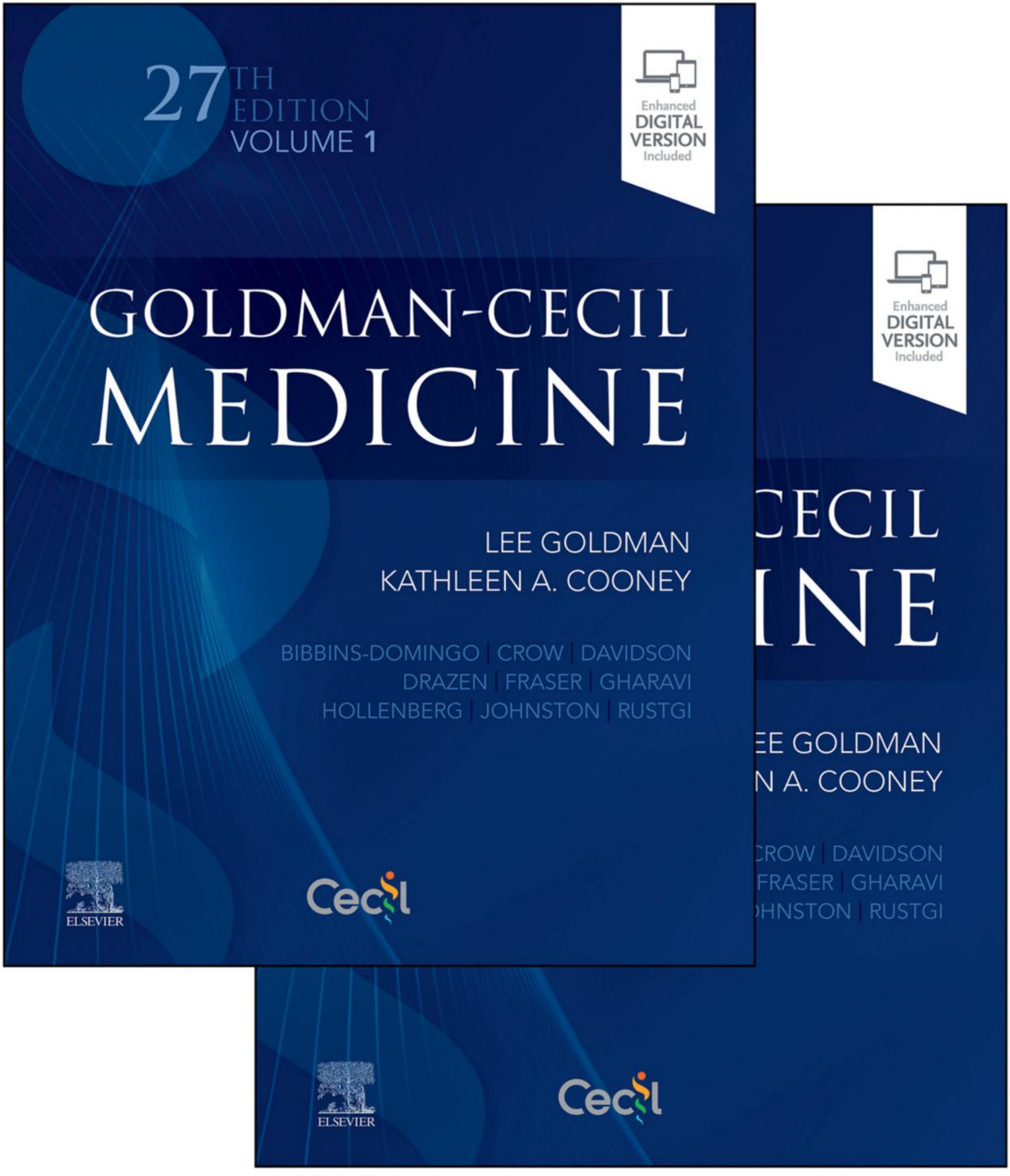

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GOLDMAN-CECIL MEDICINE

27TH EDITION

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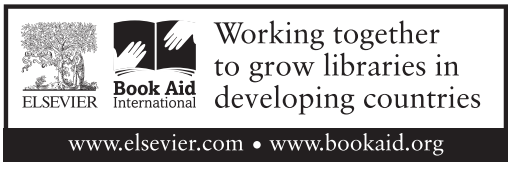

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PREFACE

In the more than 95 years since the first edition of the *Cecil Textbook of Medicine* was published, almost everything we know about internal medicine has changed. Progress in medical science is now occurring at an ever-accelerating pace, and it is doing so within the framework of transformational changes in biomedical science, clinical practice, and the delivery of health care at individual, societal, and global levels. This textbook and its associated electronic products incorporate the latest medical knowledge in multiple formats that should appeal to students and seasoned practitioners, regardless of how they prefer to access this rapidly changing information.

Even as *Cecil*'s specific information has changed, however, we have remained true to the tradition of a comprehensive textbook of medicine that carefully explains the *why* (the underlying genetics, genomics, and pathobiology of disease) and the *how* (now expected to be evidence-based from randomized controlled trials and meta-analyses). Descriptions of physiology and pathophysiology include the latest genetic advances in a practical format that strives to be useful to the nonexpert so that care can truly be as precise and personalized as possible.

Medicine has entered an era when the acuity of illness and the limited time available to evaluate a patient threaten the ability of physicians to satisfy their intellectual curiosity. As a result, the acquisition of information, quite easily achieved in this era, is often confused with knowledge. We have attempted to address this dilemma with a textbook that not only informs but also stimulates new questions and gives a glimpse of the future path to new knowledge. Grade A evidence is specifically highlighted in the text and referenced at the end of each chapter.

In addition to the information provided in the printed textbook and its electronic version, *Cecil* is commonly accessed on Elsevier's electronic Clinical Key platform. *Cecil* content and graphics are specifically organized to optimize not only its readability but also the searchability and utility of these electronic versions, which are continuously updated to incorporate new Grade A references and other evidence.

The section for each organ system begins with a chapter that summarizes an approach to patients with suspected or known dysfunction of that organ system. As summarized in E-Table 1-1, the text specifically provides clear, concise information regarding how a physician should approach more than 150 common symptoms, signs, and laboratory abnormalities, usually with a flow diagram, a table, or both for easy reference. In this way, *Cecil* remains a comprehensive text to guide diagnosis and therapy, not only for patients with suspected or known diseases, but also for patients who may have undiagnosed symptoms or signs that require an initial evaluation.

Just as each edition brings new authors, it also reminds us of our gratitude to past editors and authors. Previous senior editors of *Cecil* include a short but remarkably distinguished group of leaders of American medicine: Russell Cecil, Robert Loeb, Paul Beeson, Walsh McDermott, James Wyngaarden, Lloyd H. Smith, Jr., Fred Plum, J. Claude Bennett, Dennis Ausiello, and Andrew Schafer. As we welcome a group of outstanding new editors—Kathleen A. Cooney, Kirsten Bibbins-Domingo, Victoria J. Fraser, Ali G. Gharavi, Anthony N. Hollenberg, and S. Claiborne Johnston—we also express our appreciation to Robert C. Griggs, Donald W. Landry, Wendy Levinson, W. Michael Scheld, Allen M. Spiegel, and other associate editors from previous editions on whose foundation we continue to build. Our returning associate editors—Mary K. Crow, Nancy E. Davidson, Jeffrey M. Drazen, Anil K. Rustgi—continue to make critical contributions to the selection of authors and the review and approval of all chapters in their respective sections.

The tradition of *Cecil* is that all chapters are written by distinguished experts in each field. All told, our 409 chapters and the Appendix are written by approximately 570 individual authors. Steven A. Seifert, an author of the chapter on "Envenomation, Bites, and Stings," passed away after submitting his chapter, and we deeply mourn his passing.

The editors are most grateful for the superb editorial assistance of Maribel Lim, who expertly coordinated a team that included Caroline Davidson, Pamela Ehn, Julie Mangoff, and Joan Dupont, and without whose dedication, perseverance, and attention to detail this book never would have been possible. At Elsevier, we are most indebted to Dolores Meloni, Laura Schmidt, Daniel Fitzgerald, and Maggie Reid—dedicated professionals who have been critical to the planning and production of this edition.

This edition of *Goldman-Cecil Medicine* includes many new authors. We would also like to thank outgoing authors, who often provided figures that are included in this edition as well as tables that have been included or modified for this edition. Furthermore, because of the templated format and extensive editing that are characteristic of *Goldman-Cecil Medicine*, some new chapters incorporate principles, concepts, and organizational aspects from those prior chapters, often revised extensively prior to publication. Prior authors whose 26th edition coauthors have revised and updated their chapters include: Jeffrey L. Anderson, Gerald B. Appel, David Atkins, Richard L. Barbano, Stephen G. Baum, Hasan Bazari, George A. Beller, Paul D. Berk, Philip J. Bierman, Michael R. Bishop, William A. Blattner, William Bonnez, David M. Buchner, Edgar M. Carvalho, Troy E. Daniels, W. Lawrence Drew, George L. Drusano, David O. Freedman, John N. Galgiani, Jeffrey S. Ginsberg, Colleen Hadigan, Frederick G. Hayden, Douglas C. Heimburger, Edward W. Hook, III, Michael R. Jaff, Alain Joffe, Sian Jones, Carol A. Kauffman, Anthony E. Lang, Geoffrey S.F. Ling, Kieren A. Marr, Eric L. Matteson, William J. McKenna, Theodore E. Nash, Lindsay E. Nicolle, David L. Paterson, Srinivasa N. Raja, Daniel E. Rusyniak, George Sakoulas, Robert A. Salata, William Schaffner, W. Michael Scheld, Harry Shamoon, Richard M. Siegel, David P. Steensma, Raymond A. Strikas, and Ronald B. Turner. Special thanks also to Morton J. Kern, Gary S. Firestein, and Stephanie M. Stanford, whose excellent chapters were eliminated to save space, with their key information shortened and incorporated into other chapters. We also thank other non-returning authors from the 26th edition, many of whom had contributed to multiple editions: Grover C. Bagby, Thomas P. Bleck, Olaf A. Bodamer, Patrick J. Bosque, Lucy Breakwell, John C. Byrd, Clara Camaschella, Jane A. Cauley, William P. Cheshire, Jr., Arun Chockalingam, Steven L. Cohn, David S. Cooper, Joseph Craft, Mark R. Cullen, Stephen C. Dreskin, Thomas D. DuBose, Jr., Herbert L. DuPont, George M. Eliopoulos, Jerrold J. Ellner, Joel D. Ernst, Gregory T. Everson, Amelia Evoli, Martyn A. French, Susan I. Gerber, Dale N. Gerding, Matthew R. Golden, Richard M. Gore, Leslie C. Grammer, M. Lindsay Grayson, Lev M. Grinberg, Rajesh Gupta, H. Hunter Handsfield, David J. Hunter, Karen R. Jacobson, Stuart Johnson, Jacqueline Jonklaas, Gerald T. Keusch, Alexander Kratz, Virginia Byers Kraus, Frank A. Lederle, William M. Lee, James E. Leggett, Glenn N. Levine, Marc S. Levine, Bennett Lorber, Daniel R. Lucey, Peter Manu, Xavier Mariette, Thomas J. Marrie, Emeran A. Mayer, Stephan A. Mayer, Graeme Meintjes, Jonathan W. Mink, William E. Mitch, Bruce A. Molitoris, José G. Montoya, Daniel M. Musher, Stanley J. Naides, Anne T. Neff, Anne B. Newman, Gaetane Nocturne, James R. O'Dell, Pablo C. Okhuysen, Pankaj Jay Pasricha, Manisha Patel, Michael A. Pesce, James D. Ralston, Adam J. Ratner, Susan E. Reef, David B. Reuben, Karen Rosene-Montella, Renato M. Santos, Sam Schulman, Wun-Ju Shieh, Michael S. Simberkoff, Eric J. Small, Magdalena E. Sobieszczyk, Roland W. Sutter, Ronald G. Victor, Angela Vincent, Tonia L. Vincent, Edward H. Wagner, John T. Watson, David A. Weinstein, Anita K.M. Zaidi, Sherif Zaki, and Thomas Ziegler. We also thank Peter S. Aronson, who contributed to the chapter on "Acid-Base Disorders"; Ghada Hijazi, who contributed to the chapter on "Glycogen Storage Diseases"; Alexander Hillel, who contributed to the chapter on "Throat Disorders"; and Jason Pan, who contributed to the chapter on "Hepatic Failure and Liver Transplantation." Chapters written by public employees reflect recommendations and conclusions of

the authors and do not necessarily reflect the official position of the entity for which they work.

My work on this and previous editions would not have been possible without mentors such as Robert Gifford, Eugene Braunwald, P. Roy Vagelos, and the late Lloyd H. Smith, Jr. I am also especially indebted to Jill and the entire Goldman family (Jeff, Abigail, Mira, Samuel, Daniel, Morgan, Quincy, Robyn, Tobin, Dashel, and Alden), who have not only tolerated but actually inspired the countless hours required to edit a book that attempts to sustain the *Cecil* tradition and to meet the needs of today's physicians.

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The Thalassemias

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Valvular Heart Disease

ALGrawany

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Anaphylaxis; Drug Allergy

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Malnutrition: Assessment and Support

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Alcoholic and Nonalcoholic Steatohepatitis

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Staphylococcal Infections

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Hematopoietic Cell Transplantation

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Leishmaniasis

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Hemorrhagic Cerebrovascular Disease

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Approach to the Patient Before and After Travel

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Cryptococcosis

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Urticaria, Drug Hypersensitivity Rashes, Nodules and Tumors, and Atrophic Diseases

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Physical and Chemical Injuries of the Lung

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Neoplasms of the Small and Large Intestine

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Bioterrorism

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Diseases of the Visual System

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Measuring Health and Health Care

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Gram-Positive Rod Infections

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Fibromyalgia

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Approach to the Patient with Endocrine Disease

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Vascular Disorders of the Kidney

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Treatment of Irreversible Renal Failure

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Varicella-Zoster Virus (Chickenpox, Shingles)

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Approach to the Patient with a Sexually Transmitted Infection; COVID-19: Epidemiology, Clinical Manifestations, Diagnosis, Community Prevention, and Prognosis; Prevention of Human Immunodeficiency Virus Infection

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Pain

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Hodgkin Lymphoma

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Approach to the Patient in a Critical Care Setting

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Retroviruses Other Than Human Immunodeficiency Virus

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Approach to Medicine, the Patient, and the Medical Profession: Medicine as a Learned and Humane Profession; Prostate Cancer

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Approach to Inborn Errors of Metabolism

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Leishmaniasis

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Approach to Medicine, the Patient, and the Medical Profession: Medicine as a Learned and Humane Profession; The Innate and Adaptive Immune Systems; Approach to the Patient with Rheumatic Disease; Systemic Lupus Erythematosus

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Salmonella *Infections (Including Enteric Fever)*

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Amyotrophic Lateral Sclerosis and Other Motor Neuron Diseases

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Primary Immunodeficiency Diseases

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Osteonecrosis, Osteosclerosis/Hyperostosis, and Other Disorders of Bone

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Smallpox, Monkeypox, and Other Poxvirus Infections

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Nutritional and Alcohol-Related Neurologic Disorders

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Envenomation, Bites, and Stings

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Approach to Medicine, the Patient, and the Medical Profession: Medicine as a Learned and Humane Profession; Breast Cancer and Benign Breast Disorders

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Laboratory Testing in the Rheumatic Diseases

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Tumors of the Central Nervous System

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Interventional and Surgical Approaches to Lung Disease

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Microcytic and Hypochromic Anemias

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COVID-19: Epidemiology, Clinical Manifestations, Diagnosis, Community Prevention, and Prognosis; Prevention of Human Immunodeficiency Virus Infection

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Approach to the Patient with Neurologic Disease

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Systemic Antifungal Agents

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Rhabdomyolysis

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Aplastic Anemia and Related Bone Marrow Failure States

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Diabetes Mellitus

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Principles of Drug Therapy

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Nematode Infections

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Headaches and Other Head Pain

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Noninvasive Cardiac Imaging

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Syphilis and Nonsyphilitic Treponematoses

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Von Willebrand Disease and Hemorrhagic Abnormalities of Platelet and Vascular Function

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Amyloidosis

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Leprosy (Hansen Disease)

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Approach to the Patient with Cancer

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Papillomavirus

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Approach to Medicine, the Patient, and the Medical Profession: Medicine as a Learned and Humane Profession; Asthma

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Approach to the Patient with Urinary Tract Infection

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Clostridial and Clostridioides *Infections*

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Urinary Incontinence

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Zoonoses

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Urticaria, Drug Hypersensitivity Rashes, Nodules and Tumors, and Atrophic Diseases

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Effects of Climate Change on Health

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Parainfluenza Viral Disease

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Crystal Deposition Diseases

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Venous Thrombosis and Embolism

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Testicular Cancer

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Diseases of the Myocardium and Endocardium

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Diane v.S. Levy & Robert M. Levy Professor and Vice Provost for Global Initiatives, University of Pennsylvania, Philadelphia, Pennsylvania
Bioethics in the Practice of Medicine

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Pseudomonas *and* Burkholderia *Infections*

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Diseases of the Esophagus

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ST-Elevation Acute Myocardial Infarction and Complications of Myocardial Infarction

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Haemophilus *and* Moraxella *Infections*

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Intimate Partner Violence

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Interventional and Surgical Approaches to Lung Disease

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Streptococcus pneumoniae *Pulmonary Infections*

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Principles of Electrophysiology

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Arterial Hypertension

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Approach to the Patient with Suspected Enteric Infection

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Overview of Anesthesia

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Throat Disorders

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Diseases of the Gallbladder and Bile Ducts

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Liver Failure and Transplantation

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Pancreatitis

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Rickettsial Infections

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Infective Endocarditis

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Rotaviruses, Noroviruses, and Other Gastrointestinal Viruses

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Approach to Medicine, the Patient, and the Medical Profession: Medicine as a Learned and Humane Profession; Introduction to Microbial Disease: Pathophysiology and Diagnostics; Legionella *Infections*

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Autonomic Disorders

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Approach to Women's Health

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Chronic Poisoning: Trace Metals and Others

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Hemolytic Anemias: Red Blood Cell Membrane and Metabolic Defects

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COVID-19: Epidemiology, Clinical Manifestations, Diagnosis, Community Prevention, and Prognosis

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COVID-19 Treatment and Vaccination

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Ventricular Arrhythmias

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Cirrhosis and Its Sequelae

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Diseases Caused by Chlamydiae

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Eczemas, Photodermatoses, Papulosquamous (Including Fungal) Diseases, and Figurate Erythemas

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Regenerative Medicine, Cell Therapy, and Gene Therapy

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Amyloidosis

ALGrawany

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Syphilis and Nonsyphilitic Treponematoses

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Approach to Medicine, the Patient, and the Medical Profession: Medicine as a Learned and Humane Profession; Approach to the Patient with Renal Disease

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Whooping Cough and Other Bordetella *Infections*

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Applications of Molecular Technologies to Clinical Medicine

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Systemic Manifestations of HIV/AIDS

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Herpes Simplex Virus Infections

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Mycoplasma *Infections*

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Approach to Medicine, the Patient, and the Medical Profession: Medicine as a Learned and Humane Profession; Approach to the Patient with Possible Cardiovascular Disease; Bradycardias and Conduction System Delays; Supraventricular Ectopy and Tachyarrhythmias

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Approach to Cerebrovascular Diseases; Ischemic Cerebrovascular Disease

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Shock Syndromes Related to Sepsis

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Polycythemia Vera, Essential Thrombocythemia, and Primary Myelofibrosis

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Cholera and Other Vibrio *Infections*

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Principles of Occupational and Environmental Medicine

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Rotaviruses, Noroviruses, and Other Gastrointestinal Viruses

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Coma, Disorders of Consciousness, and Brain Death

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Medical Care of Patients with Psychiatric Diseases

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Overview of Pneumonia

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Approach to the Patient with Neurologic Disease

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Contraception

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Hereditary Nephropathies and Developmental Renal/Urinary Abnormalities

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Nonpneumococcal Streptococcal Infections and Rheumatic Fever

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Diabetes and the Kidney

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Diet and Nutrition

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Effects of Climate Change on Health

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Whooping Cough and Other Bordetella *Infections*

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The Porphyrias

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Giardiasis

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Respiratory Monitoring in Critical Care

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Transfusion Medicine

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Polyomaviruses

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Pulmonary Hypertension

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Pericardial Diseases

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Complement System in Disease

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The Nontuberculous Mycobacteria

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John Wade Professor and Chair, Department of Medicine, Boston University Chobanian & Avedisian School of Medicine; Physician-in-Chief, Boston Medical Center, Boston, Massachusetts
Approach to Medicine, the Patient, and the Medical Profession: Medicine as a Learned and Humane Profession; Thyroid

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Cardiogenic Shock

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Sickle Cell Disease and Other Hemoglobinopathies

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Osteoarthritis

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Hypoglycemia

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Sarcoidosis

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Spondyloarthritis

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Delirium and Changes in Mental Status

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Influenza; Adenovirus Diseases

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Neuro-Ophthalmology; Smell and Taste; Hearing and Equilibrium

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Gastrointestinal Hemorrhage

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Obesity

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Neuroendocrine Neoplasms

ALGrawany

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Approach to Medicine, the Patient, and the Medical Profession: Medicine as a Learned and Humane Profession; Approach to the Patient with Neurologic Disease

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Malignant Bone Tumors, Sarcomas, and Other Soft Tissue Neoplasms

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Diseases of the Mouth and Salivary Glands

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Vascular Diseases of the Gastrointestinal Tract

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Viral Hemorrhagic Fevers

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Disorders of Neuromuscular Transmission

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Malaria

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Chronic Poisoning: Trace Metals and Others

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Benign Prostatic Hyperplasia and Prostatitis

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The Systemic Autoinflammatory Diseases

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Diseases of the Esophagus

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Adolescent Medicine

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Hematopoiesis and Hematopoietic Growth Factors

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Diseases Caused by Acinetobacter *and* Stenotrophomonas *Species*

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Hematopoietic Cell Transplantation

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Liver and Biliary Tract Tumors

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Rubella (German Measles)

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Lung Cancer and Other Pulmonary Neoplasms

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Gram-Positive Rod Infections

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Chagas Disease

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Medical Epidemiologist, National Center for Immunization and Respiratory Diseases, US Centers for Disease Control and Prevention; Assistant Professor, Department of Medicine, Emory University, Atlanta, Georgia
Pre-2019 Coronaviruses

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Interventional Diagnosis and Treatment of Coronary Artery Disease

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Glycogen Storage Diseases

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Neisseria gonorrhoeae *Infections*

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Eosinophilic Syndromes

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Overview of Pneumonia

David S. Knopman, MD
Robert H. and Susan M. Rewoldt Professorship in Neurology Honoring Bradley F. Boeve, M.D., Mayo Clinic College of Medicine and Science, Rochester, Minnesota
Regional Cerebral Dysfunction: Higher Mental Functions; Cognitive Impairment and Dementia

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Approach to Skin Diseases

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Valvular Heart Disease

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Robert C. Hickey Chair in Clinical Care and Deputy Head, Division of Internal Medicine, The University of Texas MD Anderson Cancer Center, Houston, Texas
Mucormycosis; Mycetoma and Dematiaceous Fungal Infections

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Nutritional and Alcohol-Related Neurologic Disorders

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Approach to the Patient with Jaundice or Abnormal Liver Tests

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Principles of Genetics

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Bioterrorism

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Toxoplasmosis

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Antiviral Therapy (Non-HIV)

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Pneumocystis *Pneumonia*

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Gastrointestinal Hemorrhage

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Iron Overload (Hemochromatosis)

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Murray M. Rosenberg Professor and System Chair, Samuel Bronfman Department of Medicine, Icahn School of Medicine at Mount Sinai and Mount Sinai Health System, New York, New York
Approach to the Patient with Respiratory Disease

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Noninvasive Cardiac Imaging

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Lysosomal Storage Diseases

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Physical Activity

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Babesiosis and Other Protozoan Diseases

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Immunization

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Macular, Papular, Purpuric, Vesiculobullous, and Pustular Diseases

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Inflammatory and Anatomic Diseases of the Intestine, Peritoneum, Mesentery, and Omentum

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Acid Peptic Disease

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Professor of Medicine, University of Colorado School of Medicine, Aurora, Colorado
Palliative Care

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Pancreatic Cancer

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Cardiac Arrest and Life-Threatening Arrhythmias

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Geriatric Assessment

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Prevention of Human Immunodeficiency Virus Infection

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Approach to the Patient with Renal Disease

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Acute Coronary Syndrome: Unstable Angina and Non–ST Elevation Myocardial Infarction

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Psychiatric Disorders in Medical Practice

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Influenza

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Chronic Kidney Disease

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Alveolar Filling Disorders

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Inflammatory Bowel Disease

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Diseases of the Visual System

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Drug Use Disorders

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Eczemas, Photodermatoses, Papulosquamous (Including Fungal) Diseases, and Figurate Erythemas

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Cryptosporidiosis

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Cytomegalovirus

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Ray L Watts Heersink Endowed Chair and Professor, Departments of Neurology and of Epidemiology; Director, Translational Pharmacogenomics Program and Associate Director, Hugh Kaul Precision Medicine Institute, University of Alabama Birmingham Heersink School of Medicine, Birmingham, Alabama
Principles of Genetics

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Electrocardiography

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Staphylococcal Infections

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Eileen M. Foell Professor of Heart Research; Professor of Preventive Medicine, Medicine, and Pediatrics; Chair, Department of Preventive Medicine; Northwestern University Feinberg School of Medicine, Chicago, Illinois
Epidemiology of Cardiovascular Disease

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Tularemia and Other Francisella *Infections*

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Antibacterial Chemotherapy

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Psychiatric Disorders in Medical Practice

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C. Ronald MacKenzie Chair in Ethics and Medicine, Hospital for Special Surgery; Professor of Clinical Medicine and Medical Ethics, Weill Medical College of Cornell University, New York, New York
Surgical Treatment of Joint Diseases

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Shigellosis

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Intimate Partner Violence

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Diseases of the Rectum and Anus

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Alcoholic and Nonalcoholic Steatohepatitis

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Physical and Chemical Injuries of the Lung

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Pathobiology of Human Immunodeficiency Viruses

Atul Malhotra, MD
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Disorders of Ventilatory Control

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Helene B. Roberson Professor of Pediatrics, Washington University, St. Louis, Missouri
Severe Malnutrition

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Trematode Infections

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Congenital Heart Disease in Adults

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Cardiac and Circulatory Function

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Legionella *Infections*

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Approach to the Patient with Liver Disease

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Interstitial Lung Disease

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Vitamins, Trace Minerals, and Other Micronutrients

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Microbial Complications of HIV/AIDS

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Enterobacterales: Non-Enteric Infections and Multidrug Resistance

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Acute Respiratory Failure

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Diseases of the Diaphragm, Chest Wall, Pleura, and Mediastinum

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Rheumatoid Arthritis

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Pulmonary Hypertension

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Infections, Pigmentation Disorders, Regional Dermatology, and Distinctive Lesions in Black Skin

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Heart Failure: Treatment and Prognosis

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Approach to the Patient with Gastrointestinal Disease

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Plague and Other Yersinia *Infections*

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Approach to the Anemias

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Approach to Fever or Suspected Infection in the Normal Host

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Tumors of the Central Nervous System

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Professor of Surgery, University of Minnesota Medical School, Minneapolis, Minnesota
Diseases of the Rectum and Anus

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Systemic Manifestations of HIV/AIDS

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Endemic Mycoses

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Autoimmune and Intravascular Hemolytic Anemias

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Measuring Health and Health Care

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Acute Coronary Syndrome: Unstable Angina and Non–ST Elevation Myocardial Infarction

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Approach to the Patient with Nose, Sinus, and Ear Disorders

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Cardiac Arrest and Life-Threatening Arrhythmias

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Approach to the Patient with Allergic or Immunologic Disease

A L G r a w a n y

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Meningitis: Bacterial, Viral, and Other; Brain Abscess and Parameningeal Infections

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Menopause

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Interstitial Nephritis

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Plague and Other Yersinia *Infections*

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Medical Issues in Pregnancy

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Acute Poisoning

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Biology of Addiction

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COVID-19 Treatment and Vaccination

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Approach to the Patient with Endocrine Disease; Adrenal Cortex; Polyglandular Disorders

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Respiratory Testing and Function

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Heart Failure: Epidemiology, Pathobiology, and Diagnosis

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Disorders Due to Heat and Cold; Rhabdomyolysis

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Alcohol Use Disorders

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Bronchiectasis, Atelectasis, Cavitary, or Cystic Lung Diseases

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Von Willebrand Disease and Hemorrhagic Abnormalities of Platelet and Vascular Function

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Pericardial Diseases

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Parkinsonism; Other Movement Disorders

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Papillomavirus

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Approach to the Patient with Suspected Arrhythmia

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Diseases of the Myocardium and Endocardium

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Biologic Agents and Signaling Inhibitors

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Immunization

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Antithrombotic and Antiplatelet Therapy

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Biologic Agents and Signaling Inhibitors

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Infections of Bursae, Joints, and Bones

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Parkinsonism; Other Movement Disorders

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Mucormycosis

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Measles

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Rubella (German Measles)

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Candidiasis; Mycetoma and Dematiaceous Fungal Infections

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Introduction to Microbial Disease: Pathophysiology and Diagnostics

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Acute Viral Hepatitis; Chronic Viral and Autoimmune Hepatitis

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Statistical Interpretation of Data for Clinical Decision Making

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Thyroid

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Antiparasitic Therapy

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Enterococcal Infections

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Smallpox, Monkeypox, and Other Poxvirus Infections

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Relapsing Fever and Other Borrelia *Infections; African Sleeping Sickness; Amebiasis*

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Heart Failure: Treatment and Prognosis

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Laboratory Testing in the Rheumatic Diseases

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Approach to the Patient with Nose, Sinus, and Ear Disorders

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Pre-2019 Coronaviruses

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Rubella (German Measles)

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Disorders of Ventilatory Control

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Inherited Diseases of Connective Tissue

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Epidemiology and Diagnosis of Human Immunodeficiency Virus Infection and Acquired Immunodeficiency Syndrome; Acute Clinical Manifestations and Diagnosis of HIV

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COVID-19: Virology and Pathology

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Disorders of Sodium and Water; Glomerular Disorders and Nephrotic Syndromes

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Chronic Myeloid Leukemia

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Pseudomonas *and* Burkholderia *Infections*

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Paget Disease of Bone

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Bartonella *Infections; Rickettsial Infections*

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Gram-Positive Rod Infections

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Bacterial, Parasitic, Fungal, and Granulomatous Liver Diseases

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Chronic Obstructive Pulmonary Disease

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Zoonoses

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Diseases Caused by Chlamydiae

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Urinary Incontinence

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Principles of Anti-Infective Therapy

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Developmental and Neurocutaneous Disorders

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Disorders of Lipid Metabolism

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Immunomodulatory Drugs

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Heart Failure: Epidemiology, Pathobiology, and Diagnosis

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Bartonella *Infections*

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Histiocytoses

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Mumps

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Malaria

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Shock Syndromes Related to Sepsis

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Approach to Medicine, the Patient, and the Medical Profession: Medicine as a Learned and Humane Profession; Neoplasms of the Esophagus and Stomach

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Tissue Injury and Repair

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Menopause

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Disorders Due to Heat and Cold

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Respiratory Testing and Function

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Thrombotic Disorders: Hypercoagulable States; Approach to the Patient with Bleeding or Thrombosis; Disseminated Intravascular Coagulation and Bleeding in Liver Failure

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Homocystinuria and Hyperhomocysteinemia

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Wilson Disease

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Whipple Disease

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Approach to the Patient with Abnormal Vital Signs

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Melanoma and Nonmelanoma Skin Cancers

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Potassium Disorders; Acid-Base Disorders

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Approach to the Patient with Diarrhea and Malabsorption

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Approach to Fever and Suspected Infection in the Immunocompromised Host

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Principles of Medical Consultation

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Approach to the Patient with a Sexually Transmitted Infection

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Endemic Mycoses

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Nutritional and Alcohol-Related Neurologic Disorders

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A L G r a w a n y

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CONTENTS

VOLUME 1

SECTION I: SOCIAL AND ETHICAL ISSUES IN MEDICINE

1 Approach to Medicine, the Patient, and the Medical Profession: Medicine as a Learned and Humane Profession 2
LEE GOLDMAN, KATHLEEN A. COONEY, KIRSTEN BIBBINS-DOMINGO, MARY K. CROW, NANCY E. DAVIDSON, JEFFREY M. DRAZEN, VICTORIA J. FRASER, ALI G. GHARAVI, ANTHONY N. HOLLENBERG, S. CLAIBORNE JOHNSTON, AND ANIL K. RUSTGI

2 Bioethics in the Practice of Medicine 5
EZEKIEL J. EMANUEL

3 Palliative Care 11
ROBERT M. ARNOLD AND JEAN S. KUTNER

4 Disparities in Health and Health Care 17
JOHN Z. AYANIAN

5 Global Health 21
ALI H. MOKDAD

SECTION II: PRINCIPLES OF EVALUATION AND MANAGEMENT

6 History and Physical Examination 28
DAVID L. SIMEL

7 Approach to the Patient with Abnormal Vital Signs 32
DAVID L. SCHRIGER

8 Statistical Interpretation of Data for Clinical Decision Making 35
THOMAS H. PAYNE

9 Measuring Health and Health Care 40
CAROLYN M. CLANCY AND ERNEST MOY

10 Quality, Safety, and Value 43
ROBERT M. WACHTER AND KAVEH G. SHOJANIA

11 Population Health 47
KIRSTEN BIBBINS-DOMINGO

SECTION III: PREVENTIVE AND ENVIRONMENTAL ISSUES

12 The Preventive Health Visit 52
MARY B. BARTON AND TRACY A. WOLFF

13 Diet and Nutrition 57
DONALD D. HENSRUD

14 Physical Activity 61
WILLIAM E. KRAUS

15 Immunization 64
ANDREW T. KROGER AND WALTER A. ORENSTEIN

16 Principles of Occupational and Environmental Medicine 84
JUDITH GREEN-MCKENZIE

17 Effects of Climate Change on Health 89
JEREMY HESS AND KRISTIE EBI

18 Radiation Injury 91
DAVID J. BRENNER

19 Bioterrorism 95
MARK G. KORTEPETER AND THEODORE J. CIESLAK

20 Chronic Poisoning: Trace Metals and Others 101
LOUISE W. KAO, LAURA TORMOEHLEN, AND BLAKE A. FROBERG

SECTION IV: AGE-SPECIFIC AND GERIATRIC MEDICINE

21 Adolescent Medicine 110
DEBRA K. KATZMAN AND S. TODD CALLAHAN

22 Epidemiology of Aging 114
LOUISE ARONSON

23 Geriatric Assessment 116
C. SETH LANDEFELD

24 Common Clinical Sequelae of Aging 120
JEREMY D. WALSTON

SECTION V: CLINICAL PHARMACOLOGY

25 Principles of Drug Therapy 126
ROBERT B. DIASIO

26 Pain 133
STEVEN P. COHEN

27 Biology of Addiction 142
ERIC J. NESTLER

28 Immunomodulatory Drugs 144
ANNE R. BASS AND INEZ ROGATSKY

29 Biologic Agents and Signaling Inhibitors 149
NANCY J. OLSEN AND JOHN J. O'SHEA

30 Complementary and Integrative Medicine 153
FREDERICK M. HECHT

SECTION VI: GENETICS

31 Principles of Genetics 158
BRUCE R. KORF AND NITA A. LIMDI

32 Clinical Genomics—Genome Structure and Variation 160
LESLIE G. BIESECKER

33 Applications of Molecular Technologies to Clinical Medicine 165
GEOFFREY S. GINSBURG

34 Regenerative Medicine, Cell Therapy, and Gene Therapy 169
LIOR GEPSTEIN AND KARL SKORECKI

SECTION VII: PRINCIPLES OF IMMUNOLOGY AND INFLAMMATION

35 The Innate and Adaptive Immune Systems 182
MARY K. CROW

36 Tissue Injury and Repair 191
JANE E. SALMON

37 Complement System in Disease 196
JOHN P. ATKINSON AND V. MICHAEL HOLERS

38 Transplantation Immunology 203
MEGAN SYKES

SECTION VIII: HEART DISEASES

39 Approach to the Patient with Possible Cardiovascular Disease 210
LEE GOLDMAN

40 Epidemiology of Cardiovascular Disease 219
DONALD M. LLOYD-JONES

41 Cardiac and Circulatory Function 223
ANDREW R. MARKS

Copyrighted material

42 Electrocardiography 228
LEONARD GANZ AND MARK S. LINK

43 Echocardiography 235
CATHERINE M. OTTO

44 Noninvasive Cardiac Imaging 244
CHRISTOPHER M. KRAMER, VASKEN DILSIZIAN, AND KLAUS D. HAGSPIEL

45 Heart Failure: Epidemiology, Pathobiology, and Diagnosis 254
JOSEPH G. ROGERS AND CHRISTOPHER M. O'CONNOR

46 Heart Failure: Treatment and Prognosis 262
JOHN J.V. MCMURRAY AND MARC A. PFEFFER

47 Diseases of the Myocardium and Endocardium 279
PERRY M. ELLIOTT AND IACOPO OLIVOTTO

48 Principles of Electrophysiology 298
GLENN I. FISHMAN

49 Approach to the Patient with Suspected Arrhythmia 303
JEFFREY E. OLGIN

50 Cardiac Arrest and Life-Threatening Arrhythmias 312
ROBERT J. MYERBURG AND RACHEL LAMPERT

51 Bradycardias and Conduction System Delays 317
PETER ZIMETBAUM AND LEE GOLDMAN

52 Supraventricular Ectopy and Tachyarrhythmias 322
PETER ZIMETBAUM AND LEE GOLDMAN

53 Ventricular Arrhythmias 332
HASAN GARAN

54 Electrophysiologic Procedures and Surgery 340
PETER A. SANTUCCI AND DAVID J. WILBER

55 Congenital Heart Disease in Adults 347
JUDITH THERRIEN AND ARIANE J. MARELLI

56 Angina Pectoris and Chronic Ischemic Heart Disease 356
WILLIAM E. BODEN

57 Acute Coronary Syndrome: Unstable Angina and Non–ST Elevation Myocardial Infarction 370
RICHARD A. LANGE AND DEBABRATA MUKHERJEE

58 ST-Elevation Acute Myocardial Infarction and Complications of Myocardial Infarction 380
FREDERICK G.P. WELT AND JAMES C. FANG

59 Interventional Diagnosis and Treatment of Coronary Artery Disease 393
PAUL S. TEIRSTEIN AND AJAY J. KIRTANE

60 Valvular Heart Disease 400
BLASE A. CARABELLO AND SUSHEEL KODALI

61 Infective Endocarditis 413
VANCE G. FOWLER, JR., ARNOLD S. BAYER, AND LARRY M. BADDOUR

62 Pericardial Diseases 423
BRIAN D. HOIT AND JAE K. OH

SECTION IX: VASCULAR MEDICINE

63 Diseases of the Aorta 436
JOSHUA A. BECKMAN

64 Arterial Hypertension 444
JOHN M. FLACK

65 Atherosclerotic Peripheral Arterial Disease 461
CHRISTOPHER J. WHITE

66 Other Peripheral Arterial Diseases 467
JOHN R. BARTHOLOMEW

67 Thrombotic Disorders: Hypercoagulable States 475
ANDREW I. SCHAFER

68 Venous Thrombosis and Embolism 482
JEFFREY I. WEITZ AND JOHN W. EIKELBOOM

69 Pulmonary Hypertension 493
MARIUS M. HOEPER AND VALLERIE MCLAUGHLIN

70 Antithrombotic and Antiplatelet Therapy 501
RICHARD C. BECKER AND THOMAS L. ORTEL

SECTION X: RESPIRATORY DISEASES

71 Approach to the Patient with Respiratory Disease 512
MONICA KRAFT

72 Imaging in Pulmonary Disease 519
PAUL STARK

73 Respiratory Testing and Function 528
PAUL D. SCANLON AND ALEXANDER S. NIVEN

74 Disorders of Ventilatory Control 534
ATUL MALHOTRA AND FRANK POWELL

75 Asthma 537
JEFFREY M. DRAZEN AND ELISABETH H. BEL

76 Chronic Obstructive Pulmonary Disease 547
JOHN REILLY

77 Cystic Fibrosis 556
HARTMUT GRASEMANN

78 Bronchiectasis, Atelectasis, and Cavitary or Cystic Lung Diseases 560
ANNE E. O'DONNELL

79 Alveolar Filling Disorders 566
STEPHANIE M. LEVINE

80 Interstitial Lung Disease 570
GANESH RAGHU AND FERNANDO J. MARTINEZ

81 Occupational Lung Disease 584
SUSAN M. TARLO AND CARRIE A. REDLICH

82 Physical and Chemical Injuries of the Lung 591
DAVID C. CHRISTIANI AND LISA A. MAIER

83 Sarcoidosis 599
MICHAEL C. IANNUZZI

84 Acute Bronchitis and Tracheitis 605
GONZALO M. BEARMAN AND RICHARD P. WENZEL

85 Overview of Pneumonia 606
LINDSEY R. BADEN, MARIE R. GRIFFIN, AND MICHAEL KLOMPAS

86 Diseases of the Diaphragm, Chest Wall, Pleura, and Mediastinum 619
F. DENNIS MCCOOL

87 Interventional and Surgical Approaches to Lung Disease 630
DAVID J. FELLER-KOPMAN AND MALCOLM M. DECAMP

SECTION XI: CRITICAL CARE MEDICINE

88 Approach to the Patient in a Critical Care Setting 636
DEBORAH J. COOK

89 Respiratory Monitoring in Critical Care 639
JAMES K. STOLLER AND NICHOLAS S. HILL

90 Acute Respiratory Failure 642
MICHAEL A. MATTHAY AND LORRAINE B. WARE

91 Mechanical Ventilation 652
LAURENT BROCHARD AND ARTHUR S. SLUTSKY

92 Approach to the Patient with Shock 658
DEREK C. ANGUS

93 Cardiogenic Shock 665
STEVEN M. HOLLENBERG AND CLYDE W. YANCY

94 Shock Syndromes Related to Sepsis 669
ANTHONY C. GORDON AND JAMES A. RUSSELL

95 Disorders Due to Heat and Cold 678
MICHAEL N. SAWKA AND FRANCIS G. O'CONNOR

96 Acute Poisoning 682
LEWIS S. NELSON AND DIANE P. CALELLO

97 Medical Aspects of Trauma and Burns 698
ROBERT L. SHERIDAN

98 Envenomation, Bites, and Stings 704
STEVEN A. SEIFERT, RICHARD C. DART, AND JULIAN WHITE

99 Rhabdomyolysis 714
FRANCIS G. O'CONNOR AND PATRICIA A. DEUSTER

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SECTION XII: RENAL AND GENITOURINARY DISEASES

100 Approach to the Patient with Renal Disease 720
ALI G. GHARAVI AND DONALD W. LANDRY

101 Structure and Function of the Kidneys 729
QAIS AL-AWQATI AND JONATHAN BARASCH

102 Disorders of Sodium and Water 733
QAIS AL-AWQATI AND JAI RADHAKRISHNAN

103 Potassium Disorders 745
JULIAN LAWRENCE SEIFTER

104 Acid-Base Disorders 752
JULIAN LAWRENCE SEIFTER

105 Disorders of Magnesium and Phosphorus 766
ALAN S.L. YU

106 Acute Kidney Injury 770
ANUPAM AGARWAL AND JONATHAN BARASCH

107 Glomerular Disorders and Nephrotic Syndromes 776
JAI RADHAKRISHNAN AND M. BARRY STOKES

108 Interstitial Nephritis 790
CYBELE GHOSSEIN AND ERIC G. NEILSON

109 Diabetes and the Kidney 795
RAYMOND C. HARRIS

110 Vascular Disorders of the Kidney 799
THOMAS M. COFFMAN AND STEPHEN R. SMITH

111 Nephrolithiasis 803
DAVID A. BUSHINSKY

112 Cystic Kidney Diseases 808
M. AMIN ARNAOUT

113 Hereditary Nephropathies and Developmental Renal/Urinary Abnormalities 815
LISA M. GUAY-WOODFORD

114 Benign Prostatic Hyperplasia and Prostatitis 821
STEVEN A. KAPLAN

115 Urinary Incontinence 827
NEIL M. RESNICK AND CATHERINE E. DUBEAU

116 Chronic Kidney Disease 831
ANDREW S. LEVEY AND MARK J. SARNAK

117 Treatment of Irreversible Renal Failure 840
DAVID COHEN AND ANTHONY MICHAEL VALERI

SECTION XIII: GASTROINTESTINAL DISEASES

118 Approach to the Patient with Gastrointestinal Disease 850
KENNETH R. MCQUAID

119 Diagnostic Imaging Procedures in Gastroenterology 866
LAURA R. CARUCCI

120 Gastrointestinal Endoscopy 875
KENNETH K. WANG

121 Gastrointestinal Hemorrhage 882
THOMAS O. KOVACS AND DENNIS M. JENSEN

122 Disorders of Gastrointestinal Motility 887
MICHAEL CAMILLERI

123 Irritable Bowel and Functional Upper Gastrointestinal Syndromes 892
LIN CHANG

124 Diseases of the Esophagus 901
GARY W. FALK AND DAVID A. KATZKA

125 Acid Peptic Disease 913
ERNST J. KUIPERS

126 Approach to the Patient with Diarrhea and Malabsorption 923
CAROL E. SEMRAD

127 Inflammatory Bowel Disease 941
GARY R. LICHTENSTEIN

128 Inflammatory and Anatomic Diseases of the Intestine, Peritoneum, Mesentery, and Omentum 951
JOHN F. KUEMMERLE

129 Vascular Diseases of the Gastrointestinal Tract 959
CHARLES J. KAHI

130 Pancreatitis 969
CHRIS E. FORSMARK

131 Diseases of the Rectum and Anus 977
ROBERT D. MADOFF AND GENEVIEVE B. MELTON

SECTION XIV: DISEASES OF THE LIVER AND BILIARY SYSTEM

132 Approach to the Patient with Liver Disease 986
PAUL MARTIN

133 Approach to the Patient with Jaundice or Abnormal Liver Tests 993
KEVIN M. KORENBLAT

134 Acute Viral Hepatitis 1002
JEAN-MICHEL PAWLOTSKY

135 Chronic Viral and Autoimmune Hepatitis 1009
JEAN-MICHEL PAWLOTSKY

136 Drug-Induced Liver Injury 1017
PAUL B. WATKINS

137 Bacterial, Parasitic, Fungal, and Granulomatous Liver Diseases 1022
K. RAJENDER REDDY

138 Alcoholic and Nonalcoholic Steatohepatitis 1031
NAGA P. CHALASANI AND JACQUELYN MAHER

139 Cirrhosis and Its Sequelae 1035
GUADALUPE GARCIA-TSAO

140 Liver Failure and Transplantation 1043
ROBERT J. FONTANA

141 Diseases of the Gallbladder and Bile Ducts 1049
EVAN L. FOGEL AND STUART SHERMAN

SECTION XV: HEMATOLOGIC DISEASES

142 Hematopoiesis and Hematopoietic Growth Factors 1064
KENNETH KAUSHANSKY

143 The Peripheral Blood Smear 1066
BARBARA J. BAIN

144 Approach to the Anemias 1074
ROBERT T. MEANS, JR.

145 Microcytic and Hypochromic Anemias 1082
THOMAS G. DELOUGHERY

146 Autoimmune and Intravascular Hemolytic Anemias 1086
MARC MICHEL

147 Hemolytic Anemias: Red Blood Cell Membrane and Metabolic Defects 1093
PATRICK G. GALLAGHER

148 The Thalassemias 1102
MARIA DOMENICA CAPPELLINI

149 Sickle Cell Disease and Other Hemoglobinopathies 1109
JO HOWARD

150 Megaloblastic Anemias 1117
SALLY P. STABLER

151 Aplastic Anemia and Related Bone Marrow Failure States 1125
AMY E. DEZERN AND ROBERT A. BRODSKY

152 Polycythemia Vera, Essential Thrombocythemia, and Primary Myelofibrosis 1130
JASON GOTLIB

153 Leukocytosis and Leukopenia 1140
NANCY BERLINER

154 Approach to the Patient with Lymphadenopathy or Splenomegaly 1148
JANE N. WINTER

155 Histiocytoses 1154
BARRETT J. ROLLINS AND NANCY BERLINER

156 Eosinophilic Syndromes 1162
AMY D. KLION

Copyrighted material

157 Approach to the Patient with Bleeding or Thrombosis 1165
ANDREW I. SCHAFER

158 Thrombocytopenia 1170
CHARLES S. ABRAMS

159 Von Willebrand Disease and Hemorrhagic Abnormalities of Platelet and Vascular Function 1180
JORGE DI PAOLA AND JAMES S. O'DONNELL

160 Coagulation Factor Deficiencies 1187
MARGARET V. RAGNI

161 Disseminated Intravascular Coagulation and Bleeding in Liver Failure 1195
ANDREW I. SCHAFER

162 Transfusion Medicine 1199
BETH H. SHAZ AND CHRISTOPHER D. HILLYER

163 Hematopoietic Cell Transplantation 1206
NELSON J. CHAO AND ARMAND KEATING

SECTION XVI: ONCOLOGY

164 Approach to the Patient with Cancer 1214
JAMES H. DOROSHOW

165 Epidemiology of Cancer 1243
RULLA M. TAMIMI

166 Cancer Biology and Genetics 1247
BEN HO PARK

167 Myelodysplastic Syndromes 1252
RICHARD M. STONE

168 The Acute Leukemias 1259
ROLAND B. WALTER AND FREDERICK R. APPELBAUM

169 Chronic Lymphocytic Leukemia 1266
JENNIFER R. BROWN

170 Chronic Myeloid Leukemia 1272
JERALD RADICH

171 Non-Hodgkin Lymphomas 1278
JULIE M. VOSE AND JAMES O. ARMITAGE

172 Hodgkin Lymphoma 1289
JOSEPH M. CONNORS AND KERRY J. SAVAGE

173 Plasma Cell Disorders 1294
S. VINCENT RAJKUMAR

174 Amyloidosis 1305
MORIE A. GERTZ AND ANGELA DISPENZIERI

175 Tumors of the Central Nervous System 1310
INGO K. MELLINGHOFF AND LISA M. DEANGELIS

176 Head and Neck Cancer 1320
JULIE E. BAUMAN

177 Lung Cancer and Other Pulmonary Neoplasms 1329
FADLO R. KHURI

178 Neoplasms of the Esophagus and Stomach 1337
ADAM J. BASS AND ANIL K. RUSTGI

179 Neoplasms of the Small and Large Intestine 1343
EDWARD CHU

180 Pancreatic Cancer 1354
DANIEL LAHERU

181 Liver and Biliary Tract Tumors 1357
ROBIN K. KELLEY AND ALAN P. VENOOK

182 Tumors of the Kidney, Bladder, Ureters, and Renal Pelvis 1362
DEAN F. BAJORIN

183 Breast Cancer and Benign Breast Disorders 1368
NANCY E. DAVIDSON

184 Gynecologic Cancers 1375
DEBORAH K. ARMSTRONG

185 Testicular Cancer 1382
LAWRENCE H. EINHORN

186 Prostate Cancer 1384
KATHLEEN A. COONEY AND ELISABETH I. HEATH

187 Malignant Bone Tumors, Sarcomas, and Other Soft Tissue Neoplasms 1387
ROBIN L. JONES

188 Melanoma and Nonmelanoma Skin Cancers 1390
LYNN M. SCHUCHTER

VOLUME 2

SECTION XVII: METABOLIC DISEASES

189 Approach to Inborn Errors of Metabolism 1398
WILLIAM J. CRAIGEN

190 Disorders of Lipid Metabolism 1404
JENNIFER G. ROBINSON

191 Glycogen Storage Diseases 1415
PRIYA S. KISHNANI

192 Lysosomal Storage Diseases 1418
DONNA M. KRASNEWICH AND ELLEN SIDRANSKY

193 Homocystinuria and Hyperhomocysteinemia 1425
MANUEL SCHIFF AND HENK J. BLOM

194 The Porphyrias 1428
RICHARD J. HIFT

195 Wilson Disease 1436
MICHAEL L. SCHILSKY

196 Iron Overload (Hemochromatosis) 1438
KRIS V. KOWDLEY

SECTION XVIII: NUTRITIONAL DISEASES

197 Severe Malnutrition 1444
MARK J. MANARY AND INDI TREHAN

198 Malnutrition: Assessment and Support 1446
TOMMY E. CEDERHOLM AND INGVAR G. BOSAEUS

199 Vitamins, Trace Minerals, and Other Micronutrients 1451
JOEL B. MASON AND SARAH L. BOOTH

200 Eating Disorders 1461
EVELYN ATTIA, MARIAN TANOFSKY-KRAFF, AND B. TIMOTHY WALSH

201 Obesity 1463
MICHAEL D. JENSEN AND DANIEL H. BESSESEN

SECTION XIX: ENDOCRINE DISEASES

202 Approach to the Patient with Endocrine Disease 1472
DAVID R. CLEMMONS AND LYNNETTE K. NIEMAN

203 Principles of Endocrinology 1473
ALLEN M. SPIEGEL

204 Neuroendocrinology and the Neuroendocrine System 1476
ROY E. WEISS

205 Anterior Pituitary 1482
ROY E. WEISS

206 Posterior Pituitary 1498
JOSEPH G. VERBALIS

207 Thyroid 1504
ELIZABETH N. PEARCE AND ANTHONY N. HOLLENBERG

208 Adrenal Cortex 1520
LYNNETTE K. NIEMAN

209 Adrenal Medulla, Catecholamines, and Pheochromocytoma 1529
WILLIAM F. YOUNG, JR.

210 Diabetes Mellitus 1534
KETAN K. DHATARIYA, GUILLERMO E. UMPIERREZ, AND JILL P. CRANDALL

211 Hypoglycemia 1551
KHALID HUSSAIN

212 Polyglandular Disorders 1558
LYNNETTE K. NIEMAN AND ALLEN M. SPIEGEL

213 Neuroendocrine Neoplasms 1561
EDWARD M. WOLIN AND ROBERT T. JENSEN

Copyrighted material

214 Sexual Development 1569
PERRIN C. WHITE

215 Transgender Medicine 1577
JOSHUA D. SAFER

216 The Testis and Male Hypogonadism, Infertility, and Sexual Dysfunction 1580
RONALD S. SWERDLOFF AND CHRISTINA WANG

217 Ovaries and Pubertal Development 1591
WILLIAM H. CATHERINO

218 Reproductive Endocrinology and Infertility 1595
WILLIAM H. CATHERINO

SECTION XX: WOMEN'S HEALTH

219 Approach to Women's Health 1606
KAREN M. FREUND

220 Contraception 1610
BEVERLY WINIKOFF AND DANIEL GROSSMAN

221 Medical Issues in Pregnancy 1618
CATHERINE Y. SPONG AND DAVID B. NELSON

222 Menopause 1628
NANETTE SANTORO AND GENEVIEVE NEAL-PERRY

223 Intimate Partner Violence 1633
GENE FEDER AND HARRIET L. MACMILLAN

SECTION XXI: DISEASES OF BONE AND MINERAL METABOLISM

224 Approach to the Patient with Metabolic Bone Disease 1638
THOMAS J. WEBER

225 Osteoporosis 1639
THOMAS J. WEBER

226 Osteomalacia and Rickets 1647
ROBERT S. WEINSTEIN

227 The Parathyroid Glands, Hypercalcemia, and Hypocalcemia 1652
RAJESH V. THAKKER

228 Paget Disease of Bone 1662
STUART H. RALSTON

229 Osteonecrosis, Osteosclerosis/Hyperostosis, and Other Disorders of Bone 1665
MICHAEL P. WHYTE AND KATHRYN M. DAHIR

SECTION XXII: DISEASES OF ALLERGY AND CLINICAL IMMUNOLOGY

230 Approach to the Patient with Allergic or Immunologic Disease 1672
KARI C. NADEAU

231 Primary Immunodeficiency Diseases 1676
CHARLOTTE CUNNINGHAM-RUNDLES

232 Urticaria and Angioedema 1687
SARBJIT S. SAINI

233 Anaphylaxis 1691
LAWRENCE B. SCHWARTZ AND MARIANA CASTELLS

234 Drug Allergy 1695
MARIANA CASTELLS

235 Mastocytosis 1699
CEM AKIN

SECTION XXIII: RHEUMATIC DISEASES

236 Approach to the Patient with Rheumatic Disease 1706
VIVIAN P. BYKERK AND MARY K. CROW

237 Laboratory Testing in the Rheumatic Diseases 1712
KEVIN D. DEANE AND DAVID S. PISETSKY

238 Imaging Studies in the Rheumatic Diseases 1717
RONALD S. ADLER

239 Inherited Diseases of Connective Tissue 1724
REED E. PYERITZ

240 The Systemic Autoinflammatory Diseases 1730
DANIEL L. KASTNER

241 Osteoarthritis 1737
DAVID J. HUNTER

242 Bursitis, Tendinopathy, Other Periarticular Disorders, and Sports Medicine 1742
JOSEPH J. BIUNDO AND JUAN J. CANOSO

243 Rheumatoid Arthritis 1749
IAIN B. MCINNES

244 Spondyloarthritis 1760
ROBERT D. INMAN AND PROTON RAHMAN

245 Systemic Lupus Erythematosus 1767
MARY K. CROW

246 Systemic Sclerosis (Scleroderma) 1775
JOHN VARGA

247 Sjögren Syndrome 1783
E. WILLIAM ST. CLAIR

248 Inflammatory Myopathies 1787
STEVEN A. GREENBERG

249 The Systemic Vasculitides 1791
JOHN H. STONE

250 Giant Cell Arteritis and Polymyalgia Rheumatica 1801
ROBERT SPIERA

251 Infections of Bursae, Joints, and Bones 1804
DOUGLAS R. OSMON

252 Crystal Deposition Diseases 1810
N. LAWRENCE EDWARDS

253 Fibromyalgia 1816
DANIEL J. CLAUW

254 Systemic Diseases in Which Arthritis Is a Feature 1820
STERLING G. WEST AND S. LOUIS BRIDGES, JR.

255 Surgical Treatment of Joint Diseases 1826
C. RONALD MACKENZIE AND EDWIN P. SU

SECTION XXIV: INFECTIOUS DISEASES

256 Introduction to Microbial Disease: Pathophysiology and Diagnostics 1833
ROBIN PATEL AND VICTORIA J. FRASER

257 The Human Microbiome 1836
VINCENT B. YOUNG

258 Principles of Anti-Infective Therapy 1840
LOUIS B. RICE

259 Approach to Fever or Suspected Infection in the Normal Host 1845
MICHAEL T. MELIA

260 Approach to Fever and Suspected Infection in the Immunocompromised Host 1851
COSTI D. SIFRI

261 Prevention and Control of Health Care–Associated Infections 1862
DAVID P. CALFEE

262 Approach to the Patient with Suspected Enteric Infection 1868
JAMES M. FLECKENSTEIN

263 Approach to the Patient with Urinary Tract Infection 1873
DIMITRI DREKONJA

264 Approach to the Patient with a Sexually Transmitted Infection 1878
HEIDI SWYGARD AND MYRON S. COHEN

265 Approach to the Patient Before and After Travel 1885
LIN H. CHEN

266 Antibacterial Chemotherapy 1891
ARNOLD LOUIE

267 Staphylococcal Infections 1902
CATHERINE LIU, BO SHOPSIN, AND HENRY F. CHAMBERS

Copyrighted material

268 *Streptococcus pneumoniae* Pulmonary Infections 1910
THOMAS MCDONALD FILE, JR.

269 Nonpneumococcal Streptococcal Infections and Rheumatic Fever 1913
DENNIS L. STEVENS, AMY E. BRYANT, AND MELISSA M. HAGMAN

270 Enterococcal Infections 1920
PATRICE SAVARD AND TRISH M. PERL

271 Clostridial and *Clostridioides* Infections 1924
MARK H. WILCOX AND ERIK R. DUBBERKE

272 Gram-Positive Rod Infections 1930
ROSE KIM, HEATHER CLAUSS, AND ANNETTE C. REBOLI

273 Diseases Caused by Non–Spore-Forming Anaerobic Bacteria 1938
ITZHAK BROOK

274 *Neisseria meningitidis* Infections 1941
DAVID S. STEPHENS

275 *Neisseria gonorrhoeae* Infections 1946
JEFFREY D. KLAUSNER AND STEPHANIE N. TAYLOR

276 Chancroid 1950
STANLEY M. SPINOLA

277 *Haemophilus* and *Moraxella* Infections 1952
MONICA M. FARLEY

278 Cholera and Other *Vibrio* Infections 1955
EDUARDO GOTUZZO AND CARLOS SEAS

279 *Campylobacter* Infections 1958
BAN MISHU ALLOS

280 *Escherichia coli* Enteric Infections 1960
THEODORE S. STEINER

281 Enterobacterales: Non-Enteric Infections and Multidrug Resistance 1964
AMY J. MATHERS

282 *Pseudomonas* and *Burkholderia* Infections 1968
MATTHEW E. FALAGAS AND PETROS I. RAFAILIDIS

283 Diseases Caused by *Acinetobacter* and *Stenotrophomonas* Species 1973
KEITH S. KAYE AND ROBERT A. BONOMO

284 *Salmonella* Infections (Including Enteric Fever) 1976
JOHN A. CRUMP

285 Shigellosis 1980
CALMAN A. MACLENNAN

286 Brucellosis 1983
EDSEL MAURICE T. SALVANA

287 Tularemia and Other *Francisella* Infections 1985
KAREN C. BLOCH AND FRED A. LOPEZ

288 Plague and Other *Yersinia* Infections 1988
PAUL S. MEAD AND CHRISTINA A. NELSON

289 Whooping Cough and Other *Bordetella* Infections 1994
CHRISTOPHER J. GILL AND ERIK L. HEWLETT

290 *Legionella* Infections 1996
JONAS MARSCHALL AND VICTORIA J. FRASER

291 *Bartonella* Infections 2000
JEAN-MARC ROLAIN AND DIDIER RAOULT

292 Granuloma Inguinale (Donovanosis) 2004
WALTER BELDA, JR.

293 *Mycoplasma* Infections 2005
DAVID L. GOLDMAN

294 Diseases Caused by Chlamydiae 2009
HILARY E.L. RENO AND WILLIAM M. GEISLER

295 Syphilis and Nonsyphilitic Treponematoses 2014
JODIE A. DIONNE AND KHALIL G. GHANEM

296 Lyme Disease 2022
GARY P. WORMSER

297 Relapsing Fever and Other *Borrelia* Infections 2027
WILLIAM A. PETRI, JR.

298 Leptospirosis 2029
DAVID A. HAAKE

299 Tuberculosis 2031
THOMAS C. BAILEY AND JENNIFER A. PHILIPS

300 The Nontuberculous Mycobacteria 2044
STEVEN M. HOLLAND AND KENNETH N. OLIVIER

301 Leprosy (Hansen Disease) 2047
SUNIL DOGRA

302 Rickettsial Infections 2054
PIERRE-EDOUARD FOURNIER AND DIDIER RAOULT

303 Zoonoses 2063
MEGAN E. RELLER AND J. STEPHEN DUMLER

304 Actinomycosis 2066
ITZHAK BROOK

305 Whipple Disease 2069
THOMAS RUDOLF SCHNEIDER

306 Nocardiosis 2072
FREDERICK S. SOUTHWICK

307 Systemic Antifungal Agents 2074
DAVID W. DENNING AND DAVID A. STEVENS

308 Endemic Mycoses 2080
GEORGE R. THOMPSON, III, AND MARISA H. MICELI

309 Cryptococcosis 2087
SHARON C-A CHEN

310 Candidiasis 2089
PETER G. PAPPAS

311 Aspergillosis 2093
THOMAS J. WALSH AND THOMAS F. PATTERSON

312 Mucormycosis 2098
DIMITRIOS P. KONTOYIANNIS AND LUIS OSTROSKY-ZEICHNER

313 *Pneumocystis* Pneumonia 2101
JOSEPH A. KOVACS

314 Mycetoma and Dematiaceous Fungal Infections 2108
PETER G. PAPPAS AND DIMITRIOS P. KONTOYIANNIS

315 Antiparasitic Therapy 2111
PHILIP J. BUDGE AND RICHARD D. PEARSON

316 Malaria 2118
PHILIP J. ROSENTHAL AND MOSES R. KAMYA

317 African Sleeping Sickness 2123
WILLIAM A. PETRI, JR.

318 Chagas Disease 2126
LOUIS V. KIRCHHOFF

319 Leishmaniasis 2130
PIERRE A. BUFFET, SIMON L. CROFT, AND MITALI CHATTERJEE

320 Toxoplasmosis 2136
ANITA A. KOSHY

321 Cryptosporidiosis 2141
CIRLE A. WARREN AND ALDO A.M. LIMA

322 Giardiasis 2144
DAVID R. HILL

323 Amebiasis 2146
WILLIAM A. PETRI, JR.

324 Babesiosis and Other Protozoan Diseases 2151
SAM R. TELFORD, III, AND PETER J. KRAUSE

325 Cestodes 2157
A. CLINTON WHITE, JR., AND ENRICO BRUNETTI

326 Trematode Infections 2163
LUIS A. MARCOS

327 Nematode Infections 2169
DAVID J. DIEMERT

328 Antiviral Therapy (Non-HIV) 2181
JOHN H. BEIGEL AND SHYAMASUNDARAN KOTTILIL

329 The Common Cold 2192
BRUCE BARRETT

Copyrighted material

330 Respiratory Syncytial Virus and Human Metapneumovirus 2194
H. KEIPP TALBOT AND EDWARD E. WALSH

331 Parainfluenza Viral Disease 2196
GEOFFREY A. WEINBERG AND KATHRYN M. EDWARDS

332 Influenza 2198
MICHAEL G. ISON AND NELSON LEE

333 Adenovirus Diseases 2204
MICHAEL G. ISON

334 Pre-2019 Coronaviruses 2206
FIONA P. HAVERS, HANNAH KIRKING, AND IAN D. PLUMB

335 COVID-19: Virology and Pathology 2209
VINCENT RACANIELLO

336 COVID-19: Epidemiology, Clinical Manifestations, Diagnosis, Community Prevention, and Prognosis 2213
CARLOS DEL RIO, MONICA GANDHI, AND MYRON S. COHEN

337 COVID-19 Treatment and Vaccination 2216
RAJESH T. GANDHI AND KATHLEEN M. NEUZIL

338 Measles 2220
MARTIN G. OTTOLINI

339 Rubella (German Measles) 2224
GREGORY A. POLAND, INNA G. OVSYANNIKOVA, AND RICHARD B. KENNEDY

340 Mumps 2225
JENNIFER B. ROSEN AND JANE R. ZUCKER

341 Polyomaviruses 2227
HANS H. HIRSCH

342 Parvovirus 2233
NEAL S. YOUNG

343 Smallpox, Monkeypox, and Other Poxvirus Infections 2236
BRETT W. PETERSEN AND INGER K. DAMON

344 Papillomavirus 2240
SEAN T. O'LEARY AND JOHN M. DOUGLAS, JR.

345 Herpes Simplex Virus Infections 2244
RICHARD J. WHITLEY AND JOHN W. GNANN, JR.

346 Varicella-Zoster Virus (Chickenpox, Shingles) 2247
JEFFREY COHEN

347 Cytomegalovirus 2250
GUY BOIVIN AND AJIT P. LIMAYE

348 Epstein-Barr Virus Infection 2253
ROBERT T. SCHOOLEY AND UPTON D. ALLEN

349 Enteroviruses 2256
JOSÉ R. ROMERO

350 Rotaviruses, Noroviruses, and Other Gastrointestinal Viruses 2261
MANUEL A. FRANCO AND HARRY B. GREENBERG

351 Viral Hemorrhagic Fevers 2264
DANIEL G. BAUSCH AND LAURENT KAISER

352 Arboviruses Causing Fever, Rash, and Neurologic Syndromes 2274
J. DAVID BECKHAM

SECTION XXV: RETROVIRUSES

353 Epidemiology and Diagnosis of Human Immunodeficiency Virus Infection and Acquired Immunodeficiency Syndrome 2286
LARRY W. CHANG AND THOMAS C. QUINN

354 Pathobiology of Human Immunodeficiency Viruses 2291
JOEL N. BLANKSON, ROBERT F. SILICIANO, AND FRANK MALDARELLI

355 Acute Clinical Manifestations and Diagnosis of HIV 2295
THOMAS C. QUINN AND LARRY W. CHANG

356 Prevention of Human Immunodeficiency Virus Infection 2298
RAPHAEL J. LANDOVITZ, CARLOS DEL RIO, AND MYRON S. COHEN

357 Antiretroviral Treatment of Human Immunodeficiency Virus Infection 2300
ROY M. GULICK

358 Microbial Complications of HIV/AIDS 2305
HENRY MASUR

359 Systemic Manifestations of HIV/AIDS 2312
SAMUEL T. MERRICK AND MARSHALL J. GLESBY

360 Retroviruses Other Than Human Immunodeficiency Virus 2324
CHARLES R.M. BANGHAM AND LUCY B.M. COOK

SECTION XXVI: BEHAVIORAL MEDICINE

361 Delirium and Changes in Mental Status 2330
SHARON K. INOUYE

362 Psychiatric Disorders in Medical Practice 2336
JEFFREY M. LYNESS AND HOCHANG B. LEE

363 Nicotine and Tobacco 2349
TONY P. GEORGE

364 Alcohol Use Disorders 2353
PATRICK G. O'CONNOR

365 Drug Use Disorders 2360
ROGER D. WEISS AND JANE M. LIEBSCHUTZ

SECTION XXVII: NEUROLOGY

366 Approach to the Patient with Neurologic Disease 2368
GABRIELE C. DE LUCA, ROBERT C. GRIGGS, AND S. CLAIBORNE JOHNSTON

367 Headaches and Other Head Pain 2376
KATHLEEN B. DIGRE

368 Traumatic Brain Injury and Spinal Cord Injury 2385
JEFFREY J. BAZARIAN

369 Mechanical and Other Lesions of the Spine, Nerve Roots, and Spinal Cord 2392
J.D. BARTLESON

370 Regional Cerebral Dysfunction: Higher Mental Functions 2407
DAVID S. KNOPMAN

371 Cognitive Impairment and Dementia 2412
DAVID S. KNOPMAN

372 The Epilepsies 2425
SAMUEL WIEBE

373 Coma, Disorders of Consciousness, and Brain Death 2437
DAVID M. GREER AND JAMES L. BERNAT

374 Sleep Disorders 2443
BRADLEY V. VAUGHN AND ROBERT C. BASNER

375 Approach to Cerebrovascular Diseases 2454
LARRY B. GOLDSTEIN

376 Ischemic Cerebrovascular Disease 2464
LARRY B. GOLDSTEIN

377 Hemorrhagic Cerebrovascular Disease 2474
SEEMANT CHATURVEDI AND MAGDY SELIM

378 Parkinsonism 2483
JILL L. OSTREM AND MICHAEL S. OKUN

379 Other Movement Disorders 2489
MICHAEL S. OKUN AND JILL L. OSTREM

380 Multiple Sclerosis and Demyelinating Conditions 2498
PETER A. CALABRESI

381 Meningitis: Bacterial, Viral, and Other 2510
AVINDRA NATH

382 Brain Abscess and Parameningeal Infections 2525
AVINDRA NATH AND JOSEPH R. BERGER

383 Encephalitis 2531
ALLEN J. AKSAMIT, JR.

384 Nutritional and Alcohol-Related Neurologic Disorders 2537
BARBARA S. KOPPEL, LOUIS H. WEIMER, AND MICHAEL DARAS

385 Developmental and Neurocutaneous Disorders 2545
E. STEVE ROACH

Copyrighted material

386 Autonomic Disorders 2553
EDUARDO E. BENARROCH AND ROY FREEMAN

387 Amyotrophic Lateral Sclerosis and Other Motor Neuron Diseases 2561
PAMELA J. SHAW AND MERIT E. CUDKOWICZ

388 Peripheral Neuropathies 2566
A. GORDON SMITH AND MICHAEL E. SHY

389 Muscle Diseases 2580
DUYGU SELCEN

390 Disorders of Neuromuscular Transmission 2588
HENRY J. KAMINSKI

SECTION XXVIII: EYE, EAR, NOSE, AND THROAT DISEASES

391 Diseases of the Visual System 2596
GEORGE A. CIOFFI AND JEFFREY M. LIEBMANN

392 Neuro-Ophthalmology 2614
ROBERT W. BALOH AND JOANNA C. JEN

393 Diseases of the Mouth and Salivary Glands 2620
RICHARD C. JORDAN

394 Approach to the Patient with Nose, Sinus, and Ear Disorders 2627
ANDREW H. MURR AND STEVEN D. PLETCHER

395 Smell and Taste 2639
ROBERT W. BALOH AND JOANNA C. JEN

396 Hearing and Equilibrium 2641
ROBERT W. BALOH AND JOANNA C. JEN

397 Throat Disorders 2648
PAUL W. FLINT

SECTION XXIX: MEDICAL CONSULTATION

398 Principles of Medical Consultation 2656
GERALD W. SMETANA AND BARBARA A. SLAWSKI

399 Preoperative Evaluation 2659
ANDREW D. AUERBACH

400 Overview of Anesthesia 2668
JEANINE P. WIENER-KRONISH AND LEE A. FLEISHER

401 Postoperative Care and Complications 2672
DONALD A. REDELMEIER

402 Medical Care of Patients with Psychiatric Diseases 2677
MARSHA N. WITTINK AND S. RYAN GREYSEN

SECTION XXX: SKIN DISEASES

403 Approach to Skin Diseases 2686
CHRISTINE J. KO

404 Principles of Therapy of Skin Diseases 2697
VICTORIA P. WERTH AND APRIL W. ARMSTRONG

405 Eczemas, Photodermatoses, Papulosquamous (Including Fungal) Diseases, and Figurate Erythemas 2702
HENRY W. LIM AND JOEL M. GELFAND

406 Macular, Papular, Purpuric, Vesiculobullous, and Pustular Diseases 2712
DANIELA KROSHINSKY

407 Urticaria, Drug Hypersensitivity Rashes, Nodules and Tumors, and Atrophic Diseases 2724
MADELEINE DUVIC AND SUSAN Y. CHON

408 Infections, Pigmentation Disorders, Regional Dermatology, and Distinctive Lesions in Black Skin 2738
JEAN BOLOGNIA AND AMY MCMICHAEL

409 Diseases of Hair and Nails 2747
ANTONELLA TOSTI

APPENDIX

Reference Intervals and Laboratory Values e1
JORGE SEPULVEDA

Index I-1

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VIDEO CONTENTS

This icon appears throughout the book to indicate chapters with accompanying video available on Elsevier eBooks+.

HEART DISEASES

Standard Echocardiographic Views: Long Axis Image Plane
Chapter 43, Video 1A – CATHERINE M. OTTO

Standard Echocardiographic Views: Short Axis Image Plane
Chapter 43, Video 1B – CATHERINE M. OTTO

Standard Echocardiographic Views: Short Axis Image Plane
Chapter 43, Video 1C – CATHERINE M. OTTO

Standard Echocardiographic Views: Four-Chamber Image Plane
Chapter 43, Video 1D – CATHERINE M. OTTO

Dilated Cardiomyopathy: Long Axis View
Chapter 43, Video 2A – CATHERINE M. OTTO

Dilated Cardiomyopathy: Short Axis View
Chapter 43, Video 2B – CATHERINE M. OTTO

Dilated Cardiomyopathy: Apical Four-Chamber View
Chapter 43, Video 2C – CATHERINE M. OTTO

Three-Dimensional Echocardiography
Chapter 43, Video 3 – CATHERINE M. OTTO

Stress Echocardiography: Normal Reaction
Chapter 43, Video 4A – CATHERINE M. OTTO

Stress Echocardiography: Proximal Stenosis of the Left Anterior Descending Coronary Artery
Chapter 43, Video 4B – CATHERINE M. OTTO

Pericardial Effusion: Parasternal Long Axis
Chapter 43, Video 5A – CATHERINE M. OTTO

Pericardial Effusion: Parasternal Short Axis
Chapter 43, Video 5B – CATHERINE M. OTTO

Pericardial Effusion: Apical Four-Chamber Views
Chapter 43, Video 5C – CATHERINE M. OTTO

Secundum Atrial Septal Defect
Chapter 55, Video 1 – ARIANE J. MARELLI

Perimembranous Ventricular Septal Defect
Chapter 55, Video 2 – ARIANE J. MARELLI

Coronary Stent Placement
Chapter 59, Video 1 – PAUL S. TEIRSTEIN

Guidewire Passage
Chapter 59, Video 2 – PAUL S. TEIRSTEIN

Delivering the Stent
Chapter 59, Video 3 – PAUL S. TEIRSTEIN

Inflating the Stent
Chapter 59, Video 4 – PAUL S. TEIRSTEIN

Final Result
Chapter 59, Video 5 – PAUL S. TEIRSTEIN

RESPIRATORY DISEASES

Wheezing
Chapter 75, Video 1 – RAYMOND MURPHY

Inhaler Use
Chapter 75, Video 2 – LESLIE HENDELES, GENE L. COLICE, AND ROBERT J. MEYER

VATS Wedge Resection
Chapter 87, Video 1 – MALCOLM M. DECAMP

CRITICAL CARE MEDICINE

Ventilation of an Ex Vivo Rat Lung
Chapter 91, Video 1 – ARTHUR S. SLUTSKY, GEORGE VOLGYESI, AND TOM WHITEHEAD

GASTROINTESTINAL DISEASES

Ulcerative Colitis, Moderately Severe
Chapter 127, Video 1 – GARY R. LICHTENSTEIN

CMI Stents
Chapter 129, Video 1 – CHARLES J. KAHI

DISEASES OF THE LIVER AND BILIARY SYSTEM

Endoscopic Ultrasound of Biliary Ascariasis, Endoscopic Retrograde Cholangiopancreatography of Biliary Ascariasis, and Extraction of the Helminthic Worm
Chapter 137, Video 1 – K. RAJENDER REDDY

ONCOLOGY

Laparascopic Assisted Double Balloon Enteroscopy with Polypectomy of a Jejunal Adenoma Followed by Surgical Oversew of the Polypectomy Site
Chapter 179, Video 1 – SHABANA PASHA

Snare Polypectomy of a Colon Adenoma
Chapter 179, Video 2 – JONATHAN LEIGHTON

Endoscopic Mucosal Resection Using Saline Lift Polypectomy of a Colon Adenoma, Followed by Closure of the Mucosal Defect with Clips
Chapter 179, Video 3 – WAJEEH SALAH

ENDOCRINE DISEASES

Pituitary Surgery
Chapter 205, Video 1 – IVAN CIRIC

BEHAVIORAL MEDICINE

Confusion Assessment Method
Chapter 361, Video 1 – SHARON K. INOUYE

NEUROLOGY

Focal Seizure Disorder - Temporal Lobe Epilepsy
Chapter 366, Video 1 – GABRIELE C. DE LUCA, ROBERT C. GRIGGS, AND S. CLAIBORNE JOHNSTON

Generalized Seizure Disorder - Myoclonic Epilepsy
Chapter 366, Video 2 – GABRIELE C. DE LUCA, ROBERT C. GRIGGS, AND S. CLAIBORNE JOHNSTON

Pronator Drift
Chapter 366, Video 3 – GABRIELE C. DE LUCA, ROBERT C. GRIGGS, AND S. CLAIBORNE JOHNSTON

Parkinsonism
Chapter 366, Video 4 – GABRIELE C. DE LUCA, ROBERT C. GRIGGS, AND S. CLAIBORNE JOHNSTON

Internuclear Ophthalmoplegia
Chapter 366, Video 5 – GABRIELE C. DE LUCA, ROBERT C. GRIGGS, AND S. CLAIBORNE JOHNSTON

Spastic-Ataxic Gait
Chapter 366, Video 6 – GABRIELE C. DE LUCA, ROBERT C. GRIGGS, AND S. CLAIBORNE JOHNSTON

Sustained Clonus
Chapter 366, Video 7 – GABRIELE C. DE LUCA, ROBERT C. GRIGGS, AND S. CLAIBORNE JOHNSTON

Fasciculations (Tongue and Lower Limb)
Chapter 366, Video 8 – GABRIELE C. DE LUCA, ROBERT C. GRIGGS, AND S. CLAIBORNE JOHNSTON

Brachial Plexopathy
Chapter 366, Video 9 – GABRIELE C. DE LUCA, ROBERT C. GRIGGS, AND S. CLAIBORNE JOHNSTON

Length-Dependent Peripheral Neuropathy
Chapter 366, Video 10 – GABRIELE C. DE LUCA, ROBERT C. GRIGGS, AND S. CLAIBORNE JOHNSTON

Fatigable Ptosis, Dysarthria, and Dysphonia
Chapter 366, Video 11 – GABRIELE C. DE LUCA, ROBERT C. GRIGGS, AND S. CLAIBORNE JOHNSTON

Myotonic Dystrophy
Chapter 366, Video 12 – GABRIELE C. DE LUCA, ROBERT C. GRIGGS, AND S. CLAIBORNE JOHNSTON

Facioscapulohumeral Muscular Dystrophy
Chapter 366, Video 13 – GABRIELE C. DE LUCA, ROBERT C. GRIGGS, AND S. CLAIBORNE JOHNSTON

Cervical Provocation
Chapter 369, Video 1 – J.D. BARTLESON

Spurling Maneuver
Chapter 369, Video 2 – J.D. BARTLESON

Cervical Distraction Test
Chapter 369, Video 3 – J.D. BARTLESON

Straight Leg Raise
Chapter 369, Video 4 – J.D. BARTLESON

Contralateral Straight Leg Raise
Chapter 369, Video 5 – J.D. BARTLESON

Seated Straight Leg Raise
Chapter 369, Video 6 – J.D. BARTLESON

Discectomy
Chapter 369, Video 7 – J.D. BARTLESON

Typical Absence Seizure
Chapter 372, Video 1 – SAMUEL WIEBE

Left Rolandic Seizure
Chapter 372, Video 2 – SAMUEL WIEBE

Left Temporal Focal Impaired Awareness Seizure
Chapter 372, Video 3 – SAMUEL WIEBE

Left Temporal Focal Impaired Awareness Seizure, Postictal Confusion
Chapter 372, Video 4 – SAMUEL WIEBE

Left Temporal Focal Impaired Awareness Seizure
Chapter 372, Video 5 – SAMUEL WIEBE

Supplementary Sensory-Motor Seizure
Chapter 372, Video 6 – SAMUEL WIEBE

Right Posterior Temporal Seizure—Dramatic Hyperkinetic Semiology
Chapter 372, Video 7 – SAMUEL WIEBE

Right Mesial Frontal Hyperkinetic Seizure
Chapter 372, Video 8 – SAMUEL WIEBE

Generalized Nonconvulsive Status Epilepticus
Chapter 372, Video 9 – SAMUEL WIEBE

GTC Seizure Tonic Phase
Chapter 372, Video 10 – SAMUEL WIEBE

GTC Seizure Clonic Phase
Chapter 372, Video 11 – SAMUEL WIEBE

Myoclonic Facial Seizure
Chapter 372, Video 12 – SAMUEL WIEBE

Tonic Seizure Lennox Gastaut
Chapter 372, Video 13 – SAMUEL WIEBE

Atonic Seizure Lennox Gastaut
Chapter 372, Video 14 – SAMUEL WIEBE

Reflex Auditory Seizure
Chapter 372, Video 15 – SAMUEL WIEBE

Early Parkinson's Disease
Chapter 378, Video 1 – JILL L. OSTREM AND MICHAEL S. OKUN

Freezing of Gait in Parkinson's Disease
Chapter 378, Video 2 – JILL L. OSTREM AND MICHAEL S. OKUN

Gunslinger Gait in Progressive Supranuclear Palsy
Chapter 378, Video 3 – JILL L. OSTREM AND MICHAEL S. OKUN

Supranuclear Gaze Palsy in Progressive Supranuclear Palsy
Chapter 378, Video 4 – JILL L. OSTREM AND MICHAEL S. OKUN

Applause Sign in Progressive Supranuclear Palsy
Chapter 378, Video 5 – JILL L. OSTREM AND MICHAEL S. OKUN

Apraxia of Eyelid Opening in Progressive Supranuclear Palsy
Chapter 378, Video 6 – JILL L. OSTREM AND MICHAEL S. OKUN

Cranial Dystonia in Multiple System Atrophy
Chapter 378, Video 7 – JILL L. OSTREM AND MICHAEL S. OKUN

Anterocollis in Multiple System Atrophy
Chapter 378, Video 8 – JILL L. OSTREM AND MICHAEL S. OKUN

Stridor in Multiple System Atrophy
Chapter 378, Video 9 – JILL L. OSTREM AND MICHAEL S. OKUN

Alien Limb Phenomenon in Corticobasal Syndrome
Chapter 378, Video 10 – JILL L. OSTREM AND MICHAEL S. OKUN

Myoclonus in Corticobasal Syndrome
Chapter 378, Video 11 – JILL L. OSTREM AND MICHAEL S. OKUN

Levodopa-Induced Dyskinesia in Parkinson's Disease
Chapter 378, Video 12 – JILL L. OSTREM AND MICHAEL S. OKUN

Essential Tremor
Chapter 379, Video 1 – MICHAEL S. OKUN AND JILL L. OSTREM

Huntington's Disease
Chapter 379, Video 2 – MICHAEL S. OKUN AND JILL L. OSTREM

Hemiballism
Chapter 379, Video 3 – MICHAEL S. OKUN AND JILL L. OSTREM

Blepharospasm
Chapter 379, Video 4 – MICHAEL S. OKUN AND JILL L. OSTREM

Oromandibular Dystonia
Chapter 379, Video 5 – MICHAEL S. OKUN AND JILL L. OSTREM

Cervical Dystonia
Chapter 379, Video 6 – MICHAEL S. OKUN AND JILL L. OSTREM

Writer's Cramp
Chapter 379, Video 7 – MICHAEL S. OKUN AND JILL L. OSTREM

Embouchure Dystonia
Chapter 379, Video 8 – MICHAEL S. OKUN AND JILL L. OSTREM

Sensory Trick in Cervical Dystonia
Chapter 379, Video 9 – MICHAEL S. OKUN AND JILL L. OSTREM

Generalized Dystonia
Chapter 379, Video 10 – MICHAEL S. OKUN AND JILL L. OSTREM

Tics
Chapter 379, Video 11 – MICHAEL S. OKUN AND JILL L. OSTREM

Tardive Dyskinesia
Chapter 379, Video 12 – MICHAEL S. OKUN AND JILL L. OSTREM

Hemifacial Spasm
Chapter 379, Video 13 – MICHAEL S. OKUN AND JILL L. OSTREM

Eye Movements (Nystagmus) of Wernicke Encephalopathy
Chapter 384, Video 1 – BARBARA S. KOPPEL

Eye Movements (Nystagmus) of Wernicke Encephalopathy
Chapter 384, Video 2 – BARBARA S. KOPPEL

Eye Movements (Slow Dysconjugate Horizontal Movements) of Osmotic Demyelination Syndrome
Chapter 384, Video 3 – BARBARA S. KOPPEL

Limb Symptoms and Signs in ALS
Chapter 387, Video 1 – PAMELA J. SHAW

Bulbar Symptoms and Signs in ALS
Chapter 387, Video 2 – PAMELA J. SHAW

Video Fluoroscopy of Normal Swallowing and of Swallowing in an ALS Patient with Bulbar Dysfunction
Chapter 387, Video 3 – PAMELA J. SHAW

Charcot-Marie-Tooth Disease Examination and Walk
Chapter 388, Video 1 – A. GORDON SMITH AND MICHAEL E. SHY

EYE, EAR, NOSE, AND THROAT DISEASES

Skin Testing
Chapter 394, Video 1 – LARRY BORISH

Nasal Endoscopy
Chapter 394, Video 2 – LARRY BORISH

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SOCIAL AND ETHICAL ISSUES IN MEDICINE

1 APPROACH TO MEDICINE, THE PATIENT, AND THE MEDICAL PROFESSION: MEDICINE AS A LEARNED AND HUMANE PROFESSION

2 BIOETHICS IN THE PRACTICE OF MEDICINE

3 PALLIATIVE CARE

4 DISPARITIES IN HEALTH AND HEALTH CARE

5 GLOBAL HEALTH

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1

APPROACH TO MEDICINE, THE PATIENT, AND THE MEDICAL PROFESSION: MEDICINE AS A LEARNED AND HUMANE PROFESSION

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APPROACH TO MEDICINE

THE HISTORIC EVOLUTION

Medicine is a profession that incorporates science and the scientific method with the art of being a physician. The art of tending to the sick is as old as humanity itself. Even in modern times, the art of caring and comforting, guided by common sense over millennia as well as by a more recent, systematic approach to medical ethics (Chapter 2), remains the cornerstone of medicine. Without these humanistic qualities, the application of the modern science of medicine is suboptimal, ineffective, or even detrimental.

However, the essential humanistic qualities of caring and comforting can achieve full benefit only if they are coupled with an understanding of how medical science can and should be applied to all individuals regardless of their race, sex, sexual orientation, or other characteristics. Without this knowledge, comforting may be inappropriate or misleading and caring may be ineffective or counterproductive if it inhibits a sick person from obtaining appropriate, scientific medical care.

The concept of *internal medicine*, which began in 19th-century Germany, was to emphasize the underlying pathobiologic causes of disease, not just the patterns or progression of clinical manifestations. Modern medicine is based on increasingly accelerated discoveries made with this approach over the past 150 years, during which time human life expectancy has approximately doubled.[1] *Goldman-Cecil Medicine* incorporates this tradition by showing how pathobiologic abnormalities cause clinical manifestations and by emphasizing how therapies can modify this underlying pathophysiology and improve the patient's well-being.

CONTEMPORARY MEDICAL SCIENCE

The contemporary practice of medicine now includes an increasingly detailed understanding of cellular, subcellular, molecular, genetic, and epigenetic mechanisms of health and disease. For example, the understanding of microbial pathogenesis as well as that of many noninfectious (as we understand them now) inflammatory diseases (Chapter 236) is now guided by a detailed understanding of the human immune system and its response to foreign antigens (Chapters 35 to 37).

Health, disease, and an individual's interaction with the environment are also substantially determined by genetics and epigenetics. In addition to monogenic conditions, medical science increasingly understands the complex interactions that underlie multigenic traits, including diabetes mellitus, cancer, and other common health conditions (Chapter 32). The decoding of the human genome holds the promise that personalized health care increasingly can be targeted according to an individual's genetic profile, in terms of screening and presymptomatic disease management, as well as in terms of specific medications, their complex interactions, and their adjusted dosing schedules.[2]

Knowledge of the structure and physical forms of proteins helps explain abnormalities as diverse as sickle cell anemia (Chapter 149) and prion-related diseases (Chapter 371). Proteomics, which is the large-scale analysis of proteins produced by an organism, also holds extraordinary promise for developing drug targets for more specific and effective therapies. Increasingly, the effects of nurture and the environment, expressed as epigenetic modifications of DNA or chromatin, are also being deciphered, with the potential for future therapeutic interventions. A striking illustration is evolving evidence that the gut microbiome is shaped at the time of birth during vaginal delivery. Advances in our understanding of the human microbiome also raise the possibility that our complex interactions with microbes, which outnumber the cells in the human body by a factor of 10, will help explain conditions ranging from inflammatory bowel disease (Chapter 127) to obesity (Chapter 201).

EVIDENCE-BASED MEDICINE

Concurrent with these advances in fundamental human biology has been a dramatic shift in methods for evaluating the application of scientific advances to the individual patient and to populations. The randomized controlled trial, sometimes with thousands of patients at multiple institutions, has replaced anecdote as the most robust method for measuring the benefits and optimal uses of diagnostic and therapeutic interventions (Chapter 8). Yet this approach to the evaluation of therapeutics and diagnostics is being challenged. To reduce costs as well as overcome inefficiencies, redundancies, and the late failure of many clinical trials (at the phase III stage) inherent in classic randomized controlled trials, technologic advances are enabling new methods, tools, and approaches to bring clinical trials into the 21st century. These methods include disease modeling and simulation, alternative trial methods such as response-adaptive randomized designs (Chapter 8), real-world pragmatic trials, population-based studies, use of artificial intelligence and data science, implementation science, community-engaged research, novel objective outcome measures, and engagement of clinical trial "participants" (rather than "human subjects") to expand the pool of individuals willing to be involved in clinical research.

As research progresses from studies that show biologic effect, to studies that elucidate dosing schedules and toxicity, and finally to controlled trials that assess true clinical benefit, the metrics of measuring outcome has also improved from subjective impressions of physicians or patients to reliable and valid measures of morbidity, quality of life, functional status, and other patient-oriented outcomes (Chapter 9). These marked improvements in the scientific methodology of clinical investigation have expedited extraordinary changes in clinical practice, such as recanalization therapy for acute myocardial infarction (Chapter 58) and aspiration therapy for cerebrovascular clots (Chapter 377), which focus on important outcomes, including not only death but also physical function and quality of life. Just as physicians in the 21st century must understand advances in fundamental biology, similar understanding of the fundamentals of clinical study design as it applies to diagnostic and therapeutic interventions is important.

An understanding of human genomics and genetics can also help stratify and refine the approach to clinical trials by helping researchers identify fewer patients with a more homogeneous disease pattern to study the efficacy of an intervention. Such an approach has been especially relevant in cancer, in which tumors with certain genetic mutations can respond to a drug specifically designed for that target, whereas other tumors with similar histologic but different molecular characteristics will not. Germline genetic testing is now common in clinical practice, and molecular biomarkers are increasingly important for screening, surveillance, early detection, risk stratification, and therapy. Systems biology, which is the integration of all these techniques, can enable the development of new predictive, preventive, and personalized approaches to disease.

CHANGES IN MEDICAL PRACTICE

This explosion in medical knowledge and clinical research has led to increasing specialization and subspecialization, defined initially by organ system and more recently by locus of principal activity (inpatient as compared with outpatient), reliance on manual skills (proceduralist vs. nonproceduralist), or participation in research. Sophisticated computerized analyses of radiographs,[3] computed tomographic scans, magnetic resonance images, retinal images,[4] and histopathologic specimens are also poised to revolutionize the interpretation of these tests, much as computerized electrocardiographic interpretation (Chapter 42) changed clinical cardiology.

Computerized health records can avoid duplication of tests, ensure that care is coordinated among the patient's various health care providers, and increase the value of health care. Real-time electronic monitoring can be used to alert physicians about patients whose vital signs (Chapter 7) might warrant urgent evaluation to avoid more serious clinical decompensation.[5] Data derived from electronic medical records can detect patterns of drug side effects or interactions that can then guide molecular analyses that confirm new risks or even genetic diseases.[6]

Although it is too soon to know whether patients would routinely benefit from sequencing and analysis of their exome or full genome, such information is increasingly becoming affordable and more accurate, with potential usefulness for identifying Mendelian disease patterns[7] and informing reproductive planning. Despite much hope, however, genetic profiling of germline sequences has had limited positive impact on drug selection and dosing.

ABSTRACT

The medical profession incorporates both the science of medicine as well as the art of being a physician. Physicians cannot help patients unless they are well-grounded in the latest information about medical diagnosis and management, which increasingly is based on randomized clinical trials as well as on patient-specific information, including genetics and genomics. However, this scientific expertise also must be applied in the context of understanding the patient as an individual person. In applying both scientific knowledge and medical professionalism, physicians must recognize the importance of the social determinants of health and be champions for diversity, equity, inclusion, and social justice as they advocate for and take care of individual patients in the context of broader societal issues.

KEYWORDS

medical professionalism
scientific medicine
evidence-based medicine
approach to the patient
signs and symptoms

NEW THERAPEUTICS

Gene therapy is currently approved by the U.S. Food and Drug Administration (FDA) for only a few diseases—Leber congenital amaurosis (Chapter 391), retinal dystrophy, beta thalassemia, hemophilia (Chapter 160), and spinal muscular atrophy (Chapter 387) are examples—but many more gene therapies are in development and clinical testing. Specific DNA sequences can now be targeted with clustered regularly interspaced short palindromic repeats (CRISPR)-associated nucleases to inactivate genes or to correct a pathogenic mutation back to the reference sequence. This technique has already demonstrated durable benefits for patients with hemophilia (Chapter 160).

Cell-based therapy is now beginning to provide vehicles for the delivery of cells engineered to address a patient's particular chimeric antigen receptor (CAR).[8] CAR-T cell therapy is FDA-approved for conditions such as non-Hodgkin lymphoma (Chapter 171), acute lymphoblastic leukemia (Chapter 168), multiple myeloma (Chapter 173), melanoma (Chapter 188), and prostate cancer (Chapter 186), and it is being actively tested in other conditions. Although effective in many cases, cost and severe side effects, especially the so-called cytokine release syndrome, currently limit its widespread use.

Regenerative medicine to help heal injured or diseased organs, by the administration of cells modified to meet a patient's needs, is in its infancy. However, cultured chondrocytes are now FDA-approved to repair cartilaginous defects of the femoral condyle and the knee.

Immune checkpoint inhibitors have revolutionized the approach to treating cancer, initially melanoma (Chapter 188),[9] but now also a wide range of malignancies, with future potential efficacy for the treatment of refractory infectious diseases, autoimmune diseases, and serious allergic disorders.[10] Messenger RNA (mRNA) vaccines, which deliver antigen-encoding mRNA into immune cells, where they stimulate an adaptive immune response, have revolutionized the approach to preventing severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2; Chapter 337) and are increasingly being applied to other infections.[11]

SOCIETAL IMPLICATIONS

Extraordinary advances in the science and practice of medicine have transformed the global burden of disease. For example, vaccines and other population-wide interventions, such as screening for and treating hypertension and hypercholesterolemia, have greatly reduced the burden of infectious and cardiovascular diseases. In many countries, life expectancies for men and women have been increasing, a greater proportion of deaths are occurring among people older than age 70 years, and far fewer children are dying before the age of 5 years. In the United States, however, overall life expectancy has declined in the last several years. Explanations include not only the unprecedented SARS-CoV-2 pandemic and the coronavirus-2019 (COVID-19) disease it causes, but also obesity-related diseases[12] as well as so-called deaths of despair owing to alcohol, drug overdoses, and suicide.[13] Disability from conditions such as substance abuse, mental health disorders, injuries, diabetes, musculoskeletal disease, and chronic respiratory disease have become increasingly important issues for all health systems.

Globally, but also within the United States, substantial health disparities persist based on geography, race, ethnicity, socioeconomic status, and often sexual orientation and gender identity.[14] Physicians must understand historic as well as current health disparities and the social determinants of health. They must strive to understand the benefits and needs of diverse populations and individual patients, and they must be advocates for equity, inclusion, access, and social justice in all aspects of medicine and health care.[15]

APPROACH TO THE PATIENT

Patients commonly have complaints (symptoms), but at least one third of these symptoms will not be readily explainable by any detectable abnormalities on examination (signs) or on laboratory testing. Even in the modern era of advanced diagnostic testing, the history and physical examination are estimated to contribute at least 75% of the information that informs the evaluation of symptoms, and symptoms that are not explained on initial comprehensive evaluation rarely are manifestations of a serious underlying disease. Conversely, asymptomatic patients may have signs or laboratory abnormalities, and laboratory abnormalities can occur in the absence of symptoms or signs.

Symptoms and signs commonly define *syndromes*, which may be the common final pathway of a wide range of pathophysiologic alterations. The fundamental basis of internal medicine is that diagnosis should elucidate the pathophysiologic explanation for symptoms and signs so that therapy may improve the underlying abnormality, not just attempt to suppress the abnormal symptoms or signs.

When patients seek care from physicians, they may have manifestations or exacerbations of known conditions or they may have symptoms and signs that suggest malfunction of a particular organ system. Sometimes the pattern of symptoms and signs is highly suggestive or even pathognomonic for a particular disease process. In these situations, in which the physician is focusing on a particular disease, *Goldman-Cecil Medicine* provides scholarly yet practical approaches to the epidemiology, pathobiology, clinical manifestations, diagnosis, treatment, prevention, and prognosis of entities such as acute myocardial infarction (Chapter 58), chronic obstructive lung disease (Chapter 76), inflammatory bowel disease (Chapter 127), gallstones (Chapter 141), rheumatoid arthritis (Chapter 243), hypothyroidism (Chapter 207), and tuberculosis (Chapter 299), as well as newly described disorders such as emerging zoonoses (Chapter 303), small fiber neuropathies (Chapter 388), mitochondrial diseases (Chapter 389), autoinflammatory diseases (Chapter 240), and clonal disorders of indeterminate potential (Chapter 142).

Many patients, however, have undiagnosed symptoms, signs, or laboratory abnormalities that cannot be immediately ascribed to a particular disease or cause. Whether the initial manifestation is chest pain (Chapter 39), diarrhea (Chapter 126), neck or back pain (Chapter 369), or a variety of more than 100 common symptoms, signs, or laboratory abnormalities, *Goldman-Cecil Medicine* provides tables, figures, and entire chapters to guide the approach to diagnosis and therapy (see E-Table 1-1 or the table on the inside back cover of the printed book). By virtue of this dual approach to known disease as well as to undiagnosed abnormalities, this textbook, similar to the modern practice of medicine, applies directly to patients regardless of their mode of manifestation or degree of previous evaluation.

CLINICAL REASONING AND DECISION-MAKING

The patient-physician interaction proceeds through many phases of clinical reasoning and decision making. The interaction begins with an elucidation of complaints or concerns in a respectful and socially conscious approach, followed by inquiries or evaluations to address these concerns in increasingly precise ways. The process commonly requires a careful history or physical examination (Chapter 6), ordering of diagnostic tests, integration of clinical findings with test results, understanding of the risks and benefits of the possible courses of action, and careful consultation with the patient and family to develop future plans. Physicians can increasingly call on a growing literature of evidence-based medicine to guide the process so that benefit is maximized while respecting individual variations in different patients. Throughout *Goldman-Cecil Medicine*, the best current evidence is highlighted with specific grade A references that can be accessed directly in the electronic version.

The increasing availability of evidence from randomized trials to guide the approach to diagnosis and therapy should not be equated with "cookbook" medicine. Evidence and the guidelines that are derived from it emphasize proven approaches for patients with specific characteristics. Substantial clinical judgment is required to determine whether the evidence and guidelines apply to individual patients and to recognize the occasional exceptions. Even more judgment is required in the many situations in which evidence is absent or inconclusive.[16] Evidence must be tempered by patients' preferences, although it is a physician's responsibility to avoid pre-judgment and to emphasize evidence when presenting alternative options to the patient. The adherence of a patient to a specific regimen is likely to be enhanced if the patient also understands the rationale and evidence behind the recommended option.

To optimize medical care, the physician must understand the patient as a person. This fundamental precept of doctoring includes an understanding of the patient's sexual orientation and gender identity, cultural background, social situation, family issues, financial constraints, access to health insurance, trust in the health care system, and preferences for different types of care and outcomes, ranging from maximum prolongation of life to the relief of pain and suffering (Chapters 2 and 3). If the physician does not appreciate and address these issues, the science of medicine cannot be applied appropriately, and even the most knowledgeable physician will fail to achieve the desired outcomes.

Even as physicians become increasingly aware of new discoveries, patients can obtain their own information from a variety of sources, some of which are of questionable reliability.[17] The increasing use of alternative and complementary therapies (Chapter 30) is an example of patients' frequent dissatisfaction with prescribed medical therapy. Physicians should keep an open mind regarding unproven options but must advise their patients carefully if such options may carry any degree of potential risk, including the risk that they may be relied on to substitute for proven approaches.

The principle of patient autonomy asserts that physicians make recommendations but patients make the final decisions (Chapter 2). The physician is an

E-TABLE 1-1 GUIDE TO THE APPROACH TO COMMON SYMPTOMS, SIGNS, LABORATORY ABNORMALITIES, SCREENING, AND TREATMENTS

	CHAPTER	SPECIFIC TABLES OR FIGURES
SYMPTOMS		
Constitutional		
Poor appetite	118	Table 118-1
Fever	259, 260	Figures 260-1, 260-2, 260-3, 260-4; Tables 259-1, 259-2, 259-3, 259-4, 259-5, 259-6, 259-7
Obesity	201	Figure 201-1; Table 201-4
Snoring, sleep disturbances	374	Figures 374-5, 374-6
Weight loss	118, 200	Figure 118-4; Table 118-4
Head, Eyes, Ears, Nose, Throat		
Headache	367	Tables 367-1, 367-2, 367-3
Visual loss, transient	391, 392	Tables 391-2, 392-1
Ear pain	394	Table 394-8
Hearing loss	396	Figure 396-1
Ringing in ears (tinnitus)	396	Figure 396-2
Vertigo	396	Figure 396-3
Loss of smell or taste	395	Table 395-1
Nasal congestion, rhinitis, or sneezing	394	Figure 394-5; Tables 394-3, 394-5, 394-7
Dry mouth	393	Table 393-7
Hoarseness	397	
Sore throat	397	Tables 397-1, 397-2
Cardiopulmonary		
Cardiac arrest	50	Figures 50-2, 50-3; Table 50-1
Chest pain	39, 123	Tables 39-2, 123-8, 123-9
Cough	71	Figure 71-1; Tables 71-2, 71-3
Dizziness	39, 49, 396	Figure 49-1; Table 396-1
Hemoptysis	71	Figure 71-3; Tables 71-6, 71-7
Palpitations	39, 49	Figure 49-1; Tables 39-4, 49-8
Shortness of breath	39, 71	Figure 71-2; Table 71-5
Syncope	49	Figure 49-1; Tables 49-1, 49-2, 49-3, 49-4, 49-6, 49-7, 49-8
Gastrointestinal		
Abdominal pain		
Acute	118, 128	Figures 118-1, 118-2; Tables 118-2, 118-3, 128-1
Chronic	118, 123	Figure 118-3; Table 118-2
Anal pain	131	
Constipation	122, 123	Figures 122-3, 123-1; Table 122-2
Diarrhea	123, 126	Figures 123-1, 126-1, 126-2, 126-3, 126-4
Dysphagia, odynophagia	118, 124	Table 118-1
Fecal incontinence	131	Figure 131-5
Heartburn/dyspepsia	118, 123, 124, 125	Figures 118-6, 124-2; Tables 123-3, 123-4, 125-1
Hematemesis	121, 139	Figure 121-3; Table 121-1
Melena, blood in stool	121	Figures 121-3, 121-4, 121-6; Table 121-4
Nausea and vomiting	118	Figure 118-5; Table 118-5
Genitourinary		
Dysuria	263, 264	Tables 263-3, 263-5, 264-2
Erectile dysfunction	216	Figure 216-4; Table 216-9
Frequency	263	Table 263-3
Genital ulcers or warts	264	Table 264-1
Hematuria	100	Figure 100-3
Hot flashes	222	Tables 222-3, 222-4
Incontinence	115	Tables 115-1, 115-2, 115-3
Infertility, female	218, 222	Table 218-5
Infertility, male	216	Figures 216-2, 216-3; Table 216-7
Menstrual irregularities	218	Figure 218-3; Tables 218-4, 218-5, 218-6

E-TABLE 1-1 GUIDE TO THE APPROACH TO COMMON SYMPTOMS, SIGNS, LABORATORY ABNORMALITIES, SCREENING, AND TREATMENTS—cont'd

	CHAPTER	SPECIFIC TABLES OR FIGURES
Polyuria	102	Figure 102-5; Table 102-10
Renal colic	111	Figure 111-1
Scrotal mass	185	Figure 185-1
Vaginal discharge	264	
Musculoskeletal		
Neck pain	369	Figures 369-4, 369-7; Tables 369-3, 369-4
Back pain	369	Figures 369-4, 369-5, 369-6; Tables 369-3, 369-5
Joint pain	236	Figures 236-1, 236-3; Tables 236-1, 236-3
Extremities		
Edema		
Bilateral	39	Figure 39-7
Unilateral	68	Figure 68-2; Table 68-2
Claudication	65	Tables 65-3, 65-4
Limb ischemia (acute)	65	Figure 65-4; Table 65-2
Neurologic		
Gait abnormalities	366	Table 366-2
Memory loss	371	Figures 371-1, 371-2; Tables 371-1, 371-2, 371-3, 371-4, 371-5, 371-6, 371-7, 371-8
Seizures	372	Tables 372-1, 372-2, 372-3, 372-4, 372-5, 372-6
Sensory loss	366, 388	Figure 388-1; Tables 388-1, 388-3
Weakness	366, 388, 389, 390	Tables 366-1, 388-2, 389-1, 389-2, 389-4
Integumentary		
Alopecia	409	Tables 409-1, 409-3
Bleeding abnormalities	157	Tables 157-1, 157-2, 157-3
Hirsutism	409	
Hives	232, 407	Figure 232-2; Tables 232-1, 407-1, 407-2
Nail disorders	409	Table 409-4
Pigmentation abnormalities	408	Table 408-2
Rash	259, 403, 408	Figure 403-1; Tables 259-2, 403-1, 403-2, 403-3, 403-4, 403-5, 403-6, 403-8, 408-5
SIGNS		
Vital Signs		
Abnormal vital signs	7	Tables 7-1, 7-2, 7-3
Fever	259, 260	Figures 260-1, 260-2, 260-3, 260-4; Tables 259-1, 259-2, 259-3, 259-4, 259-5, 259-6, 259-7, 260-2
Heat illness/hyperthermia	95	Tables 95-1, 95-2, 95-3
Hypothermia	7, 95	Tables 95-4, 95-5, 95-6
Bradycardia	7, 49, 51	Figures 49-2, 49-3; Tables 51-1, 51-2, 51-3
Tachycardia	7, 49, 52, 53	Figures 49-2, 49-3; Tables 52-1, 52-2, 52-3, 53-2
Hypertension	64	Tables 64-4, 64-5, 64-6, 64-7, 64-8, 64-9, 64-10, 64-11, 64-12
Hypotension/shock	7, 92	Figures 92-1, 92-2, 92-3, 93-2, 94-1; Tables 92-1, 93-1, 93-2, 93-3
Respiration alteration	7, 74, 90	Tables 74-1, 74-2, 90-2
Head, Eyes, Ears, Nose, Throat		
Eye pain	391	Table 391-3
Jaundice	133	Figure 133-1; Tables 133-1, 133-2, 133-3
Nystagmus	392	Table 392-4
Papilledema	391, 392	Figure 391-25; Table 392-2
Pupillary dilatation	392	Figure 392-4
Red eye	391	Tables 391-4, 391-6
Strabismus	392	Figure 392-6
Rhinitis	394	Tables 394-1, 394-3
Sinusitis	394	Tables 394-2, 394-4, 394-5
Oral ulcers and discolorations	393	Tables 393-1, 393-2, 393-3, 393-4
Salivary gland enlargement	393	Table 393-6

E-TABLE 1-1 GUIDE TO THE APPROACH TO COMMON SYMPTOMS, SIGNS, LABORATORY ABNORMALITIES, SCREENING, AND TREATMENTS—cont'd

	CHAPTER	SPECIFIC TABLES OR FIGURES
Neck		
Lymphadenopathy	154	Tables 154-1, 154-2, 154-3, 154-4
Neck mass	176	Figure 176-2
Thyroid nodule	207	Figure 207-5
Thyromegaly/goiter	207	Figures 207-1, 207-3
Breast		
Breast mass	183	
Lungs		
Wheezes	71	Table 71-4
Cardiac		
Carotid pulse abnormalities	39	Figure 39-4
Heart murmur or extra sounds	39	Figure 39-5; Tables 39-7, 39-8
Jugular venous distention	39	Table 39-6
Abdomen		
Abdominal swelling/ascites	128, 139	Table 139-3
Acute abdomen	118, 128	Figure 118-2; Table 128-1
Hemorrhoids	131	Figures 131-1, 131-2; Table 131-1
Hepatomegaly	132	Figure 132-5
Rectal bleeding/positive stool	121, 179	Figures 121-3, 121-4, 121-6; Table 121-4
Splenomegaly	154	Table 154-5
Musculoskeletal/Extremities		
Arthritis	236	Figures 236-1, 236-2; Table 236-3
Clubbing	39, 254	Figures 39-9, 254-1
Cyanosis	39, 66	Figures 39-8, 66-12
Edema	39	Figure 39-7
Raynaud phenomenon	66	Figure 66-9
Neurologic		
Autism spectrum	385	Table 385-1
Coma	373	Tables 373-1, 373-2, 373-3, 373-4, 373-5, 373-6
Delirium	361	Figure 361-1; Tables 361-1, 361-2, 361-3
Movement disorders	378, 379	Tables 378-1, 378-2, 378-3, 378-4, 379-1, 379-2, 379-3, 379-4, 379-5, 379-6, 379-7, 379-8
Neuropathy	388	Figure 388-1; Tables 388-1, 388-2, 388-3, 388-4
Psychiatric disturbances	362	Tables 362-1, 362-2, 362-3, 362-4, 362-5, 362-6, 362-7, 362-8, 362-9, 362-10, 362-11, 362-12, 362-13, 362-14
Stroke	376, 377	Figure 376-1; Tables 376-2, 376-5, 376-6, 377-5, 377-6
Skin and Nails		
Mole	188	Table 188-1
Nail diseases	409	Table 409-4
COMMON LABORATORY ABNORMALITIES		
Hematology/Urinalysis		
Anemia	144	Figure 144-3; Tables 144-2, 144-3, 144-4, 144-5, 144-6, 144-7, 144-8, 144-9
Eosinophilia	156	Figure 156-1; Tables 156-1, 156-2
Leukocytosis	153	Figure 153-4; Table 153-1
Lymphocytosis	153	Table 153-3
Monocytosis	153	Table 153-2
Neutropenia	153	Figure 153-7; Tables 153-4 and 153-5
Neutropenia with fever	260	Figures 260-1, 260-2, 260-3, 260-4
Polycythemia	152	Table 152-4
PT or PTT prolongation	157	Figure 157-4
Thrombocytopenia	158	Figure 158-1; Tables 158-1, 158-3
Thrombocytosis	152	Table 152-5
Urinalysis	100, 106	Figure 100-3; Tables 100-2, 106-5

E-TABLE 1-1 GUIDE TO THE APPROACH TO COMMON SYMPTOMS, SIGNS, LABORATORY ABNORMALITIES, SCREENING, AND TREATMENTS—cont'd

	CHAPTER	SPECIFIC TABLES OR FIGURES
Chemistries		
Acid-base disturbances	104	Figures 104-1, 104-2, 104-3; Tables 104-1, 104-2, 104-3, 104-4, 104-5, 104-6, 104-7
BUN/creatinine elevation		
Acute	106	Figure 106-1; Tables 106-1, 106-2, 106-3, 106-4, 106-5, 106-6
Chronic	116	Table 116-1
Hypercalcemia	227	Figure 227-2; Tables 227-2, 227-3, 227-4
Hyperglycemia	210	Tables 210-1, 210-2
Hypocalcemia	227	Figure 227-3; Table 227-6
Hypoglycemia	211	Figure 211-3; Tables 211-1, 211-2
Hypo- and hyperkalemia	103	Figure 103-3; Tables 103-2, 103-3
Hypo- and hypernatremia	102	Figure 102-3; Tables 102-5, 102-6, 102-7, 102-8, 102-9
Hypo- and hyperphosphatemia	105	Figures 105-1, 105-2; Tables 105-2, 105-3
Hypo- and hyperthyroidism	207	Figures 207-1, 207-3; Tables 207-1, 207-2, 207-3
Liver enzymes	133	Figures 133-1, 133-2, 133-3; Tables 133-1, 133-3
Magnesium deficiency	105	Table 105-1
P_{CO_2} elevation	74	Figure 74-2
ECG/Chest Radiograph		
ECG abnormalities	42	Tables 42-2, 42-3, 42-4, 42-5
Incidental masses		
Adrenal incidentaloma	208	
Hepatic mass	132	Figure 132-6
Mediastinal mass	86	Table 86-6
Renal mass	182	
Pleural effusion	86	Tables 86-3, 86-4, 86-5
Solitary pulmonary nodule	177	Figure 177-2

BUN = blood urea nitrogen; ECG = electrocardiogram; PT = prothrombin time; PTT = partial thromboplastin time.

expert advisor who must inform and empower the patient to make decisions by integrating scientific data with their preferences and values. The physician must have an open dialogue with the patient and family regarding the full range of options and encourage shared decision-making whenever appropriate.

The rise of telemedicine, stimulated by the social distancing in response to the COVID-19 pandemic, promises to increase accessibility but at the potential detriment of the personal closeness of the patient-doctor relationship.[18] Physicians and the medical profession have the opportunity to use this indisputably convenient tool to extend health care to underserved and vulnerable populations worldwide, but they must remain vigilant to benefit from its virtues, minimize its limitations, and not exacerbate health disparities based on access to digital technology.[19]

INCORPORATING A PUBLIC HEALTH FOCUS

The physician does not exist in a vacuum, but rather as part of a complicated and extensive system of medical care and public health. In premodern times and even today in some resource-limited countries, the most important ways to promote health and reduce disease are to ensure basic hygiene, clean water, and adequate nutrition (Chapter 11). In resource-limited and high-income countries, adoption of healthy lifestyles, including better diet (Chapter 13) and appropriate exercise (Chapter 14), are the keys to reducing the epidemics of obesity (Chapter 201), coronary disease (Chapter 40), and diabetes (Chapter 210). Public health interventions to provide immunizations (Chapter 15) and to reduce injuries and the use of tobacco (Chapter 363), illicit drugs (Chapter 365), and excess alcohol (Chapter 364) can collectively produce more health benefits than nearly any other imaginable health intervention. As emphasized by the COVID-19 pandemic (Chapters 335 to 337), the public health system must play a key role in informing the populace and in promoting guidelines for individuals as well as for the health care profession.

APPROACH TO THE MEDICAL PROFESSION

Medical professionalism should emphasize three fundamental principles: the primacy of patient welfare, patient autonomy, and social justice. As modern medicine brings a plethora of diagnostic and therapeutic options, the interactions of the physician with the patient and society become more complex and potentially fraught with ethical dilemmas (Chapter 2). To help provide a moral compass that is not only grounded in tradition but also adaptable to modern times, the primacy of patient welfare emphasizes the fundamental principle of the medical profession. The physician's altruism, which begets the patient's trust, must be impervious to the social, economic, bureaucratic, and political challenges that are faced by the physician and the patient (Chapter 4).

To promote these fundamental principles, a series of professional responsibilities (Table 1-1) represents practical, daily traits that benefit the physician's own patients and society as a whole. Physicians who use these and other attributes to improve their patients' satisfaction with care are not only promoting professionalism but also reducing their own risk for liability and malpractice. Physicians have a responsibility to stay current in their field[20] and to know when a patient's best interests are served by a referral to another physician or health care clinician.

TEAMWORK, STANDARDS, AND ACCOUNTABILITY

An interesting new aspect of professionalism is the increasing reliance on team approaches to medical care, as exemplified by physicians whose roles are defined by the location of their practice—historically in the intensive care unit or emergency department and now on the inpatient general hospital floor. Quality care requires coordination and effective communication across inpatient and outpatient sites among physicians who themselves may now typically work defined hours. This transition from reliance on a single, always available physician to a team, ideally with a designated coordinator, places new challenges on physicians, the medical care system, and the medical profession. Many teams comprise health care professionals who have complementary skills, including physicians, nurses, advanced practice providers, and pharmacists. This new model emphasizes the relevance of interprofessional education that focuses on core competencies, roles, responsibilities, communication, and teamwork.[21]

The changing medical care environment is also placing increasing emphasis on standards, outcomes, and accountability. As purchasers of insurance become more cognizant of value rather than just cost (Chapter 10), outcomes ranging from patients' satisfaction to rates of screening mammography (Chapter 183) and even to mortality rates with coronary artery bypass graft surgery (Chapter 59) have become metrics by which rational choices can be made. Clinical guidelines and critical pathways derived from randomized controlled trials and evidence-based medicine can potentially lead to more cost-effective care and better outcomes.

TABLE 1-1 PROFESSIONAL RESPONSIBILITIES

Commitment to:
- Professional competence
- Honesty
- Patient confidentiality
- Maintaining appropriate relationships
- Improving the quality of care
- Improving access to care
- Just distribution of finite resources
- Scientific knowledge
- Maintaining trust by managing conflicts of interest
- Professional responsibilities

From Brennan T, Blank L, Cohen J, et al. Medical professionalism in the new millennium: a physician charter. *Ann Intern Med*. 2002;1136:243-246.

SOCIAL JUSTICE

The importance of social justice acknowledges that the patient-physician interaction does not exist in a vacuum. The physician has a responsibility to the individual patient and to broader society to promote equitable access to health care, to eliminate disparities in health and health care delivery, and to bring science to even the most contentious political issues. For example, research into the relationship of firearms to rates of murder and suicide[22] can be useful for preventive medicine and public policy regardless of an individual's position on background checks and licensing for gun owners. The promotion of masks and vaccines to slow the COVID-19 pandemic was an example of how science should guide behaviors, even in times of uncertainty.

Medical schools,[23] medical research,[24] the medical profession,[25] and all medical institutions must embrace the principles of diversity, equity, inclusion, and social justice in education and the workplace. These principles optimize the profession's ability to mirror the populations it serves and to maximize the ability to address disparities and inequalities in care.

These major changes in many Western health care systems bring with them many risks and concerns. If the concept of limited choice among physicians and health care providers is based on objective measures of quality and outcome, channeling of patients to better providers is one reasonable definition of better selection and enlightened competition. If the limiting of options is based overwhelmingly on cost rather than measures of quality, outcomes, and patient satisfaction, physicians and their patients can be seriously disadvantaged.

Another risk is that the same genetic information that can lead to earlier diagnosis and to more effective, personalized medicine may be used against the very people whom it is supposed to benefit—by creating a stigma, potentially raising health insurance costs, or sometimes even making someone unable to obtain life or long-term care insurance. The ethical approach to medicine (Chapter 2), genetics (Chapter 31), and genetic counseling provides means to protect against this adverse effect of scientific progress.

BALANCING PROFESSIONAL RESPONSIBILITIES

In the modern environment, the physician often has a dual responsibility: to the health care system as an expert who helps create standards, measures of outcome, clinical guidelines, and mechanisms to ensure high-quality, cost-effective care; and to individual patients who entrust their well-being to that physician to promote their best interests within the reasonable limits of the system. A health insurance system that emphasizes cost-effective, value-based care, that gives physicians and health care providers responsibility for the health of a population and the resources required to achieve these goals, that must exist in a competitive environment in which patients can choose alternatives if they are not satisfied with their care, and that places increasing emphasis on health education and prevention can have many positive effects. In this environment, however, physicians must beware of overt and subtle pressures that could entice them to underserve patients and abrogate their professional responsibilities by putting personal financial reward ahead of their patients' welfare. The physician's responsibility to represent the patient's best interests and avoid financial conflicts by doing too little in the newer systems of capitated care provides different specific challenges but an analogous moral dilemma to the historical American system in which the physician is rewarded financially for doing too much.

An ongoing challenge for a profession that values dedication, attention to detail, and selflessness is the increasing risk of suffering burnout, which is characterized by emotional exhaustion and depersonalization. For example, the medical profession's heroic response to COVID-19, despite the personal health risks and significant psychological challenges, was inspiring. Nevertheless, the longer-term effects on physicians' resiliency will be a challenge to individual physicians and the profession as a whole.[26,27] Hopefully, both individual-focused and structural or organizational modifications in the work environment can result in clinically meaningful reductions in physician burnout.[28]

In the current health care environment, all health care professionals must strive to retain and expand their scientific knowledge base, redouble their commitment to the principles of their profession, and preserve their own well-being so they can serve others. In this spirit, *Goldman-Cecil Medicine* seeks to be a comprehensive approach to the ethos, foundation, and modern practice of internal medicine.

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Many physicians are taught that four main principles can be invoked to address bioethical dilemmas: autonomy, nonmaleficence, beneficence, and justice. Autonomy is the idea that people should have the right and freedom to choose, pursue, and revise their own life plans. Nonmaleficence is the idea that people should not be knowingly harmed or injured. This principle is encapsulated in the oft-repeated phrase "first, do no harm"—*primum non nocere*. Beneficence refers to the positive actions that a physician should undertake to promote the well-being of his or her patients. In clinical practice, this obligation arises from the implicit and explicit commitments and promises central to the physician-patient relationship. Finally, the principle of justice is defined by the fair distribution of benefits and burdens that result from clinical interactions.

Although helpful in providing an initial framework, these principles are too broad to have more than limited value. The principles are also frequently underdeveloped and likely to conflict with each other, thereby resulting in bioethical dilemmas. The principles themselves do not offer guidance on how they should be balanced to resolve dilemmas. Given that they are focused on physician-patient encounters, the principles are also unhelpful when addressing bioethical issues at the system or institutional level, such as the allocation of scarce vaccines. Finally, these four principles are not comprehensive and fail to encapsulate all critical values. As the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) pandemic has made clear, other fundamental ethical principles and values include a focus on equity and priority to the worst off, duties to future generations, and professional integrity.[1]

There is no formula that can magically determine how to solve bioethical dilemmas.[2] Instead, medical professionals should follow an orderly analytic process. First, practitioners need to obtain the facts relevant to the situation. Second, they must delineate the fundamental bioethical issue. Third, they must identify all the crucial principles and values that relate to, and potentially conflict with, the case. Fourth, because many ethical dilemmas have been previously analyzed and subjected to empirical study, practitioners should examine the relevant literature so they may potentially identify new values, understand existing principles, reformulate the issue at hand, and see if there is an accepted resolution. Fifth, with this information, the practitioner must distinguish clearly unethical practices from a range of ethically permissible actions. Finally, it is important not only to come to a resolution but also to state clearly the justification for such decisions. Although unanimous decisions are ideal, the reality remains that such consensus may be elusive. Reasonable physicians must therefore take care to explain what principles they weighted highly and what interpretations they relied upon to resolve ethical dilemmas.

A multitude of bioethical dilemmas arise in medical practice each year, including issues of genetics, conscientious objection by providers, and termination of care. In clinical practice, the most common issues revolve around informed consent, termination of life-sustaining treatments, euthanasia and physician-assisted suicide, allocation of scarce resources (featured prominently during the SARS-CoV-2 pandemic and in transplantation), and conflict of interest.

PHYSICIAN-PATIENT RELATIONSHIP: INFORMED CONSENT

HISTORY

The requirement of informed consent dates as far back as Plato. The first recorded legal case on informed consent took place in England in 1767 when a patient complained that he had not given his consent for two surgeons to refracture his leg after it had healed improperly. The judge ultimately ruled that obtaining a patient's consent prior to a procedure was the "rule of the profession" and thus a legal obligation of surgeons. Failure to obtain consent, the court declared, was inexcusable. In more contemporary times, a landmark 1957 U.S. court ruling stated that physicians have a positive legal obligation to disclose information about risks, benefits, and alternative treatments to patients; this decision popularized the term *informed consent*.

DEFINITION AND JUSTIFICATION

Informed consent is a person's autonomous authorization to permit a physician—or other health professional—to undertake diagnostic or therapeutic interventions for himself or herself. The patient understands that he or she is taking responsibility for the decision while empowering someone else, the physician, to implement it. However, agreement to a course of medical treatment does not necessarily qualify as informed consent.

The four fundamental requirements for valid informed consent are: mental capacity, disclosure, understanding, and voluntariness. First, informed consent assumes that people have the mental capacity to make decisions; disease, development, or medications can compromise patients' mental capacity to provide informed consent. Adults are presumed to have the legal competence to make medical decisions, and whether an adult is incompetent to make medical decisions is a legal determination. Practically, physicians usually decide whether patients are competent based on whether they can understand the information disclosed, appreciate its significance for their own situation, and use logical and consistent thought processes in decision making. Incompetence in medical decision making does not mean a person is incompetent in all types of decision making and vice versa. Second, crucial information relevant to the decision must be disclosed, usually by the physician, to the patient. Third, the patient should understand the information and its implications for his or her interests and life goals. Finally, the patient's decision must be made voluntarily, without coercion or manipulation by the physician.

It is a mistake to view informed consent as a one-time event, such as the signing of a form. Informed consent is viewed more accurately as a process that evolves throughout the course of a patient's diagnosis and subsequent treatment.

Typically, a patient's autonomy is the value invoked to justify informed consent. Other values, such as bodily integrity and beneficence, have also been cited, especially in early legal rulings.

EMPIRICAL DATA

Extensive research on informed consent shows that physicians frequently do not communicate all the relevant information needed for patients to make an

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2

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ABSTRACT

It commonly is argued that the bioethical dilemmas physicians face today result primarily from modern advances in medical technology. In reality, however, concerns about ethical issues are as old as the practice of medicine itself. The Hippocratic Oath, composed sometime around 400 BC, attests to the need even of ancient Greek physicians for advice on how to address the many bioethical dilemmas that they confronted. Technology may make these issues more common and change the context in which they arise, but many, if not most, bioethical issues that physicians regularly confront are timeless. Indeed, the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) pandemic (Chapter 336) has further highlighted the central role of medical ethics in medical practice. A multitude of bioethical dilemmas arise in medical practice each year, including issues of genetics, conscientious objection by providers, and termination of care. In clinical practice, the most common issues revolve around informed consent, termination of life-sustaining treatments, euthanasia and physician-assisted suicide, allocation of resources, and conflicts of interest.

KEYWORDS

bioethics
informed consent
life-sustaining treatment
euthanasia
physician-assisted suicide
conflict of interest

informed decision in clinical settings. The more complex the medical decisions, the more likely it is that physicians will obtain all the elements of informed consent.

Interestingly, data suggest that disclosure, both in informed consent documents and in discussion, is better in research than clinical settings, likely because of the research-specific requirement of having a written document to guide a process overseen by an independent committee, such as an institutional review board or a research ethics committee.

Patients frequently fail to recall crucial information disclosed during the process of obtaining informed consent, although they usually think they have sufficient information to make a decision. Whether patients fail to recall key information because they are overwhelmed by the information or because they find much of it not salient to their decision is unclear. The issue therefore lies more in determining what patients understand at the point of decision making, rather than what they recall later. For common medical interventions, such as elective surgery, the ideal informed consent would include the risks and benefits as quantified in randomized controlled trials, relevant data on the surgeon, the institution's clinical outcomes for the procedure, and a list of acceptable alternatives.[3]

Studies aimed at improving informed consent in clinical settings suggest that interactive media, such as interactive computer software and videos, improve patients' understanding of competing alternatives.[A1] Typically, patients who use a decision aid have greater knowledge of the evidence, feel more clear about what matters to them, have more accurate understanding of risks and benefits, and participate more in the decision-making process. Computer and web-based decision aids are now available for hundreds of common conditions and procedures.

A more modern challenge in obtaining informed consent is the introduction of electronic methods into the process, including smartphone applications in acute situations such as ischemic stroke.[A2] Digital models for informed consent often are not user-friendly for older patients, and evidence suggests that most people do not read click-through agreements on computers and mobile devices. Concern also exists that it may be challenging to obtain true voluntary choice without being able to assess the body language, tone, and emotion that can be observed during a person-to-person interaction.

One of the most important results of empirical research on informed consent is that there is a gap between the desire for information and the desire for actual decision making. Studies suggest that although most patients want information, far fewer actually want to make decisions about their own care. In one study, for example, only one third of patients desired decision-making authority, and patients' decision-making preferences were not correlated with their information-seeking preferences. Patients' preferences for decision-making authority generally increase with higher educational levels and decline with age. Most importantly, the more serious the illness, the more likely patients are to prefer that physicians make the decisions. Several studies suggest that patients who have less of a desire to make their own decisions generally are more satisfied with how the decisions are ultimately made.

PRACTICAL CONSIDERATIONS

Physicians who implement informed consent are usually concerned about the extent to which information should be disclosed and how to disclose it so it is well understood.[4] Physicians should disclose at least six fundamental elements of information to patients (Table 2-1). Because risk is usually a physician's principal concern, physicians also should disclose (1) the nature of the risks, (2) their magnitude, (3) the likelihood that the risks will occur, and (4) when the consequences might occur. Increasingly, these disclosures should include data both from clinical trials and from the institution and physician performing the test and treatments. In general, all serious risks, such as death, paralysis, stroke, infections, or chronic pain, even if rare, should be disclosed, as should common risks.

The key challenge in providing this information is doing so within reasonable time constraints and without overwhelming the patient with unnecessarily technical details. Fortunately, time constraints can be somewhat ameliorated by using interactive electronic media that allow patients to view information on their own schedules while facilitating the transfer of basic information.

The question of how much physicians should disclose is a state-level determination. Generally, states have adopted one of two divergent legal standards. The *physician* or *customary* standard, adapted from malpractice law, states that the physician should disclose all information "which a reasonable medical practitioner would make under the same or similar circumstances." Conversely, the *reasonable person* or *lay-oriented* standard states that physicians should disclose all information that a "reasonable person in the patient's circumstances would find material" to the medical decision. The physician standard is factual and can be determined empirically, but the patient-oriented standard, which is meant to engage physicians with patients, is hypothetical. Currently, each standard is used by about half of the United States.

The requirement of informed consent has no exceptions. In emergency situations, consent can be assumed under the belief that patients' interests are in survival and retaining maximal mental and physical functioning; as a result, reasonable persons would want treatment. In some circumstances, physicians may believe the process of informed consent could pose a serious psychological threat. In rare cases, the "therapeutic privilege" of promoting a patient's well-being trumps autonomy, but physicians should be wary of invoking this exception too readily.

If patients are deemed mentally incompetent to make medical decisions, family members—in order from spouse, children, parents, siblings, then more distant relatives—usually are selected as surrogates or proxies,[5] although there may be concerns about conflicting interests or knowledge of the patient's wishes. In the relatively rare circumstance in which a patient has formally designated a proxy, that person has decision-making authority.

The *substituted judgment* standard states that the proxy should choose what the patient would choose if he or she were competent. The *best interests* standard states that the proxy should choose what is best for the patient. However, it is often not clear what the patient would have decided, because the situation was not discussed with the patient and he or she left no advance care directive. Similarly, what is considered "best" for a patient can be controversial because of tradeoffs between quality of life and pure survival. These problems are complicated by the poor ability of many proxies to predict a patient's quality of life; proxies also tend to underestimate patients' future functional status and satisfaction. Similarly, a proxy's predictions on a mentally incapacitated patient's life-sustaining preferences are often inaccurate. In cases in which the patient is diagnosed with dementia, families tend to agree with patients on decisions regarding life-sustaining treatment two thirds of the time, better but not much better than the 50% agreement based on chance alone. Such confusion on how to decide for incapacitated patients can create conflicts among family members or between the family and medical providers. In such circumstances, an ethics consultation may be helpful.

TABLE 2-1 FUNDAMENTAL ELEMENTS FOR DISCLOSURE TO PATIENTS

Diagnosis and prognosis
Nature of proposed intervention
Reasonable alternative interventions
Risks associated with each alternative intervention
Benefits associated with each alternative intervention
Probable outcomes of each alternative intervention

TERMINATION OF MEDICAL INTERVENTIONS

HISTORY

Since the origins of medicine, withholding medical treatment from terminally ill patients while still providing palliative care, thereby allowing "nature to take its course," has been deemed ethical. Hippocrates argued that physicians should "refuse to treat those [patients] who are overmastered by their disease." In the 19th century, prominent American physicians advocated withholding cathartic and emetic "treatments" from the terminally ill. In 1900, the editors of *The Lancet* argued that physicians should intervene to ease the pain of death and that they did not have an obligation to prolong a clearly terminal life. The contemporary debate on terminating care began in the United States in 1976 with the *Quinlan* case, in which the New Jersey Supreme Court ruled that patients had a right to refuse life-sustaining interventions on the basis of a right to privacy, and that the family could exercise that right for a patient in a persistent vegetative state.

DEFINITION AND JUSTIFICATION

It generally is agreed that all patients have a right to refuse medical interventions. Ethically, this right is based on the patient's right to autonomy and is implied by the doctrine of informed consent. Legally, state courts have cited the right to privacy, the right to bodily integrity, and common law to justify the right to refuse medical treatment. In the 1990 *Cruzan* case, and in the subsequent physician-assisted suicide cases, the U.S. Supreme Court affirmed that there is a "constitutionally protected right to refuse lifesaving hydration and nutrition." The Court stated that "[A] liberty interest [based on the 14th Amendment] in refusing unwanted medical treatment may be inferred from

our prior decisions." All patients have both a constitutional and an ethical right to refuse medical interventions. These rulings were the basis of consistent state and federal court rulings in the *Schiavo* case to permit the husband to terminate artificial nutrition and hydration for his terminally ill wife in a vegetative state (Chapter 373).

EMPIRICAL DATA

Data show that termination of medical treatments is now the norm, and the trend has shifted toward stopping medical interventions based on the preferences of patients and their surrogate decision makers. Over 85% of Americans and 90% of decedents in intensive care units do not receive cardiopulmonary resuscitation. Of decedents in intensive care units, more than 85% die after the withholding or withdrawal of medical treatments, with an average of 2.6 interventions being withheld or withdrawn per decedent.

Despite extensive public support for use of advance care directives, passage of the Patient Self-Determination Act mandating that health care institutions inform patients of their right to complete such documents, and the 2016 policy to reimburse physicians for discussing end-of-life preferences with patients, less than 40% of Americans appear to have completed any written form of end-of-life decisions. Among Americans ages 75 and older, about 20% have neither written nor talked with someone about their wishes for medical treatment at the end of life. Data suggest that although over 40% of patients required active decision making about terminating medical treatments in their final days, more than 70% lacked actual decision-making capacity, thereby highlighting the importance of completing advance directives.

Efforts to improve completion of advance care directives have generated mixed results. In La Crosse County, Wisconsin, for example, after health care organizations in the county added an "Advance Directive" section to their electronic medical records, 90% of decedents had some type of advance directive. Unfortunately, successful pilot efforts like La Crosse County's have not been widely adopted or easily scaled. A persistent problem has been that even when patients complete advance care directives, the documents frequently are not readily available, physicians do not know they exist, or they tend to be too general or vague to guide decisions. The increasing use of electronic health records should make it possible for advance directives to be available whenever and wherever the patient presents to a health care provider. Although electronic health records will help in making existing advance directives available, they will not solve the problem of actually initiating a conversation among the physician, patient, and family about advance care planning. Starting that conversation still seems to be a persistent barrier.

Just as proxies are poor at predicting patients' wishes, data show that physicians are even worse at determining patients' preferences for life-sustaining treatments. In one study, for example, 30% of family conferences between clinicians and surrogates did not discuss preferences for end-of-life decision making for patients who were at high risk of death. In many cases, life-sustaining treatments are continued even when patients or their proxies desire them to be stopped. Conversely, many physicians discontinue or never begin interventions unilaterally without the knowledge or consent of patients or their surrogate decision makers. These discrepancies emphasize the importance of engaging patients early on in their care about treatment preferences.

PRACTICAL CONSIDERATIONS

Many practical considerations are applicable to enacting the right to terminate medical treatment (Table 2-2). First, patients have a right to refuse any and all medical interventions. The question of what medical interventions can be terminated—or not started—is a recurrent topic of debate. Courts have made clear that any treatment prescribed by a physician and administered by a health care provider can be stopped if it is more harmful than beneficial. The issue is not whether the treatment is ordinary, extraordinary, or heroic, or whether it is high-technology or low-technology. Treatments that can be stopped include not only ventilators, artificial nutrition, and hydration, but also dialysis, pacemakers, ventricular assist devices, antibiotics, and any medication.[6]

Second, there is no ethical or legal difference between withholding an intervention and withdrawing it. If a respirator or other treatment is started because physicians are uncertain whether a patient would have wanted it, they always can stop it later when information clarifies the patient's wishes. Although physicians and nurses might find stopping a treatment to be more difficult psychologically, withdrawal is ethically and legally permitted—and required—when it is consonant with the patient's wishes.

Third, competent patients have the exclusive right to make decisions about terminating their own care. If there is a conflict between a competent patient and his or her family, the patient's wishes are to be followed. It is the patient's right to refuse treatment, not the family's right. For mentally incompetent patients, the situation is more complex. If the patients left clear indications of their wishes, whether as explicit oral statements or as written advance directives, these wishes should be followed. Physicians should not be overly concerned about the precise form patients use to express their wishes; because patients have a constitutional right to refuse treatment, the focus should be whether the wishes are clear and relevant to the situation. If an incompetent patient did not leave explicit indications of his or her wishes or designate a proxy, the physician should identify a surrogate decision maker and rely upon that person's judgment. Some state courts have restricted what treatments a proxy decision maker can terminate, thereby requiring the incompetent patient to have given very specific instructions about the particular treatments he or she does not want to receive and the conditions under which care should be withheld or withdrawn. This requirement severely limits the authority and power of proxy decision makers.

Fourth, the right to refuse medical treatment does not translate into a right to demand any treatment, especially treatments that have no pathophysiologic rationale, have already failed, or are known to be harmful. Futility has become a justification to permit physicians unilaterally to withhold or withdraw treatments despite the family's requests for treatment. Some states, such as Texas, have enacted futility laws, which prescribe procedures by which physicians can invoke futility either to transfer a patient or to terminate interventions. However, the principle of futility is not easy to implement in medical practice. Initially, some commentators advocated that an intervention was futile when the probability of success was 1% or lower. This threshold seems to be based on empirical data, but it is a covert value judgment. Futility is meant to justify unilateral determinations by physicians, so it generally has been viewed as an inappropriate assertion that undermines physician-patient communication and violates the principle of shared decision making. Similar to the distinction between ordinary and extraordinary care, futility is increasingly viewed as more obfuscating than clarifying and is therefore being invoked much less often.

TABLE 2-2 PRACTICAL CONSIDERATIONS IN TERMINATION OF MEDICAL TREATMENTS

PRACTICAL QUESTION	ANSWER
Is there a legal right to refuse medical interventions?	Yes. The U.S. Supreme Court declared that competent people have a constitutionally protected right to refuse unwanted medical treatments based on the 14th Amendment.
What interventions can be legally and ethically terminated?	Any and all interventions (including respirators, antibiotics, pacemakers, ventricular assist devices, intravenous or enteral nutrition and hydration) can be legally and ethically terminated.
Is there a difference between withholding life-sustaining interventions and withdrawing them?	No. The consensus is that there is no important legal or ethical difference between withholding and withdrawing medical interventions. Stopping a treatment once begun is just as ethical as never having started it.
Whose view about terminating life-sustaining interventions prevails if there is a conflict between the patient and family?	The views of a competent adult patient prevail. It is the patient's body and life.
Who decides about terminating life-sustaining interventions if the patient is incompetent?	If the patient appointed a proxy or surrogate decision maker when competent, that person is legally empowered to make decisions about terminating care. If no proxy was appointed, there is a legally designated hierarchy, usually (1) spouse, (2) adult children, (3) parents, (4) siblings, and (5) available relatives.
Are advance care directives legally enforceable?	Yes. As a clear expression of the patient's wishes, they are a constitutionally protected method for patients to exercise their right to refuse medical treatments. In almost all states, clear and explicit oral statements are legally and ethically sufficient for decisions about withholding or withdrawing medical interventions.

ASSISTED SUICIDE AND EUTHANASIA

HISTORY

Even in Hippocrates' era, euthanasia and physician-assisted suicide were controversial issues. In 1905, a bill was introduced into the Ohio legislature to legalize euthanasia; it was defeated. In the mid-1930s, similar bills were introduced and defeated in the British Parliament and the Nebraska legislature. In 1997, the U.S. Supreme Court stated that there is no constitutional right to euthanasia or physician-assisted suicide, but that there also is no constitutional prohibition against states legalizing these interventions. As of 2021, nine U.S. states and the District of Columbia have legalized physician-assisted suicide—but no state has legalized euthanasia. The Montana Supreme Court did not recognize a constitutional right to physician-assisted suicide, but it ruled that the law permitting the termination of life-sustaining treatment protected physicians from prosecution if they helped hasten the death of a consenting, rational, terminally ill patient. Importantly, the American College of Physicians does not currently support the legalization of physician-assisted suicide. Both euthanasia and physician-assisted suicide are legal in many other countries, including the Netherlands, Belgium, Luxembourg, Canada, New Zealand, and Spain, and physician-assisted suicide is legal in Switzerland and Germany. Both euthanasia and physician-assisted suicide are illegal under English law.

DEFINITION AND JUSTIFICATION

The terms *euthanasia* and *physician-assisted suicide* require careful definition (Table 2-3). So-called passive and indirect euthanasia are misnomers and not actual instances of euthanasia; rather, they are ethical and legal ways to terminate care.

Four general arguments are made against permitting euthanasia and physician-assisted suicide. First, Kant and Mill, the philosophical champions of individual autonomy, believed that autonomy itself did not allow a person voluntarily to end conditions that made them autonomous. As a result, both philosophers were against voluntary enslavement and suicide. They therefore argued that the exercise of autonomy cannot include the ending of life, which would mean ending the possibility of exercising autonomy. Second, many dying patients may experience pain and suffering as the result of not receiving appropriate care. It is therefore possible that adequate care and pain management (Chapter 26) might relieve suffering without the need for euthanasia or physician-assisted suicide (Chapter 3). Although some patients may experience uncontrolled pain despite optimal end-of-life care, relatively few give pain as the justification for seeking euthanasia or physician-assisted suicide. Third, there is a clear ethical distinction between intentionally ending a life and terminating life-sustaining treatments. Both the motivations and physical acts are different. Injecting a life-ending medication, or providing a prescription for one, is not the same as removing or refraining from introducing a bodily invasive medical intervention. Finally, permitting euthanasia and physician-assisted suicide may introduce adverse consequences. For example, disturbing reports of involuntary euthanasia and euthanasia of depressed patients have come from the Netherlands and Belgium, and many worry about coercion of expensive or burdensome patients to accept euthanasia or physician-assisted suicide. Permitting euthanasia and physician-assisted suicide is likely to lead to further intrusions of lawyers, courts, and legislatures into the physician-patient relationship.

Four parallel arguments are forwarded to permit euthanasia and physician-assisted suicide. First, it is argued that autonomy justifies euthanasia and physician-assisted suicide. To respect autonomy requires permitting individuals to decide when and how it is better to end their lives. Second, beneficence—furthering the well-being of individuals—supports permitting euthanasia and physician-assisted suicide. In some cases, living can create more pain and suffering than death; ending a painful life relieves more suffering and produces a net good for the patient. Just the reassurance of having the option of euthanasia or physician-assisted suicide, even if not used, can provide "psychological insurance" and be beneficial to people. Third, euthanasia and physician-assisted suicide are no different from termination of life-sustaining treatments that are recognized as ethically justified. In both cases, the patient consents to die; in both cases, the physician intends to end the patient's life and takes some action to end the patient's life; and in both cases, the final result is the same: the patient's death. With no difference in the patient's consent, the physician's intention, or the final result, there can be no difference in the ethical justification. Fourth, the supposed slippery slope that would result from permitting euthanasia and physician-assisted suicide is unlikely. The idea that permitting euthanasia and physician-assisted suicide would undermine the physician-patient relationship or lead to forced euthanasia is completely speculative and not borne out by the available data.

TABLE 2-3 DEFINITIONS OF ASSISTED SUICIDE AND EUTHANASIA

TERM	DEFINITION
Voluntary active euthanasia	Intentional administration of medications or other interventions to cause the patient's death with the patient's informed consent
Involuntary active euthanasia	Intentional administration of medications or other interventions to cause the patient's death when the patient was competent to consent but did not consent (e.g., the patient may not have been asked)
Nonvoluntary active euthanasia	Intentional administration of medications or other interventions to cause the patient's death when the patient was incompetent and was mentally incapable of consenting (e.g., the patient might have been in a coma)
Passive euthanasia	Withholding or withdrawal of life-sustaining medical treatments from a patient to let him or her die (termination of life-sustaining treatments)—a poor term that should not be used
Indirect euthanasia	Administration of narcotics or other medications to relieve pain with the incidental consequence of causing sufficient respiratory depression to result in the patient's death
Physician-assisted suicide	A physician provides prescription medications or other interventions to a patient with the understanding that the patient can use them to commit suicide
Physician-assisted death	Either voluntary, active euthanasia or physician-assisted suicide. This term is preferred in the United States by advocates of these practices, but the term is not used in Europe.

EMPIRICAL DATA

Attitudes and practices related to euthanasia and physician-assisted suicide have been studied extensively. Two thirds of Americans say there are some situations in which a patient should be allowed to die, but 30% say that medical professionals should always do everything possible to save a patient's life. About 60% of adults think that these interventions are moral for a person who has an incurable disease and is suffering great pain with no hope of improvement. However, public support dramatically decreases to below 40% for patients who are ready to die because living is a burden or for patients who are burdensome to their families.

Physicians and medical societies tend to be much less supportive of euthanasia and physician-assisted suicide than the public,[7] with oncologists, palliative care physicians, and geriatricians among the least supportive. Among American and British physicians, the majority opposes legalizing either practice.

Approximately 25% of American physicians have received requests for euthanasia or physician-assisted suicide, including about 50% of oncologists and a growing number of neurologists.[8] Studies also indicate that less than 5% of American physicians have performed euthanasia or physician-assisted suicide. Surveys of oncologists indicate that about 4% have performed euthanasia and about 11% have performed physician-assisted suicide during their careers.

Safeguards for euthanasia and physician-assisted suicide are frequently violated. For example, one study found that about 55% of euthanasia requests came from the family. In about 40% of euthanasia and 20% of physician-assisted suicide cases, the patient was depressed; in only half of the cases was the request repeated, irrespective of treatment.

In Oregon and Washington state, over 70% of patients receiving physician-assisted suicide had cancer. Other characteristics strongly linked to requests for physician-assisted suicide included age over 65 years,[9] White race, more formal education, and having medical insurance.

Since physician-assisted suicide was legalized in Oregon over 20 years ago, less than 0.7% of all dying patients died by physician-assisted suicide. In the Netherlands and Belgium, where both euthanasia and physician-assisted suicide are legal, less than 5% of all deaths are by these measures, with 0.4 to 1.8% of all deaths as the result of euthanasia without the patient's consent.[10]

Counterintuitively, in all jurisdictions where it has been studied, pain is not the primary motivation for requesting euthanasia or physician-assisted suicide. In Oregon, loss of autonomy, dignity, and fear of being a burden are cited by patients as the predominant motives. In addition, psychological

A L G r a w a n y

distress, especially depression and hopelessness, seem to be more important than pain. Interviews with physicians and with patients with amyotrophic lateral sclerosis, cancer, or infection with human immunodeficiency virus show that pain is not associated with interest in euthanasia or physician-assisted suicide; instead, depression and hopelessness are the strongest predictors of interest. These findings raise important issues about the involvement of mental health experts in attempts to determine whether psychiatric treatment would change a patient's views.

Finally, data from the Netherlands and the United States suggest that there are problems in performing euthanasia and physician-assisted suicide. Dutch researchers reported that physician-assisted suicide causes complications in 7% of cases. Furthermore, the patients did not die, awoke from coma, or vomited up the medication in 15% of cases. Ultimately, in nearly 20% of physician-assisted suicide cases, the physician ended up injecting the patient with life-ending medication, converting physician-assisted suicide to euthanasia. These data raise serious questions about how to address complications of physician-assisted suicide when euthanasia is illegal or unacceptable.

PRACTICAL CONSIDERATIONS

There is widespread agreement that if euthanasia and physician-assisted suicide are used, they should be considered only after all reasonable attempts at physical and psychological palliation have failed.[11] A consensus—with slight differences—among American states and European countries has emerged on safeguards. These safeguards include: (1) the patient must be competent and must request euthanasia or physician-assisted suicide repeatedly and voluntarily; (2) in the Netherlands and other European countries, the patient must have unbearable pain or other suffering that cannot be relieved by optimal palliative interventions; by comparison, there is no requirement for unremitting suffering in the United States, but the patient must be terminally ill; (3) there should be a waiting period to ensure that the patient's desires are stable and sincere; and (4) the physician should obtain a second opinion from an independent physician. Although there have been some prosecutions in the United States, there have been no convictions—except for Dr. M. Jack Kevorkian in 1999—when physicians have participated in euthanasia and physician-assisted suicide.

ALLOCATION OF SCARCE MEDICAL RESOURCES

HISTORY

As with other medical ethical issues, decisions about the allocation of resources are not new. In 1792, Dominique Jean Larrey, Surgeon in Chief to Napoleon's Imperial Guard, devised a plan for sorting injured soldiers for emergency transport and medical treatment based on the severity of their wounds. During World War II, penicillin was finally produced in larger, but still quite limited quantities. Winston Churchill decided that priority for treatment should be given to soldiers who could be rapidly returned to active duty at the frontlines. Consequently, soldiers with sexually transmitted diseases were prioritized to receive penicillin over soldiers with severe wounds. Only a small fraction of the penicillin supply was allocated to civilians.

In the early 1960s, chronic renal dialysis was first developed in Seattle, Washington, but the number of machines was limited. To select which patients with chronic renal failure would receive dialysis, a committee used social value criteria, such as whether the person was employed, had dependents, or went to religious services. After publication of a *Life* magazine article about this so-called "God Committee," the process and criteria were roundly condemned. Eventually, Congress eliminated the allocation issue by funding all chronic renal dialysis through Medicare. Well before SARS-CoV-2 created the need to determine which patients should receive priority for ventilators and vaccines,[12] the most visible type of allocation decisions in the United States have been for solid organ transplantation, where demand for organs has regularly outstripped supply.

DEFINITION AND JUSTIFICATION

Rationing occurs in situations in which the supply of some resource (whether a medication, hospital bed, protective equipment, or operating room time) is insufficient to meet the needs of all patients who could medically benefit from the resource. Allocation or distribution is the process of determining which patients should receive priority in getting the medical resource.

Sometimes, an *absolute* scarcity of resources means that no matter how much money is spent, the supply will not be sufficient. Examples include the limited availability of organs for transplantation and, at least initially, vaccines and therapeutics for COVID. In some cases, the problem is a *relative* scarcity, where spending more money can eventually increase the supply of the resource but choices must be made in the meantime. An example was the supply of personal protective equipment or vaccines at points during the SARS-CoV-2 pandemic. Historically, many different criteria have been used for allocating scarce medical resources, including age, income, social usefulness (such as ability to fight in war), first come–first served, time on a waiting list, and medical urgency.

Fair allocation of scarce medical resources relies on four fundamental ethical values: (1) maximizing the benefits from the scarce resources, (2) treating people equally, (3) giving priority to the worst off, and (4) promoting and rewarding social value. Each of these can be interpreted and realized in at least two different ways (Table 2-4).

At least four important conclusions can be drawn about applying these ethical values and principles to allocating scarce medical resources. First, there is widespread agreement that an individual's wealth should not determine who receives scarce medical resources. Second, first come–first served should not be used because it almost invariably prioritizes people who live near medical facilities or who are wealthy and well-connected. Third, no single principle is sufficient to encapsulate all ethical values; a multi-principled allocation scheme will be required. Fourth, the combination of principles must be adopted to the particular medical situation. To save the most lives in the SARS-CoV-2 pandemic in the United States and Europe, for example, older individuals were prioritized for vaccines because they were the most likely to become severely ill and die if infected. For other illnesses, from which children are the most likely to die or transmit infections, younger people should be prioritized.

TABLE 2-4 ETHICAL VALUES FOR ALLOCATING SCARCE MEDICAL RESOURCES

VALUE	DEFINITION	PRINCIPLES OR DIFFERENT WAYS OF REALIZING THE VALUE	EXAMPLES
Maximizing benefit	Priority for resources should be given to individuals who have the best prospects of survival, as well as individuals who are likely to live for many more years if saved.	Save the most lives	Giving resources to individuals with the best chance of survival, disaster response
		Prognosis after treatment or save the most life years	Giving resources to the individuals predicted to survive the longest
Treating people equally	Nondiscrimination based irrelevant factors such as race or religion. Age can be a relevant factor if it influences prognosis or other value.	First come–first served	Time on a waiting list used in kidney transplantation
		Random selection or lottery	Selecting among otherwise equally qualified people (e.g., draft)
Giving priority to the worst off	Worst off can be defined as individuals who are sickest now or who have had the least of a critical good, such as the shortest life.	Sickest first	Severity score for liver transplantation
		Youngest first	Prioritized for influenza vaccine because they are integral to transmission
Promoting and rewarding social value	Giving resources to individuals who have helped or will help the most in the medical response.	Retrospective—reward individuals who contributed the most in the past	Prioritizes individuals who have donated organs or who have participated in prior medical research studies
		Prospective—reward individuals who are likely to contribute most in the future	Prioritize health care workers

EMPIRICAL DATA

Decisions about the allocation of medical resources are common, and different criteria are deployed in different circumstances. In the emergency department, for example, the fundamental allocation decision is which patients receive immediate attention. The primary allocation criterion used medical urgency rather than prognosis, so the sickest patient typically gets the most attention and preempts other patients. In SARS-CoV-2, priority for both personal protective equipment and vaccines was given to health care workers, who were socially useful because they could help save the lives of others, so as to follow the principle of maximizing benefit. After health care workers, the next priority for vaccines was older individuals, so as to maximize benefit by maximally reducing mortality.

The criteria for the transplantation of different organs emphasize different principles. For example, for liver transplantation (Chapter 140) the emphasis is on sickest patients, specifically those with the highest severity scores. This approach is controversial: it minimizes death on the waiting list but does not maximize lives saved with transplantation or the post-transplantation length of life saved. Conversely, in 2014, a new kidney transplant (Chapter 117) allocation scheme was introduced to emphasize the principle of prognosis or more life years by giving "higher quality" kidneys to patients with longer expected post-transplantation survival. This new approach retained the principle first come–first served but changed how "first-come" was determined. Rather than using time on the transplantation waiting list, the allocation scheme uses the time on dialysis to reduce racial and socioeconomic disparities, thereby emphasizing the principle of giving priority to the worst off. Although racial disparities have diminished, particularly for getting onto the waitlist, access disparities have persisted in part because poorer and minority patients may have barriers related to completing needed preoperative testing or receiving financial clearance.[13]

In the United States, reports on prioritizing limited SARS-CoV-2 vaccines (Chapter 337) generally invoked the principles of social usefulness and maximizing benefits by minimizing mortality. The resulting recommendations were to provide vaccines initially to health care workers and residents of long-term care facilities, with other groups prioritized by their risk of mortality (Table 2-5). Ultimately, however, the allocation was determined by individual states. For example, Florida extended the recommendations to include all persons ages 65 and older, as well as persons deemed by hospitals to be extremely vulnerable.

PRACTICAL CONSIDERATIONS

The process for implementing any allocation scheme typically has two stages. The first stage is to establish priority groups based upon the four ethical values. The second stage is to specify which priority group applies to each particular individual. For SARS-CoV-2, both stages were fulfilled. For organ transplantation, the national Organ Procurement and Transplantation Network establishes different criteria for determining priority groups, but then transplantation teams at each center determine which individual patients qualify to receive available organs based on the allocation criteria.

TABLE 2-5 ADVISORY COMMITTEE ON IMMUNIZATION POLICY'S INITIAL RECOMMENDATIONS FOR THE ALLOCATION OF COVID-19 VACCINES*

TIER OR PHASE	GROUPS RECOMMENDED	TOTAL PERSONS IN EACH GROUP (MILLIONS)
1a	Health care workers	21
	Residents of long-term care facilities	3
1b	Frontline essential workers (e.g., grocery store workers and police)	30
	Persons over age 75 years	19
1c	Persons ages 65-74 years	28
	Persons ages 16-64 years with high-risk medical conditions	81
	Essential workers not recommended for vaccination in Phase 1b (e.g., construction workers and bank tellers)	20
2	All persons over age 16 years not previously recommended	All others

*https://www.cdc.gov/mmwr/volumes/69/wr/pdfs/mm695152e2-H.pdf.

Each of these steps can be done less than ethically. The established priority groups may not adhere to the four key ethical values. For example, the decision by Florida's governor to open up initial allocation of SARS-CoV-2 vaccines for all people over age 65 years rather than for younger minority individuals with high-risk conditions was widely viewed as politically motivated. Another example is that wealthy patients often can pick organ transplant centers with shorter waiting lists or may be listed for organ transplantation at multiple centers. This ability to be listed multiple times favors the wealthy, who also can afford to be evaluated at multiple centers and fly to them when a suitable organ becomes available.

FINANCIAL CONFLICTS OF INTEREST

HISTORY

Worrying whether payment structures and fees compromise the integrity of medical decision making is not new. In 1899, a physician reported that more than 60% of surgeons in Chicago were willing to provide a 50% commission to physicians for referring cases. He subsequently argued that in some cases, this fee splitting led to unnecessary surgical procedures. A 1912 study by the American Medical Association confirmed that fee splitting was a common practice and it added to the list of physicians' financial conflicts of interest acts, which included selling patented medicines and patenting surgical instruments. In the 1990s, the ethics of pharmaceutical and biotech companies paying clinical researchers and physicians again raised the issue of financial conflicts of interest.

DEFINITION AND JUSTIFICATION

A conflict of interest occurs when a physician's secondary interests, such as making money, risks compromising or undermining a physician's primary interest, especially promoting a patient's well-being. Physicians not only have several primary interests (Table 2-6), they also have multiple secondary interests, such as earning income, raising a family, contributing to the profession, and pursuing avocational interests, such as hobbies. These secondary interests are not evil; typically, they are legitimate, even admirable. A conflict of interest occurs when one of these secondary interests could compromise pursuit of a primary interest, especially the patient's well-being.

Conflicts of interest are problematic because they can or appear to compromise the integrity of physicians' judgment, the patient's well-being, or the integrity of research. Conflicts of interest can induce a physician to do something—perform a procedure, fail to order a test, or distort data—that may not be in a patient's best interest. These conflicts can undermine the trust of both the patient and the public, not only in an individual physician but also in the medical profession at large.

Some people may believe in a distinction between actual and potential conflicts of interest, as well as claim that a conflict exists only when a physician's judgment is actually distorted or undermined. This distinction is wrong.[14] An actual conflict of interest occurs when a reasonable person could suspect that a physician's judgment could have been altered by the secondary interest. Appearances can be damaging, because it is difficult for patients and the public to determine what motives influence a physician's decision and it often is impossible to know whether judgment actually has been distorted. Financial conflicts of interest are of particular concern, not because they are worse than other types of conflicts, but because they are more pervasive, identifiable, and regulated compared with other conflicts. Since ancient times, the ethical norm has been clear: the physician's primary obligation is to the patient's well-being, and a physician's personal financial well-being comes second and should never compromise this duty.

EMPIRICAL DATA

Financial conflicts are common, and they are often underreported. The more imaging facilities and specialty referrals a practice has, the greater the utilization of medical services and the higher the health care spending—often without any benefit to the patients. In Florida, nearly 40% of physicians are owners of freestanding facilities to which they refer patients. In one study, 4 to 4.5

TABLE 2-6 PRIMARY INTERESTS OF PHYSICIANS

Promotion of the health and well-being of their patients
Advancement of biomedical knowledge through research
Education of future physicians and health care providers
Promotion of public health

times more imaging studies were ordered by self-referring physicians than by physicians who referred patients to radiologists. Similarly, urologists who had integrated radiation facilities into their practices increased their radiation use by 2.5 times compared with urologists who did not have such financial interests.

Similarly, multiple studies have shown that physicians' interaction with pharmaceutical representatives can lead to prescribing of new drugs, nonrational prescribing, and decreased use of generic drugs.[15] Industry funding for travel to continuing medical education symposia increases prescribing of the sponsor's drug. A study of 1400 FDA advisory committee members found that 13% had some financial interest in a drug company whose product was being reviewed by that committee; these members had a 63% chance of voting for its approval and an 84% chance of doing so if they sat on advisory boards for that company. A separate study found that 80% of U.S.-based hematologist-oncologists who use Twitter, often to tweet about pharmaceutical products, have at least one financial conflict of interest, with median payments of over $1000.

Regarding researcher conflicts of interest, the available data suggest that corporate funding does not appear to compromise the design and methodology of clinical research; in fact, commercially funded research may be methodologically more rigorous than government- or foundation-supported research. Conversely, data suggest that financial interests do distort researchers' interpretations and, most importantly, dissemination of research studies. Growing evidence suggests the suppression or selective publication of data unfavorable to corporate sponsors but the repeated publication of favorable results.

PRACTICAL CONSIDERATIONS

First, financial conflicts of interest are inherent in any profession in which the professional earns income from rendering a service. Second, conflicts come in many different forms, from legitimate payment for services rendered and ownership of medical laboratories and facilities, to drug company dinners, payment for attendance at pharmaceutical meetings, and consultation with companies.

Third, in considering how to manage conflicts, it is important to note that people are poor judges of their own potential conflicts. Individuals often cannot distinguish the various influences that guide their judgments, do not think of themselves as inherently bad, and do not imagine that payment shapes their judgments. Physicians tend to be defensive about charges of conflicts of interest. In addition, conflicts tend to act insidiously, subtly changing practice patterns so that they then become what appear to be justifiable norms.

Fourth, rules—whether laws, regulations, or professional standards—to regulate conflicts of interest are based on two considerations: (1) the likelihood that payment or other secondary interests would create a conflict, with greater financial interest tending to increase the risk of compromised judgment, and (2) the magnitude of the potential harm if judgment is compromised. Rules tend to be of three types: (1) disclosure of conflicts, (2) management of conflicts, and (3) outright prohibition. Federal law bans certain types of self-referral of physicians in the Medicare program. The American Medical Association and the Pharmaceutical Research and Manufacturers of America have established joint rules that permit physicians to accept gifts of minimal value but "refuse substantial gifts from drug companies, such as the costs of travel, lodging, or other personal expenses … for attending conferences or meetings." Additionally, the Physician Payment Sunshine Act, which was passed in 2010 as part of the Affordable Care Act and went into effect in August 2013, requires that drug and device manufacturers report all payments and transfers of value given to physicians to the Centers for Medicare and Medicaid Services so that such information can be published on a searchable public website.

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Finally, some conflicts can be avoided by a physician's own action. Physicians can refuse to engage in personal investments in medical facilities or to accept gifts from pharmaceutical companies at relatively little personal cost. In other circumstances, the conflicts may be institutionalized, and minimizing them can occur only by changing the way organizations structure reimbursement incentives. Capitation encourages physicians to limit medical services, and its potentially adverse effects are likely to be managed by institutional rules rather than by personal decisions.

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3 PALLIATIVE CARE

ROBERT M. ARNOLD AND JEAN S. KUTNER

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The burden associated with these illnesses and their treatments is high. Chronically ill patients report multiple physical and psychological symptoms that lower their quality of life. The economic pressures associated with medical care adversely affect patients' socioeconomic status and cause family stress, especially among caregivers who spend 20 or more hours a week helping their loved ones.

Palliative care, which was developed to decrease the burden associated with chronic illness, emphasizes patient- and family-centered care that optimizes quality of life by anticipating, preventing, and treating suffering. Palliative care throughout the continuum of illness addresses physical, intellectual, emotional, social, and spiritual needs while facilitating the patient's autonomy, access to information, and choice.

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times more imaging studies were ordered by self-referring physicians than by physicians who referred patients to radiologists. Similarly, urologists who had integrated radiation facilities into their practices increased their radiation use by 2.5 times compared with urologists who did not have such financial interests.

Similarly, multiple studies have shown that physicians' interaction with pharmaceutical representatives can lead to prescribing of new drugs, nonrational prescribing, and decreased use of generic drugs.[15] Industry funding for travel to continuing medical education symposia increases prescribing of the sponsor's drug. A study of 1400 FDA advisory committee members found that 13% had some financial interest in a drug company whose product was being reviewed by that committee; these members had a 63% chance of voting for its approval and an 84% chance of doing so if they sat on advisory boards for that company. A separate study found that 80% of U.S.-based hematologist-oncologists who use Twitter, often to tweet about pharmaceutical products, have at least one financial conflict of interest, with median payments of over $1000.

Regarding researcher conflicts of interest, the available data suggest that corporate funding does not appear to compromise the design and methodology of clinical research; in fact, commercially funded research may be methodologically more rigorous than government- or foundation-supported research. Conversely, data suggest that financial interests do distort researchers' interpretations and, most importantly, dissemination of research studies. Growing evidence suggests the suppression or selective publication of data unfavorable to corporate sponsors but the repeated publication of favorable results.

PRACTICAL CONSIDERATIONS

First, financial conflicts of interest are inherent in any profession in which the professional earns income from rendering a service. Second, conflicts come in many different forms, from legitimate payment for services rendered and ownership of medical laboratories and facilities, to drug company dinners, payment for attendance at pharmaceutical meetings, and consultation with companies.

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ABSTRACT

Palliative care, which was developed to decrease the burden associated with chronic illness, emphasizes patient- and family-centered care that optimizes quality of life by anticipating, preventing, and treating suffering. It is both a subspecialty and a key component of good medical care for seriously ill patients. Palliative care should be delivered throughout the course of a patient's illness—from diagnosis through death. The specialty involves a multidisciplinary group of clinicians who work with the patients' primary clinicians to provide an extra layer of support. When caring for patients with serious illness, good palliative care requires that the following questions be addressed: (1) is the patient's care consistent with his or her goals; (2) is the patient physically comfortable or psychologically suffering; and (3) is the family suffering.

KEYWORDS

palliative care
serious illness
end-of-life
supportive care
advance directives
living wills
quality of life

about care needs while focusing on peace and dignity throughout the course of illness, during the dying process, and after death.

Given that most seriously ill patients are not seen by a palliative care subspecialist, every clinician should have basic competency in palliative care. For example, all primary care clinicians should know the basic tenets of treating pain (Chapter 26) as well as how to discuss advance directives (Chapter 2) and give "bad" news. Specialties with a high prevalence of seriously ill patients, such as critical care, cardiology, pulmonology, neurology, nephrology, and oncology, should have more advanced skills.[2–5] Interventions to promote both specialty and primary palliative care are associated with improvements in the patient's burden of symptoms and reductions in the utilization of acute care services, although its effects on quality of life and on the caregiver are less consistent.[A1-A4]

Six points deserve special emphasis. First, palliative care can be delivered at any time during the course of an illness and is often provided concomitantly with disease-focused, life-prolonging therapy. For example, most elderly patients with chronic incurable illnesses, who might benefit from palliative care, are in the last 10 years of their lives but do not consider themselves to be dying. Moreover, prognostication is an inexact science (E-Fig. 3-1). If palliative care is to have an impact on patients' lives, it should be integrated into patients' treatment plans early in the illness. The strongest data for early integration of specialty palliative care is from patients early in the course of oncologic disease.[6,A5] Second, although the specialty of palliative care has grown exponentially over the past 25 years, most patients with serious illness will never see a palliative care specialist because of shortages in the palliative care workforce. Some of the shortages may be addressed by telehealth,[7] but data on palliative care delivered this way are inconclusive.[A6] All clinicians must integrate palliative care principles if the care of seriously ill patients is to be improved. Third, palliative care primarily focuses on the burden of illness rather than treating the disease itself. Because these burdens can be physical, psychological, spiritual, or social, good palliative care requires a transdisciplinary approach. Fourth, palliative care takes the family unit (however defined by the patient) as the central focus of care. Treatment plans thus must be developed for both the patient and the family. Given data on prolonged grief disorder, treatment should continue for the family after the patient's death. Fifth, palliative care recognizes that medical treatments do not uniformly reverse the progression of disease and that patients die. At some point in a patient's illness, the treatments may be associated with more risks and cause more burden than benefit. Palliative care recognizes this reality and starts with a discussion of the patient's goals and the development of an individualized treatment plan that is consistent with these goals. Finally, disparities in palliative care mirror the inequities in health care generally.[8] Black patients have poorer symptom management, fewer discussions of goals of care, and less access to hospice.[A7] In addition, Black physicians receive less palliative care training and rate their training in palliative care as less good than their general medical education.

Many people confuse palliative care with hospice—an understandable confusion because hospice epitomizes the palliative care philosophy. The two, however, are different. In the United States, hospice services and eligibility criteria are largely driven by the Medicare Hospice Benefit. Although exceptions exist, hospice in the United States provides palliative care, primarily at home, for patients who have a life expectancy of 6 months or less and who are willing to forgo life-prolonging treatments. However, the requirement that patients must have a life expectancy of 6 months or less limits hospice's availability, as does the requirement that patients relinquish potentially life-prolonging treatments. Moreover, because doctors often are unwilling to cease these treatments until very late in the disease course, so are most patients.

PALLIATIVE CARE DOMAINS

Palliative care is a philosophy of and approach to care that addresses physical, psychological, spiritual, existential, social, and ethical domains. When caring for patients with chronic life-limiting illness, good palliative care requires that the following questions be addressed.

IS THE PATIENT PHYSICALLY COMFORTABLE?

Across many chronic conditions, patients have a large number of inadequately treated physical symptoms (Table 3-1). The reasons are multifactorial and range from inadequate education of the clinician, to societal beliefs regarding the inevitability of suffering in chronic illness, to concerns regarding opioids, to the lack of evidence-based treatments in noncancer patients.

The first step to improve symptom management is a thorough assessment. Standardized instruments such as the Brief Pain Inventory (Fig. 3-1) measure both the patient's symptoms and the effect of those symptoms on the patient's life. Use of standardized instruments (such as the Edmonton Symptom Assessment Scale [E-Fig. 3-2]) ensures that clinicians will identify overlooked or underreported symptoms and, as a result, will enhance the satisfaction of both the patient and family.

The evidence for the treatment of end-stage symptoms continues to improve. For example, palliative care can improve quality of life in patients with end-stage heart failure,[A8] who often require such help.[9] The use of nonsteroidal anti-inflammatory agents and opioids can result in effective pain management in more than 75% of patients with cancer. Advances such as intrathecal pumps and neurolytic blocks are helpful in the remaining 25% (Chapter 26). Medical marijuana, while popular, has little impact on cancer pain.[A9] The use of oxygen is not helpful for refractory dyspnea except when hypoxia has been documented, whereas use of medications for depression often can be helpful in addressing refractory dyspnea (Chapter 362). Recent data also suggest that prophylactic subcutaneous scopolamine butylbromide decreases dying patients' death rattle.[A10]

IS THE PATIENT PSYCHOLOGICALLY SUFFERING?

Patients may be physically comfortable but still suffering. Psychological symptoms and syndromes such as depression, delirium, and anxiety are common in patients with life-limiting or chronic illnesses. It may be difficult to determine whether increased morbidity and mortality are caused by the physical effects of the illness or by the psychological effects of depression and anxiety on energy, appetite, or sleep. Screening questions focusing on mood (e.g., "Have you felt down, depressed, and hopeless most of the time for the past 2 weeks?") and anhedonia (e.g., "Have you found that little brings you pleasure or joy in the past 2 weeks?") have been shown to help in diagnosing depression in this population. Increasing data show that treatment of depression in chronic illness is possible and improves both morbidity and mortality.

For patients and families facing mortality, existential and spiritual concerns are common. Progressive illness often raises questions of love, legacy, loss, and meaning. A clinician's role is not to answer these questions or to provide reassurance, but rather to understand concerns of the patient and family, how they are coping, and what resources might help. Spirituality often is a source of comfort, and clinicians can ascertain a patient's beliefs using a brief instrument such as the FICA Spiritual Assessment Tool (Table 3-2). A single screening question such as "Are you at peace?" may identify patients who are in spiritual distress and facilitate referrals to chaplains.

IS THE FAMILY SUFFERING?

Families, defined broadly as those individuals who care most for the patient, are an important source of support for most patients. Families provide informal caregiving, often at the expense of their own physical, economic, and psychological health. Good palliative care requires an understanding of how the family is coping and a search for ways to provide family members with the social or clinical resources they need to improve their well-being. Comprehensive and individually targeted interventions can reduce the burden on caregivers, although the absolute benefits are relatively small.

Because patients who are receiving palliative care often die, the treating team must address bereavement and family suffering after death. Good communication and informational brochures about receiving care in an intensive care unit can decrease family members' adverse psychological outcomes after death.[A11] A letter of condolence or a follow-up phone call to the next of kin after a patient's death is respectful and offers the opportunity to clarify questions about the patient's care. Some family members suffer from complicated grief—a recently described syndrome associated with separation and traumatic distress, with symptoms persisting for more than 6 months. Primary care clinicians, who have ongoing relationships with the loved one, and hospices, which provide bereavement services for a year after the patient's death, have the opportunity to assess whether the grief symptoms persist or worsen.

IS THE PATIENT'S CARE CONSISTENT WITH THE PATIENT'S GOALS?

The *sine qua non* for palliative care is ensuring that the treatment plan is consistent with the patient's goals and values. Some patients prefer longevity over quality of life, but a large proportion of elderly, seriously ill patients are not focused on living as long as possible. Instead, they want to maintain a sense of control, relieve their symptoms, improve their quality of life, avoid being a burden on their families, and have a closer relationship with their loved ones.

Ensuring that treatment is consistent with a patient's goals requires good communication skills (Table 3-3). The approaches to giving bad news, discussing goals of care, and talking about forgoing life-sustaining treatment have similar structures.[10] First, the patient needs to understand the basic facts about the

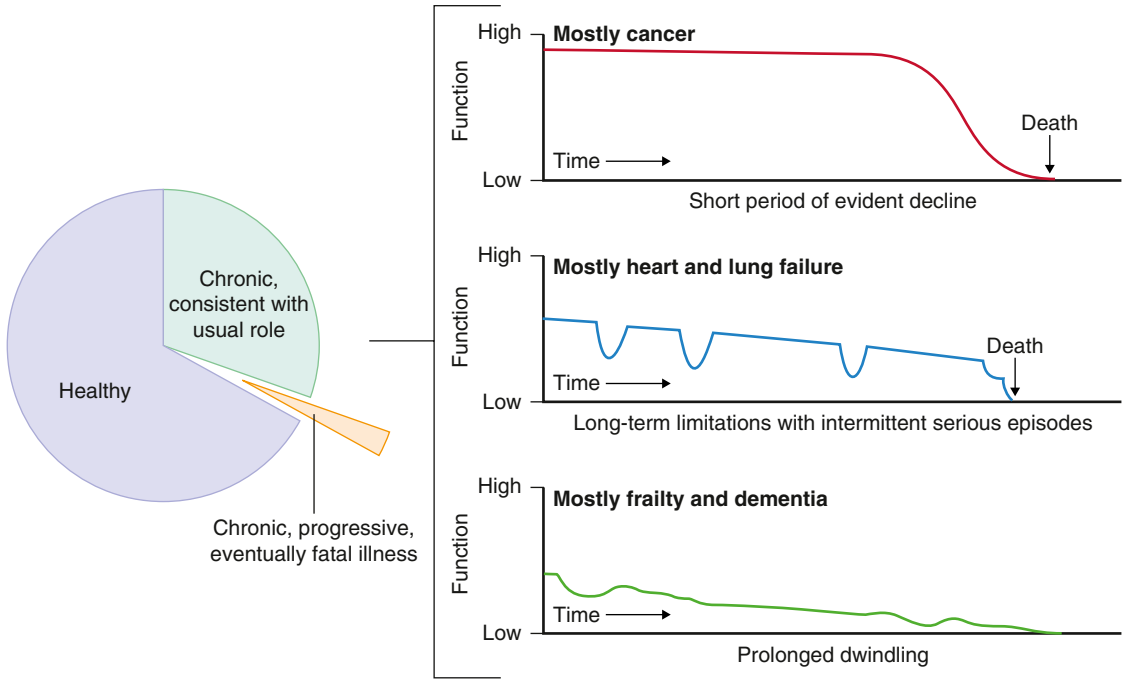

E-FIGURE 3-1. Different disease trajectories for different illnesses. (Permission obtained from RAND Corporation © Lynn J. Perspectives on care at the close of life. Serving patients who may die soon and their families: the role of hospice and other services. *JAMA*. 2001;285:925-932.)

Date: _____ Time: _____

Please circle the number that best describes your average symptom over the past 24 hours:

No Pain	0 1 2 3 4 5 6 7 8 9 10	Worst Pain
No Fatigue	0 1 2 3 4 5 6 7 8 9 10	Worst Fatigue
No Nausea	0 1 2 3 4 5 6 7 8 9 10	Worst Nausea
Not Depressed	0 1 2 3 4 5 6 7 8 9 10	Worst Depression
No Anxiety	0 1 2 3 4 5 6 7 8 9 10	Worst Anxiety
No Drowsiness	0 1 2 3 4 5 6 7 8 9 10	Worst Drowsiness
No Shortness of Breath	0 1 2 3 4 5 6 7 8 9 10	Worst Shortness of Breath
Best Appetite	0 1 2 3 4 5 6 7 8 9 10	Worst Possible
Best Feeling or Well Being	0 1 2 3 4 5 6 7 8 9 10	Worst Feeling of Well Being
Best Sleep	0 1 2 3 4 5 6 7 8 9 10	Worst Sleep

Completed by : ☐ Patient ☐ Family

Assessed by (Signature/Credentials/ID#/Date/Time) _____

Print/Stamp Name: _____

E-FIGURE 3-2. Edmonton Symptom Assessment System. (Hui D, Bruera E. The Edmonton Symptom Assessment System 25 years later: past, present, and future developments. *J Pain Symptom Manage*. 2017;53:630-643.)

TABLE 3-1 APPROACHES TO THE MANAGEMENT OF PHYSICAL AND PSYCHOLOGICAL SYMPTOMS

SYMPTOM	ASSESSMENT	TREATMENT
Pain	How severe is the symptom (as assessed with the use of validated instruments) and how does it interfere with the patient's life? What is the etiology of the pain? Is the pain assumed to be neuropathic or somatic? What has the patient used in the past (calculate previous days' equal analgesic dose)?	Prescribe medications to be administered on a standing or regular basis if pain is frequent. Consider alternative medicine, concomitant analgesics, and interventional treatments for pain to minimize the use of opiates. Concomitant analgesics (e.g., corticosteroids, anticonvulsants, tricyclic antidepressants, and bisphosphonates) should be used when applicable (particularly for neuropathic pain). For mild pain: use acetaminophen or a nonsteroidal anti-inflammatory agent. For moderate pain: titrate short-acting opioids (see Table 26-6). For severe pain: rapidly titrate short-acting opioids until pain is relieved or intolerable side effects develop; start long-acting opiates once pain is controlled. Rescue doses: prescribe immediate-release opioids—10% of the 24-hour total opiate every hour (orally) or every 30 minutes (parenterally) as needed.
Constipation	Is the patient taking opioids?	Prescribe laxatives for all patients on opiates, starting with a stimulant laxative. If ineffective, add drugs from alternative classes (e.g., stimulant, osmotic laxatives, and enemas). Prescribe methylnaltrexone if still constipated.
Shortness of breath	Ask the patient to assess the severity of the shortness of breath. Does the symptom have reversible causes?	Prescribe oxygen to treat hypoxia-induced dyspnea, but *not* if the patient is not hypoxic. Cardiopulmonary rehabilitation decreases dyspnea and improves exercise tolerance. Opioids may relieve breathlessness without measurable reductions in respiratory rate or oxygen saturation; effective doses are often lower than those used to treat pain. Aerosolized opioids do not work. Fans or cool air decrease dyspnea. Use reassurance, relaxation, distraction, cognitive behavioral therapy, and massage therapy.
Fatigue	Is the patient too tired for activities of daily living? Is the fatigue secondary to depression? Is a disease process causing the symptom or is it secondary to reversible causes?	Provide cognitive education about conserving energy use. Treat underlying conditions appropriately and as consistent with patient's goals and values. Psychostimulants may help in selected diseases for limited time periods.
Nausea	Which mechanism is causing the symptom (e.g., stimulation of the chemoreceptor trigger zone, gastric stimulation, delayed gastric emptying or "squashed stomach" syndrome, bowel obstruction, intracranial processes, or vestibular vertigo)? Is the patient constipated?	Prescribe an agent directed at the underlying cause (Chapter 118). If persistent, give antiemetic around the clock. Multiple agents directed at various receptors or mechanisms may be required.
Anorexia and cachexia	Is a disease process causing the symptom, or is it secondary to other symptoms (e.g., nausea and constipation) that can be treated? Is the patient troubled by the symptom or is the family worried about what not eating means?	A nutritionist may help find foods that are more appetizing (Chapter 13). Provide counseling about the prognostic implications of anorexia (Chapter 200).
Delirium	Is the cause reversible? Is the confusion acute, over hours to days? Does consciousness wax and wane? Is there a problem of attention? Does the patient have disorganized thinking? Does the patient have an altered level of consciousness—either agitated or drowsy?	Identify underlying causes and manage symptoms (Chapter 361). Recommend behavioral therapies, including avoidance of excess stimulation, frequent reorientation, and reassurance. Ensure presence of family caregivers and explain delirium to them. Although antipsychotics are often used, the data are meager.
Depression	Over the last 2 weeks, have you been bothered (0) not at all, (1) several days, (2) more than half the days, (3) every day by: • Little interest or pleasure in doing things • Feeling down, depressed, or hopeless	Add the points for each answer. For a score >2, further evaluation is recommended, with consideration of supportive psychotherapy, cognitive approaches, behavioral techniques, pharmacologic therapies (see Table 362-5), or a combination of these interventions. Prescribe psychostimulants for rapid treatment of symptoms (within days) or selective serotonin reuptake inhibitors, which may require 3 to 4 weeks to take effect; tricyclic antidepressants are relatively contraindicated because of their side effects.
Anxiety (applicable also for family members)	Over the last 2 weeks, have you been bothered (0) not at all, (1) several days, (2) more than half the days, (3) every day by: • Feeling nervous, anxious, or on edge • Not being able to stop or control worrying	Add the points for each answer. A score of >2 should lead to a more in-depth evaluation (see Chapter 362) and consideration of supportive counseling and benzodiazepines or selective serotonin reuptake inhibitors (Table 362-9).
Spiritual distress	Are you at peace?	Inquire about spiritual support. Offer chaplain support.

Modified from Morrison RS, Meier DE. Palliative care. *N Engl J Med*. 2004;350:2582-2590.

diagnosis, possible treatments, and prognosis. The communication skill that helps clinicians communicate information is *Ask-Tell-Ask*—exploring what the patient knows or wants to know, then explaining or answering questions, and then providing an opportunity for the patient to ask more. In the hospital, where discontinuity of care is common and misunderstandings frequent, it is important to determine what the patient knows before providing information so as to keep everyone well-coordinated. When giving serious news, knowing what the patient already knows allows the clinician to anticipate the patient's reaction. Finally, information must be titrated based on the patient's preferences. Although most patients want to hear everything about their disease, a minority do not. There is no foolproof way to ascertain what any patient wants to know other than by asking.

When giving patients information, it is important to give small pieces of information, not to use jargon, and to confirm that patients understand what they have been told.[A12] Clinicians should focus on the key message the patient should hear (the headline) rather than overwhelming the patient with

biomedical information. Giving information is like titrating medication dosing: one gives information, checks understanding, and then gives more information based on what the patient has heard.

After ensuring that the doctor and the patient have a shared understanding of the medical facts, clinicians should engage in an open-ended conversation about the patient's goals as the disease progresses. This strategy requires that the patient be asked about both hopes and fears. One might ask: "Given the medical situation, as you think about the future, what brings you joy and pleasure?" "If your time is limited, what are the things that are most important to achieve?" "What are your biggest fears or concerns?" "As you think about the future, what do you want to avoid or not have the doctors do?" The clinician can use an understanding of these goals to make recommendations about which treatments to provide and which treatments would not be helpful. As a result, palliative care provided early in the trajectory of illness can improve quality of life, mood, and even survival.

STUDY ID# _____ HOSPITAL ID# _____

DO NOT WRITE ABOVE THIS LINE

Brief Pain Inventory (Short Form)

Date: ___/___/___ Time: _____

Name: _____ _____ _____

Last First Middle Initial

1. Throughout our lives, most of us have had pain from time to time (such as minor headaches, sprains, and toothaches). Have you had pain other than these everyday kinds of pain today?

1. Yes 2. No

2. On the diagram, shade in the areas where you feel pain. Put an X on the area that hurts the most.

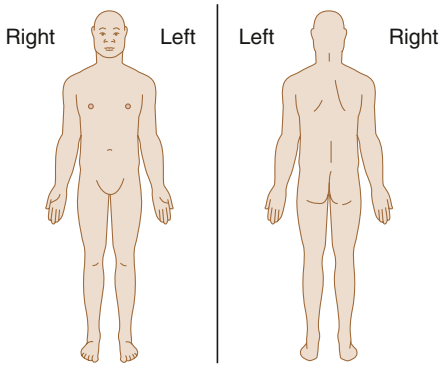

3. Please rate your pain by circling the one number that best describes your pain at its worst in the last 24 hours.

0	1	2	3	4	5	6	7	8	9	10
No pain										Pain as bad as you can imagine

4. Please rate your pain by circling the one number that best describes your pain at its least in the last 24 hours.

0	1	2	3	4	5	6	7	8	9	10
No pain										Pain as bad as you can imagine

5. Please rate your pain by circling the one number that best describes your pain on the average.

0	1	2	3	4	5	6	7	8	9	10
No pain										Pain as bad as you can imagine

6. Please rate your pain by circling the one number that tells how much pain you have right now.

0	1	2	3	4	5	6	7	8	9	10
No pain										Pain as bad as you can imagine

FIGURE 3-1. **Brief Pain Inventory (short form).** (Copyright 1991. Charles S. Cleeland, PhD, Pain Research Group. All rights reserved.)

ALGraway

7. What treatments or medications are you receiving for your pain?

8. In the last 24 hours, how much relief have pain treatments or medications provided? Please circle the one percentage that most shows how much relief you have received.

0%	10%	20%	30%	40%	50%	60%	70%	80%	90%	100%
No pain										Complete relief

9. Circle one number that describes how, during the past 24 hours, pain has interfered with your:

A. General Activity

0	1	2	3	4	5	6	7	8	9	10
Does not interfere										Completely interferes

B. Mood

0	1	2	3	4	5	6	7	8	9	10
Does not interfere										Completely interferes

C. Walking Ability

0	1	2	3	4	5	6	7	8	9	10
Does not interfere										Completely interferes

D. Normal Work (includes both work outside the home and housework)

0	1	2	3	4	5	6	7	8	9	10
Does not interfere										Completely interferes

E. Relations with Other People

0	1	2	3	4	5	6	7	8	9	10
Does not interfere										Completely interferes

F. Sleep

0	1	2	3	4	5	6	7	8	9	10
Does not interfere										Completely interferes

G. Enjoyment of Life

0	1	2	3	4	5	6	7	8	9	10
Does not interfere										Completely interferes

FIGURE 3-1, cont'd.

Clinicians often find that talking about prognosis is particularly difficult for two reasons: first, it is hard to foretell the future accurately; and second, they fear this information will "take away patients' hope." Thus, clinicians often avoid talking to patients about these issues unless specifically asked. Although some patients do not want to hear prognostic information, for many patients, this information helps them plan their lives. Patients who are told that their disease is generally terminal are more likely to spend a longer period of time enrolled in hospice and avoid aggressive treatment at the end of life, without adverse psychological consequences. Furthermore, their families usually have fewer post-death adverse psychological outcomes.

Given that one cannot guess how much information to provide, a clinician can start these conversations by asking, "Are you the kind of person who wants to hear about what might happen in the future with your illness or would you rather take it day by day?" If the patient requests the latter, the clinician can follow up by asking if there is someone else with whom he or she can talk about the prognosis. Second, before giving prognostic information, it is useful to inquire about the patient's concerns in order to provide information in the most useful manner. Finally, it is appropriate when discussing prognostic information to acknowledge uncertainty: "The course of this cancer can be quite unpredictable, and we don't have a crystal ball. I think you should be aware of the possibility that your health may deteriorate quickly, and you should plan accordingly. We probably are dealing with weeks to months, although some patients do better, and some do worse. Over time, the course may become clearer, and if you wish, I may be able to be a little more precise about what we are facing." A structured handout and conversational format, called Best Case/

TABLE 3-2 FICA SPIRITUAL ASSESSMENT TOOL

F—What is your **faith**/religion? Do you consider yourself a religious or spiritual person? What do you believe in that gives meaning/importance to life?

I—**Importance** and **influence** of faith. Is your faith/religion important to you? How do your beliefs influence how you take care of yourself? What are your most important hopes? What role do your beliefs play in regaining your health? What makes life most worth living for you? How might your disease affect this?

C—Are you part of a religious or spiritual **community**? Is this of support to you, and how? Is there a person you really love or is very important to you? How is your family handling your illness? What are their reactions/expectations?

A—How would you like me to **address** these issues in your health care? What might be left undone if you were to die today? Given the severity or chronicity of your illness, what is most important for you to achieve? Would you like me to talk to someone about religious/spiritual matters?

From Puchalski C, Romer A. Taking a spiritual history. *J Palliat Med*. 2000;3:129-137.

TABLE 3-3 CORE COMMUNICATION SKILLS

RECOMMENDED SKILL	EXAMPLE
A. IDENTIFYING CONCERNS AND RECOGNIZING CUES	
Elicit Concerns	
Open-ended questions	"Is there anything you wanted to talk to me about today?"
Active listening	Allowing patient to speak without interruption; allowing pauses to encourage patient to speak
Recognize Cues	
Informational concerns	Patient: "I'm not sure about the treatment options"
Emotional concerns	Patient: "I'm worried about that"
B. RESPONDING TO INFORMATIONAL CONCERNS	
"Ask-tell-ask"	Topic: communicating information about cancer stage
Ask	"Have any of the other doctors talked about what stage this cancer is?"
Tell	"That's right, this is a stage IV cancer, which is also called metastatic cancer…"
Ask	"Do you have questions about the staging?"
C. RESPONDING TO EMOTIONAL CONCERNS	
Nonverbal Empathy: S-O-L-E-R	
S	Face the patient **S**quarely
O	Adopt an **O**pen body posture
L	**L**ean toward the patient
E	Use **E**ye contact
R	Maintain a **R**elaxed body posture
Verbal Empathy: N-U-R-S-E	
N	**N**ame the emotion: "You seem worried"
U	**U**nderstand the emotion: "I see why you are concerned about this"
R	**R**espect the emotion: "You have shown a lot of strength"
S	**S**upport the patient: "I want you to know that I will still be your doctor whether you have chemotherapy or not"
E	**E**xplore the emotion: "Tell me more about what is worrying you"
D. DISCUSSING GOALS OF CARE	
R	**R**eframe that the status quo is not working: "I worry that more treatment will hurt you more than help"
E	**E**xpect emotion: "I can see this is not what you wanted to hear"
M	**M**ap the patient values: "Have you ever filled out a living will?" "Given the medical situation, what brings you joy and meaning?" "As you look at the future, what do you want to avoid?"
A	**A**lign with the patient values: "What I am hearing you say is…."
P	**P**ropose a plan

Adapted from Back AL, Arnold RM, Tulsky JA. *Discussing Prognosis*. Alexandria, VA: American Society of Clinical Oncology; 2008.

Worst Case, has been extensively used in surgery and nephrology,[11] both to discuss prognosis and as a way to discuss treatment alternatives (E-Fig. 3-3).

The clinician must discuss these topics in an empathic way. Palliative care conversations are as much about emotions as facts. Talking about disease progression or death may elicit negative emotions such as anxiety, sadness, or frustration. These emotions decrease a patient's quality of life and interfere with the ability to hear factual information. Empathic responses strengthen the patient-physician relationship, increase the patient's satisfaction, and make the patient more likely to disclose other concerns. The first step is recognizing when the patient is expressing emotions. Once the clinician recognizes the emotion being expressed, he or she can respond empathically.

It is also important for clinicians to recognize their own emotional reactions to these conversations. The physician's emotional reactions color impressions of the patient's prognosis, thereby making it hard to listen to the patient, and may influence the physician to hedge bad news. The clinician should become aware of her or his own emotional reactions to ensure that the conversation focuses on the patient rather than the health care provider's needs.

In addition to good communication skills, palliative care requires a basic knowledge of medical ethics and the law. For example, patients have the moral and legal right to refuse any treatment, even if refusal results in their death. There is no legal difference between withholding and withdrawing life-sustaining treatment. Differences in state laws regarding physician-assisted dying (Chapter 2), as well as use of agents such as medical marijuana or psychedelics, require clinicians to stay current regarding local legislation. When confronted with areas of ambiguity, the clinician should know how to obtain either a palliative care or ethics consultation.

During the past 50 years, a societal push has encouraged patients to designate health care proxies and to create advance care planning documents, typified by the use of living wills.[12] These documents are meant to protect patients against unwanted treatments and to ensure that as they are dying, their wishes are followed. Unfortunately, there are few empirical data showing that these documents actually change practice. Still, discussions of the documents with health professionals and family members generally provoke important conversations about end-of-life care decisions and may help families confronted with difficult situations know they are respecting their loved one's wishes.[13]

IS THE PATIENT GOING TO DIE IN THE LOCATION OF CHOICE?

Most patients say that they want to die at home. Unfortunately, most patients die in institutions—either hospitals or nursing homes. Burdensome transitions decrease quality in end-of-life care. Good palliative care requires establishing a regular system of communication to minimize transitional errors. A social worker who knows about community resources is important in the development of a dispositional plan that respects the patient's goals.

Hospice programs are an important way to allow patients to die at home. In the United States, *hospice* refers to a specific, government-regulated form of end-of-life care, available under Medicare since 1982 but subsequently adopted by Medicaid and many other third-party insurers. Hospice care typically is provided at home, a nursing home, or specialized acute care unit. Care is provided by an interdisciplinary team, which usually includes a physician, advanced practice provider, nurse, social worker, chaplain, volunteers, bereavement coordinator, and home health aides, all of whom collaborate with the primary care clinician, patient, and family. Bereavement services are offered to the family for a year after the death.

Hospices are paid on a per diem rate and are required to cover all the costs related to the patient's life-limiting illness. Because of this and the fact that the focus of hospice is on comfort rather than life prolongation, many hospices will not cover expensive treatments such as inotropic agents in heart failure or chemotherapy in cancer, even if they have a palliative effect. Not surprisingly, many hospices are experimenting with different service models that do not require patients to forgo possibly life-prolonging treatments, in an attempt to enroll patients earlier in the course of their illness and increase access to their services. The Veterans Administration and some insurance plans cover hospice services concurrently with disease-focused therapies.

Hospice care for nursing home residents is associated with less aggressive care near death but an overall increase in Medicare expenditures. By comparison, interdisciplinary palliative care for hospitalized adults with serious illness can reduce costs.[14]

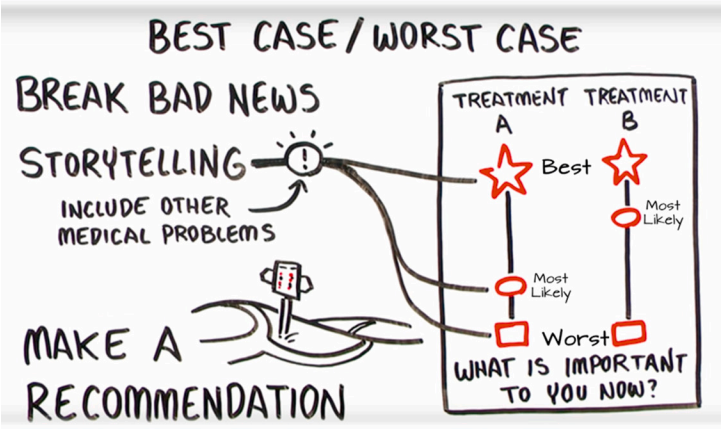

E-FIGURE 3-3. Best case/worst case communication framework. (Courtesy Gretchen Schwarze, MD.)

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4 DISPARITIES IN HEALTH AND HEALTH CARE

JOHN Z. AYANIAN

Disparities in health care and health are evident in all countries around the world. Health disparities often reflect a country's specific history, such as the legacy of conquest and colonization for American Indians and of slavery, segregation, and structural racism for Black Americans. Socioeconomic disparities in health related to poverty or lack of education occur globally and can be reduced by better educational and economic opportunities and by effective health care systems and social services.

Most efforts to understand and reduce health disparities have focused on race, ethnicity, and socioeconomic status and have sought to disentangle the relative impact of health care, health behaviors, and biologic, social, and environmental factors as contributors to these disparities. More recently, these efforts have expanded to assess a wider range of health disparities, including those faced by sexual minorities, people with disabilities, and people in disadvantaged urban or rural areas.

DEFINITIONS OF HEALTH DISPARITY AND HEALTH EQUITY

The U.S. Department of Health and Human Services defines a health disparity as a "health difference that is closely linked with economic, social, or environmental disadvantage." Conversely, health equity is defined as the "attainment of the highest level of health for all people."[1] These definitions build on U.S. National Academy of Medicine reports in which equitable health care was defined as "care that does not vary in quality due to personal characteristics, such as gender, ethnicity, geographic location, or socioeconomic status" and which identified racial and ethnic disparities in health care as an important contributor to disparities in health outcomes. Fragmented systems of care and structural racism, as well as bias and discrimination on the part of health professionals, can contribute to differential receipt of health care services, thereby leading to health disparities. However, not all differences in health care represent unacceptable disparities related to discrimination, in part because some differences in care may be related to clinical appropriateness or patients' preferences.

DEMOGRAPHIC CHANGES IN THE U.S. POPULATION

The racial and ethnic composition of the U.S. population has changed substantially in recent decades. As the population has grown from 193 million in 1965 to 332 million in 2022, almost half of this growth related to nearly 60 million new immigrants. During this time period, the non-Hispanic White proportion of the U.S. population dropped from 84 to 60% and the Black proportion rose from 11 to 13%. In contrast, the Hispanic proportion grew substantially from 4 to 18% and the Asian or Pacific Islander proportion increased from 1 to 6%. These trends are projected to continue through 2065, when the corresponding proportions of the U.S. population are projected to be 46% non-Hispanic White, 13% Black, 24% Hispanic, and 14% Asian or Pacific Islander if current immigration patterns persist.

RACIAL AND ETHNIC DISPARITIES IN HEALTH OUTCOMES

Substantial differences in life expectancy between Black and White Americans have narrowed since 1975 as life expectancy has risen.[2] Notably, as of 2018, life expectancy was about 3 years longer for Hispanic individuals relative to White individuals. In contrast, life expectancy in 2018 was 4 years shorter for Black individuals, relative to White individuals (Fig. 4-1). Overall, the all-cause mortality rate is about 25% higher in Black Americans. In 2020, coronavirus disease 2019 (COVID-19; Chapter 336) was the third leading cause of death in the United States. COVID-19 death rates have been disproportionately higher in Black and Hispanic populations, predominately because of higher infection rates rather than higher case-fatality rates.[3] As a result, during the COVID-19 pandemic in 2020, life expectancy declined from 2018 by 3.88 years for Hispanic Americans and 3.25 years for Black Americans, compared with 1.36 years for White Americans.[4] These disparities underscore the disproportionate effect that COVID-19 has had on Hispanic and Black adults.

Heart disease and cancer are the two leading causes of death for all five racial and ethnic groups officially designated by the U.S. federal government, but age-adjusted death rates for specific causes vary substantially by race and ethnicity (Table 4-1). Black Americans have the highest age-adjusted death rates, overall and due specifically to heart disease[5] and to cancer, followed by non-Hispanic White Americans. Black Americans also have the highest

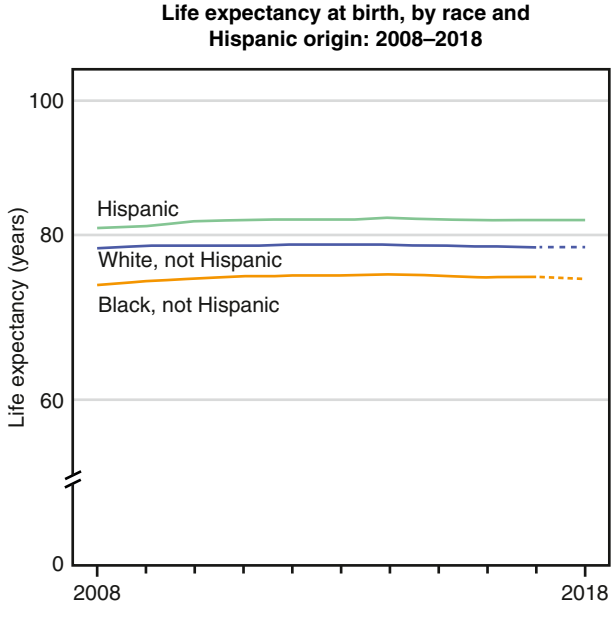

FIGURE 4-1. Life expectancy at birth. Note: Life expectancy data by Hispanic origin were available starting in 2006 and were corrected to address racial and ethnic misclassification. (Source: NCHS, *Health United States, 2019*, Figure 1 from the National Vital Statistics System [NVSS].)

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The racial and ethnic composition of the U.S. population has changed substantially in recent decades. As the population has grown from 193 million in 1965 to 332 million in 2022, almost half of this growth related to nearly 60 million new immigrants. During this time period, the non-Hispanic White proportion of the U.S. population dropped from 84 to 60% and the Black proportion rose from 11 to 13%. In contrast, the Hispanic proportion grew substantially from 4 to 18% and the Asian or Pacific Islander proportion increased from 1 to 6%. These trends are projected to continue through 2065, when the corresponding proportions of the U.S. population are projected to be 46% non-Hispanic White, 13% Black, 24% Hispanic, and 14% Asian or Pacific Islander if current immigration patterns persist.

RACIAL AND ETHNIC DISPARITIES IN HEALTH OUTCOMES

Substantial differences in life expectancy between Black and White Americans have narrowed since 1975 as life expectancy has risen.[2] Notably, as of 2018, life expectancy was about 3 years longer for Hispanic individuals relative to White individuals. In contrast, life expectancy in 2018 was 4 years shorter for Black individuals, relative to White individuals (Fig. 4-1). Overall, the all-cause mortality rate is about 25% higher in Black Americans. In 2020, coronavirus disease 2019 (COVID-19; Chapter 336) was the third leading cause of death in the United States. COVID-19 death rates have been disproportionately higher in Black and Hispanic populations, predominately because of higher infection rates rather than higher case-fatality rates.[3] As a result, during the COVID-19 pandemic in 2020, life expectancy declined from 2018 by 3.88 years for Hispanic Americans and 3.25 years for Black Americans, compared with 1.36 years for White Americans.[4] These disparities underscore the disproportionate effect that COVID-19 has had on Hispanic and Black adults.

Heart disease and cancer are the two leading causes of death for all five racial and ethnic groups officially designated by the U.S. federal government, but age-adjusted death rates for specific causes vary substantially by race and ethnicity (Table 4-1). Black Americans have the highest age-adjusted death rates, overall and due specifically to heart disease[5] and to cancer, followed by non-Hispanic White Americans. Black Americans also have the highest

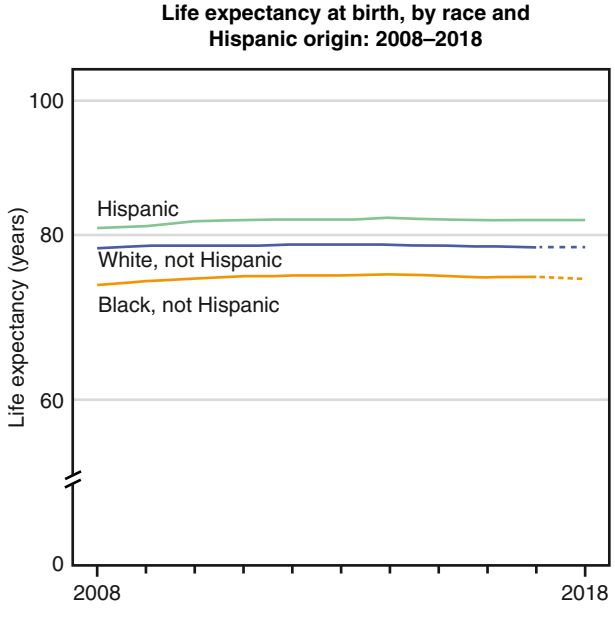

FIGURE 4-1. Life expectancy at birth. Note: Life expectancy data by Hispanic origin were available starting in 2006 and were corrected to address racial and ethnic misclassification. (Source: NCHS, *Health United States, 2019*, Figure 1 from the National Vital Statistics System [NVSS].)

ABSTRACT

Life expectancy in the United States varies substantially by race, ethnicity, and socioeconomic status. Relative to other racial and ethnic groups, Black Americans have the highest death rates overall and due to heart disease and cancer—the two most common causes of death in the United States. American adults with low incomes have substantially shorter life expectancy than more affluent adults, and the magnitude of this disparity differs widely among U.S. geographic areas. These differences arise from differences in health risk factors such as smoking and hypertension, as well as disparities in insurance coverage and access to care. The increasing diversity of the U.S. population has created new challenges and opportunities for health care providers and organizations to serve patients from diverse backgrounds by addressing interpersonal bias and discrimination, as well as the fragmented systems of care that lead to health care disparities. Trained interpreters improve care for patients with limited English proficiency, and coordinated care especially benefits disadvantaged patients by reducing fragmentation. Health care organizations should implement reporting systems to monitor disparities in the quality and outcomes of care, set measurable goals for reducing disparities, and encourage programs to meet these goals.

KEYWORDS

health disparities
health care disparities
race
ethnicity
socioeconomic factors
health outcomes
insurance coverage
access to care
quality of care

TABLE 4-1 AGE-ADJUSTED DEATH RATES FOR 10 LEADING CAUSES OF DEATH BY RACE/ETHNICITY IN THE UNITED STATES, 2018*

	ALL PERSONS	WHITE, NON-HISPANIC	BLACK OR AFRICAN AMERICAN	HISPANIC OR LATINO	ASIAN OR PACIFIC ISLANDER	AMERICAN INDIAN OR ALASKA NATIVE
All causes	723.6	745.7	852.9	524.1	390.6	571.8
Heart disease	163.6	167.5	203.7	112.3	85.0	110.8
Cancer	149.1	154.4	168.7	107.4	92.6	97.2
Chronic lung disease	39.7	45.0	29.6	17.0	11.6	28.3
Cerebrovascular disease	37.1	35.9	50.8	32.0	29.4	24.2
Alzheimer disease	30.5	32.2	26.6	25.5	15.8	15.3
Diabetes mellitus	21.4	18.8	37.6	24.6	16.4	31.0
Poisoning	19.3	23.6	19.0	11.1	3.3	19.6
Influenza and pneumonia	14.9	15.0	15.8	11.7	12.8	13.7
Suicide	14.2	18.0	7.0	7.4	6.9	13.7
Kidney disease	12.9	11.6	24.8	11.6	8.3	11.4

*Per 100,000 population, from *Health, United States, 2019*. Hyattsville, MD: National Center for Health Statistics; 2020. https://www.cdc.gov/nchs/data/hus/2019/005-508.pdf.

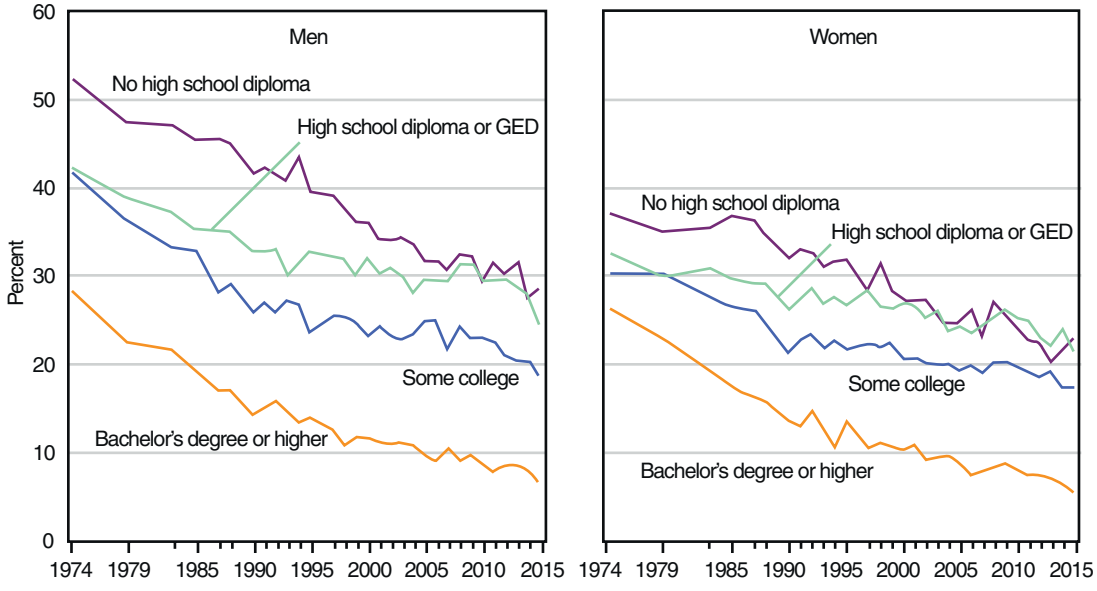

FIGURE 4-2. **Current cigarette smoking: adults aged 25+. Note: Smoked 100 cigarettes in their lifetime and now smoke every day or some days. (Source: NCHS, *Health, United States, 2016*, Figure 10 and Table 48. Data from the National Health Interview Survey [NHIS].)**

death rates from cerebrovascular disease, diabetes mellitus, and kidney disease, but lower-than-average death rates from chronic lung disease, poisoning, and suicide. Non-Hispanic White Americans, in contrast, have higher-than-average death rates from these latter three causes.

Hispanic Americans have lower-than-average death rates from all causes except diabetes mellitus (see Table 4-1). American Indians have lower-than-average death rates from most causes except diabetes mellitus and poisoning, but they also have markedly elevated death rates from chronic liver disease (27.7 deaths per 100,000 vs. 11.1 among all persons). Asian and Pacific Islander Americans together have lower-than-average death rates from each of the 10 leading causes of death, including markedly lower rates for heart disease, cancer, chronic lung disease, Alzheimer disease, poisoning, and suicide.

Major health risk factors that contribute to morbidity and mortality among adults vary substantially by race, ethnicity, and level of education.[6] Black adults have the highest age-adjusted prevalence of hypertension (43%; Chapter 64), which is a major contributor to their high rates of heart disease, cerebrovascular disease, and kidney disease, whereas the prevalence of hypertension is substantially lower among non-Hispanic White (29%), Hispanic (28%), and Asian (27%) adults. In contrast, the prevalence of diabetes mellitus is substantially higher among Black (18%), Mexican American (18%), and Asian (16%) adults than among non-Hispanic White adults (10%).[7]

Smoking rates (Chapter 363) vary widely in the United States by race/ethnicity and sex. Rates are highest among non-Hispanic White men (21%), Black men (22%), and American Indian men (28%) and women (24%). Smoking rates are intermediate among non-Hispanic White women (19%), Black women (14%), Hispanic men (16%), and Asian men (15%), and they are lowest among Hispanic women (7%) and Asian women (5%).[8]

SOCIOECONOMIC DISPARITIES IN HEALTH OUTCOMES

Socioeconomic gradients in morbidity and mortality, which are a major component of health disparities, have widened in the United States in recent years. Adults with higher educational levels and incomes have experienced substantial gains in life expectancy related to their lower smoking rates and better control of hypertension, hyperlipidemia, and other chronic health conditions and risk factors. By comparison, adults with low incomes experienced minimal gains overall prior to COVID-19.[9] For example, socioeconomic status is an independent correlate of mortality after a myocardial infarction.[10] Among middle-aged non-Hispanic White adults without postsecondary education, life expectancy has actually decreased since 1999 as a result of rising death rates from alcohol-related liver disease, drug overdoses, and suicide, and overall U.S. life expectancy has decreased since 2014.[11]

U.S. smoking rates have declined substantially since 1974, with the steepest drop among college graduates (Fig. 4-2). Higher smoking rates among less educated adults remain a major contributor to socioeconomic disparities in morbidity and mortality. The temporal improvement in smoking rates overall

has been offset by marked increases in age-adjusted death rates due to drug overdoses—particularly among non-Hispanic White adults, who have had a three-fold increase in this death rate from 1999 to 2015 primarily due to opioid overdoses (Fig. 4-3).[12]

The magnitude of socioeconomic disparities in mortality vary widely by geographic region within the United States. When considering life expectancy at age 40, for example, adults with incomes in the lowest quartile can expect to survive to age 81 years in New York City and several California cities, but only to age 77 years in some cities in Ohio, Indiana, and Michigan. These disparities in life expectancy are primarily related to regional differences in the prevalence of behavioral and metabolic risk factors, including smoking, limited physical activity, obesity, hypertension, and diabetes mellitus. Among high-income counties, cancer has become the leading cause of death, whereas heart disease remains the leading cause in poorer counties.

INSURANCE COVERAGE AND ACCESS TO CARE

Health insurance coverage is an important contributor to racial, ethnic, and socioeconomic disparities in health care and health outcomes, especially for adults who are under age 65 years and do not have near-universal insurance coverage through Medicare, as do older adults.[13] Since the Affordable Care Act was enacted in 2010, 38 states have expanded Medicaid to nonelderly adults with annual incomes below 138% of the federal poverty level (<$17,775 for a single adult in 2021). In all states, adults with incomes of 100 to 400% of the federal poverty level (about $12,900 to $51,500 in 2021) have become eligible for subsidized private insurance.

With this expanded coverage, rates of uninsurance have declined substantially for poor and near-poor adults in all racial and ethnic groups since 2010 (Fig. 4-4), although they still remain substantially higher for Hispanic and Black adults (Fig. 4-5).

Health insurance is a primary determinant of access to care because it reduces financial barriers to preventive services such as smoking cessation and cancer screening and to effective care for chronic health conditions such as hypertension, diabetes, and heart disease. Uninsured adults are three to five times more likely to delay or forgo needed care or prescription medications because of cost than are adults with private insurance or Medicaid (Fig. 4-6). Gaining insurance coverage is associated with improved access to care and better health outcomes, particularly for middle-aged adults with low incomes and chronic health conditions such as hypertension and diabetes mellitus. Life expectancy is also correlated with the local availability of physicians, especially primary care doctors, but also to a lesser degree specialists as well.[14]

QUALITY OF CARE

An extensive body of research has documented substantial racial and ethnic disparities in the quality of health care provided to patients with a wide range of major conditions, including heart disease, hypertension, diabetes mellitus, kidney disease, breast cancer, and colorectal cancer. Relative to non-Hispanic

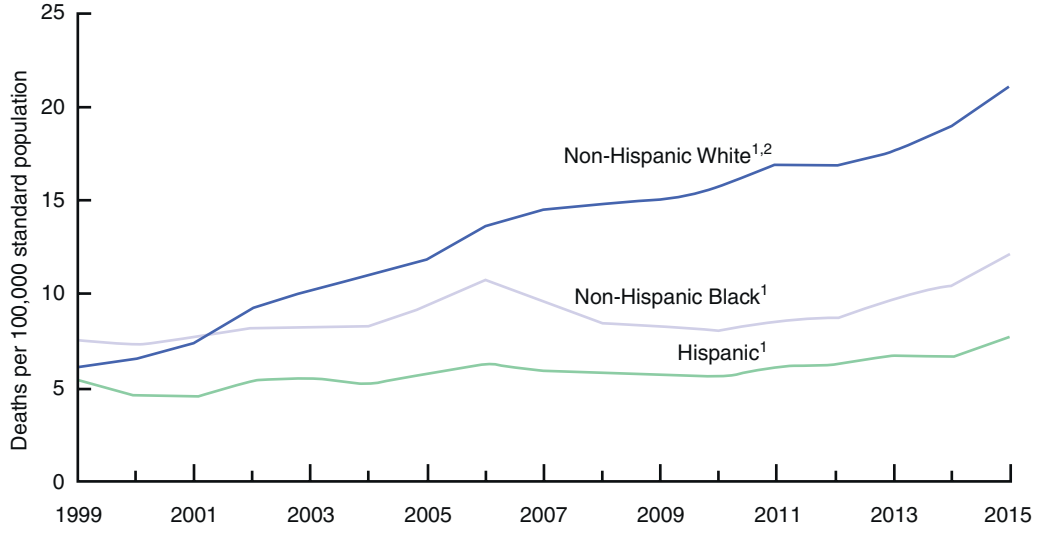

FIGURE 4-3. Age-adjusted drug overdose death rates by race and ethnicity: United States, 1999-2015. [1]Significant increasing trend, $p < 0.005$. [2]Rate for non-Hispanic White persons was significantly higher than for non-Hispanic Black and Hispanic persons, $p < 0.001$. Notes: Deaths are classified using the *International Classification of Diseases, Tenth Revision*. Drug overdose deaths are identified using underlying cause-of-death codes X40-X44, X60-X64, X85, and Y10-Y14. Deaths for Hispanic persons may be underreported by about 5%. Access data table for Figure 3 at: https://www.cdc.gov/nchs/data/databriefs/db273_table.pdf#3. (Source: Hedegaard H, Warner M, Miniño AM. *Drug overdose deaths in the United States, 1999–2015*. NCHS data brief, no 273. Hyattsville, MD: National Center for Health Statistics. 2017.)

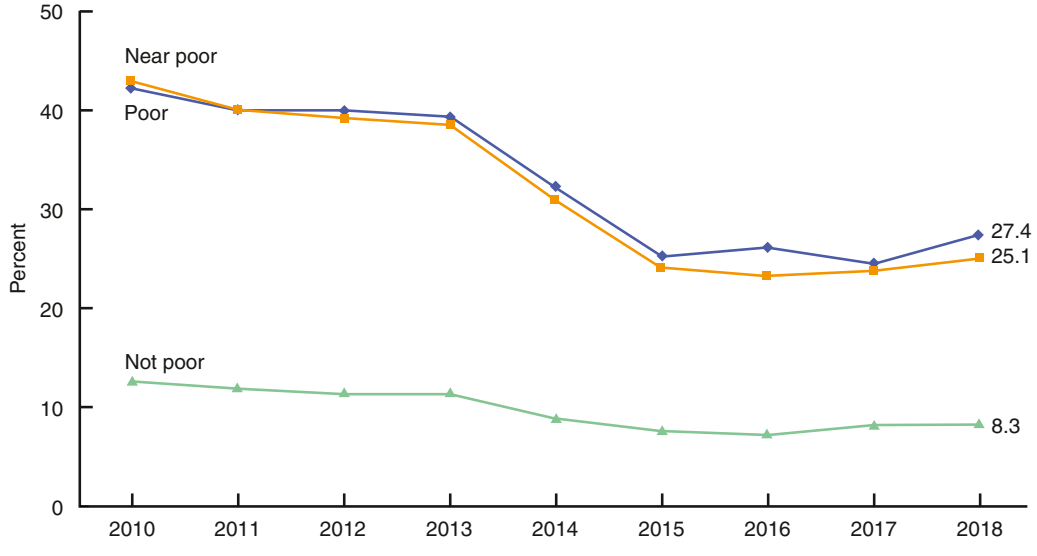

FIGURE 4-4. Percentage of adults aged 18 to 64 who were uninsured at the time of interview, by poverty status: United States, 2010-2018. Note: Data are based on household interviews of a sample of the civilian noninstitutionalized population. (Source: NCHS, National Health Interview Survey, 2010-2018, Family Core Component.)

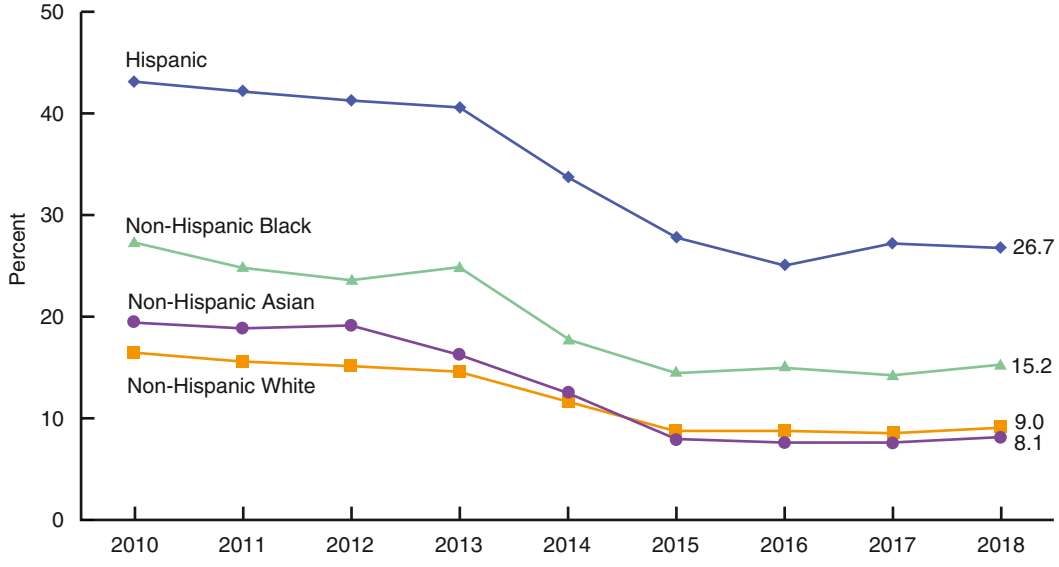

FIGURE 4-5. **Percentage of adults aged 18 to 64 who were uninsured at the time of interview, by race and ethnicity: United States, 2010-2018.** Note: Data are based on household interviews of a sample of the civilian noninstitutionalized population. (Source: NCHS, National Health Interview Survey, 2010-2018, Family Core Component.)

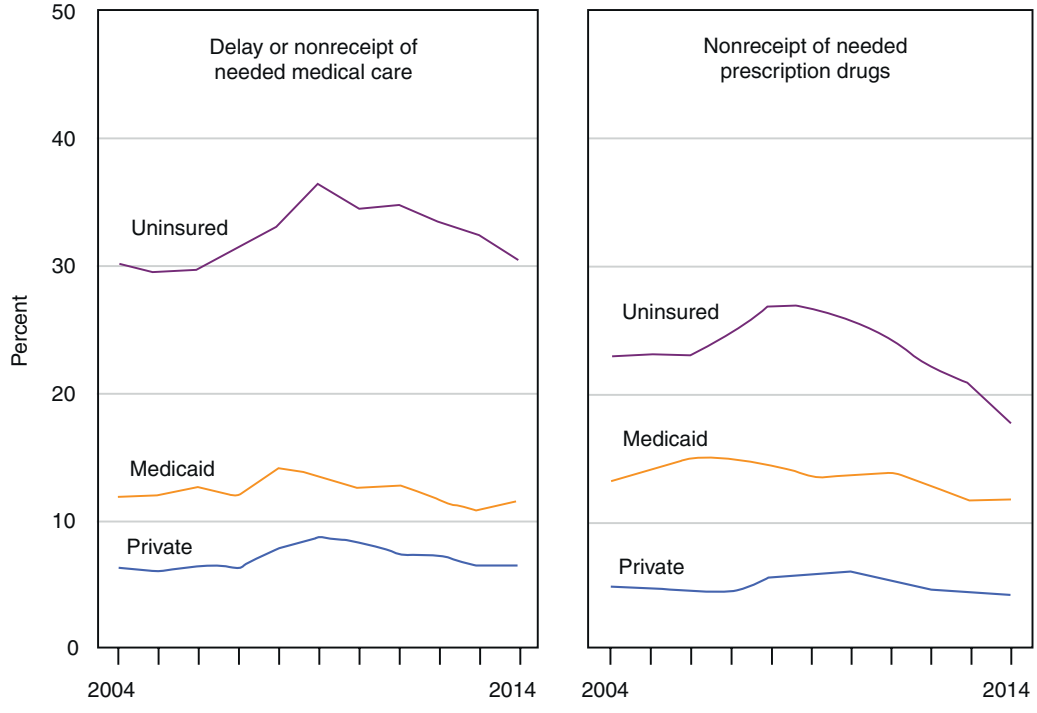

FIGURE 4-6. **Difficulty accessing care: Adults aged 18 to 64.** (Source: CDC/NCHS, Health, United States, 2015, Figure 12 and Table 63. Data from the National Health Interview Survey [NHIS].)

White adults, Black and Hispanic adults are much less likely to have good control of their hypertension or diabetes mellitus. These disparities are narrowed among Medicare enrollees nationally, and they have been eliminated in Medicare health maintenance organizations in the western United States. Over time, such improvements in the control of hypertension and diabetes mellitus may further reduce disparities in cardiovascular mortality for Black Americans relative to other racial and ethnic groups.

Similar improvements have been noted in the quality of hospital care nationally for minority patients with acute myocardial infarction, heart failure, and pneumonia, for whom the quality of hospital care is now clinically equivalent by race and ethnicity. Most notably, substantial disparities in timely percutaneous coronary interventions (Chapter 57) and in rates of influenza and pneumococcal vaccination (Chapter 15) have been eliminated for Black and Hispanic patients relative to non-Hispanic White patients.

CLINICAL APPROACHES TO REDUCE DISPARITIES

The increasing diversity of the U.S. population has created new challenges and opportunities for health care professionals and organizations to meet the needs of patients from diverse backgrounds, particularly immigrants. The federal Office of Minority Health has produced national standards for delivering culturally and linguistically appropriate health care, including the use of trained interpreters for patients with limited English proficiency. The principal standard is that health care providers should ensure quality care and services that are effective, equitable, understandable, respectful, and responsive to diverse cultural health beliefs and practices, preferred languages, health literacy, and other communication issues. Physicians and other caregivers who have undergone educational programs in cultural competencies may provide better care to diverse populations. However, this training has not clearly improved

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patients' outcomes, such as reducing disparities in control of glycemia, blood pressure, or cholesterol for Black adults with diabetes mellitus.

Disparities in health care often arise from fragmented systems of care, particularly for conditions that require complex services, such as cancer, cardiovascular disease, end-stage renal disease, and organ transplantation. When care requires multiple specialists or sites of care, disparities also can be reduced by emphasizing patient-centered approaches that provide better coordinated care with enhanced support for patients from disadvantaged backgrounds, such as those who are uninsured or have less education or limited English proficiency. This support may include multidisciplinary team-based care and enhanced outreach to patients and their families via care coordinators, patient navigators, and community health workers.[15]

It is also essential for clinical leaders in health care organizations to implement reporting systems (e.g., through enhanced electronic health records) to identify and monitor disparities related to race, ethnicity, language, and socioeconomic factors. These systems can be used to set measurable goals for reducing disparities in the quality and outcomes of care, motivate quality improvement programs to address clinically important disparities, and assess progress toward achieving these goals.

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5 GLOBAL HEALTH

ALI H. MOKDAD

Efforts to improve health and reduce death and disability in populations across the world require a comprehensive understanding of what disables and kills people across countries, time, age, and sex. Before the coronavirus disease 2019 (COVID-19) pandemic, global life expectancy was increasing despite marked disparities among and often within countries. The COVID-19 pandemic is estimated to have reduced life expectancy by about 1.7 years in the United States and globally. Addressing global health requires an understanding of the leading causes of death and disability so resources can be targeted where they can be most effective.

LIFE EXPECTANCY

Life expectancy is highly variable across the globe (Fig. 5-1), ranging from 51.8 years in Lesotho to 84.8 years in Singapore.[1] Life expectancy in Africa is markedly lower than in other parts of the world. Even within a single country, however, major disparities may exist. In the United States, for example, overall life expectancy was 78.9 years in 2019, but it ranged from 74.9 years in West Virginia to 81.7 years in Hawaii. For all racial and ethnic groups, U.S. life expectancy in 2019 ranged from 64.5 years to 91.7 years.

LEADING CAUSES OF DEATHS

Cardiovascular disease and cancers have remained the leading causes of death worldwide across the last three decades (Fig. 5-2). Compared with 1990, noncommunicable disease are more prominent and infectious diseases less prominent among leading causes of death. In general, as the sociodemographic index improves over time, the burden of noncommunicable disease increases. However, such global trends mask disparities at the country level where some countries are still dealing with a heavy infectious disease burden even as they witness a rise in noncommunicable diseases.

The leading causes of death globally vary by age of death (Fig. 5-3). Before the COVID-19 pandemic, infectious diseases were responsible for more deaths in younger age groups globally, with a greater burden of noncommunicable disease in older ages. Diarrheal and lower respiratory infections are more common in younger ages, injuries and self-harm are highest in young adults, and cardiovascular disease and cancer are the main causes of death in the older age groups. The recent declines in malnutrition deaths in some countries is attributed to improved diet, water sanitation, and access to medical care. Despite this progress, however, malnutrition is still the leading cause of burden for some countries. The COVID-19 pandemic reduced life expectancy by about 1.7 years in the U.S.[2] and by about 2.3 years worldwide.

LEADING CAUSES OF DISABILITIES

Over the past three decades, cardiovascular disease has remained the leading cause of disability worldwide (as measured by lost disability-adjusted life years [DALYs], Fig. 5-4).[3] The disability burden from cancer has risen from fourth to second, primarily as a result of longer life expectancy, whereas maternal

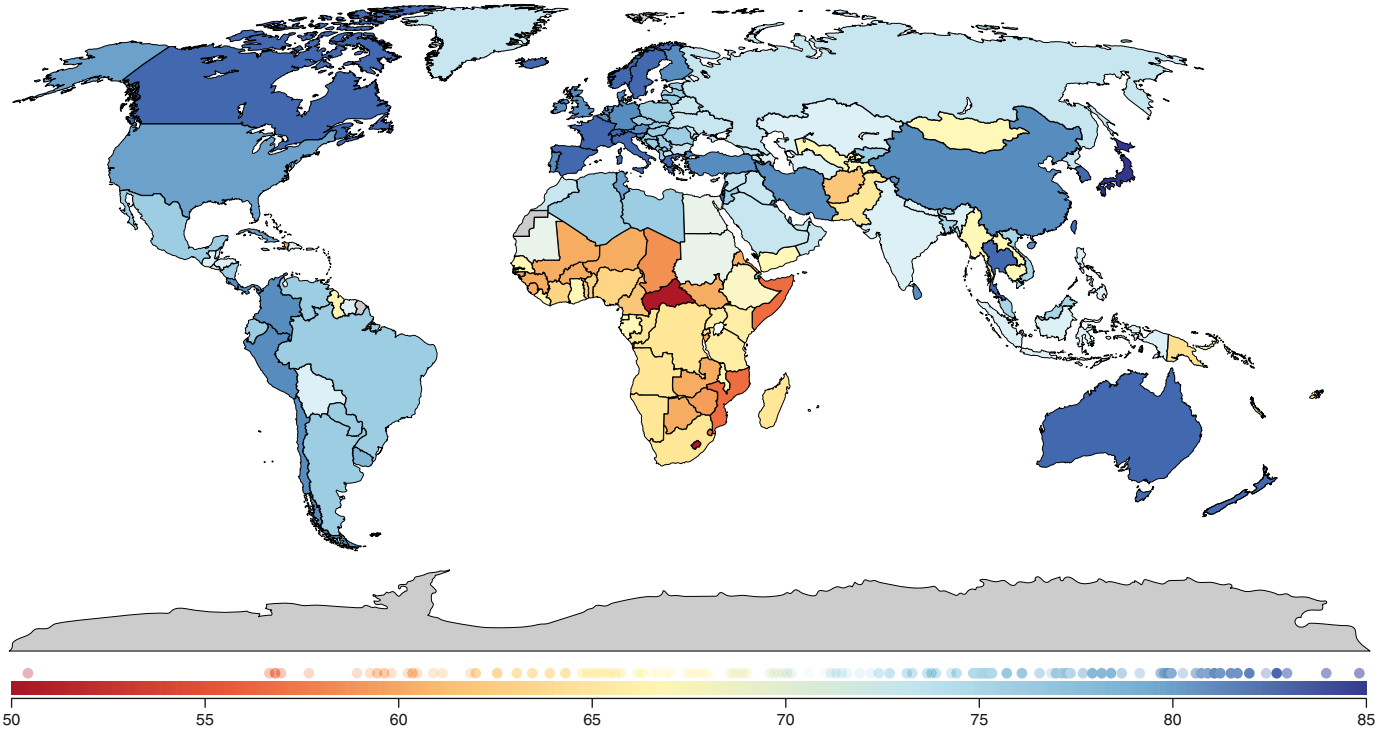

FIGURE 5-1. Life expectancy for both sexes in 2019. (Available from Global Burden of Disease 2019, Institute for Health Metrics and Evaluation. https://www.healthdata.org/data-visualization/gbd-compare. Accessed November 16, 2022.)

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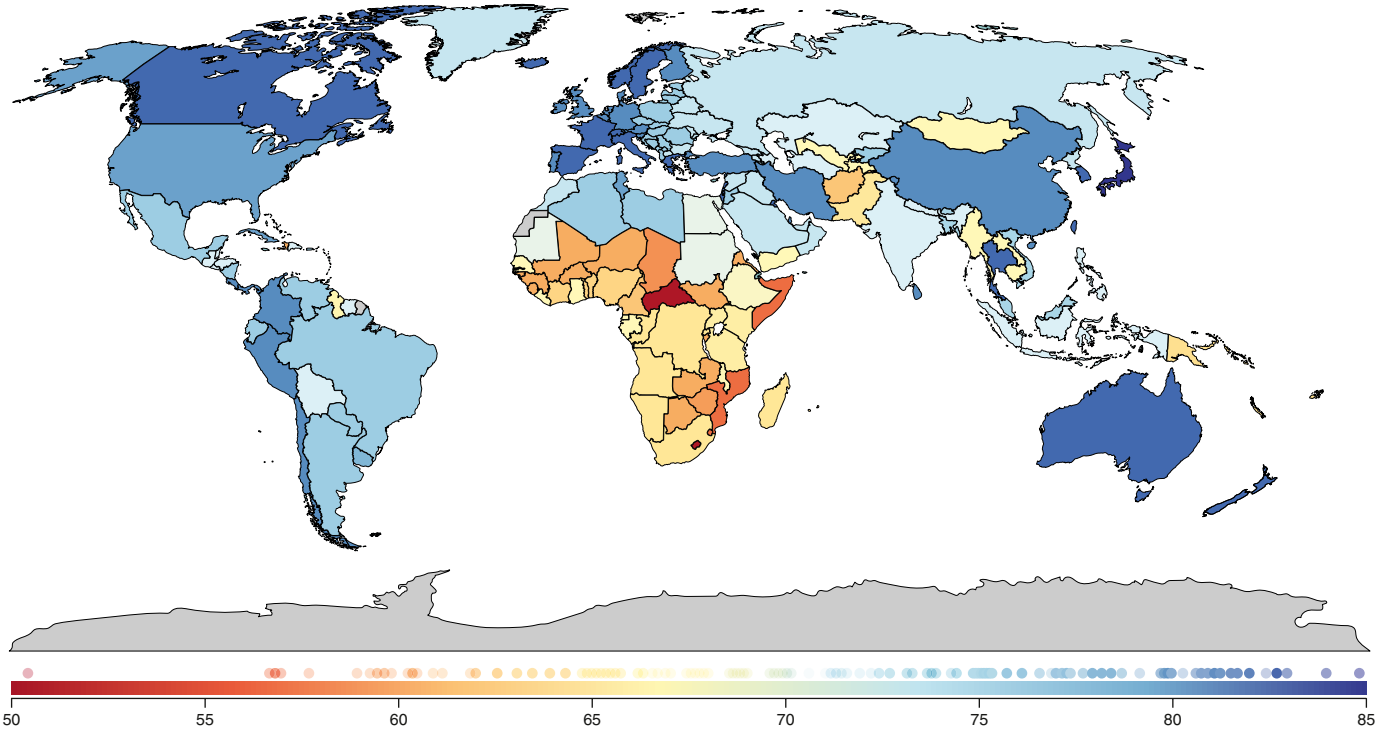

FIGURE 5-1. Life expectancy for both sexes in 2019. (Available from Global Burden of Disease 2019, Institute for Health Metrics and Evaluation. https://www.healthdata.org/data-visualization/gbd-compare. Accessed November 16, 2022.)

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KEYWORDS

global health
burden of disease
mortality
risk factors
disparity
life expectancy

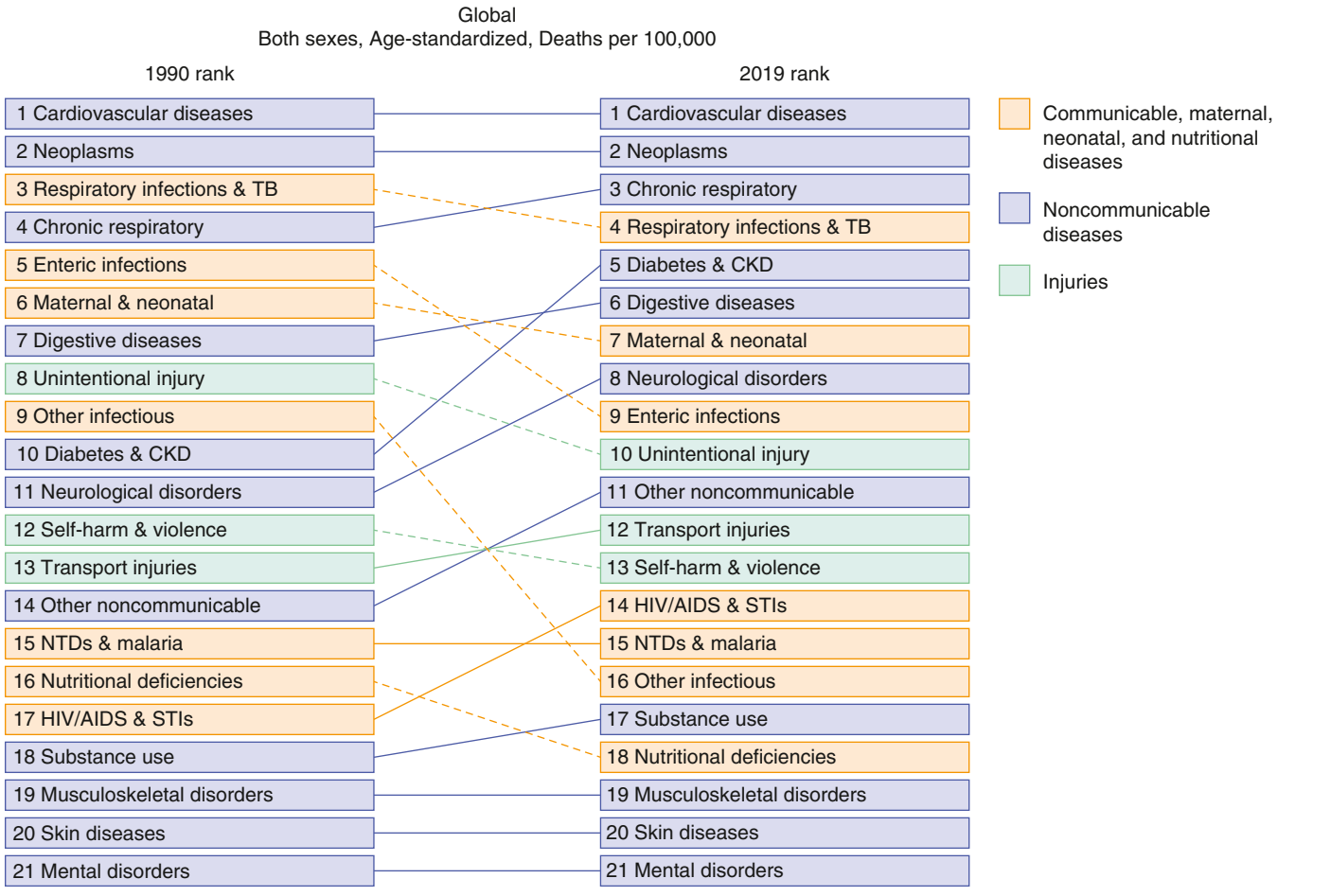

FIGURE 5-2. Leading causes of death in 1990 and 2019 for both sexes and all ages (age standardized). AIDS = acquired immunodeficiency syndrome; CKD = chronic kidney disease; HIV = human immunodeficiency virus; NTD = neglected tropical disease; STI = sexually transmitted infection; TB = tuberculosis. (Available from Global Burden of Disease 2019, Institute for Health Metrics and Evaluation. https://www.healthdata.org/data-visualization/gbd-compare. Accessed November 16, 2022.)

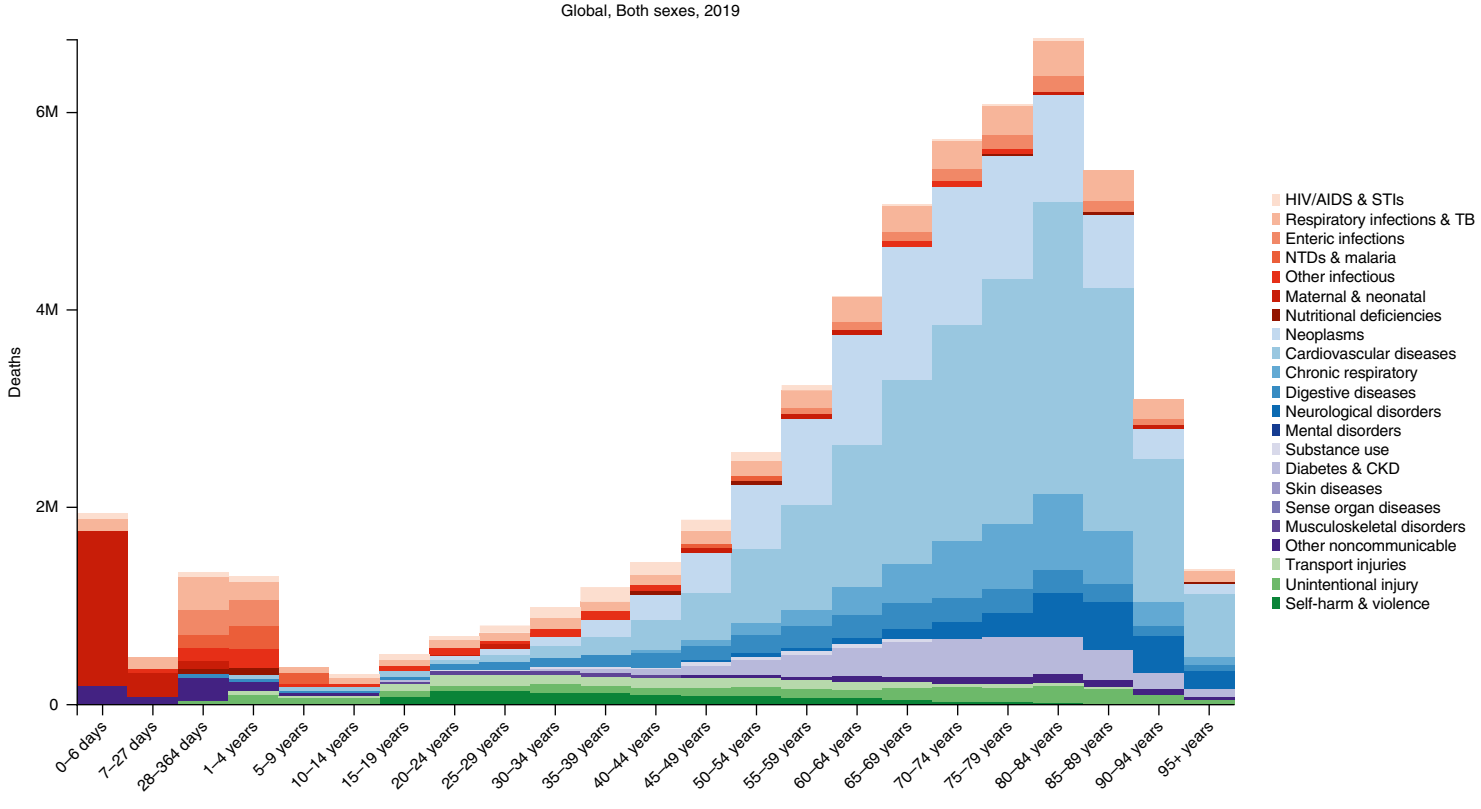

FIGURE 5-3. Causes of death globally in 2019 by 5-year incremental age groups. AIDS = acquired immunodeficiency syndrome; CKD = chronic kidney disease; HIV = human immunodeficiency virus; NTD = neglected tropical disease; STI = sexually transmitted infection; TB = tuberculosis. (Available from Global Burden of Disease 2019, Institute for Health Metrics and Evaluation. https://www.healthdata.org/data-visualization/gbd-compare. Accessed November 16, 2022.)

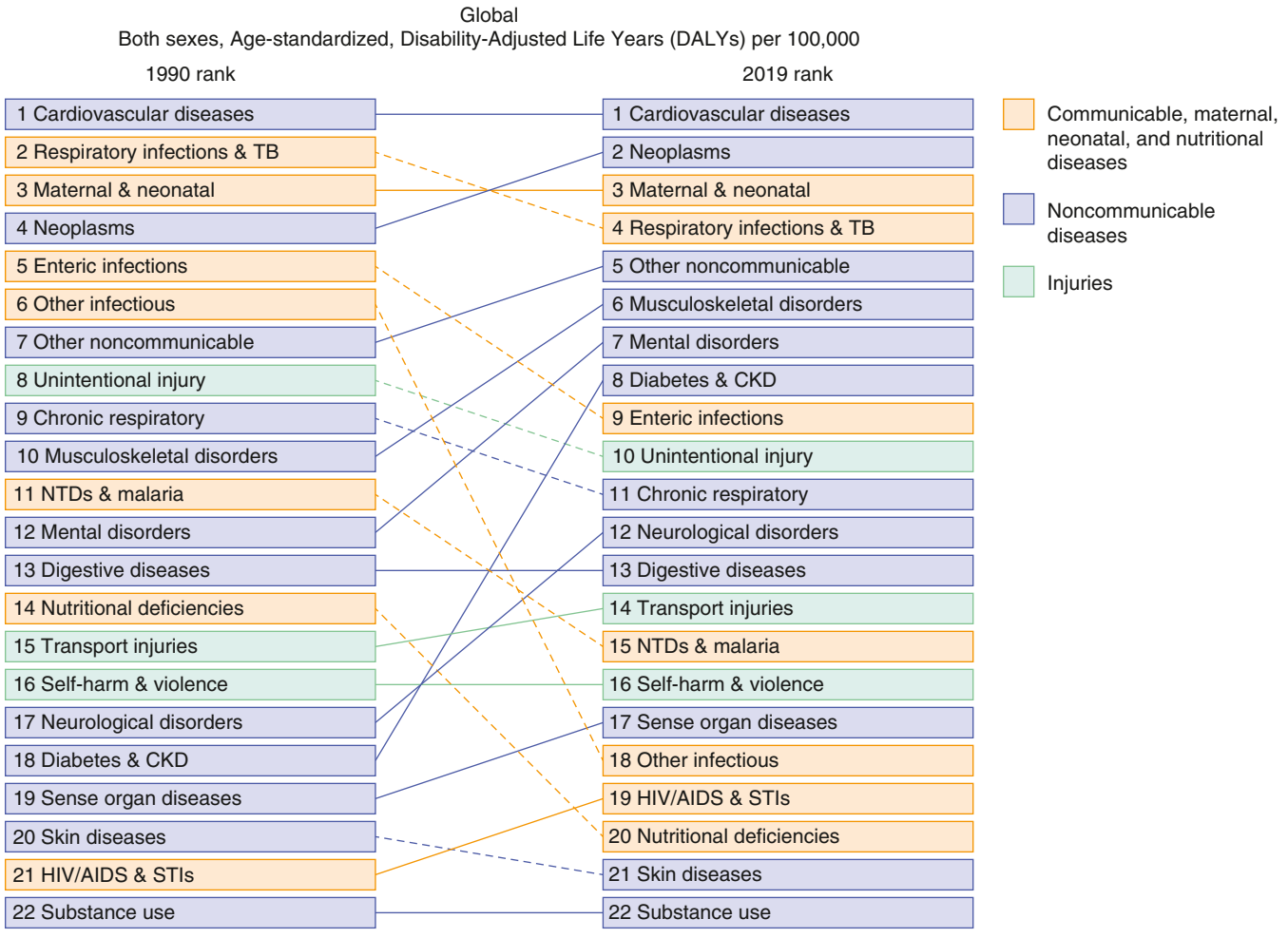

FIGURE 5-4. Leading causes of lost disability-adjusted life years 1990 and 2019 (age standardized). AIDS = acquired immunodeficiency syndrome; CKD = chronic kidney disease; HIV = human immunodeficiency virus; NTD = neglected tropical disease; STI = sexually transmitted infection; TB = tuberculosis. (Available from Global Burden of Disease 2019, Institute for Health Metrics and Evaluation. https://www.healthdata.org/data-visualization/gbd-compare. Accessed November 16, 2022.)

and neonatal diseases remained the third leading cause of lost DALYs. The burden of respiratory infections and tuberculosis has declined globally but it remains a major burden in many countries. In low-income countries, for example, respiratory infections were the second leading cause of lost DALYs.

The main contributors to increasing health loss worldwide over the past 30 years, as measured by the largest absolute increase in number of DALYs, includes six causes that largely affect older adults—ischemic heart disease (with the number of related lost DALYs increasing by 50% from 1990 to 2019), diabetes (up almost 150%), stroke (up over 30%), chronic kidney disease (up over 90%), lung cancer (up almost 70%), and age-related hearing loss (up over 80%) Additionally, four causes of disability that are common from teenage years into old age have also increased: human immunodeficiency virus (HIV; up about 130% over the past 3 decades), musculoskeletal disorders (also up about 130%), low back pain (up nearly 50%), and depressive disorders (up about 60%).

The age-standardized loss of DALYs varies substantially across the globe (Fig. 5-5).[4] In general, the burden is much higher in Africa, particularly the Central African Republic and Lesotho, compared with the remainder of the world. The burden is also high in Afghanistan. The global obesity epidemic partly explains why the number of DALYs due to ischemic heart disease rose by more than 400% in the Philippines from 1990 to 2019, and the number of lost DALYs due to diabetes rose by more than 1000% in the United Arab Emirates. In Singapore, Iceland, Norway, Ireland, Australia, New Zealand, and Qatar, more than half of all lost DALYs is now due to disability caused by noncommunicable diseases and injuries. Ethiopia, Sudan, and Bangladesh have seen 2% or greater annual reductions in age-standardized DALY rates.

LEADING UNDERLYING RISK FACTORS

Changes in mortality and morbidity reflect a variety of underlying causes.[5] Among the leading age-standardized risk factors that lead to loss of DALYs for all ages and both sexes, child and maternal malnutrition remain most prominent (Fig. 5-6). An important trend is the rise of risk factors for noncommunicable diseases, such as high systolic blood pressure, elevated fasting plasma glucose levels, and high body mass index. These risk factors vary tremendously by the sociodemographic index of countries. In countries with a low sociodemographic index, the leading risk factors for loss of DALYs are child and maternal malnutrition, air pollution, unsafe water, poor sanitation, and lack of hand-washing. By comparison, the leading risk factors in countries with high sociodemographic indexes are tobacco, high body mass index, and high fasting plasma glucose levels.

CHANGING PATTERNS OF DISEASE

Although morbidity and mortality from malnutrition and communicable diseases have declined markedly worldwide, especially in children, parts of Africa, Asia, and Latin America face not only a continued burden of persistent infectious diseases (e.g., HIV, malaria, tuberculosis, and other bacterial infections[6]) but also a rise in noncommunicable diseases (e.g., obesity, diabetes, hypertension). As the world's population ages, more and more people worldwide are now living with chronic health conditions. As a result, noncommunicable diseases, such as cardiovascular disease and diabetes, now account for nearly two-thirds of the global burden of disease, even in low- and middle-income countries.

In developing countries, malnutrition, especially in poorer and more rural areas, coexists with obesity, primarily in urban and more affluent segments of the population.[7] Rising rates of obesity (Chapter 201), diabetes (Chapter 210), smoking (Chapter 363), and often-undiagnosed hypertension (Chapter 64) in low-income countries portend a major future increase in cardiovascular diseases.[8]

THE GLOBAL HEALTH CHALLENGE

Many deaths that occur globally could have been prevented with access to high-quality health care. The Health Access and Quality of Care Index, which is

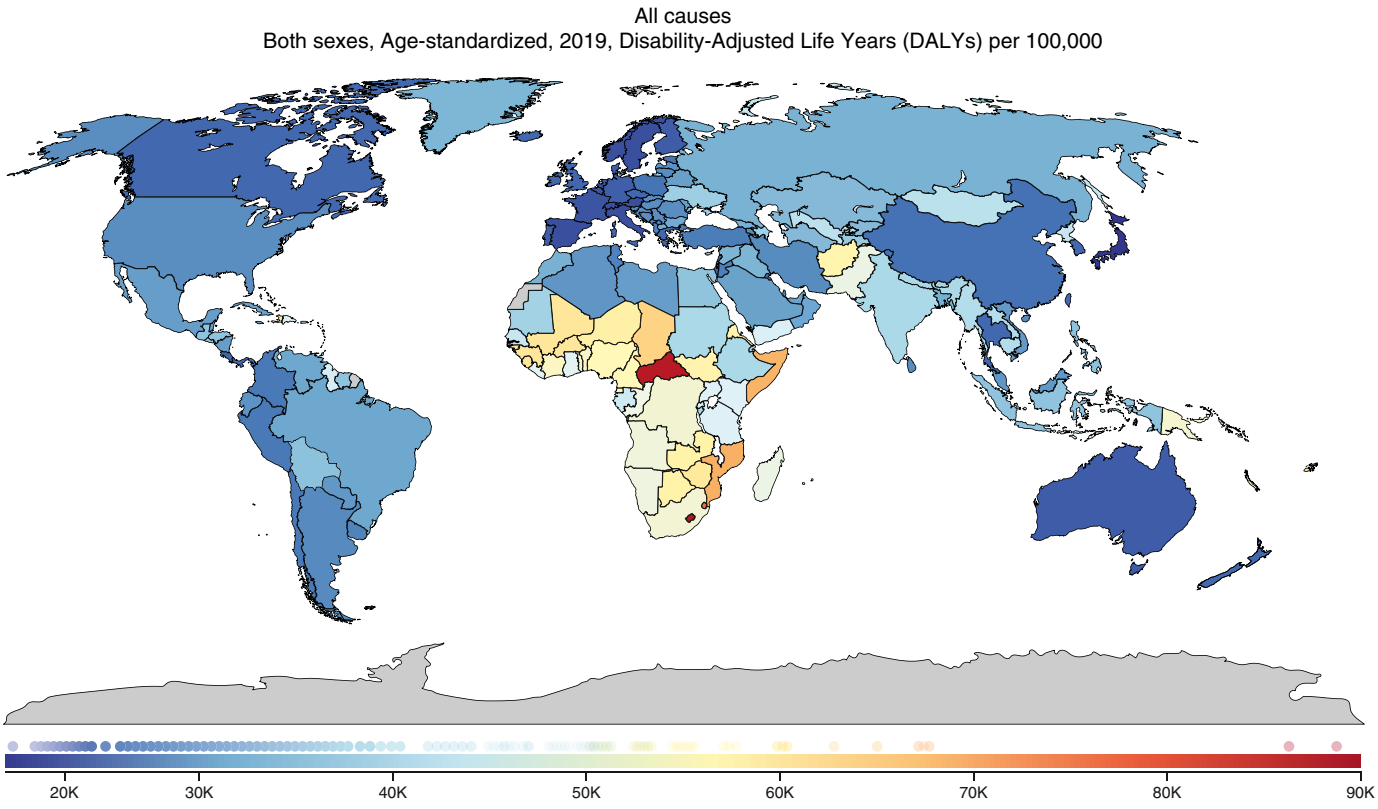

FIGURE 5-5. Age-standardized loss of disability-adjusted life years globally. (Available from Global Burden of Disease 2019, Institute for Health Metrics and Evaluation. https://www.healthdata.org/data-visualization/gbd-compare. Accessed November 16, 2022.)

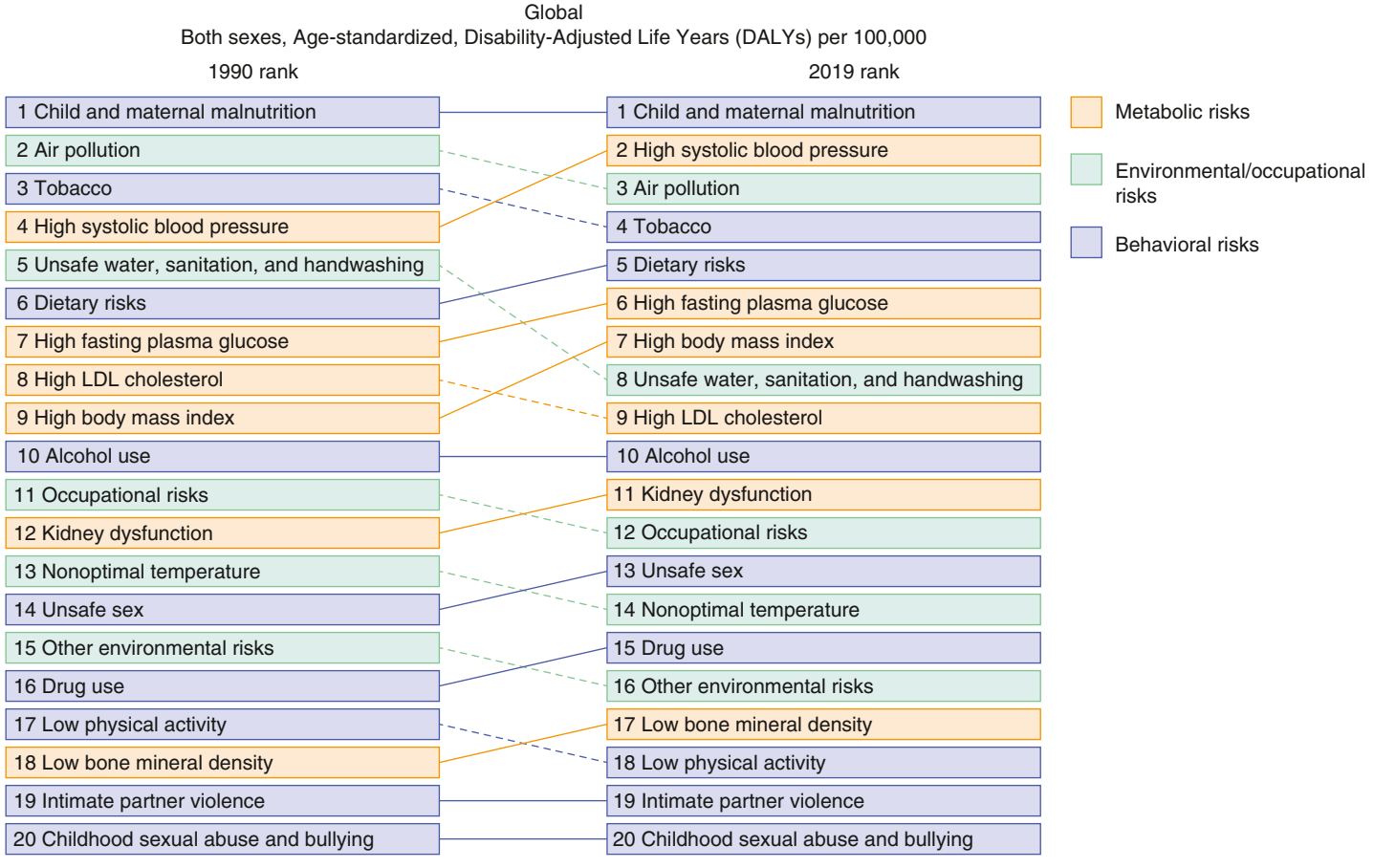

FIGURE 5-6. Age-standardized leading risk factors for loss of disability-adjusted life years globally. LDL = low-density lipoprotein. (Available from Global Burden of Disease 2019, Institute for Health Metrics and Evaluation. https://www.healthdata.org/data-visualization/gbd-compare. Accessed November 16, 2022.)

based on 32 causes of deaths that should not occur in the presence of effective health care,[9,10] range from a high of 97.1 (with 100 as the highest index of access and quality of care) in Iceland to a low of 18.6 in the Central African Republic. Second, health is strongly linked to economic development. Countries that made greater improvements in the human capital index (calculated as the number of years a person can be expected to work in the years of peak productivity, considering life expectancy, functional health, years of schooling, and learning)[11] had faster per capita economic growth. These findings highlight the need for countries to invest in health and education so as to improve their economies by improving the productivity of their labor forces.[12] Only by understanding the current health spending landscape can decision makers better allocate resources, technology, and innovation to improve health outcomes.

The COVID-19 pandemic has exacerbated already deep health disparities and demonstrated the weaknesses in worldwide public health systems. Vaccines and life-saving interventions have not been available in many parts of the world. Even in resource-rich countries, vaccination rates have often been disappointing. Excess global mortality from COVID-19 was about 17 million by the end of 2021,[13] with a huge impact on mental health[14] and gender equity.[15] Much of the recent gains in life expectancy have been reversed, with life expectancy falling to below what it was in 2013.

Global health efforts aimed to reduce infectious diseases and improve prenatal care have markedly improved the health of children under 10 years of age worldwide in the past few decades, with the overall burden of disease declining by approximately 55%. Unfortunately, this progress has not been matched in other age groups. For example, despite increased recognition of the importance of adolescent health to global development and future economic prosperity, the world failed to respond to health risks during adolescence and young adulthood (ages 10 to 24 years).[16]

Addressing social determinants of health could bring substantial health and economic benefits. Programs to improve diet quality (Chapter 13), increase physical activity (Chapter 14), and promote smoking cessation (Chapter 363) can yield large health benefits. Unfortunately, many low- and middle-income countries spend far less than 5% of their comparatively low gross domestic product on health care and, as a result, cannot address their domestic health needs.

As shown by the COVID-19 pandemic, infectious disease, like climate (Chapter 17), are worldwide issues regardless of the country or countries that may be initially or most responsible. The COVID-19 pandemic has demonstrated the importance of a strong public health infrastructure, as well as modern acute health care capabilities. However, global health threats will require not only country-specific resources and infrastructures but also general cooperation and responses. Affluent countries, which have provided poorer countries with low-cost or free treatments for HIV and onchocerciasis (Chapter 327), now must be encouraged to help countries with limited resources improve access to health care and public health programs. The sharing of expertise can also ensure that countries allocate resources to effective programs and wisely use limited resources.

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II

PRINCIPLES OF EVALUATION AND MANAGEMENT

6 HISTORY AND PHYSICAL EXAMINATION

7 APPROACH TO THE PATIENT WITH ABNORMAL VITAL SIGNS

8 STATISTICAL INTERPRETATION OF DATA FOR CLINICAL DECISION MAKING

9 MEASURING HEALTH AND HEALTH CARE

10 QUALITY, SAFETY, AND VALUE

11 POPULATION HEALTH

A L G r a w a n y

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6 HISTORY AND PHYSICAL EXAMINATION

DAVID L. SIMEL

OVERVIEW

Physicians may have multiple objectives with varying degrees of importance in their encounters with patients. These goals include, but are not limited to, the translation of symptoms and signs into diagnoses, the assessment of stability or change in known conditions, the provision of information and counseling for future prevention, and the reaffirmation or alteration of therapeutic interventions. For a healthy adult with no symptoms or signs of a problem, age-specific and risk-specific screening guidelines should be followed (Chapter 12), but a comprehensive annual physical examination is not recommended.

The interaction between the patient and physician represents not only a scientific encounter but also a social ritual centered on the locus of control of patient and physician and meeting each other's expectations. Patients expect a competent assessment of their health care needs and concerns. Physicians need to feel that they have not missed something important, an occasional need to put limits on the time available for each interaction, and a need to maintain objectivity. The expertly performed rational clinical examination enhances the social ritual and the likelihood of acquiring relevant data. It also optimizes the physician's ability to understand the patient's symptoms and concerns, as well as to facilitate the healing process. The comprehensiveness of a clinical evaluation depends on the time available, whether the episode of care was prompted by specific concerns, whether the evaluation is an intake evaluation to establish a long-term relationship with the patient, or whether the setting is in acute care. The coronavirus disease 2019 (COVID-19) pandemic rapidly advanced the use of telemedicine by clinicians who were forced to learn new creative methods for the physical examination.

MEDICAL HISTORY

The history begins by asking patients to describe, in their own words, the reason for seeking medical care (Table 6-1). Although patients may have many reasons for initiating a visit to the physician, they should be encouraged to select the one or two most important concerns they have. Physicians should reassure patients with multiple worries that other concerns will not be ignored, but emphasize that it is important to understand what worries them most.

HISTORY OF THE PRESENT ILLNESS

Open-ended questions facilitate descriptions of problems in the patient's own words. Subsequently, specific questions fill in gaps and help clarify important points. However, wise clinicians realize that when they are talking, they are not listening. Nonetheless, when the patient is acutely ill, the physician should limit the amount of time spent in open-ended discussion and move promptly to the most important features that allow quick evaluation and management. In general, the history of the problem under consideration includes the following:

- Description of onset and chronology
- Location of symptoms
- Character (quality) of symptoms
- Intensity
- Precipitating, aggravating, and relieving factors
- Inquiry into whether the problem or similar problems occurred before and, if so, whether a diagnosis was established

It is often helpful to ask patients to express what they believe is the cause of the problem or what concerns them the most. This approach often uncovers other pertinent factors and helps establish that the physician is trying to meet the patient's needs.

PAST MEDICAL AND SURGICAL HISTORY

An astute clinician recognizes that patients may not report all their prior problems because they may forget, may assume that previous events are unrelated to their current problem, or simply may not want to discuss past events. Open-ended statements such as "Tell me about other medical illnesses that we did not discuss" and "Tell me about any operations you had" prompt the patient to consider other items. The physician should ask the patient about unexplained surgical or traumatic scars.

A list of current medications includes prescriptions, over-the-counter medications, vitamins, and herbal preparations. Patients who do not recall the names of medications should bring all medication bottles to the next visit. Patients may not consider topical medications (e.g., skin preparations or eye-drops) as important, so they may need prompting.

Information about allergies (Chapter 234) is particularly important, but challenging, to collect. Patients may attribute adverse reactions or intolerances to allergies, but many supposed allergic reactions are not truly drug allergies. Eliciting the patient's actual response to medications facilitates a determination of whether the response was a true allergic reaction.

SOCIAL AND OCCUPATIONAL HISTORY AND RISK FACTORS

The social history not only reveals important information but also improves understanding of the patient's unique values, support systems, and social situation. It can be helpful to ask the patient to describe what they would do during a recent typical day when they were well, and more recently if they have been affected by changes in their health or social situation. Physicians must consider whether inherent bias, especially about race, gender, and gender identity, affects their assessment of the patient.

Data that may influence risk factors for disease should be gathered, including a nonjudgmental assessment of substance abuse (Chapter 365). The tobacco history should include the use of snuff, chewing tobacco, cigar and cigarette smoking, and electronic nicotine delivery systems (Chapter 363). Alcohol use should be determined quantitatively and by the effect that it has had on the patient's life (Chapter 364). Past or present use of prescription pain medications, sedatives, or illicit substances should be assessed (Chapter 365). The sexual history should address sexual orientation and gender identity, as well as current and past sexual activity. The best way to address sexual orientation and gender identity may be to ask the patient whether they think of themselves as "lesbian, gay, or homosexual; as straight or homosexual; as bisexual; as something else; or whether they 'don't know.'"[1] The employment history should include the current and past employment history, as well as any significant hobbies. All adult patients should be asked if they served in the military. Military veterans should be asked about their combat history, years of service, and areas of deployment.[2] In patients in whom exposure to trauma has been established, screening for post-traumatic stress disorder (PTSD; Chapter 362) can be done with several simple questions (Table 6-2). Post-traumatic stress disorder is not just a consequence of military service, so all patients should be screened for prior traumatic events and their current response to them.

The physician should obtain information on socioeconomic status, insurance, the ability to afford or obtain medications, and past or current barriers to health care (Chapter 4). Marital status and the living situation (i.e., whom the patient lives with, significant stressors for that patient) are important as risk factors for disease and to determine how best to care for the patient. A patient's culture (Chapter 4) and values should be known, including any prior advance directives or desire to overrule them (Chapter 3).

FAMILY HISTORY

The family history allows risk stratification, which affects the pretest probability for an increasing number of disorders.[3] For common diseases such as heart disease, additional inquiry into the age of onset in first-degree relatives and death attributed to the disease should be obtained (Chapter 40). Patients may lack appropriate information about the absence of disease.

REVIEW OF SYSTEMS

The review of systems elicits symptoms or signs not covered or overlooked in the history of the present illness, though no evidence suggests that a complete review of symptoms is necessary at each patient evaluation (Table 6-3).[4] The review of systems is more efficient when the questions are restricted to a specific period (e.g., "a recent change in your vision" or "shortness of breath, wheezing, or coughing this past week") or by having the patient fill out a previsit questionnaire.

PHYSICAL EXAMINATION

CHAPERONES

When a guest or friend accompanies the patient, the clinician should either ask the patient if they would like their companion to stay during the examination or ask the guest to wait outside the room. Patients can be offered the option of a chaperone, especially when the clinician and patient are of different genders and a comprehensive examination is planned. Many examiners prefer a chaperone to allay their own anxieties attributable to gender differences or to

ABSTRACT

The clinical examination provides data that are part of a scientific inquiry and is also an important social ritual that establishes and maintains a relationship between the physician and patient. As part of a scientific inquiry, the physician should focus on symptoms and signs that are of proven value, while at the same time demonstrating professionalism and caring that respects a patient's preferences and goals.

KEYWORDS

medical history
symptoms
physical examination

TABLE 6-1 PATIENT'S MEDICAL HISTORY

Description of the patient
Age, sexual orientation and gender identity, racial and ethnic background, language, occupation
Chief reason for seeking medical care
State the purpose of the evaluation (usually in the patient's words)
Other physicians involved in the patient's care
Include the clinician that the patient identifies as his or her primary provider or the physician who referred the patient. Record contact information for all physicians who should receive information about the visit
History of the reason for seeking medical care
In chronologic fashion, determine the evolution of the indication for the visit and then each major symptom. It is best to address the patient's reason for seeking care first rather than what the physician ultimately believes is most important
Be careful to avoid "premature closure," when a diagnosis is assumed before all the information is collected
Past medical and surgical history
List other illnesses and previous surgeries not related to the current problem
List all prescribed and over-the-counter medications with dose; remember to ask about vitamin and herbal supplements
Allergies and adverse reactions
List allergic reactions to medications and food. Record the specific reaction (e.g., hives). Distinguish allergies from adverse reactions or intolerance to medication (e.g., dyspepsia from nonsteroidal anti-inflammatory agents)
Social, occupational, and military history (see Table 6-2)
Describe the patient's current family and a typical day for patient
Risk factors/habits
Physical activity
Use of tobacco, alcohol, and drugs
Risk factors for sexually transmitted disease (including human immunodeficiency virus and hepatitis)
Family history
History of any diseases in first-degree relatives and a listing of family members with any conditions that could be risk factors for the patient (e.g., cardiovascular disease at a young age, malignancy, known genetic disorders, longevity)
Review of systems (see Table 6-3)

TABLE 6-2 HISTORY OF MILITARY SERVICE AND POST-TRAUMATIC STRESS

- Tell me about your military experience.
- When and where do you/did you serve?
- What do you/did you do while in the service?
- How has military service affected you?

If the patient answers "yes" to any of the questions below, ask the patient, "Can you tell me more about that?"

- Did you see combat, enemy fire, or casualties?
- Were you or a buddy wounded, injured, or hospitalized?
- Did you ever become ill while you were in the service?
- Were you a prisoner of war?

To screen for post-traumatic stress disorder, ask, "In your life, have you ever had an experience so horrible, frightening, or upsetting that, in the past month you…"

- Have had nightmares about it or thought about it when you did not want to?
- Tried hard not to think about it or went out of your way to avoid situations that reminded you of it?
- Were constantly on guard, watchful, or easily startled?
- Felt numb or detached from others, activities, or your surroundings?

From Department of Veterans Affairs. Military Health History Pocket Card for Clinicians. https://www.va.gov/oaa/archive/Military-Health-History-Card-for-print.pdf. Accessed April 6, 2021.

TABLE 6-3 REVIEW OF SYSTEMS*

FOCUS all questions on a specific time frame (e.g., within the past "month" or "now") and on items not already addressed during the clinical examination:
Change in weight or appetite
Change in vision
Change in hearing
New or changing skin lesions
Chest discomfort or sensation of skipped beats
Shortness of breath, dyspnea on exertion
Abdominal discomfort, constipation, melena, hematochezia, diarrhea
Difficulty with urination
Change in menses
Joint or muscle discomfort not already mentioned
Problems with sleep
Difficulty with sexual function
Exposure to "street" drugs or medications not already mentioned
Depression (feeling "down, depressed, or hopeless"; loss of interest or pleasure in doing things)
A sensation of unsteadiness when walking, standing, or getting up from a chair

*Start with this basic list and adapt the items by considering factors such as age, gender, medications, and the problems identified during the examination. The process is facilitated by developing a routine personal approach to these questions, typically going through the systems from "head to toe."

achieve a perceived need for protection should the patient become concerned during the procedure.

VITAL SIGNS

Vital signs include the pulse rate and rhythm, blood pressure, respiratory rate, and body temperature. Marked abnormalities require a rapid, focused evaluation that may take precedence over the typical structural approach to the remainder of the evaluation (Chapter 7).

When the blood pressure is abnormal (Chapter 64), the measurement should be repeated, assuring that the cuff size is appropriate. Because of inherent variability in blood pressure, and the prevalence of both white coat hypertension on the one hand and masked hypertension on the other, the clinician is now advised to confirm hypertension through review of measurements obtained outside of the clinical setting.[5]

Respirations should be assessed with the patient unaware that the rate is being observed. Abnormal patterns include tachypnea (rapid rate of breathing) or hypopnea (slow or shallow rate of breathing). Tachypnea is not always associated with hyperventilation, which is defined by increased alveolar ventilation resulting in a lower arterial carbon dioxide level (Chapter 89). Dyspnea is a subjective sensation claimed by the patient,[6] and patients with hypoxemia do not always complain of breathlessness. The clinician should listen for whether the patient can complete sentences without taking a breath and should observe them for increased work of breathing.

The body temperature of adults is measured with an oral electric thermometer. Tympanic thermometers vary too much in comparison with oral thermometers (−1.2° to +1.6° C vs. the oral temperature) to be reliable in hospitalized patients, but they can be useful when continuous monitoring is important.

HEAD AND NECK

Face

The examiner should note any asymmetrical facial features. Examples of asymmetry include skin lesions (Chapter 403), cranial nerve palsies (Chapter 366), parotid enlargement (Chapter 393), or the ptosis of Horner syndrome (Chapter 392). A variety of disorders may cause symmetrical, abnormal facies; examples include acromegaly (Chapter 205), Cushing syndrome (Chapter 208), and Parkinson disease (Chapter 378).

Ears

Physicians may not recognize their patient's hearing impairment (Chapter 396) unless they perform a whispered voice test. Otoscopic evaluation of the tympanic membranes should reveal a translucent membrane with an obvious cone of light reflected where the eardrum meets the malleolus (see Fig. 394-12 in Chapter 394). Cerumen impaction is an easily treated cause of diminished hearing.

Nose

Patients with nasal symptoms often incorrectly self-diagnose bacterial sinusitis (Chapter 394). The physician should inspect the nares for polyps that are obstructing, glistening, mucosal masses. Transillumination performed in a dark room is useful for diagnosing sinusitis, especially when combined with visualization of a purulent discharge, a patient's report of a poor response to decongestants or antihistamines, maxillary toothache, and the presence of discolored rhinorrhea (Chapter 394).

Mouth

The quality of the patient's dentition directly affects nutrition. Premalignant oral lesions (e.g., leukoplakia [see Fig. 393-3 in Chapter 393], nodules, ulcerations) found by generalist physicians are usually verified by dentists (Chapter 393). Patients who use smokeless tobacco products are at significantly increased risk for premalignant and malignant oral lesions (Chapter 363). Bimanual palpation of the cheeks and floor of the mouth facilitates identification of potentially malignant lesions (Chapter 393).

Eyes

The eye examination begins with simple visual inspection to look for symmetry in the lids, extraocular movements, pupil size and reaction, and the presence of redness (Chapters 391 and 392). Abnormal extraocular movements should be grouped into nonparalytic (usually chronic with onset in childhood) or paralytic causes (third, fourth, or sixth cranial nerve palsy). Pupillary abnormalities may be symmetrical or asymmetrical (anisocoria). Red eyes should be categorized by the pattern of ciliary injection, presence of pain, effect on vision, and papillary abnormalities. When the eye examination is approached systematically, the generalist physician can evaluate red eyes for conjunctivitis, episcleritis or scleritis, iritis, and acute glaucoma.

Routine determination of visual acuity can confirm a patient's report of diminished vision but does not replace the need for formal ophthalmologic evaluation in patients with visual complaints (Chapter 391). Novice examiners will find ophthalmoscopes with panoptic views easier to use than the direct ophthalmoscope, resulting in better sensitivity and specificity for optic disc abnormalities. After identifying the optic disc by ophthalmoscopy, the examiner should note the border of the disc for clarity, color, and the size of the central cup in relation to the total diameter (usually less than half the diameter of the disc). A careful observer usually can see spontaneous venous pulsations that indicate normal intracranial pressure, but about 10% of patients with normal intracranial pressure will not have spontaneous pulsations. Abnormalities of the optic disc include optic atrophy (a white disc), papilledema (see Fig. 391-25 in Chapter 391) (blurry margins with a pink, hyperemic disc), and glaucoma (a large, pale cup with retinal vessels that dive underneath and that may be displaced toward the nasal side). The generalist's examination inadequately detects early glaucomatous changes, so high-risk patients should undergo routine ophthalmologic examination for glaucoma.

After inspecting the disc, the upper and lower nasal quadrants should be examined for the appearance of vessels and the presence of any retinal hemorrhages (see Fig. 391-22 in Chapter 391) or lesions. Patients with diabetes (Chapter 210) should undergo routine examination by eye care experts because the sensitivity of a generalist's examination is not adequate to exclude diabetic retinopathy or monitor it over time.

Neck

Carotid Pulses

The carotid pulses should be palpated for contour and timing in relation to the cardiac impulse. Abnormalities in the carotid pulse contour reflect underlying cardiac abnormalities (e.g., aortic stenosis) but are generally appreciated only after detecting an abnormal cardiac impulse or murmur (Chapter 39). Many physicians listen for bruits over the carotid arteries because asymptomatic carotid bruits are associated with an increased incidence of cerebrovascular and cardiac events in older patients (Chapters 375 and 376). Unfortunately, clinical studies do not provide adequate data for judging the importance of detecting bruits in asymptomatic patients.

Jugular Veins

Inspection of the venous waveforms may facilitate the interpretation of the cardiac examination for right heart valvular lesions. The waveforms can be highlighted by shining a penlight obliquely on the vein while looking for the dynamic changes of the projected shadow on the bed linen. The examination of the neck veins is an unreliable indicator of central venous pressure or fluid responsiveness in hemodynamically unstable patients (Chapter 39). Increased respiratory collapse of the inferior vena cava seen with bedside ultrasound or increased cardiac output during passive leg raising are better examination predictors for fluid responsiveness.

Thyroid

About 4 to 7% of the general asymptomatic population will have thyroid nodules detected on physical examinations.[7] The thyroid gland is felt best when standing behind the patient and using both hands to palpate the thyroid gland gently (Chapter 207). Palpation is enhanced when the patient swallows sips of water to allow the thyroid to glide underneath the fingers. When viewed from the side, lateral prominence of the thyroid between the cricoid cartilage and the suprasternal notch indicates thyromegaly. The volume of a normal thyroid gland is no greater than the volume of the patient's distal thumb phalanx.

Lymphatic System

While palpating the thyroid, the examiner may also identify enlarged cervical lymph nodes (Chapter 154). Lymph nodes can also be palpated in the supraclavicular area, axilla, epitrochlear area, and inguinofemoral region. Simple lymph node enlargement confined to one region is common and does not usually represent an important underlying disorder. Unexpected gross lymph node enlargement in a single area or diffuse lymph node enlargement is more important. Patients with febrile illnesses, underlying malignancy, or inflammatory diseases should routinely undergo an examination of each of the aforementioned areas for lymph node enlargement.

CHEST

Inspection of the patient's posture may reveal lateral curves in the back (scoliosis) or kyphosis that may be associated with loss of vertebral height from osteoporosis (Chapter 225). When patients have back pain, the spine and paravertebral muscles should be palpated for spasm and tenderness (Chapter 369). The patient may be placed through maneuvers to assess loss of mobility associated with ankylosing spondylitis (Chapter 244), but a history of loss of lateral mobility may be just as efficient in the early stages of spondylitis.

LUNGS

The incremental value of palpation and percussion of the chest to supplement the history, auscultation, and eventual chest radiograph is unknown. Normal vesicular sounds, which approximate a 3 : 1 inspiratory : expiratory ratio with no pause between inspiration and expiration, are heard throughout most of the normal posterior chest during quiet breathing. Auscultated wheezes are continuous adventitial sounds. Crackles (formerly called rales) are discontinuous sounds heard in conditions that stiffen the lung (heart failure, pulmonary fibrosis, and obstructive lung disease[8]).

HEART

The heart examination is an important prelude to the possible ordering of further cardiac diagnostic tests.[9] The patient should be examined in the sitting and lying positions (Chapter 39). Palpation of the apical impulse in the left lateral decubitus position helps detect a displaced apical impulse and can reveal a palpable S_3 gallop. When the apical impulse is lateral to the midclavicular line, radiographic cardiomegaly and an ejection fraction of less than 50% are more likely. Most examiners auscultate in sequence the second left and right intercostal spaces, the left sternal border, and then the apex. The examiner should concentrate on the timing, intensity, and splitting of sounds with respiration. The first and second heart sounds are heard best with the diaphragm, as are pericardial rubs. Gallops (S_3 and S_4) are heard best with the stethoscope bell. High-pitched sounds are easier to hear with the diaphragm and low-pitched sounds easier to hear with the bell, while medium-pitched sounds are heard equally well with either. The location, timing, intensity, radiation patterns, and respiratory variation of murmurs should be noted. Special maneuvers during auscultation (e.g., Valsalva, auscultation during sudden squatting or standing) do not need to be performed if the results of routine precordial examination are entirely normal.

The presence of an S_3 gallop is useful for detecting left ventricular systolic dysfunction. The presence of a systolic thrill or a holosystolic murmur increases the likelihood of moderate to severe aortic stenosis or mitral regurgitation. Quiet systolic murmurs are unlikely to herald important cardiac abnormalities. A loud, early diastolic murmur or a diastolic murmur associated with an S_3 suggests severe aortic regurgitation.

BREAST

Physical breast examination by physicians is no longer recommended as a routine screening test among women at average risk. However, women may present with concerns identified through their self-examinations. The most important determinants of the accuracy of the breast examination are the duration of the examination; the patient's position; careful evaluation of the breast boundaries; the pattern of the examination; and the position, movement, and pressure of the examiner's fingers (Chapter 183). To obtain the best sensitivity, the duration of the breast examination needs to be 5 to 10 minutes' total time, but few generalist physicians perform such a lengthy examination. Clinicians should recognize that the examination may make them (or their patient) feel uncomfortable—the presence of a chaperone may give the clinician the confidence to perform an intensive examination.

The physician should palpate the breast with the pads of the fingers while the patient is supine and holding her hand first on her forehead (to flatten the lateral border of the breast) and then on her shoulder (to flatten the medial border). The examiner should make small circular motions with the fingers, moving up and down in parallel rows to span the entire breast-clavicle to the bra line. Cancerous breast lumps are difficult to distinguish from benign breast lumps, which is why breast imaging now dominates recommendations for screening and follow-up of clinical abnormalities.

ABDOMEN

When patients have an acute abdominal problem, the examination focuses initially on identifying patients who require surgical evaluation. Palpation and percussion of the abdomen of patients with no symptoms or risk factors for an abdominal disorder seldom reveal important abnormalities (Chapter 118). Palpation can reveal an asymptomatic widening of the abdominal aorta that, in older patients, suggests an abdominal aneurysm. However, palpation misses a substantial proportion of small to medium aneurysms (Chapter 63).

The presence of bowel sounds in patients with acute symptoms can be falsely reassuring because the sounds may increase early in an obstruction and then persist despite an ileus. For patients without gastrointestinal symptoms or abnormalities on palpation, auscultation for bruits is important primarily to detect renal bruits in patients with hypertension (Chapters 64 and 110). The presence of an abdominal bruit in a hypertensive patient, if heard in systole and diastole, strongly suggests renovascular hypertension.

LIVER

Detection of liver disease depends mostly on the history and laboratory evaluations (Chapter 132). By the time that signs are present on physical examination, the patient usually has advanced liver disease. The first abnormalities on physical examination associated with liver disease may be extrahepatic. The clinician should assess the patient for ascites, peripheral edema, jaundice, or splenomegaly. In patients with an enlarged liver, palpation should begin at the liver edge, but palpation of the edge below the costal margin increases the likelihood of hepatomegaly only slightly. Percussion may detect the upper border of the liver, and a span of less than 12 cm reduces the likelihood of hepatomegaly.

SPLEEN

Examination for splenomegaly in patients without findings suggestive of a disorder associated with splenomegaly almost always reveals nothing (Chapter 154). Approximately 3% of healthy teenagers may have a palpable spleen. The examination for an enlarged spleen begins first with percussion in the left upper quadrant to detect dullness. Palpation can be performed by palpating with the right hand while providing counterpressure with the left hand behind the spleen. Alternatively, the examiner can palpate with one hand without counterpressure while the patient is in the right lateral decubitus position. With the patient supine while the examiner stands cephalad to the spleen, the fingers can be hooked lightly under the left lower rib cage to feel the spleen as the patient takes a deep breath.

MUSCULOSKELETAL SYSTEM

The patient's symptoms direct the musculoskeletal examination (Chapters 236 and 242). Most patients have back pain at some point during their life (Chapter 369). The patient's history helps assess the likelihood of an underlying systemic disease (age, history of systemic malignancy, unexplained weight loss, duration of pain, responsiveness to previous therapy, intravenous drug use, urinary infection, or fever). The most important physical examination findings for lumbar disc herniation in patients with sciatica are ipsilateral straight leg raising causing pain, contralateral straight leg raising causing pain, and ankle or great toe dorsiflexion weakness. Evaluation of hip motion and pain during motion helps detect hip osteoarthritis.[10]

The generalist physician should evaluate an adult patient with knee discomfort for torn menisci or ligaments. A variety of maneuvers assess for pain, popping, or grinding along the joint line between the femur and tibia to evaluate for meniscal tears. A tear in the ligaments eliminates a discrete endpoint when the anterior, medial, or posterior ligaments are stressed. As with many musculoskeletal disorders, no single finding has the accuracy of the orthopedist's examination, which factors in the history and a variety of clinical findings.

The shoulder examination[11] is directed toward determining range of motion, maneuvers that cause discomfort, and assessment of functional disability. Hip osteoarthritis is detected by evidence of restriction of internal rotation and abduction of the affected hip. The degree of pain and disability experienced by the patient may prompt confirmation of the diagnosis and referral.

The hands and feet[12] may show evidence of osteoarthritis (local or as part of a systemic process) (Chapter 241), rheumatoid arthritis (Chapter 243), gout (Chapter 252), or other connective tissue diseases. In addition to regional musculoskeletal disorders, such as carpal tunnel syndrome, a variety of medical and neurologic conditions should prompt routine examination of the distal ends of the extremities to prevent complications (e.g., diabetes [neuropathy or ulcers] or hereditary sensorimotor neuropathy [claw toe deformity]).

SKIN

The skin should be examined under good lighting (Chapter 403). It is best to ask the patient to point out any spots on the skin of concern. Examiner agreement on some of the most important features of melanoma (asymmetry, haphazard color, border irregularity) is fair to moderate (Chapter 188). A lesion that is symmetrical, has regular borders, is only one color, is 6 mm or smaller, or has not enlarged in size is unlikely to represent a melanoma. However, an increasing number of these findings greatly enhance the likelihood of melanoma (Chapter 188).

Basal cell carcinoma and squamous cell carcinoma occur more frequently than melanoma (Chapter 188). The examiner should pay particular attention to sun-exposed areas of the nose, face, forearms, and hands.

NEUROLOGIC EXAMINATION

Full details of the neurologic examination are given in Chapter 366.

PSYCHIATRIC EVALUATION

During the general examination, much of the psychiatric assessment (including cognition) is accomplished while eliciting the routine history and performing the review of systems (Chapter 362). Observation of the patient's mannerisms, affect, facial expression, thought content, and behavior may suggest underlying psychiatric disturbances. Specific questioning for symptoms of depression (Table 362-3) is appropriate for all adult patients. Delirium (Chapter 361) is common in both medical and surgical inpatients and is recognized by fluctuating mental status. Suspect delirium when the patient has trouble carrying on a normal conversation during bedside rounds. The patient's nurse or visitors may detect delirium before the physician.

PELVIC EXAMINATION

A complete examination includes a description of the external genitalia, appearance of the vagina and cervix as seen through a speculum, and bimanual palpation of the uterus and ovaries (Chapters 184 and 219). However, current evidence is insufficient to assess whether an annual screening pelvic examination is necessary in the asymptomatic and not pregnant adult woman. In the emergency setting, all women of reproductive age with vaginal bleeding and pelvic pain should have a pregnancy test and an ultrasound to evaluate for a possible ectopic pregnancy. The diagnosis of transgender and gender incongruence should be made by clinicians with expertise in the diagnostic criteria. Likewise, the ongoing care of transgender and gender-incongruent patients is best delivered by clinicians with experience in this field (Chapter 215).[13]

MALE GENITALIA

Examination of the male genitalia should begin with a description of whether the penis is circumcised and whether there are any visible skin lesions (e.g., ulcers or warts). Palpation should confirm the presence of bilateral testes in the scrotum. The epididymis and testes should be palpated for nodules. The low incidence of testicular carcinoma means that most nodules are benign (Chapter 185).

As a screening test for prostate carcinoma, no evidence supports a digital rectal examination in the absence of an elevated serum prostate-specific antigen.[14] The generalist physician will more frequently perform a digital examination to evaluate for tenderness associated with prostatitis or enlargement causing lower urinary tract symptoms. The size of the prostate can be described by centimeters of width and height.

RECTUM

Patients can be examined while lying on their side, during a gynecologic bimanual exam, or while standing and leaning over a table. The rectal examination begins with inspection of the perianal area for skin lesions. A well-lubricated, gloved finger is placed on the anus, and while applying gentle digital pressure, the examiner asks that the patient bear down as though having a bowel movement. This maneuver facilitates entry of the finger into the rectum. A normal rectal response includes tightening of the anal sphincter around the finger. The examiner should palpate circumferentially around the length of the fully inserted finger for masses. As a screening test for colorectal carcinoma (Chapter 179), digital examination does not replace testing stool samples collected by the patient.

TELEHEALTH

The increase in telehealth visits, especially during the severe acute respiratory syndrome coronavirus 2 pandemic (Chapter 336), has made the physical examination more challenging. With the help of digital devices (for heart rate and electrocardiogram), home monitoring devices (for weight, blood

pressure, and pulse oximetry), and a caregiver (if needed), a focused physical examination can be performed virtually.[15]

SUMMARIZING THE FINDINGS FOR THE PATIENT

The clinician should summarize pertinent positive and negative findings for the patient and be willing to express uncertainty, provided that uncertainty is accompanied by a plan of action (e.g., "I will reexamine you on your next visit"). The rationale for subsequent laboratory, imaging, or other tests should be explained. A plan should be established for providing further feedback and results to the patient, especially when there is a possibility that bad news may need to be delivered. Some physicians ask the patient if there is "anything else" to be covered. Patients who express additional new concerns at the end of the visit may have been fearful to address them earlier; when the problems seem non-urgent, it is acceptable to reassure the patient and offer the promise of evaluating the patient in a follow-up phone call or at the next visit.

FUTURE DIRECTIONS

The common assumption that physicians' diagnostic skills are deteriorating is not supported by evidence. There is considerable evidence that the scientific approach to understanding what is worthwhile and what is not worthwhile during the clinical examination identifies a core set of skills for clinical diagnosticians. These skills have expanded to include bedside ultrasonography,[16] which is of proven benefit in some emergency situations (Chapters 7 and 97). Because good patient outcomes at good value are driven primarily by the quality of the information obtained during the clinical examination, continued application of scientific principles to the history and physical examination should improve diagnostic skills.

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7

APPROACH TO THE PATIENT WITH ABNORMAL VITAL SIGNS

DAVID L. SCHRIGER

Care of the patient is guided by integration of the chief complaint, history, vital signs, and findings on physical examination (Chapter 6). Physicians should be keenly aware of a patient's vital signs, because they are important markers of clinical stability. Although vital signs themselves seldom are the centerpiece of the clinical evaluation, they sometimes become the major focus of urgent care when they themselves pose a life-threatening challenge (Chapters 50, 90, 92, 95).

THE IMPORTANCE OF VITAL SIGNS

The importance of vital signs in medical care is a conundrum for proponents of an evidence-based approach to the care of patients. No experienced physician would be willing to care for patients without them, yet a formal evaluation of the utility of vital signs for making specific diagnoses would conclude that they are not particularly useful because their likelihood ratios are too close to 1 to differentiate patients who have a specific condition from those who do not (Chapter 6). For uncommon conditions, their predictive value is even worse. For example, the probability of tachycardia in a patient in thyroid storm is high, yet the probability of thyroid storm in a patient with isolated tachycardia is low. This application of Bayes theorem (Chapter 8) demonstrates why there is no justification for ordering thyroid tests for every tachycardic patient and why attempts to say "When vital sign *x* is high [low], do *y*" fail. Each vital sign can be normal or abnormal in almost every acute condition (Table 7-1), and vital signs can be transiently abnormal in healthy individuals. An algorithmic approach to testing and treatment in response to abnormal vital signs would be too vague and too complex to be of use.

TABLE 7-1 NORMAL AND PANIC RANGES FOR KEY VITAL SIGNS IN ADULTS*

	NORMAL	PANIC
Temperature	36°-38° C (96.8°-100.4° F)	40° C (104° F)
Pulse	60-100 beats/min	<45 beats/min, >130 beats/min
Respirations	12-20 breaths/min	<10 breaths/min, >26 breaths/min
Oxygen saturation	95-100%	<90%
Systolic blood pressure	90-130 mm Hg	<80 mm Hg, >200 mm Hg
Diastolic blood pressure	60-90 mm Hg	<50 mm Hg, >120 mm Hg

*Normal values are for healthy adults. Values outside these ranges are common in patients who are ill or are anxious about their health care encounter. Panic values demand the health care provider's attention in any adult patient. These values are specific (rarely present in healthy patients at rest) but not sensitive (most ill patients' vital signs will not include panic values). All vital signs must be interpreted in the context of the patient's presentation (see text).

PREDICTIVE VALUE

How can it be that vital signs are poor predictors of diagnoses but central to the practice of medicine? First, although vital signs are insufficiently predictive to be of use in rigid algorithms, these algorithms are but one of several heuristics used by physicians to diagnose and to treat patients. Pattern recognition and the hypothetical-deductive model are heuristics that are based not on average tendencies of a single factor (e.g., hypotension is present in *x*% of cases of septic shock) or a small number of factors (e.g., hypotension and tachycardia are present in *y*% of cases of septic shock) but on the complex interaction of multiple factors (e.g., because this patient is an ill-appearing elderly man with an enlarged prostate and a history of urinary tract infections, is tachycardic and hypotensive, has clear lungs and an enlarged but nontender prostate, and has an oxygen saturation of 97%, he should be treated for urosepsis [Chapter 263] while awaiting results of urinalysis and urine culture). Thus, vital signs can play an important function in medical decision making even though their likelihood ratios for specific conditions are unimpressive.

Despite their poor predictive value for any single diagnosis, abnormal vital signs help identify patients who are sicker.[1] For example, even one abnormal vital sign in the emergency department significantly increases the likelihood of adverse outcomes in elderly patients by about 50%. Abnormal vital signs on emergency department discharge increase the chance of rapid readmission, and abnormal vital signs after admission carry a 20-fold increased risk for subsequent important deterioration. Abnormal vital signs are also a key predictor of which patients are at risk of dying soon after being sent home from an emergency department or after an inpatient admission.[2]

The usefulness of vital signs is also evidenced by the finding that more severe abnormalities are associated with an even worse prognosis. For example, among hospitalized patients, one critically abnormal vital sign carries about a 1% risk for inpatient death, whereas three simultaneously abnormal vital signs carry nearly a 25% risk for inpatient death.

VITAL SIGNS AS SYMPTOMS

Abnormal vital signs are seldom the fundamental pathophysiologic problem. In shock (Chapter 92), hypotension and tachycardia are manifestations of pathophysiologic processes at cellular and molecular levels. Given the circuitous links from clinical disease to fundamental pathophysiology to abnormal vital signs, it is not surprising that the relationships between the disease states and vital signs are not strong. Until new technologies enable direct measurement of primary pathologic processes, vital signs remain an important, albeit imperfect, proxy.

The five key vital signs are temperature, pulse, blood pressure, respiratory rate, and oxygen saturation (pulse oximetry). Pulse oximetry is included because it has become widely available, is noninvasive, is relatively inexpensive, and provides information unique from the respiratory rate. Advocates have suggested that pain, smoking status, and weight be considered routine vital signs; although a case can be made for each, they are not considered here. Clinicians should never forget that the most important vital sign is what the patient looks like; general appearance is a sign that guides the intensity and urgency of the evaluation.

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ABSTRACT

Vital signs are a cornerstone of patient care. Critical abnormalities in vital signs require a rapid medical response. Other abnormalities could be completely benign, an indication of an underlying condition that requires diagnosis, or an early warning that a patient is about to decompensate. Given this wide range of significance, physicians must be aware of their patients' vital signs and think about the implications of any abnormalities. Although no simple algorithms can determine decision making, this chapter provides a general differential diagnosis for each abnormality, as well as guidance regarding the initial response to specific abnormalities.

KEYWORDS

vital signs
stability
blood pressure
respirations
heart rate
decision making

MEASURING VITAL SIGNS

Although obtaining vital signs is generally straightforward, the validity and reliability of measurement depend on proper technique and, for blood pressure and pulse oximetry, well-maintained equipment. In an era of increasing telehealth, in part because of the severe acute respiratory syndrome coronavirus 2 pandemic (Chapter 336), vital signs increasingly may be measured via home devices, including wearable sensors.[3]

Rectal and oral temperatures are generally accurate (Chapter 259), although oral temperatures can be falsely depressed in patients who breathe through their mouths. Axillary temperature is unreliable and should not be used. There is wide variability in the validity and reliability of measurements performed with tympanic membrane thermometers. A hypothermia thermometer is preferred in patients with suspected hypothermia, and core temperature should be measured with an esophageal, bladder, or rectal temperature sensor in patients with severe hypothermia or hyperthermia (Chapter 95).

Blood pressure must be measured with an appropriately sized cuff (Chapter 64). Automated blood pressure machines occasionally provide spurious results, and questionable values should be confirmed by manual auscultation and by checking other limbs. Pulse is best obtained by palpation because this technique provides the opportunity to assess regularity and contour; the pulse should be counted for sufficient time for an accurate rate to be obtained (at least 15 seconds). High heart rates or dysrhythmias detected on the digital readout of a cardiac monitor, whether watched near the patient, by off-site standardized cardiac telemetry, or a wearable electronic device,[4] must be confirmed by palpation because these monitors can spuriously count large P waves, T waves, or pacemaker spikes as R waves, thereby reporting a heart rate double the actual rate. Orthostatic vital signs—the comparison of blood pressure and pulse in the supine, sitting, and standing positions—are advocated by some but have proved to be insensitive and nonspecific for hypovolemia. Some degree of orthostatic hypotension is also common in patients whose hypertension (Chapter 64) is treated intensively but should not be a reason for de-escalating treatment unless required by the patient's symptoms.[5]

Because the typical respiratory rate is between 12 and 20 breaths per minute and because there is considerable breath-to-breath variation, the respiratory rate should be assessed for at least 30 seconds and preferably 1 minute. New technologies purporting to measure the respiratory rate have not proved clinically useful. Oxygen saturation is dependent on technology, so an understanding of the idiosyncrasies of the device being used is critical. Valid measurements are unlikely unless there is good correlation of the machine's pulse reading and the patient's pulse, and smartphone pulse oximetry readings are often unreliable.[6] The probe should be placed on a part of the body that is warm and well perfused. Pulse oximeters compare the absorption of light at two wavelengths, so readings may be spuriously high under conditions that change the color of oxygenated or deoxygenated hemoglobin, including carbon monoxide poisoning (Chapter 82), methemoglobinemia (Chapter 147), some of the less common hemoglobinopathies, and skin pigmentation. For example, pulse oximetry also slightly overestimates oxygen saturation in Black patients.[7]

ROLE OF VITAL SIGNS IN MANAGEMENT OF THE PATIENT

Abnormal vital signs should be remeasured. Certain abnormalities require prompt evaluation (Table 7-2). Other vital sign abnormalities should be rechecked in the future unless they have been previously noted, in which case a work-up can be initiated, guided by the patient's past history and physical examination findings. It is critical that physicians always "treat the patient, not the vital signs."

PATIENTS WITHOUT SYSTEMIC COMPLAINTS

In patients presenting for a routine evaluation or nonsystemic complaint (e.g., knee injury), an abnormal vital sign will seldom be the harbinger of acute illness. Most commonly, an abnormal vital sign will be a false reading or a transient finding due to random variation, pain, or anxiety that requires no evaluation or treatment and can be rechecked in the future. On occasion, an abnormal vital sign will be the only or most apparent manifestation of a chronic condition or risk factor. The measurement of an elevated blood pressure leading to a diagnosis of hypertension is the classic example of the value of vital signs in such patients.

PATIENTS WHO COMPLAIN OF SYSTEMIC ILLNESS BUT DO NOT APPEAR TO BE VERY ILL

Vital signs serve two additional roles in symptomatic patients who do not appear particularly ill. First, abnormalities in vital signs provide information that may suggest or support a diagnosis. The presence of elevated temperature in a patient with productive cough, shortness of breath, and localized rales and egophony supports a diagnosis of infectious pneumonia. Vital signs may also play a role in defining therapy and triage. For example, guidelines for patients with community-acquired pneumonia (Chapter 85) formally incorporate vital signs.

The second role of vital signs in the stable symptomatic patient is to provide warning that the patient is sicker than they appear. For example, the presence of hypotension in a well-appearing patient thought to have pyelonephritis may be an indication of sepsis or hypovolemia. For vital signs to be of use, the physician must be aware of them and must incorporate them explicitly into a thought process that considers the dangerous diagnoses associated with the abnormal vital sign. The physician then must decide whether the likelihood of each potentially dangerous diagnosis is high enough to warrant specific evaluation. Unfortunately, no quick or easy rules differentiate spurious abnormalities that can be ignored from those that should trigger additional testing or treatment. What can be said is that the well-trained physician who is aware of abnormal vital signs and is willing to contemplate a change in treatment or disposition, sometimes as stimulated by automated alert systems,[8] in response to them is less likely to make mistakes.

A few specific points bear mention. First, for most vital signs, "normal" is relative. Blood pressure must be interpreted in the context of the patient. For example, a blood pressure of 88/64 mm Hg may be reasonable for an otherwise healthy, young 50-kg woman but should cause concern in a 90-kg middle-aged man. Similarly, a blood pressure of 128/80 mm Hg would be fine in a 60-year-old man but worrisome in a 34-week pregnant woman. Second, because vital signs are insensitive measures of disease, normal vital signs should not dissuade the physician from pursuing potentially critical diagnoses. For example, young, well-conditioned adults may maintain normal vital signs well into the course of shock.

USE OF VITAL SIGNS IN PATIENTS WHO APPEAR TO BE ILL

For some patients, abnormal vital signs are expected on the basis of their appearance and their symptoms. For patients in extremis, care should proceed according to established guidelines such as Advanced Cardiac Life Support (Chapter 50), Advanced Trauma Life Support, and algorithms for the treatment of shock (Chapters 93 and 94). For hospitalized patients, markedly abnormal vital signs require urgent evaluation (Table 7-3), which in some settings may trigger a rapid response team.[9] For such ill-appearing patients, two processes must occur. In one, the physician, armed with knowledge of the differential diagnosis of each abnormal vital sign and the ability to take a thorough history and to perform an appropriate physical examination, narrows the list of potential diagnoses and decides which are of sufficient probability to warrant evaluation. Simultaneously, the physician considers the list of treatment options for all diagnoses associated with the abnormal vital sign and, before establishing a diagnosis, initiates those treatments for which the potential benefit of prompt administration exceeds potential harms. For example, antibiotics for febrile patients with suspected bacterial infection, hydrocortisone for hypotensive patients at risk for hypoadrenalism (Chapter 208), and thiamine

TABLE 7-2 ABNORMALITIES REQUIRING RAPID EVALUATION IN THE ASYMPTOMATIC PATIENT

An irregularly irregular rapid pulse (if it is not known to be chronic) should trigger an evaluation of the patient's rhythm so that atrial fibrillation can be identified, evaluated, and treated (Chapter 52), thereby decreasing the patient's risk of stroke.
A heart rate above 130 beats per minute always warrants an electrocardiogram to determine the patient's rhythm and a consideration of the differential diagnosis of tachycardia (hypovolemia, anemia, and thyroid disease in particular).
A markedly elevated diastolic blood pressure (e.g., >115 mm Hg) should stimulate an evaluation for hypertensive urgencies (Chapter 64). Note that hypertension in the absence of signs of acute end-organ damage does not require acute treatment, which can reduce intracranial perfusion pressure and cause stroke. Patients with elevated blood pressure should be offered standard evaluation and treatment for chronic hypertension (Chapter 64).
Markedly low pulse or blood pressure in patients receiving cardioactive medications should lead to a confirmation that the patient is truly asymptomatic, an inquiry into the dosing of these medications, and a reconsideration of the regimen.
Markedly low pulse in elderly patients who are not receiving rate-controlling drugs should trigger an evaluation of the patient's cardiac conduction system.
Oxygen saturation below 93% in the absence of known pulmonary problems should prompt an evaluation of the patient's pulmonary status.

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TABLE 7-3 ABNORMAL VITAL SIGNS THAT REQUIRE URGENT EVALUATION

Heart rate
- Heart rate < 40 beats/min, especially if symptoms
- Resting heart rate > 140 beats/min

Blood pressure
- Systolic blood pressure < 90 mm Hg or > 30-40 mm Hg below patient's usual stable blood pressure
- Systolic blood pressure > 200 mm Hg for >30 min
- Diastolic blood pressure > 110 mm Hg with symptoms

Respiratory rate
- Respiratory rate < 8 breaths/min or > 35 breaths/min
- New onset of marked dyspnea, compromised airway, cyanosis

Oxygenation
- O_2 saturation < 85% for >5 min (except patients with chronic severe hypoxemia)
- Need for 100% supplemental O_2 or a nonrebreathing O_2 mask

Temperature
- Body temperature < 35° C
- Body temperature > 39° C or associated with acute decompensation

for hypothermic patients at risk for Wernicke encephalopathy (Chapter 384) may improve outcome and are unlikely to cause harm even if the patient does not have the suspected condition. Although early presumptive treatment can be life-saving in selected patients, it should not be abused; physicians must avoid knee-jerk responses that can cause harm. The current COVID-19 pandemic (Chapter 336) provides a useful example of this principle. Early in the pandemic, patients who presented with low pulse oximetry values were reflexively intubated. Only later did it become clear that this approach was not optimal, but that noninvasive ventilation and sometimes putting the patient in the prone position were better responses (Chapter 337).

DIFFERENTIAL DIAGNOSIS AND TREATMENT OPTIONS

Single Abnormal Vital Signs

Because vital signs can be abnormal in virtually any disease process, no differential diagnosis can be encyclopedic. The physician should focus initially on common diseases and diseases that require specific treatment. The thought process should begin with the chief complaint and history, and then it should incorporate information about the vital signs and the remainder of the physical examination.

Multiple Abnormal Vital Signs

Patients who are acutely ill are likely to have several abnormal vital signs. Although certain patterns of abnormal vital signs predominate in specific conditions (e.g., hypotension, tachycardia, and hypothermia in profound sepsis), no pattern can be considered pathognomonic. The physician's goal is to work toward a diagnosis while simultaneously providing treatments whose benefits outweigh potential harms.

Fever is generally accompanied by tachycardia, with the general rule of thumb that the heart rate will increase by 10 beats per minute for every 1° C increase in temperature. The absence of tachycardia with fever is known as pulse-temperature dissociation and has been reported in typhoid fever (Chapter 284), legionnaires disease (Chapter 290), babesiosis (Chapter 324), Q fever (Chapter 302), infection with *Rickettsia* spp. (Chapter 302), malaria (Chapter 316), leptospirosis (Chapter 298), pneumonia caused by *Chlamydia* spp. (Chapter 294), and viral infections such as dengue fever (Chapter 352), yellow fever (Chapter 351), and other viral hemorrhagic fevers (Chapter 351), although the predictive value of this finding is unknown.

Much can be learned by comparing the respiratory rate with pulse oximetry. Hyperventilation in the presence of high oxygen saturation suggests a central nervous system process or metabolic acidosis rather than a cardiopulmonary process. Low respiratory rates in the presence of low levels of oxygen saturation suggest central hypoventilation (Chapter 74), which may respond to narcotic antagonists.

Hypertension and bradycardia in the obtunded or comatose patient are known as the Cushing reflex, a relatively late sign of elevated intracranial pressure. Physicians should strive to diagnose and treat this condition before the Cushing reflex develops.

APPROACH TO ABNORMALITIES OF SPECIFIC VITAL SIGNS

Elevated Temperature

Normal temperature is often cited as 37° C (98.6° F), but there is considerable diurnal variation and variation among individuals.[10] Furthermore, data suggest that normal human body temperature is now closer to 36.1° C (97° F),[11] so 38° C is the most commonly cited threshold for fever. Fever thought to be due to infection should be treated with antipyretics and appropriate antimicrobials (Chapter 259). The importance of early administration of antibiotics to potentially septic patients cannot be overstated (Chapters 259 and 260). Hyperthermia (temperature above 40° C) should be treated with cooling measures such as ice packs, cool misting in front of fans, cold gastric lavage, and, for medication-related syndromes, medications such as dantrolene (Chapter 95). Most hospital anesthesia departments will have a designated kit for the treatment of malignant hyperthermia (Chapter 400).

Low Temperature

The treatment of hypothermia is guided by its cause (Chapter 95). The body's temperature decreases when heat loss exceeds heat production. Every logically possible mechanism for this phenomenon has been observed. Decreased heat production can result from endocrine hypofunction (e.g., Addison disease [Chapter 208], hypopituitarism [Chapter 205], hypothyroidism [Chapter 207]) and loss of the ability to shiver (e.g., drug-induced or neurologic paralysis or neuromuscular disorders). Malfunction of the hypothalamic regulatory system can be due to hypoglycemia (Chapter 210) and a variety of central nervous system disorders (Wernicke encephalopathy [Chapter 384], stroke [Chapter 376], tumor [Chapter 175], and trauma [Chapter 368]).[12] Resetting of the temperature set point can occur with sepsis. Increased heat loss can be due to exposure, behavioral and physical disorders that prevent the patient from sensing or responding to cold, skin disorders that decrease its ability to retain heat, and vasodilators (including ethanol). A careful history and physical examination should illuminate which of these possibilities is most likely.

Several considerations are worthy of emphasis. The spine of an obtunded hypothermic patient who is "found down" must be protected and evaluated because paralysis from a fall may have prevented the patient from seeking shelter and may have diminished the ability to produce heat. The physician should not forget to administer antibiotics to patients who may be septic (Chapter 94), thiamine to those who may have Wernicke encephalopathy (Chapter 384), hydrocortisone to those who may be hypoadrenal (Chapter 208), and thyroid hormone to those who may have myxedema coma (Chapter 207). Severely hypothermic patients (Chapter 95) should be treated gently because any stimulation may trigger ventricular dysrhythmias; even in the absence of pulses, cardiopulmonary resuscitation should be used only in patients with ventricular fibrillation or asystole.

Elevated Heart Rate

The rate, rhythm, and electrocardiogram differentiate sinus tachycardia from tachyarrhythmias (Chapters 49, 50, 52, and 53). Tachyarrhythmias can be instigated by conditions that may require specific treatment (e.g., sepsis [Chapter 94], electrolyte disorders [Chapters 102, 103, and 104], endocrine disorders [Chapter 202], and poisonings [Chapters 20 and 96]) before the arrhythmia is likely to resolve. For sinus tachycardia, treatment of the underlying cause is always paramount. Treatments may include antipyretics (for fever); anxiolytics; oral or intravenous fluids (for hypovolemia); nitrates, angiotensin-converting enzyme inhibitors, and diuretics (for heart failure and fluid overload [Chapter 46]); oxygen (for hypoxemia); α-blockers (for stimulant overdose); β-blockers (for acute coronary syndromes [Chapters 57 and 58] or thyroid storm [Chapter 207]); and lysis or anticoagulation (for pulmonary embolism [Chapter 68]). Tachycardia is often an appropriate response to a clinical condition and should not be treated routinely unless it is causing or is likely to cause secondary problems.

Low Pulse

Bradycardia (Chapter 51) can be physiologic (athletes and others with increased vagal tone), due to prescribed cardiac medications (e.g., β-blockers, calcium-channel blockers, digoxin), overdoses (e.g., cholinergics, negative chronotropic agents), disease of the cardiac conducting system, electrolyte abnormalities (severe hyperkalemia), and inferior wall myocardial infarction (Chapters 51 and 58). Asymptomatic patients do not require immediate treatment. The goal of therapy is to produce a heart rate sufficient to perfuse the tissues and alleviate the symptoms (Chapter 50). Overdoses should be treated with specific antidotes (Chapter 96). Endocrine disorders should be treated with replacement therapy. In patients with acute coronary syndrome (Chapter 57), the goal is to restore perfusion and alleviate the ischemia. Patients with profound bradycardia or hypotension may require chronotropic drugs to increase perfusion even if these agents increase myocardial oxygen demand. In normotensive patients with milder bradycardia, chronotropic agents should be used only if

symptoms and ischemia cannot be resolved by other means. Atropine is the primary therapy for bradycardia; isoproterenol and cardiac pacing are reserved for those who do not respond (Chapter 51).

Elevated Blood Pressure

Elevated blood pressure does not require acute treatment in the absence of symptoms or signs of end-organ damage (Chapter 64). In patients whose blood pressure is markedly above their baseline, the history and physical examination should assess for the conditions that define "hypertensive emergency": evidence of encephalopathy, intracranial hemorrhage, ischemic stroke, heart failure, pulmonary edema, acute coronary syndrome, aortic dissection, renal failure, and preeclampsia. In the absence of these conditions, treatment should consist of restarting or adjusting the medications of patients with known hypertension and initiating a program of blood pressure checks and appropriate evaluation for those with no prior history of hypertension (Chapter 64).

The patient with a true hypertensive emergency should be treated with agents appropriate for the specific condition. Because rapid decreases in blood pressure can be as deleterious as the hypertensive state itself, intravenous agents with short half-lives, such as nitroprusside, labetalol, nitroglycerin, and esmolol, are preferred (Chapter 64).

Low Blood Pressure

Low blood pressure must be evaluated in the context of the patient's symptoms, general appearance, and physical examination findings. Treatment depends on context. The same blood pressure value may necessitate intravenous inotropic agents in one patient and no treatment in another.

In tachycardic hypotensive patients, the physician must rapidly integrate all available evidence to determine the patient's volume state, cardiac function, vascular capacitance, and the primary cause of the tachycardia (Chapter 92).[13] Not all patients with hypotension and tachycardia are in shock, and not all patients in shock will have hypotension and tachycardia. Point-of-care ultrasound (Chapter 39)[14] of the heart and inferior vena cava may be useful in differentiating the cause of shock.

Treatment of shock is based on the cause: hypovolemic, cardiogenic, or distributive (septic, neurogenic, anaphylactic) (Chapters 92 to 94). Symptomatic hypotensive patients thought to be intravascularly volume depleted should have their legs raised and receive intravenous fluid resuscitation with crystalloid or blood, depending on their hemoglobin level (Chapter 92).[15] In patients with known heart disease, patients who are frail or elderly, and patients whose volume status is uncertain, small boluses of fluid (e.g., 250 mL of normal saline), each followed by reassessment, are preferred so that iatrogenic heart failure may be avoided. Inotropic support should be reserved for patients who do not respond to fluid resuscitation. High-output heart failure should be kept in mind in patients with possible thyroid storm or stimulant overdose.

Increased Respiratory Rate

Tachypnea is a normal response to hypoxemia (see later) or acidemia (Chapter 104).[16] Treatment of tachypnea in the absence of hypoxemia is directed at the underlying cause, which often is pain (Chapter 26). Anxiolytics (e.g., diazepam, 5 to 10 mg PO or IV; lorazepam, 1 to 2 mg PO, IM, or IV) or reassurance can calm patients with behavioral causes of hyperventilation. Breathing into a paper bag has been shown to be an ineffective treatment. Pulmonary embolism (Chapter 68) does not necessarily reduce the oxygen saturation or cause a low Po_2 and should always be considered in at-risk patients with unexplained tachypnea.

Decreased Respiratory Rate

Any perturbation of the respiratory center in the central nervous system can slow the respiratory drive (Chapter 74). Narcotics and other sedatives and neurologic conditions are common causes of a decreased respiratory rate. The primary treatment of apnea is mechanical ventilation (Chapter 91), but narcotic antagonists can be tried in patients with a history or physical examination findings (miosis, track marks, opioid patch) suggestive of narcotic use or abuse (Chapter 365). In nonapneic patients, mechanical ventilation, either noninvasive or invasive (intubation), is indicated for patients who are breathing too slowly to maintain an acceptable oxygen saturation and for patients who are retaining carbon dioxide in quantities sufficient to depress mental function. Patients who are unable to protect their airway should be intubated. Oxygen should be administered to all hypopneic patients who are hypoxemic (see earlier). Patients with chronic hypoventilation (Chapter 74) may have retained HCO_3^- to compensate for an elevated Pco_2 and so may depend on hypoxia to maintain respiratory drive; in these patients, overaggressive administration of oxygen can decrease the respiratory rate, increase the Pco_2, and increase obtundation (Chapter 90).

Decreased Oxygen Saturation

In hypopneic patients, initial efforts should try to increase the respiratory rate (see earlier) and tidal volume. Regardless of etiology, oxygen, in amounts adequate to restore adequate oxygen saturation (Po_2 > 60 mm Hg, oxygen saturation > 90%), is the mainstay of therapy. When oxygen alone fails, noninvasive methods for improving ventilation or tracheal intubation are required (Chapter 90). Oxygen should increase the Po_2 in all patients except those who have severe right-to-left shunting (Chapter 55). Treatment of conditions that cause hypoxemia includes antibiotics (pneumonia), bronchodilators (asthma, chronic obstructive pulmonary disease), diuretics and vasodilators (pulmonary edema), anticoagulants (pulmonary embolism), hyperbaric oxygen (carbon monoxide poisoning), methylene blue (methemoglobinemia, sulfhemoglobinemia), and transfusion (anemia).

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8 STATISTICAL INTERPRETATION OF DATA FOR CLINICAL DECISION MAKING

THOMAS H. PAYNE

Statistical techniques are core to evidence-based medicine. The scientific method is based on generating a hypothesis and designing an experiment to test that hypothesis. This powerful approach has been at the root of advances in human endeavors and particularly within medicine. A clear description of a question, a formulation of a hypothesis, a careful design of an experiment to test the hypothesis, the gathering of unbiased data, and the appropriate analysis of the results of the experiment permit the determination of whether a test or treatment is useful or not. If these steps are not conducted in a rigorous manner, statistical tests are likely to produce inaccurate or unreliable results.

INCIDENCE AND PREVALENCE

Incidence describes the number of subjects who *contract* a disease *over time* divided by the population at risk. Incidence is usually expressed as a rate (e.g., 7 per 1000 per year), but it may sometimes be a proportion, as in lifetime incidence. *Prevalence* describes the number of subjects who *have* a disease at *one point in time* divided by the population at risk; it is always a proportion. At any point in time, the prevalence of a disease is defined by the product of incidence of the disease multiplied by the average duration of the disease.

INTERPRETING DATA

Physicians are continuously confronted with data from many sources, including clinical measurements (e.g., vital signs), laboratory tests, and imaging studies. In fact, the work of the modern-day physician is in many respects one of information management. Although the physician may not conduct independent statistical analyses unaided, knowledge of the fundamentals of data analysis is critical for the ability to evaluate whether and how to integrate information into clinical practice.

This knowledge is also essential for understanding the medical literature and incorporating it into practice. Millions of research articles are published each year, and their quality varies widely. Articles published in the leading medical journals undergo rigorous statistical review, but the same is not true for most other journals. Although it generally is inadvisable to base clinical decisions upon a single study, physicians are often confronted with new information and the dilemma of how to deal with it.

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ABSTRACT

An important and common element of the physician's role is to make decisions. Effective decision making includes gathering information, determining whether more information is worth the additional risk and expense, and interpreting results. All of these tasks depend on a physician's skill in using data optimally. Information gathering begins with the most important data: those derived from a careful patient history and physical examination. However, the variety of available laboratory tests and diagnostic procedures greatly increases the amount of information that can be obtained and that must be ordered intelligently and interpreted correctly. Appropriate use of clinical information can make important differences in patients' outcomes and in the resources required to optimize them.

KEYWORDS

clinical decision making
biostatistics

Both of these goals—interpreting clinical data and understanding the medical literature—require familiarity with the laws of probability and the field of statistics.

DATA AND THEIR CHARACTERISTICS

Variability is a constant of nature. Statistical techniques represent an effort to describe data and distinguish differences that reflect random variation from those that represent true differences. First, it is necessary to define the nature of data elements being analyzed. Numeric data can vary over a wide range, with values anywhere between the extremes of that range. Blood pressure, for example, can have values of 130, 129.3, 75, and any value in between. Such data are called *continuous*. Numeric data that can only have an integer value, such as number of siblings, are called *discrete*. Other data are reasonable only if they fall into one of several categories, such as whether someone is alive or dead. These data are *categorical*. Labeling a test as positive or negative, which may depend on a somewhat judgmental threshold rather than a continuum, is another example of categorical data.

The next step in examining data is to assess how they are distributed. The distribution of values within a population (e.g., blood pressures) is often categorized as normal (i.e., Gaussian). A normal distribution is often characterized using both measures of *central tendency* (i.e., mean, median, and mode) and measures of *dispersion* around the center of the distribution (e.g., standard deviation). However, many phenomena in medicine produce distributions that are not normal (e.g., Poisson, binomial, etc.), and their analysis requires non-parametric approaches.[1]

HYPOTHESIS TESTING

In medical research, the goal is typically to discern whether two groups differ in a meaningful way, such as whether an outcome in a group that received a particular treatment differs from the outcome in a group that received no treatment or a placebo. This comparison begins with a hypothesis that is stated formally as the *null hypothesis* and is phrased in relation to an alternative hypothesis. The two hypotheses are mutually exclusive and exhaustive. So if a study compares change in blood pressure between a group that received an intervention and one that did not (controls), the null hypothesis would be that the intervention had no effect on blood pressure and the alternative hypothesis would be that it did have an effect.

A study should be designed to determine whether to accept or reject the null hypothesis. In the analysis of data collected in the study, the challenge is to determine whether differences seen in the distribution of blood pressure in people who received the treatment differed from those who did not; and if there is a difference, whether that difference is due to chance. The appropriate techniques for testing hypotheses vary depending on the nature of the data that are collected (Table 8-1).

Since blood pressure measurements vary, any true difference between intervention subjects and control subjects may be difficult to detect if there is only a small number of study subjects; the natural, biologic dispersion of blood pressure may obscure a true difference between the two. However, if the number of subjects is increased, the ability to detect a true difference also increases, and some number should be sufficient to detect a meaningful difference if it truly exists. Below that number, the study may fail to detect a difference between blood pressure readings of the intervention and control groups even though a difference genuinely exists. This level is termed *beta* and represents the probability of a *Type II error* (i.e., failure to detect a true difference when one truly exists). When the number of subjects exceeds the minimum number, there can be greater confidence that a difference will be observed if one truly exists. The probability below which the null hypothesis can be rejected is termed the *alpha* level and represents the probability of rejecting the null hypothesis when the null hypothesis is actually true. A *Type I error* occurs when a null hypothesis is rejected although it is true. To eliminate any possibility of a Type I error would necessitate an infinite number of subjects, so by convention, a 5% or lower chance of this error is considered acceptable. Thus, at an alpha level of 0.05, a difference that is detected will be a true difference 95% of the time, but 5% of the time a random difference will be mistakenly classified as a true difference.

Because falsely concluding that a difference exists (e.g., concluding that a treatment is helpful when it is actually ineffective) is considered a more serious error than the reverse (concluding that a treatment is ineffective when, in fact, it is potentially helpful), levels for beta error typically are set much lower than those for alpha (e.g., 80%). *Power analysis* is a method for estimating the minimum sample size necessary to detect the minimum difference between groups that is defined as clinically meaningful at a specified alpha level (typically 0.05) and beta level.

TABLE 8-1 TYPES OF VARIABLES AND COMMONLY USED STATISTICAL METHODS

		ASSOCIATED STATISTICAL METHODS	
TYPE OF OUTCOME VARIABLE	**EXAMPLES**	**BIVARIATE**	**MULTIVARIATE**
Categorical (dichotomous)	Alive; readmission to the hospital within 30 days	2 × 2 table, chi-square analysis	Logistic regression
Categorical (nominal)	Race; cancer, tumor type	Chi-square analysis	Nominal logistic regression
Categorical (ordinal)	Glasgow Coma Scale	Mann-Whitney-Wilcoxon, Kruskal-Wallis	Ordinal logistic regression
Numerical (continuous)	Cholesterol; SF-36 scales*	*t* Test, analysis of variance	Linear regression
Numerical (count)	Number of times pregnant; number of mental health visits in a year	Mann-Whitney-Wilcoxon, Kruskal-Wallis	Poisson regression, linear models
Time to event regression	Time to breast cancer; time to viral rebound in HIV-positive subjects	Log rank	Cox proportional hazards

*Numerical scores with many values are often treated as though they were continuous.
HIV = human immunodeficiency virus; SF-36 = short-form 36-item health survey.
Courtesy of Thomas B. Newman, MD, MPH, and Charles E. McCulloch, PhD.

P values, which are often reported in medical studies, answer the question, "If the null hypothesis were true, what would be the probability of obtaining, by chance alone, a value of the test statistic this large or larger?" For a fixed level alpha, the power of a test increases with sample size and increases with the true difference between the null hypothesis and a specified alternative.

In essence, the foundation of hypothesis testing is determining whether there is a difference and whether any difference is explained by chance. This determination hinges on probability, as well as conventions regarding tolerance for false-positive (calling a difference real when it actually is a chance effect) and false-negative (not finding a true difference) conclusions.

Study Design

When testing the hypothesis that an intervention is effective, there may be other reasons unrelated to the intervention as to why that outcome measurement might have changed. A *covariate* is another factor, different than the tested intervention, that can potentially influence the outcome under study. For example, in evaluating a medication to treat hypertension, subjects also may have been exposed to a campaign to reduce dietary salt intake. The reduction in salt intake, which could have contributed to any observed changes in blood pressure, would be considered a covariate. It is essential to adjust, or control, for these covariates. The most straightforward way is to assign the intervention to one group but also to measure the change in outcome in an otherwise similar *control* group as well. The strongest research design is the *randomized, double-blinded controlled trial* in which individuals are randomly assigned either to receive the intervention to be tested or to receive an inert or inactive substitute. Subjects in both the intervention and control groups are kept uninformed as to whether they are receiving the active intervention or substitute, and the investigator observing the outcomes is also kept unaware of who is assigned to which group. Thus, neither the subject nor the person recording results knows which arm of the intervention is being observed, and so the reporting and recording of results are insulated from belief in the power of the intervention. This approach is regarded as the most accurate way to assess the effect of an intervention, because any effect of covariates would be expected to occur nearly equally in both the intervention and control groups. Furthermore, any placebo effect is minimized by masking whether or not the subject is receiving the treatment. The advantages of randomized controlled trials make this design the accepted "gold standard" for the evaluation of new pharmacologic treatments.

However, randomized controlled trials are not always practical for many reasons, and much medical knowledge is derived from different study designs

in which it is difficult to know all of the influences on the outcome. Nonrandomized studies can never guarantee adequate control for all covariates, even in very large observational data sets.[2] For example, consider whether hospital mortality rates increased or declined after a large process change, such as the installation of new computer systems to enter and communicate orders. Any changes in error rates may be due to the new computer system, but they also could be explained by heightened awareness of the risk for errors. Investigators can attempt to control for known covariates, but other covariates may not be known. For this reason, randomized trials provide the strongest evidence for causality.

A variety of other *quasi-experimental* study designs have been applied. For example, an intervention might be applied to an entire practice rather than to individual patients. Although it would be ideal to assign the intervention randomly to participating practices, such an approach may be impractical or impossible. One approach would be to introduce an intervention sequentially to individual practices in a systematic manner—which is termed a *stepped wedge* design. If this approach cannot be done in a systematic manner or if the evaluation is being conducted post hoc, the data can be retrospectively segmented into short, consecutive time periods so that the analysis can try to distinguish temporal trends from actual effects of the intervention. This design is termed an *interrupted time-series*.

When evaluating health care interventions, it is often desirable to include both a quantitative measurement of outcomes (such as mortality or hospital admissions) and observational or qualitative methods, such as surveys or structured interviews. These data are often complementary. If, for example, a study fails to show that an intervention was effective, qualitative information may reveal whether it was properly implemented and what problems prevented implementation. Qualitative methods also are important to understand the attitudes and reactions of health care personnel and patients.

Time to Event Data

A common study design is to follow a sample of patients who receive a treatment until a prespecified outcome has occurred, such as death or hospital admission. The analysis uses the time between the subject's participation in the study until the outcome. Results are often displayed graphically as a survival distribution. Some subjects may contribute data to the study but not complete it. A *Kaplan-Meier analysis* allows estimation of survival in a manner that uses data from patients who drop out of the study. A *Cox proportional hazards model* compares the survival between or among groups.[3]

Noninferiority Trials

In some research, the goal is not to find a more effective treatment but one that has other advantages, such as fewer side effects or lower cost. In these studies, called *noninferiority trials*, the purpose is to evaluate a new treatment against an existing one with the goal of demonstrating that it is at least as good. An example is comparing a new treatment with a standard treatment, in which the goal is not to find an approach that is more effective, but to find a therapy that has lower cost or fewer adverse effects with at least similar efficacy to the standard treatment.[4]

CAUSALITY

There is an important difference between association and causality. The rooster's crow is *associated* with, but does not cause, sunrise. Anoxia *causes* death. An investigator's—and the public's—belief that a treatment is beneficial is powerful, and the scientific method can help us determine the difference between belief and reality. Belief can influence biology. The placebo effect is the concept that effects can be due to belief and not to the intervention itself.

Confounding

If a covariate is related to both the outcome and to the exposure or risk factor being studied, and if it is unequally distributed between the groups being compared, it becomes a *confounder*. Since most health outcomes have many contributing causes, there often are many possible confounders. For example, in a study of the association between obesity and heart disease, age may be a confounder. Age is related to obesity and also to heart disease. If the obese subjects are older than the nonobese subjects, then differences in the outcome of heart diseases may be due to the older age of the obese subjects rather than to their obesity.

In observational studies in which randomization is not possible, steps to reduce bias due to confounding should be considered in the analysis. In an observational study of the effect of a treatment on an outcome of interest, it may be that the treatment is given to some subjects (patients) because of their characteristics, such as age or severity of illness. A variety of sophisticated statistical techniques are applied in an effort to reduce bias in observational studies. For example, a *propensity score* is the probability that a study subject would receive the exposure or treatment of interest, based on the subject's characteristics and the clinical environment.[5] Using the propensity score, it is possible to adjust for the effect of known confounding variables so that it is less likely the difference in outcome is due to confounding bias. Nevertheless, all techniques to reduce confounding depend entirely on data about relevant covariates. If such data are missing, statistical adjustment cannot produce an accurate result. A limitation of the propensity score in reducing confounding bias is that many confounders may be unknown or difficult or even impossible to measure.[6]

Machine Learning

Machine learning approaches problems by learning rules from data in contrast with expert systems. Starting with patient-level observations, algorithms sift through vast numbers of variables, looking for combinations that reliably predict outcomes.[7] This process in some ways resembles traditional regression models: there are outcomes, covariates, and statistical functions linking the two. Machine learning can handle enormous numbers of predictors and combine them in nonlinear and highly interactive ways. Optimism for machine learning should be tempered by understanding that association is not the same as causation and that vast biomedical data available to apply to these techniques may have insufficient breadth—lacking, for example, social determinants of health—or insufficient quality or biases that can make the results unreliable or even not valid.[8] Another limitation can be the difficulty in understanding and interpreting results because of the complexity and opacity of the model. Before they are of clinical use, machine learning models must be independently validated in prospective clinical trials in sites other than those in which the model was developed.[9]

STATISTICAL APPROACHES AND CHALLENGES

Multivariable Statistics

In many cases, researchers are interested in the effects of multiple predictor variables on an outcome. Particularly in observational studies, in which investigators cannot assign values of a predictor variable experimentally, it will be of interest to estimate the effects of a predictor variable of interest independent of the effects of other variables.[10] For example, in studying whether breastfeeding reduces a mother's risk for subsequent breast cancer, investigators would try to take differences in age, race, family history, and parity into account. Trying to stratify by all these variables would require a massive data set. Instead, multivariable models are used to enable the information about individual predictors to be summarized using the full data set.

Multiple Comparisons

Analyses in which multiple statistical tests are conducted can lead to a false conclusion that one of them is a positive result. The more tests conducted, the more likely it becomes that one will be positive based on chance alone even though the P value may be set to 0.05. One way to correct for this problem is to use the *Bonferroni correction*, which divides the P value for rejecting the null hypothesis by the number of hypothesis tests performed.[11]

Meta-analysis

Meta-analysis is a statistical method for drawing inferences from a sample of *studies* to derive a summary estimate and confidence interval for a parameter measured by the included studies. Meta-analysis allows for a formal combination of results while estimating and accommodating both the within-study and between-study variations.[12,13]

USING DATA FOR CLINICAL DECISIONS

An important and common element of the physician's role is to make decisions.[14] Effective decision making includes gathering information, determining whether more information is worth the additional risk and expense, and interpreting results. All of these tasks depend on a physician's skill in using data optimally. Information gathering begins with the most important data: those derived from a careful patient history and physical examination. However, the variety of available laboratory tests and diagnostic procedures greatly increases the amount of information that can be obtained and that must be ordered intelligently and interpreted correctly.[15] Appropriate use of clinical information can make important differences in patients' outcomes and in the resources required to optimize them.

TABLE 8-2 PRINCIPLES OF TEST ORDERING AND INTERPRETATION

The interpretation of test results depends on what is already known about the patient.
No test is perfect; clinicians should be familiar with its diagnostic performance and never believe that a test "forces" them to pursue a specific management strategy.
Tests should be ordered if they may provide *additional* information beyond that already available.
Tests should be ordered if there is a reasonable chance that the data will influence the patient's care.
Two tests that provide similar information should not be ordered.
In choosing between two tests that provide similar data, use the test that has lower costs or causes less discomfort and inconvenience to the patient.
Clinicians should seek all of the information provided by a test, not just an abnormal or normal result.
The cost-effectiveness of strategies using noninvasive tests should be considered in a manner similar to that of therapeutic strategies.

Courtesy of Thomas H. Lee, MD.

Evaluating a patient who presents with new breathlessness (Chapter 71) presents an example of decision-making principles. A thorough history and physical examination set the foundation, and a spectrum of choices are considered. Is this a temporary problem or a life-threatening condition for which immediate and potentially risky testing and treatment should be recommended? (Table 8-2) The sequence in which testing is undertaken also has implications for safety and cost. Some tests are simple and fast to perform and most helpful when results are negative; others involve substantial risk and expense but can give a definitive answer.

Theories and Principles Useful in Decision Making

Much of medical practice involves risk and uncertainty. When discussing uncertainty, the concept of *probability* is useful. Probability is the likelihood that something occurs; a probability of 1.0 means it is certain to occur, and a probability of 0 means it will not occur. The term *odds* refers to a ratio of probabilities of an event (p): Odds = p/(1 – p). If the probability of the event is 50% or 1 in 2, as in a coin flip, then odds of the event are 1 (or 1 : 1). If the probability is 1 in 3, or 0.33, then the odds are 0.33/0.66 or one half (1 : 2).

A simple yet instructive model of decision making is a 2 × 2 table (Fig. 8-1). A group (or *population)* of patients is divided into 4 cells. The table shows the presence or absence of a disease across the top and test results on the left. The cells in this 2 × 2 table are labeled with letters beginning with a in the upper left and d in the lower right. The *sensitivity* of a test, which is defined as the probability of positive results when the disease is known to be present, is calculated in the table as a/(a + c). Test *specificity*, which is the probability of a negative test result when the disease is absent, is calculated as d/(b + d). Sensitivity and specificity are referred to as *test characteristics* because they explain how a test performs in the presence or absence of disease. In clinical practice, however, tests are usually used to determine whether a disease or condition is present or absent, or at least how likely it is based on a given test result. In the 2 × 2 table, this probability, which can be calculated as a/(a + b), is referred to as the *positive predictive value*. Similarly, d/(c + d), which is the *negative predictive value* of the test, indicates how likely it is that the disease is absent given a negative test result.

Inspection of this 2 × 2 table shows another very important finding: how common the disease is in this population, shown as (a + c)/(a + b + c + d). This calculation is analogous to the *prevalence* of the disease in the population.

A special insight from this simple 2 × 2 table is that positive and negative predictive values depend on the test characteristics, but importantly they also depend on the prevalence of the disease in this particular population of patients. Different positive and negative predictive values result when the same test is used in a population in which the disease is rare compared with when it is used in a population in which the disease is common.

This insight is the essence of *Bayes theorem*: the likelihood of the disease given a positive test result depends on both the test characteristics and on the prevalence of the disease in the population. Bayes theorem is often expressed by the formula $P(A|B) = (P(B|A) * P(A))/P(B)$, (probability of disease A given test result B is the probability of result B given disease A times the probability of disease A, divided by probability of result B), but the essence of the greatest value of Bayes theorem to physicians can be understood from the simple 2 × 2 table. Bayes theorem also implies that any new information, as from a new research result, should be interpreted in the context of prior knowledge.[16]

Another useful concept is the *likelihood ratio*, which is the prevalence of a sign (or any test result) in patients with the diagnosis of interest divided by the prevalence of the identical finding (or test result) in patients without the target diagnosis. The positive likelihood ratio is expressed by the formula $P(B|A)/P(B|\bar{A})$ (or [sensitivity] ÷ [1 – specificity]) (E-Table 8-1).

Other common measures used in decision making can be derived from these simple building blocks that come from the 2 × 2 table. *Pretest probability* in the 2 × 2 model is the same as the prevalence of disease—how common it is in that population. Before doing any test, the probability of disease is simply the prevalence in that population. After performing the test, the probability may be different—the *post-test probability*—which is why and how the test can be useful.[17]

In the 2 × 2 model, a test is defined as either positive or negative. However, it may not be clear where to draw the line (or threshold) between positive and negative. Fig. 8-2 shows three possible divisions between a positive and negative test result. The vertical line on the left excludes all patients who do not have the disease, but it classifies only half of the patients with the disease as positive. The one on the right results in all patients with the disease having a positive result but at the cost of including half of the patients who do not have the disease in the positive result. The middle line achieves a compromise—most of the patients with the disease are defined as having a positive result, and most of the patients without the disease are defined as having a negative result. Which of the three lines is chosen depends on how the test is being used. A plot of all such possible lines with the sensitivity and specificity creates a curve showing how sensitivity and specificity are related for the test: a *receiver operator characteristic (ROC)* curve. Fig. 8-3 is a common way to display this relationship. An ideal test would have a curve closer to A than to B—a high sensitivity and a high specificity. ROC curves can also be used to compare the ability of different tests to distinguish between the presence or absence of disease. Tests with higher *areas under the curve* are considered better tests.

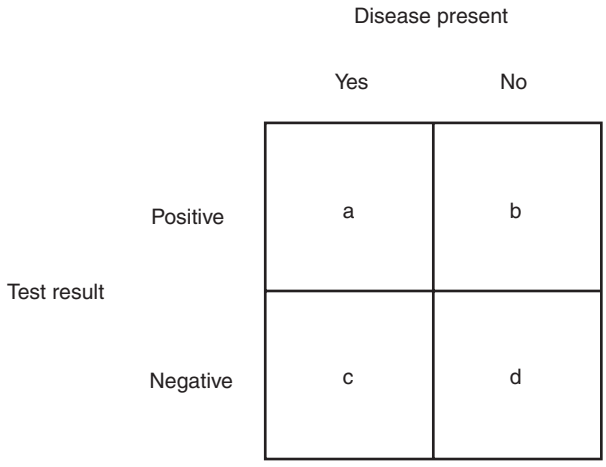

From these data, one can also calculate:

Risk ratio or relative risk (RR)	$\frac{a}{(a+b)} \div \frac{c}{c+d}$
Relative risk reduction (RRR)	1 – RR
Risk difference or absolute risk reduction (ARR)	$\frac{a}{(a+b)} - \frac{c}{(c+d)}$
Number needed to treat (NNT)	$\frac{1}{ARR}$
Odds ratio (OR)	$\frac{ad}{bc}$

FIGURE 8-1. **A 2 × 2 table evaluating use of a test to determine if a disease is present. In this model, test sensitivity is a/(a + c), specificity is d/(b + d), and disease prevalence is (a + b)/(a + b + c + d). Positive predictive value can then be calculated as a/(a + b) and negative predictive value as d/(c + d).**

E-TABLE 8-1 KEY DEFINITIONS FOR BAYES THEOREM*

Probability	A number between 0 and 1 that expresses an estimate of the likelihood of an event
Odds	The ratio of [the probability of an event] to [the probability of the event's not occurring]
BAYESIAN ANALYSIS	
Pretest (or prior) probability	The probability of a disease before the information is acquired
Post-test (or posterior) probability	The probability of a disease after new information is acquired
Pretest (or prior) odds	(Pretest probability of disease)/(1 – pretest probability of disease)
Likelihood ratio	(Probability of result in diseased persons)/(Probability of result in nondiseased persons)

*Disease can mean a condition, such as coronary artery disease, or an outcome, such as postoperative cardiac complications.

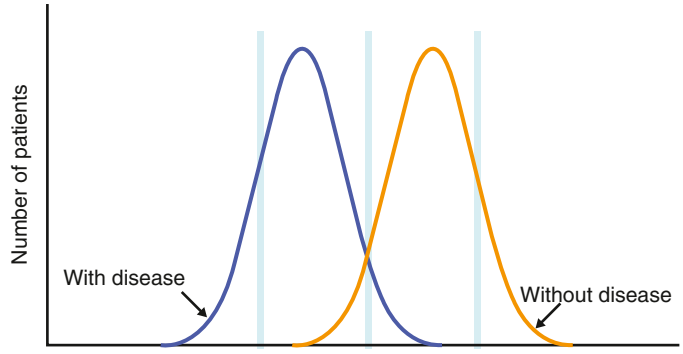

FIGURE 8-2. For each of the vertical lines, those results to the left indicate a positive result, while results on the right indicate a negative result.

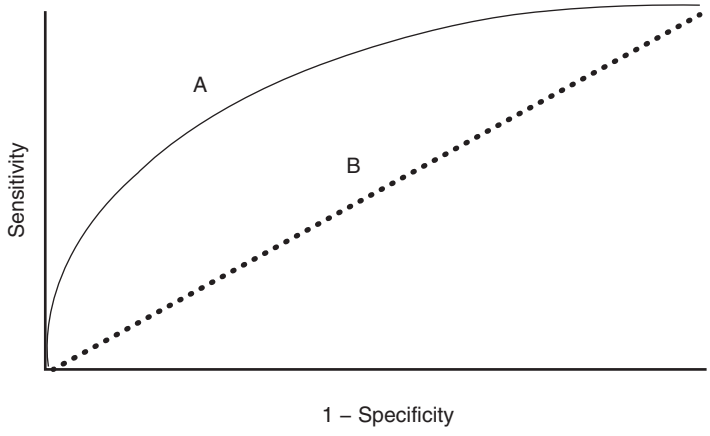

FIGURE 8-3. A receiver operator characteristic (ROC). This curve displays all the possible decision thresholds based on a test's sensitivity and specificity. The best test has very high sensitivity and specificity. In this example, A is a better test than B.

In most cases, physicians do not rely on a single test to determine whether or not a condition or disease is present. Rather, several test results and other data (which may include portions of the patient's history and findings on the physical examination), as well as findings from past records, are incorporated into that judgment. This multiplicity of information highlights one of the limitations of Bayes theorem. The results of multiple tests may not be independent of each other, but Bayes theorem assumes that they are. It is also important to be aware that it is difficult to determine the accuracy of historical and examination data—particularly if not gathered first-hand but obtained from an electronic health record, which may contain errors. Some laboratory, imaging, and pathology results may vary depending on the subjective assessment of the person who creates the report. Astute clinicians understand that data may be inaccurate or subject to differing interpretation.

When should a test be ordered? Gathering additional information—whether from history, repeated examinations, tests, or imaging—can change the likelihood of disease, as is demonstrated by the 2 × 2 table. In general terms, additional data should be obtained only if they would change the likelihood of a disease or condition at an acceptable cost and risk and if such a change in probability would affect what is recommended to the patient. "Will it change therapy?" is a common question that summarizes such thinking: Will the test lead to a diagnosis that would be treated differently? If not, then the value of the test is lower. Sometimes the most important choice is to defer further testing and to observe the patient over time—the "test of time."

Utility

The results of diagnosis and treatment vary, and the importance or value of those outcomes also varies. For example, the value of surviving may depend on quality of life and side effects endured to achieve survival. Quantifying this value can be difficult, but ultimately the most important quantification is from the patient. The term *utility* describes the value or importance of the outcome as judged by the patient or measured in some other way. In some analyses, the length of survival is adjusted by a measure of the quality of life, described as *quality-adjusted life years* or *QALYs*.[18]

DECISION-MAKING STRATEGIES

Shared Decision Making

Physicians make many decisions, some of which are simple and many of which are complex. A good physician does not make all of these decisions independently. Especially for decisions that involve risks or preferences, the wise physician involves the patient in decision making when possible. Shared decision making considers the utility of different outcomes and the patient's desires, which may vary widely from one person to the next. Shared decision making is an important element of physician-patient interaction and also has direct ties to the decision-making process.[19]

Decision Analysis

Answers to some questions involve a series of questions and probabilities that are not practical to answer with a single study or test. As a result, an approach known as *decision analysis* can be useful (E-Fig. 8-1). This analysis begins with a question, such as "should a drug be given?", which then leads to branches stemming from the yes and no answers, each of which has its own branching from what is called a chance node. Chance nodes may lead to other branches. Each chance node has several probabilities that, by definition, must add up to one. The end of each of the branches is assigned a utility. To determine, for example, if a drug should be given, the utility of each end branch is multiplied by the probability of ending on that branch, and this process is continued (or folded back) until each of the original choices is assigned a score. Using this model, the best choice is the choice with the highest score. Decision analysis can be applied to decisions in which prospective trials are impractical, such as a public health policy decision, or when a randomized controlled trial would be impractical, such as developing a strategy for screening for cervical cancer. Since probabilities assigned to some of the nodes may not be known and could plausibly be within a range, a technique known as *sensitivity analysis* can be used to determine if the key conclusions of the decision analysis model would change as the chance node probabilities change within that range. Including benefit and cost in decision analysis permits a cost-benefit (or cost-effectiveness) analysis[20] that can lead to informed decisions regarding what strategy or approach should be pursued, or whether a new technology or treatment should be adopted.

Aids to Decision Making

As the volume of text, test results, images, and genomic data rises, the limitations of human cognition often are reached. For example, most physicians are able to keep several data elements in mind when making a decision, but decision-making aids become worth considering when the number of facts to be considered rises to include a dozen or more. Some of these aids are simple *prediction rules*,[21] which can use clinical data to estimate the pretest probability of a condition. In other cases, automated systems, as simple as smartphone applications and as complex as cloud-based systems, can be helpful for diagnostic and therapeutic decision making. With progressively rising volumes of health care data and computing power, machine learning, artificial intelligence, and other analytical tools and techniques may increasingly provide additional aid to clinician decision making. Periodic modifications of decision aids and testing them using prospective (ideally randomized controlled) trials can increase their value.

To apply these concepts, consider a patient with breathlessness. Does this patient have a pulmonary embolism or some other condition? Although data derived from the history and physical examination individually have a low sensitivity, the pretest probability of pulmonary embolism (Chapter 68) can be classified as high, moderate, or low when used together to calculate a Wells score (Chapter 68). In patients so classified as having low risk, the D-dimer test has high sensitivity and therefore a high negative predictive value; as a result, a negative test reduces the risk of pulmonary embolism substantially. The D-dimer test carries a trivial risk to the patient, and its cost is low. Based on its test characteristics, a negative D-dimer result can safely exclude venous thromboembolism and limit the number of patients requiring further evaluation with imaging techniques. Conversely, in a patient with high pretest probability, a test with higher risk and expense may be warranted, such as computed tomographic pulmonary angiography, which has both a high sensitivity and a high specificity. By balancing the patient's pretest probability, as determined using a prediction rule, with a test's expenses, risks, and operating characteristics, an appropriate decision-making strategy can be developed and applied to an individual patient.

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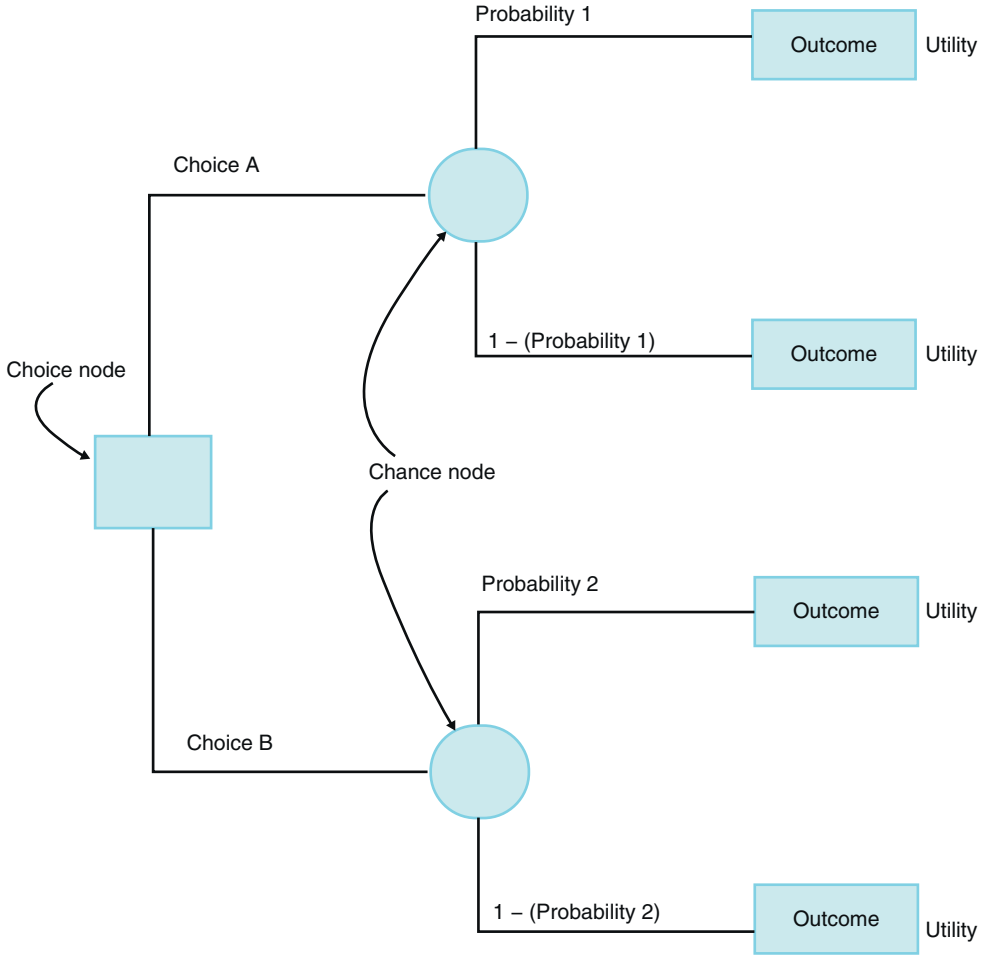

E-FIGURE 8-1. Example of decision analysis. The model begins with a choice (choice node) leading to chance nodes. The probability of branches from each choice node add up to 1. At the end of all branches is an outcome with a utility value. By "folding back" each chance node—adding probability × utility successively—a value is assigned to both choices.

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9 MEASURING HEALTH AND HEALTH CARE

CAROLYN M. CLANCY AND ERNEST MOY

Physicians routinely quantify a variety of health measures, including symptoms, vital signs, and findings on physical examination, to improve diagnosis, treatment, and prognostication. Similarly, measures of health care efficacy and quality of health care can and should be prioritized for several reasons.

First, the quality of care delivered is often suboptimal. Persistent variations in practice for patients with the same diagnosis reflect a combination of clinical uncertainty, individualized practice styles, patients' preferences and characteristics (age, race, ethnicity, education, income), and other factors. Both suboptimal care and varied care for the same condition undermine the historical assumption that a combination of highly trained health professionals and accredited facilities is sufficient to ensure consistent high-quality care.

Second, a major challenge in health care today, largely attributable to the successes of biomedical sciences, is the management of chronic disease for a population with an increasing life expectancy. For chronic conditions, health benefits are often and more appropriately measured in improvements in functional status or quality of life, rather than simply using mortality rates or life expectancy.

Third, increasing costs of health care are now threatening public budgets and investments in other social goals, such as education. Although the United States spends more per capita on health care than any other developed nation, the achieved outcomes lag far behind.

Finally, advances in communication and information technologies have inspired more people to play an active role in their health and health care. These innovations have accelerated demands for transparency and shared decision-making.

As health insurance and health care regulation have expanded, requirements to track and justify health care services have grown. Intensifying urgency to improve the quality of health care, reduce disparities, control costs, and enhance transparency will likely lead patients and insurers to demand more data and to link quality measures to payments for services.

Fortunately, modern technology can help to meet the demand for data. Patients can record and submit their health parameters using handheld devices connected to personal health records. Automated billing programs can track health care services, and electronic health records can assess the quality of physician care. Ultimately, fully integrated health information systems will allow patient information to be retrieved instantly and seamlessly whenever and wherever it is needed. For example, the Department of Veterans Affairs has substantial clinical and demographic data on veterans who receive care at their facilities. These data allowed rapid identification and outreach to at-risk groups early in the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) pandemic, so that vaccines could be targeted to patients at need without ethnic, socioeconomic, or geographic disparities.[1] In addition to assessing the quality of care today, these tools offer enormous promise for learning as a byproduct of care delivery.

HOW ARE HEALTH AND HEALTH CARE MEASURED?

Three types of measures typically assess health and health care. Measures of *health* quantify the sickness or well-being of a person. Measures of *health care quality* quantify the extent to which a patient receives needed care and does not receive unnecessary care. Health care quality is assessed using measures of *structure* (e.g., education and credentialing of clinicians), *process* (adherence to professional standards and evidence-based recommendations), and *outcomes* (or end results of care, including how patients experience their care and their self-reported health and function). Measures of *health care resources* quantify the resources used (e.g., imaging, surgery, medication, intensive care) to improve the health of a patient. All measures can be summed across populations within a practice or community (Table 9-1).

Measures of health and health care often overlap (E-Fig. 9-1). Health measures that can be improved by health care, such as blood pressure or blood glucose levels, are often used as health care quality outcome measures. The delivery of quality health care requires the use of resources and the generation of direct health care costs, which may or may not improve health care at the margins of spending. Impaired health that reduces the ability to do work and earn wages but that could have been prevented by the delivery of health care contributes to the indirect costs of health care. At the intersection of health, health care quality, and health care resources are measures of health care value. These measures compare the health benefits of specific health care services with their costs.

WHY MEASURE HEALTH AND HEALTH CARE?

Measures of health and health care can be used for many purposes by different stakeholders (Table 9-2). Patients can use their own health information to track their progress, adjust their lifestyle, and plan for their future health

TABLE 9-1 MEASURES OF HEALTH AND HEALTH CARE

MEASURES OF HEALTH

- *Mortality:* rates of death typically adjusted for age and sex
- *Morbidity:* incidence and prevalence rates of diseases and their sequelae
- *Functional status:* assessments of a patient's ability to perform various actions such as activities of daily living or instrumental activities of daily living as observed by a provider or reported by the patient
- *Self-reported health status:* a patient's assessment of his or her health and well-being

MEASURES OF HEALTH CARE QUALITY

- *Health care outcomes:* the end results or health benefits derived from good health care or the health loss attributable to poor health care
- *Health care processes:* assessments of whether the right care was delivered at the right time and in the right way
- *Health care infrastructure:* the availability of resources needed to deliver high-quality health care
- *Patient perceptions of health care:* a patient's assessment of health care received, usually emphasizing patient-provider communication and shared decision making
- *Access to health care:* the ability of patients to gain entry into health care and navigate to needed resources

MEASURES OF HEALTH CARE RESOURCES

- *Health care utilization:* the quantity of health care services that are used
- *Direct costs:* the costs of providers, supplies, and equipment needed to deliver health care
- *Indirect costs:* the costs of lost wages and decreased productivity due to illness or injury that could have been prevented by appropriate health care
- *Nonmedical costs:* the costs of health care not related to the delivery of services, such as administration, advertising, research, and profits earned by health industries

TYPE OF MEASURE	EXAMPLE
HEALTH	
Mortality	Deaths due to colorectal cancer per 100,000 population
Morbidity	New AIDS cases per 100,000 population
Functional status	% of people unable to perform one or more activities of daily living
Self-reported health status	% of people reporting that their overall health is excellent
HEALTH CARE QUALITY	
Health care outcomes	Deaths per 1000 hospitalizations with pneumonia
Intermediate outcomes	% of adults with diabetes whose blood pressure is <140/80 mm Hg
Health care processes	% of children who were given all recommended vaccinations
Health care infrastructure	% of office-based physicians with computerized systems for recording clinical notes
Patient perceptions of health care	% of patients who always reported good communication with their regular providers
Access to health care	% of patients who were unable or delayed in receiving medical care
HEALTH CARE RESOURCES	
Health care utilization	% of people with an emergency department visit in the past year
Direct costs	Expenditures for the treatment of depression
Indirect costs	Lost wages and productivity while caring for children with asthma
Nonmedical costs	Profits earned by pharmaceutical companies

ABSTRACT

Measuring health, health care quality, and health care resources is an essential dimension of contemporary health care organizations. This chapter describes the different approaches to measurement; the evidence base for those measures; and how to match available measures to the needs and interests of patients, policymakers, and other stakeholders.

KEYWORDS

health care quality
health care value
evidence-based health care

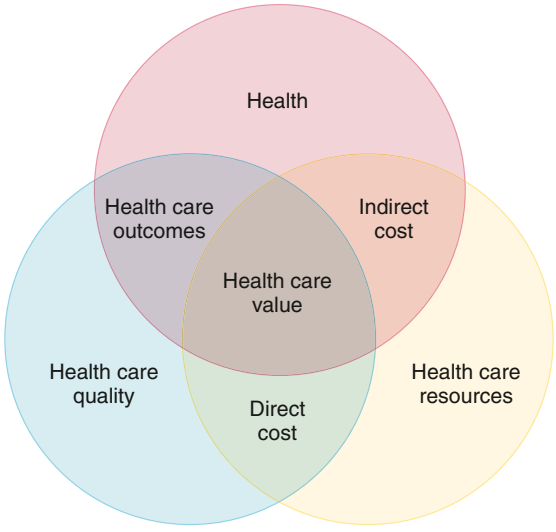

E-FIGURE 9-1. **Types of measures of health and health care.**

TABLE 9-2 USES OF HEALTH AND HEALTH CARE MEASURES BY USER AND UNIT OF ANALYSIS

	USES BY PROVIDERS	USES BY POLICYMAKERS	USES BY PATIENTS
Patient-level measures	Diagnosis and prognosis Monitoring treatment response and compliance	Identifying sentinel events	Tracking health and health needs Retirement and estate planning
Provider practice or health plan–level measures	Improving quality Improving efficiency Reducing disparities	Public reporting Paying for performance Provider credentialing	Selecting providers and health plans
Community-level measures	Selecting practice location	Resource allocation Policy evaluation	Selecting place to live

care needs. Patient-level measures are important to physicians, hospitals, health plans, and policymakers, whether they are used to identify sentinel events that represent quality defects (e.g., amputating the wrong leg or giving a patient the wrong medication), to initiate root cause analyses to improve health care quality, or to assess how quality output is linked to cost input (Chapter 10).

Hospitals and health plans aggregate measures over their practices to identify opportunities for raising quality, improving efficiency, and reducing care disparities. For measures for which physicians are primarily accountable, these data can be used to acknowledge and reward high-performing physicians, select physicians for inclusion on panels, and produce report cards to inform the public. Patients can use these report cards to select physicians and health plans that best match their health care needs. Regulators may examine measures to assess qualification for licensure and to identify physicians who might benefit from remedial instruction. Credentialing organizations may construct measures to demonstrate the superior performance of physicians who meet their high standards. For example, the National Committee for Quality Assurance maintains the Healthcare Effectiveness Data and Information Set that is widely used to accredit health plans, and the American Board of Internal Medicine and other specialty boards include measures of practice performance as well as measures of medical knowledge for the maintenance of certification. Measures that are aggregated to the community level can help policymakers allocate health care resources to locales with the greatest need and assess the success of any interventions.

SELECTING MEASURES BASED ON EVIDENCE

Data used to measure the structure, process, and outcomes of health care can be gathered as part of hypothesis-driven research, as a part of quality improvement, or from secondary sources of data initially collected for routine clinical care billing. The data's rigor and integrity are critical to the reliability of analyses performed on them.

In addition to the quality of the data themselves, however, the method of study design is also critical to the validity of reported findings. The most robust measures are supported by the concurrence of evidence derived from different research methodologies. In randomized controlled trials, random assignment of the intervention ensures that both patients who do and do not receive it are as similar as possible. In double-blind studies, neither the patient nor the patient's physician knows the assigned treatment. For more complex interventions, such as the use of a team to manage depression, blinding is impractical. In all settings, controls typically receive the best standard care. In some situations, patients may serve as their own controls in a time-series randomized trial. Adaptive designs incorporate strategies that assign more participants to treatment groups that are performing well, assign fewer participants to groups that are performing poorly, and investigate wide dose ranges to identify the most effective dose.[2] Pragmatic trials inform a clinical or policy decision by determining the usefulness of an intervention for real-world clinical practice. Noninferiority trials are designed to prove the equivalence of two strategies.[3]

Although the randomized trial is a rigorous way to assess treatment effects, enrollment is often limited to selected individuals who meet strict entry criteria. This approach enhances a trial's internal validity but limits its generalizability. As a result, randomized trials are ideal for establishing an intervention's efficacy, which is its potential benefit under ideal conditions, but not necessarily its *effectiveness* in the real world. *Cluster randomized trials*, which randomize the level of the provider or system, represent a practical approach to determining effectiveness.

Although randomized trials are critical for assessing efficacy and effectiveness, *observational* and *case-control* studies are also important. In a *cohort study*, persons or patients are followed to determine their outcomes as a function of whether or not they possess a particular attribute or have been exposed to a particular condition or intervention. Cohort studies can provide a direct estimate of the absolute risk for an outcome in exposed patients but cannot guarantee whether such differences are related to interventions that were not randomly allocated.[4]

In *case-control studies*, cases are defined based on having experienced an outcome not experienced by controls (Chapter 8). Information that is gleaned from existing records or interviews can determine the proportion of case and control patients who experienced an exposure of interest. Case-control studies can achieve the same or higher statistical power as cohort studies despite enrolling fewer subjects, so they are especially attractive for investigating uncommon outcomes, such as serious adverse effects of medications when the events are too rare to study with clinical trials or cohort studies. Case-control studies are subject to misclassification bias and recall bias, and they provide estimates of relative risk but not absolute risk.

Cross-sectional studies collect data at just one point in time. They can be used to estimate the prevalence of a condition or outcome but not to make valid inferences about whether a given outcome is related to any causal attribute or event.

There are additional methodologic issues beyond the credibility and quality of the source of data for quality measures. When presented with reports suggesting less-than-perfect performance, many physicians believe that their patients are sicker or are less likely to adhere to treatment recommendations. To address these concerns, risk adjustment for severity of illness, accurate identification of patient characteristics, and assessment of outcomes over time are all critical. Case-mix adjustment methods commonly use sophisticated statistical approaches (Chapter 8) in an attempt to adjust for such potential differences and to estimate whether observed differences result from differing patient populations rather than true differences in quality of care.[5]

The precision of specific measures is also a challenge. Many stakeholders, especially payers and policymakers, are increasingly impatient and are generally more enthusiastic about the use of measures that are only "pretty good" than are providers whose care is being judged.

SELECTING MEASURES: WHICH MEASURES ARE RIGHT FOR WHAT PURPOSE?

Creating measures is different from selecting which measures are most important and meaningful. Numerous publicly available sources provide a wealth of health and health care information (E-Table 9-1). The most prominent consensus-based organization that endorses measures is the National Quality Forum, which convenes panels of experts to assess the quality of a proposed measure based on criteria that include importance, scientific acceptability, feasibility, and usability. Endorsed measures are reassessed periodically to ensure they remain up-to-date and applicable.

The National Institutes of Health Patient Reported Outcomes Measurement Information System (http://www.nihpromis.org) is a repository of standardized patient-reported health status measures and collection instruments. Domains include physical, mental, and social well-being. The Agency for Healthcare Research and Quality National Quality Measures Clearinghouse (http://www.qualitymeasures.ahrq.gov) is an inventory of evidence-based measures of health care quality. Domains include clinical quality, efficiency,

E-TABLE 9-1 EXAMPLES OF PUBLICLY AVAILABLE SOURCES OF SECONDARY DATA

FEDERAL AGENCIES

Agency for Health Care Research and Quality (AHRQ): http://www.ahrq.gov
- Healthcare Cost and Utilization Project—the largest collection of longitudinal hospital care data in the United States, with all-payer, encounter-level information beginning in 1988: http://www.hcup-us.ahrq.gov/
- Medical Expenditure Panel Survey (MEPS)—a set of large-scale surveys of U.S. families and individuals, medical providers, and employers: http://meps.ahrq.gov/mepsweb
- National CAHPS benchmarking database—the national repository for data from the CAHPS family of surveys: https://cahpsdatabase.ahrq.gov
- National Healthcare Quality and Disparities Reports—the database of the National Reports including the State Snapshots and NHQR/DR query tool: http://nhqrnet.ahrq.gov/inhqrdr/

Centers for Disease Control and Prevention (CDC): https://www.cdc.gov
- CDC Wonder: https://wonder.cdc.gov
- DATA2020—the Healthy People 2020 interactive data tool that allows users to explore the data and technical information related to the Healthy People 2020 objectives: https://www.healthypeople.gov/2020/data-search/

Centers for Medicare and Medicaid Services (CMS): http://www.cms.gov/
- A family of consumer-oriented websites that provide information on quality of care delivered in various settings:
- Dialysis Facility Compare: http://www.medicare.gov/DialysisFacilityCompare/search.html
- Home Health Compare: http://www.medicare.gov/homehealthcompare/search.html
- Hospital Compare: http://www.medicare.gov/hospitalcompare/search.html
- Nursing Home Compare: http://www.medicare.gov/nursinghomecompare/search.html

Indian Health Service: http://www.ihs.gov

U.S. Census Bureau American Fact Finder: http://factfinder2.census.gov/faces/nav/jsf/pages/index.xhtml

Cancer Data from the National Cancer Institute SEER program: http://seer.cancer.gov

Department of Veterans Affairs: ASPIRE is a web-based dashboard that documents quality and safety goals for all VA hospitals. These data show strengths and opportunities for improvement at the national, regional, and local hospital level. The data are updated regularly.
- ASPIRE: http://www.hospitalcompare.va.gov/HOSPITALCOMPARE/aspire/index.asp

PRIVATE, NONPROFIT ORGANIZATIONS

Commonwealth Foundation/IPRO Why Not the Best?—measures of hospital quality that are publicly reported by Centers for Medicare and Medicaid Services: http://www.whynotthebest.org

National Quality Forum (NQF) Quality Positioning System—inventory of quality measures endorsed by NQF: http://www.qualityforum.org/QPS/QPSTool.aspx

The Joint Commission Quality Check—provides hospital-specific quality data from a variety of sources, including Joint Commission core measures (ORYX): http://www.qualitycheck.org/consumer/searchQCR.aspx

TABLE 9-3 ATTRIBUTES OF MEASURES OF HEALTH AND HEALTH CARE

MEASURE ATTRIBUTES	CRITERIA FOR PROVIDERS	CRITERIA FOR POLICYMAKERS	CRITERIA FOR PATIENTS
Measure is scientifically sound			
Based on strong evidence	Based on high-quality studies?		
Valid	Measures what is intended and includes key elements?		
Reliable	Reproducible by different measurers and providers?		
Clearly specified	Numerator, denominator, exclusions, and risk adjustment defined?		
Endorsed by independent experts	Well-accepted by scientific and medical communities?		
Condition is important			
Affects many people Causes high mortality or morbidity Is costly Is very unequal across populations	Important for my practice or the population I serve?	Important for population that will be affected by my policy?	Important to me?
Data collection is feasible			
Already available Could be collected at low cost relative to potential benefit Auditable	Available for my practice or the population I serve?	Available before and after policy implementation for affected population?	Available to me?
Findings are actionable			
Can be understood Can be improved Have been used successfully Have few unintended consequences	Do I know what actions I must change to improve quality? Used in practices like mine to improve quality with few unintended consequences?	Do I know what policies I must change to improve quality? Used for policies like mine to improve quality with few unintended consequences?	Do I know what actions I must take to improve my health? Used by patients like me to improve health with few unintended consequences?
When used as part of measure set, measures are:	Represents multiple conditions, settings of care, populations, types of data (survey, administrative data, medical records), types of measures (structure, process, outcomes), and perspectives (patient, provider, system, society) as appropriate?		
Balanced Able to be disaggregated	Identifies individual measures that can be improved?		

and population health. Also related are the National Guidelines Clearinghouse (http://www.guideline.gov) and the Health Care Innovations Exchange (http://www.innovations.ahrq.gov), collections of clinical guidelines and descriptions of successful uses of measures, respectively.

Potential users should examine the attributes of specific measures to ensure that they are appropriate for their intended application (Table 9-3) and can measure change reliably and validly.[6] A number of organizations have developed scales or rating systems that summarize performance across multiple dimensions. Sometimes referred to as composite measures (e.g., a letter grade from the Leapfrog Group for hospital safety), these scales vary in comprehensiveness with little consensus regarding how components of a summary scale should be weighted. Indeed, it is not uncommon for a hospital to receive an "F" from one group and be rated a "top performer" by another. Thus, although appealing in their simplicity, the optimal use of these approaches remains unresolved.

MEASURING HEALTH AND HEALTH CARE AS PARTS OF A SYSTEM

Measuring health and health care together is also important for understanding the system as a whole. Patients, providers, and policymakers generally agree that the paramount goal of the health system is to improve health. At the population health level, however, factors other than medical care are highly influential. For example, population health is affected as much by health behaviors—such as diet, physical activity, smoking, and alcohol and drug use—as by the direct provision of medical care. Social characteristics (e.g., poverty, education, crime, and residential segregation) and physical determinants (e.g., housing and the natural and built environment) also impact population health to a greater extent than medical care (Chapter 4). Discrimination and bias have adverse effects on population health, including structural racism in social policies, such as housing and education, and algorithmic biases in clinical decision-support tools that may advantage some groups over others.[7] These issues must be addressed locally and systematically to enable all patients to derive maximal benefit from medical care and to achieve health equity. Explicitly measuring and rewarding equitable care is one component of achieving excellent care for all patients.[8,9]

Viewing medical care as a component of a system for generating and preserving population health has many implications for physicians and other health care providers. First, it emphasizes the importance of services to encourage healthy lifestyles and prevent the development of disease. For example, efforts to prevent tobacco use (Chapter 363) among adolescents (Chapter 21) may yield greater population health benefits than treating the complications of nicotine addiction later in life. Second, it serves as a reminder that patients who seek care have widely varying attributes and resources, factors that may affect their ability to comply with treatment recommendations. As a consequence, it may be important to consider medications with lower out-of-pocket costs for low-income patients and to simplify instructions to a patient's level of health literacy. Third, it recognizes how environmental factors outside of the control of physicians often have a large impact on population health. When health care measures are used to assess quality, adjustment for these factors is critical to ensure that comparisons are not biased. Fourth, it stresses the need for a culturally competent, diverse, and inclusive provider workforce. For example, in a randomized controlled trial, Black men were more likely to opt for indicated preventive services after consultation with a Black male doctor than with a non-Black male doctor.[10]

The SARS-CoV-2 pandemic has emphasized the relevance of telehealth for quality of care,[11] especially for a geographically dispersed population. However, telehealth also has the potential to worsen disparities because of differential access to and comfort with suitable devices.[12] In the Department of Veterans Affairs health care system, for example, explicit attention to the digital divide enabled rapid substitution of virtual care for in-clinic care with few disparities so that veterans with lower income, higher disability, and more chronic conditions were equally likely to receive virtual care during the pandemic.[13]

Another virtue of measuring health and health care together is to assess the value of components of the health system or the health system as a whole. U.S. national health expenditures have increased over 100 times from $27 billion (5.0% of the gross domestic product) in 1960 to $3.2 trillion in 2015 (17.8% of the gross domestic product) (Fig. 9-1). They are projected to exceed $5.5 trillion in 2025 and account for 20% of the gross domestic product. Expenditures on hospital care, physician and clinical services, prescription drugs, and the administration of health insurance account for 70% of total national health expenditures. Payers and employers can examine the cost-effectiveness of specific services and promote those that yield the largest health benefits for each dollar spent. U.S. health care processes rank much higher than health outcomes, despite the world's highest health care expenditures. In the United States the differential between the world's highest per capita expenditures but only the 46th longest life expectancy is in part because social conditions, such as poverty and lack of health insurance, may prevent even excellent medical care from achieving the best health outcomes.[14]

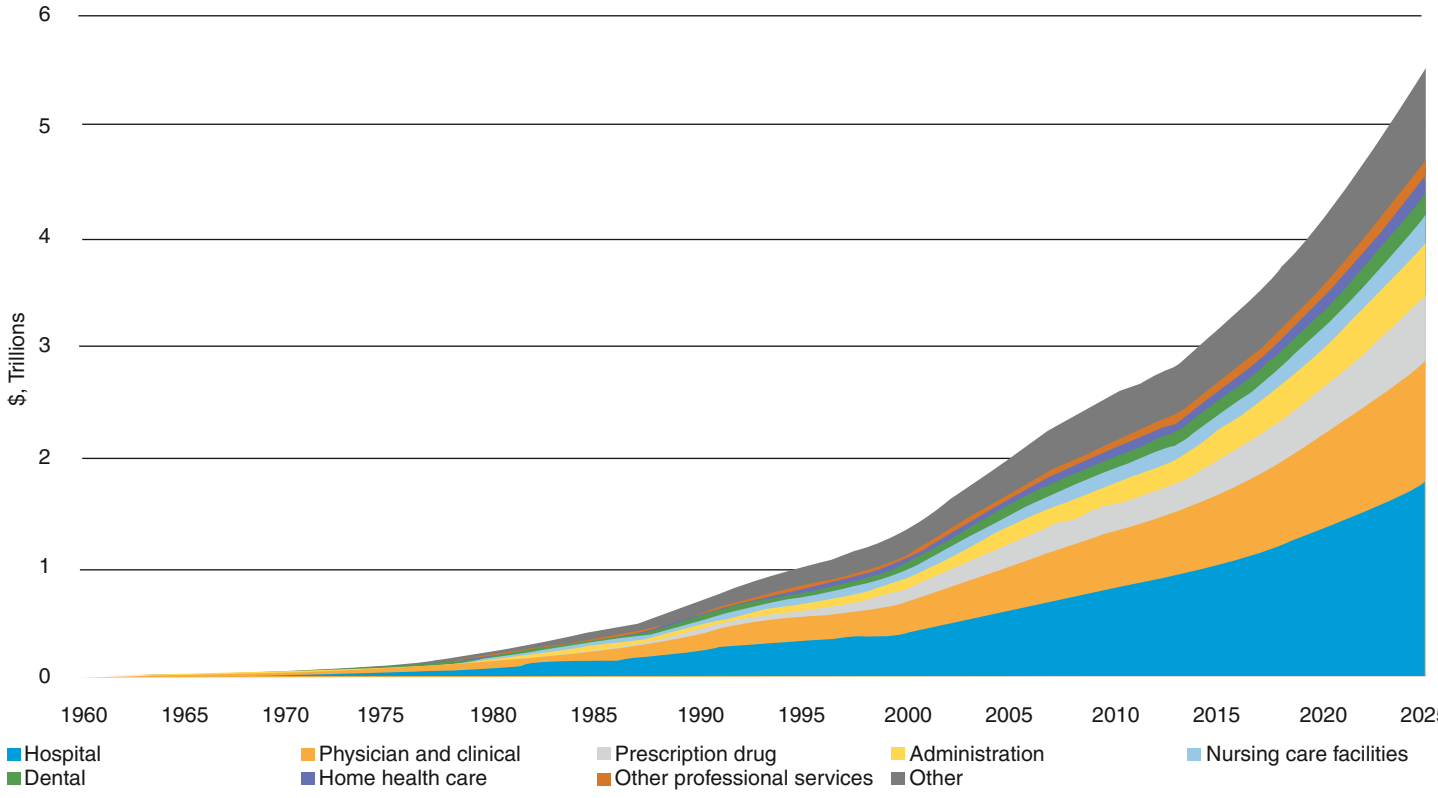

FIGURE 9-1. National health expenditures by select components, 1960-2025. Estimates for 1960-2015 are based on historical data; estimates for 2016-2025 are projections. Expenditures do not adjust for inflation. Administration includes health insurance expenditures other than health benefits paid as well as administration of government programs. (Source: CMS National Health Expenditure Data, https://www.cms.gov/Research-Statistics-Data-and-Systems/Statistics-Trends-and-Reports/NationalHealthExpendData/index.html. Accessed May 10, 2019.)

Physicians also have a critical role in ensuring that health resources are allocated wisely.[15] Unfortunately, about one third of U.S. health care expenditures probably do not improve health. As just one example, about 10% of patients in intensive care units are identified by critical care specialists as receiving clearly futile care. Physicians commonly overestimate the benefits and underestimate the harms of screening, tests, and treatments. As a result, unnecessary tests or procedures add to costs and can also increase morbidity or even mortality. Attempts to reduce such unnecessary and even harmful medical care must, of course, be balanced by being sure that potentially beneficial care is not reduced.

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10 QUALITY, SAFETY, AND VALUE

ROBERT M. WACHTER AND KAVEH G. SHOJANIA

Scores of studies demonstrate that the quality and safety of modern health care leave much to be desired, despite the fact that most physicians are well trained and work very hard. Undeniable evidence clearly documents stunning variations in patterns of care that are neither supported by evidence nor justified by outcomes, major gaps between the scientific evidence and its application in clinical practice, and staggering numbers of serious medical errors. The recognition of these quality and safety problems has catalyzed major transformations in thinking and practice, with new technologies, regulations, training models, incentive systems, and more.

To appreciate the problem and address it requires an understanding of quality measurement and improvement, the safety of patients, and value, which is the confluence of safety, quality, and cost.

QUALITY

DEFINITION

The National Academy of Medicine has defined quality of care in terms of "the degree to which health services for individuals and populations increase the likelihood of desired health outcomes and are consistent with current professional knowledge." It also identified six distinct dimensions of quality (Table 10-1). Estimates that 44,000 to 98,000 Americans died each year from medical error—the equivalent of a jumbo jet crashing every day and a half—meant patient safety received most of the initial attention,[1] even if many of these preventable deaths may occur in very sick patients with less than a 3-month life expectancy. Attention to other dimensions of effectiveness, efficiency, and patient-centeredness has subsequently followed, with a significant subsequent decline in adverse inpatient events.[2] Nevertheless, adverse events are noted in about 25% of inpatient admissions, about one fourth of which are preventable,[3] and in about 2% of emergency department visits.[4] The lesser attention paid to equity over the past two decades has changed as a result of the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) pandemic and support for antiracism movements, both of which have highlighted long-standing disparities (Chapter 4) in health care and health outcomes by race and other socioeconomic factors.[5] The climate crisis (Chapter 17) also threatens to exacerbate existing disparities.

Historically, the lack of clinical evidence and the apprenticeship model of medical training promoted an idiosyncratic practice style by which a senior clinician or a marquee medical center determined the standard of care—a tradition now sometimes termed *eminence-based medicine*. Without discounting the value of experience and mature clinical judgment, the modern paradigm for determining optimal practice has changed, driven by the explosion in clinical research during the past 30 years. For example, the number of clinical trials registered on clinicaltrials.gov grew from about 2000 in the year 2000 to more than 360,000 in 2020. This research has helped define "best practices" in many areas of medicine, from preventive strategies for a healthy 62-year-old

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A L G r a w a n y

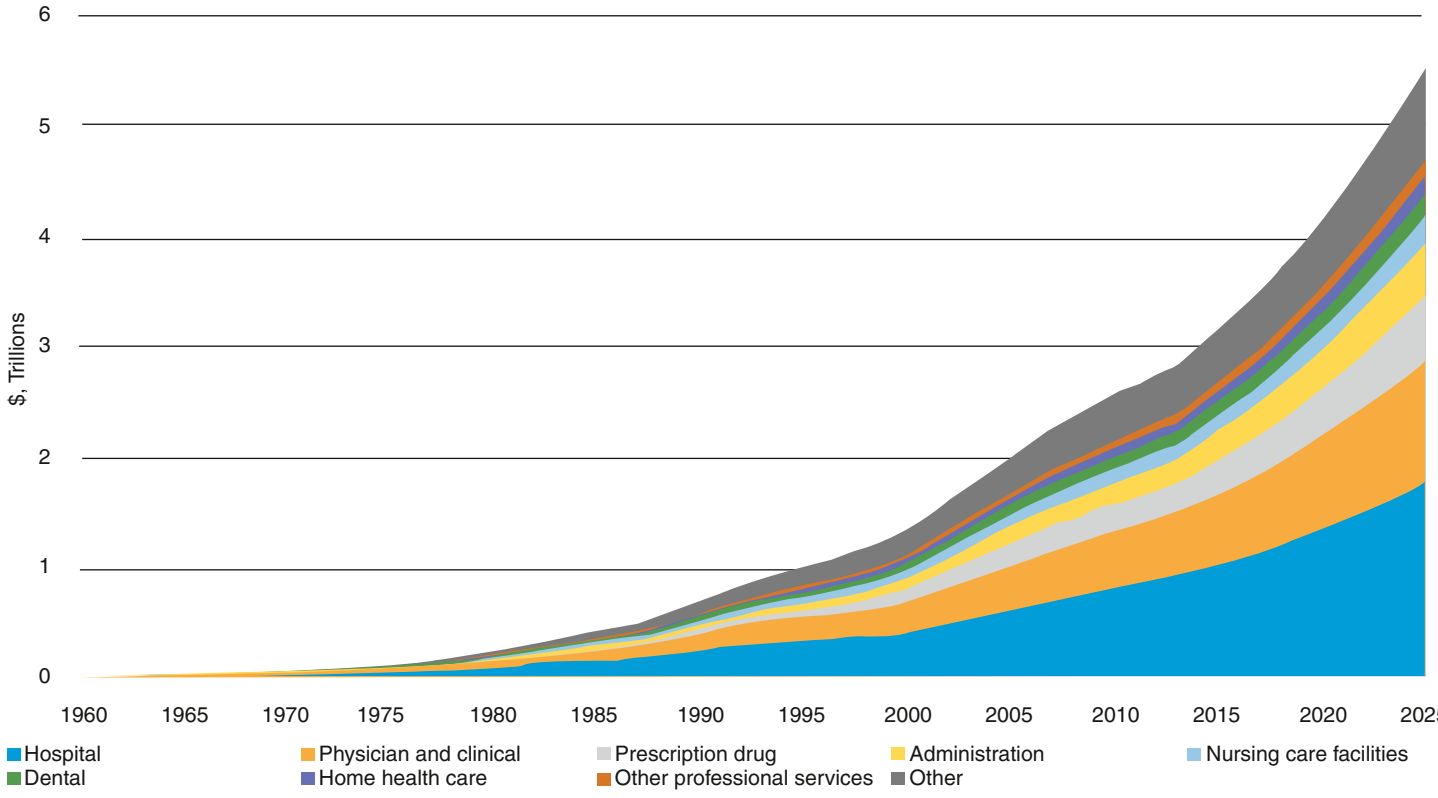

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Physicians also have a critical role in ensuring that health resources are allocated wisely.[15] Unfortunately, about one third of U.S. health care expenditures probably do not improve health. As just one example, about 10% of patients in intensive care units are identified by critical care specialists as receiving clearly futile care. Physicians commonly overestimate the benefits and underestimate the harms of screening, tests, and treatments. As a result, unnecessary tests or procedures add to costs and can also increase morbidity or even mortality. Attempts to reduce such unnecessary and even harmful medical care must, of course, be balanced by being sure that potentially beneficial care is not reduced.

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10 QUALITY, SAFETY, AND VALUE

ROBERT M. WACHTER AND KAVEH G. SHOJANIA

Scores of studies demonstrate that the quality and safety of modern health care leave much to be desired, despite the fact that most physicians are well trained and work very hard. Undeniable evidence clearly documents stunning variations in patterns of care that are neither supported by evidence nor justified by outcomes, major gaps between the scientific evidence and its application in clinical practice, and staggering numbers of serious medical errors. The recognition of these quality and safety problems has catalyzed major transformations in thinking and practice, with new technologies, regulations, training models, incentive systems, and more.

To appreciate the problem and address it requires an understanding of quality measurement and improvement, the safety of patients, and value, which is the confluence of safety, quality, and cost.

QUALITY

DEFINITION

The National Academy of Medicine has defined quality of care in terms of "the degree to which health services for individuals and populations increase the likelihood of desired health outcomes and are consistent with current professional knowledge." It also identified six distinct dimensions of quality (Table 10-1). Estimates that 44,000 to 98,000 Americans died each year from medical error—the equivalent of a jumbo jet crashing every day and a half—meant patient safety received most of the initial attention,[1] even if many of these preventable deaths may occur in very sick patients with less than a 3-month life expectancy. Attention to other dimensions of effectiveness, efficiency, and patient-centeredness has subsequently followed, with a significant subsequent decline in adverse inpatient events.[2] Nevertheless, adverse events are noted in about 25% of inpatient admissions, about one fourth of which are preventable,[3] and in about 2% of emergency department visits.[4] The lesser attention paid to equity over the past two decades has changed as a result of the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) pandemic and support for antiracism movements, both of which have highlighted long-standing disparities (Chapter 4) in health care and health outcomes by race and other socioeconomic factors.[5] The climate crisis (Chapter 17) also threatens to exacerbate existing disparities.

Historically, the lack of clinical evidence and the apprenticeship model of medical training promoted an idiosyncratic practice style by which a senior clinician or a marquee medical center determined the standard of care—a tradition now sometimes termed *eminence-based medicine*. Without discounting the value of experience and mature clinical judgment, the modern paradigm for determining optimal practice has changed, driven by the explosion in clinical research during the past 30 years. For example, the number of clinical trials registered on clinicaltrials.gov grew from about 2000 in the year 2000 to more than 360,000 in 2020. This research has helped define "best practices" in many areas of medicine, from preventive strategies for a healthy 62-year-old

ABSTRACT

The goal of medicine is to deliver care that is high quality, safe, timely, equitable, and patient-centered and to do so at the lowest possible cost. Studies over the past generation have demonstrated important gaps in all of these areas. In response to these gaps, increasing emphasis is being placed on implementing strategies—at both the individual clinician and the system level—to improve quality, safety, and health care value. Such strategies tend to emphasize a systems approach to improvement, teamwork, and learning from mistakes and quality gaps, in part by taking advantage of technology and tools such as electronic health records. The policy and payment environments also play important roles in creating appropriate accountabilities and incentives for both clinicians and health care systems to emphasize care improvement as a core activity and an imperative.

KEYWORDS

quality of care
patient safety
clinical informatics
health care value
organization of care
outcomes
safety culture

TABLE 10-1 THE INSTITUTE OF MEDICINE'S SIX QUALITY AIMS

Patient safety	Avoiding harm from medical care
Patient centeredness	Providing care that respects and responds to an individual patient's preferences, needs, and values
Effectiveness	Providing evidence-based care
Efficiency	Avoiding waste
Timeliness	Reducing waits and harmful delays
Equity	Care that does not vary in quality because of gender, ethnicity, geographic location, or socioeconomic status

From Committee on Quality of Health Care in America, Institute of Medicine. *Crossing the Quality Chasm: A New Health System for the 21st Century*. Washington, DC: National Academy Press; 2001.

outpatient (Chapter 12) to the treatment of a patient with acute myocardial infarction and cardiogenic shock (Chapters 58 and 93).

The Donabedian triad, which divides quality measures into *structure* (how care is organized), *process* (what is done), and *outcomes* (what happens to the patient), remains the most popular construct for quality measurement. Each element of the triad has important advantages and disadvantages (Table 10-2). Many widely used quality indicators are process measures for which clinical research has established a link between such processes and improved outcomes. An example is the rate at which aspirin or a β-blocker is given to survivors of a myocardial infarction before hospital discharge (Chapter 58). However, when processes are less relevant and the science of case-mix adjustment is suitably advanced (e.g., cardiac bypass surgery; Chapter 59), outcome measurement (e.g., risk-adjusted mortality rate or 30-day readmission rate) is increasingly used. In other areas involving complex processes, structural measures are used as proxies for quality; examples here include the presence of intensivists to staff critical care units, a dedicated stroke service, and computerized physician order entry systems. Nevertheless, outcomes remain the key issue for patients and payers, so some experts advocate greater emphasis on outcome-based measurements.

THE EPIDEMIOLOGY OF QUALITY-RELATED PROBLEMS

It is now well established that there are large and clinically indefensible variations in care from one city or region to another. Furthermore, U.S. practice achieves guideline-based targets for controlling common chronic conditions, such as diabetes and hypertension, for only about 50% of patients.[6,7]

LEVERS FOR CHANGE

For physicians, policymakers, administrators, and patients, evidence of major problems with quality has led to the recognition of structural problems that prevent the delivery of the highest quality of care. These problems include the lack of information regarding the performance of a provider or institution, the absence of incentives for quality improvement, the challenge for practicing physicians to stay abreast of modern evidence-based medicine, and the absence of an information technology support system for quality.

The first step in quality improvement is the creation of practice standards against which to measure quality. Scores of such measures have been promulgated by a variety of organizations, including payers (such as the Centers for Medicare and Medicaid Services), accreditors (such as The Joint Commission), and medical societies. These measures have identified many opportunities for improvement among individual physicians, practices, and hospitals.

Given the volume of new literature published each year, individual physicians cannot keep up with all the evidence-based advances in their fields. *Practice guidelines*, such as those for the treatment of community-acquired pneumonia (Chapter 85) or the prophylaxis of deep venous thrombosis (Chapter 68), aim to synthesize evidence-based best practices into a set of summary recommendations. Although concerns about "cookbook medicine" linger, there is a growing consensus that best practices should be "hard wired" if possible. The major challenges are to update guidelines as new knowledge accumulates and to recognize the complexity of guidelines when patients have multiple, potentially overlapping illnesses. *Clinical pathways* are similar to guidelines but attempt to codify a series of steps, usually temporally (on day 1, do the following; on day 2, do the following; and so forth), making them more useful for stereotypical processes such as the postoperative management of patients after hip replacement. As more health care delivery organizations become computerized, pathways and guidelines are often translated into *order sets* or *clinical decision support systems* to guide clinicians at the point of care.

TABLE 10-2 COMPARISON OF THREE MEASURES OF CLINICAL QUALITY: THE DONABEDIAN TRIAD

MEASURE	SIMPLE DEFINITION	ADVANTAGES	DISADVANTAGES
Structure	How was care organized?	May be highly relevant in a complex health system	May fail to capture the quality of care by individual physicians Difficult to determine the "gold standard"
Process	What was done?	More easily measured and acted on than outcomes May not require case-mix adjustment No time lag—can be measured when care is provided May directly reflect quality (if carefully chosen)	A proxy for outcomes Not all may agree on "gold standard" processes May promote "cookbook" medicine, especially if physicians and health systems try to "game" their performance
Outcomes	What happened to the patient?	What we really care about	May take years to occur May reflect patient factors more than quality of care Requires case-mix and other adjustment to prevent "apples-to-oranges" comparisons

Modified from Donabedian A. The quality of care. How can it be assessed? *JAMA*. 1988;270:1743-1748; and Shojania KG, Showstack J, Wachter R. Assessing hospital quality: a review for clinicians. *Eff Clin Pract*. 2001;4:82-90.

Although professionalism (Chapter 1) should be a sufficient incentive for physicians to provide high-quality care, physicians are only human. Momentary lapses in attention can lead to forgetting to check for allergies before prescribing medications or ensuring a new inpatient's order is entered into the correct patient's record. Emotions can also play a role. Disruptive patients may induce doctors to make more errors,[A1] and rudeness from colleagues can degrade the performance of entire teams.

As a result, the reliable delivery of high-quality care depends on creating systems and organizational cultures that reduce predictable problems in human performance. Such systems require significant investments in educating physicians, hiring case managers or clinical pharmacists, building digital capacity, and developing guidelines. The historical payment model in the United States, which compensates physicians and hospitals on the basis of volume rather than quality, provides no incentive to make the requisite investments, but this situation is changing.

THE CHANGING ENVIRONMENT FOR QUALITY

The recognition of major gaps in quality and of the need for systemic change to improve quality has led to a variety of initiatives to catalyze improvements. Virtually all involve several steps: defining reasonable quality measures (evidence-based measures; capturing appropriate structures, process, or outcomes), measuring the performance of providers or systems, and using these results to promote change. This final imperative creates the greatest degree of uncertainty and experimentation.

Although one might hope that simply giving a physician information about prior performance would generate meaningful improvement, this strategy yields only modest change at best. Increasingly, a more aggressive and transparent strategy, such as disseminating the results of quality measurement to key stakeholders, is being adopted. In some cases, simple transparency is the main strategy—the rationale being that providers will find the exposure of their gaps in quality to be sufficiently concerning or embarrassing to motivate improvement. Although there is little evidence that patients use such data to choose among physicians or hospitals, transparency itself has frequently resulted in impressive improvements in some publicly reported quality measures.

Some health systems have tried to improve quality by linking payments to achieving specific performance targets (pay for performance, or P4P). These P4P programs have produced surprisingly modest gains beyond the improvements achieved by simple transparency.[8] P4P also raises a host of concerns, including whether presently captured quality data are accurate,

whether payments should go to the best performers or those with the greatest improvements, whether existing measures adequately measure quality in patients with complex diseases, and whether P4P will create undue focus on certain measurable practices, leading to relative inattention to other important processes that are not being compensated. Another concern is that an overemphasis on "extrinsic" motivation (i.e., bonus payments) can actually extinguish "intrinsic" motivation (i.e., professionalism). The loss of improvements after removal of performance payments reaffirms this concern.[9] One variation on the P4P theme is Medicare's "no pay for adverse events" program, in which hospital payments are withheld for certain "preventable" adverse events, such as injuries from falls or health care–associated infections. As with P4P more generally, the impact of such programs on quality and safety has been surprisingly modest.

QUALITY IMPROVEMENT STRATEGIES

Whether the motivation is professionalism, embarrassment, or economics, the next question is how actually to improve the quality of care. There is no simple answer; successful institutions and physicians have used a variety of strategies. In general, most use a variation of a "plan, do, study, act" cycle, recognizing that quality improvement activities must be carefully planned and implemented, that their impact needs to be measured, and that the results of these activities often fall short and require iterative refinement.

"Plan, do, study, act" cycles can also optimize "off-the-shelf" interventions, such as computerized decision support systems and performance report cards, in which performance data are fed back to individual providers or teams ("audit and feedback").[A2] In some randomized trials, such interventions have shown dramatic improvements,[A3] but others have been disappointingly negative.[A4] As a result, meta-analyses of randomized trials evaluating these interventions over a range of quality measures show only small average gains in the percentages of patients who receive recommended care.[A5]

For quality improvement practices that require predictable repetition, efforts to "hard wire" the practice or to use alternative providers who focus on the activity are often beneficial. For example, the best strategy to increase the rate of pneumococcal vaccination (Chapter 15) among hospitalized patients with pneumonia is to embed it in a standard order set, either paper-based or computerized. Another example: having a nurse remove patients' shoes before the physician's entry can increase rates of diabetic foot examinations in an outpatient practice (Chapter 210). Now that the vast majority of hospitals and office practices have electronic health records, it has become easier to measure performance, to deliver real-time feedback to providers, and to "hard wire" evidence-based practices into clinicians' workflow.

Nevertheless, electronic health records also produce workflow problems of their own by generating as much as 5 hours of record keeping for every 8 hours of scheduled clinical time.[10] Electronic alerts are often inappropriate and can generate "alert fatigue" among clinicians.[11] More generally, a lesson of the last two decades is that improvement interventions can cause harms. In one noteworthy example, transition support and self-management tools for patients hospitalized with chronic obstructive pulmonary disease (COPD) were associated with significantly greater COPD-related hospitalizations and emergency department visits, without improvements in quality of life.[A6]

More complex and interdependent clinical situations pose even greater challenges for quality improvement. In these circumstances, bringing teams together to examine their practices and learn from each other can augment the applications of tools such as "plan, do, study, act" cycles. Many organizations have also adopted more sophisticated methodologies, such as Lean or Six Sigma, which involve mapping out all of the steps of a complex process (e.g., hospital discharge) in an attempt to reduce waste and imperfections in care. For a hospital or outpatient practice, the precise methodology chosen is probably less important than the decision to adopt a systematic approach to analyze complex processes and to identify potential opportunities for improvement.

PATIENT SAFETY

EPIDEMIOLOGY

The definition of quality includes safety, but it is sometimes important to emphasize safety per se. The millennia-old concept of "first, do no harm" further adds to the justification for giving special attention to safety.

This age-old interest in avoiding harm historically manifested itself in the form of periodic forums, such as morbidity and mortality conferences, to discuss errors. Now, however, there is a recognition of the need to teach about the nature of medical mistakes, invest in safety research, regulate safety standards, and emphasize safety improvements.

This emphasis is driven by a startling reality: 5 to 10% of hospitalized patients and 2 to 3% of ambulatory patients suffer preventable harm from their medical care.[12] These harms can result from medication errors, gaps in the discharge process, communication problems in intensive care units, or retained sponges in surgical patients—in short, virtually every aspect of modern medical care. Moreover, detailed clinical and statistical evidence of suboptimal safety has been reinforced by several high-profile and disquieting errors, sometimes apparently related to inadequate supervision and prolonged duty hours of trainees. These errors include the wrong patient undergoing a major procedure, the wrong limb being operated on, chemotherapy overdoses, mistaken mastectomies, and more. In the past few years, new classes of errors have emerged because of poorly designed health care information systems. In addition, increasing attention is focusing on areas that were previously underemphasized, such as diagnostic errors. Of note is that about 1% of all physicians account for 32% of malpractice claims paid nationally.

Because patients may be harmed despite receiving perfect care (i.e., from an accepted complication of surgery or a side effect of medication), it is important to separate *adverse events* from *errors*. The patient safety literature commonly defines an error as "an act or omission that leads to an unanticipated, undesirable outcome or to substantial potential for such an outcome." Adverse events, in contrast, are injuries due to medical management rather than the patient's underlying illness. This distinction is crucial. For example, when a patient who was appropriately prescribed vancomycin for a serious methicillin-resistant staphylococcal infection develops kidney injury despite a therapeutic serum level, an adverse event, not a medical error, has occurred. Conversely, if the serum level of antibiotic was supratherapeutic because the patient had simultaneously been given other nephrotoxic agents, then a medical error would have occurred.

THE MODERN APPROACH TO PATIENT SAFETY

The historical approach to medical errors often has been to blame the clinician who was most proximate: whoever performed the surgery, hung the intravenous medication, or mixed the chemotherapy. It is now recognized that this approach fails to appreciate that most errors are committed by hardworking, well-trained individuals, and such errors are unlikely to be prevented by admonishing people to be more careful or by shaming and suing them. Instead, the modern approach, known as *systems thinking*, holds that humans will inevitably err and that safety depends on creating systems that anticipate errors and either prevent or catch them before they cause harm. Such an approach has been the cornerstone of safety improvements in other high-risk industries for some time.

The "Swiss cheese" model of accidents, drawn from innumerable investigations of accidents in commercial aviation and the nuclear power industry, for example, emphasizes that single errors by one individual working in an otherwise safety-conscious system rarely cause harm. Instead, such errors must penetrate multiple incomplete layers of protection ("layers of Swiss cheese") to cause terrible harm. The lesson is to focus not on the futile goal of trying to perfect human behavior, but rather on creating multiple overlapping layers of protection to decrease the probability that the holes in the Swiss cheese will ever align, allowing an error to slip through.

HOW TO IMPROVE PATIENT SAFETY

Drawing on these models, modern thinking emphasizes efforts to design and implement systems to prevent or catch errors. For example, errors in routine behaviors can best be prevented by building in redundancies and crosschecks in the form of checklists, read-backs, and other standardized safety procedures, such as counting sponges in the operating room, signing a surgical site before an operation, or asking patients their names before administering a medication. The use of checklists for the placement of central lines and to prepare patients for surgery has produced some remarkable reductions in morbidity and mortality. Yet even this obvious intervention has shown inconsistent benefit across studies.[13,14]

One way to decrease errors at the person-machine interface is by the use of "forcing functions," engineering solutions that decrease the probability of human error. The classic example outside of medicine is the modification of automobile braking systems to make it impossible to place a car in reverse when the driver's foot is off the brake. In health care, forcing functions include changing the gas nozzles and connectors so that anesthesiologists cannot mistakenly hook up the wrong gas (such as nitrogen instead of oxygen) and administer it to a patient. Given the ever-increasing complexity of modern medicine, building in such forcing functions in intravenous pumps, defibrillators, mechanical ventilators, and computerized order entry systems will be crucial to safety.

In addition to better systems, communication and teamwork must be improved. All commercial pilots must take "crew resource management" courses, in which they train for emergencies with other crew members, learn to flatten hierarchies that might stifle open communication, communicate clearly with standard language, and use checklists and other systematic approaches. The evidence that such interventions in medical care will improve the safety of patients is persuasive.[15] The goal is a "culture of safety"—an environment in which teamwork, clear communication, and openness about errors, both with other health care professionals and with patients, is the norm.

Another key principle in ensuring the safety of patients is to learn from one's mistakes. Safe systems have a culture in which errors are openly discussed, often in morbidity and mortality conferences. To be most useful, these discussions should be interdisciplinary (involving physicians and other health professionals), identify when the errors occurred, and emphasize systems thinking and solutions; they should not be punitive. In addition to open discussions during conferences, safe organizations build in mechanisms to hear about errors from frontline staff, often through "incident reporting systems"; they also perform detailed "root cause" analyses of major errors or "sentinel events" in an effort to define all the layers of Swiss cheese that need improvement. The importance of open communication extends to patients as well. Disclosure of errors is now required by The Joint Commission. Patients and families value such openness, and reasonably strong evidence indicates that disclosure of errors might decrease the chance of a malpractice suit.

Finally, there is increasing appreciation of the importance of a well-trained, well-staffed, well-rested, and experienced[16] work force for the delivery of safe care. Lower nurse-to-patient ratios,[17] lack of residents, low procedural volumes, and lack of board certification are all linked to poor outcomes for patients. Safer systems cannot be created if the providers are overextended or poorly trained or supervised. In the United States, the Accreditation Council for Graduate Medical Education has limited duty hours for residents and has prohibited first-year residents from working 24-hour shifts. Evidence to date confirms that these standards have improved residents' quality of life but not patient safety, probably because of the concomitant increase in risky handoffs (in fact, the ban on 24-hour shifts was lifted in 2017 based on such studies).[A7,A8]

In the absence of comparative evidence and in light of the high cost of interventions such as improved staffing, computerized order entry, and teamwork training, even institutions committed to safety must often make difficult choices. For example, medication reconciliation represents a widely promoted patient safety intervention. The typical version generates small reductions in unintentional medication changes and unclear reductions in actual harm.[18] By contrast, a more intensive version, involving ongoing involvement from clinical pharmacists after hospital discharge, can improve patient outcomes and reduce visits to the hospital.[A9] Given the natural tendency to focus on practices that are measured, publicly reported, and compensated, institutions and physicians tend to focus first on areas that are subject to regulation or on initiatives with multiple potential benefits, such as computerization. For example, computerization was promoted in the United States by a federal incentive program, which between 2010 and 2015 provided billions of dollars to hospitals and physicians that implemented computer systems meeting certain "Meaningful Use" standards. Today, more than 90% of U.S. hospitals and 80% of office practices use electronic health records, with some evidence of improved safety as a result.

Because improving culture is difficult to measure and to regulate, there is concern that it will not be as high a priority as it should be. Moreover, a safe culture depends on balancing the imperative to improve systems with the need to define and enforce accountability. The safety field is increasingly emphasizing more active enforcement of policies that address problems such as disruptive behavior by clinicians and failure to adhere to evidence-based safety practices. Organizations that are particularly adept at recovering from mistakes and ensuring safety have been called "high reliability" organizations. The term "learning health system" is used to refer to organizations that iteratively learn from both successes and failures.

QUALITY AND SAFETY DURING A PANDEMIC

The coronavirus disease 2019 (COVID-19) pandemic (Chapters 335 to 337) created enormous stresses on health care and public health systems, and it also raised important issues regarding quality and safety. First, the pandemic had disproportionate impacts on communities of color and on older individuals,[19] particularly people living in congregate care facilities. Although some of these health care disparities may have been explained by different levels of exposure to the virus, they may also reflect disparities in the quality and safety of care for these communities and in these settings (Chapter 4). In geographic areas that experienced rapid surges in cases, quality and safety were undoubtedly compromised by an overwhelmed health care system, most likely mediated by availability of resources, such as staff and hospital beds.[20] In addition, the pandemic led to a sharp rise in the use of telemedicine, and with it came considerable debate about the quality and safety of virtual care.[21] This latter topic will remain a key issue as health care becomes increasingly digital.

VALUE: CONNECTING SAFETY AND QUALITY TO COST

Outside of health care, most purchasing decisions are based on perceived value: quality ÷ cost. Health care decisions historically have not been made this way, in part because of the limited ability of patients and payers to make rational judgments about the quality and safety of a given provider or system, and in part because health care insurance insulates patients from the full cost of care. In the United States, which spends nearly 20% of its Gross Domestic Product and about twice as much as other high-income countries on health care,[22] policy pressures are increasingly being brought to bear on the entire value equation, that is, promoting value, not volume. Such initiatives are especially timely given the consolidation of U.S. hospital systems by mergers and acquisitions that generally have mixed impacts on the quality of care and the patient experience.[23] For example, Medicare's Value-based Purchasing program modifies hospital reimbursement on the basis of quality, safety, and patient satisfaction scores. The organization's readmission initiative threatens substantial cuts in reimbursement to hospitals with higher-than-expected 30-day readmission rates. Other federal programs seek to drive physicians and hospitals into arrangements in which they accept a fixed payment to manage a population of patients (Accountable Care Organizations) or for an episode of illness (bundled payments). Although such programs are controversial and of variable success,[24] they reflect a growing focus on quality, safety, the patient's experience, and the costs of care. Interestingly, the care of Medicare patients at major teaching hospitals is associated with better outcomes without higher costs.[25]

Recent years have seen increased efforts to identify and eliminate low-value care—care that adds costs but no, or insufficient, benefit.[26] Many of the techniques described earlier (audit and feedback, "hard wiring" best practices, improving culture) are applicable to these efforts. Nevertheless, the fact that physicians and health care organizations may benefit financially from such care (such as in the case of unneeded procedures) or that patients may request it (such as in unnecessary antibiotics for viral infections) means that efforts to eliminate low-value care often take on a public, even political, dimension. Whether attempts to understand such overutilization[27] can offset these pressures nationally is currently unknown.

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11 POPULATION HEALTH

KIRSTEN BIBBINS-DOMINGO

In addition to understanding the biology of health, the pathobiology of disease, and the principles of diagnosis and individual therapy, clinicians also must be familiar with the concept of population health. Population health can be defined as the health outcomes of a group of individuals, whether based on geography (Chapter 5), ethnicity or socioeconomic status (Chapter 4), age (Chapters 21 and 24), gender or gender identity (Chapter 214), or other attributes, such as employment (Chapter 16), disability, homelessness, or incarceration. The field of population health includes health outcomes, patterns of the determinants that influence health, and the policies and interventions that link these two.

Population health is also a priority for health care organizations. Improving the U.S. health care system requires simultaneous pursuit of three aims: improving the experience of care for patients, reducing per capita costs of health care, and improving the health of populations.[1] In this conceptualization, the improvement of population health is central to high-quality health care (Chapter 10), potentially augmented by changing health care financing toward rewarding value over volume and specifically incentivizing improvements in population-based outcomes. These changes in payment models have led to the creation of an infrastructure that is often referred to as "population health management."

POPULATION HEALTH MANAGEMENT

Population health management describes how a health care organization that is interested in quality, value, and improvements in population health can deploy its resources to address areas of need within a population. Population health management strategies focus not only on the care that is provided to an individual during an outpatient visit or hospitalization but also on managing the health of all patients with a particular condition as well as the entire population for which an organization has responsibility. The scope of these strategies generally includes expanded preventive services, care models that detect and intercede when early signs of health deterioration are identified, and community-based programs that address care for complex conditions outside of clinical settings, including the social issues that often complicate the management of chronic conditions.

Data suggest that population health management strategies can improve health outcomes. For example, consider the delivery of a preventive intervention such as evidence-based cancer screening to an entire population for which a health care organization has responsibility. When fecal immunochemical tests are directly mailed to all patients in a health care system, rates of screening for colon cancer increase. To be effective, however, such screening must be accompanied by rigorous plans for evaluating individuals who have a positive test result.[A1] Identifying all patients with a particular risk profile (e.g., obesity [Chapter 201] or pre-diabetes [Chapter 210]) may allow for more efficient enrollment of such patients into preventive care interventions (e.g., a diabetes prevention program). A population health management program can achieve 80 to 90% control rates for hypertension (Chapter 64) in an integrated health delivery system by focusing on structured treatment algorithms, team-based care, and an active management of hypertension registries. Online digital tools and telemedicine may allow for effective management of chronic conditions such as asthma,[A2] obesity,[A3] or diabetes.

Inherent in many population health management care models is the importance of team-based care that includes nonphysicians (e.g., nurses, nurse practitioners, pharmacists, and social workers, among others). Health care workers who work outside traditional clinical settings may be particularly important. For example, community health workers, who are trained to have basic knowledge of clinical conditions, can provide health coaching and psychosocial support, augment patient engagement by strengthening connections to outpatient care, facilitate navigation during transitions in care (e.g., from inpatient to outpatient or from primary care to specialty care), and identify relevant resources to address unmet social needs (e.g., food, housing, transportation). Outpatient models that include community health workers in the care of patients with multiple chronic conditions (e.g., diabetes, obesity, tobacco dependence, and hypertension) can improve control of these chronic conditions, improve mental health outcomes, improve quality of care, and decrease subsequent hospitalizations.[A4,A5] Similar approaches for high-risk patients at the time of hospital discharge demonstrate improvements in access to primary care and reductions in recurrent readmissions. Community health workers also have shown promise for mental health conditions such as depression (Chapter 362)[2] and geriatric conditions such as hearing loss.[A6] Economic analyses show positive returns on investment for models of care that incorporate community health workers,[3] but more widespread adoption has been limited by variability in the health care reimbursement, variability in training and licensing, and limited studies on the standardization of such interventions.[A7]

BEYOND POPULATION HEALTH MANAGEMENT TO POPULATION HEALTH

Population health management is being incorporated into traditional health systems that are seeking to improve clinical prevention, management of chronic disease, value, and quality. However, inherent in the broader concept of population health is the recognition that clinical care accounts only for about 20% of the factors responsible for health outcomes. Even after also accounting for individual behaviors that might be addressed in the health care setting, other factors (often referred to as the social determinants of health) account for far more (Fig. 11-1). These social drivers of health pose specific challenges for the delivery of health care. Patients at highest risk for poor clinical outcomes often have the highest degree of need with respect to these social drivers of health, and individual clinicians often feel ill-equipped to address these needs. The systemic nature of many social drivers of health are best addressed with broader policies and programs that are widely available to groups of individuals with similar needs rather than by simply addressing the unmet needs of an individual patient at one point in time.[4] This recognition has led to an increased interest in how physicians and health systems might move beyond targeted population health management programs to address social and structural determinants of health more directly.

Interventions focused on the social determinants of health or addressing social needs of patients in health care settings have had variable success. Increasing attention is focusing on screening all patients for social needs, with the goal of addressing any unmet needs,[A8] but interventions to address food insecurity, financial strain, and housing instability have not yet resulted in replicable approaches to guide their widespread implementation.[5] For example, a trial of providing rideshare transportation to patients with transportation needs failed to improve attendance at outpatient visits,[A9] suggesting that addressing a single determinant of health may be insufficient in patients who may also have multiple additional needs (e.g., economic, food, shelter). Providing permanent supportive housing for chronically homeless individuals who are high users of health care services can increase outpatient follow-up for mental health, decrease emergency psychiatric visits, and decrease the use of homeless shelters, but not reduce overall emergency department visits or hospitalizations.[A10] Sustainable models for addressing social needs such as housing within the context of health care delivery generally require partnerships with institutions for whom housing is their primary focus. Similarly, data on addressing food insecurity for diabetic patients in health care settings support the use of partnerships with food pantries.[A11] However, the difficulties of addressing complex social needs in high-risk patients is exemplified by the failure of an intervention based on a team of nurses, social workers, and community health workers to reduce hospital readmissions among high users of health care with medically and socially complex problems,[A12] despite high engagement of patients with the program.

Although the importance of addressing the social drivers of health is critical for improving population health, the most effective means for addressing such challenges within the context of health care delivery remains uncertain. However, data suggest five types of interventions are most likely to address social needs and thereby improve individual and population health (Fig. 11-2). All clinicians and health care organizations should be *aware* of the social determinants of health and the potential needs and assets of patients with respect to these social factors. In the context of health care delivery, clinical teams may identify and address the social needs of an individual patient by providing direct *assistance* (e.g., providing a voucher for transportation or referral to a food assistance program). *Adjustments* to clinical care may also be appropriate to minimize the burden of social need (e.g., telehealth visits for patients with transportation needs or a lower-cost diagnostic evaluation or treatment regimen for patients with limited resources). Since addressing social needs one patient at a time may not be effective or cost-effective, changes in structural factors that result in social needs for larger populations of patients are usually better addressed by *alignment* with other sectors (e.g., partnerships with housing agencies and social services to develop programs for permanent supportive housing following hospitalization) or joint *advocacy* for changes in housing policies.

ABSTRACT

Population health refers to the health outcomes of groups of individuals, where the group may be defined by geography, age, ethnicity, socioeconomic status, or other attributes. The field of population health includes not only the study of the health outcomes for populations, but also the patterns of determinants that influence these outcomes, as well as the policies and interventions that link the two. Clinicians must have an understanding of population health, particularly how social and structural determinants of health may impact their patients' health and the optimal provision of individualized health care. Population health has also become a priority of U.S. health systems and has motivated the creation of infrastructure referred to as population health management and often including expanded preventive services, team-based care models that detect and intercede on early signs of health deterioration, and community-based programs that address care of complex conditions outside of traditional clinical care settings. Emerging evidence supports that such programs improve health outcomes for individual patients, particularly related to the prevention and the care of chronic conditions.

KEYWORDS

population health
health equity
social determinants of health
population health management

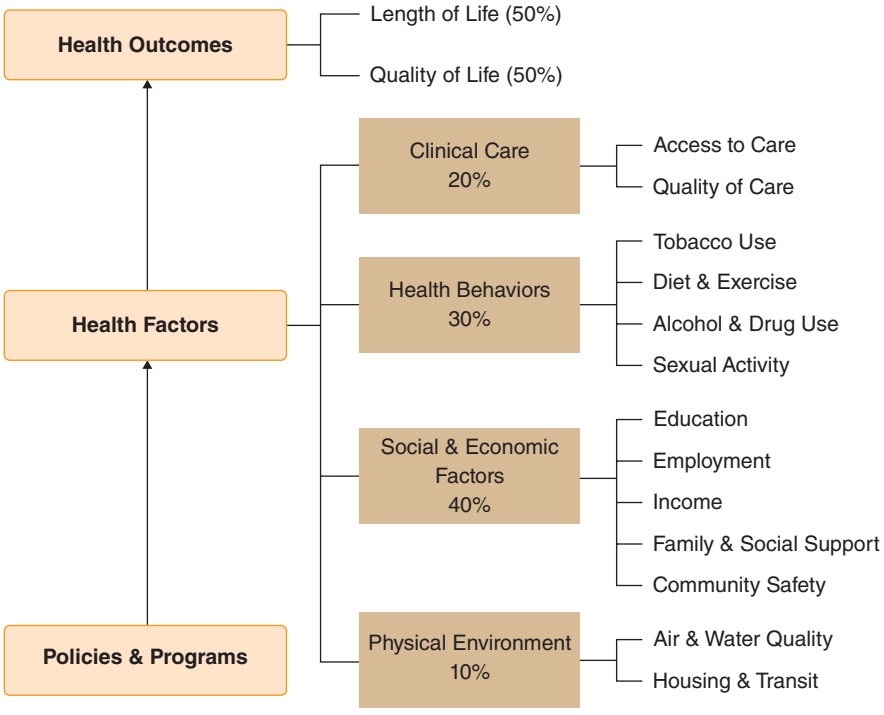

FIGURE 11-1. Relative contribution of clinical care, individual behaviors, and social determinants of health to health outcomes. (Adapted from National Academies of Sciences, Engineering, and Medicine Population Health Roundtable Discussion Paper.)

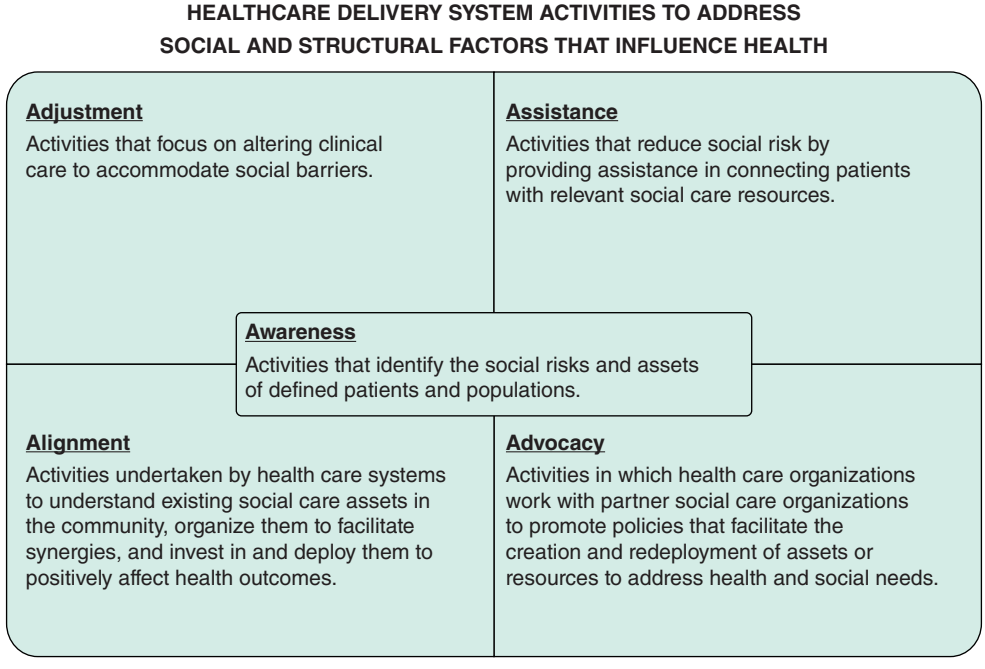

FIGURE 11-2. The Five As: Activities of health delivery systems to address social needs and social determinants of health to improve population health. (Adapted from the National Academies of Sciences, Engineering, and Medicine report: *Integrating Social Care into the Delivery of Health Care: Moving Upstream to Improve the Nation's Health.*)

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III

PREVENTIVE AND ENVIRONMENTAL ISSUES

12 THE PREVENTIVE HEALTH VISIT

13 DIET AND NUTRITION

14 PHYSICAL ACTIVITY

15 IMMUNIZATION

16 PRINCIPLES OF OCCUPATIONAL AND ENVIRONMENTAL MEDICINE

17 EFFECTS OF CLIMATE CHANGE ON HEALTH

18 RADIATION INJURY

19 BIOTERRORISM

20 CHRONIC POISONING: TRACE METALS AND OTHERS

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12 THE PREVENTIVE HEALTH VISIT

MARY B. BARTON AND TRACY A. WOLFF

A general health check-up for adults has not been proven to reduce mortality, but it is associated with better recognition and treatment of chronic diseases as well as better patient-reported outcomes.[1] The value of the periodic health visit is increased by a focus on primary and secondary prevention. The appropriate preventive services, including screening and lifestyle counseling, as well as their frequency, vary with the age, sex, and individual risk factors of each patient.

The U.S. Preventive Services Task Force (USPSTF) recommendations are used by major primary care groups, many health plans, and quality organizations, and their A and B recommendations guide preventive services that are covered under the Affordable Care Act. The USPSTF bases its recommendations on two factors: an estimate of the *net benefits* (benefits minus harms) of a service and an assessment of the *certainty* of that estimate, based on the rigor of supporting studies. Grade A recommendations require high certainty of a substantial net benefit, most often from large, prospective, controlled studies that measure morbidity or mortality.[2] Grade B recommendations have at least moderate certainty of at least a moderate benefit. USPSTF recommendations are thus more conservative than those of some subspecialty organizations that may give more weight to indirect evidence, such as earlier detection of disease, and less weight to potential harms of interventions. Clinicians can draw several general conclusions from an evidence-based approach to prevention: we should be selective in our use of screening tests, especially in older patients, and involve patients in decisions about specific services for which a small chance of benefit must be balanced against possible harm.

HISTORY AND RISK ASSESSMENT

The history and risk assessment are important tools to identify individuals who may need additional screening tests or immunizations not generally recommended for their age group or who may benefit from specific counseling to promote healthy behaviors. Formal health risk appraisals should be linked to a system to provide specific feedback and targeted interventions. Risk assessment should address the following:

- Use of tobacco, alcohol, and other drugs (especially injection drugs) (Chapters 363, 364, and 365)
- Diet (Chapters 13 and 201)
- Physical activity (Chapter 14)
- Sexual behavior that may increase the risk for sexually transmitted diseases or unintended pregnancy (Chapters 264, 353, and 356)
- Family history of cancer and heart disease
- Birthplace and current residence (community risk for infectious diseases)
- Presence of chronic diseases, such as diabetes, and of other cardiovascular risk factors
- Presence of social risk factors, such as housing instability, food insecurity, financial strain

SCREENING FOR EARLY DISEASE OR ASYMPTOMATIC RISK FACTORS

Every year, new screening tests are introduced and marketed on the basis of their ability to detect unrecognized diseases or risk factors for disease. Other conditions need to be fulfilled for a screening test to be worthwhile for routine use, however (Table 12-1). Benefits of screening must be balanced against the potential harms, including false-positive results and the risks and costs of follow-up procedures or treatments. Even when tests have high specificity, the majority of positive results will be false-positive results if the test is used to screen healthy populations for uncommon conditions such as cancer (Chapter 8). There is evidence that cancer screening can lead to "overdiagnosis"—detection of slow-growing cancers that would never have caused clinical symptoms in a patient's lifetime. Overdiagnosis subjects patients to the side effects of treatment with no benefits. A relatively small number of screening tests have been proved beneficial for the general population (Table 12-2), but several screening tests are indicated for specific populations at risk (Table 12-3). Many commonly used screening tests are not recommended by the USPSTF (Table 12-4) because they provide little benefit or lack sufficient evidence to prove

TABLE 12-1 REQUIREMENTS OF AN EFFECTIVE SCREENING TEST

The disease being screened for is an important cause of morbidity and mortality.
Screening can detect disease in an early, asymptomatic phase.
Screening and treatment of patients with early disease or risk factors produce better health outcomes than does treatment of patients when they present with symptoms.
Screening test is acceptable to patients and clinicians—safe, convenient, acceptable false-positive rate, acceptable costs.
Benefits of early detection and asymptomatic treatment are sufficient to justify potential harms and costs of screening.

TABLE 12-2 PREVENTION RECOMMENDATIONS FOR THE GENERAL POPULATION: FROM THE U.S. PREVENTIVE SERVICES TASK FORCE AND OTHER SOURCES

SCREENING
Height, weight, and body mass index (BMI) calculation: periodically
Blood pressure: at least every 2 yr
Screen for alcohol misuse
Screen for unhealthy drug use
Brief screen for depression*
Total blood cholesterol, LDL, and HDL cholesterol: every 5 yr for men and women ≥20 yr with CHD risk factors and men ≥35 yr without CHD risk factors
Colorectal cancer screening: age 45-75 yr
Mammogram: at least every 2 yr for women 50-74 yr
Cervical cancer: Papanicolaou (Pap) test every 3 yr for women aged 21-29 yr; for women aged 30-65 yr, either Pap test every 3 yr or human papillomavirus (HPV) test with or without Pap every 5 yr
HIV test: at least once in all adults; repeat based on high-risk sexual activity
Hepatitis C screening at least once for persons ages 18 to 79 years, repeat based on continued risk
Chlamydia and gonorrhea: sexually active women ≤24 yr and older women at risk
Screening for bacteriuria in pregnant persons
Bone mineral density test: women ≥65 yr and high-risk women <65 yr
COUNSELING
Substance use
Tobacco cessation
Reduction of risky or harmful alcohol use
Diet and exercise
Limit saturated fat; maintain calorie balance; emphasize grains, fruits, and vegetables†
Regular physical activity
Sexual behavior
Unintended pregnancy: contraception
Interventions during pregnancy and after birth to support breastfeeding
Dental health: floss, brush with fluoride toothpaste daily
IMMUNIZATIONS
Pneumococcal vaccine (two preparations, administered 1 yr apart, age ≥65 yr)
Influenza vaccine (annual)
Tetanus-diphtheria (Td) boosters (every 10 yr)
Measles, mumps, rubella (MMR) vaccine (susceptible adults aged 19-49 yr)‡
Varicella (two doses, susceptible adults born after 1980)‡
Herpes zoster vaccine, two doses after age 50 yr
HPV vaccine (two doses, boys and girls ages 12-13 yr; three doses if given at ages 15-26 yr)
COVID-19 vaccine, with booster age >5 yr
PREVENTIVE MEDICATIONS
Multivitamin with folic acid (women planning or capable of pregnancy)

*Screening is most effective where adequate systems exist to ensure effective treatment and appropriate follow-up.

†Diet counseling is most effective when it targets at-risk groups (overweight or with CHD risk factors).

‡Immunity can be verified by serologic testing, documented history of illness, or vaccination.

CHD = coronary heart disease; COVID = coronavirus disease; HDL = high-density lipoprotein; HIV = human immunodeficiency virus; HPV = human papillomavirus; LDL = low-density lipoprotein.

USPSTF recommendations:

Sources: https://www.uspreventiveservicestaskforce.org/; other sources for Tables 12-2 and 12-3 include U.S. Department of Health and Human Services (diet, physical activity), Centers for Disease Control and Prevention (injury prevention, immunizations, dental health), and Health Resources and Services Administration (contraception).

ABSTRACT

Primary and secondary prevention is an essential part of primary care and the patient-centered medical home; the appropriate services and their frequency vary with the age, sex, and the risk factors of each individual patient. A preventive health visit should focus on screening tests with strong evidence of effectiveness; lifestyle counseling directed toward healthy diet, physical activity, and avoiding tobacco use and risky use of alcohol and other drugs; and discussion of possible preventive medications such as aspirin and statins. The most comprehensive prevention recommendations are produced by the U.S. Preventive Services Task Force (USPSTF). The USPSTF bases its recommendations on two factors: an estimate of the *net benefits* of a service and an assessment of the *certainty* of that estimate. Importantly, these recommendations apply to patients who do not have signs or symptoms of disease and who are at average risk for the particular disease that is the focus of the preventive intervention.

KEYWORDS

preventive health visit
periodic health examination
screening
prevention
immunization
behavioral counseling

TABLE 12-3 RECOMMENDED SCREENING AND INTERVENTIONS FOR SELECTED POPULATIONS

POTENTIAL INTERVENTION	POPULATION
SCREENING	
Diabetes screen	Adults aged 35 to 70 yr with overweight or obesity
Ultrasound examination for abdominal aortic aneurysm	Males aged 65-75 yr with current or previous smoking history
Low-dose computed tomography for lung cancer	Adults with at least 20 pack-year smoking history (current adults who smoke, and those who quit smoking within past 15 years)
Syphilis (RPR/VDRL)	High-risk sexual behavior; consider local epidemiology*
Gonorrhea screen	High-risk sexual behavior; consider local epidemiology*
Tb screening	Persons who were born in, or are former residents of, high-risk countries, congregate settings, immunosuppressed
COUNSELING	
Exercise to prevent falls	Community dwelling adults ≥65 yr at increased risk for falls
Counseling to prevent STIs	Adults at increased risk
IMMUNIZATIONS	
Hepatitis B vaccine	Exposure to blood products; IV drug use; high-risk sexual behavior; travelers to high-risk areas
Hepatitis A vaccine	Persons living in or traveling to high-risk areas; institutionalized persons and workers in these institutions; those with certain chronic medical conditions
Meningococcal vaccine	First-year college students in dormitories; military recruits; those with asplenia; travelers to high-risk areas
Varicella vaccine	Adults born after 1980 without evidence of immunity
PREVENTIVE MEDICATIONS	
Statin	Adults over 40 yr at increased risk of cardiovascular disease
Breast cancer preventive medications	Women at increased risk for breast cancer and with low risk for thromboembolic complications
HIV preexposure prophylaxis	Adults at high risk of HIV acquisition

*Routine screening may be indicated in communities or settings where infection is prevalent.
HIV = human immunodeficiency virus; IV = intravenous; RPR = rapid plasma reagin; STI = sexually transmitted infection; Tb = tuberculosis; VDRL = Venereal Disease Research Laboratory.

TABLE 12-4 INTERVENTIONS NOT RECOMMENDED FOR ROUTINE USE IN ASYMPTOMATIC AVERAGE-RISK ADULTS*

PHYSICAL EXAMINATION
Oral examination for oral cancer (I)
Brief tests of mental status to detect dementia (I)
Vision and hearing tests in older adults (I)
Screening testicular examination (D)
BLOOD TEST
Routine blood tests for anemia
Blood level of C-reactive protein to predict coronary risk (I)
Blood tests for celiac disease (I)
Herpes serology (D)
Blood tests for ovarian cancer (D)
RADIOLOGY
Chest radiograph for lung cancer
Ultrasound examination for asymptomatic carotid artery stenosis (D)
Whole body computed tomographic scan
Ultrasound examination for ovarian cancer
Helical computed tomography for asymptomatic coronary disease (I)
OTHER
Resting or exercise electrocardiography (D) of asymptomatic coronary disease
Pulmonary function tests for chronic obstructive pulmonary disease (D)
Routine urine tests (for infection, cancer, or chronic kidney disease) (I)
Vitamin supplements (I, D)

*These services have either insufficient evidence to support routine use (I) or at least fair evidence that they provide no benefit or that harms outweigh benefits (D).

or disprove their value. Because only about 50% of U.S. adults see a primary care physician each year,[3] the responsibility for providing preventive services may increasingly fall to other clinicians.

DEPRESSION

Depression is common and frequently undetected in primary care (Chapter 362), and screening is specifically recommended in the adult general population, including pregnant and postpartum women. The most commonly used screen, and one of the simplest, is the Patient Health Questionnaire (PHQ)-9 (Table 12-5), which has nine items, each scored from 0 to 3. The PHQ-9 takes 5 to 10 minutes to administer.[4] A total score of 10 indicates moderate depression, whereas a score of 20 generally corresponds to severe depression. To improve outcomes, however, screening for depression must be linked to an organized system with staff support to ensure follow-up diagnostic assessment and treatment.

COGNITIVE IMPAIRMENT

By comparison, routine screening for cognitive impairment is more complicated. Despite excellent screening tools (Chapters 361 and 371),[5] no specific interventions have substantial impact on progression, so the USPSTF found insufficient evidence to support screening.[A1] Nevertheless, identification of cognitive impairment is included in Medicare's wellness visits and can guide family and other caregivers in ways that are likely to benefit the patient.

HIGH BLOOD PRESSURE, ABNORMAL LIPIDS, AND OTHER CARDIOVASCULAR RISK FACTORS

Overall cardiovascular disease (CVD) risk, based on age, sex, blood pressure, lipid levels, diabetes and smoking status, should be calculated at regular intervals to guide treatment decisions to reduce cardiovascular risk. Blood pressure should be measured at least every 2 years (Chapter 64), and home measurement[6] is recommended rather than beginning treatment based on an office measurement alone.[A2] The value of blood pressure screening in adolescents (Chapter 21) is less clear.[A3]

For lipids, the most commonly used risk estimation tool relies on measures of total cholesterol and high- and low-density lipoprotein cholesterol (Chapter 190) to estimate 10-year risk of coronary heart disease (http://tools.acc.org/ASCVD-Risk-Estimator). Statins are routinely recommended for patients who already have known atherosclerotic cardiovascular disease (Chapter 190). By comparison, the USPSTF, which focuses on primary prevention for individuals at risk for developing cardiovascular disease, recommends low- to moderate-dose statins for adults ages 40 to 75 years who have at least a 10% 10-year risk of CVD and at least one CVD risk factor.[A4] Recommendations from the American Heart Association and American College of Cardiology favor treatment for those with an estimated 10-year risk as low as 7.5%, whereas the USPSTF recommends individualizing treatment decisions for adults with a 10-year CVD risk of 7.5 to 10%.[7] The USPSTF concluded evidence was insufficient to recommend for or against beginning treatment after age 75 in adults with no evidence of CVD. Although factors such as C-reactive protein, homocysteine, and coronary calcification as assessed by computed tomography (CT) are associated with an increased risk for heart disease, the USPSTF has, at least so far, found insufficient evidence to recommend their routine use in risk assessment.

ABDOMINAL AORTIC ANEURYSM

Between 5 and 9% of men older than 65 years have an abdominal aortic aneurysm (Chapter 63). The risk for aneurysm is highest in smokers and is substantially lower in women (1%). The USPSTF recommends one-time screening with ultrasound examination in men aged 65 to 75 years who are current or former smokers,[8] based on trials demonstrating as much as a 40% lower death rate from abdominal aortic aneurysm rupture in screened men, even though it does not decrease all-cause mortality.[A5]

TABLE 12-5 PATIENT HEALTH QUESTIONNAIRE-9 (PHQ-9)

Over the last 2 weeks, how often have you been bothered by any of the following problems?

USE "✔" TO INDICATE YOUR ANSWER	NOT AT ALL	SEVERAL DAYS	MORE THAN HALF THE DAYS	NEARLY EVERY DAY
1. Little interest or pleasure in doing things	0	1	2	3
2. Feeling down, depressed, or hopeless	0	1	2	3
3. Trouble falling or staying asleep, or sleeping too much	0	1	2	3
4. Feeling tired or having little energy	0	1	2	3
5. Poor appetite or overeating	0	1	2	3
6. Feeling bad about yourself—or that you are a failure or have let yourself or your family down	0	1	2	3
7. Trouble concentrating on things, such as reading the newspaper or watching television	0	1	2	3
8. Moving or speaking so slowly that other people could have noticed. Or the opposite—being so fidgety or restless that you have been moving around a lot more than usual	0	1	2	3
9. Thoughts that you would be better off dead or of hurting yourself in some way	0	1	2	3
FOR OFFICE CODING	*0*	+___	+___	+___
		=Total Score:_____		

Developed by Drs. Robert L. Spitzer, Janet B.W. Williams, Kurt Kroenke, and colleagues.

COLORECTAL CANCER

Screening can reduce both the incidence of and mortality from colorectal cancer. Options for screening men and women older than 45 years include an annual highly sensitive fecal occult blood test (FOBT) or fecal immunochemical test, a multitargeted stool DNA test every 1 to 3 years, flexible sigmoidoscopy every 5 years (or every 10 years with annual FOBT), CT colonography every 5 years, or colonoscopy every 10 years (Chapter 179).[A6]

Colonoscopy combines detection with the opportunity for biopsy and removal of lesions, so it is preferred in some guidelines. It carries higher costs and risks, however, and no single strategy has proved to be more effective or cost-effective than the alternatives. The USPSTF recommends routine screening for adults ages 45 to 75 years and selective screening in adults ages 75 to 85 years.[9]

BREAST CANCER

In large trials, mammography screening (at intervals of 1 to 2 years, with or without clinical breast examination) reduces breast cancer mortality by 15 to 30% (Chapter 183). Most trials suggest that the benefits of screening extend to women in their 40s, but the benefits are smaller and the risks for false-positive results are higher than in women aged 50 to 70 years. If a woman aged 40 to 49 years has a two-fold increased risk for breast cancer compared with the average in her age group, she will have a similar benefit-to-harm ratio for biennial screening mammography as an average-risk woman aged 50 to 74 years. No studies provide data on the benefits of screening women aged 75 and older. In a collaborative study, six independent models predicted that an average of 80% of the benefit of mammography could be achieved with biennial rather than annual mammography, whereas national mammography surveillance data indicate that false-positive results and other harms of screening would be reduced by about half if women were screened every other year instead of yearly. The USPSTF recommends biennial screening mammography for women aged 50 to 74 years, that the decision to start screening mammography in women before age 50 years should be an individual decision, and that the current evidence is insufficient to assess the balance of benefits and harms of screening mammography in women aged 75 years or older.

Although many cancers are discovered by patients, teaching women to perform breast self-examination increases the likelihood that a woman will undergo further evaluation for an unimportant finding, but it does not improve outcomes. Widespread screening for *BRCA1* or *BRCA2*, inherited mutations that increase the risk for breast cancer, is not recommended, but the USPSTF recommends that primary care providers assess risk in women who have family members with breast, ovarian, tubal, or peritoneal cancer by using one of several family history risk assessment tools designed to identify women at risk for potentially harmful mutations. Women with a positive result on risk assessment should be referred for genetic counseling.[10]

CERVICAL CANCER

Papanicolaou (Pap) screening is highly effective in preventing invasive cervical cancer, but many women in the United States are screened more often than needed. The USPSTF and a multispecialty-society collaborative endorse starting screening at age 21 years and then screening women aged 21 to 30 years every 3 years, regardless of their sexual history or HPV vaccination status (Chapter 184). In women ages 30 to 65 years, the USPSTF recommends either Pap testing every 3 years or human papillomavirus (HPV) testing with or without Pap testing every 5 years[11] (Chapters 15 and 344).[A7] Aside from its value for performing a Pap test, evidence is inadequate for recommending a pelvic examination in asymptomatic, nonpregnant women. Women who have adequate screening histories and who are not otherwise at high risk should discontinue screening after 65 years of age. Screening is not indicated in women who have undergone a total hysterectomy for benign disease. Whether women who have received the HPV vaccine (Chapter 15) need different screening strategies is not yet known.

PROSTATE CANCER

Screening with prostate-specific antigen (PSA) can increase the detection of organ-confined prostate cancer, but three large trials provided conflicting results as to whether screening lowers morbidity or mortality from prostate cancer (Chapter 186). Based on long-term follow-up of those trials and studies of early treatment of screen-detected cancer,[A8] the USPSTF concluded that PSA-based screening programs in men ages 55 to 69 years may prevent up to 1 to 2 deaths from prostate cancer and up to 3 cases of metastatic prostate cancer per 1000 men screened over 13 years.[A9] These benefits are offset by harms of screening, including an approximate 1% risk of hospitalization after biopsy. More importantly, an estimated 20 to 50% of screen-detected cancers are "overdiagnosed" (i.e., they may subject patients to risks of unnecessary treatment). Men undergoing prostatectomy have 1 in 8 chance of developing long-term urinary incontinence, and 1 in 3 men experience long-term sexual impotence. More than 1 in 7 men who have radiation therapy experience long-term erectile dysfunction, and up to 30% or so of men experience long-term bothersome bowel symptoms, including bowel urgency and fecal incontinence. Because of the small benefit of screening with the PSA and potential harms of overdiagnosis and overtreatment, the USPSTF recommends individual decision making among men aged 55 to 69 years. The USPSTF recommends against PSA screening in men aged 70 years and older due to lack of benefits and increased harms.[12]

LUNG CANCER

The USPSTF recommends annual screening with low-dose CT in adults aged 50 to 80 years who have at least a 20 pack-year smoking history and who currently smoke or have quit within the last 15 years, based on trials that reported

relative reductions of death from lung cancer by 16 to 25% and of all-cause mortality by about 7%.[A10] The overall benefit of screening takes into account that individuals would have about two false positive CT scans over a lifetime of screening.[13] As many as 40% of screened persons will have another finding on CT, such as coronary artery calcification, a mass in the kidney or adrenal gland, or an aortic aneurysm.[14] These findings are of uncertain significance, but they may lead to additional procedures to evaluate them.

OSTEOPOROSIS

Tests of bone mineral density can identify men and women with a high risk for fracture as a result of osteoporosis and who may benefit from medications proved to lower the risk for fracture (Chapter 225). The USPSTF recommends screening for osteoporosis in women older than 65 years as well as in younger women who have risk factors that put them at comparable risk. The most widely used screening tool for the risk of hip fracture is bone mineral density of the hip assessed with dual-energy x-ray absorptiometry (DXA), although peripheral DXA and quantitative ultrasound are acceptable and have the advantage of portability. A tool developed by the World Health Organization (http://www.shef.ac.uk/FRAX/) incorporates bone mineral density and other risk factors, such as age and fracture history, to guide decisions.

THYROID DISEASE

Routine thyroid testing occasionally identifies patients with symptomatic but undiagnosed hypothyroidism (Chapter 207), but it more often detects subclinical hypothyroidism, which presents in 5% of women and 3% of men in the United States and is characterized by elevations in thyroid-stimulating hormone with normal levels of free thyroxine.

Because the benefits of treating subclinical hypothyroidism remain uncertain, the USPSTF does not recommend routine thyroid testing in the absence of symptoms. Clinicians should be alert to subtle signs of thyroid disease and have a low threshold for testing patients in high-risk groups, including postpartum and postmenopausal women.

DIABETES

Although the treatment of impaired fasting glucose or impaired glucose tolerance can delay progression to diabetes (Chapter 210), screening for type 2 diabetes does not improve mortality rates after 10 years of follow-up.[A11] Routine screening for diabetes beginning at age 45 years is recommended by some groups, but the USPSTF recommends screening for overweight or obese adults ages 35 to 70 years of age.[15] Clinicians should refer patients with abnormal blood glucose to intensive behavioral counseling interventions that can lower CVD risk. Although tight glucose control can reduce the incidence of microvascular disease, the benefit of early asymptomatic detection on clinically important retinopathy, neuropathy, and nephropathy is likely to be small.

HIV INFECTION

The USPSTF and Centers for Disease Control and Prevention (CDC) recommend screening for HIV infection (Chapters 356, 357, and 358) in all adolescents and adults aged 15 to 65 years,[16] including pregnant women.[17] Whether to continue screening after age 65 years depends upon risk factors such as new sexual partners. The optimal screening interval is unclear, but annual screening is reasonable in persons at very high risk, such as individuals who are actively engaged in risky sexual behaviors. Rescreening is not necessary in seronegative patients who have not been at increased risk since the last screen.

HEPATITIS B AND C INFECTIONS

Drugs for chronic hepatitis C and B infection (Chapter 135) have increased the ability to achieve viral suppression and prevent the complications of chronic liver disease in infected individuals.[A12] As a result, screening is recommended for hepatitis C in all adults ages 18 to 79 years, usually as just a one-time screen.[18] For hepatitis B, the evidence of a benefit is less clear,[A13] but screening is still recommended in adolescents and adults who are at increased risk of infection,[19] especially individuals born in countries with a high prevalence of hepatitis B or with a history of past or current injection drug use.

SEXUALLY TRANSMITTED DISEASE

Behavioral counseling is recommended to prevent sexually transmitted disease in sexually active adolescents and adults who are at increased risk.[A14,20] Screening for chlamydia and gonorrhea (Chapter 294) is recommended for all women aged 24 years and younger who are sexually active and for older women at risk.[A15,21] Nucleic acid amplification tests for chlamydia can be performed on cervical or urine specimens. Early detection of chlamydia can reduce pelvic inflammatory disease (Chapter 264), a risk factor for infertility and ectopic pregnancy. Similar benefits are likely from screening women for gonorrhea (Chapter 275). Women older than 25 years are at increased risk based on their current sexual behaviors and those of their partners. Syphilis testing is recommended in persons who are at increased risk for infection, such as persons with HIV, men who have sex with men, and people whose communities have an elevated prevalence of the disease.

VISION AND HEARING

Undetected but correctable vision (Chapter 391) and hearing (Chapter 396) problems are common in older adults and can be discovered by asking about problems and performing simple tests of visual acuity and hearing. Unfortunately, evidence is limited to show that regular screening leads to measurable benefits in function. Regular visual acuity testing is recommended for older adults by many organizations, but a large trial did not find any lasting benefits of screening, despite detecting many correctable causes of vision problems. The USPSTF concluded that evidence was insufficient[A16] to recommend routine vision or hearing screening.[22,23]

BEHAVIORAL INTERVENTIONS

Lifestyle factors contribute to a large proportion of preventable deaths in the United States. Brief interventions are effective for some behaviors such as smoking and problem drinking, but changing other behaviors usually requires more intensive approaches. The *5 As* framework—ask, assess, advise, assist, and arrange—which was developed from smoking cessation research, provides a useful framework for counseling.

TOBACCO USE

Brief interventions can produce small but clinically important increases in quit rates among people who use tobacco. Effects increase with more intensive counseling and support, including the use of medication (Chapter 363).

MISUSE OF ALCOHOL AND DRUGS

The USPSTF recommends screening all adults 18 years or older for alcohol misuse (Chapter 364) with one of three tools: the 10-question AUDIT instrument, its 3-question version AUDIT-C (http://www.integration.samhsa.gov/images/res/tool_auditc.pdf), or a single question: "How many times in the past year have you had five (for men) or four (for women and adults over 65 years old) or more drinks in a day?" Brief multicontact behavioral interventions can successfully reduce alcohol consumption in at-risk adults who drink. The USPSTF also recommends screening for unhealthy drug use (Chapter 365), primarily based on the benefits of treating people with opioid use disorder.[24]

DIET AND PHYSICAL ACTIVITY

Counseling to promote a healthful diet (Chapter 13) and to promote physical activity (Chapter 14) can reduce the intake of saturated fat, increase the consumption of fruits and vegetables, and increase weekly physical activity. Studies of counseling also demonstrate small but potentially important improvements in CVD risk factors, including blood pressure, low-density lipoprotein cholesterol, and adiposity. Effects are most consistent with more intensive counseling (multiple sessions with trained counselors) and in higher-risk patients, such as those who have overweight or obesity or CVD risk factors (Chapters 14 and 13).

INJURY PREVENTION

Motor vehicle injuries are the leading cause of years of potential life lost before age 65 years. In older persons, falls are a leading cause of unintentional injury and can be reduced with exercise in community-dwelling seniors and targeted multicomponent interventions in highest-risk groups (Chapter 24). The USPSTF recommends that women of childbearing age be screened for intimate partner violence (Chapter 223)[25] but found insufficient evidence to recommend screening all elderly or other vulnerable adults for abuse and neglect.

IMMUNIZATIONS

Recommendations regarding immunization (Chapter 15) are regularly updated by the Advisory Committee on Immunization Practices of the CDC (http://www.cdc.gov/vaccines).[26]

Vaccination for COVID-19 is recommended (Chapter 337) for all adults and for children and adolescents 5 to 18 years, including a booster shot for adults. These recommendations are likely to be updated as the virus mutates or immunity wanes.

Annual influenza immunization is recommended for all adults. Pneumococcal vaccination is recommended for adults ages 65 years and older and is also indicated for younger adults with chronic heart, lung, or kidney disease; asthma; diabetes; asplenia and other immune disorders; as well as those who smoke. Two doses of varicella vaccine are recommended for all adults born in the United States after 1980 without other evidence of immunity, and two doses of zoster vaccine are recommended for all adults at age 60 years. Adults should be revaccinated once with the Tdap vaccine (tetanus, diphtheria, acellular pertussis) and every 10 years with Td; if their vaccination history is uncertain, complete primary immunization with two additional doses of Td is recommended. A series of three doses of a vaccine against HPV is recommended for young men and women ages 15 to up to age 26 years (only two doses are required for vaccination at ages 11 to 14 years) to reduce the risk for cervical cancer and genital warts, as well as to decrease transmission of the virus.

PREVENTIVE MEDICATIONS AND SUPPLEMENTS

Aspirin, postmenopausal hormone replacement therapy, breast cancer preventive medications, HIV preexposure prophylaxis (PrEP), and supplements of vitamins or minerals can carry both benefits and risks. Decisions need to consider the likely benefits (which increase with the underlying risk of the disease being prevented), the probability of harm, and the individual preferences of each patient.

ASPIRIN

In men and women without known vascular disease, aspirin reduces the risk for nonfatal myocardial infarction and ischemic stroke, but these benefits are often offset by an increased risk for serious gastrointestinal bleeding and hemorrhagic stroke.[A17] In men and women who have an elevated risk of CVD (10-year risk at least 10%), the benefits of aspirin outweigh risks by a small amount for adults ages 40 to 59 years. As a result, decisions regarding aspirin in this age range should be individualized based on additional consideration of risks and patients' values.[27] By comparison, the USPSTF found evidence that the harms outweigh the benefits in older adults[A18] and recommends against initiating aspirin therapy in adults ages 60 years or older (Chapter 70).

PREVENTIVE MEDICATIONS FOR BREAST CANCER

Tamoxifen, raloxifene, and aromatase inhibitors can reduce the incidence of invasive breast cancer in women at increased risk, but all have some harms. Tamoxifen and raloxifene increase the risk for thromboembolic events and worsen menopausal symptoms, tamoxifen also increases the risk for endometrial cancer (Chapter 184). Aromatase inhibitors worsen menopausal symptoms and are associated with gastrointestinal symptoms and musculoskeletal pain. The USPSTF recommends clinicians discuss the balance of benefits and harms of these medications with women over age 35 years who are at increased risk for breast cancer. Women most likely to benefit are those who are at low risk for the adverse effects of medications and whose 5-year risk of invasive breast cancer is 3% or higher. Online tools can be used to assess this risk (http://www.cancer.gov/bcrisktool/).

POSTMENOPAUSAL HORMONE THERAPY

Estrogen-only therapy in women over the age 50 years reduces the risk for developing diabetes and fractures in the near term, but it is also associated with a higher risk of gallbladder disease, stroke, and venous thromboembolism (Chapter 222).[A19] Combination therapy with estrogen and progestin, by comparison, reduces the risk of diabetes and fractures as well as colorectal cancer, but it increases the risk for invasive breast cancer, coronary heart disease, stroke, pulmonary embolism, gallbladder disease, urinary incontinence, and dementia.[A20] Hormone therapy is an option for younger menopausal women with persistent, troublesome menopausal symptoms (Chapter 222), but the USPSTF recommends against its routine use for preventive purposes.

HIV PREEXPOSURE PROPHYLAXIS

The use of daily tenofovir-based medications reduces the risk of HIV acquisition by about 50% in individuals who are at increased risk of HIV infection (Chapter 356).[A21] Adherence to daily use is a strong predictor of benefit. The USPSTF recommends HIV preexposure prophylaxis for persons at high risk of HIV infection, including persons with serodiscordant partners, who use condoms inconsistently with partners at high risk, or who have had a recent sexually transmitted infection. Preexposure prophylaxis is also recommended for persons who inject drugs and share needles (Chapter 365).[28]

VITAMIN AND MINERAL SUPPLEMENTATION

The USPSTF does not recommend routine use of vitamin or mineral supplements because there is no convincing evidence that multivitamins or individual or paired supplements (e.g., vitamin A, C, and D; folic acid; selenium; or calcium) reduce CVD, cancer, or all-cause mortality in community-dwelling average-risk adults. For vitamin E or beta-carotene, routine supplements are documented to be harmful. The USPSTF found insufficient evidence to support screening for vitamin D deficiency in adults[A22,29] or to suggest the routine use of calcium and vitamin D supplements for the primary prevention of fractures in ambulatory adults.

FUTURE ISSUES

Preventive care recommendations often vary based on a patient's characteristics such as age, sex, gender, and clinical risk factors, including behavior and race or ethnicity. Given well-described epidemiologic differences in the prevalence of diseases and their health impacts, prevention and treatment guidelines will likely become more specific for populations if and when sufficient evidence exists. Genomic testing has the potential for guiding personal recommendations for screening and prevention, but currently available genomic screening in average-risk individuals is limited by an incomplete understanding of the predictive value of specific genotypes in the general population, the uncertain effect of such information on clinical decisions, and concerns about the possible adverse effects of screening (e.g., anxiety, false reassurance, or discrimination). The USPSTF issues an annual report to Congress about research priorities: recent reports have focused on the need for more evidence about adult and child mental health, substance abuse and intimate partner violence, and health equity.[30]

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TABLE 13-1 APPROXIMATE DAILY CALORIC NEEDS

GENDER	AGE (YEARS)	CALORIES NEEDED FOR EACH ACTIVITY LEVEL: SEDENTARY*	MODERATELY ACTIVE†	ACTIVE‡
Female	19–30	2000	2000–2200	2400
	31–50	1800	2000	2200
	51+	1600	1800	2000–2200
Male	19–30	2400	2600–2800	3000
	31–50	2200	2400–2600	2800–3000
	51+	2000	2200–2400	2400–2800

*Only light physical activity in a typical day.
†Physical activity equal to walking about 1 to 3 miles a day at 3 to 4 miles per hour, plus light physical activity.
‡Physical activity equal to walking more than 3 miles per day at 3 to 4 miles per hour, plus light physical activity.

13

DIET AND NUTRITION

DONALD D. HENSRUD

DIETARY REQUIREMENTS

The recommended dietary allowances for essential nutrients are the average daily level of intake shown to be sufficient to meet the nutrient requirements of nearly all (97 to 98%) healthy people. By comparison, the dietary reference intakes take into consideration the accumulating evidence on the relationships of diet and nutritional status to chronic diseases, such as coronary heart disease, cancer, diabetes, and the other leading causes of death. Dietary reference intakes recommend intake levels that not only prevent deficiencies but also may promote long-term health and disease prevention.

In this way, dietary guidelines have expanded from focusing on preventing deficiencies of isolated nutrients to preventing chronic disease, a goal that is especially important now that about 50% of all adult Americans have one or more preventable chronic diseases and over 70% of adults are overweight or obese. The 2020-2025 Dietary Guidelines for Americans translates average caloric requirements (Table 13-1) into specific recommendations that can reduce the likelihood of becoming overweight or obese.

NUTRITION'S INFLUENCE ON MORTALITY AND MORBIDITY

EVIDENCE OF CONNECTIONS BETWEEN DIET AND DISEASE

Deficiency conditions of specific nutrients have been well documented, but establishing conclusive relationships between diet and chronic diseases often relies on epidemiologic studies that are susceptible to unrecognized confounding and cannot infer causality. Nevertheless, the totality of consistent evidence from large population studies and randomized trials in at-risk individuals have brought clarity to the characteristics of dietary patterns that promote optimal health.

Diet should not be considered in isolation because other lifestyle factors also influence the risk of chronic diseases. The greatest nutritional public health problems in the United States and in many other parts of the world are overweight and obesity, with their associated comorbidities. Body weight is ultimately determined by the balance between energy intake through diet and energy expenditure through physical activity (Chapter 14). Recommendations for health promotion and disease prevention must include diet and physical activity, as well as other lifestyle factors.

DISEASES INFLUENCED BY NUTRITION

Of the 10 leading causes of death in the United States (Table 13-2),[1] 6 are related to diet, 4 to excess alcohol use (Chapter 364), and 6 to obesity (Chapter 201). Major causes of morbidity that often underlie causes of death (e.g., obesity, chronic liver disease, and hypertension) are also directly related to diet and nutrition.

TABLE 13-2 MAJOR CAUSES OF DEATH (2019) AND MORBIDITY IN THE UNITED STATES RELATED TO DIETARY FACTORS

CAUSE OF DEATH	NUMBER	%
1. Heart disease*,†	659,000	23
2. Cancer*,†,‡	600,000	21
3. Accidents‡	173,000	6
4. Chronic lower respiratory diseases†	157,000	6
5. Cerebrovascular diseases*,†,‡	150,000	5
6. Alzheimer disease*,†	121,000	4
7. Diabetes mellitus*,†	88,000	3
8. Kidney disease*	52,000	2
9. Pneumonia/influenza	50,000	2
10. Suicide‡	48,000	2
MORBIDITY		
1. Obesity*		
2. Chronic liver disease and cirrhosis†,‡		
3. Hypertension*,†		
4. Diverticular disease and constipation*		
5. Osteoporosis*		

*Related to diet and nutrition.
†Related to obesity.
‡Related to excess alcohol use.

The 2020-2025 Dietary Guidelines for Americans (Table 13-3)[2] outline critical ways for health professionals to help Americans make healthy choices. Although dietary recommendations promulgated by major professional societies for risk reduction and/or management of the major chronic diseases vary somewhat in their details (E-Table 13-1),[3–6] the close agreement among these recommendations enhances their credibility.

Cardiovascular Disease

Of the seven major risk factors for coronary heart disease, four are related to diet: hypercholesterolemia (Chapter 190), hypertension (Chapter 64), obesity (Chapter 201), and diabetes (Chapter 210). Elevated plasma low-density lipoprotein (LDL) cholesterol is a strong risk factor for coronary heart disease and is raised by increasing consumption of dietary saturated fat and *trans* fat. *Trans* fat also lowers high-density lipoprotein (HDL) cholesterol. Saturated fat is found in meat, full-fat dairy products, and tropical oils. *Trans* fat, which comes almost entirely from partially hydrogenated oils and has no health benefits, was removed from processed foods in 2018 by the U.S. Food and Drug Administration. Less emphasis is placed on limiting dietary cholesterol in recent guidelines because dietary cholesterol has a lesser effect on LDL cholesterol than saturated fat and is often found in the same foods. Limiting foods that contain saturated fat also limits dietary cholesterol. LDL cholesterol levels can be lowered by substituting healthier unsaturated fats (polyunsaturated or monounsaturated oils) or carbohydrates (preferably whole

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TABLE 13-1 APPROXIMATE DAILY CALORIC NEEDS

GENDER	AGE (YEARS)	CALORIES NEEDED FOR EACH ACTIVITY LEVEL: SEDENTARY*	MODERATELY ACTIVE†	ACTIVE‡
Female	19–30	2000	2000–2200	2400
	31–50	1800	2000	2200
	51+	1600	1800	2000–2200
Male	19–30	2400	2600–2800	3000
	31–50	2200	2400–2600	2800–3000
	51+	2000	2200–2400	2400–2800

*Only light physical activity in a typical day.
†Physical activity equal to walking about 1 to 3 miles a day at 3 to 4 miles per hour, plus light physical activity.
‡Physical activity equal to walking more than 3 miles per day at 3 to 4 miles per hour, plus light physical activity.

13

DIET AND NUTRITION

DONALD D. HENSRUD

DIETARY REQUIREMENTS

The recommended dietary allowances for essential nutrients are the average daily level of intake shown to be sufficient to meet the nutrient requirements of nearly all (97 to 98%) healthy people. By comparison, the dietary reference intakes take into consideration the accumulating evidence on the relationships of diet and nutritional status to chronic diseases, such as coronary heart disease, cancer, diabetes, and the other leading causes of death. Dietary reference intakes recommend intake levels that not only prevent deficiencies but also may promote long-term health and disease prevention.

In this way, dietary guidelines have expanded from focusing on preventing deficiencies of isolated nutrients to preventing chronic disease, a goal that is especially important now that about 50% of all adult Americans have one or more preventable chronic diseases and over 70% of adults are overweight or obese. The 2020-2025 Dietary Guidelines for Americans translates average caloric requirements (Table 13-1) into specific recommendations that can reduce the likelihood of becoming overweight or obese.

NUTRITION'S INFLUENCE ON MORTALITY AND MORBIDITY

EVIDENCE OF CONNECTIONS BETWEEN DIET AND DISEASE

Deficiency conditions of specific nutrients have been well documented, but establishing conclusive relationships between diet and chronic diseases often relies on epidemiologic studies that are susceptible to unrecognized confounding and cannot infer causality. Nevertheless, the totality of consistent evidence from large population studies and randomized trials in at-risk individuals have brought clarity to the characteristics of dietary patterns that promote optimal health.

Diet should not be considered in isolation because other lifestyle factors also influence the risk of chronic diseases. The greatest nutritional public health problems in the United States and in many other parts of the world are overweight and obesity, with their associated comorbidities. Body weight is ultimately determined by the balance between energy intake through diet and energy expenditure through physical activity (Chapter 14). Recommendations for health promotion and disease prevention must include diet and physical activity, as well as other lifestyle factors.

DISEASES INFLUENCED BY NUTRITION

Of the 10 leading causes of death in the United States (Table 13-2),[1] 6 are related to diet, 4 to excess alcohol use (Chapter 364), and 6 to obesity (Chapter 201). Major causes of morbidity that often underlie causes of death (e.g., obesity, chronic liver disease, and hypertension) are also directly related to diet and nutrition.

TABLE 13-2 MAJOR CAUSES OF DEATH (2019) AND MORBIDITY IN THE UNITED STATES RELATED TO DIETARY FACTORS

CAUSE OF DEATH	NUMBER	%
1. Heart disease*,†	659,000	23
2. Cancer*,†,‡	600,000	21
3. Accidents‡	173,000	6
4. Chronic lower respiratory diseases†	157,000	6
5. Cerebrovascular diseases*,†,‡	150,000	5
6. Alzheimer disease*,†	121,000	4
7. Diabetes mellitus*,†	88,000	3
8. Kidney disease*	52,000	2
9. Pneumonia/influenza	50,000	2
10. Suicide‡	48,000	2
MORBIDITY		
1. Obesity*		
2. Chronic liver disease and cirrhosis†,‡		
3. Hypertension*,†		
4. Diverticular disease and constipation*		
5. Osteoporosis*		

*Related to diet and nutrition.
†Related to obesity.
‡Related to excess alcohol use.

The 2020-2025 Dietary Guidelines for Americans (Table 13-3)[2] outline critical ways for health professionals to help Americans make healthy choices. Although dietary recommendations promulgated by major professional societies for risk reduction and/or management of the major chronic diseases vary somewhat in their details (E-Table 13-1),[3–6] the close agreement among these recommendations enhances their credibility.

Cardiovascular Disease

Of the seven major risk factors for coronary heart disease, four are related to diet: hypercholesterolemia (Chapter 190), hypertension (Chapter 64), obesity (Chapter 201), and diabetes (Chapter 210). Elevated plasma low-density lipoprotein (LDL) cholesterol is a strong risk factor for coronary heart disease and is raised by increasing consumption of dietary saturated fat and *trans* fat. *Trans* fat also lowers high-density lipoprotein (HDL) cholesterol. Saturated fat is found in meat, full-fat dairy products, and tropical oils. *Trans* fat, which comes almost entirely from partially hydrogenated oils and has no health benefits, was removed from processed foods in 2018 by the U.S. Food and Drug Administration. Less emphasis is placed on limiting dietary cholesterol in recent guidelines because dietary cholesterol has a lesser effect on LDL cholesterol than saturated fat and is often found in the same foods. Limiting foods that contain saturated fat also limits dietary cholesterol. LDL cholesterol levels can be lowered by substituting healthier unsaturated fats (polyunsaturated or monounsaturated oils) or carbohydrates (preferably whole

ABSTRACT

The relationships of diet and nutrition with health and disease have evolved over time. Rather than focusing on isolated nutrients and preventing nutritional deficiencies, dietary guidelines now emphasize healthy dietary patterns to prevent chronic disease and promote health. The optimum dietary pattern is higher in vegetables, fruits, whole grains, low- or nonfat dairy, seafood, legumes, and nuts; it is also lower in red and processed meats, salt, sugar-sweetened foods and drinks, refined grains, and alcohol. Each of these recommendations is based on increasingly solid evidence.

KEYWORDS

diet
nutrition
chronic disease
disease prevention
health promotion

E-TABLE 13-1 DIETARY GUIDELINES PROMULGATED BY NATIONAL ORGANIZATIONS*

INDICATION OR OBJECTIVE	U.S. DEPARTMENT OF AGRICULTURE AND DEPARTMENT OF HEALTH AND HUMAN SERVICES: DIETARY GUIDELINES FOR AMERICANS (2020-2025)*	2019 ACC/AHA GUIDELINE ON THE PRIMARY PREVENTION OF CARDIOVASCULAR DISEASE: EXECUTIVE SUMMARY†	AMERICAN CANCER SOCIETY (2020)‡	AMERICAN DIABETES ASSOCIATION (2019)§
	GENERAL HEALTH PROMOTION AND DISEASE PREVENTION	*HEART DISEASE PREVENTION*	*CANCER PREVENTION*	*DIABETES PREVENTION AND TREATMENT*
NUTRIENT/FOOD GROUP				
Total energy	Stay within calorie needs at each life stage	In individuals with overweight and obesity, weight loss is recommended Counseling and comprehensive lifestyle interventions, including calorie restriction, are recommended for achieving and maintaining weight loss	Achieve and maintain a healthy body weight throughout life	Adults with overweight/obesity and prediabetes or diabetes should include an individualized eating plan in a format that results in an energy deficit
Fruits and vegetables	Include 1½-2½ cup-equivalents of fruits, at least half from whole fruit rather than juice, and 2-4 cup-equivalents of a variety of vegetables from all the subgroups daily, depending on calorie level	Emphasize vegetables and fruits	Include a variety of vegetables—dark green, red, and orange, fiber-rich legumes (beans and peas), and others; include fruits, especially whole fruits with a variety of colors	
Meat	Choose a variety of protein foods, including 5-7 oz-equivalents of seafood, lean meat and poultry, eggs, beans, peas, lentils, and nuts, seeds, and soy products	Minimize processed meats	Limit or do not include red and processed meats	
Dairy	3 cup-equivalents daily of fat-free or low-fat dairy including milk, yogurt, cheese, and/or fortified soy beverages			
Grains, fiber	Consume 5-10 oz-equivalents daily with at least half as whole grains	Emphasize whole grains	Include whole grains Limit or do not include refined grain products	Consume at least the amount of fiber recommended by the Dietary Guidelines Achieve fiber intake preferably through food
Fat	Include 22-44 g daily of PUFA and MUFA oils Limit saturated fats and *trans* fats			Macronutrient distribution should be based on individualized assessment
Saturated fats	Limit to <10% of daily calories, by replacing them with monounsaturated and polyunsaturated fats	Replace saturated fat with dietary monounsaturated and polyunsaturated fats		Replace saturated fat with unsaturated fats
Trans-fats	Limit	Avoid		Minimize to the greatest extent possible
Cholesterol	Keep as low as possible	Reduce cholesterol intake		
Carbohydrates		Minimize refined carbohydrates		Macronutrient distribution should be based on individualized assessment Replace refined carbohydrates and added sugars with whole grains, legumes, vegetables, and fruits
Sugar	<10% of calories	Minimize sweetened beverages	Limit or do not include sugar-sweetened beverages	Minimize added sugars and replace sugar-sweetened beverages with water as often as possible
Protein	Choose a variety of protein foods, which include eggs, beans, peas, lentils, soy products, and unsalted nuts and seeds (for more, see Meat)	Emphasize fish, legumes, and nuts		Macronutrient distribution should be based on individualized assessment
Alcohol	Up to 2 drinks/day for men and up to 1 drink/day for women; persons in special circumstances (e.g., pregnancy, history of alcoholism) should abstain		Best not to consume alcohol. People who choose to drink alcohol should limit their consumption to no more than 1 drink/day for women and 2 drinks/day for men	Adults with diabetes or prediabetes who drink alcohol do so in moderation (two drinks or less per day for adult men and one drink or less per day for adult women) Glucose monitoring after drinking alcohol beverages to reduce hypoglycemic risk
Processed food			Limit or do not include processed foods	Choose whole foods over highly processed foods to the extent possible
Sodium	Reduce daily sodium intake to less than 2300 mg	Reduce sodium intake		<2300 mg/day

**Dietary Guidelines for Americans, 2020-2025*. 9th ed. U.S. Department of Agriculture and U.S. Department of Health and Human Services. December 2020. https://www.dietaryguidelines.gov/.

†American Heart Association. https://www.heart.org/; Arnett DK, Blumenthal RS, Albert MA, et al. 2019 ACC/AHA guideline on the primary prevention of cardiovascular disease: executive summary: a report of the American College of Cardiology/American Heart Association Task Force on Clinical Practice Guidelines. *J Am Coll Cardiol*. 2019;74:1376-1414.

‡American Cancer Society. https://www.cancer.org/; Rock CL, Thomson C, Gansler T, et al. American Cancer Society guideline for diet and physical activity for cancer prevention. *CA Cancer J Clin*. 2020;70:245-271.

§American Diabetes Association. https://diabetes.org/; Evert AB, Dennison M, Gardner CD, et al. Nutrition therapy for adults with diabetes or prediabetes: a consensus report. *Diabetes Care*. 2019;42:731-754.

ACC = American College of Cardiology; AHA = American Heart Association; MUFA = monounsaturated fatty acid; PUFA = polyunsaturated fatty acid.

grains) for saturated fat. LDL cholesterol can also be lowered modestly by increasing the intake of soluble fiber and phytosterols from legumes, fruits, vegetables, and flax seed, as well as by consuming proteins and isoflavones from soy foods.

TABLE 13-3 DIETARY GUIDELINES FOR AMERICANS, 2020-2025: KEY RECOMMENDATIONS

1. Follow a healthy dietary pattern at every life stage.
   - For about the first 6 months of life, exclusively feed infants human milk.
   - At about 6 months, introduce infants to nutrient-dense complementary foods.
   - From 12 months through older adulthood, follow a healthy dietary pattern.
2. Customize and enjoy nutrient-dense food and beverage choices to reflect personal preferences, cultural traditions, and budgetary considerations.
3. Focus on meeting food group needs with nutrient-dense foods and beverages, and stay within calorie limits.
   - The core elements that make up a healthy dietary pattern include:
     - Vegetables of all types—dark green; red and orange; beans, peas, and lentils; starchy; and other vegetables
     - Fruits, especially whole fruit
     - Grains, at least half of which are whole grain
     - Dairy, including fat-free or low-fat milk, yogurt, and cheese, and/or lactose-free versions and fortified soy beverages and yogurt as alternatives
     - Protein foods, including lean meats, poultry, and eggs; seafood; beans, peas, and lentils; and nuts, seeds, and soy products
     - Oils, including vegetable oils and oils in food, such as seafood and nuts
4. Limit foods and beverages higher in added sugars, saturated fat, and sodium, and limit alcoholic beverages.
   - Added sugars—Less than 10% of calories per day starting at age 2. Avoid foods and beverages with added sugars for those less than 2 years of age
   - Saturated fat—Less than 10% of calories per day starting at age 2
   - Sodium—Less than 2300 milligrams per day, and even less for children younger than age 14
   - Alcoholic beverages—Adults of legal drinking age can choose not to drink or to drink in moderation by limiting intake to 2 drinks or less in a day for men and 1 drink or less in a day for women

Adapted from the *Dietary Guidelines for Americans, 2020-2025*. 9th ed. U.S. Department of Agriculture and U.S. Department of Health and Human Services. December 2020. https://www.dietaryguidelines.gov/. Accessed January 24, 2022.

Diet also can influence the risk of coronary heart disease in ways independent of LDL cholesterol and traditional risk factors, such as inflammation, oxidative stress, endothelial function, insulin sensitivity, and others. Consistent evidence from meta-analyses of large cohort studies has shown decreased cardiovascular and total mortality with increasing consumption of fruits and vegetables, whole grains, and nuts, as well as decreased incident coronary heart disease and total mortality from fish and olive oil.[7,8] Randomized trials are generally consistent with cohort studies, and a Mediterranean dietary pattern (Fig. 13-1) composed of many of these food groups can favorably affect cardiovascular risk factors and outcomes.[A1–A3] Diets such as the Dietary Approaches to Stop Hypertension (DASH) diet (Table 13-4) can reduce the incidence of cardiovascular disease by 30%.[A4] Higher-carbohydrate diets also can lower the risk of coronary heart disease in men by 20%, whereas the higher–unsaturated fat and higher-protein diets can reduce the risk by 30%.

Sodium intake clearly influences blood pressure, but much controversy has surrounded whether reducing sodium intake would truly be beneficial. In a cluster randomized trial in China, providing a salt substitute that was 75% sodium chloride and 25% potassium chloride to persons over age 60 years or with a history of stroke reduced cardiovascular events and death by 12 to 13% over a mean follow-up of 4.75 years.[A5] These data support the salt recommendations in Table 13-3.[9]

Moderate consumption of alcohol, defined as no more than one drink daily for women and two for men, has been associated with reduced risk of coronary heart disease, primarily by raising HDL cholesterol, inhibiting platelet aggregation, and stimulating fibrinolytic activity. National dietary data indicate that added sugar is associated with increased cardiovascular mortality. In addition, consumption of red and particularly processed meat has been associated with increased cardiovascular and total mortality.[10]

Cancer

About one third of cancers are due to suboptimal habits in diet,[11] physical activity, and weight management. Because cancer consists of many different conditions that share a common feature of uncontrolled abnormal cell division, risk factors, including diet, vary among different types of cancer. Nutrients, non-nutritive dietary constituents, and nutritional status can influence the risk for cancer through many different mechanisms, such as free radical scavenging

The Mediterranean Diet

Food/Food Group	Recommended Intake*	Tips
Vegetables	4 or more servings each day (one portion each day should be raw vegetables)	Eat a variety of colors and textures; a serving is 1 cup raw or ½ cup cooked vegetables.
Fruits	3 or more servings each day	Make fruit your dessert
Grains	4 or more servings each day	Choose mostly whole grains. 1 serving = 1 slice bread or ½ cup cooked oatmeal
Fats/Oils	Olive oil: 4 Tablespoons or more each day	Choose extra virgin olive oil and use in salad dressings and cooking; choose avocado or natural peanut butter instead of butter or margarine
Dried Beans/Nuts/Seeds	Nuts/Seeds: 3 or more servings each week Beans/Legumes: 3 or more servings each week	1 ounce or 1 serving = 23 almonds or 14 walnut halves; 1 serving of beans = ½ cup
Fish and Seafood	2-3 times each week	Choose salmon, sardines, and tuna, which are rich in omega-3 fatty acids
Herbs and Spices	Use daily	Season foods with herbs, garlic, onions, and spices instead of salt
Yogurt/Cheese/Egg and Poultry	Choose daily to weekly	Choose low-fat yogurt and cheeses; choose skinless chicken or turkey instead of red meat
Alcohol/Wine	Men: 1-2 glasses each day Women: 1 glass each day	Always ask your clinician if alcohol is ok for you to consume.

FIGURE 13-1. Mediterranean Diet. Choosing a diet similar to one eaten by people living around the Mediterranean Sea may lower the risk of cardiovascular disease and have additional health benefits. The diet is mostly plant-based with high amounts of fresh vegetables, fruits, nuts, dried beans, olive oil, and fish. *Serving sizes should be individualized to meet energy and nutrient needs. Red meats, processed meats, and sweets should be limited. (Adapted from Mediterranean Diet. https://www.nutrition.va.gov/docs/UpdatedPatientEd/Mediterraneandiet.pdf. U.S. Department of Veterans Affairs. Accessed January 24, 2022.)

TABLE 13-4 DIETARY APPROACHES TO STOP HYPERTENSION (DASH)

FOOD GROUP	SERVINGS PER DAY 1600 CALORIES	2000 CALORIES	2600 CALORIES	SERVING SIZES	EXAMPLES AND NOTES	SIGNIFICANCE OF EACH FOOD GROUP TO THE DASH EATING PLAN
Grains*	6	6–8	10–11	1 slice bread 1 oz dry cereal† ½ cup cooked rice, pasta, or cereal	Whole wheat bread and rolls, whole wheat pasta, English muffin, pita bread, bagel, cereals, grits, oatmeal, brown rice, unsalted pretzels, and popcorn	Major sources of energy and fiber
Vegetables	3–4	4–5	5–6	1 cup raw leafy vegetable ½ cup cut-up raw or cooked vegetable ½ cup vegetable juice	Broccoli, carrots, collards, green beans, green peas, kale, lima beans, potatoes, spinach, squash, sweet potatoes, tomatoes	Rich sources of potassium, magnesium, and fiber
Fruits	4	4–5	5–6	1 medium fruit ¼ cup dried fruit ½ cup fresh, frozen, or canned fruit ½ cup fruit juice	Apples, apricots, bananas, dates, grapes, oranges, grapefruit, grapefruit juice, mangoes, melons, peaches, pineapples, raisins, strawberries, tangerines	Important sources of potassium, magnesium, and fiber
Fat-free or low-fat milk and milk products	2–3	2–3	3	1 cup milk or yogurt 1½ oz cheese	Fat-free (skim) or low-fat (1%) milk or buttermilk; fat-free, low-fat, or reduced-fat cheese; fat-free or low-fat regular or frozen yogurt	Major sources of calcium and protein
Lean meats, poultry, and fish	3–6	6 or less	6	1 oz cooked meats, poultry, or fish 1 egg‡	Select only lean meats; trim away visible fat; broil, roast, or poach; remove skin from poultry	Rich sources of protein and magnesium
Nuts, seeds, and legumes	3 per week	4–5 per week	1	⅓ cup or 1½ oz nuts 2 Tbsp peanut butter 2 Tbsp or ½ oz seeds ½ cup cooked legumes (dry beans and peas)	Almonds, hazelnuts, mixed nuts, peanuts, walnuts, sunflower seeds, peanut butter, kidney beans, lentils, split peas	Rich sources of energy, magnesium, protein, and fiber
Fats and oils§	2	2–3	3	1 tsp soft margarine 1 tsp vegetable oil 1 Tbsp mayonnaise 2 Tbsp salad dressing	Soft margarine, vegetable oil (such as canola, corn, olive, or safflower), low-fat mayonnaise, light salad dressing	The DASH study had 27% of calories as fat, including fat in or added to foods
Sweets and added sugars	0	5 or less per week	<2	1 Tbsp sugar 1 Tbsp jelly or jam ½ cup sorbet, gelatin 1 cup lemonade	Fruit-flavored gelatin, fruit punch, hard candy, jelly, maple syrup, sorbet and ices, sugar	Sweets should be low in fat

*Whole grains are recommended for most grain servings as a good source of fiber and nutrients.
†Serving sizes vary between ½ cup and 1¼ cups, depending on cereal type. Check the product's Nutrition Facts label.
‡Because eggs are high in cholesterol, limit egg yolk intake to no more than four per week; two egg whites have the same protein content as 1 oz of meat.
§Fat content changes serving amount for fats and oils. For example, 1 Tbsp of regular salad dressing equals one serving; 1 Tbsp of a low-fat dressing equals one-half serving; 1 Tbsp of a fat-free dressing equals zero servings.
oz = ounce; Tbsp = tablespoon; tsp = teaspoon.
Adapted from National Heart, Lung and Blood Institute. In brief: your guide to lowering your blood pressure with DASH. NIH Publication No. 06-5834. https://www.nhlbi.nih.gov/files/docs/public/heart/dash_brief.pdf. Accessed January 24, 2022.

and DNA repair. Supplementation with individual nutrients has had limited success in preventing and treating cancer. Therefore, as with heart disease, a focus on foods and dietary patterns provides the best nutritional approach to preventing cancer.

Obesity (Chapter 201) is now recognized as a major risk factor for at least 12 cancers, perhaps by elevating serum levels of insulin and leptin, inducing insulin resistance, and creating a chronic inflammatory state (Chapter 164). Excess alcohol intake (Chapter 364) also increases the risk for many cancers, including liver, breast, and the entire gastrointestinal tract.

Lung Cancer

Although the most important causal factor in the number-one cancer killer, lung cancer (Chapter 177), is cigarette smoking, consumption of fruit is inversely associated with the risk of lung cancer in both smokers and nonsmokers. Two large, randomized trials of supplementation with β-carotene reported increased mortality from lung cancer and all causes, primarily in smokers and former smokers, so β-carotene supplementation should be avoided.

Breast Cancer

The number-two cause of cancer deaths in women is breast cancer (Chapter 183). Postmenopausal breast cancer is positively associated with obesity, especially when excess adiposity is located predominantly in the abdomen. Paradoxically, the risk of premenopausal breast cancer is decreased with obesity. Alcohol increases and lactation probably decreases the risk of both types of breast cancer.

Colorectal Cancer

Colorectal cancer (Chapter 179) is the third leading cause of cancer mortality in men and women. The risk for colorectal cancer correlates positively with the intake of red and processed meats, obesity, and alcohol. The World Health Organization has classified processed meat as a carcinogen and red meat as a probable carcinogen. Foods that contain dietary fiber (as opposed to fiber per se), dairy products, and calcium appear to decrease risk.[12,13]

Prostate Cancer

Although studies have evaluated different dietary factors on the risk of prostate cancer, the clearest risk factor is obesity.

Liver Cancer

The strongest risk factor for liver cancer is alcohol, but obesity also increases risk in part via nonalcoholic fatty liver disease (Chapter 138). Aflatoxins are a strong risk factor, primarily outside the United States where they are more prevalent in the food supply. Coffee appears to be protective against liver cancer.

Pancreas Cancer

Associations exist between pancreas cancer and various dietary factors, but causality is not clear except for obesity, which increases risk.

Recommendations

Although there are differences among dietary risks for different cancers, the American Cancer Society Guidelines for Cancer Prevention are generally

similar to other major dietary guidelines: consuming a plant-based diet, regular physical activity, and maintenance of a healthy body weight. Alcohol intake is the primary difference between guidelines to prevent heart disease, for which moderate consumption may be beneficial, and guidelines to prevent cancer, for which consumption increases risk even at low levels for some cancers, such as breast cancer and head and neck cancer. Randomized trials with isolated nutrients including carotenoids, vitamins C and E, folic acid, selenium, and even dietary fiber have not shown a benefit for reducing the risk of cancer. Whole plant foods contain hundreds of different vitamins, nutrients, and other phytochemicals that may collectively reduce the risk of cancer more than specific nutrients.

Hypertension

Elevated blood pressure (Chapter 64) is a major risk factor for stroke (Chapters 376 and 377), coronary heart disease (Chapter 40), heart failure (Chapter 45), peripheral vascular disease (Chapter 65), and renal disease (Chapter 116). Five lifestyle factors can reduce blood pressure: weight loss if overweight or obese, the DASH diet, increased physical activity, sodium restriction, and alcohol restriction. Obesity, especially abdominal obesity, is associated with hypertension, and weight reduction is the strongest lifestyle change that decreases blood pressure. The DASH diet (see Table 13-4) can lower blood pressure as much as drug treatment (11.6/5.3 mm Hg) in individuals with hypertension.

Diabetes Mellitus

Type 2 diabetes mellitus (Chapter 210) is strongly associated with obesity, especially abdominal obesity, so maintenance of a desirable body weight throughout life is of major importance in both preventing and treating type 2 diabetes. Sugar consumption does not have a large impact on developing diabetes, except to the extent that it may promote weight gain. However, sugar-sweetened beverages contribute to weight gain and an increased risk of type 2 diabetes. A high–glycemic index (a measure of the amount a food increases blood glucose) diet also increases risk. Red and particularly processed meats increase the risk of type 2 diabetes. Coffee intake decreases the risk of diabetes in a dose-dependent fashion. A Mediterranean dietary pattern (see Fig. 13-1) higher in healthy fat can lead to slightly better glucose control than a high-carbohydrate diet. However, a higher-carbohydrate diet can still be utilized, provided that calories are controlled and preferably whole grains are emphasized. An overall healthy eating pattern helps also reduce the risk for cardiovascular disease, which is the main cause of death in patients with diabetes.

Osteoporosis

Adequate intake of calcium, vitamin D, and protein in childhood is important for achieving optimal peak bone mass in adulthood and preventing osteoporosis (Chapter 225) later in life. Dairy products are the primary source of calcium for most children. Adults should try to achieve the recommended dietary allowance for calcium (1000 mg/day until age 50 for women and age 70 for men, then 1200 mg/day), primarily through dietary calcium with supplemental calcium as necessary. The optimum intake and blood level of vitamin D are controversial. Adults should try to achieve an intake of vitamin D at the level of the recommended dietary allowance (600 IU/day until age 70, then 800 IU/day). Fruit and vegetable intake is associated with increased bone density through various mechanisms. Vitamin K, magnesium, and zinc are involved in bone metabolism, but supplementation has not been demonstrated to be beneficial to bone health. Excessive supplementation with vitamin A increases the risk of fracture, as does excess alcohol consumption.

Other Conditions

Obesity

Obesity is the most prevalent nutritional disorder in the United States (see Chapter 201). The metabolic syndrome (a constellation that includes obesity with a large waist circumference, increased levels of serum glucose and triglycerides, high blood pressure, and a reduced HDL cholesterol level) is strikingly prevalent in the United States and is a major risk factor for coronary heart disease, cancer, type 2 diabetes, and hypertension (Chapter 64). Globally, and even in some locales in the United States, malnutrition (Chapter 198) may exist in close proximity to overweight and obesity.[14,15]

Intestinal Diverticular Disease

Low dietary fiber intake causes constipation (Chapter 118), and it is thought to be a cause of intestinal diverticular disease (Chapter 128).

Dementia

Although physical activity is the strongest lifestyle factor that is associated with the avoidance of cognitive decline, dietary factors also play a role. Observational studies suggest that Mediterranean and DASH diets may help preserve cognitive function, in part by reducing the risk of cerebrovascular disease. Limited data raise the probability that even more emphasis on increasing the intake of green leafy vegetables, berries, fish, nuts, and olive oil, as well as limiting the intake of red meats, pastries, and sweets, may be even more beneficial.

Congenital Neural Tube Defects

Inadequate maternal folic acid intake (Chapter 199) has been definitively proven to be a major risk factor for congenital neural tube defects, such as spina bifida and myelomeningocele. For this reason, cereal and grain products have been fortified with folic acid in the United States since 1998, and supplementation with folic acid is recommended in all women capable of becoming pregnant (Chapter 219).

Dietary Supplements

Relatively few dietary supplements have demonstrated benefit in preventing disease. Although higher blood concentrations of vitamin C, carotenoids, and vitamin E are associated with lower mortality, this finding appears to be because they are markers of a better diet.[16] Meta-analyses of randomized, controlled trials of antioxidants have reported increased total mortality from vitamin A, vitamin E, and β-carotene. Vitamin D and calcium are necessary for adequate bone health, and vitamin D may have other health benefits, but the evidence is inconclusive. For example, vitamin D supplementation does not improve musculoskeletal health,[A6] reduce the risk of depression,[A7] or reduce the risk of cancer, cardiovascular disease, or mortality in adults.[A8] Although multivitamins are one of the most widely used dietary supplements, with over one third of Americans taking them, there is little evidence that they prevent cardiovascular disease or cancer. Fish consumption is associated with decreased cardiovascular disease, yet randomized trials have found no benefit from omega-3 supplementation,[A9] with the exception of icosapent ethyl (a highly purified eicosapentaenoic acid ethyl ester at 4 g daily), which can reduce future cardiovascular events by 25% in patients who already have very high-risk cardiovascular disease and have elevated serum triglyceride levels (135 to 499 mg/dL).[A10] By comparison, dietary supplements with vitamins C and E, zinc, copper, lutein, and zeaxanthin may benefit patients with early macular degeneration.[A11]

TRANSLATING EVIDENCE INTO DIETARY CHANGE

The evidence is strong that dietary habits can influence the incidence and severity of many incapacitating or lethal diseases.[17–19] No justification exists for the belief that modification of the "usual" American diet is unnecessary or futile. The following statement from the Scientific Report of the 2020 Dietary Guidelines Advisory Committee concisely outlines the optimal dietary pattern based on current evidence: "Common characteristics of dietary patterns associated with positive health outcomes include higher intake of vegetables, fruits, legumes, whole grains, low- or non-fat dairy, lean meat and poultry, seafood, nuts, and unsaturated vegetable oils and low consumption of red and processed meats, sugar-sweetened foods and drinks, and refined grains."[20] Various organizations have provided dietary recommendations generally consistent with this statement (see E-Table 13-1). The U.S. Departments of Agriculture and of Health and Human Services have developed and periodically revised the Dietary Guidelines for Americans (see Table 13-3). The Dietary Guidelines list three dietary patterns of eating that are consistent with the guidelines and people can use as a practical template to follow: the Healthy U.S., Healthy Vegetarian, and Healthy Mediterranean. A food guidance system, now called MyPlate (Fig. 13-2), is part of a larger communications initiative to help consumers make better food choices. Physicians can influence their patients' health by encouraging them to optimize their dietary habits and providing them with instructional materials, assistance from dietitians, or behavioral counseling,[A12] particularly in patients who are overweight, obese, or have other cardiovascular risk factors.[21]

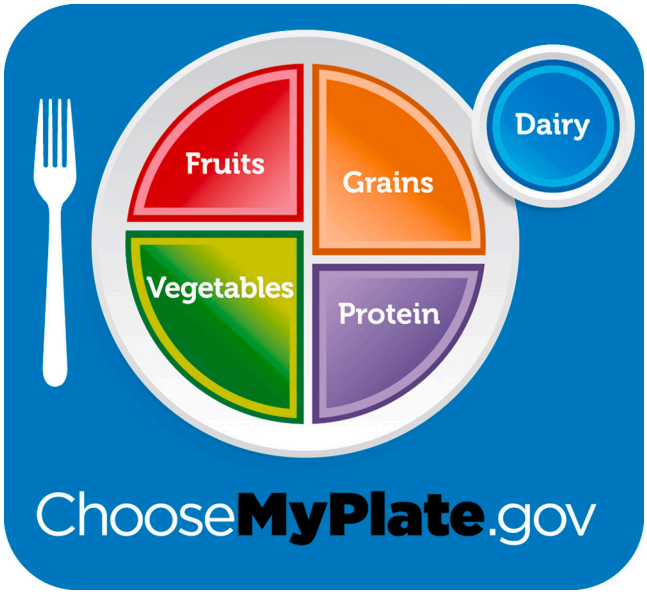

FIGURE 13-2. U.S. Department of Agriculture's MyPlate. MyPlate illustrates that a substantial proportion of dietary intake should be derived from vegetables, fruits, and grains, as contrasted with many Americans' expectation that protein sources should dominate. For more information, see www.ChooseMyPlate.gov.

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14 PHYSICAL ACTIVITY

WILLIAM E. KRAUS

DEFINITIONS

Physical activity can be broadly defined as bodily movement produced by skeletal muscles. *Exercise* refers to the subset of physical activity involving a structured program to improve physical fitness. *Health-enhancing physical activity* refers to the subset of physical activities that result in health benefits—generally activity involving large muscle groups of the body and substantial expenditures of energy. The two most important types of health-enhancing physical activity are moderate- to vigorous-intensity aerobic physical activity and moderate- to vigorous-intensity muscle strengthening activity.

TABLE 14-1 EXAMPLES OF MET LEVEL REQUIREMENTS

PHYSICAL ACTIVITY	MET	ACTIVITIES OF DAILY LIVING
LIGHT-INTENSITY ACTIVITIES	**<3**	**LIGHT ACTIVITIES**
Sleeping	0.9	Bathing in tub/eating
Watching television	1.0	Writing, desk work, typing
Walking, 1.7 mph (2.7 km/h), level ground, strolling, very slow	2.3	Light housework Warm shower - sitting
Walking, 2.5 mph (4 km/h)	2.9	Fixing meals
MODERATE-INTENSITY ACTIVITIES	**3 TO 6**	**MODERATE ACTIVITIES**
Bicycling, stationary, 50 watts, very light effort	3.0	Washing floors
Walking 3.0 mph (4.8 km/h)	3.3	Warm shower - standing
Calisthenics, home exercise, light or moderate effort general	3.5	Grocery shopping/vacuuming
Walking 3.4 mph (5.5 km/h)	3.6	Mowing lawn - riding
Bicycling, <10 mph (km/h), leisure, to work or for pleasure	4.0	Gardening - weeding and raking Gardening - digging
Bicycling, stationary, 100 watts, light effort	5.5	Snow shoveling
VIGOROUS-INTENSITY ACTIVITIES	**>6**	**VIGOROUS ACTIVITIES**
Jogging, general	7.0	Mowing lawn - walking
Calisthenics (e.g., push-ups, sit-ups, pull-ups, jumping jacks), heavy, vigorous effort	8.0	Chopping wood
Running jogging, in place	8.0	Carpentry work
Rope jumping	10.0	

MET = metabolic equivalents.
Data from St. Mary's General Hospital.

Regular physical activity improves *health-related physical fitness*—the physiologic components of fitness that influence the risk of disease, functional limitations, disability, and premature mortality. These components include cardiorespiratory endurance (aerobic capacity); skeletal muscle strength, power, and endurance; body composition and bone strength; balance, flexibility, and reaction time.

The primary attributes of physical activity are *type* (mode), *frequency, duration*, and *intensity*. Types of physical activity (e.g., walking, swimming, lifting, stretching) are grouped according to their main physiologic effects into well-known categories: *aerobic* (or "cardio"), *muscle strengthening, flexibility*, and *balance*. Intensity is the effort level during activity. For aerobic activity, the *absolute intensity* is measured in metabolic equivalents (METs). One MET is the resting metabolic rate, which is commonly taken to be 3.5 mL O_2/kg/minute in adults. The *relative intensity* is measured as the percentage of oxygen uptake reserve (aerobic capacity) required to perform an activity (Table 14-1). In practice, the generally linear relationship between heart rate and oxygen uptake makes it reasonable to use the heart rate to monitor the relative intensity of exercise. When the heart rate is not monitored, options for estimating relative intensity (Table 14-2) include the "talk test" and Rating of Perceived Exertion scale, where 6 equals no exertion and 20 equals maximal exertion.

The *volume* (or amount) of activity is the product of frequency, duration, and intensity. Volume can be measured (e.g., by questionnaires) as MET-minutes per week (a sum of the MET intensity of all activities multiplied by the minutes each activity is performed). Volume can also be assessed using wearable devices, such as accelerometers, which are calibrated to translate body movement into measures of volume.

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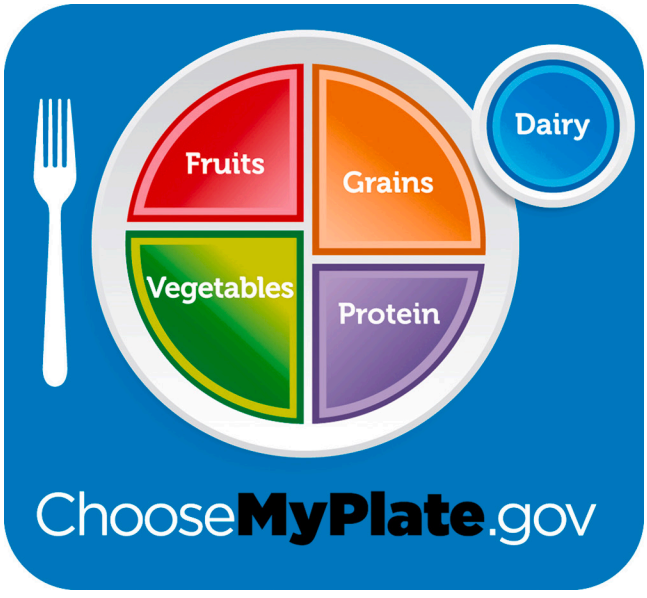

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ABSTRACT

Regular physical activity has numerous and substantial health benefits—both preventive and therapeutic. Major preventive health benefits include reduced risk of all-cause mortality, coronary heart disease, hypertension, stroke, colon cancer, breast cancer, type 2 diabetes, and fall-related fractures. The marginal benefit of even low physical activity is large, and the marginal benefit actually decreases with greater amounts of activity. The two most importance types of health-enhancing physical activity are moderate- to vigorous-intensity aerobic activity, which has a curvilinear dose-response relationship with health outcomes, and moderate- to vigorous-intensity muscle strengthening activity. Public health guidelines recommend the equivalent of at least 150 minutes of moderate-intensity aerobic activity each week, as well as muscle-strengthening activities on at least two days each week. Unfortunately, only about 20% of American adults currently meet both guidelines. Although physical activity involves risks of adverse events—primarily musculoskeletal injuries—the risk is low, especially if activity increases gradually over time. Health care providers can play an important role in promoting appropriate physical activity in their patients.

KEYWORDS

physical activity
exercise
chronic disease prevention
musculoskeletal injury

A L G r a w a n y

TABLE 14-2 CRITERIA FOR ASSESSING RELATIVE AND ABSOLUTE INTENSITY OF AEROBIC ACTIVITY

	RELATIVE INTENSITY			ABSOLUTE INTENSITY
Intensity	Percentage of heart rate reserve or oxygen uptake reserve	Rating of Perceived Exertion	Talk Test	MET Level
Sedentary behavior	<20*	<9	Can sing	1.0-≤1.5
Light	20-39*	9-11	Can sing	>1.5-<3.0
Moderate	40-<60	12-14	Can talk without pausing for breath, but cannot sing	3.0-<6.0
Vigorous	>60	14-17	Cannot talk without pausing for breath	≥6.0

*Information in table adapted from multiple sources, including guidelines by the American College of Sports Medicine (ACSM) (*ACSM's Guidelines for Exercise Testing and Prescription*. Eleventh Edition. Lippincott Williams & Wilkins: 2022). Note ACSM classifies >90%-100% of heart rate reserve and rating of perceived exertion levels of 18-20 as "near maximal to maximal." The table provides guidelines for individuals to characterize the intensity of physical activity.
MET = metabolic equivalents (see text for details).

TABLE 14-3 KEY PHYSICAL ACTIVITY GUIDELINES FOR ADULTS

All adults should avoid inactivity. Some physical activity is better than none, and adults who participate in any amount of physical activity gain some health benefits.

For substantial health benefits, adults should do at least 150 min (2.5 hr)/wk of moderate-intensity aerobic activity or 75 min (1.25 hr)/wk of vigorous-intensity aerobic activity, or an equivalent combination of moderate- and vigorous-intensity aerobic activity. However, recent evidence shows that bouts of exercise lasting less than 10 minutes also have health benefits.

For additional and more extensive health benefits, adults should increase their aerobic physical activity to 300 min (5 hr)/wk of moderate-intensity or 150 min (2.5 hr)/wk of vigorous-intensity aerobic physical activity, or an equivalent combination of moderate- and vigorous-intensity activity. Additional health benefits are gained by engaging in physical activity beyond this amount.

Adults should also do muscle-strengthening activities that are moderate or high intensity and involve all major muscle groups on 2 or more days/wk, as these activities provide additional health benefits.

Adapted from U.S. Department of Health and Human Services. 2018 Physical Activity Guidelines for Americans. https://health.gov/paguidelines/pdf/paguide.pdf. Washington, DC: U.S. Accessed January 4, 2022.

EPIDEMIOLOGY

Physical Activity Levels

About 50% of U.S. adults report that they meet public health guidelines (Table 14-3) for moderate-to-vigorous physical activity, about 25% report that they meet guidelines for muscle-strengthening activity, and about 25% of adults report that they meet both guidelines.[1] Among U.S. men and women ages 17 to 42 years, about 70% report adequate physical activity for military service, but only about one third are both adequately active and eligible based on their body mass index.[2] In the United States, men, White individuals, younger people, and people with greater incomes and education on average report more physical activity. Furthermore, although recreational physical activity is either stable or slightly improving, Americans have experienced a steady decline in occupational physical activity over the past five decades, and it is likely that levels of physical activity around the home have also declined.

Preventive Health Benefits in Adults

There is strong evidence that health-enhancing physical activity (Table 14-2) reduces the risk for premature mortality and coronary artery disease (Chapter 59), stroke (Chapter 376), high blood pressure (Chapter 64), adverse lipid profile (Chapter 190), type 2 diabetes mellitus (Chapter 210), metabolic syndrome, osteoporosis (Chapter 225), colon cancer (Chapter 179), breast cancer (Chapter 183), obesity (Chapter 201), and depression (Chapter 362).[3,4] The reduction in risk is substantial: for example, when active and inactive adults are compared, the risk reduction is greater than or equal to 30% for all-cause mortality, cardiovascular disease,[5] stroke, hypertension, colon cancer, and type 2 diabetes. Randomized trials show that multicomponent exercise programs, most commonly focused on balance training and muscle-strengthening activity, reduce the risk of falls and fall-related fractures by as much as 40%,[A1] and balance training likely improves physical function in older adults.[A2] Randomized trials show that exercise in older adults reduces the risk of hospitalization and mortality by 30%.[A3] Health-enhancing aerobic and muscle-strengthening activities also reduce the risk for cognitive impairment in older adults and improve cognition in adults over age 50 years,[A4] in part because levels of glycosylphosphatidylinositol, which is produced in the liver, increase with exercise and mitigate aging in the brain.[6] However, exercise does not slow cognitive decline in patients with mild to moderate dementia (Chapter 371).[A5] Some evidence also suggests that physical activity reduces the risk for anxiety disorders, osteoarthritis, sleep disorders, and back pain, as well as many types of cancer.

By some estimates, 10% or more of aggregate U.S. health care expenditures are related to inadequate physical activity. The benefits of physical activity are independent of other risk factors. For example, a sedentary obese smoker achieves health benefits from exercise, even if they continue to smoke and remain obese. When a healthy diet, regular activity, and abstinence from smoking occur together, the lifestyle effects are dramatic.

Mechanisms of Effect and Dose Response

The health benefits of physical activity are due to multiple incompletely understood physiologic effects. For example, physical activity reduces blood pressure in people with hypertension (Chapter 64).[A6] Possible mechanisms include reducing sympathetic activity and increasing vagal tone, reducing norepinephrine levels, releasing vasodilators such as endorphins, reducing insulin resistance, reducing plasma renin levels, and preventing overweight and obesity. In adults with type 2 diabetes, the effects of physical activity on skeletal muscle include changes in contractile protein isoforms, mitochondrial volume and functional capacity, metabolic regulation, intracellular signaling, and neuromuscular function.[A7]

Rather than its intensity or frequency, the dominant determinant of the health benefits of physical activity is likely the total weekly volume (amount) of moderate-to-vigorous physical activity. Substantial health benefits begin to accrue with a volume of 500 to 1000 MET-minutes/week. An adult can accumulate 500 MET-minutes by walking at 3.0 miles per hour (a 3.3-MET activity) on 3 days a week for 50 minutes (3.3 METs × 3 × 50 minutes = ≈500 MET-minutes). When measured by caloric expenditure, this volume of walking in a 75-kg (165-lb) adult expends an extra 430 kcal in addition to the 190 kcal that would have been expended at rest.

The dose-response relationship between moderate-to-vigorous physical activity volume and health benefits is curvilinear. The marginal benefit of activity at even low amounts is substantial, and the marginal benefit decreases with greater amounts of activity. Mortality risks fall by 20% with minimal activity, by 30% in people who meet the minimum recommendation of 7.5 MET hours of activity per week, and by about 40% in people who perform more than twice that amount.

The dose of moderate-to-vigorous physical activity reflects both energy expenditure (amount) and intensity. Thus, some health benefits should occur at low energy expenditure (i.e., low doses of moderate-to-vigorous physical activity) and at low intensity (i.e., light intensity). For example, 15 minutes per day (90 minutes per week) of moderate-intensity activity is associated with about a 15% decrease in mortality. Even at lower levels of moderate-to-vigorous physical activity, more energy expenditure from light-intensity activity, as indicated by less sitting time, is associated with lower mortality. However, greater amounts of moderate-to-vigorous physical activity (e.g., about 60 to 75 minutes per day) may be sufficient to eliminate the adverse effects of sitting. Muscle-strengthening activity also appears to be associated with lower risk of all-cause mortality, independent of the

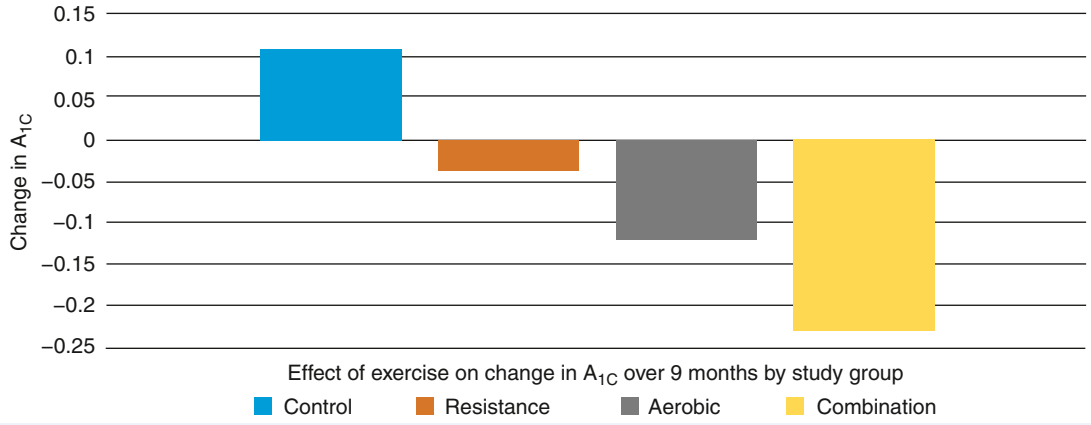

FIGURE 14-1. **Changes in hemoglobin A_{1c} levels in a 9-month randomized trial comparing three exercise interventions to a control in adults with type 2 diabetes (total N = 262). The largest improvement in A_{1c} occurred with combined aerobic exercise and resistance training (muscle-strengthening activity). (Data from Church TS, Blair SN, Cocreham S, et al. Effects of aerobic and resistance training on hemoglobin A_{1c} levels in patients with type 2 diabetes: a randomized controlled trial. *JAMA*. 2010;304:2253-2262.)**

amount of aerobic activity. Additionally, a combination of strength training and aerobic training produces greater health benefits than either alone to promote physical function in older adults, to lower hemoglobin A_{1c} levels in people with diabetes (Fig. 14-1), and to improve insulin sensitivity in adults with metabolic syndrome.

TREATMENT

Therapeutic Health Benefits in Adults

Clinical practice guidelines assign a substantial therapeutic role to physical activity in patients with coronary heart disease, high blood pressure (Chapter 64), type 2 diabetes (Chapter 210), obesity (Chapter 201), osteoporosis (Chapter 225), osteoarthritis (Chapter 241), claudication (Chapter 65), and chronic obstructive pulmonary disease (Chapter 76). Physical activity also plays a role in the management of depression and anxiety disorders (Chapter 362), elevated cholesterol levels (Chapter 190), pain (Chapter 26), heart failure (Chapter 46),[A8] syncope (Chapter 50), stroke (Chapter 375), back pain (Chapter 369), dementia (Chapter 371), and constipation (Chapter 123), as well as in the prophylaxis of venous thromboembolism (Chapter 68). Although there is more evidence for the therapeutic effects of aerobic exercise, muscle strengthening exercise also can have therapeutic effects, which can be additive or synergistic to those of aerobic exercise alone.

Health Risks of Physical Activity

Physical activity and exercise have some risks. Musculoskeletal injuries are by far the most common type of activity-related adverse event. The risk of injury depends on the type and volume of activity. The weekly volume of activity is directly related to the risk of musculoskeletal injuries, but when following public health guidelines of about 500 to 1000 MET-minutes/week, the risk of injury is low. The risk of injury is directly related to the rate of increase in the dose of activity, with more rapid increases having greater risk. Previous musculoskeletal injuries, excess weight, and low physical fitness also increase the risk of injury.

Relatively vigorous physical activity acutely increases the risk for sudden cardiac death (Chapter 50) and acute myocardial infarction (Chapter 58). However, the risk of sudden death and nonfatal events during and immediately after physical activity is extremely low—well below 1 event per 1,000,000 person-hours of activity. Importantly, physically active adults are protected from fatal and nonfatal cardiac events, with about 70% reduction in their risk of sudden death. This protection occurs because the time spent in vigorous activity per day is relatively small, so the risk of sudden cardiac death secondary to vigorous activity is far outweighed by the protective effect on cardiac events during the remainder of the day.

Recommended Amounts of Aerobic Activity for Prevention

To obtain substantial health benefits from physical activity, adults should partake in at least 150 minutes/week of moderate-intensity aerobic activity or 75 minutes/week of vigorous-intensity activity. Adults can do a combination of both moderate- and vigorous-intensity activity, using the rule of thumb that 1 vigorous-intensity minute of activity is equivalent to 2 moderate-intensity minutes.[7,8] Although previous recommendations were for bouts of aerobic activity of at least 10 minutes, bouts less than 10 minutes also appear to provide health benefits.

Recommended Amounts of Muscle-Strengthening Activity for Prevention

Adults should perform activities that strengthen the major muscle groups of the body at least 2 days each week. The major muscle groups are the legs, hips, back, chest, abdomen, shoulders, and arms.

Flexibility Activity

Flexibility activities are an important part of a complete physical activity regimen, but there is insufficient evidence that flexibility activities provide any health benefits, even for preventing injuries. Flexibility training may facilitate the types of physical activity that have health benefits. If so, flexibility training may be more important for people with reduced flexibility, such as older adults with age- and disease-related changes in range of motion.

Balance Activity

Balance training is recommended for adults at increased risk for falls, such as those older than 65 years with impaired gait or balance or frequent falls. Examples of balance exercises include sideways walking, backward walking, heel walking, and standing using a narrow base of support. Tai chi is an evidence-based approach to prevent falls. Preferably, adults at risk for falls should do balance training at least 3 days/week in the context of an evidence-based fall prevention program.

Sedentary Behavior

Increasing light-intensity activities by decreasing sedentary behavior is helpful for achieving and maintaining a healthy weight and reducing adverse health events. For example, more sedentary time is associated with greater risk of all-cause mortality, cardiovascular disease, some cancers, and type 2 diabetes.

Guidelines for Weight Management

The amount of activity required to maintain a healthy body weight varies widely among adults. For some adults, the amount of physical activity recommended in the guidelines will result in a stable, healthy body weight. Many adults, however, need greater amounts of activity to achieve a healthy weight.[9] These individuals should restrict their caloric intake and gradually increase their weekly physical activity to the point that is effective in achieving and maintaining a healthy body weight for them.

Additional Guidelines for Older Adults

In addition to balance training, older adults should be encouraged to be as active as feasible.[A9] For example, older adults who cannot do 150 minutes/week of moderate-intensity activity should be as active as their abilities and conditions allow. Resistance training and tai chi may be especially beneficial.[A10] Older adults should determine their level of physical activity using relative intensity, not absolute intensity. This latter guideline seeks to avoid inappropriately high levels of effort in older adults who have low fitness.

Recommending Physical Activity in Clinical Settings

Promoting physical activity in clinical settings involves essentially the same steps as the "5 A's" of smoking cessation (Chapter 363): ask, advise, assess, assist, arrange. Consistent with this approach, physicians should be knowledgeable in four domains: how to assess physical activity; how to make safe recommendations/prescriptions for physical activity in both healthy people and people with chronic conditions[10]; how to use effective behavioral interventions; and how to engage in their own active lifestyle for professional balance and as role models for patients.

Health care providers should ask and advise patients about physical activity regularly.[A11,11] One quality-of-care measure assesses whether asking and advising are done at least once a year in older adults. Some recommend that physical activity should be a "vital sign" that is assessed at every visit. Adults—especially older adults—identify their health care providers as an important source of advice on physical activity. Behavioral counseling is recommended for adults even if they have no cardiovascular risk factors. Intensive behavioral counseling is recommended for adults who are overweight or obese and have additional risk factors for cardiovascular disease. Such counseling should be a component

of community programs that promote physical activity in people at increased risk for type 2 diabetes.

Lifestyle Prescription

A lifestyle prescription refers to approaches that integrate physical activity into daily life. For example, rather than walking specifically for exercise, a person walks to work or walks for pleasure as a recreational activity. Common ways to integrate physical activity into daily life are walking and biking for transportation, performing yard work, and gardening. Use of wearable devices such as pedometers to track physical activity can increase steps per day by about 2000 above baseline and increase adherence to lifestyle prescriptions. More total steps per day are associated with lower all-cause mortality, whereas step intensity is not, after controlling for total steps.[12]

Tailoring the Recommendation

Recommendations should be tailored to individual abilities, individual preferences, medical conditions, and behavior techniques that improve adherence. Interventions are more likely to be successful if they include mutual goal setting, regular feedback, graded tasks, and use of equipment, such as a step monitor.[A12] Most people prefer home-based programs, which can provide health benefits that are similar to those of programs conducted elsewhere.[A13]

A target level of physical activity below that of preventive recommendations is appropriate for adults who have very low physical fitness, a large burden of chronic disease (e.g., severe chronic obstructive lung disease), or major functional limitations. An assessment of the nature of the activity limitation and the individual's capabilities and preferences can determine the target activity level and other details of the activity recommendation. Often, promoting physical activity in such adults relies on health care and community resources designed for people with preexisting limitations, such as cardiac rehabilitation, pulmonary rehabilitation, and exercise classes for adults with arthritis.

Risk Management

Strategies to reduce injury during physical activity include increasing physical activity gradually over time, selecting activities in which collision or contact with people or objects is unusual, increasing physical fitness, using appropriate gear and sports equipment (e.g., bike helmets), engaging in activities in safe environments, and following basic safety rules and policies. Popular activities such as walking, biking, swimming, and gardening have a low risk of injury. When individuals are increasing their level of physical activity, they should start with relatively moderate-intensity activity, increase the duration and frequency first, and then the intensity later. In general, adding 5 to 15 minutes of moderate-intensity activity per session, two to three times a week, to a person's usual activities carries a low risk of musculoskeletal injury and no known risk of sudden cardiac death.

There is no evidence of any protective value for medical consultation or of supervised exercise in healthy people of any age who seek to increase their level of physical activity. The U.S. Preventive Services Task Force recommends against routine screening for coronary disease in adults at low risk. Even in adults who are at high risk for coronary disease, there is insufficient evidence to recommend for or against screening with resting electrocardiography, exercise treadmill testing, electron-beam computed tomography, or C-reactive protein concentrations.

Coordination between Medical Care and the Community

Many factors that affect physical activity levels in Americans, such as the characteristics of the communal environment (e.g., parks and recreational facilities) and the social environment (e.g., crime and social support), are difficult to influence in medical care settings. Community-level interventions that address such characteristics are essential to promoting physical activity. Effective community-based interventions include school physical education, social support interventions, community-wide campaigns, and enhancement of access to places where physical activity is possible. Medical care and community efforts should be synergistic and mutually supportive. For example, health plans should advocate for evidence-based community interventions. Community programs should serve as resources for evidence-based therapeutic activity for selected chronically ill adults, such as exercise classes designed to reduce the risk of falls.

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15 IMMUNIZATION

ANDREW T. KROGER AND WALTER A. ORENSTEIN

GENERAL CHARACTERISTICS OF IMMUNIZATIONS

Immunization protects against disease or the sequelae of disease through the administration of an immunobiologic—a vaccine, toxoid, immune globulin preparation, or antitoxin. Protection induced by immunization can be active or passive (Tables 15-1 and 15-2).

ACTIVE IMMUNIZATION

Administration of a vaccine or toxoid causes the body to produce an immune response against the infectious agent or its toxins. Active immunization generally results in long-term immunity, although the onset of protection may be delayed because it takes time for the body to respond. Vaccines consist of suspensions of live (usually attenuated) microbes, nonlive microbes, or proteins of microbes. Nonlive recombinant vaccines[1] are genetically engineered, so they cannot be considered inactivated because they never consisted of whole microbes. By comparison, nonlive vaccines that are not produced via genetic engineering retain the characterization "inactivated." Toxoids are modified bacterial toxins that retain immunogenic properties but lack toxicity. With live attenuated vaccines, small quantities of living organisms multiply within the recipient until an immune response cuts off replication. In most recipients, a single dose of most live vaccines generally induces a long-term immune response that closely parallels natural infection. Additional doses are recommended to ensure high rates of population immunity.

PASSIVE IMMUNIZATION

Passive immunization using immune globulins or antitoxins delivers preformed antibodies to provide rapid temporary immunity. Immune globulins obtained from human blood may contain antibodies to a variety of agents, depending on the pool of human plasma from which they are prepared. Specific immune globulins are made from the plasma of donors with high levels of antibodies to

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ABSTRACT

Immunization is one of the most cost-effective methods of preventing morbidity and mortality from infectious diseases. In the United States, routine immunization, particularly of children, has resulted in decreases of 90% or more in reported cases of measles, mumps, rubella, congenital rubella syndrome, poliomyelitis, tetanus, invasive *Haemophilus influenzae* type b, varicella, hepatitis A, diphtheria, and pertussis. In many circumstances, immunization in children and adults not only prevents morbidity and mortality but also reduces long-term health care costs.

KEYWORDS

vaccines
active immunization
passive immunization
contraindications
precautions
adverse reactions

TABLE 15-1 PASSIVE IMMUNIZATIONS FOR ADULTS

DISEASE	NAME OF MATERIAL*†§	COMMENTS AND USE
Acquired immunodeficiency syndrome (AIDS)	Immune globulin intravenous (IGIV)	To prevent bacterial infection
Botulism	For non-infant botulism: in the United States, equine botulism antitoxin (BAT) against toxin types A, B, C, D, E, F, G For infant botulism: in the United States, botulism immune globulin types A and B; BabyBIG	Equine heptavalent antitoxin for treatment of non-infant botulism; available from CDC through state or local health department—contact emergency number of local or state health department. Human immune globulin for treatment of infant botulism available from the California Department of Health, Infant Botulism Treatment and Prevention Program, (510)231-7600
Chronic immune demyelinating polyneuropathy (CIDP)	Immune globulin intravenous (IGIV)	To improve neuromuscular ability
Chronic lymphocytic leukemia (CLL)	Immune globulin intravenous (IGIV)	To prevent bacterial infection
Cytomegalovirus	Cytomegalovirus immune globulin intravenous	Prophylaxis for bone marrow and kidney transplant recipients
Digoxin intoxication	Digoxin immune Fab, ovine	
Diphtheria	Diphtheria antitoxin, equine	Treatment of established disease; allergic reactions possible to serum of equine origin, available only from CDC
Erythroblastosis fetalis	Rho (D) immune globulin, intramuscular Rho (D) immune globulin, intravenous	Rh-negative women who are pregnant with Rh-positive infants
Hepatitis A	Immune globulin, intramuscular (IGIM)	Preexposure and postexposure prophylaxis for travelers and others who need protection before immunity can be achieved with hepatitis A vaccination
Hepatitis B	Hepatitis B immune globulin	Prophylaxis for needle stick or mucous membrane contact with HBsAg-positive persons, for sexual partners with acute hepatitis B or carriers of hepatitis B, for infants born to mothers who are carriers of HBsAg, for infants whose mother or primary caregiver has acute hepatitis B
Hypogammaglobulinemia	Immune globulin, intravenous, subcutaneous, intramuscular	Maintenance therapy
Idiopathic thrombocytopenic purpura	Immune globulin, intravenous (IGIV)	Therapy for acute episodes
Measles	Immune globulin, intramuscular (IGIM) Immune globulin, intravenous (IGIV)	Prevention or modification of disease in exposed persons, not for control of outbreaks; particularly indicated for unvaccinated infants aged <6 months, pregnant persons without evidence of measles immunity, and severely immunocompromised persons
Multifocal motor neuropathy	Immune globulin intravenous (IGIV)	To improve muscle strength
Rabies	Rabies immune globulin	Postexposure prophylaxis of animal bites
Scorpion sting	Centruroides (scorpion) immune F(ab')2, equine	Specific for *Centruroides* genus scorpions (e.g., Arizona bark scorpion)
Snakebite, coral snake	Antivenin (*Micrurus fulvius*), equine; North American coral snake antivenin	Specific for North American coral snake, *Micrurus fulvius*
Snakebite, crotalidae	Antivenin (Crotalidae) polyvalent, equine Crotalidae immune F(ab')2, equine	Effective for viper and pit viper bites, including rattlesnakes, copperheads, moccasins
Spider bite, black widow	Antivenin (*Lactrodectus mactans*), equine	Specific for black widow spider, *Latrodectus mactans*, and other members of the genus
Tetanus	Tetanus immune globulin	Management of tetanus-prone wounds in persons without adequate prior active immunization and treatment of tetanus
Vaccinia	Vaccinia immune globulin, intravenous (IGIV)	Treatment of eczema vaccinatum, vaccinia necrosum, and severe inadvertent inoculations such as ocular vaccinia after vaccinia (smallpox) vaccination; available only from CDC
Varicella	Varicella-zoster immune globulin	Prevention or modification of disease in exposed persons. Indicated for persons who are at high risk for complications from varicella, who have not had varicella or varicella vaccine, and who are exposed to varicella or herpes zoster: immunocompromised persons, newborn infants whose mothers have varicella around the time of delivery (i.e., 5 days before to 2 days after), hospitalized premature infants born at ≥28 weeks of gestation whose mothers do not have evidence of immunity to varicella, hospitalized premature infants born at <28 weeks of gestation or who weigh ≤1,000 g at birth, regardless of their mothers' evidence of immunity to varicella, pregnant persons; should be given as soon as possible after exposure and within 10 days

*All products to be administered intramuscularly, unless otherwise indicated.
†All products derived from humans unless otherwise specified.
§Table revisions provided by John Grabenstein.
CDC = Centers for Disease Control and Prevention; HBsAg = hepatitis B surface antigen.

TABLE 15-2 SELECTED IMMUNIZING AGENTS INDICATED FOR ADULTS*

DISEASE	IMMUNIZING AGENT	INDICATIONS	SCHEDULE	MAJOR CONTRAINDICATIONS (C) AND PRECAUTIONS (P)	COMMENTS
Adenovirus	Adenovirus type 4 and type 7 live oral vaccine	Military: for prevention of febrile acute respiratory disease caused by type 4 and type 7 adenovirus	One oral dose (two tablets)	C: Pregnancy C: Severe allergic reaction (e.g., anaphylaxis) to a vaccine component C: Inability to swallow whole tablets without chewing P: Altered immunocompetence P: Moderate or severe acute illness	Avoid pregnancy for 6 weeks after vaccination Virus may be shed in stool: exercise caution for 28 days after vaccination in contact with children younger than 7 years, pregnant persons, or immunosuppressed persons
Anthrax	Anthrax vaccine, adsorbed, inactivated vaccine	Preexposure prophylaxis of persons at high risk of exposure (e.g., military, certain laboratory workers) Consider with antibiotics for postexposure prophylaxis	0.5-mL dose IM at 0, 4, and 6 weeks and boosters at 12 and 18 months, then booster every 3 years thereafter If used after exposure, three doses at 0, 2, and 4 weeks with 60 days of antimicrobial therapy; antibiotics should be continued for 14 days after third dose	C: Severe allergic reaction to a vaccine component or after a prior dose P: Moderate or severe acute illness	Effectiveness against aerosol exposure inferred primarily from animal data A dose-sparing schedule of two doses with 2-4 week interval exists if there is a supply shortage
Cholera	Cholera vaccine, live attenuated oral cholera vaccine		One 100-mL oral dose before travel; booster doses are not presently recommended	C: Severe allergic reaction to a vaccine component or after a prior dose P: Moderate or severe acute illness Limited or lack of data on use of vaccine in: • Pregnant persons • Immunocompromised persons • Children <18 yr and adults 65 yr and older	All travelers to cholera-affected areas should follow safe food and water precautions and proper sanitation and personal hygiene measures as primary strategies to prevent cholera
COVID-19 (three types of vaccines)	1. mRNA vaccine (non-live messenger RNA encoding the novel SARS-2 coronavirus [NCoV2] spike protein)	Pfizer-BioNTech COVID-19 vaccine: authorized for ages 6 months through 11 years and approved for ages 12 years and older Moderna COVID-19 vaccine approved for ages 18 years and older	The information in this row/column is current for ADULTS only: Two brands (no preference) BNT162b2 two 0.3-mL doses separated by 3-8 weeks mRNA-1273 two 0.5-mL doses separated by 4-8 weeks A third dose of mRNA vaccine is recommended 28 days after the primary series for persons ages 5 years and older who are immunosuppressed. A booster dose of mRNA vaccine is recommended at least 2 months after the primary series for persons ages 12 years or older. The dose must be Pfizer-BioNTech for persons 12 years through 17 years of age. A booster dose is also recommended for persons ages 12 years old and older who were immunosuppressed upon receipt of the primary series and received an additional dose. The booster dose should be administered at least 2 months after the additional dose	C: History of severe allergic reaction to a prior dose of vaccine C: History of a known allergy to a component of the COVID-19 vaccine P: History of an immediate allergic reaction to any vaccine other than COVID-19 vaccine or to any injectable therapy (i.e., intramuscular, intravenous, or subcutaneous vaccines or therapies [excluding subcutaneous immunotherapy for allergies, i.e., "allergy shots"]) P: A history of a nonsevere, immediate (onset less than 4 hours) allergic reaction after a dose of one type of COVID-19 vaccine (i.e., mRNA or Janssen) is a precaution only to like-type vaccine (i.e., if the history is to an mRNA vaccine, this precaution is to any mRNA vaccine; if the history is to a COVID-19 vector vaccine, this precaution is to any COVID-19 vector vaccine) P: An allergy-related contraindication to one type of a COVID-19 vaccine is a precaution to other-type COVID-19 vaccine (i.e., if the contraindication is to mRNA vaccine, the precaution is to any COVID-19 vector vaccine; if the contraindication is to COVID-19 vector vaccine, the precaution is to any mRNA vaccine) P: History of myocarditis or pericarditis after a dose of an mRNA or Novavax COVID-19 vaccine P: Moderate or severe acute illness P: History of multisystem inflammatory syndrome	If a precaution on the basis of allergy, observe patient for 30 minutes instead of just 15 minutes Increased risk (3.5 cases per 1 million doses) of myocarditis and pericarditis. The highest risk is in males ages 12 years to 29 years

TABLE 15-2 SELECTED IMMUNIZING AGENTS INDICATED FOR ADULTS*—cont'd

DISEASE	IMMUNIZING AGENT	INDICATIONS	SCHEDULE	MAJOR CONTRAINDICATIONS (C) AND PRECAUTIONS (P)	COMMENTS
	2. Non-replicating adenovirus vector vaccine	Not licensed: Emergency Use Authorization Only: 18 years of age and older	One 0.5-mL dose	C: History of severe allergic reaction to a prior dose of vaccine C: History of a diagnosed allergy to a component of the COVID-19 vaccine C: Thrombosis with thrombocytopenia following receipt of a previous Janssen COVID-19 vaccine (or other COVID-19 vaccines not currently authorized in the United States that are based on adenovirus vectors, e.g., AstraZeneca) is a contraindication for Janssen COVID-19 only P: History of an immediate allergic reaction to any vaccine other than COVID-19 vaccine or to any injectable therapy (i.e., intramuscular, intravenous, or subcutaneous vaccines or therapies [excluding subcutaneous immunotherapy for allergies, i.e., "allergy shots"]) P: A history of a nonsevere, immediate (onset less than 4 hours) allergic reaction after a dose of one type of COVID-19 vaccine (i.e., mRNA or Janssen) is a precaution only to like-type vaccine (i.e. if the history is to an mRNA vaccine the precaution is to any mRNA vaccine; if the history is to a COVID-19 vector vaccine, the precaution is to any COVID-19 vector vaccine) P: An allergy-related contraindication to one type of a COVID-19 vaccine is a precaution to other-type COVID-19 vaccine (i.e., if the contraindication is to mRNA vaccine, the precaution is to any COVID-19 vector vaccine; if the contraindication is to COVID-19 vector vaccine, the precaution is to any mRNA vaccine) P: History of Guillain-Barré syndrome within 6 weeks of Janssen COVID-19 vaccine P: Moderate or severe acute illness	If a precaution on the basis of allergy, observe patient for 30 minutes instead of just 15 minutes Increased risk (7 cases in 1 million doses in persons ages 18 years to 49 years, and 1 case per million doses in persons age 50 years and older) of thrombosis with thrombocytopenia. An increased risk is in females age 18 to 49 years Increased risk (7.8 cases per million doses) of Guillain-Barré syndrome, especially in males ages 50 to 64 years

TABLE 15-2 SELECTED IMMUNIZING AGENTS INDICATED FOR ADULTS*—cont'd

DISEASE	IMMUNIZING AGENT	INDICATIONS	SCHEDULE	MAJOR CONTRAINDICATIONS (C) AND PRECAUTIONS (P)	COMMENTS
	3. Protein subunit vaccine	Novavax COVID-19 vaccine authorized for 12 years and older	NVX-CoV2373 two 0.5-mL doses separated by 3-8 weeks. A booster is recommended at least 2 months after the primary series (preferentially the booster dose should be an mRNA vaccine)	C: History of severe allergic reaction to a prior dose of vaccine C: History of a known allergy to a component of the COVID-19 vaccine P: History of an immediate allergic reaction to any vaccine other than COVID-19 vaccine or to any injectable therapy (i.e., intramuscular, intravenous, or subcutaneous vaccines or therapies [excluding subcutaneous immunotherapy for allergies, i.e., "allergy shots"]) P: A history of a nonsevere, immediate (onset less than 4 hours) allergic reaction after a dose of one type of COVID-19 vaccine (i.e., mRNA or Janssen) is a precaution only to like-type vaccine (i.e., if the history is to an mRNA vaccine, this precaution is to any mRNA vaccine; if the history is to a COVID-19 vector vaccine, this precaution is to any COVID-19 vector vaccine). Note that Janssen and Novavax vaccines contain polysorbate. mRNA vaccines do not contain polysorbate P: An allergy-related contraindication to one type of a COVID-19 vaccine is a precaution to other-type COVID-19 vaccine (i.e., if the contraindication is to mRNA vaccine, the precaution is to any COVID-19 vector vaccine; if the contraindication is to COVID-19 vector vaccine, the precaution is to any mRNA vaccine). Note that Janssen and Novavax vaccines contain polysorbate. mRNA vaccines do not contain polysorbate P: History of myocarditis or pericarditis after a dose of an mRNA or Novavax COVID-19 vaccine P: Moderate or severe acute illness P: History of multisystem inflammatory syndrome	

TABLE 15-2 SELECTED IMMUNIZING AGENTS INDICATED FOR ADULTS*—cont'd

DISEASE	IMMUNIZING AGENT	INDICATIONS	SCHEDULE	MAJOR CONTRAINDICATIONS (C) AND PRECAUTIONS (P)	COMMENTS
Diphtheria	Tetanus and diphtheria toxoids combined Adult preparation of pertussis antigens combined with tetanus and diphtheria toxoids (Tdap)	All adults	For incompletely immunized adults, three total 0.5-mL doses IM needed for primary series: two doses IM 4 weeks apart, third dose 6-12 months after second dose; it is preferable that the first dose is Tdap, subsequent doses can be Tdap or Td Booster (Tdap or Td) every 10 years No need to repeat if schedule is interrupted	C: History of neurologic reaction after a previous dose (Tdap only) C: Severe allergic reaction to a vaccine component or after a prior dose P: Moderate or severe acute illness	Tetanus and diphtheria toxoids combined with acellular pertussis vaccine (Tdap) preferred as one-time booster for all persons who have not previously received Tdap
Ebola	Live, recombinant viral vector vaccine: backbone: vesicular stomatitis virus (VSV), with gene encoding for envelope glycoprotein of *Z. ebolavirus*	Responders to an outbreak of Ebola In United States, health care workers in federally designated Ebola Treatment Centers or other staff working in biosafety level 4 facilities	One 1-mL dose	C: Hypersensitivity or allergy to a vaccine component P: Moderate or severe acute illness	Avoid kissing or sharing razors, eating utensils, toothbrushes, drinking cups, or needles for 2 weeks Avoid donating blood or contact with high-risk persons, or exposure of livestock to blood or body fluids for 6 weeks Use barrier methods for sexual interaction for 2 months
Haemophilus influenzae type b	Hib conjugate vaccines	Adults who have anatomic or functional asplenia and who are vaccine naïve or hematopoietic cell transplant recipients	Adults who have functional and anatomic asplenia and who are vaccine naïve: 1 dose Adults who have received a hematopoietic cell transplant: 3 doses at 1-month intervals	C: Severe allergic reaction to a vaccine component or after a prior dose P: Moderate or severe acute illness	
Hepatitis A	Inactivated hepatitis A vaccine	Travelers to highly or intermediately endemic countries Men who have sex with men Persons who use illegal drugs (injection and noninjection) Persons who work with hepatitis A virus–infected primates or who do research with the virus Persons with chronic liver disease Homeless persons HIV-infected persons	Two 0.5-mL doses at least 6 months apart for persons aged ≥1 year	C: Severe allergic reaction to a vaccine component or after a prior dose P: Moderate or severe acute illness	Should be considered for outbreak control Should be administered to all adults in settings where patients with indications are seen Adults with HIV can be tested at least 1 month after receipt of HepA vaccine to confirm immunity. If negative, a revaccination dose can be considered.

TABLE 15-2 SELECTED IMMUNIZING AGENTS INDICATED FOR ADULTS*—cont'd

DISEASE	IMMUNIZING AGENT	INDICATIONS	SCHEDULE	MAJOR CONTRAINDICATIONS (C) AND PRECAUTIONS (P)	COMMENTS
Hepatitis B	Three inactivated hepatitis B virus subunit vaccines containing HBsAg; one vaccine containing HBsAg and a CpG 1018 adjuvant	All adults ages 18 through 59 years Adults ages 60 years and older with any of the following health conditions: 1. Health care and public safety workers potentially exposed to blood 2. Clients and staff of institutions for the developmentally disabled 3. Hemodialysis patients 4. Men who have sex with men 5. Users of illicit injectable drugs 6. Recipients of clotting factors 7. Household and sexual contacts of HBV carriers 8. Inmates of long-term correctional facilities 9. Persons treated for sexually transmitted diseases or with multiple sexual partners 10. Travelers with close contact for ≥6 months with populations with high prevalence of HBV carriage 11. Persons with chronic liver disease 12. HIV-infected persons 13. Persons with diabetes mellitus 14. Incarcerated persons	Vaccine without CpG adjuvant: three doses IM at 0, 1, and 6 months volume of dose (Recombivax-HB and Engerix-B, 18- to 19-year-olds: 0.5 mL; 20-year-olds and older: 1 mL; PreHevbrio: 18-year-olds and older: 1 mL) Vaccine with CpG adjuvant: two 0.5-mL doses 1 month apart	C: Severe allergic reaction to a vaccine component or after a prior dose C: Hypersensitivity to yeast P: Moderate or severe acute illness	Pregnancy is not a contraindication Health care workers who have contact with patients or blood, sexual contacts of persons with chronic HBV infection, hemodialysis patients, and other immunosuppressed persons should be tested 1-2 months after vaccination to determine serologic response Consider vaccination in any adult age 60 years and older
Herpes zoster	Recombinant zoster vaccine (RZV), a subunit vaccine containing varicella-zoster virus glycoprotein E	All adults age 50 years and older Immunocompromised adults ages 19 through 49 years of age	Two 0.5-mL doses IM 2-6 months apart	C: Allergy to vaccine components P: Moderate or severe acute illness P: Active zoster disease	
Human papillomavirus (HPV)	Noninfectious recombinant vaccine prepared from purified virus-like particles of L1 capsid proteins of HPV types 6, 11, 16, 18, 31, 33, 45, 52, and 58 (nine-valent; bivalent and quadrivalent vaccines, while licensed, are no longer available in the United States)	Routine vaccination of adolescents with catch-up vaccination for adults through age 26 years. Shared clinical decision-making regarding HPV vaccination is recommended for some adults ages 27 through 45 years	Two 0.5-mL doses IM at 0 and 6-12 months if the first dose was administered before the 15th birthday Three 0.5-mL doses IM at 0, 1 to 2, and 6 months if first dose was administered at age 15 years or older Three 0.5-mL doses IM at 0, 1 to 2, and 6 months for persons who are immunocompromised, have an autoimmune disease, or have a malignant neoplasm, regardless of age at first dose	C: Severe allergic reaction to a vaccine component or to a prior dose P: Moderate or severe acute illness	The vaccine will not protect against existing infections Because vaccines do not protect against all HPV types, screening for cervical cancer among vaccinated persons should occur as for unvaccinated persons

TABLE 15-2 SELECTED IMMUNIZING AGENTS INDICATED FOR ADULTS*—cont'd

DISEASE	IMMUNIZING AGENT	INDICATIONS	SCHEDULE	MAJOR CONTRAINDICATIONS (C) AND PRECAUTIONS (P)	COMMENTS
Influenza (three types of vaccines: inactivated virus vaccine [IIV] exists as high-dose influenza vaccine, adjuvanted influenza vaccine, and standard-dose influenza vaccine)	Inactivated virus vaccine (IIV)	All adults, with greatest priority for those at higher risk for influenza complications (e.g., ≥50 years old, persons with underlying medical conditions, pregnant persons) or in contact with those at higher risk (e.g., health care workers, and persons with close contact with children <5 years)	Annual vaccination; see annual ACIP recommendation The volume of the dose varies by brand and age: 0.5 mL or 0.7 mL	C: Severe allergic reaction to an influenza vaccine component (except eggs) or after a prior dose P: Moderate or severe acute illness P: Guillain-Barré syndrome within 6 weeks of prior dose of influenza vaccine	Optimum timing of vaccination for most people is by the end of October. However, vaccination can occur throughout the influenza season, particularly for persons at high risk for complications and their contacts who were not vaccinated earlier. Only one dose of influenza vaccine per season is recommended for adults
	Live attenuated influenza virus (LAIV)	Adults through 49 years of age	Administered intranasally (0.2 mL) See annual ACIP recommendations	C: Persons <2 years or ≥50 years C: Pregnant persons C: Hypersensitivity to components of vaccine (except eggs) C: Anatomic or functional asplenia (including sickle cell disease) C: Cochlear implant C: Cerebrospinal fluid (CSF) leak C: Use of influenza antivirals C: Use of high-dose aspirin or high-dose aspirin-containing therapy C: Close contacts or a caregiver of someone with severe immunocompromise (requiring a protective environment) P: Persons with underlying disorders that place them at high risk of influenza complications (including asthma) P: Have history of Guillain-Barré syndrome within 6 weeks of prior dose of influenza vaccine P: Moderate or severe acute illness	Can be used for household contacts and health care workers caring for immunocompromised patients if the patient does not require a protected environment
	Recombinant influenza vaccine (RIV)	Adults	Annual vaccination (one 0.5-mL dose)	C: Severe allergic reaction to any component of the vaccine P: Moderate or severe acute illness P: Guillain-Barré syndrome within 6 weeks of prior dose of influenza vaccine	
Japanese encephalitis	Inactivated Japanese encephalitis virus vaccine	Travelers to Asia spending at least 1 month in endemic areas during transmission season	Two 0.5-mL doses IM on days 0 and 28. The FDA approved an alternate 0- and 7-day schedule	C: Pregnancy P: Moderate or severe acute illness	
Measles	Live virus vaccine (with mumps and rubella [MMR])	All adults born after 1956 without history of live vaccine on or after first birthday, laboratory confirmation of disease, or detectable measles antibody Persons born before 1957 generally can be considered immune	One 0.5-mL dose sufficient for most adults; two doses at least 1 month apart indicated for persons entering college or medical facility employment, traveling abroad, or at risk of measles during outbreaks	C: Altered immunity (e.g., leukemia, lymphoma, generalized malignant disease, congenital immunodeficiency, immunosuppressive therapy) C: Anaphylactic hypersensitivity to neomycin or gelatin C: Pregnancy P: Thrombocytopenia P: Immune globulin or other blood products within prior 3-11 months P: Untreated tuberculosis P: Moderate or severe acute illness	Persons with anaphylactic allergies to eggs may be vaccinated (see text) Vaccine should be administered to persons with asymptomatic HIV infection and should be considered for other patients with HIV infection except those with severe immunocompromise

TABLE 15-2 SELECTED IMMUNIZING AGENTS INDICATED FOR ADULTS*—cont'd

DISEASE	IMMUNIZING AGENT	INDICATIONS	SCHEDULE	MAJOR CONTRAINDICATIONS (C) AND PRECAUTIONS (P)	COMMENTS
Meningococcal disease (two types of vaccines)	1. Meningococcal conjugate vaccines containing polysaccharide of serogroups A, C, W, and Y	All persons with persistent complement component deficiencies or complement inhibitor use, HIV infection, or anatomic or functional asplenia Persons who will travel to areas where meningococcal infection is hyperendemic or epidemic Microbiologists routinely exposed to *Neisseria meningitidis* People at increased risk during an outbreak (e.g., unvaccinated or undervaccinated first-year college students living in residence halls, military recruits) Other persons at risk during an outbreak	A two-dose primary series recommended for individuals with complement component deficiency or complement inhibitor use, HIV infection, or anatomic or functional asplenia; others should receive a single dose Individuals at ongoing increased risk of meningococcal disease should receive a booster dose every 5 years	C: Allergic reactions to a component of the vaccine, including diphtheria or tetanus toxoid, or to other diphtheria toxoid-, CRM197-, or tetanus-toxoid-containing vaccines (depending on vaccine) P: Moderate or severe acute illness	
	2. Recombinant meningococcal B protein vaccines containing either two alleles of one protein (MenB-FHbp) or three proteins as well as one protein-containing outer membrane vesicle (MenB-4 C) (ages 10 years and older)	All persons with persistent complement component deficiencies or complement inhibitor use or anatomic or functional asplenia Certain laboratory workers May be useful during localized outbreaks May be administered to young adults before age 24 years to provide short-term protection against most strains of serogroup B meningococcal disease	For healthy persons who are not at increased risk for meningococcal disease, either a 2-dose series of MenB-4C at 0 and 1 mo, or a 2-dose series of MenB-FHbp at 0 and 6 months (each dose 0.5 mL). For persons at increased risk for meningococcal disease, including during serogroup B outbreaks, MenB-FHbp should be given as a 3-dose series at 0, 1-2, and 6 months. For persons at increased risk, the 2-dose series of MenB-4C at 0 and 1 month remains in effect. The same vaccine product should be used for all doses Booster dose is recommended 1 year after the primary series and every 2-3 years thereafter for those who continue to be at increased risk Booster dose is indicated in an outbreak of serogroup B disease if 6 months or more have passed since completion of the primary series	C: Severe allergic reaction to a vaccine component or after a prior dose P: Latex sensitivity (MenB-4C only) P: Moderate or severe acute illness P: Pregnancy	Evidence supports use of MenB vaccines in all persons at increased risk for serogroup B meningococcal disease Shared clinical decision making for young adults not at increased risk
Mumps	Live virus vaccine (measles and rubella [MMR])	All adults born after 1956 without history of live vaccine on or after first birthday, laboratory confirmation of disease, or detectable mumps antibody Persons born before 1957 generally can be considered immune	One 0.5-mL dose sufficient for most adults Two doses at least 1 month apart indicated for persons entering college or medical facility employment or traveling abroad, or at risk of mumps during outbreaks	C: Altered immunity (e.g., leukemia, lymphoma, generalized malignant disease, congenital immunodeficiency, immunosuppressive therapy) C: Anaphylactic hypersensitivity to neomycin or gelatin C: Pregnancy P: Immune globulin or other blood products within prior 3 to 11 months P: Thrombocytopenia if administered with measles vaccine P: Moderate or severe acute illness	Persons with anaphylactic allergies to eggs may be vaccinated Persons previously vaccinated with two doses of a mumps-containing vaccine who are identified by public health as at increased risk for mumps because of a mumps outbreak should receive a third dose of a mumps-containing vaccine to improve protection against mumps disease and related complications

TABLE 15-2 SELECTED IMMUNIZING AGENTS INDICATED FOR ADULTS*—cont'd

DISEASE	IMMUNIZING AGENT	INDICATIONS	SCHEDULE	MAJOR CONTRAINDICATIONS (C) AND PRECAUTIONS (P)	COMMENTS
Pertussis	Adult preparation of pertussis antigens combined with tetanus and diphtheria toxoids (Tdap)	Catch-up vaccination for all persons ≥13 years May be given whenever tetanus-toxoid–containing vaccine is indicated One dose per pregnancy	One 0.5-mL dose Pregnant persons: one dose during each pregnancy preferably early in the period between 27 and 36 weeks of gestation	C: History of neurologic reaction after a previous dose (Tdap only) C: Severe allergic reaction to a vaccine component or after a prior dose P: Moderate or severe acute illness	Two preparations are available, one licensed for all persons ≥10 yr, one for 10 to 64 yr olds
Pneumococcal disease (three vaccines)	15-valent pneumococcal conjugate vaccine (PCV15) 23-valent pneumococcal polysaccharide vaccine (PPSV23) 20-valent pneumococcal conjugate vaccine (PCV20)	All adults age 65 years or older and adults ages 19 to 64 years at risk for invasive pneumococcal disease (including asthma), diabetes mellitus, alcohol use disorder, cirrhosis, cerebrospinal fluid leaks, splenic dysfunction or anatomic asplenia, Hodgkin disease, lymphoma, multiple myeloma, chronic renal failure, nephrotic syndrome, immunosuppression, HIV infection, cigarette smokers ages 19 years and older), who previously have not received PCV13 or whose pneumococcal vaccination history is unknown	Choose either: PCV20 or PCV15 followed by PPSV23 1 year later (can consider an 8-week interval between PCV15 and PPSV23)	C: Severe allergic reaction to a vaccine component or after a prior dose P: Moderate or severe acute illness	Persons who have previously received PCV13 should receive PPSV23. If PPSV23 is unavailable, they may receive PCV20
Poliomyelitis	Inactivated poliovirus vaccine (IPV)	Certain adults who are at greater risk of exposure to wild-type or vaccine-derived poliovirus than the general population, including laboratory workers, health care workers, and travelers to countries where poliomyelitis is epidemic or endemic or specific populations with disease caused by poliovirus	For unvaccinated adults, two 0.5-mL doses IM or SQ 4 weeks apart and a third dose 6-12 months after the second; if <4 weeks available before protection is needed, a single dose of IPV and ensure that the series is complete after travel For incompletely immunized adults, complete primary series of three doses of IPV or prior oral poliovirus vaccine (OPV); no need to restart interrupted series; a mixed series can be considered complete A single dose of IPV can be given to adults who previously received a primary series but now are at high risk, such as those traveling to an endemic area	C: Severe allergic reaction to a vaccine component or after a prior dose P: On theoretical grounds, pregnant persons should not receive IPV, but if immediate protection is needed, IPV can be used P: Moderate or severe acute illness	
Rabies	Inactivated vaccine, HDCV or PCECV	High-risk persons, including animal handlers, selected laboratory and field workers, and persons traveling for ≥1 month to areas with high risk of rabies	Preexposure prophylaxis: for persons 18 years old and older, two doses of 1 mL IM on days 0 and 7 Confirmation of immunity recommended for laboratory workers, bat handlers, and animal handlers	C: History of severe hypersensitivity reaction P: Moderate or severe acute illness	Further doses needed after exposure Persons traveling to high-risk areas should receive booster dose at 1 to 3 years

TABLE 15-2 SELECTED IMMUNIZING AGENTS INDICATED FOR ADULTS*—cont'd

DISEASE	IMMUNIZING AGENT	INDICATIONS	SCHEDULE	MAJOR CONTRAINDICATIONS (C) AND PRECAUTIONS (P)	COMMENTS
Rubella	Live virus vaccine (with mumps and measles [MMR])	Adults, particularly persons of childbearing age, who lack history of rubella vaccine, laboratory confirmation of disease, and detectable rubella-specific antibodies in serum Persons in institutions where rubella outbreaks may occur, such as hospitals, the military, and colleges Persons born before 1957, except those who can become pregnant, generally can be considered immune	One 0.5-mL SQ dose	C: Pregnancy, altered immunity (e.g., leukemia, lymphoma, generalized malignant disease, congenital immunodeficiency, immunosuppressive therapy) C: Anaphylactic hypersensitivity to neomycin C: Administration of blood products should not contraindicate postpartum vaccination P: Thrombocytopenia if administered with measles vaccine P: Immune globulin or other blood products within prior 3 to 11 months P: Moderate or severe acute illness	People who can become pregnant should be counseled to avoid pregnancy for 1 month after vaccination
Smallpox (two types of vaccines)	Live vaccinia virus	Persons working with orthopox viruses	One 0.0025-mL dose intracutaneously with a bifurcated needle Boosters every 10 years and perhaps every 3 years for persons working with virulent orthopox viruses	C: History or presence of eczema or other acute, chronic, or exfoliative skin condition in patient or a close household or personal contact C: Immunosuppression or pregnancy in patient or a close household or personal contact C: Breast-feeding C: Allergy to a vaccine component P: History of heart disease P: Moderate or severe acute illness No contraindications if exposed to smallpox	Some complications of vaccination are treatable with vaccinia immune globulin Vaccine is effective 3-4 days after exposure to variola and perhaps longer to prevent or to modify the illness Serious adverse events are rare but significant, including eczema vaccinatum, progressive vaccinia, myopericarditis, autoinoculation, and encephalitis Vaccinia is transmissible
	Live, nonreplicating vaccinia vector vaccine	Adults at risk for smallpox or monkeypox infection	Two 0.5-mL doses SQ, 4 weeks apart	P: Allergy to a vaccine component (based on FDA package insert) P: Altered immunocompetence	
Tetanus	Tetanus and diphtheria toxoids combined (Td) Adult preparation of pertussis antigens combined with tetanus and diphtheria toxoids (Tdap)	All adults	For incompletely immunized adults, three total 0.5-mL doses IM needed for primary series: two doses IM 4 weeks apart, third dose 6-12 month after second dose; preferable that first dose is Tdap, subsequent doses can be Tdap or Td Booster (Tdap or Td) every 10 years No need to repeat if schedule is interrupted	C: History of neurologic or severe allergic reaction after a prior dose C: History of neurologic reaction after a previous dose (Tdap only) P: Moderate or severe acute illness P: Guillain-Barré syndrome <6 weeks after previous dose of tetanus-toxoid–containing vaccine	Special recommendations for wound treatment (see text) Persons with Guillain-Barré syndrome within the first 6 weeks after immunization, particularly adults who received a prior primary series, probably should not be revaccinated in most circumstances One-time booster of Tdap for all adults
Typhoid fever	Vi capsular polysaccharide vaccine Live attenuated Ty21a oral vaccine	Travelers to areas where the risk of prolonged exposure to contaminated food and water is high May be considered for family and intimate contacts of carriers and laboratory workers who work with *Salmonella* Typhi	Vi polysaccharide vaccine: one dose IM 0.5 mL; boosters every 2 years Oral vaccine: four doses on alternate days; repeat series every 5 years if risk continues	C: Severe local or systemic reaction to a prior dose C: Ty21a vaccine should not be administered to persons with altered immunity or those receiving antimicrobial agents P: Moderate or severe acute illness	Cumulative efficacy at 2.5 to 3.0 years: Vi capsular polysaccharide: 55%, Ty21a: 48% Food and water precautions essential

TABLE 15-2 SELECTED IMMUNIZING AGENTS INDICATED FOR ADULTS*—cont'd

DISEASE	IMMUNIZING AGENT	INDICATIONS	SCHEDULE	MAJOR CONTRAINDICATIONS (C) AND PRECAUTIONS (P)	COMMENTS
Varicella (primary infection; see herpes zoster for secondary prevention)	Live attenuated Oka strain of varicella-zoster virus (VAR)	All persons without evidence of varicella immunity	Two 0.5 mL doses SQ 4-8 weeks apart for adults A second dose is recommended for all persons who previously received one dose	C: Immunocompromise C: Pregnancy C: Allergy to vaccine components P: Immune globulin or other blood products within prior 3 to 11 months P: Moderate or severe acute illness	Adults born in the United States before 1980 (except health care workers, pregnant persons, and immunocompromised persons), or persons with clinician-diagnosed or verified history of varicella or herpes zoster can be considered immune Vaccine virus has rarely been transmitted to contacts from healthy vaccinees in whom rash developed Persons who receive vaccine should not become pregnant for 1 month
Yellow fever	Live attenuated virus (17D strain)	Persons living or traveling in areas where yellow fever exists	One 0.5 mL dose SQ booster every 10 years for at-risk laboratory personnel and certain travelers (pregnant persons, hematopoietic stem cell transplant recipients vaccinated before transplant, HIV-infected persons, and travelers who will be in a higher-risk setting based on season, location, activities, and duration of their travel, such as travelers who plan to spend a prolonged period in endemic areas or those traveling to highly endemic areas such as rural West Africa during peak transmission season or an area with an ongoing outbreak)	C: Immunocompromised persons C: History of anaphylactic allergies to eggs P: Pregnancy on theoretical grounds, although may be given if risk is high P: Moderate or severe acute illness	Fever, jaundice, and multiple-organ system failure (viscerotropic disease) have been rarely reported in first-time recipients of 17D-derived yellow fever vaccinations Vaccinate only persons traveling to areas where yellow fever is endemic.

*See the text and package inserts for further details, particularly regarding indications, dosage, administration, side effects, and adverse reactions and contraindications.

ACIP = Advisory Committee on Immunization Practices; COVID = coronavirus disease; FDA = U.S. Food and Drug Administration; HBsAg = hepatitis B surface antigen; HBV = hepatitis B virus; HDCV = human diploid cell vaccine for rabies; HIV = human immunodeficiency virus; HPV = human papillomavirus; IM = intramuscularly; IPV = inactivated poliovirus vaccine; MMR = measles, mumps, and rubella vaccine; OPV = live trivalent, bivalent, or monovalent oral poliovirus vaccine; PCECV = purified chick embryo cell culture rabies vaccine; SARS = severe acute respiratory syndrome; SQ = subcutaneously.

specific antigens (such as tetanus immune globulin). Most immune globulins must be injected intramuscularly, although intravenous and subcutaneous preparations are also available. Antitoxins are solutions of antibodies derived from animals immunized with specific antigens (e.g., diphtheria antitoxin). Passive immunization usually is indicated to protect individuals immediately before anticipated exposure or shortly after known or suspected exposure to an infectious agent (see Table 15-1), when active immunization either is not possible or has not been adequate.

ROUTE AND TIMING OF VACCINATION

Each immunobiologic has a preferred site and route of administration. In adults, vaccines intended for intramuscular injection should preferably be administered in the deltoid muscle. For most adults, intramuscular injections should be administered with a 1- to 1½-inch, 22- to 25-gauge needle. Use of the buttocks is discouraged except when volumes larger than 4 mL per injection are required because of the potential for damage to the sciatic nerve and because of diminished immune response to some vaccines (such as hepatitis B), probably because vaccine is injected into fat rather than into muscle. Subcutaneous vaccines are usually administered in the triceps area. In general, inactivated vaccines and toxoids can be given at the same visit at different sites. Live and inactivated vaccines usually can be administered at the same time. For example, measles, mumps, and rubella (MMR) vaccine can be administered at the same time as inactivated poliovirus vaccine and live attenuated varicella vaccine. In general, injected and intranasally administered live vaccines not delivered on the same day should be separated by at least 4 weeks to avoid interference with viral replication of the second vaccine by the first vaccine; if viral replication is hampered, a reduced immune response will occur. Orally administered live vaccines (such as oral typhoid vaccine) can be administered at any interval before or after live injected or intranasal vaccines. Immune globulin may interfere with the replication of injected live vaccine viruses; ideally, most live vaccines should be administered at least 2 weeks before or 3 to 11 months after receipt of immune globulin. Immune globulin does not interfere with the response to yellow fever vaccine and is not believed to interfere with orally or intranasally administered live virus vaccines.

CONTRAINDICATIONS AND PRECAUTIONS

Persons who administer vaccines should screen patients for contraindications and precautions to the vaccine before each dose of vaccine is administered (see Table 15-2). Screening is facilitated by consistent use of screening questionnaires, which are available from some state vaccination programs and other sources (e.g., Immunize.org, https://www.immunize.org). A contraindication is a condition that increases the risk for a serious adverse reaction. A vaccine should not be administered when a contraindication is present; for example, MMR vaccine should not be administered to severely immunocompromised persons. The only contraindication applicable to all vaccines is a history of a severe allergic reaction (e.g., anaphylaxis) after a previous dose of that vaccine or a vaccine component (unless the recipient has been desensitized). In addition, severely immunocompromised persons generally should not receive live vaccines. Because of the theoretical risk to the fetus, persons known to be pregnant generally should not receive live, attenuated vaccines.

A precaution is a condition that may increase the risk for a serious adverse reaction (i.e., a person may experience a more severe reaction to the vaccine than would have otherwise been expected, but the risk is less than the risk expected with a contraindication); may compromise the ability of the vaccine to produce immunity (e.g., administering measles vaccine to a person with passive immunity to measles from a blood transfusion); or may interfere with the diagnosis of another condition. In most cases, vaccinations should be deferred when a precaution is present. However, a vaccination may be indicated despite a precaution if the benefit of protection from the vaccine outweighs the risk for an adverse reaction. For example, a dose of combined tetanus toxoid, reduced diphtheria toxoid, and acellular pertussis (Tdap) should be considered for a person in a community with a pertussis outbreak even if that person previously developed Guillain-Barré syndrome (Chapter 388) after a dose of pertussis-containing vaccine. The presence of a moderate or severe acute illness with or without a fever is a precaution to administration of all vaccines.

The egg protein contained in vaccines grown in chicken eggs (influenza [except cell-culture and recombinant] and yellow fever vaccines) may cause reactions in persons severely allergic to eggs. Persons who have experienced only hives following egg exposure should receive influenza vaccines as recommended. Persons whose reactions to eggs include symptoms other than hives, such as angioedema, respiratory distress, lightheadedness, or recurrent emesis, or who required epinephrine or another emergency medical intervention may similarly receive any licensed influenza vaccine that is otherwise appropriate for their age and health status, but such individuals should be vaccinated in an inpatient or outpatient medical setting, supervised by a health care provider who is able to recognize and manage severe allergic reactions.

If a person has a severe egg sensitivity or has a positive skin test to yellow fever vaccine but the vaccination is recommended because of the travel destination–specific risk, desensitization can be performed under direct supervision of a physician experienced in the management of anaphylaxis. For such persons receiving influenza and/or yellow fever vaccines, the vaccines should be administered in an inpatient or outpatient medical setting (including, but not necessarily limited to, hospitals, clinics, health departments, and physicians' offices) and be supervised by a health care provider who is able to recognize and manage severe allergic conditions. Although measles and mumps vaccines are grown in chick embryo tissue culture, the risk of anaphylaxis even in persons with severe hypersensitivity to eggs is low, so they can be vaccinated without prior skin testing.

Vaccine providers should consider observing patients for 15 minutes following administration of any vaccine to decrease the risk for injury should syncope occur.

ADVERSE REACTIONS

All vaccines are associated with some adverse reactions. Adverse reactions fall into three general categories: local, systemic, and allergic, including anaphylactic. Local reactions, such as pain or redness at the injection site, are generally the most frequent but least severe. Systemic adverse reactions include fever, malaise, myalgias (muscle pain), headache, and loss of appetite. These symptoms, which are common and nonspecific, may occur in vaccinated persons because of the vaccine or because of something unrelated to the vaccine. Antipyretics should not be administered routinely before or at the time of vaccination because they appear to reduce the immune response,[A1,A2] but they can be used for the treatment of fever and local discomfort that may occur after vaccination. Anaphylactic allergic reactions, which are the least frequent but most severe of such reactions, may be caused by the vaccine antigen itself; by another component of the vaccine, such as the cell culture material, stabilizer (e.g., gelatin), preservative, or antibiotic used to inhibit bacterial growth; or by vaccine packaging content (i.e., latex). Life-threatening anaphylactic reactions occur at a rate of about one per million doses.

Suspected adverse events temporally related to vaccinations should be reported to the Vaccine Adverse Event Reporting System (at www.vaers.hhs.gov). The National Vaccine Injury Compensation Program was established in the 1980s to compensate individuals who experience certain health events after vaccination on a "no-fault" basis. No-fault means that persons filing claims are not required to prove negligence on the part of either the health care provider or manufacturer to receive compensation. The program covers all routinely recommended childhood vaccinations, although adults who receive a covered vaccine may also file a claim. Claims may be based on the Vaccine Injury (see https://www.hrsa.gov/sites/default/files/hrsa/vaccine-compensation/vaccine-injury-table.pdf), which lists the adverse events associated with vaccines and is updated periodically.

GENERAL CONSIDERATIONS

The major group in the United States that makes comprehensive, detailed, evidence-based recommendations regarding immunization of adults is the Advisory Committee on Immunization Practices (ACIP) of the Centers for Disease Control and Prevention, which publishes its recommendations in the *Morbidity and Mortality Weekly Report* (also available at http://www.cdc.gov/vaccines/schedules/hcp/adult.html). Immunizations for adults depend on age, lifestyle, occupation, and medical conditions. Two adult immunization schedules are available, one based on age group (Fig. 15-1 and E-Table 15-1 and 15-2) and one based on underlying risk (Fig. 15-2 and see Table 15-2). Other vaccines recommended for travel and bioterrorism exposures are not included in these two figures but are discussed later.

All adults who have not received a primary series of diphtheria-tetanus-pertussis–containing vaccine as children should receive a series of three tetanus and diphtheria toxoid–containing vaccines, with the preferred schedule of 1 dose of Tdap, followed by 1 dose of either Td or Tdap at least 4 weeks afterward, and 1 dose of either Td or Tdap 6–12 months later.[2–4] All adults who received a diphtheria-tetanus-pertussis (DTaP) vaccine series as children should receive a dose of Tdap followed by decennial doses of Tdap or Td. In circumstances where a tetanus-toxoid–containing or diphtheria-toxoid–containing vaccine is recommended, such as for wound care, either Tdap or Td may be administered.

In circumstances where Td is recommended, either Tdap or Td can be administered. Persons born in or after 1957 should have evidence of immunity to measles, mumps, and rubella (e.g., documentation of vaccination or presence of antibodies considered compatible with protection). Adults without evidence of immunity to varicella (documentation of age-appropriate vaccination with two doses of a varicella-containing vaccine [varicella vaccine or MMRV]; laboratory evidence of immunity or confirmation of disease; birth in the United States before 1980, except for health care personnel or pregnant persons; or diagnosis or verification of a history of varicella or herpes zoster disease by a health care provider) should receive the varicella vaccine. Adults 50 years and older should receive two doses of the recombinant zoster subunit vaccine.

All persons younger than age 27 years should receive a human papillomavirus (HPV) vaccine series. Catch-up vaccination is not recommended for all adults; instead, shared clinical decision making, which requires a conversation between a provider and a potential vaccine recipient, is recommended for persons 27 through 45 years.

All persons ages 65 years or older and adults ages 19 years through 64 years who are at high risk for invasive pneumococcal disease (see Table 15-2), who have not received PCV13, or whose pneumococcal vaccination history is unknown should receive either a dose of PCV20 or a dose of PCV15 followed by PPSV23 1 year later (providers may consider an interval of 8 weeks between PCV15 and PPSV23).

Influenza vaccination is recommended annually for all persons 6 months of age or older, including all health care personnel. Health care workers exposed to blood or blood products should receive hepatitis B vaccine. Health care workers should also be immune to measles, mumps, rubella, tetanus, diphtheria, pertussis, and varicella.

ALTERED IMMUNOCOMPETENCE

Patients with altered immunocompetence (also referred to as immunocompromise, immunodeficiency, and immunosuppression) include persons with immunodeficiency diseases, leukemia, lymphoma, and generalized malignant disease and those who are immunosuppressed from therapy with corticosteroids, alkylating agents, antimetabolites, and radiation generally should not receive live vaccines (E-Table 15-3). Qualifications exist with one type of altered immunocompetence, infection with HIV. Two doses of MMR vaccine are recommended for all persons aged 12 months and older who have HIV infection and do not have evidence of immunity to measles, rubella, and mumps and who are not severely immunosuppressed (i.e., a CD4 percentage ≥15% and $CD4^+$ lymphocyte counts ≥200 cells/μL for ≥6 months for persons aged >5 years). Varicella vaccination (two doses, 3 months apart) may be considered in HIV-infected persons with $CD4^+$ T-lymphocyte counts above 200 cells/μL. Patients with leukemia in remission who have not been receiving any chemotherapy for at least 3 months may receive live virus vaccines. Short-course therapy (<2 weeks) with corticosteroids, alternate-day regimens with low to moderate doses of short-acting corticosteroids, and topical applications or tendon injections are not ordinarily contraindications to the administration of live vaccines.

Immunocompromised patients can receive inactivated vaccines and toxoids, although the efficacy of such preparations may be diminished.[5] Patients with

E-TABLE 15-1 FOOTNOTES: RECOMMENDED IMMUNIZATION SCHEDULE FOR ADULTS AGED 19 YEARS OR OLDER, UNITED STATES, 2023

Notes

For vaccine recommendations for persons 18 years of age or younger, see the Recommended Child and Adolescent Immunization Schedule.

COVID-19 vaccination

Routine vaccination
- **Primary series:** 2-dose series at 0, 4-8 weeks (Moderna) or 2-dose series at 0, 3-8 weeks (Novavax, Pfizer-BioNTech)
- **Booster dose:** see www.cdc.gov/vaccines/covid-19/clinical-considerations/interim-considerations-us.html

Special situations

Persons who are moderately or severely immunocompromised
- **Primary series**
  - 3-dose series at 0, 4, 8 weeks (Moderna) or 3-dose series at 0, 3, 7 weeks (Pfizer-BioNTech)
  - 2-dose series at 0, 3 weeks (Novavax)
- **Booster dose:** see www.cdc.gov/vaccines/covid-19/clinical-considerations/interim-considerations-us.html
- **Pre-exposure prophylaxis (e.g., monoclonal antibodies)** may be considered to complement COVID-19 vaccination. See www.cdc.gov/vaccines/covid-19/clinical-considerations/interim-considerations-us.html#immunocompromised

For Janssen COVID-19 Vaccine recipients see COVID-19 schedule at www.cdc.gov/vaccines/covid-19/clinical-considerations/interim-considerations-us.html.

Note: Current COVID-19 schedule available at www.cdc.gov/vaccines/covid-19/downloads/COVID-19-immunization-schedule-ages-6months-older.pdf.

For more information on Emergency Use Authorization (EUA) indications for COVID-19 vaccines, please visit www.fda.gov/emergency-preparedness-and-response/coronavirus-disease-2019-covid-19/covid-19-vaccines

***Haemophilus influenzae* type b vaccination**

Special situations
- **Anatomical or functional asplenia (including sickle cell disease):** 1 dose if previously did not receive Hib; if elective splenectomy, 1 dose, preferably at least 14 days before splenectomy
- **Hematopoietic stem cell transplant (HSCT):** 3-dose series 4 weeks apart starting 6–12 months after successful transplant, regardless of Hib vaccination history

Hepatitis A vaccination

Routine vaccination
- **Not at risk but want protection from hepatitis A** (identification of risk factor not required): 2-dose series HepA (Havrix 6–12 months apart or Vaqta 6–18 months apart [minimum interval: 6 months]) or 3-dose series HepA-HepB (Twinrix at 0, 1, 6 months [minimum intervals: dose 1 to dose 2: 4 weeks / dose 2 to dose 3: 5 months])

Special situations
- **At risk for hepatitis A virus infection:** 2-dose series HepA or 3-dose series HepA-HepB as above
  - **Chronic liver disease** (e.g., persons with hepatitis B, hepatitis C, cirrhosis, fatty liver disease, alcoholic liver disease, autoimmune hepatitis, alanine aminotransferase [ALT] or aspartate aminotransferase [AST] level greater than twice the upper limit of normal)
  - **HIV infection**
  - **Men who have sex with men**
  - **Injection or noninjection drug use**
  - **Persons experiencing homelessness**
  - **Work with hepatitis A virus** in research laboratory or with nonhuman primates with hepatitis A virus infection
  - **Travel in countries with high or intermediate endemic hepatitis A** (HepA-HepB [Twinrix] may be administered on an accelerated schedule of 3 doses at 0, 7, and 21–30 days, followed by a booster dose at 12 months)
  - **Close, personal contact with international adoptee** (e.g., household or regular babysitting) in first 60 days after arrival from country with high or intermediate endemic hepatitis A (administer dose 1 as soon as adoption is planned, at least 2 weeks before adoptee's arrival)
  - **Pregnancy** if at risk for infection or severe outcome from infection during pregnancy
  - **Settings for exposure,** including health care settings targeting services to injection or noninjection drug users or group homes and nonresidential day care facilities for developmentally disabled persons (individual risk factor screening not required)

Hepatitis B vaccination

Routine vaccination
- **Age 19 through 59 years: complete a 2- or 3- or 4-dose series**
  - 2-dose series only applies when 2 doses of Heplisav-B* are used at least 4 weeks apart
  - 3-dose series Engerix-B, PreHevbrio*, or Recombivax HB at 0, 1, 6 months [minimum intervals: dose 1 to dose 2: 4 weeks / dose 2 to dose 3: 8 weeks / dose 1 to dose 3: 16 weeks])
  - 3-dose series HepA-HepB (Twinrix at 0, 1, 6 months [minimum intervals: dose 1 to dose 2: 4 weeks / dose 2 to dose 3: 5 months])
  - 4-dose series HepA-HepB (Twinrix) accelerated schedule of 3 doses at 0, 7, and 21–30 days, followed by a booster dose at 12 months

***Note:** Heplisav-B and PreHevbrio are not recommended in pregnancy due to lack of safety data in pregnant persons.

- **Age 60 years or older with** known risk factors for hepatitis B virus infection **should** complete a HepB vaccine series.
- **Age 60 years or older without** known risk factors for hepatitis B virus infection **may** complete a HepB vaccine series.
  - **Risk factors for hepatitis B virus infection include:**
    - **Chronic liver disease** (e.g., persons with hepatitis C, cirrhosis, fatty liver disease, alcoholic liver disease, autoimmune hepatitis, alanine aminotransferase [ALT] or aspartate aminotransferase [AST] level greater than twice upper limit of normal)
    - **HIV infection**
    - **Sexual exposure risk** (e.g., sex partners of hepatitis B surface antigen [HBsAg]-positive persons; sexually active persons not in mutually monogamous relationships; persons seeking evaluation or treatment for a sexually transmitted infection; men who have sex with men)
    - **Current or recent injection drug use**
    - **Percutaneous or mucosal risk for exposure to blood** (e.g., household contacts of HBsAg-positive persons; residents and staff of facilities for developmentally disabled persons; health care and public safety personnel with reasonably anticipated risk for exposure to blood or blood-contaminated body fluids; persons on maintenance dialysis, including in-center or home hemodialysis and peritoneal dialysis, and persons who are predialysis; patients with diabetes)
    - **Incarceration**
    - **Travel in countries with high or intermediate endemic hepatitis B**

Special situations
- **Patients on dialysis:** complete a 3- or 4-dose series
  - 3-dose series Recombivax HB at 0, 1, 6 months (note: use Dialysis Formulation 1 mL = 40 mcg)
  - 4-dose series Engerix-B at 0, 1, 2, and 6 months (note: use 2 mL dose instead of the normal adult dose of 1 mL)

E-TABLE 15-1 FOOTNOTES: RECOMMENDED IMMUNIZATION SCHEDULE FOR ADULTS AGED 19 YEARS OR OLDER, UNITED STATES, 2023—cont'd

Human papillomavirus vaccination

Routine vaccination

- **HPV vaccination recommended for all persons through age 26 years:** 2- or 3-dose series depending on age at initial vaccination or condition:
  - **Age 15 years or older at initial vaccination:** 3-dose series at 0, 1–2 months, 6 months (minimum intervals: dose 1 to dose 2: 4 weeks / dose 2 to dose 3: 12 weeks / dose 1 to dose 3: 5 months; repeat dose if administered too soon)
  - **Age 9–14 years at initial vaccination and received 1 dose or 2 doses less than 5 months apart:** 1 additional dose
  - **Age 9–14 years at initial vaccination and received 2 doses at least 5 months apart:** HPV vaccination series complete, no additional dose needed
- **Interrupted schedules:** If vaccination schedule is interrupted, the series does not need to be restarted
- **No additional dose recommended when any HPV vaccine series has been completed using the recommended dosing intervals.**

Shared clinical decision-making

- **Some adults age 27–45 years:** Based on shared clinical decision-making, 2- or 3-dose series as above

Special situations

- **Age ranges recommended above for routine and catch-up vaccination or shared clinical decision-making also apply in special situations**
  - **Immunocompromising conditions, including HIV infection:** 3-dose series, even for those who initiate vaccination at age 9 through 14 years.
  - **Pregnancy:** Pregnancy testing is not needed before vaccination; HPV vaccination is not recommended until after pregnancy; no intervention needed if inadvertently vaccinated while pregnant.

Influenza vaccination

Routine vaccination

- **Age 19 years or older:** 1 dose any influenza vaccine appropriate for age and health status annually
- **Age 65 years or older:** Any one of quadrivalent high-dose inactivated influenza vaccine (HD-IIV4), quadrivalent recombinant influenza vaccine (RIV4), or quadrivalent adjuvanted inactivated influenza vaccine (aIIV4) is preferred. If none of these three vaccines is available, then any other age-appropriate influenza vaccine should be used.
- For the 2022–2023 season, see www.cdc.gov/mmwr/volumes/71/rr/rr7101a1.htm
- For the 2023–2024 season, see the 2023–2024 ACIP influenza vaccine recommendations.

Special situations

- **Egg allergy, hives only:** any influenza vaccine appropriate for age and health status annually
- **Egg allergy–any symptom other than hives** (e.g., angioedema, respiratory distress or required epinephrine or another emergency medical intervention): Any influenza vaccine appropriate for age and health status may be administered. If using egg-based IIV4 or LAIV4, administer in medical setting under supervision of health care provider who can recognize and manage severe allergic reactions.
- **Close contacts (e.g., caregivers, healthcare workers) of severely immunosuppressed persons who require a protected environment:** these persons should not receive LAIV4. If LAIV4 is given, they should avoid contact with/caring for such immunosuppressed persons for 7 days after vaccination.
- **Severe allergic reaction (e.g., anaphylaxis) to a vaccine component or a previous dose of any influenza vaccine:** see Appendix listing contraindications and precautions
- **History of Guillain-Barré syndrome within 6 weeks after previous dose of influenza vaccine:** Generally, should not be vaccinated unless vaccination benefits outweigh risks for those at higher risk for severe complications from influenza

Measles, mumps, and rubella vaccination

Routine vaccination

- **No evidence of immunity to measles, mumps, or rubella:** 1 dose
  - **Evidence of immunity:** Born before 1957 (health care personnel, see below), documentation of receipt of MMR vaccine, laboratory evidence of immunity or disease (diagnosis of disease without laboratory confirmation is not evidence of immunity)

Special situations

- **Pregnancy with no evidence of immunity to rubella:** MMR contraindicated during pregnancy; after pregnancy (before discharge from health care facility), 1 dose
- **Nonpregnant persons of childbearing age with no evidence of immunity to rubella:** 1 dose
- **HIV infection with CD4 percentages ≥15% and CD4 count ≥200 cells/mm^3 for at least 6 months and no evidence of immunity to measles, mumps, or rubella:** 2-dose series at least 4 weeks apart; MMR contraindicated for HIV infection with CD4 percentage <15% or CD4 count <200 cells/mm^3
- **Severe immunocompromising conditions:** MMR contraindicated
- **Students in postsecondary educational institutions, international travelers, and household or close, personal contacts of immunocompromised persons with no evidence of immunity to measles, mumps, or rubella:** 2-dose series at least 4 weeks apart if previously did not receive any doses of MMR or 1 dose if previously received 1 dose MMR
- **In mumps outbreak settings,** for information about additional doses of MMR (including 3rd dose of MMR), see www.cdc.gov/mmwr/volumes/67/wr/mm6701a7.htm
- **Health care personnel:**
  - **Born before 1957 with no evidence of immunity to measles, mumps, or rubella:** Consider 2-dose series at least 4 weeks apart for protection against measles or mumps or 1 dose for protection against rubella
  - **Born in 1957 or later with no evidence of immunity to measles, mumps, or rubella:** 2-dose series at least 4 weeks apart for protection against measles or mumps or at least 1 dose for protection against rubella

Meningococcal vaccination

Special situations for MenACWY

- **Anatomical or functional asplenia (including sickle cell disease), HIV infection, persistent complement component deficiency, complement inhibitor (e.g., eculizumab, ravulizumab) use:** 2-dose series MenACWY-D (Menactra, Menveo, or MenQuadfi) at least 8 weeks apart and revaccinate every 5 years if risk remains
- **Travel in countries with hyperendemic or epidemic meningococcal disease, or microbiologists routinely exposed to *Neisseria meningitidis*:** 1 dose MenACWY (Menactra, Menveo, or MenQuadfi) and revaccinate every 5 years if risk remains
- **First-year college students who live in residential housing (if not previously vaccinated at age 16 years or older) or military recruits:** 1 dose MenACWY (Menactra, Menveo, or MenQuadfi)
- For MenACWY **booster dose recommendations** for groups listed under "Special situations" and in an outbreak setting (e.g., in community or organizational settings and among men who have sex with men) and additional meningococcal vaccination information, see www.cdc.gov/mmwr/volumes/69/rr/rr6909a1.htm

Shared clinical decision-making for MenB

- **Adolescents and young adults age 16–23 years (age 16–18 years preferred) not at increased risk for meningococcal disease:** Based on shared clinical decision-making, 2-dose series MenB-4C (Bexsero) at least 1 month apart or 2-dose series MenB-FHbp (Trumenba) at 0, 6 months (if dose 2 was administered less than 6 months after dose 1, administer dose 3 at least 4 months after dose 2); MenB-4C and MenB-FHbp are not interchangeable (use same product for all doses in series)

Special situations for MenB

- **Anatomical or functional asplenia (including sickle cell disease), persistent complement component deficiency, complement inhibitor (e.g., eculizumab, ravulizumab) use, or microbiologists routinely exposed to *Neisseria meningitidis*:** 2-dose primary series MenB-4C (Bexsero) at least 1 month apart or 3-dose primary series MenB-FHbp (Trumenba) at 0, 1–2, 6 months (if dose 2 was administered at least 6 months after dose 1, dose 3 not needed; if dose 3 is administered earlier than 4 months after dose 2, a fourth dose should be administered at least 4 months after dose 3); MenB-4C and MenB-FHbp are not interchangeable (use same product for all doses in series); 1 dose MenB booster 1 year after primary series and revaccinate every 2–3 years if risk remains
- **Pregnancy:** Delay MenB until after pregnancy unless at increased risk and vaccination benefits outweigh potential risks
- For MenB **booster dose recommendations** for groups listed under "Special situations" and in an outbreak setting (e.g., in community or organizational settings and among men who have sex with men) and additional meningococcal vaccination information, see www.cdc.gov/mmwr/volumes/69/rr/rr6909a1.htm

Note: MenB vaccines may be administered simultaneously with MenACWY vaccines if indicated, but at a different anatomic site, if feasible.

E-TABLE 15-1 FOOTNOTES: RECOMMENDED IMMUNIZATION SCHEDULE FOR ADULTS AGED 19 YEARS OR OLDER, UNITED STATES, 2023—cont'd

Pneumococcal vaccination

Routine vaccination

- **Age 65 years or older who have:**
  - **Not previously received a dose of PCV13, PCV15, or PCV20 or whose previous vaccination history is unknown:** 1 dose PCV15 OR 1 dose PCV20. If PCV15 is used, this should be followed by a dose of PPSV23 given at least 1 year after the PCV15 dose. A minimum interval of 8 weeks between PCV15 and PPSV23 can be considered for adults with an immunocompromising condition,* cochlear implant, or cerebrospinal fluid leak to minimize the risk of invasive pneumococcal disease caused by serotypes unique to PPSV23 in these vulnerable groups.
  - **Previously received only PCV7:** follow the recommendation above.
  - **Previously received only PCV13:** 1 dose PCV20 at least 1 year after the PCV13 dose OR complete the recommended PPSV23 series as described here: www.cdc.gov/vaccines/vpd/pneumo/downloads/pneumo-vaccine-timing.pdf
  - **Previously received only PPSV23:** 1 dose PCV15 OR 1 dose PCV20 at least 1 year after the PPSV23 dose. If PCV15 is used, it need not be followed by another dose of PPSV23.
  - **Previously received both PCV13 and PPSV23 but NO PPSV23 was received at age 65 years or older:** 1 dose PCV20 at least 5 years after their last pneumococcal vaccine dose OR complete the recommended PPSV23 series as described here: www.cdc.gov/vaccines/vpd/pneumo/downloads/pneumo-vaccine-timing.pdf
  - **Previously received both PCV13 and PPSV23, AND PPSV23 was received at age 65 years or older:** Based on shared clinical decision-making, 1 dose of PCV20 at least 5 years after the last pneumococcal vaccine dose.
  - For guidance on determining which pneumococcal vaccines a patient needs and when, please refer to the mobile app which can be downloaded here: www.cdc.gov/vaccines/vpd/pneumo/hcp/pneumoapp.html

Special situations

- **Age 19–64 years with certain underlying medical conditions or other risk factors** who have**
  - **Not previously received a PCV13, PCV15, or PCV20 or whose previous vaccination history is unknown:** 1 dose PCV15 OR 1 dose PCV20. If PCV15 is used, this should be followed by a dose of PPSV23 given at least 1 year after the PCV15 dose. A minimum interval of 8 weeks between PCV15 and PPSV23 can be considered for adults with an immunocompromising condition,* cochlear implant, or cerebrospinal fluid leak
  - **Previously received only PCV7:** follow the recommendation above
  - **Previously received only PCV13:** 1 dose PCV20 at least 1 year after the PCV13 dose OR complete the recommended PPSV23 series as described here: www.cdc.gov/vaccines/vpd/pneumo/downloads/pneumo-vaccine-timing.pdf
  - **Previously received only PPSV23:** 1 dose PCV15 OR 1 dose PCV20 at least 1 year after the PPSV23 dose. If PCV15 is used, it need not be followed by another dose of PPSV23
  - **Previously received both PCV13 and PPSV23 but have not completed the recommended series:** 1 dose PCV20 at least 5 years after their last pneumococcal vaccine dose OR complete the recommended PPSV23 series as described here: www.cdc.gov/vaccines/vpd/pneumo/downloads/pneumo-vaccine-timing.pdf
- For guidance on determining which pneumococcal vaccines a patient needs and when, please refer to the mobile app which can be downloaded here: www.cdc.gov/vaccines/vpd/pneumo/hcp/pneumoapp.html

*__Note:__ Immunocompromising conditions include chronic renal failure, nephrotic syndrome, immunodeficiency, iatrogenic immunosuppression, generalized malignancy, human immunodeficiency virus, Hodgkin disease, leukemia, lymphoma, multiple myeloma, solid organ transplants, congenital or acquired asplenia, sickle cell disease, or other hemoglobinopathies.

**__Note:__ Underlying medical conditions or other risk factors include alcoholism, chronic heart/liver/lung disease, chronic renal failure, cigarette smoking, cochlear implant, congenital or acquired asplenia, CSF leak, diabetes mellitus, generalized malignancy, HIV, Hodgkin disease, immunodeficiency, iatrogenic immunosuppression, leukemia, lymphoma, multiple myeloma, nephrotic syndrome, solid organ transplants, or sickle cell disease, or other hemoglobinopathies.

Polio vaccination

Routine vaccination

Routine poliovirus vaccination of adults residing in the United States is not necessary.

Special situations

- Adults at increased risk of exposure to poliovirus with:
  - No evidence of a complete polio vaccination series (i.e., at least 3 doses): administer remaining doses (1, 2, or 3 doses) to complete a 3-dose series
  - Evidence of completed polio vaccination series (i.e., at least 3 doses): may administer one lifetime IPV booster

For detailed information, see: www.cdc.gov/vaccines/vpd/polio/hcp/recommendations.html

Tetanus, diphtheria, and pertussis (Tdap) vaccination

Routine vaccination

- **Previously did not receive Tdap at or after age 11 years:** 1 dose Tdap, then Td or Tdap every 10 years

Special situations

- **Previously did not receive primary vaccination series for tetanus, diphtheria, or pertussis:** 1 dose Tdap followed by 1 dose Td or Tdap at least 4 weeks later, and a third dose of Td or Tdap 6–12 months later (Tdap can be substituted for any Td dose, but preferred as first dose), Td or Tdap every 10 years thereafter
- **Pregnancy:** 1 dose Tdap during each pregnancy, preferably in early part of gestational weeks 27–36
- **Wound management:** Persons with 3 or more doses of tetanus-toxoid-containing vaccine: For clean and minor wounds, administer Tdap or Td if more than 10 years since last dose of tetanus-toxoid-containing vaccine; for all other wounds, administer Tdap or Td if more than 5 years since last dose of tetanus-toxoid-containing vaccine. Tdap is preferred for persons who have not previously received Tdap or whose Tdap history is unknown. If a tetanus-toxoid-containing vaccine is indicated for a pregnant woman, use Tdap. For detailed information, see www.cdc.gov/mmwr/volumes/69/wr/mm6903a5.htm

Varicella vaccination

Routine vaccination

- **No evidence of immunity to varicella:** 2-dose series 4–8 weeks apart if previously did not receive varicella-containing vaccine (VAR or MMRV [measles-mumps-rubella-varicella vaccine] for children); if previously received 1 dose varicella-containing vaccine, 1 dose at least 4 weeks after first dose
  - **Evidence of immunity:** U.S.-born before 1980 (except for pregnant persons and health care personnel [see below]), documentation of 2 doses varicella-containing vaccine at least 4 weeks apart, diagnosis or verification of history of varicella or herpes zoster by a health care provider, laboratory evidence of immunity or disease

Special situations

- **Pregnancy with no evidence of immunity to varicella:** VAR contraindicated during pregnancy; after pregnancy (before discharge from health care facility), 1 dose if previously received 1 dose varicella-containing vaccine or dose 1 of 2-dose series (dose 2: 4–8 weeks later) if previously did not receive any varicella-containing vaccine, regardless of whether U.S.-born before 1980
- **Health care personnel with no evidence of immunity to varicella:** 1 dose if previously received 1 dose varicella-containing vaccine; 2-dose series 4–8 weeks apart if previously did not receive any varicella-containing vaccine, regardless of whether U.S.-born before 1980
- **HIV infection with CD4 percentages ≥15% and CD4 count ≥200 cells/mm^3 with no evidence of immunity:** Vaccination may be considered (2 doses 3 months apart); VAR contraindicated for HIV infection with CD4 percentage <15% or CD4 count <200 cells/mm^3
- **Severe immunocompromising conditions:** VAR contraindicated

E-TABLE 15-1 FOOTNOTES: RECOMMENDED IMMUNIZATION SCHEDULE FOR ADULTS AGED 19 YEARS OR OLDER, UNITED STATES, 2023—cont'd

Zoster vaccination

Routine vaccination

- **Age 50 years or older*:** 2-dose series recombinant zoster vaccine (RZV, Shingrix) 2–6 months apart (minimum interval: 4 weeks; repeat dose if administered too soon), regardless of previous herpes zoster or history of zoster vaccine live (ZVL, Zostavax) vaccination.

*__Note:__ Serologic evidence of prior varicella is not necessary for zoster vaccination. However, if serologic evidence of varicella susceptibility becomes available, providers should follow ACIP guidelines for varicella vaccination first. RZV is not indicated for the prevention of varicella, and there are limited data on the use of RZV in persons without a history of varicella or varicella vaccination.

Special situations

- **Pregnancy:** There is currently no ACIP recommendation for RZV use in pregnancy. Consider delaying RZV until after pregnancy.
- **Immunocompromising conditions (including persons with HIV regardless of CD4 count)**:** 2-dose series recombinant zoster vaccine (RZV, Shingrix) 2–6 months apart (minimum interval: 4 weeks; repeat dose if administered too soon). For detailed information, see www.cdc.gov/shingles/vaccination/immunocompromised-adults.html

**__Note:__ If there is no documented history of varicella, varicella vaccination, or herpes zoster, providers should refer to the clinical considerations for use of RZV in immunocompromised adults aged ≥19 years and the ACIP varicella vaccine recommendations for further guidance: www.cdc.gov/mmwr/volumes/71/wr/mm7103a2.htm

E-TABLE 15-2 VACCINES IN THE ADULT IMMUNIZATION SCHEDULE

VACCINES	ABBREVIATIONS	TRADE NAMES
Haemophilus influenzae type b vaccine	Hib	ActHIB Hiberix PedvaxHIB
Hepatitis A vaccine	HepA	Havrix Vaqta
Hepatitis A and hepatitis B vaccine	HepA-HepB	Twinrix
Hepatitis B vaccine	HepB	Engerix-B Recombivax HB Heplisav-B PreHevbrio
Human papillomavirus vaccine	HPV	Gardasil 9
Influenza vaccine (inactivated)	IIV	Many brands
Influenza vaccine (live, attenuated)	LAIV4	FluMist Quadrivalent
Influenza vaccine (recombinant)	RIV4	Flublok Quadrivalent
Measles, mumps, and rubella vaccine	MMR	M-M-R II Priorix
Meningococcal serogroups A, C, W, Y vaccine	MenACWY-D MenACWY-CRM MenACWY-TT	Menactra Menveo MenQuadfi
Meningococcal serogroup B vaccine	MenB-4C MenB-FHbp	Bexsero Trumenba
Pneumococcal 13-valent conjugate vaccine	PCV13	Prevnar 13
Pneumococcal 15-valent conjugate vaccine	PCV15	Vaxneuvance
Pneumococcal 20-valent vaccine	PCV20	Prevnar 20
Pneumococcal 23-valent polysaccharide vaccine	PPSV23	Pneumovax 23
Tetanus and diphtheria toxoids	Td	Tenivac Tdvax
Tetanus and diphtheria toxoids and acellular pertussis vaccine	Tdap	Adacel Boostrix
Varicella vaccine	VAR	Varivax
Zoster vaccine, recombinant	RZV	Shingrix

E-TABLE 15-3 SPECIAL POPULATIONS THAT NEED ADDITIONAL CONSIDERATIONS

- **Pregnant persons.** Pregnant persons should receive the tetanus, diphtheria, and acellular pertussis vaccine (Tdap) during every pregnancy and the influenza vaccine during or before pregnancy. Live vaccines (e.g., measles, mumps, and rubella vaccine [MMR]) are contraindicated.
- **Asplenia.** Adults with anatomic or functional asplenia have specific vaccination recommendations because of their increased risk for infection by encapsulated bacteria. Anatomic or functional asplenia includes congenital or acquired asplenia, splenic dysfunction, sickle cell disease and other hemoglobinopathies, and splenectomy.
- **Altered immunocompetence.** Adults with high-level immunosuppression should generally avoid live vaccines. Inactivated vaccines (e.g., pneumococcal vaccines) are generally acceptable. High-level immunosuppression includes human immunodeficiency virus (HIV) infection with a CD4 cell count <200 cells/μL, receipt of daily corticosteroid therapy with ≥20 mg of prednisone or equivalent for ≥14 days, primary immunodeficiency disorder (e.g., severe combined immunodeficiency or complement component deficiency), and receipt of cancer chemotherapy. Other immunocompromising conditions and immunosuppressive medications to consider when vaccinating adults can be found in *IDSA Clinical Practice Guideline for Vaccination of the Immunocompromised Host.*[*] Additional information on vaccinating immunocompromised adults is in *General Best Practice Guidelines for Immunization.*[†]

*Rubin LG, Levin MJ, Ljungman P, et al. 2013 IDSA clinical practice guideline for vaccination of the immunocompromised host. *Clin Infect Dis*. 2014;58:e44-e100.

†Advisory Committee on Immunization Practices. Centers for Disease Control and Prevention. Available at https://www.cdc.gov/vaccines/hcp/acip-recs/general-recs/index.html.
Adapted from https://www.cdc.gov/vaccines/schedules/downloads/adult/adult-combined-schedule.pdf.

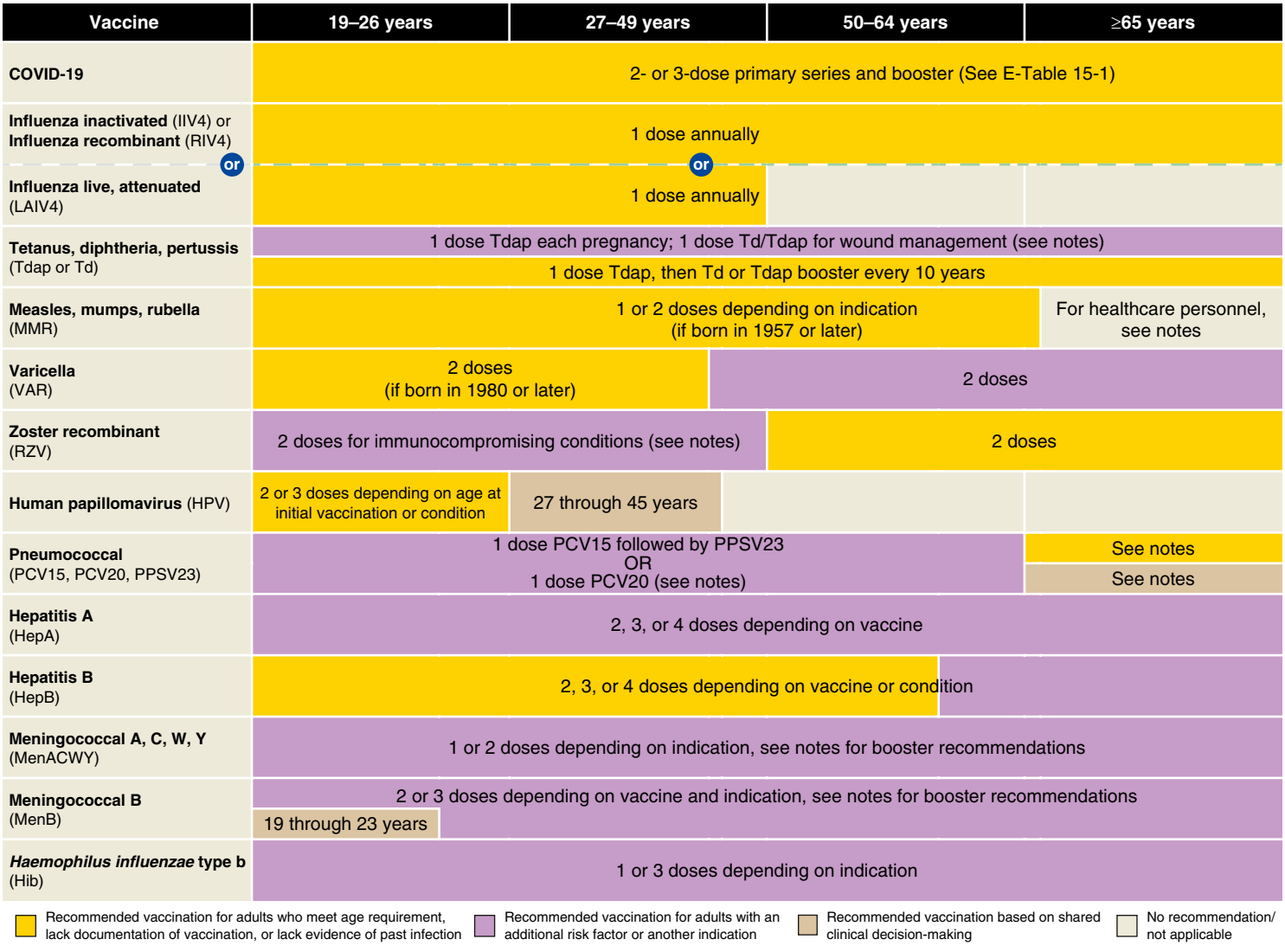

FIGURE 15-1. Recommended adult immunization schedule by age group, United States, 2023. See E-Table 15-1 for footnotes. COVID-19 = coronavirus disease 2019. (Adapted from https://www.cdc.gov/vaccines/schedules/downloads/adult/adult-combined-schedule.pdf.)

known HIV infection should receive PCV15 with PPSV23 1 year later (or PCV20 with no PPSV23); meningococcal serogroup ACWY vaccine; hepatitis A vaccine; hepatitis B vaccine; three doses of HPV vaccine (if not already vaccinated); and annual influenza vaccination.

PREGNANCY

In general, live vaccines should not be given to pregnant persons because of the theoretical concern that the vaccines could adversely affect the fetus (see E-Table 15-3). No significant adverse events have been documented as attributable to vaccination of pregnant persons with rubella-containing or varicella vaccines; nevertheless, pregnant persons should not receive MMR or varicella vaccine, and persons who do receive these vaccines should wait 1 month before becoming pregnant. Poliomyelitis and yellow fever vaccines usually should not be given to pregnant persons unless the risk of disease is substantial. Tdap vaccination is indicated for pregnant persons during each pregnancy, preferably early in the period between 27 and 36 weeks of gestation, to prevent pertussis in their infants and themselves. All pregnant persons should be screened for hepatitis B surface antigen (HBsAg). If HBsAg is positive, their infants should receive hepatitis B vaccine and hepatitis B immune globulin within 12 hours of birth. For persons who are pregnant, HPV vaccination should be delayed until after pregnancy; however, pregnancy testing is not needed before vaccination. Persons who are breast-feeding or lactating can receive the HPV vaccine. All persons who are or will be pregnant during the influenza season should receive inactivated influenza vaccine before or during pregnancy to protect themselves and their babies.

INDIVIDUAL IMMUNOBIOLOGICS

Immunobiologics for adults lacking evidence of prior infection, immunity, or documented vaccination, either for all adults at a certain age or because of one or more risk factors (health condition, lifestyle, occupation, or other indication), are discussed in the following sections.

COVID-19

In the United States as of April 2022, four intramuscular vaccines are available for prevention of coronavirus disease 2019 (COVID-19), infection with severe acute respiratory syndrome coronavirus 2 [SARS-CoV-2; Chapter 337]). Two of the vaccines (Pfizer BioNTech COVID-19 vaccine; Moderna COVID-19 vaccine) are messenger RNA (mRNA) vaccines consisting of SARS-CoV-2 mRNA. Following injection, the mRNA is translated by the host to generate SARS-CoV-2 spike protein, which acts as the antigen. A third vaccine (Johnson & Johnson's Janssen COVID-19 vaccine) is a non-replicating vector vaccine consisting of a non-replicating adenovirus vector with genes encoding for the coronavirus spike protein, which again is the antigen generating the immune response. A fourth vaccine (Novavax) consists of a recombinant spike protein nanoparticle.[6] After two doses 2 or more weeks apart, Pfizer-BioNTech COVID-19 vaccine and Moderna COVID-19 have 90 to 95% efficacy in preventing clinical disease in persons ages 16 years and older (Pfizer-BioNTech COVID-19 vaccine) and ages 18 years and older (Moderna COVID-19).[A3–A6] One dose of the Janssen vaccine has 66% efficacy in preventing laboratory-confirmed COVID-19 illness in persons 18 years old and older. All three vaccines have high efficacy against severe disease and death from COVID-19. A person is

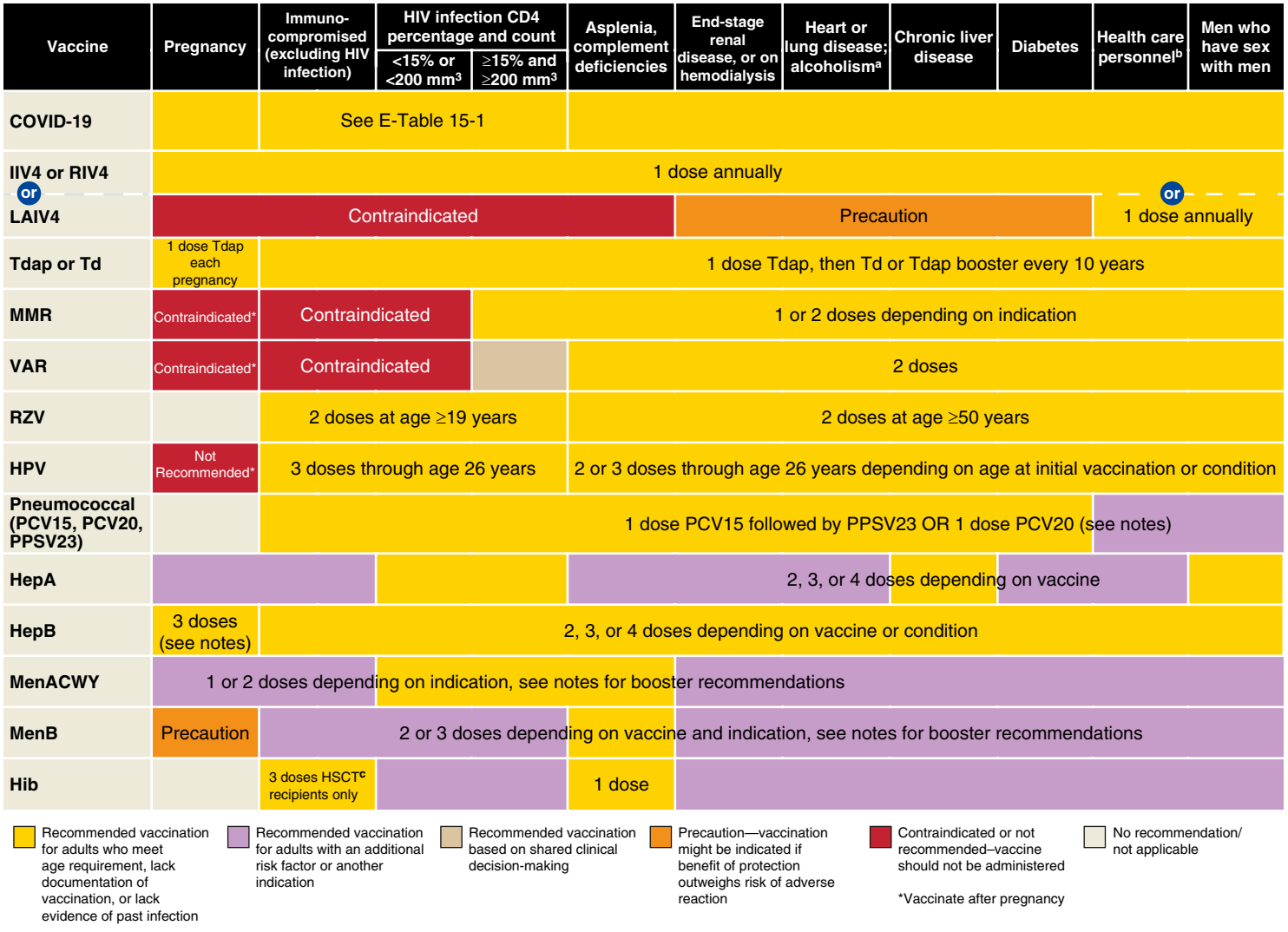

FIGURE 15-2. Recommended adult immunization schedule by medical condition or other indication, United States, 2023. [a]Precaution for LAIV4 does not apply to alcoholism. [b]See notes for influenza; hepatitis B; measles, mumps, and rubella; and varicella vaccinations. [c]Hematopoietic stem cell transplant. See E-Table 15-1 for footnotes. COVID-19 = coronavirus disease 2019. (Adapted from http://www.cdc.gov/vaccines/schedules/downloads/adult/adult-combined-schedule.pdf.)

considered fully vaccinated at 2 weeks or more after receipt of the recommended dose series.

Indications

COVID-19 vaccines are FDA-approved for a primary series in persons ages 12 years and older (Pfizer-BioNTech vaccine) and age 18 years and older (Moderna vaccine). COVID-19 vaccines are also FDA-authorized for emergency use as a primary series in persons ages 5 through 15 years (Pfizer-BioNTech COVID-19 vaccine), 12 years and older (Novavax COVID-19 vaccine), or ages 18 years or older (Janssen COVID-19 vaccine), as additional doses for immunosuppressed persons age 12 years and older (Pfizer-BioNTech and Moderna) and as booster doses (the mRNA vaccines COVID-19 vaccines).[7] Although mRNA vaccines are preferred as booster doses, Novavax may be used as a booster dose, but only if mRNA vaccines are unavailable or not desired. Novavax may only be used as a first booster dose.

COVID-19 vaccine is recommended for the prevention of SARS-CoV-2 infection. mRNA vaccines are preferred over Janssen COVID-19 vaccine.

The vaccines can be administered simultaneously with or at any interval from other vaccines. A third dose of an mRNA vaccine is recommended 28 days after the primary series for persons ages 5 years and older who are immunosuppressed.

A booster dose should be administered at least 2 months after the additional dose.[A7] A booster dose of mRNA vaccine is recommended at least 2 months after the primary series for persons ages 12 years or older. A booster dose is also recommended for persons 12 years old and older who were immunosuppressed upon receipt of the primary series and who received an additional dose. The current effectiveness of the booster against the most common circulating strain is 37 to 52% depending on the age of the adult.[8]

Adverse Reactions

After vaccination, about 35 to 90% of vaccine recipients experience local reactions and about 45 to 85% experience systemic reactions. Most of these reactions are mild and self-limited. Rare serious adverse events (Chapter 337) include anaphylactic reactions (presumably to vaccine components polyethylene glycol and polysorbate) and lymphadenopathy, Bell palsy (all vaccines), swelling at the site of previously implanted dermal fillers (Moderna COVID-19 vaccine), a syndrome of thrombosis with thrombocytopenia (Janssen COVID-19 vaccine), myopericarditis and pericarditis (mRNA COVID-19 vaccines), and Guillain-Barré syndrome (Janssen COVID-19 vaccine).[9] With the exception of the risk of anaphylaxis, which is low and exists with every vaccine, the low rate of these serious adverse reactions to date has not resulted in changes to the recommended use of these vaccines.

HAEMOPHILUS INFLUENZAE TYPE B VACCINE

*Haemophilus influenza*e type b (Hib) vaccines are composed of a polysaccharide capsule conjugated to a protein. There are two single-component vaccines (ActHib and PedvaxHib). ActHib is Hib polysaccharide from type b conjugated to a tetanus protein. PedvaxHib is Hib polysaccharide conjugated to an outer membrane protein of a strain of *Neisseria meningitidis*. There are two combination vaccines, ActHib combined with DTaP and IPV (Pentacel) and PedvaxHib combined with DTaP, IPV, and HepB (Vaxelis).

Indications

H. influenzae type b vaccine is recommended for adults who have anatomic and functional asplenia (e.g., sickle cell disease) who are vaccine naïve and adults who have received a haematopoietic cell transplant (HCT; Chapter 163). For naïve adults with functional and anatomic asplenia, one dose of Hib is recommended. For all adults post-HCT, regardless of previous vaccination, three doses of Hib are recommended with intervals of 1 month.

Adverse Reactions

The contraindication to Hib vaccine is a severe allergic reaction (e.g., anaphylaxis) following a prior dose or to a vaccine component. The precaution to Hib vaccine is severe or moderate acute illness.

HEPATITIS A

Two inactivated hepatitis A (Chapter 134) vaccines are available in the United States. Seroconversion rates after a single dose of either vaccine in persons older than 1 year exceed 95%, and protection is expected to persist for at least 25 years.

Indications

For adults, the vaccine is indicated primarily for persons traveling to countries (generally those in the developing world) with high or intermediate endemicity for hepatitis A, but it is also recommended for other groups at high risk for infection or for development of severe hepatitis. In addition, vaccine is routinely recommended for children 12 to 23 months of age, with catch-up through 18 years of age. Vaccination also is recommended for unvaccinated persons 1 year of age and older for postexposure prophylaxis after close contact with an infected person or exposure to a contaminated food or water source. For postexposure prophylaxis, persons 40 years of age and older who have altered immunocompetence or chronic liver disease should receive immune globulin in addition to hepatitis A vaccine. Health care workers have not been shown to be at higher risk than the general population for hepatitis A and do not need routine immunization. Although food handlers are not at increased risk for hepatitis A compared with the general population, the consequences of infection or suspected infection in this group, which can lead to extensive public health investigations, may make vaccination cost-effective in some settings. Doses vary by age and product. All schedules call for a second dose at least 6 months after the first dose.

Adverse Reactions

The most common adverse reaction after hepatitis A vaccination is tenderness and soreness at the injection site. Although rare and more serious adverse events have been reported in temporal association with vaccination, no causal relationships have been established.

HEPATITIS B

Hepatitis B (Chapter 134) vaccine was the first vaccine known to prevent cancer. It also can prevent acute and chronic complications of hepatitis B, including an estimated 1800 deaths annually in the United States from liver cancer, cirrhosis, and fulminant hepatic disease. Currently produced vaccines contain HBsAg derived from insertion of the gene for HBsAg into *Saccharomyces cerevisiae*. When it is administered in a three-dose series, hepatitis B vaccine produces adequate antibody responses (anti-HBs ≥10 mIU/mL) in more than 90% of healthy adults younger than 40 years and in more than 95% of healthy infants, children, and adolescents. By age 60 years, protective levels of antibody develop in only 75% of vaccinated persons. A new adjuvanted hepatitis B vaccine was licensed in 2017. It consists of recombinant HBsAg, produced in yeast cells *(Hansenula polymorpha)* combined with a novel cytosine phosphoguanine (CpG)–enriched oligodeoxynucleotide (ODN) phosphorothioate immunostimulatory adjuvant (CpG 1018 adjuvant). It is administered in a two-dose series, 1 month apart. The duration of vaccine-conferred immunity is not known, although follow-up of vaccinees for more than 20 years indicates persistence of protection against clinically significant infections (i.e., detectable viremia and clinical disease). Booster doses are not currently recommended. Vaccine must be injected intramuscularly in the deltoid.

Indications

Hepatitis B vaccine is indicated for all adults ages 18 through 59 years and for adults ages 60 years of age and older who are at increased risk of infection or increased risk of complications from hepatitis B infection (see Fig. 15-1 and E-Table 15-1), including all persons ages 19 through 59 years with diabetes. Vaccination of persons who are below age 60 years and without risk factors is based on shared clinical decision making. Universal screening for HBsAg is recommended for all pregnant persons; three doses of vaccine and one dose of hepatitis B immune globulin are recommended for infants of acutely or chronically infected mothers.

Postvaccination serologic testing is recommended for health care workers, immunosuppressed persons, and sexual contacts of persons with chronic hepatitis B infection. If the test is negative, one additional dose of vaccine should be given and the individual should be retested. If this second test is negative, the remaining doses of the series should be given. If the individual still has a negative serology, they are considered a nonresponder. Postvaccination serologic testing is recommended for patients on dialysis 1 year after the final dose in the series. If the test is negative, one booster dose should be given, with follow-up testing 1 year later and then annually.

Adverse Reactions

The most common adverse reaction is soreness at the injection site. Rare instances of Guillain-Barré syndrome, leukoencephalitis, optic neuritis, transverse myelitis, rheumatoid arthritis, type 1 diabetes, and autoimmune disease have been reported, but causal associations have not been confirmed with any systemic immune complications.

HUMAN PAPILLOMAVIRUS

Three licensed HPV vaccines (Chapter 344) contain virus-like particles of the L1 capsid protein of HPV types 16 and 18, which account for about 66% of cases of cervical cancer in the United States. HPV vaccines are prophylactic (i.e., they prevent new infections). These vaccines have reduced the incidence of vaccine-type HPV infection,[A8] as well as the risk of cervical intraepithelial neoplasia.[10] Two of these vaccines, bivalent and quadrivalent, remain licensed but are no longer available in the United States. The nine-valent vaccine (9vHPV) also contains virus-like particles of the L1 capsid protein of HPV types 6 and 11, which are the most common causes of anogenital warts. This vaccine also contains L1 capsid proteins of types 31, 33, 45, 52, and 58, which cause an additional 15% of cervical cancers. HPV type 16 accounts for most of the other cancers caused by HPV infection. Overall, 9vHPV can prevent over 90% of cancers that are caused by HPV.

Indications

Routine vaccination of 11- to 12-year-old girls and boys is recommended in a two-dose schedule at 0 and 6 to 12 months for persons initiating vaccination before age 15 years and a three-dose schedule at 0, 1 to 2, and 6 months for persons initiating vaccination at age 15 years or older or who are immunosuppressed. Vaccine can be given to persons starting at age 9 years. Catch-up vaccination is recommended for all persons through 26 years. Shared clinical decision making is recommended for adults who are age 27 through 45 years and who are not adequately vaccinated.

Adverse Reactions

The most commonly reported local symptoms are injection site pain, redness, and swelling. The most common generalized symptoms are dizziness, syncope, nausea, vomiting, fatigue, headache, fever, and urticaria.

INFLUENZA

Influenza vaccines for seasonal influenza include intramuscular inactivated influenza vaccine, recombinant influenza vaccine, containing the same four virus types as the inactivated vaccine, and intranasal live attenuated influenza vaccine. Live attenuated vaccine (LAIV), which consists of four cold-adapted, temperature-sensitive attenuated viruses, one for each of the expected circulating strains, uses viruses that have been reassorted with circulating strains to contain six internal genes from the parent virus and genes for the surface hemagglutinin and neuraminidase of an A(H3N2), A(H1N1), and two B strains.

Indications

Annual influenza (Chapter 332) vaccination is indicated for all adults, but especially persons at high risk of complications from the disease: all persons aged 50 years and older; adults who have chronic pulmonary, cardiovascular, renal, hepatic, neurologic, hematologic, or metabolic disorders; persons who are immunosuppressed; women who are or will be pregnant during the influenza season; residents of long-term care facilities; American Indians or Alaska Natives; and persons who are morbidly obese. To reduce transmission of influenza to high-risk patients, health care personnel and household contacts of high-risk patients, including contacts of children younger than 5 years, also should be vaccinated annually. Providers should offer vaccination

by the end of October, if possible. Pregnant persons in the third trimester should be vaccinated as soon as vaccine becomes available. Vaccination levels are still low in most adult populations in the United States and require more aggressive vaccination efforts.

The efficacy of inactivated influenza vaccine varies with the host's condition and the degree to which antigens in the vaccine match viruses that circulate during the following season. A high-dose inactivated vaccine consists of four times the hemagglutinin for each of the four strains compared with standard-dose vaccine. An inactivated adjuvanted vaccine contains standard doses of each of the four hemagglutinins but also contains MF59 as an adjuvant. Both the high-dose and adjuvanted vaccine are produced in eggs.

In recent years, the effectiveness of the vaccine has averaged about 30% for preventing laboratory-confirmed outpatient illness in persons 50 years and older and about 45% for preventing influenza-like illness in residents of long-term care facilities.[11] Protection often varies depending upon the type of influenza, and protection is higher with higher vaccine doses.[12] Live attenuated vaccine is licensed only for nonpregnant persons aged 2 through 49 years without underlying conditions that place them at high risk of complications from influenza. LAIV may be used for appropriately aged contacts of high-risk persons but is generally not recommended for contacts of severely immunosuppressed patients, such as patients with bone marrow transplants.

The high-dose and adjuvanted vaccines are recommended only for adults over age 65 years. Aside from LAIV, which is recommended only for persons ages 2 to 49 years, there is no preference for one vaccine over another for the general population. All influenza vaccines can be used in all adults provided they have no contraindications.

Influenza vaccination also reduces cardiovascular events. Vaccination efforts should begin as soon as the vaccine becomes available and should continue throughout the season. Peak influenza activity usually recurs in January or February, and influenza season continues through March.

Adverse Reactions

The most common side effect of inactivated vaccine is soreness at the injection site. Fever, malaise, and myalgia may begin 6 to 12 hours after vaccination and persist for 1 or 2 days, although such reactions are most common in children exposed to vaccine for the first time. The most common adverse events after live attenuated influenza vaccine in adults are runny nose, headache, and sore throat. Guillain-Barré syndrome may occur at a rate of about one case per 1 million doses.

MEASLES

Indications

Measles (Chapter 338) immunization is recommended for all persons born in or after 1957 without laboratory evidence of immunity, laboratory confirmation of prior disease, or documentation of prior appropriate vaccination. Most adults are considered to have been appropriately vaccinated if they received one dose of vaccine on or after their first birthday. However, adults who are at increased risk of exposure to measles or transmission of it (e.g., health care personnel, college students, international travelers) should receive a second dose if they did not get a second dose as children, unless they have serologically documented immunity, have laboratory confirmation of disease, or were born before 1957. Persons embarking on foreign travel should have received two doses of MMR vaccine or have other evidence of measles immunity as defined before. Persons born before 1957 are usually immune as a result of natural infection and do not require vaccination, although vaccination is not contraindicated if they are believed to be susceptible.

During educational institutional outbreaks of measles, all persons who have not received two doses or who lack other evidence of measles immunity should be vaccinated. Although measles vaccine can be administered only with mumps and rubella as MMR, individuals already immune to one or more of the components may receive MMR without harm.

Measles vaccine is contraindicated for pregnant persons on theoretical grounds, for persons with altered immunocompetence (except those with HIV infection who are not severely immunocompromised), and for persons with a history of severe allergic reaction (e.g., anaphylaxis) to a prior dose or to a vaccine component. Patients with anaphylactic reactions to eggs can be vaccinated without prior skin testing.

Adverse Reactions

MMR vaccine can cause fever (<15%), rash (5%), transient lymphadenopathy (20%), or parotitis (<1%). Febrile reactions, which usually are otherwise asymptomatic, generally occur 7 to 12 days after vaccination and persist for 1 or 2 days. MMR vaccination can rarely cause anaphylaxis, febrile seizures in children, thrombocytopenic purpura, transient arthralgia, and measles inclusion body encephalitis in persons with demonstrated immunodeficiencies.

MENINGOCOCCAL DISEASE

Three quadrivalent meningococcal vaccines are available against disease caused by serogroups A, C, W, and Y of *Neisseria meningitidis* (Chapter 274). One conjugate vaccine consists of each serogroup-specific polysaccharide covalently linked to 48 μg of diphtheria toxoid and is licensed for persons 9 months to 55 years of age. The second conjugate vaccine consists of the polysaccharides linked to CRM_{197} and is licensed for persons 2 months to 55 years of age. The third conjugate vaccine consists of the polysaccharides linked to tetanus toxoid and is licensed for persons 2 years old and older. The four serogroups in each vaccine account for approximately half of meningococcal disease cases in the United States, including in persons 11 years of age or older (Chapter 274). Conjugate vaccines induce immunologic memory and result in higher and more durable levels of high-avidity antibodies. The duration of immunity for MenACWY is estimated at between 3 and 5 years.

Two recombinant meningococcal serogroup B vaccines are licensed in the United States for persons 10 through 25 years of age. One vaccine (MenB-4C) contains three outer membrane proteins as well as protein-containing outer membrane vesicles, and the other (MenB-FHbp) contains two different alleles of the outer membrane protein (FHbp). Because of the low incidence of serogroup B meningococcal disease, evidence of vaccine effectiveness was inferred based on demonstration of immune response, as measured by serum bactericidal activity using human complement, against a small number of serogroup B strains.

Indications

Routine vaccination with MenACWY is recommended for all adolescents at 11 through 18 years of age, with a first dose administered at age 11 or 12 years and revaccination at age 16 years. For adolescents who receive a first dose between ages 13 and 15 years, a booster dose is recommended at age 16 to 18 years. Meningococcal vaccination is also recommended for unvaccinated and undervaccinated college freshmen who will live in dormitories, for military recruits, for persons at risk during a community outbreak attributable to a vaccine serogroup, and for persons who travel to or live in areas with hyperendemic or epidemic disease (e.g., the "meningitis belt" of sub-Saharan Africa, stretching from Mauritania to Ethiopia). For persons at ongoing increased risk of meningococcal disease (i.e., microbiologists with frequent exposure to *N. meningitidis* in culture and persons with persistent complement component deficiencies, splenic dysfunction, asplenia, or HIV infection), MenACWY vaccination is also recommended, with revaccination every 5 years.

MenB vaccines are recommended for a narrower group of persons at increased meningococcal disease risk compared with MenACWY: persons with persistent complement component deficiencies (including inherited or chronic deficiencies in C3, C5 to C9, properdin, factor D, factor H, or who are taking eculizumab or ravulizumab); anatomic or functional asplenia; microbiologists routinely exposed to isolates of *N. meningitidis;* and those at increased risk because of a serogroup B meningococcal disease outbreak. MenB vaccines are not recommended routinely for first-year college students in residence halls, military recruits, or international travelers. A MenB vaccine series may be administered on the basis of shared vaccine decision making to adolescents and young adults aged 16 to 23 years to provide short-term protection against most strains of serogroup B meningococcal disease. The preferred age for MenB vaccination is 16 to 18 years.

Both MenB-4C and MenB-FHbp are administered in a two-dose series for healthy individuals. For individuals at increased risk of serogroup B meningococcal disease, one of the MenB vaccines (MenB-FHbp) is recommended in a three-dose series. For individuals at continued increased risk, a booster dose is recommended 1 year after completion of the primary series and then every 2 to 3 years thereafter based on continuing risk. For persons at risk in an outbreak who may have received previous doses of MenB vaccine, a booster dose may be given 1 year after the primary series or as little as 6 months after the primary series if recommended by public health officials. MenB vaccines are not interchangeable, and the same brand of MenB vaccine should be used for all primary series doses and the booster doses. The current low prevalence of disease, coupled with lack of data for making policy recommendations for MenB vaccines, resulted in ACIP's determining insufficient evidence exists to make a routine public health recommendation that all adolescents be vaccinated

with MenB vaccine. Given the seriousness of meningococcal disease and the availability of licensed vaccines, ACIP agreed sufficient evidence exists to encourage shared clinical decision making about MenB vaccination for adolescents and young adults who are not otherwise at increased risk for serogroup B meningococcal disease.

Adverse Reactions

The most common adverse reactions to MenACWY are injection site reactions and systemic symptoms, such as headache and malaise, which generally persist for 1 or 2 days. An excess risk of Guillain-Barré syndrome was initially reported after vaccination with one of the three MenACWY vaccines but has not been confirmed in subsequent studies.

Injection site reactions are common with MenB vaccines. The most common systemic adverse reactions observed within the 7 days after receipt of MenB vaccines are fatigue, headache, and myalgia.

MUMPS

Indications

Mumps (Chapter 340) vaccine is indicated for all persons without evidence of immunity. For most adults, such evidence consists of a prior history of vaccination on or after the first birthday, laboratory evidence of immunity, or laboratory confirmation of disease. For adults at high risk, including health care personnel, international travelers, and students at post–high school educational institutions, two doses of mumps vaccine constitute acceptable evidence of immunity. Most persons born before 1957 can be considered immune as a result of natural infection, although vaccination is not contraindicated if such persons are thought to be susceptible. Persons who were previously vaccinated with two doses of a mumps-containing vaccine and who are identified by public health officials as at increased risk for mumps because of a mumps outbreak should receive a third dose of a mumps-containing vaccine to improve protection against mumps disease and related complications.

Mumps vaccine is contraindicated for pregnant persons on theoretical grounds, for persons with moderate to severe acute febrile illnesses, and for persons with altered immunocompetence. When it is combined with measles vaccine, it may be given to persons with asymptomatic HIV infection and considered for persons with symptomatic infection if they are not severely immunocompromised. Patients with anaphylactic reactions to eggs can be vaccinated without skin testing.

Adverse Reactions

Adverse events after the vaccine strain used in the United States are uncommon but include fever, parotitis, and allergic reactions. Thrombocytopenic purpura has been reported rarely after MMR (see also, Measles, Adverse Reactions).

PERTUSSIS

Each of the two vaccines licensed for boosting immunity to pertussis (Chapter 289) in adults is combined with tetanus and diphtheria toxoids as Tdap, which has a lower content of pertussis antigens compared with the childhood pertussis-containing vaccines (DTaP). Boostrix (GlaxoSmithKline), which is licensed for adolescents and adults 10 years of age and older, contains three pertussis antigens—toxoid (PT), filamentous hemagglutinin (FHA), and pertactin (PRN). Adacel (Sanofi Pasteur), which is licensed for 10 through 64 years of age, contains five pertussis antigens: PT, FHA, PRN, and two fimbriae. Both vaccines, when they are administered to previously vaccinated adolescents and adults, induce serologic responses that are comparable to those induced with effective childhood vaccination.

Indications

A single dose of Tdap is indicated for all adolescents at 11 to 12 years of age. All adults who have not received Tdap should receive it regardless of the interval since their last tetanus or diphtheria toxoid–containing vaccine. Tdap can be given at any interval after a prior Td. All pregnant persons should receive one dose of Tdap vaccine during each pregnancy, optimally early in the period between 27 and 36 weeks of gestation to maximize maternal antibody response and passive antibody transfer to the infant. Persons not vaccinated during pregnancy should receive Tdap postpartum if they have never previously been vaccinated with it. With the exception of pregnant persons, booster doses of Tdap are not recommended. However, in any circumstance in which a tetanus-toxoid vaccine is indicated generally, Tdap may substitute for Td, unless there is a contraindication to the pertussis component.

Adverse Reactions

Adverse events, usually local reactions, are similar to the adult preparation of Td alone compared with Tdap vaccine (see the section on tetanus and diphtheria later).

PNEUMOCOCCAL DISEASE

Pneumococcal polysaccharide vaccine (PPSV23) consists of purified polysaccharide capsular antigens from 23 types of *Streptococcus pneumoniae* (Chapter 268). Most adults, including elderly patients and those with alcoholic cirrhosis and diabetes mellitus, have a two-fold or greater rise in type-specific antibodies within 2 to 3 weeks of vaccination. Vaccination is approximately 60% effective against invasive pneumococcal disease, but its efficacy against pneumonia in high-risk populations, such as patients with alcoholic cirrhosis or Hodgkin disease, is not clear.[A9]

Pneumococcal conjugate vaccines (PCV15) contains conjugated capsular antigen from the serotypes for which the previously recommended PCV13 is protective, plus serotypes 22F and 33F. PCV20 contains conjugated capsular antigen from the serotypes for which the previously recommended PCV13 is protective, plus serotypes 8, 10A, 11A, 12F, 15B, 22F, and 33F.

Three pneumococcal vaccines are currently recommended for all adults ages 65 years and older. For patients who are PCV13-naïve, clinicians may choose PCV20 or choose PCV15 followed by PPSV23 a year later. Adults ages 19 through 64 years who have a high-risk condition for invasive pneumococcal disease (asthma, diabetes mellitus, cirrhosis, cerebrospinal fluid leaks, splenic dysfunction or anatomic asplenia, Hodgkin disease, lymphoma, multiple myeloma, chronic renal failure, nephrotic syndrome, immunosuppression, HIV infection, cigarette smoking) and who previously have not received PCV13 should receive either a dose of PCV20 or PCV15 followed by PPSV23 8 weeks to a year later.

Indications

The preponderance of information supports the use of pneumococcal vaccines in high-risk populations, including all persons 65 years and older and persons 19 years or older with conditions (Table 15-2). Special efforts should target hospitalized patients. Approximately two thirds of patients who are admitted later with pneumococcal disease had been hospitalized for other reasons within the preceding 5 years.

Because immunity may decrease 5 years or more after initial vaccination with PPSV23, a single booster dose of PPSV23 should be considered at that time for adults at highest risk of disease (such as asplenic patients) and for adults who lose antibody rapidly (such as patients with nephrotic syndrome or renal failure). Persons 65 years or older who received a dose more than 5 years earlier when they were younger than 65 years also should be revaccinated. Because of the rarity of severe reactions in revaccinated patients, persons with indications for vaccination but with unknown histories of prior vaccination should be vaccinated.

Adverse Reactions

Local reactions to PPSV23 are frequent, but less than 3% of vaccinees experience severe local reactions or systemic symptoms such as fever and malaise. Severe events, such as anaphylaxis or Arthus-like reactions at the site of injection, are rare. PCV13 reactions include pain, redness, and swelling at the injection site; limitation of movement of the injected arm; fatigue; and headache.

POLIOMYELITIS

Since 2000, inactivated poliovirus vaccine (IPV) has replaced the live attenuated oral poliovirus vaccine (OPV) in the United States because OPV vaccine caused about eight to nine polio cases per year in the United States among recipients or their contacts (Chapter 349). Trivalent OPV containing types 1, 2, and 3 has been replaced by bivalent OPV containing types 1 and 3 in all countries using OPV. In addition, there is a recommendation that all countries should include at least one dose of IPV in their immunization schedules.

Indications

Routine vaccination of persons 18 years of age or older is not recommended. If adults who are unvaccinated, are incompletely vaccinated, or have unknown vaccination status travel to areas where wild poliovirus is endemic or epidemic, they should receive a series of three doses: two doses of IPV administered at an interval of 4 to 8 weeks, with a third dose administered 6 to 12 months after the second. If three doses of IPV cannot be administered, alternatives include the following: three doses of IPV administered 4 weeks or more apart; two doses of IPV administered 4 weeks or more apart if less than 8 weeks remain before protection is needed; and, if less than 4 weeks remain before protection is needed, a single dose of IPV. If fewer than three doses are administered, the remaining doses needed to complete a three-dose

series should be administered when feasible, at the intervals recommended, especially if the person remains at increased risk for poliovirus exposure.

As a precaution, adults (≥18 years of age) who are traveling to areas where poliomyelitis cases are occurring and who have received a routine series with either IPV or OPV in childhood should receive another dose of IPV before departure. For adults, available data do not indicate the need for more than a single lifetime booster dose with IPV.

Adverse Reactions

Minor local reactions (pain, redness) commonly occur after IPV. Because IPV contains trace amounts of streptomycin, polymyxin B, and neomycin, allergic reactions may occur in persons allergic to these antibiotics.

RABIES

Two inactivated rabies vaccines are licensed in the United States. Human diploid cell vaccine (HDCV), which is prepared from the Pitman-Moore strain of rabies virus, also contains small amounts of neomycin sulfate, albumin, and phenol red indicator. The purified chick embryo cell vaccine (PCECV), which is prepared from the Flury LEP rabies virus strain, also contains small amounts of polygeline, human serum albumin, potassium glutamate, and sodium ethylenediamine tetra-acetic acid (EDTA). Both vaccines are given intramuscularly.

Indications

Rabies (Chapter 383) vaccine is indicated for preexposure prophylaxis of high-risk persons, including animal handlers, selected laboratory and field workers, and persons traveling for more than 1 month to areas where rabies is a constant threat. For both rabies vaccines, the preexposure regimen consists of two 1-mL intramuscular injections on days 0 and 7, followed by a titer at regular intervals depending on risk. If the titer is negative, a booster dose should be administered. Adults at intermediate risk (veterinarians, travelers) may receive a third dose of vaccine instead of a titer, provided that it is administered between 21 days through 3 years following the first dose.[13] Postexposure treatment depends on prior exposure to vaccine (Chapter 383). Persons being treated for the first time should be given human rabies immune globulin as well as four doses of vaccine at days 0, 3, 7, and 14.

Adverse Reactions

Local reactions (e.g., pain at the injection site, redness, swelling, and induration) are common after both rabies vaccine preparations. Hypersensitivity reactions have been reported in up to 6% of persons after booster doses of HDCV.

RUBELLA

Indications

One dose of rubella vaccine (Chapter 339) is indicated for adults born in 1957 or later without evidence of immunity and for women of any age who lack evidence of immunity and who are considering becoming pregnant. Persons without a prior history of vaccination on or after the first birthday, laboratory evidence of immunity, or laboratory confirmation of disease should be considered as lacking evidence of immunity. A single dose of vaccine is 95% or more effective. Many persons receive two doses of rubella vaccine by the two-dose schedule of MMR.

Rubella vaccine is contraindicated for persons with moderate to severe acute illnesses and persons with reduced immunocompetence. When it is given with measles vaccine, it may be administered to persons with asymptomatic HIV infection and considered for symptomatic persons who are not severely immunocompromised. Rubella vaccine is grown in human diploid cells and can be administered without problems to persons with egg allergies.

Adverse Reactions

Follow-up of pregnant persons who had no evidence of immunity and who received rubella vaccines within 3 months of the estimated date of conception showed no evidence of defects compatible with congenital rubella syndrome in their offspring. Nevertheless, vaccine is contraindicated in pregnant persons on theoretical grounds, and conception should be delayed for 1 month after rubella vaccination.

Arthralgia develops among about 25% of nonimmune postpubertal females after vaccination with rubella vaccine. Symptoms generally begin 1 to 3 weeks after vaccination, usually are mild, persist for about 2 days, and rarely recur. These symptoms are less common in postpubertal males compared with females. Other infrequent adverse events include transient peripheral neuritis and pain in the arms and legs. Thrombocytopenic purpura is rare when rubella vaccine is administered as MMR.

TETANUS AND DIPHTHERIA

Tetanus (Chapter 271) toxoid is one of the most effective immunizations, with more than 95% protection after a primary series of three doses. In persons aged 7 years or older, it should always be used in combination with diphtheria (Chapter 272) toxoid (Td), which is more than 85% effective in preventing disease. Combinations that also include pertussis antigens (Tdap) are preferred to Td for routine immunization of adolescents and adults who have yet to receive Tdap as well as for pregnant persons (for whom Tdap is recommended during every pregnancy). Doses need not be repeated if the schedule is interrupted. A booster dose of Tdap or Td is recommended every 10 years.

Indications

After a wound, persons of unknown immunization status or persons who have received fewer than three doses of tetanus toxoid should receive a dose of Tdap or Td regardless of the severity of the wound. Td also is indicated for persons who have previously received three or more doses if more than 10 years has elapsed since the last dose, in the case of clean and minor wounds, and if more than 5 years has elapsed for all other wounds. However, the benefit of an adult tetanus or diphtheria booster is probably very, very small.[14] Persons who have never received a dose of Tdap should receive it instead of Td for wound management. Tetanus immune globulin should be administered simultaneously at a separate site to persons who have wounds that are not clean and minor if they have not previously received at least three doses of toxoid.

Adverse Reactions

Most reactions to Td consist of local inflammation and low-grade fever. Exaggerated local (Arthus-like) reactions, with extensive painful swelling, often from shoulder to elbow, are occasionally reported 2 to 8 hours after receipt of a diphtheria- or tetanus-containing vaccine, particularly in persons who have received frequent doses of diphtheria or tetanus toxoid. Severe systemic reactions, such as generalized urticaria, anaphylaxis, Guillain-Barré syndrome, and other neurologic complications, rarely have been reported after receipt of tetanus toxoid.

VARICELLA: CHICKENPOX

A single dose of live attenuated varicella vaccine (Oka strain), which can be combined with MMR vaccine, protects 70 to 90% of recipients against any disease and more than 95% of recipients against severe disease, but a two-dose schedule is recommended. Whether immunity wanes with increasing time after vaccination is unclear. Use of vaccine has been associated with dramatic decreases in the incidence of varicella.

Indications

Persons 13 years or older without evidence of immunity to varicella should receive two doses at least 4 weeks apart. Evidence of immunity to varicella for adults includes documentation of two doses of varicella-containing vaccine (varicella or MMRV) at least 28 days apart, laboratory evidence of immunity or laboratory confirmation of disease, birth in the United States before 1980, or diagnosis or verification of a history of varicella or herpes zoster disease by a health care provider. Serologic screening of adults in some situations may be cost-effective, provided that identified susceptible adults are vaccinated. Serologic testing is not indicated after vaccination. The vaccine is contraindicated in persons who are immunocompromised, persons with anaphylactic allergies to vaccine components, and pregnant persons. Postexposure vaccination within 3 days of exposure can reduce the likelihood of symptomatic infection by about two-thirds. The varicella vaccine formulation marketed in the United States is temperature sensitive, so it must be stored at −50°C to −15°C to retain potency.

Adverse Reactions

The most common side effect is soreness at the injection site, which is reported in 25 to 35% of recipients 13 years or older. Varicella-like rashes at the injection site (median of two lesions) have been reported in 3% of recipients in this age group after the first dose and in 1% after the second dose. Nonlocalized rashes with a median of five lesions have been reported in 5.5% of recipients after the first dose and in 0.9% after the second dose. Although the vaccine virus can cause herpes zoster (shingles), especially in children, the incidence is substantially lower than would be expected after natural varicella (Chapter 346). More severe events in temporal relation to the vaccine have been reported rarely, but a causal relationship has not been established. Transmission of vaccine virus to a contact is extremely rare and probably occurs only from vaccinees in whom a varicella-like rash developed.

VARICELLA-ZOSTER

Recombinant zoster vaccine (RZV), a subunit vaccine containing varicella-zoster virus glycoprotein E with the $ASO1_B$ adjuvant system, is about 97% effective for the prevention of herpes zoster in persons ages 50 to 69 years and about 91% effective in persons aged 70 years and older.[15] This is the only zoster vaccine available in the United States.

Indications

Recombinant zoster subunit vaccine (RZV) is recommended for all adults ages 50 years and older and for adults ages 18 through 49 years who are immunosuppressed. The vaccine is recommended even in adults who previously received live zoster vaccine or had herpes zoster, and it is not necessary to elicit a history of varicella or to test for varicella immunity before administering RZV. The vaccine is administered intramuscularly as two doses separated by 2 to 6 months.[16]

Adverse Reactions

Local reactions (erythema, pain or tenderness, and swelling at the injection site) are common. Moderate or severe local reactions occur in about 10% of RZV vaccine recipients, and moderate or severe systemic reactions also occur in about 10%. If an individual has a reaction to the first dose, it does not affect their likelihood of a reaction to the second dose.

VACCINES INTENDED PRIMARILY FOR INTERNATIONAL TRAVELERS

Evaluation of people before travel should include a review and provision of routine vaccines recommended on the basis of age and other individual characteristics. Recommendations for specific vaccines related to travel will depend on itinerary, duration of travel, and host factors. Detailed recommendations are available at www.cdc.gov/travel.[17]

CHOLERA

Indications

Cholera (Chapter 278) vaccine is indicated for adult travelers (aged 18 to 64 years) from the United States to areas of the world with endemic or epidemic cholera caused by toxigenic *Vibrio cholerae* O1 within the past year (https://wwwnc.cdc.gov/travel/). Lyophilized CVD 103-HgR (Vaxchora, PaxVax) is a single-dose, live attenuated oral cholera vaccine. Its efficacy against severe diarrhea (defined as fecal output >3 L/24 hours) after oral toxigenic *V. cholerae* O1 challenge is estimated to be 90% at 10 days after vaccination and 80% at 3 months after vaccination.[18] There is no recommendation for use of booster doses at this time.

Adverse Reactions

Available safety data indicate no harms except for a slightly elevated risk for mild diarrhea among vaccine recipients.

JAPANESE ENCEPHALITIS

Indications

Japanese encephalitis (Chapter 352) vaccine is indicated primarily for travelers to Asia who will spend a month or longer in endemic areas during the transmission season, especially if travel will include rural areas. In all instances, travelers should be advised to take personal precautions to reduce exposure to mosquito bites. An older vaccine was reported to be 80 to 91% effective in preventing clinical disease, and the current whole virus inactivated vaccine (Ixiaro, Intercell Biomedical) was licensed on the basis of comparable immunogenicity. The primary series consists of two 0.5-mL doses given intramuscularly on days 0 and 28, for patients 2 months and older, with the second dose administered at least 1 week before travel. If the primary series was administered more than 1 year previously, a booster dose may be given before the next potential exposure to the virus. The FDA has approved an alternate 0- and 7-day schedule for persons 18 years old and older.

Adverse Reactions

Headache, myalgia, and local reactions (pain and tenderness) occur in more than 10% of vaccinees. However, the incidence rates of these events were similar to those in a comparison group that received a placebo with aluminum hydroxide.

TYPHOID

Indications

The cumulative efficacy at 2.5 to 3.0 years for the live attenuated Ty21a oral vaccine is about 50%, whereas the cumulative efficacy at 2.5 to 3.0 years for the capsular polysaccharide vaccine is about 55%. Typhoid (Chapter 284) vaccine is indicated primarily for travelers to areas where the risk of prolonged exposure to contaminated food and water is high. Because the vaccine is not always effective, food and water precautions are still essential. The vaccine also may be considered for family or other intimate contacts of typhoid carriers and laboratory workers who work with *Salmonella* Typhi. The capsular polysaccharide vaccine is approved for persons 2 years old and older. The live attenuated Ty21a oral vaccine is approved for persons ages 6 years and older. For adults and children 6 years and older, either of the vaccines may be used. For Ty21a, one enteric-coated capsule is taken every other day for four doses. Alternatively, a single dose of the ViCPS vaccine may be given. The duration of protection with Ty21a is not known; repetition of the primary series is recommended every 5 years for persons at risk. Boosters are recommended every 2 years for the ViCPS vaccine if persons continue to be at risk. The ViCPS vaccine can be given to children as young as 2 years.

Adverse Reactions

Fever and headache may occur after receipt of typhoid vaccines. Stomach pain, nausea, and rash are rarely observed.

YELLOW FEVER

Indications

Yellow fever (Chapter 351) occurs only in areas of South America and Africa. Vaccination with a single dose of the live attenuated 17D strain of virus confers protection to almost all recipients for at least 10 years. For most persons only a single dose is recommended. However, a booster dose is recommended every 10 years for at-risk laboratory personnel and certain previously vaccinated travelers (pregnant persons before travel to at-risk areas; hematopoietic stem cell transplant recipients vaccinated before transplant; HIV-infected persons; and travelers who will be in a higher-risk setting based on season, location, activities, and duration of their travel, such as travelers who plan to spend a prolonged period in endemic areas or those traveling to highly endemic areas such as rural West Africa during peak transmission season or an area with an ongoing outbreak).

Yellow fever vaccine should not be given to immunocompromised persons or persons with anaphylactic allergies to eggs. The vaccine is contraindicated in pregnant persons on theoretical grounds, although pregnant persons who must travel to a high-risk area may be vaccinated.

Adverse Reactions

Adverse reactions (fever, aches, and soreness, redness, or swelling where the injection was given) occur in up to 25% of vaccinees. Anaphylaxis has been reported in 0.8 to 1.8 persons per 100,000 doses of vaccine distributed. A rare syndrome (0.25 case per 100,000 doses distributed) of multiple organ system failure with high rates of mortality called viscerotropic disease has been reported, primarily among older adults and persons who have undergone thymectomy or have severe thymic dysfunction. Meningoencephalitis, Guillain-Barré syndrome, acute disseminated encephalomyelitis, and bulbar palsy have been reported in 1 per 125,000 doses and are more common in older vaccinees. In patients 60 years and older who are going to spend time in yellow fever–endemic zones, yellow fever vaccine should be administered with caution and only after careful counseling.

VACCINES FOR POSSIBLE BIOTERRORISM AGENTS

ANTHRAX

Anthrax (Chapter 272) vaccine adsorbed (AVA) is prepared from a cell-free filtrate of a nonencapsulated strain of anthrax and contains many cell products, including protective antigen. Protective antigen is responsible for binding to cells, allowing transport of lethal factor and edema factor into host cells. A recombinant protective antigen (rPA) vaccine is in clinical trials.

Indications

Preexposure prophylaxis consists of a three-dose primary intramuscular schedule at 0 and 4 weeks and at 6 months, with booster doses at 12 and 18 months, followed by boosters every 3 years thereafter. Protective efficacy of an earlier form of the vaccine against cutaneous anthrax was 92.5%. Animal models suggest efficacy against inhalation anthrax. Preexposure vaccination is recommended for persons engaged in work involving exposure to high concentrations of *Bacillus anthracis* or in activities with high potential for aerosol production. Vaccine is recommended in conjunction with antibiotics

for postexposure prophylaxis after exposure to aerosolized *B. anthracis* spores. The recommended regimen is three doses of AVA administered at 0, 2, and 4 weeks, combined with 60 days of antibiotics, which should be continued for at least 14 days after the third dose of vaccine (Chapter 272).

Adverse Reactions

The most common adverse events are local reactions, including subcutaneous nodules, which are thought to be due to the deposition of the aluminum-containing adjuvant in subcutaneous tissue. These adverse events are less common with intramuscular injections than with subcutaneous injections.

SMALLPOX

Two licensed vaccines are available for prevention of smallpox. ACAM 2000 vaccine uses live vaccinia virus, an orthopox virus that is distinct from variola and cowpox viruses and that provides cross-protection from smallpox. Smallpox vaccine is close to 100% effective when it is administered properly with a bifurcated needle. The skin usually does not need any special preparation. If alcohol is used for cleaning, the skin should be allowed to dry before vaccination to avoid inactivation of the vaccine. The needle is held perpendicular to the skin with 15 punctures for all vaccinees, made rapidly with enough vigor to ensure that a trace of blood appears within 15 to 20 seconds. With a primary take, the vaccination site should become reddened and pruritic within 3 or 4 days after vaccination; a large vesicle with a red areola forms and becomes pustular by 7 to 11 days. The lesion scabs by the third week.

Jynneos vaccine is a live, nonreplicating vaccinia vector vaccine, which uses the modified vaccinia Ankara strain. It is approved for persons ages 18 years and older for prevention of smallpox and/or monkeypox infection. Its efficacy is inferred through comparison of immunogenicity with ACAM 2000. It is administered as a subcutaneous injection in two doses 4 weeks apart.

Indications

The vaccine is indicated for persons who work with orthopox viruses. To increase preparedness for a smallpox attack, vaccination is often recommended for persons who will serve on public health or health care response teams. The duration of immunity is unclear. Revaccination is recommended at least every 10 years for persons who continue to be at risk. Contraindications for both vaccines include a history of severe allergic reactions (e.g., anaphylaxis) to a previous dose of vaccine or to a component. Immunosuppression is a contraindication to the ACAM 2000 live virus vaccine. Other contraindications to ACAM 2000 include history or presence of eczema, other chronic or exfoliative skin conditions, and pregnancy in the patient or a close household or other contact. Persons who are younger than 1 year, are breast-feeding, or have allergies to vaccine components should not be vaccinated. Because of reports of postvaccination cardiac events, vaccination should be deferred in persons with ischemia or other severe heart diseases or persons at high risk for ischemic heart disease events (https://www.cdc.gov/smallpox/clinicians/vaccination.htm). In the event of exposure to variola, the risk of disease outweighs any contraindications. Should variola be introduced into a community, vaccination would be indicated for all exposed persons and their close contacts to prevent further spread, and recommendations for more widespread vaccination would have to be evaluated on a case-by-case basis.

Adverse Reactions

For ACAM 2000, fever is the most common adverse event. Other more serious complications include eczema vaccinatum, which is a local or disseminated vaccinia infection in persons with a history of eczema or other exfoliative dermatitis; vaccinia necrosum, which occurs in immunocompromised persons; autoinoculation, especially of the eye, which can cause keratitis and scarring; generalized vaccinia; myopericarditis; and encephalitis. The risk for death from vaccinia is about one case per 1 million primary vaccinations. The most common adverse events to Jynneos include local reactions, myalgia, and headache.

EBOLA

Ervebo is a live attenuated vector vaccine with vesicular stomatitis virus as the vector with the gene encoding the glycoprotein of Ebola strain Zaire ebolavirus (Chapter 351). It is administered as a single intramuscular (IM) dose.

Indications

Ervebo is recommended for persons 18 years old and older who are responders to an outbreak of Ebola or who work in federally designated Ebola treatment centers in the United States. Additionally, vaccine is recommended for persons who work in biosafety level 4 facilities in the United States.

Adverse Reactions

The most common adverse reactions include local reactions, headache, and fever. Arthralgia and arthritis also occur, particularly in women and persons with a past history of arthritis. History of severe allergic reaction (e.g., anaphylaxis) to a previous dose of or to a component of the vaccine is a contraindication. After receiving a dose of vaccine, recipients should avoid kissing or sharing razors, eating utensils, toothbrushes, drinking cups, or needles for 2 weeks. Vaccine recipients should avoid donating blood, contact with high-risk persons, or exposure of livestock to blood or body fluids for 6 weeks. Barrier methods for sexual interaction should be used for 2 months.

OTHER AGENTS

Other organisms or products that have been considered potential bioterrorism threats include plague (Chapter 288) and botulinum toxin (Chapter 271). Poisoning with botulinum toxin can be treated with a trivalent antitoxin available from the Centers for Disease Control and Prevention (see https://www.cdc.gov/laboratory/drugservice/formulary.html). An experimental heptavalent botulinum toxoid can be obtained from the Centers for Disease Control and Prevention for laboratory workers at high risk for exposure to toxin. Preexposure vaccination is not warranted or feasible for the general population.

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16 PRINCIPLES OF OCCUPATIONAL AND ENVIRONMENTAL MEDICINE

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Occupational and environmental medicine is a multidisciplinary field that focuses on how to recognize, diagnose, treat, and prevent injuries and illnesses that arise from exposures at work and in the environment, as well as to improve the health, well-being, and safety of employees, their families, and their communities, locally and globally.[1] Physicians in occupational and environmental medicine collaborate with employers, safety personnel, industrial hygienists, occupational health nurses, ergonomists, human resources specialists, labor union leaders, and others. They must also be conversant with how environmental exposures can lead to illness.

Physicians who specialize in occupational and environmental medicine may have a responsibility to the employer as well as the worker.[2] All physicians who assess the possibility of work-related injury or illness also must be cognizant of the regulatory environment affecting their work.

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for postexposure prophylaxis after exposure to aerosolized *B. anthracis* spores. The recommended regimen is three doses of AVA administered at 0, 2, and 4 weeks, combined with 60 days of antibiotics, which should be continued for at least 14 days after the third dose of vaccine (Chapter 272).

Adverse Reactions

The most common adverse events are local reactions, including subcutaneous nodules, which are thought to be due to the deposition of the aluminum-containing adjuvant in subcutaneous tissue. These adverse events are less common with intramuscular injections than with subcutaneous injections.

SMALLPOX

Two licensed vaccines are available for prevention of smallpox. ACAM 2000 vaccine uses live vaccinia virus, an orthopox virus that is distinct from variola and cowpox viruses and that provides cross-protection from smallpox. Smallpox vaccine is close to 100% effective when it is administered properly with a bifurcated needle. The skin usually does not need any special preparation. If alcohol is used for cleaning, the skin should be allowed to dry before vaccination to avoid inactivation of the vaccine. The needle is held perpendicular to the skin with 15 punctures for all vaccinees, made rapidly with enough vigor to ensure that a trace of blood appears within 15 to 20 seconds. With a primary take, the vaccination site should become reddened and pruritic within 3 or 4 days after vaccination; a large vesicle with a red areola forms and becomes pustular by 7 to 11 days. The lesion scabs by the third week.

Jynneos vaccine is a live, nonreplicating vaccinia vector vaccine, which uses the modified vaccinia Ankara strain. It is approved for persons ages 18 years and older for prevention of smallpox and/or monkeypox infection. Its efficacy is inferred through comparison of immunogenicity with ACAM 2000. It is administered as a subcutaneous injection in two doses 4 weeks apart.

Indications

The vaccine is indicated for persons who work with orthopox viruses. To increase preparedness for a smallpox attack, vaccination is often recommended for persons who will serve on public health or health care response teams. The duration of immunity is unclear. Revaccination is recommended at least every 10 years for persons who continue to be at risk. Contraindications for both vaccines include a history of severe allergic reactions (e.g., anaphylaxis) to a previous dose of vaccine or to a component. Immunosuppression is a contraindication to the ACAM 2000 live virus vaccine. Other contraindications to ACAM 2000 include history or presence of eczema, other chronic or exfoliative skin conditions, and pregnancy in the patient or a close household or other contact. Persons who are younger than 1 year, are breast-feeding, or have allergies to vaccine components should not be vaccinated. Because of reports of postvaccination cardiac events, vaccination should be deferred in persons with ischemia or other severe heart diseases or persons at high risk for ischemic heart disease events (https://www.cdc.gov/smallpox/clinicians/vaccination.htm). In the event of exposure to variola, the risk of disease outweighs any contraindications. Should variola be introduced into a community, vaccination would be indicated for all exposed persons and their close contacts to prevent further spread, and recommendations for more widespread vaccination would have to be evaluated on a case-by-case basis.

Adverse Reactions

For ACAM 2000, fever is the most common adverse event. Other more serious complications include eczema vaccinatum, which is a local or disseminated vaccinia infection in persons with a history of eczema or other exfoliative dermatitis; vaccinia necrosum, which occurs in immunocompromised persons; autoinoculation, especially of the eye, which can cause keratitis and scarring; generalized vaccinia; myopericarditis; and encephalitis. The risk for death from vaccinia is about one case per 1 million primary vaccinations. The most common adverse events to Jynneos include local reactions, myalgia, and headache.

EBOLA

Ervebo is a live attenuated vector vaccine with vesicular stomatitis virus as the vector with the gene encoding the glycoprotein of Ebola strain Zaire ebolavirus (Chapter 351). It is administered as a single intramuscular (IM) dose.

Indications

Ervebo is recommended for persons 18 years old and older who are responders to an outbreak of Ebola or who work in federally designated Ebola treatment centers in the United States. Additionally, vaccine is recommended for persons who work in biosafety level 4 facilities in the United States.

Adverse Reactions

The most common adverse reactions include local reactions, headache, and fever. Arthralgia and arthritis also occur, particularly in women and persons with a past history of arthritis. History of severe allergic reaction (e.g., anaphylaxis) to a previous dose of or to a component of the vaccine is a contraindication. After receiving a dose of vaccine, recipients should avoid kissing or sharing razors, eating utensils, toothbrushes, drinking cups, or needles for 2 weeks. Vaccine recipients should avoid donating blood, contact with high-risk persons, or exposure of livestock to blood or body fluids for 6 weeks. Barrier methods for sexual interaction should be used for 2 months.

OTHER AGENTS

Other organisms or products that have been considered potential bioterrorism threats include plague (Chapter 288) and botulinum toxin (Chapter 271). Poisoning with botulinum toxin can be treated with a trivalent antitoxin available from the Centers for Disease Control and Prevention (see https://www.cdc.gov/laboratory/drugservice/formulary.html). An experimental heptavalent botulinum toxoid can be obtained from the Centers for Disease Control and Prevention for laboratory workers at high risk for exposure to toxin. Preexposure vaccination is not warranted or feasible for the general population.

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16 PRINCIPLES OF OCCUPATIONAL AND ENVIRONMENTAL MEDICINE

JUDITH GREEN-MCKENZIE

Occupational and environmental medicine is a multidisciplinary field that focuses on how to recognize, diagnose, treat, and prevent injuries and illnesses that arise from exposures at work and in the environment, as well as to improve the health, well-being, and safety of employees, their families, and their communities, locally and globally.[1] Physicians in occupational and environmental medicine collaborate with employers, safety personnel, industrial hygienists, occupational health nurses, ergonomists, human resources specialists, labor union leaders, and others. They must also be conversant with how environmental exposures can lead to illness.

Physicians who specialize in occupational and environmental medicine may have a responsibility to the employer as well as the worker.[2] All physicians who assess the possibility of work-related injury or illness also must be cognizant of the regulatory environment affecting their work.

ABSTRACT

Occupational and environmental medicine (OEM) combines clinical medicine, providing individual medical care, and public health, managing the health and safety of worker populations. A multidisciplinary field, it focuses on how to recognize, diagnose, treat, and prevent injuries and illnesses that arise from exposures at work and in the environment, as well as to improve the health, well-being, and safety of employees, their families, and their communities, locally and globally. OEM physicians collaborate with many stakeholders, including employers, safety personnel, industrial hygienists, occupational health nurses, ergonomists, human resources specialists, and labor union leaders. Workers' compensation is the main payer for work-related illnesses and injuries. The skillful OEM history clarifies the work relatedness of a condition. Appropriate medical management, using a graduated return to work process, employing accommodations where needed, will result in both reduced work disability and workers' compensation costs. OEM providers need to be knowledgeable about toxicological principles as they evaluate, monitor, and treat conditions such as heavy metal toxicity. They need to understand the impact and management of environmental factors such as exposure to hot working environments to prevent heat-related illness. Understanding the organization of work is paramount because lack of awareness or agency to effect change can create a fertile ground for burnout and expensive job turnover. Additionally, they need be cognizant of the surrounding regulatory environment where the Occupational Safety and Health Administration (OSHA) issues, promulgates, and enforces standards for workplace safety and health. These standards affect most workplaces, from medical institutions to construction, and are enforceable. Environmental standards such as The Emergency Planning and Community Right-to-Know Act are also important to consider. Emphasizing work and the environment as important social determinants of health, OEM has one of the highest satisfaction indices among medical specialties.

KEYWORDS

occupational and environmental medicine
safety
workers' compensation
work-related disability
exposure history
Agency for Toxic Substance and Disease Registry
occupational injury
occupational disease
occupational asthma
pneumoconiosis
hypersensitivity pneumonitis
asbestosis
silicosis
polyaromatic hydrocarbons
sensorineural hearing loss
musculoskeletal pain
latex allergy
toxicology
heavy metals
solvents
pesticides
heat-related illness
particulate matter
ambient air pollution
Occupational Safety and Health Administration
National Institute for Occupational Safety and Health
medical surveillance
hierarchy of controls
Resource Conservation and Recovery Act
wellness
burnout
resiliency
emergency management

OCCUPATIONAL AND ENVIRONMENTAL MEDICINE REGULATORY ENVIRONMENT

Occupational and environmental medicine grew out of a necessity to provide protections for workers in the context of the heightened awareness about industrial accidents and exposures as well as the liability of employers for workplace injuries and illnesses. Its development has been embedded in an evolving regulatory environment, and the two together have led to improved occupational health outcomes.[3]

WORKERS' COMPENSATION

Workers' compensation is a "no-fault" system in which monetary compensation is provided to workers for medical and rehabilitation costs as well as lost wages related to illnesses or injuries that arose out of or during the course of employment, regardless of cause. Employers are held responsible for compensation, and the injured worker accepts the standard amount of permitted compensation. Workers' compensation is now the third largest source of support for disabled workers after Social Security and Medicare.

WORK-RELATED DISABILITY

Physicians and other providers may be asked to determine the extent of their patient's disability under the workers' compensation system. In general, disability is an inability or limitation in performing activities, roles, and tasks within a social or physical environment. Disability differs from impairment, which refers to an anatomic or functional abnormality or loss. Individuals with the same impairment may have different degrees of disability, which may vary depending on factors such as economic demand, educational factors, job description, and age. Workers' compensation defines four types of disability:

- *Temporary total disability:* Inability to work for a period, but recovery is expected. Lost wage (indemnity) benefits are paid to the worker while on disability.
- *Permanent total disability:* Inability to undertake gainful employment, and further treatment will not lead to recovery. Indemnity benefits are paid to the worker.
- *Temporary partial disability:* The worker can perform some work duties (modified duty) and can return to work if a suitable placement can be found.
- *Permanent partial disability:* Permanent loss of one or several functions. Work is possible but in a modified duty capacity or at a different job.

Maximal medical improvement or *permanency* is said to have occurred when an injured worker has recovered as much as they are likely to recover and have likely reached a stage of permanent disability. Although the condition may improve over time, the best decision must be made with the information at hand at the time.

If an employer provides modified duty that the employee can perform, then this option can reduce payment for lost wages (indemnity costs) and thus reduce the overall cost of workers' compensation. This approach also keeps the employee in the work culture, thereby easing the way to return to full-duty work, if and when achievable. In fact, most injured workers return to full-duty work.

APPROACH TO THE PATIENT

SALIENT FEATURES OF THE OCCUPATIONAL AND ENVIRONMENTAL MEDICINE HISTORY

Two simple initial questions during the history taking—"What is your job? and "Where do you work?"—can help clinicians ascertain whether work may play a role in the patient's present illness and past medical history. If the condition is work related, a directed occupational and environmental history is essential to document any relationship to work so as to establish the background for any future workers' compensation claim. Otherwise the worker may be denied workers' compensation if the case is not clearly presented, or may at least experience a delay in receiving such benefits.

When a workers' compensation claim is filed, the adjuster who reviews the case relies greatly on the provider's initial medical note to determine whether to accept the claim. The physician and document must query about the mechanism of the injury or the nature of the exposure to assess any potential work-relatedness. In addition to usual questions to explore an injury, additional information should be elicited for a work-related claim:

- Reason for visit: chief complaint, which will guide future questions
- Mechanism of injury: helps ascertain work-relatedness
- Age: can help estimate time to recovery
- Handedness (right/left): may affect modified duty assigned by the provider
- Place of work: to appraise type of work potentially available (e.g., options that the worker may be able to perform)
- Job title: may help determine if modified duty is necessary
- Description of job duties: helps determine how to design modified duty work
- Prior injuries: can help the clinician determine longevity at work (e.g., if the employee had similar prior surgery, the clinician can explore potential preventive measures with the employee and the employer)
- Whether others are injured similarly: may suggest population level prevention
- Comorbid conditions: can influence current and future injuries and return-to-work arrangements
- Social history: determine living arrangements and whether help at home or duties at home may affect recovery
- Is the employee currently working: may help infer severity of injury or illness, thereby informing return to work status (modified or full duty)

In addition to detailed questions exploring an exposure, the clinician should elicit information about:

- The nature of exposure: agent and place of exposure (work, home, community)
- A standard exposure history: such as with the Exposure Survey created by the Agency for Toxic Substance and Disease Registry (E-Fig. 16-1)
- A safety data sheet (SDS): contains physical data, potential hazards, and handling and safety precautions data on all the potential toxins at work
- Symptom temporality: to determine if symptoms improve away from work or in a different environment, as in occupational asthma compared with asthma that has environmental triggers (Chapter 75)
- Time of peak symptoms: helps with temporality if during work hours
- Duration of symptoms: recent or remote onset
- Organ system involved (e.g., skin manifestations may suggest an agent with direct contact)
- Type of personal protective equipment used: determine adequacy
- Current work duties: help assess degree of potential exposure
- Occupational history using a standard survey (see E-Fig. 16-1): to determine exposures from prior jobs (e.g., sensitizers such as diisocyanate or beryllium)
- Length of employment: potential for sustained exposure
- Similar symptoms in other employees: ascertain if presentation is unique
- Smoking history: may be synergistic for a respiratory agent
- Family history of allergy: to determine atopy

CLINICAL IMPLICATIONS

ACUTE INJURIES

In the United States, approximately three million nonfatal workplace injuries and illnesses are reported annually. Over 50% of these injuries require modified duty, job transfer, or time away from work. The most commonly reported injuries are sprains, strains, and tears; soreness or pain; cuts, lacerations, and punctures; bruises and contusions; and fractures (Table 16-1).[4] Fractures result in the most lost work days. Initial management is basic first aid followed by referral, as necessary, to emergency care or an appropriate specialist.

Eye injuries are common and may be prevented with the use of appropriate personal protective equipment, such as eye protection for healthcare personnel conducting a procedure where a splash from a body fluid is possible or the use of welding goggles to prevent photokeratoconjunctivitis in a welder.

CLINICAL SYNDROMES

Environmental and occupational hazards especially affect individuals who have underlying diseases, chronic health conditions, or habits that increase their risk. For example, individuals who smoke have a higher risk of developing more severe lung disease from occupational exposures (Chapter 81).

Occupational or environmental diseases may be difficult to distinguish from other diseases that cause similar symptoms or signs. For acute syndromes, proximal exposure to toxins, often with similar symptoms in others, is a helpful clue. For more recurrent symptoms, a cyclic pattern in which symptoms worsen on workdays and improve on days off, is helpful. For chronic symptoms, such as hepatic dysfunction or neurologic findings, a more long-standing work or environmental exposure or toxin should be considered, and such a link is more likely if multiple individuals are affected.

For potential exposure to heavy metals (Chapter 20), blood levels can be diagnostic. For other exposures, a trial of withdrawal followed by re-challenge can be very helpful when it can be safely implemented.

Taking an Exposure History

Exposure History Form

Date:

Part 1. Exposure Survey **Name:** **Address:**

Please select the appropriate answer. **Birth date:** **Sex (select one):** ○ Male ○ Female

1. Are you currently exposed to any of the following?

metals	○ no ○ yes
dust or fibers	○ no ○ yes
chemicals	○ no ○ yes
fumes	○ no ○ yes
radiation	○ no ○ yes
biologic agents	○ no ○ yes
loud noise	○ no ○ yes
vibration	○ no ○ yes
extreme heat	○ no ○ yes
extreme humidity	○ no ○ yes
extreme cold	○ no ○ yes

2. Have you been exposed to any of the above in the past? ○ no ○ yes

3. Do any household members have contact with metals, dust, fibers, chemicals, fumes, radiation, or biologic agents? ○ no ○ yes

If you answered *yes* to any of the items above, describe your exposure in detail–how you were exposed, to what you were exposed, how much, how often, and how long you were exposed?

4. Do you know the names of the metals, dusts, fibers, chemicals, fumes, or radiation that you are/were exposed to? ○ no ○ yes → If *yes*, list them below

5. Do you get the material on your skin or clothing? ○ no ○ yes

6. Are your work clothes laundered at home? ○ no ○ yes

7. Do you shower at work? ○ no ○ yes

8. Can you smell the chemical or material you are working with? ○ no ○ yes

9. Do you use protective equipment such as gloves, masks, respirator, or hearing protectors? ○ no ○ yes → If *yes*, list the protective equipment used

10. Have you been advised to use protective equipment? ○ no ○ yes

11. Have you been instructed in the use of protective equipment? ○ no ○ yes

E-FIGURE 16-1. Exposure History Form. PBBs = polybrominated biphenyls; PCBs = polychlorinated biphenyls; MDI = methylene diphenyl diisocyanate; TDI = toluene diisocyanate.

12. Do you wash your hands with solvents?	○ no	○ yes
13. Do you smoke at the workplace?	○ no	○ yes
at home?	○ no	○ yes
14. Are you exposed to secondhand tobacco smoke at the workplace?	○ no	○ yes
at home?	○ no	○ yes
15. Do you eat at the workplace?	○ no	○ yes
16. Do you know of any co-workers experiencing similar or unusual symptoms?	○ no	○ yes
17. Are family members experiencing similar or unusual symptoms?	○ no	○ yes
18. Has there been a change in the health or behavior of family pets?	○ no	○ yes
19. Do your symptoms seem to be aggravated by a specific activity?	○ no	○ yes
20. Do your symptoms get either worse or better at work?	○ no	○ yes
at home?	○ no	○ yes
on weekends?	○ no	○ yes
on vacation?	○ no	○ yes
21. Has anything about your job changed in recent months (such as duties, procedures, overtime)?	○ no	○ yes
22. Do you use any (such as herbs or natural supplements) alternative medicines?	○ no	○ yes
23. Have you or your child ever eaten non-food items such as paint, plaster, dirt, and/or clay?	○ no	○ yes
24. Do you know how to access the Safety Data Sheet (SDS) at your workplace?	○ no	○ yes

If you answered *yes* to any of these questions, please explain.

E-FIGURE 16-1, cont'd

Taking an Exposure History

Part 2. Work History

A. Occupational Profile

The following questions refer to your current or most recent job:

Job title:

Type of industry:

Name of employer:

Date job began:

Are you still working in this job? ○ yes ○ no

If *no*, date job ended?

Describe this job:

Fill in the table below listing all jobs you have worked including short-term, seasonal, part-time employment, and military service. Begin with your most recent job.

Dates of Employment	Job Title and Description of Work	Exposures*	Protective Equipment

*List the chemicals, dusts, fibers, fumes, radiation, biologic agents (i.e., molds or viruses), and physical agents (i.e., extreme heat, cold, vibration, or noise) that you were exposed to at this job.

Have you ever worked at a job or hobby in which you came in contact with any of the following by breathing, touching, or ingesting (swallowing)? If *yes*, please select beside the name.

- ☐ Acids
- ☐ Alcohols (industrial)
- ☐ Alkalies
- ☐ Ammonia
- ☐ Arsenic
- ☐ Asbestos
- ☐ Benzene
- ☐ Beryllium
- ☐ Cadmium
- ☐ Carbon tetrachloride
- ☐ Chlorinated naphthalenes
- ☐ Chloroform
- ☐ Chloroprene
- ☐ Chromates
- ☐ Coal dust
- ☐ Dichlorobenzene
- ☐ Ethylene dibromide
- ☐ Ethylene dichloride
- ☐ Fiberglass
- ☐ Halothane
- ☐ Isocyanates
- ☐ Ketones
- ☐ Lead
- ☐ Mercury
- ☐ Methylene chloride
- ☐ Nickel
- ☐ PBBs
- ☐ PCBs
- ☐ Perchloroethylene
- ☐ Pesticides
- ☐ Phenol
- ☐ Phosgene
- ☐ Radiation
- ☐ Rock dust
- ☐ Silica powder
- ☐ Solvents
- ☐ Styrene
- ☐ Talc
- ☐ Toluene
- ☐ TDI or MDI
- ☐ Trichloroethylene
- ☐ Trinitrotoluene
- ☐ Vinyl chloride
- ☐ Welding fumes
- ☐ X-rays
- ☐ Other (specify)

E-FIGURE 16-1, cont'd

B. Occupational Exposure Inventory *Please select the appropriate answer.*

1. Have you ever been off work for more than 1 day because of an illness related to work? ○ no ○ yes
2. Have you ever been advised to change jobs or work assignments because of any health problems or injuries? ○ no ○ yes
3. Has your work routine changed recently? ○ no ○ yes
4. Is there poor ventilation in your workplace? ○ no ○ yes
5. Has your workplace flooded? ○ no ○ yes
6. Is your workplace damp? ○ no ○ yes
7. Do you perform outdoor work? ○ no ○ yes

Part 3. Environmental History *Please select the appropriate answer.*

1. Do you live next to or near an industrial plant, commercial business, dump site, or nonresidential property? ○ no ○ yes
2. Which of the following do you have in your home?
   Please select those that apply.
   ☐ Air conditioner ☐ Air purifier ☐ Central heating (○ Gas ○ Oil) ☐ Gas stove
   ☐ Electric stove ☐ Fireplace ☐ Wood stove ☐ Humidifier
3. Have you recently acquired new furniture or carpet, refinished furniture, or remodeled your home? ○ no ○ yes
4. Have you weatherized your home recently? ○ no ○ yes
5. Are pesticides or herbicides (bug or weed killers; flea and tick sprays, collars, powders, or shampoos) used in your home or garden, or on pets? ○ no ○ yes
6. Do you (or any household member) have a hobby or craft? ○ no ○ yes
7. Do you work on your car? ○ no ○ yes
8. Have you ever changed your residence because of a health problem? ○ no ○ yes
9. Does your drinking water come from a private well? ○ no ○ yes
   City water supply? ○ no ○ yes
   Grocery store? ○ no ○ yes
   Other (specify) [ ] ○ no ○ yes
10. Approximately what year was your home built? [ ]
11. Does your food come from somewhere other than a grocery store? ○ no ○ yes
12. Do you live in a rural area? ○ no ○ yes
13. Do you live in a suburban area? ○ no ○ yes
14. Do you live in the city? ○ no ○ yes
15. Has your home flooded? ○ no ○ yes
16. Is your home damp? ○ no ○ yes

If you answered *yes* to any of these questions, please explain.

[ ]

Save Data Print Reset Form Submit

E-FIGURE 16-1, cont'd

TABLE 16-1 COMMON OCCUPATIONAL MUSCULOSKELETAL INJURIES

ANATOMICAL LOCATION	INJURY
Neck and Back Injury	Acute back or neck pain Disk herniation
Shoulder	Acromioclavicular joint separation Adhesive capsulitis Brachial plexus neuropathy Impingement syndrome Labral tear Rotator cuff tear Rotator cuff tendinosis Shoulder dislocation Subacromial bursitis Supraspinatus tendinitis
Elbow	Anterior interosseous syndrome Elbow dislocation Elbow fracture Lateral and medial epicondylitis Olecranon bursitis Pronator syndrome Radial tunnel entrapment Ulnar collateral ligament injury Ulnar nerve entrapment at elbow
Hand	Carpal tunnel syndrome De Quervain tenosynovitis Dupytren contracture Mallet finger Radius fracture Scaphoid fracture Trigger finger Ulnar fracture Wrist sprain
Hip	Bursitis Labral tear Tendonitis
Knee	Anterior cruciate ligament injury Collateral ligament injury Knee pain Medial and lateral meniscal injury Patellofemoral pain Posterior cruciate ligament injury
Ankle	Fracture Inversion or inversion injury
Eye Injury	Cataract Chemical or thermal burn Corneal abrasion Foreign body Splash to eye of infectious fluid Trauma
Ear Injury	Hearing loss due to acoustic or physical trauma Ototoxic hearing loss Sensorineural noise induced hearing loss
Occupational Infections	Bloodborne pathogen exposures Hepatitis B and C Herpes B virus Human immunodeficiency virus Influenza virus Severe acute respiratory syndrome coronavirus 2 Tuberculosis
Occupational Skin Manifestations	Allergic dermatitis from allergens such as latex and chromate Bedbugs Infectious agents such as herpes simplex Irritant contact dermatitis from cleansers and solvents Scabies Skin cancer from arsenic or polycyclic aromatic hydrocarbons

Common Clinical Syndromes

Although environmental and occupational exposures can cause or exacerbate many clinical syndromes, certain syndromes are especially common or problematic (Table 16-2).

TABLE 16-2 COMMON OCCUPATIONAL AND ENVIRONMENTAL HEALTH CONDITIONS IN GENERAL PRACTICE

CONDITION	EXPOSURE SETTINGS	COMMENT
Asthma	Virtually any indoor or outdoor workplace	New-onset, recrudescent, or exacerbated asthma
Interstitial, parenchymal, and inflammatory lung disorders	Dusts, metals, and organic materials	All parenchymal disorders have one or more environmental causes
Cancers of the respiratory tract	Asbestos, radon, silica, combustion fumes, tars, and some metals	Smokers are more likely to be affected
Sensorineural hearing loss	Noise, metals, and solvents	High-frequency loss, especially in younger workers
Musculoskeletal disorders of trunk and limbs	Heavy or repetitive activities or postures	Cold, vibration, and work stress contribute
Upper airway irritation	Dust and fumes	More common in smokers and atopic persons
Nonspecific building-related illness	Office work	Must exclude *specific* causes
Dermatitis, allergic or irritant	Repeated exposure to unprotected skin	Work and environmental exposures should be considered in every case
Multiple chemical sensitivities	Any	Complication of adverse environmental exposure

From Cullen MR. Principles of occupational and environmental medicine. In: Goldman L, Schafer AI, eds. *Goldman-Cecil Medicine*, 26th ed. Philadelphia: Elsevier; 2020: Chapter 16.

Asthma

Numerous workplace antigens ranging from animal dander, to latex, to small molecules are responsible for as much as 20% of adult-onset asthma (Chapter 75). The temporal relationship of symptoms to work may be the only clue, and resolution after removal from the toxic environment is the only way to establish the diagnosis.

Chronic Lung Diseases

Coal workers' pneumoconiosis (Chapter 81), silicosis (Chapter 81), and chronic berylliosis can all resemble sarcoidosis (Chapter 83) on a chest radiograph, and all may exacerbate any underlying chronic obstructive pulmonary disease (Chapter 76).[5,6] Asbestosis (Chapter 81) resembles idiopathic pulmonary fibrosis (Chapter 80) except for its pleural involvement. Hypersensitivity pneumonitis (Chapters 80 and 81) occurs in agricultural settings or wherever microbes contaminate work materials. Bronchiolitis obliterans is seen in workers in facilities that produce microwave popcorn or coffee as a result of exposure to diacetyl or 2,3-pentanedione. Inorganic chemicals can cause allergic alveolitis.

Respiratory Cancers

Occupational exposure to coal dust, asbestos, silica, polyaromatic hydrocarbons, diesel exhaust, pitch, asphalt, radon, chromium, and formaldehyde have been implicated in lung cancer (Chapter 177), and their risks are synergistic with cigarette smoking. Asbestos is also the major risk factor for malignant mesothelioma (Chapters 86 and 177).

Sensorineural Hearing Loss

Noise is second only to aging as a cause of high-frequency sensorineural hearing loss (Chapter 394).[7] Hearing protection can mitigate or prevent hearing loss and is required for major occupational noise exposure. Exposure to ototoxic workplace chemicals, such as aniline dyes used commercially to dye fabric, also may lead to hearing loss.

Musculoskeletal Disorders

Low back pain (Chapter 369) is the most common work-related musculoskeletal complaint. In addition to usual care, workplace preventive measures are key.

Other chronic musculoskeletal injuries include carpal tunnel syndrome (Chapter 388), epicondylitis, and De Quervain tenosynovitis. Physical therapy and medications are often helpful, but modifying the causal work and leisure activities is a key intervention.

Skin Conditions

Erythematous rashes commonly are caused by workplace or other exposures to latex, plastics, irritating chemicals, heat pressure, or friction. Identification and elimination of the precipitant is critical. Allergy testing (Chapter 230) by a consultant is helpful in difficult cases.

Common Exposures

Thousands of toxins (Table 16-3) and other hazards can potentially cause or exacerbate a wide range of conditions, but certain basic principles and clinical approaches can guide the assessment of their role in causing signs or symptoms in individual workers. The major determinants of the risk for clinical disease are exposure and absorption, which together determine the dose of the toxin.

Sick Building Syndrome

The inability to provide safe heating, air-conditioning, and air exchange in indoor spaces can result in nonspecific symptoms such as headache, fatigue, cough, and even skin rashes in multiple occupants in the affected building.[8] Molds and other microbial materials may be the cause, but a specific irritant may not be discovered despite extensive testing. Remediation of identifiable sources usually alleviates the problem, but sometimes empirical cleaning or replacement of systems may be required.

Metals

Exposures to lead and arsenic (Chapter 20) are now uncommon in the workplace but have been associated with contamination of drinking water in the United States and globally. Mercury (Chapter 20) is found in large ocean fish. Manganese (Chapter 20) in welding fumes and various alloys can cause extrapyramidal Parkinson-like symptoms and autonomic dysfunction. Blood or urine levels are generally the best way to make the diagnosis.

Solvents, Organohalides, Herbicides, and Pesticides

Petroleum derivatives, which are commonly components of workplace and household products, are irritating and sometimes neurotoxic or hepatotoxic (Chapter 96). Dioxin, which is produced by the combustion of chlorine-containing materials, can cause soft tissue sarcomas (Chapter 187) and perhaps other cancers. Glyphosate, which had been a common herbicide, is associated with about a 40% increased risk of non-Hodgkin lymphoma (Chapter 171). Exposure to pyrethroid insecticides is associated with increased mortality.[9]

Particulate Matter

Ambient air pollution is a major contribution not only to lung disease but also to cardiovascular disease[10,11] and all-cause mortality.[12] Some estimates suggest that indoor and outdoor air pollution cause 6 to 7 million annual deaths worldwide, about two-thirds of which are attributable to outdoor pollution. Respiratory irritants include sulfur dioxide, and small particulate matter that may be laden with proinflammatory polyaromatic hydrocarbons, which especially result from burning wood, coal, or diesel fuel.

Water

In addition to toxins such as lead and arsenic, more than 800 million people worldwide consume unclean drinking water that can be contaminated with bacteria, nontuberculous mycobacteria, and protozoa. Such contaminated water causes about 3.75 million deaths worldwide each year.

Disease outbreaks attributable to water can result in serious acute, chronic illness as well as result in a fatality, especially if one is immunocompromised. Water contamination is not distributed evenly. It may depend on seasonality, for example, where enteric infection and water-related illnesses occur more commonly during the periods of rain abundance, as in areas where bimodal rainfall patterns are experienced. Besides climatic events, the degree of contamination can also depend on the number of pathogens present in the water source, how old and well maintained the system is, and whether the water quality is inspected regularly.

Molds and Dusts

Molds, with or without a detectable odor, often stimulate an allergic airway response[13] (Chapter 230), sometimes as part of a broader contamination of indoor air handling systems. Mineral dusts include silica,[14] fibrous glass, mineral wool, and other synthetic fibers.

Radiation

Radiation exposure is discussed in Chapter 18.

Global Warming and Climate Change

Please see Chapter 17.

OCCUPATIONAL SAFETY STANDARDS

The Occupational Safety and Health Administration (OSHA) issues, promulgates, and enforces standards for workplace safety and health. The National Institute of Occupational Safety and Health (NIOSH), which is part of the Centers for Disease Control and Prevention, does not have authority to set standards, but its reviews regarding chemicals, toxicology, and other hazards provide evidence to help inform the process of setting standards to protect workers' health and safety. These evidence-based standards were created to protect workers and are enforced through workplace inspections and penalties that are assessed for noncompliance. Even for hazards for which clear standards do not exist, the employer is required to protect employees from potentially dangerous exposures.

MEDICAL SURVEILLANCE

Medical surveillance is the systematic, ongoing monitoring of workers who have exposure or potential exposure to occupational hazards. This measurement and assessment then inform secondary prevention measures and the ability to evaluate the effectiveness of prevention strategies.

HIERARCHY OF CONTROLS

The hierarchy of hazard controls, developed through the National Institute of Occupational Safety and Health, is a 5-tiered system that describes the most to least robust ways by which workers can be protected from a hazard. First is elimination, such as banning dichlorodiphenyltrichloroethane (DDT) use in agriculture. Next is substitution, such as using sesquisulfide in lieu of white phosphorus in matches, thereby successfully eliminating jawbone necrosis in workers. Third is the use of engineering controls to eliminate the hazard, as in using safety devices to reduce needlestick exposures in health care personnel. Fourth are administrative controls, such as social distancing to reduce the spread of coronavirus-19 (COVID-19) infection. Finally is the use of personal protective equipment, such as hearing protection to reduce noise exposure, when the hazard itself cannot be eliminated.

ENVIRONMENTAL MEDICINE

Physicians and other providers may be called upon to understand and manage medical concerns that arise from environmental exposures.[15] Tasks may include conducting a risk assessment, managing and communicating risk, making recommendations about possible human health effects, and assessing, understanding, and interpreting regulatory issues. The severity and urgency of environmental issues, such the adverse ramifications of a changing climate (Chapter 17) or environmental justice (e.g., neighborhoods being differentially affected by toxic waste), may vary geographically but remain major challenges. Being able to elicit a detailed environmental history may help reveal presenting diagnoses. Examples include a cardiac event precipitated by exposure to particulate matter 2.5 ($PM_{2.5}$) air pollution, heat-related illness from working in a hot environment without acclimatization or with inadequate access to shade and/or hydration, or a vector-borne disease (e.g., Lyme disease) in an area where the organism was not previously found but has emerged because of climate change.

ENVIRONMENTAL STANDARDS

Key statutes to address these environmental hazards include:

- The Resource Conservation and Recovery Act, which created the framework for the proper management of hazardous and nonhazardous solid waste.
- The Comprehensive Environmental Response, Compensation, and Liability Act, which established the federal Superfund program in 1980 to clean up uncontrolled or abandoned hazardous waste sites as well as accidents, spills, and other emergency releases of pollutants and contaminants into the environment.
- The Emergency Planning and Community Right-to-Know Act of 1986, which addressed the environmental and safety hazards posed by the storage and handling of toxic chemicals.

WELLNESS AND RESILIENCY

Workplaces must not only treat and prevent illness and injury but also promote health and well-being. Wellness, resiliency, and prevention of burnout have

TABLE 16-3 SELECT OCCUPATIONAL AND ENVIRONMENTAL HAZARDS

GROUP	HAZARD	EFFECT/SYMPTOMS	OCCUPATION/POTENTIAL SOURCE
Noxious Gases	Argon	Simple asphyxiant	Welder
	Ammonia	Pulmonary irritant, acute respiratory distress syndrome	Refrigeration; ammonia injection into soil as nitrogen-containing plant nutrient
	Carbon monoxide	Chemical asphyxiant	Mechanic, firefighter, blast furnace
	Helium	Simple asphyxiant	Electronics, aircraft manufacture
	Hydrogen cyanide	Chemical asphyxiant	Agricultural workers, plastics industry
	Hydrogen fluoride	Pulmonary irritant, ARDS	Glass etching
	Nitrogen	Simple asphyxiant, silo-fillers' disease	Welder, firefighter
Industrial Dusts Pneumonoconioses	Asbestos	Asbestosis, mesothelioma, lung cancer, pleural plaques, colon, renal and stomach cancer	Mining
	Coal	Emphysema, coal workers' pneumoconiosis	Coal mining, welders, diesel exhaust
	Silica	Silicosis	Sand blasting, granite countertop manufacture
Other Inorganic Dusts	Iron	Siderosis	Welding
	Tin	Stannosis	Tin
Vegetable Dusts	Cotton, flax, hemp	Byssinosis	Yarn and cotton manufacturer
	Flour dust	Occupational asthma	Baker
	Fungi in moldy hay	Farmer lung	Farming, agriculture
	Organic dusts or aerosols	Hypersensitivity pneumonitis	Mushroom farming, composting installations, vegetable storage
	Plicatic acid from western red cedar	Occupational asthma	Logging, house construction
	Sugar cane (fungus)	Bagassois	Sugar cane farming
Metals	Beryllium	Beryllium disease	Foundries, metal fabricators
	Cadmium	Pulmonary edema	Battery manufacturing, silver soldering
	Chromium	Lung cancer, nasal sinus cancer, sensitization	Welding on stainless steel, spray painting, operating chrome plating baths
	Cobalt	Asthma, allergic contact dermatitis, cardiomyopathy	Knee/hip replacement degradation
	Copper	Metal fume fever	Welding
	Lead	Lead toxicity, lethargy, wrist drop, lead line, anemia	Environmental lead, Ayurveda medication, battery production, glazes
	Magnesium	Metal fume fever	Welding, brazing
	Manganese	Parkinsonian syndrome	Welding, ore crushing, metallurgy
	Mercury—inorganic	Erethism, tremor, proteinuria	Amalgam workers, battery maker, fluorescent lamp maker
	Mercury—organic	Paresthesias, cognitive changes, cerebral palsy	Food chain: biomethylation of inorganic mercury by aquatic organisms
	Nickel	Sensitizer, dermatitis, asthma, nasal cancer	Welding alloys, stainless steel, plating
	Vanadium pentoxide	Pneumonitis, bronchitis, eye irritation	Cleaning fireboxes under boilers
	Zinc	Metal fume fever	Welding
Organic Compounds	Aliphatic hydrocarbon-n-hexane	Neuropathy, lipoid pneumonia	Solvent use, industrial cleaner and degreaser, mineral oil lubricants use
	Aromatic hydrocarbons—benzene	Aplastic anemia, leukemia	Shoe cements use, printing, fuel component
	Chlorinated hydrocarbons (e.g., trichloroethylene)	Headache, irritability, CNS depression, beverage/alcohol intolerance	Dry cleaning, chemical synthesis
	Chlorinated aromatics (e.g., dioxin)	Chloracne	Pulping and pesticide manufacturing
	Fluorinated hydrocarbons (e.g., perfluorochemicals)	Possibly carcinogen	Stain-resistant textiles and carpeting, water-repellent clothes, ski wax, Teflon manufacture
	Halogenated hydrocarbons (e.g., chloroform)	Nephrotoxicity, respiratory depression	Building, paper and board industries
Plastics	Acrylates/methacrylates	Irritant, contact allergen	Plexiglass manufacture, caulk use
	Fluoropolymers (e.g., Teflon)	Polymer fume fever	Teflon manufacture
	Vinyl chloride	Hepatic angiosarcoma	Vinyl chloride monomer, polymerization operations
Pesticides	Carbamates (e.g., carbaryl [Sevin])	Acetylcholine esterase inhibition	Pesticide manufacturing and application, forestry, pest management
	Fumigants (e.g., dibromochloropropane)	Oligospermia	Soil fumigant
	Fungicides (e.g., pentachlorophenol)	Aplastic anemia, chloracne	Wood preservative (telephone poles), dock, pier, and wharf structures
	Herbicides (e.g., paraquat)	Pulmonary fibrosis	Agriculture, forestry
	Organophosphates (e.g., parathion)	Acetylcholine esterase inhibition, paresthesias	Pesticide, agriculture, forestry
	Pyrethrins (e.g., permethrin)	Paresthesias with skin contact, dermatitis	Forestry, agriculture
Physical Hazards	Cold	Hypothermia, frostbite	Construction worker, outdoor trades
	Dysbarism	Fatigue, mottled skin, eardrum rupture	Commercial and sport divers
	Heat	Heat-related illness	Outdoor worker, athlete, farm worker
	Infrared radiation	Lens, cornea, retinal damage, skin burns	Glass blowing, smelting, foundry and forge operations
	Ionizing radiation	Cancer	Nuclear medicine, x-ray technician
	Lasers	Mild burns, cataracts	Welding, cosmetic surgery
	Noise	Hearing loss	Construction, mining, animal worker
	Radiofrequency radiation (radio waves and microwaves)	Burns	Telecommunications, electrosurgery
	Ultraviolet radiation	Photokeratoconjunctivitis or welders flash, cataracts	Plumbers, welders, machinery fitters, assemblers, toolmaker
	Vibration	Vibration white finger	Jackhammering, chainsawing

ARDS = acute respiratory distress syndrome; CNS = central nervous system.

become key issues throughout the workforce, and especially among health care workers, exacerbated by the COVID-19 pandemic.[16] For example, the provision of physical relaxation options can reduce stress among health care workers.[A1] Building collective and individual wellness and resiliency is a valuable skill to prevent burnout, which is an important occupational hazard that affects the personal and professional lives of employees and can have a substantial negative impact on patients, clients, and the financial well-being of institutions. The organization of work is a significant factor in causing and propagating burnout, and addressing such issues requires surveillance to identify the magnitude of the problem, careful consideration of key potential explanations, and a coordinated effort among front-line workers, mental health services, institutional leadership, and relevant stakeholders.[17,18]

EMERGENCY PREPAREDNESS AND DISASTER MANAGEMENT

The key roles for occupational and environmental medicine, as highlighted during the early months of the COVID-19 pandemic, include skills in emergency preparedness, emergency management, assessment of exposures, identification of hazards, disease prevention, surveillance, and population health. Knowledge of specific threats (including chemical, biologic, radiologic, and physical hazards) and bioterrorism agents (Chapter 19) can help protect employees, families, and the population at large. Emergency management planning includes resource mobilization, communication, procurement of medical products, financing, and contingency planning, often with the collaboration with local, state, or federal agencies. Addressing the mental health and safety needs of employees and responders is also critical.

ROLE OF THE INDIVIDUAL CLINICIAN

Clinicians must be agile to meet the challenges presented by the changing nature of work and our environment. They must recognize that care extends beyond merely attending to the clinical ailment in one worker to consider workplace risks that might affect other workers. Clinicians must consider both work-related and nonoccupational causes of illnesses, with the understanding, for example, that orthopedic or neurologic conditions may predispose to workplace injuries, and vice versa, that underlying lung disease may predispose to environmental pulmonary disease, and that preexisting anxiety or depression can exacerbate burnout. Referral to an occupational and environmental medicine specialist, who is trained in preventing, mitigating, and controlling hazards and managing workforces on a population level, is indicated when the degree of complexity rises above the scope of the general clinician.

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17 EFFECTS OF CLIMATE CHANGE ON HEALTH

JEREMY HESS AND KRISTIE EBI

Climate is an important contextual element for human health and well-being. Anthropogenic climate change has demonstrated that long-held assumptions about the climate's stationarity are no longer valid, and our health systems and activities urgently need to be adjusted, in some cases fundamentally, to accommodate the ongoing shift in weather patterns. Health care education and practice must change, as well. To reduce harm, the health sector as a whole has an obligation to reduce its greenhouse gas emissions aggressively, and individual clinicians should acquire basic familiarity with the drivers and impacts of climate change, as well as priority strategies to reduce and manage risk.[1] Clinicians should understand how climate change will affect their patients and the communities in which they practice, and they should become proactive in improving the sustainability of health systems and services.

HOW CLIMATE CHANGE AFFECTS HEALTH

Climate, which is the multi-decade average of weather patterns in a given location, is the basis for long-term expectations, whereas weather is more variable and shapes day-to-day experiences. However, the implicit assumption that past climate is predictive of future weather patterns is no longer true. Anthropogenic climate change, driven by human emissions of greenhouse gases into the atmosphere, is undermining the assumption of stationarity.

Climate, which is a fundamental driver of health and disease,[2] determines the ecology of life in a particular place, including the social ecology of human settlement. Despite usual climatic variability, such as the recurring El Niño southern oscillation, the earth's climate has been quite stable within a relatively narrow range for millennia.[3]

Because of human emissions of greenhouse gases into the atmosphere, climatic expectations are no longer based on historical experience, with potentially profound implications for human health and, therefore, for public health and medical practice. Climate change affects health security, health determinants, risks for specific diseases, and how the health system's infrastructure and capacity will be able to respond to the challenges of the 21st century.

Anthropogenic climate change operates through simple physical principles. As a result of increased emissions of greenhouse gases (principally carbon dioxide but also methane, hydrofluorocarbons, and a host of other short-lived species), the earth's atmosphere is retaining a larger fraction of the sun's energy. This energy is transferred into land, water, and the atmosphere. For example, with more energy from warmer oceans, storms are stronger, contain more precipitation, and create more floods. Increased atmospheric heat dries out soils more quickly, and heat waves are stronger and persist for longer. Warming melts land-based ice and snow, thereby raising sea levels. Warming also speeds the photochemical reactions that are responsible for the formation of ground-level ozone, which is an air pollutant. Carbon dioxide levels in the oceans equilibrate with levels in the atmosphere, thereby increasing the concentration of carbonic acid; this weak acid dissolves calcium carbonate, thereby threatening collapse of marine ecosystems built on animals with shells. These impacts are already discernible with global average surface warming of 1.2° C above preindustrial temperatures. High-emission scenarios for the duration of the 21st century would result in 5.7° C of warming by the end of the century. Widespread, catastrophic impacts become increasingly likely with each additional unit of warming. For example, up to 90% of warm water corals are projected to die at 1.5° C of warming.

The implications for human health and well-being are significant. Health impacts result from a combination of underlying population-level vulnerability based on socio-demographics and health status, climate sensitivity of relevant disease pathways, and lack of investments in protective measures that could reduce exposure and promote prompt recovery in the event of expected adverse impacts.

The environmental impacts from climate change (Fig. 17-1) affect a wide range of pathways. Some pathways are relatively direct, such as heat exposure, which causes heat exhaustion and heat stroke (Chapter 95), as well as exacerbating stress on the cardiovascular, respiratory, and renal systems. Heat also affects determinants of health by reducing economic productivity and increasing the likelihood of violent crime. Extreme weather, including heat waves, storms, floods, wildfire, and climatic events such as droughts have significant health impacts by increasing injuries, exacerbations of chronic disease, anxiety, and depression.

Climate change also affects a wide range of other, less direct pathways that are important to human health, from air pollution (heat and sunlight affect the development of ground-level ozone and wildfires release particulate air pollution) to aeroallergens (the onset and intensity of pollen season are correlated with temperature).[4] Infectious diseases are particularly sensitive to climatic shifts as a result of changes in the reproductive rates and geographic distribution of pathogens (Chapter 303) including vectors that can transmit waterborne and foodborne diseases, such as the tick that can carry Lyme

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Climate change also affects a wide range of other, less direct pathways that are important to human health, from air pollution (heat and sunlight affect the development of ground-level ozone and wildfires release particulate air pollution) to aeroallergens (the onset and intensity of pollen season are correlated with temperature).[4] Infectious diseases are particularly sensitive to climatic shifts as a result of changes in the reproductive rates and geographic distribution of pathogens (Chapter 303) including vectors that can transmit waterborne and foodborne diseases, such as the tick that can carry Lyme

ABSTRACT

Climate is an important contextual element for human health and well-being. Anthropogenic climate change has demonstrated that long-held assumptions about the climate's stationarity are no longer valid, and our health systems and activities urgently need to be adjusted, in some cases fundamentally, to accommodate the ongoing shift in weather patterns. Health care education and practice must change, as well. To reduce harm, the health sector as a whole has an obligation to reduce its greenhouse gas emissions aggressively, and individual clinicians should acquire basic familiarity with the drivers and impacts of climate change, as well as priority strategies to reduce and manage risk. Clinicians should understand how climate change will affect their patients and the communities in which they practice, and they should become proactive in improving the sustainability of health systems and services.

KEYWORDS

climate change
health systems
greenhouse gas emissions
heat stress
infectious diseases
health care education

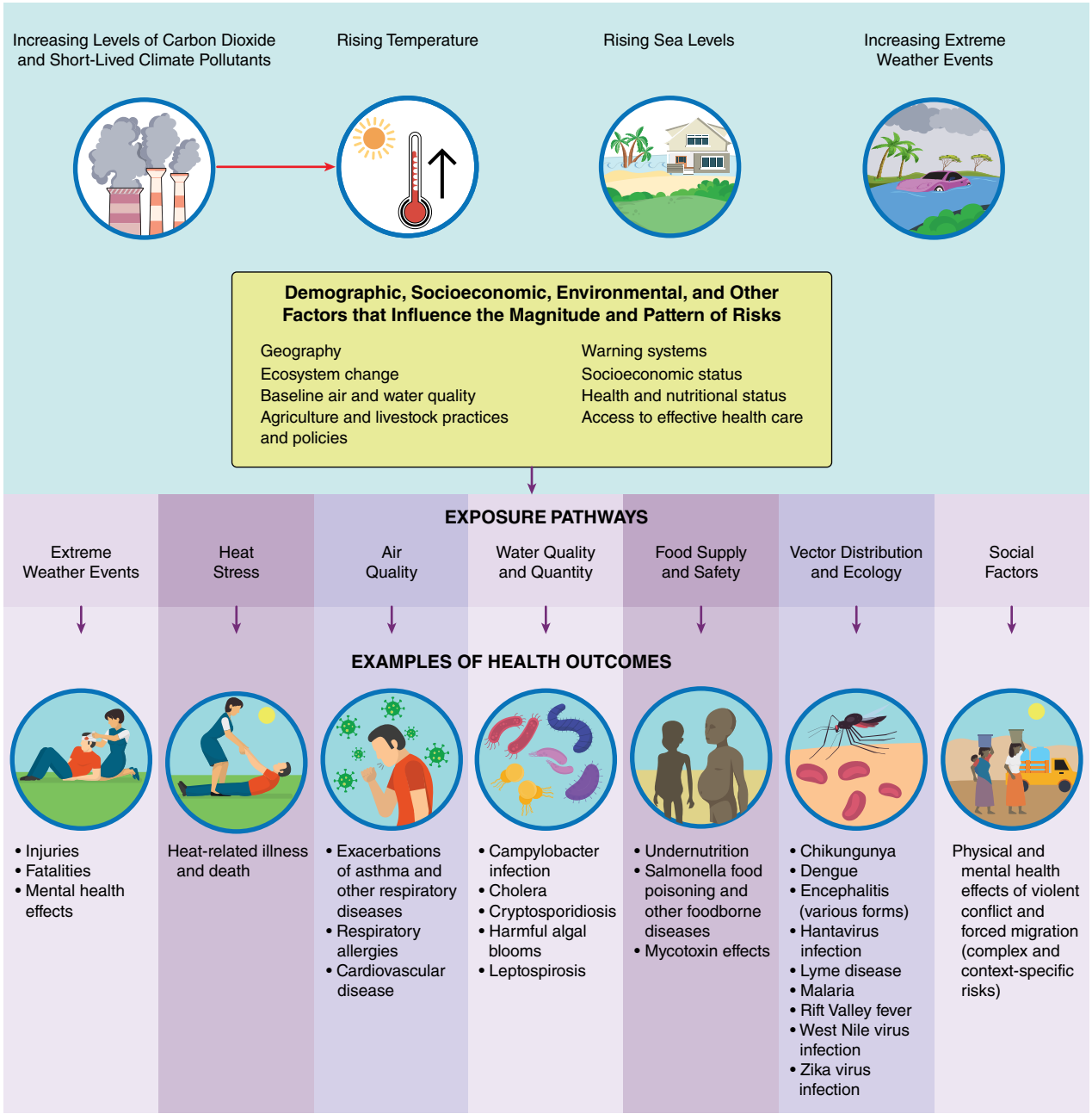

FIGURE 17-1. Major health risks associated with climate change. (From Haines A, Ebi K. The imperative for climate action to protect health. *N Engl J Med*. 2019;380:263-273. Reproduced with permission.)

disease (Chapter 296) and the mosquitoes that can carry dengue fever, Zika virus, chikungunya, and yellow fever (Chapters 351 and 352), and skin and soft tissue infections.[5] Nutritional impacts derive from several different pathways, including disruption of food production from extreme weather, decreased protein and micronutrient content of staple crops, and collapse of productive ecosystems that are key for subsistence.[6] On a macro level, rising sea levels and ecologic stressors are expected to lead to widespread and challenging migration and displacement.

RECENT EVIDENCE AND PROJECTED IMPACTS OF CLIMATE CHANGE ON HEALTH

Health impacts of climate change are already apparent. Patterns of emergence include sentinel events and outbreaks (Table 17-1), shifts in endemicity, introduction and establishment of new diseases, and changing patterns of underlying risks and stressors that affect determinants of health. For instance, heat-related mortality rates are increasing globally, and 37% of heat-related mortality can now be attributed to climate change.[7]

An outbreak of *Vibrio parahaemolyticus* (Chapter 278) in Alaska in 2004 shifted the range of that pathogen over 1000 km to the north; Lyme disease (Chapter 296) is moving steadily northward on the North American continent[8]; ragweed allergy (Chapter 230), historically rare in Europe, is becoming increasingly prevalent[9]; and rising sea levels are requiring relocation from a wide range of coastal communities (see Fig. 17-1).[10] Other shifts, such as changes in the range of *Aedes albopictus,* which transmits Zika, dengue, and chikungunya (Chapters 351 and 352), and *Phlebotomus,* which transmits leishmaniasis (Chapter 319), are driven by climate change and increase risk of these infectious diseases.[11]

The timing and magnitude of the most severe impacts will depend on multiple choices made at the societal level in coming decades. Substantial future warming is inevitable based on greenhouse gas emissions to date. Through roughly mid-century, choices regarding health and social protections, including the degree to which societies invest in basic physical and mental health care, health systems, education, economic protection, and climate-resilient infrastructure, will be the primary determinant of climate impacts. The extent to which climatic hazards and associated stresses could cause severe impacts after mid-century, overwhelming protections in many locations, is a function of preparedness and of how successfully the world is able to reduce greenhouse gas emissions in the next two decades.

HEALTH CARE PROFESSIONALS AND CLIMATE CHANGE

Clinicians should have a basic understanding of what constitutes a climate-resilient health system and how climate change may affect the populations for which they care. Practitioners should advocate for reducing the health sector's substantial greenhouse gas emissions and participate in building climate-resilient health systems (E-Fig. 17-1).

Although this framework is primarily designed for public health officials and leaders of health systems, it has clear relevance to clinicians across the health sector. An emphasis on leadership, for example, highlights the need for clinicians to speak publicly about preparing for climate change and its impacts so as to prioritize planning and public-facing policies, measures, and engagements.[12] The emphasis on ensuring climate-smart risk monitoring and early warning encompasses a wide range of activities, from surveillance of indicators of climate change (e.g., extreme heat events and heat-related illness; pollen season parameters and allergic respiratory disease) to an understanding of how shifts in climate may affect individual and community health. Other important aspects of adapting to climate change in the health sector include engagement in disaster planning and preparedness exercises (in anticipation of more frequent and severe extreme heat events, storms, wildfires, and power failures), as well as the development and implementation of early warning systems[13] for extreme events, and promoting disaster risk reduction to prevent and limit adverse health impacts from disasters.

Reducing greenhouse gas emissions from the health sector is also an important priority.[14] The health sector's emission of greenhouse gases constitutes approximately 4% of the global total,[15] larger than global emissions from air travel. In the United States, the percentage is even higher—the health sector is responsible for nearly 10% of emissions.[16] These emissions are clearly associated with health harms from co-emitted air pollution. In the United States, for example, air pollution from health care causes the loss of nearly 400,000 disability-adjusted years of life[17] and approximately 4.2 million premature deaths globally each year. The harms from air pollution associated with the health care sector in the United States are of the same order of magnitude as harms associated with medical errors.

RESEARCH PRIORITIES FOR CLIMATE CHANGE AND HEALTH

The health sector also must develop additional evidence to support the practice innovations that will be needed to respond to the challenges that climate change presents.[18,19] Areas of emphasis include understanding how climate change harms health; how to diagnose these harms in individuals and across populations; how to devise, implement, and evaluate interventions to reduce these harms; and how to make more accurate prognostic estimates about how current trends and potential interventions could affect the future.

TABLE 17-1 EXAMPLES OF CLIMATE-RELATED HAZARDS, UNDERLYING VULNERABILITIES, AND INFECTIOUS DISEASE OUTCOME

HAZARD	VULNERABILITY	INFECTIOUS DISEASE OUTBREAKS
U.S. hurricane Katrina	Lack of water, sanitation, and hygiene in large shelters for evacuees	Norovirus gastroenteritis
Mozambique cyclones Idai and Kenneth	Lack of water, sanitation, and hygiene and overcrowding in camps for displaced	Diarrheal diseases, malaria
128 flooding, storm, and drought events	Displacement	Measles, cholera, cutaneous leishmaniasis, dengue
Yemen heavy rainfall and elevated temperature	Contamination of surface water	Cholera
Pakistan monsoon flooding	Record-breaking floods	Acute diarrhea, leptospirosis, malaria, leishmaniasis
European heavy rain	Overwhelmed water treatment and distribution systems	Waterborne diseases, such as cryptosporidium
African drought	Water scarcity and hygiene	Cholera

Source: Modified from Semenza JC, Rocklov J, Ebi KL. Climate change and cascading risks from infectious diseases. *Infect Dis Ther*. 2022;11:1371-1390; https://doi.org/10.1007/s40121-022-00647-3.

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18 RADIATION INJURY

DAVID J. BRENNER

IONIZING RADIATION

DEFINITIONS

The ionizing radiations are x- and gamma rays, alpha and beta particles, and (indirectly) neutrons. Unlike non-ionizing radiations such as radio waves, microwaves, infrared light, visible light, and ultraviolet (UV) radiation, ionizing radiations have enough energy to knock electrons out of atomic or molecular orbits, thereby potentially breaking chemical bonds in key biomolecules such as DNA.

A key difference among the various ionizing radiations is their ability to penetrate matter (Fig. 18-1). For example, alpha particles have very limited range, measured in micrometers. Because alpha particles cannot penetrate skin, their health significance is entirely in the context of internal exposure by inhalation or ingestion of alpha-emitting radioactive materials. Beta particles, which have intermediate ranges, can typically be stopped by a piece of paper. By contrast, x-rays, gamma rays, and neutrons are highly penetrating and are hard to shield.

Ionizing radiations are emitted by radioactive materials, which can either be naturally occurring or can be man-made, using machines such as nuclear reactors. The amount of ionizing radiation emitted by a radioactive material is determined by its activity, measured in becquerels (1 Bq = 1 radioactive disintegration/second) or Curies (Ci).

Radioactivity should be distinguished from absorbed dose, which is a measure of how much ionizing energy is actually absorbed by a structure of interest, such as a person or an organ. The basic measurement unit of absorbed dose, which is the energy deposited per unit mass, is the Gray (1 Gy = 1 J/kg). *Equivalent dose* takes into account the fact that not all types of radiation are equally effective, *effective dose* takes into account the fact that not all organs in the body are equally sensitive to ionizing radiation, and *collective dose* is a measure of the effective dose delivered summed over a whole exposed population (Table 18-1).

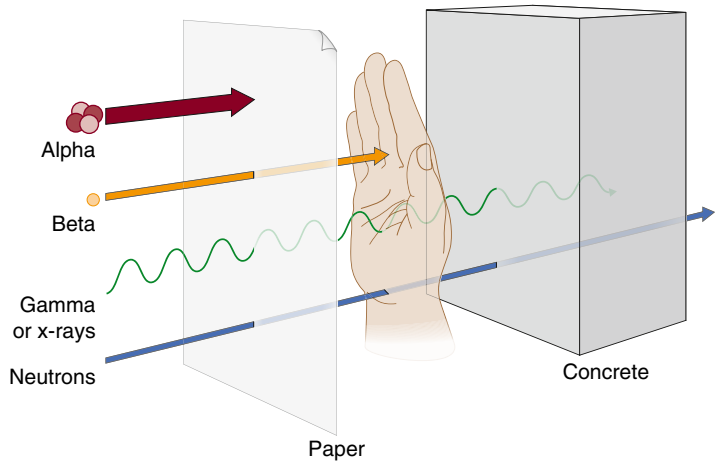

FIGURE 18-1. Schematic illustration of the relative ranges of alpha particles, beta rays, x- or gamma rays, and neutrons as they penetrate through matter.

E-FIGURE 17-1. **World Health Organization operational framework for climate resilient health systems.**

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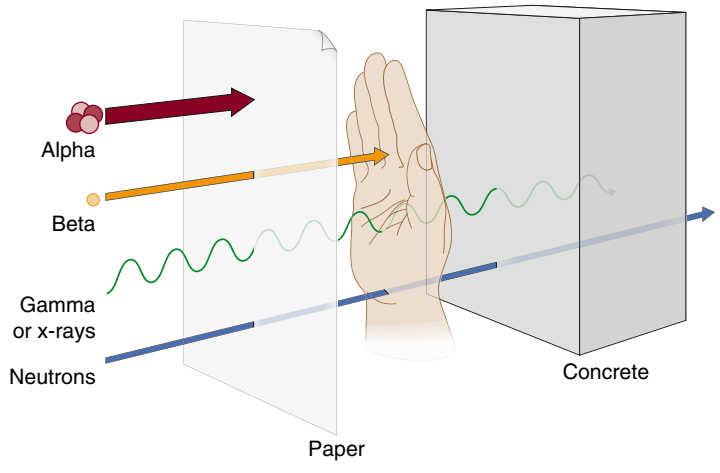

FIGURE 18-1. Schematic illustration of the relative ranges of alpha particles, beta rays, x- or gamma rays, and neutrons as they penetrate through matter.

ABSTRACT

Both ionizing and non-ionizing radiations can cause radiobiologic damage to a variety of tissues. Some of these damages can be mitigated by preventive measures. Radiation can also be used therapeutically as a disinfectant.

KEYWORDS

ionizing radiation
non-ionizing radiation
radiation sources
radiobiologic mechanisms
clinical radiation effects
diagnosis and treatment of radiation effects
prevention of radiation effects

TABLE 18-1 STANDARD QUANTITIES AND UNITS ASSOCIATED WITH EXPOSURE TO IONIZING RADIATION

QUANTITY	DEFINITION	UNITS
Absorbed dose	Energy per unit mass	Gray (Gy)
Equivalent dose	Average dose × radiation-type-specific radiation weighting factor	Sievert (Sv)
Effective dose	Sum of equivalent doses to all exposed organs, each multiplied by an appropriate organ-relative sensitivity factor	Sievert (Sv)
Collective dose	Sum of effective doses to a population of exposed individuals	Person-Sv

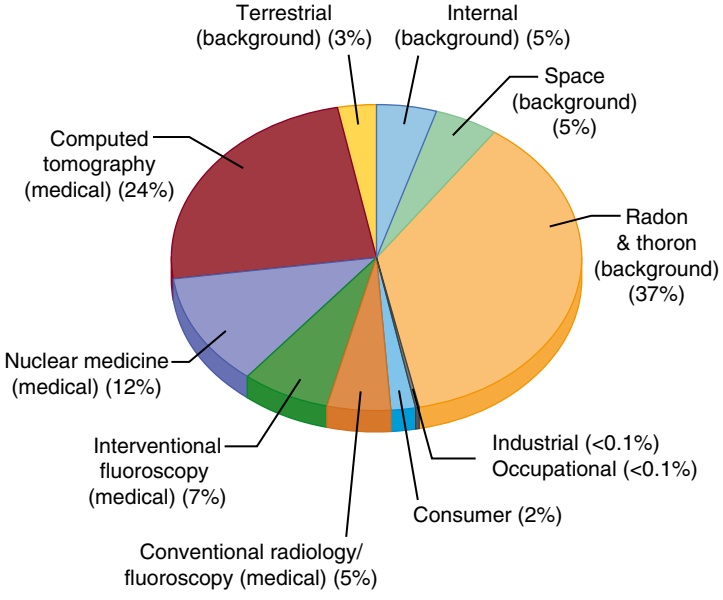

FIGURE 18-2. The major sources of radiation exposure to an average individual in the United States. (From Hall EJ, Giaccia AJ. *Radiobiology for the Radiologist*. 7th ed. Philadelphia: Lippincott Williams & Wilkins; 2012.)

EPIDEMIOLOGY

Radiation exposure can come from natural sources, therapeutic or diagnostic medical exposures, or accidental exposures to individuals or to large populations. Natural sources and radiologic examinations are the major (and about equal) contributors to the overall collective radiation dose to the U.S. population (Fig. 18-2).

Natural Sources of Ionizing Radiation

The largest naturally occurring source of radiation is from radon gas, which is an alpha-particle emitter. Radon is a constituent component of all rocks, particularly granite-type rocks. Radon is a member of a chain of radioactive elements that starts with naturally occurring uranium and radioactively decays from one element to the next; uniquely in this chain of elements, radon is a gas, which can emerge from the ground and result in high levels in the basement and higher floors of houses. Long-term exposure to radon gas can cause lung cancer because emitted alpha particles in the lung can damage cells in the bronchial epithelium. The three other main sources of naturally occurring radiation exposure are from terrestrial exposure (gamma rays emitted from naturally occurring radioactive materials in the ground), from space radiations (mainly intergalactic cosmic rays that penetrate through the atmosphere), and internal radiation (from naturally occurring radioactive elements in the body, such as potassium-40).

Medical Exposures

The single largest source of medical exposure is computed tomography (CT), which on average contributes about 25% of the collective dose to the U.S. population. This source of exposure is recent because CT has been commonly used only since the 1980s. Now, however, about 70 million CT scans are performed annually in the United States. In addition to CT, nuclear medicine, interventional fluoroscopy, and conventional radiography together constitute about 25% of the overall collective dose to the U.S. population.

TABLE 18-2 ESTIMATED RELEASES OF RADIOACTIVE IODINE AND RADIOACTIVE CESIUM FROM THE FOUR HISTORICALLY BIGGEST NUCLEAR POWER PLANT ACCIDENTS

	^{131}I (TBq)	$^{137/134}$Cs (TBq)
Windscale, 1957	750	20
Three Mile Island, 1979	1	0.000001
Chernobyl, 1986	1,800,000	110,000
Fukushima, 2011	~500,000	~20,000

Radiologic Accidents

Since the widespread introduction of nuclear power plants, major radiologic accidents have become an intermittent, although rare, source of radiation exposure. The accidents at Chernobyl in 1986 and at Fukushima in 2011 released far more radioactivity than any other accidents (Table 18-2). For those individuals exposed to low radiation doses, many common symptoms reported in the immediate aftermath were not necessarily physical health problems directly attributable to radiation exposure but rather psychological and psycho-social effects.[1]

Radiologic Terrorism

In the broadest of terms, two different types of such threats exist, one from an improvised nuclear device and the other from a radiologic dispersal device, sometimes called a *dirty bomb*.[2,3] The two are very different in terms of their potential consequences and also their likelihood of occurrence.

The consequences of exploding an improvised nuclear device, perhaps similar to those detonated at Hiroshima or Nagasaki, although more likely exploded at ground level, would be devastating in terms of loss of life and major injuries. For example, a 20-kT daytime surface improvised nuclear device explosion in midtown Manhattan might involve 2.2 million people exposed to high radiation doses, of whom perhaps only 1.6 million might survive.

By contrast, the consequences of exploding a radiologic dispersal device or dirty bomb, dispersing what could be very small or very large amounts of radioactive material, would likely involve a relatively small spatial area in which individuals are significantly exposed, as well as a much larger area in which individuals are exposed to very low levels of radioactivity. The significance of a dirty bomb depends on the amount of radioactivity in the device and the efficiency with which the explosion aerosolizes and disperses the radioactive material. Of course, the consequences of a radiologic dispersal device extend beyond health effects and could potentially involve large-scale social and economic disruption.

PATHOBIOLOGY

Ionizing radiation can both mutate cells and cause cell death. The key initial damage site is a DNA double-strand break, although other types of damage are possible. This double-strand break is generally repaired by a variety of mechanisms, the most important of which for ionizing radiation damage is nonhomologous end rejoining. Imprecise nonhomologous end rejoining can lead to small mutations, whereas double-strand break misrepair (i.e., the wrong ends of breaks being rejoined to each other) can lead to chromosomal translocations, inversions, telomere fusions, and other large-scale chromosomal structural alterations.

Although chromosomal translocations, inversions, and point mutations are typically nonlethal lesions, such radiation-induced chromosomal aberrations can be the initial lesions associated with carcinogenesis. For example, the initial event in many hematopoietic cancers (Chapters 168 and 170) is often a recurrent translocation, which in turn results in the fusion of genes located at the translocation breakpoints. Radiation-induced point mutations and deletions also are often associated with loss of heterozygosity in tumor suppressor genes.

Misrepair of double-strand breaks can also result in dicentric chromosome aberrations and centric rings (Chapter 166), which are generally lethal lesions that cause reproductive cell death in which a cell loses its ability to divide. A second, quite different mechanism of radiation-induced cell death is apoptosis, or programmed cell death, that, for example, is important after radiation exposure of hematopoietic cells and jejunal crypt cells.

CLINICAL MANIFESTATIONS

The consequences of radiation exposure are dose dependent and are also dependent on whether the exposure is to the whole body or only part of the body. After high doses of whole-body exposure, the major consequences are acute radiation syndromes, which may be fatal. After high doses of partial-body exposure, such as after radiotherapy, the consequences are highly organ specific. These high-dose tissue reactions are deterministic, meaning that there typically is a threshold below which the effects are not seen, with the severity of the effect increasing with increasing dose. By contrast, the major concern at lower doses is with stochastic effects, in which there is no dose threshold, and it is the probability of the effect that increases with increasing dose. The most important example here is radiation-induced cancer.

Acute Radiation Syndromes

The radiation dose needed to mitotically kill active dividing cells is far less than the dose needed to remove the functioning ability of differentiated cells. As a result, acute radiation syndromes generally relate to the failure of precursor cells to provide replacements for functional cells within an organ, when the latter need replacement. Acute radiation syndromes typically progress through four stages: prodromal, clinical latency, manifest illness, and recovery or death.

Prodromal Stage

Prodromal (early) symptoms occur shortly after irradiation, with the radiation dose determining the severity, duration, and onset. Typical prodromal symptoms include nausea, vomiting, anorexia, fatigue, diarrhea, abdominal cramping, and dehydration. At very high doses, these symptoms can appear within a few minutes of exposure; but at somewhat lower doses, they may not appear for many hours, if at all.

Latency Period

After the prodromal stage, a latency period typically precedes manifest illness. This delay occurs because the subsequent syndromes (hematopoietic or gastrointestinal) involve the failure of relevant tissues to self-renew, and manifest illness does not occur until after the typical cellular turnover times in these tissues.

Manifest Illness

The *hematopoietic syndrome* results from whole-body or significant partial-body exposure to 3 to 9 Gy. At these doses, radiation kills mitotically active hematopoietic precursor cells. Symptoms then result from lack of circulating blood elements some 4 to 8 weeks later as circulating cells die and are not replaced. The hematopoietic syndrome may manifest as infections and possible hemorrhage, impairment of immune mechanisms, and potentially multiple-organ failure.

The *gastrointestinal syndrome* usually occurs after whole-body or significant partial-body exposure of about 8 Gy and above. These doses lead to death of intestinal stem cells in the regenerating crypts. Symptoms then result when differentiated cells of the villi are naturally sloughed off, but stem cells are unable to produce new cells, thereby leading to depopulation of the epithelial lining of the gastrointestinal tract. After a latency period of about 7 days, loss or significant shortening of the villi on the intestinal epithelium leads to bacterial growth and increased risk for sepsis. Common symptoms include anorexia, nausea, vomiting, prolonged bloody diarrhea, abdominal cramps, dehydration, and weight loss. Should death occur, it is typically 7 to 10 days later.

At extremely high radiation doses, death is typically from the *cerebrovascular syndrome* within a few days after exposure. The cause of death is believed to be because changes in permeability of small blood vessels in the brain lead to cerebral edema.

Organ-Specific Late Effects after Radiotherapy

Iatrogenic organ-specific late effects follow quite predictably after targeted radiation therapy in which the organ in question is irradiated, although the severity of the response is less predictable.[4] These tissue effects can be divided into global organ responses and focal responses, in which a particular part of the organ is differentially irradiated (Table 18-3).

As one example, significant radiation exposure to the heart increases the risk for subsequent major heart disease.[5,6] These risks have been most notable in women who have had radiotherapy for left-sided breast cancer (Chapter 183), patients treated with mantle radiation for Hodgkin lymphoma (Chapter 172), and some patients treated for lung tumors adjacent to the heart. Radiation effects to the heart can be wide ranging, including to the coronary arteries, the myocardium, the heart valves, and the pericardial sac. The increased risk, which is proportional to the cardiac dose, begins a few years after exposure and continues throughout life. These radiation risks appear to be multiplicative of the natural background cardiac risks, so patients with preexisting cardiac risk factors are likely to have greater absolute increases in their risk for radiation-induced cardiac disease. Radiation damage to the lungs (Chapter 82)[7] and colorectal area (Chapter 128)[8] also can cause significant morbidity.

TABLE 18-3 TYPICAL ORGAN-SPECIFIC DETERMINISTIC LATE EFFECTS AFTER HIGH-DOSE RADIOTHERAPY

ORGAN	LOCAL END POINT	GLOBAL END POINT
Brain, cranial nerves	Focal weakness, vision loss	Neurocognitive deficit
Lung	Bronchial stricture	Shortness of breath
Heart	Coronary stenosis	Pericarditis, cardiomyopathy
Bladder	Bleeding	Urinary frequency, diarrhea
Bowel	Ischemia, bleeding	Enteritis

Adapted with changes from Rubin P, Constine LS, Marks LB, eds. *ALERT—Adverse Late Effects of Cancer Treatment*. Vol. 1: General Concepts and Specific Precepts. Heidelberg: Springer; 2014.

Stochastic Effects of Radiation

In contrast to the deterministic organ-based effects of radiation, ionizing radiation also produces stochastic effects, whereby the severity of the disease is not dose dependent, but the probability of an effect increases with increasing dose. These effects are largely due to radiation-induced mutations of target cells, as opposed to cell killing, with by far the most important effect being radiation carcinogenesis. Other potential radiation-induced stochastic health effects include deleterious radiation-induced genetic effects to subsequent generations.

Radiation Carcinogenesis

In general, radiation acts as a multiplier of natural background cancer rates, although there are exceptions, such as radiation-induced breast cancer, in which the radiation risks are largely independent of the natural background rates, and prostate cancer, which generally is not a radiogenic tumor. Most radiation-induced cancers occur many years after radiation exposure, typically in the same "cancer-prone" years (about 55 to 75 years of age), as do naturally occurring cancers. Exceptions include radiation-induced hematopoietic cancers and radiation-induced thyroid cancers, both of which typically occur within a few years of radiation exposure. Sensitivity to radiation-induced cancer is age dependent, with people exposed at younger ages having higher lifetime cancer risks.

Most of what is known quantitatively about the radiation-induced risks for cancer comes from studies of atomic bomb survivors, who had measurable increased subsequent risks for cancer: at a 1 Gy dose at follow-up more than 50 years later, atomic bomb survivors showed a 64% increased risk of solid cancer in females and a 20% increase in males. Despite much study, hereditary effects in the children of atomic bomb survivors was not detected.

Long-term survivors of radiation therapy also have a small but significantly increased risk of radiation-associated second cancers.[9] At low radiation doses, for example, below 0.1 Gy, epidemiologic studies are difficult to perform and interpret because of the difficulty in quantifying a small excess cancer risk above the natural human lifetime cancer risk of about 40%. However large-scale epidemiologic studies in children who have received CT scans or had small radioactive iodine exposures at Chernobyl showed an increased risk of radiation-induced cancer.

Radiation Cataractogenesis

Ionizing radiation induces ocular cataracts (Chapter 391) with a probability, severity, and latency related to the radiation dose.[10] Studies of atomic bomb survivors, Chernobyl cleanup workers, astronauts, and radiologic technicians have all shown increased incidence of cataracts, even at radiation doses below 1 Gy. Radiation cataractogenesis is a result of radiation damage to dividing cells in the lens. Because there are essentially no mechanisms in the lens for removal of damaged cells, the resulting nontranslucent lens fibers migrate toward the posterior pole of the lens, where they represent the first stage of a cataract. Posterior subcapsular cataracts are less common than nuclear or cortical cataracts in the general population but are the type most commonly associated with ionizing radiation.

DIAGNOSIS

The diagnosis of radiation injury can be considered in two different contexts. The first context is when the radiation dose is not known, and the goal is to estimate the dose that was delivered in order to optimize treatment. Examples

include accidents and radiologic terrorism scenarios. The second context is when the radiation dose is known, in particular after radiotherapy. Here the sequelae (see Table 18-3) are predictable, but the timing and the severity of the injury are less predictable.

Radiation Biodosimetry

For an individual exposed to a large whole-body radiation dose, the first critical task is to estimate the radiation dose that the individual received, because different syndromes (hematopoietic, gastrointestinal, cerebrovascular) are associated with different radiation dose ranges. The technique for estimating exposures to individuals is known as *radiation biodosimetry*. In this diagnostic process, a small amount of a body tissue, such as blood or urine, is analyzed, and dose-dependent end points in the sample are measured to provide an estimated dose. The most common end point of DNA damage, such as micronuclei, in blood samples, can now be assessed by commonly available high-throughput technologies. Other practical endpoints include gene expression in blood or induction of metabolites in urine.

Post-Radiotherapy Sequelae

Deterministic radiation-induced organ syndromes are seen at reasonably predictable intervals after radiation therapy. For example, radiation pericarditis (Chapter 62) can develop during treatment or months to years later, initially with an effusion and progressing to pericardial constriction. Radiation enterocolitis (Chapter 126) can develop 6 to 12 months after radiation doses of 40 to 60 Gy for prostate cancer or gynecologic malignancies. Radiation-induced pulmonary injury can be detected in up to 50% of patients who receive thoracic radiation therapy, but only a minority of them will develop clinical symptoms (Chapter 82). In addition, the majority of all radiotherapy patients experience acute skin or mucosal toxicity, in particular radiation dermatitis, oral mucositis, and xerostomia.

TREATMENT

Whole-Body Exposure Syndromes

For exposures below 2 Gy, no immediate treatment is needed (Fig. 18-3). For patients with potential hematopoietic syndrome (doses between 2 and 10 Gy), the two primary treatment approaches are: first, antibiotics and barrier nursing, which can raise the human LD_{50} (the dose at which 50% of exposed individuals die) from about 4 Gy to 8 Gy; and second, granulocyte colony-stimulating factor (G-CSF).[11] Subcutaneous G-CSF, filgrastim (10 μg/kg daily for up to 2 weeks), or pegfilgrastim (two 6-mg doses one week apart) are approved by the U.S. Food and Drug Administration (FDA) for the treatment of patients with radiation-induced myelosuppression following a radiologic/nuclear incident. A placenta-derived adherent stromal cell has been approved by the FDA for emergency treatment of acute radiation exposure in a possible nuclear event.[12]

The role of bone marrow transplantation in treating individuals with the hematopoietic syndrome is probably quite limited at doses less than about 9 Gy. In the aftermath of the Chernobyl accident, for example, 13 individuals underwent bone marrow transplantation, and three deaths were directly attributed to the sequelae of the procedure in patients in whom the transplantation was not indicated based on their exposure. Conservative treatment regimens, including antibiotics, cytokine therapy, transfusions, and nursing, are clearly effective, but current treatment options are very limited at doses above about 10 Gy, when the gastrointestinal syndrome becomes the dominant cause of death.

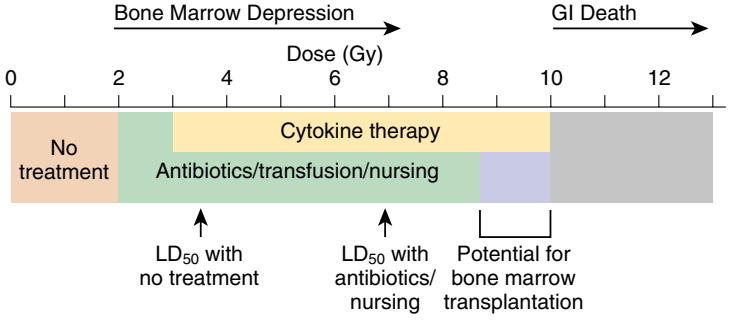

FIGURE 18-3. Schematic recommended treatment for acute radiation syndromes, as a function of the estimated dose that the individual received. Note the very narrow dose window for which bone marrow transplantations are potentially useful. GI = gastrointestinal; Gy = Gray units; LD_{50} = dose of radiation expected to kill 50% of exposed cells within 30 days. (Adapted with changes from Hall EJ. *Radiobiology for the Radiologist*. 7th ed. Philadelphia: Lippincott Williams & Wilkins; 2012.)

Radiotherapy Sequelae

Proton beam therapy may have the potential to reduce side effects compared with other modern versions of radiation therapy.[A1] However, these benefits appear to be limited to specific situations, especially locally advanced esophageal cancer and pediatric brain tumors,[13] and the cost-benefit ratio of proton beam therapy is uncertain. Comparatively few drugs have been approved by the FDA for minimizing radiotherapy-associated sequelae. Amifostine (200 mg/m^2 given intravenously daily before each fraction of radiation therapy)[14] is FDA-approved for minimizing radiotherapy-associated xerostomia, but its use has been limited by significant toxicity, and data on its efficacy are conflicting.[15] Several drugs have been designed to mitigate or treat the damage caused by radiation therapy, particularly to the mucosal barrier. Palifermin, which is a recombinant human keratinocyte growth factor, is FDA-approved (60μg/kg/day administered as an IV bolus injection for 3 consecutive days before therapy and 3 consecutive days after therapy for leukemia or lymphoma) to decrease the incidence or duration of severe oral mucositis.[A2] Avasopasem (a superoxide dismutase mimetic at 90mg given before each therapy) can reduce mucositis in patients who receive radiation therapy for head and neck cancer.[A3] Oral glutamine[A4] and zinc[A5] have shown some benefit for reducing the severity of radiation-induced oral mucositis. However, no medications have been consistently effective for reducing the gastrointestinal side effects of pelvic radiotherapy.[A6]

For radiotherapy-induced dermatitis, mucositis, and xerostomia, treatments include topical agents for dermatitis (Chapter 405), analgesics for mucositis, and saliva substitutes for xerostomia. Beyond dermatitis, mucositis, and xerostomia, radiation-induced deterministic tissue effects are typically treated in the same way as their non-radiation-induced counterparts. For example, the treatment of radiation-induced coronary artery disease is no different than the approach to coronary diseases in general (Chapters 56 to 59). However, the management of acute and chronic gastrointestinal symptoms after radiotherapy requires a more specialized approach because of the risk for local stricture (Chapter 128).

PREVENTION

Countermeasures after Radiologic Accidents or Terrorism

Three FDA-approved pharmaceuticals can limit the radiation dose caused by exposures to specific radioisotopes: potassium iodide for radioactive iodine; Prussian blue for radioactive cesium or thallium; and diethylenetriamine pentaacetate (DTPA) for plutonium, americium, or curium. Although these pharmaceutical countermeasures can limit the organ doses and therefore the health consequences produced by these specific radioisotopes, they cannot be used to treat any of the adverse clinical effects caused by them.

The administration of potassium iodide (KI), which contains nonradioactive iodine, saturates the thyroid with nonradioactive iodine and thereby prevents radioactive iodine from being absorbed into the thyroid, where it can cause thyroid cancer (Chapter 207). The protective effects of KI last about 24 hours, so it should be taken daily (130 mg for adults, 65 mg for children >3 years of age, 32 mg for children 1 to 3 years of age, 16 mg for infants) while there is a likelihood of exposure.

Prussian blue (Radiogardase: ferric hexacyanoferrate [II]) binds cesium in the gastrointestinal tract and limits its reabsorption into the blood stream, thereby reducing the biologic half-life of cesium in the body from about 110 days to about 30 days and limiting the organ toxicities that it produces. The recommended dose of Prussian blue is 3 g orally three times daily for adults and 1 g orally three times daily for children 2 to 12 years of age, for a minimum of 30 days.

DTPA is a chelating agent that binds to radioactive plutonium, americium, and curium, thereby decreasing their persistence in the body. DTPA comes in two forms, Ca-DTPA and Zn-DTPA, with the calcium form considered more effective over the first 24 hours of exposure, and the zinc form preferable at later times, although both are effective over several weeks. They are administered intravenously (or with a nebulizer), with a daily intravenous dose of 1 g for adults and 14 mg/kg for children younger than 12 years.

Several radiation countermeasure drugs have been developed to counteract the symptoms of acute radiation syndromes, have been demonstrated effective in animal models, and are undergoing trials prior to FDA approval.

Medical Imaging

CT is a superb diagnostic tool, and individual CT radiation–associated risks are small; as a result, a great majority of the approximately 90 million CT scans performed annually in the United States generally provide far more benefits than risks. However, organ doses from CT are typically far larger than those from conventional radiographic examinations, so CT should operate under the dual principles of optimization and justification. Optimization involves reducing the radiation dose per CT, using improved protocols and technology.

In terms of justification—making sure that all CT scans are clinically justified, a substantial proportion of CT scans could potentially be replaced by other modalities, such as magnetic resonance imaging for some head examinations and selective use of ultrasound for diagnosing appendicitis. For example, CT scans performed in patients who undergo appendectomy are associated with about a 25% higher risk of subsequent hematologic malignancy.[16] In addition, many CT scans could be avoided entirely by following usage appropriateness criteria.

NON-IONIZING RADIATION INJURY

Ionizing radiations uniquely have sufficient energy to cause DNA strand breaks, which in turn can lead to cell killing and mutations. By contrast, non-ionizing radiations, such as radio waves, microwaves, infrared radiation, and visible light, do not have sufficient energy to break DNA strands, and none of these radiations have been associated with health hazards. One exception is ultraviolet (UV) radiation, which is generally a mutagen and a carcinogen. A second possible exception is radiofrequency radiation, although in this case the epidemiologic evidence and mechanistic considerations do not provide strong evidence of health risks.

ULTRAVIOLET RADIATION

UV radiations, which are part of the non-ionizing electromagnetic spectrum, cover a wavelength from about 150 to 400 nm (intermediate between visible light and x-rays). In turn, these UV wavelengths are subcategorized as UVA (400 to 320 nm), UVB (315 to 280 nm), and UVC (280 to 150 nm).

Sunlight is by far the largest source of UV radiation to humans. Because of filtering in the atmosphere, about 95% of the UV spectrum that reaches the earth's surface is UVA, the remainder is nearly all UVB, and almost no UVC penetrates the ozone layer to reach the earth. Other sources of UV exposures include tanning beds and booths. Industrial exposures include welding arcs, plasma torches, germicidal and blacklight lamps, electric arc furnaces, hot-metal operations, mercury-vapor lamps, and some lasers.

PATHOBIOLOGY

UV radiations do not penetrate deeply into human tissues, so the injuries they cause are principally to the skin and eyes. The biologic effects of UV radiation are primarily attributable to its absorption in DNA, where pyrimidine dimers and their products are produced. These products are generally very efficiently removed, primarily through nucleotide excision repair but also through base excision repair, but errors in these repair processes ultimately can result in mutations. Although most UV radiation in sunlight is UVA, UVB is much more efficiently absorbed by nucleic acids, and most of the biologic effects of sunlight are associated with UVB.

The damaging effects of UV radiation are exacerbated in patients who have underlying defects in nucleotide excision repair. For example, studies of patients with xeroderma pigmentosum have provided key evidence of the link between UV light and skin cancer. In addition, the effects of UV are often enhanced in patients who are taking medications that contain photodynamic agents, such as tetracyclines, fluoroquinolones, nonsteroidal anti-inflammatory drugs, diuretics, statins, phenothiazines, thioxanthenes, and antifungals. Such drug-related phototoxic reactions typically resolve after the drug is discontinued.

CLINICAL MANIFESTATIONS

The major acute effects of UVB exposure are sunburn and erythema, whereas UVA exposure is rarely the direct cause of sunburn. All UV radiations are well-established skin carcinogens (Chapter 188). Squamous cell carcinomas and basal carcinomas are typically associated with multiple or chronic exposures to sunlight, whereas melanoma is linked primarily to episodes of acute sunburn. Lighter-skinned individuals, whose skin and eyes contain less melanin, are more prone to all UV effects because melanin acts as a photoprotector. Acute exposures of the eye to UVB (Chapter 391) can cause "welder flash" (photokeratitis), and chronic exposures are associated with cataracts as well as pterygium.

PREVENTION

Excessive exposure to sunlight or other sources of UV radiation should be avoided, especially in fair-skinned individuals. UV radiation–screening lotions or creams and UV radiation–blocking sunglasses should be used when appropriate.

During significant exposure to sunlight, it is important to use a broad-spectrum sunscreen that provides protection from UVB as well as UVA. Standard recommendations are use of sunscreen with a sun protection factor (SPF) of 30, with reapplication at least every 2 hours. Likewise, sunglasses should be rated to block 99% or 100% of UVB and UVA radiation.

FAR-UVC RADIATION

A particular UV wavelength, far UVC (207 to 222 nm), is an effective antibactericidal and antiviral agent, including against severe acute respiratory syndrome coronavirus 2 (Chapter 336).[17] Because of its very limited penetration, it may be safe for human exposure, unlike typical UVC radiation.

RADIOFREQUENCY RADIATIONS

Radiofrequency radiations are also part of the non-ionizing electromagnetic spectrum (E-Fig. 18-1). Examples are radiation emitted from mobile phones (800 to 2000 MHz),[18] electric power lines (50/60 Hz),[19] low-frequency magnetic fields,[20] and airport whole-body scanners (24 to 30 GHz). Biologic studies of these low-level radiofrequency exposures have generally not shown measurable genotoxicity.

Numerous epidemiologic studies have focused on the effects of electric power line proximity and of cell phone usage. Although some early studies showed positive associations between exposure and health detriment, these studies have generally not proved consistent or repeatable. Further studies are, however, warranted, and an ongoing prospective European study is following 290,000 adult cell phone users over a 20-year period.

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19 BIOTERRORISM

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As with any other outbreak, the response to a potential act of bioterrorism relies on public health fundamentals.[1,2] Except for direct evidence of a release, no other single feature can be considered definitive proof of bioterrorism, but multiple simultaneous features should raise the suspicion of an unnatural event (Table 19-1).

Victims of a chemical or conventional weapon attack would likely become ill shortly after a release or explosion, whereas victims of a silent biologic weapon attack would likely present for care in a delayed fashion to different

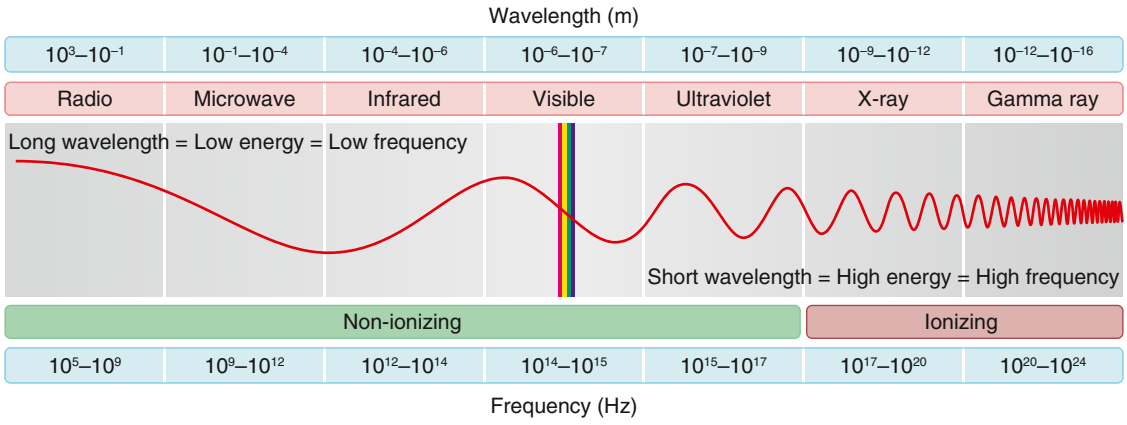

E-FIGURE 18-1. **The electromagnetic spectrum.**

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Victims of a chemical or conventional weapon attack would likely become ill shortly after a release or explosion, whereas victims of a silent biologic weapon attack would likely present for care in a delayed fashion to different

ABSTRACT

Although a terrorist or criminal may seek to use a number of infectious pathogens or toxins to cause illness or disability of humans, certain pathogens have properties that make them potentially better suited to cause large numbers of casualties when released on a population. These properties include the ability to be grown in large quantities, stability in the air, stability for storage, and ease of infection by the aerosol route. Of these potential pathogens or toxins, six have been deemed the highest potential threats if utilized properly: anthrax, smallpox, plague, tularemia, botulism, and viral hemorrhagic fevers. This chapter discusses these specific agents.

KEYWORDS

bioterrorism
anthrax
viral hemorrhagic fever
plague
botulism
tularemia
smallpox

care providers, dispersed in space and time due to the pathogen's incubation period. One way in which a bioterror attack might differ from a natural outbreak is in the unusual presentation of illness. For example, a disease that typically occurs on the skin or causes gastrointestinal illness might instead exhibit respiratory features (e.g., anthrax, plague). Another clue could be illnesses that are unresponsive to standard therapies because of an unusual antibiotic sensitivity profile. Suspicion should also be raised by finding a disease outside the location or season in which it typically occurs.

AGENTS OF CONCERN

Among the myriad human infectious pathogens, a relatively small number possess the requisite properties to be considered potential weapons that could cause widespread disease, so-called weapons of mass destruction. The U.S. Centers for Disease Control and Prevention (CDC) has designated six as category A due to their ability to cause large-scale disruption, the need for preparedness, and fear their release might engender (Table 19-2).[3] These agents can be formulated to remain stable in aerosol, which allows their potential efficient spread via the air over a large population.

TABLE 19-1 EPIDEMIOLOGIC CLUES OF A BIOWEAPON ATTACK

A large outbreak, especially in a discrete population
Many cases of unexplained illness or deaths
More severe disease than expected for a specific pathogen or failure to respond to standard therapy
Unusual manifestation of illness, such as inhalational disease from agents not typically causing clinical illness
An unusual disease for a given geographic area or transmission season, especially in the absence of a competent vector
Multiple simultaneous or serial epidemics
A single case of a rare disease (smallpox, some viral hemorrhagic fevers, inhalational anthrax, pneumonic plague)
Unusual strains or variants of organisms, or antimicrobial resistance patterns different from those known to be circulating
Higher attack rates among those outside a protected area or lower rates among those inside a protected area or shelter
Outbreaks of the same disease occurring simultaneously in noncontiguous areas
A zoonotic disease occurring in humans but not in animals
Direct evidence or intelligence of a release (equipment, munitions, tampering) or other identified vehicle of spread (spray device, contaminated letter)
A downwind pattern of casualty location

Modified from Stanek SA, Saunders D, Alves DA, et al. *USAMRIID's Medical Management of Biological Casualties Handbook*, 9th ed. September 2020. Found at www.usamriid.army.mil under reference materials tab. Accessed October 30, 2021.

ANTHRAX

EPIDEMIOLOGY

Anthrax, caused by infection with the gram-positive bacillus *Bacillus anthracis* (Chapter 272), is a worldwide scourge of herbivores. Most human cases have had direct occupational contact with infected animals or their hides, hair, or bone, although a recent outbreak occurred among injection drug users in the United Kingdom. Endemic areas include underdeveloped parts of sub-Saharan Africa and Southeast Asia, where humans interact closely with animals that have not been vaccinated. Sporadic cases occur in the United States, typically along the trails of the historic cattle drives in the central plains. Animals are typically infected while grazing in areas contaminated with anthrax spores, which can survive in the soil for decades and can be formulated as a stable desiccated powder. Although most cases worldwide are cutaneous, the spore form of the organism can be milled into the ideal particle size (2 to 6 μm) for infecting the lungs and causing inhalational disease.

PATHOBIOLOGY AND CLINICAL MANIFESTATIONS

Exposure to spores can occur through a break in the skin, through the gastrointestinal tract, or by inhalation. Spores are taken up by macrophages and replicate in the local skin, or are transported to the regional lymph nodes in the gastrointestinal tract or lungs. While replicating, the bacilli secrete lethal toxin, which causes local necrosis, and edema toxin, which causes significant local edema. Untreated or unrecognized infection can result in bacteremia, systemic toxemia, and death.

Cutaneous anthrax can be readily recognized by the astute clinician based on two clinical manifestations caused by its toxins: a black eschar, from which anthrax gets its name (from the Greek *anthrakis*, for coal), and surrounding edema that is out of proportion to the size of the lesion. The lesion starts as a papule that becomes a vesicle and eventually develops a central, black, necrotic area. Although this form of disease is readily treatable, it can lead to a 20% case-fatality rate if it is not recognized and treated appropriately. Gastrointestinal anthrax, which occurs after ingestion of infected, undercooked meat, is much more difficult to recognize and can have a case-fatality rate

TABLE 19-2 CENTERS FOR DISEASE CONTROL AND PREVENTION CATEGORY A BIOTERROR AGENTS

DISEASE (AND AGENT)	DIAGNOSTIC ASSOCIATIONS	WEAPONIZATION RATIONALE	TREATMENT* (SEE TEXT FOR DETAIL)
Anthrax (*Bacillus anthracis*; Chapter 272)	Hemorrhagic mediastinitis	Highly lethal inhalational disease; stable spores survive desiccation; can be formulated as aerosol	**Ciprofloxacin** (400 mg q8h) or (a) levofloxacin (750 mg q24h) or moxifloxacin (400 mg q24h) plus either (b) **meropenem** (2 g q8h) or imipenem (1 g q6h) or doripenem (500 mg q8h) plus (c) **linezolid** (600 mg q12h) or clindamycin (900 mg q8h) or rifampin (600 mg q12h) or chloramphenicol (1 g q6-8h)†
Smallpox (variola virus; Chapter 343)	Synchronous exanthem	Virions stable in environment; population immunologically naïve	Supportive care; brincidofovir and tecovirimat are now licensed treatments
Plague (*Yersinia pestis*; Chapter 288)	Hemoptysis	Contagious through respiratory droplets; "Black Death" conjures fear	Gentamicin (5 mg/kg qd) or ciprofloxacin (400 mg q12h), doxycycline (200 mg × 1, then 100 mg q12h), or levofloxacin 500 mg q24h or moxifloxacin 400 mg q24h
Tularemia (*Francisella tularensis*; Chapter 287)	Plague-like illness	Bacteria stable in environment; very low infectious dose	Same as for plague‡
Botulism (botulinum toxins; Chapter 271)	Descending, flaccid paralysis	Highly potent toxin; lends itself to food and water use; cases consume vast resources	Supportive care; ventilator support; botulinum antitoxin may halt (but will not reverse) symptom progression
Viral hemorrhagic fevers (Chapter 351; see E-Table 19-1)	Hemorrhagic diatheses	Fear factor is paramount; few countermeasures exist	Supportive care; ribavirin may be beneficial in select cases (e.g., Lassa fever, New World arenaviruses, Crimean-Congo hemorrhagic fever virus, hemorrhagic fever renal syndrome) when it is given under an experimental protocol: 30 mg/kg load, then 16 mg/kg q6h for 4 days, then 8 mg/kg q8h for 6 days; for Ebola virus (Zaire), two approved therapies are either REGN-EB3 or mAb114

*All therapeutic agents listed in this table should be administered intravenously.
†Preferred treatments are in **bold**.
‡Note that levofloxacin and moxifloxacin are now licensed by the U.S. Food and Drug Administration for the treatment of plague, but not for tularemia.
qd = once daily.

of 50% or more. Reported in the United States for the first time after an animal-hide drum circle event in 2009, the disease causes fever, abdominal pain, diarrhea, hematochezia, hematemesis, and ascites. Paracentesis may yield hemorrhagic ascites.

Inhalational anthrax is of greatest concern after an aerosolized bioweapon attack. After an incubation period that averages 1 to 6 days but can be up to 43 days, patients present with fever, profound drenching sweats, nausea, vomiting, diarrhea, shortness of breath, cough, and chest pain. Without prompt recognition and appropriate therapy, individuals can deteriorate rapidly with increasing dyspnea, stridor, cyanosis, and respiratory failure. Engorgement and hemorrhage of mediastinal lymph nodes with accompanying mediastinitis lead to the clinical hallmark of a widened mediastinum on the chest radiograph in about 60% of cases. Patients may also develop large hemorrhagic pleural effusions and infiltrates. Bacteremic dissemination can lead to widely metastatic infection in the gastrointestinal tract and meninges.

DIAGNOSIS

B. anthracis can be identified by Gram stain or culture of tissue or body fluids, including skin biopsy for cutaneous disease, peripheral blood, pleural effusions, and cerebrospinal fluid but not sputum. A chest radiograph may provide initial clues to inhalational disease with manifestations such as hilar or paratracheal fullness and pleural effusions. A chest computed tomography scan can confirm mediastinal adenopathy. Other techniques, such as fluorescent antibody staining or polymerase chain reaction (PCR), may provide more rapid diagnosis.

TREATMENT

The approach to the management of patients[4] infected with or exposed to anthrax differ among patients with meningitis and patients in whom meningitis has been excluded. For patients in whom meningitis is present or cannot be excluded, three antibiotics are administered intravenously (preferred drugs are in bold):

- **Ciprofloxacin** (400 mg q8h) or levofloxacin (750 mg q24h) or moxifloxacin (400 mg q24h) plus
- **Meropenem** (2 g q8h) or imipenem (1 g q6h) or doripenem (500 mg q8h) plus
- **Linezolid** (600 mg q12h) or clindamycin (900 mg q8h) or rifampin (600 mg q12h) or chloramphenicol (1 g q6-8h).

If meningitis has been excluded, a two-drug regimen can be used:

- **Ciprofloxacin** or levofloxacin or moxifloxacin or meropenem or imipenem or doripenem or vancomycin (penicillin G or amoxicillin can also be used if the infecting strain is known to be susceptible) plus
- **Clindamycin or linezolid** or doxycycline or rifampin

A monoclonal antibody, raxibacumab (single dose of 40 mg/kg IV during 2 hours and 15 minutes after premedicating with diphenhydramine 25 to 50 mg IV), is approved for additional therapy of inhalational anthrax along with antibiotics on the basis of animal efficacy data. Intravenous anthrax immune globulin, which has been given as adjunctive therapy to a small number of patients, is approved in the United States for use in addition to antibiotics for inhalational anthrax. Another antibody, obiltoxaximab (16 mg/kg IV), is also approved by the Food and Drug Administration (FDA) to treat inhalational anthrax in combination with appropriate antibacterial drugs or to prevent inhalational anthrax based on its efficacy in animals and safety in healthy human volunteers.[5]

PREVENTION

The anthrax vaccine,[6] which is effective at preventing all forms of disease, has been reserved primarily for at-risk ranchers or veterinarians who have regular contact with herbivores, as well as for laboratory research personnel and military personnel. The vaccine is given as five doses intramuscularly over 18 months (day 0, followed by 1, 6, 12, and 18 months), with annual boosters if continued risk exists.

After a known exposure, chemoprophylaxis is recommended with ciprofloxacin (500 mg orally twice daily) or doxycycline (100 mg orally twice daily) for 60 days, although shorter durations are likely to be effective, especially if combined with vaccination. If the vaccine is available, three doses may be given concomitantly with antibiotics, but it is not licensed for this purpose and must be administered under an investigational protocol. Raxibacumab (dosed as before) is also approved for prophylaxis if antibiotics are not available.[7]

PROGNOSIS

Factors associated with survival from anthrax include administration of a multiple-drug antibiotic regimen or anthrax antiserum given during the prodromal phase, as well as pleural fluid drainage. Case-fatality rates in untreated patients approach 100%, although 55% of the victims of inhalation anthrax survived in a 2001 outbreak, likely owing to the use of multiple antibiotics and modern intensive care.

SMALLPOX

EPIDEMIOLOGY

Although smallpox was declared eradicated in 1980, concerns exist about undeclared stores outside approved repositories in the United States and Russia. The recent discoveries of unaccounted for vials of variola in the United States provide some credence to this concern. In addition to near-universal susceptibility, the environmental stability of smallpox viral particles makes it a formidable potential weapon.[8]

Smallpox is caused by variola virus, an orthopoxvirus (Chapter 343) that is closely related to cowpox, vaccinia, monkeypox, and Alaskapox. Variola generally spreads to household and other close contacts, but it can spread via aerosolized droplet nuclei as well as by direct contact with patient secretions or fomites. Health care providers who are caring for patients or unsuspecting individuals who have contact with contaminated objects are also at risk.

PATHOBIOLOGY AND CLINICAL MANIFESTATIONS

Infection initially occurs in the respiratory mucosa, is followed by replication in the regional lymph nodes, and leads to an asymptomatic primary viremia that seeds the reticuloendothelial system. Approximately 1 week after infection (range, about 1 to 2 weeks), a secondary viremia seeds the skin. At this time, the sudden onset of illness includes fever, headache, backache, and vomiting. Within 2 or 3 days of this prodrome, and often as the temperature falls, the characteristic rash begins with small papules in a centrifugal pattern (more on the face and extremities than on the trunk) that progress in synchronous fashion during the next week to vesicles, umbilicated pustules, and finally scabs. Lesions are deep seated and can be intensely painful. Individuals are contagious at the onset of the rash and are considered free of contagion only after the scabs have separated.

DIAGNOSIS

Chickenpox (varicella; Chapter 346), which might be confused with early or mild smallpox, occurs predominantly on the trunk rather than on the extremities (a centripetal pattern), and the lesions occur in successive crops, so macules, papules, pustules, and scabs can be seen simultaneously. In addition, varicella is transmissible before onset of the rash, but contagiousness abates when all the lesions are scabbed. Other diseases in the differential diagnosis of smallpox include monkeypox (Chapter 343), Alaskapox, other poxviruses, disseminated vaccinia in a vaccine recipient or contact, disseminated herpes zoster (Chapter 346) or herpes simplex (Chapter 345), impetigo (Chapter 408), drug eruptions (Chapter 407), contact dermatitis (Chapter 405), erythema multiforme (Chapter 406), and rickettsialpox (Chapter 302).

Clinical recognition of the characteristic rash (Fig. 19-1) should raise suspicion of smallpox. Diagnosis would likely come from PCR or viral culture of skin or blood samples or from acute and convalescent serologies.

TREATMENT

The primary therapy for smallpox remains supportive care, although tecovirimat (600 mg orally every 12 hours for 14 days) is approved by the U.S. FDA to treat all poxvirus infections and is included in the strategic national stockpile.[9] Brincidofovir (4 mg/kg, once weekly for two doses, maximum 200 mg), which is an oral analog of cidofovir, is also an approved treatment.

PREVENTION

Vaccination uses vaccinia, an orthopoxvirus related to variola. In the event of an outbreak, postexposure vaccination within 4 days can prevent or ameliorate disease and might be applied in a method of surveillance and containment, as was used during global eradication. The U.S. government has stockpiled enough doses for the entire U.S. population of a live replicating cell-culture-derived product (ACAM2000) for use in a national emergency. The surveillance and containment, or ring, vaccination method combines active case finding with vaccination of potential contacts within a certain radius around the cases. Health care providers would need to be vaccinated, and airborne

FIGURE 19-1. **Smallpox. A**, Demonstrates centrifugal nature of the rash. **B**, Demonstrates coalescences of some pustules. **C**, Demonstrates umbilicated pustules. (From Fenner F, Henderson DA, Arita A, et al. *Smallpox and its Eradication*. Geneva: World Health Organization; 1988.)

and contact precautions (HEPA filter masks, negative-pressure rooms, gowns, gloves, eye protection) would be recommended in the hospital environment. Because the vaccine is a live agent, it is contraindicated in individuals who are immunocompromised and in individuals who have eczema or significant exfoliative skin conditions. Even in normal hosts, the vaccine can be associated with inoculation of other locations on the body, spread to close contacts, disseminated disease, postvaccine encephalitis, progressive vaccinia in individuals with defective cell-mediated immunity, eczema vaccinatum in people with prior eczema, and pericarditis or myocarditis.[10] In the postexposure setting, risks and benefits must be weighed regarding which individuals at risk for complications might receive vaccine and whether vaccinia immune globulin might be administered concomitantly. First-line therapy for significant vaccine reactions is vaccinia immune globulin. A novel live, but nonreplicating, vaccinia-based vaccine, Jynneos, was recently approved by the FDA for the prevention of smallpox as well as monkeypox. Although this product is expected to alleviate some of the concerns associated with the replicating vaccine, its requirement for two doses would complicate its use in a postexposure setting.[A1]

PROGNOSIS

The case-fatality rate for the typical form of smallpox, variola major, is approximately 30%, but wide variations exist. In the minority of individuals who develop hemorrhagic smallpox or flat-type smallpox, the case-fatality rate approaches 100%. A different viral strain, variola minor, has case-fatality rates of only about 1%. Survivors of smallpox are often left with lifelong scarring from the lesions. Blindness and bone deformities, especially in children, are also known complications.

PLAGUE

EPIDEMIOLOGY

Plague, which is caused by the gram-negative coccobacillus *Yersinia pestis* (Chapter 288), was responsible for hundreds of millions of deaths during three historic pandemics. Plague was used as a weapon by the Japanese before World War II when they released infected fleas in Chinese cities, and it was included in the former Soviet Union's biologic weapon arsenal. Plague is transmissible through the respiratory route, so an aerosol release could have devastating effects.

Each year in the United States, several human cases are reported, usually in the Southwest. Most of these cases are bubonic, although occasional pneumonic plague has been linked to infections in domestic cats.

PATHOBIOLOGY AND CLINICAL MANIFESTATIONS

Plague is manifested in three ways.[11] Bubonic plague, which is the most common form, occurs after the bite of an infected flea. The organism spreads through the local lymphatics to the regional lymph nodes. As replication occurs, the lymph node or group of lymph nodes becomes swollen and extremely tender. Because most flea bites occur on the lower extremities, the inguinal and femoral lymph nodes are most often affected. Untreated bubonic plague can progress to septicemic plague after organisms gain entry to the blood stream. In addition, patients can develop necrosis of cooler areas of the body, such as the tip of the nose, ears, or digits, due to a temperature-dependent coagulase produced by the organism.

Septicemic plague may also occur in the absence of an antecedent bubo. Meningitis may occur from seeding through the blood stream.

In pneumonic plague, the lungs are seeded secondarily by bacteremia from septicemic plague or primarily when a person inhales infectious droplets. Although naturally occurring pneumonic plague is rare, this form of disease is the major concern after intentional release of aerosol. In patients with pneumonic plague, the disease can be spread to others. One of the hallmarks of the disease is the potential for purulent sputum to become hemorrhagic. Although hemoptysis can certainly be seen with other diseases (Chapter 71), the presentation of clusters of multiple patients with hemoptysis should prompt the clinician to consider plague.

DIAGNOSIS

Plague bacilli are readily identified by their bipolar appearance or Gram, Wright-Giemsa, or Wayson stains, and they can be cultured from sputum or other infected body fluid, such as blood, fluid from a bubo, or cerebrospinal fluid. Other diagnostic methods include PCR for the F1 antigen, direct fluorescent antibody staining of body fluids, and serology by enzyme-linked immunosorbent assay or passive hemagglutination. However, serology is primarily useful in retrospect, because patients must be treated empirically before a serologic response occurs.

TREATMENT

Drug options include streptomycin (if available, 1 g IM twice daily for 7 to 10 days or for 3 days after the fever remits) or gentamicin (5 mg/kg IM or IV daily or a 2-mg/kg load followed by 1.7 mg IM or IV three times daily also for 7 to 10 days). Alternative choices (all for 7 to 10 days or for 3 days after fever and symptoms have resolved) include doxycycline (200-mg IV load, then 100 mg IV every 12 hours), ciprofloxacin (400 mg IV every 12 hours), levofloxacin (500 to 750 mg IV once daily), and moxifloxacin (400 mg IV once daily) (Table 19-2).[12] The drug of choice for plague meningitis is chloramphenicol (25- to 30-mg/kg IV load, followed by 50 to 60 mg/kg/day every 6 hours; on favorable clinical response, the dose can be reduced to 25 to 30 mg/kg/day every 6 hours). CDC now recommends the addition of either levofloxacin (750 mg once daily) or moxifloxacin (400 mg once daily) to chloramphenicol, when feasible.

PREVENTION

Use of standard precautions is appropriate for bubonic plague. Droplet precautions should be applied for patients with pneumonic plague, including a private room where caregivers wear masks, gowns, gloves, and eye protection within 3 to 6 feet of the patients. These precautions should be continued until the patient demonstrates improvement and has been receiving effective antibiotics for 72 hours. Oral ciprofloxacin (500 to 750 mg twice daily), levofloxacin (500 to 750 mg once daily), doxycycline (100 mg twice daily), or moxifloxacin (400 mg once daily) is recommended for postexposure prophylaxis for 7 days beyond the period of exposure in household contacts or individuals suspected of exposure in either the endemic or bioterrorism setting.[13]

No licensed vaccine for plague currently exists in the United States, and a previously licensed whole-cell killed vaccine is no longer available. New vaccines are being studied.

PROGNOSIS

Case-fatality rates are 50% or more for untreated bubonic plague and nearly 100% for untreated septicemic and pneumonic plague. These fatality rates can be significantly reduced with prompt recognition and appropriate therapy.

TULAREMIA

Tularemia (Chapter 287) is caused by infection with the gram-negative, aerobic nonmotile coccobacillary organism *Francisella tularensis*.[14] A zoonotic disease of rabbits, ground squirrels, and other small mammals, tularemia can infect humans by skin or mucous membrane contact with body fluids or tissues of infected animals or from the bite of infected deerflies, mosquitoes, or ticks. Disease rarely occurs by inhalation of contaminated dusts or ingestion of contaminated food or water. One outbreak was associated with groundskeepers in Martha's Vineyard. Fewer than 150 cases of naturally occurring human tularemia are typically reported each year. However, the environmental stability of *F. tularensis* as well as its very low infectious dose (as few as 10 organisms) makes it a potential weaponization threat.

CLINICAL MANIFESTATIONS AND DIAGNOSIS

Clinical manifestations of tularemia depend on the route of exposure. Although six different forms have been described, tularemia is perhaps more simplistically compared with plague, with glandular forms analogous to bubonic plague, as well as pneumonic and typhoidal forms that present a clinical picture similar to what is seen in pneumonic and septicemic plague. A preponderance of these latter forms would be expected after an intentional release by aerosol. After an incubation period of 2 to 10 days, symptoms begin with fever and proceed to include severe exhaustion, substernal chest pain, nonproductive cough, and weight loss.

A diagnosis can be made by isolating the organism from blood, sputum, skin, or mucus membrane lesions, but culture may be difficult because of unusual growth requirements and overgrowth of commensal organisms. Molecular technologies are available in specialized laboratories, but serology is the most common method of diagnosis, often in retrospect. Because of the risk of spread to microbiology laboratory personnel, it is important to notify the laboratory if infection with this organism is suspected.

TREATMENT AND PROGNOSIS

Treatment of tularemia is similar to that of plague, with aminoglycosides for 7 to 10 days; streptomycin and gentamicin are considered the drugs of choice, although ciprofloxacin is a newer potential alternative (Table 19-2). Doxycycline/tetracycline and chloramphenicol are second-line choices because their use has been associated with relapses, and the recommended duration of therapy is 14 to 21 days.

Person-to-person spread is unusual, and standard precautions are adequate in caring for ill individuals. For known exposures, consensus recommendations in a bioterrorism setting call for doxycycline (100 mg) or ciprofloxacin (500 mg) orally twice a day for 14 days as postexposure prophylaxis. A live attenuated vaccine has proven efficacy in preventing disease due to laboratory exposures and aerosol challenge in human volunteers, but it is not readily available to the public.

The case-fatality rate for untreated pneumonic and typhoidal tularemia is 35%, but this rate can be reduced to less than 5% with appropriate treatment.

BOTULISM

Botulism is caused by exposure to one of eight related neurotoxins (A to H) produced by strains of *Clostridium botulinum* (Chapter 271), a ubiquitous, anaerobic, spore-forming, gram-positive bacillus. Botulinum toxins, which are among the most toxic substances known, can be lethal in doses as low as 0.001 μg/kg. These toxins block release of acetylcholine from presynaptic nerve terminals, thereby resulting in a generalized flaccid paralysis with autonomic dysfunction. Although most toxins are unstable in the environment and thus constitute dubious weaponization threats, the potent nature of botulinum toxin, coupled with the ease with which it might be used to contaminate food and water, makes it a concern. Naturally occurring human botulism is limited to types A, B, and E, although other toxin serotypes can produce an identical clinical syndrome. For this reason, a heptavalent antitoxin with activity against serotypes A to G was licensed in 2013.

CLINICAL MANIFESTATIONS AND DIAGNOSIS

Botulism typically develops after a latent period ranging from hours to several days. Initial manifestations involve bulbar palsies, ptosis, photophobia, blurred vision, and other signs of cranial nerve dysfunction.[15] Symptoms progress craniocaudally, thereby leading to dysphonia, dysphagia, and, ultimately, a descending symmetrical paralysis. In fatal cases, death typically results from respiratory muscle failure.

Although botulism may mimic other neurologic disorders, such as myasthenia gravis (Chapter 390) and Guillain-Barré syndrome (Chapter 388), the occurrence of an outbreak involving multiple cases of descending, symmetrical, flaccid paralysis should make diagnosis of botulism relatively straightforward.

TREATMENT AND PROGNOSIS

Supportive care measures, including meticulous attention to ventilatory support, are the mainstay of botulism management. Patients may require such support for several months, so the management of a large-scale botulism outbreak would be resource intensive. Antitoxin should be administered as soon as possible to prevent progressive disease. Botulism is not contagious, so standard precautions are appropriate. The first victims of an outbreak may have higher case-fatality rates because of delays in recognition. Patients who recover can have long-term sequelae, such as dyspnea on exertion, fatigue, and weakness.

VIRAL HEMORRHAGIC FEVERS

EPIDEMIOLOGY

Viral hemorrhagic fever (Chapter 351) describes a clinical syndrome caused by four families of RNA viruses: filoviruses (Ebola and Marburg), arenaviruses ("Old World" Lassa fever and "New World" South American viruses, Machupo, Junin, and others), bunyaviruses (hantaviruses, Crimean-Congo hemorrhagic fever, and Rift Valley fever), and flaviviruses (yellow fever and dengue) (E-Table 19-1). Agents of greatest concern from a bioterrorism perspective include the filoviruses and arenaviruses, which are infectious by the aerosol route, can replicate well in cell culture for large-scale production, and have a clinical syndrome of hemorrhage and fever that engenders fear. The massive outbreak of Ebola virus disease in West Africa in 2013-2016 and a subsequent outbreak in eastern Democratic Republic of the Congo in 2018-2020 demonstrated the devastation that a hemorrhagic fever virus can have on a population, even in the absence of an intentional release, in an environment conducive to spread, including limited medical infrastructure, mobile populations, mistrust of government, and close contact during burial practices, among other factors.[16]

PATHOBIOLOGY AND CLINICAL MANIFESTATIONS

Once virus gains entry through the skin, mucous membranes, or respiratory tract, replication occurs in macrophages and dendritic cells. Organisms are then transported to regional lymph nodes and eventually through the lymphatics and blood stream to target organs, such as the liver and spleen, where local necrosis occurs. The body responds with activation of cytokines and chemokines, and massive depletion of lymphocytes disables the host's adaptive immune response. A sepsis-like picture ensues, with

E-TABLE 19-1 COMPARISON OF VIRAL HEMORRHAGIC FEVER AGENTS*

FAMILY	VIRUS	ENDEMIC AREA	FATALITY RATE	NOSOCOMIAL TRANSMISSION	COUNTERMEASURES
Filoviruses	Ebola	Africa, Philippines (Reston)	18.5-90% (Sudan/ Zaire)	Yes	Reduced fatality rates with supportive care, including fluid and electrolyte management. Two newly licensed monoclonal antibody treatments against Ebola (Zaire) virus. Lower fatality rates occurred in U.S. and European intensive care settings compared with endemic settings. Licensed vaccine (Ervebo).
	Marburg	Africa	23-70%	Yes	
Arenaviruses	Lassa	West Africa	1-2%	Yes	Ribavirin effective in a clinical trial with nonrandomized controls
	Junin	Argentine Pampas	30%	Rare	Immune plasma; reports of benefit with ribavirin; Candid#1 vaccine protective; not available in the United States
	Machupo	Bolivia	25-35%	Rare	Immune plasma; reports of benefit with ribavirin
Bunyaviruses	Crimean-Congo hemorrhagic fever	Africa, southeast Europe, Central Asia, India	30%	Yes	Anecdotal success with ribavirin treatment
	Rift Valley fever	Africa	<0.5%	No	Livestock vaccines in Africa; U.S. Department of Defense has two experimental vaccines
	Hantaviruses	Europe, Asia, South America (rare)	5% (Asian hemorrhagic fever with renal syndrome)	No†	Vaccines available in Asia; ribavirin effective in randomized trial for hemorrhagic fever renal syndrome but not licensed for that purpose
Flaviviruses	Yellow fever	Africa, South America	3-12% (20-50% if second phase develops)	No	17D live attenuated vaccine
	Kyasanur Forest	Southern India	3-5%	No	Formalin-inactivated vaccine in India
	Omsk	Siberia	0.2-3%	No	Tick-borne encephalitis vaccines (not in United States) may offer some cross protection

*Adapted from Stanek SA, Saunders D, Alves DA, et al. *USAMRIID's Medical Management of Biological Casualties Handbook*, 9th ed. September 2020. Fort Detrick, MD. Accessed from www.usamriid.army.mil on October 30, 2021.

†Exception is Andes, which causes hantavirus pulmonary syndrome (not addressed in this chapter).

declining mean arterial pressure, increased vascular permeability, and a bleeding diathesis.

Clinical features of the hemorrhagic fevers include the acute onset of malaise, sore throat, fever, skin flushing, conjunctival injection, prostration, myalgias, and nonbloody diarrhea. These viruses have significant differences in the prominence of individual clinical findings. For example, dengue, the filoviruses, and Lassa more commonly cause a maculopapular rash in the first week. The filoviruses and South American viruses more typically cause obtundation and encephalitis. Although all of these viruses produce modest elevations of aminotransferase levels, yellow fever and Rift Valley fever are known for causing significant hepatic dysfunction, thereby resulting in icterus and jaundice. Depending on a number of factors, including virulence, route of exposure, inoculum, and other host factors, illness can progress in the second week to overt signs of bleeding, including petechiae, purpura, ecchymoses, and oozing from venipuncture sites. Electrolyte abnormalities and large-volume gastrointestinal losses were reported during the 2013-2016 West Africa Ebola outbreak. Massive bleeding occurs uncommonly; but if it does, the source is usually the gastrointestinal tract. Severe cases will demonstrate a combination of neurologic and hematologic abnormalities.

DIAGNOSIS

Numerous common diseases should be considered in the differential diagnosis of a viral hemorrhagic fever, including rickettsial infections (Rocky Mountain spotted fever, ehrlichia, anaplasma, and African tick typhus; Chapter 302), leptospirosis (Chapter 298), meningococcemia (Chapter 274), typhoid (Chapter 284), and falciparum malaria (Chapter 316). However, a viral hemorrhagic fever should be considered in patients who present with a clinically compatible syndrome, especially if a cluster of cases is seen.

Laboratory features may include thrombocytopenia, elevated aminotransferase levels, leukopenia, anemia (although an elevated hematocrit may be seen in patients with significant vascular leakage, as is sometimes seen with dengue and hantaviruses), hematuria, and proteinuria.

PCR, viral culture, immunoglobulin M–specific enzyme-linked immunosorbent assay, acute and convalescent serology, or immunohistochemistry on autopsy specimens can establish the diagnosis. Routine clinical specimens and any attempt at viral isolation require a biosafety level 3 or 4 laboratory with expert consultation from the CDC or the U.S. Army Medical Research Institute of Infectious Diseases.

TREATMENT

Two licensed therapies now exist for Ebola virus: Inmazeb (a cocktail of three monoclonal antibodies) and Ebanga (a single monoclonal antibody). Both showed significantly decreased fatality rates in the 2018-2020 outbreak in eastern Democratic Republic of Congo.[A2] Even with this success, however, supportive care remains a primary means of management for all viral hemorrhagic fevers, with close attention to fluid status, electrolytes, avoidance of procedures that cause bleeding and medications that impair platelet function, use of blood products as necessary, use of vasopressors for hypotension, and dialysis for renal failure. Close attention to fluid status has significantly reduced mortality from dengue, and aggressive fluid repletion has been needed to address significant loss of fluid volume due to diarrhea, electrolyte abnormalities, and protein/nutritional depletion in Ebola infections.[17] Oral ribavirin or intravenous ribavirin (see Table 19-2) under an approved experimental protocol can reduce mortality in Lassa hemorrhagic fever and also appears to be beneficial against Argentine hemorrhagic fever (Junin virus) and hantaviruses that cause hemorrhagic fever with renal syndrome. Ribavirin has no apparent efficacy against filoviruses (Ebola or Marburg) or flaviviruses (dengue, yellow fever).

PREVENTION

Vaccines licensed by the U.S. FDA are available against only two specific agents, yellow fever and Ebola.[A3] Experimental vaccines exist against Junin virus and Rift Valley fever virus, but these vaccines have been used primarily to protect laboratory workers.

Certain viral hemorrhagic fevers (primarily Ebola, Marburg, Lassa, and Crimean-Congo hemorrhagic fever) produce high-level viremia during the period of greatest bleeding risk and body fluid production, thereby making them notorious for causing nosocomial outbreaks. In general, these outbreaks occur in environments, such as sub-Saharan Africa, where basic infection control practices are inadequate because of limited resources (e.g., lack of gowns, gloves, and eye protection as well as reuse of unsterilized needles and syringes). Spread of these viruses in the nosocomial environment can be significantly reduced with standard precautions that limit contact with blood and body fluids. In caring for patients who may spread disease, the use of masks, gowns, gloves, and eye protection is recommended. Many cases in the United States and Europe are cared for in biocontainment units specifically designed to reduce nosocomial spread to caregivers.[18]

PROGNOSIS

Hemorrhagic viruses exhibit a wide range of mortality rates, ranging from less than 1% with Rift Valley fever to 80 to 90% with untreated Ebola Zaire (E-Table 19-1). Despite the notoriety of these viruses for causing hemorrhage, the majority of individuals do not die of blood loss. Rather, death results from a sepsis-like picture (Chapter 94), including a loss of vascular hemostasis, disseminated intravascular coagulation, hypotension, renal failure, shock, and death. Provision of intensive care appears to have benefit.

RESPONSE TO A BIOTERRORISM ATTACK

Even a relatively small bioterror event can have profound consequences. After the 2001 anthrax mailings, thousands of people were prescribed antibiotic prophylaxis, and government buildings were closed for decontamination. Since that event, significant improvements in future responses to a bioterrorism event include the licensure, manufacture, and storage of enough smallpox vaccine for everyone in the United States; production of anthrax and botulinum antitoxins for the strategic national stockpile; and development of protocols and authority for response.

The early detection of the release of a pathogen remains a significant challenge. The 2013-2016 Ebola outbreak also identified shortcomings in preparedness, which may be mitigated, in part, by establishing a network of biocontainment units.

A framework for pandemic preparedness, which applies to bioterrorism preparedness as well,[19] includes four main features: ensuring the global community commits appropriate financial resources and monitors progress; reinforcing national public health capabilities and infrastructure; strengthening the leadership role of the World Health Organization; and enhancing the scientific armory against infectious diseases.

Unfortunately, the response to the coronavirus-2019 (COVID-19) pandemic demonstrated that, despite lessons learned from both the 2001 anthrax attacks and the 2013-2016 Ebola outbreak, significant challenges remain in public health preparedness. There is a critical need to reassess our response capability and capacity for the next public health emergency.[20]

In any future bioterror attack,[21] early warning signs might include clusters of patients with mediastinal adenopathy or widened mediastinum on the chest radiograph, a centrifugal pustular rash (smallpox), pneumonia and hemoptysis (plague), descending flaccid paralysis (botulism), or hemorrhagic manifestations and impaired clotting (viral hemorrhagic fever). Should such a cluster be identified or suspected, physicians should contact the local county or city health department, the state health department, and potentially the CDC. Unlike a natural outbreak, a potential bioterror outbreak also requires a rapid dialogue between public health and law enforcement authorities, because patient and environmental samples constitute evidence against a perpetrator and must be handled under chain of custody. Physicians also must be prepared not only to protect themselves and their patients but also to serve as community resources, regardless of whether an outbreak is natural or terrorist in origin.

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20 CHRONIC POISONING: TRACE METALS AND OTHERS

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About 80% of the elements in the periodic table are metals or metalloids, and various metals are in contact with humans in the home, workplace, and environment. Metals are part of a number of normal physiologic processes, such as iron in hemoglobin, but also can cause a number of toxic adverse effects.[1–3]

LEAD TOXICITY

EPIDEMIOLOGY

Lead (Pb) is a silver-gray, malleable metal that is resistant to corrosion. It has no known physiologic use, so any lead in the human body should be considered contamination.

The most common sources of lead poisoning are lead-based paints, lead-contaminated dust, and lead-contaminated soil. Other sources include plumbing, solder, batteries, retained bullets, toys, curtain weights, necklace charms, food containers, and cosmetics, including Nigerian eyeliners. Adults in occupations such as battery manufacturing, welding, construction, mining, glass blowing, rifle ranges, and shipbuilding have the highest lead exposures. Other less common but important routes of exposure include lead-contaminated moonshine and lead-containing ethnic folk remedies (e.g., greta and azarcon in Mexico).

Children in lower socioeconomic areas have the highest exposures to lead,[4] and the majority of the scientific literature is biased toward pediatric studies. Much of what we have learned, however, is applicable to adults.

PATHOBIOLOGY

Lead's most devastating effects are on the central nervous system (CNS) of children. By disrupting the intracellular junction of capillary endothelium, lead impairs the blood-brain barrier and further increases its CNS absorption. Lead also increases capillary leak, which in severe cases can result in cerebral edema.

Lead inhibits several enzymes involved in heme synthesis: aminolevulinic acid synthetase, δ-aminolevulinic acid dehydratase, coproporphyrinogen decarboxylase, and ferrochelatase. Lead also inhibits the enzyme erythrocyte pyrimidine-5-nucleotidase and, as a result, impairs RNA degradation and contributes to red cell hemolysis. Collectively, the inhibition of these enzymes results in decreased concentrations of hemoglobin and a shorter lifespan of red blood cells.

By depositing lead-protein complexes in renal proximal tubular cells, lead interferes with normal mitochondrial function, thereby resulting in decreased reabsorption of glucose, amino acids, and phosphate. Chronically exposed persons can develop renal failure from tubular atrophy, interstitial fibrosis, and glomerular sclerosis.

Although lead has not been associated with specific bone-related disorders, the skeletal system serves as the main reservoir for lead; with chronic exposure, lead stores in bone can have a half-life of 5 to 19 years. As a result, tissues may be subjected to increased lead exposure during times of accelerated bone turnover, such as during childhood growth, after fracture of a long bone, or during pregnancy.

CLINICAL MANIFESTATIONS

Lead poisoning can be subtle and difficult to diagnose because many of its historical clinical associations (e.g., neuropathy, gout, abdominal colic) are rarely seen today. In children, the most concerning long-term complications of environmental lead exposure are developmental cognitive deficits, especially when lead concentrations in young children exceed 100 µg/dL. Subacute neurologic problems include ataxia, lethargy, seizures, and coma. Adults can also experience severe neurologic symptoms (e.g., seizures and cerebral edema) with plumbism, but typically only when whole blood lead levels are higher than 150 µg/dL. More commonly, the neurologic problems caused by lead in adults are manifested as memory problems,[5] insomnia, depression, personality changes, and an increased risk of cardiovascular disease. Higher childhood blood levels are also associated with changes on measures of brain structure seen on magnetic resonance imaging (MRI).[6]

Other clinical effects of lead poisoning, in both children and adults, include a normocytic or microcytic anemia, abdominal pain, hepatotoxicity, and pancreatitis. The classic finding of peripheral neuropathy with footdrop and wristdrop is well described in adults but only occasionally seen in children. Nephrotoxicity most commonly is manifested as Fanconi syndrome (Chapter 113) with aminoaciduria, glycosuria, and phosphaturia. A consequence of this toxicity is impaired uric acid clearance and gout (Chapter 252). High lead levels may increase the risk of hypertension.

DIAGNOSIS

Existing evidence is insufficient to recommend screening for elevated blood lead levels in asymptomatic individuals,[7] so the diagnosis of lead intoxication involves a high level of clinical suspicion. The best initial test is a whole blood lead level collected in a certified lead-free tube (Table 20-1). The blood lead level can be falsely elevated in individuals who have received chelation therapy in the prior 7 days. Capillary lead levels can be falsely elevated by skin contaminated with lead.

Radiographic imaging can support the diagnosis of lead poisoning and sometimes detect a lead-containing object or a retained bullet. Bone x-ray fluorescence technology can estimate bone lead levels, which can reflect chronic lead exposure, but this test is not commonly available.

TREATMENT

The first step in the management of patients with elevated lead levels is prompt removal of the source, although the effectiveness of household environmental clean-up and educational initiatives is disappointing.[A1,A2] If lead comes from a work-related source, the Occupational Safety and Health Administration should be contacted. Chelation increases excretion of lead in a 24-hour urine sample and thereby decreases blood concentrations, but studies to date with the chelating agent succimer (2,3-dimercaptosuccinic acid, DMSA) in children have not shown improved neuropsychological function despite success in reducing blood lead levels. The current recommendation is that asymptomatic adults with blood lead levels of less than 70 µg/dL do not require chelation, patients with mild symptoms or blood lead levels between 70 and 100 µg/dL should receive oral chelation, and patients with lead-induced encephalopathy or blood lead levels above 100 µg/dL should receive parenteral chelation. Although DMSA is approved by the Food and Drug Administration only for children, it also is commonly used in adults (Table 20-2).

Whole bowel irrigation with a polyethylene glycol–electrolyte solution should be considered if a patient has retained a gastrointestinal lead object. Patients who have lead-containing bullet fragments lodged in soft tissues or joint spaces may need to have them surgically removed.

PROGNOSIS

Despite controversy about long-term recovery from lead-associated cognitive deficits in children, adults with neurologic symptoms improve with removal of the exposure. The hematologic and nephrotoxic effects of lead also are reversible.

TABLE 20-1 DIAGNOSTIC TESTING FOR METALS: REFERENCE RANGES

METAL	SERUM LEVEL	WHOLE BLOOD LEVEL	SPOT URINE	24-HOUR URINE
Lead		<5 µg/dL		
Mercury		<10 µg/L	<20 µg/L	<5 µg/L creatinine
Arsenic		<5 µg/L		<50 µg/L or <100 µg/g creatinine
Cadmium		<5 µg/L		<3 µg/g creatinine
Aluminum	<2 µg/L	<12 µg/L		<4-12 µg/g creatinine
Bismuth	<1 µg/dL	<5 µg/dL	<20 µg/L	
Cobalt	0.1-1.2 µg/L		0.1-2.2 µg/L	
Manganese	0.4-0.85 µg/L	4-15 µg/L		<10 µg/L
Silver	<0.5 µg/L			<1 µg/L
Thallium		<2 µg/L		<5 µg/L
Zinc	109-130 µg/dL	600-1000 µg/dL		<500 µg/day

Modified from Nelson L, Howland M, et al., eds. *Goldfrank's Toxicologic Emergencies*. 11th ed. New York: McGraw-Hill Medical; 2019.

ABSTRACT

Comprising 80% of the periodic table, heavy metals are an integral part of human life and physiology. Chronic exposure to many metals, however, can result in systemic toxicity. In this chapter, we will discuss clinical manifestation and pathophysiology of poisoning from lead, mercury, arsenic, cadmium, aluminum, cobalt, silver, thallium, zinc, and manganese.

KEYWORDS

lead
mercury
arsenic
trace metals
chronic toxicity
chelation

TABLE 20-2 CHELATORS FOR ADULT HEAVY METAL POISONING

SYMPTOMS	CHELATOR	RECOMMENDED DOSE[†]	ADVERSE EFFECTS
LEAD			
Asymptomatic, BLL[*] < 70 µg/dL	None		
Mild-moderate, BLL 70-100 µg/dL	DMSA	10 mg/kg tid PO × 5 days, then bid for 14 days	Nausea, vomiting, diarrhea, rash, elevations in aminotransferase levels, neutropenia
Encephalopathy, BLL > 100 µg/dL	BAL +	4 mg/kg deep IM q4h × 5 days	Local injection site (pain, redness, sterile abscess); nausea, vomiting, diarrhea; anxiety, hypertension, tachycardia, fever; contraindicated in peanut allergy
	$CaNa_2EDTA$[‡]	1500 mg/m^2/day (approximately 50-75 mg/kg/day, maximum 3 g) either continuous infusion or in 2-4 divided IV doses for 5 days, adjusted for renal insufficiency	Renal toxicity (from metal chelate), constitutional symptoms, transient hypotension
MERCURY			
Acute (elemental or inorganic, but not organic) with moderate/severe symptoms	BAL	5 mg/kg deep IM q4h for 2 days, then 2.5 mg/kg q6h for 2 days, then 2.5 mg/kg bid for 7 days or until symptoms improve and the patient is able to take oral medication, at which point DMSA should be considered	Local injection site (pain, redness, sterile abscess); nausea, vomiting, diarrhea; anxiety, hypertension, tachycardia, fever; contraindicated in peanut allergy
Chronic (elemental or inorganic) or organic with symptoms	DMSA	10 mg/kg tid PO × 5 days, then bid for 14 days	Nausea, vomiting, diarrhea; mild elevations in aminotransferase levels
ARSENIC			
Acute exposure with moderate to severe symptoms	BAL	3 mg/kg deep IM q4h × 2 days, then bid for 7 to 10 days	Local injection site (pain, redness, sterile abscess); nausea, vomiting, diarrhea; anxiety, hypertension, tachycardia, fever; contraindicated in peanut allergy
Chronic exposure with moderate symptoms[§]	DMSA	10 mg/kg tid PO × 5 days, then bid for 14 days	Nausea, vomiting, diarrhea; mild elevations in aminotransferase levels
ALUMINUM			
Acute or chronic exposure in dialysis patient with encephalopathy	Deferoxamine	See *http://kidneyfoundation.cachefly.net/professionals/KDOQI/guidelines_bone/guide12.htm*	Hypotension, increased risk of sepsis, acute lung injury
THALLIUM			
Acute thallium poisoning with moderate to severe symptoms	Prussian Blue	3 g tid PO until the urinary thallium excretion is less than 0.5 mg/day	Constipation, blue stool

*Adult recommendations.
[†]Chelation doses in general are not well studied or validated, with the exception of lead in children. Optimal dosing is not well established, particularly for BAL. Doses listed are author's suggestions.
[‡]Start 4 hours after first dose of BAL is administered.
[§]Benefit in this setting is not established.
BAL = British anti-Lewisite, dimercaprol; bid = twice daily; BLL = blood lead level; DMSA = 2,3-dimercaptosuccinic acid, succimer; EDTA = ethylenediaminetetraacetic acid; h = hour; IM = intramuscularly; IV = intravenously; PO = orally; qd = daily; tid = three times daily.

MERCURY TOXICITY

EPIDEMIOLOGY

Mercury (Hg) is a naturally occurring metal with three distinct forms. Although all forms are neurotoxic, elemental mercury (Hg^0) also causes pulmonary toxicity, inorganic mercury (Hg^+ or Hg^{++}) causes gastrointestinal and renal toxicity, and organic mercury (ethyl, methyl, alkyl, or phenyl) is a teratogen.

Elemental mercury is found in dental amalgams, thermometers, fluorescent lamps, batteries, and some paints. Occupational exposures may occur in dentists and dental hygienists, painters, gold extractors, bronzers, electroplaters, metallurgists, paper pulp manufacturers, miners, ceramic workers, and other workers who use mercury in processing. Mercury thermometers are becoming increasingly rare, and many countries have banned them because of potential mercury toxicity. Toxicity from elemental mercury is caused primarily from breathing its volatilized vapor.

Inorganic mercury has been used historically as a medicinal, cosmetic, and topical antiseptic in the forms of HgCl (calomel) and $HgCl_2$ (mercuric chloride). It is also used in the tanning industry, in taxidermy, in manufacturing of fireworks, and in dye manufacturing. Inorganic mercury may also be found in patent medicines, folk remedies (such as empacho among Mexican Americans), skin lightening creams, and Asian herbal remedies. Toxicity may occur from ingestion, inhalation, or dermal absorption.[8]

Organic mercury compounds can be classified as short-chain alkyl (such as methyl mercury), long-chain alkyl, and aryl compounds. The aryl compounds, such as thimerosal, behave like inorganic mercurial compounds. Methyl mercury has caused several large-scale human poisoning epidemics.

Soil and marine organisms methylate inorganic mercury from the air and industrial waste. Through a process known as bioamplification, methyl mercury concentrates in the tissues of marine life, reaching highest concentrations in large predatory fish such as tuna and swordfish. Fish consumption is now the largest route of organic mercury exposure in the general population, and organic mercury levels have been increasing in the United States even as levels of inorganic mercury have been declining.[9] Organic mercury is also used as a fungicide, pesticide, wood preservative, and medicinal antiseptic or preservative (Mercurochrome and thimerosal). Toxicity is typically by ingestion.

PATHOBIOLOGY

The pathophysiology of mercury poisoning is related to its disruption of cell physiology by binding to sulfhydryl, phosphoryl, carboxyl, and amide groups, thereby causing widespread dysfunction of normal cellular mechanisms. Each type of mercury causes differential effects depending on its route of exposure, solubility, and lipophilicity.

Elemental mercury is poorly absorbed by ingestion. If gastrointestinal motility or mucosal integrity is compromised, however, elemental mercury may ionize into more readily absorbed forms. Elemental mercury toxicity occurs primarily by inhalation of the vapor into the alveoli, where it is well absorbed in the pulmonary circulation and readily crosses the blood-brain barrier. In the brain, it interferes with multiple cellular processes, including protein and nucleic acid synthesis. Mercury also inhibits catechol-*O*-methyltransferase, thereby elevating circulating catecholamine levels.

Inorganic mercury is absorbed after ingestion, initially binds the gastrointestinal mucosa, and accumulates in the kidneys, where it exerts direct oxidative damage. Although it does not readily cross the blood-brain barrier, CNS toxicity can be seen with chronic exposures because of the prolonged elimination rate. Mercuric ions do not appear to cross the placental barrier.

Organic mercury compounds are readily absorbed after ingestion and inhalation and are moderately absorbed after dermal exposure, particularly if skin

is not intact. Owing to its high lipid solubility, organic mercury crosses the blood-brain barrier and concentrates in the CNS. It can also cross the placental barrier and concentrate in the fetus. Organic mercury concentrates in red blood cells, distributes throughout the body, and is primarily eliminated in the feces. Some forms of organic mercury are metabolized in the body to inorganic mercury compounds. Toxicity results from its inhibition of enzyme systems and interference with cellular maturity, microtubule function, and neurotransmitter synthesis and uptake.

CLINICAL MANIFESTATIONS

Elemental Mercury

The manifestations of elemental mercury toxicity vary depending on the dose and chronicity of the exposure. Inhalation of high concentrations of mercury vapor, as may occur in an industrial setting, may result in cough, chills, fever, and shortness of breath. Nausea, vomiting, and weakness may result. This syndrome may progress to a severe acute lung injury and respiratory as well as renal failure. Chronic exposure to lower concentrations of mercury vapor produces a classic triad of tremor, gingivostomatitis, and neuropsychiatric disturbances. The mercurial tremor may be both static and intentional. Sudden episodic bursts of tremor, also called tetanus mercurialis, have been described. Neuropsychiatric manifestations of mercury poisoning, also known as erethism, include fatigue, insomnia, memory dysfunction, social withdrawal, shyness, and depression. Acrodynia, or pink disease, has been described after elemental or inorganic mercury exposure, most notably in children after exposure to mercurial teething powder and diaper ointment. This syndrome is manifested as an erythematous, hyperkeratotic, often desquamating rash on the palms, soles, and face in conjunction with a papular rash. Acrodynia is also associated with an idiosyncratic hypersensitivity to mercury ions and mercury poisoning, which itself can increase circulating catecholamines and mimic pheochromocytoma (Chapter 209). Common findings include tremor, diaphoresis, tachycardia, and hypertension.

Inorganic Mercury

Inorganic mercury poisoning can occur after dermal or mucosal absorption of mercury-containing cosmetics and teething powders as well as after accidental or intentional ingestion of mercuric chloride antiseptics. After acute ingestion, a hemorrhagic gastroenteritis is typically followed by renal failure from acute tubular necrosis. Chronic exposure is associated with erethism, renal dysfunction, and neurologic manifestations such as sensorimotor neuropathy, constriction of visual fields, tremor, and delirium.

Organic Mercury

Human toxicity from organic mercury was first recognized when the dumping of mercury-containing waste into Minamata Bay in Japan led to a large-scale poisoning of the population, whose primary dietary staple was fish from the bay. In what is now called Minamata disease, patients presented with paresthesia, ataxia, dysarthria, tremor, and constriction of visual fields or "tunnel vision."[10] These symptoms can be progressive and sometimes fatal. Children born to these exposed mothers (congenital Minamata disease) suffered mental retardation, limb deformities, chorea, seizures, and microcephaly. In a large Korean study, higher mercury levels were associated with depression in women but not men, and even then only in women with low fish consumption.[11] In the United States, organic mercury exposure from seafood has not been significantly associated with cardiovascular or all-cause mortality.[12] Nevertheless, higher circulatory levels of mercury (along with aluminum and cadmium) are found in patients with Alzheimer disease than in controls.

With organic mercury toxicity, symptoms are typically delayed for weeks to months. Other symptoms that follow organic mercury poisoning include mucous membrane irritation after ingestion and dermatitis after cutaneous exposure. However, no cardiovascular toxicities have been reported with up to moderate elevation in blood mercury levels.

DIAGNOSIS

The diagnosis of mercury poisoning should be considered on recognition of the characteristic signs and symptoms coupled with a known or suspected exposure. Whole blood and urine mercury levels can confirm the exposure, but the correlation between levels and symptoms is inconsistent. In the setting of elemental mercury ingestion or injection, radiographs may also be useful. In a nonoccupationally exposed patient, whole blood mercury concentration should not exceed 10 μg/L, and a 24-hour urine mercury concentration should not exceed 20 μg/L (Table 20-1); urine must be collected in an acid-washed container. In general, urine concentrations are more reliable for monitoring of exposure and the response to therapy, but whole blood concentration is the preferred monitoring test for methyl mercury poisoning.

The ratio of red blood cells to plasma mercury can differentiate organic mercury toxicity from inorganic mercury toxicity because organic mercury concentrates significantly in red blood cells. Hair analysis is unreliable because of the potential for external contamination. The practice of obtaining urine mercury levels after a chelation challenge is not recommended because levels obtained in this way are difficult to interpret.

TREATMENT

Treatment is primarily symptomatic and supportive, with removal from the source of exposure. In cases of acute exposure, decontamination may be required. In cases of occupational or environmental exposure, environmental decontamination and surveillance by local or federal agencies may be necessary. After inhalation of elemental mercury vapor, support of respiratory function is crucial. After ingestion of inorganic mercury salts, fluid resuscitation, usually with normal saline, is needed to correct intravascular depletion, and renal replacement therapy may be required in cases of oliguric renal failure. Mercury compounds are poorly cleared by extracorporeal elimination measures, such as hemodialysis or peritoneal dialysis.

If dietary fish is the likely cause of an elevated mercury level, affected individuals should avoid eating any fish or shellfish for 1 month, after which blood or urine mercury levels should be reanalyzed. If mercury levels have declined into the normal range, as is usually the case, low-mercury fish (shrimp, canned light tuna, salmon, pollock, catfish) can be reintroduced into the diet at a frequency of no more than two meals per week.

Chelation therapy will increase urinary elimination of mercury (Table 20-2), and limited clinical data support its use early after acute poisonings. Oral DMSA, which is the chelator of choice, is generally well tolerated. If oral administration is not possible, dimercaprol (British anti-Lewisite, BAL) can be used except after methyl mercury exposure, in which it is contraindicated because it may shift mercury into the brain.

PROGNOSIS

The neurotoxicity that follows significant poisoning from all types of mercury may be irreversible, particularly in the setting of organic mercury poisoning, in which the diagnosis is often delayed. Nevertheless, 33 of 40 symptomatic children affected in the contaminated grain outbreak of 1971 in Iraq improved during a 2-year observation period. Acute renal failure after elemental or inorganic mercury poisoning can sometimes resolve. Patients with acrodynia have been reported to recover completely after chelation therapy and removal of the exposure.

ARSENIC TOXICITY

EPIDEMIOLOGY

Arsenic (As), which is found in soil, minerals, rocks, and metal ores, is present in all living organisms. It exists in several forms: elemental, inorganic (As^{3+} trivalent arsenite and As^{5+} pentavalent arsenate), gaseous (arsine, AsH^3), and organic. Elemental and organic arsenic have low toxicity, whereas gaseous arsine and inorganic arsenic are highly toxic. Arsenic's medicinal properties were recognized as early as 400 BC, and it has been used throughout history as a medicinal as well as a component of pigments, cosmetics, and famously as a poison.

Human exposure to arsenic may occur through contaminated air, groundwater, soil, and food, particularly seafood, rice, and produce.[13] Marine organisms, especially shellfish, contain organic arsenicals arsenobetaine and arsenocholine, which are commonly reported in laboratory assays as elevated arsenic level but exert no known toxic effects.

In Bangladesh, ongoing epidemic arsenic poisoning from contaminated groundwater has affected millions of persons. Taiwan, Chile, the Cordoba province in Argentina, West Bengal, and other regions in the Ganga plain also have elevated levels of naturally occurring arsenic and cases of arsenic poisoning.

Occupational exposure to arsenic occurs in the microelectronics industry, where arsenide crystals are used to etch circuits on microchips. Arsine gas is liberated when inorganic arsenic contacts acid, as may occur in occupations such as metal smelting, galvanizing, and semiconductor manufacturing. Arsenic compounds are also used in the production of paint, fungicide, insecticide, pesticide, herbicide, wood preservatives, ceramics, and glass, and employees in these industries may also be potentially exposed.

Arsenic compounds may still be found in folk remedies and patent medicines. Modern medicinal uses of arsenic include arsenic trioxide (Trisenox) for the treatment of acute promyelocytic leukemia and other hematologic

malignancies (Chapter 168), and melarsoprol (which is not commercially available in the United States), for the treatment of African trypanosomiasis (Chapter 317).

PATHOBIOLOGY

The toxicologically significant arsenic compounds are inorganic (trivalent and pentavalent). Arsine gas, which is also toxic, causes acute hemolysis. After absorption, inorganic arsenic binds to hemoglobin and is distributed to the liver, kidney, heart, and lungs. In the liver, arsenic is methylated to form monomethylarsonic and dimethylarsinic acid, both of which are less toxic. Arsenic concentrates in keratin-rich tissues, such as hair, skin, and nails. Much of an ingested dose of arsenic is eliminated in the urine. The mechanism of toxicity is by binding sulfhydryl groups of critical enzymes, including those of the Krebs cycle, thereby resulting in impaired gluconeogenesis, impaired oxidative phosphorylation, and ultimately depletion of cellular energy stores. DNA damage and an impaired DNA repair mechanism contribute to carcinogenic effects. Pentavalent arsenate may substitute for phosphate in biochemical reactions and disrupt normal oxidative phosphorylation. Arsenic also affects cardiac conduction by blocking cardiac potassium channels. Arsenic can alter gene expression through induction, downregulation, and upregulation of various genes involved in apoptosis, cell signaling, and growth factor response.

Arsine is a colorless, nonirritating gas. After inhalation, it is absorbed rapidly and binds to erythrocytes, where it exerts oxidative stress and causes severe Coombs-negative intravascular hemolysis. Renal failure is due to hemoglobin pigment deposition as well as to the direct toxic effects of arsine on renal tubular cells.

CLINICAL MANIFESTATIONS

The initial clinical features after acute ingestion of inorganic arsenic are nausea, vomiting, bloody diarrhea, and abdominal pain. Severe manifestations such as seizures, delirium, and coma are seen after large exposures. Within several days, hematologic findings such as pancytopenia can be seen. QT prolongation, which can develop acutely or chronically, can lead to dysrhythmias such as torsades de pointes. After gastrointestinal symptoms improve, distal symmetrical peripheral neuropathy develops, potentially accompanied by weakness or encephalopathy.

Chronic exposures affect the bone marrow, skin, and peripheral nervous system.[14] Dermatologic effects include patchy or diffuse alopecia, hyperpigmentation, and melanosis as well as hyperkeratosis on the palms and soles. The pigmentation of chronic poisoning commonly appears in a finely freckled, "raindrop" pattern of symmetrical pigmentation or depigmentation that is particularly pronounced on the trunk and extremities. Nails may exhibit transverse white bands, which are known as Mees lines (Chapter 409) and reflect growth interruption during poisoning. Anemia, pancytopenia, neutropenia, thrombocytopenia, and eosinophilia can be seen. Neuropathy, which is a hallmark of arsenic poisoning, is a diffuse, symmetrical, ascending, painful sensorimotor neuropathy, most prominent in a stocking-glove distribution. In severe poisoning, ascending weakness and paralysis may result in respiratory failure that mimics Guillain-Barré syndrome (Chapter 388). Arsenic exposure also causes a dose-dependent decline in lung function.[15] Peripheral vascular disease, including peripheral vascular gangrene (black foot disease), can develop in chronically exposed patients. Even low to moderate chronic arsenic exposure increases the long-term risk of cardiovascular disease. Arsenic is a human carcinogen, and exposed populations have an increased risk of developing malignant neoplasms in the lung, skin, and bladder.[16]

Arsine gas produces a clinical triad of abdominal pain, hemolysis, and hematuria, typically occurring hours after exposure. Patients may initially have headache, weakness, nausea, and vomiting. Several weeks after an acute exposure, peripheral neuropathy may develop.

DIAGNOSIS

Blood arsenic, urine arsenic, and urine arsenic metabolites can be used to confirm recent or ongoing exposure. In the unexposed individual, blood arsenic should be below 1 μg/L; hair and nail levels should be less than 1 ppm.[17]

However, arsenic clears from the blood quickly, so urine levels are most helpful to diagnose chronic or past exposure. Arsenic levels above 50 μg in a spot urine test warrant a 24-hour test. Urine is collected in a metal-free polyethylene container, and levels exceeding 50 μg or 100 μg/g creatinine in a 24-hour collection require further scrutiny (Table 20-1). Patients who have recently ingested seafood may have urine arsenic levels exceeding 1500 μg/L exclusively from organic arsenic, so differentiating inorganic from nontoxic organic arsenic is often critical. Total arsenic levels in hair or nails, where arsenic accumulates, are useful indicators of past exposures.

In patients with chronic arsenic exposure, a complete blood count may show anemia (normocytic, normochromic, or megaloblastic), leukopenia, and thrombocytopenia. A peripheral smear may show basophilic stippling (see Fig. 143-14) or karyorrhexis. Renal dysfunction, hepatic enzyme elevation, and hyperbilirubinemia may be seen as well. The electrocardiogram may show QT prolongation and nonspecific ST-T wave changes. Nerve conduction studies typically show evidence of a distal symmetrical sensorimotor axonopathy. Conduction slowing may be seen in severe poisoning.

TREATMENT

Initial treatment of arsenic toxicity includes supportive care, fluid repletion, decontamination if needed, and removal of the source of exposure. Hemodialysis may be required in patients who have significant renal dysfunction.

In cases of severe acute poisoning from inorganic arsenic, chelation is beneficial if it is instituted early. Dimercaprol (BAL; see Table 20-2), which is the traditional chelating agent for arsenic, is effective in decreasing morbidity and mortality if it is administered within minutes to hours of acute exposure. The oral analogue of BAL, dimercaptosuccinic acid (DMSA, succimer) is also useful for subacute or chronic arsenic poisoning. 2,3-dimercapto-1-propanesulfonic acid (DMPS) has also been used successfully but is neither approved by the Food and Drug Administration nor commercially available in the United States. In chronic inorganic arsenic intoxication, however, a clear benefit of chelation therapy has not been demonstrated.

Hemolysis caused by arsine gas poisoning should be treated with prompt exchange transfusion. Exchange transfusion can restore functional erythrocytes, remove hemoglobin pigments, remove arsenic itself, and remove toxic products formed in the arsine-hemoglobin reaction.

PROGNOSIS

Outcomes after arsenic poisoning are influenced by the dose, type of arsenic compound, and route and chronicity of exposure. Acute high-dose arsine gas inhalation with severe and rapid systemic toxicity can be fatal. With appropriate treatment, however, recovery has been reported. After acute inorganic arsenic ingestion, rapid diagnosis and treatment, including chelation, can significantly reduce mortality. After acute or chronic arsenic poisoning, electrocardiographic abnormalities and bone marrow suppression are generally reversible after exposure ceases, but encephalopathy and neuropathy may be permanent. Skin changes, such as hyperpigmentation and hyperkeratoses, can progress to cancer but also can improve with mitigation of exposure.

CADMIUM TOXICITY

EPIDEMIOLOGY

Cadmium (Cd) is primarily found in zinc ores as cadmium sulfide. Serious human exposures usually come from industrial use, including the production of nickel-cadmium batteries, electroplating, soldering, and welding. Workplace exposures occur through inhalation of dust containing oxides of cadmium or fumes from welding or smelting of metals containing cadmium.[18] Depending on the particle size, more than 50% of cadmium can be absorbed through the lungs, but little cadmium is absorbed through the gastrointestinal tract. Many plants take up cadmium from the environment, but poor oral bioavailability and relatively low food concentrations make ingestion of food an unlikely source of significant cadmium. An exception is when cadmium-containing industrial waste is dumped in agricultural regions, such as happened in Japan in the 1950s, when cadmium-containing mining waste in waterways that irrigated rice fields caused a large outbreak of osteomalacia, painful fractures, and renal disease ("itai-itai", or ouch-ouch syndrome). Today, a common source of environmental cadmium exposure is through smoking, because tobacco concentrates cadmium from the soil. Compared with nonsmokers, an average smoker has twice the concentration of total body cadmium.

PATHOBIOLOGY

Cadmium commonly exists as a divalent ion (Cd^{2+}) in salts such as cadmium sulfide and cadmium oxide. As with other divalent metals, it binds to and inhibits sulfhydryl-containing proteins and enzymes, thereby resulting in oxidative stress, cellular apoptosis, or necrosis. To survive in an environment where metals are ubiquitous, mammals have developed numerous antioxidant systems for protection. The one best studied in cadmium is the protein metallothionein, which is an intracellular, cysteine-rich protein especially found in the liver and kidney, where it is a potent protective antioxidant that binds to ionized

cadmium.[19] Slow release of cadmium from the cadmium-metallothionein complex results in a long biologic half-life of over 20 years.

CLINICAL MANIFESTATIONS

The most life-threatening manifestation of cadmium toxicity is acute chemical pneumonitis (Chapters 81 and 82). In persons who are exposed to high concentrations of cadmium fumes (e.g., smelter or welders), cadmium pneumonitis is manifested like metal fume fever with fever, malaise, myalgias, and elevated white blood cell counts that develop within 12 hours of exposure. Unlike metal fume fever, which typically resolves within a few days, cadmium pneumonitis can progress, with symptoms of dyspnea, hemoptysis, pulmonary edema, and respiratory distress, as well as diffuse bilateral alveolar infiltrates on the chest radiograph.

The most problematic manifestation of chronic cadmium exposure is renal failure. As with lead, cadmium can damage the proximal tubules of the kidney and result in Fanconi syndrome (Chapter 113). Cadmium, bound to metallothionein, accumulates in the kidney; once metallothionein binding is saturated, toxicity can develop. Unlike the acute pulmonary manifestations, renal symptoms of cadmium toxicity may have a latency of decades. Clinically, the signs of renal disease from cadmium are not different from those of other causes of proximal tubular disease, with proteinuria being the most common finding. Patients will often manifest secondary symptoms of renal dysfunction, such as osteoporosis, osteomalacia, or ureteral stones owing to impaired calcium metabolism. Hypertension and anemia from cadmium exposure are also likely secondary to its renal toxicity.

DIAGNOSIS

No laboratory tests can aid in the diagnosis of cadmium pneumonitis, so physicians must rely on their clinical suspicion or on alveolar infiltrates on a chest radiograph in a cadmium-exposed worker who presents with influenza-like symptoms. Patients may present with an initially benign clinical picture and progress to respiratory failure.

Diagnosis of renal toxicity from chronic cadmium exposure relies predominantly on a 24-hour urine cadmium level standardized to grams of creatinine in a certified laboratory experienced in heavy metal testing (Table 20-1). In nonexposed nonsmokers, cadmium values should average about 0.08 μg/g creatinine. For patients with levels above 3 μg cadmium/g creatinine, a medical evaluation and renal testing are indicated. Levels at or above 7 μg cadmium/g creatinine require removal from the workplace. Urinary β_2-microglobulin levels increase as proximal tubular function worsens and can serve as a useful early marker of toxicity; levels above 300 μg/g creatinine should raise concern for early kidney disease.

TREATMENT

Because of the progression of potentially life-threatening pulmonary symptoms in cadmium pneumonitis, any patient presenting with influenza-like symptoms after working with heated cadmium should be admitted for observation. If the metal a patient was welding or cutting is not known, any clinical or radiographic signs of noncardiogenic pulmonary edema would also warrant hospital admission for supplemental oxygen and pulmonary support.

There are no effective specific treatments for acute or chronic cadmium toxicity. Chelation therapy is not recommended. Cessation of exposure is recommended but is not likely to reverse renal or pulmonary damage.

PROGNOSIS

Patients with cadmium pneumonitis can survive with aggressive supportive treatment, but severe cases can result in death, and survivors can have persistent restrictive lung disease. Because of its long half-life in the kidney, cadmium-induced renal damage is largely irreversible unless it is detected early when body burden is low (urinary cadmium < 10 μg/g creatinine).

SYNDROMES SPECIFIC TO OTHER TOXIC METALS

ALUMINUM (DIALYSIS DEMENTIA)

In the 1970s, patients who had renal failure and who were exposed to aluminum-containing phosphate binders or aluminum-contaminated dialysis fluid developed progressive neurologic impairment and seizures. Also known as dialysis dementia, this syndrome developed during weeks to years and was often fatal if undetected. Aluminum-containing phosphate binders and dialysis fluids are no longer used in patients with renal failure, and at-risk dialysis patients are screened for aluminum toxicity. As a result, this phenomenon has decreased over time,[20] but occasional outbreaks continue to be reported, typically owing to contamination of dialysis fluid with aluminum from electric pumps or drums.

Aluminum is found in air, soil, and water and is a component of metal alloys used in the home, such as cookware. Aluminum is also found in some antacids (sucralfate) and as aluminum potassium sulfate (Alum), which is used to treat hemorrhagic cystitis. Additional iatrogenic sources of aluminum include total parenteral nutrition solutions and vaccines. Ingested aluminum is not metabolized by the body and is excreted unchanged by the kidney. In patients who have impaired renal function, aluminum is bound to transferrin and concentrates primarily in bone. Smaller amounts, however, are distributed to the heart, liver, kidney, and brain. Ingested aluminum is thought to affect several biochemical functions, including neurotransmitter manufacture, uptake, and release. Aluminum also affects erythropoiesis and the normal function of bone, likely partially by interference with parathyroid function.

CLINICAL MANIFESTATIONS AND DIAGNOSIS

Clinical effects in patients with chronic exposures include anemia, osteomalacia, and neurologic effects including memory loss, tremor, dyspraxia, encephalopathy, and seizures.[21] A relationship between aluminum and Alzheimer dementia has been proposed, but the complex characteristics of aluminum bioavailability make it difficult to produce conclusive evidence.

Serum and urine aluminum levels can be obtained to estimate exposure. A serum aluminum concentration should not exceed 2 μg/L, and a 24-hour urine concentration is expected to be 4 to 12 μg per gram of creatinine in a patient with typical background aluminum exposure (Table 20-1).

TREATMENT AND PROGNOSIS

Management of aluminum toxicity centers on removal of the source of exposure. The only chelator with proven benefit is deferoxamine (Table 20-2), which has a high affinity for aluminum and forms a dialyzable aluminum-deferoxamine complex. If neurologic dysfunction is detected early, successful treatment and full recovery have been reported with deferoxamine.

BISMUTH (BISMUTH ENCEPHALOPATHY)

Bismuth salts used to treat gastrointestinal disorders include bismuth subgallate, bismuth citrate, bismuth subnitrate, and bismuth subsalicylate (the active ingredient in Pepto-Bismol). Bismuth (Bi) is poorly absorbed from the gastrointestinal tract and is still used today to treat peptic ulcer disease and diarrhea. It also is used as an oral deodorant for patients with colostomies. Idiopathic bismuth toxicity is almost always associated with the chronic ingestion of over-the-counter preparations.

CLINICAL MANIFESTATIONS AND DIAGNOSIS

Bismuth toxicity is manifested primarily as a subacute encephalopathy with ataxia and incoordination followed by progressive memory loss, behavioral changes, insomnia, and muscle cramps. As symptoms progress, a common feature is limb myoclonus when patients are startled or as they fall asleep. As symptoms worsen, myoclonus can progress to involve the entire body, including the tongue, and can occur without stimulus. Seizures can also develop.

The diagnosis of bismuth encephalopathy can be difficult. Blood and urine levels can indicate exposure to bismuth (Table 20-1) but do not correlate with symptoms. Furthermore, electroencephalographic findings, laboratory tests, and imaging studies are not specific. Because of its similarity in onset and symptoms, bismuth encephalopathy is often misdiagnosed as Creutzfeldt-Jakob disease (Chapter 371) or other progressive encephalopathies. Therefore, any patient in whom these diagnoses are being entertained should be screened for the use of bismuth products. Because bismuth causes black stools, the finding of heme-negative black stool in a patient with a rapidly progressing encephalopathy warrants an investigation for bismuth toxicity.

TREATMENT AND PROGNOSIS

The treatment of bismuth encephalopathy is to stop the use of the offending agent. Although case reports have reported benefits with metal chelators (e.g., DMSA, BAL, and 2,3-dimercapto-1-propanesulfonic acid; see Table 20-2), the rarity of the disorder makes a clinical trial impossible. Ethylenediaminetetraacetic acid (EDTA) may increase brain bismuth concentrations, so it should not be used. Although deaths have occurred from bismuth encephalopathy, full recovery is possible if the offending drug is stopped and if the patient receives modern supportive care.

COBALT (THYROID AND CARDIAC TOXICITY)

Cobalt (Co) is an essential trace element that serves as the catalytic center of vitamin B_{12}. Toxicity is associated with chronic ingestion of cobalt salts and more recently from cobalt-containing metal prostheses. One of the side effects of chronic ingestion is polycythemia (Chapter 152). By stabilizing hypoxia-inducible transcription factors that normally respond to low concentrations of oxygen, cobalt mimics hypoxia and stimulates erythropoietin production. In the 1950s, cobalt chloride was used to treat iron deficiency anemia. Some of these patients developed hypothyroidism and goiter because of cobalt's ability to inhibit tyrosine iodinase. In addition, cobalt has caused dilated cardiomyopathy with pericardial effusions in adults who consumed large amounts of beer in which cobalt salts had been added as a foam stabilizer. Cobalt can cause neurotoxicity with symptoms of hearing loss, visual impairment, and polyneuropathy.

Current concern for cobalt toxicity is predominately for patients who have cobalt-chromium prosthetic joints. Cobalt liberated from a prosthesis has been linked to hypothyroidism (Chapter 207), dilated cardiomyopathy (Chapter 47), and neurotoxicity with metal-on-ceramics arthroplasty and metal-on-metal prosthetics.

DIAGNOSIS AND TREATMENT

The diagnosis in a patient with a cobalt-containing joint replacement requires symptoms of polycythemia, hypothyroidism, cardiomyopathy, and neurotoxicity. In these patients, a blood chromium level above 7 μg/L should stimulate a referral for a possible joint revision.

There is little evidence that chelation improves outcomes in cobalt-poisoned patients.

SILVER (ARGYRIA)

Silver (Ag) is a precious metal long used in coinage and for its antibacterial properties. Silver is a broad-spectrum antimicrobial and commonly used as a topical antimicrobial in bandages, catheters, and medical devices. The ingestion of colloidal silver preparations as a "natural" supplement accounts for the majority of recent cases of significant toxicity.

When it is ingested continually, silver will be deposited in the skin and the liver.[22] The primary chronic toxicity of silver is argyria, which is a permanent blue-gray discoloration of the skin owing to silver deposition over time (Fig. 20-1). Argyria can result from inhalation, ingestion, mucosal absorption, or dermal application or exposure. Argyria may be localized to the site of exposure, such as with corneal argyria, which was seen in the past from the use of colloidal silver–containing eye drops, or at the site of silver earrings and rings. Rarely, argyria has been reported after the implantation of silver-containing medical devices.

DIAGNOSIS AND TREATMENT

The diagnosis of argyria is primarily based on history and physical examination. Localized skin biopsy, typically to differentiate argyria from malignant lesions, will show characteristic black-brown globules that are adherent to the dermal elastic fibers, blood vessels, basement membranes, hair follicles, and sweat glands on light microscopy; refractile particles on darkfield microscopy; and the presence of silver on scanning electron microscopy with energy dispersive radiography.

Chelation therapy is not effective for argyria, but successful laser treatment has been reported.[23]

THALLIUM (NEUROPATHY AND ALOPECIA)

Thallium (Tl) has no beneficial role in the human body. Its salts are odorless, tasteless, well absorbed in the gastrointestinal tract, and very toxic. These characteristics make it a potential homicidal agent, and patients with thallium poisoning should always be considered potential victims of a crime. By interfering with potassium and sulfhydryl-containing enzymes, thallium interrupts normal energy production. Although it is toxic to all organs, the peripheral nervous system and integumentary system are the most sensitive.

The earliest clinical sign of thallium poisoning is a rapidly progressive, painful sensory polyneuropathy. Within 2 or 3 days of exposure, patients will describe painful burning paresthesias in their feet. These paresthesias can progress up the legs and, over time, can involve the hands. Motor nerves can also be affected, and profound weakness, including in respiratory muscles, can be misdiagnosed as Guillain-Barré syndrome (Chapter 388). Cranial neuropathies have also been reported. Thallium toxicity causes painless hair loss, typically beginning 5 to 14 days after exposure and sometimes progressing to total body alopecia. Skin and nails can also be affected, with scaling of palms, acne-like lesions of the face, and Mees lines in the nails. Other neurologic symptoms of thallium poisoning include hallucinations, altered mental status, insomnia, psychosis, ataxia, and coma. Constipation, myalgias, pleuritic chest pain, arrhythmias, and hypotension can also occur.

Systemic toxicities often develop before hair loss and because not all patients lose their hair, clinicians should consider thallium as a possible cause of any rapidly progressive painful neuropathy. In patients with thallium poisoning, a pulled hair will often have darkening of the hair root when visualized under a low-power light microscope.

FIGURE 20-1. Frontal and side views of a 36-year-old woman with argyria show the gray discoloration of her face and neck. (From Jacobs R. "Argyria: my life story," *Clin Dermatol*. Elsevier, 2006;24:66-69. Figure 3.)

DIAGNOSIS AND TREATMENT

The diagnosis of thallium poisoning requires the identification of elevated concentrations of thallium in a 24-hour urine sample (normal, <20 μg/specimen). Because thallium undergoes enterohepatic circulation and is eliminated in the feces, treatment requires binding of thallium in the gut. The most effective antidote is Prussian blue (a complex of potassium hexacyanoferrate), with recommended doses ranging from 3 g orally three times a day up to 250 mg/kg three times a day. Patients with thallium toxicity have received plasma exchange and continuous renal replacement therapy, but the benefit of these therapies is unknown.[24]

ZINC (MYELOPATHY)

Zinc (Zn) is an essential mineral that is necessary for normal cellular functioning. It is involved in the catalytic activity of more than 200 enzymes and plays an important role in olfaction, taste, immune function, protein synthesis, and DNA synthesis. It is found naturally in a wide variety of foods and is absorbed in the jejunum, where it binds to metallothioneins. Patients at risk for zinc deficiency include those with intestinal bypass, Crohn disease, and patients receiving total parenteral nutrition without adequate zinc supplementation. Zinc deficiency is manifested as a triad of dermatitis, diarrhea, and alopecia, which is reversible after zinc repletion.

In the setting of zinc overload, metallothioneins are upregulated; because copper has a higher affinity for metallothioneins, the result is increased copper binding and subsequent elimination of copper. Zinc-induced copper deficiency has been reported after overuse of zinc-containing supplements, with the improper use of zinc-containing denture adhesives, and from the presence of retained zinc-containing coins such as pennies.

The hematologic manifestations of zinc-induced copper deficiency include sideroblastic anemia, leukopenia, neutropenia, and myelodysplastic syndrome, all of which are reversible with zinc cessation alone. In addition, a syndrome of myeloneuropathy,[25] characterized by a spastic gait and sensory ataxia, is also associated with zinc overload/copper deficiency and may improve with copper supplementation and zinc cessation.[26]

Diagnostic testing in patients suspected of zinc overload should include serum or urine zinc concentrations (Table 20-1), serum copper levels, and ceruloplasmin levels. In patients with myeloneuropathy, nerve conduction studies may show a sensory neuropathy, and MRI may show increased T2 signal in the dorsal columns of the cervical spinal cord.

TREATMENT

Treatment of zinc overload–induced copper deficiency is primarily by cessation of zinc exposure and repletion of copper. Although there is no standard dosing regimen, a common recommendation is 2 to 8 mg/day of oral elemental copper. Various chelation regimens have been reported, but data are insufficient to support their routine use in the setting of chronic toxicity.

MANGANESE (PARKINSONISM)

Manganese (Mn) is an essential element necessary for the function of several enzymes, including superoxide dismutase and glutamine synthetase. Although there is no clear syndrome associated with manganese deficiency, a well-described constellation of symptoms and findings is associated with manganese toxicity. Dose-dependent manganese toxicity, primarily with chronic occupational exposure, results from inhalation of high concentrations of either manganese dust (e.g., in miners) or manganese fumes (e.g., smelting, grinding, and rarely welding). Toxicity has also been reported with overuse of supplements or use of illicit methcathinone synthesized with potassium permanganate.

The mechanism of neurotoxicity from manganese exposure is likely multifactorial, including neuroinflammation, dysregulation of mitochondrial function and cell signaling, oxidative stress, altered metabolism of neurotransmitters, and alterations in manganese transporters and homeostasis.[27] Manganese causes selective toxicity in the globus pallidus, striatum, and substantia nigra pars reticulata.

CLINICAL MANIFESTATIONS

The symptoms of manganism develop insidiously after years of exposure. Patients first develop changes in appetite, muscle weakness, and apathy. On occasion, patients will develop signs of central excitation and can have what is termed manganese psychosis. Symptoms often progress to difficulties with gait, speech, and facial expression.[28] The gait abnormalities involve a slow and clumsy gait with the inability to walk backward. Patients often freeze while turning and frequently fall. Symptoms can progress to muscle hypertonia in extension and a peculiar gait in which patients walk on the balls of the feet with their ankles extended. Patients also develop stuttering speech, masked facies, sleep disturbances, and myalgias. Unlike with idiopathic Parkinson disease (Chapter 378), patients with manganism do not typically develop a resting tremor or resting dementia, and their symptoms do not typically respond to levodopa therapy.[29]

DIAGNOSIS

Although there is no definitive test of manganese toxicity, a history of exposure, confirmatory laboratory testing (Table 20-1), radiographic studies, and clinical symptoms can support the diagnosis. The best laboratory test is a whole blood manganese level (normal, <15 μg/L), with elevated levels indicative of exposure but not necessarily correlating directly with symptoms. Because manganese can concentrate in the globus pallidus, MRI often will show an intense T1-weighted signal in the globus pallidus bilaterally. However, MRI is indicative of manganese exposure but does not correlate with clinical symptoms. Because of the differences in the affected brain regions between manganese toxicity and Parkinson disease, fluorodopa positron emission tomography (PET) scanning can help differentiate between these disorders: patients with manganese toxicity will typically have normal PET scans, whereas patients with Parkinson disease have abnormal scans.

TREATMENT

Manganism is not typically responsive to treatment, but removal from exposure is important. Although chelation with $CaNa_2EDTA$ has been associated with increased urinary elimination of manganese, patient outcomes would not be expected to improve with chelation.

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IV

AGE-SPECIFIC AND GERIATRIC MEDICINE

21 ADOLESCENT MEDICINE

22 EPIDEMIOLOGY OF AGING

23 GERIATRIC ASSESSMENT

24 COMMON CLINICAL SEQUELAE OF AGING

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21 ADOLESCENT MEDICINE

DEBRA K. KATZMAN AND S. TODD CALLAHAN

Adolescence, a period of transition between childhood and adulthood, is marked by critical biologic, psychological, social, and cognitive changes. During this unique developmental period, patterns of behaviors and lifestyle choices are established that can influence current and future health, and unique medical and psychological problems can emerge. Adult-oriented health care providers play a pivotal role in engaging youth in their health and in providing health care to adolescents.

NORMAL PHYSICAL GROWTH AND DEVELOPMENT

Biologic growth and development in adolescents are signified by the onset of puberty (Chapter 217), which varies temporally among adolescents and explains why adolescents of the same chronologic age can vary greatly in physical appearance. The first visible sign of puberty among girls is usually thelarche, or the development of breast buds, which occurs on average at 10 years in White girls and 1 year earlier in African American girls (Chapter 217).

Menarche occurs 2 to 4 years after the initial appearance of breast buds and pubic hair. The average age of menarche is 12.9 years for White American girls and 12.2 years for African American girls. Menstrual periods are not always regular during the first 2 years after menarche. At menarche, only 20% of cycles are ovulatory; it may take up to another 4 years for 80% of cycles to be ovulatory. The average time for completion of puberty in girls is 4 years (range, 1.5 to 8.0 years).

Puberty begins about 1 year later in boys than in girls. The first physical signs of puberty in boys, testicular enlargement and thinning of the scrotum, occur at 10 years. Adrenarche usually begins about 6 months later (Chapter 216), and facial hair appears about 3 years after the appearance of pubic hair. The completion of puberty in boys averages 3 years (range, 2 to 5 years).

Pubertal weight gain accounts for about half of a person's ideal adult body weight. Peak weight gain follows the linear growth spurt by 3 to 6 months in adolescent girls and by about 3 months in adolescent boys. The average weight gain during puberty among adolescent girls is 15 to 55 lb or 7 to 25 kg (mean gain, 38.5 lb or 17.5 kg). Overall, adolescent boys gain 15 to 65 lb or 7 to 30 kg during puberty (mean gain, 52.2 lb or 23.7 kg).

Boys' body fat levels decrease during adolescence, dropping to 12% body fat by the end of puberty. On average, adolescent girls' lean body mass falls from 80 to 75%, whereas their average body fat levels increase from 16 to 27% by the end of adolescence. By the time adolescent girls are 16 years of age and adolescent boys are 18 years of age, they have accrued more than 90% of their adult skeletal mass.

Sexual maturity ratings (SMRs), also known as Tanner stages, are used to describe the progression of secondary sexual characteristics that occur in adolescents, irrespective of chronologic age. SMR is based on the development of breasts and the appearance of pubic hair among girls (E-Fig. 21-1) and on testicular and penile development and the appearance of pubic hair among boys (E-Fig. 21-2). SMR 1 corresponds to the prepubertal stage: puberty has not begun and no sexual development has occurred. SMR 2 to SMR 5 indicates the progression of puberty to adulthood. Once young people reach SMR 5, they have fully developed secondary sexual characteristics. Sexual maturation correlates with linear growth, changes in weight and body composition, and hormonal changes.[1] Sexual maturation provides important assurance of the normal progression of puberty or identification of abnormal pubertal development.

NORMAL PSYCHOSOCIAL DEVELOPMENT

Adolescence is often divided into three psychosocial developmental phases: early adolescence (11 to 13 years), middle adolescence (14 to 16 years), and late adolescence (17 to 21 years). In early adolescence, adolescents begin to separate from their parents and establish an individual identity. As adolescents pull away from parents in search of their own identity, their peer group begins to take on increasing salience.

At the beginning of adolescence, cognitive abilities are dominated by concrete thinking. Young adolescents lack abstract reasoning capabilities, problem-solving skills needed to overcome barriers to behavioral changes, and the ability to appreciate how current behaviors can affect future health status.

Middle adolescence is characterized by growth in emotional autonomy and increasing separation from family. The adolescents' peer groups play a powerful role, and adolescents are increasingly involved in partnering relationships that include dating, sexual experimentation, and adverse health behaviors such as smoking cigarettes, drinking alcohol, using street drugs, and being truant. Abstract reasoning skills emerge but often regress to concrete thinking when adolescents are faced with stressful situations. These adolescents begin to understand the relationship between health behaviors and future health status, but peer pressure may make it challenging for them to make appropriate health-related choices.

During late adolescence, young people become increasingly more emotionally independent. Peer group values become less important, and young people spend more time in a relationship with one person. This late stage of adolescence is characterized by the development of a strong personal identity. Abstract reasoning skills expand, and older adolescents have problem-solving skills that help them overcome challenges to behavioral change.

VITAL STATISTICS

Morbidity and mortality among 10- to 19-year-olds are often the result of risky behaviors and environmental factors (Table 21-1).[2] Unintentional injury is the leading cause of death in this age group. Malignant neoplasms, suicide, and homicide are the next three leading causes. Most deaths due to intentional injury (i.e., suicide and homicide) are theoretically preventable.

UNINTENTIONAL AND INTENTIONAL INJURIES

Unintentional injuries account for 25 to 35% of all deaths among 10- to 19-year-olds. Major causes of unintentional injuries include motor vehicle accidents, drowning, fire, poisoning, and falls. Factors that contribute to adolescent injuries include socioeconomic factors (adolescents from low-income families are at greatest risk for injury), environmental factors (hazards such as all-terrain vehicles, backyard swimming pools, firearms, kerosene heaters, and gang activity), school environment, and developmental factors.

Suicide (Chapter 362) rates have been increasing among 10- to 19-year-olds since 1999, and suicide is now the second leading cause of death among youth 10- to 14-year-olds and 15- to 19-year-olds. In both age groups, Native Americans have the highest rates, followed by White American youth; African American and Asian American youth have substantially lower rates. The rate of attempted suicide is almost five times greater among gay, lesbian, and transgender (sexual minority) students (29%) compared with heterosexual students (6.4%).[3] The estimated ratio of attempted-to-completed suicides among adolescents ranges between 50:1 and 100:1. The most common methods used in suicide attempts are drugs and alcohol, whereas suffocation, hanging, or use of firearms is associated with completed suicides. Suicide death rates caused by firearms are almost seven times higher in 15- to 19-year-old boys than in comparably aged girls.

Homicide is the third leading cause of death among 15- to 19-year-olds and the fourth leading cause among younger adolescents. Among African American males, however, it is the leading cause of death among 15- to 19-year-olds

TABLE 21-1 LEADING CAUSES OF DEATH AMONG 10- TO 19-YEAR-OLDS, U.S., 2019

AGES 10-14		*AGES 15-19*	
CAUSE	**NUMBER (%)**	**CAUSE**	**NUMBER (%)**
All causes	3,164 (100)	All causes	10,258 (100)
Unintentional injury	778 (24.6)	Unintentional injury	3,537 (34.5)
Suicide	534 (16.9)	Suicide	2,210 (21.5)
Malignant neoplasms	404 (12.8)	Homicide	1,877 (18.3)
Homicide	191 (6.0)	Malignant neoplasms	589 (5.7)
Congenital anomalies	189 (6.0)	Heart disease	288 (2.8)
Heart disease	87 (2.7)	Congenital anomalies	188 (1.8)
Chronic lower respiratory disease	81 (2.6)	Influenza and pneumonia	71 (0.7)
All others	900 (28.4)	All others	1,498 (14.6)

Data from the Centers for Disease Control and Prevention's Web-based Statistics Query and Reporting System (WISQARS™). Available at https://wisqars.cdc.gov/data/lcd/home. Accessed March 13, 2023.

ABSTRACT

Adolescence, a period of transition between childhood and adulthood, is marked by critical biologic, psychological, social, and cognitive changes. During this developmental period, behaviors and lifestyle choices can influence current and future health, and medical and psychological problems can emerge. Adult-oriented health care providers play a pivotal role in engaging youth in their health and in delivering health care to adolescents.

KEYWORDS

adolescent
adolescence
transition
physical growth and development
mental health
confidentiality
sexual maturity rating

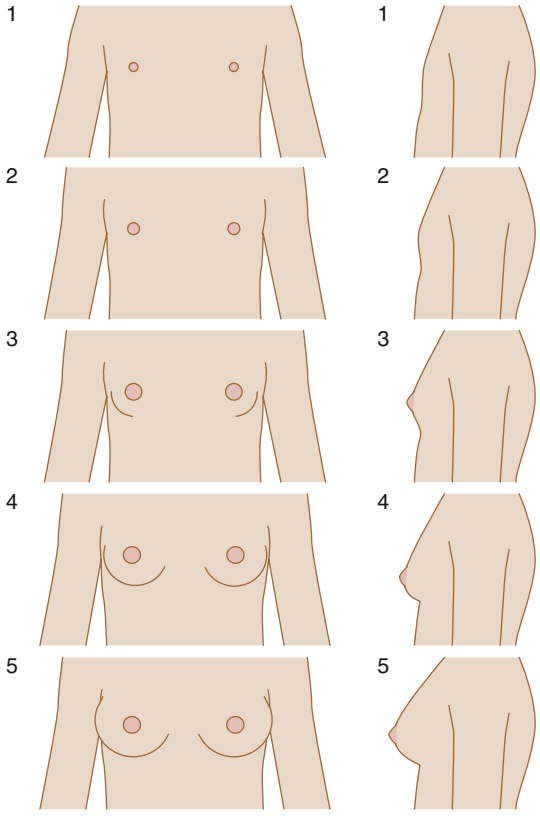

E-FIGURE 21-1. Female breast development. *Sexual maturity rating 1 (SMR 1):* Preadolescent; no glandular tissue. Areola and papilla: Areola conforms to general chest line. *SMR 2:* Breast buds appear; areola is slightly widened and projects as small mound. *SMR 3:* Enlargement of the entire breast with protrusion of the papilla or of the nipple. Breast and areola enlarge with no separation of their contours. *SMR 4:* Enlargement of the breast and projection of areola and papilla as a secondary mound. *SMR 5:* Adult configuration of the breast with protrusion of the nipple; areola no longer projects separately from remainder of breast. (Redrawn from Daniel WA, Paulshock BZ. A physician's guide to sexual maturity rating. *Patient Care*. 1979;30:122. Original illustration by Paul Singh-Roy.)

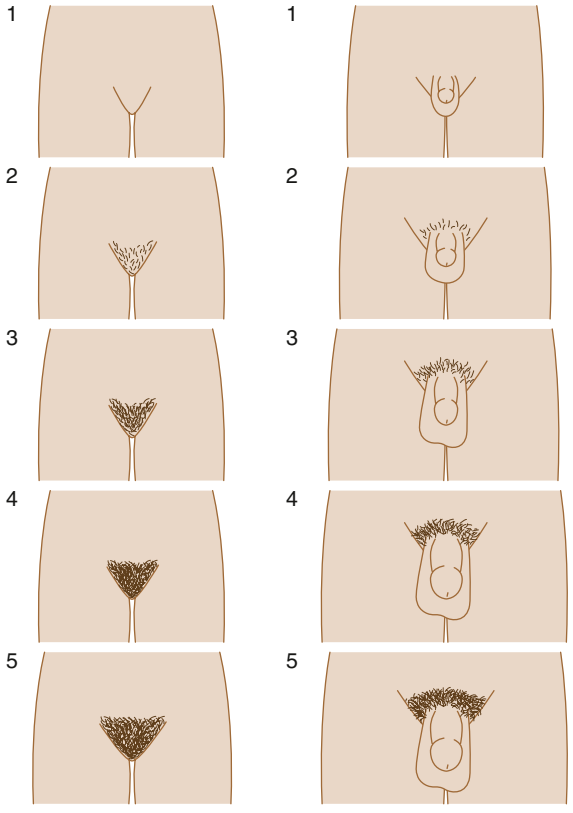

E-FIGURE 21-2. Female *(left)* and male *(right)* pubic hair development. *Sexual maturity rating 1 (SMR 1):* Prepubertal; no pubic hair. *SMR 2:* Small amount of scanty, long, slightly pigmented, along the base of the scrotum and phallus in the male and the medial border of the labia majora in females. *SMR 3:* Darker, coarser, starts to curl, small amount, extending laterally. *SMR 4:* Coarse, curly; resembles adult type but does not extend to the medial surface of the thighs. *SMR 5:* Abundant, adult-type pattern; hair extends onto the medial aspect of the thighs. *Right*, Male genital development. *SMR 1:* Penis preadolescent. Testicular volume <4 mL. *SMR 2:* Penis slight or no enlargement. Beginning enlargement of testes; testicular volume 4 to 8 mL; scrotal skin reddened, thinner. *SMR 3:* Penis increased in length. Testicular volume 10 to 15 mL. Further enlargement of scrotum. *SMR 4:* Penis larger in breadth, glans penis develops. Testes and scrotum nearly adult; testicular volume 12-20 mL. *SMR 5:* Penis adult size; testicular volume greater than 25 mL. (Redrawn from Daniel WA, Paulshock BZ. A physician's guide to sexual maturity rating. *Patient Care*. 1979;30:122. Original illustration by Paul Singh-Roy.)

(97% involving firearms) and the second leading cause among those 10 to 14 years old (92% firearm-related).

Approximately 1 in 8 9th- to 12th-grade students who dated or "went out with someone" report being the victim of physical or sexual dating violence in the prior 12 months.[4] For both physical and dating violence, the prevalence is higher among females than males (9 versus 7% and 13 versus 4%, respectively). Among 9th- to 12th-grade students, almost 16% report being electronically bullied and 20% report being bullied on school property. Being the victim of bullying is associated with a wide variety of mental health problems. When adolescent bullies become adults, they are more likely than their peers to become violent or abusive towards partners, spouses, and children.

OTHER DISEASES

Excluding intentional and unintentional injuries, cancer is the leading cause of death in adolescents. Cancers of major importance in adolescents include Hodgkin lymphoma (Chapter 172), germ cell tumors (Chapter 185), central nervous system tumors (Chapter 175), non-Hodgkin lymphoma (Chapter 171), thyroid cancer (Chapter 207), malignant melanoma (Chapter 188), and acute lymphoblastic leukemia (Chapter 168).

In adolescents, the course of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection tends to be much milder than in adults, but severe illness, death, and long-term adverse effects can occur.[5] Vaccines against SARS-CoV-2 are at least as effective in adolescents as in young adults.[6]

APPROACH TO THE ADOLESCENT PATIENT

When interviewing adolescent patients, the clinician should consider their physical, cognitive, and psychosocial developmental stage; their growing autonomy and increasing role in taking responsibility for managing their own health and well-being; and their individual progression from childhood to adulthood. Chronologic age is not a guarantee that all adolescents will be at the same stage of development. The clinician should offer adolescent health care in a sensitive, flexible, and developmentally and culturally appropriate manner.

The clinician can meet with the adolescent alone at first to give the message that the adolescent is the patient and the clinician is most eager to hear what the adolescent has to say. This is also an opportunity to assess the adolescent's capacity for autonomous decision making. Conversely, the clinician can meet with the adolescent and their parents or guardians together for the initial part of the interview and then meet with the adolescent alone; this approach permits the clinician to develop an understanding of the reason for the visit from the perspective of the adolescent and the adolescent's parents or guardians and to communicate that input from both the adolescent and the parents or guardians is highly valued. This approach also provides an opportunity for the clinician to observe the interaction between the adolescent and parents or guardians. The final approach to the interview is to greet the adolescent and family and request a meeting with the parents or guardians alone. This approach allows the parents or guardians to discuss concerns about the adolescent that they may not feel comfortable raising in the presence of the adolescent. Having this information may improve the focus of the visit. In this approach, the encounter with the parents or guardians is then followed by the clinician's meeting with the adolescent alone. With this interview structure, it is important that the adolescent be present from the time the adolescent meets with the clinician until the end of the visit, so that the adolescent does not perceive a breach of confidentiality.

CONFIDENTIALITY

Issues of consent and confidentiality are central in the clinician-adolescent interaction. When confidentiality is guaranteed, adolescents are more likely to seek necessary medical care, to disclose sensitive information, and to trust their clinician. Under these circumstances, most adolescents will involve their parents in their care at some point. Parents appreciate education about the concept of confidentiality and recognize the importance of allowing the adolescent the opportunity to speak alone with the clinician. Confidentiality is also important for clinicians to make an accurate diagnosis and to provide treatment.

Confidentiality and defining the limits of confidentiality should be discussed with the adolescent and their parents or guardians at the beginning of the interview. The adolescent and family need to know that the clinician will intervene if the clinician believes that the adolescent's actions may cause the adolescent, or another person, significant harm or that the adolescent is in imminent danger. Examples of situations in which the clinician would not maintain confidentiality when dealing with young people include disclosure of current suicidal or homicidal intent. The legal definition of confidentiality varies, depending on geographic location, and clinicians should be familiar with local laws.

Another goal of the interview is to build rapport with the adolescent and their parents or guardians. Clinicians can establish rapport at the start of the interview by creating an environment that is nonjudgmental, unintimidating, and supportive. It is helpful to encourage the adolescent to talk about themself—friends, hobbies, school. The clinician should listen carefully to the adolescent's statements and feelings. Sensitivity to and understanding of the adolescent's developmental stage, sexual orientation, gender identity, and cultural background are important in interviewing and interpreting answers accurately. The clinician should be respectful of the adolescent's growing need to be independent and desire to be treated as an individual person. Taking the time to build rapport is key to engaging the adolescent in a discussion of their personal health concerns with the clinician.

PREVENTIVE HEALTH CARE

Preventive health care for adolescents (Chapters 12 and 15) should promote physical and mental health and healthy physical, psychological, and social growth and development. Positive behaviors such as exercise (Chapter 14) and nutritious eating (Chapter 13) should be encouraged, and health risk behaviors such as unsafe driving, high-risk sexual behaviors, and use of tobacco (Chapter 363), drugs, and alcohol (Chapter 364) should be discouraged. Because lifelong health habits are established during adolescence, it is an important time to invest in health promotion and preventive services.

The U.S. Preventive Services Task Force recommends screening and counseling of all adolescents about depression[7] and obesity and ensuring that all adolescents are up-to-date on their immunizations for tetanus, diphtheria, pertussis, varicella, measles, mumps, rubella, hepatitis A and B, meningococcus (A, C, Y, W-135), influenza, polio, and human papillomavirus (HPV; Chapter 15). In addition, at-risk adolescents should be counseled about sexually transmitted infections (e.g., human immunodeficiency virus [HIV], chlamydia, gonorrhea, and syphilis) and advised about immunizations for pneumococcus and meningococcal serotype B.

COMPONENTS OF THE ADOLESCENT CARE HEALTH VISIT

History

Open-ended, nonjudgmental, developmentally appropriate, and gender-neutral questions help put the adolescent at ease and produce informative answers (Chapter 12). In addition to a standard medical history, the assessment should include a psychosocial history from the adolescent, either through a screening questionnaire or during the interview with the adolescent alone. The HEEADSSS assessment, a valuable screening tool for obtaining a comprehensive psychosocial history, covers the following topics:

- **H**ome: family members, living arrangements, and relationships
- **E**ducation/**E**mployment: academic or vocational success and future plans
- **E**ating: concerns about weight or body image or disordered eating attitudes and behaviors; dietary intake
- **A**ctivities: recreational activities, dating, and relationships
- **D**rugs: use of tobacco or e-cigarettes, alcohol, illicit drugs, anabolic steroids, nonmedical use of prescription medications, and driving while intoxicated or after using drugs
- **S**exuality: sexual orientation, sexual behaviors (including abstinence), and sexual abuse
- **S**uicide (mental health): feelings of sadness, loneliness, depression; or suicidal ideation, attempts, and nonsuicidal self-injury
- **S**afety: risk of unintentional injury or violence, fighting; or weapon carrying; seat belts when driving motor vehicles; bicycle helmets, and sports-related protective gear.

Physical Examination

In general, the adolescent physical examination should occur without a parent or guardian present. In some situations, the adolescent is asked whether they would prefer to have a chaperone in the room during the physical examination. A male clinician should request that a female chaperone be present during the physical examination of a female patient, especially during the breast and genital examination. In theory, a female clinician should request a male chaperone be present during the genital examination of a male patient.

Care should be taken to ensure the adolescent's privacy. Providing an examination gown that covers the trunk and genital area is important. Talking with the adolescent during the examination also tends to increase comfort; explaining the procedures and commenting on the results are helpful. A comprehensive physical examination (Chapter 12) should include measuring the adolescent's weight and height, calculating their body mass index, plotting these measurements on standardized growth charts, and determining the adolescent's SMR.

Adolescent cardiovascular risk factors are associated with adult cardiovascular events.[8] However, the U.S. Preventive Services Task Force currently states that it cannot make recommendations for or against screening adolescents for high blood pressure.[9]

A thorough sexual history must be obtained to determine which anatomic sites (oral, anal, vaginal, urethral) should be screened for sexually transmitted infections. Annual screening for *Chlamydia trachomatis* and *Neisseria gonorrhoeae* is recommended for sexually active adolescents. A self-collected vaginal swab is the preferred specimen for testing women, whereas a first-catch urine specimen is preferred for men to screen for urethral infection (and is acceptable for women as well). Adolescents 13 years and older should be screened at least once for HIV infection. Screening intervals for all sexually transmitted infections should be based on the patient's sexual behaviors.

Routine cervical cancer screening is not recommended in adolescents.[10] However, screening is appropriate in young women with HIV infection, human papillomavirus infection, immune deficiency, or a prior abnormal cervical screening result. Indications for a pelvic examination in an adolescent include symptoms of vaginal or uterine infection, menstrual irregularities (e.g., amenorrhea, dysfunctional uterine bleeding, menorrhagia, and severe dysmenorrhea), undiagnosed abdominal or pelvic pain, tenderness, mass, trauma, sexual abuse, or assault.

Conclusion of the Health Visit

At the conclusion of the adolescent health visit, the clinician should review the findings with the adolescent and talk about what happens next. The adolescent should have the opportunity to ask questions, get clarification, make comments, and respond to suggestions. The clinician should discuss with the adolescent what information will remain confidential. The clinician should then meet with the adolescent and the parents or guardians (if they have accompanied the adolescent to the health visit) to review the outcomes and to discuss the nonconfidential issues.

SEXUAL AND REPRODUCTIVE HEALTH

Care related to sexual and reproductive health includes issues of adolescent sexual development, sexual orientation, sexual behaviors, gender identity (Chapter 214), pregnancy, and, if indicated, contraception. When obtaining a sexual history, it is important that clinicians avoid assumptions about a teen's gender identity, gender expression, or sexual attraction; doing so will likely preclude receiving correct information.

In the United States, the percentage of teens having sex before the age of 13 is 3.4%: 2.0% of girls and 4.8% of boys.[11] The proportion of young people who have had sexual intercourse increases as they age through adolescence: one in five 15-year-olds and two-thirds of 18-year-olds report having had sex.[12] About 40% of adolescents aged 15 to 19 years reported ever having had penile-vaginal intercourse, 45% ever having had oral sex with a different-sex partner, and 9% ever having had anal sex with a different-sex partner. Among adolescents aged 15 to 19 years who had had penile-vaginal sex, 75% of females and 48% of males reported that their first intercourse was with a steady partner.[13] About 10% of adolescents have had four or more sex partners during their lives, and over 50% of sexually active high-school students report condom use during their last sexual encounter. Nearly 12% of adolescent females between 9th and 12th grade report having been forced to have intercourse. Adolescents are more likely to report engaging in oral than in vaginal sex because they perceive oral sex as significantly less risky (fewer health, social, and emotional consequences) than vaginal sex, but adolescents who engage in oral sex also are more likely to engage in vaginal sex.

In 2019, about 170,000 babies were born to women aged 15 to 19 years in the United States. This birth rate of 16.7/1,000 women in this age group represented an historic low for the United States.[14] Even so, the United States has the highest adolescent birth rate of any developed country. Adolescent pregnancy is more common among American Indian/Alaska Native, Black, and Hispanic girls, as well as among girls from low-income families. Abortion rates in this age group have decreased by almost 50% since 1990, mostly attributable to decreased sexual activity and increased use of effective contraception.

CONTRACEPTION

The use of effective contraceptive methods is a cornerstone of preventing adolescent pregnancy. Sexually active teens require ready access to confidential care that offers effective, safe, and affordable types of birth control. The most commonly used contraceptive method in adolescents is the condom, followed by withdrawal and oral contraceptive pills.[15] Hormonal delivery systems, such as transdermal patches, vaginal rings, and long-acting reversible contraceptives, are convenient and effective (Chapter 220). Long-acting reversible contraceptive methods (intrauterine devices and contraceptive implants) are now recommended as the contraceptive method of choice for young women because of their high effectiveness. In choosing a method of contraception, dual protection against HIV and other sexually transmitted infections should be recommended. Routine counseling about and advance provision of emergency contraception is an important part of the public health strategy to reduce teen pregnancy rates (Chapter 220).

SEXUALLY TRANSMITTED INFECTIONS

Young people ages 15 to 24 account for over half (55%) of all new sexually transmitted infections in the United States (Chapter 264). In 2019, adolescents 15 to 19 years of age accounted for 25% of the reported cases of chlamydia (Chapter 294) and 15% of the cases of gonorrhea (Chapter 275) in the United States. The overall prevalence of *Chlamydia trachomatis* infections among 14- to 19-year-olds is approximately 2%, but the prevalence varies and is higher among young women than men. In adolescents, HIV infection (Chapter 353) is contracted primarily as a sexually transmitted infection, and youth 13 to 24 years of age represent over 20% of all new diagnoses of HIV infection in the United States. HPV (Chapter 344), which is the most prevalent of all sexually transmitted infections in 15- to 24-year-olds, has a prevalence of about 20% in adolescent girls 14 to 17 years of age. HIV and syphilis are of particular concern among African American and Hispanic male adolescents with same-sex partners.

Adolescents are at increased risk for acquiring sexually transmitted infections for several reasons, including elevated rates among sex partners and inconsistent or incorrect condom use. Sexual minority youth may have particular difficulty accessing appropriate sexual health services. Adolescent girls may have persistent cervical columnar epithelium that is more susceptible than squamous epithelium to infection with *Neisseria gonorrhoeae, Chlamydia trachomatis*, and HPV as well as lower levels of immunoglobulin A in their cervical mucus. For many adolescents, treatment may be delayed owing to an inability to access confidential health care services, lack of health insurance, stigma, shame, poverty, and drug use.

Chlamydial infections (Chapter 294) are overwhelmingly asymptomatic. When symptoms are present, they may be so mild or short-lived that they are easily ignored. Otherwise, clinical presentations and treatments of sexually transmitted infections (Chapter 264) in adolescents are similar to those in adults.

To maximize the likelihood of successful treatment of these infections, an observed single-dose therapy is preferred, when available. In addition, whenever possible, expedited partner therapy, which is the treatment of sexual partners without requiring a prior clinical evaluation or prevention counseling, reduces the risk of recurrent sexually transmitted infections better than standard management and should be used within 60 days wherever state law permits. Clinicians should consider the use of expedited partner therapy for partners exposed to heterosexual males and females with chlamydia or gonorrhea infections, especially when in-person evaluation and treatment are unlikely (Chapter 264).[16] For prevention, the U.S. Preventive Services Task Force recommends behavioral counseling for sexually active adolescents.[17]

OBESITY

The prevalence of obesity among adolescents between ages 16 and 19 years is 20%.[18] Obese adolescents are significantly more likely to become severely obese in adulthood. The health consequences of adolescent obesity include sleep apnea, diabetes and its complications,[19] and cardiovascular diseases. Interventions should focus on changing behavior, modifying diet,[A1] increasing physical activity, reducing screen time, assessing for obesity-related physical and mental health issues, and improving sleep patterns. Pharmacotherapy can be considered after a formal program of intensive lifestyle modifications has failed to limit weight gain or to ameliorate comorbidities.[A2] Bariatric surgery may be considered as an option for adolescents with severe obesity (Chapter 201).

MENTAL HEALTH

About 25% of female adolescents and about 10% of male adolescents in the United States have depression.[20] Approximately 75% of lifetime cases of depression[21] and anxiety (Chapter 362) start by age 24 years. The most common mental disorders in adolescents (age 13 to 18 years) in the United States by lifetime prevalence are anxiety (32%), behavior (19%), and mood disorders (14%). About 10% of adolescents have attention-deficit/hyperactivity disorder,[22] about half of whom are on medications.[23] Adolescents diagnosed with one of these mental health problems often have other comorbid disorders.

Screening for anxiety[24] and depression[25] is recommended in adolescents. Left undiagnosed or untreated, these disorders can influence development, education, social relationships, and participation in the workforce.

EATING DISORDERS

Eating disorders (Chapter 200) commonly begin during adolescence. For adolescent-onset eating disorders, early recognition and aggressive treatment are critical to a successful outcome. The medical complications of eating disorders in adolescents include faltering growth, pubertal delay, low bone mineral density, and changes in brain structure and cognitive function. These complications, which occur early in the disease process, may not be completely reversible.

The goals of treatment are to restore physical health, normal eating behavior patterns, and mental health and to reduce the impact of the eating disorder on the quality of life. Adolescents should be treated at a facility where the health professionals understand eating disorders and have experience in treating adolescents. Successful management strategies for adolescents with eating disorders include early restoration of a normal nutritional and physiologic state, involvement of the family in the treatment, and incorporation of an interdisciplinary team in the treatment. Family-based therapy is an effective first-line, outpatient treatment for adolescents with eating disorders and helps protect against relapse.

SUBSTANCE USE AND SUBSTANCE USE DISORDERS

Nearly half of adolescents try an illicit drug (Chapter 365) by the time they finish high school. Just over 60% of adolescents consume alcohol (Chapter 364) by the end of high school, and about 40% report having been drunk at least once in their life. Adolescents who begin using alcohol or drugs before 15 years of age are more than five times more likely to develop an addiction later in life compared with those who first use alcohol at 21 years of age.

Nearly 30% of 12th-grade students report vaping in the last 30 days, with 25% vaping nicotine and 12% vaping marijuana. About 25% of U.S. adolescents have used marijuana in the past year, a percentage that has remained relatively stable over the last decade with an increasing proportion using e-cigarettes or vaping systems as the delivery device. Similarly, adolescents are now more likely to use e-cigarettes than to smoke conventional cigarettes (Chapter 363); however, those who use e-cigarettes are more likely than nonusers to initiate conventional cigarette use as well.[26] In 2004, almost 10% of 12th-graders reported nonmedical use of prescription opioids (Chapter 365), but that number dropped to 2% in 2020.[27]

Adolescent drug use is the result of a complex interaction among genetic, social, environmental, and personal risk factors. Boys tend to initiate drug and alcohol use at younger ages than girls do, but once girls begin to experiment, they are just as likely as boys to use drugs. Boys are more likely to consume marijuana, steroids, and smokeless tobacco, whereas girls are more likely to use amphetamines and methamphetamine.

Adolescents with poor self-esteem and low motivation, as well as those without an attachment to school and/or with poor academic achievement, have a greater propensity for alcohol and drug use compared with those without these characteristics. Adolescents with a family history of alcohol or other drug use are also at greater risk. Adolescents are less likely to succumb to external pressures toward drug use if they have a strong sense of attachment to parents who clearly communicate their disapproval of drug use.

Signs and symptoms suggestive of substance use or substance use disorders include changes in physical appearance, poor hygiene or dress, wearing long-sleeved shirts to hide scarring at injection sites, persistent cough or bronchitis, difficulty sleeping, sudden weight loss or weight gain, sudden changes in personality, aggressive behavior, irritability, nervousness, giddiness, changes in peer group, increased isolation from peers or family, depression, loss of interest in once-favorite activities, decline in performance or attendance at school or work, forgetfulness, increased secretiveness, money or objects disappearing from the household, and prescription drugs that seem to be used up too quickly.

A validated screening tool for alcohol and substance use (Table 21-2) should be used in adolescents.[28] Those answering yes to one question should receive feedback regarding the adverse effects of substance use. Those who answer yes to two or more questions are at high risk for substance use problems and require further assessment or referral (Chapters 364 and 365).[A3] Urine drug testing has low sensitivity for detection of drug use, and there is no consensus about its role for screening of adolescents.

Alcohol and drug use contributes to more than 40% of adolescent deaths from motor vehicle crashes, to suicide attempts, and to an increased risk for subsequent use and dependence and related problems in adulthood. Historically, treatment for substance use disorders in adolescents and young adults has been based on abstinence. More recently, however, a harm-reduction approach has gained acceptance. Adolescents discontinue drug and alcohol use mainly because of concern about their negative effects, and community-based interventions can be effective. Individual interventions appear to have a larger effect size than family-based interventions[A4] in reducing alcohol abuse, with the effect size decreasing over time.

TABLE 21-2 CRAFFT SCREENING TOOL FOR DRUG AND ALCOHOL USE IN ADOLESCENTS

The adolescent is instructed, "Please answer these next questions honestly. Your answers will be kept confidential. During the past 12 months, did you …"
- Drink any alcohol (more than a few sips)?
- Smoke any marijuana or hashish?
- Use anything else to get high?

If the adolescent answers no to the three opening questions, the provider only needs to ask the adolescent the first question—the CAR question. If the adolescent answers yes to any one or more of the three opening questions, the provider asks all six CRAFFT questions.
- **C**—Have you ever ridden in a CAR driven by someone (including yourself) who was "high" or had been using alcohol or drugs?
- **R**—Do you ever use alcohol or drugs to RELAX, feel better about yourself, or fit in?
- **A**—Do you ever use alcohol/drugs while you are by yourself, ALONE?
- **F**—Do you ever FORGET things you did while using alcohol or drugs?
- **F**—Do your family or FRIENDS ever tell you that you should cut down on your drinking or drug use?
- **T**—Have you gotten into TROUBLE while you were using alcohol or drugs?

CRAFFT is a mnemonic acronym of the first letters of key words in the six screening questions. The questions should be asked exactly as written.

CHRONIC ILLNESS AND TRANSITION

The prevalence of chronic diseases in adolescents has increased significantly because advances in medical technology and treatments have increased the survival of young people with childhood diseases formerly considered lethal. About 18% of adolescents in the United States live with a chronic illness. Chronic illness may affect the adolescent's development, or the adolescent's development may affect the illness. For example, cystic fibrosis (Chapter 77) may delay puberty and hinder normal peer development. Puberty can exacerbate diabetes mellitus (Chapter 210). Increased risk-taking by adolescents with diabetes, asthma, or chronic renal failure can hinder their compliance with their medication regimen.

Adolescents in general, and those with special health care needs in particular, require a smooth, seamless, coordinated, and developmentally appropriate transition to support their engagement in the adult health care system.[29] The patient, family, and pediatric and adult health care systems should view the transition as a natural part of the developmental process of care for all adolescents. The recommended elements of a transition plan include early individualized planning and preparation of patient, family, and health care teams; tailored written transition plans; coordination by both the transferring and receiving physicians; introductory meetings for young adults with their new providers before transfer; transfer at a time of disease stability rather than during a period of instability; and the introduction of transition coordinators who act as liaisons between the pediatric and adult health care system.

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22 EPIDEMIOLOGY OF AGING

LOUISE ARONSON

DEMOGRAPHY

For decades, the world's population has aged at an unprecedented rate. Both proportions and absolute numbers of people living into old age have increased. As of 2020, 1 billion people were age 60 years or older, and by 2050 people over age 65 years are projected to account for 1 in 6 people worldwide. Between 1990 and 2019, people over age 80 nearly tripled, a number expected to triple again by 2050, thereby reaching 426 million. As a result of these marked shifts, the World Health Organization declared 2020 to 2030 the Decade of Healthy Ageing, and the United Nations has recognized aging as one of four global population "mega-trends."[1]

In 2021 in the United States, people ages 65 years and older accounted for 16% of the population, and people over age 80 years comprised 4% of the population, with those numbers expected to double and triple, respectively, by 2050.[2] So-called baby boomers (i.e., people born between 1946 and 1964 and one of the largest generations in American history) play a key role in shaping national demographic trends. By the 2030s, when all baby boomers are over age 65 years, older Americans will constitute 21% of the population, and the country will have more elderly people than children. Since millennials (people born between 1981 and 1995) outnumber baby boomers, these trends are projected to continue for generations.

Three demographic factors within this larger transformation have important implications for health. First, marked inequalities in life expectancies persist across ethnic and racial groups (Chapter 4), among sexual minorities, and in geographic location within the United States.[3] Second, a somewhat smaller but still significant gender gap exists in longevity. In 2019, for example, average life expectancy at age 65 years was 18.2 years for males and 20.8 years for females. Third, the longevity curve has flattened since 2010 as a result of a leveling of the decline in mortality from cardiovascular disease (Chapter 40) despite increases in deaths from drug overdose (Chapter 365), suicide (Chapter 362), obesity (Chapter 201), and Alzheimer disease (Chapter 371), as well as the emergence of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2; Chapter 336).[4] Improvements in life expectancy will therefore require attention to social determinants of health across the life span.

DISEASE AND DISABILITY IN OLDER ADULTS

MORBIDITY AND MULTIMORBIDITY

Over 85% of older adults have one or more chronic health conditions (Table 22-1), the most common of which are hypertension (Chapter 64), hyperlipidemia (Chapter 190), arthritis (Chapter 236), heart disease (Chapter 40), and diabetes (Chapter 210). The prevalence of individual diseases varies by sex, race, and ethnicity. For example, more older Black adults than White adults report hypertension (about 70% vs. about 55%), and more women have arthritis than men (about 60% vs. about 45%). Nevertheless, over 82% of adults ages 65 to 74 years and 73% of adults ages 75 years and older describe their overall health as good to excellent. Self-reported health worsens not only with advanced age but also by race; 12 to 14% of Native, Black, and Latino Americans report fair to poor health compared with just over 8% of White or Asian Americans. Over age 70 years, nearly 14% of Americans have dementia (Chapter 371) and a majority have sensory impairments, including problems with balance (75%), hearing (26%), and vision (15%). The lifetime risk of dementia increases with age, is higher in women than in men (for reasons that include greater longevity as well as hormonal and environmental factors), and is nearly two times higher in Black adults than White adults.

Multimorbidity, which is the state of having multiple comorbid conditions, is the norm with advancing age. About 65% of adults over age 65 years have two or more chronic health conditions, nearly a quarter have four or more such conditions, and the prevalence of multiple chronic conditions is increasing. After adjustment for other factors, Black adults have earliest onset and highest prevalence of multimorbidity, whereas Latino adults develop multimorbidity most rapidly with aging. Quality care of older adults requires consideration of sociodemographic risk, the impact of the treatment of one condition on others, the masking of diseases by symptoms of other diseases, and burden of the treatment.

The degree of multimorbidity predicts future disability. The proportion of older adults with self-reported difficulty in activities of daily living increases stepwise as their number of medical conditions increases. Multimorbidity is also associated with poorer lower extremity strength and balance, which are predictors of disability, and slower gait speed, which is a powerful predictor of mortality in old age. Multiple chronic diseases have more than an additive effect on physical functioning and hence disability.

GERIATRIC SYNDROMES

Geriatric syndromes (Chapter 24), which are common and highly morbid conditions in older adults, are not linked to a single disease or pathologic process but rather occur when accumulated impairments across multiple domains result in a single, recognizable phenomenon. For example, falls (Chapter 24) occur in people with a wide range of risk factors: poor vision, foot problems, cognitive impairment, disorders of gait and balance, fear of falling, sarcopenia, neurologic diseases, polypharmacy, and medications that can cause orthostatic hypotension. Other geriatric syndromes include urinary incontinence (Chapter 115), frailty (Chapter 24), impaired sleep (Chapter 374), delirium (Chapter 361), pressure ulcers (Chapter 24), cognitive impairment (Chapter 371), and malnutrition (Chapter 197). Geriatric syndromes adversely affect health outcomes and may be caused or exacerbated by medical treatments.

SUBCLINICAL DISEASE

The risks of disability and mortality among older adults are elevated by asymptomatic or unrecognized disease. Nonspecific symptoms may be inaccurately attributed to aging or a comorbid condition. For example, magnetic resonance imaging reveals subclinical vascular changes consistent with a prior stroke in about one third of older adults without a history of stroke. Although subclinical cardiovascular disease doubles the risk of falls, frailty, dementia, and death, when and how to intervene to prevent these outcomes remains unclear. Noninvasive testing also yields higher rates of conditions such as hypothyroidism (Chapter 207), peripheral arterial disease (Chapter 65), chronic obstructive pulmonary disease (Chapter 76), and osteoarthritis (Chapter 241) than are documented clinically, perhaps in part because other limitations mask their subclinical impact.

OBESITY

Obesity (Chapter 201) is a major cause of preventable life-years lost, and its impact on morbidity (e.g., physical limitations, diabetes) and mortality (e.g., cardiovascular disease, cancer) increases with age. Over age 60 years, about one third of White adults, 40% of Latino adults, and 50% of Black adults are obese. Obesity disproportionately affects older women, especially Black women and low-income women, in whom it increases the risk of disability, low quality of life, nursing home placement, and death. However, the prevalence of obesity declines after age 75 years, in part because of selective survivorship and in part because of the increasing prevalence of serious comorbid diseases that result from the pro-inflammatory state of obesity.

TABLE 22-1 U.S. ADULTS WITH CHRONIC CONDITIONS, MULTIMORBIDITY, 2018

	NO CHRONIC CONDITIONS		*1 CHRONIC CONDITION*		*≥2 CHRONIC CONDITIONS*	
AGE	**% POPULATION**	**N**	**% POPULATION**	**N**	**% POPULATION**	**N**
18 to 44 years	73%	83,444	21%	23,841	7%	7,723
45 to 64 years	37%	30,404	30%	25,250	33%	27,383
≥65 years	12%	6,382	24%	12,280	64%	32,748

Source: National Center for Chronic Disease Prevention and Health Promotion. https://www.cdc.gov/pcd/issues/2020/20_0130.htm.

DISABILITY

Disability in older adults can be slowly progressive and chronic (e.g., arthritis), subacute and potentially reversible (e.g., post-hospitalization), or sudden and catastrophic (e.g., after a stroke). Levels of disability range from challenges in work, social, or recreational activities, thereby requiring adaptation or substitution, to an inability to be independent in household tasks, to the loss of basic self-care capabilities and the need for long-term personal care (see Chapter 23).

Fortunately, most older adults are not disabled. Although some degree of loss in physical function with advancing age is inevitable, the effects of age are highly variable, both between and within individuals. For example, self-reported physical limitations are about 6.5% through age 45 years, but they increase to 17% between ages 46 to 64 years, to 27% at age 65 years, and to 45% at age 75 years and beyond. After age 65 years, the prevalence of physical disability is higher among women in each age subgroup, as well as in American Indians, Alaska Natives, Latinos, people below the federal poverty level, and people living in the South U.S. Census region. Between the ages of 65 to 74 years, just 4% of Americans need personal care, but that number rises to 21% in Americans over age 85 years.

Noncatastrophic disability has a preclinical phase, during which people limit or modify their function but are not yet disabled. The onset of disability occurs with frequent transitions between independent and dependent states, thereby often offering multiple opportunities for intervention.[5] Major disabling conditions include arthritis, cardiovascular disease, chronic back pain, and dementia. However, joint and cardiac disease do not always cause limitations in the elderly, whereas sensory impairment and falls have substantial impact on disability.

FRAILTY

Frailty (Chapter 24) is defined as an age-related syndrome of decreased physiologic reserve, increased vulnerability to stress, and adverse health outcomes. Its phenotype has been described as including at least three of the following: weakness, fatigue, low activity, slow movement, and weight loss.[6] Frailty is also characterized by poor physical function, accumulation of physical deficits, and the cumulative burden of disease. Loss of muscle mass, which is termed sarcopenia, is also a key component of frailty.[7] Experimental data suggest that sestrins, which are stress-induced regulators that affect cell metabolism, may be critical for maintaining muscle mass and strength.

The prevalence of frailty, which increases with age, is under 5% below age 70 years but rises steeply thereafter to over 30% above age 80 years. In all older age groups, frailty is more common in women than men, and it is more prevalent in populations with high rates of chronic disease and socio-demographic disadvantage.[8] Importantly, frailty is not a steady state; both progression and reversion are common, although it eventually usually becomes a pre-death condition.

In clinical settings, frailty can be assessed using a validated instrument (see Table 24-1). Weakness can be assessed in an office setting by measuring grip strength (<30 kg in men and <20 kg in women). Although frailty itself is a risk factor for poorer outcomes and high health care costs, it also is associated with falls, fractures, cognitive decline, depression, low quality of life, loneliness, disability, nursing home admission, and hospitalization.

MORTALITY

Mortality rises with age. U.S. death rates are 1.7% per year between the ages of 65 to 74 years, increasing to 4.3% per year between the ages of 75 to 84 years, and to 13.2% per year in Americans age 85 years and older.[9] Before the coronavirus-2019 (COVID-19) pandemic, the top five causes of death for Americans ages 65 and older were cardiovascular disease (37%), cancer (about 27%), chronic lower respiratory disease (about 8%), cerebrovascular disease (about 8%), and Alzheimer disease (about 8%). Since 1980, cardiovascular disease and cancer have remained the top causes of death, whereas death rates for Alzheimer disease, diabetes, and unintentional injuries have increased (Table 22-1). Cancer was the leading cause of death and diabetes the fifth most common among the young-old ages 65 to 74 years, whereas Alzheimer disease and stroke are more common in the old-old ages 85 years and older. In 2020, however, COVID-19 became the third leading cause of death among all older age subgroups (Fig. 22-1),[10] and especially in frail elderly.[11]

HEALTHY AGING

LONGEVITY AND HEALTHY AGING

About 15 to 25% of longevity is estimated to be heritable. Other key determinants include a mother's health during pregnancy, lifetime exposures to infectious diseases and environmental hazards, psychosocial stress, nutrition (Chapter 13), physical activity (Chapter 14), and avoidance of smoking

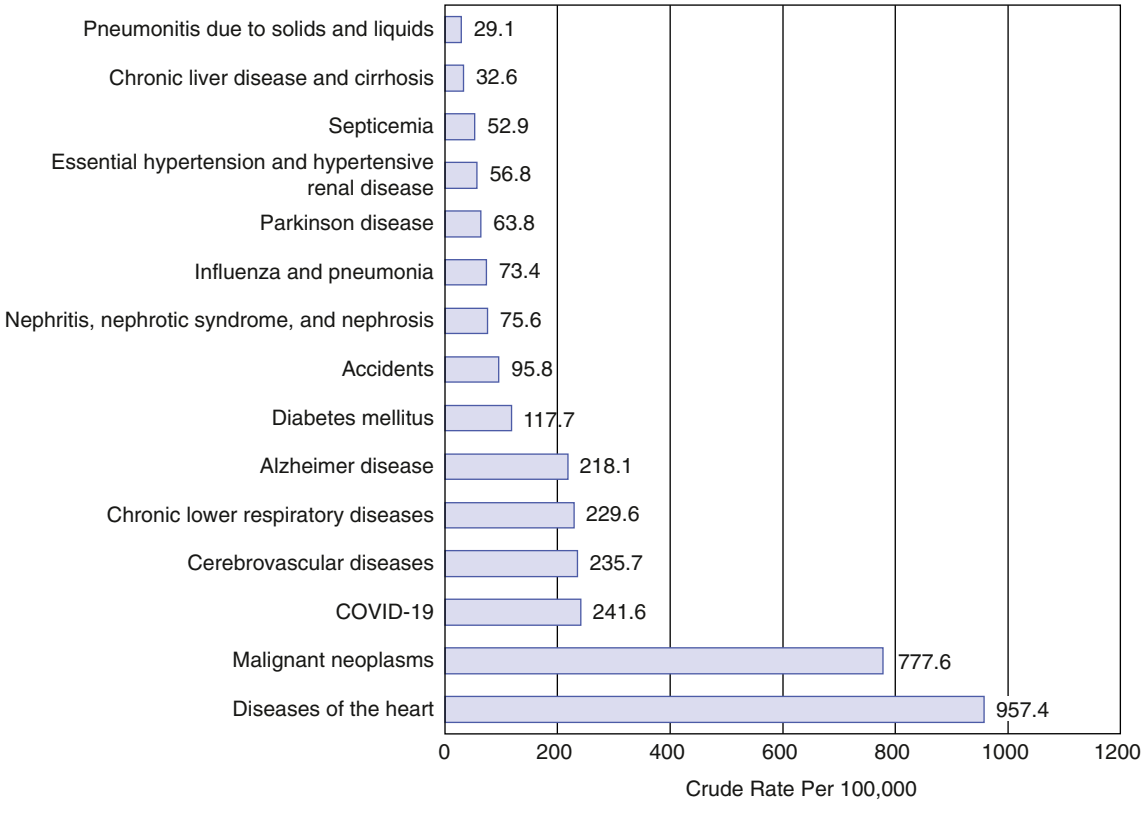

FIGURE 22-1. Underlying causes of death in Americans over age 65 years. (Centers for Disease Control and Prevention, National Center for Health Statistics. Provisional Multiple Cause of Death on CDC WONDER Online Database, released 2021. Data are from the final Multiple Cause of Death Files, 2018-2019, and from provisional data for years 2020-2021, as compiled from data provided by the 57 vital statistics jurisdictions through the Vital Statistics Cooperative Program. Accessed at http://wonder.cdc.gov/mcd-icd10-provisional.html on Dec 20, 2021 2:16:53 PM.)

TABLE 22-2 LIFE EXPECTANCY AND HEALTH EXPECTANCY AT AGE 60 BY GENDER AND GEOGRAPHY

	LIFE EXPECTANCY (IN YEARS)		*HEALTH LIFE EXPECTANCY (IN YEARS)*	
REGION	**MALE**	**FEMALE**	**MALE**	**FEMALE**
Global	**18.3**	**21.0**	**14.1**	**16.1**
Africa	16.0	17.6	12.1	13.3
Americas	19.8	22.9	15.5	17.7
Eastern Mediterranean	18.0	19.7	13.4	14.4
Europe	19.7	23.6	15.5	18.3
Southwest Asia	17.7	20.1	13.2	14.8
Western Pacific	18.5	21.6	14.4	16.6

Source: World Health Organization and United States Census Bureau. https://www.census.gov/library/stories/2021/05/long-life-does-not-always-mean-a-healthy-life-in-old-age.html.

(Chapter 363) and drugs of abuse (Chapter 365). Primary molecular pathways involved in aging include insulin and insulin growth factor-1, sirtuins, mechanistic target of rapamycin (mTOR), and AMP-activating protein kinase (AMPK). Each of these mechanisms affects autophagy, the catabolic process that enables cells to recycle dysfunctional material and maintain energy homeostasis. Metabolism, proteostasis, inflammation, epigenetics, macromolecular damage, and stem cells are among the critical, interrelated factors affecting healthy aging.

Emerging geroscience suggests the possibility that biological rate of aging may be slowed by nutritional, behavioral, genetic, and pharmacological interventions. Senolytics are compounds, such as flavonoids, that are being evaluated as potential supplements to slow the progression of aging.[12] Although many hormone levels decline with aging, hormone replacement with estrogen (Chapter 222), growth hormone (Chapter 205), testosterone (Chapter 216), and adrenal androgens (Chapter 208) have not been proven beneficial for longevity and have known harms.

Critical to consideration of longevity is the concept of "health span," defined by the World Health Organization as the average number of years lived in full health. Worldwide, life expectancy at age 60 years is 18.3 years in men and 21 years in women, but health life expectancy is only about 14 years in men and 16 years in women (Table 22-2).

Between 1991 and 2018, the health span of older Americans increased, with fewer elderly individuals reporting fair or poor health. Despite these overall gains, however, considerable disparities persist based on economic status, with fair or poor health reported by 21% of Americans age 65 years and older below the poverty level compared with just 4% of Americans in that age range with incomes at 400% of the poverty level or higher.

PREVENTION

Intensive blood pressure control to systolic blood pressure to less than 130 mm Hg lowers cardiovascular events in adults ages 60 to 80 years.[A1] Statins effectively reduce cardiovascular and all-cause mortality when used for primary prevention, even in individuals up to at least age 75 years.[A2] In healthy elderly, low-dose aspirin not only does not improve disability-free survival but also actually increases all-cause mortality.[A3] Antiresorptive and anabolic agents can slow the progression of osteoporosis and reduce the risk of fractures in women.[A4] Multifactorial interventions to prevent falls, fractures, and serious fall injuries do not appear to be helpful as currently designed.[A5,A6] Exercise reduces functional decline in community-dwelling elderly persons.[A7] Tai Chi continues to be the most effective exercise for preventing falls in community-dwelling older adults, whereas resistance training is useful to reduce the risk of disability.[A8] Biobehavioral approaches can decrease disability in low-income elders.[A9] Hearing aids significantly improve hearing-related function, but their long-term benefit to prevent disability or dementia is not yet known.[A10]

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23 GERIATRIC ASSESSMENT

C. SETH LANDEFELD

The goal of geriatric assessment is to improve quality of life, independence, and longevity by identifying conditions that may be ameliorated and by informing patients' decisions. Geriatric assessment evaluates specific domains that are often impaired in older people and that reduce quality of life, ability to live independently, and life expectancy; and the personal and social context of the older person.

RATIONALE

The premise of geriatric assessment is that older individuals desire "life, liberty, and the pursuit of happiness." Fulfillment of these desires depends on the older person's abilities, their environment, and the person-environment fit, all of which should be assessed and managed to achieve the older person's goals.

Geriatric assessment and management by a clinician or multidisciplinary team identifies conditions that are often undetected but can be ameliorated; they also provide information about prognosis, patients' values, and preferences.[1] Geriatric assessment improves outcomes in hospitalized older adults and in older adults with advanced cancer, and possibly in others.[A1–A5]

FUNCTION

Decline in the function of every organ system occurs at a rate of about 1% per year after age 30 years. Geriatric assessment evaluates functions that directly affect how older people live in the world each day. These functions generally depend on the central or peripheral nervous system, although they can be affected by dysfunction in other organ systems.

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Southwest Asia	17.7	20.1	13.2	14.8
Western Pacific	18.5	21.6	14.4	16.6

Source: World Health Organization and United States Census Bureau. https://www.census.gov/library/stories/2021/05/long-life-does-not-always-mean-a-healthy-life-in-old-age.html.

(Chapter 363) and drugs of abuse (Chapter 365). Primary molecular pathways involved in aging include insulin and insulin growth factor-1, sirtuins, mechanistic target of rapamycin (mTOR), and AMP-activating protein kinase (AMPK). Each of these mechanisms affects autophagy, the catabolic process that enables cells to recycle dysfunctional material and maintain energy homeostasis. Metabolism, proteostasis, inflammation, epigenetics, macromolecular damage, and stem cells are among the critical, interrelated factors affecting healthy aging.

Emerging geroscience suggests the possibility that biological rate of aging may be slowed by nutritional, behavioral, genetic, and pharmacological interventions. Senolytics are compounds, such as flavonoids, that are being evaluated as potential supplements to slow the progression of aging.[12] Although many hormone levels decline with aging, hormone replacement with estrogen (Chapter 222), growth hormone (Chapter 205), testosterone (Chapter 216), and adrenal androgens (Chapter 208) have not been proven beneficial for longevity and have known harms.

Critical to consideration of longevity is the concept of "health span," defined by the World Health Organization as the average number of years lived in full health. Worldwide, life expectancy at age 60 years is 18.3 years in men and 21 years in women, but health life expectancy is only about 14 years in men and 16 years in women (Table 22-2).

Between 1991 and 2018, the health span of older Americans increased, with fewer elderly individuals reporting fair or poor health. Despite these overall gains, however, considerable disparities persist based on economic status, with fair or poor health reported by 21% of Americans age 65 years and older below the poverty level compared with just 4% of Americans in that age range with incomes at 400% of the poverty level or higher.

PREVENTION

Intensive blood pressure control to systolic blood pressure to less than 130 mm Hg lowers cardiovascular events in adults ages 60 to 80 years.[A1] Statins effectively reduce cardiovascular and all-cause mortality when used for primary prevention, even in individuals up to at least age 75 years.[A2] In healthy elderly, low-dose aspirin not only does not improve disability-free survival but also actually increases all-cause mortality.[A3] Antiresorptive and anabolic agents can slow the progression of osteoporosis and reduce the risk of fractures in women.[A4] Multifactorial interventions to prevent falls, fractures, and serious fall injuries do not appear to be helpful as currently designed.[A5,A6] Exercise reduces functional decline in community-dwelling elderly persons.[A7] Tai Chi continues to be the most effective exercise for preventing falls in community-dwelling older adults, whereas resistance training is useful to reduce the risk of disability.[A8] Biobehavioral approaches can decrease disability in low-income elders.[A9] Hearing aids significantly improve hearing-related function, but their long-term benefit to prevent disability or dementia is not yet known.[A10]

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23 GERIATRIC ASSESSMENT

C. SETH LANDEFELD

The goal of geriatric assessment is to improve quality of life, independence, and longevity by identifying conditions that may be ameliorated and by informing patients' decisions. Geriatric assessment evaluates specific domains that are often impaired in older people and that reduce quality of life, ability to live independently, and life expectancy; and the personal and social context of the older person.

RATIONALE

The premise of geriatric assessment is that older individuals desire "life, liberty, and the pursuit of happiness." Fulfillment of these desires depends on the older person's abilities, their environment, and the person-environment fit, all of which should be assessed and managed to achieve the older person's goals.

Geriatric assessment and management by a clinician or multidisciplinary team identifies conditions that are often undetected but can be ameliorated; they also provide information about prognosis, patients' values, and preferences.[1] Geriatric assessment improves outcomes in hospitalized older adults and in older adults with advanced cancer, and possibly in others.[A1–A5]

FUNCTION

Decline in the function of every organ system occurs at a rate of about 1% per year after age 30 years. Geriatric assessment evaluates functions that directly affect how older people live in the world each day. These functions generally depend on the central or peripheral nervous system, although they can be affected by dysfunction in other organ systems.

ABSTRACT

Geriatric assessment aims to improve quality of life, independence, and longevity of older people by identifying conditions that may be ameliorated, informing a management plan, and guiding patients' decisions. Geriatric assessment broadens conventional management of chronic diseases and focuses on geriatric syndromes that worsen quality of life and shorten it. Geriatric assessment has four components. First, it assesses functions that are often impaired in older people. These functions include the ability to perform activities needed to live independently (functional status), continence, cognition, competency, mood, hearing, vision, mobility, risk of fall, nutrition, and sexual function. Medications are assessed, and evidence of self-neglect or abuse is sought. Second, the person's built and social environments are evaluated. Third, prognosis is determined. Fourth, the person's values, goals, and preferences are determined. Recommendations that can improve quality of life and lengthen survival are based on the assessment, as well as the person's prognosis and preferences. Recommendations incorporate preventive services for which evidence confirms that the benefits exceed the harms. Geriatric assessment and management can increase survival, independent living, and quality of life, especially in older people with serious diseases.

KEYWORDS

geriatric assessment
functional status
prognosis
medication review
patient goals and preferences
preventive services for older people

INITIAL OBSERVATION

Geriatric assessment begins with observation of the patient and companions, looking for signs of geriatric syndromes such as dementia (Chapter 371), depression (Chapter 362), impaired mobility (Chapter 24), or elder abuse. Is the patient alone or accompanied? Bright or dulled? Well groomed? Conversant? At ease with a companion? Does the patient stand briskly and without assistance? Is the gait normal?

FUNCTIONAL STATUS

Functional status refers to the ability of an individual to perform activities that are needed to fulfill social and community roles. These activities, which are acquired during childhood, are often lost in reverse order with progressive failure of the brain or another organ. For example, children learn first to feed themselves, later to dress, and later to work, whereas a person with dementia may first lose the ability to work, later to dress, and later to feed.

Activities of daily living (ADLs) are performed daily: feeding, maintaining continence, toileting, transferring, bathing, grooming, and dressing. People with an impairment, such as difficulty standing, may maintain independence in ADLs by using an appliance, such as a raised toilet seat and support stand. ADL dependency—needing the help of another person to perform an activity—can be caused by an acute illness but often results from a neurologic condition such as neurodegenerative disease or stroke.

Instrumental ADLs are performed to live at home: preparing meals, housework, laundry, shopping, driving or using public transportation, using the telephone, and handling medications and finances. Dependency in instrumental ADLs can be caused by physical limitations from chronic disease or by dementia (Chapter 371), and it is often an early sign of undiagnosed dementia. Dependency in instrumental ADLs often can be ameliorated by a variety of public and private services (e.g., taxis or rideshare, laundry and cleaning services, and Meals on Wheels).

Dependency in ADLs and instrumental ADLs are present in about 10% and 20%, respectively, of people ages 75 years or older living in the community and are very frequent in hospitalized elders. These dependencies are strong predictors of long-term institutionalization and death.

Advanced ADLs are the ability to fulfill societal, community, and family roles. They can be assessed by asking the person whether they perform an activity, such as playing a musical instrument, or performed it previously. Loss of advanced ADLs may indicate mild cognitive impairment, dementia, or physical limitations.

COGNITION AND COMPETENCY

Mild cognitive impairment does not interfere with independent ADLs. By comparison, dementia (Chapter 371), which is cognitive decline in one or more domains not explained by delirium (Chapter 361) or another mental disorder (Chapter 362, interferes with independence in instrumental ADLs.

The incidence of dementia increases from less than 1% per year at age 65 years to 5% per year at age 85 years. Treating hypertension with a target of 120 mm Hg systolic (Chapter 64) is the only intervention demonstrated to reduce the incidence of dementia and mild cognitive impairment.

Although screening for cognitive impairment is not recommended, detection can lead to identification of treatable conditions (e.g., medication side effects, depression, or hearing impairment). Symptoms of cognitive decline, such as forgetfulness, disorientation, and changes in personality, require cognitive testing. Disorientation to year is about 85% sensitive and 95% specific for cognitive impairment. The Mini-Cog test (Table 361-5), also has high sensitivity and specificity.

Decision-making capacity is specific to each decision. Patients are competent when they can do all of the following:

- Make and express personal preferences.
- Comprehend the risks and benefits of the intervention.
- Comprehend the implications of the decision.
- Give rational reasons for the decision.

If the patient is not competent, the decision should be made by a surrogate or, if a surrogate is not available, by the physician, as specified by state law (Chapter 2).

MOOD AND AFFECT

Universal screening is recommended to assess mood and affect.[2] A positive answer to either of these two questions has a 95% sensitivity and 65% specificity for a major depressive disorder:

1. During the past month, have you often been bothered by feeling down, depressed, or hopeless?
2. During the past month, have you often been bothered by little interest or pleasure in doing things?

All patients should be screened once and also after major life events, such as retirement or a serious illness, and whenever the clinician senses sadness or aversion on seeing a patient.

VISION

Impaired visual acuity is associated with worse functional status, worse quality of life, falls, depression, and social isolation. The prevalence of impaired visual acuity with refractive correction increases from 1% at age 65 years to nearly 20% in persons aged 80 years or older.

Although screening has not been recommended for older adults,[A6] it is useful for the clinician to ask a simple question: whether the patient has difficulty driving, watching television or reading, or doing any of their daily activities because of their eyesight, even while wearing eyeglasses. Impaired visual acuity is determined using the Snellen eye chart (E-Fig. 391-1) as worse than 20/40; 20/200 is the legal threshold for blindness.

HEARING

Hearing loss (Chapter 396) is common, often unrecognized and untreated, and associated with social isolation, functional decline, depressive symptoms, and cognitive impairment. Presbycusis initially affects high frequencies and often-associated central auditory processing disorders can further decrease the ability to understand words over background noise. Routine screening for hearing loss is not recommended,[3] but hearing tests are warranted when the patient, the caregiver, or the physician visit reveals a potential loss of hearing because amplification with a hearing aid, cochlear implant, or assisted listening device can be very helpful.[4]

To detect hearing loss, the clinician can ask, "Do you feel you have hearing loss or have any difficulty hearing?" The whisper test has high sensitivity and specificity: the clinician stands 2 feet behind the patient, occludes one ear, rubs the tragus, whispers a combination of 6 numbers and letters, and then asks the patient to repeat the sequence. The whisper test is positive if fewer than 3 numbers and letters are repeated correctly. Hearing loss also can be detected by a handheld otoscope with a built-in audiometer and by tests on personal computers and smartphones.

When hearing loss is detected, the patient's companion can be asked about its severity and effects on functioning. When hearing is diminished, it is important to examine the ear. If substantial cerumen is found, it must be removed, sometimes by a specialist, and then the hearing evaluation can be performed again.

NUTRITION

The patient should be asked whether a change in weight has occurred over the last year and whether any change was intentional. Weight should be measured and the body mass index (BMI) calculated in kg/m^2 (Chapter 201): BMI of less than 18.5 is underweight, 18.5 to 24.9 is normal, 25 to 29.9 is overweight, 30 to 39.9 is obese, and 40.0+ is severely obese.

Obesity (Chapter 201) affects more than 40% of older Americans and is associated with poorer function and mobility, many chronic diseases, and decreased life expectancy. Obesity and its adverse effects are ameliorated by intensive, multicomponent interventions that may include bariatric surgery.

Unintentional weight loss (Chapter 118) of 5% or more is associated with increased mortality and should prompt evaluation for an underlying cause of malnutrition (Chapter 198), including depression, dementia, dental disease, cancer, malabsorption, poverty, and neglect. Protein and energy supplementation (Chapter 198) increase survival in hospitalized patients who are undernourished on admission. Screening for deficiency of vitamin D or B_{12} is not recommended because of insufficient evidence.[5]

MOBILITY AND LIFE SPACE

Mobility without the assistance of another person depends on the environment and assistive devices. For example, a person may walk the aisles of a grocery store with a shopping cart but be unable to walk across a parking lot without assistance. Life-space mobility, which is the distance through which a person moves over a month, varies from being restricted to a room to traveling outside the region.

Gait speed predicts survival, although less in the very old: for example, 65 year-old men with gait speeds of 1.6 meter (m) per second (s) and 0.8 m/second have median survivals of 32 years and 15 years, respectively; 90-year-old men with gait speeds of 1.6 m/second and 0.8 m/second have median survivals of 8 years and 6 years, respectively. Gait speed also predicts survival in women, and survival in women is generally 20% or more longer than in men of the same age and gait speed.

Mobility can be assessed with two questions:

1. For health or physical reasons, do you have difficulty climbing up 10 steps? Walking ¼ mile?
2. Because of underlying health or physical reasons, have you modified how you climb 10 steps or how frequently? Walk ¼ mile?

The clinician should then evaluate risk factors for impaired mobility, including low physical activity, obesity, symptoms that limit mobility, and chronic diseases that cause organ failure. By observing how the patient arises from a chair, the patient's gait, and the strength of major muscle groups, the clinician can assess the likely causes of poor mobility and whether they may be amenable to physical therapy or other interventions.

RISK OF FALLS

Poor balance is associated with high all-cause mortality,[6] and falls (Chapter 24), which are the 11th most frequent cause of death among people ages 75 years or older, kill almost as many people as prostate cancer and breast cancer combined. One third of community-dwelling persons older than age 65 years fall each year, and the risk increases with age.

On an annual basis, patients should be asked: "Have you fallen in the last year?, Are you afraid of falling?" If the answer to either question is yes, the clinician could measure orthostatic blood pressure, determine nutritional status, assess visual acuity, and examine the feet and knees (for causes of mobility impairment), the strength of the legs and arms, sensation and proprioception of the feet, balance, gait, and cognition. The Timed Up and Go approach measures how long it takes a person to stand up from a chair, walk 10 feet, turn, return, and sit down again; if the sequence requires more than 12 seconds or reveals any gait abnormalities, the patient is at increased risk for falls.[7]

When possible, any medications that affect balance, alertness, or judgement should be discontinued. Older people at increased risk for falls benefit from exercise programs.[A7]

CONTINENCE

Incontinence of urine (Chapter 115) or stool (Chapter 131) and urinary tract symptoms decrease quality of life, limit social function and life space, and can lead to falls and admission to long-term care facilities. Urinary incontinence, which occurs in one third of older women, usually improves with specific interventions, often without medication or surgery.[A8,A9] Three quarters of older men experience urinary frequency, nocturia, or urgency, almost always related to prostate conditions (Chapter 115). Fecal incontinence with at least monthly loss of stool occurs in 8% of men and women aged 50 years and older.

Every elderly patient should be asked: "Have you had urinary incontinence to the extent that it is bothersome?" Further questions determine the frequency and severity of the symptoms and often the pattern (overflow, urge, stress, or mixed incontinence; Chapter 115).

FRAILTY

Frailty (Table 24-1) is global decline in physical function associated with unintentional weight loss of 10 pounds in the last year, self-reported exhaustion, low physical activity, weak grip strength, and slow walking speed.[8] The presence of three or more of these characteristics predicts a five-fold increase in mortality as well as hip fractures, cognitive decline, and adverse outcomes of surgery and hospital care.

SEXUALITY

Among older people in excellent or very good health, nearly 80% of individuals ages 66 to 75 years old and nearly 40% of individuals ages 76 to 85 years old are sexually active. Sexual activity is associated with better cardiovascular health, greater self-esteem, and higher life enjoyment.[9] Nonetheless, sexual problems are common, and sexually transmitted infections have increased in older adults.

Each elderly patient should be asked: "Do you have sex?" The risk for sexually transmitted infections should be assessed (Chapter 264), with behavioral counseling for patients who are at risk.

SELF-NEGLECT AND ABUSE

More than 10% of older people suffer mistreatment, which includes emotional, financial, physical, and sexual abuse, as well as self-neglect and neglect by others. Self-neglect is most common, especially among persons ages 75 years or older and individuals with lower socioeconomic status, cognitive impairment, or physical disability.

To identify difficulties that can lead to self-neglect, patients should be asked how they manage their daily lives: "Are you afraid of anyone?, Has anybody hurt you?, Is anyone taking or using your money without your permission?" Family caregivers should be asked: "Are your elder's needs more than you are able to handle? Are you worried that you might hit your elder? Have you hit your elder?"

Most states have laws that require clinicians to report a reasonable suspicion of abuse or self-neglect to adult protective services.

MEDICATION REVIEW

Polypharmacy is common and can cause drug-drug interactions as well as other adverse effects such as nonadherence. The patient and caregiver should be asked to bring all prescribed and over-the-counter medicines to each visit. The physician should record all the medications and determine which may lead to drug-drug interactions or potentially have harms that exceed their benefits; commercially available drug interaction programs are useful (e.g., Drug Interactions Checker for Drugs, Food and Alcohol: https://www.drugs.com/drug_interactions.html). Drug safety can be improved by goal-directed programs and by explicit deprescribing, which is the process of withdrawing medications, usually one at a time under the supervision of a health professional, with the goal of improving outcomes and minimizing potential harms of polypharmacy.[10,11]

THE BUILT AND SOCIAL ENVIRONMENTS

BUILT ENVIRONMENT

The ability of an older person to live safely as they wish depends on how their home environment and community fit their abilities and needs. Inability to access needed services can lead to self-neglect. Decisions about the appropriateness of the home environment often involve a tension between safety and autonomy. This determination can be based on two questions:

1. Is the home safe, given the patient's cognitive and functional abilities?
2. Can the patient access needed community services, such as stores and a bank?

Home safety to reduce risk for falls can be assessed by a home health agency or by the patient using a brochure from the Centers for Disease Control and Prevention (CDC). (Check for Safety: A Home Fall Prevention Checklist for Older Adults: https://www.cdc.gov/steadi/pdf/check_for_safety_brochure-a.pdf).

SOCIAL SUPPORT

Older persons with loss of independence of ADLs or instrumental ADLs usually require help with important decisions and with daily activities. Informal (i.e., unpaid) support from family and friends is an important source of help,[12] but the clinician should also determine who is available to help the patient and who has durable power of attorney for health care and finances.

FINANCIAL ASSESSMENT

Insufficient money to pay for food, housing, and medical care increases the risk for functional decline and death. If financial security is in doubt, the patient should be asked: "Do you have enough money to pay for groceries? Bills? Medication? Medical/dental bills? A small emergency? A major emergency?" The answers can guide further questions as to whether the patient is a beneficiary of Medicare or Medicaid, is a veteran, or has private health or long-term care insurance. For example, insurance or veterans' benefits can pay for home assistance and daycare.

PROGNOSIS

Prediction of functional status, ability to live independently, and survival inform planning and decisions by older persons and their families. Life expectancy, which is the median length of survival for a group of people, varies according to age, gender, and race (E-Table 23-1 and https://www.cdc.gov/nchs/data/nvsr/nvsr69/nvsr69-12-508.pdf). Life expectancy can be estimated more precisely by incorporating clinical characteristics with online calculators (e.g., see https://eprognosis.ucsf.edu/calculators/). For example, just a few criteria such as male sex (1 point), dependent ADL (2 points for 1 to 4 ADLs and 5 points for 5 dependent ADLs), and 4 clinical characteristics (heart failure, 2 points; serum creatinine >3 mg/dL, 2 points; albumin level 3.0 to 3.4 g/dL or <3.0 g/dL, 1 or 2 points, respectively; nonmetastatic or metastatic cancer, 3 or 8 points, respectively) can classify hospitalized older adults into groups with median 1-year mortality rates of 4% (0 or 1 point), 19% (2 or 3 points), 34% (4 to 6 points), and 64% (>6 points), respectively.

For treatments and screening tests, it is important to determine whether the "time to benefit" (how long it will take for the long-term benefit to exceed the short-term risk) exceeds the life expectancy.[13] For example, an intervention for which benefit exceeds harm after 5 to 10 years (e.g., cancer screening) is unlikely to benefit a person with a life expectancy of 3 years.

GOALS AND PREFERENCES

Life goals often change over time, and advance care planning unfortunately does not necessarily improve end-of-life care.[14] Each year and after major

E-TABLE 23-1 LIFE EXPECTANCY (Y) BY AGE (UNITED STATES), 2018*

AGE	*MEN*									*WOMEN*								
	HISPANIC			NON-HISPANIC WHITE			NON-HISPANIC BLACK			HISPANIC			NON-HISPANIC WHITE			NON-HISPANIC BLACK		
	PERCENTILE																	
	25TH	50TH	75TH	25TH	50TH	75TH	25TH	50TH	75TH	25TH	50TH	75TH	25TH	50TH	75TH	25TH	50TH	75TH
65	13	20	26	13	20	26	8	16	22	17	23	29	14	21	27	12	20	26
70	10	16	22	9	16	21	6	12	18	13	19	24	11	17	22	9	16	22
75	7	12	17	7	12	17	5	10	15	9	14	19	7	12	17	7	12	17
80	5	9	13	4	8	13	3	7	11	6	11	15	5	9	13	4	9	14
85	3	6	9	3	5	9	2	5	8	3	7	11	3	6	9	3	6	10
90	2	4	6	1	3	6	1	3	6	2	4	7	1	4	6	2	4	7
95	1	2	4	1	2	4	1	2	4	1	3	5	1	2	4	1	3	5

*Figures indicate the number of years in which a percentage of the corresponding age, sex, and race/ethnicity cohort will die. For example, in a cohort of Hispanic men aged 65 years, 25% will be dead in 13 years, 50% will be dead in 20 years, and 75% will be dead in in 26 years.

Arias E, Xu JQ. United States life tables, 2018. National Vital Statistics Reports; vol 69, no 12. Hyattsville, MD: National Center for Health Statistics. 2020.

TABLE 23-1 FUNCTIONAL ASSESSMENT ELDERLY INDIVIDUALS

	PREVISIT QUESTIONNAIRE		*ADMINISTERED BY INTERVIEW*	
ASPECT BEING ASSESSED	**LENGTH OF SCREEN IN MINUTES**	**INSTRUMENTS**	**LENGTH OF SCREEN IN MINUTES***	**INSTRUMENTS**
Functional status	<2	Activities of daily living* Instrumental activities of daily living*		
Advance directives	<2	Single question about having advance directives		
MEDICAL ASSESSMENT				
Visual impairment	<2	Single question*	<2	Snellen eye chart (see E-Fig. 391-1)
Hearing impairment	<2	Single question*	<2 (if needed)	Whisper test*
Cognitive problems	<2		≥5	Mini-cog (see Table 361-5)
Mind, affective problems	≥5	PHQ-2* and 9 (see Table 12-5)	<2	
Falls, mobility, balance	<2	Simple questions	<2	Timed Up and Go test*
Medication review	≥5	Inspection of medication bottles		
Malnutrition	<2	Single question*	<2	Weight
Urinary incontinence	<2	Single question*	<2	International Consultation on Incontinence Modular Questionnaire short form if single question is positive (see Chapter 115)
Frailty	<2	Questions (see Table 24-1)	<2	Gait speed, grip strength
Preventive services	≥5	Specific questions		
OTHER DIMENSIONS				
Environment	≥5	Home safety checklist		
Social support	<2	Single question		
Financial status			<2	Insurance status

*See text.
PHQ = Patient Health Questionnaire (see text).
Modified from Reuben DB. Geriatric Assessment. In: Goldman L, Schafer A, eds. *Goldman-Cecil Medicine*. 26th ed. Philadelphia: Elsevier; 2020.

life events, a patient should be asked questions such as: "As you look to the future, what is important to you?," and "What can I do for you today and over the coming months?" Goals may include long-term survival, survival to an event in the foreseeable future, living at home, maintenance of a role, or control of symptoms (e.g., pain or dyspnea). Clinicians can suggest what goals are achievable, what actions can achieve specific goals, and the risks of actions and their possible consequences. Symptom-focused management can improve survival.[A10]

PREVENTIVE SERVICES

Preventive services that benefit older people include vaccinations, screening tests for selected asymptomatic diseases, and behavioral counseling. Vaccinations recommended by the CDC for older adults (Chapter 15) are annual inactivated or recombinant influenza vaccination, two one-time pneumococcal vaccinations (PCV13 and PPSV23 administered 1 year apart), herpes zoster recombinant vaccination (two doses of RZV), and tetanus-diphtheria (Td) or tetanus-diphtheria-pertussis (Tdap) vaccination every 10 years.

Preventive services for which current evidence demonstrates net benefit are recommended by U.S. Preventive Services Task Force for older adults (Chapter 12; http://epss.ahrq.gov/ePSS/search.jsp). Screening is recommended for colorectal cancer and breast cancer to age 75 years and for lung cancer in past or current smokers up to age 80 years. Other recommendations (E-Table 23-2) pertain to screening for hypertension (Chapter 64), abdominal aortic aneurysm (Chapter 63), prediabetes or diabetes (Chapter 210), osteoporosis (Chapter 225), depression (Chapter 362), unhealthy use of alcohol or drugs (Chapters 364 and 365), and certain infections (e.g., human immunodeficiency virus, syphilis, gonorrhea and chlamydia, hepatitis B, hepatitis C, and latent tuberculosis). Aspirin for primary prevention is not recommended in adults ages 60 years or older.[A11]

GERIATRIC ASSESSMENT IN PRACTICE

Geriatric assessment asks questions that can be completed by the patient, caregiver, or office staff, as well as by clinicians (a physician, advanced practice nurse, social worker, and/or physical therapist). Tests can be completed by office staff or a clinician (Table 23-1). Geriatric assessment identifies syndromes, impairments, and disabilities that require a targeted plan to guide management by the principal physician or other clinician over time.

Geriatric assessment is especially useful in hospitalized older adults, but it is reasonable to perform it annually in individuals over age 75 years, patients with multiple chronic diseases, and patients who have survived after major illnesses. Many elements of geriatric assessment are included in Medicare's Initial Preventive Physical Exam and the Annual Wellness Visit (see Medicare Wellness Visits – ICN MLN6775421 February 2021 [https://www.cms.gov] for covered services).

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For the General References and other additional features, please visit Elsevier eBooks+ at https://ebooks.health.elsevier.com.

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E-TABLE 23-2 ALL PREVENTIVE SERVICES RECOMMENDED BY THE UNITED STATES PREVENTIVE SERVICES TASK FORCE FOR OLDER ADULTS, ACCORDING TO THE GRADE OF RECOMMENDATION

RECOMMENDED PREVENTIVE SERVICE*	GROUP OF OLDER ADULTS	GRADE OF RECOMMENDATION†
Colorectal Cancer Screening	Adults aged 50-75 years Selected adults aged 76-85 years	A C
Hypertension Screening	All adults	A
Tobacco Smoking Cessation	All adults	A
Syphilis Infection Screening	Adults at increased risk for infection	A
Chlamydia and Gonorrhea Screening	All women at increased risk for infection	B
Pre-diabetes and Type 2 Diabetes Screening	Adults aged 70 years or younger who have overweight or diabetes	B
Lung Cancer Screening	Adults aged 50-80 years with a 20 pack-year history who smoked within the past 15 years	B
Hepatitis B Virus Infection Screening	Adults at increased risk of infection	B
Healthy Diet & Physical Activity	Adults with cardiovascular disease risk factors	B
Sexually Transmitted Infections Counseling	Adults at increased risk for sexually transmitted infections	B
Unhealthy Drug Use Screening	All adults	B
Hepatitis C Infection Screening	Adults aged <80 years	B
Abdominal Aortic Aneurysm Screening	Men aged 65-75 years who have ever smoked Selected men aged 65-75 years who have never smoked	B C
Medicines to Reduce Risk for Breast Cancer	Women at increased risk for breast cancer aged 35 years or older	B
BRCA-Related Cancer Assessment & Counseling	Women with a personal or family history of breast, ovarian, tubal, or peritoneal cancer or an ancestry associated with *BRCA1/2* gene mutation	B
Unhealthy Alcohol Use Screening, Interventions	All adults	B
Weight Loss to Prevent Obesity-related Events	Adults with a body mass index of ≥30	B
Osteoporosis Screening	Women aged 65 years and older	B
Fall Prevention Interventions	Community-dwelling adults aged 65 years or older	B
Statin Use	Adults aged 40-75 years with no cardiovascular risk factors, ≥1 CVD risk factor, and a 10-year CVD event risk ≥10% Adults aged 40-75 years with no cardiovascular risk factors, ≥1 CVD risk factor, and a 10-year CVD event risk 7.5–10%	B C
Latent Tuberculosis Infection Screening	Adults at increased risk for infection	B
Depression Screening	All adults	B
Breast Cancer Screening	Women aged 50-74 years	B
Prostate Cancer Screening	Men aged 55-69 years	C
Skin Cancer Prevention	Adults with fair skin types	C
Healthful Diet and Physical Activity	Adults without obesity or cardiovascular disease risk factors	C

*Several preventive services are not recommended for older adults because there is evidence that the service does not have net benefit or because there is insufficient evidence of net benefit. Evidence is insufficient to recommend screening for the following: impaired visual acuity, primary open-angle glaucoma, atrial fibrillation, vitamin D deficiency, hearing loss, cognitive impairment, abdominal aortic aneurysms in women, abuse or neglect, obstructive sleep apnea, skin cancer, thyroid dysfunction, suicide risk, oral cancer, and bladder cancer. Screening for the following is not recommended because of evidence of lack of net benefit: COPD, carotid artery stenosis, asymptomatic bacteriuria in older adults, pancreatic cancer, ovarian cancer, and testicular cancer.

†Grade of Recommendation: A = there is high certainty that the net benefit is substantial. B = there is high certainty that the net benefit is moderate or there is moderate certainty that the net benefit is moderate to substantial. C = there is at least moderate certainty that the net benefit is small.

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24 COMMON CLINICAL SEQUELAE OF AGING

JEREMY D. WALSTON

EPIDEMIOLOGY

Older adults make up the majority of patients actively treated in the health care system, in large part owing to their increased burden of chronic diseases but also because of their marked vulnerability to adverse health outcomes, such as functional and cognitive decline (Chapter 361), falls, delirium (Chapter 361), and frailty. This age-related vulnerability is thought to have its basis in altered biology that results in tissue and physiologic system changes, which in turn may contribute to many of these conditions and to the chronic disease states commonly seen in older adults. Importantly, these biologic changes are likely to be heterogeneous and to occur at different chronologic ages and in different organs at different rates (Fig. 24-1). These complex age-related biologic changes represent a source of vulnerability that sets the stage for the marked increase in clinical sequelae observed in older adults.

PATHOBIOLOGY

Age-Related Cellular and Molecular Changes

The multiple biologic changes of aging affect important homeostatic functions and can lead to altered cellular function, declines in tissue resiliency, and cellular dropout. Although the exact contributions of each of these biologic changes are not yet known, improvements in precision medicine approaches may facilitate future targeted prevention and treatment strategies. For example, autophagy, an intracellular process responsible for the recycling of damaged or redundant organelles or proteins, becomes less effective with aging.[1] The result is an intracellular accumulation of dysfunctional mitochondria and proteins, which in turn can trigger cellular dysregulation through increased levels of free radicals, lower mitochondrial energy production, and programmed cell death or apoptosis. Senescent cell populations arise with increasing age and lead to alterations in tissue and immune system function.[2] For example, some fibroblasts and fat cells evolve toward a senescent cell phenotype whereby reproduction and cell death are less likely to take place and survival persists in an altered, less functional state. These senescent cells secrete inflammatory cytokines and other bioactive molecules that pathologically alter surrounding tissues. Senescent T-cell populations also evolve with increasing age, perhaps related to early-life viral infections. Senescent T cells are less able to respond appropriately to immunogenic signals, thereby increasing vulnerability to infections. Another biologic age-related change is an increasing tendency for apoptosis, or programmed cell death. Although apoptosis is a normal cellular program that kills and disassembles damaged or redundant cells in all tissues, it accelerates with age and likely contributes to the vulnerability to chronic disease states, such as Parkinson disease (Chapter 378), heart failure (Chapter 45), and the generalized loss of cell number in many tissues. Finally, evidence suggests that increased activity in transforming growth factor-β signaling may play an important role in the fibrotic changes that are observed in the heart, skeletal muscle, and lung tissue and that result in functional decrements with increasing age. Importantly, these aging-related molecular and cellular changes are heterogeneous and may affect individuals at different ages and in different tissues. However, the end results are increased susceptibility to chronic disease states, frailty, declines in function and cognition, and ultimately mortality.

Physiologic System Dysregulation and Its Consequences

Dysfunction in multiple physiologic stress response systems also plays a role in late-life vulnerability. Chronic diseases such as diabetes, vascular disease, chronic obstructive pulmonary disease, depression, and heart failure activate the innate immune system, the sympathetic nervous system, and the hypothalamic-pituitary-adrenal axis, which in turn increases the production of cortisol and the inflammatory cytokine interleukin-6 (IL-6). These responses further exacerbate aging-related clinical conditions, such as osteoporosis and hypertension, and increase vulnerability to frailty, functional decline, accidental injury, and worsening chronic disease states (E-Fig. 24-1).

CLINICAL MANIFESTATIONS

Some clinical manifestations are related not to physiologic aging but rather to cumulative exposures, such as with sun-related skin cancer (Chapter 188), or the delayed expression of genetic abnormalities, such as Huntington disease (Chapter 379) or polycystic kidney disease (Chapter 112). However, many organs and systems become less functional with age. For example, a healthy 70-year-old will have only about 50% of the lung function (Chapter 71) and renal function (Chapter 101) of a young adult. The resultant lack of physiologic reserve capacity does not affect day-to-day function but can greatly affect the ability to recover from a severe illness that exhausts the body's reserve capacity.

Despite normal baseline temperatures, older adults are more susceptible to hypothermia or hyperthermia (Chapter 95) after environmental exposure, even though they are less likely to develop fever with infections. For example, patients with pneumonia (Chapter 85) may present with confusion and dehydration rather than with fever and cough. Among older persons with critical illness, more than half die within 1 month or experience significant functional decline over the following year.

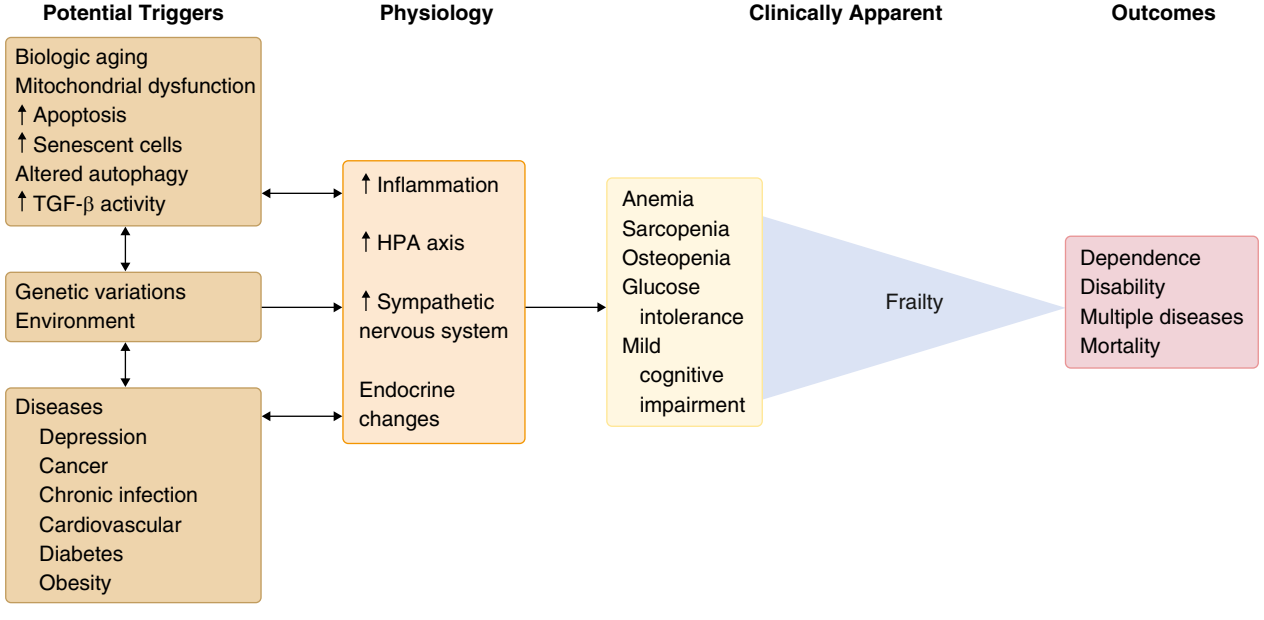

FIGURE 24-1. **Comprehensive model pathway for biologic vulnerability to adverse outcomes in aging.** HPA = hypothalamic-pituitary-adrenal; TGF-β = transforming growth factor-β.

ABSTRACT

Older adults comprise the majority of medical patients and have many more iatrogenic complications compared with younger adults. Complex physiologic and biologic aging-related changes, as well as chronic disease states, contribute to this vulnerability. Common organ- and tissue-specific age-related changes contribute to cardiovascular disease, urinary tract conditions, and musculoskeletal changes. Many of these changes contribute to frailty and to related late-life vulnerability to adverse health outcomes and mortality.

KEYWORDS

aging
frailty
risk assessment
chronic wounds
age-related biologic changes
chronic diseases

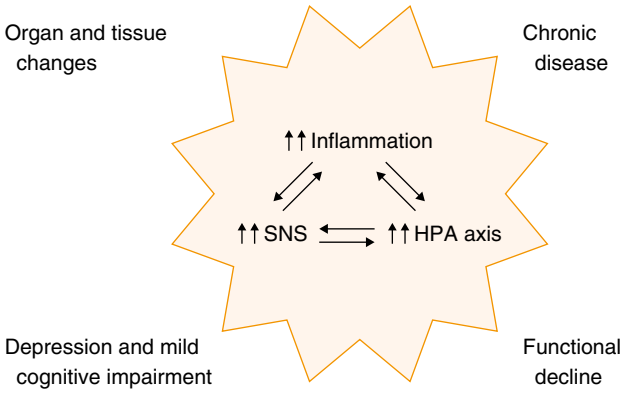

E-FIGURE 24-1. Dysregulation of stress response systems and their influence on vulnerability to adverse outcomes. HPA = hypothalamic-pituitary-adrenal; SNS = sympathetic nervous system.

EFFECTS OF AGING ON SPECIFIC ORGANS AND SYSTEMS

CARDIOVASCULAR SYSTEM

Between the ages of 20 and 80 years, left ventricular systolic function does not change, but the left ventricle gradually thickens. The result is that left ventricular filling in early diastole declines by 50%, and ventricular filling becomes more dependent on atrial contraction (Chapter 41).[3] Although atherosclerosis is the most important cause of symptomatic cardiac disease in elderly people, the age-associated vascular stiffness results in an age-related increase in heart failure despite normal systolic function (Chapter 45). With the gradual loss of up to 90% of sinus node pacemaker cells by the age of 80 years, both the resting heart rate and the maximal heart rate with exercise decline. Conduction system dysfunction contributes to an increase in the prevalence of atrial fibrillation, which is seen in about 4% of community-dwelling older individuals (Chapter 52) and can develop in up to one third of the elderly after surgery (Chapter 401). Heart valves thicken and stiffen, and the prevalence of aortic stenosis and mitral annular calcifications rises (Chapter 60), often causing heart murmurs.

Stiffening of the aorta causes an increase in systolic blood pressure, whereas diastolic blood pressure often stays stable or even declines (Chapter 64). Hypertensive patients age 80 years and older should generally be treated according to current recommendations for people older than 65 years, with a systolic blood pressure goal of less than 120 mm Hg likely associated with lower cardiovascular and all-cause mortality for otherwise healthy older adults.[A1,A2] However, some older adults, especially frail elders, may not tolerate systolic blood pressures this low without side effects, so treatment must be individualized. For some patients over age 80 years, a modest reduction in their multidrug regimen may sustain target blood pressure levels with fewer side effects.[A3] Blood pressure control reduces the incidence of cognitive impairment and dementia (Chapter 371) in older persons with mild cognitive deficits,[A4] and discontinuation of antihypertensive treatment does not improve cognitive, psychological, or general daily functioning.[A5] There is little evidence, however, of the impact of maintaining a lower blood pressure on those who are over age 90 years.

The combination of impaired ventricular filling and the inability to increase the heart rate with stress contributes to the postural hypotension that is seen in 20% of older individuals (Chapter 49), as well as their predisposition to falls and syncope with stresses that younger individuals would tolerate. The reduced ability of the elderly to tolerate cardiovascular stress must be recognized and anticipated whenever they experience a major illness. In addition, coronary artery disease can limit cardiac reserve and increase the risk that hypotension will cause a secondary myocardial infarction.

Hyperlipidemia is common in older adults, and statins are effective in this age group for reducing coronary heart disease events.[A6,A7] However, their favorable cost-effectiveness for primary prevention in persons over age 75 years can be offset by even minor geriatric-specific side effects, and these drugs can be discontinued safely in the setting of advanced, life-limiting illness.[A8] Low-dose aspirin is not beneficial in healthy elderly people because its side effects outweigh its benefits.[A9,A10] However, low-dose edoxaban (15 mg daily) may be a safe and effective option to prevent systemic embolization in elderly patients who otherwise seem not to be safe candidates for anticoagulation.[A11]

All adult cardiac conditions become more common with aging. Exercise training can improve endurance and decrease age-related cardiac stiffness.[A12] Treatment recommendations for specific cardiac abnormalities must balance the potential benefit of targeted interventions against the common multimorbidities seen with aging.[4]

RESPIRATORY SYSTEM

The chest wall stiffens with advancing age, and the lungs lose elastic recoil (Chapter 73).[5] Maximal vital capacity declines by about 40%, but oxygen exchange declines by about 50% because of the additive effect of progressive ventilation-perfusion mismatching (Chapter 73). As a result, the arterial Po_2 of many 80-year-olds is about 70 to 75 mm Hg. The clinical manifestations are often progressive shortness of breath with exercise (Chapter 71) and an increased susceptibility to community-acquired pneumonia (Chapter 85) and even to aspiration pneumonia.

GASTROINTESTINAL SYSTEM

Taste and smell (Chapter 395) decline with advancing age. Food tends to taste less sweet and more bitter.

The esophageal sphincter can become lax (Chapter 124), thereby increasing reflux and even aspiration. Atrophic gastritis reduces the risk of duodenal ulcer but also the absorption of iron (Chapter 145) and vitamin B_{12} (Chapter 150). Delayed gastric emptying can lead to a sense of early satiety and decreased appetite.

A gradual decline in the number of hepatocytes decreases the weight of the liver by about one third by the age of 90 years and decreases the liver's ability to metabolize drugs (Chapter 25). Distal colonic motility from the rectosigmoid to the anal canal declines, and more than 60% of elderly individuals develop constipation (Chapter 122). Diverticula (Chapter 128) become more common with age and are seen in up to 50% of people older than age 80 years.

URINARY SYSTEM

Glomerular filtration declines by about 1% per year, and kidney size declines by about one third in older adults (Chapter 101). Maximal concentrating capacity declines, and it becomes more difficult to excrete a salt load or to conserve water in the face of dehydration.

The bladder becomes more irritable with advancing age and may generate less power, which is especially a problem in men with prostatic hypertrophy (Chapter 114). By comparison, urinary incontinence (Chapter 115) is more prevalent in women. Residual bladder urine volume increases, and nocturia is common. Vaginal and urethral atrophy predispose women to urinary tract infections (Chapter 263).

The kidney is more susceptible to the effects of medications, particularly nonsteroidal anti-inflammatory drugs, which can result in sodium and fluid retention and subsequent hypertension. In elderly individuals, a slight acidemia results from impaired acid excretion and may contribute to the development of osteoporosis.

ENDOCRINE SYSTEM

Growth hormone levels fall with advancing age (Chapter 205), thereby resulting in decreased muscle strength, thinning of bones and skin, and increased central fat. However, growth hormone replacement does not appear to result in improved muscle strength. Levels of thyroid hormones do not decline with age (Chapter 207). Parathyroid hormone levels, however, commonly increase, especially in women, probably in response to the kidney's declining ability to maintain normal serum levels of phosphorus and calcium (Chapters 184 and 227).

The ability of the pancreas to release insulin is blunted with advancing age (Chapter 210), but the kidney's clearance of insulin also decreases. The net result is maintained plasma insulin levels in the fasting state but an increased likelihood of postprandial or stress-induced hyperglycemia. Dramatic declines in estrogen and progesterone production precipitate menopause at an average age of 51 years (Chapter 222). Testosterone levels begin to decrease in men by about 50 years of age, often with resulting declines in sexual function but not in the potency of semen (Chapter 216). Testosterone supplements reverse the muscle loss and sexual implications of declining testosterone levels, but their safety and effect on the risk of cardiovascular complications are uncertain.[6,7]

IMMUNE SYSTEM

Declines in the responsiveness of the immune system explain why the incidence of autoimmune conditions, such as systemic lupus erythematosus (Chapter 245) and multiple sclerosis (Chapter 380), declines in the elderly. However, this same decline explains increased morbidity and mortality with infectious diseases and the increased risk of reactivating infections such as tuberculosis (Chapter 299) and herpes zoster (Chapter 346). These risks emphasize the importance of vaccination against herpes zoster, influenza, pneumococcal pneumonia, and tetanus in the elderly (Chapter 15).

HEMATOPOIETIC SYSTEM

Hematopoiesis (Chapter 142) is generally sustained with aging, except in response to marked stress and inflammatory pathway activation. The one exception is that the hematocrit declines somewhat in older men, presumably owing to their lower testosterone levels. Clonal hematopoiesis, which is the proliferation of a single cell, is more common with aging and increases the risk of cancer, cardiovascular disease, and all-cause mortality.[8]

INTEGUMENTARY SYSTEM

With aging, the epidermis and dermis adhere less tightly and the subcutaneous tissue thins, thereby making the skin feel looser and more likely to wrinkle and ulcerate. Clinical sequelae include senile purpura (Fig. 24-2) as tears in small venules after bumps or abrasions (Chapter 407). Ultraviolet light exposure also predisposes to skin cancer (Chapter 188), rosacea (Chapter 406), xerosis, and hair loss (Chapter 409). Wound healing is also compromised, and complete skin healing can take 5.5 weeks instead of 3.5 weeks in individuals older than age 65 years.

FIGURE 24-2. Senile purpura is a common and benign condition that results from impaired collagen production and capillary fragility in some older adults. In the absence of other signs of disease, no investigation is necessary. (From Forbes CD, Jackson WF. *Color Atlas and Text of Clinical Medicine*. 3rd ed. London: Mosby; 2003.)

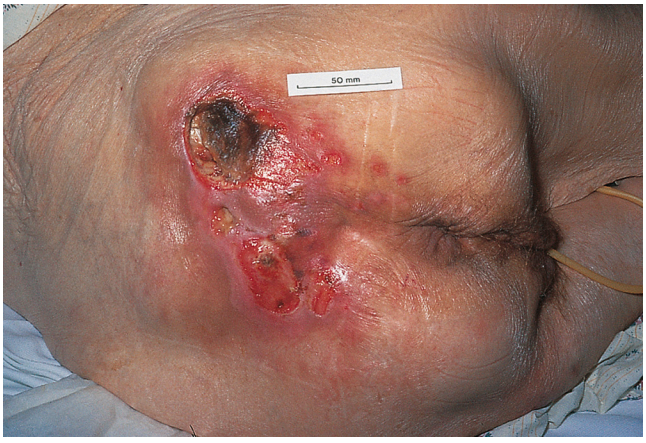

FIGURE 24-3. Severe sacral pressure sore, one of the serious but preventable complications of immobility. (From Forbes CD, Jackson WF. *Color Atlas and Text of Clinical Medicine*. 3rd ed. London: Mosby; 2003.)

Pressure Sores

Older adults are more prone to pressure sores when they are bedridden. Pressure sores, which are necrotic areas of muscle, subcutaneous fat, and skin, usually occur between underlying bone and a hard surface (or a soft surface during a prolonged time) as a result of compression and subsequent ischemia (Fig. 24-3). A continuous-pressure threshold of only 30 to 35 mm Hg is needed to cause pressure sores, and a standard mattress can generate pressures five times as high. In addition to pressure injury, other contributing factors include shear injury from rubbing constantly against underlying surfaces, burning injury from friction of the superficial skin layers, and moisture that softens the skin, makes it stick to underlying surfaces, and provides easy access for infection.

TREATMENT AND PREVENTION

Safe positioning, regular turning, avoidance of direct pressure, pressure-reducing beds, and advanced static mattresses or advanced static overlays can reduce the incidence of pressure sores. Alternating air mattresses or overlays are not recommended.[9] Pressure sores should be photographed to establish a baseline. The wound should be freed of any pressure to prevent additional pressure ulcers. Wet-to-dry dressings are a mainstay, and semiocclusive and occlusive dressings also can be helpful. Protein or amino acid supplementation enriched with zinc and antioxidants,[A13] hydrocolloid or foam dressings, and adjunctive electrical stimulation may be useful. Surgical or chemical débridement is often required. Topical or systemic antibiotics (Chapter 261) may be needed. Pressure ulcers usually heal within 6 months, but surgical repair is sometimes required.

MUSCULOSKELETAL SYSTEM

Bone mass and density decrease by about 1% per year but by up to 2 to 3% per year in the first 5 to 10 years after menopause in women (Chapters 222 and 225). In older women with osteopenia, bisphosphonate therapy (e.g., zoledronate, four 5-mg infusions at 18-month intervals)[A14] significantly reduces the risk of nonvertebral or vertebral fractures within 1 year[A15] and therefore is useful in women with a life expectancy longer than 1 year. Tendons and ligaments become less elastic, thereby contributing to a higher incidence of rupture, especially of the Achilles tendon. Sarcopenia is common in older adults.[10] For example, muscle mass declines by about 25% by the age of 70 years and by 30 to 40% by the age of 80 years unless it is offset by exercise.

CLINICAL PHARMACOLOGY

Older adults take a disproportionate share of all prescription (Chapter 25) and nonprescription (Chapter 30) medications, and they are at increased risk of drug-drug interactions. Because older adults have less muscle mass and more fat as a proportion of total body weight, they are more sensitive to the effects of water-soluble drugs and have prolonged effects from lipophilic drugs. Declines in renal and hepatic function reduce the clearance of most drugs, although drugs that are conjugated and glucuronidated are cleared relatively normally. Older people also are more likely to be nonadherent to prescribed regimens owing to the number of medications and their cost, mental impairment, and medication side effects.

SENSORY AND SLEEP

In addition to age-related cognitive decline (Chapters 361 and 361), hearing loss develops in about 25% of individuals older than 65 years (Chapter 396), with decreased neural transmission leading to difficulty in discriminating important sounds from background noise. Presbycusis diminishes the ability to hear high-frequency sounds.

The thickening and stiffening of the lens diminish the ability to focus on nearby objects and increase glare (Chapter 391). Transmission of light through the lens may decline by 50% or more, so elderly individuals require more ambient light. Vitreal detachment causes floaters that also can interfere with vision. Decreased tear production causes dryness of the eyes. All of these conditions contribute to a decline in visual acuity to the extent that 40% of men and 60% of women older than 65 years have a visual acuity of 20/70 or worse.

Older adults tend to have difficulty in sleeping (Chapter 374) yet spend much more time in bed. Sleep apnea also becomes more common with advancing age (Chapter 374).

FRAILTY

EPIDEMIOLOGY

Frailty in older adults is a geriatric syndrome of weakness, slowness, and weight loss, owing to an aggregate of comorbid conditions. Frailty serves as a clinical indicator of which older adults are at high risk for adverse outcomes, including delirium (Chapter 361), falls, and mortality.[11,12] Measures of frailty are also increasingly utilized to identify older adults who are at highest risk for adverse health outcomes related to procedures or medical treatments, including intensive care,[13] general surgery,[14] hip fracture surgery,[15] or coronavirus disease 2019 (COVID-19) infection.[16]

PATHOBIOLOGY

The biology that differentiates vulnerable or frail older adults from resilient or robust older adults is complex and multisystemic in nature. For example, diminished heart rate variability, which is a marker of dysregulated sympathetic nervous system activity, is associated with aging, frailty, and cardiac arrhythmias. Frail older adults have significantly higher levels of salivary cortisol during the afternoon nadir period, thereby suggesting chronically increased activity of the hypothalamic-pituitary-adrenal axis. Elevated levels of inflammatory cytokines, especially IL-6, tumor necrosis factor-α receptor 1 (TNFR1), and C-reactive protein, are strongly related to functional decline, frailty, chronic disease, and mortality in older adults, probably owing to increased fat, more senescent cells, and free radical production from altered mitochondria. IL-6 is likely to have a negative impact on stem cells and satellite cells, which in turn may contribute to the chronic anemia and age-related declines in skeletal muscle (sarcopenia) and bone mass (osteopenia) commonly observed in frail, older adults. TNFR1 stimulates apoptosis and necroptosis, which are cell programs that lead to cell death and possibly tissue depletion and vulnerability later in life. In addition to stress response systems, endocrine factors that normally maintain muscle mass play a role in frailty. For example, the adrenal androgen dehydroepiandrosterone sulfate and insulin-like growth

factor 1 are significantly lower in frail adults. Future preventive or treatment strategies to reduce frailty and improve resiliency may target some of these stress responses or endocrinologic changes.

CLINICAL MANIFESTATION AND DIAGNOSIS

Validated frailty screening tools (Table 24-1) enable physicians to identify patients at highest risk of side effects, adverse outcomes, and mortality and to develop preventive interventions that will decrease risk and improve quality of life. One approach is to measure physiologic parameters such as grip strength, walking speed, and weight loss, as well as to gather information about activity and fatigue levels. With use of this approach, the prevalence of frailty rises with increasing age; approximately 10% of community-dwelling adults older than 65 years meet these frailty criteria and subsequently are at increased risk of functional decline, falling, hospitalization, and death, even after adjustment for age, socioeconomic and smoking status, and multiple common disease states.

TREATMENT AND PREVENTION

Interventions should be targeted to the specific characteristics of a patient's frailty. Increasing physical exercise is the mainstay of most programs.[A16] Focused prevention of iatrogenic injuries or recurrent hospitalizations and remediation of symptoms are often warranted for frail vulnerable older adults (Fig. 24-4). Physical activity, exercise interventions, and nutritional supplementation can reduce disability and symptoms and improve quality of life across the spectrum of robust to frail older adults. In addition, exercise and weight loss together improve function in obese and frail older adults. Other options include a team-based approach that engages the patient, family members, caregivers, health care providers, and social workers. Classic palliative care (Chapter 3), with appropriate pain management, less invasive treatment plans, limited hospital visits, and organized home care plans, can greatly improve quality of life. If the patient has frequently been admitted to an inpatient setting, a program for all-inclusive care or a medical daycare setting may help prevent recurrent admissions and improve quality of life. Once admitted to the hospital, frail older adults may benefit from being congregated in a unit that specializes in their care and can provide attention to their functionality, continence, sleep disturbances, delirium, and palliative care issues.

TABLE 24-1 FOUR COMMONLY USED INSTRUMENTS TO MEASURE FRAILTY IN OLDER ADULTS, WITH RELEVANT MEASUREMENT DOMAINS AND SCORING CRITERIA

INSTRUMENT	DOMAINS	SCORING
Physical frailty (biologic syndrome model)*	Physical function (slowness, low activity, weakness), nutritive (weight loss), and exhaustion	Score range: 0-5 Frail = ≥3 criteria present Intermediate/pre-frail = 1-2 criteria present Robust = 0 criteria present
Cumulative Deficit Frailty Model (comorbidity model)†	Diseases, ability in ADL, health attitudes/values, and symptoms/signs from the clinical and neurologic examinations	Number of deficits present and divided by the number of deficits taken into consideration Higher proportion equates to a higher level of frailty
Vulnerable Elders Survey (VES-13)‡	Physical function and ADL/IADL disability	Score range: 0-10 Frail = score ≥3
1994 Frailty measure (functional domains model)§	Physical function, nutritive function, cognitive function, sensory problems	Subject scoring a 3 or higher on at least one item in any domain is considered to have a problem or difficulty in that domain Frail = problems/difficulties in ≥2 domains

*Fried LP, Tangen CM, Walston J, et al. Frailty in older adults: evidence for a phenotype. *J Gerontol A Biol Sci Med Sci*. 2001;56:M146-M156.

†Rockwood K, Andrew M, Mitnitski A. A comparison of two approaches to measuring frailty in elderly people. *J Gerontol A Biol Sci Med Sci*. 2007;62:738-743.

‡Saliba D, Elliott M, Rubenstein LZ, et al. The Vulnerable Elders Survey: a tool for identifying vulnerable older people in the community. *J Am Geriatr Soc*. 2001;49:1691-1699.

§Strawbridge WJ, Shema SJ, Balfour JL, et al. Antecedents of frailty over three decades in an older cohort. *J Gerontol B Psychol Sci Soc Sci*. 1998;53:S9-S16.

Details on the use and implementation of these tools can be found in the referenced articles.
ADL = activities of daily living; IADL = instrumental activities of daily living.

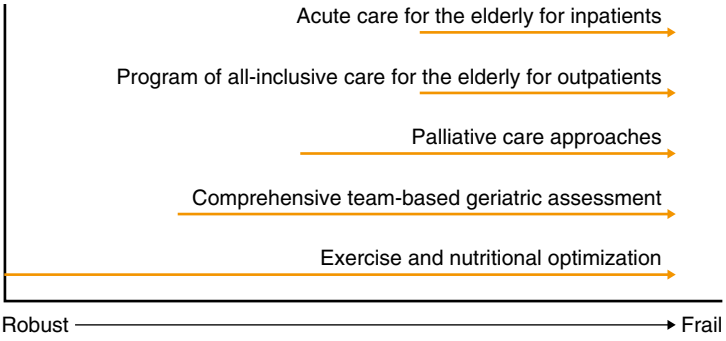

FIGURE 24-4. Assessment and treatments in frail and vulnerable older adults.

PROGNOSIS

Frailty increases the likelihood for development of influenza or influenza-like illness in the 6 months after vaccination; the likelihood of requiring care in a skilled nursing or long-term care facility after hospitalization for general surgery; the likelihood of poor outcomes in patients with cardiovascular disease; poor renal transplant graft function and early hospital readmission after transplantation; falls, hospitalization, and mortality in patients on hemodialysis for chronic renal failure; and the risk of death in aging intravenous drug users. Biologic differences between frail and non-frail older adults (see Fig. 24-1) drive the marked vulnerability to adverse outcomes observed in the frail subjects.

FALLS

Falls are a common manifestation of frailty. Contributing factors include cardiopulmonary disease, poor eyesight, hearing loss, balance disturbances, weakness, movement disorders, neuropathies, poor judgment, depression, osteoporosis, arthritis, and foot disorders.[17] The risk of falling also increases in patients who take more prescription medications, especially hypnotics, muscle relaxants, antihypertensive agents, diuretics, and antidepressant medications. Environmental risks include stairs, loose objects, rugs, poor lighting, poorly fitting shoes, uneven pavements, and slippery surfaces.

Patients who have fallen or have a fear of falling should have a falls assessment, including measuring orthostatic blood pressure, assessing vision, reviewing medications, and testing balance, gait, and lower extremity strength.[18,19] Exercise alone and exercise combined with other interventions (e.g., vision assessment and treatment; environmental modification) lower the risk compared with usual care,[A17–A19] but intensive, nurse-led, individualized plans may not provide incremental benefit over good baseline care.[A20,A21] Data on vitamin D supplementation to reduce falls have been inconclusive, but recent trials indicate no benefit.[A22,A23]

GENERAL REFERENCES

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Grade A References

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25 PRINCIPLES OF DRUG THERAPY

ROBERT B. DIASIO

Depending on the conditions, a drug may produce different effects ranging from no effect to a desirable effect to an undesirable toxic effect. Clinicians must learn how to choose the correct drug dosage for different conditions to ensure effective and safe therapy. To do so, clinicians must understand pharmacokinetics—the movement of a drug over time through the body—and pharmacodynamics—the relationship between drug concentration and drug effect (Fig. 25-1), as well as drug interactions and adverse drug responses. Genomics is increasingly helpful both for individualizing therapy as well as in the design of new drugs.[1]

PHARMACOKINETIC PRINCIPLES

Administration

The most efficient and straightforward means of administering a drug into the systemic circulation is by intravenous injection of a bolus. With this route, the full amount of a drug is delivered into the systemic circulation almost immediately. The same dose also may be administered as an intravenous infusion over a longer period, thereby resulting in a decrease in the peak plasma concentration and an accompanying increase in the time the drug is present in the circulation. Many other routes of administration can be used, including sublingual, oral, transdermal, rectal, inhalational, subcutaneous, and intramuscular; each of these routes carries not only a potential delay in the time it takes the drug to enter the circulation but also the possibility that a large fraction of it will never reach the circulation.

Absorption

Absorption refers to the transfer of a drug from the site of administration to the systemic circulation. Many drugs cross a membrane barrier by passive diffusion and enter the systemic circulation. Because passive diffusion in this setting depends on the concentration of the solute at the membrane surface, the rate of drug absorption is affected by the concentration of free drug at the absorbing surface. Factors that influence the availability of free drug thus affect drug absorption from the administration site; this effect can be exploited to design medications that release a drug slowly into the circulation by prolonging drug absorption. With certain sustained-released oral preparations, the rate of dissolution of the drug in the gastrointestinal tract determines the rate at which the drug is absorbed (e.g., timed-release antihistamines). Similarly, a prolonged drug effect can be obtained by the use of transdermal medications (e.g., nitroglycerin) or intramuscular depot preparations (e.g., benzathine penicillin G).

First-Pass Effect

Some drugs that are administered orally are absorbed relatively efficiently into the portal circulation but are metabolized by the liver before they reach the systemic circulation. Because of this "first-pass" or "presystemic" effect, the oral route may be less suitable than other routes of administration for such drugs. A good example is nitroglycerin, which is well absorbed but efficiently metabolized during the first pass through the liver. However, the same drug can achieve adequate systemic levels when it is given sublingually or transdermally.

Bioavailability

The extent of absorption of a drug into the systemic circulation may be incomplete. The bioavailability of a particular drug is the fraction (F) of the total drug dose that ultimately reaches the systemic circulation from the site of administration. This fraction is calculated by dividing the amount of the drug dose that reaches the circulation from the administration site by the amount of the drug dose that would enter the systemic circulation after direct intravenous injection into the circulation (essentially the total dose). Bioavailability can range from 0, in which no drug reaches the systemic circulation, to 1.0, in which essentially all of the drug is absorbed. The bioavailability of a drug may vary in different formulations because the overall absorption differs. This variability is a concern with the increasing use of generic preparations.

Distribution

After delivery of a drug into the systemic circulation, either directly by intravenous injection or after absorption, the drug is transported throughout the body, initially to well-perfused tissues and later to areas that are less perfused. This distribution phase can be assessed best by plotting the drug's plasma concentration on a log scale versus time on a linear scale (Fig. 25-2). For an intravenously administered drug, for which absorption is not a factor, the initial phase—from immediately after administration through the rapid fall in concentration—represents the distribution phase, during which a drug rapidly disappears from the circulation and enters the tissues. This phase is followed by the elimination phase (see later), when drug in the plasma equilibrates with drug in the tissues. During this latter phase, the drug's plasma concentration is thought to be related to drug effect.

Volume of Distribution

The volume of distribution relates the amount of drug in the body to the concentration of drug in the plasma. It is calculated by dividing the dose that ultimately gets into the systemic circulation by the plasma concentration at time zero (C_{p0}):

$$\text{volume of distribution} = \text{dose}/C_{p0} \quad (1)$$

The C_{p0} can be calculated by extrapolating the elimination phase back to time zero (see Fig. 25-2). The volume of distribution is best considered the "apparent volume of distribution" because it represents the apparent volume

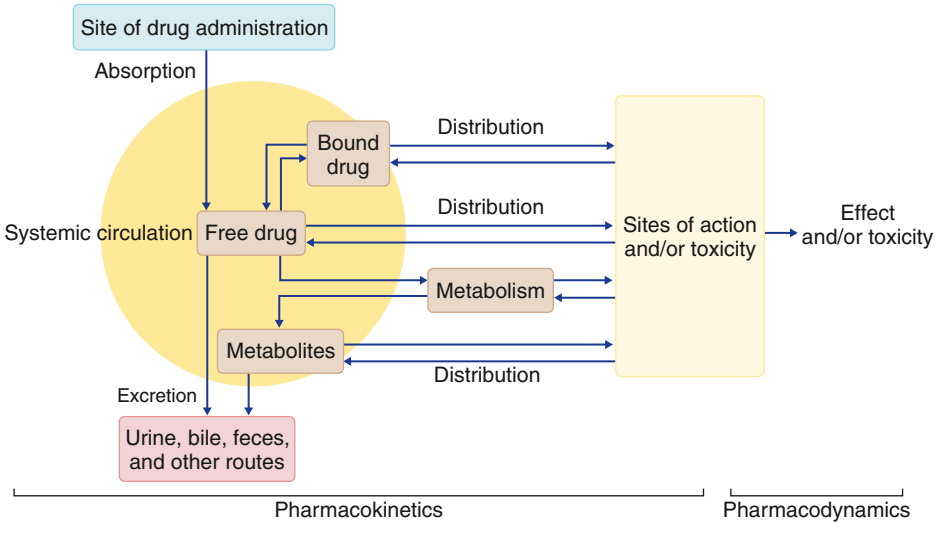

FIGURE 25-1. Schematic of a drug's movement through the body, from the site of administration to production of a drug effect. The relationship between pharmacokinetics and pharmacodynamics is shown.

ABSTRACT

The principles of pharmacokinetics help clinicians manage drug dosing and levels, including calculating a loading dose, determining a maintenance dose, and calculating how to decrease the drug level. Drug monitoring guides how to adjust dosing in various conditions, such as renal insufficiency, liver disease, and altered hemodynamic states. Knowledge of drug interactions and adverse reactions can help avoid these complications. Genomics is increasingly important, both to guide rational therapeutic decisions and for the design of new drugs.

KEYWORDS

pharmacokinetics
drug monitoring
drug overdose
drugs in the elderly
drug interactions
adverse drug reactions
pharmacogenomics

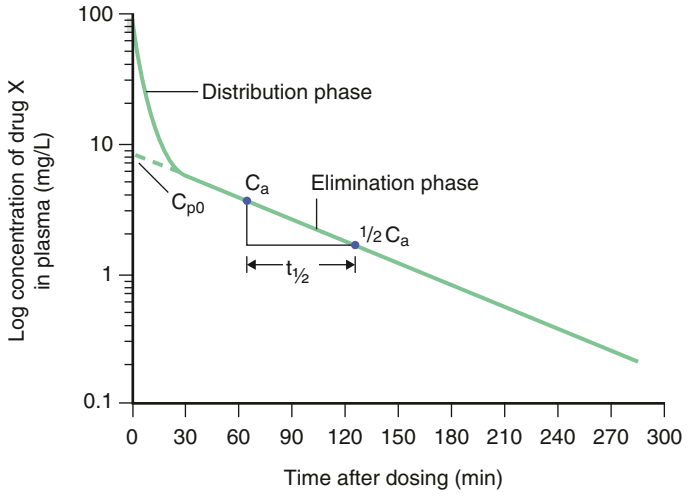

FIGURE 25-2. Representative drug concentration versus time plot used in pharmacokinetic studies. Concentration of drug is plotted with a logarithmic scale on the ordinate, and time is plotted with a linear scale on the abscissa. The resultant curve has two phases: the distribution phase, which is the initial portion of the plotted line when the concentration of drug decreases rapidly; and the later elimination phase, during which there is an exponential disappearance of drug from the plasma over time. The *dotted line* extrapolated from the elimination phase back to time zero is used to calculate plasma concentration at time zero (C_{p0}). During the elimination phase, the half-life ($t_{½}$) can be calculated as the time it takes to decrease the concentration by half (shown here as the time needed to decrease from concentration C_a to ½ C_a).

needed to contain the entire amount of the drug, assuming it is distributed throughout the body at the same concentration as in the plasma. Volume of distribution can vary widely for commonly used drugs (E-Table 25-1). Volume of distribution is useful for calculating a loading dose and appreciating how various changes can affect a drug's half-life.

Elimination

Drugs are removed from the body by two major mechanisms: hepatic elimination, in which drugs are metabolized in the liver and excreted through the biliary tract; and renal elimination, in which drugs are removed from the circulation by either glomerular filtration or tubular secretion. For most drugs, the rates of hepatic and renal elimination are proportional to its plasma concentration, a relationship that is often described as a "first-order" process. Two measurements, clearance and half-life, are used to evaluate elimination.

Clearance

The efficiency of elimination can be assessed by quantifying how fast the drug is cleared from the circulation. Drug clearance is a measure of the volume of plasma cleared of drug per unit of time. It is similar to the clinical measurement used to assess renal function—creatinine clearance, which is the volume of plasma from which creatinine is removed per minute. Total drug clearance (Cl_{tot}) is the rate of elimination by all processes (El_{tot}) divided by the plasma concentration of the drug (C_p):

$$Cl_{tot} = El_{tot}/C_p \quad (2)$$

Drugs may be cleared by several organs, but renal clearance and hepatic clearance are the two major mechanisms, so total drug clearance (Cl_{tot}) for most drugs is essentially the sum of renal clearance and hepatic clearance:

$$Cl_{tot} = Cl_{Ren} + Cl_{Hep} \quad (3)$$

Some drugs have clearances as low as <3 mL/minute, whereas aspirin is cleared at greater than 500 mL/minute. Aminoglycosides are cleared almost entirely by the kidneys, whereas aspirin, carbamazepine, and phenytoin are cleared less than 5% by the kidneys.

Drug clearance is affected by several factors, including blood flow through the organ of clearance, protein binding to the drug, and activity of the clearance processes in the organs of elimination (e.g., glomerular filtration rate and tubular secretion in the kidney, enzyme activity in the liver). Drug clearance is not affected by the volume of distribution of drug throughout the body because clearance mechanisms act only on drug in the circulation.

Half-Life

The amount of time needed to eliminate a drug from the body depends on the clearance and the volume of distribution. The first-order elimination constant (K_e) represents the proportion of the apparent volume of distribution that is cleared of drug per unit of time during the drug's exponential disappearance from the plasma over time (elimination phase):

$$K_e = \text{Cl/volume of distribution} \quad (4)$$

The value of this constant for a particular drug can be determined by plotting drug concentration versus time on a log-linear plot (see Fig. 25-2) and measuring the slope of the straight line obtained during the exponential (elimination) phase.

The time needed to eliminate the drug is best described by its half-life ($t_{1/2}$), which is the time required during the elimination phase (see Fig. 25-2) for the plasma concentration of the drug to be decreased by half. Mathematically, the half-life is equal to the natural logarithm of 2 (representing a reduction of drug concentration to half) divided by K_e. Substituting for K_e from Equation 4 and calculating the natural logarithm of 2, the half-life can be represented by the following equation:

$$t_{1/2} = 0.693 \text{ volume of distribution/Cl} \quad (5)$$

From this equation, one can predict that at any given clearance, as the volume of distribution increases, the half-life increases. Similarly, at a given volume of distribution, the half-life decreases as the clearance increases. Because a disease may affect volume of distribution and clearance differently, the half-life may increase, decrease, or not change much at all.

The half-life is useful to predict how long it takes for a drug to be eliminated from the body. For any drug that has a first-order elimination, one would expect that by the end of the first half-life, the drug would be reduced to 50%; by the end of the second half-life, to 25%; by the end of the third half-life, to 12.5%; by the end of the fourth half-life, to 6.25%; and by the end of the fifth half-life, to 3.125%. In general, a drug can be considered essentially eliminated after five half-lives, when less than 5% of the effective concentration remains.

CLINICAL APPLICATION OF PHARMACOKINETIC PRINCIPLES

Using a Loading Dose

To attain a desired therapeutic concentration rapidly, a loading dose is often used. In determining the amount of drug to be given, the clinician must consider the volume of distribution within the body into which the drug will be distributed.

$$\text{Loading dose} = \text{desired concentration} \times \text{volume of distribution} \quad (6)$$

Rapid administration of an entire loading dose may produce an initially high peak concentration that results in toxicity. This problem can be avoided either by administering the loading dose as a divided dose, by administering the drug as an infusion (with an intravenous drug), or by taking advantage of the slower access to the circulation from various other routes (e.g., oral dosing). For example, phenytoin may require a loading dose to achieve a therapeutic level (10 to 20 mg/L) rapidly. Because the volume of distribution for phenytoin is approximately 0.6 L/kg, the loading dose (see Equation 6) is 420 mg/L to attain a minimally therapeutic level of 10 to 20 mg/L in a 70-kg adult. However, administration of 420 mg of phenytoin by intravenous bolus carries the risk for cardiac arrest and death. By taking advantage of the reduced bioavailability (F = 0.8) and slow absorption of oral phenytoin, the loading dose can be administered safely as an oral dose of 500 mg.

The equation for the loading dose can also be used to calculate the dose needed to "boost" an inadequate blood level of drug to a desired therapeutic range. If therapeutic monitoring (see later under Drug Monitoring as a Guide to Therapy) shows that the phenytoin level is 5 mg/L and the desired level is 15 mg/L, it is necessary to multiply the difference needed to achieve the desired concentration (15 mg/L) by the volume of distribution (0.6 L/kg) to determine the dose (in mg/kg) necessary to achieve this drug level. In a 70-kg individual, 0.6 mg/kg is multiplied by 70 kg to obtain the calculated loading dose (420 mg) that can be administered safely. A 500-mg oral dose with a bioavailability of less than 1 (e.g., F = 0.8) would deliver to the systemic circulation the approximate amount needed and avoid the risks associated with rapid intravenous administration.

E-TABLE 25-1 PHARMACOKINETIC PARAMETERS FOR SOME COMMONLY USED DRUGS

DRUG	VD (L/kg)	PROTEIN BINDING (%)	TOTAL CLEARANCE (mL/min)	% OF TOTAL CLEARANCE AS RENAL CLEARANCE	HALF-LIFE (hr)	THERAPEUTIC RANGE (mg/L)*
Amoxicillin	0.47	17-18	417	86	1.2	2-8
Aspirin (acetylsalicylic acid)	0.14-0.18	80-90	575-725	<2	0.2-0.3	20-250
Carbamazepine	1.2	75-90	50-125	1-3	12-17	4-12
Lithium carbonate	0.7-1	0	20-40	95-99	20-270	0.1-0.4
Phenytoin	0.4-0.8	88-93	167	<5	7-42	10-20
Vancomycin	0.4-1	52-60	65	85	4-6	5-40

*Therapeutic range may vary according to the indication for the drug. For example, lithium carbonate in the range of 0.4-1.3 mg/L is appropriate for affective schizophrenia disorder, whereas a range of 1.0-1.4 mg/L is appropriate for mania. NOTE: The therapeutic range is listed to provide a sense of values often seen rather than an idealized therapeutic drug level range to be attained.
VD = volume of distribution.

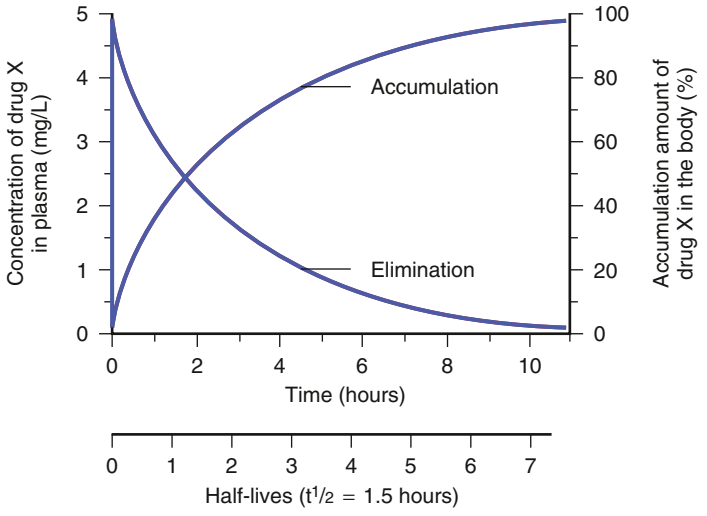

FIGURE 25-3. **Representative plot of the mirror-image relationship between the elimination of drug (after drug is discontinued) and the accumulation of drug (during infusion).** The plot shows the concentration on the left *y*-axis and time on the upper *x*-axis. The lower *x*-axis shows the time in half-lives, and the *y*-axis on the right shows the percentage of drug in the body. After five half-lives, elimination is essentially complete, and accumulation is essentially at a steady state.

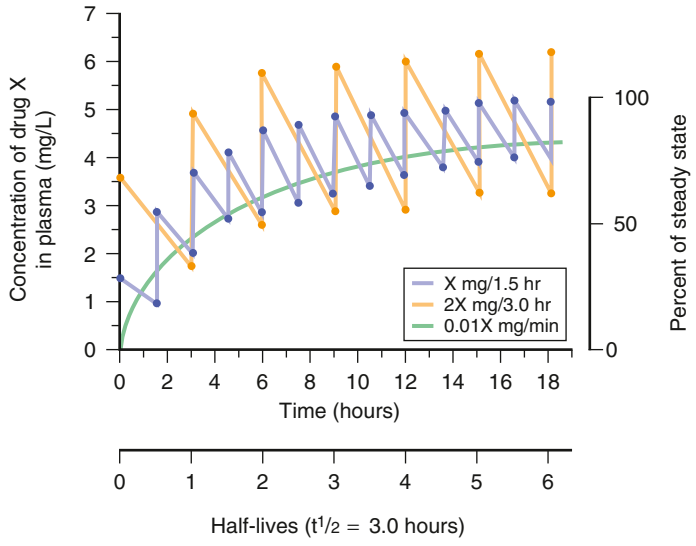

FIGURE 25-4. **Accumulation of drug over time, approaching a steady state.** Time is depicted in hours (upper *x*-axis) and half-lives (lower *x*-axis, showing that steady state is reached in approximately five half-lives). The *green line* depicts the pattern produced by an infusion of a hypothetical drug at a dose of 0.01X. The *orange line* shows the pattern resulting from oral administration of a 2X dose every 3 hours, and the *blue line* represents the pattern produced by oral administration of dose X every 1.5 hours.

Determining Drug Accumulation

Continuing to administer a drug, either as a prolonged infusion or as repeated doses, results in accumulation until the drug level reaches a steady state at which plasma and tissue levels remain constant because the amount of drug being administered equals the amount being eliminated. The elimination half-life determines not only the time course of drug elimination but also the time course of drug accumulation (Fig. 25-3). As with drug elimination, five half-lives is the approximate time needed to reach steady state during drug accumulation. Whereas drugs with short half-lives accumulate rapidly, drugs with long half-lives require a longer time to accumulate, thereby potentially delaying the achievement of therapeutic levels. For drugs with long half-lives, a loading dose may be needed to obtain rapid drug accumulation and a more rapid therapeutic effect.

With each change in drug dose or rate of infusion, a change in steady state occurs. Although it is not obvious for drugs with short half-lives, the effects of dose adjustments for drugs with longer half-lives are delayed, and the time varies directly with the drug's half-life.

Using a Maintenance Dose

After steady state is reached in approximately five half-lives, with either a continuous infusion or intermittent doses, the rate of drug administered equals the rate of drug eliminated. For an intravenous drug, the administration rate is the infusion rate (I); for a drug administered by another route (e.g., orally), the administration rate is the dose per unit of time (D/t). Equation 7 shows that the rate of elimination (total) equals $Cl_{tot} \times C_p$. With an intravenously administered drug, because the infusion rate equals the elimination rate at steady state, it follows that

$$I = Cl_{tot} \times C_p \quad (7)$$

Similarly, with an orally administered drug, the dose administered per unit of time equals the elimination rate at steady state, with the result that

$$D/t = Cl_{tot} \times C_p \quad (8)$$

These equations show the direct relationship between the dose and the resultant plasma concentration at steady state. This relationship is independent of the distribution of the drug. By use of these equations, it is possible to determine the infusion rate or the interval and dose needed to achieve and maintain a specified drug concentration in the plasma.

When a drug is administered intermittently, it approaches steady-state concentration over time, with a pattern similar to that observed with continuous infusion (Fig. 25-4). With intermittent drug administration, such as with an oral dose, the drug concentration fluctuates; the magnitude of fluctuation between the peak and trough concentrations depends on the interval of administration, drug half-life, absorption characteristics, and site of administration. As the intervals decrease below the half-life, the fluctuation decreases and approaches the curve produced by an intravenous infusion. With timed-release formulations, orally administered drugs reach peak concentration more slowly but persist longer in the plasma.

Decreasing the Drug Level

At times, it may be necessary to decrease the plasma drug level while maintaining therapy (e.g., when signs of toxicity become apparent or a potentially dangerously high concentration of drug is noted; see later). The most effective and rapid response is to discontinue the drug; the length of time for which the drug is discontinued is determined by the estimated half-life of the drug in the specific patient. After discontinuation of the drug for a time based on its half-life, the total clearance (Cl_{tot}) of the drug can be used to determine what infusion rate (I, Equation 7) or dose and interval (D/t, Equation 8) must be used to achieve the new desired concentration (C_p).

Effect of Dose Increases on Elimination Kinetics

Not all drugs behave the same when the dose is increased. For most drugs, elimination follows first-order or linear kinetics; the amount of drug eliminated is directly proportional to the concentration of drug in the plasma (Fig. 25-5A). However, a few drugs have a different pattern of elimination. For example, ethanol, phenytoin, and aspirin have dose-dependent, nonlinear saturation kinetics. As the dose of drug increases and the concentration of drug in the plasma rises, the relative amount of drug being eliminated falls (i.e., the clearance decreases) until the rate of drug metabolism is at its maximum. At this point, drug elimination is said to be zero order, and the drug concentration in plasma starts to increase much more (no longer linearly) with each subsequent increase in dose (Fig. 25-5B).

DRUG MONITORING AS A GUIDE TO THERAPY

Although published pharmacokinetic data (usually population averages) are useful to determine initial drug dosing, modification of the dose may be needed in an individual patient. For some drugs (e.g., certain antihypertensive agents or anticoagulants), the therapeutic effects (e.g., blood pressure or coagulation) can be quantified easily over a range of concentrations, thereby permitting adequate drug adjustment. For many other drugs (e.g., some antiarrhythmic or antiseizure medications), therapeutic effects over a range of concentrations are not readily detectable. With these drugs, the plasma concentration may provide further guidance in optimizing therapy if the plasma concentration of the drug is a reflection of its concentration at the site of action and the drug effects are reversible. A third, much smaller group of drugs produces irreversible effects (e.g., aspirin inhibition of platelet aggregation). With these drugs, plasma drug concentration does not correlate with drug effect, and drug monitoring is not useful.

To use drug concentration as a guide to therapy, the range of effective but safe concentrations, or the *therapeutic window*, is usually determined from a dose-response curve generated from a population of patients who have been examined closely for therapeutic and toxic effects (Fig. 25-6). The *therapeutic*

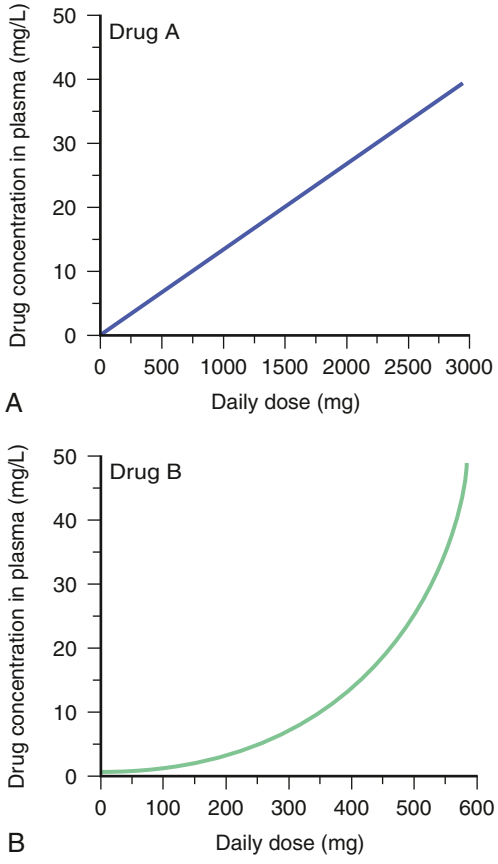

FIGURE 25-5. **Effect of increasing the dose of a drug on its serum concentration. A, Drug A follows first-order or linear kinetics. B, Drug B follows zero-order or nonlinear (or saturable) kinetics.**

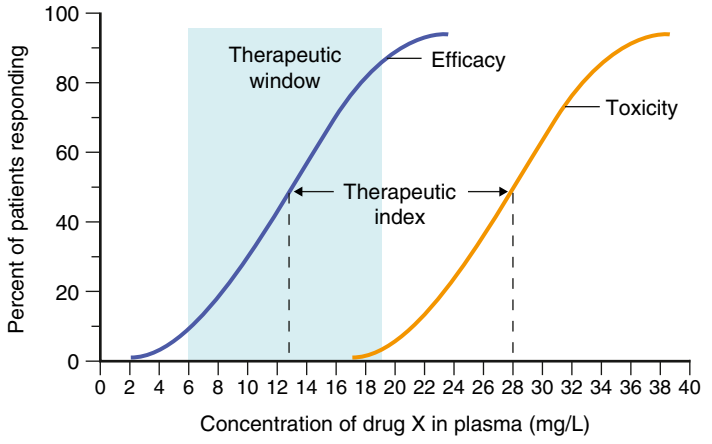

FIGURE 25-6. **Pattern produced in a dose-response population study in which both effect and toxicity are measured. The therapeutic window is shown as the range of therapeutically effective concentrations, which includes most of the efficacy curve and less than 10% of the toxicity curve. The therapeutic index is calculated by dividing the 50% value on the toxicity curve by the 50% value on the efficacy curve.**

index, which is a useful measure of drug toxicity, is calculated by dividing the 50% value from the toxicity curve by the 50% value from the efficacy curve. Because these curves are generated from population data, the values may not be applicable to all individuals.

Drug monitoring is especially useful when a drug is used to treat a serious or life-threatening disease and it is essential to avoid inadequate doses (because a therapeutic effect is often critical) as well as excessive doses (because of the risk for toxicity). In contrast, it is not necessary to assay levels of drugs used to treat noncritical diseases (when inadequate treatment is not a serious problem) or for which the therapeutic index is large (when relative overtreatment is not likely to produce toxicity).

Problems with Interpreting Drug Concentration

The time of blood collection, perhaps more than any other factor, contributes to the misinterpretation of drug levels. If sampling is performed too early, while the drug is still in the distribution phase, the drug level may be high and not reflect drug concentration at the site of action. It is therefore important to sample after the distribution phase.

For many drugs administered intermittently, such as intravenous antibiotics (e.g., vancomycin), a trough level, which is obtained immediately before the next dose is administered, is most useful for making decisions about dose adjustments. For drugs administered by infusion or intermittently at short intervals, the best time to draw blood is during steady state.

Protein binding is another major factor that contributes to the misinterpretation of drug levels. Free drug (not bound to protein and able to equilibrate with tissues and to interact with the site of action) is the critical drug concentration when therapeutic decisions are being made. Many drugs are tightly bound to plasma protein, however. Many commonly used drugs (e.g., aspirin, carbamazepine, and phenytoin), have protein binding of more than 75%, so assessment of the total drug level may not be helpful. Unfortunately, assessment of the "true" free drug concentration also may be inaccurate, particularly if the fraction of drug bound to protein varies. In addition, the drug's binding may be decreased by disease or by other drugs, thereby leading to increased unbound drug levels that alter the interpretation of the measured drug concentrations. Kidney and liver disease can change the binding of certain drugs (e.g., phenytoin) to protein because of a decrease in protein (e.g., decreased albumin, as in nephrotic syndrome or liver disease) or as a result of competition for protein binding by endogenously produced substances (e.g., uremia in kidney disease, hyperbilirubinemia in liver disease). Similarly, other drugs being administered may compete for binding to protein. A major problem secondary to these changes in protein binding is that free drug is not typically measured in many of the common drug assays used by clinical laboratories. Lastly, changes in drug binding to protein can affect the pharmacokinetics of the drug; the volume of distribution increases as protein binding decreases.

The usefulness of a drug assay is also limited by physiologic changes that may alter the response at a particular drug concentration. An example is the response produced by increasing levels of phenytoin in the presence of reduced protein binding (e.g., with hypoalbuminemia or renal impairment), where changes in phenytoin's blood concentration will be exaggerated.

Tolerance, which is a reduced response to a given concentration of drug with continued use, is commonly observed with the continued use of opioids (e.g., in terminal cancer patients). After long-term administration, the same drug concentration is no longer associated with the same pain relief. Positive (placebo) or negative (nocebo) effects may also be associated with many drugs and may mimic their known benefits or toxicities.[2]

ADJUSTMENTS OF DRUG DOSE WITH DISEASE

Kidney Disease

The major questions to be answered when determining whether a drug dosage needs to be adjusted in the setting of kidney disease are: is the drug primarily excreted through the kidneys, and are increased drug levels likely to be associated with toxicity? If the answer to both questions is yes, a drug is likely to accumulate and become toxic as renal clearance decreases unless the drug dose is reduced.

To obtain the desired concentration over time in the presence of decreased clearance, adjustments can be made by decreasing the dose while maintaining the dose interval, maintaining the dose but increasing the interval between doses, or a combination of both (E-Table 25-2). With these adjustments, it may be possible to achieve an average concentration similar to that obtained with normal renal function, but there may be concomitant marked changes in the magnitude of peak and trough values. In choosing the type of drug adjustment, the clinician should consider not only the therapeutic index of the drug but also whether an effective concentration must be achieved quickly and maintained within a narrow range (i.e., maintaining an average drug concentration and avoiding trough levels at which the drug is ineffective); and whether toxicity is associated with elevated (i.e., peak) drug concentrations.

Renal drug clearance correlates with creatinine clearance (whether the drug uses glomerular filtration or tubular secretion), so any adjustment of drug dose in kidney disease can use the creatinine clearance to estimate the dose needed. The creatinine clearance (Cl_{cr}), which is used as an estimate of glomerular filtration rate, may be calculated directly from the serum creatinine concentration by the following equation:

$$Cl_{cr} = [(140 - \text{age}) \times \text{weight (kg)}] / [72 \times \text{serumcreatinine (mg/dL)}] \quad (9)$$

E-TABLE 25-2 EXAMPLES OF ADJUSTMENTS TO DRUG DOSES IN RENAL FAILURE

		HALF-LIFE (HR)			*ADJUSTMENT FOR RENAL FAILURE*			
DRUG	**TYPE OF ELIMINATION**	**NORMAL**	**END-STAGE RENAL DISEASE**	**METHOD***	**GFR > 50 mL/min**	**GFR 10-50 mL/min**	**GFR < 10 mL/min**	**REMOVED BY DIALYSIS†**
Amikacin	Renal	2-3	30	DD II	60-90% 12 hr	30-70% 12-18 hr	20-30% 24 hr	Yes
Aspirin	Hepatic (renal)	2-19	Unchanged	II	4 hr	4-6 hr	Avoid	Yes
Carbamazepine	Hepatic (renal)	35	?	DD	Unchanged	Unchanged	75%	No
Lithium carbonate	Renal	14-28	Prolonged	DD	Unchanged	50-75%	25-50%	Yes
Phenytoin	Hepatic (renal)	24	8	DD	Unchanged	Unchanged	Unchanged	No
Tobramycin	Renal	2.5	56	DD II	60-90% 8-12 hr	30-70% 12 hr	20-30% 24 hr	Yes
Vancomycin	Renal	6-8	200-250	II	24-72 hr	72-240 hr	240 hr	No

*DD (alone) = decrease dose (maintain same interval); II (alone) = increase interval between doses (maintain dose); DD and II (together) = combination of both approaches.
†Dialysis refers to hemodialysis.
GFR = glomerular filtration rate.

The calculated creatinine clearance should be multiplied by 0.85 for females when the serum creatinine concentration is less than 5 mg/dL and renal function is not rapidly changing.

Using Clearance for Dose Adjustment

The dose of a drug used in renal insufficiency ($dose_{D\text{-}RI}$) is proportional to the dose used with normal renal function ($dose_D$) in the same ratio as clearance of the drug in renal insufficiency ($Cl_{D\text{-}RI}$) to clearance with normal renal function (Cl_D). By rearranging, $dose_{D\text{-}RI}$ is defined as:

$$Dose_{D\text{-}RI} = dose_D \times [Cl_{D\text{-}RI}/Cl_D] \quad (10)$$

The $Cl_{D\text{-}RI}$ can be estimated by multiplying Cl_D by the ratio of the creatinine clearance in renal insufficiency ($Cl_{cr\text{-}RI}$) over Cl_{cr} with normal renal function:

$$Cl_{D\text{-}RI} = Cl_D \times [Cl_{cr\text{-}RI}/Cl_{cr}] \quad (11)$$

As shown in Equation 3, total clearance is the sum of clearance by renal and nonrenal (typically hepatic) mechanisms. Any nonrenal clearance is assumed to remain normal, and only the renal clearance is adjusted, with total clearance being reduced only to the extent that renal clearance is reduced. The dose may be calculated from the total (adjusted) clearance and the desired plasma concentration by either Equation 7 or Equation 8.

However, the calculated dose is only an initial guide to the needed dose. By monitoring the drug response or the plasma drug concentration at various times after initial dosing, further dose adjustments can be made as necessary. From a practical perspective, most clinical dose adjustments in the presence of renal dysfunction can be guided by published tables based on changes in glomerular filtration rate and the effectiveness of dialysis in removing the drug. Computerized decision support systems are particularly effective in guiding medication dosing for inpatients with renal insufficiency.

Loading Dose in Renal Insufficiency

For drugs that are typically administered with a loading dose in patients with normal renal function, the same approach can be used in patients with renal insufficiency to ensure that the desired concentration is achieved rapidly. For drugs typically administered without a loading dose, the prolonged half-life that results from renal insufficiency may delay the time required to reach a steady state. In this setting, a loading dose (equal to the amount needed to reach steady state with normal renal function) should be followed by lower or less frequent maintenance doses.

Liver Disease

Although many drugs are biotransformed in the liver, no useful laboratory test can guide dose adjustments. If the liver's capacity to produce protein (reflected by a low albumin concentration and prolonged prothrombin time) is reduced significantly, the clearance of drugs metabolized by the cytochrome P-450 enzymes is probably reduced as well.

One special situation that can develop with chronic liver disease and may require dose adjustment is portal hypertension with a portacaval shunt (Chapter 139). In this situation, hepatic blood flow decreases and hepatic clearance also decreases, thereby reducing the first-pass effect and resulting in higher concentrations of drug reaching the systemic circulation. Drugs with a large hepatic extraction that are typically administered orally (e.g., propranolol to lower portal vein pressure) may appear in the systemic circulation at higher, potentially toxic concentrations.

Hemodynamic Diseases

Decreased cardiac output and hypotensive conditions lead to decreased perfusion of the organs, including those responsible for eliminating drugs. The drug dose can be adjusted for decreased renal perfusion by the use of creatinine clearance. The effect of decreased hepatic blood flow on pharmacokinetics is more difficult to assess. For drugs that have a high hepatic extraction (e.g., lidocaine), decreased hepatic blood flow suggests a need for dose reduction.

Altered hemodynamics also may affect the distribution of selected drugs. Drugs that have a relatively large volume of distribution (e.g., lidocaine) may be affected by conditions leading to hypotension, such as shock, thereby resulting in a decrease in the apparent volume of distribution and a need to reduce the loading dose to avoid potentially toxic drug levels.

In general, in the setting of severely compromised hemodynamics, it is advisable to be conservative and to avoid potentially toxic loading and maintenance doses. Drug levels and the clinical status should be monitored closely, and drug doses should be adjusted as necessary.

TABLE 25-1 GENERAL RECOMMENDATIONS FOR DRUG USE IN ELDERLY PATIENTS

- Clearance of drugs eliminated by the kidneys may be reduced by 50%.
- Drugs eliminated primarily by the liver typically do not require dose adjustments for age, except for drugs with high hepatic clearances, which may be affected by the age-related decrease in hepatic blood flow.
- Because of the potential for increased target organ sensitivity in elderly people, only the lowest effective dose should be used.
- Frequent reviews of the patient's drug history should be conducted, including both prescription and over-the-counter medications, keeping in mind the increased potential risk for drug interactions and adverse drug responses.

APPROACH TO DRUG OVERDOSE

The pharmacokinetic principles discussed earlier can be used to determine the best approach for drug removal in the setting of a drug overdose (Chapter 96), particularly if hemodialysis or hemoperfusion remove a substantial fraction of the total body load of drug. For drugs with a large volume of distribution (e.g., warfarin), only a small amount can be removed because clearance affects only the amount of drug present in the plasma, and a large portion of the drug is outside the plasma compartment. Similarly, for a drug with high clearance value (e.g., metformin), hemoperfusion may increase the overall clearance only minimally and is not indicated.

DRUG USE IN ELDERLY PATIENTS

Administering drugs to elderly patients (Chapter 24) is perhaps the most challenging area of adult therapeutics because of several factors: the increasing likelihood of multiple illnesses, often with multisystemic involvement; the need for these patients to take multiple drugs (often prescribed by different physicians); and the increasing probability of altered pharmacokinetics and pharmacodynamics. These factors together contribute to a significantly increased frequency of drug interactions and adverse drug responses in this group of patients (Table 25-1).

Pharmacokinetic Changes with Age

Pharmacokinetic changes can be secondary to the general physiologic effects of aging, such as alteration in body composition, or to specific changes in pharmacokinetically important organs (e.g., kidneys, liver). The distribution of drugs tends to change dramatically with age, mainly because of changes in body composition. Most typical is the increase in total body fat, with the accompanying decrease in lean body mass and total body water. The concentration of plasma proteins may also change; in particular, the albumin level may decrease as the liver ages. For water-soluble drugs that are not bound to plasma proteins, the apparent volume of distribution is reduced; in contrast, for lipid-soluble drugs, the volume of distribution is increased. Changes in metabolism also accompany aging, but these changes alone do not typically account for altered pharmacokinetics.

The clearance of many drugs is decreased in the elderly because cardiac output and blood flow to the kidneys and liver may be decreased. Glomerular filtration rate may be reduced by 50%. Hepatic elimination of drugs is less affected, except for drugs with a high hepatic clearance (e.g., lidocaine). The elimination half-life of many drugs is increased with aging as a consequence of a larger apparent volume of distribution and a decreased hepatic or renal clearance (see Equation 5).

Pharmacodynamic Changes with Age

Pharmacodynamic changes are a result of changes in the responsiveness of the target organ. Elderly individuals typically require lower drug doses, even if the pharmacokinetics are little changed. For example, antianxiety drugs and drugs from the sedative-hypnotic class may produce increased central nervous system depression in elderly patients at concentrations that are well tolerated in younger adults.

INTERACTIONS AMONG DRUGS

Because patients are typically treated with multiple agents, even for a single disease, the possibilities for drug interactions are great. Many clinically important drug interactions typically involve a drug with a low therapeutic index (e.g., warfarin) and an easily detectable pharmacologic effect (e.g., bleeding), such that a small increase in the amount of drug produces a significant effect (toxicity).

It is difficult to assess the prevalence of drug interactions in either the inpatient or the ambulatory setting, particularly because no formal and comprehensive

surveillance mechanism is available. However, the risk for drug interactions seems to be increasing, particularly for critically ill, hospitalized patients who are frequently taking more than 10 medications.[3]

There are basically two types of drug interaction: pharmacokinetic drug interactions, caused by a change in the amount of drug or active metabolite at the site of action; and pharmacodynamic drug interactions (without a change in pharmacokinetics), caused by a change in drug effect.

Pharmacokinetic Drug Interactions

Less Drug at the Site of Action

Decreased Absorption

The gastrointestinal lumen is perhaps the best example of an area where drug interactions can result in decreased drug absorption. Some commonly used drugs can illustrate this type of interaction. For many drugs, a physicochemical interaction prevents the drug from being absorbed. For example, metal ions (e.g., aluminum, calcium, and magnesium in antacids and iron in supplements to treat iron deficiency) form insoluble complexes with tetracyclines and can act as chelating agents. Other commonly used medications that decrease absorption include kaolin-pectin suspensions, which are used to treat diarrhea and can significantly inhibit the absorption of coadministered drugs.

Drugs that are particularly susceptible to changes in pH may have decreased absorption when they are administered with other drugs that either affect gastric acidity or alter the extent of exposure to low pH. Proton pump inhibitors or histamine-2 receptor antagonists may elevate gastric pH, which can inhibit the dissolution and subsequent absorption of drugs that are weak bases (e.g., ketoconazole). Medications that delay gastric emptying (e.g., belladonna alkaloids) can increase the degradation of a coadministered acid-labile drug (e.g., levodopa), thereby resulting in decreased absorption.

Altered Distribution

Drugs that use the same active transport process to reach their site of action can compete at the level of transport, thereby resulting in lower levels of drug reaching that site. Examples of this type of interaction include the interaction of phenothiazines (e.g., chlorpromazine) with tricyclic antidepressants (e.g., amitriptyline).

Increased Metabolism

Many drugs (e.g., phenytoin, ethanol, griseofulvin, rifampin) and toxic compounds (e.g., cigarette smoke, certain chlorinated hydrocarbons) can increase the hepatic metabolism of other drugs (e.g., corticosteroids, cyclophosphamide, cyclosporine, certain β-adrenergic blockers, theophylline, warfarin) by inducing the activity of the cytochrome P-450 super family of monooxygenase enzyme (see medicine.iupui.edu/clinpharm/ddis/ for more information).

More Drug at the Site of Action

Increased Absorption

Any drug that increases the rate of gastric emptying (e.g., metoclopramide) can potentially increase the absorption of acid-unstable drugs. Also, drugs that decrease intestinal motility (e.g., anticholinergics) may increase the absorption of drugs that are relatively poorly absorbed (e.g., metformin) by increasing the drug's contact time with the absorbing surface.

Altered Distribution

Drugs bound to protein are limited in their distribution (particularly at the site of action) and are not available for metabolism or excretion. Drugs can compete with each other for binding to plasma proteins, resulting in drug interactions. Phenytoin and warfarin are both greater than 90% bound to protein. When both are coadministered, phenytoin can displace warfarin, thereby leading to an increased anticoagulant effect and possible bleeding.

Decreased Metabolism

One of the most impressive drug interactions is produced when one drug inhibits the metabolism of another, thereby leading to the second drug's accumulation and a significant risk for toxicity. An example of this type of interaction occurs when 6-mercaptopurine, an antileukemic drug with a low therapeutic index, is used with allopurinol, often administered to control hyperuricemia. The interaction may result in potentially life-threatening toxicity.

Some drugs can inhibit the metabolism of many other drugs because many drugs share the same metabolic pathway. This consideration is particularly relevant for drugs that share CYP-450 pathways. It is estimated that CYP2D6 accounts for the metabolism of approximately 25% of all currently prescribed drugs, including antidepressants, neuroleptics, β-blockers, opioids, antiemetics, antiarrhythmics, and even some cancer chemotherapy drugs. Some commonly used drugs such as cimetidine can inhibit the metabolism of drugs from several different classes, such as diazepam, imipramine, lidocaine, propranolol, theophylline, and warfarin. Agents such as amiodarone inhibit the metabolism of calcium-channel blockers, phenytoin, and warfarin. Of particular importance with amiodarone is its half-life of 1 to 2 months; it continues to inhibit drug metabolism for several months after it has been discontinued.

Other drugs are notable because their metabolism is inhibited by a variety of different drugs. The metabolism of warfarin is inhibited not only by cimetidine and amiodarone but also by many other drugs, including alcohol, allopurinol, disulfiram, metronidazole, phenylbutazone, sulfinpyrazone, and trimethoprim-sulfamethoxazole. Similarly, the metabolism of phenytoin is inhibited by chloramphenicol, clofibrate, disulfiram, isoniazid (slow acetylators; see Table 25-3), phenylbutazone, and valproic acid.

Although most of these examples involve enzymes that metabolize the drug within the liver, drug-metabolizing enzymes outside the liver also may be affected by certain drugs. Perhaps the best-known example is monoamine oxidase, which can be affected by nonspecific monoamine oxidase inhibitors, thereby resulting in the accumulation of catecholamines at multiple sites after their release in response to the eating of tyramine-containing foods such as aged cheese, aged or cured meats, and any spoiled meat, poultry, or fish.

Decreased Excretion

Drugs can compete for the active transporters present in the kidney. Most of these interactions involve the acid transporters. The best-known interaction is probenecid's inhibition of penicillin transport, thereby leading to decreased penicillin clearance and thus higher plasma levels, an interaction that was helpful when penicillin was in short supply. A similar inhibitory effect on the renal excretion of methotrexate can be produced by salicylates, phenylbutazone, and probenecid. The active transport of basic drugs (e.g., metformin and dofetilide) can also be inhibited by other drugs (e.g., cimetidine).

Pharmacodynamic Drug Interactions

With pharmacodynamic interactions, drugs interact at the level of the receptor (target) or may produce additive effects by acting at separate sites on cells. An example of the first is the interaction of a β-blocker with epinephrine, which blocks β-adrenergic receptors; as a result, the α-adrenergic effects of epinephrine are unopposed. This undesirable interaction can result in severe hypertension. The additive effects of drugs are exemplified by aspirin, which can increase the bleeding time by acting on platelets, and direct-acting oral anticoagulants, which affect clotting (Chapter 70). The result is an increased risk for hemorrhage. Similarly, β-adrenergic blockers and calcium-channel blockers have additive negative inotropic effects when they are coadministered.

DIAGNOSIS AND PREVENTION OF DRUG INTERACTIONS

For a drug interaction to be recognized, the index of suspicion must be high, particularly whenever multiple drugs are used together. Several clinical settings should raise concern about the possibility of drug interactions and alert the clinician as to how to avoid them (Table 25-2). Because of the ever-increasing list of known and suspected drug interactions, it is impossible for a clinician to remember all or even many of the possible interactions, so it is best to consult one of a number of websites (e.g., www.drugs.com/drug_interactions.html and reference.medscape.com/drug-interactionchecker) that maintain current information on drug interactions.

Another type of drug interaction is between components of food (e.g., grapefruit juice) or natural products (e.g., herbs) and drugs. By inhibiting the intestinal CYP-450 3A4 enzyme system, grapefruit juice can raise levels of drugs metabolized by this pathway (e.g., saquinavir, cyclosporine, verapamil) and result in toxicity or adverse drug effects. It is now recognized that a number of foods and herbs can affect drug-metabolizing enzymes, such as the CYP-450s (see medicine.iupui.edu/clinpharm/ddis/).

ADVERSE REACTIONS TO DRUGS

An adverse drug response is an undesired effect produced by a drug at standard doses, which typically necessitates reducing or stopping the suspected agent and may require treatment of the noxious effect produced. Further harm may occur with continued or future therapy with the drug.

EPIDEMIOLOGY

The financial impact of adverse drug responses is estimated to be more than $100 billion per year. The actual incidence of adverse drug responses is difficult to quantify because many cases are either not recognized or not

TABLE 25-2 HIGH-RISK SITUATIONS THAT RAISE CONCERNS ABOUT POSSIBLE DRUG INTERACTIONS AND HOW TO PREVENT THEM

HIGH-RISK SITUATIONS

- The use of any drug with a low therapeutic index (e.g., anticoagulant agents, antiarrhythmic agents, anticonvulsant agents, lithium carbonate, oral hypoglycemic agents).
- As the number of drugs being used concurrently increases, the risk for drug interactions disproportionately increases, particularly with more than 10 drugs.
- Critically ill patients who have multisystemic disease with compromised renal, hepatic, cardiac, or pulmonary function.
- Patients who have the acquired immunodeficiency syndrome or an immunocompromised state.
- Patients with various behavioral and psychiatric disorders (e.g., patients who take many prescription drugs as well as illicit drugs and alcohol).

STEPS CAN BE TAKEN TO PREVENT DRUG INTERACTIONS

- When taking the medical history, document all drugs the patient is taking (and has recently taken), including prescription, over-the-counter, and other addictive drugs.
- Minimize the number of drugs being taken by frequently reviewing the patient's drug list to ensure that each drug continues to be needed.
- Have a high degree of suspicion when medications that have a low therapeutic index and are known to have a high risk for drug interactions are used.
- Be especially alert in high-risk clinical settings, such as occur with critically ill patients.
- Consider adverse drug interactions in the differential diagnosis whenever any change occurs in a patient's course.

reported. The incidence may approach 20% for outpatients (even higher for patients taking more than 15 drugs) and 2 to 7% for inpatients. The incidence of adverse drug responses increases exponentially with more than four drugs. Meta-analyses of several prospective studies suggest that adverse drug responses are now the fourth leading cause of death in hospitalized patients. Each year, adverse drug events cause an estimated four emergency department visits per 1000 individuals in the United States, with an estimated 100,000 drug-related emergency hospitalizations just in patients older than age 65 years. The most common drug classes implicated are anticoagulants, antibiotics, diabetes drugs, and opioid analgesics.[4] The incidence of adverse drug responses is likely to increase because of more prescribed and over-the-counter medications being used. Electronic medical records have the potential to predict adverse drug events and hopefully to prevent them.[5,6]

PATHOBIOLOGY

Most adverse drug responses are caused by an exaggerated (but predictable) pharmacologic effect of the drug or by a toxic or immunologic effect of the drug or a metabolite (not typically expected).

Predictable Toxic Responses to Drugs

Exaggerated drug responses that cause adverse drug effects may be due to any condition, including genetic factors,[7] that alter pharmacokinetics or pharmacodynamics. Molecular changes in the genes coding for drug-metabolizing enzymes include autosomal recessive polymorphisms associated with the debrisoquine-sparteine, *N*-acetylation, and mephenytoin types or classes of drugs (Table 25-3). Individuals with autosomal recessive genes are typically "poor metabolizers," with potentially altered pharmacokinetics that result in elevated plasma drug concentrations and can lead to toxicity. For example, the variability of response to warfarin (Chapter 70) is now understood to be due to single-nucleotide polymorphisms in the cytochrome P-450 2C9 *(CYP2C9)* and vitamin K epoxide reductase *(VKOR)* genes.

A particularly impressive example occurs with certain cancer chemotherapeutic agents that have a relatively narrow therapeutic window and the potential to produce severe cytotoxicity (e.g., deficiency in dihydropyrimidine dehydrogenase activity can result in life-threatening toxicity after the administration of 5-fluorouracil). These defects typically are not recognized until the patient is given the drug. They are often described as "pharmacogenetic" syndromes.

Other genetic alterations do not affect metabolism specifically and do not produce a range of quantitative changes. These defects can produce "qualitative" defects and are often associated with structural defects. The classic example is glucose-6-phosphate dehydrogenase. Individuals who are deficient in this enzyme cannot tolerate the oxidative stress produced by some drugs, thereby leading to hemolysis (Chapter 147). Drugs that can produce this clinical picture include aspirin, nitrofurantoin, primaquine, probenecid, quinine, sulfonamides, sulfones, and vitamin K. Another similar defect is deficiency of methemoglobin reductase, which results in an inability to maintain iron in hemoglobin in the ferrous state, causing methemoglobinemia (Chapter 144) after exposure to oxidizing drugs such as nitrites, sulfonamides, and sulfones.

Unpredictable Toxic Responses to Drugs

Other toxic or immunologic adverse drug responses are not predictable and are not obviously due to an increase in drug concentration (pharmacokinetic) or drug effect (pharmacodynamic). Unpredictable toxic responses include direct reactions between a drug and a specific organ (e.g., platinum-containing drugs, such as cisplatin, can produce direct toxicity in the kidney and the eighth cranial nerve, and a wide range of drugs can cause liver injury [Chapter 136]). With other drugs, metabolism to an active intermediate must occur first. With a standard dose of acetaminophen, no untoward effects occur because the relatively small amount of reactive metabolite formed by oxidative metabolism is detoxified rapidly by reduced glutathione. In the presence of an overdose (Chapter 96), the glutathione is depleted, and the remaining reactive metabolite can damage the liver.

Immunologic reactions to drugs are generally not produced by the drug alone. Similar to other low-molecular-weight compounds (<1000 D), they are typically not antigenic themselves. When a drug or reactive metabolite combines with a protein to form a drug-protein complex, it can become antigenic, capable of eliciting an immune response.

Perhaps the most impressive form of drug allergy (Chapter 234) is anaphylaxis (Chapter 233), which is due to an immunoglobulin E–mediated hypersensitivity. Many drugs from different classes have been shown to produce this type of drug allergy. The best-known example is the anaphylactic response produced by penicillin, which can occur after its administration by any route. Skin testing with penicillin G, penicilloic acid, or penicilloyl polylysine can identify patients at risk and should be performed in those with a suspected penicillin allergy who need treatment with penicillin. If the skin test result is

TABLE 25-3 GENETIC POLYMORPHISMS OF DRUG-METABOLIZING ENZYMES

TYPE	PRIMARY DRUG EXAMPLES	OTHER DRUGS THAT ARE SUBSTRATES	INCIDENCE OF "POOR METABOLIZERS" (%)	ENZYME INVOLVED
Debrisoquine-sparteine polymorphism	Amitriptyline, codeine, tamoxifen	Antidepressants, antiarrhythmics, β-adrenergic receptor–blocking drugs, codeine, dextromethorphan, neuroleptics	5-10 (Whites)	Cytochrome P-450 IID6 (CYP2D6)
Mephenytoin polymorphism	Mephenytoin	Mephobarbital, hexobarbital, diazepam, omeprazole	4 (Japanese, Chinese, 15-20)	Cytochrome P-450 IIC (CYP2C)
N-acetylation polymorphism	Isoniazid, sulfadiazine	Hydralazine, phenelzine, procainamide, dapsone, sulfamethazine, sulfapyridine, aminoglutethimide, aminosalicylic acid, sulfasalazine	40-70 (Japanese, 10-20)	*N*-acetyltransferase (NAT2)
Methyl conjugation polymorphism	Catecholamines	L-Dopa, methyldopa	25-30 (Whites)	Catechol-*O* methyltransferase (COMT)

positive, the patient must undergo desensitization before receiving penicillin. If the skin test result is negative, penicillin can be administered with caution.

DIAGNOSIS AND PREVENTION OF ADVERSE DRUG RESPONSES

Although many of the well-known adverse drug effects are due to a relatively small group of drugs, every drug has the potential to cause an adverse reaction. A physician should always consider the possibility of an adverse drug reaction in the differential diagnosis even if none has been previously reported to an updated website (e.g., www.fdable.com) for the particular drug. Health care professionals are encouraged to report any adverse events or product problems on a one-page form that can be sent by mail, fax, or electronically to the U.S. Food and Drug Administration (https://www.fda.gov/safety/medical-product-safety-information/medwatch-forms-fda-safety-reporting).

In many instances, it is readily apparent that a specific drug has produced an adverse reaction, such as the appearance of a rash in an otherwise healthy patient who was recently prescribed a single drug (e.g., penicillin).[8] In other cases, the effect produced by the drug may be difficult to discern from other disease states. In still other cases, the adverse effect may mimic the illness being treated (e.g., development of an arrhythmia in a patient being treated with an antiarrhythmic drug).

A patient's list of prescription drugs should be reviewed at each visit, and potential interactions with any nonprescription drugs should also be assessed. Screening tools[9] that can identify potentially inappropriate or unnecessary drug prescriptions can also reduce the risks of adverse drug reactions.[A1,A2]

The recent severe acute respiratory syndrome coronavirus 2 pandemic (Chapters 335 to 337) has resulted in external pressures to bring new drugs to market quickly. However, this public health crisis has also emphasized the need for the careful application of basic principles of clinical pharmacology in drug development.[10]

USEFULNESS OF GENOMIC DATA

In addition to being useful for avoiding adverse drug effects (see earlier), genomic data (e.g., the presence of a specific genetic variant) can also help inform the clinician of the optimal drug or dose for a specific patient. With oncologic drugs, genomic data from the tumor of an individual patient often can be useful in making a specific therapeutic decision (see www.fda.gov/drugs/science-and-research-drugs/table-pharmacogenomic-biomarkers-drug-labeling) (Chapter 164). An example is vemurafenib, which is an orally bioavailable, adenosine triphosphate (ATP)-competitive, small-molecule inhibitor of BRAF(V600E) kinase and which is effective against melanoma and potentially other malignancies[A3] that have a specific mutation in their *BRAF* gene—a valine-to-glutamic acid mutation at residue 600 (V600E) that results in the oncogene protein product, BRAF(V600E) kinase and markedly elevates activity in the MAPK signaling pathway.

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26 PAIN

STEVEN P. COHEN

DEFINITION

In 2020, the International Association for the Study of Pain redefined pain as "an unpleasant sensory and emotional experience associated with, or resembling that associated with, actual or potential tissue damage."[1] This definition removes the connection between the perception of pain and its stimulus, and it also acknowledges that pain may occur in the absence of ongoing tissue damage, such as with fibromyalgia or phantom limb pain.[2] One implication of this construct is that pain is always subjective. Hence, a patient's report of pain should be accepted at face value in the absence of evidence to the contrary, even though some treatments may be tailored to objective evidence.

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Populations at high risk for chronic pain include the elderly, people residing in rural areas, minority individuals, service members and veterans, and individuals with physical and psychological morbidities. Reasons for these disparities may include cultural issues, access to care, and differential treatment. Many chronic pain conditions including headaches, abdominal pain, and widespread pain disorders are more common in females.

PATHOBIOLOGY

The biopsychosocial model posits that biological, psychological, and social factors play a role in chronic pain (Fig. 26-1). The relationship between psychopathology in pain is bidirectional, with many conditions strongly associated with the persistence of pain after acute injury. Social factors that can negatively affect treatment include low job satisfaction, smoking, sedentary lifestyle, and secondary gain. Functional imaging has demonstrated that the brains of chronic pain patients are different than normal individuals, and that they undergo morphologic alterations such as general and disease-specific diminutions in gray matter as a consequence of chronic pain.

Nociception is the physiologic activation of specialized peripheral receptors *(nociceptors)* by stimuli that are potentially damaging to tissue (e.g., mechanical [tumor growth, incision], thermal, or chemical [ischemia or infection]). In addition to nociceptors that respond to specific stimuli, polymodal nociceptors respond to multiple modalities.

In contrast, pain is a conscious experience that results not only from activation of nociceptive pathways (sensory-discriminative component) but is also influenced by alterations in somatosensory processing following tissue injury, psychosocial factors (affective-motivational component), past experience, and expectations (cognitive-evaluative component). Once a stimulus is detected, it is converted into an electrical nerve signal through activation of transduction channels (e.g., transient receptor potential channels) expressed on the axonal membrane *(transduction)*. These action potentials are conveyed along the axons of unmyelinated (C) or thinly myelinated (A-delta) nerve fibers through specific pathways *(transmission)*. Modulation refers to the attenuation

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positive, the patient must undergo desensitization before receiving penicillin. If the skin test result is negative, penicillin can be administered with caution.

DIAGNOSIS AND PREVENTION OF ADVERSE DRUG RESPONSES

Although many of the well-known adverse drug effects are due to a relatively small group of drugs, every drug has the potential to cause an adverse reaction. A physician should always consider the possibility of an adverse drug reaction in the differential diagnosis even if none has been previously reported to an updated website (e.g., www.fdable.com) for the particular drug. Health care professionals are encouraged to report any adverse events or product problems on a one-page form that can be sent by mail, fax, or electronically to the U.S. Food and Drug Administration (https://www.fda.gov/safety/medical-product-safety-information/medwatch-forms-fda-safety-reporting).

In many instances, it is readily apparent that a specific drug has produced an adverse reaction, such as the appearance of a rash in an otherwise healthy patient who was recently prescribed a single drug (e.g., penicillin).[8] In other cases, the effect produced by the drug may be difficult to discern from other disease states. In still other cases, the adverse effect may mimic the illness being treated (e.g., development of an arrhythmia in a patient being treated with an antiarrhythmic drug).

A patient's list of prescription drugs should be reviewed at each visit, and potential interactions with any nonprescription drugs should also be assessed. Screening tools[9] that can identify potentially inappropriate or unnecessary drug prescriptions can also reduce the risks of adverse drug reactions.[A1,A2]

The recent severe acute respiratory syndrome coronavirus 2 pandemic (Chapters 335 to 337) has resulted in external pressures to bring new drugs to market quickly. However, this public health crisis has also emphasized the need for the careful application of basic principles of clinical pharmacology in drug development.[10]

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ABSTRACT

Pain is the most common reason people seek medical attention and the leading cause of disability. Pain can be classified in a variety of ways, including acuity (chronic pain is pain persisting >3 months) and cause. Nociceptive pain results from actual or potential tissue injury, neuropathic pain results from an injury or disease that affects the somatosensory system, and nociplastic pain arises from altered nociception despite no clear evidence of tissue damage or abnormalities that affect the somatosensory system. Acuity is a strong predictor of outcome, whereas the cause of pain informs treatment decisions at all levels of care. Pain differs from the physical process of nociception in that it represents the denouement of a complex perceptual experience affected by myriad factors that include not only nociceptor activation, but also emotions, cognition, social and cultural context, and expectations.

Currently, no biomarkers or diagnostic tests can reliably identify or measure pain, so a patient's subjective pain complaints must be taken seriously, even though objective findings can and should influence treatment decisions. The goals of treatment should ideally include elucidating the cause of pain, mitigating nociception, improving quality of life, and alleviating suffering. The treatment of pain can be divided into four classes: conservative, which includes physical and psychotherapy; pharmacotherapy, which includes opioids and nonopioid analgesics; procedural interventions, which include injections and surgery; and increasingly popular integrative treatments, which include acupuncture, yoga, and chiropractic. Despite a paucity of studies evaluating an integrative approach, a widespread consensus supports that an interdisciplinary model is beneficial.

KEYWORDS

chronic pain
nociception
neuropathic
nociplastic
injections
surgery
spinal pain
biopsychosocial

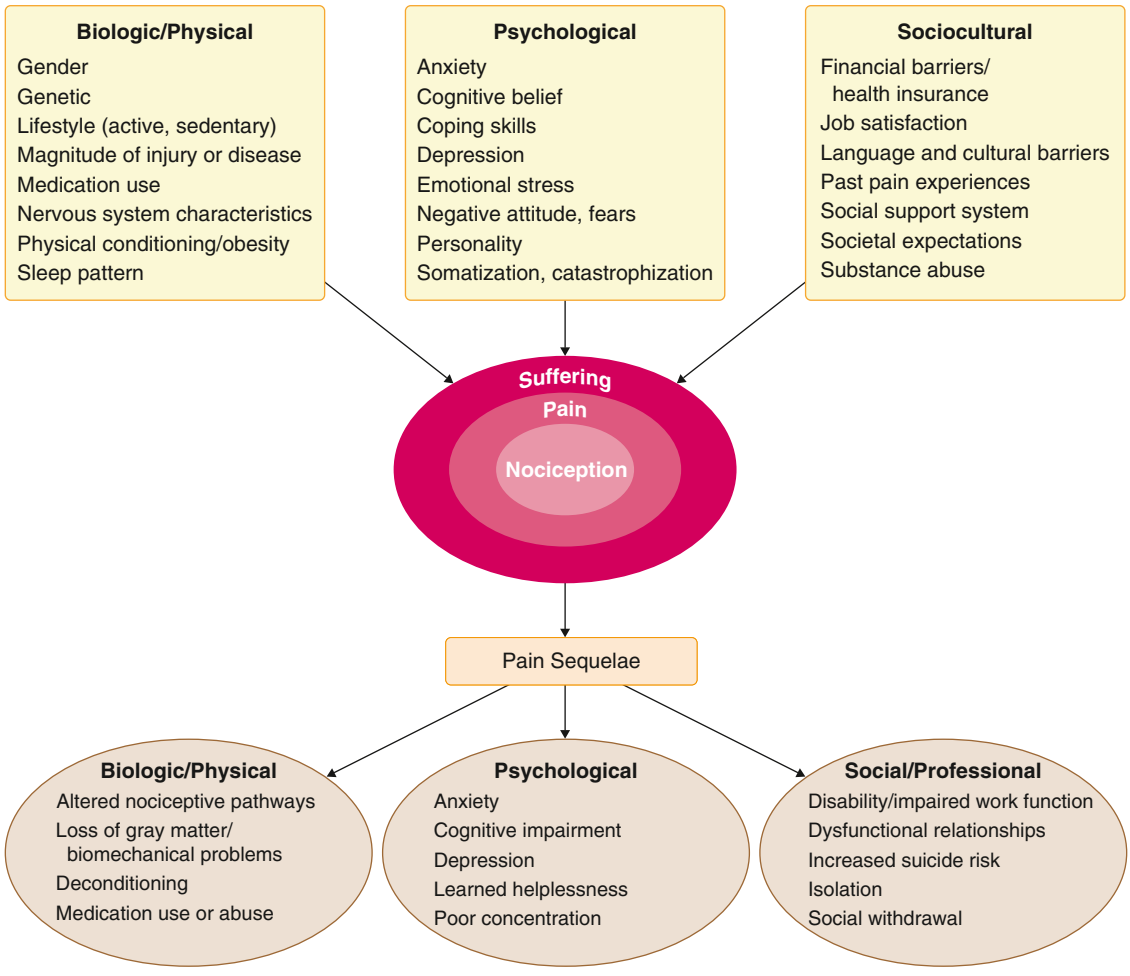

FIGURE 26-1. **Biopsychosocial model of pain.**

(or amplification) of pain signals through intrinsic inhibitory activity within the peripheral and central nervous systems (e.g., intrinsic brain and spinal neurons that release a plethora of neurotransmitters) before being perceived as unpleasant *(perception),* though in some cases pain signals may be enhanced during this process (e.g., wind-up). Pathologic pain results when injury- or disease-induced changes in the peripheral and/or central nervous systems lead to enhanced pain signaling. One example is *peripheral sensitization,* which is characterized by spontaneous ectopic activity in injured nerves and dorsal root ganglion cells, as well as enhanced sensitivity to stimuli.

Prolonged and repeated activation of nociceptive afferent fibers produces *central sensitization,* a state of hyperexcitability of central pain-signaling neurons with activation of *N*-methyl-D-aspartate (NMDA) receptors by glutamate. Loss of inhibitory interneurons and altered balance between descending inhibitory and excitatory modulatory mechanisms play a key role in the maintenance of pain. Other central neuroplastic changes that contribute to neuropathic pain include deafferentation hyperactivity following spinal cord or avulsion injuries, loss of large fiber inhibition, and reorganization of central connections of primary afferent fibers. Central and peripheral sensitization are considered to be the prime culprits responsible for pain induced by innocuous stimuli (allodynia) and increased pain to normally noxious stimuli (hyperalgesia), both of which are commonly observed in neuropathic pain. In some patients, this nociplastic process serves as the primary mechanism (e.g., fibromyalgia).

Nature versus Nurture

Chronic pain is a prototypical example of the interplay between genes and environment. Heritability is estimated to account for between 30% and 60% of the variance in pain response and plays a role in both the perception of acute pain and the transition to chronic pain.

A pain syndrome can result from a single gene mutation with high penetrance (e.g., primary erythromelalgia; Chapter 66), but multiple gene abnormalities usually promote a predisposition to pain, which requires a subsequent inciting event. For example, back pain, despite the large influence of environmental and psychosocial factors, is estimated to have a heritability of between 21% and 67%. Chronic pain in parents and a parent's pain-related cognitions are associated with pain in early adolescence, before degenerative processes typically manifest, and may have a genetic as well as environmental explanation.

Neuropathic, Nociceptive, Nociplastic, and Mixed Pain

Pain can be etiologically classified as nociceptive, neuropathic, nociplastic, or mixed (Tables 26-1 and 26-2). This distinction is important because it affects decision making at all levels of care (e.g., whether to obtain magnetic resonance imaging [MRI] for subacute spinal pain, what type of medications to prescribe, and prognosis).

Nociceptive pain, which is the most common type of pain, results from an injury or disease affecting somatic structures and includes conditions such as arthritis and mechanical spine pain.[4] Nociceptive pain can be subdivided into somatic pain involving injury to skin, muscles, and joints, and visceral pain, which results from pathology affecting internal organs (e.g., pancreatitis, angina, renal stones). In contrast to somatic pain, visceral pain is usually poorly localized, referred to somatic regions (e.g., myocardial ischemia radiating into the arm), and tends to be associated with a greater affective-motivational component than somatic pain. Reasons for these differences include a lower density and different types of nociceptors, and convergence with afferent pathways in the spinal cord.

Neuropathic pain,[5] which accounts for between 15% and 25% of chronic pain, is caused by a lesion or disease that affects the somatosensory system. Neuropathic pain may be associated with a greater decrement in quality of life than comparable degrees of nociceptive pain. One subtype of neuropathic pain is central pain, which manifests as a constellation of sensory, motor, and sometimes autonomic symptoms following a lesion or disease affecting the central nervous system.

Nociplastic pain[6] arises from altered nociception despite no clear evidence of actual or threatened tissue damage, no biomarkers, and no evidence of a disease or lesions affecting the somatosensory system. Formerly known as

TABLE 26-1 CLASSIFICATION AND PREVALENCE OF COMMON PAIN CONDITIONS

NEUROPATHIC		*NOCICEPTIVE*		*NOCIPLASTIC*[1]	*MIXED*
PERIPHERAL[2]	**CENTRAL**	**SOMATIC**	**VISCERAL**		
Peripheral neuropathy (1-3%) Postherpetic neuralgia (annual incidence 0.1-0.2%), lower with varicella zoster vaccine Chronic postsurgical pain (2-10% after surgery) Phantom limb pain (30-60%) Trigeminal neuralgia (0.01%) Radiculopathy/spinal stenosis (3-10%) Nerve entrapment syndromes (e.g., carpal tunnel, thoracic outlet, meralgia paresthetica; 5-10% collectively)	Central post-stroke pain (8%) Spinal cord injury (30-50%) Multiple sclerosis (25%) Parkinson disease (10%) Seizure disorder (1-3%)	Arthritis (25-40% in people >40 yr) Myofascial pain (5%-10%) Connective tissue disorders (0.2-0.5%) Burn pain[3] (annual incidence of burns requiring hospitalization 0.01%)	Endometriosis (10% in women of reproductive age) Interstitial cystitis[1,4] (0.2-1% of women) Ulcers/gastritis/esophagitis (3-9%) Cholecystitis/appendicitis (10-20% of people have gallstones and up to one third develop cholecystitis)	Irritable bowel syndrome[1] (5-15%) Fibromyalgia[1] (3-6%), generalized diffuse pain 7-13% Complex regional pain syndrome type I[1] (0.006-0.05%, 3-20% after orthopedic surgery) Temporomandibular disorder (5-12%)[1]	Headache[1] (15% for migraine, 20-30% for tension-type) Cancer[5] (lifetime prevalence 30-40%) Low back pain[6] (annual prevalence rate 15-45%) Neck pain[6] (annual prevalence rate 15-40%) Ischemic pain[7] (5-10% prevalence for peripheral vascular disease)

[1]Strong female predominance.
[2]Prevalence rates represent the proportion of the population who suffers from the condition except for phantom limb pain in which the prevalence is based on those with limb amputation.
[3]Third-degree burns may be associated with neuropathic pain.
[4]Also sometimes considered nociplastic pain (bladder pain syndrome).
[5]Neuropathic pain occurs in 20-50% of cases and may occur secondary to tumor invasion, surgery, chemotherapy, and radiation treatment.
[6]Neuropathic pain may predominate or accompany nociceptive pain in 20-50% of cases.
[7]Typically nociceptive, but long-standing pain may result in ischemic neuropathy.

TABLE 26-2 CATEGORIZATION OF PAIN STATES

CLINICAL CHARACTERISTIC	NEUROPATHIC PAIN	NOCICEPTIVE PAIN	NOCIPLASTIC PAIN
Etiology	Disease or injury affecting the nervous system	Tissue or potential tissue damage	Maladaptive changes that affect nociceptive processing
Descriptors	Lancinating, shooting, electrical-like	Throbbing, aching, pressure-like	Similar to neuropathic pain; visceral pain (irritable bowel syndrome, bladder pain syndrome) may be diffuse, aching, gnawing, or sharp
Sensory deficits	Frequent (e.g., numbness, tingling, pricking)	Infrequent and in nondermatomal or non-nerve distribution	Common, in nondermatomal or non-nerve distribution
Motor deficits	Neurologic weakness may be present	May have pain-induced weakness	Generalized fatigue common; weakness due to deconditioning
Hypersensitivity	Pain frequently evoked with nonpainful (allodynia) stimuli	Uncommon except for hypersensitivity in the immediate area of an acute injury	Very common and diffuse
Pain pattern	Distal radiation common	Distal radiation less common; proximal nondermatomal radiation frequent around anatomic structure	Diffuse spread not following anatomic referral pattern; patients often have multiple nociplastic conditions
Paroxysms	Exacerbations common and unpredictable	Exacerbations less common and associated with activity	Common, often related to psychosocial stressors
Autonomic signs	Can occur in ⅓ to ½ of patients	Uncommon	Sympathetic nervous system hyperactivity common

"functional pain syndromes," these conditions include fibromyalgia (Chapter 253), irritable bowel syndrome (Chapter 123), and some forms of chronic headache. Coexisting conditions may include augmented sensory processing (e.g., photophobia), diminished inhibitory pathways, and a higher co-prevalence of mood and sleep disorders. For example, over 50% of patients with chronic pain exhibit some form of sleep disturbance (Chapter 374), with the prevalence being even higher in nociplastic pain states.

Mixed pain disorders[7] contain components of neuropathic, nociceptive, and sometimes nociplastic pain (e.g., nonspecific low back pain). An example is cancer-related pain, which can result from tissue invasion or as a consequence of therapy (e.g., surgery, chemotherapy, and radiation therapy), can involve sensory nerves, and can be exacerbated by anxiety and sleep disorders. In some studies, mixed pain conditions account for more than 50% of chronic pain.

CLINICAL MANIFESTATIONS AND DIAGNOSIS

Multiple classification systems describe pain based on duration, anatomic source, and mechanisms. Acute pain results from injury or inflammation, has survival value, and plays a role in healing by preventing reinjury. In contrast, chronic pain is perhaps best construed as a "disease" that serves no useful purpose. Although no clear threshold defines when acute pain becomes pathologic, it is generally accepted that pain persisting beyond the expected healing period, or lasting over 3 months, constitutes chronic pain.

History

The evaluation of pain begins with a thorough history. Since no test or biomarker can reliably identify pain, a patient's pain complaints should always be taken seriously in the absence of objective evidence to the contrary.

A comprehensive history should include the location of pain, its quality, inciting event(s), exacerbating and relieving factors, associated symptoms and signs (e.g., numbness), magnitude, interference with activities, and response to prior treatments. The severity of pain should be assessed, usually on a 0 to 10 visual analogue scale, as mild (1-3), moderate (4-7), or severe (>7 on a 0-10 scale). Because there are subtle differences among pain scales, repeat assessments or response to therapy are ideally gauged using the same instrument. For mentally incapacitated patients, age-appropriate substitute scales or facial expressions can be used. In assessing response to therapy, a 30% or greater reduction in pain constitutes meaningful improvement. However, pain also must be considered in the context of functional capacity, psychologic and emotional well-being, sleep status, and ability to work.

Neuropathic pain is characterized by positive and negative symptoms. Positive symptoms reflect abnormal excitability of the nervous system, whereas negative symptoms, such as a loss of sensation, are usually the result of loss of axons/neurons. Paresthesias and other symptoms suggestive of sensory dysfunction are indicative of neuropathic pain, especially when they occur in a dermatomal or nerve distribution. Descriptors such as "shooting" and "electrical" are more apt to be associated with neuropathic pain. Other positive symptoms observed in neuropathic pain states include pain evoked by normally innocuous stimuli (allodynia) and an exaggerated or prolonged pain response to noxious stimuli (hyperalgesia/hyperpathia).

Nociceptive pain is classically exacerbated by movements that stress the anatomic structure (e.g., walking for arthritis, head movements for neck pain). "Throbbing" and "aching" tend to be identified with nociceptive pain states such as arthritis.

Nociplastic pain is typically characterized by diffuse symptoms (e.g., widespread pain, coexisting nociplastic conditions, or multiple pain locations). It is often accompanied by concomitant symptoms such as fatigue, insomnia, multiple chemical sensitivities, mild cognitive impairment (e.g., memory difficulties), and sensitivity to light and/or sound. *Mixed pain syndromes* in conditions such as cancer are characterized by more than one type of pain.

The evaluation of a patient in pain also must include a psychosocial history. Between half and two thirds of patients with chronic pain have depression (Chapter 362), anxiety disorders, somatoform disorders, or substance abuse disorders (Chapters 364 and 365).

Physical Examination

Since pain is a frequent manifestation of systemic disease, examination of the patient in pain should encompass all bodily systems. Although a finding on examination is almost never pathognomonic, it frequently helps guide diagnostic testing or treatment. Unlike acute pain, chronic pain is usually not associated with autonomic activation and altered vital signs. Numbness in the distribution of a nerve or nerve root suggests neuropathic pain, but nondermatomal sensory changes can accompany nociplastic and nociceptive pain as well. Focal allodynia and hyperalgesia are hallmarks of neuropathic pain. The most common forms of neuropathy are associated with sensory deficits in a glove-stocking distribution, but other patterns occur as well (Chapter 388).

When evaluating muscle strength, a distinction should be made between pain-induced and neurologic weakness (Chapter 366), with the latter often occurring in conjunction with muscle atrophy or asymmetric reflexes. Widespread physical findings such as diffuse tenderness or nonanatomic pain patterns may indicate central sensitization, opioid-induced hyperalgesia, a somatic symptom disorder, or another psychiatric illness (e.g., new-onset depression).

Psychologic Assessment

The lifetime prevalence of coexisting psychiatric illness in patients with chronic pain ranges from 50% to over 80%, and 30% to 60% of chronic pain sufferers experience symptoms of depression, anxiety, or posttraumatic stress (Chapter 362). These psychiatric conditions are strong predictors for the development of chronic pain after an episode of acute pain and are associated with poorer treatment outcomes. The clinician must screen all pain patients for psychological conditions that can adversely affect treatment (Table 26-3), including maladaptive behaviors and secondary diagnoses such as somatic symptom disorders and poor coping skills.

Diagnostic Tests

Imaging can be helpful in diagnosing the cause of pain, but it lacks specificity. For example, the correlation between findings on MRI and the intensity of spinal pain is modest at best, with more than 50% of asymptomatic individuals having abnormalities on lumbar, thoracic, and cervical films (Chapter 369). Musculoskeletal imaging should be reserved for patients who have serious or progressive deficits or "red flags," such as suspected malignancy, infection, or fractures.[8] For chronic pain disorders such as primary headaches, abdominal pain, or pelvic pain, imaging should be reserved for the evaluation of new-onset symptoms or a significant change in symptoms.

Electromyography and nerve conduction studies (Chapter 366) can diagnose injury to large nerve fibers. However, these studies are associated with both false-negative and false-positive results and are not sensitive for detecting impairment of small nerve fibers. For small-fiber neuropathies, a skin biopsy demonstrating decreased nerve fiber density can be valuable.

TABLE 26-3 PSYCHOSOCIAL FACTORS ASSOCIATED WITH CHRONIC PAIN

Multiple pain complaints
Poor job satisfaction/low pay
Inadequate coping skills, catastrophization
Fear-avoidance behavior
Manual labor/physically stressful job
Obesity
Somatization
Smoking
Low resiliency
Low baseline activity levels
Secondary gain (e.g., worker's compensation, ongoing litigation)
Older age
Low education level
High disease burden (e.g., pain intensity/disability, opioid use)
Substance misuse, including opioids
Neurologic symptoms
Anxiety
Depressed mood
Emotional distress

TREATMENT

In managing pain, realistic goals must be established, and individually tailored treatment regimens should be developed to achieve these ends. A key goal is to alleviate suffering, which can be the consequence of loss of physical function, social isolation, familial distress, and a sense of inadequacy.

Interdisciplinary pain programs can be more effective than unidimensional approaches and cost-effective when properly administered. The stepped care model recommends starting therapy with the least resource-intensive services and progressing to specialty care within a biopsychosocial framework. Within this paradigm, self-care can include weight loss if appropriate; a healthy lifestyle, including exercise[A1] and proper sleep hygiene; smoking cessation; and ergonomic modifications when indicated (Fig. 26-2). Whenever possible, nonopioid options are preferred.[9]

Pharmacologic Therapies

Antipyretic Analgesics

Acetaminophen, aspirin, and other nonsteroidal anti-inflammatory drugs (NSAIDs) form a cornerstone of pain pharmacotherapy (Table 26-4). These antipyretic analgesics exert their antinociceptive effects by inhibiting cyclooxygenase, the rate-limiting enzyme in the production of prostaglandins, which sensitize nociceptors and regulate inflammation. Whereas aspirin and NSAIDs act both centrally and peripherally, thereby making them effective topical agents for inflammatory conditions, acetaminophen is a weaker analgesic that acts primarily in the central nervous system (and possibly also via cannabinoid 1 and transient receptor potential cation channel subfamily V member 1 receptors) and is largely devoid of anti-inflammatory effects.

The main drawback of these nonopioid analgesics is their relatively limited therapeutic efficacy. Acetaminophen is often ineffective for spinal pain and usually provides only minimal, short-term benefit for knee or hip osteoarthritis.[A2] NSAIDs generally provide limited benefit for spinal pain and osteoarthritis compared with placebo.[A3]

A major concern for antipyretic agents is their side effects. For NSAIDs, these include bleeding, gastrointestinal ulceration, renal toxicity, and an increased risk of cardiovascular events. Cyclooxygenase-2 selective inhibitors such as celecoxib or the addition of a protein pump inhibitor (Table 124-1) may attenuate the risk of gastrointestinal bleeding, but the incidence of adverse renal or cardiovascular events remains increased, especially in patients who are elderly, have multiple comorbid conditions, and take many medications. In these and other situations, topical NSAIDs (e.g., diclofenac) can be useful for focal rheumatologic disorders, with fewer side effects.[A4]

Adjuvant Analgesics

For the treatment of neuropathic pain (Table 26-5), antidepressants and anticonvulsants (gabapentin and pregabalin) should be the two first-line classes of medications.[A5] Depending on the drug and condition, these medications can provide significant pain relief beyond that observed with placebo in 15% to 30% of patients with neuropathic pain, and may provide preemptive effects before surgery. In terms of efficacy, tricyclic antidepressants are superior to serotonin and norepinephrine reuptake inhibitors, which in turn are more efficacious

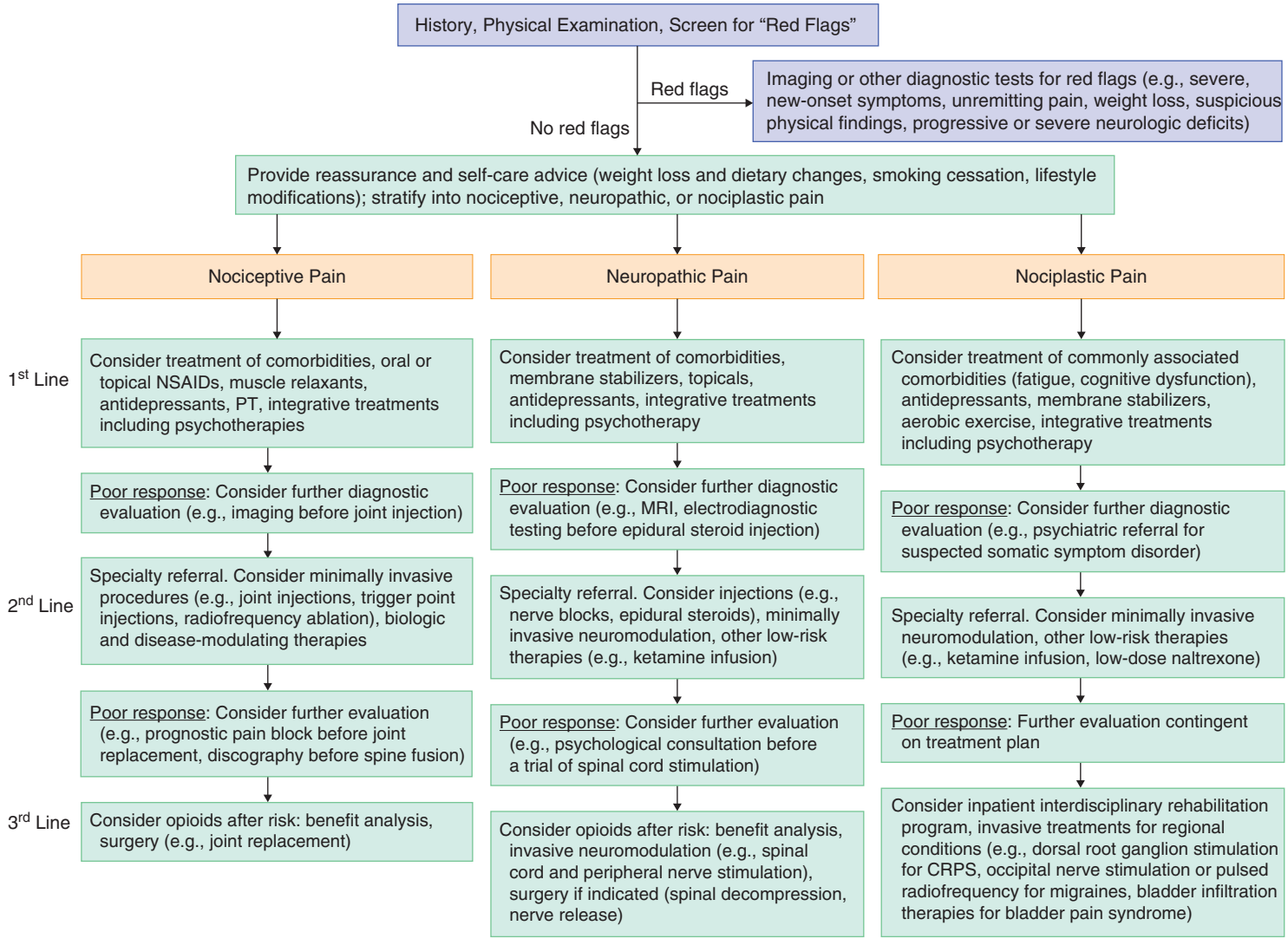

FIGURE 26-2. Approach to patient with chronic pain. CRPS = complex regional pain syndrome; MRI = magnetic resonance imaging; NSAIDs = nonsteroidal anti-inflammatory drugs; PT = physical therapy.

than serotonin specific reuptake inhibitors. Nortriptyline and imipramine have fewer side effects than amitriptyline and are preferable first-choice agents for neuropathic pain. Antidepressants are also effective for headaches (Chapter 367), nociplastic pain, and musculoskeletal disorders.

Although antidepressants are more versatile in that they have proven benefit in myriad pain conditions, gabapentin and pregabalin may be better than antidepressants for prototypical "lancinating-type" neuropathic pain. Gabapentin and pregabalin also act additively with antidepressants and opioids.[10]

When gabapentin and pregabalin are ineffective or intolerable, alternative anticonvulsants that act via different mechanisms may be tried. For trigeminal neuralgia (Chapter 367), carbamazepine remains the treatment of choice, though adverse effects such as agranulocytosis limit its utility. Other adjuvants that may be effective in certain contexts include topical agents such as lidocaine and capsaicin,[A6] NMDA antagonists (e.g., ketamine), and skeletal muscle relaxants/antispasticity drugs (e.g., baclofen).

Cannabinoids can treat chronic pain by binding to two receptors: CB1, which is expressed in high concentrations in the central nervous system (and is responsible for most of their euphoric effects) and along pain pathways, and CB2, which is found mainly on immune cells in peripheral tissue and contains anti-inflammatory properties.[11] FDA-approved cannabinoids are dronabinol, nabilone, and cannabidiol, none of which is currently approved for pain. Unfortunately, controlled trials have found that cannabinoids have limited benefit for chronic pain and a high rate of adverse effects.[A7] Nevertheless, some patients may benefit from their antiemetic and appetite-stimulating properties, as well as improved sleep and decreased anxiety. Serious side effects of cannabinoids may include cognitive and motivational impairment and psychological effects such as delusions, hallucinations, panic disorders, depression, and addiction.

Opioid Analgesics

Opioid analgesics (Table 26-6) are a mainstay of treatment for cancer pain but are no longer considered first-line treatment for any noncancer pain because of limited evidence that they improve quality of life compared with nonopioid analgesics despite their abuse potential.[A8] For nociplastic pain, opioids may be less effective than for other pain categories, and some evidence actually supports the efficacy of opioid antagonists (e.g., low-dose naltrexone) for nociplastic pain.

Optimizing therapy with opioid analgesics requires carefully balancing the beneficial and undesirable effects (Table 26-7), including not only addiction but also nausea, constipation, sedation, itch, respiratory depression, and endocrine deficiency that leads to sexual dysfunction and accelerated osteoporosis.[12] Opioids that are predominantly eliminated by the kidneys, such as morphine, must be used with caution in patients with renal dysfunction; in this situation, alternatives include fentanyl and methadone.

The increasing use of prescription opioids for chronic pain has been associated with a dramatic increase in opioid-related deaths, a trend that has been amplified by the coronavirus disease 2019 (COVID-19) pandemic (Chapter 365). The long-term use of opioids can be associated with tolerance, hyperalgesia, physical dependence, and addiction. The rates of abuse and addiction, which vary substantially across studies, are heavily dependent on the population selected, surveillance, and differences in applying definitions. Rates of misuse are estimated at between 20% and 30%, and the incidence of addiction is less than 8% in carefully selected populations (E-Fig. 26-1). Sometimes the only way to distinguish between tolerance and opioid-induced hyperalgesia is with a long-term drug holiday. Cross-tolerance among opioids is incomplete, and a strategy often used to combat tolerance is opioid rotation, which may result in a 30% to 50% reduction in the equi-analgesic dose.

Tramadol and tapentadol represent a class of analgesic drugs that have dual mechanisms of action. Tramadol is a weak agonist that inhibits the reuptake of norepinephrine and serotonin. Along with the typical opioid-related side effects, seizures have been reported. Tapentadol, which is about twice as strong as tramadol, functions as a mu opioid agonist with a ceiling effect and as a norepinephrine reuptake inhibitor.

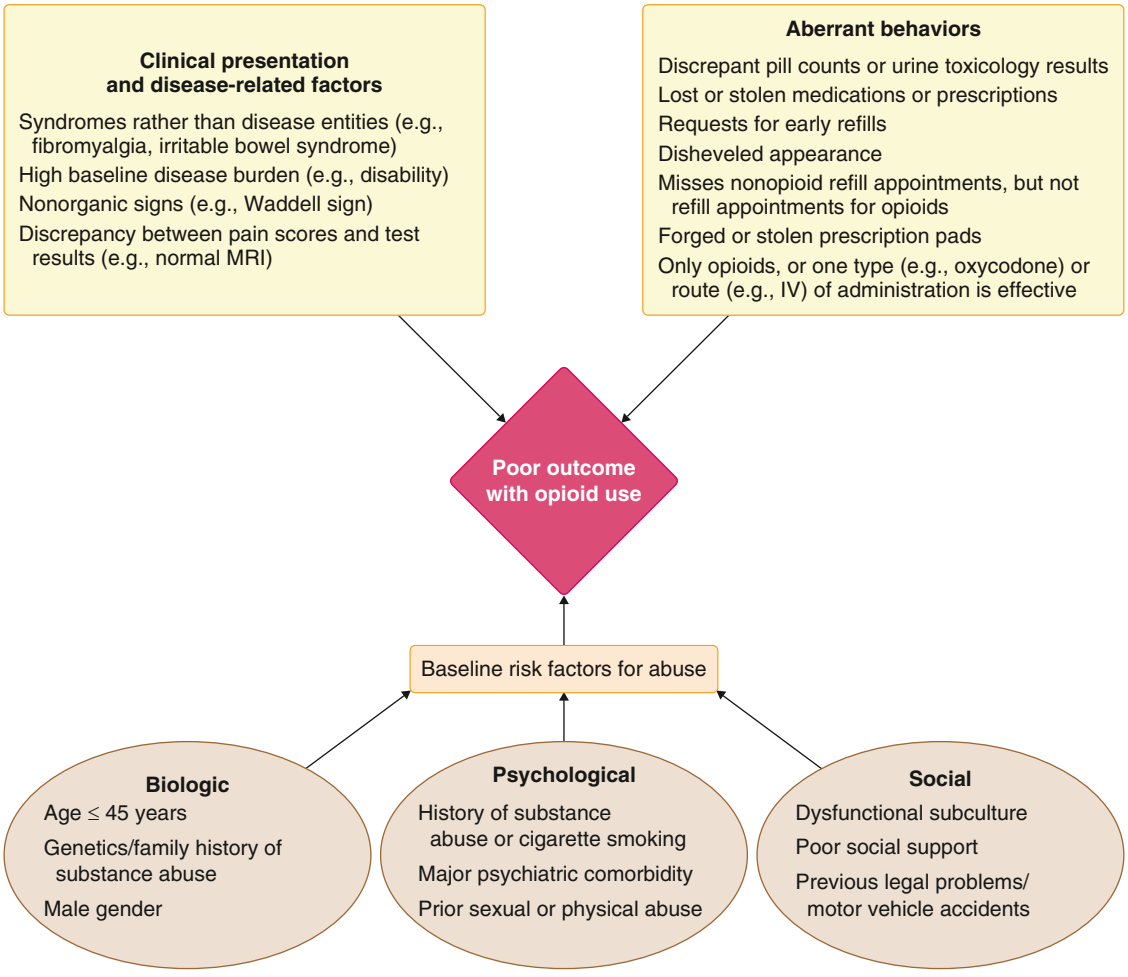

E-FIGURE 26-1. Factors associated with opioid abuse and/or treatment failure. IV = intravenous; MRI = magnetic resonance imaging.

TABLE 26-4 COMMONLY USED NONSTEROIDAL ANTI-INFLAMMATORY DRUGS (NSAIDS)

DRUG SUBSTANCE	USUAL DOSE
OVER-THE-COUNTER	
Acetaminophen	325-650 mg orally q4-6h 650 mg q4h PRN IV or up to 1000 mg q6h PRN IV
Acetylsalicylic acid	325-650 mg orally q4-6h
Ibuprofen	200-800 orally q6-8h (200 mg available over-the-counter) 400-800 mg q6h IV PRN
Naproxen	220-550 mg orally q12h (220 mg available over-the-counter); extended release: 750-1000 mg orally q24h; 1500 mg orally may be given if well-tolerated
ORAL PRESCRIPTION	
Celecoxib (COX-2 selective)	100-200 mg orally q12-24h
Diclofenac	50 mg orally q8h 75 mg q24h IM
Diflunisal	Initial dose 500-1000 mg orally then 250-500 mg orally q8-12h
Etoricoxib (COX-2 selective; not available in United States)	30-90 mg orally daily
Etodolac (COX-2 selective)	300 mg orally q8-12h or 400-500 mg orally q12h; extended release 400-1000 mg orally q24h
Ketoprofen	25-50 mg orally q6-12h; extended release 100-200 mg orally daily
Ketorolac	Initial dose 20 mg orally, then 10 mg orally q4-6h 10-30 mg q4-6h IM or IV
Indomethacin	25-50 mg orally q6-8h; extended release 75 mg orally q12-24h
Mefenamic acid	Initial dose 500 mg orally, then 250 mg orally q6h, for up to 1 wk
Meloxicam (COX-2 selective)	5-15 mg orally in once or twice per day dosing 30 mg daily IV
Nabumetone (COX-2 selective)	1000-2000 mg orally daily
Oxaprozin	600-1200 mg orally daily
Piroxicam	Initial dose 40 mg orally, then 20 mg orally daily
Sulindac	150-200 mg orally q12h
TOPICAL CREAM	
Diclofenac	Apply up to 4 g q6h as needed; available over-the-counter in United States
Ketoprofen	Apply 2-4 g q6-12h as needed; not available in United States

h = hour; IM = intramuscular; IV = intravenous.

TABLE 26-5 RECOMMENDATIONS FOR THE PHARMACOLOGIC TREATMENT OF CHRONIC NEUROPATHIC PAIN

FIRST-LINE DRUGS/DRUG CLASSES	TYPICAL TOTAL DAILY DOSE AND REGIMEN
Gabapentin	1200–3600 mg, in three divided doses
Gabapentin extended release	1200–3600 mg, in one or two divided doses
Pregabalin	300–600 mg, in two divided doses
Duloxetine	60–120 mg, in one or two divided doses
Tricyclic antidepressants (e.g., nortriptyline, amitriptyline)	25–150 mg, usually once per day
SECOND-LINE DRUGS	
Capsaicin 8% patches (for peripheral neuropathic pain)	1-4 patches to the painful area for 30-60 min once every 3 mo
Lidocaine patches (for peripheral neuropathic pain)	1-3 patches to the region of pain once per day for up to 12 h
THIRD-LINE DRUGS AND THOSE RECOMMENDED IN SELECTIVE CIRCUMSTANCES	
Botulinum toxin A (subcutaneously)	50–200 units to the painful area once every 3 mo
Lamotrigine	200-400 mg in two divided doses
Carbamazepine	400-1200 mg in two divided doses
Oxcarbazepine	1200-2400 mg in two divided doses
Venlafaxine	150-225 mg in two or three divided doses
Ketamine (infusion)	No standard therapy for chronic pain in terms of rate or number of treatments, though higher cumulative doses (e.g., >400 mg) appear more effective
Baclofen (intrathecal, oral)	15-80 mg in three or four divided doses. Oral to intrathecal ratio 100 : 1
Tramadol, tapentadol, and pure mu-agonist opioids	See Table 26-6

All medications are oral unless otherwise indicated.

Recommendations based on Schlereth T. Guideline "diagnosis and non interventional therapy of neuropathic pain" of the German Society of Neurology (Deutsche Gesellschaft für Neurologie). *Neurol Res Pract*. 2020;2:16.

Butorphanol, nalbuphine, and pentazocine are opioid agonist-antagonist drugs. These drugs should be used with caution, particularly in patients who are receiving other opioid agonists, because they may precipitate withdrawal or reduce the effectiveness of pure opioid agonists. Buprenorphine, which is a long-acting partial agonist at the mu opioid receptor and an antagonist at other opioid receptors, is available in various formulations as a stand-alone analgesic and in combination with naloxone for treatment of opioid addiction.

Combination Pharmacotherapies

Guidelines suggest that when monotherapy is ineffective, multiple agents that act at different sites and ideally have antagonistic adverse effects may be combined (E-Fig. 26-2). Controlled trials have found that gabapentin plus nortriptyline, gabapentin plus morphine, nortriptyline plus morphine, and mirtazapine plus pregabalin provide superior benefit than either drug alone for neuropathic pain.[A9]

Psychologic Treatment

Relaxation techniques such as biofeedback and guided imagery are effective for a wide array of acute and chronic pain conditions but may be especially useful in individuals with high levels of anxiety. Cognitive-behavioral therapy, which is a structured form of psychotherapy predicated on the replacement of negative thought patterns and behaviors with more constructive ones, enhances inhibitory pain signals and also can be effective for associated symptoms such as fatigue and insomnia.[A10,A11] Ideal candidates include motivated patients in whom distorted thinking (e.g., catastrophization) and counterproductive behaviors (e.g., fear-avoidance) amplify pain. In patients with personality disorders and ingrained maladaptive behaviors, which may also predispose to pain and pain-related disability, long-term psychotherapy may be necessary.

Physical Treatments

The use of physical therapies to provide pain relief and enhance function is a cornerstone of integrative treatment. Physical therapists evaluate, educate, and provide minimally invasive procedural interventions to help prevent and alleviate pain and dysfunction. These interventions include addressing causes of pain (e.g., correcting gait abnormalities) and providing treatments (e.g., hot and cold packs, joint manipulation).

Exercise is an effective treatment for many forms of chronic pain, and it also is a means to prevent injury. Exercise reduces the sensitivity to pain but is more beneficial for improving function than for relieving pain and more beneficial for musculoskeletal and diffuse pain than for neuropathic pain.[A12]

Interventional therapies

Local Injections and Nerve Blocks

Local injections of lidocaine may be tried for diagnostic, therapeutic, and prognostic purposes. In appropriate patients (especially trigger point injections for myofascial pain, intra-articular injections for osteoarthritis, and nerve blocks with corticosteroids for nerve entrapment syndromes), injections can provide intermediate-term pain relief, facilitate rehabilitation, and improve quality of life. For radicular leg pain, spinal injections can provide limited benefit.[A13] Patients

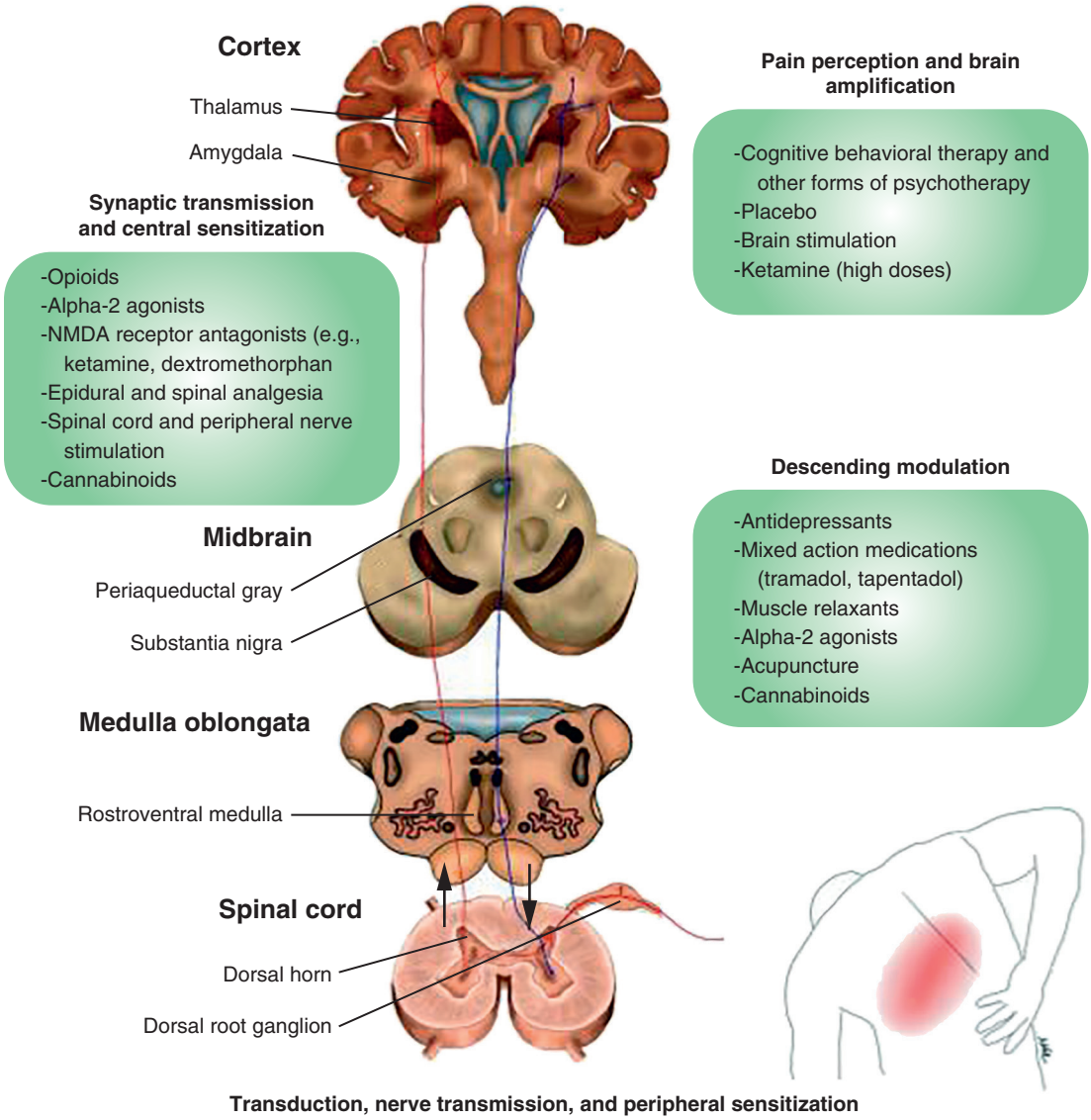

E-FIGURE 26-2. **Rational choice of pharmacologic therapies for pain should be based on the mechanisms of drug actions.** Combining drugs with disparate sites of action can have additive or synergistic analgesic effects and minimize adverse effects. NMDA = N-methyl-D-aspartate. (Drawing courtesy of Seffrah Cohen.)

TABLE 26-6 FORMULATIONS, DOSAGES, AND PHARMACOLOGIC INFORMATION ON COMMONLY PRESCRIBED OPIOIDS

PURE OPIOID AGONISTS

DRUG	EQUIANALGESIC DOSAGE (ORAL UNLESS SPECIFIED)	READILY AVAILABLE ROUTES OF ADMINISTRATION	DURATION OF ACTION	COMMENTS
Morphine	30 mg	IV, IM, PO, PR; SR formulation	3-6 h for short-acting, 8-12 h for SR	Reference standard for all opioids. Renally excreted active metabolite
Oxycodone	20 mg	PO, PR; SR formulation	3-6 h for short-acting, 8-12 h for SR	Widely available in combination form with nonopioid analgesics. Greater euphoric effects than morphine. Popular among recreational users
Hydromorphone	3-6 mg	PO, PR, IV, IM, SR formulation	3-6 h, 18-24 h for SR	Higher PO: IV conversion ratio than other opioids. SR form reserved for opioid-tolerant patients, and contraindicated in patients with recent monoamine oxidase inhibitor use
Hydrocodone	30-60 mg	PO, SR formulation	3-6 h, 12-24 h for SR	Wide variation in morphine equivalent dose. Most commonly prescribed opioid in United States. Typically used in combination form with nonopioid analgesic acetaminophen. IR products containing <15 mg hydrocodone are Schedule III in the United States. SR form available without acetaminophen
Oxymorphone	10 mg	PO, IV, IM, PR; SR formulation	4-8 h, 8-12 h for SR	Coingestion of alcohol with SR formulation can lead to rapid increase in plasma levels and overdose. Very low (10%) oral bioavailability
Methadone	2-10 mg (see comments)	PO, PR, IV	6-12 h for pain	Morphine: methadone conversion varies according to dose and length of opioid use, ranging from 3 : 1 to > 20 : 1 in patients on very high doses. Any physician with a Schedule II DEA license may prescribe for pain. May take 5-7 days to reach steady state due to long half-life. ECG monitoring recommended with higher doses. Other properties such as NMDA receptor antagonism and reuptake inhibition of serotonin and norepinephrine may slow tolerance and increase efficacy for neuropathic pain
Levorphanol	3 mg	PO, IM, IV	4-10 h	2 : 1 oral to IV conversion ratio. Agonist at mu, kappa, and delta receptors. Multiple mechanisms of action, including inhibition of serotonin and norepinephrine reuptake, NDMA receptor antagonism and sigma receptor agonism. Long half-life exceeded only by methadone
Fentanyl	12.5 µg/h (TD) = 30 morphine milliequivalents/day Dosing 100-1200 µg for TM Potency for TM formulations varies from 1/8 that of morphine for buccal or sublingual tablets or lozenges to 1/5 for films or oral sprays	TD, TM	72 h for TD; 1.5-3 h for TM	TD and TM formulations may be useful in patients with poor bowel function. Rapid onset (<10 min) iontophoretic TD system available for postoperative pain TD: Wide variation in conversion ratios and doses depending on route. Delivery system may be associated with fewer gastrointestinal side effects, and include buccal, sublingual, and intranasal routes TM delivery associated with more rapid (10 min) onset than immediate-release oral opioids. FDA approved for breakthrough cancer pain in opioid-tolerant patients
Sufentanil	15-30 µg (~7.5 times as potent as fentanyl)	TM	1-3 h	Rapid onset, wide variation in conversion ratio. For use only in health care and battlefield settings. 15 and 30 µg dosages approved in Europe and United States. Not approved for home use or for longer than 72 h
Propoxyphene	200 mg	PO, PR	3-6 h	Removed from market in United States. Wide variation in morphine equivalent dose. Often used in combination form with nonopioid analgesics. Toxic metabolite may accumulate with excessive use, especially in elderly. Weak antagonist at NMDA receptor
Meperidine	300 mg	PO, PR, IM, IV	2-4 h	Toxic metabolite may accumulate with excessive use, especially in patients with renal insufficiency. Associated with tachycardia and hypertension. Concurrent use with monoamine oxidase inhibitors may result in fatal reactions. May cause more "euphoria" than other opioids. IM absorption erratic

TABLE 26-6 FORMULATIONS, DOSAGES, AND PHARMACOLOGIC INFORMATION ON COMMONLY PRESCRIBED OPIOIDS—cont'd

DRUG	TYPICAL DOSING/ ANALGESIC POTENCY	READILY AVAILABLE ROUTES OF ADMINISTRATION	DURATION OF ACTION	COMMENTS
AGONIST-ANTAGONISTS, PARTIAL AGONISTS				
Buprenorphine Buprenorphine/ Naloxone (4 : 1 ratio for opioid addiction)	0.3-24 mg SL 5-70 µg/h (TD) 2-24 mg/day (tablets and films about 30 times as potent as morphine; TD patch 10-15 times as potent)	TM, PR, IV, TD	8-12 h for TM, 7 days for SR, once daily for stable buprenorphine/ naloxone combination	Partial mu agonist and kappa antagonist that may precipitate withdrawal in opioid-dependent patients on high doses. Lower abuse potential and fewer side effects than pure agonists. Not readily reversed by naloxone. Schedule III drug in United States. Primarily used in combination with naloxone as sublingual or buccal tablets and films for opioid dependence. May prolong QT interval
Butorphanol	1 mg/spray, repeat after 60-90min (IN) 1-2 mg (IV/IM) (~7 times as potent as morphine)	IN, IM, IV, PO	3-5 h	Mixed agonist-antagonist at mu receptor and antagonist at kappa receptor. Commonly used as nasal spray to treat migraine headache, and less commonly for labor pain. Significant abuse potential
Nalbuphine	1 : 1 parenteral analgesic potency ratio to morphine (~0.8 : 1.0 [equianalgesic] times as potent as morphine)	SQ, IM, IV	3-6 h	Mixed agonist-antagonist, often used for labor and delivery. Sometimes used to treat refractory opioid-induced pruritus
Pentazocine Pentazocine/ Naloxone (Talwin) (100 : 1 ratio of pentazocine to naloxone)	90 mg (~3 times as potent as morphine)	PO, SQ, IM, IV	3-4 h parenteral, 3-8 h PO	Mixed agonist-antagonist. (–) enantiomer is kappa agonist. Naloxone added in 1970s (Talwin) to prevent abuse. Commonly prescribed in preparation with acetaminophen
WEAK, DUAL-ACTION OPIOID AGONISTS				
Tramadol	50-100 mg, up to 400 mg/day (1/10th as potent as morphine)	PO	4-6 h, 24 h for SR	Dual action involves inhibition of serotonin and norepinephrine reuptake. Affinity for mu opioid receptor 6000× less than morphine. Analogue of codeine with active metabolite in which differences in metabolism may influence drug effects. Available in combination form with acetaminophen. Maximum recommended dose of 400 mg/day. Avoid concurrent use of monoamine oxidase inhibitors. Recently moved to FDA category Schedule IV in United States
Tapentadol	50-100 mg, up to 600 mg/day (⅓ to ⅔ as potent as morphine)	PO	4-6 h, 12 h for SR	Dual action involves inhibition of norepinephrine reuptake. May have fewer of certain side effects than morphine, such as gastrointestinal and respiratory depression. Maximum dose 600 mg/day. Avoid concurrent use of monoamine oxidase inhibitors. Schedule II in United States. Approved for diabetic neuropathy

DEA = Drug Enforcement Administration; ECG = electrocardiogram; FDA = U.S. Food and Drug Administration; IM = intramuscular; IN = intranasal; IR = immediate release; IV = intravenous; NMDA = N-methyl-D-aspartate; PO = oral; PR = rectal; SL = sublingual; SR = sustained release; TD = transdermal; TM = transmucosal.

who have concomitant psychosocial issues (e.g., secondary gain, untreated depression) or a greater burden of disease, are taking opioids, and have a discordance between their symptoms and the findings on physical examination or imaging are unlikely to benefit. Although the theoretical benefits of adding a corticosteroid to lidocaine include blocking the inflammatory cascade (thereby suppressing ectopic discharges from injured nerves and inhibiting the synthesis of prostaglandins), the incremental benefit of adding corticosteroids to a local anesthetic for nerve blocks or to epidural or joint injections is small.[A14] In patients who benefit from local injections, translating the temporary relief into long-term improvement necessitates addressing the underlying cause, which often requires rehabilitation and psychotherapy.

Biologic therapies such as bone marrow concentrate and platelet-rich plasma have shown inconsistent results in the treatment of musculoskeletal disorders and peripheral nerve injuries.[A15] In patients with lumbar facet joint pain, sacroiliac joint pain, or knee osteoarthritis, evidence supporting radiofrequency denervation is mixed.[13] In patients with cancer pain, neurolytic procedures targeting the celiac plexus for upper abdominal pain and the superior hypogastric plexus for pelvic pain may provide significant benefit lasting several months.

Electrical Stimulation

The most common form of electrical stimulation[14] is transcutaneous electrical nerve stimulation. The evidence supporting transcutaneous electrical nerve stimulation to treat chronic pain is mixed, with evidence of limited, short-term benefit for neuropathic pain[A16] but not for back pain. Spinal cord stimulation is a neuromodulatory technique in which an electrode is inserted epidurally to stimulate the dorsal column. Conventional, high-frequency, and burst stimulation have all been shown to be effective for chronic pain, with mixed evidence supporting one modality over another. The strongest evidence for spinal cord stimulation is to treat complex regional pain syndrome, ischemic pain, and back pain with predominantly radicular pain after unsuccessful back surgery.

Peripheral nerve stimulation is used for patients with neuropathic pain in the distribution of one or two nerves and for headaches (Chapter 367), with relief sometimes persisting for more than 1 year for neuropathic pain but mixed evidence for efficacy in migraine headaches.[15] In patients with intractable chronic pain unresponsive to conservative measures, deep brain and motor cortex stimulation may be considered, with the strongest evidence for neuropathic pain.

Surgery

Surgical interventions are often advocated in patients who have failed conservative measures. A traumatic neuroma is an inexorable consequence of cutting or burning a nerve, formed as a result of unregulated and disorganized nerve regeneration. Neuromas have been shown to fire ectopic pain signals and are often quite painful. Hence, neurolytic procedures are rarely successful in the

TABLE 26-7 GUIDELINES FOR OPIOID THERAPY

1. Nonpharmacologic and nonopioid pharmacologic therapy are preferred for subacute and chronic pain and should be used before initiating opioid therapy. For acute pain, consider opioid therapy only if the benefits are anticipated to outweigh the risks.
2. Establish realistic goals before starting opioid therapy and discuss how therapy will be discontinued.
3. Before starting opioids and during treatment, risk factors for harm should be evaluated, and strategies to mitigate risk (e.g., offering naloxone) should be incorporated in patients who are at risk of overdose.
4. Initiate therapy with immediate-release opioids.
5. Start with the lowest effective dose; carefully reassess benefits and risks when dosage is increased. Avoid increasing doses to levels likely to yield diminishing benefits relative to risks.
6. For patients who are already receiving higher opioid dosages, clinicians should carefully weigh benefits and risks and exercise care when reducing or continuing the opioid dosage. If risks outweigh benefits of continued opioid therapy, clinicians should optimize other therapies and work closely with patients to taper to lower dosages gradually or, if warranted, appropriately taper and discontinue opioids. In the absence of life-threatening or extenuating circumstances, opioid therapy should not be discontinued abruptly, and clinicians should not abruptly or rapidly reduce opioid dosages.
7. For the treatment of acute pain, clinicians should prescribe no greater quantity than needed for the expected duration of pain severe enough to require opioids.
8. Evaluate the patient within 1 to 4 weeks after starting opioids, and reevaluate the benefits and harms within 3 months or more frequently as indicated.
9. When prescribing opioids for acute, subacute, or chronic pain, review the patient's history of use of controlled substance with a prescription drug monitoring program.
10. When prescribing opioids for subacute or chronic pain, consider toxicology testing to assess for prescribed medications as well as other prescribed and nonprescribed controlled substances.
11. Clinicians should use extreme caution when prescribing opioids and benzodiazepines concurrently and consider whether the benefits outweigh risks when concurrently prescribing opioids and other central nervous system depressants.
12. For patients with opioid use disorder (Chapter 365), offer or arrange treatment with medications (e.g., buprenorphine or methadone).

Adapted from Dowell D, Ragan KR, Jones CM, Baldwin GT, Chou R. CDC guideline for prescribing opioids—United States, 2022. Available at https://www.cdc.gov/mmwr/volumes/71/rr/pdfs/rr7103a1-H.pdf.

long-term treatment of neuropathic pain. Total joint replacement (Chapter 255) is an increasingly common treatment for osteoarthritis of the knee or hip, but up to 40% of patients will experience significant pain following arthroplasty. Surgery done solely to remove a painful body part (e.g., orchiectomy, limb amputation) rarely results in long-term benefit.

Complementary and Alternative Therapies

Pain is the most common indication for complementary and alternative medical treatments (Chapter 30), with utilization rates approaching 40%. Some of the most popular modalities are acupuncture, chiropractic, nutraceuticals, Tai Chi, and yoga, all of which are beneficial in certain contexts. However, the magnitude of benefit tends to be modest, and little evidence supports one modality over another or against conventional medical treatments. Other supplements that have been used to treat chronic pain include omega-3 polyunsaturated fatty acids, natural eggshell membrane, turmeric, ginger, magnesium, and vitamin B_{12}.

Back Pain

In many populations, back pain is the leading cause of pain worldwide. Careful diagnostic assessment is required. For pain that has a clear anatomic cause and does not respond to medications, physical therapy, injections, and surgery may all be considered (Chapter 369).[A17]

Pain Management in Vulnerable Populations

Persons at particularly high risk for chronic pain include individuals with intellectual disabilities, older adults, indigent people, and torture survivors.[16] For these vulnerable populations, focus should be on the utilization of tools to assess pain and monitor treatment compatible with cognitive abilities, adapting therapy to individual circumstances, understanding age-related differences in drug pharmacokinetics, and ensuring autonomy and dignity.

Older adults have higher pain thresholds and lower pain tolerance; they are more likely to report pain, often with multiple comorbid conditions, than are younger adults. The increased risk for drug-related adverse effects in this population is the basis for the popular recommendation, "start low and go slow" in the titration of drugs. Age-related physiologic factors that can decrease the therapeutic dose of opioid and nonopioid analgesics include changes in volume of distribution and protein binding, decreased metabolism, decreased excretion, and increased pharmacologic sensitivity. Thus, nonpharmacologic interventions such as ergonomic modifications, tailored physical therapy and exercise programs, nutritional consultation, psychobehavioral approaches, and injections should be considered in appropriate patients.[17]

FUTURE DEVELOPMENTS

Research is addressing the genotyping and phenotyping of chronic pain patients both to identify individuals at high risk for chronification of pain and to guide treatment. Neuroimaging and molecular biomarkers may, in the future, help to measure nociception and pain, and also function as objective indicators of treatment response.

Regenerative therapies (Chapter 34) seek to facilitate the body's ability to repair, replace, restore, and/or regenerate diseased or damaged tissue. Some treatments, such as platelet-rich plasma, are commonly used to treat musculoskeletal conditions with mixed results. Others, such as stem cell therapy, are also being investigated for nerve injury and degenerative conditions. The approach to managing pain must consider the reality of spiraling health care costs and opioid addiction (Chapter 365).

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27 BIOLOGY OF ADDICTION

ERIC J. NESTLER

DEFINITION

Drug addiction involves compulsive substance use despite serious negative consequences. Harmful drug use and addiction are significant contributors to medical morbidity and mortality both directly as a result of the toxic effects of abused drugs and indirectly through accidents, violence, nonsterile needle use, smoking, and other health hazards. By far the greatest contributors to illness and death are the widely used legal drugs, tobacco (Chapter 363) and alcohol (Chapter 364), although illegal addictive drugs and abused prescription drugs also exact a significant toll. An increasing impact of cannabinoids is expected as legal restrictions against such drugs are eased and their use increases. In addition, addiction creates enormous burdens on society by impairing the function of the addicted person in multiple life roles, disrupting families and neighborhoods, and motivating crime.

Compulsive use, the cardinal feature of addiction, means that the affected person cannot control substance use for a significant period of time despite powerful reasons to do so, such as drug-related health problems, drug-associated arrests, or the threat of losing one's job or spouse.[1] In the outpatient setting, addiction can be remarkably frustrating to treat: drug seeking and administration are apparently voluntary behaviors that an otherwise sentient person seems unwilling to control. Even after significant efforts have been exerted to get an addicted patient into drug treatment, relapse is common, even long after the last withdrawal symptom has cleared. Relapses are often precipitated by stress or by reminders of drug use (cues) that may range from familiar drug use contexts (such as smoking after a meal) to interactions with drug-using friends, the smell of marijuana or tobacco smoke, and body feelings previously associated with drug seeking (so-called interoceptive cues).

Drug users may repeatedly take drugs to gain pleasure or to escape from negative feelings, including the aversive feelings that may occur when drugs wear off.[2,3] As a result of repeated drug administration over time, initial protein targets for the drugs and their downstream signaling pathways (Table 27-1) are excessively stimulated and may thus undergo homeostatic adaptations. These adaptations can produce tolerance (the need for increasing drug doses to achieve desired affects) or dependence (revealed by withdrawal symptoms between drug doses or with drug cessation). Both tolerance and dependence can contribute to ongoing drug use and to dosage increases; however, neither tolerance nor dependence alone explains compulsive use. First, tolerance and dependence occur not only with repeated use of many addictive drugs (e.g., heroin, alcohol) but also with many nonaddictive drugs (e.g., β-adrenergic antagonists, α_2-adrenergic agonist antihypertensive agents, nitrates, selective serotonin reuptake inhibitor antidepressants). Second, some highly addictive drugs, such as cocaine, may produce little physical dependence and withdrawal in some individuals who nonetheless exhibit compulsive use. Finally, if dependence and withdrawal were necessary factors in addiction, the phenomenon of late, post-detoxification relapse would not be the major clinical problem that it is. Although these forms of homeostatic adaptation play a role in addiction, other types of plasticity within the nervous system are more significant.

RISK FACTORS FOR ADDICTION

Only a minority of individuals who use drugs go on to become addicted. The best-established risk factors for addiction are male sex and family history. Across countries and cultures, males have a greater risk for both heavy drug use and addiction, with risk ratios in the range of 1.4:1 to 2:1, but the sex ratios have narrowed in many countries, especially for tobacco use and alcohol. Moreover, females who succumb to addiction tend to do so more quickly after initial drug exposures, and drug use during pregnancy can have enormously deleterious effects on the fetus.[4]

Genes play a major role in familial risk as evidenced by twin and adoption studies. Twin studies consistently show higher rates of concordance for heavy drug use and addiction within monozygotic twin pairs than within dizygotic twin pairs. Adoption studies demonstrate that individuals adopted early in life tend to resemble their biologic rather than their adoptive parents with respect to patterns of alcohol use. Large population genetic studies suggest that the heritable risk for addiction to any of several substances, including opioids, stimulants, nicotine, alcohol, and marijuana, is roughly the same and varies between 30 and 60%, depending on the study. Adverse life events (e.g., stress, trauma) are important noninherited factors that also determine an individual's risk for addiction.

Although genes clearly play a significant role in vulnerability to addiction, only a small portion (<10%) of the specific genetic variants that confer risk have been identified with certainty. Like all common neuropsychiatric disorders, addiction risk is highly genetically complex; there is evidence from linkage and association studies for contributions by many hundreds of genetic variants, each with a very small effect.[5–7] The strongest genetic risk factors identified to date are variations in genes that encode acute drug targets, such as nicotinic cholinergic receptor subunits, although each contributes only a very small portion of the overall heritable risk. However, the task of gene identification is complicated by the challenges of phenotype definition. There are no objective medical tests with which to make the diagnosis, and there may be independent genetic and nongenetic risk factors for different stages of substance use disorders, such as drug experimentation, addiction, and treatment responsiveness. Moreover, twin and family studies suggest that there may be both shared and unshared genetic risk factors as well as epigenetic changes[8] underlying addictions to different drugs. As in other genetically complex disorders, it is hoped that with the identification of numerous risk-conferring variants, it will be possible to identify key biochemical pathways involved in addiction pathogenesis, which will then suggest potential targets for new and more effective treatments.

REWARD CIRCUITRY: THE NEURAL SUBSTRATE OF ADDICTION

The survival and perpetuation of species require that animals, including humans, learn to predict threats and also learn the circumstances under which they can

TABLE 27-1 PROPERTIES OF ADDICTIVE DRUGS

DRUG	NEUROTRANSMITTER	DRUG TARGET	EFFECT AFTER BINDING
Opioids (morphine, heroin, oxycodone, fentanyl)	Endorphins; enkephalins	μ and δ opioid receptor (agonist)	Activate G_i/G_o; activate K^+ channels
Psychostimulants (cocaine, amphetamines)	Dopamine (DA)	Dopamine transporter (DAT)* (antagonist)	Increase synaptic DA; stimulate presynaptic and postsynaptic DA receptors
Nicotine	Acetylcholine	Nicotinic acetylcholine receptor (nAChR) (agonist)	Stimulate cation channel (may desensitize)
Alcohol†	γ-Aminobutyric acid (GABA) Glutamate	$GABA_A$ receptor (agonist) *N*-methyl-D-aspartate (NMDA) receptor (antagonist)	Activate Cl^- channel Inhibit Na^+/Ca^{2+} entry
Marijuana (Δ^9-tetrahydrocannabinol)	Anandamide; 2-arachidonoylglycerol	Cannabinoid CB_1 (agonist)	Activate G_i/G_o; activate K^+ channels
Phencyclidine, ketamine	Glutamate	NMDA receptor (antagonist)	Inhibit Na^+/Ca^{2+} entry

*The psychostimulants also interact with the norepinephrine and serotonin transporters, but under normal conditions, it is the DAT that is critical for rewarding and addictive properties. Unlike cocaine, amphetamines enter dopamine nerve terminals through the DAT and interact with a second target, the vesicular monoamine transporter (VMAT), to release DA into the cytoplasm and thence, through the DAT, to release it into the synapse.

†Alcohol binds to and affects many other protein targets (e.g., several types of ion channels) that also contribute to its overall actions.

Modified from Hyman SE, Malenka RC, Nestler EJ. Neural mechanisms of addiction: the role of reward-related learning and memory. *Annu Rev Neurosci*. 2006;29:565-598.

ABSTRACT

Only a minute fraction of the approximately billion compounds known in chemical space share the property of inducing addiction: compulsive drug intake despite adverse consequences. Such compounds are termed drugs of abuse. Despite their very different chemical structures and very different initial protein targets in the brain, all drugs of abuse converge on the brain's reward circuity, which evolved to regulate responses to natural rewards in the environment such as food, sex, and social interaction. This convergent action includes increasing dopaminergic neurotransmission from the midbrain ventral tegmental area to the nucleus accumbens and other regions of the forebrain, as well as the activation of several other reward-related neurotransmitter systems. Repeated exposure to drugs of abuse, with repeated activation of these acute reward mechanisms, induces pathologic changes in individual reward neurons and associated glial cells, as well as in the functioning of the overall brain reward circuitry. These effects then drive an individual's compulsive drug use. The ability of a drug to induce such changes, and therefore addiction, is highly heritable, with about 50% of the risk being genetic, apparently via hundreds of specific genes.

KEYWORDS

reward
ventral tegmental area
nucleus accumbens
dopamine
opioid peptides
endocannabinoids
acetylcholine

obtain "rewards," such as food, water, shelter, and opportunities for mating. A simple operational definition of reward is a stimulus that elicits approach and consummatory behaviors. Several interconnected neural circuits, highly conserved in evolution, control an individual's responses to rewarding and aversive stimuli (E-Fig. 27-1). Dopamine-releasing neurons in the ventral tegmental area of the midbrain and their major target neurons in the nucleus accumbens in the ventral striatum serve as a rheostat that detects and drives responses to rewards and threats. The amygdala and hippocampus are crucial for forming reward- and fear-related memories. The dorsal striatum (caudate and putamen) mediates well-learned behaviors and habits. Finally, several regions of the prefrontal cortex exert executive control over these subcortical systems. Addiction involves abnormal functioning of this entire circuit.[9,10]

The neurotransmitter dopamine, released from ventral tegmental area nerve terminals in the nucleus accumbens, plays the key (albeit not the only) role in binding rewards and reward-associated cues to adaptive reward-seeking responses. In animals, implanted electrodes can record firing of dopamine neurons; microdialysis catheters and electrochemical methods can be used to detect dopamine that has been released from presynaptic terminals. In humans, positron emission tomography (PET) permits indirect measures of dopamine release by observing the displacement of a positron-emitting D_2 dopamine receptor ligand previously bound to receptors after a stimulus or pharmacologic challenge. Such methods show that natural rewards cause firing of neurons in the ventral tegmental area and release of dopamine in the nucleus accumbens and other forebrain regions. When dopamine action does not occur because of lesions in dopamine neurons, blockade of postsynaptic dopamine receptors, or inhibition of dopamine synthesis, rewards no longer motivate the behaviors necessary to obtain them.

The role of dopamine has been elucidated in patients with Parkinson disease (Chapter 378), which results from the death of midbrain dopamine neurons; however, neurons within the substantia nigra, which project to the dorsal striatum, are more severely affected than neurons within the ventral tegmental area. Patients are generally treated with l-dopa, a dopamine precursor, but as the disease progresses, other drugs may be needed, including selective D_2 dopamine receptor agonists. A minority of patients treated with these D_2 dopamine receptor agonists develop new risky, goal-directed behaviors, such as compulsive gambling or shopping. These behaviors generally cease when the D_2 dopamine receptor agonist is withdrawn, presumably because these agents can combine with endogenous dopamine from preserved neurons in the ventral tegmental area to overstimulate the nucleus accumbens and other components of the reward circuitry. These observations not only underscore the role of dopamine in motivation and reward seeking but also suggest that behavioral addictions share neural substrates with drug addiction.[11,12]

The precise pattern of firing of dopamine neurons and the resulting synaptic release of dopamine in forebrain circuits shape behavior so as to maximize future reward. In a basal state, dopamine neurons have a slow tonic pattern of firing. When a new, unexpected, or greater-than-expected reward is encountered, a phasic burst of firing of dopamine neurons causes a transient increase in synaptic dopamine. When a reward is predicted from known cues and is exactly as expected, there is little change from the tonic pattern of firing, that is, only small additional dopamine release. When a predicted reward is omitted or less than expected, dopamine neurons pause their firing to levels below their tonic rate. Phasic increases in synaptic dopamine signify that the world is better than expected, facilitate learning of new predictive information, and bind the newly learned predictive cues to action.

Dopamine is not the only neurotransmitter that signals reward. Other neurotransmitters, including acetylcholine, endogenous opioid peptides (e.g., enkephalin and endorphin), and endogenous lipid substances called endocannabinoids (because cannabinoid drugs like marijuana are agonists at their receptors), are also released in the reward circuitry in response to natural rewards.

PROPERTIES OF ADDICTIVE DRUGS

Addictive drugs are chemically diverse, and these interact with different molecular targets in the nervous system (Table 27-1). They also exhibit significant differences from each other in many of their physiologic and behavioral effects.[13–15] For example, cocaine and amphetamines are stimulants that increase arousal, may cause anxiety, and at lower doses enhance cognitive performance. Alcohol, which is a depressant, is anxiolytic at low doses and degrades cognitive performance. Heroin and other opioids, which are analgesic, cause drowsiness, constipation, and pupillary constriction. The shared behavioral effect of all addictive drugs is the liability, in vulnerable individuals, of causing compulsive use. The shared pharmacologic property that is a major mediator of addiction is the ability to increase levels of synaptic dopamine in the nucleus accumbens and other regions of the forebrain. For example, cocaine blocks the dopamine uptake transporter that normally clears dopamine from synapses. Amphetamines cause reverse transport of dopamine into synapses through the dopamine uptake transporter. Opioids, nicotine, cannabinoids, and alcohol cause dopamine release, and they act by different initial mechanisms to stimulate dopamine neurons in the ventral tegmental area or to release them from resting inhibitory control. The first three of these drugs also induce reward through nondopamine mechanisms (i.e., by activating cholinergic, opioid, or cannabinoid receptors). By comparison, alcohol directly affects γ-aminobutyric acid and glutamate receptors within the reward circuitry (Table 27-1).

Natural rewards, such as food or sexual opportunities, regulate the firing of dopamine neurons through highly processed sensory information, both external and interoceptive. Addictive drugs short-circuit this kind of information processing by acting directly on proteins that control dopamine and other signals in the reward circuitry. Acting by such direct pharmacologic mechanisms, addictive drugs typically produce greater quantities of synaptic dopamine and other reward-related neurotransmitters over longer times compared with natural rewards. In addition, addictive drugs provide a grossly pathologic learning signal by occluding pauses in dopamine and other neuron firing, even when drug use proves less pleasurable than expected or even aversive. For example, when the inhalation of smoke causes painful coughing, it might seem that the brain would signal an experience that is worse than expected with a resulting decrement in the firing rate of neurons in the ventral tegmental area. However, because nicotine causes dopamine release pharmacologically, independent of the smoker's actual experience, reward circuits, unavailable to conscious introspection, still receive a positive message that reinforces nicotine-seeking and nicotine use. In short, addictive drugs, by virtue of their effects on dopamine and related neurotransmitters, always signal "better than expected."

DRUG-INDUCED NEURAL PLASTICITY RELEVANT TO ADDICTION

Neurobiologic research on addiction has focused intensely on compulsive aspects of drug use, the ability of specific cues to activate drug seeking and craving, and the long persistence of stress- and cue-dependent relapse risk. As described previously, compulsive drug use and the power of drug-associated cues reflect the usurpation of the brain's reward circuitry by drugs of abuse. The persistence of addiction reflects long-term changes in neurons and synapses, as well as their interacting circuits. These long-lived alterations in gene expression can be attributed to drug-induced epigenetic mechanisms, such as modifications of chromatin.[16]

Long-term changes in gene expression may render the addicted person susceptible to stress and may also create persistent changes in hedonic state and mood regulation that may motivate drug taking. By themselves, however, changes in gene expression do not explain the ability of exquisitely specific cues to activate drug seeking or, if seeking is impeded, intense subjective drug craving. The ability of specific cues to activate drug seeking and wanting is based on long-term associative memories consolidated under the influence of dopamine and other reward signals, in part via changes in gene expression.[17,18] Long-term memory formation represents perhaps the most persistent changes in brain function that may occur in adult life. The neural substrates of memory are likely to include alterations in synaptic weights, such as long-term potentiation or long-term depression, and physical remodeling of dendritic spines.

Cues that can reinitiate drug use include environmental stimuli (e.g., persons with whom drugs have been used, drug paraphernalia) and body feelings. Because addictive drugs reliably increase synaptic dopamine and other reward-related neurotransmitters as a result of their direct pharmacologic actions—indeed, they produce excessive and grossly distorted reward signals—the brain receives a powerful impetus to connect the circumstances in which the drugs have been used with the motivation to take drugs again. Addictive drugs also activate transcription factors, such as the cyclic adenosine monophosphate response element binding protein, and alter the composition of activator protein 1 complexes in brain reward circuits.[19] Cocaine, opioids, and other addictive drugs regulate many genes downstream of these and other transcription factors. Even if the drug is no longer pleasurable, these signals continue to reinforce drug wanting and seeking. Moreover, the certainty and magnitude of these signals give drugs a marked advantage over natural rewards and other learned goals, including prosocial activities.

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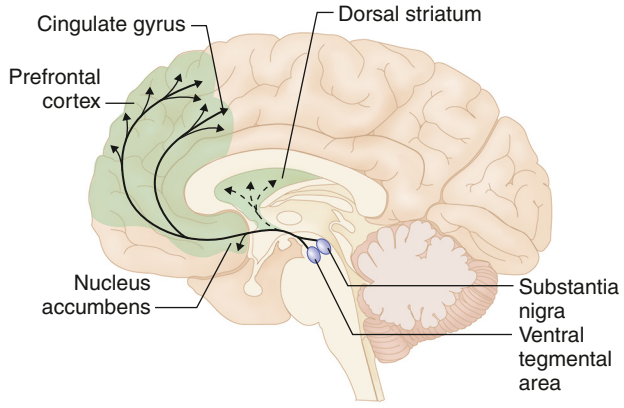

E-FIGURE 27-1. Brain reward circuits. The major dopaminergic projections to the forebrain that underlie brain reward are shown superimposed on a diagram of the human brain: projections from the ventral tegmental area to the nucleus accumbens, amygdala (not shown), hippocampus (not shown), and prefrontal cerebral cortex. Also shown are projections from the substantia nigra to the dorsal striatum (caudate and putamen and related structures) that play a role in habit formation and drug consumption. (From Hyman SE, Malenka RC, Nestler EJ. Neural mechanisms of addiction: the role of reward-related learning and memory. *Annu Rev Neurosci*. 2006;29:565-598.)

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28 IMMUNOMODULATORY DRUGS

ANNE R. BASS AND INEZ ROGATSKY

Even with the availability of targeted biologic treatments (Chapter 29), synthetic immunomodulatory drugs remain the cornerstone of therapy for many autoimmune conditions, including rheumatoid arthritis, juvenile inflammatory arthritis, psoriatic arthritis, and systemic lupus erythematosus (Table 28-1). When used for rheumatic diseases, these agents are often referred to as disease-modifying antirheumatic drugs (DMARDs). Orally bioavailable and relatively inexpensive, these agents target intracellular processes important for the survival and/or function of immune cells. Many, although not all, of these agents are immunosuppressive; that is, they predispose patients to infection. With the exception of glucocorticoids, synthetic immunomodulatory agents are slow acting, generally taking 2 to 3 months to have their therapeutic effect. Some synthetic immunomodulatory drugs are U.S. Food and Drug Administration (FDA)–approved for a narrow group of conditions but are used more widely in clinical practice. For example, mycophenolate mofetil is FDA-approved for the prevention of transplant rejection but is often used to treat systemic lupus erythematosus.

GLUCOCORTICOIDS

First introduced into clinical practice in the early 1950s, glucocorticoids remain among the most commonly prescribed class of medications worldwide, primarily due to their extremely potent immunosuppressive and anti-inflammatory properties and very low cost. Despite their efficacy, serious side effects associated with glucocorticoid use prompted the race for "selective," less toxic, glucocorticoid-like compounds; however, no such new-generation glucocorticoids have yet become available. A fundamental difference setting glucocorticoids apart from other anti-inflammatory medications is that they are modeled after endogenously produced steroid hormones with numerous functions in normal mammalian physiology. Hence, "adverse effects" of their administration are not "off-target" but rather reflect expected responses of biologic systems receiving these hormones in excess of their physiologic levels and irrespective of the normal circadian cycle of glucocorticoid secretion. Endogenous glucocorticoids are produced from cholesterol by the adrenal cortex along with structurally similar mineralocorticoids (the unifying term *corticosteroids* refers to both types of molecules). These hormones signal through the glucocorticoid and mineralocorticoid receptors, respectively; however, the main endogenous glucocorticoid, cortisol, can bind both receptors. Most synthetic clinically used glucocorticoids have much higher affinity for the glucocorticoid receptors.[1]

GLUCOCORTICOID RECEPTOR

The human glucocorticoid receptor gene (*NR3C1*) encodes the main 795–amino acid GRα protein that is responsible for the majority of glucocorticoid activities and a GRβ splice variant that differs from GRα in its unique C-terminus beyond amino acid 728 and does not bind hormone. The physiologic significance of the β-isoform has been debated and likely differs between cell types depending on how much β-isoform is expressed; it has been reported to function as a dominant-negative inhibitor of GRα in certain contexts. In addition, the alternate translation start sites of GRα may give rise to different isoform combinations present in different tissues. GRα protein is a member of the nuclear receptor family—the largest family of mammalian transcription factors. Upon activation by its endogenous or synthetic hormonal ligand, cytoplasmic heat-shock protein-bound GRα undergoes structural changes and translocates to the cell nucleus, where it either binds DNA directly—typically, a specific palindromic sequence known as a glucocorticoid response element—or is tethered to DNA through protein:protein interactions with other DNA-bound regulators, particularly those of the activator protein-1 (AP1) and nuclear factor-κB (NF-κB) families (Fig. 28-1). In each case, GRα can activate or repress transcription. Commonly, however, GRα binding to palindromic glucocorticoid response elements leads to activation of associated genes, whereas binding to AP1/NF-κB represses transcription of their target genes (Fig. 28-1). Anti-inflammatory and immunosuppressive properties of glucocorticoids result both from direct activation of anti-inflammatory (interleukin [IL]-10, dual specificity phosphatase-1 [Dusp1], glucocorticoid-inducible leucine-zipper [Gilz], TNFAIP3/A20, and others) and repression of AP1- and/or NF-κB–driven pro-inflammatory genes.

The extremely broad consequences of glucocorticoid actions stem from the fact that the GRα protein is expressed essentially in every cell in the body. In each cell type, the glucocorticoid receptor activates and represses hundreds of genes, thereby leading to specific physiologic effects. Recent genome-wide analyses of GRα binding and glucocorticoid-regulated transcriptomes revealed a striking level of specificity in the glucocorticoid receptor's actions, whereby even in closely related cell types (e.g., different types of white blood cells), glucocorticoid receptor–regulated genes display a mere 15% overlap. This finding indicates that cell-specific variables (e.g., chromatin packaging and accessibility to transcription factor binding), the composition of GRα interacting accessory proteins (e.g., coactivators and corepressors that associate with GRα in a cell- and binding site–specific manner), and the physiologic state of the cell play major roles in specifying glucocorticoid function (Fig. 28-1).

TABLE 28-1 RECOMMENDED GLUCOCORTICOID DOSE TAPERING SCHEDULES, SUBJECT TO INDIVIDUAL VARIABILITY AND REQUIRING MONITORING OF PATIENT'S CLINICAL RESPONSE*

STARTING DOSE OF PREDNISONE (OR EQUIVALENT)	PROGRESSIVE DECREASE OF DAILY DOSE
>40 mg daily	5-10 mg daily every 1-2 weeks
20-40 mg daily	5 mg daily every 1-2 weeks
10-19 mg daily	2.5 mg daily every 2-3 weeks
5-9 mg daily	1 mg daily every 2-4 weeks
<5 mg daily	0.5 mg daily every 2-4 weeks

*Recommended schedules can be modified for individual patients, depending on the disease and the duration of glucocorticoid treatment.

Adapted from Guerrero Pérez F, Marengo AP, Villabona Artero CV. The unresolved riddle of glucocorticoid withdrawal. *J Endocrinol Invest*. 2017;40:1175-1181.

PHYSIOLOGIC AND PHARMACOLOGIC EFFECTS OF GLUCOCORTICOIDS IN DIFFERENT TISSUES

Glucocorticoids and Inflammation

One of the most well-known effects underlying the widespread use of glucocorticoids is suppression of inflammation. This effect stems from dramatic reduction

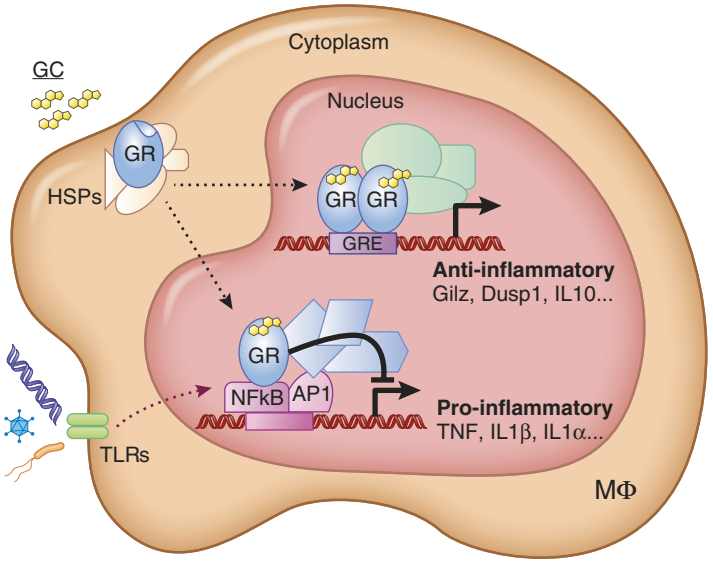

FIGURE 28-1. Glucocorticoid receptor (GR) signaling pathway. Unliganded GR is cytoplasmic and bound by heat-shock proteins (HSPs) that maintain its competence for glucocorticoid (GC) ligand binding. When GC-bound, GR undergoes structural change, translocates to the nucleus, and associates with specific genomic glucocorticoid response elements (GREs) (two hexameric head-to-tail [inverted] half-sites separated by three base pairs) or tethers to DNA through protein:protein interactions with AP1 and NF-κB, the effector pro-inflammatory transcription factors downstream of toll-like receptors (TLRs). In each case, a number of coactivator and corepressor proteins associate with GR in a binding site–specific manner. Some proteins encoded by genes activated and repressed by GR in a macrophage (MΦ) through direct DNA binding and tethering, respectively, are listed. AP1 = activator protein 1; IL = interleukin; NFκB = nuclear factor kappa light chain enhancer of activated B cells; TNF = tumor necrosis factor.

ABSTRACT

Synthetic immunomodulatory drugs are oral agents that target intracellular processes important for the survival and/or function of immune cells. Glucocorticoids are the most widely used (and least expensive) of these agents. Glucocorticoids bind to glucocorticoid receptors that are expressed not only on inflammatory cells but also on cells of the cardiovascular system, bone, muscle, liver, adipose tissue, and central nervous system. As a consequence, they have both profound immunosuppressive and anti-inflammatory effects but can also result in significant toxicity. Methotrexate, leflunomide, and mycophenolate mofetil are immunosuppressive drugs commonly used to treat rheumatic diseases, while the immunophilin-binding agents, cyclosporine, tacrolimus, and sirolimus, are most commonly used to prevent transplant rejection.

KEYWORDS

glucocorticoid
methotrexate
disease-modifying antirheumatic drugs (DMARDs)
transplant
rheumatic disease

in the transcription of genes encoding inflammatory cytokines (tumor necrosis factor [TNF], IL-1α, IL-1β, IL-12p40, IL-6), chemokines (Cxcl10, Ccl2, Ccl3, Ccl4, Ccl5), and cell adhesion molecules (ICAM, ELAM), along with other mediators of inflammation (such as those produced through the activity of cyclooxygenase-2 and phospholipase A2: prostaglandins, leukotrienes, and arachidonic acid metabolites) produced by macrophages, endothelial cells, fibroblasts, and other cell types. These changes yield a less inflammatory environment, reducing leukocyte and lymphocyte trafficking, as well as their numbers, due to both a decrease in proliferation and an increase in apoptosis for certain cell subsets. It should be noted that glucocorticoid receptor–mediated apoptosis, specifically of immature and transformed lymphocytes, makes glucocorticoids the drug of choice for numerous hematologic malignancies.

Physiologically, glucocorticoid production in inflammatory conditions is triggered through the activation of the hypothalamic-pituitary-adrenal (HPA) axis by inflammatory cytokine signaling when the local mechanisms to control inflammation fail. This effect is transient and self-limited due to a negative feedback loop back to the hypothalamus that suppresses excessive HPA activity.[2] Pharmacologically, prolonged or high-dose glucocorticoid administration is not susceptible to HPA-mediated inhibition and may lead to immunosuppression and increased susceptibility to infections. It is important to note that the effect of glucocorticoids on immune cell types is not indiscriminately suppressive but modulatory and generally favors Th2-type T-cell responses while suppressing Th1; similarly, glucocorticoids inhibit the function of inflammatory macrophages while promoting macrophage commitment to the homeostatic anti-inflammatory phenotype.

Glucocorticoids and Metabolism in the Liver, Adipose Tissue, and Muscle

As the name suggests, endogenous glucocorticoids are critical mediators of glucose, as well as lipid and protein metabolism. In the liver, glucocorticoids are essential for maintaining normal blood glucose levels during fasting, awakening, and periods of stress, partly by increasing the hepatic responsiveness to glucagon. This occurs through stimulation of gluconeogenesis (indeed, GR activates genes encoding rate-limiting enzymes of gluconeogenesis such as *PEPCK*). Glucocorticoids have also been implicated in the regulation of fatty acid metabolism in the liver. In the adipose tissue, glucocorticoids both increase adipocyte differentiation and decrease lipolysis upon chronic exposure; the result is to promote visceral fat accumulation. Finally, in the skeletal muscle, glucocorticoids inhibit protein synthesis while promoting proteolysis to provide amino acids for gluconeogenesis.

The compound systemic effects of glucocorticoid excess on the key metabolic tissues—the liver, adipose tissue, and muscle—are perhaps best highlighted in patients with Cushing syndrome (Chapter 208) resulting from pituitary or adrenocortical adenomas or long-term administration of glucocorticoid medications. These include glucose intolerance due to increased gluconeogenesis in the liver and antagonism of the effects of insulin on peripheral glucose utilization, fasting and postprandial hyperglycemia, and reduced insulin sensitivity[3]—typical signs of type 2 diabetes and metabolic syndrome (Chapter 210). Patients with Cushing syndrome often present with dyslipidemia due to both an increase in triglyceride and total cholesterol levels and adipocyte differentiation in the visceral adipose tissue, ultimately leading to centripetal adiposity. Finally, catabolic effects of high circulating glucocorticoids in the muscle result in skeletal muscle atrophy and weakness.

Glucocorticoids and the Cardiovascular System

Glucocorticoids are required to maintain blood volume and pressure, as well as normal arteriolar tone and cardiac output. Consequently, sustained exposure to high-dose glucocorticoids results in elevated blood pressure—an effect observed both in patients with Cushing syndrome and in individuals treated with glucocorticoids. Of note, in Cushing syndrome, a part of this effect is a consequence of increased retention of water and sodium by the kidneys—an activity of mineralocorticoid receptors, rather than glucocorticoid receptors, activated by endogenous cortisol. However, synthetic glucocorticoids lacking any mineralocorticoid receptor–binding activity have an independent glucocorticoid receptor–mediated effect on blood pressure by suppressing the production of vasodilators (e.g., prostaglandins and endothelial nitric oxide) while stimulating the responsiveness to vasoconstrictors (e.g., vasopressin and catecholamines) and augmenting the expression of angiotensin II receptors, ultimately increasing peripheral vascular resistance (Chapter 64).

Glucocorticoids and the Bones

Two of the most debilitating adverse effects of glucocorticoid treatment are osteoporosis (Chapter 225)[4] and osteonecrosis (Chapter 229). Glucocorticoids have a spectrum of functions in normal bone physiology by acting upon both key cell types: osteoblasts and osteoclasts (Chapter 225). Glucocorticoids are required for normal bone growth and remodeling; they stimulate osteoclastogenesis, in part, by activating the expression of RANK ligand—a critical growth factor for osteoclast maturation—while inhibiting the expression of its decoy receptor osteoprotegerin in surrounding osteoblasts and stromal cells, ultimately leading to bone resorption. At the same time, glucocorticoids inhibit osteoblast proliferation and differentiation (by shifting stromal cell differentiation from osteoblasts to adipocytes) and promote their apoptosis. Clinically, these activities may result in significant bone loss and an increased risk of fractures, especially with prolonged use (>3 months) of oral corticosteroids or high cumulative doses of potent topical corticosteroids.[5] Fortunately, however, these effects can be lessened by co-administration of bisphosphonates, denosumab (a RANK ligand inhibitor at 60 mg subcutaneously every 6 months), or teriparatide (a recombinant parathyroid hormone at 20 μg subcutaneously daily).[A1]

Glucocorticoids and the Central Nervous System

At normal levels, glucocorticoids have long been known to be critical in the hippocampus, where they facilitate memory and learning. There is also extensive evidence that excessive glucocorticoids (including endogenous glucocorticoids during a sustained period of stress) are associated with decreased hippocampal cellularity, impaired memory, and changes in mood, cognition, and reasoning. Similarly, although adequate levels of glucocorticoids are protective against acute traumatic stress, repeated high-dose glucocorticoid treatment mimics chronic stress and induces dendritic lengthening in the basolateral amygdala—a region responsible for developing fear, anxiety, and aggression. Notably, experimental evidence also shows that exposure of the brain to increased amounts of glucocorticoids early in life or even in utero may have long-lasting consequences for the HPA axis and glucocorticoid-regulated processes such as metabolism and cardiovascular function.

Overall, while physiologic, diurnal, or acute stress-induced secretion of glucocorticoids is essential for normal brain functions and protection from stress-induced damage, sustained elevated levels of glucocorticoids cause a spectrum of central nervous system pathologies whose severity depends on the dose, duration, and time of exposure, as well as genetic, epigenomic, and environmental factors at play.

Clinical Use

Glucocorticoids are approved for use in a wide variety of inflammatory conditions at a range of doses and durations. Glucocorticoids can be used for short-term management of disease flares, such as in patients with asthma, gout, rheumatoid arthritis, juvenile inflammatory arthritis, or psoriatic arthritis, and for patients experiencing acute allergic reactions. A short course of corticosteroids also improves outcomes in ventilated patients with coronavirus 2019 diseases (Chapter 337). Other conditions require sustained glucocorticoid use to maintain disease remission, such as sarcoidosis, ulcerative colitis, eczema, minimal change glomerulonephritis, systemic lupus erythematosus, dermatomyositis, temporal arteritis, and polymyalgia rheumatica. Low doses (≤10 mg) are often adequate for rheumatoid arthritis and polymyalgia rheumatica, whereas high doses (e.g., prednisone 1 mg/kg) are required for the acute management of giant cell arteritis, lupus nephritis, and dermatomyositis. Inhaled glucocorticoids can be used for the management of asthma and chronic obstructive pulmonary disease, whereas intra-articular glucocorticoids are used to control localized joint symptoms in patients with inflammatory arthritis and osteoarthritis. Repeated intra-articular glucocorticoid injections can be associated with more rapid cartilage loss in osteoarthritis patients, however. Finally, glucocorticoids can be administered topically for the treatment of psoriasis, eczema, and other skin conditions.

Management of glucocorticoids in the perioperative period for patients on chronic steroid therapy has been traditionally based on an assumption that supraphysiologic dose increases are always required to avoid the development of adrenal insufficiency. Based on the negative results of a small number of randomized trials to test this assumption and more recent clinical experience, along with the risks of hypertension, fluid retention, hyperglycemia, and infection with the routine use of high-dose glucocorticoid supplementation, this practice should be reserved for special situations. With (1) major surgical procedures, (2) the presence of volume-refractory hypotension, or (3) in patients requiring chronic physiologic replacement therapy for adrenal insufficiency, it has been recommended that patients should receive their steroid dose right up to the time of surgery, followed by hydrocortisone 50 to 100 mg intravenously started prior to surgery, followed by a 200-mg continuous infusion

over 24 hours or by 50 to 100 mg repeated every 8 hours for at most 48 to 72 hours postoperatively (based on the known normal secretory rate of cortisol of 75 to 150 mg daily during anesthesia and major surgery).[6] Either of these regimens should be immediately followed by replacement with the patient's oral glucocorticoid therapy. Conversely, perioperative supplemental glucocorticoids are not indicated for minor or intermediate-intensity surgical procedures, for patients who are chronically taking prednisone (or equivalent) at doses of 10 mg or less daily, for patients who are on every-other-day steroids, or for patients who are using only topically administered steroids. In all these cases, treating physicians should be promptly reactive, with exogenous glucocorticoids administered in case of unexpected postoperative hypotension or other manifestations of adrenocortical insufficiency. The recommendations for withholding supraphysiologic steroid therapy perioperatively in the settings described earlier do not apply to individuals taking chronic glucocorticoid replacement for adrenal failure or to generally any surgery in children chronically treated with glucocorticoids.

Toxicity and Monitoring

Glucocorticoid toxicity is dose and duration dependent. Even inhaled glucocorticoids for asthma (Chapter 75) have metabolomic side effects,[7] and just a short burst of high-dose oral glucocorticoid therapy increases the short-term risk of gastrointestinal bleeding, heart failure, and sepsis by about three-fold.[8] Common toxicities include weight gain, Cushing syndrome, osteoporosis, osteonecrosis, diabetes, hypertension, hyperlipidemia, posterior subcapsular cataracts, increased intraocular pressure, skin fragility, poor wound healing, gastrointestinal tract bleeding and perforation, mood changes, myopathy, and predisposition to infection, including opportunistic ones. Glucocorticoids administered to children can also result in growth retardation. Patients starting glucocorticoids should be counseled to take supplemental calcium and vitamin D; additional treatments to prevent osteoporosis depend on the anticipated dose and duration of glucocorticoid treatment, the patient's age, and baseline osteoporosis risk.

Because patients on exogenous glucocorticoids can develop secondary adrenal insufficiency, the dose of glucocorticoids should be tapered gradually to accommodate a slow return of adrenal function (Table 28-1). Different tapering regimens for glucocorticoids in different diseases are based on a very low quality of evidence. Considering the sizable individual variation in response to tapering, it is unlikely that a secure, uniform glucocorticoid tapering schedule applicable to all patients will be determined in the foreseeable future, as recently summarized. A systematic, broadly based review estimated the risk of clinical or subclinical adrenal insufficiency after glucocorticoid withdrawal to be approximately 30% after use of a variety of types of glucocorticoids in several underlying diseases. The problem of this apparently high rate of adrenal insufficiency is compounded by its difficulty in recognition, because symptoms and signs are usually nonspecific (e.g., nausea, vomiting, abdominal cramps, fatigue) and insidious in onset. Dosage, duration of treatment, administration route, age, fragility, underlying disease, and even laboratory testing of serum cortisol level are not completely useful in predicting adrenal insufficiency. Some generalizations can be made regarding glucocorticoid withdrawal[9]:

1. Hypothalamic-pituitary-adrenal (HPA) axis suppression mostly occurs after oral or parenteral glucocorticoid treatment that leads to higher systemic levels of glucocorticoids, but it may also appear with cutaneous, ototopical, or ophthalmic administration.
2. HPA suppression is improbable in patients who have received glucocorticoid treatment for less than 3 weeks.
3. HPA suppression is improbable in patients who have received daily prednisone at a dose of less than 5 mg (or equivalent) or alternate-day prednisone at doses of less than 10 mg (or equivalent).
4. Repeated biochemical monitoring for adrenal insufficiency with glucocorticoid withdrawal is impractical. If needed, a first assessment that measures morning serum cortisol level (between 8:00 and 9:00 AM) may be helpful but not conclusive in most cases. Among classical stimulatory tests to diagnose adrenal insufficiency, the insulin tolerance test is considered the gold standard, but it requires medical supervision because of its risk and is contraindicated in several populations. A standard-dose corticotropin analog test may be more reliable and accurate than the morning cortisol level, but it is cumbersome.
5. Patients who have adrenal insufficiency upon glucocorticoid withdrawal usually respond symptomatically to reinstitution of glucocorticoid therapy.
6. During the year after discontinuing glucocorticoids, patients should be well educated on the risks of adrenal insufficiency[10] and know that they may require glucocorticoids in situations of stress (such as surgery or significant medical illness) to compensate for reduced adrenal glucocorticoid production.

Notwithstanding the complex variables that determine the effectiveness and safety of glucocorticoid tapering, which may also include genetic determinants, an example of a general tapering scheme might be a stable reduction of 10 to 20% with monitoring of clinical response of the patient (see Table 28-1).

Glucocorticoid use in pregnancy can be associated with low-birthweight babies and may slightly increase the risk of cleft palate, but glucocorticoids are commonly used in pregnancy when needed by the mother (Chapter 221). Prednisone and prednisolone are metabolized to an inactive form by placental 11β-hydroxysteroid dehydrogenase and do not reach the fetus. In contrast, fluorinated glucocorticoids such as dexamethasone and betamethasone do cross the placenta and are used predelivery to treat the fetus and induce fetal lung maturation.

IMMUNOMODULATORY AGENTS

Hydroxychloroquine

Mechanism of Action

The mechanism of action of hydroxychloroquine is not fully understood, but the drug is known to reduce lysosomal activity and autophagy (the process in which organelles and proteins are sequestered into vesicles that fuse with lysosomes to be broken down and used as fuel for other cellular needs). Hydroxychloroquine also reduces the presentation of class II major histocompatibility complex autoantigens, as well as signaling through toll-like receptors 7 and 9. Hydroxychloroquine is given as a once- or twice-daily oral dose; it is readily absorbed and has a long half-life due to extensive tissue uptake.

Clinical Use

Hydroxychloroquine was developed to treat malaria but is also approved for the treatment of systemic lupus erythematosus (Chapter 245) and rheumatoid arthritis (Chapter 243). Hydroxychloroquine can help to control lupus skin disease, arthritis, serositis, and mild hematologic abnormalities, and discontinuing hydroxychloroquine increases the risk of a lupus flare. Hydroxychloroquine is not used as primary treatment for lupus nephritis, but the drug can help reduce the risk of end-stage renal disease in these patients. Hydroxychloroquine also reduces the risk of type 2 diabetes and venous thromboembolism, lowers cholesterol levels, and improves overall lupus survival. In patients with rheumatoid arthritis, hydroxychloroquine is a component of "triple therapy" (along with sulfasalazine and methotrexate), which is as effective as methotrexate plus a TNF inhibitor. Hydroxychloroquine is also used in some inflammatory and rheumatic skin diseases, mainly as a steroid-sparing agent.

Toxicity and Monitoring

Hydroxychloroquine can cause retinopathy, which is treatment dose and duration related. Retinopathy risk can be minimized by using a dose less than or equal to 5 mg/kg and by referring the patient for ophthalmologic screening. Hydroxychloroquine can also be associated with pruritus, areas of blue-gray "bruiselike" skin pigmentation, particularly on the lower extremities, cardiomyopathy, prolongation of the QT interval, proximal myopathy, and peripheral neuropathy. Hydroxychloroquine is not associated with fetal malformations and is generally continued during pregnancy in lupus patients in order to prevent a disease flare.

Sulfasalazine

Mechanism of Action

Sulfasalazine is metabolized by intestinal bacteria to sulfapyridine and 5-aminosalicylic acid (5-ASA). Sulfapyridine is well absorbed, whereas most of the 5-ASA remains in the intestine. 5-ASA appears to be responsible for the therapeutic effect of sulfasalazine in ulcerative colitis (Chapter 127) through an unknown mechanism. It should be noted that 5-ASA is a weak cyclooxygenase 1 and 2 inhibitor, and traditional nonsteroidal anti-inflammatory agents, which strongly inhibit cyclooxygenase, actually worsen colitis. How sulfasalazine ameliorates rheumatoid arthritis is unknown. Sulfasalazine is given in split daily doses ranging from 2 to 4 g/day.

Clinical Use

Sulfasalazine is approved for the treatment of ulcerative colitis (Chapter 127), as well as polyarticular juvenile inflammatory arthritis and rheumatoid arthritis. In rheumatoid arthritis, sulfasalazine is a component of "triple therapy" (along with hydroxychloroquine and methotrexate), which has been shown

to be as effective as methotrexate plus a TNF inhibitor. Sulfasalazine is also used in the treatment of psoriatic arthritis.

Toxicity and Monitoring

Sulfasalazine can be associated with severe hypersensitivity reactions and should never be given to individuals with sulfa or aspirin allergy. Sulfasalazine can also cause agranulocytosis (Chapter 153) and aplastic anemia (Chapter 151). More common side effects of sulfasalazine include gastrointestinal upset, headache, and liver dysfunction.

Sulfasalazine has not been associated with fetal abnormalities; however, because sulfasalazine can inhibit folate absorption, folic acid supplementation is especially important in pregnant women taking the drug. Sulfasalazine can cause reversible oligospermia, and alternative treatments should be considered in male patients attempting to conceive a child.

IMMUNOSUPPRESSIVE AGENTS

Methotrexate

Mechanism of Action

Methotrexate inhibits dihydrofolic acid reductase, which results in antiproliferative effects via reduced synthesis of purines, pyrimidines, and polyamines. Methotrexate polyglutamates (metabolites) also inhibit aminoimidazole carboxamide ribonucleotide transformylase, an inhibitor of adenosine deaminase. This results in high intracellular levels of adenosine, which, when released, can have anti-inflammatory effects on neutrophils, macrophages, and lymphocytes. Oral absorption of methotrexate is dose dependent and varies among individuals. Subcutaneous dosing can be used to ensure bioavailability and helps to reduce gastrointestinal side effects. Methotrexate is excreted largely through glomerular filtration and active tubular secretion, and dose reduction is important in individuals with renal insufficiency, such as the elderly. Methotrexate is administered weekly as either a single dose or in three divided doses 12 hours apart over a 24-hour period. Although high-dose methotrexate (20 to 25 mg per week) is associated with greater efficacy than lower doses (5 to 15 mg per week), dosages are generally "ramped up" while monitoring for dose-dependent toxicities.

Clinical Use

Along with cyclosporine and acitretin, methotrexate is approved as one of the conventional systemic immunomodulatory treatments of psoriasis (Chapter 405). Several biologic agents have since emerged for the treatment of moderate to severe psoriasis. Methotrexate is FDA-approved for the treatment of rheumatoid arthritis,[11] polyarticular juvenile inflammatory arthritis, and psoriatic arthritis. Methotrexate monotherapy is recommended as the first-line treatment in patients with early rheumatoid arthritis, with or without glucocorticoid therapy (Chapter 243). If disease activity remains high, then methotrexate can be combined with hydroxychloroquine and/or sulfasalazine or combined with a biologic DMARD, generally a TNF inhibitor or a Janus kinase inhibitor. In patients with psoriatic arthritis (Chapter 244), methotrexate is effective in treating peripheral arthritis and psoriasis but is not effective in treating enthesitis, dactylitis, or nail or spine involvement.

Toxicity and Monitoring

In addition to predisposing patients to infection, methotrexate can cause liver toxicity and bone marrow suppression.[12] Complete blood counts and liver function testing should be performed monthly for 3 months at the initiation of therapy (and after changes in dose) and every 3 to 4 months thereafter. Renal function should also be monitored because a fall in glomerular filtration rate reduces methotrexate clearance. Alcohol should be avoided in patients on methotrexate, and methotrexate should not be prescribed to individuals with underlying liver disease. Patients with psoriasis (Chapter 405), particularly patients who have diabetes or who are obese, appear to be at higher risk of liver toxicity than patients with rheumatoid arthritis. Liver biopsy may be recommended in psoriatic patients who have received a cumulative methotrexate dose between 1.5 and 4 grams, depending on their level of risk. Non-Hodgkin lymphoma (Chapter 171) has been reported in patients treated with methotrexate, including some cases that regressed without additional treatment upon withdrawal of methotrexate. Methotrexate can be associated with acute pneumonitis or pulmonary fibrosis, and smokers are at increased risk for pulmonary toxicity. In patients with rheumatoid arthritis, methotrexate-induced lung injury can sometimes be difficult to distinguish from rheumatoid lung disease. Stomatitis, nausea, malaise, and fatigue are other relatively common side effects of methotrexate. Toxicity can be lessened by administration of folic acid 1 mg daily or folinic acid 5 mg weekly 12 to 24 hours after each methotrexate dose.

Methotrexate is teratogenic and can also cause fetal death. It is contraindicated in pregnant women and nursing mothers, and it should not be used for at least 3 months before planned conception in either men or women.

PURINE AND PYRIMIDINE INHIBITORS

Leflunomide

Mechanism of Action

Leflunomide inhibits dihydro-orotate dehydrogenase and thereby results in decreased pyrimidine synthesis and antiproliferative effects. Leflunomide is given as a daily 20-mg dose. It has a long half-life (≈2 weeks) due to biliary recycling, and using a loading dose (100 mg daily × 3 days) at treatment initiation leads to a more rapid clinical response. Leflunomide has both renal (early) and fecal (late) elimination, and in cases of severe leflunomide toxicity, a cholestyramine washout (cholestyramine 8 g three times daily × 11 days) causes rapid drug elimination. Without a washout, leflunomide metabolites remain detectable in the blood for up to 2 years.

Clinical Use

Leflunomide is FDA-approved for the treatment of rheumatoid arthritis (Chapter 243), where it improves signs and symptoms of the disease and prevents structural damage. Leflunomide is also used in the management of peripheral arthritis in patients with psoriatic arthritis.

Toxicity and Monitoring

Leflunomide can cause severe liver injury, including fatal liver failure. Leflunomide can also cause marrow suppression and predispose patients to infection. Liver function testing and complete blood counts should be performed monthly for 3 to 6 months at the initiation of therapy and every 2 to 3 months thereafter. If there is a three-fold rise in aminotransferase levels, then leflunomide should be discontinued and a cholestyramine washout used. As with methotrexate, there are reports of leflunomide-associated interstitial lung disease. Leflunomide commonly causes diarrhea and mild alopecia. Minor side effects may resolve with leflunomide dose reduction. Although there are no data specifically linking leflunomide to the development of malignancy, the risk of lymphoma may be increased in any patient on immunosuppressive therapy.

Leflunomide is teratogenic and can also cause fetal death; it is contraindicated in pregnant women and nursing mothers, and it should not be used in women of childbearing age who are not using contraception. Women planning pregnancy should stop leflunomide and use a cholestyramine washout. Pregnancy should not be attempted until the blood leflunomide M1 metabolite level is less than 0.02 mg/L on two separate tests at least 2 weeks apart.

Mycophenolate Mofetil

Mechanism of Action

Mycophenolate mofetil is rapidly metabolized to mycophenolic acid, the active metabolite.[13] Mycophenolic acid blocks the function of inosine monophosphate dehydrogenase and thereby inhibits the de novo pathway of guanosine synthesis. Because T and B lymphocytes lack salvage pathways to synthesize purines, mycophenolate mofetil acts preferentially on lymphocytes. In addition to these antiproliferative effects, mycophenolate mofetil reduces antibody formation by B cells. Mycophenolate mofetil is given orally twice daily, with dose reduction in patients with severe renal impairment.

Clinical Use

Mycophenolate mofetil is approved for use in kidney, liver, and heart transplant (Chapter 38) recipients in combination with cyclosporine and glucocorticoids. Mycophenolate mofetil has also been shown to be as effective as cyclophosphamide in inducing remission of lupus nephritis and superior to azathioprine in maintaining remission of lupus nephritis (Chapter 245). Mycophenolate mofetil is as effective as cyclophosphamide in the management of scleroderma-related interstitial lung disease.

Toxicity and Monitoring

Mycophenolate mofetil can cause neutropenia and other cytopenias. Nausea and diarrhea are common with the drug. Mycophenolate mofetil increases the risk of infection and may also increase the risk of lymphoma.

Mycophenolate mofetil is a pregnancy category D drug that has been associated with congenital malformations and miscarriages and is contraindicated in pregnancy. Reliable contraception should be used in women of childbearing

age on mycophenolate mofetil, and contraception should be continued for at least 6 weeks after discontinuing the drug. Breast-feeding should also be avoided in mothers on mycophenolate mofetil.

Azathioprine and 6-Mercaptopurine

Mechanism of Action

Azathioprine is a derivative of 6-mercaptopurine (6-MP), and their effects are similar. Both drugs are activated by hypoxanthine-guanine phosphoribosyltransferase (HGPRT) to form 6-thioguanine nucleotides that can be incorporated into DNA, causing cytotoxicity. Other drug metabolites inhibit the enzyme glutamine-5-phosphoribosylpyrophosphate amidotransferase, required for de novo purine synthesis. Both drugs result in dose-dependent suppression of delayed-type hypersensitivity and cytotoxicity. Azathioprine and 6-MP are metabolized in the liver and in erythrocytes via two pathways, one using thiopurine S-methyltransferase (TPMT) and the other using xanthine oxidase. Ten percent of the population is heterozygous for a nonfunctioning TPMT allele and 0.3% are homozygous for this allele, resulting in intermediate or low to absent TPMT levels, respectively. Patients with low or absent TPMT can experience life-threatening myelosuppression when given azathioprine or 6-MP, while those with intermediate levels benefit from lower drug dosages. TPMT testing (level or genotype) can help identify individuals at increased risk of myelotoxicity, but because myelotoxicity can occur even in the presence of normal TPMT levels, all patients require close monitoring of complete blood counts, particularly at the initiation of therapy and with any dose change. The second route of azathioprine and 6-MP inactivation, via xanthine oxidase, can be inhibited by xanthine oxidase inhibitors, such as allopurinol or febuxostat, used in the treatment of gout. The dose of azathioprine or 6-MP must be reduced when one of these drugs is used. Azathioprine and 6-MP are given as a single or split daily dose. The daily dose of azathioprine in patients with autoimmune diseases and as maintenance to prevent transplant rejection is 1 to 3 mg/kg.

Clinical Use

Azathioprine is approved for the treatment of rheumatoid arthritis, though rarely used for this indication, and as adjunctive therapy in the prevention of renal transplant rejection (Chapter 117). 6-MP is approved for the treatment of acute lymphatic leukemia as part of a combination regimen. Azathioprine and 6-MP can help to maintain remission in ulcerative colitis[14] and are sometimes used as steroid-sparing agents in Crohn disease (Chapter 127). Azathioprine is most commonly used as a steroid-sparing agent in systemic lupus erythematosus (Chapter 245).

Toxicity and Monitoring

Bone marrow suppression is common and dose-related in patients receiving azathioprine or 6-MP, and it can result in leukopenia, anemia, and thrombocytopenia. Gastrointestinal side effects, including nausea, vomiting, diarrhea, and elevated liver enzymes, are common, and azathioprine can also cause pancreatitis. Complete blood counts and measurement of liver enzymes should be performed every 1 to 2 weeks during the first month of treatment and with every change in dose, every 2 weeks for an additional 2 months, and then every 3 months thereafter. Azathioprine and 6-MP are associated with an increased risk of infections, lymphoma, and skin cancer. Rare cases of hepatosplenic T-cell lymphoma have been reported in inflammatory bowel disease patients receiving azathioprine.

Azathioprine and 6-MP are categorized as pregnancy category D drugs because they can be associated with prematurity, low birthweight, neonatal leukopenia, thymic hypoplasia, and hypogammaglobulinemia. However, immunologic effects on the fetus generally normalize within 1 year, and azathioprine is not associated with fetal malformations. For this reason, azathioprine is often continued in pregnant lupus patients, especially if they have a recent history of nephritis.

IMMUNOPHILIN-BINDING AGENTS, INCLUDING CALCINEURIN INHIBITORS

Cyclosporine

Mechanism of Action

Cyclosporine binds to cyclophilin A, the predominant immunophilin in T cells, and this binding enhances cyclophilin's inhibition of calcineurin. Calcineurin is stimulated during T-cell activation to activate nuclear factor of activated T cells (NFAT), which in turn leads to the production of IL-2 and other cytokines important in the immune response. Calcineurin also indirectly enhances activation of NFκB, which is critical for T-cell function and survival. Cyclosporine also has calcineurin-independent inhibitory effects on the mitogen-activated protein kinase (MAPK) pathway. Cyclosporine is metabolized by cytochrome P-450 3A (CYP3A) in the liver, and 95% of excretion is biliary. Drug clearance is also strongly stimulated by P-glycoprotein expression on intestinal enterocytes. Cyclosporine is given twice daily as a divided oral dose. Daily dosages for patients with rheumatic diseases are lower than maintenance doses used to prevent transplant rejection (2 to 4 mg/kg vs. 7 to 9 mg/kg, respectively). Trough drug levels should be measured to determine the optimal therapeutic dose, especially in transplant patients. Therapeutic drug concentrations differ with the measurement technique, institution, indication, and protocol. Drug interactions occur when cyclosporine is co-administered with inhibitors or inducers of CYP3A or P-glycoprotein. Azole antifungal agents, macrolide antibiotics, and calcium-channel blockers increase cyclosporine levels, whereas many anticonvulsants and St. John's wort decrease cyclosporine levels.

Clinical Use

Cyclosporine is FDA-approved for the treatment of severe plaque psoriasis (Chapter 405) and to prevent allogeneic kidney, heart, and liver transplant rejection (Chapter 38). It is also approved for the treatment of active rheumatoid arthritis but is not commonly used for this indication. In patients with psoriasis, cyclosporine is generally used intermittently and for less than 12 weeks to avoid cumulative toxicity. Cyclosporine is also a first-line treatment for pure red cell aplasia (Chapter 151). Voclosporin, a cyclosporine analogue, is approved for the treatment of active lupus nephritis in patients who are on background therapy with mycophenolate mofetil.

Toxicity and Monitoring

Cyclosporine can cause hypertension, renal insufficiency, hyperkalemia, and hyperuricemia. In patients with rheumatoid arthritis and psoriasis, blood pressure and creatinine levels should be monitored every 2 weeks during initiation of treatment and every 1 to 3 months during long-term use. If the creatinine level rises 25% above baseline, then testing should be repeated and the dosage reduced 25 to 50% if there is no improvement. Nonsteroidal anti-inflammatory drugs (NSAIDs) should be avoided in patients taking cyclosporine. Psoriasis patients treated with cyclosporine who have been previously treated with PUVA or methotrexate are at increased risk of skin cancer. Cyclosporine also increases the risk of lymphoma and predisposes patients to infection. More common side effects of cyclosporine include hypertrichosis, gum hyperplasia, and tremor.

Cyclosporine is a pregnancy category C drug. Limited experience in pregnant transplant recipients suggests that cyclosporine is not associated with fetal malformations but is associated with low-birthweight babies. Breast-feeding should be avoided in mothers on cyclosporine.

Tacrolimus

Mechanism of Action

Tacrolimus binds to the T-cell immunophilin FK-binding protein 12 (FKBP-12), and this complex inhibits activation of calcineurin (see Cyclosporine, Mechanism of Action). As with cyclosporine, tacrolimus also has calcineurin-independent inhibitory effects on the MAPK pathway. Tacrolimus is metabolized by CYP3A in the liver and is more than 90% excreted in feces. Drug interactions occur when tacrolimus is co-administered with inhibitors or inducers of CYP3A. Tacrolimus is given twice daily as a divided oral dose, with dose adjustments made based on trough levels.

Clinical Use

Tacrolimus is approved for the prevention of allogeneic kidney, heart, and liver transplant rejection, and graft survival is similar to that achieved with cyclosporine-based regimens. Tacrolimus should be used in combination with azathioprine or mycophenolate mofetil in heart and kidney transplant recipients.

Toxicity and Monitoring

Tacrolimus, particularly at high doses, can cause nephrotoxicity and hypertension and should not be used in combination with cyclosporine. Like cyclosporine, tacrolimus can also cause hyperkalemia, headache, and tremor, and it is associated with an increased risk of infections, lymphoma, and skin cancers. Tacrolimus is associated with new-onset type 2 diabetes in approximately 20% of transplant recipients, but it reverses in about one third of them by 1 year post-transplant. Tacrolimus has been associated with cardiac hypertrophy,

which is reversible upon dose reduction or drug discontinuation. Tacrolimus given by injection can be associated with anaphylaxis, likely due to castor oil derivatives contained in the IV formulation, and should be avoided unless oral administration is impossible.

Tacrolimus has not been associated with fetal malformations, but it has been associated with preterm birth, as well as hyperkalemia and renal impairment during pregnancy. Breast-feeding should be avoided in mothers taking tacrolimus.

Sirolimus

Mechanism of Action

Sirolimus, like tacrolimus, binds to the immunophilin FKBP-12. However, unlike tacrolimus, the sirolimus/FKBP-12 complex inhibits activation of the mammalian target of rapamycin (mTOR) and has no effect on calcineurin. mTOR inhibition blocks antigen- and cytokine-driven T-cell proliferation and also inhibits antibody production. mTOR is also an important modulator for aging and age-related diseases. mTOR inhibitors may have anticancer activity for many types of malignancies. Sirolimus is given once daily as an oral dose, and excretion is over 90% in feces. Sirolimus has a long half-life, and dose adjustments should not be more frequent than every 7 to 14 days, guided by trough levels. A loading dose more rapidly achieves therapeutic levels, both when sirolimus treatment is initiated and when dose adjustments are made. Like cyclosporine, sirolimus is a substrate for CYP3A4 and P-glycoprotein, and concomitant use of strong inducers or inhibitors of CYP3A4 or P-glycoprotein should be avoided when possible. When given concomitantly with cyclosporine, sirolimus should be administered 4 hours after cyclosporine to minimize their interaction. The dose of sirolimus often needs to be increased after cyclosporine is withdrawn.

Clinical Use

Sirolimus is approved for the prevention of allogeneic renal transplant rejection and is used in combination with cyclosporine and glucocorticoids starting at the time of transplant (Chapter 117). Cyclosporine can be withdrawn 3 to 12 months after transplant, depending on the patient's risk of rejection. Sirolumus is also approved for the treatment of patients with lympangioleiomyomatosis (Chapter 80).

Toxicity and Monitoring

Patients taking sirolimus are at increased risk of lymphoma and infection. Sirolimus can be associated with angioedema (particularly when used together with ACE inhibitors), fluid accumulation, and delayed wound healing. Sirolimus can be associated with renal insufficiency, particularly when used with cyclosporine, and the new onset of proteinuria. Patients on sirolimus can develop hyperlipidemia and are at risk for rhabdomyolysis when given HMG-CoA reductase inhibitors, particularly if they are receiving concomitant cyclosporine.

Sirolimus is contraindicated in pregnancy, given its antiproliferative effects. Breast-feeding should also be avoided in mothers taking sirolimus.

ALKYLATING AGENTS

Cyclophosphamide

Mechanism of Action

Cyclophosphamide is a prodrug that is metabolized in the liver by CYP-450 enzymes to alkylating molecules that cause DNA cross-linking. This occurs preferentially in rapidly proliferating cells, such as tumor and hematopoietic cells.

Clinical Use

Cyclophosphamide is approved for the treatment of a variety of malignancies, as well as minimal change nephrotic syndrome, but is also used in the treatment of lupus nephritis and antineutrophil cytoplasmic antibodies (ANCA)–associated vasculitis. The use of cyclophosphamide for these conditions has declined, however, as less toxic therapies, such as mycophenolate mofetil for lupus nephritis and rituximab for ANCA-associated vasculitis, have been shown to be equally efficacious.

Toxicity and Monitoring

Cyclophosphamide causes myelosuppression and predisposes patients to infections (including opportunistic ones), and cyclophosphamide metabolites can cause hemorrhagic cystitis. Cardiac toxicity is also seen. Cyclophosphamide increases the risk of secondary malignancies and increases the risk of bladder cancer even in patients who do not experience hemorrhagic cystitis during treatment. Cyclophosphamide commonly causes nausea and hair loss. Cyclophosphamide should not be used together with a TNF inhibitor because of an increased risk of solid tumors with this combination.

Cyclophosphamide can cause infertility, and the risk is higher the older the patient and the greater the cumulative cyclophosphamide dose. Treatment with a GnRH agonist prior to each dose of cyclophosphamide can help to protect gonadal function. Cyclophosphamide causes fetal malformations and miscarriages and should not be used in pregnancy or during lactation.

GENERAL REFERENCES

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A1. Ding L, Hu J, Wang D, et al. Efficacy and safety of first- and second-line drugs to prevent glucocorticoid-induced fractures. *J Clin Endocrinol Metab*. 2020;105:600-613.

29

BIOLOGIC AGENTS AND SIGNALING INHIBITORS

NANCY J. OLSEN AND JOHN J. O'SHEA

Many of the drugs used by clinicians, even if effective and safe, were discovered empirically, meaning their molecular target was not necessarily known in advance. By comparison, therapeutic agents derived from biologic molecules and other targeted therapies have transformed many areas of medicine over the past two decades. A significant advantage of this new type of drug is the possibility of acting on specific molecules directly involved in disease pathogenesis. The concept of targeted agents carried with it the promise of reduced toxicity compared to empirically generated agents. Although this promise may not have been universally fulfilled, most targeted drugs have relatively good margins of safety and their usage in many areas of medicine has steadily increased. The efficacy (or lack thereof) of targeted therapies has also contributed to understanding of disease mechanisms.

Targeted therapeutics can be broadly classified as "biologics," meaning that they are produced from natural sources or living organisms. In this chapter though, we will be focusing on products engineered to be produced by cells using biotechnology methods. In general, these are large molecules administered by intravenous or subcutaneous routes. Newer additions to this class are small molecules synthesized and designed for specific targets. The targeting of specific signaling pathways was challenging given the similarities of some of these molecules, such as kinases, which may contribute to many intracellular processes. Nevertheless, many of these obstacles have been successfully overcome, resulting in a class of novel therapeutics.

Targeted therapies such as biologic agents and signaling inhibitors have applications in many areas of medicine, including cancer as well as immune-mediated dermatologic, rheumatologic, infectious, neurologic, hematologic, and cardiovascular disease. The range of possible and approved indications is almost endless and will continue to be an area of intense research and development.

BIOLOGIC AGENTS

Several types of biologics have been used as targeted therapies (Table 29-1; Fig. 29-1). One widely used class of drugs is recombinant proteins, including cytokines, interferons, growth factors, and colony-stimulating factors. Examples include granulocyte colony-stimulating factor (G-CSF; filgrastim, lenograstim), used to treat neutropenia, and interleukin (IL)-2 (aldesleukin), approved for treatment of melanoma and renal cell carcinoma. Classic endocrine mediators that engage receptors and activate intracellular signaling pathways, such as growth hormone, can be considered in this category as well (Chapter 205).

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BIOLOGIC AGENTS

Several types of biologics have been used as targeted therapies (Table 29-1; Fig. 29-1). One widely used class of drugs is recombinant proteins, including cytokines, interferons, growth factors, and colony-stimulating factors. Examples include granulocyte colony-stimulating factor (G-CSF; filgrastim, lenograstim), used to treat neutropenia, and interleukin (IL)-2 (aldesleukin), approved for treatment of melanoma and renal cell carcinoma. Classic endocrine mediators that engage receptors and activate intracellular signaling pathways, such as growth hormone, can be considered in this category as well (Chapter 205).

ABSTRACT

Therapeutics derived from biologic molecules have transformed many areas of medicine. The development of these new agents is a major shift from previous, largely empirical, approaches to drug development. Biologics, including monoclonal antibodies, recombinant and fusion proteins, and engineered cells, are designed to target pathways involved in disease pathogenesis from cancer and autoimmunity to cardiovascular, neurologic, and infectious disease. In recent years, small molecule inhibitors of intracellular signaling pathways have been added to the list of available targeted therapeutics. Many of these drugs also have been shown in rigorous clinical trials to have efficacy and safety in the treatment of a wide range of conditions ranging from malignancies to autoimmune diseases. This chapter will discuss specific agents in these broad categories, focusing on approved treatments and using selected examples to illustrate molecular targets, mechanisms, and clinical applications. This is a fast-moving area with great potential for even wider clinical applications in the future.

KEYWORDS

biologic agents
signaling inhibitors
monoclonal antibodies
cytokines
growth factors
targeted therapies

In addition to cytokines, humans produce endogenous cytokine antagonists. An example is anakinra, which is a recombinant version of a naturally occurring protein, the IL-1 receptor antagonist. The drug, like the natural protein, blocks binding of IL-1 to its receptor, thereby preventing signaling. It differs from the native human protein by the addition of one terminal amino acid. It is approved to treat rheumatoid arthritis (Chapter 243) and some childhood inflammatory syndromes.

Many of the commonly used biologics are monoclonal antibodies, which were initially derived from mice using hybridoma technology. By comparison, chimeric immunoglobulins are engineered to have murine variable regions of the component heavy and light chains attached to human constant regions. An example is infliximab, which targets the cytokine tumor necrosis factor-α (TNF-α). However, antichimeric antibodies develop in some treated patients and have the potential to block their efficacy. Further refinements using phage display techniques led to development of completely humanized monoclonal immunoglobulin Gs (IgGs); the TNF-α–targeting product adalimumab was an early example. More than 100 monoclonal antibodies have now been approved for diverse indications.[1]

A variation on monoclonal antibody therapy is the creation of antibody drug conjugates, meaning that other moieties, including small molecules, are chemically linked to the antibodies; examples include brentuximab vedotin and trastuzumab emtansine. The former is used in Hodgkin's lymphoma (Chapter 172) and targets CD30 with an antibody coupled to monomethyl auristatin E to effect cell killing. The latter targets *HER2* on cancer cells by the antibody and kills the cells with its "warhead."

Another approach to designing biologic therapeutics is with fusion proteins. Most of these agents are receptors that are fused to other human proteins like the Fc portion of immunoglobulins. These agents may target soluble or cell-bound molecules such as cytokines by functioning as decoy receptors that prevent binding of the mediator to its receptor. The first major therapeutic application of this technology was etanercept, which combines the human TNF-α receptor with a human Fc portion of the IgG molecule. An alternative strategy is to graft biologically active peptides onto the Fc domain of IgG, as in romiplostim, a thrombopoietin receptor agonist, approved for treatment of immune thrombocytopenia (Chapter 158). Cytokine fusion molecules also can be created. An example is IL-2 linked to a peptide of diphtheria toxin that was

TABLE 29-1 CLASSES OF BIOTHERAPEUTICS

CLASS	TYPES	EXAMPLES
Recombinant proteins	Cytokines Growth factors IL-1 receptor antagonist	Aldesleukin (IL-2) Filgrastim Anakinra
Monoclonal antibodies	Murine Chimeric Humanized	OKT3 Infliximab Adalimumab
Antibody-drug conjugates	Tumor cytotoxics	Brentuximab vedotin
Fusion proteins	Decoy receptors Immunotoxins	Etanercept Denileukin diftitox
Engineered cells	CAR-T cells	Tisagenlecleucel

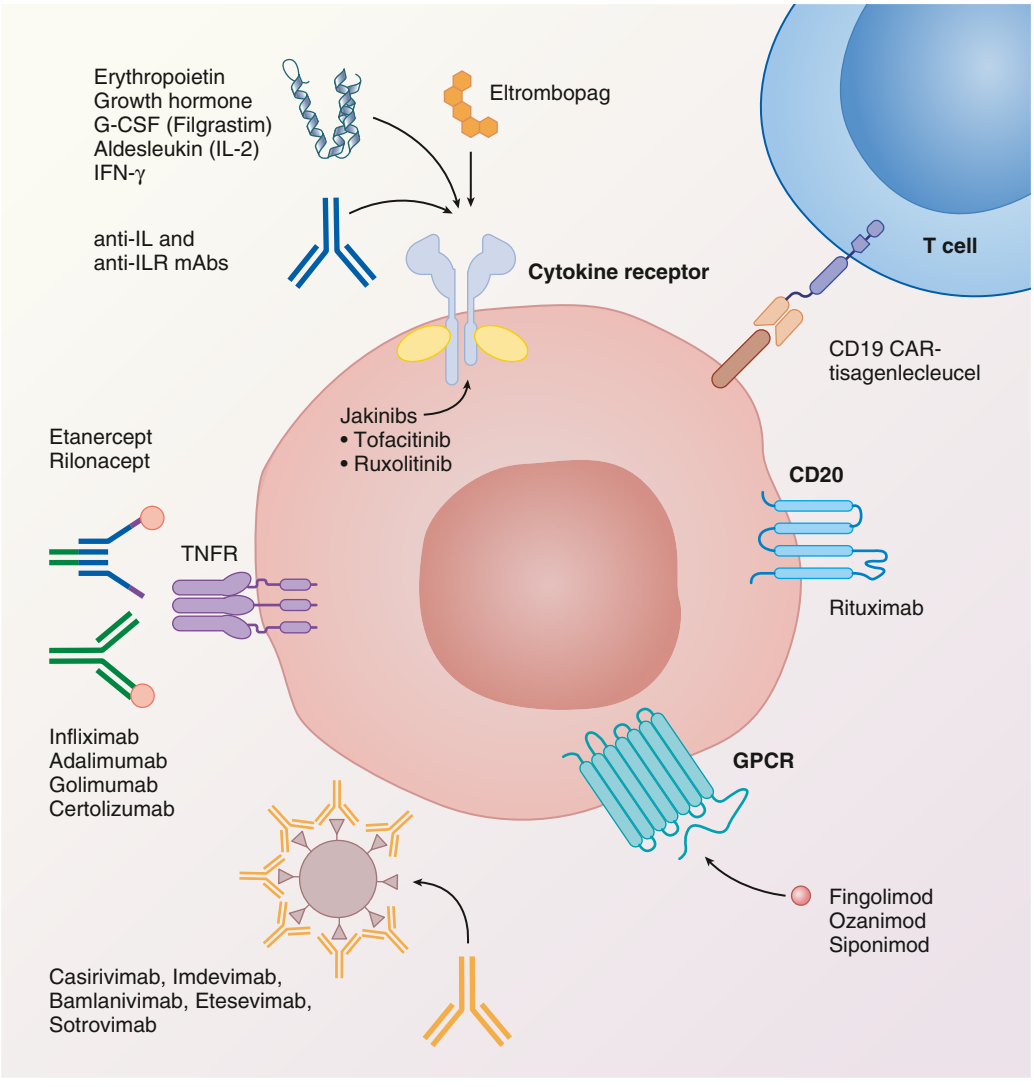

FIGURE 29-1. Biologics and signaling inhibitors that have clinical applications as targeted therapeutics take many forms. Recombinant cytokines and growth factors, monoclonal antibodies, and fusion proteins may target small molecules or cells. Newer approaches include cells that are engineered to target tumors and small molecular weight kinase inhibitors that block intracellular signaling pathways. The clinical applications of these therapies are numerous, ranging from malignancies to autoimmune diseases. CAR = chimeric T cell antigen receptor; G-CSF = granulocyte colony-stimulating factor; GPCR = G protein–coupled receptor; IFN = interferon; IL = interleukin; ILR = interleukin receptor; TNFR = tumor necrosis factor receptor.

approved for treatment of cutaneous T-cell lymphoma but was subsequently removed from the market because of toxicities, especially visual loss.

A more recently developed class of biologics is engineered cells. Perhaps the most exciting example of this therapy is chimeric antigen receptor (CAR)-T cells.[2,3] Such cells are a remarkable example of gene therapy in which T cells are directed to tumor cells by transduction with engineered antigen receptors. Approved CAR-T cells include tisagenlecleucel, axicabtagene ciloleucel, and lisocabtagene maraleucel, all of which target malignant B cells and represent the first examples of engineered living cells being approved.

SPECIFIC TYPES OF BIOLOGIC AGENTS

Biologic agents also can be considered in groups defined by their corresponding targets. Examples include soluble mediators (e.g., cytokines, complement proteins, antibodies, and growth factors), viruses,[4] and cells (including malignant cells and normal cells, especially T and B lymphocytes).

BIOLOGICS THAT TARGET SOLUBLE PROTEINS

Cytokines

The cytokine TNF-α binds to two receptors (TNFR55 and TNFR75), where it contributes to host responses against infection. When TNF-α production is uncontrolled, chronic inflammation can cause subsequent tissue damage in diseases such as rheumatoid arthritis (Chapter 243). Both monoclonal antibodies and soluble TNF-α receptor molecules are efficacious in inhibiting the activity of TNF-α (Table 29-2). These biologics all neutralize soluble TNF-α, but the monoclonal antibodies are more effective at also binding and preventing signaling of transmembrane forms of the cytokine. Efficacy of these approved biologics in rheumatoid arthritis and other conditions was shown in large, randomized, placebo-controlled trials in combination with methotrexate or as monotherapy.[A1,A2] However, these agents are not completely interchangeable,[5] as shown by the lack of utility of etanercept in treatment of granulomatous diseases such as Crohn disease (Chapter 127), for which infliximab is efficacious.[A3] Adverse effects of TNF blockade include an increased risk of infection, especially reactivation of latent tuberculosis, and therefore screening tests to exclude tuberculosis are required before its use.

RANKL, which is another member of the TNF superfamily, promotes osteoclast differentiation and bone resorption. Denosumab is a recombinant human monoclonal antibody that targets RANKL, which interferes with differentiation, activation, and survival of osteoclasts. It is indicated for treatment of postmenopausal osteoporosis (Chapter 225) and in men and women at high risk of bone loss after treatment with androgen deprivation therapy or aromatase inhibitors, respectively. Conversely, sclerostin, which is a product of osteocytes, inhibits bone formation; romosozumab targets sclerostin and is approved for the treatment of postmenopausal osteoporosis.

B cell activating factor (BAFF, aka Blys, CD257) is also in the TNF family. Belimumab is an anti-BAFF monoclonal antibody approved to treat adults with active systemic lupus erythematosus (Chapter 245). A fusion protein targeting CD257, blisibimod, is being investigated as a treatment for IgA nephropathy (Chapter 107).

IL-1 is an important driver of fever and induction of acute phase protein synthesis. Three approved therapeutics for IL-1 blockade are available at this time (Table 29-2): recombinant human IL-1 receptor antagonist (anakinra), a receptor fusion molecule (rilonacept) displaying both the IL-1 receptor and the IL-1 receptor accessory protein, and a fully human monoclonal antibody against IL-1β (canakinumab). Efficacy of anakinra in adult rheumatoid arthritis was somewhat disappointing, but subsequent studies in children with inflammatory arthritis showed significant therapeutic effects. It has become clear that IL-1β is the key inflammatory mediator of the autoinflammatory syndromes (Chapter 240), and IL-1 blockade using these agents has been approved for treatment of these conditions. An advantage of IL-1 blockade is a lower risk of infections than with TNF-α inhibitors. Canakinumab also has been shown to prevent recurrent cardiovascular events in patients who have suffered a myocardial infarction and who have elevated C-reactive protein (CRP) levels (Chapter 58).

Daclizumab, a humanized monoclonal IgG1 that targets the high-affinity IL-2 receptor by binding IL-2R alpha chain is approved for the prevention of acute renal transplant rejection but was discontinued in 2009. In 2016 it was approved for relapsing forms of multiple sclerosis (Chapter 380).

Dupilumab binds to the alpha chain subunit that is shared by the IL-4 and IL-13 receptors and inhibits signaling of both of these type 2 cytokines. It is approved for treatment of atopic dermatitis, asthma, and rhinosinusitis with polyps.

TABLE 29-2 APPROVED BIOTHERAPEUTICS TARGETING TNF-α, INTERLEUKIN-1, AND INTERLEUKIN-6

TARGET	THERAPEUTIC	DESCRIPTION	APPROVED INDICATIONS
TNF-α	Infliximab	Chimeric mAb	Rheumatoid arthritis, psoriatic arthritis, psoriasis, ankylosing spondylitis, Crohn disease
	Etanercept	Receptor fusion molecule	Rheumatoid arthritis, psoriatic arthritis, psoriasis, ankylosing spondylitis, polyarticular juvenile idiopathic arthritis
	Adalimumab	Humanized mAb	Rheumatoid arthritis, psoriasis, hidradenitis suppurativa, adult and pediatric Crohn disease, ankylosing spondylitis, polyarticular juvenile idiopathic arthritis
	Golimumab	Human IgG1 mAb	Rheumatoid arthritis, psoriatic arthritis, ankylosing spondylitis, ulcerative colitis
	Certolizumab pegol	Pegylated Fab′ fragment of a mAb	Rheumatoid arthritis, psoriatic arthritis, Crohn disease
IL-1	Anakinra	Recombinant human IL-1 receptor antagonist	Rheumatoid arthritis, cryopyrin-associated periodic syndromes
	Rilonacept	Recombinant receptor fusion molecule	Cryopyrin-associated periodic syndromes
	Canakinumab	Human IgG1 mAb	Systemic juvenile idiopathic arthritis, adult and pediatric familial Mediterranean fever, TNF receptor-associated periodic syndrome, hyper IgD syndrome
IL-6	Tocilizumab	Recombinant humanized mAb	Rheumatoid arthritis, giant cell arteritis, systemic juvenile idiopathic arthritis, polyarticular juvenile idiopathic arthritis
	Sarilumab	Human IgG1 mAb	Rheumatoid arthritis

IgD = immunoglobulin D; IgG = immunoglobulin G; IL = interleukin; mAb = monoclonal antibody; TNF = tumor necrosis factor.

IL-5 is important for eosinophil maturation and activation. Three anti-IL-5 monoclonal antibodies, mepolizumab, reslizumab, and benralizumab are approved for the treatment of asthma (Chapter 75) and eosinophilia (Chapter 156).

Similar to IL-1, IL-6 is a prototypic inflammatory cytokine, which drives production of TNF-α, IL-1, and IL-17.[6] Therapeutic blockade of IL-6R with tocilizumab and sarilumab is approved for treatment of inflammatory joint conditions in adults and children (Table 29-2). Subcutaneous tocilizumab is approved for the treatment of giant cell arteritis (Chapter 250). Tocilizumab use is associated with increased risk of varicella zoster virus infection as well as liver and cholesterol abnormalities. Satralizumab is an IL-6R monoclonal antibody approved for neuromyelitis optica (Chapter 392). Siltuximab is an IL-6 antibody approved for multicentric Castleman disease (Chapter 171).

IL-12 and IL-23 are dimeric cytokines that share a subunit (p40). Ustekinumab targets this common p40 chain, preventing binding of both cytokines to their corresponding receptors, which are expressed primarily on activated T cells. Ustekinumab is an approved treatment for psoriasis (Chapter 405), psoriatic arthritis (Chapter 244), and Crohn disease (Chapter 127). Agents that target the p19 subunit of IL-23, including guselkumab, tildrakizumab, and risankizumab are approved for the treatment of psoriasis and psoriatic arthritis.

The IL-17 family includes 6 members, with IL-17A and IL-17F sharing sequence similarities and having the greatest role in development of autoimmunity. Neutralizing antibodies to IL-17A (secukinumab and ixekizumab) and IL-17R (brodalumab) are approved by the U.S. Food and Drug Administration to treat ankylosing spondylitis, psoriasis, and psoriatic arthritis.[A4,7]

Interferons are important for host defense, especially against viruses but are overexpressed in autoimmune disease, particularly systemic lupus erythematosus. Anifrolumab binds to IFN-alpha receptor 1 (IFNAR1) and thereby blocks IFN-α and IFN-β. In phase III trials, anifrolumab reduced lupus disease activity, improved skin rash and arthritis, and reduced corticosteroid use. It is now approved for treatment of moderate or severe systemic lupus erythematosus.[A5] Emapalumab targets IFN-γ and is approved for hematophagocytic lymphohistiocytosis (Chapter 155).[8]

Thymic stromal lymphopoietin (TSLP) is an epithelial-derived cytokine that has a role in allergic disease, upregulates other cytokines and is elevated in the airways of patients with asthma. A recent phase II trial showed efficacy of an anti-TSLP monoclonal antibody, tezepelumab, in patients with noneosinophilic asthma.

Antibodies

IgE antibodies mediate allergic diseases by binding through the Fc portion of the molecule to specific receptors, FcεRI and CD23/FcεRII. Omalizumab is an approved humanized IgG1 monoclonal antibody that binds free IgE and prevents receptor binding and signaling. Indications for treatment with omalizumab include allergic asthma that has failed other therapies and chronic spontaneous urticaria (Chapter 232). Because of the elevated risk of allergic reactions, subcutaneous injections of this drug must be administered in a medical office rather than in the home.

Complement

Tissue damage in allergic and immune disorders is often mediated by complement proteins, so targeting these molecules is a useful therapeutic approach. Eculizumab and ravulizumab are anti-C5 monoclonal antibodies that prevent the formation of the membrane attack complex and block chemotactic activity of C5a. They are approved to treat paroxysmal nocturnal hemoglobinuria (Chapter 146) and are available in some countries for the treatment of atypical hemolytic uremic syndrome. Investigational applications include age-related macular degeneration. An inhibitor of C5a, avacopan, is being investigated for treatment of antineutrophil cytoplasm antibody (ANCA)-associated vasculitis.[A6]

BIOLOGIC AGENTS THAT TARGET CELLS

B Lymphocytes

The humoral arm of the immune response mediates many autoimmune disorders through production of autoantibodies. Therefore, blockade or targeted elimination of B lymphocytes and inhibition of B cell–derived cytokines has been used therapeutically in diseases such as systemic lupus erythematosus (Chapter 245) and rheumatoid arthritis.[9] Rituximab is a chimeric monoclonal antibody that targets CD20 B cells for deletion. It was first used for treatment of B-cell lymphomas (Chapter 171) and is now also approved for treatment of rheumatoid arthritis. Consensus documents also suggest that rituximab may be useful as treatment for organ-damaging systemic lupus erythematosus that has failed other therapies. Ocrelizumab is a humanized monoclonal antibody that targets an overlapping epitope of CD20 and is an FDA-approved treatment for multiple sclerosis (Chapter 380). Obinutuzumab and ofatumumab are anti-CD20 monoclonal antibody approved for lymphoma and being studied for autoimmune disease. Targeting CD19 rather than CD20 is of interest as an alternative approach because of the potential for depleting long-lived plasma cells and early B cells that are not CD20-positive, while at the same time sparing regulatory B cells. Anti-CD19 antibodies are currently in trials for autoimmune diseases and malignancies. Blinatumomab is a bispecific agent that targets CD3 on T cells and CD19 on B cells and is approved for acute lymphoblastic leukemia (Chapter 168).

T Lymphocytes

The central role of T lymphocytes in the immune response makes this cell subset an attractive target for treatments of autoimmune disease and graft rejection as well as cancer immunotherapy. Therapies targeting the T-cell surface marker CD3 have been available for several decades and are still in limited use for the treatment of transplant rejection. The first humanized therapeutic monoclonal antibody was alemtuzumab, which targeted the CD52 molecule on T and B lymphocytes. An unexpected and as yet unexplained consequence of this treatment was long-standing lymphopenia, limiting its use. Ibalizumab is anti-CD4 monoclonal antibody for treatment of human immunodeficiency virus (HIV).

Costimulatory and Checkpoint Molecules

Another approach is inhibition of costimulatory signals required for full T-cell activation. The best example is the fusion protein abatacept, in which the extracellular portion of cytotoxic T lymphocyte antigen-4 (CTLA-4) is coupled to the extracellular portion of human IgG1. This molecule, which inhibits costimulatory signals between CD28 and CD80/86, is FDA approved for the treatment of rheumatoid arthritis (Chapter 243). Addition of abatacept to cyclophosphamide, however, did not improve the outcome of lupus nephritis in a trial. In general, infectious complications associated with abatacept are lower than with drugs that block TNF-α. Physiologically, CTLA4 binds CD80/CD86 and delivers a signal that inhibits T-cell activation. Antibodies that target CTLA4 and other negative regulators of T-cell activation (PD1, PDL1) represent a new class of drugs, checkpoint inhibitors, that are currently in use to treat various cancers (Chapter 164).[10] Examples include ipilimumab, nivolumab, atezolizumab, pembrolizumab, cemiplimab, avelumab, and durvalumab. Checkpoint inhibitors may induce immune-related adverse effects and can exacerbate autoimmune diseases.[11]

Adhesion Molecules

Another way to manipulate T cells in the immune response is to block migration to sites of inflammation. Natalizumab, which is a human monoclonal antibody against α_4-integrin, achieves this effect and is approved to treat relapsing/remitting forms of multiple sclerosis. A safety concern with natalizumab is the risk of progressive multifocal leukoencephalopathy (Chapter 341), a fatal condition associated with reactivation of the JC virus in immunosuppressed individuals. Vedolizumab is a monoclonal antibody that targets α4β7 integrin and is approved for ulcerative colitis and Crohn disease.[A7]

Growth Factor Receptors

Growth factor receptors, also known as receptor tyrosine kinases, are key regulators of normal cellular function but can also have major roles in cancer. Multiple monoclonal antibodies that target epidermal growth factor receptors (EGFRs) are approved, including trastuzumab and pertuzumab (breast cancer; Chapter 183); cetuximab and panitumumab (colorectal cancer; Chapter 179); and necitumumab (small cell lung cancer).

The vascular endothelial growth factor (VEGF) family of growth factors is involved in angiogenesis and has been implicated in pathogenesis of malignant disease, the development of metastases, and in forms of retinopathy. Bevacizumab and ramucirumab are biologics that target VEGF to treat malignancies including metastatic colon cancer (Chapter 179). VEGF inhibitors ramucirumab, brolucizumab, and ranibizumab are approved for treatment of macular degeneration (Chapter 391). Another approach to targeting VEGF is with the recombinant fusion protein aflibercept, which is composed of binding domains of the two human receptors for VEGF fused to human IgG1 Fc.

Other Therapeutic Targets Engaged By Monoclonal Antibodies

Aside from cancer, autoimmunity, and allergic disease, biologics are used in the treatment of a wide variety of additional disorders. For instance, the proprotein convertase subtilisin/kexin type 9 (PCSK9) binds to low-density lipoprotein (LDL) receptors and facilitates their degradation. The PSCK9 monoclonal antibodies alirocumab and evolocumab promote recycling LDL receptors and are approved for treatment of hypercholesterolemia (Chapter 190). Caplacizumab is a monoclonal antibody that targets von Willebrand factor and is used for the treatment of acquired thrombocytopenic purpura (Chapter 158). Crizanlizumab targets P-selectin approved for vaso-occlusive crisis in sickle cell disease, and lanadelumab targets kallikrein for treatment of hereditary angioedema (Chapter 232). Litifilimab, a monoclonal antibody to blood dendritic cell antigen 2 (BDCA2), has shown potential for the treatment of cutaneous lupus erythematosus.[A8]

Calcitonin gene–related peptide (CGRP) is a potent vasodilator involved in the pathophysiology of migraine (Chapter 367). Galcanezumab and fremanezumab target CGRP and erenumab targets CGRP receptor for migraine prevention. Aducanumab binds aggregated amyloid β and is approved for the treatment of Alzheimer disease, although controversy remains regarding its efficacy and cost-effectiveness (Chapter 371).

Biologics are also used in the treatment of infectious disease. Raxibacumab is a monoclonal antibody directed against the protective antigen component of lethal toxin of *Bacillus anthracis* (Chapter 272). Palivizumab is a monoclonal antibody that binds the F protein of respiratory syncytial virus (Chapter 330) and is used to prevent severe disease. For severe acute respiratory syndrome coronavirus 2, antispike monoclonal antibodies, including casirivimab, imdevimab, bamlanivimab, etesevimab, and sotrovimab, have been used for prevention and treatment (Chapter 337).

SMALL MOLECULE TARGETED THERAPIES

In addition to recombinant cytokines, small molecule agonists of cytokine receptors have been generated. Eltrombopag is a small molecule thrombopoietin receptor agonist that is approved for treatment of cases of immune thrombocytopenia (ITP) that are resistant to other therapies. It has the advantage of oral dosing (Chapter 158). The original approval for ITP was subsequently expanded with addition of severe aplastic anemia (Chapter 151), in which efficacy is due to actions on stem cells that result in production of other cell lines. This interesting precedent suggests that many other small molecule cytokine receptor agonists and antagonists might be useful therapeutics.

Seven-transmembrane receptors, including chemokine receptors, are very "druggable" targets. Two examples of drugs that target chemokine receptors include maraviroc, a small, orally available molecule that targets the chemokine receptor CCR5. This receptor is an essential cofactor for HIV entry into the cell, which is the mechanism of its antiretroviral effects. Fingolimod, ozanimod, and siponimod are small molecule receptor modulators that target sphingosine-1-phosphate receptor (S1PR1), which is critical for trafficking of T cells and vascular integrity. These agents are approved for multiple sclerosis, and ozanimod is also approved for treatment of ulcerative colitis.[12]

SIGNALING INHIBITORS

An alternative to targeting cytokines extracellularly is to use small molecules that block intracellular signaling pathways activated by binding of cytokines to their specific receptors. An advantage of this approach is that the drugs are administered orally. Because of the ultimately similar downstream cytokine targets, a basic safety principle is that biologics and signaling inhibitors are generally not recommended for use in combination. Janus kinases (JAKs) are critical for signaling by a large family of cytokines, presenting an especially attractive therapeutic target.[13,14] First-generation JAK inhibitors, or jakinibs, inhibit multiple JAKs and thus a large number of cytokines (Table 29-3). Jakinibs are approved for the treatment of rheumatoid arthritis, psoriatic arthritis, juvenile arthritis, and ulcerative colitis and are being investigated for the treatment of a number of other autoimmune and dermatologic conditions.[15,16] Polycythemia vera and related myeloproliferative neoplasms are due to gain-of-function *JAK2* mutations. Ruxolitinib inhibits JAK1 and JAK2 and is approved for the treatment of myeloproliferative neoplasms (Chapter 152) and acute graft-versus-host disease. First-generation jakinibs inhibit JAK2, which mediates signaling of many cytokines, including growth hormone, erythropoietin, thrombopoietin, IL-11, granulocyte colony-stimulating factor (G-CSF), and granulocyte macrophage (GM)-CSF; as a result, treated patients may develop anemia and other cytopenias. Although these effects are not usually severe enough to lead to discontinuation of treatment, newer selective jakinibs are being developed that spare JAK2.

Bruton tyrosine kinase has a critical role in B-cell function.[17] The Bruton tyrosine kinase inhibitors ibrutinib, acalabrutinib, and zanubrutinib are FDA approved to treat chronic lymphocytic leukemia (Chapter 169), Waldenström macroglobulinemia, and lymphoma. In all, more than 35 kinase inhibitors have been approved for multiple indications, including many cancers.

CONCLUSION

The use of biologic agents and signaling inhibitors has led to major improvements in the treatment of a wide variety of diseases, ranging from autoimmunity to malignancies. These targeted therapies have also provided insights into basic pathogenetic mechanisms in many of these disorders. Future directions are likely to focus on improved targeting, with greater selectivity for disease processes while sparing normal pathways, thereby reducing off-target effects. Expansion into other areas of medicine is also likely, with borrowed, modified, or completely new agents.

TABLE 29-3 APPROVED JANUS KINASE INHIBITORS

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Upadacitinib	JAK1	RA
Filgotinib	JAK1	RA (approved in EU, Japan)
Peficitinib	Multiple JAKs	RA (approved in Japan, Korea)
Fedratinib	JAK2/FLT3/RET/BRD4	MPN

COVID = coronavirus disease; EU = European Union; GvHD = graft versus host disease; JIA = juvenile idiopathic arthritis; MPN = myeloproliferative neoplasms; PsA = psoriatic arthritis; RA = rheumatoid arthritis; UC = ulcerative colitis.

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30 COMPLEMENTARY AND INTEGRATIVE MEDICINE

FREDERICK M. HECHT

In addition to the pharmaceutical and surgical therapies that have been central to advances in medical care, a large proportion of people across the globe also use health care treatments that fall outside of conventional medical care. The United States' National Center for Complementary and Integrative Health of the National Institutes of Health has defined complementary health care as "health care approaches developed outside of mainstream Western, or conventional, medicine" when they are used together with conventional medicine, and as alternative medicine when they are used in place of conventional medicine. Integrative medicine is an approach to medical practice that includes conventional medical therapies as well as nonpharmaceutical and nonsurgical therapies that have not always been incorporated or emphasized in conventional medicine but for which some evidence base now exists. This approach typically includes the use of lifestyle, mind-body practices, or natural products. Because these therapies typically receive little or no attention during medical

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ABSTRACT

Complementary medicine emphasizes health care approaches outside of mainstream Western or conventional medicine, whether instead of or in addition to conventional medicine. Integrative medicine coordinates complementary and conventional medicine in a unified approach. Each year, over 30% of U.S. adults use complementary medicine therapies, including natural products (e.g., vitamins and mineral supplements, probiotics, and prebiotics) and mind and body practices (e.g., meditation, yoga and tai chi, manual therapies, acupuncture). In the United States natural products are regulated under the Dietary Supplement Health and Education Act, not the Food and Drug Administration (FDA). Increasing evidence is becoming available to guide the use of these complementary therapies.

KEYWORDS

complementary and alternative medicine
integrative medicine
mind and body practices
yoga
tai chi
manual therapies
acupuncture
natural products
vitamin and mineral supplements
probiotics and prebiotics

education and because of conflicting claims and limitations in the quality of existing evidence, counseling patients about these therapies can be challenging.

USE OF INTEGRATIVE AND COMPLEMENTARY TREATMENTS

An estimated one third of Americans over 18 years of age have used some form of integrative health approach in the past 12 months, and the percentage appears to be increasing. The most commonly used practices included natural products, yoga and tai chi, deep breathing, meditation, chiropractic and osteopathic manipulation, and massage. Integrative medicine techniques have also become a common component of pain management in patients with cancer.[1]

MIND AND BODY PRACTICES

MEDITATION

Meditation and related contemplative practices involve various techniques to self-regulate attention. Often derived from different spiritual traditions, meditation has been used for centuries to achieve states of mental and emotional calm, increased awareness of physical sensations and emotional states, and improved attention. More recently, meditation practices are often used in the secular arena, increasingly within health care settings, to help manage stress, improve emotional regulation skills, and address other mental and physical health issues.

Among the different approaches to meditation, the two general types that have received the most study are *mindfulness-based* meditation and *concentration-mantra* meditation. Mindfulness meditation involves practices aimed at "paying attention in a particular way, on purpose, in the present moment, and nonjudgmentally." For example, the Mindfulness-based Stress Reduction program and related programs in health care settings aim to improve the ability of patients to cope with chronic pain. This approach is at least as effective as approaches such as cognitive-behavioral therapy for treating chronic low back pain (Chapter 369), and both approaches are more effective than usual medical care alone.[A1] In patients treated with opiates for chronic pain, mind-body therapies can reduce the intensity of pain and reduce opioid doses, with the largest effect sizes from meditation approaches.[A2]

Another important application of mindfulness-based approaches has been to address mood regulation, particularly in conditions such as depression (Chapter 362). In patients who have experienced at least one prior episode of significant depression, mindfulness-based cognitive therapy, which combines some elements of cognitive-behavioral therapy with mindfulness practices, can reduce relapse rates by about 20% compared with continuing antidepressant medication alone,[A3] without increasing costs. As a result, mindfulness-based cognitive therapy is now recommended as one of the standard-of-care approaches to prevent relapse of depression in the United Kingdom. Mindfulness-based interventions are also increasingly integrated into the workplace in a variety of ways, including web-based programs and classes on yoga or meditation.

A common form of mantra-based meditation is transcendental meditation. A more generic form is mantra meditation, which may evoke a relaxation response. Limited evidence suggests that this approach can lower blood pressure and improve depressive symptoms.

YOGA AND TAI CHI

Although yoga, tai chi, and qigong are practiced for different purposes and with a variety of styles, their goal is to achieve health benefits that go beyond general physical fitness. The focused attention during movement practices can be viewed as a form of moving meditation.

Tai chi can improve balance and reduce the risk of falls by about 50% in the elderly.[A4] In addition, regular tai chi can significantly improve psychological outcomes, including reductions in stress[A5] and depression. Yoga also is effective for low back pain and has been incorporated into guidelines for managing chronic low back pain.[A6] In patients with hypertension, yoga has been reported to decrease systolic blood pressure by up to 10 mm Hg,[A7] although the quality of data is low.

Yoga can be practiced in a variety of ways, and the actual yoga practices are important when suggesting yoga to patients. For example, yoga that is effective for low back pain has been specifically tailored to low back pain—a gentle yoga style to avoid postures that might exacerbate back pain, while focusing on postures and methods that are thought to be useful. Yoga programs designed for conditions such as low back pain are available at some medical centers and yoga studios. If specifically tailored classes are not available, many yoga studios offer restorative yoga classes, which are less likely to include postures and movements that may exacerbate low back pain and are more likely to include a focus on mindful movement and body awareness that may be helpful for low back pain.

MANUAL THERAPIES

Manual therapies include a broad range of physical treatments commonly used by physical therapists, massage therapists, chiropractors, and osteopaths. These therapies typically include massage and manipulation of muscles, as well as techniques to mobilize joints.

Massage therapy is effective for conditions such as neck and shoulder pain,[2] and massage is commonly used for sports injuries, delayed-onset muscle soreness after strenuous exercise, and other causes of muscle pain. The mechanisms though which massage therapy works are not fully understood. However, studies using muscle biopsies after exercise-induced muscle injury have found that massage decreases the production of inflammatory cytokines and increases indicators of cell repair such as mitochondrial biogenesis. Massage therapy has also been shown to reduce anxiety and blood pressure. One important issue for clinicians to understand is the wide range of massage techniques and different types of expertise among massage therapists. Some forms, such as Swedish massage, are aimed largely at relaxation. Other forms of massage, such as sports massage and deep tissue massage, tend to use greater pressure and techniques specifically aimed at enhancing recovery from muscle injury. When referring a patient for massage for issues such as sports injury, it may be helpful to make sure the massage therapist has specific training and experience in working with sports injuries.

Spinal manipulation, which involves applying a controlled force to a joint of the spine, is typically performed by chiropractors or osteopathic physicians but also can be performed by physical therapists and some physicians. Although spinal manipulation has sometimes been viewed with suspicion in conventional medicine, a growing body of evidence supports its use in specific conditions.[3] For example, spinal manipulative therapy is somewhat effective for reducing acute low back pain,[A8,A9] and is now included in the American College of Physicians recommendations for treatment of acute low back pain. Although serious adverse events after spinal manipulation, such as vertebral artery dissection, appear to be very rare, they emphasize the need for skilled practitioners who are properly trained to perform it.[4]

ACUPUNCTURE AND TRADITIONAL CHINESE MEDICINE

Acupuncture,[5] which has been practiced in China for thousands of years, involves placing thin needles in specific sites, or acupuncture points, which are often stimulated in a variety of ways, such as by spinning the needle. Controversy exists as to whether the benefits of acupuncture are due to a placebo effect versus actual effects of the needle insertion. Data from meta-analysis suggest that about 50% of its benefits are consistent with a placebo effect, but it still improves pain compared with sham treatment, such as stimulation of an acupuncture point without a needle penetrating the skin.[A10,A11] Substantial evidence also indicates that acupuncture can decrease the duration of postoperative ileus,[A12] as well as nausea and vomiting after chemotherapy or surgery.[6]

Other components of traditional Chinese medicine include an assessment of potential imbalances or blockages in the circulation of *qi*, or vital energy, through the body; the use of herbal medicine; and recommendations for diet and exercise (including qigong). Evidence for these broader elements of traditional Chinese medicine is still limited. Data are also limited for the true benefit of Ayurveda (traditional medicine from the Indian subcontinent), which includes some elements of yoga along with components parallel to traditional Chinese medicine.

NATURAL PRODUCTS

Natural products encompass vitamins, minerals, herbs (also known as botanicals), and probiotics, all of which are often sold as dietary supplements. Although many of these products have anecdotal support, evidence of efficacy is limited for most of them.[7] Under the 1994 Dietary Supplement Health and Education Act, dietary supplements are considered to be food, so manufacturers are not required to obtain Food and Drug Administration (FDA) approval before marketing any supplement that was already available before 1994 ("grandfathered status"). By comparison, new dietary ingredients introduced after 1994 require reasonable evidence of safety, which must be reviewed before marketing.

Some dietary supplements can cause severe adverse effects, in part due to impurities or excessive levels of certain active ingredients,[8] and in aggregate they represent the second most common cause of drug-induced liver disease (Chapter 136). The Dietary Supplement and Nonprescription Drug Consumer Protection Act of 2006 requires that physicians in hospitals report any serious

adverse event associated with a dietary supplement (using a form available on the FDA website: MedWatch Form 3500 A). The updated status of different natural products is available on the National Center for Complementary and Integrative Health website (https://nccih.nih.gov/health/herbsataglance.htm), and the National Institutes of Health Office of Dietary Supplements has additional information on the current status of different dietary supplements (https://ods.od.nih.gov/factsheets/list-all/).

Although rigorous research has not found evidence that clearly supports the use of many nutritional supplements, intriguing exceptions exist. An example is turmeric (a traditional medicine from the Indian subcontinent), which is high in curcumin, a curcuminoid that has substantial anti-inflammatory and antioxidant properties. Data suggest that a curcuminoid preparation may be more effective than placebo for decreasing pain and improving postexercise recovery.[9]

Potential Interactions with Drug Therapies

One reason for medical providers to be aware of dietary supplements their patients are taking is that some supplements may have potential interactions with other medications. An example is St. John's wort, which may improve depression, although well-designed studies have failed to show that it is more effective than placebo. St. John's wort induces several cytochrome P-450 isoenzymes, and it has significant interactions with a variety of medications that are metabolized through this system, including warfarin, cyclosporine, oral contraceptives, certain antiretrovirals, and selective serotonin reuptake inhibitors. Other herbal supplements with significant potential for drug interactions include goldenseal and ginseng.

VITAMIN AND MINERAL SUPPLEMENTS

Vitamin and mineral supplements are popular and widely used. Observational studies have linked consumption of various micronutrients, or measurements of these micronutrients in blood, to a reduced risk of certain diseases. However, supplementation of vitamins and minerals for the general population has been disappointing, and a number of randomized trials of nutrient supplementation have not only failed to find evidence of benefit but have actually demonstrated harm (Chapter 199).

Together, these considerations suggest that clinicians should focus on having patients follow an overall healthy eating pattern (Chapter 13) that is low in processed foods and high in nutrient-rich foods, rather than relying on dietary supplements. A Mediterranean diet pattern (Fig. 13-1), for example, can reduce cardiovascular risk, and this type of diet should provide adequate micronutrients for most patients. Special conditions in which evidence suggests benefit from micronutrient supplementation include pregnancy (Chapter 221) and conditions such as chronic pancreatitis with pancreatic insufficiency (Chapter 130).

Probiotics and Prebiotics

Growing evidence shows that the human gut microbiome (Chapter 257) has a variety of important influences on health. Probiotics, which are live microorganisms that are thought to be beneficial in the human gut, are available naturally in yogurt and other fermented foods or as dietary supplements. Prebiotics, which are nondigestible food ingredients that promote the growth of beneficial microorganisms, are another potential approach to improving the gut microbiome.

The most impressive evidence for how changing the gut microbiome can treat a medical condition comes from the studies in which fecal transplants from healthy individuals have been used to treat recurrent *Clostridioides difficile*–associated colitis (Chapters 261 and 271).[A13] Probiotics also can reduce the incidence of antibiotic-induced diarrhea.[A14] For irritable bowel syndrome, data have found probiotics may improve global symptoms by about 20%[10] but overall are mixed, and so are the recommendations of professional societies. In trials showing benefit, the most frequently included strains have been *Lactobacillus acidophilus*, followed by *Streptococcus thermophilus*, *Bifidobacterium breve*, and *Bifidobacterium longum*.

OVERVIEW

Although more evidence is needed on many fronts, evidence-based integrative health therapies are increasingly being included in medical practice. When used appropriately, these approaches may expand the tools available to health care practitioners and the options that can be recommended to patients. Many patients may appreciate choices other than drugs in different conditions. For some conditions, such as pain, the use of nonpharmacologic treatments may reduce the risk of harm from conventional treatments, such as overuse of narcotics. Yoga, tai chi, mindfulness-based meditation, self-massage, and acupressure also can be incorporated into telemedicine.[11]

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31 PRINCIPLES OF GENETICS

BRUCE R. KORF AND NITA A. LIMDI

The elucidation of the structure and function of the genome is one of the great triumphs of modern science. The relevance of inheritance to health and disease probably has been recognized throughout history, but now the rules governing inheritance and the mechanisms whereby genetic information is stored and used are coming to light. Application of this knowledge to medical practice had long been focused on rare monogenic and chromosomal disorders. Major contributions have been made in these areas in genetic testing, genetic counseling, prenatal diagnosis, newborn screening, carrier screening, and, to an increasing extent, treatment. The era of genomic medicine[1] provides powerful new approaches to the management of both rare and common disorders.

GENETIC ARCHITECTURE OF DISEASE

It may be argued that no disorder is completely determined either by genetic or nongenetic factors. Even monogenic conditions, such as phenylketonuria, are modified by the environment, in this case by dietary intake of phenylalanine. Genetically determined host factors are known to modify susceptibility to infection or other environmental agents. Even individuals who are victims of trauma may find themselves at risk in part because of genetic traits that affect behavior or ability to perceive, escape, or recover from danger.

The number of genetic variants that contribute to a disease phenotype, the degree to which each contributes, and the frequency of these variants in the population is referred to as the genetic architecture of disease (Fig. 31-1).[2] Conditions may be largely determined by a single gene, with other genes playing a smaller role in modifying the phenotype, or may result from the accumulation of small effects of many genes. From a medical perspective, it is helpful to divide the genetic contribution to disease into three categories: (1) high-penetrance monogenic or chromosomal disorders; (2) monogenic versions of common disorders; and (3) complex, multifactorial disorders. Each of these affects medical practice in distinctive ways.

HIGH-PENETRANCE MONOGENIC OR CHROMOSOMAL DISORDERS

High-penetrance monogenic or chromosomal disorders are what most clinicians think of as "genetic conditions." They include rare but familiar single-gene disorders, such as neurofibromatosis, Marfan syndrome, and cystic fibrosis, and chromosomal abnormalities, such as trisomy 21 (Down syndrome). Several thousand distinct human genetic disorders have been described and catalogued in Mendelian Inheritance in Man (available at www.omim.org). These disorders include dominant, recessive, and sex-linked disorders, as well as conditions due to variants within the 16.6-kilobase mitochondrial genome. These disorders also include chromosomal syndromes that are associated with duplication or deletion of small regions of the genome and that may result in specific syndromes, such as Williams syndrome (deletion of contiguous loci from a region of chromosome 7), intellectual disability, or autism spectrum disorder.

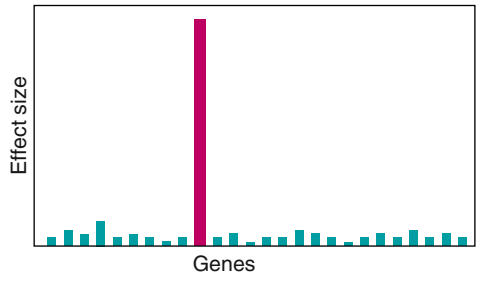

FIGURE 31-1. Diagram illustrating concept of genetic architecture. Different genes are indicated on the x-axis, and their effect size (the degree to which a particular gene contributes to the phenotype) is shown on the y-axis. A disorder associated with variants in a single gene shows a large effect size from that single gene (shown in red). Many other genes (shown in blue) with smaller effect sizes may modify the phenotype, but the major gene is alone sufficient to cause the phenotype.

ROLE OF THE NONSPECIALIST IN MANAGEMENT OF RARE GENETIC DISORDERS

Most clinicians have limited experience with specific rare genetic disorders and are likely to need to refer such patients to a specialist for assistance with diagnosis and management. Nevertheless, the nonspecialist has an important role in the care of these patients. This role begins with realization that the patient may have such a disorder and arrangement for diagnostic evaluation. Many genetic disorders produce obvious signs or symptoms that should prompt referral even if they are not immediately suggestive of a diagnosis. Others can be more subtle, with nevertheless significant consequences if the diagnosis is missed. An example is Marfan syndrome (Chapter 239). The physician needs to be alert to the physical characteristics of patients with Marfan syndrome because life-threatening aortic dissection can be avoided with appropriate monitoring and treatment.

The management of patients with rare genetic disorders may require the assistance of a specialist, but the nonspecialist is likely to be the first contact when an affected individual is ill. The primary care physician should be familiar with the disorder and major potential complications. For example, patients who have neurofibromatosis type 1 (Chapter 385) and who experience chronic back pain require more aggressive evaluation than would be typical for an unaffected individual with back pain because they may be presenting with a malignant peripheral nerve sheath tumor. A good working relationship between the specialist and nonspecialist is crucial to effective care.

The nonspecialist also has an important role in supporting the patient and helping to explain the choices that may be offered for management. This role includes providing support for patients who have disorders that cannot be treated and for the emotional impact that accompanies knowledge that a disorder may be transmitted to one's offspring or shared with other relatives. Most patients have little understanding of the mechanisms of genetics and genetic disease. Although the responsibility to explain these issues may reside with specialists and counselors, the primary care physician has an important supportive role.

GENOMIC APPROACHES TO RARE DISORDERS

Identification of genes that underlie rare disorders enables molecular diagnostic tests to detect pathogenic variants. A database of testing laboratories can be found at www.ncbi.nlm.nih.gov/gtr/. Cytogenomic microarray analysis can reveal small deletions or duplications in individuals with conditions such as autism spectrum disorder, for whom standard chromosomal analysis is unrevealing. Sequencing the entire coding region of the genome (exome sequencing) or the entire genome (genome sequencing) is now being applied clinically.[3] Screening for carrier status for autosomal recessive disorders has been offered for many years, with specific ancestry groups being offered testing for conditions of high prevalence in their group. Genomic approaches are now making it possible to increase the number of conditions tested, thereby enabling a comprehensive screen of dozens or even hundreds of genes regardless of ancestry.[4] Prenatal screening for trisomy and some pathologic copy number changes can be offered noninvasively by analysis of fetal DNA in maternal blood.[5] Newborn screening is being expanded beyond inborn errors of metabolism such as phenylketonuria and galactosemia, with the advent of tandem mass spectrometry and the availability of a standardized panel of tests.[6] Genome sequencing is also effective for identifying genetic disorders in newborns in intensive care nurseries, thereby providing information that can guide management.[7] Genome sequencing has also been evaluated as an approach to newborn screening,[8,A1] though challenges include the inability to detect all pathologic variants associated with treatable newborn diseases, as well as concerns about identification of currently untreatable or later-onset disorders.

Finally, treatment of some monogenic disorders is becoming feasible. Therapies that use either pharmaceuticals or gene or enzyme replacement strategies are in use or being tested for many conditions. The principles of management of genetic disorders are evolving rapidly, and care of patients increasingly requires active partnership among specialists, primary care physicians, and patient advocates. Moreover, individuals with congenital disorders such as Down syndrome are routinely surviving to adulthood and require primary care physicians who are familiar with their special needs.

ABSTRACT

Genetics and genomics are increasingly being incorporated into the day-to-day practice of medicine. Rare diseases have long been the domain of medical genetics, and new techniques of genome sequencing have vastly increased the power of genetic diagnosis. In some cases, targeted therapies are now available or are in development. A proportion of apparently "common disorders" such as cancer and cardiovascular disorders can be attributed to single gene changes as well. Tools are now at hand to identify individuals at risk, in some cases based on genetic testing, but also from analysis of family history. The genetics of multifactorial common disorders are the most difficult to elucidate. Genetic factors associated with risk of common conditions are beginning to be applied clinically in polygenic risk scores. Genetic tests that interrogate variations in drug metabolism can also be used to individualize the selection of medications and their dosing for conditions such as cancer, cardiovascular disease, epilepsy, and psychiatric disorders. As the clinical utility of genomic medicine is gradually established, virtually all areas of medical practice will include genetics and genomics in routine medical decision making.

KEYWORDS

genetics
genomic medicine
genome sequencing
genetic testing
pharmacogenetics

MONOGENIC VERSIONS OF COMMON DISORDERS

Not all monogenic disorders produce rare phenotypes, and not all common disorders have complex multifactorial causes. Some common disorders occur in families as single-gene traits, mostly with an autosomal dominant inheritance. Age of onset can be variable, and penetrance is usually incomplete (i.e., not all individuals who carry a pathogenic variant become symptomatic). Examples include several cancer predisposition syndromes (e.g., hereditary breast and ovarian cancer, Lynch syndrome, familial adenomatous polyposis, Li-Fraumeni syndrome, and various multiple endocrine neoplasia syndromes), inherited forms of cardiomyopathy, long QT syndrome, and maturity-onset diabetes of the young.[9]

GENETIC TESTING FOR MONOGENIC COMMON DISORDERS

Genetic tests for disorders associated with inherited forms of common disorders are now available, usually as panels that test for variants in multiple genes known to be associated with specific disorders. As with any medical test, the physician must consider the clinical utility of testing before a test is ordered. For example, compelling evidence supports the value of making an early diagnosis of hemochromatosis because the complications can be prevented, but not reversed, by phlebotomy and subsequent monitoring of iron stores. Individuals at risk for colon cancer can be offered surveillance with colonoscopy or surgical resection of the colon to reduce the risk for cancer. Individuals at risk for breast and ovarian cancer likewise can be offered surveillance, chemoprevention, or surgery.

Potential risks of genetic testing, such as guilt or stigmatization, also must be considered. The Genetic Information Nondiscrimination Act of 2008 (GINA)[10] protects individuals in the United States from the use of genetic information as a basis for determining eligibility for employment or health insurance in most instances. Protection does not, however, extend to life insurance or disability insurance. Some states have genetic nondiscrimination laws that exceed the protections of GINA.

ROLE OF THE NONSPECIALIST IN MANAGEMENT

The role of the physician in dealing with monogenic disorders includes recognition of individuals at risk and participation in the creation of a plan of care.[11] The most valuable screening tool is the family history. Directed questioning about a family history of monogenic disorders (especially breast, ovarian, and colon cancer, as well as hypercholesterolemia, hypertension, cardiomyopathy, arrhythmia, deep vein thrombosis, cirrhosis, kidney disease, and diabetes) can help identify the occasional patient with Mendelian segregation of these conditions. Even if the information is of uncertain reliability, eliciting a family history can prompt referral for further evaluation, documentation of the family history, and consideration for genetic testing.

The advent of exome or genome sequencing for diagnosis of rare disorders has opened the possibility of identification of individuals at risk based on secondary findings. The American College of Medical Genetics and Genomics has recommended that testing laboratories evaluate a list of genes for which identification of a pathogenic variant can lead to management to reduce risk, if the patient or parent opts into receiving this information.[12] This information would be shared even if the individual being sequenced is a child, because the condition may have relevance to the eventual health of the child, as well as parents and other relatives.

COMPLEX, MULTIFACTORIAL DISORDERS

Understanding the genetics of common disorders is one of the great challenges of modern medicine, with the promise of major returns in terms of prevention, diagnosis, and treatment. The etiology of these disorders is complex in that they result from an interplay of genes, environment, and individual lifestyles.

GENOME-WIDE ASSOCIATION STUDIES

Dissection of the genetic contribution to common disease cannot be accomplished by study of rare variants or family-based linkage studies. Most efforts have focused on study of large patient cohorts, comparing the association of genetic variants in affected cases as compared with control subjects. The ability to test millions of genetic variants rapidly across the genome has enabled genome-wide association studies (GWAS) to identify variants associated with common disorders. Hundreds of such associations have been found, either because genetic variants themselves contribute to risk or are closely linked with other variants that are involved in the disorder (linkage disequilibrium).

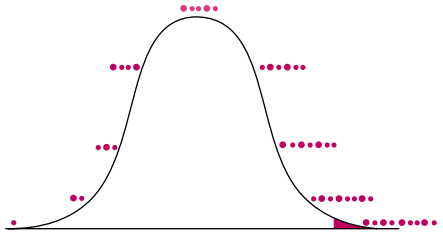

FIGURE 31-2. Concept of polygenic risk score. Individual variants are indicated by red dots, with the effect size depicted by the size of the dot. The phenotype is indicated as showing a normal distribution in the population, with the least affected individuals to the left and the most affected to the right. There is a gradient of numbers of genomic variants along the distribution, with the most severely affected, indicated by the red area under the curve to the right, having the highest polygenic risk score (i.e., the sum of all associated genetic variants weighted by their effect size). In reality, the number of variants incorporated into a polygenic risk score is far larger than shown here.

GENETIC RISK ASSESSMENT

The goal of genetic risk assessment is the identification of individuals at risk for disease before the onset of signs or symptoms. In principle, the genetic factors could be identified at any time in life by testing a DNA sample. Persons found to be at risk can be offered treatment in advance of onset of the disease to avoid complications or might be advised to modify their lifestyle to avoid exposure to dietary or environmental factors that might increase risk of disease.

Polygenic Risk Scores

The contribution to multifactorial disease risk of any one genetic variant is too small to be clinically useful, but risk is additive across multiple variants. Summing the number of risk-associated variants, each weighted by effect size (i.e., the odds ratio of disease in carriers of a specific allele compared with noncarriers) results in a polygenic risk score (Fig. 31-2).[13] Individuals at the upper end of the distribution of a polygenic risk score for a particular trait may have a risk comparable to persons with a single gene Mendelian trait, and they likewise can be offered management to mitigate that risk. Studies are underway to test the clinical utility of polygenic risk scores and determine how they can be integrated into clinical care.[14,15] Specific risk alleles and effect sizes may differ in populations of different ancestry, thereby limiting the portability of polygenic scores across populations. To date most GWAS studies have been performed on populations of European ancestry, so a major effort is required to engage populations historically under-represented in genetics research to enable application of polygenic scores across diverse populations and to avoid exacerbating health disparities.[16]

POPULATION SCREENING

The possibility of early identification of individuals at risk of disease raises the question of the utility of population screening. Some research-based population screening programs have been instituted, based on lists of actionable genomic variants (i.e., variants that are highly predictive of disease for which treatment is beneficial prior to onset of symptoms). The Centers for Disease Control and Prevention have identified a list of "Tier 1 conditions" (specifically hereditary breast and ovarian cancer, Lynch syndrome, and hypercholesterolemia) for which population screening may be beneficial. Low-cost genotyping has also spawned an industry of direct-to-consumer genomic testing for a limited repertoire of tests subject to approval by the Food and Drug Administration.

PHARMACOGENETIC TESTING

Response to medications, the principal treatment modality for acute and chronic diseases, is highly variable, ranging from inadequate efficacy to adverse drug reactions. Variations in genes associated with drug pharmacodynamics and pharmacokinetics (absorption, distribution, metabolism, and excretion) has a significant effect on response and dose requirements (Table 31-1). The Clinical Pharmacogenetic Implementation Consortium (https://cpicpgx.org/guidelines/) and the Food and Drug Administration (https://www.fda.gov/medical-devices/precision-medicine/table-pharmacogenetic-associations) provide clinical guidance on the use of genotypic information to optimize medication regimens. With approximately 15 to 30% of response variability explained by genetic variants, pharmacogenetics has become a valuable tool for optimizing the selection and dosing of medications, and it is poised to

TABLE 31-1 GENES IN WHICH COMMON POLYMORPHISMS AFFECT RATES OF DRUG METABOLISM OR ACTION

GENE	EXAMPLES OF AFFECTED DRUG(S)
CYP2B6	efavirenz
CYP2C19	amitriptyline, clopidogrel, citalopram, escitalopram
	omeprazole, rabeprazole, lansoprazole, pantoprazole
	voriconazole
CYP2C9	lornoxicam, meloxicam, phenytoin, piroxicam, tenoxicam
	fosphenytoin, phenytoin
	warfarin
CYP2D6	doxepin, clomipramine, amitriptyline, nortriptyline, desipramine, metoprolol, imipramine
	atomoxetine, codeine, fluvoxamine, ondansetron, oxycodone, paroxetine, tamoxifen, tramadol, tropisetron
CYP3A5	tacrolimus
CYP4F2	warfarin
DPYD	capecitabine, fluorouracil
G6PD	rasburicase, tafenoquine
HLA-A	carbamazepine, oxcarbazepine
HLA-B	abacavir
	allopurinol
	phenytoin, carbamazepine, oxcarbazepine
IFNL3	peginterferon-alpha-2a/2b
NUDT15	azathioprine, thioguanine, mercaptopurine
SLCO1B1	simvastatin
TPMT	azathioprine, thioguanine, mercaptopurine
UGT1A1	atazanavir, irinotecan
VKORC1	warfarin

17 play an increasing role in clinical care.[17] Benefits include customizing drug selection and dosing, increasing the likelihood of therapeutic benefit without a prolonged trial and error period, and improving safety and cost-effectiveness.

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Grade A **Grade A Reference**

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32 CLINICAL GENOMICS—GENOME STRUCTURE AND VARIATION

LESLIE G. BIESECKER

CLINICAL GENOMICS

Genomics is a biomedical discipline that addresses the structure, function, evolution, mapping, and editing of all of the DNA of an organism. Genomics also encompasses a broad and rapidly changing suite of technologies that use 1 high-throughput assays to assess the molecular basis of heritable disease.[1]

The growth of genomic medicine is exemplified by the more than 3 million individuals who already have been evaluated using genome sequencing and many others using exome sequencing. At least 1 of every 25 of patients has a mendelian genetic disorder, and many more have polygenic disorders. This simple arithmetic indicates that practicing clinicians are likely to have sequenced patients in their practices and must learn to recognize and manage individuals with inherited diseases.

A genome is the nuclear DNA included in 23 pairs of chromosomes: 22 autosomes plus two sex chromosomes (XX in females and XY in males). The diploid genome (2n) comprises two haploid copies, each of about 3 billion base pairs (bp). Two haploid genomes are reconstituted in the fertilized embryo as a diploid genome, for a total of 6 billion nucleotides. The protein coding genetic sequences include about 23,000 genes and comprise a minority (about 2%) of the human genome. The many other biologically relevant sequences include noncoding RNAs and conserved regulatory elements. In spite of this biologic complexity, clinicians can focus on the 2% of the genome that encode genes, because those genes harbor the variations that are currently best understood as being important for diagnosing and managing patients.

GENE

Genes, which are the units of heredity, are the biologic basic of the transmission of genetic traits and diseases. Genes comprise segments of DNA that encode the information carried by the gene. Precisely mapping the gene onto the nucleotides of the genome can be challenging, because it can be difficult to appreciate all of the disparate DNA elements, such as enhancers and promoters, that contribute to gene regulation and function.

Genomic DNA is configured in a two-stranded, double-helical macromolecule. A DNA strand comprises millions of one of four nucleotides: two purine bases, adenine (A) and guanine (G), and two pyrimidine bases, thymine (T) and cytosine (C). Two such strands, in opposite orientation and with an elegant twist, compose the double helix. Three consecutive nucleotides (triplet codon) of coding DNA specify an amino acid. The 64 possible different codons code for only 20 amino acids, so more than one codon triplet can code for a single amino acid. The information that codes for proteins in most protein-coding genes is broken up into several segments, referred to as exons, which are separated by noncoding introns (Fig. 32-1). The entire gene (exons and introns) is transcribed into messenger RNA (mRNA) by RNA polymerase. In the subsequent splicing process, the intervening introns are deleted; then the spliced, mature mRNA is translated into a polypeptide. At the end of the open reading frame of the gene, the polypeptides are terminated by one of three termination codons.

PATTERNS OF INHERITANCE

MENDELIAN INHERITANCE

Many heritable traits in humans can be attributed to variation of a single gene (monogenic) and segregate in a mendelian inheritance pattern[2]: autosomal 2 dominant, autosomal recessive, or sex-linked. An understanding of inheritance begins with understanding the genotype, which is the status (normal or variant) of a given pair of alleles of genes in an individual. For females, inheritance is straightforward because they have 23 pairs of homologous chromosomes (22 pairs of autosomes and one pair of X chromosomes), whereas males have 22 pairs of autosomes, but only one X and one Y chromosome. Thus, in females, the status of all genes is either homozygous normal (both normal), homozygous variant (both variant), heterozygous (one of each), or compound heterozygous (two different, but both variant). By comparison, genes on the X chromosome of males can be either hemizygous normal or hemizygous variant, to denote the fact that they only have one X chromosome. Only a few genes have alleles on the X and the Y chromosome.

Autosomal dominant inheritance is the pattern that results from a disorder in which the gene is located on an autosome (i.e., not a sex chromosome) and harbors just one copy of an abnormal allele (heterozygote) that is sufficient to cause the phenotype (Fig. 32-2A). The phenotype of an individual who harbors two identical abnormal alleles (homozygote) or two different abnormal alleles (compound heterozygote) is also abnormal. The heterozygous genotype is much more common than the homozygous or compound heterozygous genotype. If a parent is heterozygous, the variant is present in only one of their two alleles, and there is a 50% chance of transmission to each offspring. In pedigree analysis, autosomal dominant inheritance is recognized as a vertical transmission of the trait—from parent to child. However, there is a nuance in dominant inheritance. A trait is formally called autosomal dominant only when the phenotype of the heterozygote is the same as the homozygous variant (see Fig. 32-2A). In reality, this relationship is true for very few human disorders, Huntington

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TABLE 31-1 GENES IN WHICH COMMON POLYMORPHISMS AFFECT RATES OF DRUG METABOLISM OR ACTION

GENE	EXAMPLES OF AFFECTED DRUG(S)
CYP2B6	efavirenz
CYP2C19	amitriptyline, clopidogrel, citalopram, escitalopram
	omeprazole, rabeprazole, lansoprazole, pantoprazole
	voriconazole
CYP2C9	lornoxicam, meloxicam, phenytoin, piroxicam, tenoxicam
	fosphenytoin, phenytoin
	warfarin
CYP2D6	doxepin, clomipramine, amitriptyline, nortriptyline, desipramine, metoprolol, imipramine
	atomoxetine, codeine, fluvoxamine, ondansetron, oxycodone, paroxetine, tamoxifen, tramadol, tropisetron
CYP3A5	tacrolimus
CYP4F2	warfarin
DPYD	capecitabine, fluorouracil
G6PD	rasburicase, tafenoquine
HLA-A	carbamazepine, oxcarbazepine
HLA-B	abacavir
	allopurinol
	phenytoin, carbamazepine, oxcarbazepine
IFNL3	peginterferon-alpha-2a/2b
NUDT15	azathioprine, thioguanine, mercaptopurine
SLCO1B1	simvastatin
TPMT	azathioprine, thioguanine, mercaptopurine
UGT1A1	atazanavir, irinotecan
VKORC1	warfarin

17 play an increasing role in clinical care.[17] Benefits include customizing drug selection and dosing, increasing the likelihood of therapeutic benefit without a prolonged trial and error period, and improving safety and cost-effectiveness.

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Grade A **Grade A Reference**

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32 CLINICAL GENOMICS—GENOME STRUCTURE AND VARIATION

LESLIE G. BIESECKER

CLINICAL GENOMICS

Genomics is a biomedical discipline that addresses the structure, function, evolution, mapping, and editing of all of the DNA of an organism. Genomics also encompasses a broad and rapidly changing suite of technologies that use 1 high-throughput assays to assess the molecular basis of heritable disease.[1]

The growth of genomic medicine is exemplified by the more than 3 million individuals who already have been evaluated using genome sequencing and many others using exome sequencing. At least 1 of every 25 of patients has a mendelian genetic disorder, and many more have polygenic disorders. This simple arithmetic indicates that practicing clinicians are likely to have sequenced patients in their practices and must learn to recognize and manage individuals with inherited diseases.

A genome is the nuclear DNA included in 23 pairs of chromosomes: 22 autosomes plus two sex chromosomes (XX in females and XY in males). The diploid genome (2n) comprises two haploid copies, each of about 3 billion base pairs (bp). Two haploid genomes are reconstituted in the fertilized embryo as a diploid genome, for a total of 6 billion nucleotides. The protein coding genetic sequences include about 23,000 genes and comprise a minority (about 2%) of the human genome. The many other biologically relevant sequences include noncoding RNAs and conserved regulatory elements. In spite of this biologic complexity, clinicians can focus on the 2% of the genome that encode genes, because those genes harbor the variations that are currently best understood as being important for diagnosing and managing patients.

GENE

Genes, which are the units of heredity, are the biologic basic of the transmission of genetic traits and diseases. Genes comprise segments of DNA that encode the information carried by the gene. Precisely mapping the gene onto the nucleotides of the genome can be challenging, because it can be difficult to appreciate all of the disparate DNA elements, such as enhancers and promoters, that contribute to gene regulation and function.

Genomic DNA is configured in a two-stranded, double-helical macromolecule. A DNA strand comprises millions of one of four nucleotides: two purine bases, adenine (A) and guanine (G), and two pyrimidine bases, thymine (T) and cytosine (C). Two such strands, in opposite orientation and with an elegant twist, compose the double helix. Three consecutive nucleotides (triplet codon) of coding DNA specify an amino acid. The 64 possible different codons code for only 20 amino acids, so more than one codon triplet can code for a single amino acid. The information that codes for proteins in most protein-coding genes is broken up into several segments, referred to as exons, which are separated by noncoding introns (Fig. 32-1). The entire gene (exons and introns) is transcribed into messenger RNA (mRNA) by RNA polymerase. In the subsequent splicing process, the intervening introns are deleted; then the spliced, mature mRNA is translated into a polypeptide. At the end of the open reading frame of the gene, the polypeptides are terminated by one of three termination codons.

PATTERNS OF INHERITANCE

MENDELIAN INHERITANCE

Many heritable traits in humans can be attributed to variation of a single gene (monogenic) and segregate in a mendelian inheritance pattern[2]: autosomal 2 dominant, autosomal recessive, or sex-linked. An understanding of inheritance begins with understanding the genotype, which is the status (normal or variant) of a given pair of alleles of genes in an individual. For females, inheritance is straightforward because they have 23 pairs of homologous chromosomes (22 pairs of autosomes and one pair of X chromosomes), whereas males have 22 pairs of autosomes, but only one X and one Y chromosome. Thus, in females, the status of all genes is either homozygous normal (both normal), homozygous variant (both variant), heterozygous (one of each), or compound heterozygous (two different, but both variant). By comparison, genes on the X chromosome of males can be either hemizygous normal or hemizygous variant, to denote the fact that they only have one X chromosome. Only a few genes have alleles on the X and the Y chromosome.

Autosomal dominant inheritance is the pattern that results from a disorder in which the gene is located on an autosome (i.e., not a sex chromosome) and harbors just one copy of an abnormal allele (heterozygote) that is sufficient to cause the phenotype (Fig. 32-2A). The phenotype of an individual who harbors two identical abnormal alleles (homozygote) or two different abnormal alleles (compound heterozygote) is also abnormal. The heterozygous genotype is much more common than the homozygous or compound heterozygous genotype. If a parent is heterozygous, the variant is present in only one of their two alleles, and there is a 50% chance of transmission to each offspring. In pedigree analysis, autosomal dominant inheritance is recognized as a vertical transmission of the trait—from parent to child. However, there is a nuance in dominant inheritance. A trait is formally called autosomal dominant only when the phenotype of the heterozygote is the same as the homozygous variant (see Fig. 32-2A). In reality, this relationship is true for very few human disorders, Huntington

ABSTRACT

Human genomics is a biomedical discipline that addresses the structure, function, evolution, mapping, and editing of all of the DNA of a patient by using high-throughput assays to assess the molecular basis of heritable disease. Genomics is changing the practice of medicine today, and all clinicians are likely to have patients with genetic diseases in their practice. Clinicians must know the fundamentals of gene and genome structure, as well as the myriad types of genomic variation and how those variations are correlated with inherited patterns of disease. Such knowledge can guide the ordering of genetic testing and the understanding of its results.

KEYWORDS

gene
genome
genetic variation
inheritance patterns
mutation
inherited disease

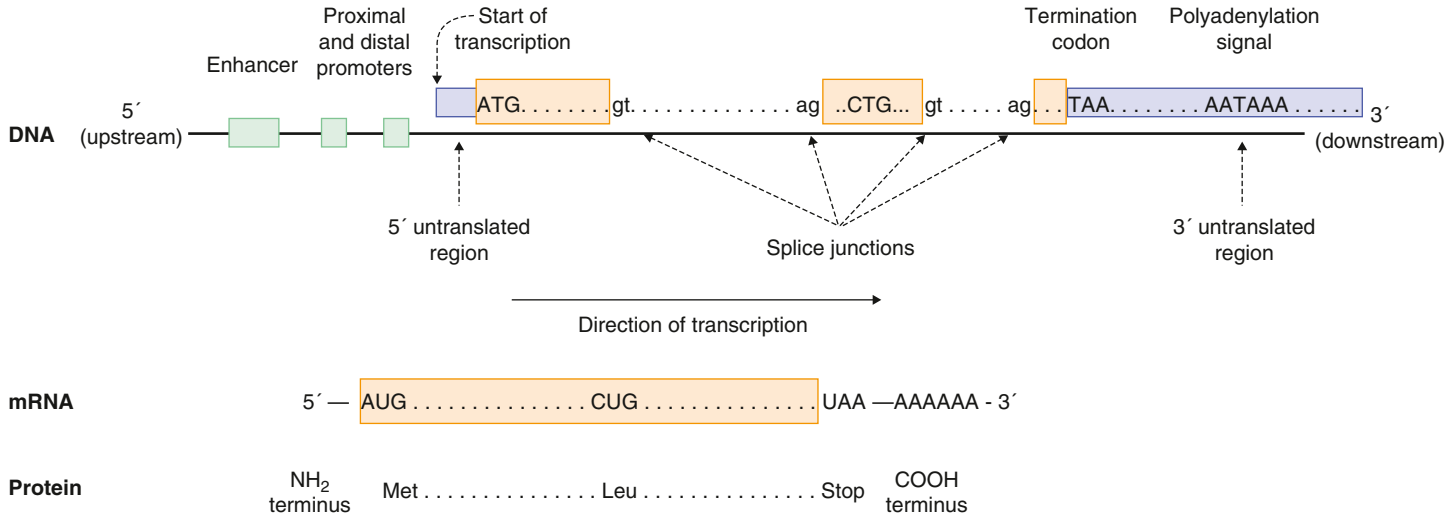

FIGURE 32-1. Gene structure. Illustration of the general structure of a gene. Three exons are depicted as rectangles, comprising sequences that code for proteins *(orange)* or are noncoding *(blue)*. Note that the translation typically starts with an ATG triplet, which encodes the amino acid methionine. The upstream portion of a gene corresponds to the NH_2 terminus, and the downstream portion encodes the COOH terminus of the encoded protein. Enhancers and promoters are shown as *green* rectangles. A = adenine; C = cytosine; G = guanine; T = thymine; u = uracil.

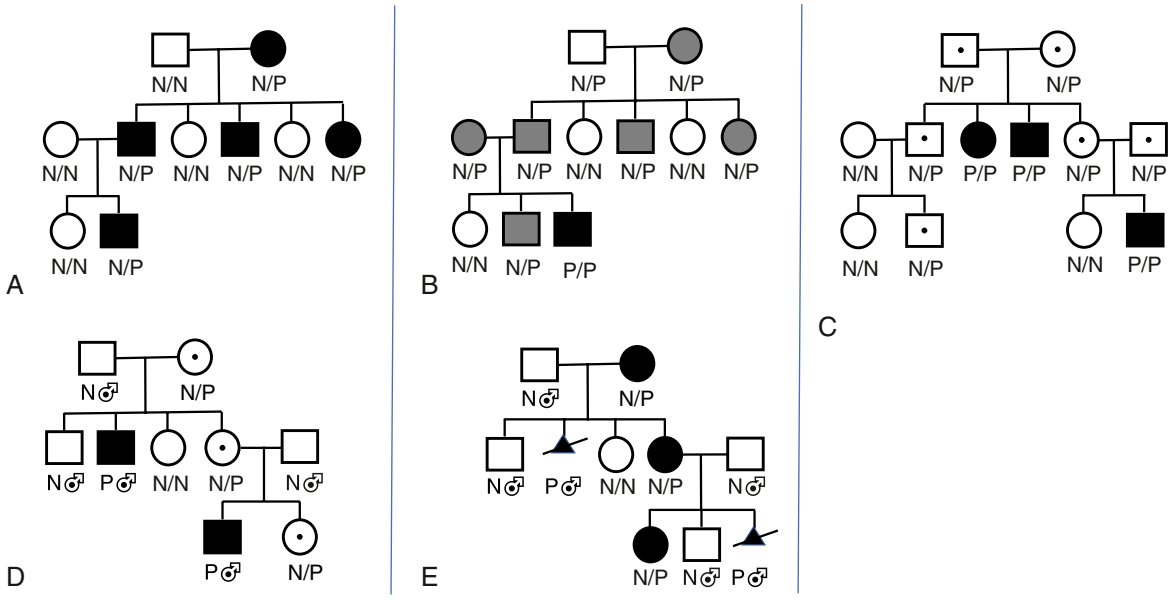

FIGURE 32-2. Modes of inheritance. In the classic mendelian modes of inheritance, the inheritance pattern that is observed in families is determined by the biologic effects of the variants in the gene. In autosomal dominant inheritance (**A**), the pattern reflects the fact that the abnormal variant allele causes a phenotype when only one copy is present and it overrides the normal allele. Two copies of the variant can cause the same severity as one, or it may be more severe (see **B**). In semidominant inheritance (**B**), the effects of the abnormal variants are additive—so two copies of the variant are more severe than one. In autosomal recessive inheritance, (**C**) one copy of the abnormal variant causes little or no abnormality, and so only individuals with two variant alleles have the disorder. The sex-linked inheritance patterns (**D, E**) parallel the same ideas as for the autosomal patterns, with the caveat that males only have one copy of the gene, and thus have fewer combinations of alleles. Squares = male; circles = female; black symbols = affected individuals; symbols with a dot in center = carriers; white symbols = unaffected individuals; gray symbols = individuals affected with phenotype of intermediate severity; black triangle crossed out = terminated pregnancy.

disease being one. For most disorders that are described as having autosomal dominant inheritance, the phenotype of the heterozygote is intermediate in severity between that of the two homozygous states (normal and variant) (see Fig. 32-2B). The classic example is familial hypercholesterolemia, in which the heterozygote phenotype has moderate hypercholesterolemia (low-density cholesterol levels of 190 to 500 mg/dL), whereas the homozygous (or compound heterozygous) variant phenotype is much more severe (levels >500 mg/dL). The formal term for this characteristic is semidominant (or incompletely dominant) inheritance. In humans, most pathogenic variants of this type are sufficiently rare that there are very few matings in which both parents are heterozygous for pathogenic variants in the same gene, so homozygosity is not commonly observed in their offspring. In common usage, all human traits that follow either the "true" autosomal dominant or the semidominant patterns are called autosomal dominant. One final type of dominant inheritance is codominant, best known as the inheritance pattern of the ABO blood type system, in which both alleles are expressed independently, and neither dominates the other.

Autosomal recessive inheritance is the pattern that results from variants in which the phenotype of the heterozygote (termed a "carrier") is unaffected (Fig. 32-2C). This characteristic is the main distinction between autosomal recessive inheritance as compared with autosomal dominant inheritance. In autosomal recessive inheritance, the affected individuals have two pathogenic variants at a single locus, one on each chromosome. These variants can either be the same (homozygous) or distinct (compound heterozygous). Typically, both pathogenic variants are inherited, one each, from an unaffected carrier parent. Because there is a 1 in 2 chance of transmission of the pathogenic variant from each parent, there is a 1 in 4 chance that an offspring will inherit the pathogenic variants from both parents (½×½). Autosomal recessive inheritance is observed as horizontal occurrence of the trait—that is, multiple affected siblings, but no parent-to-child transmission because the carrier parents are unaffected. Occasionally heterozygotes may manifest a mild phenotype, which is indeed the same situation described above for what was termed semidominant inheritance. However, if the heterozygous phenotype is very mild

or only detectable with sophisticated and sensitive phenotyping, the trait is considered to have an autosomal recessive inheritance pattern.

In sex-linked inheritance, the gene is on the X chromosome (it is sometimes called X-linked inheritance). Father-to-son transmission is not observed because if a father is affected, he harbors the pathogenic variant on his sole X chromosome; he can either transmit his X chromosome with the pathogenic variant (in which case the offspring must be female) or he can transmit his Y chromosome, which cannot have the pathogenic variant (in which case the offspring is male). Males only have one X chromosome, so when they harbor an abnormal allele, their genotype is said to be hemizygous. All daughters of affected fathers are therefore heterozygotes for the pathogenic variant. The clinical manifestations of sex-linked inherited disorders is complicated by X-inactivation. This X-inactivation process provides a degree of similarity in gene expression between the sexes—males only have one X chromosome, so gene dosage is 1.0. The X-inactivation process balances expression between males and females by randomly silencing the expression of most genes on X on one of the two chromosomes in females, leading to a functional gene dosage of 1.0.

Taking X-inactivation into account and the various combinations of genotype and phenotype that can manifest in sex-linked disorders, there are two classic patterns. The sex-linked recessive inheritance pattern (see Fig. 32-2D) is typically associated with a partial loss of function allele, which reduces, but does not abrogate gene function and is not cell-lethal. This inheritance pattern typically only manifests in affected males. Female heterozygotes, having one normal allele of the gene, are unaffected because 50% dosage is sufficient for normal function. This principle assumes random X-chromosome inactivation. However, females with incomplete X-inactivation can manifest the phenotype of what is typically a sex-linked recessive inheritance pattern disorder. In sex-linked recessive inheritance, heterozygous (carrier) females have a 1 in 2 probability that each male offspring is affected and a 1 in 2 probability that each female offspring is a heterozygous carrier. If the disorder is such that affected males can reproduce, all of their male offspring are unaffected, and all their female offspring are heterozygous carriers. The classic description of sex-linked dominant inheritance (see Fig. 32-2E) is typically associated with more severe alleles, which are cell-lethal. This lethality leads to nonviability of the male embryos, so the pathogenic variant is not observed in males. Female heterozygotes are affected and have a 1 in 2 chance that each female offspring will also be affected; there is also a 1 in 2 chance a male will receive the variant, but all affected males die early in development.

Formally, the terms autosomal dominant, autosomal recessive, and sex-linked describe inheritance patterns, not genes, diseases, alleles, or variants. Although this distinction may seem arcane, it is important because the inheritance pattern descriptor can be confused with the descriptor for the cellular basis of the disease. This is most obvious for cancer susceptibility traits caused by variants in tumor suppressor genes (see Chapter 166). The inheritance pattern of the clinical trait, which is increased susceptibility to cancer, is autosomal dominant. Biologically, however, such disorders are often described as cellular recessives, because the phenotype of cancer only manifests following a secondary, somatic variant in the gene, thereby causing the cells to be homozygous or compound heterozygous for variants in the gene. As well, it is best to associate disease or abnormal phenotypes to pathogenic variants in the gene, not to the gene itself. In this respect, one should describe a patient as "having a pathogenic variant in a Lynch syndrome gene," instead of saying the person "has the Lynch syndrome gene." It is also nonsensical to say that a patient "has the Lynch syndrome gene" because in fact essentially all humans have two copies of such genes. As well, it is incorrect to say that colon cancer is "caused by the Lynch syndrome gene." Genes do not cause disease—they "cause" normal and abnormal physiology.

NONMENDELIAN INHERITANCE

Genetic disorders can present with multiple occurrences in a family (multiplex) or as a single occurrence (simplex). Simplex occurrence of disease can be explained by a classic mendelian autosomal recessive, X-linked recessive, or autosomal dominant inheritance pattern. For the autosomal recessive pattern, it may be simply by chance in the family; for the X-linked recessive pattern, it may have been inherited silently through females in prior generations; and in either, it may develop through a de novo (new) mutation. However, simplex occurrence disease also might be due to nonmendelian inheritance such as genomic imprinting, uniparental disomy, digenic inheritance, mosaicism, and mitochondrial DNA variants. For these reasons, the clinician should be alert for families in which only a single individual is apparently affected. Other atypical modes of inheritance not further considered here include mitochondrial inheritance, imprinting, digenic inheritance, and uniparental disomy.

Mosaicism

An important exception to mendelian inheritance is the concept of mosaicism.[3] 3 Mosaicism is defined as the presence of two or more cell lines that originated from the same zygote but have distinct chromosomal or gene variant complements. A chimera is when the cells originated from different zygotes, as is the case in an individual who receives transplanted tissue. Some mosaic disorders can manifest patchy pigmentary abnormalities that follow the lines of Blaschko. Mosaicism is common in a number of well-recognized disorders, such as seborrheic keratoses of the skin, which are caused by somatic variants in *PIK3CA* or *FGFR3,* and paroxysmal nocturnal hemoglobinuria, which is associated with somatic variants in *PIGA*. Mosaicism is also the genomic basis of cancer—a clone of cells with extensive variants that originated from a normal cell in an individual (see Chapter 166). Mosaicism can also arise in the hematopoietic lineage with age. This phenomenon has become important in internal medicine in the phenomenon of clonal hematopoiesis of indeterminant potential (CHIP). This condition causes an elevated risk of myelodysplastic conditions, vascular disease, and other disorders, most commonly in older individuals.[4,5] 4 5

Mosaicism can also affect the risk of recurrence for genetic diseases. A parent can harbor two or more cell lines in the gonads (germline mosaicism) or in somatic cells. The level of mosaicism in the somatic cells may be low enough or limited to non-critical tissues or organs such that the parent appears unaffected, or they may be affected in a patchy pattern (Fig. 32-3). Mosaicism should be suspected when two or more children of healthy parents develop a disease that is typically inherited in an autosomal dominant pattern.

GENOMIC VARIATION IN HUMANS

Variation in the genome is the fundamental biologic basis of all heritable traits and diseases.[6] This spectrum of genomic variation runs the gamut from one base 6 pair (a single nucleotide variant [SNV]) to 3×10^9 base pairs (triploidy, which is three copies of a genome, rather than the normal two), and everything in between. The categories of genomic variation that are described later represent slices of that spectrum of variation, and are handy categorical clusters of this variation (much as red, orange, yellow, green, cyan, blue, and violet are useful but arbitrary slices of the continuous, visible electromagnetic spectrum). Another dimension of the broad and continuous spectrum of genomic variation is the relationship of this variation to health and disease. A given single nucleotide variant can be so devastating that it is 100% lethal early in embryonic development. On the other extreme, each of us has over a million single nucleotide variants that have no known biologic consequences.

MUTATION AND VARIANTS

The process of changing a genome from one state to another is termed a mutation. Mutation is a process, not a state. Mutation is defined as the process of a change in nucleotide sequence owing to errors of DNA replication, recombination, or repair, radiation, chemical mutagens, or transposons. A variant is a state of the genome such that one or more nucleotides differ from the reference sequence. At first this may seem arbitrary and unsatisfying—it seems to be dodging the issue of whether a variant is normal or abnormal, disease-associated, or benign. But there is utility and merit to this approach because it is not so simple that at a given position an adenine is normal whereas a cytosine, guanine, or thymine is abnormal. Genetic variation can be complex and subtle, so the new formulation is simply to define a reference sequence, but not necessarily call it normal or abnormal. Because the reference is based on sequences from actual human beings, it is a mix of both. Then a variant is simply described as being different from, or the same as, the reference. Genomic variants can be inherited from a parent (hereditary, constitutional, or germline variants; see Fig. 32-2A–D) and thus be present in every cell, or variants can be acquired in only some tissues during development or any time during life (somatic or mosaic variants) (see Fig. 32-3).

SINGLE NUCLEOTIDE VARIANTS AND OTHER SMALL VARIANTS

Single nucleotide variants are defined as a change of one nucleotide at a given position. Nonsynonymous variants are gene changes that can either lead to a single amino acid change (missense); alter the reading frame and thereby lead to alteration in the downstream protein structure (frameshift) or introduce a stop codon (premature termination codon) that truncates the protein prematurely (nonsense); or abolish the specific site at which splicing of an intron takes place during the processing of precursor mRNA into mature mRNA (splice site). Most mRNAs with nonsense variants are inactivated and

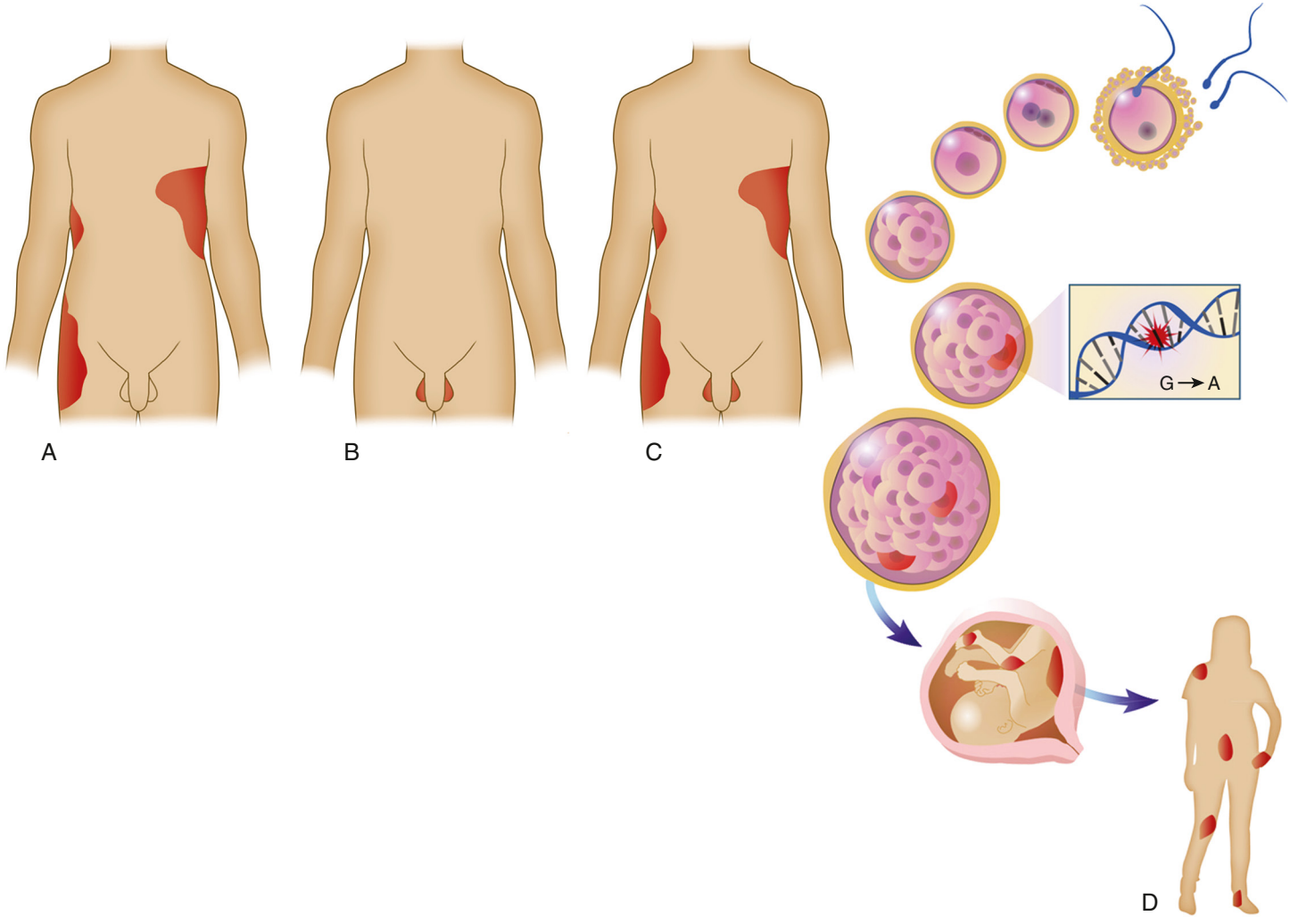

FIGURE 32-3. Types of mosaicism. Mosaicism is categorized into germline and somatic. A given individual can harbor a mosaic variant in one of two general categories of cells: germline or nongermline (somatic) cells. Thus, an individual can harbor in either (**A** or **B**) or both (**C**) of these compartments. How mosaicism is generated is illustrated in **D**. After fertilization, in a multicellular embryo, one cell undergoes a mutation and all of the cells that derive from that cell harbor the variant. (From Spinner N, Biesecker LG. Mosaicism in human disease. *Nat Rev Genet*. 2013;14:307-320.)

removed from cells by a surveillance mechanism called nonsense mediated decay. The most common mutation, cytosine to thymine, is about 10-fold more common than other base changes and occurs in the methylated CpG dinucleotide (a cytosine-guanine sequence) because methylated cytosine can be deaminated and converted to thymine.

Any two unrelated humans differ on average by about 3.5 million single nucleotide variants (≈0.1% of the 3 billion bp reference haploid genome). Whereas most of these single nucleotide variants lie outside of the exons, on average about 20,000 single nucleotide variants occur in coding regions; among these variants, about 7000 to 10,000 are nonsynonymous (i.e., change the encoded amino acid). Single nucleotide variants located outside of the protein-coding regions can still have phenotypic effects, such as by modifying gene regulatory elements, altering the binding sites for transcription factors, generating splicing variants, or affecting noncoding RNAs. The former term, single nucleotide polymorphism (SNP), was initially defined as a DNA variation that is present in greater than 1% of the population, but this term is now discouraged because "polymorphism" carried with it connotations of being "benign," which is clearly false for a substantial number of single nucleotide polymorphisms.

Variants are divided into substitutions, insertions, and deletions. Variants in protein-coding sequence that change the protein structure are termed nonsynonymous, whereas those that do not lead to protein changes are termed synonymous. Synonymous variants can still have functional consequences, such as by generating a new (abnormal) splice site or an exon splice enhancer, or by affecting regulatory elements. A set of consecutive single nucleotide variants (or other variants) that lie on a single chromosome is defined as a haplotype. A nonrandom association of markers in a population not interrupted by meiotic recombination (crossing over) is described as linkage disequilibrium. More than 100,000 single nucleotide variants have been shown to cause mendelian disorders. Many of these disorders are cataloged in locus-specific databases (http://www.hgvs.org/locus-specific-mutation-databases), the Human Gene Mutation Database (http://www.hgmd.cf.ac.uk/ac/index.php), and ClinVar (https://www.ncbi.nlm.nih.gov/clinvar/).

DELETIONS, INSERTIONS, AND INDELS

These variations are less common than single nucleotide variants. They comprise small nucleotide alterations, including deletions of one to a moderate number of nucleotides, insertions of one or a moderate number of nucleotides (which may be a duplication of adjacent DNA or nucleotides from elsewhere in the genome), and variants that comprise both a deletion of one or more nucleotides and an insertion of one or more nucleotides. Many of these variants are cataloged in the same databases as described earlier for single nucleotide variants.

TANDEM REPEATS

The genome contains a large number of repetitive elements, the most clinically important of which are the short tandem repeats (e.g., dinucleotides, trinucleotides, and tetranucleotides—$[GT]_n$, $[CAA]_n$, or $GATA]_n$—called microsatellites). These highly polymorphic repeats can have a wide range of copy numbers of their repeating subunits.[7] A number of these markers can be used to derive a nearly unique pattern of genotypes for each individual, as is used in identification for criminal forensic and paternity analysis (https://www.fbi.gov/services/laboratory/biometric-analysis/codis).

The instability of these repeats leads them to be unstable (dynamic) within individuals; humans can be complex mosaics of a range of repeat lengths among their cells. Pathogenic dynamic expansion of trinucleotide, tetranucleotide, and

pentanucleotide repeat sequences can cause disease whether located in coding regions (e.g., $[CAG]_n$ triplet in *HTT*-related Huntington disease), noncoding introns (e.g., $[GAA]_n$ in *FXN*-related Friedreich ataxia), in the upstream noncoding part of the gene (e.g., $[CGG]_n$ in *FMR1*-related fragile X syndrome), or in the downstream noncoding part of the gene (e.g., $[CTG]_n$ in myotonic dystrophy) regions. These variants can cause disease in an autosomal dominant pattern (e.g., *DMPK*-related myotonic dystrophy), autosomal recessive pattern (e.g., *FXN*-related Friedreich ataxia), or sex-linked pattern (e.g., *FMR1*-related fragile X syndrome) owing to a gain or loss of function of the encoded protein that is altered by the repeat mutation. For each of the unstable repeat diseases, a repeat number threshold exists, above which the disease is manifested. The number of repeats below that threshold but greater than normal is referred to as a pre-mutation. However, in some of these genes, pre-mutations are also associated with a milder, later onset, and sometimes distinct phenotype (e.g., ovarian failure in females and late-onset neurologic disorders in males with premutations in the *FMR1*-related fragile X syndrome). The number of repeats tends to expand in subsequent generations—a phenomenon called anticipation, which typically occurs in a sex-specific manner.

STRUCTURAL VARIANTS AND COPY NUMBER VARIANTS

It has long been recognized that genomes can have large-scale variation in the amount of DNA or the arrangement of DNA, as delineated by microscopic chromosomal analysis. Recent technologic advances (Chapter 33) have improved the ability to identify and characterize these variations. High-resolution analysis of human genome sequences has identified both moderate scale and higher order architectural features, with a potential to cause genomic instability and extensive submicroscopic structural variations. Copy number variant is the term used to describe a larger scale gain or loss of DNA from a chromosome, as compared to an insertion, deletion, or indel, as described above. Again, all of these categories are arbitrarily defined, and some of these categories more reflect how they are detected rather than a biologically based categorization. On average, each individual harbors about 1000 copy number variants, with sizes ranging from 500 bp to 1.2 Mb (million base pairs). These structural variations consist of copy number gains or losses, including deletions, insertions, duplications, and triplications, as well as balanced rearrangements such as genomic inversions and balanced translocations. The frequency of smaller copy number variants (<1 kb, kilobase pair) and indels (insertion or deletion of bases <100 bp) is higher than the larger rearrangements, because they are biologically better tolerated. The number of copy number variants is far smaller than the number of single nucleotide variants, but if one counts the base pairs that are abnormal, more base pairs are in copy number variants than in single nucleotide variants in any given individual.

Copy number variants are associated with mendelian diseases, nonmendelian traits (e.g., complex diseases), and common traits (including neurobehavioral traits),[8] but they also can be benign. Copy number variants can cause disorders by disrupting the gene structure or by changing the copy number of dosage-sensitive genes. However, copy number variants that involve nongenic sequences and leave a gene intact also can have long-range effects by changing the expression of neighboring genes. The Toronto Database of Genomic Variants (http://projects.tcag.ca/variation) summarizes copy number variants, and many clinically relevant copy number variants are also included in the Database of Chromosomal Imbalance and Phenotype in Humans using Ensembl Resources (DECIPHER) (https://www.deciphergenomics.org/).

CHROMOSOMAL ABERRATIONS

Chromosomal aberrations are the class of genomic variation that causes the greatest perturbation of DNA. Chromosomal aberrations, which can be divided into numerical and structural aberrations, occur in about 1 in 160 live births. Although many of the associated phenotypes are rare, the general clinician is likely to have individuals with the more common disorders in their practice.

Most numerical chromosome aberrations result in prenatal lethality. Numerical aberrations are classified as either polyploidy (number of chromosomes are in multiples of the haploid set of 23 chromosomes) or aneuploidy (with extra or missing chromosomes not in multiples of the haploid set). A normal female chromosome complement is 46,XX and male is 46,XY. Polyploidies such as triploidies (69,XXX, 69,XXY, and 69,XYY) are caused by abnormal fertilization of the egg by two sperms, whereas tetraploidies (92,XXYY or 92,XXXX) are caused by a failure in zygote division. Among *viable* chromosomal aneuploidies, the most common trisomies and monosomies involve chromosomes X, Y, 21, 18, and 13 and arise as a result of meiotic nondisjunctions. These aneuploidies are the most common because these four chromosomes have the smallest number of biallelically transcribed genes. The only autosomal trisomies compatible with life are Down syndrome (trisomy 21, 1 in every 670 newborns) (E-Fig. 32-1A),[9,10] Edwards syndrome (trisomy 18, 1 in 7500 newborns), and Patau syndrome (trisomy 13, 1 in every 22,700 newborns). In contrast to trisomies, all monosomies are lethal.

Sex chromosome aneuploidies are found in 1 in 440 newborns. Monosomy X (45,X) in females causes Turner syndrome (Chapter 214), which occurs in 1 in every 4000 female newborns. However, this observed birth rate represents only 1% of all 45,X fetuses because more than 99% of such fetuses result in miscarriage. In most live patients, the 45,X cell line is a mosaic with another cell line that has either a normal karyotype or a structural rearrangement of the X chromosome (e.g., deletion of the short arm, ring chromosome, or isochromosome of the long or short arms). About one in every 1000 males is either 47,XXY Klinefelter syndrome (Chapter 214) or 47,XYY (typically with at most phenotypic manifestations).

STRUCTURAL ABERRATIONS

Chromosomal deletions and duplications have been categorized as microscopically visible or submicroscopic, as terminal or interstitial, and as recurrent or nonrecurrent. Balanced reciprocal translocations, which result from an exchange of the DNA material between two chromosomes, are found in about 1 in 600 individuals. During meiosis, the translocation chromosomes segregate and lead to the transmission of either balanced or unbalanced products being transmitted to progeny. The unbalanced products often lead to either spontaneous miscarriage or birth of a child with typically serious clinical consequences. When a fragment of one chromosome is translocated internally into another chromosome's arm, the aberration is termed an insertion or insertional translocation. Insertional translocations occur more than 100 times more frequently than originally recognized. The carrier of a balanced translocation has up to a 50% chance of abnormal progeny. Other less common structural chromosomal abnormalities include inversions, ring chromosomes, isochromosomes, complex chromosome rearrangements, and heterochromatin variants.

ASSAYING GENETIC VARIATION

Genomic assays vary based upon the size of the aberration that is being targeted. Chromosomal aberrations longer than about 5 Mb can be detected by light microscopy (cytogenetics) after specific staining that generates a characteristic banding pattern (e.g., G-banded karyotype analysis). Submicroscopic rearrangements, such as microdeletions or microduplications (30 kb to 5 Mb), can be analyzed using fluorescence in situ hybridization (FISH).[11] Overall, light microscopic techniques are declining in favor of molecular assays but are still necessary to detect balanced rearrangements.

The development of array-based comparative genomic hybridization (array CGH) or single nucleotide polymorphism chip-based testing allows determination of chromosome imbalances and copy number variants, with the level of resolution depending only on the number, size, and distance between the arrayed interrogating probes. Millions of these oligonucleotide probes can be synthesized on one glass slide. Oligonucleotide probes are also used on single nucleotide polymorphism arrays, which, unlike microarray-based CGH, can generate association studies or detect uniparental disomies. The widespread diagnostic use of array CGH and single nucleotide polymorphism chips has not only increased the sensitivity for detecting diseases associated with copy number variants but also has led to the discovery of many additional copy number variant–associated disorders. To detect genomic imbalances, an alternative is a quantitative polymerase chain reaction–based technique called multiplex ligation-dependent probe amplification (MLPA). MLPA provides a simple, rapid, and sensitive method to detect dosage alterations in selected genomic regions.

Most recently, several next-generation sequencing technologies enabled simultaneous and massively parallel DNA sequencing (Chapter 33). These technologies facilitate panel testing (simultaneous assay of multiple genes implicated in a particular phenotype), exome sequencing (the coding regions of the genome), and genome sequencing. Next-generation sequencing methods generate far larger quantities of data at less expense; however, the raw sequence data that are generated from individual amplified DNA template sequences have shorter read lengths, which can be difficult to map uniquely to the genome. Thus, neither exome sequencing nor genome sequencing is truly "whole exome" or "whole genome." Nevertheless, next-generation sequencing of a patient's genome (e.g., 30-fold coverage with respect to the haploid human reference genome sequence) can generate robust and accurate individual genomic evaluation. These next-generation sequencing technologies have led to an explosion in gene discovery and an increasing understanding of the mechanistic bases of

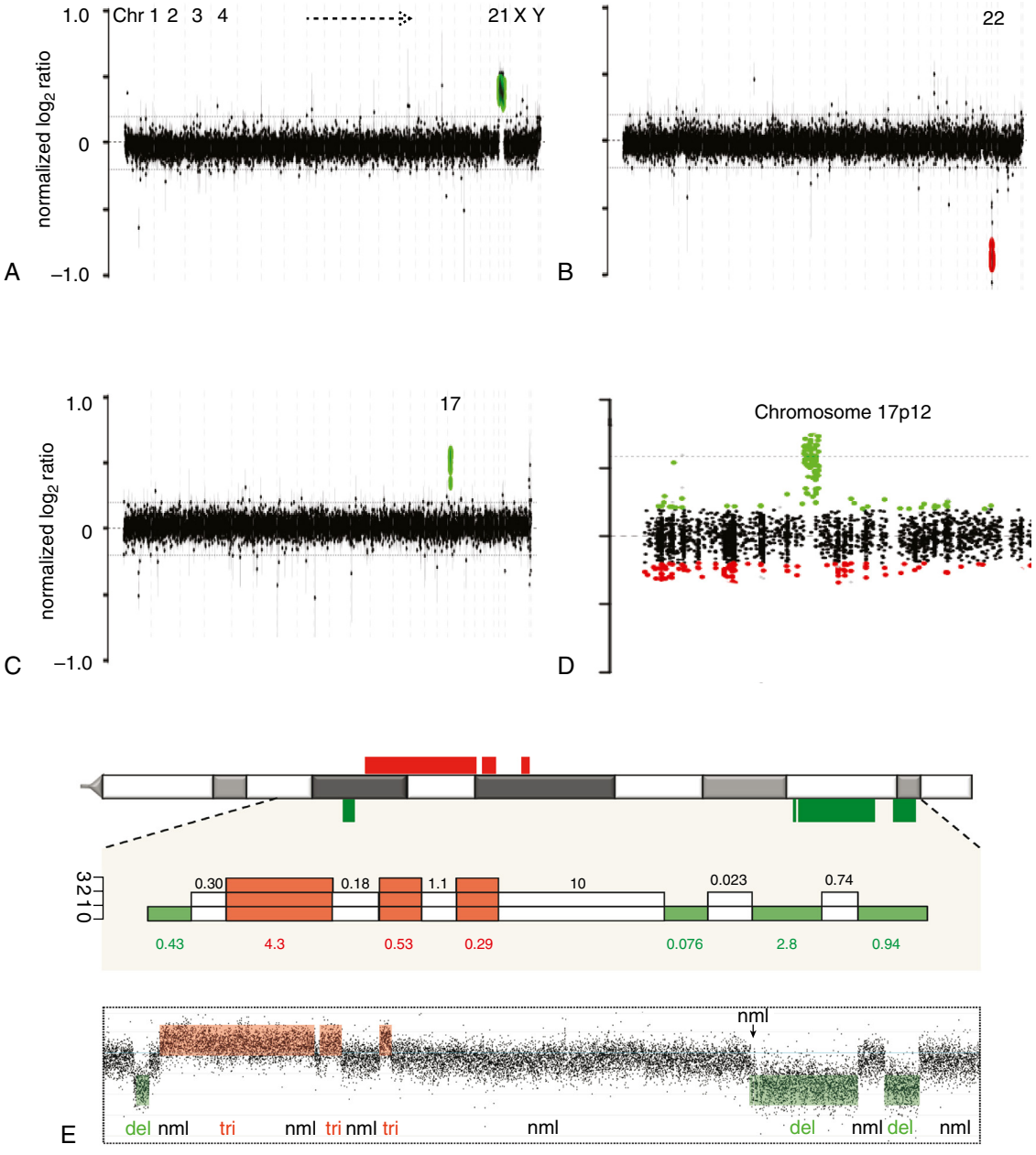

E-FIGURE 32-1. **Assaying copy-number variants (CNVs).** Plots of array-based comparative genomic hybridization from patients with genomic rearrangements. Each "dot" on the plot represents an oligonucleotide that interrogates specific regions of the human genome from chromosome 1 (depicted on *left*) to the sex chromosomes depicted on the *right*). Gain of copy number is depicted in *green,* and loss of copy number is depicted in *red.* **A**, Patient with Down syndrome showing gain (three copies) of chromosome 21. **B**, Patient with congenital heart disease and velocardiofacial syndrome with a 3-Mb deletion of chromosome 22q11.2. **C**, Patient with autosomal dominant sensorimotor neuropathy (CMT1A) with a gain of copy number (duplication) on chromosome 17p12. **D**, Expanded view of the 17p12 duplication shown in **C**. **E**, Complex genomic rearrangement in a pediatric patient with epilepsy and hypotonia showing multiple breakpoints in a single chromosome. The rectangular boxes below the ideogram of the chromosome show copy number of genomic segments, and the numbers depict the size of the copy number variants in Mb. del = deletion; nml = normal; tri = triplication.

genetic disorders. Exome sequencing alone currently has about a 25% yield for clinical diagnosis in patients with phenotypic syndromes of unknown cause—a significant improvement over previously available testing modalities.

Recent advances and the relatively widespread use of array CGH, single nucleotide polymorphism-chips, and next-generation sequencing technologies have transformed the understanding and diagnosis of human disease (Chapter 33). As sequencing becomes less expensive and more available, the understanding of human evolution, disease, and treatment is advancing rapidly.

GENETIC TEST REPORTS

Whereas gene changes formerly were termed "polymorphism" if they are benign and "mutation" if they are disease- or trait-associated, these terms have been replaced. Instead, a gene state different from reference is termed a variant, and the term variant is modified by an adjective such as "benign," "likely benign," of "unknown significance," "likely pathogenic," or "pathogenic."[12] Clinicians will increasingly encounter genetic test reports with descriptors such as "likely pathogenic variant" or "benign variant," or "variant of unknown significance." The involvement of genetic counselors can greatly improve the transmission of genetic information to patients and their families.[13]

As with all forms of medical testing, genetic test results are probabilistic. Some, such as the finding of nonmosaic trisomy 21, confer an extremely high likelihood (for all practical purposes, 100%) of phenotypic abnormality in the patient. Others, such as a novel nonsense variant in a patient with suspected *BRCA1*-related hereditary breast and ovarian cancer susceptibility, may be reported as likely pathogenic.

Distinct variants in a gene can cause the same phenotype (allelic heterogeneity) or distinct phenotypes (phenotypic heterogeneity). By contrast, the same abnormal clinical phenotype can be caused by variants in different genes (genetic or locus heterogeneity). This complexity has led to a proposal to designate human single gene diseases by the dyad of gene and phenotype. For example, *MSH2*-related Lynch syndrome.

Based on the functional consequences, variants are also categorized by their consequences into loss-of-function or gain-of-function variants. The former—also known as hypomorphic (partial loss) or amorphic (null) loss of function (complete loss)—affect the dosage-sensitive or haploinsufficient genes, in which decreased production of a protein is not sufficient for normal function. Gain-of-function variants increase the function or add a new function for the protein (neomorphic), whereas dominant negative variants encode a protein that interacts antagonistically with the normal product from the other allele (antimorphic).

Adult medicine practitioners are increasingly likely to encounter genetic testing results in their practices, whether in a diagnostic setting (e.g., an individual with early onset cancer), a secondary findings setting (e.g., a parent of a child sequenced for autism found to have malignant hyperthermia), or in a direct-to-consumer testing setting (e.g., an unanticipated breast and ovarian cancer susceptibility result from ancestry testing). Familiarity with genetic and genomic test results will allow clinicians to integrate these results seamlessly into their practices and use them to improve the care of their patients.

GENOMICS AND GENETICS AS A NORMAL PART OF MEDICINE

Nongeneticists are sometimes intimidated or concerned about using genetic diagnostics in their practices, and there is some historical basis for this concern. Clinical genetics is associated with a tragic legacy of eugenics, the thoroughly discredited concept that our species should be "improved" by preventing the reproduction of individuals deemed to be genetically undesirable or unfit. The modern clinical practice of genetics seeks to improve the health and lifespan of individuals with genetic disorders, theoretically increasing the frequency of pathogenic variants in the population because successfully treated individuals can live longer and reproduce.[14] The theoretical qualifier is important because, in the larger picture, this effect on the population is much smaller than that of the natural mutation rate. Nevertheless, reproductive genetics can still elicit concerns of eugenic tendencies. Although no overtly eugenic laws or medical practices persist, concerns linger that the very availability of prenatal testing and selective termination, coupled with social and economic pressures against disease and disability, comprise a subtle eugenic bias in reproductive medicine.

The important takeaway from this history and sociology of genetics is that adult medicine clinicians seeking to improve the health of their patients should not hesitate to use genetic and genomic diagnosis and targeted therapeutics because of any lingering fears of the eugenic history of the field. In this respect, genetics is just like any other technologically advanced component of modern medicine. It can have bioethical conundrums (Chapter 2), which may be different from those in other specialties, but these issues are not overall greater or more worrisome than those in other disciplines. Clinicians should ignore protestations that genetics and genomics is somehow exceptional from all other aspects of medicine, or something to be avoided or discouraged. A genetic or genomic test used to diagnose and treat an adult with cardiac disease is no different than a catheter, an ultrasound, or a troponin level—another arrow in the modern biomedical quiver that has great potential to improve health and extend longevity.

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33

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MOLECULAR TECHNOLOGIES ALONG THE CONTINUUM FROM HEALTH TO DISEASE

In 2015, the United States embarked on a Precision Medicine Initiative to enroll over 1 million people in what is now called the "*All of Us*" research program (https://allofus.nih.gov/). The shared data from sequencing, electronic medical records (EMRs), personal reported information, and digital health technologies provide a platform for assessing the biology of disease as well as a paradigm that will allow for more informed decisions along the continuum from health to disease (Fig. 33-1). Precision health care is now being used in clinical practice across the lifespan (Table 33-1). DNA testing is used for reproductive counseling for couples who are planning a pregnancy and for prenatal testing with sequencing assays of fetal DNA in the maternal circulation to assess for mendelian and developmental disorders. Sequencing in the neonatal intensive care unit (ICU) is becoming more common for diagnoses and determination of treatment options for gravely ill infants. Sequencing is also being used to end the diagnostic odyssey for many children (and some adults) with rare and undiagnosed diseases. For the early assessment of disease risk, family history still may be the most powerful tool. However, genomic risk scores are being defined to complement family history for certain chronic diseases. Although lagging the dramatic decline in cost and increase in throughput of DNA sequencing, technology platforms that measure the "expressed genome" (RNA, proteins, metabolites) are increasingly being used to define physiologic states in response to the environment, to classify disease states, to diagnose current disease, and to predict future clinical outcomes. These approaches, which form the basis for a new molecular classification and taxonomy of disease and diagnosis, can provide more precise ways to screen for

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33

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MOLECULAR TECHNOLOGIES ALONG THE CONTINUUM FROM HEALTH TO DISEASE

In 2015, the United States embarked on a Precision Medicine Initiative to enroll over 1 million people in what is now called the "*All of Us*" research program (https://allofus.nih.gov/). The shared data from sequencing, electronic medical records (EMRs), personal reported information, and digital health technologies provide a platform for assessing the biology of disease as well as a paradigm that will allow for more informed decisions along the continuum from health to disease (Fig. 33-1). Precision health care is now being used in clinical practice across the lifespan (Table 33-1). DNA testing is used for reproductive counseling for couples who are planning a pregnancy and for prenatal testing with sequencing assays of fetal DNA in the maternal circulation to assess for mendelian and developmental disorders. Sequencing in the neonatal intensive care unit (ICU) is becoming more common for diagnoses and determination of treatment options for gravely ill infants. Sequencing is also being used to end the diagnostic odyssey for many children (and some adults) with rare and undiagnosed diseases. For the early assessment of disease risk, family history still may be the most powerful tool. However, genomic risk scores are being defined to complement family history for certain chronic diseases. Although lagging the dramatic decline in cost and increase in throughput of DNA sequencing, technology platforms that measure the "expressed genome" (RNA, proteins, metabolites) are increasingly being used to define physiologic states in response to the environment, to classify disease states, to diagnose current disease, and to predict future clinical outcomes. These approaches, which form the basis for a new molecular classification and taxonomy of disease and diagnosis, can provide more precise ways to screen for

ABSTRACT

Scientific advances in the genome and data sciences in the past decade have provided an opportunity to deliver health care in a distinctly patient-centered way. Precision medicine uses individual molecular information as well as highly specific clinical information to assess individual risks and develop tailored prevention and treatment strategies. Genome-based technologies (i.e., assays of RNA, proteins, and metabolites) are augmenting diagnosis and treatment as well as changing the taxonomy of disease. Genetic variation associated with drug response, or pharmacogenomics, now provides more precise targeting of therapeutics to an individual's genetic background to optimize the benefit and reduce the risks associated with drug therapies. Despite progress and momentum in the discovery of genomic information with great potential to affect health care, significant challenges and barriers have limited the broad use of genomics in clinical practice. Four of these barriers are: (1) evidence generation; (2) implementation and education; (3) data ownership, sharing, and infrastructure; and (4) participant diversity, engagement, and trust. Until these are challenges are fully addressed, precision medicine may remain a futuristic concept rather than being fully integrated into mainstream medicine.

KEYWORDS

precision medicine
precision health
genomics
pharmacogenomics
genomic medicine
implementation
policy

and to detect disease at its earliest molecular manifestations, often preclinically. In addition, the selection of certain drugs increasingly can be guided by a patient's underlying genetic makeup as well as by the molecular makeup of the disease. Given that a disease's evolution from baseline risk often occurs over many years (see Fig. 33-1), periodic molecular and digital profiling defines a novel form of health care that focuses on health assessments and disease prevention with proactive management rather than the current paradigm of acute intervention and crisis management.

GENOMES, DISEASE, AND TREATMENT

A key question in medicine is to what extent genetic variation influences the likelihood of disease onset, affects the natural history of disease in combination with the environment and social factors, or provides clues relevant to the management of disease. Genome sequencing is providing new approaches for the diagnosis, study, and treatment of disease.

NEWBORN SCREENING, PRENATAL DIAGNOSIS, AND PRE-CONCEPTION CARRIER TESTING

A natural outcome of identifying genes for rare mendelian disorders (Chapter 32) is the application of these findings to earlier detection, at birth (newborn screening), in utero (prenatal diagnosis), or pre-conception (carrier testing).

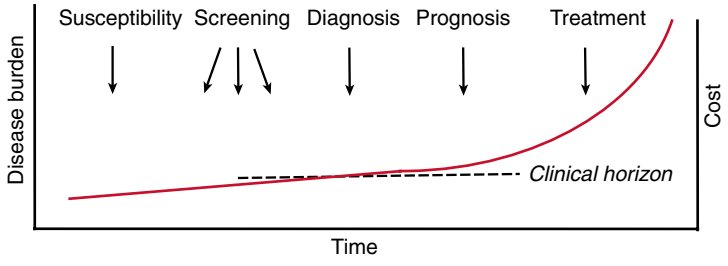

FIGURE 33-1. Use of molecular technologies across the continuum from health to disease. Various molecular technologies may now be used to complement the traditional approach to evaluating health and disease across the lifespan. The *red curve* indicates the course of a chronic disease over time. The *dashed line* indicates when clinical symptoms are manifest. Overall, the goal is to shift the detection and treatment paradigm to the left. (Adapted from Ginsburg GS, Willard H. eds. *Genomic and Personalized Medicine*. 3rd ed. Academic Press; 2016.)

Newborn screening—mandatory, state-supported public health programs meant to protect newborn children by screening them for rare, treatable (and thus preventable) disorders at birth—has been steadily increasing from an average of five conditions in 1995 to a panel of 35 core disorders currently recommended by the U.S. Department of Health and Human Services.[2] Rapid genome sequencing (about 19.5 hours from test to result) has been used to treat patients with undiagnosed and potentially fatal disorders in the neonatal ICU.[3] As the number of conditions considered for newborn screening will undoubtedly grow, rapid sequencing can potentially broaden and foreshorten differential diagnosis, thereby resulting in fewer empirical treatments as well as faster progression to genetic and prognostic counseling.[4,5]

Cell-free fetal DNA circulating in maternal blood can be analyzed by next-generation sequencing technologies to identify fetal aneuploidy from cell-free fetal DNA in maternal plasma. Noninvasive prenatal testing of trisomy 21 eliminates the need for invasive procedures, while also greatly expanding the number of genetic variants that have traditionally been detected in utero.

Before conception, carrier screening enables couples to assess their risk of having a child with a recessive mendelian disorder (Chapter 32) and use this information to guide their reproductive decisions. There are over 1000 rare, *recessive* mendelian disorders for which the underlying genetic mutation is known. Though individually rare, these mutations can have a sizable public health impact considering that each person is estimated to carry on average 2.8 mutations[6] for known severe recessive disorders.

SEQUENCING: A DRIVER OF PRECISION MEDICINE

Genome-wide association studies (GWASs) have identified over 275,000 unique single nucleotide variant trait associations from large cohorts of patients and controls across numerous diseases (https://www.ebi.ac.uk/gwas/). GWAS has been a transformative approach to identifying common genetic variation across the entire human genome in an unbiased fashion, thereby offering an unprecedented opportunity to uncover new biologic pathways of disease. Gene editing technologies using Clustered Regularly Interspaced Short Palindromic Repeats (CRISPR) and Transcription Activator-Like Effector Nucleases (TALEN) are changing the approach to defining the biology of genetic variants discovered by GWAS and sequencing.[7,8]

Since 2001, the cost of sequencing a human genome has dropped from more than $3 billion per genome to $500. Using next-generation sequencing technology, a sequencing laboratory can sequence more than 60 genomes

TABLE 33-1 APPLICATION OF MOLECULAR DIAGNOSTICS ALONG THE CONTINUUM FROM HEALTH TO DISEASE

TIME POINT IN CLINICAL DECISION MAKING	*CANCER*		*CARDIOVASCULAR DISEASE*	
	TEST	**INDICATION**	**TEST**	**INDICATION**
Risk/susceptibility	*BRCA1, BRCA2* *HNPCC* *TP53, PTEN*	Breast, ovarian Colon Sarcomas	*9p21*, GeneSeq, various polygenic risk scores LongQTNext/RhythmNext	CAD LQTS
Screening	HPV genotypes	Cervical	*APOB, LDLR, LDLRAP1, PCSK9*	Familial hypercholesterolemia
Diagnosis	Cancer origin OVA1	Cancer of unknown primary Ovarian mass malignancy	*ABCC9, AKAP9, ANK2, CACNA1C, CACNA2D1, CACNB2, CALM1, CALM2, CALM3, CASQ2, CAV3, DES, DSC2, DSG2, DSP, GPD1L, HCN4, JUP, KCND3, KCNE1, KCNE1L, KCNE2, KCNE3, KCNH2, KCNJ2, KCNJ5, KCNJ8, KCNQ1, LMNA, NKX2-5, PKP2, PLN, RANGRF, RYR2, SCN10A, SCN1B, SCN2B, SCN3B, SCN4B, SCN5A, SNTA1, TGFB3, TMEM43, TRDN, TRPM4, TTN* TnI, BNP, CRP	Long QT syndrome ACS
Prognosis	Oncotype DX (21-gene assay) MammaPrint (70-gene assay) HER2/neu, ER, PR	Breast	Under development	
Drug response*	*BCR-ABL* *EML4-ALK*	Imatinib (CML) Crizotinib (NSCL)	*CYP2C19* *CYP2C9, VKORC1*	Clopidogrel Warfarin
Monitoring	CTCs	Tumor recurrence or progression	AlloMap	Transplant rejection

*Additional drug-gene pairs can be found in E-Table 33-1.

ACS = acute coronary syndromes; BNP = brain natriuretic peptide; CAD = coronary artery disease; CRP = C-reactive protein; CTCs = circulating tumor cells; ER = estrogen receptor; HPV = human papillomavirus; LQTS = long QT syndrome; PR = progesterone receptor; TnI = troponin I.

Data from Ginsburg GS, Willard H. eds. *Genomic and Personalized Medicine*. 3rd ed. Academic Press; 2016.

per day, thereby allowing direct measurement not just of common variants, but also theoretically of all variation in a genome. It is estimated that the population frequency of germline variants is approximately 1 in every 1000 of the 3.2 billion nucleotide positions, thereby giving rise to approximately 3 million variants in a given human genome. The challenge lies in determining the meaning of variants, many of which occur in noncoding regions of the genome whose function is largely unknown, and their potential for causing disease. The significance of the noncoding variants remains poorly understood. As a result, the focus clinically has been on exome sequencing (which examines variation in the coding sequences that constitute 1 to 2% of the genome), in which mutations may have predictable effects on downstream protein structure. Genome interpretation is a key bottleneck in the ubiquitous application of sequencing to clinical medicine.[9] With increasing efforts to encourage data sharing and the creation of interoperable data stores, definitive diagnoses from genomic data should become more common.[10] Of note, the American Colleges of Medical Genetics and Genomics currently defines 73 actionable variants in the human genome (https://www.ncbi.nlm.nih.gov/clinvar/docs/acmg/) that, when found, should be discussed with the patients who harbor them.

RISK PREDICTION FOR COMMON COMPLEX DISEASES

Despite strong statistical associations linking genetic variants with complex diseases in GWAS, the low relative risk of the disease allele (generally <2) limits their use for risk assessment. Notable exceptions include the genetic variations underlying inherited breast cancer syndromes, Lynch syndrome, and familial hypercholesterolemia, for which some variants have enabled preventive treatment or screening of family members as well as their consideration as part of population screening programs.

Despite the advancements in genetic testing, a simple family history continues to be among the best tools to identify risks for common diseases.[11] In fact, for conditions with high heritability, such as cardiovascular disease, family history is a much stronger predictor of disease than any single or combination of genetic/genomic markers. One model suggests that neither family history nor genetic testing should be used as a standalone but that the real power for disease prediction, risk assessment, and differential diagnosis comes from their combined use. Recently, polygenic risk scores have been derived from GWAS and sequencing data to enhance the prediction of genetic susceptibility of individuals to disease. Polygenic risk scores for an individual are calculated as weighted counts of thousands of risk variants that they carry, where the risk variants and their weights have been identified in GWASs. Whether polygenic risk scores are ready for clinical use is a matter of debate because many of them have been derived on data from individuals of European ancestry and may not apply to other ancestral groups. In addition, the utility of polygenic risk scores has not always been compared with more traditional risk calculators or family history, so it is not clear whether polygenic risk scores are superior to other risk assessment tools that are already available clinically.

CLINICAL SEQUENCING FOR RARE DISEASES AND DIAGNOSTIC DILEMMAS

Nearly 7000 mendelian disorders have a known molecular basis (http://omim.org/). However, there are nearly as many suspected mendelian traits for which the molecular basis remains to be identified. The potential for clinical sequencing to find the underlying cause and identify treatment options for these rare, sometimes debilitating diseases has led to the formation of various large national and international rare disease consortia. In some specialized clinical centers and through programs such as the National Human Genome Research Institute's Undiagnosed Diseases Program (http://www.genome.gov/27544402), clinical sequencing is being offered to patients with suspected genetic diseases, the so-called "diagnostic dilemmas." To date, about 30% of the more than 1500 participants have received a diagnosis based on their genome sequencing data.[12,13]

PHARMACOGENOMICS: GERMLINE GENETIC VARIANTS AND DRUG RESPONSE

Over the past decade a plethora of genomic markers of efficacy, adverse events, and dosing of therapeutics have been discovered and recommended for clinical use (see E-Table 33-1), but their uptake into clinical practice has been variable, despite their clear actionability. In some cases, such as with the *HLA-B**5701 genotype for the drug abacavir for the treatment of human immunodeficiency virus (HIV) and *HLA-B**1502 for the antiseizure drug carbamazepine, carriers of these genotypes should avoid the drug entirely to eliminate a specific serious adverse event. In other cases, such as *TPMT* for mercaptopurine or *CYP2C9/VKORC1* for warfarin, adjusting the dose of drug based on genotype can help to avoid toxicity and improve efficacy. *Actionability* is not enough to ensure uptake of pharmacogenomics testing as exemplified with the anti-platelet drug clopidogrel, for which despite having an FDA "black box warning" for efficacy in individuals carrying the *CYP2C19* genetic variant, there is often no clear consensus among physicians on its use. Genetic markers that predict reduced therapeutic efficacy may face a high hurdle for established drugs, unless there is strong evidence of the test's clinical validity and utility.

One barrier to implementation of pharmacogenetic testing in clinical practice is the difficulty in translating genetic laboratory test results into actionable prescribing decisions for affected drugs. The Clinical Pharmacogenomics Implementation Consortium was formed to address this barrier to clinical implementation of pharmacogenetic tests by creating, curating, and posting freely available, peer-reviewed, evidence-based, updatable, and detailed gene/drug clinical practice guidelines (https://cpicpgx.org/). These guidelines follow standardized formats, include systematic grading of evidence and clinical recommendations, use standardized terminology, and are peer-reviewed.

CANCER PHARMACOGENOMICS: SOMATIC SEQUENCING OF TUMOR DNA FOR TARGETING DRUG THERAPIES

Cancer arises as a result of somatic DNA mutations that confer a growth advantage upon the cells in which they have occurred, thereby giving rise to tumors (Chapter 166). Comparison of the genetic profiles of tumors and the surrounding normal tissue can reveal the acquired DNA variations that drive growth and that may reveal targets for treatment. The idea of pairing medicines with specific tumor markers in a targeted fashion was first demonstrated when detailed molecular studies of breast tumors led to the discovery of human epidermal growth factor receptor 2 (HER-2), a biomarker overexpressed in approximately 30% of breast tumors and associated with adverse outcomes. Subsequently, trastuzumab (Herceptin), a humanized monoclonal antibody targeting HER-2, was developed and shown to have increased efficacy in patients whose tumors tested positive. HER-2 testing is now part of the standard evaluation and management of breast cancer (Chapter 183). In the past decade, other examples of cancer therapies with companion diagnostics emerged (https://www.mycancergenome.org/). For example, *EGFR* mutation testing has markedly improved the efficacy of gefitinib and erlotinib, small molecule drugs for the treatment of non–small cell lung cancer (Chapter 177) that target *EGFR*. In metastatic colorectal cancer (Chapter 179), tumors with mutated *KRAS* are usually resistant to treatment with cetuximab and panitumumab, thereby leading the American Society of Clinical Oncologists and the U.S. Food and Drug Administration (FDA) to recommend withholding the drugs in these patients. Next-generation sequencing now allows a comprehensive assessment of actionable tumor markers that indicate the potential for a specific therapeutic to have efficacy in a given tumor (https://www.mycancergenome.org/). In 2011, two cancer drugs received accelerated approval by the FDA for use with a companion diagnostic test: crizotinib for the treatment of patients with locally advanced or metastatic non–small cell lung cancer (Chapter 177) with its companion diagnostic designed to detect the *EML4-ALK* fusion gene, and vemurafenib for the treatment of patients with metastatic or unresectable melanoma positive for *BRAF* V600E mutations (Chapter 188). The International Cancer Genome Consortium (https://www.icgc.org/) and the Cancer Genome Atlas (http://cancergenome.nih.gov/) represent international collaborative efforts to define the spectrum of mutations found in tumors, mapping the genomic landscape of cancer. These efforts provide a foundation from which to develop additional therapeutic strategies against new targets; however, even when successful, the results may be short-lived as therapeutic resistance evolves. Despite the promise of next-generation sequencing, an integrated interdisciplinary approach is needed to select the best therapeutic option for any given patient. Molecular tumor boards have become a powerful platform to foster debate, discussions, and overall communication and decision making for the use of next-generation sequencing data to select therapy.[14]

MICROBIAL SEQUENCING FOR INFECTIOUS DISEASE DIAGNOSIS

In infectious disease, diagnosis of pathogens by next-generation sequencing may supplant the need to first grow microorganisms in culture, previously a major impediment to pathogen identification. For example, in 2003,

E-TABLE 33-1 DRUG-GENE PAIRS TO GUIDE PHARMACOGENOMIC TESTING

GENE	DRUG	GENE	DRUG
HLA-B	abacavir	*SLCO1B1*	cerivastatin
HLA-B	allopurinol	*G6PD*	chloramphenicol
CYP2C19	amitriptyline	*G6PD*	chloroquine
CYP2D6	amitriptyline	*G6PD*	chlorpropamide
UGT1A1	atazanavir	*G6PD*	ciprofloxacin
TPMT	azathioprine	*CYP2C19*	clomipramine
DPYD	capecitabine	*CYP2D6*	clomipramine
HLA-A	carbamazepine	*G6PD*	dapsone
HLA-B	carbamazepine	*CYP2D6*	desipramine
CYP2C19	clopidogrel	*CYP2C19*	dexlansoprazole
CYP2D6	codeine	*G6PD*	dimercaprol
CACNA1S	desflurane	*POLG*	divalproex sodium
RYR1	desflurane	*CYP2C19*	doxepin
DPYD	fluorouracil	*CYP2D6*	doxepin
CYP2D6	fluvoxamine	*CYP2B6*	efavirenz
UGT1A1	irinotecan	*CYP2D6*	eliglustat
CACNA1S	isoflurane	*CYP2C19*	esomeprazole
RYR1	isoflurane	*G6PD*	glibenclamide
CFTR	ivacaftor	*G6PD*	glimepiride
TPMT	mercaptopurine	*G6PD*	glipizide
CYP2D6	nortriptyline	*G6PD*	hydroxychloroquine
CYP2D6	ondansetron	*CYP2C19*	imipramine
CYP2D6	oxycodone	*CYP2D6*	imipramine
CYP2D6	paroxetine	*CYP2C19*	lansoprazole
CYP2C9	phenytoin	*G6PD*	levofloxacin
HLA-B	phenytoin	*G6PD*	mafenide
G6PD	rasburicase	*G6PD*	mefloquine
CACNA1S	sevoflurane	*G6PD*	mesalazine
RYR1	sevoflurane	*CYP2B6*	methadone
SLCO1B1	simvastatin	*G6PD*	methylene blue
CACNA1S	succinylcholine	*CYP2D6*	methylphenidate
CYP3A5	tacrolimus	*CYP2D6*	mirtazapine
CYP2D6	tamoxifen	*G6PD*	moxifloxacin
DPYD	tegafur	*HPRT1*	mycophenolic acid
TPMT	thioguanine	*G6PD*	nalidixic acid
CYP2D6	tramadol	*CYP2B6*	nevirapine
CYP2D6	tropisetron	*G6PD*	nitrofurantoin
CYP2C19	voriconazole	*G6PD*	norfloxacin
CYP2C9	warfarin	*CYP2C19*	omeprazole
CYP4F2	warfarin	*HLA-B*	oxcarbazepine
VKORC1	warfarin	*CYP2C19*	pantoprazole
CYP2C19	citalopram	*G6PD*	pegloticase
CYP2C19	escitalopram	*G6PD*	phenazopyridine
IFNL3	peginterferon alfa-2a	*CYP4F2*	phenprocoumon
IFNL3	peginterferon alfa-2b	*SCN1A*	phenytoin
IFNL3	ribavirin	*CYP2D6*	pimozide
CYP2C9	acenocoumarol	*G6PD*	primaquine
CYP4F2	acenocoumarol	*G6PD*	probenecid
HLA-A	allopurinol	*CYP2D6*	protriptyline
CYP2D6	aripiprazole	*G6PD*	quinine
CYP2D6	atomoxetine	*CYP2C19*	rabeprazole
UGT1A1	belinostat	*CYP2D6*	risperidone
CYP2D6	brexpiprazole	*CYP2C19*	sertraline
SCN1A	carbamazepine	*CYP2D6*	sertraline
NAGS	carglumic acid	*G6PD*	sodium nitrite
CYP2C9	celecoxib	*RYR1*	succinylcholine

E-TABLE 33-1 DRUG-GENE PAIRS TO GUIDE PHARMACOGENOMIC TESTING—cont'd

GENE	DRUG	GENE	DRUG
G6PD	sulfacetamide	*CYP2D6*	duloxetine
G6PD	sulfadiazine	*F5*	eltrombopag
G6PD	sulfamethoxazole and trimethoprim	*SERPINC1*	eltrombopag
G6PD	sulfasalazine	*CYP2D6*	fesoterodine
CYP2C19	trimipramine	*CYP2D6*	flecainide
CYP2D6	trimipramine	*CYP2C19*	flibanserin
ABL2	valproic acid	*CYP2C9*	flibanserin
ASL	valproic acid	*CYP2D6*	flibanserin
ASS1	valproic acid	*MTHFR*	fluorouracil
CPS1	valproic acid	*CYP2D6*	fluoxetine
NAGS	valproic acid	*CYP2D6*	haloperidol
OTC	valproic acid	*F5*	hormonal contraceptives for systemic use
POLG	valproic acid	*NAT2*	isoniazid
GBA	velaglucerase alfa	*HLA-DQA1*	lapatinib
CYP2D6	venlafaxine	*CYP2C9*	lesinurad
CYP2D6	vortioxetine	*MTHFR*	leucovorin
CYP4F2	warfarin	*HLA-B*	methazolamide
CYP2D6	dextromethorphan	*HLA-C*	methazolamide
CYP2D6	quinidine	*HLA-B*	methimazole
G6PD	erythromycin	*MTHFR*	methotrexate
G6PD	sulfisoxazole	*SLCO1B1*	methotrexate
CYP2C19	brivaracetam	*CYP2D6*	metoprolol
CYP2C19	carisoprodol	*CYP3A5*	midazolam
SLC6A4	citalopram	*CYP2D6*	modafinil
G6PD	dabrafenib	*HLA-B*	nevirapine
UGT1A1	dolutegravir	*HLA-DRB1*	nevirapine
CYP2D6	donepezil	*UGT1A1*	nilotinib
SLC6A4	escitalopram	*CYP2D6*	olanzapine
CYP2C9	flurbiprofen	*MTHFR*	oxaliplatin
CYP2D6	iloperidone	*CYP2D6*	palonosetron
G6PD	lidocaine	*SLCO1B1*	pravastatin
UGT1A1	pazopanib	*CYP2D6*	propafenone
CYP2D6	perphenazine	*CYP2D6*	propranolol
HLA-C	allopurinol	*HLA-B*	propylthiouracil
MT-RNR1	aminoglycoside antibacterials	*CYP2D6*	quinine
MC4R	antipsychotics	*DRD2*	risperidone
HLA-DPB1	aspirin	*SLCO1B1*	rosuvastatin
CFTR	ataluren	*COMT*	selective serotonin reuptake inhibitors
CYP3A5	atazanavir	*CYP3A5*	sirolimus
MTHFR	capecitabine	*CYP3A4*	tacrolimus
HLA-B	carbimazole	*CYP2D6*	tamsulosin
MTHFR	carboplatin	*CYP2D6*	terbinafine
CYP2D6	carvedilol	*CYP2D6*	tetrabenazine
CYP2D6	cevimeline	*CYP2D6*	thioridazine
XPC	cisplatin	*CYP2D6*	timolol
CYP2C19	clobazam	*CYP2D6*	tiotropium
CYP2D6	clozapine	*CYP2D6*	tolterodine
MTHFR	cyclophosphamide	*TNF*	tumor necrosis factor-alpha (TNF-alpha) inhibitors
CYP3A5	cyclosporine	*G6PD*	vitamin c
HLA-B	dapsone	*CYP2D6*	zuclopenthixol
CYP2D6	darifenacin	*OPRM1*	alfentanil
CYP2C19	diazepam	*COMT*	cisplatin
CYP2C9	diclofenac	*CES1*	clopidogrel
CYP2D6	dolasetron	*GSTP1*	cyclophosphamide

E-TABLE 33-1 DRUG-GENE PAIRS TO GUIDE PHARMACOGENOMIC TESTING—cont'd

GENE	DRUG	GENE	DRUG
ABCB1	digoxin	*FLOT1*	carbamazepine
CYP2A7P1	efavirenz	*EGF*	cetuximab
GSTP1	epirubicin	*FCGR3A*	cetuximab
OPRM1	ethanol	*GSTM1*	cisplatin
ABCB1	fentanyl	*TMEM43*	cisplatin
OPRM1	fentanyl	*TP53*	cisplatin
GSTP1	fluorouracil	*GRIK4*	citalopram
ITPA	interferon alfa-2b, recombinant	*HTR2A*	citalopram
ABCB1	methadone	*HTR2C*	clozapine
OPRM1	methadone	*SOD2*	cyclophosphamide
ABCB1	methotrexate	*TP53*	cyclophosphamide
ABCB1	morphine	*ANKK1*	ethanol
OPRM1	morphine	*DYNC2H1*	etoposide
OPRM1	naloxone	*NQO1*	fluorouracil
OPRM1	naltrexone	*TYMS*	fluorouracil
ABCB1	nevirapine	*UMPS*	fluorouracil
CYP2A7P1	nevirapine	*CRHR1*	fluticasone propionate
COMT	nicotine	*CRHR1*	fluticasone/salmeterol
ABCB1	ondansetron	*ADD1*	furosemide
GSTP1	oxaliplatin	*CYP2D6*	galantamine
ABCB1	oxycodone	*NT5C2*	gemcitabine
GSTP1	platinum compounds	*CETP*	HMG-CoA reductase inhibitors
CYP2C8	rosiglitazone	*HMGCR*	HMG-CoA reductase inhibitors
ADRB2	salbutamol	*LPA*	HMG-CoA reductase inhibitors
ADRB2	salmeterol	*NEDD4L*	hydrochlorothiazide
ABCB1	simvastatin	*PRKCA*	hydrochlorothiazide
BCHE	succinylcholine	*YEATS4*	hydrochlorothiazide
ABCB1	sunitinib	*C8orf34*	irinotecan
ABCB1	tramadol	*SEMA3C*	irinotecan
OPRM1	tramadol	*UGT1A4*	lamotrigine
KCNIP4	ACE inhibitors, plain	*PTGFR*	latanoprost
NQO1	alkylating agents	*C11orf65*	metformin
CBR3	anthracyclines and related substances	*SLC47A2*	metformin
HAS3	anthracyclines and related substances	*ATIC*	methotrexate
NQO1	anthracyclines and related substances	*MTRR*	methotrexate
SLC28A3	anthracyclines and related substances	*CYB5R1*	metoclopramide
FKBP5	antidepressants	*CYB5R2*	metoclopramide
GRIK4	antidepressants	*CYB5R3*	metoclopramide
HTR2A	antidepressants	*CYB5R4*	metoclopramide
ANKK1	antipsychotics	*CCHCR1*	nevirapine
GP1BA	aspirin	*CHRNA3*	nicotine
LTC4S	aspirin	*HTR2C*	olanzapine
PTGS1	aspirin	*GSTM1*	oxaliplatin
APOE	atorvastatin	*UGT2B15*	oxazepam
COQ2	atorvastatin	*HTR1A*	paroxetine
KIF6	atorvastatin	*VDR*	peginterferon alfa-2b
LDLR	atorvastatin	*XRCC1*	platinum
FDPS	bisphosphonates	*DYNC2H1*	platinum compounds
CRHR1	budesonide	*ERCC1*	platinum compounds
ANKK1	bupropion	*NQO1*	platinum compounds
ADORA2A	caffeine	*KIF6*	pravastatin
TYMS	capecitabine	*TANC1*	radiotherapy
ACE	captopril	*VDR*	ribavirin
EPHX1	carbamazepine	*HTR2C*	risperidone

E-TABLE 33-1 DRUG-GENE PAIRS TO GUIDE PHARMACOGENOMIC TESTING—cont'd

GENE	DRUG	GENE	DRUG
FCGR3A	rituximab	*GGCX*	warfarin
ABCG2	rosuvastatin	*PROC*	warfarin
COQ2	rosuvastatin	*PROS1*	warfarin
COL22A1	salbutamol	*NAT1*	hydralazine
CRHR2	salbutamol	*NAT2*	hydralazine
TXNRD2	selective serotonin reuptake inhibitors	*NAT1*	isosorbide dinitrate
GNB3	sildenafil	*NAT2*	isosorbide dinitrate
ADD1	spironolactone	*IFNL4*	peginterferon alfa-2a
TCF7L2	sulfonamides	*IFNL4*	peginterferon alfa-2b
ABCC4	tenofovir	*ABCB1*	antidepressants
CRHR1	triamcinolone	*NUDT15*	azathioprine
CALU	warfarin	*NUDT15*	mercaptopurine

Adapted from https://cpicpgx.org/.

sequencing of samples from infected patients with the severe acute respiratory syndrome (SARS) identified the causative agent as a coronavirus. Comparison of sequences of multiple isolates of an organism from a single epidemic gives a picture of the organism's evolution, thereby allowing inference as to where the outbreak began and how the infection spread.[15] Sequencing has been a key for diagnosis, rapid vaccine development, and population health surveillance during the SARS-coronavirus-2 (SARS-CoV-2) pandemic.[16] The clinical application of next-generation sequencing to infectious disease also has been highlighted when the source of a carbapenem-resistant *Klebsiella pneumoniae* outbreak at the National Institutes of Health Clinical Center was identified by sequencing isolates of the bacteria in real time and tracing the source to a single individual who had been discharged 3 weeks earlier.

THE EXPRESSED GENOME

COMPLEX MULTIMARKER GENOMIC TESTS FOR DISEASE DIAGNOSIS AND PROGNOSIS

Beyond DNA sequence, measures of gene expression, proteins, metabolites, and epigenetic changes are being used to generate comprehensive profiles of biologic systems in health and disease. Many of the computational challenges of analyzing these large, complex datasets are being addressed to yield next-generation biomarkers that are multianalyte, diagnostic, prognostic, and predictive. A growing number of marketed tests now typically measure protein or RNA levels, often with complex algorithms, thereby enabling diagnosis and prognosis. One example examines expression of 21 genes in tumor tissue to determine the likelihood of disease recurrence in women with early-stage hormone estrogen receptor–positive breast cancer. The test analyzes expression levels and converts them to a recurrence risk score, which has been shown to help guide treatment in patients, reduce overall health care costs, and improve outcomes and is currently covered by many major insurance companies. Other examples include MammaPrint (Agendia, Inc.), which analyzes the expression of 70 genes to determine whether patients are at high or low risk of breast cancer recurrence; and AlloMap (CareDx, Inc.), an 11 blood gene RNA signature for monitoring rejection following cardiac transplant.

Some, but not all, of the marketed in vitro diagnostic multianalyte index assays have demonstrated analytical and clinical validity, but evidence of clinical utility is usually lagging. Moreover, the very nature of these tests presents challenges to insurers, who grapple not only with limited data on clinical utility, but also how to reimburse such tests that are composed of both a laboratory component and an associated algorithm used to score risk, the latter part being integral to realizing the test's value.

METABOLIC AND PROTEIN PROFILING

Endophenotypes are the various molecular domains that exist at intermediate levels of organization between the genotype and the phenotype, including metabolomics and proteomics.[17] A metabolic profile is very similar to some of the traditional targeted profiles, such as a lipid profile, although it is more comprehensive. Metabolomics measures changes in the metabolic or chemical milieu that are downstream of genomic and proteomic alterations. Humans contain an estimated 5000 or so discrete small molecule metabolites, and the identification of metabolic fingerprints for specific diseases may have particular practical utility for the development of therapies because metabolic changes immediately suggest enzymatic drug targets. Similar to genomics and proteomics, metabolomics may be useful in disease diagnosis, prognosis, and drug development. In particular, metabolomics likely will be a valuable tool in assessing drug toxicity. These tools are being applied to diverse areas such as diabetes, obesity, cardiovascular disease, cancer, and mental disorders.

The large-scale study of proteins, termed proteomics, allows for the identification of proteins and of their differential expression between two physiologic states (e.g., health and a specific disease). Quantitative proteomics, in which global differences in protein abundances are measured, continues to be a priority area for biomarker discovery and molecular medicine. This area has been dominated by stable isotope approaches, but recent label-free quantitative methods rely on the measured intensity of a peptide ion and compare this intensity to intensity in other samples. Label-free methods have the advantage of higher throughput and fewer sample manipulation steps. Multiple- or selected-reaction monitoring of specific peptides within biofluids allows quantitation of absolute abundance of proteins in clinical samples. Although this technology is relatively immature in its applications to human health and disease compared with RNA and metabolic profiling, it is anticipated that these methods, combined with the development of mass spectroscopy technology, will advance proteomics to more routine use in diagnosis, prognosis, and pharmacogenomics within the coming years.[18]

IMPLEMENTING PRECISION MEDICINE IN CLINICAL PRACTICE

Despite progress and momentum in the discovery of genomic information with great potential to affect health care, significant challenges and barriers have limited the broad use of genomics in clinical practice (Table 33-2).[19]

EVIDENCE GENERATION

The adoption of genomic medicine is significantly hampered by gaps in the evidence of its clinical utility or impact on health and economic outcomes. Evidence is needed to demonstrate that genomic approaches deliver improved health outcomes in a cost-effective and affordable manner. As genome-based technologies mature scientifically, mechanisms must be put into place to ensure ongoing assessment and evidence generation of their value to patients, providers, and health systems. The pace of discovery far outweighs the ability to assess the value of each technology using traditional approaches such as randomized controlled clinical trials. Advancing the field likely will be best served by drawing upon a range of evidence sources, including randomized trials, pragmatic clinical trials, observational studies, and mining of data from EMRs.[20]

One strategy for developing the evidence base is to use continuous data collection among diverse populations after a drug or diagnostic test has entered the marketplace. A framework that guides implementation and ensures ongoing evidence generation, either after these products have been approved by regulators and entered the market or across a dedicated genomic medicine implementation network, could ultimately enhance the pace of adoption. Ongoing post-market data capture and evidence development is a paradigm that has been broadly underutilized but could be used to assess the economic impact of genomic medicine approaches.

IMPLEMENTATION OF PRECISION MEDICINE IN HEALTH CARE SYSTEMS

Generating the evidence base for precision medicine requires overcoming many practical and logistic challenges such as the absence of supporting information

TABLE 33-2 CHALLENGES AND SOLUTIONS TO ENABLE PRECISION MEDICINE IN PRACTICE

CHALLENGE	POTENTIAL SOLUTIONS
Evidence generation	• Balance the use of evidence generated from randomized controlled trials, the analysis from large datasets, and observational studies • A framework that ensures ongoing evidence generation once products have been approved by regulators and entered the market • Final regulatory and payer approval contingent on the inclusion of a health economic analysis
Implementation and education	• Standardized structured data and common data elements in EMRs • A centralized global genomic medicine toolbox to include optimized decision support tools • Increased investment in implementation science and diffusion research, as well as the outcomes and public health impact • Incentives to encourage adoption of precision medicine best practices by clinicians and health care delivery systems • Modular genomic medicine education programs for clinicians • Integration of genomics into core curricula in professional training • Educational programs, beginning at early educational stages, to emphasize precision and related concepts
Data ownership, privacy, and sharing	• Incentives among the public, private industry, academics, and government • Data governance and ownership frameworks • Privacy measures and risks associated with data breaches
Participant diversity, engagement, and trust	• A research agenda to understand participant preferences, beliefs, literacy, and values in precision medicine research and clinical care • Programs should reach out and engage underserved populations • Community advisors and ambassadors

Adapted from Ginsburg GS, Finkelman E, Balatbat C, et al. *Precision Medicine: A Global Action Plan for Impact*. Doha, Qatar: World Innovation Summit for Health; 2016.

technology (IT) infrastructure, data standards and interoperability, decision support technology, and funding for implementation and translational research. EMRs can enable linkage between genetic information and other health information to produce new understandings of health and disease. EMRs have been suggested as a possible solution for delivering actionable genomic information to providers. However, even where EMRs are available, they are largely unprepared to handle genomic information. Compounding this problem is a lack of standards for how such data should be stored. This challenge is referred to as interoperability, or the ability of IT programs to communicate with other systems both in terms of the data and codes they contain and the operating systems they use. In addition, standards for structured data, or common data elements, to be captured in EMRs must be developed. Having these structured data will allow datasets to be aggregated across health systems and research cohorts to be created across institutions. An example of work being done to enable the integration of genomic information is the DIGITizE Action Collaborative of the National Academies of Science, Medicine and Engineering (http://www.nationalacademies.org/hmd/Activities/Research/GenomicBasedResearch/Innovation-Collaboratives/EHR.aspx).

Clinical decision support is becoming more relevant as the sheer volume of information providers need to have "just in time" increases and also as clinical conditions continue to be subdivided and treated differently. Clinical decision support has the power to use genetic information to guide decision making, reduce cognitive load, and potentially limit medication errors. Clinical decision support, empowered by a robust IT infrastructure, represents an important approach for ensuring adherence to evidence-based precision medicine in clinical practice as well as a platform from which to share clinical success and cost-savings information.

Education of key stakeholder groups is a critical need for implementation and adoption of genomic medicine technologies. Most health professional educational programs are devoid of the practical information for understanding the use of genomic medicine testing, interpretation of the results, and how to counsel patients. These gaps must be filled for both the workforce currently in practice and for the workforce of the future.

DATA OWNERSHIP, PRIVACY, AND SHARING

Data sharing among health care systems, industry, researchers, clinicians, and patients is integral to evidence generation and to advancing the understanding of health and disease. Prototypes for sharing genomic and clinical data on a centralized platform are being developed (E-Table 33-2), but the IT costs prohibit some health care systems from participating in data sharing. As a result, underserved populations may be underrepresented in or completely absent from the shared datasets. Amassing larger and more diverse datasets and sharing these data with smaller or resource-limited health settings will be critical for their inclusion in precision medicine strategies in the future.

Policy and regulatory frameworks must address participants' concerns related to data ownership and privacy. Given the intrinsic identifiable nature of genomic
21 data, patients have concerns about their privacy and rights.[21] Because obtaining participant consent is a necessary first step to gathering research data, the informed consent process could be made more standardized and streamlined globally, including implementing and standardizing nontraditional electronic consent tools to make it easier on patients and researchers.

Legislation prohibiting discrimination based on genetic information, such as
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34

REGENERATIVE MEDICINE, CELL THERAPY, AND GENE THERAPY

LIOR GEPSTEIN AND KARL SKORECKI

CELL THERAPY

DEFINITION

A remarkable clinical need exists for the development of methods to facilitate the regeneration of injured or diseased tissues and organs. This need stems from the unrelenting prevalence of trauma, congenital disorders, ischemia, and degenerative processes, which becomes increasingly urgent as the global population expands and ages. Cancer also is tied to this field, both directly (replacement of lost vital organ function as a result of cancer invasion or treatment modalities, cell-based delivery of cancer immune and gene therapies) and indirectly (e.g., role of stem cells in cancer pathogenesis and risk of tumorigenesis in stem cell–based therapies). Recent developments in stem cell biology, molecular interventions, biopolymers, and other related biological and engineering disciplines have paved the way to the emerging research and clinical discipline of regenerative medicine.

REGENERATIVE MEDICINE

Regenerative medicine seeks to harness methods for the replacement or repair of dysfunctional cells, tissue, or organs in an attempt to restore normal function. It therefore draws upon therapies from the three conventional pillars of medical therapeutics (pharmaceuticals, biologics, and medical devices) as well as from the newest technology platforms, namely, cell therapy, tissue engineering, and molecular therapies. The long-term goal of regenerative medicine is to replace the lost functions of tissues and organs, and, consequently, to develop curative strategies for unmet clinical needs such as diabetes, heart failure, chronic kidney disease, traumatic and ischemic tissue loss, and neurodegenerative disorders, among others.

Cell Therapies

Cell therapies involve the application of cells to achieve a therapeutic benefit. Although achieving tissue and organ regeneration through cell replacement represents an important goal of cell therapy, additional therapeutic benefits could be obtained by immunomodulatory effects (e.g., for prevention of graft-versus-host disease), by acting as a vehicle for the delivery of genes or gene

E-TABLE 33-2 ADDITIONAL RESOURCES

WEBSITE	URL	DESCRIPTION
CPIC	http://www.pharmgkb.org/page/cpic	Provides freely available, peer-reviewed, updatable, and detailed gene/drug clinical practice guidelines
EGAPP	https://www.cdc.gov/egappreviews	Synthesizes scientific evidence and makes recommendations on appropriate use of genetic tests in clinical practice
FDA Biomarkers	https://www.fda.gov/drugs/science-and-research-drugs/table-pharmacogenomic-biomarkers-drug-labeling	List of pharmacogenomic biomarkers on drug labels (link to drug labels provided)
Genetic Testing Registry	http://www.ncbi.nlm.nih.gov/gtr/	Central location for voluntary submission of genetic test information by providers; includes information on test methodology, validity, evidence of the test's usefulness, and laboratory contacts and credentials
PharmGKB	http://www.pharmgkb.org	Information on potentially clinically actionable gene-drug associations and genotype-phenotype relationships
IGNITE	https://gmkb.org/	A toolbox for implementation of genomics into diverse care practices

CPIC = Clinical Pharmacogenetics Implementation Consortium; EGAPP = Evaluation of Genomic Applications in Practice and Prevention; FDA = Food and Drug Administration; IGNITE = Implementing GeNomics In pracTicE

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technology (IT) infrastructure, data standards and interoperability, decision support technology, and funding for implementation and translational research. EMRs can enable linkage between genetic information and other health information to produce new understandings of health and disease. EMRs have been suggested as a possible solution for delivering actionable genomic information to providers. However, even where EMRs are available, they are largely unprepared to handle genomic information. Compounding this problem is a lack of standards for how such data should be stored. This challenge is referred to as interoperability, or the ability of IT programs to communicate with other systems both in terms of the data and codes they contain and the operating systems they use. In addition, standards for structured data, or common data elements, to be captured in EMRs must be developed. Having these structured data will allow datasets to be aggregated across health systems and research cohorts to be created across institutions. An example of work being done to enable the integration of genomic information is the DIGITizE Action Collaborative of the National Academies of Science, Medicine and Engineering (http://www.nationalacademies.org/hmd/Activities/Research/GenomicBasedResearch/Innovation-Collaboratives/EHR.aspx).

Clinical decision support is becoming more relevant as the sheer volume of information providers need to have "just in time" increases and also as clinical conditions continue to be subdivided and treated differently. Clinical decision support has the power to use genetic information to guide decision making, reduce cognitive load, and potentially limit medication errors. Clinical decision support, empowered by a robust IT infrastructure, represents an important approach for ensuring adherence to evidence-based precision medicine in clinical practice as well as a platform from which to share clinical success and cost-savings information.

Education of key stakeholder groups is a critical need for implementation and adoption of genomic medicine technologies. Most health professional educational programs are devoid of the practical information for understanding the use of genomic medicine testing, interpretation of the results, and how to counsel patients. These gaps must be filled for both the workforce currently in practice and for the workforce of the future.

DATA OWNERSHIP, PRIVACY, AND SHARING

Data sharing among health care systems, industry, researchers, clinicians, and patients is integral to evidence generation and to advancing the understanding of health and disease. Prototypes for sharing genomic and clinical data on a centralized platform are being developed (E-Table 33-2), but the IT costs prohibit some health care systems from participating in data sharing. As a result, underserved populations may be underrepresented in or completely absent from the shared datasets. Amassing larger and more diverse datasets and sharing these data with smaller or resource-limited health settings will be critical for their inclusion in precision medicine strategies in the future.

Policy and regulatory frameworks must address participants' concerns related to data ownership and privacy. Given the intrinsic identifiable nature of genomic
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34

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ABSTRACT

The significant developments in the areas of stem cell biology, molecular interventions, and tissue engineering have opened a new medical discipline, regenerative medicine. This therapeutic approach seeks to replace or repair lost or dysfunctional cells, tissue, or organs using adult-origin or pluripotent stem cells. Proven or still experimental procedures include the use of bone marrow- and blood-derived stem/progenitor cells; delivery of extracellular vesicles, the activation of tissue-specific resident stem/progenitor cells or induction of cell proliferation to induce endogenous regeneration; the use of transcription-factor reprogramming to convert one cell type into another; and the engraftment of fetal tissue or ex vivo predifferentiated cell derivatives from pluripotent stem cells. An alternative therapeutic approach is gene therapy, which involves the transfer of genetic material (DNA, siRNA, or modified RNA) into cells in order to correct inherited disorders through the expression of the missing proteins, or to alter cellular function for treatment of nongenetic diseases through overexpression or inactivation of a specific protein. Recent clinical trials of gene therapy have shown encouraging benefits and an excellent safety record. Ongoing studies aim to move from uncontrolled overexpression of the missing protein to directly correcting the mutation at the DNA level through the use of gene-editing strategies such as the CRISPR-Cas9 system.

KEYWORDS

regenerative medicine
cell therapy
stem cells
tissue engineering
gene therapy
gene editing
siRNA
CRISPR-Cas9

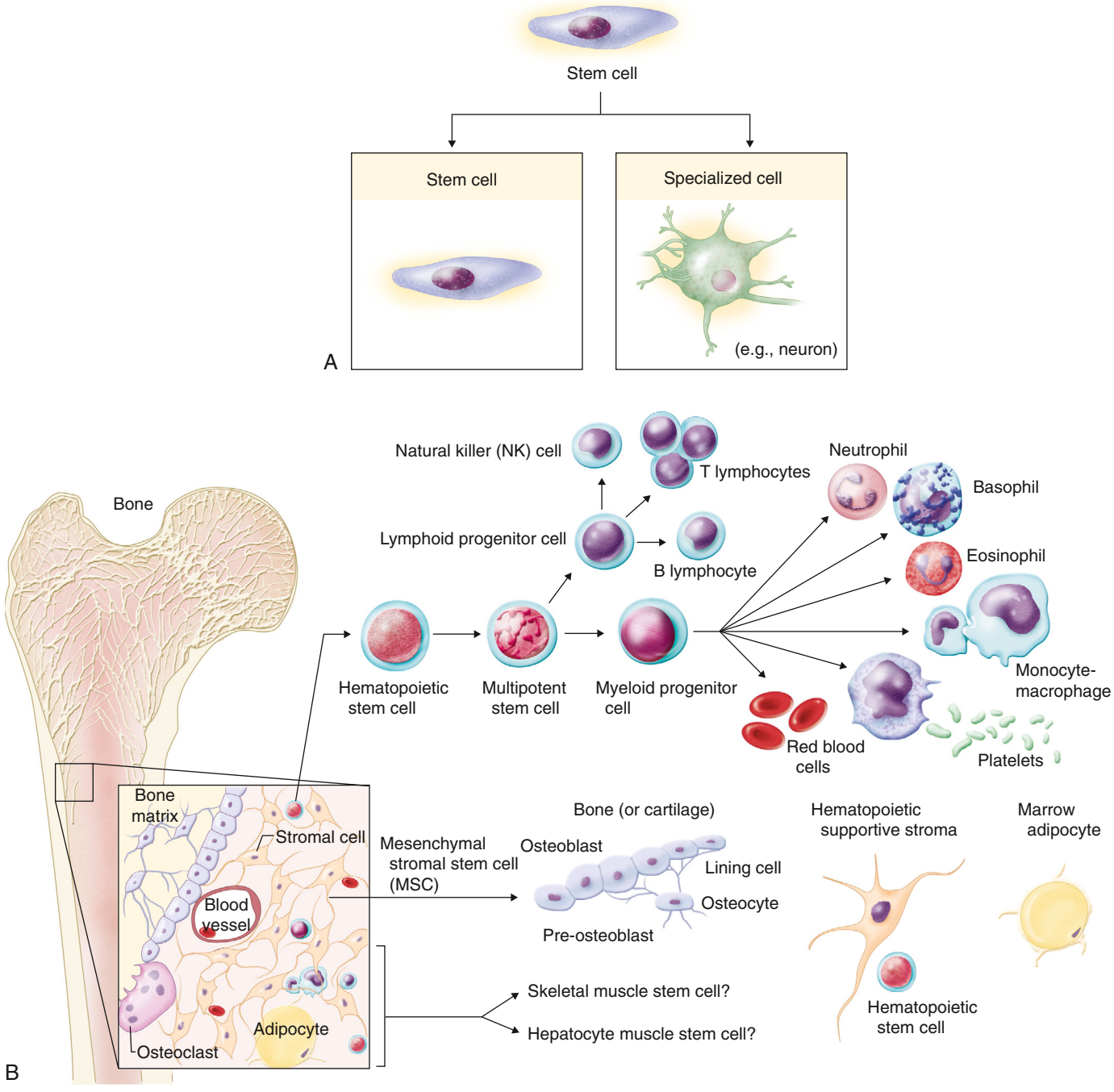

FIGURE 34-1. **A, Asymmetrical cell division. Although this property was considered a required characteristic for stem cells based on their original description in the adult hematopoietic system, not all cell types currently named as stem cells necessarily display this property. For instance, human embryonic stem cells divide by symmetrical cell division. B, Adult stem cells. Adult stem cells can be multipotent and have the capacity to differentiate into a limited number of different cell types, often restricted to a given tissue or organ system, as in the case of adult hematopoietic or epidermal stem cells. Two stem cell types have been isolated from adult bone marrow: the hematopoietic stem cell (HSC) that can give rise to all blood cell types and the supporting mesenchymal stromal cell (MSC). MSCs have immunomodulatory effects and can give rise to some differentiated cell types.**

products, and by the genetic engineering of immune cells (e.g., in chimeric antigen receptor [CAR] T-cell–based therapies).

Stem Cells

Stem cells possess two defining properties: (1) the capacity for self-renewal and (2) the ability to differentiate into cell types with specialized cellular functions (Fig. 34-1A). Their effects may occur through the process of asymmetrical cell division at the individual stem cell level or at the cell population level wherein a subset of cells differentiates and the remaining stem cells remain dormant or replicate themselves as stem cells. After asymmetrical cell division, non–stem cell derivatives may either generate a pool of organ system–restricted, transit-amplifying cells with enhanced proliferative capacity or continue to differentiate by epigenetic and gene expression profile changes until reaching the terminally differentiated state. For example, bone marrow cells are capable of reconstituting the adult hematopoietic system (Fig. 34-1B). These hematopoietic stem cells constitute the basis for hematopoietic stem cell transplantation, the only form of stem cell therapy performed routinely in clinical practice (Chapter 163).

The different stem cell types can be classified based on the protein or transcription factors they express, but also according to their replicative capacity (limited versus unlimited), the scope or potency of differentiation (e.g., pluripotent, multipotent, oligopotent, unipotent), and their place in the life history of the organism (developmental or post-developmental).

ADULT (POSTNATAL) STEM CELLS. After birth, many tissues are thought to contain a subpopulation of cells with the capacity for extended self-renewal, combined with the ability to differentiate into more mature cell types with specialized functions (Fig. 34-1). Adult stem cells, thought to represent less than 0.01% of the total number of cells, are located in specialized supportive

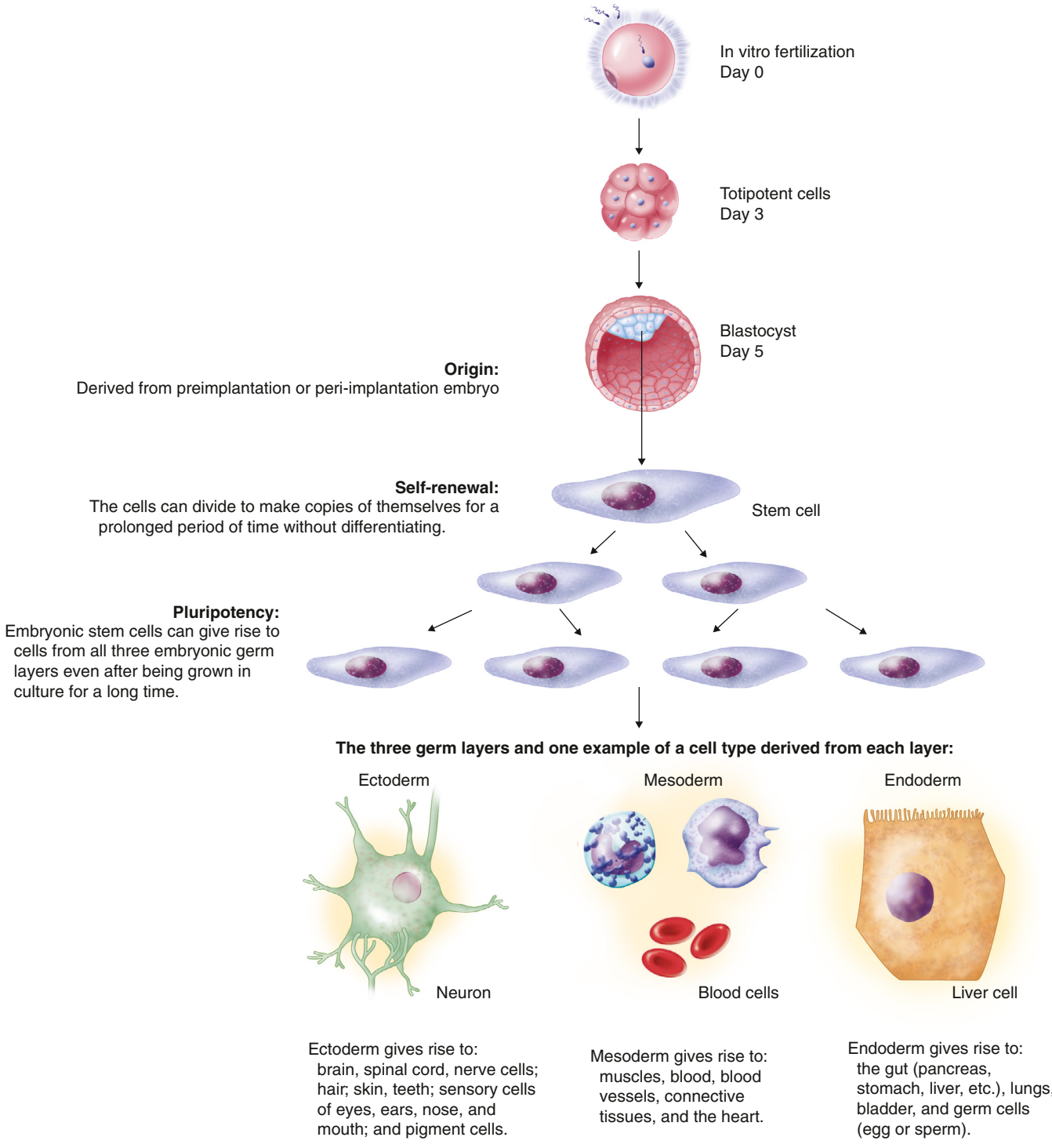

FIGURE 34-2. Embryonic stem cells. Totipotency refers to the capacity to differentiate into all cell types in an organism, including extraembryonic tissues, placenta, and umbilical cord, a property confined to the fertilized egg itself, including the cells derived from the first few cell divisions after fertilization. Pluripotency refers to the capacity to differentiate into all the specialized cell types derived from the three germ layers (ectoderm, mesoderm, endoderm) of the developing embryo and is a hallmark feature of embryonic stem cells, derived from the inner cell mass of the preimplantation blastocyst.

niche compartments and respond to cues in their local microenvironment. Adult tissues reported to contain putative stem cells include bone marrow (hematopoietic and mesenchymal compartments), blood vessel endothelium, dental pulp, epithelia of the skin, adipose tissue, digestive system, cornea, retina, testis, and liver. Similar stem/progenitor cells were also reported in organs historically not thought to contain such cells, such as the central nervous system. Whether adult stem cells represent remnants of developmental stem cells that persist into adulthood for the purposes of organ maintenance and repair or represent a distinct cell type dedicated for this latter purpose is not clear. Importantly, in many organs, despite the presence of such tissue-specific stem cells, their regenerative capacity is still inadequate to deal with massive cell loss, such as occurs following ischemic brain injury.

EMBRYONIC AND INDUCED PLURIPOTENT STEM CELLS. In contrast to adult stem cells that have relatively limited differentiation potency, cells in the developing preimplantation embryo retain the capacity to differentiate into all tissues in the body. Consequently, human embryonic stem cells, which can be isolated from the inner cell mass of human blastocysts generated for in vitro fertilization, can be propagated indefinitely in the undifferentiated state using special culture conditions, while retaining the capacity to differentiate into cell derivatives of all three germ layers (ectoderm, mesoderm, and endoderm) (Fig. 34-2). Using combinations of different growth factors, human embryonic stem cells can be induced to differentiate into several cell types, including neurons and glia, cardiomyocytes, vascular endothelial and smooth muscle cells, pancreatic β-cells, hepatocytes, and blood cells (e.g., platelets, red blood cells).

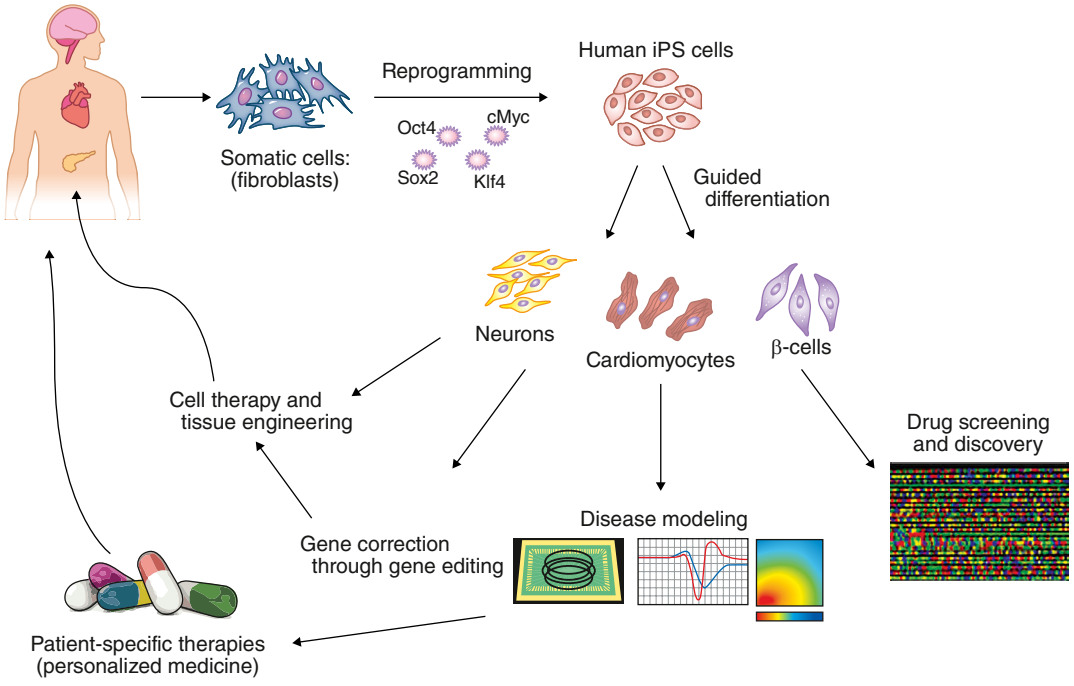

FIGURE 34-3. Potential applications of human induced pluripotent stem cells (hiPSCs). Patient-specific hiPSCs can be generated by reprogramming adult-somatic cells (e.g., fibroblasts) with a set of transcription factors and then coaxing them to differentiate into a variety of cell lineages. The patient-specific hiPSC cell derivatives can then be transplanted back into the patient in an autologous manner for regenerative medicine applications. In a similar manner, disease/patient-specific hiPSC-based models of inherited disorders can be generated ("disease-in-a-dish models") and used to improve the understanding of genetic disorders, to develop drugs, and to optimize patient-specific therapies. Gene editing techniques can be used to correct mutations and for transplantation of healthy cells.

One of the limitations in using human embryonic stem cells is the inability to derive such cells from adult individuals, thereby preventing their utilization in a patient-specific manner. This limitation was overcome with the introduction of the human induced pluripotent stem cell technology. This approach allows adult somatic cells (such as fibroblasts or blood cells) to be reprogrammed into pluripotent stem cells through the transient expression of a set of transcription factors linked to pluripotency. The human induced pluripotent stem cells generated can then be coaxed to differentiate into a wide variety of cell types. Importantly, since hiPSCs can be generated in a patient-specific manner, the technology can be used to develop autologous cell-replacement strategies that can preempt immunologic rejection, to generate patient/disease-specific models of genetic disorders, and to establish screens for drug testing and drug discovery (Fig. 34-3).

Conceptual Cell Therapy Approaches for Regenerative Medicine

Historically, the field of cell therapy can be traced to the transfusion of blood and blood products, solid organ transplantation, in vitro fertilization, and bone marrow transplantation. Nevertheless, beyond the aforementioned therapies and the recent emergence of CAR T-cell therapy for hematologic malignancies, additional cell therapy approaches are considered experimental and are still at different stages of preclinical and clinical development (Fig. 34-4).[1]

BONE MARROW–DERIVED STEM/PROGENITOR CELLS AND MESENCHYMAL STROMAL CELLS. Studies of bone marrow–derived hematopoietic or mesenchymal stem cells were based initially on the assumption that these adult stem cells may display some degree of plasticity, thereby allowing them to transdifferentiate into the relevant cell types (such as heart cells, nerve cells, and liver cells) following engraftment into the appropriate tissue environment. Although mounting evidence suggests that such transdifferentiation probably does not occur to a significant extent, many of these studies reported varying degrees of functional improvement in different organs. It now seems that the clinical benefit relates to growth factors that are secreted by the engrafted cells ("paracrine hypothesis") and augment endogenous tissue repair, improve tissue vascularization, modulate inflammation, and protect tissues at risk. Nevertheless, despite numerous trials for several indications, no mesenchymal stromal cell therapies are currently FDA approved in the United States.

DELIVERY OF EXTRACELLULAR VESICLES. Extracellular vesicles are intrinsic mediators of intercellular communication and allow functional transfer of biomolecules (lipids, proteins, DNA, mRNA, and microRNAs) between diverse locations.[2] Extracellular vesicles represent a collective term for vesicles that are secreted or shed by cells and can be categorized into groups, either by their size or mechanisms of formation and release. Examples include apoptotic bodies (1 to 5 μm), microparticles (100 to 1000 nm), and exosomes (<100 nm). Extracellular vesicles have attracted considerable interest both as potential biomarkers for disease and as therapeutic agents.

Many stem cells may exert their beneficial effect in tissue repair/regeneration by a paracrine effect, potentially acting by transferring biologically active molecules via extracellular vesicles. Delivery of extracellular vesicles may possess several advantages over stem cell therapy, such as reduced cost, easier manufacturing and delivery, and limited immunogenicity. Extracellular vesicles can also be used as a novel drug delivery approach by engineering the cells from which they are created to confer unique properties tailored for specific applications.

DELIVERY OR ACTIVATION OF TISSUE-SPECIFIC STEM CELLS OR INDUCTION OF CELL PROLIFERATION. In contrast to the conventional dogma, recent evidence suggests that several organs believed to lack regenerative capacity (such as the brain, pancreas, and kidney) do possess such ability, albeit at a limited capacity. Whether this capability is due to the presence of tissue-specific stem/progenitor cells or due to the replication capability of terminally differentiated cells is still a matter of debate.

Significant efforts have been made in recent years to isolate such putative tissue-specific stem/progenitor cells based on the expression of general or specific stem cell markers or unique culturing properties. Current efforts to utilize these findings for regenerative medicine are focused either on the isolation, ex vivo expansion, and transplantation of such putative stem/progenitor cells back to their respective native organs or on the augmentation of their endogenous reparative potential in vivo.

The final strategy aims to boost endogenous organ repair through the replication of terminally differentiated tissue-specific cells. Such strategies can either augment the inherent physiologic capability of a given organ (for example, insulin secretagogues for pancreatic β-cells) or attempt to induce replication in cells that have already withdrawn from the cell cycle, such as in the case of cardiomyocytes. Such regeneration strategies in the heart, for example, focus on attempting to replicate molecular and cellular pathways involved in the transient regeneration capacity reported in the neonatal mammalian heart[3] or by genetic approaches promoting adult cardiomyocytes to reenter the cell cycle.

ENGRAFTMENT OF HUMAN FETAL TISSUES OR XENOTRANSPLANTATION USING GENETICALLY MODIFIED ANIMALS. The most straightforward

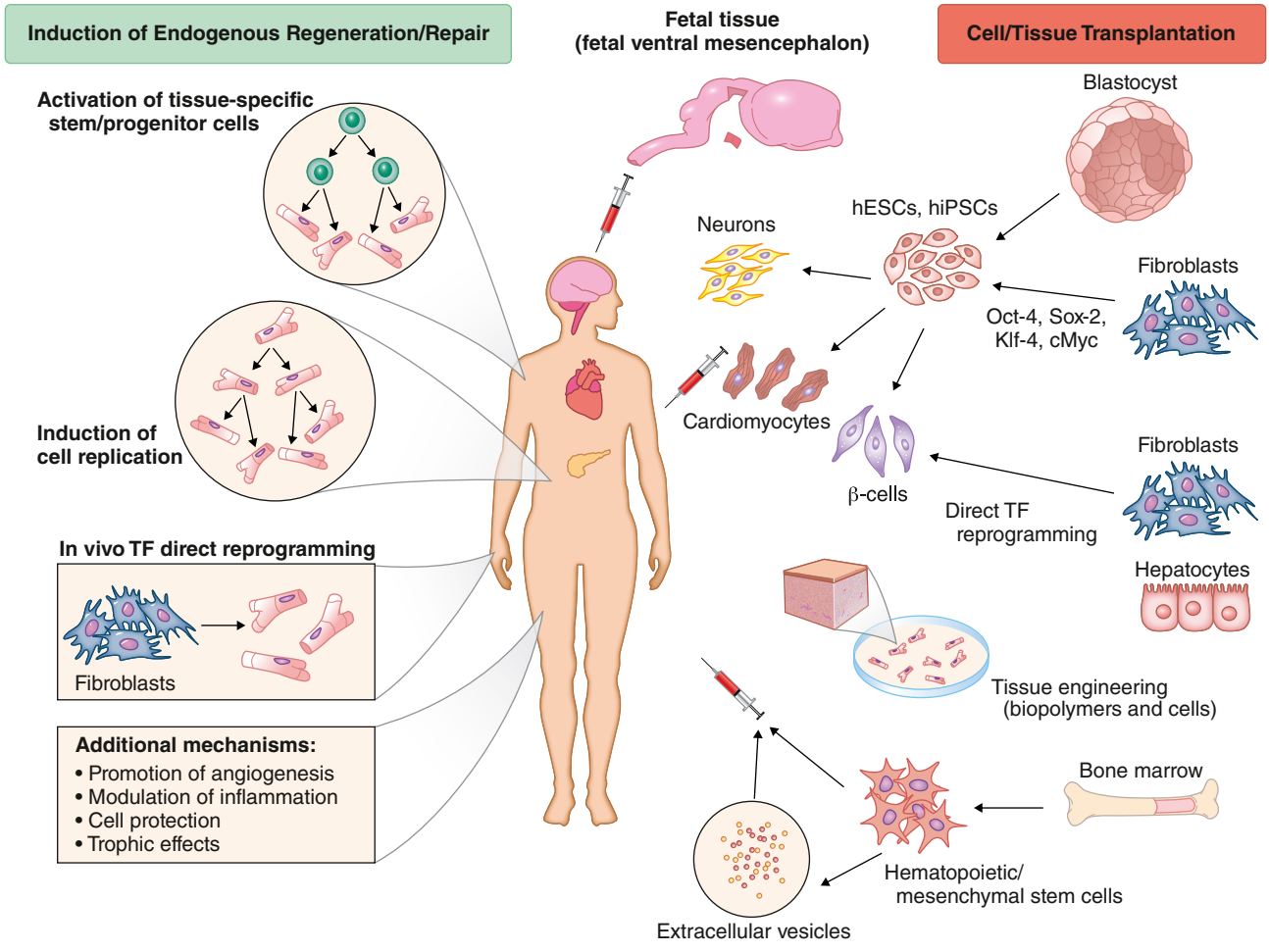

FIGURE 34-4. Conceptual framework for regenerative medicine approaches. These strategies can be divided into those attempting to augment endogenous regeneration or those focusing on transplantation of cells. The former could be achieved through the activation of putative tissue-specific stem/progenitor cells, through induction of cell replication, by in vivo transcription factor (TF)–based direct reprogramming (directly converting one somatic cell type such as fibroblasts into another), and by several other indirect means (e.g., modulation of inflammation, induction of angiogenesis, trophic effect, protection of tissue at risk). Cell sources that can be used for cell transplantation include fetal tissues (e.g., dopaminergic-rich fetal ventral mesencephalon for Parkinson disease), pluripotent stem cell (hESCs and hiPSCs)–derived cell lineages, and somatic cells that can be generated ex vivo by direct transcription factor–based reprogramming of fibroblasts. More recently, delivery of extracellular vesicles (EVs) derived from such cell sources were suggested as a potential alternative to cell therapy. Finally, the aforementioned cell sources can be combined with biopolymers as a tissue-engineering strategy. hESC = human embryonic stem cell; hiPSC = human induced pluripotent stem cell.

approach for organ repair would be to replace the missing cells/tissues/organs with identical counterparts. During prenatal human development, cells of fetal origin often show enhanced proliferative capacity as well as the ability to differentiate into more than one type of mature or specialized cell. Moreover, animal studies have demonstrated that transplantation of tissues harvested from developing organs may give rise to entire functioning organs such as kidneys, lungs, and pancreas. Nevertheless, to date, the only fetal-derived cells that have been used in human clinical applications are the dopaminergic cells derived from the developing fetal nervous system for the treatment of Parkinson disease, with conflicting evidence for success (Chapter 378).

An alternative to the use of human tissue/organ donors may be xenotransplantation, focusing on the use of transgenic pigs as sources for organ transplantation. Several genetically modified pig lines have been generated (most recently using the CRISPR/Cas9 genome editing system), aiming to overcome the main obstacles of immune rejection of the xenografts, physiologic incompatibilities, and transmission of zoonotic pathogens. These advancements have allowed proof-of-concept implantation of kidneys derived from such genetically modified pigs into two legally dead people with no discernible brain function.[4] More recently, a heart from a genetically modified pig was implanted in a patient who had terminal heart failure and was not a candidate for conventional heart transplantation.[5] The pigs were genetically modified to knock out three endogenous swine genes and to knock in six human genes, thereby reducing the immune rejection of the xenografts and particularly the hyperacute rejection associated with the presence of highly immunogenic glycoprotein derivatives in the vasculature of the pig's organs.

TRANSPLANTATION OF EX VIVO DIFFERENTIATED HUMAN PLURIPOTENT STEM CELLS. Numerous preclinical studies have demonstrated the ability of human embryonic stem cell derivatives to engraft, survive, and improve organ performance in a wide spectrum of relevant animal disease models (including, for example, heart failure, Parkinson disease, and diabetes). Nevertheless, the inability to create patient-specific human embryonic stem cells from adult individuals, the ethical issues arising from destructive use of human embryos, and the anticipated immune rejection associated with such allogeneic cell transplantation may hinder their clinical utilization. The human induced pluripotent stem cell technology may provide a potential solution to these challenges, since it generates patient-specific cells that could be coaxed to differentiate into a variety of lineages and subsequently transplanted in an autologous or allogeneic manner.

A flurry of clinical trials using human embryonic stem cells or human induced pluripotent stem cell lineages[6] have focused on the retina (transplantation of retinal pigmented epithelial cells for the treatment of macular degeneration) and other ophthalmologic disorders (retinitis pigmentosa and corneal disorders),[7] on spinal cord injury (using oligodendrocyte progenitors), and on neurodegenerative disorders such as Parkinson disease (using dopaminergic neurons) and amyotrophic lateral sclerosis. Additional targeted disorders include heart failure, pancreatic type 1 diabetes, cartilage defects, and cancer. Early clinical trials indicate that these procedures are safe and well tolerated, but many technical, regulatory, and conceptual challenges remain.

DIRECT REPROGRAMMING. In contrast to approaches involving human induced pluripotent stem cells, which seek to initially reprogram somatic cells into a pluripotent state followed by differentiation into specific cell lineages, direct reprogramming aims to convert the phenotype of one mature cell type directly into another. The prototype for such a strategy was the demonstration that *MyoD*, a master regulator of skeletal muscle formation, can convert

fibroblasts directly to skeletal muscle. Based on the experimental approach used to identify the combination of transcription factors that can reprogram somatic cells into human induced pluripotent stem cells, researchers identified a combination of lineage-specific developmental transcription factors that can convert terminally differentiated fibroblasts or other somatic cells into neuronal cells, β-cells, different hematopoietic cell lineages, and cardiomyocyte-like cells. Despite the unique potential of such strategies, direct reprogramming has not yet reached clinical trials, and in many cases the transdifferentiated cells cannot recapitulate the full extent of the phenotypic properties of the native cells.

Tissue Engineering

Tissue engineering is an interdisciplinary technology that combines principles from life sciences and engineering with the goal of developing functional substitutes for damaged tissues and organs. Regardless of the specific clinical application, tissue-engineering strategies usually involve the utilization of combinations of biomaterials (to generate supporting three-dimensional scaffolds), cells, and biologically active factors. The scaffold serves many purposes, including the control of the shape and size of the engrafted tissue, the delivery of biologic signals and adequate biomechanical support to the cells, the induction of vascularization of the graft, and the protection of the cells from physical damage. Scaffolds used in tissue engineering approaches are commonly divided into two general categories: cellular scaffolds that are seeded ex vivo with cells prior to the in vivo transplantation and acellular scaffolds that depend on cells in the recipient to repopulate the scaffold with subsequent reconstitution. Efforts have mainly concentrated on the musculoskeletal system (bone and cartilage repair) but have also targeted other organs such as the heart and even complex organ structures such as the esophagus, trachea, and urinary bladder. More recently, advances in organ decellularization/recellularization methodologies and three-dimensional bioprinting have allowed the generation of clinically relevant, anatomically accurate engineered tissues and organs.

Specific Disease Applications in Cell Therapy

Although a growing number of experimental cell therapies have reached various stages of clinical trials, as yet none have become established or approved treatments, with the aforementioned exception of hematopoietic stem cells, CAR T cells, and solid organ transplantation. Nonetheless, significant advances may be on the horizon.

NEURODEGENERATIVE DISORDERS. The central nervous system has limited capacity for regenerating lost tissue in both slowly progressive degenerative neurologic conditions (e.g., Parkinson disease, Alzheimer disease, or amyotrophic lateral sclerosis) and in acute injuries that lead to rapid cell loss (e.g., ischemic stroke or traumatic spinal cord injury). Stem cell–based therapies are being explored as potential novel therapeutic paradigms for both acute and chronic neurodegenerative disorders. These procedures could potentially act through the following mechanisms: (1) cell replacement, whereby cells (precommitted to a specific neuronal or glial lineages) are transplanted to replace the specific subtypes of cells that were lost (i.e., dopaminergic neurons in Parkinson disease, motor neurons in amyotrophic lateral sclerosis, or a mixture of different neuronal and glial subtypes in other disorders); (2) trophic support, whereby the engrafted cells are used to promote the survival of affected neurons or glia or stimulate endogenous repair of the diseased brain through the secretion of neurotrophic factors; and (3) modulation of the inflammatory process thought to contribute to the pathogenesis of many neurodegenerative processes.

In Parkinson disease (Chapter 378) cell-replacement therapy suggested significant improvement in motor function after intrastriatal implantation of fetal mesencephalic dopamine-rich tissue obtained from aborted human fetuses aged 6 to 9 weeks. Further progress, however, has been limited by lack of sufficient tissue to treat a large number of affected patients, the variability in functional outcome, reports of serious dyskinesias in a subset of treated patients, and ethical considerations.

Given these limitations, stem cell derivatives could offer a viable alternative by either replacing the dopaminergic neurons or by slowing the degeneration process and restoring the integrity of the nigrostriatal pathway through the release of trophic factors. Preclinical engraftment studies demonstrate that such cells can survive in animal models of Parkinson disease and exert beneficial functional effects following cell maturation. Initial clinical trials using human pluripotent stem cells have begun. The program that has advanced the most has been the transplantation of retinal pigment epithelium derived from human embryonic stem cells and human induced pluripotent stem cells for the treatment of macular degeneration (Chapter 391).

DIABETES MELLITUS. Successful pancreatic transplantation and improved glucocorticoid-free protocols for transplantation of islets of Langerhans can not only restore glucose control in patients with diabetes mellitus but can also prevent or even reverse some of the disease's complications (Chapter 210).[8] However, whole organ or islet-based transplantation approaches are limited both by immunologic rejection and an available source of transplantable tissues. These challenges have motivated the search for cell types that can replace or augment deficient β-cell function.

The differentiation of human embryonic stem cells and human induced pluripotent stem cells into precursor or early-stage β-cells is a potential option. The engraftment of either β-cell progenitors (which are expected to develop and mature in vivo) or more mature β-cells/islet-like tissues can sometimes normalize glucose levels in treated patients.

One of the problems in using β-cells for cell-replacement therapy is that the autoimmune destruction of endogenous β-cells, which underlies the pathogenesis of type 1 diabetes, will probably also result in the destruction of the human induced pluripotent stem cell–derived β-cells. To overcome this challenge, efforts are being made either to genetically manipulate the transplanted cells or to develop encapsulation biotechnologies to deliver the cells in an immunoprotective environment.

Beyond the derivation of new β-cells from pluripotent stem cells, progress has also been made in reprogramming closely related cell types to β-cells by overexpressing master regulatory transcription factors. An additional regenerative strategy focuses on increasing pancreatic β-cell mass by inducing their replication. This therapeutic approach would mainly target type 2 patients with diabetes by decreasing the burden on existing but overworked β-cells.

Finally, several clinical trials have explored the efficacy of mesenchymal stem cells, both as supporting cells to protect existing β-cells and as a source for newly generated β-cells. There is some evidence to suggest that transplantation of mesenchymal stem cells can be effective to a certain degree in type 2 diabetes, but its efficacy in type 1 diabetes is controversial.

STEM CELL–DERIVED PLATFORMS FOR DISEASE MODELING, PERSONALIZED MEDICINE, AND DRUG DISCOVERY. In addition to the generation of cells for regenerative applications, the ability to grow a wide variety of different specialized cell types of human origin in culture (in combination with advances in organ-on-a-chip, tissue engineering, and three-dimensional bioprinting technologies) provides unparalleled opportunities for disease modeling, gene and drug discovery, and drug testing. The advent of human induced pluripotent stem cell technology has further revolutionized this field. Different types of patient-specific human induced pluripotent stem cell–derived neurons, cardiomyocytes, skeletal muscle, blood cells, hepatocytes, and other cell types propagated in cell culture recapitulate disease-relevant phenotypes of a wide array of genetic disorders. Mechanistic insights derived using this approach have enabled predictive testing of existing therapies in a patient-specific manner (personalized medicine) as well as development and preclinical testing of evolving therapies.

GENE THERAPY

Gene therapy can be broadly defined as the transfer of genetic material into cells to restore or correct a cellular dysfunction or to provide a new cellular function in an attempt to cure a disease or to improve the clinical status of a patient. Recent clinical successes include entirely novel initiatives in treating primary immunodeficiency syndromes,[9] blood disorders,[10,11] and leukodystrophies; the improvement of vision in patients with retinal disease[12]; innovative approaches targeting chronic and acute viral infections; and highly encouraging outcomes in treating cancer.[13]

Clinically approved gene therapy agents include fomivirsen for the treatment of cytomegalovirus retinitis, the viral delivery of the lipoprotein lipase (*LPL*) gene for the treatment of LPL deficiency, voretigene neparvovec-rzyl for the treatment of Leber retinal dystrophy, and onasemnogene abeparvovec for the treatment of spinal muscular atrophy. An alternative to the direct in vivo gene delivery approach is the ex vivo genetic engineering of cells that are then engrafted to the patient.[14] The first clinical approval of this strategy involved the ex vivo genetic modification of harvested hematopoietic stem cells to express a functional product of the adenosine deaminases gene for the treatment of severe combined immunodeficiency. A turning point in the field was the development of CAR T cells,[15] which are a genetically modified cellular immunotherapy that can rescue patients who have hematologic malignancies (and recently also certain solid tumors) and who have failed prior conventional therapies.

Classifications and Mechanisms of Action

In general, somatic gene therapy applications can be divided into those aiming to correct or treat genetic disorders and those targeting nongenetic diseases by altering cell, tissue, and organ function. Traditional gene therapy efforts for inherited disorders have mainly focused on the exogenous expression of genes encoding the missing or abnormal proteins. Current and future efforts are expected to shift the focus from uncontrolled overexpression of the missing protein to correcting the mutation at the DNA level (gene editing strategies). For nongenetic disorders, efforts are aimed at overexpressing various proteins in an attempt to alter cellular function (e.g., to increase contractility in heart failure by expressing proteins related to calcium handling), to protect tissue at risk (e.g., in acute kidney injury), to exert paracrine effects through local secretion of specific proteins by the engineered cells (e.g., to promote angiogenesis in ischemic tissues or to induce neurotrophic effects in neurodegenerative disorders), and even to secrete certain proteins and hormones (e.g., to correct bleeding disorders by secreting coagulation factors or to treat anemia by secreting erythropoietin). Finally, major efforts have focused on using gene therapy tools for cancer immunotherapies.

Gene therapy efforts can be divided into ex vivo strategies and direct in vivo strategies. The former involve initial harvesting of cells from a patient, followed by their genetic modification, selection, and amplification in the laboratory, and eventually delivery of the modified cells back to the patient to achieve the desired therapeutic effect. This strategy is attractive for the genetic modification of stem cells or other cell types that could reconstitute relevant tissues and organs following transplantation. Prominent examples include the genetic modification of hematopoietic stem cells for treatment of hematopoietic disorders and various CAR T-cell strategies. Finally, next-generation therapeutic strategies are expected to use genetically engineered cells also to carry drugs and oncolytic viruses to treat intractable tumors and to modulate several tissue processes through the secretion of angiogenic, neurotrophic, and anti-inflammatory molecules.

The in vivo gene therapy approach involves the delivery of the relevant transgene (via different vectors) directly to the targeted tissue. The stable or transient expression of the transgene only in the relevant cells/tissues can be achieved by combining localized delivery, tropism of the vector used to the tissue of interest, and expression of the transgene under the control of a cell/tissue-specific promoter.

Gene Therapy Delivery Methods

Gene therapy agents are often composed of two elements: the genetic material itself (i.e., the DNA expression cassette, short interfering RNA, or an antisense molecule) and the vector delivery system. The latter is often the more complex and limiting component. It is therefore important to tailor the specific vector type for each gene therapy application to allow the most efficient delivery with minimal adverse effects. Vectors used for gene therapy can be classified into nonviral or viral vectors.

Gene therapy mediated by nonviral vectors is referred to as transfection and consists of the direct delivery of naked DNA by injection or in combination with liposomes (cationic lipids mixed with nucleic acids), nanoparticles, and other means. Although nonviral vectors are less toxic and immunogenic and can be produced in large amounts, their efficacy may be transient and insufficient. The efficiency of nonviral vector delivery could be enhanced by different physical methods, such as electroporation (for muscle, skin, and tumors), gene gun (for DNA vaccination), and ultrasound-assisted delivery (for cardiovascular and tumor-related applications).

Gene therapy mediated by viral vectors is referred to as transduction and has become the dominant clinical delivery approach. The idea is to harness the innate ability of viruses to deliver genetic material into the infected cell. Viruses used in gene therapy have been modified to enhance safety, increase specific uptake, and improve efficiency. Viral vectors are derived from viruses with either RNA (retroviruses and lentiviruses) or DNA (adenovirus, adeno-associated virus [AAV], herpes simplex virus [HSV], and poxvirus [vaccine virus]) genomes. Viral vectors can also be integrating, by inserting themselves into the recipient's genome, or nonintegrating, by forming an extrachromosomal genetic element. Integrating vectors, such as gamma-retroviral vectors and lentiviral vectors, are generally used to transfect actively dividing cells. Integrating vectors, however, may carry the risk of insertional mutagenesis, with clinical oncogenic transformations reported for retroviruses. Nonintegrating vectors, such as adenoviral vectors and adeno-associated virus vectors, can be used to transduce quiescent or slowly dividing cells, but they are quickly (in the case of adenoviral vectors) lost from cells that divide rapidly.

Adenoviral vectors and retroviral vectors featured prominently in early gene therapy trials. There has been a movement away from both, however, because of a death that was linked to the toxicity of the adenoviral vector and the leukemic transformation associated with the retroviral vector. These vectors have been replaced with adeno-associated virus and lentiviral vectors. Other viral vectors may be tailored for specific settings. For example, in gene therapies for pain management a replication-defective herpes simplex virus vector is used due to its tropism for nerves, whereas different oncolytic viruses are used in oncology because of their tropism to cancer cells.

Diseases Treated by Gene Therapy

HUMAN STEM CELL–BASED GENE THERAPY. Human stem cells are the preferred target for ex vivo gene therapy since their genetic modification would ensure a steady supply of their gene-corrected progeny in the body. Consequently, such approaches have the potential to treat conditions in which mature hematopoietic lineages fail to develop or to function correctly. The process of hematopoietic stem cell–based gene therapy involves the initial isolation of these progenitors from the bone marrow or peripheral blood using antibodies targeting the CD34 surface marker, followed by ex vivo genetic modification (using lentiviral vectors or gene editing techniques) for expression of the corrective transgene. Before the modified cells are administered back to the patient, the recipient is usually treated with a preconditioning chemotherapy regimen to deplete endogenous progenitors and to favor engraftment of the gene-corrected cells.

Despite the convincing clinical improvement observed in the first-generation human stem cell–based gene therapies for immunodeficiency, the adverse consequences resulting from the random integration of retroviruses have stalled progress in this field for many years. The recent shift to the use of lentiviral vectors and gene editing tools with improved efficacy and safety has renewed interest in the approach. Consequently, human stem cell–based gene therapies have been successfully tested in severe inherited diseases of the immune system (Wiskott-Aldrich syndrome and X-linked severe combined immunodeficiency) and in diseases of the blood (β-thalassemia) and nervous system (adrenoleukodystrophy and metachromatic leukodystrophy).

LIVER. A striking gene therapy success has been to induce the liver to produce coagulation factors for the treatment of coagulopathies, such as hemophilia B (Chapter 160), in which raising circulating coagulation factor levels from <1% (in affected individuals) into the range of 5% may be sufficient for effective treatment.

Cardiovascular disease. The cardiovascular system is emerging as an attractive target for nucleic acid–based therapies.[16] These efforts have focused on novel lipid-lowering approaches, on achieving therapeutic angiogenesis for chronic ischemic heart disease and critical limb ischemia, on improving cardiac function in heart failure, and on correcting monogenic cardiovascular diseases. 16

The use of traditional gene therapy strategies and emerging RNA and genome editing therapies have led to the development of clinical programs for the prevention and management of atherosclerotic cardiovascular diseases by targeting lipid metabolism. These include early-stage clinical trials employing recombinant adeno-associated virus (rAAV)–based liver-directed human LDL receptor (LDLR) gene delivery for the treatment of homozygous familial hypercholesterolemia. The emerging role of RNA-based therapies resulted in development of antisense oligonucleotides or short interfering RNA strategies for lowering apolipoprotein (a), proprotein convertase subtilisin/kexin type 9, *apoCIII*, and *ANGPTL3*. These highly successful lipid-altering strategies have either reached advanced clinical trials or were already approved clinically (i.e., inclisiran, a siRNA-based therapy targeting PCSK9 (Chapter 190).[A1] A1

The use of genes to promote angiogenesis to augment perfusion of the ischemic myocardium or to treat critical limb ischemia has been the focus of two decades of preclinical research using a variety of angiogenic mediators. Overall, these gene therapy approaches were very successful in various animal models, but human trials provided inconsistent results. Another important gene therapy target has been heart failure and various cardiomyopathies. One effort that reached advanced clinical trials was the expression of the sarcoplasmic reticulum calcium ATPase (SERCA2a), which led to the restoration of abnormal calcium transients and improved cardiac contractility in animal models with heart failure. However, human trials failed to demonstrate clinical benefits, most probably due to inefficient myocardial transgene expression. Nevertheless, efforts focusing on additional targets are ongoing.

CANCER (SEE ALSO CHAPTER 164). One of the most exciting opportunities for gene therapy lies in the cancer arena. Gene therapy strategies targeting cancer include the use of naturally occurring or modified viruses to induce

cytotoxic or growth inhibitory effects in cancer cells, gene therapies to boost the immune response to tumor antigens, and mRNA antitumor vaccines.

Antitumor cytotoxicity and growth inhibition. Oncolytic viruses are therapeutically useful anticancer viruses that preferentially infect and damage malignant tissues without causing harm to normal tissues. Cancer selectivity takes advantage of deficiencies characterizing many tumor types, such as deficient innate antiviral response mechanisms, susceptibility to cell injury pathways (e.g., reactive oxygen species), deficient tumor suppressors, and restoration of defective cell death pathways such as apoptosis. Several viruses such as the Newcastle disease virus (which activates the innate or adaptive immune response), reovirus (which activates host protein kinases to shut down protein production), and mumps virus preferentially target cancer cells, thereby causing cell death and tumor regression. Other oncolytic viruses include modified versions of Coxsackie, herpes, vaccinia, adeno, rhabdo, and measles viruses.

Although the foregoing approaches have inherent anticancer activity, viruses such as vesicular stomatitis poliovirus can be genetically engineered to engender oncolytic activity. Beyond the direct viral cytopathic effect, viral vectors can be engineered to deliver genes to cancer cells that will result in tumor cell death. Tumor cell selectivity for activation of such genes can be achieved using promoters that are activated only in cancer cells (e.g., human telomerase or survivin) or in specific types of tumors (e.g., probasin in prostate cancer, ceruloplasmin in ovarian cancer, or HER2 in breast cancer). Suicide gene therapy involves delivery of a pro-drug activating enzyme (suicide gene) that converts nontoxic pro-drugs to cytotoxic metabolites.

Oncorine, which is a recombinant oncolytic virus that selectively replicates in p53-deficient tumors, is used in China for patients with squamous head and neck or esophageal cancer. Talimogene laherparepvec is a recombinant human herpes simplex virus modified to optimize local spread and elaboration of human granulocyte-macrophage colony stimulating factor. This agent is an oncolytic virus approved by the FDA for the treatment of locally advanced or metastatic cutaneous melanoma and is under study for the treatment of hepatocellular, pancreatic, and other solid tumors.

Gene therapies aiming to boost the immune response to tumor antigens. Immunotherapeutic approaches are rapidly emerging as the "fifth pillar" (along with surgery, radiation, chemotherapy, and growth factor pathway–targeted therapies) in the treatment of cancer. Among these approaches, CAR T-cell anticancer therapy can be considered a form of combined gene and cell therapy. The approach is based upon ex vivo genetic engineering of T cells from the cancer patient (Fig. 34-5). CAR T-cell therapy requires drawing blood from the patient, separating the T cells, and genetically engineering the T cells ex vivo to express surface CARs and then expanding them in vitro. CARs are synthetic molecules which enable the engineered T cells to recognize and attach to a specific protein, or antigen, on tumor cells. Following a prior chemotherapy immunodepletion step, the CAR T cells are infused into the patient. Infused CAR T cells multiply in the patient, where they target, attack, and kill cells expressing the surface antigen corresponding to the genetically engineered CAR. This process may elicit an extensive massive cytokine release response, which is an "on-target" adverse effect, whose clinical management using corticosteroids and anti–interleukin-6 drugs, along with the treatment of other adverse effects (e.g., neurotoxicity), is a *sine qua non* for the overall success of this novel anticancer therapy approach.

The CAR T-cell therapies, which have been extensively studied and approved for clinical use, target the CD19 surface antigen on B cells and are effective for B-cell malignancies, including childhood acute lymphocytic leukemia and diffuse B-cell lymphomas. The remarkable success of CAR T-cell therapy to achieve durable remissions, even in relapsed or poor prognosis disease, has now led to the successful extension of CAR T-cell therapy targeting the CD22 and CD123 antigens in leukemias and the BCMA protein in myeloma.[A2] A2

RNA-Based Therapeutics

Recent advances in the generation, purification, and cellular delivery of RNA have allowed the development of several types of RNA-based therapeutics.[17] 17 These diverse RNA-based therapies include approaches that (1) inhibit protein generation by promoting RNA degradation and/or inhibition of protein translation (antisense oligonucleotides, small interfering RNAs, or microRNAs); (2) bind receptors and inhibit signal transduction (aptamers); or (3) induce protein expression (mRNA therapeutics) (Fig. 34-6).

Antisense Oligonucleotide, Small Interfering RNAs, and microRNAs

ANTISENSE OLIGONUCLEOTIDES. Antisense oligonucleotides are short, single-stranded oligonucleotides that can pair with complementary sequences in endogenous messenger RNA (mRNA) transcripts, thereby altering their processing and eventually affecting specific protein translation (Fig. 34-6).[18] 18 By binding to their targets, antisense oligonucleotides can modulate the splicing of pre-mRNAs (allowing skipping or inclusion of a targeted exon), induce the degradation of target mRNAs (by the RNase H-mediated degradation process), or block the translation of mRNAs into proteins (by steric hindrance of ribosomal activity).

Several antisense oligonucleotide drugs have already received clinical approval, and several others are in advanced clinical trials, Eteplirsen is a representative of a group of morpholino-oligos approved to treat Duchenne muscular dystrophy (Chapter 389), which is caused by mutations that produce a premature stop codon and a nonfunctional dystrophin protein (most commonly in exon 51 of the *DMD* gene). Eteplirsen recognizes and hybridizes to exon 51 of the dystrophin gene, thereby modulating the pre–messenger RNA splicing process to exclude exon 51 from the mature mRNA. This process restores the reading frame and leads to translation of a shortened, but functional, dystrophin protein. Similarly, nusinersen is used to treat spinal muscular atrophy (Chapter 387) by binding to the *SMN2* gene pre-mRNA, thereby inducing the inclusion of exon 7 and, consequently, the stability of the translated protein as an alternative to the mutated SMN1 protein.[A3] Mipomersen induces the degradation of A3
apolipoprotein B mRNAs to treat familial hypercholesterolemia (Chapter 190), whereas inotersen is used to treat familial amyloid polyneuropathy (Chapter 174) caused by the mutations in the transthyretin (*TTR*) gene.[A4] A4

SMALL INTERFERING RNA (siRNA). RNA interference (RNAi) regulates gene expression through a highly precise mechanism of sequence-directed gene silencing by specific mRNA degradation. Whereas the antisense oligonucleotide techniques are based on single-stranded RNA, the molecule utilized in the RNAi pathway is small interfering RNA (siRNA), a short-sized,

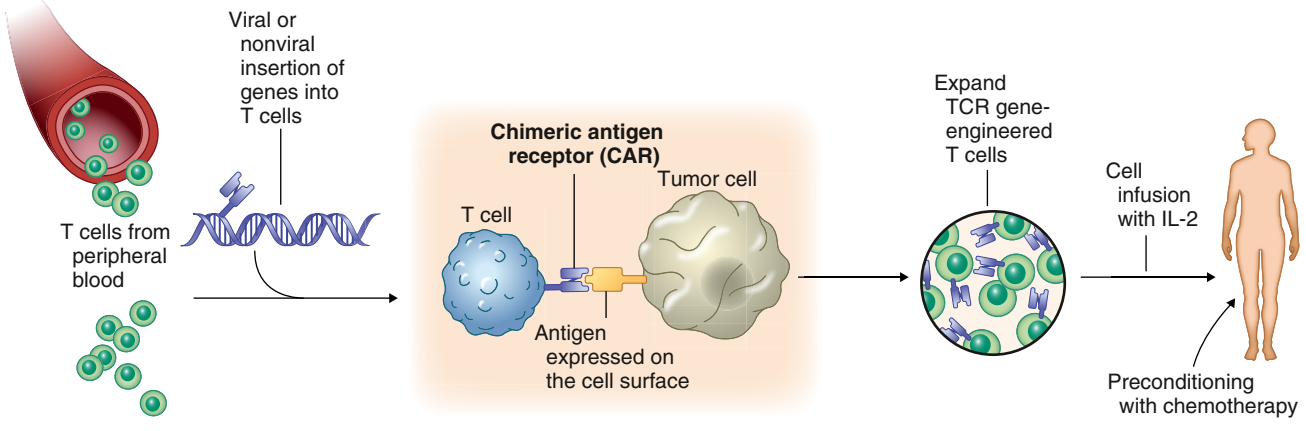

FIGURE 34-5. CAR T-cell anticancer therapy. CAR T cells are genetically engineered ex vivo to produce chimeric antigen receptors (CARs) on their surfaces. They are then expanded in the laboratory and reinfused into the patient. IL = interleukin; TCR = T-cell receptor. (Adapted from National Cancer Institute publication at https://www.cancer.gov/about-cancer/treatment/research/car-t-cells. Credit: National Cancer Institute.)

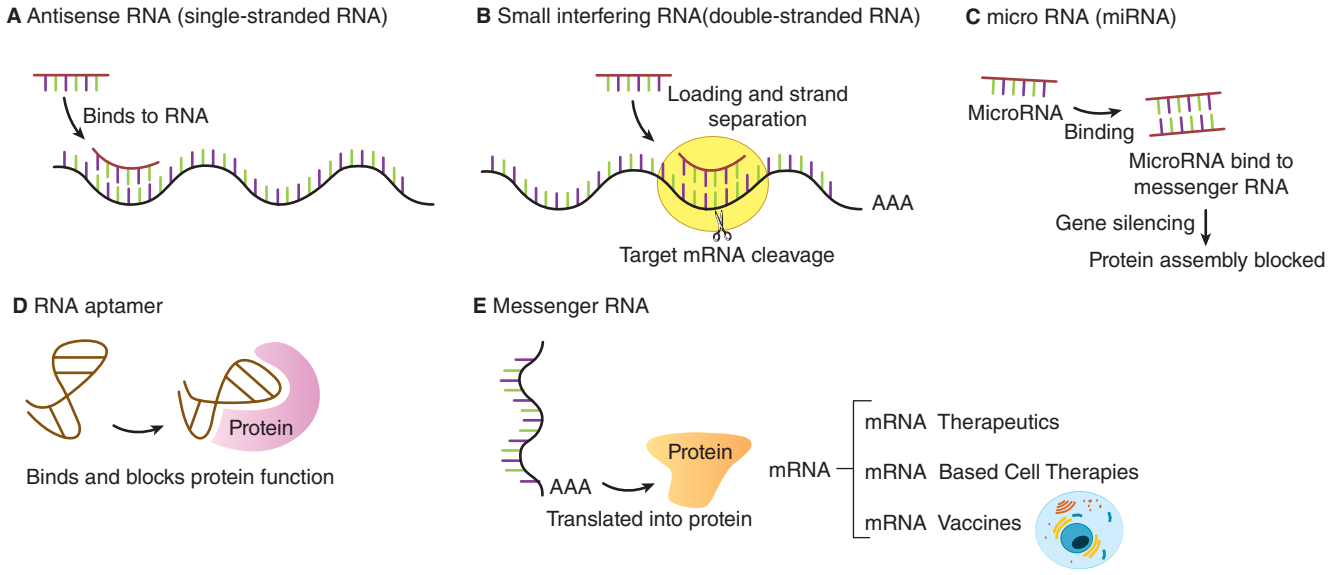

FIGURE 34-6. RNA therapies. A, Antisense RNA. The single-stranded antisense RNA hybridizes to the target mRNA. After binding, it modulates the splicing of pre-mRNA and/or induces the degradation of mRNA and/or inhibits the translation of mRNA into protein. **B,** Small interfering RNA (siRNA). siRNAs are short (20 to 25 nucleotides), double-stranded RNA molecules that use the RNAi pathway to degrade a target mRNA in a sequence-specific manner. After loading into the RNA-induced silencing complex (RISC), one strand is removed after strand separation. The guide strand then guides the RISC to the target mRNA, which is recognized and cleaved. **C,** microRNA (miRNA). miRNAs are small, noncoding RNA molecules that regulate the expression of multiple mRNAs by blocking translation or promoting degradation of the target mRNAs. **D,** RNA aptamers. The RNA aptamer can bind to a specific protein and block its function. **E,** Synthetic messenger RNA. After the messenger RNA (mRNA) is introduced into the cells, cellular machinery, including the ribosome, translates its information into a protein, the final product that can work as an enzyme or antigen. The mRNA-based therapies can be divided into three conceptual groups: (1) replacement therapy (mRNA therapeutics), (2) mRNA-based vaccines, and (3) mRNA-based cell therapy. mRNA = messenger RNA.

double-stranded RNA (Fig. 34-6). After being loaded into the cell's RNA-induced silencing complex (RISC), the double strands of siRNA are separated and one strand is discarded. The remaining RNA strand binds to the target mRNA sequence specifically, and the RISC machinery induces its degradation.

The use of RNAi for therapeutic applications is based on repressing the function of proteins implicated in several disease states such as cancer, age-related macular degeneration, and amyloidosis. In addition, siRNA-based, allele-specific silencing (resulting in reduced expression of the mutated "toxic" allele) can be used to target a variety of dominant-negative genetic disorders, such as Huntington disease (Chapter 379).

Currently, several siRNA-based therapeutics received FDA approval. The first approved siRNA drug, patisiran, exerts its effect by targeting the 3' untranslated region of transthyretin mRNA in the liver. By suppressing the expression of TTR, patisiran can prevent the systemic deposition of amyloid aggregates and is indicated to treat adult patients with polyneuropathy due to hereditary TTR amyloidosis (Chapter 174).[A5] Givosiran, which is intended to treat acute hepatic porphyria (Chapter 194),[A6] targets aminolevulinate synthase 1 mRNA in the liver and reduces the levels of the disease-causing neurotoxic intermediate proteins. Inclisiran binds to and cleaves the mRNA sequence of proprotein convertase subtilisin/kexin type 9 (PCSK9), thereby interfering with LDL receptor recycling in the liver and reducing LDL levels for more than 6 months (Chapter 190). Similarly, olpasiran was shown to reduce the levels of lipoprotein(a), another cardiovascular risk factor.[A7] Lumasiran, which targets glycolate oxidase,[19] reduces hepatic oxalate production for the treatment of primary hyperoxaluria type 1 (Chapter 189).

MICRORNA (MIRNA) MIMICS AND INHIBITORS. MicroRNAs are small, noncoding RNA molecules that regulate the expression of multiple mRNAs by blocking their translation or inducing their degradation. The miRNA-based therapeutics can be categorized into miRNA mimics and miRNA inhibitors (Fig. 34-6). The former are double-stranded RNA molecules that mimic the function of endogenous miRNAs, whereas the latter are single-stranded RNA oligos designed to interfere with specific endogenous miRNAs. Although no miRNA-based drugs are currently approved, promising candidates in clinical trials include miRNA inhibitors targeting specific miRNAs thought to play a role in hematologic malignancies, in solid tumors such as glioblastoma multiforme, in chronic hepatitis C, and in tissue repair. Potential therapeutic targets of miRNA mimics include keloid and pathologic fibrosis as well as modulation of the tumor microenvironment of different solid cancers.

APTAMERS. Aptamers are short, single-stranded nucleic acids that can bind to a variety of proteins, peptides, carbohydrates, and other molecules by virtue of their tertiary structure (Fig. 34-6). Consequently, aptamers can serve as agonists, antagonists, bispecific activity, and even carriers for other drugs. In this regard, aptamers have the potential to replace monoclonal antibody–based therapies. Pegaptanib, the first RNA aptamer drug, was developed to treat the wet type of age-related macular degeneration (Chapter 391). It acts by binding to vascular endothelial growth factor (VEGF), thereby preventing the formation of abnormal and leaky blood vessels. Other aptamers are currently in clinical trials for indications ranging from diabetic nephropathy, to multiple type of cancers (lung, pancreatic, and glioblastoma), to coagulation disorders.

MESSENGER RNA-BASED THERAPEUTICS. mRNAs serve as the intermediates between the coding genomic DNA and the encoded proteins. Synthetic mRNA is engineered to mimic naturally occurring mRNA, so as to prevent it from being recognized as foreign biologic material and being destroyed by the immune system. One of the most advanced approaches is to encase the mRNA in lipid nanoparticles. However, the activity of synthetic mRNAs is still transient, ranging from days to weeks.

Replacement therapy. In replacement therapy, modified RNA is administered to replace or compensate for a defective gene or protein or to supply therapeutic proteins. Many rare genetic diseases can be targeted using this approach. In cystic fibrosis (Chapter 77), for example, the mRNA encoding CFTR, a chloride channel that is defective in this disease, is delivered to lung epithelial cells by nebulization. Other mRNA-based therapeutic applications are being developed for different metabolic, infectious, and cardiac diseases. The largest number of mRNA-based applications are in the cancer arena, focusing mainly on immuno-oncology applications.

mRNA-based vaccines. Synthetic mRNAs encoding specific antigens can be used for vaccination to induce immunity against infections (prophylactic vaccines) or to harness the immune system to fight specific cancer types (therapeutic vaccines). For the former, the SARS-CoV-2 pandemic revealed the potential of the modified RNA technology for prophylactic vaccination (Chapter 337).[A8,A9]

MRNA ANTI-TUMOR VACCINES. Once in the body, the delivered mRNA directs cells that take up the mRNA (such as dendritic cells) to produce proteins that may stimulate an immune response against targeted proteins present in tumor cells. After taking up and translating the mRNA, dendritic cells present the resulting proteins, or antigens, to immune cells such as T cells, thereby starting the immune response. As in the case of CAR T-cell therapy, personalizing the vaccine for the antigens relevant to a given patient tumor, or developing banks for vaccines relevant to characterized tumor neo-antigens, are likely to be the future manner in which antitumor mRNA vaccines join in the repertoire of gene and cell therapy for malignant disease.

Cell therapy. Cell therapy may be enhanced by the mRNA approach by generation of engineered cells with unique properties tailored for specific applications. The cells may be obtained in an autologous manner, from pluripotent stem cells, or from a cell bank. Subsequently, candidate cells are therapeutically modified ex vivo with mRNA encoding the desired proteins (such as CARs or reprogramming or transdifferentiation factors) and delivered to the patient. In contrast to genetically modified cells with DNA plasmids, the effects achieved by mRNA expression are temporary.

GENOME EDITING

The center of gravity for gene therapy may be shifting from the addition of a therapeutic gene by conventional gene therapy strategies to genome editing, whereby a pathogenic mutation can be corrected at its natural location in the genome using programmable nucleases. Such programmable nucleases include zinc-finger nucleases (ZFNs), transcription activator-like effector nucleases (TALENs), and the more recently described clustered regularly interspaced
20 short palindromic repeat associated nuclease Cas9 (CRISPR-Cas9).[20] These genome-editing methodologies can be used not only to correct mutations but also to inactivate (or knock out) deleterious mutations in diseased cells, to disrupt viral DNA, and to add therapeutic transgenes. Such genome-editing therapies have already entered advanced preclinical and clinical testing for a
21 variety of indications.[21]

Genome Editing Mechanisms of Action

Programmable nucleases act as highly specific molecular scissors engineered to target a specific sequence in the genome and introduce a double-strand break in the DNA just proximal to the targeted site (Fig. 34-7). The predominant cellular pathway to repair double-stranded DNA breaks is nonhomologous end-joining, which joins two double-stranded break ends by direct ligation with no or little homology between the joined ends. As a result, nonhomologous end-joining is associated with a high probability for error by resulting in the insertion or deletion of a few nucleotides at the break site. The resulting insertion-deletion (*indel*) mutations can therefore be exploited to selectively inactivate genes (Fig. 34-7A) and specifically genes that are responsible for the abnormal clinical phenotype.

The same logic can also be extended to protect against infectious or genetic diseases by inactivating wild-type genes that favor the pathologic processes. Examples include inducing loss-of-function mutations in the CCR5 T-cell receptor to treat HIV infection, in the *PCSK9* gene to treat hypercholesterolemia, and in the *TTR* gene to treat ATTR amyloidosis-related polyneuropathy.[22] The first approved gene editing clinical trial involved the use of 22
zinc finger nucleases to target the *CCR5* locus in autologous CD4+ T cells ex vivo by adenoviral vectors for the treatment of HIV infection. Clinical follow-up revealed that the transfer of the gene-edited T cells into patients was well tolerated and that the *CCR5*-knockout cells were protected to a certain extent from infection with CCR5-tropic HIV. Similarly, programmable nucleases may also be used to target foreign DNA, such as viral genomes, thereby specifically targeting and inactivating viral-specific genes without affecting host human-specific DNA. Such an approach is in clinical trials targeting human papilloma virus (HPV). Finally, targeting of two nucleases to make two double-stranded breaks around an insertion (Fig. 34-7B) may be useful for treatment of nucleotide expansion disorders such as spino-cerebellar ataxia and Huntington disease.

An alternative mechanism to resolve the DNA cleavage is by homology directed repair between the endogenous DNA and an exogenously introduced donor fragment containing the normal nucleotide sequence (Fig. 34-7C). In this fashion, the pathogenic mutation is permanently corrected back to the normal sequence. This mutation correction approach preserves the architecture of the genome and maintains gene control under the normal cellular regulatory elements and could therefore be used to target a wide array of genetic disorders.

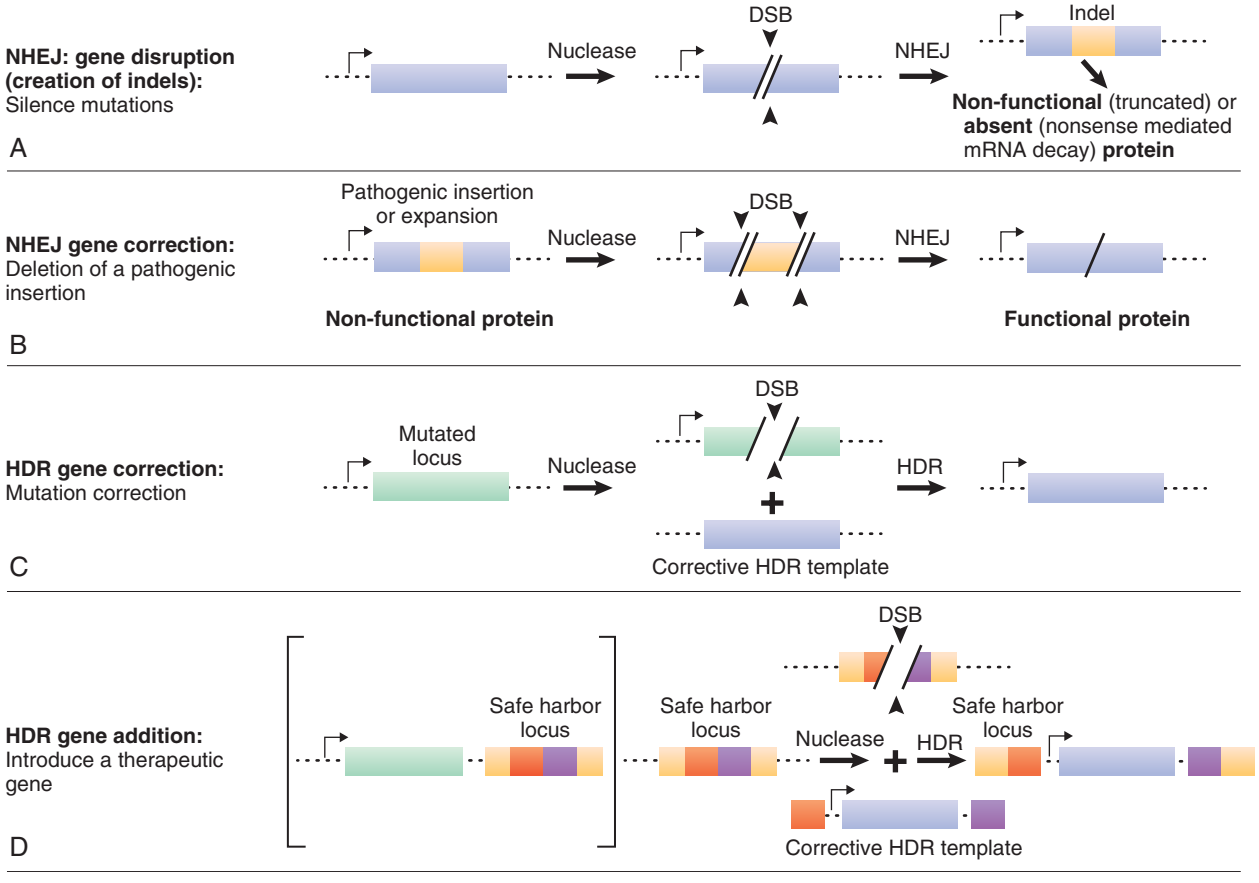

FIGURE 34-7. Conceptual therapeutic genome-editing modifications. The specific type of genome-editing therapeutic strategy depends on the nature of the mutation/disease. **A,** Nonhomologous end-joining (NHEJ) gene disruption. For gene disruption, expression of the pathologic protein is suppressed by introducing a double-stranded break (DSB) at the desired gene locus. The ineffective endogenous NHEJ repair mechanism leads to formation of indels in the gene of interest, often resulting in frameshift mutations that create premature stop codons and a nonfunctional protein product (truncated protein) or nonsense mediated decay of transcripts (no protein). **B,** NHEJ gene correction. Two DSBs targeted to both sides of a pathogenic expansion or insertion may be resolved by NHEJ, causing a deletion of the intervening sequences to mediate therapy. **C,** Homology directed repair (HDR) gene correction. For mutation correction, the HDR gene correction mechanism is used. A DSB is induced near the mutation site. HDR repair of the break site is achieved with an exogenous template, correcting the mutation and restoring normal gene function. **D,** Gene editing. This approach introduces a therapeutic transgene into either the native or a non-native (safe harbor site) locus in the genome. A DSB is induced at the desired locus, and an HDR template containing the relevant transgene and associated transcription control elements is introduced to the nucleus. mRNA = messenger RNA.

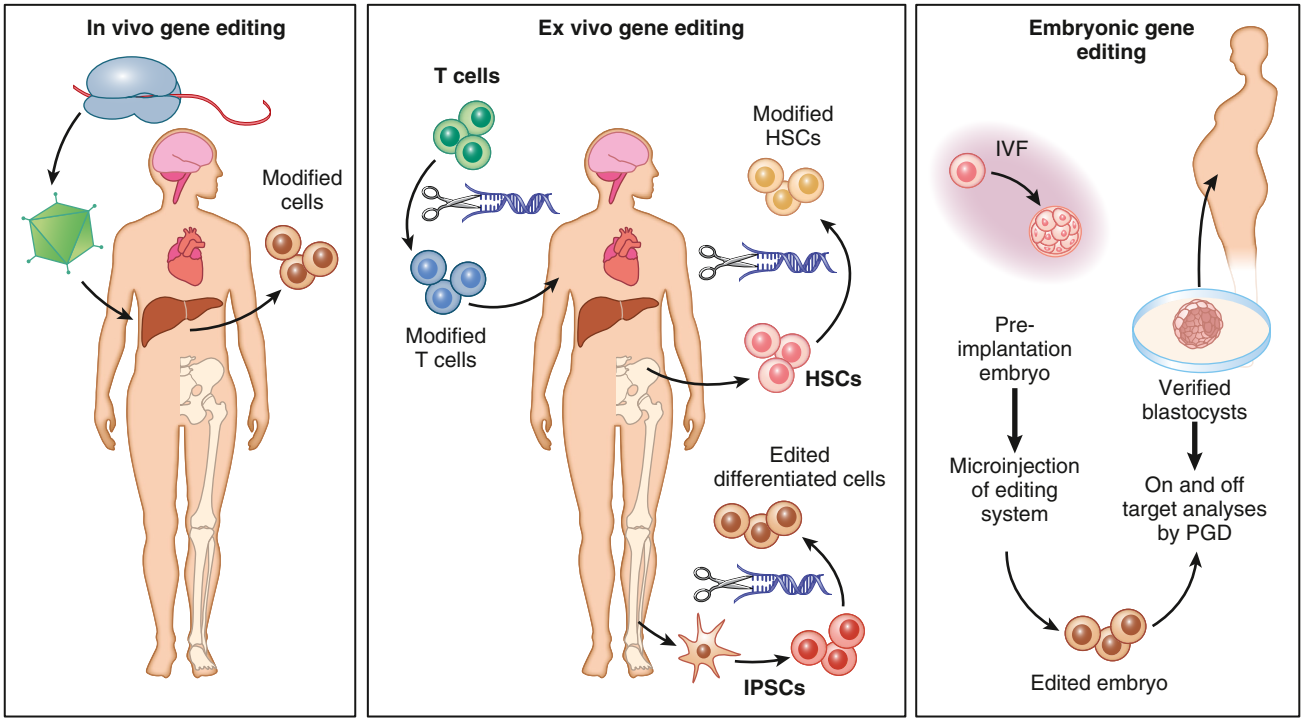

FIGURE 34-8. Ex vivo versus in vivo therapeutic genome therapy strategies. In ex vivo editing therapy, cells are removed from a patient, undergo genome editing, are expanded, and are then engrafted back to the patient to repopulate the diseased organ/tissues with healthy cells. Unique candidates for such an approach are HSCs, which can then be reintroduced by bone marrow transplantation. Alternative candidates are patient-specific iPSCs, which can be generated from a diseased individual, genetically modified, coaxed to differentiate into the desired cell lineage (e.g., heart cell, nerve cells, liver cells) and then transplanted back to the same patients. In vivo therapy involves genome editing of cells in situ. Delivery could be systemic or localized, with the preferred candidate organs being the liver, muscle, brain, and eye. For embryonic correction, the early-stage embryo formed during in vitro fertilization can undergo gene editing, and the corrected blastocyst can then be returned to the mother. HSCs = hematopoietic stem cells; iPSCs = induced pluripotent stem cells; IVF = in vitro fertilization; PGD = preimplantation diagnosis.

Finally, site-specific nucleases may also bring a unique value by enabling insertion of therapeutic transgenes (Fig. 34-7D) into specific safe harbor locations in the human genome, thereby ensuring long-term expression of the transgene, achieving better control over transgene copy number and expression levels, and reducing the potential for random insertional mutagenesis. Gene insertion may be used to secrete certain factors or to favorably alter the phenotype of the genetically modified cell.

The aforementioned strategies for gene modifications can be utilized either via a direct in vivo approach to modify existing cells (e.g., targeting liver cells) or alternatively by an initial ex vivo cell modification step followed by in vivo transplantation of genetically modified cells (Fig. 34-8).

The first clinical trials involving CRISPR/Cas9 in China and later in the United States involved the ex vivo disruption of the programmed death 1 (PD-1) gene in extracted T cells, which were then reinjected into the patients to generate more efficacious cancer immunotherapies to treat multiple myeloma, pancreatic and lung cancer, or glioblastoma. More than 100 ongoing clinical trials of CRISPR/Cas gene editing and other gene editing technologies in different disease types have confirmed the safety and feasibility of the technique for human gene therapy. These trials focus primarily on five clinical fields: blood disorders, cancer, ophthalmologic disorders, chronic infections, and protein-folding disorders.

Efforts in treating blood disorders have focused on development of CRISPR-based treatments of sickle cell anemia (Chapter 149) and β-thalassemia (Chapter 148).[23] Both hemoglobinopathies could theoretically be cured by isolating hematopoietic stem cells from the patients and using genome editing to either correct the disease-causing mutation in β-globin or to activate the expression of γ-globin, a fetal form of hemoglobin that could substitute for defective β-globin. The edited stem cells are then transplanted back into the patient. All patients treated so far showed normal or near-normal hemoglobin levels. The challenge for these approaches will be to achieve efficient, robust, and specific gene modification of the ex vivo hematopoietic stem cells since they cannot undergo effective clonal expansion. CRISPR/Cas9 may also be used to improve cell-based immunotherapies such as next-generation CAR T cells, which are safer, more controllable, and more efficacious.

In cases in which somatic approaches do not look promising, researchers are considering a third approach by making permanent changes to the genomes of human embryos. From a medical perspective, this approach has the advantage that gene correction will be permanent, so neither the treated person nor any of their descendants will carry the disease allele. In principle, the procedure would involve manipulating embryos at a very early stage, in conjunction with in vitro fertilization (Fig. 34-8). In a proof-of-concept study, a genetic mutation in the *MYBPC3* gene (causing hypertrophic cardiomyopathy) was corrected in viable preimplantation human embryos. In this and other studies, the embryos were never implanted, but the feasibility of this controversial approach was demonstrated.

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35 THE INNATE AND ADAPTIVE IMMUNE SYSTEMS

MARY K. CROW

THE IMMUNE SYSTEM IN HOST DEFENSE

The immune system, comprising cells, the molecules they produce, and the organs that organize those components, evolved over millions of years in response to infections with pathogenic microorganisms. Its essential role in maintaining health is based on recognition and elimination or control of those foreign microbes. Central to its efficacy is its capacity to distinguish foreign and dangerous invaders from self-components.[1] In addition to host defense, the immune system is involved in the prevention of malignancy by surveying and recognizing self-cells that express novel antigens,[2] as well as in resolution and repair of tissue damage.

The immune system is described as including an *innate immune system* and an *adaptive immune system*. The former provides the first and rapid line of defense to a foreign stimulus.[3] The latter, dependent on activation by cells of the innate immune system, develops a more specific response targeted to the offending organism and generates memory for that stimulus that can be elicited rapidly should that organism be encountered on a later occasion.[4]

Immune system cells derive from precursor cells of the hematopoietic lineage in the bone marrow (Chapter 142) and populate discrete lymphoid organs, including lymph nodes, spleen, and thymus, as well as skin and intestine. Cells of the innate immune system serve as sentinels at locations that are likely to encounter foreign organisms, and after activation they often travel to a local lymphoid organ. The induction of the adaptive immune response occurs in the context of structured aggregates of innate and adaptive immune cells in the lymphoid organs. Once activated and differentiated to produce effector molecules, immune system cells can be sampled in blood as they travel to sites of infection or tissue damage. There they interact directly with target cells to mediate cell death. Alternatively, they provide activating signals to expand or regulate a response or secrete high local levels of immunomodulatory proteins called cytokines. Cytokines communicate among cells within the immune system or between immune system cells and cells in other tissues.[5]

Important advances in characterization of the cell surface and intracellular pattern recognition receptors, particularly the Toll-like receptor (TLR) family and signaling pathways used by innate immune cells to implement a defensive response, are now understood to have relative specificity for pathogen-associated molecular patterns that are characteristic of categories of microbes.[6] In contrast to those receptor systems that initiate an innate immune response, the protein products that implement the response, whether to expand the reaction, promote cell trafficking to the most relevant location, or shape the differentiation programs of adaptive immune system cells, do not show specificity based on the initial triggering stimulus. The products of the innate immune system can be highly effective at ablating or limiting the extent of infection and can generate a tissue repair program that establishes a satisfactory resolution of the episode of infection.

In contrast to recognition of structural patterns common in the microbial world by cells of the innate immune system, the adaptive immune system is designed to respond to the entire continuum of antigens.[7] This goal is achieved through two principal types of antigen recognition receptors: T-cell receptors and antibodies. α/β T-cell receptors, which are the most abundant class of T-cell receptors, interact specifically with epitopes formed by a small linear peptide embedded in major histocompatibility complex (MHC) molecules on the surface of antigen-presenting cells. Antibodies, or immunoglobulins, are expressed as cell surface receptors on B cells or are secreted, with both having the same specificity for antigen by recognizing conformational structures formed by the tertiary configuration of proteins.

The cells and products of the immune system function as an exquisitely regulated complex system. Inherited variations in hundreds of genes have evolved, under pressure of microbial challenge, to ensure adequate defense against pathogenic organisms across the human population. However, in any one individual, the composite genetic profile can generate vulnerability to infection or, alternatively, autoimmune or inflammatory disease.

CELLULAR ELEMENTS OF THE INNATE IMMUNE SYSTEM

Monocytes and Macrophages

Monocytes circulate in the peripheral blood with a half-life of 1 to 3 days. Macrophages arise from circulating patrolling monocytes that have migrated out of the circulation and have proliferated and differentiated in tissue. Tissue-resident macrophages may represent a separate yolk sac–derived cell lineage, with their differentiation influenced by tissue-specific factors, and include alveolar macrophages in the lung, Kupffer cells in the liver, osteoclasts in bone, microglia in the central nervous system, and type A synoviocytes in the synovial membrane.[8] Macrophages secrete myriad products, including hydrolytic enzymes, reactive oxygen species, cytokines, and chemokines. Macrophages engulf microorganisms and foreign particles directly and can be activated by protein complexes containing antibodies that bind to cell surface receptors for the Fc portion of immunoglobulin molecules (Fc receptors, or FcRs). These encounters activate intracellular signaling pathways that induce transcription of target genes, primarily those encoding mediators that promote inflammation or enzyme-mediated death of the microbe. Cytokines from other immune system cells, including interferon (IFN)-γ or interleukin (IL)-4, can drive macrophage differentiation toward the production of mediators that are primarily pro-inflammatory or to a wound healing functional profile. Researchers have characterized those functional phenotypes as M1 or M2, although it is recognized that the context of an innate immune response will determine the functional response, with composite profiles common. In addition to responding to foreign microbes,[9] macrophages contribute to the elimination of senescent or apoptotic cells through a process called efferocytosis and in a manner that avoids induction of an inflammatory response.[10] Macrophages also interact with other cell types through complementary cell surface adhesion or costimulatory receptors. After capturing antigen, they can function as antigen-presenting cells for T lymphocytes, and they can interact with non–immune system cells such as endothelial cells or fibroblasts.

Dendritic Cells

Dendritic cells comprise a complex family of cells that perform essential functions in the innate immune response and serve as a bridge to activation of an adaptive immune response. Myeloid dendritic cells incorporate antigens derived from invading microbes, travel to nearby lymph nodes, and present processed antigenic peptides to T cells in the form of peptide–MHC molecule complexes. They are the most effective antigen-presenting cells[11] based on expression of cell surface costimulatory molecules, and they produce cytokines, including IL-12 and IL-23, after interaction with pathogen-associated molecular patterns (PAMPs). They thereby contribute to the shaping of the T-cell differentiation program to generate effector cell functions. Plasmacytoid dendritic cells are highly efficient producers of type I IFN, a key mediator of host defense against viral infections, after interaction of nucleic acids with their endosomal Toll-like receptors.

Natural Killer Cells

Natural killer (NK) and NK T cells provide early defense against viral infections and other intracellular pathogens while adaptive responses are developing. NK cells are sensitized by cytokines, including type I IFNs, released from plasmacytoid dendritic cells and macrophages, and secrete abundant IFN-γ, which activates macrophages and other cells. They also are poised to kill virus-infected cells by injecting pore-forming enzymes and granzymes. Activation of NK cells is inhibited by interaction with self-MHC class I molecules on target cells. When those self-histocompatibility antigens are not present, NK cell–mediated killing is implemented. NK cells are important in tumor surveillance because they are able to kill MHC class I–deficient tumor cells that are no longer susceptible to adaptive immune responses. In addition to NK cells, innate lymphoid cells, a type of lymphocyte that participates early in innate immune responses but does not express rearranged receptors, are a focus of current study and are particularly important in immune responses in the gut.[12]

Neutrophils

Neutrophils are the most abundant circulating white blood cells. They are recruited rapidly to inflammatory sites and can phagocytose and digest microbes (Chapter 153). Activation of neutrophils and phagocytosis is facilitated through the triggering of FcRs or complement receptors. Microbe-containing phagosomes fuse with lysosomes, which contain enzymes, proteins, and peptides that inactivate and digest microbes. Beyond their phagocytic capability, neutrophils produce a variety of toxic products in the respiratory burst, which

ABSTRACT

The innate immune system provides a fast-acting first line of defense in response to a foreign insult. Cells of the innate immune system serve as sentinels at locations that are likely to encounter foreign organisms, recognize structural patterns common in the microbial world, and implement a defensive response to those microbes. After the initial response they provide a bridge toward activation of the adaptive immune response. The products of the innate immune response can be highly effective at limiting the extent of infection and can generate a tissue repair program that resolves the episode. However, for most infections the adaptive immune system is required to ensure effective host defense and the generation of immune memory. The adaptive immune system expands the repertoire and effectiveness of the immune response through T-cell receptor recognition of linear peptides associated with major histocompatibility molecules on antigen-presenting cells, and recognition of conformational structures of proteins by immunoglobulins expressed on the surface of B cells or secreted. Together, the innate and adaptive immune systems can restore homeostasis after a microbial challenge, but when their response is sustained or poorly regulated, they can mediate autoimmune and inflammatory diseases.

KEYWORDS

toll-like receptors
nucleic acid sensors
cytokines
type I interferon
tumor necrosis factor
macrophages
T cells
B cells
memory
autoimmunity

is a process accompanied by an increase in oxygen consumption. During the respiratory burst, oxygen radicals are generated by nicotinamide adenine dinucleotide phosphate (NADPH) oxidases. Neutrophils also contribute to host defense through extrusion of DNA and associated proteins in the form of neutrophil extracellular traps to which bacteria can stick, facilitating their clearance. Despite their effective contributions to the innate immune response and microbial host defense, neutrophils can generate considerable collateral damage. Neutrophil extracellular traps have the capacity to induce production of cytokines by plasmacytoid dendritic cells and may damage vascular endothelial cells.[13] Secretion of neutrophil granule contents, particularly their enzymes (myeloperoxidase, elastase, collagenase, and lysozyme), causes direct cellular injury and damages macromolecules at inflamed sites.

Eosinophils

In contrast to macrophages and neutrophils, eosinophils are only weakly phagocytic but are potent cytotoxic effector cells against parasites. Their major effector mechanism is the secretion of cationic proteins (major basic protein, eosinophil cationic protein, and eosinophil-derived neurotoxin). These proteins are released into the extracellular space, where they directly destroy the invading microorganism but can also damage host tissue (Chapter 156).

Basophils and Mast Cells

Basophils and tissue mast cells secrete inflammatory mediators such as histamine, prostaglandins, leukotrienes, and some cytokines. Release of these substances is triggered when cell surface immunoglobulin E (IgE) receptors encounter monomeric IgE. They play a role in atopic allergies, in which allergens bind immunoglobulin (IgE) and cross-link FcεRs. Mast cells have been observed in rheumatoid arthritis synovial tissue and have been implicated in local inflammatory responses (Chapter 235). Like plasmacytoid dendritic cells and macrophages, mast cells express Toll-like receptors and FcRs and produce cytokines after encountering immune complexes composed of Toll-like receptor ligands.

PRINCIPLES OF INNATE IMMUNE SYSTEM ACTIVATION: RECOGNITION OF IMMUNE STIMULI AND GENERATION OF EFFECTOR FUNCTION

Recognition Receptors and Triggers of an Innate Immune Response

Toll-like Receptors

The innate immune system uses both cell surface and intracellular pattern recognition receptors to recognize conserved structures on microbes (PAMPs). Examples of PAMPs are bacterial lipopolysaccharides, peptidoglycans, mannans, bacterial DNA, double-stranded RNA, and glucans. The discovery and characterization of the Toll-like receptor (TLR) family of receptors and their relevant ligands have focused attention on the mechanisms that allow an innate immune response to shape the nature of the resulting inflammatory or repair programs, as well as the T-cell effector functions that follow recognition of antigens from the relevant pathogen. The Toll-like receptors have in common leucine-rich domains and bind PAMPs common to classes of pathogenic organisms. For example, TLR-4, a cell surface–expressed pattern recognition receptor, binds lipopolysaccharide of gram-negative bacteria, and TLR-2 recognizes bacterial peptidoglycans and lipoproteins, often based on dimerization with other Toll-like receptor family members. Important advances in understanding systemic autoimmune diseases have followed the characterization of endosomal Toll-like receptors with relative specificity for single-stranded RNA (TLR-7 and TLR-8), demethylated 5′-cytosine-phosphate-guanine-3′ (CpG)-enriched DNA (TLR-9), and double-stranded RNA (TLR-3, which has both cell surface and endosomal forms). The distribution of particular Toll-like receptors among cells of the innate immune system varies, contributing to the distinct roles played by those cells in immune responses. The Toll-like receptors alert the immune system that a microbe, typically a bacterium in the case of TLR-2 and TLR-4 or a virus in the case of TLR-3, TLR-7, TLR-8, and TLR-9, is threatening the host. But in some cases, when an immune complex with self-nucleic acid gains access to an endosomal Toll-like receptor, a self-directed innate immune response can be initiated or amplified.[14]

Cytoplasmic Nucleic Acid Sensors

Following the description of the Toll-like receptor family and their capacity to recognize microbial and self-nucleic acids, a second category of intracellular innate immune system receptors was defined that recognize RNA or DNA from microbes, primarily viruses, that gain access to the cell cytoplasm. The DExD/H-box family of helicases include retinoic acid–inducible gene I (RIG-I) and melanoma differentiation–associated protein 5 (MDA5), described as members of the RIG-I–like receptor (RLR) family that recognizes viral RNAs with particular structural characteristics that distinguish them from most host RNAs (Fig. 35-1). Cytoplasmic DNA receptors also have been defined, with cyclic guanosine monophosphate–adenosine monophosphate synthase (cGAS) identified as an important sensor of cytoplasmic DNA that triggers an innate immune response after interacting with the stimulator of IFN genes (STING). Whether RNA or DNA triggers these cytoplasmic sensors, the results are transcription and production of IFN-β and other pro-inflammatory cytokines that orchestrate the early phase of an antiviral immune response. The aryl hydrocarbon receptor represents an additional cytosolic receptor that can be triggered by various ligands and demonstrates crosstalk with other intracellular pathways.[15]

NOD Receptors

The nucleotide-binding oligomerization domain (NOD)–like receptor (NLR) family comprises components of an intracellular structure called the inflammasome, a signaling platform that organizes innate immune system activation in response to some stimuli.[16] The inflammasome can activate caspase 1, an enzyme important for maturation of the pro-inflammatory cytokines IL-1β and IL-18. The NLRP3-containing inflammasome has been best studied and implicated in the inflammatory response to monosodium urate crystals, the triggers of gout attacks (Chapter 252). Mutations in the *NLRP3* gene are the basis of chronic autoinflammatory syndromes that are associated with exaggerated production of IL-1 (reviewed in Chapter 240).

C-Type Lectin Receptors

Members of the C-type lectin receptor family have a carbohydrate recognition domain and a calcium-binding domain that promotes signaling after interaction with carbohydrate-expressing microbes as well as self-molecules. Dendritic cell–specific intracellular adhesion molecule-3 grabbing non-integrin (dendritic cell-SIGN) is an example of a family member that recognizes high–mannose-containing structures on foreign antigens and supports dendritic cell activation. Mannose receptors on macrophages, dendritic cells, and other cell types, such as renal mesangial cells, participate in clearance of microbes as well as antigen trapping for presentation to adaptive immune system cells. The selectin family of proteins has a lectin domain, binds to carbohydrate ligands, and mediates the first steps of leukocyte migration. L-selectin is present on virtually all leukocytes; P-selectin and E-selectin are expressed on activated endothelial cells, and P-selectin is also stored in platelets. Selectins capture floating leukocytes and initiate their attachment and rolling on activated endothelial cells.

Scavenger Receptors

Scavenger receptors comprise a diverse family of receptors with the common functional role of binding various ligands and transporting or removing nonself or altered-self targets. They can participate in clearance of microorganisms and cholesterol transport but also contribute to disease pathology. For example, among the scavenger receptors is the receptor for oxidized low-density lipoproteins, which can promote generation of lipid-laden macrophages and atherosclerosis when accumulated in excess, and receptors for relatively inert substances such as silicon, which drive an inflammatory response once taken into phagocytic cells. Scavenger receptors also participate in activation of the inflammasome, as can occur after binding serum amyloid A protein.

Immunoglobulin-like Domain-Containing Receptors

The immunoglobulin-like killer inhibitory receptor (KIR) family of receptors participates in distinguishing self-cells from cells of foreign origin or tumor cells expressing modified self-molecules. NK cells are ready to produce their toxic mediators, but they are held in check by inhibitory receptors that recognize MHC class I or MHC class I–like molecules. The observation that NK cells kill target cells lacking MHC class I molecules recognized as self led to the missing-self hypothesis. By screening cell surfaces for the expression of MHC class I molecules, the innate immune system collects information about the intactness of tissues, emphasizing the crucial role of MHC class I molecules as markers of tissue integrity. The Triggering Receptors Expressed by Myeloid cells (TREM) family of cell surface receptors has emerged as important regulators of inflammation.[17] TREM-1 synergizes with other pathogen-recognizing receptors in anti-viral responses, and TREM-2 participates in innate immunity in Alzheimer disease.[18]

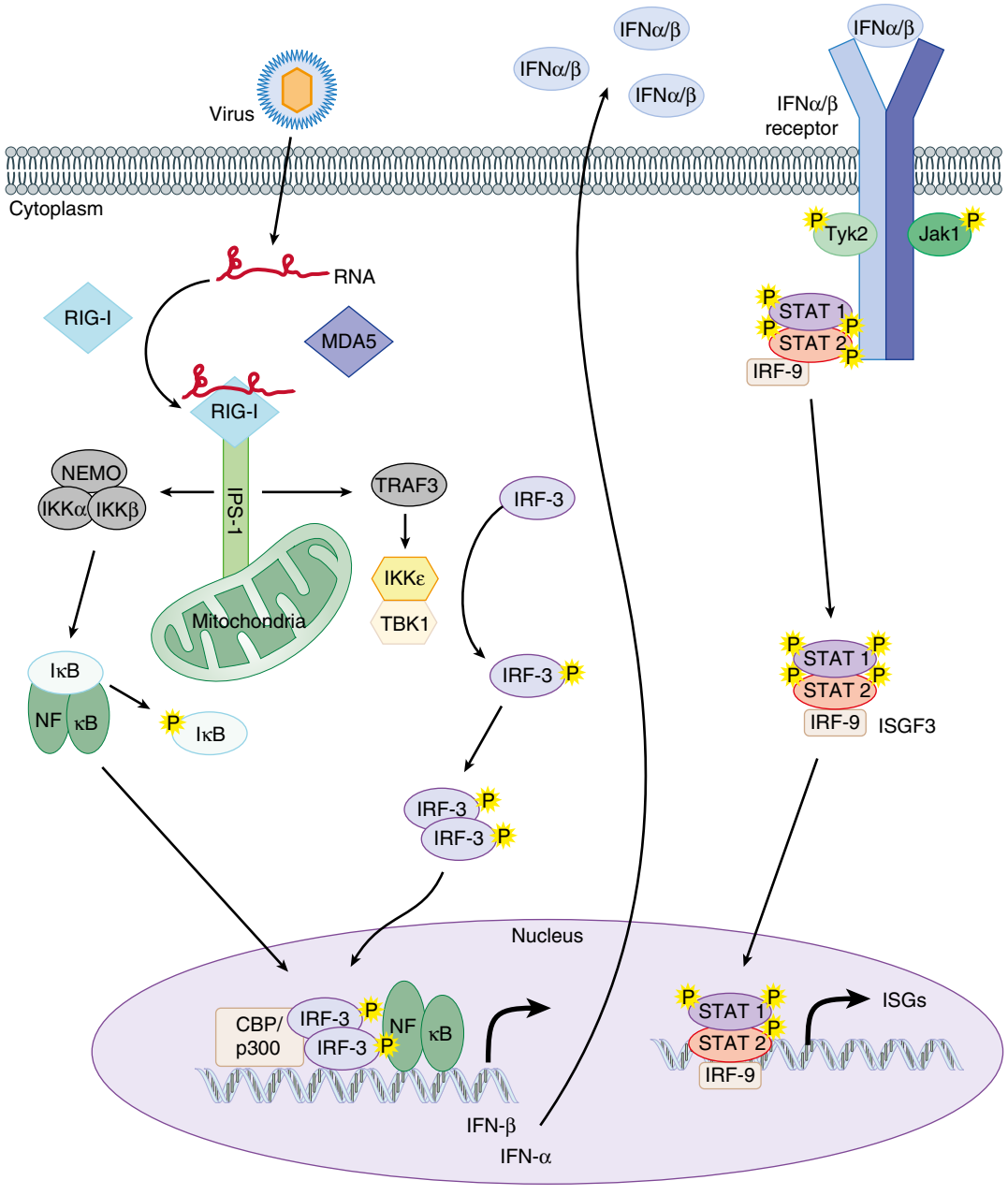

FIGURE 35-1. Induction of an antiviral type I interferon (IFN) response. Cytoplasmic sensors of RNA, including retinoic acid–inducible gene 1 (RIG-I) and melanoma differentiation-associated protein 5 (MDA5), trigger a signaling cascade that results in translocation of interferon regulatory factor 3 (IRF-3) to the nucleus and transcription of interferons. Those cytokines promote an antiviral immune response after binding to their receptor and activating the Janus kinase (JAK)–signal transducer and activator of transcription (STAT) pathway. CBP/p300 = CREB binding protein; IFN = interferon; IκB = inhibitor of κB; IKK = inhibitor of nuclear factor κB kinase subunit; IPS-1 = interferon-β promoter stimulator-1; IRF = interferon regulatory factor; ISG = interferon-stimulated gene; ISGF3 = interferon-stimulated gene factor 3; NEMO = nuclear factor-κB essential modulator; NF-κB = nuclear factor κB; P = phosphate; RIG-1 = retinoic acid-inducible gene 1; RNA = ribonucleic acid; STAT = signal transducer and activator of transcription; TBK1 = TANK-binding kinase 1; TRAF3 = TNF (tumor necrosis factor) receptor–associated factor; Tyk = tyrosine kinase. (From Wilkins C, Gale M Jr. Recognition of viruses by cytoplasmic sensors. *Curr Opin Immunol*. 2010;22:41-47.)

Fc and Complement Receptors

Most cells of the innate immune system possess FcRs that specifically interact with the constant region (Fc portion) of immunoglobulins and can bind antibodies attached to antigens. The isotype of the antibody determines which cell type is activated in a given response. Triggering of most FcRs transmits activating signals; however, inhibitory FcRs on B cells and macrophages can limit responses. Ligation of an FcγR on macrophages or neutrophils triggers phagocytosis of the antigen, activation of the respiratory burst, and induction of cytotoxicity. On NK cells, FcγRs initiate antibody-dependent cell-mediated cytotoxicity. FcRs on plasmacytoid dendritic cells are important for bringing immune complexes into endosomes containing Toll-like receptors. FcRs on mast cells, basophils, and activated eosinophils bind monomeric IgE with extremely high affinity. Cross-linking of the constitutively cell surface–bound IgE induces cell activation and the release of cytoplasmic granules. Some immunoglobulin isotypes fix complement, and complement receptors on monocytes amplify cell activation induced by antigen-antibody-complement immune complexes (Chapter 37). Complement receptor 1 (CR1) binds C3b and C4b, initial degradation products of complement activation, and when activated promotes phagocytosis of a complement-bearing immune complex. CR3 and CR4 are β_2-integrins and bind the degradation product iC3b.

Cytokine and Chemokine Receptors

Cells of the innate immune system express receptors for many cytokines, soluble low-molecular-weight glycoproteins that derive from many cellular sources. Binding of IFN-γ, produced by NK or type 1 helper T cells (T_H1 cells), by its receptor on monocytes activates a differentiation program that expands an inflammatory response. Receptors for IL-4 on monocytes induce a gene transcription program that is more supportive of a wound healing and repair program. Tumor necrosis factor-α (TNF-α) is a product of activated macrophages but also binds to those same cells through its specific receptor, expanding an inflammatory response. Innate immune cells also express receptors for IL-6, which induces acute phase reactants, and type I IFN. These

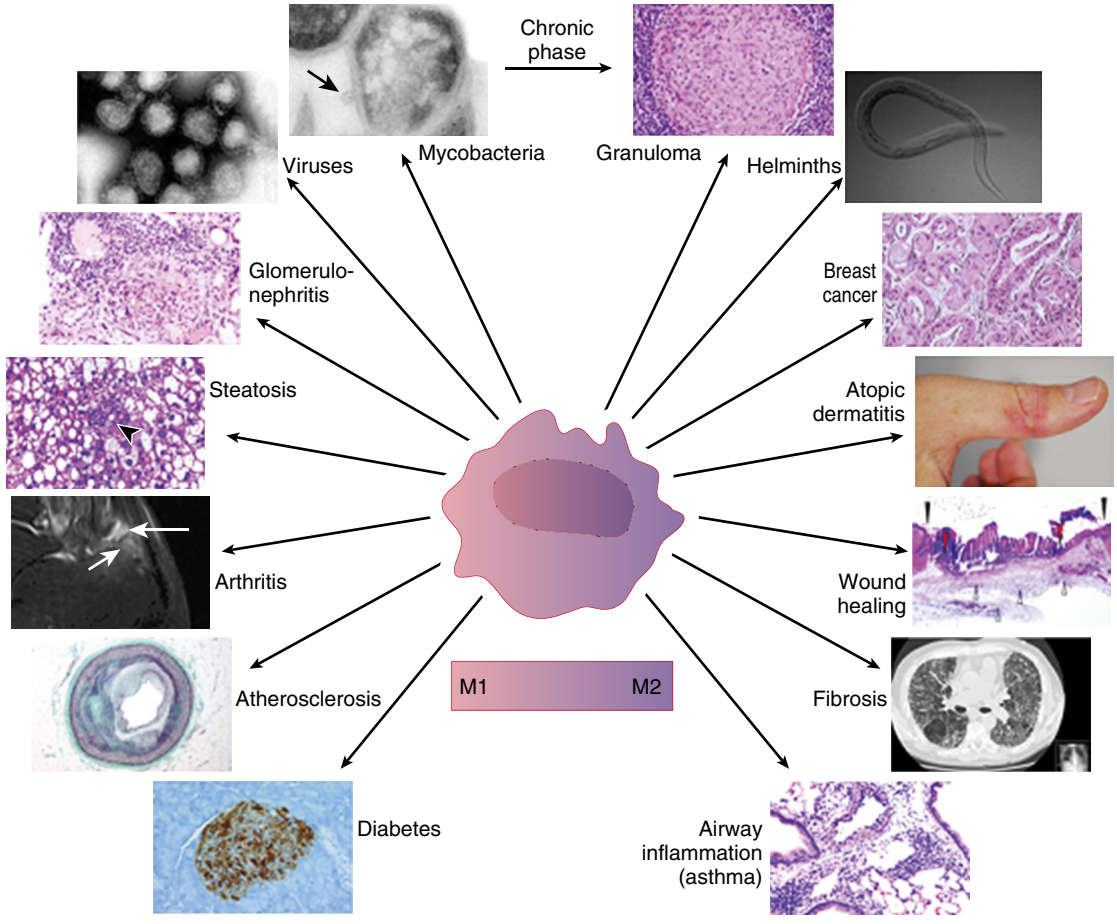

FIGURE 35-2. Schematic representation of macrophage plasticity and polarization in pathology. Dynamic changes occur over time with evolution of pathology: a switch from M1 (pro-inflammatory/classically activated) to M2 (anti-inflammatory/alternatively activated) macrophage polarization characterizes the transition from early to chronic phases of infection. Moreover, mixed phenotypes or populations with different phenotypes can coexist. (From Sica A, Mantovani A. Macrophage plasticity and polarization: in vivo veritas. *J Clin Invest*. 2012;122:787-795.)

mediators orchestrate a broad host defense program in response to virus infection (Fig. 35-2). Chemokine receptors include many family members that are differentially distributed among immune system cells and sense the gradient generated by soluble chemokines, resulting in attraction of cells to sites where they are needed to implement inflammatory or immune functions.

Signaling Pathways, Cell Differentiation, and Effector Mediators of the Innate Immune System

Each family of innate immune system receptors uses a complex network of molecules to transmit information from the cell surface or its cytoplasm to the nucleus, resulting in induction of a broad gene transcription and protein synthesis program that implements the next phase of the response. The contributions of each of the signal transduction pathways to the overall innate immune response will depend on the proteins produced and will determine whether the resulting cell products focus on ablating the damaging effects of virus infection on the host, limiting the inflammation and tissue damage that follow a bacterial or fungal infection, or healing a tissue wound through the production of scar tissue.

Receptor-Mediated Signaling Pathways

Certain common cell signaling systems are used by many cells and receptor systems. Arguably the most important is the nuclear factor κ light chain enhancer of activated B cells (NF-κB) pathway. NF-κB is a rapid-acting transcription factor because it preforms in cells of the innate immune system and does not require new protein synthesis to take action. Its activity is induced by ligation of Toll-like receptors and many cytokine receptors. Its component transcription factors translocate to the cell nucleus after degradation of an inhibitory component, inhibitor of κB (IκB), and bind to promoter regions of genes encoding mediators of inflammation and cell proliferation. Other important pathways are mediated by the IFN regulatory factor (IRF) family, including transcription factors that are activated by endosomal Toll-like receptors or by cytoplasmic nucleic acid sensors in response to ligation by DNA or RNA, usually from viral sources. IRF-3 is particularly important for promoting transcription of IFN-β, typically produced early in an antivirus innate immune response. IRF-7 is particularly supportive of IFN-α production induced by endosomal Toll-like receptors and is constitutively present in plasmacytoid dendritic cells, the most active producers of IFN-α.

The Janus kinase (JAK)–signal transducer and activator of transcription (STAT) pathway is used by many cytokine receptors and involves sequential enzymatic reactions by kinases that eventuate in translocation of STAT proteins to the nucleus, where they bind to gene promoters and induce transcription and synthesis of products important in implementing immunoregulation and inflammation.[19]

TNF receptor family members activate a complex signaling pathway that involves proteins called TNF receptor–associated death domain (TRADD) proteins and TNF receptor–associated factors (TRAFs), ultimately activating the NF-κB and the mitogen-activated protein (MAP) kinase pathways.

The TGF-β receptor is a serine/threonine receptor kinase that phosphorylates cytoplasmic proteins of the SMAD family, which act as transcription factors after receptor engagement by TGF-β. TGF-β signaling can play an important role in terminating an innate immune response and initiating a wound healing or tissue repair program.

It is apparent that common intracellular signaling strategies are used by many of the receptor systems that activate and regulate the innate immune system, with ligand-receptor engagement triggering the activation of kinases that phosphorylate downstream pathway proteins, and result in translocation of important transcription factors from cytoplasm to nucleus where new gene transcription takes place.

Soluble Products of the Innate Immune Response

Cells of the innate immune system are the principal producers of many proinflammatory and regulatory cytokines already mentioned and are also their targets. In addition to the cytokines described, cells of the innate immune system produce chemokines that attract immune system cells to sites of tissue

damage or infection, and they produce cell survival and differentiation factors that help to develop an adaptive immune response. Macrophages and dendritic cells produce IL-12 and IL-23 to support the development of effector T-cell programs, and they produce B-cell–activating factor (BAFF), a soluble member of the TNF family.[20] BAFF supports B-cell survival and can provide costimulatory signals to B cells that have received antigen-specific activation signals through their surface B-cell antigen receptors, promoting differentiation to antibody-producing plasma cells.

Components of the complement system, a group of plasma enzymes and regulatory proteins that are converted from inactive pro-enzymes to active enzymes in a controlled and systematic cascade, are crucial in linking microbial recognition to cellular effector function (Chapter 37). Mannose-binding lectin circulates in the plasma, functioning as an opsonin, and is involved in activation of the complement pathway. C-reactive protein, an acute phase protein, participates in opsonization by binding to bacterial phospholipids. Macrophages and neutrophils are important in the initiation phase of an innate immune response through their production of antimicrobial defensins, cysteine-rich cationic proteins, and cathelicidin peptides, such as LL37. Both categories of mediators can assist in killing of microbes in phagosomes. Neutrophils extrude stimulatory DNA in the form of neutrophil extracellular traps or release mitochondrial DNA, along with DNA-associated proteins like high-mobility group box 1 (HMGB1) that amplifies Toll-like receptor responses in plasmacytoid dendritic cells or macrophages.

Role of the Innate Immune System in Localization, Expansion, and Resolution of the Immune Response

Localization of Innate Immune System Cells

Most cells of the innate immune response are free agents, moving through blood or lymph in transit from one site to another. Mobility of those cells is required for effective initiation of a response to invading microbes. Cells use a multistep process of adherence and activation. Initially, leukocytes roll on activated endothelial cells, activate chemokine receptors, increase adhesiveness, and eventually migrate through the endothelial layer across a chemokine gradient. The selectin family of proteins mediates the first steps of leukocyte migration. P-selectin and E-selectin are expressed on activated endothelial cells, and P-selectin is also stored in platelets. Selectins capture floating leukocytes and initiate their attachment and rolling on activated endothelial cells. To transform attachment and rolling into firm adhesion, the concerted action of chemokines, chemokine receptors, and integrins is necessary. Integrins are heterodimers formed of many different α chains and β chains; different α/β combinations are expressed on different cell subsets. Only after activation can integrins interact with ligands on endothelial cells. Activation involves modification of the cytoplasmic domain of the β chain, which leads to a structural change of the extracellular domains. This process is termed *inside-out signaling*. The last step of homing is transendothelial migration. Here, the firmly attached leukocytes migrate through the endothelial cell monolayer and the basement membrane of the vessel wall.

Transition to an Adaptive Immune Response

Movement of innate immune system cells is also required to transition a host response from primarily one depending on cells of the innate immune system to one that engages T and B lymphocytes. Dendritic cells resident in the skin and gut serve as sentinels and a first line of defense against invading organisms. When those cells are activated following sensing of PAMPs by pattern recognition receptors and following uptake of microbial components by those cells, the dendritic cells migrate to local lymph nodes where their contents can be sampled by T cells. As noted, activated macrophages, dendritic cells, and plasmacytoid dendritic cells produce cytokines that shape the differentiation program of T cells. In addition, cell surface costimulatory molecules induced after Toll-like receptor-mediated activation, such as CD80 and CD86, provide essential accessory activation signals to T cells to ensure their effective activation. Macrophages and dendritic cells also support the development of an adaptive immune response through their production of survival and differentiation factors.

Role of Innate Immune System Cells in Resolution of an Immune Response and Wound Repair

Macrophages are particularly important in resolving an immune response and organizing the repair of damaged tissue. A classic paradigm describing pro-inflammatory/classically activated (M1) and anti-inflammatory/alternatively activated (M2) macrophages (see earlier under Monocytes and Macrophages) is likely to be overly simplistic. Yet it is clear that in the course of a chronic infection, macrophages can shift their functional profile from M1 to M2, in some cases promoted by the T-cell cytokines IL-4 and IL-13, to develop a gene expression program that includes production of TGF-β, supportive of a fibrotic response, and IL-10, a cytokine that inhibits antigen-presenting cell function. Although an M1-like profile driven by IFN-γ is highly productive in achieving initial control over a pathogenic invading microbe, and M2-derived mediators promote wound healing, it should be recognized that either macrophage phenotype, and complex in-between profiles, also can be associated with pathologic states (see Fig. 35-2). A family of polyunsaturated fatty acid (PUFA)-derived innate immune system mediators, termed specialized pro-resolving mediators, includes lipoxins, resolvins, protectins, and maresins.[21] These mediators stimulate clean up of inflammatory sites, limit further inflammation, and help to restore homeostasis following an episode of immune system activation. Current research is investigating the innate immune mechanisms that account for such diverse diseases as atherosclerosis (Chapter 65), viewed as associated with M1 macrophages, and idiopathic pulmonary fibrosis (Chapter 80), possibly involving M2-like macrophages, as well as the role of resolvins at sites of chronic inflammation such as rheumatoid synovial tissue.

CELLULAR ELEMENTS OF THE ADAPTIVE IMMUNE SYSTEM

T Cells

T precursor cells are derived from hematopoietic progenitors that migrate to the thymus, a primary lymphoid tissue, where all the subsequent stages of T-cell maturation occur (Fig. 35-3). Pre-T cells express two enzymes, RAG recombinase and terminal deoxynucleotidyl transferase, enabling them to recombine T-cell receptor genes. The β chain of the T-cell receptor is rearranged first and is expressed together with a pre-T-cell receptor α chain. Signals from the immature T-cell receptor complex induce thymocyte proliferation

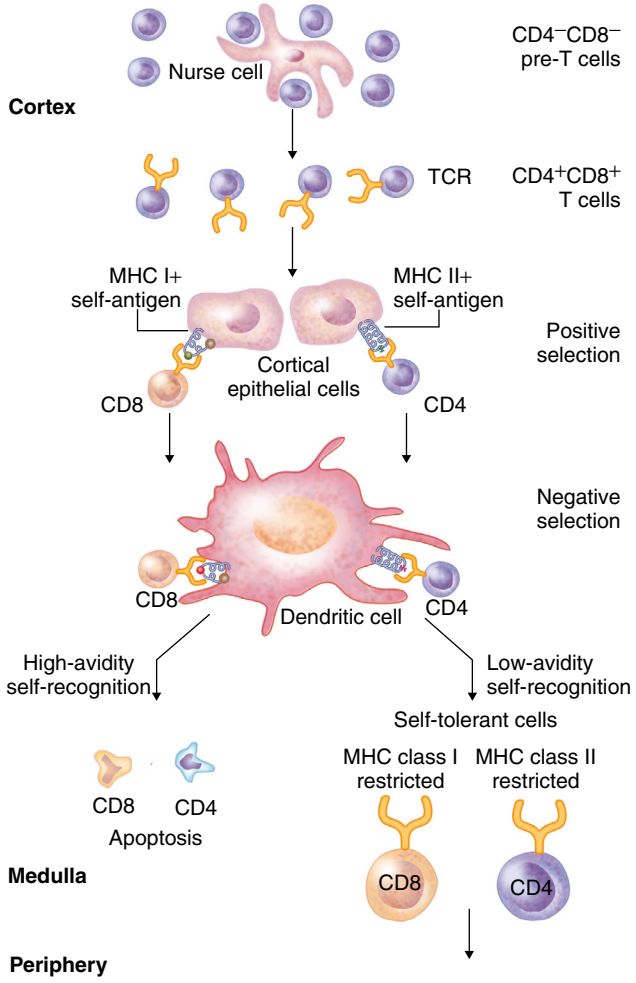

FIGURE 35-3. Maturation of T cells in the thymus. Precursors committed to the T-cell lineage arrive in the thymus and begin to rearrange their T-cell receptor (TCR) genes. Immature T cells with receptors binding to self–major histocompatibility complex (MHC) on cortical epithelial cells receive signals for survival (positive selection). At the corticomedullary junction, surviving T cells probe self-antigens presented by dendritic cells and macrophages. T cells reacting strongly to self-antigens are deleted by apoptosis (negative selection). T cells released into the periphery are tolerant toward self and recognize foreign antigens in the context of self-MHC.

and expression of both CD4 and CD8 molecules, so-called double-positive thymocytes. Subsequently, the T-cell receptor α chain is recombined, with formation of a mature T-cell receptor. From here, the thymocyte undergoes differentiation and selection steps modulated by the thymic microenvironment, thereby resulting in formation of a T cell that can migrate to secondary lymphoid tissues and is poised to recognize antigenic peptides.

Early-stage thymocytes reside in the thymic cortex, where they mostly interact with epithelial cells. They then migrate toward the medulla, encountering dendritic cells and macrophages at the corticomedullary junction. Thymic stromal cells regulate T-cell proliferation by secreting lymphopoietic growth factors, such as IL-7. Interactions of the T-cell receptor with MHC molecules expressed on epithelial cells and on dendritic cells or macrophages determine the fate of the thymocyte. Low-avidity recognition of peptide-MHC complexes on thymic cortical cells by the T-cell receptor results in positive selection, thereby rescuing cells from apoptotic cell death. Following positive selection, thymocytes migrate toward thymic medullary epithelial cells, which selectively express and present peripheral tissue antigens in order to mediate negative selection of autoreactive T cells. Thymocytes that express a receptor not fitting any MHC antigen complex die by neglect. High-affinity interaction between the T-cell receptor and peptide-MHC complex induces apoptotic death of the recognizing T cell. This process of negative selection eliminates T cells with specificity for self-antigens and is responsible for central tolerance to many autoantigens. While undergoing selection, T cells continue to differentiate. Double-positive thymocytes expressing both CD4 and CD8 engage either MHC-I or MHC-II with low-moderate affinity T-cell receptors, thereby resulting in differentiation to CD8 or CD4 single-positive T cells, respectively. These single-positive cells are now mature and ready for exit and migration to secondary lymphoid organs, including the spleen, lymph nodes, and mucosal lymphoid tissues, following chemokine cues and using adhesion molecules to enter. They exist in these tissues as quiescent naïve cells until receiving the appropriate antigenic signal for activation and development of subsequent effector function.

B Lymphocytes

Lymphoid stem cells differentiate into B-lineage cells in the bone marrow, supported by a specialized microenvironment of nonlymphoid stromal cells that supply necessary chemokines, including stromal cell–derived factor 1 (CXCL12) and cytokines (IL-7). Precursor B cells undergo sequential rearrangements of heavy chain and light chain immunoglobulin genes. On pre-B cells, the membrane μ chain is associated with a surrogate light chain to form a pre-B-cell receptor. Signals provided through this receptor induce proliferation of progeny that subsequently rearrange different light chain gene segments.

Immature B cells that express receptors directed against self-antigens are lost through negative selection and clonal deletion. Cross-linking of surface IgM by multivalent self-antigens causes immature B cells to die. Such self-reactive B cells can be rescued from death by replacing the light chain with a newly rearranged light chain that is no longer self-reactive, a process named *receptor editing*. On maturation, B cells begin additionally to express surface IgD. B cells positive for IgD and IgM are exported from the bone marrow and migrate to peripheral lymphoid tissues following a chemokine gradient (Fig. 35-4). Colocalization of T and B cells in secondary lymphoid tissues facilitates their interaction following a pathogen challenge. This response enables B cells to receive T-cell help for the former's activation and differentiation to generate memory cells and allows the antibody secretion that is required for responses to protein antigens.

PRINCIPLES OF ADAPTIVE IMMUNE SYSTEM ACTIVATION: RECOGNITION OF ANTIGEN AND GENERATION OF EFFECTOR FUNCTION

Lymphocytes and Lymphoid Tissue

The immune system uses specialized lymphoid microstructures to bring antigens to the site of lymphocyte traffic and accumulation. Secondary lymphoid organs include the spleen for blood-borne antigens, the lymph nodes for antigens encountered in peripheral tissues, and the mucosa-associated, bronchial-associated, and gut-associated lymphoid tissues, where antigens from epithelial surfaces are collected. Lymphocytes circulate through secondary lymphoid organs, constantly searching for their antigen.[22] Their homing to lymph nodes is facilitated by specialized microvessels, called high endothelial venules, which provide the proper structure for them to leave the circulation and enter the tissue. Secondary lymphoid tissues have developed several

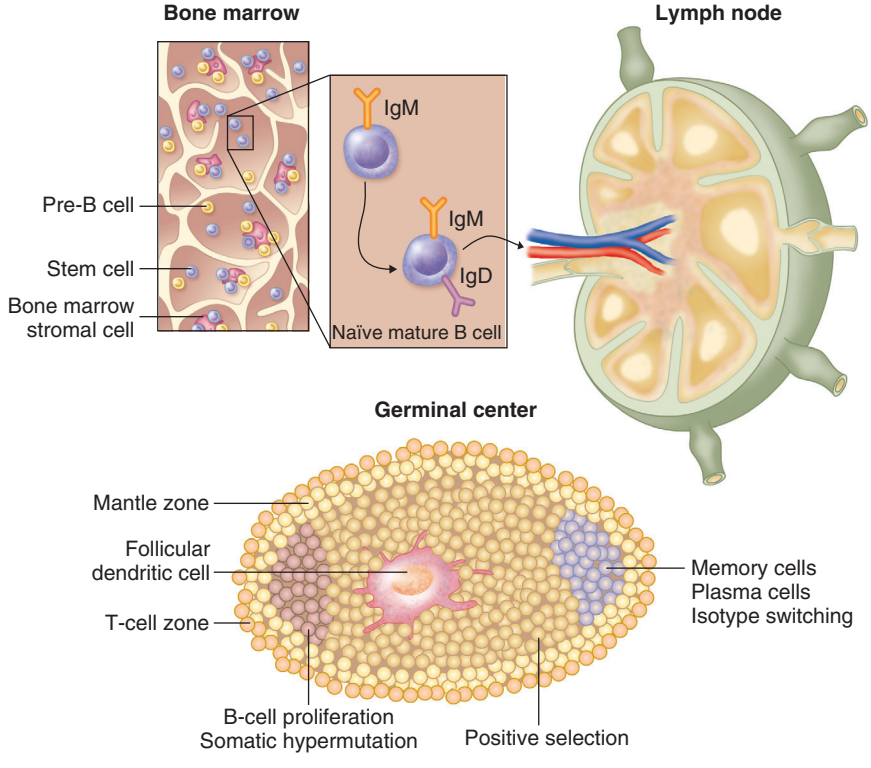

FIGURE 35-4. B-cell development and differentiation. The early stages of B-cell development occur in the bone marrow, with cells progressing through a developmental program determined by the rearrangement and expression of immunoglobulin (Ig) genes. Immature B cells with receptors for multivalent self-antigens die in the bone marrow. Surviving B cells coexpress IgD and IgM surface receptors. They are seeded into peripheral lymphoid organs, where they receive signals to survive. Antigen-binding B cells and antigen-presenting B cells that receive help from antigen-specific T cells are activated through membrane-bound and secreted molecules. Activated B cells migrate into the follicles, forming germinal centers, and undergo somatic hypermutation of immunoglobulin genes. Cells with high affinity for antigens presented on the surface of follicular dendritic cells are selected to differentiate into long-lived antibody-secreting plasma cells that migrate to the bone marrow. Cells differentiating into long-lived memory B cells have a range of antigen affinities, enabling more diverse responses upon reinfection by pathogens.

strategies to sequester the relevant antigen. Antigens in peripheral tissue are encountered first by dendritic cells that, after activation, are mobilized to transport antigens into the local lymph nodes by the draining lymph. These antigen-bearing dendritic cells enter the lymph nodes through the afferent lymphatic vessel and settle in the T-cell–rich zones to present processed antigens to T cells. The net result of this process is an accumulation and concentration of the antigen in an environment that can be readily screened by infrequent antigen-specific T cells.

B cells are segregated from T cells in the lymph nodes and are localized in follicles. Naïve B cells may engage antigen as they circulate through secondary lymphoid tissues, for example as presented to them by migratory dendritic cells or macrophages in the subcapsular region of lymph nodes. If, on antigen engagement, B cells find their cooperating (cognate) T cells at the borders of the T-cell–rich areas and the follicle, they both receive cues to enter germinal centers and send similar signals back to their cognate follicular helper T cells. Germinal centers contain a network of follicular dendritic cells that capture particulate antigen or immune complexes on the cell surface. This unprocessed antigen is taken up by antigen-specific B cells, processed and presented, and recognized by antigen-specific T_{FH} cells. Germinal centers are essential for generating long-lived antibody-secreting plasma cells and memory B cells.

Antigen Processing and Presentation

T cells bearing α/β T-cell receptors recognize peptide fragments that are displayed in the context of MHC class I and class II molecules through a process termed antigen presentation. The two classes of MHC molecules are used as restriction elements by two different subsets of T cells. $CD4^+$ T cells recognize antigenic peptides embedded into MHC class II molecules, whereas $CD8^+$ T cells bind peptides complexed with MHC class I molecules. Generally, MHC class II molecules are expressed only on specialized, so-called professional, antigen-presenting cells, such as dendritic cells, monocytes, macrophages, and B cells, whereas class I proteins are displayed by virtually all nucleated cells, facilitating recognition by $CD8^+$ T cells of peptides from viruses that often have a broad range of target tissues. Peptides bound to MHC class II molecules typically derive from extracellular antigens that are captured and internalized into endosomes to be digested by proteinases, notably cathepsin. Occasionally, however, intracellular proteins or membrane proteins are also funneled into this pathway. MHC class II molecules are assembled in the endoplasmic reticulum in association with a protein called the invariant chain (Fig. 35-5). The molecules are transported to the endosome, where the invariant chain is removed from the peptide-binding cleft, making the cleft accessible to peptides derived from extracellular proteins. MHC class II molecules, stabilized by peptides of 10 to 30 amino acids in length, are displayed on the cell surface, where they are recognized by $CD4^+$ T cells.

MHC class I–associated peptides are generated in the cytosol by the proteasome, a large cytoplasmic multiprotein enzyme complex (see Fig. 35-5), thereby allowing killer $CD8^+$ T cells to recognize microbial peptides produced within infected cells. Specialized transporter proteins, called transporter in antigen processing (TAP), facilitate translocation of peptides from the cytosolic proteasome to the endoplasmic reticulum. There, the peptides bind to newly formed MHC class I molecules and are transported to the cell surface, where they are recognized by antigen-specific $CD8^+$ T cells. MHC class I–associated peptides may also originate in the extracellular environment and be presented to T cells through the appropriately named cross-presentation pathway. This pathway enables $CD8^+$ T cells to recognize foreign peptides (e.g., from viruses) that are derived from infected and dying cells that are ingested by myeloid cells and then presented by MHC class I molecules.

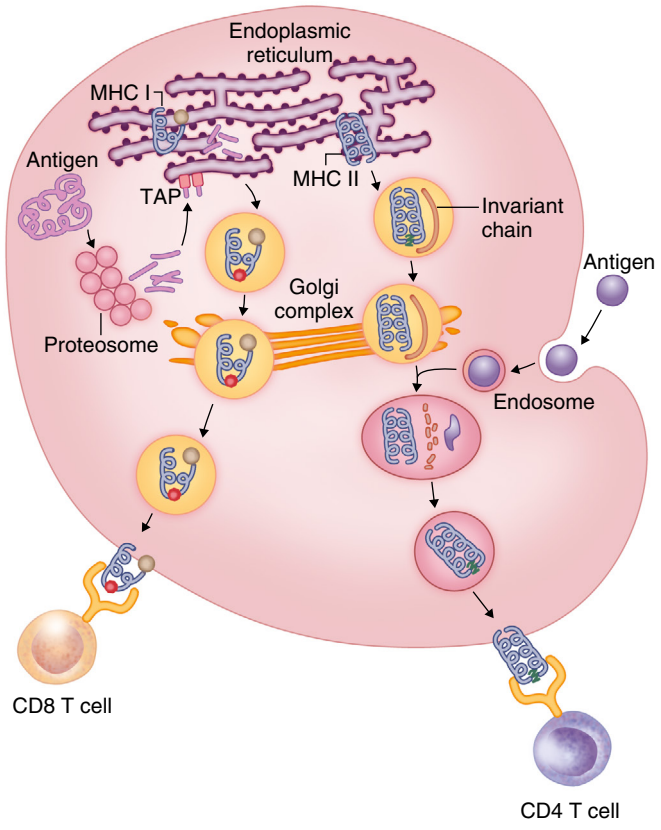

FIGURE 35-5. Pathways of antigen processing and delivery to major histocompatibility complex (MHC) molecules. Cytosolic proteins are broken down by the proteosome to generate peptide fragments, which are transported into the endoplasmic reticulum by specialized peptide transporters (TAP). After peptides are bound to MHC class I molecules, MHC-peptide complexes are released from the endoplasmic reticulum and travel to the cell surface, where they are ligands for $CD8^+$ T-cell receptors (TCRs). Extracellular foreign antigens are taken into intracellular vesicles, called *endosomes*, and proteases are activated that digest antigens into peptide fragments. After fusing with vesicles that contain MHC class II molecules, antigenic peptides are placed in the antigen-binding groove. Loaded MHC class II–peptide complexes are transported to the cell surface, where they are recognized by the TCRs of $CD4^+$ T cells.

Structure of Antigen-Specific Receptors

T-Cell Receptors

T-cell receptors are dimers of α chains and β chains or of γ chains and δ chains, each of which contains three complementarity-determining binding sites in the N-terminal domain. These complementarity-determining sites define the specificity of the T-cell receptor. Most α/β T-cell receptors recognize peptide fragments in the context of MHC molecules, although certain ones bind glycolipid antigens, for example, from mycobacteria, displayed by molecules with structural similarity to MHC. γ/δ T-cell receptors are more variable and can recognize peptides or certain glycolipid antigens in the context of MHC-like molecules, or even unprocessed antigens.

Antibodies

Antibodies consist of two identical heavy chains and two identical light chains, which are covalently linked by disulfide bonds. The amino (N)-terminal domain of each chain is variable and represents the recognition structure that interacts with the antigen. Each antibody has two binding arms of identical specificity. The carboxy (C)-terminal ends of the heavy and light chains form the constant region, which defines the subclass of the antibody (κ or λ for light chains; IgM, IgA, IgD, IgE, or IgG for heavy chains). Additional subclasses can be distinguished for IgG and IgA. The constant region of antibodies includes the Fc region. Fc regions can polymerize (IgA) or pentamerize (IgM), both in the presence of a J (joining) chain. Fc regions are also the ligand for Fc receptors (FcRs) on cells of the innate immune system.

Specificities of T-Cell Receptors and Antibodies

The repertoires, or total number of specificities, of T-cell receptors and antibodies are extremely diverse and have been estimated in the human to account for up to 10^{18} or higher and 10^{11} combinations, respectively. This enormous diversity reflects the anticipatory nature of adaptive immune receptors and must be acquired; it cannot be genetically encoded in contrast to that of innate receptors. T-cell receptor β chains and δ chains are assembled by the recombination of variable, diversity, joining, and constant region segments of T-cell receptor genes. Immunoglobulin heavy chains are formed from four gene segments—the variable, diversity, joining, and constant region gene segments. Also, immunoglobulin light chains and T-cell receptor α chains and γ chains lack the diversity segment and are composed of three gene segments. During T-cell receptor or antibody rearrangement, gene segments are cut out by nucleases and recombined at the DNA level to form linear coding units for each receptor gene. An enormous diversity of receptors is generated as each receptor or antibody uses a different combination of gene segments; the recombination and repair process is imprecise, introducing nucleotide variations at the variable-diversity, diversity-joining, and variable-joining junctions; and random nucleotides can be inserted at the junctional region by an enzyme, terminal deoxyribonucleotidyl transferase.

Once generated, T-cell receptor sequences remain unchanged. This rule does not apply to immunoglobulins, which undergo modification, including replacement of an entire variable region, or receptor editing, to modify those receptors that inadvertently bind self-antigens; class switching, in which the variable-diversity-joining unit combines with different constant region genes; or somatic hypermutation, in which the antigen-contact areas of the antibody undergo mutations to improve the affinity. The latter two events occur in secondary lymphoid tissues, such as the spleen, lymph nodes, and mucosal lymphoid tissue, where immune responses to antigens are initiated.

T-Cell Stimulation and Accessory Molecules

MHC-peptide recognition by the T-cell receptor, the first signal for T-cell activation, leads to receptor clustering and phosphorylation of the intracellular portion of the CD3 protein complex, the signaling component of the receptor, by receptor-associated tyrosine kinases. These events transmit signals to the nucleus and initiate activation of the T cell. The coreceptors CD4 and CD8, through their interaction with MHC class II and class I molecules, respectively, support CD3-mediated signals. This first activation signal delivered by the T-cell receptor and coreceptors needs to be complemented by the interaction of accessory molecules on the T cell and their ligands on the antigen-presenting cell. A spectrum of accessory molecules has been identified, of which the best known is CD28, which are engaged by CD80 and CD86 on antigen-presenting cells. Engagement of CD28 provides to the T cells a second, or costimulatory, signal that ensures T-cell survival and expansion. CD28-mediated signals are mandatory for the expression of many activation markers on the responding T cells and, in particular, for the secretion of IL-2. In the absence of such a second signal, T cells are rendered nonresponsive and anergic or undergo apoptosis. Additionally, adhesion molecules (integrins) stabilize the interactions between T cells and antigen-presenting cells. Signals from the T-cell receptor result in the activation of many genes and entry of the T cell into the cell cycle.

Three major variables determine the outcome of T-cell receptor stimulation: the duration and affinity of the T-cell receptor-antigen interaction, the maturation stage of the responding T cell, and the nature of the antigen-presenting cell. Antigen-presenting cells are gatekeepers in the initiation of T-cell responses. They can upregulate the expression of accessory molecules that provide costimulatory signals. MHC-peptide complexes are particularly dense on dendritic cells, enabling them to activate naïve T cells. In contrast, memory and effector cells have a lower threshold for activation and can react to antigens presented on peripheral tissue cells.

Another set of accessory molecules can limit the activation of T cells and have been identified as therapeutic targets, with inhibitors promoting activation and expansion of T cells with potential to inhibit or eliminate tumor cells.[23] CTLA-4 and PD-1 are expressed on T cells after cell activation and limit their expansion when ligated by CD80 or CD86 or PD-L1, respectively, but the so-called immune checkpoint inhibitors block those accessory molecules, with the goal of reversing peripheral tolerance to tumor antigens.

B-Cell Stimulation and Accessory Molecules

Mature, but naïve, B cells in secondary lymphoid organs are activated by soluble and cell-bound antigens to develop into antibody-secreting effector cells. B cells respond to a large variety of antigens, including proteins, polysaccharides, and lipids. Binding of antigen to cell surface IgM molecules induces B-cell receptor clustering, the initial step in B-cell activation. In addition to the antigen-binding immunoglobulin, the B-cell receptor comprises two proteins, Ig-α and Ig-β. The Ig-α/Ig-β heterodimer functions to transduce a signal and initiates the intracellular signaling cascade, analogous to the CD3 molecule of the T-cell receptor. Thus, the composition of the B-cell receptor, with ligand-binding and signal-transducing units, and the signaling events that lead to gene induction, are similar to those of the T-cell receptor. Both receptors are enhanced by coreceptors. The B-cell receptor-coreceptor complex is composed of CD81, CD19, and CD21, analogous to the T-cell receptor coreceptors CD4 and CD8. CD21 binds to complement fragments on opsonized antigens that are bound by the B-cell receptor, thereby resulting in phosphorylation of the intracellular tail of CD19 by tyrosine kinases and augmentation of the B-cell receptor–mediated signal.

Like naïve T cells, naïve B cells require accessory signals in addition to triggering of their antigen-binding receptor. They receive second signals either from follicular helper T cells or from thymus-independent antigens such as bacterial polysaccharides that can induce antibody production in the absence of helper T cells.[24] In contrast, in the case of protein antigens, which are thymus- or T-dependent, the initial B-cell receptor stimulation prepares the cell for subsequent interaction with follicular helper T cells. These activated B cells start to enter the cell cycle; upregulate cell surface molecules, such as CD80 and CD86, which provide costimulatory signals to T cells; and upregulate certain cytokine receptors. As such, these B cells are prepared to activate helper T cells and to respond to cytokines secreted by those T cells, but they cannot differentiate into antibody-producing cells in the absence of T-cell help. Survival and differentiation factors produced by myeloid cells, such as B-cell–activating factor, also stimulate B cells and help to maintain the B-cell pool.

Signaling Pathways, Cell Differentiation, and Effector Mediators of the Adaptive Immune System

T-Cell Differentiation

T-cell activation induces T-cell proliferation, with the goal of clonally selecting and expanding antigen-specific T cells. Antigen-specific $CD8^+$ T cells expand several thousand–fold; $CD4^+$ T cells expand somewhat less. During the phase of rapid growth, T cells differentiate from naïve T cells that are essentially devoid of effector functions into effector T cells that are needed for clearance of infectious organisms, or pathogens. The transition into effector cells is associated with a fundamental shift in functional profiles. First, effector T cells do not require costimulation to function and can scan tissues that lack professional antigen-presenting cells. Second, they switch the expression of chemokine receptors and adhesion molecules to gain access to peripheral tissues. Finally, they gain effector functions.

The principal effector function of $CD8^+$ T cells is to lyse infected, antigen-bearing target cells. On activation, $CD8^+$ T cells acquire cytotoxic functions and, using a variety of receptors and adhesion molecules, can emigrate from secondary lymphoid organs to peripheral tissue sites seeking cells infected by viruses or intracellular bacteria displaying pathogen-derived peptides on MHC class I molecules. On recognizing the appropriate MHC class I–peptide complex, $CD8^+$ T cells induce apoptosis of target cells using specialized lytic granules. A pore-forming protein, perforin, is released from the lytic granules and inserted into the target cell membrane. Proteases (granzymes) are injected into the target cells to initiate the apoptotic process by activating enzyme cascades. $CD4^+$ T cells can also induce apoptosis but by a different mechanism. On activation, they express cell surface molecules such as Fas ligand (CD178) and TRAIL, which initiate the apoptotic cascade selectively in cells expressing the respective ligands Fas (CD95) or the death receptors DR4 and DR5.

Compared with $CD8^+$ T cells, the spectrum of options for $CD4^+$ T cells is larger. They are generally characterized as helper T, or T_H, cells because they produce cytokines and express cell surface molecules that promote the effector function of other lymphocytes and phagocytes. On activation, different subsets of $CD4^+$ effector T cells can be distinguished based on the preferential production of certain cytokines (see E-Table 35-1). T_H1 T cells predominantly produce IFN-γ and tumor necrosis factor-α (TNF-α) and are involved in cell-mediated immunity, such as delayed-type hypersensitivity reactions. These cytokines, among other actions, promote macrophage activation that is critical for protective responses against intracellular pathogens such as mycobacteria and listeria. T_H2 T cells preferentially produce IL-4, IL-5, and IL-13, cytokines that promote eosinophil maintenance, expansion, and tissue accumulation, as well as macrophage function; these are all important for host protection following infection with helminths, such as schistosomes and other worms. T_H17 T cells produce IL-17, critical for neutrophil expansion and function, with killing of extracellular bacteria, such as streptococci, and pathogenic fungi. These cells may also produce IL-22 that promotes host-protective function at barrier surfaces, such as the skin and gut. Follicular helper T (T_{FH}) cells home to lymphoid follicles, where B cells congregate, where they express CD40 ligand (CD154) and other surface proteins along with cytokines, including IL-21, IL-4, and IFN-γ, that are critical for B-cell maturation to plasma cells and memory B cells. The decision as to which differentiation pathway to take is made during the early stages of naïve T-cell activation by antigen-presenting cells in secondary lymphoid organs. Pathway differentiation depends on several factors, including (1) the cytokines produced by the activating antigen-presenting cell and other innate cells in the microenvironment, (2) the nature of costimulatory signals, and (3) the avidity of the T-cell receptor-MHC antigen interaction. $CD4^+$ T-cell subset, or lineage, development is generally correlated with the expression of specific transcription factors (T-bet for T_H1, GATA3 for T_H2, RORγt for

E-TABLE 35-1 CYTOKINES AND CYTOKINE FUNCTION

CYTOKINES	MAJOR PRODUCER CELLS	PRINCIPAL ACTION
HEMATOPOIETIN FAMILY		
IL-2	T cells	Proliferation of T cells, B cells, and NK cells
IL-3	T cells	Early hematopoiesis
IL-4	T cells, mast cells	B-cell activation, IgE switch, inhibition of T_H1 cells
IL-5	T cells, mast cells	Eosinophil growth and differentiation
IL-6	Macrophages, endothelial cells	T-cell and B-cell growth and differentiation, induction of acute phase proteins
IL-7	Bone marrow, thymic epithelium	Growth of pre-B cells and pre-T cells
IL-9	T cells	Stimulation of mast cells and T_H2 cells
IL-11	Stromal fibroblasts	Hematopoiesis
IL-13	T cells	B-cell growth and differentiation, inhibition of T_H1 cells and macrophages
G-CSF	Fibroblasts and monocytes	Neutrophil development and differentiation
IL-15	Non-T cells	Growth of T cells and NK cells
GM-CSF	Macrophages, T cells	Growth and differentiation of myelomonocytic lineage cells
INTERFERON FAMILY		
IFN-α	Plasmacytoid dendritic cells, other leukocytes	Antiviral, induction of coordinated interferon-stimulated gene transcriptional response
IFN-β	Fibroblasts	Antiviral, induction of coordinated interferon-stimulated gene transcriptional response
IFN-γ	T cells, NK cells	Macrophage activation, increases expression of MHC molecules, Ig class switching, inhibition of T_H2 cells
TUMOR NECROSIS FACTOR FAMILY		
TNF-α	Macrophages, NK cells, T cells	Induction of pro-inflammatory cytokines, endothelial cell activation, apoptosis
TNF-β (LT-α)	T cells, B cells	Cell death, endothelial activation, lymphoid organ development
LT-β	T cells, B cells	Cell death, lymphoid organ development
OTHERS		
TGF-β	Monocytes, T cells	Anti-inflammatory, inhibits cell growth, induces IgA secretion
IL-1α, IL-1β	Macrophages, endothelial cells	Acute phase response, fever, macrophage activation, costimulation
IL-10	T cells, macrophages	Suppression of macrophage functions
IL-12	Macrophages, dendritic cells	NK cell activation, T_H1 cell differentiation
IL-16	T cells, mast cells, eosinophils	Chemoattractant for CD4 T cells, monocytes, and eosinophils
IL-17	CD4 T cells	Cytokine production by epithelia, endothelial cells, and fibroblasts
IL-18	Macrophages	IFN-γ production by T cells and NK cells
IL-23	Macrophages, dendritic cells	T_H17 cell differentiation

CD = cluster of differentiation; G-CSF = granulocyte colony-stimulating factor; GM-CSF = granulocyte-macrophage colony-stimulating factor; IFN = interferon; Ig = immunoglobulin; IL = interleukin; LT = lymphotoxin; MHC = major histocompatibility complex; NK = natural killer; TGF = transforming growth factor; T_H = helper T lymphocyte; TNF = tumor necrosis factor.

T_H17, and Bcl6 for T_{FH} cells). However, lineage commitment among differentiated $CD4^+$ T cells is not absolute, and transition between different effector types is possible.

Regulatory T Cells

Depending on their cytokine profile, $CD4^+$ T cells have the ability to cross-regulate each other, influence T-cell differentiation, and suppress T-cell effector activity. T cells with regulatory activity generated during the normal immune response are IL-10– and transforming growth factor-β (TGF-β)–producing cells. In addition, specialized subsets of regulatory T (Treg) cells are characterized by expression of the transcription factor forkhead box P3 (Foxp3).[25] Naturally occurring $Foxp3^+$ Treg cells are generated during T-cell development in the thymus and recognize self-antigens. $Foxp3^+$ Treg cells can also arise from conventional $CD4^+$ T cells in the periphery. Treg cells are important in peripheral tolerance, controlling the expansion of autoreactive T cells. They also play a role in immune responses to pathogens by virtue of their ability to suppress T-cell effector function and consequently downmodulate the inflammatory response incited by the former, a natural consequence of pathogen elimination. Treg cells may also specialize according to their tissue environment, for example, selectively to regulate inflammation promoted by T_H1, T_H2, and T_H17 cells, respectively, and to regulate T_{FH} cells that drive production of autoantibodies by B cells in autoimmune diseases. A principal difference between natural and induced Treg cells is that the latter largely survey mucosal and other environmentally exposed surfaces.

In addition to secretion of IL-10 and TGF-β, which can dampen inflammatory responses, and functioning as a sink for pro-inflammatory cytokines such as IL-2, Tregs may also express the T-cell molecule cytotoxic T-lymphocyte antigen (CTLA)-4 (CD152) that, like CD28, engages CD80 and CD86 on antigen-presenting cells. In contrast to CD28, which receives a positive signal from CD80 and CD86, engagement of these molecules on antigen-presenting cells by CTLA-4 on Tregs suppresses the ability of antigen-presenting cells to activate naïve T cells.

T-Cell Homeostasis

Effective immunity depends on the ability of the immune system to generate large numbers of antigen-specific T cells rapidly, yet the space in the T-cell compartment is limited. To avoid competition for space and resources and to prevent perturbation of T-cell diversity by lifelong exposure to antigens, the adaptive immune system employs several counterbalancing mechanisms. In the later stages of the activation process, a strong negative signal derives from interaction of CTLA-4 with CD80/CD86 on antigen-presenting cells. In addition, T cells undergo activation-induced cell death. Activated $CD4^+$ T cells begin to secrete Fas ligand and acquire sensitivity to Fas-mediated death, inducing apoptotic suicide and fratricide in neighboring T cells. These mechanisms impose constraints in the early stages of the T-cell antigen response. Other mechanisms control the rapid decline of expanded antigen-specific T cells when elimination of the antigen has been achieved. Removal of the driving antigen causes a deprivation of cytokines and costimulatory molecules, and growth factor–deprived T cells die from apoptosis. It has been estimated that only 5% of the antigen-expanded population survives after antigen clearance, becoming memory cells that are poised to respond if the host is again challenged by the same offending pathogen.

B-Cell Differentiation

Differentiation of B cells activated by protein antigens depends on interaction with helper T cells. B cells use their antigen receptor not only to recognize antigens but also to internalize them. After processing endocytosed antigens, MHC class II–peptide complexes appear on the cell surface, where antigen-specific $CD4^+$ T cells detect them. Also, B cells express costimulatory molecules and provide optimal conditions for T-cell activation. On activation, $CD4^+$ T cells express CD154, also known as CD40 ligand, on their surface and are able to stimulate the CD40 molecule on their B-cell partner. CD40-CD154 interaction is essential for subsequent B-cell proliferation and differentiation. Cytokines secreted by the helper T cells act in concert with CD154 to amplify B-cell differentiation and to determine the antibody type by controlling isotype switching. Cytokines drive isotype switching by stimulating the transcriptional activation switch regions upstream of heavy chain constant region genes and ultimately facilitating excision of the IgM heavy chain gene and recombination of the VDJ segments with one of the downstream constant regions, IgG, IgA, or IgE. A population of B cells that is prominent in aging, in autoimmune disease and after virus infection or vaccination, called age-associated B cells (ABCs), appears to require signals through endosomal TLR-7, along with B-cell receptor and cytokine signals, for differentiation to autoantibody-secreting cells.[26]

T-cell–dependent B-cell differentiation and maturation take place in germinal centers, specialized areas in secondary lymphoid tissues where B cells rapidly proliferate and mutate the variable, or antigen-binding portion, of their immunoglobulin surface receptors. Those B cells bearing receptors with mutations that confer the highest affinity for antigen are selected for survival with the help of specific signals delivered by follicular helper T cells, whereas those with mutations conferring lesser affinity die by apoptosis. This process enables affinity maturation of B cells that most efficiently bind antigen and thereby facilitate antigen removal and pathogen clearance.

Generating Memory and Tolerance

Memory

An important consequence of adaptive immunity is the generation of immunologic memory, the basis for long-lived protection after a primary infection. Memory induction by vaccination is one of the landmark successes in medicine. Immunologic memory is defined as the ability to respond more rapidly and effectively to pathogens that have been encountered previously. As a direct result of clonal expansion and selection in antigen-driven responses, the frequencies of antigen-specific memory B cells and memory T cells are increased 10-fold to 1000-fold compared with the naïve repertoires. In addition to increased frequencies, memory T cells and B cells are functionally different from their naïve counterparts. Memory cells are long-lived and survive in the presence of certain cytokines without the need for continuous antigenic stimulation, guaranteeing immunologic memory for the life expectancy of the individual cell. Memory B cells produce predominantly IgG and IgA antibodies with evidence of somatic hypermutation and high affinity for the antigen. High-affinity IgE antibodies are also produced upon challenge with certain pathogens, such as helminths, and upon allergen exposure. Cell surface expression of high-affinity antibodies allows more efficient antigen uptake, thereby enhancing the crucial interaction with T cells. On antigen encounter, memory B cells change to antibody-secreting plasma cells, or re-enter the germinal center, where the high affinity of their immunoglobulin receptor gives them a competitive advantage over naïve B cells in antigen binding, leading to affinity maturation of somatically mutated antibody molecules.

Because the T-cell receptor does not undergo isotype switching or affinity maturation, memory T cells are more difficult to distinguish from naïve or effector T cells. Memory T cells lack activation markers and need antigen stimulation to resume effector functions. In contrast to naïve T cells, memory T cells have a lower activation threshold and are less dependent on costimulatory signals. In essence, their requirements for antigen stimulation are fewer, and their clonal size is larger, permitting fast, efficient responses to secondary antigen encounters.

Tolerance

Unresponsiveness to self is a fundamental property of the immune system and is required to maintain tissue integrity of the host. Because of the extraordinary complexity and variability of the repertoires of T- and B-cell antigen receptors, mechanisms of self/nonself discrimination are particularly applicable to the adaptive immune system. For T and B cells, antigen-specific receptors are generated randomly, and the entire spectrum of antigens can be recognized. Several different mechanisms are used, collectively called *tolerance*.[27] Tolerance in the adaptive immune system is antigen specific, and failure of self-tolerance results in immune responses against self-antigens. In central tolerance, self-reactive lymphocytes are deleted during development. In the bone marrow, B cells that express receptors directed against self-antigens are eliminated through clonal deletion. The process of negative selection is particularly important for T cells, and mutations in a gene called *AIRE* are associated with failure to delete self-reactive cells effectively in the thymus.[28] Even in the healthy setting, not all self-reactive T cells are centrally purged from the repertoire, and all T cells have some degree of self-reactivity, which is necessary for positive selection in the thymus and peripheral survival. Mechanisms of peripheral T-cell tolerance include (1) anergy, (2) peripheral deletion, (3) clonal ignorance, and (4) suppression of immune responses by regulatory T cells. T-cell anergy is transient and is actively maintained. MHC-peptide presentation to T cells by immature or inactivated, resting antigen-presenting cells or on cells other than peripheral antigen-presenting cells results in anergy because of the lack of expression of costimulatory molecules. Peripheral deletion is induced as a consequence of hyperstimulation.

Hyperstimulation of T cells (e.g., by high doses of antigen and high concentrations of IL-2) preferentially activates pro-apoptotic pathways and causes elimination of the responding T-cell specificity. Clonal ignorance is defined as the presence of self-reactive lymphocytes that fail to recognize or respond to peripheral antigens. These cells remain responsive to antigenic challenge if given in the right setting. An example of clonal ignorance is nonresponsiveness to sequestered antigens that are not accessible to the immune system. Treg cells play a pivotal role in maintaining peripheral tolerance. Harnessing the frequencies and function of Foxp3 $CD4^+$ T cells may offer a promising approach to restoring peripheral tolerance in treating autoimmune diseases or facilitating transplantation tolerance.

A critically important mechanism of peripheral B tolerance is maintained through the absence of T-cell help. B lymphocytes that recognize self-antigens in the periphery in the absence of T-cell help are rendered anergic or are unable to enter lymphoid follicles, where they could receive T-cell help, effectively excluding them from immune responses.

CONTRIBUTION OF THE INNATE AND ADAPTIVE IMMUNE RESPONSES TO PATHOGENESIS OF DISEASE

Immunodeficiency and Autoimmunity

Characterization of genetic polymorphisms and mutations in immune system genes that are associated either with apparent vulnerability to infection or inappropriate self-reactivity and autoimmunity has provided important insights into immune mechanisms that are essential for host defense and maintenance of immune tolerance. Mutations in components of innate and adaptive immune system pathways that recognize, respond to, or regulate the response to viruses or bacteria characterize immunodeficiencies that can be life-threatening (see Chapter 231).[29] In some cases, those vulnerabilities are revealed only in the setting of an infection with an agent not previously encountered. For example, recent reports describe previously healthy men who developed severe disease in the setting of severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2) infection and were found to have mutations in the *TLR7* gene, thereby impairing the type I IFN response.[30]

Autoimmune and inflammatory diseases occur in about 5% of the general population. The mechanisms that account for the generation of autoreactive T cells, responses directed to modified self-antigens, and the well-established associations of certain MHC alleles with autoimmune diseases are areas of active investigation.[31] Although many autoimmune diseases may result from failure of tolerance mechanisms or dysfunction of the regulatory pathways that control adaptive immune responses, excessive activation of an innate immune response can set the stage for a self-reactive T- or B-cell response. Polymorphisms in genes encoding components of innate immune signaling pathways can amplify an immune response, thereby resulting in increased and sustained production of type I IFN, IL-1, or TNF-α. Endogenous ligands with potential to activate Toll-like receptors can act as effective immune stimuli in the setting of a pro-inflammatory environment associated with oxidative or apoptotic cell damage. Alterations in degradation of endogenous RNA and DNA based on single-gene mutations can result in activation of cytosolic nucleic acid sensors, sustained type I IFN production, skin lesions, and central nervous system involvement in diseases termed type I interferonopathies.[32] The inflammasome and its component proteins, including the NOD-like receptors, are recognized as mediators of inflammatory responses induced in some autoinflammatory syndromes (Chapter 240).

Many models of autoimmunity rely on the hypothesis that peripheral anergy is broken. Microbial infection or bacterial components in the gut microbiome (Chapter 257) may trigger an immune response that primes the immune system for an exaggerated and self-directed response to a subsequent trigger through epigenetic modifications.[33] Autoreactive B cells that recognize self-antigen complexed with foreign antigen may result in activation of T cells specific for the foreign antigen that then provide help to B cells specific for the self-antigen. Tolerance mechanisms of anergy or clonal ignorance can fail if a foreign antigen is sufficiently different from a self-antigen to initiate an immune response but sufficiently similar for activated T cells to elicit T-cell and B-cell effector functions (molecular mimicry).

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36

TISSUE INJURY AND REPAIR

JANE E. SALMON

THE INFLAMMATORY RESPONSE: INNATE IMMUNE MECHANISMS

Inflammation is a vital physiologic response triggered by noxious agents that challenge homeostasis of the body. The innate immune system provides the first level of defense against signals of danger, including pathogenic microorganisms and sterile incursions such as trauma, cancer, ischemia, and metabolic perturbations. Host defense mechanisms generate a rapid protective response, render pathogens harmless, and repair damaged tissue. These highly controlled responses normally protect against further injury, but pathologic inflammation can be inappropriately triggered or inadequately controlled and, in some cases, lead to marked destruction of the extracellular matrix as well as to organ dysfunction.

Invading pathogens or environmental stresses stimulate tissue resident cells by engaging receptors that activate innate immunity. Innate immune responses are also required to initiate specific adaptive immune responses. Designed for rapid responses (minutes to hours), innate immunity relies on the body's ability to recognize conserved features that are present in pathogens but not in the uninfected host. Common motifs trigger innate immune responses, in contrast to the exquisite antigen specificity and precision of adaptive responses, which are slow to develop (days to weeks; Chapter 35).

An adaptive immune response is essential for host protection when innate mechanisms fail to contain the pathogen or injury.

INITIATORS AND EFFECTORS

Triggers of an innate inflammatory response can be classified as pathogen-associated molecular patterns (PAMPs), conserved molecular motifs of infectious agents, and damage-associated molecular patterns (DAMPs), which are signals of host cellular distress. A variety of pattern recognition receptors and cells of innate and adaptive immunity sense PAMPs and DAMPs. PAMP receptors, such as toll-like receptor (TLR) proteins, that are expressed on the cell surface or the inner leaflet of cytoplasmic vesicles, serve as sentinels that rapidly activate innate immune responses, thereby protecting the host from infection. DAMP recognition receptors within the cytoplasm sense "danger" signals that originate from stress, whether toxic environmental (e.g., urate) or cellular (e.g., adenosine triphosphate [ATP]), and respond to microenvironmental damage. Tissue injury induced by trauma or noxious stimuli triggers DAMP receptors to initiate inflammatory responses, thereby leading to microvascular damage, extravasation of leukocytes, and leakage of plasma proteins into the tissue (Fig. 36-1).

Upon encountering a pathogenic agent or tissue injury, the innate immune system is challenged to integrate multiple signals to initiate a proper protective response. Inflammasomes are cytoplasmic multiprotein complexes that comprise a sensor protein, inflammatory caspases, and, in some cases, an adapter protein that connects the two. Inflammasomes (Chapter 35) constitute fundamental processing units that contribute to PAMP and DAMP sensing and coordinate downstream signaling. Inflammasomes are activated by a range of endogenous and exogenous stimuli, thereby leading to enzymatic activation of a caspase and resulting in secretion of interleukin-1β (IL-1β) and IL-18, as well as apoptotic and pyroptotic cell death.

Resident tissue cells, mainly macrophages, dendritic cells, eosinophils, and mast cells that are activated by pattern recognition receptors, are the initiators of acute inflammation. These cells express surface or cytoplasmic pattern recognition receptors and, at the onset of an infection or other injury, they are activated and release inflammatory mediators that are responsible for the clinical signs of inflammation and tissue damage (see Fig. 36-1). Chemical factors produced during inflammation, including histamine, bradykinin, serotonin, leukotrienes, and prostaglandins, sensitize pain receptors, cause local vasodilation, and attract phagocytes, especially neutrophils. Neutrophils help to eliminate microbes but also can damage tissues owing to phagocytosis, the generation of reactive oxygen species, and degranulation, which releases proteases. Neutrophils also extrude chromatin fibers that contain antimicrobial peptides and enzymes, called neutrophil extracellular traps (NETs),[1] and that immobilize and kill invading

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An adaptive immune response is essential for host protection when innate mechanisms fail to contain the pathogen or injury.

INITIATORS AND EFFECTORS

Triggers of an innate inflammatory response can be classified as pathogen-associated molecular patterns (PAMPs), conserved molecular motifs of infectious agents, and damage-associated molecular patterns (DAMPs), which are signals of host cellular distress. A variety of pattern recognition receptors and cells of innate and adaptive immunity sense PAMPs and DAMPs. PAMP receptors, such as toll-like receptor (TLR) proteins, that are expressed on the cell surface or the inner leaflet of cytoplasmic vesicles, serve as sentinels that rapidly activate innate immune responses, thereby protecting the host from infection. DAMP recognition receptors within the cytoplasm sense "danger" signals that originate from stress, whether toxic environmental (e.g., urate) or cellular (e.g., adenosine triphosphate [ATP]), and respond to microenvironmental damage. Tissue injury induced by trauma or noxious stimuli triggers DAMP receptors to initiate inflammatory responses, thereby leading to microvascular damage, extravasation of leukocytes, and leakage of plasma proteins into the tissue (Fig. 36-1).

Upon encountering a pathogenic agent or tissue injury, the innate immune system is challenged to integrate multiple signals to initiate a proper protective response. Inflammasomes are cytoplasmic multiprotein complexes that comprise a sensor protein, inflammatory caspases, and, in some cases, an adapter protein that connects the two. Inflammasomes (Chapter 35) constitute fundamental processing units that contribute to PAMP and DAMP sensing and coordinate downstream signaling. Inflammasomes are activated by a range of endogenous and exogenous stimuli, thereby leading to enzymatic activation of a caspase and resulting in secretion of interleukin-1β (IL-1β) and IL-18, as well as apoptotic and pyroptotic cell death.

Resident tissue cells, mainly macrophages, dendritic cells, eosinophils, and mast cells that are activated by pattern recognition receptors, are the initiators of acute inflammation. These cells express surface or cytoplasmic pattern recognition receptors and, at the onset of an infection or other injury, they are activated and release inflammatory mediators that are responsible for the clinical signs of inflammation and tissue damage (see Fig. 36-1). Chemical factors produced during inflammation, including histamine, bradykinin, serotonin, leukotrienes, and prostaglandins, sensitize pain receptors, cause local vasodilation, and attract phagocytes, especially neutrophils. Neutrophils help to eliminate microbes but also can damage tissues owing to phagocytosis, the generation of reactive oxygen species, and degranulation, which releases proteases. Neutrophils also extrude chromatin fibers that contain antimicrobial peptides and enzymes, called neutrophil extracellular traps (NETs),[1] and that immobilize and kill invading

ABSTRACT

Many clinically important diseases are characterized by normal immune responses directed against an inappropriate antigen, typically in the absence of infection. Hypersensitivity reactions are overreactions of the immune system to innocuous environmental antigens. The four types of hypersensitivity reactions are distinguished by the effector responses mediated by immunologic mechanisms that cause tissue damage. Types I to III are antibody mediated and are distinguished by the different types of antigens recognized and different classes of antibodies involved. Receptors for Ig (Fc receptors) play a crucial role in triggering the effector functions. Type I is mediated by IgE, which induces mast cell activation, whereas types II and III are mediated by IgG, which can engage phagocyte activation and complement activation, depending upon the antigens and antibody subclasses involved. Type II reactions are directed against cell surface or matrix antigens, whereas type III reactions are directed against soluble antigens. Damage to cells and tissues is caused by responses triggered by immune complexes. Type IV hypersensitivity reactions are T cell mediated. The means of antigen recognition that lead to tissue damage in autoimmune disease are similar to the mechanisms elicited in response to pathogens and environmental antigens, and the effector mechanisms of autoimmunity resemble those causing some types of hypersensitivity reactions.

KEYWORDS

allergic reaction
hypersensitivity
immune complex
Fcγ receptor
Fcε receptor

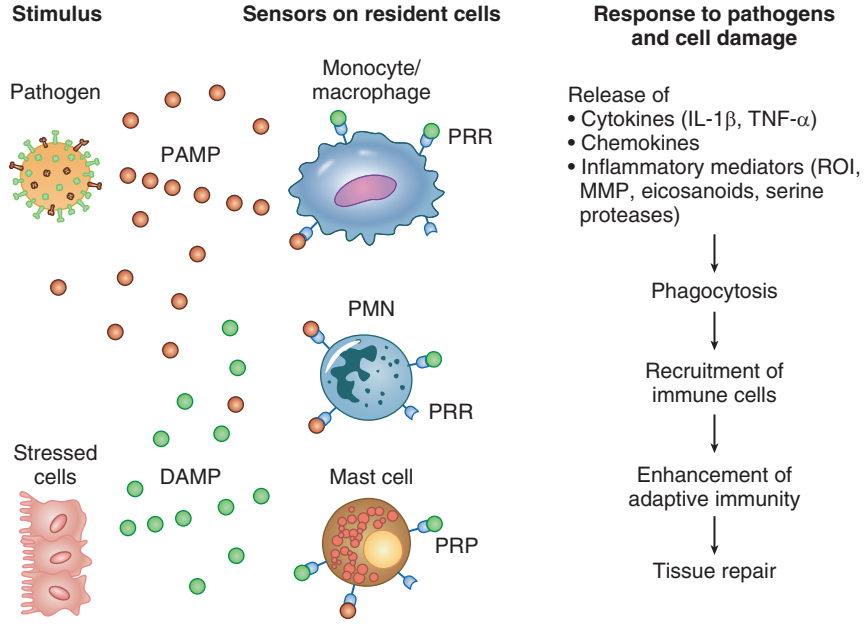

FIGURE 36-1. **Pathogens release PAMPs and stressed, injured cells release DAMPS, both of which bind to pattern recognition receptor on immune cells and stimulate an innate immune response that is accompanied by inflammation, activation of adaptive immunity, and eventually processes to resolve the infection injury and allow for tissue repair.** DAMP = damage-associated molecular pattern; IL-1β = interleukin-1beta; MMP = matrix metalloproteinase; PAMP = pathogen-associated molecular pattern; PMN = polymorphonuclear leukocytes; PRR = pattern recognition receptor; ROI = reactive oxygen intermediate; TNF-α = tumor necrosis factor-alpha.

microorganisms. NETs also may contribute to autoimmunity by binding to and presenting extracellular autoantigens or by stimulating thrombus formation. Neutrophils trigger other parts of the immune system by releasing factors that summon additional leukocytes and lymphocytes.

Local activation of the innate immune response quickly triggers a variety of signals that recruit other inflammatory cells (see Fig. 36-1). Resident vascular endothelial cells, mast cells, dendritic cells, and interstitial fibroblasts also release soluble mediators, including eicosanoids, chemokines, and pro-inflammatory cytokines. Pro-inflammatory members of the IL-1 family (IL-1α, IL-1β, IL-18, and IL-33) and tumor necrosis factor-α (TNF-α) have pleiotropic activities; they enhance adhesion molecule expression on endothelial cells, induce proliferation of endogenous cells, stimulate antigen presentation, and amplify the inflammatory response. Newly arrived inflammatory cells and locally stimulated cells also produce reactive toxic intermediates plus a variety of proteases (e.g., matrix metalloproteinases, serine proteases, and cysteine proteases). Enzymes that degrade the extracellular matrix regulate inflammatory tissue turnover, thereby damaging tissue, releasing matrix-bound growth factors and cytokines, and promoting the retention of newly recruited cells. In most situations, the normal physiologic response is an exquisitely coordinated program that uses proteolytic enzymes to remodel the extracellular matrix and promote a supportive environment for wound healing rather than tissue damage.

THE INFLAMMATORY RESPONSE: ADAPTIVE IMMUNE MECHANISMS

The adaptive immune response is a crucial component of host defense against infection, but unlike the innate response, it is learned rather than intrinsic. Its distinguishing and unique feature is the ability to recognize pathogens specifically, based on clonal selection of lymphocytes bearing antigen-specific receptors. Effector mechanisms that eliminate pathogens in adaptive immune responses are essentially identical to those of innate immunity. The specific antigen recognition feature of the adaptive immune response seems to have been appended to the preexisting innate defense system. As a result, the inflammatory cells and molecules of the innate immune system are essential for the effector functions of B and T lymphocytes.

In addition to initiating protective responses, antigens unassociated with infectious agents also may elicit adaptive immune responses. Many clinically important diseases are characterized by normal immune responses directed against an inappropriate antigen, typically in the absence of infection. Immune responses directed at noninfectious antigens occur in allergy and hypersensitivity, in which the antigen is an innocuous foreign substance, and in autoimmunity, in which the response is to a self-antigen. Adaptive immune responses mediate tissue injury in allergy, hypersensitivity, and autoimmunity.

INITIATORS AND EFFECTORS

Effector actions of antibodies depend on recruiting cells and molecules of the innate immune system. Antibodies are adapters that bind antigens to nonspecific inflammatory cells and direct their destructive effector responses. Antibodies also activate the complement system (Chapter 37), which enhances opsonization of antigens, recruits phagocytic cells, and amplifies (or "complements") antibody-triggered damage. The isotype or class of antibodies produced determines which effector mechanisms are engaged.

Cell-bound receptors for immunoglobulin (Ig) constitute the link between humoral and cellular aspects of the immune cascade and play an integral part in the process by which foreign and endogenous opsonized material is identified and destroyed. These cell-based binding sites for antibodies, termed *Fc receptors,* interact with the constant region (Fc portion) of the immunoglobulin heavy chain of a particular antibody class regardless of its antigen specificity. Accessory cells that lack intrinsic specificity, such as neutrophils, macrophages, and mast cells, are recruited to participate in inflammatory responses through the interaction of their Fc receptors with antigen-specific antibodies. Distinct receptors for different immunoglobulin isotypes are expressed on different effector cells.

Receptors for IgG (FcγRs) are a diverse group of receptors expressed as hematopoietic cell surface molecules on phagocytes (macrophages, monocytes, neutrophils), platelets, mast cells, eosinophils, and natural killer (NK) cells.[2] FcγRs often are expressed as stimulatory and inhibitory pairs. Triggering of stimulatory FcγRs initiates a series of events, including phagocytosis; antibody-dependent, cell-mediated cytotoxicity; secretion of granules; and release of inflammatory mediators, such as cytokines, reactive oxidants, and proteases. Extensive structural diversity among FcγR family members leads to differences in binding capacity, signal transduction pathways, and cell type–specific expression patterns. The structure of the Fc domain of IgG dictates interactions with FcγRs and can lead to pro- or anti-inflammatory responses. The strength of interactions between immune complexes and various FcγRs is determined by structural diversity within IgG subclasses (IgG1, IgG2, IgG3, IgG4) and post-translational modifications of their Fc domains.[3] This diversity allows IgG complexes to activate a broad program of cell functions relevant to inflammation, host defense, and autoimmunity. Phagocyte activation is triggered by stimulatory FcγRs, facilitating the recognition, uptake, and destruction of antibody-coated targets, whereas multivalent IgG binding to FcγRs on platelets leads to platelet aggregation and thrombosis, and binding to FcγRs on NK cells mediates cytotoxicity of antibody-coated targets.

IgE binds to high-affinity FcεRs on mast cells, basophils, and activated eosinophils.[4] In contrast to FcγRs, which are low affinity and bind to multivalent IgG rather than circulating individual IgG molecules, FcεRs can bind monomeric IgE. A single mast cell may be armed with IgE molecules specific for different

antigens, all bound to surface FcεRs. Mast cells, localized beneath the mucosa of the gastrointestinal and respiratory tracts and the dermis of the skin, await exposure to multivalent antigens, which cross-link surface IgE bound to FcεRs and cause release of histamine-containing granules and generation of cytokines and other inflammatory mediators (Chapter 235). IgE-mediated activation of eosinophils, which are normally present in the connective tissue of underlying respiratory, urogenital, and gut epithelium, leads to the release of highly toxic granule proteins, free radicals, and chemical mediators such as prostaglandins, cytokines, and chemokines (Chapter 156). These mediators amplify local inflammatory responses by activating endothelial cells and recruiting and activating more eosinophils and leukocytes. Prepackaged granules and high-affinity FcεRs that bind to free monomeric IgE enable an immediate response to pathogens or allergens at the first site of entry, a location where FcεR-bearing cells reside.

Inhibitory FcγRs, which modulate activation thresholds and terminate stimulating signals, are key elements in the regulation of effector function. Given that inhibitory and stimulatory Fc receptors are often coexpressed on the same cells, the effector response to a specific stimulus in a particular cell represents the balance between stimulatory and inhibitory signals. Inhibitory FcγRs can dampen responses triggered by FcεRs on mast cells and FcγR-mediated inflammation at sites of immune complex deposition.

Effector activities targeted by IgG and IgM also may be mediated by components of the complement system (Chapter 37). Antigen-bound multimeric immunoglobulin can initiate activation of the classic pathway of complement, causing enhanced phagocytosis of antigen-antibody complexes, increased local vascular permeability, and recruitment and activation of inflammatory cells. The target of injury is specified by the antibody, and the extent of damage is determined by the synergistic activities of immunoglobulin and complement.

Antigen-specific effector T cells also may initiate tissue injury. On exposure to an appropriate antigen, memory T cells are stimulated to release cytokines and chemokines that activate local endothelial cells and recruit and activate macrophages and other inflammatory cells. The effector cells directed by T-cell-derived cytokines, or cytolytic T cells themselves, mediate tissue damage. T helper 1 (T_H1) cells produce interferon-γ (IFN-γ) and activate macrophages to cause injury, whereas T_H2 cells produce IL-4, IL-5, and eotaxin (an eosinophil-specific chemokine) and trigger inflammatory responses in which eosinophils predominate. T_H17 cells secrete several effector molecules, including IL-17, which act on both immune and nonimmune cells to trigger differentiation; release of antimicrobial molecules, cytokines, and chemokines; and recruitment to sites of inflammation.[5] T_H effector subsets, more recently identified, include follicular T helper cells (T_{FH}), which provide help to B cells in germinal centers and thus are key regulators of humoral responses and antibody production.

HYPERSENSITIVITY REACTIONS

In predisposed individuals, innocuous environmental antigens may stimulate an adaptive immune response, immunologic memory, and, on subsequent exposure to the antigen, inflammation. Damage to epithelial surfaces lies at the origin of various manifestations of allergic disease. The epithelium of the lungs, gut, and skin are sensors of environmental stimuli, and alterations to their epithelial surfaces drives a type 2 immune response that underlies atopic diseases.[6] These "overreactions" of the immune system to harmless environmental antigens (allergens), called *hypersensitivity* or *allergic reactions* (Chapter 230), produce tissue injury and can cause serious disease. Hypersensitivity reactions are grouped into four types according to the effector mechanisms by which they are produced (Table 36-1). The effectors for types I, II, and III hypersensitivity reactions are antibody molecules, whereas type IV reactions are mediated by antigen-specific effector T cells.

Autoimmune disease is characterized by the presence of antibodies and T cells specific for self-antigens expressed on target tissues. The mechanisms of antigen recognition and effector function that lead to tissue damage in autoimmune disease are similar to the mechanisms elicited in response to pathogens and environmental antigens. These mechanisms resemble certain hypersensitivity reactions and may be classified accordingly. Autoimmune disease caused by antibodies directed against cell surface or extracellular matrix antigens corresponds to type II hypersensitivity reactions; disease caused by formation of soluble immune complexes that subsequently are deposited in tissue corresponds to type III hypersensitivity; and disease caused by effector T cells corresponds to type IV hypersensitivity. Typically, several of these pathogenic mechanisms are operative in autoimmune disease. However, IgE responses are not associated with damage in autoimmunity.

Type I Hypersensitivity Reactions

Type I hypersensitivity reactions (Fig. 36-2) are triggered by the interaction of antigen with antigen-specific IgE bound to FcεRs on mast cells, which causes mast cell activation. Proteolytic enzymes and toxic mediators, such as histamine, are released immediately from preformed granules, and chemokines, cytokines, and leukotrienes are synthesized after activation. Together, these mediators increase vascular permeability, break down tissue matrix proteins, promote eosinophil production and activation (IL-3, IL-5, and granulocyte-macrophage colony-stimulating factor [GM-CSF]), and cause influx of effector leukocytes (TNF-α, platelet-activating factor, and macrophage inflammatory protein [MIP-1]), constriction of smooth muscle, stimulation of mucus secretion, and amplification of T_H2 cell responses (IL-4 and IL-13). Eosinophils and basophils, which are activated through cell surface FcεRs, rapidly release highly toxic granular proteins (major basic protein, eosinophil peroxidase, and collagenase) and, over a longer period, produce cytokines (IL-3, IL-5, and GM-CSF), chemokines (IL-8), prostaglandins, and leukotrienes that activate epithelial cells, leukocytes, and eosinophils to augment local inflammation and tissue damage.

FcεR-bearing effectors act in a coordinated fashion. The immediate allergic inflammatory reaction initiated by mast cell products is followed by a late-phase response that involves recruitment and activation of eosinophils, basophils, and T_H2 lymphocytes. The manifestations of IgE-mediated reactions depend on

TABLE 36-1 FOUR MAJOR TYPES OF IMMUNOLOGICALLY MEDIATED HYPERSENSITIVITY REACTIONS*

IMMUNOLOGIC SPECIFICITY	TYPE I (IgE ANTIBODY)	TYPE II (IgG ANTIBODY)	TYPE III (IgG ANTIBODY)	TYPE IV (T CELLS)			
				T_H1 CELLS	T_H2 CELLS	T_H17 CELLS	T CELLS
Antigen	Soluble antigen allergen	Cell- or matrix-associated antigen	Soluble antigen	Soluble antigen	Soluble antigen	Soluble antigen	Cell-associated antigen
Effector mechanism	FcεRI- or FcγRIII-dependent mast cell activation, with release of mediators/cytokines	$Fc\gamma R^+$ cells (phagocytes, NK cells), complement	$Fc\gamma R^+$ cells, complement	Macrophage activation	Eosinophil activation	Macrophage activation, neutrophil activation	Direct cytotoxicity
Examples	Systemic anaphylaxis, asthma, allergic rhinitis, urticaria, angioedema	Certain drug reactions and reactions to incompatible blood transfusions	Arthus reaction and other immune complex–mediated reactions (e.g., serum sickness, subacute bacterial endocarditis)	Contact dermatitis, tuberculin reaction	Chronic allergic inflammation (e.g., chronic asthma, chronic allergic rhinitis)	Contact dermatitis, atopic dermatitis, asthma, rheumatoid arthritis	Contact dermatitis (e.g., poison ivy), reactions to certain virus-infected cells, some instances of graft rejection

*Hypersensitivity reactions were classified into four types by Coombs and Gell (1963) and modified by Janeway and colleagues (2001).
FcγR = Fc receptor for immunoglobulin G; FcεR = Fc receptor for immunoglobulin E; Ig = immunoglobulin; NK = natural killer.
From Coombs RRA, Gell PGH. Classification of allergic reactions responsible for clinical hypersensitivity and disease. In: Gell PGH, Coombs RA, eds. *Clinical Aspects of Immunology*. Oxford, UK: Blackwell; 1963; and Janeway C, Travers P, Walport M, Shlomchick M. *Immunobiology: The Immune System in Health and Disease*. 5th ed. New York: Garland Publishing; 2001.

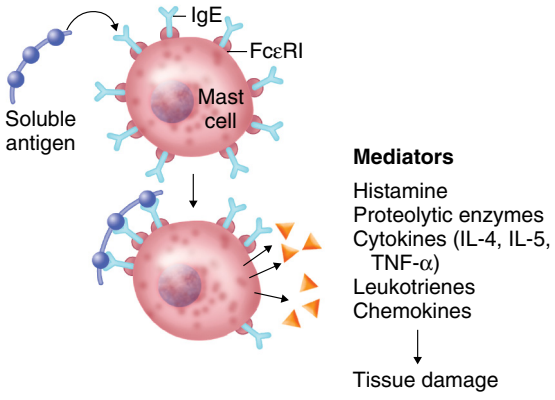

FIGURE 36-2. Type I hypersensitivity. Type I responses are mediated by immunoglobulin E (IgE), which induces mast cell activation. Cross-linking of the Fc receptor for IgE (FcεR) on mast cells, triggered by the interaction of multivalent antigen with antigen-specific IgE bound to FcεR, causes the release of preformed granules containing histamine and proteases. Cytokines, chemokines, and lipid mediators are synthesized after cell activation. IL = interleukin; TNF = tumor necrosis factor.

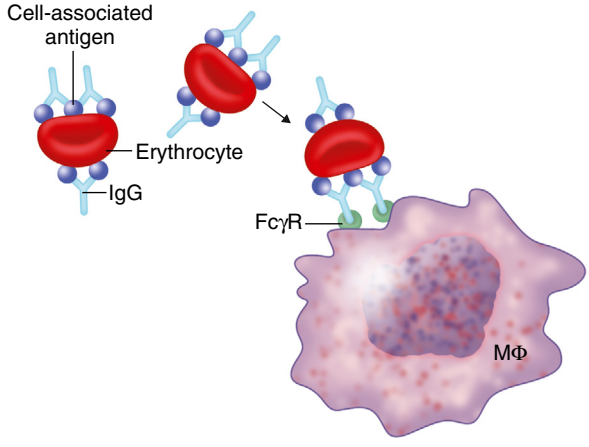

FIGURE 36-3. Type II hypersensitivity. Type II responses are mediated by immunoglobulin G (IgG) directed against cell surface or matrix antigens, which initiates effector responses through the Fc receptor for IgG (FcγR) and complement. The relative contributions of these pathways vary with the IgG subclass and the nature of the antigen. Only FcγR-mediated phagocytosis by macrophages (MΦ) is depicted in this figure. Activation of complement components would result in binding of C3b to the red blood cell membrane, rendering red blood cells susceptible to phagocytosis and leading to formation of the membrane attack complex and cell lysis.

the site of mast cell activation. Mast cells reside in vascular and epithelial tissue throughout the body. In a sensitized host (an individual with IgE responses to antigens), re-exposure to antigen leads to type I hypersensitivity responses only in the mast cells exposed to the antigen. Inhalation of antigens produces bronchoconstriction and increased mucus secretion (asthma and allergic rhinitis); ingestion of antigens causes increased peristalsis and secretion (diarrhea and vomiting); and the presence of subcutaneous antigens initiates increased vascular permeability and swelling (urticaria and angioedema). Blood-borne antigens cause systemic mast cell activation, increased capillary permeability, hypotension, tissue swelling, and smooth muscle contraction—the characteristics of systemic anaphylaxis.[7]

Type II Hypersensitivity Reactions

Type II hypersensitivity reactions (Fig. 36-3) are caused by chemical modification of cell surface or matrix-associated antigens that generates "foreign" epitopes to which the immune system is not tolerant. B cells respond to this antigenic challenge by producing IgG, which binds to these modified cells and renders them susceptible to destruction through complement activation, phagocytosis, and antibody-dependent cytotoxicity This phenomenon is seen clinically when drugs interact with blood constituents and alter their cellular antigens. Hemolytic anemia caused by immune-mediated destruction of erythrocytes (Chapter 146) and thrombocytopenia caused by destruction of platelets (Chapter 158), both type II hypersensitivity reactions, are adverse effects of certain drugs. Chemically reactive drug molecules bind covalently to the surface of red cells or platelets creating new epitopes that in a small subset of individuals are recognized as foreign antigens by the immune system and stimulate production of IgM and IgG antibodies reactive with the conjugate of drug and cell surface protein. Penicillin-specific IgG binds to penicillin-modified proteins on red blood cells and triggers activation of the complement cascade. Activation of complement components C1 through C3 results in covalent binding of C3b to the red cell membrane and renders circulating red cells susceptible to phagocytosis by FcγR and complement receptor–bearing macrophages in the spleen or liver. Activation of complement components C1 through C9 and formation of the membrane attack complex cause intravascular lysis of red cells. The factors that predispose only some people to drug-induced type II hypersensitivity reactions are unknown. Penicillin, quinidine, and methyldopa have been associated with hemolytic anemia and thrombocytopenia through this mechanism. Another example is heparin-induced thrombocytopenia or thrombosis, a severe, life-threatening complication that occurs in 1 to 3% of patients exposed to heparin (Chapter 158). Interactions among heparin, human platelet factor 4, antibodies to the human platelet factor 4–heparin complex, platelet FcγRIIA, and splenic FcγRs (which remove opsonized platelets) are involved in the pathogenesis of this disease.

Autoantibodies directed at antigens on the cell surface or extracellular matrix cause tissue damage by mechanisms similar to type II hypersensitivity reactions. IgG or IgM antibodies against erythrocytes lead to cell destruction in autoimmune hemolytic anemia because opsonized cells (coated with IgG or IgM and complement) are removed from the circulation by phagocytes in the liver and spleen or are lysed by formation of the membrane attack complex. Platelet destruction in autoimmune thrombocytopenic purpura occurs through a similar process. Because nucleated cells express membrane-bound complement regulatory proteins, they are less sensitive to lysis through the membrane attack complex, but when coated with antibody, they become targets for phagocytosis or antibody-dependent cytotoxicity. This mechanism is responsible for autoimmune and alloimmune neutropenia (Chapter 153).

IgM and IgG antibodies recognizing antigens within tissue or binding to extracellular antigens cause local inflammatory damage through FcγR and complement mechanisms.[8] Pemphigus vulgaris (Chapter 406) is a serious blistering disease that results from a loss of adhesion between keratinocytes caused by autoantibodies against the extracellular portions of desmoglein 3, an intercellular adhesion structure of epidermal keratinocytes. Another example of a type II hypersensitivity reaction is Goodpasture disease (Chapter 79), in which antibodies against the α_3-chain of type IV collagen (the collagen in basement membranes) are deposited in glomerular and lung basement membrane. Tissue-bound autoantibodies activate monocytes, neutrophils, and basophils through FcγRs, initiating release of proteases, reactive oxidants, cytokines, and prostaglandins. Local activation of complement, particularly C5a, recruits and activates inflammatory cells and amplifies tissue injury. Neighboring cells are lysed by assembly of the membrane attack complex or by FcγR-initiated, antibody-dependent cytotoxicity.

Autoantibodies against cell surface receptors produce disease by stimulating or blocking receptor function. In myasthenia gravis (Chapter 390), autoantibodies against the acetylcholine receptors on skeletal muscle cells bind the receptor and induce its internalization and degradation in lysosomes, thereby reducing the efficiency of neuromuscular transmission and causing progressive muscle weakness. In contrast, Graves disease (Chapter 207) is characterized by autoantibodies that act as agonists. Autoantibodies to thyroid-stimulating hormone receptors bind the receptor, mimicking the natural ligand, inducing thyroid hormone overproduction, disrupting feedback regulation, and causing hyperthyroidism.

Type III Hypersensitivity Reactions

Type III hypersensitivity reactions (Fig. 36-4) are caused by tissue deposition of small soluble immune complexes that contain antigens and high-affinity IgG antibodies directed at these antigens. Localized deposition of immune complexes activates FcγR-bearing mast cells and phagocytes and initiates the complement cascade, all effectors of tissue damage.

Immune complexes are generated in all antibody responses. The formation and the fate of immune complexes depend on the biophysical and immunologic properties of the antigen and the antibody. Larger aggregates fix complement more efficiently, present a broader multivalent array of ligands for complement and FcγRs to bind, and are taken up more readily by mononuclear phagocytes in the liver and spleen and thereby removed from the circulation. Smaller immune complexes, which form in antigen excess—as occurs early in an immune response—circulate in the blood and are deposited in blood

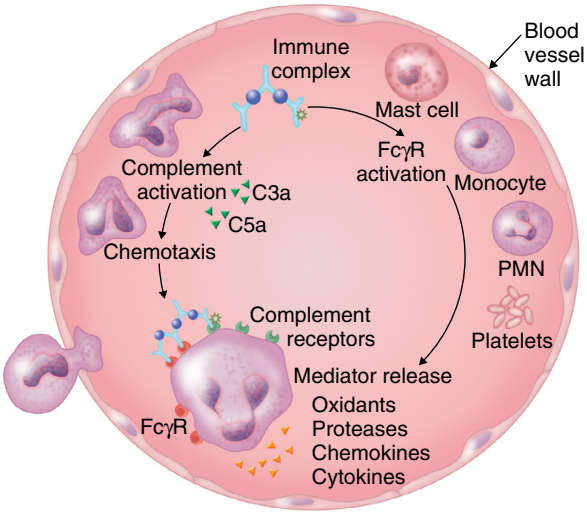

FIGURE 36-4. Type III hypersensitivity. Type III responses are mediated by immunoglobulin G (IgG) directed against soluble antigens. Localized deposition of immune complexes activates mast cells, monocytes, neutrophils, and platelets bearing the Fc receptor for IgG (FcγR), and initiates the complement cascade, all effectors of tissue damage. Generation of complement activation products C3a and C5a recruits and stimulates inflammatory cells and amplifies effector functions. PMN = polymorphonuclear leukocyte (also called *neutrophil*).

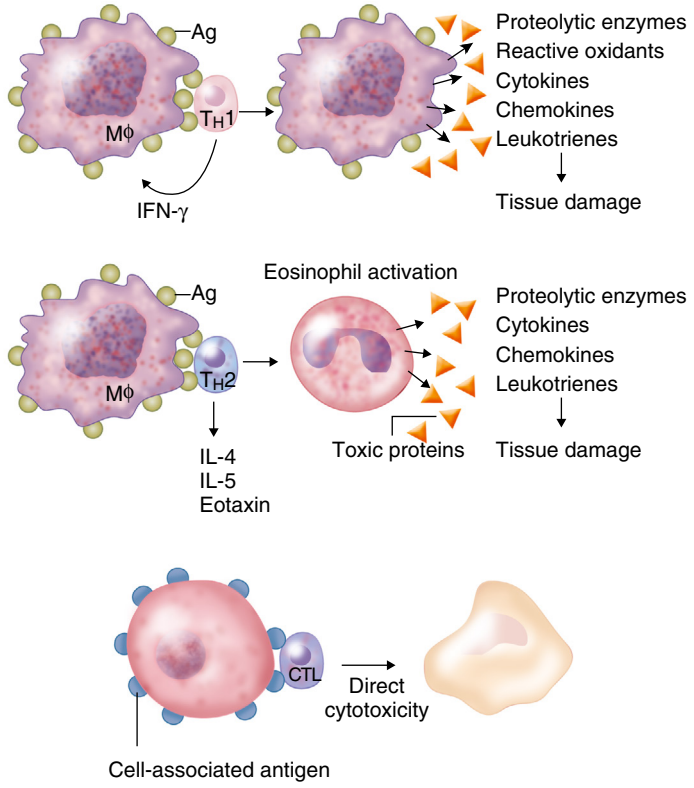

FIGURE 36-5. Type IV hypersensitivity. Type IV responses are mediated by T cells through three different pathways. In the first, type 1 helper T (T_H1) cells recognize soluble antigens (Ag) and release interferon-γ (IFN-γ) to activate effector cells, in this case macrophages (MΦ), and cause tissue injury. In T_H2-mediated responses, eosinophils predominate. T_H2 cells produce cytokines to recruit and activate eosinophils, leading to their degranulation and tissue injury. In the third pathway, damage is caused directly by cytolytic T lymphocytes (CTL). IL = interleukin.

vessels, where they initiate inflammatory reactions and tissue damage through interactions with FcγRs and complement receptors.

Serum sickness (Chapter 230)[9] is a systemic type III hypersensitivity reaction, historically described in patients injected with therapeutic horse antiserum for the treatment of bacterial infections. In general, serum sickness occurs after the injection of large quantities of a soluble antigen. Clinical features include chills, fever, rash, urticaria, arthritis, and glomerulonephritis. Disease manifestations become evident 7 to 10 days after exposure to the antigen, when antibodies are generated against the foreign protein and form immune complexes with these circulating antigens. Immune complexes are deposited in blood vessels, where they activate phagocytes and complement, producing widespread tissue injury and clinical symptoms. The effects are transient, however, and resolve after the antigen is cleared.

A syndrome similar to serum sickness occurs in chronic infections in which pathogens persist in the face of continued immune response. In subacute bacterial endocarditis (Chapter 61), antibody production continues but fails to eliminate the infecting microbes. As the pathogens multiply, generating new antigens, immune complexes form in the circulation and are deposited in small blood vessels, where they lead to inflammatory damage of skin, kidney, and nerve. Hepatitis B virus infection (Chapters 134 and 135) may be associated with immune complex deposition early in its course, during a period of antigen excess, because antibody production in response to hepatitis B surface antigen is as yet relatively insufficient; some anicteric patients may present with acute arthritis. Mixed essential cryoglobulinemia, which may be associated with hepatitis C viral infection (Chapters 134 and 135), is an immune complex–mediated vasculitis in which deposition of complexes containing IgG, IgM, and hepatitis C antigens causes inflammation in peripheral nerves, kidneys, and skin. Serum sickness also can develop in transplant recipients who are treated with mouse monoclonal antibodies specific for human T cells to prevent rejection, and in patients with myocardial infarction who are treated with the bacterial enzyme streptokinase to effect thrombolysis.

Systemic lupus erythematosus (Chapter 245), the prototypical immune complex–mediated autoimmune disease, is characterized by circulating IgG directed against common cellular constituents, typically DNA and DNA-binding proteins. Small immune complexes are deposited in skin, joints, and glomeruli and initiate local tissue damage.

Type IV Hypersensitivity Reactions

Type IV hypersensitivity reactions (Fig. 36-5), also known as *delayed-type hypersensitivity reactions*, are mediated by antigen-specific effector T cells.[10] These reactions are distinguished from other hypersensitivity reactions by the lag time from exposure to the antigen until the response is evident (1 to 3 days). Antigen is taken up, processed, and presented by macrophages or dendritic cells. T_H1 effector cells that recognize the specific antigen (these are scarce and take time to arrive) are stimulated to release chemokines, which recruit macrophages to the site, release cytokines that mediate tissue injury and growth factors that stimulate monocyte production. IFN-γ activates macrophages and enhances their release of inflammatory mediators, whereas TNF-α and TNF-β activate endothelial cells, enhance vascular permeability, and damage local tissue. The prototypical type IV hypersensitivity reaction is the tuberculin test, but similar reactions can occur after contact with sensitizing antigens (e.g., poison ivy, certain metals) and lead to epidermal reactions characterized by erythema, cellular infiltration, and vesicles. $CD8^+$ T cells also may mediate damage by direct toxicity.

In contrast to T_H1-mediated hypersensitivity reactions, in which the effectors are macrophages, eosinophils predominate in T_H2-mediated responses. T_H2 effector T cells are associated with tissue damage in chronic asthma (Chapter 75). T_H2 cells produce cytokines to recruit and activate eosinophils (IL-5 and eotaxin), leading to degranulation, further tissue injury, and chronic, irreversible airway damage.

Additional T_H effector cells, such as T_H17 cells, mediate tissue damage. T_H17 cells produce IL-17 family cytokines, as well as IL-21, IL-22, and GM-CSF, that regulate innate effectors and orchestrate local inflammation by inducing release of pro-inflammatory cytokines and chemokines, proliferation and activation of effector cells and other target cells, recruitment of neutrophils, and enhanced T_H2-mediated inflammation, all of which amplify allergic and autoimmune responses. T_H17 cells have been implicated in allergic disorders (atopic dermatitis, asthma) and autoimmune and inflammatory diseases (psoriasis, inflammatory bowel disease, rheumatoid arthritis, systemic lupus erythematosus, multiple sclerosis), and chronic transplant rejection.

In some autoimmune diseases, effector T cells specifically recognize self-antigens to cause tissue damage, either by direct cytotoxicity or by inflammatory responses mediated by activated macrophages. In type 1 insulin-dependent diabetes mellitus, T cells mediate destruction of β cells of the pancreatic islets. IFN-γ–producing T cells specific for myelin basic proteins have been implicated in multiple sclerosis. Rheumatoid arthritis (Chapter 243) is another autoimmune disease caused, at least in part, by activated T_H1 cells.

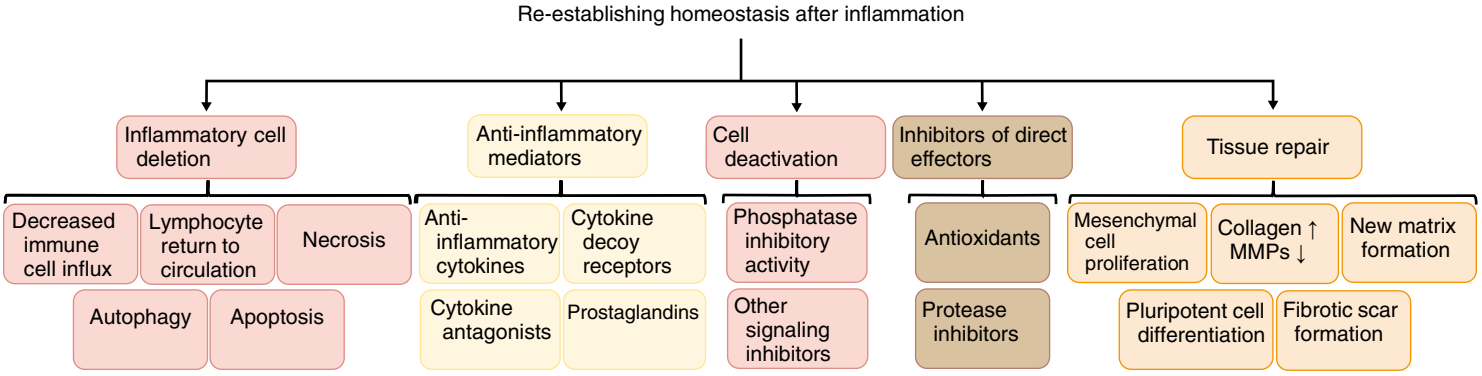

FIGURE 36-6. Mechanisms that resolve inflammation and lead to repair of the extracellular matrix. MMPs = matrix metalloproteinases.

TISSUE REPAIR AND RESOLUTION OF INFLAMMATION

Transient inflammation is a normal physiologic response, but serious injury results when unabated inflammation persists. After an inflammatory response is initiated, homeostasis must be reestablished by removing or deactivating mediators and effector cells, thereby permitting damaged tissues to repair. This resolution process requires cellular responses such as apoptosis and necrosis, the generation of anti-inflammatory cytokines and antioxidants, and the production of protease inhibitors (Fig. 36-6).

CELLULAR RESPONSES

Removal of inflammatory cells is accomplished by suppressing the production of chemotactic factor and the expression of vascular adhesion molecules, thereby releasing cells (particularly lymphocytes) from tissues so they can return to the circulation through the lymphatic system or by directly causing cell death via necrosis, apoptosis, or autophagy. However, the release of cellular contents by dying cells may be deleterious, and defective apoptosis or the persistence of apoptotic cells can contribute to chronic inflammation and to autoimmune diseases.

Some immune cells disappear during the resolution phase, whereas other cells expand.[11] For example, mesenchymal cells, such as fibroblasts, typically proliferate to produce new matrix, which in turn contracts to form fibrotic scar tissue. DNA synthesis in these stromal cells is induced by locally produced growth factors, such as platelet-derived growth factor. TGF-β stimulates fibroblasts to proliferate and changes their phenotype to healing by driving matrix formation through increased production of collagen and suppressed expression of matrix metalloproteinases. Mesenchymal stem cells also can differentiate into organ-specific lineages and, in the appropriate milieu, become bone cells, chondrocytes, adipocytes, or other terminally differentiated stromal cells.

SOLUBLE MEDIATORS AND INHIBITORS OF DAMAGING EFFECTORS

Resident and infiltrating cells release anti-inflammatory cytokines. TGF-β and IL-10 are produced by macrophages, interstitial fibroblasts, or T cells. T-cell cytokines (e.g., IL-4, IL-10, and IL-13) suppress the expression of matrix metalloproteinases by IL-1- or TNF-stimulated cells. TGF-β suppresses the production of collagenase, increases the deposition of collagen, and induces the tissue production of metalloproteinase inhibitors, thereby decreasing the activity of matrix metalloproteinases.

In addition, intracellular safety mechanisms regulate inflammatory signaling pathways to ensure that the process is self-limited. For example, kinases in growth factor receptors and other intracellular pathways activated by pro-inflammatory cytokines require phosphorylation to amplify enzyme activity, but phosphatases remove these phosphates so that kinases return to their resting inactive form.

Catalase and superoxide dismutase, which are antioxidant enzymes, inactivate toxic reactive oxygen intermediates released by phagocytes. The removal of toxic metabolites is facilitated by glutathione peroxidases and glutathione reductase.

Protease inhibitors are produced to regulate endogenous proteases and thereby to reduce the likelihood that collateral tissue damage will occur. For example, serine protease inhibitors (e.g., antithrombin III, plasminogen activator inhibitors 1 and 2, and α_1-antitrypsin) attenuate inflammation and resolve blood clots. Tissue inhibitors of metalloproteinases bind to activated matrix metalloproteinases and irreversibly block their catalytic sites to inhibit enzyme function. Examples of disease states characterized by an unfavorable balance between tissue inhibitors of metalloproteinases and matrix metalloproteinases include loss of cartilage in arthritis and progression of tumor metastases. Inhibition of pro-inflammatory cytokines and growth factors is associated with increased production of matrix protein and decreased activity of matrix metalloproteinases.

GENERAL REFERENCES

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37 COMPLEMENT SYSTEM IN DISEASE

JOHN P. ATKINSON AND V. MICHAEL HOLERS

The complement system consists of plasma and membrane proteins that participate in host defense against infections and in clearance of cellular and extracellular debris, as well as in a wide variety of autoimmune and inflammatory states (Fig. 37-1).[1–3] Complement is essential in innate immunity and a potent effector arm of adaptive (humoral) immunity. It is a *first* responder, especially in blood, to bacterial and viral invasion (Table 37-1). It helps to maintain sterility ("guardian of the intravascular space") by depositing within seconds its opsonic and membrane-perturbing fragments on a pathogen's surface. A second major activity of complement is to promote the inflammatory response via the release of soluble fragments *(anaphylatoxins)* that act in both extracellular and intracellular sites. These fragments bind to their receptors, thereby leading to cellular activation, including chemokinesis and chemotaxis by phagocytic cells, and enhancing protection against infections. Furthermore, the deposition of complement fragments on immune complexes keeps them from precipitating and promotes their adherence to red blood cells (RBCs) for a hand-off to monocytes and dendritic cells in the liver and spleen.

Through these interactions, complement also instructs the adaptive immune response. Antigens decorated by complement proteins are more efficiently taken up by, or held in place for presentation to, monocytes, follicular-dendritic cells, B lymphocytes, and other antigen-presenting cells, thereby resulting in an adaptive immune response (Chapter 35). For example, complement activation is required for an optimal antibody response to most foreign antigens. In this way, the complement system is often called "nature's adjuvant." Individuals lacking a functional complement system are predisposed to bacterial infections, predominantly by encapsulated organisms, including streptococcus, staphylococcus, *Haemophilus* spp, and *Neisseria* spp. Surprisingly, a complete deficiency of C1q, which is an early component of the classical complement

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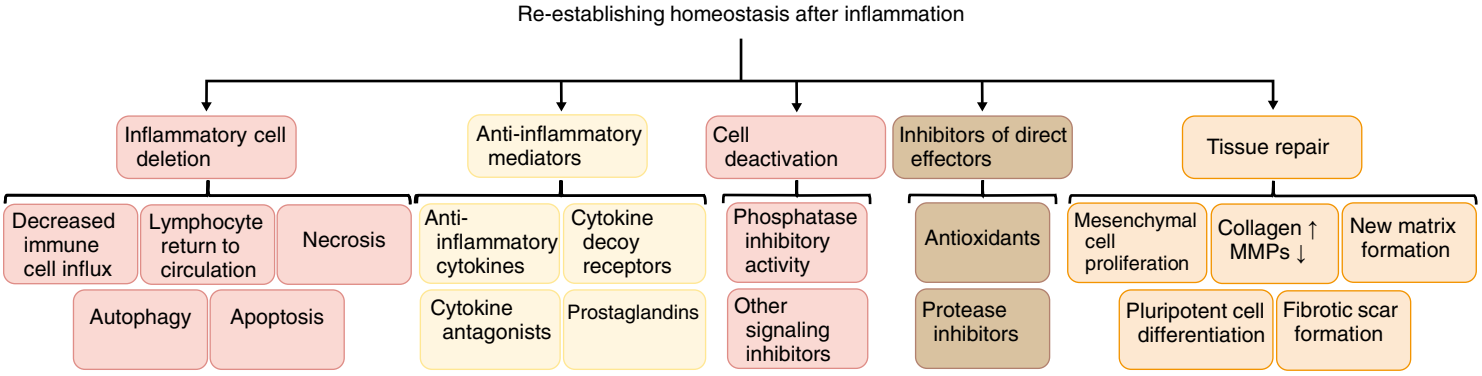

FIGURE 36-6. Mechanisms that resolve inflammation and lead to repair of the extracellular matrix. MMPs = matrix metalloproteinases.

TISSUE REPAIR AND RESOLUTION OF INFLAMMATION

Transient inflammation is a normal physiologic response, but serious injury results when unabated inflammation persists. After an inflammatory response is initiated, homeostasis must be reestablished by removing or deactivating mediators and effector cells, thereby permitting damaged tissues to repair. This resolution process requires cellular responses such as apoptosis and necrosis, the generation of anti-inflammatory cytokines and antioxidants, and the production of protease inhibitors (Fig. 36-6).

CELLULAR RESPONSES

Removal of inflammatory cells is accomplished by suppressing the production of chemotactic factor and the expression of vascular adhesion molecules, thereby releasing cells (particularly lymphocytes) from tissues so they can return to the circulation through the lymphatic system or by directly causing cell death via necrosis, apoptosis, or autophagy. However, the release of cellular contents by dying cells may be deleterious, and defective apoptosis or the persistence of apoptotic cells can contribute to chronic inflammation and to autoimmune diseases.

Some immune cells disappear during the resolution phase, whereas other cells expand.[11] For example, mesenchymal cells, such as fibroblasts, typically proliferate to produce new matrix, which in turn contracts to form fibrotic scar tissue. DNA synthesis in these stromal cells is induced by locally produced growth factors, such as platelet-derived growth factor. TGF-β stimulates fibroblasts to proliferate and changes their phenotype to healing by driving matrix formation through increased production of collagen and suppressed expression of matrix metalloproteinases. Mesenchymal stem cells also can differentiate into organ-specific lineages and, in the appropriate milieu, become bone cells, chondrocytes, adipocytes, or other terminally differentiated stromal cells.

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ABSTRACT

"Complement" is an ancient innate immune system. Initially, it was likely designed to handle cellular debris and invasion by pathogens, even in single-cell organisms. In host defense, its two major functions are mediated by opsonization and membrane perturbation (including the lysis of gram-negative bacteria and enveloped viruses). In parallel, small protein fragments (anaphylatoxins) are liberated that engage receptors to promote the inflammatory response. Through these activities, the complement system also serves as nature's adjuvant to trigger the adaptive immune system. The three pathways evolved to work in seconds to protect the circulation from infections. In evolution, lectins and then antibodies became more rapid and specific triggers of their respective pathways. Complete deficiency of a complement system activating component predisposes to recurrent bacterial infections (particularly pneumococcal for early and meningococcal for late pathways) and autoimmunity, namely systemic lupus erythematosus. If a regulator is deficient secondary to a rare genetic mutation, excessive activation in response to a given degree of injury predisposes to paroxysmal nocturnal hemoglobinuria, atypical hemolytic uremic syndrome, and age-related macular degeneration. Therapeutic agents, particularly monoclonal antibodies to components of each of the three major pathways, are in development. A monoclonal antibody to C5 is Food and Drug Administration–approved to treat paroxysmal nocturnal hemoglobinuria, atypical hemolytic uremic syndrome, myasthenia gravis, and neuromyelitis optica spectrum disorder. The complement system's role in the pathophysiology of many chronic inflammatory conditions and in autoantibody-mediated diseases remains to be defined.

KEYWORDS

innate immunity
opsonization
lysis
immune-complex interactions
lectins
inhibitors
debris clearance
autoimmunity

pathway, strongly predisposes to autoimmune diseases, particularly systemic lupus erythematosus (SLE).[4] This association suggests that complement is required not only for host defense against foreign agents but also to identify and safely clear self-materials (debris removal), particularly RNA and DNA species[5] in conditions such as rhabdomyolysis.[6]

A remarkable feature of the complement system is that it reacts within seconds (Table 37-2). In less than 2 minutes, it can coat an encapsulated gram-positive bacterium with several million C3b opsonic fragments and lyse gram-negative bacteria by insertion of its terminal components (the membrane attack complex). It works faster if driven by immunoglobulin M (IgM) or IgG binding to an antigen on a microbial membrane to activate and focus the cascade. Antibodies and lectins direct the activation process to the pathogen's surface. Overall, the complement cascade is designed to become engaged on the surface of a pathogen, particularly bacteria. Plasma and membrane *regulators of complement activation* inhibit formation on normal "self" cells.

Much of complement-mediated pathology revolves around the alternative pathway's amplification loop. This loop is key in triggering activation early in an immune response; however, it must be rigorously regulated to prevent activation on normal self and excessive activation on injured self.[7] Approximately half of the proteins associated with the complement system are dedicated to the control of its activation and effector functions, especially to maintain homeostasis of the alternative pathway's amplification loop.

In clinical medicine, the complement system participates in three pathologic processes: (1) an inherited decrease in functional activity leading to increased susceptibility to bacterial infections and to autoimmunity, (2) undesirable tissue damage upon activation by autoantibodies and immune complexes, and (3) excessive activation at sites of tissue injury in individuals carrying genetic variants in regulators (Tables 37-3 and 37-4).

Knowledge of how complement is activated and how it can be controlled points to opportunities for the development of therapeutic agents such as anti-C5 monoclonal antibody therapy, which has been approved to treat complement-dependent hemolytic and autoimmune disorders.

ACTIVATION OF COMPLEMENT

CLASSICAL PATHWAY

The binding of IgM or IgG to a target antigen activates this exceptionally powerful and quick-acting pathway to destroy microbes (Figs. 37-2 and 37-3). The classical pathway reaction cascade is designed to opsonize and perturb the surface membrane of microorganisms. Of course, autoantibodies also trigger this highly efficient classical pathway. Complement action mediated by immune complexes may then lead to cellular and tissue damage. Instructive examples of autoantibodies and complement-mediated diseases are immune hemolytic anemias, myasthenia gravis, and bullous pemphigoid. The basic problem or pathologic defect in this type of human disease is the formation of the autoantibody. A misidentification of self has occurred because of a breaking of tolerance. In this pathologic situation, the complement system is working at the behest of the autoantibody.

TABLE 37-1 COMPLEMENT SYSTEM IN HOST DEFENSE AGAINST BACTERIA AND VIRUSES

THE ACTIVITY	THE PLAYERS
Opsonization	(C3b > C4b, C1q, MBL)*
Membrane perturbation including lysis (the membrane attack complex)	(C5b-C9)
Pro-inflammatory via cellular activation (the anaphylatoxins and their receptors)	(C3a, C4a, C5a)

*C3b is the major opsonin of the complement system. C1q and MBL (mannose- or mannan-binding lectin) both participate in classical and lectin pathway activation, respectively, but also bind to their specific receptors upon attachment to a target.

TABLE 37-2 SALIENT FEATURES OF THE COMPLEMENT SYSTEM

- Ancient innate system of immunity predominantly found in blood (the "guardian of the intravascular space")
- Capable of rapidly opsonizing and lysing bacteria and viruses (millions of active fragments can be deposited on a target)
- Works in seconds!
- Most proteins are synthesized by the liver, but local production is also important to outcomes
- Constantly turning over (AP protein C3 "ticks over" at a rate of 1 to 2%/hr)
- The AP also features a feedback or amplification loop, which requires tight control
- Effector arm of the humoral immune system (IgM, IgG, and IgA)
- Critical for clearance of self-debris (garbage removal)
- After immunoglobulins and albumin, complement proteins are among the most abundant in blood
- Nature's adjuvant (almost all foreign antigens are coated with complement fragments); instructs the adaptive immune response
- A deficiency of an activator leads to bacterial infections or autoimmunity (SLE)
- A deficiency of a regulator leads to undesirable cellular and tissue damage at sites of injury or degeneration (excessive activation): atypical hemolytic uremic syndrome, age-related macular degeneration

aHUS = atypical hemolytic uremic syndrome; AMD = age-related macular degeneration; AP = alternative pathway; Ig = immunoglobulin; SLE = systemic lupus erythematosus.

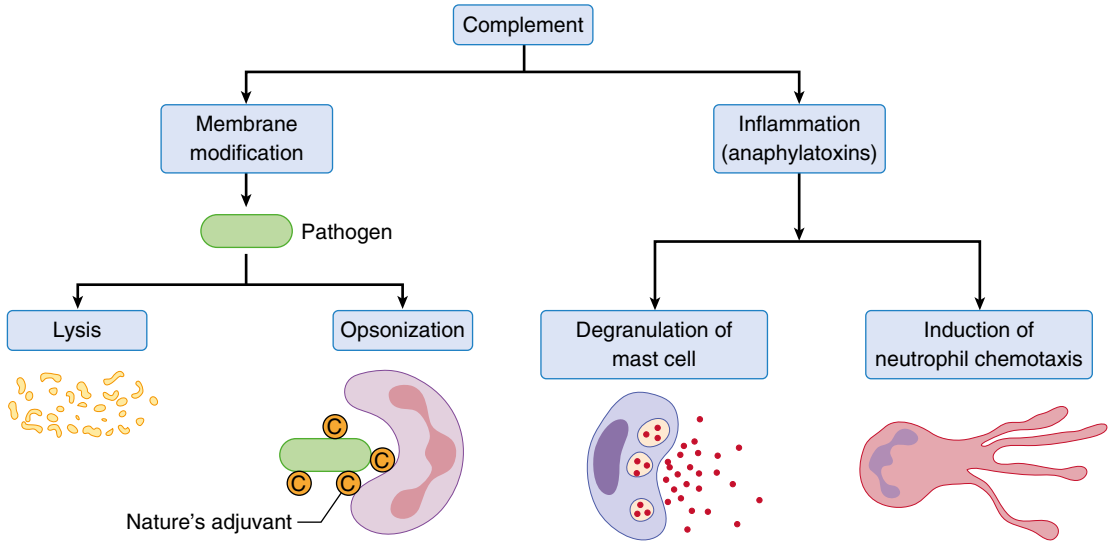

FIGURE 37-1. Function of the complement system. The most important function of the complement system is to alter the membrane of the pathogen by coating its surface with clusters of activation fragments. In one case, they facilitate the key process of opsonization in which C4b and C3b interact with complement receptors. In the other case, as with certain gram-negative bacteria and viruses, the membrane attack complex lyses the organism. The second critical function of complement is to activate cells and thus promote inflammatory and immune responses. The complement fragments C3a and C5a (known as anaphylatoxins) stimulate many cell types such as mast cells to release their contents and stimulate phagocytic cells to migrate to sites of inflammation (chemotaxis) and T cells to modulate metabolism and promote polarization. Through these phenomena of opsonization and cell activation, complement serves as nature's adjuvant to prepare, facilitate, and instruct the host's adaptive immune response. Because extracellular complement activation occurs in a few seconds, this innate immune system initially engages most pathogens, especially those that try to enter the vascular space. As will be illustrated, these basic functions are also required to handle immune complexes and prevent autoimmunity. (Modified from Arthritis Foundation. *Primer on the Rheumatic Diseases*, 12th ed. Atlanta, GA: Arthritis Foundation; 2001.)

The classical pathway is also activated by means other than the formation of IgM- and IgG-bearing immune complexes. β-Amyloid in the neuritic plaques of patients with Alzheimer disease directly engages the classical pathway via an interaction with C1q (Table 37-5). Likewise, C-reactive protein (CRP) and serum amyloid protein bind to chromatin and other ribonucleoprotein complexes released from apoptotic cells, and these types of complexes activate the classical pathway. The classical pathway also plays a key role in the opsonization and removal of nuclear debris. Approximately 80% of patients with hereditary absence of C1q or C4 develop SLE. Deposits of CRP and activated C1 have been demonstrated in ischemic tissue such as infarcted human myocardium. These observations indicate that classical pathway activation via these antibody-independent means is critical in protecting against autoimmune responses by facilitating debris clearance.

Regulation of classical pathway activation occurs at two levels. First, the *ser*ine *p*rotease *in*hibitor (serpin) known as the C1-inhibitor (C1-INH) blocks the activity of many proteases, including factor XIIa, kallikrein, and factor XIa of the clotting system as well as C1r, C1s, and MASP2 of the complement system. The importance of C1-INH is exemplified by its role in hereditary angioedema (Table 37-6). In this dominantly inherited disease, a deficiency of C1-INH allows uncontrolled proteolysis of C4 and C2 and generation of bradykinin, leading to recurrent swelling episodes. This serpin prevents chronic activation of the classical pathway cascade and, after a few minutes, helps to shut down the system. Classical pathway activation is also regulated by multiple inhibitors at the key step of C3 activation. These plasma and membrane proteins inhibit C3 convertase formation on healthy self. Membrane regulators are highly expressed on most cell types, where they prevent activation on normal self and overexuberant activation on altered self.

TABLE 37-3 PARTICIPATION OF THE COMPLEMENT SYSTEM IN HUMAN DISEASE

Activation by autoantibody (formation of immune complexes)
Engagement with modified self (clearance of debris or garbage) • Degenerative processes (diseases of aging such as age-related macular degeneration) • Cell and tissue damage (ischemia-reperfusion injury; atypical hemolytic uremic syndrome)

TABLE 37-4 PATHOLOGIC CONDITIONS ASSOCIATED WITH COMPLEMENT ACTIVATION

Examples of diseases in which complement activation contributes to the immunopathology:
Atypical hemolytic uremic syndrome*†
Paroxysmal nocturnal hemoglobinuria†
Age-related macular degeneration*†
Membranoproliferative glomerulonephritis (types 1, 2, and 3)†‡
Myasthenia gravis‡
Neuromyelitis optica spectrum disorder
Bullous pemphigoid‡
Systemic lupus erythematosus/antiphospholipid syndrome‡
Rheumatoid arthritis‡
Immune hemolytic anemias‡
Immune vasculitis (ANCA-positive syndromes)‡
Ischemia reperfusion injury*†
Allotransplantation‡
Amyotrophic lateral sclerosis†
Transplantation rejection‡
Serum sickness‡
Exposures to foreign materials (e.g., membranes, nanoparticles, gene therapy viruses)*

*Injury, ischemia, trauma, degeneration, or foreign body is the trigger (innate immune activation).
†Lack of adequate regulation contributes to disease pathogenesis.
‡Antibody-dependent activation of the complement system (adaptive humoral immune activation).
ANCA = antineutrophil cytoplasmic antibody.

LECTIN PATHWAY

The protein mannose-binding lectin (MBL) is a member of the collectin family that also includes pulmonary surfactants A and D. MBL has a structure similar to C1q in that it consists of several subunits; namely, a globular recognition head domain for carbohydrates and a collagen-like tail that interacts with serine proteases. In the case of MBL, the globular domain is a lectin (protein) that binds to repeating mannose and *N*-acetylglucosamine residues on the surface of pathogens (see Figs. 37-2 and 37-3). Many microorganisms are recognized by MBL, including gram-positive and gram-negative bacteria, mycobacteria, fungi, parasites, and viruses (including human immunodeficiency virus 1 [HIV-1]). In general, as would be expected, mammalian glycoproteins and glycolipids are not readily recognized by MBL and the related lectins (ficolins and collectins) that activate the lectin pathway.

Three serine proteases, MASP-1, MASP-2, and MASP-3, associate with MBL (and the ficolins and collectins) through their collagen-like domain. This is analogous to the association of C1r and C1s with C1q. Activation of MASP-2, with some help from MASP-1, results in cleavage of C2 and C4, leading to formation of the classical/lectin pathway C3 convertase (C4b2a).

Genetic variations in the structural and regulatory portions of the MBL gene lead to wide differences in serum levels. A low level of MBL is associated with recurrent infections in children and adults and is a risk factor for the development of SLE. More striking is the association of low levels of MBL with infections in the setting of the treatment of SLE. For example, heterozygous MBL deficiency has been associated with a four-fold increase in the risk of bacterial pneumonia and homozygous deficiency with a more than 100-fold increase.[8]

ALTERNATIVE PATHWAY

The alternative pathway takes advantage of the fact that C3 undergoes spontaneous, chronic, low-grade activation (Fig. 37-4; see also Figs. 37-2 and 37-3). This C3b may covalently attach to any cell; however, on normal self, amplification of the cascade is blocked by inhibitors. In contrast, deposition on polysaccharides of bacterial membranes and to other targets, such as endotoxin and virally infected cells, leads to a rapid engagement of this pathway. These sites, similar to immune complexes and almost any type of biomaterial (cardiopulmonary bypass and hemodialysis membranes, nanoparticles, and so on), lack regulators, so rapid, massive activation may occur. IgA also has the capacity to promote activation of the alternative pathway.

During spontaneous activation, called *tickover*, small amounts of activated C3 are continuously generated (C3 turns over in blood at 1 to 2%/hour). It can initiate a feedback loop and cleave more C3 to C3b. Also, the initial C3b may be derived from either the classical or lectin pathway. Thus, activation of complement by any one of the three pathways has the potential to be rapidly magnified. The alternative pathway C3 convertase is negatively controlled (to maintain homeostasis), both in the fluid phase and on host cells, by two abundant plasma proteins and two widely expressed membrane proteins.[9]

The central role of the alternative pathway as an amplifier of complement activation is borne out by its association with a number of clinicopathologic states in the setting of deficient regulation (Tables 37-6 and 37-7). For example, multiple forms of membranoproliferative glomerulonephritis (Chapter 107)

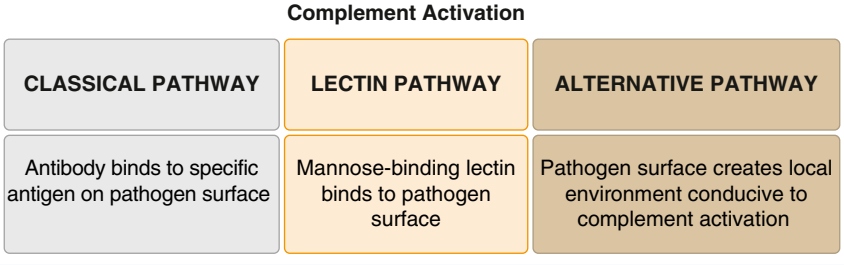

FIGURE 37-2. The three pathways of complement activation. The system is designed to be most efficient on a membrane surface. However, complement activation in the fluid phase, as, for example, in serum sickness, also occurs. In addition, the alternative pathway is continuously at a low level turning over (tickover) in the fluid phase (see Fig. 37-3).

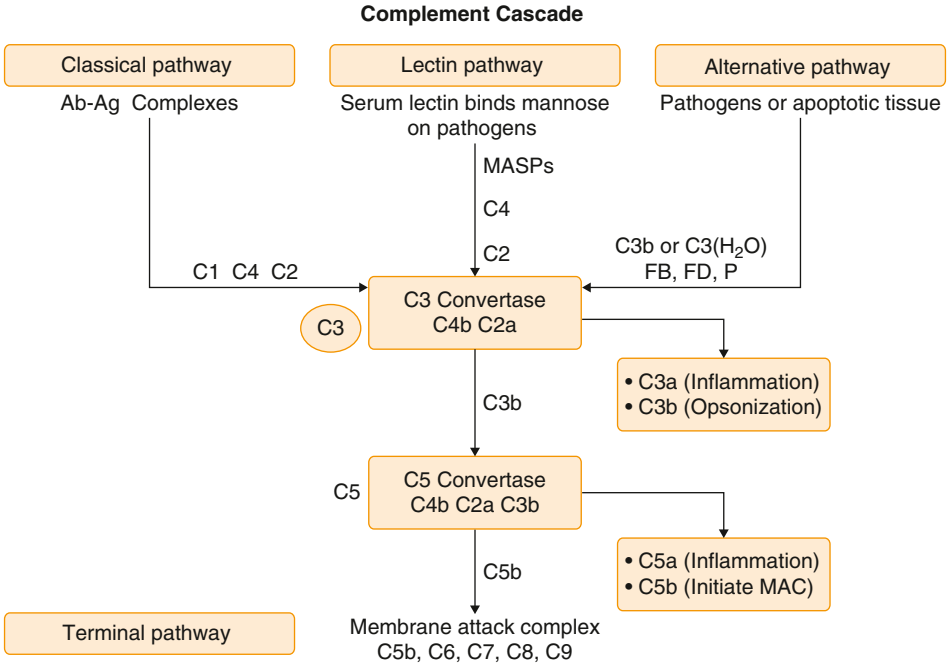

FIGURE 37-3. Classical and lectin pathway activation. Ab = antibody; Ag = antigen; FB = pro-enzyme factor B; FD = protease factor D; MAC = membrane attack complex; MASP = mannan-associated serine protease; P = complement factor P.

TABLE 37-5 TISSUE INJURY OR DEGENERATION AND COMPLEMENT ACTIVATION*

Age-related macular degeneration
Osteoarthritis (degenerative joint disease)
Ischemic stroke
Myocardial infarction
Traumatic injury (e.g., brain, liver, kidney, gut)
Ischemia-reperfusion injury
Burns
Acute respiratory distress syndrome
Septic shock
Multiorgan failure syndromes
Alzheimer disease

*In these conditions, complement activation leads to deposition of fragments at the site of injury; however, how much of the tissue injury is attributable to complement system is unknown. In many cases, animal models support a pathologic role for the complement system. Only in age-related macular degeneration is there also powerful genetic evidence in humans to indicate a key role for the complement system.

are associated with excessive deposition of C3 fragments in the kidney because of either the presence of autoantibodies (C3 or C4 nephritic factors) that stabilize C3 convertases or a genetic deficiency in complement regulatory protein (factor H or factor I). Likewise, atypical hemolytic uremic syndrome[10] (i.e., not associated with a preceding enteropathic infection featuring a Shiga-like toxin) occurs (Chapter 158) in individuals who harbor heterozygous missense mutations in factor H, membrane cofactor protein (MCP), or factor I or have gain-in-function mutations in factor B or C3. Genome-wide association and targeted deep sequencing studies have also linked age-related macular degeneration and diabetic retinopathy[11] (Chapter 391) to functional coding mutations in factor H and factor I and, more uncommonly, in factor B and C3. Finally, rodent models of rheumatoid arthritis, SLE, and antineutrophil cytoplasmic antibody (ANCA)–positive vasculitic syndromes[12] are ameliorated if the alternative pathway is disrupted.

C3 AND C5 CONVERTASES

The three activation pathways converge at C3. A remarkable feature of C3 is the presence of a thioester bond. Buried within the three-dimensional structure of the C3 protein lies a γ-carboxy group of a reactive glutamic acid residue linked to a cysteine in an "internal thioester." Upon its cleavage, for a few microseconds, a covalent attachment can occur via an ester or amide linkage to any nearby hydroxyl or amino group. Most of the cleaved thioester bonds are hydrolyzed by water to produce a form of C3 (known as C3 [H_2O]); however, a substantial percentage forms an amide or ester bond to amino groups or carbohydrates, thereby covalently attaching C3b to a target's surface. Also, the addition of a C3b to C4b2a (classical/lectin pathway C3 convertase) or to C3bBb (alternative pathway C3 convertase) then forms a convertase for C5 (C3bBbC3b for the alternative pathway and C4bC2aC3b for the classical/lectin pathway).

REGULATORS OF COMPLEMENT ACTIVATION AT THE C3 AND C5 STEPS

The regulators of complement activation (see Table 37-6) limit the production of C3b, primarily by the alternative pathway C3 convertases. Because the addition of C3b to a C3 convertase makes it a C5 convertase, regulation of the two enzyme complexes is linked. Modulation of their activity on host cells limits tissue destruction and the production of inflammatory mediators.

The complement activation regulatory proteins control complement activation by two processes. *Decay-accelerating activity* refers to when the inhibitor transiently binds to C3b or C4b in the convertase and thereby dissociates the other members of the complex, rendering it enzymatically inactive (as the component released is the catalytic domain of the protease). The second is cofactor activity, which requires recognition of C3b or C4b by a plasma cofactor protein. Upon this interaction, the protease, factor I, cleaves C3b or C4b. Cleavage of C3b by factor I renders the convertase irreversibly inactive (generates iC3b, which cannot participate in convertase formation).

MEMBRANE ATTACK COMPLEX

The cleavage of C5 generates C5a, the most potent of the complement anaphylatoxins, and C5b. C5b associates with C6 and C7 to create a lipophilic trimer as the initial part of the membrane attack complex (see E-Fig. 37-1). The C5b67 trimer inserts into the lipid bilayer and serves as a binding site for C8 and C9. C9 self-polymerizes, leading to 12 to 18 C9 molecules that form a ring structure, completing the membrane attack complex. The membrane attack complex resembles a doughnut with a 10-nm pore running through the center. This pore allows water and ions to enter the cells, ultimately leading to osmotic lysis. Many pathogens such as gram-positive bacteria possess a capsule that makes them resistant to lysis. Opsonization leading to phagocytosis is thus the major means of eliminating such organisms.

The membrane attack complex appears to be essential only for elimination of *Neisseria* spp. Individuals completely deficient in C5, C6, C7, C8, or C9 are at an increased risk only for meningococcal and gonococcal infections (Chapters 274 and 275). C9 deficiency is a common immunodeficiency in Japan, with a heterozygote frequency of 3 to 5%. Thus, heterozygous deficiency seems to not be deleterious to the population in general but may have a selective advantage.

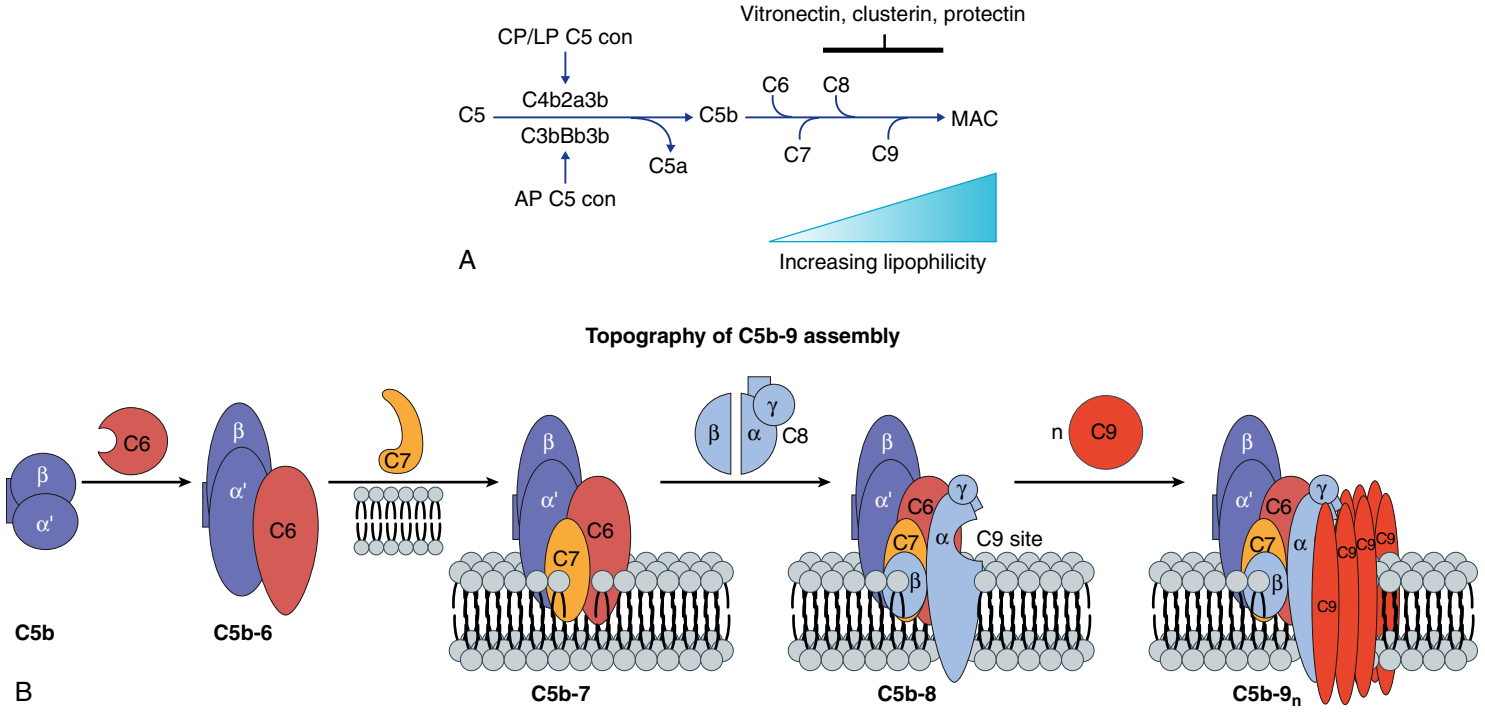

E-FIGURE 37-1. **Activation of C5 and the membrane attack complex (MAC). A,** The C5 convertases (con) are the same as C3 convertases except a C3b has been attached to C4bC2a or a second C3b in the case of alternative pathway (AP) C5 convertase. **B,** Schematic representation of the assembly of the MAC on a cell membrane. C5b (composed of two chains) binds C6 and then C7. The C5b-7 complex can insert into a membrane and then bind C8 (composed of three chains) and multiple C9s to form a pore or channel in the membrane. A complete lack of C5, C6, C7, C8, or C9 predisposes the individual to *Neisseria* infections, especially with the meningococcus (Chapter 274), but no other infectious or immune disorders. Not shown (but see Fig. 37-4) is that properdin stabilizes both C5 convertases and is usually required for efficient C3 and C5 convertase activity. CP = classical pathway; LP = lectin pathway. (Modified from Liszewski MK, Atkinson JP. Regulatory proteins of complement. In: Volanakis JE, Frank MM, eds. *The Human Complement System in Health and Disease*. New York: Marcel Dekker; 1998.)

TABLE 37-6 SOLUBLE AND MEMBRANE FACTORS REGULATING COMPLEMENT

SOLUBLE FACTORS REGULATING COMPLEMENT			
NAME	**LIGAND OR BINDING FACTOR**	**FUNCTIONAL ACTIVITY**	**PATHOLOGY, IF DEFICIENT**
C1-INH	C1r, C1s, mannan-binding lectin-associated serine protease (MASP-2)	Binds to and displaces C1r and C1s from C1q and mannan-binding lectin-associated serine protease (MASP-2) from mannan or mannose binding lectin (MBL)	Hereditary angioedema
C4bp* (C4 binding protein)	C4b, glycosaminoglycans	Displaces C2a (decay-accelerating activity); cofactor for C4b cleavage by factor I (cofactor activity)	No clinical syndrome clearly defined
CPN-1 (carboxypeptidase-N)	C3a, C5a	Inactivates C3a and C5a	Urticaria and angioedema
Factor H*†	C3b, C3d, glycosaminoglycans	Displaces Bb from alternative pathway C3 and C5 convertases (decay-accelerating activity) and is a cofactor for factor I to cleave C3b (cofactor activity)	Age-related macular degeneration, atypical hemolytic uremic syndrome, C3 glomerulopathies, bacterial infections secondary to low C3
Factor I†	C3b, C4b	Serine protease; cleaves C3b and C4b, requires a cofactor protein (cofactor activity)	Age-related macular degeneration, atypical hemolytic uremic syndrome, bacterial infections secondary to low C3
Protein S (vitronectin)	C5b67	Inhibits membrane attachment by C5b67	None defined
MEMBRANE-BOUND FACTORS REGULATING COMPLEMENT			
NAME	**LIGAND OR BINDING FACTOR**	**FUNCTIONAL ACTIVITY**	**DISEASE, IF DEFICIENT**
Decay-accelerating factor (CD55)	C3 and C5 convertases	Prevents binding and displaces Bb from alternative pathway convertase and C2a from CP or LP convertases, respectively	Paroxysmal nocturnal hemoglobinuria Polyneuropathy syndromes CD55 deficiency with hyperactivation of complement, angiopathic thrombosis, and protein-losing enteropathy (CHAPLE syndrome)
Membrane cofactor protein (MCP, CD46)	C3b, C4b	Cofactor for factor I (cofactor activity)	Atypical hemolytic uremic syndrome, immune deficiency
Protectin (CD59)	C8, C9	Inhibits MAC formation and insertion	Paroxysmal nocturnal hemoglobinuria
Complement receptor type 1 (CD35) (immune adherence or C4b/C3b receptor)	C3b, C4b, C3, and C5 convertases	Cofactor for factor I to cleave C4b and C3b (cofactor activity); displaces Bb from C3b and C2a from C4b to inhibit convertases (decay-accelerating activity)	No complete deficiency described; decreased levels in immune complex–mediated diseases such as lupus
Complement receptor of the immunoglobulin superfamily (CRIg)	C3b, iC3b, C3c	Inhibits activation of alternative pathway	None defined

*Factors H and C4bp also bind to surfaces, particularly at sites of tissue and cellular injury, where they carry out regulatory activity.
†If heterozygous deficient, the individual is predisposed to age-related macular degeneration and atypical hemolytic uremic syndrome. If homozygous deficient, the AP turns over excessively, resulting in kidney disease (C3 glomerulopathies) and bacterial infections (secondary to the very low C3).
$(C3b)_2$ Bb = alternative pathway C5 convertase; C3bC4bC2a = classical and lectin pathway C5 convertase; C4bC2a = classical and lectin pathway C3 convertase; MAC = membrane attack complex.

Extensive complement activation during an inflammatory response can result in sufficient membrane attack complex deposition to produce host cell lysis. Host cells, however, have mechanisms in place to resist the osmotic changes caused by the membrane attack complex and to block assembly of the membrane attack complex as it is formed (the protein is known as protectin or CD59). Rather, the nonlethal effects of sublytic membrane attack complex deposition are more likely to contribute to pathology. In most cells, this occurs through a general activation of multiple cell signaling pathways.

The response to membrane attack complex deposition at sites of complement activation depends on the cell type (Table 37-8). In phagocytic cells, such as neutrophils or macrophages, sublytic membrane attack complex insertion leads to the production of reactive oxygen species (e.g., superoxide, hydrogen peroxide) as well as release of prostaglandins and leukotrienes. Platelets undergoing a "membrane attack complex insertion" expose phosphatidylserine on their outer membrane, facilitating assembly of blood coagulation enzyme complexes on their surfaces with a potentially procoagulant effect. On endothelial cells, membrane attack complex deposition induces the synthesis of interleukin-1α (IL-1α), which leads to further autocrine and paracrine endothelial cell activation. It stimulates a procoagulant state by (1) altering the phospholipid composition of the endothelial membrane; (2) inducing the synthesis of tissue factor and upregulating the synthesis of plasminogen activator inhibitor; (3) upregulating the expression of adhesion molecules, including intercellular adhesion molecule 1 (ICAM-1) and E-selectin; and (4) stimulating endothelial cells to proliferate through growth factor production. In summary, although cell death does not usually occur, deposition of the sublytic levels of membrane attack complex leads to a potentially dangerous situation, with increased inflammation, a procoagulant state, and cellular proliferation. Of course, part of this response is necessary at sites of injury to eliminate pathogens and debris and to facilitate wound repair. The short duration of complement activation and the presence of inhibitors help to maintain homeostasis.

Regulation of membrane attack complex formation is important clinically (Fig. 37-5). Two plasma proteins, S-protein (vitronectin) and possibly clusterin, bind the C5b-7 complex and prevent its association with the lipid membrane. C8 and multiple C9 molecules adhere to this soluble complex, termed *soluble C5b-9*, which is lytically inactive. CD59 (protectin) is a membrane-bound inhibitor of membrane attack complex formation. This small glycoprotein is attached to the cell membrane through a glycosyl phosphatidylinositol tail (GPI anchor). It binds to C5b-8, inserted in the cell membrane, to prevent binding to and polymerization of C9. The expression of CD59 is defective in patients with paroxysmal nocturnal hemoglobinuria (Chapter 146), owing to the failure to synthesize the GPI anchor used by this and many other membrane proteins (including decay-accelerating factor [DAF]) to insert on the cell. The clinical features of paroxysmal nocturnal hemoglobinuria are primarily chronic hemolysis and intermittent thrombosis. Hemolysis is caused by complement activation on red cells because of a lack of DAF and particularly CD59. Thrombosis (Chapter 67) is likely secondary to intravascular complement activation, leading to endothelial cell activation. The primary defect is an acquired somatic hematopoietic stem cell mutation of a gene on the X chromosome responsible for encoding the first enzyme in the pathway to synthesize a GPI anchor.

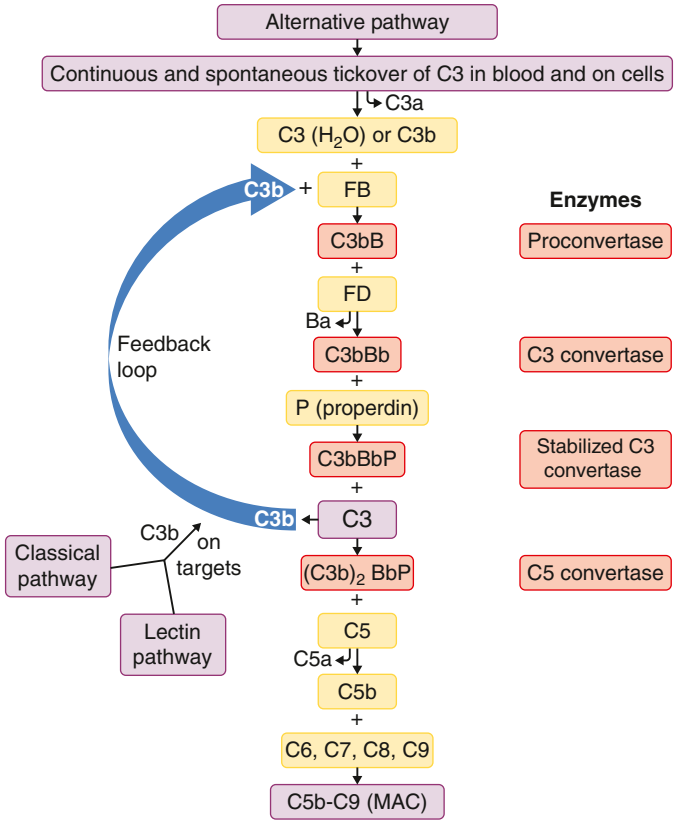

FIGURE 37-4. Complement activation pathways. In the reaction cascade shown, C3b or C3 (H_2O) binds the pro-enzyme factor B (FB), and the C3bB or C3 (H_2O)B complex then is cleaved by the protease factor D (FD). FD is generated by the cleavage of inactive pro-FD to active FD by the protease MASP-3. The addition of properdin (P) to the enzyme complex increases the half-life of the enzyme complex approximately 10-fold. Although the source of the C3b can be from spontaneous turnover or via lectin pathway (LP) and classical pathway (CP) activation, the alternative pathway (AP) feedback loop commonly takes over to generate much of C3b that binds to a target. The alternative pathway is continuously turning over. If activated C3b or C3 (H_2O) remains in the fluid phase, it is rapidly inhibited by the plasma regulators factor H and factor I. If activated C3b binds to normal or healthy self, it is prevented from forming a convertase by the ubiquitously expressed membrane cofactor protein (MCP [CD46]) and decay-accelerating factor (DAF [CD55]) (not shown). DAF both prevents B from binding to C3b and "kicks out" the catalytic Bb domain (a temporary stop), but MCP is a permanent stop because, upon its binding, the C3b is proteolytically cleaved to inactive C3b (iC3b) by the serine protease factor I. The feedback loop is a powerful amplification system. A single *Escherichia coli* organism in blood can be coated with several million C3bs in a couple of minutes!

ANAPHYLATOXINS

The anaphylatoxins serve a key early role in initiating a local inflammatory response as they trigger pathways to prepare a cell to face a pathogen or injury (Table 37-9). Similar to the membrane attack complex, anaphylatoxins are another major source of potential pathologic damage to self that results from complement activation. These peptides, C3a and C5a, are cleaved from their respective proteins during complement activation. They are 77 (C3a) or 74 (C5a) amino acids long and contain a key carboxy (C)-terminal arginine. They interact with the anaphylatoxin receptors. In plasma, the C-terminal arginine is removed by carboxypeptidase-N from anaphylatoxins not bound to their receptors. Depending on the response studied, this removal totally inactivates the anaphylatoxin or reduces its potency by about 1000-fold.

TABLE 37-8 RESPONSES TO SUBLYTIC MEMBRANE ATTACK COMPLEX ACTIVATION

CELL TYPE	EFFECTS
Most cells	Increased intracellular calcium flux Activation of G proteins Activation of protein kinases Activation of transcription factors Proliferation
Neutrophils and macrophages	Release of reactive oxygen species Activation of phospholipase A_2 Release of prostaglandins, thromboxane, and leukotrienes
Platelets	Release of adenosine triphosphate Increased P-selectin expression Procoagulant membrane changes
Endothelial cells	Increased synthesis of IL-1α Increased release of tissue factor Increased release of von Willebrand factor Increased synthesis of basic fibroblast and platelet-derived growth factors
Synoviocytes	Increased synthesis of prostaglandins Increased synthesis of interleukin-6 Increased production of matrix metalloproteinase
Glomerular epithelium	Activation of phospholipase A_2 Synthesis of prostaglandin Increased synthesis of collagen and fibronectin
Oligodendrocytes	Increased synthesis of myelin basic protein and proteolipids Increased proliferation

TABLE 37-7 COMPLEMENT SYSTEM MEDIATES THE DISEASE PROCESS AND ITS INHIBITION TREATS THE CONDITION

DISEASE	PATHOPHYSIOLOGY	ETIOLOGY	TREATMENT	FDA APPROVED
Paroxysmal nocturnal hemoglobinuria (Chapter 146)	Lyse red blood cells	Acquired hematopoietic somatic stem cell mutation in gene required for synthesis of glycosylphosphatidylinositol (GPI) anchor	Monoclonal antibody to C5 Peptide C3 convertase inhibitor	Yes Yes
Atypical hemolytic uremic syndrome (Chapter 158)	Damage to endothelial cells	Inherited loss-of-function variants in alternative pathway regulators or gain of function variants in alternative pathway activators	Monoclonal antibody to C5	Yes
Hereditary angioedema (Chapter 232)	Bradykinin generation	Autosomal dominant variants in the C1-inhibitor gene	C1 inhibitor replacement Bradykinin receptor blockage Kallikrein inhibitors	Yes Yes Yes
Age-related macular degeneration (Chapter 391)	Degeneration of the retina	Inherited variants in a regulator (factor H or factor I) or gain-in-function in an alternative pathway component (C3 or factor B)	Clinical trials in progress	No
Neuromyelitis optica spectrum disorder (Chapter 392)	Damage to spinal cord and optic nerve	Complement-fixing autoantibodies to aquaporin-4 typically found	Monoclonal antibody to C5	Yes
Myasthenia gravis (Chapter 390)	Degeneration of neuromuscular junction	Complement-fixing autoantibodies to acetylcholine receptor	Monoclonal antibody to C5	Yes

FDA = Food and Drug Administration.

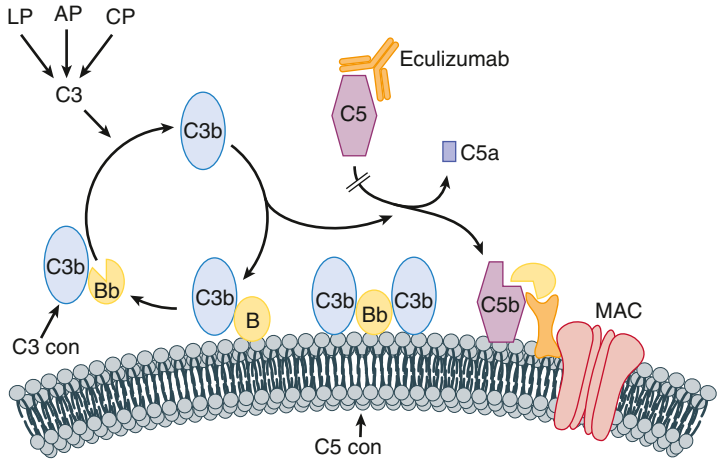

FIGURE 37-5. Complement activation and the mechanism of action of eculizumab (monoclonal antibody [mAb] to C5). The alternative pathway (AP) constantly undergoes "tickover" but can also be primed by the classical pathway (CP) and lectin pathway (LP). The C3b that is formed interacts with factor B (B), which is then cleaved by factor D to form a C3 convertase (C3Bb). As more C3b is generated, a fraction binds to the C3 convertase to form a C5 convertase. Monoclonal antibody to C5 (eculizumab) prevents the cleavage of C5 by the C5 convertase. Not shown is that properdin binds to both the C3 and C5 convertases to increase their half-lives approximately five- to 10-fold (from ≈30 seconds to several minutes). (Modified from Wong EK, Goodship TH, Kavanagh D. Complement therapy in atypical haemolytic uraemic syndrome [aHUS]. *Mol Immunol*. 2013;56:199-212.)

TABLE 37-9 DISTRIBUTION OF ANAPHYLATOXIN RECEPTORS AND THEIR CELLULAR RESPONSES

CELL TYPE	RESPONSES
C5aR (CD88)	
Neutrophils	Chemotaxis
Eosinophils	Enzyme release
Basophils	Generation of reactive oxygen species
Mast cells	Upregulation of adhesion molecules
Monocytes	Increased synthesis of interleukin-1, interleukin-6, and interleukin-8
	Prostaglandin and leukotriene synthesis
Hepatocytes	Increased synthesis of acute phase reactants
Pulmonary epithelium	Increased interleukin-8
Neuronal cells	Cellular activation
Endothelial cells	Increased expression of P-selectin
Renal epithelial/mesangial cells	Proliferation and synthesis of growth factors
C3aR	
Eosinophils	Chemotaxis
Mast cells	Enzyme release
Platelets	Generation of reactive oxygen species
	Upregulation of adhesion molecules
Epithelial, endothelial, etc.	Cellular activation

IL = interleukin.

The C5a receptor (C5aR [CD88]) is a seven-transmembrane-spanning protein that couples ligand binding to G-protein signaling. Expressed on myeloid cells, particularly neutrophils and eosinophils, it mediates the potent chemoattractant property of C5a for both of these cell types. Signaling through CD88 leads to rapid secretion of all granule contents. These contents include lipases and proteases as well as lactoferrin from neutrophils and peroxidase, major basic protein, and cationic protein from eosinophils. C5a also induces the release of cytokines, such as tumor necrosis factor (TNF), IL-1, IL-6, IL-8, and adhesion molecules, promoting the inflammatory response. The C5aR is expressed by numerous other tissues, including hepatocytes, bronchial and alveolar epithelium, vascular endothelium, renal mesangial and tubular epithelial cells, and brain neuronal cells. These cells are activated by receptor engagement, leading to production and release of cytokines, chemokines, and prostaglandins and to cellular proliferation.

The C3a receptor is also a seven-transmembrane-domain protein. It is expressed on almost all myeloid cells, including mast cells, where it mediates the release of allergic mediators. The C3aR also has been detected on many tissues, including in the brain and lung.

The anaphylatoxins have multiple biologic effects. In general, they cause smooth muscle contraction and recruitment of granulocytes, monocytes, and mast cells. In theory, they can contribute to the pathophysiology of any inflammatory condition. In disease models, C3a and C5a have been shown to play a role in diseases such as acute respiratory distress syndrome (ARDS), multisystem organ failure, septic shock, myocardial ischemia-reperfusion injury, ANCA-associated vasculitis, asthma, rheumatoid arthritis, SLE, and inflammatory bowel disease. The anaphylatoxin peptides also are responsible for the "postpump" syndrome seen in patients undergoing cardiopulmonary bypass or hemodialysis. Exposure of blood to dialysis or perfusion membranes leads to complement activation. Within minutes of starting bypass, there is a sharp increase in the levels of C3a and C5a in the extracorporeal circuit being returned to the patient. This increase can be associated with respiratory distress, pulmonary hypertension, and pulmonary edema. It has been shown that the length of time that patients stay on the ventilator after bypass surgery correlates with the level of C3a generated during reperfusion.

C3a and C5a have been implicated in the initiation and prolongation of ARDS (Chapter 90) and multisystem organ failure. After severe trauma, levels of C3a have been measured that suggest activation of the entire circulating C3 pool. This activation leads to bronchoconstriction, increased vascular permeability, hypotension, and vascular plugging with leukocytes. The activation of white blood cells continues the cycle of tissue damage with further complement activation. Continued elevation of C3a in shock or ARDS is a poor prognostic sign. C3a and C5a also appear to play a major role in the pathogenesis of asthma (Chapter 75).

COMPLEMENT RECEPTORS

Opsonization of target by C4b and C3b is effective in preventing infections because these two complement fragments (and the further cleavage products in the case of C3b) are ligands for complement receptors (E-Fig. 37-2). After covalent attachment of C4b and C3b, immune adherence occurs between the opsonized microbe and immune cells, predominantly neutrophils, monocytes, and macrophages. Complement opsonins are highly effective mediators of immune adherence. On phagocytic cells, this is the prelude to the ingestion and destruction of the target antigen. On red cells, immune adherence is followed by transfer of the C4b/C3b-coated cargo to monocytes and macrophages in the liver and spleen. CR1 is particularly efficient at immune adherence. Proteolytic modification of C3b leads to iC3b, which is a ligand for the highly phagocytic CR3 and CR4. A further degradation of iC3b to C3d leads to an interaction with CR2 to lower the threshold of B-cell activation. Overall, the process is designed with two goals in mind: (1) destruction by phagocytosis of the microbe and (2) coating of microbial antigens for an adaptive immune response. For example, follicular dendritic cells and B lymphocytes express CR1, CR2, CR3, and CR4 that facilitate complement-coated antigens to be bound, internalized, and presented to other immune cells. CR3 and CR4 facilitate phagocytosis, and CR2 on follicular dendritic cells facilitates immunologic memory generation.

COMPLEMENT INHIBITORS

Given the many disease states in which complement is one of the central mediators of pathology, it is no surprise that complement inhibitors are in preclinical or clinical development for treatment of human diseases (see Table 37-2 and E-Fig. 37-2). These inhibitors take several different forms. Whereas some are variations of physiologic inhibitors, others are the products of molecular biologic searches for novel compounds.[13,14]

It is important to consider where in the complement pathway to design an inhibitor to act. Inhibition of the activation pathways limits the production of biologically active peptides. Inhibiting the activation of C3 not only prevents the generation of the C3a anaphylatoxin but also may leave the patient susceptible to infection by limiting the deposition of C3b on targets as an opsonin. Inhibition of C3b deposition would decrease the patient's ability to clear immune complexes, potentially resulting in renal, pulmonary, and vascular damage. It also might promote the development of antibodies to self-antigens.

Inhibition of the C5 convertases is an attractive goal because it would prevent the generation of the C5a anaphylatoxin and the membrane attack complex (see Fig. 37-5). This strategy would inhibit complement activation without limiting C3b deposition. Inhibitors based on this concept have been successful; the monoclonal antibody to C5 is approved by the U.S. Food and Drug Administration (FDA) to treat paroxysmal nocturnal hemoglobinuria and atypical hemolytic-uremic syndrome (Chapter 158) as well as neuromyelitis optica spectrum disorder (Chapter 392) and myasthenia gravis (Chapter 390).

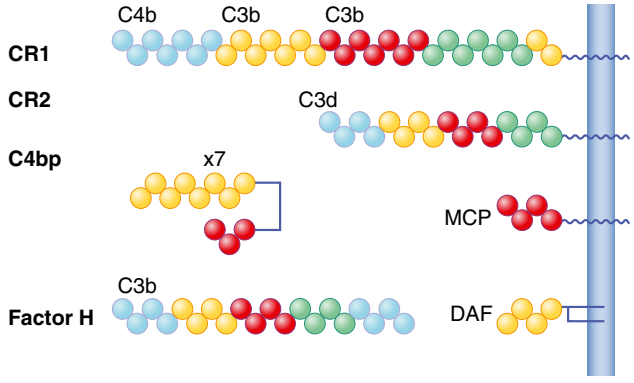

E-FIGURE 37-2. Model of the complement regulators required to inhibit complement activation on self at the steps of C3 and C5 cleavage. *Circles* represent individual complement control repeats (~60 amino acids each), and *shading* indicates higher organizational units composed of several repeats. The approximate locations for binding of C3b and C4b fragments are indicated. Factor H and C4bp are plasma proteins. C4bp = C4-binding protein; CR = complement receptor; DAF = decay-accelerating factor; MCP = membrane cofactor protein.

Other concerns about complement inhibition include whether it is short or long term and whether it is systemic or local. Long-term inhibition of complement, particularly at one of the early steps, is likely to predispose to infection and possibly autoimmunity. Short-term (hours to days) inhibition at any step is unlikely to cause problems. Given that inflammation is usually a local phenomenon, several mechanisms are being tested to target complement inhibitors to these sites. In this way, higher levels of inhibition can be achieved when needed and with lower doses of inhibitor.

NATURAL COMPLEMENT INHIBITORS

Naturally occurring compounds that control complement activation include products or extracts of plants, fungi, insects, bacteria, viruses, and venoms. The mechanism of complement inhibition by some of these natural products is known and is of clinical and experimental importance. In particular, to protect themselves from the host's complement system, poxviruses, herpesviruses, and flaviviruses produce either mimics of the human regulators that they at one time hijacked from their hosts or proteins that bind the hosts' regulators such as the plasma protein factor H. Bacteria also express a wide variety of inhibitors of the human complement system. *Staphylococcus aureus,* for example, synthesizes up to 10 distinct proteins that inhibit at almost every key step of the complement cascade. Cobra venom factor (CVF) is a modified form of cobra C3b secreted by venom glands in the oral cavity. It is a 144,000-dalton glycoprotein that forms an alternative pathway convertase in association with host factor B. Upon injection, CVF leads to massive activation of the alternative pathway, resulting in shock and pulmonary microvascular injury in experimental animals. It is resistant to the host's inhibitors because the site for that interaction is altered on CVF. Perhaps the most widely used natural inhibitor of complement activation is heparin. It decreases activation of the classical pathway and alternative pathway. In clinical practice, the anticomplementary effect of heparin has been used to prevent complement activation during cardiopulmonary bypass. Measurement of complement activation products such as C3a or soluble C5b-9 after bypass showed decreases of 35 to 70% for adult and pediatric patients when heparin-coated extracorporeal circuits were used. Although numerous studies have looked at the decrease in complement activation by heparin-coated bypass circuits, there have been few attempts to correlate this with clinical outcome.

ANTI-C5

The complement inhibitor that has achieved the widest attention as a therapeutic agent to stop complement activation is a monoclonal antibody that targets C5 and prevents its cleavage to C5a (potent anaphylatoxin) and C5b (initiator of the membrane attack complex) (see Fig. 37-5). The generation of the C3b and C4b still occurs, allowing opsonization of pathogens and formation of immune complexes. Because activation of early complement components is also important for the maintenance of tolerance to self-antigens, inhibition of C5 activation is less worrisome than inhibition of C3 activation. The one consequence of C5 deficiency in humans is an increased risk of *Neisseria* infections (Chapters 274 and 275) that can largely be mitigated through vaccination. The anti-C5 monoclonal antibody eculizumab has been approved for use in patients with paroxysmal nocturnal hemoglobinuria, atypical hemolytic uremic syndrome, neuromyelitis optica, and myasthenia gravis. Additional inhibitors targeting the C3 convertase, specific complement receptors, and early pathway-specific activation mechanisms are all under active development and clinical trials.

The complement system is undergoing a renaissance. There are several reasons but probably the foremost is the discovery of mutations in complement regulators leading to atypical hemolytic uremic syndrome and age-related macular degeneration. Second is the therapeutic success of a monoclonal antibody to C5 in the treatment of atypical hemolytic uremic syndrome and paroxysmal nocturnal hemoglobinuria. Third is the introduction of purified C1-INH, kallikrein inhibitors, and a bradykinin receptor antagonist to prevent and treat swelling attacks in hereditary angioedema. Last, intriguing recent data implicate the complement system in the pathophysiology of multiple disorders, including age-related macular degeneration, ischemia/reperfusion injury, organ regeneration, brain development (pruning of undesirable synapses), intracellular metabolomics and polarization processes, obesity, asthma, T-cell activation phenomena associated with allergic and rheumatic diseases,[15,16] and more.

GENERAL REFERENCES

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38 TRANSPLANTATION IMMUNOLOGY

MEGAN SYKES

DEFINITION

Clinical transplantation encompasses transplantation of organs and islets of Langerhans containing insulin-producing β cells, in which it is necessary to overcome the host-versus-graft (HVG) immune response to avoid rejection, as well as hematopoietic cell transplantation (Chapter 163), in which it is necessary to contend with not only the HVG but also the graft-versus-host (GVH) immune response. Because preparations of bone marrow or mobilized peripheral blood stem cells contain mature T cells, their administration to conditioned and consequently immunoincompetent recipients is associated with the risk for GVH disease (GVHD). Transplanted organs and tissues include corneas, kidneys, livers, hearts, lungs, small intestines, pancreases, hands, and faces. Uterine, penile, and laryngeal transplantation are composite tissue transplants that have only recently become possible, and the numbers performed are consequently quite low.

Transplants originating from a member of the same species are referred to as *allotransplants*. However, transplants from other species, termed *xenografts*, provide a promising solution to the severely inadequate supply of allogeneic organs and tissues, and may be used in the future. Transplants of tissues or cells originating from the recipient, either by processing of cells from the recipient's own organ (e.g., islets of Langerhans following pancreatectomy for chronic pancreatitis) or cell populations (e.g., $CD34^+$ hematopoietic progenitor and stem cells collected from leukapheresis products following mobilization from the bone marrow before high-dose radiation or chemotherapy to treat cancer) are referred to as *autologous*. In the future, these transplants may include stem cell–derived autologous cells used for therapeutic purposes.

ANTIGENS IN TRANSPLANTATION

The major antigens recognized during graft rejection and the cell types targeting them are summarized in Table 38-1.

MAJOR HISTOCOMPATIBILITY ANTIGENS

The major histocompatibility complex (MHC; human leukocyte antigens [HLAs] in the human) controls adaptive and some innate immune responses and is of central importance in many immune-mediated diseases. The MHC also presents the strongest immunologic obstacle to all types of allografts. The HLA molecules include two major isoforms, termed class I and class II, and are all encoded in the MHC complex of chromosome 6. Although all HLA molecules have a similar general structure, class I and class II molecules show different expression patterns, with class I MHC expressed on most cells of the body, whereas class II antigens are expressed mainly on antigen-presenting cell populations, such as dendritic cells, macrophages, and B cells, as well as thymic epithelial cells involved in T-cell selection. Class II MHC can also be expressed on human vascular endothelial cells and activated T cells.

The function of both classes of MHC molecules is to present peptide antigens to T-cell receptors, allowing adaptive immune responses to occur (Chapter 35). Class I molecules typically present eight- to nine-amino acid peptides derived from cytosolic proteins (e.g., viral proteins) that are transported into the endoplasmic reticulum, where they are processed and loaded onto class I molecules. CD8 molecules interact with the α_3 domain of the class I heavy chain, thereby strengthening the interaction of $CD8^+$ T cells that recognize class I–peptide complexes. Peptides presented by class II MHC molecules, on the other hand, are mostly 10- to 20-mers derived from exogenous proteins (e.g., phagocytosed bacteria) that are processed through the endosomal processing pathway, and these are recognized by receptors of T cells whose CD4 molecules strengthen the overall T cell–antigen-presenting cell interaction. The class I presentation pathway is of particular importance in allowing destruction of virally infected cells, consistent with the expression of class I MHC on almost all cell types in the body. An exception occurs when class I molecules present peptides from exogenous antigens, thereby resulting in cross-presentation and cross-priming of T cells. Class II MHC presentation of exogenous antigens takes place primarily on professional antigen-presenting cells and B cells, consistent with the role of $CD4^+$ T cells in initiating immune responses by activating antigen-presenting cells, providing direct and indirect

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Other concerns about complement inhibition include whether it is short or long term and whether it is systemic or local. Long-term inhibition of complement, particularly at one of the early steps, is likely to predispose to infection and possibly autoimmunity. Short-term (hours to days) inhibition at any step is unlikely to cause problems. Given that inflammation is usually a local phenomenon, several mechanisms are being tested to target complement inhibitors to these sites. In this way, higher levels of inhibition can be achieved when needed and with lower doses of inhibitor.

NATURAL COMPLEMENT INHIBITORS

Naturally occurring compounds that control complement activation include products or extracts of plants, fungi, insects, bacteria, viruses, and venoms. The mechanism of complement inhibition by some of these natural products is known and is of clinical and experimental importance. In particular, to protect themselves from the host's complement system, poxviruses, herpesviruses, and flaviviruses produce either mimics of the human regulators that they at one time hijacked from their hosts or proteins that bind the hosts' regulators such as the plasma protein factor H. Bacteria also express a wide variety of inhibitors of the human complement system. *Staphylococcus aureus,* for example, synthesizes up to 10 distinct proteins that inhibit at almost every key step of the complement cascade. Cobra venom factor (CVF) is a modified form of cobra C3b secreted by venom glands in the oral cavity. It is a 144,000-dalton glycoprotein that forms an alternative pathway convertase in association with host factor B. Upon injection, CVF leads to massive activation of the alternative pathway, resulting in shock and pulmonary microvascular injury in experimental animals. It is resistant to the host's inhibitors because the site for that interaction is altered on CVF. Perhaps the most widely used natural inhibitor of complement activation is heparin. It decreases activation of the classical pathway and alternative pathway. In clinical practice, the anticomplementary effect of heparin has been used to prevent complement activation during cardiopulmonary bypass. Measurement of complement activation products such as C3a or soluble C5b-9 after bypass showed decreases of 35 to 70% for adult and pediatric patients when heparin-coated extracorporeal circuits were used. Although numerous studies have looked at the decrease in complement activation by heparin-coated bypass circuits, there have been few attempts to correlate this with clinical outcome.

ANTI-C5

The complement inhibitor that has achieved the widest attention as a therapeutic agent to stop complement activation is a monoclonal antibody that targets C5 and prevents its cleavage to C5a (potent anaphylatoxin) and C5b (initiator of the membrane attack complex) (see Fig. 37-5). The generation of the C3b and C4b still occurs, allowing opsonization of pathogens and formation of immune complexes. Because activation of early complement components is also important for the maintenance of tolerance to self-antigens, inhibition of C5 activation is less worrisome than inhibition of C3 activation. The one consequence of C5 deficiency in humans is an increased risk of *Neisseria* infections (Chapters 274 and 275) that can largely be mitigated through vaccination. The anti-C5 monoclonal antibody eculizumab has been approved for use in patients with paroxysmal nocturnal hemoglobinuria, atypical hemolytic uremic syndrome, neuromyelitis optica, and myasthenia gravis. Additional inhibitors targeting the C3 convertase, specific complement receptors, and early pathway-specific activation mechanisms are all under active development and clinical trials.

The complement system is undergoing a renaissance. There are several reasons but probably the foremost is the discovery of mutations in complement regulators leading to atypical hemolytic uremic syndrome and age-related macular degeneration. Second is the therapeutic success of a monoclonal antibody to C5 in the treatment of atypical hemolytic uremic syndrome and paroxysmal nocturnal hemoglobinuria. Third is the introduction of purified C1-INH, kallikrein inhibitors, and a bradykinin receptor antagonist to prevent and treat swelling attacks in hereditary angioedema. Last, intriguing recent data implicate the complement system in the pathophysiology of multiple disorders, including age-related macular degeneration, ischemia/reperfusion injury, organ regeneration, brain development (pruning of undesirable synapses), intracellular metabolomics and polarization processes, obesity, asthma, T-cell activation phenomena associated with allergic and rheumatic diseases,[15,16] and more.

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38 TRANSPLANTATION IMMUNOLOGY

MEGAN SYKES

DEFINITION

Clinical transplantation encompasses transplantation of organs and islets of Langerhans containing insulin-producing β cells, in which it is necessary to overcome the host-versus-graft (HVG) immune response to avoid rejection, as well as hematopoietic cell transplantation (Chapter 163), in which it is necessary to contend with not only the HVG but also the graft-versus-host (GVH) immune response. Because preparations of bone marrow or mobilized peripheral blood stem cells contain mature T cells, their administration to conditioned and consequently immunoincompetent recipients is associated with the risk for GVH disease (GVHD). Transplanted organs and tissues include corneas, kidneys, livers, hearts, lungs, small intestines, pancreases, hands, and faces. Uterine, penile, and laryngeal transplantation are composite tissue transplants that have only recently become possible, and the numbers performed are consequently quite low.

Transplants originating from a member of the same species are referred to as *allotransplants*. However, transplants from other species, termed *xenografts*, provide a promising solution to the severely inadequate supply of allogeneic organs and tissues, and may be used in the future. Transplants of tissues or cells originating from the recipient, either by processing of cells from the recipient's own organ (e.g., islets of Langerhans following pancreatectomy for chronic pancreatitis) or cell populations (e.g., $CD34^+$ hematopoietic progenitor and stem cells collected from leukapheresis products following mobilization from the bone marrow before high-dose radiation or chemotherapy to treat cancer) are referred to as *autologous*. In the future, these transplants may include stem cell–derived autologous cells used for therapeutic purposes.

ANTIGENS IN TRANSPLANTATION

The major antigens recognized during graft rejection and the cell types targeting them are summarized in Table 38-1.

MAJOR HISTOCOMPATIBILITY ANTIGENS

The major histocompatibility complex (MHC; human leukocyte antigens [HLAs] in the human) controls adaptive and some innate immune responses and is of central importance in many immune-mediated diseases. The MHC also presents the strongest immunologic obstacle to all types of allografts. The HLA molecules include two major isoforms, termed class I and class II, and are all encoded in the MHC complex of chromosome 6. Although all HLA molecules have a similar general structure, class I and class II molecules show different expression patterns, with class I MHC expressed on most cells of the body, whereas class II antigens are expressed mainly on antigen-presenting cell populations, such as dendritic cells, macrophages, and B cells, as well as thymic epithelial cells involved in T-cell selection. Class II MHC can also be expressed on human vascular endothelial cells and activated T cells.

The function of both classes of MHC molecules is to present peptide antigens to T-cell receptors, allowing adaptive immune responses to occur (Chapter 35). Class I molecules typically present eight- to nine-amino acid peptides derived from cytosolic proteins (e.g., viral proteins) that are transported into the endoplasmic reticulum, where they are processed and loaded onto class I molecules. CD8 molecules interact with the α_3 domain of the class I heavy chain, thereby strengthening the interaction of $CD8^+$ T cells that recognize class I–peptide complexes. Peptides presented by class II MHC molecules, on the other hand, are mostly 10- to 20-mers derived from exogenous proteins (e.g., phagocytosed bacteria) that are processed through the endosomal processing pathway, and these are recognized by receptors of T cells whose CD4 molecules strengthen the overall T cell–antigen-presenting cell interaction. The class I presentation pathway is of particular importance in allowing destruction of virally infected cells, consistent with the expression of class I MHC on almost all cell types in the body. An exception occurs when class I molecules present peptides from exogenous antigens, thereby resulting in cross-presentation and cross-priming of T cells. Class II MHC presentation of exogenous antigens takes place primarily on professional antigen-presenting cells and B cells, consistent with the role of $CD4^+$ T cells in initiating immune responses by activating antigen-presenting cells, providing direct and indirect

ABSTRACT

Clinical transplantation encompasses allogeneic organs such as kidneys, livers, intestines, hearts, and lungs; composite tissues such as limbs; tissues such as islets of Langerhans; and cells such as bone marrow or mobilized peripheral blood hematopoietic cells. Allograft rejection due to host-versus-graft immune responses is driven largely by T cells and may also involve humoral responses. When hematopoietic cells are transplanted, rejection in the opposite direction may cause graft-versus-host disease. The most potent allograft responses in both directions are mediated by recognition of allogeneic human leukocyte antigen (HLA) molecules, which are highly polymorphic. When HLA is identical between the donor and recipient, responses to multiple minor histocompatibility antigens still pose significant barriers in both directions. New approaches to preventing graft-versus-host disease have recently permitted extension of hematopoietic cell transplantation to include alternative, HLA-mismatched donors. The mainstay of successful organ and tissue transplantation has been chronic nonspecific immunosuppressive therapy. Despite its overall success in advancing transplantation, this approach is associated with significant toxicity and has made little progress in preventing chronic rejection. Induction of allograft tolerance, which would obviate the need for lifelong immunosuppression while preventing both early and late rejection, is a major goal in the transplantation field. Several advances have recently been made toward this goal, and small trials of combined hematopoietic cell and kidney transplantation have successfully induced allograft tolerance. The inadequate supply of human organs for transplantation presents a major hurdle, resulting in exploration of xenotransplantation as a promising alternative for the future.

KEYWORDS

transplantation
HLA
allograft
allotransplants
xenografts
rejection
graft-versus-host disease
immune tolerance

TABLE 38-1 LYMPHOCYTES INVOLVED IN GRAFT REJECTION

CELL TYPE	ANTIGENS RECOGNIZED	FUNCTION	RELEVANCE
$CD4^+$ T cells	Allogeneic class II MHC (+ peptide) Self class II MHC + donor peptide	Antigen-presenting cell activation Help (cytokines and costimulation) Proinflammatory cytokine production Cytotoxicity Regulatory function	Organ allografts Cellular allografts Xenografts GVHD
$CD8^+$ T cells	Allogeneic class I MHC (+ peptide) Self class I MHC + donor peptide	Cytotoxicity Cytokine production Regulatory function	Organ allografts Cellular allografts Xenografts GVHD
NK cells	Class I MHC (activates or inhibits NK cell function) Other activating ligands	Cytotoxicity Cytokine production	Organ allografts Cellular allografts Xenografts
B cells	Class I and class II MHC Blood group antigens Xenogeneic carbohydrates	Antibody-mediated rejection (hyperacute, acute humoral, and chronic rejection)	Organ and hematopoietic cell allografts Cellular allografts Xenografts GVHD

CTL = cytotoxic T lymphocyte; GVHD = graft-versus-host disease; MHC = major histocompatibility complex; NK = natural killer.

(through activated antigen-presenting cells that also present peptides on class I molecules) "help" for $CD8^+$ cytotoxic T lymphocytes, and providing help for antibody-producing B cells. B cells are able to focus the antigens recognized by their specific surface immunoglobulin receptors by binding and internalizing these antigens, which enter the endosomal antigen-processing pathway and become presented by class II molecules on that B cell. This ability of B cells preferentially to present peptides derived from their cognate antigens to CD4 T cells recognizing those alloantigens is very important in driving alloantibody production.

A number of MHC molecules have been crystallized, both alone and with T-cell receptors that recognize them. The structure of class I and II MHC molecules is similar overall and includes both the peptide-binding cleft formed by a β-pleated sheet and two α-helices forming the sides of the cleft (E-Fig. 38-1). However, class I and II MHC molecules also have significant structural differences, as summarized in E-Table 38-1. T-cell receptors interact physically with both the α-helices of the MHC molecules and side chains of the peptide that is bound in the groove, thereby representing a trimolecular MHC-peptide–T-cell receptor interaction (see E-Fig. 38-1). The most variable ("hypervariable") portion of the T-cell receptor, which is produced by V-D (for TCRβ)-J somatic rearrangements and N insertions in the T-cell receptor α and β chains, known as complementarity-determining region 3 (CDR3), recognizes specific MHC-peptide complexes.

The HLA molecules are all encoded within a 3.6-million base-pair region that encodes more than 200 genes, including complement and tumor necrosis factor (TNF) genes and many others in addition to MHC that have immunologic functions. The organization of the HLA region is illustrated in E-Figure 38-2. The class II region contains two α- and β-chain genes, only one of which is functional, for each of HLA-DQ and DP. However, the DR locus contains different numbers of β-chains for different HLA alleles. Some of these DR β-chains are pseudogenes, but various HLA-DR alleles contain either one or two functional β-chain genes.

One of the striking features of HLA molecules (and the MHC of most mammalian species) is their extensive polymorphism.[1] The class I and class II regions contain thousands of defined HLA alleles. Because the primary function of antigen presentation to T cells is to permit responsiveness to and clearance of pathogenic microorganisms, this polymorphism may have evolved to maintain the diversity of immune responsiveness to various pathogens within a population, thereby avoiding annihilation of that population by a single microorganism that might not be presented well by a particular MHC. According to the most recently accepted nomenclature, HLA alleles are identified by the locus (e.g., HLA-A), followed by an asterisk, and then a unique number with up to four sets of digits separated by colons.[2] The first set describes the allele group (e.g., HLA-A*02), which usually corresponds to a serologically defined antigen, and the second set indicates the specific allele (e.g., HLA-A*02:101). The third and fourth sets of digits are of less practical importance because they identify silent nucleotide substitutions in different alleles and variations in the nontranslated regions of the gene, respectively.

Within certain populations, however, the level of diversity within allele groups may be quite limited because of the common genetic origin of the allele. For example, for the originally serologically defined HLA-DR3 allele group, there is little diversity among Northern Europeans, such that most carry the DRB1*0301 allele. Thus, for this population, it is reasonable to refer to the serologic HLA-DR3 type as defining this allele. Certain alleles predominate within racial groups. For example, as few as five DRB1 alleles predominate among Northern Europeans, with each allele represented in 10 to 30% of this population (E-Table 38-2).

Most organ transplantations are performed across HLA disparities, and the strong immunosuppressive regimens used in transplant recipients are designed to prevent rejection by this exceptionally strong immune response. In contrast to T-cell responses to peptide antigens derived from foreign proteins, which are recognized by a very small fraction of naïve T cells (in the range of 1 in 10^5), a very high proportion, estimated at 1 to 10% of the T-cell repertoire, recognizes MHC alloantigens. The application of high-throughput sequencing of the hypervariable regions of T-cell receptors of those T cells that proliferate to allogeneic MHC has directly demonstrated the large number of T-cell clones contributing to this response.[3] The strong immunogenicity of allogeneic MHC molecules relates to the manner in which T cells are selected in the thymus; developing thymocytes do not survive unless they can weakly recognize a self MHC/peptide complex on a thymic stromal cell. This process is termed *positive selection*. Thymocytes whose receptors have high affinity for self/MHC complexes are deleted, however, so strongly autoreactive T cells rarely make it into the peripheral T-cell pool. Allogeneic antigens are not part of this *negative selection* process. The net result of these two selection steps and the inherent cross-reactivity of T-cell receptors is that the T-cell "repertoire" recognizes allogeneic MHC molecules, providing a barrier to organ and hematopoietic cell transplantation. In the case of organ transplantation, in which long-term pharmacotherapy with powerful immunosuppressive drugs is used in an effort to prevent graft rejection, this can translate into improved results with HLA-matched organs. Despite the disadvantage of prolonged cold ischemia associated with transportation of a deceased donor graft, a pediatric kidney transplant study has shown superior outcomes with well-matched deceased donor kidneys compared with poorly matched living donor transplants.[4] Because of the high rates of late graft loss associated with de novo anti-HLA antibody formation, efforts have aimed to reduce this outcome by identifying HLA mismatches that are less likely to induce these alloantibodies.

For hematopoietic cell transplantation (Chapter 163), the risks for GVHD and marrow graft failure are so greatly amplified in the presence of extensive HLA mismatches that such transplantations have been largely avoided in the past. Disparities in the highly polymorphic class I and class II molecules predispose to GVHD. The risk of GVHD is increased by HLA-DPB1 mismatching, despite its lower polymorphism, especially when the regulatory region variant rs9277534 is a high-expression allele in recipients but low-expression in donors. If a sufficiently matched, related donor is unavailable, a search has typically been conducted through large registries containing millions of volunteer unrelated donors. Because of its extensive polymorphism, truly MHC-identical, unrelated donors can be difficult to find in the human population at large. For individuals with common HLA genotypes, the likelihood of finding a matched unrelated donor is markedly greater than that for individuals with

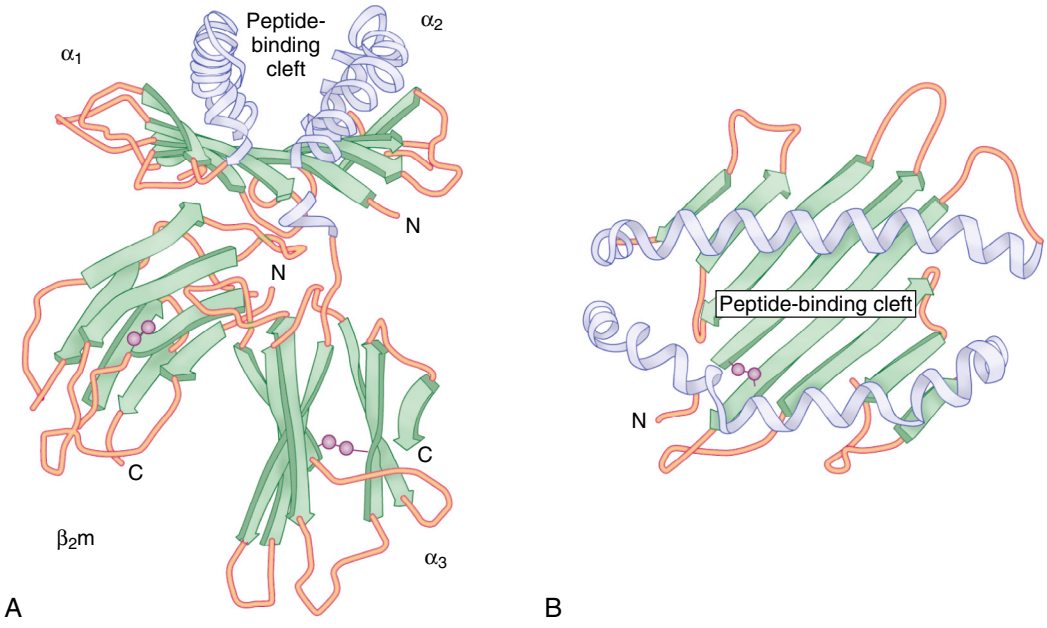

E-FIGURE 38-1. Two views of an HLA class I molecule. A, Ribbon diagram showing the x-ray crystallographic structure of an HLA class I molecule (side view). The β-strand structures are indicated by *thick green arrows* (oriented in an amino to carboxy direction), whereas connecting loops are indicated as *thin lines*. The α-helices are shown flanking a peptide-binding cleft at the top (membrane distal portion) of the molecule. The base (membrane proximal portion) of the molecule is formed by the noncovalent association between the α_3 domain of the class I α-chain and β_2-microglobulin (β_2m). **B,** View from the top of the molecule emphasizing that the base of the peptide-binding cleft consists of β-pleated sheets flanked by α-helical structures. C = C terminal; N = N terminal. (Adapted from Bjorkman PJ, Saper MA, Samraoi B, et al. Structure of the class I histocompatibility antigen HLA-A2. *Nature*. 1987;329:506-512.)

E-TABLE 38-1 COMPARISON OF STRUCTURAL AND FUNCTIONAL FEATURES OF HLA CLASS I AND CLASS II ISOTYPES

FEATURE	HLA CLASS I	HLA CLASS II
Chain structure of heterodimer	45-kD α-chain 12-kD β_2-microglobulin	34-kD α-chain 28-kD β-chain
Tissue distribution	All nucleated cells	Antigen-presenting cells (monocytes, B cells, dendritic cells, Langerhans cells), thymic epithelium, and some T cells; inducible on other cell types by interferon-γ
Size of bound peptides	8-9 amino acids	10-20 amino acids
Source peptides	Cytosolic	Endosomal
Functions	Presentation of antigenic peptides to $CD8^+$ T cells; ligands for natural killer cell receptors	Presentation of antigenic peptides to $CD4^+$ T cells

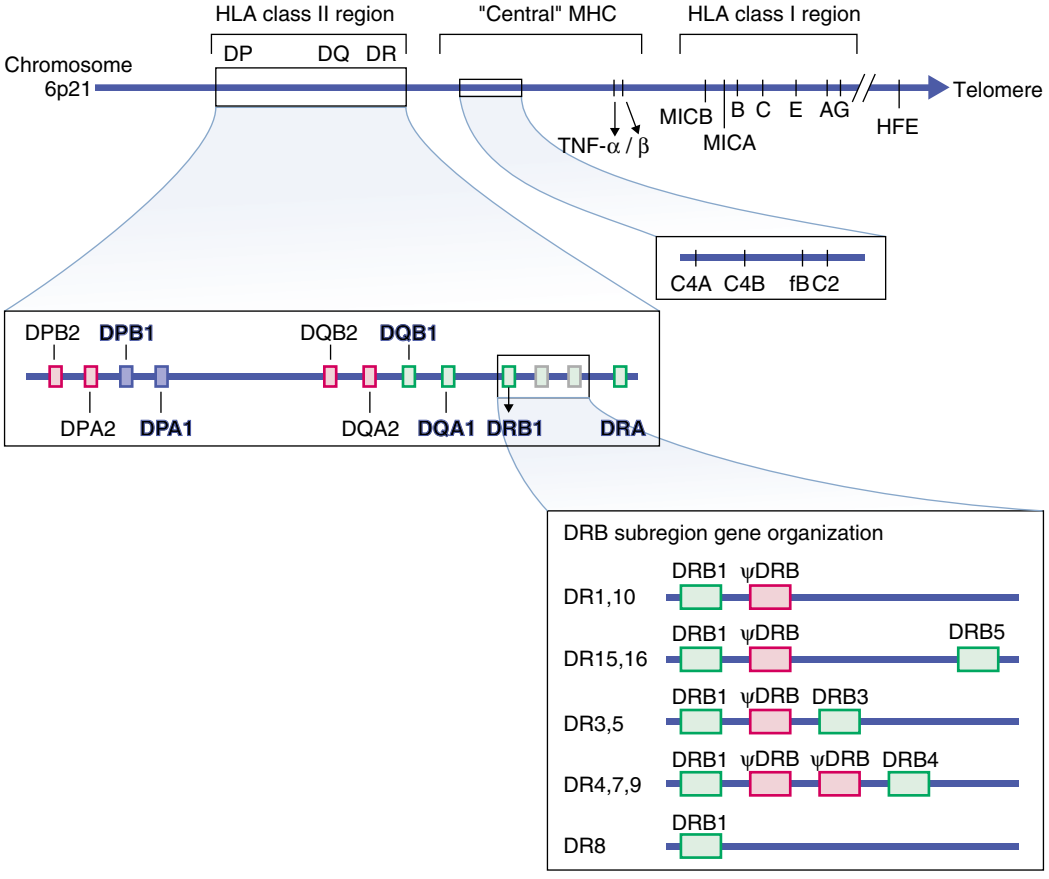

E-FIGURE 38-2. Map of the human major histocompatibility complex (MHC) spanning approximately 3.5 million base pairs on the short arm of chromosome 6. The HLA class I and class II molecules are encoded in distinct regions of the MHC. The HLA class II region contains three subregions: DR, DQ, and DP. Each of these subregions contains a variable number of α- and β-chain genes. HLA class II loci with known functional protein products are labeled in bold. In the case of DR, different numbers of DRB genes are present in different haplotypes, some of which are nonfunctional pseudogenes (ψ). A summary of the most common of these is shown in the *box*. The DQ and DP subregions each contain one pair of functional α- and β-chain genes. The HLA class I region contains the three "classic" class I genes—HLA-A, HLA-B, and HLA-C—as well as other related "nonclassic" class I molecules such as MICA, MICB, HLA-E, and HLA-G. The gene for familial hemochromatosis (HFE) is found just telomeric to the HLA class I region, about 3 million base pairs distant from HLA-A. The "central" MHC also contains a number of genes related to immune function, including the complement components (C4A, C4B, C2, and factor B), as well as tumor necrosis factor (TNF)-α and -β. Not shown in the figure are more than 100 additional genes, many of which are located in the central MHC. (A complete listing of MHC-encoded genes can be found in Horton R, Wilming L, Rand V, et al. Gene map of the extended human MHC. *Nat Rev Genet*. 2004;5:889-899.)

E-TABLE 38-2 SUMMARY OF MAJOR ALLELIC GROUPS AT THE DRB1 LOCUS AND THEIR RELATIONSHIP TO COMMON DRB1 ALLELES DEFINED AT THE SEQUENCE LEVEL

ALLELIC GROUPS (SEROLOGIC TYPING)		EXAMPLES OF COMMON ALLELES (NORTHERN EUROPEAN WHITE INDIVIDUALS) DEFINED BY SEQUENCE*
MAJOR GROUPS	**SEROLOGIC "SPLITS"**	
DR1		DRB1* **0101**, 0102, 0103
DR2	DR15 DR16	DRB1* **1501**, 1502 DRB1*1601
DR3		DRB1* **0301**
DR4		DRB1* **0401**, 0402, 0403, 0404, 0405, 0406, 0407, 0408
DR5	DR11 DR12	DRB1*1101, 1102, 1103, 1104 DRB1*1201
DR6	DR13 DR14	DRB1*1301, 1302, 1303 DRB1*1401
DR7		DRB1* **0701**
DR8		DRB1*0801, 0802, 0803, 0804, 0806
DR9		DRB1*0901
DR10		DRB1*1001

*Alleles in bold are found in at least 10% of individuals in the population.

From Williams F, Meenagh A, Single R, et al. High resolution HLA-DRB1 identification of a Caucasian population. *Hum Immunol*. 2004;65:66-77.

rare genotypes. This situation relates in part to the phenomenon of *linkage disequilibrium*, wherein alleles at nearby loci are found together on the same chromosomal segment, or *haplotype*, more frequently than would be predicted by chance. The pattern of linkage disequilibrium is different in different racial groups, so the chance of finding a truly genotypically identical haplotype is greatest within the same population.

Advances in the ability to perform transplants from alternative donors have increased the availability of hematopoietic cell transplantation in individuals who lack an HLA-identical related donor (Chapter 163). Advances in avoiding GVHD in haploidentical related donor hematopoietic cell transplantation have increased the safety of HLA-mismatched hematopoietic cell transplantation, thereby yielding outcomes that may be superior to those using matched unrelated donors in some cases and comparable to results using matched sibling donors.

MINOR HISTOCOMPATIBILITY ANTIGENS

"Minor" histocompatibility antigens are peptides derived from polymorphic proteins presented by an MHC molecule. Even genotypically HLA-identical siblings have many different minor histocompatibility antigens that are sufficient to induce graft rejection if immunosuppressive pharmacotherapy is not used. Additionally, significant GVHD frequently (about 30 to 50% of the time) complicates hematopoietic cell transplantation between HLA-identical siblings, even with the use of pharmacologic immunoprophylaxis. Minor histocompatibility antigens, which can result from genetic polymorphisms in protein-coding regions or from homozygous loss-of-function variants in hematopoietic cell transplant donors or organ transplant recipients, render recipient and donor organs more susceptible to GVHD and rejection, respectively. An example of the latter is the *LIMS1* locus, which encodes a cell surface protein for which a homozygous loss-of-function variant is associated with anti-LIMS1 IgG2 and IgG3 antibodies and an increased risk of kidney allograft rejection. Another example is Y chromosome-encoded genes, which result in significantly increased graft rejection rates and GVHD in male-to-female and female-to-male organ and hematopoietic cell transplants, respectively.

OTHER ANTIGENS

The major blood group (ABO) antigens can be the targets of a dramatic "hyperacute" rejection process that occurs when mismatched vascularized grafts are transplanted. Recognition of blood group antigens on the endothelial surface of the graft vessels by recipient "natural" antibodies (antibodies that are present without known sensitization to the antigens) activates the complement and coagulation cascades, resulting in rapid graft thrombosis and ischemia. A similar outcome can occur after transplantation to an individual with preformed antidonor HLA antibodies resulting from presensitization by prior transplantations, transfusions, or pregnancies. Antibodies against other polymorphic antigens, such as MHC class I–related chain A (MICA), have been associated with graft rejection. In the past, transplantation could not be successfully performed in the presence of a positive antidonor crossmatch. However, considerable success has been achieved in the transplantation of ABO-mismatched kidneys, livers, and hearts (the latter in the neonatal period only) and in transplantation of kidneys to highly presensitized patients. In the case of kidney and liver transplantation, initial removal of the antibody and sometimes depletion of B cells, as well as the infusion of intravenous immunoglobulin (IVIG), has led to these successes.[5] Additional agents under investigation include proteosome inhibitors, interleukin-6 blockers, complement inhibitors, and IgG-degrading enzymes.[6] ABO-mismatched neonatal heart transplantation has succeeded because the transplantations are performed before the recipient has developed high levels of anti–blood group antigen antibodies, and the B cells seem to be rendered tolerant to the donor blood group antigen by the grafting process. Recognition of blood group antigens can also be of significance in hematopoietic cell transplantation, in which ABO barriers are routinely crossed in both directions. This can cause hemolysis of recipient erythrocytes if the mismatch is in the GVH direction, but this complication can be avoided by washing the cellular product before infusion. Mismatches in the HVG direction can cause more persistent problems due to ongoing destruction of donor erythropoietic cells, resulting in pure red cell aplasia. More often, however, donor erythropoiesis is successfully established, and antidonor isohemagglutinins disappear from the circulation. With the increasing application of HLA-mismatched donor hematopoietic cell transplantation, the importance of HLA alloantibodies in causing graft failure has recently been recognized and may require similar desensitization procedures to those used in sensitized organ allograft recipients.[7]

A and B blood group antigens are the consequence of the presence or absence of specific glycosylation enzymes in different individuals. Likewise, an antigenic specificity of the utmost importance in xenotransplantation is a carbohydrate epitope, Galα1–3Galβ1–4GlcNAc (αGal), which is produced by a specific galactosyl transferase. Humans and Old World monkeys lack a functional αGal transferase and produce high levels of natural antibodies against the ubiquitous αGal epitope. Because animals of interest as xenograft sources (e.g., pigs) express αGal at high levels on their vascular endothelium, transplantation of vascularized organs from pigs results in hyperacute rejection. The development of αGal-knockout pigs, therefore, was an important milestone that advanced the field of xenotransplantation. The more recent recognition of non-Gal carbohydrate natural antibody targets on cells of αGal-knockout pigs has led to further genetic modifications of these potential source animals, a procedure that has been greatly facilitated by current gene editing techniques.

In another type of transplant reaction, recognition as foreign results not from the presence of an antigen, but paradoxically from the absence of a self MHC molecule. Natural killer (NK) cells express a series of surface inhibitory and activating receptors that, collectively, determine whether the NK cell does or does not kill a potential target cell. The ligands for the inhibitory receptors are MHC class I molecules, and the receptors recognize specific groups of alleles. An NK cell may kill an allogeneic target that lacks a self MHC inhibitory ligand. This phenomenon can result in rapid bone marrow rejection in animal models and may be of significance in HLA-mismatched hematopoietic cell transplantation. The possible role of NK cells in organ allograft rejection is controversial, but they are thought to be of importance in organ xenotransplantation. NK cells clearly play a strong role in the rejection of xenogeneic hematopoietic cells, an observation that is relevant in one approach to inducing tolerance (see later discussion).

MECHANISMS OF REJECTION AND GRAFT-VERSUS-HOST DISEASE

CELLULAR MEDIATORS

Many different cell types participate in rejection responses, and considerable redundancy exists. T cells are key players in most forms of rejection, with the exception of rejection induced by antibodies in the absence of T-cell help, such as hyperacute and acute vascular rejection induced by natural antibodies. Several studies have suggested a dominant role for memory T cells in causing rejection, but it is difficult to distinguish whether "memory" T cells detected after a transplant converted from naïve T cells before or after the transplant.

DIRECT, SEMIDIRECT, AND INDIRECT ALLORECOGNITION

T-cell responses are induced by antigen-presenting cells that present alloantigens. Alloantigen recognition may be categorized as *direct*, *semidirect*, and *indirect* (Fig. 38-1). Direct allorecognition denotes recognition of donor antigens on donor antigen-presenting cells provided by the graft. The extraordinarily high frequency of T cells with alloreactivity is caused by direct recognition of allogeneic MHC. However, T cells with these specificities may also detect their ligands on recipient antigen-presenting cells, as these may pick up intact donor MHC-peptide complexes transferred in exosomes. This "semidirect" pathway may be important in maintaining strong direct alloresponses long after donor antigen-presenting cells in a grafted organ have been replaced by those of the recipient. Indirect recognition is the recognition of donor antigens

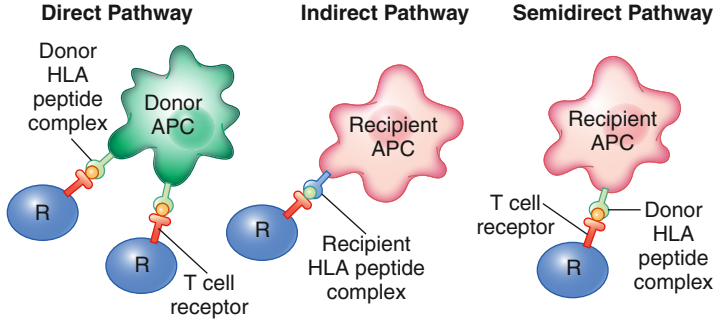

FIGURE 38-1. Direct and indirect allorecognition. Direct allorecognition involves the recognition by a T-cell receptor of major histocompatibility complex (MHC) molecules (with or without a peptide) on a donor antigen-presenting cell. Indirect allorecognition involves recognition by the T-cell receptor of a donor peptide presented on a recipient antigen-presenting cell that has picked up and processed donor antigens.

that are picked up, processed, and presented on recipient MHC molecules on recipient antigen-presenting cells. The indirect response is more similar to "normal" T-cell responses, in which professional antigen-presenting cells present peptide antigens to T cells that are present at relatively low frequency in the naïve repertoire. The indirect response, like the semidirect response, can be maintained by the constantly renewed pool of recipient antigen-presenting cells. The indirect response is of particular importance in inducing antibody responses.

EFFECTOR MECHANISMS OF REJECTION

T cells can promote graft rejection through several effector mechanisms. One is the antibody-dependent processes that have already been discussed. CD4 T cells provide cognate help to B cells when their T-cell receptors (TCRs) recognize complexes of self MHC with donor MHC–derived peptide antigens produced by B cells whose surface Ig receptors recognize and pick up the donor MHC antigen. Antidonor antibody can lead to the pathologic picture of acute humoral rejection and may also participate in a slower process of chronic rejection. Chronic rejection of kidney and heart allografts is characterized by unique vascular lesions with intimal thickening and loss of the vessel space. Chronic rejection of lung allografts is termed obliterative bronchiolitis. The mechanisms underlying these chronic rejection lesions are not well understood, and several different immune processes may in fact lead to similar lesions. Induced responses to autoantigens exposed by injured graft tissue have been implicated in several forms of chronic rejection.

Another major effector pathway leading to graft rejection involves cytotoxic T lymphocytes, which are predominantly $CD8^+$ but also include $CD4^+$ T cells. Several effector mechanisms lead to killing of target cells by cytotoxic T lymphocytes, including granzyme/perforin-mediated and Fas/Fas ligand (FasL) pathways and other members of the TNF/TNF-receptor families. Because $CD8^+$ cells recognize class I MHC molecules, which are widely expressed, it is not difficult to envision graft destruction by $CD8^+$ cytotoxic T lymphocytes. $CD8^+$ cytotoxic T lymphocytes may be activated through an antigen-presenting cell that is stimulated initially through contact with an alloreactive $CD4^+$ cell. This is one form of CD4 "help" for $CD8^+$ cells. In addition, $CD8^+$ cells may be dependent on cytokines such as interleukin-2 (IL-2) produced by $CD4^+$ cells for their expansion and cytotoxic differentiation. However, there are also many examples of $CD8^+$ cell–mediated rejection that is independent of "help" from $CD4^+$ cells. Class II MHC, which is recognized by $CD4^+$ T cells, is less widely expressed on graft tissues than is class I MHC, although it may be induced on endothelial cells and graft parenchymal cells in the presence of inflammatory cytokines such as interferon-γ (IFN-γ).

In addition to cytotoxic mechanisms resulting from direct allorecognition, $CD4^+$ and $CD8^+$ T cells with indirect specificity seem also to be capable of causing graft destruction under some circumstances. Cytokines such as IFN-γ and TNF-α, as well as innate cellular mediators, have been implicated in some instances, but in general, the pathways of indirect graft destruction are not well understood.

THE ROLE OF T-CELL TRAFFICKING

Rejection processes require trafficking of T cells into the graft, which occurs after the initial activation of naïve T cells in the lymphoid tissues. Naïve T cells can migrate into lymph nodes because of their expression of the CCR7 chemokine receptor and the adhesion molecule L-selectin. These T cells are activated by migratory graft antigen-presenting cells that also enter the lymph nodes. T-cell activation is associated with loss of CCR7 and L-selectin expression and acquisition of a new set of chemokine receptors and adhesion molecules that allow rolling and adhesion on the graft endothelium and entry into the graft parenchyma. Inflammation in the graft, such as that induced by ischemia-reperfusion injury and the transplantation procedure, as well as that induced by initially responding T cells, is associated with upregulation of chemokines and adhesion ligands that promote entry of lymphocytes into the graft. Nevertheless, well-healed-in grafts can be slowly rejected by adoptively transferred memory T cells, demonstrating that acute graft injury and inflammation are not essential for rejection in the presence of an established memory T-cell response. Rejection of hematopoietic cell grafts may involve many of the same mechanisms as those discussed for solid organs, although less detailed work has been done in this area.

MECHANISMS OF GRAFT-VERSUS-HOST DISEASE

Initiation of GVHD (Chapter 163) requires that donor T cells recognize host alloantigens. Donor T cells infiltrate a variety of recipient epithelial tissues, namely skin, the intestine, and liver. Animal models have demonstrated clear roles for both $CD4^+$ and $CD8^+$ cells in initiating GVHD, and each subset is able to do so independently of the other. The mechanisms of GVHD include activation of alloreactive donor T cells by recipient antigen-presenting cells within the recipient lymphoid tissues, leading to the differentiation of effector cells with direct cytotoxic activity and cytokine production in response to host antigens. A prominent role is played by TNF-α, whose production is induced in part by the translocation of bacteria across the intestinal wall, promoting innate immune system activation through toll-like receptors (Chapter 35). An intensely pro-inflammatory environment is produced by the combination of conditioning-induced tissue injury and disruption of mucosal barriers, bacterial activation of the innate immune system, and the GVH alloresponse. An important role is now appreciated for the inflamed microenvironment in target tissues in promoting the trafficking of GVH-reactive T cells into these tissues.

STRATEGIES TO PREVENT GRAFT-VERSUS-HOST DISEASE

In view of the critical role of donor T cells in inducing GVHD, an obvious strategy for preventing this complication is to remove mature T cells from the marrow graft. This approach has indeed been shown in both animal models and clinical studies to prevent GVHD effectively. However, there are several disadvantages to this approach. One is that adult humans, particularly those who have undergone prior chemotherapy and radiotherapy, have little remaining thymic tissue and therefore demonstrate sluggish T-cell recovery, leading to serious opportunistic infections. For example, the inclusion of antihuman T-lymphocyte immune globulin in a myeloablative conditioning regimen for patients with acute leukemia significantly lowers the rate of chronic GVHD but does not significantly improve survival.[A1]

T-cell depletion of hematopoietic cell grafts used to treat hematologic malignancies may be associated with an increased relapse rate due to loss of a graft-versus-tumor (GVT) effect, which is in large part mediated by GVH alloreactivity. Separation of GVHD from GVT effects is a major goal of research in hematopoietic cell transplantation, and some promising strategies are being explored (E-Table 38-3).[8] For example, Janus kinase inhibitors show promise for prevention of GVHD[9] and for the treatment of steroid-refractory GVHD after hematopoietic cell transplantation (Chapter 163).[A2,A3] Trials of low-dose IL-2 have shown efficacy in preventing chronic GVHD, apparently by expanding regulatory T cells. Infusion of expanded regulatory T cells has also entered clinical trials,[10] and infusion of mesenchymal stromal cells has shown benefit in treating refractory GVHD.[11] Preventing T-cell trafficking into epithelial target tissues of GVHD is a particularly promising approach because of the theoretical preservation of graft-versus-tumor effects in lymphohematopoietic tissues. Chemokine receptor blockade is a promising approach to achieving this goal.

A third disadvantage of T-cell depletion is that it eliminates the engraftment-promoting effect conferred by alloreactive T cells, resulting in increased rates of allograft failure, especially in the setting of HLA-mismatched transplantation. NK-cell recognition in the GVH direction resulting from the absence in the recipient of a class I MHC ligand (E-Fig. 38-3) that can trigger a donor NK-cell inhibitory receptor (KIR) may promote donor hematopoietic cell engraftment and antitumor effects against acute myeloid leukemias in the setting of T-cell–depleted, HLA-mismatched hematopoietic cell transplantation. The role of donor-recipient KIR mismatch and of polymorphisms in KIR genotype and expression in antitumor effects, GVHD, and infectious immunity in hematopoietic cell transplantation is complex and may vary with different diseases and types of transplant conditioning, in addition to different types of donor-recipient mismatch.

Clinically, pharmacologic immunosuppressive prophylaxis is usually used in at least the first 6 months after hematopoietic cell transplantation to minimize the complication of GVHD. Posttransplant cyclophosphamide significantly reduces the risk of GVHD although it does not increase overall survival.[A4] Additionally, HLA-matched or closely matched donors are chosen whenever possible because GVHD increases in frequency and severity as increased HLA barriers are transgressed. These measures, nevertheless, are insufficient, and GVHD remains a major complication of hematopoietic cell transplantation. Therefore, many of the new strategies being explored in organ transplantation and other fields are also being examined for the prevention of GVHD in experimental models. It should be borne in mind, however, that tolerance of donor T cells to recipient alloantigens (see later discussion) might not be entirely beneficial in the hematopoietic cell transplantation setting for the treatment of malignant

E-TABLE 38-3 EXPERIMENTAL STRATEGIES TO PREVENT GRAFT-VERSUS-HOST DISEASE

STRATEGY	ADVANTAGES	LIMITATIONS
Donor T-cell T_H2 polarization (e.g., conditioning with ATG and TLI; in vitro stimulation with cytokine exposure)	May preserve GVL	May limit GVL; T_H2 can contribute to acute and chronic GVHD
Tolerance induction of donor T cells (e.g., costimulatory blockade; activation pathway inhibitors)	Some strategies may selectively tolerize GVH-reactive T cells (e.g., in vitro antigen exposure with costimulatory blockade)	Global immunosuppression may limit GVL and anti-infectious immunity; tolerance (i.e., GVH protection) may be incomplete
Regulatory cell infusion or induction (e.g., low-dose IL-2)	GVL and infectious immunity may be preserved Does not compromise engraftment	GVL might be compromised by reduced alloreactivity
Depletion of naïve donor T cells	May preserve GVL and memory responses to infection	Incomplete protection from GVHD
Donor T-cell depletion plus NK-cell infusion with class I mismatched transplantation	NK cells do not cause GVHD but may mediate antitumor effects; donor NK cells may eliminate host APCs that trigger GVHD	Antitumor effect against only certain types of malignancies; requires appropriate MHC disparity and expression of polymorphic NK-cell receptors; insufficient T-cell immunity to infection
Donor T-cell depletion followed by delayed donor lymphocyte infusion (DLI)	Preserves high level of GVL due to GVH reactivity. GVHD does not occur if host inflammation from conditioning has subsided and initial HCT was devoid of donor T cells	Antitumor effect delayed until time of DLI; most applicable for indolent lymphohematopoietic tumors. GVHD more difficult to control in humans than animal models, probably owing to occult or overt infection resulting from T-cell deficiency before DLI
Depletion of donor T cells recognizing host alloantigens by in vitro or in vivo activation/depletion (i.e., "allodepletion")	Preserves anti-infectious immunity and tumor antigen–specific responses while limiting GVHD	Loss of GVH reactivity will limit GVL and engraftment; highly efficient allodepletion methods not yet available. Residual T cells may cause GVHD
Donor T-cell depletion with infusion of expanded infection-specific T cells (e.g., CMV or EBV specific)	Reduces GVHD potential while protecting against significant infectious organisms	Lack of GVL effect; lack of broad anti-infectious immunity; expense and inefficiency of in vitro T-cell expansion; loss of survival/homing potential of cultured T cells
Donor T-cell depletion with infusion of expanded tumor antigen-specific T cells (expanded from natural repertoire or transduced with a T-cell receptor or chimeric antigen receptor)	GVL without GVHD	Lack of anti-infectious immunity; expense and inefficiency of in vitro expansion of tumor-specific T cells; loss of survival/homing potential of cultured T cells
Insertion of suicide gene (e.g., thymidine kinase) into donor T cells	Drug targeting inserted gene (e.g., ganciclovir) kills donor T cells to treat GVHD after GVL initiated	Expense and inefficiency of in vitro transduction of T cells; loss of function/survival/homing potential of cultured T cells; risk for GVHD if transduction incomplete; curtailment of GVL when donor T cells killed in vivo
Block T-cell trafficking to epithelial GVHD target tissues (e.g., blockade of adhesion molecules or chemokines, sphingosine 1 phosphate agonists)	Permits lymphohematopoietic GVH reactions to occur, with associated GVL effects. Preserves infectious immunity	Redundancy of trafficking pathways in inflammatory environment may limit efficacy; tumors outside of lymphohematopoietic system not targeted
Block injury/promote repair in epithelial target tissues (e.g., keratinocyte growth factor)	Permits lymphohematopoietic GVH reactions to occur, with associated GVL effects. Preserves infectious immunity	Efficacy may be limited

APC = antigen-presenting cell; ATG = antithymocyte globulin; CMV = cytomegalovirus; DLI = donor lymphocyte infusion; EBV = Epstein-Barr virus; GVHD = graft-versus-host disease; GVL = graft-versus-leukemia effects; HCT = hematopoietic cell transplantation; MHC = major histocompatibility complex; NK = natural killer; T_H2 = helper T lymphocytes type 2; TLI = total lymphoid irradiation.

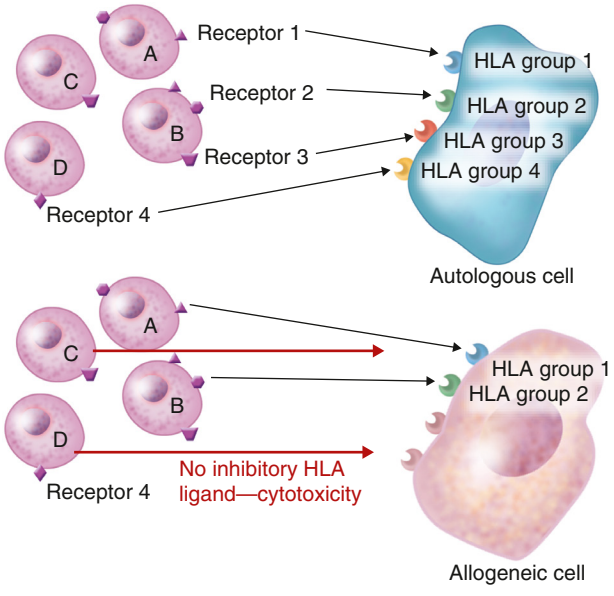

E-FIGURE 38-3. Killing of allogeneic targets by natural killer (NK) cells due to "missing self." NK cells express clonally distributed inhibitory receptors (KIRs) with specificity for different groups of major histocompatibility complex (MHC) class I alleles, referred to in the figure as human leukocyte antigen (HLA) groups 1, 2, 3, and 4. Four different NK cells (A, B, C, and D) are shown, each with a different set of KIRs (referred to as receptors 1, 2, 3, and 4). Examples of HLA allele groups in the human are the HLA-Cw4, HLA-Cw3, and HLA-Bw4 groups; examples of KIRs are the ligands for these allele groups—namely, KIR2DL1, KIR2DL2/3, and KIR3DL1, respectively. Each functional NK cell has one or more inhibitory receptors that recognize a "self" (autologous) HLA molecule. Although some of the NK cells (e.g., cells A and B in the figure) will also find an HLA ligand to which their receptors bind on allogeneic cells, others (e.g., cells C and D) will not. The latter cells therefore will not receive inhibitory signals from the allogeneic cells and will kill them due to recognition by other (activating) receptors.

disease because loss of GVH alloreactivity is likely to come with loss of antitumor effects.

STRATEGIES TO PREVENT ALLOGRAFT REJECTION

NONSPECIFIC IMMUNOSUPPRESSION

Immunosuppressive drugs are the mainstay of clinical organ transplantation, and improvements in these drugs following the discovery of cyclosporine have extended organ transplantation to include hearts, lungs, pancreases, livers, and other organs and tissues in the past 40 years. The mechanisms of action of these agents, which typically include a calcineurin inhibitor, an anti-proliferative drug, and corticosteroids, are discussed in Chapter 28. However, it is noteworthy that, despite these improvements and their enormous impact on early graft survival, pharmacologic agents have been less effective in attenuating late graft loss. Because chronic immunologic rejection processes and side effects of the immunosuppressive drugs themselves are responsible for much of this late graft loss, improved immunosuppressive agents and induction of immune tolerance (see later discussion) are major research goals in transplantation.

COSTIMULATORY BLOCKADE

As understanding of immune responses has increased, recent years have seen the exploration of numerous biologic agents, including antibodies and small molecules targeting receptors of the immune system, as well as cell-based therapies,[12] in efforts to improve allograft survival. Because of the central role played by T cells in the immune response, considerable attention has been focused on blockers of T-cell costimulation. When a naïve T cell recognizes antigen through its unique TCR, additional "costimulatory" signals are required to allow full activation, expansion, and differentiation to occur. These signals are provided by antigen-presenting cells in the form of ligands (e.g., B7-1, B7-2) for costimulatory receptors (e.g., CD28) on the T cell. Cross-talk between the T cell and the antigen-presenting cell (e.g., due to CD40 activation by CD154 upregulation on the activated T cell) further amplifies the costimulatory activity of the antigen-presenting cell, allowing it to effectively activate other T cells as well. The CD154 (T cell)–CD40 (B cell) interaction also promotes Ig class switching and functioning of B cells as antigen-presenting cells. Blockade of these processes (e.g., by CTLA4Ig and anti-CD154 or CD40 monoclonal antibodies [mAbs]) has led to marked prolongation of allograft survival in stringent rodent and large-animal models. Robust, systemic tolerance to donor antigens has been achieved in rodents receiving bone marrow transplantation with costimulatory blockade and little or no additional conditioning. Some of these agents have joined the armamentarium of immunosuppressive agents in clinical trials in transplantation and autoimmune diseases. Although the optimal protocol for its use is still in development, CTLA4Ig has permitted sparing of nephrotoxic calcineurin inhibitors, with improved long-term patient and renal allograft survival.[13] Although anti-CD154 antibodies have been associated with thromboembolic complications, precluding further evaluation in transplantation trials, recently developed nonthrombogenic anti-CD154 and anti-CD40 antibodies have shown promise in preclinical studies and have entered clinical trials.[14] Numerous additional costimulatory and inhibitory pathways that affect T-cell responses have been described, and these all are potential targets for further manipulation of the alloresponse.

IMMUNE TOLERANCE

Immune tolerance denotes a state in which the immune system is specifically unreactive to the donor graft (or recipient in the case of GVH reactivity) while remaining normally responsive to other antigens.[15] Tolerance is distinct from the state produced by nonspecific immunosuppressive agents, which increase risks for infection and malignancy. Numerous approaches to tolerance induction have been described in rodent models, largely owing to the strong tolerogenicity of primarily vascularized heart, liver, and kidney grafts in these animals. Such grafts are less tolerogenic in humans, and few of these strategies have been effectively applied clinically to date. Since the test for tolerance is graft acceptance without continuous immunosuppressive therapy (i.e., without the standard of care), tolerance protocols being evaluated clinically should first demonstrate efficacy in stringent animal models, including highly immunogenic grafts such as MHC-mismatched skin in rodents and vascularized organ graft models in large animals.

The three major mechanisms of T-cell tolerance are deletion, anergy, and suppression (often referred to as "regulation"). *Deletion* denotes the destruction of T cells with receptors that recognize donor antigens; it can be achieved during T-cell development in the thymus, for example, by induction of mixed chimerism in T-cell–depleted hosts. Deletion can also be applied to mature T cells in the periphery, for example, by transplantation of a tolerogenic organ or marrow graft in combination with blockade of costimulatory molecules. *Anergy* denotes the inability of T cells to respond fully to antigens they recognize, and it can be induced by antigen presentation without costimulation. *Suppression* has attracted considerable interest since the discovery that constitutively $CD25^+$ T cells of the $CD4^+$ subset have suppressive activity that is dependent on expression of the transcription factor Forkhead Box Protein 3 (FoxP3). These and other types of suppressive T cells (e.g., NKT cells, regulatory $CD8^+$ cells and B cells, myeloid-derived suppressor cells, regulatory monocytes, and dendritic cells) have been implicated in rodent transplantation tolerance models and in prevention of autoimmunity. The use of expanded regulatory cells has recently entered clinical trials in both transplantation and autoimmune disease, including both antigen-specific and nonspecific ("polyclonal") regulatory cell therapy,[16] as well as chimeric antigen receptor (CAR) Tregs.[17] Other regulatory cell types, including tolerogenic monocytes and dendritic cells, have demonstrated safety in early clinical trials.[18] However, in the absence of large animal studies demonstrating the efficacy of these cellular therapies in achieving tolerance and without validated biomarkers for tolerance, rapid immunosuppression withdrawal to test tolerance induction is not the goal of these studies. There is also interest in strategies for activating or expanding regulatory T cells in vivo, thereby favoring the suppressive immune response over destructive alloimmunity.

The developments in animal models and understanding of immune mechanisms described here have provided impetus for efforts to achieve immune tolerance in clinical transplantation. Every transplantation center has anecdotal cases of patients who have removed themselves from chronic immunosuppression without experiencing graft rejection. However, for every such patient, there are dozens more who have experienced rejection on dose reduction or removal of immunosuppressive drugs. Trials of slow withdrawal of nonspecific immunosuppressive therapy have had very little success in renal allograft recipients and higher success rates in a very highly selected group of liver allograft recipients, especially children with long-term rejection-free graft survival.[A5,19] Application of this approach to a larger subset of patients will depend on future advances in the ability to identify biomarkers that are predictive of success. "Tolerance signatures" with sufficient predictive value to allow such withdrawal to be safely undertaken have not yet been identified.

One approach developed in animal models has been successfully applied to the induction of immune tolerance in a small group of patients receiving renal allografts. This approach, involving bone marrow transplantation after nonmyeloablative conditioning, which is less toxic than standard hematopoietic cell transplantation conditioning, was shown to be effective in the most stringent rodent and large-animal models before being evaluated clinically. Initial success using combined kidney and bone marrow transplantation in patients with renal failure due to multiple myeloma led to pilot studies in patients with renal failure without malignant disease, with encouraging results. This protocol involved induction of transient chimerism in combination with a kidney allograft from HLA-mismatched related donors and was free of the complication of GVHD. Mechanistic studies, including a high-throughput sequencing-based approach to identifying and tracking donor-reactive T-cell clones, implicated an early role for regulatory T cells followed by gradual clonal deletion in the long-term tolerance.[20] Another nonmyeloablative approach has succeeded in achieving more durable chimerism and tolerance, but only in the HLA-identical sibling transplant setting,[21] and a third approach has led to full donor chimerism across extensive HLA barriers, but with significant toxicity, including GVHD.[22] With further refinements of this approach and proof of efficacy in large animal models, it is hoped that transplantation of all organ types might ultimately be routinely performed without the need for chronic immunosuppressive therapy, with its attendant complications and limited ability to control chronic rejection. Because autoimmune diseases are major contributors to end-stage renal disease, β-cell loss in type 1 diabetes, and other types of organ failure, the potential for tolerance strategies to reverse autoimmunity while inducing allograft tolerance is also a source of hope. All these approaches must, however, be undertaken with the caution that successful regimens could also lead to immune tolerance to active infectious organisms.

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39 APPROACH TO THE PATIENT WITH POSSIBLE CARDIOVASCULAR DISEASE

LEE GOLDMAN

Patients with cardiovascular disease may present with a wide range of symptoms and signs, each of which may be caused by noncardiovascular conditions. Conversely, patients with substantial cardiovascular disease may be asymptomatic. Because cardiovascular disease is a leading cause of death in the United States and other developed countries, it is crucial that patients be evaluated carefully to detect early cardiovascular disease, that symptoms or signs of cardiovascular disease be evaluated in detail, and that appropriate therapy be instituted.

In evaluating a patient with known or suspected heart disease, the physician must determine quickly whether a potentially life-threatening condition exists. In these situations, the evaluation must focus on the specific issue at hand and be accompanied by the rapid performance of appropriately directed additional tests. Examples of potentially life-threatening conditions include acute myocardial infarction (MI) (Chapter 58), unstable angina (Chapter 57), suspected aortic dissection (Chapter 63), pulmonary edema (Chapter 46), and pulmonary embolism (Chapter 68).

USING THE HISTORY TO DETECT CARDIOVASCULAR SYMPTOMS

Patients may complain spontaneously of a variety of cardiovascular symptoms (Table 39-1), but sometimes these symptoms are elicited only by obtaining a careful, complete medical history. In patients with known or suspected cardiovascular disease, questions about cardiovascular symptoms are key components of the history of present illness; in other patients, these issues are a fundamental part of the review of systems.

CHEST PAIN

Chest discomfort or pain is the cardinal manifestation of myocardial ischemia resulting from coronary artery disease or any condition that causes myocardial ischemia by an imbalance of myocardial oxygen demand compared with myocardial oxygen supply (Chapter 56). Women[1] and older individuals may be less likely to complain of classic anginal pain despite equivalent or even more advanced coronary disease.

New, acute, often ongoing pain may indicate an acute myocardial infarction, unstable angina, or aortic dissection; a pulmonary cause, such as acute pulmonary embolism or pleural irritation; a musculoskeletal condition of the chest wall, thorax, or shoulder; or a gastrointestinal abnormality, such as esophageal reflux or spasm, peptic ulcer disease, or cholecystitis (Table 39-2). The chest discomfort of an acute coronary syndrome (Chapter 57) or a myocardial infarction commonly occurs without an immediate or obvious precipitating clinical cause and builds in intensity for at least several minutes; the sensation can range from annoying discomfort to severe pain (Chapter 58).[2,3] Although a variety of adjectives may be used by patients to describe the sensation, physicians must be suspicious of any discomfort, especially if it radiates to the neck, shoulder, or arms.

The chest discomfort of unstable angina is clinically indistinguishable from that of an acute myocardial infarction except that the former may be precipitated more clearly by activity and may be more rapidly responsive to antianginal therapy (Chapter 57). Aortic dissection (Chapter 63) classically presents with the sudden onset of severe pain in the chest and radiating to the back; the location of the pain often provides clues to the location of the dissection. Ascending aortic dissections commonly present with chest discomfort radiating to the back, whereas dissections of the descending aorta commonly present with back pain radiating to the abdomen. The presence of back pain or a history of hypertension or other predisposing factors, such as Marfan syndrome, should prompt a careful assessment of peripheral pulses to determine whether the great vessels are affected by the dissection and of the chest radiograph to evaluate the size of the aorta. If this initial evaluation is suggestive, further testing with transesophageal echocardiography, computed tomography (CT), or magnetic resonance imaging (MRI) is indicated. The pain of pericarditis (Chapter 62) may simulate the pain of an acute myocardial infarction, may be primarily pleuritic, or may be continuous; a key physical finding is a pericardial rub. The pain of pulmonary embolism (Chapter 68) is commonly pleuritic in nature and is associated with dyspnea; hemoptysis also may be present. Pulmonary hypertension (Chapter 69) of any cause may be associated with chest discomfort with exertion; it commonly is associated with severe dyspnea and often is associated with cyanosis.

Recurrent, episodic chest discomfort may be noted with angina pectoris and with many cardiac and noncardiac causes (Chapter 56). A variety of stress tests (Table 39-3) can be used to provoke reversible myocardial ischemia in susceptible individuals and to help determine whether ischemia is the pathophysiologic explanation for the chest discomfort (Chapter 56).

TABLE 39-1 CARDINAL SYMPTOMS OF CARDIOVASCULAR DISEASE

Chest pain or discomfort
Dyspnea, orthopnea, paroxysmal nocturnal dyspnea, wheezing
Palpitations, dizziness, syncope
Cough, hemoptysis
Fatigue, weakness
Pain in extremities with exertion (claudication)

DYSPNEA

Dyspnea, which is an uncomfortable awareness of breathing, is commonly caused by cardiovascular or pulmonary disease. A systematic approach (see Fig. 71-2) with selected tests nearly always reveals the cause.[4] Acute dyspnea can be caused by myocardial ischemia, heart failure, severe hypertension, pericardial tamponade, pulmonary embolism, pneumothorax, upper airway obstruction, acute bronchitis or pneumonia, or some drug overdoses (e.g., salicylates). Subacute or chronic dyspnea is also a common presenting or accompanying symptom in patients with pulmonary disease (Chapter 71). Dyspnea also can be caused by severe anemia (Chapter 144) and can be confused with the fatigue that often is noted in patients with systemic and neurologic diseases (Chapters 236 and 366).

In heart failure, dyspnea typically is noted as a hunger for air and a need or an urge to breathe. The feeling that breathing requires increased work or effort is more typical of airway obstruction or neuromuscular disease. A feeling of chest tightness or constriction during breathing is typical of bronchoconstriction, which is commonly caused by obstructive airway disease (Chapters 75 and 76) but also may be seen in pulmonary edema. A feeling of heavy breathing, a feeling of rapid breathing, or a need to breathe more is classically associated with deconditioning.

In cardiovascular conditions, chronic dyspnea usually is caused by increases in pulmonary venous pressure as a result of left ventricular failure (Chapters 45 and 46) or valvular heart disease (Chapter 60). Orthopnea, which is an exacerbation of dyspnea when the patient is recumbent, is caused by increased work of breathing because of either increased venous return to the pulmonary vasculature or loss of gravitational assistance in diaphragmatic effort. Paroxysmal nocturnal dyspnea is severe dyspnea that awakens a patient at night and forces the assumption of a sitting or standing position to achieve gravitational redistribution of fluid. Of note is that acute diuresis relieves the dyspnea of severe heart failure, but the degree of relief is not always directly related to the amount of diuresis.

PALPITATIONS

Palpitations (Chapter 49) describe a subjective sensation of an irregular or abnormal heartbeat. Palpitations may be caused by any arrhythmia (Chapters 52 and 53) with or without important underlying structural heart disease. Palpitations should be defined in terms of the duration and frequency of the episodes; the precipitating and related factors; and any associated symptoms of chest pain, dyspnea, lightheadedness, or syncope. The history can determine whether the palpitations are caused by an irregular or a regular heartbeat. The feeling associated with a premature atrial or ventricular contraction, often described as a "skipped beat" or a "flip-flopping of the heart," must be distinguished from the irregularly irregular rhythm of atrial fibrillation or the rapid but regular rhythm of supraventricular tachycardia. Associated symptoms of chest pain, dyspnea, lightheadedness, dizziness, or diaphoresis suggest an important effect on cardiac output and mandate further evaluation. In general, evaluation begins with ambulatory electrocardiography (ECG; Table 39-4), which is always indicated in patients who have palpitations in

ABSTRACT

The approach to the patient with possible cardiovascular disease begins with a careful history. Chest pain may be of cardiac origin (e.g., ischemic heart disease, pericarditis, aortic dissection, pulmonary embolism, or pulmonary hypertension) or from noncardiac causes, ranging from pulmonary diseases (e.g., pneumonia with pleurisy, spontaneous pneumothorax), musculoskeletal diseases, gastrointestinal conditions (e.g., esophageal reflux, peptic ulcer, gall bladder disease), or anxiety states. Acute dyspnea may be a symptom of myocardial ischemia, heart failure, pericardial tamponade, pulmonary embolism, pneumothorax, a variety of pulmonary diseases, or even severe anemia. Palpitations can be caused by arrhythmias, with or without important underlying structural heart disease. Light-headedness or syncope can be caused by arrhythmias but also can be the result of other conditions that decrease cardiac output (e.g., left ventricular/right ventricular failure or inflow or outflow obstruction, cardiac tamponade, aortic dissection), reflex-mediated vasomotor instability (e.g., vasovagal, situational, or carotid sinus syncope), or hypostatic hypotension. Cough can be an early manifestation of heart failure. Fatigue and weakness are common in advanced cardiac disease. Claudication suggests possible peripheral arterial disease. Careful physical examination includes assessment of the jugular venous pressure and carotid pulse, as well as cardiac auscultation. The timing, quality, and duration of a heart murmur provide clues to its cause. Evaluation of the abdomen, extremities, and skin may demonstrate evidence of hypoperfusion, heart failure, or infective endocarditis. Careful laboratory testing, noninvasive imaging, and cardiac catheterization may help determine the cause of cardiovascular symptoms and signs, as well as how best to treat them.

KEYWORDS

chest pain
palpitations
heart murmurs
cardiovascular functional class palpitations
cardiac physical examination

TABLE 39-2 CAUSES OF CHEST PAIN

CONDITION	LOCATION	QUALITY	DURATION	AGGRAVATING OR RELIEVING FACTORS	ASSOCIATED SYMPTOMS OR SIGNS
CARDIOVASCULAR CAUSES					
Angina	Retrosternal region; radiates to or occasionally isolated to neck, jaw, epigastrium, shoulder, or arms (left common)	Pressure, burning, squeezing, heaviness, indigestion	<2-10 min	Precipitated by exercise, cold weather, or emotional stress; relieved by rest or nitroglycerin; atypical (Prinzmetal) angina may be unrelated to activity, often early morning	S_3 or murmur of papillary muscle dysfunction during pain
Rest or unstable angina	Same as angina	Same as angina but may be more severe	Usually <20 min	Same as angina, with decreasing tolerance for exertion or at rest	Similar to stable angina but may be pronounced; transient heart failure can occur
Myocardial infarction	Substernal and may radiate like angina	Heaviness, pressure, burning, constriction	≥30 min but variable	Unrelieved by rest or nitroglycerin	Shortness of breath, sweating, weakness, nausea, vomiting
Pericarditis	Usually begins over sternum or toward cardiac apex and may radiate to neck or left shoulder; often more localized than the pain of myocardial ischemia	Sharp, stabbing, knifelike	Lasts many hours to days; may wax and wane	Aggravated by deep breathing, rotating chest, or supine position; relieved by sitting up and leaning forward	Pericardial friction rub
Aortic dissection	Anterior chest; may radiate to back	Excruciating, tearing, knifelike	Sudden onset, unrelenting	Usually occurs in setting of hypertension or predisposition, such as Marfan syndrome	Murmur of aortic insufficiency, pulse or blood pressure asymmetry; neurologic deficit
Pulmonary embolism (chest pain often not present)	Substernal or over region of pulmonary infarction	Pleuritic (with pulmonary infarction) or angina-like	Sudden onset; minutes to <1 hr	May be aggravated by breathing	Dyspnea, tachypnea, tachycardia; hypotension, signs of acute right ventricular failure, and pulmonary hypertension with large emboli; rales, pleural friction rub, hemoptysis with pulmonary infarction
Pulmonary hypertension	Substernal	Pressure; oppressive	Similar to angina	Aggravated by effort	Pain usually associated with dyspnea; signs of pulmonary hypertension
NONCARDIAC CAUSES					
Pneumonia with pleurisy	Localized over involved area	Pleuritic, localized	Brief or prolonged	Painful breathing	Dyspnea, cough, fever, dull to percussion, bronchial breath sounds, rales, occasional pleural friction rub
Spontaneous pneumothorax	Unilateral	Sharp, well localized	Sudden onset, lasts many hours	Painful breathing	Dyspnea; hyperresonance and decreased breath and voice sounds over involved lung
Musculoskeletal disorders	Variable	Aching	Short or long duration	Aggravated by movement; history of muscle exertion or injury	Tender to pressure or movement
Herpes zoster	Dermatomal in distribution	Burning, itching	Prolonged	None	Vesicular rash appears in area of discomfort
Esophageal reflux	Substernal, epigastric	Burning, visceral discomfort	10-60 min	Aggravated by large meal, postprandial recumbency; relief with antacid	Water brash
Peptic ulcer	Epigastric, substernal	Visceral burning, aching	Prolonged	Relief with food, antacid	
Gallbladder disease	Epigastric, right upper quadrant	Visceral	Prolonged	May be unprovoked or follow meals	Right upper quadrant tenderness may be present
Anxiety states	Often localized over precordium	Variable; location often moves from place to place	Varies; often fleeting	Situational	Sighing respirations, often chest wall tenderness

Modified from Andreoli TE, Carpenter CCJ, Griggs RC, et al. Evaluation of the patient with cardiovascular disease. In: *Cecil Essentials of Medicine*, 6th ed. Philadelphia: WB Saunders; 2004:34-35.

the presence of coronary artery disease, structural heart disease, or substantial accompanying symptoms.[§] In such patients, more detailed evaluation is also warranted (see Fig. 49-3).

Lightheadedness or *syncope* (Chapter 49) can be caused by any condition that decreases cardiac output (e.g., bradyarrhythmia, tachyarrhythmia, obstruction of the left ventricular or right ventricular inflow or outflow, cardiac tamponade, aortic dissection, or severe pump failure), by reflex-mediated vasomotor instability (e.g., vasovagal, situational, or carotid sinus syncope), or by orthostatic hypotension (see Table 49-1). Neurologic diseases (e.g., migraine headaches, transient ischemic attacks, or seizures) also can cause transient loss of consciousness. The history, physical examination, and ECG can often diagnose the cause of syncope (see Table 49-2). Syncope caused by a cardiac arrhythmia usually occurs with little warning. Syncope with exertion or just after conclusion of exertion is typical of aortic stenosis and hypertrophic obstructive cardiomyopathy. In many patients, additional testing is required to document central nervous system disease, the cause of reduced cardiac output, or carotid sinus syncope. When the history, physical examination, and ECG do not provide helpful diagnostic information that points toward a specific cause of syncope, it is imperative that patients with heart disease or an abnormal ECG be tested with continuous ambulatory ECG monitoring to diagnose a

TABLE 39-3 COMMON EXERCISE TEST PROTOCOLS*

PROTOCOL	STAGE	DURATION (min)	GRADE (%)	RATE (mph)	METABOLIC EQUIVALENTS AT COMPLETION	FUNCTIONAL CLASS
Modified Bruce protocol†	1	3	0	1.7	2.5	III
	2	3	10	1.7	5	II
	3	3	12	2.5	7	I
	4	3	14	3.4	10	I
	5	3	16	4.2	13	I
Naughton protocol‡	0	2	0	2	2	III
	1	2	3.5	2	3	III
	2	2	7	2	4	III
	3	2	10.5	2	5	II
	4	2	14	2	6	II
	5	2	17.5	2	7	I

*Ramp protocols in which the workload is gradually increased on the basis of the patient's estimated functional capacity to achieve maximal effort in approximately 10 minutes are also useful.
†Commonly used in ambulatory patients.
‡Commonly used in patients with recent myocardial infarction, unstable angina, or other conditions that are expected to limit exercise.
Modified from Braunwald E, Goldman L, eds. *Primary Cardiology*. 2nd ed. Philadelphia: WB Saunders; 2003.

TABLE 39-4 INDICATIONS FOR AMBULATORY ELECTROCARDIOGRAPHIC MONITORING

History, physical examination, or 12-lead electrocardiogram suggests a possible arrhythmia
Known coronary or structural heart disease or a family history of genetic arrhythmia or sudden cardiac death
Symptoms warrant targeted therapy that depends on diagnosing the specific arrhythmia
Patient requires reassurance or a specific diagnosis because of anxiety or other concerns

possible arrhythmia; in selected patients, formal electrophysiologic testing may be indicated (Chapter 49). In patients with no evident heart disease, tilt testing (Chapter 49) can help detect reflex-mediated vasomotor instability.

OTHER SYMPTOMS

Nonproductive *cough* (Chapter 71), especially a persistent cough (see Fig. 71-1), can be an early manifestation of elevated pulmonary venous pressure and otherwise unsuspected heart failure. *Fatigue* and *weakness* are common accompaniments of advanced cardiac disease and reflect an inability to perform normal activities. A variety of approaches have been used to classify the severity of cardiac limitations, ranging from class I (little or no limitation) to class IV (severe limitation) (Table 39-5). *Hemoptysis* (Chapter 71) is a classic presenting finding in patients with pulmonary embolism, but it is also common in patients who have mitral stenosis, pulmonary edema, pulmonary infections, and malignant neoplasms (see Table 71-6). *Claudication*, which is pain in the extremities with exertion, should alert the physician to possible peripheral arterial disease (Chapters 65 and 66).

COMPLETE MEDICAL HISTORY

The complete medical history should include a thorough review of systems, family history, social history, and past medical history (Chapter 12). The review of systems may reveal other symptoms that suggest a systemic disease as the cause of any cardiovascular problems. The family history should focus on premature atherosclerosis or evidence of familial abnormalities, such as may be found with various causes of the long QT syndrome (Chapter 53) or hypertrophic cardiomyopathy (Chapter 47).

The social history should include specific questioning about cigarette smoking, alcohol intake, and use of illicit drugs. The past medical history may reveal prior conditions or medications that suggest systemic diseases, ranging from chronic obstructive pulmonary disease, which may explain a complaint of dyspnea, to hemochromatosis, which may be a cause of restrictive cardiomyopathy. A careful history to inquire about recent dental work or other procedures is crucial if bacterial endocarditis is part of the differential diagnosis.

PHYSICAL EXAMINATION FOR DETECTION OF SIGNS OF CARDIOVASCULAR DISEASE

The cardiovascular physical examination, which is a subset of the complete physical examination (Chapter 6), provides important clues to the diagnosis of asymptomatic and symptomatic cardiac disease and may reveal cardiovascular manifestations of noncardiovascular diseases. The cardiovascular physical examination begins with careful measurement of the pulse and blood pressure (Chapter 7). If aortic dissection (Chapter 63) is a consideration, blood pressure should be measured in both arms and, preferably, in at least one leg. When coarctation of the aorta is suspected (Chapter 55), blood pressure must be measured in at least one leg and in the arms. Discrepancies in blood pressure between the two arms also can be caused by atherosclerotic disease of the great vessels. Pulsus paradoxus, which is more than the usual 10-mm Hg drop in systolic blood pressure during inspiration, is typical of pericardial tamponade (Chapter 62).

GENERAL APPEARANCE

The respiratory rate may be increased in patients with heart failure. Patients with pulmonary edema are usually markedly tachypneic and may have labored breathing. Patients with advanced heart failure may have Cheyne-Stokes respirations.

Systemic diseases, such as hyperthyroidism (Chapter 207), hypothyroidism (Chapter 207), rheumatoid arthritis (Chapter 243), scleroderma (Chapter 246), and hemochromatosis (Chapter 196), may be suspected from the patient's general appearance. Marfan syndrome (Chapter 239), Turner syndrome (Chapter 217), Down syndrome (Chapter 32), and a variety of congenital anomalies also may be readily apparent.

OPHTHALMOLOGIC EXAMINATION

Examination of the fundi may show diabetic (see Fig. 391-22) or hypertensive retinopathy (see Fig. 391-24) or Roth spots (see Fig. 391-26) typical of infectious endocarditis. Beading of the retinal arteries is typical of severe hypercholesterolemia. Osteogenesis imperfecta, which is associated with blue sclerae, also is associated with aortic dilation and mitral valve prolapse. Retinal artery occlusion (see Fig. 391-27) may be caused by an embolus from clot in the left atrium or left ventricle, a left atrial myxoma, or atherosclerotic debris from the great vessels. Hyperthyroidism may present with exophthalmos and typical stare (see Fig. 391-5), whereas myotonic dystrophy, which is associated with atrioventricular block and arrhythmia, often is associated with ptosis and an expressionless face (see Fig. 389-2).

JUGULAR VEINS

The external jugular veins help in assessment of mean right atrial pressure, which normally varies between 5 and 10 cm H_2O; the height (in centimeters) of the central venous pressure is measured by adding 5 cm to the height of the observed jugular venous distention above the sternal angle of Louis (Fig. 39-1). The normal jugular venous pulse, best seen in the internal jugular vein (and not seen in the external jugular vein unless insufficiency of the jugular venous valves is present), includes an *a* wave, caused by right atrial contraction; a *c* wave, reflecting carotid artery pulsation; an *x* descent; a *v* wave, which corresponds to isovolumetric right ventricular contraction and is more marked in the presence of tricuspid insufficiency; and a *y* descent, which occurs as the tricuspid valve opens and ventricular filling begins (Fig. 39-2). Abnormalities of the jugular venous pressure (Fig. 39-3) as detected on physical examination or point-of-care ultrasonography[6] are useful in detecting heart failure, and they

TABLE 39-5 A COMPARISON OF THREE METHODS OF ASSESSING CARDIOVASCULAR DISABILITY

CLASS	NEW YORK HEART ASSOCIATION FUNCTIONAL CLASSIFICATION	CANADIAN CARDIOVASCULAR SOCIETY FUNCTIONAL CLASSIFICATION	SPECIFIC ACTIVITY SCALE
I	Patients with cardiac disease but without resulting limitations of physical activity Ordinary physical activity does not cause undue fatigue, palpitation, dyspnea, or anginal pain	Ordinary physical activity, such as walking and climbing stairs, does not cause angina Angina with strenuous or rapid or prolonged exertion at work or recreation	Patients can perform to completion any activity requiring ≥7 metabolic equivalents, for example, can carry 24 lb up 8 steps; carry objects that weigh 80 lb; do outdoor work (shovel snow, spade soil); do recreational activities (skiing, basketball, squash, handball, jog or walk 5 mph)
II	Patients with cardiac disease resulting in slight limitation of physical activity They are comfortable at rest Ordinary physical activity results in fatigue, palpitations, dyspnea, or anginal pain	Slight limitation of ordinary activity Walking or climbing stairs rapidly, walking uphill, walking or stair climbing after meals, in cold, in wind, or when under emotional stress, or only during the few hours after awakening Walking >2 blocks on the level and climbing >1 flight of ordinary stairs at a normal pace and in normal conditions	Patient can perform to completion any activity requiring ≥5 metabolic equivalents but cannot and does not perform to completion activities requiring ≥7 metabolic equivalents, e.g., have sexual intercourse without stopping, garden, rake, weed, roller skate, dance foxtrot, walk at 4 mph on level ground
III	Patients with cardiac disease resulting in marked limitation of physical activity They are comfortable at rest Less than ordinary physical activity causes fatigue, palpitations, dyspnea, or anginal pain	Marked limitation of ordinary physical activity Walking 1 or 2 blocks on the level and climbing >1 flight in normal conditions	Patient can perform to completion any activity requiring ≥2 metabolic equivalents but cannot and does not perform to completion any activities requiring ≥5 metabolic equivalents, for example, shower without stopping, strip and make bed, clean windows, walk 2.5 mph, bowl, play golf, dress without stopping
IV	Patients with cardiac disease resulting in inability to carry on any physical activity without discomfort Symptoms of cardiac insufficiency or of the anginal syndrome may be present even at rest If any physical activity is undertaken, discomfort is increased	Inability to carry on any physical activity without discomfort—anginal syndrome may be present at rest	Patient cannot or does not perform to completion activities requiring ≥2 metabolic equivalents; cannot carry out activities listed above (Specific Activity Scale, class III)

From Goldman L, Hashimoto B, Cook EF, et al. Comparative reproducibility and validity of systems for assessing cardiovascular functional class: advantages of a new specific activity scale. *Circulation*. 1981;64:1227-1234. Reproduced by permission of the American Heart Association.

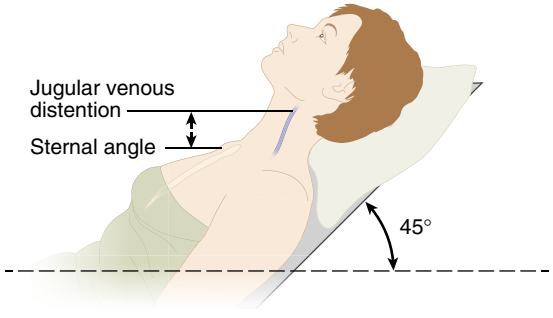

FIGURE 39-1. Jugular venous distention is defined by engorgement of the internal jugular vein more than 5 cm above the sternal angle at 45 degrees. The central venous pressure is the observed venous distention above the sternal angle plus 5 cm.

correlate well with brain natriuretic peptide levels (Chapter 45) and echocardiographic evidence of an elevated pulmonary artery pressure (Chapter 43). The jugular venous pressure also helps in the diagnosis of pericardial disease, tricuspid valve disease, and pulmonary hypertension (Table 39-6).

CAROTID PULSE

The carotid pulse should be examined in terms of its volume and contour. The carotid pulse (Fig. 39-4) may be increased in frequency and may be more intense than normal in patients with a higher stroke volume secondary to aortic regurgitation, arteriovenous fistula, hyperthyroidism, fever, or anemia. In aortic regurgitation or arteriovenous fistula, the pulse may have a bisferious quality. The carotid upstroke is delayed in patients with valvular aortic stenosis (Chapter 60) and has a normal contour but diminished amplitude in any cause of reduced stroke volume.

CARDIAC INSPECTION AND PALPATION

Inspection of the precordium may reveal the hyperinflation of obstructive lung disease or unilateral asymmetry of the left side of the chest because of right ventricular hypertrophy before puberty. Palpation may be performed with the patient either supine or in the left lateral decubitus position; the

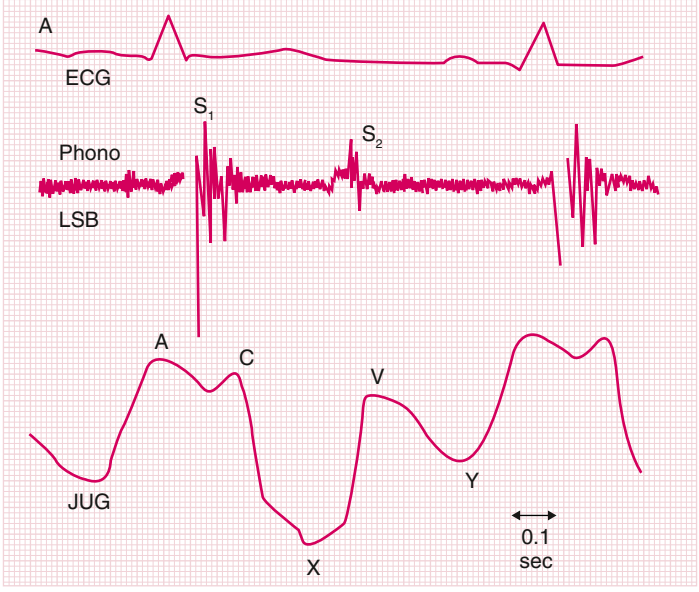

FIGURE 39-2. Normal jugular venous pulse. ECG = electrocardiogram; JUG = jugular vein; LSB = left sternal border; phono = phonocardiogram; S_1 = first heart sound; S_2 = second heart sound.

latter position moves the left ventricular apex closer to the chest wall and increases the ability to palpate the point of maximal impulse and other phenomena. Low-frequency phenomena, such as systolic heaves or lifts from the left ventricle (at the cardiac apex) or right ventricle (parasternal in the third or fourth intercostal space), are felt best with the heel of the palm. With the patient in the left lateral decubitus position, this technique also may allow palpation of an S_3 gallop in cases of advanced heart failure or an S_4 gallop in cases of poor left ventricular distensibility during diastole. The left ventricular apex is more diffuse and sometimes may be frankly dyskinetic in patients

FIGURE 39-3. Typical distention of the internal jugular vein. (From http://courses.cvcc.vccs.edu/WisemanD/jugular_vein_distention.htm.)

TABLE 39-6 ABNORMALITIES OF VENOUS PRESSURE AND PULSE AND THEIR CLINICAL SIGNIFICANCE

Positive hepatojugular reflux	Suspect heart failure, particularly left ventricular systolic dysfunction (echocardiography recommended)
Elevated systemic venous pressure without obvious *x* or *y* descent, quiet precordium, and pulsus paradoxus	Suspect cardiac tamponade (echocardiography recommended)
Elevated systemic venous pressure with sharp *y* descent, Kussmaul sign, and quiet precordium	Suspect constrictive pericarditis (cardiac catheterization and MRI or CT recommended)
Elevated systemic venous pressure with a sharp brief *y* descent, Kussmaul sign, and evidence of pulmonary hypertension and tricuspid regurgitation	Suspect restrictive cardiomyopathy (cardiac catheterization and MRI or CT recommended)
A prominent *a* wave with or without elevation of mean systemic venous pressure	Exclude tricuspid stenosis, right ventricular hypertrophy caused by pulmonary stenosis, and pulmonary hypertension (echo-Doppler study recommended)
A prominent *v* wave with a sharp *y* descent	Suspect tricuspid regurgitation (echo-Doppler or cardiac catheterization to determine etiology)

CT = computed tomography; MRI = magnetic resonance imaging.
From Braunwald E, ed. *Heart Disease: A Textbook of Cardiovascular Medicine*. 5th ed. Philadelphia: WB Saunders; 1997.

with advanced heart disease. The distal palm is best for feeling thrills, which are the tactile equivalent of cardiac murmurs. By definition, a thrill denotes a murmur of grade 4/6 or louder. Higher-frequency events may be felt best with the fingertips; examples include the opening snap of mitral stenosis or the loud pulmonic second sound of pulmonary hypertension.

AUSCULTATION

The first heart sound (Fig. 39-5), which is largely produced by closure of the mitral and—to a lesser extent—the tricuspid valves, may be louder in patients with mitral valve stenosis and intact valve leaflet movement and less audible in patients with poor closure caused by mitral regurgitation (Chapter 60). The second heart sound is caused primarily by closure of the aortic valve, but closure of the pulmonic valve is also commonly audible. In normal individuals, the louder aortic closure sound occurs first, followed by pulmonic closure. With expiration, the two sounds are virtually superimposed. With inspiration, by comparison, the increased stroke volume of the right ventricle commonly leads to a discernible splitting of the second sound. This splitting may be fixed in patients with an atrial septal defect (Chapter 55) or a right bundle branch block. The split may be paradoxical in patients with left bundle branch block or other causes of delayed left ventricular emptying. The aortic component of the second sound is increased in intensity in the presence of systemic hypertension and decreased in intensity in patients with aortic stenosis. The pulmonic second sound is increased in the presence of pulmonary hypertension.

Early systolic ejection sounds are related to forceful opening of the aortic or pulmonic valve. These sounds are common in congenital aortic stenosis, with a mobile valve; in hypertension, with forceful opening of the aortic valve; and in healthy young individuals, especially when cardiac output is increased. Midsystolic or late systolic clicks are caused most commonly by mitral valve prolapse (Chapter 60). Clicks are relatively high-frequency sounds that are heard best with the diaphragm of the stethoscope.

An S_3 corresponds to rapid ventricular filling during early diastole. It may occur in normal children and young adults, especially if stroke volume is increased. After about 40 years of age, however, an S_3 should be considered abnormal; it is caused by conditions that increase the volume of ventricular filling during early diastole (e.g., mitral regurgitation) or that increase pressure in early diastole (e.g., advanced heart failure).[7] A left ventricular S_3 gallop is heard best at the apex, whereas the right ventricular S_3 gallop is heard best at the fourth intercostal space at the left parasternal border; both are heard best with the bell of the stethoscope. An S_4 is heard rarely in young individuals but is common in adults older than 40 or 50 years because of reduced ventricular compliance during atrial contraction; it is a nearly ubiquitous finding in patients with hypertension, heart failure, or ischemic heart disease.

The opening snap of mitral and, less commonly, tricuspid stenosis (Chapter 60) occurs at the beginning of mechanical diastole, before the onset of the rapid phase of ventricular filling. An opening snap is high pitched and is heard best with the diaphragm; this differential frequency should help distinguish an opening snap from an S_3 on physical examination. An opening snap commonly can be distinguished from a loud pulmonic component of the second heart sound by the differential location (mitral opening snap at the apex, tricuspid opening snap at the left third or fourth intercostal space, pulmonic second sound at the left second intercostal space) and by the longer interval between S_2 and the opening snap.

Heart murmurs may be classified as systolic, diastolic, or continuous (Table 39-7).[8] Murmurs are graded by intensity on a scale of 1 to 6. Grade 1 is faint and appreciated only by careful auscultation; grade 2, readily audible; grade 3, moderately loud; grade 4, loud and associated with a palpable thrill; grade 5, loud and audible with the stethoscope only partially placed on the chest; and grade 6, loud enough to be heard without the stethoscope on the chest. Systolic ejection murmurs usually peak in early to mid-systole when left ventricular ejection is maximal; examples include fixed valvular, supravalvular, or infravalvular aortic stenosis and pulmonic stenosis. The murmur of hypertrophic obstructive cardiomyopathy has a similar ejection quality, although its peak may be later in systole when dynamic obstruction is maximal (Chapter 47). Pansystolic murmurs are characteristic of mitral or tricuspid regurgitation or with a left-to-right shunt from conditions such as a ventricular septal defect (left ventricle to right ventricle). A late systolic murmur is characteristic of mitral valve prolapse (Chapter 60) or ischemic papillary muscle dysfunction. Ejection quality murmurs also may be heard in patients with normal valves but increased flow, such as occurs with marked anemia, fever, or bradycardia secondary to congenital complete heart block; they also may be heard across a valve that is downstream from increased flow because of an intracardiac shunt. Maneuvers such as inspiration, expiration, standing, squatting, and hand gripping can be especially useful in the differential diagnosis of a murmur; however, echocardiography commonly is required to make a definitive diagnosis of cause and severity (Table 39-8).

High-frequency, early diastolic murmurs are typical of aortic regurgitation and pulmonic regurgitation from a variety of causes. The murmurs of mitral and tricuspid stenosis begin in early to mid-diastole and tend to diminish in intensity later in diastole in the absence of effective atrial contraction, but they tend to increase in intensity in later diastole if effective atrial contraction is present.

Continuous murmurs may be caused by any abnormality that is associated with a pressure gradient in systole and diastole. Examples include a patent ductus arteriosus, ruptured sinus of Valsalva aneurysm, arteriovenous fistula (of the coronary artery, pulmonary artery, or thoracic artery), and a mammary souffle. In some situations, murmurs of two coexistent conditions (e.g., aortic stenosis and regurgitation, atrial septal defect with a large shunt and resulting flow murmurs of relative mitral and pulmonic stenosis) may mimic a continuous murmur.

Although experienced examiners may still be able to diagnose meaningful valvular heart disease accurately by auscultation, most general physicians are not nearly so accurate, even after training. As a result, echocardiography (Chapter 43) is critical to the evaluation of patients with suspected structural heart disease.

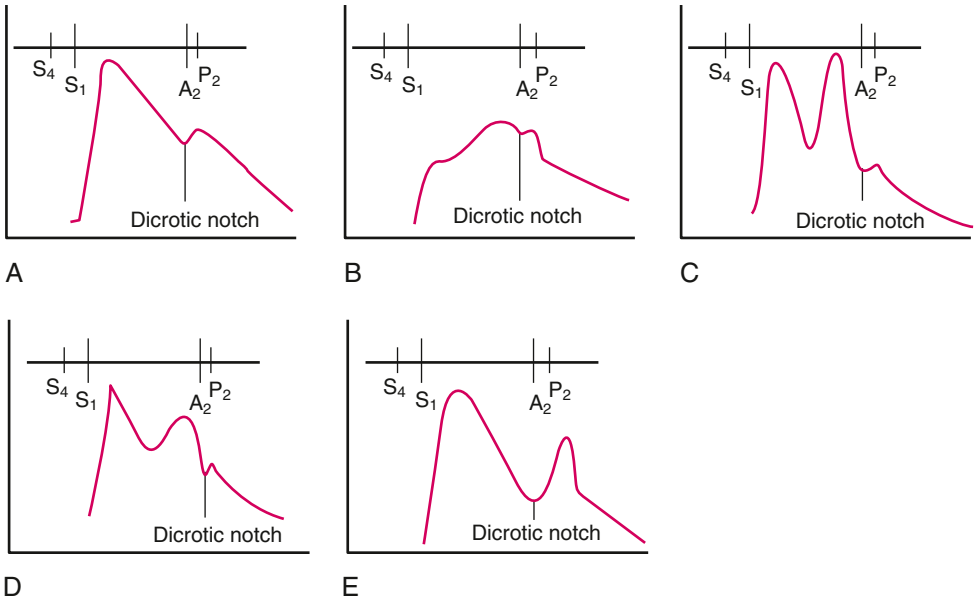

FIGURE 39-4. Schematic diagrams of the configurational changes in the carotid pulse and their differential diagnosis. Heart sounds also are illustrated. **A**, Normal. **B**, Anacrotic pulse with slow initial upstroke. The peak is close to the second heart sound. These features suggest fixed left ventricular outflow obstruction, such as valvular aortic stenosis. **C**, Pulsus bisferiens, with percussion and tidal waves occurring during systole. This type of carotid pulse contour is observed most frequently in patients with hemodynamically significant aortic regurgitation or combined aortic stenosis and regurgitation with dominant regurgitation. It rarely is observed in patients with mitral valve prolapse or in normal individuals. **D**, Pulsus bisferiens in hypertrophic obstructive cardiomyopathy. This finding rarely is appreciated at the bedside by palpation. **E**, Dicrotic pulse results from an accentuated dicrotic wave and tends to occur in sepsis, severe heart failure, hypovolemic shock, and cardiac tamponade and after aortic valve replacement. A_2 = aortic component of the second heart sound; P_2 = pulmonary component of the second heart sound); S_1 = first heart sound; S_4 = atrial sounds. (From Chatterjee K. Bedside evaluation of the heart: the physical examination. In: Chatterjee K, Chetlin MD, Karliner J, et al, eds. *Cardiology: An Illustrated Text/Reference*. Philadelphia: JB Lippincott; 1991:3.11-3.51.)

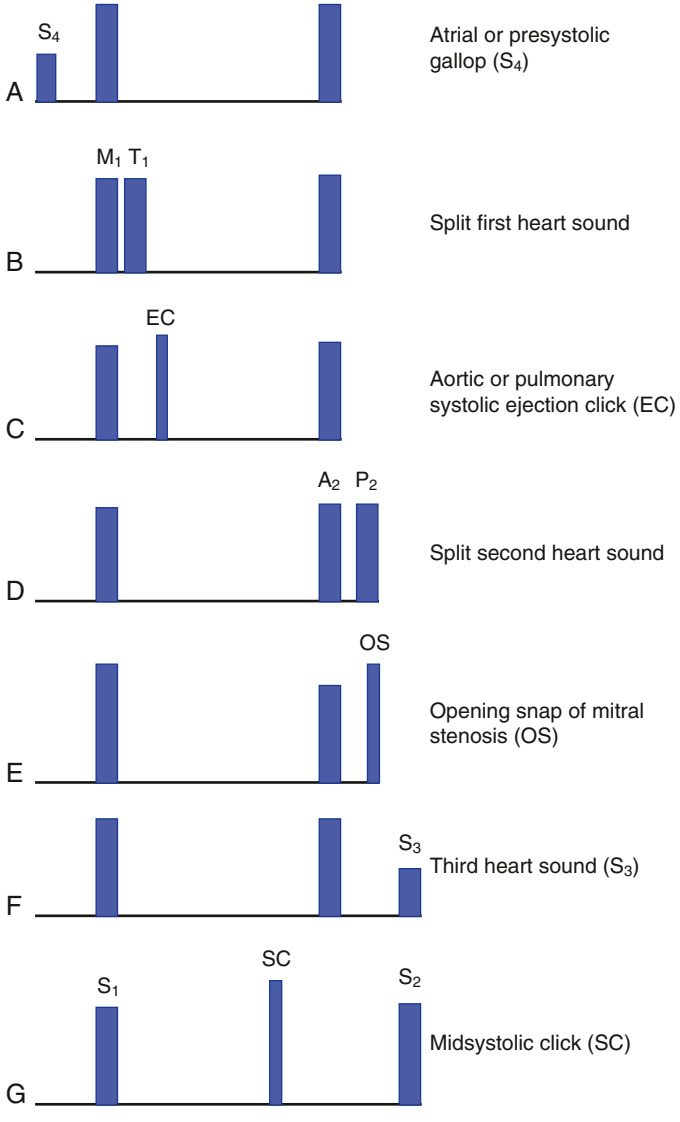

FIGURE 39-5. Timing of the different heart sounds and added sounds. (Modified from Wood P. *Diseases of the Heart and Circulation*. 3rd ed. Philadelphia: JB Lippincott; 1968.)

ABDOMEN

The most common cause of hepatomegaly in patients with heart disease is hepatic engorgement from elevated right-sided pressures associated with right ventricular failure of any cause. Hepatojugular reflux is elicited by pressing on the liver and showing an increase in the jugular venous pressure; it indicates advanced right ventricular failure or obstruction to right ventricular filling. Evaluation of the abdomen also may reveal an enlarged liver caused by a systemic disease, such as hemochromatosis (Chapter 196) or sarcoidosis (Chapter 83), which also may affect the heart. In more severe cases, splenomegaly and ascites also may be noted. Large, palpable, polycystic kidneys (Chapter 112) commonly are associated with hypertension. A systolic bruit suggestive of renal artery stenosis (Chapter 110) or an enlarged abdominal aorta (Chapter 63) is a clue of atherosclerosis.

EXTREMITIES

Extremities should be evaluated for peripheral pulses, edema, cyanosis, and clubbing. Diminished peripheral pulses suggest peripheral arterial disease (Chapters 65 and 66). Delayed pulses in the legs are consistent with coarctation of the aorta and are seen after aortic dissection.

Edema (Fig. 39-6) is a cardinal manifestation of right-sided heart failure. When it is caused by heart failure, pericardial disease, or pulmonary hypertension, the edema is usually symmetrical and progresses upward from the ankles; each of these causes of cardiac edema commonly is associated with jugular venous distention and often with hepatic congestion.[9] Unilateral edema suggests thrombophlebitis or proximal venous or lymphatic obstruction (Fig. 39-7).[10] Edema in the absence of evidence of right-sided or left-sided heart failure suggests renal disease, hypoalbuminemia, myxedema, or other noncardiac causes. Among unselected patients with bilateral edema, about 40% have an underlying cardiac disease, about 40% have an elevated pulmonary blood pressure, about 20% have bilateral venous disease, about 20% have renal disease, and about 25% have idiopathic edema. In patients who have chronic leg edema with recurrent cellulitis, leg compression therapy can reduce the risk of subsequent cellulitis.[A1]

Cyanosis (Fig. 39-8) is a bluish discoloration caused by reduced hemoglobin exceeding about 5 g/dL in the capillary bed. Central cyanosis is seen in patients with poor oxygen saturation resulting from a reduced inspired oxygen concentration or inability to oxygenate the blood in the lungs (e.g., as a result of advanced pulmonary disease, pulmonary edema, pulmonary arteriovenous fistula, or right-to-left shunting); it also may be seen in patients with marked erythrocytosis. Methemoglobinemia (Chapter 144) also can present with cyanosis. Peripheral cyanosis may be caused by reduced blood flow to the extremities secondary to vasoconstriction, heart failure, or shock.

TABLE 39-7 SOME COMMON CAUSES OF HEART MURMURS*

	USUAL LOCATION	COMMON ASSOCIATED FINDINGS
SYSTOLIC		
Holosystolic		
Mitral regurgitation	Apex → axilla	↑ with handgrip; S_3 if marked mitral regurgitation; left ventricular dilation common
Tricuspid regurgitation	LLSB	↑ with inspiration; right ventricular dilation common
Ventricular septal defect	LLSB → RLSB	Often with thrill
Early to midsystolic		
Aortic valvular stenosis	RUSB	Ejection click if mobile valve; soft or absent A_2 if valve immobile; later peak associated with more severe stenosis
Fixed supravalvular or subvalvular	RUSB	
Dynamic infravalvular	LLSB → apex + axilla	Hypertrophic obstructive cardiomyopathy; murmur louder if left ventricular volume lower or contractility increased, softer if left ventricular volume increased†; can be later in systole if obstruction delayed
Pulmonic valvular stenosis	LUSB	↑ with inspiration
Infravalvular (infundibular)	LUSB	↑ with inspiration
Supravalvular	LUSB	↑ with inspiration
"Flow murmurs"	LUSB	Anemia, fever, increased flow of any cause‡
Mid to late systolic		
Mitral valve prolapse	LLSB or apex → axilla	Preceded by click; murmur lengthens with maneuvers that decrease left ventricular volume†
Papillary muscle dysfunction	Apex → axilla	Ischemic heart disease
DIASTOLIC		
Early diastolic		
Aortic regurgitation	RUSB, LUSB	High-pitched, blowing quality; endocarditis, diseases of the aorta, associated aortic valvular stenosis; signs of low peripheral vascular resistance
Pulmonic valve regurgitation	LUSB	Pulmonary hypertension as a causative factor
Mid to late diastolic		
Mitral stenosis, tricuspid stenosis	Apex, LLSB	Low pitched; in rheumatic heart disease, opening snap commonly precedes murmur; can be caused by increased flow across normal valve‡
Atrial myxomas	Apex (L), LLSB (R)	"Tumor plop"
Continuous		
Venous hum	Over jugular or hepatic vein or breast	
Patent ductus arteriosus	LUSB	
Arteriovenous fistula		
Coronary	LUSB	
Pulmonary, bronchial, chest wall	Over fistula	
Ruptured sinus of Valsalva aneurysm	RUSB	Sudden onset

*See also Chapters 55 and 60.

†Left ventricular volume is decreased by standing or during prolonged, forced expiration against a closed glottis (Valsalva maneuver); it is increased by squatting or by elevation of the legs; contractility is increased by adrenergic stimulation or in the beat after an extrasystolic beat.

‡Including a left-to-right shunt through an atrial septal defect for tricuspid or pulmonic flow murmurs and a ventricular septal defect for pulmonic or mitral flow murmurs.

LLSB = left lower sternal border (fourth intercostal space); LUSB = left upper sternal border (second and third intercostal spaces); RLSB = right lower sternal border (fourth intercostal space); RUSB = right upper sternal border (second and third intercostal spaces).

TABLE 39-8 SENSITIVITY AND SPECIFICITY OF BEDSIDE MANEUVERS IN THE IDENTIFICATION OF SYSTOLIC MURMURS

MANEUVER	RESPONSE	MURMUR	SENSITIVITY (%)	SPECIFICITY (%)
Inspiration	↑	RS	100	88
Expiration	↓	RS	100	88
Valsalva maneuver	↑	HC	65	96
Squat to stand	↑	HC	95	84
Stand to squat	↓	HC	95	85
Leg elevation	↓	HC	85	91
Handgrip	↓	HC	85	75
Handgrip	↑	MR and VSD	68	92
Transient arterial occlusion	↑	MR and VSD	78	100

HC = hypertrophic cardiomyopathy; MR = mitral regurgitation; RS = right sided; VSD = ventricular septal defect.

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Clubbing (Fig. 39-9), which is loss of the normal concave configuration of the nail as it emerges from the distal phalanx, is seen in patients with cyanotic congenital heart disease (Chapter 55), but in adults it is usually related to pulmonary abnormalities such as lung cancer (Chapter 177).[11]

EXAMINATION OF THE SKIN

Examination of the skin may reveal bronze pigmentation typical of hemochromatosis (Chapter 196); jaundice (see Fig. 132-1) characteristic of severe right-sided heart failure or hemochromatosis; or capillary hemangiomas typical of hereditary hemorrhagic telangiectasia (see Fig. 159-3), which also is associated with pulmonary arteriovenous fistulas and cyanosis. Infectious endocarditis may be associated with splinter hemorrhages (Fig. 39-10),[12] Osler nodes (see Fig. 61-2), or Janeway lesions (Chapter 61). Xanthomas (E-Fig. 39-1) are subcutaneous deposits of cholesterol seen on the extensor surfaces of the extremities or on the palms and digital creases; they are found in patients with severe hypercholesterolemia.

LABORATORY STUDIES

All patients with known or suspected cardiac disease should have an ECG. The ECG (Chapter 42) helps identify rate, rhythm, conduction abnormalities, and possible myocardial ischemia or myocardial infarction. Blood testing in patients with known or suspected cardiac disease should be targeted to the conditions in question. In general, a complete blood cell count, thyroid indices, and lipid levels are part of the standard evaluation. Genetic screening

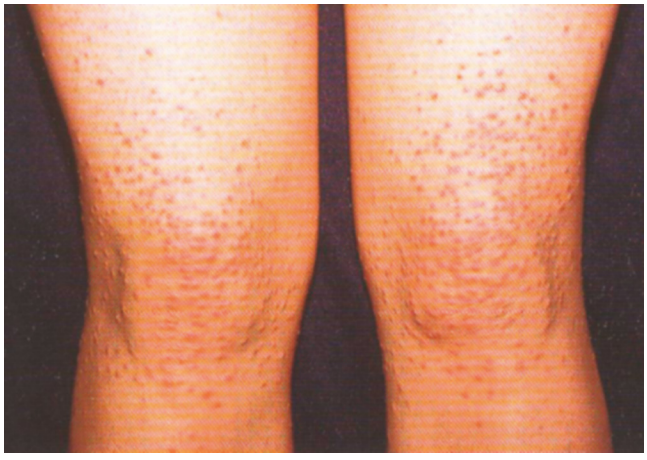

E-FIGURE 39-1. Eruptive xanthomas of the extensor surfaces of the lower extremities. This patient had marked hypertriglyceridemia. (From Massengale WT, Nesbitt LT Jr. Xanthomas. In: Bolognia JL, Jorizzo JL, Rapini RP, eds. *Dermatology*. Philadelphia: Mosby; 2003:1449.)

has become increasingly useful in individuals who have a family history of cardiomyopathy, arrhythmias, or sudden death.[13]

The chest radiograph (Chapter 44) yields important information on chamber enlargement, pulmonary vasculature, and the great vessels. Point-of-care ultrasonography is increasingly being used in acute care settings to distinguish heart failure from pulmonary causes of dyspnea,[14] to diagnose severe valvular heart disease, and to evaluate suspected pericardial tamponade.[15]

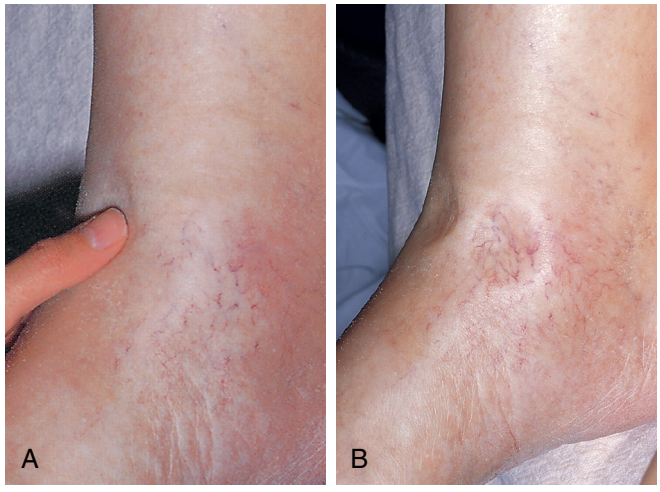

FIGURE 39-6. **A and B, Pitting edema in a patient with cardiac failure.** A depression ("pit") remains in the edema for some minutes after firm fingertip pressure is applied. (From Forbes CD, Jackson WD. *Color Atlas and Text of Clinical Medicine*. 3rd ed. London: Mosby; 2003.)

For patients who have acute chest pain or other symptoms that suggest acute myocardial ischemia, the probability of an acute myocardial infarction can be estimated by integrating information from the history, physical examination, and ECG. If the ECG shows evidence of ST-segment or T-wave changes that are consistent with myocardial ischemia and that are not known to be old, admission is mandatory, and acute interventions are often required (Chapters 57 and 58). In other patients who have suggestive symptoms but a nondiagnostic ECG, rapid testing with a high-sensitivity troponin assay is very helpful for guiding triage decisions (Chapter 57). An undetectable high-sensitivity troponin level at presentation reduces the probability of acute MI or an acute coronary event to less than 1%.[16] A protocol in which the ECG and troponin level are repeated in 2 hours is as good as longer observation periods for evaluating patients with acute chest pain and suspected myocardial infarction. However, the advent of high-sensitivity troponin assays has also greatly increased the risk for a false-positive diagnosis of myocardial infarction, especially because of chronic troponin elevations in many cardiac conditions and in some elderly patients (Chapter 57). In this acute setting, early CT angiography does not improve clinical outcomes compared with invasive coronary angiography (Chapter 57).[A2]

In patients who have dyspnea or other symptoms or signs of potential heart failure, a pro–B-type natriuretic peptide level (Chapter 45) is very useful for their emergency evaluation. A level <300 pg/mL nearly excludes the diagnosis of heart failure.[17]

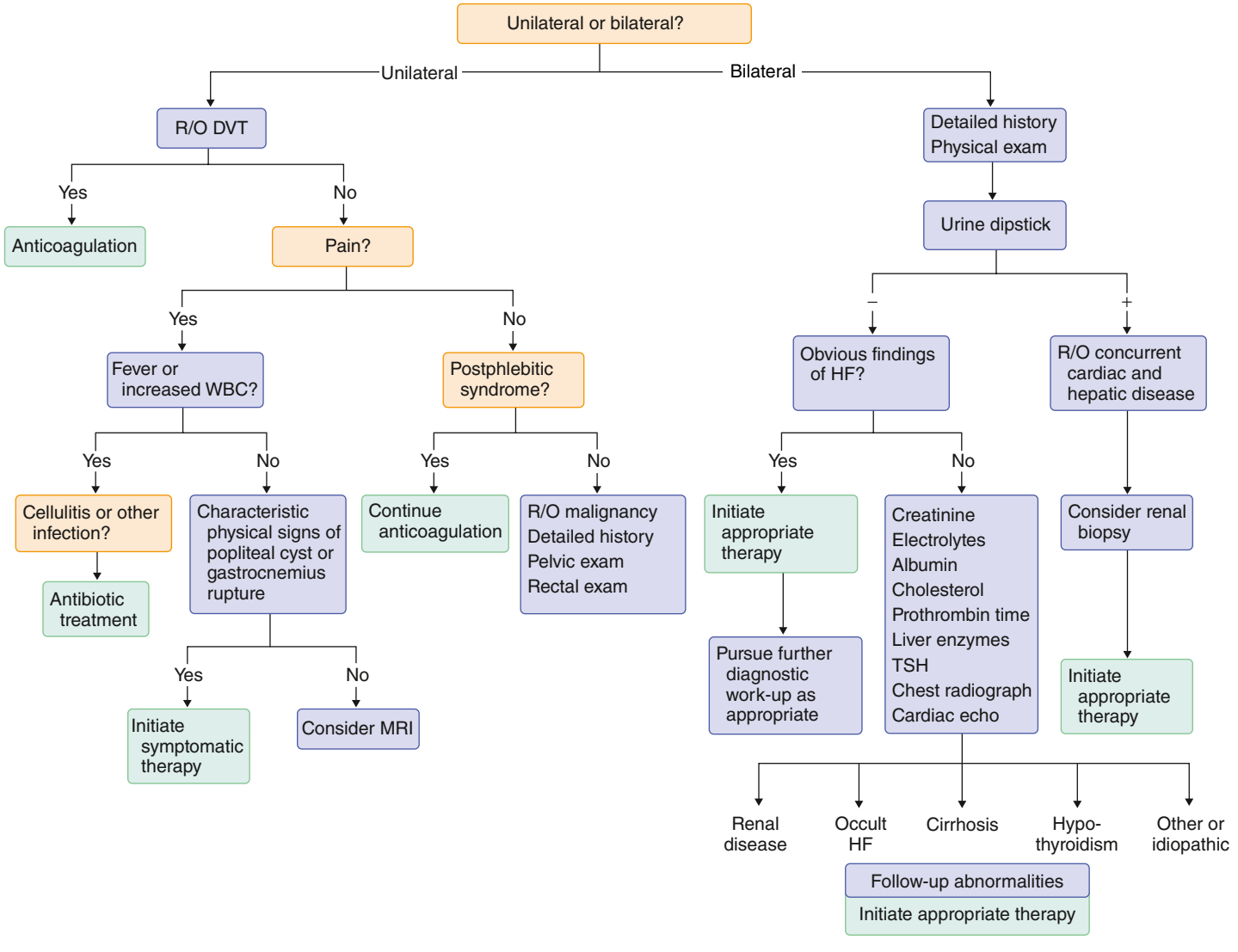

FIGURE 39-7. **Diagnostic approach to patients with edema.** DVT = deep vein thrombosis; HF = heart failure; MRI = magnetic resonance imaging; R/O = rule out; TSH = thyroid-stimulating hormone; WBC = white blood cell count. (From Chertow G. Approach to the patient with edema. In: Braunwald E, Goldman L, eds. *Primary Cardiology*. 2nd ed. Philadelphia: WB Saunders; 2003.)

FIGURE 39-8. Arterial embolism causing acute ischemia and cyanosis of the leg. Initial pallor of the leg and foot was followed by cyanosis. (From Forbes CD, Jackson WD. *Color Atlas and Text of Clinical Medicine*. 3rd ed. London: Mosby; 2003.)

FIGURE 39-9. Severe finger clubbing in a patient with cyanotic congenital heart disease. (From Forbes CD, Jackson WD. *Color Atlas and Text of Clinical Medicine*. 3rd ed. London: Mosby; 2003.)

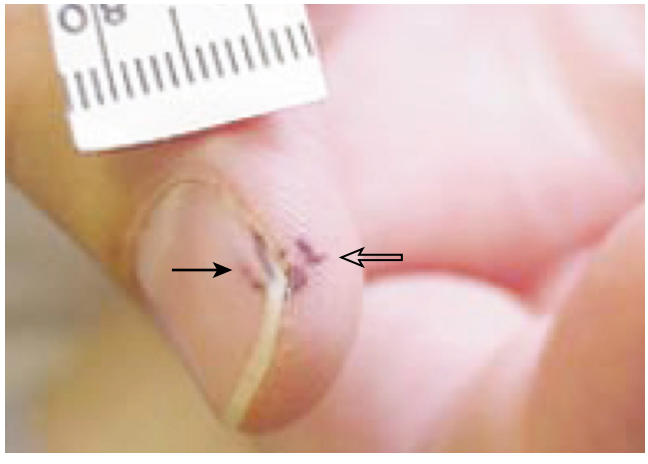

FIGURE 39-10. Splinter hemorrhage (*solid arrow*) and Janeway lesions (*open arrow*). These findings should stimulate a work-up for endocarditis. (Courtesy of Daniel L. Stulberg, MD.)

Echocardiography (Chapter 43) is the most useful test to analyze valvular and ventricular function. By use of Doppler flow methods, stenotic and regurgitant lesions can be quantified. Handheld ultrasonography performed by generalists can improve the assessment of left ventricular function, cardiomegaly, and pericardial effusion. Transesophageal echocardiography is the preferred method to evaluate possible aortic dissection and to identify clots in the cardiac chambers. Radionuclide studies (Chapter 44) can measure left ventricular function, assess myocardial ischemia, and determine whether ischemic myocardium is viable. CT can detect coronary calcium, which is a risk factor for symptomatic coronary disease (Chapter 44).[18]

Multislice CT scanning can diagnose coronary disease. In a randomized trial of emergency department patients at low to intermediate risk for a possible acute coronary syndrome, coronary CT angiography resulted in a higher rate of discharge from the emergency department (50% vs. 23%), a shorter length of stay (median, 18 vs. 24.8 hours), and a higher rate of detection of coronary disease (9% vs. 3.5%) without any change in the rate of serious adverse events. However, in a subsequent randomized trial of emergency department patients with symptoms suggestive of acute coronary syndromes but without ischemic ECG changes or an initially positive troponin test, incorporating coronary CT angiography into the triage strategy did not decrease overall costs of care.

Stress testing by exercise or pharmacologic stress is useful to precipitate myocardial ischemia that may be detected by ECG abnormalities, perfusion abnormalities on radionuclide studies, or transient wall motion abnormalities on echocardiography. These tests are often crucial for the diagnosis of possible myocardial ischemia (see Figs. 56-1, 56-2, and 56-3) and for understanding the prognosis in patients with known ischemic heart disease.

In symptomatic patients with suspected coronary disease, the strategies of initial coronary CT angiography and functional testing using exercise electrocardiography, nuclear stress testing, or stress echocardiography provide equivalent clinical outcomes over a median follow-up of 2 years,[A3] but CT angiography may be preferable when follow-up is extended to 5 years.[A4] In patients whose chest pain portends an intermediate risk for stable underlying coronary artery disease, CT coronary angiography is as good as invasive coronary angiography in terms of guiding therapy over at least 3.5 years.[A5] However, none of these tests are currently recommended in asymptomatic individuals, either routinely or prior to participation in sports or other physical activities.

Cardiac catheterization (Chapter 59) can measure precise gradients across stenotic cardiac valves, judge the severity of intracardiac shunts, and determine intracardiac pressures. Coronary angiography provides a definitive diagnosis of coronary disease and is a necessary prelude to coronary revascularization with a percutaneous coronary intervention or coronary artery bypass graft surgery (Chapter 59).

Continuous ambulatory ECG monitoring can help diagnose arrhythmias. A variety of newer technologies allow longer-term monitoring in patients with important but infrequently occurring symptoms (Chapter 49). Formal invasive electrophysiologic testing can be useful in the diagnosis of ventricular or supraventricular wide-complex tachycardia, and it is crucial for guiding a wide array of new invasive electrophysiologic therapies (Chapter 54).

APPROACH TO THERAPY

The history, physical examination, and laboratory evaluation should help the physician establish the cause of any cardiovascular problem; identify and quantify any anatomic abnormalities; determine the physiologic status of the valves, myocardium, and conduction system; determine functional capacity; estimate prognosis; and provide primary or secondary prevention. Improvements in diagnosis, therapy, and prevention have contributed to a 70% or so decline in age-adjusted cardiovascular death rates in the United States since the 1960s. Key preventive strategies that should be part of the approach to every patient, with or without heart disease, include dietary modification (Chapter 13), recognition and treatment of hypertension (Chapter 64) and hyperlipidemia (Chapter 190), cessation of cigarette smoking (Chapter 363), and adequate physical exercise (Chapter 14).

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For the General References and other additional features, please visit Elsevier eBooks+ at https://ebooks.health.elsevier.com.

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40 EPIDEMIOLOGY OF CARDIOVASCULAR DISEASE

DONALD M. LLOYD-JONES

Cardiovascular diseases remain the leading causes of death, disability, and medical costs in the world, and they are expected to remain so for the foreseeable future. Cardiovascular disease manifests in a number of different ways, including: congenital heart and vascular malformations (Chapter 55); coronary heart disease (Chapters 56, 57, 58, and 59); heart failure (Chapter 46); cardiomyopathies (Chapter 47); valvular heart disease (Chapter 60); dysrhythmias (Chapters 49, 50, 51, 52, and 53); pericardial diseases (Chapter 62); aortic (Chapter 63), peripheral (Chapter 65), and cerebrovascular diseases (Chapter 375); systemic hypertension (Chapter 64); vasculitides (Chapter 249); venous thromboembolic disease (Chapter 68); and pulmonary vascular hypertension (Chapter 69). Of these, coronary heart disease, stroke, and heart failure, which share many common underlying risk factors, have by far the largest impact on the population in terms of incidence, prevalence, quality of life, and medical costs.

BURDEN IN THE UNITED STATES

Cardiovascular diseases have been the leading cause of death in the United States in every year of the 20th and 21st centuries except for 1918, when the influenza epidemic surpassed them. Even during the severe acute respiratory disease coronavirus 2 (SARS-CoV-2) pandemic (Chapter 336), cardiovascular disease remained the leading cause of death. Cardiovascular diseases account for 1 in 3 deaths in the United States annually, or more than 850,000 deaths, including about 420,000 women and slightly more men. The overall age-adjusted annual rate of death due to cardiovascular disease in the United States is about 219 per 100,000 persons, with higher rates in men than in women and in Black than in White, Hispanic, or Asian Americans.[1] Because of secular trends in risk factors and the development of effective treatments over the last 50 years, cardiovascular disease mortality rates declined by approximately 70% from their peak in the 1960s, but rates have been constant since 2011.[2]

Cardiovascular diseases also are the leading cause of hospitalizations and medical costs in the United States. Each year about 5 million Americans are hospitalized for cardiovascular disease, over 1 million of which are due to coronary heart disease and approximately 1 million more each are due to heart failure and stroke. The United States currently spends approximately $360 billion annually on direct costs for cardiovascular diseases, and total costs are projected to exceed $800 billion annually by 2030.

In the United States, about 20.1 million adults (7.2%) have coronary heart disease, 45% of whom have had a myocardial infarction. Each year, Americans suffer over 1 million new and recurrent myocardial infarctions, with about 365,000 deaths due to coronary heart disease, a large percentage of which are sudden cardiac deaths. There are 7.6 million stroke survivors (2.7%) in the United States, with the proportion twice as high in Black than in White Americans, and 795,000 new or recurrent strokes occur every year. Stroke rates are especially high in the so-called "stroke belt" in the southeastern United States. At present, 6 million Americans (2.1%) have chronic heart failure, with prevalence 50% higher in men than women and in individuals who identify as Black. With aging, the risks for stroke and heart failure tend to increase at younger ages in women and Black Americans than in White men, whose coronary risk increases earlier.

GLOBAL BURDEN

Cardiovascular diseases, including coronary heart disease and stroke, became the leading cause of death and disability globally in the early 21st century (E-Fig. 40-1). About 80% of cardiovascular deaths and events now occur in low- and middle-income countries, and the onset of cardiovascular disease tends to be at an earlier age in these countries.[3] For example, about 50% of coronary deaths occur before age 70 years in India, whereas only 25% occur by that age in high-income countries.[4] Unfavorable global trends in eating patterns, high rates of smoking, and increasing burdens of obesity, diabetes, and hypertension are driving the burden of cardiovascular disease. Although stroke was the dominant cause of death and disability in East Asian countries for decades owing to high sodium intake and resulting hypertension, recent changes in diet, activity levels, and smoking have made coronary heart disease an equivalent or greater health burden in this area of the world.

RISK FACTORS FOR CARDIOVASCULAR DISEASE

ESTABLISHED RISK FACTORS

A number of causal factors have been established for cardiovascular disease based on their strength and consistency of associations, specificity, temporality, and biologic plausibility. Furthermore, these established risk factors explain the vast majority of risk for incident myocardial infarction. Longitudinal cohort studies demonstrate that 90% of individuals who suffer a myocardial infarction have at least one established clinical risk factor prior to their first event, and adverse levels of nine risk factors and behaviors collectively account for 90% or more of the risk for myocardial infarction in men and women, in older and younger individuals, and in all regions of the world. These nine risk factors and behaviors include smoking (Chapter 363), elevated apolipoprotein B/apolipoprotein A1 ratio (Chapter 190), hypertension (Chapter 64), diabetes (Chapter 210), abdominal obesity (Chapter 201), psychosocial factors, lower consumption of fruits and vegetables (Chapter 13), alcohol intake (Chapter 364), and physical inactivity (Chapter 14). Many of the established risk factors tend to cluster in a *metabolic syndrome*, which is characterized by abdominal adiposity, insulin resistance, hyperglycemia, elevated blood pressure, elevated triglyceride levels, and lower high-density lipoprotein (HDL)-cholesterol levels. This clustering of cardiovascular risk factors can lead to synergistic increases in the risk for events.

Age is the most powerful risk factor for the development of most cardiovascular diseases, especially stroke (Chapter 376), heart failure (Chapters 45 and 46), and atrial fibrillation (Chapter 52). Chronologic age integrates a person's aggregate exposure to multiple physiologic and environmental factors on the cardiovascular system. The incidence of cardiovascular disease at least doubles with each additional decade of age in adulthood until the oldest ages, when the heavy burden of competing causes of mortality (Chapter 22) limits further progression. Newer methods of assessing biologic age, as compared with chronologic age, may lead to improved assessment of cardiovascular risk.[5]

The impact of a person's *sex* on cardiovascular disease is important. Women tend to develop risk factors later in life than do men, and women's cardiovascular disease incidence rates lag men's by approximately 10 years. The precise contributions of sex hormones to these age trends are uncertain, but many women develop worsening risk factor levels, particularly with regard to lipids, blood pressure, weight, and insulin resistance, during and after the menopausal transition (Chapter 222). Pregnancy is a cardiovascular stress test, and adverse outcomes of pregnancy are markers of risk for future cardiometabolic disease.[6]

Large disparities in cardiovascular disease are noted by *self-identified race* or ethnicity, but the established causal risk factors have broadly similar effects in all racial and ethnic groups. Hypertension tends to be more prevalent in individuals of African ancestry, especially in environments with higher sodium intake, and to have a somewhat stronger association with cardiovascular events, especially heart failure and stroke. Compared with Whites, individuals of East Asian and South Asian descent have a greater risk for developing metabolic syndrome, insulin resistance, and diabetes at a lower overall body mass index. A substantial proportion of the differences in cardiovascular risks and outcomes observed across race and ethnic groups can be attributed to differences in social determinants of health (education, socioeconomic position, health care access; Chapter 4),[7] but racial differences still exist after considering these factors.[8]

Blood lipid levels (Chapter 190), including the total serum cholesterol level and its subfractions, particularly low-density lipoprotein (LDL) cholesterol, have significant, continuous, and graded associations with the risk of coronary heart disease. Cumulative exposure is more predictive than any single measurement, elevated levels earlier in life are associated with greater risk,[9] and earlier reduction in lipid levels will have greater absolute benefit.[10] By comparison, independent, direct associations of blood lipids with stroke and heart failure events are much weaker. Apolipoprotein B–containing particles comprise the subpopulation of circulating cholesterol-containing particles that represent the atherogenic lipoprotein fractions. These particles are considered to be the central actors in the initiation and promotion of atherogenesis on the basis of a substantial body of epidemiologic, clinical, and basic science evidence. Among U.S. adults aged 20 years and older, 38.1% (or about 94 million) have total cholesterol levels above the desirable range of less than 200 mg/dL, and 11.5% (28 million) have elevated levels at or over 240 mg/dL. Mean total cholesterol levels have been falling sharply in recent decades, because of changes in dietary composition but also because of more widespread use of lipid-lowering medications. In the 1970s, mean total cholesterol concentrations

ABSTRACT

Despite decades of progress in prevention and treatment, cardiovascular disease remains the leading cause of mortality, morbidity, and health care costs in high-income countries, and it has emerged as the leading cause in low- and middle-income countries. A number of modifiable, causal risk factors for cardiovascular disease have been identified, including blood lipid levels, blood pressure, tobacco, dysglycemia, excess body weight, adverse diet, and physical inactivity; collectively they account for the vast majority of excess risk in populations. Individuals who avoid the development of risk factors have very favorable long-term health outcomes and longevity, whereas it is difficult to restore low risk once risk factors have developed. The causal risk factors also tend to cluster and interact additively or synergistically to increase risk. Together, these factors are used to estimate short- and long-term risks for cardiovascular events in individuals and in populations in order to predict the burden of disease and scale the intensity of prevention efforts. Numerous novel blood-based risk markers have been proposed to refine risk assessment, but they have proven less useful than noninvasive imaging modalities (especially measurement of the coronary artery calcium score using computed tomographic imaging) that directly assess the presence and extent of subclinical atherosclerosis disease burden. The advent of genomic and systems biology approaches to studying health and disease in populations, as well as the availability of "big data" phenotypes from electronic health records, are revolutionizing our ability to perform cardiovascular epidemiology on a large scale and with greater precision.

KEYWORDS

cardiovascular disease
epidemiology
risk factors
risk prediction
coronary artery calcium
prevention

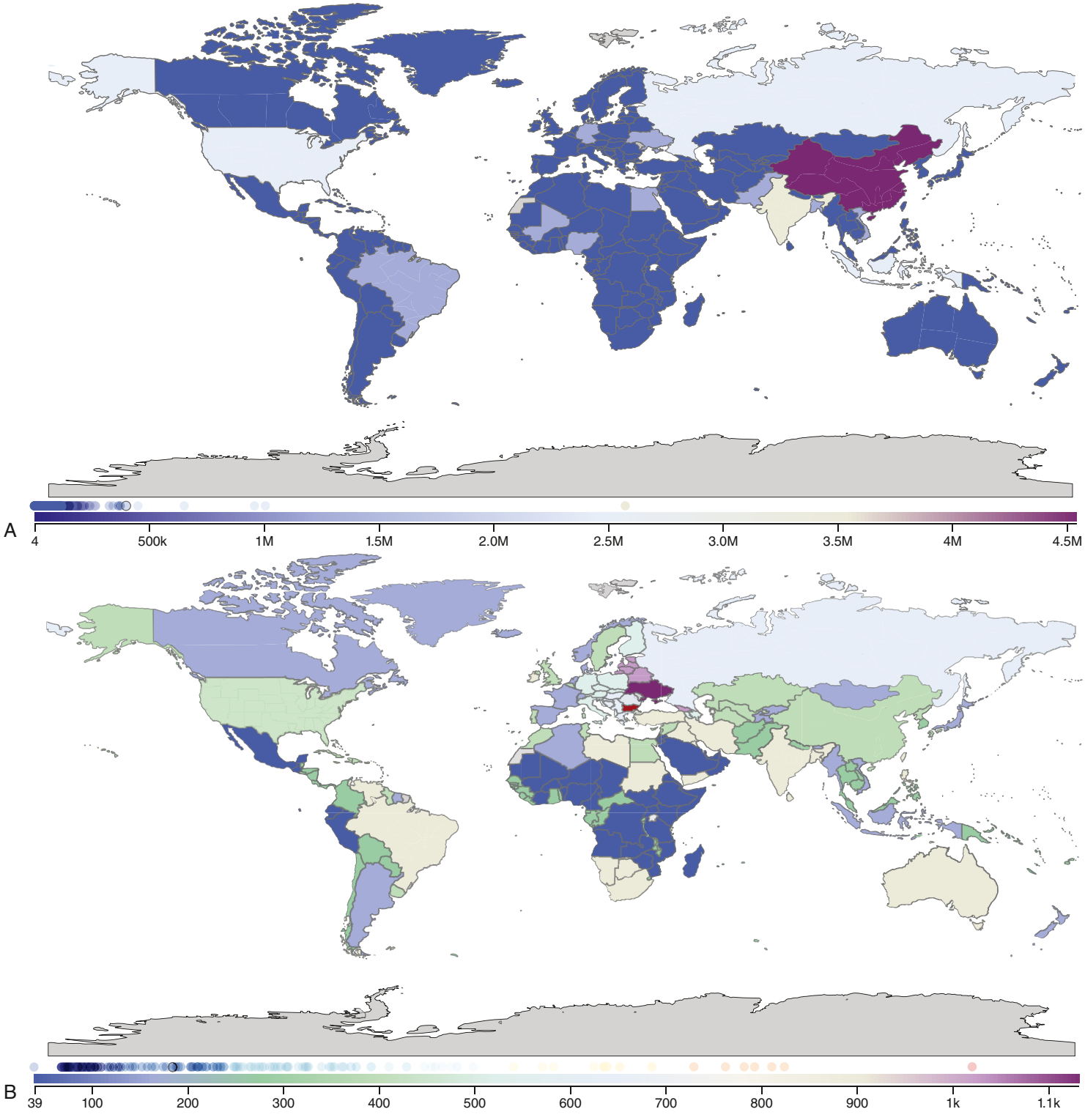

E-FIGURE 40-1. Global burden of cardiovascular disease deaths in 2019 in terms of total deaths (A) and death rates per 100,000 population (B). (Data and visualization from the Global Burden of Disease Study, https://vizhub.healthdata.org/gbd-compare/.)

were approximately 220 mg/dL, whereas currently they are just under 200 mg/dL. These improvements have been a major contributor to the decline in coronary death rates over the same time period. Randomized clinical trials have unequivocally established LDL cholesterol (and the particles that carry it) as a causal agent for coronary heart disease, and LDL cholesterol-lowering therapies (Chapter 190) are effective at reducing rates of both coronary heart disease and stroke significantly and substantially.[A1,11]

Blood pressure (Chapter 64) has a strong, continuous, and independent association with incident coronary heart disease, stroke, and heart failure events. In worldwide studies of nearly one million individuals, the risk at every age for all types of cardiovascular disease death doubled with each 20 mm Hg higher systolic blood pressure and each 10 mm Hg higher diastolic blood pressure, beginning at a blood pressure of 115/75 mm Hg. In 2017, U.S. blood pressure guidelines lowered the definition of hypertension to 130 mm Hg systolic or higher or 80 mm Hg diastolic or higher; under this definition nearly half of U.S. adults have hypertension, and its prevalence has been increasing owing to the obesity epidemic. In the United States, rates of treatment and control were gradually increasing prior to the SARS-CoV-2 pandemic, which caused a significant decline.[12] Hypertension has stronger relative associations with stroke and heart failure than with coronary heart disease, in part because of its effects on myocardial and cerebrovascular remodeling. The effective treatment of hypertension reduces the risk of stroke, heart failure, and coronary heart disease events. Current data suggest that a treatment goal of lower than 120 mm Hg systolic (with an average achieved systolic pressure of 120 to 124 mm Hg) reduces cardiovascular events and all-cause mortality compared with a goal of lower than 140 mm Hg systolic in patients without preexisting heart failure or diabetes.[13] For patients with diabetes, a goal of lower than 130 mm Hg is reasonable.[14]

Cigarette smoking (Chapter 363) is one of the strongest risk factors for cardiovascular disease events. After adjustment for other risk factors, smoking confers two- to three-fold higher risk for all manifestations of cardiovascular disease, especially coronary heart disease and peripheral arterial disease. Fortunately, consistent public health efforts have reduced the prevalence of smoking in the United States from about 45% in the 1960s to just under 15% currently. The prevalence of smoking remains higher in many European and Asian countries, and its continued increase in some parts of the world drives unfavorable trends in cardiovascular morbidity and mortality. A large body of evidence indicates that environmental exposure to tobacco smoke in nonsmokers ("second hand" or "passive" smoking) also increases risk for cardiovascular events substantially (Chapter 363) and contributes to the population burden of disease. Substantial data also support the benefits of smoking cessation for reducing the risks of a subsequent coronary event and death.[15,16]

Overweight and obesity have been increasing in the United States and worldwide. Prior to 1985, fewer than 10% of Americans were obese, defined as having a body mass index of 30 kg/m^2 or higher. Now, however, approximately 70% (170 million) of U.S. adults are overweight or obese, with 40% being obese (Chapter 201). Thirty-five percent (26 million) of U.S. children ages 2 to 19 years are overweight or obese (Chapter 201), with roughly half in each stratum. Major societal changes in the availability of food and in dietary content, coupled with reductions in physical activity, have produced this unprecedented epidemic. Although overweight and obesity themselves tend to be weak independent predictors of cardiovascular events in the short term, they are major drivers of elevated blood pressure, elevated blood glucose levels, and adverse lipid profiles that are themselves major contributors to the incidence of cardiovascular disease in the short and long term. The existence of an "obesity paradox," in which individuals diagnosed with cardiovascular disease who are overweight or obese appear to live longer than normal weight individuals, appears to represent earlier onset of cardiovascular disease owing to overweight, with shorter total longevity and more time spent with cardiovascular disease.[17]

Blood glucose (Chapter 210) and its surrogate marker for chronic levels, hemoglobin A_{1c}, have a continuous and independent association with cardiovascular events.[18] People with diabetes, whether diagnosed or undiagnosed, have two- to three-fold higher adjusted risk for cardiovascular events compared with persons without diabetes, and they also have substantially higher risks for developing chronic kidney disease (Chapter 116). Whereas diabetes was relatively uncommon before the 1980s, the obesity epidemic has led to a dramatic increase in the prevalence of type 2 diabetes and of impaired fasting glucose levels, termed *prediabetes*, with worsening of glycemic control in the United States over the past 20 or so years.[19] At present in the United States, 26 million people, representing 9.8% of all adults, have diagnosed diabetes, and another 9.4 million (about 3.7% of adults) have undiagnosed diabetes. Fully 92 million more adults, or about 38% of adults, currently have prediabetes. Diabetes disproportionately affects non-White racial and ethnic groups, such as American Indians, Black Americans, South Asians, East Asians, and Latinos, who appear to have greater probability of insulin resistance at lower body mass index, in much greater proportions than Whites. Unfortunately, tight control of glucose levels in persons with diabetes has not been associated consistently with significant reductions in risk for macrovascular cardiovascular disease (Chapter 210). However, treatment of type 2 diabetes with sodium-glucose cotransporter-2 inhibitors or glucagon-like peptide-1 receptor agonists can reduce the risk of cardiovascular events (Chapter 210).[A2,20]

Adverse diet (Chapter 13) is a major contributor to obesity, diabetes, hypertension, and dyslipidemia. Healthy eating patterns emphasize a lower caloric intake and focus on fruits and vegetables, healthy fats from nuts and olive oil, lean sources of protein such as fish, whole grains, a reduced sodium intake, and limiting the intake of processed foods, unhealthy fats, and simple sugars.[21] This eating pattern is typical of the Mediterranean diet (Fig. 13-1), which has been shown to be associated with lower cardiovascular disease incidence,[A3,A4] and the similar DASH (Dietary Approaches to Stop Hypertension) eating pattern (Table 13-4). The consumption of more sodium and less potassium is associated with a higher risk of cardiovascular disease,[22] and using a salt substitute (75% sodium chloride, 25% potassium chloride) in patients who have a history of stroke or who are over age 60 years and have hypertension can reduce cardiovascular events and all-cause death.[A5] By comparison, supplemental vitamins, minerals, and n-3 fatty acids, independent of eating pattern, have not been shown conclusively to reduce cardiovascular risk,[A6,A7] even in patients with diabetes or preexisting heart disease.[A8-A10]

Alcohol (Chapter 364) has a complex association with cardiovascular events. Moderate intake of one serving of alcohol per day is associated with a modestly lower risk for cardiovascular disease, but it is unlikely that this association is causal.[23] At higher levels of intake, however, risks for total mortality, hypertension, stroke, and heart failure clearly increase. Whereas heavy alcohol use and patterns of binge use are associated with heart failure and atrial fibrillation, alcohol's association with atherosclerotic cardiovascular disease is less clear.

Physical inactivity (Chapter 14) *and a sedentary lifestyle* are significant risk factors for cardiovascular disease.[24] Individuals who participate in no physical activity are at highest risk for events. The risk is significantly lower for people who participate in even minimal physical activity, and risks decrease further with greater activity levels, particularly to the extent they contribute to higher objective physical fitness. The biology and risks of sedentary time may be more than just the absence of physical activity, since sedentary lifestyle, as measured best by the hours of time spent in front of a television or computer screen, seems to have an adverse effect independent of time spent doing physical activity.

Family history is clearly an important cardiovascular risk factor, independent of other measurable risk factors. Genetic variants that influence cardiovascular risk factors over the lifespan, such as blood pressure and lipid levels, affect lifetime risk even more than would be estimated by adult epidemiologic or intervention studies. However, ideal levels of cardiovascular health do not appear to be genetically programmed. The heritability of ideal cardiovascular health is less than 20%, thereby suggesting strong environmental and behavioral influences on the development of cardiovascular disease.

NOVEL RISK MARKERS

Blood markers of inflammation and *target organ damage* such as C-reactive protein, high-sensitivity troponin, or natriuretic peptide levels have demonstrated significant associations with incident and recurrent cardiovascular events, independent of established risk factors. However, inflammatory markers have contributed very little additional utility for the identification of patients at risk for cardiovascular disease. Measures of myocardial damage in apparently healthy individuals appear to have more potential clinical utility.

Noninvasive cardiac testing and imaging have demonstrated ability to detect preclinical disease and guide appropriate preventive pharmacotherapeutic decisions for higher risk individuals, or avoidance of drug therapy in individuals who are thought to be at risk but do not have evidence of preclinical disease. For example, electrocardiographic evidence of left ventricular hypertrophy confers significant excess risk for coronary heart disease over and above the presence of hypertension and other risk factors. Higher levels of coronary calcification on computed tomographic (CT) imaging of the heart (Chapter 44) or greater carotid intima-media thickness measured by B-mode ultrasound of the carotid arteries portend a higher risk of future cardiovascular events. Because these imaging markers detect evidence of the actual underlying diseases of interest (i.e., left ventricular hypertrophy or atherosclerosis), rather than nonspecific

risk factors, they are more effective at identifying individuals at high risk for incident clinical events, such as heart failure, stroke, and myocardial infarction. Of the available modalities, CT screening for coronary artery calcification is the preferred and widely available means for detecting individuals at near-term risk. For example, asymptomatic individuals with coronary artery calcium scores of more than 100 Agatston units have relative hazards for a coronary event that are 7- to 10-fold higher than in individuals without any coronary calcification, even after adjustment for major established risk factors. Coronary calcium scoring is the most effective and reliable means for reclassifying risk after a quantitative risk assessment using established risk factors,[25] with the ability to more correctly classify lower-risk individuals who nonetheless will have a cardiovascular event as well as higher-risk individuals who will not.

Polygenic risk scores, which can quantify genetic variation across the entire genome, have been examined for their ability to predict risk above and beyond the traditional, routinely measured clinical risk factors. To date, such scores have demonstrated statistically significant but clinically modest ability to add value to cardiovascular risk stratification in middle-aged and older individuals.[26,27]

ASSESSMENT OF RISK FOR CARDIOVASCULAR DISEASE

Estimation of Short-Term Risk

Adverse levels of any single risk factor or risk marker are associated with elevated risk for incident cardiovascular events. However, combinations of adverse risk factors are additive and sometimes synergistic for increasing risk. To improve the prediction of cardiovascular events and provide quantitative risk assessment, a number of multivariable risk equations or scores, such as the Pooled Cohort Equations,[28] have been developed. The vast majority of risk scores available have focused on predicting 10-year absolute risk, and essentially all include age, sex, smoking status, cholesterol, and blood pressure, with some also including diabetes, family history, body mass index, socioeconomic status, or novel biomarkers. The end points of interest for diverse risk equations have varied widely, from the prediction of cardiovascular death alone to the prediction of fatal and nonfatal major coronary events, major atherosclerotic events (coronary disease and stroke), or a broader range of cardiovascular events (including heart failure, coronary revascularization, angina, or claudication). As an example, the 10-year risk for incident atherosclerotic cardiovascular disease can be predicted in 50-year-old men and women according to sex, race, and different levels of risk factors (E-Fig. 40-2), and the risks are dramatically higher with a greater risk factor burden.

Lifetime Risk Estimation

Despite the widespread use of 10-year risk estimates to guide prevention strategies, this approach has important limitations. For example, one consequence of the substantial weighting of age in 10-year risk equations is that younger men and women, even those with substantial risk factor burden, do not tend to have a high short-term risk. When treatment thresholds are applied to quantitative risk estimates for clinical guidelines, men younger than 50 years of age and women under 60 years of age will infrequently exceed those thresholds. Therefore, recent guidelines have considered longer risk horizons, such as 30 years or the remaining lifespan. The established risk factors are all associated with lifetime risks for cardiovascular disease, but the nature of the relationships sometimes differs from short-term associations because of competing risks. For example, smoking is a strong risk factor for near-term cardiovascular events but a weaker discriminator of lifetime risk for cardiovascular events because of the simultaneous and substantial risk for cancer death, which limits the lifetime risk for cardiovascular disease among smokers. As a result, lifetime risk estimates may enhance communication for individual patients, but how they should be used in decision making regarding the institution of preventive drug therapy in younger individuals is less certain.

PREVENTION OF CARDIOVASCULAR DISEASE

Because patients with prevalent cardiovascular disease are at the highest risk, preventive interventions such as lifestyle modifications and drug therapy to reduce risk are most effective and cost-effective when used as therapy for secondary prevention of recurrent events, or complications such as heart failure. Examples of intensive lifestyle modification and of proven therapies include cardiac rehabilitation, antiplatelet therapy, LDL cholesterol–lowering therapy, antihypertensive medications, mineralocorticoid receptor antagonists, and certain classes of diabetes medications, as well as implantable devices that may prevent complications such as fatal ventricular dysrhythmias (Chapter 54).

For primary prevention, asymptomatic individuals may be at risk because of a heritable family history of premature cardiovascular disease, one or more markedly elevated risk factors, or multiple modestly elevated risk factors. Aspirin has no net benefit over placebo in healthy elderly individuals, in whom it actually reduces disability-free survival and overall survival,[A11,A12,29] without significantly reducing the risk of cardiovascular disease.[A13] Even in patients with diabetes or patients at moderate risk of cardiovascular disease, any benefits for preventing future cardiovascular events are offset by aspirin's side effects.[A14-A16]

The current primary prevention paradigm is to match the intensity of prevention efforts to the absolute risk of the patient.[A17] Appropriate lifestyle interventions (e.g., smoking cessation, weight loss, dietary modification) are recommended for all individuals, whereas drug therapy is recommended only for individuals in whom the absolute benefits can be expected to outweigh any potential adverse drug effects and to be cost-effective in doing so. In underserved or resource-limited settings, polypill formulations containing a statin plus several blood pressure–lowering medications in one pill, with or without aspirin, have been effective in reducing lipid levels, blood pressure,[A18] and even major cardiovascular events[A19-A21] compared with placebo or usual care. Treatment that restores optimal risk factor levels, however, does not imply that the treated individual will now have the very low incidence rates observed in people who have maintained optimal risk factor levels throughout young adulthood and into middle age. As a result, a concept gaining in importance is *primordial prevention*, which is the prevention of the development of risk factors in the first place. Primordial prevention requires a focus on health behaviors that may prevent the development of dyslipidemia, diabetes, and hypertension, as well as population-level strategies that attempt to create an environment conducive to favorable health behaviors. Mobile applications may help with the self-management that is likely critical for such efforts.[29]

CARDIOVASCULAR HEALTH: A NEW PARADIGM

In addition to resuming declines in mortality rates from cardiovascular diseases and stroke in the United States, a newer goal is to promote cardiovascular health in individuals and the population, monitor it over time, and improve it by concerted action. Central to the concept of cardiovascular health is the observation that optimal levels of seven health behaviors and health factors (Table 40-1) are associated with ideal cardiovascular health. Although about 40% of American adults believe they are in ideal cardiovascular health, fewer than 1% have all seven metrics at ideal levels, principally because of a poor-quality diet. Persons who maintain high levels of cardiovascular health from young age to middle age have extremely favorable outcomes from middle to older ages,[30] including: a markedly increased longevity; a better quality of life; a substantially lower incidence of fatal and nonfatal cardiovascular disease events; a lower incidence of other chronic diseases of aging, including cancer, dementia, and venous thromboembolism; a lower burden of subclinical atherosclerosis (e.g., carotid intima-media thickness, coronary artery calcification); higher levels of cognitive function in middle and older ages; and reduced medical care costs. These outcomes are observed in all segments of the population, as well as across all ages and both sexes.

People who pursue healthy lifestyles from young adulthood to middle age are far more likely to preserve ideal cardiovascular health than those who pursue none: 60% of the former group compared with only 3% of the latter group maintained ideal cardiovascular health factors into middle age. Cardiovascular health promotion thus represents a major paradigm shift and opportunity in public health efforts. If even 50% of U.S. adults could preserve ideal cardiovascular health into mid-life, an estimated 900,000 events would be prevented annually.[31]

FUTURE OF CARDIOVASCULAR EPIDEMIOLOGY

Decades of success in observational epidemiology research continue to provide novel insights into trends and risk markers for cardiovascular disease, as well as the influence of in utero and early life exposures on the life course of cardiovascular diseases. New techniques to characterize environmental and behavioral exposures, physiology, health status, and precursors of disease include epigenetics, proteomics, metabolomics, and high-resolution imaging. With these tools, epidemiologic research has advanced to improve the characterization of the life course of cardiovascular diseases in living individuals and populations and to understand the complex interplay of genes and environment. For example, studies of the genotypes of individuals at the extremes of the distribution of LDL cholesterol levels led to the discovery of polymorphisms in the proprotein convertase subtilisin/kexin type 9 (*PCSK9*) gene. Although such polymorphisms are uncommon, specific missense and nonsense mutations in White and Black men and women are associated with significantly lower lifelong levels of LDL cholesterol and substantially lower lifetime risks for coronary heart disease. *PCSK9* has since become an established therapeutic target for reducing atherosclerotic cardiovascular risk. Other genes discovered

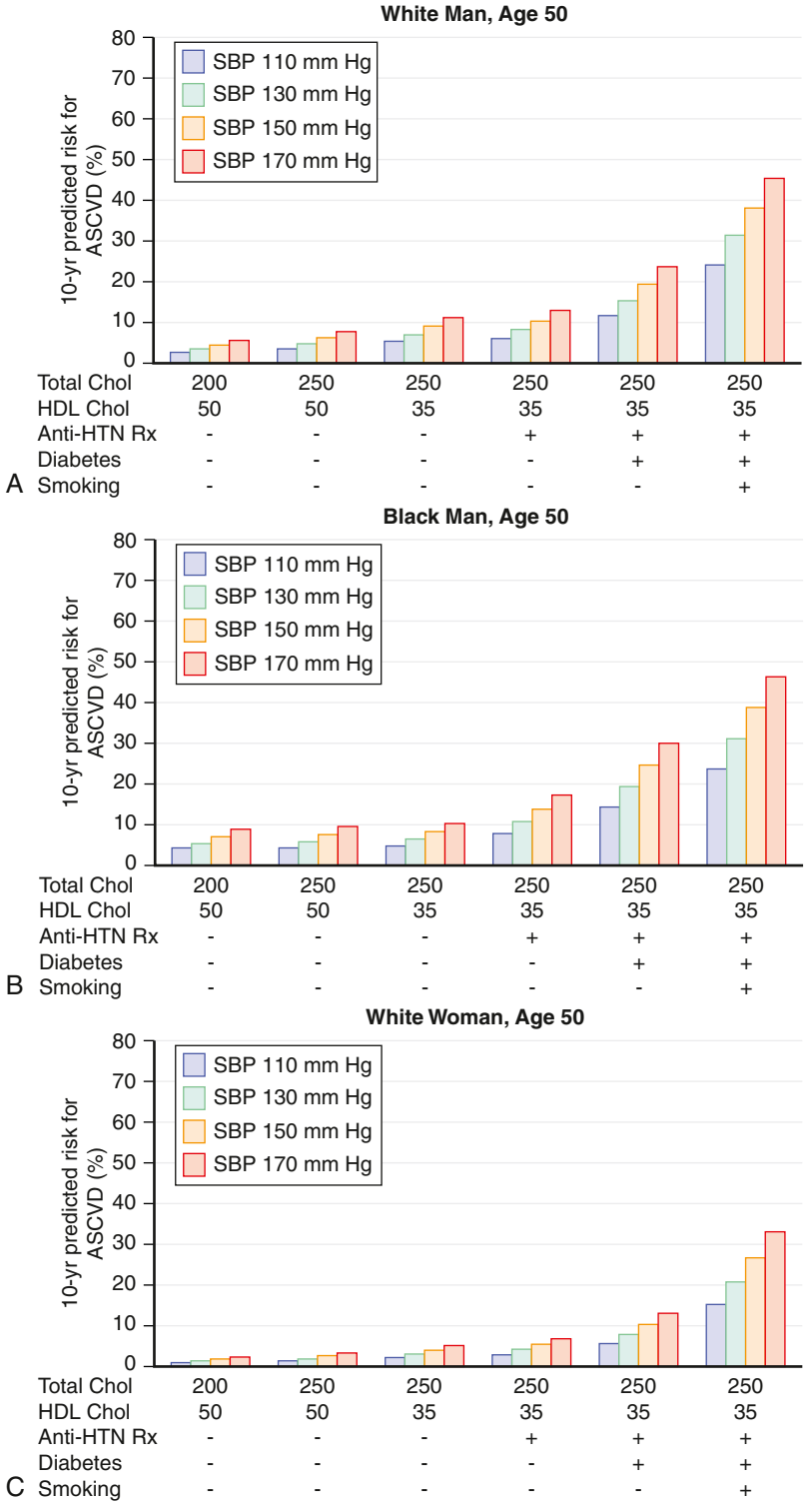

E-FIGURE 40-2. **Predicted 10-year risks for atherosclerotic cardiovascular disease, including fatal coronary heart disease, nonfatal myocardial infarction, and fatal or nonfatal stroke, as a function of selected risk factor levels in a 50-year-old White man (A), Black man (B), White woman (C) or Black woman (D).** (Predicted risks are derived from the Pooled Cohort Equations used in Arnett DK, Blumenthal RS, Albert MA, et al. 2019 ACC/AHA Guideline on the Primary Prevention of Cardiovascular Disease. *Circulation*. 2019;140:e596-e646.)

Continued

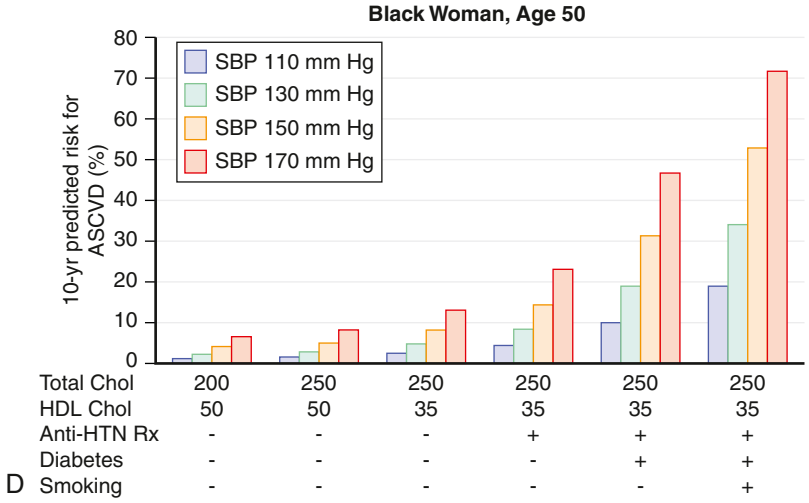

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E-FIGURE 40-2. Cont'd

TABLE 40-1 DEFINITIONS OF POOR, INTERMEDIATE, AND IDEAL CARDIOVASCULAR HEALTH FOR EACH OF SEVEN METRICS IN ADULTS AND CHILDREN

METRIC	POOR	INTERMEDIATE	IDEAL
CURRENT SMOKING			
Adults	Yes	Former, ≤12 mo	Never or quit >12 mo
Children	Tried in last 30 days	—	Never tried; never smoked whole cigarette
BODY MASS INDEX			
Adults	30 kg/m^2	25-29.9 kg/m^2	<25 kg/m^2
Children	>95th percentile	85th-95th percentile	<85th percentile
PHYSICAL ACTIVITY			
Adults	None	1-149 min moderate or 1-74 min vigorous activity per week	≥150 min moderate or ≥75 min vigorous activity per week
Children	None	1-59 mins moderate or vigorous activity daily	≥60 mins moderate or vigorous activity daily
HEALTHY DIET SCORE*			
Adults	Meets 0-1 components	Meets 2-3 components	Meets 4-5 components
Children	Meets 0-1 components	Meets 2-3 components	Meets 4-5 components
TOTAL CHOLESTEROL			
Adults	≥240 mg/dL	200-239 mg/dL or treated to goal	<200 mg/dL untreated
Children	≥200 mg/dL	170-199 mg/dL	<170 mg/dL untreated
BLOOD PRESSURE			
Adults	SBP ≥140 mm Hg or DBP ≥90 mm Hg	SBP 120-139 mmHg or DBP 80-89 mm Hg or treated to goal	<120/<80 untreated
Children	>95th percentile	90th-95th percentile or SBP ≥120 mm Hg or DBP ≥80 mm Hg	<90th percentile untreated
FASTING GLUCOSE			
Adults	≥126 mg/dL	100-125 mg/dL or treated to goal	<100 mg/dL untreated
Children	≥126 mg/dL	100-125 mg/dL or treated to goal	<100 mg/dL untreated

*Healthy diet score consists of five components, including low sodium intake, low sugar-sweetened beverage consumption, and higher consumption of fruits/vegetables, fish, and whole grains.
DBP = diastolic blood pressure; SBP = systolic blood pressure.
Adapted from Coorey GM, Neubeck L, Mulley J, et al. Effectiveness, acceptability and usefulness of mobile applications for cardiovascular disease self-management: systematic review with meta-synthesis of quantitative and qualitative data. *Eur J Prev Cardiol*. 2018;25:505-521.

through genetic epidemiology investigations, such as the angiopoietin-like 3 gene (*ANGPTL3*), are also rapidly becoming therapeutic targets.[A22]

A second emerging focus in cardiovascular epidemiologic research has been the study of effects of interventions in populations through public health and social policies. For example, studies have demonstrated marked reductions in hospitalizations for acute myocardial infarction occurring rapidly after the initiation of indoor smoking bans in diverse settings. Modeling studies have synthesized data from numerous epidemiologic sources to show that approximately 50 to 75% of the reductions in coronary death rates in Western countries may be attributable to population changes in risk factor levels, despite being offset by a recent worsening in obesity and diabetes prevalence, with the remainder likely attributable to advances in medical and surgical therapies. The widespread availability of electronic health records and wearable device technologies offer substantial promise for future cardiovascular epidemiology studies in ever-larger and well-defined segments of the population.

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For the General References and other additional features, please visit Elsevier eBooks+ at https://ebooks.health.elsevier.com.

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41 CARDIAC AND CIRCULATORY FUNCTION

ANDREW R. MARKS

The heart has the daunting task of pumping sufficient amounts of blood to meet both its own metabolic demands and those of the other organs. Unique among all the organs, the heart's failure to perform its task for even a few minutes causes death. The heart continuously fulfills this physiologic role with a variety of electrical, contractile, and structural functions that control the flow of blood to the organs.

STRUCTURE OF THE HEART

CARDIAC DEVELOPMENT

In humans, the formation of a linear heart tube from the primary cardiac crescent occurs between days 21 and 23 of gestation. Looping of the heart tube and trabecular formation of the ventricle occur at 26 days of gestation (E-Fig. 41-1). At 6 weeks, the embryonic interventricular communication closes, followed by thickening and remodeling of the ventricular walls in the first trimester. By the end of week 7, heart development is essentially finished, although the heart continues to enlarge throughout gestation.

ELECTRICAL CELLS

The heart is a muscular pump controlled by regular electrical discharges from specialized muscle cells in the conduction system (Chapter 48). The molecular basis for the electrical activity of the heart is the activation of specific ion-conducting channels (Fig. 41-1). Coordinated activation and inactivation of cardiac ion channels regulate the membrane potential of the cardiac cells, thereby resulting in a rapid sequence of depolarization followed by repolarization. This electrical activity, which is manifested on the body surface as the electrocardiogram (ECG), is known as the action potential, and it is responsible for activating the contraction of the cardiac muscle. At a typical heart rate of 70 beats per minute, the heart beats about 100,000 times per day, or 37 million beats a year, corresponding to 3 billion beats during a lifespan of 80 years. Failure to propagate the signal throughout the heart (e.g., heart block) or abnormal rhythms (arrhythmias) that are either too slow (bradycardia) or too fast (tachycardia) can result in death (Chapter 49). Studies indicate that cardiac arrhythmias may be triggered by leak of calcium inside the cardiomyocytes, thereby suggesting a possible novel therapeutic target for a new generation of antiarrhythmic agents.

ION CHANNELS

Sodium, potassium, and calcium channels determine the electrical activity of the heart by opening and closing in a highly choreographed pattern that determines the action potential of the heart. The electrical regulation of the heart, which is reflected in the relative concentrations of ions inside and outside the heart muscle cells, determines the five phases of the action potential (Chapter 48). The action potential is initiated when the opening of sodium channels results in a rapid influx of sodium (phase 0) down its concentration gradient (≈145 mmol outside the heart muscle cell, ≈10 mmol inside). After a brief early repolarization due to activation of potassium channels (phase 1), the rapid sodium influx depolarizes the cell, thereby activating calcium channels that allow calcium influx (phase 2) down its concentration gradient (≈3 mmol outside, ≈100 nmol inside). This calcium influx triggers excitation-contraction coupling that results in pumping by the heart. Potassium channels then open and cause repolarization (phase 3) as potassium fluxes out of the cell down its concentration gradient (≈4 mmol outside, ≈135 mmol inside). The membrane potential returns to the resting level of about −90 mV (phase 4). Genetic mutations in the genes encoding ion channels have been linked to inherited forms of ventricular and atrial arrhythmias (Chapters 52 and 53).

CONDUCTION SYSTEM

Specialized pacemaker cells in the sinoatrial node (Fig. 41-2) have slightly higher (less negative) resting potentials and gradually depolarize during phase 5 owing to the activity of the potassium and calcium channels and the hyperpolarization-activated cyclic nucleotide–gated channels that are responsible for a small inward (depolarizing) current. In the normal heart, pacemaker cells are the first cells to depolarize, and they trigger the subsequent depolarization of the cells in specialized conducting fibers that propagate the electrical signal throughout the heart muscle in a highly regular and integrated fashion. Electrical activation (depolarization) spreading through the atria to the atrioventricular (AV) node is reflected as the P wave on the ECG (Chapter 42). The slowing of conduction in the AV node accounts for the PR interval on the ECG. After passing through the AV node, the depolarizing signal enters the bundle of His,

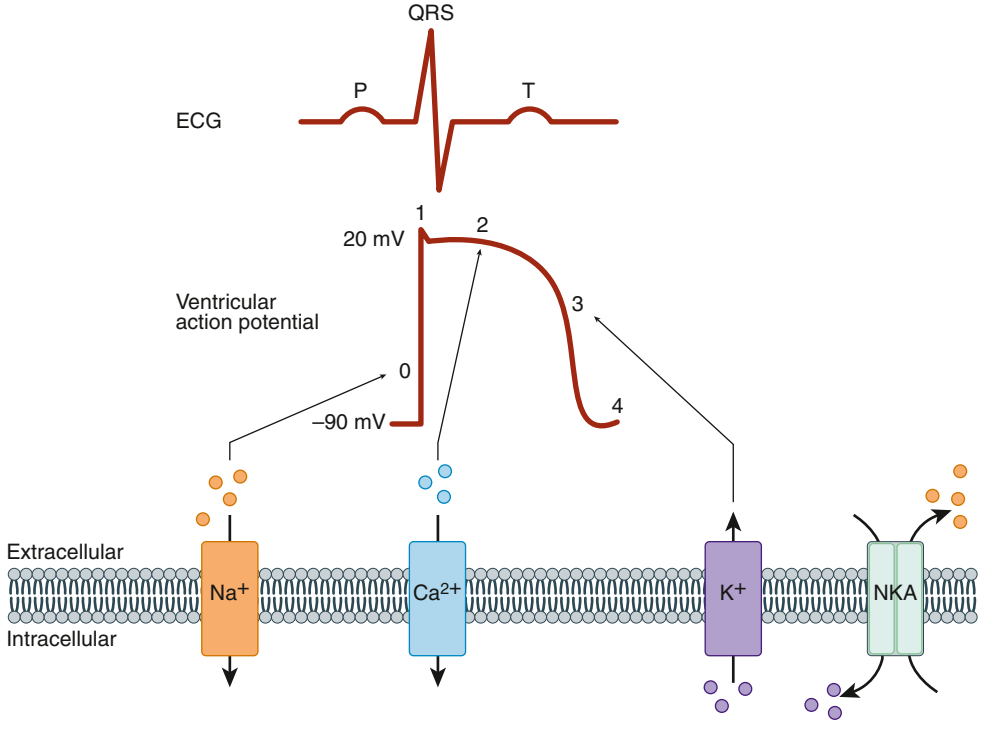

FIGURE 41-1. Cardiac action potential and ion channels. Myocardial contraction begins when sodium channels open and positively charged sodium ions flow into the cell and cause membrane depolarization (phase 0). During phases 1, 2, and 3, calcium ions flow into the cell through L-type calcium channels, while potassium flows out of the cell through voltage-gated potassium channels. These three phases correspond to myocardial contraction, which corresponds to the QRS complex on the surface electrocardiogram (ECG). The sodium-potassium adenosine triphosphatase (NKA) helps return the system to its resting state.

ABSTRACT

The heart is a large muscle with four chambers and a complex electrical system that activates contraction to supply blood flow to all organs. A reduction in heart-driven blood flow quickly results in organ failure and ultimately in death. Over the past two centuries, detailed understanding of heart development and function has been accumulated. Moreover, we also have learned a great deal about the circulatory system, how it develops, and how it is regulated. However, there is much we do not understand. For example, occlusion of coronary arteries that supply blood to the heart muscle by atherosclerosis cause heart muscle death. Loss of heart muscle leads to heart failure, but few effective drugs are available to treat this leading cause of death. Similarly, the electrical system of the heart, controlled by ion channels, results in fatal heart rhythms when ion channel function is defective. Understanding of this system also remains limited, such that safe and effective drug treatments for arrhythmias are largely lacking. Nevertheless, the heart performs an amazing function, beating steadily, for the most part, throughout life.

KEYWORDS

cardiac physiology
heart muscle
ion channels
contraction
coronary artery disease

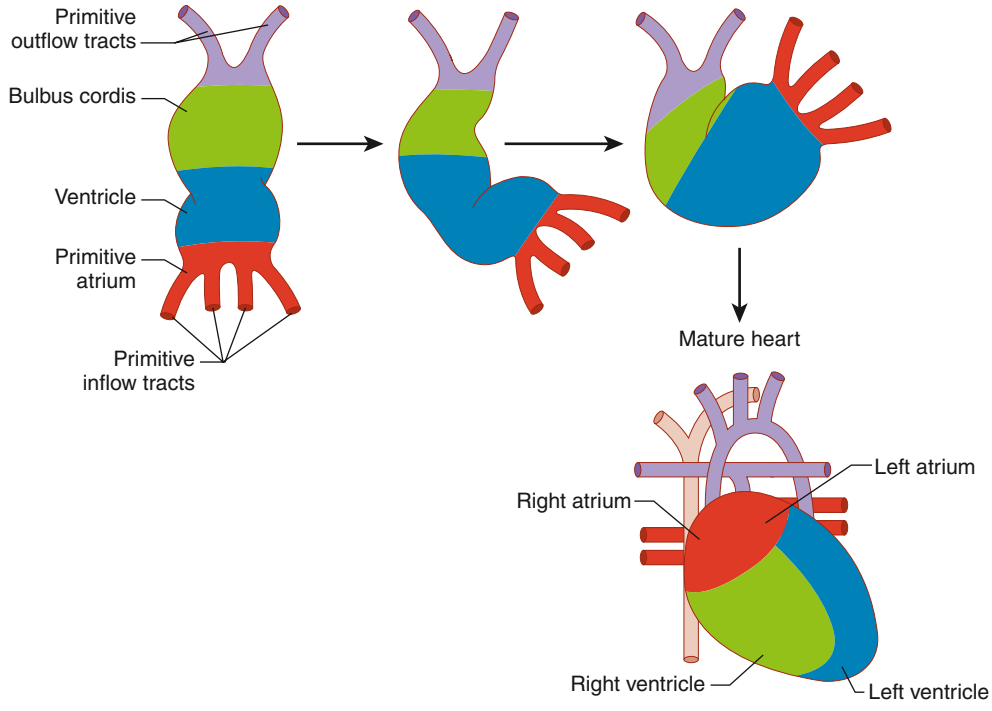

E-FIGURE 41-1. Folding of the heart tube during development. The primitive outflow tracts develop into the pulmonary artery and aorta. The left and right atria, along with the pulmonary veins and the superior and inferior vena cava, arise from the primitive inflow tracts. The area covered by the bulbus cordis and ventricle contributes to the development of the left and right ventricles.

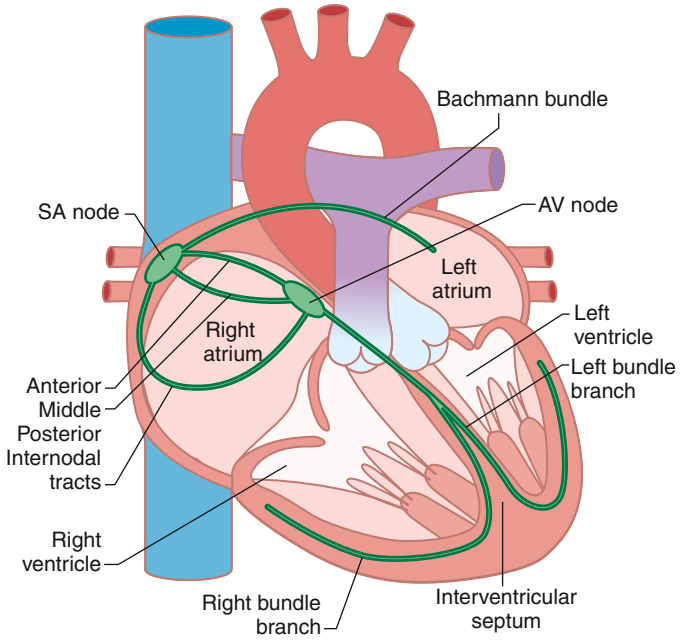

FIGURE 41-2. Cardiac anatomy. Cardiac anatomy comprises electrical and structural components. The electrical impulse that directs cardiac contraction originates in the sinoatrial (SA) node and is rapidly conducted through the atria by specialized conduction tracts. The impulses merge at the atrioventricular (AV) node, where, after a brief pause, they are rapidly conducted into the ventricles through the bundle of His, which is composed of specialized Purkinje cells. Blood moves from the atria into the ventricles through the tricuspid and mitral valves, respectively, during diastole. During systole, blood from the ventricles is pumped into the pulmonary artery and aorta through the pulmonic and aortic valves, respectively.

where conduction is rapid. The bundle of His divides into the right and left bundle branches, which conduct the depolarizing signals into the ventricles and account for the QRS complex on the ECG. Repolarization is represented by the ST segment and the T and U waves of the ECG.

CONTRACTILE CELLS

Heart muscle is composed of billions of individual cells known as cardiomyocytes, which contain an elaborate machinery required for coordinated contraction that pumps blood. Each cardiomyocyte is connected to its neighbors through specialized junctions that enable them to work as a single contractile unit.

The cardiomyocytes are filled with specialized contractile proteins arranged in highly regulated units, called sarcomeres, that give the muscles characteristic patterns known as striations (E-Fig. 41-2). Hence, like skeletal muscle, cardiac muscle is termed striated, as opposed to smooth muscles that form the vasculature and other organs such as the bladder, uterus, and stomach. Cardiomyocytes are also loaded with mitochondria that provide the energy (adenosine triphosphate [ATP]) required to fuel the heart's lifelong contractions (systole) and relaxations (diastole).

ULTRASTRUCTURE

The basic unit of the contractile system is the sarcomere, which is defined anatomically as the distance between two Z lines that anchor thin filaments composed of actin, tropomyosin, and troponin. Thin filaments slide past thick filaments (composed of myosin and titin) in a calcium-dependent manner to shorten the sarcomere length. Mutations in the genes encoding contractile proteins have been linked to dilated and hypertrophic cardiomyopathies (Chapter 47).[1,2] The contractile proteins are surrounded by a calcium-filled membrane called the sarcoplasmic reticulum. The sarcoplasmic reticulum forms specialized associations with the transverse tubules, which are invaginations of the plasma membrane and contain voltage-gated calcium channels. When the muscle is activated by depolarization of its membrane, this electrical signal travels deep into the muscle through the transverse tubules. Inside the muscle, the electrical depolarizing signal activates the voltage-gated channels, which open to allow a small amount of calcium to enter the muscle cells. This influx of calcium in turn activates the type 2 ryanodine receptor (RyR2), calcium-release channels on the sarcoplasmic reticulum. The RyR2 channels open and release enough calcium from the sarcoplasmic reticulum to raise the calcium concentration in the myoplasm about 10-fold. As a result, calcium binds to troponin C in the thin filaments and causes a conformational change that enables cross-bridging between actin and myosin, thereby leading to sliding of the filaments, shortening of the sarcomere, and muscle contraction. Hydrolysis of ATP provides the energy required for the generation of force by the actin-myosin interaction. The conversion of electrical energy (depolarization of the cell membrane) to mechanical energy is known as excitation-contraction coupling. Relaxation of the heart muscle occurs when calcium is pumped back into the sarcoplasmic reticulum through the sarcoendoplasmic reticulum ATPase.

Signals That Regulate Contraction

Contractile force can be enhanced during stress by activation of the β-adrenergic pathway, which increases both the amount of calcium released and the rate of calcium uptake in the sarcoplasmic reticulum (E-Fig. 41-3). β-Agonists (e.g., epinephrine or norepinephrine) bind to β-adrenergic receptors to activate adenylyl cyclase, which generates cyclic adenosine monophosphate and activates protein kinase A. Protein kinase A phosphorylates phospholamban, the voltage-gated calcium channel, the ryanodine receptor/calcium release channel, and sarcomeric regulatory proteins, thereby resulting in increased release of calcium from the sarcoplasmic reticulum and enhanced contractility of the heart.

Nonmuscle Cells

Although the heart is a muscular pump, 60 to 70% of its cells are cardiac fibroblasts, not muscle cells. These fibroblasts provide critical components of the extracellular matrix that determine the structure of the heart. Collagen, which is produced by the cardiac fibroblasts, is a major component of the extracellular matrix, where it forms a network that surrounds the cardiomyocytes and creates tissue that is able to withstand the stress of constant pumping. In certain pathologic conditions, including hypertension, myocardial infarction, and heart failure, the cardiac fibroblasts respond to stress by generating excess extracellular matrix, resulting in fibrosis, which can impair cardiac function.[3] Indeed, a number of commonly used therapies for heart disease, including lipid lowering with statins or fibrates and antihypertensive treatments with angiotensin-converting enzyme inhibitors, β-blockers, and angiotensin receptor blockers, exert part of their beneficial effects on cardiac fibroblasts by reducing fibrosis, thereby resulting in favorable "reverse" remodeling of the heart. Resident fibroblast lineages mediate pressure overload–induced cardiac fibrosis.

ANATOMY OF THE HEART

The primary pumping chamber of the heart is the thick-walled left ventricle, which is composed of billions of cardiomyocytes connected end to end through gap junctions. The right ventricle is a thinner-walled chamber, divided from the left ventricle by the *interventricular septum*. Above the ventricles are the right and left atria, which are thin-walled chambers that receive low-pressure venous blood; they are separated from the ventricles by the *tricuspid valve* on the right side and the *mitral valve* on the left side. These valves are attached to *papillary muscles* that emerge from the ventricular walls through *chordae tendineae*. The pressure gradient between the ventricles and the atria opens the AV valves. The papillary muscles help establish the positions of the valve leaflets and prevent regurgitant flow during contraction. The *aortic and pulmonary valves* separate the left and right ventricles from their arterial connections and enable blood flow out of the ventricles.

CORONARY BLOOD FLOW

The coronary arteries receive blood from the aorta, directly above the aortic valve, and travel through the epicardium that surrounds the heart to supply blood to the heart muscle (see Fig. 59-1 in Chapter 59). The diastolic blood pressure in the ascending aorta just above the aortic valve determines most of the flow of blood into the normal (nonstenosed) coronary arteries while the heart is relaxed. During systole, coronary flow is determined by the left ventricular intracavitary pressure, which equals the pressure within the inner myocardial wall, where coronary arteries are compressed during systole. Coronary blood flows to the epicardium during both systole and diastole but flows to the endocardium predominantly during diastole.

METABOLIC REGULATION OF THE CARDIOVASCULAR SYSTEM

Cardiac muscle requires constant coronary perfusion to supply oxygen and other metabolites. Increased energy consumption due to enhanced contractility necessitated by increased pressures or higher heart rates (e.g., during exercise) can be met only by increased coronary blood flow. Signals that augment coronary blood flow (by up to six-fold) include nitric oxide, adenosine, bradykinins, prostaglandins, and carbon dioxide. The breakdown of ATP is the

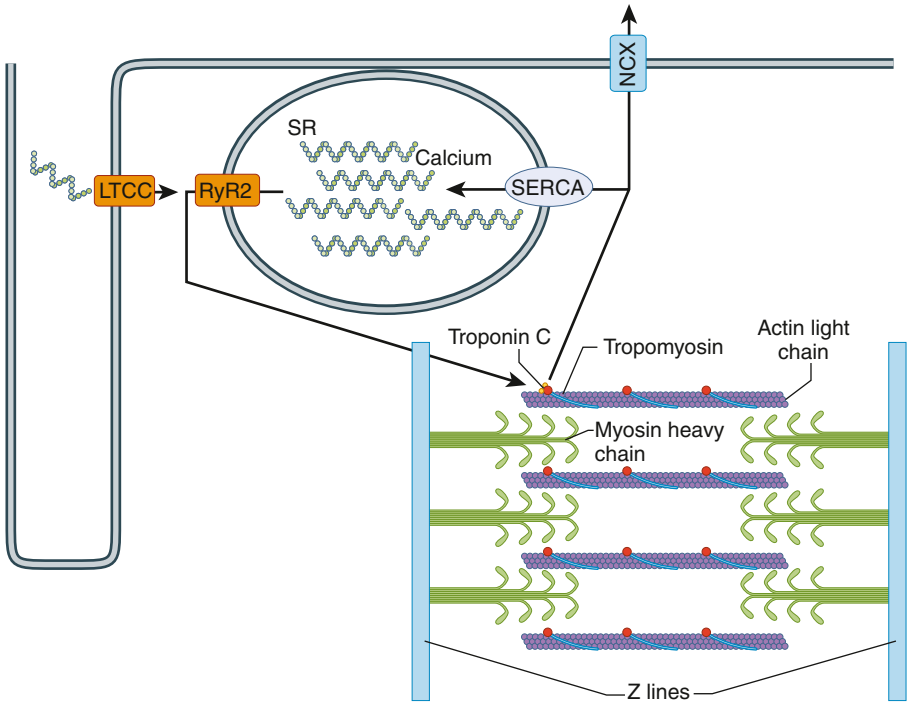

E-FIGURE 41-2. Sarcomere and excitation-contraction coupling. Depolarization of the cell membrane leads to calcium influx through L-type calcium channels (LTCC), which activate ryanodine receptors (RyR2) to release the large calcium stores from the sarcoplasmic reticulum (SR). Calcium binds to troponin C and induces a conformational change in tropomyosin, which enables myosin heads to interact with actin filaments and to cause contraction. During relaxation, calcium is pumped back into the sarcoplasmic reticulum through the sarcoendoplasmic reticulum calcium ATPase (SERCA) and out of the cell through the sodium-calcium exchanger (NCX).

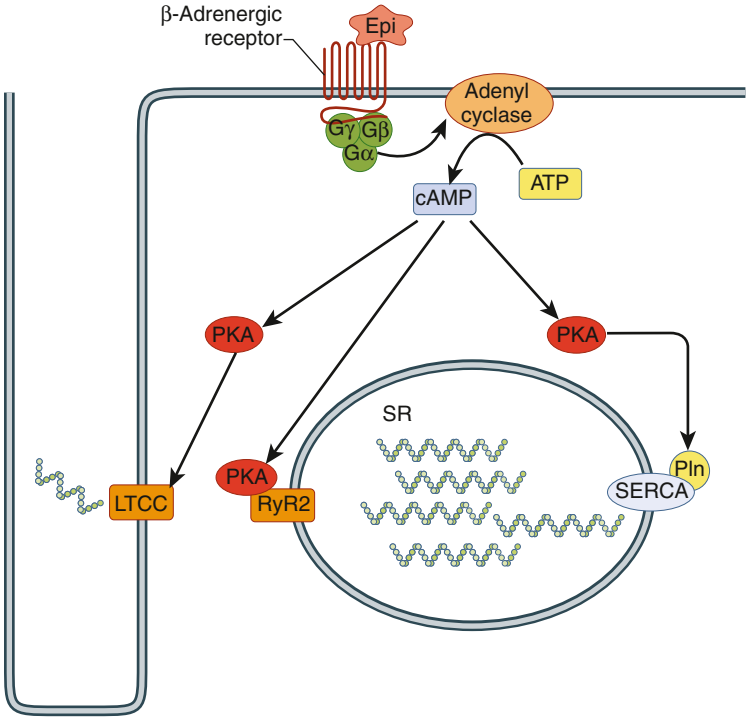

E-FIGURE 41-3. Cardiomyocyte signaling. Binding of catecholamines (epinephrine, norepinephrine) to β-adrenergic receptor, a G-coupled protein receptor, leads to activation of adenyl cyclase, which converts adenosine triphosphate (ATP) to cyclic adenosine monophosphate (cAMP). cAMP activates protein kinase A (PKA), which phosphorylates multiple calcium-handling proteins, including L-type calcium channels (LTCC), ryanodine receptors (RyR2), and phospholamban (Pln), leading to a general increase in their activity and greater contractility. Epi = epinephrine; SERCA = sarcoendoplasmic reticulum calcium ATPase; SR = sarcoplasmic reticulum.

source of adenosine, whereas nitric oxide is produced by the action of nitric oxide synthases that metabolize the amino acid L-arginine. Autoregulatory mechanisms, including constriction in response to increased luminal pressures and dilation in response to reduced pressure, also play a role in determining coronary artery blood flow. Other metabolic factors that cause vasoconstriction include endothelin peptides, serotonin, 5-hydroxytryptamine, thromboxane, angiotensin II, and β_1-adrenergic stimulation.

Sympathetic and parasympathetic pathways of the autonomic nervous system and the renin-angiotensin system exert potent regulatory effects on cardiovascular function. The sympathetic nervous system plays the key role in the response to stress (e.g., the fight-or-flight response) by increasing heart rate and myocardial contractility and decreasing vascular tone. Regulation of cardiovascular function by the sympathetic nervous system is mediated by norepinephrine that is released at the nerve endings and by epinephrine from the adrenal gland. β-Adrenergic signaling is mediated by epinephrine, which increases the heart rate and vasodilates the central arterial bed, thereby resulting in reduced afterload, which in turn helps augment cardiac output.

The sinoatrial and AV nodes are regulated by parasympathetic innervation that slows the pacemaker's rate of firing and conduction through the AV node by the release of acetylcholine. Vasoconstriction of the venous system is mediated by the sympathetic nervous system, which limits fluid and blood loss after trauma.

The renin-angiotensin system also regulates blood pressure, peripheral vasoconstriction, and contractility in coordination with the sympathetic nervous system. Both the sympathetic nervous system and the renin-angiotensin system are chronically activated in heart failure (Chapter 45), in which the resulting maladaptive remodeling of the cardiovascular system promotes the progression of heart failure. Decreased perfusion to the kidney, decreased delivery of sodium to the macula densa, or increased sympathetic activity results in the release of the hormone renin from the macula densa cells within the juxtaglomerular apparatus of the kidney. Renin results in the production of angiotensin II, a potent constrictor of peripheral and coronary arteries. In turn, angiotensin II causes the release of the sodium-retaining hormone aldosterone from the adrenal gland (Chapter 208). Together, these signals result in sodium retention and increased arterial blood pressure.

PHYSIOLOGY OF THE HEART AND CIRCULATORY CONTROL

CARDIAC ENERGETICS

The major immediate source of energy in the heart is the oxidation of fatty acids and glucose. When oxygen supply is limited, glucose metabolism is favored because it generates more ATP per oxygen consumed. The heart has virtually no ability to conduct anaerobic metabolism (i.e., glycolysis) and therefore is dependent on oxygen for its function. For example, heart function deteriorates immediately under conditions of hypoxia, ischemia, and carbon monoxide poisoning.

Basal metabolism, total mechanical work performed by the heart, contractility, and heart rate determine the oxygen and energy consumption of the heart. During excitation-contraction coupling, two key steps require energy consumption (ATP hydrolysis): release of the myosin head–actin interaction and reuptake of calcium into the sarcoplasmic reticulum.

The mechanical work of the heart is determined by the total *pressure-volume area*, which is related to the number of actin-myosin cross-bridges formed during the contraction. It is the sum of the external work performed by the heart in pumping blood from the ventricle to the aorta (represented by the area inside the pressure-volume loop) plus energy stored in the myocardium at the end of contraction. Enhanced contractility requires increased oxygen consumption because an increased amount of calcium released from the sarcoplasmic reticulum requires increased ATP and oxygen consumption to pump the released calcium back into the sarcoplasmic reticulum through the sarcoplasmic reticular ATPase. On the basis of these principles, increasing the heart rate requires increased oxygen consumption. If the heart rate increases from 70 to 140 beats per minute during exercise or stress, oxygen consumption increases almost two-fold above the basal value.

CONTRACTILITY AND RELAXATION

The Cardiac Cycle

In resting humans, the heart beats approximately once per second. With each beat, the heart cycles through a series of four hemodynamic events represented by changes in pressures and volumes (E-Fig. 41-4) as well as electrical activity as represented by the ECG. When the heart muscle is relaxed at end diastole, the ventricular pressure is at its resting level (*end-diastolic pressure*) and the ventricular volumes are at their maximal value (*end-diastolic volume*). Aortic pressure declines as the blood ejected into the aorta during the previous ventricular contraction flows to the peripheral circulation. Atrial contraction provides a final boost to ventricular volume immediately before ventricular systole. Ventricular contraction increases the pressure in the ventricle; when this pressure exceeds the pressure in the atrium, the mitral valve closes. However, because ventricular pressure remains less than aortic pressure, the aortic valve remains closed, and no blood enters or leaves the ventricle during this first phase of the cardiac cycle, the *isovolumic contraction* phase. During systole, ventricular pressure eventually exceeds aortic pressure, at which time the aortic valve opens, blood is ejected into the aorta, and ventricular volume decreases during the *ejection* phase of the cycle. At the end of systole when contraction is maximum, ejection ends, and the ventricular volumes are at their lowest (*end-systolic volume*). The volume of the ejected blood, which is termed the stroke volume (SV), is defined as the difference between the end-diastolic and end-systolic volumes. The ejection fraction (EF), defined as the percentage of end-diastolic volume (EDV) ejected during a contraction ($EF = 100 \times SV/EDV$), is an index of heart function. The next phase in the cycle occurs when the heart muscle relaxes, ventricular pressures are less than the aorta pressure, and the aortic valve closes. During this *isovolumic relaxation* phase, ventricular volumes remain constant because, once again, both the mitral and aortic valves are closed. When ventricular pressures fall below atrial pressures, the mitral and tricuspid valves open, and blood flows from the atria into the ventricles during the *filling* phase.

These four phases of the cardiac cycle can be represented by a *pressure-volume diagram* (E-Fig. 41-5), which plots the instantaneous ventricular pressure versus volume to calculate the *pressure-volume loop*. Similar effects occur on the left and right sides of the heart, but with higher pressures on the left side (Table 41-1).

Pressure-Volume Relationships

The volume of a ventricular chamber correlates with length of its muscles and sarcomeres. In the left ventricle, with its circular cross section, Laplace's law defines the relationship among pressure in the chamber (P), muscle tension (T, force/unit cross-sectional area of the muscle), chamber wall thickness (h), and internal radius of the chamber (R): $P \approx 2 \cdot T \cdot h/R$. Both calcium and the length of the heart muscle determine force (Fig. 41-3). Each muscle is composed of a linear array of sarcomere bundles. Maximal force is achieved at a sarcomere length of about 2.2 to 2.3 μm, which results in the optimal overlap of thick and thin filaments. When the sarcomere length is less than 2.0 μm, the ends of the thin filaments contact each other, thereby resulting in a reduction in force. Conversely, when sarcomeres are stretched beyond 2.3 μm, force decreases owing to reduced overlap between myosin heads and actin.

Force-length relationships, which are determined by measuring the force developed at different muscle lengths while preventing the muscle from shortening (isometric contractions), characterize the systolic and diastolic contractile properties of cardiac muscle. With increasing muscle length, end-systolic force increases to a greater degree than does end-diastolic force. The

TABLE 41-1 RANGE OF NORMAL RESTING HEMODYNAMIC VALUES

PRESSURE
Central venous (mean): 0-5 mm Hg
Right atrial (mean): 0-5 mm Hg
Right ventricular (systolic/diastolic): 20-30/0-5 mm Hg
Pulmonary artery (systolic/diastolic): 20-30/8-12 mm Hg
Left atrial (mean): 8-12 mm Hg
Left ventricular (systolic/diastolic): 100-150/8-12 mm Hg
Aortic (systolic/diastolic): 100-150/70-90 mm Hg
VOLUME-RELATED MEASURES
Right ventricular end-diastolic volume: 70-100 mL
Left ventricular end-diastolic volume: 70-100 mL
Stroke volume: 40-70 mL
Cardiac index: 2.5-4 L/min/m^2
Ejection fraction: 55-70%
ARTERIAL RESISTANCE
Systemic vascular resistance: 10-20 mm Hg · min/L
Pulmonary vascular resistance: 0.5-1.5 mm Hg · min/L

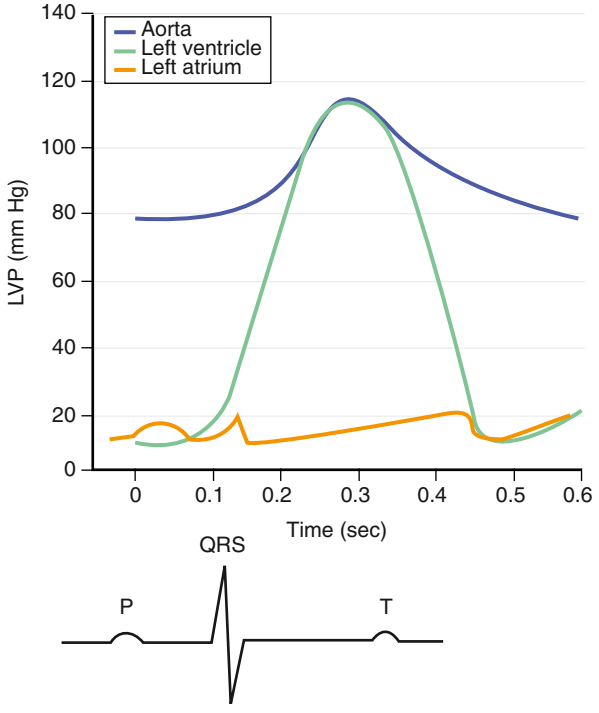

E-FIGURE 41-4. **Wiggers diagram.** Changes in aortic, left ventricular, and left atrial pressures represented graphically as a function of time, with the corresponding electrocardiogram signal for each. LVP = left ventricular pressure.

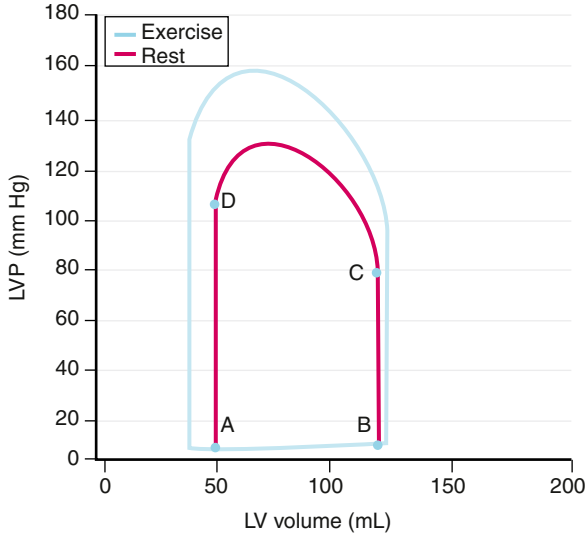

E-FIGURE 41-5. **Pressure-volume loop.** The left ventricle (LV) begins to fill when pressure in the chamber falls below that of the left atrium, and the mitral valve opens (point A). Pressure in the ventricle slowly rises as the muscle fibers are stretched by the increasing volume. When the myocardium contracts (point B), pressure in the left ventricle rises, causing the mitral valve to close and trapping the blood inside the chamber (isovolumic contraction). When the pressure in the left ventricle is higher than in the aorta, the aortic valve opens (point C), and blood is ejected out of the left ventricle. As the left ventricle stops contracting, pressure in the aorta becomes higher than that in the left ventricle, and the aortic valve closes (point D). During this period of isovolumic relaxation, the ventricle rapidly relaxes until it starts filling again. During exercise, the release of norepinephrine from sympathetic nerve terminals leads to enhanced myocardial contractility. As a result, the left ventricle generates higher pressures and ejects a greater volume of blood during each beat. LVP = left ventricular pressure.

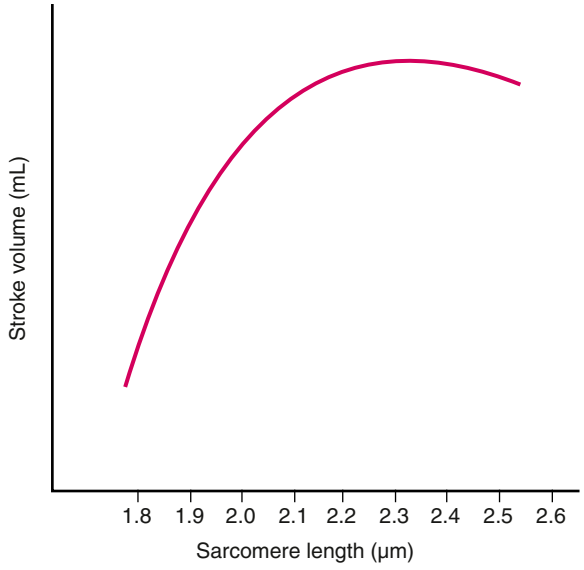

FIGURE 41-3. Frank-Starling law. Cardiac output, represented as stroke volume (end-systolic volume minus end-diastolic volume), as a function of initial sarcomere stretch. The greater the initial stretch on the fibers during diastole, referred to as preload, the more force is generated during systole.

difference in force at end diastole versus end systole increases as muscle length increases as a result of the greater developed force of the stretched muscle. This relationship of force to length is referred to as the Frank-Starling law of the heart.

Work of the Heart

Cardiovascular performance is reflected in the arterial blood pressure and cardiac output (mean arterial blood flow), which in turn are dependent on four factors: preload, afterload, ventricular contractility, and heart rate.

Preload, which refers to the degree to which sarcomeres are stretched just before systole, is defined as the end-diastolic pressure or volume. The Frank-Starling law of the heart dictates that ventricular pressure and output vary with preload, so a decrease in preload decreases end-diastolic volume and pressure, peak pressure, and stroke volume. Conversely, increased preload increases ventricular pressure and output, subject to the limits to which preload pressures can be increased. Left ventricular end-diastolic pressures of 20 to 25 mm Hg and greater cause exudation of fluid into the alveoli and pulmonary edema (Chapter 45).

Afterload refers to the stress that the ventricle must overcome to eject blood. Peak arterial pressure reflects the peak stress imposed on cardiomyocytes according to Laplace's law (described previously as $P \approx 2 \cdot T \cdot h/R$). As long as there is no left ventricular outflow obstruction, arterial pressure reflects myocyte afterload, as does *total peripheral resistance* (TPR), which corresponds to the tone of the resistance vessels. TPR is the ratio between the mean pressure decrease across the arterial system (mean arterial pressure [MAP] minus mean central venous pressure [CVP]) and cardiac output (CO): TPR = (MAP − CVP)/CO. When TPR is increased, the pressure-volume relationship shifts such that peak pressure is increased, whereas stroke volume and ejection fraction are decreased.

Contractility of cardiac muscle (*myocardial contractility*) or a ventricle (*ventricular contractility*) is the intrinsic ability to generate force independent of preload or afterload. When ventricular contractility is increased, the pressure-volume relationship shifts so that pressure, stroke volume, and ejection fraction are increased at constant preload volume and arterial resistance. By comparison, ventricular contractility is decreased in dilated cardiomyopathy (Chapter 47), and atrial contractility is decreased by the atrial myopathy that may precede and commonly follow atrial fibrillation.[3]

Cardiac output is measured in liters per minute and is equal to the amount of blood ejected at each heartbeat (stroke volume in liters per beat) multiplied by the number of beats per minute. As a result, *heart rate* is a powerful determinant of cardiac performance. Cardiac output and mean arterial pressure can be related to preload, afterload, contractility, and heart rate through the Frank-Starling curves, which plot end-diastolic pressure versus cardiac output or mean arterial pressure, to yield an overall picture of left ventricular function.

CARDIOVASCULAR RESPONSES TO STRESSORS

EXERCISE

Exercise requires dramatic increases in cardiac function combined with remodeling of the peripheral circulation to meet the enhanced metabolic demands of critical organs and to redirect blood flow to those organs. Indeed, the oxygen consumption during exercise can increase as much as 18-fold. About one third of the requirement for increased oxygen consumption is met by improved extraction of oxygen from the blood in the muscles (reducing venous saturation from about 75% to about 25%) and the remainder by increasing cardiac output as much as six-fold. Increased cardiac function is achieved largely through sympathetic stimulation and reduction in vagal tone, which combine to increase the heart rate, contractility, ejection fraction, filling rates, and systolic blood pressure and to decrease aortic impedance. In young healthy individuals, heart rate can increase from a baseline of 60 to 70 beats per minute at rest to as much as 170 to 200 beats per minute with exercise. To increase rather than to decrease cardiac output at these high heart rates, which can limit ventricular filling and stroke volume, contractility must also increase through a phenomenon known as the positive force frequency relationship, or Bowditch phenomenon. Along with increased cardiac contractility, arterial vasodilation in the aorta and other major arteries reduces the resistance to cardiac outflow. Both enhanced cardiac contractility and arterial vasodilation are triggered by the same sympathetic nervous system signals. With increased cardiac outflow, venous return also must increase so that preload can be maintained as well as possible to enhance cardiac function by the Frank-Starling mechanism. In response to the stress of repeated exercise (e.g., in trained athletes), the heart may undergo physiologic hypertrophy, which should be distinguished from the pathologic hypertrophy that is triggered by hypertension, myocardial infarction, and chronic activation of neurohormonal pathways (e.g., the renin-angiotensin system) (E-Fig. 41-6).

HEART FAILURE

Heart failure can be defined as the inability of the heart to provide sufficient blood flow to meet the metabolic demands of the organs (Chapter 45). Heart failure can be due to systolic dysfunction with volume overload, most often as the consequence of ischemic heart disease (myocardial infarction) or as the end-stage consequence of hypertension. Systolic heart failure is characterized by increases in the size of the various cardiac chambers (rightward shift of the end-diastolic pressure-volume relationship). In another form of heart failure, known as *diastolic heart failure*, the heart is not necessarily increased in size, and systolic function is preserved.[4] Emerging data implicate altered regulation of calcium inside the cardiomyocyte in the pathogenesis of both the cardiac and skeletal muscle weakness that is seen in heart failure, as well as in atrial fibrillation,[5] which is the most common arrhythmia associated with heart failure.

AGING

Prolongation of contraction and relaxation times, which are common abnormalities in older individuals, may be related to cardiac hypertrophy as a consequence of the high prevalence of hypertension with advancing age (Chapter 64). A progressive "stiffening" of the large arteries with advancing age increases resistance, although the mechanism underlying this change is not understood. The heart rate and contractile responses to sympathetic signals are reduced and lead to a diminished ability to respond to conditions of acute overload, such as increased blood pressure or an acute myocardial infarction.

CARDIAC REGENERATION

Some animals, such as zebrafish, can regenerate substantial portions of their hearts after injury, sometimes by recruiting atrial myocytes to replace damaged ventricular myocytes. In mammals, however, cardiomyocytes stop proliferating right after birth. Any subsequent enlargement of the heart in response to stress (e.g., hypertension) or loss of myocardium (e.g., myocardial infarction) is limited to hypertrophy of existing cardiomyocytes. Studies, however, have shown that micro-RNAs (miRNAs) can activate cardiomyocyte proliferation and repair by enabling the terminally differentiated cardiomyocytes to re-enter the cell cycle and proliferate. These miRNAs are short, noncoding RNAs that downregulate target messenger RNAs by binding to partially complementary sequences and reducing the expression of the encoded proteins. In mice, miRNAs can induce cardiac regeneration and prevent loss of heart function after myocardial infarction, thereby raising the possibility for a better understanding and potential treatment of cardiac diseases. To date, however, stem cell therapy has been disappointing for heart failure[A1] and for acute myocardial infarction.[6]

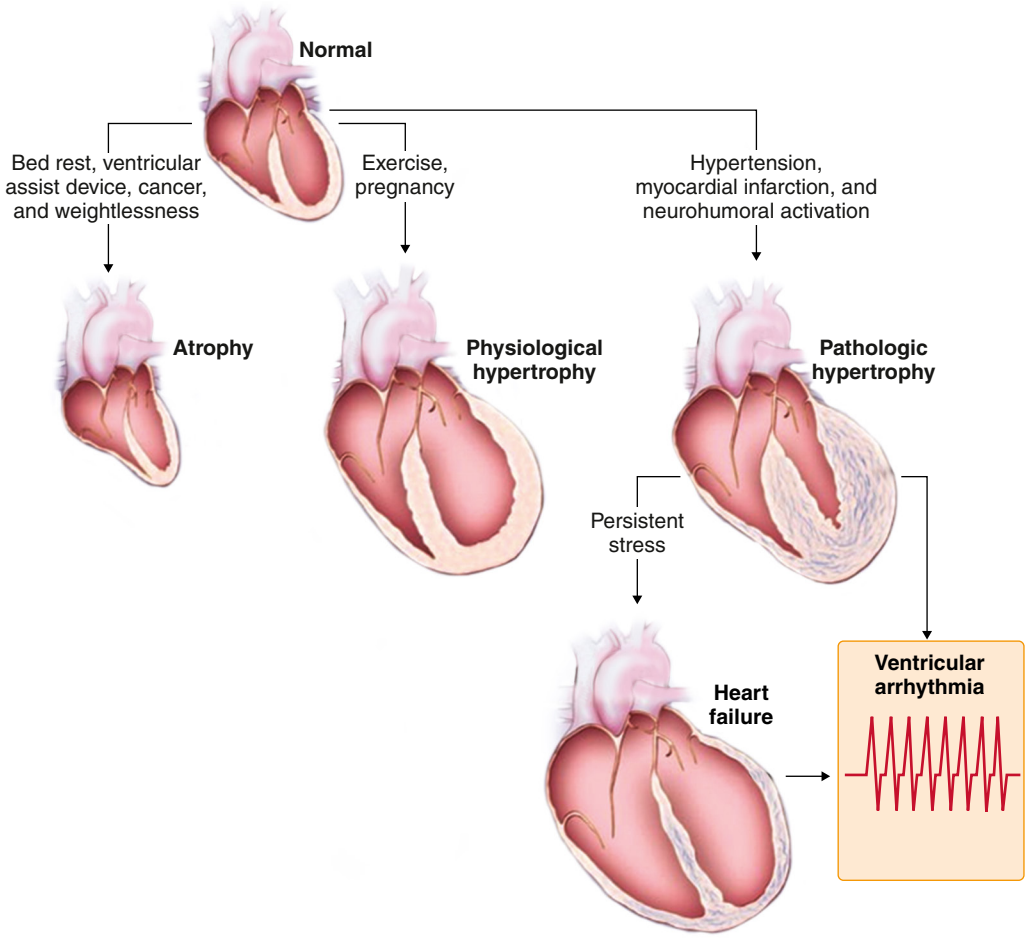

E-FIGURE 41-6. Remodeling of the heart in response to stress. The heart can undergo physiologic remodeling in response to normal stress (repeated exercise), or it can undergo pathophysiologic remodeling after a myocardial infarction or in response to chronic hypertension. Atrophy, or shrinking of the heart, can occur in microgravity (space travel), weight loss, cancer cachexia, and other conditions in which the pumping work of the heart is diminished. (From Hill JA, Olson EN. Cardiac plasticity. *N Engl J Med*. 2008;358:1370-1380.)

IMPAIRED CIRCULATORY FUNCTION: ATHEROSCLEROSIS

Atherosclerosis, which is an age-dependent process of progressive damage to arterial vessels, can impair coronary blood flow and result in myocardial ischemia (Chapter 56) and infarction (Chapters 57 and 58). Atherosclerosis is linked to cardiac risk factors including elevated cholesterol levels, hypertension, cigarette smoking, obesity, genetics (positive family history), and diabetes. Atherosclerosis can lead to partial or complete blockages of arteries due to formation of atherosclerotic plaques comprised of lipoproteins, inflammatory cells, and connective tissue. Atherosclerotic plaques may rupture, thereby leading to thromboses and arterial occlusions that result in myocardial infarction (Chapters 57 and 58), ischemic stroke (Chapter 376), and peripheral arterial disease (Chapter 65). Repeated atherosclerotic-induced ischemic attacks can result in dilated cardiomyopathy and heart failure (Chapter 45). An estimated 90% of cases of myocardial infarction (Chapter 58), 60% of strokes (Chapter 376), most cases of heart failure (Chapter 45), and up to one third of all cases of dementia (Chapter 371) are due to atherosclerosis.

RISK FACTORS FOR ATHEROSCLEROSIS

The major risk factors that promote the development of atherosclerosis are an elevated low-density lipoprotein (LDL) cholesterol level (Chapter 190); cigarette smoking (Chapter 363); diabetes (Chapter 210); hypertension (Chapter 64); and a family history of coronary heart disease, ischemic stroke, or peripheral arterial disease. Other conditions that increase the risk of atherosclerotic disease or events include a low high-density lipoprotein (HDL) level (Chapter 190), obesity, hyper-triglyceridemia, high plasma levels of lipoprotein (a), hyperfibrinogenemia, homocystinuria, and physical inactivity (Chapter 40).

An atherogenic lipoprotein phenotype (characterized by the predominance of small, dense LDL particles, hypertriglyceridemia, and low plasma HDL cholesterol concentration) with the metabolic syndrome is associated with atherogenic and thrombotic factors, including raised levels of plasma fibrinogen, plasminogen activator inhibitor-1, and coagulation factor VII, as well as platelet hyperactivity. The inflammatory biomarker C-reactive protein does not cause atherosclerosis but reflects ongoing inflammation that may accelerate the atherosclerotic process.[7]

PATHOPHYSIOLOGY OF ATHEROSCLEROSIS

When LDL accumulates in the inner wall of arteries (intima), it becomes oxidized, thereby resulting in the release of chemokines and adhesion molecules that promote inflammation, chiefly marked by the recruitment of monocytes, which become macrophages (E-Fig. 41-7). Macrophages accumulate cholesterol and become cholesterol-laden foam cells. Other macrophages produce proinflammatory mediators, including tumor necrosis factor (TNF), interleukin-1, proinflammatory eicosanoids, oxygen and nitrogen free radicals, and prothrombotic factors.

PLAQUE ACTIVATION, THROMBOSIS, AND INFARCTION

The atherosclerotic process typically is silent for months, years, and even decades, and it may never result in clinical manifestations.[8] However, if the plaque ruptures thrombotic occlusion of the artery may ensue (Fig. 41-4). Platelet aggregates that form on these exposed surfaces are stabilized by a fibrin network. Tissue factor, expressed in the vascular smooth muscle cells and macrophages of the atherosclerotic plaque, is the primary cellular initiator of the blood coagulation cascade that leads to fibrin formation. Atherothrombi expand rapidly and can fill the lumen within minutes, thereby leading to ischemia and infarction.

Matrix metalloproteinases and cysteine proteinases, which are produced by macrophages, are found at sites of plaque rupture and have been implicated in rupture, but their effects on the composition and size of lesions are complex. Cell death may be an important trigger of plaque rupture. Apoptotic cells contained in the plaque are usually removed by efferocytosis. If this process fails, secondary necrosis ensues, thereby leading to reduced mechanical integrity and accumulation of prothrombotic material from dead cells.

ANTIATHEROSCLEROTIC THERAPY

Current treatment of atherosclerosis focuses on reduction of risk factors, including smoking cessation, dietary and pharmacologic reduction of LDL cholesterol (Chapter 190), management of blood pressure (Chapter 64), treatment of hyperglycemia (Chapter 210), hypertriglyceridemia (Chapter 190), obesity (Chapter 201), and physical inactivity (Chapter 14).

Cholesterol-lowering with statins,[A2] ezetimibe,[A3] and proprotein convertase subtilisin kexin type 9 (PCSK9) antibodies[A4] can reduce atherosclerotic lesions, inhibit their progression, and lower the rate of subsequent coronary events and all-cause mortality. More recently, inhibition of the hepatic synthesis of PCSK9 using a single subcutaneous injection of inclisiran has resulted in LDL cholesterol reductions of 50% or so for 18 months.[A5,A6]

Aspirin[A7] and other inhibitors of platelet aggregation,[9] β-adrenergic receptor blockers, and angiotensin-converting enzyme inhibitors or angiotensin II antagonists are also part of the routine secondary prevention of coronary heart disease (Chapters 56, 57, and 58). Inhibitors of platelet aggregation are widely used for secondary prevention of atherosclerotic cardiovascular disease. Aspirin inhibits formation of proaggregatory prostaglandins, whereas other inhibitors of platelet aggregation modulate expression of platelet adhesion molecules. In addition to medical therapies, interventional therapies such as stenting and coronary artery bypass surgery (Chapter 59) also have greatly impacted the health burden of atherosclerosis.

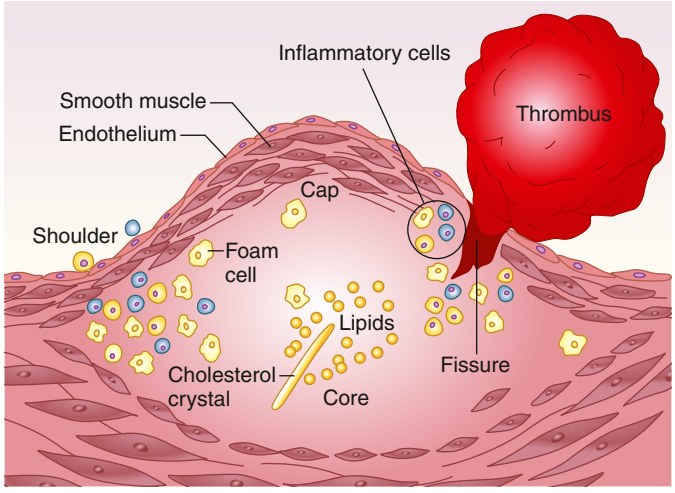

FIGURE 41-4. Plaque rupture and atherothrombosis. The advanced atherosclerotic plaque has a central core with lipids (especially cholesterol), live and dead cells, necrotic material from dead foam cells, and calcium salts. The plaque is overlaid by a fibrous cap that consists of smooth muscle cells and collagen (produced by the muscle cells) and covered by an intact layer of endothelial cells. Inflammatory cells (macrophages, T cells, mast cells, dendritic cells, and occasional B cells) are interspersed with these components and are particularly abundant in the shoulder regions of plaques, where fissures (also called ruptures) may expose thrombogenic core material (e.g., lipids, collagen, tissue factor) to blood components. This event triggers platelet aggregation and humoral coagulation, thereby leading to thrombus formation at the site of fissuring. Thrombi may expand locally to obstruct blood flow or they may detach to cause embolization.

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For the General References and other additional features, please visit Elsevier eBooks+ at https://ebooks.health.elsevier.com.

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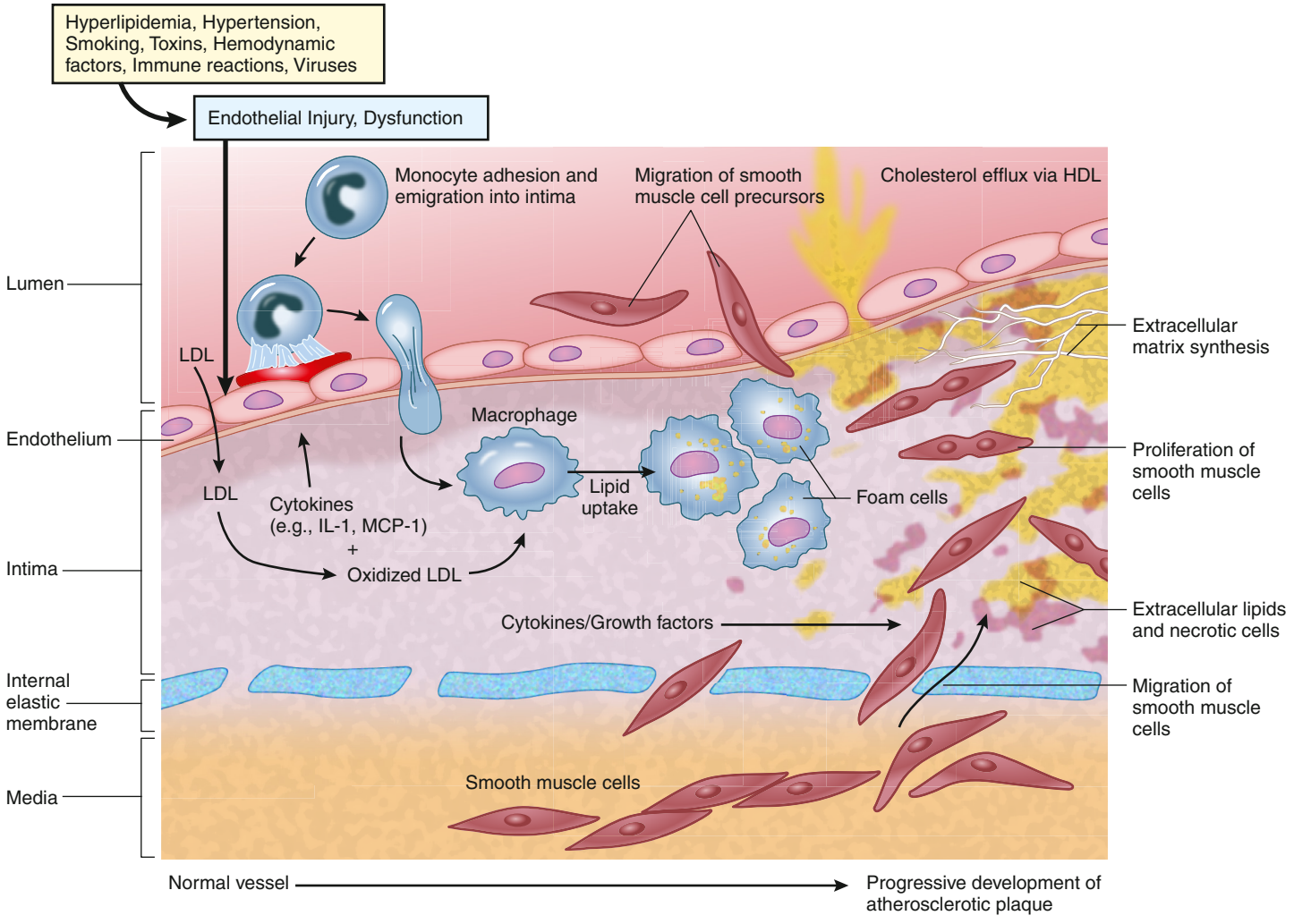

E-FIGURE 41-7. Formation of atherosclerotic plaques. Low-density lipoproteins (LDL) transit from the blood stream to the arterial intima and accumulate under the endothelial cell layer. LDL particles undergo oxidative modification in the intima (denoted by spikes on LDL particles), thereby leading to their binding to scavenger receptors and uptake by macrophages, which accumulate cholesterol and develop into foam cells. Cholesterol efflux to high-density lipoprotein (HDL) counteracts the tendency to foam cell formation. Molecules released from oxidatively modified LDL activate endothelial cells to express leukocyte adhesion molecules that promote binding of monocytes and T cells to the surface of the artery. Chemokines stimulate monocytes and T cells to migrate into the intima, where the monocytes differentiate into macrophages and cytokines promote vascular smooth muscle cell proliferation. Some macrophages are activated, thereby leading to release of proinflammatory cytokines, eicosanoids, radicals, and proteases. T cells entering through mechanisms similar to those of monocytes can recognize local antigens, such as LDL components, which are presented to them by antigen-presenting cells (dendritic cells and macrophages) that express human leukocyte antigen (HLA) molecules. T cells whose receptors can recognize local antigens are activated, thereby leading to release of a host of cytokines that can activate macrophages and enhance vascular inflammation. Triglyceride-rich lipoprotein remnant particles, which have adverse effects on endothelial function, penetrate into the subendothelial space of normal intima and form atherosclerotic plaques. Conversely, antiatherogenic HDL particles mediate cholesterol efflux from cells by acting as acceptors of cholesterol delivered from specific transport proteins termed adenosine triphosphate–binding cassette (ABC) A1 and G1. (From Kumar et al. *Robbins Basic Pathology*, 8e.)

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42 ELECTROCARDIOGRAPHY

LEONARD GANZ AND MARK S. LINK

Electrocardiography, which itself has changed surprisingly little since initially introduced by Einthoven in the early 1900s, allows simultaneous recording of myocardial activation from multiple vantage points on the body's surface, thereby permitting analysis of electrical activation in different myocardial regions. Surface electrocardiography may be supplemented with intracardiac recordings, which are particularly helpful in the diagnosis and management of cardiac arrhythmias (Chapter 49). With the advent of computerized readings and artificial intelligence, the interpretations of electrocardiograms are becoming more accurate and potentially more diagnostic of certain disease conditions.

NORMAL FUNCTION AND ELECTROCARDIOGRAM

NORMAL CARDIAC ACTIVATION

Electrical activation of the heart depends on the spread of a depolarizing wave front from pacemaker cells through cardiac muscle, as well as via specialized conducting tissues (Fig. 42-1). Under normal circumstances, cells in the sinoatrial (SA) nodal complex in the high lateral epicardial right atrium near the superior vena cava spontaneously depolarize at the highest rate and therefore constitute the dominant cardiac pacemaker (Chapter 48). This electrical wave front spreads throughout the right and left atria; specialized conducting tracts called the Bachmann bundle speed the depolarizing wave front to the left atrium. Electrical atrial activation triggers atrial muscular contraction, thereby propelling blood through the tricuspid and mitral valves into the right and left ventricles. Normally, the atrioventricular (AV) node, where conduction delay is physiologic, serves as the only electrical connection linking the atria and ventricles; the AV valve rings are insulated. The depolarizing wave front exits the AV node into the bundle of His, a specialized conducting tissue capable of rapid conduction. The bundle of His bifurcates into right and left bundle branches; the left bundle branch divides into the left anterior and left posterior fascicles. The bundle branches and their more distal ramifications of specialized conducting tissue are called the Purkinje system. From these specialized conducting tissues, the depolarizing wave front enters into and then moves through ventricular muscle. As in the atria, ventricular electrical depolarization initiates muscular contraction, which pumps blood through the semilunar valves into the pulmonary and systemic circulations. After electrical depolarization, a period of electrical recovery, or repolarization, is necessary before repeated depolarization.

At the cellular level, a complex orchestration of ion channels opening and closing determines the membrane potential throughout this process. The flow of ions into and out of the myocardial cells inscribes an action potential, which reflects depolarization and repolarization, as well as the spontaneous depolarization of pacemaker cells (Chapter 48).

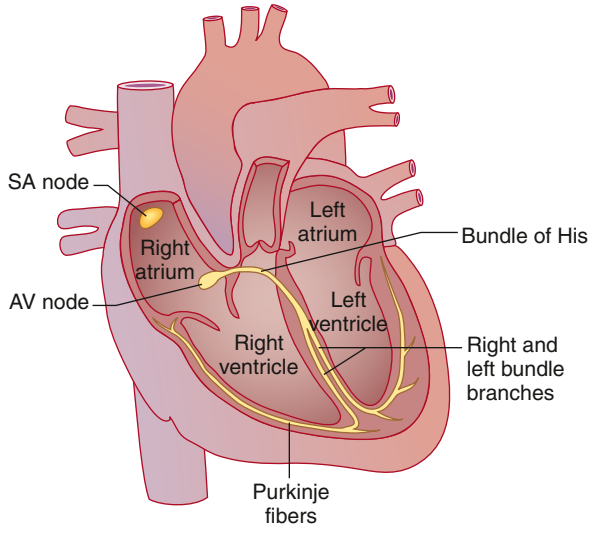

FIGURE 42-1. Cardiac conduction system. The normal conducting system consists of pacemaker cells in the sinoatrial (SA) nodal complex, specialized intra-atrial conducting tracts (including Bachmann bundle), the atrioventricular (AV) node, the His-Purkinje system, and working atrial and ventricular myocardium.

THE ELECTROCARDIOGRAPHIC WAVES

Labeled alphabetically, beginning with the P wave, the basic waves of the electrocardiogram (ECG) correspond to these electrical events (Fig. 42-2). The P wave represents atrial muscular depolarization. The morphology of the P wave is reflective of atrial structure. Under normal circumstances, the PR interval, which is the segment from the onset of the P wave to the onset of the QRS complex, represents the delay between atrial and ventricular depolarization. The QRS complex represents ventricular muscular depolarization; the disparity between ventricular and atrial muscle mass typically yields a QRS complex much larger in voltage amplitude than the P wave. Recorded from multiple vantage points, the QRS complex harbors tremendous information about the structure and function of ventricular tissue. The ST segment and T wave (and occasionally the U wave) reflect ventricular repolarization, a process of electrical recovery that must take place before the ventricle can be depolarized again. The J (junction) point denotes the end of the QRS complex and beginning of the ST segment. Atrial muscle also requires repolarization before the next depolarizing wave front. Because ventricular mass far exceeds atrial muscular mass, the low-amplitude atrial repolarization wave is buried underneath the QRS complex and therefore not manifested on the ECG.

One rarely seen ECG finding, the J wave (of Osborn), breaks with the alphabetic convention of the other electrocardiographic waves. Defined as a positive deflection on the QRS downstroke or at the J point, the J wave is seen most commonly in hypothermia (see Fig. 42-3). It also has been described in hypercalcemia and brain injury, and it may connote risk of idiopathic ventricular fibrillation (see later).

ELECTROCARDIOGRAPHY STANDARDS

A standard ECG is recorded on paper (and frequently digitally) with 1-mm ("small" boxes) as well as 5-mm ("big" boxes) gridlines (see Fig. 42-2). Voltage amplitude is measured on the vertical axis (typically 10 mm equaling 1 mV) and time on the horizontal axis. Because the usual ECG recording speed is 25 mm/sec, each 1-mm gridline (small box) represents 0.04 second

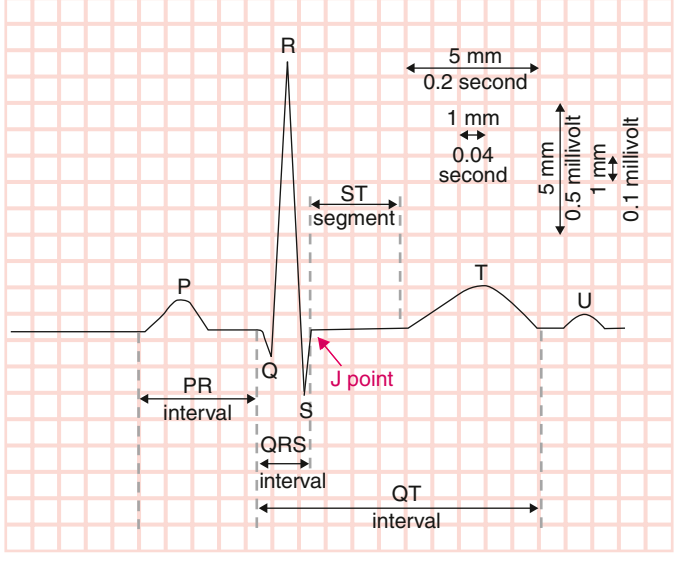

FIGURE 42-2. Inscription of a normal electrocardiogram (ECG). Sinoatrial nodal depolarization is not visible on the surface ECG; the P wave corresponds to atrial muscular depolarization. The PR interval denotes conduction through the atrial muscle, atrioventricular node, and His-Purkinje system. The QRS complex reflects ventricular muscle depolarization. The ST segment and T wave correspond to ventricular repolarization. The J point lies at the junction of the end of the QRS complex and beginning of the ST segment. The QT interval is measured from QRS onset to T wave offset. Note the gridlines. On the horizontal axis, each 1-mm line ("small" box) denotes 0.04 second (40 msec); a "big" box denotes 0.2 second (200 msec). On the vertical axis, 1 mm (small box) corresponds to 0.1 mV; 10 mm (two big boxes) therefore denotes 1 mV.

ABSTRACT
A comprehensive introduction to the theory, practice, and interpretation of the electrocardiogram.

KEYWORDS
electrocardiography
electrocardiogram
ECG
EKG

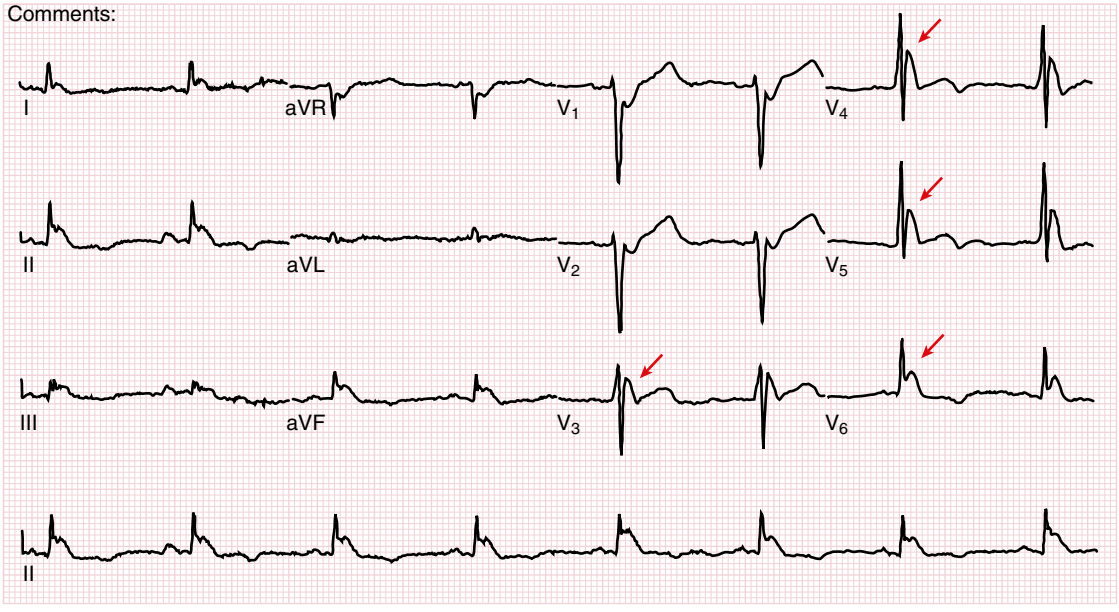

FIGURE 42-3. **J wave (of Osborn).** This ECG was recorded in a 40-year-old diabetic woman with profound hypothermia (26.6° C), diabetic ketoacidosis, and hypokalemia. Note the massive J waves in leads V_3-V_6, and smaller J waves in leads I, II, III, and aVF. Other notable findings include sinus bradycardia and QT prolongation.

(40 msec), and each 5-mm gridline (big box) equals 0.2 second (200 msec). These parameters, which are typically printed on the ECG to aid in proper interpretation, are the usual calibration or standardization, but they can be modified in unusual circumstances.

A standard ECG is recorded over a 10-second period, although a rhythm or monitor strip can be recorded for substantially longer if necessary. Multiple leads are typically recorded simultaneously from the top to the bottom of the page. The usual groupings of leads include I, II, and III; aVR, aVL, and aVF; V_1, V_2, and V_3; and V_4, V_5, and V_6 (see later). Each group of leads is recorded for 2.5 seconds. A single lead (or multilead) rhythm strip is recorded below for the entire 10 seconds. Thus, as the ECG is scanned from left to right, one sees 10 seconds of cardiac activity, with each complex recorded simultaneously in multiple leads.

NORMAL INTERVALS

Each of the various ECG waves and intervals has normal ranges, defined from large numbers of electrocardiographic recordings in (presumably) healthy subjects (Table 42-1; see Fig. 42-2).

The RR interval (identical to the PP interval in sinus rhythm), which is the measurement from R wave to R wave (or P wave to P wave), allows calculation of the heart rate. Because there are 60,000 msec in a minute, the heart rate (HR) in beats per minute can be easily calculated from the RR or PP interval in milliseconds:

$$HR = \frac{60{,}000}{RR}$$

Although traditionally the normal resting adult heart rate range has been defined as 60 to 100 beats per minute, a range of 50 to 90 at rest may actually be more reflective of normal physiology. Various stressors (exercise, pain, fever, anemia, etc.) increase the heart rate; a lower heart rate is noted after eating and during sleep. Resting heart rates tend to decrease with age. When the heart rate is grossly irregular, as in atrial fibrillation (Chapter 52), the RR interval can be averaged over a number of cardiac cycles to estimate the heart rate. Because a standard ECG records 10 seconds in time, the heart rate (beats per minute) will equal the number of beats recorded on a standard ECG multiplied by 6. Alternatively, in a regular rhythm, the heart rate can be estimated by counting the number of big boxes between consecutive QRS complexes or P waves (i.e., 2 large boxes = 150 beats per minute, 3 large boxes = 100 beats per minute, 4 large boxes = 75 beats per minute, 5 large boxes = 60 beats per minute, and so on.).

TABLE 42-1 NORMAL ELECTROCARDIOGRAPHIC INTERVALS

Heart rate	50-100 beats per minute
P wave duration	<0.12 sec (120 msec)
PR interval	0.09-0.20 sec (90-200 msec)
QRS duration	0.075-0.11 sec (75-110 msec)
QTc	males: 0.39-0.45 sec (390-450 msec); females: 0.39-0.46 sec (390-460 msec)
QRS axis	−30 to +90 degrees

P Wave Duration

The P wave duration, from the beginning to the end of a P wave, is typically less than 0.12 second (120 msec, three small boxes) in length. A broader P wave reflects an intra-atrial and/or interatrial conduction delay. Abnormalities in P wave amplitude, morphology, and axis may reflect atrial enlargement.

PR Interval

The PR interval, measured from the onset of the P wave to the onset of the QRS complex, normally lasts between 0.09 and 0.2 second (90 to 200 msec). One-to-one AV conduction with a PR interval greater than 0.2 second has traditionally been called *first-degree AV block*, but *delayed AV conduction* may be a more appropriate term. Conduction through the atrial tissue, the AV node, and the His-Purkinje system all contribute to the PR interval. When the PR interval is prolonged, delay is usually present in the AV node, although other sites of delay are possible. A short PR interval may reflect ventricular preexcitation (Wolff-Parkinson-White syndrome), a junctional rhythm, or enhanced AV nodal conduction (Chapters 49 and 52).

QRS Complex

The QRS complex, which reflects ventricular muscular electrical activation, carries important information in patients with coronary artery disease, cardiomyopathy, metabolic abnormalities, and other conditions. Capital letters (Q, R, S) denote large-amplitude deflections (≥5 mm or 0.5 mV), whereas lowercase letters (q, r, s) signify low-amplitude deflections (<5 mm or 0.5 mV). Q, q, S, and s waves are negative excursions from the isoelectric baseline, whereas R and r waves are positive deflections. Q and q waves are initial negative deflections, and S and s waves are negative deflections that follow a positive deflection (R or r wave); a QS complex is an entirely negative deflection. Q waves may reflect prior infarction (Chapters 56-58). An R′ or r′ wave refers to a second positive deflection after an S (or s) wave. The duration of the QRS complex reflects the time required for ventricular depolarization. Ventricular activation usually requires at least 0.075 second (75 msec, nearly two small boxes). There is some debate regarding the upper limit of the normal range for QRS duration; a recent consensus document specified 0.11 second (110

msec, nearly three small boxes). If the QRS duration is prolonged, an intraventricular and/or interventricular conduction delay is present. Particular patterns of interventricular conduction delay have been termed bundle branch block (see later).

QT Interval

The QT interval is measured from the onset of the QRS complex to the end of the T wave. Although the QT interval is generally felt to reflect ventricular repolarization, it also includes the time required for ventricular depolarization (QRS duration). The QT interval is generally measured in leads II, V_5, and V_6 (see later) and reported as the longest interval among the three, averaged over three to five cycles. If the QT interval cannot be accurately measured in these leads, other leads may be used. The QT interval must be corrected to allow comparison of this interval at differing heart rates. The most commonly used approach, Bazett's formula, defines a corrected QT interval (QTc):

$$QTc = \frac{QT}{\sqrt{RR}}$$

Bazett's formula works reasonably well at heart rates in the normal range but overcorrects at high rates and undercorrects at low rates. Irregular rhythms (notably atrial fibrillation) complicate calculation of the QTc. Some investigators recommend measuring at least three QT intervals to get an average, and then using an RR interval averaged over 10 cycles. More complex regression formulas have been developed to correct the QT interval at different heart rates. For example, the Fridericia formula

$$QTc = \frac{QT}{\sqrt[3]{RR}}$$

may be more accurate than Bazett's formula in atrial fibrillation and better at predicting adverse outcomes, but it has not achieved widespread clinical use.

The presence of a U wave complicates measurement of the QT (and therefore QTc) interval; it may be unclear where the T wave ends and where the U wave begins. In general the U wave should not be included as part of the QT interval; instead, the slope of the T wave to the baseline (before the P wave) should be extrapolated to determine the true QT interval. The QTc in a given patient may vary somewhat during the course of the day and is slightly longer in young and middle-aged women than in men. The upper limit of a normal QTc is somewhat debatable, but a cutoff of 0.45 second (450 msec) in men and 0.46 second (460 msec) in women is generally used. Repolarization and thus the QT interval are sensitive to drug effects as well as to abnormal electrolytes, coronary ischemia, and central nervous system events. Patients with widened QRS complexes frequently have prolonged QT and QTc intervals. In these patients, the JT interval (from J point to the end of T wave) may be a more accurate index of repolarization, but normal standards have not been established. However, a reasonable correction factor is to subtract the excess QRS interval (i.e., measured QRS – 80) from the QT interval. Patients with a prolonged QTc, whether congenital or acquired, may be at risk for torsades de pointes ventricular tachycardia (Chapter 53). A very short QTc interval (<320 to 340 msec) is unusual, and the very rare patient with the short QT syndrome is also at risk for malignant ventricular arrhythmias.

ELECTROCARDIOGRAPHIC LEADS

Recording a single ECG lead allows calculation of the heart rate and, frequently, accurate diagnosis of the heart rhythm. When the ECG is recorded from multiple skin leads simultaneously, the direction (or vector) of activation as the electrical wave front moves through the heart can be inferred. Although a number of different lead systems are possible (and some are actually used in research settings), standard electrocardiography uses 12 vantage points (i.e., leads), derived from 10 electrodes, 6 on the chest wall and 4 on the limbs. In reality, only three limb leads are actually used to generate recordings; the right leg lead serves as an electrical ground. The limb leads, called the frontal plane leads, generate bipolar and augmented unipolar lead recordings. The chest or precordial electrodes record unipolar recordings. Bipolar leads record the potential difference between two skin electrodes. In unipolar recordings, the lead of interest, the exploring electrode, is compared with a reference electrode. By convention, a positive deflection is recorded if the electrical wave front is moving toward the positive electrode in a bipolar pair or toward the exploring electrode in a unipolar lead.

The bipolar limb leads measure potential differences between electrodes on pairs of limb electrodes and closely resemble Einthoven's original string galvanometer recordings. Lead I compares the right arm (negative) and left arm (positive), lead II the right arm (negative) and left leg (positive), and lead III the left arm (negative) and left leg (positive) (E-Fig. 42-1). Because the direction of both atrial and ventricular depolarization is away from the right arm and toward the left arm, a positive P wave and QRS complex are generally recorded in lead I. Similarly, the P wave and QRS complexes are positive in leads II and III in normal sinus rhythm because atrial and ventricular activation proceeds in a craniocaudal direction.

Leads aVR, aVL, and aVF are augmented unipolar leads in which the potential in each limb is compared with a reference electrode. For lead aVR, the potential of the right arm is compared with a reference composed of the left arm and left leg electrodes. Lead aVL compares the left arm potential with a reference combining the right arm and left leg; aVF compares the left leg with a right and left arm reference. Because atrial and ventricular activation normally moves from right to left and in a craniocaudal direction, the P wave and QRS complex are negative in lead aVR but positive in lead aVF. In lead aVL, P waves and QRS complexes are generally upright, although an rS complex may be recorded, particularly in young patients.

The precordial electrodes are positioned at specific points on the chest wall (E-Fig. 42-2A). These unipolar leads compare electrical potential between the chest electrode and a reference electrode called the Wilson central terminal. The Wilson central terminal combines the right arm, left arm, and left leg potentials through 5000-Ω resistors. The six precordial leads define atrial and ventricular activation with respect to a somewhat transverse plane through the chest wall (E-Fig. 42-2B). In this plane, atrial activation moves from right to left. Initial ventricular activation involving the septum is directed from left to right; left ventricular depolarization, which dominates right ventricular depolarization because of the differential in myocardial mass, then moves apically and laterally. In lead V_1, to the right of the sternum, the P wave is biphasic (reflecting right and then left atrial activation). Initial ventricular activation of the septum inscribes an r wave, whereas subsequent activation away from lead V_1 records a dominant S wave. In lead V_6, the P wave is positive, and initial ventricular septal depolarization inscribes a tiny "septal" q wave (usually ≤0.02 second). Subsequent ventricular depolarization records a dominant R wave.

Right-sided chest leads should be recorded when right ventricular abnormalities are suspected. RV_3, the reflection of lead V_3 in the right chest, is routinely recorded in pediatric patients because of the possibility of congenital heart disease. In adults, ST elevation in lead RV_3 is quite specific for acute right ventricular infarction in patients who are being evaluated for an acute inferior wall myocardial infarction.

AXIS

An axis of electrical activation can be defined in the frontal plane axis by combining the bipolar and augmented unipolar limb leads (E-Fig. 42-3A). By convention, the axis parallel to lead I, toward the left, is called 0 degrees. A frontal plane axis between −30 and +90 degrees is normal; other axes are abnormal (E-Fig. 42-4). Mild right axis deviation beyond +90 degrees is a normal variant in children and adolescents. The frontal plane axis can be estimated by identifying the limb lead in which the QRS complex is most nearly isoelectric (a similar amplitude of positive and negative deflections); the axis is perpendicular to this lead (see E-Fig. 42-3B). Because two lines pointing 180 degrees apart can be drawn perpendicular to any given line, examination of the other limb leads defines the direction in which the axis points. If the QRS complex is positive in any given limb lead, the axis will be oriented toward that limb lead, not away from it. Alternatively, the axis is in the normal range if the QRS complexes are primarily positive in both leads I and II.

An axis per se is not defined in the precordial leads. Rather, because the typical progression from leads V_1 to V_6 is from a predominantly negative to a positive QRS complex, the transition point is usually defined as the point at which the amplitude of the R wave first exceeds the amplitude of the S wave. Clockwise rotation (transition zone at V_4 or later) may portend a higher risk of future coronary events, and counterclockwise rotation (transition zone at V_3 or earlier) a lower risk of events.

APPROACH TO INTERPRETING THE ELECTROCARDIOGRAM

Physicians' deficiencies in ECG interpretation[1] can be reduced by using a stepwise approach to ensure that no features of the tracing will be overlooked (Table 42-2).[2]

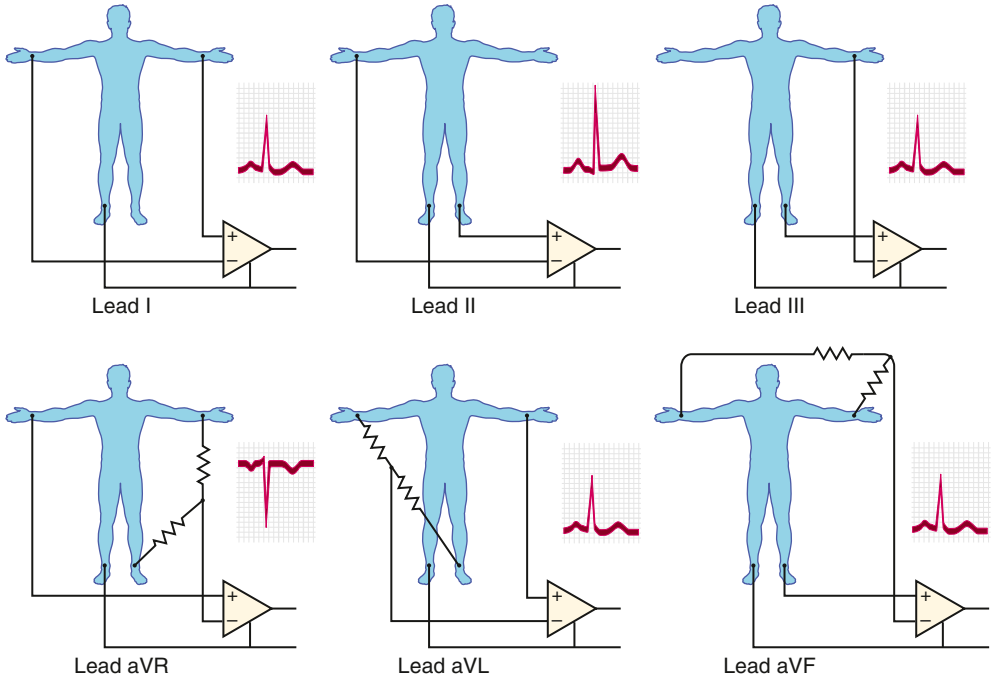

E-FIGURE 42-1. Normal cardiac activation as manifested in the limb leads. Under normal circumstances, P waves and QRS complex are typically upright in leads I, II, III, and aVF and inverted in aVR. In lead aVL, P waves are usually upright, although QRS complexes may be either upright or inverted. The right leg electrode serves to ground the system.

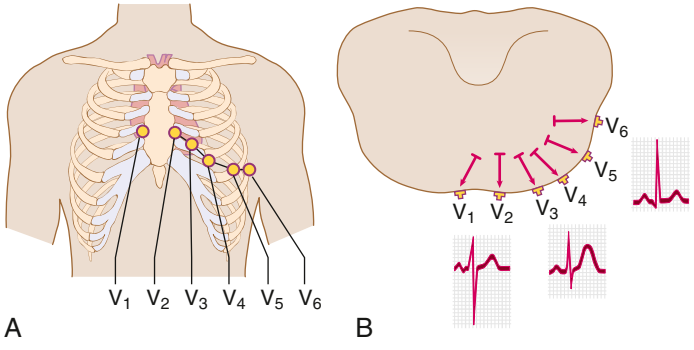

E-FIGURE 42-2. Precordial leads. A, Positioning of the precordial leads on the chest wall. **B,** Normal cardiac activation as manifested in the precordial leads. Note the small r wave and deep S wave in lead V_1, the transition at around V_3 or V_4, and the "septal" q wave and large R wave in lead V_6.

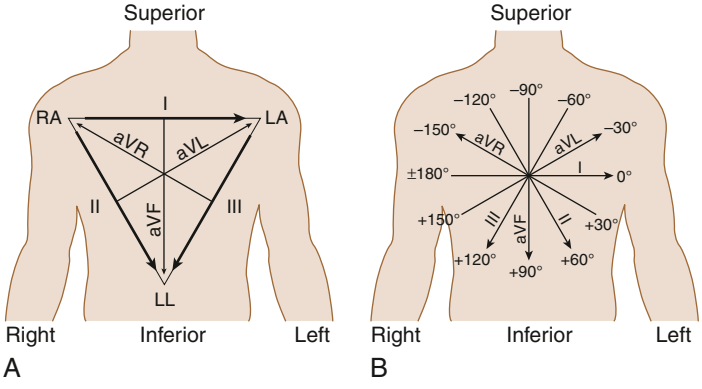

E-FIGURE 42-3. Axis of electrical activation. A, Vectors for the limb leads in the frontal plane. **B,** Hexaxial reference for determining the frontal plane axis. Note that the vectors for leads I, II, and III are in the same direction as in **A**, but now, like the augmented limb leads, these standard limb lead vectors have been moved so that they emanate from the center of the figure.

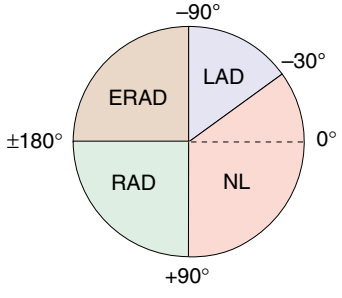

E-FIGURE 42-4. Chart of frontal plane axes. Normal (NL) = –30 to +90 degrees; left axis deviation (LAD) = –30 to –90 degrees (moderate –30 to –45 degrees; marked –45 to –90 degrees); right axis deviation (RAD) = +90 to +180 degrees (moderate +90 to +120 degrees; marked +120 to +180 degrees); extreme right axis deviation (ERAD) = –90 to ±180 degrees. Mild RAD is considered normal in children, adolescents, and young adults.

TABLE 42-2 STEPWISE APPROACH TO INTERPRETING THE ELECTROCARDIOGRAM

Estimate the heart rate
Define the heart rhythm as regular vs. irregular
  Note the relationship of P waves to QRS complexes
  Identify any pauses or premature beats
  If an unsustained arrhythmia is present, note its rate, onset (gradual vs. acute), and termination
Measure intervals (PR, QRS duration, QT)
Calculate/estimate QTc
Estimate QRS axis
Examine P wave morphology, duration, and axis
Examine QRS progression and transition in precordial leads
Examine QRS complexes in regional groupings (septal leads [V_1, V_2], anterior leads [V_2, V_3, V_4], lateral leads [I, aVL, V_5, V_6], inferior and posterior leads [II, III, aVF, V_1, V_2])
Examine ST segments in regional groupings
Examine T waves in regional groupings

NORMAL ELECTROCARDIOGRAM

Figure 42-4 is an example of a normal ECG. Sinus rhythm occurs at about 78 beats per minute, with minor variations in the RR intervals (sinus arrhythmia). The PR interval, QRS duration, and QTc are all normal. The QRS complex is most nearly isoelectric in lead aVL, so the QRS axis will be perpendicular to lead aVL. Because aVL points to −30 degrees, the QRS axis must be approximately −120 or +60 degrees. Because the QRS complex is positive in leads I and II (large R waves), the QRS axis is approximately +60 degrees. The transition in the precordial leads is typically at lead V_3 or V_4. The P wave is biphasic in lead V_1 and then positive in the other precordial leads. Septal q waves, reflecting not lateral infarction but rather normal early septal depolarization, are present in leads V_5 and V_6. Small q waves in the inferior leads are a normal variant.

ABNORMAL ELECTROCARDIOGRAM

Electrocardiography in patients with coronary artery disease is reviewed in Chapters 56 to 58 and in patients with arrhythmias in Chapters 48 to 54.

Conduction Abnormalities and Axis Deviation

Abnormalities of the specialized conduction system (i.e., His-Purkinje system) reflect slow or absent conduction in a particular structure (Table 42-3 and Fig. 42-5). Left anterior or posterior fascicular block does not prolong QRS duration beyond 120 msec. Incomplete bundle branch refers to QRS patterns that are morphologically similar to left or right bundle branch block, but with a duration of less than 0.12 second (120 msec). An interventricular conduction delay is generally defined as a QRS duration of more than 0.11 second (110 msec). When the QRS has a duration of at least 0.12 second (120 msec), it often has the configuration of a specific bundle branch block. An isolated left bundle branch block in an otherwise healthy person is associated with a two-fold higher risk for development of a cardiovascular event or dying of a cardiovascular cause. As a result, this finding should trigger an evaluation for possible cardiac disease. By comparison, a complete right bundle branch block generally has not traditionally been associated with an increased risk, although one study suggested up to a 30% increased risk in cardiovascular mortality.

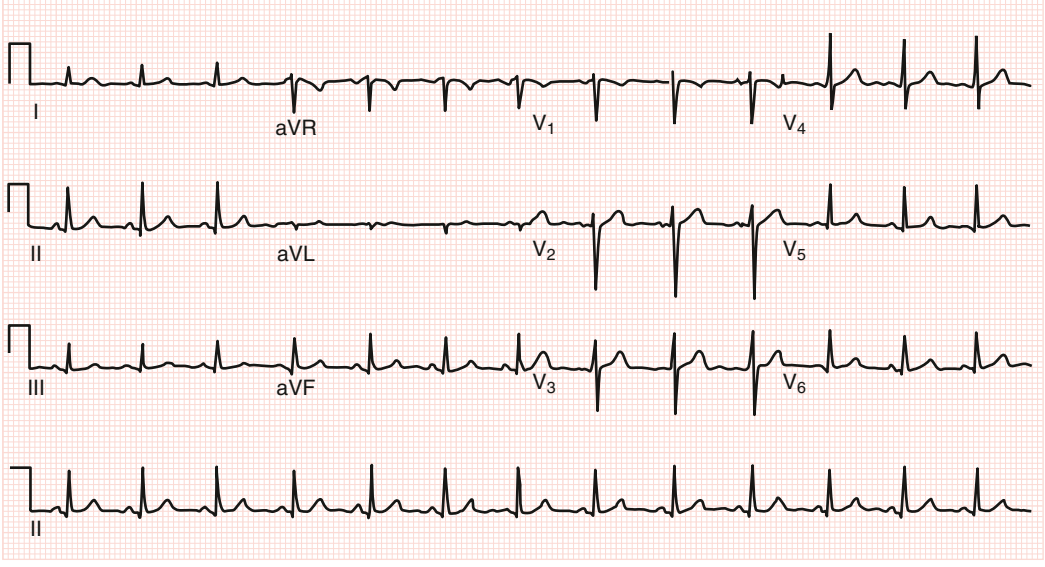

FIGURE 42-4. Normal electrocardiogram. The heart rate is approximately 78 beats per minute, with minor irregularity. Sinus arrhythmia is present. The axis is approximately +60 degrees. The PR, QRS, and QT intervals are approximately 140, 90, and 360 msec, respectively. P wave morphology, duration, and axis are normal. The transition is at lead V_4. No abnormal Q waves are present. ST segments are isoelectric, and T waves are concordant with QRS complexes.

TABLE 42-3 FASCICULAR AND BUNDLE BRANCH BLOCKS

	QRS DURATION	AXIS	QRS MORPHOLOGY	ST SEGMENTS AND T WAVES
LAFB	<0.12 sec (120 msec)	−45 to −90 degrees	Delayed transition across the precordium qR aVL	Normal
LPFB	<0.12 sec (120 msec)	+90 to +180 degrees	Delayed transition across the precordium rS I, aVL qR in III, aVF	Normal
RBBB	≥0.12 sec (120 msec)	Normal	rsr′, rsR′, rSR′ in V_1 (and usually V_2); wide S in V_6 and I	Discordant in V_1 and V_2
RBBB with LAFB	≥0.12 sec (120 msec)	−45 to −90 degrees	rsr′, rsR′, rSR′ in V_1 (and usually V_2); wide S in V_6 and I	Discordant in V_1 and V_2
RBBB with LPFB	≥0.12 sec (120 msec)	+90 to +180 degrees	rsr′, rsR′, rSR′ in V_1 (and usually V_2); wide S in V_6 and I	Discordant in V_1 and V_2
LBBB	≥0.12 sec (120 msec)	Variable	rS or QS in V_1 (S wide and notched); wide notched R without q in V_5, V_6, and I Wide notched R with or without small q in aVL	Discordant in V_1 to V_6

LAD = left axis deviation; LAFB = left anterior fascicular block; LBBB = left bundle branch block; LPFB = left posterior fascicular block; RBBB = right bundle branch block.

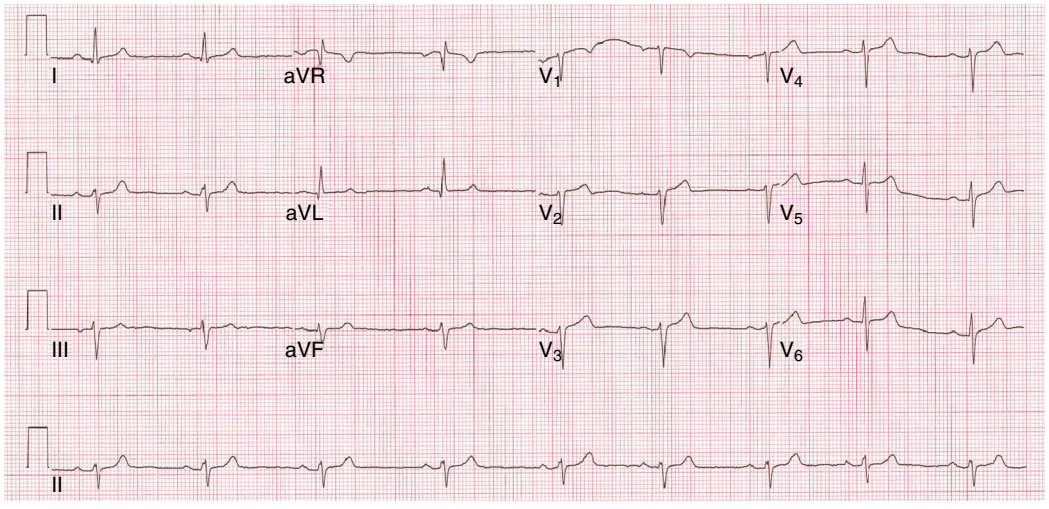

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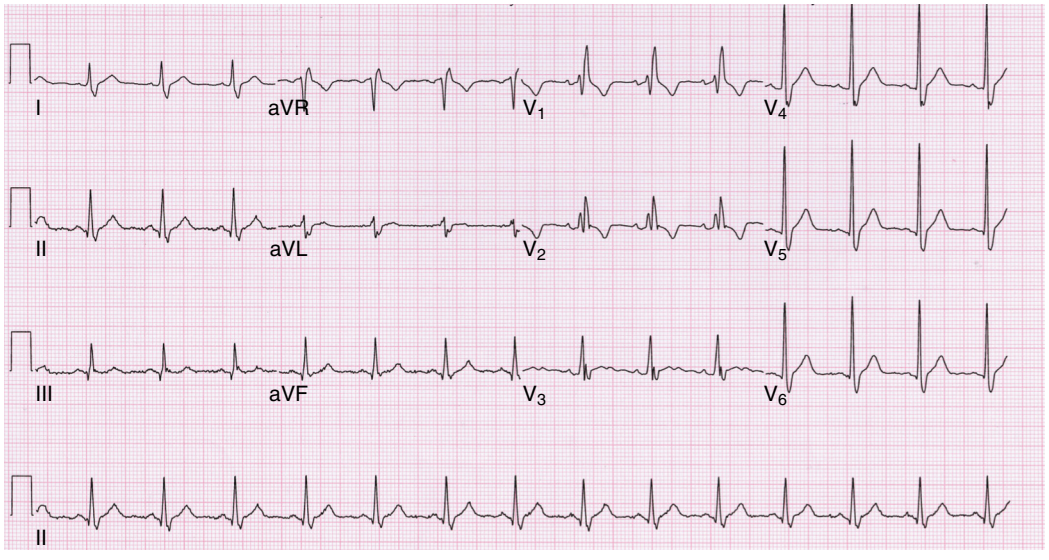

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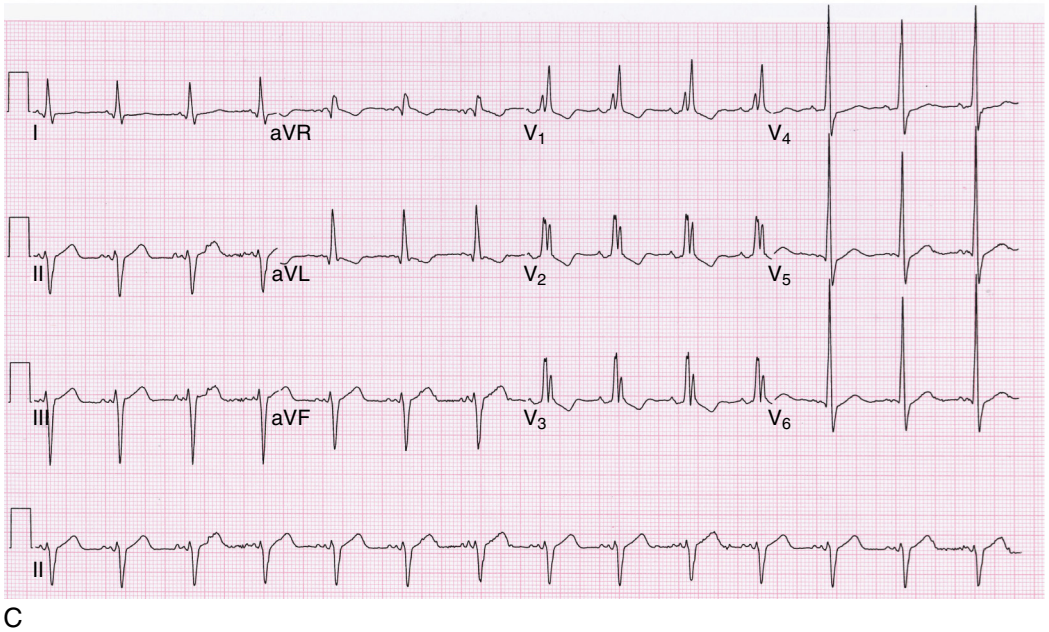

C

FIGURE 42-5. Fascicular and bundle branch blocks. A, Left anterior fascicular block (LAFB). Left axis deviation is present; the axis is approximately −60 degrees. The QRS duration is normal, and there is a delay in R wave progression across the precordial leads (late transition). Small q waves are present in leads I and aVL and small r waves in leads II, III, and aVF. **B,** Right bundle branch block (RBBB). The QRS is widened, with an rsR′ pattern in lead V_1 and a wide terminal S wave in lead V_6. ST segments are downsloping, and T waves are discordant with the QRS complex in the right precordial leads. The axis is normal, and signs of normal septal activation (q waves in lead V_6) are present. **C,** RBBB and LAFB. In addition to features diagnostic of RBBB, an axis of −60 degrees is present.

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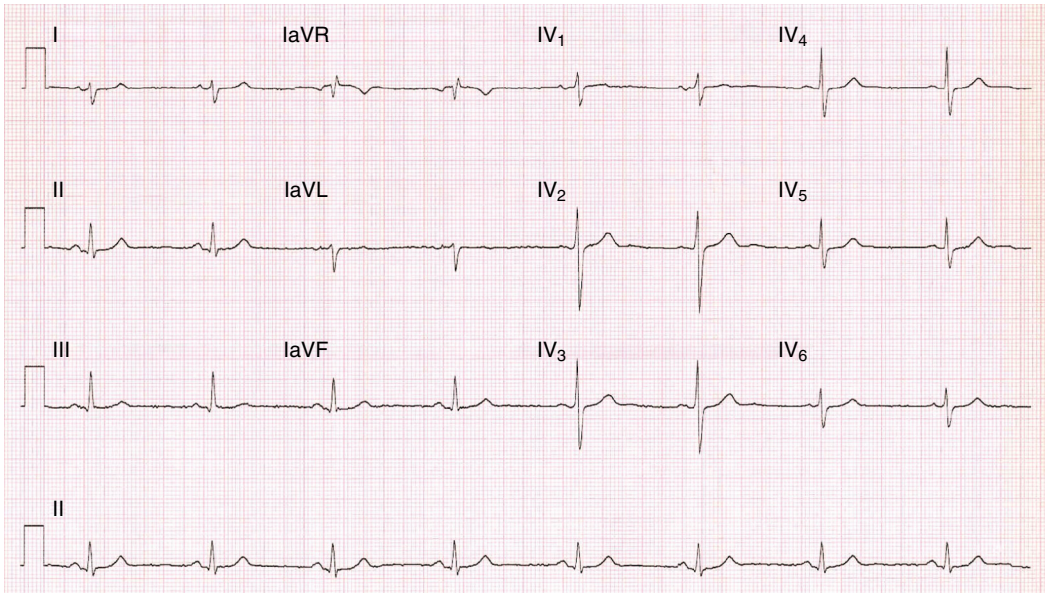

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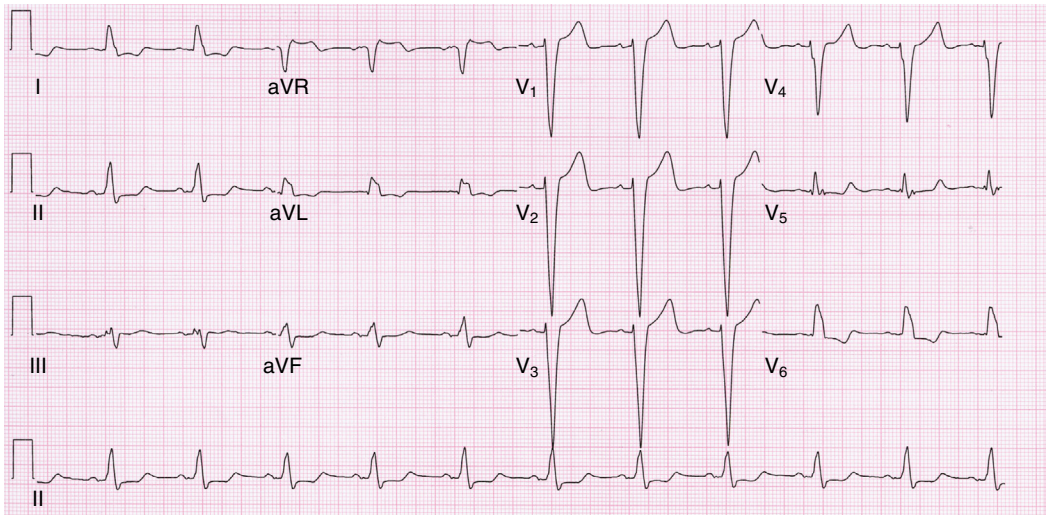

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FIGURE 42-5, cont'd. **D, Left posterior fascicular block (LPFB). Right axis deviation (+120 degrees) is present. QRS duration is normal, and R wave progression across the precordial leads is delayed. Leads I and AVL have rS complexes, and the inferior leads have insignificant q waves. E, Left bundle branch block (LBBB). The QRS is widened, with a broad, notched complex in leads I, aVL, and the left precordial leads. Small r waves and broad, deep S waves are present in the right precordial leads. With LBBB, the axis is usually normal or deviated to the left. ST segments and T waves are discordant with the QRS complex throughout the precordium.**

Chamber Hypertrophy

A number of criteria for defining left ventricular hypertrophy (LVH; Fig. 42-6) and right ventricular hypertrophy (RVH) have been proposed. All of the LVH criteria suffer from poor sensitivity (ranging from 30 to 50%), although the specificity is reasonable (85 to 95%). The Cornell voltage criterion, developed with an echocardiographic standard for LVH, simply adds the S wave amplitude in V_3 and the R wave amplitude in aVL; a total greater than 2.0 mV in women and 2.8 mV in men implies LVH. In many clinical settings, the Cornell criterion has replaced the more complicated Romhilt-Estes criteria, which assign points for QRS amplitude, repolarization abnormalities ("strain" pattern), left axis deviation, and other electrocardiographic features. These criteria adjusted for body weight also appear to be the preferred method for detecting LVH in obese individuals. RVH is much less common than LVH. Electrocardiographic criteria for diagnosing RVH have even lower sensitivity (10 to 20%) than for LVH, although the specificity is similar. The Sokolow-Lyon criterion for RVH adds the R wave amplitude in V_1 to the S wave amplitude in lead V_5 or V_6; a sum of 1.05 mV or greater implies RVH.

Low QRS Voltage

Low QRS voltage is defined as limb lead voltage less than 5 mm (0.5 mV) in all leads or precordial voltage less than 10 mm (1 mV) in all leads. The differential diagnosis is broad (Table 42-4), and many patients will not have a clinically apparent underlying explanation.

Repolarization Abnormalities

Abnormalities of the ST segment or T waves, or both, are extremely common (Table 42-5). T waves may be in the same direction (concordant) with the QRS complex or discordant. Electrolyte and other metabolic abnormalities, drug effects (particularly digoxin and antiarrhythmic drugs), and secondary effects caused by LVH, bundle branch block, or pacing are all commonly encountered. Abnormal depolarization patterns frequently beget abnormal repolarization.

Early repolarization, which is a relatively common pattern of ST segment elevation and which was previously thought to be benign, occurs more commonly in patients who have idiopathic ventricular fibrillation compared with controls and also has been associated with an increased relative risk of cardiac mortality. The absolute risk of sudden death in apparently healthy patients with the early repolarization pattern remains quite low, however. Whether the "early repolarization syndrome" is a distinct arrhythmic syndrome or a predisposing factor in patients with other arrhythmic substrate(s) is unclear.

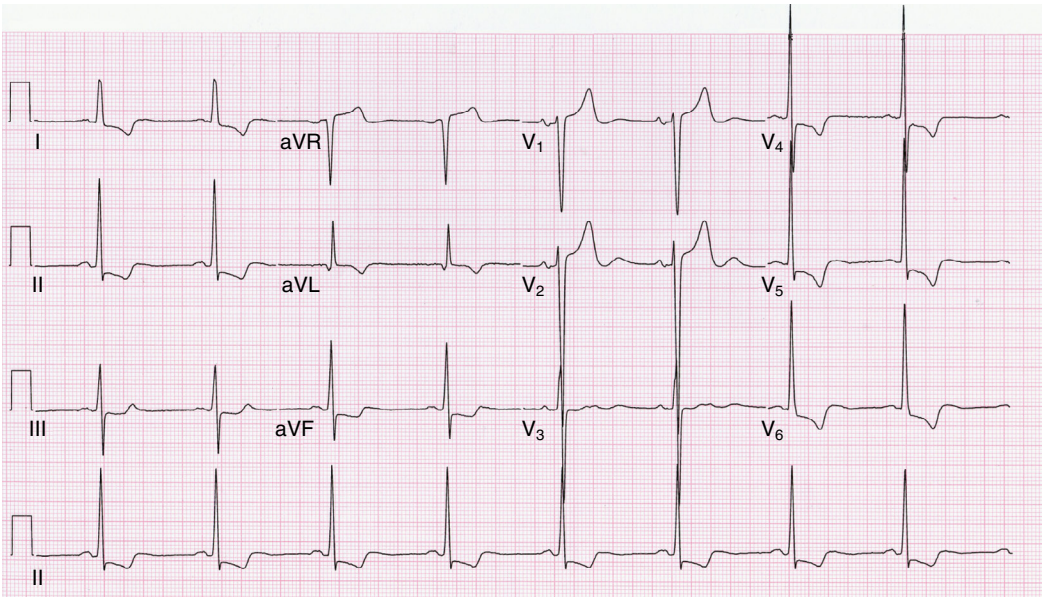

FIGURE 42-6. Left ventricular hypertrophy. Note the striking S wave amplitude in the right precordial leads and R wave amplitude in the left precordial leads. Repolarization abnormalities are present in the left precordial leads, as well as the limb leads. The S wave amplitude in V_3 (2.4 mV) plus the R wave amplitude in aVL (1.0 mV) total 3.4 mV, easily satisfying the Cornell voltage criteria in this 76-year-old hypertensive man. Sinus bradycardia (50 beats per minute) is present as well.

TABLE 42-4 CAUSES OF LOW QRS VOLTAGE

Normal variant
Pericardial effusion
Myocardial infarction
Cardiomyopathy
Hypothyroidism
Obesity
Sarcoidosis
Amyloidosis
Chronic obstructive pulmonary disease
Anasarca

TABLE 42-5 CAUSES OF REPOLARIZATION ABNORMALITIES

Athlete's heart
Early repolarization (normal variant)
Myocardial ischemia/injury
Pericarditis
Electrolyte abnormalities
Left ventricular hypertrophy
Intraventricular conduction delay/bundle branch block
Drug effects (digitalis, antiarrhythmic drugs, etc.)
Long QT syndrome
Stroke/neurologic catastrophe

TABLE 42-6 GENERALLY BENIGN FINDINGS IN ATHLETES' ECGS

Sinus arrhythmia, sinus bradycardia, wandering atrial rhythm, junctional rhythm
First-degree AV block
Mobitz I (Wenckebach) second-degree AV block
Incomplete RBBB
Isolated voltage criteria for LVH (without repolarization abnormalities, left axis deviation, left atrial abnormality, pathologic Q waves, etc.)
Early repolarization pattern

COMPUTERIZED ELECTROCARDIOGRAPHIC READINGS

Automatic computerized ECG interpretations are generally accurate for calculating heart rates, axes, and intervals, but most if not all such systems require over-reading by a physician who will also compare the current ECG to older ECGs. In one large study of patients who received a prehospital ECG, automated interpretation for ST elevation MI (STEMI) had sensitivity and specificity of about 93% and 99%, respectively. False-positive interpretations were due primarily to artifact and nonischemic causes of ST elevation; false-negatives were rare, but related primarily to algorithmic shortcomings. Another study comparing three automated algorithms, however, reported much lower sensitivities and specificities. However, computerized readings are not reliable for diagnosis of rhythm disturbances,[3] and an over-reading by a physician remains mandatory to confirm the cardiac rhythm.

Despite these current limitations, emerging artificial intelligence systems are more accurate than cardiologists with regard to a number of ECG characteristics, such as timing intervals, P-wave morphology, QRS morphology, and left ventricular hypertrophy.[4,5] For example, artificial intelligence ECG analysis can diagnose left ventricular systolic dysfunction in patients who present with dyspnea,[6] predict which patients are at risk for developing atrial fibrillation or ischemic stroke,[7,8] and diagnose hypertrophic cardiomyopathy. These and other enhancements are likely to revolutionize ECG reading in the future.

ELECTROCARDIOGRAMS IN ATHLETES

Extensive physical training leads to structural, electrophysiologic, and autonomic adaptations that can appear abnormal on an uninformed ECG reading.[9] Among the most important are rhythms suggesting hypervagotonia, early repolarization, and increased chamber size (Table 42-6 and Fig. 42-7). Differentiation between physiologic adaptations to exercise and potentially life-threatening abnormalities can be difficult and often requires expert consultation. The early repolarization pattern is seen frequently in athletes and may not necessarily imply significant risk in this setting.

ELECTROCARDIOGRAM IN CORONAVIRUS-19 DISEASE

Patients with coronavirus-19 disease (COVID-19; Chapter 336) may have a variety of tachyarrhythmias related to fever, hypoxia, and myocardial

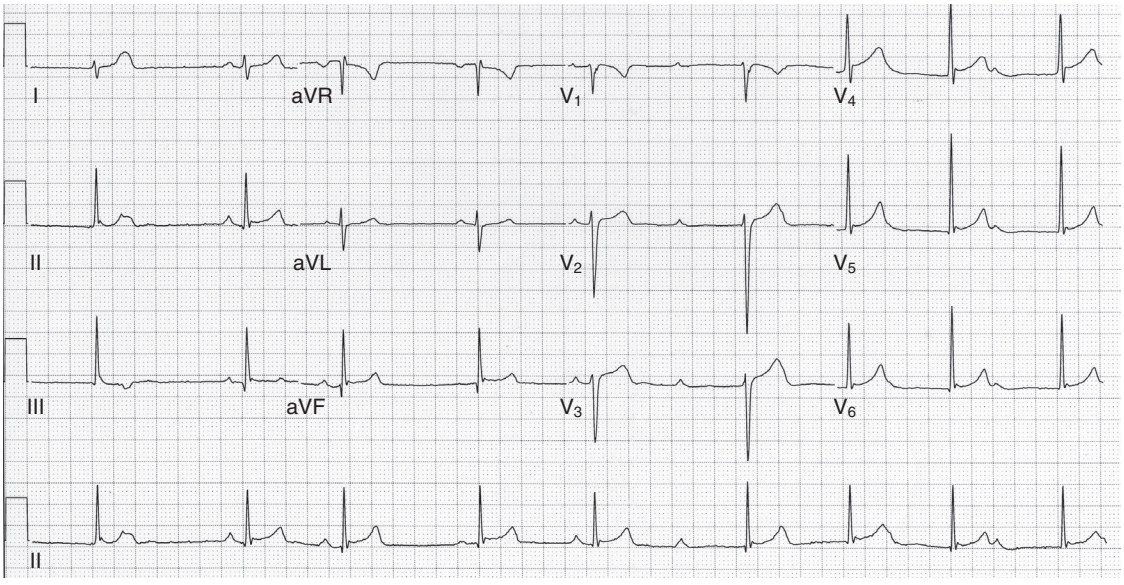

FIGURE 42-7. Athlete's heart. Bradycardia, variable P wave morphology, Mobitz I (Wenckebach) second-degree AV block, and junctional escape beats all reflect hypervagotonia in this thin, 18-year-old athlete. Mild right axis deviation is present, not uncommon in adolescents and young adults. Prominent S waves are present in leads V_2 and V_3, though formal voltage criteria for LVH are absent. Note sinus P waves following junctional beats that are blocked; this is not abnormal physiology.

involvement. New-onset atrial fibrillation (Chapter 52), QT-interval prolongation, ST-segment and T-wave changes, and ventricular arrhythmias (Chapter 53) are associated with a poorer prognosis, although they likely are markers of a poor prognosis rather than mediators.[10,11]

SCREENING ELECTROCARDIOGRAMS

Though frequently recommended by cardiologists and primary care physicians, screening ECGs and exercise ECGs (i.e., exercise stress test) have not been shown to improve outcomes in asymptomatic adults. The U.S. Preventive Services Task Force recommends against obtaining a screening resting or exercise ECG in asymptomatic adults who are at low risk of coronary heart disease events (Chapter 12).[A1,12] For asymptomatic adults at intermediate or high risk, evidence is insufficient to make a recommendation. The American College of Cardiology specifically recommends against performing pre-procedure ECG screening in low-risk, asymptomatic patients (Chapter 399).[13] Electrocardiographic screening of competitive athletes prior to participation remains controversial,[14] as does whether improved ECG interpretation should lead to reconsidering a screening ECG in the military.[15]

AMBULATORY ELECTROCARDIOGRAPHY

Ambulatory electrocardiography (Chapter 49) is used primarily to correlate symptoms, such as palpitations and light-headedness, with intermittent cardiac arrhythmias. Wearable devices such as smartwatches to screen for arrhythmias, especially atrial fibrillation, can increase the ability to detect asymptomatic events by about 10-fold and can guide the institution of prophylactic anticoagulant treatment, with about a 1% net absolute benefit in persons age 75 years after 7 years of follow-up.[A2] The reliability and validity of wearable devices to detect myocardial ischemia is less proven.[16]

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For the General References and other additional features, please visit Elsevier eBooks+ at https://ebooks.health.elsevier.com.

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43 ECHOCARDIOGRAPHY

CATHERINE M. OTTO

Echocardiography is the clinical standard for evaluation of cardiac function in patients with known or suspected heart disease.[1] This chapter reviews the basic principles of echocardiography, standard imaging approaches, quantitative measurements, and clinical indications.[2,3] The specific indications for echocardiography and additional echocardiographic images are presented in other chapters on individual types of cardiovascular diseases.

ECHOCARDIOGRAPHIC IMAGING PRINCIPLES

Echocardiography is based on the use of a piezoelectric crystal that converts electrical to mechanical energy, and vice versa, allowing both transmission and reception of an ultrasound signal. The frequency of ultrasound waves used for diagnostic imaging ranges from 2 to 10 MHz, with lower frequencies having greater tissue penetration and higher frequencies providing better image resolution. Each transducer consists of a complex array of piezoelectric crystals arranged to provide images in a fanlike two- or three-dimensional image, with the narrow top of this sector scan indicating the origin of the ultrasound signal. Transducers also include an acoustic lens that determines the focal depth, height, and width of the ultrasound beam.

Images are generated on the basis of the reflection of ultrasound from acoustic interfaces, for example, the boundary between the blood in the left ventricle and the myocardium. The time delay between transmission and reception is used to determine the depth of origin of the ultrasound reflection. The depths of the reflected signals from multiple ultrasound beams are combined to generate an image. The speed of signal analysis allows acquisition of two-dimensional images at slower frame rates. Ultrasound is strongly attenuated by bone and air, so echocardiography relies on acoustic "windows," where ultrasound can penetrate to the heart while avoiding the ribs and lungs. With transthoracic imaging, the patient is positioned to bring the cardiac structures close to the chest wall, usually in a left lateral decubitus position, and the transducer is placed on the chest, with use of gel to provide acoustic coupling between the transducer and skin. Standard transthoracic acoustic windows are parasternal, apical, subcostal, and suprasternal notch.

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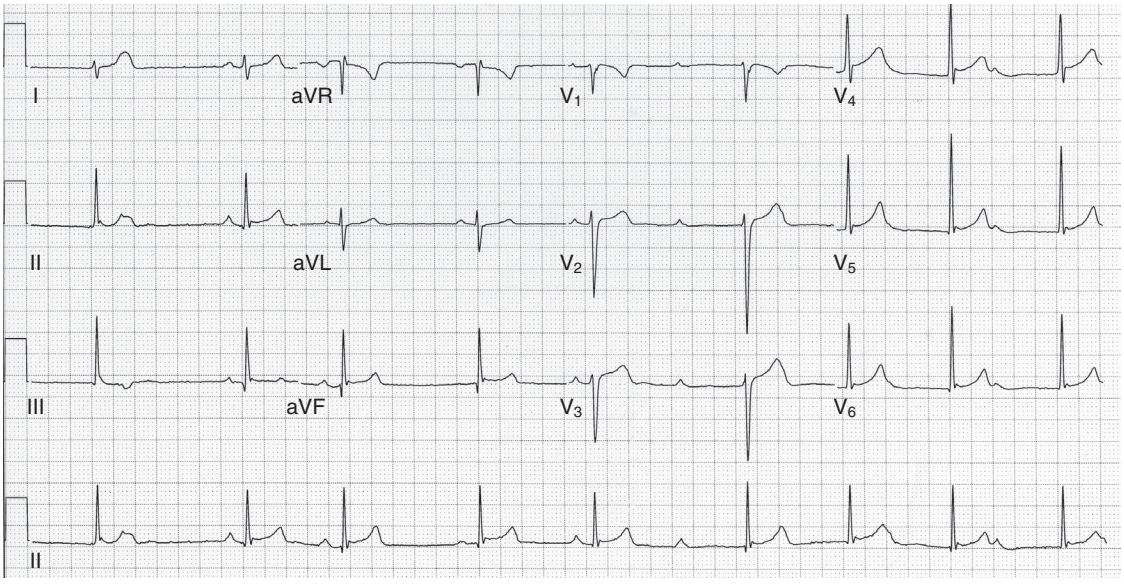

FIGURE 42-7. Athlete's heart. Bradycardia, variable P wave morphology, Mobitz I (Wenckebach) second-degree AV block, and junctional escape beats all reflect hypervagotonia in this thin, 18-year-old athlete. Mild right axis deviation is present, not uncommon in adolescents and young adults. Prominent S waves are present in leads V_2 and V_3, though formal voltage criteria for LVH are absent. Note sinus P waves following junctional beats that are blocked; this is not abnormal physiology.

involvement. New-onset atrial fibrillation (Chapter 52), QT-interval prolongation, ST-segment and T-wave changes, and ventricular arrhythmias (Chapter 53) are associated with a poorer prognosis, although they likely are markers of a poor prognosis rather than mediators.[10,11]

SCREENING ELECTROCARDIOGRAMS

Though frequently recommended by cardiologists and primary care physicians, screening ECGs and exercise ECGs (i.e., exercise stress test) have not been shown to improve outcomes in asymptomatic adults. The U.S. Preventive Services Task Force recommends against obtaining a screening resting or exercise ECG in asymptomatic adults who are at low risk of coronary heart disease events (Chapter 12).[A1,12] For asymptomatic adults at intermediate or high risk, evidence is insufficient to make a recommendation. The American College of Cardiology specifically recommends against performing pre-procedure ECG screening in low-risk, asymptomatic patients (Chapter 399).[13] Electrocardiographic screening of competitive athletes prior to participation remains controversial,[14] as does whether improved ECG interpretation should lead to reconsidering a screening ECG in the military.[15]

AMBULATORY ELECTROCARDIOGRAPHY

Ambulatory electrocardiography (Chapter 49) is used primarily to correlate symptoms, such as palpitations and light-headedness, with intermittent cardiac arrhythmias. Wearable devices such as smartwatches to screen for arrhythmias, especially atrial fibrillation, can increase the ability to detect asymptomatic events by about 10-fold and can guide the institution of prophylactic anticoagulant treatment, with about a 1% net absolute benefit in persons age 75 years after 7 years of follow-up.[A2] The reliability and validity of wearable devices to detect myocardial ischemia is less proven.[16]

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43 ECHOCARDIOGRAPHY

CATHERINE M. OTTO

Echocardiography is the clinical standard for evaluation of cardiac function in patients with known or suspected heart disease.[1] This chapter reviews the basic principles of echocardiography, standard imaging approaches, quantitative measurements, and clinical indications.[2,3] The specific indications for echocardiography and additional echocardiographic images are presented in other chapters on individual types of cardiovascular diseases.

ECHOCARDIOGRAPHIC IMAGING PRINCIPLES

Echocardiography is based on the use of a piezoelectric crystal that converts electrical to mechanical energy, and vice versa, allowing both transmission and reception of an ultrasound signal. The frequency of ultrasound waves used for diagnostic imaging ranges from 2 to 10 MHz, with lower frequencies having greater tissue penetration and higher frequencies providing better image resolution. Each transducer consists of a complex array of piezoelectric crystals arranged to provide images in a fanlike two- or three-dimensional image, with the narrow top of this sector scan indicating the origin of the ultrasound signal. Transducers also include an acoustic lens that determines the focal depth, height, and width of the ultrasound beam.

Images are generated on the basis of the reflection of ultrasound from acoustic interfaces, for example, the boundary between the blood in the left ventricle and the myocardium. The time delay between transmission and reception is used to determine the depth of origin of the ultrasound reflection. The depths of the reflected signals from multiple ultrasound beams are combined to generate an image. The speed of signal analysis allows acquisition of two-dimensional images at slower frame rates. Ultrasound is strongly attenuated by bone and air, so echocardiography relies on acoustic "windows," where ultrasound can penetrate to the heart while avoiding the ribs and lungs. With transthoracic imaging, the patient is positioned to bring the cardiac structures close to the chest wall, usually in a left lateral decubitus position, and the transducer is placed on the chest, with use of gel to provide acoustic coupling between the transducer and skin. Standard transthoracic acoustic windows are parasternal, apical, subcostal, and suprasternal notch.

ABSTRACT

Echocardiography is the clinical standard for evaluation of cardiac function. Imaging allows accurate diagnosis of structural heart disease and measurement of left ventricular ejection fraction. Doppler velocity data provide quantitative measures of cardiac output, diastolic function, valve stenosis and regurgitation, and congenital heart disease. Stress echocardiography is appropriate for diagnosis of coronary disease based on inducible wall motion abnormalities with stress. Transesophageal echocardiography is more accurate than transthoracic imaging for diagnosis of endocarditis, evaluation of prosthetic valves, and visualization of posteriorly located cardiac structures. Point-of-care echocardiography increasingly is used by many clinicians in the acute care setting but does not replace a complete diagnostic study for clinical decision making.

KEYWORDS

echocardiography
Doppler
stenosis
systolic function
diastolic function
regurgitation

STANDARD IMAGE PLANES

From the parasternal window, the image plane is adjusted manually by an experienced health care provider to obtain long and short axis views. Standard cardiac imaging planes are aligned relative to the axis of the heart, with the long axis defined as the plane that intersects the cardiac apex and the middle of the aortic valve. Short axis views are perpendicular to this long axis, with standard image planes at the cardiac base (aortic valve level), mitral valve, and midventricular levels. From the apical window, the transducer is rotated to provide three views oriented 60 degrees from each other, producing a four-chamber, a two-chamber, and a long axis view (Fig. 43-1; Video 43-1). These image planes also can be acquired with three-dimensional ultrasound transducers, which allow structures to be seen in a cutaway three-dimensional anatomic view or in reconstructed standard two-dimensional planes.

MEASUREMENTS

Echocardiography provides accurate cardiac dimensions and volumes from 3D and 2D recordings. The measurements typically provided include left ventricular end-diastolic and end-systolic chamber diameter and wall thickness, left atrial diameter or volume, and aortic sinus diameter. Left ventricular ejection fraction (EF) is determined from three-dimensional data sets or two orthogonal two-dimensional views (Figs. 43-2 and 43-3; Video 43-2). End-diastolic and end-systolic ventricular volumes (EDV and ESV, respectively) are calculated by validated formulas, and the EF is calculated as:

$$EF = (EDV - ESV)/EDV$$

LIMITATIONS

Echocardiography is an accurate, widely available imaging approach. In some patients, image quality may be suboptimal because of poor tissue penetration (e.g., excessive adipose tissue, position of the lungs relative to the heart), but images are nondiagnostic in less than 5% of patients. Reflections are stronger when the interface is perpendicular to the ultrasound beam, so structures that are parallel to the beam may not be visible, an artifact called *echo dropout*. This potential limitation is avoided by using multiple transducer positions and imaging planes. Ultrasound artifacts, such as beam width, shadowing, and reverberations, may be misinterpreted by inexperienced observers.

DOPPLER ECHOCARDIOGRAPHY

PRINCIPLES

Ultrasound energy that is backscattered from moving red blood cells is shifted to a higher frequency when the blood is moving toward the transducer and a lower frequency when it is moving away. The magnitude of this Doppler shift corresponds to the velocity of blood flow.

MODALITIES

Pulsed Doppler allows measurement of flow velocity at a specific intracardiac site with the advantages of high spatial and temporal resolution. However, spatial localization is based on intermittent sampling at a time interval corresponding to the depth of interest. The sampling frequency, which is depth dependent, limits the maximum detectable velocity because of a phenomenon called *signal aliasing*. Pulsed Doppler usually allows recording of normal intracardiac flow velocities, which are about 1 m/second.

Continuous-wave Doppler allows measurement of high velocities along the entire length of the ultrasound beam, but the origin of the high-velocity signal must be inferred from the two-dimensional images. With stenotic and regurgitant valves, blood flow velocities may be as high as 5 to 6 m/second, requiring the use of the continuous-wave Doppler mode. Both pulsed and continuous-wave Doppler velocities are displayed as a graph of velocity versus time, with the density of the spectral display corresponding to signal strength.

Color Doppler flow imaging is a modification of pulsed Doppler in which the flow velocity is displayed across a two-dimensional or three-dimensional image with a color scale to indicate direction and velocity. The advantage is a visually appealing display of intracardiac flow patterns. Disadvantages are low temporal resolution (frame rates of 10 to 30 per second) and poor velocity resolution due to signal aliasing.

Tissue Doppler uses the Doppler principle to record the velocity of motion of the myocardial wall. Tissue Doppler recordings of the myocardium adjacent to the mitral annulus are used to evaluate diastolic ventricular function. Speckle tracking strain imaging allows direct evaluation of myocardial mechanics (E-Fig. 43-1).

MEASUREMENTS

A standard echocardiographic study includes pulsed Doppler measurement of antegrade flow velocities (transmitral and transaortic), evaluation for valve regurgitation by continuous-wave and color Doppler modalities, and estimation

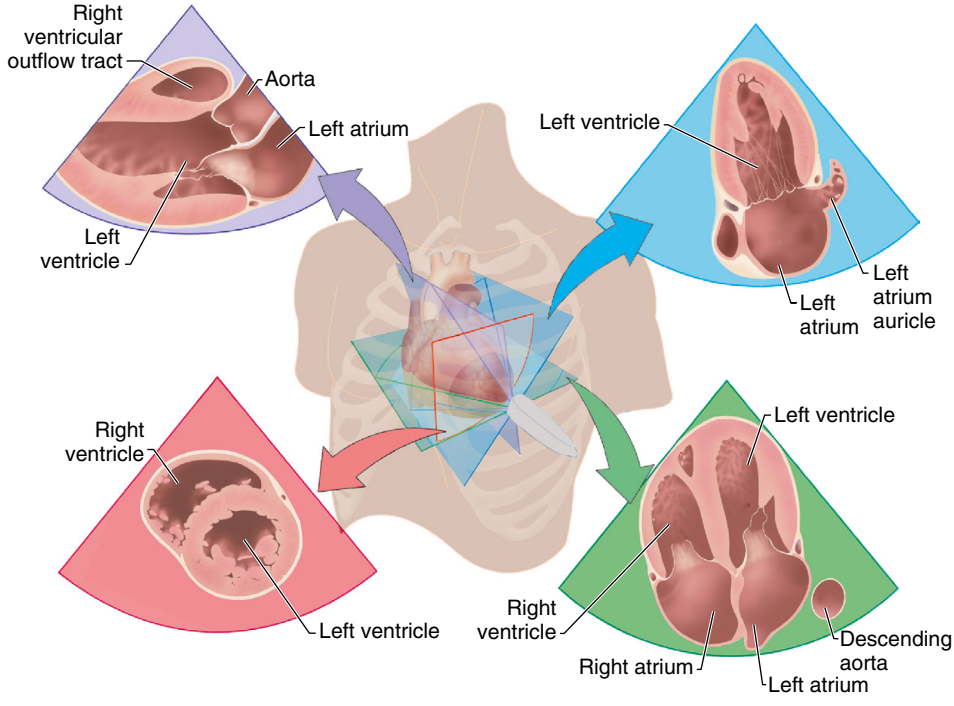

FIGURE 43-1. The four basic image planes used in transthoracic echocardiography. A parasternal transducer position, or "window," is used to obtain long and short axis views. The long axis view (*purple outline*) extends from the left ventricular apex through the aortic valve plane. The short axis view is perpendicular to the long axis view, resulting in a circular view of the left ventricle (*red outline*). The transducer is placed at the ventricular apex to obtain the two-chamber (*blue outline*) and four-chamber (*green outline*) views, each of which is about a 60-degree rotation from the long axis view and perpendicular to the short axis view. The four-chamber view includes both ventricles and both atria. The two-chamber view includes the left ventricle and left atrium; sometimes the atrial appendage is visualized. See Video 43-1. (From Otto CM. *Textbook of Clinical Echocardiography*. 6th ed. Philadelphia: Elsevier; 2018.)

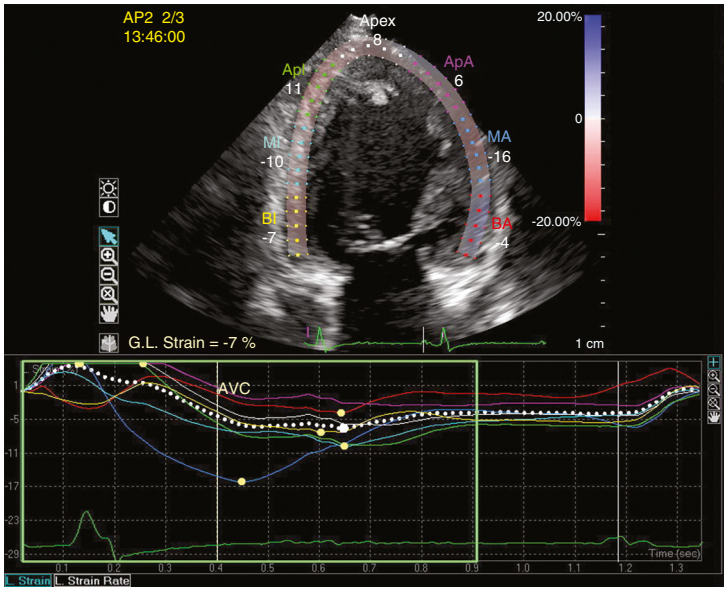

E-FIGURE 43-1. Speckle tracking strain imaging. In an apical four-chamber view, myocardial strain is calculated by the change in distance (divided by the original distance) between echogenic myocardial speckles for each segment as shown by the colored dots. The relationship of time (*x*-axis) with strain (*y*-axis) is shown in colors corresponding to the colors on the two-dimensional image, with global longitudinal strain shown in white. This image is from the same patient as in Figs. 43-2 and 43-3 and shows reduced (only 7%) global longitudinal strain (normal is −16% to −22%).

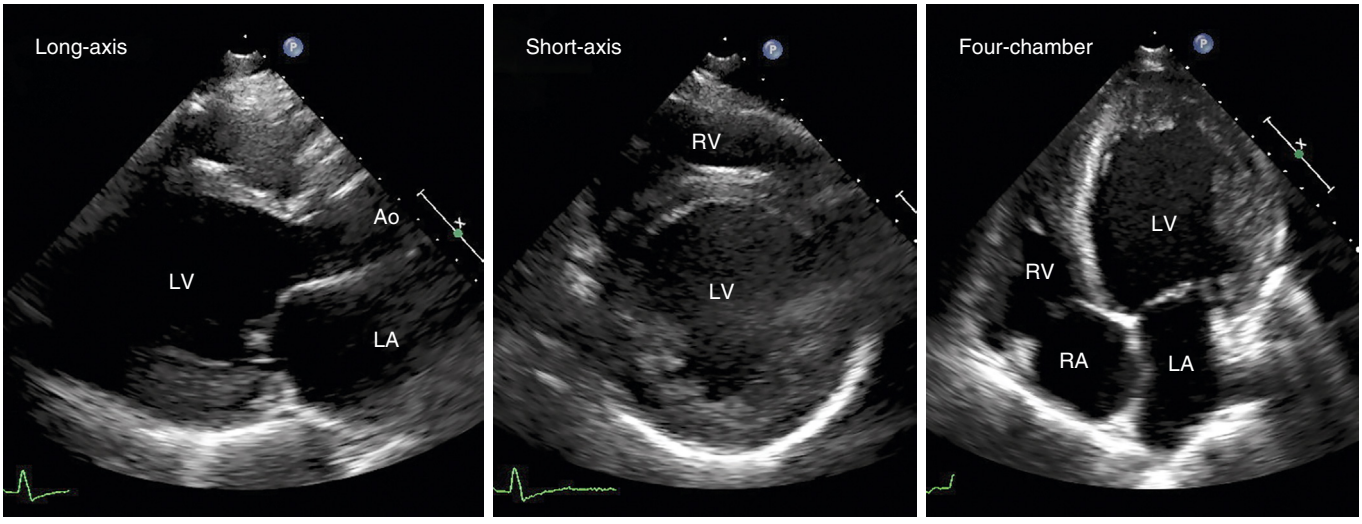

FIGURE 43-2. Dilated cardiomyopathy on echocardiography. This example shows severe left ventricular dilation and systolic dysfunction in standard image planes of the (A) parasternal long axis (*left*), (B) parasternal short axis (*center*), and (C) apical four chamber (*right*). Ao = aorta; LA = left atrium; LV = left ventricle; RA = right atrium; RV = right ventricle. See Video 43-2.

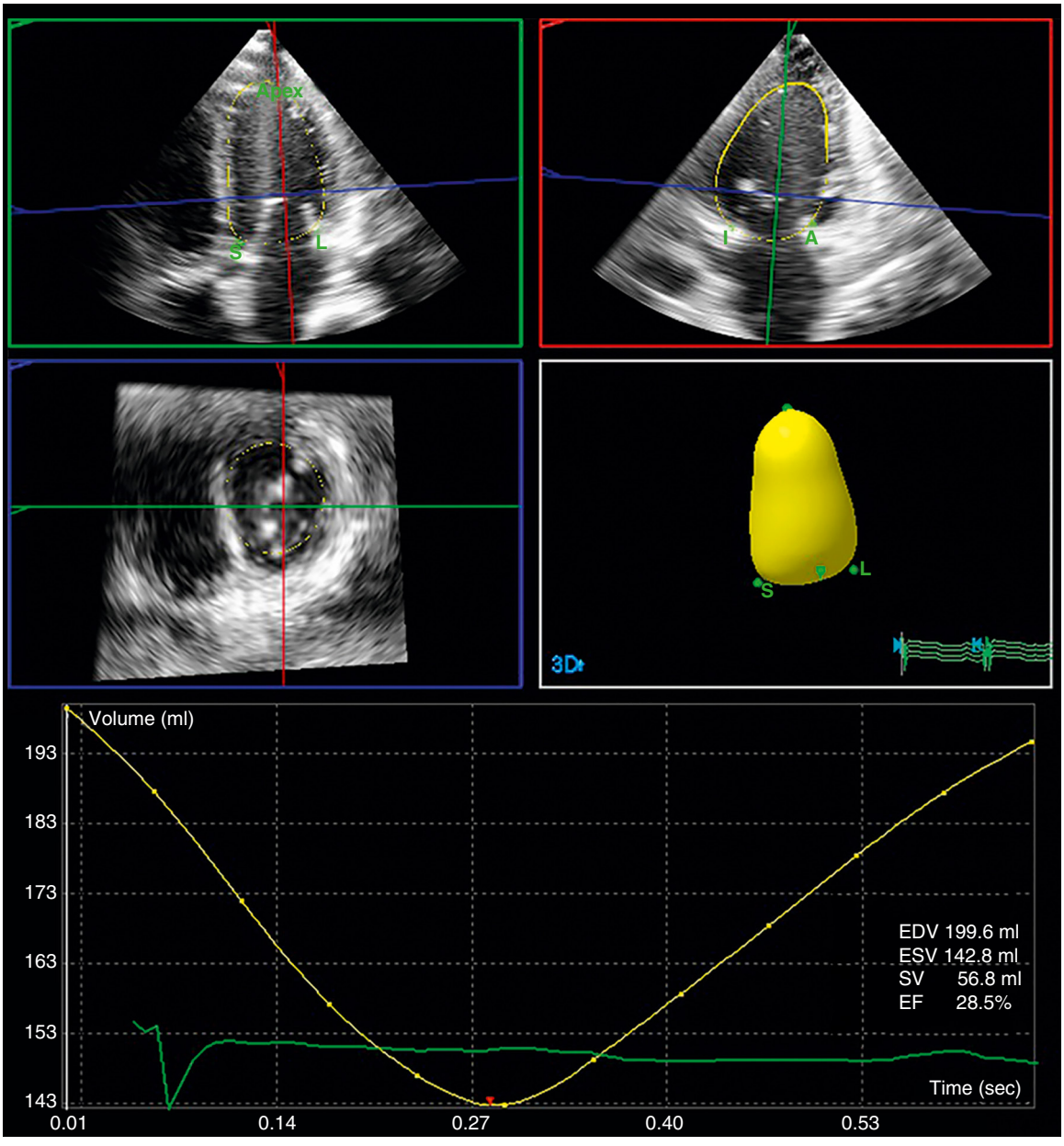

FIGURE 43-3. Three-dimensional echocardiographic measurement of left ventricular volumes and ejection fraction. Three-dimensional imaging shows the ventricle in four-chamber (*upper left*), two-chamber (*upper right*), and short axis (*lower left*) views derived from the three-dimensional image acquisition. The left ventricular chamber is reconstructed in the lower right. The ejection fraction is 28.5%.

of pulmonary systolic pressure based on the velocity of tricuspid regurgitation. Other Doppler measurements depend on the specific clinical indication.

Quantitative measurements using Doppler data are derived from two basic concepts: volume flow rate and the pressure-velocity relationship. Stroke volume (SV, in cubic centimeters) is calculated as the volume of a cylinder, where the base is the spatial cross-sectional area (CSA, in square centimeters) of flow, determined as the area of a circle from a two-dimensional diameter measurement. The height of the cylinder is the distance the average blood cell travels in one cardiac cycle, which is the velocity-time integral (VTI, in centimeters) of flow. Therefore,

$$SV\,(cm^3) = CSA\,(cm^2) \times VTI\,(cm)$$

This approach has been validated to measure transaortic, transmitral, and transpulmonic flow. Measurement of volume flow rate at two different intracardiac sites allows quantitation of intracardiac shunts and valvular regurgitation.

The relationship between the pressure gradient (ΔP) across a narrowing and the velocity (v) of blood flow is described by the simplified Bernoulli equation:

$$\Delta P = 4v^2$$

This equation calculates the maximum and mean gradients across stenotic valves, estimates pulmonary systolic pressure, and evaluates intracardiac hemodynamics with regurgitant valves.

ECHOCARDIOGRAPHIC APPROACHES

Transthoracic echocardiography is the standard clinical approach in most patients with suspected or known cardiac disease (Table 43-1). Advantages are that it is noninvasive, has no known adverse effects, and provides detailed data on cardiac anatomy and physiology. Limitations include poor image quality in some patients, limited visualization of structures distant from the transducer (e.g., atrial septum, left atrial appendage), and inability to visualize structures distal to prosthetic heart valves due to acoustic shadowing.

Transesophageal echocardiography offers superior image quality because of a shorter distance between the transducer and the heart, the absence of interposed bone or lung, and the use of a higher-frequency transducer (Table 43-2). Transesophageal echocardiography usually is well tolerated, but it entails some risk, because most clinicians do this procedure with the patient under moderate sedation. Transesophageal echocardiography is much more sensitive than transthoracic echocardiography for detection of left atrial thrombus (95% vs. 50%), valvular vegetations (99% vs. 60%), and prosthetic mitral valve regurgitation (Fig. 43-4).

Point-of-care ultrasound refers to the use of smaller, less expensive ultrasound systems carried by the physician to perform quick, limited examinations in the emergency department, at the inpatient bedside, or in the outpatient setting (Table 43-3).[4] Point-of-care echocardiography units range from pocket sized to laptop sized. Some are very simple, with only two-dimensional imaging and limited controls; other systems provide high-quality imaging and all Doppler modalities. Point-of-care imaging does not replace a complete echocardiogram but instead serves as an adjunct to the physical examination, particularly in the acute care setting, such as to distinguish ventricular dilation from a pericardial effusion, to estimate ventricular systolic performance, or to screen for aortic stenosis.

Contrast echocardiography may be performed with intravenous injection of agitated saline to opacify the heart chambers. These microbubbles are relatively large and do not pass through pulmonary capillaries. Therefore, appearance of contrast material in the left atrium within one or two beats after right heart opacification is consistent with an intracardiac shunt. Although blood flow occurs predominately from the left to right atrium for most atrial-level shunts, a small amount of right-to-left shunting, which is the basis of this approach, also occurs.

Contrast echocardiography also may be performed with commercially available microbubbles in the range of 1 to 5 μm. Because these microbubbles are smaller than the pulmonary capillaries, opacification of the right heart chambers is followed by opacification of the left ventricle, which can enhance the evaluation of systolic function when image quality is suboptimal, especially during stress echocardiography (Fig. 43-5).

Three-dimensional echocardiography is recommended to quantify left ventricular function and to evaluate complex structural heart disease. It also is essential to guide complex transcatheter interventions (Fig. 43-6; Video 43-3).

Stress echocardiography is a standard approach for evaluating patients with known or suspected coronary artery disease with a high sensitivity (85 to 95%) and specificity (80 to 90%).[5] Although myocardial infarction results in thinning and akinesis of the affected wall, resting myocardial function is normal in the absence of infarction, even when severe epicardial coronary disease is present. The increased myocardial demand associated with exercise or pharmacologic stress leads to myocardial ischemia, which results in a regional wall motion abnormality, often before the onset of chest pain or electrocardiographic changes (Fig. 43-7; Video 43-4).

In patients who can exercise, standard views of the left ventricle are recorded at baseline and immediately after maximal treadmill or bicycle exercise, with the rest and exercise images compared in a side-by-side format. Myocardial ischemia is present if resting wall motion is normal but hypokinesis or akinesis is seen after exercise. The pattern of regional wall motion accurately identifies the area of myocardium at risk and is reasonably reliable for identification of the affected coronary artery. With three-vessel coronary disease, rather than a regional wall motion abnormality, the only clue on imaging may be an absence of the expected decrease in chamber size at peak exercise, caused by diffuse ischemia. Interpretation of an exercise echocardiogram includes exercise duration, hemodynamic response, symptoms, and electrocardiographic changes in addition to the echocardiographic images.

TABLE 43-1 INDICATIONS FOR TRANSTHORACIC ECHOCARDIOGRAPHY IN PATIENTS WITH CARDIAC SIGNS OR SYMPTOMS AND IN THE ACUTE CARE SETTING

CARDIAC SIGNS AND SYMPTOMS
• Cardiac symptoms including chest pain, shortness of breath, palpitations, syncope/presyncope, TIA, stroke, or peripheral embolic event • Abnormal cardiac murmur (any diastolic murmur or systolic murmur grade 3 or louder) • Atrial fibrillation, SVT, VT, frequent or exercise-induced VPCs • Evaluation of pulmonary hypertension • Suspected infective endocarditis (native or prosthetic valve) with positive blood cultures or a new murmur
ACUTE CARE SETTING
• Hypotension or hemodynamic instability of suspected cardiac etiology • Acute chest pain with suspected MI but nondiagnostic ECG • Elevated cardiac biomarkers without other features of ACS • Suspected complications of acute MI • Evaluation of ventricular function after ACS • Respiratory failure of uncertain etiology • Guidance of therapy with acute pulmonary embolism

ACS = acute coronary syndrome; ECG = electrocardiogram; MI = myocardial infarction; SVT = supraventricular tachycardia; TIA = transient ischemic attack; VPCs = ventricular premature contractions; VT = ventricular tachycardia.
Modified from Otto CM. *Textbook of Clinical Echocardiography*. 6th ed. Philadelphia: Elsevier; 2018.

TABLE 43-2 INDICATIONS FOR TRANSESOPHAGEAL ECHOCARDIOGRAPHY AS THE INITIAL OR SUPPLEMENTAL TEST

• Suspected endocarditis with a moderate or high pretest probability (e.g., staphylococcal bacteremia, fungemia, prosthetic heart valve, or intracardiac device) • Suspected complications of endocarditis (e.g., abscess, fistula) • Suspected prosthetic mitral valve dysfunction • Evaluation of posterior structure (e.g., atrial baffles) in patients with congenital heart disease • Evaluation of patients with atrial fibrillation or flutter to facilitate clinical decision making with regard to anticoagulation, cardioversion, or radio frequency ablation • Evaluation for cardiac source of embolus with no identified source on TTE • Evaluation of valve structure and function to evaluate suitability for surgical or transcatheter valve interventions • Suspected acute aortic disease, including dissection and transection (although CT preferred for this indication) • Guidance for transcatheter interventions for structural heart disease, such as closure of a patent foramen ovale or atrial septal defect, or transcatheter edge-to-edge repair for valve regurgitation • Reevaluation for interval changes compared with prior TEE when a change in therapy is anticipated

CT = computed tomography; PFO/ASD = patent foramen ovale/atrial septal defect; TEE = transesophageal echocardiography; TTE = transthoracic echocardiography.
Modified from Otto CM. *Textbook of Clinical Echocardiography*. 6th ed. Philadelphia: Elsevier; 2018.

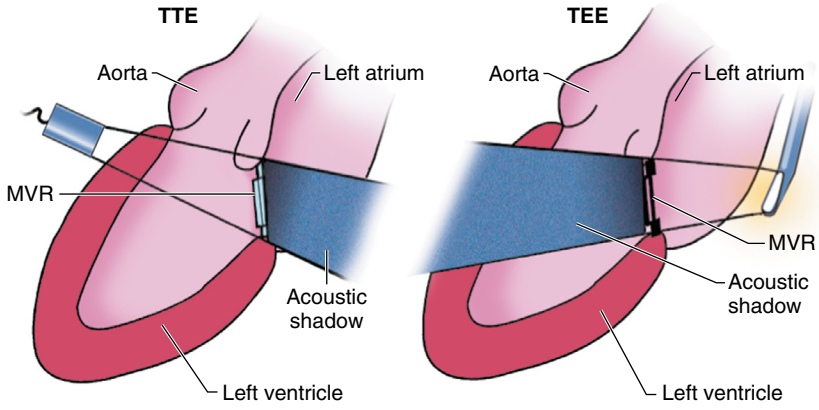

FIGURE 43-4. **The problem of acoustic shadowing from a prosthetic mitral valve replacement (MVR).** ***Left***, **With transthoracic echocardiography (TTE), the acoustic shadow distal to the prosthetic valve obscures the left atrium, limiting assessment of valve regurgitation by Doppler techniques.** ***Right***, **With transesophageal echocardiography (TEE), the left atrium now can be evaluated for valvular regurgitation. However, the acoustic shadow now obscures the left ventricle. (From Otto CM.** ***Textbook of Clinical Echocardiography*****. 5th ed. Philadelphia: Elsevier; 2018.)**

TABLE 43-3 INDICATIONS FOR POINT-OF-CARE ECHOCARDIOGRAPHY

Urgent clinical evaluation (emergency department or intensive care unit)
- Left ventricular size (volume status) and systolic function
- Right ventricular size and systolic function
- Pericardial effusion/tamponade

Screening at-risk populations (athletes, rheumatic heart disease, etc.)
Frequent serial exams for known abnormality (e.g., response to heart failure therapy)

In patients who are unable to exercise, stress testing can be performed with a graded intravenous infusion of dobutamine, beginning at 5 to 10 μg/kg/minute and gradually increasing to a maximum dose of 40 μg/kg/minute. If needed, atropine is used to achieve 85% of the maximum predicted heart rate. In addition to evaluation for myocardial ischemia, myocardial viability is evidenced by an improvement in endocardial motion from baseline to low-dose dobutamine, with subsequent worsening of function at higher doses—the "biphasic" response.

Intracardiac echocardiography is performed with an ultrasound probe on a catheter that is inserted into the right side of the heart through the femoral vein. Intracardiac echocardiography is used in the cardiac catheterization laboratory to guide percutaneous closure of a patent foramen ovale (PFO) and other procedures. In the electrophysiology laboratory, intracardiac echocardiography can help guide catheter positioning and identify complications.

CARDIAC FUNCTION MEASUREMENTS

In addition to qualitative descriptions of cardiac anatomy and physiology, echocardiography provides precise and accurate quantification of cardiac function (including ventricular systolic and diastolic function), the severity of valve stenosis and regurgitation, and a noninvasive estimate of pulmonary pressures.[6]

SYSTOLIC VENTRICULAR FUNCTION

Left ventricular volumes and ejection fractions are routinely measured by two-dimensional biplane or three-dimensional imaging approaches. When actual measurements are not possible, overall left ventricular systolic function is graded by visual estimation, with an approximate correspondence to EF as follows: normal (EF > 55%), mildly reduced (EF, 40 to 55%), moderately reduced (EF, 20 to 40%), and severely reduced (EF < 20%). Cardiac output calculations are not routine but may be helpful for noninvasive monitoring of therapy in patients with heart failure. Because EF measurements are affected by preload and afterload, measures that are less dependent on loading conditions, including the end-systolic dimension or volume, are generally preferred for clinical decision making in situations such as the timing of surgery for chronic valvular regurgitation.

Speckle tracking strain imaging is less load-dependent than standard imaging and allows evaluation of global and regional ventricular function. A reduction in global longitudinal strain may be seen before a detectable reduction in the ejection fraction in patients with inherited cardiomyopathies or after treatment with cardiotoxic chemotherapy.[7]

Quantitative evaluation of right ventricular function by echocardiography is difficult because of the complex shape of the chamber. Useful measurements include the basal diameter, the tricuspid annular plane systolic excursion, and the systolic Doppler tissue velocity at the annulus. Cardiac magnetic resonance imaging provides more accurate quantitation of right ventricular volumes and function when it is clinically needed.

DIASTOLIC VENTRICULAR FUNCTION

Evaluation of diastolic ventricular function is challenging because the patterns of ventricular filling are affected by preload, heart rate, and coexisting valvular regurgitation in addition to the diastolic properties of the ventricle. However, echocardiography can classify diastolic function on the basis of the combination of left ventricular inflow, pulmonary vein flow, tissue Doppler velocities, and isovolumic relaxation time. An estimate of left ventricular filling pressure (e.g., left ventricular end-diastolic pressure) also can be inferred by these approaches.

VALVULAR STENOSIS

Echocardiography is the clinical standard for evaluating patients with known or suspected valvular heart disease and is far more accurate than cardiac auscultation for diagnosis.[8] When significant valvular stenosis is a concern but echocardiography is not diagnostic or seems discordant with other clinical information, measurement of valve calcification by computed tomography (Chapter 44) or of a serum brain natriuretic protein level may be helpful. In current practice, cardiac catheterization is rarely performed to diagnose the severity of valve stenosis, although coronary arteriography may be indicated before valve surgery to evaluate the coronary anatomy and to determine whether concomitant myocardial revascularization may be indicated (Chapter 56).

In patients with aortic stenosis, the most direct measure of stenosis severity is the antegrade velocity across the valve, indicating mild (<3 m/second), moderate (3 to 3.9 m/second), or severe (≥4 m/second) valve obstruction. The maximum and mean transaortic pressure gradients also can be calculated by the Bernoulli equation. Accurate evaluation depends on a careful examination by an experienced echocardiographer.

Aortic valve area (AVA) is calculated by the continuity equation, based on the concept that volume flow rates proximal to and within the narrowed orifice are equal:

$$AVA \times VTI_{AS} = CSA_{LVOT} \times VTI_{LVOT}$$

or

$$AVA = (CSA_{LVOT} \times VTI_{LVOT}) / VTI_{AS}$$

where LVOT is left ventricular outflow tract, VTI is velocity-time integral, CSA is cross-sectional area, and AS is aortic stenosis (Fig. 43-8). It is especially important to calculate the AVA when left ventricular systolic dysfunction accompanies aortic valve disease. In some patients, low-dose dobutamine stress echocardiography is helpful in distinguishing ventricular dysfunction caused by severe aortic stenosis from primary myocardial disease with concurrent moderate stenosis.

The evaluation of mitral stenosis (see Fig. 60-4) focuses on the calculation of valve area, both from direct planimetry of the area of the orifice on three-dimensional or two-dimensional images and from the deceleration slope of the

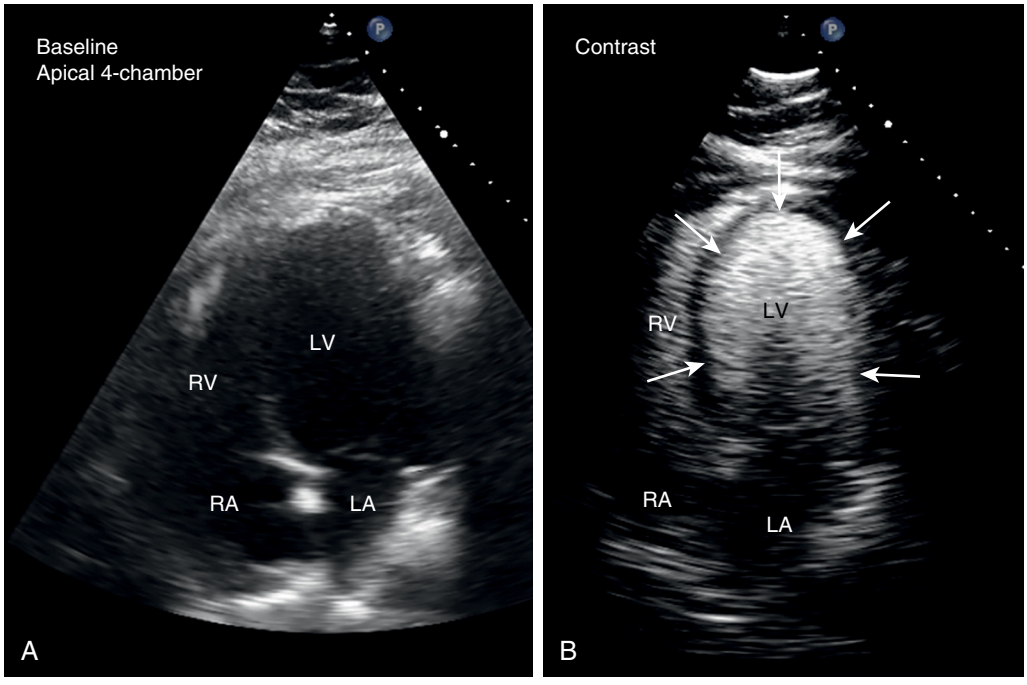

FIGURE 43-5. **Poor-quality apical view (A) with marked improvement in definition of the left ventricular cavity after opacification by contrast echocardiography (B).** The arrows indicate improved identification of the left ventricular endocardial border for calculation of ejection fraction. LA = left atrium; LV = left ventricle; RA = right atrium; RV = right ventricle.

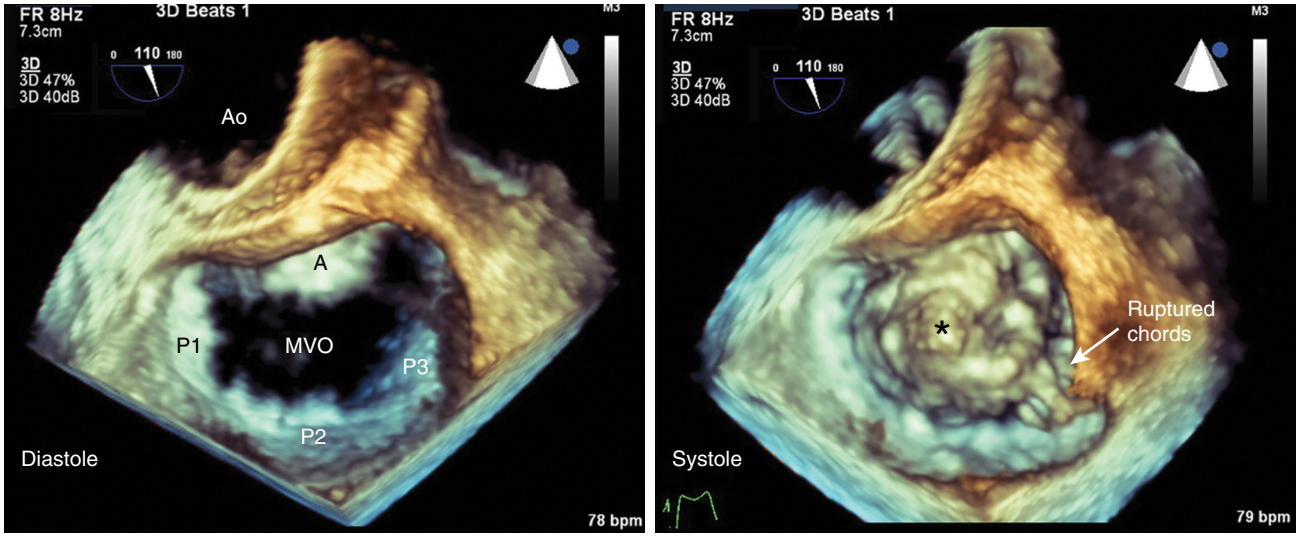

FIGURE 43-6. **The surgeon's three-dimensional view of the mitral valve from the left atrial side of the valve with the aortic valve at the top of the image.** In diastole, the anterior (A) leaflet and posterior leaflet (with P1, P2, and P3 scallops) are seen in the open position, with the normal mitral valve orifice (MVO). In systole (B), severe prolapse of the anterior leaflet is seen, particularly one bulging section (*asterisk*), and a flail segment with two small ruptured chords (*arrow*) is well visualized. These abnormalities cause severe, posteriorly directed mitral regurgitation. Ao = aorta. See Video 43-3. (From Otto CM. *Textbook of Clinical Echocardiography*. 6th ed. Philadelphia: Elsevier; 2018.)

Doppler curve (pressure half-time method). The mean transmitral gradient, which is dependent on the heart rate and volume flow rate as well as the severity of the stenosis, is not recommended to define the severity of mitral stenosis.

VALVULAR REGURGITATION

The current approach to evaluating valvular regurgitation (see Figs. 60-5 and 60-8) is based on the proximal geometry of the regurgitant jet, with measurement of the narrowest jet width (vena contracta). When further quantification is needed, regurgitant volume, regurgitant fraction, and regurgitant orifice area are calculated. Although color flow visualization of the flow disturbance may be helpful for detecting regurgitation and for understanding the mechanism of valve dysfunction, this approach should no longer be used to evaluate severity.

For aortic regurgitation, a narrow vena contracta (<3 mm) indicates mild regurgitation, whereas a wide vena contracta (>6 mm) indicates severe regurgitation. Additional evaluation of the severity of aortic regurgitation is based on the presence of holodiastolic flow reversal in the abdominal aorta and the density and slope of the continuous-wave Doppler velocity curve. The approach to evaluating mitral regurgitation (see Fig. 60-5) is similar, beginning with measurement of the vena contracta. In addition to calculation based on transmitral versus transaortic volume flow rates, the proximal acceleration of flow into the regurgitant orifice allows evaluation with central regurgitant jets based on the proximal isovelocity surface area method.

PULMONARY PRESSURES

Estimation of pulmonary artery systolic pressure (PAP) is a standard component of any echocardiographic study. The systolic pressure difference between the right ventricle and right atrium is calculated from the peak velocity in the tricuspid regurgitant (V_{TR}) jet, with use of the Bernoulli equation. Then, the right atrial pressure (RAP) is estimated from the size and appearance of the inferior vena cava. Because right ventricular and pulmonary artery systolic pressures are equal (in the absence of pulmonic stenosis),

$$PAP = 4(V_{TR})^2 + RAP$$

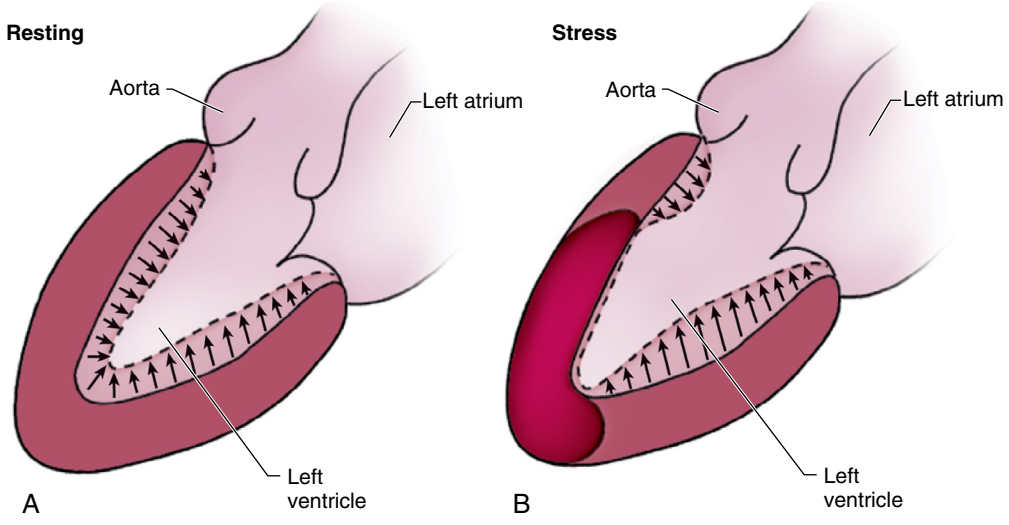

FIGURE 43-7. **The concept of stress echocardiography in a patient with 70% stenosis in the proximal third of the left anterior descending coronary artery.** At rest (A), endocardial motion and wall thickening are normal. After stress (B), either exercise or pharmacologic, the middle and apical segments of the anterior wall become ischemic, showing reduced endocardial wall motion and wall thickening. If the left anterior descending coronary artery extends around the apex, the apical segment of the posterior wall also will be affected, as shown here. The normal segment of the posterior wall shows compensatory hyperkinesis. See Video 43-4. (From Otto CM. *Textbook of Clinical Echocardiography*. 6th ed. Philadelphia: Elsevier; 2018.)

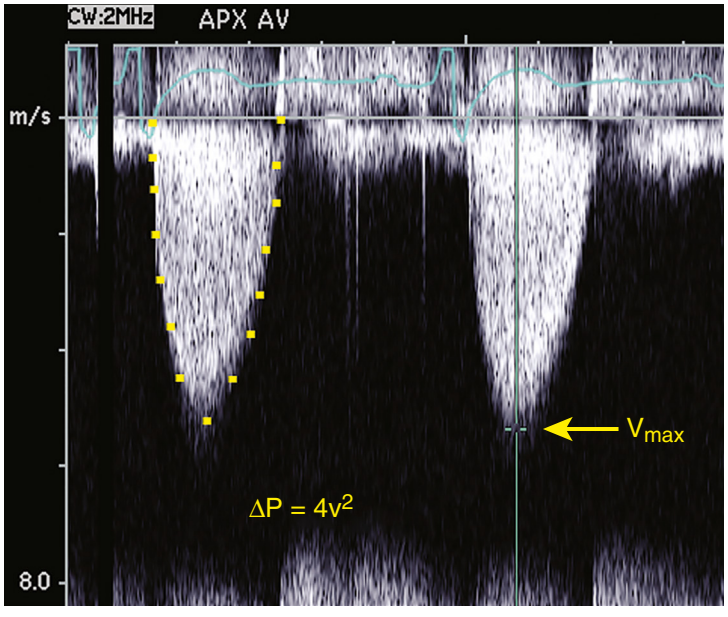

FIGURE 43-8. **In a patient with aortic stenosis, the aortic jet velocity is recorded with continuous-wave Doppler from the window that yields the highest-velocity signal.** Maximum velocity (V_{max}) is used to calculate the maximum systolic gradient. The Doppler curve is traced, as shown, to calculate the mean systolic gradient with the Bernoulli equation, by which the pressure gradient (ΔP) equals four times the square of the velocity.

A small amount of tricuspid regurgitation is present in most patients, so pulmonary pressures can be estimated with this approach in more than 90% of patients. Because this approach measures only pulmonary systolic pressure, not pulmonary vascular resistance, invasive evaluation may still be needed in some clinical situations (Chapter 69).

THE ECHOCARDIOGRAPHIC EXAMINATION

CLINICAL INDICATIONS

Currently, echocardiography is not recommended for screening of the general population in developed countries, but it is an effective approach to the initial evaluation of many cardiac signs and symptoms (Table 43-4),[9] with a better sensitivity than the clinical evaluation for detecting left ventricular dysfunction and valvular heart disease. Screening can also be effective in low-resource settings with a high prevalence of rheumatic heart disease.[10] A transthoracic examination is appropriate initially in most patients, although transesophageal imaging is needed for some specific diagnoses, such as concern for para-valvular abscess in patients with infected endocarditis and to exclude left atrial thrombosis before cardioversion (Chapter 52). Resting echocardiography is not helpful for diagnosis of coronary artery disease; stress imaging is needed if this diagnosis is suspected (Chapter 56). In patients with known cardiac disease, echocardiography is used to evaluate severity, to assess the results of medical and surgical interventions, and to guide procedures. Point-of-care ultrasound is useful for rapid screening to evaluate overall left ventricular function and to detect pericardial effusion (Fig. 43-9; Video 43-5).[11–13]

NORMAL FINDINGS

Trace to mild valve regurgitation is considered "physiologic" and is seen with 70 to 80% of mitral valves, 80 to 90% of tricuspid valves, and 70 to 80% of pulmonic valves in normal individuals. The prevalence of aortic regurgitation increases with age, but it is found in only 5% of young normal adults; the presence of aortic regurgitation raises the possibility of subtle aortic valve or root abnormalities.

A patent foramen ovale (Chapter 55) is present in 25 to 35% of normal individuals and may be identified by color Doppler or by contrast echocardiography. Use of the Valsalva maneuver enhances identification of a patent foramen ovale because the slight elevation in right atrial pressure may lead to a brief right-to-left shunt. The significance of a patent foramen ovale in patients without clinical events is unclear. Other common anatomic variants seen on echocardiography include aberrant chords (or "webs") in the left ventricle; small, linear, mobile echoes associated with the valves (Lambl's excrescences); and normal ridges in the left and right atria.

Unexpected abnormal findings also may be found on studies requested for other indications. A bicuspid aortic valve is present in 1 to 2% of the population; most of these patients are asymptomatic until late in life, so many cases are diagnosed "incidentally" by echocardiography. Aortic valve sclerosis, which is a frequent unexpected echocardiographic diagnosis, is a marker of cardiovascular disease and an increased risk of myocardial infarction even if valve function is normal.

INTEGRATING THE ECHOCARDIOGRAPHIC AND CLINICAL FINDINGS

The echocardiographic request should indicate the specific reason for the study and any relevant symptoms or signs. The echocardiographic examination then can be tailored to answer the clinical question.

The echocardiographic results should be interpreted in conjunction with other clinical data. If the echocardiographic data seem discrepant with the clinical data, the requesting physician should review the images with the echocardiographer to identify areas of uncertainty and to determine the next best diagnostic step.

TABLE 43-4 INDICATIONS FOR TRANSTHORACIC ECHOCARDIOGRAPHY (TTE) BY KNOWN DIAGNOSIS

CLINICAL DIAGNOSIS	KEY ECHOCARDIOGRAPHIC FINDINGS	LIMITATIONS OF ECHOCARDIOGRAPHY	ALTERNATIVE APPROACHES
VALVULAR HEART DISEASE (CHAPTER 60)			
Valve stenosis	Cause of stenosis, valve anatomy Transvalvular ΔP, valve area Chamber enlargement and hypertrophy LV and RV systolic function Associated valvular regurgitation	Possible underestimation of the stenosis severity Possible coexisting coronary artery disease	Cardiac catheterization; CMR
Valve regurgitation	Mechanism and cause of regurgitation Severity of regurgitation Chamber enlargement LV and RV systolic function PA pressure estimate	TEE may be needed to evaluate mitral regurgitant severity and valve anatomy (especially before MV repair)	Cardiac catheterization; CMR
Prosthetic valve function	Evidence for stenosis Detection of regurgitation Chamber enlargement Ventricular function PA pressure estimate	TTE is limited by shadowing and reverberations TEE is needed for suspected prosthetic MR due to "masking" of the LA on TTE	Cardiac catheterization; fluoroscopy
Endocarditis (Chapter 61)	Detection of vegetations (TTE sensitivity, 70-85%) Presence and degree of valve dysfunction Chamber enlargement and function Detection of abscess Possible prognostic implications	TEE more sensitive for detection of vegetations (>90%) A definite diagnosis of endocarditis also depends on bacteriologic criteria TEE more sensitive for detection abscess	Blood cultures and clinical findings also are diagnostic criteria for endocarditis
CORONARY ARTERY DISEASE			
Acute myocardial infarction (Chapters 57 and 58)	Segmental wall motion abnormality reflects "myocardium at risk" Global LV function (EF) Complications: Acute MR vs. VSD Pericarditis LV thrombus, aneurysm, or rupture RV infarct	Coronary artery anatomy itself is not directly visualized	Coronary angiography (by catheterization or CT) Radionuclide or PET imaging for myocardial perfusion
Angina (Chapter 56)	Global and segmental LV systolic function Exclude other causes of angina (e.g., AS, HCM)	Resting wall motion may be normal despite significant CAD Stress echocardiography is needed to induce ischemia and wall motion abnormality	Coronary angiography Radionuclide or PET imaging ETT
Pre-revascularization/ post-revascularization (Chapter 59)	Assess wall thickening and endocardial motion at baseline Improvement in segmental function after procedure	Dobutamine stress or contrast echocardiography is needed to detect viable but nonfunctioning myocardium	CMR Coronary angiography Radionuclide or PET imaging Contrast echocardiography
End-stage ischemic disease	Overall LV systolic function (EF) PA pressures Associated MR LV thrombus RV systolic function	—	Coronary angiography (by catheterization or CT) Radionuclide or PET imaging CMR for myocardial viability
CARDIOMYOPATHY (CHAPTERS 45-47)			
Dilated	Chamber dilation (all four) LV and RV systolic function (qualitative and EF) Coexisting atrioventricular valve regurgitation PA systolic pressure LV thrombus	Indirect measures of LVEDP Accurate EF may be difficult if image quality is poor	CMR for LV size, function, and myocardial fibrosis LV angiography with left and right heart hemodynamics
Restrictive	LV wall thickness LV systolic function LV diastolic function PA systolic pressure	Must be distinguished from constrictive pericarditis	Cardiac catheterization with direct, simultaneous RV and LV pressure measurement after volume loading CMR
Hypertrophic	Pattern and extent of LV hypertrophy Dynamic LVOT obstruction (imaging and Doppler) Coexisting MR Diastolic LV dysfunction	Exercise echo to detect inducible LV outflow tract obstruction	CMR Strain and strain rate imaging
HYPERTENSION (CHAPTER 64)			
	LV wall thickness and chamber dimensions LV hypertrophy LV diastolic dysfunction LV systolic function Aortic valve sclerosis Mitral annular calcification	Diastolic dysfunction precedes systolic dysfunction, but detection is challenging because of age and other factors	Speckle tracking; strain and strain rate imaging LV twist and torsion
PERICARDIAL DISEASE (CHAPTER 62)			
	Pericardial thickening Detection, size, and location of PE Two-dimensional signs of tamponade physiology Doppler signs of tamponade physiology	Diagnosis of tamponade is a hemodynamic and clinical diagnosis Constrictive pericarditis is a difficult diagnosis Not all patients with pericarditis have an effusion	Intracardiac pressure measurements for tamponade or constriction CMR or CT to detect pericardial thickening

TABLE 43-4 INDICATIONS FOR TRANSTHORACIC ECHOCARDIOGRAPHY (TTE) BY KNOWN DIAGNOSIS—cont'd

CLINICAL DIAGNOSIS	KEY ECHOCARDIOGRAPHIC FINDINGS	LIMITATIONS OF ECHOCARDIOGRAPHY	ALTERNATIVE APPROACHES
DISEASES OF THE AORTA (CHAPTER 63)			
Aortic root dilation	Cause of aortic dilation Accurate aortic root diameter measurements Anatomy of sinuses of Valsalva (especially Marfan syndrome) Associated aortic regurgitation	The ascending aorta is only partially visualized on TTE in most patients	CT CMR TEE
Aortic dissection	Two-dimensional images of ascending aorta, aortic arch, descending thoracic and proximal abdominal aorta Imaging of dissection "flap" Associated aortic regurgitation Ventricular function	TEE more sensitive (97%) and more specific (100%) Cannot assess distal vascular beds	Aortography CT CMR TEE
CARDIAC MASSES (CHAPTER 47)			
LV thrombus	High sensitivity and specificity for diagnosis of LV thrombus Suspect with apical wall motion abnormality or diffuse LV systolic dysfunction	Technical artifacts can be misleading 5-MHz or higher frequency transducer and angulated apical views needed	LV thrombus may not be recognized on radionuclide or contrast angiography
LA thrombus	Low sensitivity for detection of LA thrombus, although specificity is high Suspect with LA enlargement, MV disease	TEE needed to detect LA thrombus reliably	TEE
Cardiac tumors	Size, location, and physiologic consequences of tumor mass	Extracardiac involvement is not well seen Cannot distinguish benign from malignant tumor or tumor from thrombus	TEE CT CMR (with cardiac gating) Intracardiac echocardiography
PULMONARY HYPERTENSION (CHAPTER 69)			
	PA pressure estimate Evidence of left-sided heart disease to account for increased PA pressures RV size and systolic function (cor pulmonale) Associated TR	Indirect PA pressure measurement Difficult to determine pulmonary vascular resistance accurately	Cardiac catheterization
CONGENITAL HEART DISEASE (CHAPTER 55)			
	Detection and assessment of anatomic abnormalities Quantitation of physiologic abnormalities Chamber enlargement Ventricular function	No direct intracardiac pressure measurements Complicated anatomy may be difficult to evaluate if image quality is poor (TEE is helpful)	CMR with three-dimensional reconstruction Cardiac catheterization TEE Three-dimensional echocardiography

AS = aortic stenosis; CAD = coronary artery disease; CMR = cardiac magnetic resonance; CT = computed tomography; EF = ejection fraction; ETT = exercise treadmill test; HCM = hypertrophic cardiomyopathy; LA = left atrium; LV = left ventricle; LVEDP = left ventricular end-diastolic pressure; LVOT = left ventricular outflow tract; MR = mitral regurgitation; MV = mitral valve; ΔP = pressure gradient; PA = pulmonary artery; PE = pericardial effusion; PET = positron emission tomography; RV = right ventricle; TEE = transesophageal echocardiography; TR = tricuspid regurgitation; TTE = transthoracic echocardiography; VSD = ventricular septal defect.

From Otto CM. *Textbook of Clinical Echocardiography*. 6th ed. Philadelphia: Elsevier; 2018.

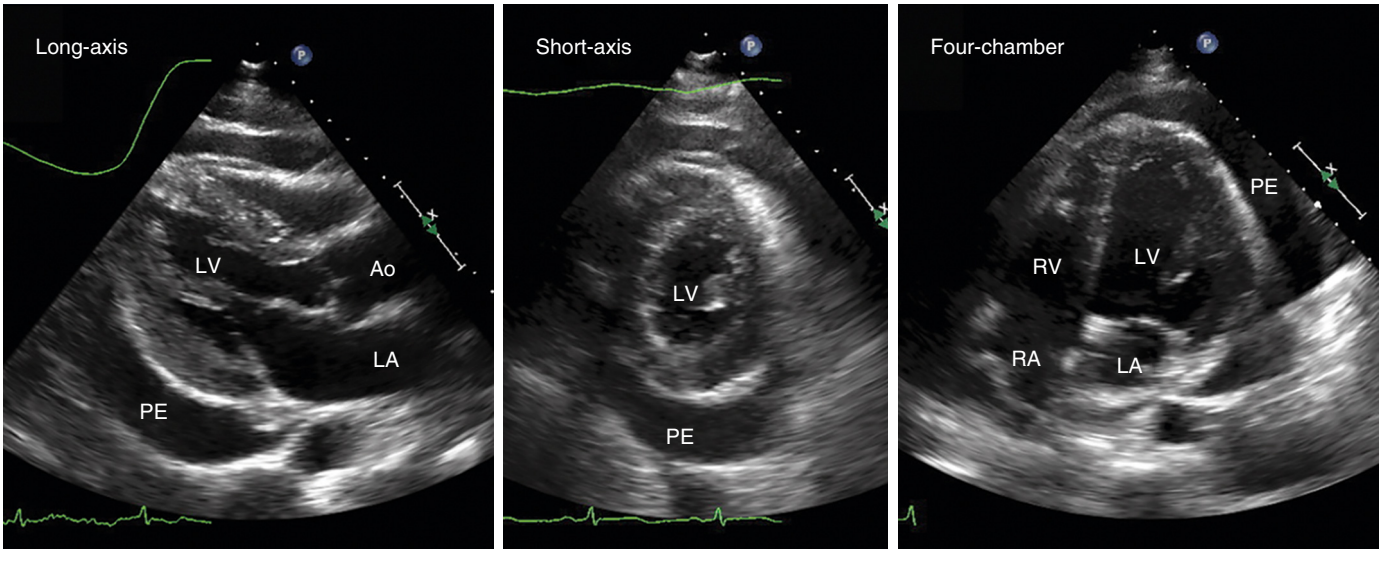

FIGURE 43-9. Pericardial effusion. A large echo-free space is seen anterior and posterior to the cardiac structure in the (A) parasternal long axis view (*left*), (B) short axis view (*center*), and (C) apical four-chamber view (*right*) consistent with a pericardial effusion (PE). Ao = aorta; LA = left atrium; LV = left ventricle; RA = right atrium; RV = right ventricle. See Video 43-5.

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44 NONINVASIVE CARDIAC IMAGING

CHRISTOPHER M. KRAMER, VASKEN DILSIZIAN, AND KLAUS D. HAGSPIEL

RADIOGRAPHY OF THE HEART

Chest radiography is a widely available, relatively inexpensive, and rapid imaging modality, with an average effective radiation dose of 0.03 to 0.1 mSv. The heart is best evaluated on posteroanterior (PA) and lateral radiographs, with the heart closest to the image detector.

On the chest radiograph, the heart appears as a homogeneous shadow surrounded by lungs, so diagnostic assessment of the heart and great vessels is based on the size and shape of the cardiac silhouette, rather than on direct visualization of the heart's internal anatomy. Nevertheless, the size and shape of the heart and their changes over time, together with the appearance of the pulmonary vasculature, aid in the diagnosis of cardiac diseases. The radiographic appearance of the heart is also influenced by the radiographic technique, projection, body habitus, degree of inspiration, and whether the patient is supine or erect during the examination.

On the PA projection, the normal heart is located in the middle mediastinum, with approximately two thirds projecting to the left of the midsternum (Fig. 44-1). The superior segment of the right heart border is a more or less straight line formed by the superior vena cava and right innominate vein. The inferior segment is convex and formed by the right atrium. The left heart border consists of three segments: the aortic arch superiorly, the main pulmonary artery in the middle, and the left ventricle inferiorly. The left atrial appendage is situated in the junction between the lower and middle segments; if enlarged, it can appear as a separate, prominent segment. The inferior border of the heart sometimes is not well differentiated from the diaphragm (see Fig. 44-1).

On lateral chest images, the right ventricle and its outflow tract form the anterior heart border, with the right ventricle in contact with the lower third of the sternum. Lung between the sternum and the posteriorly curving right ventricle and its outflow tract forms the retrosternal clear space. The posterior heart border, which is seen between the carina and the diaphragm on lateral images, consists of the left atrium superiorly and the left ventricle inferiorly. The inferior vena cava courses obliquely upward before it joins the right atrium. The ascending aorta, aortic arch, and proximal descending thoracic aorta are usually well seen on lateral images (see Fig. 44-1).

Alterations of the contour of the heart are generally caused by dilation of the atria, ventricles, or blood vessels. Chest images are not sensitive for detecting cardiac hypertrophy unless it is severe.

Comprehensive cardiovascular analysis of chest radiographs requires evaluation of the size and morphology of the heart and the great vessels, the pulmonary vasculature, and the presence and positioning of any calcifications or implanted devices such as valves, pacemakers, and defibrillators.

RADIOGRAPHIC ASSESSMENT OF HEART SIZE

The cardiothoracic ratio (see Fig. 44-1) estimates the size of the heart. A value of less than 0.5 is considered normal on a radiograph taken during

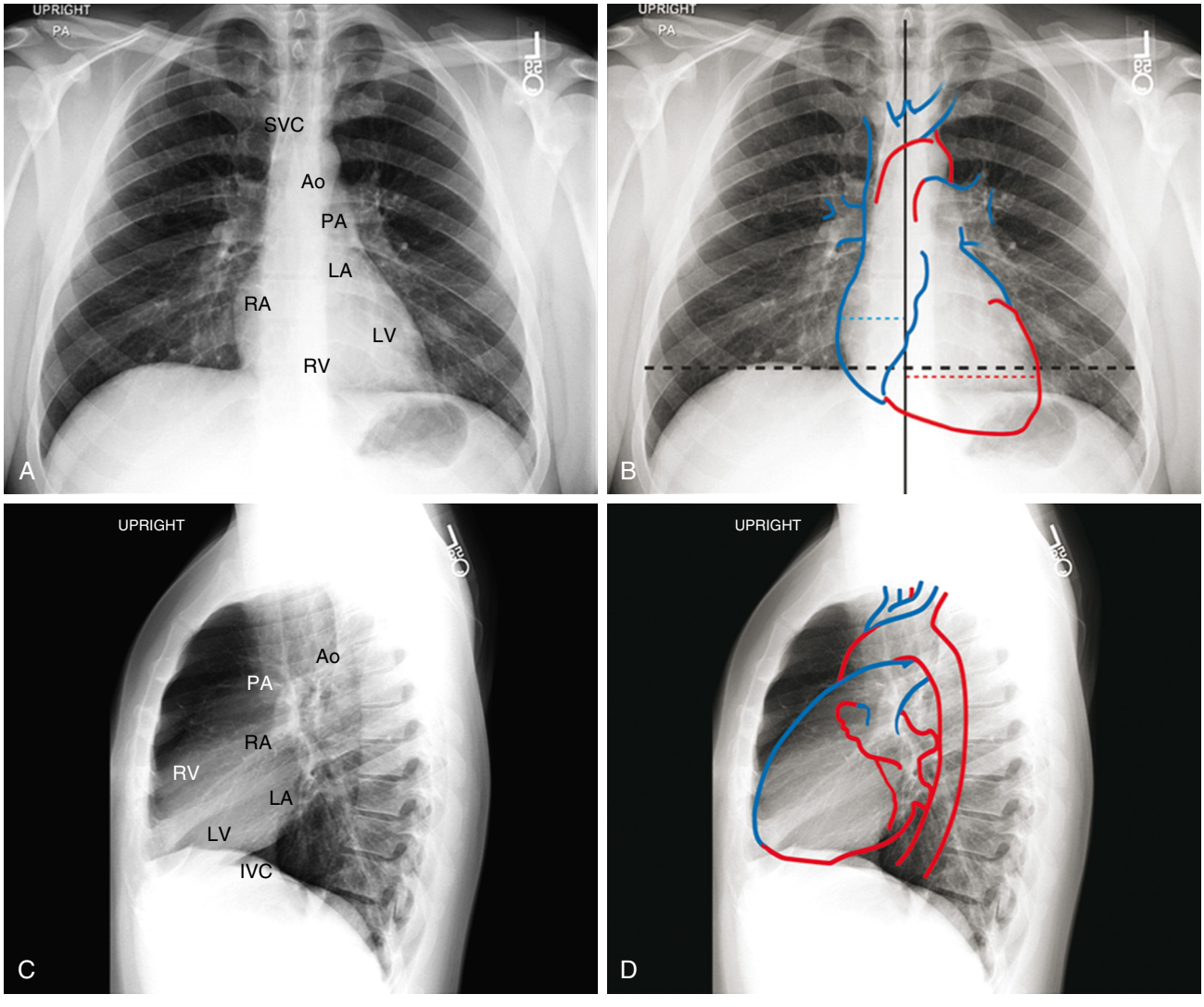

FIGURE 44-1. Normal anatomy. Posteroanterior (**A**) and lateral (**B**) chest radiograph projections in a healthy 28-year-old man. The cardiac chambers and the great vessels are marked on the corresponding drawings (**B, D**). The cardiothoracic ratio (**C**) is calculated by dividing the maximum transverse diameter of the cardiac silhouette (*blue line:* widest distance of the right heart border from the midpoint of the spine; *red line:* widest distance from the left heart border to the midpoint of the spine) through the distance between the internal margin of the ribs at the top of the right diaphragm (*black line*). Ao = aorta; IVC = inferior vena cava; LA = left atrium; LV = left ventricle; PA = pulmonary artery; RA = right atrium; RV = right ventricle; SVC = superior vena cava. WWW.BOOKBAZ.IR

ABSTRACT

This chapter reviews noninvasive cardiac imaging technologies other than echocardiography. Chest radiography is a widely available, relatively inexpensive, and rapid imaging modality that can be used to assess heart size, presence of a pulmonary effusion, size of the pulmonary vasculature, calcifications, and location of cardiac devices. Nuclear cardiology permits the noninvasive imaging of myocardial perfusion under stress and resting conditions and of resting regional and global function to assess myocardial viability and prognosis. Coronary computed tomography (CT) angiography can capture a three-dimensional image of the heart in one to two heartbeats and provide coronary artery calcium scoring without the use of contrast and with little radiation. Recent studies demonstrate the equivalence of coronary CT to stress testing in the initial evaluation of patients with low-intermediate-risk chest pain. Cardiac magnetic resonance is a versatile and flexible imaging modality that is accurate in the evaluation of myocardial ischemia and viability in coronary heart disease, as well as the cause and prognosis of cardiomyopathies, congenital heart disease, aortic disease, pericardial disease, and cardiac masses.

KEYWORDS

chest radiography
single-photon emission computed tomography
positron emission tomography
CT coronary angiography
coronary artery calcium scoring
cardiac magnetic resonance

deep inspiration. Pectus excavatum deformities (Chapter 86) and epicardial fat pads can result in an abnormally large cardiothoracic ratio despite a normal-sized heart. Dilation of the left ventricle, which increases the cardiothoracic ratio, appears as a concave mid-left heart border and lengthening of the entire left heart border, with a downward pointing apex projecting below the diaphragm on PA views (Fig. 44-2). Extension of the posterior margin of the left ventricle more than 2 cm posterior to the inferior vena cava on the lateral film is considered a sign of left ventricular enlargement. Localized rather than global left ventricular enlargement usually indicates the presence of ventricular aneurysms (Chapter 58). Left ventricular hypertrophy without dilation usually is not detectable on chest radiographs.

The most common cause of left atrial enlargement is secondary to left ventricular dysfunction, especially left ventricular dilation. Isolated enlargement of the left atrium is usually a sequela of mitral valve abnormalities or atrial fibrillation. Enlargement of the left atrium can also occur with left ventricular hypertrophy without dilation in patients with aortic stenosis (Chapter 60) or hypertrophic cardiomyopathy (Chapter 47). Straightening of the left heart border between the main pulmonary artery and the left ventricle just below the left main bronchus owing to enlargement of the left atrial appendage is one of the earliest signs of left atrial enlargement; with increasing size, this segment becomes convex. A double contour within the right cardiac border (double density sign), splaying of the carina, and elevation of the right main bronchus are less frequent signs (Fig. 44-3).

The right ventricle normally does not form part of the heart's border on PA radiographs, but significant right ventricular enlargement can lead to an abnormal convexity of the left heart border, with elevation and leftward displacement of the cardiac apex. The best radiographic indication of right ventricular enlargement is obliteration of the retrosternal clear space in the lateral view owing to dilation of the right ventricular outflow tract (Fig. 44-4).

Dilation of the right atrium causes the lower segment of the right heart border to become more prominent and increasingly round. In more severe cases, the entire right heart border is enlarged, and in extreme cases, the right atrium can become border-forming on the lateral view (see Fig. 44-3).

PERICARDIAL EFFUSION

Large pericardial effusions cause significant enlargement of the cardiac silhouette despite a normal superior mediastinum—the so-called water-bottle sign. The fluid in the pericardial sac will obscure the hilar vessels on a PA chest film (Fig. 44-5), unlike cardiomegaly without effusion, in which the hilar structures often are relatively conspicuous. Posterior displacement of the pericardial fat line on lateral images is also a valuable finding for the detection of pericardial effusions.

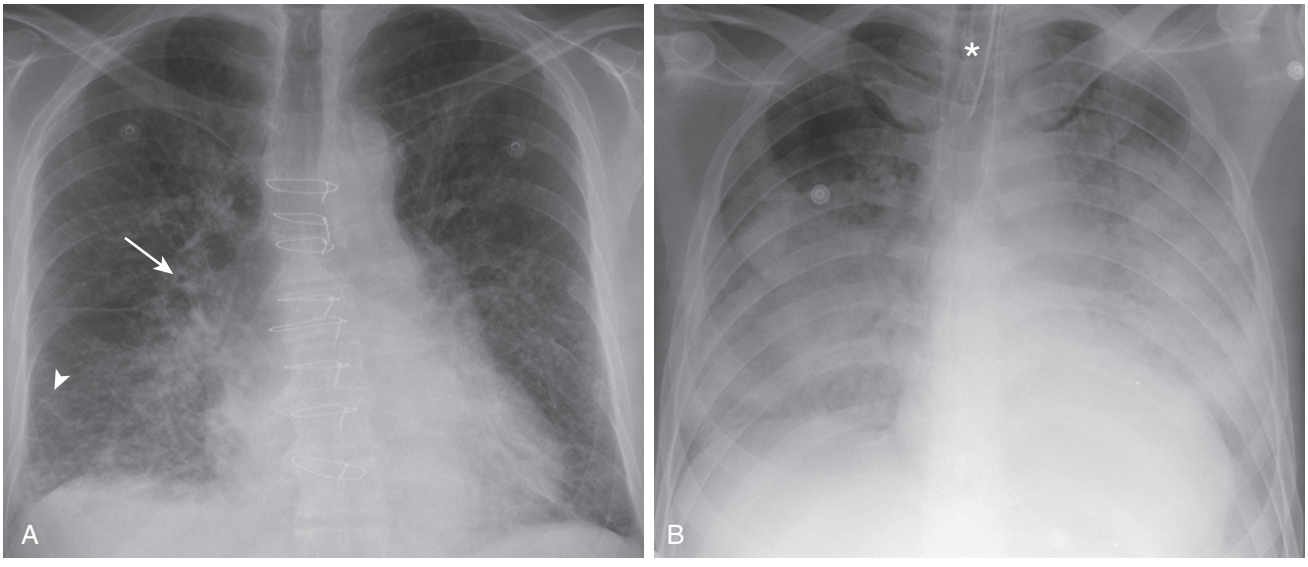

FIGURE 44-2. Left ventricular enlargement and pulmonary edema in two different patients. The image on the left (**A**) was obtained in a patient who had acute myocardial infarction and who had previously undergone aortic bypass grafting (sternotomy wires and bypass clips are seen). Interstitial edema is evidenced by the presence of vascular redistribution, Kerley B lines (*arrowhead*), and peribronchial cuffing (*arrow*). The image on the right (**B**) was obtained in a patient with cardiogenic alveolar edema. The left ventricle is significantly enlarged, and there is extensive bilateral air space consolidation with air bronchogram. Note normal position of an endotracheal tube (*asterisk*) and a nasogastric tube.

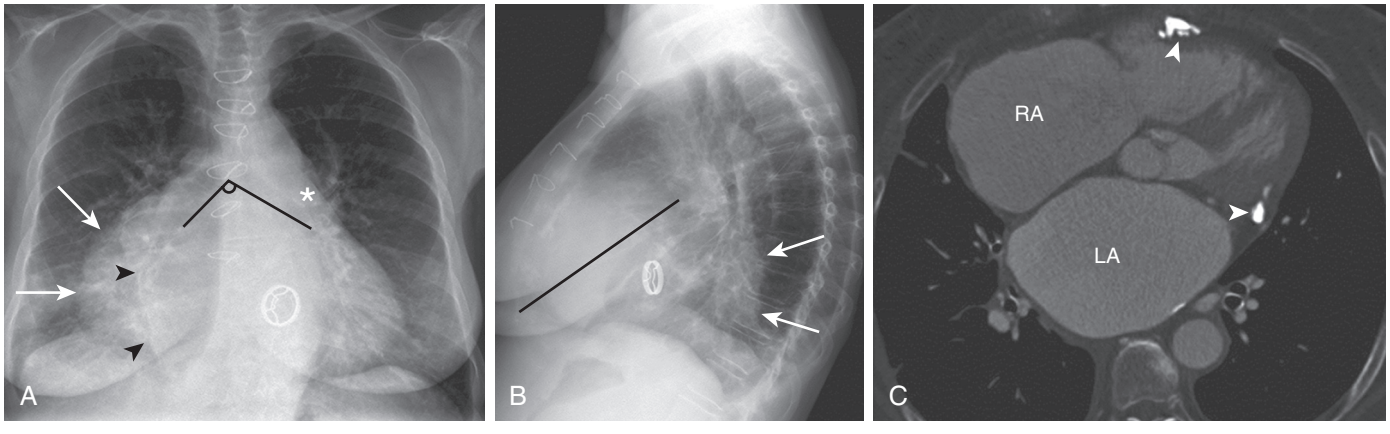

FIGURE 44-3. Biatrial enlargement in a patient who has undergone mitral valve repair. The posteroanterior (**A**) chest radiograph shows a prominent left atrial appendage (*asterisk*), the double density sign (*arrowheads*), and splaying of the carina. There is also enlargement of the right atrium, as evidenced by prominence and round shape of the right side border on the posteroanterior view (*arrows*). Posterior bulging of the heart (*arrows*) owing to biatrial enlargement is seen on the lateral view (**B**). Interstitial pulmonary edema is present. The location of the cardiac valves is best assessed on a lateral view (**B**) by drawing a line from the carina to the anterior costophrenic recess (*black line*). The pulmonic and aortic valves usually are positioned superior to this line, and the tricuspid and mitral valves are inferior to it. A computed tomographic image (**C**) also demonstrates biatrial enlargement as well as pericardial calcifications (*arrowheads*). LA = left atrium; RA = right atrium.

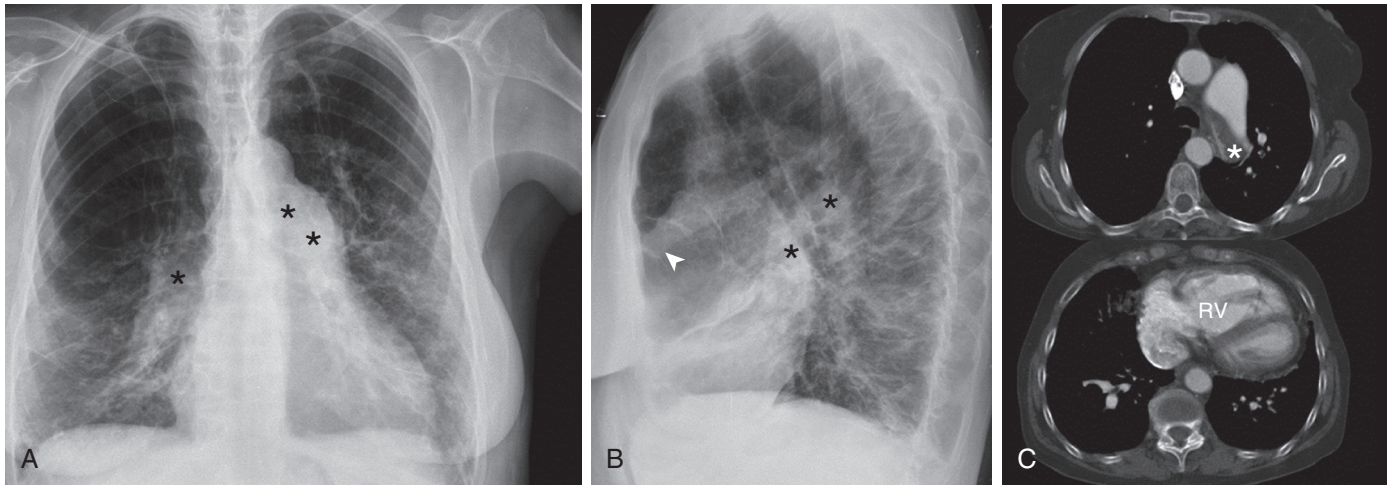

FIGURE 44-4. Pulmonary arterial hypertension in a patient with severe pulmonary emphysema and chronic pulmonary embolism. Enlarged central pulmonary arteries (*asterisks*) and the pruned-tree sign can be seen on the posteroanterior (**A**) and lateral (**B**) projections. Hyperlucency in both upper lobes is present owing to extensive pulmonary emphysema. Right ventricular enlargement has obliterated the retrosternal clear space on the lateral view (*arrowhead*) (**B**). The computed tomographic scan demonstrates dilated central pulmonary arteries with wall-adherent chronic pulmonary embolus (*asterisk*) (**C**) as well as right ventricle (RV) dilation and hypertrophy.

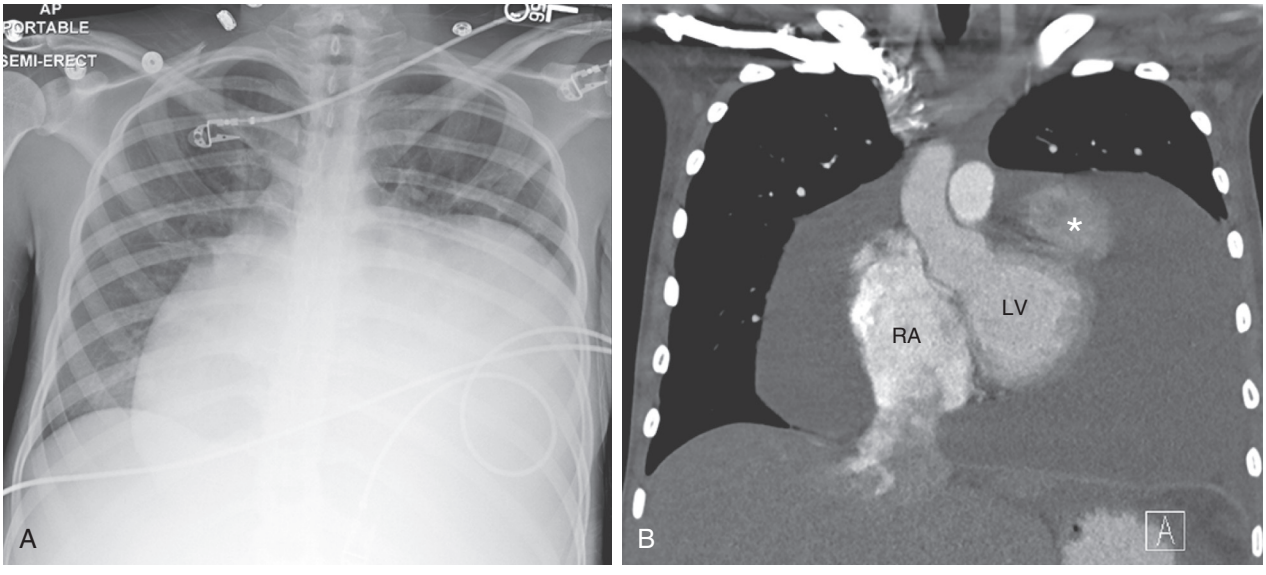

FIGURE 44-5. A 17-year-old girl presenting with massive pericardial effusion. The posteroanterior radiograph (**A**) shows the water-bottle sign; the hilar vessels are obscured. A coronal reformatted computed tomographic scan (**B**) shows the fluid in the pericardial sac as well as dilation of the right atrium and the left atrial appendage (*asterisk*). LV = left ventricle; RA = right atrium.

PULMONARY VASCULATURE

The large and medium-sized pulmonary arteries and veins can be seen on the radiograph as linear shadows, and their size and appearance correlate with pulmonary blood flow and pulmonary venous pressure. The vessels in the lower lung zones are normally larger than in the upper zones as a result of the normal distribution of pulmonary blood flow (see Fig. 44-1). In patients with right-to-left shunts (Chapter 55), the pulmonary vasculature is decreased in caliber. In left-to-right shunts, the vascularity is increased, and the vessels are sharply outlined if the patient does not have heart failure (Fig. 44-6). With increasing pulmonary venous pressure, as is seen in heart failure (Chapters 45 and 46), the vessels in the upper zone enlarge on the chest radiograph. With further increases in pulmonary venous pressures, fluid extravasates into the pulmonary interstitium, and the pulmonary vessels lose their sharp demarcation. Horizontal lines in the periphery of the lungs (Kerley B) and vertical lines in the upper lobes (Kerley A) represent thickened interlobular septae. Fluid in the interstitium of the bronchial walls causes peribronchial thickening or cuffing (see Fig. 44-2). In more advanced cases, the lungs show a diffuse ground-glass appearance that masks the vascular structures, and pulmonary edema ultimately develops (see Fig. 44-2). Long-standing pulmonary arterial hypertension leads to dilation of the central pulmonary arteries with abrupt change in caliber instead of the normal tapering. The size and number of the peripheral arterial branches diminish, resulting in a pruned-tree appearance (see Fig. 44-4).

CALCIFICATIONS

Calcifications can often be seen on chest radiographs. In the heart, calcifications most frequently involve the valves and the mitral annulus (Chapter 60). Most aortic valvular calcifications are degenerative in nature and occur in otherwise normal valves, but their incidence is increased in bicuspid valves or in patients who have had rheumatic fever. Calcification of the mitral annulus is common and usually an asymptomatic finding. Coronary artery calcifications are frequent but are rarely seen on chest radiographs. Calcifications of the ventricles are most often seen in patients with prior myocardial infarction or ventricular aneurysms (Fig. 44-7). Pericardial calcifications tend to be thicker than calcifications in the myocardium and, in severe cases, can entirely surround the heart (see Fig. 44-3).

IMPLANTED DEVICES

A great number of devices can be seen on a chest radiograph, and it is important to be familiar with their appearance to assess their correct position and integrity. The accurate assessment of device position can occasionally require cross-sectional imaging (see Figs. 44-2, 44-3, and 44-7).

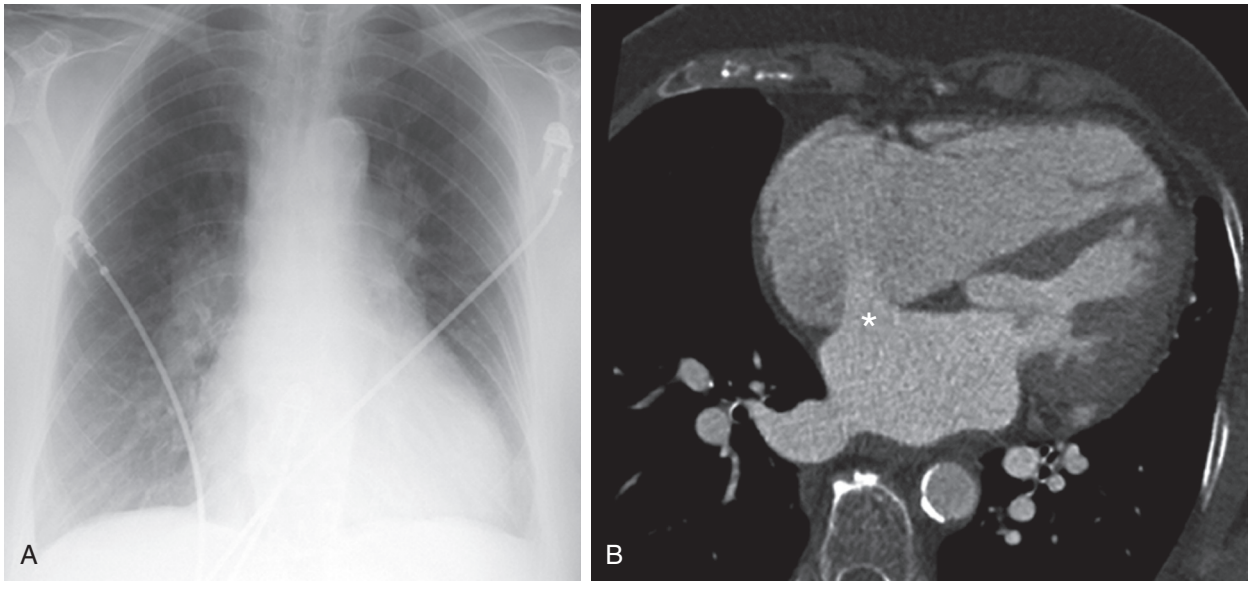

FIGURE 44-6. Female patient with known secundum type atrial septal defect. The posteroanterior radiograph (**A**) shows enlargement of the pulmonary arteries, shunt vascularity, and enlargement of the right heart border. A computed tomographic scan (**B**) shows the septal defect (*asterisk*) with left-to-right shunt. Enlargement of the right heart is also seen.

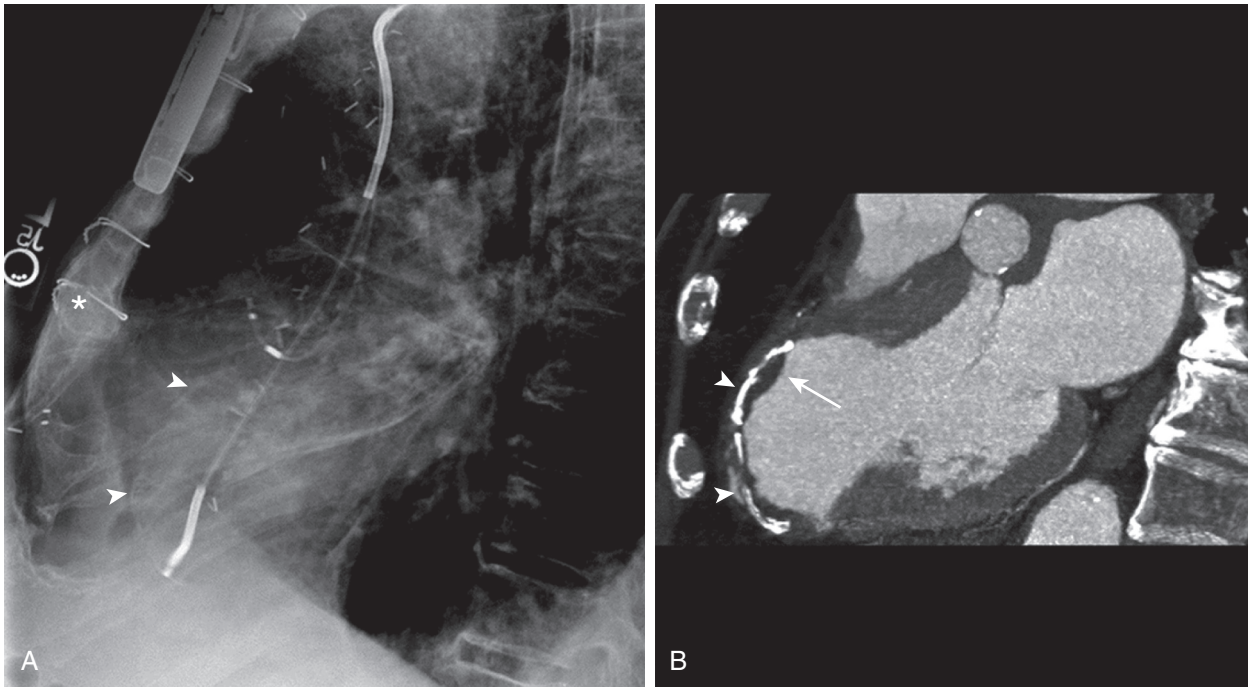

FIGURE 44-7. Calcified chronic myocardial infarction. Lateral radiograph (**A**) demonstrates thin curvilinear calcifications (*arrowheads*) in the region of the left ventricular apex. A reformatted cardiac computed tomographic scan (**B**) shows aneurysmal dilation and thinning of the apex, curvilinear calcifications, and thrombus (*arrow*). Dual-chamber pacer leads, aortocoronary bypass clips, and fracture of the most inferior sternotomy wire (*asterisk*) are also seen on the lateral radiograph (**A**).

CHARACTERISTIC APPEARANCE OF CARDIAC SILHOUETTE

Certain constellations of findings on chest radiographs can be characteristic of specific disorders. For example, in mitral stenosis, left atrial enlargement, pulmonary venous hypertension, a small aortic knob, and enlargement of the main pulmonary artery are typical findings. In aortic stenosis, left ventricular enlargement, calcifications of the aortic valve, and dilation of the ascending aorta are often present. In pulmonic valve stenosis, enlargement of the pulmonary trunk is the most common radiographic sign, with or without signs of right ventricular enlargement. In atrial septal defects, the heart is usually normal in size, with prominent pulmonary vasculature (shunt vascularity). In ventricular septal defects, the left atrium and left ventricle are prominent, and shunt vascularity is present. A number of classic chest radiographic signs have been described for patients with more complex congenital heart disease (Chapter 55). These findings include the egg-on-a-string sign in transposition of the great arteries, the gooseneck sign in endocardial cushion defects, the boot-shaped heart in tetralogy of Fallot (E-Fig. 44-1), the figure-of-3 and reversed figure-of-3 signs in coarctation of the aorta, the box-shaped heart in Ebstein anomaly, the snowman sign in total anomalous pulmonary venous return, and the scimitar sign in partial anomalous pulmonary venous return. Due to earlier diagnosis and treatment of congenital heart disease, the diagnostic role of chest radiography for these conditions is limited today, but it remains a useful technique for monitoring the progression of disease and its response to treatment.

NUCLEAR CARDIOLOGY

The techniques of nuclear cardiology permit the noninvasive imaging of myocardial perfusion, function, metabolism, and innervation by use of radionuclide imaging agents and gamma or positron cameras with associated computer processing.[1,2] All these techniques are based on acquiring images of radioactivity

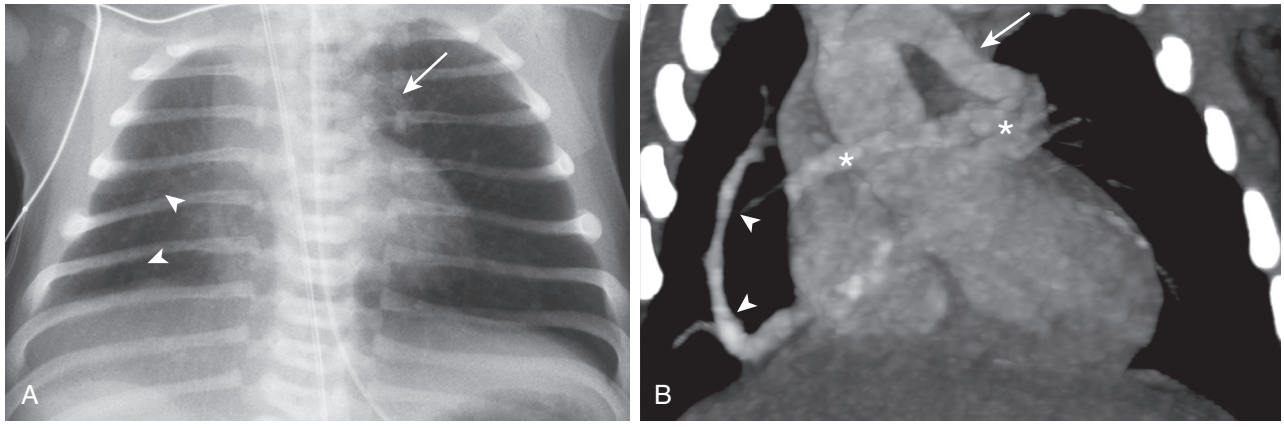

E-FIGURE 44-1. Infant with tetralogy of Fallot, pulmonary atresia, and partial anomalous pulmonary venous return. Anteroposterior radiograph (**A**) shows the classic boot-shaped heart seen with tetralogy of Fallot; the scimitar sign, owing to abnormal right pulmonary vein draining into the inferior vena cava (*arrowheads*); and abnormal superior parasternal left-sided mediastinal density caused by a left upper pulmonary vein draining into the left innominate vein (*arrow*). Coronal reformatted computed tomography (**B**) confirms these findings. The pulmonary arteries are diminutive (*asterisks*).

emanating from tracers localized in heart muscle or in the blood pools of the left and right ventricles. Myocardial perfusion imaging is the most commonly performed nuclear cardiology technique, most often in conjunction with either exercise or pharmacologic stress intended to produce flow heterogeneity between relatively hypoperfused and normally perfused myocardial regions.

MYOCARDIAL PERFUSION IMAGING

AGENTS AND TECHNIQUES

For the assessment of myocardial perfusion using single-photon emission computed tomography (SPECT) technology, ^{99m}Tc-labeled perfusion agents or thallium-201 (^{201}Tl) are used for exercise or pharmacologic stress perfusion imaging to evaluate patients with suspected or known coronary heart disease (CHD). Of the various ^{99m}Tc-labeled agents, ^{99m}Tc-sestamibi and ^{99m}Tc-tetrofosmin are the most common. These ^{99m}Tc agents permit simultaneous assessment of regional and global left ventricular function and volumes with ECG-gated SPECT technology. Advantages of positron emission tomography (PET) myocardial perfusion imaging compared with SPECT include higher sensitivity and specificity for the detection of coronary artery disease at a lower radiation dose, reduced image acquisition time (less likelihood of patient motion), higher resolution images, and better soft tissue attenuation (such as for the breast and diaphragm), with added information regarding absolute quantitative hyperemic myocardial blood flow and reserve flow (Chapter 59).

In patients with chest pain or shortness of breath, myocardial perfusion imaging is commonly performed with exercise so as to induce coronary hyperemia and link the symptoms during exercise to the location, extent, and severity of abnormal perfusion patterns. In patients who are unable or incapable of exercising to greater than 85% of the maximum predicted heart rate for their age, pharmacologic stress testing with a vasodilator can be used to induce coronary hyperemia. Vasodilator stress typically causes a modest increase in heart rate and decline in arterial pressure. Options include dipyridamole, adenosine, the selective A_{2A} adenosine receptor agonist regadenoson, or the inotropic/chronotropic agent dobutamine. Dobutamine stress is preferred in patients who have bronchospasm or a history of asthma, or who have consumed caffeine, which is an adenosine receptor antagonist, within 12 hours before testing. Patients who experience side effects such as hypotension and chest pain during vasodilator infusion should be treated with intravenous aminophylline, which is an adenosine antagonist. Unlike exercise stress, however, the perfusion defect induced with pharmacologic vasodilator stress may merely represent the heterogeneity in coronary flow rather than true myocardial ischemia.

Exercise or pharmacologic stress myocardial perfusion images are compared with images acquired at rest. Stress-induced perfusion abnormalities in regions that exhibit normal perfusion at rest are termed reversible perfusion defects, and such regions represent viable, ischemic myocardium with blunted coronary blood flow reserve (Fig. 44-8). Conversely, perfusion abnormalities that are seen both on stress and rest myocardial perfusion images are termed fixed or irreversible defects and most often suggest an area of prior myocardial infarction, particularly if the defect is severe.

CLINICAL APPLICATIONS

The major indications for stress and rest myocardial perfusion imaging are to diagnose coronary heart disease, to assess prognosis, and to detect myocardial viability.

Detection of Coronary Heart Disease

Exercise or pharmacologic stress myocardial perfusion imaging in patients with chest pain yields a sensitivity for detecting coronary heart disease of 88% for SPECT and 93% for PET. The specificity for excluding coronary heart disease is 76% for SPECT and 81% for PET. Exercise or pharmacologic stress SPECT perfusion imaging has sensitivities and specificities that are superior to those of exercise electrocardiography (ECG) testing alone.

SPECT and PET cameras can help combined with a computed tomography (CT) scanner, which allows for multimodality hybrid imaging of anatomy and physiology. Myocardial perfusion imaging can be added to coronary CT angiography (see later) if the latter shows an intermediate coronary stenosis of 50 to 70% in diameter. Conversely, the CT angiogram can be performed after an equivocal SPECT or PET study to distinguish between true-positive and false-positive perfusion defects. Hybrid imaging also permits combined coronary artery calcium scoring with myocardial perfusion.

Assessment of Prognosis

Stress myocardial perfusion imaging does not appear to add any useful prognostic information over exercise ECG testing alone in patients who achieve 10 metabolic equivalents or more of workload (Chapter 39) without ischemic ST segment depression on the exercise ECG or in low-risk women with good physical capacity. In other situations, however, the extent of fixed and reversible defects on SPECT and PET perfusion image can provide important incremental prognostic information when added to clinical characteristics, the resting left ventricular ejection fraction, and exercise ECG stress test variables. For example, nondiabetic patients with chest pain and a normal stress myocardial perfusion scan have a less than 1% per year rate of subsequent cardiac death or myocardial infarction and are generally appropriate candidates for medical therapy (Chapter 56) or even further diagnostic evaluation to search for a noncardiac cause of chest pain (Chapters 39 and 123). Conversely, patients with high-risk stress imaging results, such as transient ischemic left ventricular cavity dilation on stress images (E-Fig. 44-2), may benefit from early referral for coronary angiography and possible coronary revascularization (Chapter 59), even if symptoms are mild.

One significant limitation of SPECT myocardial perfusion imaging is its inability to identify multivessel and left main coronary artery disease in some patients who have balanced ischemia, in which uptake of the imaging agent at peak stress is homogeneously diminished throughout the left ventricular

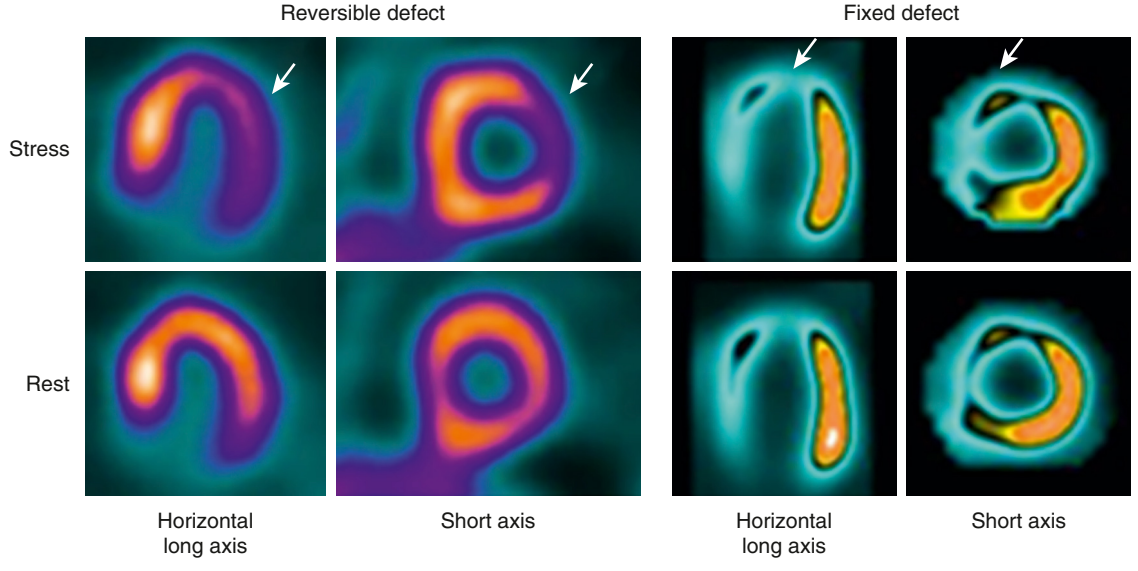

FIGURE 44-8. Examples of reversible and fixed myocardial perfusion defects. A, Paired stress and rest images show a reversible defect in the lateral region, thereby indicating myocardial ischemia related to the left circumflex coronary artery territory. **B,** Fixed defects in the anterior, apical, and interventricular septum, representing prior transmural myocardial infarction related to the left anterior descending coronary artery.

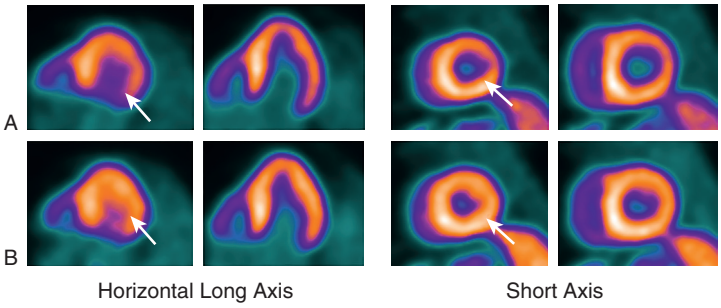

E-FIGURE 44-2. Exercise (A) and resting (B) myocardial perfusion images. Note stress-induced transient ischemic dilatation of the left ventricular cavity (see *arrows* in exercise panels) associated with extensive multivessel myocardial ischemia.

myocardium because of diffusely reduced flow in regions supplied by all three major coronary arteries. Quantitative PET myocardial perfusion imaging will identify these patients by demonstrating regional and/or global reduction in absolute hyperemic myocardial blood flow and an abnormal coronary flow reserve.[3]

Determination of Myocardial Viability

In some patients, fixed perfusion defects may not represent permanently infarcted myocardium but rather represent stunned or hibernating viable myocardium that has the potential to recover function after coronary revascularization. Myocardial viability usually is assessed using PET technology, with fluorine-18-labeled 2-deoxyglucose (FDG) to assess regional myocardial metabolism, and either nitrogen-13 (^{13}N) ammonia or rubidium-82 (^{82}Rb) to assess regional myocardial perfusion. FDG is a glucose analogue that is taken up initially in myocardial cells and is trapped by conversion to FDG-6-phosphate. In dysfunctional myocardial regions, increased FDG activity on clinical PET images in areas of diminished regional blood flow (termed mismatch defect) is indicative of hibernating but viable myocardium. After coronary revascularization, the left ventricular ejection fraction can improve by about 10 percentage points in such patients. However, this postintervention improvement in ejection fraction does not predict which patients with ischemic cardiomyopathy will have better survival after coronary revascularization.[A1,A2] Conversely, decreased (or absent) glucose utilization in dysfunctional myocardial regions with concomitant reduction of blood flow (termed match defect) is indicative of permanently scarred, infarcted myocardium.

INFILTRATIVE CARDIOMYOPATHIES

CARDIAC SARCOIDOSIS

The combination of PET perfusion imaging with FDG can diagnose the inflammation of cardiac sarcoidosis (E-Fig. 44-3) and monitor its response to therapy (Chapters 47 and 83).[4] The high cellular uptake of FDG in sarcoidosis is related to the inflammatory cell infiltrates that have high glycolytic activity to satisfy their large energy demands.

CARDIAC AMYLOIDOSIS

Transthyretin cardiac amyloidosis (Chapters 47 and 174) can be diagnosed with Tc-99m-pyrophosphate (^{99m}Tc-PYP) scintigraphy. In a patient with typical features of cardiac amyloid on echocardiography or cardiac magnetic resonance (MR), Grade 2 or 3 ^{99m}Tc-PYP uptake in the absence of a clonal plasma cell process (Chapter 173) is diagnostic of transthyretin cardiac amyloidosis (E-Fig. 44-4).[5]

IMAGING OF VENTRICULAR FUNCTION

Although echocardiography (Chapter 43) is the dominant noninvasive tool for measuring ventricular function, it can also be measured with radionuclide angiography using technetium-99m (^{99m}Tc)-labeled red blood cells or other ^{99m}Tc-labeled agents that are injected intravenously. Because ^{99m}Tc remains within the blood pool, serial imaging studies can be acquired during several hours. Acquisition of the images is synchronized with the QRS complex on the ECG through a multigated approach by which each cardiac cycle is divided into multiple frames. A uniform diminution of left ventricular systolic function without regional wall motion abnormalities suggests nonischemic dilated cardiomyopathy (Chapter 47), whereas depressed global function associated with regional wall motion abnormalities suggests ischemic heart disease. Left ventricular function can also be assessed by gated SPECT myocardial perfusion imaging.

CARDIAC COMPUTED TOMOGRAPHY

For CT, imaging with high spatial and temporal resolution and ECG gating during a breath-hold yields snapshots of the heart reconstructed from the same phase of the cardiac cycle.[6] Coronary CT angiography can capture a three-dimensional image of the heart in one to two heartbeats on the latest generation scanners as well as provide coronary artery calcium scoring without the use of contrast and with little radiation. Coronary CT angiography requires 60 to 80 mL of iodinated contrast. With latest generation scanners, radiation doses of 1 to 2 mSv are achievable although radiation can still be on the order of 5 to 20 mSv on older 64-detector scanners. β-Blockade is often used to achieve a heart rate of 60 beats per minute or less to optimize imaging, and irregular rhythms such as atrial fibrillation may diminish image quality.

CORONARY ARTERY CALCIUM SCORING

Coronary calcium is an indicator of the burden of atherosclerotic plaque, although there is no correlation of the amount of local coronary calcium with the physiologic or anatomic significance of an underlying coronary stenosis. Calcium scores are generally calculated as an Agatston score, which corresponds to each coronary lesion's calcium area multiplied by the maximal CT attenuation value of that lesion, and then summed for the entire coronary tree (Fig. 44-9). High scores confer an increased risk for future cardiac events and death, with overall 15-year mortality rates in asymptomatic patients ranging from 3 to 28% with coronary artery calcification scores from 0 to 1000 or greater.[7] Calcium scores are age, gender, and race dependent, but they predict coronary heart disease events independently of standard risk factors. The utility of calcium scoring is highest in patients who are at intermediate risk for coronary heart disease, based on Framingham risk data (Chapter 40). By comparison, a calcium score in otherwise low- or high-risk patients will rarely change management, although very high calcium scores may sometimes encourage cardiac stress testing.

CORONARY COMPUTED TOMOGRAPHIC ANGIOGRAPHY

Coronary CT angiography is an excellent technique to diagnose anomalous coronary arterial anatomy in adults (E-Fig. 44-5). For detection of coronary artery disease, positive-predictive values are in the range of 64 to 91%, and negative-predictive values approach 99%. Thus, the technique is an excellent

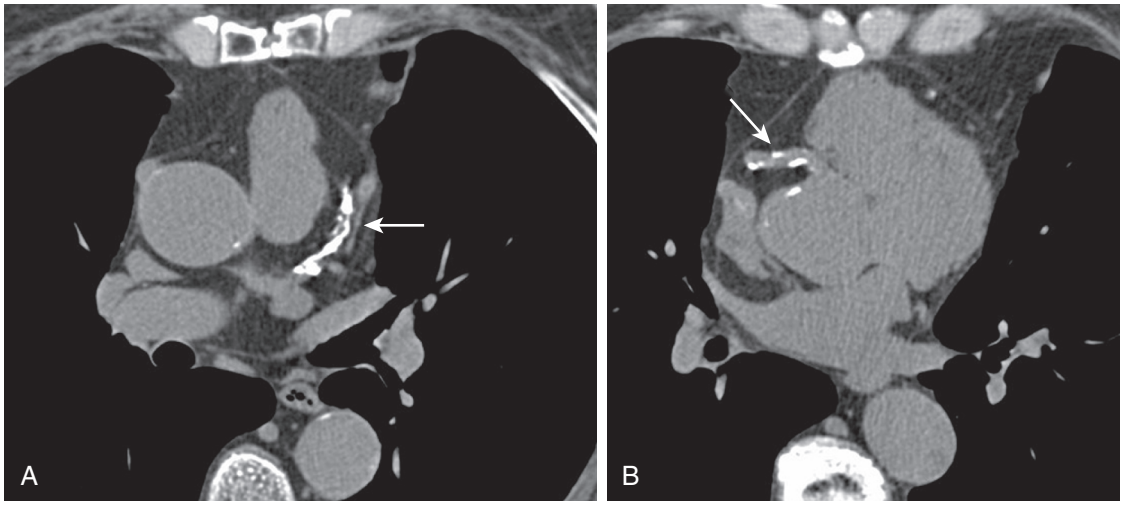

FIGURE 44-9. Non-contrast-enhanced computed tomography axial slices through the heart at two locations for coronary calcium scoring as risk assessment in an asymptomatic patient. A, The slice includes the left anterior descending artery with extensive calcification in its proximal portion (*arrow*). **B,** The slice includes the right coronary artery with proximal spotty calcification (*arrow*). This patient's calcium score was 457, putting him in a higher risk group regardless of his Framingham risk score.

Stages	Perfusion/FDG Patterns			
	Perfusion Defect		FDG-Uptake	
Normal	None	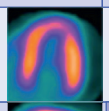	No/ Low	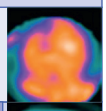
Early	None	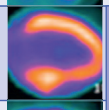	FDG uptake high	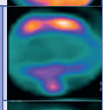
Progressive	Mild	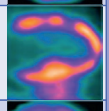		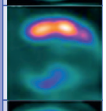
Peak active	Moderate	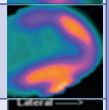		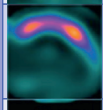
Progressive myocardial impairment	Severe	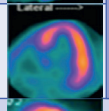		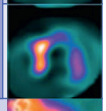
Fibrosis	Severe		Low	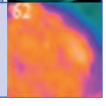

E-FIGURE 44-3. Cardiac sarcoidosis. Various stages of cardiac sarcoidosis with associated patterns of perfusion defects and fluorine-18-labeled 2-deoxyglucose (FDG) metabolism. In the normal stage, no regional perfusion defect is seen with FDG in the cardiac blood pool. As the disease progresses, variable combinations of regional perfusion and metabolic patterns are seen. In the fibrosis/scarred stage, a focal perfusion defect represents a non-caseating granuloma without a corresponding inflammatory FDG metabolic signal in the myocardium. (Adapted from Skali H, Schulman AR, Dorbala S. 18F-FDG PET/CT for the assessment of myocardial sarcoidosis. *Curr Cardiol Rep*. 2013;15:352.)

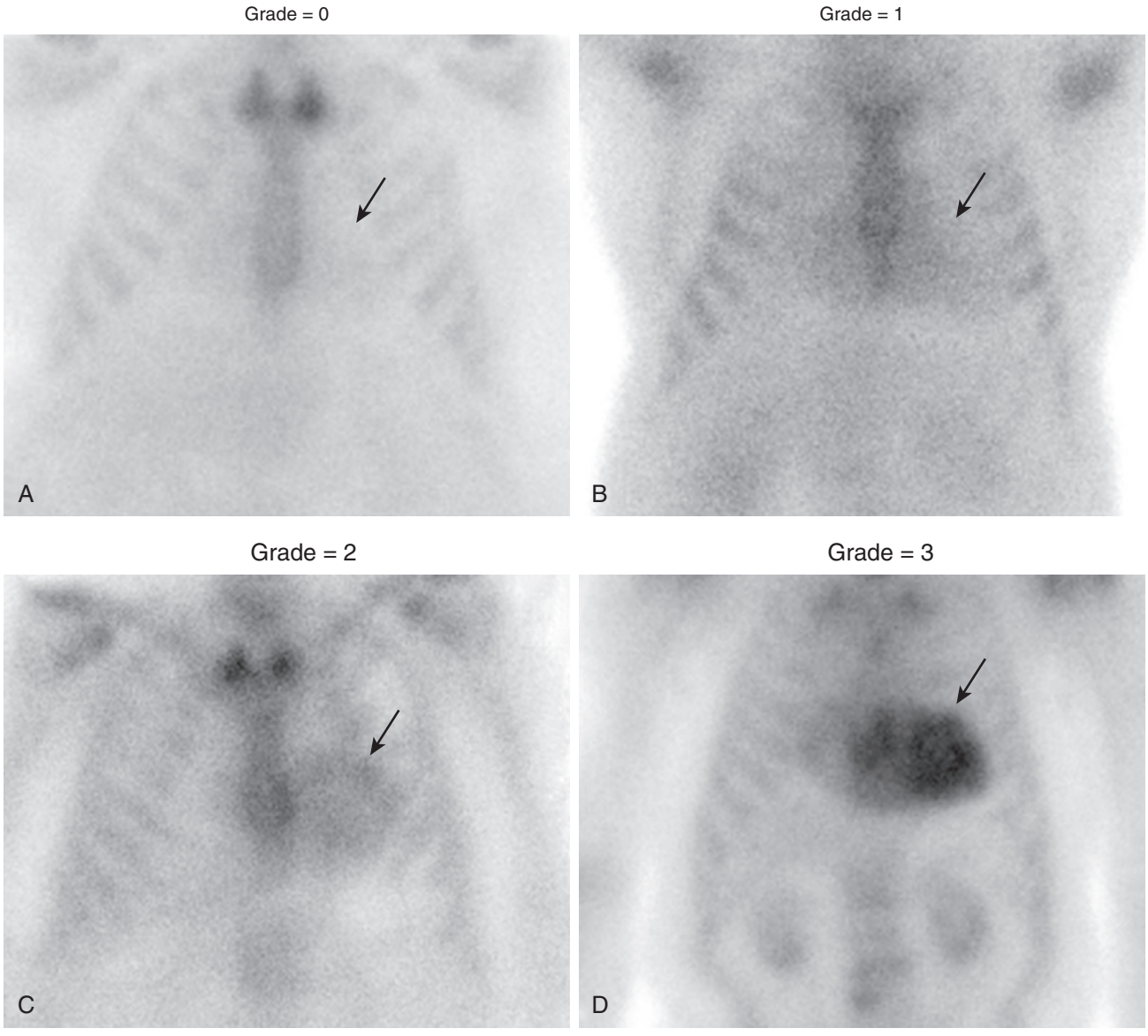

E-FIGURE 44-4. Cardiac amyloidosis. Representative images of ^{99m}Tc pyrophosphate uptake in transthyretin cardiac amyloidosis. **A,** No uptake, grade = 0. **B,** Mild uptake (*arrow*) less than bone, grade = 1. **C,** Moderate uptake (*arrow*) equal to bone, grade = 2. **D,** High uptake (*arrow*) greater than bone, grade = 3. (Adapted from Chen W, Ton VK, Dilsizian V. Clinical phenotyping of transthyretin cardiac amyloidosis with bone seeking radiotracers in heart failure with preserved ejection fraction. *Curr Cardiol Rep*. 2018; 8;20:23.)

E-FIGURE 44-5. Contrast-enhanced computed tomographic angiogram in a young patient with chest pain and an anomalous right coronary artery (RCA). The RCA originates with a slitlike origin from the left coronary cusp (*arrow*) and passes anteriorly between the aorta and right ventricular outflow tract. The left main coronary artery originates normally from the left cusp.

way to exclude (Fig. 44-10) or detect significant coronary artery disease in the three major coronary vessels (Fig. 44-11). A limitation of the technique, however, is its lower specificity in heavily calcified vessels, which are more common in elderly patients. The accuracy for detecting stenoses in bypass grafts is quite high, although evaluation of native vessel coronary artery disease is limited in these patients owing to extensive calcification and smaller size vessels. Imaging within most coronary stents has proved difficult. Measurement of coronary artery-specific fractional flow reserve using computational flow dynamics can improve upon the accuracy (especially specificity) of angiography (E-Fig. 44-6).

Coronary CT angiography is not recommended as a routine screening test in asymptomatic patients, even those with diabetes. However, it is especially useful in selected situations, such as in low- or low-intermediate-risk patients with chest pain, patients who present to the emergency department with chest pain but without ECG changes or elevations of cardiac biomarkers (Chapters 39 and 57), or patients with equivocal or nondiagnostic stress testing. Some guidelines recommend CT angiography as the initial test for diagnosing coronary diseases in symptomatic patients.[8,9] In patients who have acute non-ST elevation MI, CT angiography has a high positive and negative predictive value as compared with invasive angiography and may be an alternative in lower risk patients with this clinical presentation.[10]

In symptomatic patients with suspected coronary disease, the strategies of initial coronary CT angiography and functional testing using exercise electrocardiography, nuclear stress testing, or stress echocardiography provide equivalent clinical outcomes at an equivalent cost over a median follow-up of 2 years.[A3,A4] CT angiography is associated with similar outcomes and fewer complications or revascularizations compared with invasive angiography in patients who have intermediate-risk chest pain.[A5] However, CT angiography can improve outcomes compared with standard care in patients with stable chest pain by stimulating the use of more aggressive medical therapies without increasing rates of coronary angiography or coronary revascularization.[A6] The extent and severity of coronary disease found at CT angiography correlate with subsequent all-cause mortality in a similar fashion to catheter-based coronary angiography. Low-attenuation, noncalcified plaque is the most potent predictor of subsequent myocardial infarction,[11] whereas progression of calcification is associated with a mildly increased risk of subsequent events after adjusting for other risk factors.[12] In asymptomatic patients, however, CT angiography does not improve risk stratification over calcium scoring.

OTHER CARDIAC APPLICATIONS

The same data acquired by coronary CT angiography can be reformatted and used for functional cardiac imaging, including measurement of left ventricular volumes, ejection fraction, wall thickness, and global and segmental wall motion. CT angiography can complement echocardiography to evaluate cardiac anatomy in patients with congenital heart disease. CT can evaluate pericardial thickness and calcification in patients with suspected constrictive pericarditis (see Fig. 62-9) and can evaluate native and prosthetic valvular structures (E-Fig. 44-7) and cardiac masses when imaging with other modalities is inadequate.

CT angiography is often used to image the left atrium and pulmonary venous anatomy and to exclude left atrial thrombus prior to electrical cardioversion or pulmonary vein ablation for atrial fibrillation (Chapter 54). CT is an important

FIGURE 44-11. Contrast-enhanced computed tomographic coronary angiogram of the left anterior descending artery (LAD) in a 54-year-old man who presented to an emergency department with risk factors but atypical chest pain. The mid LAD demonstrates mixed obstructive plaque with calcified and noncalcified components.

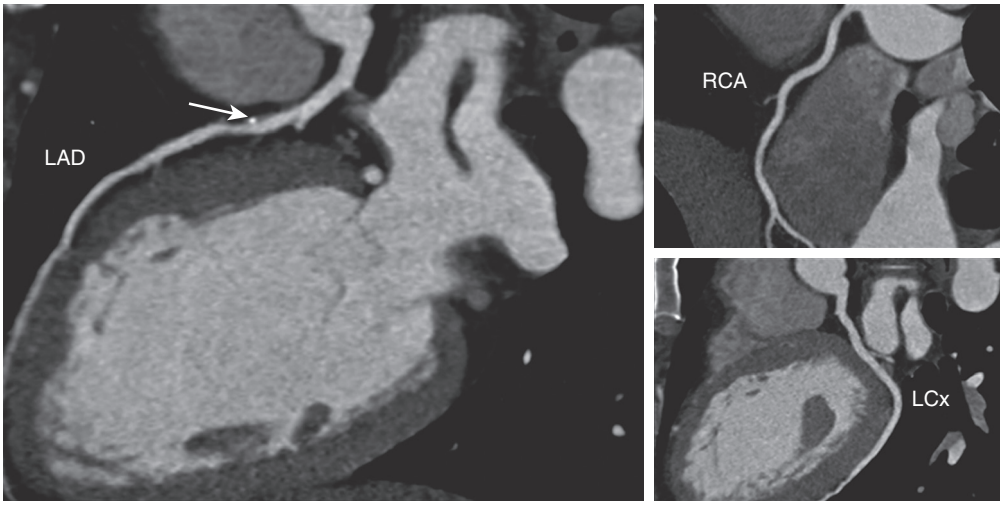

FIGURE 44-10. Contrast-enhanced computed tomographic coronary angiogram obtained on a dual-source 64-detector scanner in a patient with atypical chest pain. The left anterior descending (LAD) artery has a nonobstructive lesion (*arrow*) containing both noncalcified (soft) plaque, which appears dark, and a focal area of calcification. The right coronary artery (RCA) and left circumflex coronary artery (LCx) are normal.

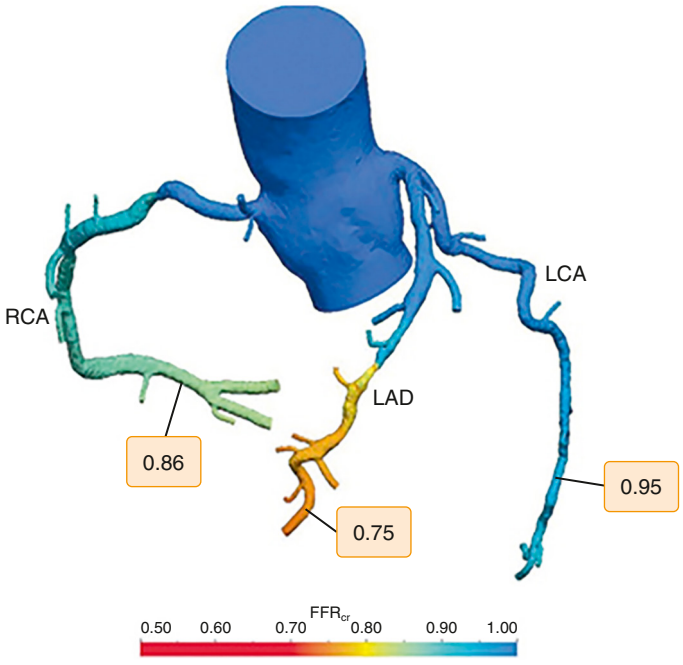

E-FIGURE 44-6. Fractional flow reserve (FFR) data computed from a typical computed tomographic coronary angiogram. A FFR value of 0.8 or higher is considered normal. Thus the left anterior descending (LAD) coronary artery demonstrates reduced FFR at 0.75 and therefore is considered to have a significant stenosis whereas the right coronary artery (RCA) and left circumflex coronary artery (LCA) do not.

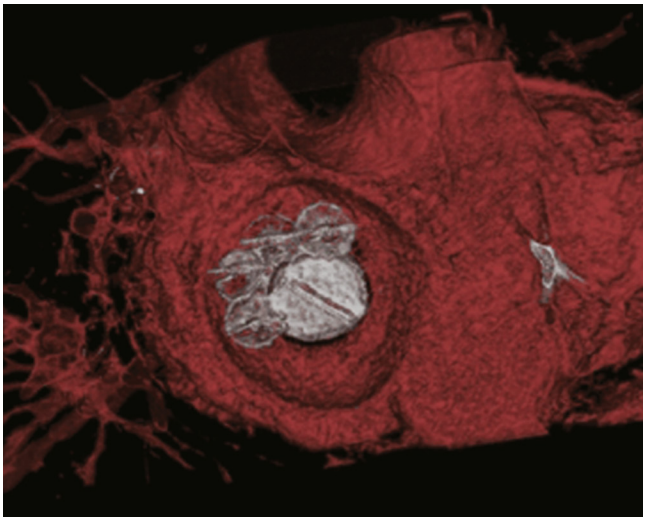

E-FIGURE 44-7. Three-dimensional reconstruction of a computed tomographic angiogram in a patient with a St. Jude's mechanical mitral valve with a paravalvular leak that has been closed with four Amplatzer devices.

tool for peri-preprocedural planning in patients being considered for transcatheter valve replacement (Chapter 60).

CARDIOVASCULAR MAGNETIC RESONANCE IMAGING

INDICATIONS, CONTRAINDICATIONS, AND PULSE SEQUENCES

Cardiac MR is a versatile and flexible imaging modality that can be applied in diverse cardiovascular conditions using either 1.5- or 3-Tesla (T) scanners. Advantages of cardiac MR include the lack of ionizing radiation, the variety of tissues that can be characterized, and the ability to image the heart in any arbitrary plane. Images typically are obtained using ECG gating and breath-hold techniques.

Although some metallic devices are contraindications to cardiac MR, patients with newer pacemaker and defibrillator systems can be imaged by carefully following the manufacturer's instructions. In addition, some non-pacemaker-dependent patients with older pacemaker and defibrillator models can be scanned safely with close monitoring and testing, as well as reprogramming of the device after the procedure. Cardiac MR is safe for all prosthetic heart valves and intracoronary stents. Gadolinium-based contrast agents can be associated with nephrogenic systemic fibrosis in patients with a glomerular filtration rate of less than 30 mL/minute/1.83 m^2 (Chapter 246), but this risk is very low with current cyclic contrast agents.

A comprehensive cardiac MR study includes evaluation of cardiac structure, function, tissue characteristics (T1, T2, T2*, and extracellular volume [ECV]) mapping, perfusion, and scarring or fibrosis. Cardiac MR is highly accurate for the noninvasive quantitative assessment of ventricular volumes and ejection fraction. The components of the examination are tailored to the particular diagnostic question at hand.

SPECIFIC CLINICAL APPLICATIONS

CORONARY ARTERY DISEASE

For detection of myocardial ischemia, first-pass gadolinium perfusion imaging during vasodilator stress with adenosine or regadenoson shows defects, generally in the subendocardium, that persist for at least five heartbeats during the first pass of contrast in patients with CHD (Fig. 44-12). Imaging is often repeated at rest after approximately 10 minutes to be sure any defect seen with stress was not either artifactual or caused by an infarct (the latter is excluded in combination with late gadolinium enhancement). Cardiac MR stress testing is more accurate than SPECT, is a strong predictor of cardiac events and survival, and is cost-effective in the evaluation of patients with chest pain.[13] In patients with suspected angina, cardiac MR can reduce unnecessary angiography within 12 months compared with routine clinical care but not compared with myocardial perfusion scintigraphy.[A7] Cardiac MR perfusion can be used to assess coronary flow. In patients with stable angina, cardiac MR perfusion is as good as the measurement of fractional flow reserve by invasive angiography for predicting future coronary events and may reduce referral for coronary revascularization.[A8] Coronary CT angiography has superior spatial resolution and accuracy compared with cardiac MR for imaging of the coronary arteries, but cardiac MR coronary imaging is useful for the diagnosis of anomalous coronary arteries.

Cardiac MR with late gadolinium enhancement is the gold standard technique for assessment of myocardial scar caused by myocardial infarction, with a better accuracy than nuclear imaging approaches, especially for smaller non–Q wave infarctions (Fig. 44-13). In acute myocardial infarction, cardiac MR T2-weighted techniques can assess the myocardium at risk and estimate the amount of salvaged myocardium owing to reperfusion. Areas of low signal in the subendocardial core of the infarction represent regions of microvascular obstruction with severe capillary destruction and are a marker of subsequent adverse left ventricular remodeling and poorer outcome. To assess myocardial viability in patients with chronic coronary heart disease, cardiac MR with late gadolinium enhancement has the best sensitivity for recovery of function with revascularization, but low-dose dobutamine contractile reserve has better specificity.

CARDIOMYOPATHIES

Cardiac MR should not be routinely performed in all patients with new onset heart failure,[A9] but it is very helpful in identifying patterns of scar or fibrosis that typify specific causes of cardiomyopathy (Chapter 57). Cardiac MR measurements of left ventricular mass and left atrial volume can be used to estimate left ventricular filling pressures and to predict survival in patients who have heart failure.[14] In nonischemic dilated cardiomyopathy, late gadolinium enhancement is associated with an adverse prognosis,[15] regardless of the left ventricular ejection fraction. In patients who have chest pain, elevated

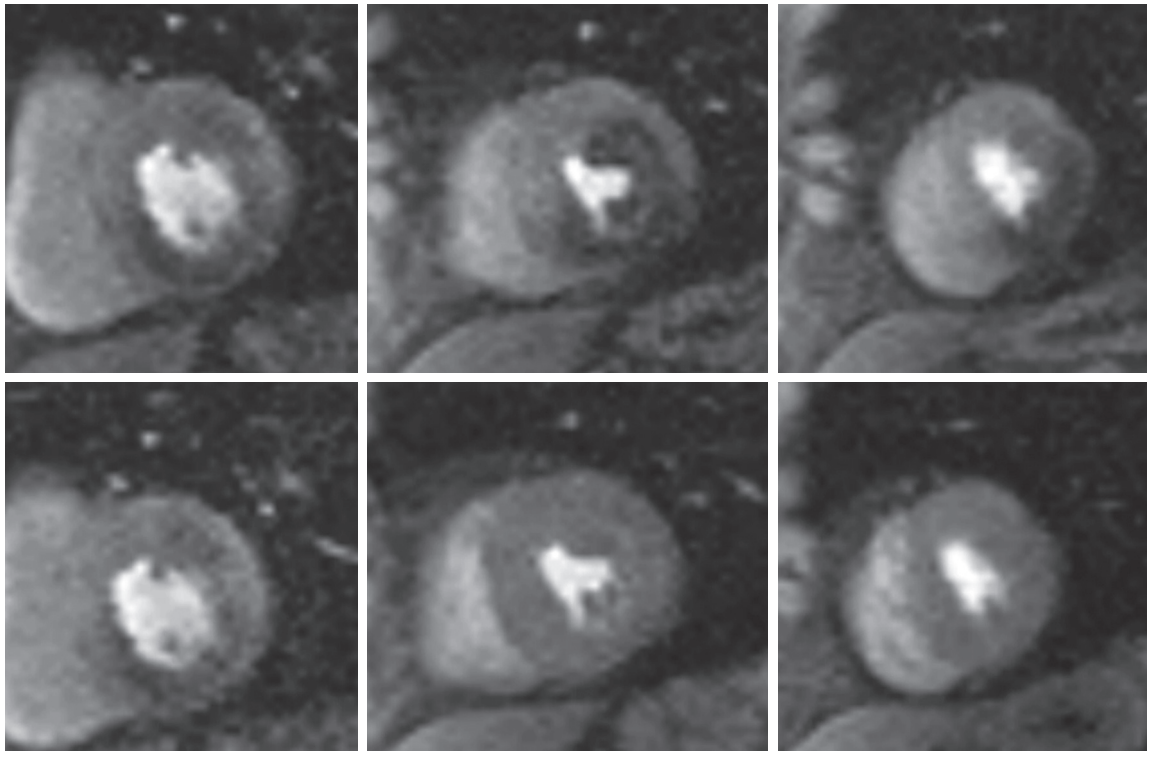

FIGURE 44-12. **Set of first-pass gadolinium-enhanced magnetic resonance perfusion images during adenosine stress (*top row*) and at rest (*bottom row*) at the base (*left*), mid-ventricle (*center*), and apex (*right*). The stress images demonstrate a large perfusion deficit in the anterolateral and inferolateral walls (from 1 o'clock to 7 o'clock), especially in the mid-ventricle and apex, whereas the same regions appear normal at rest.**

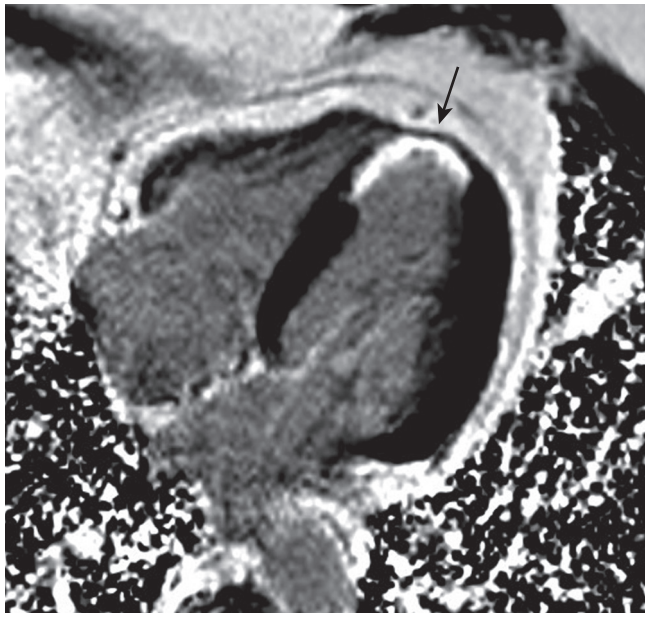

FIGURE 44-13. Late gadolinium-enhanced four-chamber long axis image in a patient with a scar (*arrow*) from a prior anterior myocardial infarction.

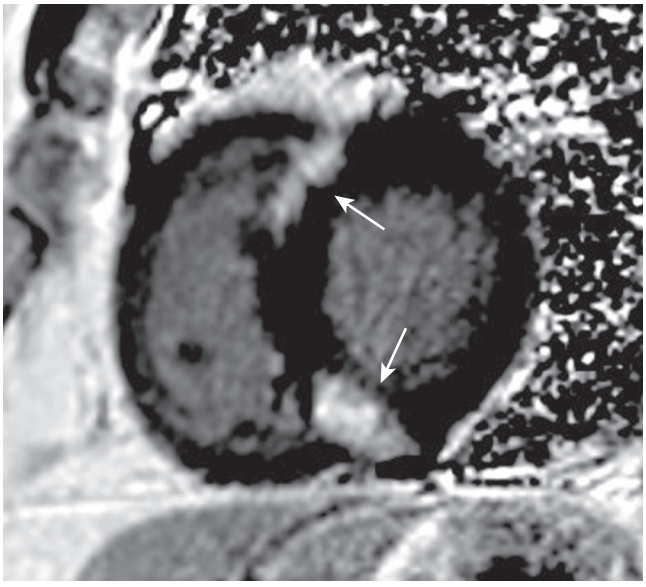

FIGURE 44-15. Late gadolinium-enhanced magnetic resonance short axis image of a 35-year-old man with hypertrophic cardiomyopathy demonstrates a classic pattern of enhancement, which identifies fibrosis (*arrows*) in the right ventricular insertion sites.

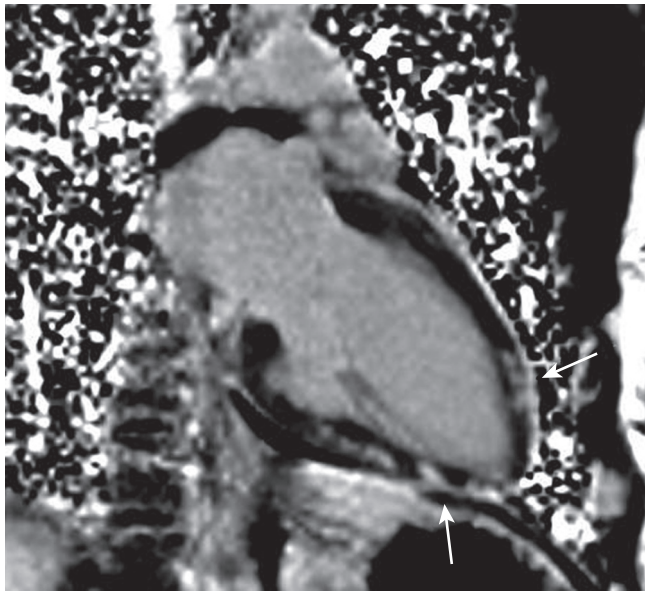

FIGURE 44-14. Gadolinium-enhanced image in a 22-year-old man shows patchy subepicardial enhancement (*arrows*) characteristic of acute myocarditis.

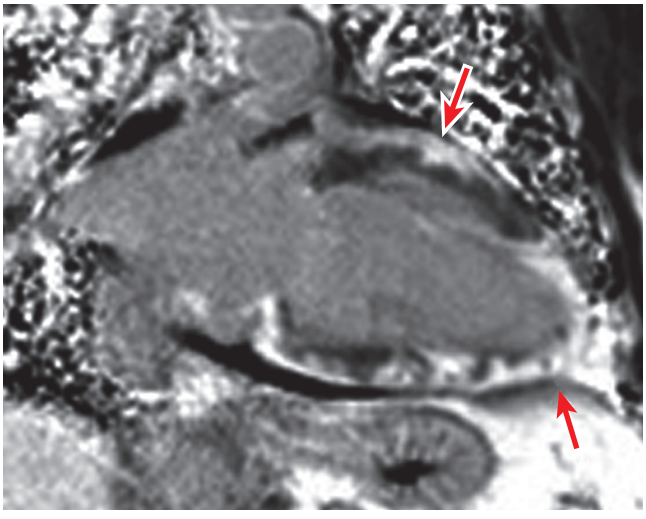

FIGURE 44-16. Late gadolinium-enhanced magnetic resonance image in a 47-year-old man with heart failure, heart block, and hilar lymphadenopathy shows patchy late gadolinium enhancement in a noncoronary distribution, including subepicardial anterior wall enhancement (*upper arrow*) and near transmural apical enhancement (*lower arrow*) consistent with myocardial sarcoidosis.

troponin levels, but a negative coronary arteriogram, cardiac MR is ideally suited to identify myocarditis or unusual causes of myocardial infarction,[16] (Fig. 44-14) (Chapter 47). In patients with hypertrophic cardiomyopathy (Chapter 47), cardiac MR is more sensitive than echocardiography for identifying increased regional wall thickness and can demonstrate late gadolinium enhancement (Fig. 44-15), the extent of which correlates with the risk of sudden death. Cardiac amyloidosis (Chapters 47 and 174) can be seen as diffuse subendocardial, transmural, or patchy late gadolinium enhancement. In cardiac sarcoidosis (Chapters 47 and 83; Fig. 44-16), patchy midwall and/or subepicardial fibrosis is readily identified, is complementary to PET (see earlier), and is more sensitive than endomyocardial biopsy. Cardiac MR is also useful for diagnosing the myocarditis associated with coronavirus disease 2019 (Chapter 336).[17]

Cardiac MR is often used to diagnose arrhythmogenic ventricular cardiomyopathy (Fig. 44-17; Chapters 47 and 53), which is characterized by global right ventricular dilation and regional akinesis or dyskinesis. In iron overload conditions such as thalassemia (Chapter 148), imaging of T2* can identify the extent of iron overload and can be used to follow the effects of chelation therapy. Rarer causes of cardiomyopathy, such as ventricular noncompaction and Chagas disease (Chapters 47 and 318), also have characteristic cardiac MR findings.

AORTIC DISEASE, PERICARDIAL DISEASE, AND MASSES

Cardiac MR is an excellent test to image aneurysms but is a second-line test to detect acute aortic dissection or intraluminal aortic hematoma (see Fig. 63-5) in stable patients. Cardiac MR is also an excellent test for the evaluation of chronic pericardial disease (Fig. 44-18) because it accurately identifies pericardial thickness as well as adherence of the pericardium to the epicardium in constrictive pericarditis. Real-time imaging can demonstrate ventricular interdependence, a hallmark of this disease. Cardiac MR is also an ideal tool to diagnose intracardiac (Fig. 44-19) and extracardiac masses such as myxomas, thrombus, and tumors (Chapter 47), owing to its high spatial resolution and ability to perform tissue characterization.

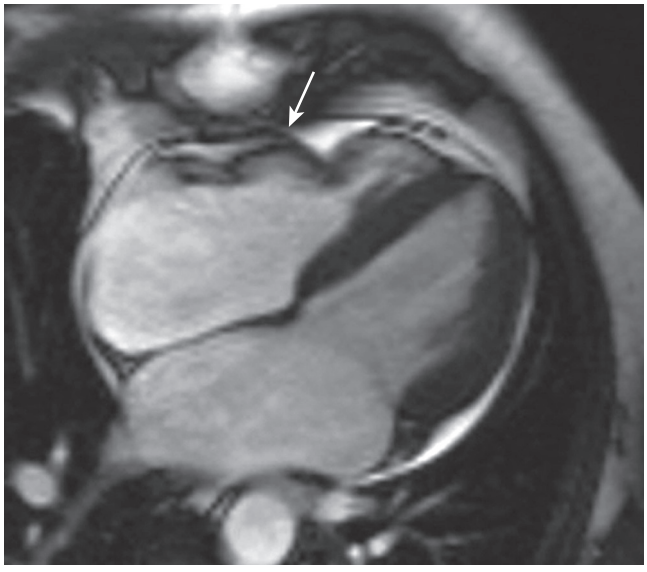

FIGURE 44-17. Magnetic resonance image in a 27-year-old woman with arrhythmogenic ventricular cardiomyopathy demonstrates regional right ventricular (RV) systolic dysfunction, which is the hallmark of the disease. The *arrow* points to a region of RV dyskinesis at end systole, and the RV appears like an accordion at end systole.

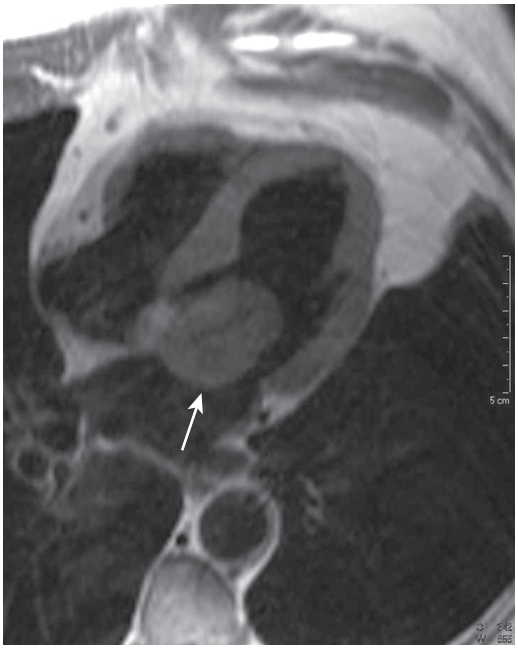

FIGURE 44-19. Diastolic magnetic resonance image of a large left atrial myxoma (*arrow*) showing that it is attached to the atrial septum and is prolapsing across the mitral valve.

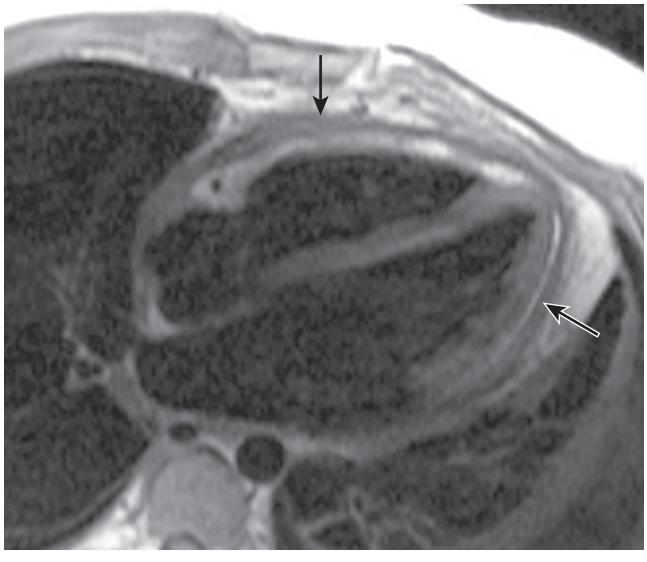

FIGURE 44-18. Magnetic resonance image of a 35-year-old man with dyspnea many years after mantle radiation for Hodgkin lymphoma shows a thickened pericardium (*arrows*) circumferentially around the left and right ventricles.

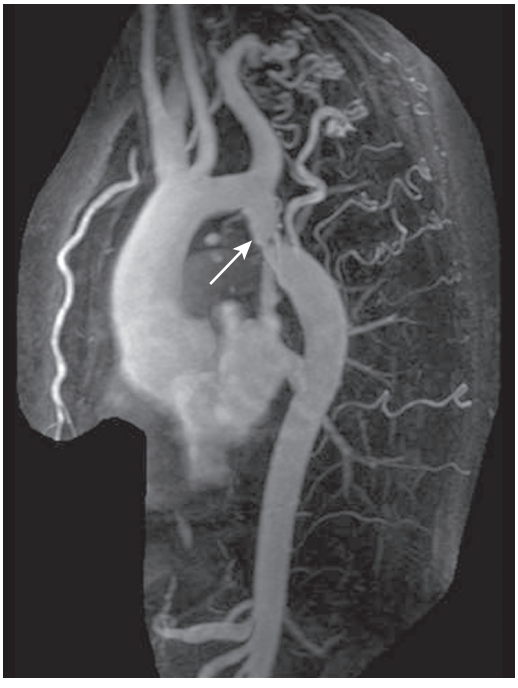

FIGURE 44-20. Three-dimensional contrast-enhanced magnetic resonance angiogram in a patient with an aortic coarctation (*arrow*).

CONGENITAL HEART DISEASE

Cardiac MR is useful for the assessment of both simple and complex congenital heart disease and is often used as an adjunct to echocardiography (Chapter 55). For example, phase velocity cardiac MR readily quantifies blood flow through the major blood vessels, thereby facilitating accurate assessment of the ratio of pulmonary to systemic blood flow in the presence of shunts. Cardiovascular MR is particularly valuable for assessing abnormalities of the great vessels, such as aortic coarctation (Fig. 44-20), extracardiac anatomy, or anomalous pulmonary venous drainage, and in patients with complex congenital heart disease who have undergone prior corrective or palliative shunt surgery, such as in tetralogy of Fallot or hypoplastic left heart syndrome. Cardiac MR is uniquely able to measure right ventricular volumes accurately, an often important determination in this setting.

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45 HEART FAILURE: EPIDEMIOLOGY, PATHOBIOLOGY, AND DIAGNOSIS

JOSEPH G. ROGERS AND CHRISTOPHER M. O'CONNOR

DEFINITION

Heart failure is a clinical syndrome that results when abnormalities in myocardial structure and function impair cardiac output or decrease filling of the ventricles. Clinical characteristics of the heart failure syndrome include dyspnea, fatigue, impaired exercise performance, and edema. Congestion is a common but not universal feature, so the term *congestive heart failure* is no longer used.

EPIDEMIOLOGY

Current estimates are that more than 64 million people worldwide have heart failure.[1] Most studies estimate the prevalence of heart failure to be 1 to 2% of the total adult population, with a lifetime risk that ranges between 20 to 45% depending upon age, race, and geography. Although the overall prevalence of the disease appears to be stabilized or decreasing, it is increasing in younger and older individuals as well as individuals with a preserved ejection fraction. Heart failure is the leading cause of hospitalization in patients older than age 65 years, and once a patient is hospitalized for heart failure, the 30-day risk of rehospitalization is 25%, with a 10% risk of 30-day postdischarge mortality. Although survival has improved, the absolute mortality rates for heart failure remain approximately 50% within 5 years of diagnosis.

Nearly half of patients with heart failure have a preserved ejection fraction. Compared with patients who have heart failure with reduced ejection fraction, heart failure patients with a preserved ejection fraction tend to be older and are more likely to be women with a prior history of hypertension and diabetes. The mortality rate of patients who have heart failure with a preserved ejection fraction is similar to the rate for patients with reduced ejection fraction.[2] Hospitalization and rehospitalization rates are comparable for heart failure patients regardless of their ejection fractions.

Disparities

Black Americans are at increased risk for incident heart failure compared with White Americans and also have more frequent hospitalizations. Black patients with heart failure also have a higher mortality rate than White populations. The reasons for these disparities include racial differences in risk factors, the causes of heart failure, access to care, and response to therapies. However, there is a growing literature to support systemic racial inequities and even racism as an important underlying explanation.[3] Hispanics represent a growing population of heart failure patients in the United States with an incidence rate between those of Black and White Americans.

Classification

The classification of heart failure considers the disease state and progression, degree of exercise intolerance (Chapter 39), measurement of the left ventricular ejection fraction, and its underlying cause.[4] In the first approach, heart failure is classified by its progression through four stages from pre-disease to advanced symptoms (Fig. 45-1). The second approach evaluates functional states by standardized classification systems such as the New York Heart Association classification, the Canadian Cardiovascular Society system, or other validated measures of exercise tolerance (see Table 39-5). Functional status is the most appropriate way to understand a patient's limitations and the impact of heart failure on quality of life. It also correlates with prognosis and is commonly used as a secondary end point in clinical trials. A third approach is to describe heart failure based upon ejection fraction. This method stratifies patients into those with reduced (<40%), midrange (40 to 50%), and preserved (>50%) ejection fraction. This approach also helps in understanding the patient's underlying pathophysiologic process and in guiding therapeutic decisions. Classification based on etiology, usually ischemic versus nonischemic (Chapter 47), is useful in guiding the diagnostic evaluation and in tailoring treatment.

Causes of Heart Failure

Heart failure has numerous causes (Table 45-1). In developed countries, coronary artery disease, usually with a prior myocardial infarction, accounts for nearly 70% of heart failure cases (Chapter 58). Comorbid conditions such as hypertension (Chapter 64),[5] diabetes (Chapter 210),[6] and obesity (Chapter 201)[7] are commonly associated with heart failure. Diseases of the myocardium

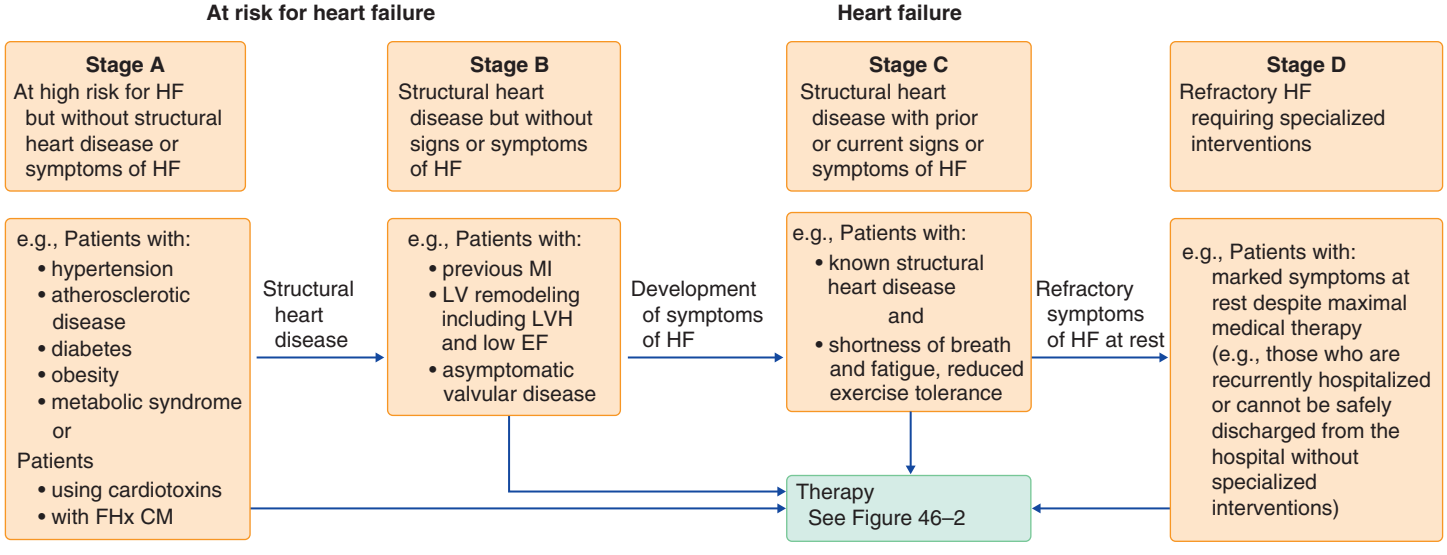

FIGURE 45-1. Stages of heart failure. EF = ejection fraction; FHx CM = family history of cardiomyopathy; HF = heart failure; LV = left ventricle; LVH = left ventricular hypertrophy; MI = myocardial infarction. (Modified from Heidenreich PA. 2022 AHA/ACC/HFSA guideline for the management of heart failure: a report of the American College of Cardiology/American Heart Association Joint Committee on Clinical Practice Guidelines. *Circulation*. 2022;145:e895-e1032.)

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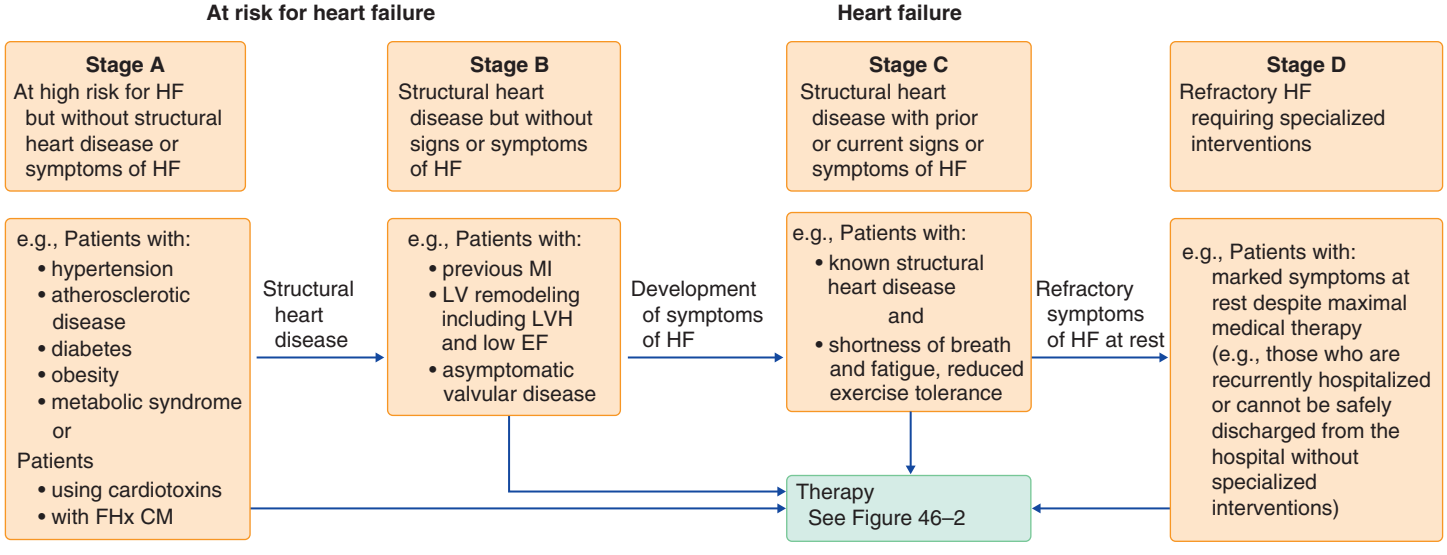

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ABSTRACT

The prevalence of heart failure is increasing worldwide owing to the aging population and development of more effective treatments of many heart diseases that injure the myocardium. Heart failure is now classified by the presence or absence of left ventricular systolic dysfunction, with a growing appreciation for the complexity of patients who have heart failure with preserved left ventricular systolic function. The evaluation of heart failure integrates a carefully performed history and physical examination, a thorough knowledge of general medicine, and the appropriate use of diagnostic testing.

KEYWORDS

heart failure
heart failure with reduced ejection fraction
heart failure with preserved ejection fraction
biomarkers
cardiac imaging

TABLE 45-1 CAUSES OF HEART FAILURE

Coronary artery disease or prior myocardial infarction or ischemic injury
Hypertension
Familial and genetic disorders, including dilated cardiomyopathies, hypertrophic cardiomyopathies, storage diseases, and muscular dystrophies
Valvular disease: valvular stenosis or regurgitation
Toxic/drug-induced damage, including prior chemotherapy
Infiltrative processes, such as sarcoid, amyloid, and hemochromatosis (i.e., restrictive cardiomyopathy)
Arrhythmia-related dysfunction, including premature ventricular contraction–induced cardiomyopathy and atrial tachyarrhythmia–related dysfunction
Arrhythmogenic right ventricular cardiomyopathy
Pulmonary heart disease, including cor pulmonale
Infectious agents, including viral infections and Chagas disease
Immunologically mediated myocardial injury
Intra- and extra-cardiac shunts
Constrictive pericarditis (i.e., nonmyocardial processes)
Nutritional disorders, such as beriberi
Inflammatory heart disease such as systemic lupus erythematosus
High-output states, such as chronic anemia, thyrotoxicosis

TABLE 45-2 FACTORS THAT MAY PRECIPITATE ACUTE DECOMPENSATION OF CHRONIC HEART FAILURE

Myocardial ischemia or infarction
Arrhythmias
Worsening hypertension
Worsening mitral or tricuspid regurgitation
Initiation of medications that worsen heart failure (calcium antagonists, β-blockers, nonsteroidal anti-inflammatory drugs, antiarrhythmic agents, chemotherapeutic drugs, antidiabetic drugs)
Failure to adhere to guideline-directed management
Dietary indiscretion
Iatrogenic volume overload (transfusion, fluid administration)
Alcohol consumption
Fever or infection
Anemia
Thyroid abnormalities
Exposure to environmental toxins
Exposure to high altitude
Pregnancy

(Chapter 47), valves (Chapter 60), and pericardium (Chapter 62), as well as endocrinopathies, metabolic abnormalities, and genetic conditions,[8] may cause heart failure. Chemotherapy (e.g., anthracyclines and trastuzumab; Chapter 164) and chest radiation (Chapter 18) may damage the myocardium. Reversible myocardial dysfunction from toxin exposure (e.g., cocaine [Chapter 365] and excessive alcohol intake [Chapter 364]), persistent tachycardia (Chapters 52 and 53), and severe mental/emotional stress (e.g., takotsubo cardiomyopathy [Chapter 47]) may cause ventricular dysfunction that typically resolves following withdrawal of the inciting etiology. Right-sided heart failure is most commonly caused by left-sided heart failure, but it also can result from pulmonary thromboembolic disease (Chapter 68), chronic lung disease (Chapters 76 and 80), and pulmonary arterial hypertension (Chapter 69).[9]

The underlying causes of heart failure vary by region. For instance, Chagas cardiomyopathy (Chapter 47) is prevalent in Central and South America. Rheumatic valvular disease is a common cause of heart failure in developing countries but is infrequent in developed countries.

Acute decompensation of heart failure may be related to worsening of the primary cause, a new cardiac or pulmonary condition, the influence of other disease states that require increased cardiac output, poor adherence to medical therapies, or the addition of medications used to treat other conditions (Table 45-2). As a result, a systematic approach to the clinical evaluation is critical. Some patients will have decompensated heart failure that requires hospitalization, whereas others will have heart failure as a comorbidity during hospitalization for another problem.

PATHOBIOLOGY

A number of factors contribute to the development and progression of heart failure (Table 45-3). The relative contribution of these mechanisms to the overall pathophysiologic manifestations of heart failure (E-Fig. 45-1) varies in individual patients.

Heart Failure with a Reduced Ejection Fraction

A central tenet of heart failure is that myocardial dysfunction limits the heart's ability to pump blood at a rate commensurate with the requirements of metabolizing tissues or that it can do so only in the setting of elevated cardiac filling pressures. The pathobiology of the failing heart results in maladaptive regulation of multiple neurohormonal pathways that reduce intrinsic cardiac contractility and cause prototypical ventricular remodeling (Chapter 41). Alterations in cardiac extracellular matrix and replacement fibrosis increase the connective tissue content and further impair systolic and diastolic function (Chapter 41). Several neurohormonal pathways regulate myocardial fibrosis, including aldosterone, matrix metalloproteinases, tissue inhibitors of metalloproteinases (TIMPS), TNF-alpha, and ST2.

Adrenergic nervous system activation plays a pivotal role in the development and progression of left ventricular dysfunction. Reduced pulse pressure

TABLE 45-3 PATHOBIOLOGIC MECHANISMS OF HEART FAILURE

Hemodynamics
Neurohormones
Cardiorenal interactions
Abnormal calcium cycling
Cell death
Myocardial genetics

activates arterial baroreceptors and stimulates sympathetic nervous system activity, elevated levels of circulating norepinephrine, and increased release of norepinephrine by several organs, including the heart. Exposure of cardiac myocytes to chronically elevated levels of norepinephrine reduces the density of their β-adrenergic receptors, downregulates signaling pathways, and is directly toxic to the cells. The renin-angiotensin-aldosterone system, which is also activated relatively early in heart failure, causes vasoconstriction and sodium retention. The presumptive mechanisms of induction include renal hypoperfusion, β-adrenergic system stimulation, and hyponatremia. Adrenergic and renin-angiotensin-aldosterone system activation stimulate the failing heart and support the circulation in the short term. Over time, however, the prolonged activation of these systems causes maladaptive remodeling and further ventricular dysfunction. In addition, the sympathetic nervous system and renin-angiotensin-aldosterone system are co-regulated, such that increased activity of each pathway stimulates a simultaneous increase in the other.

Natriuretic peptides counterbalance the vasoconstricting and sodium-retaining properties of the renin-angiotensin-aldosterone system and sympathetic nervous systems by causing both arterial and venous vasodilation, natriuresis, and diuresis. The extent of natriuretic pathway activation is a marker of the severity of heart failure and is associated with adverse outcomes, including the risk for hospitalization and death.

Many patients with heart failure have elevated levels of endothelin and arginine vasopressin. Arginine vasopressin induces vasoconstriction through a vascular (V_1) receptor and reduces free water clearance through a renal tubular (V_2) receptor. Endothelin causes prolonged vasoconstriction, reductions in glomerular filtration, and pulmonary arteriolar constriction.

Cardiorenal interactions highlight the integral role of kidney dysfunction in the worsening of heart failure, with both organs contributing to the retention of sodium and water. In most patients with chronic heart failure, the kidneys are anatomically and structurally normal, but passive venous congestion and reduced renal perfusion lead to worsening renal function and a vicious cycle of progressive dysfunction of both organ systems. Renal failure may limit the ability to use inhibitors of the renin-angiotensin-aldosterone system to treat heart failure.

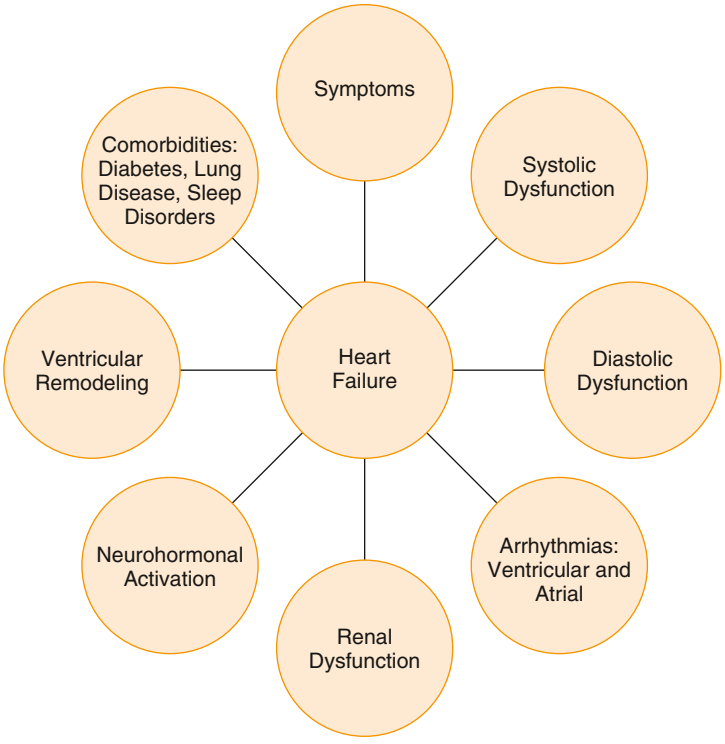

E-FIGURE 45-1. Pathophysiology of heart failure. The contributing and exacerbating factors to the pathophysiologic process of heart failure.

Abnormal calcium cycling reduces the calcium content in the cardiac sarcoplasmic reticulum owing to diastolic leak through altered ryanodine receptors. The reduced calcium content of the sarcoplasmic reticulum alters the contraction interactions between cardiac myosin and actin myofilaments. In addition, a loss of function of cardiac SERCA2a (sarcoendoplasmic reticulum calcium transport ATPase 2a) pumps, which are responsible for removal of cytoplasmic calcium, affects ventricular relaxation and causes diastolic dysfunction.

In all forms of heart failure, a variety of stimuli (e.g., elevated neurohormone levels, adrenergic activation, inflammatory mechanisms, and toxin exposure) accelerate cell death. Elevated serum levels of proinflammatory cytokines (including tumor necrosis factor-α, interleukin-1β, and interleukin-6) induce contractile dysfunction, myocardial fibrosis, and myocyte necrosis, perhaps by mediating some of the deleterious responses to catecholamines and angiotensin II.

Persistent tachycardia (e.g., atrial fibrillation with rapid ventricular response) also can result in heart failure, presumably related to chronic hyperadrenergic stimulation.[10] In some patients, the tachycardic response to heart failure may itself contribute to worsening heart failure. These forms of heart failure may be reversible, depending on the relative contribution of the tachycardia to the underlying myocardial dysfunction.

Genetic mutations are increasingly identified as important mediators of the cardiac structural and functional abnormalities linked to symptomatic heart failure (see E-Table 47-1). The majority of familial cardiomyopathies (Chapter 47), most of which are inherited in an autosomal dominant fashion, are related to defects in cytoskeletal or nuclear proteins. Inherited cardiomyopathies are also associated with muscular dystrophies, infiltrative diseases such as hemochromatosis, and mitochondrial disorders. A low plasma transthyretin concentration is a marker of transthyretin tetramer instability associated with a higher risk of heart failure in the general population even in the absence of amyloidosis.[11]

Heart Failure with a Preserved Ejection Fraction

The pathophysiologic mechanism of heart failure with a preserved ejection fraction is complex and includes alterations in cardiac structure and function, vascular abnormalities, end-organ dysfunction, and interrelated comorbidities (Table 45-4).[12] In principle, diastolic dysfunction in heart failure with a preserved ejection fraction can result from increased ventricular stiffness due to hypertrophy and interstitial fibrosis as well as from abnormal ventricular relaxation due to dysfunctional calcium cycling. Although there are many potential causes of heart failure with preserved ejection fraction, most patients have current or prior hypertension; the resulting left ventricular hypertrophy and fibrosis are responsible for increased chamber stiffness. Ischemic heart disease also may contribute to heart failure with a preserved ejection fraction by virtue of subendocardial fibrosis or as a result of intermittent ischemic dysfunction. Age itself is a crucial predisposing factor because it causes loss of myocytes (apoptosis), increased fibrosis with shifts to more rigid forms of collagen, and loss of vascular compliance.

Myocardial relaxation is an energy-dependent process. Processes that interfere with myocardial energy metabolism, such as ischemia, compromise myocardial relaxation. These changes reduce ventricular compliance and increase filling pressures. Elevated filling pressures raise the pulmonary capillary wedge pressure and contribute to the sensation of dyspnea. Diastolic dysfunction may remain asymptomatic for years, but increasing age, renal dysfunction, hypertension, and progressive left ventricular dysfunction are associated with the development of symptomatic heart failure. The resting hemodynamic profile in heart failure with preserved ejection fraction is frequently normal, but physiologic perturbations such as tachycardia or exercise result in exaggerated increases in filling pressures. This phenomenon accounts for the exertional limitations seen in this syndrome.[13] Furthermore, because atrial contraction is responsible for a disproportionately large proportion of ventricular diastolic filling into a noncompliant ventricle, atrial fibrillation can exacerbate symptoms. Abnormalities in ventricular relaxation and myocardial stiffness limit ventricular filling, so patients may have a narrow window for optimal fluid volume. Modest volume overload can substantially exacerbate symptoms of dyspnea, and diuresis may precipitate symptomatic hypotension owing to ventricular underfilling. Although isolated diastolic dysfunction can occur, the majority of patients with ventricular dysfunction have both systolic and diastolic components. As a result, it is preferable to characterize patients as having heart failure with a preserved ejection fraction or heart failure with a reduced ejection fraction rather than as having systolic or diastolic heart failure.

High-output heart failure is seen in severe anemia and hyperthyroidism (Chapter 207). It is also seen in patients with vasodilative states such as obesity (Chapter 201), late-stage liver disease (Chapter 140), arteriovenous shunts, hypoxic-hypercapnic lung disease, and myeloproliferative/myelofibrotic disorders with extramedullary hematopoiesis (Chapter 152).

TABLE 45-4 CONTRIBUTIONS TO HEART FAILURE WITH PRESERVED EJECTION FRACTION

Left ventricular hypertrophy
Hypertension
Myocardial fibrosis
Subendocardial fibrosis (from intermittent ischemia, especially with diabetes)
Arterial stiffness
Endothelial dysfunction
Inflammation

CLINICAL MANIFESTATIONS

The diagnosis of heart failure may be apparent when patients present with classic symptoms of shortness of breath in combination with a clinical examination consistent with volume overload. A previous history of a myocardial infarction or poorly controlled hypertension should increase the clinician's suspicion for the diagnosis. In contrast, the diagnosis may be missed or delayed in patients who experience a more insidious course with vague symptoms, such as fatigue and exercise intolerance. The use of biomarkers such as natriuretic peptides has significantly improved diagnostic accuracy in recent years.

The evaluation of a patient with suspected heart failure should proceed in an organized and focused manner (Fig. 45-2 and Table 45-5).

Symptoms

Shortness of Breath

Dyspnea (Chapter 71) is the most common but nonspecific symptom of heart failure, and patients with predominant lung disease or anemia may have similar symptoms. In most heart failure patients, dyspnea is present only with activity. It is the most common reason that patients seek care for heart failure, both during the chronic state and with acutely decompensated heart failure. The most important cause of dyspnea is pulmonary congestion that increases the accumulation of interstitial or intra-alveolar fluid, reduces lung compliance, and increases the work of breathing (E-Fig. 45-2). The relief of dyspnea is a primary treatment goal because of its effect on quality of life and its association with worse in-hospital and postdischarge outcomes.

When dyspnea occurs in the recumbent position, it is called *orthopnea*. Orthopnea results from the increase in venous return from the extremities and splanchnic circulation to the central circulation with changes in posture. The increase in ventricular preload raises pulmonary venous and pulmonary capillary hydrostatic pressures. Orthopnea is clinically characterized by the number of pillows a patient requires to sleep comfortably without shortness of breath. Patients with orthopnea may report an inability to sleep in a bed and instead may sleep sitting upright. Orthopnea is a specific symptom of heart failure, and it correlates well with the severity of pulmonary congestion.

Bendopnea is defined as dyspnea that occurs while bending over. The mechanism of bendopnea is poorly defined but appears to be related to increases in left ventricular filling pressures during bending in patients with a baseline elevation in pulmonary capillary wedge pressure. There appears to be an association between bendopnea and baseline mismatch of left- and right-sided filling pressures (i.e., elevated wedge pressure out of proportion to right atrial pressure). The clinical spectrum of this symptom and its relationship to outcomes are not well understood, but recent data suggest that this symptom may be more common than has previously been recognized.

Paroxysmal nocturnal dyspnea is acute, severe shortness of breath that awakens the patient from sleep. Paroxysmal nocturnal dyspnea usually occurs about 1 hour after the patient lies in a recumbent position and subsides with sitting or standing. Paroxysmal nocturnal dyspnea results from increased venous return and the mobilization of interstitial fluid from the splanchnic circulation and lower extremities, with accumulation of alveolar edema. Paroxysmal nocturnal dyspnea is relatively uncommon but almost always represents severe heart failure, and it appears to be associated with increased mortality.

Fatigue

Fatigue occurs in more than 90% of patients with heart failure. Although nonspecific and difficult to quantify, it can be an occult and troublesome manifestation of heart failure.

Chest Pain

Chest pain (Chapter 39) may be mediated by myocardial ischemia related to underlying coronary artery disease or increased wall stress that is proportional

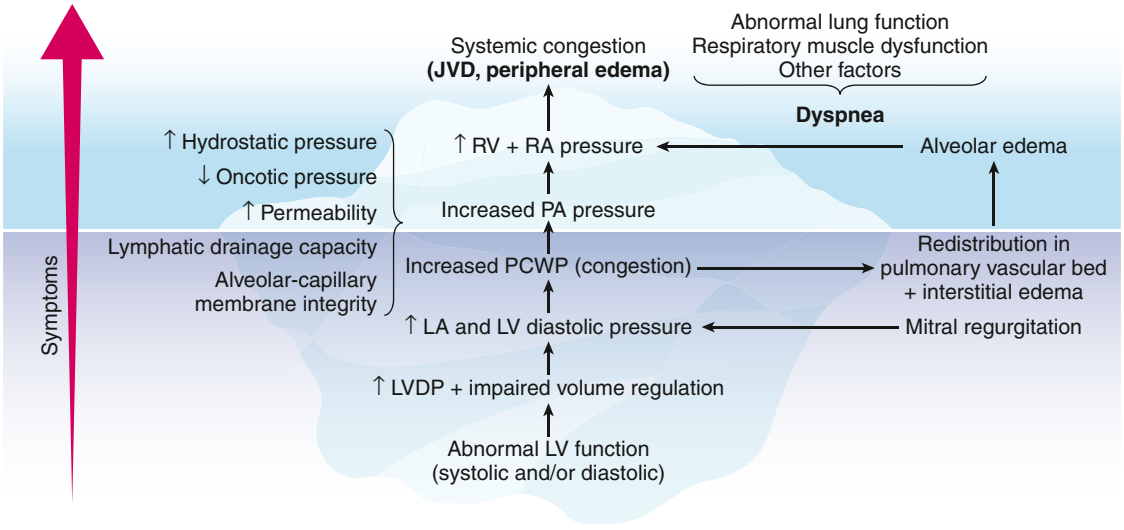

E-FIGURE 45-2. **Role of congestion in heart failure.** JVD = jugular venous distention; LA = left atrial; LV = left ventricular; LVDP = left ventricular diastolic pressure; PA = pulmonary artery; PCWP = pulmonary capillary wedge pressure; RA = right atrial; RV = right ventricular. (From Gheorghiade M, Follath F, Ponikowski P, et al. Assessing and grading congestion in acute heart failure: a scientific statement from the Acute Heart Failure Committee of the Heart Failure Association of the European Society of Cardiology and endorsed by the European Society of Intensive Care Medicine. *Eur J Heart Fail*. 2010;12:423-433.)

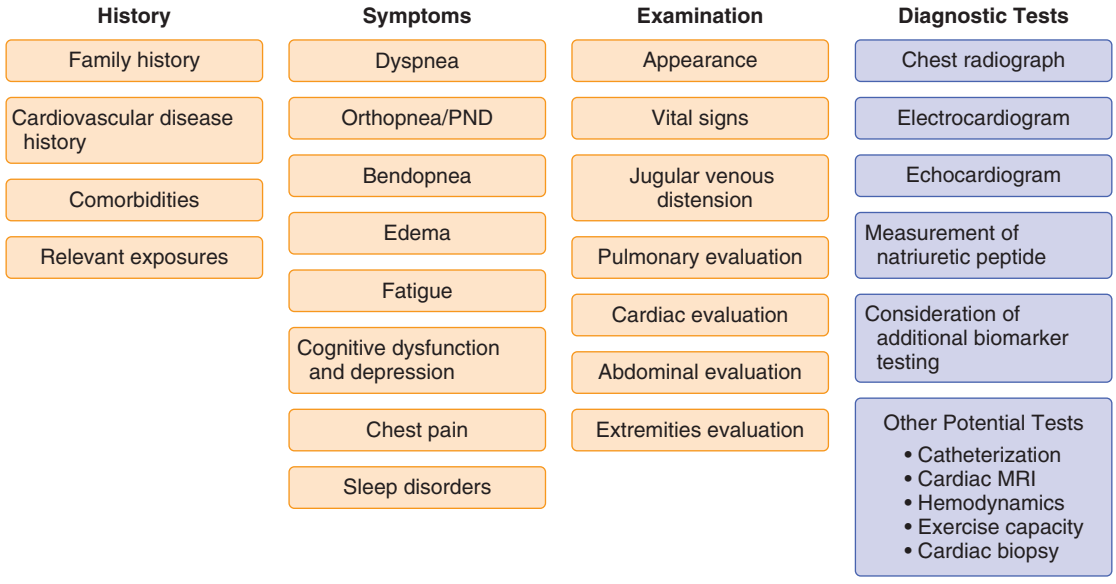

FIGURE 45-2. Diagnostic evaluation of heart failure. The various components of the diagnostic evaluation of heart failure patients are presented from the history, symptoms, and examination to diagnostic testing. MRI = magnetic resonance imaging; PND = paroxysmal nocturnal dyspnea.

TABLE 45-5 APPROACH TO THE DIAGNOSIS OF HEART FAILURE

Obtain a history and physical examination to identify disorders or behaviors that might cause or exacerbate heart failure.
Obtain a family history to aid in diagnosis of heritable causes of heart failure.
Assess volume status and vital signs at each encounter.
Patients with suspected new-onset or acute heart failure should undergo chest radiography to assess heart size and pulmonary congestion and to detect other diseases that may cause or contribute to the patient's symptoms.
A 12-lead electrocardiogram should be obtained for all patients presenting with heart failure.
Echocardiography should be performed during the initial evaluation of patients with heart failure to assess ventricular function and valve function.
Measurement of natriuretic peptides is recommended for the following indications: To support the diagnosis of heart failure in ambulatory patients with dyspnea as well as in those with possible acute heart failure, especially in the setting of an uncertain diagnosis. To establish prognosis or disease severity in heart failure.
The initial evaluation of patients presenting with heart failure should include a complete blood count, urinalysis and renal function, serum electrolytes, glucose and lipid profile, liver function tests, and thyroid-stimulating hormone.
Hemodynamic monitoring is recommended to guide therapy in patients who have respiratory distress or clinical evidence of impaired perfusion in whom the adequacy or excess of intracardiac filling pressures cannot be determined from clinical assessment.

Modified from Yancy CW, Jessup M, Bozkurt B, et al. 2013 ACCF/AHA guideline for the management of heart failure: a report of the American College of Cardiology Foundation/American Heart Association Task Force on Practice Guidelines. *J Am Coll Cardiol.* 2013;62:e147-e239.

to the degree of left ventricular dilation. Left ventricular hypertrophy may cause chest pain from a mismatch between oxygen supply and demand. Patients with amyloid heart disease can have chest pain owing to transient ischemia caused by deposition of amyloid protein in the medial layer of myocardial arterioles.

Cardiac Cachexia

As heart failure progresses, patients may develop constitutional symptoms, including nausea, vomiting, anorexia, abdominal pain, and muscle wasting. The development of cardiac cachexia is associated with a poor prognosis.[14] In many patients, these symptoms arise from right-sided heart failure, with or without concomitant tricuspid regurgitation, and resulting passive venous congestion in the abdominal vasculature or liver. Patients with significant hepatic congestion may develop right upper quadrant abdominal pain and jaundice that can be difficult to distinguish clinically from gallbladder disease or other abdominal conditions (Chapter 141). In patients with advanced cardiogenic shock (Chapter 93), severe abdominal pain can be a particularly ominous sign of abdominal ischemia (Chapter 129).

Cognitive Dysfunction and Mood Disorders

Cognitive dysfunction (Chapter 371) is common, particularly in elderly heart failure patients. Confusion can be a manifestation of worsening heart failure related to relative hypotension or precipitated by medications used to treat heart failure. Although intrinsic brain function itself is not affected in most patients with heart failure, cerebral hypoperfusion in advanced heart failure can cause memory impairment, limited attention span, and altered mentation.

Depressive symptoms (Chapter 362) occur in up to 25% of patients with heart failure. Depressive symptoms can be detected by simple questions such as the Patient Health Questionnaire depression module (see Chapter 23), which has an 80% predictive value for depression and is associated with worse outcomes in heart failure patients.

Sleep Disorders

Sleep-disordered breathing is observed in upward of 70% of heart failure patients and is associated with increased morbidity and mortality. Patterns of sleep-disordered breathing include obstructive sleep apnea and central sleep apnea/Cheyne-Stokes respiration (Chapter 74). Patients may have both types, and the relative proportion of each type varies with the severity of heart failure and its treatment. Nocturnal rostral fluid movement from the lower extremities of heart failure patients may worsen obstructive sleep apnea. Central sleep apnea is due in part to the instability of the ventilatory control systems in heart failure.

Chronic sleep-disordered breathing also causes a series of derangements that may precipitate or exacerbate heart failure. Sleep-disordered breathing increases blood pressure and the risk of arrhythmias.

Symptoms of sleep-disordered breathing (Chapter 374) include hypersomnolence, choking or gasping during sleep, recurrent awakenings, unrefreshing sleep, daytime fatigue, and impaired concentration or memory. The symptoms may be difficult to distinguish from other symptoms of heart failure, including unrefreshing sleep due to orthopnea and paroxysmal nocturnal dyspnea. Treatment of sleep-disordered breathing with continuous positive airway pressure ventilation improves quality of life and left ventricular ejection fraction, but these effects are attenuated after 3 months.[A1] The use of adaptive servo-ventilation increases mortality and should be avoided in this patient population.[A2]

Physical Examination

A carefully performed physical examination is critical to make an accurate diagnosis, assess comorbid conditions, understand the patient's underlying hemodynamic state, and estimate prognosis.[15]

Global Observation and Vital Signs

The patient's general appearance may provide details related to the acuity and severity of the heart failure. Patients with severe symptoms may be pale or

diaphoretic and unable to speak in complete sentences. In extreme circumstances, they may be unable to lie recumbent in bed because of severe dyspnea. The heart rate may be elevated (>100 beats per minute), and premature ventricular beats or atrial arrhythmias are common. Approximately 30% of heart failure patients have atrial fibrillation (Chapter 52). Pulsus alternans (alternating amplitude of successive beats) is an uncommon sign but is virtually diagnostic for advanced heart failure. Blood pressure is most commonly normal or high, but it may be low (systolic blood pressure <90 mm Hg) in advanced low-output heart failure. Blood pressure has historically been identified as an important prognostic marker (i.e., higher blood pressure is associated with improved long-term outcomes), but these associated data may not be applicable to all subgroups of patients, especially the elderly. A narrow pulse pressure (e.g., <30 to 35 mm Hg) is indicative of more severe heart failure. Weight should be assessed and compared with the patient's known dry weight or recent weight trajectory. The assessment of weight not only helps the clinician to appreciate the severity of volume overload, but it may also assist with quantifying the degree of cardiac cachexia. The respiratory rate should be measured. Both low rates and high rates may be seen in heart failure. Likewise, both hypothermia and hyperthermia can be informative of impending shock or secondary causes of heart failure.

Jugular Veins

Examination of the jugular veins assesses right atrial pressure (see Fig. 39-2). Right atrial pressure can be estimated by measuring the height of the jugular pulse in centimeters above the sternal angle and adding 5 cm H_2O (normal = 8 cm H_2O; see Fig. 39-3). An alternative is to assess the height of the veins in relationship to the clavicle. Jugular pulsations can be distinguished from carotid pulsations by their more lateral location, lack of palpability, and a visible double waveform. It may also be useful to compare the timing to the contralateral carotid or radial pulse. If the jugular pulsation is not seen in the neck, the right atrial pressure may be either very high or low. The presence of abdominal-jugular reflux, which is a sign of abnormally elevated right-sided filling pressures, should be assessed by putting sustained pressure on the right upper quadrant of the abdomen for 30 seconds; a positive finding is at least a 1-cm rise in the jugular pressure, which then slowly declines when abdominal pressure is removed. Either an elevated jugular venous pressure or an abnormal abdominal jugular reflux has been reported in 80% of patients with advanced heart failure.

An additional important finding in the neck is evidence of tricuspid regurgitation, which is visualized as a large *cv* wave (see Fig. 39-3). This finding is often corroborated by hepatic pulsations, which can be detected during the abdominal examination. Difficulty palpating the carotid pulses may suggest low cardiac output from heart failure, aortic stenosis, or carotid artery disease (see Fig. 39-4).

Pulmonary Examination

Despite elevated left ventricular filling pressures that are transmitted back into the left atrium and pulmonary circulation, most patients with heart failure do not have evidence of pulmonary congestion on physical examination. The lungs of chronic heart failure patients undergo adaptive changes and have robust lymphatic drainage to compensate for elevated filling pressures. However, a subset of patients may develop alveolar fluid accumulation, which is appreciated as rales (Chapter 71) and which are an independent predictor of prognosis among patients with heart failure and a reduced ejection fraction.[16] These findings are more common in patients with acute pulmonary edema due to sudden decompensation from an inciting event.

Fluid may also accumulate in the pleural space related to the increased transudation of fluid and impaired lymphatic drainage in the setting of elevated systemic venous pressures (Chapter 86). The clinician should listen and percuss for the possible presence of pleural effusions (Chapter 86), which tend to lateralize to the right side owing to the greater surface area of the lungs and the position of the diaphragm.[17] The diagnosis of a moderate or large pleural effusion is critical because draining the effusion may improve dyspnea.

Cardiac Examination

The cardiac examination is the cornerstone of the evaluation of the patient with heart failure. Visual inspection and palpation may reveal a right ventricular heave, suggestive of right ventricular dysfunction and underlying pulmonary hypertension. The location, size, and duration of the point of maximal impulse against the chest wall may provide details related to the degree of left ventricular dilation; the impulse is typically laterally displaced in the setting of left ventricular enlargement and may be sustained in the setting of left ventricular hypertrophy.

Auscultation of the heart sounds provides important information related to the underlying rhythm and frequency of ectopic beats. Auscultation of a loud P2 or the ability to hear a P2 beyond the pulmonic listening area suggests pulmonary hypertension. The presence (or worsening) of valvular disorders (Chapter 60) can be characterized for their potential contribution to cardiac dysfunction. An apical S_3 gallop (see Fig. 39-5 in Chapter 39) is common in severe LV dysfunction, and its presence is correlated with an elevated left ventricular end-diastolic pressure and a poor prognosis. An S_4 gallop is common in patients who have ischemic heart disease and hypertension, and it is more likely indicative of diastolic dysfunction. Pericardial effusions (Chapter 62) may also occasionally occur in the setting of heart failure, particularly in inflammatory cardiomyopathies.

Abdomen

The physical examination should estimate the size of the liver and spleen and elicit the presence of ascites (Chapter 132). Abdominal venous congestion may cause renal venous hypertension and subsequent renal dysfunction. An enlarged and pulsatile liver is seen in individuals with markedly elevated right heart pressures and in patients with significant tricuspid insufficiency. In the setting of irreversible liver disease (i.e., cardiac cirrhosis), patients with heart failure are at a substantially increased risk during surgical interventions. Thus, a thorough abdominal examination represents a critical component of the evaluation of heart failure patients.

Extremities

Edema (Chapter 39) results from the retention of sodium due to low cardiac output and reduced renal perfusion pressures, which ultimately result in elevated right-sided filling pressures, increased hydrostatic pressures in the venous circulation, and transudation of fluid into dependent interstitial spaces, especially in the ankles or lower extremities. Edema is commonly measured on a scale of 0 to 3+, but this system has marked interobserver variation. Peripheral edema is a nonspecific finding, and edema due to heart failure must be distinguished from edema related to medication use (e.g., calcium-channel blockers, thiazolidinediones, or nonsteroidal anti-inflammatory drugs), venous insufficiency, or hypoproteinemia.

The temperature of the extremities should also be assessed. Cool extremities suggest low cardiac output or concomitant peripheral arterial disease (Chapter 65).

DIAGNOSIS

Patterns of Presentation

The initial presentation ranges from subtle outpatient findings to acute decompensation that requires hospitalization (see Figs. 45-3 and 45-4). In critically ill patients with respiratory compromise, the distinction between cardiac pulmonary edema compared with acute respiratory distress syndrome (Chapter 90) can be challenging.[18]

An initial presentation of heart failure may represent the gradual progression of known but previously asymptomatic (stage A or B) heart failure or be the first indication of altered cardiac function. In patients without an antecedent history of heart failure, precipitating factors, such as acute myocardial infarction (Chapter 58), tachyarrhythmias (Chapters 52 and 53), previously unrecognized or new valvular abnormalities (Chapter 60), toxic injury (including alcohol excess), or acute myocarditis (Chapter 47), should be considered.

When patients with stage C or D heart failure present with worsening symptoms, precipitating factors may also include myocardial ischemia, arrhythmias, or worsening of valvular function (see Table 45-2). Other conditions can include anemia, infection, thyroid abnormalities, and any disease process that may accompany or require a higher cardiac output. In many patients, however, the worsening may be gradual, augured by subtle signs and symptoms (Fig. 45-5).

Electrocardiography

A 12-lead electrocardiogram (Chapter 42) should be obtained for all patients who present with possible heart failure to evaluate the cardiac rhythm, identify current ischemia or prior myocardial infarction, and detect evidence of left ventricular hypertrophy. Rhythm abnormalities may be responsible for the development or exacerbation of underlying cardiac dysfunction. For example, an underlying tachyarrhythmia can lead to the development of left ventricular systolic dysfunction that is reversible with appropriate intervention. Q waves suggest coronary artery disease as a likely contributor to ventricular dysfunction. Voltage criteria for left ventricular hypertrophy support a diagnosis of hypertensive heart disease, including heart failure with a preserved ejection fraction. Underlying conduction abnormalities, such as delayed ventricular conduction (i.e., bundle branch morphology), determine eligibility criteria for cardiac resynchronization therapy in appropriate patients (Chapters 46 and 54) and have important prognostic implications. Holter monitoring sometimes may be helpful to determine the burden of ventricular arrhythmias or ectopic beats because tachycardia-mediated cardiomyopathies may be reversible with medical or ablation therapy.

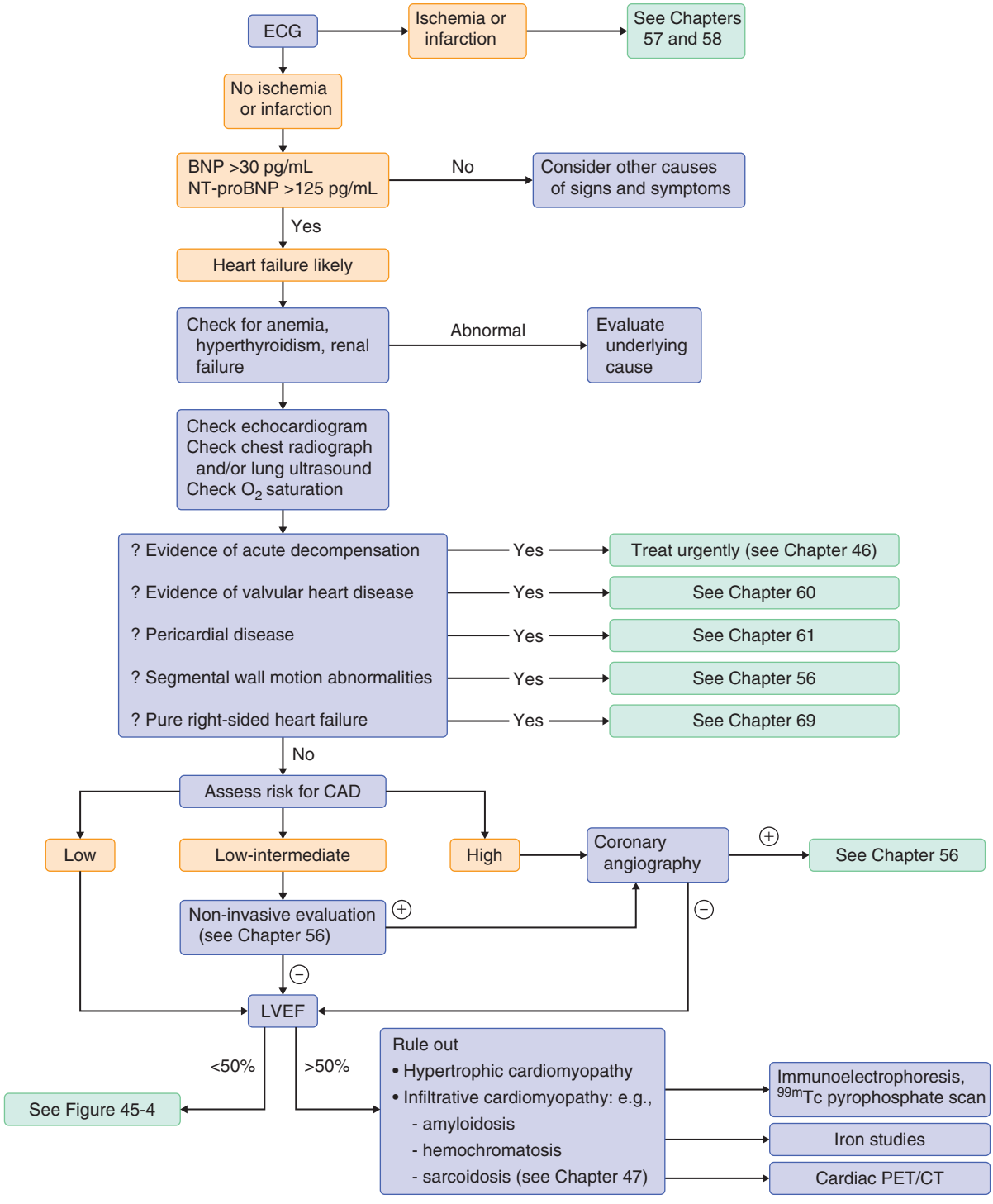

FIGURE 45-3. **Diagnostic approach to the patient with suspected heart failure.** BNP = brain natriuretic peptide; CAD = coronary artery disease; CT = computed tomographic scan; ECG = electrocardiogram; LVEF = left ventricular ejection fraction; NT-proBNP = N-terminal pro-B-type natriuretic peptide; PET = positron emission tomography.

Chest Radiography

Patients with suspected new-onset or worsening heart failure should undergo chest radiography to assess heart size and pulmonary congestion as well as to detect other diseases that may cause or contribute to the patient's symptoms. Many patients with acute heart failure but only a minority of those with chronic heart failure have clear evidence of pulmonary venous hypertension (upper lobe vascular redistribution, enlarged pulmonary veins) or pulmonary edema (perihilar or patchy peripheral infiltrates; see Fig. 44-2). Pleural effusions, usually on the right if unilateral but often bilateral, are also identified on the chest radiograph (see Fig. 86-3). Chest radiography may also play a role in identifying the location of the lead placement of intracardiac devices, such as biventricular pacemakers. Inappropriate lead placement may be observed in patients with worsening heart failure symptoms.

Laboratory Testing

The initial evaluation of patients presenting with heart failure should include a complete blood count to detect anemia and systemic diseases with hematologic manifestations; urinalysis and tests of renal function to assess underlying renal disease; serum electrolyte values to identify abnormalities needing treatment and to provide a baseline for subsequent therapy; glucose level and lipid profile to diagnose diabetes and dyslipidemia, which should be carefully managed in patients with heart failure; and thyroid-stimulating hormone level. Markers of hepatic congestion, such as elevated serum aminotransferase and bilirubin levels (Chapter 133), also should be measured because they have prognostic importance. Screening for hemochromatosis (Chapter 196) or human immunodeficiency virus (HIV) infection is reasonable in selected patients with heart failure. Diagnostic tests for rheumatologic diseases (Chapter 236), amyloidosis (Chapter 174), or pheochromocytoma (Chapter 209) are

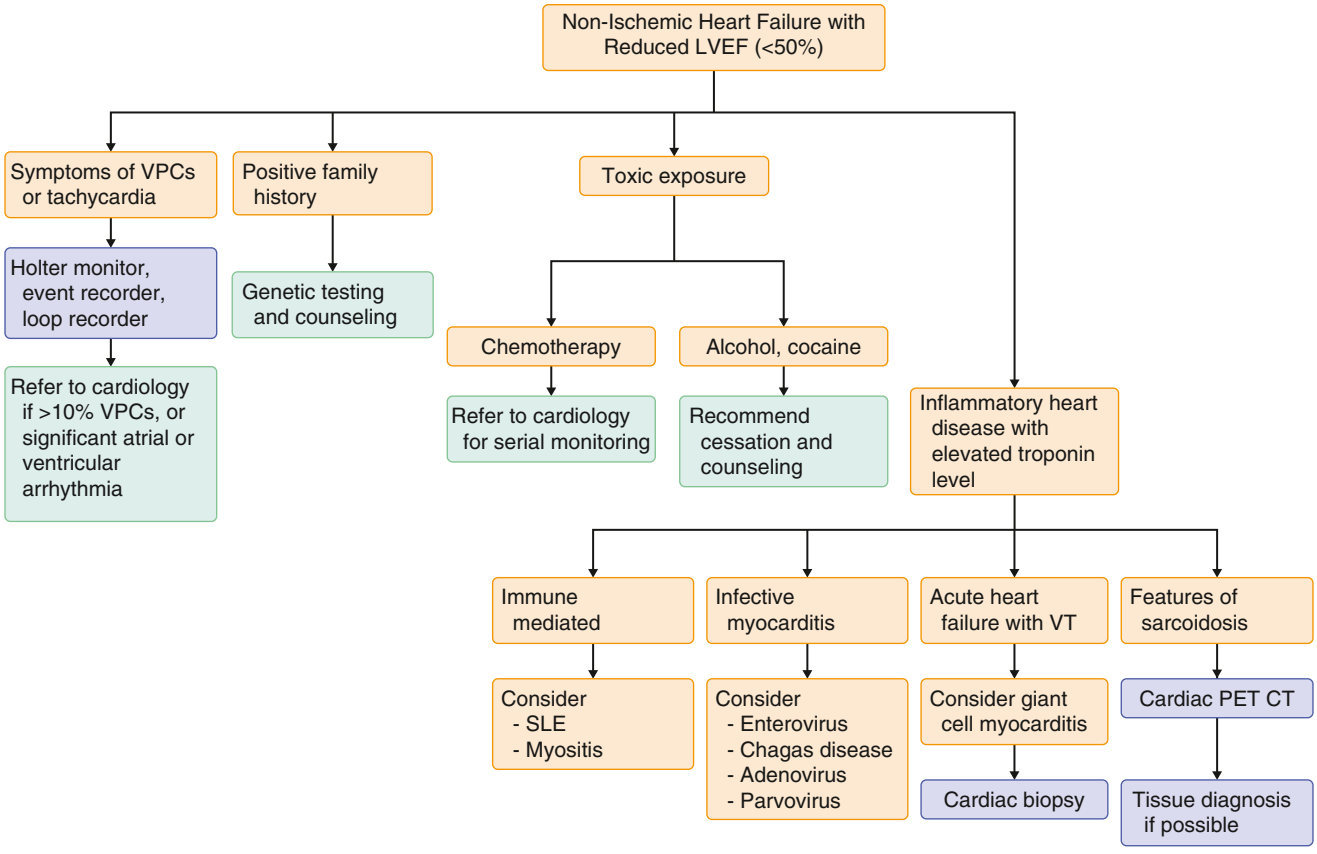

FIGURE 45-4. **Diagnostic approach to the patient with nonischemic heart failure and a reduced left ventricular ejection fraction.** CT = computed tomographic scan; LVEF = left ventricular ejection fraction; PET = positron emission tomography; SLE = systemic lupus erythematosus; VPC = ventricular premature contraction; VT = ventricular tachycardia.

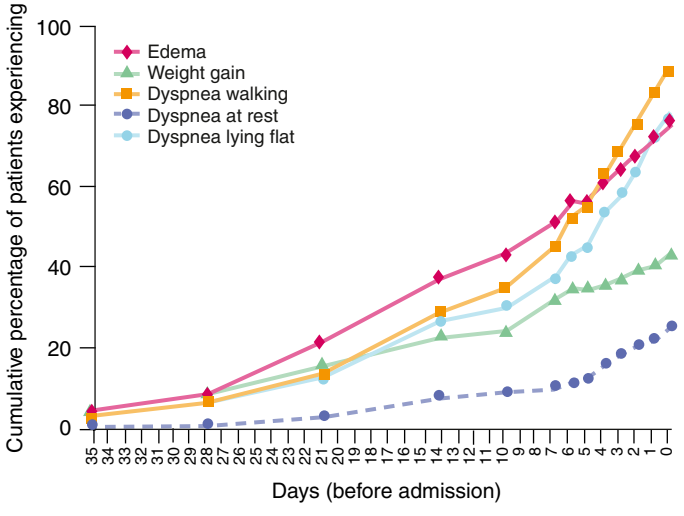

FIGURE 45-5. **Number of days from onset of worsening of selected symptoms of heart failure to admission to the hospital: cumulative percentage of patients.** (From Schiff GD, Fung S, Speroff T, et al. Decompensated heart failure: symptoms, patterns of onset, and contributing factors. *Am J Med*. 2003;114:625-630.)

not routinely indicated but rather should be targeted to patients with other ancillary findings suggestive of these conditions. Viral antibody titers yield relatively little incremental information and are rarely indicated in the evaluation of heart failure.

Natriuretic Peptides

Brain natriuretic peptide (BNP) and its amino-terminal fragment (NT-proBNP) provide incremental diagnostic and prognostic information above and beyond the history and physical examination in patients with heart failure. A natriuretic peptide level should be measured to support the diagnosis of heart failure in ambulatory patients with dyspnea, as well as in patients with possible acute heart failure, especially in the setting of an uncertain diagnosis. It also is useful to estimate the severity of heart failure and its prognosis.

BNP levels are relatively sensitive (about 95 to 99%) but less specific (about 50 to 60%) markers for diagnosing clinically confirmed heart failure. Circulating levels are influenced by comorbid processes. For example, obesity reduces BNP levels, whereas advancing age and renal dysfunction are associated with higher levels. Most heart failure therapies reduce BNP levels, but the usefulness of BNP-guided heart failure therapy is not well established.[A3,A4]

Troponin

Owing to the increased sensitivity of currently available troponin assays, the majority of patients admitted with acute heart failure have elevations in circulating troponin even without any obvious myocardial ischemia. These elevations, which suggest ongoing myocyte injury or necrosis, are associated with worse clinical outcomes and mortality.[19]

Other Biomarkers: Galectin-3 and ST2

A number of additional biomarkers characterize inflammation, myocyte injury, neurohormonal upregulation, and extracellular matrix turnover in patients with heart failure (E-Table 45-1). In the future, strategies that combine multiple biomarkers into a risk stratification model may prove additive to clinical judgment.

Echocardiography

An echocardiogram should be obtained during the initial evaluation of patients with heart failure to assess ventricular and valvular function. Repeated echocardiograms are also indicated when patients have a significant change in their clinical status or receive treatment that may have had a significant effect on cardiac function. In contrast, routine repeated measurements of left ventricular function in the absence of a change in clinical status or treatment should not be performed.

Echocardiography (Chapter 43) allows the assessment of systolic and diastolic ventricular function (see Figs. 43-2 and 43-3). Wall thickness, chamber size, and regional wall motion abnormalities provide evidence of the underlying etiology of heart failure with a diminished or preserved ejection fraction.[20] Echocardiography also evaluates valvular dysfunction (Chapter 60), which may be the result of or cause worsening ventricular

E-TABLE 45-1 EMERGING BIOMARKERS IN CHRONIC HEART FAILURE

BIOMARKER	PROPOSED PATHOPHYSIOLOGY	POTENTIAL ROLE IN PATIENTS WITH CHRONIC HF
Copeptin	Stable plasma surrogate for vasopressin, which is released from the hypothalamus in response to changes in plasma osmolarity and reduced cardiac output Elevated levels of vasopressin contribute to development of hyponatremia, vasoconstriction, and adverse cardiac remodeling	Independent role as a prognostic marker in patients with chronic HF Potential role of molecular marker for tailored therapies with vasopressin antagonism
Cystatin C	Cysteine protease inhibitor that is more sensitive and specific to changes in GFR than creatinine Produced at a constant rate by all nucleated cells of the body	Independent predictor of mortality in patients with chronic HF Identifies poor prognosis even in patients with a normal creatinine level, pointing to a role as a marker of the CRS
Endothelin 1	Produced by the endothelium in response to ATII, inflammation, and vascular shear stress Causes vasoconstriction and adverse cardiac remodeling	Independent predictor of mortality in patients with chronic HF Clinical application requires measurement of the more stable precursor (CT-proET-1) Whether patients with elevated levels of CT-proET-1 would benefit from endothelin 1 antagonism is unclear
Galectin-3	β-Galactoside–binding lectin produced by several tissues Promotes cardiac fibroblast proliferation and collagen synthesis (maladaptive remodeling)	Predicts mortality independent of natriuretic peptides in patients with chronic HF Does not appear to be modified by treatment Potential role as a target for therapy
GDF-15	Member of the TGF-β cytokine family Expressed in most tissues Expression in myocytes is triggered by ischemia, stretch, inflammation, and neurohormonal activation May protect myocytes against apoptosis and hypertrophy	Predictive of mortality in patients with chronic HF independent of established biomarker Serial changes are associated with prognosis Could lead to the development of unique treatments for patients with chronic HF
hs-cTn	Proteins involved in the regulation of cardiac and skeletal muscle contraction Released after loss of myocytes from necrosis, apoptosis, or reversible injury with increased membrane permeability	Predictive of chronic HF mortality in patients with no known CHD Independently predictive of mortality in patients with chronic HF The effect of serial changes in hs-cTn levels on prognosis, and how therapy should be modified on the basis of increased levels of hs-cTn, is unknown
MR-proADM	Produced by various tissues within the cardiovascular system in response to hemodynamic stress Favorable effects on the vasculature—positive inotropy and vasodilation	May add prognostic value to predictive models for patients with chronic HF beyond that provided by natriuretic peptides and traditional clinical risk factors
Neuregulin 1	Belongs to a family of growth factors with an important role in cardiac development and the pathogenesis of chronic HF Has an important role in promoting cardiomyocyte growth in function and regulation of the stress response	Preliminary studies show independent associations with disease severity and risk of adverse outcomes in patients with chronic HF A promising target for drug therapy Trials with recombinant neuregulin are already under way, with a phase II trial showing improvement in cardiac structure and function
NGAL	Small glycoprotein released by multiple cell types during inflammation and injury Involved in cell survival, inflammation, and matrix degradation Early marker of renal tubular damage Increased levels found in patients with chronic HF	Early detection of renal injury in patients with chronic HF A more effective marker of CRS than creatinine Independent predictor of mortality in patients with chronic HF
sST2	Member of the IL-1 receptor family that is secreted from myocytes during biomechanical strain Possible mediator of myocardial hypertrophy and fibrosis by compromising the favorable effects of IL-33/ST2 signaling	Independent predictor of morbidity and mortality in patients with chronic HF Possible role as a novel therapeutic target

ATII = angiotensin II; CHD = coronary heart disease; CRS = cardiac-renal syndrome; CT-proET-1 = C-terminal pro-endothelin 1; GDF = growth differentiation factor; GFR = glomerular filtration rate; HF = heart failure; hs-cTn = cardiac troponins measured by a highly sensitive assay; IL = interleukin; MR-proADM = mid-regional pro-adrenomedullin; NGAL = neutrophil gelatinase–associated lipocalin; TGF = transforming growth factor.

From Ahmad T, Fiuzat M, Felker GM, et al. Novel biomarkers in chronic heart failure. *Nat Rev Cardiol*. 2012;9:347-359.

function or symptoms. Quantitative measurements of pulmonary artery pressure and central venous pressure help characterize the degree of pulmonary hypertension and may guide diuretic therapies in circumstances in which the jugular veins are difficult to visualize. Detection of atrial or ventricular thrombi requires anticoagulation. Novel methods using ventricular strain analysis and three-dimensional echocardiography can provide additional insights about myocardial performance.

Point-of-Care Ultrasound

Point-of-care ultrasonography has gained increasing acceptance as a noninvasive tool for the detection and quantification of jugular venous distention[21] and pulmonary congestion[22] in both ambulatory and hospitalized patients with potential heart failure. However, adding ultrasound to the standard clinical evaluation has not been shown to reduce admission rates or mortality, although it may reduce future urgent visits for worsening symptoms.[A5]

Nuclear Cardiology and Coronary Angiography

Significant coronary artery disease is common in adults with heart failure and should prompt careful evaluation for ischemia, which is common not only in patients who have heart failure with a reduced ejection fraction but is also found (either as epicardial stenosis or microvascular dysfunction) in about 90% of patients who have heart failure with a preserved ejection fraction[23] (Chapters 39, 43, 44, and 56). When myocardial ischemia may be contributing to heart failure, coronary arteriography (Chapter 59) is reasonable to assess eligibility for revascularization.

The most powerful predictors of prognosis for patients with ischemic cardiomyopathy are a history of prior myocardial infarction, stenosis of 75% or greater of the left main or proximal left anterior descending artery, stenosis of 75% or greater of two or more epicardial vessels, and the severity of ventricular dysfunction. Coronary computed tomographic angiography (Chapter 44) may represent a noninvasive modality for assessing coronary disease in appropriately selected patients.

Noninvasive imaging (Chapter 44) to detect myocardial ischemia and viability is reasonable in patients who present with de novo heart failure and in patients who have known coronary artery disease and no angina, unless they are not eligible for revascularization. Viability assessment is reasonable in select situations in planning revascularization for patients who have heart failure and coronary artery disease.[24] However, stress testing to assess myocardial viability so far has not been able to identify patients who will benefit from revascularization compared with medical therapy alone.

For suspected cardiac transthyretin amyloidosis (Chapters 47 and 174), which is responsible for about 6% of cases of heart failure with a preserved ejection fraction,[25] a ^{99m}Tc-pyrophosphate scan is highly sensitive and specific. Typical findings avoid the need for a confirmatory biopsy.[26]

The single-photon emission computed tomography tracer *m*-iodobenzylguanidine (mIBG) has been widely used for studying causes and effects of cardiac sympathetic hyperactivity. Cardiac sympathetic imaging with mIBG is a noninvasive tool that may assist with the risk stratification of patients with heart failure. With mIBG imaging, the myocardial uptake and distribution can be visually assessed and quantified by calculating a heart-to-mediastinum ratio. This approach provides a highly reproducible index of cardiac sympathetic activity. Further study is required to determine the role of this imaging modality in heart failure risk stratification and clinical care.

Cardiac Magnetic Resonance Imaging

Cardiac magnetic resonance imaging (Chapter 44) provides accurate measurements of left ventricular volume and ejection fraction, and it is useful when echocardiography is inadequate. It is also helpful to assess for potential infiltrative cardiomyopathies when the cause of heart failure, especially heart failure with a preserved ejection fraction, is unclear. Late gadolinium enhancement (see Fig. 44-16) adds important prognostic information related to the risks of ventricular arrhythmias and mortality.

Myocardial Biopsy

Guidelines indicate that endomyocardial biopsy should not be performed in the routine evaluation of patients with heart failure. However, endomyocardial biopsy may be useful in patients who present with heart failure when a specific suspected diagnosis would influence therapy. For example, in patients with acute myocarditis or giant cell myocarditis and in patients with sarcoid or amyloid cardiomyopathy (Chapter 47), the appropriate pathologic diagnosis may inform treatment recommendations and prognosis. In certain circumstances, biopsy may be performed along with genetic testing (e.g., transthyretin gene mutation) to inform decisions on management and counseling of family members.

Assessment of Exercise Capacity

A heart failure patient's exercise capacity can be quantified by several testing modalities, including 6-minute walk distance and cardiopulmonary exercise testing (Chapter 73). Although these tests are not routinely recommended, they are helpful for determining the relative contribution of cardiac compared with pulmonary causes of functional limitation. The results of cardiopulmonary exercise testing are critical to determine candidacy for heart transplantation or placement of a ventricular assist device (Chapter 46). A maximal oxygen consumption of less than 14 mL/kg/minute is associated with a sufficiently poor prognosis that transplantation or implantation of a left ventricular assist device is warranted. Serial cardiopulmonary exercise testing, the 6-minute walk test, or the 60-foot walk test also can be useful to follow the disease course of specific patients objectively.

Invasive Diagnostics and Hemodynamic Monitoring

Invasive monitoring may be useful in selected patients who have acute heart failure, who have persistent symptoms despite adjustment of standard therapies, and whose fluid status or perfusion is uncertain. However, the routine use of pulmonary artery catheters should be discouraged.

Up to 30% of patients with heart failure with a reduced ejection fraction have an implantable device that detects arrhythmias and can provide hemodynamic assessment. Indirect measures, such as changes in impedance or heart rate variability, are precursors to worsening heart failure symptoms. Chronic hemodynamic monitors (i.e., direct measures of pulmonary pressures and right ventricular pressures) have been approved by the U.S. Food and Drug Administration and are now available for the serial measurement of left ventricular filling pressure surrogates. Interrogation of these devices may become part of the routine diagnostic follow-up to guide therapy[27] in patients who have respiratory distress or clinical evidence of impaired perfusion in whom the adequacy or excess of intracardiac filling pressures cannot be determined by clinical assessment.

CONSEQUENCES OF MISDIAGNOSIS

The diagnosis of heart failure may be straightforward in a patient with dyspnea, signs of congestion, and an elevated BNP level. Conversely, many patients have multiple comorbid conditions that make the assessment of shortness of breath a diagnostic dilemma. Pulmonary conditions such as chronic obstructive pulmonary disease (Chapter 76) represent the most common reason for misdiagnosis. The BNP level and echocardiogram provide useful information to make this distinction. Other potential causes of edema or volume overload include renal failure (Chapter 117), venous thrombosis (Chapter 68), and venous insufficiency. If left ventricular systolic function is normal, it may be difficult to make a conclusive determination of the relative role of heart failure with preserved ejection fraction compared with other concomitant conditions, such as pericardial constriction, severe obesity, deconditioning, chronic anemia, or other systemic illnesses. BNP levels may be helpful in some circumstances. In other situations, exercise testing or invasive hemodynamic testing may be necessary to establish the appropriate diagnosis. Misdiagnosis can result in excessive and unnecessary diagnostic testing, higher costs, and increased morbidity and mortality because of the inappropriate use or nonuse of heart failure therapies.

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For the General References and other additional features, please visit Elsevier eBooks+ at https://ebooks.health.elsevier.com.

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46 HEART FAILURE: TREATMENT AND PROGNOSIS

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EVALUATION AND MANAGEMENT OF HEART FAILURE

Heart failure is an overarching term for a syndrome (i.e., a constellation of signs and symptoms) that encompasses a vast spectrum of cardiovascular disorders and is associated with a greatly heightened risk for death and nonfatal adverse cardiovascular events (Chapter 45). Treatment is initially directed toward prevention of cardiac injury (e.g., due to hypertension or myocardial infarction) or toward limiting structural progression if cardiac damage has already occurred (e.g., left ventricular remodeling with declining left ventricular ejection fraction) and delaying the development of symptomatic heart failure. When symptoms develop, treatments are also directed at improving functional status as well as prognosis.

At least one in five adults will develop heart failure. In the United States, 6.5 million people have heart failure, and 1.25 million patients are discharged from U.S. hospitals annually with a primary diagnosis of heart failure.[1] The estimated cost of heart failure in the United States exceeds $30 billion per year. Randomized controlled clinical trials (RCTs) supply the framework for quantifying what different therapeutic approaches can offer. Even when they are definitive, RCTs generate data only about average risks and benefits of the tested therapeutic option in a selected cohort. Because an individual patient's responses can only be inferred from the overall estimated group responses, RCTs cannot definitively direct the approach of every patient or answer the myriad questions that confront the practitioner regarding the specific circumstances of the patient. Another major limitation of RCTs is the relatively narrow time frame of observation, generally only months to several years, compared with epidemiologic experiences during decades. Despite these limitations, RCTs are the premier tool of evidence-based medicine, and the field of heart failure has fortunately been the focus of relatively high-quality RCTs that have provided robust evidence to improve clinical care and prognosis (Table 46-1). Indeed, the implementation of evidence from RCTs into clinical practice has resulted in impressive temporal improvements in survival after discharge from a first hospital admission for heart failure. Moreover, the age at which symptomatic heart failure first becomes evident has increased. Despite these tangible advances, heart failure continues to be a leading cause of morbidity and mortality in elderly people.

STAGES OF HEART FAILURE

Guidelines for the evaluation and management of chronic heart failure use a staging classification to underscore the evolution and progression of heart failure severity (Fig. 46-1).[2,3] This classification emphasizes the use of different strategies and therapeutic options across the full spectrum of the syndrome, from prevention of heart failure to palliation of patients with end-stage disease.

TABLE 46-1 THERAPIES OF PROVEN BENEFIT IN HEART FAILURE

Angiotensin-converting enzyme inhibitors
Angiotensin receptor blockers
β-Blockers
Mineralocorticoid receptor antagonists
Sacubitril-valsartan
Sodium-glucose cotransporter 2 inhibitors
Hydralazine-isosorbide dinitrate
Ivabradine
Digitalis
Vericiguat
Cardiac resynchronization therapy
Cardioverter-defibrillator
Ventricular assist device
Heart transplantation
Exercise training

INDIVIDUALS AT RISK FOR DEVELOPMENT OF HEART FAILURE (STAGE A)

Stage A designates patients at risk for development of heart failure based on concomitant cardiovascular diseases such as hypertension, coronary artery disease, and diabetes mellitus. Also included in stage A are individuals with prior exposure to cardiotoxic agents such as doxorubicin (Chapter 164) and those with a family history of a cardiomyopathy (Chapter 47). Although these predisposing factors do not by themselves technically constitute the syndrome of heart failure, the guidelines stress the importance of identifying individuals with modifiable factors because this represents an important opportunity to reduce the reservoir of patients at risk.

Population-based preventive approaches can reduce the incidence of heart failure. For example, public health programs targeting the eradication of the insect vector for *Trypanosoma cruzi* (Chapter 318) have reduced the incidence of Chagas cardiomyopathy (Chapter 47) in endemic regions of South and Central America.

Other population-based approaches to reduce the incidence of heart failure require specific screening efforts to identify individuals with modifiable risk factors. The most important, although unfortunately nonmodifiable, risk factor for the development of heart failure is advanced age; the incidence of heart failure rises sharply per decade after the age of 45 years (Chapter 45). For each decade of age after 45 years, the incidence of heart failure doubles, and heart failure is the leading hospital diagnosis for patients older than 65 years in the United States.

HYPERTENSION

Of the modifiable factors, hypertension (Chapter 64) undoubtedly contributes the greatest population-attributable risk for heart failure. In other words, even though the increased risk for heart failure in an individual with hypertension is modest, the high prevalence of hypertension in the general population means that at a population level, hypertension is the major cause of heart failure.

The contribution of hypertension to the risk for heart failure was a consistent finding from all major cardiovascular epidemiologic studies, and the earliest RCTs of antihypertensive therapy showed unambiguous reductions in the risk for heart failure. Of the components of blood pressure, elevated systolic pressure has a greater influence on the incidence of heart failure than does diastolic pressure. In fact, aging is associated with a progressive rise in systolic blood pressure and fall in diastolic pressure as the compliance of the arterial tree diminishes (Chapter 64). In community-based studies, isolated systolic hypertension and elevated pulse pressure have been the most predictive blood pressure measurements for development of heart failure. Antihypertensive treatment to a systolic blood pressure goal of 130 mm Hg appears to reduce the risk of developing heart failure.[A1] Reduction to lower than 120 mm Hg systolic provides additional benefit for reducing nonfatal cardiovascular events and all-cause mortality in patients without diabetes or prior heart failure,[A2] but at the cost of more hypotension, electrolyte abnormalities, and renal impairment. The current blood pressure goal is lower than 120 mm Hg for selected patients at high cardiovascular risk without diabetes or prior heart failure and lower than 130 mm Hg otherwise (Chapter 64).

DIABETES

Individuals with diabetes (Chapter 210) are also at heightened risk for premature cardiovascular mortality and morbidity, including heart failure. Type 2 diabetes frequently clusters with hypertension, obesity, and a sedentary lifestyle, thereby exacerbating the risks associated with each condition. However, the glucose level is an independent risk factor for cardiovascular events, including heart failure. Unlike hypertension, where pharmacologic therapy has had a generally favorable impact on reducing the risk of heart failure, historically, glucose-lowering therapy has not been shown to reduce this risk. However, sodium-glucose cotransporter 2 (SGLT2) inhibitors (e.g., dapagliflozin 10 mg daily; Chapter 210) reduce the risk of heart failure hospitalization in patients with type 2 diabetes and cardiovascular risk factors, preexisting cardiovascular disease, or chronic kidney disease (Chapter 116) with or without type 2 diabetes.[A3] The glucagon-like peptide-1 (GLP-1) receptor agonists may also reduce the risk of developing heart failure,[A4] but not to the extent seen with SGLT2 inhibitors.[A5] The α-glucosidase inhibitor acarbose, insulin, and the meglitinide nateglinide do not increase the risk of developing heart failure in patients with impaired glucose tolerance, diabetes, or both.[A6] An increase in risk of heart failure was reported with saxagliptin, although this increased risk has not been seen with other dipeptidyl peptidase-4 (DPP-4) inhibitors.[4]

By comparison, thiazolidinediones cause retention of sodium and water and should not be used in patients at risk for developing heart failure.

ABSTRACT

The treatment of heart failure is guided by its stage: patients at risk of heart failure (stage A), asymptomatic structural or functional heart disease (stage B; pre-heart failure), structural heart disease with prior or current symptoms of heart failure (stage C), and advanced heart failure requiring specialized interventions (stage D). Treatment of hypertension and lipid disorders, smoking cessation, regular exercise, discouraging alcohol intake, and control of weight and hyperglycemia are cornerstones of therapy for all stages. An ACE inhibitor or an angiotensin receptor blocker and often an SGLT2 inhibitor are indicated for stages A and B. β-Blockers are added in stages B and C, implantable defibrillators oftentimes in stages B and C, and sacubitril/valsartan, mineralocorticoid antagonists, cardiac resynchronization therapy, and sometimes other medications in stage C. For stage D, left ventricular mechanical support, heart transplantation, and compassionate and often palliative care are indicated.

KEYWORDS

heart failure
reduced ejection fraction
mildly reduced ejection fraction
preserved ejection fraction
angiotensin converting enzyme inhibitor
beta-blocker
aldosterone
neprilysin
ivabradine
sodium-glucose cotransporter 2 inhibitor
vericiguat

Trials

Therapy	Stage A	Stage B	Stage C	Stage D
Antihypertensive agents	✓	✓	✓	
Statins	✓	✓	(✓)	(✓)
β-blockers		✓	✓	✓
ACE inhibitors	✓	✓	✓	✓
Angiotensin II receptor blockers (ARBs)		✓	✓	✓
Sodium glucose cotransporter 2 inhibitors (SGLT2i)	✓	✓	✓	
Hydralazine/ nitrates			✓	✓
ARNI			✓	✓
Digoxin			✓	✓
Ivabradine			✓	✓
Mineralocorticoid antagonists			✓	✓
Implantable cardioverter-defibrillator (ICD)		✓	✓	(✓)
Cardiac resynchronization therapy (CRT)			✓	✓
Left ventricle assist device (LVAD)				✓

Stage A High risk for HF without structural heart disease or symptoms of HF	**Stage B** Structural heart disease but without signs or symptoms of HF	**Stage C** Structural heart disease with prior or current symptoms of HF	**Stage D** Refractory HF requiring specialized interventions
Patients with • Hypertension • Atherosclerotic disease • Diabetes • Obesity • Metabolic syndrome or • Patients using cardiotoxins with family history of cardiomyopathy (FHx CM)	Patients with • Previous MI • LV remodeling including LVH and low EF • Asymptomatic valvular disease	Patients with • Known structural heart disease • Shortness of breath and fatigue, reduced exercise tolerance	Patients with marked symptoms at rest despite maximal medical therapy (e.g., those who are recurrently hospitalized or cannot be safely discharged from the hospital without specialized interventions)
THERAPY **Goals** • Treat hypertension • Encourage smoking cessation • Treat lipid disorders • Encourage regular exercise • Discourage alcohol intake, illicit drug use • Control metabolic syndrome **Drugs** • ACE inhibitor or ARB as appropriate for patients with vascular disease or diabetes • SGLT2i in patients with type 2 diabetes	**THERAPY** **Goals** • Treat hypertension • Encourage smoking cessation • Treat lipid disorders • Encourage regular exercise • Discourage alcohol intake, illicit drug use • Control metabolic syndrome **Drugs** • ACE inhibitor or ARB as appropriate for patients with vascular disease or diabetes • β-blockers in appropriate patients • SGLT2i in patients with type 2 diabetes **Devices in selected patients** • Implantable defibrillators	**THERAPY** **Goals** • Treat hypertension • Encourage smoking cessation • Treat lipid disorders • Encourage regular exercise • Discourage alcohol intake, illicit drug use • Control metabolic syndrome • Dietary salt restriction **Drugs for routine use** • Diuretics for fluid retention • ACE inhibitor or ARNI • β-blockers • Mineralocorticoid antagonists • SGLT2i **Drugs in selected patients** • ARBs • Digitalis • Hydralazine/nitrates • Ivabradine **Device in selected patients** • Biventricular pacing (CRT) • Implantable defibrillators	**THERAPY** **Goals** • Appropriate measures under stages A,B,C • Decision re: appropriate level of care **Options** • Compassionate end-of-life care/hospice • Extraordinary measures • Heart transplantation • Chronic inotropes • Permanent mechanical support • Experimental surgery or drugs

FIGURE 46-1. Stages of heart failure and therapies at various stages of heart failure (HF). Check marks indicate therapies proved by randomized trials to be beneficial; check marks in brackets indicate benefits uncertain. ACEI = angiotensin converting enzyme inhibitor; ARB = angiotensin receptor blocker; ARNI = angiotensin receptor/neprilysin inhibitor; CRT = cardiac resynchronization therapy; EF = ejection fraction; FHx CM = family history of cardiomyopathy; HF = heart failure; LV = left ventricle; LVH = left ventricular hypertrophy; MI = myocardial infarction; SGLT2i = sodium glucose cotransporter 2 inhibitors.

OTHER RISK FACTORS

Treatment of atherosclerotic risk factors, such as hypercholesterolemia (Chapter 190), and promotion of measures that encourage healthier lifestyles, such as smoking cessation (Chapter 363), weight control (Chapter 201), adoption of a Mediterranean diet (Chapter 13), and aerobic exercise (Chapter 14), should also reduce the number of individuals who progress from stage A to stage B (structural heart disease but without symptoms of heart failure). ACE inhibitors and SGLT2 inhibitors protect against the development of heart failure in patients with diabetes mellitus or with evidence of atherosclerosis. Elevated natriuretic peptide levels and elevated troponin levels may help identify patients with an elevated risk of developing heart failure.

Many anticancer drugs can cause myocardial damage and heart failure, as can mediastinal radiotherapy. Pericardial constriction can be a result of previous radiotherapy, and malignant pericardial involvement can cause effusion and tamponade (Chapter 62).

PRE–HEART FAILURE (STAGE B): ASYMPTOMATIC STRUCTURAL OR FUNCTIONAL HEART DISEASE

Stage B identifies asymptomatic (New York Heart Association or Canadian Cardiovascular Society class I; Chapter 45) patients who have a structural or functional cardiac disorder (e.g., left ventricular hypertrophy, enlargement, or dysfunction and valvar abnormalities) but do not have the signs and symptoms, such as dyspnea and fatigue, of the heart failure syndrome. In addition to history, physical examination, and electrocardiography (Chapter 42), more extensive screening with echocardiography (Chapter 43) or other imaging modalities (Chapter 44) is often required to detect patients with asymptomatic cardiac structural abnormalities.

A patient who has an acute myocardial infarction not complicated by early heart failure is an obvious example of someone who transitions from stage A to stage B. Rapid mechanical or pharmacologic coronary reperfusion is one of the immediate goals of therapy, with the aim of limiting the extent of myocardial injury and reducing the risk for death and future development of heart failure (Chapters 57 and 58). Survivors of the acute phase of myocardial infarction, a well-studied stage B cohort, are at particularly high risk for the future development of heart failure, with an overall annual incidence of 2% per year—but higher in patients who are older, have a lower left ventricular ejection fraction, do not routinely perform at least moderate exercise, or have concomitant hypertension or diabetes mellitus. For example, a clinically stable asymptomatic patient who has recovered from a myocardial infarction but who is older than 60 years with a left ventricular ejection fraction of less than 50% and a history of diabetes and hypertension has an estimated 30% 5-year likelihood of experiencing death or heart failure; without diabetes or hypertension, the 5-year estimated rate becomes 12%. By comparison, a younger myocardial infarction survivor who has a left ventricular ejection fraction over 50% and does not have hypertension or diabetes would be anticipated to have a 5-year rate for heart failure or death of only 3%. Measures of right ventricular function and biomarkers such as natriuretic peptides and troponin provide further independent incremental prediction for the risk for developing heart failure. With the continued improvements in care of patients with acute myocardial infarction (Chapters 57 and 58) and the use of implantable cardioverter-defibrillators (ICDs) after myocardial infarction in patients with reduced left ventricular ejection fraction, this pool of stage B patients, who represent a reservoir for new-onset heart failure, has been expanding. An ICD is recommended in patients who have a left ventricular ejection fraction of 30% or less and who survive at least 40 days after an acute myocardial infarction to reduce the risk for death (Chapter 58).

The impaired left ventricle, often due to a prior myocardial infarction, can undergo progressive chamber enlargement. This process, also termed left ventricular remodeling, describes the time-dependent and often insidious structural alterations of the impaired left ventricle, whereby the relationship of the left ventricular cavity volume increases out of proportion to mass, so the overall ventricular geometry becomes more distorted, usually more spherical. This distortion of left ventricular geometry often leads to mitral regurgitation. These structural changes produce regional and global increases in myocardial wall stress, which can promote further remodeling and contribute to the progressive deterioration of cardiac function and structure often associated with the later stages of symptomatic heart failure.

TREATMENT

The treatment of heart failure is guided by the stage of symptoms and signs (see Fig. 46-1) as well as a robust literature on therapies proved to be beneficial by randomized trials (Fig. 46-2).[5]

Angiotensin-Converting Enzyme Inhibitors and Angiotensin Receptor Blockers

Mechanistic studies confirm that ACE inhibitors inhibit progressive left ventricular enlargement by reducing wall stress during the entire cardiac cycle as well as by more direct inhibition of the intracellular signaling pathways involved in myocardial hypertrophy and interstitial fibrosis. This attenuation of ventricular remodeling by ACE inhibitors reduces the development of symptomatic heart failure or death, including sudden and unexpected deaths, in stage B asymptomatic patients with left ventricular dysfunction by about 20%.

Several ACE inhibitors are effective as prophylactic therapy for high-risk stage B patients, and the target dose of each agent is established (Table 46-2). Therefore, patients with left ventricular systolic dysfunction, heart failure, or both complicating acute myocardial infarction should receive an ACE inhibitor to reduce the risk for chronic heart failure, reinfarction, stroke, and death. The angiotensin receptor blocker (ARB) valsartan is as effective as captopril in reducing risk for cardiovascular death and other nonfatal cardiovascular outcomes, thereby providing an alternative pharmacologic class of agents for patients who cannot tolerate an ACE inhibitor because of cough or angioedema. Importantly, in patients with left ventricular dysfunction or acute heart failure in the context of a myocardial infarction, the combination of an ACE inhibitor and ARB is not better than either alone, so combination therapy is not recommended in this setting. Unlike in stage C heart failure, sacubitril/valsartan is not clearly superior to an ACE inhibitor.[A7]

β-Blockers

β-Adrenergic receptor blockers (β-blockers) have long been known to reduce death and recurrent myocardial infarction when they are administered during the acute phase of myocardial infarction in patients without pulmonary congestion (Chapter 58). However, carvedilol (Table 46-3) also improves survival, reduces subsequent nonfatal myocardial infarctions, and has a favorable trend for reduced hospitalizations for heart failure in patients with a recent myocardial infarction and reduced left ventricular ejection fraction (≤40%) when it is added to an ACE inhibitor and should be considered in such patients. For stage B patients whose left ventricular dysfunction does not have an ischemic etiology, the evidence for β-blockers is less firm.

Treatment of Arrhythmias

Functional as well as structural problems may lead to the development of heart failure. For example, a persistently rapid ventricular rate in patients with atrial fibrillation can cause a rate-related (tachycardia-induced) cardiomyopathy (Chapter 52). Adequate pharmacologic control of the ventricular rate or interventions to restore sinus rhythm or to ablate re-entry pathways (Chapter 54) may reduce the risk for heart failure.

Other Therapies

Any treatments that control hypertension or reduce the risk for myocardial infarction will benefit stage B patients. Examples include statins, antiplatelet agents, and smoking cessation. Sodium glucose cotransporter 2 (SGLT2) inhibitors also reduce the risk that patients with type 2 diabetes, established cardiovascular disease, or chronic kidney disease will develop heart failure.

SYMPTOMATIC HEART FAILURE (STAGES C AND D)

The development of symptoms and signs of the heart failure syndrome defines the transition from patients in the asymptomatic "at-risk" stages (A and B) to those who fulfill the clinical diagnosis of symptomatic heart failure (Chapter 45). This transition to the symptomatic phase underscores the progressive nature of heart failure and heralds a marked decline in prognosis. In one study, for example, the 2-year mortality rate was 27% in symptomatic patients compared with 10% in asymptomatic patients despite similarly reduced left ventricular ejection fractions and comorbidities.

HEART FAILURE PHENOTYPES BASED ON LEFT VENTRICULAR EJECTION FRACTION

Patients with heart failure are divided into three main categories defined by their left ventricular ejection fraction: heart failure with a reduced ejection fraction (HFrEF, ≤40%),[6] mildly reduced ejection fraction (HFmrEF, 41% to 49%),[7] or preserved ejection fraction (HFpEF, ≥50%).[8] Some patients with an ejection fraction ≤40% have a follow-up measurement >40%, often as a result of treatment. This fourth group of patients are said to have heart failure with improved ejection fraction (HFimpEF). Strong evidence helps guide the treatment of patients who have heart failure with a reduced ejection fraction, but less robust evidence is available for the other subtypes of heart failure.

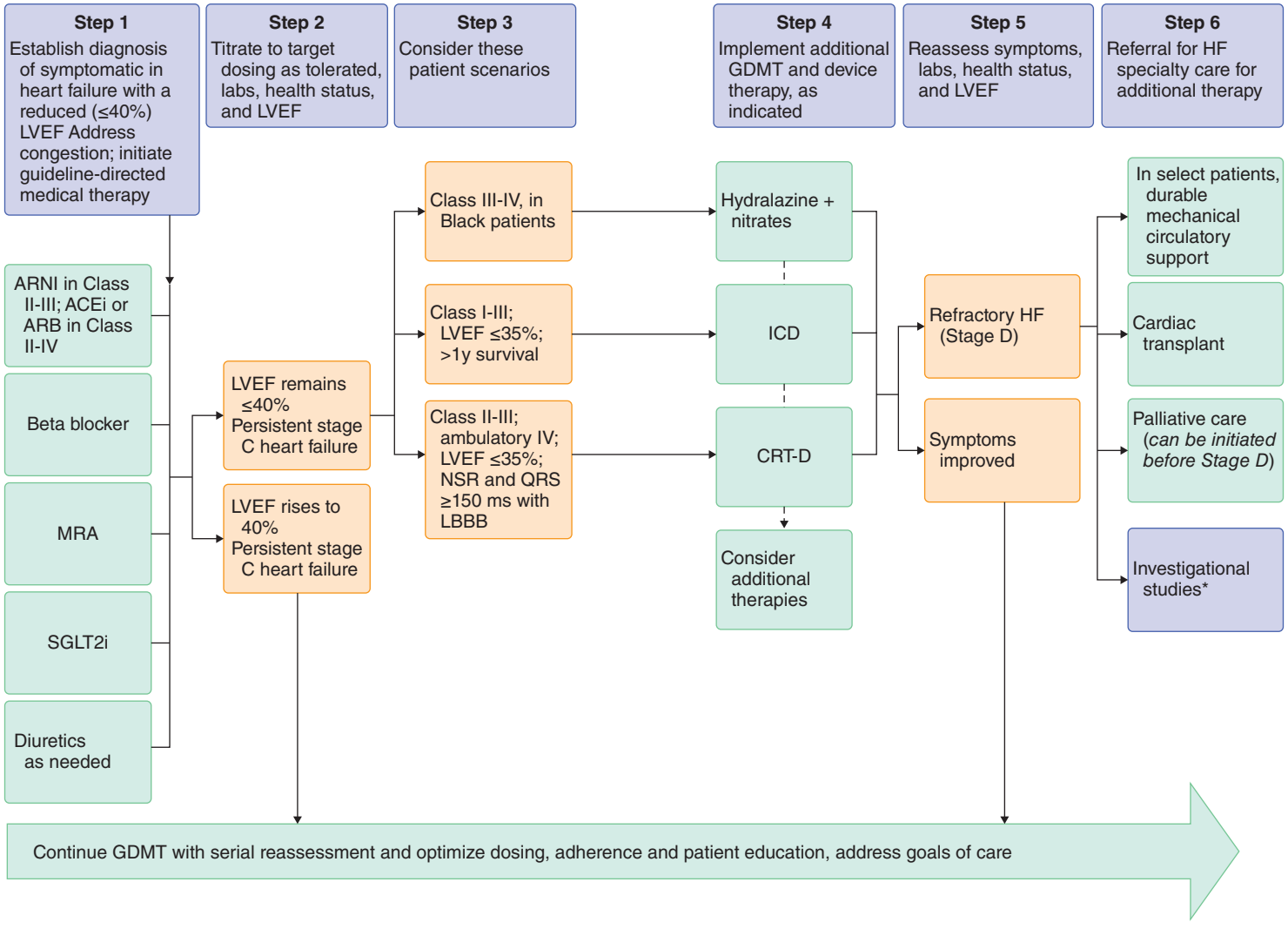

FIGURE 46-2. General approach to stage C heart failure with a reduced ejection fraction. *Participation in investigational studies is appropriate for stage C, NYHA class II and III heart failure (HF). ACEI = angiotensin-converting enzyme inhibitor; ARB = angiotensin-receptor blocker; ARNI = angiotensin receptor-neprilysin inhibitor; CRT-D = cardiac resynchronization therapy with defibrillator; eGFR = estimated glomerular filtration rate; GDMT = guideline-directed medical therapy; HR = heart rate; ICD = implantable cardiovascular-defibrillator; LBBB = left bundle branch block; LVEF = left ventricular ejection fraction; MRA = mineralocorticoid receptor antagonist; NSR = normal sinus rhythm; SGLT2i = sodium glucose cotransporter 2 inhibitor. (From Heidenreich PA, Bozkurt B, Aguilar D, et al. 2022 AHA/ACC/HFSA guideline for the management of heart failure: a report of the American College of Cardiology/American Heart Association Joint Committee on Clinical Practice Guidelines. *Circulation*. 2022;145:e895-e1032.)

TREATMENT

The goals of treatment for patients with stage C and stage D heart failure are relief of symptoms, avoidance of hospital admission or other manifestations of worsening heart failure, and prevention of premature death. In general, the preventive measures that are of value during stages A and B should be sustained in patients with stages C and D heart failure.

Heart Failure with Reduced Left Ventricular Ejection Fraction

Pharmacologic Treatment

Drugs are the mainstay of the treatment of patients with symptomatic heart failure on the basis of the cumulative experiences from RCTs, particularly for patients with reduced left ventricular ejection fraction.[9] However, devices and surgery have an important and increasing role in patients with advanced symptomatic heart failure (stages C and D; see Fig. 46-1). Exercise clearly improves well-being and clinical outcomes, but the evidence base for other lifestyle interventions is less robust. The organization and delivery of care can also have a substantial impact on outcomes.

Although diuretics are required to control fluid retention in most patients who have symptomatic heart failure with a reduced ejection fraction, four other life-saving foundational therapies should be prescribed in any order for all patients, wherever possible: an angiotensin receptor neprilysin inhibitor, a β-blocker, a mineralocorticoid receptor antagonist, and a sodium-glucose cotransporter 2 (SGLT2) inhibitor. The key principles guiding the use of these therapies are that all should be initiated as quickly as possible, usually starting at low doses, and up-titrated to the evidence-based target (see later).

Diuretics

MECHANISM OF ACTION. Conventional diuretics (see Table 102-4 in Chapter 102) act by blocking sodium reabsorption in the loop of Henle and distal renal tubule, thereby enhancing urinary excretion of sodium and water.

CLINICAL BENEFITS. Although not proven to improve mortality and morbidity in large trials, diuretics are required in nearly all patients with symptomatic heart failure (stages C and D) to relieve dyspnea and the signs of sodium and water retention ("congestion"), that is, peripheral and pulmonary edema.[10] No other treatment relieves symptoms and the signs of sodium and water overload as rapidly and effectively. Once a patient needs a diuretic, treatment is usually necessary for the rest of the patient's life, although the dose and type of diuretic may vary.

PRACTICAL USE. The key principle is to prescribe the minimum dose of diuretic needed to maintain an edema-free state ("dry weight"). Excessive use can lead to electrolyte imbalances, such as hyponatremia, hypokalemia (and risk for digitalis toxicity), hyperuricemia (and risk for gout), and uremia. The risk for renal dysfunction is increased by concomitant use of nonsteroidal anti-inflammatory drugs (NSAIDs). Diuretic-induced hypovolemia may also cause symptomatic hypotension and prerenal azotemia. Restriction of dietary sodium intake may help reduce, but does not eliminate, the requirement for diuretics. Diuretic dosing should be flexible, with temporary increases for evidence of fluid retention (e.g., increasing symptoms, weight gain, edema) and decreases for evidence of hypovolemia (e.g., as a consequence of increased electrolyte loss due to gastroenteritis, decreased fluid intake, or both).

In some patients with milder symptoms of heart failure and preserved renal function (stage C), a thiazide diuretic such as chlorthalidone may suffice. In

TABLE 46-2 PRACTICAL GUIDANCE ON THE USE OF ANGIOTENSIN-CONVERTING ENZYME INHIBITORS AND ANGIOTENSIN RECEPTOR BLOCKERS IN PATIENTS WITH HEART FAILURE DUE TO LEFT VENTRICULAR SYSTOLIC DYSFUNCTION

WHY?

Randomized trials have conclusively shown that angiotensin-converting enzyme (ACE) inhibitors increase survival, reduce hospital admissions, and improve New York Heart Association (NYHA) class and quality of life in patients with *all* grades of symptomatic heart failure. Other randomized trials in patients with systolic dysfunction after acute myocardial infarction show that ACE inhibitors increase survival. In patients with heart failure, the composite end point of death or hospital admission is reduced by higher doses of an ACE inhibitor compared with lower doses. ACE inhibitors also delay or prevent the development of symptomatic heart failure in patients with *asymptomatic* left ventricular systolic dysfunction.

In patients who are intolerant of an ACE inhibitor, an angiotensin receptor blocker (ARB) is indicated. For example, candesartan reduces the risk for the composite outcome of cardiovascular death or heart failure hospitalization, reduces the risk of hospital admission for heart failure, and improves functional class. Valsartan is as effective as the ACE inhibitor captopril in reducing mortality and cardiovascular morbidity in patients with left ventricular systolic dysfunction, heart failure, or both complicating acute myocardial infarction.

IN WHOM AND WHEN?

ACE Inhibitors/ARBs

Indications
- Potentially all patients with heart failure and a low ejection fraction, although usually an angiotensin receptor-neprilysin inhibitor (ARNI) is the preferred treatment (see later).
- First-line treatment (along with a β-blocker, mineralocorticoid receptor antagonist [MRA], and sodium glucose cotransporter 2 [SGLT2] inhibitor) in patients with NYHA class II to IV heart failure; start as early as possible in course of disease.
- ACE inhibitors (and probably ARBs) are also of benefit in patients with asymptomatic left ventricular systolic dysfunction (NYHA class I).

Contraindications
- ACE inhibitors only—history of angioedema
- Known bilateral renal artery stenosis
- Combination with an angiotensin receptor blocker-neprilysin inhibitor (valsartan/sacubitril)—risk of angioedema if combined with an ACE inhibitor (and renal dysfunction and hyperkalemia when combined with an ACE inhibitor or an ARB)

Cautions/seek specialist advice
- Significant hyperkalemia ($K^+ > 5.0$ mmol/L)
- Significant renal dysfunction (creatinine 221 μmol/L or >2.5 mg/dL)
- Symptomatic or severe asymptomatic hypotension (systolic blood pressure <90 mm Hg)

Potential drug interactions of particular concern
- K^+ supplements/K^+-sparing diuretics (e.g., amiloride and triamterene [beware combination preparations with furosemide])
- Mineralocorticoid receptor antagonists (spironolactone, eplerenone), ARBs, NSAIDs*
- "Low-salt" substitutes with a high K^+ content
- Angiotensin receptor blocker-neprilysin inhibitor (sacubitril/valsartan)—see earlier (contraindicated)

WHERE?

In the community for most patients
Exceptions—see Cautions/seek specialist advice

WHICH ACE INHIBITOR AND WHAT ORAL DOSE?

	STARTING DOSE	TARGET DOSE
Captopril	6.25 mg three times daily	50 mg three times daily
Enalapril	2.5 mg twice daily	10-20 mg twice daily
Lisinopril	2.5-5.0 mg once daily	20-35 mg once daily
Ramipril	2.5 mg once daily	5 mg twice daily or 10 mg once daily
Trandolapril	0.5 mg once daily	4 mg once daily

WHICH ARB AND WHAT ORAL DOSE?

	STARTING DOSE	TARGET DOSE
Candesartan	4 or 8 mg once daily	32 mg once daily
Valsartan	40 mg twice daily	160 mg twice daily
Losartan	50 mg once daily	150 mg daily

HOW TO USE?

Start with a low dose (see doses in previous column).
Double dose typically at 2-week intervals.
Aim for target dose (see doses in previous column) or, failing that, the highest tolerated dose.
Remember: *some* ACE inhibitor/ARB is better than *no* ACE inhibitor/ARB.
Monitor blood pressure and blood chemistry (urea/blood urea nitrogen, creatinine, K^+).
Check blood chemistry 1 to 2 weeks after initiation and 1 to 2 weeks after final dose titration.
When to stop up-titration, reduce dose, stop treatment—see Problem Solving.
A specialist heart failure nurse or pharmacist may assist with education of the patient, follow-up (in person or by telephone), biochemical monitoring, and dose up-titration.

ADVICE TO PATIENT

Explain expected benefits (see Why?).
Treatment is given to improve symptoms, to prevent worsening of heart failure leading to hospital admission, and to increase survival.
Symptoms improve within a few weeks to a few months of starting treatment.
Advise patients to report principal adverse effects, (i.e., dizziness/symptomatic hypotension, cough)—see Problem Solving.
Advise patients to avoid NSAIDs* not prescribed by a physician (self-purchased over-the-counter) and salt substitutes high in K^+—see Problem Solving.

PROBLEM SOLVING

Asymptomatic low blood pressure
- Does not usually require any change in therapy

Symptomatic hypotension
- If dizziness, lightheadedness, or confusion and a low blood pressure, reconsider need for nitrates, calcium-channel blockers,† and other vasodilators.
- If no signs or symptoms of congestion, consider reducing diuretic dose.
- If these measures do not solve problem, seek specialist advice.

Cough
- Cough is common in patients with heart failure, many of whom have smoking-related lung disease.
- Cough is also a symptom of pulmonary edema, which should be excluded when a new or worsening cough develops.
- ACE inhibitor–induced cough rarely may not require treatment discontinuation.
- When a troublesome cough does develop (e.g., one stopping the patient from sleeping) and can be proved to be due to ACE inhibition (i.e., recurs after ACE inhibitor withdrawal and rechallenge), substitution of an ARB should be considered.

Worsening renal function
- Some rise in urea (blood urea nitrogen), creatinine, and potassium is to be expected after initiation of an ACE inhibitor/ARB; if an increase is small and asymptomatic, no action is necessary.
- An increase in creatinine of up to 50% above baseline, or 266 μmol/L (3 mg/dL), whichever is the smaller, is acceptable.
- An increase in potassium to ≤5.5 mmol/L is acceptable but must be rechecked.
- If urea, creatinine, or potassium does rise excessively, consider stopping concomitant nephrotoxic drugs (e.g., NSAIDs*) and other potassium supplements or retaining agents (triamterene, amiloride, spironolactone-eplerenone) and, if no signs of congestion, reducing the dose of diuretic.
- If greater rises in creatinine or potassium than those outlined earlier persist despite adjustment of concomitant medications, the dose of the ACE inhibitor should be halved and blood chemistry rechecked within 1 to 2 weeks; if there is still an unsatisfactory response, specialist advice should be sought.
- If potassium rises to >5.5 mmol/L or creatinine increases by >100% or to above 310 μmol/L (3.5 mg/dL), the ACE inhibitor/ARB should be stopped and specialist advice sought. Concomitant use of a K^+ binder (e.g., patiromer; see Chapter 103) may allow an ACE inhibitor/ARB (or ARNI) to be continued in patients developing hyperkalemia.
- Blood chemistry should be monitored frequently and serially until potassium and creatinine have plateaued.

*Avoid nonsteroidal anti-inflammatory drugs (NSAIDs) unless essential.
†Calcium-channel blockers should be discontinued unless absolutely essential (e.g., for angina or hypertension).
Note: It is rarely necessary to stop an ACE inhibitor/ARB, and clinical deterioration is likely if treatment is withdrawn. Ideally, specialist advice should be sought before treatment discontinuation.
Modified from McMurray J, Cohen-Solal A, Dietz R, et al. Practical recommendations for the use of ACE inhibitors, β-blockers, mineralocorticoid receptor antagonists and angiotensin receptor blockers in heart failure: putting guidelines into practice. *Eur J Heart Fail*. 2005;7:710-721.

TABLE 46-3 PRACTICAL GUIDANCE ON THE USE OF B-BLOCKERS IN PATIENTS WITH HEART FAILURE DUE TO LEFT VENTRICULAR SYSTOLIC DYSFUNCTION

WHY?

Several major randomized controlled trials have shown conclusively that certain β-blockers increase survival, reduce hospital admissions, and improve New York Heart Association (NYHA) class and quality of life when added to standard therapy (diuretics, digoxin, and angiotensin-converting enzyme [ACE] inhibitors) in patients with heart failure. Carvedilol is substantially more effective than a low dose of short-acting metoprolol.*

IN WHOM AND WHEN?

Indications
- Potentially *all* patients with *euvolemic* heart failure with mild to moderate symptoms; patients with severe heart failure should be referred for specialist advice.
- First-line treatment (along with an angiotensin receptor-neprilysin inhibitor [ARNI] or ACE inhibitor or angiotensin receptor blocker [ARB], mineralocorticoid receptor antagonists [MRA], and sodium-glucose cotransporter 2 [SGLT2] inhibitor) in patients with *euvolemic* NYHA class II to III heart failure; start as early as possible in course of disease.

Contraindications
- Asthma
- Second- or third-degree atrioventricular block

Cautions/seek specialist advice
- Severe (NYHA class IV) heart failure
- Current or recent (<4 weeks) exacerbation of heart failure (e.g., hospital admission with worsening heart failure, heart block, or heart rate <60 beats/minute).
- Persisting signs of congestion, hypotension/low blood pressure (systolic < 90 mm Hg), raised jugular venous pressure, ascites, marked peripheral edema

Potential drug interactions of particular concern
- Verapamil, diltiazem (should be discontinued)†
- Digoxin, amiodarone

WHERE?

In the community in stable patients (NYHA class IV/severe heart failure patients should be referred for specialist advice)
Not in unstable patients hospitalized with worsening heart failure
Other exceptions—see Cautions/seek specialist advice

WHICH β-BLOCKER AND WHAT ORAL DOSE?

	STARTING DOSE	TARGET DOSE
Bisoprolol	1.25 mg once daily	10 mg once daily
Carvedilol	3.125 mg twice daily	25-50 mg twice daily
Metoprolol CR/XL	12.5-25 mg once daily	200 mg once daily*
Nebivolol	1.25 mg once daily	10 mg once daily

HOW TO USE?

Start with a low dose (see dose shown in previous column).
Double dose at *not less than* 2-week intervals.
Aim for target dose (see dose shown in previous column) or, failing that, the highest tolerated dose.
Remember: *some* β-blocker is better than *no* β-blocker.
Monitor heart rate, blood pressure, and clinical status (symptoms, signs—especially signs of congestion, increased body weight).
Check blood chemistry 1 to 2 weeks after initiation and 1 to 2 weeks after final dose titration.
When to stop up-titration, reduce dose, stop treatment—see Problem Solving.
A specialist heart failure nurse may assist with education of the patient, follow-up (in person or by telephone), and dose up-titration.

ADVICE TO PATIENT

Explain expected benefits (see Why?).
Treatment is given to improve symptoms, to prevent worsening of heart failure leading to hospital admission, and to increase survival.
Symptomatic improvement may develop slowly after starting treatment, and treatment for 3 to 6 months or longer may be required before the full effects on left ventricular size and function are observed.
Temporary symptomatic deterioration *may* occur during initiation or up-titration phase; in the long term, β-blockers improve well-being.
Advise patient to report deterioration (see Problem Solving) and that deterioration (tiredness, fatigue, breathlessness) can usually be easily managed by adjustment of other medication; patients should be advised not to stop β-blocker therapy without consulting the physician.
To detect and to treat deterioration early, patients should be encouraged to weigh themselves daily (after waking, before dressing, after voiding, before eating) and to increase their diuretic dose should their weight increase persistently (>2 days) by >1.5-2.0 kg.‡

PROBLEM SOLVING

Worsening symptoms or signs (e.g., increasing dyspnea, fatigue, edema, weight gain)
- If increasing congestion, increase dose of diuretic or halve dose of β-blocker (if increasing diuretic does not work).
- If marked fatigue (or bradycardia—see later), halve dose of β-blocker (rarely necessary); review patient in 1 to 2 weeks; if not improved, seek specialist advice.
- If serious deterioration, halve dose of β-blocker or stop this treatment (rarely necessary); seek specialist advice.

Low heart rate
- If <50 beats/minute and worsening symptoms, halve dose of β-blocker or, if severe deterioration, stop β-blocker (rarely necessary).
- Review need for other heart rate–slowing drugs (e.g., digoxin, amiodarone, diltiazem, or verapamil†).
- Arrange electrocardiogram to exclude heart block.
- Seek specialist advice.

Asymptomatic low blood pressure
- Does not usually require any change in therapy.

Symptomatic hypotension
- If dizziness, lightheadedness, or confusion and a low blood pressure, reconsider need for nitrates, calcium-channel blockers,† and other vasodilators.
- If no signs or symptoms of congestion, consider reducing diuretic dose.
- If these measures do not solve problem, seek specialist advice.

*Metoprolol tartrate should not be used in preference to an evidence-based β-blocker in heart failure.
†Calcium-channel blockers should be discontinued unless absolutely necessary, and diltiazem and verapamil are generally contraindicated in heart failure.
‡This is generally good advice for all patients with heart failure.
Note: β-Blockers should not be stopped suddenly unless absolutely necessary (there is a risk for a "rebound" increase in myocardial ischemia or infarction and arrhythmias). Ideally, specialist advice should be sought before treatment discontinuation.
Modified from McMurray J, Cohen-Solal A, Dietz R, et al. Practical recommendations for the use of ACE inhibitors, β-blockers, mineralocorticoid receptor antagonists and angiotensin receptor blockers in heart failure: putting guidelines into practice. *Eur J Heart Fail*. 2005;7:710-721.

more advanced heart failure (stage D) or in patients with concomitant renal dysfunction, a loop diuretic such as furosemide is often needed. Loop diuretics cause a rapid onset of an intense but relatively short-lived diuresis compared with the longer lasting but gentler effect of a thiazide diuretic. The timing of administration of a loop diuretic, which need not be taken first thing every morning, can be adjusted according to the patient's social activities. The dose may be postponed or even temporarily omitted if the patient has to travel or has another activity that might be compromised by the prompt action of the diuretic. In severe heart failure (stage D), the effects of long-term administration of a loop diuretic may be diminished by increased sodium reabsorption at the distal tubule. This problem can be offset by use of the combination of a loop diuretic and a thiazide or thiazide-like diuretic (e.g., hydrochlorothiazide or metolazone), which act in synergy with a loop diuretic by blocking sodium reabsorption in different segments of the nephron.[A8] This combination requires more frequent monitoring of electrolytes and renal function for diuretic-induced hyponatremia, abnormalities of the serum potassium level, and prerenal azotemia. The combination of a loop diuretic with the proximally acting carbonic anhydrase inhibitor acetazolamide can augment decongestion in the acute setting.[A9]

A period of intravenous loop diuretic, given either as bolus injections or by continuous infusion, may be required either in the ambulatory setting or as an in-patient in patients who become resistant to the action of oral diuretics. Why this resistance develops is uncertain, but factors thought to be important include impaired absorption of oral diuretics due to gut edema, hypotension,

reduced renal blood flow, renal venous congestion, and adaptive changes in the nephron. In cases of severe resistant volume overload, mechanical removal of fluid by ultrafiltration may be considered.

Patients receiving a combination of diuretics require careful monitoring of blood chemistry and clinical status.

Although they are highly effective in relieving symptoms and signs, diuretics alone are not sufficient for treatment of heart failure. The addition of other disease-modifying treatments will slow structural progression, better maintain clinical stability, and reduce the risk for hospital admission and premature death.

ACE Inhibitors and Angiotensin Receptor Blockers (ARBs)

MECHANISM OF ACTION. ACE inhibitors inhibit the enzyme that converts the inactive decapeptide angiotensin I to the active octapeptide angiotensin II (and that also breaks down bradykinin). In patients with heart failure, excessive angiotensin II is thought to exert myriad harmful actions mediated through stimulation of the angiotensin II type 1 receptor subtype (AT1R), including vasoconstriction (which increases ventricular afterload), excessive growth of myocytes and the extracellular matrix (contributing to maladaptive left ventricular remodeling), activation of the sympathetic nervous system, prothrombotic actions, and augmentation of the release of arginine vasopressin and the retention of sodium (both directly and through stimulation of secretion of aldosterone, which activates the mineralocorticoid receptor). ARBs selectively block the action of angiotensin II at the AT1 receptor. Although pharmacologically distinct from ACE inhibitors, their clinical effects are similar.

ACE inhibitors also reduce the breakdown of bradykinin, and the resultant accumulation of bradykinin is directly or indirectly responsible for two of the specific adverse effects of ACE inhibitors: cough and angioedema. ARBs do not inhibit kininase II or the breakdown of bradykinin, so they do not cause cough and are associated with lower rates of angioedema than are ACE inhibitors. This difference between ARBs and ACE inhibitors explains why the combination of neprilysin (which also breaks down bradykinin and may itself cause angioedema) and an ARB is safe (and why the combination of an ACE inhibitor and a neprilysin inhibitor poses a significant risk of angioedema and is not recommended).

CLINICAL BENEFITS. Clinical trials have shown that treatment with an ACE inhibitor, when it is used alone or added to diuretics and digoxin, decreases left ventricular size, improves ejection fraction, reduces symptoms and hospital admissions, and prolongs survival. These agents also reduce the risk of developing myocardial infarction and possibly diabetes and atrial fibrillation. Consequently, treatment with an ACE inhibitor is recommended for all patients with left ventricular systolic dysfunction, irrespective of symptoms or etiology. ACE inhibitors are not a substitute for a diuretic but mitigate diuretic-induced hypokalemia.

When used as the sole agent in heart failure, ARBs produce benefits similar to those of ACE inhibitors. An ARB may be used as a substitute in patients who have cough or angioedema with an ACE inhibitor. When they are used in clinically effective doses, other adverse effects such as hypotension, renal dysfunction, and hyperkalemia are encountered as frequently as with an ACE inhibitor.

PRACTICAL USE. As early as possible in a patient's treatment, the combination of an ARB with a neprilysin inhibitor (i.e., sacubitril/valsartan) is preferred because of the additional benefit of neprilysin inhibition. If the combination is not tolerated, an ACE inhibitor or an ARB can be used. The only contraindications are a history of angioedema (for an ACE inhibitor), current symptomatic hypotension, and bilateral renal artery stenosis (Chapter 110); the latter is often associated with a prompt and marked increase in serum levels of blood urea nitrogen and creatinine when renal perfusion is reduced precipitously by inhibiting the production and actions of angiotensin II. Combined use of an ACE inhibitor and an ARB is contraindicated because it results in increased side effects without an increase in efficacy.

Treatment should be started in a low dose (see Table 46-2), with the dose gradually increased toward a target dose of proven benefit in a clinical trial. The patient should be evaluated for symptomatic hypotension, uremia, and hyperkalemia after each dose increment; these adverse effects are uncommon and can usually be resolved by reduction in the dose of diuretic (if the patient is edema free) or concomitant hypotensive or nephrotoxic medications (e.g., nitrates, calcium-channel blockers, or NSAIDs). A dry, nonproductive cough occurs in approximately 5% of patients treated with an ACE inhibitor, and if it is troublesome, substitution of an ARB is recommended. In the rare cases of angioedema (Chapter 232), the ACE inhibitor should be stopped and not used again; an ARB can be cautiously substituted (see later).

Neprilysin Inhibition

Neprilysin is an enzyme that breaks down natriuretic peptides and other vasoactive substances, including adrenomedullin and bradykinin. Inhibiting neprilysin augments the concentrations of these substances, which have vasodilator and natriuretic actions, and also inhibits pathologic growth, including hypertrophy and fibrosis. Because neprilysin also degrades angiotensin II, a neprilysin inhibitor must be combined with an agent that blocks the renin-angiotensin system. Because ACE and neprilysin each degrade bradykinin, inhibiting both enzymes leads to a significant increase in the risk of angioedema. Consequently, an ARB (valsartan) combined with a neprilysin inhibitor (sacubitril), termed an angiotensin receptor neprilysin inhibitor (ARNI), is preferred. When added to a β-blocker and a mineralocorticoid receptor antagonist, sacubitril/valsartan (97/103 mg twice daily) reduces heart failure hospitalization, cardiovascular mortality, death from all causes, and other measures of progressive worsening of heart failure compared with adding enalapril (10 mg twice daily).[A10] Compared with enalapril, sacubitril/valsartan causes more hypotension and slightly more angioedema but less renal dysfunction and hyperkalemia. Neprilysin inhibition increases levels of B-type natriuretic peptide but not NT pro-B-type natriuretic peptide.

PRACTICAL USE. Sacubitril/valsartan, which is recommended as first-line starting therapy instead of an ACE inhibitor or an ARB, can be initiated in patients hospitalized with decompensated heart failure.[A11] Switching to sacubitril/valsartan should be considered in patients who have persisting symptoms despite tolerating treatment with an ACE inhibitor or ARB (Table 46-4). Because neprilysin inhibition with sacubitril increases bradykinin, a history of angioedema is a contraindication to sacubitril/valsartan. Sacubitril/valsartan should never be combined with an ACE inhibitor, and a "wash-out" period of 36 hours is required between stopping an ACE inhibitor and starting the ARNI. Because neprilysin inhibition increases a number of vasodilator peptides, hypotension is more common with sacubitril/valsartan than with an ACE inhibitor or ARB, and switching is not recommended in a patient with a systolic blood pressure lower than 95 mm Hg.

β-Blockers

MECHANISM OF ACTION. Heart failure is characterized by excessive activation of the sympathetic nervous system, which causes vasoconstriction and sodium retention, thereby increasing cardiac preload and afterload and often inducing myocardial ischemia or arrhythmias. In addition, norepinephrine can cause hypertrophy of myocytes and augment their apoptosis. β-Blockers counteract many of these harmful effects of the hyperactivity of the sympathetic nervous system. A rapid heart rate is an important prognostic factor in heart failure among patients in sinus rhythm, and β-blockers reduce heart rate.

CLINICAL BENEFITS. The long-term addition of a β-blocker to an ARNI, an SGLT2 inhibitor, a diuretic, and a mineralocorticoid receptor antagonist further improves left ventricular systolic function and symptoms, reduces hospital admissions, and strikingly improves survival. Consequently, a β-blocker is recommended for all patients with symptomatic systolic dysfunction, irrespective of etiology and severity, and the combination of a β-blocker with an ARNI (or an ACE inhibitor or ARB) is a cornerstone of the treatment of symptomatic heart failure (see Fig. 46-1). Treatment with a β-blocker, added to an ARNI (or ACE inhibitor or ARB), a mineralocorticoid receptor antagonist, and an SGLT2 inhibitor is generally recommended for all patients with symptoms (functional classes II to IV) and left ventricular systolic dysfunction, irrespective of etiology.

In a retrospective analysis of pooled data from 11 randomized trials in patients with heart failure, β-blockers improved the left ventricular ejection fraction but did not appear to reduce all-cause mortality in patients with atrial fibrillation, whereas they reduced mortality by 27% in patients who were in sinus rhythm.[A12] Although the interpretation of these results is controversial, β-blockers remain the preferred treatment for control of the ventricular rate in patients who have both atrial fibrillation and heart failure with a reduced ejection fraction because of their excellent safety profile.

PRACTICAL USE. The major contraindications to use of a β-blocker are asthma (although it is important to note that the dyspnea caused by pulmonary congestion can be confused with reactive airway disease) and second- or third-degree atrioventricular block. Initiation of treatment during an episode of acute decompensated heart failure should also be avoided until the patient is stabilized. In addition, caution is advised in patients with a heart rate below 60 beats per minute or a systolic blood pressure below 90 mm Hg. It is recommended that a β-blocker shown to produce benefits in a randomized trial be used.

As with an ARNI (or an ACE inhibitor or ARB), mineralocorticoid receptor antagonist, and SGLT2 inhibitor, β-blockers should be introduced as early as possible in a patient's treatment, started in a low dose (see Table 46-3), and increased gradually toward a target dose used in a clinical trial (the "start low–go slow" approach). The patient should be checked for symptomatic hypotension and excessive bradycardia after each dose increment, but both of these side effects are uncommon, and hypotension can often be resolved by reduction in the dose of other nonessential blood pressure–lowering medications (e.g., nitrates and calcium-channel blockers). Bradycardia is more likely in patients who are also taking digoxin or amiodarone, and the simultaneous use of these agents should be reviewed if excessive bradycardia occurs. On occasion, symptomatic worsening and fluid retention (e.g., weight gain or edema) may occur after initiation of a β-blocker or during dose up-titration; these side effects usually can be resolved by a temporary increase in the diuretic dose without necessitating discontinuation of the β-blocker.

Treatment with a β-blocker should be given for life, although the dose may need to be decreased (or, rarely, treatment discontinued) temporarily during

TABLE 46-4 PRACTICAL GUIDANCE ON THE USE OF A COMBINED ANGIOTENSIN RECEPTOR BLOCKER-NEPRILYSIN INHIBITOR (SACUBITRIL/VALSARTAN) IN PATIENTS WITH HEART FAILURE DUE TO LEFT VENTRICULAR SYSTOLIC DYSFUNCTION

WHY?

In one major randomized trial, patients who had symptomatic heart failure and who were previously treated with an angiotensin-converting enzyme (ACE) inhibitor or angiotensin receptor blocker (ARB) were randomized to an ARB plus a neprilysin inhibitor (ARNI) sacubitril/valsartan or the ACE inhibitor enalapril, added to standard pharmacologic therapy (diuretics, β-blockers, mineralocorticoid receptor antagonists [MRAs], and digoxin). Patients treated with sacubitril/valsartan had a better survival, fewer hospital admissions, and improved New York Heart Association (NYHA) class and quality of life compared with patients who were treated with enalapril.

IN WHOM AND WHEN?

Indications
- Potentially all patients with heart failure and a low ejection fraction
- First-line treatment (along with a β-blocker, MRA, and SGLT2 inhibitor) in patients with functional class II to IV heart failure as the preferred alternative to an ACE inhibitor or ARB.

Contraindications
- History of angioedema
- Known bilateral renal artery stenosis
- Combination with an ACE inhibitor or ARB—risk of angioedema if combined with an ACE inhibitor (and renal dysfunction and hyperkalemia when combined with ACE inhibitor or an ARB)

Cautions/seek specialist advice
- Significant hyperkalemia ($K^+ > 5.0$ mmol/L)
- Significant renal dysfunction (creatinine 221 μmol/L or >2.5 mg/dL)
- Symptomatic or asymptomatic hypotension (systolic blood pressure < 95 mm Hg)

Potential drug interactions of particular concern
- K+ supplements/K+-sparing diuretics (e.g., amiloride and triamterene [beware combination preparations with furosemide])
- Mineralocorticoid receptor antagonists (spironolactone, eplerenone), NSAIDs*
- "Low-salt" substitutes with a high K+ content
- ACE inhibitor/ARB—see earlier (contraindicated)

WHERE?

In the community for most patients
Exceptions—see Cautions/seek specialist advice

WHAT ORAL DOSE?

STARTING DOSE usually sacubitril/valsartan 49 mg/51 mg twice daily if switching from ACE inhibitor/ARB (24 mg/26 mg twice daily if starting de novo)
TARGET DOSE sacubitril/valsartan 97/103 mg twice daily

HOW TO USE?

As for ACE inhibitors/ARBs
ACE inhibitor treatment must be stopped for 36 hours before starting sacubitril/valsartan (to minimize risk of angioedema)

ADVICE TO PATIENT

As for ACE inhibitors/ARBs

PROBLEM SOLVING

As for ACE inhibitors/ARBs (manage cough related to neprilysin inhibition in same way as ACE inhibitor–induced cough)

*Avoid nonsteroidal anti-inflammatory drugs (NSAIDs) unless essential.
SGLT2 = sodium glucose cotransporter 2.

episodes of acute decompensation if the patient shows signs of circulatory underperfusion or refractory congestion.

Mineralocorticoid Receptor (Aldosterone) Antagonists (MRAs)

MECHANISM OF ACTION. Aldosterone, which is the second effector hormone in the renin-angiotensin-aldosterone cascade, has detrimental vascular, renal, autonomic, and cardiac actions when it is produced in excess in patients with heart failure. Excessive aldosterone promotes sodium retention and hypokalemia, and it is believed to contribute to myocardial fibrosis, all of which predispose to arrhythmias. Aldosterone mediates its effects by activating the mineralocorticoid receptor, which is also stimulated by other endogenous corticosteroids. Mineralocorticoid receptor antagonists block these undesirable actions and, at high doses, also act as potassium-sparing diuretics.

CLINICAL BENEFITS. The mineralocorticoid receptor antagonist spironolactone improves symptoms, reduces hospital admissions, and increases survival when it is added to an ACE inhibitor (and diuretics and digoxin) in patients with a reduced left ventricular ejection fraction and severely symptomatic heart failure. Eplerenone, another mineralocorticoid receptor antagonist, reduces mortality and morbidity when it is added to both an ACE inhibitor and β-blocker in patients with a reduced left ventricular ejection fraction and heart failure with mild symptoms (NYHA class II). Consequently, a mineralocorticoid receptor antagonist should be considered in all patients with symptomatic (class II to IV) heart failure and reduced ejection fraction in addition to an ARNI (or ACE inhibitor or ARB), β-blocker, and an SGLT2 inhibitor.[A13] When begun, a mineralocorticoid receptor antagonist should be given indefinitely.

PRACTICAL USE. Treatment with a mineralocorticoid receptor antagonist should be initiated with a low dose (Table 46-5) with careful monitoring of serum electrolytes and renal function. Hyperkalemia and uremia are the adverse effects of greatest concern (as with ACE inhibitors, ARBs, or an ARNI), and a mineralocorticoid receptor antagonist should not be given to patients with a serum potassium concentration of more than 5.0 mmol/L, serum creatinine concentration above 2.5 mg/dL (>221 μmol/L), or other evidence of markedly impaired renal function. The importance of selection of patients and dose is underscored by reports of a worrisome incidence of serious hyperkalemia in community practice settings. Spironolactone can have antiandrogenic effects, especially painful gynecomastia, in men; because eplerenone has less of an action on the androgen receptor, it is a reasonable substitute in patients who experience this adverse effect.

Sodium Glucose Cotransporter 2 (SGLT2) Inhibitors

MECHANISM OF ACTION. The SGLT2 is found in the renal proximal tubule, where it is responsible for the reabsorption of glucose filtered at the glomerulus. Inhibition of SGLT2 results in increased urinary excretion of glucose and sodium, along with an osmotic diuresis. Whether this action completely or partly explains the benefit of these drugs in patients with heart failure (and chronic kidney disease) is unknown. In addition to increased glycosuria and a resultant reduction in blood glucose, the other consistent effects of SGLT2 inhibitors are an increase in hematocrit, reduced rate of long-term decline in glomerular filtration rate (after an initial dip in this measure), and a modest decrease in blood pressure.[11] Many other actions of SGLT2 have been speculated, but not confirmed, in humans.

CLINICAL BENEFITS. Clinical trials have shown that adding an SGLT2 inhibitor to a renin-angiotensin system blocker (or ARNI), β-blocker, and a mineralocorticoid receptor antagonist decreases left ventricular size, improves ejection fraction, reduces symptoms and hospital admissions, and prolongs survival in men and women, regardless of whether or not they have type 2 diabetes, chronic renal disease, or a recent worsening of their heart failure.[A14–A17] These agents also reduce the risk of worsening kidney function[A18] and possibly of developing diabetes. Consequently, treatment with an SGLT2 inhibitor is recommended for all patients with symptomatic heart failure and a reduced ejection fraction, irrespective of diabetes status. SGLT2 inhibitors mitigate MRA-induced hyperkalemia.

PRACTICAL USE. As with an ARNI (or an ACE inhibitor or ARB), β-blocker, and mineralocorticoid receptor antagonist, an SGLT2 inhibitor should be introduced as early as possible in a patient's treatment. The only contraindications are type 1 diabetes, a history of diabetic ketoacidosis, and severe renal dysfunction (estimated glomerular filtration rate <20 mL/min/1.73 m^2). In patients with type 2 diabetes (Chapter 210), other glucose-lowering therapy may need to be adjusted, especially if there is a recent history of hypoglycemia. The dose of insulin should not be decreased by more than 25%, and it is prudent to discuss changes in insulin dosage with an endocrinologist before commencing an SGLT2 inhibitor.

Unlike other treatments for heart failure, SGLT2 inhibitors are prescribed as a single dose, and no up-titration is required (Table 46-6). Treatment may lead to a modest initial, but short-lived, diuresis and small decline in estimated glomerular filtration rate, although neither of these is usually a clinical problem. It is advisable to check kidney function within a month of starting treatment, especially in patients with a very low baseline estimated glomerular filtration rate. A clinically meaningful change in blood pressure is rare. Genital skin fungal infections may occur in 5 to 10% of patients, are rarely troublesome, and can usually be treated with an antifungal cream. In the rare cases of ketoacidosis (Chapter 210), the SGLT2 inhibitor should be discontinued immediately. Patients at greatest risk of ketoacidosis are those who are concurrently taking insulin or who may be insulin-deficient (e.g., as a result of previous pancreatitis). SGLT2 inhibitors should be temporary withheld in situations that might trigger ketoacidosis (i.e., illness leading to decreased food and fluid intake or stopping or reducing the dose of insulin), including elective surgery, for which SGLT2 inhibitors should be discontinued 3 days preoperatively.

Second-Line Treatments for Heart Failure with Reduced Left Ventricular Ejection Fraction

Several secondary agents are available for selected patients with heart failure (Fig. 46-3).

TABLE 46-5 PRACTICAL GUIDANCE ON THE USE OF MINERALOCORTICOID RECEPTOR ANTAGONISTS (MRAS) IN PATIENTS WITH HEART FAILURE DUE TO LEFT VENTRICULAR SYSTOLIC DYSFUNCTION

WHY?

Treatment with an MRA (spironolactone or eplerenone) increases survival, reduces hospital admissions, and improves New York Heart Association (NYHA) class when added to standard therapy (diuretic, digoxin, ACE inhibitor/ARB, and β-blocker) in patients with symptomatic (NYHA class II to IV) heart failure. Eplerenone also increases survival and reduces hospital admission for cardiac causes in patients with left ventricular systolic dysfunction and heart failure (or diabetes) complicating *acute* myocardial infarction.

IN WHOM AND WHEN?

Indications
- Potentially all patients with symptomatic heart failure (NYHA class II to IV)
- First-line therapy (along with an angiotensin receptor-neprilysin inhibitor [ARNI], an ACE inhibitor, or an ARB], plus a β-blocker and an SGLT2 inhibitor) in patients with symptomatic heart failure (NYHA class II to IV) and an LVEF ≤40%

Cautions/seek specialist advice
- Significant hyperkalemia ($K^+ > 5.0$ mmol/L)†
- Significant renal dysfunction (creatinine >221 μmol/L or 2.5 mg/dL)†

Potential drug interactions of particular concern
- K^+ supplements/K^+-sparing diuretics (e.g., amiloride and triamterene; beware combination preparations with furosemide)
- ACE inhibitor, ARBs, ARNIs, NSAIDs‡
- "Low-salt" substitutes with a high K^+ content

WHERE?

In the community or in the hospital
Exceptions—see Cautions/seek specialist advice

WHICH ORAL DOSE?†

	STARTING DOSE	TARGET DOSE
Spironolactone	25 mg once daily or on alternate days	25-50 mg once daily
Eplerenone	25 mg once daily	50 mg once daily

HOW TO USE?

Start with a low dose (see dose shown in previous column).
Check blood chemistry at 1, 4, 8, and 12 weeks; 6, 9, and 12 months; 6-monthly thereafter.
If K^+ rises above 5.5 mmol/L or creatinine rises to 221 μmol/L (2.5 mg/dL), reduce dose to 25 mg on alternate days and monitor blood chemistry closely.
If K^+ rises to >6.0 mmol/L or creatinine to >310 μmol/L (3.5 mg/dL), stop MRA immediately and seek specialist advice.
A specialist heart failure nurse may assist with education of the patient, follow-up (in person or by telephone), biochemical monitoring, and dose up-titration.

ADVICE TO PATIENT

Explain expected benefits (see Why?).
Treatment is given to improve symptoms, to prevent worsening of heart failure leading to hospital admission, and to increase survival.
Symptom improvement occurs within a few weeks to a few months of starting treatment.
Avoid NSAIDs‡ not prescribed by a physician (self-purchased over-the-counter agent) and salt substitutes high in K^+.
If diarrhea or vomiting occurs, patients should stop the MRA and contact the physician.

PROBLEM SOLVING

Worsening renal function/hyperkalemia
- See How to Use? section.
- Major concern is hyperkalemia (>6.0 mmol/L)
- Conversely, a high-normal potassium level may be desirable in patients with heart failure, especially if they are taking digoxin.
- It is important to avoid other K^+-retaining drugs (e.g., K^+-sparing diuretics such as amiloride and triamterene) and nephrotoxic agents (e.g., NSAIDs‡)

Concomitant use of a K^+ binder (e.g., patiromer [Chapter 103] may allow an MRA to be continued in patients who develop hyperkalemia with an MRA.
Some "low-salt" substitutes have a high K^+ content.
Male patients treated with spironolactone may develop breast discomfort or gynecomastia (these problems are significantly less common with eplerenone).

†It is extremely important to adhere to these cautions and doses in light of recent evidence of serious hyperkalemia with spironolactone in usual clinical practice in Ontario.
‡Avoid nonsteroidal anti-inflammatory drugs (NSAIDs) unless essential.
ACE = angiotensin converting enzyme; ARB = angiotensin receptor blocker; ARNI = angiotensin receptor/neprilysin inhibitor; MRA = mineralocorticoid receptor antagonist; NSAID = nonsteroidal anti-inflammatory drug; SGLT2 = sodium-glucose cotransporter 2.
Modified from McMurray J, Cohen-Solal A, Dietz R, et al. Practical recommendations for the use of ACE inhibitors, β-blockers, aldosterone antagonists and angiotensin receptor blockers in heart failure: putting guidelines into practice. *Eur J Heart Fail*. 2005;7:710-721.

Sinus Node Inhibitors: Ivabradine

MECHANISM OF ACTION. Ivabradine is the first of a new class of drugs developed to inhibit the mixed sodium-potassium channel or current (also known as the funny channel, abbreviated as I_f or I_{kf}) in the sinoatrial node and, in so doing, reduce heart rate. Reduction in heart rate is the only known cardiac action of ivabradine, which has this effect only in patients in sinus rhythm.

CLINICAL BENEFITS. In patients with symptomatic heart failure (NYHA class II to IV), a reduced ejection fraction (≤35%), and sinus rhythm with a rate of 70 beats per minute or higher, ivabradine improves symptoms and ejection fraction and reduces the risk for hospitalization for heart failure (but not mortality) when added to an ACE inhibitor (or ARB or, presumably, ARNI), a β-blocker, and a mineralocorticoid receptor antagonist.[A19]

PRACTICAL USE. Ivabradine should be considered in patients who have persistent symptoms (NYHA class II to IV) despite treatment with a diuretic and other disease-modifying therapies (i.e., an ARNI [or ACE inhibitor or ARB], β-blocker, and a mineralocorticoid receptor antagonist) and who are in sinus rhythm with a heart rate of 70 beats per minute or greater. Ivabradine is not a substitute for a β-blocker and is not effective in atrial fibrillation. Treatment should be started at 5 mg twice daily, increased to 7.5 mg twice daily after 14 days unless the heart rate is 60 beats per minute or less, and reduced usually to 2.5 mg twice daily if the rate is less than 50 beats per minute. Symptomatic bradycardia and visual disturbance (phosphenes) are uncommon but require the dose be reduced or ivabradine be discontinued. Ivabradine also may increase the risk of developing atrial fibrillation, which should prompt discontinuation of the drug. Ivabradine should not be used in combination with agents that prolong the QT interval (e.g., amiodarone) and must be used cautiously with inhibitors (including grapefruit juice) or inducers of CYP3A4.

Soluble Guanylate Cyclase Stimulator: Vericiguat

MECHANISM OF ACTION. Vericiguat stimulates soluble guanylate cyclase, thereby converting guanosine triphosphate to cyclic guanosine monophosphate and increasing phosphokinase G levels. Phosphokinase G levels cause relaxation of vascular and cardiac muscle. Stimulation of this pathway may also prevent pathologic fibrosis and muscle hypertrophy, which contribute to adverse vascular and cardiac remodeling.

CLINICAL BENEFITS. In patients with symptomatic heart failure, a reduced ejection fraction (<45%), and a recent hospital admission (or intravenous diuretic) for worsening heart failure, vericiguat reduces the risk for hospitalization for heart failure (but not mortality) when added to an ACE inhibitor (or ARB or ARNI), a β-blocker, and a mineralocorticoid receptor antagonist.[A20]

PRACTICAL USE. Vericiguat may be considered in patients who have persistent symptoms (functional class II to IV) despite treatment with a diuretic and other disease-modifying therapies (i.e., an ARNI [or ACE inhibitor or ARB], β-blocker, a mineralocorticoid receptor antagonist and an SGLT2 inhibitor) following a hospitalization for heart failure or need for outpatient intravenous diuretics. Treatment should be started at 2.5 mg orally once daily with food, and the dose should be doubled approximately every 2 weeks as tolerated to reach the target maintenance dose of 10 mg once daily. Hypotension is the most common side effect. Vericiguat also increases the risk of anemia. Concomitant use of vericiguat with a phosphodiesterase type 5 inhibitor is not recommended because of the potential for hypotension.

Digoxin

MECHANISM OF ACTION. Digitalis glycosides inhibit the cell membrane Na^+, K^+-ATPase pump, thereby increasing intracellular calcium and myocardial contractility. In addition, digoxin is thought to enhance parasympathetic and reduce sympathetic nervous activity as well as to inhibit renin release.

CLINICAL BENEFITS. In the only large RCT that examined the effects of starting (as opposed to withdrawing) digoxin, digoxin did not reduce mortality but did decrease the risk for admission to hospital for worsening heart failure and improve quality of life when it was added to a diuretic and an ACE inhibitor. In patients in sinus rhythm, the addition of digoxin can be considered if heart failure remains symptomatic despite standard treatment with a diuretic

TABLE 46-6 PRACTICAL GUIDANCE ON THE USE OF SODIUM GLUCOSE COTRANSPORTER 2 (SGLT2) INHIBITORS IN PATIENTS WITH HEART FAILURE DUE TO LEFT VENTRICULAR SYSTOLIC DYSFUNCTION

WHY?

Treatment with SGLT2 inhibitors (dapagliflozin or empagliflozin) increases survival, reduces hospital admissions, and improves symptoms/quality of life class when added to standard therapy (diuretic, an angiotensin receptor blocker-neprilysin inhibitor [ARNI] or ACE inhibitor/ARB], a β-blocker, and an MRA) in patients with symptomatic (NYHA class II to IV) heart failure. SGLT2 inhibitors also slow the rate of decline in estimated glomerular filtration rate over time.

IN WHOM AND WHEN?

Indications
- Potentially all patients with symptomatic heart failure (NYHA class II to IV)
- First-line therapy (along with ARNI [or ACE inhibitor/ARB], β-blocker and MRA) in patients with symptomatic heart failure (NYHA class II to IV) and an LVEF ≤40%

Contraindications
- Previous diabetic ketoacidosis
- Estimated glomerular filtration rate <20 mL/min/1.73 m^2

Cautions/seek specialist advice
- Significant renal dysfunction (estimated glomerular filtration rate <30 mL/min/1.73 m^2)
- Recurrent hypoglycemia
- Insulin treatment if hypoglycemia or if "tight" glycemic control (i.e., glycated hemoglobin <7%)
- Possible pancreatic insufficiency (e.g., due to previous pancreatitis)
- History of genital fungal infection
- Possibility that excessive alcohol consumption and ketogenic low-carbohydrate diets may increase the risk of ketoacidosis (or cause diagnostic confusion)

Potential drug interactions of particular concern
- Glucose-lowering therapy, especially insulin or insulin secretagogues (such as sulfonylureas) because of small risk of hypoglycemia if "tight" glycemic control (i.e., glycated hemoglobin <7%)

WHERE?

In the community or in the hospital
Exceptions—see Cautions/seek specialist advice

WHICH ORAL DOSE?

	STARTING DOSE	TARGET DOSE
Dapagliflozin	10 mg once daily	10 mg once daily
Empagliflozin	10 mg once daily	10 mg once daily

HOW TO USE?

Start with dose shown earlier
Check kidney function at 4-8 weeks; earlier if baseline estimated glomerular filtration rate <30 mL/min/1.73 m^2. Regular monitoring not needed unless concerning initial decline in kidney function (rare).
A specialist heart failure nurse may assist with education of the patient, follow-up (in person or by telephone), and biochemical monitoring.

ADVICE TO PATIENT

Explain expected benefits (see Why?).
Treatment is given to improve symptoms, to prevent worsening of heart failure leading to hospital admission, and to increase survival.
Symptomatic improvement occurs within a few weeks to a few months after starting treatment.
Advise of small (5-10%) risk of genital fungal skin infection—more common in women and in noncircumcised men. Probably less common in people without diabetes. Genital skin hygiene important.
Advise of small (<5%) risk of hypoglycemia—only in patients with type 2 diabetes and probably only in those treated with insulin or insulin secretagogues. More likely in individuals with "tight" glycemic control (i.e., glycated hemoglobin <7%).
Advise temporary withholding of SGLT2 inhibitor and/or stopping/reducing insulin dose in situations that might trigger diabetic ketoacidosis (e.g., illness leading to decreased food and fluid intake). For example, stop SGLT2 inhibitors 3 days preoperatively. Ketoacidosis has not been observed in patients without type 2 diabetes, and the greatest risk is in patients treated with insulin or insulin secretagogues.

PROBLEM SOLVING

Most common problem is genital fungal skin infection
- Can usually be treated with an antifungal cream and does not usually require treatment interruption; oral antifungal therapy is an alternative.

Major concern is ketoacidosis, which is rare but serious
- Diagnosis may be delayed because blood glucose may not be elevated (or greatly elevated).
- Symptoms and signs that should raise concern are abdominal pain, vomiting, confusion, "pear drop/fruity" breath
- Other typical problems (e.g., breathlessness, thirst) are not helpful in patients with heart failure
- Some increase in ketones with SGLT inhibitors is common (up to 1 mmol/L)

ACE = angiotensin converting enzyme; ARB = angiotensin receptor blocker; ARNI = angiotensin receptor/neprilysin inhibitor; LVEF = left ventricular ejection fraction; MRA = mineralocorticoid receptor antagonist; SGLT2 = sodium glucose cotransporter 2.

and key disease-modifying drugs (i.e., an ARNI [or ACE inhibitor or ARB], a β-blocker, a mineralocorticoid receptor antagonist, and an SGLT2 inhibitor). However, digoxin has not been as well studied and may not be as safe as ivabradine when used in conjunction with contemporary therapies. In patients with atrial fibrillation, digoxin may be used at an earlier stage if a β-blocker fails to control the ventricular rate during exercise (Chapter 52). Digoxin can also be used to control the ventricular rate when β-blocker treatment is being initiated or up-titrated.

If the effect of digoxin is needed urgently, loading with 10 to 15 μg/kg lean body weight, given in three divided doses 6 hours apart, may be used. The maintenance dose should be one third of the loading dose. Smaller maintenance doses (e.g., one fourth of the loading dose and not more than 62.5 μg/day) should be used in elderly patients and in patients with reduced renal function as well as in patients with a low body mass. Monitoring of the serum digoxin concentration is recommended because of the narrow therapeutic window. A steady state is reached 7 to 10 days after treatment is started; blood should be collected at least 6 hours (and ideally 8 to 24 hours) after the last dose. The currently recommended therapeutic range is 0.5 to 1.0 ng/mL.

Digoxin can cause anorexia, nausea, arrhythmias, confusion, and visual disturbances, especially if the serum concentration is above 2.0 ng/mL. Hypokalemia increases susceptibility to the adverse effects. The dose of digoxin should be reduced in elderly patients and in patients with renal dysfunction. Certain drugs increase serum digoxin concentration, including amiodarone.

Hydralazine and Isosorbide Dinitrate

MECHANISM OF ACTION. Hydralazine is a powerful direct-acting arterial vasodilator. Its mechanism of action is not understood, although it may inhibit enzymatic production of superoxide, which neutralizes nitric oxide and may induce nitrate tolerance. Nitrates dilate both veins and arteries, thereby reducing preload and afterload by stimulating the nitric oxide pathway and increasing cyclic guanosine monophosphate in vascular smooth muscle. Neither drug on its own, nor any other direct-acting vasodilator, has been demonstrated to be beneficial in heart failure.

CLINICAL BENEFITS. The addition of hydralazine and isosorbide dinitrate reduces mortality, hospital admissions for heart failure, and heart failure symptoms when added to standard disease-modifying drugs (i.e., an ACE inhibitor [or presumably an ARB or ARNI, a β-blocker, mineralocorticoid receptor antagonist, and an SGLT2 inhibitor) in Black patients with functional class III or IV symptoms and an ejection fraction of 45% or less. The dose is a fixed combination of 37.5 mg of hydralazine and 20 mg of isosorbide dinitrate; if one tablet is tolerated, a second is given 12 hours later. Then the tablet is given three times daily for 3 to 5 days, at which point the dose is increased to the target maintenance of two tablets three times daily (i.e., a daily dose of 225 mg hydralazine and 120 mg isosorbide dinitrate). It is uncertain whether hydralazine/isosorbide dinitrate is an effective addition to standard therapy in non–African American patients.

PRACTICAL USE. Other than for Black patients, the main indication for hydralazine and isosorbide dinitrate is as a substitute in patients who are intolerant to an ARNI (or ACE inhibitor or ARB), primarily because of renal dysfunction. However, many patients who cannot tolerate these three drugs because of hypotension also do not tolerate hydralazine and isosorbide dinitrate. Hydralazine and isosorbide dinitrate can also be used as additional treatment in non–African Americans who remain symptomatic with other proven therapies. The main dose-limiting adverse effects of hydralazine and isosorbide dinitrate are headache and dizziness. A rare adverse effect of higher doses of hydralazine, especially in slow acetylators, is a systemic lupus erythematosus–like syndrome (Chapter 245).

Omega-3 Polyunsaturated Fatty Acids

In one trial, 1 gram of n-3 PUFA (850 to 852 mg eicosapentaenoic acid and docosahexaenoic acid as ethyl esters in the average ratio of 1 : 1.2) per day led to a

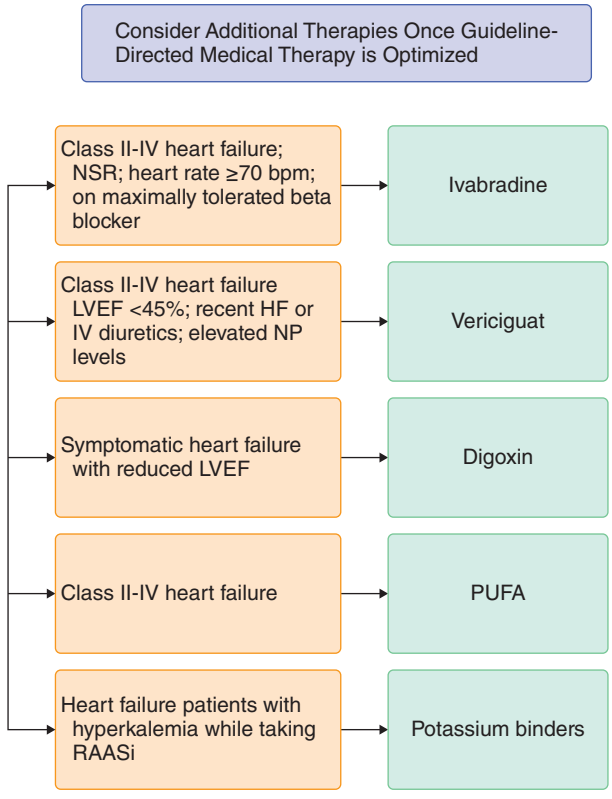

FIGURE 46-3. Second-line treatments for heart failure with reduced left ventricular ejection fraction. bpm = beats per minute; HR = heart rate; IV = intravenous; LVEF = left ventricular ejection fraction; NP = natriuretic peptide; NSR = normal sinus rhythm; PUFA = polyunsaturated fatty acids; RAASi = renin-angiotensin-aldosterone system inhibitor. (Reprinted with permission *Circulation*. 2022;145:e895-e1032 ©2022 American Heart Association, Inc.)

small reduction in cardiovascular morbidity and mortality in patients with heart failure. Although this agent may have beneficial anti-inflammatory and antiarrhythmic effects, its current role in the treatment of heart failure is uncertain, especially because trials in survivors of acute myocardial infarction have not shown benefit (Chapter 58).

Other Agents

The selective cardiac myosin activator omecamtiv mecarbil has shown inconsistent effects and is not approved by the U.S. Food and Drug Administration to treat heart failure. Other treatments have been tested in randomized trials and have been shown to have a neutral (e.g., amlodipine) or uncertain (e.g., bosentan and etanercept) effect on mortality and morbidity or to increase mortality (e.g., dronedarone, milrinone, flosequinan, vesnarinone, and moxonidine). The direct renin inhibitor aliskiren is inferior to an ACE inhibitor and is not recommended as an alternative to an ACE inhibitor (or ARB or ARNI) in patients with heart failure and a reduced ejection fraction. The potential role of cardiac stem cell therapy remains uncertain.[12]

Other Pharmacologic Issues

Some therapies that are of proven value for cardiovascular conditions that underlie or are associated with heart failure are of uncertain benefit (antiplatelet treatment, Chapter 70) or do not improve outcomes (statins, Chapter 190) in patients with persistent, symptomatic heart failure. Newer direct-acting oral anticoagulants or warfarin is indicated in patients with atrial fibrillation to reduce the risk for thromboembolism, unless patients have contraindications to their use (Chapter 52). Anticoagulants may also be used in patients with evidence of intracardiac thrombus (e.g., detected during echocardiographic examination) or systemic thromboembolism but otherwise are not indicated in patients who are not in atrial fibrillation.[A21] The many interactions of warfarin with other drugs, including some statins and amiodarone (Chapter 70), must always be considered. Heparin prophylaxis (Chapter 70) against deep vein thrombosis is indicated when patients with heart failure are bed bound, such as during hospital admission. Vaccination against influenza,[A22] pneumococcal infection, and severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) is advised (Chapter 15) in all patients with heart failure because these infections can lead to severe clinical deterioration.

Refractory Heart Failure and Pulmonary Edema

Patients presenting with acute heart failure include those who develop heart failure de novo as a consequence of another cardiac event, usually a myocardial infarction,[13] and those who present for the first time with decompensation of previously asymptomatic and often unrecognized cardiac dysfunction (patients previously with pre–heart failure [stage B], a transition with profound prognostic implications). However, because of frequent recurrences, most episodes of decompensation occur in patients with established, chronic heart failure that has worsened as a result of the unavoidable natural progression of the syndrome, with an intercurrent cardiac (e.g., arrhythmia) or noncardiac (e.g., pneumonia) event, or as a consequence of an avoidable reason, such as nonadherence with treatment or use of an agent that can alter renal function. Although it is not always identified, searching for a reversible precipitant is an important aspect of the initial therapy plan (Table 46-7). Many patients with decompensated heart failure experience worsening over a period of days or weeks before presenting to their doctor, during which time rising pulmonary artery pressure may be detected by an implantable pressure sensor.

TABLE 46-7 SOME COMMON PRECIPITATING CAUSES OF HEART FAILURE

Myocardial ischemia or infarction
Atrial fibrillation or other supraventricular tachycardias
Uncontrolled hypertension
Valvular disease
Ventricular tachycardia
Pulmonary embolism
Pericardial disease
Sepsis
Anemia
Poor dietary or medical adherence
Adverse drug effects
Hyperthyroidism or hypothyroidism
Unknown/unexplained*

*Commonly, no clear precipitant is identified.

Adapted from Kimmelstiel CD, DeNofrio D, Konstam MA. Heart failure. In: Wachter RM, Goldman L, Hollander H, eds. *Hospital Medicine,* 2nd ed. Philadelphia: Lippincott Williams & Wilkins; 2005:360.

Most patients with decompensated heart failure require admission to the hospital, especially if pulmonary edema is present. In contrast to the ambulatory setting, data from RCTs generally are not available to guide effective therapy for worsening of chronic heart failure or new-onset acute heart failure.[14] The principal goals of management of this heterogeneous group of patients are to relieve symptoms, the most important of which is extreme dyspnea, and to maintain or to restore vital organ perfusion. Importantly, using the acute admission period as an opportunity to commence evidence-based therapy and to titrate it rapidly after discharge results in a significant reduction in the risk of readmission and death.[A23]

The early administration of an intravenous bolus or infusion of a loop diuretic and, in hypoxemic patients, oxygen are the key first-line treatments. A small RCT suggested that high-dose diuretic (more than 2.5 times the previous oral dose) resulted in greater relief of dyspnea and congestion compared with low-dose diuretic (same intravenous dose as prior oral dose), but at the expense of more, albeit transient, renal dysfunction. Torsemide and furosemide are equally effective.[A24] A continuous infusion of furosemide may increase urine output compared with intermittent boluses but has not been shown to reduce mortality. An intravenous opiate may also be used cautiously in selected patients to relieve anxiety and distress, but at the risk of reducing ventilatory drive.

Noninvasive ventilation using a tight-fitting mask to provide positive-pressure ventilation reduces respiratory distress and metabolic disturbances more rapidly than standard oxygen therapy but has not reduced short-term mortality. Intravenous infusion of a nitrate (e.g., continuous intravenous infusion of 20 to 200 μg/mm of nitroglycerin, titrated according to the symptomatic response and hemodynamic measurements, particularly arterial blood pressure) may also be valuable in patients with hypertension or myocardial ischemia (Fig. 46-4).

Intravenous nesiritide can reduce the pulmonary capillary wedge pressure more promptly than intravenous nitroglycerin but has minimal effect on dyspnea and does not improve other clinical outcomes, and early intensive ventilator therapy is no better than usual care. In volume-overloaded patients with severe heart failure unresponsive to diuretics, ultrafiltration is an option at specialized centers, although it was not superior to intensified pharmacologic therapy in a recent trial.

In patients with marked hypotension or other evidence of organ hypoperfusion, an inotropic agent such as dobutamine (continuous intravenous infusion of 2.5 to 25 μg/kg/min, titrated according to hemodynamic and heart rate response and induction of arrhythmias or myocardial ischemia) or a phosphodiesterase inhibitor (e.g., milrinone) should be considered, although neither treatment has ever been shown to reduce in-hospital deaths. In some countries, the calcium

sensitizer levosimendan is also available for use in these patients. In general, potent inotropic agents should be used in a cardiac-monitored setting at the lowest clinically effective dose and for the shortest duration possible (Chapter 93). Although low-dose dopamine (intravenous infusion of 2.5 μg/kg/mm) is often administered in an attempt to improve diuresis and renal function, such benefits have not been confirmed in RCTs.

Devices and Surgery

In critically ill patients (Chapter 93), temporary percutaneous mechanical circulatory support guided by invasive hemodynamic measurements may also be considered. The aim of treatment is to support the patient's circulation and vital organ function until either the patient's own heart recovers or a definitive operative procedure can be performed (e.g., percutaneous coronary intervention, implantation of a ventricular assist device, or cardiac transplantation).

Implantable Cardioverter-Defibrillators

About half of patients with heart failure die suddenly, mainly as the result of a ventricular arrhythmia. The relative risk for sudden death, as opposed to death from progressive heart failure, is greatest in patients with milder symptoms. In patients with more advanced heart failure, progressive pump failure deaths are relatively more common. Antiarrhythmic drugs do not improve survival in heart failure. ICDs (Chapter 54), however, reduce the risk for death in selected patients after myocardial infarction (Chapter 58) and, in one large RCT, improved survival in patients with class II to III heart failure and systolic dysfunction who were otherwise treated with what was considered optimal medical therapy at the time. However, a large RCT with longer follow-up found no reduction in all-cause mortality when an ICD was added to excellent contemporary pharmacologic and device therapy in older patients with nonischemic heart failure.[A25] Currently, in addition to their role in patients with an ischemic etiology, the balance of evidence also favors use of an ICD in patients who have nonischemic heart failure,[A26] limited comorbidity (i.e., a low risk of noncardiovascular death), an anticipated survival of at least a year, and a left ventricular ejection fraction remaining at 35% or less despite at least 3 months of treatment with disease-modifying therapy (i.e., an ARNI [or ACE inhibitor or ARB], β-blocker, mineralocorticoid receptor antagonist, and an SGLT2 inhibitor).

Cardiac Resynchronization Therapy

About 30% of patients with heart failure and a reduced ejection fraction have substantial prolongation of the QRS duration on the surface electrocardiogram, which is a marker of abnormal electrical activation of the left ventricle

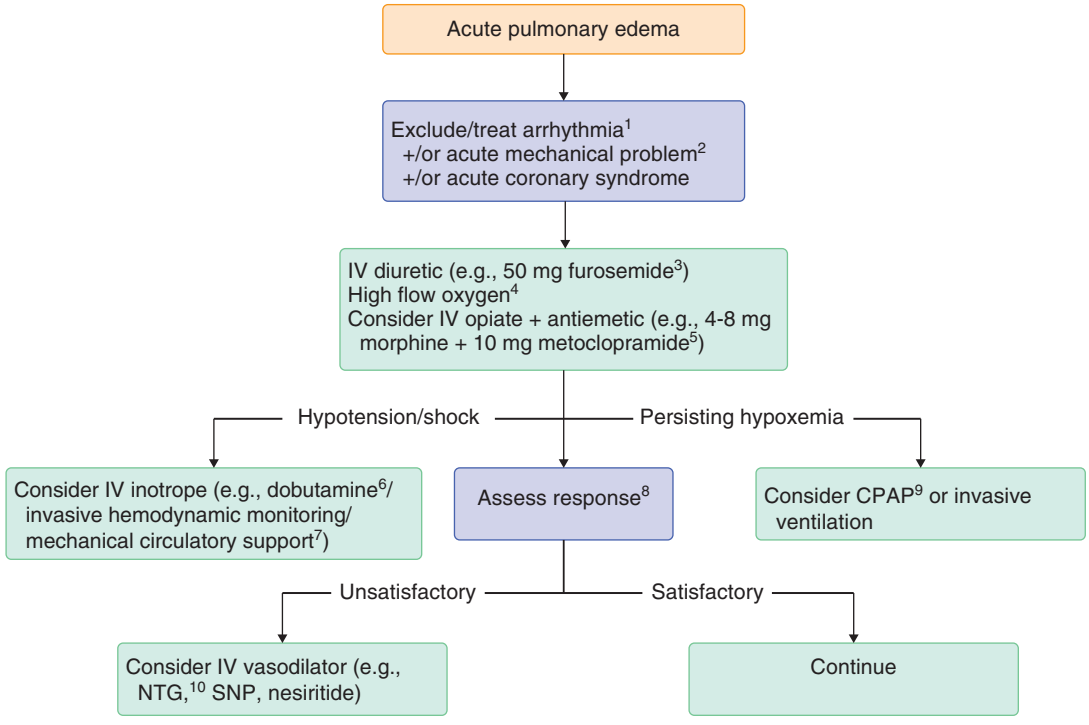

[1] Casual arrhythmia (e.g., ventricular tachycardia). It can be difficult to determine whether atrial fibrillation is a primary cause of acute pulmonary edema or secondary to it. An ECG is an essential investigation.

[2] Acute mechanical problems include ventricular septal rupture and mitral valve papillary muscle rupture. Mechanical support (e.g., an intra-aortic balloon pump) and urgent surgery should be considered. An echocardiogram should be performed as soon as possible, especially in a patient without a prior diagnosis of heart failure/other relevant heart disease (e.g., prior myocardial infarction or valve disease).

[3] Dose of diuretic depends on prior diuretic use and renal function—a lower dose may suffice if preserved renal function and no prior diuretic use.

[4] Oxygen causes an increase in systemic vascular resistance and a reduction in heart rate and cardiac output and should only be administered to patients with hypoxemia.

[5] Consider if patient is agitated/distressed/in pain; may cause respiratory depression and dose should be reduced in very elderly.

[6] An intravenous infusion of dobutamine may be started at a dose of 2.5 μg/kg/min, doubling every 15 minutes according to response and tolerability (dose titration usually limited by excessive tachycardia, arrhythmias, or ischemia). A dose above 20 μg/kg/min is rarely needed.

[7] For example, an intra-aortic balloon pump

[8] Improvement in symptoms and peripheral perfusion and adequate urine output—patient should be monitored closely, and usually a response will occur within 30 minutes. Bladder catheterization may help in monitoring urine output.

[9] Continuous positive airways pressure (CPAP) is valuable in severe pulmonary edema, especially if associated with hypoxemia. Endotracheal intubation and invasive mechanical ventilation should be considered in patients with persisting hypoxemia and physical ventilatory exhaustion.

[10] If systolic blood pressure is adequate (>100 mm Hg), an intravenous infusion of nitroglycerin (NTG) can be considered. Start at a dose of 10 μg/min and double every 10 minutes according to response and tolerability (usually dose up-titration is limited by hypotension). A dose of more than 100 μg/min is rarely needed.

Approach to the patient with acute pulmonary edema. IV = intravenous; NTG = nitroglycerin; SNP = sodium nitroprusside.

causing dyssynchronous contraction, less efficient ventricular emptying, and, often, mitral regurgitation. Atrioventricular coupling may also be abnormal, as reflected by a prolonged PR interval, as may interventricular synchrony. Cardiac resynchronization therapy (CRT) with atrial-biventricular or multisite pacing optimizes atrioventricular timing and improves synchronization of cardiac contraction. In symptomatic patients (NYHA class II to IV) who are in sinus rhythm, have marked systolic dysfunction (left ventricular ejection fraction ≤35%), and have a wide QRS, the addition of CRT to optimal medical therapy and an ICD improves pump function, reduces mitral regurgitation, relieves symptoms, and significantly prolongs exercise capacity. CRT also substantially reduces the risk for death and for hospital admission for worsening heart failure in such patients.[15] Many other outcome measures, including quality of life, are also improved. Whether CRT is beneficial in patients in atrial fibrillation or with non–left bundle branch block (LBBB) QRS widening is uncertain. All patients in sinus rhythm with persistent symptoms (NYHA class II to IV) and an ejection fraction of 35% or less despite optimal disease-modifying medical therapy (ARNI [or ACE inhibitor or ARB], β-blocker, mineralocorticoid receptor antagonist, and an SGLT2 inhibitor) should be considered for CRT if they have a QRS duration 130 msec or longer, especially if they have LBBB morphology, with the greatest benefit seen in patients with a QRS duration 150 msec or longer. Conversely, patients with a QRS duration less than 130 msec may be harmed by CRT. The value of new pacing modes, such as left bundle branch or[A27] His-bundle pacing,[A28] is also being explored in heart failure.

Surgery

With the exception of cardiac transplantation and ventricular assist devices, there are no generally accepted criteria for surgical intervention. Use of operative procedures is variable among centers and greatly dependent on local experience and expertise. Expert imaging and detailed hemodynamic and functional assessments are usually required when any patient with heart failure is considered for surgery, and close liaison between the relevant experts in these fields is essential. The collective expertise in surgical centers is often used to make highly individualized decisions about whether to operate and what procedures will be attempted. "Established" operative treatments for patients with heart failure include coronary artery bypass grafting, surgery, surgical or percutaneous interventions for aortic valve stenosis and mitral valve incompetence (Chapter 60), implantation of ventricular assist devices,[16] and heart transplantation.

PERCUTANEOUS CORONARY INTERVENTION OR CORONARY ARTERY BYPASS GRAFTING. Percutaneous coronary intervention or coronary artery bypass grafting (Chapter 59), as appropriate, is indicated for relief of angina. The extent of ischemia and residual myocardial viability can be determined by noninvasive assessments such as dobutamine echocardiography (Chapter 43), magnetic resonance imaging (Chapter 44), and positron emission tomographic scanning (Chapter 44) in patients with impaired left ventricular ejection fraction. Coronary artery bypass grafting reduces the risk for cardiovascular death and cardiovascular hospitalization (including heart failure hospitalization) in patients with ischemic cardiomyopathy, an ejection fraction of 35% or less, and coronary artery disease amenable to coronary-artery bypass grafting.[A29] The net benefit is not apparent until approximately 2 years after randomization because of the perioperative mortality related to surgery. Coronary artery bypass grafting is therefore recommended in such patients who are otherwise fit for surgery and have an anticipated life expectancy of 2 years or more. Percutaneous coronary revascularization has not been proven to have similar benefits in this situation.[A30]

CARDIAC TRANSPLANTATION. Cardiac transplantation remains the most accepted (Table 46-8) surgical intervention in end-stage heart failure.[17] Selection criteria usually focus on patients with refractory heart failure, that is, those with severe symptoms and functional limitations (peak oxygen consumption of less than 12 mL/kg per minute), as well as a particularly worrisome clinical course and prognosis attributed to their cardiac condition. These patients are often dependent on intravenous inotropic agents and mechanical support.

Over 3800 heart transplants are performed annually in the United States. The major limitation is the scarcity of donor organs, although increasing acceptance of heart donation after circulatory death has helped ease this problem. Cardiac xenotransplantation is experimental but a potentially promising additional way to address this shortage.[18] Absolute and relative exclusion criteria for heart transplantation (Table 46-9) include advanced age, serious comorbid conditions, and nonreversible pulmonary vascular resistance of more than 6 Wood units.

To diagnose allograft rejection, which can be antibody-mediated or cell-mediated, transjugular endomyocardial biopsies are usually performed weekly for 1 month, every other week for 2 months, and then every 1 to 2 months for the first year. In patients who are asymptomatic on low doses of corticosteroids, a gene expression profile of peripheral blood[19] can provide equivalent clinical outcomes despite fewer biopsies.[A31] Cellular rejection is usually easily treated with high-dose corticosteroids, but humoral rejection may require more aggressive immunosuppression (Chapter 38).

Another form of chronic rejection is transplant vasculopathy, which occurs at an annual rate of 5 to 10%. Patients are more likely to present with fatigue, heart failure, myocardial infarction, ventricular arrhythmia, or sudden death than with exertional angina. Patients are typically screened with annual coronary angiography, stress echocardiography, or positron emission tomography. Treatment emphasizes high-dose statins (see Table 190-2 in Chapter 190) and mTOR inhibitors (e.g., sirolimus or everolimus), but repeat transplantation may be required.

The survival rate after heart transplantation is currently about 85 to 90% at 1 year, 70 to 75% at 5 years, and 20% at 20 years. Transplant vasculopathy and malignancies account for about one third of deaths among patients who survive for 10 or more years.

MECHANICAL CIRCULATORY SUPPORT. Given the scarcity of organ donors, durable mechanical circulatory support using a left ventricular (or biventricular) assist device (LVAD) may be used as a "bridge to transplantation" or, in some centers, as a permanent and definitive alternative to transplantation ("destination therapy").[20] Mechanical circulatory support may also be used as

TABLE 46-8 INDICATIONS FOR HEART TRANSPLANTATION

Indications for referral of ambulatory patients with chronic heart failure

1. Patients who have limiting symptoms on exertion despite optimal medical therapy
2. Patients who require frequent hospital admission (two or more in 12 months) despite adequate therapy and adherence
3. Deteriorating renal function or inability to clear congestion without adversely affecting renal function
4. The need to decrease the dose or discontinue prognostically beneficial medication due to symptoms (often hypotension) or side effects such as renal dysfunction
5. Worsening right ventricular function or rising pulmonary artery pressure
6. High or rising natriuretic peptide levels despite optimal therapy
7. Frequent episodes of ventricular arrhythmias despite optimal drug and electrophysiologic therapy
8. Anemia, weight loss, hyponatraemia, or liver dysfunction attributable to heart failure

Indications for urgent inpatient referral

1. Inability to wean intravenous inotropic therapy
2. Need for percutaneous mechanical circulatory support to treat a patient in cardiogenic shock
3. Ventilatory support with use of positive airway pressure for intractable pulmonary edema
4. Refractory ventricular arrhythmias

From Bhagra SK, Pettit S, Parameshwar J. Cardiac transplantation: indications, eligibility and current outcomes. *Heart*. 2019;105:252-260.

TABLE 46-9 CARDIAC TRANSPLANTATION CONTRAINDICATION CRITERIA

1. Active infection (patients with chronic viral infection such as hepatitis B, hepatitis C, and human immunodeficiency virus may be considered if viral titres are undetectable on treatment or following treatment without evidence of other organ damage).
2. Symptomatic cerebral or peripheral vascular disease.
3. Diabetes mellitus with end-organ damage (e.g., nephropathy, neuropathy, proliferative retinopathy). Poorly controlled diabetes with glycosylated hemoglobin persistently >7.5% or 58 mmol/mL is a relative contraindication.
4. Current or recent neoplasm: risk of recurrence should be discussed with the oncologist.
5. Severe lung disease: FEV1 and FVC <50% predicted or evidence of parenchymal lung disease.
6. Irreversible renal dysfunction with estimated glomerular filtration rate <30 mL/min/1.73 m^2.
7. Irreversible liver dysfunction (e.g., cirrhosis).
8. Recent pulmonary thromboembolism (generally in the last 3 months).
9. Pulmonary hypertension with pulmonary artery systolic pressure >60 mm Hg, transpulmonary gradient ≥15 mm Hg and/or pulmonary vascular resistance >5 Wood units. If irreversible with either pharmacologic manipulation or mechanical unloading of the left ventricle, this is an absolute contraindication to isolated heart transplantation.
10. Psychosocial factors including history of non-compliance with medication, inadequate social support, ongoing or recent drug or alcohol use disorder, current smoker.
11. Obesity (body mass index >35 kg/m^2 or weight >140% of ideal body weight).
12. Other multisystem disease with poor long-term survival.

FEV1 = forced expiratory volume in one second; FVC = forced vital capacity.
From Bhagra SK, Pettit S, Parameshwar J. Cardiac transplantation: indication, eligibility and current outcomes. *Heart*. 2019;105:252-260.

a "bridge to candidacy" (i.e., to try to improve a patient's clinical status sufficiently to become eligible for transplantation). A continuous axial-flow device can provide a 65% 2-year survival free of repeat device surgery or disabling stroke. A newer ventricular magnetically levitated centrifugal-flow pump may provide better short-term and 2-year outcomes than the axial-flow pump.[A32]

Because not every hospital could or should be expected to offer all these levels of support for patients with advanced heart failure, there is a general recognition that such services should be concentrated in a limited number of tertiary centers. Centers implanting these devices use criteria such as persistent (>2 months) severe symptoms despite optimal drug and device therapy and other features placing patients at high risk for death (e.g., left ventricular ejection fraction <25%, three or more heart failure hospitalizations in the prior 12 months, peak oxygen consumption <12 mL/kg per minute, dependence on intravenous inotropic therapy, progressive end-organ dysfunction, and deteriorating right ventricular function) to decide who should be considered for mechanical circulatory support.

Organization of Care and Remote Monitoring

Several studies have shown that organized, nurse-led, multidisciplinary care can improve outcomes in patients with heart failure, particularly by reducing recurrent hospital admissions. Thus it is recommended that all patients with heart failure be enrolled in a disease management program. The most successful disease management approach seems to involve education of the patients, their families, and caregivers about heart failure and its treatment (including flexible diuretic dosing and reinforcing the importance of adherence), recognizing (and acting on) early deterioration (dyspnea, sudden weight gain, edema), and optimizing proven pharmacologic treatments. Both home-based and office-based approaches are effective. Even telephone follow-up is of value. New technology enabling noninvasive home telemonitoring of physiologic measures (e.g., heart rate and rhythm, blood pressure, temperature, respiratory rate, weight, and estimated body water content) and implanted devices, which collect similar data and may be interrogated remotely, are also being tested as aids to monitoring and management, but studies to date have not given consistent results. An alert embedded into the electronic health record can provide outpatients with personalized recommendations for increasing the use of guideline-directed medical therapies.[A33] Despite the usefulness of brain-type natriuretic peptide (BNP) in the diagnosis of heart failure and as a prognostic measure, treatment guided by BNP levels has not been shown in randomized trials to be consistently better than standard, evidence-based care.[A34] Conversely, treatment based on hemodynamic data transmitted from an implantable pulmonary artery pressure sensor may reduce heart failure hospitalizations over a 6- to 12-month period.[A35]

Education

Education of the patient, family, and caregivers is valuable (Table 46-10). Self-detection of early signs and symptoms of deterioration provides for earlier intervention. Counseling on the proper use of therapies, with an emphasis on adherence, is critical.

Useful patient-oriented material is available from several reliable sources: the Heart Failure Society of America (https://hfsa.org/patient-hub/heart-failure-facts-information), American Heart Association (http://www.heart.org/HEARTORG/Conditions/HeartFailure/Heart-Failure_UCM_002019_SubHomePage.jsp), National Heart, Lung and Blood Institute (http://www.nhlbi.nih.gov/health/dci/Diseases/Hf/HF_WhatIs.html), the Heart Failure Association of the European Society of Cardiology (https://www.heartfailurematters.org/), and other organizations.

Medication Use Counseling

When appropriate, a patient should be taught how to adjust the dose of diuretic within individualized limits. The dose should be increased (or a supplementary diuretic added) if there is evidence of fluid retention (symptoms of congestion) and decreased if there is evidence of hypovolemia (e.g., increased thirst associated with weight loss or postural dizziness, especially during hot weather or an illness causing decreased fluid intake or sodium and water loss). If hypovolemia is more marked, the doses of other medications also will have to be reduced.

The expected effects, beneficial and adverse, of other drugs should also be explained in detail (e.g., possible association of cough with ACE inhibitor). It is useful to inform patients that improvement with many drugs is gradual and may become fully apparent only after several weeks or even months of treatment. It is also important to explain the need for up-titration of the dose of an ARNI (or ACE inhibitor or ARB), a β-blocker, a mineralocorticoid receptor antagonist, and an SGLT2 inhibitor to the evidence-based target level, a goal that again may require weeks or even months to achieve. Patients should be advised not to use NSAIDs without consultation and to be cautious about using herbal or other nonproprietary preparations (Chapter 30).

Adherence

Education and counseling of the patient, caregiver, and family promote adherence, which is associated with better outcomes. Drug adherence can also be helped by home visits, specialized follow-up programs, and certain pharmacy aids, such as dose allocation (pill-organizing) boxes.

TABLE 46-10 TOPICS THAT SHOULD BE DISCUSSED WITH A PATIENT WITH HEART FAILURE AND WITH HIS OR HER FAMILY AND CAREGIVERS

GENERAL ADVICE
Explain what heart failure is and why symptoms occur
Causes of heart failure
How to recognize symptoms
What to do if symptoms occur
Self-weighing (to identify fluid retention)
RATIONALE FOR TREATMENTS
Importance of adhering to pharmacologic and nonpharmacologic (e.g., dietary) treatments
Smoking advice
Prognosis
DRUG COUNSELING
Rationale (i.e., benefits of individual drugs)
Dose and time of administration
Potential adverse effects (and what, if any, action to take)
What to do in case of missed or skipped doses
Self-management (e.g., flexible diuretic dosing)
REST AND EXERCISE
Rest
Exercise and activities related to work
Daily physical activity
Sexual activity
Rehabilitation
PSYCHOSOCIAL ASPECTS
Depression
Cognitive function
Social support
VACCINATIONS AND IMMUNIZATIONS
Influenza
Pneumococcal
OTHER
Travel
Driving
Dietary and social habits
Control sodium intake when necessary (e.g., some patients with severe heart failure)
Avoid excessive fluids in severe heart failure
Avoid excessive alcohol intake and illicit drugs

Modified from McMurray JJ, Adamopoulos S, Anker SD, et al. ESC Guidelines for the diagnosis and treatment of acute and chronic heart failure 2012: the Task Force for the Diagnosis and Treatment of Acute and Chronic Heart Failure 2012 of the European Society of Cardiology. Developed in collaboration with the Heart Failure Association (HFA) of the ESC. *Eur Heart J*. 2012;33:1787-1847.

Lifestyle Modification

Exercise

Tailored, structured, supervised aerobic exercise is safe and improves functional capacity and quality of life in patients with heart failure.[A36] An appropriate exercise prescription may also reduce hospitalizations and mortality in patients with heart failure. Regular physical activity or exercise training, if available, is recommended for all patients with heart failure who are able to participate.

Diet, Nutrition, and Alcohol

Most guidelines advocate avoidance of foods containing relatively high salt content in the belief that doing so may reduce the need for diuretic therapy, although the benefits of severe sodium restriction to less than 1 gram of sodium per day are unproven.[A37] This recommendation is based on clinical experience, which suggests that excess sodium intake can be a precipitant of clinical decompensation. Some salt substitutes have a high potassium content, which can lead to hyperkalemia.

Restriction of fluid intake is indicated only during episodes of decompensation associated with peripheral edema or hyponatremia. In these situations, daily intake should be restricted to 1.5 to 2.0 L to help facilitate reduction in extracellular fluid volume and to avoid hyponatremia.

Reducing excessive weight will reduce the work of the heart and may lower blood pressure (Chapter 64). Conversely, malnutrition is common in severe heart failure, and the development of cardiac cachexia is an ominous sign. Reduced food intake is sometimes caused by nausea (e.g., related to digoxin use or hepatosplenic congestion) or abdominal bloating (e.g., due to ascites). In these cases, small frequent meals and high-protein and high-calorie liquids may be helpful.

In severe decompensated heart failure, eating and bending may be difficult because of dyspnea—so called "bendopnea."

Moderate alcohol intake is not thought to be harmful in heart failure, although excessive intake can cause cardiomyopathy and atrial arrhythmias in susceptible individuals. In patients with suspected alcoholic cardiomyopathy, abstinence from alcohol may improve cardiac function.

Smoking

Smoking causes peripheral vasoconstriction, which is detrimental in heart failure. Nicotine replacement therapy (Chapter 363) is believed to be safe in heart failure. The safety of bupropion in heart failure is uncertain, especially because it is known to increase blood pressure, and varenicline may increase cardiovascular risk.

Sexual Activity

Sexual activity need not be restricted in patients with compensated heart failure, although dyspnea may be limiting. In men with erectile dysfunction (Chapter 216), treatment with a cyclic guanine monophosphate phosphodiesterase type 5 inhibitor can be useful, but these drugs must not be taken within 24 hours of prior nitrate use, and nitrates must not be restarted for at least 24 hours afterward. Caution should be exercised when sildenafil or another type-5 phosphodiesterase inhibitor is used in addition to sacubitril/valsartan and vericiguat because of the risk of hypotension.

Driving

Patients with heart failure can continue to drive, provided their condition does not induce undue dyspnea, fatigue, or other incapacitating symptoms. Patients with recent syncope, cardiac surgery, percutaneous coronary intervention, or device placement may be restricted from driving, at least temporarily, according to local regulations. Patients holding an occupational or commercial license may also be subject to additional restrictions.

Traveling

Short flights are unlikely to cause problems for a patient with compensated heart failure. For patients with an LVAD, travel should be planned in advance and in conjunction with the heart failure team.[21] Cabin pressure is generally maintained to provide an oxygen level no lower than equivalent to 6000 feet above sea level, which should be well tolerated in patients without severe pulmonary disease or pulmonary hypertension. Longer journeys may cause limb edema and dehydration, owing to insensible fluid loss, aggravated by caffeinated drinks and alcohol, thereby predisposing to venous thrombosis. Avoidance of dehydration is especially important in patients with an LVAD because the function of these devices is sensitive to blood volume. Adjustment of the dose of diuretics and other treatments should be discussed with the patient wishing to travel to a warm climate or a country where the risk for gastroenteritis is high. It is also advisable for heart failure patients to carry a list of medications and contact information for their health care provider and device cards for airport security. In those with an LVAD, contact with a health care provider at the patient's destination may be advisable.

Comorbidity

Comorbid conditions, which are common and important in patients with heart failure, may be due to the underlying cardiovascular disease that caused or contributed to heart failure (e.g., hypertension, coronary artery disease, diabetes mellitus), may arise as a complication of heart failure (e.g., arrhythmias), or can result from an adverse effect of treatment given for heart failure (e.g., gout). The exact causes of other comorbidities in heart failure, such as diabetes (Chapter 210), depression (Chapter 362), sleep apnea (Chapter 374), renal dysfunction (Chapter 116), and anemia (Chapter 144), are complex and uncertain. These and other comorbid conditions, such as chronic obstructive pulmonary disease and asthma, are important because they are a major determinant of prognosis and may limit the use of certain treatments for heart failure (e.g., renal dysfunction limiting use of ACE inhibitors or asthma limiting β-blockers) and because treatment of comorbidities may affect the stability of heart failure (e.g., NSAIDs needed for rheumatic conditions can cause salt and water retention and renal dysfunction). Both prevention (e.g., diabetes mellitus) and treatment (e.g., anemia) of comorbidities are being evaluated as a potential new therapeutic goal in heart failure.

Angina and Ischemia

β-Blockers are of benefit in both angina (Chapter 56) and heart failure. Similarly, ivabradine, which reduces heart rate by inhibiting the I_f current in the sinus node, is also beneficial in both angina and heart failure. Nitrates relieve angina but on their own are not of proven value in chronic heart failure. Calcium-channel blockers should generally be avoided in heart failure because they have a negative inotropic action and cause peripheral edema; only amlodipine has been shown to have no adverse effect on survival, but it may increase the risk for pulmonary edema. Trimetazidine, ranolazine, and nicorandil are antianginal drugs that are available in certain countries; their safety in patients with heart failure is uncertain. Percutaneous and surgical (Chapter 59) revascularization is also of value in relieving angina in selected patients with heart failure (see later). Coronary artery bypass grafting may reduce the risk for death from cardiovascular causes and cardiovascular hospitalization (including heart failure hospitalization) in selected heart failure patients with angina and a reduced ejection fraction.

Atrial Fibrillation

Atrial fibrillation (Chapter 52) may be the cause of or a consequence of heart failure in a patient presenting with atrial fibrillation and a rapid ventricular rate, and the distinction can be difficult, especially because prolonged atrial fibrillation may lead to a rate-related cardiomyopathy. Thyrotoxicosis (Chapter 207) and mitral valve disease (Chapter 60), especially stenosis, must be excluded. Alcohol abuse should also be considered. β-Blockers and digoxin are given to control the ventricular rate. The patient should be supervised closely after the initiation of these treatments because underlying sinus node dysfunction may raise the risk for bradycardia. If the patient presents emergently with severe heart failure, shock, or myocardial ischemia, urgent electrical or pharmacologic cardioversion may be considered (Chapter 54). Catheter ablation (Chapter 52) can reduce hospitalizations and mortality in selected patients with heart failure and atrial fibrillation,[A38] even if the left ventricular ejection fraction is normal,[A39] whereas a strategy of maintaining sinus rhythm with antiarrhythmic drug therapy alone is not superior to controlling the ventricular rate in patients with atrial fibrillation and heart failure. If pharmacologic therapy fails to control the ventricular rate and catheter ablation is contraindicated or unsuccessful, atrioventricular node ablation and pacing may be required (Chapter 54).[22] There is a strong indication for thromboembolism prophylaxis with a direct-acting anticoagulant or warfarin in patients who have heart failure with paroxysmal, persistent, or permanent atrial fibrillation (Chapter 52).

Asthma and Reversible Airway Obstruction

Asthma is a contraindication for use of a β-blocker, but most patients with chronic obstructive pulmonary disease (Chapter 76) can tolerate a β-blocker. Pulmonary congestion can mimic chronic obstructive pulmonary disease. Systemic administration of a corticosteroid to treat reversible airway obstruction may cause sodium and water retention and exacerbate heart failure, whereas inhalation therapy is better tolerated.

Diabetes Mellitus

The prevalence and incidence of diabetes mellitus are high in heart failure. β-Blocker treatment is not contraindicated and is of benefit in patients with diabetes and heart failure. In patients who have heart failure and type 2 diabetes, the SGLT2 inhibitors are the preferred antidiabetic agents.[23] Using sacubitril/valsartan reduces the glycated hemoglobin level and the need to institute insulin treatment compared with using an ACE inhibitor.

Neither insulin nor glucagon-like peptide-1 (GLP-1) receptor agonists (GP-1 Ras) increase the risk of developing heart failure, and both are considered to be safe in patients with heart failure. By comparison, several agents are not recommended in patients with severe heart failure. Thiazolidinediones cause sodium and water retention, metformin may cause lactic acidosis in patients with severe heart failure, and saxagliptin, which increases the risk for developing heart failure, should be avoided. Although there is no evidence of a similar risk with other dipeptidyl peptidase-4 inhibitors, these medications also are not recommended.

Abnormal Thyroid Function

Both thyrotoxicosis and hypothyroidism can cause heart failure (and thyrotoxicosis can cause atrial fibrillation, which may precipitate heart failure). Amiodarone can also induce both hypothyroidism and hyperthyroidism, the latter being particularly difficult to diagnose. The risk for thyroid dysfunction may be less with the related antiarrhythmic agent dronedarone, but dronedarone increases mortality in severe heart failure and should be avoided in patients with stage C or D heart failure or recently decompensated heart failure.

Gout and Hyperuricemia

Hyperuricemia and gout (Chapter 252) are common in heart failure and can be caused or aggravated by diuretic treatment. Sacubitril/valsartan and SGLT2 inhibitors reduce serum uric acid levels. Acute gout attacks are better treated with colchicine, oral steroids, or intra-articular steroids rather than with an NSAID. Allopurinol can prevent gouty attacks more safely than febuxostat.[A40]

Renal Dysfunction

Most patients with heart failure have a reduced glomerular filtration rate. ACE inhibitors, ARBs, sacubitril/valsartan, mineralocorticoid receptor antagonists, and SGLT2 inhibitors often cause an early, but small, further reduction in glomerular filtration rate and rise in serum blood urea nitrogen and creatinine levels, which, if limited, should not lead to discontinuation of treatment. Marked increases in blood urea nitrogen and creatinine, however, should prompt consideration of underlying renal artery stenosis (Chapter 110). Renal dysfunction may also be caused by sodium and water depletion (e.g., due to excessive diuresis, diarrhea, and vomiting) that leads to relative hypovolemia and hypotension. Conversely, renal venous congestion can contribute to renal impairment in patients who are markedly volume-overloaded. Nephrotoxic

agents such as NSAIDs are also a common cause of renal dysfunction in heart failure.

Prostatic Obstruction

For prostatic disease (Chapter 114), a 5α-reductase inhibitor may be preferable to an α-adrenoceptor antagonist, which can cause hypotension and salt and water retention.

Iron Deficiency and Anemia

Iron deficiency is very common in heart failure, for reasons that are uncertain, and may be present without concomitant anemia. Several trials have shown that intravenous ferric carboxymaltose or ferric derisomaltose (Chapter 145) improves symptoms, quality of life, and functional capacity when administered to patients who have a serum ferritin level <100 ng/mL or serum ferritin 100 to 299 ng/mL with a transferrin saturation <20%. In patients with heart failure, this treatment can substantially reduce the risk of hospital readmission for heart failure.[A41,A42]

A normocytic, normochromic anemia (Chapter 144) is also common in heart failure, in part because of the high prevalence of renal dysfunction. Malnutrition, blood loss, and underlying iron deficiency may be contributing factors. SGLT2 inhibitors increase the hematocrit and hemoglobin and often correct anemia, possibly by reducing plasma volume and increasing erythropoiesis. The erythropoiesis-stimulating agent darbepoetin is not of benefit in heart failure patients with anemia.

Depression

Depression (Chapter 362) is common in patients with heart failure, perhaps partly owing to disturbance of the hypothalamic-pituitary axis and other neurochemical pathways but also as a result of social isolation and the adjustment to chronic disease. Depression is associated with worse functional status, reduced adherence to treatment, and poor clinical outcomes. Both psychosocial interventions and pharmacologic treatment are helpful. Selective serotonin reuptake inhibitors are believed to be the best-tolerated pharmacologic agents, whereas tricyclic antidepressants should be avoided because of their anticholinergic actions and potential to cause arrhythmias.

Sleep Apnea

Sleep-disordered breathing, including both obstructive and central sleep apnea (Chapter 374), is common in patients with heart failure. Continuous positive airway pressure can improve the symptoms of obstructive sleep apnea in selected patients (Chapter 374), but adaptive servo-ventilation increases the risk of death in patients with heart failure and central sleep apnea.

Drugs to Use with Caution in Heart Failure

Patients with heart failure, especially if it is severe, often have renal and hepatic dysfunction, so any drug excreted predominantly by the kidneys or metabolized by the liver may accumulate (Chapter 25). Similarly, because of their extensive comorbidity, patients with heart failure are inevitably treated with multiple drugs, thereby increasing the risk for drug interactions.

Drugs that should be avoided, if possible, in heart failure include most antiarrhythmic drugs (including dronedarone, although amiodarone and dofetilide may be used), most calcium-channel blockers (with the possible exception of amlodipine, although this drug may increase the risk for pulmonary edema), corticosteroids, NSAIDs, cyclooxygenase-2 inhibitors, thiazolidinediones, saxagliptin, metformin, many antipsychotics (e.g., clozapine), and antihistamines. The U.S. Food and Drug Administration recently raised the concern that the dopamine agonist pramipexole used to treat Parkinson disease (Chapter 378) also might increase the risk for developing heart failure. Some salt substitutes contain substantial amounts of potassium and must be used cautiously. Other dietary constituents (e.g., grapefruit and cranberry juice) and supplements such as St. John's wort can interact with drugs taken by patients with heart failure, especially warfarin and digoxin. α-Adrenoceptor antagonists, commonly given for prostatic symptoms (Chapter 114), may cause hypotension and fluid retention. A variety of anticancer drugs, including trastuzumab, may aggravate heart failure (see Table 164-2).

Other Subtypes of Heart Failure

Heart Failure with Mildly Reduced Left Ventricular Ejection Fraction

In patients with heart failure and a left ventricular ejection fraction >40%, the SGLT2 inhibitors dapagliflozin and empagliflozin (each 10 mg once daily)[24] reduce the risk of heart failure hospitalization substantially and also improve symptoms and health-related quality of life.[A43,A44] In addition, retrospective analyses of several trials suggest that patients with a left ventricular ejection fraction in the range of 41 to 49% respond favorably to other treatments (e.g., an ARNI [or ACE inhibitor or ARB], a β-blocker, and a mineralocorticoid receptor antagonist) shown to be effective in patients with heart failure and a reduced ejection fraction. These therapies can be used to treat patients with heart failure and mildly reduced ejection fraction, along with diuretics as needed to control fluid retention (Fig. 46-5).

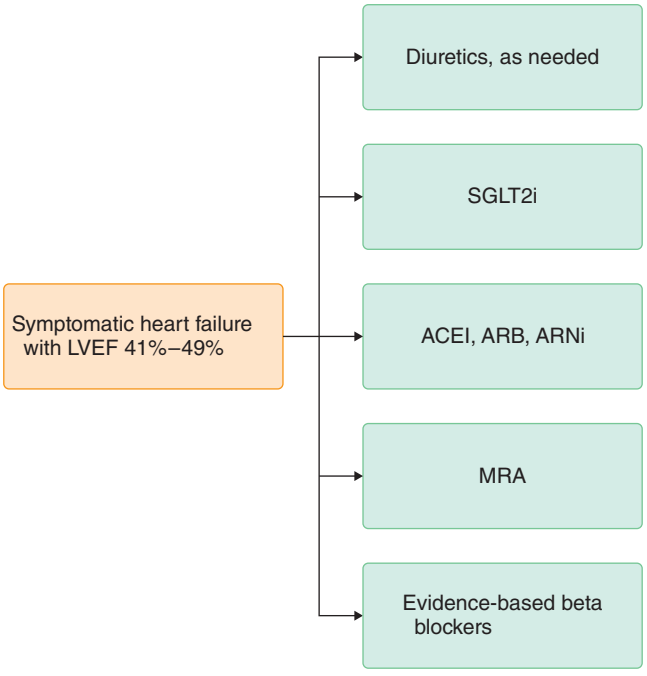

FIGURE 46-5. Treatments for heart failure with mildly reduced left ventricular ejection fraction. ACEI = angiotensin-converting enzyme inhibitor; ARB = angiotensin-receptor blocker; ARNI = angiotensin receptor-neprilysin inhibitor; LVEF = left ventricular ejection fraction; MRA = mineralocorticoid receptor antagonist; SGLT2i = sodium glucose cotransporter 2 inhibitor. (Reprinted with permission *Circulation*. 2022;145:e895-e1032 ©2022 American Heart Association, Inc.)

Heart Failure with Preserved Left Ventricular Ejection Fraction

For patients with heart failure and a left ventricular ejection fraction ≥50%, SGLT2 inhibitors (e.g., dapagliflozin 10 mg once daily or empagliflozin 10 mg once daily) reduce the risk of hospitalization for heart failure and improve symptoms and health-related quality of life. Diuretics, as needed to control fluid retention, are also valuable. However, no international consensus exists regarding other pharmacologic therapy (Fig. 46-6). Treatment of the underlying cardiovascular and other disorders that contribute to symptomatic stage C and stage D of heart failure with preserved left ventricular ejection fraction, such as hypertension, myocardial ischemia, and diabetes, is critical and is as for stages A and B (see earlier). In patients with atrial fibrillation, restoration of sinus rhythm or control of the ventricular rate with a β-blocker or a rate-limiting calcium-channel blocker can help control symptoms, although excessive rate control of atrial fibrillation or sinus rhythm may make these patients worse rather than better (Chapter 52). In patients with heart failure and preserved ejection fraction, ivabradine has no benefit on exercise capacity, and isosorbide mononitrate treatment tends to worsen activity levels. Infiltrative cardiomyopathies such as amyloidosis respond to disease-specific therapies (Chapter 47).

Heart Failure Due to Valvular Heart Disease

Heart failure also can arise as a result of regurgitant and stenotic valve disease (Chapter 60). It can sometimes be difficult to determine whether mitral regurgitation is primary or secondary in a patient with heart failure and left ventricular dilation, although a prior history of known valve disease or rheumatic fever may suggest a primary valve problem. The objective of treatment of primary valve disease is the prevention of heart failure by surgical repair or replacement of the diseased valve or valves (Chapter 60). The development of overt heart failure is an ominous sign, sometimes requiring emergent valve replacement (e.g., aortic stenosis) but sometimes indicating that valve replacement may not be possible (e.g., because of severe pulmonary hypertension).

Aortic Stenosis

Evaluation of the aortic valve (Chapter 60) can be difficult in patients with poor left ventricular systolic function. Such patients may have insufficient cardiac output to generate a high gradient across even a severely stenotic valve. Conversely, a calcified and degenerate but nonstenotic aortic valve may appear stenosed simply because it does not open normally in patients with very low cardiac output. A calculated valve area provides a better assessment of the severity of aortic stenosis in these patients. Stress echocardiography (Chapter 43) may help assess the potential for ventricular recovery after relief of aortic stenosis. Transcatheter valve replacement is a valuable technique for patients who have aortic stenosis but are at very high risk for open valve replacement.

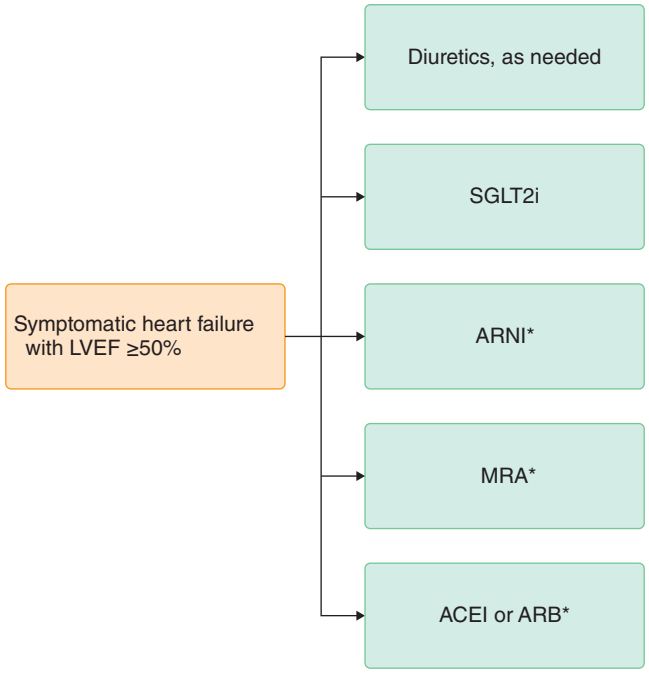

*Greater benefit in patients with LVEF closer to 50%.

FIGURE 46-6. Treatments for heart failure with preserved left ventricular ejection fraction. ACEI = angiotensin-converting enzyme inhibitor; ARB = angiotensin-receptor blocker; ARNI = angiotensin receptor-neprilysin inhibitor; LVEF = left ventricular ejection fraction; MRA = mineralocorticoid receptor antagonist; SGLT2i = sodium glucose cotransporter 2 inhibitor. (Reprinted with permission *Circulation*. 2022;145:e895-e1032 ©2022 American Heart Association, Inc.)

Mitral and Tricuspid Regurgitation

Mitral regurgitation can be a primary cause (organic) or a secondary manifestation (functional) in a patient with heart failure and left ventricular dilation (Chapter 60). In primary mitral regurgitation, surgery sometimes will result in clinical improvement, but some patients with advanced left ventricular dysfunction will not achieve substantial benefit (e.g., mitral valve surgery in a patient with long-standing severe mitral regurgitation). Valve repair is preferable to valve replacement, although neither procedure is proven to improve survival. Generally, medical and device therapy (e.g., CRT) is preferred to isolated valve surgery for secondary regurgitation. The role of transcatheter mitral valve repair is still evolving. Two recent trials have reported conflicting findings, but one suggested that this approach could provide a durable reduction in the risk of death and hospitalization for heart failure in carefully selected patients.[A45] Concomitant tricuspid valve repair may also provide some benefit in patients who have heart failure with both mitral and tricuspid valve regurgitation,[A46] but more data will be required before it can be routinely recommended.

Heart Failure Due to Nonischemic Dilated Cardiomyopathy

Patients with heart failure and normal coronary arteries should be evaluated for possible reversible causes. Untreated hypertension is now an unusual cause of dilated cardiomyopathy in the United States, but hypertension was once a leading cause in the United States and remains a major consideration in many parts of the world. Infiltrative cardiomyopathies (e.g., hemochromatosis, amyloid, sarcoid) and arteritides sometimes have specific recommended therapies (Chapters 47, 83, 174, and 196). Chagas disease (Chapter 318) must be considered in patients from endemic areas. Alcohol and other toxins (e.g., chemotherapeutic agents) are other recognized causes of dilated cardiomyopathy. Dilated cardiomyopathy can also develop in the peripartum period. Most cases of nonischemic dilated cardiomyopathy are usually labeled "idiopathic" (i.e., no specific etiology can be determined), although many may have a genetic origin, especially if there is a positive family history. In many centers routine genetic testing is undertaken in younger patients with unexplained dilated cardiomyopathy, especially in individuals with a family history of heart failure or sudden death and in those with conduction disease (e.g., bundle branch block). First-degree relatives of patients with genetic cardiomyopathies should be counseled and screened. Irrespective of etiology, nonischemic dilated cardiomyopathy should be treated in the same way as dilated ischemic cardiomyopathy.

Heart Failure Due to Hypertrophic Cardiomyopathy

Heart failure can arise in patients with hypertrophic cardiomyopathy because of predominant diastolic dysfunction, associated mitral incompetence, or the development of systolic dysfunction. The management of hypertrophic cardiomyopathy and its complications is often very different from the management of dilated cardiomyopathy (Chapter 47), thereby underscoring the value of echocardiography in the evaluation of the patient with heart failure.

Outpatient Follow-Up

In patients being sent home from the hospital, discharge planning and subsequent management to reduce the risk for readmission are important. Ideally, an effective oral diuretic regimen should have been identified, and fluid-volume and biochemical stability should have been achieved. This optimization of volume status and development of a stable oral regimen before discharge is thought to reduce the risk for early readmission. Treatment with an ARNI (or ACE inhibitor or ARB), a β-blocker, a mineralocorticoid receptor antagonist, and SGLT2 inhibitor should be started in the stabilized patient before discharge. Outpatient follow-up should be arranged to ensure that any of those treatments that have not been started before discharge are initiated after discharge and that the dose of each drug is increased, as tolerated, to the appropriate target.

The key to successful follow-up is the careful tracking of clinical symptoms and the patient's weight, which often involves interviewing not only the patient but also family members, who may be more aware of changes in status than the patient is. Treatment of established heart failure based on natriuretic peptide levels does not appear to improve outcomes compared with best standard care. Continuity of care and seamless transitions from the inpatient to the outpatient setting are crucial aspects of optimal management. Patients with advanced heart failure and patients requiring frequent hospitalization require special attention. Programs that provide telephone-based tracking of daily weights and symptoms can detect deterioration in time to intervene before the need for hospitalization, and an implanted pulmonary artery pressure monitor may be valuable in selected patients. Although these programs may be costly, several evaluations have found them to be cost-effective. Because the care of these patients requires considerable experience and expertise, specialized disease management programs and clinics have been developed and may provide additional benefit compared with traditional care.

PROGNOSIS

The prognosis of patients with heart failure has improved with advances in therapy. Although it is difficult to predict prognosis in individual patients, until recently patients with symptoms at rest (NYHA class IV) have a 30 to 50% annual mortality rate, patients who are symptomatic with mild activity (class III) have mortality rates of 10 to 20% annually, and patients with symptoms only with moderate activity (class II) have a 5 to 10% annual mortality rate. Mortality rates are higher in older patients, men, patients with a reduced left ventricular ejection fraction[25] or underlying coronary heart disease, and patients with higher serum levels of certain biomarkers (e.g., natriuretic peptides and high-sensitivity troponin).[26]

End-of-Life Considerations

Although predicting the trajectory of illness in patients with advanced heart failure is notoriously difficult, it is often apparent when a patient has progressed to end-stage heart failure, commonly associated with concomitant renal failure. In these circumstances, the expertise of the palliative care team may be especially helpful (Chapter 3).[27] Useful websites providing information on palliative care relevant to heart failure are available (https://getpalliativecare.org/whatis/disease-types/congestive-heart-failure-palliative-care/, http://www.goldstandardsframework.org.uk/, and http://www.palliativecarescotland.org.uk/content/links, https://www.hospiceuk.org/what-we-offer/clinical-and-care-support/heart-failure-and-hospice-care). Medications such as parenteral opiates (with an antiemetic) and benzodiazepines may be particularly helpful in relieving dyspnea, anxiety, and pain that arises from ascites, hepatic congestion, lower limb edema, and pressure points. At this stage in the patient's illness, it may be appropriate to discuss withdrawal of conventional treatment, deactivation of an ICD to avoid undesired and unpleasant electrical discharges, and a do-not-resuscitate order if the patient and others involved in the patient's care agree that comfort care is appropriate. Hospice care may be chosen by some at this point.

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For the General References and other additional features, please visit Elsevier eBooks+ at https://ebooks.health.elsevier.com.

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47 DISEASES OF THE MYOCARDIUM AND ENDOCARDIUM

PERRY M. ELLIOTT AND IACOPO OLIVOTTO

MYOCARDIAL DISEASE

A substantial minority of cases of heart failure result from familial (genetic) or nonfamilial (acquired) disorders, which can be confined to the heart or be multisystem disorders. The term *cardiomyopathy* refers to myocardial disorders in which the heart muscle is structurally and functionally abnormal in the absence of coronary artery disease (Chapter 58), hypertension (Chapter 64), valvular disease (Chapter 60), or congenital heart disease (Chapter 55) sufficient to cause the observed myocardial abnormality. Cardiomyopathies are classified according to ventricular morphology and pathophysiology into four major types: dilated cardiomyopathy, hypertrophic cardiomyopathy, restrictive cardiomyopathy, and arrhythmogenic cardiomyopathy (Table 47-1 and Fig. 47-1). Diseases that do not fit into these groups (such as endocardial fibroelastosis and left ventricular noncompaction) are termed unclassified cardiomyopathies. Mixed phenotypes can exist; for example, patients with hypertrophic and dilated cardiomyopathies frequently have a restrictive left ventricular physiology or develop ventricular dilation.

HYPERTROPHIC CARDIOMYOPATHY

DEFINITION AND EPIDEMIOLOGY

Hypertrophic cardiomyopathy is defined as unexplained left ventricular hypertrophy in the absence of abnormal loading conditions (valve disease, hypertension, congenital heart defects) sufficient to explain the degree of hypertrophy. The disease occurs worldwide and in all racial groups, with a prevalence of between 0.2 and 0.5%.

PATHOBIOLOGY

Hypertrophic cardiomyopathy is usually familial with autosomal dominant inheritance. Mutations in sarcomeric contractile protein genes (E-Table 47-1) account for approximately 50 to 60% of cases.[1] More than 1400 different mutations have been identified, with marked variation in disease penetrance and clinical expression. The most common involved genes are *MYH7*, which

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47 DISEASES OF THE MYOCARDIUM AND ENDOCARDIUM

PERRY M. ELLIOTT AND IACOPO OLIVOTTO

MYOCARDIAL DISEASE

A substantial minority of cases of heart failure result from familial (genetic) or nonfamilial (acquired) disorders, which can be confined to the heart or be multisystem disorders. The term *cardiomyopathy* refers to myocardial disorders in which the heart muscle is structurally and functionally abnormal in the absence of coronary artery disease (Chapter 58), hypertension (Chapter 64), valvular disease (Chapter 60), or congenital heart disease (Chapter 55) sufficient to cause the observed myocardial abnormality. Cardiomyopathies are classified according to ventricular morphology and pathophysiology into four major types: dilated cardiomyopathy, hypertrophic cardiomyopathy, restrictive cardiomyopathy, and arrhythmogenic cardiomyopathy (Table 47-1 and Fig. 47-1). Diseases that do not fit into these groups (such as endocardial fibroelastosis and left ventricular noncompaction) are termed unclassified cardiomyopathies. Mixed phenotypes can exist; for example, patients with hypertrophic and dilated cardiomyopathies frequently have a restrictive left ventricular physiology or develop ventricular dilation.

HYPERTROPHIC CARDIOMYOPATHY

DEFINITION AND EPIDEMIOLOGY

Hypertrophic cardiomyopathy is defined as unexplained left ventricular hypertrophy in the absence of abnormal loading conditions (valve disease, hypertension, congenital heart defects) sufficient to explain the degree of hypertrophy. The disease occurs worldwide and in all racial groups, with a prevalence of between 0.2 and 0.5%.

PATHOBIOLOGY

Hypertrophic cardiomyopathy is usually familial with autosomal dominant inheritance. Mutations in sarcomeric contractile protein genes (E-Table 47-1) account for approximately 50 to 60% of cases.[1] More than 1400 different mutations have been identified, with marked variation in disease penetrance and clinical expression. The most common involved genes are *MYH7*, which

ABSTRACT

Diseases of the myocardium and endocardium commonly present with heart failure and/or arrhythmia. Myocardial diseases are termed cardiomyopathies when they are unexplained by coronary artery, hypertensive, valvular, or congenital heart disease and are classified by their predominant phenotype. Most cardiomyopathies are heritable, with autosomal dominant inheritance, and have a defined genetic cause with pathogenic variants in sarcomere, cytoskeletal, and desmosomal genes that cause hypertrophic, dilated, restrictive, and arrhythmogenic cardiomyopathy. Other uncommon genetic disorders may present with overlapping phenotypes but different inheritance patterns and genetic bases (e.g., hypertrophic cardiomyopathy in Anderson-Fabry disease or Noonan syndrome). Diagnosis of the cardiomyopathies relies on electrocardiography (ECG) and imaging and exclusion of significant abnormalities related to more common cardiac disorders. Management focuses on familial evaluation and counseling regarding genetic and clinical risk, treatments to improve symptoms, assessment of the risk of arrhythmias, and, when necessary, treatments (e.g., implantable defibrillators) to prevent sudden death. Molecular genetic analysis is recommended when there is a diagnostic phenotype and is particularly valuable when cascade screening of family members is feasible. Myocarditis, an inflammatory process of the myocardium, is most often caused by infections (e.g., Chagas disease, virus), toxins (e.g., chemotherapy, recreational drugs), and immunologic disease (e.g., systemic lupus erythematosus). Definitive diagnosis relies on demonstration of inflammation in the myocardium; more often a presumptive diagnosis is made based on clinical and ECG features, because endomyocardial biopsy is usually only performed in the deteriorating patient or to exclude giant cell myocarditis, which is usually fatal if not treated with prolonged immunosuppression. Endocardial disease, characterized as with or without hypereosinophilia, and primary cardiac tumors are rare.

KEYWORDS

hypertrophic cardiomyopathy
dilated cardiomyopathy
arrhythmogenic cardiomyopathy
myocarditis
genetics of cardiomyopathy
heart failure
sudden death

E-TABLE 47-1 SOME GENETIC CAUSES OF CARDIOMYOPATHY

PROTEIN NAME	GENE SYMBOL	INHERITANCE	PHENOTYPE	ESTIMATED FREQUENCY
SARCOMERIC PROTEINS				
Cardiac β-myosin heavy chain	MYH7	AD	HCM; DCM; LVNC; RCM; Laing distal myopathy	HCM 30-40%; DCM 4-6%
Cardiac myosin-binding protein C	MYBPC3	AD	HCM; DCM; LVNC	HCM 30-40%; DCM ~1%
Cardiac troponin T	TNNT2	AD	HCM, DCM, RCM	HCM 10-15%; DCM 3-5%
Cardiac troponin I	TNNI3	HCM: AD; DCM: AD, AR	HCM; RCM; DCM	HCM 2-5%; RCM frequent; DCM < 1%
α-Tropomyosin	TPM1	AD	HCM; DCM	HCM ~1-2%; DCM <1%
Regulatory myosin light chain	MYL2	AD	HCM; DCM	HCM ~1%; DCM rare
Cardiac actin	ACTC1	AD	LVNC; DCM; HCM; CHD	DCM ~1%; HCM ~1%
Essential myosin light chain	MYL3	AD	HCM; DCM	Rare
Cardiac troponin C	TNNC1	AD	HCM; DCM	HCM <1%
Actin, alpha 1, skeletal muscle	ACTA1	AD	HCM, DCM, skeletal/nemaline myopathy	Rare
SARCOMERE AND Z-DISC–RELATED PROTEINS				
Titin	TTN	AD	DCM; LVNC; skeletal myopathy	DCM 15-25%
BCL2-associated athanogene 3	BAG3	AD	DCM; skeletal myopathy	2-4%
FH1/FH2 domain-containing protein 3	FHOD3	AD	HCM	HCM 1-2%
Titin-cap or telethonin	TCAP	AD	HCM; DCM; skeletal myopathy	Rare
Cysteine and glycine-rich protein 3 (cardiac LIM protein)	CSRP3	AD; AR	HCM; DCM	Rare
Four-and-a-half LIM protein 1	FHL1	X linked	HCM, muscular dystrophy	Rare
Myozenin 2	MYOZ2	AD	HCM	Rare
CYTOSKELETAL PROTEINS				
Desmin	DES	AD, AR	DCM; RCM; ACM; skeletal myopathy; CCD	DCM <1%
Filamin C	FLNC	AD	ACM; DCM; RCM; skeletal myopathy	DCM 1%; ACM ~5%
Dystrophin	DMD	XL	DCM; skeletal myopathy	DCM <1%
Caveolin-3	CAV3	AD	HCM; DCM; skeletal myopathy	Rare
α-B crystallin	CRYAB	AD	DCM; skeletal myopathy	Rare
α-, β-, γ-, and δ-sarcoglycans	SGCA, SGCB, SGCG, SGCD	AR; SGCD: AD	DCM; muscular dystrophy	Rare
Striated muscle preferentially expressed protein kinase	SPEG	AR	DCM; skeletal myopathy	Rare
NUCLEAR PROTEINS				
Lamin A/C	LMNA	AD	DCM; skeletal myopathy; CCD; ACM	DCM 4-8%
Emerin	EMD	XL recessive	DCM; skeletal myopathy; CCD	DCM <1%
Dystrobrevin alpha	DTNA	AD	DCM; LVNC	Rare
α-Kinase 3 deficiency	ALPK3	AR/AD	HCM; DCM	HCM 1-2%
PR domain-containing protein 16	PRDM16	AD	LVNC; DCM	Rare
Transmembrane protein 43	TMEM43	AD	ACM; DCM; skeletal myopathy	Rare
ION CHANNEL AND ION CHANNEL RELATED				
Cardiac sodium channel	SCN5A	AD	DCM; CCD; Brugada syndrome, LQTS	DCM <1%
Potassium/sodium hyperpolarization-activated cyclic nucleotide-gated channel 4	HCN4	AD	LVNC; CCD; Brugada syndrome	Rare
Regulatory SUR2A subunit of the cardiac K(ATP) channel	ABCC9	AD	DCM; HCM in Cantú syndrome	Rare
Anoctamin-5	ANO5	AR	DCM; skeletal myopathy	Rare
Voltage-dependent L-type calcium channel subunit alpha-1C	CACNA1C	AD	HCM in Timothy syndrome; LQTS	Rare
DESMOSOMAL PROTEINS				
Plakophilin 2	PKP2	AD, AR	ARVC; DCM	AD 30-40%; AR rare
Desmoglein 2	DSG2	AD	ARVC; ACM; DCM	12-40%
Desmoplakin	DSP	ARVC: AD; Carvajal syndrome: AR	ACM; ARVC; DCM in Carvajal syndrome	ACM/ARVC 6-39%

E-TABLE 47-1 SOME GENETIC CAUSES OF CARDIOMYOPATHY—cont'd

PROTEIN NAME	GENE SYMBOL	INHERITANCE	PHENOTYPE	ESTIMATED FREQUENCY
Desmocollin 2	DSC2	AD	ARVC	Rare
Junction plakoglobin	JUP	ARVC: Naxos disease: AR	ARVC in Naxos disease	Rare
Phospholamban	PLN	AD	ACM; DCM; HCM	DCM founder effect in Holland, otherwise rare
Junctophilin 2	JPH2	AD	HCM	Rare
METABOLIC PROTEINS				
Amylo-1,6-glucosidase	AGL	AR	HCM in Forbes disease	Rare
Acid α-1,4-glucosidase	GAA	AR	HCM, DCM in Pompe disease	Rare
α-Galactosidase A	GLA	XL dominant	HCM in Anderson-Fabry disease	Rare
Lysosomal-associated membrane protein 2	LAMP2	XL dominant	HCM, DCM in Danon disease	Rare
Protein kinase, AMP- activated, γ2 noncatalytic subunit	PRKAG2	AD	HCM; Wolff-Parkinson-White syndrome	Rare
Frataxin	FXN	AR	HCM in Friedreich ataxia	Rare
Hereditary hemochromatosis	HFE	AR	DCM and RCM in hereditary hemochromatosis	Rare
Mitochondrial genes encoding mitochondrial components	MT-TG, MT-TY, MT-ND5, others	Maternal	HCM in MELAS, MERRF syndromes	Rare
Dolichol kinase	DOLK	AR	DCM	Rare
Tafazzin	TAZ	XL recessive	DCM; LVNC in Barth syndrome	Rare
1-Acyl-sn-glycerol-3-phosphate acyltransferase beta	AGPAT2	AR	HCM in Berardinelli-Seip syndrome	Rare
Fumarylacetoacetase	FAH	AR	HCM	Rare
β-Galactosidase	GLB1	AR	HCM in Morquio syndrome A	Rare
β-Glucuronidase	GUSB	AR	HCM in mucopolysaccharidosis VII	Rare
Glycogenin-1	GYG1	AR	HCM; DCM; skeletal myopathy	Rare
Malonyl-CoA decarboxylase, mitochondrial	MLYCD	AR	HCM; LVNC; DCM	Rare
Phosphopantothenate--cysteine ligase	PPCS	AR	DCM	Rare
Solute carrier family 22 member 5	SLC22A5	AR	HCM, DCM long and short QT in primary systemic carnitine deficiency	Rare
Alanine-tRNA ligase, mitochondrial	AARS2	AR	HCM, DCM in combined oxidative phosphorylation deficiency 8	Rare
Acyl-CoA dehydrogenase family member 9, mitochondrial	ACAD9	AR	HCM/DCM in mitochondrial complex I deficiency	Rare
Very long-chain specific acyl-CoA dehydrogenase, mitochondrial	ACADVL	AR	HCM/DCM in very long-chain acyl-CoA dehydrogenase deficiency	Rare
Acylglycerol kinase, mitochondrial	AGK	AR	HCM in Sengers syndrome	Rare
ATP synthase mitochondrial F1 complex assembly factor 2	ATPAF2	AR	Syndromic HCM	Rare
Cytochrome c oxidase assembly factor 5	COA5	AR	Syndromic HCM	Rare
Cytochrome c oxidase assembly factor 6 homolog	COA6	AR	Syndromic HCM	Rare
4-Hydroxybenzoate polyprenyltransferase, mitochondrial	COQ2	AR	Syndromic HCM	Rare
Cytochrome c oxidase assembly protein COX15 homolog	COX15	AR	Syndromic HCM	Rare
Cytochrome c oxidase subunit 6B1	COX6B1	AR	Syndromic HCM	Rare
Dihydrolipoyl dehydrogenase, mitochondrial	DLD	AR	Syndromic HCM	Rare
Mitochondrial import inner membrane translocase subunit TIM14	DNAJC19	AR	Syndromic DCM; LVNC	Rare
Zinc phosphodiesterase ELAC protein 2	ELAC2	AR	Syndromic HCM; DCM	Rare

E-TABLE 47-1 SOME GENETIC CAUSES OF CARDIOMYOPATHY—cont'd

PROTEIN NAME	GENE SYMBOL	INHERITANCE	PHENOTYPE	ESTIMATED FREQUENCY
FAD-dependent oxidoreductase domain-containing protein 1	FOXRED1	AR	Syndromic HCM	Rare
Elongation factor G, mitochondrial	GFM1	AR	Syndromic DCM; HCM; CHD	Rare
Lipoyl synthase, mitochondrial	LIAS	AR	HCM in Leigh syndrome	Rare
39 S ribosomal protein L3, mitochondrial	MRPL3	AR	Syndromic HCM	Rare
39 S ribosomal protein L44, mitochondrial	MRPL44	AR	Syndromic HCM	Rare
28 S ribosomal protein S22, mitochondrial	MRPS22	AR	Syndromic HCM	Rare
Protein MTO1 homolog, mitochondrial	MTO1	AR	Syndromic HCM	Rare
Inorganic pyrophosphatase 2, mitochondrial	PPA2	AR	Syndromic DCM	Rare
Glutamyl-tRNA(Gln) amidotransferase subunit A, mitochondrial	QRSL1	AR	Syndromic HCM	Rare
Protein SCO2 homolog, mitochondrial	SCO2	AR/AD	Syndromic HCM	Rare
Succinate dehydrogenase [ubiquinone] flavoprotein subunit, mitochondrial	SDHA	AR	LVNC; DCM; HCM in Leigh syndrome	Rare
Phosphate carrier protein, mitochondrial	SLC25A3	AR	Syndromic HCM	Rare
Surfeit locus protein 1	SURF1	AR	DCM, HCM in Leigh syndrome	Rare
Transmembrane protein 70, mitochondrial	TMEM70	AR	Syndromic HCM	Rare
ADP/ATP translocase 1	SLC25A4	AR/AD	Syndromic HCM; encephalopathy	Rare
Pyruvate dehydrogenase E1 component subunit alpha, somatic form, mitochondrial	PDHA1	XL dominant	HCM, CCD	Rare
Phosphorylase b kinase regulatory subunit alpha, skeletal muscle isoform	PHKA1	XL	HCM	Rare
Seipin	BSCL2	AR	HCM in Berardinelli-Seip syndrome	Rare
Phosphomannomutase 2	PMM2	AR	Syndromic HCM	Rare
OTHER GENES				
RNA-binding protein 20	RBM20	AD	DCM; LVNC	3-5%
Homeobox protein Nkx-2.5	NKX2-5	AD	LVNC; CHD	<1%
Muscle RING Finger 1 (MuRF1)	TRIM63	AR	HCM; skeletal myopathy	Rare
Transcription factor TBX20	TBX20	AD	DCM; LVNC; CHD	<1%
Hereditary amyloidosis	TTR	AD	HCM and RCM in hereditary amyloidosis	Rare
Alström syndrome protein 1	ALMS1	AR	DCM in Alström syndrome	Rare
Eyes absent 4	EYA4	AD	DCM	Rare
Fukutin-related protein	FKRP	AD, AR	DCM; skeletal myopathy	Rare
Fukutin	FKTN	AD, AR	DCM; skeletal myopathy	Rare
F-box–only protein 32	FBXO32	AR	DCM	Rare
Laminin α2	LAMA2	AR	DCM; skeletal myopathy	Rare
Transcription factor GATA-4	GATA4	AD	DCM; CHD	Rare
Transcription factor GATA-6	GATA6	AD	DCM; CHD	Rare
Kelch-like protein 24	KLHL24	AD/AR	DCM in epidermolysis bullosa	Rare
Cardiotrophin 1	CTF1	AD	DCM	Rare
αT-catenin	CTNNA3	AD	ARVC; ACM	Rare
RAS-MAPK pathway	PTPN11, RAF1, SOS1, KRAS, HRAS, BRAF, NRAS, MEK1-2, RIT1, SHOC2, SOS2, SPRY1, others	AD-de novo	HCM in Noonan, LEOPARD, Costello and CFC syndromes	Rare
Leucine-zipper–like transcriptional regulator 1	LZTR1	AR	HCM in Noonan syndrome	Rare

E-TABLE 47-1 SOME GENETIC CAUSES OF CARDIOMYOPATHY—cont'd

PROTEIN NAME	GENE SYMBOL	INHERITANCE	PHENOTYPE	ESTIMATED FREQUENCY
Dual specificity mitogen-activated protein kinase kinase 1	MAP2K1	AD	HCM in CFC syndrome	Rare
Dual specificity mitogen-activated protein kinase kinase 2	MAP2K2	AD	HCM in CFC syndrome	Rare
E3 ubiquitin-protein ligase CBL	CBL	AD	HCM in Noonan-like syndrome	Rare
Non-POU domain-containing octamer-binding protein	NONO	XL-dominant	LVNC; CHD	Rare
Pleckstrin homology domain	PLEKHM2	AR	DCM; LVNC	Rare

ACM = arrhythmogenic cardiomyopathy; AD = autosomal dominant; AR = autosomal recessive; ARVC = arrhythmogenic right ventricular cardiomyopathy; CCD = cardiac conduction disease; CFC = cardiofaciocutaneous; CHD = congenital heart disease; CPVT = catecholaminergic polymorphic ventricular tachycardia; DCM = dilated cardiomyopathy; HCM = hypertrophic cardiomyopathy; LQTS = long QT syndrome; LVNC = left ventricular noncompaction; MELAS = mitochondrial encephalomyopathy, lactic acidosis, and strokelike episodes; MERRF = myoclonic epilepsy with ragged red fibers; RCM = restrictive cardiomyopathy; SGCD = sarcoglycan delta; XL = X-linked.

TABLE 47-1 PROFILES OF MYOCARDIAL DISEASE

	HYPERTROPHIC	DILATED	RESTRICTIVE	ARRHYTHMOGENIC
Causes	Genetic (see E-Table 47-1) Infiltrative or storage disease	Myocarditis (see Table 47-3) Metabolic/endocrine Genetic (see E-Table 47-1)	Infiltrative or storage diseases (see Table 47-7) Endomyocardial (e.g., Löffler, carcinoid) Genetic (see E-Table 47-1)	Genetic (see E-Table 47-1)
LV ejection fraction	Increased or normal	Reduced	Normal or reduced	LV and RV normal or mildly reduced until end stage
LV end-diastolic dimension	Usually decreased	Increased	Normal	LV and RV normal or mildly increased until end stage
LV wall thickness	Increased	Normal	Normal or mildly increased	Normal
Atrial size	Increased	Increased	Increased; may be massive	Atria normal until end stage
Valvular disease	Mitral regurgitation (SAM)	Mitral (functional); tricuspid regurgitation in late stages	Mitral and tricuspid regurgitation, rarely severe	
Common symptoms	Dyspnea; chest pain, syncope, palpitation, fatigue Late: orthopnea, PND	Dyspnea, fatigue Late: orthopnea, PND	Dyspnea Late: orthopnea, PND, right-sided heart failure	Palpitations, syncope End stage: right and/or left heart failure
Arrhythmia	Atrial fibrillation, ventricular tachycardia; conduction block in *PRKAG2*, mitochondrial; Fabry disease	Ventricular tachyarrhythmias; heart block in Chagas disease, giant cell myocarditis, laminopathies	Atrial fibrillation; conduction block in sarcoidosis, amyloidosis, desminopathy	Biventricular ectopy and tachycardia

LV = left ventricle; PND = paroxysmal nocturnal dyspnea; PRKAG2 = protein kinase, AMP-activated, gamma 2 noncatalytic subunit mutation; RV = right ventricle; SAM = systolic anterior motion of mitral valve.

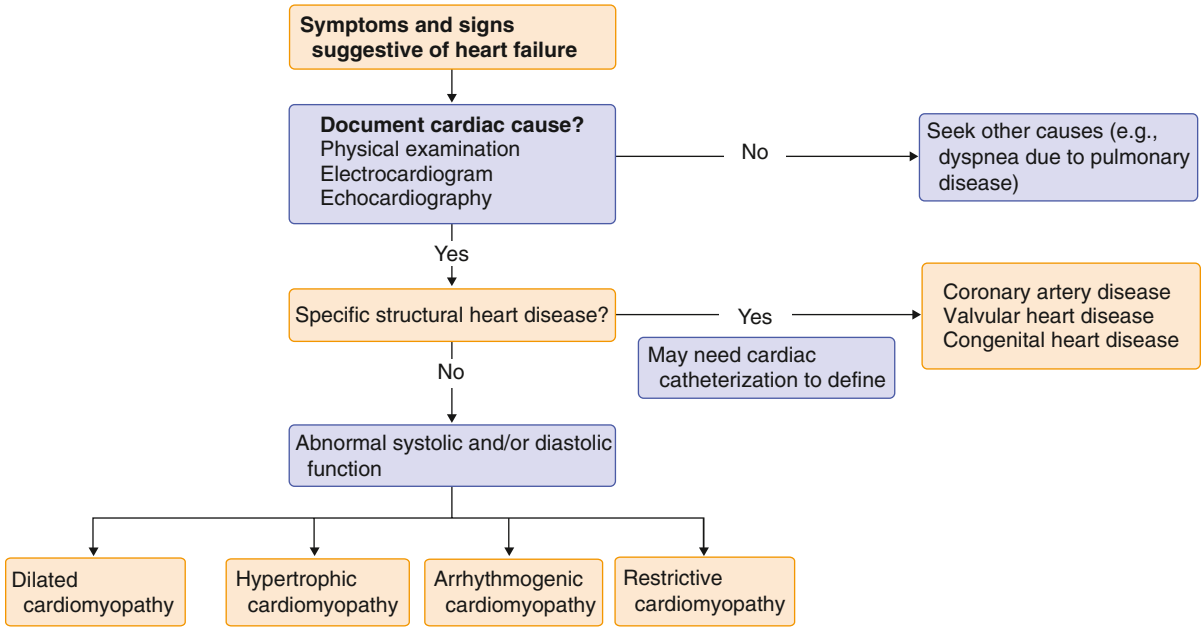

FIGURE 47-1. Initial approach to classification of cardiomyopathy. The evaluation of symptoms or signs consistent with heart failure first includes confirmation that they can be attributed to a cardiac cause. Although this conclusion is often apparent from routine physical examination and electrocardiography, echocardiography serves to confirm cardiac disease and provides clues to the presence of other cardiac diseases, such as valve disease or congenital heart disease. Having excluded these conditions, cardiomyopathy is generally considered to be dilated, restrictive, or hypertrophic, as shown in Table 47-1. Patients with apparently normal cardiac structure and contraction are occasionally found to demonstrate abnormal intracardiac flow patterns consistent with diastolic dysfunction but should also be evaluated carefully for other causes of their symptoms. Most patients with so-called diastolic dysfunction also demonstrate at least borderline criteria for left ventricular hypertrophy, frequently in the setting of chronic hypertension and diabetes. A moderately decreased ejection fraction without marked dilation or a pattern of restrictive cardiomyopathy may represent either a distinct entity or a transition between acute and chronic disease.

codes for the cardiac β-myosin heavy chain, and *MYBPC3*, which codes for myosin binding protein C. A similar clinical phenotype is seen in association with other uncommon genetic disorders, including Noonan syndrome (Chapter 55), Friedreich ataxia (Chapter 389), neurofibromatosis (Chapter 385), hereditary spherocytosis (Chapter 147), respiratory chain disorders, glycogen storage diseases (Chapter 191), and lysosomal storage disorders (Chapter 192), especially Fabry and Danon disease.

Pathology

In its original classical form, hypertrophic cardiomyopathy causes asymmetric myocardial hypertrophy preferentially involving the anteroseptal wall. However, a wide spectrum of patterns is now recognized, including concentric, midventricular, and apical. Older individuals often have hypertrophy that is limited to the basal portion of the sigmoid-shaped septum, frequently in the context of sporadic, genotype-negative disease. The right ventricular free wall and papillary muscles are often involved. The papillary muscles are often hypertrophied, are displaced anteriorly, may be bifid, and occasionally are implanted directly into the mitral leaflet, with poorly developed or absent chordae. The mitral leaflets are consistently elongated, irrespective of the degree of hypertrophy, and are prone to developing systolic anterior motion and dynamic outflow obstruction. Myocardial crypts, apical hypertrabeculation, and apical-septal myocardial bundles constitute ancillary phenotypic traits, which can be found

also in genotype-positive individuals who lack myocardial hypertrophy. Apical aneurysms may develop, particularly in patients with mid-apical hypertrophy and mid-ventricular obstruction.

At the histologic level, hypertrophic cardiomyopathy is characterized by hypertrophy of cardiomyocytes, areas of myocytic disarray, and interstitial fibrosis. Myocyte disarray refers to architectural disorganization of the myocardium, with adjacent myocytes aligned obliquely or perpendicular to each other in association with increased interstitial collagen. The myofibrillar architecture within the myocyte is also disorganized. The coronary microcirculation is affected, with medial and intimal hyperplasia that can obliterate the vessel's lumen and impair vasodilatation.

Pathophysiology

Genetic mutations associated with hypertrophic cardiomyopathy can result in an overall gain of function of the sarcomere, thereby leading to abnormal cellular metabolism and an inefficient utilization of energy. Myocardial hypertrophy, which is a compensatory mechanism to this altered metabolic state, contributes to diastolic dysfunction. Myocardial fibrosis is common and contributes to progressive systolic dysfunction.

About 50% of patients develop left ventricular outflow tract obstruction at rest or with exercise owing to systolic anterior movement of the mitral valve leaflets. Obstruction may also occur at the mid-ventricular level in patients who have distal hypertrophy because of systolic obliteration of the ventricular cavity with the interposition of an abnormally positioned papillary muscle; this type of obstruction is associated with the development of apical aneurysms. The occurrence and severity of obstruction typically vary over time in individual patients and are exacerbated by dehydration, standing, increased adrenergic states, vasodilators, and ingestion of food and alcohol.

CLINICAL MANIFESTATIONS

Most patients are asymptomatic or have only mild or intermittent symptoms, and the diagnosis is often made as a result of family screening or the incidental detection of a heart murmur or an electrocardiographic (ECG) abnormality. However, a lack of symptoms may reflect the patient's long-term adaptation to diminished exercise. Symptoms can develop at any age, even many years after the appearance of ECG or echocardiographic manifestations of left ventricular hypertrophy. On occasion, sudden death or syncope may be the initial presentation.

Symptomatic progression is usually slow and associated with a gradual deterioration in left ventricular function over decades, often associated with the development of atrial fibrillation. Less than 5% of patients have rapid, symptomatic deterioration and often develop refractory heart failure owing to hypokinetic and/or restrictive evolution.

Approximately 20 to 30% of adults develop chest pain (Chapters 39 and 56), which may occur on exertion, at rest, or nocturnally. Postprandial angina associated with mild exertion is typical. Mild to moderate dyspnea on exertion is relatively common. Occasionally, patients may develop paroxysmal nocturnal dyspnea, often due to paroxysmal arrhythmias such as atrial fibrillation. Approximately 20% of patients experience syncope (Chapters 39 and 49),[2] and a similar proportion complain of presyncope. Angina and syncope are most frequent in patients who have dynamic left ventricular outflow obstruction. Palpitations (Chapter 49) are frequent and are usually attributable to supraventricular or ventricular ectopy.

DIAGNOSIS

The initial diagnostic evaluation must include a comprehensive medical history focusing on cardiovascular symptoms, a family history focusing on premature cardiac disease or death, a careful physical examination, a 12-lead ECG, and a two-dimensional echocardiogram.[3] A three- to four-generation family history, which should be obtained in all patients with a new diagnosis of cardiomyopathy, helps determine the probability of familial disease and its mode of inheritance.

Clinical examination of the cardiovascular system is often normal. In the presence of left ventricular outflow tract obstruction, the arterial pulse has a rapid upstroke and downstroke (sometimes with a bisferiens character), the apex beat is sustained or double (reflecting a palpable atrial impulse followed by left ventricular contraction), and auscultation will demonstrate a systolic ejection murmur that is heard loudest at the left sternal edge and that radiates to the right upper sternal edge and apex (Chapter 39). Most patients with left ventricular outflow tract obstruction also have the murmur of functional mitral regurgitation, which results from failure of the mitral valve leaflets to coapt due to the systolic anterior motion of the mitral valve. Physiologic and pharmacologic maneuvers that decrease afterload or venous return (e.g., standing, Valsalva maneuver, inhalation of amyl nitrite) or increase contractility (e.g., a post-extrasystole beat) will increase the intensity of the murmur, whereas interventions that increase afterload and venous return (e.g., squatting or handgrip) will reduce it (see Table 39-8). In contrast, physical signs in most patients who do not have left ventricular outflow tract obstruction are subtle and are limited to features that reflect the hyperdynamic contraction (rapid upstroke pulse) and poorly compliant right (prominent *a* wave in jugular venous pressure) and left (S_4 gallop, double-apex beat) ventricles (Chapter 39).

The general evaluation must always include an overview of potential extracardiac manifestation, which may help distinguish classic disease from rare genotypes that have radically different pathobiology, clinical course, and therapeutic strategies. These diseases include lysosomal storage diseases such Fabry, Danon, and Pompe diseases (Chapter 191); syndromes such as Noonan and LEOPARD; and mitochondrial diseases. Noonan syndrome is characterized by short stature, developmental delay, cutaneous abnormalities, hypertelorism, ptosis, low-set posteriorly rotated ears, and webbed neck. These features are shared with the less common LEOPARD syndrome (Noonan syndrome with multiple lentigines [NSML]). Angiokeratomas, anhidrosis, Raynaud-like symptoms with neuropathy, cornea verticillata, retinal vascular dilation, tinnitus, diarrhea, and proteinuria are typical features of Fabry disease (Chapter 192). Patients with mitochondrial diseases such as mitochondrial encephalomyopathy, lactic acidosis, and strokelike episodes (MELAS) have a matrilinear pattern of inheritance and present with short stature, lactic acidosis, severe exercise intolerance, neurosensory deafness, juvenile-onset diabetes, and strokelike episodes.

Diagnostic Testing

More than 95% of patients have abnormal ECG findings, but no changes are disease specific. The most common abnormalities are increased QRS voltage consistent with left ventricular hypertrophy, left axis deviation (15 to 20%), abnormal Q waves (25 to 30%, most commonly in inferolateral leads), and ST segment or T wave changes (>50%). An isolated increase in the QRS voltage without ST segment changes or T wave inversion is rare in hypertrophic cardiomyopathy. The presence of predominantly distal or apical thickening is associated with giant negative T wave inversion, which is maximal in leads V_3 and V_4.

Two-dimensional echocardiography (Chapter 43), which is the mainstay of diagnostic imaging, may be complemented by magnetic resonance imaging (MRI; Chapter 44) and computed tomography (CT; Chapter 44) for more precise definition of the extent and distribution of the hypertrophy and other relevant phenotypic features. The hypertrophy is often asymmetric and involves the anterior and posterior intraventricular septum (Fig. 47-2). The hypertrophy, however, may be more generalized and involve the free wall of the left ventricle, or it may be localized and confined to areas other than the septum, such as the apex (E-Fig. 47-1), lateral wall, or posterior wall of the left ventricle. Hypertrophy can completely obliterate the left ventricular outflow tract (E-Fig. 47-2). Systolic anterior motion of the mitral valve prevents normal coaptation of the mitral leaflets and results in mitral regurgitation (E-Fig. 47-3).

The echocardiogram also can measure left ventricular outflow tract obstruction, both at rest and after provocative maneuvers. Patients with an outflow tract gradient of 30 mm Hg or more are considered to have obstructive disease, with severe obstruction defined as a gradient ≥50 mm Hg. Exercise echocardiography is essential to assess the severity of dynamic obstruction on effort, particularly in physically active individuals, because resting values may be falsely reassuring.

Most patients with hypertrophic cardiomyopathy have left atrial enlargement as well as echocardiographic evidence of diastolic dysfunction. Magnetic resonance imaging provides accurate characterization of tissue and allows the identification of edema and replacement fibrosis (E-Fig. 47-4), while also aiding in the exclusion of rare mimics of hypertrophic cardiomyopathy such as amyloidosis (Chapter 174). Late in the disease, patients often develop left ventricular dilation (E-Fig. 47-5.)

When it is available, cardiopulmonary exercise testing with metabolic gas exchange measurements provides an accurate and reproducible assessment of exercise capacity, which can be followed serially, and it is most useful in patients who have evidence of myocardial fibrosis and progressive heart failure. Cardiac catheterization is rarely required for diagnosis or management, but it may be indicated when measurement of intracardiac pressures is required to guide therapeutic decisions (e.g., in patients with severe mitral regurgitation) and for the exclusion of coexistent coronary artery disease in patients with chest pain.

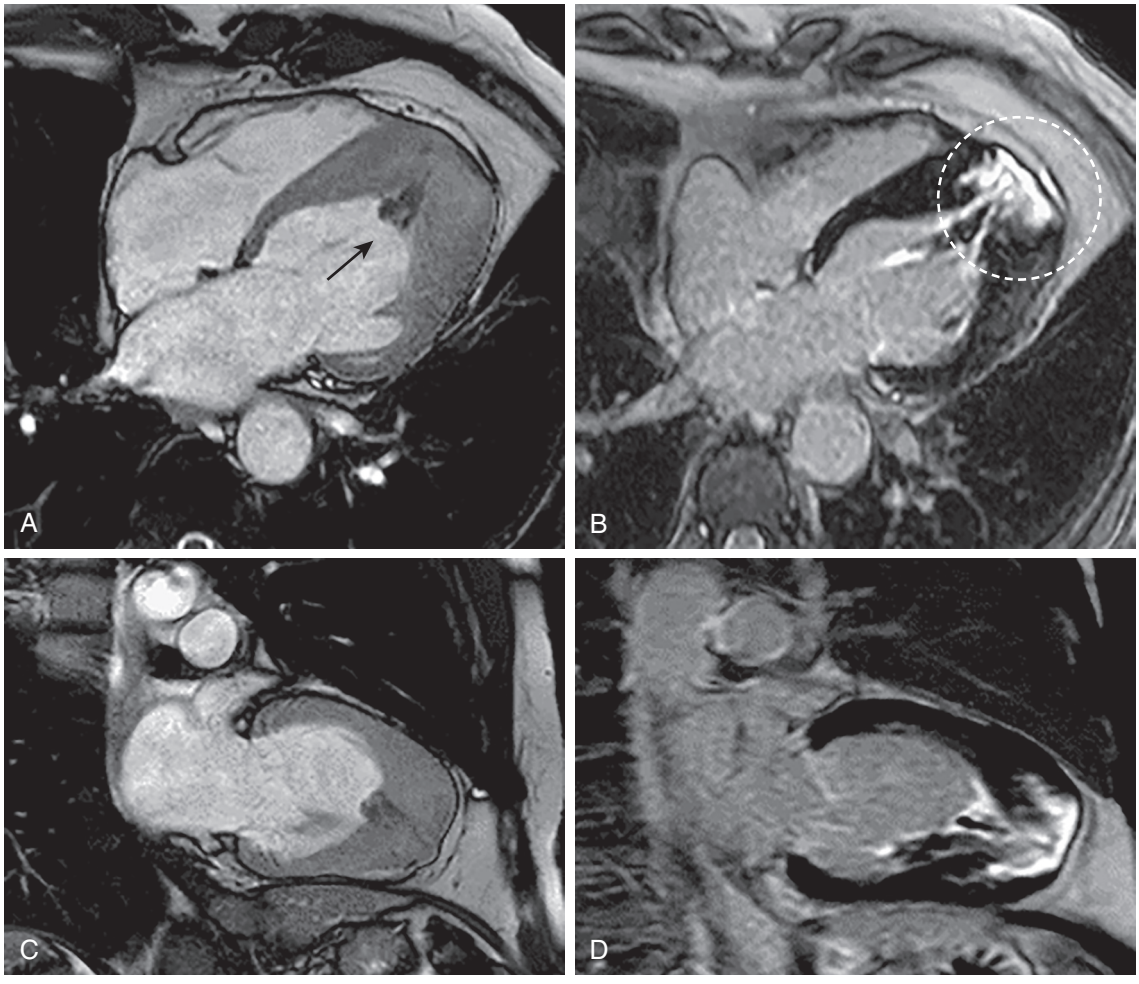

E-FIGURE 47-1. Apical hypertrophic cardiomyopathy. Magnetic resonance imaging shows apical hypertrophy with thrombosis *(small arrow)* and fibrosis *(dotted circle)*.

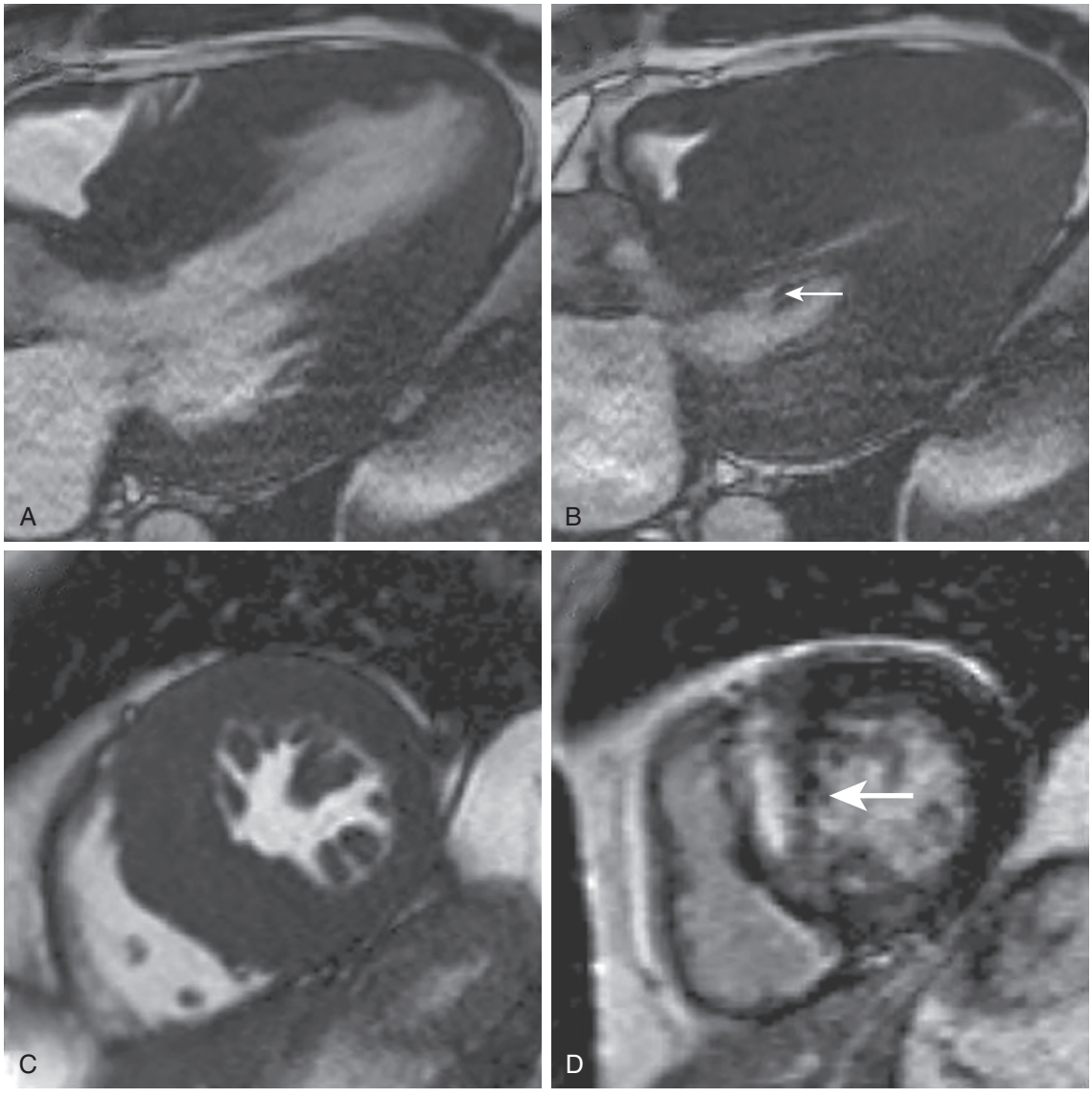

E-FIGURE 47-2. Cardiac magnetic resonance image in a 40-year-old man with hypertrophic cardiomyopathy. Three-chamber cine in diastole (**A**) and systole (**B**). There is mid-cavity obliteration and left ventricular outflow tract obstruction with complete systolic anterior motion of the mitral valve *(small arrow)*. The basal short axis cine (**C**) in diastole measures 30 mm, and there is mid-myocardial scar, visualized as late gadolinium enhancement *(large arrow)* (**D**).

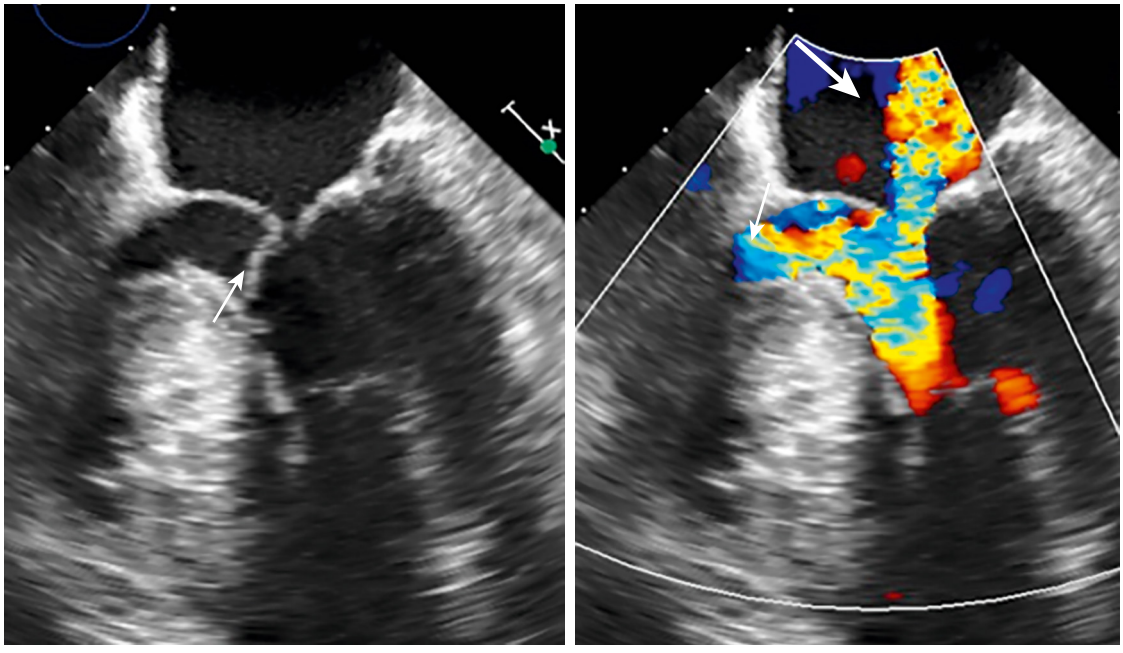

E-FIGURE 47-3. Transesophageal echocardiogram in a patient with hypertrophic cardiomyopathy. Systolic anterior motion of the mitral valve *(small arrow)* prevents normal coaptation and results in functional mitral regurgitation *(large arrow)*.

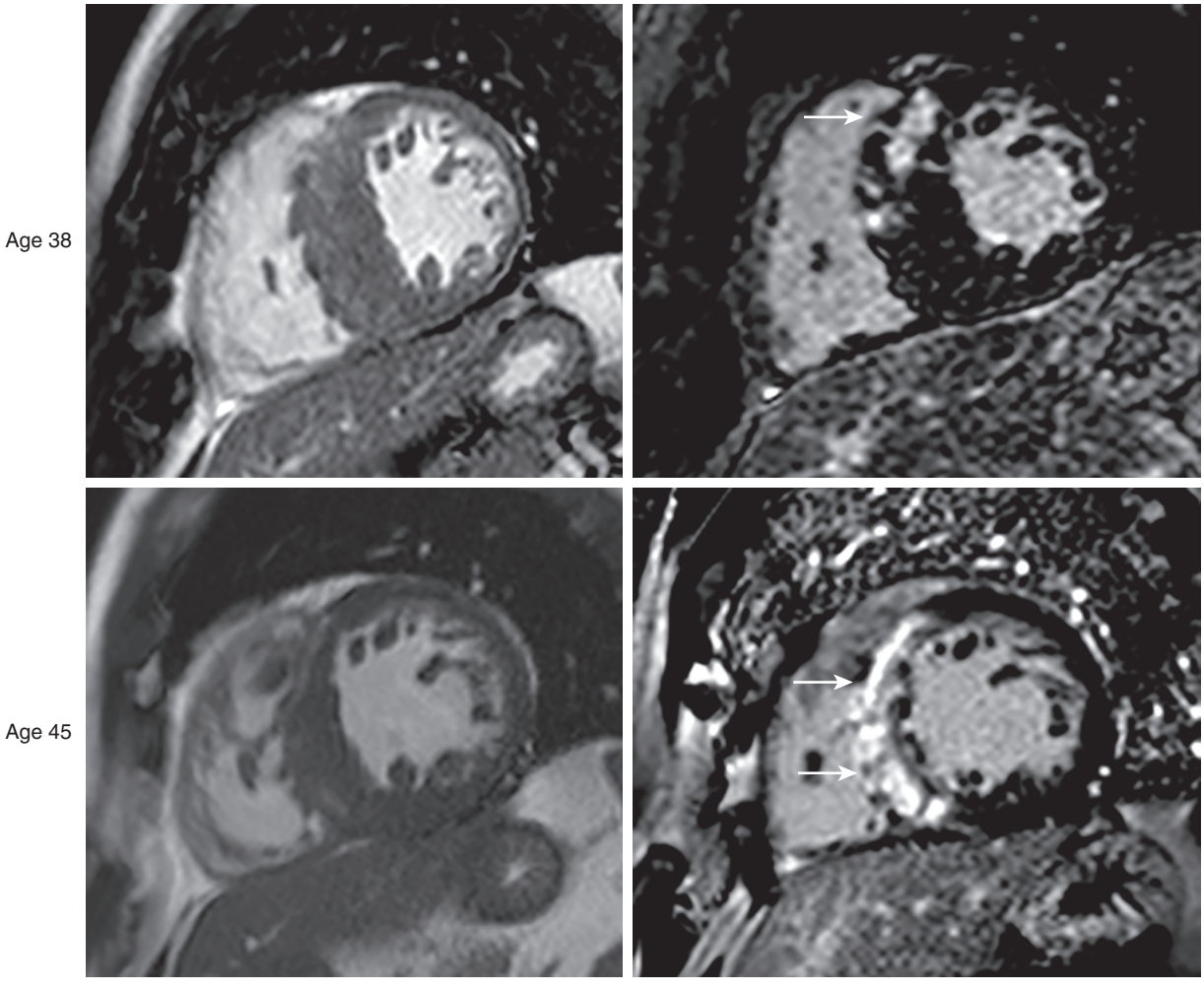

E-FIGURE 47-4. Progression of myocardial fibrosis from age 38 years to age 45 years. Diffuse septal fibrosis progressed in this patient as shown by late gadolinium enhancement on cardiac magnetic resonance imaging *(arrows)*.

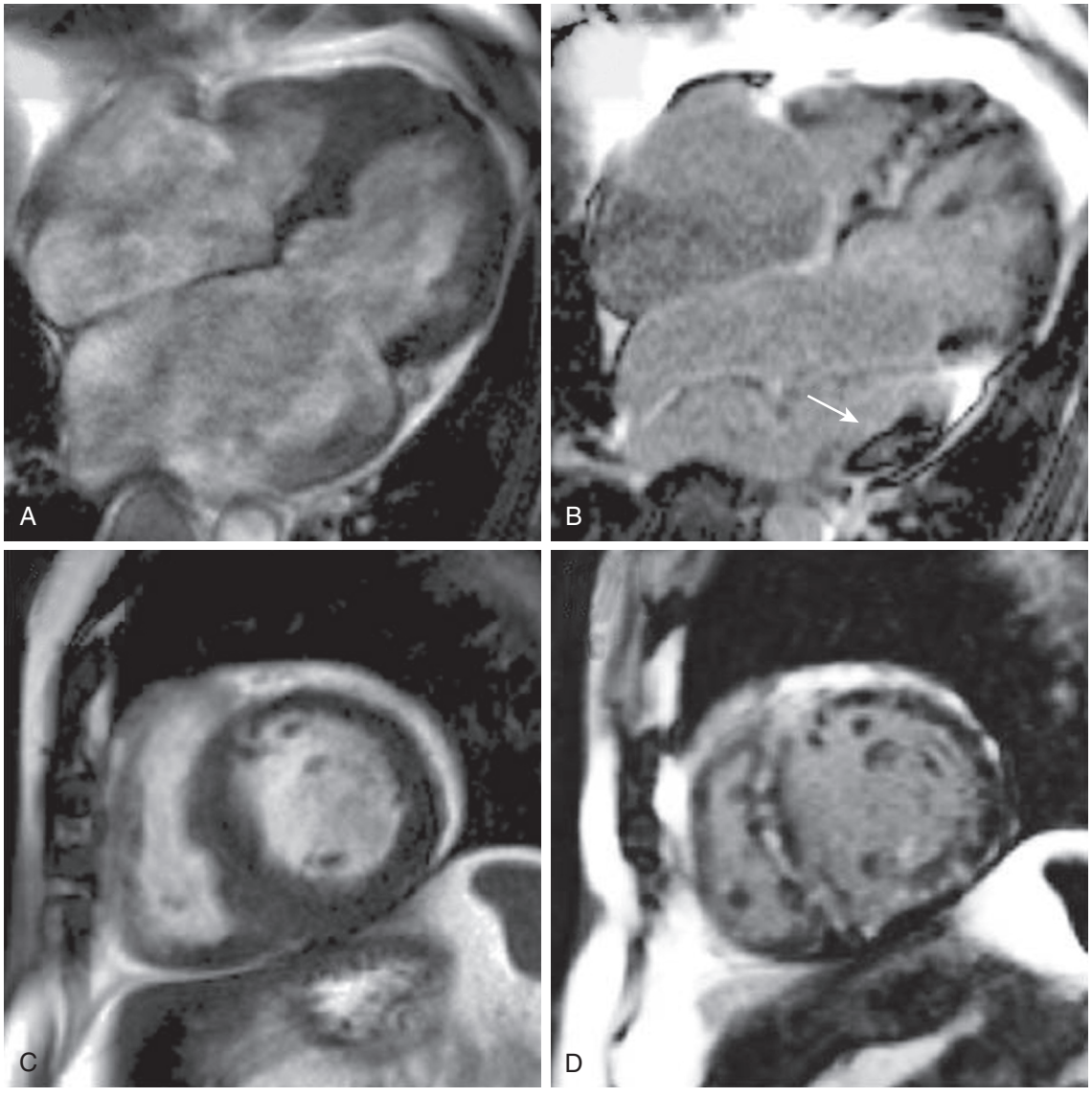

E-FIGURE 47-5. A 50-year-old man with hypertrophic cardiomyopathy in a progressive (dilated) disease phase. The left ventricular ejection fraction is 35%. There is left ventricular dilation, particularly for hypertrophic cardiomyopathy, and severe atrial dilation (**A**, diastolic frame). The maximal wall thickness is known to have reduced during recent follow-up (**C**, was 23 mm, now 18 mm). An extensive, nonischemic myocardial scar comprises an estimated 40% of the myocardium (**B, D**) and left atrial thrombus (*arrow*, **B**).

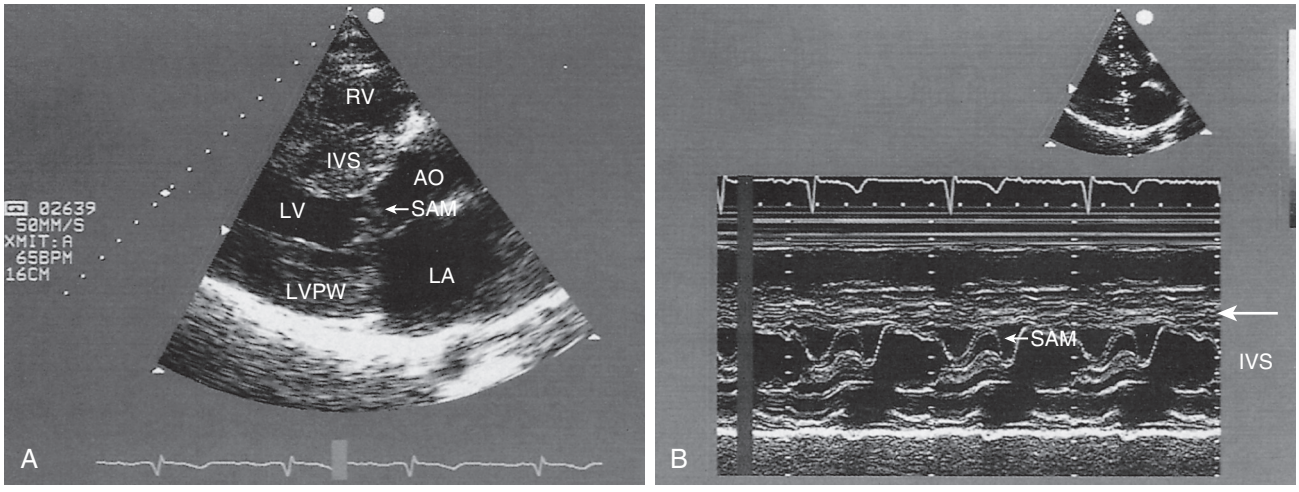

FIGURE 47-2. Hypertrophic obstructive cardiomyopathy. A, The two-dimensional long axis parasternal view shows the chambers of the heart. The left ventricle posterior wall (LVPW) is thickened, and the most striking abnormality is the hypertrophy of the interventricular septum (IVS). In 25% of patients, systolic anterior motion of the mitral valve (SAM) causes dynamic obstruction to left ventricular outflow. **B,** This phenomenon is more clearly shown in the parasternal long axis M-mode echocardiogram. The massive thickening of the septum is also obvious in the M-mode image (IVS). AO = aorta; LA = left atrium; LV = left ventricle; RV = right ventricle. (From Forbes CD, Jackson WF. *Color Atlas and Text of Clinical Medicine,* 3rd ed. London: Mosby; 2003.)

Diagnostic Criteria

Hypertrophic cardiomyopathy is defined by a maximal left ventricular wall thickness value of 15 mm or more. A value of 13 mm is considered diagnostic in relatives of probands with an unequivocal diagnosis, particularly if they have a defined genotype. In children, a wall thickness of more than 2 standard deviations above the mean, corrected for age and body size, is generally accepted as diagnostic. In the presence of other causes of left ventricular hypertrophy, such as long-standing systemic hypertension or aortic stenosis, the diagnosis of hypertrophic cardiomyopathy may be problematic. However, secondary hypertrophy rarely exceeds 15 mm, tends to be concentric, and usually lacks the typical valvular and subvalvular mitral abnormalities of hypertrophic cardiomyopathy. Hypertrophy in the highly trained athlete is mild, is rare in women, and typically occurs in association with increased left ventricular dimensions and stroke volume. An ECG tracing showing Q waves or inferolateral repolarization changes in an athlete favors the diagnosis of hypertrophic cardiomyopathy.

TREATMENT

No medical treatments have proven benefit to modify the underlying pathobiology of hypertrophic cardiomyopathy or to slow the long-term progression of the disease. As a result, medical therapy is directed at the control of symptoms, outflow obstruction, and arrhythmias (Fig. 47-3).[4,5] Exceptions include specific therapies for lysosomal storage diseases, such as Pompe disease (Chapter 191) and Fabry disease (E-Fig. 47-6; Chapter 192), and for Friedreich ataxia (Chapter 389). The treatment of the remaining patients with hypertrophic cardiomyopathy focuses on the counseling of family members, the management of symptoms, lifestyle advice related to exercise,[A1] and the prevention of disease-related complications.

Genetic Testing and Familial Screening

Genetic counseling should be offered to all newly diagnosed patients with hypertrophic cardiomyopathy. Genetic testing using next-generation sequencing panels or whole-exome sequencing can exclude rare genotypes and guide cascade screening in families in whom a pathogenic or likely pathogenic variant is identified. However, such variants are found in less than 50% of probands, and a negative test does not exclude the diagnosis of hypertrophic cardiomyopathy. When a pathogenic or likely pathogenic variant is identified, family members may be tested. However, genetic testing remains controversial in minors in the absence of clinical abnormalities, and the pros and cons of early genotyping (versus clinical follow-up) should be carefully considered on an individual basis. Individuals who test positive should be followed at regular intervals, even when the clinical evaluation is negative, because late onset of the disease has been described. Healthy family members in whom the genetic variant is excluded can be reassured and avoid such follow-up evaluations.

Screening with a 12-lead electrocardiogram and echocardiogram takes place at intervals of 12 to 18 months, usually starting at the age of 12 years (unless there is a family history of premature sudden death, the child is symptomatic or a competitive athlete, or there is a clinical suspicion of left ventricular hypertrophy), until full growth and maturation are achieved (usually by the age of 18 to 21 years). Thereafter, if there are no signs of disease expression, screening approximately every few years is advised because the onset of left ventricular hypertrophy may be delayed until well into adulthood in some families. Modified diagnostic criteria (see Table 47-2) consider the high probability that otherwise unexplained ECG and echocardiographic findings in first-degree relatives reflect incomplete disease expression.

Symptomatic Management

Medical Therapy

In patients who have nonobstructive cardiomyopathy, β-blockade may improve chest pain and dyspnea. The dose (starting at a dose equivalent to metoprolol 150 mg/day or propranolol 120 mg/day) should be titrated to achieve a target heart rate of 50 to 70 beats per minute at rest and 130 to 140 beats per minute at peak exercise. Non-dihydropyridine calcium antagonists such as verapamil (starting at a dose of 120 mg/day) and diltiazem (starting at a dose of 180 mg/day) are useful alternatives, particularly in patients with refractory chest pain, but high doses (e.g., verapamil >480 mg/day, diltiazem >360 mg/day) may be required.

In patients with symptoms caused by left ventricular outflow tract obstruction, the main aim of treatment is to reduce intraventricular gradients. Approximately 60 to 70% of patients improve with β-blockers,[A2] although high doses (equivalent to propranolol at 480 mg/day) are frequently required, and side effects are often limiting. When β-blockade alone is ineffective, disopyramide (a negative-inotropic antiarrhythmic agent), titrated to the maximal tolerated dose (usually between 400 and 600 mg/day), may be effective in up to two thirds of patients, but side effects related to the anticholinergic effects (e.g., dry eyes and mouth, urinary retention) limit its use. Disopyramide should be given concomitantly with a β-blocker (e.g., propranolol 120 to 240 mg/day), which will slow the heart rate and also blunt rapid atrioventricular nodal conduction should supraventricular arrhythmias develop. In patients who have left ventricular outflow tract obstruction and are taking a β-blocker and disopyramide, other QT-prolonging drugs (e.g., sotalol or amiodarone) must be avoided because of the potential proarrhythmic effect. In patients with outflow tract gradients, verapamil can be effective, but caution is required in patients with severe obstruction or elevated pulmonary pressures.

Allosteric inhibitors of cardiac myosin, such as mavacamten (at doses as low as 5 mg orally daily), can reduce obstruction and improve both exercise capacity and quality of life.[A3–A5] Data suggest a benefit in patients with nonobstructive hypertrophic cardiomyopathy as well.[6]

Diuretics (e.g., furosemide, 20 to 40 mg orally, followed by 20 mg/day) are seldom required; if needed in patients who have pulmonary congestion caused by elevated pulmonary pressures due to left ventricular dysfunction, the dose and duration of diuretic therapy should be minimized because injudicious use of these drugs can be dangerous, particularly in patients who have severe diastolic impairment or labile obstruction.

Losartan (100 mg/day) and valsartan (320 mg/day) are safe and may somewhat improve cardiac structure and function, but they have no benefit in terms of slowing the progression of disease.[A6,A7] Similarly, ranolazine (1000 mg twice daily) is safe for reducing ventricular ectopy, but it does not change exercise performance, plasma prohormone brain natriuretic peptide levels, diastolic function, or quality of life.[A8]

Interventional Therapy

Surgical myectomy or percutaneous alcohol septal ablation is indicated in patients who have refractory, symptomatic outflow obstruction (gradient

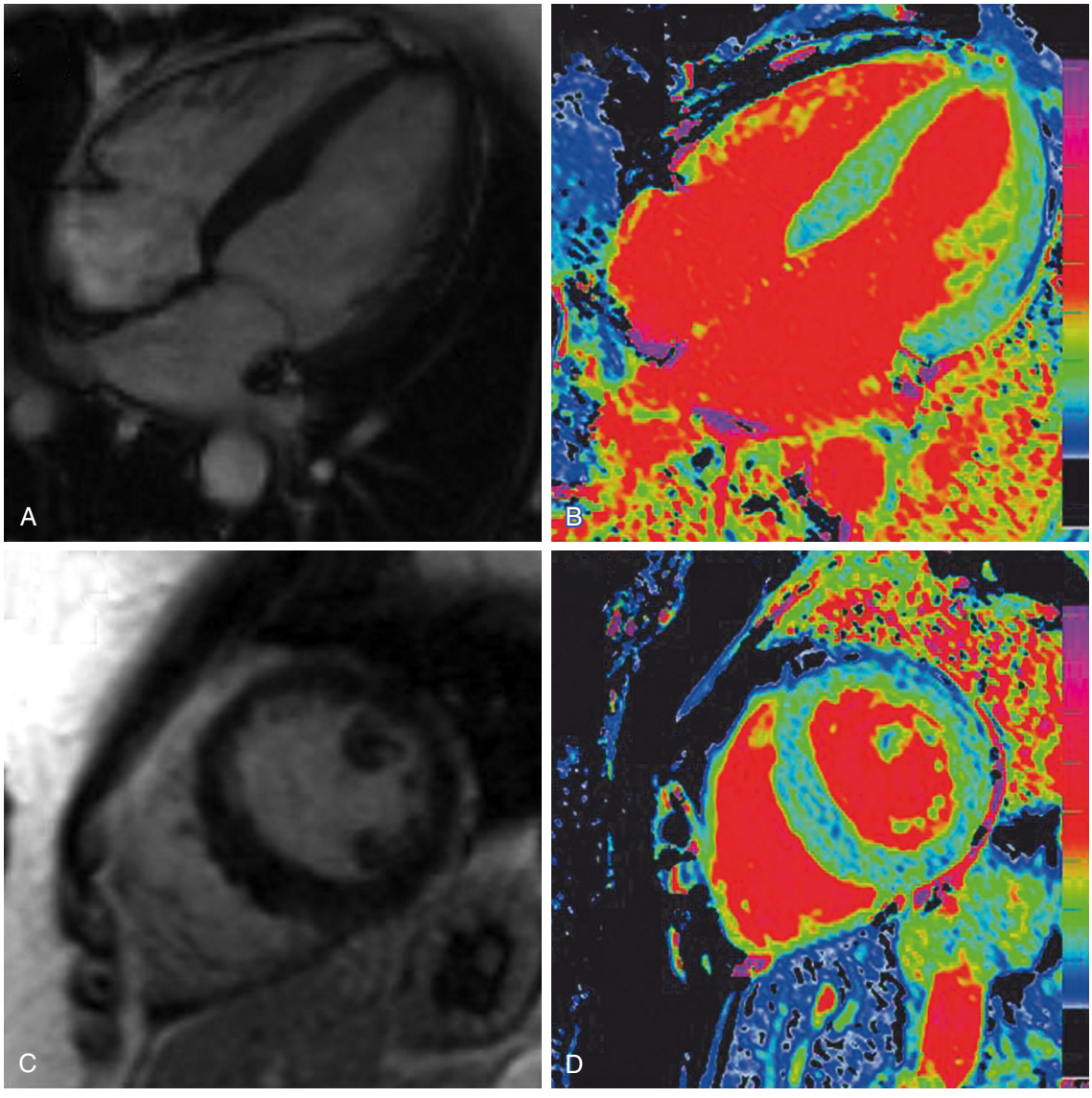

E-FIGURE 47-6. A 38-year-old man with Fabry disease and cardiac involvement. Cardiac magnetic resonance image shows a mild hypertrophy in the four-chamber (**A**) and short axis end-diastolic (**C**) views. The non–contrast-enhanced T1 map shows blue areas (T1 lowering) present circumferentially at the basal segments (**B, D**). This finding is in keeping with accumulation of glycosphingolipid in myocytes. This case does not have high T1 in the basal inferolateral wall (in many such patients, a red signal indicating fibrosis on this color scale is seen here in an area matched by scarring after contrast enhancement).

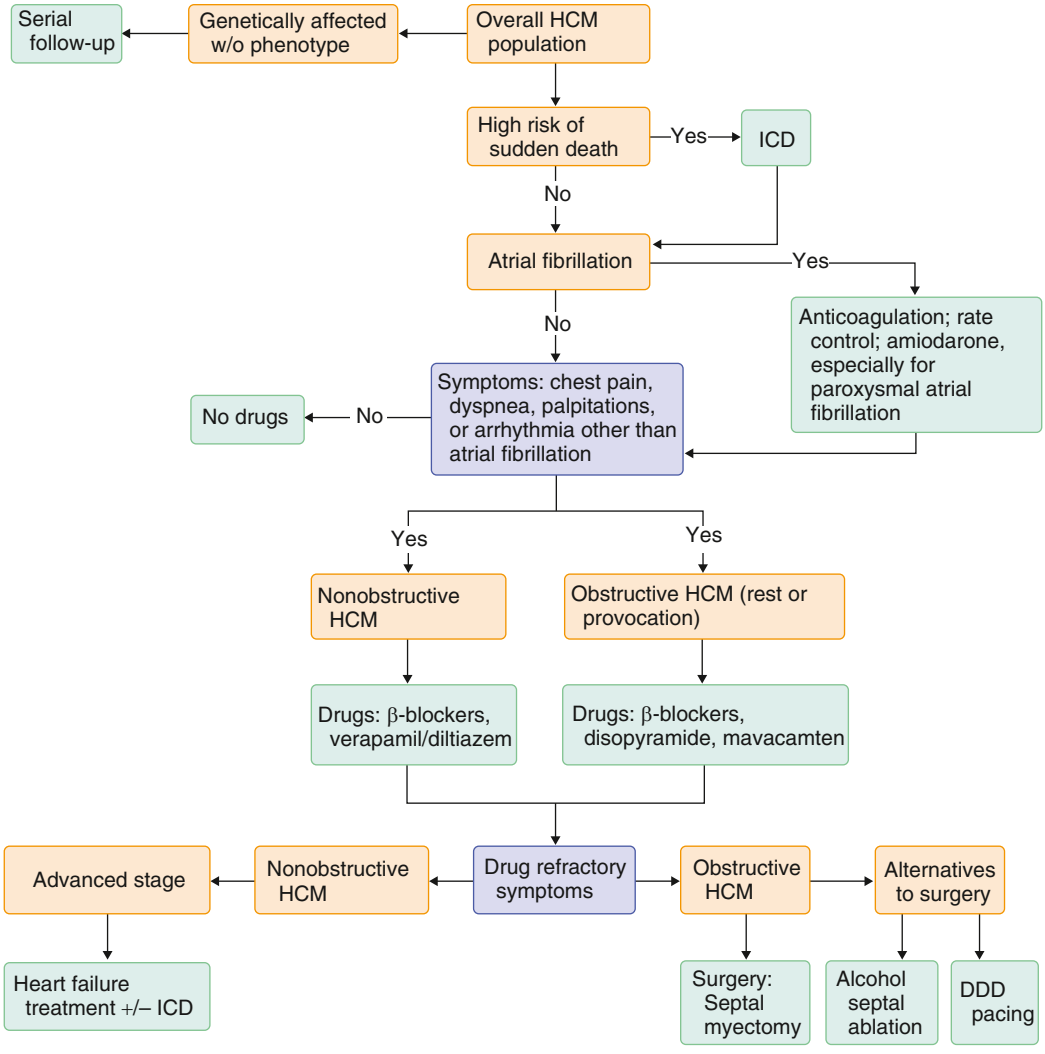

FIGURE 47-3. **Approach to the management of hypertrophic cardiomyopathy (HCM).** DDD = dual chamber; ICD = implantable cardioverter-defibrillator. **(Modified from Maron BJ, McKenna WJ, Danielson GK, et al. American College of Cardiology/European Society of Cardiology clinical expert consensus document on hypertrophic cardiomyopathy. *J Am Coll Cardiol*. 2003;42:1687-1713.)**

>50 mm Hg) despite optimized medical therapy or who are intolerant to it, with data suggesting that alcohol septal ablation may be preferred.[7] Both procedures are safe and effective in expert hands, although surgery is more effective for relieving gradients. Multidisciplinary evaluation by an expert team is advisable to determine the most appropriate therapeutic strategy for an individual patient.

The most commonly performed surgical procedure, which is extended ventricular septal myectomy, either abolishes or substantially reduces the gradient in 95% of cases, reduces mitral regurgitation, and improves exercise capacity and symptoms. Surgery should be performed in an experienced center, where mortality rates should be less than 1% for isolated myectomy. The main complications (atrioventricular block, ventricular septal defects) are uncommon (2 to 5%). When concomitant procedures (e.g., mitral valve repair or replacement, coronary artery bypass grafting) are required or when other significant comorbidities are present, perioperative mortality rates are higher (4 to 5%).

In experienced centers, the selective injection of alcohol into a septal perforator branch of the left anterior descending coronary artery to create a localized septal scar has benefits and risks that are comparable to surgery. The main nonfatal complication is atrioventricular block requiring a pacemaker in 5 to 20% of patients.

In the presence of end-stage disease with extensive myocardial fibrosis and refractory symptoms, heart transplantation is the only therapeutic option. Conversely, a left ventricular assist device is technically challenging to implant and is rarely used because of the small size of the left ventricle.

Atrial Fibrillation

Atrial fibrillation, which is one of the most common complications of hypertrophic cardiomyopathy, occurs in about 25% of patients. In general, the principles of managing atrial fibrillation in patients with hypertrophic cardiomyopathy are similar to those in other conditions (Chapter 52), including the use of anticoagulation because of the significant risk of systemic embolization. Treatment with low-dose amiodarone, 1000 to 1400 mg/week, is effective in maintaining sinus rhythm and in controlling the ventricular response during breakthrough episodes, but it is usually avoided in young patients because of its toxicity. Disopyramide, dofetilide, or sotalol (see Table 52-2) are safe but less effective. In patients who have permanent atrial fibrillation, a ß-blocker, verapamil, or diltiazem are usually required for rate control (see Chapter 52). Transcatheter ablation may be considered in selected patients, but its long-term efficacy is less than 50%, and repeated procedures are often necessary. Marked left atrial dilatation, older age, and worse symptomatic status predict failure to maintain sinus rhythm following ablation.

Prevention of Sudden Death

The overall risk for sudden death in children and adults with hypertrophic cardiomyopathy is approximately 0.5 to 1% per year, but a minority of individuals have a much greater risk for life-threatening ventricular arrhythmia. All patients with hypertrophic cardiomyopathy should be advised to avoid competitive sports and intense physical exertion, which are typical precipitants of sudden death.

The most powerful predictor of sudden cardiac death in hypertrophic cardiomyopathy is a history of previous cardiac arrest. Such patients should receive an implantable cardioverter-defibrillator (ICD; Chapter 54).

In patients without such a history, the identification of high-risk patients can be challenging. The most useful predictors of the risk for sudden death (https://doc2do.com/hcm/webHCM.html) are a family history of premature (<40 years of age) sudden cardiac death, unexplained syncope (unrelated to neurocardiogenic mechanisms), flat or hypotensive blood pressure response to upright exercise, nonsustained ventricular tachycardia on ambulatory ECG monitoring or during exercise, and severe left ventricular hypertrophy on echocardiography (defined as a maximal left ventricular wall thickness of 30 mm or more). Patients without any risk factors do not warrant an ICD. For patients with one risk factor, decisions about an ICD should be individualized on the basis of the patient's age and severity of disease and level of risk that is acceptable to the patient.

TABLE 47-2 DIAGNOSTIC CRITERIA FOR HYPERTROPHIC CARDIOMYOPATHY IN FIRST-DEGREE RELATIVES OF AFFECTED PATIENTS*

MAJOR CRITERIA	MINOR CRITERIA
ECHOCARDIOGRAPHY	
Left ventricular wall thickness ≥13 mm in the anterior septum or posterior wall or ≥15 mm in the posterior septum or free wall	Left ventricular wall thickness of 12 mm in the anterior septum or posterior wall or of 14 mm in the posterior septum or free wall
Severe SAM of the mitral valve (septal-leaflet contact)	Moderate SAM of the mitral valve (no mitral leaflet–septal contact) Redundant mitral valve leaflets
ELECTROCARDIOGRAPHY	
Left ventricular hypertrophy with repolarization changes (Romhilt and Estes)	Complete bundle branch block or (minor) interventricular conduction defects (in left ventricular leads)
T wave inversion in leads I and aVL (≥3 mm with QRS-T wave axis difference ≥30 degrees), V_3-V_6 (≥3 mm), or II and III and aVF (≥5 mm)	Minor repolarization changes in left ventricular leads Deep S wave in lead V_2 (>25 mm)
Abnormal Q waves (>40 msec or >25% R wave) in at least two leads from II, III, aVF (in absence of left anterior hemiblock), and V_1-V_4; or I, aVL, V_5-V_6	Unexplained chest pain, dyspnea, or syncope

*The diagnosis of hypertrophic cardiomyopathy in first-degree relatives of patients with the disease is based on the presence of one major criterion, two minor echocardiographic criteria, or one minor echocardiographic criterion and two minor electrocardiographic criteria.

aVF = augmented voltage unipolar left foot lead; aVL = augmented voltage unipolar left arm lead; SAM = systolic anterior motion.

Modified from McKenna WJ, Spirito P, Desnos M, et al. Experience in clinical genetics in hypertrophic cardiomyopathy. *Heart*. 1997;77:130-132.

PROGNOSIS

Most patients with hypertrophic cardiomyopathy follow a stable and benign course with a low risk for adverse events and a survival similar to that of age- and gender-matched normal populations, but many experience progressive symptoms caused by atrial arrhythmia and gradual deterioration in left ventricular systolic and diastolic function (E-Fig. 47-7). With modern therapy, heart failure–related deaths have become more common than sudden deaths. The mortality rate related specifically to hypertrophic cardiomyopathy is 0.53% per year, with 5- and 10-year cardiomyopathy-related survival rates of 98% and 94%, respectively. The annual incidence of stroke varies from 0.56 to 0.8% per year, rising to 1.9% in patients older than 60 years, and 23% of strokes are fatal. The development of severe systolic heart failure is associated with a poor prognosis, with an overall mortality rate of up to 11% per year. The incidence of infective endocarditis is 1.4 per 1000 person-years overall but 3.8 per 1000 person-years in patients with obstruction.

MYOCARDITIS

DEFINITION AND EPIDEMIOLOGY

Myocarditis, which is an inflammatory process involving the myocardium, can be caused by infections, immune-mediated damage, or toxins (Table 47-3).[8] The incidence and prevalence of myocarditis are difficult to estimate because the clinical presentation varies from asymptomatic ECG abnormalities to hemodynamic collapse and sudden death. Population estimates of the prevalence of myocarditis range from 1 in 100,000 to 1 in 10,000, whereas postmortem studies report myocarditis in up to 12% of young victims of sudden cardiac death. Myocarditis may also be the clinical presentation of the inflammatory phase of an arrhythmogenic cardiomyopathy.

Worldwide, the most common infective myocarditis is Chagas disease, caused by *Trypanosoma cruzi*, a protozoan organism endemic in rural areas of South and Central America (Chapter 318).[9] In the Western world, viral myocarditis is the most common cause of inflammatory heart disease. Human immunodeficiency virus (HIV) infection (Chapter 353) is associated with lymphocytic myocarditis and is a strong predictor of poor prognosis. Smallpox vaccination (Chapter 15) causes myopericarditis with a reported incidence of 7.8 cases per 100,000 vaccine administrations. Other rare myocarditides include giant cell myocarditis, myocarditis complicating autoimmune disorders such as systemic lupus erythematosus (Chapter 245), cocaine abuse (Chapter 365), and as a complication of combination immune checkpoint inhibitor therapy (Chapter 164).

TABLE 47-3 CAUSES OF MYOCARDITIS

INFECTION
Viral
Coxsackievirus, human immunodeficiency virus, echovirus, severe acute respiratory syndrome coronavirus-2, adenovirus, influenza, measles, mumps, parvovirus, poliovirus, rubella, varicella-zoster virus, herpes simplex virus, cytomegalovirus, hepatitis C virus, rabies virus, respiratory syncytial virus, vaccine virus, dengue virus, yellow fever virus
Protozoal
Trypanosoma cruzi, Toxoplasma gondii
Bacterial
Brucella, Corynebacterium diphtheriae, Salmonella, Haemophilus influenzae, Mycoplasma pneumoniae, Neisseria meningitidis (meningococcus), *Streptococcus pneumoniae, Staphylococcus, Mycobacterium, Neisseria gonorrhoeae* (gonococcus), *Vibrio cholerae*
Spirochetal
Treponema pallidum, Borrelia, Leptospira
Fungal
Aspergillus, Candida, Cryptococcus, Actinomyces, Blastomyces, Histoplasma, Coccidioides
Rickettsial
Coxiella burnetii, Rickettsia rickettsii, Rickettsia tsutsugamushi
Parasitic
Trichinella spiralis, Echinococcus granulosus, Taenia solium
IMMUNE-MEDIATED DISORDERS
Alloantigens
Heart transplant rejection
Autoantigens
Eosinophilic granulomatosis with polyangiitis (formerly Churg-Strauss syndrome), celiac disease, Whipple disease, giant cell myocarditis, Kawasaki disease, systemic lupus erythematosus, systemic sclerosis, sarcoidosis, scleroderma, polymyositis, thrombocytopenic purpura
Allergens (Drugs)
Penicillin, sulfonamides, tetracycline, methyldopa, streptomycin, tricyclic antidepressants, thiazide diuretics, dobutamine, indomethacin
TOXIC CAUSES
Drugs
Anthracyclines, catecholamines, amphetamines, cocaine, cyclophosphamide, 5-fluorouracil, trastuzumab, interferon, interleukin-2, checkpoint inhibitors, clozapine
Physical Agents
Electric shock, radiation, hyperpyrexia
Heavy Metals
Copper, iron, lead
Others
Arsenic, snake bite, scorpion bite, wasp and spider stings, phosphorus, carbon monoxide
GENETIC DISORDERS
Inherited cardiomyopathies with immune-mediated pathogenesis (dilated and right ventricular cardiomyopathy)

PATHOBIOLOGY

Myocarditis is defined histologically by the presence of myocyte injury, with degeneration or necrosis, and an inflammatory infiltrate not due to ischemia. Four patterns are recognized: *active myocarditis*, with myocyte degeneration or necrosis and definite cellular infiltrate with or without fibrosis; *borderline myocarditis*, with a definite cellular infiltrate without evidence of myocardial cellular injury; *persistent myocarditis*, with continued

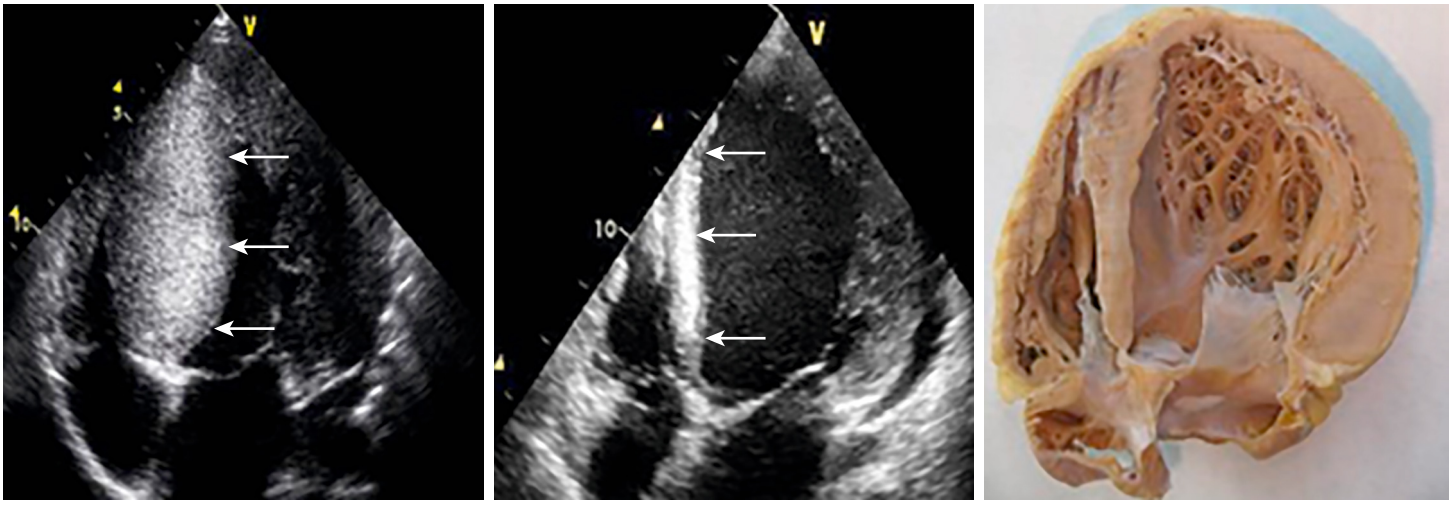

E-FIGURE 47-7. Progression to end-stage hypertrophic cardiomyopathy. LV = left ventricle; LVEF = left ventricular ejection fraction. (From Pasqualucci D, Fornaro A, Castelli G, et al. Clinical spectrum, therapeutic options, and outcome of advanced heart failure in hypertrophic cardiomyopathy. *Circ Heart Fail*. 2015;8:1014-1021; Olivotto I, Cecchi F, Poggesi C, et al. Patterns of disease progression in hypertrophic cardiomyopathy. *Circ Heart Fail*. 2012;5:535-546; Galati G, Leone O, Pasquale F, et al. Histological and histometric characterization of myocardial fibrosis in end-stage hypertrophic cardiomyopathy: a clinical-pathological study of 30 explanted hearts. *Circ Heart Fail*. 2016;9:e003090.)

active myocarditis on repeated biopsy; and *resolving or resolved myocarditis*, characterized by a diminished or absent infiltrate with evidence of connective tissue healing on repeated biopsy. Despite their widespread use, the so-called Dallas criteria have low specificity and sensitivity, with a diagnostic yield as low as 10 to 20% in some series. Therefore, newer virology techniques used in conjunction with conventional light microscopy include nested polymerase chain reaction or reverse transcription polymerase chain reaction on RNA and DNA extracted from endomyocardial biopsy specimens and immunohistochemical staining for subtypes of infiltrating lymphocytes and abnormal expression of cellular adhesion molecules on interstitial or endothelial cells.

VIRAL MYOCARDITIS

Most data on the pathology of viral myocarditis come from murine models. Initially, there is direct invasion of the myocardium by cardiotropic viruses, which enter the cardiomyocyte through receptor-mediated endocytosis. The viral genome, which is translated intracellularly to produce viral protein or is incorporated into the host cell genome, may contribute to myocyte dysfunction by cleaving dystrophin. In the second phase, activation of the host immune system, including recruitment of natural killer cells and macrophages, increases the expression of proinflammatory cytokines such as interleukin-1 and tumor necrosis factor. Activation of $CD4^+$ T lymphocytes promotes clonal expansion of B lymphocytes, thereby resulting in further myocardial cell damage, inflammation, and the production of circulating antiheart antibodies directed against contractile, structural, and mitochondrial proteins. This autoimmune response may result in long-term ventricular remodeling by direct effects on myocardial structural components or alterations in the extracellular matrix.

CLINICAL MANIFESTATIONS

Some patients report prodromal symptoms of viremia, including fever, myalgia, coryzal symptoms, and gastroenteritis, but many individuals with myocarditis are asymptomatic and manifest only transient ECG abnormalities, such as nonspecific ST segment and T wave abnormalities, pathologic Q waves, and low QRS voltages. Less common presentations include acute myocardial infarction with angiographically normal coronary arteries (Chapter 58), atrioventricular block (Chapter 52), and ventricular arrhythmias (Chapter 53). Patients with impairment of left ventricular function may present with symptoms and signs of fulminant cardiogenic shock (Chapter 93) with acute cardiovascular collapse. In some cases, sudden cardiac death is the first presentation.

DIAGNOSIS

The diagnosis of myocarditis requires a high index of suspicion because it may mimic other common conditions.[10] There are no typical features on echocardiography, but impaired left or right ventricular systolic performance (with or without ventricular dilation), regional wall motion abnormalities, left (or right) ventricular thrombus, diastolic impairment, and pericardial effusions may be present. Cardiac magnetic resonance imaging can detect myocardial inflammation and myocyte injury, with pericellular and cellular edema.

Routine blood tests, such as full blood count and erythrocyte sedimentation rate, are usually unhelpful. Serum markers of myocardial injury, such as troponins T and I, may be elevated, but myocarditis may be proven by biopsy even in the absence of elevated serum troponin levels. Increased levels of autoantibodies against myocardial proteins (such as myosin and the adenine nucleotide translocator protein) are biomarkers of autoimmune myocarditis and correlate with progressive worsening of ventricular function. A microRNA designated as has-miR-Chr8:96 is seen in myocarditis but rarely in myocardial infarction.[11]

Cardiac magnetic resonance imaging with gadolinium enhancement can show evidence of myocarditis (Fig. 47-4), but cardiac catheterization with right ventricular endomyocardial biopsy remains the "gold standard" diagnostic test. In the United States, biopsy has generally been reserved for patients with heart failure refractory to standard management, features suggestive of systemic disease (e.g., connective tissue disease [Chapter 239], amyloidosis [Chapter 174], hemochromatosis [Chapter 196], sarcoidosis [Chapter 83]), or suspicion of giant cell myocarditis because of new-onset heart failure associated with tachyarrhythmias or conduction disease. By comparison, a European consensus statement recommends endomyocardial biopsy to achieve an etiologic diagnosis and to guide potential novel treatment options in patients with "clinically suspected myocarditis."

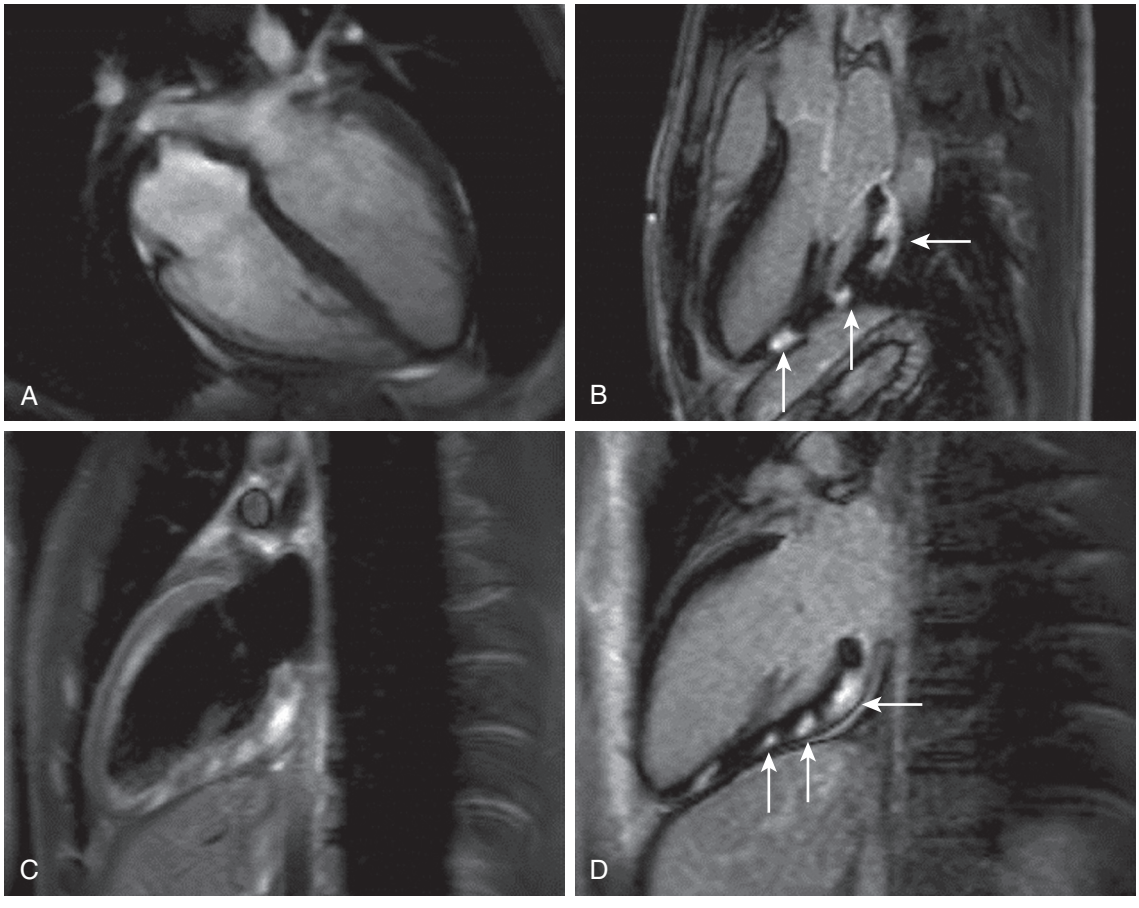

FIGURE 47-4. A 17-year-old man presenting with apparent acute myopericarditis. The four-chamber end-diastolic view (**A**) presents a mildly dilated left ventricle. There is patchy late gadolinium enhancement involving the inferior and lateral walls (**B, D**, *arrows*). Edema is seen on T1 imaging (**C**), and there is extensive late enhancement. The differential diagnosis of this appearance also includes sarcoid and giant cell myocarditis.

Specific Causes

Viral myocarditis may be suspected from the clinical picture of recent febrile illness, often with prominent myalgias, followed by angina-like chest pain, dyspnea, or arrhythmias. Elevated troponin levels support the diagnosis, and increasing viral titers (to coxsackievirus, echovirus, adenovirus, or influenza virus) are consistent with recent infection. The correlation with biopsy-proven myocarditis is strongest with HIV and Lyme disease. Clinical cardiomyopathy occurs in 10 to 40% of patients infected with HIV due to the HIV infection itself or to coinfection with cytomegalovirus.

Giant Cell Myocarditis

Giant cell myocarditis, which accounts for 10 to 20% of biopsy-positive cases of myocarditis, is manifested with the rapid onset of chest pain, fever, and hemodynamic compromise, often with ventricular tachycardia or atrioventricular block. When ventricular tachyarrhythmias or progressive heart failure are major features of clinically suspected myocarditis, particularly in a young person, endomyocardial biopsy is recommended to determine whether giant cell myocarditis is present.

Lyme Disease and Toxoplasmosis

Lyme carditis (Chapter 296)[12] is classically manifested with conduction system abnormalities resulting from infection with *Borrelia burgdorferi*, which is diagnosed serologically. Toxoplasmosis (Chapter 320) myocarditis, due to intermittent rupture of cysts in the myocardium, can cause atypical chest pain, arrhythmias, pericarditis, and symptomatic heart failure. Diagnosis is made from antibody titers.

Severe Acute Respiratory Syndrome Coronavirus-2

Myocarditis is a rare complication of SARS-CoV-2 infection (Chapter 336), with an apparent excess incidence rate of 40 extra events per million persons.[13] The risk of myocarditis also appears to be increased (1 to 10 per million persons) within a week of receiving the first dose of both adenovirus and mRNA vaccines, with a higher increased risk after the second dose of mRNA vaccines (Chapter 337). The risk of vaccine-associated myocarditis after vaccination seems to be higher in people under age 40 years.

Immune-Mediated Myocarditis

Many systemic immune-mediated diseases may present as myocarditis with lymphocytic, eosinophilic, and granulomatous myocardial infiltrates.[14] Specific disorders include sarcoidosis (Chapter 83), systemic lupus erythematosus (Chapter 245), systemic sclerosis (Chapter 246), the antiphospholipid syndrome (Chapter 160), dermato-polymyositis (Chapter 248), eosinophilic granulomatosis with polyangiitis, and other vasculitis syndromes (Chapter 249). Myocarditis can also occur in some organ-specific immune-mediated diseases such as chronic inflammatory bowel diseases (Chapter 127). Hypersensitivity reactions, especially to drugs (Chapter 234), can cause myocarditis that is often associated with peripheral eosinophilia and can be confirmed by endomyocardial biopsy.

TREATMENT

The first-line treatment of myocarditis is supportive with afterload reduction and diuresis (Chapter 46). Patients with fulminant acute myocarditis may require inotropic support, mechanical assist devices, or extracorporeal membrane oxygenation (Chapter 93). After initial stabilization, patients with symptoms and signs of heart failure should receive angiotensin-converting enzyme inhibitors, diuretics, β-blockers, and anticoagulants in accordance with standard guidelines (Chapter 46). Patients with intractable and deteriorating heart failure may require cardiac transplantation (Chapter 46).

The role of immunosuppression is uncertain. In one randomized, placebo-controlled trial of 111 adults with biopsy-proven myocarditis, there was no difference in mortality or improvement in left ventricular function in patients treated with prednisolone plus either cyclosporine or azathioprine. Conversely, in a randomized trial of patients who had major histocompatibility complex expression on endomyocardial biopsy samples and who were randomized to prednisolone (1 mg/kg/day tapering to a maintenance dose of 0.2 mg/kg/day for a total of 90 days) and azathioprine (1 mg/kg/day for a total of 100 days) versus placebo, left ventricular ejection fraction improved in the immunosuppressed group, but no difference was observed in mortality or rates of transplantation or rehospitalization during a 2-year follow-up period. Immunosuppression appears to be beneficial for patients with giant cell myocarditis, and current recommendations extend immunosuppression to other biopsy-proven, infection-negative immune-mediated forms of myocarditis including eosinophilic myocarditis, cardiac sarcoidosis, and lymphocytic myocarditis that is refractory to conventional heart failure therapy.[A9] The optimal regimens remain to be determined, and intravenous immune globulin therapy is not helpful.

PROGNOSIS

Patients with acute myocarditis with mild heart failure or symptoms suggestive of myocardial ischemia or infarction typically improve within weeks without sequelae. An acute presentation of myocarditis with advanced heart failure (ejection fraction <35%) may resolve but can lead to chronic left ventricular dysfunction (dilated cardiomyopathy) or progress to death or cardiac transplantation. Patients who present with acute fulminant myocarditis, however, may have an excellent prognosis, with survival rates of more than 90%. Overall, however, biopsy-proven viral myocarditis is associated with a long-term mortality of almost 20% at 4.7 years, and the presence of biventricular dysfunction at presentation is the best predictor of all-cause mortality. Giant cell myocarditis is usually fatal without heart transplantation, but it can be stabilized by early diagnosis and prompt introduction of immunosuppression.[15]

DILATED CARDIOMYOPATHY

DEFINITION AND EPIDEMIOLOGY

Dilated cardiomyopathy is a heart muscle disorder defined by dilation and impaired systolic function of the left ventricle or both ventricles, in the absence of coronary artery disease, valvular abnormalities, or pericardial disease. In adults, the estimated prevalence is 1 in 250.[16] In children, dilated cardiomyopathy is the most common cardiomyopathy, accounting for up to 58% of cases. Overall, males and females are approximately equally affected, except for dilated cardiomyopathy associated with neuromuscular disorders or inborn errors of metabolism, for which there is male predominance because some of these conditions have an X-linked inheritance.

PATHOBIOLOGY

A number of conditions are associated with dilated cardiomyopathy, including neuromuscular disorders, inborn errors of metabolism, and malformation syndromes. When no identifiable cause is found, the disease is termed idiopathic dilated cardiomyopathy.

Genetic Dilated Cardiomyopathy

Between 20 and 50% of individuals with dilated cardiomyopathy have evidence of familial disease (see E-Table 47-1).[17] Autosomal dominant inheritance, which accounts for the majority of familial cases, has two major forms: isolated dilated cardiomyopathy, which is manifested with a clinical picture of heart failure, and dilated cardiomyopathy, in which an associated arrhythmia (i.e., atrial fibrillation, conduction system disease, ventricular tachycardia, or fibrillation) is usually the initial manifestation. The latter cardiomyopathy may also result in heart failure or be associated with a skeletal myopathy. Genes implicated in nonsyndromic dilated cardiomyopathy include cytoskeletal and sarcomeric protein genes. Truncating mutations in *TTN*, the gene encoding the sarcomere protein titin, occur in approximately 25% of familial cases of dilated cardiomyopathy and in 18% of sporadic cases. Genes implicated in arrhythmogenic forms of dilated cardiomyopathy include desmosomal, intermediate filament, nuclear envelope, and ion channel genes. Mutations in the lamin A/C gene, which encodes a nuclear envelope protein, cause atrial and ventricular arrhythmia and progressive atrioventricular conduction disease, which may precede the development of dilated cardiomyopathy. Truncating in the filamin C gene, which encodes an important intermediate filament protein, causes a mixed arrhythmogenic and dilated cardiomyopathy phenotype, typically with lethal ventricular arrhythmias in adolescents and young adults and with subsequent heart failure in survivors.

X-linked inheritance accounts for between 2 and 5% of familial cases of dilated cardiomyopathy. Neuromuscular disorders account for 26% of cases, 90% of which are Duchenne, Becker, and Emery-Dreifuss muscular dystrophies (Chapter 389). Isolated X-linked dilated cardiomyopathy, also caused by mutations in the dystrophin gene, is characterized by raised serum creatine kinase muscle isoforms but does not result in clinical signs or symptoms of skeletal muscular dystrophy.

Acquired Dilated Cardiomyopathy

Common acquired causes of dilated cardiomyopathy include infectious myocarditis, chemotherapy (Chapter 164), radiation therapy (Chapter 18), alcohol (Chapter 364), cocaine (Chapter 365), nutritional deficiencies (Chapter 197), iron overload (Chapter 196), inflammatory and autoimmune disorders (Chapters 245 and 249), endocrinopathies (Chapter 207), and pregnancy (Chapter 221). Tachycardia-mediated cardiomyopathy (tachycardiomyopathy) is rare and usually reverses once the tachycardia is controlled.

CLINICAL MANIFESTATIONS

The symptoms and signs associated with dilated cardiomyopathy depend on the age of the patient and the degree of left ventricular dysfunction. Although the first presentation may be with sudden death or a thromboembolic event, most patients present with symptoms of high pulmonary venous pressure or low cardiac output (Chapter 45), which can be acute, sometimes precipitated by intercurrent illness or arrhythmia, or chronic. Increasingly, dilated cardiomyopathy is diagnosed incidentally in asymptomatic individuals during family screening.

Adults initially present with reduced exercise tolerance and dyspnea on exertion. With worsening left ventricular function, patients may develop dyspnea at rest, orthopnea, paroxysmal nocturnal dyspnea, peripheral edema, and ascites. Symptoms related to mesenteric ischemia, such as abdominal pain after meals, nausea, vomiting, and anorexia, may dominate, especially in children. Arrhythmia symptoms, such as palpitations, presyncope, and syncope, can occur at any age.

In advanced disease, features of low cardiac output include sinus tachycardia, weak peripheral pulses, and hypotension. The jugular venous pressure may be elevated, and the apical impulse is displaced. Peripheral edema, hepatomegaly, and ascites are common in patients with heart failure. Auscultation of the chest typically reveals basal crackles. Auscultation of the heart may reveal the presence of a third (and sometimes also a fourth) heart sound. In patients with functional mitral regurgitation, a pansystolic murmur may be heard at the apex and radiate to the axilla, but frequently no murmurs are heard, even in the presence of mitral incompetence, especially if cardiac output is very low.

DIAGNOSIS

The electrocardiogram may be normal but more typically shows sinus tachycardia, nonspecific ST segment and T wave changes (most commonly in the inferior and lateral leads), atrial enlargement, and voltage criteria for ventricular hypertrophy. Atrioventricular block raises the possibility of mutations in the lamin A/C or desmin gene. Supraventricular and ventricular arrhythmias are common, particularly in patients who have pathogenic variants in *TTN*, *DSP*, *RBM20*, *LMNA*, and *FLNC*. The chest radiograph is usually abnormal, with an increased cardiothoracic ratio (>0.5) reflecting left ventricular and left atrial dilation. Patients with pulmonary edema have increased pulmonary vascular markings and pleural effusion.

On echocardiography, the presence of ventricular end-diastolic dimensions greater than 2 standard deviations above body surface area–corrected means (or greater than 112% of predicted dimension) and fractional shortening less than 25% are sufficient to make the diagnosis. Other common features include functional mitral and tricuspid regurgitation and abnormalities of diastolic left ventricular function. Cardiac magnetic resonance imaging may show areas of myocardial fibrosis (E-Fig. 47-8).

Other recommended tests (Table 47-4) include a complete blood count and tests of renal, thyroid, and hepatic function. Levels of serum creatine kinase should be measured in all patients with dilated cardiomyopathy because this may provide important clues to the etiology. For example, dystrophin-linked dilated cardiomyopathy has been diagnosed in up to 8% of men with dilated cardiomyopathy and should be considered in men with increased serum creatine kinase levels and an X-linked family history. Other cardiac biomarkers, such as troponin I and troponin T, can be elevated. Plasma B-type natriuretic peptide levels predict survival, hospitalization rates, and listing for cardiac transplantation. Symptom-limited exercise testing, combined with respiratory gas analysis, is a useful technique to assess functional limitation and disease progression in patients with stable dilated cardiomyopathy.

Cardiac catheterization is rarely needed except perhaps to exclude severe coronary artery disease or to provide more precise information about possible valvular heart disease. Endomyocardial biopsy may be diagnostic for myocarditis and for some metabolic or mitochondrial disorders but is rarely advised. Hemodynamic assessment of left ventricular end-diastolic and pulmonary artery pressures may be necessary before transplantation.

TABLE 47-4 LABORATORY EVALUATION OF CARDIOMYOPATHY

CLINICAL EVALUATION
History and physical examination to identify cardiac and noncardiac disorders*
Assessment of ability to perform routine and desired activities*
Assessment of volume status*
LABORATORY EVALUATION
Electrocardiogram*
Chest radiograph*
Ambulatory electrocardiographic monitoring
Two-dimensional and Doppler echocardiogram*
Chemistry
Serum sodium,* potassium,* glucose, creatinine,* blood urea nitrogen,* calcium,* magnesium*
Albumin,* total protein,* liver function tests,* serum iron, ferritin, creatine kinase, thyroid-stimulating hormone,* brain natriuretic peptide, troponin level
Urinalysis
Hematology
Hemoglobin/hematocrit*
White blood cell count with differential,* including eosinophils
Erythrocyte sedimentation rate
INITIAL EVALUATION IN SELECTED PATIENTS ONLY
Titers for suspected infection
Acute viral titers
Human immunodeficiency virus, Epstein-Barr virus
Lyme disease, toxoplasmosis
Chagas disease
Catheterization with coronary angiography in patients with angina who are candidates for intervention*
Serologic studies for active rheumatologic disease
Endomyocardial biopsy

*Level I recommendations.

Adapted from Hunt SA, Abraham WT, Chin MH, et al. ACC/AHA 2005 guideline update for the diagnosis and management of chronic heart failure in the adult. *Circulation*. 2005;112:e154-e235.

TREATMENT

Supportive therapy includes sodium and fluid restriction, avoidance of alcohol and other toxins, and use of established heart failure medications (Chapter 46). Rest and avoidance of exercise should be recommended only for patients who have myocarditis, peripartum cardiomyopathy, or desmosomal or lamin AC mutations. For other patients, a submaximal exercise regimen is desirable to sustain mobility, to avoid deconditioning, and to maintain physical and psychological health. Patients with atrial fibrillation or with echocardiographic evidence of a left atrial or left ventricular mural thrombosis should be anticoagulated, preferably with a direct-acting anticoagulant (Table 70-6), or with warfarin to an international normalized rate of 2.0 to 3.0 (Table 70-4). An ICD is preferred to medication for primary prevention against sudden cardiac death from ventricular arrhythmia,[A10] and some patients require management for advanced heart failure (Chapter 46) with cardiac resynchronization therapy, inotropic medications, ventricular assist devices, and cardiac transplantation (Chapter 46).

Family Screening

When a pathogenic gene variant has been identified in a proband, cascade genetic testing should be considered in first-degree relatives.[18] The detection of early disease in a family member offers an opportunity to initiate treatment, usually with an angiotensin-converting enzyme inhibitor (e.g., ramipril or perindopril 5 mg daily) or ß-blocker (e.g., bisoprolol 5 mg daily or carvedilol 12.5 or 25 mg twice daily), although the efficacy of such therapy remains to be proven. Precise algorithms to guide the interval of serial evaluation remain to be determined. Even in the absence of a positive genetic test, evaluation of first-degree relatives by history, physical examination, a 12-lead ECG, and a two-dimensional echocardiogram should be considered.

PROGNOSIS

The prognosis of idiopathic and genetically determined dilated cardiomyopathy is related to the etiology, the severity of disease at the time of presentation, and the response to treatment. Most patients improve with treatment, but the 5-year survival is less than 50% in patients who present with severe disease (e.g., ejection fraction <25%, left ventricular end-diastolic dimension >65 mm, peak oxygen consumption <12 mL/kg/minute).

Specific Causes of Dilated Cardiomyopathy

Alcoholic Cardiomyopathy

In the United States, excess alcohol consumption (Chapter 364) contributes to more than 10% of cases of heart failure.[19] Alcohol and its metabolite, acetaldehyde, are cardiotoxins. Myocardial depression is initially reversible but, if alcohol consumption is sustained, can lead to myocyte vacuolization, mitochondrial

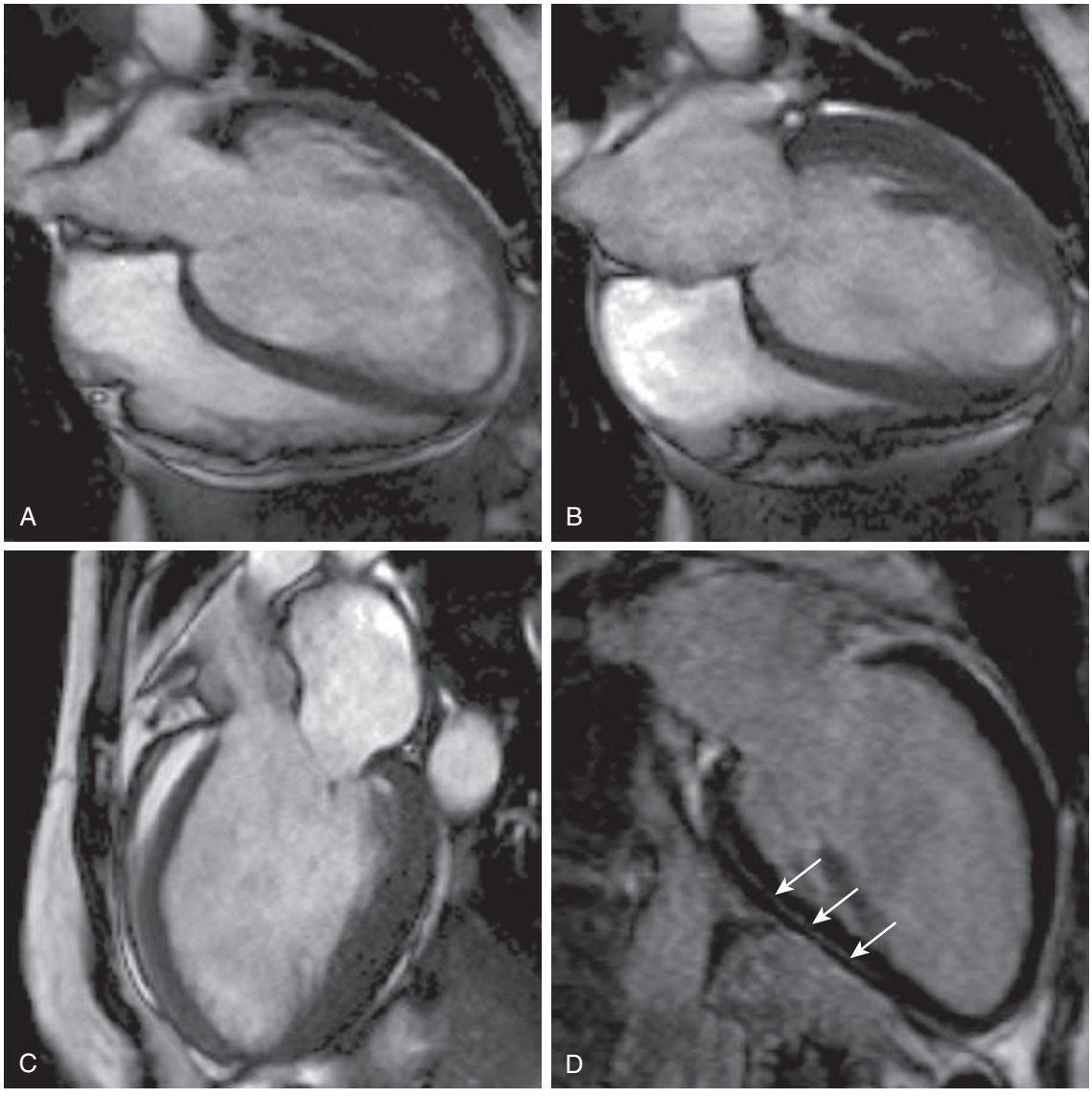

E-FIGURE 47-8. A 45-year-old woman with dilated cardiomyopathy, left bundle branch block, and heart failure. The left ventricular ejection fraction is 27%, and the left ventricle is severely dilated (diastolic volume of 288 mL; **A**, diastolic; **B, C**, systolic frames). There is a rim of mid-myocardial late gadolinium enhancement at the inferior wall (*arrows*, **D**).

abnormalities, and myocardial fibrosis. Even in chronic stages, however, the heart failure represents a sum of both reversible and irreversible myocardial dysfunction. The amount of alcohol necessary to produce symptomatic cardiomyopathy in susceptible individuals is not known but has been estimated to be six drinks (~4 oz of pure ethanol) a day for 5 to 10 years. Frequent binging without heavy daily consumption may also be sufficient. Alcoholic cardiomyopathy can develop in patients without social evidence of an alcohol problem. Abstinence leads to improvement in at least 50% of patients with severe symptoms, some of whom normalize their left ventricular ejection fractions. Patients with other causes of heart failure also should limit alcohol consumption.

Chemotherapy

Anthracycline (doxorubicin, daunorubicin, epirubicin) cardiotoxicity (Chapter 164) causes characteristic histologic changes on endomyocardial biopsy with overt heart failure in 5 to 10% of patients who receive doses of 450 mg/m^2 of body surface area or more. Most cardiotoxicity occurs within the first year and is associated with a higher anthracycline dose and a lower left ventricular ejection fraction. Patients who have received anthracyclines in the prepubertal period without apparent cardiotoxicity may develop cardiac failure in young adulthood. The risk is higher in patients who have lower baseline ejection fractions, concomitant radiation therapy, or higher doses of anthracycline. Cyclophosphamide and ifosfamide can cause acute severe heart failure and malignant ventricular arrhythmias. Some tyrosine kinase inhibitors (e.g., sunitinib) cause a reduction in systolic function, especially in the presence of coronary artery disease, but there is good response to withdrawal and conventional medical therapy (Chapter 164). 5-Fluorouracil can cause coronary artery spasm and depressed left ventricular contractility. Up to 11% of patients who receive trastuzumab (Chapter 183), a recombinant monoclonal antibody that binds to human epidermal growth factor type 2, develop dilated cardiomyopathy, which is reversible after withdrawal and conventional drug treatment. The risk for cardiotoxicity increases with previous anthracycline and radiation treatment. Interferon alfa may be associated with hypotension and arrhythmias in up to 10% of patients, and interleukin-2 rarely has been associated with cardiotoxicity. Immune checkpoint inhibitors, which activate antitumor T lymphocytes that then attack cancer cells, can lead to off-target effects, including myocarditis, heart failure, and cardiogenic shock.

The use of ß-blockers (e.g., carvedilol, starting at 6.25 mg twice daily and increasing to 25 mg twice daily in the absence of heart failure, bradycardia, or atrioventricular block)[A11] or renin–angiotensin system blockers (e.g., enalapril, starting at 1.25 mg or 2.5 mg twice daily, increasing to 10 mg twice daily as tolerated with systolic blood pressure >90 mm Hg) with chemotherapy has been associated with better subsequent left ventricular function. However, small sample sizes and potential publication bias limit the clinical interpretability of these findings.

Metabolic and Endocrine Disease

Excess catecholamines, as in pheochromocytoma (Chapter 209), may injure the heart by compromising the coronary microcirculation or by direct toxic effects on myocytes. *Cocaine* (Chapter 365) increases synaptic concentrations of catecholamines by inhibiting reuptake at nerve terminals; the result may be an acute coronary syndrome or chronic cardiomyopathy.

Thiamine deficiency from poor nutrition or alcoholism (Chapter 199) can cause beriberi heart disease, with vasodilation and high cardiac output followed by low output. Calcium deficiency (Chapter 227) resulting from hypoparathyroidism, gastrointestinal abnormalities, or chelation directly compromises myocardial contractility.

Hypophosphatemia (Chapter 105), which may occur in alcoholism, during recovery from malnutrition, and in hyperalimentation, also reduces myocardial contractility. Patients with magnesium depletion (Chapter 105) due to impaired absorption or increased renal excretion (Chapter 105) also may present with left ventricular dysfunction.

Hypothyroidism (Chapter 207) depresses contractility and conduction and may cause pericardial effusions, whereas *hyperthyroidism* increases cardiac output, can worsen underlying heart failure, and may rarely be the sole cause of heart failure. The presenting sign of diabetes (Chapter 210) can be cardiomyopathy, especially with diastolic dysfunction, independent of epicardial coronary atherosclerosis, for which it is a major risk factor. Obesity (Chapter 201) can cause cardiomyopathy with increased ventricular mass and decreased contractility, which improve after weight loss, or it can aggravate underlying heart failure from other causes.

Peripartum Cardiomyopathy

Peripartum cardiomyopathy appears in the last month of pregnancy or in the first 5 months after delivery in the absence of preexisting cardiac disease (Chapter 221).[20] The incidence is between 1 in 3000 and 1 in 15,000 deliveries, with increased risk in older mothers or in the setting of twins, malnutrition, tocolytic therapy, toxemia, or hypertension. Lymphocytic myocarditis, which is found in 30 to 50% of biopsy specimens, suggests an immune component, perhaps cross-reactivity between uterine and cardiac myocyte proteins or an enhanced susceptibility to viral myocarditis. Enhanced oxidative stress triggers activation of cathepsin D, which is a ubiquitous lysosomal enzyme that cleaves serum prolactin in its antiangiogenic and proapoptotic 16-kD form, and that appears to promote endothelial inflammation and impair metabolism and contraction of cardiomyocytes. About 15% of patients have truncating mutations in the same genes that have been implicated in dilated cardiomyopathy, especially the *TTN* gene. Presentation is usually with orthopnea and dyspnea on minimal exertion, most often within the first weeks after delivery when the excess volume of pregnancy would normally be mobilized. Preexisting cardiac disease must be excluded.

TREATMENT

Diuretics facilitate postpartum diuresis, and angiotensin-converting enzyme inhibitors improve symptoms (Chapter 46).[21] Oral bromocriptine (2.5 mg twice daily for 2 weeks, then daily for 6 weeks) can significantly improve the recovery of left ventricular function and may reduce deaths.[A12] The prognosis is improvement to normal or near-normal ejection fraction during the next 6 months in more than 50% of patients. About 4% require heart transplantation, and about 9% die suddenly or from complications of heart transplantation.

Overlap with Restrictive Cardiomyopathy

Diseases causing primarily restrictive cardiomyopathies can occasionally overlap to cause a picture consistent with dilated cardiomyopathy. For example, hemochromatosis (Chapter 196) and sarcoidosis (Chapter 83) should be considered in evaluating any patient with a cardiomyopathy. Amyloidosis (Chapter 174) is less commonly confused with dilated than with hypertrophic cardiomyopathy but should be considered in a patient who has a thick-walled ventricle with depressed contractile function.

ARRHYTHMOGENIC RIGHT VENTRICULAR CARDIOMYOPATHY

DEFINITION AND EPIDEMIOLOGY

Arrhythmogenic right ventricular cardiomyopathy (ARVC; Chapter 53) is a genetically determined type of cardiomyopathy that is characterized histologically by loss of cardiomyocytes with replacement by fibrous or fibrofatty tissue in the right ventricular myocardium; clinically by ventricular arrhythmias, heart failure, and sudden cardiac death; and histologically by cardiomyocyte loss and replacement. The disease is seen in patients of European, African, and Asian descent, with an estimated prevalence between 1 in 1000 and 1 in 5000 adults.

PATHOBIOLOGY

Arrhythmogenic right ventricular cardiomyopathy is inherited as an autosomal dominant disease with incomplete penetrance, although recessive forms with cutaneous manifestations are recognized (see E-Table 47-1). Most cases are caused by heterozygous mutations in genes encoding components of the desmosomal junction of cardiomyocytes. The most common occur in plakophilin 2, desmocollin 2, desmoplakin, and desmoglein 2. Homozygous mutations in plakoglobin and desmoplakin are responsible for the rare autosomal recessive forms (Naxos disease and Carvajal syndrome, respectively). A highly penetrant and lethal mutation in the transmembrane cytoplasmic protein 43 (TMEM43) has been described in families from Newfoundland. Other genes that rarely cause arrhythmogenic right ventricular cardiomyopathy include desmin (*DES*), phospholamban (*PLN*), and lamin (*LMNA*).

Pathology

The main pathologic feature is progressive loss of right ventricular myocardium, which is replaced by adipose and fibrous tissue. These changes begin in the inflow, outflow, and apical regions of the right ventricle. Aneurysm formation in these areas is typical. Progressive myocardial involvement may lead to global right ventricular dilation. Right ventricular disease is often associated with fibrofatty substitution of the left ventricular myocardium, with the posterolateral wall preferentially affected.

Mutations in desmosomal protein genes may increase the susceptibility of the myocardium to the damaging effects of mechanical stress. The acute phase

of myocardial injury may be accompanied by inflammation. The predilection for the right ventricle has been explained by its thin wall and greater distensibility. As desmosomal proteins interact with many other proteins, including components of the cellular cytoskeleton and intermediate filaments, it is possible that ventricular dysfunction occurs as the result of reduced cytoskeletal integrity and impaired force transduction. Some desmosomal proteins, in particular plakoglobin, are also important signaling molecules that regulate the transcription of many other genes.

Inflammatory infiltrates are present in about 70% of patients in autopsy series. People with arrhythmogenic right ventricular cardiomyopathy also have raised levels of cytokines and anti-DSG2 (desmoglein) antibodies.

CLINICAL MANIFESTATIONS

By convention, the natural history of arrhythmogenic right ventricular cardiomyopathy is divided into phases, but it is not inevitable that patients will progress through all phases. In the early phase, patients are usually asymptomatic, but resuscitated cardiac arrest and sudden death may be the initial manifestations, particularly in adolescents and young adults. The overt arrhythmic phase usually begins in adolescents and young adults, when patients note palpitations or syncope. Symptomatic sustained arrhythmias are usually accompanied by ECG, morphologic, and functional abnormalities of the right ventricle sufficient to fulfill diagnostic criteria for arrhythmogenic right ventricular cardiomyopathy. A small proportion of patients progress to a more advanced phase, which is characterized by diffuse right or left ventricular impairment that requires conventional treatment for heart failure (Chapter 46). Cardiac sarcoidosis (Chapter 83; see later) has many similarities with arrhythmogenic right ventricular cardiomyopathy in terms of presentation and clinical features, and it is sometimes clinically indistinguishable.

DIAGNOSIS

Clinical evaluation includes inquiry for symptoms of arrhythmia (syncope, presyncope, sustained palpitation); a family history of premature cardiac symptoms or sudden death; 12-lead, 24-hour, and maximal exercise ECG testing; and two-dimensional echocardiography with specific right ventricular views. Contrast echocardiography may be required to obtain better endocardial definition of the right ventricular myocardium and apex of the left ventricle. Magnetic resonance imaging (Chapter 44) provides accurate assessment of ventricular volumes as well as noninvasive characterization of the characteristic fibrous tissue and fat that establish the diagnosis and provide prognostic information (Figs. 44-17 and 47-5).[22]

Ventricular arrhythmias with a left bundle branch block morphology, consistent with a right ventricular origin, are characteristic. However, the ECG and arrhythmic manifestations are not specific to arrhythmogenic right ventricular cardiomyopathy and overlap with many other disease states, so standard criteria are recommended for diagnosis (Table 47-5). Because these criteria are highly specific but lack sensitivity for detection of early disease, more sensitive criteria are recommended for first-degree relatives of known cases (Table 47-6). The diagnosis in a proband also raises the possibility of mutation analysis in the family to identify those at risk and in need of serial evaluation as well as those who need no specific follow-up.

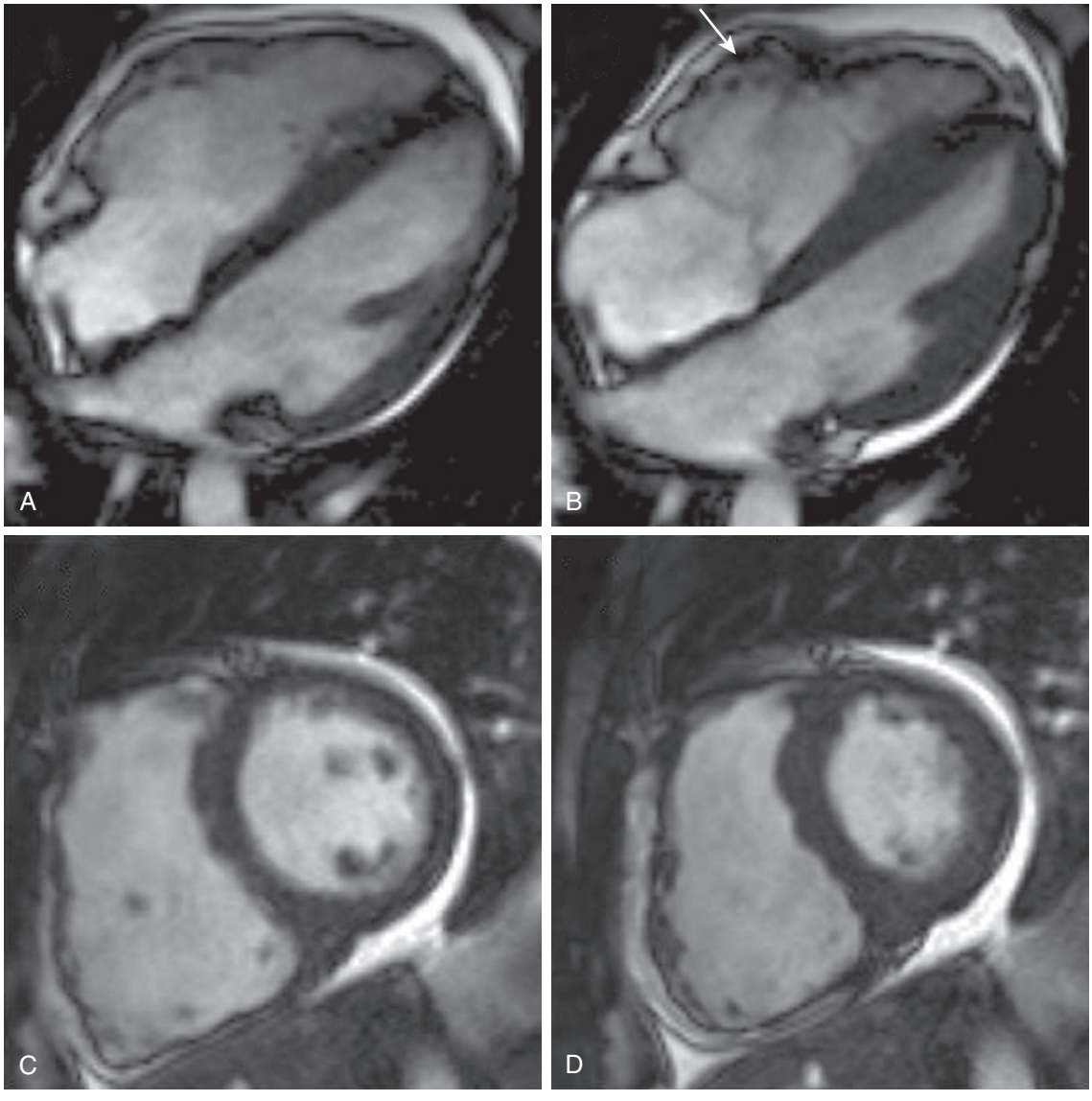

FIGURE 47-5. A 21-year-old man with arrhythmogenic right ventricular cardiomyopathy. End-diastolic (**A**) and end-systolic (**B**) frames from a four-chamber view, with a dilated and impaired right ventricle with a basal wall motion abnormality (*arrow*), confirmed on end-diastolic (**C**) and end-systolic (**D**) short axis views. This individual had no scar in the left ventricle with well-preserved systolic function; scar imaging in the thin right ventricle (with adjacent fat and small effusion) was equivocal.

TABLE 47-5 REVISED TASK FORCE CRITERIA FOR ARRHYTHMOGENIC RIGHT VENTRICULAR CARDIOMYOPATHY IN PROBANDS*

CRITERIA	
MAJOR	**MINOR**
I. GLOBAL OR REGIONAL DYSFUNCTION AND STRUCTURAL ALTERATIONS*	
By Two-Dimensional Echo • Regional RV akinesia, dyskinesia, or aneurysm • *and* 1 of the following (end diastole): PLAX RVOT ≥32 mm (corrected for body size [PLAX/BSA] ≥19 mm/m^2) PSAX RVOT ≥36 mm (corrected for body size [PLAX/BSA] ≥21 mm/m^2) *or* fractional area change ≤33%	**By Two-Dimensional Echo** • Regional RV akinesia or dyskinesia • *and* 1 of the following (end diastole): PLAX RVOT ≥29 to <32 mm (corrected for body size [PLAX/BSA] ≥16 to <19 mm/m^2) PSAX RVOT ≥32 to <36 mm (corrected for body size [PSAX/BSA] ≥18 to <21 mm/m^2) *or* fractional area change >33% to ≤40%
By MRI • Regional RV akinesia or dyskinesia or dyssynchronous RV contraction • *and* 1 of the following: RV end-diastolic volume indexed to BSA ≥110 mL/m^2 (male) or ≥100 mL/m^2 (female) *or* RV ejection fraction ≤40%	**By MRI** • Regional RV akinesia or dyskinesia or dyssynchronous RV contraction • *and* 1 of the following: RV end-diastolic volume indexed to BSA ≥100 to <110 mL/m^2 (male) or ≥90 to <100 mL/m^2 (female) *or* RV ejection fraction >40% to ≤45%
By RV angiography • Regional RV akinesia, dyskinesia, or aneurysm	
II. TISSUE CHARACTERIZATION OF WALL	
• Residual myocytes <60% by morphometric analysis (or <50% if estimated), with fibrous replacement of the RV free wall myocardium in ≥1 sample, with or without fatty replacement of tissue on endomyocardial biopsy	• Residual myocytes 60% to 75% by morphometric analysis (or 50% to 65% if estimated), with fibrous replacement of the RV free wall myocardium in ≥1 sample, with or without fatty replacement of tissue on endomyocardial biopsy
III. REPOLARIZATION ABNORMALITIES	
• Inverted T waves in right precordial leads (V_1,V_2, and V_3) or beyond in individuals >14 years of age (in the absence of complete right bundle branch block QRS ≥120 msec)	• Inverted T waves in leads V_1 and V_2 in individuals >14 years of age (in the absence of complete right bundle branch block) or in V_4, V_5, or V_6 • Inverted T waves in leads V_1, V_2, V_3, and V_4 in individuals >14 years
IV. DEPOLARIZATION/CONDUCTION ABNORMALITIES	
• Epsilon wave (reproducible low-amplitude signals between end of QRS complex to onset of the T wave) in the right precordial leads (V_1 to V_3)	• Late potentials by SAECG in ≥1 of 3 parameters in the absence of a QRS duration ≥110 msec on the standard ECG • Filtered QRS duration (fQRS) ≥114 msec • Duration of terminal QRS <40 μV (low-amplitude signal duration) ≥38 msec • Root-mean-square voltage of terminal 40 msec ≥20 μV • Terminal activation duration of QRS ≥55 msec measured to the end of the QRS, including R′, in V_1, V_2, or V_3, in the absence of complete right bundle branch block
V. ARRHYTHMIAS	
• Nonsustained or sustained ventricular tachycardia of left bundle branch morphology with superior axis (negative or indeterminate QRS in leads II, III, and aVF and positive in lead aVL)	• Nonsustained or sustained ventricular tachycardia of RV outflow configuration, left bundle branch block morphology with inferior axis (positive QRS in leads II, III, and aVF and negative in lead aVL) or of unknown axis • >500 ventricular extrasystoles per 24 hours (Holter)
VI. FAMILY HISTORY	
• ARVC confirmed in a first-degree relative who meets current Task Force criteria • ARVC confirmed pathologically at autopsy or surgery in a first-degree relative • Identification of a pathogenic mutation† categorized as associated or probably associated with ARVC in the patient under evaluation	• History of ARVC in a first-degree relative in whom it is not possible or practical to determine whether the family member meets current Task Force criteria • Premature sudden death (<35 years of age) due to suspected ARVC in a first-degree relative

*Hypokinesis is not included in this or subsequent definitions of right ventricular (RV) regional wall motion abnormalities for the proposed modified criteria.

†A pathogenic mutation is a DNA alteration associated with ARVC that alters or is expected to alter the encoded protein, is unobserved or rare in a large non-ARVC control population, and either alters or is predicted to alter the structure or function of the protein or has demonstrated linkage to the disease phenotype in a conclusive pedigree.

ARVC = arrhythmogenic right ventricular cardiomyopathy; aVF = augmented voltage unipolar left foot lead; aVL = augmented voltage unipolar left arm lead; BSA = body surface area; ECG = electrocardiogram; MRI = magnetic resonance imaging; PLAX = parasternal long axis view; PSAX = parasternal short axis view; RVOT = right ventricular outflow tract; SAECG = signal-averaged electrocardiogram. Diagnostic terminology for original criteria: this diagnosis is fulfilled by the presence of 2 major, 1 major plus 2 minor, or 4 minor criteria from different groups. Diagnostic terminology for revised criteria: definite diagnosis: 2 major, 1 major and 2 minor, or 4 minor criteria from different categories; borderline: 1 major and 1 minor or 3 minor criteria from different categories; possible: 1 major or 2 minor criteria from different categories.

From Marcus FI, McKenna WJ, Sherrill D, et al. Diagnosis of arrhythmogenic right ventricular cardiomyopathy/dysplasia: proposed modification of the task force criteria. *Circulation*. 2010;121:1533-1541.

Differential Diagnosis

The differential diagnosis includes other inherited cardiomyopathies, the inherited arrhythmia syndromes (long QT syndrome, Brugada syndrome, and catecholaminergic polymorphic ventricular tachycardia; Chapter 53), cardiac sarcoidosis, myocarditis, and causes of right ventricular dilation such as intracardiac or extracardiac shunts (Chapter 55). The differentiation from so-called benign right ventricular outflow tract tachycardia may be problematic, although the 12-lead ECG and right ventricular imaging studies are typically normal, and no familial disease is present. Some patients with desmosomal protein gene mutations demonstrate left ventricular involvement early in the disease (e.g., truncating variants in desmoplakin), whereas survivors may develop a predominant left ventricular dilated cardiomyopathy phenotype with a risk of lethal arrhythmias.

TREATMENT

Pharmacologic treatment is the first-line therapy for patients with well-tolerated, non–life-threatening ventricular arrhythmias, such as frequent ventricular extrasystoles. Treatment of patients with symptomatic ventricular arrhythmias is with an ICD,[23] with supplemental sotalol (160 to 240 mg/day) or even amiodarone (maintenance dose of 200 mg/day). Catheter ablation (Chapter 54) may be required in patients with drug-refractory incessant ventricular arrhythmia

TABLE 47-6 ARRHYTHMOGENIC RIGHT VENTRICULAR CARDIOMYOPATHY: CRITERIA FOR DIAGNOSIS OF FIRST-DEGREE RELATIVES WHO DO NOT FULFILL CRITERIA AS PROBANDS*

ARVC in a first-degree relative plus one of the following:	
ECG	T wave inversion in right precordial leads (V_2 and V_3)
Signal-averaged ECG	Late potentials seen on signal-averaged ECG
Arrhythmia	Left bundle branch block–type ventricular tachycardia on ECG, on Holter monitoring, or during exercise testing; >200 extrasystoles during a 24-hour period
Structural or functional abnormality of the right ventricle	Mild global right ventricular dilation or reduction in ejection fraction with normal left ventricle; mild segmental dilation of the right ventricle; regional right ventricular hypokinesia

*Any one criterion is adequate for the diagnosis.
ARVC = arrhythmogenic right ventricular cardiomyopathy; ECG = electrocardiogram.
From Hamid MS, Norman M, Quraishi A, et al: Prospective evaluation of relatives for familial arrhythmogenic right ventricular cardiomyopathy reveals a need to broaden diagnostic criteria. *J Am Coll Cardiol*. 2002;40:1445-1450.

TABLE 47-7 CAUSES OF RESTRICTIVE CARDIOMYOPATHIES

INFILTRATIVE DISORDERS
Amyloidosis
Sarcoidosis
STORAGE DISORDERS
Hemochromatosis
Fabry disease
Glycogen storage diseases
FIBROTIC DISORDERS
Radiation
Scleroderma
Drugs (e.g., doxorubicin, serotonin, ergotamine)
METABOLIC DISORDERS
Carnitine deficiency
Defects in fatty acid metabolism
ENDOMYOCARDIAL DISORDERS
Endomyocardial fibrosis
Hypereosinophilic syndrome (Löffler endocarditis)
MISCELLANEOUS CAUSES
Carcinoid syndrome

or frequent recurrences of ventricular tachycardia after implantation of an ICD, although recurrence is common.

Retrospective analyses of clinical and pathologic series have identified a number of possible predictors of adverse outcome in probands, including an early age at onset of symptoms, competitive sporting activity, severe right ventricular dilation, left ventricular involvement, syncope, episodes of complex ventricular arrhythmias or VT, and increased QRS dispersion on the 12-lead electrocardiogram. ICD implantation is recommended for the prevention of sudden cardiac death in patients with documented sustained ventricular tachycardia or ventricular fibrillation and a reasonable expectation of survival with a good functional status for longer than 1 year. ICD implantation may also be appropriate in patients with extensive disease, including those with left ventricular involvement, or undiagnosed syncope when ventricular tachycardia or ventricular fibrillation has not been excluded as the cause.

Standard heart failure therapy, including diuretics, angiotensin-converting enzyme inhibitors, and β-blockers, is indicated in patients in whom arrhythmogenic right ventricular cardiomyopathy has progressed to severe heart failure or biventricular systolic dysfunction (Chapter 46). Anticoagulation should be considered in the presence of atrial fibrillation (Chapter 52), marked ventricular dilation, or ventricular aneurysms. In patients in whom heart failure is refractory, cardiac transplantation (Chapter 46) should be considered.

PROGNOSIS

Most data on prognosis are derived from small, high-risk populations. By the age of 40 years, event-free survival is 50 to 60% in patients with Naxos disease and some autosomal dominant forms. In patients who have syncope or sustained ventricular arrhythmias and are treated with an ICD, freedom from appropriate shock therapy is about 75% at 48 months after implantation, with 96% of patients alive. Risk factors for sudden cardiac death include genotype,[24] severe right ventricular disease, left ventricular involvement, and a history of unexplained syncope.

RESTRICTIVE CARDIOMYOPATHY

DEFINITION AND EPIDEMIOLOGY

Restrictive cardiomyopathies (Table 47-7) are characterized by stiffness, impaired filling, elevated left ventricular diastolic pressures, and reduced diastolic volume of the left or right ventricle despite normal or near-normal systolic function and wall thickness.[25] Primary (idiopathic) forms are very uncommon, whereas secondary forms, in which the heart is affected as part of a multisystem disorder, usually present at the advanced stage of an infiltrative disease (e.g., amyloidosis or sarcoidosis) or a systemic storage disease (e.g., hemochromatosis). Idiopathic restrictive cardiomyopathy affects both male and female patients and may be manifested in children and young adults.

PATHOBIOLOGY

Approximately 30% of patients with idiopathic restrictive cardiomyopathy have familial disease, and most of these patients will have mutations in the cardiac sarcomere protein genes, particularly *TNNI3* and *MYH7*. These individuals may present with phenotypes that overlap with hypertrophic cardiomyopathy (Fig. 47-6). Mutations in the gene (*DES*) that encodes desmin, which is an intermediate filament, cause restrictive cardiomyopathy associated with skeletal myopathy and cardiac conduction system abnormalities. Wild-type, transthyretin-related cardiac amyloidosis (Chapter 174) is the most prevalent form of restrictive cardiomyopathy, and it increases in frequency in older patients. However, restriction is present only in the late stages of disease, when patients have extensive amyloid infiltration of the myocardial interstitium.

Restrictive cardiomyopathy is seen in hemochromatosis (Chapter 196) and sarcoidosis (Chapter 83), and it also is increasingly seen in cancer survivors as a consequence of diffuse biventricular fibrosis, most often with a nonischemic pattern, caused by chemotherapy (especially high-dose anthracyclines) and chest radiotherapy (Chapter 18).

The macroscopic features of restrictive cardiomyopathy include biatrial dilation and small ventricular cavities. In many hearts, there is thrombus in the atrial appendages and patchy endocardial fibrosis. The histologic features of restrictive cardiomyopathy vary, depending on the cause, but patchy interstitial fibrosis and myocyte disarray can be seen in patients with pure restrictive cardiomyopathy. Amyloidosis, hemochromatosis, and sarcoidosis are among the systemic diseases that cause restrictive cardiomyopathy (see later).

CLINICAL MANIFESTATIONS

Most patients present with symptoms and signs of heart failure and supraventricular arrhythmias, including atrial fibrillation (Chapter 52) and heart block (Chapter 51). Common symptoms include dyspnea on exertion, recurrent respiratory tract infections, general fatigue, and weakness. Symptoms may progress rapidly to dyspnea at rest, orthopnea, paroxysmal nocturnal dyspnea, and abdominal discomfort due to hepatic engorgement. Many patients complain of chest pain and palpitation. Rarely, sudden death is the initial manifestation of the disease.

Physical examination typically reveals an elevated jugular venous pressure, which has a prominent *y* descent and fails to fall (or rises) during inspiration (Kussmaul sign). On cardiac auscultation, the pulmonary component of the second heart sound may be loud if pulmonary vascular resistance is high. A third heart sound and occasionally a fourth heart sound commonly produce a gallop rhythm. Peripheral edema, ascites, and hepatomegaly are common.

DIAGNOSIS

No ECG findings are diagnostic, but the most frequent ECG abnormalities include P mitrale and P pulmonale, nonspecific ST segment and T wave abnormalities, ST segment depression, and T wave inversion, usually in the inferolateral leads. Voltage criteria for left and right ventricular hypertrophy may be present. Some patients with amyloidosis have low-voltage QRS complexes. Conduction abnormalities include intraventricular conduction delay and abnormal Q waves.

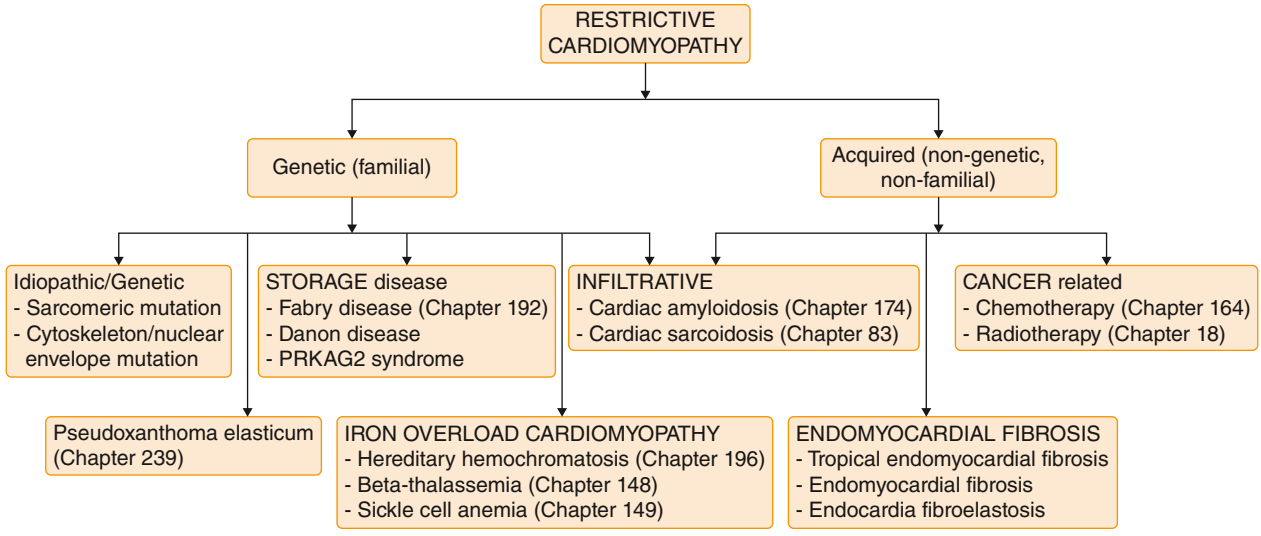

FIGURE 47-6. Classification of restrictive cardiomyopathies. (Adapted from Ditaranto R, Caponetti AG, Ferrara V, et al. Pediatric restrictive cardiomyopathies. *Front Pediatr.* 2022;9:745365.)

On cardiac imaging, both atria are markedly dilated and can dwarf the size of the ventricles in patients with normal global systolic function and a nonhypertrophied, nondilated left ventricle. Pulsed-wave Doppler velocities typically show increased early diastolic filling velocity, decreased atrial filling velocity, increased ratio of early diastolic filling to atrial filling, decreased E wave deceleration time, and decreased isovolumic relaxation time. Pulmonary vein and hepatic vein pulsed-wave Doppler velocities demonstrate higher diastolic than systolic velocities, increased atrial reversal velocities, and atrial reversal duration greater than mitral atrial filling duration. Tissue Doppler imaging usually shows reduced diastolic annular velocities and an increased ratio of early diastolic tissue Doppler annular velocity to mitral early diastolic filling velocity, reflecting elevated left ventricular end-diastolic pressures.

The characteristic hemodynamic feature on cardiac catheterization is a deep and rapid early decline in ventricular pressure at the onset of diastole (Table 62-6 and E-Fig 47-9), with a rapid rise to a plateau in early diastole ("dip-and-plateau" or "square root sign") (Fig. 47-7). Left ventricular end-diastolic, left atrial, and pulmonary capillary wedge pressures are markedly elevated, usually 5 mm Hg or more above right atrial and right ventricular end-diastolic pressures. Volume loading and exercise accentuate the difference between left-sided and right-sided pressures.

The diagnostic evaluation aims to exclude potentially reversible conditions and to distinguish restrictive cardiomyopathy from constrictive pericarditis (Chapter 62). Definitive etiologic diagnosis relies on the demonstration of disease-specific features, such as amyloid protein in amyloidosis (Chapter 174), noncaseating granulomas in sarcoidosis (Chapter 83), abnormal iron studies in hemochromatosis (Chapter 196), or reduced α-galactosidase A levels in Fabry disease (Chapter 192). Endomyocardial biopsy is rarely required to make these diagnoses.

TREATMENT

Diuretics are the main therapy for heart failure symptoms (Chapter 46), but they must be carefully administered so as not to reduce left ventricular filling pressures to the point of hypotension. Angiotensin-converting enzyme inhibitors and β-blockers are commonly recommended despite few data on their benefit. However, all atrioventricular blocking agents, including β-blockers, must be used with caution, because an increase in heart rate is the only mechanism to increase cardiac output in the face of augmented oxygen requirements (e.g., during physical activity). In patients with secondary restrictive cardiomyopathies, specific treatment of the underlying systemic disease is indicated whenever possible (see later). Referral for assessment for possible heart transplantation should be considered early before refractory pulmonary hypertension may develop.

PROGNOSIS

In adults with restrictive cardiomyopathy, the clinical course is usually slow and protracted. Survival from the time of diagnosis is often 10 years or more, except for AL amyloidosis, which progresses much more rapidly. Symptoms of heart failure are generally progressive and respond poorly to treatments for heart failure.

SPECIFIC CLINICAL SYNDROMES

SARCOIDOSIS

The frequency of myocardial involvement in patients with sarcoidosis (Chapter 83) is difficult to determine because it is frequently subclinical and patchy in nature. Postmortem studies suggest that the heart is involved in at least 25% of patients, but clinical cardiac involvement occurs in less than 10% of patients. Clinical manifestations of ventricular dysfunction include heart failure, conduction abnormalities, atrial and ventricular arrhythmias, pericardial effusion, valvular dysfunction, and, rarely, sudden cardiac death. Right-sided heart failure secondary to pulmonary hypertension may occur in patients with extensive fibrotic lung disease. Myocardial infiltration by sarcoid granulomas results in restrictive or dilated cardiomyopathy. The most common site is in the lateral wall of the left ventricle. Papillary muscle involvement is responsible for the most common valvulopathy, mitral regurgitation. Granuloma formation in the basal interventricular septum may cause conduction abnormalities. Ventricular arrhythmias, usually monomorphic ventricular tachycardia, are frequent and may be life-threatening.

DIAGNOSIS

The diagnosis of cardiac sarcoidosis can be challenging given its patchy involvement of the heart.[26] Magnetic resonance imaging identifies areas of edema and fibrosis (the latter evident as patchy areas of late gadolinium enhancement [Fig. 44-16]), whereas ^{18}F-Fluorodeoxyglucose positron emission tomography/computed tomography may demonstrate cardiac inflammation in the active phase of disease (E-Fig. 44-3). In patients with such noninvasive findings, histologic confirmation then may be obtained by a biopsy of other affected organs, such as mediastinal lymph nodes or the liver.

TREATMENT AND PROGNOSIS

Corticosteroid therapy (Chapter 83) may improve arrhythmias. However, heart failure may worsen despite such therapy, so immunosuppressants such as mycophenolate mofetil, methotrexate, or azathioprine may be required. An ICD is generally indicated for ventricular arrhythmias. Estimates for 1-, 5-, and 10-year transplantation-free cardiac survival are 97%, 90%, and 83%, respectively, but heart failure at presentation predicts a poor outcome, with a 10-year transplantation-free cardiac survival of only 53%.

AMYLOIDOSIS

EPIDEMIOLOGY AND PATHOBIOLOGY

Amyloidosis can result in deposition of amyloid protein in the atria, ventricles, coronary vessels, conduction system, and valves. The degree of cardiac involvement varies among subtypes. Hematologic disorders (Chapter 173) associated with excessive light chain (AL) immunoglobulin production are a common cause of cardiac amyloid. Familial forms caused by the accumulation of mutant proteins (transthyretin or apolipoprotein A) (Chapter 174)

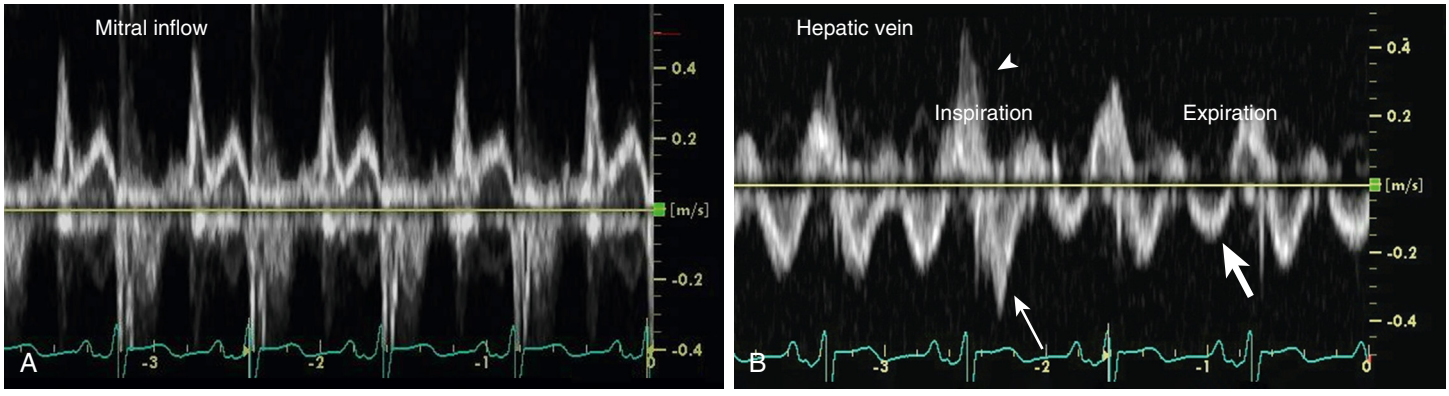

E-FIGURE 47-9. **Differentiation between constrictive pericarditis and restrictive cardiomyopathy. A,** Pulsed-wave Doppler of the mitral inflow shows a restrictive pattern, with early diastolic mitral inflow Doppler velocity greater than late velocity and short deceleration time. **B,** Hepatic vein pulsed-wave Doppler shows increased inspiratory forward velocities *(arrow)*, inspiratory diastolic flow reversals *(arrowhead)*, and minimal expiratory diastolic flow reversals *(thick arrow)*. (From Geske JB, Anavekar NS, Nishimura RA, et al. Differentiation of constriction and restriction: complex cardiovascular hemodynamics. *J Am Coll Cardiol*. 2016;68:2329-2347.)

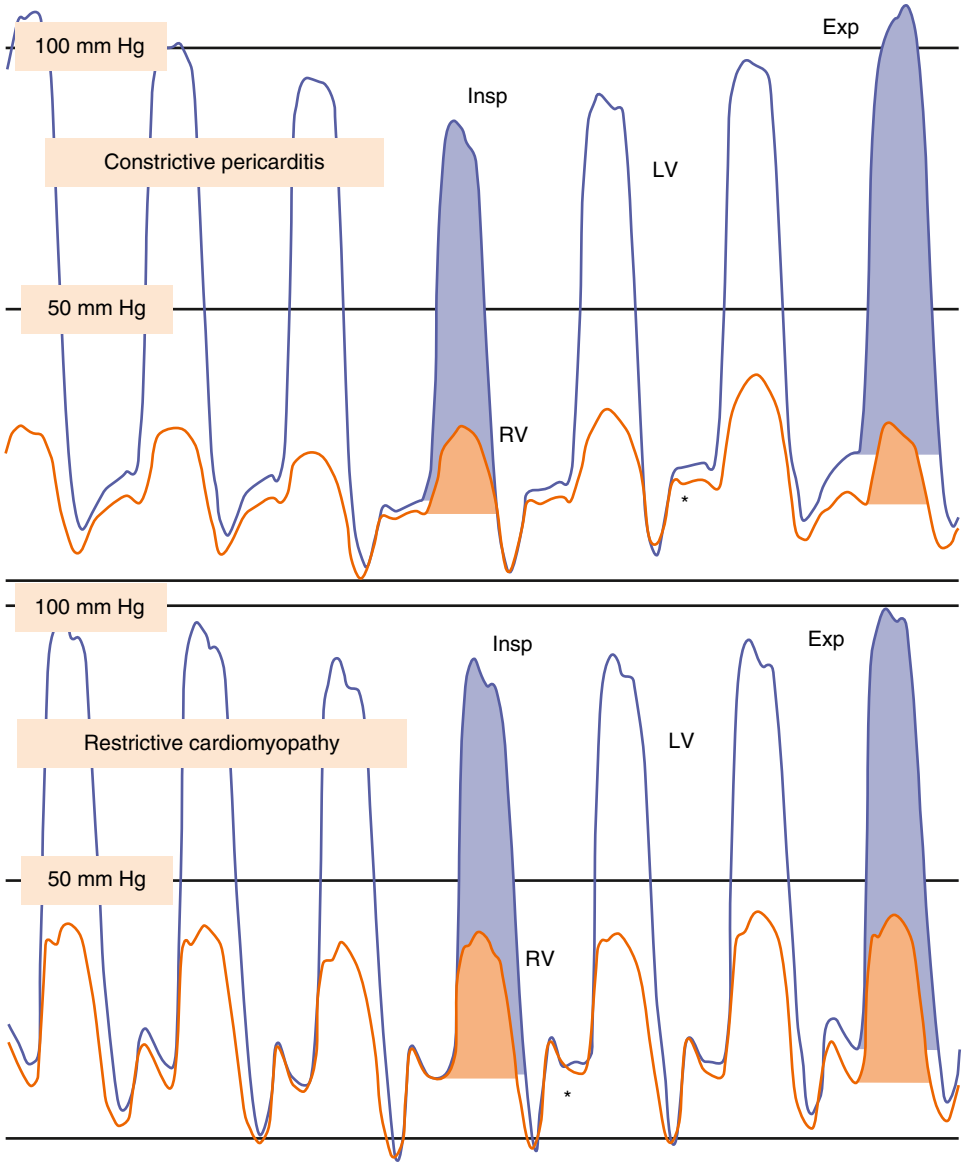

FIGURE 47-7. Simultaneous RV and LV hemodynamic assessment in constrictive pericarditis and restrictive cardiomyopathy. *Top*, Left ventricular (LV) (blue) and right ventricular (RV) (orange) hemodynamic pressure tracings in constrictive pericarditis. End-diastolic filling pressures are elevated and a "square root" sign is present on both pressure tracings (*). Enhanced ventricular interdependence is present, demonstrated by visualization of the systolic area index; RV (gray) and LV (dark gray) areas under the curve are shown for both inspiration (Insp) and expiration (Exp). During inspiration, there is an increase in the area of the RV pressure curve and decrease in the area of the LV pressure curve. *Bottom*, LV and RV pressure tracings in restrictive cardiomyopathy. Although end-diastolic filling pressures are elevated and a square root sign (*) is present, there is no evidence of enhanced ventricular interdependence, with parallel changes in LV and RV pressure curve areas. (Adapted from Geske JB, Anavekar NS, Nishimura RA, et al. Differentiation of constriction and restriction: complex cardiovascular hemodynamics. *J Am Coll Cardiol*. 2016;68:2329-2347.)

have variable cardiac involvement. Secondary amyloidosis, due to deposition of serum amyloid A protein in chronic inflammatory diseases, rarely affects the heart. In late-onset systemic amyloidosis, cardiomyopathy is caused by deposition of normal wild-type transthyretin (TTR); this disease nearly always affects elderly persons (>70 years), with a clinical course that is considerably slower than with other types of amyloid.

DIAGNOSIS

If cardiac amyloidosis is suspected, blood and urine should be analyzed for evidence of a plasma cell dyscrasia (Chapters 173 and 174). The ECG tracing in most forms of cardiac amyloid characteristically shows decreased voltage despite increased wall thickness on echocardiography. Characteristic two-dimensional echocardiographic findings in advanced cardiac amyloidosis are biventricular hypertrophy, thickened valves and interatrial septum, dilated atria, and a small pericardial effusion. The myocardium has a hyperreflective granular texture (Fig. 47-8), best seen on digital image analysis.[27] Echo Doppler in advanced disease demonstrates a restrictive left ventricular filling pattern. Cardiac magnetic resonance imaging may show subendocardial late gadolinium enhancement with abnormal gadolinium kinetics, but it has a 10 to 20% false-negative and false-positive rate.

Transthyretin-related cardiac amyloidosis is particularly avid for 99mTc-phosphate bone tracers (see E-Fig. 44-4). In the setting of a positive 99mTc-phosphate scan without evidence for a plasma clone on blood and urine testing, a diagnosis of transthyretin cardiomyopathy can be made without a biopsy. If both the phosphate scan and blood tests are negative, cardiac amyloidosis is very unlikely. For patients with evidence for a plasma cell dyscrasia, a histologic diagnosis is still required because the presence of uptake on a 99mTc-phosphate scan is not 100% specific for amyloid transthyretin cardiomyopathy.

A definitive diagnosis of amyloidosis requires a tissue biopsy specimen, which can be obtained from other sites. For example, fine-needle aspiration of abdominal fat is positive for amyloid deposits in more than 80% of patients with AL amyloidosis, but is less sensitive for diagnosing other forms of amyloid. If the result is negative, endomyocardial biopsy has a very high sensitivity.

TREATMENT AND PROGNOSIS

Specific therapies to impede precursor protein production and fibril formation should be implemented whenever possible (Chapter 174).[28] Tafamidis (20 to 80 mg daily) can reduce the rate of functional decline and all-cause mortality in transthyretin amyloid cardiomyopathy, but the survival benefit may not be

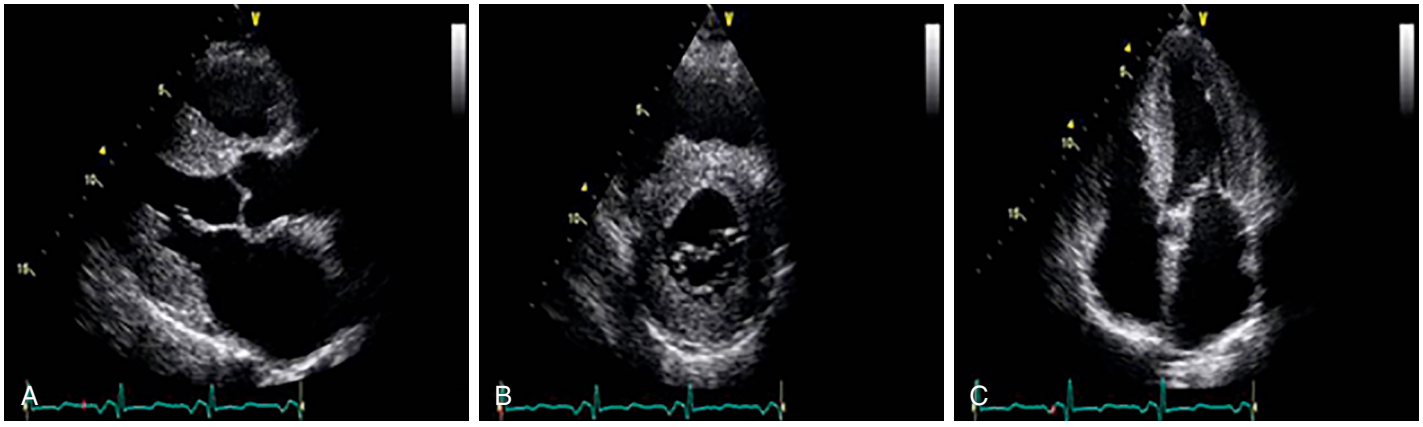

FIGURE 47-8. **Typical echocardiographic features of cardiac amyloidosis. A,** Parasternal long axis showing concentric left ventricular hypertrophy, bright myocardium, and left atrial dilatation. **B,** Parasternal short axis showing concentric left ventricular hypertrophy and bright myocardium. **C,** Apical four-chamber view showing concentric left ventricular hypertrophy and biatrial dilatation. (Images courtesy of Professor Elliott.)

evident until after 2 years of treatment.[A13,A14] Patisiran (0.3 mg/kg intravenously every 3 weeks) may reduce functional decline and adverse cardiac outcomes.[A15] All patients with atrial fibrillation (Chapter 52) should receive anticoagulation (Chapter 70) because of the high intrinsic risk of thromboembolism.

For heart failure (Chapter 46), diuretics, often in high doses (e.g., furosemide, 40 to 80 mg daily), are the mainstay of the palliative heart failure regimen. ß-blockers, angiotensin-converting enzyme inhibitors, and angiotensin II receptor blockers should be used cautiously because they are often poorly tolerated and of unproven efficacy in cardiac amyloidosis. Aldosterone inhibitors might be helpful in advanced cases. Patients may be hypersensitive to digoxin because of enhanced drug binding with amyloid fibrils. Cardiac transplantation remains controversial, but heart transplantation (Chapter 46) with high-dose chemotherapy and with stem cell transplantation (Chapter 163) has been used in patients with AL amyloidosis.

Patients with amyloidosis with heart failure have had a median survival time of less than 1 year and a 5-year survival rate of less than 5%, but new therapies such as tafamidis have reduced mortality by about 30%. Most deaths occur suddenly. Patients with familial amyloidosis have a slower course than do patients with a monoclonal gammopathy.

HEREDITARY HEMOCHROMATOSIS

Hereditary hemochromatosis (Chapter 196) is an autosomal recessive disorder caused by excessive iron deposition in various organs, including the liver, spleen, pancreas, endocrine glands, and heart. In Whites, its prevalence is between 1 in 200 and 1 in 500, with an even higher prevalence in the Irish population. The most common form is caused by mutations in the *HFE* gene, with two missense mutations (*C282Y* and *H63D*) accounting for most cases.

Most patients with classic disease present between the ages of 40 and 60 years with hyperpigmentation, diabetes mellitus, and hepatomegaly. Up to 35% of patients with hemochromatosis experience heart failure, and 36% develop arrhythmias.[29] Restrictive physiologic features dominate early in the disease, followed by ventricular dilation.

DIAGNOSIS

The diagnosis is generally made from the clinical picture, an elevated serum iron level, and a high transferrin saturation. Because paramagnetic ferritin and hemosiderin interact with nearby hydrogen nuclei in tissue water, appropriate MRI sequences evaluating the relaxation time T_2^* is highly sensitive for detecting myocardial iron deposition. Genetic testing is essential, and the diagnosis can be confirmed by endomyocardial biopsy.

TREATMENT

Phlebotomy and iron chelation therapy with deferoxamine (Chapter 196) may improve cardiac function before cell injury becomes irreversible. Standard heart failure treatment (Chapter 46) is generally recommended. Death from hemochromatosis results more often from cirrhosis and liver carcinoma than from cardiac disease.

UNCLASSIFIED CARDIOMYOPATHIES

LEFT VENTRICULAR NONCOMPACTION

Left ventricular noncompaction (LVNC) refers to an abnormal ventricular morphology that is characterized by a thin outer layer of normal or compacted myocardium with an inner noncompacted layer consisting of prominent muscular trabeculae and intra-trabecular recesses that communicate with the ventricular cavity. Current evidence suggests that the compact wall grows by intrinsic proliferation rather than by compaction of the preexisting trabecular layer. For this reason, the term excessive trabeculation is being used to describe the phenomenon.

Left ventricular noncompaction can be caused by genetic variants, most commonly in cardiac sarcomeric proteins *MYH7*, *MYBPC*, and *TTN*,[30] in approximately one-third of patients. However, left ventricular noncompaction has also been reported in athletes, healthy controls, and pregnant women, and it is more frequent in Black individuals.

CLINICAL MANIFESTATIONS AND DIAGNOSIS

When extensive areas are involved, ventricular systolic performance may be impaired and lead to an increased risk of ventricular arrhythmias and systemic emboli. Various diagnostic imaging criteria have been proposed, with MRI (Fig. 47-9) being more sensitive than echocardiography, Excessive trabeculation can be seen in isolation or in association with congenital heart anomalies, cardiomyopathies, and even in physiologic conditions such as pregnancy and highly trained athletes. As a result, extreme caution is needed when diagnosing left ventricular noncompaction, particularly in situations in which physiologic remodeling of the ventricle results in prominent ventricular trabeculae.

TREATMENT AND PROGNOSIS

Treatment, when necessary, is for associated heart failure (Chapter 46), arrhythmias (Chapters 50 and 53), and the risk of emboli (Chapter 70). Natural history and prognosis are not well-established.

TAKOTSUBO SYNDROME

Takotsubo syndrome causes transient left ventricular apical dysfunction that mimics myocardial infarction (Chapter 58).[31] About 90% of affected patients are women, especially postmenopausal women.

Catecholamines play a central role in the pathobiology, with acute episodes often triggered by sudden, unexpected stress or major physical illness or trauma. Many patients have abnormalities in both the structure and activity of brain areas that are related to both emotions and the sympathetic nervous system. Microvascular dysfunction and abnormal vasomotor reactivity are common findings, but it is not clear if these findings are the cause or consequence of an acute episode. Myocardial inflammation, which occurs during the acute phase, may persist in the chronic phase and may contribute to long-term morbidity.

CLINICAL PRESENTATION AND DIAGNOSIS

About 35% of events are triggered by emotional events and about 30% of events are triggered by physical events, with no obvious triggers in the remainder of

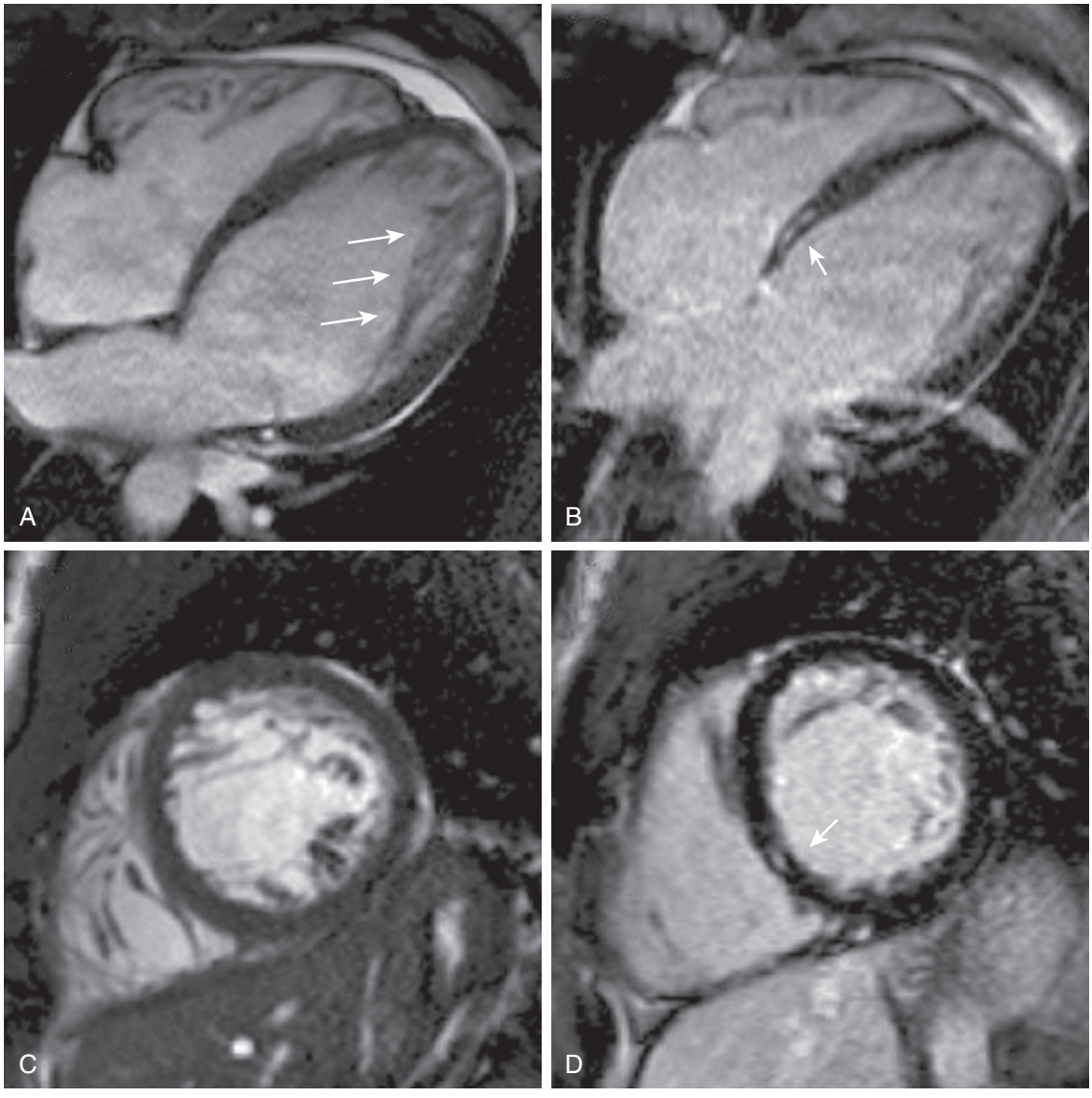

FIGURE 47-9. A 23-year-old White man with left ventricular noncompaction. Four-chamber end-diastolic (**A**) and short axis (**C**) views show left ventricular dilation, prominent trabeculae (*long arrows*), and poorly formed papillary muscles. The ejection fraction was 55%. There is limited mid-myocardial septal late gadolinium enhancement (**B, D**, *short arrows*).

patients. The clinical presentation is usually similar to acute myocardial infarction (Chapter 58), with chest pain, dyspnea, ST-segment elevation or depression, and T-wave inversion on the resting ECG, as well as elevation of serum cardiac troponin levels. Coronary arteriography, which reveals normal epicardial vessels, differentiates Takotsubo syndrome from acute myocardial infarction.

TREATMENT

Conservative treatment with rehydration and removal of the determinants of stress usually results in resolution of the symptoms, ECG changes, and wall motion abnormalities within hours.[32] Patients with left ventricular systolic dysfunction (ejection fraction <40%) should be treated with angiotensin-converting enzyme inhibitors and β-blockers, as in patients who have had an ST elevation myocardial infarction (Chapter 58). Patients may be weaned from both medications once left ventricular function has recovered if patients have no other complications such as tachyarrhythmias or hypertension.

PROGNOSIS

Takotsubo syndrome has a 4 to 5% in-hospital mortality related to cardiogenic shock and cardiac arrest. Survivors may experience long-term cardiac and noncardiac health problems, with an increased long-term mortality.

DISEASES OF THE ENDOCARDIUM

Endocardial fibrosis, fibroelastosis, and thrombosis are subclassified into endomyocardial diseases with hypereosinophilia (hypereosinophilic syndromes) and endomyocardial disease without hypereosinophilia (e.g., endomyocardial fibrosis) (see Table 47-7).

HYPEREOSINOPHILIC SYNDROME

Hypereosinophilic syndromes are a rare and heterogeneous group of disorders defined as persistent blood eosinophilia ($>1.5 \times 10^9$/L) for more than 6 consecutive months, associated with evidence of eosinophil-induced organ damage in the absence of causes of hypereosinophilia, such as allergic drug reactions, parasitic, and malignant disorders (Chapter 156). Pathogenic mechanisms include stem cell mutations that lead to expression of PDGFRA-containing fusion genes, mainly the *FIP1L1-PDGFRA* fusion gene, with constitutive tyrosine kinase activity and sustained overproduction of interleukin-5 by activated T-cell subsets. Clinically, hypereosinophilic syndrome can be classified into chronic eosinophilic leukemia, lymphocytic hypereosinophilic syndrome, myeloproliferative hypereosinophilic syndrome, and idiopathic hypereosinophilic syndrome. The term organ-restricted eosinophilic disease, such as eosinophilic gastroenteritis, dermatitis, or pneumonia, is used when a specific organ or tissue is the exclusive target of eosinophilic infiltration and damage. The term Löffler fibroplastic endocarditis with eosinophilia has been used to describe cardiac damage caused by direct toxicity of circulating eosinophils in patients with persistent hypereosinophilia, but its use is now discouraged.

CLINICAL MANIFESTATIONS AND DIAGNOSIS

Hypereosinophilic syndrome is a rare disorder that tends to occur in patients 20 to 50 years of age, but all age groups are affected. Cardiac involvement generally evolves in three phases: an early necrotic stage that involves the

endomyocardium, which is usually asymptomatic but can be manifested as acute heart failure; a thrombotic stage, in which thrombi develop on the ventricular endocardium, sometimes causing peripheral emboli; and the final fibrotic stage, endomyocardial fibrosis, which causes restrictive cardiomyopathy and damage to atrioventricular valves.[33] Chest pain, cough, dyspnea or orthopnea, and edema of the lower extremities are typical symptoms. Some patients may develop arrhythmias.

The characteristic two-dimensional echocardiographic findings include endocardial thickening, apical obliteration of one or both ventricles by an echogenic material, hyperdynamic contraction of the spared ventricular walls with bilateral atrial enlargement, and a restrictive pattern on echo Doppler. Endomyocardial biopsy, which should be considered when myocardial involvement is suspected and which remains the gold standard for diagnosis, shows eosinophils and/or their granular products in cardiac tissue.

TREATMENT

Patients should be treated as for the hypereosinophilic syndrome (Chapter 156). Heart failure (Chapter 46) and cardiac arrhythmias (Chapter 52 and 53) should be managed in accordance with consensus guidelines. Chronic oral anticoagulation (Chapter 70) is indicated in patients who have an intracavitary thrombus and/or recurrent thromboembolic events.

TROPICAL ENDOMYOCARDIAL FIBROSIS

Tropical endomyocardial fibrosis is probably the most common type of restrictive cardiomyopathy worldwide.[34] The disease occurs predominantly within the tropics and affects mostly children and adolescents, usually from low socioeconomic backgrounds. Its cause is unknown, but potential contributors include infection, autoimmunity, genetic predisposition, ethnicity, diet, climate, and poverty.

Severe hypereosinophilia is found in some patients early in the initial stage of the illness; it is characterized by febrile illness, pancarditis, facial and periorbital swelling, pruritus, urticaria, and neurologic symptoms. This phase is followed by ventricular thrombosis that affects the apices and the subvalvular apparatus and then evolves to endocardial fibrosis. The final stage is characterized by restrictive physiology, atrioventricular valve regurgitation, and marked atrial dilation. Death results from complications of chronic heart failure but can occur suddenly from thromboembolism or arrhythmia.

Atrial fibrillation is common at presentation. In advanced disease, the electrocardiogram shows low-voltage QRS complexes, nonspecific ST-T wave changes, and conduction abnormalities. Echocardiography demonstrates apical obliteration, reduction of ventricular cavity size, and tethering or retraction of mitral or tricuspid leaflets or both. There is no specific laboratory test, and hypereosinophilia is present only early in the disease.

There is no specific treatment for endomyocardial fibrosis. Medical treatment is used to control the heart failure (Chapter 46) and arrhythmias (Chapters 52 and 53). Surgical endocardial resection, combined with valve repair or replacement, has an early postoperative mortality between 15 and 30%. The overall prognosis is poor, with about a 45% mortality rate at 1 year, increasing to nearly 90% at 3 years.

CARCINOID SYNDROME

EPIDEMIOLOGY AND PATHOBIOLOGY

Carcinoid tumors are rare (1 in 100,000) neuroendocrine malignant neoplasms originating mostly from enterochromaffin cells in the gastrointestinal tract (Chapter 213). Carcinoid syndrome, with flushing, diarrhea, and bronchospasm, occurs after tumor cells metastasize to the liver and the vasoactive substances produced by the tumors enter the systemic circulation through the hepatic vein. Carcinoid heart disease occurs in up to 70% of cases of carcinoid syndrome.

The typical cardiac lesion is the carcinoid plaque, which is composed of smooth muscle cells, myofibroblasts, and elastic tissue that forms a fibrous layer on the endocardial surface of the right ventricle and atrium, the valve leaflets, and the subvalvular apparatus, including the chordae and papillary muscles. The tricuspid valve plaques tend to develop on the ventricular side of the leaflets, where they adhere to the mural endocardium and cause valvular regurgitation. On the pulmonary valve, the predominant lesion is stenosis. In patients with a patent foramen ovale, left-sided valvular involvement can occur. Occasional patients may have concomitant myocardial metastases and pericardial effusions from direct tumor invasion.

The most common presentation is dyspnea with signs and symptoms of right-sided heart failure. The electrocardiogram and radiograph are nonspecific. Echocardiography shows thickening of the tricuspid valve, the subvalvular apparatus, and the pulmonary valve. In severe disease, the tricuspid leaflets are retracted and fixed, with loss of normal coaptation. Similar findings can be seen on cardiac magnetic resonance imaging.

TREATMENT AND PROGNOSIS

Treatment of the underlying carcinoid with a somatostatin analogue can improve systemic symptoms (Chapter 213).[35] Valve replacement now has an operative mortality of less than 10% (Chapter 213). Without treatment, patients with carcinoid heart disease have a mean life expectancy of 1.6 years, but cardiac surgery for valve disease is associated with a better outcome.[36]

NONBACTERIAL THROMBOTIC (MARANTIC) ENDOCARDITIS

EPIDEMIOLOGY AND PATHOBIOLOGY

Platelet-fiber masses that are adherent to the mitral or aortic valves are seen in about 20% of patients with malignant tumors, especially mucin-producing adenocarcinomas, melanomas, leukemias, and lymphomas. The lesions are sterile, commonly verruciform, and without accompanying inflammation.

CLINICAL MANIFESTATIONS AND DIAGNOSIS

Nonbacterial thrombotic endocarditis is virtually always asymptomatic but occasionally is a source of systemic emboli. Because of the small size of many of the emboli, the first presentation is often with cerebral symptoms. Larger lesions are detectable by echocardiography, but even transesophageal echocardiography is not sufficiently sensitive to identify lesions that may be found at autopsy and that may have been the source of systemic emboli.

TREATMENT

No treatment has been proved efficacious. However, systemic anticoagulation similar to that used in patients with tumor-associated deep venous thrombosis is often tried (Chapters 68 and 157).

CARDIAC TUMORS

Cardiac tumors can involve any part of the heart (Fig. 47-10).

MYOCARDIAL TUMORS

Most primary cardiac tumors (Table 47-8) are benign. However, all tumors that extend from other tissues into the heart are malignant, as are metastatic lesions.[37]

EPIDEMIOLOGY AND PATHOBIOLOGY

Primary tumors of the heart are unusual, with a prevalence of 1 in 2000 to 1 in 4000 in autopsy series. Nearly all these primary tumors are benign myxomas, although fibromas, lipomas, and fibroelastomas also occur. Rhabdomyomas are seen in children, especially with tuberous sclerosis (Chapter 385). The rare primary malignant tumors include sarcomas, especially angiosarcomas (see Table 47-8). Rarely, a primary mesothelioma or lymphoma may originate in the heart.

Up to 20% of advanced cancers may involve the pericardium, epicardium, or cardiac chambers either by direct extension of the primary tumor or by metastatic disease. Direct extension occurs principally from cancers of the lung, breast, esophagus, and mediastinum. Extension through the inferior vena cava to the right atrium and even to the right ventricle occurs with cancers of the kidney, adrenal gland, and liver. Metastatic spread is most common with melanomas or lymphomas.

PERICARDIAL TUMORS

CLINICAL MANIFESTATIONS

Pericardial tumors almost always result from direct extension of tumors, principally lung and breast, which produce a pericardial effusion that can progress to cardiac tamponade (Chapter 62). Patients typically are asymptomatic or minimally symptomatic in terms of the cardiac involvement until the effusion is large, although they often may be very ill because of progressive tumor elsewhere.

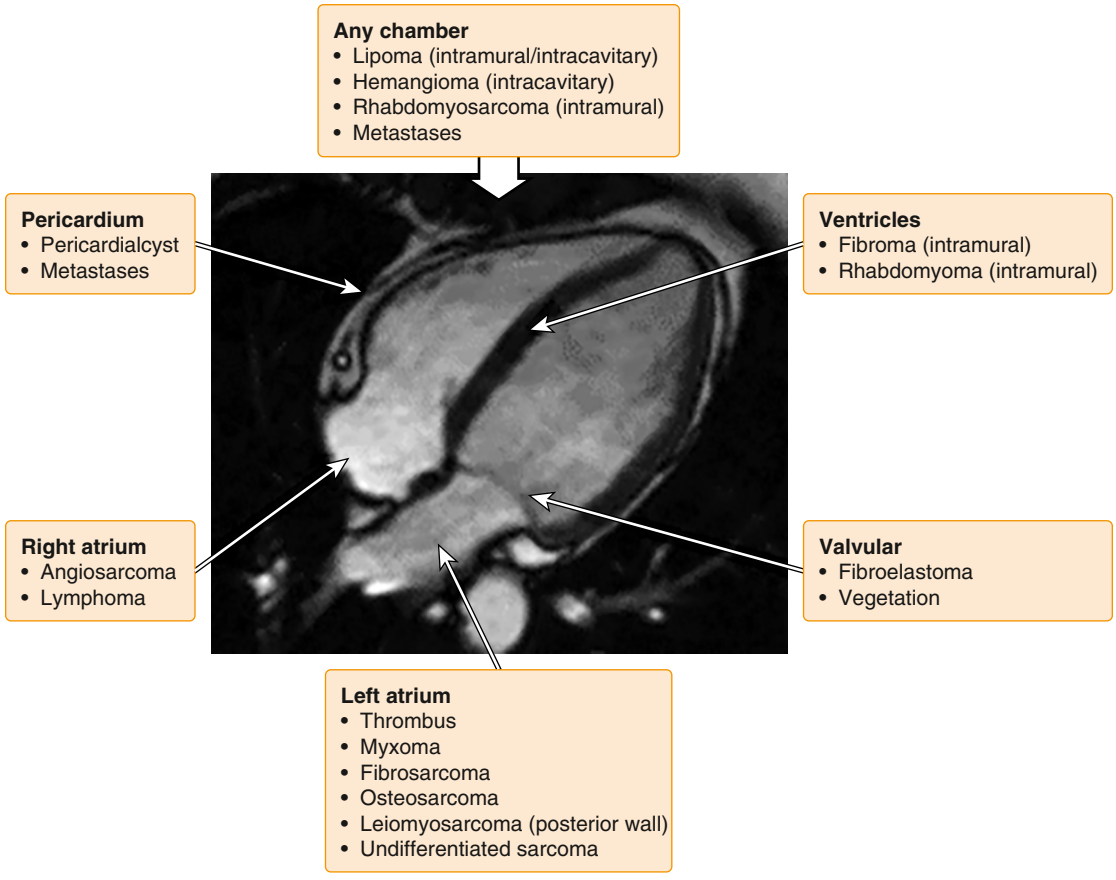

FIGURE 47-10. The typical locations of the most common cardiac tumors. Note, however, that the location of the various conditions can vary, and many cardiac tumors can occur in any chamber. (From Motwani M, Kidambi A, Herzog BA, et al. MR imaging of cardiac tumors and masses: a review of methods and clinical applications. *Radiology*. 2013;268:26-43.)

TABLE 47-8 CARDIAC TUMORS

PRIMARY
Benign
Myxoma
Lipoma
Fibroma
Rhabdomyoma
Fibroelastoma
Malignant
Sarcoma
Mesothelioma
Lymphoma
SECONDARY
Direct Extension
Lung cancer
Breast cancer
Mediastinal tumors
Metastatic Tumors
Malignant melanoma
Leukemia
Lymphoma
Venous Extension
Renal cell cancer
Adrenal cancer
Liver cancer

DIAGNOSIS

The diagnosis is often suspected in a patient with advanced malignant disease on the basis of evidence of heart failure, hypertension, or arrhythmia and is confirmed by echocardiography. The differentiation between pericardial involvement by tumor and postradiation pericarditis depends on pericardiocentesis, often guided by echocardiography, and cytologic examination.

TREATMENT

Cardiac tamponade must be treated with urgent pericardiocentesis, preferably under echocardiographic or radiologic guidance (Chapter 62). Although such a procedure can be life-saving and provide short-term to intermediate-term palliation, control of the effusion often requires prolonged drainage, administration of intrapericardial chemotherapeutic agents, or limited or full pericardiectomy (Chapter 62). Some patients with pericardial tumors may respond to aggressive systemic chemotherapy, but recurrent accumulation of fluid is sufficiently likely that creation of a pericardial window should be considered before hospital discharge.

PROGNOSIS

In many cases, a tumor that is causing pericarditis has extended or will eventually extend through the pericardial space and into the myocardium, so no therapy is likely to be successful. The prognosis is very poor, except in unusual cases in which the tumor responds dramatically to systemic therapy.

INTRACAVITARY TUMORS

MYXOMA

DEFINITION AND EPIDEMIOLOGY

A myxoma is a benign polypoid neoplasm that originates from endocardial cells and is attached to the interatrial septum, usually protruding into the left atrium but occasionally into the right atrium and rarely into the ventricles. Myxomas are more common in women, especially between the ages of 30 and 60 years, than in men. These tumors can be familial and are rarely associated with other systemic abnormalities.

CLINICAL MANIFESTATIONS

Myxomas are slow growing and usually do not produce symptoms or signs until they enlarge. The typical presentation is with a tumor embolus, whereby usually small portions of the myxoma break loose and cause a single embolism or a shower of emboli. However, a large embolism from a

myxoma can be of sufficient size to obstruct a medium-sized artery. Some patients have systemic symptoms, including fever, malaise, and arthralgias, as part of a clinical syndrome that may be confused with bacterial endocarditis (Chapter 61) or a collagen vascular disease. Large myxomas can prolapse into the mitral valve orifice during diastole, or they may obstruct blood flow from the left atrium to the left ventricle and mimic rheumatic mitral stenosis.

DIAGNOSIS

A myxoma large enough to obstruct the mitral orifice can produce an audible "tumor plop" when the myxoma prolapses and obstructs blood flow during diastole, at the same time that the opening snap of mitral stenosis would typically be heard. If obstruction is incomplete, the tumor plop may be followed by a diastolic rumble. As obstruction becomes more severe, cardiac output may fall precipitously. Echocardiography (Chapter 43) is usually definitive; transesophageal echocardiography provides a higher sensitivity than does transthoracic echocardiography, and magnetic resonance imaging can be helpful.

TREATMENT

Surgical removal is generally curative, although myxomas can be multiple or recur in about 5% of cases. Follow-up postoperative echocardiography is generally recommended. However, the optimal frequency and duration for follow-up screening are uncertain.

OTHER PRIMARY INTRACAVITARY TUMORS

Papillary fibroelastomas are rare, typically frondlike tumors that may arise from a cardiac valve, often the mitral valve, and are generally detected incidentally by echocardiography. However, like myxomas, they can be manifested with systemic or even coronary emboli. Surgical excision is usually successful.

Angiosarcomas, which are more frequent in men than in women, typically involve the pericardium and right atrium. They cause obstruction with clinical signs and symptoms of right-sided heart failure. These sarcomas are generally not amenable to therapy.

EXTENSION OF TUMOR INTO THE CARDIAC CAVITIES

Direct extension of tumor up the inferior vena cava into the right atrium can be seen with renal cell carcinomas and less commonly with liver and adrenal cancers. In some cases, tumor extension is accompanied by adherent clot, and either the tumor or the clot may cause obstruction or pulmonary emboli (Chapter 68). No treatments are generally successful, and the prognosis is grim.

INTRAMYOCARDIAL TUMORS

Primary malignant intracardiac tumors are rare, with an incidence rate of about 35 per 100 million. The most common tumors are sarcomas (Chapter 187), lymphomas (Chapters 171 and 172), and mesotheliomas (Chapters 86 and 177). Current overall survival rates for these tumors at 5 years are about 10%, 35%, and 25%, respectively.

Benign tumors in the myocardium include lipomas, fibromas, and rhabdomyomas. Primary malignant tumors include sarcomas, lymphomas, and mesotheliomas. Metastatic tumors include melanomas, lymphomas, and leukemias. The tumors may be clinically silent, or they may produce arrhythmias or even impinge on coronary arteries, thereby causing ischemic syndromes. Large tumors may protrude into the cardiac chamber and cause obstruction. Therapies are not successful, except for occasional patients whose metastatic tumors may respond to systemic chemotherapy or whose primary tumors have been cured by heart transplantation.

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48 PRINCIPLES OF ELECTROPHYSIOLOGY

GLENN I. FISHMAN

The rhythmic beating of the heart reflects the tightly regulated and exquisitely integrated activity of numerous protein complexes that control the flow of ions across cell membranes, including channels, transporters, exchangers, and gap junction channels.[1] The human heart beats almost 3 billion times during a normal lifespan, and even brief periods of dysfunction may lead to life-threatening consequences. Thus, the failure rate of cardiac rhythmicity is exceptionally low. Nonetheless, inherited syndromes, as well as acquired heart disease, may affect cardiac rhythmicity, and these disorders lead to substantial morbidity and mortality, including sudden cardiac death (Chapter 50). This chapter reviews the molecular, cellular, and organ-level determinants of cardiac rhythmicity and relates these principles to fundamental mechanisms responsible for clinically important arrhythmias.

BASIC CONCEPTS

The function of the heart as a highly dynamic pump is intricately entwined with the tightly regulated electrical activation of its constituent cardiomyocytes. During each cardiac cycle, an electrical impulse known as an *action potential* is spontaneously generated by a relatively small number of pacemaker cells in the sinoatrial node, which is located at the junction of the right atrium and the superior vena cava. The impulse then propagates through the right and left atrium, which is represented by the P wave on the electrocardiogram (ECG; Chapter 42). After depolarizing the atria, the impulse enters the atrioventricular (AV) node, which is located in the inferior septal region of the right atrium, where a delay occurs. This delay allows time for the atria to contract and fill the ventricles. The delay in the AV node represents most of the isoelectric portion of the PR interval on the ECG (Fig. 42-2). The usual duration of atrial activation, including delay in the AV node, is up to 140 msec and can be measured directly as the atrial-His interval. The impulse then travels into the specialized infranodal conducting system, which is composed of the His bundle, right and left bundle branches, and Purkinje network. The Purkinje network, which extends throughout the ventricular endocardium, rapidly conducts impulses, thereby allowing nearly simultaneous activation of the ventricles. Once out of the Purkinje network, the impulse proceeds relatively slowly from the endocardial to epicardial surface of the ventricles.

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myxoma can be of sufficient size to obstruct a medium-sized artery. Some patients have systemic symptoms, including fever, malaise, and arthralgias, as part of a clinical syndrome that may be confused with bacterial endocarditis (Chapter 61) or a collagen vascular disease. Large myxomas can prolapse into the mitral valve orifice during diastole, or they may obstruct blood flow from the left atrium to the left ventricle and mimic rheumatic mitral stenosis.

DIAGNOSIS

A myxoma large enough to obstruct the mitral orifice can produce an audible "tumor plop" when the myxoma prolapses and obstructs blood flow during diastole, at the same time that the opening snap of mitral stenosis would typically be heard. If obstruction is incomplete, the tumor plop may be followed by a diastolic rumble. As obstruction becomes more severe, cardiac output may fall precipitously. Echocardiography (Chapter 43) is usually definitive; transesophageal echocardiography provides a higher sensitivity than does transthoracic echocardiography, and magnetic resonance imaging can be helpful.

TREATMENT

Surgical removal is generally curative, although myxomas can be multiple or recur in about 5% of cases. Follow-up postoperative echocardiography is generally recommended. However, the optimal frequency and duration for follow-up screening are uncertain.

OTHER PRIMARY INTRACAVITARY TUMORS

Papillary fibroelastomas are rare, typically frondlike tumors that may arise from a cardiac valve, often the mitral valve, and are generally detected incidentally by echocardiography. However, like myxomas, they can be manifested with systemic or even coronary emboli. Surgical excision is usually successful.

Angiosarcomas, which are more frequent in men than in women, typically involve the pericardium and right atrium. They cause obstruction with clinical signs and symptoms of right-sided heart failure. These sarcomas are generally not amenable to therapy.

EXTENSION OF TUMOR INTO THE CARDIAC CAVITIES

Direct extension of tumor up the inferior vena cava into the right atrium can be seen with renal cell carcinomas and less commonly with liver and adrenal cancers. In some cases, tumor extension is accompanied by adherent clot, and either the tumor or the clot may cause obstruction or pulmonary emboli (Chapter 68). No treatments are generally successful, and the prognosis is grim.

INTRAMYOCARDIAL TUMORS

Primary malignant intracardiac tumors are rare, with an incidence rate of about 35 per 100 million. The most common tumors are sarcomas (Chapter 187), lymphomas (Chapters 171 and 172), and mesotheliomas (Chapters 86 and 177). Current overall survival rates for these tumors at 5 years are about 10%, 35%, and 25%, respectively.

Benign tumors in the myocardium include lipomas, fibromas, and rhabdomyomas. Primary malignant tumors include sarcomas, lymphomas, and mesotheliomas. Metastatic tumors include melanomas, lymphomas, and leukemias. The tumors may be clinically silent, or they may produce arrhythmias or even impinge on coronary arteries, thereby causing ischemic syndromes. Large tumors may protrude into the cardiac chamber and cause obstruction. Therapies are not successful, except for occasional patients whose metastatic tumors may respond to systemic chemotherapy or whose primary tumors have been cured by heart transplantation.

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48 PRINCIPLES OF ELECTROPHYSIOLOGY

GLENN I. FISHMAN

The rhythmic beating of the heart reflects the tightly regulated and exquisitely integrated activity of numerous protein complexes that control the flow of ions across cell membranes, including channels, transporters, exchangers, and gap junction channels.[1] The human heart beats almost 3 billion times during a normal lifespan, and even brief periods of dysfunction may lead to life-threatening consequences. Thus, the failure rate of cardiac rhythmicity is exceptionally low. Nonetheless, inherited syndromes, as well as acquired heart disease, may affect cardiac rhythmicity, and these disorders lead to substantial morbidity and mortality, including sudden cardiac death (Chapter 50). This chapter reviews the molecular, cellular, and organ-level determinants of cardiac rhythmicity and relates these principles to fundamental mechanisms responsible for clinically important arrhythmias.

BASIC CONCEPTS

The function of the heart as a highly dynamic pump is intricately entwined with the tightly regulated electrical activation of its constituent cardiomyocytes. During each cardiac cycle, an electrical impulse known as an *action potential* is spontaneously generated by a relatively small number of pacemaker cells in the sinoatrial node, which is located at the junction of the right atrium and the superior vena cava. The impulse then propagates through the right and left atrium, which is represented by the P wave on the electrocardiogram (ECG; Chapter 42). After depolarizing the atria, the impulse enters the atrioventricular (AV) node, which is located in the inferior septal region of the right atrium, where a delay occurs. This delay allows time for the atria to contract and fill the ventricles. The delay in the AV node represents most of the isoelectric portion of the PR interval on the ECG (Fig. 42-2). The usual duration of atrial activation, including delay in the AV node, is up to 140 msec and can be measured directly as the atrial-His interval. The impulse then travels into the specialized infranodal conducting system, which is composed of the His bundle, right and left bundle branches, and Purkinje network. The Purkinje network, which extends throughout the ventricular endocardium, rapidly conducts impulses, thereby allowing nearly simultaneous activation of the ventricles. Once out of the Purkinje network, the impulse proceeds relatively slowly from the endocardial to epicardial surface of the ventricles.

ABSTRACT

The rhythmic beating of the heart reflects the tightly regulated and exquisitely integrated activity of numerous protein complexes that control the flow of ions across cell membranes, including channels, transporters, exchangers, and gap junction channels. The human heart beats almost 3 billion times during a normal lifespan, and even brief periods of dysfunction may lead to life-threatening consequences. Thus, the failure rate of cardiac rhythmicity is exceptionally low. Nonetheless, inherited syndromes, as well as acquired heart disease, may affect cardiac rhythmicity, and these disorders lead to substantial morbidity and mortality, including sudden cardiac death (Chapter 50). This chapter reviews the molecular, cellular, and organ-level determinants of cardiac rhythmicity and relates these principles to fundamental mechanisms responsible for clinically important arrhythmias.

KEYWORDS

cardiac electrophysiology
ion channel
action potential
impulse propagation
arrhythmia
conduction

The QRS complex on ECG represents depolarization of the bundle branches and ventricular myocardium.

Subpopulations of myocytes within the heart have unique electrical properties that reflect regional specialization. Myocytes within the sinoatrial and AV nodes produce spontaneous action potentials that reflect their pacemaking function. Cells within the His-Purkinje network are optimized to rapidly deliver excitatory current to the large mass of ventricular myocardium, whereas ventricular myocytes display action potentials optimized to facilitate excitation-contraction coupling, that is, to trigger the release of calcium ions from the sarcoplasmic reticulum and to promote the actomyosin cross-bridge formation that underlies cardiac contraction (Chapter 41). Abnormalities in cardiac electrophysiology, whether the result of mendelian disorders, oligogenic syndromes, or environmental stressors that evoke acquired heart disease, can lead to disturbances in the initiation, propagation, or conduction of electrical impulses and, as a result, to a wide variety of arrhythmic syndromes.

IONIC BASIS OF CARDIAC ELECTROPHYSIOLOGY

THE CARDIAC ACTION POTENTIAL

The cardiac action potential (Fig. 48-1) is a recording of a cell's membrane potential, V_m, versus time. During each cardiac cycle, ions move back and forth across the cardiomyocyte cell membrane, thereby changing V_m. The cardiac action potential, which reflects the integrated behavior of numerous individual ionic currents, is largely dominated by the movement of Na^+, Ca^{2+}, and K^+ ions. These ions traverse the cell membrane through ion-selective pores formed by assemblies of integral membrane-spanning proteins and accessory proteins. The behavior of these ionic pathways is highly regulated, and permeation of specific ions is influenced by multiple factors, the most prominent of which are changes in membrane potential (i.e., voltage gating), ligand binding, second messengers such as cyclic adenosine monophosphate, and post-translational modification. Channel function and, by extension, action potential behavior are dynamically tuned in response to normal physiologic factors, especially heart rate. However, a number of pathologic stressors influence channel activity, including acquired syndromes that are associated with cardiac hypertrophy and failure, as well as an ever-growing number of congenital diseases. Regardless of the underlying pathology, the effects on action potential behavior may trigger arrhythmic activity.

The cardiac action potential is divided into phases, each reflecting the major ionic movements that take place. In working cardiomyocytes, such as ventricular or atrial myocytes, the *resting membrane potential* during diastole, or phase 4 of the cardiac action potential, is determined by the baseline ionic and charge gradients that exist across the sarcolemmal membrane. These gradients are generated by pumps and transporters, the most important of which is the Na^+, K^+-ATPase. This energy-requiring electrogenic pump, which is the major target of ouabain-like compounds such as digoxin, extrudes three Na^+ ions from the intracellular compartment in exchange for two K^+ ions, thereby resulting in directionally opposite gradients of Na^+ ions (outside > inside) and K^+ ions (inside > outside). Under resting conditions, a subset of membrane channels highly permeable to K^+ is open, but those that allow for the passage of other ions such as Na^+ or Ca^{2+} are only minimally permeable. As a consequence, the concentration gradient promotes the movement of potassium ions from inside to outside of the cell, until the resulting excess of negative charge within the cell balances the diffusional forces and an electrochemical equilibrium is established. The equilibrium potential for a given ion is calculated by the *Nernst equation*, where E_{eq} is the equilibrium potential, R is the universal gas constant, T is the absolute temperature, z is the valence of the ionic species, and F is Faraday constant:

$$E_{eq} = \frac{RT}{zF} ln\left(\frac{[X]_{out}}{[X]_{in}}\right)$$

If the cell membrane were *only* permeable to K^+ ions, at the measured concentrations of intracellular and extracellular K^+, the resting membrane potential would be approximately −100 mV. However, because of the slight but measurable permeability to other ionic species, which have Nernst potentials that are less negative than that for K^+, the actual resting membrane potential in a typical ventricular cardiac myocyte is closer to −85 mV.

When the cardiac cell is depolarized to its excitatory threshold, an action potential is triggered through a series of highly regulated time-dependent changes in ionic conductances (see Fig. 48-1B). The fast sodium current is activated and very rapidly depolarizes the membrane during phase 0 of the

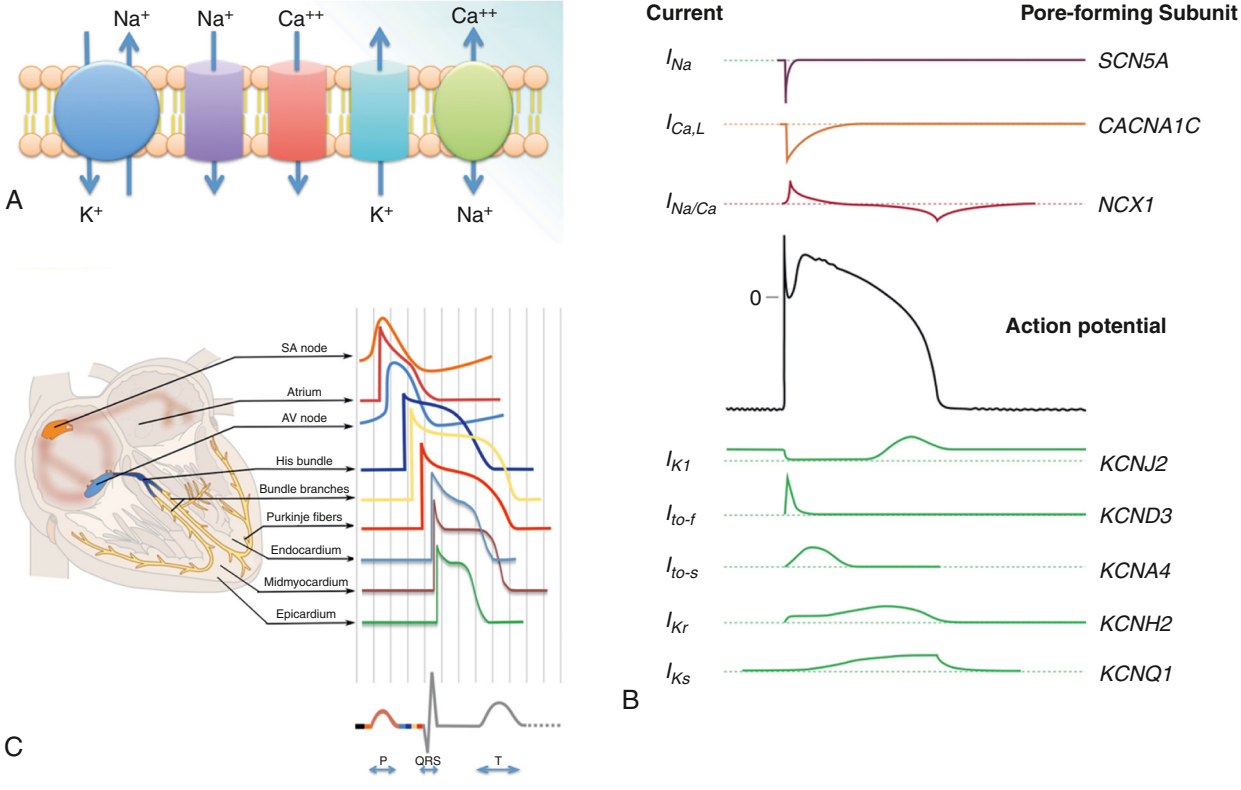

FIGURE 48-1. Ion channels and the cardiac action potential. A, Key channels involved in cardiac excitability and generation of the cardiac action potential. Inward currents are carried by Na^+ channels *(purple)* and Ca^{2+} channels *(red)*. Repolarizing currents are primarily carried by K^+ channels *(blue)*. The Na^+/K^+ ATPase is an energy-requiring exchanger that pumps Na^+ out of the cell in exchange for K^+ and is essential for establishing resting ionic gradients and the resting membrane potential. **B,** Time course and relative magnitude of ionic currents active during the cardiac action potential. Inward currents are represented by downward deflections and outward currents by upward deflections. **C,** Action potentials from different regions of the heart and their relationship to the surface electrocardiogram are indicated. (Adapted from Marbán E. Cardiac channelopathies. *Nature*. 2002;415:213-218.)

action potential. The sodium current is inactivated at the peak of depolarization, which is approximately +40 mV. The increase in V_m during phase 0 activates several additional voltage-gated currents. A transient outward potassium current, or I_{to}, partially *re*polarizes the cell, thereby producing a small notch in the action potential, denoted as phase 1. The increase in V_m during phase 0 also activates, albeit more slowly, the inward L-type calcium current, $I_{Ca\text{-}L}$. It is this trigger for Ca^{2+} that is responsible for Ca^{2+}-induced release from the sarcoplasmic reticulum and is integral to the process of excitation-contraction coupling (Chapter 41). The inward Ca^{2+} current is balanced by several outward repolarizing currents, including the rapid component of the delayed rectifier potassium current I_{Kr}, the slow component of the delayed rectifier potassium current I_{Ks}, and the electrogenic Na^+-Ca^{2+} exchanger, thereby resulting in a plateau in the action potential known as phase 2. When the outward potassium currents increase and the calcium current decreases at the end of phase 2, the action potential progresses to phase 3, which is the phase of rapid repolarization. The inward rectifier potassium current I_{K1} contributes significantly to this final phase of repolarization and brings the action potential back to its resting membrane potential, or phase 4, at which point the cell is primed for another action potential.

Action potential recordings from atrial cardiomyocytes and from cells of the His-Purkinje system are qualitatively similar to those described previously, but with some notable differences that primarily reflect the differential expression of repolarizing potassium currents that tend to abbreviate (in the case of atrial cells) or lengthen (for Purkinje cells) the action potential duration (see Fig. 48-1C).

The relatively small populations of cells in the sinoatrial node (SAN) and atrioventricular node (AVN) express unique complements of ionic currents that are responsible for spontaneous depolarization during phase 4 and the triggering of action potentials. Pacemaker cells express substantially less I_{K1} compared with ventricular myocytes, and as a consequence, their minimum V_m is −65 mV, and they do not repolarize to the same extent as working ventricular cardiomyocytes. In addition, pacemaker cells display what is known as the funny current, I_f, which is activated by *hyper*polarization and carried by sodium. Activation of I_f during phase 4 slowly depolarizes the cell membrane. In addition, a subsarcolemmal calcium clock contributes to diastolic depolarization through the spontaneous, rhythmic release of Ca^{2+} from the sarcoplasmic reticulum, a process that is linked to the voltage clock through the activity of the sodium-calcium exchange current, I_{NCX}. Inasmuch as there is minimal fast inward I_{Na} expressed in nodal cells, the action potential triggered by this spontaneous phase 4 depolarization is due to activation of calcium currents carried by $I_{Ca,L}$ and $I_{Ca,T}$. The magnitude of I_f and I_{Ca}, and hence the slope of phase 4 depolarization as well as the upstroke velocity of the action potential in pacemaker cells, is augmented by adrenergic stimulation, which produces a chronotropic response.

Owing to considerable regional heterogeneity in the density of individual ionic currents, even within distinct compartments of the heart such as the ventricular myocardium, not all ventricular action potentials are identical (see Fig. 48-1C). Much of this heterogeneity is due to differences in the magnitude of various repolarizing K^+ currents. For example, although electrotonic coupling through gap junction channels mitigates this intrinsic heterogeneity, action potentials recorded from epicardial, mid-myocardial, and endocardial cells show substantial differences in morphology, both at rest and especially in response to provocative stimuli such as changes in rate or pharmacologic agents. Moreover, action potential morphology is not static; it varies in response to changes in physiologic state. *Action potential duration adaptation*, which reflects the normal shortening of the action potential observed during increased heart rate, provides a mechanism to preserve adequate time for ventricular filling during diastole. Action potential duration shortening in this setting is due to a net increase in repolarizing currents, primarily from increased I_{Ks} and reverse-mode I_{NaCa}. This adaptation is regulated, at least in part, by the kinetics of activation and inactivation of the channels that are responsible for these currents, as well as their modulation by various signaling cascades, such as those regulated by the autonomic nervous system. However, maladaptive regulation of ionic currents is a frequent manifestation of acquired forms of heart disease, and this pathologic electrical remodeling may amplify intrinsic heterogeneities in cardiac electrophysiology and form a substrate that promotes arrhythmic behavior.

IMPULSE PROPAGATION

In the intact heart, action potentials not only must be generated but also must propagate from cell to cell as a wave of excitation throughout the atrial and ventricular myocardium. For successful propagation, the upstream excited cell must provide sufficient charge to bring the membrane potential, V_m, of downstream cells up to their excitation threshold potential. Gap junctions, which comprise arrays of intercellular channels, provide the structural basis for this electrotonic flow of current from cell to cell. For propagation to be successful, the ratio of the charge generated to charge consumed during the excitation cycle, known as the safety factor, must be greater than 1.

Unlike nerves, the action potential duration of human cardiomyocytes is quite long, on the order of 200 msec. This longer action potential duration is required so that each myocyte has sufficient time for contraction and relaxation before the next heartbeat. Impulses that arrive too early in the cardiac cycle will not produce normal action potentials. If the impulse occurs during the upstroke or plateau phase (phases 0 to 2), the sodium channels will not have had sufficient time to recover from fast inactivation, and the cell displays *absolute refractoriness*. If the impulse occurs somewhat later, during phase 3 of the action potential, a supranormal stimulus is required to overcome the potassium currents that remain active during the terminal portion of the action potential, a phenomenon known as *relative refractoriness*. Moreover, because not all of the sodium channels will have recovered from inactivation, the rate of rise of voltage during phase 0 of the premature beat may be diminished.

MOLECULAR BASIS OF CARDIAC ELECTROPHYSIOLOGY

The individual currents that are responsible for cardiac excitability reflect the integrated behavior of various protein complexes that are assembled into ion-specific channels, transporters, and exchangers.[2,3] At the molecular level, ion channels comprise multi-subunit glycoproteins, including a pore-forming major, or α-subunit, and one or several accessory proteins (E-Fig. 48-1). The latter influence a range of channel properties, including trafficking of the major subunit to the sarcolemmal membrane, as well as regulation of channel biophysical properties, that is, the opening and closing of the channel in response to various factors such as membrane voltage, ligands, mechanical stimuli, second messengers, or post-translational modification.

SODIUM CHANNELS

Voltage-gated sodium channels are responsible for the activation and propagation of the cardiac action potential. Not surprisingly, acquired and inherited syndromes that affect the function of voltage-gated sodium channels in the heart are responsible for a broad range of arrhythmic phenotypes. Cardiac sodium channels activate extremely rapidly, within 1 msec, and begin to inactivate almost completely within several milliseconds. The very small proportion of channels that remain active for several hundred milliseconds results in the persistent or late Na^+ current, I_{NaL}.

The most abundant cardiac sodium channel comprises a pore-forming α-subunit known as $Na_v1.5$ and several smaller accessory subunits, or β-subunits, designated $Na_v\beta1$ to 4. The α-subunit is an approximately 260-kD protein that consists of four homologous domains, each comprising six transmembrane segments.[4] Substantial experimental work has identified the key regions of the protein that regulate channel properties, including voltage dependence, activation, and inactivation, as well as the binding sites for pharmacologic agents such as local anesthetics, antiarrhythmic drugs, and neurotoxins. The β-subunits are single-membrane-spanning proteins that associate with $Na_v1.5$ through their extracellular immunoglobulin-fold domains. They serve to increase the delivery of the α-subunit to the sarcolemmal membrane and to influence channel function. The β-subunits also enhance the subcellular localization of the channel and its interactions with various adaptors, signaling molecules, and cytoskeletal proteins. In addition to $Na_v1.5$, several "neuronal" α-subunits are expressed at low levels in the heart and likely contribute to regional heterogeneity in sodium channel function. Mutations in $Na_v1.5$, in specific β-subunits, and in several interacting regulatory and scaffolding proteins all may influence the behavior of the sodium current in the heart and thereby produce a range of arrhythmic syndromes, including long QT syndrome type 3 (LQT3) and Brugada syndrome (Chapter 53).[5]

The I_f current contributes to phase 4 depolarization in pacemaker cells and is a reflection of the activity of hyperpolarization-activated cyclic nucleotide gated, or *HCN* channels. The full channels are composed of dimers of *HCN* proteins, each of which has six transmembrane domains. *HCN4* and *HCN1* are the predominant isoforms found in the nodes, whereas *HCN2* is found throughout the conduction system. Binding of cyclic adenosine monophosphate, a key second messenger in the adrenergic signaling cascade, to the carboxy terminus of the channel shifts activation positively, thereby

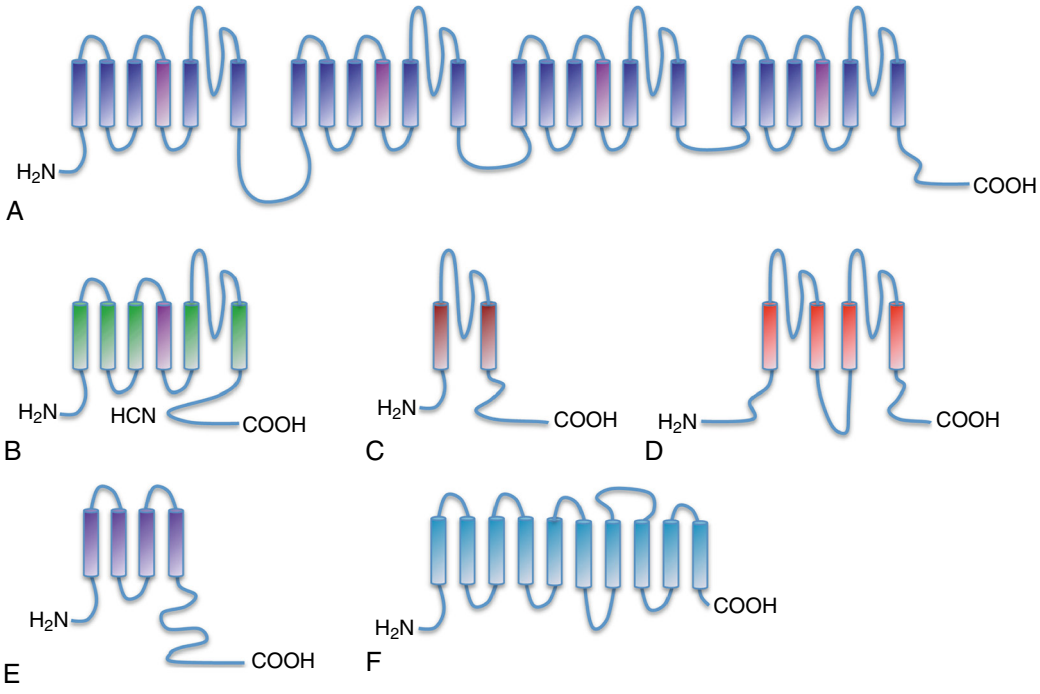

E-FIGURE 48-1. Structure of the pore-forming subunits of ion channels expressed in the heart. Individual barrels represent transmembrane domains. In all cases, the amino and carboxy-terminal domains reside within the cytoplasmic compartment. **A**, Voltage-gated sodium and calcium channels. **B**, Voltage-gated potassium channel. **C**, Inwardly rectifying potassium channel. **D**, Two-pore domain potassium channel. **E**, Gap junction channel. **F**, Sodium-potassium adenosine triphosphatase.

increasing the slope of phase 4 depolarization and linking autonomic tone to heart rate.

CALCIUM CHANNELS

Voltage-gated calcium channels are important for generating the action potential in the sinoatrial and atrioventricular nodes and for excitation-contraction coupling in virtually all contractile cardiomyocytes.[6] The dominant forms expressed in the heart are the L-type (large and long-lasting) and the T-type (tiny and transient) calcium channels, both of which include pore-forming α-subunits, similar in overall structure to that of voltage-gated sodium channels.

L-type Ca^{2+} channels comprise an α_1 subunit, a noncovalently bound β accessory subunit ($Ca_v\beta 1$-4), and an alternatively spliced α_2-δ-subunit that is post-translationally processed through cleavage and disulfide bond formation. The dominant α_1-subunit in the heart is $Ca_v1.2$, whereas $Ca_v1.3$ is restricted primarily to nodal and atrial cells. Both α_1-subunits are alternatively spliced to produce variants that are uniquely regulated.

The related T-type calcium channels are also found in the heart but display distinct biophysical properties compared with L-type Ca^{2+} channels; they activate at more negative voltages (−70 mV) and inactivate more rapidly. The major isoform expressed in the heart is $Ca_v3.1$ and, to a lesser extent, $Ca_v3.2$. These channels are normally restricted to the nodes, Purkinje cells, and atrial myocytes. In pacemaking cells, the T-type currents contribute to phase 4 depolarization. Mutations in Ca^{2+} channel subunits are also responsible for a number of arrhythmic syndromes, including Timothy syndrome (LQT8) and a subset of individuals with Brugada syndrome.

POTASSIUM CHANNELS

Numerous classes of potassium channels are expressed in the heart, where they contribute to repolarization and maintenance of the resting membrane potential.[7] The heterogeneous expression of potassium channels in different regions and cell types is largely responsible for the variable action potential morphologies that are observed. As with sodium and calcium channels, potassium channels are formed from the assembly of pore-forming subunits along with various accessory β-subunits. However, α-subunits of potassium channels include between two and six transmembrane domains, and the full channel is formed as a dimer or tetramer, depending on the specific subfamily. Dysregulation of expression and function of potassium channels is quite common in many acquired forms of heart disease. The resulting loss of repolarizing currents leads to action potential duration prolongation and acquired long QT syndrome. In addition, heritable mutations that diminish potassium currents are responsible for several forms of inherited long QT syndrome, whereas gain of function mutations may produce the short QT syndrome.

Voltage-gated potassium channels, or *Kv* channels, are activated by membrane depolarization. Numerous classes of *Kv* channels have been identified in the heart. The α-subunits are six transmembrane domain proteins. Unlike sodium and calcium channels, functional potassium channels are formed by the assembly of four such subunits and various β-subunits. The transient outward current is composed of two components, $I_{to,fast}$ and $I_{to,slow}$; both are rapidly activated and contribute to phase 1 of the cardiac action potential, but their recovery kinetics differ. $I_{to,fast}$ is particularly prominent in the epicardial layer of the ventricles, especially in the right ventricle. This differential expression is thought to contribute to the pathology of J wave syndromes, including Brugada syndrome.

The other major class of voltage-gated potassium channels in the heart is responsible for the delayed rectifier currents, broadly classified as I_K currents.[8] These channels include the ultra-rapidly activating I_{Kur}, which is restricted to atrial myocytes, and the delayed rectifier currents, I_{Kr} and I_{Ks}, both of which contribute to phase 3 repolarization of the cardiac action potential. I_{Kr} activates and inactivates rapidly and shows strong inward rectification; that is, current moves more easily (but not exclusively) in the inward direction than in the outward direction, although it is the outward current that is physiologically relevant. I_{Ks} activates slowly and does not display inward rectification. Both currents also show marked regional heterogeneity. Numerous cardiac and noncardiac medications, as well as heritable syndromes that reduce the magnitude of these currents (particularly I_{Kr}), result in action potential duration prolongation and acquired or heritable long QT syndrome.

The second major class of potassium currents in the heart are the *Kir* currents carried by inwardly rectifying potassium channels. I_{K1} is observed in both atrial and ventricular cardiomyocytes. Conductance through these channels is high at negative membrane potentials, so this current is critical for terminal repolarization (phase 3) and for setting the resting membrane potential (phase 4). Another inwardly rectifying potassium current is carried by I_{KATP} channels. The full channels include not only the pore-forming subunit but also auxiliary *SUR* subunits, which are targets for channel inhibition by the sulfonylurea class of drugs. Because I_{KATP} currents are inhibited by intracellular adenosine triphosphate, they are activated in the setting of ischemia. The augmented outward current shortens action potential duration and abbreviates systole, thereby diminishing energetic requirements. Thus I_{KATP} channels provide a link between metabolic state and membrane excitability. Importantly, the resulting action potential duration shortening diminishes refractoriness, which may enhance the risk for re-entrant arrhythmias. The last major class of inward rectifiers includes the acetylcholine- and adenosine-activated potassium channels, which are encoded by $K_{ir}3.1$ and $K_{ir}3.4$. These channels, which are enriched in nodal and atrial cardiac myocytes, are activated when ligands bind to muscarinic or purinergic G protein–coupled receptors, which facilitate the uncoupling of $G_{\beta\gamma}$ from G_α and the activation of the K_{ir} channels by the released $G_{\beta\gamma}$.

GAP JUNCTION CHANNELS

Gap junction channels, which are responsible for the electrotonic coupling of cardiac myocytes, are essential for normal impulse propagation throughout the myocardium. The channels are formed by the hexameric assembly of connexin monomers, each of which is a tetramembrane spanning protein. Connexin 43[9] is the dominant isoform expressed in ventricular and atrial myocardium, whereas connexin 40 is also abundantly expressed in the atrium. The nodes express variable amounts of connexin 45 and connexin 30.2, and the bundle branches and Purkinje fibers express significant levels of connexin 40. Gap junctions in the node integrate the intrinsic beating rate of each nodal cell into a single functional unit. Abnormalities in connexin expression and function, a process known as pathologic gap junction remodeling, are observed in atrial and ventricular myocardium in many acquired forms of heart disease. The remodeling contributes to aberrant impulse propagation and predisposes to arrhythmic behavior. In addition, germline or somatic mutations in cardiac connexin genes are associated with arrhythmic syndromes, especially atrial fibrillation.

MECHANISMS OF ARRHYTHMOGENESIS

Cardiac arrhythmias, which are disturbances in the rate or rhythm of the heartbeat, are a reflection of abnormal impulse formation or conduction. Inasmuch as cardiac myocytes reside within a complex multicellular environment and are electrotonically coupled by gap junction channels, arrhythmic syndromes almost always reflect a complex interplay of individual, or *cell autonomous*, properties within a multicellular network. Most clinically important arrhythmias arise in the setting of acquired heart disease, in which pathologic *electrical remodeling*, resulting from dysregulation of ion channel expression or function, accompanies *structural remodeling*. However, many arrhythmic syndromes, including those that are drug-induced, result from, or are exacerbated by, genetic variations, including disease-causing alterations in coding regions that directly affect the function of proteins, which regulate cardiac electrophysiology, as well as sequence variants in regulatory or other noncoding genome regions, which appear to regulate transcriptional and post-transcriptional behavior.

DISORDERS OF IMPULSE FORMATION

In the healthy heart, the sinus node, which is located at the junction of the right atrium and the superior vena cava, is the predominant pacemaker. Secondary pacemakers with intrinsically slower pacing rates are found further downstream in the specialized conduction system within the atrioventricular node and the His-Purkinje system. The firing rate of pacemaker cells is regulated primarily by autonomic tone: sympathetic stimulation increases the slope of phase 4 depolarization, whereas parasympathetic stimulation decreases the slope by augmenting repolarizing currents. Nodal suppression may result from pharmacologic agents, such as β-adrenergic blockers, calcium channel blockers, or digitalis, as well as from fibrotic diseases. Moreover, mutations in several genes that affect the voltage clock (*SCN5A* and *HCN4*), the calcium clock (*RYR2* and *CASQ2*), or both (*ANKB*) may cause familial sinus node dysfunction.

Conversely, under pathologic conditions, myocardial cells outside the specialized conduction system may exhibit spontaneous activity, a phenomenon termed *abnormal automaticity*. Abnormal automaticity is

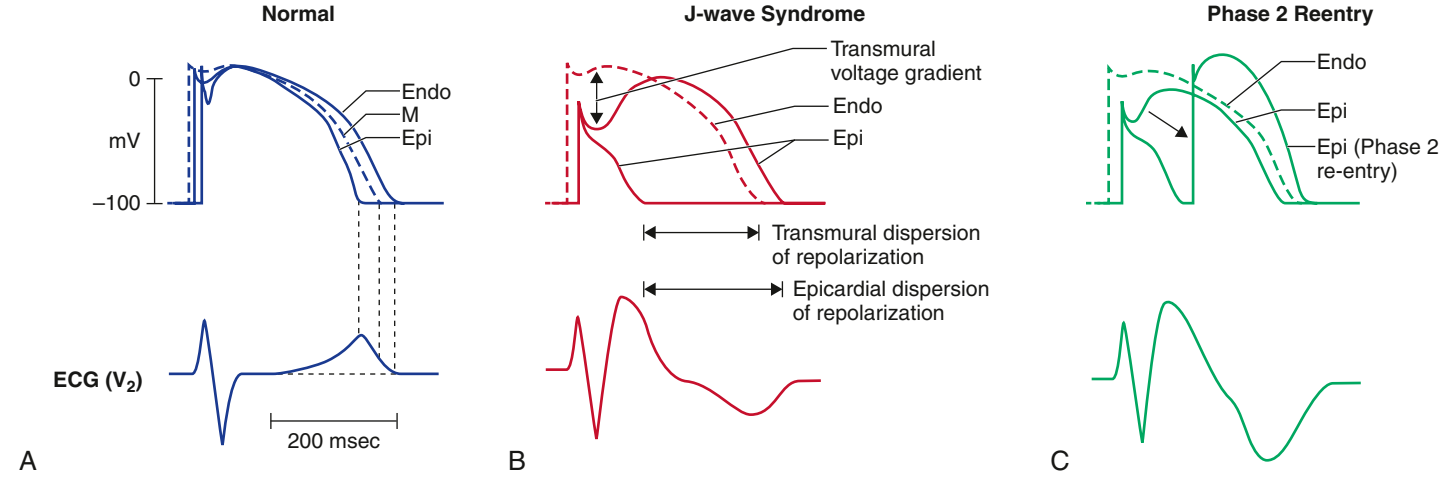

FIGURE 48-2. Cellular basis for J-wave syndromes and phase 2 re-entry. Under normal conditions, the ST segment is isoelectric because of the absence of transmural voltage gradients at the level of the action potential plateau. Accentuation of the phase I notch under pathophysiologic conditions, such as loss-of-function of I_{Na} or gain-of-function of I_{to} leads to loss of the action potential dome at some epicardial sites but not others, producing ST and T wave changes typically observed in Brugada syndrome. Loss of the action potential dome in epicardium but not endocardium results in the development of a marked transmural dispersion of repolarization and conduction of the action potential dome, from sites at which it is maintained to sites at which it is lost, thereby causing local reexcitation via a phase 2 re-entry mechanism. (Modified from Antzelevitch C, Brugada P, Brugada J, et al. Brugada syndrome: from cell to bedside. *Curr Probl Cardiol*. 2005;30:9-54.)

most often seen with ischemia or reperfusion, in which maximum diastolic potentials are reduced to approximately −60 mV to −50 mV, a level at which Na^+ or Ca^{2+} channels may reach their activation threshold and trigger action potentials.

AFTERDEPOLARIZATIONS AND TRIGGERED ACTIVITY

During cardiac repolarization, a number of inward and outward currents are active, and small changes in conductance of individual channels can markedly affect the trajectory of repolarization. *Afterdepolarizations*, which are abnormal oscillations in membrane potential, occur either during (early afterdepolarizations) or after (delayed afterdepolarizations) an action potential.[10] Afterdepolarizations of sufficient magnitude to evoke an action potential produce triggered activity. Early afterdepolarizations are almost always observed in the setting of abnormal action potential duration prolongation, which provides sufficient time for *re*-activation of L-type Ca^{2+} channels during the plateau phase of the action potential. Thus, congenital syndromes, as well as bradycardia, hypokalemia, hypomagnesemia, antiarrhythmic medications, and many noncardiac drugs, are associated with QT prolongation and promote early afterdepolarizations. Conversely, rapid pacing and drugs that shorten the action potential duration tend to suppress early afterdepolarizations. Early afterdepolarizations in the setting of action potential duration prolongation often trigger *torsades de pointes* (Chapter 53), a polymorphic ventricular tachycardia, especially when there is increased dispersion of repolarization. Delayed afterdepolarizations, in contrast, are usually the result of intracellular Ca^{2+} overload and are typically seen in the setting of catecholamine excess, ischemia, toxic concentrations of digitalis-like agents, and some congenital syndromes, including catecholaminergic polymorphic ventricular tachycardia. The excessive Ca^{2+} load activates the electrogenic Na^+-Ca^{2+} exchanger, producing a depolarizing transient inward current, I_{TI}.

DISORDERS OF IMPULSE CONDUCTION

During each cardiac cycle, impulses must be generated in pacemaker cells within the sinus node, and a wave of excitation must propagate throughout the atria, travel down the specialized conduction system (including the atrioventricular node and His-Purkinje network), and then activate the ventricular myocardium. Processes that diminish intercellular coupling, such as fibrosis or calcification of the specialized conduction system, can diminish the safety factor for conduction and produce varying degrees of heart block. Inherited defects in conduction have been observed with mutations in sodium channel subunits *SCN5A* and *SCN1B*, which affect phase 0 of the cardiac action potential; in *KCNJ2*, which affects terminal repolarization and the resting membrane potential; and in a number of developmental disorders that affect the cardiac conduction system, such as Holt-Oram syndrome, Emery-Dreifuss muscular dystrophy, and myotonic dystrophy type 1. Conduction block may also be seen with the secondary electrical remodeling that is associated with structural heart disease and with many cardioactive drugs.

RE-ENTRY

Re-entry is considered the most common mechanism responsible for clinically significant cardiac arrhythmias, including both supraventricular and ventricular disorders. Fundamentally, re-entry involves self-perpetuating waves of excitation that circulate around an inexcitable obstacle. Depending on the number of re-entrant waves within a tissue (one or multiple), their size, and their spatial stability, the surface ECG may reveal a relatively organized rhythm, such as atrial flutter or monomorphic ventricular tachycardia, or a seemingly disorganized rhythm, such as atrial fibrillation or polymorphic ventricular tachycardia. Re-entry normally requires the presence of unidirectional block within a "fast" conducting pathway around an obstacle, combined with recirculation of the impulse from a second "slow" pathway in the retrograde direction, as might be the case at a bifurcating Purkinje-ventricular junction or around scar tissue of a healed myocardial infarction (E-Fig. 48-2). However, the "obstacle" may also be viable myocardium that is inexcitable owing to its intrinsic electrophysiologic properties, such as cellular uncoupling or refractoriness, a phenomenon referred to as *functional block*. Because refractoriness is critically dependent on the action potential duration, areas of myocardium with prolongation of the action potential duration may form a suitable substrate for functional re-entry.

Heterogeneity in action potential duration and the concomitant *dispersion of refractoriness* also play critical roles in the maintenance of arrhythmic behavior, especially through a phenomenon known as *phase 2 re-entry*. This term refers to the flow of current during phase 2 of the cardiac action potential from a depolarized cell to neighboring cells that are more fully repolarized and not refractory to reexcitation. This principle is best characterized in the J wave syndromes,[11] especially Brugada syndrome, in which loss of function of inward currents (I_{Na} or I_{Ca}) or gain of function of outward currents (I_{to}, $I_{K\text{-}ATP}$) causes loss of the action potential dome during phase 2 and an abbreviated action potential duration in a subset of cardiac myocytes. Current can then flow into these cells from neighboring cells in which the action potential dome is maintained, thereby causing local reexcitation, a closely coupled extrasystole, and the initiation of re-entry. In Brugada syndrome, this process is thought to arise in the right ventricular outflow tract, where the transient outward current density is significantly greater in the epicardium compared with the endocardium (Fig. 48-2).

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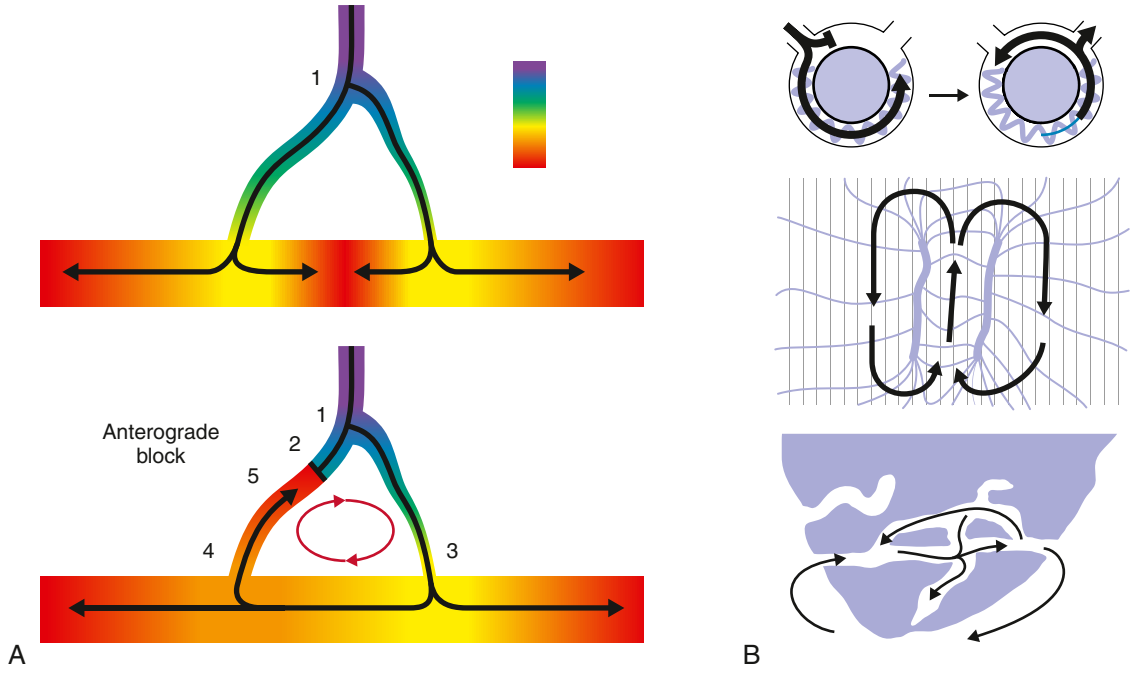

E-FIGURE 48-2. **Re-entrant cardiac arrhythmias. A**, Re-entry at the Purkinje-ventricular junction. *Upper panel:* Normally an impulse propagates along a Purkinje fiber and divides into two pathways (1), and together they activate the underlying ventricular myocardium. *Lower panel:* The impulse propagates along the right pathway (3) but is blocked within the left pathway (2). The original impulse travels within the ventricular myocardium, re-enters the left pathway in the retrograde direction (4), and successfully propagates through the area with block (5). Continued propagation throughout this circuit *(red circle)* would produce re-entrant ventricular tachycardia. **B**, Re-entry associated with myocardium scar. *Upper panel:* Diagram representing a single circuit of re-entry that initiates with unidirectional block. The circuit length must be longer than the longest refractory period in the circuit. *Middle panel:* A figure 8, in which re-entry is established owing to dispersion of refractoriness during tachycardia. *Lower panel:* Anatomic labyrinth circuit, created by strands of viable myocardium within the scar, with potential for multiple re-entry circuits. (The image to the right is reproduced from Benito B, Josephson ME. Ventricular tachycardia in coronary artery disease. *Rev Esp Cardiol [Engl Ed]*. 2012;65:939-955.)

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49 APPROACH TO THE PATIENT WITH SUSPECTED ARRHYTHMIA

JEFFREY E. OLGIN

CLINICAL MANIFESTATIONS

Patients with suspected arrhythmias can present in a variety of ways. Typical symptoms include palpitations, syncope, and presyncope (dizziness). On occasion, arrhythmias can manifest more subtly as exercise intolerance, lethargy, and vague complaints of malaise or without any symptoms at all. Conversely, arrhythmias occasionally manifest as aborted sudden cardiac death (cardiac arrest; Chapter 50). The specific differential diagnosis, prognosis, and treatment of these symptoms are determined by the severity of the symptom (i.e., whether it results in syncope) and whether the patient has underlying structural heart disease. In general, the likelihood of a life-threatening arrhythmia, such as ventricular tachycardia or ventricular fibrillation, in a patient with symptoms of palpitations or syncope is significantly greater in a patient who has structural heart disease. Therefore, the determination of whether structural heart disease is present is a key step in the diagnosis and prognosis of patients with suspected arrhythmias. The exception to this general rule is in patients with a significant family history suggestive of an inherited arrhythmia syndrome (e.g., long QT syndrome, Brugada syndrome), for whom a family history of syncope and/or sudden death should prompt referral to a cardiac electrophysiologist.

Palpitations

Palpitations, defined as an awareness of an irregular or rapid heartbeat, are most commonly due to ectopic beats—namely, premature atrial contractions (PACs; Chapter 52) and premature ventricular contractions (PVCs; Chapter 53)—or to tachyarrhythmias. A careful history can often distinguish benign palpitations from those that need further evaluation. It can be useful to have the patient tap out with a finger what the palpitations feel like. An irregularly irregular pattern suggests atrial fibrillation, whereas a more regular, rapid pattern suggests a sustained tachycardia. A reliable symptom suggesting that palpitations are caused by a tachyarrhythmia, particularly a supraventricular tachycardia, is the sensation of a regular, rapid-pounding sensation in the neck. Conversely, most patients who complain of symptoms from PACs or PVCs are often more aware of the post-extrasystolic pause or the accentuated output of the post-extrasystolic beat than of the actual premature beat itself. Most patients who have symptoms suggestive of premature beats but not of sustained tachycardia do not require further evaluation if they have no other symptoms and no evidence of structural heart disease—that is, an otherwise normal cardiac history, physical examination, and electrocardiogram (ECG; see Table 39-4). If, however, the symptoms are not due to a single occasional extrasystole or are accompanied by presyncope or syncope, further evaluation is required (Fig. 49-1). Antiarrhythmic therapy is usually not necessary to treat PACs or PVCs unless the symptoms are frequent or severe. β-Blockers (e.g., metoprolol 25 mg/day or atenolol 25 mg/day) are first-line therapy in highly symptomatic patients with documented PACs or PVCs. Recent data suggest that patients in whom PVCs exceed 24% of beats during 24-hour monitoring may have a higher risk of developing PVC-induced cardiomyopathy.[1]

Palpitations are the most common presentation of tachyarrhythmias, whereas bradyarrhythmias rarely manifest as palpitations. Most tachyarrhythmias in patients without structural heart disease are due to supraventricular tachycardias (Chapter 52) that resolve spontaneously within several seconds. When the tachyarrhythmia is more prolonged, it often resolves with simple interventions that increase vagal (parasympathetic nervous system) influence on the heart (generally the atrioventricular [AV] node). Patients themselves can cough several times, perform the Valsalva maneuver, exhale forcefully against a closed glottis for several seconds, immerse their face in ice water, or even rub gently on their eyeballs. A physician can use carotid sinus massage (Chapter 52), performed by pressing and rubbing the carotid pulse just below the angle of the mandible for 5 to 15 seconds. This maneuver should be avoided in elderly patients and in patients with a history of cerebrovascular accident, known carotid artery stenosis, or carotid bruit on auscultation. In patients with structural heart disease, palpitations may signify ventricular tachycardia (Chapter 53), particularly if they occur with syncope or presyncope. An occasional patient without structural heart disease may have idiopathic ventricular

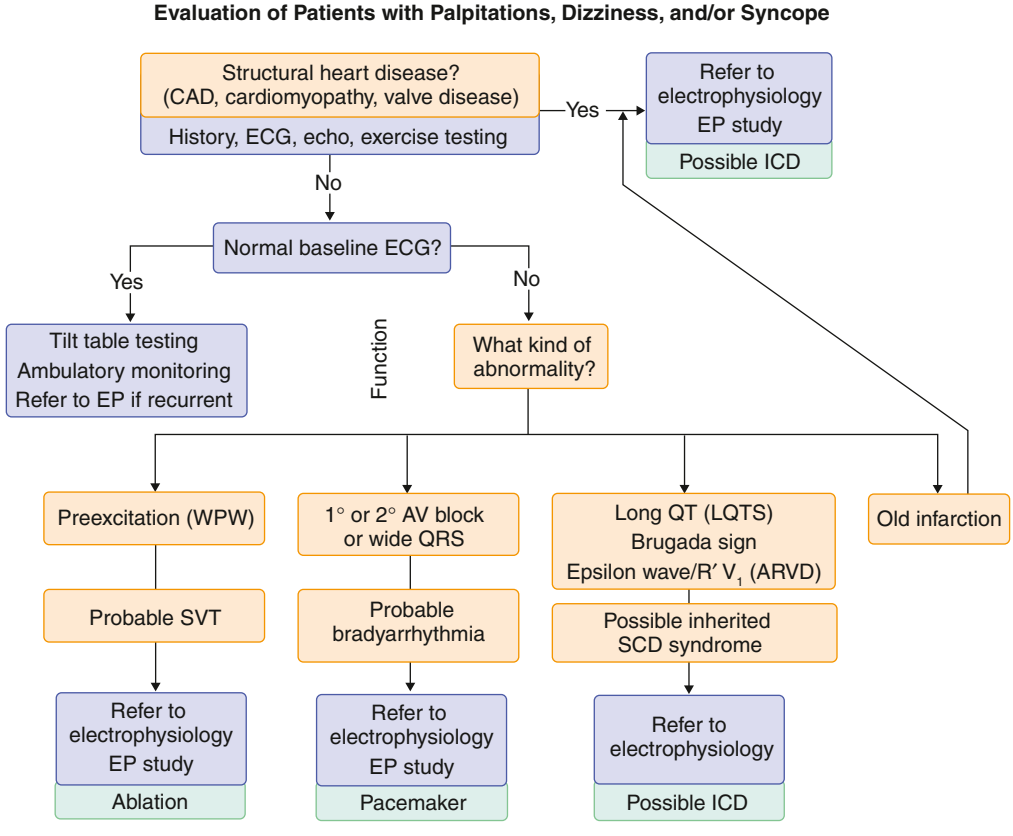

FIGURE 49-1. Algorithm for evaluating patients with symptoms of palpitation, dizziness, or syncope. ARVD = arrhythmogenic right ventricular dysplasia; AV = atrioventricular; CAD = coronary artery disease; ECG = electrocardiogram; echo = echocardiogram; EP = electrophysiology; ICD = implantable cardioverter-defibrillator; LQTS = long QT syndrome; SCD = sudden cardiac death; SVT = supraventricular tachycardia; WPW = Wolff-Parkinson-White syndrome.

ABSTRACT

Patients with suspected arrhythmias can present in a variety of ways. Typical symptoms include palpitations, presyncope (dizziness), and syncope. On occasion, arrhythmias can manifest more subtly as exercise intolerance, lethargy, and vague complaints of malaise or without any symptoms at all. Conversely, arrhythmias occasionally manifest as aborted sudden cardiac death (cardiac arrest). This chapter discusses the causes, diagnosis, and treatment of these conditions.

KEYWORDS

syncope
palpitations
arrhythmia
neurocardiogenic
bradycardia
tachycardia

TABLE 49-1 CAUSES OF SYNCOPE AND THEIR PREVALENCE

NEUROCARDIOGENIC CAUSES
Vasovagal (8-41% of patients)
Situational (1-8% of patients)
Micturition
Defecation
Swallow
Cough
Carotid sinus syncope (0.4% of patients)
Neuralgias
Psychiatric disorders
Medications, exercise
ORTHOSTATIC HYPOTENSION (4-10% OF PATIENTS)
DECREASED CARDIAC OUTPUT
Obstruction to flow (1-8% of patients)
Obstruction to left ventricular outflow or inflow: aortic stenosis, hypertrophic obstructive cardiomyopathy, mitral stenosis, myxoma
Obstruction to right ventricular outflow or inflow: pulmonic stenosis, pulmonary embolism, pulmonary hypertension, myxoma
Other heart disease
Pump failure, myocardial infarction, coronary artery disease, coronary spasm, tamponade, aortic dissection
ARRHYTHMIAS (4-38% OF PATIENTS)
Bradyarrhythmias: sinus node disease, second- and third-degree atrioventricular block, pacemaker malfunction, drug-induced bradyarrhythmias
Tachyarrhythmias: ventricular tachycardia, torsades de pointes (e.g., associated with congenital long QT syndrome or acquired QT prolongation), supraventricular tachycardia
NEUROLOGIC AND PSYCHIATRIC DISEASES (3-32% OF PATIENTS)
Migraine
Transient ischemic attacks
UNKNOWN (13-41% OF PATIENTS)

Adapted from Kapoor W. Approach to the patient with syncope. In: Braunwald E, Goldman L, eds. *Primary Cardiology*, 2nd ed. Philadelphia: Saunders; 2003.

TABLE 49-2 CLINICAL FEATURES SUGGESTING SPECIFIC CAUSES

DIAGNOSTIC CONSIDERATION
Neurocardiogenic
Symptoms after prolonged motionless standing; sudden unexpected pain; fear; or unpleasant sight, sound, or smell
Syncope in a well-trained athlete after abrupt cessation of exertion (without heart disease)
Situational syncope during or immediately after micturition, cough, swallowing, or defecation
Syncope with throat or facial pain (glossopharyngeal or trigeminal neuralgia)
Organic Heart Disease (e.g., coronary artery disease, aortic stenosis, primary arrhythmia, obstructive hypertrophic cardiomyopathy, pulmonary hypertension)
Brief loss of consciousness, no prodrome, history of heart disease
Syncope during exertion
Family history of sudden death
Neurologic
Seizures: confusion for >5 min after regaining consciousness
Transient ischemic attack, subclavian steal, basilar migraine: syncope associated with vertigo, dysarthria, diplopia, arm exercise
Migraine: syncope associated with antecedent headaches
Other Vascular
Carotid sinus: syncope with head rotation or pressure on the carotid sinus (as in tumors, shaving, tight collars)
Orthostatic hypotension: syncope immediately on standing
Subclavian steal or aortic dissection: differences in blood pressure or pulse between the two arms
Drug-Induced
Patient is taking a medication that may lead to long QT syndrome, orthostasis, or bradycardia
Psychiatric Illness
Frequent syncope, somatic complaints, no heart disease, inconstant circumstances of events

Adapted from Kapoor WN. Syncope. *N Engl J Med*. 2000;343:1856-1862.

tachycardia (typically arising from the ventricular outflow tracts; Chapter 53), but such patients generally have a more benign course than patients with structural heart disease and are readily curable with ablation (Chapter 54).

Presyncope and Syncope

Syncope, defined as a sudden loss of consciousness, and presyncope, or lightheadedness, are caused by global impairment of blood flow to the brain (Table 49-1). Syncope can be a manifestation of tachyarrhythmias, bradyarrhythmias, or neurocardiogenic syncope, or it can be unrelated to any arrhythmia. A careful history and physical examination are necessary to exclude other cardiac causes (e.g., acute ischemia, aortic stenosis) or neurologic causes. Important historical features that suggest an arrhythmic cause are an association with palpitations and the lack of any neurologic deficits preceding or following the event. Left ventricular outflow obstruction, due either to aortic stenosis (Chapter 60) or hypertrophic obstructive cardiomyopathy (Chapter 47), can present as syncope, often during or just after exertion.

Important differential diagnoses include conditions other than lightheadedness that may be termed dizziness by the patient. Vertigo (Chapter 396), a sense of imbalance or of the "room spinning," and ataxia (Chapter 379) can usually be distinguished by the history and physical examination. The possibility of seizures (Chapter 372) must also be evaluated; syncope from an arrhythmia or neurocardiogenic syncope occasionally results in seizure-like activity, and seizures can sometimes be confused with syncope. The most important distinguishing feature is that postictal symptoms, a key feature of seizure disorders, are absent when syncope is the result of an arrhythmia or a neurocardiogenic event. Patients with syncope from an arrhythmia usually awaken without any neurologic residual, unless the patient experienced a cardiac arrest with prolonged hypoxia and required resuscitation. Among patients who are hospitalized with a first episode of syncope and in whom pulmonary embolism cannot be excluded based on a low Wells score (see Table 68-3) and a negative D-dimer assay, pulmonary embolism may be found in 25% of patients who do not have another obvious cause of their syncope and in about 13% of patients who do have an alternative explanation for their syncope. By comparison, among all patients who present to an emergency department with syncope, only about 1.5% of patients appear to have pulmonary emboli.[2]

Because most spells of episodic loss of consciousness occur outside medical observation, the history is the most critical part of the evaluation (Table 49-2).[3] Each syncopal episode should be reviewed in detail, with special attention to symptoms preceding the episode, events during unconsciousness, and the symptoms and time course of regaining orientation after consciousness is restored. Information from a witness can be essential to the evaluation. About 20% of syncopal events are associated with an injury, but recurrent neurocardiogenic events are less likely to result in injury.[4]

The patient's presymptomatic activity and positioning, as well as symptoms when the syncopal episode began, are important clues to diagnosis. Seizures or cardiac arrhythmias can occur in any body position, but recumbent patients rarely develop neurocardiogenic (vasovagal) syncope and never have orthostatic hypotension. Prodromal lightheadedness, dizziness (but uncommonly vertigo), bilateral tinnitus, nausea, diffuse weakness, and dimming of vision are symptoms of cerebral hypoperfusion and support the diagnosis of syncope, which may be from a cardiac, orthostatic, or neurocardiogenic cause. Loss of consciousness so rapid that a prodrome is absent may occur with seizures and with some cardiac arrhythmias such as asystole, which typically causes loss of consciousness within 4 to 8 seconds in the upright position but usually requires 12 to 15 seconds in the recumbent position. Palpitations during the prodrome suggest a tachyarrhythmia. The activity of the patient immediately before the onset of symptoms may also provide clues. Syncope associated with the cessation of exertion or with anxiety or pain suggests neurocardiogenic syncope, whereas symptoms during exertion suggest an arrhythmia or left ventricular outflow obstruction due to aortic stenosis (Chapter 60) or hypertrophic obstructive cardiomyopathy (Chapter 47). Syncope associated with a change in posture suggests orthostatic causes, whereas syncope while straining at urination suggests situational neurocardiogenic syncope.

A witness's description of the events during the episode of unconsciousness is very helpful. Although body stiffening and limb jerking occur with generalized seizures, similar movements can result from cerebral hypoperfusion, especially if perfusion is not restored rapidly. Such muscle jerking is often multifocal and can be synchronous or asynchronous. In contrast to epileptic seizures,

which generally produce tonic-clonic activity for at least 1 to 2 minutes, muscle jerking in syncope rarely persists for longer than 30 seconds. If an arrhythmia continues or the patient is physically maintained upright, tonic stiffening of the body followed by jerking movements of the limbs can occur. Occasionally, motor movements identical to a tonic-clonic seizure occur, and a mistaken diagnosis of epilepsy can be made. Urinary incontinence during the spell is frequently used to support or refute a diagnosis of epilepsy; however, fainting with a full bladder can result in incontinence, whereas seizures with an empty bladder will not. Tongue biting favors seizures.

The time frame over which consciousness and orientation are regained is perhaps the most important clue in differentiating seizures from syncope. Recovery of orientation after neurocardiogenic syncope occurs within seconds of regaining consciousness. Recovery of orientation after self-reversible arrhythmia-associated syncope is usually proportional to the duration of the unconsciousness and is usually rapid (0 to 10 seconds). Life-threatening arrhythmias (e.g., prolonged asystole or ventricular fibrillation) usually do not resolve without resuscitation, and the confusion after regaining consciousness may be permanent owing to ischemic brain injury (Chapter 50). By comparison, the period of confusion after seizures, often accompanied by agitation, continues for 2 to 20 minutes after recovery of consciousness.

DIAGNOSIS

The likelihood of an arrhythmic cause of syncope is higher in patients with underlying heart disease, a systolic blood pressure below 90 or above 180 mm Hg, a QRS duration >130 msec, or a QTc interval >480 msec. Arrhythmias are generally categorized as bradyarrhythmias (slow heart rates; see Chapter 51), tachyarrhythmias (fast heart rates; see Chapters 52 and 53), or premature beats (single extrasystoles from the atrium or the ventricle—PACs [see Fig. 52-1 or PVCs [see Fig. 53-1], respectively) (see Table 49-1). Although not a primary arrhythmia, neurocardiogenic syncope is a related diagnostic and management issue because its symptoms are frequently similar to those of arrhythmias and because neurocardiogenic syncope secondarily results in bradycardia (see later). A systematic approach can optimize the likelihood of identifying the cause of transient loss of consciousness (Table 49-3).[5]

Bradyarrhythmias

Bradyarrhythmias (Chapter 51) can be due to dysfunction in the sinoatrial node, AV node, or His-Purkinje system (below the AV node). Sinus bradycardia manifests as a slow atrial (sinus) rate and can occur at rest or as an inappropriately slow rate during exercise (chronotropic incompetence). Sinus arrest can be intermittent, when transient loss of sinus activity (loss of the P wave on the ECG) causes brief sinus pauses, or persistent, with prolonged loss of atrial activation. The sinus rate and even the presence of sinus pauses are influenced by autonomic tone. Therefore, healthy individuals—particularly younger patients and well-trained athletes (with high vagal tone)—have occasional sinus slowing, often during sleep. A sinus pause of more than 3 seconds is considered pathologic if it is associated with symptoms while a patient is awake. Sinus bradycardia and sinus arrest can also be the result of medications, typically β-blockers and calcium-channel blockers. When not "physiologic" or due to medications, sinus bradycardia and sinus arrest are the result of intrinsic conduction system disease. Sinus bradycardia, especially if it is intermittent, can also signify disease of the right coronary artery.

Bradyarrhythmias from AV nodal disease result from the failure of impulse conduction from the atrium to the ventricle. Like the sinus node, the AV node is dramatically affected by autonomic tone. Mobitz type I second-degree AV block (Wenckebach block; see Fig. 51-6) can be seen during periods of high vagal tone (such as while sleeping) and is not necessarily pathologic; for example, it does not progress to complete heart block and is not associated with a widened QRS. Many drugs, such as β-blockers and calcium-channel blockers, commonly cause first-degree AV block and should be considered a potential cause of any degree of AV block. Mobitz type II block (see Fig. 51-7) signifies that the level of AV block is below the AV node in the His-Purkinje system, which is not sensitive to autonomic tone; the resulting QRS is widened, and there is a high likelihood of progression to complete heart block (third-degree AV block; see Figs. 51-8 and 51-9). Idiopathic paroxysmal AV block, detected by continuous ECG monitoring, can also cause syncope. Intermittent complete heart block, which can result in drop attacks or Stokes-Adams attacks, is usually preceded by abnormal baseline findings on the ECG, such as a bundle branch block or second-degree AV block.

Tachyarrhythmias

Tachyarrhythmias can arise from the atrium or AV node (supraventricular tachycardias) or from the ventricle (ventricular tachycardias). Supraventricular tachyarrhythmias that may be associated with palpitations, presyncope, or syncope include atrial tachycardia (see Fig. 52-11), AV nodal re-entrant tachycardia (see Fig. 52-8), AV junctional tachycardia (see Fig. 52-9), atrial flutter (see Fig. 52-12), atrial fibrillation (see Fig. 52-13), or sometimes in association with accessory conduction pathways that facilitate the re-entry needed to sustain the arrhythmia (AV reciprocating tachycardia). Ventricular tachyarrhythmias include the various forms of ventricular tachycardia (see Figs. 53-1 through 53-6).

TABLE 49-3 SUMMARY OF CLINICAL RECOMMENDATIONS FOR TRANSIENT LOSS OF CONSCIOUSNESS

TOPIC	RECOMMENDATIONS
Initial assessment	Detailed history, especially from witnesses Full clinical examination 12-lead ECG
Uncomplicated faints	Suggestive features include: Posture: occurrence during prolonged standing or similar previous episodes avoided by lying down Provoking factors, such as pain or a medical procedure Prodromal symptoms, such as sweating or feeling warm or hot before TLoC Further investigation and specialist referral are not needed.
Epilepsy	Suggestive features are a bitten tongue; head turning to one side during TLoC; no memory of abnormal behavior that occurred before, during, or after TLoC; unusual posturing; prolonged limb jerking (brief seizure-like activity often occurs during syncope, including uncomplicated faints); confusion after the event; or prodromal déjà vu or jamais vu. If features of epilepsy are present, arrange for early review by an epilepsy specialist. Do not arrange for EEG before neurologic assessment. Note that brief seizure-like activity often occurs during syncope, including uncomplicated faints. Do not suspect epilepsy unless suggestive features are present. Arrange for cardiovascular assessment if the cause of TLoC is unclear.
Urgent specialist referral	Give immediate treatment for clinically urgent problems (such as complete AV block or severe bleeding). Arrange for urgent specialist cardiovascular assessment for patients at risk for a severe adverse event (such as those with long QT interval, cardiac arrhythmia, or structural heart disease).
Further cardiovascular assessment	Focus on specific disorders that may cause TLoC, such as orthostatic hypotension, the carotid sinus syndrome, structural heart disease, or cardiac arrhythmia. Assessment should include repeated history, clinical examination, and 12-lead ECG. For suspected cardiac arrhythmia or unexplained TLoC, use ambulatory ECG for further assessment: Very frequent episodes: use 24- to 48-hour Holter monitoring. Moderately frequent episodes: use external event monitoring. Infrequent episodes: use an implantable event recorder. In patients who are sick or worrisome enough for hospital admission and do not have both a low Wells score (see Chapter 68) and a negative D-dimer assay, evaluate for possible pulmonary embolism (computed tomographic pulmonary angiography or ventilation-perfusion lung scanning).

AV = atrioventricular; ECG = electrocardiography; EEG = electroencephalogram; TLoC = transient loss of consciousness.

Adapted from Cooper PN, et al. Synopsis of the National Institute for Health and Clinical Excellence Guideline for management of transient loss of consciousness. *Ann Intern Med*. 2011;155:543-549.

Neurocardiogenic Syncope and Related Syndromes

Neurocardiogenic syncope is the sudden onset of lightheadedness or loss of consciousness as a result of autonomic reflexes and is more common in younger patients (teenage to third decade of life). It is sometimes called a vasovagal episode, a common faint, or situational syncope if it is clearly induced by a particular activity (e.g., micturition syncope). Some families have autosomal dominant vasovagal syncope, which is genetically heterogeneous but seems to be linked to chromosome 15q26.

In neurocardiogenic syncope, heightened parasympathetic output, either due to direct stimulation (e.g., micturition, defecation, abdominal pain, or other gastrointestinal conditions) or as a reflex in response to sympathetic stimulation (e.g., seeing blood, abrupt cessation of exercise), results in arterial dilation (called the vasodilatory response) and an inhibition of sinus and

AV node activity (the cardioinhibitory response). The result is a transient decrease in blood pressure, often manifested as lightheadedness or syncope. Because they are associated with parasympathetic (vagal) output, episodes are frequently accompanied by nausea, diaphoresis, and salivation. Twin analyses provide strong evidence for genetic factors in vasovagal syncope.

Rarely, situational syncope is associated with swallowing or coughing. Swallowing can trigger brain stem reflexes that lead to vagally induced bradyarrhythmias, with resultant syncope. This phenomenon may or may not be associated with severe pain in the tonsillar pillar, which may radiate to the ear (i.e., glossopharyngeal neuralgia; Chapter 367). Cough-related syncope can occur with severe, repeated coughing, which may increase thoracic pressure and result in increased vagal tone or a transient reduction in outflow from the intracranial veins, followed by a transient increase in intracranial pressure and impaired blood flow.

A related cause of syncope is carotid body hypersensitivity, in which vagal tone is increased by direct stimulation of the carotid body. This condition is frequently seen in older patients (particularly men older than 60 years), in whom episodes are associated with mechanical stimulation of the neck (e.g., turning the head, shaving, wearing a tight collar or necktie). Use of β-blockers, calcium-channel blockers, and digitalis can exacerbate or predispose to this condition. This form of syncope is diagnosed by documenting pauses longer than 3 seconds in response to carotid sinus massage.

Postural or orthostatic hypotension can result in recurrent syncope. The history confirms that the patient is in the upright posture during spells, that the prodromal symptoms are those of cerebral hypoperfusion, and that the symptoms are relieved with recumbency. The diagnosis is supported by detecting a decrease of 30 mm Hg or greater in systolic blood pressure or a decrease of 10 mm Hg or greater in diastolic blood pressure between recumbent and upright postures. The many causes include drugs, polyneuropathies (Chapter 388), postural orthostatic tachycardia syndrome (a ≥30 beat per minute increase in heart rate when standing),[6] and neurodegenerative disorders (Chapter 378).

Cerebrovascular syncope results from cerebral hypoperfusion due to vascular phenomena, as opposed to generalized hypotension caused by arrhythmias or neurocardiogenic reflexes. Loss of consciousness can be a component of a basilar artery transient ischemic attack, but other brain stem symptoms nearly always precede or accompany the unconsciousness. Vertigo is most frequent, but diplopia or visual field disturbances, hemifacial or perioral numbness, and dysarthria or ataxia are also common. Recovery of consciousness may require 30 to 60 minutes. Although the diagnosis is suggested by the history and clinical presentation, imaging studies can be useful to confirm the diagnosis. Carotid Doppler studies may show various degrees of stenosis, especially in older patients. However, unconsciousness requires bihemispheric dysfunction; thus, unilateral carotid stenosis alone does not cause syncope. Transcranial Doppler studies or magnetic resonance angiography of the basilar artery is indicated only if brain stem ischemic symptoms are present in addition to loss of consciousness; false-positive tests are common, especially with increasing age.

Other syndromes that can cause syncope include subclavian artery stenosis, which may result in retrograde blood flow from the vertebral artery to one arm, with resultant brain stem hypoperfusion (i.e., subclavian steal syndrome). Asymmetry in upper extremity systolic blood pressure, typically averaging 45 mm Hg, is nearly always present. Brain stem symptoms are similar to those in basilar transient ischemic attacks, including loss of consciousness, but a subsequent stroke from subclavian steal is rare. Syncope may also occur in up to 10% of patients with basilar artery migraine (Chapter 367). It can have a postural (orthostatic) manifestation or be associated with other basilar artery symptoms.

Neuropsychiatric syncope is a diagnosis of exclusion but is suggested by young age, frequent spells, multiple symptoms (e.g., dizziness, vertigo, lightheadedness, numbness), and duplication of the patient's symptoms by hyperventilation with the mouth open for 2 to 3 minutes. Whereas syncope and seizures occur with the eyes open, often with gaze deviation, psychogenic events frequently begin with eye closing.

Seizures (Chapter 372) can cause loss of consciousness and occasionally present clinically as syncope. However, seizures usually have a characteristic presentation and include a postictal phase, whereas most patients experiencing a syncopal episode quickly regain consciousness, except when cerebral perfusion is so compromised as to cause a secondary seizure or persistent anoxia and brain damage.

Diagnostic Tests

Electrocardiography

The baseline ECG is critical in the evaluation of a patient with palpitations or syncope. The presence of ventricular preexcitation, as manifested by a short PR interval and a delta wave (see Fig. 52-10), establishes the likely diagnosis of Wolff-Parkinson-White syndrome in a patient with palpitations and AV reciprocating tachycardia (Chapter 52); a 12-lead ECG can also be used to determine the location of the responsible accessory pathway. The baseline ECG provides useful predictive information about the likelihood of conduction system abnormalities being responsible for bradyarrhythmias (e.g., sinus bradycardia suggests sinus node dysfunction, a prolonged PR interval suggests AV nodal disease, and a widened QRS suggests disease below the AV node). The ECG is also useful in diagnosing prior myocardial infarction (i.e., pathologic Q waves), which raises the likelihood of ventricular tachycardia as a potential cause of syncope or palpitations. Abnormalities such as a prolonged QT interval in a patient with syncope and a family history of syncope or sudden death suggest one of the congenital long QT syndromes (Chapter 50). An incomplete right bundle branch block with coved ST segment elevation in ECG lead V_1 or V_2 in a patient with syncope or palpitations suggests Brugada syndrome, whereas an epsilon wave, incomplete right bundle branch block, and inverted T waves in V_1 are suggestive of right ventricular dysplasia (Chapter 47). All these syndromes carry an increased risk for recurrent syncope and sudden death if untreated (Chapters 50 and 53). The short QT syndrome (QTc ≤330 msec or QTc ≤360 plus a family history of sudden death) also predisposes to ventricular arrhythmias. Since some of these ECG findings (especially those suggestive of Brugada syndrome and even long QT syndrome) may be transient or episodic, lack of these findings does not exclude these syndromes in patients with syncope and a strong family history.

In one study, electrocardiographic screening for 14 days increased the detection of atrial fibrillation in older adults and led to a small reduction in adverse events.[A1] However the U.S. Preventive Services Task Force found evidence to be insufficient to recommend such screening.[7]

Performing an ECG during an episode of palpitations is extremely useful in making a definitive diagnosis. For narrow–QRS complex tachycardias, the specific supraventricular tachycardia can often be surmised from the 12-lead ECG obtained during symptoms (Fig. 49-2). Moreover, for wide–QRS complex tachycardias, the 12-lead ECG is useful in distinguishing a supraventricular tachycardia (with aberrancy) from a ventricular tachycardia (Fig. 49-3). The presence of fusion beats or AV dissociation during a wide–QRS complex tachycardia leads to the diagnosis of ventricular tachycardia. For ventricular tachycardias, the morphology of the QRS complex is useful in determining the location of the ventricular tachycardia focus and in identifying idiopathic ventricular tachycardia (right ventricular outflow tract or fascicular), which has a much more benign course than ventricular tachycardia in the setting of coronary disease (Chapter 53).

The effect of carotid sinus massage, vagal maneuvers, or adenosine (given as a rapid intravenous bolus of 6 mg and repeated at a dose of 12 mg if the initial dose is ineffective) is also useful in narrowing the differential diagnosis of a tachycardia. These maneuvers slow conduction through the AV node. Therefore, tachycardias that terminate with either maneuver are likely to involve the AV node as a critical component of the re-entrant circuit (AV nodal re-entrant tachycardia or AV re-entrant tachycardia). If the maneuver induces AV block but does not immediately terminate the arrhythmia, likely causes are atrial fibrillation, atrial flutter, and atrial tachycardias (or occasionally ventricular tachycardia if the QRS is wide). On rare occasions, atrial tachycardias and some idiopathic ventricular tachycardias terminate in response to adenosine (but usually not at precisely the same time as AV block). Important clues to the specific mechanism can be obtained at the onset or termination of tachycardia, so obtaining a continuous 12-lead ECG during carotid sinus massage or the administration of adenosine is very useful.

During bradycardias, the ECG is useful in determining the level of the conduction system (sinus node, AV node, or His bundle) responsible for the bradycardia. Sinus bradycardia is diagnosed when a slow (<50/minute at rest) atrial rate (P wave) conducts to the ventricle. Sinus arrest or sinus pauses are diagnosed by absent or dropped P waves. First-degree AV block (see Fig. 51-5) is defined as a prolonged PR interval (>200 msec), and second-degree AV block is defined by P waves that occasionally do not conduct to the ventricle (P wave without an ensuing QRS); Mobitz type I second-degree AV block (also known as Wenckebach block; see Fig. 51-6) is characterized by progressive lengthening of the PR interval until one P wave does not conduct to the ventricle. This form of AV block is often seen in younger patients, is usually benign, and rarely progresses to complete AV (third-degree) block. Mobitz type II second-degree AV block (see Fig. 51-7), which is characterized by the sudden, unexpected loss of conduction of a P wave to the ventricle (dropped QRS), signifies disease of the His-Purkinje system and often progresses to complete heart block. Complete heart block or third-degree AV block (see Figs. 51-8 and 51-9) is diagnosed by the dissociation of P waves from QRS complexes, with an atrial rate faster than the ventricular rate.

Ambulatory Monitoring

For intermittent symptoms such as palpitations, dizziness, or syncope, it is often difficult to obtain a 12-lead ECG while the symptoms are occurring.

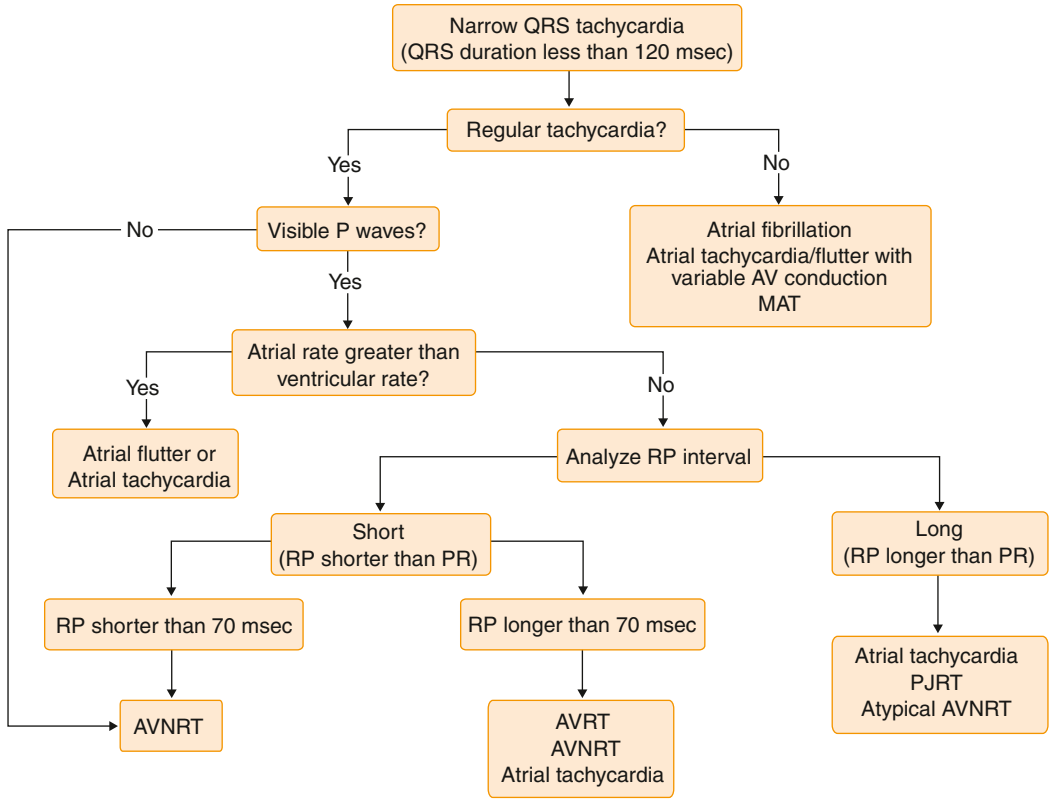

FIGURE 49-2. ECG algorithm for diagnosis of narrow-complex tachycardias. AVNRT = atrioventricular nodal reciprocating tachycardia; AVRT = atrioventricular reciprocating tachycardia; MAT = multifocal atrial tachycardia; PJRT = permanent form of junctional reciprocating tachycardia. (From Blomstrom-Lundqvist C, Scheinman MM, Aliot EM, et al. ACC/AHA/ESC guidelines for the management of patients with supraventricular arrhythmias—executive summary. *Circulation*. 2003;108:1871-1909.)

Therefore, ambulatory monitoring, which allows ECG monitoring over long periods, is a vital diagnostic tool. There are currently four general types of ambulatory monitors: Holter monitors, which continuously record the ECG for 24 to 48 hours (or extended monitors that can record continuously for longer); event recorders, which are wearable loop recorders that record only during specific events (when the patient activates the recorder because of symptoms or the recorder detects a heart rate above or below a specified threshold) and can be worn for 1 month or more; mobile cardiac outpatient telemetry that functions similarly to external event recorders but transmits data in real time through a wireless network to a central monitoring center and can be worn for up to 1 month; and implantable loop recorders, which function similarly to event recorders but can be used for up to 3 years. More recently, consumer-directed smartphone ECGs attach to a smartphone and can record an on-demand single-lead ECG rhythm strip or can use light-sensing photoplethysmography to detect irregular heart rhythms (such as atrial fibrillation) and heart rates. The choice among ambulatory monitoring methods is largely determined by the frequency and severity of the symptoms and the likelihood of capturing an episode during a given monitoring period.

Ambulatory monitoring is diagnostic only if abnormalities occur during symptoms or if the patient has typical symptoms without any concurrent abnormalities. A "normal" monitoring record is nondiagnostic if the patient does not have symptoms during the period.

Holter Monitors

Holter monitors use either a tape (in older devices) or digital media (in newer devices) to record a 3-, 5-, or 12-lead surface ECG continuously, usually for 24 to 48 hours but for 3 weeks or more when indicated. Processing, printing, and analysis of the recordings are performed offline with commercial systems. In addition to recording the rhythm, analyses of heart rate variability and ST segment changes and accurate counts of PACs and PVCs can be automated. Some systems allow extrapolation to produce a "virtual" 12-lead recording at any time during the monitoring period. Holter monitoring is useful for detecting symptoms that are frequent (multiple times daily) and for diagnosing sinus node dysfunction (sinus node arrest, sick sinus syndrome) or intermittent AV block. It can also be useful to assess the adequacy of ventricular rate control in a patient with atrial fibrillation or burden of PVCs. New form factors have enabled longer, more comfortable monitors (such as a self-contained patch) that can record for several weeks.

Traditional Holter monitors have largely been replaced by the more convenient and longer-lasting extended monitors using a single-lead patch. Traditional Holters remain useful, however, for situations in which having more than one simultaneous lead is helpful, for example, in differentiating supraventricular tachycardia (SVT) with aberrancy from ventricular tachycardia (VT) or localizing the source of a PVC or VT.

Event Monitors

Event monitors, also known as loop recorders, are designed to record intermittent episodes during long periods (weeks to months) and are thus useful for patients with less frequent symptoms. The system records the ECG into a loop buffer that is continuously updated and overwritten. The duration of memory varies from a few seconds to a few minutes and is usually programmable. When activated, the information is "locked" into memory and continues to record forward for a preprogrammed amount of time. Newer systems allow both patient-activated (when symptoms occur) and event-triggered (when the heart rate is above or below a preset threshold) recording.[8] Some recorders have algorithms to detect and record atrial fibrillation automatically, regardless of the heart rate. After episodes have been recorded, the patient transmits the recording over the telephone to centralized receivers. Some event monitors require leads similar to Holter monitors, whereas others are worn on the wrist or are put into small credit card–sized devices that are placed on the chest during symptoms. The latter type is useful only in patients whose symptoms last for several minutes and who do not have syncope.

Mobile Cardiac Outpatient Telemetry

Mobile cardiac outpatient telemetry units are similar to external event monitors, except that data are transmitted wirelessly in real time to a monitoring center. These devices are useful for patients in whom intermittent symptoms are severe or the differential diagnosis includes potentially dangerous arrhythmias that should be diagnosed expeditiously. For example, a wearable ECG sensor patch can expedite the diagnosis of atrial fibrillation in patients at high risk for it.[A2] The monitoring center also has the ability to dispatch emergency medical services if necessary.

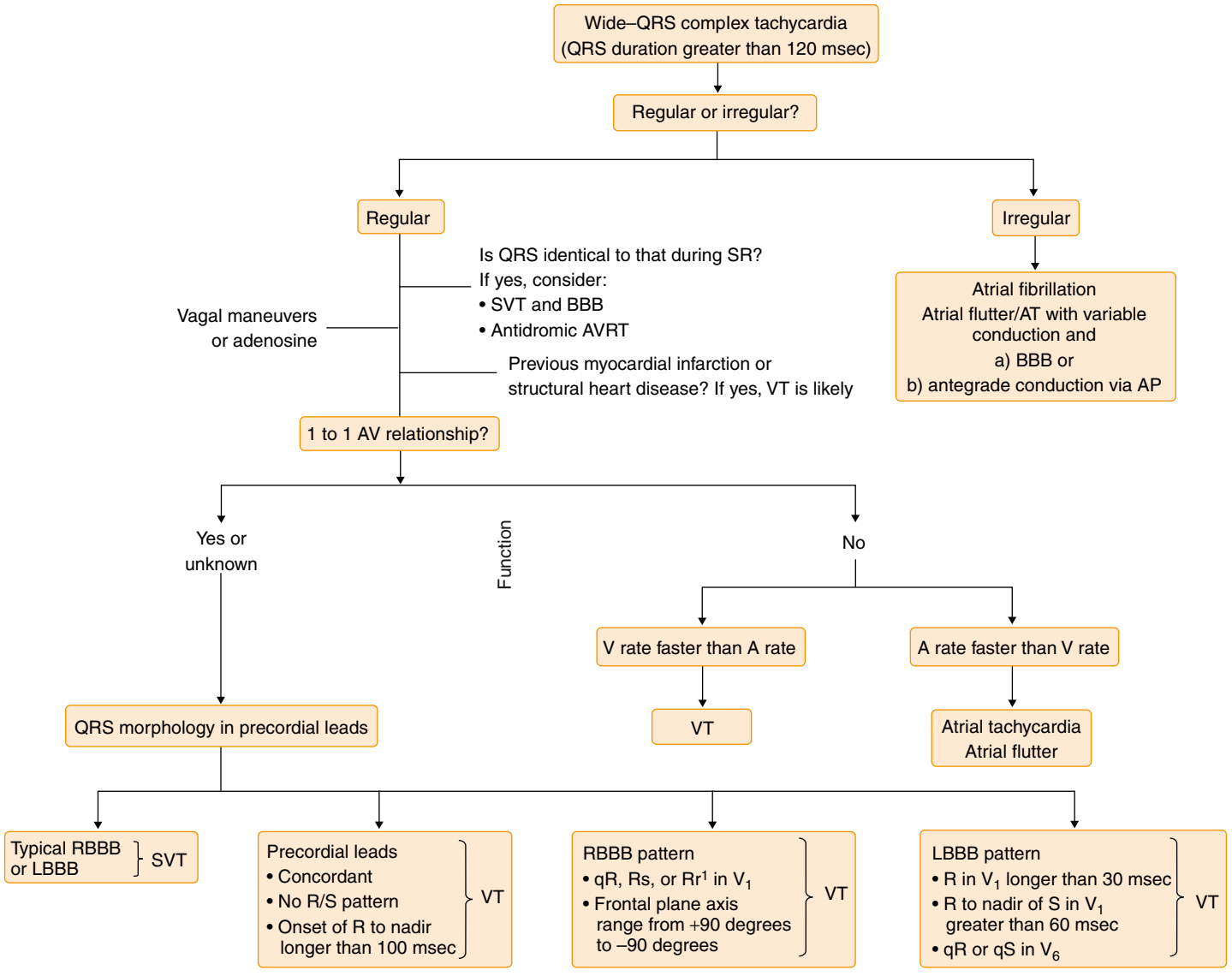

FIGURE 49-3. ECG algorithm for diagnosis of wide-complex tachycardias. A = atrial; AP = accessory pathway; AT = atrial tachycardia; AV = atrioventricular; AVRT = atrioventricular reciprocating tachycardia; BBB = bundle branch block; LBBB = left bundle branch block; RBBB = right bundle branch block; SR = sinus rhythm; SVT = supraventricular tachycardia; V = ventricular; VT = ventricular tachycardia. (From Blomstrom-Lundqvist C, Scheinman MM, Aliot EM, et al. ACC/AHA/ESC guidelines for the management of patients with supraventricular arrhythmias—executive summary. *Circulation*. 2003;108:1871-1909.)

Implantable Loop Recorders

Implantable loop recorders are small devices with integrated leads that are placed in a small subcutaneous pocket during a simple surgery, usually performed in the electrophysiology laboratory. They function similarly to event recorders in terms of recording ECGs. Patients can activate the device with a small transmitter, or the device can be autotriggered on the basis of preprogrammed heart rates. The device can be interrogated by a computer, similar to the way pacemakers are interrogated to program the device's parameters and to retrieve ECGs that have been recorded. Newer devices can wirelessly communicate with a telephone-connected base station in the home to upload data after an event. In patients with recurrent, difficult-to-diagnose syncope, an implantable loop recorder is better than the combination of tilt testing, an external loop recorder, and electrophysiologic testing for establishing an arrhythmic diagnosis. In patients ages 70 to 79 years or with a history of ischemic stroke, implantable loop recorders are significantly more likely than prolonged external monitoring to detect paroxysmal atrial fibrillation,[A3-A5] but the clinical benefits of better diagnosis appear to be negligible.

Consumer-Based Rhythm Monitors

With the growth of smartphones and wearable devices, patients can purchase consumer-grade devices to monitor their heart rate and heart rhythm. These devices use one of two general approaches[9,10]: use of the light sensor on the back of a smartwatch to measure *pulse* rate and rhythm using photoplethysmography or single-lead ECG devices that connect to a smartphone or are integrated into a smartwatch. Both of these devices use internal algorithms to provide automated simple interpretations of the heart rhythm (e.g., normal, possible atrial fibrillation or undetermined) and heart rate to the user. The ECG devices also record a single-lead ECG, which may be useful for a physician to interpret for possible arrhythmias. Currently, these devices are designed and approved to screen for atrial fibrillation but not other abnormal rhythms. These devices should not generally substitute for other, more established types of ambulatory monitoring to diagnose patients with suspected arrhythmias, with the possible exception of screening for atrial fibrillation.

Tilt Table Testing

Tilt table testing is used to confirm the diagnosis of neurocardiogenic syncope.[11] The test involves continuous heart rate and blood pressure monitoring during head-up tilting. After baseline measurements in the supine position, the patient is tilted head-up at 60 to 80 degrees for 60 minutes. Some laboratories use isoproterenol or nitroglycerin as additional provocation. A positive result is a sudden and precipitous fall in blood pressure and heart rate, with concurrent reproducibility of symptoms (syncope). Because there is an appreciable false-positive rate, the test is best used as a confirmatory test in patients with a history suggestive of neurocardiogenic syncope or in patients with syncope in whom structural heart disease and other causes of syncope have been excluded.

Electrophysiologic Studies

Electrophysiologic studies involve the placement of several transvenous catheters in the heart to make temporary measurements of intracardiac electrograms and to perform pacing. Electrophysiologic studies are useful to identify the

precise mechanism of tachyarrhythmias and are a necessary prelude to curative ablation (Chapter 54). Most arrhythmias, especially those with re-entrant mechanisms, can be readily induced during electrophysiologic studies. In addition, the existence and characteristics of accessory AV pathways (i.e., those responsible for Wolff-Parkinson-White syndrome or other re-entrant tachyarrhythmias) can be readily assessed by an electrophysiologic study. In patients with previous myocardial infarction, electrophysiologic studies are useful in determining the existence of a substrate for ventricular arrhythmias (Chapter 53), which may be treated with ablation or implantable defibrillators (Chapter 54). Electrophysiologic studies are also useful to determine the integrity of the conduction system and the precise mechanism of bradyarrhythmias that may be causing syncope. Therefore, electrophysiologic studies may be indicated in patients with documented or suspected tachyarrhythmias as a prelude to curative ablation in patients with documented or suspected supraventricular tachycardia or idiopathic ventricular tachycardia; in patients with a previous myocardial infarction (but left ventricular ejection fraction >30 to 35%) and syncope, presyncope, or palpitations to exclude ventricular tachycardia; and in patients with severe or prolonged symptoms and no apparent diagnosis by history or ambulatory monitoring in the setting of an abnormal ECG. However, with the advent of implantable loop recorders capable of prolonged electrocardiographic monitoring and the known benefit of implantable cardioverter-defibrillator therapy in many patients with depressed left ventricular function, the role of invasive diagnostic cardiac electrophysiologic studies has been substantially reduced in patients with unexplained syncope in patients with reduced left ventricular function.

Other Tests

Echocardiography

Echocardiography (Chapter 43) can be useful to ensure that a patient does not have underlying structural heart disease, which can be an important prognostic factor in patients with ventricular tachycardia or syncope. Echocardiography should be performed in patients who present with near-syncope or syncope that is not obviously neurocardiogenic to ensure that there is no valvular or myocardial cause.

Exercise Testing

Exercise testing (Chapters 39 and 56) can be useful to assess arrhythmias, particularly in patients whose symptoms are exercise related. Exercise testing can also be useful in the evaluation of patients with bradyarrhythmias to diagnose chronotropic incompetence, and it can differentiate AV block due to autonomic tone (improves with exercise) from intrinsic conduction disease (generally worsens with an increasing rate).

Neurologic Testing

Routine electroencephalography (Chapter 366) is not helpful because a single study may be normal, even in epileptic patients. Structural brain diseases rarely cause episodic loss of consciousness, and routine brain imaging studies are indicated only in patients with focal neurologic findings. Carotid Doppler (Chapter 376) studies can document stenosis, but unconsciousness requires bihemispheric dysfunction. Transcranial Doppler or magnetic resonance angiography of the basilar artery is indicated only in patients with symptoms suggestive of brain stem ischemia.

TREATMENT

Treatment of syncope depends on the underlying cause (Chapters 52 and 53),[12,13] as well as the risk of recurrence. One approach to risk stratification is the Canadian Syncope Risk Score (Tables 49-4 and 49-5).[14] Immediate hospital admission (e.g., observation in a chest pain unit, syncope unit, or the equivalent) is recommended when the patient has a Canadian Syncope Risk Score of greater than 3 or high-risk characteristics (see Table 49-6); the cause of syncope is unclear (especially in elderly patients, otherwise fragile, or worrisome patients); the syncope resulted in significant injury; the patient is suspected of having a cardiac or cerebrovascular cause of syncope; or the patient meets criteria established by professional societies (Table 49-7). Patients at highest risk have a systolic blood pressure below 90 mm Hg, a history of myocardial infarction or heart failure, a complaint of shortness of breath, an abnormal initial ECG, or a hematocrit less than 30%.

Until the cause of the syncope is determined and treated, patients should be instructed to avoid situations that may cause injury as a result of the syncope, especially if there is no prodrome and episodes are frequent. Careful consideration should be given to driving restrictions, which may be mandatory depending on local laws, and restrictions on dangerous work-related activity (e.g., for pilots, heavy machine operators, bus drivers) until definitive therapy is given.

TABLE 49-4 THE CANADIAN SYNCOPE RISK SCORE

	POINTS
History and physical examination	
Vasovagal characteristics*	−1
History of heart disease†	1
Systolic blood pressure < 90 mm Hg or > 180 mm Hg‡	2
Laboratory data	
Troponin level elevated	2
QRS axis < −30° or > 100°	1
QRS duration > 130 ms	1
Corrected QT interval > 480 ms	2
Emergency department clinical diagnosis	
Vasovagal syncope	−2
Cardiac syncope	2
Total score (−3 to 11)	

*Triggered by prolonged standing, fear, emotion, pain, or being in a warm crowded place.
†Coronary or valvular heart disease, heart failure, cardiomyopathy, history of ventricular or atrial arrhythmias, or cardiac rhythm device.
‡At any time from presentation until emergency department discharge.
Thiruganasambandamoorthy V, Kwong K, Wells GA, et al. Development of the Canadian Syncope Risk Score to predict serious adverse events after emergency department assessment of syncope. *CMAJ*. 2016;188:E289-E298.

TABLE 49-5 SERIOUS 30-DAY OUTCOMES BASED ON THE CANADIAN SYNCOPE RISK SCORE

RISK	# OF POINTS	SERIOUS OUTCOMES*	DEATHS
Very low	−3 to −2	0.2%	0
Low	−1 to 0	0.7%	0
Medium	1 to 3	8%	0.1%
High	4 to 5	19%	3%
Very High	6 to 11	51%	9%

*Serious arrhythmia (e.g., pacemaker/defibrillator, cardioversion to treat an arrhythmia) or nonarrhythmic serious conditions such as myocardial infarction, new serious structural heart disease, aortic dissection, pulmonary embolism, severe pulmonary hypertension, significant hemorrhage, subarachnoid hemorrhage, any other serious condition causing syncope, or death.
Thiruganasambandamoorthy V, Kwong K, Wells GA, et al. Development of the Canadian Syncope Risk Score to predict serious adverse events after emergency department assessment of syncope. *CMAJ*. 2016;188:E289-E298.

Cardiac Syncope

In patients with a cardiac cause of syncope, targeted treatments include valve replacement for aortic stenosis (Chapter 60); medications for hypertrophic cardiomyopathy (Chapter 47); a pacemaker for bradyarrhythmias (Chapters 52 and 54) and for carotid body hypersensitivity; cardioversion, an implantable cardioverter-defibrillator, ablation, or medications for tachyarrhythmias (Table 49-8; Chapters 50 through 53); and fluid repletion for orthostatic hypotension. Even when a pacemaker is implanted in a patient with syncope attributed to bradycardia, the 5-year incidence of recurrent syncope approaches 20%.[15]

Neurocardiogenic Syncope

In patients with neurocardiogenic syncope, the most effective therapies are behavioral: avoidance of triggers, wearing of compression stockings, and maintenance of adequate hydration and salt intake. Lying down with the feet elevated and performing isometric hand exercises may abort an acute episode. Patients should specifically be taught how to tense their arms and legs and grip their hands during prodromal symptoms to increase peripheral resistance and systemic blood pressure.

If neurocardiogenic syncope recurs despite education and lifestyle changes, fludrocortisone (0.1 mg/day, starting dose, increasing to 0.2 mg daily if tolerated or decreasing to 0.05 mg daily if not) can expand intravascular volume and reduce syncopal episodes[A6] but has not been definitively proven to prevent syncope. Midodrine (usually 5 to 10 mg three times daily), an α_1-receptor agonist and vasoconstrictor, has shown benefit,[A7] but other α-agonists have not. Fluoxetine (10 to 40 mg daily) may be useful in patients with recurrent neurocardiogenic syncope triggered by anxiety.[A8] β-blockers (e.g., pindolol 5 to 15 mg twice daily) can be of limited benefit. High dietary sodium intake is useful for reducing the change in heart rate in the postural tachycardia syndrome.[A9]

Pacemakers reduce recurrent neurocardiogenic syncope in selected patients with primarily a cardioinhibitory component or with severely asystolic neurally mediated syncope. For example, in patients older than 40 years with frequent syncopal episodes (at least three episodes in 2 years) and either (a) demonstrated bradycardia (asystole or AV block) during an event (≥3 seconds during a

TABLE 49-6 CHARACTERISTICS OF HIGH-RISK SYNCOPE, GENERALLY REQUIRING MONITORING, ADMISSION, AND/OR SPECIALIST CONSULTATION

HISTORY
During exertion
In supine position
New onset of chest discomfort
Palpitations before syncope
Family history of sudden death
Heart failure or left ventricular ejection fraction <35%
Aortic stenosis or left ventricular outflow obstruction
Cardiomyopathy (dilated or hypertrophic)
Arrhythmogenic right ventricular cardiomyopathy
Previously documented ventricular arrhythmia
Coronary artery disease
Congenital heart disease
Pulmonary hypertension
Previous ICD implantation
PHYSICAL EXAMINATION
Lowest systolic blood pressure <90 mm Hg
Sinus bradycardia (<40 bpm)
Suspected valvular heart disease
LABORATORY EVALUATION
Anemia (hemoglobin <9 g/dL)
Hypoxia
ELECTROCARDIOGRAM
New (or previously unknown) ischemic changes, left bundle branch block, or nonsinus rhythm
Bifascicular block
Prolonged QTc (>450 ms)
Brugada pattern

Adapted from Costantino G, Sun BC, Barbic F, et al. Syncope clinical management in the emergency department: a consensus from the first international workshop on syncope risk stratification in the emergency department. *Eur Heart J*. 2016;37:1493-1498.

TABLE 49-7 INDICATIONS FOR INITIAL OBSERVATION AND RAPID EVALUATION OF SYNCOPE

EUROPEAN SOCIETY OF CARDIOLOGY*	CANADIAN CARDIOVASCULAR SOCIETY†
Known coronary or structural heart disease, heart failure, or prior arrhythmia	Heart failure or history of ischemic, arrhythmic, obstructive, or valvular heart disease
ECG showing nonsustained ventricular tachycardia, bifascicular block, sinus bradycardia <50 beats/min, sinoatrial block, preexcitation, or evidence of an inherited disease	Abnormal ECG: arrhythmia, conduction disease, new ischemia, or evidence of prior myocardial infarction
Syncope during exertion or when supine, palpitations preceding syncope, family history of sudden cardiac death	Systolic blood pressure <90 mm Hg
Important comorbidities (e.g., severe anemia, electrolyte disturbance)	Comorbid conditions: age >60 years, dyspnea, hematocrit <30%, hypertension, cerebrovascular disease, family history of sudden death before age 50 years, syncope while supine, syncope during exercise, syncope with no prodromal symptoms

*Moya A, Sutton R, Ammirati F, et al. Guidelines for the diagnosis and management of syncope (version 2009): the Task Force for the Diagnosis and Management of Syncope of the European Society of Cardiology (ESC). *Eur Heart J*. 2009;30:2631-2671.

†Sanatani S, Chau V, Fournier A, et al. Canadian Cardiovascular Society and Canadian Pediatric Cardiology Association Position Statement on the Approach to Syncope in the Pediatric Patient. *Can J Cardiol*. 2017;33:189-198.

ECG = electrocardiogram.

TABLE 49-8 ARRHYTHMIC CAUSES OF PALPITATIONS AND SYNCOPE

ETIOLOGY	SPECIFIC ARRHYTHMIA	*SYMPTOMS*			TREATMENT	COMMENTS
		PALPITATIONS	DIZZINESS	SYNCOPE		
BRADYARRHYTHMIAS						
Sinus node dysfunction	Sinus bradycardia	No	Occasional	Rare	Pacemaker if symptoms	Can be seen in association with neurocardiogenic syncope
	Sinus arrest	Occasional	Yes	Occasional	Pacemaker	Pause >3 sec
	Sick sinus syndrome	Occasional	Yes	Occasional	Pacemaker	
AV nodal disease	First-degree AV block	No	No	No	None	
	Type I second-degree AV block	Occasional	No	No	None	Can be seen in association with neurocardiogenic syncope
	Type II second-degree AV block	Occasional	Rare	No	Pacemaker if severe	Can progress to complete heart block
	Third-degree AV block	Yes	Yes	Yes	Pacemaker	
Tachy-brady syndrome		Yes	Yes	Occasional	Treat tachycardia if possible Pacemaker	Can also be manifestation of sick sinus syndrome

TABLE 49-8 ARRHYTHMIC CAUSES OF PALPITATIONS AND SYNCOPE—cont'd

ETIOLOGY	SPECIFIC ARRHYTHMIA	SYMPTOMS			TREATMENT	COMMENTS
		PALPITATIONS	DIZZINESS	SYNCOPE		
TACHYARRHYTHMIAS						
SVT	Atrial tachycardia	Yes	Occasional	Rare	Ablation β-Blockers (e.g., metoprolol, atenolol)* Calcium-channel blockers (e.g., diltiazem)*	
	Atrial flutter	Yes	Occasional	Rare	Ablation Antiarrhythmic drugs (e.g., amiodarone)* Cardioversion (acute episode)	Often difficult to control rate
	Atrial fibrillation	Yes	Occasional	Rare	Ventricular rate control Warfarin Antiarrhythmic drugs (e.g., amiodarone)* Cardioversion (acute episode) Ablation	
	AV nodal re-entrant tachycardia	Yes	Yes	Rare	Ablation β-Blockers (e.g., metoprolol, atenolol)* Calcium-channel blockers (e.g., diltiazem)*	
	AV re-entrant tachycardia (WPW)	Yes	Yes	Rare	Ablation Antiarrhythmic drugs*	
VT	Idiopathic (RV outflow tract, fascicular)	Yes	Yes	Occasional	Ablation	Absence of structural heart disease Low risk for sudden death
	VT secondary to CAD, cardiomyopathy	Yes	Yes	Yes	ICD Amiodarone (400 mg qd)* Ablation	Increased incidence of sudden death
	Bundle branch re-entry	Yes	Yes	Yes	Ablation	Usually in the setting of LV dysfunction and baseline intraventricular conduction delay
	Genetic syndromes (e.g., long QT syndrome, Brugada, arrhythmic right ventricular dysplasia)	Occasional	Yes	Yes	ICD	Not always a clear family history Increased incidence of sudden death
Ectopy	PACs	Occasional	No	No	None β-Blockers (e.g., atenolol, metoprolol) if symptomatic*	
	PVCs	Occasional	No	No	None β-Blockers (e.g., atenolol, metoprolol) if symptomatic*	Benign in absence of structural heart disease
NEUROCARDIOGENIC SYNCOPE		No	Yes	Yes	Behavioral (hydration, avoid triggers, abort episodes) Midodrine (10 mg tid)	

*See Table 52-2 for drug doses.

AV = atrioventricular; CAD = coronary artery disease; ICD = implantable cardioverter-defibrillator; LV = left ventricle; PACs = premature atrial contractions; PVCs = premature ventricular contractions; RV = right ventricle; SVT = supraventricular tachycardia; VT = ventricular tachycardia; WPW = Wolff-Parkinson-White syndrome.

syncopal episode or ≥6 seconds during a presyncopal episode) or (b) a positive tilt test, dual-chamber pacing reduces subsequent syncope significantly.[A10, A11]

In syncope related to glossopharyngeal neuralgia (Chapter 367), the pain can usually be prevented by carbamazepine (400 to 1000 mg/day total in divided doses of 2 to 3 times per day orally). In refractory cases, 300 mg/day in divided doses of 1 to 4 times per day of phenytoin can be added.

Neurological Syncope

Patients who are at risk for basilar artery stroke should be treated with aspirin and should be considered for other treatments (e.g., surgery, stent placement) appropriate for their symptoms and anatomy (Chapter 376). For subclavian stenosis, repair of the stenosis is the treatment of choice. For other patients with cerebrovascular disease, the potential value of antithrombotic therapy and cerebral revascularization procedures must be considered according to standard criteria (Chapter 376). Seizures require anti-epileptic medications (Chapter 372). Basilar artery migraine requires careful medical therapy (Chapter 367).

PROGNOSIS

One syncopal event predicts a substantial risk for recurrent syncope. Although a history of syncope itself does not appear to increase the risk for a motor vehicle crash,[16] patients with cardiac or cerebrovascular causes have higher mortality rates than patients with definable noncardiac causes or those without a definable cause. For otherwise healthy individuals discharged with a primary diagnosis of syncope, the subsequent risk for all-cause mortality is increased by 6%, with stroke increased by 35%, and a cardiovascular hospitalization by 75%. Among patients who come to an emergency department, the overall death rate is about 7.5% at 1 year. In patients with inherited arrhythmias, such as long QT syndrome (Chapter 53), syncope worsens prognosis. Compared with other patients with supraventricular tachycardia, syncope per se does not increase mortality but does increase the likelihood of needing medical or ablation therapy (Chapter 54).

TABLE 49-9 DRIVING IN PATIENTS WITH ARRHYTHMIAS

CARDIOVASCULAR DISORDER	DRIVING RESTRICTION
SVT: atrial fibrillation, atrial flutter, narrow-complex SVT, wide-complex SVT	No driving if symptomatic Can drive if asymptomatic for 1 month (3-6 months for wide-complex SVT)
VT, VF	No driving for 6 months
Bradyarrhythmias	No restriction if asymptomatic; no driving if syncope occurs
After successful catheter ablation	Can drive after recovery from procedure
After pacemaker implantation	No driving for 1 week (4 weeks for commercial drivers)
After ICD implantation	No driving for 6 months (barred from commercial driving)

ICD = implantable cardioverter-defibrillator; SVT = supraventricular tachycardia; VF = ventricular fibrillator; VT = ventricular tachycardia.

Adapted from Banning AS, Ng GA. Driving and arrhythmia: a review of scientific basis for international guidelines. *Eur Heart J*. 2013;34:236-244.

In patients with arrhythmias, a key issue is whether they should be allowed to drive a motor vehicle. Consensus recommendations vary depending on the arrhythmia and its treatment (Table 49-9).

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50 CARDIAC ARREST AND LIFE-THREATENING ARRHYTHMIAS

ROBERT J. MYERBURG AND RACHEL LAMPERT

Sudden cardiac arrest is characterized by an abrupt loss of consciousness because of absence of cerebral blood flow owing to loss of cardiac pumping action. If not treated promptly, it will lead to central nervous system injury within minutes and a progressively increasing risk of death. Sudden cardiac arrest is often forewarned by a change in cardiovascular status, as indicated by the onset or worsening of symptoms related to transient arrhythmias, such as palpitations, lightheadedness, or near-syncope or syncope (Chapter 49). Other forewarnings may include new or worsening chest pain, dyspnea, or weakness. In individual patients, however, these warning symptoms have limited sensitivity and predictive power for sudden cardiac arrest because they also predict acute coronary syndromes (Chapter 57) and acute myocardial infarction (MI) (Chapter 58) in the absence of expressed arrhythmia. Further, sudden cardiac arrest is often the first manifestation of cardiac disease.

EPIDEMIOLOGY

The population burden of sudden cardiac arrest leading to sudden cardiac death is described by the rule of 50 s—specifically, sudden cardiac death accounts for about 50% of all cardiovascular deaths, about 50% of which are first cardiac events in apparently healthy individuals with unrecognized disease, and resulting in 50% of the loss of years of productivity owing to cardiovascular diseases.[1] The incidence in the general population over the age of 35 years is 1 to 2 per 1000 per year. Among adolescents and young adults, it is 1 per 100,000 per year. Most sudden cardiac arrests occur out of hospital (>375,000/year in the United States, with an average survival rate of 10%), and an additional 200,000 or so occur in hospital, with about a 25% survival rate.

Coronary artery disease is the most common cause of sudden cardiac arrest, either during acute events or as a consequence of chronic disease. Patients with advanced ischemic and nonischemic cardiomyopathies (Chapter 47) and with heart failure (Chapters 45 and 46) are at higher risk, although the incidence in heart failure appears to be decreasing as a result of improved long-term therapies. Patients with either common or rare acquired and inherited arrhythmia syndromes (Chapters 52 and 53) are also at increased risk for sudden cardiac arrest. In addition, both competitive athletes and individuals participating in high-intensity recreational athletic activities have a low but finite increase in risk for sudden cardiac arrest. Risk is higher in males and in association with specific sports, such as basketball and football in the United States and cycling, jogging, and soccer in Europe. In adolescents and young adults in the United States, hypertrophic cardiomyopathy (Chapter 47) is the most commonly identified structural cause in competitive athletes.[2] In individuals under 35 years, 40% of patients have no structural cardiac abnormalities at autopsy ("sudden unexplained death"), among whom about 25% have a clinically relevant variant in postmortem genetic testing.[3] Beyond the age of 30 to 35 years, coronary artery disease is more common (Chapter 58). Offspring in families in which sudden cardiac arrest was the initial manifestation of heart disease are themselves at increased risk for arrest as the initial manifestation of heart disease, thereby emphasizing the importance of a careful family history for assessing risk.[4]

PATHOBIOLOGY

In the past, ventricular fibrillation (VF) and pulseless ventricular tachycardia (VT) were the most common initially identified electrical mechanisms of sudden cardiac arrest (Chapter 53), largely in association with acute MI. However, asystole and pulseless electrical activity are now the first recorded rhythm in the majority of both in-hospital and out-of-hospital cases. Asystole may be primary or may follow deterioration or active termination of VF by electrical cardioversion. Pulseless electrical activity is defined as primary when it is the initial rhythm noted in patients with predisposing cardiac disorders and as secondary when it occurs in the setting of noncardiac predisposing factors, such as hypoxemia, metabolic disorders, massive pulmonary embolism, or blood loss.

Premature ventricular contractions (PVCs) and short runs of nonsustained VT may forewarn a long-term risk for sudden cardiac arrest, primarily when associated with advanced structural heart disease, but there is no evidence that suppression of chronic PVCs is protective. In contrast, sustained wide-QRS tachycardias are of greater concern and should be considered of ventricular origin, because of their potentially high immediate risk, until determined otherwise (Chapter 49).

It is important to recognize that not all out-of-hospital sudden deaths are cardiac in origin. Other causes include pulmonary embolism (Chapter 68), ruptured aortic aneurysm (Chapter 63), aortic dissection (Chapter 63), and acute neurologic events such as intracerebral or subarachnoid hemorrhage (Chapter 377).[5,6]

CLINICAL MANIFESTATIONS AND DIAGNOSIS

Pulselessness, in conjunction with the absence of respiratory efforts or only gasping or agonal respirations and absence of responsiveness, is diagnostic of

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CLINICAL MANIFESTATIONS AND DIAGNOSIS

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ABSTRACT

Sudden cardiac arrest, as the mechanism for unexpected deaths, accounts for 50% of all cardiovascular deaths and is the first clinically recognized cardiovascular event in 50% of these victims. Electrical mechanisms of sudden cardiac arrest are shockable rhythms, including ventricular fibrillation (VF) and pulseless ventricular tachycardia (pulseless VT), and nonshockable rhythms, such as pulseless electrical activity and asystole. Shockable rhythms provide a better opportunity for return of spontaneous circulation and survival. The most common causes of cardiac arrest are consequences of coronary artery disease, such as acute ischemia and ischemic cardiomyopathy. The various nonischemic cardiomyopathies, and other acquired or inherited disorders, account for a smaller proportion of the events. Survival from sudden cardiac arrest free of neurologic dysfunction is dependent upon a rapid return of spontaneous circulation. Cardiopulmonary resuscitation (CPR) initiated by bystanders immediately after summoning emergency rescue and rapid defibrillation with community-based automated defibrillators improve survival. Advanced life support includes activities—such as intubation, administration of antiarrhythmic drugs, and other therapies—that may restore circulation when return of spontaneous circulation is not immediate. An important consequence of sudden cardiac arrest is brain damage, due to ischemic encephalopathy and resulting coma. Among out-of-hospital cardiac arrest victims who are resuscitated and hospitalized, brain damage is the most important cause of subsequent in-hospital death and long-term disabilities. Outcomes can be improved by preventing hyperthermia in the comatose cardiac arrest victim. Among those whose sudden cardiac arrest is not secondary to reversible causes, implantable cardioverter-defibrillators provide long-term protection against death from recurrent sudden cardiac arrest.

KEYWORDS

cardiac arrest
sudden cardiac death
ventricular fibrillation
ventricular tachycardia
cardiopulmonary resuscitation
defibrillation
antiarrhythmic drugs

cardiac arrest. Although the absence of a carotid or femoral pulse is a primary diagnostic criterion for health care professionals, palpation for a pulse is no longer recommended for lay responders. The absence of respiratory efforts or severe stridor with persistence of a pulse suggests a primary respiratory arrest that may lead to cardiac arrest in a short time.

In the out-of-hospital setting, the rhythm can be diagnosed by an automatic external defibrillator, when available. In the inpatient setting, electrocardiographic monitoring should be started immediately. The underlying arrhythmia can be VF, VT, supraventricular tachycardia, bradycardia, asystole, or pulseless electrical activity, with the latter implying electrical activity during which no pulse is generated (Fig. 50-1). VF is recognized by the disorganized electrical activity with no recognizable QRS. If the electrocardiogram (ECG) reveals pulseless electrical activity, potentially treatable causes include hypovolemia (Chapter 102), hypoxia (Chapter 90), cardiac tamponade (Chapter 62), tension pneumothorax (Chapter 86), drug overdose (Chapter 96), hypothermia (Chapter 95), and hyperkalemia (Chapter 103). For a wide-complex tachycardia, differentiating VT from a supraventricular tachycardia can be more challenging (see Fig. 49-3 and Table 53-2).

For at least 50% of survivors of a cardiac arrest, the arrest represents the first manifestation of cardiac disease, and diagnosing the underlying cause is critical for treatment to and prevent recurrence. The leading causes of out-of-hospital cardiac arrest are ischemic heart disease, structural heart disease, and primary arrhythmias (Table 50-1), but a variety of severe noncardiac conditions can also be responsible and are more frequent when a patient arrests in a hospital.

Systematic clinical testing should start with an ECG, blood testing for electrolytes and toxicology, echocardiography, and imaging for coronary artery disease or coronary artery anomalies. Cardiac magnetic resonance imaging (Chapter 44) is more sensitive than echocardiography and should also be performed if the diagnosis remains elusive. If the underlying diagnosis remains unclear after initial testing, provocative stress testing may reveal arrhythmic syndromes such as catecholaminergic ventricular tachycardia (Chapter 53) or a subclinical arrhythmogenic cardiomyopathy, and pharmacologic testing may unmask other rare arrhythmic syndromes. Genetic testing can reveal an underlying abnormality in about 10 to 30% of patients whose other tests have been unrevealing.[6]

TREATMENT

The management of a patient during cardiac arrest emphasizes actions to maintain blood flow to preserve the viability of the central nervous system, heart, and other vital organs, while striving to restore spontaneous circulation as quickly as possible. These goals are accomplished by assessing the patient and contacting an emergency response system (EMS), followed quickly by initiating basic life support (BLS), early defibrillation for patients with VF or pulseless VT, advanced life support (ACLS) as needed, and post–cardiac arrest care.

Cardiopulmonary resuscitation (CPR) performed by bystanders in the community or at sporting events before EMS arrival is associated with a 30-day

TABLE 50-1 CAUSES OF OUT-OF-HOSPITAL CARDIAC ARREST

CARDIAC CAUSES
- Ischemic heart disease with or without acute myocardial infarction
- Cardiomyopathy (e.g., myocarditis, hypertrophic, infiltrative, dilated), arrhythmogenic right ventricular cardiomyopathy
- Valvular heart disease
- Pericardial tamponade
- Congenital heart disease, including coronary artery anomalies
- Arrhythmia without ischemic or structural heart disease (e.g., Wolff-Parkinson-White syndrome, long QT syndrome, Brugada syndrome, catecholaminergic polymorphic ventricular tachycardia)

NONCARDIAC CAUSES
- Traumatic or nontraumatic bleeding
- Cerebrovascular accident
- Aortic dissection or rupture
- Hypoxia (e.g., pulmonary embolism, pneumonia, carbon monoxide poisoning, asthma, or chronic obstructive pulmonary disease)
- Drug overdose
- Hypoglycemia
- Hypothermia or hyperthermia
- Epilepsy
- Tension pneumothorax
- Septic shock
- Electrolyte abnormalities
- Severe dehydration

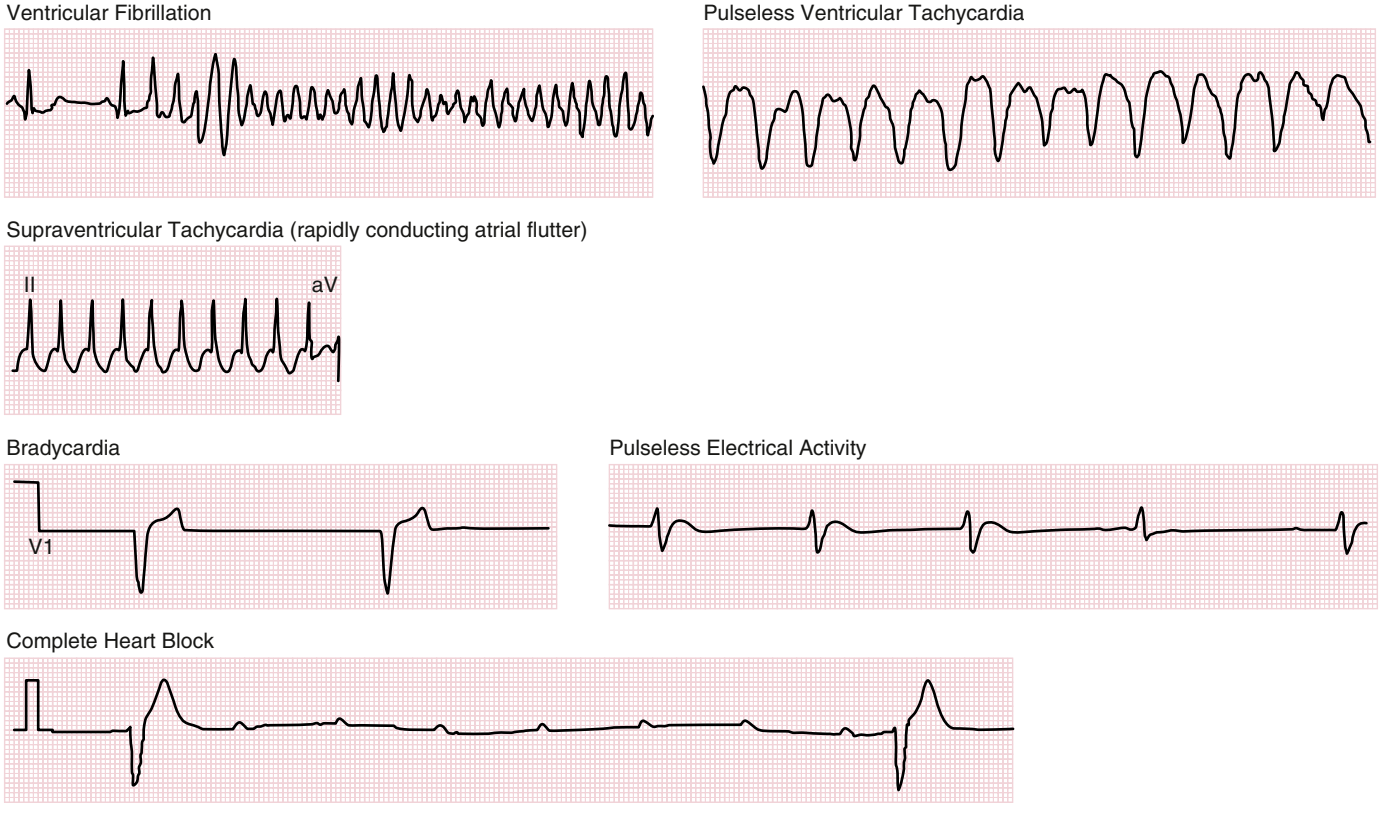

FIGURE 50-1. Electrical mechanisms associated with cardiac arrest. Shockable mechanisms include ventricular fibrillation and pulseless ventricular tachycardia. Pulseless electrical activity (as distinct from pulseless ventricular tachycardia) is a mechanical rather than an electrical disorder, and shocks are not indicated.

survival rate that is more than twice as high as that associated with no CPR before the arrival of EMS.[7,8] A mobile-phone system dispatch of lay volunteers trained in CPR and located within about one third of a mile of the victim can increase the rate of lay response by about 40%.[A1] In the United States, however, Black and Hispanic persons are 20 to 35% less likely to receive bystander CPR regardless of the location of their arrest.[9]

Basic Life Support

After an initial evaluation for response to voice or tactile stimulation, observation for respiratory movements and skin color, and simultaneous palpation of major arteries for the presence of a pulse, the determination that a life-threatening incident is in progress should prompt immediate contact with EMS (911).

When a cardiac arrest is confirmed, the goal of BLS is to establish perfusion as quickly as possible using CPR or the concept of cardiocerebral resuscitation (see later). The algorithm of BLS is compression-airway-breathing, based on the recognition that compression alone is the primary maneuver because the patient is better perfused by minimizing interruptions between compressions and can be harmed by excessive ventilation.

A precordial thump may be attempted by a trained rescuer as part of an initial response, although its added benefit is questionable. The technique involves one or two blows delivered firmly to the junction of the middle and lower thirds of the sternum from a height of 8 to 10 inches. It should not be used in an unmonitored patient with a perceptible rapid tachycardia or without complete loss of consciousness because of concern about converting organized electrical activity into VF.

Prompt initiation of CPR, which can be performed by professional and paraprofessional personnel, by emergency medical technicians, and by trained laypersons, is the key element for successful resuscitation. The delay between diagnosis and starting CPR should be minimal. If only one witness is present, the only activity that should precede BLS is telephone contact (911) of EMS. The untrained lay bystander can be prompted on how to perform CPR by the EMS telecommunicator.

Clearing the airway includes tilting the head backward and lifting the chin, in addition to exploring the airway for foreign bodies—including dentures—and removing them. The Heimlich maneuver, which entails wrapping the arms around the victim from the back and delivering a sharp thrust to the upper part of the abdomen with a closed fist, should be performed if there is reason to suspect a foreign body lodged in the oropharynx, as suggested by severe respiratory stridor, in contrast to slow agonal respirations or apnea, especially in a patient who is eating at the time of the arrest. When the person at the scene has insufficient physical strength to perform the maneuver, mechanical dislodgment of a foreign body can sometimes be achieved by abdominal thrusts with the unconscious patient in a supine position. If there is suspicion that respiratory arrest precipitated the cardiac arrest, particularly in the presence of a mechanical airway obstruction, a second precordial thump should be delivered after the airway has been cleared.

With the head properly positioned and the oropharynx clear, mouth-to-mouth respiration can be initiated. With the exception of Heimlich maneuvers, however, mechanical ventilation strategies are now reserved for EMS responders and medical professionals, rather than bystanders. Devices for establishing ventilation include plastic oropharyngeal airways, esophageal obturators for establishing ventilation, a masked Ambu bag, and endotracheal tubes. Intubation is the preferred procedure, but time should not be sacrificed, even in the in-hospital setting, while awaiting an endotracheal tube or a person trained to insert it. Temporary support with Ambu bag ventilation is the usual method in the hospital until endotracheal intubation can be accomplished. When ventilatory support is provided by EMS responders in the out-of-hospital setting, the lungs should be inflated twice in succession after every 30 chest compressions.

Circulatory support, which is the primary element of BLS, is intended to maintain blood flow until definitive steps can be taken to restore effective cardiac contractions. The rationale is based on the hypothesis that chest compression maintains an externally driven pump function by sequential emptying and filling of its chambers, with competent valves favoring forward flow. The palm of one hand is placed over the lower sternum while the heel of the other rests on the dorsum of the lower hand. The sternum is then depressed with the resuscitator's arms straight at the elbows to provide a less tiring and more forceful fulcrum at the junction of the shoulders and back. A force sufficient to depress the sternum at least 2 inches (>5cm) should be applied, with abrupt relaxation. The cycle is carried out at a rate of about 100 compressions per minute. Compression-only CPR is as good as, if not perhaps slightly better than, compression plus rescue breathing, in part because it may be more effective than compression-ventilation sequences, encourages more bystander CPR by untrained or remotely trained bystanders who lack confidence, and also allays concerns about mouth-to-mouth ventilation of unknown victims in the absence of mechanical airway devices.[A2,A3] An alternative is a compression-ventilation ratio of 30:2 for single responders to victims through adulthood and for two responders to adult victims. For two-rescuer CPR for infants and children, the recommended compression-ventilation ratio is 15 : 2. Another recently suggested modification is the "hands-only" (cardiac-only, compression-only) technique, which uses 200 successive compressions without interruption. In the prehospital setting, therapeutic hypothermia is not beneficial.[A4]

Intermediate Life Support: Automated External Defibrillators

Despite the benefit of BLS, time to defibrillation is the major determinant of survival for victims in VF or pulseless VT. Because ACLS strategies are generally implemented by in-hospital personnel or out-of-hospital EMS responders, an intermediate strategy is for nonconventional first responders to use automated external defibrillators. These devices prompt the user to deliver a defibrillation shock when deemed appropriate by a computerized rhythm detection system integrated into the device. The operators can be trained police officers, security guards, airline personnel, or trained or untrained lay bystanders (Table 50-2). A number of studies have suggested improved survival rates when such strategies are deployed in public sites,[A5] but an initial study of a home deployment strategy was disappointing. Further study is warranted because 70 to 80% of out-of-hospital cardiac arrests occur at home, with survival rates less than 6%. Automated external defibrillators, which serve as an intermediate supplement to the BLS-ACLS sequence, are intended to attempt earlier defibrillation while awaiting the arrival of ACLS-trained emergency personnel.

Advanced Cardiac Life Support

ACLS methods, other than those directly related to control of tachyarrhythmias, are guided by comprehensive protocols to aid responders over a broad expanse of clinical circumstances and mechanisms of cardiac arrest, ranging from transient clinical events to end-stage multisystem disease. The primary goals of ACLS are to restore a hemodynamically effective cardiac rhythm, optimize ventilation, and maintain and support the restored circulation. During ACLS, the first priority is prompt cardioversion or defibrillation of persisting pulseless VT or VF, if appropriate equipment is immediately available. If cardiac arrest has occurred for 4 to 5 minutes before the availability of a defibrillator, a short period of cardiac compressions immediately before defibrillation increases the probability of survival. The administration of epinephrine in this setting to all patients can increase 30-day overall survival but not survival with a favorable neurologic outcome.[A6] In the in-hospital setting, vasopressin (20 IU) plus methylprednisolone (40 mg) similarly can increase the likelihood of a return to spontaneous circulation but not of a favorable neurologic outcome.[A7] If the initial attempt to restore circulation is

TABLE 50-2 AUTOMATED EXTERNAL DEFIBRILLATOR STRATEGIES FOR RAPID RESPONSE TO CARDIAC ARRESTS CAUSED BY VENTRICULAR FIBRILLATION

DEPLOYMENT	EXAMPLES	RESCUERS	ADVANTAGES	LIMITATIONS
Emergency vehicles	Police cars Fire engines Ambulances	Trained emergency personnel	Experienced users Broad deployment Objectivity	Deployment time Arrival delays Community variations
Public access sites	Public buildings Stadiums, malls Airports Airliners	Security personnel Designated rescuers Random laypersons	Population density Shorter delays Lay and emergency personnel access	Low event rates Inexperienced users Panic and confusion
Multifamily dwellings	Apartments Condominiums Hotels	Security personnel Designated rescuers Family members	Familiar locations Defined personnel Shorter delays	Infrequent use Low event rates Geographic factors
Single-family dwellings	Private homes Apartments Neighborhood "heart watch"	Family members	Immediate access Familiar setting	Acceptance Victim may be alone One-time user; panic

unsuccessful, continued on-scene resuscitation may be preferred to immediate transfer to a hospital.[10] In patients who do not respond to standard defibrillation, either rapid sequential shocks from two defibrillators or switching the pads to an anterior-posterior position is preferable to repeated standard shocks.[A8]

After the initial attempt to restore a hemodynamically effective rhythm, the patient is intubated and oxygenated, if needed. Electrical pacing of the heart should be attempted if a severe bradyarrhythmia or asystole is present (Chapter 54). An intravenous line is established to deliver medications. After intubation, the goal of ventilation is to reverse hypoxemia and not merely to achieve a high alveolar P_{O_2}. When available, oxygen rather than room air should be used to ventilate the patient, and arterial O_2 saturation should be monitored, when possible. In the out-of-hospital setting, a face mask or an Ambu bag by means of an endotracheal tube is generally used.

Approach to Specific Arrhythmias

Tachyarrhythmic Cardiac Arrest

Slow, well-tolerated monomorphic VTs, especially in the absence of structural heart disease, can usually be treated with antiarrhythmic drugs or β-adrenergic blocking agents in some circumstances (see Tables 52-2 and 52-3 in Chapter 52). In contrast, when rapid VT or VF is identified on a monitor or by telemetry, immediate cardioversion or defibrillation should be performed (Fig. 50-2). When a reversible cause, such as an acute ischemic syndrome or electrolyte disturbance, is the apparent mechanism, normal rhythm can be successfully restored in up to 90% of VF victims weighing up to 90 kg with a direct current (DC) biphasic shock of up to 200 joules delivered within 2 to 3 minutes, or if such equipment is not available, a monophasic shock of up to 360 joules. Failure of the initial shock to restore an effective rhythm is a poor prognostic sign.

After a single shock, the patient should be checked immediately for restoration of a spontaneous pulse; CPR should be continued for five cycles if a pulse remains absent. Subsequently, a second shock should be delivered, followed by epinephrine 1 mg intravenously (IV). If a pulse is still absent, CPR is repeated for five cycles before the next shock. Epinephrine may be repeated at 3- to 5-minute intervals with defibrillator shocks in between, but high-dose epinephrine does not appear to provide added benefit. Vasopressin (40 U given IV once) is an equally good alternative to epinephrine,[A8] but the combination does not appear to be better than either alone.

SVTs can precipitate cardiac arrest in two circumstances. One is in patients with high-grade coronary artery disease, in whom rapid heart rates can cause myocardial ischemia because of the dependence of coronary blood flow on the diastolic interval. In this setting, the arrhythmia should be treated urgently by restoring sinus rhythm or slowing the heart rate, either by medical therapy (e.g., intravenous adenosine, β-blockers, or calcium channel blockers) (Chapter 52) or by electrical DC cardioversion (Chapter 54). The second mechanism of concern is atrial fibrillation in patients with Wolff-Parkinson-White syndrome, who may have ventricular rates greater than 240 beats per minute when the accessory pathway has a short refractory period (see Fig. 52-10 in Chapter 52). This abnormality, which can trigger VF or cause hypotensive VT, requires prompt slowing or termination of the SVT (Chapter 52).

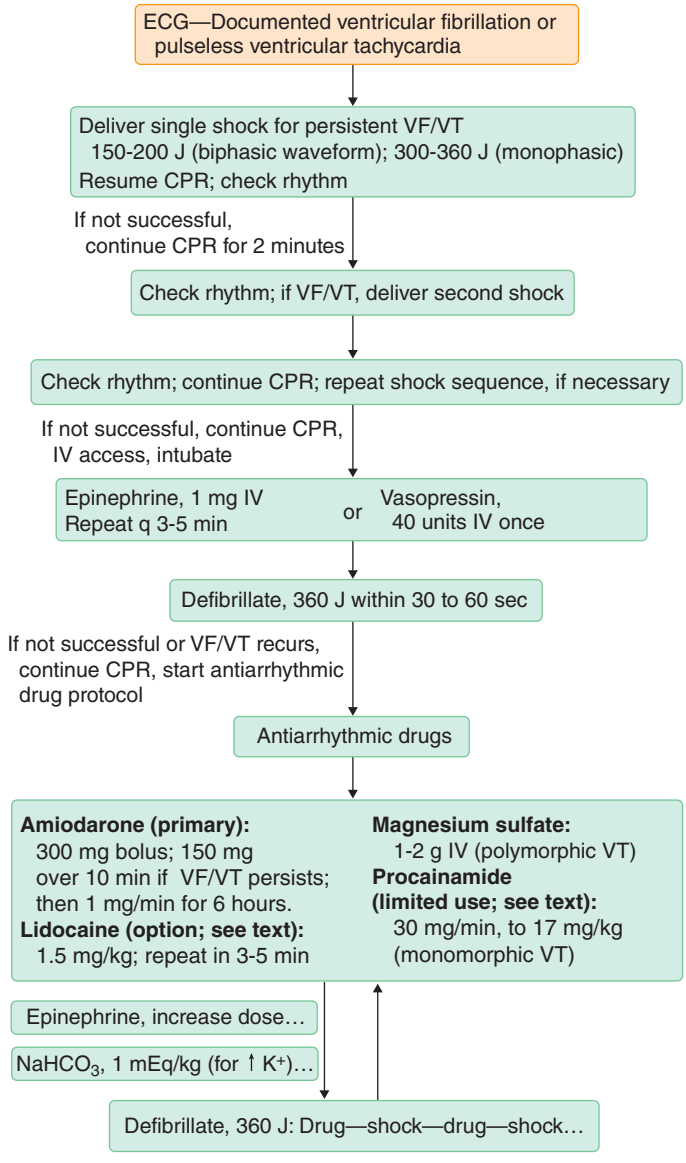

FIGURE 50-2. General algorithm for advanced cardiac life support (ACLS) response to ventricular fibrillation (VF) or pulseless ventricular tachycardia (VT). For more detail, see the ACLS guidelines in the Grade A References. *Note:* In a 2008 advisory, 200 compression-only sequences were suggested as an alternative to standard cardiopulmonary resuscitation (CPR) cycles between shocks, and this approach is under consideration for future guidelines. ECG = electrocardiogram; IV = intravenous; K^+ = potassium; $NaHCO_3$ = sodium bicarbonate.

Pharmacotherapy for Resistant Arrhythmias

For a patient who continues in VF or pulseless VT despite multiple attempts at DC cardioversion after epinephrine, or who has recurrent episodes of VF or VT after cardioversion, the likelihood of return of spontaneous circulation and survival to hospitalization may be increased by administering intravenous antiarrhythmic agents while continuing resuscitative efforts (see Fig. 50-2). Amiodarone and lidocaine are equivalent to each other and better than placebo when the cardiac arrest is witnessed by bystanders or EMS, but neither is better than placebo for patients who suffer unwitnessed arrests.[A9]

Amiodarone is given as a 150-mg intravenous bolus over a 10-minute period, followed by 1 mg/minute for up to 6 hours and 0.5 mg/minute thereafter. Additional bolus dosing, to a maximum of 500 mg, can be tried if the initial bolus is unsuccessful. The lidocaine dose is a 1.0- to 1.5-mg/kg intravenous bolus, with the dose repeated in 2 minutes. Neither drug needs to be given as a routine to individuals who respond to initial defibrillation with a persistently stable rhythm. For patients who remain electrically unstable or have recurrent episodes of VT or VF after initial defibrillation and oxygenation, continued antiarrhythmic therapy is indicated.

If there is sufficient clinical evidence that the cardiac arrest was associated with an acute coronary syndrome or that recurrent arrhythmias are precipitated by ischemia, lidocaine may be used in preference to amiodarone. Under other circumstances, intravenous amiodarone may be the preferred initial drug. Under all circumstances, the alternative drug may be tried if the initial choice fails. Intravenous procainamide (loading infusion of 100 mg/5 minutes to a total dose of 500 to 800 mg, followed by a continuous infusion at 2 to 5 mg/minute) is now rarely used but may be tried in those with persisting, hemodynamically unstable arrhythmias.

In patients with acute hyperkalemia as the triggering event for resistant VF, hypocalcemia, or arrest potentially caused by excess doses of calcium-blocking drugs, 10% calcium gluconate (5 to 20 mL infused at a rate of 2 to 4 mL/minute) may be helpful. Otherwise, calcium should not be used routinely during resuscitation, even though ionized Ca^{2+} levels may be low during resuscitation from cardiac arrest.

Resistant forms of polymorphic VT (*torsades de pointes*), rapid monomorphic VT, ventricular flutter (rate >260/minute), or resistant VF may respond to magnesium sulfate ($MgSO_4$) (1 to 2 g given IV over a 1- to 2-minute period) or to β-blocker therapy (propranolol, 1-mg boluses IV to a total dose of up to 15 to 20 mg or metoprolol 5 mg IV, up to 20 mg). $MgSO_4$ is specifically indicated for polymorphic VTs due to inherited or acquired (drug-induced) long QT patterns (Chapter 53). This VT pattern also occurs with marked hypokalemia. Potassium chloride (20 mEq/hour intravenously) should be included in the treatment of patients with these arrhythmias if their serum potassium level is less than 3 mEq/L. However, hypokalemia also may follow the acid-base and electrolyte shifts associated with prolonged arrests and should not be considered a primary cause of the cardiac arrest in that circumstance.

Asystole, Bradyarrhythmias, and Pulseless Electrical Activity

The approach to a patient with symptomatic bradyarrhythmia, asystolic arrest, or pulseless electrical activity differs from the approach to patients with tachyarrhythmic events (pulseless VT or VF). Effective CPR is critical because no electrical strategies are effective for restoring circulation. As soon as this mechanism of cardiac arrest is recognized, efforts should focus on continuous CPR, intubation, and establishing intravenous access. Possible reversible causes, including hypovolemia, hypoxia, cardiac tamponade, tension pneumothorax, preexisting

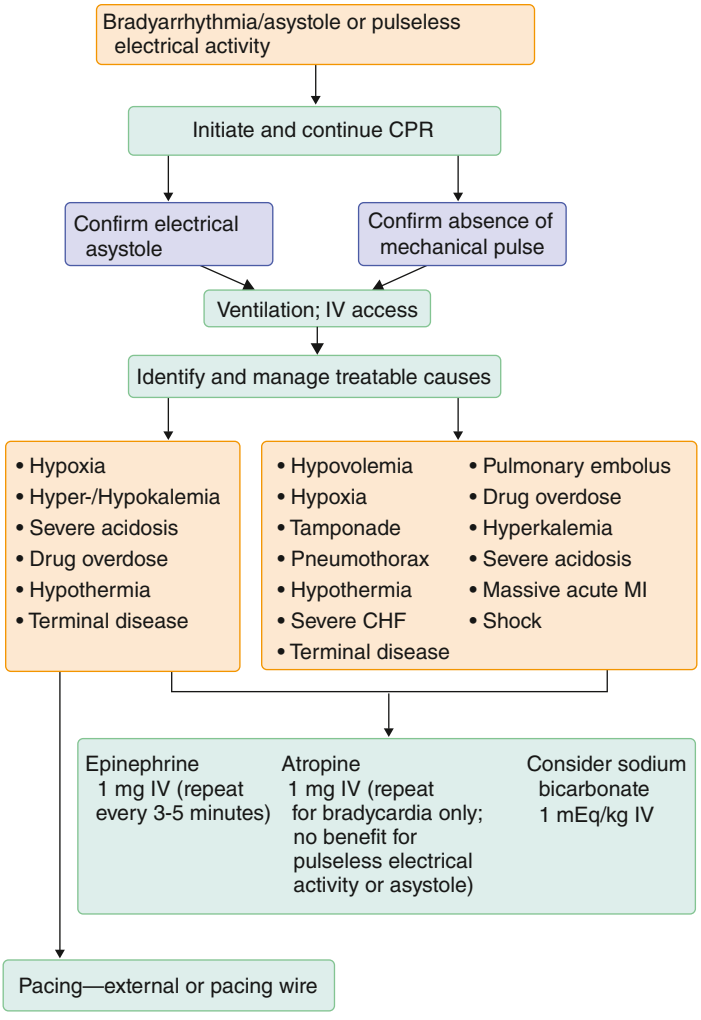

FIGURE 50-3. General algorithm for advanced cardiac life support response to bradycardic or asystolic cardiac arrest or pulseless electrical activity. For more detail, see the Grade A References. CHF = congestive heart failure; CPR = cardiopulmonary resuscitation; IV = intravenous; MI = myocardial infarction.

acidosis, drug overdose, hypothermia, and hyperkalemia, must be identified and treated immediately (Fig. 50-3). Respiratory causes of pulseless electrical activity or asystole may respond promptly to appropriate interventions, as do tamponade and hypovolemic causes. Epinephrine (1.0 mg IV every 3 to 5 minutes) or isoproterenol (up to 15 to 20 μg/minute IV), which are commonly used in an attempt to elicit spontaneous electrical activity or increase the rate of a bradycardia, have only limited success. However, one randomized trial of patients with cardiac arrest requiring vasopressors showed that combined vasopressin-epinephrine plus methylprednisolone during CPR and stress-dose hydrocortisone in postresuscitation shock improved survival to hospital discharge with favorable neurologic status compared with epinephrine-saline placebo. In the absence of an intravenous line, epinephrine (1 mg, i.e., 10 mL of a 1 : 10,000 solution) may be given by the intracardiac route, despite the danger of coronary artery or myocardial laceration. Sodium bicarbonate (1 mEq/kg) may be tried for known or strongly suspected preexisting hyperkalemia or bicarbonate-responsive acidosis but is no longer recommended for routine use. Atropine is no longer recommended for management of bradyarrhythmic cardiac arrests because of lack of efficacy.

External pacing (Chapter 54) should be tried for out-of-hospital bradycardic or asystolic cardiac arrests, although existing data suggest little effect on outcome. In-hospital, external pacing is generally used during the initial response to a bradycardic or asystolic arrest, but it should be superseded by transvenous pacing if the arrest is prolonged, if continuous pacing is needed, or if the external device fails to pace. Unfortunately, an *asystolic* patient continues to have a very poor prognosis.

Postresuscitation Care

After return of spontaneous circulation, particularly following a prolonged resuscitation, attention shifts to the elements of injury caused by cardiac arrest. The four components of the post–cardiac arrest syndrome include brain injury,[11] myocardial dysfunction, systemic ischemia-reperfusion responses, and control of persistent precipitating factors. The therapeutic goal is to maintain a stable electrical, hemodynamic, and central nervous system status. Specific therapy is determined by the clinical circumstances. The most pressing issue is the presence of anoxic encephalopathy, which is a strong predictor of in-hospital death and postarrest disability. To prevent postarrest encephalopathy, therapeutic cooling to prevent hyperthermia improves neurologic outcomes, but a target of 36°C appears to be as good as targeted hypothermia.[A10,A11] After 24 to 48 hours of cooling, patients should be gradually rewarmed to 37°C. For patients who suffer in-hospital cardiac arrest, therapeutic hypothermia does not appear to be beneficial.

During or after therapy targeted to restoration of an electrically stable cardiac rhythm, the patient's general metabolic state should be addressed by improving oxygenation and reversing acidosis. Intravenous sodium bicarbonate (1 mEq/kg), with up to 50% of this dose repeated every 10 to 15 minutes during the course of CPR, is recommended for patients with known or suspected preexisting bicarbonate-responsive causes of acidosis, for certain drug overdoses (Chapter 96), and after prolonged and unsuccessful attempts at resuscitation. Caution must be exercised, however, because excessive quantities of sodium bicarbonate can be deleterious by causing alkalosis, hypernatremia, and hyperosmolality. Furthermore, goal-directed optimization of oxygenation does not improve neurologic outcomes.[A12] When possible, arterial pH, P_{O_2}, and P_{CO_2} should be monitored during the resuscitation. Myocardial injury (Chapter 58) and hemodynamic dysfunction (Chapter 93) are managed by standard techniques, and a mean arterial blood pressure target of 63 mm Hg is as good as a target of 77 mg Hg.[A13]

In parallel with postarrest therapeutic support, diagnostic actions are also indicated, especially when the arrest is suspected to be due to an acute coronary syndrome (Chapter 57). The most pressing is cardiac catheterization followed by coronary interventions (Chapter 59) to help control unstable rhythms associated with persisting ischemia and to preserve myocardium in survivors.[12] However, in patients without ST elevation, immediate angiography is no better than delaying angiography until after neurologic recovery.[A14,A15] These activities require EMS transport to hospitals capable of advanced care on a 24-7 basis. An added transport time of less than 15 minutes to achieve prompt advanced care has been suggested as an appropriate tradeoff. A 2-day course of amoxicillin-clavulanate (1 g, 200 mg) can reduce the risk of ventilator-associated pneumonia but not mortality at 28 days.[A16]

PREVENTION

Prevention of sudden cardiac arrest should focus on preventing the underlying diseases whenever possible. Since coronary artery disease is the most common cause of sudden cardiac arrest, treatment of the modifiable risk factors of atherosclerosis (e.g., serum lipids, blood pressure, smoking, and exercise; see Chapter 40) is the cornerstone of prevention. In addition, patients who have known cardiac diseases, such as patients with a history of myocardial infarction or heart failure, and clinical characteristics indicative of a high risk of ventricular arrhythmias, can benefit from insertion of an implantable cardioverter defibrillator (Chapters 46 and 53). Screening of highly competitive and professional athletes with a history and physical examination is recommended to detect undiagnosed cardiac disease, and an ECG adds further diagnostic sensitivity.[13]

Public health initiatives can improve survival after cardiac arrest by increasing the number of people trained in CPR and in how to use automated external defibrillators, as well as by increasing the availability of defibrillators in public places. Innovative strategies, such as the use of drones to deliver automated external defibrillators when needed, may further improve survival.

PROGNOSIS

The probability of survival after a prompt intervention is about 25 to 30% for VF/pulseless VT compared with about 10 to 15% for pulseless electrical activity and less than 5% for asystole. In the hospital, the probability of survival is determined by the specific patient category (acute syndromes better than end-stage diseases), the mechanism of cardiac arrest (better for tachyarrhythmias than for bradyarrhythmias, asystole, or pulseless electrical activity), and the hospital site (better in intensive care units or other monitored settings than on an unmonitored general care unit).[14] Immediate defibrillation in highly protected settings, such as a cardiac catheterization laboratory where response times of less than 60 seconds are the norm, is associated with greater than a 90% survival rate for VF in the absence of pathophysiologic conditions that tend to perpetuate the potentially fatal arrhythmia. In many acute care settings, including patients with acute

coronary syndromes (Chapters 57 and 58), outcomes also can be excellent. For other in-hospital settings and most out-of-hospital settings, the absolute number and proportion of survivors remain low.

The most important determinant of survival from sudden cardiac arrest is time to CPR and defibrillation. Some public locations amenable to very rapid response times achieve survival rates of 50% or higher. If, however, 3 to 4 minutes elapse from the onset of sudden cardiac arrest to attempted defibrillation, the survival rate falls below 50% in most in-hospital and out-of-hospital circumstances. Survival rates continue to fall rapidly thereafter, decreasing to 25% or less by 4 to 6 minutes and to less than 10% by 10 minutes. Although immediate defibrillation is preferred within the first few minutes after the onset, a brief period of CPR improves survivability when the time to defibrillation exceeds 4 to 5 minutes.

The 10-year survival among patients who are discharged alive is about 60%.[15] Long-term prognosis after discharge is determined by a number of factors, including pre-event ventricular function, history of heart failure, and the severity of residual neurologic injury. Bystander resuscitation and defibrillation not only improve survival but also reduce the rate of brain damage and nursing home admission.

Overall, about 40% of patients who survive out-of-hospital cardiac arrest have good quality of life and functional status. Patients whose sudden cardiac arrests are due to a transient arrythmia, who have preserved left ventricular function, and who have minimal, if any, neurologic defects, have a good prognosis. In contrast, patients with advanced heart disease have annual mortality rates that range from 10 to 50%. Most patients who survive but who do not have a predictably reversible cause will receive an implantable cardioverter defibrillator for secondary prevention (Chapter 54). Survivors who receive an implantable defibrillator after a sudden cardiac arrest not due to transient factors (Chapter 54) achieve a relative risk reduction of 25 to 30%, with absolute risk decreasing from 21 to 25% to 15 to 18% over a 2-year follow-up.[A17]

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For the General References and other additional features, please visit Elsevier eBooks+ at https://ebooks.health.elsevier.com.

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51

BRADYCARDIAS AND CONDUCTION SYSTEM DELAYS

PETER ZIMETBAUM AND LEE GOLDMAN

BRADYCARDIAS

DEFINITION

The normal human heart rate is typically defined as 60 to 100 beats per minute, and rates below 60 per minute are defined as bradycardia. Bradycardias can be a result of sinus node dysfunction or of atrioventricular (AV) block (Table 51-1). However, many individuals have heart rates below 60 per minute at rest and especially during sleep without any symptoms or signs of hypoperfusion. A bradyarrhythmia is best defined as a heart rate below 60 per minute associated with signs or symptoms, or an awake non–sinus rhythm rate below 60 per minute even in the absence of symptoms.

EPIDEMIOLOGY

Bradycardia (heart rate below 60 beats per minute) is very common, with an estimated prevalence of about 15% in adult males and 7% in adult females.[1] It is even more common (50 to 80% prevalence) in endurance athletes.[2] The prevalence of bradycardia actually diminishes with age, presumably because of age-related declines in parasympathetic activity. During sleep, bradycardia is even more common, with studies of healthy adults showing sinus bradycardia below 40 beats per minute in 20 to 25% of individuals, sinus pauses of two seconds or more in 5 to 10%, first-degree AV block in 8 to 12%, and second-degree Wenckebach block in about 5 to 10%.

However, an overwhelming majority of bradycardias are asymptomatic in individuals who can raise their heart rates to meet increased cardiac demands when needed. As a result, only an estimated 0.26% of U.S. adults have a cardiac pacemaker implanted for any indication, including bradycardia.

PATHOBIOLOGY

The normal cardiac impulse begins in the sinus node complex, which is located at the junction of the right atrium and the superior vena cava. It then travels through the right atrium and primarily activates the left atrium through the coronary sinus. The time it takes to activate the atria is represented by the P wave on the electrocardiogram (ECG). After depolarizing the atria, the impulse enters the AV node, which is located in the inferior septal region of the right atrium, where a delay occurs. This delay allows time for the atria to contract and fill the ventricles. In most individuals, the impulse travels through the AV node over a uniform functional pathway or route. Some people have two or more functional pathways called dual AV nodal pathways (fast and slow pathways). The delay in the AV node represents most of the isoelectric portion of the PR interval on the ECG (E-Fig. 51-1). The usual duration

TABLE 51-1 BRADYCARDIAS

SINUS NODE DYSFUNCTION
Sinus bradycardia <45 beats/min
Sinoatrial exit block
First-degree
Second-degree
Third-degree
Sinus arrest
Bradycardia-tachycardia syndrome
ATRIOVENTRICULAR BLOCK
First-degree
Second-degree
Mobitz type I (Wenckebach phenomenon)
Mobitz type II
Higher degree (e.g., 2 : 1, 3 : 1)
Third-degree
Atrioventricular node
His-Purkinje system

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coronary syndromes (Chapters 57 and 58), outcomes also can be excellent. For other in-hospital settings and most out-of-hospital settings, the absolute number and proportion of survivors remain low.

The most important determinant of survival from sudden cardiac arrest is time to CPR and defibrillation. Some public locations amenable to very rapid response times achieve survival rates of 50% or higher. If, however, 3 to 4 minutes elapse from the onset of sudden cardiac arrest to attempted defibrillation, the survival rate falls below 50% in most in-hospital and out-of-hospital circumstances. Survival rates continue to fall rapidly thereafter, decreasing to 25% or less by 4 to 6 minutes and to less than 10% by 10 minutes. Although immediate defibrillation is preferred within the first few minutes after the onset, a brief period of CPR improves survivability when the time to defibrillation exceeds 4 to 5 minutes.

The 10-year survival among patients who are discharged alive is about 60%.[15] Long-term prognosis after discharge is determined by a number of factors, including pre-event ventricular function, history of heart failure, and the severity of residual neurologic injury. Bystander resuscitation and defibrillation not only improve survival but also reduce the rate of brain damage and nursing home admission.

Overall, about 40% of patients who survive out-of-hospital cardiac arrest have good quality of life and functional status. Patients whose sudden cardiac arrests are due to a transient arrythmia, who have preserved left ventricular function, and who have minimal, if any, neurologic defects, have a good prognosis. In contrast, patients with advanced heart disease have annual mortality rates that range from 10 to 50%. Most patients who survive but who do not have a predictably reversible cause will receive an implantable cardioverter defibrillator for secondary prevention (Chapter 54). Survivors who receive an implantable defibrillator after a sudden cardiac arrest not due to transient factors (Chapter 54) achieve a relative risk reduction of 25 to 30%, with absolute risk decreasing from 21 to 25% to 15 to 18% over a 2-year follow-up.[A17]

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51

BRADYCARDIAS AND CONDUCTION SYSTEM DELAYS

PETER ZIMETBAUM AND LEE GOLDMAN

BRADYCARDIAS

DEFINITION

The normal human heart rate is typically defined as 60 to 100 beats per minute, and rates below 60 per minute are defined as bradycardia. Bradycardias can be a result of sinus node dysfunction or of atrioventricular (AV) block (Table 51-1). However, many individuals have heart rates below 60 per minute at rest and especially during sleep without any symptoms or signs of hypoperfusion. A bradyarrhythmia is best defined as a heart rate below 60 per minute associated with signs or symptoms, or an awake non–sinus rhythm rate below 60 per minute even in the absence of symptoms.

EPIDEMIOLOGY

Bradycardia (heart rate below 60 beats per minute) is very common, with an estimated prevalence of about 15% in adult males and 7% in adult females.[1] It is even more common (50 to 80% prevalence) in endurance athletes.[2] The prevalence of bradycardia actually diminishes with age, presumably because of age-related declines in parasympathetic activity. During sleep, bradycardia is even more common, with studies of healthy adults showing sinus bradycardia below 40 beats per minute in 20 to 25% of individuals, sinus pauses of two seconds or more in 5 to 10%, first-degree AV block in 8 to 12%, and second-degree Wenckebach block in about 5 to 10%.

However, an overwhelming majority of bradycardias are asymptomatic in individuals who can raise their heart rates to meet increased cardiac demands when needed. As a result, only an estimated 0.26% of U.S. adults have a cardiac pacemaker implanted for any indication, including bradycardia.

PATHOBIOLOGY

The normal cardiac impulse begins in the sinus node complex, which is located at the junction of the right atrium and the superior vena cava. It then travels through the right atrium and primarily activates the left atrium through the coronary sinus. The time it takes to activate the atria is represented by the P wave on the electrocardiogram (ECG). After depolarizing the atria, the impulse enters the AV node, which is located in the inferior septal region of the right atrium, where a delay occurs. This delay allows time for the atria to contract and fill the ventricles. In most individuals, the impulse travels through the AV node over a uniform functional pathway or route. Some people have two or more functional pathways called dual AV nodal pathways (fast and slow pathways). The delay in the AV node represents most of the isoelectric portion of the PR interval on the ECG (E-Fig. 51-1). The usual duration

TABLE 51-1 BRADYCARDIAS

SINUS NODE DYSFUNCTION
Sinus bradycardia <45 beats/min
Sinoatrial exit block
First-degree
Second-degree
Third-degree
Sinus arrest
Bradycardia-tachycardia syndrome
ATRIOVENTRICULAR BLOCK
First-degree
Second-degree
Mobitz type I (Wenckebach phenomenon)
Mobitz type II
Higher degree (e.g., 2 : 1, 3 : 1)
Third-degree
Atrioventricular node
His-Purkinje system

ABSTRACT

Bradyarrhythmias can be a result of sinus node dysfunction or blocked conduction of a sinus impulse, usually at or below the level of the atrioventricular node. Causes include intrinsic disease within the conducting system, medications, iatrogenic injury, and occasionally infiltrative or infectious cause. Except for cases that respond to the elimination of precipitating medications, symptomatic patients nearly always require a cardiac pacemaker. Delays in intraventricular conduction are usually asymptomatic but can be markers of underlying coronary or myocardial disease and can progress to higher degrees of conduction block.

KEYWORDS

complete heart block
sick sinus syndrome
bradycardia

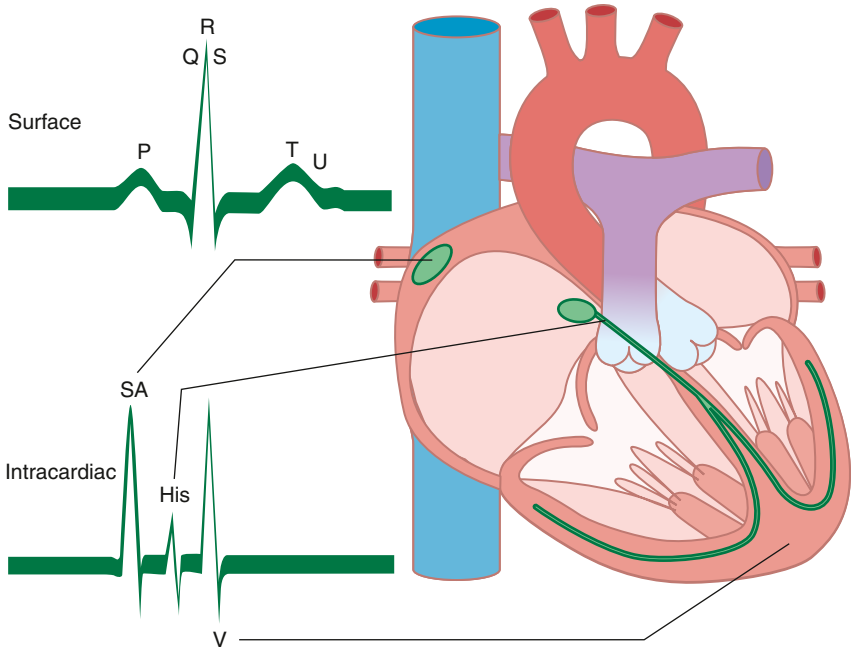

E-FIGURE 51-1. Diagram of the surface electrocardiogram (P, QRS, T, and U waves) and the related intracardiac electrograms (SA, His, and V). The atrial (SA) electrogram represents intra-atrial conduction. The His bundle electrogram (His) represents the recording of a His potential, and the ventricular (V) electrogram represents activation of the ventricles. The SA-His interval corresponds to intra-atrial conduction and delay in the atrioventricular node. The His-V interval represents conduction between the His bundle and the ventricles (infranodal conduction).

of atrial activation including delay in the AV node is up to 140 msec and can be measured directly as the atrial-His interval. The impulse then travels into the specialized infranodal conducting system, that is, through the His bundle, then right and left bundle branches, and into the Purkinje network. The Purkinje network extends or fans out throughout the ventricular endocardium. Impulses conduct rapidly through the Purkinje network, thereby allowing nearly simultaneous activation of the ventricles. A small portion of the isoelectric segment of the PR interval represents infranodal conduction. This infranodal conduction through the His-Purkinje system (HPS) also can be measured directly (His-ventricle interval) and should take between 40 and 60 msec. Once out of the Purkinje network, the impulse proceeds relatively slowly from the endocardial to epicardial surface of the ventricles. The QRS complex on ECG represents depolarization of the bundle branches and ventricular myocardium.

The normal heart rate is generated by tissues or pacemaker cells with intrinsic automaticity. The sinus node cells produce the greatest rate (60 to 100 beats per minute) of automaticity and suppress other potentially automatic (AV junctional, 40 to 55 beats per minute; His-Purkinje cells, 15 to 40 beats per minute) tissues with slower rates of depolarization. The sinus node and AV node are heavily influenced by the parasympathetic (vagal) and sympathetic (adrenergic) nervous systems. At rest, the parasympathetic system controls sinus node automaticity. With exertion or emotional or physical stress, a withdrawal of parasympathetic tone and an increase in heart rate, which is then perpetuated by sympathetic tone, further increase heart rate. Sinus arrhythmia refers to the normal variation in heart rate with inspiration and expiration. With inspiration, a withdrawal of vagal tone increases heart rate; by comparison, expiration is associated with a drop in heart rate (Fig. 51-1). During sleep, a dominance of vagal tone slows heart rate.

Most bradyarrhythmias are caused by intrinsic idiopathic fibrocalcific degeneration of the cardiac conduction system (Table 51-2). Some patients have congenital heart block,[3] and familial bradycardia can occur. The conduction system also can be damaged by ischemia and myocardial infarction, especially below the AV node. Infiltrative diseases, such as amyloidosis (Chapter 174). Sarcoidosis (Chapter 83)[4] and collagen vascular diseases, such as scleroderma (Chapter 246) or advanced rheumatoid arthritis (Chapter 243), can affect any part of the conduction system. Hypothyroidism (Chapter 207) is also commonly associated with sinus bradycardia.

Systemic infections such as Lyme disease (Chapter 296) can affect the cardiac conduction system. A myocardial abscess in bacterial endocarditis (Chapter 61) can present with acute conduction delays. Iatrogenic causes include medications (Table 51-3),[5] valve replacement surgery (whether open or catheter-based), and intracardiac procedures.[6] Even percutaneous placement of a pulmonary artery catheter can precipitate transient heart block.

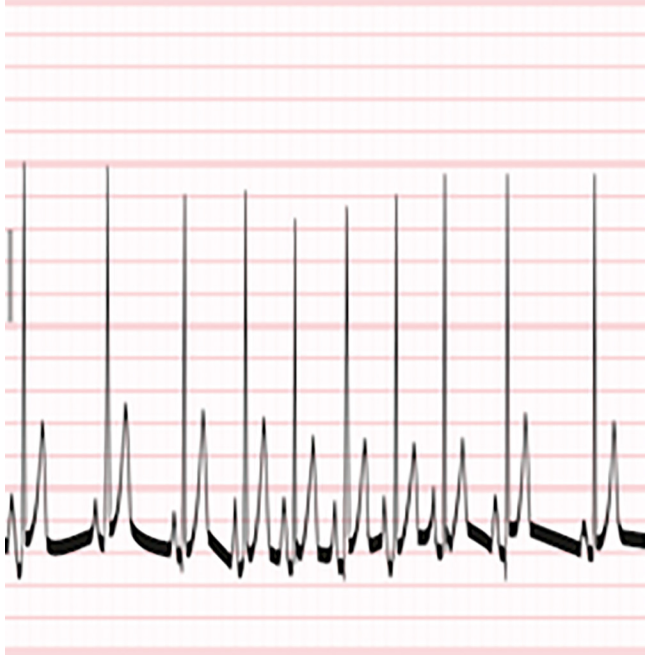

FIGURE 51-1. Sinus arrhythmia. Note the variation in sinus rates, which fluctuate with normal variations in autonomic tone.

BRADYARRHYTHMIAS

Bradyarrhythmias may be caused by dysfunction of the sinus node, AV node, or His-Purkinje system (see Table 51-1).

CLINICAL MANIFESTATIONS

Sinus bradycardia and various degrees of AV nodal blocks can occur asymptomatically during sleep in healthy individuals. Asymptomatic first- and second-degree AV block, particularly when partially or completely reversed by exercise, is usually benign. Persistent second-degree and third-degree AV nodal block is abnormal and is often associated with dizziness, fatigue, exertional dyspnea, worsening of heart failure, near-syncope, or syncope. Third-degree AV block with a good junctional escape mechanism that accelerates during exercise, as often noted in patients with congenital AV block, may remain asymptomatic. Patients with congenital heart block may not appreciate their potential for a more active lifestyle because of the lack of a reference point but often feel much better when an appropriate heart rate acceleration can be achieved after pacemaker therapy.

DIAGNOSIS

Bradycardias are typically diagnosed by the ECG. In symptomatic patients with symptoms suggestive of bradyarrhythmia, 24-hour Holter monitoring or prolonged loop monitoring usually can make the diagnosis, but some patients may require formal electrophysiologic testing (Chapter 49). Any bradycardias,

TABLE 51-2 CONDITIONS ASSOCIATED WITH BRADYCARDIA AND CONDUCTION DISORDERS

DEGENERATIVE FIBROSIS
ISCHEMIA/INFARCTION
CARDIOMYOPATHY/MYOCARDITIS
INFILTRATIVE DISORDERS
Amyloidosis
Hemochromatosis
Lymphoma
Sarcoidosis
INFECTION
Chagas disease
Diphtheria
Infectious endocarditis
Lyme disease
Toxoplasmosis
RHEUMATOLOGIC CONDITIONS
Rheumatoid arthritis
Scleroderma
Systemic lupus erythematosus
NEUROMUSCULAR CONDITIONS
Myotonic dystrophy
Emery Dreifuss syndrome
CARDIAC PROCEDURES
Valve surgery (open or percutaneous)
Passage of a pulmonary artery catheter
CONGENITAL
Congenital anatomic lesions
Arrhythmic mutations*
NEUROCARDIOGENIC EPISODES
Increased vagal tone
Carotid sinus hypersensitivity
Physical conditioning
ENDOCRINE/METABOLIC
Hypothyroidism
Acidosis
Hyperkalemia or hypokalemia
Hypothermia
Hypoxia

*For example, *HCN4, KCNQ1, SCN5A.*
Source: American Heart Association, Inc.

TABLE 51-3 COMMONLY USED MEDICATIONS THAT CAN PRECIPITATE OR UNMASK SINUS BRADYCARDIA OR ATRIOVENTRICULAR NODE ABNORMALITIES

CARDIAC DRUGS
β-blockers (including β-blocker eye drops for glaucoma)
Non-dihydropyridine calcium channel blockers (e.g., diltiazem, verapamil)
ANTIARRHYTHMIC DRUGS
Sotalol
Propafenone
Amiodarone
Dronedarone
Flecainide
PSYCHOACTIVE DRUGS
Opioid analgesics
Selective serotonin reuptake inhibitors
Tricyclic antidepressants
Lithium
Phenothiazine
Phenytoin
Cannabis
Cholinesterase inhibitors (e.g., donepezil)
OTHER
Uncommonly used agents, including clonidine, digoxin, ivabradine, methyldopa, propofol, reserpine, remdesivir

Source: American Heart Association, Inc.

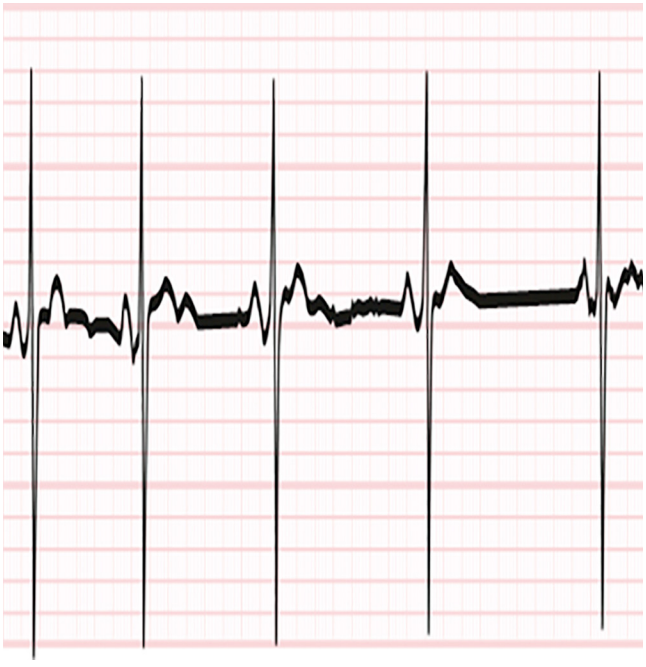

FIGURE 51-2. Sinus bradycardia. Progressive sinus bradycardia, in this case related to heightened vagal tone while sleeping.

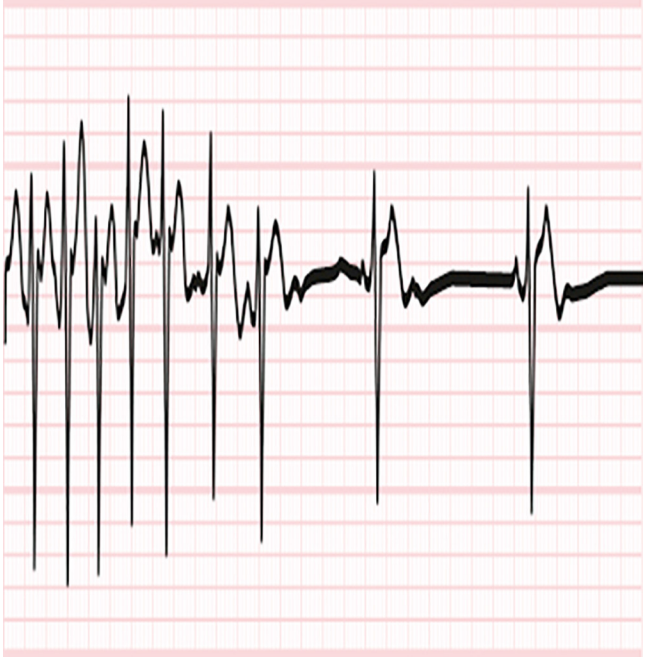

FIGURE 51-3. Electrocardiographic evidence of tachy-brady syndrome. Atrial fibrillation with a tachycardic ventricular response followed by conversion to sinus bradycardia.

including sinus node dysfunction and AV nodal block, can be caused at least in part by vagal influences, such as vasovagal episodes, vomiting, abdominal surgery, and upper and lower gastrointestinal invasive procedures. Syncope, sometimes caused by the bradycardia and sometimes by vasodepression with hypotension, may result (Chapters 39 and 49). Medications, infiltrative diseases, fibrocalcific degeneration, and a variety of other causes must be considered. Lyme disease also is a common cause of reversible complete heart block, usually localized to the AV node.

The evaluation should also include echocardiography (Chapter 43) to evaluate for structural heart disease and cardiac function. If myocardial ischemia is suspected, exercise testing (Chapters 44 and 56) should be performed. If an underlying endocarditis (Chapter 61), an infiltrative or inflammatory cardiomyopathy (Chapter 47), or adult congenital heart disease (Chapter 55) is suspected, either cardiac computed tomography or cardiac magnetic imaging should be performed (Chapter 44).

SPECIFIC BRADYARRHYTHMIAS

SINUS BRADYCARDIA AND SINUS NODE DYSFUNCTION

Sinus bradycardia (Fig. 51-2) is generally defined as a sinus rate of less than 60 beats per minute. It should be noted, however, that sinus rates as low as 45 to 50 beats per minute, particularly at rest, can be physiologically normal. Sinus node dysfunction[7] encompasses a group of disorders including sinus bradycardia, sinoatrial exit block, sinus arrest (pause of >2 to 3 seconds) during sinus rhythm, chronotropic incompetence, and tachycardia-bradycardia (tachy-brady) syndrome.[8] Sinus node dysfunction in combination with symptoms such as fatigue, dizziness, near or complete syncope (Chapters 39 and 49), or worsening of heart failure (Chapter 45) is called sick sinus syndrome. The tachy-brady syndrome is often identified by a prolonged delay in sinus node recovery following the termination of atrial fibrillation (AF) (Fig. 51-3). Sinoatrial exit block refers to the electrophysiologic phenomenon of sinus node firing with delay or block of the impulse as it travels from the sinus node to the surrounding atrial tissue (Fig. 51-4). Sinoatrial exit block can be first degree, second degree (type 1 or 2), and third degree. First-degree sinoatrial block is difficult to diagnose from the surface ECG. Second-degree sinoatrial exit block type 1 is manifest by progressive PP shortening preceding the sinus pause. The PP interval following the pause must be greater than twice the PP interval that preceded the pause. Second-degree sinoatrial exit block type 2 is characterized by a pause equaling an exact multiple of the sinus rate (i.e., constant PP interval before and after the pause). High-degree sinoatrial exit block refers to the absence of multiple P waves with a pause still corresponding to an absolute multiple of the underlying PP intervals, and third-degree AV block results in a complete absence of sinus P waves.

Chronotropic incompetence refers to the inability to increase the sinus rate appropriately in response to exercise or other physiologic demand. In most patients, chronotropic incompetence is manifest by a maximal heart rate of less than 100 beats per minute.

ATRIOVENTRICULAR CONDUCTION DISTURBANCES

AV conduction disturbances refer to abnormal conduction in the AV node or in the HPS below the AV node. Electrical transmission through the AV conduction system is primarily limited by the AV node, which conducts in a decremental fashion to prevent excessively rapid conduction to the ventricles. The normal AV node rarely conducts faster than 200 beats per minute and

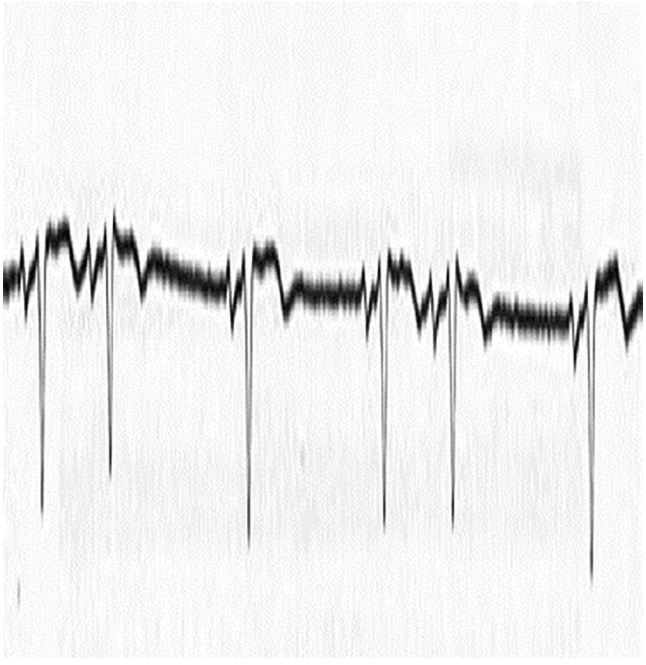

FIGURE 51-4. Sinoatrial block. Sinoatrial exit block, probably type 2, is characterized by a pause equaling an exact multiple of the sinus rate.

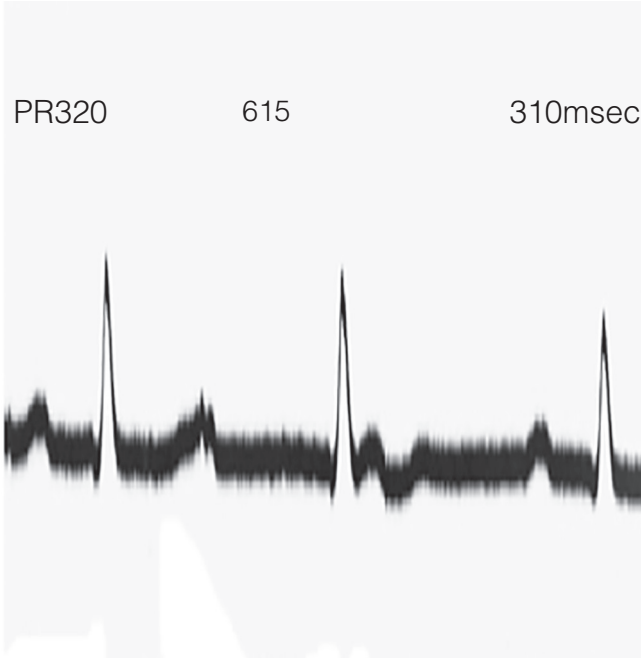

FIGURE 51-6. Mobitz I block. Progressive PR prolongation from 320 to 615 msec, followed by a blocked P wave. The subsequent conducted PR interval is less than the PR interval before the dropped P wave.

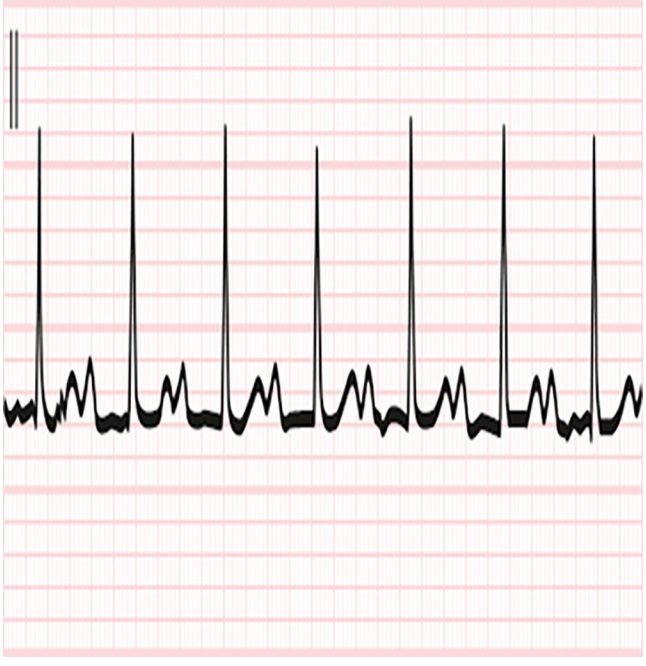

FIGURE 51-5. First-degree atrioventricular (AV) block. Note the prolonged (>200 msec) AV conduction.

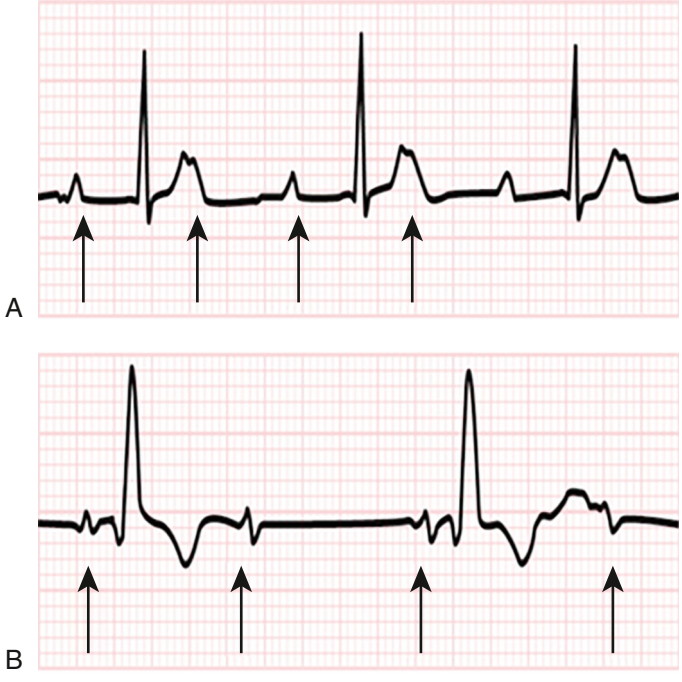

FIGURE 51-7. Two-to-one conduction in the atrioventricular (AV) node and below the AV node. A, Two-to-one conduction, with the conducted beats demonstrating a prolonged PR interval (>300 msec) and a narrow QRS, indicating Mobitz I block in the AV node. **B,** Normal-duration conducted PR interval and a wide QRS duration favoring Mobitz II block into an infranodal site of block.

slows with aging. The AV node is heavily influenced by autonomic tone and may conduct more than 200 beats per minute in the presence of heightened sympathetic and withdrawal of parasympathetic tone. Conduction through the HPS is faster and nondecremental.

The AV blocks are classified as first, second, high, and third degree.[9] First-degree AV block is a misnomer because nothing is actually blocked; rather, there is delay, usually in the AV node, manifest by a prolonged PR interval (Fig. 51-5). However, 50% or more of patients who have first-degree AV block either have detectable higher-degree AV block on prolonged monitoring or develop higher-grade block within about a year after the detection of asymptomatic first-degree AV block.[10] Second-degree AV block is divided into Mobitz type I (Wenckebach) or Mobitz type II. Mobitz type I is defined by progressive PR prolongation with eventual block after a P wave (Fig. 51-6). The initial PR prolongation is longest, the subsequent RR intervals shorten, and the PR interval following the blocked P wave is shorter than the last conducted PR interval before the blocked P wave. Mobitz type I usually occurs in the AV node. Mobitz type II, which is characterized by the abrupt failure of conduction after a P wave without preceding PR prolongation, usually represents conduction disease below the AV node. In patients with 2 : 1 block (two P waves for every QRS), it can be difficult to determine whether the block is Mobitz I in the AV node or Mobitz II below the AV node. Clues to conduction disease in the AV node include a prolonged PR interval (i.e., >300 msec) and a narrow QRS duration. Clues to conduction disease below the node include a normal PR interval but with bundle branch block (Fig. 51-7).

FIGURE 51-8. High-degree atrioventricular block. Periods of complete heart block with three nonconducted P waves (the first of which is buried in the first QRS complex) followed by two P waves, the second of which is conducted to the ventricle with a long PR interval. The subsequent three P waves are once again nonconducted, with the last P wave buried in the last QRS complex.

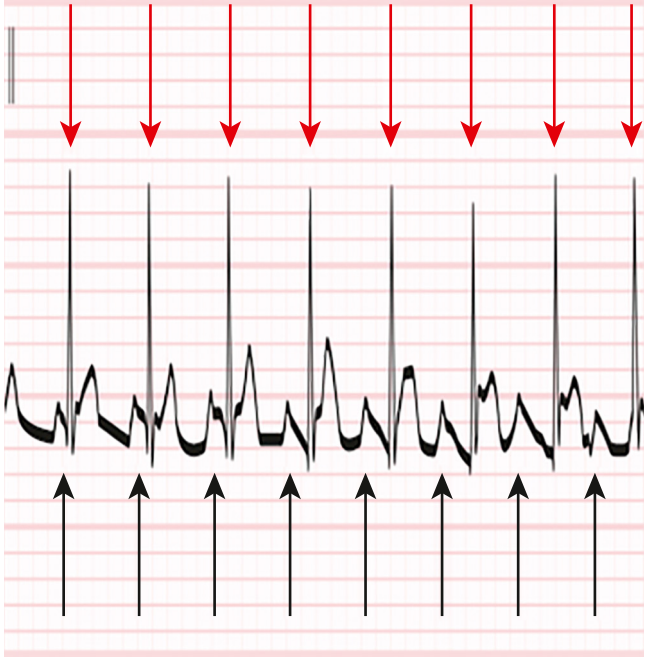

FIGURE 51-9. Complete heart block with the atrial beats *(black arrows)* dissociated from the ventricular beats *(red arrows)*. Note the ST elevation in leads III and aVF indicating acute inferior myocardial infarction as the cause of complete heart block.

High-degree or advanced AV block, which is a form of second-degree block with multiple or successive nonconducted P waves, or both (Fig. 51-8), frequently recurs or persists. Third-degree block (or complete heart block) refers to a rhythm in which the atrial and ventricular activity occurs independently, and the atrial rate usually exceeds the ventricular rate.[11] Third-degree heart block can be seen with sinus rhythm or any atrial tachyarrhythmia with a regular escape rhythm in the AV junction or below (Fig. 51-9). Sometimes there is no escape rhythm, and heart block results in asystole. Complete heart block, particularly when it is acute and accompanied by an escape rhythm, can be associated with marked QT prolongation, which signifies a risk for torsades de pointes (Chapter 53). For this reason, patients who undergo AV node ablation have their pacemakers set at 80 beats per minute for at least 6 weeks after the procedure to prevent QT prolongation and torsades de pointes. Eventually, the pacing rate can be reduced to more physiologic levels without the ongoing risk for ventricular arrhythmia. Complete heart block and other types of severe bradyarrhythmia may present with syncope if there is a prolonged pause before an escape rhythm develops. More often, these rhythms present with fatigue and dyspnea. The blood pressure is often elevated owing to peripheral vasoconstriction, and there may be renal insufficiency secondary to reduced cardiac output.

The term AV dissociation refers to any rhythm in which the atria and ventricles beat independently of one another. If the atrial rate is faster than the ventricular rate, it is called complete heart block or third-degree AV block. AV dissociation with an atrial rate slower than the subsidiary pacemaker is usually seen with junctional or ventricular tachycardias.

TREATMENT

The treatment of sinus node dysfunction and AV blocks consists of first removing any medications that may precipitate dysfunction (see Table 51-3).[12] Although some patients will recover normal conduction, the susceptibility to medications usually indicates an underlying conduction abnormality that may worsen over time. For example, asymptomatic sinus bradycardia (<50 per minute) in middle-aged or older adults does not appear to be associated with incident cardiovascular disease or mortality except in patients who take heart rate–modifying drugs.

Asymptomatic sinus node dysfunction requires no therapy. Asymptomatic AV nodal block, particularly if the QRS escape complex is narrow, also can be managed without intervention unless the QT interval is markedly prolonged, in which case a pacemaker should be considered.

For acutely symptomatic sinus node dysfunction and second- and third-degree AV block, urgent management includes intravenous atropine (1 mg) or isoproterenol (usually 1 to 2 µg/minute infusion) to increase the heart rate. Temporary cardiac pacing (Chapter 54) may be required. If sinus node dysfunction or AV block is due to transient abnormalities, such as drug-induced or acute ischemic syndromes, temporary pacing is usually sufficient; however, when intra-His or infra-His block is suspected (e.g., exercise-induced AV block or asymptomatic Mobitz type II block) and the site can be documented with His bundle recording, permanent pacing (see Tables 54-1 and 54-2) is the only effective long-term therapy, and consensus recommendations for pacemaker implantation should guide its use (Chapter 54).

For all forms of persistent symptomatic sinus node dysfunction or second- or third-degree AV block, permanent pacing is the therapy of choice (Chapter 54). However, recurrent syncope occurs despite a pacemaker in about 20% of patients over the subsequent 5 years.[13] In patients who have the tachy-brady syndrome, permanent pacing is usually required to prevent symptomatic bradycardia if medications are required to treat the tachycardia (Chapter 52).[14] In patients with AV block and systolic dysfunction, biventricular pacing is preferred. The only exception is Lyme disease, in which most cases of heart block resolve within a week of antibiotic therapy (Chapter 296). A newer form of physiologic pacing paces the His or left bundle branch region of the right ventricle (Chapter 54). This type of pacing stimulates the native conduction system and results in more synchronous contraction of the left and right ventricles than occurs with placement of a pacemaker into the apex or wall of the right ventricle. Cardiac neural ablation attempts to improve sinus node and AV node conduction by ablating the parasympathetic ganglia that innervate the sinus and AV nodes. This therapy has been used to treat neurocardiogenic syncope (Chapter 49) and is also being investigated for patients with sinus node dysfunction and varying degrees of AV nodal block.

INTRAVENTRICULAR BLOCKS

Given the anatomy of the intraventricular cardiac conduction system, patients can have conduction blocks or delays in either of the two fascicles (anterior or posterior) of the left bundle branch, a block or delay in the right bundle branch, or any combination of these three. As long as any one of the three conducts adequately, the patient's ECG will show the delays in the other(s): left anterior block (see Fig. 42-5A), with an axis of −45° or more negative; left posterior fascicular block (see Fig. 42-5D), with an axis of +120° or more positive; complete left bundle branch block (see Fig. 42-5E); or right bundle branch block (see Fig. 42-5B). Right bundle branch block also can occur in combination with either left anterior or left posterior fascicular block (see Fig. 42-5C). If all are delayed but at least one conducts, the patient will also have Mobitz type II block as described earlier. If all three are blocked, the patient has complete heart block (as described earlier). These intraventricular conduction delays or blocks can be caused by any of the structural (non-neurogenic, nonmedication) causes of AV block. However, by far the most common causes are ischemic heart disease, especially for the left bundle, and intrinsic degenerative changes.

In aggregate, about 1% of individuals have a bundle branch block at age 50 years, but the prevalence increases to about 17% by age 80 years. Left posterior

fascicular block[15] is unusual and nearly always associated with right bundle branch block; it must be distinguished from much more common causes of right axis deviation, such as right ventricular hypertrophy, pulmonary embolism, and lateral wall myocardial infarction. Left anterior fascicular block, defined as an axis of −45° to −90°, is found in about 1% of otherwise healthy adults. However, it can be associated with degenerative disease of the conduction system, myocardial fibrosis, coronary artery disease, and structural heart diseases.

Complete left bundle branch block[16] is seen in fewer than 0.1 to 0.5% of healthy individuals but up to 25% of patients with heart failure. About 50 to 60% of patients have underlying coronary or structural heart disease.

Right bundle branch block is present in about 0.5 to 1% of the normal adult population.[17] Potential underlying causes include degenerative or infiltrative or inflammatory heart diseases, prior myocardial infarction, or severe lung disease. Transient right bundle branch block can be precipitated by the passage of pulmonary artery catheter.

CLINICAL MANIFESTATIONS AND DIAGNOSIS

Intraventricular conduction delays themselves are typically asymptomatic. However, left bundle branch block causes ventricular dyssynchrony, whereby the right ventricle contracts before the left ventricle. In some patients, this dyssynchrony also leads to mitral regurgitation. The result can be the precipitation or worsening of heart failure.

The evaluation centers on determining the risk for progression to complete heart block and determining cause, especially otherwise undiagnosed ischemic heart disease. When an intraventricular conduction delay is found on an ECG, the first task is to seek any prior ECGs to determine if the abnormality is new, whether the abnormality is or is not associated with hitherto undiagnosed underlying heart disease.[18] In patients who are presenting with suspected myocardial ischemia, a new left bundle branch block is the equivalent of ischemic ECG changes and warrants appropriate evaluation for a possible acute myocardial infarction (Chapters 57 and 58). In the setting of a possible pulmonary embolism (Chapter 68), a new right bundle branch block suggests right ventricular strain and severe pulmonary hypertension. Symptoms of syncope or presyncope suggest that the intraventricular blocks may be associated with high-degree heart block.

The routine evaluation should include echocardiography and a stress test (using echocardiography or radionuclides). Cardiac magnetic resonance imaging is recommended if there is any suspicion of an infiltrative cardiomyopathy. Rhythm monitoring (Chapter 49) is indicated if the intraventricular conduction abnormality is associated with prolongation of the PR interval, evidence of alternating right and left intraventricular blocks, or any symptoms of light-headedness or presyncope.

TREATMENT

Treatment for intraventricular conduction delays is targeted at any underlying cause. However, rhythm-specific treatments are sometimes indicated. In patients with heart failure (Chapter 46), for example, left bundle branch block is often an indication for biventricular pacing (Chapter 54). For patients with bifascicular block and syncope, pacemaker implantation is preferable to an implantable cardiac monitor,[A1] regardless of the morphology of the block or the PR interval.[19] For patients with new bifascicular block (either left bundle branch block alone or right branch block plus a left fascicular block) in combination with PR prolongation, a pacemaker is often placed prophylactically because of the high risk for progression to complete heart block, especially in the setting of an acute myocardial infarction (Chapter 47).

PROGNOSIS

The risk of all-cause mortality is increased by about two- to three-fold in individuals with left bundle branch block, about six-fold higher in the presence of underlying heart disease, and probably only minimally if exercise testing and cardiac magnetic resonance imaging show no evidence of underlying heart disease.[20] For right bundle branch block, mortality is increased in the presence of underlying heart disease; for idiopathic cases, the risk of mortality is not increased, but the long-term risk of requiring a cardiac pacemaker may be higher. The combination of right bundle branch block with either left anterior or left posterior fascicular block portends a high risk for needing a pacemaker, but prophylactic pacing is not indicated in the absence of symptoms such as syncope.

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52 SUPRAVENTRICULAR ECTOPY AND TACHYARRHYTHMIAS

PETER ZIMETBAUM AND LEE GOLDMAN

SUPRAVENTRICULAR ARRHYTHMIAS WITH A NORMAL RATE

Atrial premature beats (APBs) can arise from the right or left atrium or the pulmonary veins. The P wave, which differs from the P wave of sinus rhythm unless the APB originates near the sinus node, always precedes the QRS complex (Fig. 52-1). If the P wave is blocked, however, it is not followed by a QRS complex. A blocked premature atrial contraction may be confused with second-degree atrioventricular (AV) block, unless its prematurity is recognized, or with sinus node dysfunction, if it is inconspicuous. Altered appearance of the ST-T segment is often a clue to the presence of a P wave. A premature QRS complex with the morphology of the underlying sinus rhythm in the absence of a premature P wave represents an AV junctional beat (Fig. 52-2).

An ectopic atrial rhythm refers to a nonsinus atrial rhythm from a single focus with a single P wave morphology (Fig. 52-3). Wandering atrial pacemaker refers to an ectopic atrial rhythm with at least three distinct P wave morphologies at rates between 50 and 100 beats per minute (Fig. 52-4).

CLINICAL MANIFESTATIONS

APBs are most often asymptomatic but can occasionally be experienced as palpitations (Chapter 49). Similarly, ectopic atrial rhythms, including a wandering atrial pacemaker, are virtually always asymptomatic. Rarely, ectopic atrial rhythm can be very slow and associated with symptoms of fatigue.

DIAGNOSIS

The diagnoses of APBs, ectopic atrial rhythms, and wandering atrial pacemakers are all made by an electrocardiogram (ECG), an ambulatory Holter monitor, or an event recorder (Chapter 49).

FIGURE 52-1. Atrial premature beat. Sinus rhythm with an atrial premature beat as the third complex in the rhythm strip. The P wave is buried in the preceding T wave.

FIGURE 52-2. Junctional premature beat. The premature beat is narrow but slightly different in morphology compared with the surrounding sinus beats. This premature beat is from the atrioventricular junction or slightly more distal in the fascicles. The inverted P wave following the QRS represents retrograde activation of the atria.

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An ectopic atrial rhythm refers to a nonsinus atrial rhythm from a single focus with a single P wave morphology (Fig. 52-3). Wandering atrial pacemaker refers to an ectopic atrial rhythm with at least three distinct P wave morphologies at rates between 50 and 100 beats per minute (Fig. 52-4).

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DIAGNOSIS

The diagnoses of APBs, ectopic atrial rhythms, and wandering atrial pacemakers are all made by an electrocardiogram (ECG), an ambulatory Holter monitor, or an event recorder (Chapter 49).

FIGURE 52-1. Atrial premature beat. Sinus rhythm with an atrial premature beat as the third complex in the rhythm strip. The P wave is buried in the preceding T wave.

FIGURE 52-2. Junctional premature beat. The premature beat is narrow but slightly different in morphology compared with the surrounding sinus beats. This premature beat is from the atrioventricular junction or slightly more distal in the fascicles. The inverted P wave following the QRS represents retrograde activation of the atria.

ABSTRACT

Supraventricular arrhythmias include premature atrial contractions, sinus tachycardia, sinus node re-entry, atrial tachycardias, atrial flutter, and atrial fibrillation, as well as a variety of atrioventricular junctional tachycardias. These arrhythmias can be caused by intrinsic diseases of the conduction system but also may be triggered by alcohol, exercise, or stimulation of the sympathetic nervous system. Each can typically be diagnosed by a surface electrocardiogram, but electrophysiologic testing is sometimes required to distinguish among them or to exclude a ventricular arrhythmia. Treatment focuses on relieving symptoms, occasionally with medications and often with procedures. Because of the risk of systemic embolization, systemic anticoagulation is required for atrial fibrillation and atrial flutter.

KEYWORDS

supraventricular tachycardia
atrial tachycardia
atrial fibrillation
atrial flutter
Wolff-Parkinson-White syndrome
AVNRT
AVRT

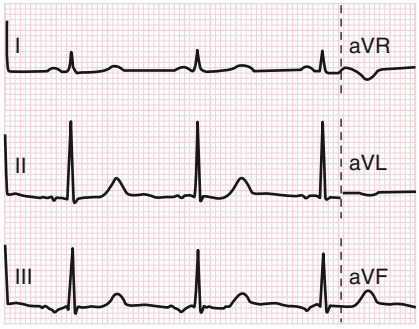

FIGURE 52-3. Ectopic atrial rhythm. The inverted P waves in leads II, III, and aVF indicate a nonsinus P wave originating in the low right atrium.

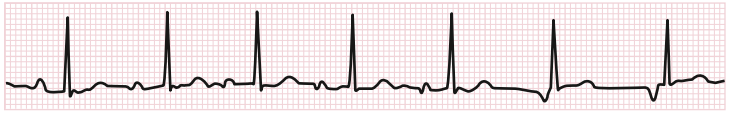

FIGURE 52-4. Wandering atrial pacemaker. Rhythm with three distinct P wave morphologies.

TREATMENT AND PROGNOSIS

Premature atrial contractions do not generally require treatment unless they are associated with significant symptoms. Treatment consists primarily of β-blockers (e.g., metoprolol XL, 25 to 100 mg daily) or calcium-channel blockers (e.g., long-acting diltiazem, 180 to 300 mg daily). Ectopic atrial rhythms and wandering atrial pacemakers are rarely symptomatic and are not treated with medications. Rarely, a slow ectopic rhythm associated with fatigue can be treated with atrial pacing at a rate faster than the ectopic atrial rhythm. Very frequent premature atrial contractions may portend a higher risk of atrial fibrillation (AF)[1] and other serious atrial arrhythmia, and they are associated with an increased long-term risk of stroke and clinical cardiovascular disease.

SUPRAVENTRICULAR TACHYARRHYTHMIAS

The supraventricular tachycardias (SVTs) are defined as arrhythmias with three or more beats at a rate of greater than 100 beats per minute (Table 52-1). In the United States, the incidence and prevalence of paroxysmal supraventricular tachycardias are estimated to be about 93 per 100,000 people and 480 per 100,000 people, respectively.[2]

The beats, which can be regular or irregular, are usually narrow complex but can be wide complex when associated with bundle branch block (aberration) or conduction over an accessory pathway. Atrial dilation, acute or chronic heart failure, pulmonary embolism, acute or chronic inflammatory states, or scars from prior surgery involving atrial myocardium or pericardium are among the causes of atrial tachyarrhythmias.

The most important clues for diagnosing the type of SVT include the ventricular response rate, regularity, and, if known, the suddenness of the onset of tachycardia. The QRS is regular during sinus tachycardia, atrial flutter, AV nodal re-entrant tachycardia, AV re-entrant tachycardia, and atrial tachycardia; it is irregular with AF, atrial flutter with variable AV block, multiple atrial premature contractions, and multifocal atrial tachycardia. Sudden onset and termination suggest acute AF, atrial flutter, AV nodal re-entrant tachycardia, AV reciprocating tachycardia, and atrial tachycardia. Gradual onset and recession are more suggestive of sinus tachycardia, nonparoxysmal junctional tachycardia and some forms of atrial tachycardia. The QRS complex during SVT is usually narrow but can be wide in the setting of aberrant conduction through the ventricles because of its very fast rate in the presence of coexisting disease in the bundle branches.[3]

SVTs can produce symptoms specifically related to the rhythm itself (Chapter 49), including fatigue, palpitations, dizziness, shortness of breath, chest discomfort, presyncope, and syncope. These symptoms are mostly related to the rapidity of the ventricular response and are most prevalent at the onset of the arrhythmia. In contrast to other forms of SVT, asymptomatic episodes of AF are common in patients who also have symptomatic AF.

TABLE 52-1 SUPRAVENTRICULAR TACHYCARDIAS

	R-R REGULARITY	P WAVE MORPHOLOGY
ATRIAL TACHYCARDIAS		
Sinus tachycardia	Regular	Positive in II, III, aVF; negative in aVR
Sinus node re-entry	Regular	Positive in II, III, aVF; negative in aVR
Atrial tachycardia, unifocal	Regular	P different from sinus
Atrial tachycardia, multifocal	Irregular	Three or more different P wave morphologies
Atrial flutter, common: Counterclockwise	Regular; irregular if variable AV block	Sawtooth flutter waves; regular waveform; negative in II, III, aVF, positive in V_1, negative in V_6
Clockwise		Positive in II, III, aVF; negative in V_1; positive in V_6
Atrial flutter: uncommon	Regular; irregular if variable AV block	Pattern different than common atrial flutter (counterclockwise or clockwise)
Atrial fibrillation	Irregularly irregular	Irregular fibrillation waves
AV JUNCTIONAL TACHYCARDIAS		
AV re-entry (using accessory pathways)		
Orthodromic	Regular	Retrograde P in ST-T wave
Antidromic	Regular preexcited, except in irregular preexcited atrial fibrillation	Retrograde P, short RP
Slow conducting	Regular	Retrograde P at end of T wave or later (long RP)
Atriofascicular (antidromic)	Regular preexcited	Retrograde P, short RP
AV nodal re-entry		
Common (slow-fast)	Regular	Retrograde P obscured by QRS or alters the end of QRS (short RP)
Uncommon (fast-slow)	Regular	Retrograde P at end of T wave or later (long RP)
Others (slow-slow)	Regular	PR-RP approximately equal
Nonparoxysmal junctional tachycardia*	Regular, slow rate	AV dissociation
Automatic junctional tachycardia*	Regular	AV dissociation

*Site of origin is usually infranodal.
AV = atrioventricular.

Incessant SVT and uncontrolled ventricular rates can cause tachycardia-related cardiomyopathy (Chapter 45), which is reversible with control of these arrhythmias. In some situations, however, the clinical presentation may be dominated by the underlying condition that precipitates the arrhythmia, such as fever, physical stress, hypovolemia, heart failure (Chapter 45), hypoxia, sympathomimetic or parasympatholytic medications, thyrotoxicosis (Chapter 207), and pheochromocytoma (Chapter 209).

The fundamental principle for the diagnosis of a supraventricular tachycardia is the identification of the rhythm on a 12-lead ECG, on a continuous ECG monitor, or on a wearable device such as a smart watch with ECG capability (Chapter 49). The latter two methods will also determine any correlation between an identified arrhythmia and a patient's symptoms. Chronically implanted devices such as pacemakers and an implantable cardioverter-defibrillator (ICD) also allow identification of SVTs.

SINUS TACHYCARDIA

Sinus tachycardia (Fig. 52-5) is an arrhythmia that is almost always a physiologic response to an emotional or physical stress such as anxiety, exercise, anemia, hypotension, hypoxemia, fever, thyrotoxicosis, or heart failure. It is

FIGURE 52-5. Sinus tachycardia at 120 beats/minute.

characterized by a gradual increase and decrease in heart rate and rarely exceeds 180 beats per minute. In rare cases, it may be a nonphysiologic condition called inappropriate sinus tachycardia, which is characterized by sinus tachycardia that develops in response to minimal stress and that continues beyond the time when the normal response would have slowed.

Sinus node re-entry is a rare form of SVT caused by re-entry in the sinus node. As opposed to physiologic sinus tachycardia, sinus node re-entry begins abruptly, is often triggered by a premature atrial beat, and ends abruptly. The P wave morphology is identical to sinus rhythm.

TREATMENT AND PROGNOSIS

Sinus tachycardia rarely should be treated directly. Instead, treatment should focus on identifying and treating any precipitating underlying conditions, especially heart failure (Chapter 46), pulmonary disease (Chapters 75 and 76), fever, anemia, thyroid disease (Chapter 207), or pheochromocytoma (Chapter 209). In the occasional patients who require treatment for symptoms that are associated with inappropriate sinus tachycardia, β-blockers (e.g., metoprolol succinate starting at 25 mg daily and titrating upward as needed) are generally chosen as first-line therapy. Alternatively, ivabradine (5 mg twice daily) provides significant improvement and can completely eliminate symptoms in approximately 50% of patients.[4] Rarely, catheter-based sinus node modification can be performed when medications are ineffective and symptoms are intractable. The prognosis is poorly understood and likely highly variable.

ATRIAL TACHYCARDIA

The term atrial tachycardia refers to a group of SVTs that originate from focal anatomic locations in the atria and propagate in a centrifugal pattern (Fig. 52-6). These locations include the pulmonary veins, crista terminalis in the right atrium, tricuspid or mitral annulus, coronary sinus, atrial septa, left atrial appendage, aortomitral continuity, or regions of scar tissue from previous cardiac surgery. Atrial tachycardias, which are usually regular rhythms that rarely exceed 200 beats per minute, may present in young age but more often develop later in life. Atrial tachycardias can be re-entrant, triggered, or automatic in mechanism.

TREATMENT AND PROGNOSIS

Some forms of atrial tachycardia are paroxysmal and may remit spontaneously without treatment. When they do not, electrical mapping and ablation (Chapter 54) of atrial tachycardia are highly effective and are increasingly offered as first-line therapy.[5] Alternatively, atrial tachycardias can be managed with medications such as β-blockers (e.g., metoprolol starting at 25 mg twice daily), calcium-channel blockers (e.g., diltiazem starting at 180 mg long-acting daily), or other antiarrhythmic drugs (see Table 52-2). Some forms of atrial tachycardia are incessant and can predispose to a tachycardia-related cardiomyopathy (Chapter 47).

MULTIFOCAL ATRIAL TACHYCARDIA

Multifocal atrial tachycardia (Fig. 52-7), which is a unique form of atrial tachycardia characterized by three or more P wave morphologies, is distinguished from wandering atrial pacemaker when the rate is 100 beats per minute or more, rather than less than 100 beats per minute. It is an irregular rhythm and occurs almost exclusively in patients with advanced pulmonary disease.

TREATMENT AND PROGNOSIS

Multifocal atrial tachycardia is relatively unresponsive to medical therapy, is very difficult to ablate, and is best treated by management of the underlying pulmonary or cardiac disorder. If absolutely required for acute symptoms, options include intravenous diltiazem, verapamil, or metoprolol (see Table 52-2). Cardioversion can restore normal sinus rhythm, but multifocal atrial tachycardia generally recurs quickly. Prognosis is largely determined by the underlying pulmonary disease.

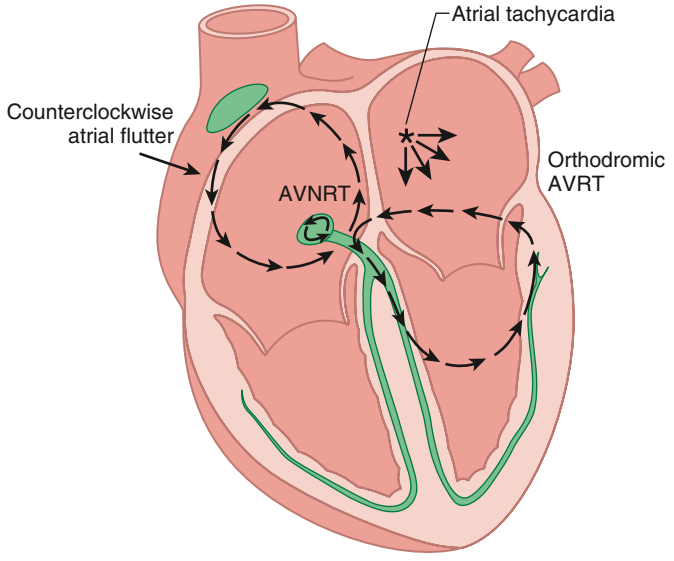

FIGURE 52-6. Diagram of the site and mechanism of common forms of supraventricular tachycardia. AVNRT = atrioventricular nodal re-entrant tachycardia; AVRT = atrioventricular re-entrant tachycardia.

ATRIOVENTRICULAR NODAL RE-ENTRANT TACHYCARDIA

AV nodal re-entrant tachycardia (also called AVNRT) is a common form of SVT in all age groups, but it presents most often in young adulthood and frequently occurs after a change in position. It is more common in women than men and may develop or be exacerbated by pregnancy or certain phases of the menstrual cycle. Patients with AV nodal re-entrant tachycardia have two functional AV nodal pathways (dual pathways). Typically, an APB blocks in one pathway (fast pathway) and conducts slowly over the other pathway (slow pathway). If this beat conducts back up the fast pathway and then re-enters the slow pathway, AV nodal re-entry occurs (Fig. 52-8). This re-entrant circuit is confined to the AV node, and the result is that both the atria and ventricles are activated nearly simultaneously. P waves may not be visible on the ECG because they are buried in the QRS complex. When P waves are present, they usually are seen just after the QRS and have a negative or superior axis (negative in leads II, III, and aVF; short RP tachycardia) (see Fig. 52-6). Atypical AV nodal re-entrant tachycardia is rare and occurs with conduction down the fast pathway and up the slow pathway, with a long interval between the preceding R wave and subsequent negative P wave (e.g., long RP tachycardia).

Symptoms associated with AV nodal re-entrant tachycardia most often include palpitations, occasionally include a sense of fullness in the neck, and may include a beat-to-beat distention of the neck veins, known as a "frog sign" and associated with contraction of the atria while the tricuspid and mitral valves are closed (cannon a waves; see Chapter 39).

TREATMENT AND PROGNOSIS

Carotid sinus massage, which has a vagal effect on the AV node, can terminate SVTs such as AV nodal re-entrant tachycardia that depend on the AV node as part of the circuit. For documented intermittent episodes of atrial tachycardia, the patient also can be instructed to try a Valsalva maneuver to terminate the arrhythmia, with higher response rates if performed in a semi-recumbent position and combined with supine repositioning and straight leg raising immediately afterward.[AT] Longer-term preventive pharmacologic management typically includes daily β-blocker or calcium channel blocker therapy (see Table 52-2). Unfortunately, use of these agents once the arrhythmia has started is usually unsuccessful. Radiofrequency ablation is the definitive approach to manage AV nodal re-entrant tachycardia and can cure more than 95% of cases, but with about a 0.5 to 1% risk of causing complete heart block that will require a pacemaker.

JUNCTIONAL TACHYCARDIA

Primary junctional tachycardia refers to a focal (non-re-entrant) tachycardia originating in the AV junction (Fig. 52-9). A number of different forms of junctional tachycardia have differing clinical patterns. Digitalis toxicity was a leading cause when it was a commonly prescribed drug.

TABLE 52-2 ANTIARRHYTHMIC DRUGS: DOSES AND SIDE EFFECTS

ANTIARRHYTHMIC DRUG AND COMMON USE	DOSE/METABOLISM	SIDE EFFECTS AND REQUIRED MONITORING	SELECTED DRUG INTERACTIONS
RATE CONTROL			
β-Blockers (selected)	Hepatic, renal Only renal (atenolol, nadolol) IV: esmolol, 250-500 µg over 1 min, then 50-300 µg/kg/min over 4 min; metoprolol, 2.5- to 5-mg bolus over 2 min, up to 3 doses 10 min apart Oral: acebutolol, 200-600 mg bid; atenolol, 25-100 mg qd; carvedilol, 3.125-50 mg bid; metoprolol, 25-150 mg bid; nadolol, 20-120 mg qd; nebivolol, 5-40 mg qd; propranolol, 10-120 mg bid	Fatigue, depression, bronchospasm, impotence	Minimal, except for carvedilol and metoprolol, whose levels may be increased by amiodarone, propafenone, quinidine, fluoxetine, haloperidol, paroxetine, and cimetidine
Calcium-channel blocker (nondihydropyridine)	Hepatic Inhibit CYP 3A4 IV: diltiazem, 20-mg bolus over 2 min, then 5-15 mg per hour maintenance infusion; verapamil, 5- to 10-mg bolus over 2 min (if no response, an additional 10 mg after 30 min and then a 0.005-mg/kg/min infusion) Oral: verapamil long-acting 120-480 mg qd Diltiazem long-acting 180-300 mg qd	Constipation, rash, peripheral edema	Inhibits CYP 3A4—will increase levels of alprazolam, carbamazepine, dihydropyridine, cyclosporine, HMG-CoA inhibitors. Verapamil (but not diltiazem) increases digoxin levels
Digoxin	Renal, hepatic, gastrointestinal, 0.125-375 mg/day orally	Anorexia, nausea, fatigue, confusion, altered vision with green-yellow halos	Levels of or sensitivity to digoxin increased by hypokalemia, quinidine, verapamil, amiodarone, propafenone, renal failure, hypoxia, decreased muscle mass Levels of or sensitivity to digoxin decreased by malabsorption, hyperkalemia, hypocalcemia
RHYTHM CONTROL			
Adenosine	Erythrocyte, endothelial cell 6-mg IV push, followed if necessary by 12 mg after 1-2 min	Nausea, headache, flushing, chest pain, bronchospasm (contraindicated if asthma)	Methylxanthines compete for adenosine receptors with adenosine Dipyridamole decreases the metabolism of adenosine
Amiodarone	Hepatic half-life 50 days PO load 10 g over 7-10 days, then 400 mg for 3 wk, then 200 mg/day for atrial fibrillation Maintenance dose of 400 mg/day for VT Dose reduce load for bradycardia or QT prolongation IV: 150- to 300-mg bolus, then 1 mg/min infusion for 6 hr, followed by 0.5 mg/min thereafter	Pulmonary (acute hypersensitivity pneumonitis, chronic interstitial infiltrates), hepatitis Thyroid (hypothyroidism or hyperthyroidism) Photosensitivity, blue-gray discoloration with chronic high dose, nausea, ataxia, tremor, alopecia Avoid if identified thyroid nodule LFTs two to three times a year, TFTs twice yearly, PFTs and CXR at initiation and CXR yearly thereafter QT prolongation expected; reduce dose if exceeds 500 msec	Inhibits CYP 450 enzymes—increases concentrations of warfarin, digoxin, cyclosporine, alprazolam, carbamazepine, HMG-CoA inhibitors, phenytoin, and quinidine
Sotalol	Renal: 80-120 mg bid orally Max dose, 240 mg bid orally	Bronchospasm QT prolongation/torsades de pointes	No significant interactions
Ibutilide	Hepatic CYP 3A4 1 mg IV over 10 min, repeat after 10 min if necessary	Nausea QT prolongation and torsades de pointes Must monitor for 4 hr after drug initiation	None
Propafenone	Hepatic 150-300 mg q8h or sustained release 225-425 mg bid orally	Metallic taste, dizziness, SIADH Atrial flutter, ventricular tachycardia	May decrease the metabolism of warfarin Increase digoxin levels
Flecainide	Renal, hepatic CYP 2D6 50-100 mg bid orally; max dose, 300-400 mg/day	Dizziness, headache, visual blurring Atrial flutter, ventricular tachycardia	May increase digoxin levels Flecainide levels increased by amiodarone, haloperidol, quinidine, cimetidine, and fluoxetine
Disopyramide	Renal, hepatic (CYP 3A4) Dose: 100-400 mg q8-12h orally; max dose, 800 mg/24 hr Reduce dose for renal or hepatic dysfunction	Anticholinergic (contraindicated for narrow-angle glaucoma): dry mouth, urinary retention, constipation, blurry vision QT prolongation/torsades de pointes	None
Procainamide	Mostly hepatic—rapid acetylators produce more NAPA; NAPA renally cleared PO dose: 50 mg/kg/24 hr IV dose: 1 g over 25 min, then 20-60 µg/kg/min infusion Reduce dose for renal dysfunction or low cardiac output	Rash, fever, arthralgias, drug-induced lupus, particularly in slow acetylators Agranulocytosis QT prolongation/torsades de pointes	Procainamide clearance reduced by trimethoprim, cimetidine, and ranitidine

TABLE 52-2 ANTIARRHYTHMIC DRUGS: DOSES AND SIDE EFFECTS—cont'd

ANTIARRHYTHMIC DRUG AND COMMON USE	DOSE/METABOLISM	SIDE EFFECTS AND REQUIRED MONITORING	SELECTED DRUG INTERACTIONS
Quinidine	Hepatic CYP 3A4 (70%), renal (30%) Dose: sulfate—600 mg tid orally, gluconate—324 to 648 mg q8h orally Dose reduced for renal failure	Thrombocytopenia, cinchonism Pruritus, rash QT prolongation/torsades de pointes	↑ Digoxin and amiodarone concentrations Quinidine inhibits CYP 2D6 and may increase drugs metabolized by this enzyme (e.g., ↑ effect of tricyclic antidepressants, haloperidol, some β-blockers, fluoxetine, opioids) Quinidine metabolism inhibited by cimetidine Quinidine metabolism increased by phenobarbital, phenytoin, and rifampicin
Dofetilide	Renal, hepatic CYP 3A4 CrCl >60 mL/min (500 µg bid orally), CrCl 40-60 (250 µg bid orally), CrCl 20-39 mL/min (125 µg bid orally)	QT prolongation and torsades de pointes Three days of in-hospital monitoring is required during drug initiation	Contraindicated with verapamil, ketoconazole, cimetidine, megestrol, prochlorperazine, and trimethoprim Hydrochlorothiazide increases dofetilide levels Must discontinue amiodarone at least 3 mo before dofetilide initiation
Ivabradine	2.5 mg starting dose, 5 mg bid orally for 1 mo followed by increase to 7.5 bid if needed	Sinus bradycardia Headaches Visual brightness	Azole antifungals, macrolide antibiotics, nefazodone, nelfinavir, ritonavir
Dronedarone	Hepatic CYP 3A4 half-life 30 hr PO 400 mg bid orally Improved absorption with food	Reduces the secretion of creatinine without a reduction in GFR Hepatic failure Avoid in heart failure	Increases digoxin levels (dose reduce digoxin by half) May increase myositis with simvastatin Avoid grapefruit

bid = twice daily; CrCl = creatinine clearance; CXR = chest radiograph; CYP = cytochrome P-450; GFR = glomerular filtration rate; HMG-CoA = 3-hydroxy-3-methylglutaryl coenzyme A; IV = intravenous administration; LFT = liver function test; max = maximum; NAPA = *N*-acetyl procainamide; PFT = pulmonary function test; PO = oral administration; qd = daily; SIADH = syndrome of inappropriate diuretic hormone; TFT = thyroid function test; VT = ventricular tachycardia.

FIGURE 52-7. Multifocal atrial tachycardia. An atrial tachycardia with three different P wave morphologies.

Nonparoxysmal junctional tachycardia is a benign arrhythmia that rarely exceeds 120 beats per minute and typically exhibits a "warm-up" and "cool-down" pattern. A more rapid paroxysmal form of junctional tachycardia occurs in young adults and is often associated with exercise. Congenital junctional ectopic tachycardia, which occurs in the pediatric population, is associated with very rapid rates and a risk for tachycardia-related cardiomyopathy.

TREATMENT AND PROGNOSIS

When junctional tachycardia is not a re-entrant arrhythmia, treatment is either medically, with amiodarone or ivabradine (see Table 52-2),[A2] or with radiofrequency catheter ablation. Reported efficacies are in the 90% range.

ACCESSORY PATHWAY TACHYCARDIAS

Tachycardias associated with an accessory pathway or bypass tract are called AV re-entrant tachycardia (also called AVRT). These tachycardias most often conduct down the normal AV conducting system and back up the accessory pathway (orthodromic AV re-entrant tachycardia) (see Fig. 52-6). Antidromic tachycardia is rare and represents conduction down the accessory pathway and back up the normal conducting system or, less commonly, a second accessory pathway. Wolff-Parkinson-White syndrome is defined by the presence of delta waves or preexcitation on the ECG in sinus rhythm (Fig. 52-10), in combination with a history of AV re-entrant tachycardia. It is important to recognize, however, that many patients with ventricular preexcitation never get AV re-entrant tachycardia. In addition, up to 40% of patients with accessory pathways have AF. Because accessory pathway tissue, unlike the AV node, is usually nondecremental, a rapidly conducting accessory pathway may allow AF to conduct to the ventricles at excessive rates and precipitate ventricular fibrillation. Drugs such as digoxin, which accelerate accessory pathway conduction, should be avoided in these patients.

The ECG during orthodromic AV re-entrant tachycardia can have a narrow complex, but a wide QRS complex will be seen if there is aberration from a bundle branch block, especially at more rapid rates. The retrograde P wave is negative in leads I and aVL if it conducts over a left lateral accessory pathway and negative in leads II, III, and aVF if it conducts over a septal or posteroseptal accessory pathway (Fig. 52-11). The P wave occurs later (after the preceding R wave) compared with AV nodal re-entrant tachycardia because in AV re-entrant tachycardia, the impulse must conduct beyond the AV node and into the ventricle before returning to the atria over an accessory pathway. In antidromic AV re-entrant tachycardia, the QRS complex is wide with a slurred upstroke and resembles that seen with ventricular tachycardia as opposed to a bundle branch block. Antidromic conduction with AF is often fast, broad, and irregular (see Fig. 52-10).

Palpitations are the most common symptoms. If AF with rapid conduction occurs over the accessory pathway (preexcited AF), more significant symptoms such as light-headedness, syncope, or even cardiac arrest may occur.

TREATMENT

The acute management of AV re-entrant tachycardia, particularly if there is evidence of preexcitation, is intravenous adenosine (6 mg intravenous push, followed by another 12 mg after 1 to 2 minutes if needed). Intravenous procainamide (1 g over 25 minutes is an alternative, but direct electrical cardioversion is a safe, effective, and generally preferred option if adenosine is unsuccessful. Intravenous calcium channel blockers and β-blockers can potentially be used (see Table 52-2), but the risk of associated vasodilation and hypotension with a resultant reflex adrenergic response can cause a dangerous acceleration in conduction over the accessory pathway, so they require great caution and should be used only under expert supervision.

The longer term management of AV re-entrant tachycardia is best accomplished with an electrophysiologic study and ablation of the accessory pathway (Chapter 54). If an invasive approach is not available or preferred by the patient or if the accessory pathway is in a location that is difficult to access or associated with high risk of damage to the conduction system (i.e., risk of complete heart block), oral medications, including β-blockers (e.g., metoprolol 25 to 50 mg daily) or antiarrhythmic drugs (e.g., flecainide 100 to 150 mg twice daily) can be considered.

ATRIAL FLUTTER

Atrial flutter is an arrhythmia with an atrial rate of approximately 300 beats per minute and a ventricular response of 150 (2 : 1), 100 (3 : 1), or slower multiples. Typical atrial flutter is a macro-re-entrant circuit that circulates in the

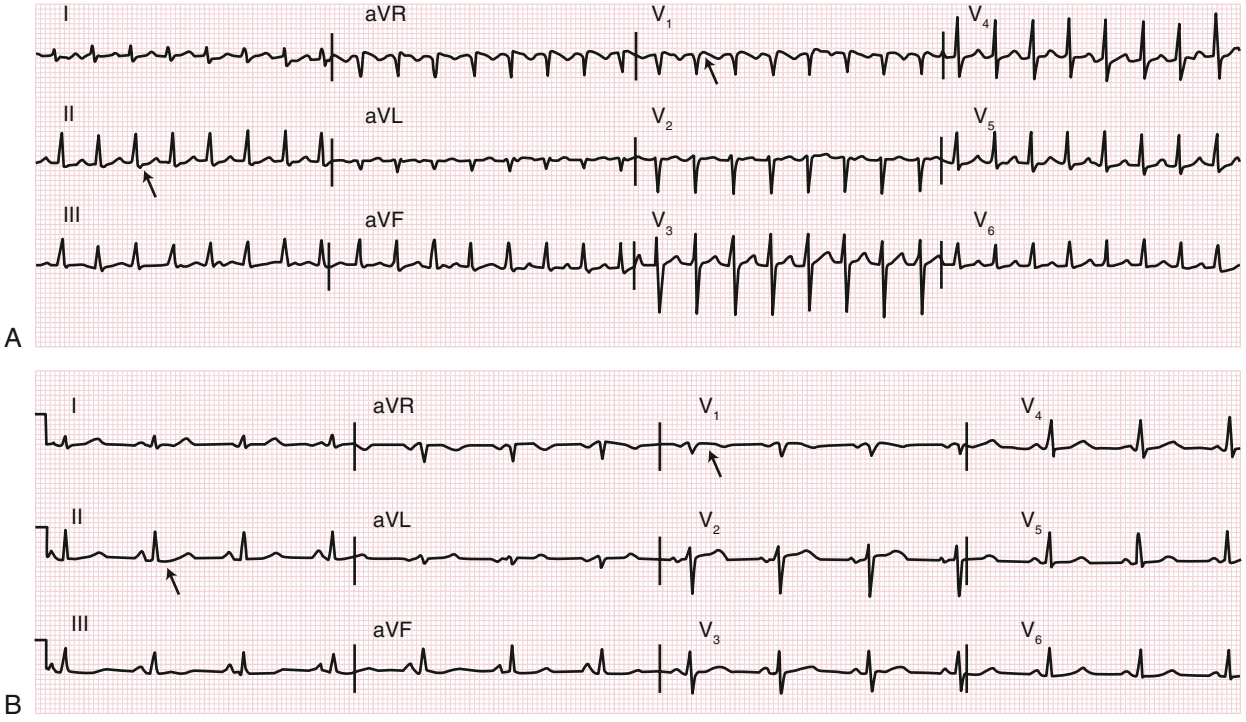

FIGURE 52-8. **Electrocardiograms demonstrating different rhythms in the same patient. A,** Atrioventricular nodal re-entrant tachycardia, with *arrows* indicating retrograde P waves (negative in lead II, positive in V_1). **B,** Same patient in sinus rhythm. The absence of a negative deflection at the end of the QRS in lead II and positive deflection in V_1 confirms that those findings in panel A were retrograde P waves.

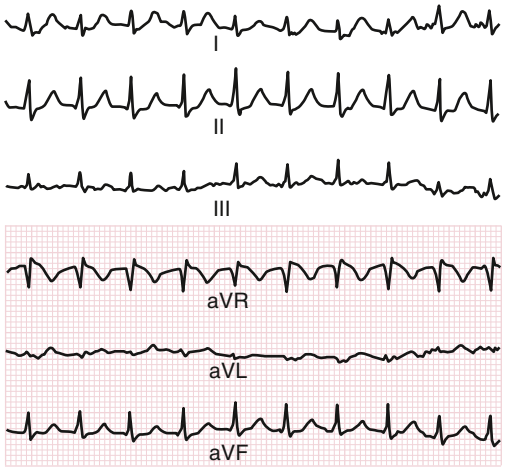

FIGURE 52-9. **Junctional tachycardia. A tachycardia without evident P waves. The negative deflections at the end of leads II, III, and aVF represent retrograde P waves. This rhythm is impossible to distinguish from atrioventricular nodal re-entrant tachycardia on the surface electrocardiogram.**

right atrium in a clockwise or counterclockwise loop (Fig. 52-12). The inferior portion of typical flutter uses the narrow region between the inferior vena cava and tricuspid annulus as a critical isthmus of conduction. Typical atrial flutter almost always occurs in patients with underlying cardiovascular or pulmonary disease. It can also develop in patients who receive antiarrhythmic drugs (e.g., sodium-channel blocking drugs) for AF. Atypical atrial flutter refers to macro-re-entrant atrial circuits that do not use this critical cavotricuspid isthmus of tissue. These atypical forms of atrial flutter often occur in the left atrium after mitral valve surgery or catheter ablation of AF. Typical atrial flutter can be recognized by a "sawtooth" P wave morphology, which is predominantly negative in leads II, III, and aVF and positive in V_1 (counterclockwise atrial flutter) or positive in leads II, III, and aVF and negative in V_1 (clockwise atrial flutter).

If the rate of atrial flutter is well controlled by effective atrioventricular block, patients may be asymptomatic. More rapid ventricular rates are associated with palpitations, light-headedness, syncope, or shortness of breath. Atrial flutter also can precipitate heart failure or myocardial ischemia in patients with underlying heart disease. If high-grade atrioventricular block develops, light-headedness and even syncope can be seen as with other bradycardias (see Chapter 51).

TREATMENT AND PROGNOSIS

It can be very difficult to control the ventricular rate of acute atrial flutter, which generally must be treated by restoring sinus rhythm. In some cases, successful treatment of precipitating problems such as hypoxia, fever, and electrolyte abnormalities will lead to spontaneous conversion, and such treatment is often required to sustain sinus rhythm once it is achieved.

Intravenous ibutilide (1 g over 10 minutes, repeated after 10 minutes if needed) is approximately 60% effective for converting atrial flutter to sinus rhythm, but direct current electrical cardioversion (Chapter 54) is the preferred approach and is highly (>95%) effective for restoring sinus rhythm. As is true of AF (see later), electrical or pharmacologic cardioversion should not be performed unless the episode of atrial flutter is believed to be less than 48 hours in duration, a transesophageal echocardiogram has excluded clot in the left atrial appendage, or the risk for stroke has been minimized by achieving a therapeutic level of anticoagulation, preferably with a direct-acting oral anticoagulant (e.g., dabigatran, rivaroxaban, apixaban, or edoxaban; see Table 70-6) or with a therapeutic international normalized ratio (INR) of 2 to 3 with warfarin (see Table 70-4), for the prior 4 weeks. Since the effective ventricular rate in atrial flutter depends on the degree of atrioventricular block, a titrated β-blocker (e.g., metoprolol starting at 25 to 50 mg daily) or calcium channel blocker (e.g., diltiazem starting at 180 to 240 mg daily) can provide temporary rate control while awaiting cardioversion. However, very careful follow-up is critical because of the challenge of balancing the degree of atrioventricular block.

As with AF, atrial flutter is rarely an isolated occurrence and can be expected to recur. Even if patients are minimally symptomatic because atrioventricular block results in a physiologic heart rate, patients are likely to have variable block, and hence an unstable heart rate, over time. For these reasons, radiofrequency ablation of the cavotricuspid isthmus is 95% curative for the typical form of atrial flutter and is the preferred choice for most patients (Chapter 54). The first-line therapy for atypical atrial flutter is also often catheter ablation, but the likelihood of success is lower,[6] so either antiarrhythmic drug therapy or simply recurrent cardioversion for infrequent recurrences are also reasonable approaches. Because patients with atrial flutter have a 3% per year risk for thromboembolism, patients at risk for recurrence should also receive long-term anticoagulation similar to what is recommended for AF (see later). If atrial flutter ablation is successful, however, the risk for recurrence is very small, and long-term anticoagulation is not necessary. Prognosis is generally related to any underlying comorbid conditions that may have precipitated the atrial flutter.

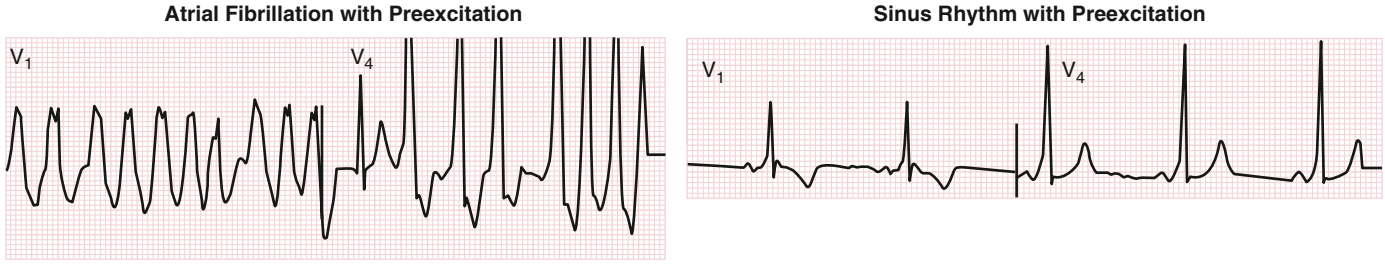

FIGURE 52-10. Two panels of the same patient with ventricular preexcitation. The rhythm on the left is fast, broad, and irregular, indicating atrial fibrillation with conduction over an accessory pathway. The rhythm on the right is sinus with conduction over an accessory pathway.

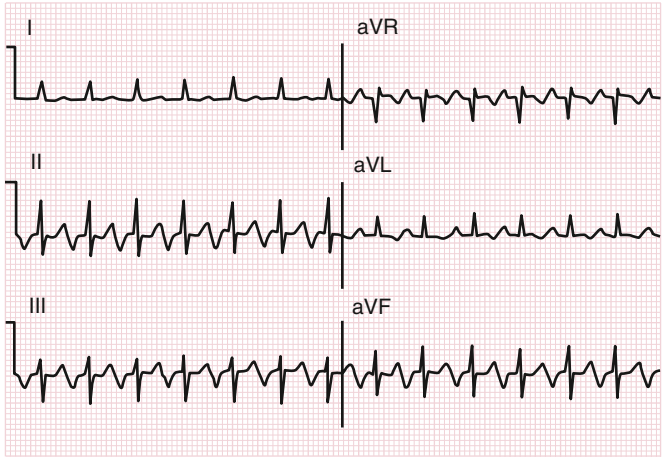

FIGURE 52-11. Atrioventricular re-entrant tachycardia. Negative P waves are seen in leads II, III, and aVF indicative of retrograde conduction to the atria over a septal accessory pathway.

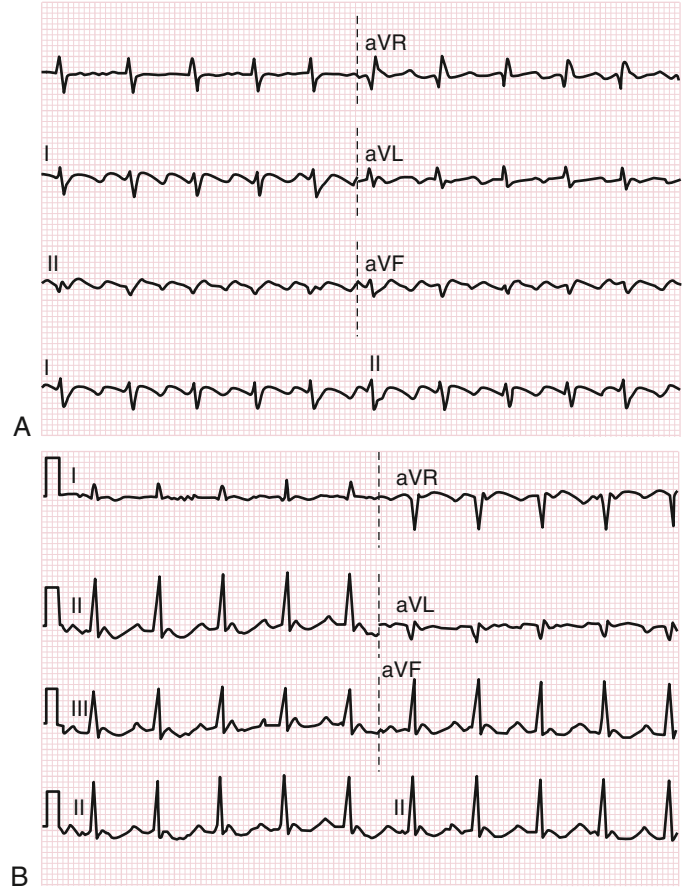

FIGURE 52-12. Two examples of atrial flutter. A, Typical counterclockwise right atrial flutter with classic sawtooth flutter waves seen in leads II, III, and aVF. **B,** Clockwise right atrial flutter.

FIGURE 52-13. Coarse atrial fibrillation. The wavy baseline is suggestive of atrial activity and can be misinterpreted as P waves or flutter waves. The irregularity of the QRS complexes indicates that this is atrial fibrillation.

ATRIAL FIBRILLATION

AF is identified by the absence of P waves and the presence of an irregularly irregular ventricular rate. Coarse AF, which describes the presence of residual atrial activity on the ECG, is generally best seen in lead V_1 with the absence of P wave–like activity in other leads (Fig. 52-13). AF can be present with a regular ventricular rate when there is concomitant AV dissociation (e.g., complete heart block or ventricular tachycardia).

AF, which is the most common arrhythmia in clinical practice,[7] afflicts more than 2 million Americans. The likelihood of developing AF increases with aging, with an anticipated three-fold increase in prevalence as the U.S. population ages in the next 20 years. AF is almost always a recurrent disorder, with the possible exception of AF that develops in association with hyperthyroidism (Chapter 207) and surgery (Chapter 401). AF can be paroxysmal (terminates spontaneously) or persistent (persists for at least 7 days or until cardioverted).

In addition to its association with aging, AF frequently occurs in association with hypertension (Chapter 64) or other comorbid conditions such as diabetes mellitus (Chapter 210), thyrotoxicosis (Chapter 207), heart failure (Chapter 45), coronary artery disease (Chapter 56), valvular heart disease (Chapter 60), or lung disease such as chronic obstructive pulmonary disease (Chapter 76)[8] or obstructive sleep apnea (Chapter 374). About 20% of patients have no associated comorbidity. Some patients develop AF after binges of alcohol use ("holiday heart")[9] or after parasympathetic surges, such as occur after vigorous exercise or a large meal (vagally induced AF). Long-term significant alcohol use can also result in an increased risk of AF. Excessive caffeine intake is an often cited but very rare cause of AF.

AF requires a trigger in the form of atrial premature depolarizations, which often originate in the pulmonary veins and which, in the susceptible individual, result in AF. The susceptibility to AF may relate to changes in the electrical function of the left atrium. Prolonged periods of AF can lead to electrical and structural remodeling of the atria and promote the further perpetuation of AF.

AF results in the loss of the atrial contribution to ventricular filling. This so-called loss of atrial kick is generally well tolerated in normal individuals, in whom only about 15% of ventricular filling is the result of atrial contraction. In patients who have stiff, noncompliant ventricles (e.g., patients with aortic stenosis, hypertrophic or restrictive cardiomyopathy, or long-standing hypertension), however, up to 40% of ventricular filling may be related to atrial contraction, so stroke volume may fall noticeably in such patients.

Silent or asymptomatic AF may be identified on a permanently placed device such as a pacemaker or implantable defibrillator or on a wearable device.[A3] By convention, at least 2 minutes of a sustained arrhythmia consistent with AF must be present to make the diagnosis of AF. Currently, the U.S. Preventive Services Task Force concludes that evidence is insufficient to determine whether screening for AF should be recommended.[10]

CLINICAL MANIFESTATIONS AND DIAGNOSIS

The most common symptoms associated with AF include palpitations, dyspnea, chest pain, and fatigue.[11] Most patients have symptoms with the new onset of AF, but it is common for these symptoms to dissipate over time with recurrent or persistent AF, especially if the heart rate is in the physiologic range. Syncope (Chapter 49) can occasionally occur and is usually a consequence of a conversion pause that occurs when AF terminates and a delay ensues before the resumption of sinus rhythm.

The primary morbidity associated with AF is thromboembolism. Thromboembolism in patients with nonvalvular AF typically results from thrombus that forms in the left atrial appendage and later dislodges from it. The risk for thromboembolism is related to the presence of underlying vascular disease but not to the pattern of AF (paroxysmal or persistent). For example, even subclinical ("silent") AF is associated with a 2.5-fold increased risk for ischemic stroke or systemic embolism. However, the risk for embolization is further increased in the first 3 to 4 weeks after cardioversion, when the gradual return of atrial mechanical function can result in a particularly high risk for thromboembolism. The risk for thromboembolism in AF increases with age, diabetes mellitus, hypertension, previous embolic episodes, vascular disease, and heart failure. The lowest incidence (<1% annually) is in patients younger than 65 years with lone AF. AF is associated with about a 1.4-fold higher risk for cognitive impairment and dementia, with or without a history of clinical stroke. About 12% of clinical embolic events are extracranial, about 70% of which affect the extremities, with most of the remainder affecting the visceral mesenteric circulation.

AF with a rapid ventricular response can also result in biventricular dysfunction, termed tachycardia-induced cardiomyopathy (Chapter 45). This complication is generally associated with ventricular rates over 120 beats per minute for at least a few weeks. In many instances, patients with this complication are relatively asymptomatic while in AF and, as such, do not seek medical attention until evidence of heart failure develops.

The initial diagnostic evaluation of AF should include blood work (hematocrit and blood levels of potassium, creatinine, and thyroid-stimulating hormone at a minimum), as well as an echocardiogram to evaluate for possible underlying ventricular dysfunction or valvular disease. A stress test to exclude ischemia is not required as a routine part of the evaluation unless the patient otherwise has clinical evidence of atherosclerosis or coronary artery disease from the history, physical examination, ECG, or echocardiogram.

TREATMENT

Recent-Onset Atrial Fibrillation

In the presence of hypotension, acute myocardial ischemia, or new or worsening heart failure, prompt cardioversion is generally indicated. However, precipitating conditions such as hypoxia, fever, and electrolyte abnormalities also should be addressed to increase the likelihood that cardioversion will be successful and the patient will remain in sinus rhythm.

For acute AF without hypotension, hemodynamic compromise, or acute ischemia, at least one attempt to restore normal sinus rhythm is almost always warranted. However, a short period of rate control is appropriate because about 50% of patients with acute-onset AF will spontaneously revert to sinus rhythm within the first 48 to 96 hours. Therefore, even in patients with mildly symptomatic recent-onset AF, a "wait-and-see" approach with delayed cardioversion if the AF does not resolve within 48hours is as good as early cardioversion in achieving a return to sinus rhythm at 1 month.[A4] Rate control is crucial and can be accomplished with esmolol, metoprolol, verapamil, or diltiazem (see Table 52-2); digoxin is usually a third-line agent (Fig. 52-14).

Before cardioversion, either pharmacologic or electrical (Chapter 54), however, the risk for clot formation must be mitigated in all patients who have AF of more than 48 hours' duration.[12] The first step generally is to perform transesophageal echocardiography (Chapter 43). If the transesophageal echocardiogram shows no evidence of a left atrial clot, cardioversion can be undertaken without systemic anticoagulation. If the patient has risk factors for stroke in association with AF, however, most clinicians administer anticoagulation during the cardioversion and for the subsequent 4 weeks. If the transesophageal echocardiogram shows evidence of clot, 4 consecutive weeks of pre-cardioversion anticoagulation is required, preferentially with therapeutic doses of dabigatran, rivaroxaban, apixaban, or edoxaban (see Table 70-6), rather than with heparin and warfarin. If warfarin is used (see Table 70-4), an international normalized ratio (INR) of at least 2.0 is required.

For a first episode of acute AF (<48 hours' duration), cardioversion can be attempted using electrical cardioversion (Chapter 54) or medications. Electrical cardioversion, which is performed with a minimum of 200 joules, is successful in more than 90% of cases.[A5] Medical options include procainamide (15mg/kg intravenously over 30 min), ibutilide (1 mg intravenously over 10 minutes, repeated after 10 minutes if necessary), or a single dose of propafenone (600 mg) or flecainide (300 mg). For recent-onset AF of less than 48 hours' duration, the success rate is approximately 50%. Approximately 3 hours of postadministration monitoring is required when these antiarrhythmic agents are used owing to a risk of proarrhythmia, including but not limited to QT prolongation and torsades de pointes. This limitation often makes this option impractical compared with treatment with immediate cardioversion.

Atrial Fibrillation of Uncertain Duration

Since the duration of AF may be hard to identify definitively, it is prudent to assume that the duration of AF has been greater than 48 hours when contemplating a cardioversion strategy (see Fig. 52-14) unless there is absolute certainty of the timing of onset. In this setting, a transesophageal echocardiogram should be performed to assess for possible clot in the left atrium. If negative, cardioversion (either medical or electrical) is as for recent-onset AF. If, however, clot is seen, then the patient must be anticoagulated for 1 month unless symptoms truly warrant urgent cardioversion. Anticoagulation also must be maintained for at least 3 to 4 weeks after successful cardioversion. Even in the absence of clot, long-term anticoagulation is commonly recommended for patients with paroxysmal or recurrent AF.

Chronic Rhythm and Rate Therapy

Catheter Ablation

After the treatment and hopefully resolution of a first episode of AF and the mandatory 1 month of anticoagulation, the strategy of rhythm control within the first year with catheter ablation to isolate the pulmonary veins electrically from the remainder of the atrium (see Chapter 54) and/or with an antiarrhythmic drug confers about a one-third lower rate of death (1.0 vs. 1.3 deaths/100 person years),[A6] due to the safety and efficacy of catheter ablation,[13] which is significantly superior to anti-arrhythmia medications,[A7–A10] and the widespread use of direct-acting oral anticoagulants. Early rhythm control with catheter ablation is especially beneficial in patients who have heart failure.[A11–A13]

Medical Rhythm Control

Rhythm control with medication alone is not superior to rate control in terms of major adverse events but may be chosen for bothersome symptoms. If catheter ablation is not selected, repeat electrical or pharmacologic cardioversion can be attempted with the same medications used for an initial episode or with oral amiodarone (typically a 10-g loading dose given in equal daily amounts over 1 to 2 weeks, followed by 400 to 600 mg a day for the remainder of a month).

To prevent recurrent AF, the pharmacologic options work by blocking sodium channels, potassium channels, or a combination of ion channels, thereby slowing cardiac conduction (sodium channels) and/or prolonging cardiac repolarization (potassium channels), as well as modulating the autonomic nervous system. The choice of antiarrhythmic drug is based on the patient's underlying clinical condition (Table 52-3).[14]

Amiodarone (usually 200 mg daily), which is the most widely used medication for the prevention of recurrent AF, has an efficacy of 60 to 70% at 1 year and is significantly more effective than propafenone, flecainide, dofetilide, or sotalol, which are the recommended alternatives. It is associated with a number of drug interactions, most notably with warfarin and digoxin. Its associated risk for thyroid, liver, and lung toxicities, related in part to the iodine moieties on this compound, necessitate careful monitoring. Dronedarone (400 mg twice daily), which is related to amiodarone but has no iodine and a shorter 15-hour half-life, is well tolerated in terms of non-cardiovascular side effects but carries an increased risk for heart failure, stroke, and death in patients with permanent AF. As a result, it should be discontinued in patients in whom sinus rhythm is not well maintained.

Quinidine, procainamide, and disopyramide are predominantly sodium-channel blocking drugs that also block potassium channels at slow heart rates. Each of these drugs is moderately successful in AF, with about 50% of treated patients in sinus rhythm at 1 year, but each also has idiosyncratic non-cardiovascular toxicities that can significantly limit their utility (see Table 52-2). Propafenone and flecainide are sodium-channel blockers that are also used for the maintenance of sinus rhythm. These drugs are moderately effective, with a 50% rate of sinus rhythm at 1 year, and are generally well tolerated, but they must be avoided in patients with structural heart disease, particularly with a history of prior myocardial infarction and impaired left ventricular function, because of a risk for drug-induced ventricular arrhythmia. Dofetilide is a potassium-channel blocking medication that is moderately effective for suppressing AF but carries a dose-dependent risk for QT prolongation and torsades de pointes.

Rate Control

If a strategy of rate control is chosen, it is important to confirm a heart rate of 70 to 100 beats per minute at rest and less than 140 beats per minute with exercise, preferably by monitoring the heart rate during exercise on an exercise treadmill test or with an ambulatory monitor. More strict rate control is not beneficial. Failure to confirm rate control can result in the development of tachycardia-induced cardiomyopathy. First-line therapy for rate control includes β-blockers (e.g., metoprolol 25 to 50 mg daily) or non-dihydropyridone calcium-channel

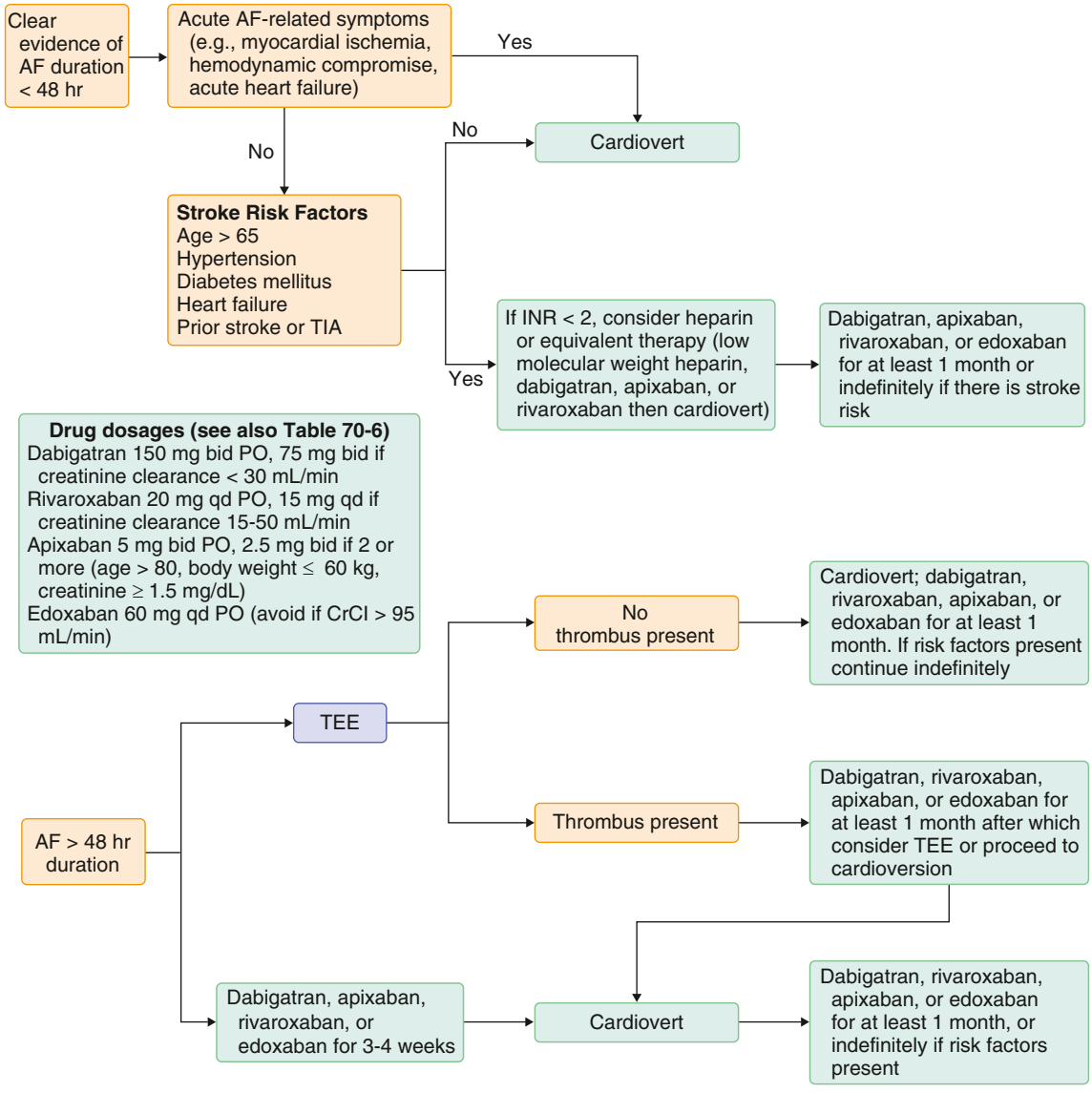

FIGURE 52-14. Management of recent-onset atrial fibrillation (AF). bid = twice daily; CrCl = creatinine clearance; INR = international normalized ratio; qd = daily; TEE = transesophageal echocardiography; TIA = transient ischemic attack.

TABLE 52-3 SELECTION OF ANTIARRHYTHMIC DRUGS

PATIENT'S CHARACTERISTICS	ANTIARRHYTHMIC DRUG CHOICES
No structural heart disease	*First line:* flecainide, propafenone, dronedarone, sotalol *Second line:* amiodarone, dofetilide
Depressed left ventricular ejection fraction with heart failure	*First line:* amiodarone, dofetilide *Avoid:* dronedarone, flecainide, propafenone
Coronary artery disease without heart failure	*First line:* sotalol, dronedarone, dofetilide, amiodarone *Avoid:* flecainide, propafenone
Hypertrophic cardiomyopathy	*First line:* amiodarone, sotalol *Second line:* disopyramide

blockers (e.g., diltiazem 180 to 240 mg daily); digoxin (usually 0.125 to 0.25 mg daily) can also be used but is generally less well tolerated.[A14] Interestingly, β-blockers do not appear to reduce all-cause mortality when used in patients whose AF is complicated by heart failure, but it is not clear whether digoxin is preferred in this setting. From a practical perspective, patients commonly require a combination of medications (e.g., metoprolol plus diltiazem) to achieve goal heart rates. In some patients, rate control is difficult to achieve because of inefficacy of or intolerance to medical therapy. In these patients, ablation of the AV junction can be performed with placement of a single chamber or biventricular pacemaker.[A15]

Chronic Persistent AF

In patients with chronic existing AF, catheter ablation is now recommended first-line therapy because of its efficacy of about 70% for preventing recurrent AF with an excellent safety profile.[A16] When available, the benefits of catheter ablation over medical therapy are even more striking in patients who have heart failure, in whom it provides a very clear survival advantage (Chapter 46). A second procedure typically is offered to patients who have recurrent AF following a first catheter-based procedure. Interestingly, continuing previously ineffective antiarrhythmic therapy after ablation can further reduce the risk of recurrent AF.[A17]

The surgical maze procedure is nearly always reserved for patients who have a concomitant reason for open heart surgery (e.g., coronary artery bypass grafting and/or a valve operation). The maze procedure is performed from an endocardial or epicardial approach with the same fundamental goal of electrical isolation of the pulmonary veins. In addition, a surgical maze procedure includes the clipping or resection of the left atrial appendage. The success rate for the procedure is comparable to or slightly better than that of catheter-based pulmonary vein isolation.

Paroxysmal AF

Paroxysmal AF refers to recurrent episodes of AF that resolve either spontaneously or with medical treatment. Paroxysmal AF may manifest as a breakthrough arrhythmia in patients who are on chronic medical therapy to suppress AF or in patients who are on no treatment or may be taking a medication (such as a β-blocker or diltiazem) to slow the rate of any future episode of AF. Unfortunately,

most behavioral efforts to limit the recurrence of AF have largely proven ineffective. One exception is in regular alcohol drinkers, for whom abstinence from alcohol can reduce the likelihood of recurrent paroxysmal AF by about one third.[A18] Prophylactic rhythm control can be tried, but outcomes are not as good as with ablation,[A19] and medication side effects often are limiting.

For paroxysmal AF, catheter ablation is preferred because it significantly reduces the risk of recurrent atrial arrhythmias and hospitalizations, significantly improves quality of life,[A20] and also results in about a one-third reduction in the risk of major adverse events.[A21] The success rate is improved if it is performed before patients with paroxysmal AF develop persistent AF.

The other option is prophylactic rate control, typically with low-dose metoprolol (25 to 50 mg daily, with the option for an additional dose at the onset of AF and again 6 hours later if rapid AF develops) or diltiazem (180 to 240 mg daily). Another option is so-called pill-in-the-pocket therapy with a single dose of propafenone (600 mg) or flecainide (300 mg) when the paroxysmal AF episode occurs (see Fig. 52-14).

Thromboembolic Prophylaxis

Long-term anticoagulation therapy (Fig. 52-15) is generally recommended in all patients who have persistent or paroxysmal AF and a CHADS VASC score of 2 or more (Table 52-4). When paroxysmal AF is detected by screening in asymptomatic individuals by intermittent electrocardiograms or an implantable loop recorder, prophylactic anticoagulation is of little or limited value in preventing major complications.[A22,A23]

For patients with a single risk factor for stroke in association with AF, the decision to anticoagulate can be at the preference of the patient and physician.[15,16] For thromboembolic prophylaxis in patients who have AF with a mechanical prosthetic valve or rheumatic heart disease, warfarin anticoagulation (Table 70-4) is the approach of choice.[A24] For other patients, however, direct-acting oral anticoagulant medications (Table 70-6 in Chapter 70) have replaced warfarin because of their ease of use, superior or equivalent efficacy, and excellent safety profile.[A25] Options include rivaroxaban (an oral factor Xa inhibitor at 20 mg per day), apixaban (an oral factor Xa inhibitor at 5 mg twice daily), dabigatran (a direct thrombin inhibitor at 150 mg twice daily), and edoxaban (30 or 60 mg once daily). All four drugs are eliminated by the kidney (apixaban 25%, edoxaban 50%, rivaroxaban 65%, and dabigatran 85%), so they are not recommended in patients with substantial renal dysfunction, and their doses should be reduced in patients with moderate renal dysfunction (see Chapter 70).[17] Even in patients older than 75 years, these agents appear to be at least as effective as warfarin with a lower risk of life-threatening bleeding.[18] In very elderly patients who are not considered candidates for full-dose anticoagulation, low-dose edoxaban (15 mg daily) is safe and efficacious.[A26] In patients who cannot take these agents because of renal failure, warfarin titrated to an INR of 2.0 (Chapter 70) is indicated.

Idarucizumab (4 to 5 g intravenously) can rapidly reverse dabigatran,[19] and andexanet alfa (400- to 800-mg bolus over 15 to 30 minutes followed by a 400- to 960-mg infusion) can reverse rivaroxaban or apixaban and achieve good to excellent hemostasis in about 75% of bleeding patients within 12 hours (Chapter 70).[20]

In patients with AF and stable coronary disease (Chapter 59), rivaroxaban (10 mg once daily for patients with a creatinine clearance of 15 to 49 mL/minute or 15 mg once daily for patients with a creatinine clearance of ≥50 mL/minute) alone is safer and as efficacious as combining it with an anti-platelet agent.[A27] In patients with AF after an acute coronary syndrome (Chapter 57) or a coronary stent, standard-dose apixaban (5 mg twice daily or 2.5 mg twice daily for patients who meet two or more of the following dose-reduction criteria: are at least 80

TABLE 52-4 CURRENT RECOMMENDATIONS FOR THROMBOEMBOLIC PROPHYLAXIS FOR PATIENTS WITH ATRIAL FIBRILLATION BASED ON RISK FACTORS FOR STROKE

RISK FACTORS*	RECOMMENDATIONS
Heart failure (1 point) Hypertension (1 point) Age ≥65 (1 point), ≥75 (2 points) Diabetes (1 point) Stroke/TIA (2 points) Vascular disease (1 point) Female sex (1 point)	2 or more points: anticoagulation with warfarin or a direct oral anticoagulant 1 point: anticoagulation or no therapy depending on the preference of the patient and treating physician 0 points: no therapy

*Based on the CHA_2DS_2-VASc risk stratification scoring system.

TIA = transient ischemic attack.

Data from January CT, Wann S, Alpert JS, et al. 2014 AHA/ACC/HRS guideline for the management of patients with atrial fibrillation: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines and the Heart Rhythm Society. *J Am Coll Cardiol.* 2014;64:e1-e76.

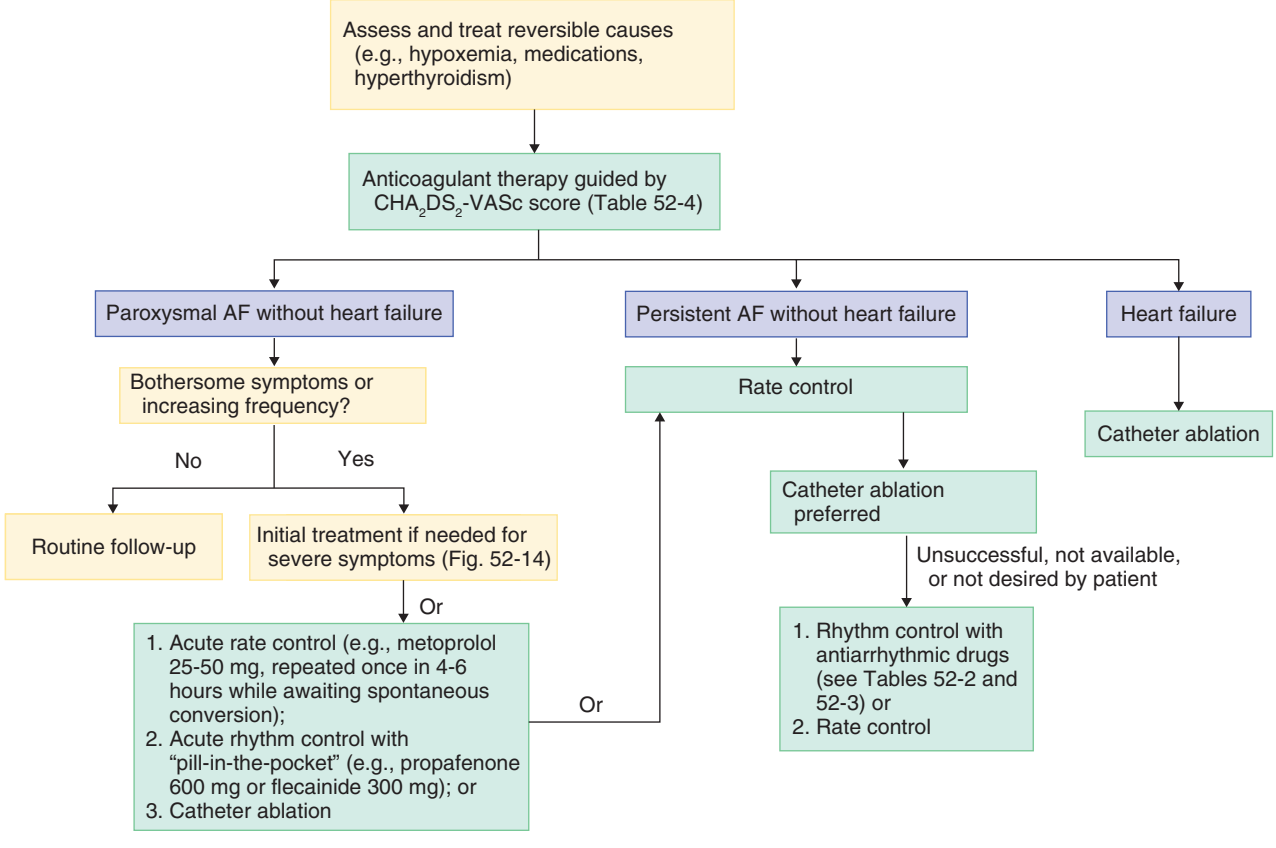

FIGURE 52-15. Treatment of recurrent paroxysmal or chronic persistent fibrillation (AF). Direct oral anticoagulants are strongly preferred over warfarin. If warfarin is used, the goal international normalized ratio is generally 2 to 3. (Adapted from Prystowsky EN, Padanilam BJ, Fogal RI. Treatment of atrial fibrillation. *JAMA.* 2015;314:278-288.)

years of age, weigh no more than 60 kg, or have a serum creatinine level of 1.5 mg/dL or higher) plus a $P2Y_{12}$ inhibitor such as clopidogrel (75 mg once daily) is safer and as efficacious as the two drugs plus aspirin.[A28] Another efficacious option for stented patients is dual therapy with dabigatran (110 or 150 mg twice daily) plus clopidogrel (75 mg once daily) or ticagrelor 180 mg once daily.[A29] The addition of dabigatran, rivaroxaban, or apixaban to aspirin under expert supervision is preferable to adding warfarin.[A30] At the time of an invasive procedure (Chapter 399), bridging anticoagulation is no better than interrupting anticoagulation[A31] except perhaps for the very highest risk patients.[21]

For patients with mechanical valves, warfarin must be used. However, rivaroxaban (20 mg daily) is safer and more effective for patients with AF and a bioprosthetic valve.[A32] Edoxaban is non-inferior to warfarin in patients who are in atrial fibrillation after transcatheter aortic valve replacement.[A33] Oral inhibition of factor XIa is a promising alternative to factor X inhibition.[A34]

For patients at very high risk of bleeding or with serious bleeding on anticoagulation, surgical removal of the left atrial appendage or exclusion of the left atrial appendage with an implanted device is a non-inferior alternative to anticoagulation.[A35,A36] Surgical exclusion of the left atrial appendage is increasingly performed when patients with AF undergo coronary artery bypass graft surgery, and in this situation it is associated with a reduction in the risk of subsequent stroke and bleeding.[A37] With this procedure, serious complications occur in about 2% of patients, and the net benefits from reduced bleeding may increase over time.[22]

PROGNOSIS

Paroxysmal AF can occur as a self-remitting arrhythmia for decades or can progress to permanent AF. Patients with persistent AF generally progress to permanent AF unless sinus rhythm is restored.

The major long-term risks of AF are stroke, which occurs at a rate of about 4% per year in the absence of anticoagulation but only about 0.5% per year with anticoagulation, with individual risks influenced by the presence of specific risk factors (see Table 52-4). The risk is about half as high with paroxysmal AF compared with persistent AF, but even a single paroxysmal AF event is clearly linked to an increased risk of stroke.[23] Persistent AF also increases the likelihood of new or worsening heart failure, especially in patients who have a poorly compliant left ventricle, because of the absence of atrial contraction. Poor rate control can result in tachyarrhythmia-induced left ventricular dysfunction. Prognosis is also linked to any underlying comorbid conditions that may precipitate AF or contribute to a rapid ventricular response.

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53 VENTRICULAR ARRHYTHMIAS

HASAN GARAN

DEFINITIONS

Ventricular arrhythmias are cardiac rhythms that originate in the ventricular myocardium or in the His-Purkinje tissue. They include a wide spectrum of arrhythmias, including isolated premature ventricular contractions (PVCs) (Fig. 53-1A), nonsustained ventricular tachycardia (Fig. 53-1B), sustained ventricular tachycardia (Fig. 53-1C), and immediately life-threatening ventricular fibrillation (VF) (Fig. 53-2).

Ventricular tachycardia (VT) is arbitrarily defined as three or more ventricular contractions in a row at a rate faster than 100 beats per minute (see Fig. 53-1B). The definition of *sustained* VT—a continuous ventricular rhythm, at a rate faster than 100 beats per minute, with no interruption for 30 seconds

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53 VENTRICULAR ARRHYTHMIAS

HASAN GARAN

DEFINITIONS

Ventricular arrhythmias are cardiac rhythms that originate in the ventricular myocardium or in the His-Purkinje tissue. They include a wide spectrum of arrhythmias, including isolated premature ventricular contractions (PVCs) (Fig. 53-1A), nonsustained ventricular tachycardia (Fig. 53-1B), sustained ventricular tachycardia (Fig. 53-1C), and immediately life-threatening ventricular fibrillation (VF) (Fig. 53-2).

Ventricular tachycardia (VT) is arbitrarily defined as three or more ventricular contractions in a row at a rate faster than 100 beats per minute (see Fig. 53-1B). The definition of *sustained* VT—a continuous ventricular rhythm, at a rate faster than 100 beats per minute, with no interruption for 30 seconds

ABSTRACT

Ventricular arrhythmias are cardiac rhythm disturbances that originate in the right or left ventricular myocardium or in the His-Purkinje (HP) tissue. The diagnosis of monomorphic ventricular tachycardia (VT) on 12-lead ECG may be challenging, and the differential diagnosis of regular-rate, wide-complex tachycardia includes any type of supraventricular tachycardia with aberrant conduction or with ventricular pre-excitation, as well as VT. The most reliable ECG observation in favor of VT is evidence of atrioventricular dissociation, but the clinical setting and the patient's background also play major roles in making an accurate diagnosis. A small proportion of the patients with documented, sustained VT have no identifiable structural heart disease. These idiopathic VTs may originate in the outflow tract of either ventricle or may arise in left fascicles of the HP system. Rare, genetically acquired ion-channel mutations may be the cause of specific types of VT, such as polymorphic torsade de pointes. Most commonly, however, VT occurs in patients with organic heart disease, such as acute or prior myocardial infarction or dilated or hypertrophic cardiomyopathy. VT may be immediately life-threatening. Heart failure from any cause significantly increases the risk of ventricular arrhythmias. Acute management of hemodynamically unstable VT and ventricular fibrillation (VF) should conform to the guidelines for advanced cardiac life support. Sustained VT or VF in patients with organic heart disease is a primary indication for implantable cardioverter-defibrillator (ICD) therapy. Catheter ablation therapy may be curative for idiopathic VTs and should be considered as a preferred alternative to long-term antiarrhythmic drug therapy. In contrast, the role of catheter ablation or antiarrhythmic drug therapy is palliative in patients with VT and advanced organic heart disease after they are protected with ICD implantation.

KEYWORDS

ventricular tachycardia
ventricular fibrillation
sudden cardiac death
antiarrhythmic therapy
catheter ablation
implantable cardioverter defibrillator

FIGURE 53-1. **Ventricular arrhythmias. A, Multifocal premature ventricular beats. B, Nonsustained monomorphic ventricular tachycardia (VT). Note dissociated P waves indicated by *arrows*. C, Sustained monomorphic VT. Dissociated P waves are indicated by *arrows*, and the eighth beat in the tracing is a fusion beat.**

FIGURE 53-2. **This electrocardiogram in a patient with idiopathic ventricular fibrillation (VF) shows recurrent, closely coupled premature ventricular contractions (PVCs) and the initiation of VF by one of these closely coupled PVCs.**

or longer—is equally arbitrary. However, most sustained VTs are much faster than 100 beats per minute (see Fig. 53-1C), persist for more than 30 seconds, and cause a substantial decrease in ventricular function and cardiac output, especially in patients with underlying organic heart disease, thereby resulting in acute heart failure, hypotension, syncope, or even circulatory collapse.

Monomorphic VT is electrocardiographically defined as a wide-complex tachycardia with no change in QRS configuration, frontal axis, or horizontal axis from one beat to the next (Fig. 53-3A). Polymorphic VT is characterized by beat-to-beat changes in the QRS morphology and axis, and very fast polymorphic VT may be difficult to distinguish from *ventricular fibrillation* (VF) (Fig. 53-3B). VF, which is a grossly irregular ventricular rhythm usually at a rate faster than 300 beats per minute, appears as low-amplitude continuous electrical activity on the surface electrocardiogram (ECG) and generates no cardiac output. Torsades de pointes and bidirectional polymorphic VT are two distinct subtypes of polymorphic VT. *Pleomorphic* VT describes the phenomenon of multiple clinical monomorphic VTs, each with distinct QRS configurations and axis observed at different times in the same patient.

EPIDEMIOLOGY

The prevalence of PVCs is a function of sampling method and duration, and PVCs may be seen in 50% of apparently healthy individuals if the monitoring time is 24 hours or longer. Asymptomatic PVCs may, however, be a marker of more serious underlying heart disease.

Nonsustained VT may be recorded in up to 3% of apparently healthy individuals with no identifiable heart disease. The prevalence of PVCs and nonsustained VT not only increases with age but also with the presence and severity of an underlying heart disease. Therefore, the finding of nonsustained VT often leads to a cardiac evaluation to exclude organic heart disease, even if it is incidentally discovered in an asymptomatic patient. The prevalence of nonsustained VT rises to 7 to 12% in the late phase of myocardial infarction (MI) and may be as high as 80% in patients with advanced heart failure owing to dilated cardiomyopathy (Chapter 47).

Approximately 10% of patients with documented sustained VT have no identifiable heart disease, in which case idiopathic VT is diagnosed. The prevalence of idiopathic VT is estimated to be only 15.5 in 100,000 in men and 12.3 in 100,000 in women.

VT or VF in patients with advanced organic heart disease accounts for an estimated 50% of all annual cardiovascular deaths in the United States. The nature of the underlying heart disease in patients dying of VT or VF is age dependent. Before 30 years of age, the heart diseases most commonly associated with VT and VF are genetically inherited cardiomyopathies or channelopathies (Chapter 47), whereas acute MI and cardiomyopathy (either ischemic or dilated nonischemic) are the most common underlying heart diseases in individuals older than 40 years. In about 15% of cases of sudden cardiac death without obvious underlying organic heart disease identifiable at autopsy, postmortem genetic analysis may identify a clinically actionable pathologic mutation in an ion channel that predisposes to VT and VF.

PATHOBIOLOGY

Based on their underlying mechanisms, ventricular arrhythmias are classified as re-entrant, triggered, or automatic (Chapter 48). Re-entry, commonly the result of activation in adjacent circuits sharing a common pathway referred to as the isthmus, is initiated by the simultaneous presence of conduction block in one pathway and abnormally slow conduction in an adjacent pathway, thereby allowing recovery of excitability in the former (E-Fig. 53-1A). One type of triggered activity results from early afterdepolarizations, which are rapidly repetitive depolarizations occurring during the late phase of the action potential in the setting of an abnormally delayed repolarization process (E-Fig. 53-1B). Another type of triggered activity results from delayed afterdepolarizations, which reach depolarization threshold and cause repetitive action potentials in the setting of elevated intracellular calcium concentrations (see E-Fig. 53-1B). Automatic arrhythmias arise from accelerated pacemaker activity (E-Fig. 53-1C).

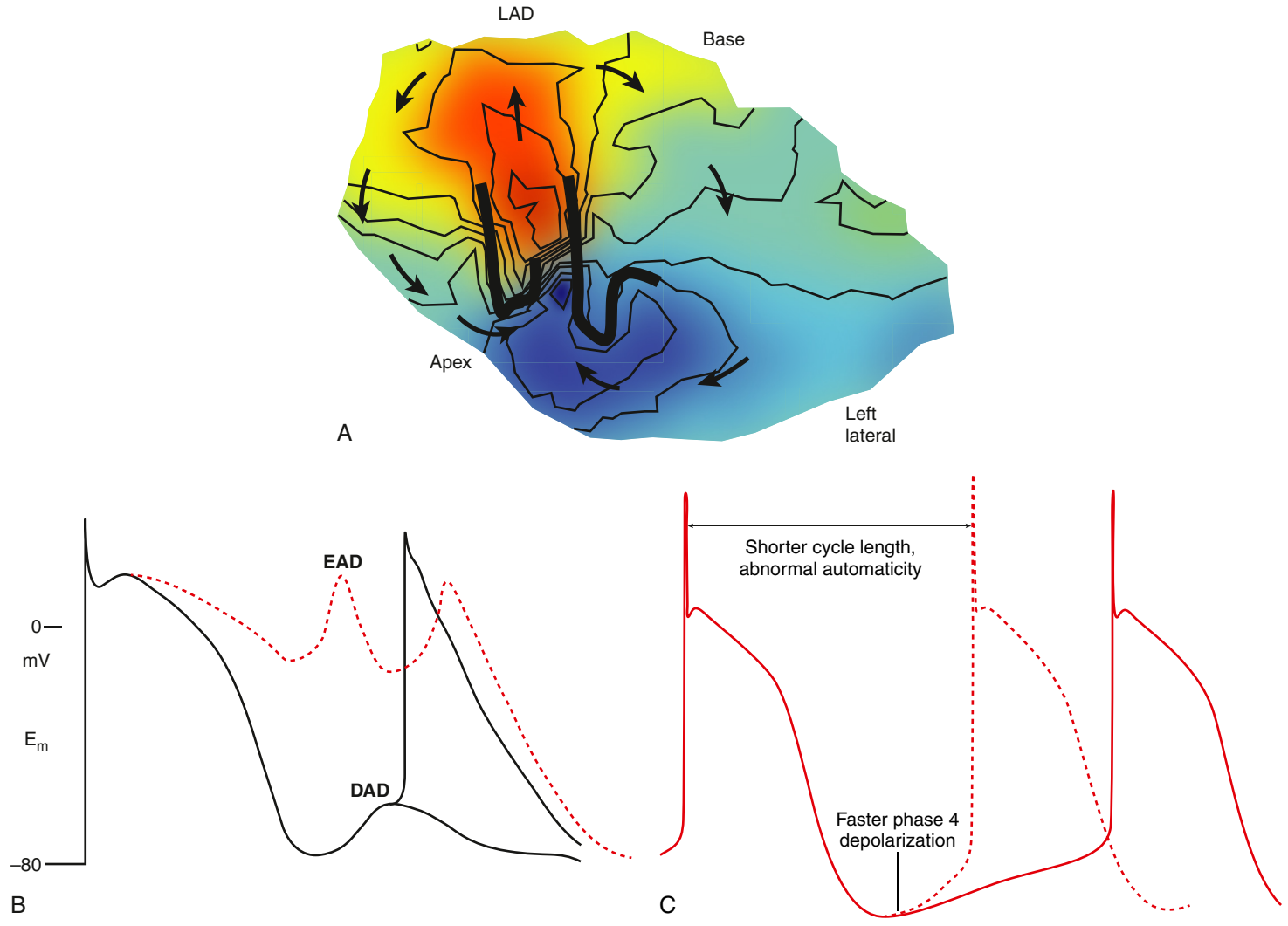

E-FIGURE 53-1. **A**, Re-entry within the myocardial infarction zone in an experimental canine model of ventricular tachycardia (VT). The central region of slow abnormal conduction, commonly referred to as the isthmus, is characterized by narrow crowded isochrones flanked by arcs of bidirectional conduction block depicted by *dark lines*, isolating the isthmus and enabling the maintenance of re-entry. The *arrows* indicate the spread of the wave of depolarization outside the central isthmus, in the shape of a figure of eight, with the red zone as the early breakthrough of activation and the dark blue area as the late activation in the VT cycle, which is also the point of re-entry into the isthmus. LAD = left anterior descending. **B**, Schematic depiction of the cardiac action potential with early afterdepolarizations (EAD) during phase 3 of a prolonged action potential *(dotted lines)* and delayed afterdepolarizations (DAD) reaching threshold and resulting in a premature action potential at the end of phase 3 and the very start of phase 4. E_m = membrane potential. **C**, Schematic depiction of cardiac action potential with an increased slope of depolarization toward the threshold during phase 4, at a site of automatic tachycardia.

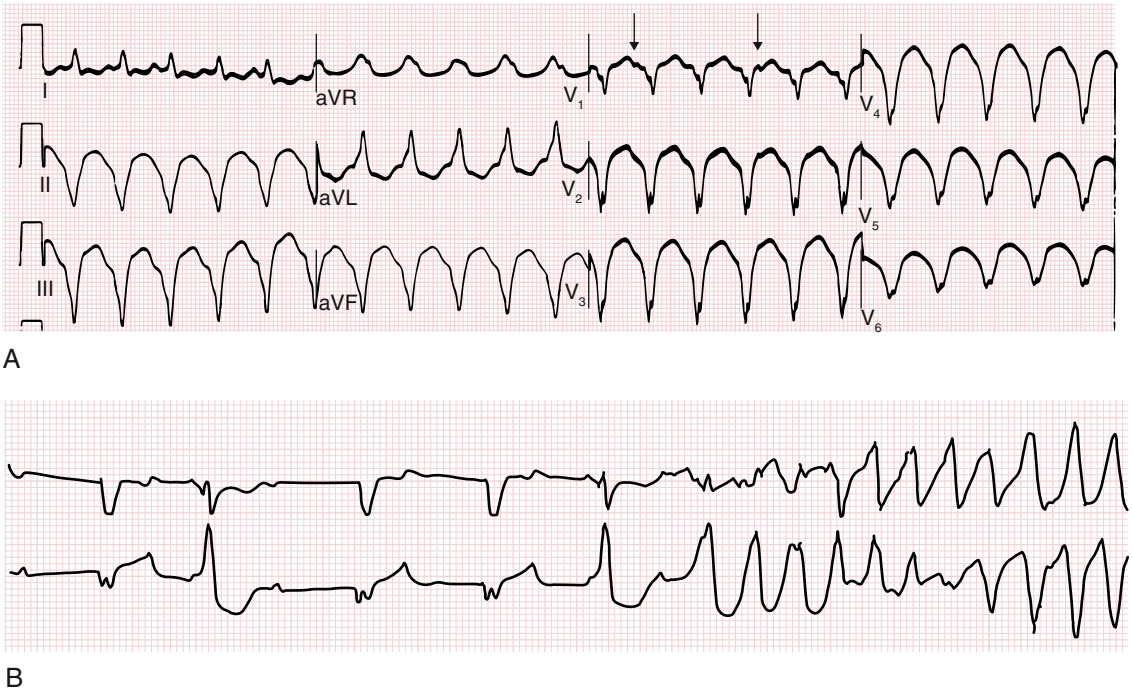

FIGURE 53-3. **A, Monomorphic ventricular tachycardia (VT) in a patient with a prior myocardial infarction. The *arrows* identify P waves in lead V_1, showing atrioventricular dissociation. No R wave is recorded in any of the precordial leads V_1 to V_6 during VT. B, Polymorphic VT in a patient with chronic ischemic cardiomyopathy and marked first-degree atrioventricular block. There is no QT prolongation before the onset of the polymorphic VT.**

Sustained re-entrant activation in the diseased myocardium is the most common cause of monomorphic VT and usually arises when scar (which may be subendocardial, transmural, or subepicardial), resulting from prior ischemic injury, creates an electrophysiologically abnormal substrate. Other pathologic conditions capable of creating a substrate for re-entry include inflammation (e.g., myocarditis), granuloma (e.g., cardiac sarcoidosis), fibrofatty infiltration (e.g., arrhythmogenic right ventricular cardiomyopathy), genetically caused sarcomeric disarray (e.g., hypertrophic cardiomyopathy), infiltration (e.g., amyloidosis, hemochromatosis), and iatrogenic scar (e.g., surgical repair of tetralogy of Fallot). These substrates may also result in polymorphic VT and VF by a similar re-entrant mechanism.

Triggered activity resulting from delayed afterdepolarizations is thought to be the underlying mechanism for most idiopathic monomorphic VT that has a focal site of origin in the right or left ventricular outflow tract, in one of the sinuses of Valsalva, the area of aortomitral continuity, or in the myocardial segment termed the left ventricular summit. Idiopathic VT from re-entry in the fascicles of the left bundle branch has a relatively narrow QRS complex that mimics right bundle branch block (RBBB) and anterior or posterior fascicular block. Idiopathic fascicular VTs may be electrocardiographically difficult to distinguish from idiopathic papillary muscle VTs. In Brugada syndrome, the primary cause is genetically acquired abnormal conduction in the epicardium of the right ventricular outflow tract.

Torsades de pointes, which is a specific type of polymorphic VT that derives its name from the rotating of the QRS axis, is caused by early afterdepolarizations that arise during a delayed repolarization process in the setting of genetic long QT syndromes or acquired long QT during therapy with QT-prolonging drugs. The cause may be either diminished outflowing repolarizing potassium currents, enhanced inflowing sodium currents due to incomplete inactivation of the sodium channel, or increased inflowing calcium currents. Although many episodes terminate spontaneously, the rates are usually very fast, and episodes of torsade can transform into sustained VF.

Bundle branch re-entry, which incorporates the right and the left bundle branches distally joined by the slowly conducting septal myocardium, may cause one or two nonsustained ventricular beats in a normal heart. However, sustained bundle branch re-entry occurs when myocardial disease causes chamber enlargement and bundle branch elongation and/or disease in the conduction system causes abnormally slow conduction, thereby creating the scenario for sustained bundle branch re-entry. The common type of bundle branch re-entry has anterograde activation over the right bundle and uses the left bundle retrogradely, thereby resulting in a left bunch branch block (LBBB) pattern on the surface ECG, but the reverse direction with RBBB pattern may also occur.

Accelerated pacemaker activity in an ectopic location, with rates exceeding the underlying sinus rhythm rate, may arise in settings such as transient inflammation, excess digoxin levels, intracellular calcium loading, electrolyte imbalance, and coronary reperfusion following occlusion. Bidirectional VT is thought to result from calcium overload of the myocytes owing to congenitally acquired, abnormal ryanodine receptor or calsequestrin function, or from digitalis toxicity, and it may transform to more malignant polymorphic VT and VF.

Finally, there is no consensus regarding the mechanisms underlying VF. Theoretically, VF may be initiated when a premature contraction falls in the vulnerable period of the action potential, thereby precipitating a re-entrant wave that breaks into sister wavelets and results in high-frequency electrical activity. In fact, VF may be regarded as an end stage for a variety of severe electrophysiologic abnormalities that result in chaotic activation.

CLINICAL MANIFESTATIONS

Ventricular arrhythmias can present in a variety of clinical settings (Table 53-1). They may be asymptomatic and detected only by an irregular pulse on a physical examination, on a routine ECG, or on an exercise test. Symptomatic ventricular arrhythmias can present as palpitations, dizziness, syncope (Chapters 39 and 49), shortness of breath, or sudden cardiac arrest (Chapter 50). The diagnosis may be confirmed by ambulatory ECG monitoring (Chapter 49), but more extended monitoring by a loop recorder may be needed to detect arrhythmias that may be rare and intermittent. Ambulatory monitoring can also help correlate arrhythmias with any symptoms they may cause. In some patients, exercise testing can be helpful for diagnosis.

Acute Myocardial Infarction

VT and VF may arise as early as minutes to hours after the onset of symptoms during coronary thrombosis, and prehospital VT and VF during acute MI are responsible for a large proportion of out-of-hospital sudden cardiac deaths (Chapter 50). The incidence of peri-infarction VF has declined over the past two decades, perhaps related to the widespread application of successful early coronary revascularization (Chapter 59) during acute MI. Among patients with ST elevation MI who now reach the hospital, about 3 to 4% develop VT, mostly during the acute phase. The incidence of VT in patients with non–ST elevation MI (Chapter 57) is lower, about 1%. Accelerated idioventricular rhythm (AIVR) is an automatic ventricular rhythm that is faster than the sinus rate but usually less than 120 beats per minute. It may occur

TABLE 53-1 VENTRICULAR TACHYCARDIA AND CARDIAC DIAGNOSIS

STRUCTURAL HEART DISEASE
Acquired heart disease
Acute myocardial infarction
Prior myocardial infarction, ischemic heart disease
Nonischemic dilated cardiomyopathy
Hypertensive heart disease
Valvular heart disease
Cardiac sarcoidosis
Cardiac amyloidosis
Other infiltrative diseases (e.g., Chagas disease)
Cardiac tumors
Congenital heart disease
Arrhythmogenic right ventricular cardiomyopathy
Hypertrophic cardiomyopathy
Genetic dilated cardiomyopathies
Iatrogenic
Surgically repaired congenital heart disease
Left ventricular assist devices
NO STRUCTURAL HEART DISEASE
Idiopathic ventricular tachycardia
Right and left ventricular outflow tract tachycardias
Left intrafascicular reentry
Papillary muscle tachycardias
Ion channel/ryanodine receptor mutations
Long QT syndromes
Catecholaminergic polymorphic ventricular tachycardia
Short QT syndrome
Mixed etiology
Brugada syndrome
Idiopathic ventricular fibrillation

TABLE 53-2 DISTINGUISHING VENTRICULAR TACHYCARDIA FROM SUPRAVENTRICULAR TACHYCARDIA WITH ABERRANT CONDUCTION

VENTRICULAR TACHYCARDIA	SUPRAVENTRICULAR TACHYCARDIA
AV dissociation	Same QRS morphology as preexisting bundle branch block in sinus rhythm
aVR: initial R > S or initial R or Q >40 msec	V_1: rsR′
Absence of any R waves in V_1 to V_6	
V_1 to V_6: onset of R to S >100 msec in any lead	
QRS duration >160 msec	
Initial R wave in aVR	

AV = atrioventricular.

immediately following coronary reperfusion after an acute MI, and it typically terminates spontaneously.

DIAGNOSIS

Not every wide-complex tachycardia is VT (Fig. 49-3). The diagnosis is straightforward when a His bundle electrogram is recorded during a wide-complex tachycardia in the cardiac electrophysiology laboratory, but diagnosis on a standard 12-lead ECG may be challenging (Table 53-2). The differential diagnosis of a sustained regular-rate wide-complex tachycardia includes any type of supraventricular tachycardia with aberrant conduction (Chapter 52), supraventricular tachycardia with ventricular preexcitation, bundle branch reentry, and myocardial VT. The clinical setting and the patient's background (e.g., history of previous MI or cardiomyopathy) play a major role in making an accurate diagnosis. A wide-complex tachycardia in a young and otherwise healthy individual with no structural heart disease is more likely to be a supraventricular tachycardia (SVT) conducted with aberration or with preexcitation, but it also may be idiopathic VT. Establishing a definitive diagnosis is critically important.

The most reliable electrocardiographic observation in favor of VT is evidence of atrioventricular (AV) dissociation, that is, the absence of any relationship between the atrial and ventricular rate, with the ventricular rate faster than the atrial rate (see Fig. 53-1C), or a regular wide-complex tachycardia with the atria fibrillating. Such findings immediately exclude SVT with aberration or preexcitation except for extremely rare cases of junctional tachycardia with aberrant conduction or nodo-fascicular/nodo-ventricular reentrant tachycardia. However, the absence of AV dissociation does not exclude VT because 1:1 ventriculoatrial conduction is present in about 50% of VTs and can be seen on the 12-lead ECG in 25% of cases. Fusion beats (which occur when an occasional sinus beat conducts through the AV node and reaches the His-Purkinje system at the same time as the VT source activates the myocardium, thereby resulting in a beat with a morphology that is the hybrid of a conducted QRS complex and the VT complex; Fig. 53-1C) also confirm AV dissociation but are observed only when VT rates are relatively slow.

Another approach is to rely on ECG lead aVR, where the presence of an initial R wave, notching on the initial downstroke of a predominantly negative QRS complex, and the width of an initial r-wave or q-wave > 40 ms strongly suggest VT. Other findings that favor VT include a QRS duration longer than 160 msec, or longer than 140 msec with an RBBB pattern. The absence of an RS complex in all precordial ECG leads or an interval of more than 100 msec from the onset of R to the nadir of S wave favors VT (Fig. 53-4; and see Fig. 53-3A). The absence of any R waves in the QRS complexes recorded from all six precordial leads (see Fig. 53-3A), described as *negative concordance*, strongly suggests VT, but is not a common finding. Prominent R waves observed in all six precordial ECG leads, termed *positive concordance*, may be seen in SVT with left ventricular preexcitation in patients without structural heart disease but otherwise also suggests VT with a basal site of origin. A wide-complex tachycardia with a QRS morphology identical to that of aberrantly conducted sinus rhythm manifesting bundle branch block (BBB) on a previously recorded ECG in the same patient should raise suspicion of bundle branch re-entry VT if the ECG shows AV dissociation, which excludes 1 : 1 aberrantly conducted supraventricular tachycardia.

If AV dissociation is not present, the differential diagnosis includes SVT with aberrant conduction, but the rare condition of preexcitation with an atriofascicular accessory pathway should also be considered in a patient with LBBB pattern and 1 : 1 AV ratio. A monomorphic wide-complex tachycardia with an irregular rate, manifested by more than 60-msec difference in cycle length from one beat to the next, is likely to be atrial fibrillation (AF) or atrial flutter, with variable AV block and aberrant conduction or with preexcitation. It is important to emphasize that severe electrolyte imbalances or the use of antiarrhythmic drugs diminishes the predictive accuracy of all of these diagnostic clues.

Sustained polymorphic wide-complex tachycardia with marked beat-to-beat changes in the QRS morphology is either atrial fibrillation with varying degrees of preexcitation from one beat to the next or ventricular tachycardia that either terminates spontaneously or transforms into VF. Torsades de pointes is frequently pause dependent—typically starting when a premature beat falls on the T wave of the beat following a long RR interval (Fig. 53-5). Finally, bidirectional VT manifesting a unique feature of beat-by-beat axis alternans may occur with digitalis toxicity or in congenital catecholaminergic polymorphic VT syndrome.

Several different algorithms based on the configurations of the QRS complexes have high sensitivity, high specificity, and acceptable predictive accuracy for distinguishing epicardial VT from endocardial VT (Table 53-3). If the site of origin is epicardial, the rapidly conducting His-Purkinje system is not available immediately, and the intramyocardial conduction delay produces a slurred initial component of the QRS complex, often called a *pseudo-delta wave*, which is manifested as a slow rate of rise of voltage before it reaches the intrinsicoid deflection (Fig. 53-6). Early recognition of ECG findings suggesting an epicardial origin of VT is important in planning and preparing a patient before a catheter ablation procedure (Chapter 54) because the epicardial approach requires a special technique in the cardiac electrophysiology laboratory.

Diagnostic cardiac electrophysiology testing (Chapter 49) may be indicated in patients who have organic heart disease and recurrent syncope but in whom the history, physical examination, ECG, echocardiogram, and ambulatory cardiac rhythm monitoring fail to clarify the cause, especially if the patient has a history of MI or cardiomyopathy, either of which increases the probability that VT may be the cause of syncope.

Identifying the Underlying Cause of Ventricular Arrhythmias

In patients with ventricular arrhythmia, the first step is to conduct a careful evaluation to exclude any underlying structural heart disease. This evaluation must include a comprehensive history and physical examination (Chapter 39),

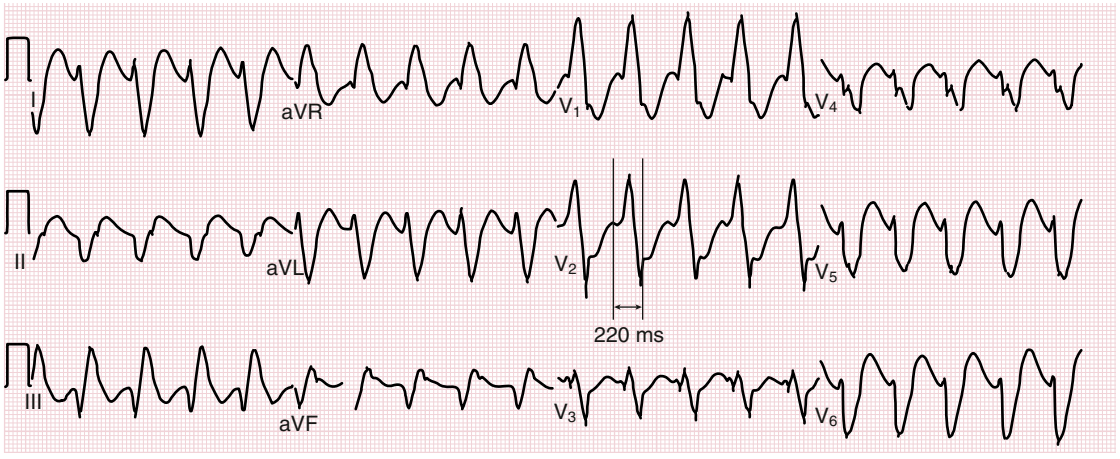

FIGURE 53-4. Monomorphic ventricular tachycardia in a patient with chronic ischemic cardiomyopathy. In lead V_2, the duration from the onset of the R wave to the nadir of the S wave is 220 msec. See text for further explanation.

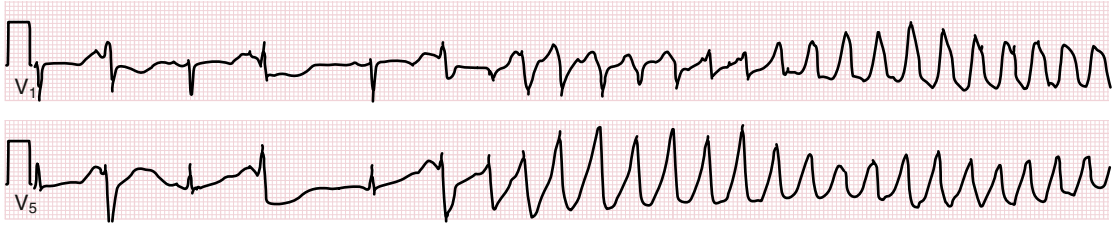

FIGURE 53-5. Torsades de pointes (TdP) in a patient with a markedly prolonged QT interval. A premature ventricular beat just after the peak of the T wave initiates TdP. As the tachycardia progresses, the rotation or the "twist" in the QRS axis is clearly observed in lead V_1, with the polarity of the signal changing gradually from negative to positive.

TABLE 53-3 ELECTROCARDIOGRAPHIC PARAMETERS TO HELP PREDICT AN EPICARDIAL ORIGIN OF VENTRICULAR TACHYCARDIA

PARAMETER	CRITERIA
Pseudo-delta wave	>75 msec favors epicardial site
Intrinsicoid deflection time	>85 msec favors epicardial site
Onset of R to nadir of S in precordial leads	>120 msec favors epicardial site
QRS duration	Epicardial longer
Q waves during VT in lead I	Favors epicardial site
Q waves during VT in II, III, aVF	Favors endocardial site
aVR/aVL amplitude ratio	Epicardial higher

VT = ventricular tachycardia.

electrocardiography, echocardiography (Chapter 43), extended cardiac rhythm monitoring (Chapter 49), and stress testing (Chapter 56). The family history may provide clues for the presence of an inherited cardiomyopathy (Chapter 47) or channelopathy. Cardiac magnetic resonance imaging (Chapter 44) is indicated in patients who are suspected of having sarcoidosis or arrhythmogenic right ventricular cardiomyopathy, and for risk stratification in patients with cardiomyopathy. Other tests to consider include 99 m technetium-pyrophosphate scan in patients suspected to have transthyretin cardiac amyloidosis (Chapters 47 and 174) and positron emission tomography to detect active myocardial inflammation (Chapter 44), conditions which predispose to ventricular tachyarrhythmias.

Despite a comprehensive evaluation, about 10 to 15% of patients will have VT with no identifiable structural or genetically identifiable cause. Most of the idiopathic monomorphic VTs are in one of two categories, distinguishable by ECG morphology. VTs that arise in the right or left ventricular outflow tract typically manifest an inferiorly directed frontal axis (E-Fig. 53-2); the QRS configurations and polarity observed in the right precordial leads (V_1 and V_2) may further discriminate the sites of origin as the right or the left ventricular outflow tract or one of the sinuses of Valsalva. VT originating in the right sinus of Valsalva closely resembles VT originating in the right ventricular outflow tract. In VT originating in the left sinus of Valsalva, the R wave duration and R/S wave amplitude ratio in leads V_1 and V_2 are significantly increased compared with VT from the right ventricular outflow tract. By comparison, idiopathic left ventricular tachycardia resulting from intrafascicular re-entry usually manifests RBBB and left axis deviation, but there may also be right axis deviation. The QRS complexes typically are not very wide because the involved region is His-Purkinje tissue adjacent to the interventricular septum. Idiopathic VT arising in one of the left ventricular papillary muscles has QRS complexes similar to those of intrafascicular re-entry (E-Fig. 53-3). Either of these typical patterns in a patient with no structural heart disease suggests idiopathic VT. Conversely, sustained VT that does not fall into either of these two broad categories should always raise a high index of suspicion that organic heart disease may be present.

Chronic Ischemic Heart Disease and Post–Myocardial Infarction Ventricular Tachycardia

In survivors of ST elevation MI (Chapter 58), the risk of sudden cardiac death is 10 times higher during the first month than later during recovery. The prevalence of sustained VT by 6 weeks is about 1%, and VT may occur as late as 15 to 20 years after the acute MI without any intervening event. VT commonly, but not invariably, reflects poor left ventricular function. The electrophysiologic substrate is the surviving but electrophysiologically abnormal tissue embedded in the infarcted zone, which creates the conditions responsible for re-entry. The areas that harbor pathways underlying re-entry may be identified by low-amplitude fractionated endocardial electrograms recorded in late systole during sinus rhythm or in mid-diastole during VT in the cardiac electrophysiology laboratory. Up to 16% of the VTs in ischemic heart disease are of epicardial origin. The same pathologic substrate may cause polymorphic VT and VF that, unlike torsades de pointes, do not depend on a long QT interval.

Nonischemic Dilated Cardiomyopathy

The most common cause of sustained monomorphic VT in nonischemic cardiomyopathy (Chapter 47) is also re-entry within the myocardium, but it differs from the post-infarction VT of chronic ischemic heart disease. The pathologic substrates tend to be located in basal, lateral, and often perivalvular

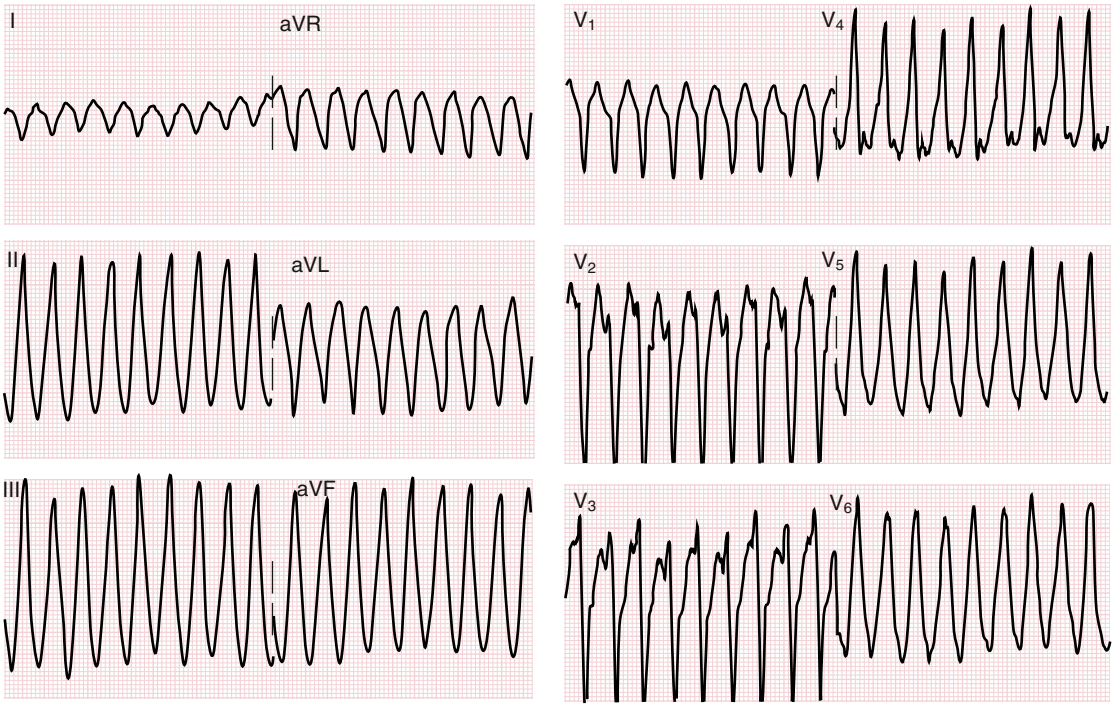

E-FIGURE 53-2. **Electrocardiogram recorded during idiopathic ventricular tachycardia originating in the right ventricular outflow tract and manifesting a deeply inferior frontal axis and left bundle branch block mimicry in the precordial leads.**

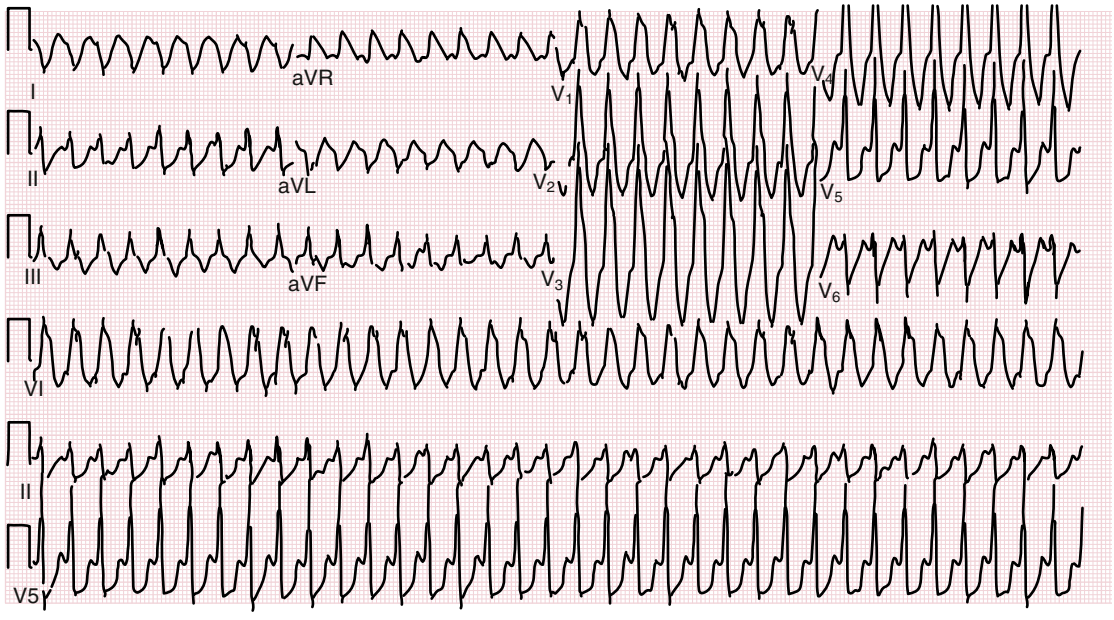

E-FIGURE 53-3. **Ventricular tachycardia (VT) originating in the anterolateral papillary muscle.** Note the right bundle branch mimicry of the QRS and the right axis deviation, similar to the electrocardiographic configuration of an interfascicular re-entrant VT.

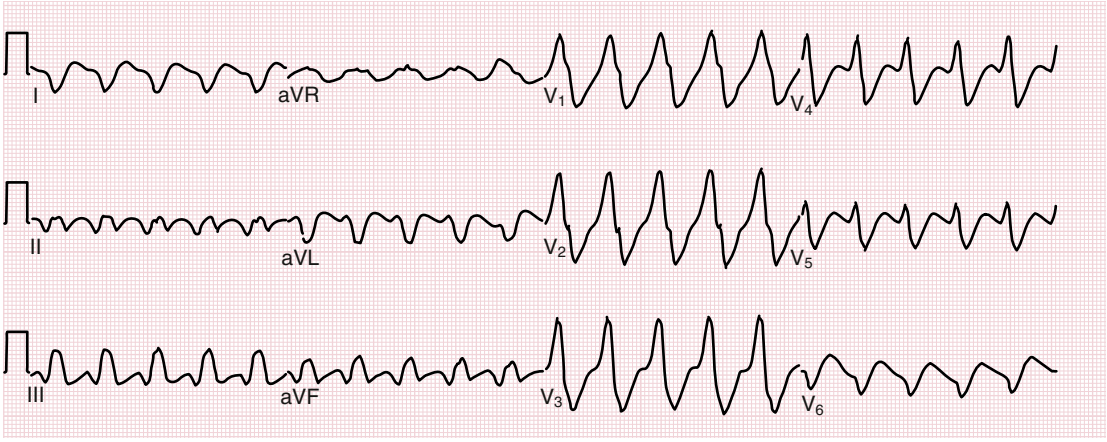

FIGURE 53-6. Monomorphic epicardial ventricular tachycardia in a patient with nonischemic dilated cardiomyopathy. The positive polarity pseudo-delta wave is prominent in the right precordial leads, and the negative polarity pseudo-delta wave is prominent in the inferior limb leads.

left ventricular areas, which may correlate with the location of intramyocardial or subepicardial scarring identified by imaging studies. The proportion of monomorphic VTs due to bundle branch re-entry is higher in nonischemic dilated cardiomyopathy compared with chronic ischemic heart disease.[1] Also, VT in nonischemic dilated cardiomyopathy is more likely to have an epicardial origin—as high as 35% overall and reaching 70% in Chagas disease.

Rapidly Reversing Cardiomyopathy

Patients with stress-induced cardiomyopathy (Chapter 47) will recover over several days to weeks, and patients with viral myocarditis may also recover relatively rapidly. Despite recovery of their ventricular systolic function, subgroups of patients with a history of myocarditis have a higher incidence of subsequent VT and mortality than the healthy controls over long-term follow-up.

Heart Failure

The failing heart from any underlying cause (Chapter 45) is highly vulnerable to ventricular arrhythmias. The proportion of sudden arrhythmic death depends on heart failure class and may be as high as 60% in class II to III heart failure. In patients with class IV heart failure, however, the fatal arrhythmia is more often an agonal bradyarrhythmia. Re-entrant VT is common, especially in patients whose heart failure is due to advanced ischemic heart disease, but triggered activity resulting from derangements of calcium homeostasis may also play a prominent role. In addition, hormonal factors, electrolyte abnormalities, and changes in autonomic nervous system activity also increase the vulnerability of the failing heart to ventricular arrhythmias.

Inflammatory and Infiltrative Disease

Among patients with sarcoidosis (Chapter 83), about 40 to 50% have cardiac involvement, which may first manifest as progressive AV block, VT, or both. Although the true prevalence of VT in sarcoidosis is not known, in the selected patients who have received implantable cardiac defibrillators (ICDs) for cardiac sarcoidosis diagnosed by endomyocardial biopsy, cardiac magnetic resonance imaging, or cardiac positron emission tomographic scans, about 15% per year have appropriate ICD discharges for sustained VT. Patients with other infiltrative heart diseases such as amyloidosis (Chapter 174), Fabry disease (Chapter 192), and hemochromatosis (Chapter 196) also have an elevated risk for VT and life-threatening ventricular arrhythmias.

Adult Congenital Heart Disease

VT may occur in the setting of any adult congenital heart disease with a ventricular surgical scar or patch, as is seen after repair of tetralogy of Fallot or a ventricular septal defect closure. It may also occur in a failing systemic right ventricle (Chapter 55). In patients with surgically repaired tetralogy of Fallot, the right ventricular outflow tract, with its scarring and artificial material, serves as an ideal milieu for re-entry and VT. In these patients, the prevalence of VT is about 5 to 10%, and about 2% have sudden cardiac death.

Genetically Inherited Cardiomyopathies

Hypertrophic cardiomyopathy (Chapter 47) is responsible for more than one third of sudden cardiac deaths in patients younger than age 25 years (Chapter 50), and mortality in young hypertrophic cardiomyopathy patients is almost exclusively due to VT and VF. Neither genetic testing nor a cardiac electrophysiology study can definitively identify patients at high risk for VT and VF, and the estimation of risk is based on findings such as a history of syncope, documented nonsustained VT especially in a young patient, a markedly thickened (>3 cm) interventricular septum, and a paradoxical decrease in blood pressure during exercise. Recent studies suggest that the extent of late gadolinium enhancement on cardiac magnetic resonance imaging may be a reliable predictor of serious ventricular arrhythmias in patients with hypertrophic cardiomyopathy.

Arrhythmogenic right ventricular cardiomyopathy[2] is a congenital cardiomyopathy (Chapter 47), usually with an autosomal dominant inheritance. The fibrofatty infiltration of the right ventricular myocardium, which may also involve the interventricular septum and the left ventricle, results in progressive electrophysiologic abnormalities, which may be manifest on the surface ECG as an epsilon wave (Fig. 53-7). The markedly altered conduction characteristics are conducive to re-entry. The incidence of VT in arrhythmic right ventricular cardiomyopathy is related to the severity of the pathologic myocardial changes and ranges from 25 to 100%, depending on the penetrance and the expressivity of the disease. VT typically is initiated by exercise and mimics LBBB in the precordial ECG leads. However, unlike idiopathic right ventricular outflow tract VT, the frontal axis may not be inferiorly directed, and multiple endocardial and epicardial sites of origin exist in about 60% of cases. Vigorous exercise may accelerate the progression of cardiomyopathy and increase the incidence of ventricular arrhythmia.

Genetically Inherited Ventricular Arrhythmias

Several genetically acquired syndromes, including the long QT syndromes, Brugada syndrome, and catecholaminergic polymorphic VT, increase the risk for sudden cardiac death due to ventricular tachyarrhythmias. Despite the remarkable genetic heterogeneity of long QT syndrome, most cases are LQT1, LQT2, and LQT3, which result from loss-of-function mutations in genes *KCNQ1* and *KCNH2* that code for two different potassium channels or gain-in-function mutations in the *SCN5A* gene that codes for the sodium channel.[3] The other genetic mutations are extremely rare. The VT of long QT syndrome is torsades de pointes, and both bradycardia and pauses increase its probability in patients who are predisposed. The incidence of torsades de pointes is influenced by multiple factors, including age, gender, the particular genetic mutation, and the magnitude of QT prolongation (Fig. 53-8A).

The electrocardiographic hallmark of Brugada syndrome, which also predisposes to ventricular tachyarrhythmias and sudden cardiac death, is coved ST segment elevations in the right precordial leads (Fig. 53-8B). In some cases, this pattern may not be present except when the patient is febrile. The inheritance is autosomal dominant, but the genetics are complex. A pathogenic variant of the *SCN5A* gene is present in less than 20% of the cases. Catecholaminergic polymorphic VT is a rare genetic condition resulting from abnormal calcium homeostasis. It is characterized by exercise-induced, wide-complex tachycardia manifesting alternating ECG axes from one beat to

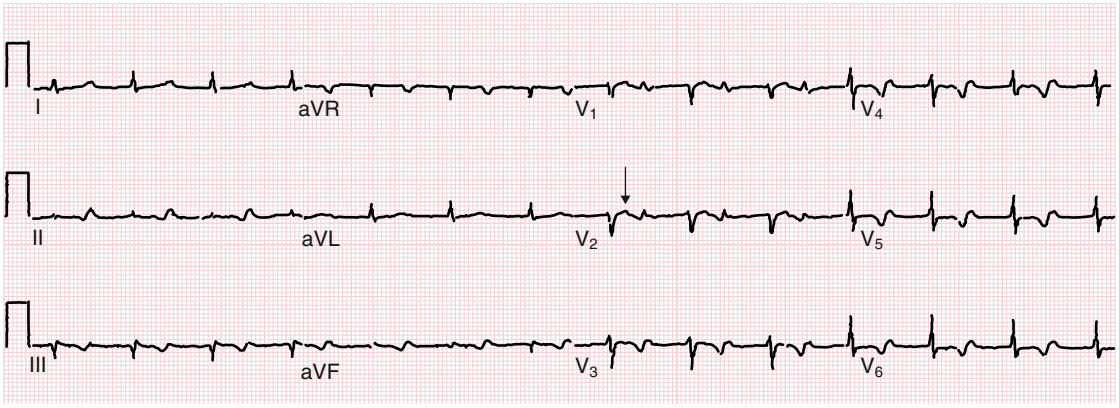

FIGURE 53-7. **This electrocardiogram was recorded in a patient with arrhythmogenic right ventricular cardiomyopathy, marked first-degree heart block, and recurrent ventricular tachycardia.** Epsilon waves, marked by the *arrow*, are visible in the right precordial leads.

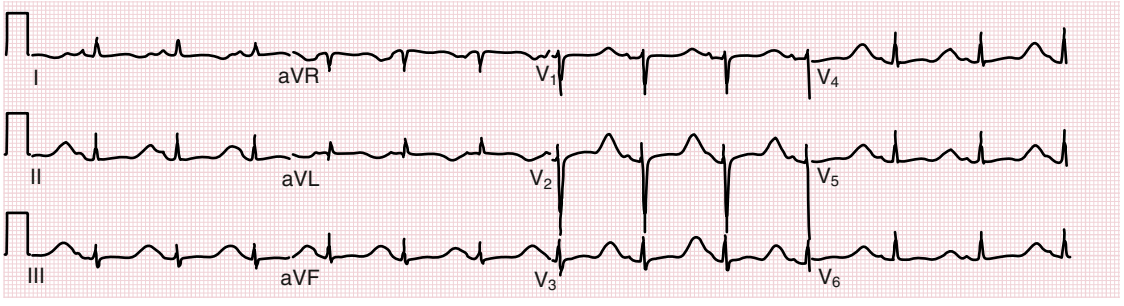

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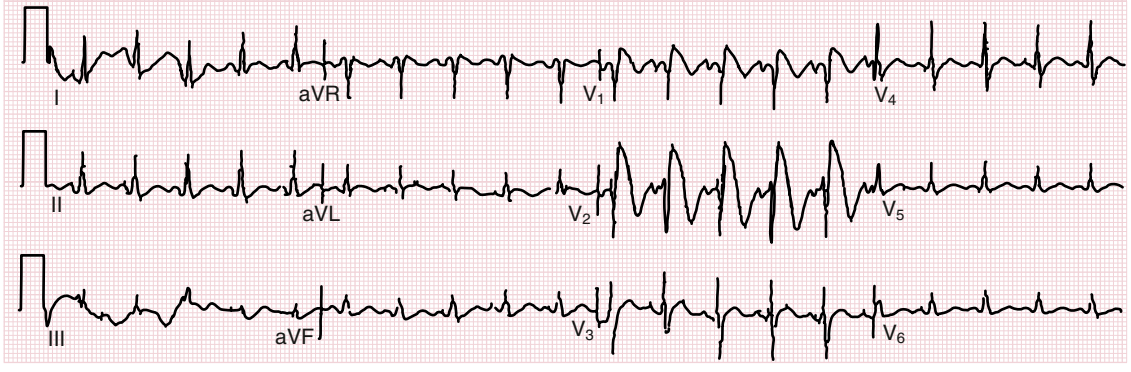

B

FIGURE 53-8. **A, Electrocardiogram showing a QT interval of 640 msec in a woman with LQT1 syndrome, with the terminal portion of the Q wave merging with the P wave. B, Electrocardiogram of a man with Brugada syndrome, showing the typical "coved" elevation in lead V_1.**

the next. This condition also predisposes the patient to exercise-induced VF. In addition, a chromosomal haplotype causing overexpression of dipeptidyl peptidase-like protein-6 has been described in one type of familial idiopathic VF,[4] which is a rare but challenging subset of inheritable arrhythmia syndromes causing sudden cardiac death.

Iatrogenic Ventricular Tachycardia and Ventricular Fibrillation

QT-prolonging drugs, including class III antiarrhythmic drugs (see www.torsades.org), may precipitate torsades de pointes and VF in genetically predisposed individuals even if the baseline QTc is normal or borderline.[5] Class IC antiarrhythmic drugs may cause life-threatening VT in patients with ischemic or any other organic heart disease and in patients with Brugada syndrome. Ventricular scarring owing to aneurysmectomy, tetralogy of Fallot repair, ventricular septal defect repair, alcohol ablation of the interventricular septum to relieve dynamic outflow tract obstruction in hypertrophic cardiomyopathy, or implantation of a left ventricular assist device may create a substrate for re-entry and VT.

TREATMENT

Acute Management of Ventricular Tachycardia and Ventricular Fibrillation

The management of hemodynamically unstable VT and VF should conform to the guidelines for advanced cardiac life support (Chapter 50), with an emphasis on prompt defibrillation. For patients who have sustained VT with modest hypotension and normal mental status, intravenous drug therapy with lidocaine (given as a 50-mg bolus), procainamide (10 mg/kg or a total of 1000 mg over 20 minutes), or amiodarone (150 mg infused intravenously over 10 minutes) may be tried. In one randomized trial, procainamide was superior to amiodarone for promptly terminating wide-complex tachycardia with fewer adverse effects.[A1] Lidocaine, which is more efficacious at faster heart rates, is effective for terminating VT, but not for preventing recurrences, except in the setting of acute ischemia. By comparison, amiodarone is more effective at slower heart rates and therefore is better for preventing recurrent VT after sinus rhythm is restored. Intravenous calcium-channel blocker therapy should not be given unless the mechanism is known with certainty to be verapamil-sensitive idiopathic left ventricular tachycardia in a patient who does not have organic heart disease.

The most important factors in preventing early recurrence are the prompt identification and reversal of any precipitating causes. Examples include hypokalemia and other electrolyte imbalances, low oxygen saturation, intravenous β-agonist agents or milrinone, acute heart failure (Chapter 46), or myocardial ischemia (Chapters 57 and 58). Heart failure should be rigorously treated (Chapter 46) and the presence of residual myocardial ischemia suspected if VF is recurrent.

Treatment of Electrical Storm

Electrical storm describes frequently recurrent VT or VF requiring repeated shocks from an implanted cardioverter-defibrillator (ICD) or external defibrillations. Electrical storm rarely occurs in nonischemic cardiomyopathy or in genetically acquired ventricular arrhythmias. When this condition is encountered in the setting of ischemic heart disease, relief of ischemia is of paramount importance. If the electrical storm continues even after coronary reperfusion, insertion of an intra-aortic balloon pump and use of an intravenous β-blocker therapy, preferably with a short half-life drug (e.g., esmolol 500 μg/kg load over 1 minute, then 50 to 200 μg/kg per minute by intravenous infusion) should be considered. Intravenous lidocaine (2 to 4 mg per minute) or intravenous amiodarone (0.5 to 1.0 mg per minute) may also be used. Catheter ablation, if possible, may reduce the recurrence rate and potentially improve survival.[6] For recurrent ventricular arrhythmias refractory to traditional therapies, noninvasive radioablation (see later) or left-sided or bilateral cardiac sympathetic denervation may be effective. Another potential option is renal denervation.[7]

Treatment of PVCs and Idiopathic Ventricular Tachycardia

In the absence of structural heart disease, there is no convincing evidence that ventricular ectopic activity influences survival. Therefore PVCs do not need treatment in asymptomatic patients.[8] If ventricular ectopy results in symptoms that substantially decrease quality of life, a cardioselective β-blocker (e.g., metoprolol 50 mg twice daily or atenolol 50 mg once daily) is a safe but not a very effective first-choice therapy. If the frequency of PVCs and nonsustained VT reaches a critical level, however, the arrhythmia itself may result in decreased systolic ventricular function even in the absence of any other cause for cardiomyopathy. These patients should be treated aggressively, including catheter mapping and ablation (Chapter 54), to avoid progressive cardiomyopathy and heart failure without subjecting the patient to the potential adverse effects of antiarrhythmic drugs.

Although cardiac arrest resulting from transformation of idiopathic VT to VF is exceedingly rare, sustained VT at a rate faster than 200 beats per minute commonly causes cardiopulmonary symptoms and may cause syncope (Chapter 49), even in the absence of structural heart disease. Idiopathic VTs of outflow tract origin may respond to β-blocker therapy (e.g., metoprolol 50 mg every 12 hours or atenolol 50 mg daily), and a few may respond to an empirical trial of calcium-channel blockers (e.g., sustained-release diltiazem 120 to 240 mg daily or sustained-release verapamil 120 to 240 mg daily). However success rates are low, ranging from 25 to 50%. The so-called idiopathic left ventricular tachycardia resulting from left fascicular re-entry frequently responds to verapamil (e.g., sustained-release 180 to 360 mg daily), but papillary muscle VT may not.

Catheter ablation therapy (Chapter 54) can cure 80 to 90% of cases of idiopathic ventricular arrhythmia with a low risk (<1%) and should be considered as a preferred alternative to long-term antiarrhythmic drug therapy.[9] If careful catheter mapping in the right ventricular outflow tract does not yield a suitable target, the left ventricular outflow tract, right or left sinus of Valsalva, or the aortomitral continuity may be the site of origin. Failures are usually due to an inability to induce the arrhythmia reliably with electrophysiologic testing or VT that originates in epicardial sites beyond safe access for an ablation catheter (e.g., close proximity to a coronary artery).

By comparison to the relatively benign prognosis of idiopathic sustained VT, idiopathic VF accounts for 5 to 10% of all cases of sudden cardiac death (Chapter 50) in patients without organic heart disease. The appropriate treatment for survivors of idiopathic VF is no different than for any other survivor of VF (i.e., ICD therapy), but some patients may have findings on electrophysiologic testing that are amenable to catheter ablation—which may decrease the risk for recurrence but still does not obviate the need for ICD protection.

Therapy for Ventricular Tachycardia and Ventricular Fibrillation in Structural Heart Disease

Implantable Cardiac Defibrillator Therapy and Antiarrhythmic Drugs

Sustained VT or VF in patients with organic heart disease is a primary indication for ICD therapy.[10,11,A2] A subcutaneous ICD is as safe and effective as a transvenous ICD for patients who do not have an indication for pacing.[A3]

After an acute MI, an ICD implanted as primary prevention therapy reduces mortality in patients who have survived more than 40 days and have a left ventricular ejection fraction of 30% or less.[A4] For patients who have class II or III heart failure regardless of the etiology of their organic heart disease and who have a left ventricular ejection fraction of less than 35%, an ICD also significantly reduces sudden cardiac death, although it may not prolong life in patients with nonischemic heart failure because of the high burden of death from other causes.[A5] By comparison, ICDs do not reduce mortality when routinely implanted soon after MI or in patients after recent coronary artery revascularization.

In patients with ischemic heart disease and a chronically depressed ejection fraction of less than 30%, insertion of an ICD reduces the mortality rate by 20%, from 36 to 29%, over the next 5 years. By comparison, amiodarone (Table 52-3) reduces the risk of sudden arrhythmic death but does not improve survival. In patients with advanced organic heart disease, the presence of frequent PVCs and nonsustained VT portend a poor prognosis, but suppression of ventricular ectopic activity with antiarrhythmic drugs does not improve prognosis; in fact, suppression of PVCs with class IC antiarrhythmic drugs in patients with prior MI increases mortality. Therefore, antiarrhythmic drugs currently serve as palliative treatment to modify the course of VT in patients with an ICD, rather than as definitive therapy. Amiodarone (100 to 400 mg daily) is more successful than β-blockers or sotalol for this palliative therapy of VT.[A6]

In patients who are clinically unstable because of incessant VT, reversible precipitating factors should be sought and, if present, corrected promptly. Intravenous β-blockers (e.g., esmolol 50 to 200 μg/kg per minute) and amiodarone (0.5 to 1.0 mg per minute) constitute first-line therapy. Intravenous lidocaine (e.g., 2 to 4 mg per minute) can be added, especially if myocardial ischemia is present, and emergent catheter ablation may be considered.

Catheter Ablation

Catheter ablation is usually also palliative rather than definitive treatment for VT in patients with structural heart disease, but it can significantly reduce the frequency of recurrent VT, ICD discharge, and adverse cardiac events.[A7,A8] Catheter ablation is most successful when clinical VT can be reproduced in the cardiac electrophysiology laboratory and tolerated for a long enough period to allow detailed catheter mapping and to validate the underlying mechanism and site of origin. Catheter ablation can be performed safely in patients with advanced heart failure. However, preventive catheter ablation before ICD implantation is not clearly better than reserving ablation for patients who need it as supplemental therapy.[A9]

Radioablation

Application of stereotactic body radiation is an investigational noninvasive method of treatment for recurrent VT,[12] especially VT storm.[13] The precise location of the target requires a synthesis of anatomic and electrophysiologic data using cardiac magnetic resonance imaging (MRI), cardiac single photon emission computed tomography (SPECT), a 12-lead ECG recorded during VT, and electrophysiologic imaging information. A single fraction of 25 Gy is delivered to the VT substrate while avoiding healthy tissue. Late postprocedure complications include exacerbation of heart failure and pericarditis.

Torsades de Pointes and Catecholinergic Polymorphic VT

In an acute setting with frequently recurrent torsades de pointes, magnesium sulfate (1 to 2 g intravenous infusion over 10 to 30 minutes) may be effective. Temporary pacing should be considered if the patient exhibits excessive bradycardia or prolonged pauses.

An ICD is recommended for patients who present with aborted cardiac arrest. Otherwise, the first line of preventive therapy for torsades de pointes in patients with long QT syndrome is β-blocker therapy (e.g., metoprolol 50 to 100 mg daily, atenolol 50 mg daily, or nadolol 40 mg daily and titrated as tolerated), but its success is influenced by gender and the magnitude of QT prolongation, as well as by the specific genotype. However, about 25% of patients continue to experience ventricular arrhythmias on full doses of β-blocker therapy and require an ICD. Left cardiac sympathetic denervation can substantially reduce the incidence of torsades de pointes and syncope in high-risk patients, as well as decrease the frequency of shocks in patients with an ICD.

β-Blockers (Table 52-3) are also the drugs of choice for catecholaminergic polymorphic VT, with ICD therapy recommended for patients with recurrent syncope or documented VT while on β-blocker therapy. Oral flecainide (Table 52-3) may be an effective adjunct in such patients.

Treatment of Genetically Acquired Ventricular Tachycardia and Ventricular Fibrillation

Most of the VTs observed in patients with arrhythmogenic right ventricular cardiomyopathy may be reproducibly induced by programmed cardiac stimulation and are amenable to catheter ablation. Nearly half of these VTs have an epicardial site of origin, and simultaneous endocardial and epicardial catheter mapping and ablation may be the most effective method of treatment. However, catheter ablation cannot substitute for concomitant ICD therapy. In patients with hypertrophic cardiomyopathy, ICD therapy is routinely recommended, especially in young high-risk patients (Chapter 47), and amiodarone may sometimes be useful.

For Brugada syndrome, catheter ablation of the electrophysiologically abnormal substrate in the right ventricular outflow tract epicardium can lead

to eventual disappearance of the pathognomonic ST elevation on the ECG. Quinidine (600 to 900 mg daily in three or four divided doses) is the only antiarrhythmic drug that appears to be useful to treat this syndrome. However, follow-up periods are not long enough to know whether catheter ablation or quinidine can obviate the need for an ICD in high-risk patients who have unprovoked Brugada pattern in their resting ECG and have a history of syncope.

Iatrogenic Ventricular Tachycardia

For sustained monomorphic VT in patients with surgically repaired congenital heart disease, catheter mapping and ablation are recommended. The techniques are similar to those used for catheter ablation of ischemic VT. Although sustained VT or VF during the course of left ventricular assist device therapy is usually well tolerated acutely, recurrent intractable VT or VF can result in right heart failure and in frequent ICD shocks, both of which may carry significant morbidity. Amiodarone (200 to 400 mg daily) and β-blocker therapy (e.g., metoprolol 100 to 200 mg daily) may be effective in at least rendering VT no longer incessant, and catheter ablation therapy has occasionally been tried in refractory VT with modest success.

PROGNOSIS

VT or VF in the early minutes or hours of acute MI has not been shown to affect the long-term prognosis in patients who survive to hospital discharge. Sustained monomorphic VT occurring after the hyperacute phase but within the next few days of an anterior wall MI portends poor prognosis, with about a seven-fold increase in subsequent mortality, because it usually occurs after the necrosis of a large amount of myocardium.

The modern natural course of untreated VT and VF perhaps can best be assessed from prospective studies of patients receiving ICD therapy. Among patients who have had documented sustained VT, appropriate ICD therapy for VT or VF occurs in about 70% of patients within 2 years and 85% of patients within 3 years. For patients who have survived cardiac arrest, the rate is about 70% at 3 years. These figures underscore the high rate of recurrence of VT and VF in patients with organic heart disease presenting with sustained ventricular arrhythmias.

The prognosis of patients with PVCs or nonsustained VT is less well known but is critically dependent on the underlying heart disease. No study to date has shown any survival benefit of treating PVCs or nonsustained VT in patients who do not have underlying organic heart disease and who do not develop a cardiomyopathy as a result of their ventricular ectopic activity. In high-risk patients who have ischemic heart disease, a left ventricular ejection fraction of less than 40%, and electrically induced sustained VT, the 2-year rate of cardiac arrest or death from ventricular arrhythmia is more than 30%.

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For the General References and other additional features, please visit Elsevier eBooks+ at https://ebooks.health.elsevier.com.

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54 ELECTROPHYSIOLOGIC PROCEDURES AND SURGERY

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TRANSTHORACIC CARDIOVERSION AND DEFIBRILLATION

Transthoracic defibrillation, which rapidly delivers a stored charge to the heart across two surface pads or paddle electrodes, is used emergently for life-threatening tachycardias (Chapter 50). Cardioversion, which refers to shock delivery synchronized with the QRS complex, is advised in patients with either supraventricular arrhythmias (Chapter 52) or ventricular tachycardia (VT; Chapter 53) because a nonsynchronized shock coincident with the vulnerable period of the T wave may precipitate ventricular fibrillation (VF). The shock extinguishes tachyarrhythmias by simultaneously depolarizing large portions of the atria and/or ventricles. Defibrillation is used for disorganized rhythms in which synchronization to the QRS complex is not appropriate, such as VF or rapid polymorphic VT. In these emergent situations, attempts to synchronize may delay delivery of the shock.

The success of cardioversion or defibrillation is affected by the shock waveform and shock strength. Biphasic shock waveforms are recommended because they are significantly more effective than monophasic waveforms at equivalent energies. Shock energies vary by indication and between defibrillator units but are generally from 50 to 360 J. Other technique-dependent variables that maximize the energy delivered to the heart include increasing paddle pressure, delivery of the shock during expiration, and repetitive shocks. Patient-related factors that may decrease the probability of successful cardioversion and defibrillation include metabolic disturbances, a longer duration of arrhythmia, cardiac enlargement, chronic obstructive pulmonary disease, barrel-chested habitus, and higher body weight. Elective cardioversion is performed with the patient in the fasting state, usually with a short-acting anesthetic agent.

PRECAUTIONS AND COMPLICATIONS

Cardioversion of atrial fibrillation (AF) and atrial flutter (Chapter 52) may be complicated by thromboembolism, but this risk can be minimized by excluding the presence of an atrial thrombus on a transesophageal echocardiogram or by therapeutic anticoagulation with a direct-acting anticoagulant for at least 3 weeks before elective cardioversion (see Fig. 52-14, and Chapters 52 and 70). All patients should be anticoagulated for 1 month after cardioversion if AF or atrial flutter has been present for longer than 48 hours.

VF may rarely occur even when shocks are synchronized to the QRS complex. The risk is increased with electrolyte disturbances and digitalis toxicity, so elective cardioversion should be delayed in such patients. Although patients may develop mild elevations of serum troponin levels after cardioversion, sometimes with transient ST segment elevation, clinical myocardial dysfunction is rare. Post-shock bradycardia or asystole sometimes can require atropine (0.5 to 3.0 mg intravenously) or emergency transcutaneous pacing. If a patient has a pacemaker or an implantable cardioverter-defibrillator (ICD), the shocking electrodes should be placed as far away from the generator as possible and at a right angle from the pacemaker leads if feasible. Both the generator and pacing threshold should be checked after the procedure.

CARDIAC IMPLANTABLE ELECTRONIC DEVICES

Pacemakers are implanted to eliminate bradycardia, and ICDs offer highly effective protection for life-threatening ventricular tachyarrhythmias (Chapter 53). Cardiac resynchronization pacing is an essential tool for managing heart failure (Chapter 46) and is available in devices with or without the capacity for defibrillation. Implantable loop recorders, which are the preferred approach for detecting occult, infrequent, and short-lived paroxysmal arrhythmias (Chapter 49), are especially useful for patients who have syncope or may have occult AF as the cause of a stroke.

Modern devices are highly programmable and provide a wealth of diagnostic information that the clinician can use to diagnose abnormalities and to tailor therapy. The diagnostic data regarding the device's performance and

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to eventual disappearance of the pathognomonic ST elevation on the ECG. Quinidine (600 to 900 mg daily in three or four divided doses) is the only antiarrhythmic drug that appears to be useful to treat this syndrome. However, follow-up periods are not long enough to know whether catheter ablation or quinidine can obviate the need for an ICD in high-risk patients who have unprovoked Brugada pattern in their resting ECG and have a history of syncope.

Iatrogenic Ventricular Tachycardia

For sustained monomorphic VT in patients with surgically repaired congenital heart disease, catheter mapping and ablation are recommended. The techniques are similar to those used for catheter ablation of ischemic VT. Although sustained VT or VF during the course of left ventricular assist device therapy is usually well tolerated acutely, recurrent intractable VT or VF can result in right heart failure and in frequent ICD shocks, both of which may carry significant morbidity. Amiodarone (200 to 400 mg daily) and β-blocker therapy (e.g., metoprolol 100 to 200 mg daily) may be effective in at least rendering VT no longer incessant, and catheter ablation therapy has occasionally been tried in refractory VT with modest success.

PROGNOSIS

VT or VF in the early minutes or hours of acute MI has not been shown to affect the long-term prognosis in patients who survive to hospital discharge. Sustained monomorphic VT occurring after the hyperacute phase but within the next few days of an anterior wall MI portends poor prognosis, with about a seven-fold increase in subsequent mortality, because it usually occurs after the necrosis of a large amount of myocardium.

The modern natural course of untreated VT and VF perhaps can best be assessed from prospective studies of patients receiving ICD therapy. Among patients who have had documented sustained VT, appropriate ICD therapy for VT or VF occurs in about 70% of patients within 2 years and 85% of patients within 3 years. For patients who have survived cardiac arrest, the rate is about 70% at 3 years. These figures underscore the high rate of recurrence of VT and VF in patients with organic heart disease presenting with sustained ventricular arrhythmias.

The prognosis of patients with PVCs or nonsustained VT is less well known but is critically dependent on the underlying heart disease. No study to date has shown any survival benefit of treating PVCs or nonsustained VT in patients who do not have underlying organic heart disease and who do not develop a cardiomyopathy as a result of their ventricular ectopic activity. In high-risk patients who have ischemic heart disease, a left ventricular ejection fraction of less than 40%, and electrically induced sustained VT, the 2-year rate of cardiac arrest or death from ventricular arrhythmia is more than 30%.

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54 ELECTROPHYSIOLOGIC PROCEDURES AND SURGERY

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TRANSTHORACIC CARDIOVERSION AND DEFIBRILLATION

Transthoracic defibrillation, which rapidly delivers a stored charge to the heart across two surface pads or paddle electrodes, is used emergently for life-threatening tachycardias (Chapter 50). Cardioversion, which refers to shock delivery synchronized with the QRS complex, is advised in patients with either supraventricular arrhythmias (Chapter 52) or ventricular tachycardia (VT; Chapter 53) because a nonsynchronized shock coincident with the vulnerable period of the T wave may precipitate ventricular fibrillation (VF). The shock extinguishes tachyarrhythmias by simultaneously depolarizing large portions of the atria and/or ventricles. Defibrillation is used for disorganized rhythms in which synchronization to the QRS complex is not appropriate, such as VF or rapid polymorphic VT. In these emergent situations, attempts to synchronize may delay delivery of the shock.

The success of cardioversion or defibrillation is affected by the shock waveform and shock strength. Biphasic shock waveforms are recommended because they are significantly more effective than monophasic waveforms at equivalent energies. Shock energies vary by indication and between defibrillator units but are generally from 50 to 360 J. Other technique-dependent variables that maximize the energy delivered to the heart include increasing paddle pressure, delivery of the shock during expiration, and repetitive shocks. Patient-related factors that may decrease the probability of successful cardioversion and defibrillation include metabolic disturbances, a longer duration of arrhythmia, cardiac enlargement, chronic obstructive pulmonary disease, barrel-chested habitus, and higher body weight. Elective cardioversion is performed with the patient in the fasting state, usually with a short-acting anesthetic agent.

PRECAUTIONS AND COMPLICATIONS

Cardioversion of atrial fibrillation (AF) and atrial flutter (Chapter 52) may be complicated by thromboembolism, but this risk can be minimized by excluding the presence of an atrial thrombus on a transesophageal echocardiogram or by therapeutic anticoagulation with a direct-acting anticoagulant for at least 3 weeks before elective cardioversion (see Fig. 52-14, and Chapters 52 and 70). All patients should be anticoagulated for 1 month after cardioversion if AF or atrial flutter has been present for longer than 48 hours.

VF may rarely occur even when shocks are synchronized to the QRS complex. The risk is increased with electrolyte disturbances and digitalis toxicity, so elective cardioversion should be delayed in such patients. Although patients may develop mild elevations of serum troponin levels after cardioversion, sometimes with transient ST segment elevation, clinical myocardial dysfunction is rare. Post-shock bradycardia or asystole sometimes can require atropine (0.5 to 3.0 mg intravenously) or emergency transcutaneous pacing. If a patient has a pacemaker or an implantable cardioverter-defibrillator (ICD), the shocking electrodes should be placed as far away from the generator as possible and at a right angle from the pacemaker leads if feasible. Both the generator and pacing threshold should be checked after the procedure.

CARDIAC IMPLANTABLE ELECTRONIC DEVICES

Pacemakers are implanted to eliminate bradycardia, and ICDs offer highly effective protection for life-threatening ventricular tachyarrhythmias (Chapter 53). Cardiac resynchronization pacing is an essential tool for managing heart failure (Chapter 46) and is available in devices with or without the capacity for defibrillation. Implantable loop recorders, which are the preferred approach for detecting occult, infrequent, and short-lived paroxysmal arrhythmias (Chapter 49), are especially useful for patients who have syncope or may have occult AF as the cause of a stroke.

Modern devices are highly programmable and provide a wealth of diagnostic information that the clinician can use to diagnose abnormalities and to tailor therapy. The diagnostic data regarding the device's performance and

ABSTRACT

Interventional procedures and surgery have become commonplace and crucial in managing a variety of heart rhythm disorders. These approaches include cardioversion/defibrillation, implantable electronic devices, catheter and surgical ablation, and closure of the left atrial appendage. Cardiac resynchronization therapy is a critical tool in the management of patients who have heart failure with reduced ejection fraction and a widened QRS.

Catheter ablation has become a mainstay of treatment for patients suffering from many forms of tachyarrhythmias and symptomatic ectopy, including AV nodal reentry, reciprocating tachycardias due to accessory pathways, focal atrial tachycardias, typical and complex atrial flutters, paroxysmal and persistent atrial fibrillation, and ventricular tachycardia. Arrhythmia surgery is an option for atrial fibrillation, both for rhythm control and for the reduction of embolic risk, particularly in patients undergoing cardiac surgery for other reasons. Catheter-based left atrial appendage occlusion can reduce the risk of stroke in patients who have persistent atrial fibrillation and who are poor candidates for long-term anticoagulation.

KEYWORDS

electrophysiology interventions
catheter ablation
atrial fibrillation
cardiac implantable electronic devices
pacemakers
implantable cardioverter defibrillator

the presence of arrhythmias can be routinely transmitted directly from home to the appropriate health care provider.

An important issue is the use of magnetic resonance imaging (MRI) in patients with an implanted cardiac device. Historically, such devices were considered a contraindication to MRI, but most newer devices and leads are now engineered to be classified as "MRI conditional." These patients can safely undergo MRI with appropriate management. Even patients with more modern MRI nonconditional devices often can safely undergo MRI for both thoracic and nonthoracic indications,[1] provided that the patients are appropriately screened and that their devices are reprogrammed according to standard protocols.[A1]

TEMPORARY PACING

Temporary pacing is used in patients who may not require long-term pacing as well as in emergencies, such as asystolic cardiac arrest (Chapter 50). Transcutaneous pacing with electrode pads applied to the chest wall may be the quickest option and can be life-saving, but it is uncomfortable and should be used sparingly. Usually, however, time allows for temporary pacemaker leads to be inserted percutaneously, typically through an internal jugular or subclavian vein, and to be positioned gently in the right ventricular apex, ideally under fluoroscopic guidance. Another indication for temporary pacing is to maintain a higher heart rate (typically 85 to 100 beats per minute) in order to suppress torsades de pointes (Chapter 53) until the causative factor, such as an offending drug, has been eliminated. Prophylactic temporary pacing is used in patients who have high-degree atrioventricular (AV) block in the setting of an acute myocardial infarction (Chapter 58) and for patients who are at a high risk for developing symptomatic bradycardia during an interventional or surgical cardiac procedure (e.g., during transcatheter aortic valve replacement; Chapter 60).

The most common complication of temporary pacing is infection. The risk can be minimized by proper sterile technique, limiting temporary pacing to 48 hours, or replacing the lead at that time under optimal sterile conditions.

PERMANENT PACING

Indications for Permanent Pacemaking for Bradycardias

Pacemakers are implanted either to alleviate symptoms caused by bradycardia or to prevent severe symptoms in patients in whom symptomatic bradycardia is likely to develop (Tables 54-1 and 54-2).[2] The most common bradycardia-induced symptoms are dizziness or lightheadedness, syncope or near-syncope (Chapters 39 and 49), fatigue, and heart failure. Exercise intolerance caused by a poor heart rate response to exertion (chronotropic incompetence) is another common indication. Because these symptoms can be nonspecific, documentation of an association between symptoms and bradycardia should be obtained whenever possible before a pacemaker is recommended.[3] In some patients, a simple electrocardiogram (ECG) may be sufficient to document the need for a pacemaker. If the bradycardia is intermittent, other diagnostic testing, such as 24-hour ambulatory monitoring, a continuous external or implantable loop recorder, an implantable event monitor, or an electrophysiology test (Chapter 49), may be needed to document a relationship between symptoms and bradycardia.

Correctable causes of bradycardia (Chapter 51) should be excluded. Examples include hypothyroidism (Chapter 207), electrolyte disturbances, and medications such as β-adrenergic blocking agents, calcium-channel blocking agents, digitalis, and antiarrhythmic medications (Chapters 51 and 52). Other temporary causes of bradycardia that may not require a permanent pacemaker include acute ischemia or infarction, perioperative bradycardia following cardiac surgery, and neurocardiogenic causes. Patients with sleep-related bradycardia or transient pauses do not generally warrant permanent pacing. At times, a pacemaker is necessary to allow continued treatment with a medication that is responsible for the bradycardia, such as an antiarrhythmic medication or an AV nodal blocking agent needed for AF with a rapid ventricular response.

Pacing Systems

Permanent pacing systems most commonly consist of a pulse generator connected with one to three leads implanted into the heart to sense intrinsic activity and to deliver pacing pulses as needed. Pacemaker leads are inserted percutaneously via the axillary or subclavian vein, or by cephalic vein cutdown. Less often, leads are placed epicardially during cardiac surgery. Atrial leads are often placed in the right atrial appendage, but they may be placed in a variety of locations, in part based on local electrical threshold measurements. Ventricular leads are typically positioned in the right ventricular apex, right ventricular septum, or outflow tract, and they are commonly secured in place with a helical screw, known as "active fixation," for biventricular pacing (Fig. 54-1).

TABLE 54-1 CLASS I INDICATIONS* FOR IMPLANTATION OF A PERMANENT PACEMAKER

SINUS NODE DYSFUNCTION
Symptomatic sinus bradycardia
Symptomatic chronotropic incompetence
Symptomatic sinus bradycardia resulting from required drug therapy
ATRIOVENTRICULAR BLOCK
Third-degree and advanced second-degree AV block associated with symptomatic bradycardia
Third-degree and advanced second-degree AV block in an awake patient with asystole of >3 seconds or an escape rate of <40 beats per minute or with an infranodal escape rhythm
Atrial fibrillation with a pause of ≥5 sec
Third-degree and advanced second-degree AV block due to postoperative AV block that is not expected to resolve
Third-degree and advanced second-degree AV block with neuromuscular diseases such as myotonic muscular dystrophy, Kearns-Sayre syndrome, and Erb dystrophy
Asymptomatic third-degree AV block if cardiomegaly or left ventricular dysfunction is present, or if the block is below the AV node
CHRONIC BIFASCICULAR BLOCK
Advanced second-degree or intermittent third-degree AV block
Type II second-degree AV block
Alternating bundle branch block
AFTER ACUTE PHASE OF MYOCARDIAL INFARCTION
Second-degree infranodal AV block with alternating bundle branch block
Third-degree infranodal AV block
Transient advanced second-degree or third-degree infranodal AV block and associated bundle branch block
Persistent symptomatic second-degree or third-degree AV block
CAROTID SINUS SYNDROME
Recurrent syncope caused by spontaneous carotid sinus stimulation or carotid sinus pressure that induces asystole of >3 sec in duration

*Class I indications are conditions for which a pacemaker is indicated.
AV = atrioventricular.
Adapted from Gillis AM, Russo AM, Ellenbogen KA, et al. HRS/ACCF expert consensus statement on pacemaker device and mode selection. *J Am Coll Cardiol*. 2012;60:682-703.

TABLE 54-2 CLASS IIA INDICATIONS* FOR IMPLANTATION OF A PERMANENT PACEMAKER

SINUS NODE DYSFUNCTION
Heart rate of <40 beats per minute when a clear association between symptoms consistent with bradycardia and the actual presence of bradycardia has not been demonstrated
Syncope of unclear etiology when sinus node dysfunction is demonstrated by electrophysiologic testing
ATRIOVENTRICULAR BLOCK
Persistent third-degree AV block with an escape rate of >40 beats per minute in an asymptomatic adult without cardiomegaly
Asymptomatic second-degree infranodal AV block
First-degree or second-degree AV block associated with symptoms similar to pacemaker syndrome
Asymptomatic type II second-degree AV block with a narrow QRS
CHRONIC BIFASCICULAR BLOCK
Syncope, when other potential causes of syncope have been excluded
An HV interval of ≥100 msec
Pathologic pacing-induced infranodal AV block during electrophysiologic testing
CAROTID SINUS SYNDROME
Syncope without clear provocative events and with asystole of >3 sec during carotid sinus pressure

*Class IIA indications are conditions for which a pacemaker is reasonable.
AV = atrioventricular; HV = His-ventricle.
Adapted from Tracy CM, Epstein AE, Darbar D, et al. 2012 ACCF/AHA/HRS focused update of the 2008 guidelines for device-based therapy of cardiac rhythm abnormalities: a report of the American College of Cardiology Foundation/American Heart Association Task Force on Practice Guidelines. *J Am Coll Cardiol*. 2012;60:1297-1313.

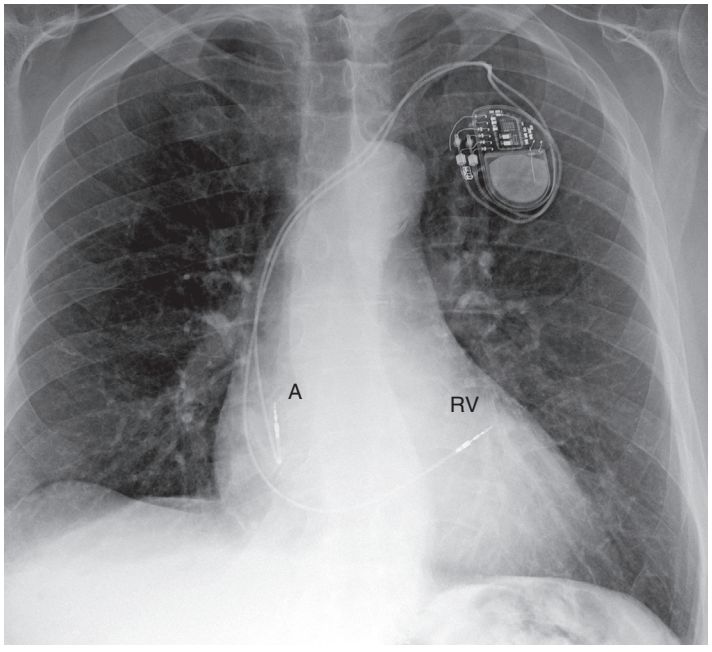

FIGURE 54-1. Chest radiograph of a patient with a dual-chamber (atrial and right ventricular) pacemaker.

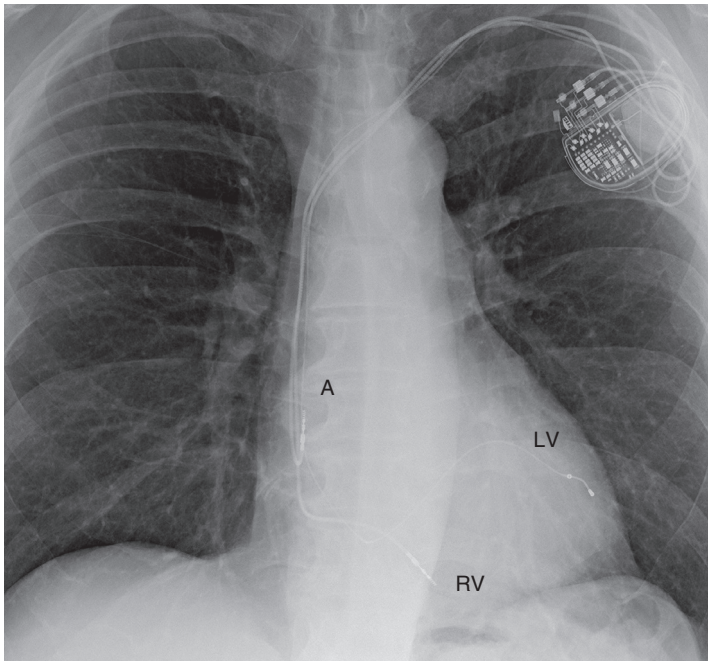

FIGURE 54-3. Chest radiograph of a patient with an atrial and biventricular pacemaker.

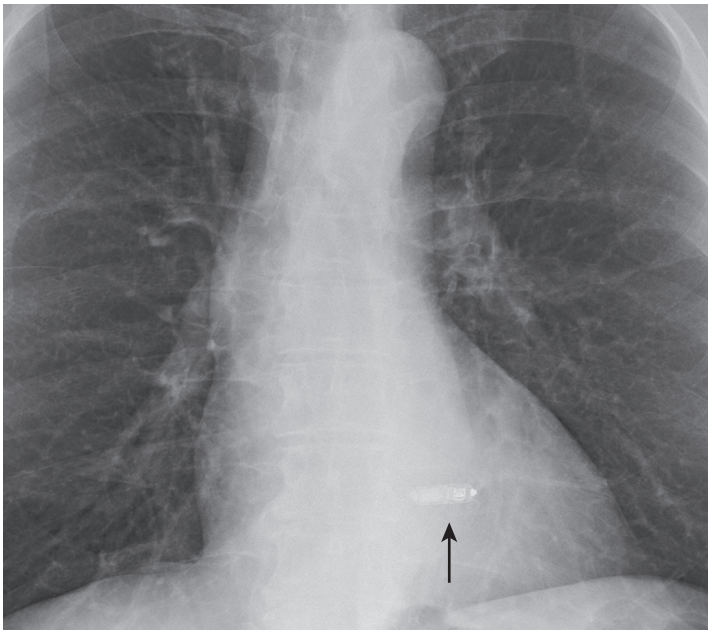

FIGURE 54-2. Chest radiograph of a leadless pacemaker (arrow) positioned in the right ventricle.

A leadless pacing system,[4] with a miniaturized generator and delivery system combined into a single unit, can be implanted, typically in the right ventricle (Fig. 54-2). These leadless pacemakers are commonly used in patients who have permanent AF and AV block. However, they also can frequently sense and track atrial mechanical activity to pace the ventricle while maintaining AV synchrony in patients with AV block and sometimes are used in patients who are in sinus rhythm with AV block.

With traditional systems, pulse generators are powered by lithium-based pacemaker batteries, which have an 8- to 12-year (or more) lifespan and can weigh less than 30 g. These generators typically are implanted subcutaneously in the infraclavicular region. The programmability of many different parameters has become standard, as has the ability of the pacemaker to provide diagnostic and telemetric data.

Synchronous biventricular pacing can preserve the ventricular synchrony that is lost when only one ventricle is paced and the other's activation is delayed. The usual option is biventricular pacing with one lead in the right ventricle and one in the coronary venous system to pace the lateral left ventricle (Fig. 54-3), typically with an atrial lead in patients who are not in permanent atrial fibrillation. Permanent His-bundle pacing is also increasingly being used to maintain the patient's intrinsic conduction system, thereby avoiding ventricular dyssynchrony.[5] Yet another emerging option for physiologic pacing is left bundle branch area pacing, which may produce lower and more stable pacing thresholds in some patients.[A2] Each paced beat will have a configuration that depends on the site of the pacing lead (Fig. 54-3).

Pacing Modes and Programming

Pacing modes are described by a simple code. The first letter represents the chamber being paced (A for atrium, V for ventricle, D for dual chamber). The second letter identifies the chamber whose depolarizations are being sensed by the pacemaker (A, V, D, or O for no sensing). The third letter indicates whether the pacemaker is functioning in an inhibited (I) mode, a tracking (T) mode, in both modes (D), or asynchronously (O). The fourth letter designates whether the pacemaker can modulate the pacing rate, usually by increasing pacing rates with physical activity (R).

The most appropriate pacing mode must be determined for each individual and may change with the patient's status. By far the most common permanent pacing modes now used in the United States are DDD and DDDR. VVI and VVIR modes are used mainly in patients who have chronic AF with symptomatic pauses or bradycardia. Mode-switching pacemakers can pace in the DDD mode during sinus rhythm and automatically switch to rate-responsive (VVIR) ventricular pacing during paroxysmal AF or other supraventricular arrhythmias. Automatic mode switching from AAI(R) to DDD(R) is also available for patients with sinus node dysfunction and intermittent AV block.

Many patients' devices are programmed at settings chosen to minimize the right ventricular pacing burden, not only to conserve the battery, but also to reduce pacing-induced ventricular dyssynchrony, which sometimes can lead to impaired ventricular function. This potential side effect is particularly a concern in patients who have a normal intrinsic QRS duration and then undergo single-chamber right ventricular pacing. However, in patients who require resynchronization therapy, a very high percentage of ventricular pacing is the goal.

In patients with sinus node dysfunction, atrial or dual-chamber pacing significantly reduces the risk for AF and improves quality of life compared with ventricular pacing. Because such patients are at substantial risk of symptomatic AV block, initial dual-chamber pacing is commonly used, although atrial pacing alone is an option for selected patients with normal AV conduction. Because chronotropic incompetence is frequent in this patient population, a rate-responsive mode (AAIR or DDDR) is usually recommended. In patients with AV block, dual-chamber pacing improves quality of life, reduces the risk for developing AF, and avoids the 7 to 25% risk for developing the pacemaker syndrome, which consists of symptoms of weakness, lightheadedness, exercise intolerance,

or palpitations owing to the absence of AV synchrony during single-chamber ventricular pacing. For these reasons, current consensus guidelines recommend dual-chamber pacing for most patients with sinus node dysfunction or AV block.

Synchronous biventricular pacing or His-bundle pacing is preferred in bradycardic patients who have a left ventricular ejection fraction of 50% or below and who are expected to need pacing for more than 40% of their heartbeats. With atrial pacing, this synchrony can simulate normal cardiac function. In patients who require permanent pacing, the risk of future ventricular arrhythmias guides the need for simultaneous insertion of an implantable cardioverter defibrillator.

The electrocardiogram of paced patients depends on the site and frequency of pacing (Fig. 54-4)

COMPLICATIONS OF PACEMAKERS

Complications can be either acute or late. About 1 to 2% of patients develop acute complications from the implantation procedure itself, including infection,[6] pneumothorax, cardiac tamponade owing to pericarditis or perforation of the atrium or ventricle, lead dislodgement, subclavian vein thrombosis, and pocket complications. The subcutaneous pocket may develop a hematoma, seroma, dehiscence, or local infection. Pocket hematomas can be painful and increase the risk of infection. Their occurrence can be minimized by meticulous operative technique and postoperative care, as well as by interrupting anticoagulation when feasible. In patients who require uninterrupted anticoagulation, a strategy of continued oral anticoagulant treatment at the time of implantation of a pacemaker or an ICD markedly reduces the incidence of clinically significant device-pocket hematoma compared with bridging therapy with heparin.

Late complications include venous thrombosis or obstruction (including the superior vena cava syndrome; Fig. 86-8), the pacemaker syndrome, pacing-induced ventricular dyssynchrony that can cause heart failure, infection, and various forms of pacemaker malfunction. The latter include failure to pace, failure to capture, and sensing abnormalities, most often resulting

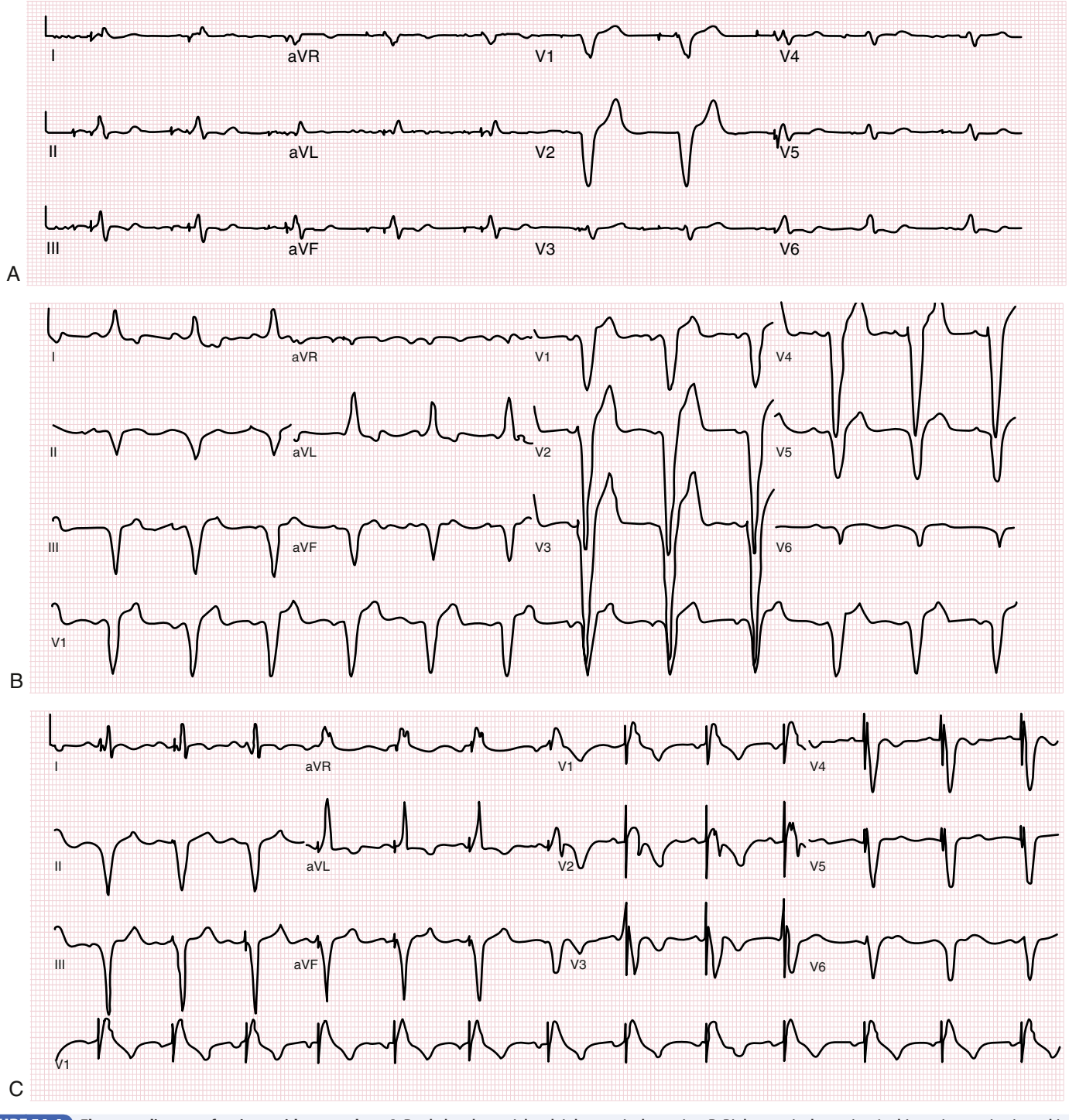

FIGURE 54-4. Electrocardiogram of patients with pacemakers. A, Dual-chamber atrial and right ventricular pacing. **B,** Right ventricular pacing. In this tracing, pacing is tracking the sinus P waves that are sensed with an atrial lead (with a single-chamber ventricular pacemaker, the P waves would be dissociated). **C,** Same patient after being upgraded to a biventricular pacemaker. Note the changes in lead V_1 and V_2 and the partial narrowing of the QRS that are often seen by adding simultaneous pacing of the left ventricle.

from lead abnormalities (conductor fractures, insulation breaks or changes at the lead-tissue interface). Pacemaker infections typically involve primarily the subcutaneous pacemaker pocket, but long-term resolution of infection generally requires removal of both the pulse generator and leads as well as extended antibiotic therapy (Chapter 61). Nearly 40% of patients have coexisting valve involvement, predominantly tricuspid valve infection (Chapter 61), with mortality rates as high as 15% in the hospital and 20 to 25% at 1 year. Less commonly, pulse generator malfunctions, including premature battery depletion, may occur. Long-term problems may also result from inappropriate programming. The emerging use of leadless pacing eliminates many of the risks of conventional pacing systems and is becoming increasingly common as experience grows and the technology advances.

IMPLANTABLE CARDIOVERTER-DEFIBRILLATORS AND CARDIAC RESYNCHRONIZATION THERAPY

Abnormal and prolonged ventricular activation, indicated by a QRS duration greater than 120 msec, may cause dyssynchronous activation of the left ventricle and, as a result, diminished systolic function. Right ventricular pacing, particularly from the apex, also is associated with a delayed activation sequence and, as a result, interventricular and intraventricular mechanical dyssynchrony. Cardiac resynchronization therapy requires synchronized pacing of both ventricles or physiologic pacing by means of His-bundle pacing or left bundle branch pacing.[7]

Implantable Cardioverter-Defibrillators

Indications

ICDs are a highly effective method for detecting and terminating life-threatening ventricular arrhythmias (Chapter 53). They are used both for secondary prevention following an episode of sustained VT or VF and for primary prevention in individuals at high risk for sudden cardiac death (Table 54-3). Examples include patients with ischemic or nonischemic dilated cardiomyopathy with a left ventricle ejection fraction of 35% or less and class II or III heart failure,[A3] as well as selected patients with conditions such as hypertrophic cardiomyopathy, Brugada syndrome, and long QT syndrome (Chapters 47, 53, and 58).[8]

ICD Pulse Generators and Leads

Procedures for implanting transvenous ICDs are analogous to those used for permanent pacemakers. The pulse generators, although still somewhat larger than pacemakers (with some models now <1 cm in thickness, <28 mL in volume, and around 60 g), deliver biphasic shocks at programmable energies while recording the electrogram during the arrhythmia and its treatment (E-Fig. 54-1). They also can provide anti-tachycardia pacing, as well as dual-chamber bradycardia pacing or cardiac resynchronization pacing therapy.

ICD implantation and lead configuration (Figure 54-5) are designed to deliver sufficient energy to the ventricular myocardium to ensure reliable defibrillation. The most common pathway for this energy is from the implanted pectoral pulse generator to a coil electrode on the distal portion of the transvenous lead that is positioned in the right ventricle (E-Fig. 54-2). The majority of transvenous ICD pulse generators can deliver up to 30 to 40 J, which exceeds the typical defibrillation energy threshold of 10 to 15 J, thereby allowing a substantial margin of safety for defibrillation.

An alternative to a transvenous ICD is the subcutaneous ICD.[9] However, subcutaneous systems currently have a larger pulse generator, somewhat shorter battery longevity, and do not provide usual bradycardic, anti-tachycardic, or resynchronization pacing therapy. The pulse generator must deliver higher stored energy (80 J) compared with transvenous defibrillation to ensure an adequate margin of safety for defibrillation, but data show that the device's effectiveness for sensing and terminating VF is comparable to that of transvenous systems.[A4] It is an attractive option for patients who have had prior complications from transvenous systems (e.g., vein thrombosis, infection) or issues with intravenous access, as well as for primary prevention in patients in whom frequent shocks or the need for pacing are not anticipated. However, the choice of an ICD system must be individualized to a patient's overall needs.

Programming of ICDs

The goals of ICD programming are to provide the appropriate detection of all arrhythmias, the discrimination of ventricular from supraventricular rhythms, and appropriate anti-tachycardia pacing and shocks only when needed for sustained arrhythmias. The shocks are programmed to provide an adequate margin of safety for reliable cardioversion and defibrillation. In addition, bradycardic pacing therapy should be optimized to provide an appropriate heart rate response to exertion while minimizing right ventricular pacing. Conversely, the ventricles are ideally paced for all beats in patients in whom cardiac resynchronization (see later) is needed.

ICD recipients may have sustained monomorphic VT that can be painlessly terminated by appropriately timed, overdrive anti-tachycardia pacing. ICD shocks

TABLE 54-3 INDICATIONS FOR IMPLANTABLE CARDIOVERTER-DEFIBRILLATOR IMPLANTATION

CLASS I*: SECONDARY PREVENTION
Cardiac arrest survivor (VF or unstable sustained VT not associated with a completely reversible cause)
Spontaneous sustained VT (irrespective of stability) and structural heart disease
Syncope of unknown origin associated with clinically relevant and hemodynamically significant sustained VT or VT induced at electrophysiologic testing
CLASS I*: PRIMARY PREVENTION
Prior myocardial infarction (≥40 days), LVEF <35%, NYHA class II or III
Prior myocardial infarction (≥40 days), LVEF <30%, NYHA class I
Nonischemic dilated cardiomyopathy, LVEF ≤35%, NYHA class II or III
Prior myocardial infarction, LVEF <40%, spontaneous NSVT, inducible sustained VT or VF at electrophysiologic testing
CLASS IIA†
Nonischemic dilated cardiomyopathy, significant LV dysfunction, and syncope
Sustained VT and normal or near-normal ventricular function
Hypertrophic cardiomyopathy and one or more risk factors for sudden death
Arrhythmogenic right ventricular cardiomyopathy and one or more risk factors for sudden death
Long QT syndrome with syncope or VT despite β-blocker therapy
Nonhospitalized patients awaiting cardiac transplantation
Brugada syndrome and syncope or VT
Catecholaminergic polymorphic VT and syncope or VT on β-blocker therapy
Cardiac sarcoidosis, giant cell myocarditis, or Chagas disease

*Class I indications are conditions for which an implantable cardioverter-defibrillator is indicated.
†Class IIA indications are conditions for which an implantable cardioverter-defibrillator is reasonable.
LVEF = left ventricular ejection fraction; NSVT = nonsustained ventricular tachycardia; NYHA = New York Heart Association; VF = ventricular fibrillation; VT = ventricular tachycardia.
Adapted from Tracy CM, Epstein AE, Darbar D, et al. 2012 ACCF/AHA/HRS focused update of the 2008 guidelines for device-based therapy of cardiac rhythm abnormalities: a report of the American College of Cardiology Foundation/American Heart Association Task Force on Practice Guidelines. *J Am Coll Cardiol*. 2012;60:1297-1313.

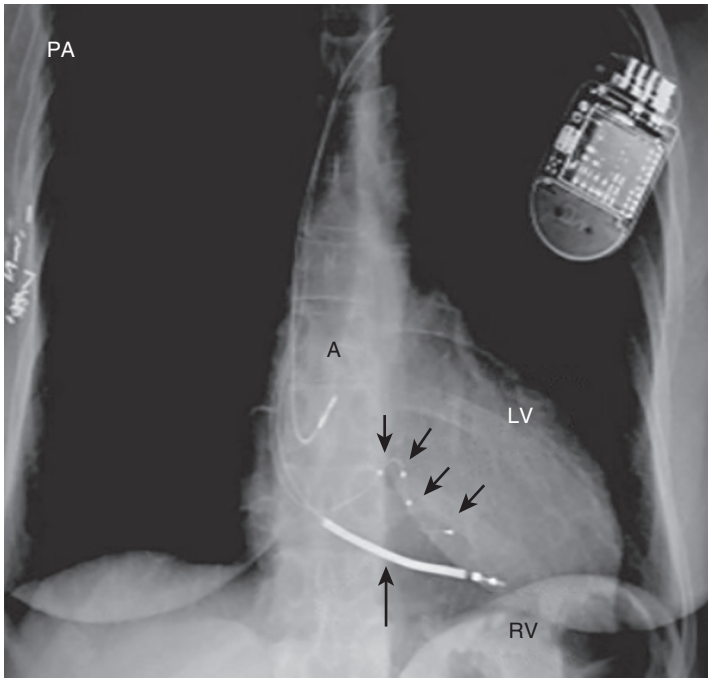

FIGURE 54-5. Typical position of the left ventricular (LV) pacing lead *(short arrows)* with four poles, in a posterolateral branch of the coronary sinus in a patient with a cardiac resynchronization device. Atrial (A) and right ventricular (RV) implantable cardioverter-defibrillator leads are also present in typical locations. Note the presence of a defibrillator coil on the distal right ventricular lead *(long arrow),* indicating that the device is also capable of defibrillation. PA = posteroanterior.

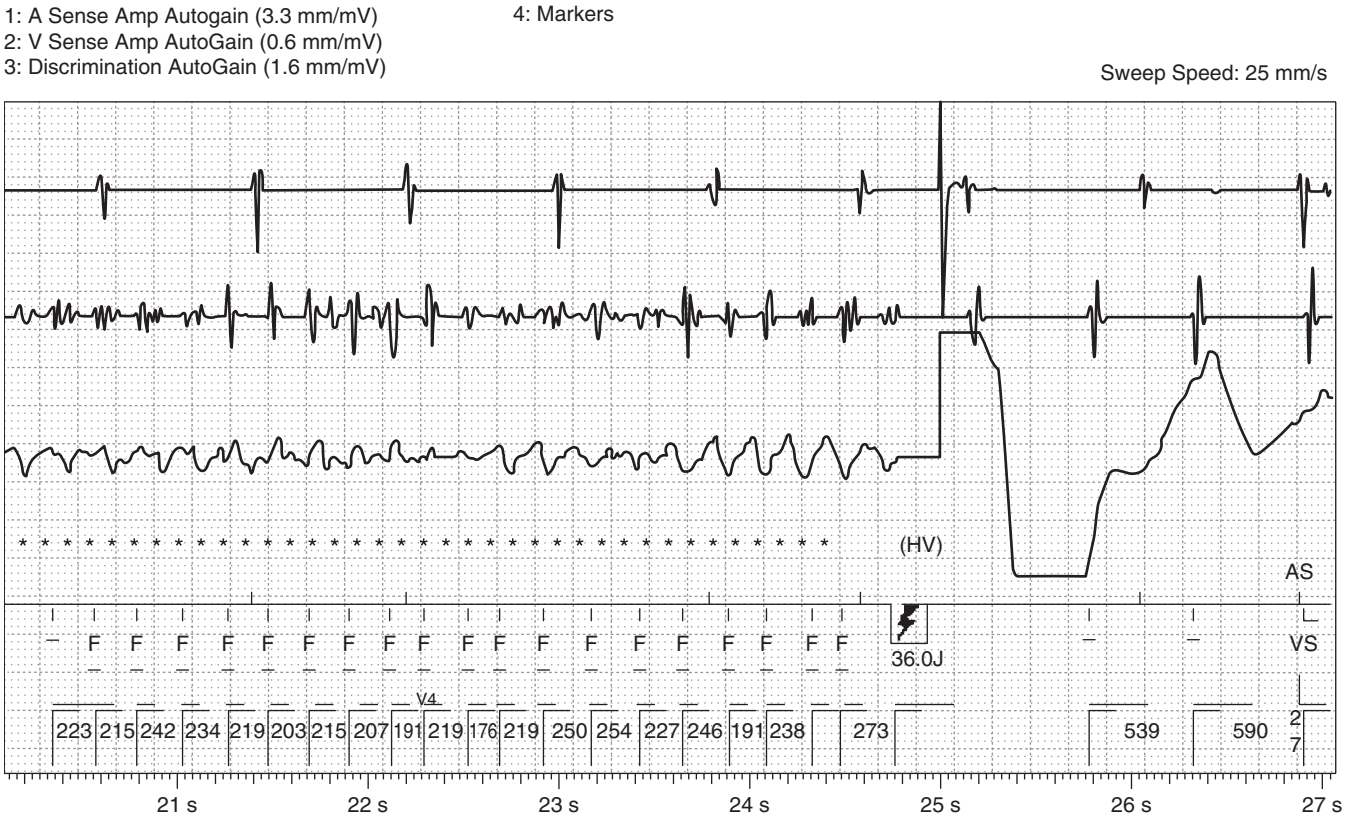

E-FIGURE 54-1. Intracardiac stored electrograms (atrial [A], ventricular [V], and marker channels) from an implantable cardioverter-defibrillator shock terminating ventricular fibrillation. Ventricular fibrillation is appropriately detected and terminated with a 36-Joule shock.

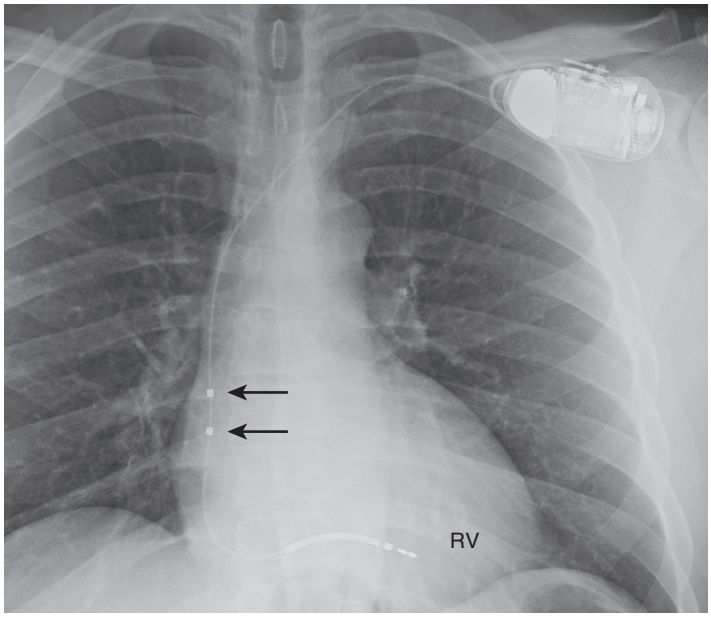

E-FIGURE 54-2. Single-chamber implantable cardioverter-defibrillator with lead in the right ventricle (RV). *Arrows* show atrial sensing poles incorporated into the single lead in this model.

are uncomfortable and are not intended for routine conversion of more benign tachycardias. Optimal anti-tachycardia pacing can successfully terminate VT without a shock while also minimizing the risk that it will accelerate into VF.

ICDs incorporate a variety of programmable discrimination algorithms designed to withhold unnecessary therapies for brief episodes of rapid supraventricular arrhythmias, especially sinus tachycardia or AF. In addition, many ventricular arrhythmias will self-terminate within seconds, so algorithms designed to delay therapy for a short time can reduce unnecessary shocks. Optimal programming reduces the patient's discomfort, maximizes the life of the pulse generator battery, and reduces the potential adverse effects of unneeded shocks. Incorporating higher rate cutoffs, detection delay, rhythm discriminators, and anti-tachycardia pacing can reduce inappropriate device shocks by 50% and mortality by 30% compared with standard ICD programming, without significantly increasing the risk for syncope. Many athletes with ICDs can engage in vigorous and competitive sports without physical injury or failure to terminate the arrhythmia.

Indications for Cardiac Resynchronization Therapy

Resynchronization therapy promotes more synchronous ventricular contraction and results in "reverse remodeling" with a reduction in ventricular volumes, improved systolic function, and clinical improvement in heart failure (Chapter 46). In clinical trials of patients with reduced systolic function, QRS duration longer than 120 msec, and class III or ambulatory class IV heart failure, the addition of cardiac resynchronization therapy to guideline-directed medical therapy is associated with an approximately 30% reduction in hospitalizations and a 24 to 36% reduction in total mortality. Functional improvement in heart failure symptoms and quality of life is seen in a majority of patients, but 30 to 40% of patients may not improve symptomatically. Superior outcomes are associated with longer QRS durations (>150 msec) and a left bundle branch block QRS configuration, whereas patients with imaging-identified mechanical dyssynchrony alone, in the absence of QRS prolongation, do not improve.

Clinical trials have also established that the benefit of cardiac resynchronization therapy extends to patients with less severe heart failure symptoms (class I or II), in whom it appears to delay the onset of symptomatic heart failure and significantly reduce heart failure events over the next 1 to 7 years if the ejection fraction is 30% or less and the QRS duration is more than 130 msec, especially in patients with left bundle branch block. As noted previously, cardiac resynchronization therapy is also recommended for the treatment of bradycardia in patients who have a left ventricular ejection fraction of 50% or less and who likely will have more than 40% paced beats. The role of physiologic His-bundle and left bundle branch pacing continues to evolve. Evidence suggests the clinical results match or exceed those of biventricular pacing.[10] Current accepted usage largely follows indications for cardiac resynchronization therapy (Table 54-4).

TABLE 54-4 INDICATIONS FOR IMPLANTATION OF A CARDIAC RESYNCHRONIZATION THERAPY (CRT) DEVICE

CLASS I INDICATIONS*
LVEF ≤35%, sinus rhythm, LBBB (≥150 msec), NYHA class II, III, or ambulatory class IV on guideline-directed medical therapy
CLASS IIA INDICATIONS†
LVEF ≤35%, sinus rhythm, LBBB (120-149 msec), NYHA class II, III, or ambulatory class IV on guideline-directed medical therapy
LVEF <35%, sinus rhythm, non-LBBB (≥150 msec), NYHA class III or ambulatory class IV on guideline-directed medical therapy
LVEF ≤35%, atrial fibrillation, on guideline-directed medical therapy, and both: • Requires ventricular pacing or otherwise meets CRT criteria • Near 100% pacing with CRT can be achieved by either atrioventricular node ablation or pharmacologic rate control
LVEF ≤35% on guideline-directed medical therapy and are undergoing new or replacement device implantation with anticipated requirement for significant (>40%) ventricular pacing
In patients who have atrioventricular block, an indication for permanent pacing, a left ventricular ejection fraction between 36 and 50%, and are expected to require ventricular pacing more than 40% of the time, it is reasonable to choose pacing methods that maintain physiologic ventricular activation (e.g., cardiac resynchronization therapy or His bundle pacing) rather than right ventricular pacing.

*Class I indications are conditions for which CRT is indicated.

†Class IIA indications are conditions for which CRT is reasonable.

LBBB = left bundle branch block; LVEF = left ventricular ejection fraction; NYHA = New York Heart Association (functional class).

Adapted from Brignole M, Auricchio A, Baron-Esquivias G, et al. 2013 ESC Guidelines on cardiac pacing and cardiac resynchronization therapy: the Task Force on cardiac pacing and resynchronization therapy of the European Society of Cardiology (ESC). Developed in collaboration with the European Heart Rhythm Association (EHRA). *Eur Heart J*. 2013;34:2281-2329; Tracy CM, Epstein AE, Darbar D, et al. 2012 ACCF/AHA/HRS focused update of the 2008 guidelines for device-based therapy of cardiac rhythm abnormalities: a report of the American College of Cardiology Foundation/American Heart Association Task Force on Practice Guidelines. *J Am Coll Cardiol*. 2012;60:1297-1313; Kusumoto FM, Schoenfeld MH, Barrett C, et al. 2018 ACC/AHA/HRS guideline on the evaluation and management of patients with bradycardia and cardiac conduction delay: executive summary: a report of the American College of Cardiology/American Heart Association task force on clinical practice guidelines, and the Heart Rhythm Society. *J Am Coll Cardiol*. 2019;74:932-987.

Combined Resynchronization and Cardioverter Defibrillator Therapy

In patients who meet criteria for both cardiac resynchronization therapy and an ICD, implantation of a device with both functions (CRT-D) may provide additional mortality benefit. The burden of comorbidity does not appear to compromise the clinical benefits of cardiac resynchronization therapy plus an ICD compared with an ICD alone.[A5] However, cardiac resynchronization therapy alone may be appropriate for some patients with more advanced heart failure, extensive comorbidity, and limited life expectancy when the primary objective is symptomatic improvement, and the added value of defibrillation is not desired or less clear.[A6]

Complications

Many of the complications related to ICDs and cardiac resynchronization therapy are similar to those associated with pacemakers. Overall, major complications occur in 2 to 3% of new ICD implants and are more common during pulse generator replacement (5 to 6%). Use of an absorbable antibiotic-eluting envelope can significantly reduce the risk of major infection and should be considered in patients at high risk.[A7]

Long-term complications are primarily related to late infection and lead failure. Given their larger size and complexity, ICD leads are more likely to fail (1 to 4% annually) than are pacemaker leads (<0.5% annually). Lead failure is most often due to insulation failure or fracture of the conductor wires. Cardiac resynchronization therapy devices have the highest likelihood of procedure-related complications or lead dislodgement, predominantly owing to dislodgement of the coronary sinus lead. Phrenic nerve stimulation, which may occur with left ventricular pacing, manifests as a left-sided thumping sensation that is generally palpable; it can often be corrected with programming adjustments. In underserved countries, a resterilized pacemaker or defibrillator can be implanted with infection and failure rates similar to new devices.[11]

Although an occasional therapeutic ICD discharge is common, flurries of discharges require urgent evaluation to determine the cause. Such causes can range from flurries of VT or VF, which may have a correctable precipitant (e.g., an electrolyte imbalance, drug toxicity), to AF or another supraventricular tachycardia (SVT) with a rapid ventricular response, lead fracture, or insulation failure. An important consideration is the potential psychological impact of ICD shocks, and some patients may require psychiatric help in managing anxiety after receiving one or more shocks. In some cases, antiarrhythmic drug therapy (see Tables 52-2 and 52-3), catheter ablation, or both may reduce or eliminate the arrhythmias associated with frequent shocks (Chapter 53).

CATHETER ABLATION

Catheter ablation is a common and often preferred method for treating various forms of tachycardia. For appropriate arrhythmias, ablation often has higher success rates and is more definitive when compared with medical therapy. In addition, the treatment can be curative for some arrhythmias and avoid the need for chronic medication or future urgent intervention. Ablation is used for arrhythmias that depend upon a critical anatomic site, region, or regions of myocardial tissue that can be selectively necrosed to eliminate the arrhythmia. Depending on the arrhythmia, the target sites for ablation may be selected based on location, by substrate, by a local electrogram during a diagnostic electrophysiologic study (Chapter 49), by various mapping techniques, or by the response to maneuvers during an episode of sustained tachycardia. For some arrhythmias, reproduction of the clinical arrhythmia during diagnostic electrophysiologic testing (Chapter 49) is critical and can be facilitated by judicious use of sedation and intravenous infusion of catecholamines or other agents. Electroanatomic mapping has facilitated the ablation of many forms of tachyarrhythmias, allowed for substantial reductions in the need for fluoroscopy, and enabled ablation of complex arrhythmias with good success rates (E-Fig. 54-3).

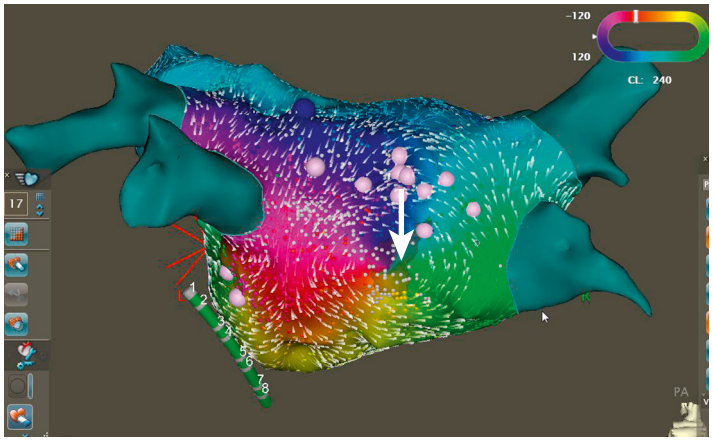

E-FIGURE 54-3. Electroanatomic map of an atypical atrial flutter around a scar *(arrow)* on the posterior left atrium. Catheter ablation restored sinus rhythm.

TISSUE EFFECTS OF APPLIED ENERGY

Catheter ablation is performed by several means, including radio frequency energy, cryoablation, and laser ablation. The most common form uses radio frequency energy, typically in the range of 300 to 750 kHz, applied in a unipolar fashion between a small catheter-tip electrode in contact with the targeted myocardium and a large dispersive cutaneous patch electrode. Irreversible myocyte injury occurs with a tissue temperature higher than 50° C, with visually apparent tissue destruction at higher than 60° C. Saline irrigation of the electrode reduces heating at the tissue-electrode interface, allows for higher energy delivery when needed, moves the zone of maximal heating deeper into the tissue, and thus can allow for larger and deeper lesions with less risk of surface char and coagulum. Among other energy sources, cryoablation is the most widely used, whereas laser, microwave, and ultrasound have limited applications at present. Pulsed field ablation, which is still investigational, utilizes non-thermal electrical fields that are rapid and tissue-selective, thereby potentially reducing the risk of collateral injury.[12]

The most common serious complication of ablation is cardiac tamponade, owing to mechanical perforation of the heart by an electrode catheter. Rarely, high-degree AV block can occur when the target is near the AV node. Pulmonary vein stenosis is a rare complication of AF ablation. Also, depending on the type of ablation, collateral injury may occur to a phrenic nerve, the esophagus, or other nearby tissues. When epicardial ablation is performed, usually via percutaneous subxiphoid pericardial access, the coronary arteries could potentially be injured if ablation is delivered too nearby.

CATHETER ABLATION OF SUPRAVENTRICULAR TACHYCARDIAS

Catheter ablation is the recommended first-line treatment for paroxysmal SVT, Wolff-Parkinson-White (WPW) syndrome, or typical atrial flutter that is symptomatic enough to warrant therapy (Chapter 52). For atypical atrial flutters, ablation is becoming more common as success rates now approach those for typical atrial flutter. Ablation is rarely recommended for inappropriate sinus tachycardia because outcomes are less predictable, often partial, and may result in undesired sinus node dysfunction.

AV nodal re-entrant tachycardia (Chapter 52), which is the most common type of paroxysmal SVT, is successfully eliminated in 98% of cases (with a <1% risk for high-degree AV block), usually by radio frequency ablation of the "slow" limb of the re-entry circuit, most often at the posteroseptal aspect of the right atrium.

Accessory pathways are the next most common cause of paroxysmal SVT and can be due to manifest accessory pathways showing preexcitation (WPW syndrome) or concealed pathways that conduct only in retrograde fashion (no preexcitation on an ECG). Left-sided accessory pathways are ablated by using either a retrograde aortic or a transseptal approach, whereas right-sided and septal lesions are ablated with a venous approach. Detailed mapping is essential to identify the optimal site to ablate the accessory pathway, usually on either the atrial or the ventricular aspect of the mitral or tricuspid annulus. For the ablation of an accessory pathway, the success rate is 90 to 98%, with an overall complication rate of 2 to 3% and a less than 0.1% risk for a fatal complication.

Atrial tachycardias often arise in the right atrium and are mapped using a venous approach, but left atrial tachycardias require a transseptal approach. Approximately 10 to 20% of patients with atrial tachycardia have more than one focus and may be associated with other forms of SVT, particularly AV nodal re-entrant tachycardia. If the atrial tachycardia originates from a single site, ablation has about a 90% success rate, and complications are rare. For patients with multiple sources of atrial tachycardia, long-term success rates are lower.

Typical atrial flutter (Chapter 52), which arises in the right atrium, can be eliminated by ablation directed at a critical isthmus located in the low right atrium, between the tricuspid annulus and the inferior vena cava. The long-term success rate is more than 90%, with a less than 1% risk for serious complications.

ABLATION FOR ATRIAL FIBRILLATION

The primary aim of ablation for AF currently is to reduce the burden of recurrent episodes of AF in patients with symptoms and thereby to improve quality of life. Catheter ablation of AF has been effective in treating paroxysmal, persistent, and long-standing persistent (>1 year) AF. The optimal approach for the ablation of AF (Chapter 52) is an area of active investigation, but pulmonary vein isolation remains the cornerstone of most AF ablation procedures. For patients with recurrent paroxysmal AF, a primary driver of the arrhythmia is from focal sources in the regions surrounding the proximal portions of the pulmonary vein and sometimes other thoracic veins as they insert into atrial myocardium. Focally triggered arrhythmias may arise from other right and left atrial sites in 10 to 20% of patients.

For patients with recurrent symptomatic paroxysmal AF despite at least one antiarrhythmic drug trial, catheter ablation significantly reduces the risk for recurrent atrial arrhythmias by 50 to 70% and significantly improves quality of life compared with continued attempts to control the arrhythmia with alternative drug therapy.[13,14] The strategy of early intervention to maintain sinus rhythm (including ablation and/or antiarrhythmic drugs) may reduce mortality and stroke compared with standard medical care[A8] (see Chapter 52). First-line ablation therapy, without the requirement for prior antiarrhythmic drug failure, results in similar improvements and may lead to lower rates of recurrences.[A9–A11] For patients with symptomatic heart failure, and especially for patients who require an ICD or cardiac resynchronization therapy, catheter ablation is clearly the preferred initial therapy because it reduces all-cause mortality.[A12–A14]

Because AF is a progressive disease, however, the window of opportunity for intervention to prevent progression from paroxysmal to permanent AF or to prevent stroke, heart failure, or death may be limited. In patients with persistent AF, pulmonary vein isolation is also commonly performed early after diagnosis because it is less successful in patients with persistent AF of longer than 1 year's duration.[15]

Due to limited responses with pulmonary vein isolation alone, a variety of additional ablation targets have been tried, with mixed and often disappointing results. However, low-voltage myocardium-guided ablation can be helpful in selected patients.[A15]

Overall, the 1-year success rate of catheter ablation is 75 to 85% for paroxysmal AF and 60 to 75% for persistent AF. The most serious complications of AF ablation are atrial perforation, thromboembolism, and atrioesophageal fistula, with an overall risk of about 2%. Other complications are phrenic nerve injury, pulmonary vein stenosis, or vascular access issues. Left atrial macro-re-entrant arrhythmias, which can be a sequela of AF ablation, may require additional ablation.

In patients with refractory AF associated with an uncontrolled ventricular rate despite pharmacologic AV node blockade, ablation of the AV node can improve symptoms, functional capacity, and left ventricular function. In AV node ablation, third-degree AV block is intentionally induced with a success rate that approaches 100%. When the ablation lesions are placed sufficiently proximal in the AV junction, a junctional escape rhythm usually can be preserved. All patients require a permanent pacemaker to provide adequate rate response to physical activity.

ABLATION OF VENTRICULAR ARRHYTHMIAS

Ablation to manage ventricular arrhythmias is most commonly used for sustained VT, idiopathic monomorphic VT, and VT associated with structural heart disease, including ischemic cardiomyopathy, nonischemic dilated cardiomyopathy, arrhythmogenic right ventricular cardiomyopathy, sarcoidosis, congenital heart disease, and the Brugada syndrome.[16] However, it also may be used in selected patients with ventricular fibrillation or frequent premature ventricular contractions.

Ablation for the treatment of idiopathic VT carries a high (85% to 100%) success rate (Chapter 53), whether it arises in the outflow tract of the right ventricle or arises from other sites, including the AV valve annuli, the sinuses of Valsalva, the left ventricular septum, or the papillary muscles. Given these outcomes, ablation is recommended in symptomatic patients, either after failure of initial drug therapy or as first-line therapy, depending in part on the patient's preference. Complications are rare, and patients can usually avoid medications or an ICD.

By comparison, VT in patients with coronary artery disease and other forms of structural heart disease usually arises in diseased tissue in either ventricle. In patients with a prior myocardial infarction, ablation is often performed endocardially adjacent to or within an area of previous infarction in the left ventricle (E-Fig. 54-3). In patients with recurrent VT despite antiarrhythmic medications, VT ablation is more effective than an escalation of drug therapy.[A16]

In other forms of structural disease, percutaneous epicardial ablation may be needed. Ablation may not always be curative, but it may markedly diminish the frequency of VT episodes and reduce discharges of an ICD. Success rates range from 65 to 95%, with serious complications in about 5% of patients.

Although radio frequency catheter ablation is the most common method, other forms of ablation are sometimes used. An emerging noninvasive option is ablation via electrophysiology-guided stereotactic body radiotherapy.[17]

ARRHYTHMIA SURGERY

ATRIAL FIBRILLATION

Surgical ablation of AF can involve isolation of the pulmonary vein or a full biatrial Maze procedure, in which a series of incisions or linear lesions created by cryoablation or radio frequency ablation subdivides the atria into smaller segments unlikely to sustain AF. The most common current indication for the Maze procedure is the treatment of symptomatic AF in patients undergoing other cardiac surgical procedures, such as coronary revascularization or valve replacement or repair. AF surgery added to mitral valve surgery significantly reduces the recurrence of AF in patients with persistent or long-standing persistent AF. A variety of simpler and even minimally invasive operative procedures have been developed for AF, but their long-term efficacy and role in the treatment of AF are still being defined.

VENTRICULAR TACHYCARDIA

Surgical treatment by subendocardial resection or cryoablation of scar tissue (Chapter 53) in patients with a prior myocardial infarction can eliminate VT in selected patients (E-Fig. 54-4), with a success rate of 85 to 90%, but it carries an operative mortality rate of 5 to 15% even in experienced centers. Because of this high mortality and the development of catheter-based techniques, this procedure is generally limited to patients who have refractory VT or who have recurrent VT and other indications for cardiac surgery, such as large aneurysms associated with heart failure or the need to implant a left ventricular assist device.

CLOSURE OF THE LEFT ATRIAL APPENDAGE

The left atrial appendage, where blood tends to stagnate, is by far the most common site of origin for thromboembolism in patients with AF. Occlusion, removal, or isolation of the left atrial appendage can protect patients from stroke and thromboembolic events. In patients who are not suitable candidates for long-term anticoagulation (typically due to a propensity for bleeding or to poor adherence), occlusion of the left atrial appendage is at least as efficacious and safe as persisting with anticoagulation.[A17] The most widely used technique deploys an endocardial occlusion device, inserted percutaneously via transeptal puncture to the ostium of the left atrial appendage. After endothelialization of the luminal surface, these devices generally do not require long-term anticoagulation. Risks include dislodgement, residual leaks, and device-related thrombus. In patients who have AF and are undergoing cardiac surgery for another indication, epicardial closure of the left atrial appendage (amputation, stapling, or clip) can significantly reduce the risk of ischemic stroke or systemic embolism compared with anticoagulation alone during a mean follow-up of nearly 4 years.[A18]

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55 CONGENITAL HEART DISEASE IN ADULTS

JUDITH THERRIEN AND ARIANE J. MARELLI

The convergence of major progress in medicine, pediatrics, and cardiovascular surgery has resulted in the survival of an increasingly large number of adult patients with congenital heart disease. An estimated 2.4 million people are currently living with congenital heart disease in the United States, two thirds of whom are adults. Adult care providers are becoming increasingly responsible for these patients, commonly in concert with a cardiologist and a tertiary care facility.

EPIDEMIOLOGY

Congenital heart defects are diagnosed in approximately 1% of births in the United States. An overall prevalence of 3 to 4 per 1000 adults has been documented. The median age of patients with *severe* lesions has increased from childhood to late adolescence. Advances in medical and surgical therapy have increased the survival of patients with congenital heart defects. Nearly 300,000 people in the United States are estimated to have severe congenital heart disease, defined as a combination of at least two or more abnormalities, typically associated with cyanosis at birth.

Bicuspid aortic valve occurs in about 2% of the general population, is the most common congenital cardiac anomaly encountered in adult populations, and accounts for up to half of surgical cases of aortic stenosis in adults (Chapter 60). Atrial septal defects (ASDs) constitute 30 to 40% of cases of congenital heart disease in adults, with ostium secundum ASD accounting for 7% of all congenital lesions. A solitary ventricular septal defect (VSD) represents 15 to 20% of all congenital lesions and is the most common lesion observed in children; its high spontaneous closure rates explain the lesser prevalence in adults. Patent ductus arteriosus (PDA) accounts for 5 to 10% of all congenital cardiac lesions in infants with a normal birthweight. Pulmonary stenosis and coarctation of the aorta represent 3 to 10% of all congenital lesions.

Tetralogy of Fallot is the most common cyanotic congenital anomaly observed in adults. Together with complete transposition of the great arteries, these lesions account for 5 to 12% of congenital heart disease in infants. More complex lesions, such as tricuspid atresia, univentricular heart, congenitally corrected transposition of the great arteries, Ebstein anomaly, and double-outlet right ventricle, account for 2.5% or less of all congenital heart disease.

PATHOBIOLOGY

Genetic Determinants

About 20% of congenital heart defects are associated with a syndrome or chromosomal anomaly, and the most common such chromosomal anomaly is Down syndrome (trisomy 21), in which about 50% of patients have defects of the endocardial cushions and the ventricular septum. VSDs also occur in 90% of patients with trisomy 13 and trisomy 18. The most frequently observed defects in patients with Turner syndrome (45,X) are aortic coarctation, aortic stenosis, and atrial septal defect. About 15% of patients with tetralogy of Fallot have a deletion on chromosome 22q11; prevalence is higher in those with a right aortic arch. Abnormalities involving the chromosomal band 22q11 can also result in a group of syndromes, the most common of which is DiGeorge syndrome. The shared phenotypic features are designated CATCH-22 syndromes, that is, a combination of *c*ardiac defects, *a*bnormal facies, *t*hymic

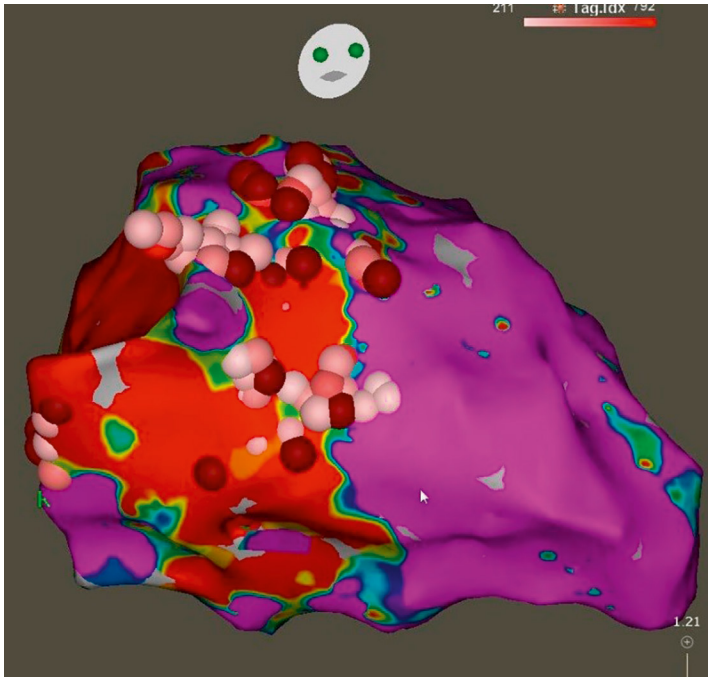

E-FIGURE 54-4. Voltage map of the left ventricle in a patient with ischemic cardiomyopathy and multiple ventricular tachycardias. Ablation of channels *(round tags)* within the anterior portion of a large anteroseptal scar (*red areas* of low voltage) was required to eliminate multiple ventricular tachycardias.

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ARRHYTHMIA SURGERY

ATRIAL FIBRILLATION

Surgical ablation of AF can involve isolation of the pulmonary vein or a full biatrial Maze procedure, in which a series of incisions or linear lesions created by cryoablation or radio frequency ablation subdivides the atria into smaller segments unlikely to sustain AF. The most common current indication for the Maze procedure is the treatment of symptomatic AF in patients undergoing other cardiac surgical procedures, such as coronary revascularization or valve replacement or repair. AF surgery added to mitral valve surgery significantly reduces the recurrence of AF in patients with persistent or long-standing persistent AF. A variety of simpler and even minimally invasive operative procedures have been developed for AF, but their long-term efficacy and role in the treatment of AF are still being defined.

VENTRICULAR TACHYCARDIA

Surgical treatment by subendocardial resection or cryoablation of scar tissue (Chapter 53) in patients with a prior myocardial infarction can eliminate VT in selected patients (E-Fig. 54-4), with a success rate of 85 to 90%, but it carries an operative mortality rate of 5 to 15% even in experienced centers. Because of this high mortality and the development of catheter-based techniques, this procedure is generally limited to patients who have refractory VT or who have recurrent VT and other indications for cardiac surgery, such as large aneurysms associated with heart failure or the need to implant a left ventricular assist device.

CLOSURE OF THE LEFT ATRIAL APPENDAGE

The left atrial appendage, where blood tends to stagnate, is by far the most common site of origin for thromboembolism in patients with AF. Occlusion, removal, or isolation of the left atrial appendage can protect patients from stroke and thromboembolic events. In patients who are not suitable candidates for long-term anticoagulation (typically due to a propensity for bleeding or to poor adherence), occlusion of the left atrial appendage is at least as efficacious and safe as persisting with anticoagulation.[A17] The most widely used technique deploys an endocardial occlusion device, inserted percutaneously via transeptal puncture to the ostium of the left atrial appendage. After endothelialization of the luminal surface, these devices generally do not require long-term anticoagulation. Risks include dislodgement, residual leaks, and device-related thrombus. In patients who have AF and are undergoing cardiac surgery for another indication, epicardial closure of the left atrial appendage (amputation, stapling, or clip) can significantly reduce the risk of ischemic stroke or systemic embolism compared with anticoagulation alone during a mean follow-up of nearly 4 years.[A18]

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55 CONGENITAL HEART DISEASE IN ADULTS

JUDITH THERRIEN AND ARIANE J. MARELLI

The convergence of major progress in medicine, pediatrics, and cardiovascular surgery has resulted in the survival of an increasingly large number of adult patients with congenital heart disease. An estimated 2.4 million people are currently living with congenital heart disease in the United States, two thirds of whom are adults. Adult care providers are becoming increasingly responsible for these patients, commonly in concert with a cardiologist and a tertiary care facility.

EPIDEMIOLOGY

Congenital heart defects are diagnosed in approximately 1% of births in the United States. An overall prevalence of 3 to 4 per 1000 adults has been documented. The median age of patients with *severe* lesions has increased from childhood to late adolescence. Advances in medical and surgical therapy have increased the survival of patients with congenital heart defects. Nearly 300,000 people in the United States are estimated to have severe congenital heart disease, defined as a combination of at least two or more abnormalities, typically associated with cyanosis at birth.

Bicuspid aortic valve occurs in about 2% of the general population, is the most common congenital cardiac anomaly encountered in adult populations, and accounts for up to half of surgical cases of aortic stenosis in adults (Chapter 60). Atrial septal defects (ASDs) constitute 30 to 40% of cases of congenital heart disease in adults, with ostium secundum ASD accounting for 7% of all congenital lesions. A solitary ventricular septal defect (VSD) represents 15 to 20% of all congenital lesions and is the most common lesion observed in children; its high spontaneous closure rates explain the lesser prevalence in adults. Patent ductus arteriosus (PDA) accounts for 5 to 10% of all congenital cardiac lesions in infants with a normal birthweight. Pulmonary stenosis and coarctation of the aorta represent 3 to 10% of all congenital lesions.

Tetralogy of Fallot is the most common cyanotic congenital anomaly observed in adults. Together with complete transposition of the great arteries, these lesions account for 5 to 12% of congenital heart disease in infants. More complex lesions, such as tricuspid atresia, univentricular heart, congenitally corrected transposition of the great arteries, Ebstein anomaly, and double-outlet right ventricle, account for 2.5% or less of all congenital heart disease.

PATHOBIOLOGY

Genetic Determinants

About 20% of congenital heart defects are associated with a syndrome or chromosomal anomaly, and the most common such chromosomal anomaly is Down syndrome (trisomy 21), in which about 50% of patients have defects of the endocardial cushions and the ventricular septum. VSDs also occur in 90% of patients with trisomy 13 and trisomy 18. The most frequently observed defects in patients with Turner syndrome (45,X) are aortic coarctation, aortic stenosis, and atrial septal defect. About 15% of patients with tetralogy of Fallot have a deletion on chromosome 22q11; prevalence is higher in those with a right aortic arch. Abnormalities involving the chromosomal band 22q11 can also result in a group of syndromes, the most common of which is DiGeorge syndrome. The shared phenotypic features are designated CATCH-22 syndromes, that is, a combination of *c*ardiac defects, *a*bnormal facies, *t*hymic

ABSTRACT

As a result of major advances in diagnosis and interventional therapy, there are now more adults than children living with congenital heart disease in the United States and other industrialized countries worldwide. More than 20 phenotypes range from defects between the atria, the ventricles, and the great arteries to well-recognized associations of defects such as tetralogy of Fallot and atrioventricular canal defects. Follow-up is often shared between internists and specialized adult congenital heart disease centers to ensure adequate surveillance for potential complications and timely interventions to prevent long-term morbidity and mortality. Common cardiovascular complications include arrhythmias, residual valvular dysfunction, heart failure, and infective endocarditis. Superimposed cardiovascular disease as a result of atherosclerosis increases the cumulative burden of heart disease. This chapter is a concise starting point for understanding the lifelong management of cardiovascular and systemic issues facing this growing group of patients and their caregivers.

KEYWORDS

congenital
heart defect
adult
cyanosis
hyperviscosity
operated
palliated

hypoplasia, cleft palate, and *h*ypocalcemia. For families with a child who carries a congenital cardiac malformation due to a chromosomal anomaly, the risk of the cardiac malformation in future children is related to the risk of recurrence of the chromosomal anomaly itself.

Typically, single mutant genes are also associated with syndromes of cardiovascular malformations, although not every patient with the syndrome has the characteristic cardiac anomaly. Examples include osteogenesis imperfecta (autosomal recessive; Chapter 239), associated with aortic valve disease; Jervell and Lange-Nielsen syndrome (autosomal recessive) and Romano-Ward syndrome (autosomal dominant), associated with a prolonged QT interval and sudden death; and Holt-Oram syndrome (autosomal dominant), in which an ASD occurs with a range of other skeletal anomalies. Osler-Weber-Rendu telangiectasias (Chapter 159) are associated with pulmonary arteriovenous fistulas. Williams syndrome (Chapters 31 and 32) occurs with supravalvular aortic stenosis in most cases. Noonan syndrome is associated with pulmonary stenosis, ASD, and hypertrophic cardiomyopathy. Although autosomal dominant inheritance has been implicated for both, most cases are sporadic. Deletion at chromosome 7q11.23 has been identified in patients with Williams syndrome, and a gene defect has been mapped to 12q22-qter in patients with Noonan syndrome (Chapter 47).

The risk for recurrence when the mother carries a sporadically occurring congenital lesion varies from 2.5 to 18%, depending on the lesion. Obstructive lesions of the left ventricular outflow tract have the highest recurrence rates in offspring. When the father carries the lesion, 1.5 to 3% of the offspring are affected. When a sibling has a congenital cardiac anomaly, the risk for recurrence in another sibling varies from 1 to 3%.

Genetic screening for the 22q11.2 microdeletion should be considered if patients with tetralogy of Fallot plan to have children. Without the 22q11 deletion, the risk of congenital heart disease in the fetus is 4 to 6%.

CLINICAL MANIFESTATIONS

History

Congenital heart disease is a lifelong condition during which the patient and the lesion evolve concurrently. The differential diagnosis of native and surgical anatomy in the adult with an unknown diagnosis depends on whether the patient is cyanotic or acyanotic. On completion of the evaluation, the following questions should be answered (Fig. 55-1): What is the native anatomy? Has this patient undergone surgery for the condition? What, if any, are the residual hemodynamic sequela?

Physical Examination

Physical examination of the heart and circulation includes the general physical appearance, the arterial pulse, the jugular venous pulse, the chest inspection, precordial percussion and palpation, and auscultation (Chapter 39).

Laboratory Investigations

A 12-lead electrocardiogram (ECG), chest radiograph, and baseline oxygen saturation should be part of every initial assessment. Two-dimensional transthoracic echocardiography (Chapter 43) and Doppler and color flow imaging are used to establish the diagnosis and to monitor the evolution of documented hemodynamic complications. Transesophageal echocardiographic examination is particularly useful in adults and is increasingly important during interventional catheter-guided therapy and surgery. Magnetic resonance imaging (Chapter 44) and computed tomography (Chapter 44) are useful adjuncts. Cardiac catheterization for congenital heart disease has shifted from pure diagnosis to include intervention. Coronary arteriography is recommended for adults older than 40 years in whom surgical intervention is contemplated.

SIMPLE LESIONS

ISOLATED SHUNT LESIONS

Hemodynamic complications of significant shunts relate to volume overload and chamber dilation of the primary chamber receiving the excess left-to-right shunt and to damage to the pulmonary vascular bed. The size and duration of the shunt determine the clinical course and therefore the indications for closure. The degree of shunting is a function of both the size of the communication and, depending on its location, biventricular compliance or pulmonary and systemic vascular resistance. Clinically apparent hemodynamic sequelae of shunts are typically apparent or can be expected to occur when pulmonary to systemic flow ratios, as inferred by Doppler echocardiography or measured by cardiac catheterization, exceed 1.5 : 1. Secondary enlargement of the cardiac chambers receiving excess shunt flow in diastole occurs if the shunt size is hemodynamically significant; in addition, the pulmonary artery becomes enlarged as pulmonary pressure rises.

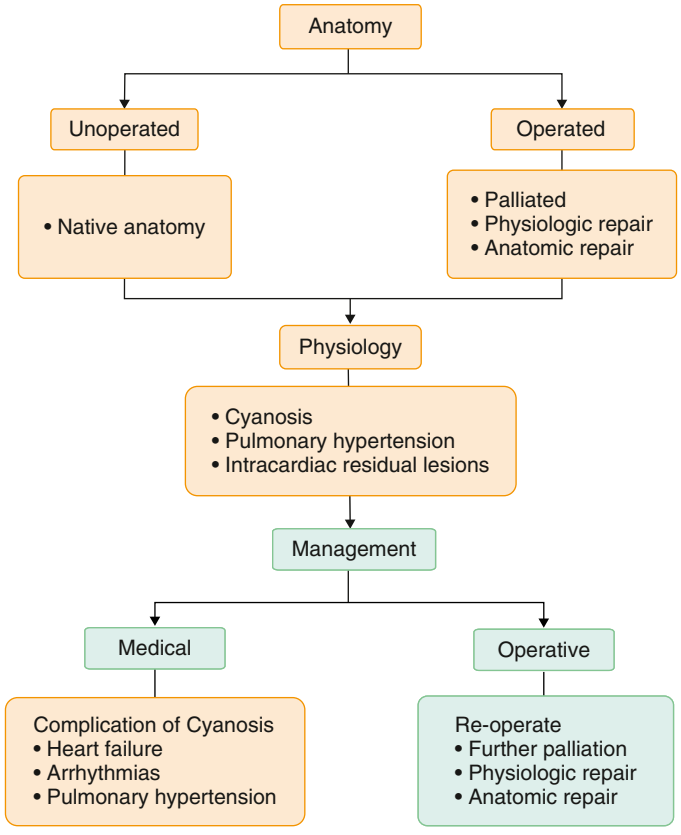

FIGURE 55-1. **The goals of complete clinical assessment in congenital heart disease are to define the anatomy and residual sequela to determine appropriate management and follow-up.**

PATENT FORAMEN OVALE AND ATRIAL SEPTAL DEFECT

Classification of ASDs is based on anatomic location. Most commonly, an ostium secundum ASD occurs in the central portion of the interatrial septum as a result of an enlarged foramen ovale or excessive resorption of the septum primum (Video 55-1). The combination of a secundum ASD and acquired mitral stenosis is known as *Lutembacher syndrome*, the pathophysiology of which is determined by the relative severity of each. Abnormal development of the embryologic endocardial cushions results in a variety of atrioventricular canal defects, the most common of which consists of a defect in the lower part of the atrial septum in the ostium primum location, typically accompanied by a cleft mitral valve and mitral regurgitation. The sinus venosus defect, which accounts for 2 to 3% of all interatrial communications, is located superiorly at the junction of the superior vena cava and right atrium and is generally associated with anomalous drainage of the right-sided pulmonary veins into the superior vena cava or right atrium. Less commonly, interatrial communications can be seen at the site of the coronary sinus, typically associated with an anomalous left superior vena cava.

The pathophysiology is determined by the effects of the shunt on the heart and pulmonary circulation. Right atrial and right ventricular dilation occurs as shunt size increases with pulmonary to systemic flow ratios greater than 1.5 : 1. Superimposed systemic hypertension and coronary artery disease modify left ventricular compliance and favor left-to-right shunting. Mitral valve disease can occur in up to 15% of patients older than 50 years. Right-sided heart failure, atrial fibrillation, or atrial flutter can occur as a result of chronic right-sided volume overload and progressive ventricular and atrial dilation. Stroke can result from paradoxical emboli, atrial arrhythmias, or both. A rise in pulmonary pressure occurs because of the increased pulmonary blood flow. Pulmonary hypertension is unusual before 20 years of age but is seen in 50% of patients older than 40 years. The overall incidence of pulmonary vascular obstructive disease is 15 to 20% in patients with ASD. Eisenmenger complex (see later) with reverse shunting, a late and rare complication of isolated secundum ASD, is reported in 5 to 10% of patients.

Up to 30% of adults have evidence of a pink-patent foramen ovale without hemodynamic evidence of shunt at rest. Clinical studies have demonstrated that the prevalence of patent foramen ovale is three times higher in patients with cryptogenic stroke (Chapter 376), particularly before the age of 55 years, because of right-to-left shunting and paradoxical embolization of material from the venous circulation.

DIAGNOSIS

Atrial Septal Defect

Although most ASDs are minimally symptomatic in the first three decades, more than 70% become impaired by the fifth decade.[1] Initial symptoms include exercise intolerance, dyspnea on exertion, and fatigue caused most commonly by right-sided heart failure and pulmonary hypertension. Palpitations, syncope, and stroke can occur with the development of atrial arrhythmias.

Precordial palpation typically discloses a normal left ventricular impulse unless the patient also has mitral valve disease. If the patient has a significant left-to-right shunt, the right ventricular impulse usually can be felt in the left parasternal area in end expiration or in the subxiphoid area in end inspiration. A dilated pulmonary artery can sometimes be felt in the second left intercostal space. On auscultation, the hallmark of an ASD is the wide and fixed splitting of the second heart sound, because the increase in venous return elevates the right atrial pressure during inspiration, thereby decreasing the degree of left-to-right shunting and offsetting the usual phasic respiratory changes. Pulmonary valve closure, as reflected by P_2, is delayed because of right ventricular overload and the increased capacitance of the pulmonary vascular bed. A soft midsystolic murmur generated by the increased flow across the pulmonary valve is usually heard in the second left interspace. In the presence of a high left-to-right shunt volume, increased flow across the tricuspid valve is heard as a mid-diastolic murmur at the lower left sternal border. With advanced right-sided heart failure, evidence of systemic venous congestion is present.

The ECG characteristically shows an incomplete right bundle branch block pattern (Fig. 55-2). Right axis deviation and atrial abnormalities, including a prolonged PR interval, atrial fibrillation, and flutter, are also seen. Typically, the chest radiograph shows pulmonary vascular plethora with increased markings in both lung fields consistent with increased pulmonary blood flow (see Fig. 44-6). The main pulmonary artery and both its branches are dilated. Right atrial and right ventricular dilation can be seen. Echocardiography is diagnostic and provides important prognostic information (E-Fig. 55-1). Ostium primum and secundum ASDs are easily identifiable with transthoracic imaging, but a sinus venosus ASD can be missed unless it is specifically sought. With Doppler study, pulmonary artery pressures can be quantified, and the interatrial shunt ratio can be estimated.

Patent Foramen Ovale

A patent foramen ovale without a resting shunt is not detectable on physical examination and is not associated with ECG abnormalities. The diagnosis is established by transesophageal Doppler echocardiography accompanied by injections of agitated saline to detect a right-to-left shunt during the Valsalva maneuver (Chapter 39).

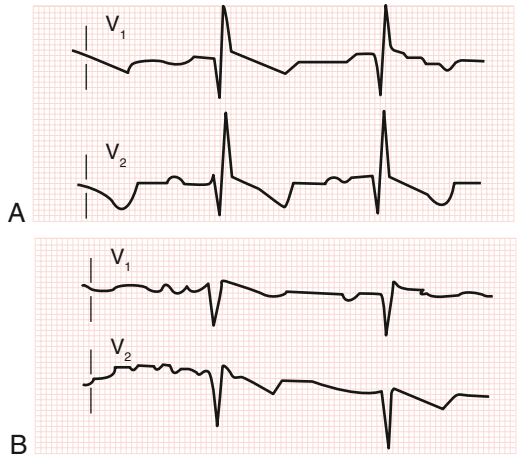

FIGURE 55-2. Electrocardiographic hallmark in atrial septal defect. Right precordial leads V_1 and V_2 illustrate two variants of an incomplete right bundle branch block pattern, the rSrT pattern (**A**) and the rsR′ pattern (**B**).

TREATMENT AND PROGNOSIS

Closure of an ASD, either percutaneously or surgically, is indicated in the presence of right-sided heart enlargement, with or without symptoms. In patients older than 40 years with symptoms and significant shunts, closure improves functional status and survival. A centrally located ASD or patent foramen ovale measuring up to 3.5 cm can be occluded by transcatheter techniques in a cardiac catheterization laboratory.[1,2] Advantages of this approach include the avoidance of sternotomy and cardiopulmonary bypass.[A1] Surgical closure is usually reserved for patients in whom concomitant repair of associated valvular anomalies is required, anomalous pulmonary veins are present, or device closure is not technically feasible.

In the presence of a significant shunt, closure of an ASD before 25 years of age without evidence of pulmonary hypertension results in a long-term outcome that is similar to that of age- and sex-matched controls. Advanced age (60 years) is not a contraindication to ASD closure in the presence of a significant shunt because a significant number of patients will show evidence of symptomatic improvement, although such late closure may not improve longevity.[3] Preoperative pulmonary artery pressure and the presence or absence of pulmonary vascular disease are important predictors of successful interventional outcome.

In patients who have had a cryptogenic stroke,[4] the presence of an atrial septal aneurysm may be more predictive of recurrent stroke than the size of the shunt.[5] Percutaneous closure of a patent foramen reduces the risk of recurrent stroke and chronic anticoagulations at the expense of a higher rate of periprocedure complications,[A2-A5] and closure is commonly recommended if the infarct appears to be embolic and no other cause can be identified.[6] A residual shunt after closure portends a higher risk of future stroke, with the risk generally proportional to the magnitude of the residual shunt.[7] By comparison, closure of a patent foramen ovale is not recommended as a treatment for migraine headache (Chapter 367).[8]

VENTRICULAR SEPTAL DEFECT

For anatomic classification of VSDs, the interventricular septum can be divided into four regions. Defects of the membranous septum, or infracristal VSDs, are located in a small translucent area beneath the aortic valve and account for up to 80% of VSDs. These VSDs typically show a variable degree of extension into the inlet or outlet septum, hence their designation as perimembranous (Video 55-2). Infundibular defects or supracristal outlet VSDs occur in the conal septum above the crista supraventricularis and below the pulmonary valve. Inlet defects are identified at the crux of the heart between the tricuspid and mitral valves and are usually associated with other anomalies of the atrioventricular canal. Defects of the trabecular or muscular septum can be multiple and occur distal to the septal attachment of the tricuspid valve and toward the apex.

Approximately half of all native VSDs are small, and more than half of them close spontaneously; moderate or even large VSDs may also close in 10% or less of cases. The highest closure rates are observed in the first decade of life; spontaneous closure in adult life is unusual.

Patients who have a small defect with trivial or mild shunts are defined as those with a shunt of less than 1.5 and normal pulmonary artery pressure and vascular resistance. Minimal or mild defects usually cause no significant hemodynamic or physiologic abnormality.

Patients with moderate defects have a shunt ratio of greater than 1.2, with elevated pulmonary artery pressure but not elevated pulmonary vascular resistance. Patients with a large and severe defect have an elevated left-to-right shunt (1.5 : 1 or higher) with high pulmonary pressure and elevated pulmonary vascular resistance. A moderate or severe defect causes left atrial and ventricular dilation consistent with the degree of left-to-right shunting. Shunting across the ventricular septum occurs predominantly during systole when left ventricular pressure exceeds that on the right; diastolic filling abnormalities occur in the left atrium. With moderate or severe defects, the right side of the heart becomes affected as a function of the rise in pulmonary artery pressure and pulmonary blood flow.

Eisenmenger complex develops in about 10% of patients with VSDs, usually when there is no resistance to flow at the level of the defect, which can be as large as the aorta. When a systolic pressure gradient is present between the ventricles, the physiologic severity may be trivial or mild but can also be moderate or severe.

DIAGNOSIS

An adult with a VSD most commonly has a small restrictive lesion that either was small at birth or has undergone some degree of spontaneous closure. Patients with a trivial or mild shunt across a small, restrictive VSD are usually asymptomatic. Physical examination discloses no evidence of systemic or

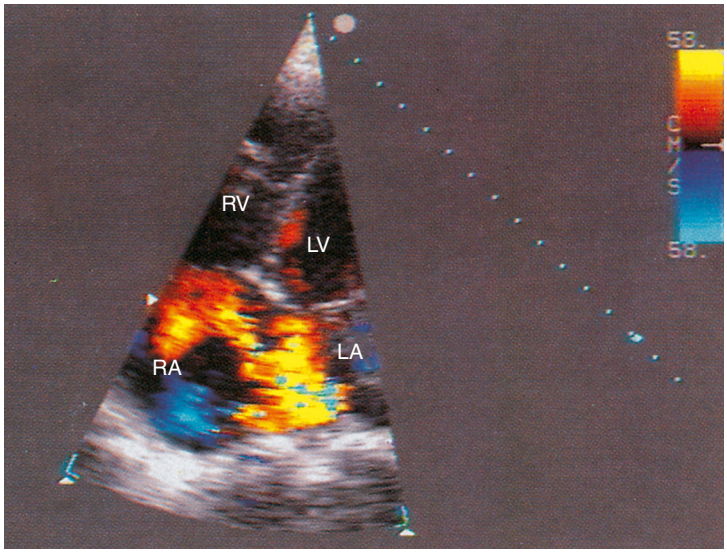

E-FIGURE 55-1. Color flow Doppler apical four-chamber view showing blood flow from the left atrium (LA) to the right atrium (RA) through a moderately sized atrial septal defect. LV = left ventricle; RV = right ventricle. (From Forbes CD, Jackson WF. *Color Atlas and Text of Clinical Medicine*. 3rd ed. London: Mosby; 2003.)

pulmonary venous congestion, and jugular venous pressure is normal. A thrill may be palpable at the left sternal border. Auscultation reveals normal S_1 and S_2 without gallops. A grade 4 or louder, widely radiating, high-frequency, pansystolic murmur is heard maximally in the third or fourth intercostal space and reflects the high-pressure gradient between the left and right ventricles throughout systole. The striking contrast between a loud murmur and otherwise normal findings on cardiac examination is an important diagnostic clue. The ECG and chest radiograph are also normal in patients with small VSDs.

Patients with moderately sized VSDs typically are symptomatic as children and are therefore more likely to have repair at a young age. Adults with large, nonrestrictive VSDs that have not been operated on typically have had Eisenmenger complex for most of their lives. If not, they usually have a combination of pulmonary hypertension and left-sided volume overload resulting from a significant left-to-right shunt. Such patients are rarely seen today in developed countries but may still be encountered in the developing world.

In adults, shortness of breath on exertion can be the result of both pulmonary venous congestion and elevated pulmonary pressure. On physical examination, a diffuse palpable left ventricular impulse occurs with a variable degree of right ventricular hypertrophy and an accentuated second heart sound. A systolic murmur persists as long as pulmonary vascular resistance is below systemic resistance. The ECG commonly shows left atrial enlargement and left ventricular hypertrophy. The chest radiograph shows shunt vascularity with an enlarged left atrium and ventricle. The degree of pulmonary hypertension determines the size of the pulmonary artery trunk.

Echocardiography can identify the defect and determine the significance of the shunt by assessing left atrial and ventricular size, pulmonary artery pressure, and presence or absence of right ventricular hypertrophy. Cardiac catheterization is reserved for those in whom surgery is considered. Adults with a small defect of no physiologic significance need not be studied invasively. Those with Eisenmenger complex have severe pulmonary vascular disease and are not surgical candidates. Patients who have a moderately sized shunt that appears hemodynamically significant and in whom pulmonary pressures are elevated are most likely to benefit from direct measurements of pulmonary vascular resistance and reactivity.

TREATMENT AND PROGNOSIS

Patients with Eisenmenger complex have pulmonary vascular resistance that is prohibitive to surgery. For this group of patients, management centers on the medical complications of cyanosis (see later). In a few patients with small defects, complications can relate to progressive tricuspid insufficiency caused by septal aneurysm formation or to acquired aortic insufficiency when an aortic cusp becomes engaged in the high-velocity jet flow generated by the defect. The intermediate group of patients with a defect of moderate physiologic significance should have their VSDs closed unless closure is contraindicated by high pulmonary vascular resistance. For a perimembranous VSD, transcatheter closure is as effective as open surgical closure and has a lower rate of minor adverse events.[9]

Cumulative survival, which is about 85% at 40 years, is slightly lower than in the general population. Cumulative event-free survival after surgery is about 70% at 40 years, and a concomitant cardiac lesion (e.g., patent ductus arteriosus) and aortic cross-clamp time are determinants of late events. Late results after operative closure of isolated VSDs include residual patency in up to 20% of patients, only about 5% of whom need a reoperation. Rhythm disturbances after surgical closure of VSDs include tachyarrhythmias and conduction disturbances. Right bundle branch block occurs in one third to two thirds of patients, whereas first-degree atrioventricular block and complete heart block occur in less than 10%. Sudden cardiac death after surgical repair of VSD occurs in 2% of patients.

PATENT DUCTUS ARTERIOSUS

The ductus arteriosus connects the descending aorta to the main pulmonary trunk near the origin of the left subclavian artery (E-Fig. 55-2). Normal postnatal closure results in fibrosis and degenerative changes in the ductal lumen, leaving in its place the residual ligamentum arteriosum, which rarely can become part of an abnormal vascular ring.

The physiologic consequences of a PDA are determined by its size and length as well as by the ratio of pressure and resistance of the pulmonary and aortic circulations on either end of the duct. If systolic and diastolic pressure in the aorta exceeds that in the pulmonary artery, aortic blood flows continuously down a pressure gradient into the pulmonary artery and then returns to the left atrium. The left atrium and subsequently the left ventricle dilate, whereas the right side of the heart becomes progressively affected as pulmonary hypertension develops.

A small PDA has continuous flow throughout the entire cardiac cycle without left-sided heart dilation, pulmonary hypertension, or symptoms. However, patients with a small PDA develop infectious endarteritis at a rate of about 0.45% per year after the second decade, and closure should be considered.

A PDA is of moderate or large size but still restrictive when a left-to-right shunt occurs throughout systole and diastole is of variable duration. Left atrial or ventricular dilation and pulmonary hypertension will vary with the quantity of left-to-right shunting, as well as with the secondary effects on the pulmonary vascular bed. Symptoms generally increase by the second and third decades and include dyspnea, palpitations, and exercise intolerance. As heart failure, pulmonary hypertension, or endarteritis develops, mortality rises to 3 to 4% per year by the fourth decade, and two thirds of patients die by 60 years of age. Eisenmenger complex with systemic or suprasystemic pulmonary pressure and a right-to-left shunt develops in 5% of patients with an isolated PDA.

DIAGNOSIS

In patients with Eisenmenger physiology, a right-to-left shunt from the pulmonary artery to the descending aorta results in decreased oxygen saturation in the lower extremities compared with the upper extremities. This difference in cyanosis and clubbing is most prominent in the toes. With a large left-to-right shunt, the pulse pressure widens as diastolic flow into the pulmonary artery lowers systemic diastolic pressure. The arterial pulse becomes bounding as a result of increased stroke volume. Precordial palpation discloses variable left and right ventricular impulses as determined by the relative degree of left-sided volume overload and pulmonary hypertension. In the presence of a continuous aortopulmonary gradient, the classic "machinery" murmur of a PDA can be heard at the first or second left intercostal space below the left clavicle. As the pulmonary pressure rises, the diastolic component of the murmur becomes progressively shorter. With the development of Eisenmenger physiology and equalization of aortic and pulmonary pressure, the entire murmur may disappear, and the clinical findings are dominated by pulmonary hypertension.

In older patients, the chest radiograph shows calcification at the location of the PDA. Characteristically, the ascending aorta and pulmonary artery are dilated, and the left-sided chambers are enlarged. Echocardiography may not directly visualize the PDA but can accurately identify it by a Doppler signal that often parallels the length of the murmur. Cardiac catheterization to assess pulmonary vascular resistance is commonly indicated before closure.

TREATMENT AND PROGNOSIS

Ibuprofen can accelerate the closure of PDA in premature infants but may not reduce the need for an interventional procedure to eliminate the shunt.[A6] After ligation of a PDA in infancy or early childhood, cardiac function is commonly normal, and no special follow-up is required. If pulmonary artery pressure and pulmonary vascular resistance are substantially elevated, preoperative evaluation should assess the degree of reversibility. With Eisenmenger complex, closure is contraindicated. Closure of a PDA either percutaneously or surgically is indicated in the presence of left-sided heart enlargement or if prior endarteritis has occurred. Reported operative mortality rates vary from less than 1 to 8%, depending on the presence of calcification and the degree of pulmonary hypertension. Transcatheter or coil occlusion is an accepted procedure in adults. Residual shunt rates vary from 0.5 to 8%, depending on the device used.

PULMONARY ARTERIOVENOUS FISTULAS

Pulmonary arteriovenous fistulas can occur as isolated congenital disorders or as part of generalized hereditary hemorrhagic telangiectasia (Osler-Weber-Rendu syndrome; Chapter 159). These fistulas typically occur in the lower lobes or the right middle lobe and can be small or large, single or multiple. The arterial supply usually comes from a dilated, tortuous branch of the pulmonary artery.

The most common finding is that of abnormal opacity on a chest radiograph in a patient with buccal ruby patches or in an otherwise healthy adult who has mild cyanosis. Shunting between deoxygenated pulmonary arterial blood and the oxygenated pulmonary venous blood results in a physiologic right-to-left shunt. The degree of shunting is typically small and not significant enough to result in dilation of the left atrium and ventricle. Heart failure is unusual. Hemoptysis can result if a fistula ruptures into a bronchus. In patients with hereditary hemorrhagic telangiectasia, angiomas occur on the lips and mouth as well as in the gastrointestinal tract and on pleural, liver, and vaginal surfaces. Epistaxis is most common, but cerebrovascular accidents can also occur. Patients with hereditary hemorrhagic telangiectasia can have symptoms that resemble those of a transient ischemic attack even in the absence of right-to-left shunting. On physical examination, cyanosis and clubbing can be notable or barely detectable. Auscultation

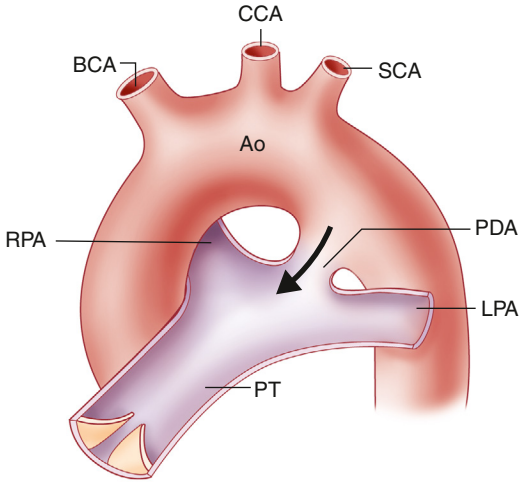

E-FIGURE 55-2. Anatomy of a patent ductus arteriosus. Note the relationships of the position of the ductus, left subclavian artery, and pulmonary artery bifurcation. Ao = aorta; BCA = brachiocephalic; CCA = common carotid artery; LPA = left pulmonary artery; PDA = patent ductus arteriosus; PT = pulmonary trunk; RPA = right pulmonary artery; SCA = subclavian artery. (From Perloff JK, ed. *Clinical Recognition of Congenital Heart Disease*. 4th ed. Philadelphia: WB Saunders; 1994:510.)

can disclose soft systolic or continuous noncardiac murmurs on the chest wall adjacent to the fistula. The murmur typically increases with inspiration. The ECG is usually normal. The chest radiograph shows one or more densities, typically in the lower lobes or in the right middle lobe. An echocardiogram can confirm the presence of the fistula by showing early opacification of the left atrium in the absence of any other intracardiac communication when saline is injected into a peripheral vein. The absence of a hemodynamically significant shunt can be confirmed by documenting normal cardiac chamber size.

If the hypoxemia is progressive or if a neurologic complication is documented to have occurred because of paradoxical emboli, fistula closure should be considered.[10] Options include percutaneous catheter techniques (e.g., embolization) if the fistula is small and accessible or a pulmonary wedge resection or lobectomy if the fistula is large. Multiple or recurrent fistulas create a major therapeutic challenge.

ISOLATED OBSTRUCTIVE LESIONS OF THE RIGHT AND LEFT VENTRICULAR OUTFLOW TRACT

Complications of obstructive lesions of the outflow tract relate to the secondary effects of exposure to pressure overload in the chamber proximal to the obstruction. The inability to increase systemic or pulmonary blood flow in the face of a fixed obstruction can cause exercise intolerance, inadequate myocardial perfusion, ventricular arrhythmias, and sudden death.

RIGHT VENTRICULAR OUTFLOW TRACT OBSTRUCTION

Obstruction of the right ventricular outflow tract can occur at the level of the pulmonary valve (see later), above it in the main pulmonary artery or its branches, or below it in the right ventricle itself. Supravalvular and branch pulmonary artery stenoses are important and common complications in patients with tetralogy of Fallot (see later). Residual supravalvular pulmonary stenosis is sometimes seen after palliative pulmonary artery banding to decrease pulmonary blood flow in patients with large left-to-right shunts. Congenital branch pulmonary artery stenosis can occur in isolation or with valvular pulmonary stenosis, shunt lesions, or a variety of syndromes.

VALVULAR PULMONARY STENOSIS

Isolated congenital valvular pulmonary stenosis (Chapter 60) is a common lesion due to a bicuspid valve in 20% of cases, a dysplastic valve caused by myxomatous changes and severe thickening in 10% of cases, and an abnormal trileaflet valve in most of the remaining cases. Fusion of the leaflets results in a variable degree of thickening and calcification in older patients.

DIAGNOSIS

A patient with moderate or even severe pulmonary stenosis may be asymptomatic. With severe stenosis, exercise intolerance can be associated with presyncope and ventricular arrhythmias. Progressive right-sided heart failure is the most common cause of death. On physical examination of patients with significant pulmonary stenosis, jugular venous pressure has a dominant *a* wave, reflecting a noncompliant right ventricle. Palpation discloses a sustained parasternal lift of right ventricular hypertrophy. An expiratory systolic ejection click is characteristic if the leaflets are still mobile. In moderate or severe stenosis, a grade 3 or louder systolic murmur can be heard and felt in the second left interspace. The length of the murmur increases as it peaks progressively later in systole with an increasing degree of obstruction. If right-sided heart failure occurs, tricuspid insufficiency and systemic venous congestion develop. The ECG can show right axis deviation and tall, peaked right atrial P waves in lead II. With more than mild stenosis, the R wave exceeds the S wave in lead V_1. On chest radiography, the main pulmonary artery can be dilated even if the stenosis is mild. Characteristically, the left pulmonary artery is more dilated than the right because of the leftward direction of the high-velocity jet. A variable degree of right ventricular hypertrophy is manifested as right-sided chamber enlargement. Echocardiography can establish the diagnosis and determine the severity by Doppler ultrasound examination, so cardiac catheterization is not required.

TREATMENT AND PROGNOSIS

The 25-year survival of patients with valvular pulmonary stenosis is greater than 95%. For patients with mild (<50 mm Hg gradients) and moderate (50 to 80 mm Hg gradients) pulmonary stenosis, bacterial endocarditis, complex ventricular arrhythmias, and progression of the stenosis are uncommon.

Depending on symptoms, percutaneous balloon valvotomy should be considered for patients with isolated valvular pulmonary stenosis and mean Doppler gradients of 30 mm Hg or greater unless there is moderate or severe pulmonary regurgitation. In the presence of a doming valve, pulmonary valvuloplasty is the procedure of choice for adults,[11] who achieve persistently good results at 10-year follow-up. When valvuloplasty cannot be performed or is unsuccessful, transcatheter pulmonary valve replacement provides good hemodynamic and clinical outcomes for at least 7 years after implantation. For patients with hypoplastic pulmonary arteries or subvalvular stenosis (double-chambered right ventricle), surgical resection of right ventricular muscle bands can be performed.

LEFT VENTRICULAR OUTFLOW TRACT OBSTRUCTION

Stenosis of the left ventricular outflow tract can occur at, below, or above the aortic valve. Discrete subaortic stenosis, most commonly caused by a fibromuscular ring just below the valve, accounts for 15 to 20% of all cases of congenital obstruction of the left ventricular outflow tract. Concomitant aortic insufficiency occurs in 50% of cases. Supravalvular aortic stenosis results from thickened media and intima above the aortic sinuses; early coronary atherosclerosis or even ostial coronary obstruction can occur.

CONGENITAL VALVULAR AORTIC STENOSIS

The normal aortic valve has three cusps and commissures. A unicuspid aortic valve accounts for most cases of severe aortic stenosis in infants (Chapter 60). A bicuspid aortic valve, which occurs in about 0.8% of infants[12] and is the most common congenital cardiac malformation, functions normally at birth but often becomes gradually obstructed as calcific and fibrous changes occur.

DIAGNOSIS

Symptoms include angina, exertional dyspnea, presyncope, and syncope and may progress to heart failure. The auscultatory hallmark of a bicuspid aortic valve in an adolescent or young adult is an audible systolic ejection click that is typically of a higher pitch than the first heart sound and is best heard not at the cardiac base but at the apex. The sound is caused by sudden movement of the stenotic valve as it moves superiorly in systole and is followed by the typical aortic stenosis murmur (Chapter 60). When significant calcification of the valve results in reduced mobility, the ejection sound is no longer heard. The diagnosis is easily confirmed by two-dimensional echocardiography, with which the number and orientation of aortic cusps can readily be identified.

TREATMENT AND PROGNOSIS

Conservative management is generally indicated for mild stenosis with a peak gradient of less than 25 mm Hg, but close supervision is required because 20% of these patients require an intervention during long-term follow-up. Unlimited athletic participation is allowed only for asymptomatic patients with peak gradients of less than 20 to 25 mm Hg, a normal ECG, and a normal exercise test result. Aortic valvuloplasty can be considered in young adults, but calcification limits its success, and valve replacement is usually required (Chapter 60). For adults, treatment decisions are similar to those for aortic stenosis from other causes. For patients with subvalvular aortic stenosis, surgical intervention is indicated in the presence of peak gradients above 50 mm Hg, symptoms, or progressive significant aortic insufficiency.

The estimated overall 25-year survival rate for patients with congenital valvular aortic stenosis diagnosed in childhood is 85%. Children with initial peak cardiac catheterization gradients of less than 50 mm Hg have long-term survival rates of higher than 90%, as opposed to survival rates of 80% in those with gradients of 50 mm Hg or greater.

COARCTATION OF THE AORTA

Aortic coarctation typically occurs just distal to the left subclavian artery at the site of the aortic ductal attachment or its residual ligamentum arteriosum. Less commonly, the coarctation ridge lies proximal to the left subclavian. A bicuspid aortic valve is the most common coexisting anomaly, but VSDs and PDAs are also seen.

The most common complications of aortic coarctation are systemic hypertension (Chapter 64) and secondary left ventricular hypertrophy with heart failure. Heart failure occurs most commonly in infants and then after 40 years of age. The high pressure proximal to the obstruction stimulates the growth of collateral vessels from the internal mammary, scapular, and superior intercostal arteries to the intercostals of the descending aorta. Collateral circulation increases with age and contributes to perfusion of the lower extremities and

the spinal cord. Aneurysms occur most notably in the ascending aorta and in the circle of Willis. Premature coronary disease is thought to be related to the resulting hypertension. Complications, including bacterial endarteritis at the coarctation site or, more commonly, endocarditis at the site of a bicuspid aortic valve, cerebrovascular complications, myocardial infarction, heart failure, and aortic dissection, occur in 2 to 6% of patients, more frequently in those with advancing age who have not undergone surgery.

DIAGNOSIS

Young adults may be asymptomatic with incidental systemic hypertension and decreased lower extremity pulses. Coarctation should always be considered in adolescents and young adult men with unexplained upper extremity hypertension. The pressure differential can cause epistaxis, headaches, leg fatigue, or claudication. Older patients have angina, symptoms of heart failure, and vascular complications.

On physical examination, the lower half of the body is typically slightly less developed than the upper half. Blood pressure measurements should be obtained in each arm and one leg; an abnormal measurement is an increase of less than 10 mm Hg in popliteal systolic blood pressure compared with arm systolic blood pressure. The diastolic pressure should be the same in the upper and lower extremities. A pressure differential of more than 30 mm Hg between the right and the left arms is consistent with compromised flow in the left subclavian artery. Right brachial palpation characteristically reveals a strong or even bounding pulse compared with a slowly rising or absent femoral, popliteal, or pedal pulse. Examination of the eyegrounds can reveal tortuous or corkscrew retinal arteries. Precordial palpation is consistent with left ventricular pressure overload. On auscultation, a systolic ejection sound reflecting the presence of a bicuspid aortic valve should be sought. The coarctation itself generates a systolic murmur heard posteriorly, in the midthoracic region, the length of which correlates with the severity of the coarctation. Over the anterior of the chest, systolic murmurs reflecting increased collateral flow can be heard in the infraclavicular areas and the sternal edge or in the axillae.

In adult coarctation, the most common finding on the ECG is left ventricular hypertrophy. On the chest radiograph, the location of the coarctation segment between the dilated left subclavian artery above and the leftward convexity of the descending aorta below results in the "3 sign" (Fig. 55-3). Bilateral rib notching as a result of dilation of the posterior intercostal arteries is seen on the posterior of the third to eighth ribs when the coarctation is below the left subclavian artery. Unilateral rib notching sparing the left ribs is observed when the coarctation occurs proximal to the left subclavian artery. Transthoracic echocardiography documents the gradient in the descending aorta and determines the presence of left ventricular hypertrophy. Magnetic resonance imaging (Chapter 44) is the best modality for visualizing the anatomy of the descending aorta. Cardiac catheterization should measure pressures and assess collaterals when surgery is contemplated.

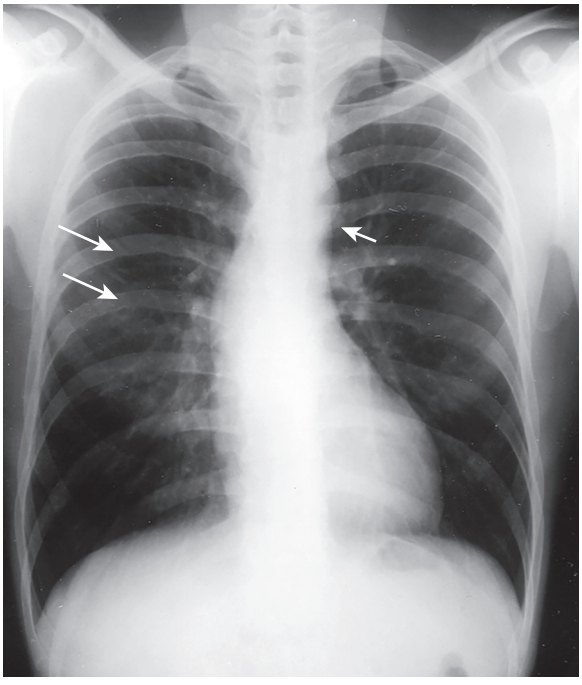

FIGURE 55-3. Chest radiograph of a patient with coarctation of the aorta. The radiographic "3 sign" formed by the dilated subclavian artery above and the dilated aorta below (*short arrow*) is shown. Note the notching, best seen at the level of the seventh and eighth ribs (*long arrows*). The dilated ascending aortic segment can also be seen.

TREATMENT AND PROGNOSIS

Intervention, typically catheter-based in adults,[13] is recommended in patients who have systemic hypertension with a peak gradient of 20 mm Hg or more on cardiac catheterization or who have evidence of significant collateral flow on imaging studies. Fifty percent of patients repaired when they are older than 40 years have residual hypertension, whereas those who have undergone surgery between the ages of 1 and 5 years have a less than 10% prevalence of hypertension on long-term follow-up.

ANOMALIES OF THE SINUSES OF VALSALVA AND CORONARY ARTERIES

SINUS OF VALSALVA ANEURYSMS

At the base of the aortic root, the aortic valve cusps are attached to the aortic wall, above which three small pouches, or sinuses, are seated. The right coronary artery originates from one sinus and the left main coronary artery from a second; the third is called the *noncoronary sinus*. A weakness in the wall of the sinus can result in aneurysm formation with or without rupture. In more than 90% of cases, the aneurysm involves the right or noncoronary cusp. Rupture typically occurs into the right side of the heart at the right atrial or ventricular level with a resulting large left-to-right shunt driven by the high aortic pressure.

A previously asymptomatic young man typically has chest pain and rapidly progressing shortness of breath sometimes after physical strain. The physical examination is consistent with significant heart failure. Even if the communication is between the aorta and the right side of the heart, biventricular failure is not unusual. The classic murmur is loud and continuous, often with a thrill. A murmur of aortic insufficiency secondary to damage to the adjacent aortic valve may be superimposed. The chest radiograph shows volume overload of both ventricles with evidence of shunt vascularity and pulmonary venous congestion. The echocardiogram is diagnostic. Cardiac catheterization can verify the integrity of the coronary artery adjacent to the ruptured aneurysm.

Even though symptoms may abate as the heart dilates, progressive cardiac decompensation typically results in death within 1 year of the rupture. A ruptured sinus of Valsalva aneurysm therefore requires urgent surgical repair.

CORONARY ARTERY FISTULAS

Fistulas arise from the right or left coronary arteries and in 90% of cases drain into the right ventricle, the right atrium, or the pulmonary artery in order of decreasing frequency. Typically, young patients are asymptomatic, but supraventricular arrhythmias are seen with progressive dilation of the intracardiac chambers. Angina can occur as the fistula creates a coronary steal by diverting blood away from the myocardium. Heart failure is seen with large fistulas. A continuous murmur heard in a young, otherwise normal acyanotic, asymptomatic patient should suggest the diagnosis. Most fistulas are associated with a small shunt, and hence the murmur is often less than grade 3 and is heard in the precordial area. Unless the shunt is large, the ECG is normal, as is the chest radiograph. The echocardiogram, especially the transesophageal echocardiogram, is diagnostic. Percutaneous transcatheter closure with coil embolization is preferred, but surgical ligation is also an alternative.

ANOMALOUS ORIGIN OF THE CORONARY ARTERIES

The left main coronary artery normally arises from the left sinus of Valsalva and courses leftward, posterior to the right ventricular outflow tract. The right coronary artery arises from the right sinus of Valsalva and courses rightward to the right ventricle. Isolated ectopic or anomalous origins of the coronary arteries (see Fig. 55-4) are seen in 0.6 to 1.5% of patients undergoing coronary angiography.[14]

The most common anomaly is ectopic origin of the left circumflex artery from the right sinus of Valsalva, followed by anomalous origin of the right coronary artery from the left sinus and anomalous origin of the left main coronary artery from the right sinus. If the anomalous coronary artery does not course between the pulmonary artery and aorta, the prognosis is favorable.

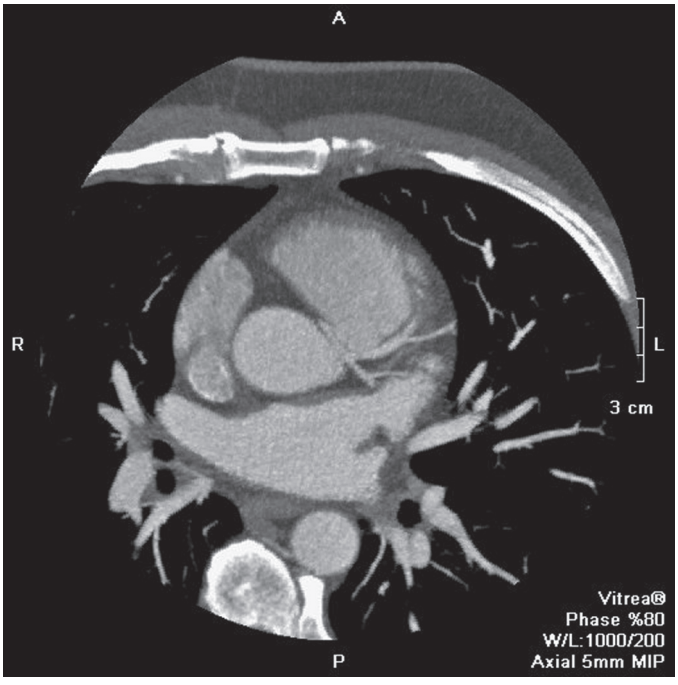

FIGURE 55-4. **Frame from a computed tomographic angiographic study showing the origin of the left main coronary artery arising from the right sinus of Valsalva and coursing anteriorly between the aorta and pulmonary artery.** (From Kern MJ, Kirtane AJ. Catheterization and angiography. In: Goldman L, Schafer AI, eds. *Goldman-Cecil Medicine*. 26th ed. Philadelphia: Elsevier; 2020.)

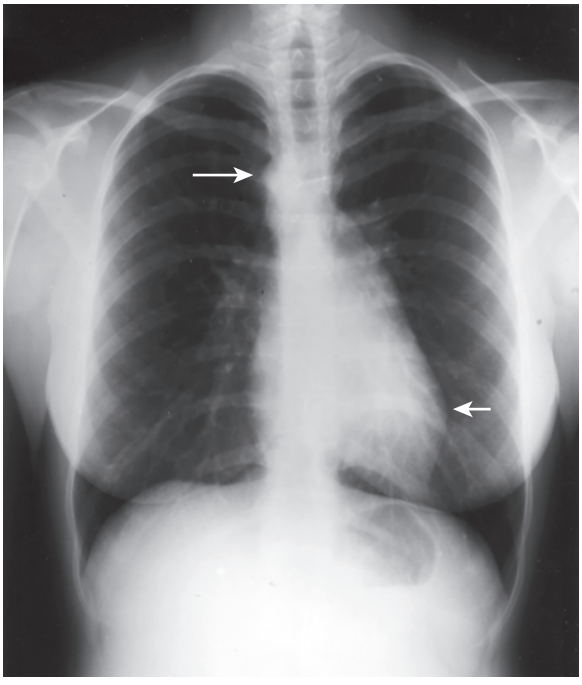

FIGURE 55-5. **Chest radiograph of an adult after tetralogy of Fallot repair.** A right aortic arch with rightward indentation of the trachea (*long arrow*) can be seen. The right ventricular apex remains upturned (*short arrow*). Note the sternal wires consistent with intracardiac repair, clarifying the fullness of the pulmonary artery segment often seen after extensive enlargement of the right ventricular outflow tract.

Risks of ischemia, myocardial infarction, and death are greatest when the left main coronary artery courses between both great vessels.

Coronary arteries can also originate from the pulmonary trunk. If both the right and left arteries originate from the pulmonary trunk, death usually occurs in the neonatal period. If only the left anterior descending coronary artery originates from the pulmonary trunk, the rate of survival to adulthood is approximately 10%, depending on the development of collateral retrograde flow to the anomalous artery from a normal coronary artery. This collateral flow may cause a continuous murmur along the left sternal border, congestive heart failure from the large shunt, and a coronary steal syndrome as blood is diverted away from the normal artery.

A single coronary ostium can provide a single coronary artery that branches into right and left coronary arteries, the left then giving rise to the circumflex and the anterior descending arteries. The ostium can originate from the right or left aortic sinus. The coronary circulation is functionally normal unless one of the branches passes between the aorta and the pulmonary artery.

Diagnostic procedures include angiography, magnetic resonance imaging, and transesophageal echocardiography. For an anomalous coronary artery that originates from the pulmonary artery, surgical reimplantation into the aorta is preferred. For an anomalous artery that courses between the pulmonary artery and aorta, a bypass graft to the distal vessel is preferred.

SPECIFIC COMPLEX LESIONS

TETRALOGY OF FALLOT

Tetralogy of Fallot, the most common cyanotic malformation, is characterized by superior and anterior displacement of the subpulmonary infundibular septum, which causes the tetrad of pulmonary stenosis, VSD, aortic override, and right ventricular hypertrophy. The VSD is perimembranous in 80% of cases. Additional cardiac anomalies include a right-sided aortic arch in up to 25% of patients. An anomalous left anterior descending artery originating from the right coronary cusp and crossing over the right ventricular outflow tract is seen in 10% of cases. Other associated anomalies include ASD, left superior vena cava, defects of the atrioventricular canal, and aortic insufficiency. With pulmonary atresia, pulmonary blood flow occurs through aortic to pulmonary collaterals.

Complete surgical repair in childhood consists of patch closure of the VSD and relief of the right ventricular outflow tract obstruction. Adequate pulmonary blood flow is ensured by reconstruction of the distal pulmonary artery bed. Previous palliative shunts are usually taken down. Complete repair in childhood yields a 90 to 95% 10-year survival rate with good functional results, and 30-year survival rates may be as high as 85%.

After repair, residual pulmonary stenosis, proximal or distal, can be seen. Some degree of pulmonary insufficiency is common, particularly if a patch has been inserted at the level of the pulmonary valve or if a pulmonary valvotomy has been performed. Residual VSDs can be found in up to 20% of patients. Patients may be asymptomatic or may have symptoms related to long-term complications after surgical repair. Symptoms can reflect residual right ventricular pressure or volume overload or arrhythmias at rest or with exercise. Angina can occur in a young patient if surgical repair has damaged an anomalous left anterior descending artery as it courses across the right ventricular outflow tract. In acyanotic adults, clubbing commonly regresses.

On physical examination, a right ventricular impulse is often felt as a result of residual pulmonary insufficiency or stenosis. A systolic murmur can represent residual pulmonary stenosis, residual VSD, or tricuspid insufficiency. A diastolic murmur can reflect aortic or pulmonary insufficiency. Ventricular arrhythmias are common after repair, with an incidence of sudden death as high as 5%.

The ECG in unrepaired tetralogy of Fallot shows right axis deviation, right atrial enlargement, and dominant right ventricular forces over the precordial leads. The most common finding after repair is complete right bundle branch block, which is seen in 80 to 90% of patients. The chest radiograph typically shows an upturned apex with a concave pulmonary artery segment giving the classic appearance of a boot-shaped heart. Figure 55-5 demonstrates the findings in an adult after repair. The apex is persistently upturned, although the pulmonary artery segment is no longer concave. Echocardiography can confirm the diagnosis and document intracardiac complications in repaired and unrepaired patients. Shunt patency can be determined by Doppler examination. Magnetic resonance imaging can accurately document stenosis in the distal pulmonary artery bed. Cardiac catheterization is reserved for patients in whom operative or reoperative treatment is contemplated or in whom the integrity of the coronary circulation needs to be verified.

Patients with a change in exercise tolerance, angina, or evidence of right-sided heart failure and those with symptomatic arrhythmias or syncope should be referred for complete evaluation. Surgical reintervention is generally considered when right ventricular pressure is more than two thirds the systemic pressure because of residual right ventricular outflow tract obstruction, free pulmonary regurgitation with right ventricular dysfunction, sustained arrhythmias, or a residual VSD causes a significant shunt.

Patients should be seen yearly by an adult congenital heart specialist for assessment of right ventricular function, pulmonary valve dysfunction, and arrhythmia. Surveillance should include a history, physical examination, and

12-lead ECG. Sudden cardiac death can occur in 3 to 6% of patients observed between 20 and 30 years, sometimes despite favorable hemodynamics.[15]

COMPLETE TRANSPOSITION OF THE GREAT ARTERIES

Complete transposition of the great arteries is the second most common cyanotic lesion, and surgically corrected adults are increasingly common. In simple transposition of the great arteries, the atria and ventricles are in their normal positions, but the aorta arises from the right ventricle, and the pulmonary artery arises from the left ventricle. When the aorta is anterior and rightward with respect to the pulmonary artery, as is most common, D-transposition is present. The native anatomy has the pulmonary and systemic circulations in parallel, with deoxygenated blood recirculating between the right side of the heart and the systemic circulation, whereas oxygenated blood recirculates from the left side of the heart to the lungs. The condition is incompatible with life unless a VSD, PDA, or ASD is present or an ASD is created; a hemodynamically significant VSD is present in 15% of cases. Subpulmonary obstruction of the left ventricular outflow tract occurs in 10 to 25% of cases.

The arterial switch operation transects the aorta and pulmonary artery above their respective valves and switches them to become realigned with their physiologic outflow tracts and appropriate ventricles. The proximal coronary arteries are translocated from the sinuses of the native aorta to the neoaorta (native pulmonary artery). The 22-year survival rate of patients with transposition of the great arteries who underwent operation between 1990 and 2009 is 93%. Long-term complications include neoaortic regurgitation, supravalvular stenosis, and coronary artery complications.

CONGENITALLY CORRECTED TRANSPOSITION OF THE GREAT ARTERIES

In congenitally corrected transposition of the great arteries, the great arteries are transposed, the ventricles are inverted, but the atria remain in their normal position. The systemic circulation (left atrium, morphologic right ventricle, and aorta) and pulmonary circulation (right atrium, morphologic left ventricle, and pulmonary artery) are in series. The patient is therefore acyanotic unless an intracardiac shunt is also present. The right ventricle is aligned with the aorta and performs lifelong systemic work, which accounts in part for its eventual failure. Patients with congenitally corrected transposition of the great arteries and no other associated defects can remain free of symptoms until the sixth decade, at which time significant atrioventricular valve regurgitation, failure of the right (systemic) ventricle, supraventricular arrhythmias, and heart block occur.

EBSTEIN ANOMALY

In Ebstein anomaly of the tricuspid valve, the right side of the heart consists of three anatomic components: the right atrium proper, the true right ventricle, and the atrialized portion of the right ventricle between the two. The displaced septal and posterior tricuspid leaflets lie between the atrialized right ventricle and the true right ventricle. Functionally, the valve is regurgitant because it is unable to appose its three leaflets during ventricular contraction. Valvular regurgitation and asynchronous, abnormal right ventricular function cause the dilation and right-sided heart failure observed in the more severe forms of the lesion. The wide spectrum of severity of the anomaly is based on the degree of tricuspid leaflet tethering and the relative proportion of atrialized and true right ventricle. The most common associated cardiac defect, a secundum ASD or patent foramen ovale, is reported in more than 50% of patients. On physical examination, a clicking "sail sound" is heard as the second component of S_1 when tricuspid valve closure becomes loud and delayed.

The 12-lead ECG typically shows highly peaked P waves with a wide, often bizarre-looking QRS complex. Preexcitation (Chapter 52) occurs in 20% of patients, whereas supraventricular tachyarrhythmias, atrial fibrillation, and atrial flutter occur in 30 to 40% of patients.

When patients of all ages are taken together, the predicted mortality is approximately 50% by the fourth or fifth decade. Complications include atrial arrhythmias, cyanosis, and, if there is an intra-atrial communication, stroke.

Intervention is considered when functional status or cyanosis worsens, significant atrial arrhythmias are documented, or a cerebrovascular accident occurs. Surgical options include replacement or repair of the tricuspid valve and closure of the ASD.

ATRIOVENTRICULAR CANAL DEFECT

A partial atrioventricular canal defect refers to an ostium primum ASD with a cleft mitral valve. The anomaly is manifested as a hemodynamic combination of an ASD with a variable degree of mitral regurgitation. The 12-lead ECG shows the typical findings of left axis deviation with a Q wave in leads I and aVL and a prolonged PR interval. The echocardiogram shows a defect in the inferior portion of the interatrial septum and a cleft mitral valve.

A complete atrioventricular canal defect is an uncommon defect consisting of a primum ASD, an inlet VSD that usually extends to the membranous interventricular septum, and a common atrioventricular valve. Adults who have not been operated on usually have Eisenmenger syndrome.

Surgical repair consists of closing the interatrial or interventricular communication with reconstruction of the common atrioventricular valve or closure of the cleft in the mitral valve. An adult who has undergone repair may have significant residual regurgitation of the mitral or tricuspid valve. Even after surgery, acquired subaortic obstruction can occur.

UNIVENTRICULAR HEART AND TRICUSPID ATRESIA

The terms *single ventricle, common ventricle*, and *univentricular heart* have been used interchangeably to describe the double-inlet ventricle, in which one ventricular chamber receives flow from both the tricuspid and mitral valves. In 75 to 90% of cases, the single ventricle is a morphologic left ventricle. Obstruction of one of the great arteries is common.

In tricuspid atresia, no orifice is found between the right atrium and right ventricle, and an underdeveloped or hypoplastic right ventricle is present. The morphologic left ventricle is consistently normally developed and therefore becomes the single functional ventricle. Typically, blood flows into the right atrium, then through an obligatory ASD and to the left atrium, where it then proceeds to the left ventricle. Variable features include a VSD, the abnormal position of the great arteries, and the relative degree of pulmonary stenosis, all of which are used to classify tricuspid atresia.

Adult patients rarely have not been operated on. They may be acyanotic after the Fontan operation. At 5-year follow-up, 80% or more of Fontan survivors are in New York Heart Association functional class I or II, with successful pregnancy reported in a small number of patients. When patients of all ages are considered together, 10-year survival rates vary from 60 to 70%. Late deaths are due to reoperation, arrhythmia, ventricular failure, protein-losing enteropathy, and liver dysfunction. Yearly follow-up with specialized imaging is recommended.

Anomalies of Pulmonary Venous Return

In partial anomalous pulmonary venous return, one or more, but not all four, pulmonary veins are not connected to the left atrium. The most common pattern has the right pulmonary veins connected to the superior vena cava, usually with a sinus venosus ASD.

In total anomalous pulmonary venous return, all the pulmonary veins connect abnormally to either the right atrium or one of the systemic veins above or below the diaphragm. Concurrent obstruction of the pulmonary veins is present when drainage occurs below the diaphragm and variable when drainage occurs above it. An ASD is essential to sustain life. One third of cases occur with major complex cardiac malformations. Surgical treatment is indicated.

In cor triatriatum, the pulmonary veins drain into an accessory chamber that is usually connected to the left atrium through an opening of variable size. The hemodynamic consequences are determined by the size of this opening and are similar to those of mitral stenosis.

Dextrocardia and Mesocardia

In dextrocardia, the heart is on the right side of the thorax with or without situs inversus. When the heart is right sided with inverted atria, the stomach is right sided, and the liver is left sided, the combination is dextrocardia with situs inversus. The heart usually functions normally, and the diagnosis is often fortuitous. The heart sounds are louder on the right side of the chest, and the liver is palpable on the left. The chest radiograph shows a right-sided cardiac apex with a lower left hemidiaphragm and a right-sided stomach bubble. The ECG shows an inverted P and T wave in lead I with a negative QRS deflection and a reverse pattern between aVR and aVL. A mirror-image progression is seen from V_1 to a right-sided V_6 lead. An echocardiogram should be performed to ensure that intracardiac anatomy is normal.

When dextrocardia with situs solitus occurs, the ventricles are inverted, but not the viscera and therefore not the atria. Associated severe cardiac malformations are typical. In mesocardia, the heart is centrally located in the chest with normal atrial and visceral anatomy. The apex is central or rightward displaced

on the chest radiograph. Typically, no associated cardiac malformations are present.

SPECIALIZED ISSUES

Pulmonary Hypertension and Its Complications

Pulmonary hypertension (Chapter 69) secondary to structural disease of the heart or circulation can occur with or without an increase in pulmonary vascular resistance. Pulmonary vascular obstructive disease occurs when pulmonary vascular resistance rises and becomes fixed and irreversible. *Eisenmenger physiology* designates the physiologic response of shunt lesions in which a right-to-left shunt occurs in response to an elevation in pulmonary vascular resistance.

In the most common congenital anomalies, pulmonary hypertension is a result of increased pulmonary blood flow because of a native left-to-right shunt. Examples include ASD, a large-sized VSD, PDA, and a variety of complex lesions. The rate at which pulmonary hypertension progresses to become pulmonary vascular obstructive disease varies from one lesion to another and depends at least in part on the source of pulmonary blood flow. Pulmonary hypertension typically develops in patients with an ASD after the fourth decade; Eisenmenger syndrome is a late complication seen in only 5 to 10% of cases. In contrast, in patients with a large VSD or persistent PDA, progressive elevation in pulmonary vascular resistance occurs rapidly because the pulmonary vascular bed is exposed not only to the excess volume of the left-to-right shunt but also to systemic arterial pressures. As a result, Eisenmenger complex develops in approximately 10% of patients with a large VSD during the first decade.

The term *Eisenmenger syndrome*[16] should be reserved for patients in whom pulmonary vascular obstructive disease is present and pulmonary vascular resistance is fixed and irreversible. These findings, in combination with the absence of left-to-right shunting, render the patient inoperable.

The clinical manifestations of Eisenmenger syndrome include dyspnea on exertion, syncope, chest pain, congestive heart failure, and symptoms related to erythrocytosis and hyperviscosity. On physical examination, central cyanosis and digital clubbing are hallmark findings. Systemic oxygen saturations typically vary between 75 and 85%. The pulse pressure narrows as the cardiac output falls. Examination of jugular venous pressure can reveal a dominant *a* wave reflecting a noncompliant right ventricle until tricuspid insufficiency is severe enough to generate a large *v* wave. A prominent right ventricular impulse is felt in the left parasternal border in end expiration or in the subcostal area in end inspiration. A palpable pulmonary artery is commonly felt. The pulmonary component of the second heart sound is increased and can be felt in most cases. Pulmonary ejection sounds are common when the pulmonary artery is dilated with a structurally normal valve. Right atrial gallop is heard more frequently when the *a* wave is dominant. A murmur of tricuspid insufficiency is common, but the inspiratory increase in the murmur (Carvallo sign) disappears when right ventricular failure occurs. In diastole, a pulmonary insufficiency murmur is often heard. The 12-lead ECG shows evidence of right atrial enlargement, right ventricular hypertrophy, and right axis deviation. Chest radiographic findings include a dilated pulmonary artery segment, cardiac enlargement, and diminished pulmonary vascular markings. Echocardiography confirms the right-sided pressure overload and pulmonary artery enlargement as well as the tricuspid and pulmonary insufficiency. Cardiac catheterization is indicated if doubt exists about the potential reversibility of the elevated pulmonary vascular resistance in a patient who might otherwise benefit from surgery.

Cyanosis occurs when persistent venous-to-arterial mixing results in hypoxemia. Adaptive mechanisms to increase oxygen delivery include an increase in oxygen content, a rightward shift in the oxyhemoglobin dissociation curve, a higher hematocrit, and an increase in cardiac output. When cyanosis is not relieved, chronic hypoxemia and erythrocytosis result in hematologic, neurologic, renal, and rheumatic complications.

TREATMENT AND PROGNOSIS

In patients with Eisenmenger syndrome, pulmonary vasodilator therapy (e.g., bosentan 62.5 mg twice daily for 4 weeks, then 125 mg twice daily) may improve hemodynamics and exercise capacity after 4 months of use. Chronic oxygen therapy is unlikely to benefit hypoxemia caused by right-to-left shunting in the setting of a fixed pulmonary vascular resistance. Oxygen therapy may be considered for cyanotic patients during long-distance flights.

Indications for phlebotomy are symptomatic hyperviscosity in an iron-replete patient and prevention of excessive bleeding perioperatively. In the iron-replete state, moderate to severe hyperviscosity symptoms typically occur when hematocrit levels exceed 65%. If no evidence of dehydration is present, removal of 500 mL of blood during a 30- to 45-minute period should be followed by quantitative volume replacement with normal saline or dextran (E-Fig. 55-3). The procedure may be repeated every 24 hours until symptomatic improvement occurs.

Treatment of spontaneous bleeding is dictated by its severity and the abnormal hemostatic parameters (E-Fig. 55-4). For severe bleeding, platelet transfusions, fresh-frozen plasma, vitamin K, cryoprecipitate, and desmopressin have been used. Reduction in erythrocyte mass also improves hemostasis, so cyanotic patients undergoing surgery should have prophylactic phlebotomy if the hematocrit is greater than 65%.

Symptomatic hyperuricemia and gouty arthritis (Chapter 252) can be treated as necessary with colchicine, probenecid, or allopurinol. Nonsteroidal anti-inflammatory drugs are best avoided, given the baseline hemostatic anomalies in these patients.

Endocarditis Prophylaxis

Prolonged survival of patients with complex congenital heart disease has resulted in a population at increased risk for infective endocarditis (Chapter 61), which usually involves left-sided heart valves.[17] Adults with congenital heart disease should be informed about the risks of endocarditis. Any unexplained fever requires blood cultures to be drawn before antibiotics are initiated. Thorough transthoracic and transesophageal echocardiograms should be performed to assess the presence of vegetations. If infection of prosthetic material is suspected, early consultation with a specialist who has access to a congenital heart surgeon should be initiated because of the potential for rapid deterioration. The risk of endocarditis is highest in patients with cyanotic congenital heart disease and prosthetic material.

Antibiotic prophylaxis before dental procedures that involve manipulation of the gingiva, periapical regions of the teeth, or mucosal tissue is indicated in patients with previous infective endocarditis, unrepaired cyanotic lesions, palliative shunts or conduits, prosthetic valves or prosthetic materials used for valve repair, repaired congenital heart disease with prosthetic material or transcatheter device within 6 months of intervention, and repaired congenital heart disease with residual lesions at or adjacent to the site of a prosthetic patch or device (Chapter 61). It is also reasonable to consider prophylaxis against endocarditis before vaginal delivery at the time of membrane rupture in such patients. Prophylaxis is not indicated for nondental procedures in the absence of active infection.

Exercise

The goal of exercise evaluation is to assess the functional results of therapeutic interventions and to provide guidelines for exercise prescriptions. Patients with residual hemodynamic lesions or unrepaired congenital cardiac anomalies should be evaluated on an annual basis with a physical examination, an ECG, and a cardiac ultrasonographic examination if indicated. Pertinent additional tests may include Holter monitoring and exercise testing. Attention should be directed to the detection of pulmonary hypertension; arrhythmias; myocardial dysfunction; and symptoms such as exercise-induced dizziness, syncope, dyspnea, or chest pain.

Patients beyond 6 months after repair of a single shunt lesion without pulmonary hypertension, arrhythmias, or evidence of myocardial dysfunction can participate in all sports (E-Table 55-1).[18] With residual shunts, if the peak pulmonary artery pressure is less than 40 mm Hg in the absence of ventricular dysfunction or significant arrhythmias, patients can enjoy a free range of activity. Patients with elevated pulmonary vascular resistance are at risk of sudden death during intense exercise; although most self-limit their activity, participation in competitive sports is contraindicated. Patients with aortic and pulmonary stenosis should be counseled as recommended earlier, according to gradient severity. For patients with uncomplicated aortic coarctation, athletic participation is permitted if the arm-leg blood pressure gradient is 20 mm Hg or less at rest and the peak systolic blood pressure during exercise is normal. For patients after tetralogy of Fallot repair, repair of transposition of the great arteries, and the Fontan operation, exercise recommendations vary according to residual ventricular function and the presence or absence of arrhythmias.

Older Patients

Overall survival is similar to the general population in patients without cyanosis, univentricular physiology, genetic disorders, ventricular dysfunction, residual hemodynamic lesions, or acquired late complications. However, median survival is only 56 years in patients with one or more of these risk factors. Among

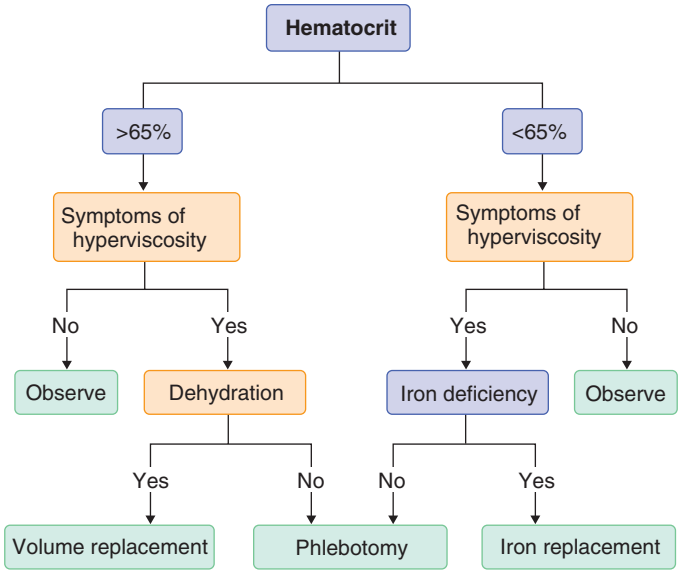

E-FIGURE 55-3. **Treatment algorithm for erythrocytosis of cyanotic congenital heart disease.**

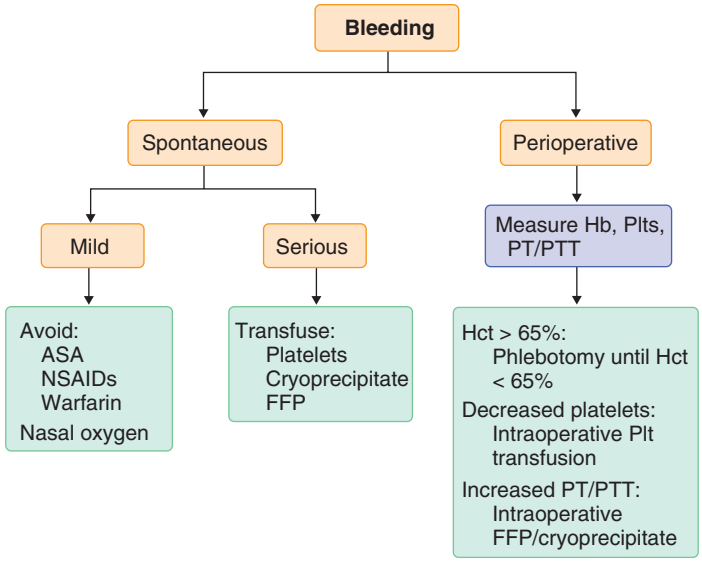

E-FIGURE 55-4. **Treatment algorithm for bleeding diathesis of cyanotic congenital heart disease.** ASA = acetylsalicylic acid; FFP = fresh-frozen plasma; Hb = hemoglobin; Hct = hematocrit; NSAIDs = nonsteroidal anti-inflammatory drugs; Plts = platelets; PT = prothrombin time; PTT = partial thromboplastin time.

E-TABLE 55-1 EXERCISE RECOMMENDATIONS IN ADULTS WITH CONGENITAL HEART DISEASE

CONDITION	UNRESTRICTED	LOW-MODERATE INTENSITY*	PROHIBITED
ASD†	No PHT; no arrhythmia; normal ventricular function	PA pressure >40 mm Hg *with* normal ETT; no arrhythmia	Eisenmenger
VSD†	Small; no PHT; no arrhythmia; normal ventricular function	Moderate VSD	Eisenmenger
PDA†	Small; no PHT; no arrhythmia; normal ventricular function	PA pressure >40 mm Hg *with* normal ETT; no arrhythmia	Eisenmenger
Coarctation‡	Gradient ≤20 mm Hg arm to leg; normal BP at rest and exercise	Gradient ≥20 mm Hg arm to leg *with* normal BP and normal ETT	Gradient ≥50 mm Hg arm to leg *or* aortic aneurysm
PS	Gradient <40 mm Hg; no arrhythmia; normal ventricular function	Gradient 40-60 mm Hg	Gradient ≥70 mm Hg *or* ventricular arrhythmia
AS	Gradient, <30 mm Hg; normal ECG; normal ETT; asymptomatic	Gradient 30-50 mm Hg *with* normal ECG, normal ETT; asymptomatic	Gradient >50 mm Hg *or* ventricular arrhythmia
TOF after repair	Normal RV pressure; no shunt; no arrhythmia	Increased RV pressure *or* moderate PR *or* SVT	RV pressure ≥65% systemic *or* ventricular arrhythmia on ETT
Mustard or Senning		No cardiomegaly, arrhythmia, or syncope; normal ETT	Cardiomegaly *or* arrhythmia at rest or exercise
c-TGA unoperated	No cardiomegaly; mild TR; no arrhythmia; normal ETT	Moderate RV dysfunction, moderate TR; no arrhythmia	Severe TR *or* uncontrolled arrhythmia
Ebstein anomaly	Mild Ebstein; no arrhythmia; operated with mild TR	Moderate TR *with* no arrhythmia	Severe Ebstein *or* uncontrolled arrhythmia
Fontan		Normal O_2 saturation *with* near-normal ETT and ventricular function	Moderate-severe MR or TR *or* uncontrolled arrhythmia

*Based on peak dynamic and static components of exercise during competition for individual sports (see credit line).

†Unoperated or 6 months after surgery.

‡Unoperated or 1 year after surgery.

AS = aortic stenosis; ASD = atrial septal defect; BP = blood pressure; c-TGA = corrected transposition of the great arteries; ECG = electrocardiogram; ETT = exercise tolerance test; MR = mitral regurgitation; PA = pulmonary artery; PDA = patent ductus arteriosus; PHT = pulmonary hypertension; PR = pulmonary regurgitation; PS = pulmonary stenosis; RV = right ventricle; SVT = supraventricular tachyarrhythmia; TOF = tetralogy of Fallot; TR = tricuspid regurgitation; VSD = ventricular septal defect.

Based on guidelines recommended in Graham TP, Driscoll DJ, Gersony WM, et al. Task Force 2: Congenital heart disease. *J Am Coll Cardiol*. 2005;45:1326-1333.

women who become pregnant, fetal growth retardation is about 30% more common if the congenital heart condition is simple, but complex congenital lesions are associated with a 60% increased risk of fetal growth retardation and an 80-fold increased risk of maternal death.

The increasing number of older adults are surgical survivors who are subject to developing the full range of age-related cardiac conditions as well as late complications from their surgically repaired congenital anomaly.[19] Careful attention to blood pressure (Chapter 64), lipid levels (Chapter 190), and other preventive approaches (Chapter 40), including physical activity (Chapter 14), diet (Chapter 13), and smoking cessation (Chapter 363), is critically important. Neurodevelopmental problems in childhood and adolescence also may contribute to detectable cognitive decline (Chapter 371) and dementia in adulthood.

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56 ANGINA PECTORIS AND CHRONIC ISCHEMIC HEART DISEASE

WILLIAM E. BODEN

DEFINITION

Angina pectoris and myocardial ischemia most commonly result from an obstruction or stenosis of one or more of the epicardial coronary arteries by atheromatous plaque, but it is increasingly recognized that both angina and ischemia can occur in the absence of epicardial coronary artery obstruction—particularly in women, who may exhibit microvascular angina and ischemia. Both coronary stenosis and obstruction can result when a plaque ruptures acutely to cause severe myocardial ischemia, thereby culminating in a myocardial infarction or an acute coronary syndrome (Chapters 57 and 58) with associated symptoms of angina, dyspnea, heart failure (Chapters 45 and 46), and arrhythmic complications (Chapters 50, 52 and 53) that may result in sudden cardiac death.

Angina pectoris results from an imbalance in myocardial oxygen supply and demand when an increase in activity or emotional stress increases cardiac workload, or "demand," with a concomitant increase in heart rate, blood pressure, and contractility, which, in turn, leads to an increase in left ventricular (LV) wall tension. However, stenotic coronary arteries are unable to augment antegrade flow, or "supply," adequately in response to this increase in demand. Such an imbalance classically results in chest discomfort (Chapter 39) of varying intensity and duration. Angina pectoris is generally defined as a discomfort in the chest or adjacent areas that occurs predictably and reproducibly at a certain level of exertion and is relieved with rest or nitroglycerin.

Chronic angina may result from epicardial coronary obstruction, vasospasm of the epicardial coronary arteries or microcirculation, or a noncoronary or nonvascular process, such as myocardial energy derangements, blood rheology abnormalities, or extravascular microcirculatory compression. Stable angina and chronic myocardial ischemia have been variably termed "chronic coronary syndromes," "stable ischemic heart disease," or "chronic coronary disease." Given the multiplicity of causes and precipitants of angina and ischemia in the nonacute setting, the term "chronic ischemic heart disease" is favored as being more accurately descriptive and inclusive of these multiple pathogenetic processes and triggers.

Grading of Angina Pectoris

The Canadian Cardiovascular Society (CCS) angina grading scale is a widely used four-point ordinal scale that classifies angina pectoris from mild (class I: angina occurring only during strenuous or prolonged physical activity) to severe (class IV: inability to perform any activity without angina, or angina at rest) and includes the full spectrum of angina from chronic stable to unstable (see Table 39-5). Operationally, the CCS angina scale permits clinicians to categorize patients as mild or stable (generally CCS classes I and II) versus severe or unstable (typically CCS classes III and IV). For classification purposes, subjects with stable ischemic heart disease generally exhibit CCS class I to II symptoms, which are typically provoked by exertion. Other grading systems include a specific activity scale, which is based on the metabolic cost of specific activities, and an anginal score, which integrates the clinical features and tempo of angina with electrocardiographic changes and offers independent prognostic information beyond that provided by age, sex, ventricular function, and coronary anatomy.

EPIDEMIOLOGY

More than 85 million American adults (more than 1 in 3) have at least one type of cardiovascular disease, which includes more than 17 million persons with coronary heart disease (Chapter 40), including 7.6 million who have survived a myocardial infarction (MI), nearly 10 million with angina pectoris, 5.7 million with heart failure, and 6.6 million with stroke (of all types). Among adults aged 60 to 79 years, approximately 25% of men and 16% of women have coronary heart disease, and among persons older than age 80 years, the percentages increase to 37% and 23%, respectively.[1] The Global Burden of Disease Study estimates that cardiovascular diseases are the leading cause of death globally. An estimated 18 million people died from cardiovascular disease in 2019, representing 32% of all global deaths.[2]

In 2019, before the severe acute respiratory syndrome coronavirus 2 pandemic, coronary heart disease accounted for 365,000 of the 650,000 or so U.S. deaths due to heart disease, or about 55%. The number of coronary heart disease deaths is expected to rise in the coming decade as a consequence of the aging of the U.S. population as well as the epidemic rise in obesity (Chapter 201), type 2 diabetes (Chapter 210), and metabolic syndrome, which may give rise to an increasing risk for premature coronary artery disease in younger generations.

PATHOBIOLOGY

Angina is the most frequent clinical expression of myocardial ischemia. Ischemia, which rapidly develops when a mismatch arises between myocardial oxygen needs and myocardial oxygen supply, can be manifested clinically in many ways besides angina, from no symptoms (e.g., silent myocardial ischemia) to unstable angina, MI, or sudden cardiac death. It may remain stable for many years in selected patients or may be rapidly progressive with an abrupt change in frequency and tempo during days to weeks. Conversely, atherosclerosis, which is the most common cause of myocardial ischemia, may evolve for years without any manifestations of ischemia.

Chronic angina and ischemia may be due to a variety of pathogenetic mechanisms, the most common of which is an obstructed or stenotic coronary artery. Alternative mechanisms include microvascular dysfunction, vasoconstriction at the site of a dynamic stenosis, or mural thrombosis, as well as noncoronary or nonvascular processes, such as derangements in myocardial energy supply or demand, abnormalities in blood rheology, and extravascular microcirculatory compression.[3,4]

Two major pathogenetic mechanisms may result in myocardial ischemia and angina in the chronic setting: so-called *demand angina*, which is caused by an increase in myocardial oxygen requirements and workload, and *supply angina*, which is caused by diminished oxygen delivery to myocardial tissue. Demand angina is a consequence of the increased myocardial oxygen requirements that occur with increased physical activity, emotion, or stress. In a patient with decreased myocardial perfusion owing to chronic atherosclerotic narrowing of a coronary artery, this increased demand may precipitate angina. Other extracardiac precipitants of angina include the excessive metabolic demands imposed by fever, thyrotoxicosis (Chapter 207), severe anemia (Chapter 144)

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Grading of Angina Pectoris

The Canadian Cardiovascular Society (CCS) angina grading scale is a widely used four-point ordinal scale that classifies angina pectoris from mild (class I: angina occurring only during strenuous or prolonged physical activity) to severe (class IV: inability to perform any activity without angina, or angina at rest) and includes the full spectrum of angina from chronic stable to unstable (see Table 39-5). Operationally, the CCS angina scale permits clinicians to categorize patients as mild or stable (generally CCS classes I and II) versus severe or unstable (typically CCS classes III and IV). For classification purposes, subjects with stable ischemic heart disease generally exhibit CCS class I to II symptoms, which are typically provoked by exertion. Other grading systems include a specific activity scale, which is based on the metabolic cost of specific activities, and an anginal score, which integrates the clinical features and tempo of angina with electrocardiographic changes and offers independent prognostic information beyond that provided by age, sex, ventricular function, and coronary anatomy.

EPIDEMIOLOGY

More than 85 million American adults (more than 1 in 3) have at least one type of cardiovascular disease, which includes more than 17 million persons with coronary heart disease (Chapter 40), including 7.6 million who have survived a myocardial infarction (MI), nearly 10 million with angina pectoris, 5.7 million with heart failure, and 6.6 million with stroke (of all types). Among adults aged 60 to 79 years, approximately 25% of men and 16% of women have coronary heart disease, and among persons older than age 80 years, the percentages increase to 37% and 23%, respectively.[1] The Global Burden of Disease Study estimates that cardiovascular diseases are the leading cause of death globally. An estimated 18 million people died from cardiovascular disease in 2019, representing 32% of all global deaths.[2]

In 2019, before the severe acute respiratory syndrome coronavirus 2 pandemic, coronary heart disease accounted for 365,000 of the 650,000 or so U.S. deaths due to heart disease, or about 55%. The number of coronary heart disease deaths is expected to rise in the coming decade as a consequence of the aging of the U.S. population as well as the epidemic rise in obesity (Chapter 201), type 2 diabetes (Chapter 210), and metabolic syndrome, which may give rise to an increasing risk for premature coronary artery disease in younger generations.

PATHOBIOLOGY

Angina is the most frequent clinical expression of myocardial ischemia. Ischemia, which rapidly develops when a mismatch arises between myocardial oxygen needs and myocardial oxygen supply, can be manifested clinically in many ways besides angina, from no symptoms (e.g., silent myocardial ischemia) to unstable angina, MI, or sudden cardiac death. It may remain stable for many years in selected patients or may be rapidly progressive with an abrupt change in frequency and tempo during days to weeks. Conversely, atherosclerosis, which is the most common cause of myocardial ischemia, may evolve for years without any manifestations of ischemia.

Chronic angina and ischemia may be due to a variety of pathogenetic mechanisms, the most common of which is an obstructed or stenotic coronary artery. Alternative mechanisms include microvascular dysfunction, vasoconstriction at the site of a dynamic stenosis, or mural thrombosis, as well as noncoronary or nonvascular processes, such as derangements in myocardial energy supply or demand, abnormalities in blood rheology, and extravascular microcirculatory compression.[3,4]

Two major pathogenetic mechanisms may result in myocardial ischemia and angina in the chronic setting: so-called *demand angina*, which is caused by an increase in myocardial oxygen requirements and workload, and *supply angina*, which is caused by diminished oxygen delivery to myocardial tissue. Demand angina is a consequence of the increased myocardial oxygen requirements that occur with increased physical activity, emotion, or stress. In a patient with decreased myocardial perfusion owing to chronic atherosclerotic narrowing of a coronary artery, this increased demand may precipitate angina. Other extracardiac precipitants of angina include the excessive metabolic demands imposed by fever, thyrotoxicosis (Chapter 207), severe anemia (Chapter 144)

ABSTRACT

Angina pectoris and myocardial ischemia generally result from an inadequate supply of blood flow and oxygen to an area of myocardium, typically resulting from a mismatch of myocardial oxygen demand and supply. Both exertional angina and dyspnea are common symptoms in the chronic setting. Obstructive coronary artery disease, which may have either acute or chronic presentations, most commonly results from a significant stenosis of greater than 70% in one or more of the major epicardial coronary arteries secondary to an atherosclerotic plaque. In acute disease expressions, the plaque may rupture or fissure, whereas symptoms of angina and objective findings of chronic ischemia typically result from a slowly advancing atherosclerotic process that compromises the arterial lumen. Increasingly, attention is being directed to ischemic manifestations that may occur in the absence of epicardial coronary artery narrowing, such as is observed in patients (most often women) who may exhibit "microvascular angina" due to involvement of the arteriolar resistance vessels, thereby resulting in impaired coronary vasodilator reserve. Other chronic manifestations of myocardial ischemia include vasospastic angina and silent myocardial ischemia (as detected electrographically or by imaging) in the absence of angina. Multiple diagnostic tests include laboratory assessments and both noninvasive and invasive approaches, which are often used in combination to risk-stratify patients and inform treatment options. These treatments include aggressive secondary prevention with both disease-modifying pharmacologic agents and drugs directed at the relief of angina/ischemia as well as intensive lifestyle interventions, which together comprise optimal medical therapy. Revascularization is also indicated in patients whose symptoms are refractory to intensive medical therapy or in patients who cannot tolerate antianginal medications. To date, data from multiple randomized controlled trials have failed to demonstrate that a strategy of routine upfront revascularization (with either percutaneous coronary intervention or coronary artery bypass graft surgery) plus optimal medical therapy reduces the rates of death or myocardial infarction or improves quality of life as compared with an intensive medical therapy alone. Thus, in the chronic setting, revascularization is principally indicated to relieve symptoms when medical therapy fails or for patients in whom quality of life remains unacceptable with a conservative approach to management.

KEYWORDS

angina pectoris
chronic stable angina
stable ischemic heart disease
noninvasive testing
diagnostic coronary angiography
risk stratification
disease-modifying therapy
myocardial revascularization

from blood loss, tachycardia from any cause (Chapters 50, 52, 53), hypoglycemia (Chapter 211), and pain (Chapter 26).

By contrast, supply angina may occur in patients with either acute coronary syndrome (Chapter 57) or chronic ischemic heart disease by transient reductions in myocardial oxygen delivery as a consequence of coronary vasoconstriction with resulting dynamic coronary stenosis. In the presence of coronary luminal narrowing due to atherosclerosis, superimposed platelet thrombi and leukocytes may elaborate vasoconstrictor substances, such as serotonin and thromboxane A_2, whereas endothelial damage in diseased coronary arteries may decrease production of vasodilator substances such as nitric oxide and adenosine. The result is an abnormal physiologic vasoconstrictor response to exercise and other stimuli, such as exogenously administered adenosine, or the paradoxical vasoconstrictor response to the typical flow-mediated reactive hyperemia associated with brachial artery compression. Some patients with normal coronary angiograms or non–flow-limiting stenoses may exhibit dynamic obstruction alone, which can cause myocardial ischemia and result in angina at rest (Prinzmetal [variant] angina). Conversely, in patients with flow-limiting coronary stenoses, only a minor increase in dynamic obstruction can reduce blood flow sufficiently to cause myocardial ischemia.

The pathophysiologic basis for angina and myocardial ischemia has important implications for the selection of anti-ischemic agents. In patients with *demand angina*—in which increases in myocardial oxygen requirements are triggered by increases in heart rate, blood pressure, and contractility—therapeutic agents that reduce heart rate and wall tension, such as β-blockers or non-dihydropyridine calcium antagonists, will often provide the most clinical benefit. By comparison, nitrates and calcium antagonists with more potent vasodilatory properties (particularly the dihydropyridines) will be more beneficial to alleviate angina and ischemia mediated by coronary vasoconstriction and reductions in myocardial oxygen delivery.

Although the most common cause of chronic ischemic heart disease is atherosclerotic coronary artery narrowing and flow-limiting obstruction to epicardial blood flow, obstructive coronary artery disease may also have nonatherosclerotic causes, including congenital abnormalities of the coronary arteries (Chapter 55), coronary artery dissection, myocardial bridging, coronary arteritis in association with systemic vasculitides (Chapter 249), and radiation-induced coronary disease (Chapter 18). Importantly, myocardial ischemia and angina pectoris may occur commonly in the absence of obstructive coronary artery disease, a syndrome that is termed ischemia with nonobstructive coronary arteries (INOCA).[5] Angina and ischemia may also be associated with aortic valve disease, principally aortic stenosis (Chapter 60), hypertrophic cardiomyopathy (Chapter 47), and dilated cardiomyopathy.

CLINICAL MANIFESTATIONS

History

It is important to recognize that there are many causes of chest discomfort (see Table 39-2), that angina-like chest pain may not represent ischemic heart disease (Fig. 56-1), that ischemic heart disease causes symptoms other than anginal pain (Table 56-1), and that nonatherosclerotic coronary artery abnormalities may cause ischemic chest pain (Table 56-2).

Angina pectoris has four cardinal clinical features: the character of the discomfort, its site and distribution, its provocation, and its duration. The character of anginal discomfort is typically described as a pressure sensation that conveys a feeling of strangling and anxiety (Chapter 39), but patients may also use descriptors such as heaviness, squeezing, constricting, viselike, suffocating, and crushing. In some patients, especially women and the elderly, the quality of the sensation is more vague and atypical. Some patients may describe the discomfort as a burning sensation in the mid-epigastrium or as an uncomfortable, numb sensation. *Anginal equivalents* (i.e., symptoms of myocardial ischemia other than angina), such as dyspnea, fatigue, lightheadedness or dizziness, and gastric eructations, also may be manifestations of ischemic heart disease.

The site and distribution of anginal discomfort are predominantly midsternal or retrosternal but can be precordial. Radiation is common, usually to the left side of the neck and shoulder and down the ulnar surface of the left arm; radiation to the right arm is less common. Throat tightness or discomfort is a very important angina equivalent and should be a warning of coronary obstruction. Discomfort radiating to the jaw is common and must be distinguished from dental pain. Epigastric discomfort alone or in association with chest pressure may occur. Provocation of angina is classically caused by physical exertion or activity, emotional stress, exposure to the cold, sexual intercourse, or eating a large meal. Angina that occurs at rest or nocturnally often heralds a change in the pattern from stable to unstable and may indicate that there is an incipient plaque rupture leading to an acute coronary syndrome (ACS). Vasospastic (or Prinzmetal) angina may occur spontaneously at rest or nocturnally without provocation.

The typical duration of an episode of angina pectoris is brief. An episode usually begins gradually and reaches its maximal intensity during a period of

TABLE 56-1 NON–CHEST PAIN SYMPTOMS OF CHRONIC ISCHEMIC HEART DISEASE

DYSPNEA
Dyspnea on exertion
Dyspnea at rest
Paroxysmal nocturnal dyspnea
Temporal change of increasing exertional dyspnea with declining effort tolerance
NON–CHEST LOCATIONS OF DISCOMFORT (EITHER EXERTIONAL OR AT REST)
Neck or mandibular discomfort or pain
Throat tightness
Shoulder discomfort
Upper arm or forearm discomfort (more often left-sided)
Interscapular or infrascapular discomfort
MID-EPIGASTRIC OR ABDOMINAL
Mid-epigastric burning, often postprandially
Sharp abdominal pain (atypical, but more common in women)
Right upper quadrant discomfort (may mimic gallbladder disease or pancreatitis)
Nausea or vomiting (often associated with increased vagal tone secondary to inferior myocardial ischemia or infarction)
DIAPHORESIS
EXCESSIVE FATIGUE AND WEAKNESS
Often a discernible prodrome of increasing fatigue with declining effort tolerance
DIZZINESS AND SYNCOPE
Uncommon, unless precipitated or exacerbated by alterations in heart rate or rhythm (e.g., bradyarrhythmia, tachyarrhythmia, heart block), blood pressure (e.g., hypotension), or cardiac output (e.g., decreased cerebral perfusion)

	Typical/Definite Anginal Pain		Atypical/Probable Anginal Pain		Non-anginal Chest Pain	
Age	Men	Women	Men	Women	Men	Women
30–39	3%	5%	4%	3%	1%	1%
40–49	22%	10%	10%	6%	3%	2%
50–59	32%	13%	17%	6%	11%	3%
60–69	44%	16%	26%	11%	22%	6%
70+	52%	27%	34%	19%	24%	10%

Dyspnea	
Men	Women
0%	3%
12%	3%
20%	9%
27%	14%
32%	12%

FIGURE 56-1. Pretest probabilities of coronary artery disease by age, sex, and symptoms. The regions shaded yellow denote the groups in which noninvasive testing is most beneficial. The regions shaded pink denote the groups with pretest probabilities of coronary artery disease between 5 and 15%, in which testing for diagnosis may be considered after assessing the overall clinical likelihood. (Adapted from Knuuti J, Wijns W, Saraste A, et al. 2019 ESC Guidelines for the diagnosis and management of chronic coronary syndromes. *Eur Heart J*. 2020;41:407-477.)

TABLE 56-2 NONATHEROSCLEROTIC CAUSES OF ISCHEMIC CHEST PAIN

PRIMARY CARDIAC CAUSES
Coronary artery abnormalities
Coronary spasm
Coronary arteritis
Coronary dissection
Coronary artery anomalies
Radiation-induced coronary disease
Myocardial bridging
Aortic stenosis
Hypertrophic cardiomyopathy
Dilated cardiomyopathy
Tachycardia
PRIMARY NONCARDIAC CAUSES
Anemia
Sickle cell disease
Hypoxemia
Carbon monoxide poisoning
Hyperviscosity (e.g., polycythemia)
Hyperthyroidism
Pheochromocytoma

minutes before abating. It is unusual for angina pectoris to peak and trough in less than a minute, and it is common that patients with exertional angina usually prefer to rest, to sit, or to stop walking during episodes that may be precipitated by the offending activity. Chest discomfort that persists for more than 15 to 20 minutes, especially at rest or nocturnally, is likely to represent ACS or MI. By contrast, features that suggest a noncardiac etiology of angina pectoris include pleuritic pain, pain reproduced by movement or palpation of the chest wall, sharp or constant pain lasting for many hours, pain or discomfort that a patient can localize to the chest wall with the tip of one finger, and very brief episodes of pain lasting seconds (Chapter 39). Typical angina pectoris is generally relieved within minutes by rest or the use of sublingual, oral, or cutaneous nitroglycerin. The response to sublingual nitroglycerin is often a helpful diagnostic tool, although some noncardiac pain (e.g., esophageal spasm) may also respond to nitroglycerin.

Although chest discomfort is usually the predominant symptom of ischemia, it is not invariably seen in all patients with chronic ischemic heart disease. Many individuals may complain predominantly or exclusively of dyspnea, diminishing exercise tolerance, fatigue, or weakness. Others will first present with an abnormal exercise test result or other evidence of myocardial ischemia without any symptoms (so-called *silent myocardial ischemia*). Some patients may present with cardiac arrhythmias or even sudden cardiac death.

Physical Examination

Many patients with chronic ischemic heart disease present with normal physical findings (Chapter 39), but a diligent physical examination may reveal findings that represent either the consequences of myocardial ischemia or evidence of risk factors for coronary heart disease. Inspection of the eyes may reveal a corneal arcus, and examination of the skin may show xanthomas (see E-Fig. 39-1). Retinal arteriolar changes are common in patients with coronary heart disease who have hypertension or diabetes mellitus (see Figs. 391-22 and 391-24).

The cardiac examination is generally of limited benefit in evaluating patients with chest discomfort or establishing a diagnosis of stable ischemic heart disease. During an episode of chest discomfort, myocardial ischemia may produce either a third or fourth heart sound.

Myocardial ischemia also can cause a transient holosystolic or mid-late systolic apical murmur due to reversible papillary muscle dysfunction that results in mitral regurgitation. These murmurs are more prevalent in patients with extensive coronary artery disease, especially with inferior or inferoposterior ischemia due to right coronary artery disease. It is important to distinguish such a murmur from the murmur of aortic stenosis or obstructive hypertrophic cardiomyopathy (see Tables 39-7 and 39-8). A displaced LV apical impulse, particularly if dyskinetic, is a sign of significant LV systolic dysfunction.

If patients have coexisting heart failure, an elevated jugular venous pressure, pulmonary rales, an S_3 gallop, and peripheral edema may be present (Chapter 45). The physical examination may reveal other implicating or contributing conditions, such as thyroid enlargement (Chapter 207) or severe anemia (Chapter 144).

DIAGNOSIS

In addition to a careful history and physical examination, assessment of patients with chronic ischemic heart disease includes the 12-lead electrocardiogram (ECG), measurement of biochemical and inflammatory markers, and noninvasive diagnostic testing (Chapter 44). The first goal is to assess the patient's probability of ischemia so that an appropriate evaluation can expedite effective therapy (Fig. 56-2). An acute syndrome with discomfort on minimal exertion or at rest requires urgent evaluation and treatment (Chapters 39 and 57), whereas a chronic syndrome with effort-related symptoms can be evaluated on an outpatient basis if an ECG does not show evidence of an acute myocardial infarction (Chapter 58), an acute coronary syndrome (Chapter 57), pericarditis (Chapter 62), or a worrisome arrhythmia (Chapters 51 to 53; Fig. 56-3).[6]

Resting Electrocardiogram

Although there may be focal, diagnostic findings of ST segment depression or T wave inversions (Fig. 56-4) on the resting ECG in patients with chronic ischemic heart disease, even those with extensive anatomic coronary artery disease may have a normal tracing at rest. In addition to myocardial ischemia, other conditions that can produce ST-T wave abnormalities include LV hypertrophy and dilation due to long-standing hypertension and valvular heart disease (e.g., aortic stenosis, hypertrophic cardiomyopathy), electrolyte abnormalities, neurogenic effects, and antiarrhythmic drugs. The presence of new ST-T wave abnormalities on the resting ECG, however, can be helpful in the diagnosis of coronary artery disease and may correlate with the severity of the underlying heart disease.

In addition to focal ST-T wave abnormalities, the ECG may reveal various conduction disturbances, most frequently left bundle branch block and left anterior fascicular block (Chapter 42). The finding of abnormal Q waves is relatively specific for the presence of previous MI but may not help determine when such an event occurred. Arrhythmias, especially ventricular premature beats (Chapter 53), may be present on the ECG but have a low sensitivity and specificity for coronary artery disease.

During a spontaneous episode of angina pectoris or during exertion or stress, the ECG becomes abnormal in 50% or more of patients with normal resting ECGs. The most common abnormality observed is focal ST segment depression, usually in one or more ECG lead groups, which signifies the presence of subendocardial ischemia. On occasion, transient but diminutive ST segment elevation and normalization of previous resting ST-T wave depression or inversion (pseudonormalization) may develop during chronic angina and ischemia, although ST segment elevation is far more commonly observed in ACS patients with plaque rupture.

Chest Radiography

Unless there is a history of prior MI, heart failure, or structural heart disease, the chest radiograph (Chapter 44) is usually normal in patients with stable angina and chronic ischemic heart disease. If an enlarged cardiac silhouette is present, it is generally indicative of a previous MI with LV dilation and cardiac remodeling. Other causes of cardiomegaly include long-standing hypertension (Chapter 64), concomitant valvular heart disease (Chapter 60), pericardial effusion (Chapter 62), and nonischemic cardiomyopathy (Chapter 47).

Laboratory Testing

In patients with new-onset or worsening symptoms, serial troponin measurements can distinguish MI and ACS from chronic ischemic heart disease (Chapters 57 and 58). The plasma levels of brain natriuretic peptide (BNP) and N-terminal pro-BNP, which increase in response to spontaneous or provoked ischemia, do not reliably distinguish stable from acute coronary syndromes but are associated with the risk of future cardiovascular events in patients who are at risk for coronary disease.

All patients with chronic angina should have biochemical evaluation of total cholesterol, low-density lipoprotein (LDL) cholesterol, high-density lipoprotein (HDL) cholesterol, triglycerides, serum creatinine (estimated glomerular filtration), and fasting blood glucose levels. In patients with known or suspected diabetes, a hemoglobin A_{1C} level should be obtained (Table 56-3). Other biochemical markers that are not routinely recommended but are associated with higher risk of future cardiovascular events include lipoprotein (a), apolipoprotein B, small dense LDL cholesterol, and lipoprotein-associated

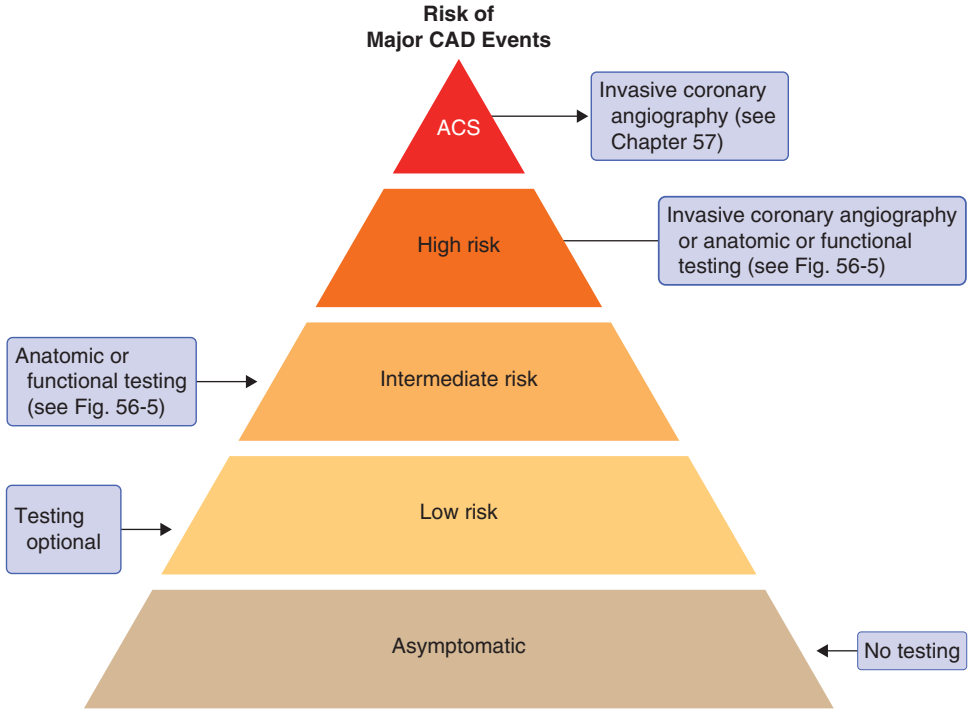

FIGURE 56-2. **Guide to when to consider noninvasive and invasive tests.** ACS = acute coronary syndrome (see Chapter 57). (From Gulati M, Levy PD, Mukherjee D, et al. 2021 AHA/ACC/ASE/CHEST/SAEM/SCCT/SCMR guideline for the evaluation and diagnosis of chest pain: a report of the American College of Cardiology/American Heart Association joint committee on clinical practice guidelines. *Circulation*. 2021;144:e368-e454.)

phospholipase A_2. Homocysteine levels correlate with the risk for development of coronary heart disease, but randomized trials have failed to demonstrate a reduction of clinical events when elevated homocysteine levels are reduced; as a result, routine screening for an elevated homocysteine level is not recommended.

High-sensitivity C-reactive protein, which is an acute-phase reactant of inflammation, has a strong and consistent relationship to the risk of future cardiovascular events, and an elevated level may warrant more aggressive diagnostic evaluation and therapy. Similarly, elevated levels of N-terminal pro-B-type natriuretic peptide can predict worse outcomes in patients with stable ischemic heart disease.

Differential Diagnosis of Angina

Many common noncardiac disorders may be manifested with clinical features that can be confused with angina pectoris (see Table 39-2). In some instances, symptoms may be indistinguishable from ischemic heart disease. For example, many patients with angina have coexisting esophageal disorders (Chapter 124), and both angina and esophageal discomfort may be relieved by nitroglycerin (Chapter 39). A distinguishing feature from angina is that esophageal discomfort is often relieved by antacids, proton pump inhibitors, or food.

Costochondritis can mimic angina but can typically be distinguished by the presence of well-localized pain on palpation. However, pressure, if it is applied too firmly to the anterior chest wall during examination of a patient with suspected angina pectoris, may elicit symptoms of discomfort even in normal subjects. Cervical radiculopathy may cause pain radiating to the shoulders, neck, or upper arms and can be confused with angina. However, this condition typically causes a constant ache that is often exacerbated by neck movement or rotation and may be accompanied by a focal sensory deficit or radiculopathy.

Pulmonary hypertension (Chapter 69) can cause exertional chest discomfort that may share many of the characteristics of angina pectoris. It is believed that right ventricular ischemia during physical exertion may cause this discomfort along with associated symptoms of exertional dyspnea, dizziness, and syncope. Findings on physical examination typically include a parasternal lift, a loud (and sometimes palpable) pulmonary component of the second heart sound, and findings of right ventricular hypertrophy on electrocardiography.

Chest discomfort may also be an important presenting clinical feature of pulmonary embolism (Chapter 68). Physical findings typically include tachycardia and tachypnea, an accentuated pulmonic component of the second heart sound, and occasionally a right-sided S_4 gallop. Pleuritic discomfort suggests pulmonary infarction, whereas a history of pain exacerbated by inspiration or deep breathing, along with a pleural friction rub, usually helps distinguish it from angina pectoris.

Acute pericarditis (Chapter 62) may be confused with the discomfort of angina pectoris, but pericarditis tends to cause chest pain that is generally sharp, is not relieved by rest or nitroglycerin, is exacerbated by movement or deep breathing, and is associated with a pericardial friction rub that may be evanescent. Aortic dissection (Chapter 63), which may be manifested with acute, severe chest pain, may be confused with an acute MI but generally not with angina.

Pretest Probability in Patients with Angina or Ischemic Equivalents

When symptoms of angina or exertional dyspnea prompt consideration of coronary heart disease and the need for additional cardiac evaluation, the clinician should first make a probability estimate of the likelihood that obstructive coronary disease is present. A number of validated risk assessment models exist that, in general, are useful in calculating this probability as follows:

- Low Pretest Probability: less than 10% pretest probability of coronary heart disease;
- Intermediate Pretest Probability: between 10% and 90% pretest probability of coronary heart disease;
- High Pretest Probability: greater than 90% pretest probability of coronary heart disease.

Recent evidence suggests that the pretest probability of detecting obstructive coronary disease among middle-aged men and women with typical angina has declined appreciably, to 32% and 44% in men aged 50 to 59 and 60 to 69 years, respectively, and to just 13% and 16% in women aged 50 to 59 and 60 to 69 years, respectively (see Fig. 56-1). These data reinforce the observation that epicardial coronary obstruction may be less common than previously believed and that other causes of chronic myocardial ischemia, such as coronary vasospasm, microvascular angina, and ischemia with nonobstructive coronary arteries, may be as frequent, if not more frequent.

Noninvasive Testing

Noninvasive stress testing with a standard electrocardiographic treadmill or bicycle exercise, radionuclide imaging (Chapter 44), stress echocardiography (Chapter 43), or newer diagnostic modalities such as cardiac magnetic resonance (CMR; Chapter 44) and positron emission tomography (PET; Chapter 44)

Pretest likelihood of CAD	Low →	No testing necessary →	Option for CAC for ASCVD risk stratification		(see Chapter 44)
	Intermediate-high →	Younger patient (age < 65 years)	**OR**	Less obstructive CAD suspected →	CCTA favored (see Chapter 44)
	Intermediate-high →	Older patient (age ≥ 65 years)	**OR**	More obstructive CAD suspected →	Stress testing favored

	Favors use of CCTA	Favors use of stress imaging
Goal	• Exclude obstructive CAD • Detect nonobstructive CAD	• Ischemia-guided management
Availability and expertise	• High-quality imaging and expert interpretation routinely available	• High-quality imaging and expert interpretation routinely available
Likelihood of obstructive CAD	• Age <65 years	• Age ≥65 years
Prior test results	• Prior functional study inconclusive	• Prior CCTA inconclusive
Other compelling indications	• Patient unable to exercise • Anomalous coronary arteries • Require evaluation of aorta or pulmonary arteries	• Suspect scar (especially if PET or stress CMR available) • Suspect coronary microvascular dysfunction (when PET or CMR available)

Stress testing information

	ETT	Stress echocardiography	SPECT MPI	PET MPI	Stress CMR MPI
Patient capable of exercise	✓	✓	✓		
Pharmacologic stress indicated		✓	✓	✓	✓
Quantitative flow				✓	✓
LV dysfunction/scar		✓	✓	✓	✓

FIGURE 56-3. Approach to choosing diagnostic testing in suspected angina pectoris or chronic ischemic heart disease. ASCVD = atherosclerotic cardiovascular disease; CAC = coronary artery calcium; CAD = coronary artery disease; CCTA = coronary computed tomography angiography; CMR = cardiovascular magnetic resonance; ETT = exercise tolerance test; LV = left ventricular; MPI = myocardial perfusion imaging; PET = positron emission tomography; SPECT = single-photon emission computed tomography. (From Gulati M, Levy PD, Mukherjee D, et al. 2021 AHA/ACC/ASE/CHEST/SAEM/SCCT/SCMR guideline for the evaluation and diagnosis of chest pain: a report of the American College of Cardiology/American Heart Association joint committee on clinical practice guidelines. *Circulation*. 2021;144:e368-e454.)

are useful and clinically important options for establishing the diagnosis and prognosis in patients with chronic ischemic heart disease (Fig. 56-5). The predictive accuracy of these tests is defined not only by their sensitivity and specificity but also by the prevalence of disease (or pretest probability) in the population under study. Noninvasive testing should be performed only if the incremental information is likely to alter the planned management strategy. Thus, the value of noninvasive stress testing is limited in patients with a very low likelihood of ischemic heart disease (Chapter 44) and is greatest when the pretest likelihood is intermediate because the test result is likely to have the greatest effect on the post-test probability of coronary artery disease and, hence, on clinical decision making.[7]

Each noninvasive test has a sensitivity and specificity (Table 56-4) that, when combined with a patient's pretest probability (see Table 56-1), can yield a post-test probability that may essentially rule in or rule out significant for coronary artery disease (Fig. 56-6).[8] The choice among tests depends on the patient's characteristics (see Figs 56-3 and 56-5). Stress testing can be performed carefully in patients with mild aortic valve stenosis or hypertrophic cardiomyopathy but generally should be avoided in patients with severe disease.

Cardiac Computed Tomographic Angiography

Cardiac computed tomographic angiography (CCTA; Chapter 44) is a highly sensitive method to detect coronary calcification (see Fig. 44-9), which is strongly associated with coronary atherosclerosis, and can also provide noninvasive angiography of the proximal coronary arteries. Although coronary calcification is a highly sensitive (approximately 90%) finding in patients with coronary artery disease, the specificity for identifying patients with obstructive coronary artery disease is much lower (approximately 50%). Because of the potential unnecessary testing from false-positive results, CCTA is currently not recommended as a routine screening approach for suspected obstructive coronary artery disease in individuals who are asymptomatic or are at low risk (<10% 10-year estimated risk of coronary events).

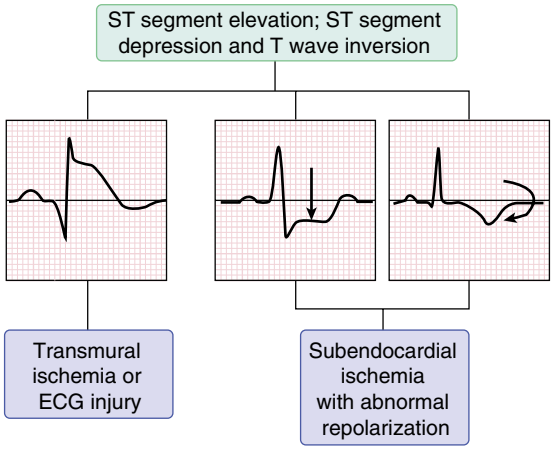

FIGURE 56-4. **Ischemic ST segment shifts and repolarization changes on electrocardiogram (ECG).**

TABLE 56-3 BLOOD TESTS TO OBTAIN ROUTINELY (OR SELECTIVELY*) IN PATIENTS WITH CHRONIC STABLE ISCHEMIC HEART DISEASE

LIPID LEVELS
Low-density lipoprotein (LDL) and high-density lipoprotein (HDL) cholesterol
Triglyceride level
*LDL electrophoresis (especially apolipoprotein B and small dense LDL)
*Lipoprotein (a)
*Lipoprotein-associated phospholipase A_2
METABOLIC EVALUATION
Fasting plasma glucose concentration
Serum creatinine level
Thyroxine level
*Hemoglobin A_{1c} in patients with known or suspected diabetes
MARKERS OF INFLAMMATION OR CARDIAC FUNCTION
*High-sensitivity C-reactive protein
*Brain natriuretic peptide
PROTHROMBOTIC ASSESSMENT
Plasma fibrinogen
Platelet count
*Factor V Leiden
*D-dimer
*Plasminogen activator inhibitor type 1
TO ASSESS OTHER POTENTIAL CARDIAC RISK FACTORS
*Serum homocysteine level

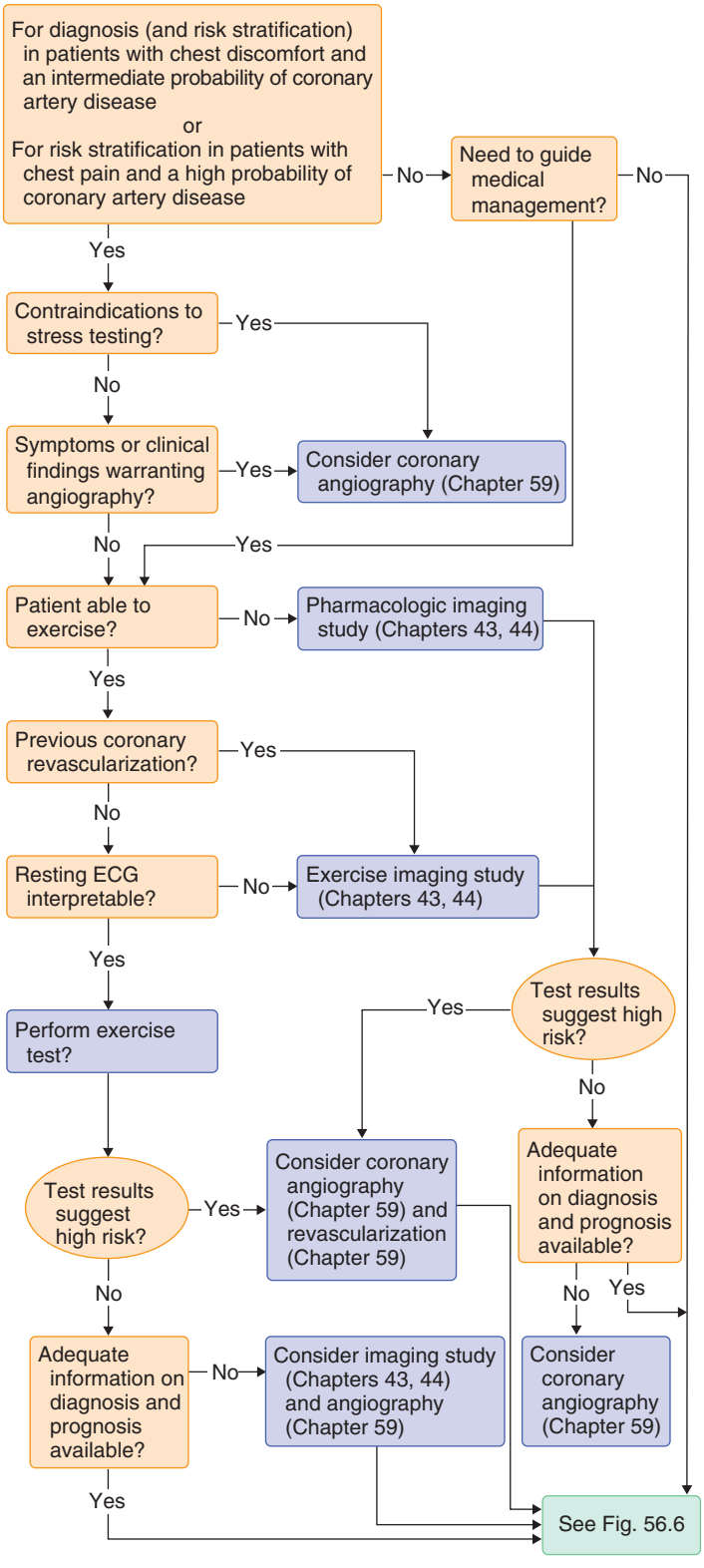

FIGURE 56-5. **Approach to the use of stress testing and angiography for the evaluation of chronic stable angina.** ECG = electrocardiogram. (Modified from American College of Cardiology/American Heart Association Task Force on Practice Guidelines. Management of patients with chronic stable angina. *ACC/AHA/ACP-ASIM Pocket Guidelines*. Philadelphia: Elsevier Science; 2000.)

By contrast, selective screening of intermediate-risk patients may be reasonable because a high calcium score may reclassify such individuals as higher risk and thereby lead to more intensive risk factor modification and treatment.[9] In symptomatic patients who have an intermediate pretest probability of obstructive coronary artery disease, stress myocardial perfusion imaging and CCTA are equivalent in predicting the composite end point of death, MI, or hospitalization for ACS.[A1,A2] A negative CCTA portends a very favorable prognosis. Since CCTA identifies both obstructive and nonobstructive coronary artery disease, however, it appears to provide better overall prognostic information[A3,A4] and has replaced functional testing in some recent guidelines. CCTA is also a diagnostic alternative to invasive coronary angiography for patients who have stable chest pain and an intermediate probability of obstructive coronary disease.[A5]

Exercise Electrocardiography

An exercise ECG is the preferred test in patients who have suspected angina pectoris and are considered to have a moderate probability of coronary artery disease if the resting ECG is interpretable (i.e., ST segments are not obscured by structural heart disease or medication), provided subjects are capable of achieving an adequate workload. Interpretation of the exercise ECG should include the exercise capacity achieved (duration and metabolic equivalents of the external workload), the magnitude and extent of ST segment deviation, the clinical and hemodynamic responses to exercise, and the rapidity with which the heart rate returns to normal after exercise (recovery phase).

The exercise test protocol is usually adjusted to a patient's tolerance, aiming for 6 to 12 minutes of exercise time (i.e., Bruce protocol stages II to IV) to achieve maximal oxygen consumption and to elicit objective evidence of inducible ischemia, if present. Exercise stress testing is generally safe,

with death or MI occurring in less than one case per 2500 tests, when such provocative testing is avoided in patients with ACS, severe aortic stenosis, severe hypertension, or uncontrolled heart failure. Other contraindications are acute MI, symptomatic arrhythmias, acute pulmonary embolism, and suspected acute aortic dissection. Relative contraindications are hypertension above 200 mm Hg systolic or 110 mm Hg diastolic, significant aortic stenosis, hypertrophic cardiomyopathy, and high-degree atrioventricular block.

Concomitant antianginal therapy (notably the use of β-blockers) reduces the sensitivity of exercise testing as a screening tool. If the purpose of the exercise test is to diagnose ischemia, it should be performed, whenever possible, before β-blockers are initiated or 2 to 3 days after their discontinuation.

TABLE 56-4 APPROXIMATE SENSITIVITIES AND SPECIFICITIES OF COMMON NONINVASIVE TESTS TO DIAGNOSE CORONARY ARTERY DISEASE

TEST	SENSITIVITY (%)	SPECIFICITY (%)
Stress ECG	58	62
Stress echocardiography	85	82
CCTA	97	78
SPECT	87	70
PET	90	85
Stress CMR	90	80

CCTA = coronary computed tomography angiography; CMR = stress cardiac magnetic resonance; ECG = electrocardiogram; PET = positron emission tomography; SPECT = single-photon emission computed tomography (exercise stress SPECT with or without dipyridamole or adenosine); stress echocardiography = exercise stress echocardiography.

Adapted from Knuuti J, Ballo H, Juarez-Orozco LE, et al. The performance of non-invasive tests to rule-in and rule-out significant coronary artery stenosis in patients with stable angina: a meta-analysis focused on post-test disease probability. *Eur Heart J*. 2018;39:3322-3330.

Nuclear Cardiology Imaging

Stress myocardial perfusion imaging (Chapter 44) with single-photon emission computed tomography (SPECT) with simultaneous electrocardiographic testing (see Fig. 44-8) is particularly helpful in the diagnosis of coronary artery disease in patients with abnormal resting ECGs and among those in whom ST segment responses cannot be interpreted accurately, such as patients with repolarization abnormalities caused by LV hypertrophy, those with left bundle branch block, and those receiving digitalis. Its sensitivity and specificity are superior to exercise electrocardiography alone in detecting coronary artery disease (especially multivessel disease), in identifying regional perfusion defects that may localize to and correlate with diseased vessels, and in delineating the magnitude and extent of ischemic and infarcted myocardium. Treadmill testing is preferred for patients who can perform such physical activity because of the additional diagnostic and prognostic information achieved with graded exercise. In the 40 to 50% of patients who are unable to exercise adequately, however, myocardial perfusion imaging with pharmacologic vasodilator stress with dipyridamole, adenosine, or regadenoson may be the preferred approach to noninvasive testing.

Stress Echocardiography (Chapter 43)

Stress two-dimensional echocardiography with exercise or pharmacologic stress can detect regional ischemia by identifying new wall motion abnormalities (see Fig. 43-7). Additional clinical information about associated structural heart disease, chamber dimensions, and valve function can be readily obtained. Exercise echocardiography can detect the presence of coronary artery disease with an accuracy similar to that achieved with stress myocardial perfusion imaging and is useful for localizing and quantifying ischemic myocardial segments. Pharmacologic stress is usually performed with dobutamine in patients who are unable to exercise and in those unable to achieve adequate heart rates with exercise.

Stress Cardiac Magnetic Resonance Imaging (Chapter 44)

Pharmacologic stress perfusion with CMR imaging is becoming increasingly available in many centers and may provide additional diagnostic capability in detecting the presence of structural heart disease, in addition to suspected coronary artery disease. CMR with gadolinium enhancement is the most accurate way to diagnose a scar from a prior MI (see Fig. 44-13). Preliminary

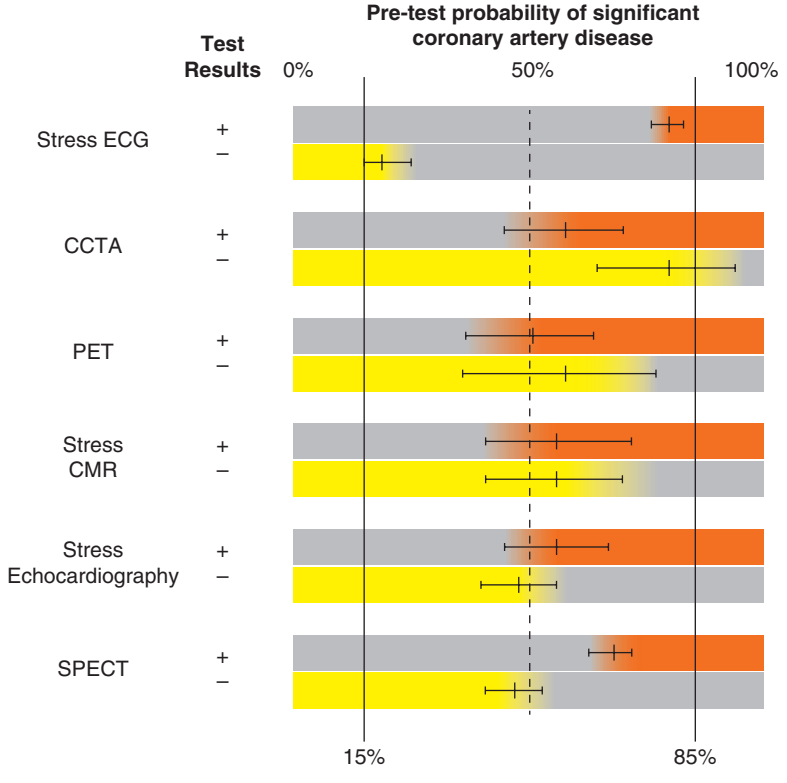

FIGURE 56-6. Ability of noninvasive tests to rule in or rule out significant coronary artery disease. Yellow = range where a negative test can rule out coronary artery disease to a threshold below 15%; red = range where a positive test can rule in coronary artery disease at a threshold above 85%. CCTA = coronary computed tomography angiography; CMR = stress cardiac magnetic resonance; ECG = electrocardiogram; PET = positron emission tomography; SPECT = single-photon emission computed tomography (exercise stress SPECT with or without dipyridamole or adenosine); stress echocardiography = exercise stress echocardiography. (From Knuuti J, Ballo H, Juarez-Orozco LE, et al. The performance of non-invasive tests to rule-in and rule-out significant coronary artery stenosis in patients with stable angina: a meta-analysis focused on post-test disease probability. *Eur Heart J*. 2018;39:3322-3330.)

TABLE 56-5 CORONARY ANGIOGRAPHY FOR DIAGNOSIS AND RISK STRATIFICATION IN PATIENTS WITH CHRONIC ANGINA AND STABLE ISCHEMIC HEART DISEASE

FOR INITIAL DIAGNOSTIC INDICATION
Recommended on the Basis of Evidence or General Consensus
Patients with suspected angina and evidence of intermediate-high risk, moderate-severe ischemia on noninvasive testing, or a changing angina pattern who have survived sudden cardiac death or serious ventricular arrhythmia
Weight of Evidence or Opinion Is in Favor
Uncertain diagnosis after noninvasive testing, and the benefit of a more certain diagnosis outweighs the risk and cost of coronary angiography
Inability to undergo noninvasive testing because of disability, illness, or morbid obesity
Occupational requirement for a definitive diagnosis
Suspected nonatherosclerotic cause of myocardial ischemia
Suspicion of a coronary spasm
High pretest probability of left main or three-vessel disease
Recurrent hospitalization for chest pain in the absence of definitive diagnosis
Overriding desire for a definitive diagnosis and a greater than low probability of CAD
Not Recommended
Significant comorbidity in patients in whom the risk of coronary arteriography outweighs the benefit of the procedure
Overriding personal desire for a definitive diagnosis and a low probability of CAD
FOR INITIAL RISK STRATIFICATION OR TREATMENT INDICATION
Recommended on the Basis of Evidence or General Consensus
With disabling (CCS class III and class IV) chronic stable angina despite medical therapy
With high-risk criteria on noninvasive testing regardless of anginal severity
Patients with angina who have survived sudden cardiac death or serious ventricular arrhythmia
Angina and symptoms and signs of congestive heart failure
Clinical characteristics that indicate a high likelihood of severe CAD
Weight of Evidence or Opinion Is in Favor
Significant left ventricular dysfunction (EF < 45%), CCS class I or class II angina, and demonstrable ischemia but less than high-risk criteria on noninvasive testing
High-risk criteria suggesting ischemia on noninvasive testing
Inadequate prognostic information after noninvasive testing
Clinical characteristics that indicate a high likelihood of severe CAD
CCS class I or class II angina, preserved left ventricular function (EF > 45%), and less than high-risk criteria on noninvasive testing
CCS class III or class IV angina that improves to class I or class II with medical therapy
CCS class I or class II angina but intolerance (unacceptable side effects) to adequate medical therapy
Not Recommended
CCS class I or class II angina in patients who respond to medical therapy and who have no evidence of ischemia on noninvasive testing
Patients who prefer to avoid revascularization after adequate explanation

CAD = coronary artery disease; CCS = Canadian Cardiovascular Society; EF = ejection fraction.
Modified from Gibbons RJ, Abrams J, Chatterjee K, et al. ACC/AHA 2002 guideline update for the management of patients with chronic stable angina—summary article: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines (Committee on Management of Patients with Chronic Stable Angina). *Circulation*. 2003;107:149-158.

TABLE 56-6 USING THE RESULTS OF NONINVASIVE RISK STRATIFICATION TO GUIDE CLINICAL DECISION MAKING

HIGH RISK (>3% ANNUAL MORTALITY RATE)
Severe resting left ventricular dysfunction (LVEF < 35%)
High-risk treadmill score (≤−11)*
Severe exercise left ventricular dysfunction (exercise LVEF <35%)
Stress-induced large perfusion defect (particularly if anterior)
Stress-induced multiple perfusion defects of moderate size
Large, fixed perfusion defect with left ventricular dilation or increased lung uptake (^{201}Tl)
Stress-induced moderate perfusion defect with left ventricular dilation or increased lung uptake (^{201}Tl)
Echocardiographic wall motion abnormality (involving more than two segments) developing at a low dose of dobutamine or at a low heart rate (<120 beats/min)
Stress echocardiographic evidence of extensive ischemia
INTERMEDIATE RISK (1-3% ANNUAL MORTALITY RATE)
Mild to moderate resting left ventricular dysfunction (LVEF = 35-49%)
Intermediate-risk treadmill score (−11 < score < 5)*
Stress-induced moderate perfusion defect without left ventricular dilation or increased lung intake (^{201}Tl)
Limited stress echocardiographic ischemia with a wall motion abnormality only at higher doses of dobutamine involving two segments or less
LOW RISK (<1% ANNUAL MORTALITY RATE)
Low-risk treadmill score (≥5)*
Normal or small myocardial perfusion defect at rest or with stress†
Normal stress echocardiographic wall motion or no change of limited resting wall motion abnormalities during stress†

*Score = (duration of exercise in minutes) − (5 × mm of ST segment depression) − (4 × angina score), where 0 = no angina, 1 = nonlimiting angina, and 2 = angina that causes discontinuation of the test.
†Although the published data are limited, patients with these findings will probably not be at low risk in the presence of either a high-risk treadmill score or severe resting left ventricular dysfunction (LVEF < 35%).
LVEF = left ventricular ejection fraction; Tl = thallium.
From Gibbons RJ, Abrams J, Chatterjee K, et al. ACC/AHA 2002 guideline update for the management of patients with chronic stable angina—summary article: a report of the American College of Cardiology/American Heart Association Task Force on practice guidelines (Committee on the Management of Patients with Chronic Stable Angina). *J Am Coll Cardiol*. 2003;41:159-168.

data suggest that cardiovascular magnetic resonance imaging may be equally sensitive but more specific than fractional flow reserve (see "Diagnostic Coronary Angiography") for determining which patients will benefit from revascularization.[A6]

Diagnostic Coronary Angiography

Despite the continued evolution of noninvasive diagnostic testing, invasive coronary angiography (Chapter 59) remains the "gold standard" for anatomic definition of obstructive coronary artery disease. Among patients who have a clinical diagnosis of stable angina and chronic myocardial ischemia and who are referred for coronary angiography, a 70% or more luminal diameter narrowing is found in one (about 25%), two (about 25%), or all three (about 25%) epicardial coronary arteries in about 75% of cases; another 5 to 10% of patients have obstruction of the left main coronary artery; and the remaining 15 to 20% have no flow-limiting coronary obstructions. These data emphasize the persisting role of coronary angiography for diagnostic purposes (Table 56-5), but angiography is also helpful for risk stratification in patients with clear-cut angina and chronic ischemic heart disease. In patients with less severe coronary stenoses (i.e., 50 to 70% on angiography), coronary intravascular ultrasonography can substantially enhance the quantification of obstruction and vulnerability of the coronary atheroma to future instability. Alternatively, an invasive physiologic approach with use of a pressure wire positioned proximal and distal to a coronary stenosis can measure the severity of the stenosis and determine whether functionally significant flow reduction (i.e., a decreased fractional flow reserve [FFR] <0.8) is present. This technique may be useful when there is a borderline (50 to 60%) visual coronary stenosis at angiography, particularly if such a stenosis subtends an ischemic myocardial segment observed on noninvasive testing. An FFR below 0.8 is generally considered to represent a sufficiently important reduction in coronary flow to justify proceeding to percutaneous coronary intervention (Chapter 59) to reduce symptoms and the subsequent need for urgent revascularization.[A7] By contrast, an FFR of 0.8 or higher would indicate that myocardial revascularization of the stenotic coronary artery would be of little benefit clinically.

Risk Stratification

Clinical and noninvasive criteria can be used in a complementary fashion to refine the estimate of risk for the individual patient with chronic ischemic heart disease (Table 56-6). Clinical characteristics that include age, male sex, diabetes mellitus, previous MI, and symptoms typical of angina are predictive of the presence of coronary artery disease. Heart failure and LV dysfunction (generally defined by an ejection fraction <50%), the severity and extent of angina, and associated symptoms such as dyspnea are also important predictors of outcome in patients with chronic ischemic heart disease.

The simple classification of disease into single-, double-, or triple-vessel or left main coronary artery disease remains the most widely used approach (Table 56-8). Additional prognostic information is provided by the severity and extent of coronary luminal narrowing and its location. For example, high-grade lesions of the left main coronary artery or its equivalent, as defined by severe proximal left anterior descending and proximal left circumflex coronary artery disease, are particularly life-threatening. The SYNTAX trial has permitted the

TABLE 56-7 TREATMENT OF PATIENTS WITH STABLE ANGINA

GENERAL MEASURES
Rule out and control aggravating conditions
Associated noncardiac diseases
Associated cardiac disease
Use of drugs aggravating angina
Smoking cessation
Dietary counseling for body weight and lipid control
Exercise prescription
Treat to targets
Hypertension
Blood lipids
Diabetes
PHARMACOLOGIC THERAPY: RECOMMENDATIONS FOR PHARMACOTHERAPY TO PREVENT MI AND DEATH AND TO REDUCE SYMPTOMS
Recommended on the Basis of Evidence or General Consensus
Aspirin in the absence of contraindications
β-Blockers as initial therapy in the absence of contraindications in patients with prior MI or without prior MI
Angiotensin-converting enzyme inhibitor in all patients with CAD who also have diabetes or left ventricular systolic dysfunction
Low-density lipoprotein–lowering therapy in patients with documented or suspected CAD, with a target <55 mg/dL using high-potency statins, ezetimibe, and PCSK9 inhibitors
Sublingual nitroglycerin or nitroglycerin spray for the immediate relief of angina
Calcium-channel antagonists or long-acting nitrates as initial therapy for reduction of symptoms when β-blockers are contraindicated
Calcium-channel antagonists or long-acting nitrates in combination with β-blockers when initial treatment with β-blockers is not successful
Calcium-channel antagonists and long-acting nitrates as a substitute for β-blockers if initial treatment with β-blockers leads to unacceptable side effects
Weight of Evidence or Opinion Is in Favor
Rivaroxaban 2.5 mg twice daily added to low-dose (81-100 mg daily) aspirin
Clopidogrel when aspirin is contraindicated
Long-acting non-dihydropyridine calcium-channel antagonists instead of β-blockers as initial therapy
Weight reduction and increased physical activity in persons with metabolic syndrome
Consider fibric acid derivatives for high-risk patients with elevated triglycerides if LDL-cholesterol is at target on statin therapy
Angiotensin-converting enzyme inhibitor in patients with CAD or other vascular disease
Not Recommended
Dipyridamole
Chelation therapy

CAD = coronary artery disease; HDL = high-density lipoprotein; LDL = low-density lipoprotein; MI = myocardial infarction; PCSK9 = proprotein convertase subtilisin/kexin type 9.

From Fihn SD, Blankenship JC, Alexander KP, et al. 2014 ACC/AHA/AATS/PCNA/SCAI/STS focused update of the guideline for the diagnosis and management of patients with stable ischemic heart disease: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines, and the American Association for Thoracic Surgery, Preventive Cardiovascular Nurses Association, Society for Cardiovascular Angiography and Interventions, and Society of Thoracic Surgeons. *J Am Coll Cardiol*. 2014;64:1929-1949.

TABLE 56-8 CURRENT RECOMMENDATIONS FOR MYOCARDIAL REVASCULARIZATION IN PATIENTS WITH CHRONIC STABLE ANGINA

CABG SURGERY VERSUS MEDICAL THERAPY
Among patients with medically refractory angina pectoris, CABG surgery is indicated for symptom improvement.
Among patients with medically stable angina pectoris, CABG surgery is indicated to prolong life in left main coronary artery disease or three-vessel disease (regardless of left ventricular function) and, possibly, to help symptoms.
CABG surgery may be indicated for prolongation of life if the proximal left anterior descending coronary artery is involved (regardless of the number of diseased vessels).
CABG surgery may reduce the composite end point of death, myocardial infarction, or stroke in diabetic patients with extensive multivessel (two- to three-vessel) coronary artery disease compared with medical therapy.
CABG surgery can reduce symptoms, cardiovascular events, and death in diabetic patients with stable angina.
PCI VERSUS MEDICAL THERAPY
For the initial management of patients with stable ischemic heart disease, PCI does not reduce the risk of death, myocardial infarction, or other major cardiovascular events when it is added to optimal medical therapy.
Among patients with symptomatic angina pectoris, PCI is indicated to improve symptoms.
PCI may be indicated in the presence of severe myocardial ischemia, regardless of symptoms. PCI does not appear to improve survival compared with medical treatment among patients with one- or two-vessel disease.
In the absence of symptoms of myocardial ischemia, PCI is not indicated (merely for the presence of an anatomic stenosis).
PCI VERSUS CABG SURGERY
For single-vessel disease, PCI and CABG surgery provide excellent symptom relief, but repeated revascularization procedures are required more frequently after PCI. Intracoronary stenting is preferred to regular PCI, but direct comparison with CABG surgery is limited.
For treating diabetic patients with two- or three-vessel disease, CABG surgery is the treatment of choice.
For nondiabetic patients, multivessel PCI and CABG surgery are acceptable alternatives. The choice of PCI or CABG surgery for initial treatment depends primarily on local expertise and the patient's and physician's preferences.
In general, PCI is preferred for patients at low risk and CABG surgery for patients at high risk.

CABG = coronary artery bypass graft; PCI = percutaneous coronary intervention.

identification of subsets of coronary artery disease patients into three tertiles of low-, moderate-, and high-risk anatomic findings based on multiple lesional characteristics (see Table 56-7). Although the plaque that is causing the most severe chronic stenosis is not necessarily the one that will subsequently rupture to cause an acute coronary syndrome or acute MI, the underlying extent and severity of the coronary stenoses are nevertheless potent predictors of the likelihood of a critical plaque rupture somewhere in the epicardial coronary arterial circulation.

TREATMENT

Comprehensive management of angina and chronic ischemic heart disease (Fig. 56-7) entails multiple therapeutic approaches to the identification and treatment of associated diseases that can precipitate or worsen angina and ischemia (Table 56-8): cardiac risk factor identification and intervention; application of pharmacologic and nonpharmacologic interventions for secondary prevention; pharmacologic and symptomatic management of angina and ischemia; and myocardial revascularization with percutaneous coronary intervention (PCI) or coronary artery bypass graft (CABG) surgery, when indicated (Table 56-8).[10,11] A multidimensional management approach integrates all of these considerations, often simultaneously, in each patient. Among pharmacotherapies, three drug classes are classified as being "disease modifying" in that they have been demonstrated to reduce mortality and morbidity in patients with chronic ischemic heart disease and preserved LV function: antiplatelet agents such as aspirin; inhibitors of the renin-angiotensin-aldosterone system, especially angiotensin-converting enzyme (ACE) inhibitors; and effective lipid-lowering agents, principally statins (Chapter 40). In patients who have type 2 diabetes, the use of either a sodium-glucose cotransporter-2 inhibitor or a glucose-like peptide-1 agonist can reduce cardiac events (Chapter 210). Other therapies, such as nitrates, β-blockers, calcium antagonists, and ranolazine, can reduce symptomatic myocardial ischemia, ameliorate or prevent angina, and improve exercise performance, but they have not been shown to reduce mortality in patients with chronic ischemic heart disease.

Medical Therapy

Careful attention to lifestyle and the management of coronary risk factors is essential (Fig. 56-8). Such secondary prevention strategies can reduce the risk of progressive coronary disease, morbidity, and mortality.

Drugs That Alter Lipid Metabolism

Each 1% increase in the LDL cholesterol level results in a 2 to 3% increase in the risk for coronary events (Chapter 40). Large, randomized clinical trials in patients with ischemic heart disease have shown a consistent and significant reduction in mortality and cardiac events with statin therapy (Chapter 190). Patients with stable angina and documented ischemic heart disease should routinely be treated with statins[A8] (see Table 190-2). Current U.S. guidelines

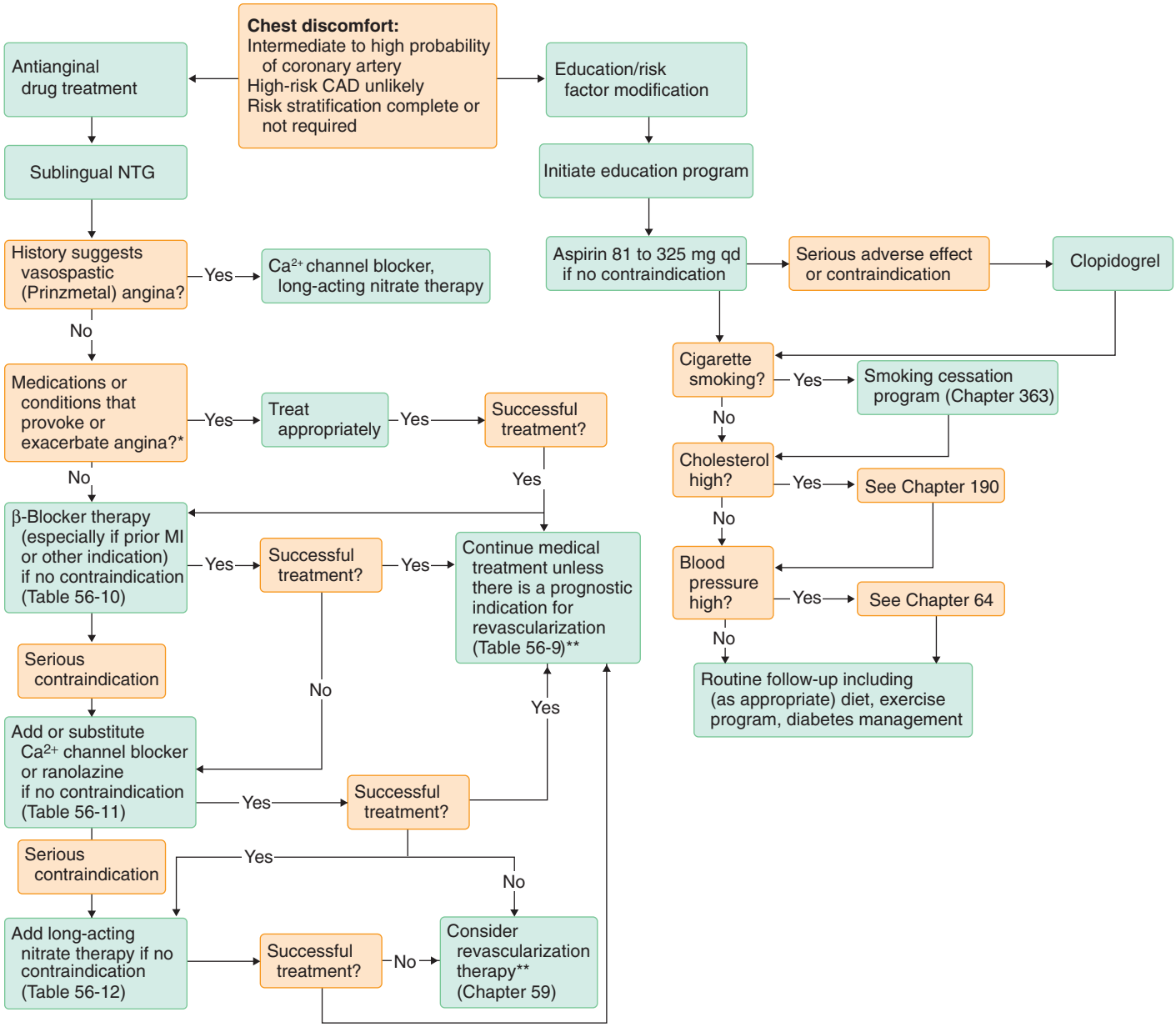

FIGURE 56-7. Algorithm for the oral treatment of stable angina. Both pathways (Antianginal Drug Treatment and Education/Risk Factor Modification) must be completed. *Conditions that exacerbate or provoke angina: medications: vasodilators, excessive thyroid replacement, vasoconstrictors; other medical problems: profound anemia, uncontrolled hypertension, hyperthyroidism, hypoxemia; other cardiac problems: tachyarrhythmias, bradyarrhythmias, valvular heart disease (especially AS), hypertrophic cardiomyopathy. **At any point in this process, based on coronary anatomy, severity of anginal symptoms, and patient preferences, it is reasonable to consider evaluation for coronary revascularization. Unless a patient is documented to have left main, three-vessel, or two-vessel CAD with significant stenosis of the proximal left anterior descending coronary artery, there is no demonstrated survival advantage associated with revascularization in low-risk patients with chronic stable angina; thus, medical therapy should be attempted in most patients before considering PTCA or CABG. AS = aortic stenosis; CABG = coronary artery bypass graft; CAD = coronary artery disease; MI = myocardial infarction; NTG = nitroglycerin; PTCA = percutaneous transluminal coronary angioplasty; qd = once daily. (Modified from American College of Cardiology/American Heart Association Task Force on Practice Guidelines. Management of Patients with Chronic Stable Angina. *ACC/AHA/ACP-ASIM Pocket Guidelines*. Philadelphia: Elsevier Science; 2000.)

recommend high-potency statin therapy (e.g., atorvastatin up to 80 mg per day or rosuvastatin up to 40 mg per day) with periodic monitoring of LDL levels to a target of less than 70 mg/dL, whereas European guidelines recommend a more stringent LDL target of less than 55 mg/dL. With the documentation of additional benefit from ezetimibe and PCSK9 antagonists, most U.S. cardiologists have also adopted these more intensive targeted levels.[12]

Ezetimibe added to statins lowers LDL and reduces subsequent cardiovascular events in patients who have survived an acute coronary syndrome,[A9] even when statins have reduced LDL levels to 50 to 100 mg/dL. PCSK9 inhibitors, which can reduce LDL levels by 60% and LDL levels to less than 30 mg/dL in most patients, are an effective option for patients with elevated LDL levels despite statins, with or without ezetimibe, and further reduce dyslipidemic residual risk, especially in high-risk patients (Chapter 190).[A10]

A pure eicosapentaenoic acid derivative (an icosapent ethyl ester) can significantly reduce cardiovascular death, MI, and stroke as well as all-cause mortality when added to statins in patients who have ischemic heart disease, well-controlled LDL levels (40 to 100 mg/dL), and elevated baseline triglyceride levels (135 to 500 mg/dL).[A11] However, bile acid sequestrants, fibrates, and various fish oil preparations (Chapters 190) targeted to reduce the triglyceride level or raise the HDL cholesterol level have failed to reduce clinical events when added to statins.[A12] Drug therapies directed specifically at raising low levels of HDL with either niacin or cholesteryl ester transfer protein inhibitors have been uniformly disappointing and are not recommended.

Angiotensin-Converting Enzyme Inhibitors

ACE inhibitors and angiotensin receptor blockers (see Table 64-7) reduce cardiac events, cardiovascular mortality, and all-cause mortality in patients with risk factors for or with previously diagnosed coronary artery disease, including high-risk patients with vascular disease or diabetes and patients with chronic ischemic heart disease and no clinical evidence of heart failure. However, the incremental benefit of such agents in otherwise well-treated patients without high-risk features remains less clear.[A13]

Antiplatelet Agents and Anticoagulants

Aspirin reduces the risk of adverse cardiovascular events in patients with angina and chronic ischemic heart disease, and in the absence of contraindications,

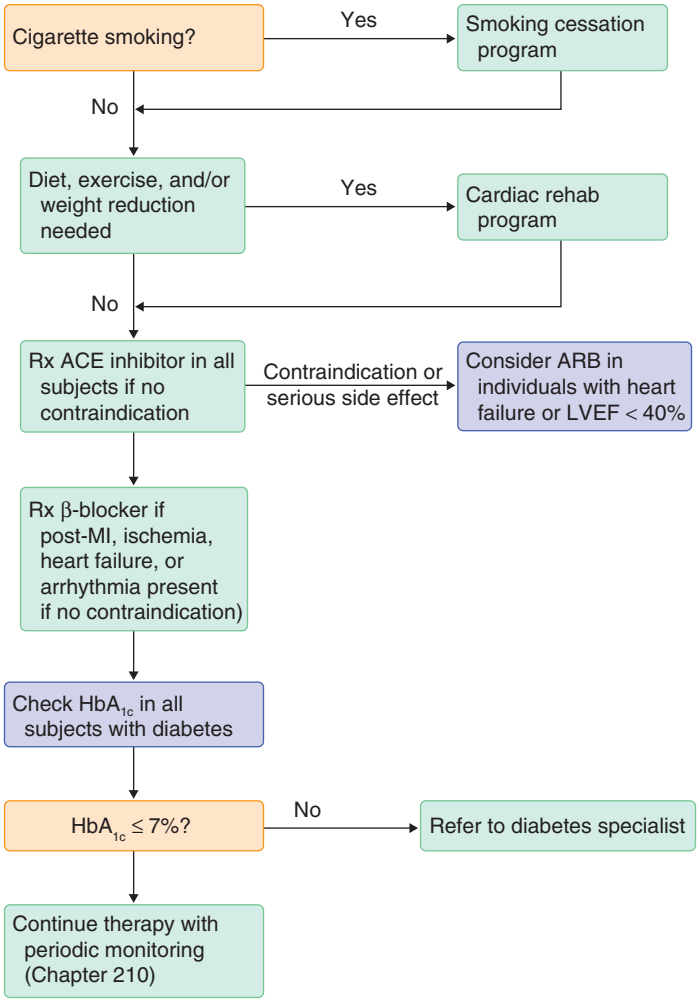

FIGURE 56-8. Approach to lifestyle interventions and pharmacotherapy. ACE = angiotensin-converting enzyme; ARB = angiotensin receptor blocker; HbA_{1c} = hemoglobin A_{1c}; LVEF = left ventricular ejection fraction; MI = myocardial infarction; Rx = prescribe.

should be administered routinely. In such patients, low-dose aspirin (81 mg daily) is as effective as 325 mg daily, with a similar bleeding risk but overall better adherence.[A14]

Although dual antiplatelet therapy with clopidogrel, prasugrel, or ticagrelor (Chapter 70) is of proven benefit when combined with aspirin to reduce the composite end point of death, MI, or stroke in ACS patients and in patients who undergo PCI,[13] especially with drug-eluting stents (Chapters 57, 58, and 59), these agents have not been shown to be superior to low-dose (75 to 162 mg/day) aspirin alone in patients who have stable angina and chronic ischemic heart disease, because any reduction in cardiovascular events is at least offset by an increase in major bleeding events.[A15] For patients who cannot tolerate aspirin or have aspirin insensitivity, clopidogrel (75 mg once daily), prasugrel (10 mg once daily), and ticagrelor (60 mg twice daily) are indicated. A direct-acting anticoagulant (see Table 70-6) is required in patients who have atrial fibrillation (Chapter 52).

Low-dose rivaroxaban (2.5 mg twice daily) combined with low-dose aspirin (81 to 100 mg daily) is superior to aspirin alone for reducing the composite primary endpoint of cardiovascular death, MI, or stroke,[A16] including a 23% reduction in death in patients with stable coronary artery disease,[A17] although it causes more bleeding. Warfarin is generally as effective as aspirin for preventing coronary events in patients with angina and is preferred to aspirin for patients with concomitant atrial fibrillation (Chapter 52), but has it been superseded by direct-acting anticoagulants, except in patients with prosthetic heart valves.

Therapeutic Agents to Reduce Angina and Ischemia

The goal of antianginal therapy is to reduce symptoms of cardiac ischemia and to improve quality of life.[14] β-Blockers, which prevent the binding of catecholamines to the β-adrenergic receptor, lower heart rate and myocardial contractility, thereby reducing myocardial workload, myocardial oxygen demand, and ischemia and anginal symptoms. β-Blockers raise the ischemic threshold and delay or prevent the onset of angina with exercise. β-Blockers also reduce the rate of secondary cardiac events and sudden cardiac death in post-MI patients, but to date there have been no placebo-controlled outcome trials in angina patients. All β-blockers appear to be equally effective in patients with chronic stable angina (Table 56-9). The β-blocker dose should be titrated to a target resting heart rate of 50 to 60 beats per minute as tolerated by the patient.

Calcium-channel blockers (Table 56-10) reduce afterload by their peripheral vasodilatory effects and thus lower myocardial workload and myocardial oxygen demand. Calcium-channel blockers also reduce coronary vascular resistance and inhibit coronary vasospasm by preventing coronary arterial smooth muscle contraction. This favorable reduction in myocardial oxygen demand, coupled with an increase in myocardial oxygen supply, results in a reduction in angina and ischemia. Non-dihydropyridine calcium-channel blockers, such as verapamil and diltiazem, also reduce heart rate. Conversely, dihydropyridine calcium-channel antagonists, such as nifedipine and amlodipine, have greater effect on vascular smooth muscle, are better peripheral and coronary vasodilators, and hence may have advantages for use in the hypertensive patient with angina. In randomized clinical trials, calcium-channel blockers and β-blockers are generally equally effective in relieving angina, improving time to onset of angina, and improving time to ischemic ST depression during exercise. Because calcium-channel blockers have not been shown to reduce death or MI in patients with stable or previously unstable ischemic heart disease, these agents are usually used in patients who cannot tolerate β-blockers or who require additional pharmacotherapy to control their symptoms. When calcium-channel blockers are used with β-blockers, care must be taken not to cause symptomatic bradycardia with verapamil and diltiazem. When calcium-channel blockers are used alone, diltiazem is often preferred because dihydropyridine calcium-channel blockers can increase the heart rate.

Nitrates (Table 56-11) continue to be widely prescribed for antianginal treatment and are effective when they are administered sublingually, orally, or topically. They act as vasodilators by entering vascular smooth muscle, where they are metabolized to nitric oxide, which relaxes vascular smooth muscle, including in coronary arteries. These effects reduce angina by improving coronary blood flow. Nitrates also lower preload because of their venodilatory effects, with a resulting reduction in LV end-diastolic pressure and wall tension, which in turn lowers subendocardial oxygen demand. When nitrates are used in patients with stable angina, they improve exercise tolerance, time to onset of angina, and ST segment depression during treadmill exercise testing. Long-acting nitrates, which are frequently combined with β-blockers and calcium-channel blockers, have additive antianginal and anti-ischemic effects in patients with stable ischemic heart disease. Sublingual nitroglycerin or oral spray can terminate an angina attack and can be used as prophylaxis to prevent exertional angina. Long-acting nitrates administered orally or transdermally are used to prevent angina and to improve exercise tolerance. For avoidance of nitrate tolerance or tachyphylaxis, an 8- to 12-hour nitrate-free interval daily is recommended. Nitroglycerin and nitrates can cause vasodilation-induced headache, a decrease in blood pressure, and, more rarely, severe hypotension with bradycardia due to activation of the vagal Bezold-Jarisch reflex. Because the vasodilation by nitroglycerin is markedly exaggerated and prolonged in the presence of the phosphodiesterase inhibitors sildenafil (Viagra), vardenafil (Levitra), tadalafil (Cialis), and avanafil (Stendra), these agents and nitrates should not be used concurrently.

Ranolazine (initiated at a dose of 500 mg twice daily and titrated up to a maximal dose of 1000 mg twice daily) acts by reducing intracellular calcium overload in ischemic myocytes by inhibiting late inward sodium current entry. The net effect of reduced late inward sodium current is a reduction in LV wall tension and myocardial oxygen demand, thereby reducing angina and ischemia. Ranolazine increases exercise tolerance in patients with stable angina, reduces episodes of recurrent ischemia, and provides additional antianginal benefit in patients who are already receiving intensive antianginal therapy with β-blockers and calcium-channel blockers, but it has not been documented to reduce the composite primary end point of cardiac death, MI, or recurrent ischemia in a trial of patients after an acute coronary syndrome.[A18]

Treating Inflammation

Low-dose colchicine (0.5 mg daily) can reduce the composite primary outcome of cardiac death, MI, stroke, and ischemia-driven revascularization by about 30% compared with placebo, but the reduction in cardiac deaths has been at least counterbalanced by an increase in noncardiovascular death.[A19,A20] Injections of a monoclonal antibody (canakinumab) targeting interleukin-1beta (IL-1β), administered in combination with standard of care (including lipid-lowering therapy) in patients with a prior MI and an hsCRP greater than or equal to 2 mg/L, reduces the primary composite end point of nonfatal MI, stroke, and cardiovascular death by 15% during a median 3.7 years of follow-up.[A21] Whether the treatment of inflammatory pathways will become a part of standard secondary prevention care remains uncertain.

Myocardial Revascularization

Coronary revascularization with CABG surgery (but not PCI) (Chapter 59) prolongs life, reduces major cardiovascular events, and improves health status, quality of life, and functional capacity in selected patients with chronic, stable ischemic heart disease who meet certain anatomic criteria: the presence of

TABLE 56-9 CLINICAL USE OF B-BLOCKERS

COMPOUND BY RECEPTOR ACTIVITY	INTRINSIC SYMPATHOMIMETIC ACTIVITY*	MEMBRANE STABILITY EFFECT	HALF-LIFE (hr)	EXCRETION	ORAL DOSE
β_1 AND β_2					
Propranolol	–	++	1-6	Hepatic	20-80 mg bid-tid
Propranolol long-acting	–	++	8-11	Hepatic	80-360 mg/day
Nadolol	–	–	40-80	Renal	40-80 mg/day
Pindolol	+	+	3-4	Renal	2.5-7.5 mg tid
Sotalol	–	–	7-18	Renal	40-160 mg bid
Timolol	–	–	4-5	Hepatic-renal	10-15 mg bid
β_1 SELECTIVE					
Acebutolol	+	+	3-4	Hepatic	200-600 mg bid
Atenolol	–	–	6-9	Renal	50-200 mg/day†
Bisoprolol	–	–	9-12	50% renal	5-20 mg/day
Metoprolol	–	–	3-7	Hepatic	50-200 mg bid
Metoprolol long-acting	–	–	14-25	Hepatic	25-400 mg
Esmolol	–	–	4.5 min	Esterases in red cells	Bolus 500 µg/kg 50-300 µg/kg/min IV
β_1, β_2, α_2					
Labetalol	+	–	6	Hepatic	200-600 mg bid
Carvedilol	–	+	6-10	Hepatic	25-50 mg bid

*Presence commonly associated with maintenance of or increase in heart rate; absence associated with decrease in heart rate.
†Atenolol may be used in older individuals at a lower dose of 25 mg once daily.
bid = twice daily; IV = intravenous; tid = three times daily.
From Théroux P. Angina pectoris. In: Goldman L, Ausiello DA, eds. *Cecil Textbook of Medicine*. 23rd ed. Philadelphia: Saunders Elsevier; 2008.

TABLE 56-10 PROPERTIES OF ORAL CALCIUM-CHANNEL BLOCKING DRUGS IN CLINICAL USE

DRUGS	USUAL DOSE	ELIMINATION HALF-LIFE (HR)	*HEMODYNAMIC EFFECT* HR	*HEMODYNAMIC EFFECT* PVR	SIDE EFFECTS
DIHYDROPYRIDINES					
Nifedipine PA*	10-40 mg bid	10	↑↑	↓↓↓	Hypotension, dizziness, flushing, edema, constipation
Nifedipine XL*	30-120 mg/day	24	↑	↓↓	
Amlodipine	2.5-10 mg/day	30-50	=	↓↓↓	Headache, edema
Felodipine	2.5-10 mg/day	11-16	↑	↓↓↓	Headache, dizziness
Isradipine	2.5-10 mg bid	8	=	↓↓↓	Headache, fatigue
Nicardipine	20-40 mg tid	2-4	↑	↓↓↓	
Nicardipine SR*	30-60 mg bid	8-10	↑	↓↓	Headache, dizziness, flushing, edema
Nisoldipine	10-40 mg/day	7-12	=	↓↓↓	Same as for nifedipine
Nitrendipine	20 mg/day or bid	5-12	↑	↓↓↓	Same as for nifedipine
OTHERS					
Bepridil	200-400 mg/day	24-40	↓	↓	Arrhythmias, dizziness, nausea
Diltiazem	30-90 mg tid	4-6	↓	↓	Hypotension, dizziness, bradycardia, edema
Diltiazem CD*	120-540 mg/day	—	↓	↓	
Verapamil	80-160 mg tid	3-8	↓	↓↓	
Verapamil SR*	120-480 mg/day	—	↓	↓↓	Hypotension, heart failure, edema, bradycardia

*PA, XL, SR, CD: long acting.
bid = twice daily; HR = heart rate; PVR = peripheral vascular resistance; tid = three times daily.
From Théroux P. Angina pectoris. In: Goldman L, Ausiello DA, eds. *Cecil Textbook of Medicine*. 23rd ed. Philadelphia: Saunders Elsevier; 2008.

TABLE 56-11 CLINICAL USE OF NITROGLYCERIN AND NITRATES

	DOSE	DURATION OF ACTION	INDICATION
NITROGLYCERIN			
Sublingual or buccal spray	0.15-1.5 mg	Relief of angina	Before or at onset of pain
Ointment	7.5-40 mg	8-12 hr	Prophylaxis of angina
Transdermal	0.1-0.8 mg/hr	8-16 hr	Prophylaxis of angina
Intravenous	5-400 μg/hr	Ongoing; increasing doses as needed	Recurrent chest pain, systemic hypertension, left-sided heart failure
ISOSORBIDE DINITRATE			
Oral	5-40 mg tid	6-8 hr	Prophylaxis of angina
ISOSORBIDE-5-MONONITRATE			
Oral	20 mg bid	8-12 hr	Prophylaxis of angina
Oral, slow release	30-240 mg/day	12-20 hr	Prophylaxis of angina

bid = twice daily; tid = three times daily.
From Théroux P. Angina pectoris. In: Goldman L, Ausiello DA, eds. *Cecil Textbook of Medicine*. 23rd ed. Philadelphia: Saunders Elsevier; 2008.

significant left main coronary artery disease, three-vessel coronary artery disease, or multivessel coronary artery disease in patients who have an LV ejection fraction below 50% or have diabetes.[15]

Comparisons of PCI with Optimal Medical Therapy

Numerous randomized clinical trials have compared PCI with medical therapy in stable angina patients. PCI improves angina symptoms but does not reduce the risk of death, MI, or other major cardiovascular events when it is added to optimal medical therapy as an initial management strategy in patients with chronic ischemic heart disease,[A22–A26] including patients with a chronic total occlusion of a major coronary artery.[A27] As a result, optimal medical therapy to control symptoms is a justifiable and more cost-effective initial management strategy for patients with chronic ischemic heart disease, even if they have diabetes,[16] with revascularization reserved only for patients in whom medical therapy is ineffective in controlling anginal symptoms.[17]

For patients who have stable angina and coronary lesions with reduced fractional flow reserve below 0.8 in one or more visually stenotic arteries (≥50% stenosis), initial PCI significantly reduces the need for hospitalization for urgent revascularization but has not been shown to reduce the composite end point of MI or death.[A28] Thus, intensive secondary prevention with proven pharmacotherapies combined with lifestyle modification is of paramount importance in reducing major cardiovascular events in such patients and must be considered the foundation of treatment.

Comparisons of CABG with Medical Therapy

Randomized trials comparing CABG with medical therapy indicate that a greater severity of ischemia, a greater extent of anatomic coronary disease, and the presence of LV systolic dysfunction favor a greater magnitude of survival benefit of CABG over medical therapy. CABG prolongs survival in patients with significant left main coronary artery disease irrespective of symptoms, in patients with multivessel coronary artery disease and impaired LV function (ejection fraction < 50%), and in patients with two- or three-vessel coronary artery disease that includes the proximal left anterior descending coronary artery. Patients with extensive multivessel coronary artery disease appear to derive a survival benefit from CABG surgery, particularly if they also have diabetes, whereas PCI may be considered appropriate for symptom relief, particularly in patients with one- or two-vessel coronary artery disease. It is also worth emphasizing, however, that the randomized trials of CABG surgery compared with medical therapy were conducted more than 40 years ago, and subsequent improvements in both medical therapy and CABG surgery make it increasingly difficult to extrapolate these earlier findings to contemporary clinical practice.

Comparisons of PCI with CABG Surgery for Multivessel Coronary Artery Disease

In patients with isolated left main disease, PCI appears to be approximately equivalent to CABG for the combined end point of death, stroke, or myocardial infarction, but there may be a survival advantage with CABG.[A29] In patients with severe three-vessel disease or left main disease with additional stenoses, however, CABG is superior to PCI, especially in patients with diabetes.[A30] In terms of death and MI, as well as the composite of death, MI, and stroke, CABG surgery is superior to both PCI and optimal medical therapy in reducing the composite outcome of death or MI in stable ischemic heart disease patients who have diabetes and two- and three-vessel coronary disease during a 5-year follow-up,[A31] but not at 10 years.[A32]

These data emphasize that, among patients who remain symptomatic despite intensive treatment or who have substantial ischemia or extensive coronary artery disease, revascularization with either PCI or CABG is appropriate. If, however, the goal of revascularization is to improve survival or reduce clinical events, CABG surgery is generally superior to PCI in symptomatic patients who have stable ischemic heart disease and who have more anatomically complex disease, including three-vessel or left main coronary artery disease and in diabetic patients with multivessel coronary disease for at least 5 years (see Table 56-8; Chapter 58).[18,19] Although PCI appears to provide equivalent survival outcomes in lower-risk patients (principally in patients with one- or two-vessel coronary disease), repeated procedures are more often needed during follow-up.

Refractory Angina

Occasional patients may have refractory angina despite medications and revascularization.[20] One alternative is enhanced external counterpulsation (EECP), which is generally administered as 35 sequential treatments (1 hour daily; 5 days/week) during 7 weeks. EECP does not reduce ischemia on myocardial perfusion imaging, and the mechanisms underlying its effects are poorly understood. Possible mechanisms include durable hemodynamic changes that reduce myocardial oxygen demand, improvement in myocardial perfusion by diastolic augmentation of retrograde coronary flow, and improved endothelial function. Although EECP increased the time to ST segment depression during exercise testing, reduced angina, and improved health-related quality of life for at least 1 year in one randomized, double-blind study of patients with chronic stable angina, its role in the treatment of angina remains unclear. In patients who have refractory angina despite medical therapy and are not candidates for revascularization, reduction of coronary venous return via the coronary sinus can potentially redistribute flow to areas of ischemic myocardium and is an experimental approach to reducing symptoms and improving quality of life.

OTHER ANGINAL SYNDROMES

VARIANT ANGINA OR PRINZMETAL ANGINA

The diagnosis of variant or Prinzmetal angina is based on the documentation of transient ST segment elevation during an episode of chest pain in the absence of a severe, fixed coronary stenosis.[21] Prinzmetal variant angina typically is caused by an occlusive spasm superimposed on a coronary artery stenosis that otherwise does not limit blood flow significantly. In some patients, however, no underlying stenoses are seen. Associated Raynaud phenomenon and migraine headache have been described in some patients, suggesting that the syndrome may be part of a more generalized vasospastic disorder.

The chest discomfort occurs predominantly at rest, although approximately one third of patients may also experience pain during exercise. There is a predilection for the pain to wake the patient in the early morning hours when sympathetic activity is increasing. The syndrome is often cyclical; periods of exacerbation with repetitive episodes of chest pain may persist only for seconds or be more prolonged and severe, alternating with periods with few or no symptoms. The symptoms are typically relieved by nitroglycerin. The ST segment elevation accompanying the pain signifies transmural ischemia due to total abrupt occlusion of a nonsignificant epicardial coronary stenosis in the absence of adequate collateral circulation. The subsequent rapid reperfusion may explain the high prevalence of severe life-threatening arrhythmias.

Coronary angiography, with a provocative test for spasm, such as injection of acetylcholine into the affected coronary artery, usually precipitates the

syndrome. Such testing is useful to establish the diagnosis and to assess the response to therapy, especially in patients with normal or nearly normal coronary angiograms, in whom the diagnosis is otherwise unclear. Dihydropyridine calcium-channel blockers (e.g., amlodipine, 5 to 10 mg orally per day) are preferred in patients with Prinzmetal angina.

MICROVASCULAR ANGINA WITH NORMAL CORONARY ANGIOGRAPHY

Angina can occur despite normal coronary arteries, even after an acetylcholine challenge.[22] The majority of patients who have angina or ischemia with nonobstructive coronary arteries on angiography have occult coronary abnormalities that can be detected by cardiac MR imaging[23] (Chapter 44) or by a detailed coronary catheterization. Such detailed testing may reveal increased coronary resistance and an inability to increase coronary resistance and to increase coronary flow in response to stimuli such as exercise, adenosine, dipyridamole, and atrial pacing.

Symptoms occur most frequently at rest and often in relation to emotional stress. Periods of exacerbation commonly alternate with symptom-free periods. The syndrome is more frequent in women, and some patients have an altered perception of pain or hypersensitivity to certain stimuli.

The diagnosis requires objective documentation of ischemia based on ST-T segment changes, a metabolic abnormality, a transient regional perfusion defect or new wall motion abnormality on echocardiography, or endothelial dysfunction that limits blood flow reserve. Abnormal endothelium-dependent vasoreactivity can be associated with regional myocardial perfusion defects on SPECT and PET imaging.

β-Blockers or heart rate–lowering calcium-channel blockers may be useful, particularly when a relative tachycardia, hypertension, or decreased heart rate variability on Holter monitoring is present. Nitroglycerin can relieve symptoms in approximately 50% of patients, and long-acting nitrates are also sometimes helpful.

The prognosis is generally favorable and not different from that of a general age-matched population in the absence of coronary artery disease.[24,25] However, some studies have indicated that an ischemic response to exercise is associated with increased mortality.

SILENT MYOCARDIAL ISCHEMIA

Up to 20% of patients with ischemic heart disease may not present with angina and are often described as having silent myocardial ischemia. Some patients are totally asymptomatic despite obstructive coronary artery disease, which may be severe. Others have silent ischemia after a prior documented MI. The third and most common form occurs in patients who may also exhibit the usual forms of chronic stable angina, unstable angina, and Prinzmetal angina. When monitored, these patients, who typically have silent ischemia episodes in addition to symptomatic ischemia, are sometimes referred to as having *mixed angina*. This mixed angina is estimated to be present in approximately one third of all treated patients with angina, although an even higher prevalence has been reported in diabetic patients. In these patients, about 85% of ambulant ischemic episodes occur without chest pain, and 66% of angina episodes are not accompanied by ST segment depression, suggesting that overt angina pectoris is merely the "tip of the ischemic iceberg." Pharmacologic agents that reduce or abolish episodes of symptomatic ischemia also reduce or abolish episodes of silent ischemia.

PROGNOSIS

Modern treatments have improved the prognosis of patients with chronic ischemic heart disease to an annual mortality rate of 1 to 3% and a 1 to 2% rate of major ischemic events. The 1-year rate of cardiovascular death is now 1.9% (95% confidence interval [CI], 1.7 to 2.1), with a 2.9% (95% CI, 2.6 to 3.2) rate of all-cause mortality and a 4.5% (95% CI, 4.2 to 4.8) rate of the combined outcome of cardiovascular death, MI, or stroke. Even in patients who have refractory angina and are not candidates for revascularization, modern medical treatment is associated with a 1-year mortality of only 4% and a 9-year mortality of 30%.

In a large majority of patients, anginal symptoms greatly improve or even resolve, often without any change in medical therapy.[26] Recurrent angina is a common subsequent complaint in many patients with chronic ischemic heart disease, even those who were initially treated successfully with PCI. About 30% of patients continue to experience angina one or more times per week, with associated greater physical limitation and worse quality of life, and almost 80% of patients who underwent initially successful PCI for chronic angina still take one or more antianginal agents at 1 year. Exercise rehabilitation may slightly increase exercise capacity but otherwise does not have any clear prognostic implications.[A33]

Patients with chronic stable angina require follow-up on a regular basis (in general, at least every 6 to 12 months). At each visit, a detailed history and physical examination should be performed to discern any important developments such as:

- A change in physical activity
- Any change in the frequency, severity, or pattern of angina
- Tolerance of and adherence to the prescribed medical regimen
- Modification of cardiac risk factors
- The development of new or worsened comorbid illnesses

In addition to a lipid profile and blood glucose level, an ECG should be obtained if medications have changed, and echocardiography as well as electrocardiography is indicated if there are new findings on the history or physical examination. However, routine noninvasive surveillance is not needed in stable patients.

Selection of optimal treatment requires a full understanding of the potential risks and benefits of each treatment approach. In patients who have stable symptoms and who have not had an adequate trial of medical therapy, there is no need to proceed to an invasive evaluation before multifaceted medical therapy and lifestyle intervention are implemented for at least 3 to 6 months.[27] Such an initial approach of aggressive medical therapy and lifestyle intervention is strongly recommended and supported by professional guidelines. Finally, it is important to emphasize that the results of randomized trials involving both pharmacotherapy and revascularization must be individualized for specific patients, while a multidisciplinary approach to clinical decision making can ensure that all therapeutic options are fully and transparently discussed so that patients are offered the most appropriate evidence-based treatment recommendations that are tailored to the level of ischemic risk and coronary anatomic findings.

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For the General References and other additional features, please visit Elsevier eBooks+ at https://ebooks.health.elsevier.com.

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57

ACUTE CORONARY SYNDROME: UNSTABLE ANGINA AND NON–ST ELEVATION MYOCARDIAL INFARCTION

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DEFINITION

The term *acute coronary syndrome* is used to describe the continuum of myocardial ischemia (unstable angina pectoris) or infarction (with or without concomitant ST segment elevation). The patient with *unstable angina* has cardiac chest pain that is new, worsening (i.e., more severe, prolonged, or frequent than previous episodes of angina), or occurring at rest, *without* serologic evidence of myocyte necrosis—that is, no elevation of serum concentrations of troponin. The patient with cardiac chest pain *with* serologic evidence of myonecrosis and without ST elevation is said to have a *non–ST elevation myocardial infarction* (MI). Because unstable angina and non–ST elevation MI are characterized by the absence of ST elevation, they are collectively termed *non–ST elevation acute coronary syndrome* (Fig. 57-1). The patient with acute-onset cardiac chest pain, serologic evidence of myonecrosis, and persistent (>20 minutes) ST segment elevation is said to have an *ST elevation MI* (Chapter 58).

EPIDEMIOLOGY

Almost 1.2 million individuals in the United States are hospitalized annually with acute coronary syndrome, of whom approximately two thirds have non–ST elevation acute coronary syndrome. More than half of patients with non–ST elevation acute coronary syndrome are older than 65 years, and almost half are women. Non–ST elevation acute coronary syndrome is more common in individuals with one or more risk factors for atherosclerosis (Chapter 40), peripheral vascular disease, or a chronic inflammatory disorder, such as rheumatoid arthritis, psoriasis, or infection.

Most patients with non–ST elevation acute coronary syndrome have so-called type 1 MI, which is precipitated by rupture of a coronary arterial atherosclerotic plaque, with subsequent platelet aggregation and thrombus formation, leading in turn to diminished blood flow in the involved artery. Type 2 MI is myocardial injury in the milieu of a mismatch between oxygen supply and demand. Substantial reductions in oxygen supply, for example, can be caused by severe systemic arterial hypotension, anemia, or hypoxemia; dramatic increases in oxygen demand can be caused by tachycardia, severe systemic arterial hypertension, or thyrotoxicosis. In patients thought to have type 2 MI, therapy should be directed at the underlying cause.

PATHOBIOLOGY

The precipitating event in almost all patients with non–ST elevation acute coronary syndrome is coronary arterial atherosclerotic plaque rupture or erosion, with subsequent platelet aggregation and thrombus formation, leading to subtotal occlusion of the involved artery (type 1 MI). In an occasional patient, total thrombotic occlusion of the artery leads to non–ST elevation acute coronary syndrome rather than to ST elevation MI when extensive collateral blood supply perfuses the region of myocardium that is distal to the occluded artery.

Some patients have a mismatch between myocardial oxygen supply and demand caused by a secondary process other than coronary artery disease (type 2 MI). For example, intense vasospasm of a segment of an epicardial coronary artery, due to focal endothelial dysfunction (i.e., Prinzmetal angina) or drug ingestion (caused, for example, by cocaine, chemotherapeutic agents, or one of the serotonin receptor agonist "triptans"), causes a transient or sustained compromise of coronary arterial blood flow, with resultant non–ST elevation acute coronary syndrome. Spontaneous coronary arterial dissection, which occurs most often in peripartum women and patients with vasculitis, also may result in non–ST elevation acute coronary syndrome.

Plaque Rupture

Coronary arterial atherosclerotic plaque rupture (Chapter 41) or erosion is the initiating event in most patients with non–ST elevation acute coronary syndrome. Several factors may play a role in the deterioration of the protective fibrous cap that separates the atheroma in the vessel wall from the coronary arterial lumen. Local and systemic inflammation, mechanical features, and anatomic changes contribute to the transformation of a stable atherosclerotic plaque to a so-called vulnerable plaque, the rupture of which triggers platelet adherence, activation, and aggregation, with subsequent thrombus formation.

The deposition of oxidized low-density lipoprotein in the coronary arterial wall stimulates an inflammatory response, which results in the accumulation of macrophages and T lymphocytes at the plaque border. These inflammatory cells secrete cytokines (e.g., tissue necrosis factor, interleukin-1, interferon-γ), which inhibit collagen synthesis and deposition, as well as enzymes (e.g., matrix metalloproteinases and cathepsins), which promote collagen and elastin degradation, thereby rendering the overlying fibrous cap vulnerable to rupture.

Systemic inflammation may play a role in plaque rupture, as evidenced by the predisposition of individuals with chronic gingivitis, psoriasis, systemic lupus erythematosus, rheumatoid arthritis, and chronic or acute infection to develop acute coronary syndrome. Angiographic and angioscopic studies of the coronary arteries of acute coronary syndrome patients often demonstrate plaque ulceration and thrombosis at more than one site, thereby suggesting that a systemic and diffuse inflammatory process is present.

The mechanical characteristics and location of coronary arterial plaques appear to influence their stability. For example, thin fibrous caps are more likely to erode or to rupture than are thick ones. Sites of low shear stress, such as vessel bifurcations, have reduced production of endothelial vasodilator substances (i.e., nitric oxide and prostacyclin), accelerated accumulation of lipids and inflammatory cells, increased degradation of the extracellular matrix, and thinning of the fibrous cap, all of which contribute to plaque instability.

Detailed histologic examination of evolving atherosclerotic plaques reveals a rich neovascularization that is the result of angiogenic peptides, such as fibroblast growth factors, vascular endothelial growth factor, placental growth factor, oncostatin M, and hypoxia-inducible factor, which are secreted by smooth muscle cells, inflammatory cells, and platelets. This neovascularization

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57

ACUTE CORONARY SYNDROME: UNSTABLE ANGINA AND NON–ST ELEVATION MYOCARDIAL INFARCTION

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DEFINITION

The term *acute coronary syndrome* is used to describe the continuum of myocardial ischemia (unstable angina pectoris) or infarction (with or without concomitant ST segment elevation). The patient with *unstable angina* has cardiac chest pain that is new, worsening (i.e., more severe, prolonged, or frequent than previous episodes of angina), or occurring at rest, *without* serologic evidence of myocyte necrosis—that is, no elevation of serum concentrations of troponin. The patient with cardiac chest pain *with* serologic evidence of myonecrosis and without ST elevation is said to have a *non–ST elevation myocardial infarction* (MI). Because unstable angina and non–ST elevation MI are characterized by the absence of ST elevation, they are collectively termed *non–ST elevation acute coronary syndrome* (Fig. 57-1). The patient with acute-onset cardiac chest pain, serologic evidence of myonecrosis, and persistent (>20 minutes) ST segment elevation is said to have an *ST elevation MI* (Chapter 58).

EPIDEMIOLOGY

Almost 1.2 million individuals in the United States are hospitalized annually with acute coronary syndrome, of whom approximately two thirds have non–ST elevation acute coronary syndrome. More than half of patients with non–ST elevation acute coronary syndrome are older than 65 years, and almost half are women. Non–ST elevation acute coronary syndrome is more common in individuals with one or more risk factors for atherosclerosis (Chapter 40), peripheral vascular disease, or a chronic inflammatory disorder, such as rheumatoid arthritis, psoriasis, or infection.

Most patients with non–ST elevation acute coronary syndrome have so-called type 1 MI, which is precipitated by rupture of a coronary arterial atherosclerotic plaque, with subsequent platelet aggregation and thrombus formation, leading in turn to diminished blood flow in the involved artery. Type 2 MI is myocardial injury in the milieu of a mismatch between oxygen supply and demand. Substantial reductions in oxygen supply, for example, can be caused by severe systemic arterial hypotension, anemia, or hypoxemia; dramatic increases in oxygen demand can be caused by tachycardia, severe systemic arterial hypertension, or thyrotoxicosis. In patients thought to have type 2 MI, therapy should be directed at the underlying cause.

PATHOBIOLOGY

The precipitating event in almost all patients with non–ST elevation acute coronary syndrome is coronary arterial atherosclerotic plaque rupture or erosion, with subsequent platelet aggregation and thrombus formation, leading to subtotal occlusion of the involved artery (type 1 MI). In an occasional patient, total thrombotic occlusion of the artery leads to non–ST elevation acute coronary syndrome rather than to ST elevation MI when extensive collateral blood supply perfuses the region of myocardium that is distal to the occluded artery.

Some patients have a mismatch between myocardial oxygen supply and demand caused by a secondary process other than coronary artery disease (type 2 MI). For example, intense vasospasm of a segment of an epicardial coronary artery, due to focal endothelial dysfunction (i.e., Prinzmetal angina) or drug ingestion (caused, for example, by cocaine, chemotherapeutic agents, or one of the serotonin receptor agonist "triptans"), causes a transient or sustained compromise of coronary arterial blood flow, with resultant non–ST elevation acute coronary syndrome. Spontaneous coronary arterial dissection, which occurs most often in peripartum women and patients with vasculitis, also may result in non–ST elevation acute coronary syndrome.

Plaque Rupture

Coronary arterial atherosclerotic plaque rupture (Chapter 41) or erosion is the initiating event in most patients with non–ST elevation acute coronary syndrome. Several factors may play a role in the deterioration of the protective fibrous cap that separates the atheroma in the vessel wall from the coronary arterial lumen. Local and systemic inflammation, mechanical features, and anatomic changes contribute to the transformation of a stable atherosclerotic plaque to a so-called vulnerable plaque, the rupture of which triggers platelet adherence, activation, and aggregation, with subsequent thrombus formation.

The deposition of oxidized low-density lipoprotein in the coronary arterial wall stimulates an inflammatory response, which results in the accumulation of macrophages and T lymphocytes at the plaque border. These inflammatory cells secrete cytokines (e.g., tissue necrosis factor, interleukin-1, interferon-γ), which inhibit collagen synthesis and deposition, as well as enzymes (e.g., matrix metalloproteinases and cathepsins), which promote collagen and elastin degradation, thereby rendering the overlying fibrous cap vulnerable to rupture.

Systemic inflammation may play a role in plaque rupture, as evidenced by the predisposition of individuals with chronic gingivitis, psoriasis, systemic lupus erythematosus, rheumatoid arthritis, and chronic or acute infection to develop acute coronary syndrome. Angiographic and angioscopic studies of the coronary arteries of acute coronary syndrome patients often demonstrate plaque ulceration and thrombosis at more than one site, thereby suggesting that a systemic and diffuse inflammatory process is present.

The mechanical characteristics and location of coronary arterial plaques appear to influence their stability. For example, thin fibrous caps are more likely to erode or to rupture than are thick ones. Sites of low shear stress, such as vessel bifurcations, have reduced production of endothelial vasodilator substances (i.e., nitric oxide and prostacyclin), accelerated accumulation of lipids and inflammatory cells, increased degradation of the extracellular matrix, and thinning of the fibrous cap, all of which contribute to plaque instability.

Detailed histologic examination of evolving atherosclerotic plaques reveals a rich neovascularization that is the result of angiogenic peptides, such as fibroblast growth factors, vascular endothelial growth factor, placental growth factor, oncostatin M, and hypoxia-inducible factor, which are secreted by smooth muscle cells, inflammatory cells, and platelets. This neovascularization

ABSTRACT

The term acute coronary syndrome is used to describe the continuum of myocardial ischemia (unstable angina pectoris) or infarction (with or without concomitant ST segment elevation). The patient with unstable angina has cardiac chest pain that is new, worsening (i.e., more severe, prolonged, or frequent than previous episodes of angina), or occurring at rest, without serologic evidence of myocyte necrosis—that is, no elevation of serum concentrations of troponin or the MB isoenzyme of creatine kinase (CK-MB). The patient with cardiac chest pain with serologic evidence of myonecrosis and without ST elevation is said to have a non–ST elevation myocardial infarction (MI). Because unstable angina and non–ST elevation MI are characterized by the absence of ST elevation, they are collectively termed the non–ST elevation acute coronary syndrome.

KEYWORDS

acute coronary syndrome
unstable angina
non–ST elevation myocardial infarction
antiplatelet therapy
percutaneous coronary intervention

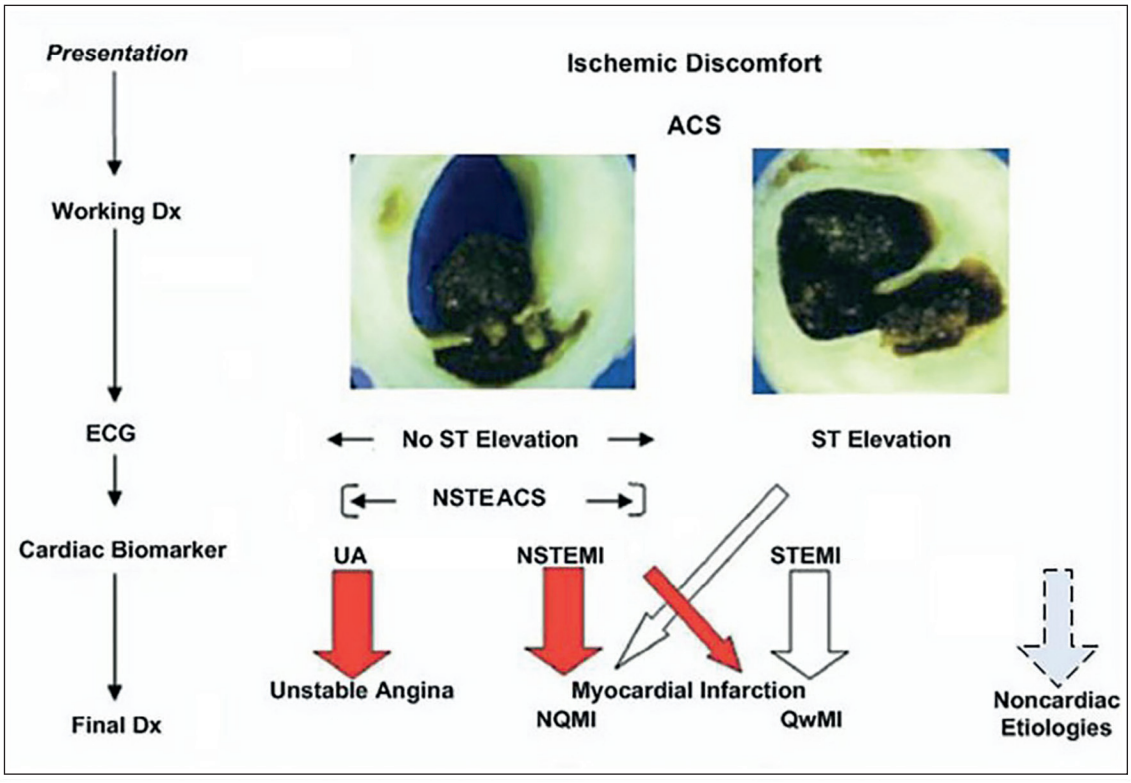

FIGURE 57-1. Acute coronary syndrome (ACS). Symptomatic, morphologic, electrocardiographic, and serologic findings in patients with various kinds of ACS. Patients with ACS usually complain of chest pain. If the involved coronary artery is totally occluded by a fresh thrombus (shown on the *right*), the patient's electrocardiogram (ECG) reveals ST segment elevation, cardiac biomarkers subsequently are elevated, and the patient is diagnosed with an ST elevation myocardial infarction (STEMI). In some cases, initial ST elevation can lead to non-Q wave myocardial infarction. If the involved coronary artery is partially occluded by fresh thrombus (shown on the *left*), the patient's ECG does not show ST segment elevation. If cardiac biomarkers are not elevated, the patient is diagnosed with unstable angina (UA). If cardiac biomarkers remain negative or are not elevated during hospitalization, the final diagnosis remains unstable angina. If cardiac biomarkers are elevated, the patient is diagnosed with a non–ST elevation MI (NSTEMI). Most patients presenting with NSTEMI develop NQMI, but a few may develop QwMI. Dx = diagnosis; NQMI = non–Q wave myocardial infarction; NSTEACS = non-ST elevation acute coronary syndrome; QwMI = Q wave myocardial infarction; UA = unstable angina.

contributes to the growth of atheroma and to leukocyte trafficking, plaque hemorrhage, and destabilization.

Thrombus Formation

Platelets play a pivotal role in the pathobiology of the acute coronary syndrome. After erosion or rupture of a vulnerable plaque, circulating platelets *adhere* to the exposed subendothelial proteins, after which they are *activated*. With activation, the platelets change shape from discoid to stellate, thereby increasing the surface area on which thrombin formation can occur. The platelets then release the contents of their intracellular granules (i.e., thromboxane, serotonin, adenosine diphosphate [ADP], von Willebrand factor, fibrinogen) into the immediate environment and promote focal vasoconstriction of the adjacent arterial segment and activation of nearby platelets. Platelets also increase the number of glycoprotein IIb/IIIa receptors on their surface and the affinity of these receptors to bind circulating fibrinogen. The result is platelet *aggregation*, which occurs as fibrinogen binds to the glycoprotein IIb/IIIa receptors of adjacent platelets, thereby creating a "platelet plug."

With formation of the platelet plug, the coagulation system activates and generates thrombin, which is a powerful stimulator of further platelet activation and aggregation. Thrombin also converts fibrinogen to fibrin, which is incorporated into the thrombus. Subtotal coronary arterial occlusion by this platelet-rich thrombus compromises blood flow in the involved artery, thereby resulting in an imbalance of oxygen supply and demand of the myocytes perfused by the artery. Distal embolization of platelet-rich thrombi from the site of a ruptured plaque may contribute to the compromise in blood flow. If the supply-demand imbalance is transient, the involved myocytes become ischemic but do not die because the ischemia is of insufficient duration to cause necrosis. The patient typically complains of cardiac chest pain at rest, but serologic evidence of myonecrosis, as evidenced by elevated serum concentrations of troponin, is absent; a diagnosis of *unstable angina* is made. In contrast, if the supply-demand imbalance is sustained, ischemic myocytes begin to die, and infarction occurs. The patient typically complains of cardiac chest pain at rest, and serologic evidence of myonecrosis confirms the diagnosis of *non–ST elevation MI*.

CLINICAL MANIFESTATIONS

Symptoms

The patient with non–ST elevation acute coronary syndrome typically complains of retrosternal pressure, squeezing, or heaviness that may be intermittent and recurrent or persistent (Chapter 39). If the episodes are intermittent and recurrent, the duration of each episode may range from only a few minutes to several hours. The chest pain may radiate to the left arm, neck, or jaw, and it may be accompanied by diaphoresis, nausea, abdominal pain, dyspnea, or syncope.

Atypical presentations are not uncommon and may include aching or vague chest discomfort, epigastric pain, acute-onset indigestion, unexplained fatigue, or dyspnea. Such atypical complaints are often observed in younger (25 to 40 years of age) and older (>75 years of age) patients; women; and patients with diabetes mellitus, chronic renal insufficiency, or dementia.

Physical Examination

The patient with non–ST elevation acute coronary syndrome often has normal findings on physical examination. On occasion, evidence of left ventricular dysfunction (Chapter 45), such as basilar rales or a ventricular gallop, hypotension, or peripheral hypoperfusion, may accompany an acute episode or appear shortly thereafter. An important goal of the physical examination is to exclude other potential causes of the patient's symptoms, including both noncardiac causes (i.e., costochondritis, pneumothorax, pulmonary embolism, pneumonia) and other cardiac disorders not attributable to myocardial ischemia (i.e., aortic dissection, pericarditis, severe systemic arterial hypertension, arrhythmias; Chapter 49). Accordingly, differences in blood pressure between the upper and lower limbs, decreased lung sounds, friction rubs, and pain on sternal palpation suggest a diagnosis other than non–ST elevation acute coronary syndrome. Other findings on physical examination—such as an elevated blood pressure, tachycardia, pallor, or increased sweating or tremor—point toward precipitating conditions, such as uncontrolled hypertension (Chapter 64), arrhythmias (Chapters 52 and 53), anemia (Chapter 144), or thyrotoxicosis (Chapter 207).

DIAGNOSIS

The patient with suspected acute coronary syndrome should be evaluated promptly because an expedient and accurate diagnosis permits the timely initiation of appropriate therapy, which can reduce the rate of complications.[1] The initial assessment should be directed at determining whether the patient's symptoms are likely to be caused by myocardial ischemia, MI, or some other disorder. The likelihood of acute coronary syndrome can be estimated from the history, physical examination, and electrocardiogram (ECG). In the acute setting, the presence or absence of traditional risk factors for atherosclerosis is less important for determining the presence or absence of acute coronary syndrome than are the patient's symptoms, ECG findings, and serologic evidence of myonecrosis. As a result, these long-term risk factors are not integral in determining whether an individual should be evaluated, hospitalized, or treated for acute coronary syndrome. Conditions that increase the likelihood that the symptomatic patient is experiencing myocardial ischemia or MI include older age, diabetes mellitus, extracardiac vascular disease, and chest pain radiating to the left arm, neck, or jaw as the presenting symptom. Myocardial ischemia is highly likely if anginal symptoms are accompanied by ECG abnormalities (i.e., Q waves, ST segment depression or elevation ≥1 mm in magnitude, or T wave inversion in multiple precordial leads) or elevated serum concentrations of troponin.

In a patient with known coronary artery disease, typical symptoms are likely to be caused by myocardial ischemia or MI rather than by another condition, particularly if the patient confirms that the symptoms are similar to previous anginal episodes. Conversely, a young individual who has a normal ECG and no risk factors for atherosclerosis is unlikely to be having acute coronary syndrome even when complaining of chest pain with features consistent with ischemia or infarction.

It is important to inquire about the use of cocaine and methamphetamines in the patient with suspected acute coronary syndrome, especially in those who are younger than 40 years or have few traditional risk factors for atherosclerosis. These drugs can increase myocardial oxygen demand and concomitantly decrease oxygen supply by causing vasospasm and thrombosis. A urine toxicologic analysis should be considered when substance abuse is suspected as a cause of acute coronary syndrome.

Electrocardiogram

An ECG, which should be performed and interpreted within 10 minutes or less of the patient's arrival at a facility, is particularly valuable if it is obtained during a symptomatic episode. If the patient has persistent (>20 minutes) ST segment elevation, prompt reperfusion therapy should be initiated (Chapter 58). Transient ST segment abnormalities that develop during a symptomatic episode at rest and resolve when the patient is asymptomatic strongly suggest non–ST elevation acute coronary syndrome. ST segment depression (or transient ST segment elevation) and T wave abnormalities occur in up to 50% of patients.

A completely normal ECG does not exclude the possibility of non–ST elevation acute coronary syndrome; in fact, about 5% of patients who are discharged from the emergency department and ultimately diagnosed with acute coronary syndrome have a normal ECG. Ischemia or infarction in the territory of the left circumflex coronary artery often escapes detection with a standard 12-lead ECG, but it may be detected with right-sided leads (V_4R and V_3R) or posterior leads (V_7 to V_9). In the patient whose initial ECG is normal, serial ECGs (e.g., 15- to 30-minute intervals during the first hour) should be performed routinely and during symptomatic episodes, and they should be compared with previous tracings to identify new ST segment or T wave abnormalities. Deep (>2 mm), symmetrical T wave inversion in the anterior chest leads is often associated with a hemodynamically significant stenosis of the left main or proximal left anterior descending coronary artery.

Serum Biomarkers

Unfortunately, the initial history, physical examination, and ECG alone cannot confirm or exclude an acute coronary syndrome. By comparison, modern high-sensitivity assays can detect troponin (Chapter 58) in the blood within 2 hours of the onset of symptoms in patients with non–ST elevation MI.

Risk Assessment and Triage

The greatest safety comes from continued observation or admission of patients who have a positive troponin level on presentation or at serial testing, have evidence of ischemia on their ECG, or have symptoms indicative of an acute exacerbation of prior coronary disease.[2,3] Because a single normal serum troponin measurement is insufficient to exclude MI in a patient with a very recent onset of symptoms, patients with suspected MI based on the clinical presentation or with ischemic ECG changes may be observed, either in the emergency department or in a chest pain evaluation unit, with a repeated troponin measurement (and a repeated ECG) at 3 or so hours after the onset of symptoms or whenever chest pain recurs.[4] A negative high-sensitivity troponin level at 2 to 3 hours after the onset of symptoms is sufficient to identify patients who do not have ST elevation or non–ST elevation MI (Fig. 57-2),[A1,A2] and patients with negative results and no ECG findings of ischemia have a sufficiently low risk (a 0.4% 30-day risk of MI or death) that they can safely complete the remainder of their evaluation as outpatients if they have no other need for hospitalization.[5–8] Noninvasive cardiac testing performed within 3 days of the initial presentation is associated with a modestly reduced subsequent risk of serious cardiac events, but its value in patients with normal troponin levels is likely small.[9]

Serum troponin concentrations can be measured with point-of-care instruments at the patient's bedside by desktop devices or handheld rapid qualitative assays.[10] The advantage of point-of-care systems for avoiding delays must be weighed against their higher costs and the need for stringent quality control. In addition, point-of-care assays are qualitative or semiquantitative and observer dependent, whereas the central laboratory provides more accurate quantitative information concerning biomarker concentrations.

Noninvasive Testing

A chest radiograph may identify pulmonary causes of chest pain and may show a widened mediastinum in aortic dissection (Chapter 63). The patient considered to have a low likelihood for acute coronary syndrome (on the basis of the history, physical examination, ECG, and serum biomarkers) should undergo timely stress testing (Chapter 39). Although stress testing does not absolutely establish or exclude the presence of coronary artery disease, it has the advantage of also defining a patient's exercise tolerance, which helps tailor therapeutic decisions. Alternatively, multidetector coronary computed tomographic angiography, which has a high (>98%) negative predictive value to exclude coronary artery disease when it is performed and interpreted at experienced centers, can help reduce the length of hospital stay when the findings are normal in emergency department patients at low to intermediate risk of possible acute coronary syndrome. However, coronary computed tomographic angiography does not have incremental value in patients with a negative troponin assay and a nonischemic ECG.[A3] Conversely, the patient who is believed to be at higher risk or who continues to have typical ischemic chest pain with ECG abnormalities or elevated cardiac biomarkers should not undergo stress testing or coronary computed tomographic angiography but rather should either undergo coronary angiography or be rendered symptom free with medical therapy before stress testing.

An echocardiogram may be helpful in the patient with chest pain if the ECG is nondiagnostic (i.e., minimal ST segment or T wave abnormalities). If left ventricular hypokinesis or akinesis is observed during an episode of chest pain and then improves when symptoms resolve, myocardial ischemia is likely. In the patient with anterior T wave inversion of uncertain etiology, hypokinesis of the left ventricular anterior wall suggests that the observed T wave abnormality is due to a severe stenosis of the left anterior descending coronary artery. Because echocardiography can help evaluate and identify alternative causes for the patient's chest pain (i.e., myocarditis [Chapter 47], aortic dissection [Chapter 63], or pulmonary embolism [Chapter 68]), it is recommended in patients whose diagnosis is uncertain.

Coronary Angiography

Coronary angiography (Chapter 59) should be performed in patients who are thought to be at high risk for death, MI, or recurrent ischemia in the ensuing days, weeks, and months (see later); in patients who have spontaneous or inducible myocardial ischemia despite appropriate medical therapy; and in patients who have a confusing or difficult clinical presentation and a subsequent inconclusive noninvasive evaluation. The results of angiography help determine whether revascularization is appropriate and, if so, whether it should be attempted by coronary artery bypass grafting or percutaneous coronary intervention (PCI) (Chapter 59).

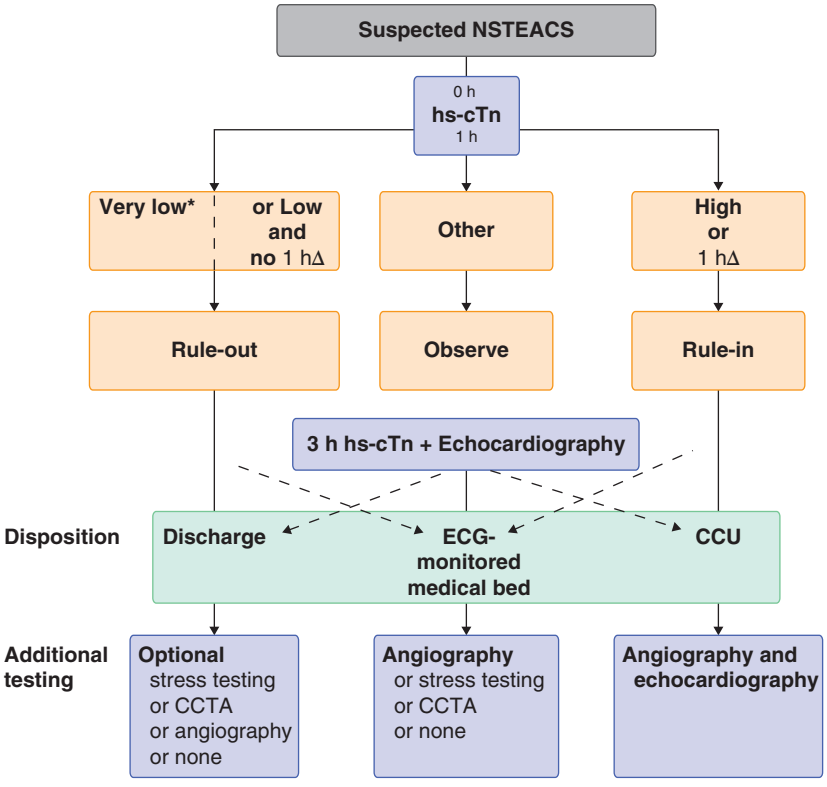

FIGURE 57-2. Initial triage for patients with symptoms suggestive of a non-ST elevation acute coronary syndrome (NSTEACS) using high-sensitivity cardiac troponin assays. 0 h/1 h rule-out and rule-in algorithm using high-sensitivity cardiac troponin assays in hemodynamically stable patients presenting with suspected NSTEACS to the emergency department. 0 h and 1 h refer to the time from the first blood test. NSTEMI can be ruled out at presentation if the hs-cTn concentration is very low. NSTEMI can also be ruled out by the combination of low baseline levels and the lack of a relevant increase within 1 h (no 1hΔ). Patients have a high likelihood of NSTEMI if the hs-cTn concentration at presentation is at least moderately elevated or hs-cTn concentrations show a clear rise within the first hour (1hΔ). CCTA = coronary computed tomography angiography; CCU = coronary care unit; hs-cTn = high-sensitivity cardiac troponin; NSTEACS = non-ST elevation acute coronary syndrome; NSTEMI = non-ST elevation myocardial infarction. *Only applicable if chest pain onset >3 h. (Adapted from Collet JP, Thiele H, Barbato E, et al. 2020 ESC guidelines for the management of acute coronary syndromes in patients presenting without persistent ST-segment elevation. *Eur Heart J*. 2021;42:1289-1367.)

In patients with non–ST elevation acute coronary syndrome, coronary angiography demonstrates significant stenosis of the left main coronary artery in about 15% of patients, of all three major epicardial coronary arteries in about 30 to 35% of patients, of two of the three epicardial arteries in about 20 to 30% of patients, and of one major epicardial artery in 20 to 30% of patients. About 15% of patients have no coronary arterial narrowing of hemodynamic significance. Women with non–ST elevation acute coronary syndrome are likely to have less extensive coronary artery disease than men have, and patients with non–ST elevation MI usually have more extensive disease than those with unstable angina.

On angiography, the coronary arterial lesion responsible for signs and symptoms (the so-called culprit lesion) typically is asymmetrical or eccentric, with scalloped or overhanging edges and a narrow base or neck, features that reflect underlying plaque disruption and thrombus formation. Although obvious thrombus is visible by angiography in only one third of patients, coronary angioscopy shows plaque rupture with overlying thrombus in the majority. Interestingly, the culprit lesion often is not severely stenotic when it is assessed on recently performed angiograms; in fact, two thirds of culprit lesions previously had less than 50% luminal diameter narrowing (and therefore would not have been considered appropriate for revascularization).

After the initial triage decision is made, therapeutic interventions are based on the risk of adverse events in the ensuing hours, days, weeks, and months—estimated by either the Thrombolysis in Myocardial Infarction (TIMI) or Global Registry of Acute Coronary Events (GRACE) risk algorithm—balanced against the risk of a bleeding complication from intensive medical therapy (Table 57-1) or an adverse event from an invasive cardiac procedure. On the basis of this initial assessment, the patient's therapy should be tailored to minimize the likelihood of adverse events.

Although serum markers of myonecrosis represent only one of the TIMI or GRACE risk variables, the presence of this variable alone identifies the patient as being at high risk. However, although elevated serum markers indicate myonecrosis, they provide no insight into its cause because myonecrosis can occur with disease entities other than coronary artery disease (e.g., pulmonary embolism, decompensated heart failure, severe hypertension or tachycardia, anemia, sepsis). Thus, in evaluation of the patient with possible acute coronary syndrome, the presence of elevated serum markers should be assessed in conjunction with other variables.

Increasing age is associated with a higher incidence of both ischemic events and of complications from intensive medical therapy and invasive cardiac procedures. Even though elderly individuals are at increased risk of treatment-related complications, they nonetheless derive a greater absolute and relative benefit from such intensive therapy compared with younger individuals. Apart from this initial risk assessment, the patient's general medical and cognitive status, anticipated life expectancy, and, most important, personal preferences should be evaluated and considered.

Differential Diagnosis

The current universal definition of MI recognizes five different types (Table 57-2),[11] including ST elevation (Chapter 58) MI or non–ST elevation MI related to an acute coronary thrombosis (type 1); MI caused by a mismatch between myocardial supply and demand (type 2); MI associated with sudden cardiac arrest but not documented antemortem (type 3, Chapter 50); and MI associated with a percutaneous coronary intervention (type 4) or coronary artery bypass graft surgery (type 5, Chapter 59). The use of high-sensitivity troponin assays increases the detection of all five types.

Cardiac injury with troponin elevation but without other evidence of ischemia can also occur after cardiac and noncardiac procedures (Chapter 401). Several cardiac and noncardiac conditions, some of which are potentially life-threatening, may mimic non–ST elevation acute coronary syndrome. The patient with a pulmonary embolism (Chapter 68) will often complain of chest pain and dyspnea and may have ECG abnormalities and an elevated serum troponin concentration. Aortic dissection (Chapter 63) should be considered and excluded because the therapies for non–ST elevation acute coronary syndrome are contraindicated in patients with this condition. Stroke (Chapter 376) and subarachnoid hemorrhage (Chapter 377) may be accompanied by ECG abnormalities, left ventricular segmental wall motion abnormalities, and elevated serum biomarker concentrations. Underlying chronic cardiac conditions, such as valvular heart disease (i.e., aortic stenosis, aortic regurgitation) and hypertrophic cardiomyopathy (Chapter 47), may be associated with symptoms similar to those of non–ST elevation acute coronary syndrome, elevated serum biomarker concentrations, and ECG abnormalities. Myocarditis (Chapter 47), pericarditis (Chapter 62), and myopericarditis often cause chest pain that resembles angina, ECG abnormalities, and elevated serum biomarker concentrations; an influenza-like or upper respiratory tract infection (including severe acute respiratory syndrome coronavirus 2) often precedes or accompanies these conditions. Patients with "stress cardiomyopathy" (takotsubo syndrome) typically have chest pain, ST segment abnormalities and deeply inverted T waves, and mildly elevated serum biomarker concentrations (Chapter 47). In rural areas without emergency medicine specialists or cardiologists, diagnostic support from a tertiary center can improve diagnostic accuracy.[A4]

TABLE 57-1 RISK VARIABLES FOR ISCHEMIC EVENTS AND BLEEDING COMPLICATIONS

RISK VARIABLES PREDICTIVE OF DEATH, MYOCARDIAL INFARCTION, OR RECURRENT ISCHEMIA
Thrombolysis in Myocardial Infarction (TIMI) Score*
Age >65 yr
Three or more risk factors for atherosclerosis
Known coronary artery disease (previous coronary arteriography or myocardial infarction)
Two or more episodes of anginal chest pain at rest in the 24 hr before hospitalization
Use of aspirin in the 7 days before hospitalization
ST segment deviation ≥0.5 mV
Elevated serum concentrations of troponin or CK-MB
Global Registry of Acute Coronary Events (GRACE)†
Age
Heart failure (Killip) class
Heart rate
Systolic blood pressure
ST segment deviation
Cardiac arrest during presentation
Serum creatinine concentration
Elevated serum markers of myonecrosis
RISK FACTORS FOR BLEEDING COMPLICATIONS WITH INTENSIVE THERAPY†
Female gender
Older age
Renal insufficiency
Low body weight
Tachycardia
Systolic arterial pressure (high or low)
Anemia
Diabetes mellitus

*Individuals with three or more of these variables are considered to be at high risk, whereas those with none, one, or two are considered to be at low risk.

†Each variable is assigned a numerical score on the basis of its specific value, and the eight scores are summed to yield a total score, which is applied to a reference nomogram to determine the patient's risk. The GRACE application tool is available online at www.outcomes-umassmed.org/grace. (From Brieger D, Fox KA, Fitzgerald G, et al. Predicting freedom from clinical events in non-ST-elevation acute coronary syndromes: the Global Registry of Acute Coronary Events. *Heart*. 2009;95:888-894.)

†The patient's bleeding risk can be estimated with the tool available at https://reference.medscape.com/calculator/53/crusade-score-for-post-mi-bleeding-risk. (From Subherwal S, Bach RG, Chen AY, et al. Baseline risk of major bleeding in non-ST-segment-elevation myocardial infarction: the CRUSADE [Can Rapid risk stratification of Unstable angina patients Suppress ADverse outcomes with Early implementation of the ACC/AHA Guidelines] Bleeding Score. *Circulation*. 2009;119:1873-1882.)

From Diez JG, Cohen M. Balancing myocardial ischemic and bleeding risks in patients with non-ST-segment elevation myocardial infarction. *Am J Cardiol*. 2009;103:1396-1402.

TABLE 57-2 UNIVERSAL DEFINITION OF MYOCARDIAL INFARCTION

TYPE 1
Rise and/or fall of cardiac troponin values, with at least one value above the 99th percentile and at least one of the following: • Symptoms of acute myocardial ischemia • New ischemic ECG changes or development of new pathologic Q waves • New loss of viable myocardium or new regional wall motion abnormality consistent with an ischemic cause on imaging • Coronary thrombus on angiography, intracoronary imaging, or autopsy
TYPE 2
Rise and/or fall of cardiac troponin values, with at least one value above the 99th percentile, evidence of an imbalance between myocardial oxygen supply and demand unrelated to acute coronary thrombosis, and at least one of the following: • Symptoms of acute myocardial ischemia • New ischemic ECG changes or development of new pathologic Q waves • New loss of viable myocardium or new regional wall motion abnormality consistent with an ischemic cause on imaging
TYPE 3
• Cardiac death in a patient with symptoms suggestive of myocardial ischemia accompanied by presumed ischemic ECG changes or ventricular fibrillation, before blood samples for biomarkers can be obtained or increases in cardiac biomarkers can be identified • Myocardial infarction detected on autopsy
TYPE 4
Myocardial infarction associated with a percutaneous coronary intervention
TYPE 5
Myocardial infarction related to coronary artery bypass graft surgery

ECG = electrocardiogram.

Thygesen K, Alpert JS, Jaffe AS, et al. Fourth universal definition of myocardial infarction (2018). *Circulation*. 2018;138:e618-e651.

TREATMENT

The goals of treatment of the patient with non–ST elevation acute coronary syndrome are to prevent recurrent ischemia (by correcting the imbalance between myocardial oxygen supply and demand), to prevent thrombus propagation, and to stabilize the vulnerable plaque.[12,13] Antianginal medications, such as nitroglycerin (see Table 56-11), β-adrenergic blockers (see Table 56-9), and calcium-channel blockers (see Table 56-10), favorably affect myocardial oxygen supply and demand, thereby preventing recurrent ischemia. Antiplatelet and antithrombotic agents retard thrombus propagation, and statins promote plaque stabilization.

Once the patient's risk status is established, therapy is initiated and tailored to the patient's risk of sustaining a subsequent ischemic cardiac event or a treatment-related complication (Table 57-3). For example, the patient considered to be at low risk of a subsequent ischemic event does not benefit from intensive antithrombotic therapy or routine coronary angiography and revascularization. Conversely, in patients considered to be at high risk of sustaining an ischemic event, optimal therapy—including coronary angiography and revascularization (if appropriate)—results in a 20 to 40% decrease in the risk of recurrent ischemia and MI and an approximately 10% reduction in mortality, with about an 18-month postponement of recurrent MI or death.[A5] An invasive approach also appears to be preferable in patients over age 75 years.[A6]

Every patient with non–ST elevation acute coronary syndrome, regardless of their level of risk, should promptly receive antianginal medications, antiplatelet therapy, and a statin, unless contraindicated. A patient considered to be at low risk may receive unfractionated heparin, but more intensive anticoagulant therapy is not necessary because such therapy increases the risk of bleeding without further reducing the risk of an ischemic cardiac event. Routine coronary angiography and revascularization are not beneficial and should be reserved for the patient with recurrent ischemia despite intensive medical therapy.

Conversely, the high-risk patient should receive antianginal medications, antiplatelet therapy, a statin, intensive anticoagulant therapy, and coronary angiography followed by revascularization (if indicated). In the patient whose coronary anatomy is suitable, revascularization reduces the incidence of ischemia and recurrent MI, and it also improves survival in certain patients (see later).

Antianginal Therapy

Nitroglycerin

Nitroglycerin (see Table 56-11), which is a venodilator at low doses and an arteriolar dilator at higher doses, may prevent recurrent ischemia in patients with unstable angina, but no studies of sufficient statistical power have determined whether it reduces the risk of MI in this population of patients. In patients who complain of recurrent symptoms, nitroglycerin should be given sublingually or by buccal spray (0.3 to 0.6 mg). Patients with ongoing or recurrent chest pain should receive intravenous nitroglycerin (5 to 10 μg/minute with use of nonabsorbable tubing), with escalation of the dose in increments of 10 μg/minute until symptoms resolve or adverse effects develop. Nitroglycerin's most common adverse effects are headache, nausea, dizziness, hypotension, and reflex tachycardia.

Nitrate tolerance can be avoided by periodically providing the patient with a nitrate-free period (i.e., a brief cessation of drug administration). Nitroglycerin should not be given to patients who have received a phosphodiesterase-5 inhibitor (i.e., sildenafil, tadalafil, or vardenafil) within the previous 24 to 48 hours, because severe hypotension may ensue.

β-Adrenergic Blockers

β-Adrenergic blockers diminish symptoms and the risk of MI in patients with acute coronary syndrome who are not already taking a β-blocker at the time of hospitalization. In the normotensive patient without ongoing chest pain or tachycardia and without contraindications to β-blockers, metoprolol should be initiated at 25 to 50 mg orally every 6 to 8 hours, with the dose increased (to 100 mg twice daily) as necessary to control heart rate, blood pressure, and symptoms. In high-risk patients and in patients with tachycardia or elevated systemic arterial pressure, metoprolol should be administered intravenously

TABLE 57-3 MANAGEMENT STRATEGIES FOR PATIENTS WITH ACUTE CORONARY SYNDROME

THERAPY	INITIATION	DURATION	DOSE, ROUTE, AND DURATION	BENEFIT VS. PLACEBO (REDUCED INCIDENCE OF …)
LOW-RISK PATIENT				
Antianginal				
β-Blocker*	Within 24 hr	Hospitalization ± indefinitely	Metoprolol, 25-50 mg orally twice daily, titrated up to 100 mg twice daily; or atenolol, 50-100 mg orally daily	Recurrent ischemia
Nitroglycerin	Immediately	Hospitalization ± indefinitely	0.3-0.6 mg sublingually or 5-10 μg/min IV initially and increased by 10 μg/min every 5 min	Not studied
Diltiazem or verapamil†	Immediately	Hospitalization ± indefinitely	30-90 mg orally four times daily or up to 360 mg of long-acting preparation orally daily	MI, recurrent ischemia
Lipid Lowering				
Statins (with other lipid-lowering medications as needed; see Chapter 190)	Immediately	Indefinitely	Atorvastatin, 40-80 mg; or rosuvastatin, 20-40 mg orally daily	Recurrent ischemia
Antiplatelet				
Aspirin	Immediately	Indefinitely	162-325 mg orally initial dose, then 81 mg orally daily	Death, MI
Clopidogrel	Immediately	1-12 mo	300 mg orally initial dose, then 75 mg orally daily	MI, recurrent ischemia
Anticoagulant				
Unfractionated heparin	Immediately	2-5 days	IV bolus of 60 U/kg, then 12 U/kg/hr IV adjusted to achieve an aPTT of 50 to 70 sec	Death or MI (combined)
HIGH-RISK PATIENT				
Antianginal				
β-Blocker*	Within 24 hr	Hospitalization ± indefinitely	Metoprolol, 25-50 mg orally twice daily, titrated up to 100 mg twice daily; or atenolol, 50-100 mg orally daily	Death, MI, recurrent ischemia
Nitroglycerin	Immediately	Hospitalization ± indefinitely	0.3-0.6 mg sublingually or 5-10 μg/min IV initially and increased by 10 μg/min every 5 min	Not studied
Diltiazem or verapamil†	Immediately	Hospitalization ± indefinitely	30-90 mg orally four times daily or up to 360 mg of long-acting preparation orally daily	MI, recurrent ischemia
Lipid Lowering				
Statin	Before hospital discharge	Indefinitely	Atorvastatin, 40-80 mg; or rosuvastatin, 20-40 mg orally daily	Recurrent ischemia
Antiplatelet				
Aspirin *and*	Immediately	Indefinitely	162-325 mg orally initial dose, then 81 mg orally	Death, MI
Clopidogrel *or*	Immediately	12 mo	300-600 mg orally initial dose, then 75 mg orally daily	MI, recurrent ischemia
Prasugrel *or*	At time of PCI	12 mo	60 mg orally initial dose, then 10 mg orally daily	Cardiovascular death, MI or stroke (combined)‡
Ticagrelor	Immediately	12 mo	180 mg orally initially, then 90 mg twice daily	Vascular death, MI or stroke (combined)‡
Glycoprotein IIb/IIIa inhibitor (eptifibatide, tirofiban, or abciximab)	At time of PCI	12-24 hr after PCI	Abciximab, IV bolus of 0.25 mg/kg, then 0.125 μg/kg/min IV (max. 10 μg/min) for 12 hr; or eptifibatide, IV bolus of 180 μg/kg, then 2.0 μg/kg/min IV for 18-24 hr; or tirofiban, 0.4 μg/kg/min IV for 30 min, then 0.1 μg/kg/min IV for 12 to 24 hr	MI
Anticoagulants				
Enoxaparin *or*	Immediately	Duration of hospitalization (up to 8 days); discontinue after successful PCI	1 mg/kg subcutaneously twice daily	MI, recurrent ischemia§
Unfractionated heparin *or*	Immediately	2 to 5 days; discontinue after successful PCI	IV bolus of 60 U/kg, then 12 U/kg/hr IV adjusted to achieve an aPTT of 50 to 70 sec	Death or MI (combined)
Bivalirudin *or*	Immediately (only in patients managed with an early invasive strategy)	Up to 72 hr; discontinue 4 hr after PCI	0.10 mg/kg loading dose followed by 0.25 mg/kg/hr	Bleeding#

TABLE 57-3 MANAGEMENT STRATEGIES FOR PATIENTS WITH ACUTE CORONARY SYNDROME—cont'd

THERAPY	INITIATION	DURATION	DOSE, ROUTE, AND DURATION	BENEFIT VS. PLACEBO (REDUCED INCIDENCE OF …)
Fondaparinux	Immediately	Duration of hospitalization (up to 8 days); if used during PCI, it must be coadministered with another anticoagulant with factor IIa activity	2.5-mg subcutaneous injection once daily	Bleeding[¶]
Invasive Management				
Coronary angiography followed by revascularization (if appropriate)	Up to 36-80 hr after hospitalization; within 24 hr in "very high risk" patients			MI, recurrent ischemia

*Avoid in the patient with signs of decompensated heart failure, evidence of low-output state, increased risk for cardiogenic shock, or other contraindications to β-blockade (e.g., PR interval >0.24 sec, second- or third-degree atrioventricular block without a cardiac pacemaker, active asthma, or reactive airway disease).
†Avoid in patients with clinically significant left ventricular dysfunction, increased risk for cardiogenic shock, PR interval >0.24 sec, or second- or third-degree atrioventricular block without a cardiac pacemaker.
‡Compared with clopidogrel.
§Compared with unfractionated heparin.
#As monotherapy compared with heparin and glycoprotein IIb/IIIa inhibitor combination.
¶Compared with enoxaparin.
aPTT = activated partial thromboplastin time; IV = intravenous; MI = myocardial infarction; PCI = percutaneous coronary intervention.
Modified from Lange RA, Hillis LD. Optimal management of acute coronary syndromes. *N Engl J Med.* 2009;260:2237-2240.

(three boluses of 5 mg each given 5 minutes apart) initially, after which an oral dose should be initiated. A reasonable target heart rate is 50 to 60 beats per minute at rest.

β-Blockers should not be administered to patients with decompensated heart failure, hypotension, hemodynamic instability, or advanced atrioventricular block. Because most patients with chronic obstructive pulmonary disease or peripheral vascular disease tolerate β-blockers without difficulty, these conditions should not automatically preclude their use.

Calcium-Channel Blockers

Calcium-channel blockers, which cause arterial vasodilation, increase coronary arterial blood flow and lower systemic arterial pressure. The non-dihydropyridine calcium-channel blockers diltiazem and verapamil slow heart rate and are recommended for the patient with a contraindication to a β-adrenergic blocker or persistent or recurrent symptoms despite treatment with nitroglycerin or a β-blocker. Oral diltiazem (30 to 90 mg four times daily of the short-acting preparation or up to 360 mg once daily of the long-acting preparation) is the preferred calcium-channel blocker because it reduces the incidence of myocardial ischemia and recurrent MI in patients with non–ST elevation acute coronary syndrome. Diltiazem is contraindicated in patients with left ventricular systolic dysfunction or pulmonary vascular congestion. Caution should be exercised when combining a β-blocker with diltiazem because the two drugs may act synergistically to depress left ventricular systolic function as well as sinus and atrioventricular nodal conduction. Patients with acute coronary syndrome should not be prescribed short-acting nifedipine unless they are already receiving a β-blocker because it may increase the risk of death. By comparison, the risks and benefits of long-acting dihydropyridines are not well defined.

Antiplatelet Agents

Patients with acute coronary syndrome should receive dual antiplatelet therapy (aspirin and a $P2Y_{12}$ ADP receptor inhibitor) acutely and for up to 1 year unless they have an aspirin allergy, active bleeding, or are at high risk of bleeding.[14] Aspirin (162 to 325 mg initially, then 81 mg daily, continued indefinitely; Chapter 70) reduces the risk of death or MI by about 50%. The choice of which ADP receptor antagonist to use in combination with aspirin is determined by each patient's characteristics (i.e., risk of bleeding), medication costs, and pharmacologic properties of the agent (see the following details). The patient who is allergic to or intolerant of aspirin should be treated with a $P2Y_{12}$ ADP receptor inhibitor (clopidogrel, ticagrelor, or prasugrel [if PCI treated]) alone. Patients who are treated with drug-eluting coronary stenting (see later) and who are at high risk of bleeding may discontinue $P2Y_{12}$ ADP receptor inhibitor therapy after 3 to 6 months.[A7] Among these three options, prasugrel and ticagrelor decrease ischemic events but increase bleeding compared with clopidogrel.[A8] De-escalation to clopidogrel or low-dose prasugrel (e.g., 5 mg rather than 10 mg daily) at 3 to 6 months can provide equivalent benefits with lower bleeding risks.[A9]

$P2Y_{12}$ ADP Receptor Inhibitors

Clopidogrel (Chapter 70) has antiplatelet activity that is synergistic with aspirin because the two agents inhibit different platelet-activating pathways. Clopidogrel is a prodrug that must be metabolized by the cytochrome P-450 system to the active form. Polymorphisms in the cytochrome P-450 isoform CYP2C19, which are present in 15 to 20% of individuals, slow metabolism of the prodrug to the active form, thereby reducing the magnitude of platelet inhibition. Drugs that are potent inhibitors of the CYP2C19 enzyme (e.g., omeprazole, esomeprazole, cimetidine, fluconazole, ketoconazole, voriconazole, etravirine, felbamate, fluoxetine, and fluvoxamine) should not be administered with clopidogrel because they affect the metabolism to its active form and reduce its antiplatelet effects. In patients with non–ST elevation acute coronary syndrome, the addition of clopidogrel (a loading dose of 300 to 600 mg, then 75 mg daily for up to 1 year) to aspirin reduces the composite end point of cardiovascular death, nonfatal MI, or stroke by 20% (2.1% reduction in absolute risk) compared with treatment with aspirin alone. The benefit of an aspirin-clopidogrel combination was seen as early as 24 hours after drug initiation and persisted for the 12 months of the study, despite an increase in minor bleeding.

Prasugrel (Chapter 70) has a greater antiplatelet effect and a more rapid onset of action than clopidogrel. In patients with acute coronary syndrome who are referred for PCI, prasugrel in combination with aspirin reduces ischemic events (i.e., a combination of cardiovascular death, nonfatal MI, and stroke) by 20% compared with concomitant clopidogrel and aspirin (2.2% absolute risk reduction) therapy. However, this benefit is obtained at a 0.5% increased risk of life-threatening bleeding and a 0.3% increased risk of fatal bleeding. Compared with ticagrelor, prasugrel can significantly reduce the 1-year risk of death, myocardial infarction, or stroke, with a slightly lower risk of bleeding.[A10] In combination with aspirin, it is administered as a 60-mg oral loading dose followed by a 10-mg daily maintenance dose. Diminishing the dose from 10 mg daily to 5 mg daily at 1 month may sustain its anti-ischemic benefits but reduce bleeding, thereby improving its net clinical benefit.[A11] Because prasugrel-associated bleeding complications are highest in patients with a previous stroke or transient ischemic attack, age older than 75 years, or a body weight of less than 60 kg, it should not be used in patients with any of these features.

Ticagrelor (Chapter 70) does not require hepatic activation, and it has more rapid onset and more pronounced platelet inhibition than clopidogrel. It is a reversible inhibitor of the $P2Y_{12}$ receptor, so platelet function returns more rapidly after discontinuation than with clopidogrel. In a randomized trial in non–ST elevation acute coronary syndrome patients, the addition of ticagrelor to aspirin reduced the composite end point of vascular death, nonfatal MI, or stroke by about 15% compared with treatment with clopidogrel and aspirin but increased non–procedure-related bleeding by an absolute 0.7%. In combination with aspirin, ticagrelor is administered as a 180-mg oral loading dose, followed by a 90-mg twice-daily maintenance dose. In patients who receive ticagrelor, the daily aspirin maintenance dose should be 100 mg or less, and ticagrelor

should not be used in patients with a history of intracranial hemorrhage. Even in patients more than 1 year after a non–ST elevation MI, treatment with ticagrelor at 60 or 90 mg twice daily in addition to aspirin significantly reduces the risk of cardiovascular death, MI, or stroke but not of overall death because of an increased risk of major bleeding.

Cangrelor, which is the only intravenous $P2Y_{12}$ receptor antagonist, is administered as a bolus (30 μg/kg before the PCI procedure), followed by an infusion (4 μg/kg per minute for at least 2 hours or through the duration of the intervention, whichever is longer), as an adjunct during PCI to reduce the risk of periprocedural MI, repeated coronary revascularization, and subacute thrombosis in patients who are not being treated with an oral $P2Y_{12}$ inhibitor and are not planned to receive a glycoprotein IIb/III inhibitor. To maintain platelet inhibition after discontinuation of the cangrelor infusion, oral options include clopidogrel (600 mg immediately after discontinuing cangrelor), prasugrel (60 mg immediately after discontinuing cangrelor), or ticagrelor (180 mg at any time during the cangrelor infusion or immediately after it).

Glycoprotein IIb/IIIa Inhibitors

Glycoprotein IIb/IIIa inhibitors (Chapter 70) block platelet aggregation in response to all potential agonists, so they are the most potent antiplatelet agents available. Three glycoprotein IIb/IIIa inhibitors, each of which must be administered parenterally, are available: abciximab is the Fab fragment of a monoclonal antibody to the receptor, eptifibatide is a peptide, and tirofiban is a peptidomimetic molecule.

Glycoprotein IIb/IIIa inhibitors reduce the incidence of recurrent ischemic events in patients with non–ST elevation acute coronary syndrome who undergo PCI but not in patients who are managed with medical therapy alone. When a glycoprotein IIb/IIIa inhibitor is administered to PCI patients, it should be initiated at the time of angiography because its routine administration beforehand carries an increased bleeding risk and no improvement in outcomes. The glycoprotein IIb/IIIa inhibitor infusion (see Table 57-3) typically is continued for 12 to 24 hours after PCI.

Anticoagulants

Anticoagulant therapy should be administered to all patients with acute coronary syndrome unless a contraindication, such as active bleeding, is present. For the patient in whom a noninvasive, ischemia-guided management strategy is selected, treatment with unfractionated heparin, low-molecular-weight heparin (LMWH), or fondaparinux is appropriate, with fondaparinux recommended for the patient at increased risk of bleeding. For the patient in whom an invasive management strategy is selected, unfractionated heparin and LMWH are the agents of choice. Although bivalirudin may be preferred in patients undergoing PCI, it is not used in the initial management of the patient with acute coronary syndrome.

Low-Molecular-Weight Heparin

LMWHs (Chapter 70), which are fragments of unfractionated heparin, exert a more predictable anticoagulant effect, have a longer half-life, and are less likely to cause thrombocytopenia compared with unfractionated heparin. Because they provide predictable and sustained anticoagulation with once- or twice-daily subcutaneous administration, monitoring of their anticoagulant effect is not required.

LMWH is superior to unfractionated heparin in preventing MI or death during hospitalization in non–ST elevation acute coronary syndrome patients who have elevated serum cardiac biomarkers, as well as in those considered to be at high risk for recurrent ischemia (see Table 57-1). In the low-risk patient, unfractionated heparin and LMWH have similar efficacy.

Two LMWHs, enoxaparin and dalteparin, are approved for the treatment of the patient with non–ST elevation acute coronary syndrome. The dose of enoxaparin is 1 mg/kg subcutaneously twice daily, and the dose of dalteparin is 120 IU/kg (maximum, 10,000 IU) subcutaneously twice daily. Therapy should be continued for the duration of the hospitalization, up to 8 days, or until revascularization is performed (whichever occurs first). In obese (>120 kg), thin (<60 kg), or renally impaired (creatinine clearance <30 mL/minute) patients, the LMWH dose should be adjusted to achieve an anti–factor Xa concentration of 0.5 to 1.5 IU/mL 4 to 6 hours after drug administration. LMWH should be avoided in the patient with a history of heparin-induced thrombocytopenia. In the patient with renal failure, treatment with LMWH has been associated with the development of hyperkalemia.

Heparin

Unfractionated heparin (Chapter 70) exerts its anticoagulant effect by accelerating the action of circulating antithrombin; it prevents thrombus propagation but does not lyse existing thrombi. In the patient with non–ST elevation acute coronary syndrome, the addition of heparin to aspirin reduces the rate of in-hospital ischemic events (i.e., death or MI) by 33%.

Unfractionated heparin should be initiated with an intravenous bolus of 60 U/kg, followed by a continuous infusion of approximately 12 U/kg/hour (maximum, 1000 U/hour), adjusted to maintain the activated partial thromboplastin time (aPTT) at 1.5 to 2.5 times control (i.e., 50 to 70 seconds) or a heparin concentration at 0.3 to 0.7 U/mL (by anti–factor Xa determinations). The infusion should be continued for 48 hours or until revascularization is performed, whichever occurs sooner. Frequent monitoring of the aPTT or heparin concentration is necessary because the anticoagulant response to a standard dose of unfractionated heparin varies widely among individuals; even when a weight-based nomogram (see Table 68-6) is followed, the aPTT is outside the therapeutic range more than one third of the time.

Mild thrombocytopenia occurs in 10 to 20% of patients treated with unfractionated heparin. In 1 to 5% of patients, a more severe form of thrombocytopenia develops. This antibody-mediated response usually occurs 4 to 14 days after the initiation of treatment (although it may appear more quickly in patients who received heparin within the preceding 6 months) and is associated with thromboembolic sequelae in 30 to 80% of patients (Chapter 158).

Fondaparinux

Fondaparinux (Chapter 70), which is a selective factor Xa inhibitor, does not require dose adjustment and monitoring. Fondaparinux does not cause thrombocytopenia. Fondaparinux is as effective as enoxaparin in preventing ischemic cardiac events but with 50% fewer major bleeding episodes (2.2% vs 4.1%). Because an increased incidence of catheter-related thrombosis has been reported after fondaparinux treatment, it is not recommended for patients who are likely to undergo coronary angiography. Fondaparinux is a desirable anticoagulant for the acute coronary syndrome patients who are managed in an ischemia-guided fashion, especially patients at higher risk of a bleeding complication with anticoagulant therapy, but not for other patients.

For the patient with acute coronary syndrome, fondaparinux is administered as a 2.5-mg subcutaneous injection once daily for up to 5 days or until hospital discharge. Its use is contraindicated in patients with severe renal impairment and in those who weigh 50 kg or less, and it should not be used as the sole anticoagulant during a PCI.

Bivalirudin

Bivalirudin, a direct thrombin inhibitor, is currently recommended as an alternative anticoagulant for patients undergoing PCI. In patients whose acute coronary syndrome is managed with an ischemia-guided strategy, its administration in a setting other than the cardiac catheterization laboratory is not recommended. In the patient undergoing PCI, bivalirudin (0.75 mg/kg intravenous bolus followed by an infusion of 1.75 mg/kg/hour for up to 4 hours after the PCI) is as effective as unfractionated heparin[A12] and as combination heparin and glycoprotein IIb/IIIa inhibitor therapy in preventing ischemic events, but it causes fewer major bleeding episodes. Bivalirudin is the anticoagulant of choice for the patient with acute coronary syndrome who has heparin-induced thrombocytopenia.

Direct-Acting Oral Anticoagulants

Adding a direct-acting oral anticoagulant (e.g., apixaban, rivaroxaban, and dabigatran) to a single antiplatelet agent appears to have little effect on bleeding or cardiovascular complications in patients with acute coronary syndrome. By comparison, adding one to dual antiplatelet therapy appears to increase significant bleeding about 2.2-fold with only a modest 14% reduction in adverse cardiac events.[A13] Factor Xa inhibition with low-dose rivaroxaban (2.5 mg twice daily) plus aspirin may be considered as a treatment option for maintenance treatment beyond 12 months after PCI for acute coronary syndrome inpatients at high thrombotic risk but without an increased risk for major or life-threatening bleeding.

Cholesterol Reduction

Prompt initiation of statin therapy is recommended in all patients with non–ST elevation acute coronary syndrome to promote plaque stabilization and to restore endothelial function. Moreover, when statin therapy is initiated during the patient's hospitalization (rather than at hospital discharge), long-term medical compliance is substantially improved. In the absence of contraindications, high-dose atorvastatin (40 to 80 mg daily) or rosuvastatin (20 to 40 mg daily) should be given orally regardless of the baseline serum low-density lipoprotein (LDL) cholesterol concentration. A lower dose is not as effective in reducing ischemic events, and the goal for LDL reduction is to 70 mg/dL or lower. If a statin alone does not achieve this goal, ezetimibe (10 mg daily) and/or an inhibitor of proprotein convertase subtilisin/kexin type 9 (e.g., alirocumab 300 mg or evolocumab 320 mg subcutaneously every 4 weeks; Chapter 190) should be added to achieve it. The addition of ezetimibe provides incremental benefit even in patients who have achieved an average LDL level of 70 mg/dL, especially if they have other high-risk characteristics such as diabetes or age over 70 years.[A14,A15]

Recurrent or Refractory Unstable Angina

In most patients hospitalized with non–ST elevation acute coronary syndrome, symptoms do not recur after the institution of appropriate antianginal therapy. The occasional patient with continued or recurrent chest pain despite optimal medical therapy is at high risk for an MI. For the patient with refractory myocardial ischemia or hemodynamic instability despite optimal medical therapy,

intra-aortic balloon counterpulsation can reduce the incidence of ischemic episodes until revascularization can be performed. Intra-aortic balloon function is synchronized with the patient's ECG so that it inflates during diastole and deflates during systole, thereby augmenting coronary arterial blood flow and reducing myocardial oxygen demand by decreasing afterload. Intra-aortic balloon counterpulsation causes lower limb ischemia in approximately 3% of patients in whom the device is placed, but this complication usually resolves with its removal.

Coronary Revascularization

Coronary revascularization is performed to relieve angina that is persistent or recurrent despite optimal medical therapy, to prevent recurrent ischemia or MI in patients at high risk for a subsequent ischemic event, and to improve survival in patients with suitable coronary arterial anatomy.

Coronary revascularization is successful in relieving symptoms in 90% of the patients with angina refractory to medical therapy. Whether coronary bypass surgery or PCI is the more appropriate method of revascularization is determined by the location and severity of coronary arterial stenoses and the presence of comorbid medical conditions that may affect the performance or safety of the revascularization procedure (Chapter 59).

The patient who has been rendered symptom free with optimal medical therapy should undergo an assessment to determine whether he or she is at high risk or relatively low risk of sustaining a cardiac ischemic event (death, MI, or recurrent ischemia) in the ensuing days, weeks, and months and a bleeding complication from intensive medical therapy or an invasive cardiac procedure. Patients who are at low risk of having a subsequent ischemic event (those with a normal serum troponin concentration; age younger than 75 years; and zero, one, or two TIMI risk variables) should be evaluated noninvasively for inducible ischemia before hospital discharge. If the patient has spontaneous or provocable ischemia, coronary angiography and, if appropriate, revascularization should be performed.

The acute coronary syndrome patient with a detectable serum troponin concentration, age older than 75 years, or three or more TIMI risk variables is considered to be at high risk for a subsequent event and should be referred for routine coronary angiography and revascularization (if appropriate) during the hospitalization because this management strategy reduces the incidence of subsequent ischemic cardiac events.[A16] In most patients, early (within 24 hours of hospitalization) invasive therapy is no better at preventing death, MI, or stroke than somewhat delayed (median, 60 hours) invasive management,[A17] although it is associated with a modest decrease in the occurrence of recurrent ischemia. In contrast, in the one third of patients considered to be at very high risk (GRACE risk score of >140, corresponding to an incidence of in-hospital death or MI of >20%), an early invasive management strategy is superior to a delayed strategy in reducing the incidence of death, MI, or stroke. The benefit of an invasive strategy appears to extend even to patients over age 80 years.[15]

The patient with clinical features or noninvasive test results suggestive of severe coronary artery disease (i.e., left ventricular dysfunction, hemodynamic instability, life-threatening ventricular arrhythmias, or extensive inducible ischemia) should be referred for coronary angiography (Table 57-4) to determine if left main or three-vessel coronary arterial disease is present because patients with these coronary anatomic findings derive a survival benefit with coronary revascularization compared with medical therapy (Chapter 59). In patients who are taking a $P2Y_{12}$ ADP receptor inhibitor and in whom coronary artery bypass grafting can be delayed, the drug should be discontinued (5 days for clopidogrel or ticagrelor and at least 7 days for prasugrel) to allow dissipation of the antiplatelet effect. The timing of coronary bypass surgery in patients treated with a $P2Y_{12}$ ADP inhibitor should balance a potential increased risk of bleeding against the risks of delaying surgery.

For PCI, a single-stage complete revascularization is probably preferred compared with staged revascularization of the culprit artery immediately followed by other significant stenoses later (Chapter 59).[A18] Stenting can be performed safely at centers without on-site cardiac surgery.

Complications

Patients with non–ST elevation acute coronary syndrome can develop recurrent ischemic events or any of the complications associated with ST elevation MI, including arrhythmias, heart failure, and mechanical complications (Chapter 58). However, the acute complications other than recurrent ischemia occur less often in patients with non–ST elevation acute coronary syndrome because the amount of myocardial damage usually is less.

Because intensive medical therapy in conjunction with invasive management can lead to life-threatening bleeding complications, the patient's risk of such should be assessed before these therapies are instituted. Female gender, older age, renal insufficiency, low body weight, tachycardia, high or low systolic arterial pressure, anemia, and diabetes mellitus predict an increased risk of major bleeding, often due to excessive dosing of antiplatelet or anticoagulant agents. The bleeding risk can be estimated with the tool available at https://www.mdcalc.com/calc/1784/crusade-score-post-mi-bleeding-risk.

TABLE 57-4 SELECTION OF INITIAL TREATMENT STRATEGY: INVASIVE VERSUS CONSERVATIVE

GENERALLY PREFERRED STRATEGY	PATIENT CHARACTERISTICS
Invasive	Recurrent angina or ischemia at rest or with low-level activities despite intensive medical therapy Elevated troponin level New or presumably new ST segment depression Signs or symptoms of heart failure or new or worsening mitral regurgitation High-risk findings from noninvasive testing Hemodynamic instability Sustained ventricular tachycardia PCI within 6 months Previous CABG High-risk score (e.g., TIMI, GRACE) Mild to moderate renal dysfunction Diabetes mellitus Reduced left ventricular systolic function (EF <40%)
Conservative	Low-risk score (e.g., TIMI [0 or 1] or GRACE [<109]) Low-risk, troponin-negative female patients Patient or physician preference in the absence of high-risk features

CABG = coronary artery bypass grafting; EF = ejection fraction; GRACE = Global Registry of Acute Coronary Events; PCI = percutaneous coronary intervention; TIMI = Thrombolysis in Myocardial Infarction.

Integrated Approach to Treatment

Although the treatment of the patient with non–ST elevation acute coronary syndrome should be individualized, taking into account the specific features of the disease and the particular circumstances of the patient, algorithms nonetheless provide a useful framework (Fig. 57-3). Smoking cessation (Chapter 363), cholesterol lowering (Chapter 190), and control of blood pressure (Chapter 64), obesity, and diabetes mellitus (Chapter 210) are important long-term prevention strategies. A polypill strategy with aspirin (100 mg daily), ramipril (2.5 to 10 mg daily), and atorvastatin (20 to 40 mg daily) is preferred to usual care for preventing recurrent myocardial ischemic events.[A19] Maintaining adherence long term with medical therapy appears to reduce the risk of a future ischemic event by up to 80%.

PROGNOSIS

Because the number of ECG leads demonstrating ST segment depression and the magnitude of such depression are indicative of the extent and severity of myocardial ischemia and MI, it is not surprising that ST segment depression correlates with the patient's prognosis. Compared with patients without ST segment depression, the patient with non–ST elevation acute coronary syndrome who has ST segment depression of 1 mm or greater in two or more leads is almost four times as likely to die within 1 year, and the patient with ST segment depression of 2 mm or greater in magnitude is almost six times as likely to die within 1 year. If ST segment depression of 2 mm or greater is present in more than one region of the ECG, the mortality is increased 10-fold. Even the 20% of patients with acute coronary syndrome who have only 0.5 to 1 mm of ST segment depression have an adverse prognosis. Patients with ST segment depression also have a higher risk for subsequent cardiac events compared with patients with only T wave inversions (>1 mm).

The magnitude of the serum troponin concentration predicts short-term (30 days) and long-term (1 year) risks of recurrent MI and death, independent of ECG abnormalities or markers of inflammatory activity. Patients with a high-sensitivity troponin level <5 ng/L are at low risk for an event in the next 30 days, but risks increase progressively into higher levels even if the levels are stable and therefore not indicative of acute coronary syndrome.

C-reactive protein measured with a highly sensitive assay, which is a widely used marker of inflammation, has no role in the diagnosis of acute coronary syndrome but is predictive of long-term (6 months) mortality among patients with troponin-negative non–ST elevation acute coronary syndrome. Elevated serum concentrations of natriuretic peptides (B-type natriuretic peptide [BNP] or its N-terminal prohormone [NT-pro-BNP]) are associated with

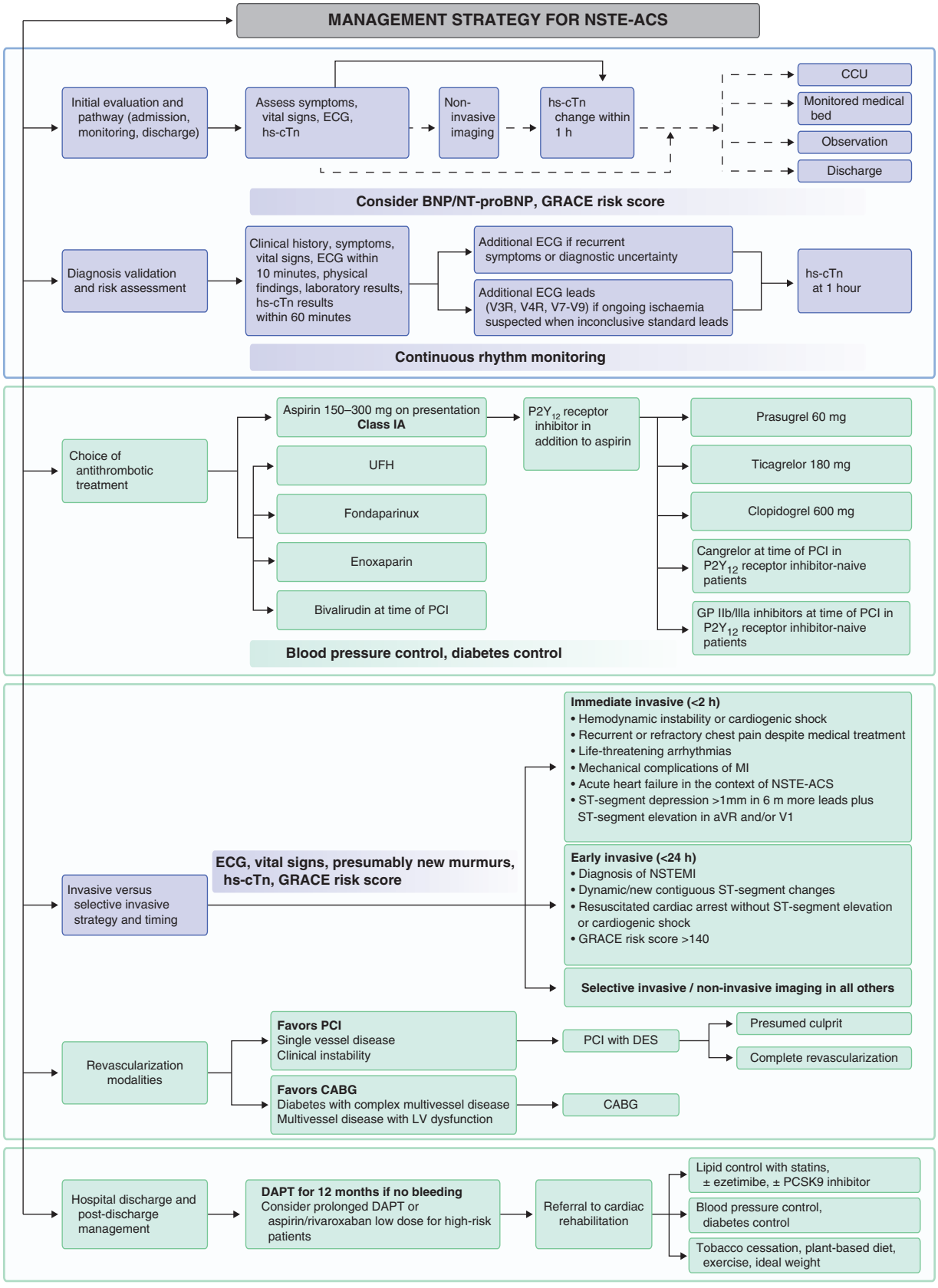

FIGURE 57-3. **Approach to the patient with non–ST elevation acute coronary syndrome (NSTE-ACS).** BNP = B-type natriuretic peptide; CABG = coronary artery bypass grafting; CCU = coronary care unit; DAPT = dual antiplatelet therapy; DES = drug-eluting stent; ECG = electrocardiogram/electrocardiography; GP = glycoprotein; GRACE = Global Registry of Acute Coronary Events; hs-cTn = high-sensitivity cardiac troponin; LV = left ventricular; MI = myocardial infarction; NSTE-ACS = non-ST elevation acute coronary syndrome; NSTEMI = non-ST elevation myocardial infarction; NT-proBNP = N-terminal pro-B-type natriuretic peptide; PCI = percutaneous coronary intervention; PCSK9 = proprotein convertase subtilisin kexin 9; UFH = unfractionated heparin. (Adapted from Collet JP, Thiele H, Barbato E, et al. ESC guidelines for the management of acute coronary syndromes in patients presenting without persistent ST-segment elevation. *Eur Heart J*. 2021;42:1289-1367.)

a three- to five-fold increased mortality in patients with non–ST elevation acute coronary syndrome, although they have limited value for diagnosis, initial risk stratification, and selection of an initial management strategy. Natriuretic peptide concentrations measured a few days after the onset of symptoms have better predictive value than those measured at the time of hospitalization. In patients with non–ST elevation acute coronary syndrome, a simultaneous assessment of troponin, high-sensitivity C-reactive protein, and BNP is superior to a single biomarker assessment at predicting short-term outcome.

In contrast to patients with ST elevation MI, in whom most events occur before or shortly after presentation to the hospital, patients with non–ST elevation acute coronary syndrome continue to be at high risk for such events during the ensuing days, weeks, and months. Although in-hospital mortality is higher in patients with ST elevation MI than among those with non–ST elevation acute coronary syndrome (7 vs. 5%, respectively), the mortality rates at 6 months are similar for the two conditions (12 vs. 13%, respectively). During long-term follow-up of hospitalized patients, rates of death are actually higher in those with non–ST elevation acute coronary syndrome than in those with ST elevation MI, with a two-fold difference after 4 years. As a result, treatment strategies for non–ST elevation acute coronary syndrome should address the issues related to both the acute event and longer-term treatment.

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58

ST-ELEVATION ACUTE MYOCARDIAL INFARCTION AND COMPLICATIONS OF MYOCARDIAL INFARCTION

FREDERICK G.P. WELT AND JAMES C. FANG

DEFINITION

Conceptually, acute myocardial infarction (MI) is myocardial necrosis caused by ischemia. Practically, MI can be diagnosed and evaluated by clinical, electrocardiographic (ECG), biochemical, radiologic, and pathologic methods. Acute MI is classified based on whether the ECG shows ST-segment elevation (ST-elevation MI) or not (non–ST-elevation MI). Acute MI can be further classified into five types: type 1, acute MI due to coronary atherothrombosis; type 2, acute MI due to a demand/supply mismatch; type 3, acute MI causing (sudden) death without the opportunity for biomarker or ECG confirmation; type 4, acute MI related to a percutaneous coronary intervention (PCI) or thrombosis of a coronary stent[1]; and type 5, acute MI related to coronary bypass graft surgery (CABG). This chapter focuses primarily on type 1 ST-elevation MI. Non–ST-elevation MI is covered in Chapter 57.

ST-elevation MI is characterized by profound ("transmural") acute myocardial ischemia affecting relatively larger areas of myocardium. The underlying cause is essentially *complete* interruption of regional myocardial blood flow. In contrast, non–ST-elevation MI is characterized by *incomplete* blockage of coronary flow, for which different acute therapies are appropriate (Chapter 57).

EPIDEMIOLOGY

The age-adjusted risk of hospitalization and death from cardiovascular disease and MI has declined since the 1960s. Data from Medicare beneficiaries show a continued reduction in rates of hospitalization for MI in patients over age 65 years.[2]

The declines in cardiovascular disease and MI have been particularly noteworthy for ST-elevation MI, with rates falling by two-thirds since 2008. ST-elevation MI currently comprises 25% or less of acute coronary syndromes. This decline is attributable to changing demographics, lifestyles, and medical therapies.

Nevertheless, cardiovascular disease remains the number one cause of mortality in the United States, with 690,000 deaths in 2020 (21% of all deaths), and it has become a leading contributor to the burden of disease worldwide (Chapter 40) as developing countries adopt a more Western lifestyle. Coronary artery disease is the leading cardiovascular disease, causing about 600,000 first acute MIs, 200,000 recurrent MIs, and an estimated 170,000 "silent" MIs annually in the United States. Each year, about 365,000 Americans die from coronary heart disease, including about 100,000 attributable to acute MI.

The lifetime risk for coronary artery disease varies dramatically depending on age, sex, lipid profile (Chapter 190), blood pressure (Chapter 64), diabetes (Chapter 210), smoking status (Chapter 363), and family history. When all modifiable risk factors are optimal, the lifetime risk of coronary artery disease for a 45-year-old is estimated to be less than 5%; with two or more major risk factors, by comparison, it is 50% for men and 31% for women. All modifiable risk factors combined (including obesity, diet, physical activity, alcohol consumption, and psychosocial factors) account for over 90% of the population-attributable risk of acute MI globally. The genetic contribution to the risk of coronary artery disease is estimated to be about 40%, and polygenic risk scores based on common genetic variants can provide supplementary prognostic information.

Pathobiology

The usual initiating mechanism of acute MI is fissure or rupture of a vulnerable, lipid-laden atherosclerotic coronary plaque, thereby resulting in exposure of circulating blood to highly thrombogenic plaque core and matrix materials (Chapter 41). Based on both postmortem pathologic techniques and in vivo optical coherence tomography, up to one third of acute MIs may be due to superficial erosion of fibrous caps both in lesions with necrotic cores and in lesions that are predominantly fibrocellular (Chapter 41). A minority of lesions responsible for MI are characterized as a calcified nodule that fractures.[3] Regardless of

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ABSTRACT

Acute myocardial infarction (MI) is defined as myocardial necrosis caused by an imbalance between oxygen supply and demand. ST-segment elevation MI (STEMI) is typically associated with abrupt cessation of flow in an epicardial coronary artery, usually as a result of atherothrombosis. Although the incidence of STEMI has declined in the last several decades, it remains a major source of morbidity and mortality. The hallmark of treatment for STEMI is rapid diagnosis and reperfusion with either fibrinolytic medications or, preferably, primary percutaneous coronary intervention (PCI). Rapid diagnosis is dependent on clinical suspicion based on symptoms and evaluation of the 12-lead ECG. Other confirmatory tests include markers of myocardial necrosis, including high sensitivity troponin assays. Considerable efforts have been made to design systems of care to ensure that STEMI patients receive prompt reperfusion therapy (within 90 minutes at hospitals with PCI programs). Postreperfusion care is centered around surveillance for immediate complications of MI and initiation of medical regimens designed to reduce secondary risks. Of particular concern is surveillance for malignant arrhythmias, recurrent ischemia, and the development of heart failure. Assessment of cardiac function is critical in the post-MI patient. Secondary prevention involves mitigation of risk from hyperlipidemia, hypertension, and diabetes as well as lifestyle modification. Prevention and treatment of heart failure are also closely linked to prognosis.

KEYWORDS

myocardial infarction
plaque rupture
acute coronary syndrome
thrombosis
reperfusion

the initiating insult, platelets adhere, are activated, and aggregate at the site of injury. Thrombin is generated, thereby accelerating platelet activation, and the resulting fibrin traps red blood cells and leads to the formation of thrombus. A totally occluding thrombus typically leads to ST-elevation MI. By comparison, partial occlusion, or occlusion in the presence of collateral circulation, results in a non–ST-segment elevation acute coronary syndrome, often with ST depression or T-wave inversion (Chapter 57). Ischemia resulting from reduced coronary flow leads to myocardial cell injury or death, ventricular dysfunction, and cardiac arrhythmias. Myocardial necrosis begins after as little as 15 to 20 minutes of coronary occlusion and proceeds rapidly in a wave front from endocardium to epicardium. Partial myocardial salvage can be achieved by reperfusion within 3 to 6 hours, the degree of salvage being inversely proportional to the duration and extent of ischemia. The extent of myocardial necrosis also depends on metabolic demand and collateral blood supply.

About 10% of acute MIs are caused by conditions other than critical epicardial coronary atherosclerosis.[4] These other mechanisms include microvascular disease, endothelial dysfunction, coronary artery dissection,[5,6] coronary emboli, in situ thrombosis, vasculitis, primary vasospasm, infiltrative or degenerative disease, diseases of the aorta, congenital anomalies of a coronary artery, or trauma (Table 58-1).

CLINICAL MANIFESTATIONS

History

Acute MI may present with typical ischemic-type chest discomfort or atypically with dyspnea, nausea, epigastric discomfort, malaise, and/or unexplained weakness. Ischemic-type chest discomfort, usually the most prominent clinical symptom in acute MI, is perceived as a persistent (>10-20 minutes), diffuse, deep, and heavy retrosternal pressure or burning sensation; it rarely is perceived as sharp pain and generally not as stabbing pain (see Table 39-2 in Chapter 39). The discomfort associated with acute MI is qualitatively similar to that of angina pectoris but more severe and persistent (Chapters 39 and 56).

The primary location of typical ischemic pain is most consistently retrosternal, but it also can present left parasternal, left precordial, or across the anterior chest (Chapter 39). On occasion, discomfort is predominantly perceived in the anterior neck, jaw, arms, or epigastrium. It generally is somewhat diffuse; highly localized pain (finger point) is rarely angina or acute MI. The most characteristic pattern of radiation is to the left arm, but the right arm or both arms can be involved. The shoulders, neck, jaw, teeth, epigastrium, and interscapular areas also are sites of radiation. Discomfort above the jaws or below the umbilicus is not typical of acute MI. Associated symptoms often include nausea, vomiting, diaphoresis, weakness, dyspnea, restlessness, and apprehension.

The discomfort of acute MI is not reliably relieved by rest or nitroglycerin. The onset of acute MI usually is unrelated to exercise or other apparent precipitating factors. Nevertheless, acute MI may begin during or within a few hours following physical or emotional stress and is more common in this situation than is explained by chance.

It is estimated that at least 20% of acute MIs are painless ("silent") or atypical (unrecognized). Elderly patients, especially women, and patients with diabetes are particularly prone to painless or atypical MI, which is the presentation of MI in as many as one third to one half of such patients. Because the prognosis is worse in elderly and diabetic patients, diagnostic vigilance is required. In these patients, acute MI can be manifested as sudden dyspnea (which can progress to pulmonary edema), weakness, lightheadedness, nausea, and vomiting. Confusional states, sudden loss of consciousness, a new rhythm disorder, and an unexplained fall in blood pressure are other uncommon presentations. The differential diagnosis of ischemic chest discomfort also should include gastrointestinal disorders (e.g., reflux esophagitis; Chapter 124), musculoskeletal pain (e.g., costochondritis), anxiety or panic attacks, pleurisy or pulmonary embolism (Chapter 68), and acute aortic dissection (see Table 39-2 in Chapter 39 and Chapter 63).

Physical Examination

No physical findings are diagnostic or pathognomonic of acute MI. The physical examination often is entirely normal or may reveal only nonspecific abnormalities. An S_4 gallop frequently is found if it is carefully sought. Blood pressure often is initially elevated, but it may be normal or low. Signs of sympathetic hyperactivity (tachycardia, hypertension, diaphoresis, or any combination of these three) often accompany anterior wall MI, whereas parasympathetic hyperactivity (bradycardia, hypotension, or both) is more common with inferior wall MI.

The examination is best focused on an overall assessment of cardiac function. Adequacy of vital signs and peripheral perfusion should be noted. Signs of cardiac failure, both left and right sided (e.g., S_3 gallop, pulmonary congestion, elevated neck veins), should be sought, and observation for arrhythmias and mechanical complications (e.g., new murmurs) is essential. If hypoperfusion is present, determination of its primary cause (e.g., hypovolemia, right-sided heart failure, left-sided heart failure) is critical to management.

DIAGNOSIS

The diagnosis of acute MI has traditionally rested on the triad of ischemic-type chest discomfort, electrocardiographic abnormalities, and elevated serum cardiac biomarkers of necrosis. Acute MI was considered present when at least two of the three were present. With their increasing sensitivity and specificity, serum cardiac troponin levels (i.e., troponin I [TnI] and troponin T [TnT])

TABLE 58-1 CONDITIONS OTHER THAN CORONARY ATHEROSCLEROSIS THAT CAN CAUSE ACUTE MYOCARDIAL INFARCTION

Coronary emboli	Causes include aortic or mitral valve lesions, left atrial or ventricular thrombi, prosthetic valves, fat emboli, intracardiac neoplasms, infective endocarditis, and paradoxical emboli
Thrombotic coronary artery disease	Can occur with oral contraceptive use, sickle cell anemia and other hemoglobinopathies, polycythemia vera, thrombocytosis, thrombotic thrombocytopenic purpura, disseminated intravascular coagulation, antithrombin III deficiency and other hypercoagulable states, macroglobulinemia and other hyperviscosity states, multiple myeloma, leukemia, malaria, and fibrinolytic system shutdown secondary to impaired plasminogen activation or excessive inhibition
Coronary vasculitis	Seen with Takayasu disease, Kawasaki disease, polyarteritis nodosa, lupus erythematosus, scleroderma, rheumatoid arthritis, and immune-mediated vascular degeneration in cardiac allografts
Coronary vasospasm	Can be associated with variant angina, nitrate withdrawal, cocaine or amphetamine abuse, and angina with "normal" coronary arteries
Infiltrative and degenerative coronary vascular disease	Can result from amyloidosis, connective tissue disorders (e.g., pseudoxanthoma elasticum), lipid storage disorders and mucopolysaccharidoses, homocystinuria, diabetes mellitus, collagen vascular disease, muscular dystrophies, and Friedreich ataxia
Spontaneous coronary dissection	Over 90% of cases occur in younger women. The dominant predisposing cause is fibromuscular dysplasia (Chapter 63); other causes include various arteriopathies and pregnancy-related conditions. Precipitating factors include extreme physical and emotional stressors, intense hormonal therapy, and labor, delivery, and postpartum status. About 50% of cases present as an ST-elevation myocardial infarction, and the estimated 10-year rate of subsequent major adverse cardiac events is about 50%.
Coronary ostial occlusion	Associated with aortic dissection, luetic aortitis, aortic stenosis, and ankylosing spondylitis syndromes
Congenital coronary anomalies	Including Bland-White-Garland syndrome of anomalous origin of the left coronary artery from the pulmonary artery, left coronary artery origin from the anterior sinus of Valsalva, coronary arteriovenous fistula or aneurysms, and myocardial bridging with secondary vascular degeneration
Trauma	Associated with and responsible for coronary dissection, laceration, or thrombosis (with endothelial damage secondary to trauma such as angioplasty) and direct myocardial injury with radiation and cardiac contusion
Augmented myocardial oxygen requirements exceeding oxygen delivery	Encountered with aortic stenosis, aortic insufficiency, hypertension with severe left ventricular hypertrophy, pheochromocytoma, thyrotoxicosis, methemoglobinemia, carbon monoxide poisoning, shock, and hyperviscosity syndromes

have assumed a dominant role in confirming the diagnosis of acute MI in patients with suggestive clinical or electrocardiographic features.

Electrocardiography

In patients with a possible acute MI, a 12-lead ECG should be obtained immediately, with a goal of less than 10 minutes after arrival at a health care facility. Although the initial ECG is neither perfectly sensitive nor specific in patients who develop acute ST-elevation MI, it plays a critical role in initial stratification, triage, and management (Chapter 39).[7] In an appropriate clinical setting, a pattern of ST-segment elevation of 2 mm (0.2 mV) or more at the J point in V_2 to V_3 in men or 1.5 mm (0.15 mV) or more in women in the absence of left ventricular (LV) hypertrophy or 1 mm (0.1 mV) or more in two or more other contiguous chest or limb leads suggests coronary occlusion causing marked myocardial ischemia. In such patients, emergency reperfusion (primary angioplasty or fibrinolysis) should be performed unless it is contraindicated. Hyperacute T-wave changes may suggest the diagnosis in the early phase of ST-elevation MI before the onset of ST elevation. A new or presumably new left bundle branch block, which may obscure ST elevation analysis, may suggest an ST-elevation MI equivalent in the appropriate clinical setting. ST depression in two or more precordial leads V_1 to V_4 may indicate transmural posterior injury due to occlusion of the left circumflex coronary artery; extending ECG analysis to leads V_7 to V_9 (i.e., over the left posterior chest) can help confirm this diagnosis. Other ECG patterns (ST-segment depression, T-wave inversion, nonspecific changes, normal ECG) in association with ischemic chest discomfort are consistent with a non–ST-segment elevation acute coronary syndrome and are treated with different triage and initial management strategies (Chapter 57).

Electrocardiographic Evolution

Serial ECG tracings improve the sensitivity and specificity of the ECG for the diagnosis of acute MI and assist in assessing the outcomes of therapy. When typical ST-segment elevation persists for hours and is followed within hours to days by T-wave inversions and Q waves, the diagnosis of acute MI can be made with virtual certainty. The ECG changes in acute ST-elevation MI evolve through three overlapping phases: hyperacute or early acute, evolved acute, and chronic (stabilized).

Early Acute Phase

This earliest phase begins within minutes, persists, and evolves during hours. T waves increase in amplitude and widen over the area of injury (hyperacute pattern). ST segments evolve from concave to straightened to convex upward patterns (acute pattern). When prominent, the acute injury pattern of blended ST-T waves can take on a tombstone appearance (Figs. 58-1 and 58-2). ST-segment depressions that occur in leads opposite those with ST-segment elevation are known as reciprocal changes and are associated with larger areas of injury and a worse prognosis but also with greater potential for benefit from reperfusion therapy.

Other causes of ST-segment elevation must be considered and excluded (Table 58-2). These conditions include pericarditis (Chapter 62), left ventricular hypertrophy with J point elevation, and normal variant early repolarization (Chapter 42). Pericarditis (or perimyocarditis) is of particular concern because it can mimic acute MI clinically, but fibrinolytic therapy is *not* indicated and can be hazardous.

Evolved Acute Phase

During the second phase, ST-segment elevation begins to regress, T waves in leads with ST-segment elevation become inverted, and pathologic Q or QS

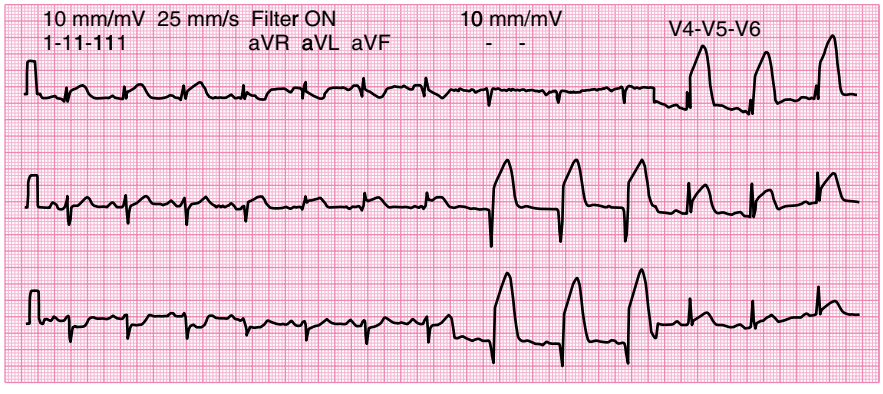

FIGURE 58-1. Electrocardiographic tracing shows an acute anterolateral myocardial infarction. Note ST-segment elevation in leads I, aVL, and V_1 to V_6 with Q waves in V_1 to V_4.

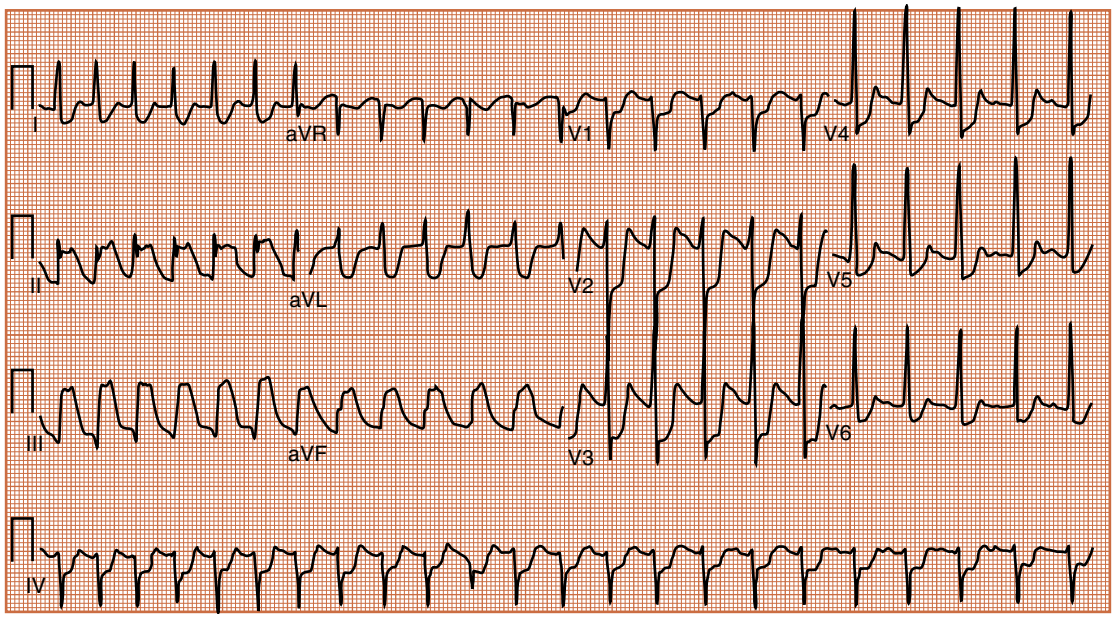

FIGURE 58-2. Electrocardiographic tracing shows an acute inferoposterior myocardial infarction.

TABLE 58-2 CONDITIONS THAT CAN MIMIC ST-SEGMENT ELEVATION MYOCARDIAL INFARCTION

Early repolarization with noncoronary chest pain
Myocarditis
Pericarditis
Takotsubo syndrome (stress cardiomyopathy)
Hyperkalemia
Brugada syndrome

waves become fully developed (>0.03-second duration or depth >30% of R wave amplitude or both).

Chronic Phase

Resolution of ST-segment elevation is variable. Resolution is usually complete within 2 weeks of inferior MI, but it can be delayed further after anterior MI. Persistent ST-segment elevation, often seen with a large anterior MI, is indicative of a large area of akinesis, dyskinesis, or ventricular aneurysm. Symmetrical T-wave inversions can resolve during weeks to months or can persist for an indefinite period; hence, the age of an MI in the presence of T-wave inversions is often termed indeterminate. Q waves usually do not resolve after anterior MI but often disappear after inferior wall MI.

Early reperfusion therapy accelerates the time course of ECG changes to minutes or hours instead of days to weeks. ST segments recede rapidly, T-wave inversions and loss of R waves occur earlier, and Q waves may not develop or progress and occasionally may regress. Indeed, failure of ST-segment elevation to resolve by more than 50 to 70% within 1 to 2 hours suggests failure of fibrinolysis and should prompt referral for urgent angiography and consideration of "rescue angioplasty."

True Posterior Myocardial Infarction and Left Circumflex Myocardial Infarction Patterns

True posterior MI presents a mirror-image pattern of ECG injury in leads V_1 to V_2 to V_4 (Fig. 58-2). The location of injury of an isolated true posterior MI by magnetic resonance imaging actually involves portions of the lateral left ventricular wall and is typically caused by occlusion of a nondominant left circumflex artery. In the precordial leads, the acute phase is characterized by ST-segment depression rather than by ST-segment elevation. The evolved and chronic phases show increased R wave amplitude and widening instead of Q waves. Recognition of an isolated true posterior acute MI pattern is challenging but important because the diagnosis should lead to an immediate reperfusion strategy. Extending the ECG to measure left posterior leads V_7 to V_9 increases sensitivity for detection of acute left circumflex–related injury patterns (i.e., ST-segment elevation) with excellent specificity (Chapter 42). Other causes of prominent upright anteroseptal forces include right ventricular hypertrophy, ventricular preexcitation variants (Wolff-Parkinson-White syndrome; Chapter 52), cardiomyopathies, right bundle branch block, and normal variants with early R wave progression. New appearance of these changes or the association with an acute or evolving inferior MI usually allows the diagnosis to be made.

Right Ventricular Infarction

Proximal occlusion of the right coronary artery before the acute marginal branch can cause right ventricular infarction as well as acute inferior MI in about 30% of cases. Because the prognosis and treatment of acute inferior MI differ in the presence of right ventricular infarction, it is important to make this diagnosis. The diagnosis is assisted by obtaining right precordial ECG leads, which are routinely indicated for inferior acute MI (Chapter 42). Acute ST-segment elevation of at least 1 mm (0.1 mV) in one or more leads V_4R to V_6R is both sensitive and specific (>90%) for identifying acute right ventricular injury, and Q or QS waves effectively identify right ventricular infarction.

Diagnosis in the Presence of Bundle Branch Block

The presence of left bundle branch block often obscures ST-segment analysis in patients with suspected acute MI. The presence of a new (or presumed new) left bundle branch block in association with clinical (and laboratory) findings suggesting acute MI is associated with high mortality; patients with new-onset left bundle branch block benefit substantially from reperfusion therapy and should undergo triage and treatment in the same way as patients with ST-elevation MI do. Certain ECG patterns, although relatively insensitive, suggest acute MI if they are present in the setting of left bundle branch block: Q waves in two of leads I, aVL, V_5, and V_6; R wave regression from V_1 to V_4; ST-segment elevation of 1 mm or more in leads with a positive QRS complex; ST-segment depression of 1 mm or more in leads V_1, V_2, or V_3; and ST-segment elevation of 5 mm or more associated with a negative QRS complex. The presence of right bundle branch block usually does not mask typical ST-T wave or Q wave changes except in rare cases of isolated true posterior acute MI, which are characterized by tall right precordial R waves and ST-segment depressions.

TABLE 58-3 NON–MYOCARDIAL INFARCTION CAUSES OF AN ELEVATED TROPONIN LEVEL

OTHER CARDIAC CAUSES
Myocardial injury: cardiac contusion, surgery, ablation, shocks
Myocardial inflammation: myocarditis, pericarditis
Heart failure
Cardiomyopathies: infiltrative, stress, hypertensive, hypertrophic
Aortic dissection
Severe aortic stenosis
Tachycardias
PULMONARY CAUSES
Pulmonary embolism
Pulmonary hypertension
Respiratory failure
NEUROLOGIC CAUSES
Stroke
Intracranial hemorrhage
OTHER
Shock: septic, hypovolemic, cardiogenic
Renal failure

Modified from Thygesen K, Alpert JS, Jaffe AS, et al. Fourth universal definition of myocardial infarction. *Circulation*. 2018;138:e618-e651.

Differential Diagnosis

Although ST-elevation MI is often an easy diagnosis to make on the basis of the presentation and test results (see later), other considerations include acute pericarditis (Chapter 62), acute myocarditis (Chapter 47), stress-induced cardiomyopathy (takotsubo syndrome) (Chapter 47), hyperkalemia, and early repolarization (see Table 58-2). All but early repolarization can be associated with abnormal biomarkers, but none are associated with a coronary occlusion. Early coronary angiography is advised when the cause of ST-segment elevation is unclear (see Table 58-1).

Serum Cardiac Biomarkers of Necrosis

Cardiac-derived troponin-I and troponin-T are proteins specific to sarcomeres. Serial measurement of cardiac troponins is the preferred biomarker approach for differentiating acute MI from unstable angina and non-acute coronary syndromes. In the appropriate clinical setting, acute MI is indicated by a rising and/or falling pattern of troponin, with one or more value(s) above the 99th percentile upper reference limit. High-sensitivity troponin assays can greatly reduce the likelihood of acute MI after a single negative sample and effectively exclude MI in 1 to 2 hours.[8] Such testing has increased the ability to diagnose type 1 MIs (attributable to atherothrombotic events) as well as type 2 MIs (attributable to acute imbalances in myocardial oxygen supply and demand). However, high-sensitivity assays also can lead to an increasing number of false-positive diagnoses of acute MI, because they sometimes can detect increased troponin levels in a number of non-MI settings: myocarditis (Chapter 47); other causes of cardiac injury, such as cardiac, renal, and respiratory failure (Chapter 90); stroke (Chapter 376) and intracranial hemorrhage (Chapter 377); septic shock (Chapter 94); and chronic structural heart diseases (Chapter 56; Table 58-3).[9] As a result, the clinician always must consider the clinical context as well as the finding of a temporal rise and fall of troponin levels.

High-sensitivity troponin assays measure troponin-T, which can be elevated in patients with renal failure (Chapter 117); in this situation, a troponin-I measurement, if available, is preferred. Troponin levels are maximally sensitive at 8 to 12 hours, peak at 10 to 24 hours, and persist for 5 to 14 days. This persistence poses a challenge for the diagnosis of an early recurrent MI, for which the measurement of more rapidly cleared MB isoenzyme of creatine kinase (CK-MB) can be useful.

Other Laboratory Tests

On admission, routine assessment of complete blood count and platelet count, standard blood chemistry studies, a lipid panel, and coagulation tests (prothrombin time, partial thromboplastin time) are useful. Results assist in assessing comorbid conditions and prognosis and in guiding therapy. Hematologic tests provide a useful baseline before initiation of antiplatelet, anticoagulant, and fibrinolytic therapy or coronary angiography or angioplasty. Myocardial injury precipitates polymorphonuclear leukocytosis, thereby commonly resulting in an elevation of the white blood cell count to up to 12,000 to 15,000/μL, which appears within a few hours and peaks at 2 to 4 days. The metabolic panel provides a useful check on electrolytes, glucose, and renal function.

Serum lipid levels may fall in the first 24 to 48 hours after an MI, but a fasting lipid panel is recommended as a baseline for lipid-lowering (statin) therapy (Chapter 190). Unless carbon dioxide retention is suspected, finger oximetry is adequate to diagnose hypoxemia and titrate oxygen therapy. B-type natriuretic peptide, which increases with ventricular wall stress and relative circulatory fluid overload, may provide useful incremental prognostic information in the setting of acute MI.

Imaging

The rapid triage of ST-elevation MI patients to reperfusion therapy, most often for coronary angiography with intent to perform percutaneous intervention (PCI), should not be delayed by routine imaging studies. A chest radiograph is the only imaging test routinely considered in the emergency department for ST-elevation MI, and its usefulness is limited to selected patients with a concern for findings that might affect initial management. Although the chest radiograph is often normal, findings of pulmonary venous congestion, cardiomegaly, or a widened mediastinum can contribute importantly to diagnosis and management decisions. For example, a history of severe, "tearing" chest and back pain in association with a widened mediastinum should raise the question of a dissecting aortic aneurysm (Chapter 63). In such cases, fibrinolytic therapy must be withheld pending more definitive diagnostic imaging of the aorta, and the approach to angiography may be modified. Other noninvasive imaging (e.g., echocardiography [Chapter 43], cardiac nuclear scanning [Chapter 44], and other testing) may be performed later during the course of hospitalization to evaluate specific clinical issues, including suspected complications of acute MI, or for predischarge risk stratification. Coronary angiography (Chapter 59) is performed urgently as part of an interventional strategy for ST-elevation MI or later for risk stratification in higher-risk patients who are initially managed medically.

Echocardiography

Two-dimensional transthoracic echocardiography with color flow Doppler imaging is the most generally useful noninvasive test obtained during the hospital course (Chapter 43). Echocardiography efficiently assesses global and regional cardiac function and enables the clinician to evaluate suspected complications of acute MI. The sensitivity and specificity of echocardiography for regional wall motion assessment are high (>90%), although the age of the abnormality (new vs. old) must be distinguished clinically or by electrocardiography. Echocardiography is helpful in determining the cause of circulatory failure with hypotension (relative hypovolemia, left ventricular failure, right ventricular failure, or mechanical complication of acute MI). Echocardiography also can assist in differentiating pericarditis and perimyocarditis from acute MI. Doppler echocardiography is indicated to evaluate a new murmur and other suspected mechanical complications of acute MI (e.g., papillary muscle dysfunction or rupture, acute ventricular septal defect, and left ventricular free wall rupture with tamponade or pseudoaneurysm). Later in the course of acute MI, echocardiography may be used to assess the degree of recovery of stunned myocardium after reperfusion therapy, the degree of residual cardiac dysfunction and indications for angiotensin-converting enzyme (ACE) inhibitors and other therapies for heart failure, and the presence of left ventricular aneurysm and mural thrombus (requiring oral anticoagulants).

Radionuclide, Magnetic Resonance, and Other Imaging Studies

Radionuclide techniques generally are too time-consuming and cumbersome for routine use in the acute setting of definite or probable acute MI. More commonly, they are used in risk stratification before or after hospital discharge to augment exercise or pharmacologic stress testing (Chapter 44). Thallium Tl 201 or technetium Tc 99 m sestamibi nuclear scans or rubidium Rb 82 positron emission tomography scans can assess myocardial perfusion and viability as well as infarct size. Cardiac magnetic resonance imaging (Chapter 44) with late gadolinium enhancement also can assess infarct size as well as myocardial function during the convalescent phase. Computed tomography and magnetic resonance imaging also can be useful to evaluate patients with a suspected dissecting aortic aneurysm (Chapter 63). When a nonatherosclerotic cause of myocardial necrosis is suspected (e.g., perimyocarditis simulating acute MI), contemporary multislice (e.g., 64-256 slice) coronary computed tomography can assess coronary artery disease qualitatively and semiquantitatively as well as distinguish other causes of chest pain syndromes (Chapters 39 and 44).

TREATMENT

Prehospital Phase

Prehospital cardiac arrest (Chapter 50) and extensive necrosis are major causes of acute MI-associated morbidity and mortality. The first hour after the onset of symptoms represents the best opportunity for myocardial salvage with reperfusion therapy. Thus the primary goals of prehospital care are to recognize symptoms promptly and seek medical attention, deploy an emergency medical system trained in emergency cardiac care, and transport the patient expeditiously to a medical facility capable of advanced coronary care, including reperfusion therapy (primary PCI or fibrinolysis).[10] Guidelines set an average system time goal for first medical contact-to-device of 90 minutes or less. For patients who initially arrive at or are transported to a non–PCI-capable hospital, the system time goal to device is 120 minutes or less. The greatest time lag to reperfusion therapy is the patient's delay in calling for help. Public education efforts aimed at reducing this delay have yielded mixed results, and innovative approaches are needed.

Expert emergency medical system teams perform prehospital ECGs, communicate preliminary diagnoses, and transport patients preferentially to a PCI-capable hospital where an ST-elevation MI team is on alert. This approach results in more rapid primary PCI (average savings of about 15 minutes) and superior clinical outcomes. Direct triage to the catheterization laboratory rather than to the emergency department also may decrease time to reperfusion. However, as many as one third of initial activations of the ST-elevation MI-team may be false positives.

Aspirin (162 to 325 mg, chewed) and sublingual nitroglycerin (0.4 mg every 5 minutes for up to three doses) are administered at first medical contact where appropriate. Administering fibrinolytic therapy in the field by physician-directed systems is feasible when the expected transit time is long (i.e., >120 min), but this practice is rare in the United States. Prehospital antiplatelet therapy of ST-elevation MI patients with ticagrelor does not improve pre-PCI coronary reperfusion.

Emergency Department Phase

The goals of emergency department care are to identify patients with acute myocardial ischemia rapidly, to stratify them into acute ST-elevation MI versus other acute coronary syndromes (Fig. 58-3), to initiate a reperfusion strategy and other appropriate medical care, to assess risk (E-Fig. 58-1), and to triage them rapidly to inpatient care (patients with suspected acute coronary syndrome) or outpatient care (patients without suspected ischemia; see Fig. 57-2).

The evaluation of patients with chest pain and other suspected acute coronary syndromes begins with a 12-lead ECG (with a goal of within 10 minutes of hospital arrival) and continues with a focused history and a targeted physical examination. Continuous ECG monitoring is started, an intravenous line is established, and admission blood tests are drawn (including a troponin level). As rapidly as possible, the patient is stratified into acute ST-elevation MI, likely or definite non–ST-elevation acute coronary syndrome, possible non–ST-elevation acute coronary syndrome (Chapter 57), or noncardiac chest pain categories.

Emergent Therapeutic Measures and Early Inpatient Care

Although troponin assays are the "gold standard" for detecting myocardial necrosis, the decision to proceed with urgent reperfusion (primary angioplasty or fibrinolysis) in ST-elevation MI should be based on the patient's clinical history, and the initial ECG and not be delayed by troponin testing. Coronary reperfusion is accomplished by primary PCI (angioplasty and stenting) or by intravenous fibrinolytic therapy.[11]

Primary PCI

Prompt PCI (with a goal of <90 minutes from first medical contact) is the preferred approach at PCI-capable hospitals for ST-elevation MI patients within 12 hours of the onset of symptoms and is reasonable for ECG and clinical evidence of ongoing ischemia within 12 to 24 hours after the onset of symptoms (Table 58-4). The preferred access site for emergent PCI is the radial artery,[A1] because it results in lower mortality as well as less bleeding compared with a femoral artery approach. Primary PCI also is indicated in patients with cardiogenic shock (Chapter 93) or severe acute heart failure regardless of time delay. Advantages of primary PCI over fibrinolysis include lower rates of early mortality, reinfarction, and intracranial hemorrhage.[A2]

Current guidelines for ST-elevation MI support implantation of advanced-generation drug-eluting stents to provide the best outcomes.[A3] Aspiration thrombectomy does not provide incremental benefit[A4] and is not indicated as a routine strategy.

Risk calculator for 6-month postdischarge mortality after hospitalization for acute coronary syndrome

Record the points for each variable at the bottom left and sum the points to calculate the total risk score. Find the total score on the x-axis of the nomogram plot. The corresponding probability on the y-axis is the estimated probability of all-cause mortality from hospital discharge to 6 months.

Medical history

① Age in years — Points

≤29	0
30–39	0
40–49	18
50–59	36
60–69	55
70–79	73
80–89	91
≥90	100

② History of congestive heart failure

③ History of myocardial infarction

Findings at initial hospital presentation

④ Resting heart rate, beats/min — Points

≤49.9	0
50–69.9	3
70–89.9	9
90–109.9	14
110–149.9	23
150–199.9	35
≥200	43

⑤ Systolic blood pressure, mm Hg

≤79.9	24
80–99.9	22
100–199.9	18
120–139.9	14
140–159.9	10
160–199.9	4
≥200	0

⑥ ST-Segment depression — 11

Findings during hospitalization

⑦ Initial serum creatinine, mg/dL — Points

0–0.39	1
0.4–0.79	3
0.8–1.19	5
1.2–1.59	7
1.6–1.99	9
2–3.99	15
≥4	20

⑧ Elevated cardiac enzymes — 15

⑨ No in-hospital percutaneous coronary intervention — 14

Points

① _____
② _____
③ _____
④ _____
⑤ _____
⑥ _____
⑦ _____
⑧ _____
⑨ _____

Total risk score _____ **(Sum of points)**

Mortality risk _____ **(From plot)**

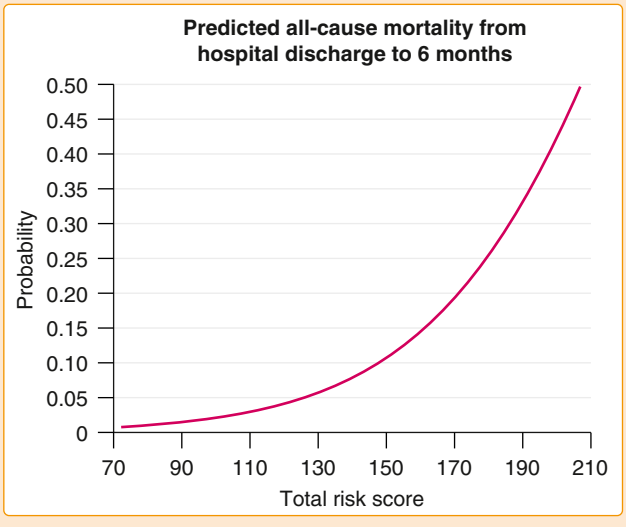

E-FIGURE 58-1. **Global Registry of Acute Coronary Events (GRACE) risk score calculator for all-cause mortality from discharge after acute coronary syndrome to 6 months.** (Reprinted with permission from Eagle KA, Lim MJ, Dabbous OH, et al. A validated prediction model for all forms of acute coronary syndrome: estimating the risk of 6-month postdischarge death in an international registry. *JAMA*. 2004;291:2727-2733.)

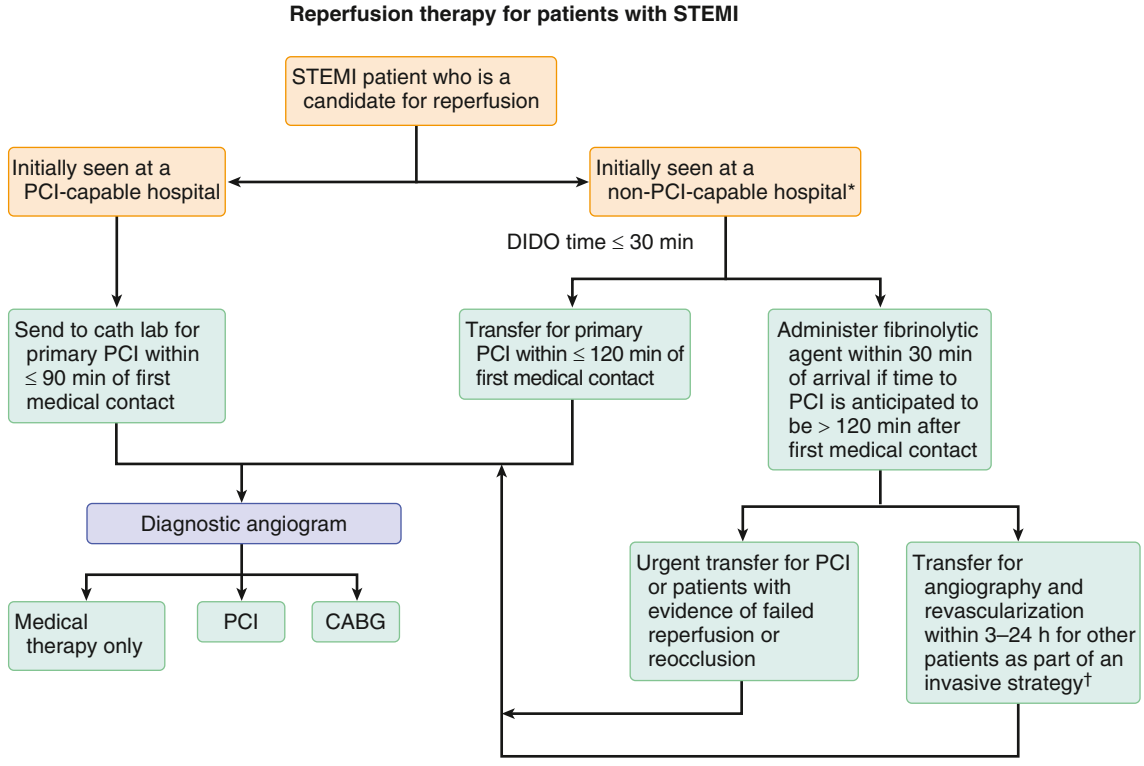

FIGURE 58-3. Reperfusion therapy for patients with ST-segment elevation myocardial infarction (STEMI). All eligible STEMI patients also are treated with dual antiplatelet therapy and an anticoagulant on admission (see text). *Patients with cardiogenic shock or severe heart failure initially seen at a non–PCI-capable hospital should be transferred for cardiac catheterization and revascularization as soon as possible, irrespective of time delay from the onset of the myocardial infarction. †Angiography and revascularization should not be performed within the first 2 to 3 hours after administration of fibrinolytic therapy. CABG = coronary artery bypass grafting; DIDO = door in–door out; PCI = percutaneous coronary intervention. (Modified from O'Gara PT, Kushner FG, Ascheim DD, et al. 2013 ACCF/AHA guideline for the management of ST-elevation myocardial infarction: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines. *Circulation*. 2013;127:e362-e425.)

TABLE 58-4 INDICATIONS FOR PRIMARY ANGIOPLASTY AND COMPARISON WITH FIBRINOLYTIC THERAPY

INDICATIONS
A preferred reperfusion strategy for ST segment elevation or LBBB acute MI within 12 hours of symptom onset (or >12 hours if symptoms persist)
Cardiogenic shock developing within 36 hours of ST-segment elevation/Q wave acute MI or LBBB acute MI in patients <75 years old who can be revascularized within 18 hours of the onset of shock
Recommended at centers performing >400 PCIs/year with backup cardiac surgery and for operators performing >75 PCIs/year
Primary PCI can be performed at centers without on-site cardiac surgery if performed on carefully selected patients by experienced operators and if arrangements are in place for rapid transfer to a surgery-capable center when needed
ADVANTAGES OF PRIMARY PCI
Higher initial reperfusion rates
Reduced risk of intracerebral hemorrhage
Less residual stenosis; less recurrent ischemia or infarction
Usefulness when fibrinolysis is contraindicated
Improvement in outcomes with cardiogenic shock
Evaluation of total burden of coronary artery disease
DISADVANTAGES OF PRIMARY PCI (COMPARED WITH FIBRINOLYTIC THERAPY)
Access, advantages restricted to high-volume centers and operators
Longer average time to treatment
Greater dependence on operators for results
Higher system complexity and costs

LBBB = left bundle branch block; MI = myocardial infarction; PCI = percutaneous coronary intervention (includes balloon angioplasty, stenting).

Randomized trials support that the emergent PCI address not only the infarct-related artery but also significant stenoses in "nonculprit" arteries,[A5] either at the time of the initial procedure or within the next month or so,[A6,A7] except in patients who are in cardiogenic shock.[A8] Such an approach reduces the need for repeat revascularization and also lowers the subsequent risk of recurrent MI and of cardiovascular death.[A9]

Thrombolysis

With the increasing availability of PCI-capable facilities, the use of fibrinolytic therapy (Table 58-5) has decreased. When PCI will be delayed by more than 120 minutes, however, fibrinolytic therapy, in the absence of contraindications, is indicated within 12 hours of the onset of symptoms. It should begin immediately in the emergency department (or ambulance, if available) with a goal of a door-to-needle time of less than 30 minutes. When PCI is not available, fibrinolysis also is reasonable for ECG and clinical evidence of ischemic injury within 12 to 24 hours of the onset of symptoms in patients who are hemodynamically unstable or have a large area of myocardium at risk (Fig. 58-3).

When fibrinolysis is used, an accelerated regimen of a tissue plasminogen activator (plus intravenous heparin) is preferred to streptokinase because the patency rate of the infarct-related artery at 90 minutes is higher and mortality is lower. Longer-acting variants of alteplase, given as single-bolus (tenecteplase) or double-bolus (reteplase) injections, now are more commonly used than alteplase in clinical practice because they are more convenient to administer, but they do not further improve survival.[A10]

The risk-to-benefit ratio should be assessed in each patient when fibrinolysis is considered and specific regimens are selected (Table 58-6). The major risk of fibrinolytic therapy is bleeding. Intracranial hemorrhage is the most serious and frequently fatal complication; its incidence rate is 0.5 to 1% with currently approved regimens. Older age (older than 70 to 75 years), female sex, hypertension, and higher relative doses of plasminogen activators and heparin increase the risk of intracranial hemorrhage. In patients over age 75 years, half-dose tenecteplase is as efficacious as full-dose tenecteplase and associated with less intracranial hemorrhage, thereby making it an attractive alternative.

If fibrinolysis fails to open the infarct-related artery, urgent transfer to a PCI-capable hospital for rescue PCI is more effective than repeated fibrinolysis.

TABLE 58-5 CHARACTERISTICS OF INTRAVENOUS FIBRINOLYTIC AGENTS APPROVED BY THE U.S. FOOD AND DRUG ADMINISTRATION

	STREPTOKINASE (SK)	ALTEPLASE (t-PA)	RETEPLASE (r-PA)	TENECTEPLASE (TNK–t-PA)
Dose	1.5 MU in 30-60 minutes	100 mg in 90 minutes*	10 U + 10 U, 30 minutes apart	30-50 mg† during 5 seconds
Circulating half-life (minutes)	≅20	≅4	≅18	≅20
Antigenic/Allergic reactions	Yes	No	No	No
Systemic fibrinogen depletion	Severe	Mild to moderate	Moderate	Minimal
Intracerebral hemorrhage	≅0.4%	≅0.7%	≅0.8%	≅0.7%
Patency (TIMI 2/3) rate, 90 minutes‡	≅51%	≅73-84%	≅83%	≅77-88%
Lives saved per 100 treated	≅3§	≅4‖	≅4	≅4
Cost per dose (approximate U.S. dollars)	300	1800	2200	2200

*An accelerated alteplase regimen is given as follows: 15-mg bolus, then 0.75 mg/kg during 30 minutes (maximum, 50 mg), then 0.50 mg/kg during 60 minutes (maximum, 35 mg).

†TNK–t-PA is dosed by weight (supplied in 5-mg/mL vials): <60 kg = 6 mL; 61-70 kg = 7 mL; 71-80 kg = 8 mL; 81-90 kg = 9 mL; >90 kg = 10 mL.

‡TIMI = Thrombolysis in Myocardial Infarction. Data from Granger CB, Califf RM, Topol EJ. Thrombolytic therapy for acute myocardial infarction: a review. *Drugs.* 1992;44:293-325; and Bode C, Smalling RW, Berg G, et al. Randomized comparison of coronary thrombolysis achieved with double-bolus reteplase (recombinant plasminogen activator) and front-loaded, accelerated alteplase (recombinant tissue plasminogen activator) in patients with acute myocardial infarction: the RAPID II Investigators. *Circulation.* 1996;94:891-898.

§Patients with ST-segment elevation or bundle branch block, treated <6 hours.

‖Based on the finding from the GUSTO trial that t-PA saves one more additional life per 100 treated than does SK. Data from The GUSTO Investigators. An international randomized trial comparing four thrombolytic strategies for acute myocardial infarction. *N Engl J Med.* 1993;329:673-682; and Simes RJ, Topol EJ, Holmes DR Jr, et al. Link between the angiographic substudy and mortality outcomes in a large randomized trial of myocardial reperfusion: importance of early and complete infarct artery reperfusion. GUSTO-I Investigators. *Circulation.* 1995;91:1923-1928.

Even for patients successfully reperfused, rapid transfer to a PCI-capable facility, where angiography and PCI are performed as early as feasible within the window of 3 to 24 hours after fibrinolysis, can reduce the risk for recurrent ischemia, reinfarction, heart failure, cardiogenic shock, or death by about 35%.

Acute Hospital Phase

Ancillary and Other Therapies

General Medical Management

Beyond prompt initiation of reperfusion and other antithrombotic therapy, initial management includes bedrest (i.e., for 12 hours or until ischemia has been relieved and hemodynamic parameters have stabilized) with ECG monitoring. Routine oxygen supplementation does not benefit normoxemic patients.[A11,A12] Oxygen should be used in doses just sufficient to avoid hypoxemia (e.g., initially at 2 to 4 L/minute by nasal cannula; fingertip oximetry may be used to monitor effect) in patients with hypoxemia (oxygen saturation <90%), respiratory distress, or other high-risk features for hypoxemia. Initiation or continuation of high-intensity statin therapy (i.e., atorvastatin 80 mg/day or rosuvastatin 20 or 40 mg/day), beginning on admission, is supported by clinical trials.

Patients with ischemic chest discomfort or pain should be given sublingual nitroglycerin (0.4 mg every 5 minutes for up to three doses). Subsequently, intravenous (IV) nitroglycerin, titrated to symptom relief and blood pressure effects, may be considered to treat ongoing discomfort, uncontrolled hypertension, or heart failure. Bradycardia is a relative contraindication for nitrates, particularly in the setting of acute inferior ST-elevation MI, in which it may slow the heart rate even more. Persistent ischemic pain may be treated with titrated intravenous doses of morphine (i.e., 1 to 4 mg intravenously, repeated in 5 to 30 minutes as needed to relieve pain).

Routine IV β-blocker therapy does not benefit ST-elevation MI patients treated with primary PCI.[A13] However, selected patients (e.g. with hypertension, persistent chest pain, left ventricular dysfunction) may benefit. In such cases, titrated oral β-blockers (e.g., metoprolol tartrate, 12.5 mg orally every 6 hours, increased to 25 to 50 mg every 6 hours as tolerated) can be started, beginning within the first 24 hours if there are no contraindications. For hypertension, intravenous therapy (e.g., metoprolol tartrate, 5 mg every 2 to 5 minutes, up to three doses, transitioning to oral therapy, e.g., 25 to 50 mg every 8 hours) may be used. β-Blockers should be avoided in patients with active heart failure or cardiogenic shock. However, β-blockade, preferably with carvedilol, should be considered in patients with a left ventricular ejection fraction <40% once the heart failure has resolved.

In the absence of contraindications (e.g., hypotension), ACE inhibitors (e.g., initially captopril 6.25 mg every 8 hours or lisinopril 2.5 mg twice daily, titrated upward as tolerated) or angiotensin receptor blockers (e.g., losartan 12.5 to 25 mg once or twice daily, titrated upward as tolerated) should be started within 24 hours in patients with an anterior MI, left ventricular dysfunction, or heart failure. Subsequently (e.g., at 3 to 14 days), patients with an ejection fraction ≤40% and either symptomatic heart failure or diabetes become candidates for the addition of an aldosterone antagonist (i.e., eplerenone; initially, 25 mg once daily) or spironolactone (12.5 to 25 mg twice daily.)

The optimal systolic blood pressure range during acute MI is generally 100 to 140 mm Hg. Excessive hypertension usually responds to titrated nitroglycerin, β-blocker therapy, and morphine. Relative hypotension could require discontinuation of these medications, fluid administration, and/or other measures as appropriate to the hemodynamic subset (Table 58-7). Atropine (0.5 to 1.5 mg intravenously) should be available to treat symptomatic bradycardia and hypotension related to hypervagotonia.

Antiplatelet Therapy

Given the critical role of coronary thrombosis in the precipitation of acute MI, antithrombotic therapy, supplemental to primary PCI or fibrinolysis, plays a key role in management of ST-elevation MI (Fig. 58-4; Table 58-7).

Aspirin (162 to 325 mg, non–enteric-coated) should be given on presentation to all patients unless it is contraindicated (see Fig. 58-4). A daily maintenance aspirin dose of 81 to 325 mg is then given and continued indefinitely. An 81 mg maintenance dose of aspirin is required with ticagrelor and preferred with prasugrel. However, a higher initial dose (325 mg daily for 30 days) of aspirin may be preferred with clopidogrel.

In addition to aspirin, a loading dose of an adenosine diphosphate receptor ($P2Y_{12}$) inhibitor (i.e., clopidogrel 600 mg, prasugrel 60 mg, or ticagrelor 180 mg)

TABLE 58-6 INDICATIONS FOR AND CONTRAINDICATIONS TO FIBRINOLYTIC THERAPY

INDICATIONS
Ischemic-type chest discomfort or equivalent for 30 minutes–12 hours with new or presumed new ST-segment elevation in two contiguous leads of ≥2 mm (≥0.2 mV) in leads V_1, V_2, or V_3 or ≥1 mm in other leads
New or presumed new left bundle branch block with symptoms consistent with myocardial infarction
Absence of contraindications
CONTRAINDICATIONS, ABSOLUTE
Active bleeding or bleeding diathesis (menses excluded)
Prior hemorrhagic stroke, ischemic stroke within 3 months, except acute ischemic stroke within 3-4.5 hours
Intracranial or spinal cord neoplasm or arteriovenous malformation
Suspected or known aortic dissection
Closed head or facial trauma within 3 months
CONTRAINDICATIONS, RELATIVE
Severe, uncontrolled hypertension by history or on presentation (>180/110 mm Hg)
Anticoagulation with therapeutic or elevated international normalized ratio (>2-3)
Old ischemic stroke (>3 months ago); intracerebral disease other than above
Recent (<3 weeks) major trauma/surgery or prolonged (>10 minutes) cardiopulmonary resuscitation or internal bleeding
Active peptic ulcer
Recent noncompressible vascular punctures
Pregnancy
For streptokinase/anistreplase: prior exposure (especially if >5 days ago) or allergic reaction

Modified from Kushner FG, Hand M, Smith SC Jr, et al. 2009 Focused updates: ACC/AHA guidelines for the management of patients with ST-elevation myocardial infarction and the ACC/AHA/SCAI guidelines on percutaneous coronary intervention. *Circulation.* 2009;120:2271-2306.

TABLE 58-7 IN-HOSPITAL DOSING OF SELECTED ANTITHROMBOTIC DRUGS

DRUG	INITIAL DOSE	MAINTENANCE DOSE
Abciximab	0.25 mg/kg IV bolus	0.125 μg/kg/min (maximum, 10 μg/min) for up to 12 hr
Aspirin	162-325 mg	81 mg*-325 mg/day
Clopidogrel	PCI: 300-600 mg* Fibrinolysis and age >75: 75-150 mg	75 mg/day (optional: 150 mg/day × 1 wk)
Eptifibatide	180 μg/kg IV bolus × 2†	2.0 μg/kg/min for up to 18 hr reduce rate by 50% for CrCl < 50 mL/min
Prasugrel	60 mg	10 mg/day
Ticagrelor	180 mg	90 mg bid (given with aspirin 81 mg/day)
Tirofiban	25 μg/kg IV bolus	0.15 μg/kg/min for up to 12 to 18 hr; reduce rate by 50% for CrCl < 30 mL/min
UFH	PCI‡: 70-100 U/kg IV bolus Fibrinolytic§: 60 U/kg IV bolus (max, 4000 U)	Repeat to achieve, maintain target ACT 12 U/kg/hr (max, 1000 U/hr) initial adjust aPTT to 1.5-2.0 × control (~50-70 sec)
Bivalirudin	PCI‡: 0.75 mg/kg IV bolus Additional 0.3 mg/kg PRN	1.75 mg/kg/hr infusion 1 mg/kg/hr for CrCl < 30 mL/min
Enoxaparin	Fibrinolytic§: 30 mg IV bolus Age >75: no bolus	1 mg/kg SQ at 15 min and q12h (max, 100 mg) 0.75 mg/kg SQ q12h (max, 75 mg) All ages, CrCl <30 mL/min: 1 mg/kg q24h
Fondaparinux	Fibrinolytic§: 2.5 mg IV	2.5 mg SQ daily, starting the next day Contraindicated if CrCl < 30 mL/min

*Generally preferred dose.
†Boluses are separated by 10 minutes.
‡Anticoagulants are generally stopped following uncomplicated PCI.
§Given for the index hospitalization (up to 48 hr [UFH] or up to 8 days [enoxaparin or fondaparinux]) or until revascularization.
ACT = activated clotting time; bid = twice daily; CrCl = creatinine clearance; IV = intravenous; max = maximum; PCI = percutaneous coronary intervention (e.g., stenting); SQ = subcutaneous; UFH = unfractionated heparin.

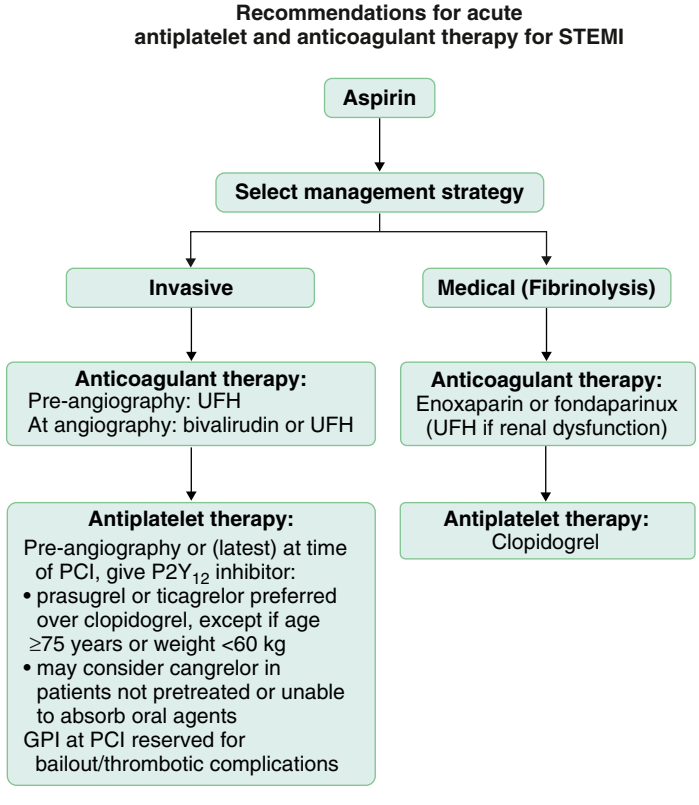

FIGURE 58-4. Recommendations for antiplatelet and anticoagulant therapy for ST-segment elevation myocardial infarction (STEMI). See text for doses. GPI = glycoprotein IIb/IIIa inhibitor; UFH = unfractionated heparin.

should be given as early as possible or at the time of primary PCI to ST-elevation MI patients for whom an invasive approach is planned, followed by a daily maintenance dose for at least 1 year. The more potent prasugrel and ticagrelor are preferred over clopidogrel for ST-elevation MI patients undergoing primary PCI when their bleeding risk is acceptable, with data suggesting that prasugrel is more effective and equally safe.[A14] By comparison, clopidogrel is preferred in patients with a history of a stroke or transient ischemic attack, and it also is recommended for at least 14 days and up to 1 year after fibrinolytic therapy. *Cangrelor*, a short-acting IV $P2Y_{12}$ inhibitor (given as a 30 μg/kg IV bolus followed immediately by a 4 μg/kg/min infusion for at least 2 hours or until the end of the procedure), has a rapid onset/offset of action (3- to 6-minute half-life) and is better than clopidogrel for preventing ischemic events, but at the cost of increased bleeding.

Glycoprotein (GP) IIb/IIIa inhibitors (Table 58-7) can provide a rapid onset of antiplatelet activity in the precatheterization laboratory setting or for the prevention and treatment of periprocedural thrombotic complications. Otherwise, their use is now limited.

Anticoagulant Therapy

Inhibition of thrombin generation is crucial to the management of occluding coronary thrombi in ST-elevation MI. Initiation of a parenteral anticoagulant thrombin inhibitor is recommended at the time of presentation for all ST-elevation MI patients (Fig. 58-4). Intravenous unfractionated heparin and bivalirudin are comparably effective alternatives for the composite end point of death, recurrent MI, and major bleeding in supporting PCI and intensive antiplatelet therapy.[A15] Anticoagulants are generally stopped after an uncomplicated PCI. Recommended options to support fibrinolytic therapy include unfractionated heparin, enoxaparin, and fondaparinux (see Table 58-7).

Combined Oral Anticoagulant and Antiplatelet Therapy

Based on limited evidence, current guidelines recommend dual antiplatelet therapy combined with an oral anticoagulant in post-MI patients with high-risk atrial fibrillation (AF; Chapter 52), a mechanical heart valve (Chapter 60), venous thromboembolism (Chapter 68), or hypercoagulable disorders (Chapter 67) but that the duration of such triple therapy be as short as possible (usually 1 week to 1 month). Warfarin (INR goal 2.0 to 2.5) is indicated as the anticoagulant for patients with a mechanical heart valve or left ventricular thrombus, typically combined with clopidogrel. For patients with AF or a history of venous thromboembolism, a direct-acting oral anticoagulant is preferred: options include low-dose rivaroxaban (15 mg daily) plus a $P2Y_{12}$ inhibitor (primarily clopidogrel), apixaban 2.5 or 5 mg twice daily (depending on renal function) plus a $P2Y_{12}$ inhibitor (primarily clopidogrel),[A16] or very-low-dose rivaroxaban (2.5 mg twice daily) plus dual antiplatelet therapy with aspirin plus a $P2Y_{12}$ inhibitor.[A17]

Coronary Intensive Care

Prompt reperfusion therapy has dramatically lowered the prevalence of MI-related ventricular arrhythmias. After early successful primary PCI, patients who have small infarcts and who are hemodynamically and electrically stable may be transferred to a telemetry step-down unit within 24 hours.

In the contemporary care of patients with an ST-elevation MI, the primary role of coronary intensive care unit admission (Table 58-8) is to manage patients with or at risk for complications of acute MI. The goals of the coronary intensive care unit include continuous electrocardiographic monitoring and therapy for serious arrhythmias (e.g., rapid defibrillation of ventricular fibrillation [VF]; Chapter 53), monitoring the success of the primary PCI, monitoring or continuing fibrinolytic therapy, initiating or continuing other acute medical therapies (as discussed earlier), appropriate hemodynamic assessment and monitoring, and diagnosis and treatment of mechanical and physiologic complications of acute MI.

General care measures in the coronary intensive care unit include attention to activity, diet and bowels, education, reassurance, and sedation. Bedrest is encouraged for the first 12 hours. In the absence of complications, dangling, bed-to-chair, and self-care activities can begin within 24 hours or earlier after successful reperfusion therapy. When stabilization has occurred, usually within 1 to 3 days, patients may be transferred to a step-down unit for progressive ambulation. The risk for emesis and aspiration or the anticipation of angiography or other procedures usually dictates nothing by mouth or clear liquids for the first 4 to 12 hours. Thereafter, a heart-healthy diet in small portions is recommended. In patients at high risk for bleeding gastric stress ulcers, a proton pump inhibitor or an H2-receptor antagonist is recommended. Many patients benefit from an analgesic (see Tables 26-4 and 26-6) to relieve ongoing pain and an anxiolytic or sedative during the acute phase. A benzodiazepine (Table 362-9) is frequently selected, but routine use of anxiolytics is neither necessary nor recommended. Sedatives should not substitute for education and reassurance from concerned caregivers to relieve emotional distress and improve behavior. Constipation often occurs with bedrest and narcotics; stool softeners and a bedside commode are advised.

The ECG should be monitored continuously during the entire hospital course to detect serious arrhythmias and to guide therapy. Measures to limit infarct size (i.e., coronary reperfusion) and to optimize hemodynamics also stabilize the heart electrically. Routine antiarrhythmic prophylaxis (e.g., with lidocaine

TABLE 58-8 SAMPLE ADMISSION ORDERS FOR ST-SEGMENT ELEVATION ACUTE MYOCARDIAL INFARCTION

Diagnosis	Acute ST-segment elevation myocardial infarction
Admit	Coronary care unit with telemetry
Condition	Serious
Vital signs	q½h until stable, then q1-4h and PRN; pulse oximetry × 24 hr; notify if heart rate <50 or >100; respiratory rate <8 or >20; SBP <90 or >150 mm Hg; O_2 saturation <90%
Activity	Bedrest × 12 hr with bedside commode; thereafter, light activity if stable
Diet	NPO except for sips of water until pain free and stable; then 2 g sodium, heart-healthy diet as tolerated, unless on call for catheterization (or other test requiring NPO)
Laboratory tests*	Troponin I or T at 2 hours, then q8h × 3; comprehensive blood chemistry, magnesium, CBC with platelets; PT/INR, aPTT; BNP; lipid profile (fasting in morning); portable CXR
IV therapy	D_5W or NS to keep vein open (increase fluids for relative hypovolemia); second IV if IV medication given
Reperfusion therapy*	Emergency primary coronary angioplasty or fibrinolysis (if appropriate and if not already performed) 1. Primary angioplasty (preferred if available within 90 minutes) 2. Tenecteplase, reteplase or alteplase (preferred); or streptokinase (see Table 58-6 for doses), if primary PCI is unavailable within 90-120 minutes
Medications	1. Nasal O_2 at 2 L/min if with or at risk of hypoxemia, titrated to keep O_2 saturation >90% 2. Aspirin 162-325 mg chewed on admission, then 81-365 mg PO daily 3. IV heparin, 60-U/kg bolus (maximum, 4000 U) and 12 U/kg/hr (maximum, 1000 U/hr), titrate to target aPTT 1.5-2.0 × control (about 50-70 seconds); *or* enoxaparin (preferred with fibrinolytic), 30 mg IV, then 1 mg/kg SQ q12h (maximum SQ doses, 100 mg on day 1; reduce to 0.75 mg/kg for age ≥75 years, increase interval to q24h for CrCl <30 mL/min); *or* bivalirudin (with primary PCI), 0.75-mg/kg IV bolus, then 1.75 mg/kg/hr (delay 30 minutes if heparin given) 4. Metoprolol, 12.5 PO q6h, incremented to 25-50 mg q6h as tolerated (hold for SBP < 100 mm Hg, pulse <50 beats/min, asthma, heart failure); may consider IV metoprolol if immediate effect required (tachyarrhythmia, severe hypertension, unrelieved pain) in the absence of heart failure 5. Consider IV nitroglycerin drip × 24-48 hr (titrated to SBP 100-140 mm Hg) 6. Morphine sulfate, 1-4 mg IV and increment at 5-30 minutes PRN for unrelieved pain 7. Stool softener 8. Anxiolytic or hypnotic if needed 9. ACE inhibitor for hypertension, anterior acute MI, or LV dysfunction, in low oral dose (e.g., captopril, 6.25 mg q8h), begun within 24 hours or when stable (SBP > 100 mm Hg) and adjusted upward 10. Lipid-lowering therapy (i.e., high-intensity statin) regardless of LDL: target LDL reduction of ≥50%; give atorvastatin 80 mg PO or rosuvastatin 20-40 mg PO on admission (pre-cath) and continue daily. 11. Antiplatelet therapy: Ticagrelor, 180 mg PO on admission, then 90 mg bid *or* prasugrel, 60 mg PO on admission, then 10 mg PO daily with a primary PCI strategy (preferred to clopidogrel if acceptable bleeding risk); *or* clopidogrel, 600 mg PO on admission for a primary PCI strategy, or 300 mg PO with fibrinolytic, then 75 mg PO daily. For specific treatments for hemodynamic subgroups, see Table 58-9.

*If not ordered in the emergency department.

ACE = angiotensin-converting enzyme; aPTT = activated partial thromboplastin time; BNP = brain natriuretic peptide; CABG = coronary artery bypass graft surgery; CBC = complete blood count; CrCl = creatinine clearance; CXR = chest radiograph; D_5W = 5% dextrose in water; daily = once daily; INR = international normalized ratio; IV = intravenous; LDL = low-density lipoprotein; LV = left ventricle; MI = myocardial infarction; NPO = nothing by mouth; NS = normal saline; PCI = percutaneous coronary intervention; PO = orally; PRN = as needed; PT = prothrombin time; SBP = systolic blood pressure; SQ = subcutaneous.

or amiodarone) is not indicated, but specific arrhythmias require treatment (see later text).

Hemodynamic evaluation is helpful in assessing prognosis and in guiding therapy (see Table 58-9). Clinical and noninvasive evaluation of vital signs is adequate for normotensive patients without pulmonary congestion. Patients with pulmonary venous congestion are at high risk and must be carefully monitored in terms of fluid status, oxygenation, and urine output (Chapter 46). Invasive hemodynamic monitoring is appropriate only when the cause of circulatory failure is uncertain or when titration of intravenous therapies depends on hemodynamic measurements (e.g., pulmonary capillary wedge pressure and cardiac output). Arterial catheters are appropriate and useful in clinically unstable, hypotensive patients who do not respond to intravenous fluids to replete or to expand intravascular volume (see the later discussion of complications).

Management of Complications

Complications of acute MI have declined with early reperfusion and modern medical therapy, but they remain an important cause of morbidity and mortality.

Recurrent Chest Pain

Recurrent chest pain can be caused by post-infarction ischemia of the border zones of the infarcted territory, acute closure of the treated infarct-related artery, non–infarct-related coronary lesions, mechanical complications (see later), and pericarditis. Characterization of the pain, physical examination, electrocardiography, echocardiography, and cardiac marker determinations assist in the differential diagnosis. Treatment should be specific to the cause.

Postinfarction angina developing spontaneously during hospitalization for acute MI despite medical therapy may indicate infarct extension or reinfarction and usually merits coronary angiography. Infarct expansion implies circumferential slippage with thinning of the infarcted myocardium. Infarct expansion can be associated with chest pain but without recurrent elevation of cardiac markers. Expansive remodeling can lead to a left ventricular aneurysm. The risk for remodeling is reduced by early reperfusion therapy and administration of ACE inhibitors. β-Blockers and nitroglycerin are recommended medical therapies.

Pain with recurrent ST-segment elevation or recurrent elevation of cardiac markers may be due to acute closure (e.g., stent thrombosis) of the treated infarct-related artery. An invasive approach is recommended and preferred to relieve discomfort that occurs hours to days after an acute MI and that is associated with objective signs of reinfarction. Other potential treatment strategies include readministration of thrombolytic therapy or a GP IIb/IIIa inhibitor, along with nitroglycerin, β-blockade, and heparin. Streptokinase, which induces neutralizing antibodies, generally should not be readministered beyond the first few days of an initial administration. Radionuclide perfusion stress testing can be helpful in patients with discomfort that is transient or of uncertain ischemic origin. For lesions with questionable degrees of stenosis at angiography, coronary pressure gradient (fractional flow reserve) or Doppler velocimetry or intracoronary ultrasound can determine whether PCI is warranted.

Acute pericarditis most commonly is manifested on days 2 to 4 when a large, transmural infarction causes pericardial inflammation. On occasion, hemorrhagic effusion with tamponade develops, so excessive anticoagulation should be avoided. Pericarditis developing later (2 to 10 weeks) after acute MI could represent Dressler syndrome, which is believed to be immune mediated. The incidence of this post-MI syndrome has decreased dramatically in the modern reperfusion era. Pericardial pain after ST-elevation MI is usually treated with aspirin, but colchicine, acetaminophen, or narcotic analgesics (Chapter 62) are reasonable if aspirin (even in high doses) is not effective. Glucocorticoids and nonsteroidal anti-inflammatory drugs are potentially harmful after ST-elevation MI and should be avoided.

Rhythm Disturbances

Ventricular Arrhythmias

Acute MI and subsequent reperfusion are associated with a proarrhythmic environment that includes heterogeneous myocardial ischemia, heightened

TABLE 58-9 HEMODYNAMIC SUBSETS OF ACUTE MYOCARDIAL INFARCTION

	BLOOD PRESSURE (RELATIVE)	TYPICAL PHYSICAL FINDINGS	CARDIAC INDEX (L/min/m^2)	PA WEDGE PRESSURE (mm Hg)	SUGGESTED INTERVENTIONS
Normal	Normal	$\pm S_4$	>2.5	≤12	None required
Hyperdynamic	Normal or high	Anxious	>3	<12	Control pain, anxiety; β-blocker; treat SBP to <140 mm Hg
Hypovolemia	Low	Dry	≤2.7	≤9	Add fluids to maintain normal pressure; can develop pulmonary edema if hypotension is caused by unrecognized LV failure
Mild LV failure	Low to high	Rales, $\pm S_3$	2-2.5	>15	Diuresis; nitrates, ACE inhibitor; consider low-dose β-blocker
Severe LV failure	Low to normal	Above $+S_3$, ± ↑ JVP, ± edema	<2	>20	Diuresis; nitrates; low-dose ACE inhibitor; avoid β-blockers; consider inotropes, urgent revascularization
Cardiogenic shock	Very low	Above + cool, clammy; ↓ mental or renal function	≤1.5	>25	Avoid hypotensive agents; place intra-aortic balloon pump or LV assist device; urgent revascularization if possible
RV infarct	Very low	↑ JVP with clear lungs	<2.5	≤12	Give IV fluids; avoid nitrates and hypotensive agents; dobutamine if refractory to fluids

↑ = increased; ↓ = decreased; ACE = angiotensin-converting enzyme; IV = intravenous; JVP = jugular venous pressure; LV = left ventricle; PA = pulmonary artery; RV = right ventricle; SBP = systolic blood pressure.

Modified from Forrester JS, Diamond G, Chatterjee K, et al. Medical therapy of acute myocardial infarction by application of hemodynamic subsets (second of two parts). *N Engl J Med*. 1976;295:1404-1413.

adrenergic tone, intracellular electrolyte disturbance, lipolysis and the production of free fatty acids, and the generation of oxygen free radicals. Micro-reentry likely is the most common electrophysiologic mechanism of early-phase arrhythmias, although enhanced automaticity and triggered activity also are observed in experimental models.

Accelerated idioventricular rhythm (60 to 100 beats per minute) frequently occurs within the first 12 hours and is generally benign (i.e., is not a risk factor for more serious ventricular arrhythmias). Indeed, accelerated idioventricular rhythm frequently heralds successful reperfusion. Antiarrhythmic therapy is not indicated except for sustained, hemodynamically compromising accelerated idioventricular rhythm.

Primary ventricular fibrillation (Chapter 50) is associated with a higher rate of 24-hour in-hospital and short-term mortality, but the longer-term risk of recurrent ventricular tachycardia or ventricular fibrillation and mortality is largely unaffected in survivors. Polymorphic ventricular tachycardia (Chapter 53) and, less commonly, monomorphic ventricular tachycardia are associated life-threatening arrhythmias that can occur in almost 6% of patients in the early phase of acute MI. Clinical features (including warning arrhythmias) are not adequately specific or sensitive to identify patients at risk for sustained ventricular tachyarrhythmias, so all patients should be continuously monitored. Prophylactic lidocaine, which reduces primary ventricular fibrillation but does not decrease (and may increase) mortality, is not recommended.

In comatose ST-elevation MI patients resuscitated from out-of-hospital cardiac arrest due to ventricular fibrillation or pulseless ventricular tachycardia, body temperature management to avoid hyperthermia is beneficial and should be considered as soon as possible after hospital arrival (Chapter 50).

Electrical cardioversion is required for ventricular fibrillation and sustained polymorphic ventricular tachycardia (unsynchronized shock) and for sustained monomorphic ventricular tachycardia (synchronized shock) that causes hemodynamic compromise (Chapters 53 and 54). Brief intravenous sedation is given to conscious, "stable" patients. For slower, stable ventricular tachycardia and nonsustained ventricular tachycardia requiring therapy, intravenous amiodarone or intravenous lidocaine is commonly used. After episodes of ventricular tachycardia or ventricular fibrillation, infusions of antiarrhythmic drugs may be given for 6 to 24 hours; the ongoing risk for arrhythmia then is reassessed. Electrolyte and acid-base imbalance and hypoxia should be corrected. β-Blockade is useful in patients with frequent polymorphic ventricular tachycardia associated with adrenergic activation ("electrical storm"). Additional, aggressive measures should be considered to reduce cardiac ischemia (e.g., emergency PCI or CABG) and to address left ventricular dysfunction (e.g., intra-aortic balloon pump or left ventricular assist device) in patients with recurrent polymorphic ventricular tachycardia despite the use of β-blockers or amiodarone or both.

Late ventricular fibrillation, which develops more than 48 hours after the onset of acute MI, portends a worse prognosis and deserves aggressive therapy (see below). Monomorphic ventricular tachycardia resulting from re-entry in the context of a recent or old MI also can appear late after MI, and patients may require long-term therapy (see below). An implantable cardioverter-defibrillator (ICD; Chapter 54) is indicated in patients with ventricular fibrillation or hemodynamically significant sustained ventricular tachycardia occurring more than 2 days after ST-elevation MI and not due to a transient or reversible cause (e.g., ischemia, reinfarction, metabolic abnormalities; Figure 58-5).

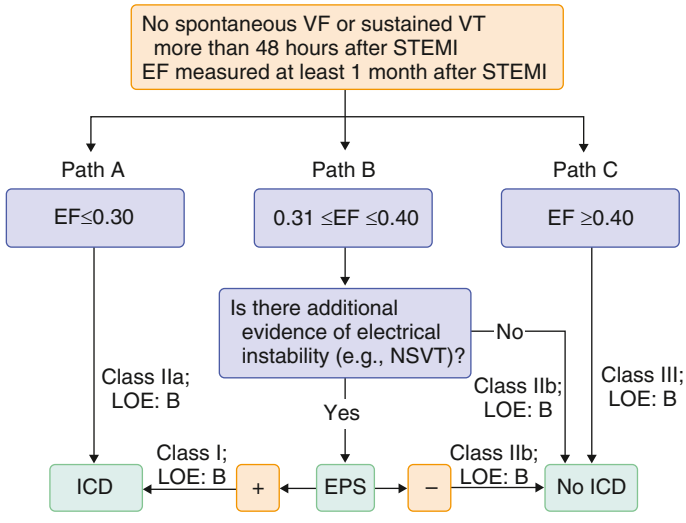

FIGURE 58-5. Algorithm to aid in selection of implantable cardioverter-defibrillator (ICD) in patients with ST-segment elevation myocardial infarction (STEMI) and diminished ejection fraction (EF). The appropriate management path is selected on the basis of left ventricular EF measured at least 1 month after STEMI. All patients, whether an ICD is implanted or not, should receive medical therapy. EPS = electrophysiologic studies; LOE = level of evidence; NSVT = nonsustained ventricular tachycardia; VF = ventricular fibrillation; VT = ventricular tachycardia. (Modified from Antman EM, Anbe DT, Armstrong PW, et al. 2004 Update: ACC/AHA guidelines for the management of patients with ST-elevation myocardial infarction—executive summary. A Report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines [Writing Committee to Revise the 1999 Guidelines for the Management of Patients with Acute Myocardial Infarction]. *Circulation*. 2004;110:588-636.)

Atrial Fibrillation and Other Supraventricular Tachyarrhythmias

Atrial fibrillation (AF), which is an important and relatively common acute MI-related arrhythmia, occurs in 5 to 10% of patients with an acute MI, often within the first day (Chapter 52). The incidence of atrial flutter and other supraventricular tachyarrhythmias is much lower. The risk for AF increases with age, larger MIs, heart failure, pericarditis, atrial infarction, hypokalemia, hypomagnesemia, hypoxia, pulmonary disease, and hyperadrenergic states. The incidence of AF is reduced by effective early reperfusion. Hemodynamic compromise with rapid rates and systemic embolism (in about 2% of cases) are adverse consequences of AF. Systemic embolism can occur on the first day, so prompt anticoagulation with heparin is indicated.

Recommendations for management of AF include electrical cardioversion for patients with hemodynamic compromise or ischemia; rate control with an intravenous β-blocker (e.g., metoprolol, 5 mg over 2 minutes to a total of 15 mg over 10 to 15 minutes) in patients without clinical ventricular dysfunction, with intravenous digoxin for patients with ventricular dysfunction (i.e., give 1.0 mg, half initially and half in 4 hours), or with intravenous diltiazem or verapamil in hemodynamically compensated patients with a contraindication to β-blockers; and anticoagulation with heparin (or low-molecular-weight heparin). Amiodarone, which is generally reserved for patients with or at high risk for AF recurrence, may be started and continued for 6 weeks if sinus rhythm is restored and maintained. Long-term chronic anticoagulation may not be necessary thereafter unless other indications exist.

Bradycardias, Conduction Delays, and Heart Block

Bradycardias caused by sinus or atrioventricular (AV) nodal delay, typically owing to increased parasympathetic tone associated with an inferior wall MI, are common and usually benign. Atropine (0.5 to 1.5 mg IV) is useful for symptomatic cases (e.g., heart rates generally <50 beats per minute associated with hypotension, ischemia, or escape ventricular arrhythmias). Temporary pacing is needed rarely. By comparison, atropine can worsen infranodal AV block (usually observed in association with anterior MI and a wide-complex escape rhythm), so it is important to differentiate the two (Chapter 52).

New-onset infranodal AV, intraventricular, and bundle branch blocks predict a four-fold to six-fold increase in in-hospital mortality, but this increase is related more to extensive myocardial damage than to the heart block itself. Temporary pacing usually is indicated, but it only modestly improves survival. Fortunately, the incidence of these arrhythmias has declined markedly in the reperfusion era (from 10 to 20% to ~4%).

Indications for permanent pacing after acute MI depend on the prognosis of the AV block and not solely on symptoms. Indications include even transient second- or third-degree AV block in association with bundle branch block and ongoing symptomatic AV block at any level. However, block at the AV nodal level (Wenckebach) rarely is persistent or symptomatic enough to warrant permanent pacing.

Heart Failure and Other Low-Output States

Of all serious acute MI-related complications, heart failure (Chapters 45 and 46) is the most common and is the leading cause of in-hospital acute MI-related death.[12] Manifestations of circulatory failure can include a weak pulse, low blood pressure, cool extremities, a third heart sound, pulmonary congestion, oliguria, and obtundation. However, pump failure has several distinct mechanisms and causes, which must be distinguished from each other as well as from volume depletion as the cause of a low cardiac output state. Each requires a specific approach to diagnosis, monitoring, and therapy (see Table 58-7).

Left Ventricular Dysfunction

The degree of left ventricular dysfunction correlates well with the extent of acute ischemia and infarction. Hemodynamic compromise becomes evident when impairment involves 20 to 25% of the left ventricle, and cardiogenic shock occurs with impairment of 40% or more (Chapter 93). Pulmonary congestion and S_3 and S_4 gallops are the most common physical findings. Early reperfusion (with fibrinolytic agents, PCI, or CABG) is the most effective therapy to reduce infarct size, ventricular dysfunction, and associated heart failure. Medical treatment of heart failure related to the ventricular dysfunction of acute MI is otherwise generally similar to that of heart failure in other settings (Chapter 46) and includes adequate oxygenation and diuresis (begun early, blood pressure permitting, and continued on a long-term basis if needed). Morphine sulfate (i.e., 1 to 4 mg intravenously, with increments as needed after 5 to 30 minutes or more) is useful for patients with pulmonary congestion. Titrated oral ACE inhibitor therapy (e.g., captopril, incremented from 3.125 to 6.25 mg three times daily to 50 mg twice daily as tolerated, or lisinopril, 1.25 to 2.5 mg once or twice daily, titrated as tolerated up to 10 to 20 mg twice daily) also is indicated for heart failure and pulmonary edema unless excessive hypotension (systolic blood pressure <100 mm Hg) is present. Nitroglycerin reduces preload as well as afterload and effectively relieves congestive symptoms; treatment can be begun sublingually (0.4 mg every 5 minutes times three), and then transition can be made to intravenous therapy (initially 5 to 10 μg/minute, incrementing by 5 to 20 μg/minute until symptoms are relieved or until mean arterial pressure falls by 10% in normotensive patients or 30% in hypertensive patients but not <90 mm Hg or >30 mm Hg lower than baseline).

Volume Depletion

Relative or absolute hypovolemia is a frequent cause of hypotension and circulatory failure and is easily corrected if it is recognized and treated promptly. Poor hydration, vomiting, diuresis, and disease- or drug-induced peripheral vasodilation can contribute to this condition. Occult gastrointestinal and/or access site bleeding should also be considered. Hypovolemia should be identified and corrected with intravenous fluids before more aggressive therapies are considered. An empirical fluid challenge may be tried in the appropriate clinical setting (e.g., for hypotension in the absence of congestion, for inferior or right ventricular infarction, and for hypervagotonia). If filling pressures are measured, cautious fluid administration to a pulmonary capillary wedge pressure 15 to 20 mm Hg may optimize cardiac output and blood pressure without impairing oxygenation.

Right Ventricular Infarction

Right ventricular ischemia and infarction occur with proximal occlusion of the right coronary artery (before the take-off of the right ventricular branches). Ten percent to 15% of inferior acute ST-elevation MIs show classic hemodynamic features, and these patients form the highest-risk inferior MI subgroup for morbidity and mortality (25 to 30% vs. <6% hospital mortality). Improvement in right ventricular function commonly occurs over time if short-term management is successful.

Hypotension in patients with clear lung fields and elevated jugular venous pressure in the setting of inferior or inferoposterior acute MI should raise the suspicion of right ventricular infarction. The Kussmaul sign (distention of the jugular veins on inspiration) is relatively specific and sensitive in this setting. ST-segment elevation in lead V_1 and in right precordial lead V_4R (Chapter 42), particularly in the first 24 hours, is the most sensitive electrocardiographic marker of right ventricular infarction. Echocardiography is helpful in confirming the diagnosis. (Right ventricular dilation and dysfunction are observed.) When right-sided heart pressures are measured, a right atrial pressure of 10 mm Hg or greater and 80% or more of the pulmonary capillary wedge pressure are relatively sensitive and specific for right ventricular ischemic dysfunction.

Management of right ventricular infarction consists of early maintenance of preload with intravenous fluids, reduction of right ventricular afterload (i.e., treatment of pulmonary congestion), early reperfusion, short-term inotropic support if needed, and avoidance of venodilators (e.g., nitrates) and diuretics used for left ventricular failure (they may cause marked hypotension). Volume loading with normal saline solution alone is often effective. If the cardiac output fails to improve after 0.5 to 1 L of fluid, inotropic support with intravenous dobutamine (starting at 2 μg/kg/minute and titrating to hemodynamic effect or tolerance, up to 20 μg/kg/minute) is recommended. High-grade AV block is common, and restoration of AV synchrony with temporary AV sequential pacing can lead to substantial improvement in cardiac output. Because the onset of AF (in up to one third of right ventricular infarcts) can cause severe hemodynamic compromise, it requires prompt cardioversion. In rare circumstances, a right ventricular assist device may be required if shock from right ventricular failure persists despite optimized hemodynamic parameters and rhythm control. Early coronary reperfusion with PCI or fibrinolysis markedly improves outcomes.

Cardiogenic Shock

Cardiogenic shock (Chapter 93) is a form of severe left ventricular failure characterized by marked hypotension (systolic pressures <90 mm Hg) and reductions in cardiac index (to <1.8 L/minute/m^2) despite high left ventricular filling pressure (pulmonary capillary wedge pressure >18 mm Hg). The cause is loss of a critical functional mass (>40%) of the left ventricle. Risk factors include age, large (usually anterior) acute MI, previous MI, and diabetes. The treatment and prognosis of cardiogenic shock are discussed in Chapter 46.

Mechanical Complications

Mechanical complications of acute MI may occur throughout the hospital course and include acute mitral valve regurgitation (often caused by papillary muscle dysfunction or rupture), ventricular septal defect, and left ventricular free wall rupture.[13,14] These mechanical complications are much less common after early reperfusion therapy: in ST-elevation MI patients treated with primary PCI, current risks are about 0.5% for free wall rupture, 0.2% for ventricular septal defect, and 0.3% for papillary muscle rupture, for a total mechanical complication rate of 1% or less. Prompt diagnosis and early surgery, although still associated with a high mortality rate, lead to better outcomes than delayed diagnosis and medical therapy alone

A left ventricular aneurysm can develop after a large, most commonly anterior, acute MI and create mechanical and electrical complications. If refractory heart failure, ventricular tachycardia, or systemic embolization occurs despite medical therapy and PCI, aneurysmectomy with CABG is indicated.

Thromboembolic Complications

Arterial thromboembolism, typically arising from the left ventricle or left atrium, is very unusual in ST-elevation MI patients who are treated with early reperfusion and aggressive antithrombotic therapies. Arterial embolism can cause dramatic clinical events, such as hemiparesis (Chapter 376), loss of a pulse, ischemic bowel (Chapter 129), or sudden changes in blood pressure, depending on the regional circulation involved.

Left ventricular mural thrombosis occurs typically in the setting of a large (especially anterior) acute ST-elevation MI and heart failure. The risk for embolism is particularly high when a mural thrombus is detected by echocardiography. Thus, in patients with anterior acute ST-elevation MI and in other high-risk patients, echocardiography should be performed during hospitalization; if results are positive, oral anticoagulation (e.g., apixiban 5 mg twice daily) should be started and continued for 3 to 6 months.[15,16]

Pulmonary emboli, which commonly arise from thrombi in leg veins, are highly unusual unless patients are immobilized for several days. Deep venous thrombosis can be prevented by lower extremity compression therapy, by

limiting the duration of bedrest, and by the use of subcutaneous heparin (in patients at risk and not receiving intravenous heparin) until patients are fully ambulatory (Chapter 68).

As noted in more detail previously (see Combined Oral Anticoagulant and Antiplatelet Therapy), adding a direct-acting oral anticoagulant to aspirin and a $P2Y_{12}$ inhibitor for the prevention of venous thromboembolic disease (Chapters 67 and 68) or the prevention of systemic embolization in patients with AF (Chapter 52) is indicated for up to about 1 month in an ST-elevation MI patient with AF and a high risk of systemic emboli, recent venous thromboembolism, or a hypercoagulable disorder. For patients with a mechanical heart valve or left ventricular mural thrombus (Chapter 70), warfarin, usually to an international normalized ratio of 2.0 to 2.5, should be added to dual antiplatelet therapy for 3 months. To minimize bleeding, careful attention must be paid to the appropriate selection and doses of antithrombotic regimens based on age, weight, renal function, and other comorbid conditions.

Late Hospital Phase

Transfer from coronary intensive care to a step-down unit usually occurs within 1 to 3 days, when the cardiac rhythm and hemodynamics are stable. The duration of this late phase of hospital care is usually an additional 1 to 3 days in uncomplicated cases. Activity levels should be increased progressively under continuous electrocardiographic monitoring. Medical therapy should progress from parenteral and short-acting agents to oral medications appropriate and convenient for long-term outpatient use. Risk stratification and functional evaluations are critical to assess prognosis and to guide therapy as the time for discharge, which may be as early as 2 to 3 days in uncomplicated, successfully reperfused patients. Functional evaluation also can be extended to the early period after hospital discharge. Education must be provided about diet, activity, smoking, and other risk factors (e.g., lipids, hypertension, and diabetes—see later).

Risk Stratification after Myocardial Infarction

Risk stratification is a continuous process that begins on admission and continues through hospital discharge. The goals of risk stratification before and early after discharge for acute MI are to assess ventricular and clinical function, latent ischemia, and arrhythmic risk; to use this information for patient education and prognostic assessment; and to guide therapeutic strategies (E-Fig. 58-1).

Cardiac Functional Assessment

An echocardiogram should be obtained to assess resting left ventricular function before discharge in all patients. Patients who initially have a reduced left ventricular ejection fraction and who are possible candidates for ICD therapy should have the ejection fraction re-evaluated 40 days or more after discharge.

Risk stratification during hospitalization or around the time of discharge should include an assessment of exertional capacity. This assessment can be formally addressed with submaximal exercise stress testing at 4 to 6 days after the infarction or limited stress testing at 2 to 6 weeks after discharge (to peak heart rate of 120 to 130 beats per minute or 70% of the predicted maximum) unless patients have unstable post-MI angina, uncompensated heart failure, or serious cardiac arrhythmias. Alternatively, patients may undergo symptom-limited stress testing at 2 to 6 weeks before they return to work or resume other increased physical activities. Abnormal test results include not only ECG ST-segment depression but also low functional capacity, exertional hypotension, and serious arrhythmias. Patients with positive test results should be considered for coronary angiography if coronary anatomy had not been previously defined. Imaging-enhanced stress testing with radionuclide perfusion tests (Chapter 44), echocardiography (Chapter 43), or cardiac magnetic resonance (Chapter 44) can increase the sensitivity for detecting latent ischemia compared with stress ECG tests, can provide information about ejection fraction and infarct size, and should be used for patients with ECG changes that preclude accurate ECG interpretation during stress. For patients unable to exercise, pharmacologic stress testing can be performed with adenosine, a long-acting bolus analogue of adenosine (e.g., regadenoson), or by dipyridamole scintigraphy.

Discharge and Post-Hospital Phase

Secondary Prevention

Advances in secondary prevention have resulted in increasingly effective measures to reduce recurrent MI and cardiovascular death. Secondary prevention should be conscientiously applied after acute MI (Table 58-10).

Lipid Reduction

A fasting lipid profile is recommended within 24 hours of admission, and high-intensity lipid-lowering therapy with a statin should start in the hospital, preferably on admission, and be continued as outpatient therapy in all patients with ST-elevation MI and no contraindication to its use (e.g., atorvastatin, 80 mg daily or rosuvastatin 20 to 40 mg daily; Chapter 190). Ezetimibe (10 mg daily) or a PCSK9 inhibitor can be considered in patients who have not achieved an LDL-cholesterol goal of 70 mg/dL or lower.

Continued smoking doubles the subsequent mortality risk after acute MI, and smoking cessation reduces the risk for reinfarction and death within 1 year (Chapter 363). An individualized smoking cessation plan should be formulated, including pharmacologic aids (nicotine gum and patches, bupropion, or varenicline).

Antiplatelet and Anticoagulation Therapies

Antiplatelet therapy (Chapter 70) is indicated in all patients, and some patients require concomitant anticoagulant therapy. After PCI for ST-elevation MI, at

TABLE 58-10 DISCHARGE MEDICATION CHECKLIST AFTER MYOCARDIAL INFARCTION*

MEDICATION	DOSES	REASONS NOT TO USE	COMMENTS
Aspirin	81 (preferred) to 325 mg daily	High bleeding risk	Reduces mortality, reinfarction, and stroke
Clopidogrel *Or*	75 mg daily	High bleeding risk; suboptimal antiplatelet response	Indicated after PCI for at least 1 year (shorter time for BMS if high bleeding risk); also reduces vascular events when added to aspirin in non–ST-segment elevation acute MI (also useful on the basis of clinical trials after ST-segment elevation acute MI) Genetic variants (CYP2C19) may reduce response Controversial interaction with proton pump inhibitors (e.g., omeprazole)
Prasugrel *Or*	10 mg daily	High bleeding risk	Avoid with history of prior stroke or TIA
Ticagrelor	90 mg bid		Consider 5 mg prasugrel daily in patients >75 years or <60 kg Avoid if history of intracranial bleed Limit daily aspirin dose to 81 mg
β-Blocker (e.g., metoprolol, carvedilol)	Metoprolol: 25-200 mg daily Carvedilol: 6.25-25 mg bid	Asthma, bradycardia, heart failure	Reduces mortality, reinfarction, sudden death, arrhythmia, hypertension, angina, atherosclerosis progression
ACE inhibitor (e.g., ramipril, lisinopril) or ARB (e.g., valsartan, losartan)	Ramipril: 2.5-10 mg daily Lisinopril: 5-10 mg daily Valsartan: 80-160 mg daily-bid Losartan: 50-100 mg daily	Hypotension, allergy, hyperkalemia	Reduces mortality, reinfarction, stroke, heart failure, diabetes, atherosclerosis progression
Lipid-lowering agent (i.e., a high-intensity statin; e.g., atorvastatin, rosuvastatin)	Atorvastatin: 80 mg daily Rosuvastatin: 20-40 mg daily	Myopathy, rhabdomyolysis, hepatitis	Goal = LDL ≥50% reduction (statins also can benefit patients with lower LDL†)
Nitroglycerin sublingual	0.4 mg SL PRN for angina	Aortic stenosis; sildenafil (Viagra) use	Instruct on PRN use and appropriate need for medical attention

*Medications given at hospital discharge improve long-term compliance. All are oral except for nitroglycerin.

†Heart Protection Study (*Lancet.* 2002;360:7); and PROVE-IT study (*N Engl J Med.* 2004;350:1495).

ACE = angiotensin-converting enzyme; ARB = angiotensin receptor blocker; bid = twice daily; BMS = bare metal stent; daily = once daily; LDL = low-density lipoprotein; MI = myocardial infarction; PCI = percutaneous coronary intervention; PRN = as needed; SL = sublingual; TIA = transient ischemic attack.

least 1 year of dual antiplatelet therapy generally has been indicated (usually aspirin [81 mg/day] plus a $P2Y_{12}$ inhibitor) to reduce ischemic events and stent thrombosis, with treatment beyond 1 year providing additional anti-ischemic benefit but at the expense of more bleeding.[A18] However, accumulating evidence with second-generation polymer-free, drug-eluting stents (Chapter 59) suggests safety with just 1 month of dual antiplatelet therapy, because stent thrombosis now is less common,[A19,A20] and that the duration and strength of antiplatelet therapy should be individualized (Chapter 59) based on bleeding and thrombotic risks. For patients who are not at a high risk of bleeding, prasugrel (10 mg/day) or ticagrelor (90 mg twice daily) is the preferred $P2Y_{12}$ inhibitor rather than clopidogrel (75 mg daily) because of greater efficacy, and prasugrel appears to be superior to ticagrelor. A genotype-guided approach to the selection of prasugrel versus clopidogrel at discharge is of uncertain benefit.[A21]

For patients with AF (Chapter 52), recent trials support a shortened period of triple antithrombotic therapy (i.e., ≤1 month) followed by dual antithrombotic therapy consisting of a direct-acting oral anticoagulant and a $P2Y_{12}$ inhibitor (e.g., dabigatran [110 or 150 mg twice daily] plus clopidogrel or ticagrelor or apixaban plus clopidogrel),[A22,A23] with clopidogrel usually preferred over ticagrelor because of its lower bleeding risk. Patients with venous thromboembolic disease (Chapter 68) can be treated similarly. For other hypercoagulable states (Chapter 67), data are sparse, but generally the antiplatelet therapy would be added to the background anticoagulant therapy. By comparison, patients with a left ventricular thrombus require a direct-acting oral anticoagulant (e.g., apixaban 5 mg twice daily), and patients with a mechanical heart valve require careful chronic warfarin anticoagulation in addition to antiplatelet therapy.

Prevention and Treatment of Heart Failure

ACE inhibitor therapy can prevent adverse myocardial remodeling after acute MI and can reduce heart failure and death; it is strongly indicated for long-term use in patients with anterior acute MI or an left ventricular ejection fraction less than 40%. ACE inhibitors also reduce recurrent MI in patients with an ejection fraction greater than 40%, except in patients who have stable coronary disease and are at low risk for a recurrent coronary event (i.e., without heart failure, hypertension, or glucose intolerance). Recommended ACE inhibitors include ramipril (2.5 mg titrated to 10 mg/day) or lisinopril (2.5 to 5 mg titrated to 10 mg/day). An angiotensin-receptor blocker (e.g., valsartan, 80 to 160 mg twice daily, or losartan, 50 to 100 mg/day) should be substituted in patients who cannot tolerate an ACE inhibitor (Chapter 46). Overt heart failure requires careful treatment (Chapter 46) titrated to symptoms and tolerance. Sacubitril plus valsartan is no better than ramipril alone in this setting.[A24]

Anti-Ischemic Therapies

Long-term β-blocker therapy does not benefit patients who have a preserved ejection fraction when added to standard modern therapy during the first year after acute MI, but it is recommended for MI survivors who have a reduced ejection fraction without other contraindications. Options include metoprolol (20 to 200 mg/day) or carvedilol (6.25 to 25 mg twice daily). However, chronic β-blocker therapy in patients at low subsequent cardiovascular risk (normal ventricular function, successful reperfusion, absence of arrhythmias) currently is viewed as reasonable but not mandatory.

Nitroglycerin (0.4 mg) is commonly prescribed for sublingual or buccal administration for acute anginal attacks (Chapter 56), although this long-standing practice has never been fully evaluated. Longer-acting oral therapy (isosorbide mononitrate, 30 to 60 mg orally every morning, or dinitrate, 10 to 40 mg orally two or three times daily) or topical nitroglycerin (e.g., start with 0.5 inch; can be titrated up to 2 inches every 6 hours for 2 days) may be added to treatment regimens for angina or heart failure (in combination with hydralazine) in selected patients.

Calcium-channel blockers are negatively inotropic and are not routinely given on a long-term basis. However, they may be used in selected patients who do not have left ventricular dysfunction (ejection fraction >0.40), who are intolerant of β-blockers, and who require these drugs for antianginal therapy (e.g., amlodipine, 5 to 10 mg/day orally, or diltiazem, 120 to 480 mg/day orally as sustained-release preparations or in divided doses; see Chapter 56) or for control of heart rate in AF (e.g., diltiazem, 120 to 480 mg/day orally, or verapamil, 180 to 480 mg/day orally, as sustained-release preparations or in divided doses). Short-acting nifedipine should be avoided.

If these medical approaches do not control post-infarction angina and complete revascularization was not performed during an acute PCI, coronary angiography should be considered in patients whose symptoms would warrant it (Chapter 56).[17]

Anti-Inflammatory Therapy

In patients who have survived an MI and have a high-sensitivity C-reactive protein level of 2 mg/L or greater, the use of canakinumab, a monoclonal antibody against interleukin-1β (150 mg subcutaneously every 3 months) reduced the risk of subsequent nonfatal MI, nonfatal stroke, or cardiovascular death.[A25] Colchicine (0.5 mg daily) also can reduce the risk of subsequent cardiovascular events in patients who have survived a myocardial infarction,[A26] especially if begun within 3 days of the MI.[A27] Whether these therapies will become a part of routine post-MI medical care is yet to be determined.

Antiarrhythmic Therapy

In patients who do not require an acute ICD (see Ventricular Rhythms, earlier), an ICD is recommended for those with severe left ventricular dysfunction (ejection fraction ≤0.30) at least 40 days after ST-elevation MI and 3 months after CABG, even without spontaneous or induced ventricular tachycardia or ventricular fibrillation.[A28] Antiarrhythmic drugs are not generally recommended after acute MI, and class I antiarrhythmic agents can increase the risk for sudden death. Class III drugs (amiodarone, sotalol, dofetilide) may be used as part of the management strategy for specific arrhythmias (e.g., AF, ventricular tachycardia) (Chapters 52 and 53).

Other Medical Therapies

Hypertension (Chapter 64) and diabetes mellitus (Chapter 210) must be assessed and tightly controlled in patients after an acute MI. ACE inhibitors or β-blockers as described earlier are usually the first-choice therapies for hypertension, with ARBs indicated when ACE inhibitors are not tolerated. ACE inhibitors and ARBs also can reduce the long-term complications of diabetes. Such drugs should be titrated to a goal blood pressure of less than 130/80 mm Hg, which is equivalent to an office goal of 120/80 mm Hg (Chapter 64).

Hormone replacement therapy (Chapter 222) with estrogen with or without progestin is not begun after an acute MI because it increases thromboembolic risk and does not prevent reinfarction. For women already receiving hormone replacement, therapy should be discontinued unless it is being given for a compelling indication.

Antioxidant supplementation (e.g., vitamin E, vitamin C) does not benefit patients after acute MI and is not recommended. The role of fish oil and related supplements is unclear, but purified agents such as eicosapentoic ethyl appear to decrease cardiovascular events in chronic coronary heart disease.

Patient Education and Rehabilitation

The hospital stay provides an important opportunity to educate patients about their MI and its treatment, coronary risk factors, and behavioral modification. Education should begin on admission and continue to and beyond discharge. At hospital discharge, a detailed, evidence-based plan of care should emphasize the importance of a healthy lifestyle, including diet (Chapter 13), exercise (Chapter 14), smoking cessation (Chapter 363), and compliance with medications. Timely outpatient health care follow-up also should be scheduled and a rehabilitation program referral provided. Exercise-based cardiac rehabilitation may reduce reinfarction by about 50% and overall mortality by about 25%, with home-based programs being as safe and effective as center-based programs.[A29] Many hospitals use case managers and prevention specialists to augment physicians and nurses, to provide educational materials, to review important concepts, to assist in formulating and actualizing individual risk reduction plans, and to ensure proper and timely outpatient follow-up. This follow-up should include early return appointments with the patient's physician (within 2 to a few weeks), which may be facilitated with virtual platforms. Instructions on activities also should be given before discharge.

PROGNOSIS

With the broad application of reperfusion and other contemporary therapies, the prognosis often myocardial infarction continues to improve.[18] The 30-day mortality after ST-elevation MI is now less than 6%, and the 1-year mortality rate is 7 to 8%. Since reductions in mortality can be directly related to the number of evidence-based therapies given, patients treated at high-performing hospitals live about 1 year longer than do patients treated at low-performing hospitals. Of note is that the long-term survival is similar in patients who do and do not have evidence of obstructive coronary disease on acute coronary arteriography.[19]

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For the General References and other additional features, please visit Elsevier eBooks+ at https://ebooks.health.elsevier.com.

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59

INTERVENTIONAL DIAGNOSIS AND TREATMENT OF CORONARY ARTERY DISEASE

PAUL S. TEIRSTEIN AND AJAY J. KIRTANE

Percutaneous coronary intervention (PCI) and coronary artery bypass graft (CABG) surgery represent alternative and sometimes complementary approaches to coronary revascularization. Each has its relative indications, advantages, disadvantages, and contraindications.

CORONARY ARTERIOGRAPHY TO ASSESS CORONARY STENOSIS

For coronary angiography, catheters are inserted into the epicardial arteries of the heart to obtain radiographic images of the coronary vasculature and to define the site and severity of any lesions or anomalies, as well as any visible collateral blood vessels beyond arterial stenoses or occlusions. Coronary arteriography often is part of a more comprehensive catheterization to assess valvular (Chapter 60), congenital (Chapter 55), or myocardial diseases (Chapter 47) or to perform a variety of catheter-based interventions (E-Table 59-1).

THE PROCEDURE

Vascular access under local anesthetic is preferably via the radial artery,[1] which is associated with less bleeding and equivalent or better outcomes compared with femoral access.[A1] A specially shaped catheter is inserted over a guidewire to facilitate atraumatic passage to a coronary artery ostium (origin at the aorta) to inject radiographic contrast media for coronary arteriography. This process is performed twice, once for the left coronary ostium and once for the right, although each may be accompanied by more than one injection as needed. Hemodynamic data may be acquired to assist in the evaluation of cardiac function at rest or sometimes after stationary exercise.

After a radial procedure, the patient can ambulate immediately and may be discharged 2 to 4 hours later. After a femoral procedure, however, the patient must remain stationary in bed for 1 to 2 hours using a vascular closure device (or otherwise for 4 hours) and can be discharged after 4 to 6 hours of recovery.

ASSESSMENT OF CORONARY STENOSES

The patient's coronary arteriographic images are compared with normal anatomy (Fig. 59-1). The degree of stenosis in any vessel is based on a visual estimate of the percentage reduction in luminal diameter at the most severely narrowed coronary segment compared with the closest angiographically unobstructed vessel segment (Fig. 59-2). The degree of coronary collateralization, which is assessed qualitatively, correlates with longer chronicity of stenoses or complete occlusion and is associated with a more favorable prognosis.

Because these estimates of the severity of stenoses may vary, even among experienced angiographers, the importance of an intermediately severe lesion (i.e., a 40 to 90% stenosis) can be determined by passing a pressure sensor guidewire to measure the pressure gradient across the stenosis after injecting adenosine to maximize flow. The ratio of post-lesion pressure to aortic pressure during maximal flow (the fractional flow reserve) indicates the percentage of normal flow across the stenosis.[2] Stenoses with fractional flow reserve (a ratio of distal hyperemic pressure to aortic pressure) above 0.80 are considered nonischemic and typically do not require revascularization, whereas a lower fractional flow reserve typically warrants percutaneous coronary intervention (PCI).

COMPLICATIONS OF CARDIAC CATHETERIZATION

Diagnostic cardiac catheterization has few contraindications and a low but not trivial risk of serious complications (Table 59-1). In the United States, for example, the overall risk is less than 0.2% for death, less than 0.5% for myocardial infarction, less than 0.07% for stroke, less than 0.5% for serious arrhythmia, and less than 1% for major vascular complications (including thrombosis or cholesterol embolization [Chapter 110]), bleeding requiring transfusion, or pseudoaneurysm.[3,4] Vascular complications are less common with the radial artery approach.

For a diagnostic catheterization, patients are not routinely anticoagulated except for the radial approach, in which preexisting anticoagulation is typically maintained or heparin is given to reduce the occurrence of radial artery occlusion. For the femoral approach, anticoagulation may be uninterrupted or held for 2 to 3 days before the procedure. For a patient who is taking warfarin after a mechanical valve replacement, warfarin is withheld for 3 days before the procedure, with consideration of bridging heparin in high-risk cases.

Most medications should be continued up to and including the morning of the procedure. For diabetic patients, 50% of the usual morning dose of insulin is usually given; metformin should be withheld.

Contrast-induced acute kidney injury, which usually is not clinically evident until 2 to 3 days after the procedure,[5] is clinically significant in about 1.2% of patients,[6] but the risk is 3 to 5 times higher in patients who have diabetes or renal insufficiency or who are dehydrated. In such patients, preprocedural hydration with sodium chloride is usually indicated to increase urine output.[A2] An oral statin (e.g., rosuvastatin, either 40 mg on admission followed by 20 mg per day for patients with an acute coronary syndrome or 10 mg for two days before and three days afterward for patients with diabetes and

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ABSTRACT

Percutaneous coronary intervention (PCI) and coronary artery bypass graft (CABG) surgery are two commonly performed procedures used to increase blood flow to cardiac muscle receiving inadequate blood supply due to coronary artery stenoses. PCI and CABG can be competitive or, at times, complementary techniques. PCI, which is one of the most widely used medical procedures based on its simplicity, usually requires entry of only a small-diameter catheter into the radial (wrist) or femoral artery under local anesthesia. In an awake patient, a thin guidewire is passed through catheter, across the arterial stenosis. A metallic stent is then passed over the wire and expanded by balloon inflation to push the plaque aside and scaffold the artery open. The balloon is then removed, thereby leaving the stent in place and creating a normal-diameter lumen. Patients are often discharged the same day. The advantages of PCI include its high effectiveness, low morbidity, very short period of observation/hospitalization, and complete recovery within hours. Its main disadvantages are restenosis, which occurs in 5 to 20% of patients, and the need for antiplatelet therapy for 3 to 12 months following the procedure.

CABG is performed using the internal thoracic artery or a reverse saphenous vein from the leg. One end of the bypass is attached to the aorta and the other to the obstructed coronary artery beyond the obstruction. Open chest surgery with general anesthesia and typically cardiopulmonary bypass is required. The advantages of CABG include its high effectiveness and the durability of the result. Its main disadvantage is the need for open chest surgery, which results in increased procedural morbidity, requires a 4- to 7-day hospital stay, and several weeks for full recovery. The decision between PCI and CABG is largely determined by clinical status and anatomic features, but in some patients the decision regarding which procedure is favored may be dictated by the patient's own preferences.

KEYWORDS

CABG
PCI
bypass surgery
angioplasty
stent
bypass graft
angina
coronary
ischemia

E-TABLE 59-1 PROCEDURES PERFORMED IN CARDIAC CATHETERIZATION LABORATORIES

Diagnostic cardiac catheterization (right and/or left heart catheterization, including drug studies)
Coronary angiography
Coronary intervention including stents
Coronary intravascular imaging and translesional hemodynamic assessment
Coronary atherectomy (rotational, orbital, laser)
Endomyocardial biopsy
Insertion of an intra-aortic balloon pump
Insertion of percutaneous ventricular assist devices
Pericardiocentesis
Alcohol septal ablation
Transseptal puncture
Balloon valvuloplasty
Percutaneous valve repair/replacement (tricuspid, pulmonic, mitral, aortic)
Percutaneous treatment of large-bore access complications (balloon occlusion, covered stenting of iliofemoral vessels)
Closure of a patient foramen ovale
Treatment of congenital heart defects (atrial septal defect, patent ductus arteriosus, coarctation, post-congenital surgery procedures)
Implantation of intra-atrial shunt devices
Closure of a left atrial appendage
Implantation of pulmonary artery pressure sensor (for remote hemodynamic monitoring)
Peripheral angiography/peripheral intervention (subclavian, lower extremity: iliac, femoral, popliteal, tibial)
Cerebral angiography and intervention
Carotid angiography and interventions (stenting)
Venous thrombectomy/intravascular thrombolysis/vena cava filter
Renal angiography and intervention
Repair of an abdominal or thoracic aortic aneurysm

From Kern MJ, Kirtane AJ. Catheterization and angiography. In: Goldman L, Schafer AI, eds. *Goldman-Cecil Medicine*. 26th ed. Philadelphia, PA: Elsevier; 2020.

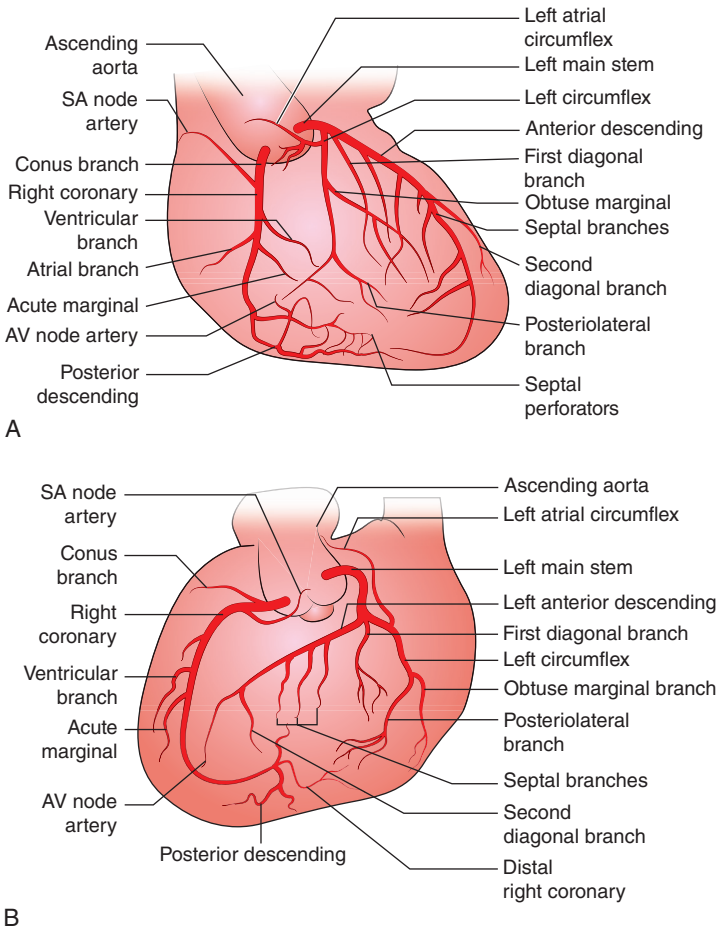

FIGURE 59-1. Coronary vessels. The right anterior oblique (A) and left anterior oblique (B) views are shown. The major arteries are the left main, left anterior descending, circumflex, and right coronary arteries. AV = atrioventricular; SA = sinoatrial. (Modified from Yang SS, Bentivoglio LG, Maranhao V, et al, eds. From *Cardiac Catheterization Data to Hemodynamic Parameters*. Philadelphia: Oxford University Press; 1988.)

TABLE 59-1 CARDIAC CATHETERIZATION: CONTRAINDICATIONS AND COMPLICATIONS

ABSOLUTE CONTRAINDICATIONS
Inadequate facilities
Patient refusal
RELATIVE CONTRAINDICATIONS
Severe uncontrolled hypertension
Ventricular arrhythmias
Recent acute stroke
Severe anemia
Active gastrointestinal bleeding
Allergy to radiographic contrast agents
Acute renal failure
Uncompensated heart failure (patient cannot lie flat)
Unexplained febrile illness or untreated active infection
Electrolyte abnormalities (e.g., hypokalemia)
Severe coagulopathy
Pregnancy
Uncontrolled arrhythmias, hypertension
Uncooperative patient or patient refusal
MAJOR COMPLICATIONS
Death
Cerebrovascular accident
Myocardial infarction, shock
Ventricular tachycardia or fibrillation
RARE BUT SERIOUS COMPLICATIONS
Aortic dissection
Cardiac perforation
Tamponade
Heart failure
Reaction to contrast agents, anaphylaxis
Nephrotoxicity
Arrhythmias, including heart block, asystole, supraventricular tachyarrhythmias
Hemorrhage, including local or retroperitoneal
Infection
Protamine reaction
Vascular complications, including thrombosis, embolus, vascular injury, pseudoaneurysm

Adapted from Kern MJ, Kirtane AJ. Catheterization and angiography. In: Goldman L, Schafer AI, eds. *Goldman-Cecil Medicine*. 26th ed. Philadelphia, PA: Elsevier; 2020.

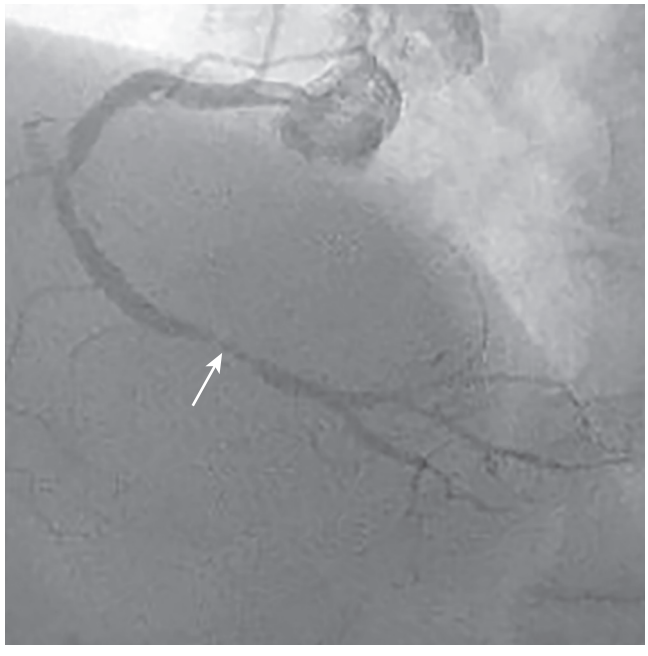

FIGURE 59-2. Example of a significant stenosis (*arrow*) in the right coronary artery. (Courtesy of Morton J. Kern, MD.)

chronic kidney disease) can reduce the risk of acute kidney injury by about 50%.[A3] Treatment with sodium bicarbonate or *N*-acetylcysteine (Mucomyst) is not of incremental value and is not routinely recommended.[A4,A5] In patients who have advanced chronic kidney disease and in whom radiocontrast is contraindicated, angiography can be avoided, with PCI guided by intravascular ultrasound and physiologic measurements.

Adverse reactions to contrast media are potentially serious but rare, with an overall incidence of 5% or less. However, adverse reactions occur in about 15% of patients with a previously reported allergic contrast reaction. Patients who have had a previous allergic reaction to contrast media should be premedicated with prednisone (60 mg orally the evening before and morning of the procedure) and diphenhydramine (25 to 50 mg orally the morning of the procedure).

Vasovagal hypotension, which is relatively common, is treated with intravenous fluids and atropine (0.5 to 1.0 mg intravenously). Hypotension that is accompanied by back pain is rare but suggests retroperitoneal bleeding and hematoma and requires emergency intervention. Hypotension also can be caused when perforation of a coronary artery leads to cardiac tamponade (Chapter 62); this emergency requires urgent pericardiocentesis and treatment of any coronary perforation. Pulmonary congestion, which may develop in patients with compromised left ventricular function or valvular heart disease, is treated with oxygen and diuretics (Chapter 46) or more intensive interventions if it progresses to cardiogenic shock (Chapter 93).

Chest pain is unusual during coronary angiography, but may be associated with myocardial ischemia and ST segment changes during PCI. Treatment (e.g., nitroglycerin, heparin, and antiplatelet medications) usually controls myocardial ischemia before revascularization (Chapter 57). Atrial or ventricular premature contractions or even brief episodes of supraventricular tachycardia

are common and usually resolve spontaneously. Ventricular tachycardia and ventricular fibrillation are rare but require prompt defibrillation (Chapter 50).

PERCUTANEOUS CORONARY INTERVENTION

Percutaneous coronary intervention is applicable to most forms of coronary artery disease, including single- and double-vessel disease, but also can be performed for multivessel disease, total occlusions, saphenous vein graft disease, unstable angina (Chapter 57), and acute myocardial infarction (MI) (Chapter 58). An estimated 2 million PCIs are performed worldwide each year, making it one of the most widely used medical procedures. Its popularity is based largely on its simplicity, the need for only local anesthesia, a short (≈1 day or even outpatient) hospitalization, and negligible postprocedure recovery time. In the United States, PCI is a cornerstone of the treatment of acute coronary syndromes (Chapters 57 and 58), but the number of nonacute PCIs has declined by over one third since 2010.

MECHANISMS AND TECHNICAL CONSIDERATIONS

Under local anesthesia, a hollow-bore needle is inserted percutaneously into a peripheral artery (usually the radial or femoral artery). A guidewire is placed through this needle and advanced into the aorta. The needle is removed, leaving the guidewire, over which a small-caliber (≈3 mm), specially shaped catheter (called a guiding catheter) is advanced under fluoroscopic guidance into the ostium of the obstructed coronary artery. By use of radiographic contrast injections that provide fluoroscopic visualization of the coronary artery lumen, a thin (≈0.014 inch), highly steerable guidewire is directed down the coronary artery and across the stenotic lesion. This guidewire becomes a "rail" over which therapeutic tools such as inflatable balloons, stents, and atherectomy catheters are passed to the diseased segment (Fig. 59-3).

Balloon catheters (Fig. 59-4) typically have two lumens, one to allow passage over the guidewire and another to carry a mixture of saline and radiographic contrast material to inflate a balloon at the distal catheter tip. Under fluoroscopy, the balloon is centered across the lesion and inflated to typically 4 to 30 atmospheres of pressure. Balloon inflation widens the narrowed lumen by stretching the vessel and, in most cases, causing a tear (a therapeutic dissection) at the edges of the plaque, where the atheroma meets the nondiseased media. Atherectomy catheters, which also are passed over a guidewire to the diseased segment, remove plaque by a shaving, grinding, slicing, or suction mechanism. Coronary stents are metallic or polymeric scaffolding devices that are crimped onto a deflated balloon catheter before insertion into the diseased vessel (Videos 59-1, 59-2, and 59-3). During balloon inflation, the collapsed stent expands to support the vessel lumen (see E-Fig. 59-1 and Video 59-4). Although balloons and atherectomy devices create an adequate, albeit rough channel through diseased arteries, the supporting structure of the stent can widen the lumen to near its predisease dimensions. With a stent, tissue flaps are "pinned" against the wall, and recoil is limited (Video 59-5). Most stents are designed so that the metallic struts comprise only about 20% of the surface area, thereby allowing for endothelialization, which reduces the risk of thrombosis.[7] In some cases (e.g., PCI of saphenous vein grafts), filters deployed within a coronary vessel beyond the target lesion can limit distal embolization of plaque, platelet aggregates, and other "debris" can further reduce ischemic complications in vessels with a friable endothelium.

During the PCI procedure, the interventional cardiologist is able to assess the target vessel fluoroscopically by injections of contrast material through the guiding catheter (Fig. 59-5). A more detailed assessment of the target vessel is often obtained using intravascular imaging technologies, with catheters that use sound waves or light to produce an image of the lumen (channel for blood flow) and vessel walls (E-Fig. 59-2). When the coronary artery has been opened successfully, all catheters are withdrawn and the arterial access site is sealed by mechanical pressure, an absorbable plug, or an external suturing device. Patients without comorbidity ambulate in 2 to 6 hours. Discharge from the hospital usually occurs 2 to 6 hours later or the morning after the procedure, when stability of the arterial access site, cardiac biomarkers, and the electrocardiogram are confirmed.

SELECTION OF PATIENTS FOR PERCUTANEOUS CORONARY INTERVENTION

Any decision to perform PCI must include a comprehensive and detailed review of the coronary angiogram by an experienced interventional cardiologist to assess the lesion's technical suitability for the procedure. Coronary flow is not significantly obstructed until a stenosis narrows the coronary artery lumen by at least 60%. A pressure drop of more than 20% (which corresponds to a fractional flow reserve <0.80) predicts a clinical benefit from PCI[A6,A7] in stable chronic ischemic heart disease but not clearly for stenting a nonculprit lesion in a patient with a non–ST elevation acute myocardial infarction.[A8]

For each patient, the benefits of PCI must be weighed against the procedural risk. Patients whose lesions are characterized by longer length, tortuous vessels, calcification, or the presence of thrombus can be treated with PCI but are at increased risk. Other patient characteristics conveying increased risk include advanced age (i.e., >75 years), diabetes, smaller vessels that are often found in women, prior MI, significant impairment of left ventricular function, and renal insufficiency.

PROCEDURAL SUCCESS AND COMPLICATIONS

With use of modern techniques in appropriately selected patients, most PCI procedures have a greater than 95% success rate. The single exception is a chronic total coronary occlusion (100% obstruction of the lumen), in which the interventional cardiologist's ability to negotiate a guidewire through the blockage is only about 60% to 90% and varies substantially with the operator's expertise. With the increased use of coronary stents and adjunctive antiplatelet agents, acute coronary artery closure is rarely encountered. When PCI is performed by an experienced interventional cardiologist in appropriately selected patients, the risk of in-hospital death is less than 0.5%, but the risk of a type 4 MI (usually a small, non–ST segment elevation MI; Chapter 57) is not negligible, especially when assessed by sensitive biomarker assays.[8] The

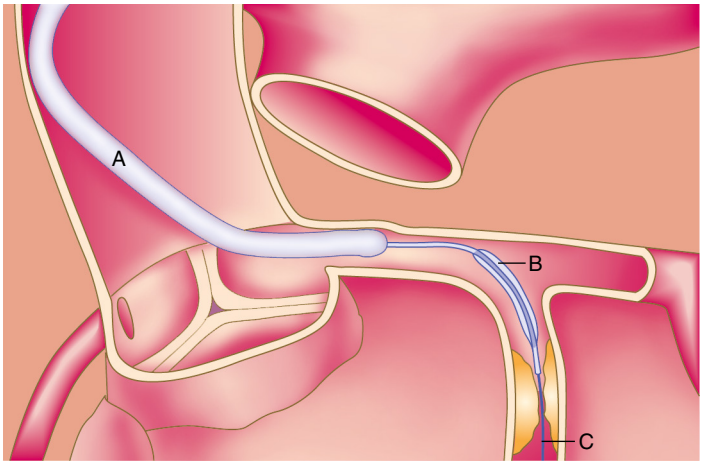

FIGURE 59-3. Schematic view of coronary angioplasty technique. A guide catheter (A) is inserted into the orifice of the coronary artery (in this figure, the left main artery), and a balloon catheter (B) is advanced over a thin guidewire (C) into the lesion. Balloon inflation dilates the stenotic region. (Modified from Baim DS. Percutaneous balloon angioplasty and general coronary intervention. In: Baim DS, ed. *Grossman's Cardiac Catheterization, Angiography, and Intervention*. 7th ed. Philadelphia: Lippincott Williams & Wilkins; 2005.)

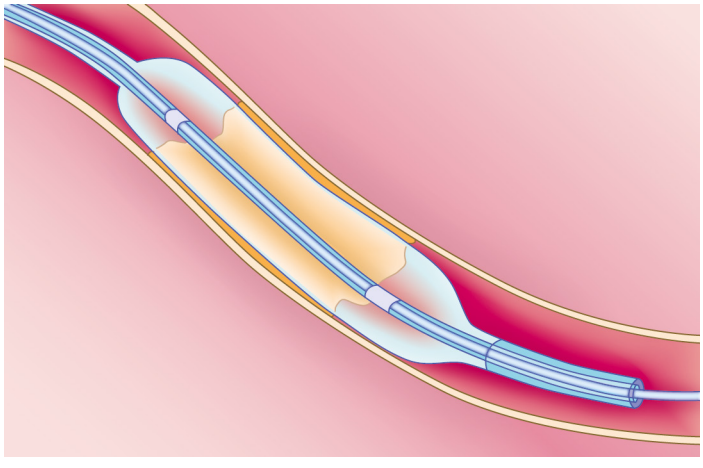

FIGURE 59-4. Balloon angioplasty catheter. The catheter consists of two lumens, an inflation lumen and a guidewire lumen. Two radiopaque markers, indicating the lateral balloon margins, aid in positioning of the balloon before inflation.

E-FIGURE 59-1. Balloon-expandable coronary stent. The stainless steel stent is crimped onto a balloon catheter to allow low-profile passage through the coronary artery. When it is positioned across the lesion, the balloon is inflated, expanding the stent (**A**). After balloon deflation and removal, the stent remains, providing a scaffold that supports the vessel lumen and conforms to the vessel's geometry (**B**).

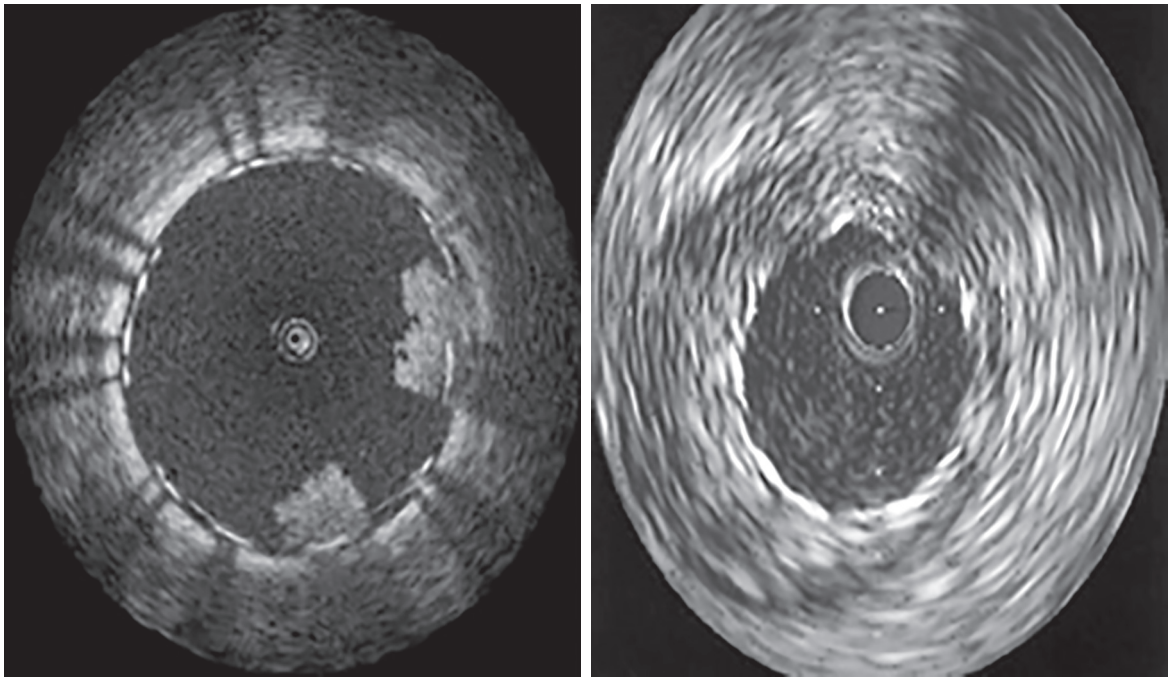

E-FIGURE 59-2. Cross-sectional image within a coronary artery by optical coherence tomography *(left)* and intravascular ultrasound *(right)*. (Courtesy of Morton J. Kern, MD.)

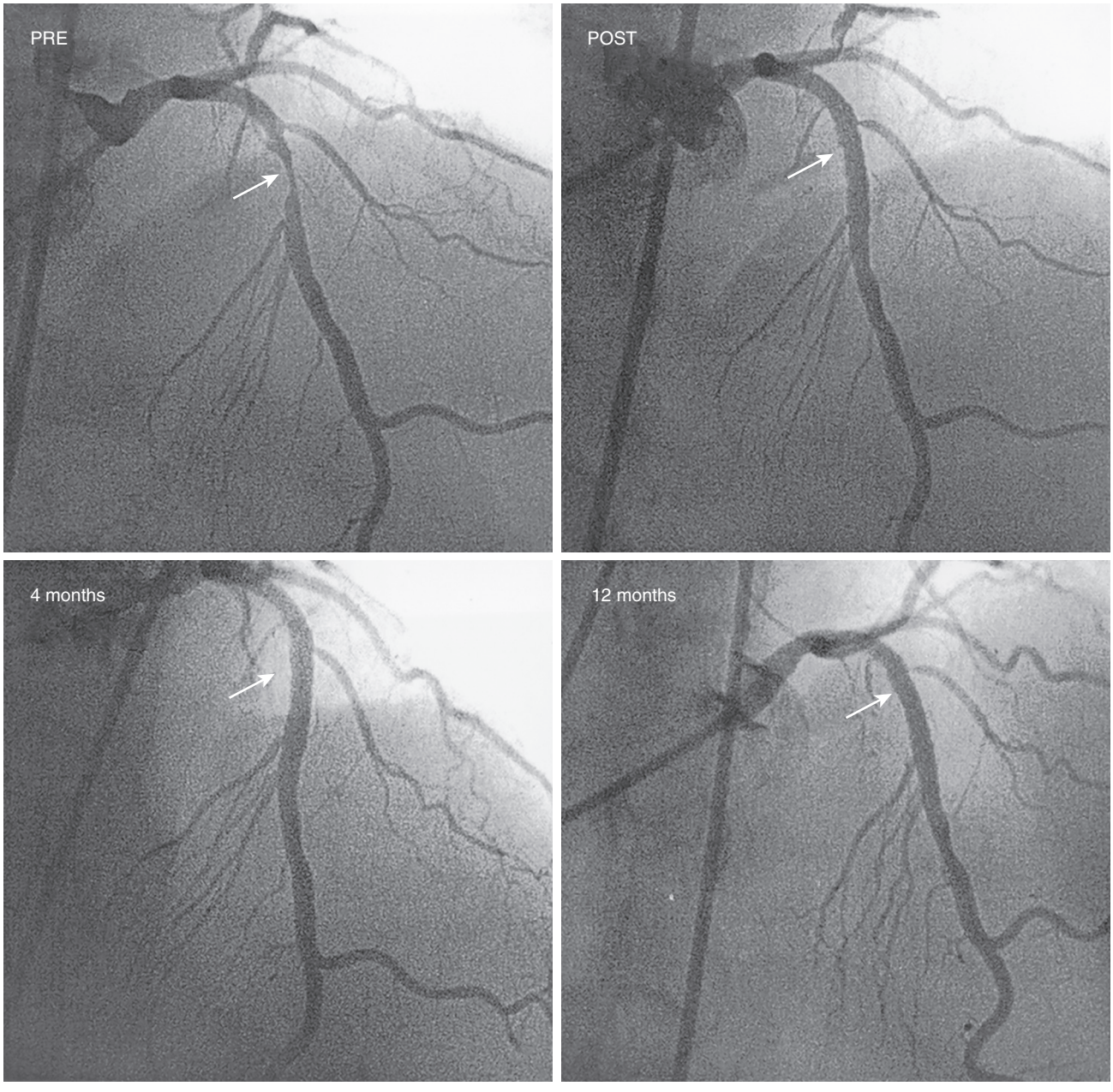

FIGURE 59-5. Angiographic images before, after, and at late follow-up after placement of a drug-eluting stent. The left anterior descending artery contains a tight stenosis *(arrow, upper left panel)*. After stent implantation *(upper right panel)*, the stenosis is abolished *(arrow)*. Follow-up at 4 and 12 months *(bottom panels)* reveals a completely open lumen with no evidence of restenosis *(arrows)*.

rate of clinically apparent MI characterized by chest discomfort, electrocardiographic changes, or a new wall motion abnormality is typically less than 2%. The need for urgent or emergent CABG surgery, stroke, and coronary perforation are less than 1%, and morbidity at the arterial access site (i.e., hematoma, pseudoaneurysm, or arteriovenous fistula) occurs in fewer than 5% of patients. As a result of these low complication rates, PCI without the availability of on-site surgery has not been demonstrably associated with higher mortality or rate of emergency CABG surgery.

Restenosis and Thrombosis

Restenosis[9] is a renarrowing of an artery after a PCI procedure, usually resulting from one of two mechanisms. The first mechanism, unfavorable remodeling and elastic recoil, is a mechanical renarrowing caused by adventitial constriction and shrinkage of the vessel lumen. The second mechanism, neointimal hyperplasia, is caused by the proliferation of smooth muscle cells and matrix in response to the injury caused by balloons, stents, or atherectomy devices. After balloon angioplasty alone without stenting, restenosis occurs in 10% to 50% of patients, usually within the first 6 months after the procedure, because of remodeling and recoil. Bare metal coronary stents, which provide a semi-rigid scaffolding within the lumen, eliminate the mechanical component of restenosis, but the proliferative component is enhanced; restenosis is reduced by about one third compared with balloon angioplasty alone. Drug-eluting stents, which contain and release antiproliferative drugs (e.g., sirolimus, everolimus, zotarolimus, and paclitaxel) reduce the need for early repeat PCI to less than 5%.[A9] Even with drug-eluting stents, however, about 10% of all PCI procedures in the United States are performed for restenosis.[10]

CHOICES RELATED TO STENTING

Balloon angioplasty is essentially always followed immediately by the insertion of a drug-eluting coronary stent.[A10] Biodegradable drug-eluting scaffolds, which completely dissolve over 2 to 3 years, were posited as a promising new technology but appear to be associated with a higher risk of in-stent thrombosis and myocardial infarction compared with metallic drug-eluting stents at 3-year follow-up.[A11]

The treatment of highly calcified vessels often requires rotational atherectomy or lithotripsy. Atherectomy (using a spinning catheter containing abrasive particles or laser energy) pulverizes plaque into microparticles that pass through the coronary microcirculation and is particularly helpful for the treatment of

heavily calcified lesions. Intravascular lithotripsy catheters deliver localized pulsatile sonic pressure waves that disrupt calcified plaque by creating microfractures. After the calcium has been cracked by lithotripsy or pulverized by atherectomy, the artery can be more easily expanded, and a drug-eluting stent is usually implanted.

DISCHARGE ISSUES

Discharge planning after PCI represents an important opportunity to emphasize evidence-based medical treatment of atherothrombotic disease and coronary risk factor modification (Chapter 40). Prolonged use of lipid-lowering agents, angiotensin-converting enzyme inhibitors, and in some cases β-blockers should be considered on the basis of randomized trials showing improved long-term outcome, particularly in patients who present with unstable coronary syndromes (Chapters 57 and 58). Smoking cessation (Chapter 363), blood pressure control (Chapter 64), stress management, exercise, weight loss, changes in dietary habits, and strict blood glucose control for patients with diabetes (Chapter 210) also are important elements of the discharge plan.

All patients should receive aspirin (81 mg/day) indefinitely. For patients receiving bare metal stents, a minimum 2-week course of a $P2Y_{12}$ receptor inhibitor (e.g., clopidogrel 75 mg/day, prasugrel 10 mg/day, or ticagrelor 90 mg/day) is mandatory. If a drug-eluting stent is deployed, aspirin plus a $P2Y_{12}$ inhibitor historically was required for a minimum of 3 to 6 months if the stent was implanted in a stable patient and 6 to 12 months if stenting was performed due to an acute coronary syndrome (unstable angina or myocardial infarction),[A12] However, switching to $P2Y_{12}$ monotherapy can be safe and effective in selected high-risk patients after 1 to 3 months of dual antiplatelet therapy.[A13] In fact, with second-generation polymer-free drug-eluting stents,[11] 1 month of dual anti-platelet therapy followed by 11 months of clopidogrel alone is a potential option to limit bleeding in patients with higher risks of bleeding. [A14,A15] Extending dual antiplatelet therapy to 30 or 36 months reduces ischemic cardiovascular events but increases bleeding. In patients with atrial fibrillation (Chapter 52), dual therapy with a direct-acting oral anticoagulant (e.g., dabigatran 110 mg or 150 mg twice daily) plus a $P2Y_{12}$ receptor inhibitor carries similar ischemic protection with a lower risk of bleeding compared with triple therapy with aspirin, warfarin, and either clopidogrel or ticagrelor.[A16]

Activity restrictions after PCI are modest. If the femoral artery was instrumented, heavy lifting is discouraged for several days. Intense aerobic exercise is usually discouraged for 2 to 4 weeks (especially after stent implantation) because exercise can activate platelets and lead to formation of thrombus at the angioplasty site. Patients may return to work 1 or 2 days after the procedure if their occupation does not include heavy lifting or excessive physical exercise. There is usually no restriction on driving an automobile. Routine postoperative functional testing has not been shown to be beneficial.[A17]

CORONARY ANGIOPLASTY VERSUS MEDICAL THERAPY

Percutaneous coronary intervention reduces angina and commonly leads to better treadmill exercise performance and improved quality-of-life measurements. However, in patients with stable angina, PCI has not been shown to reduce the risks of death, MI, or other major cardiovascular events compared with modern optimal medical therapy (Chapter 56).[A18-A22] In truly asymptomatic patients, significant ischemia first should be documented by functional testing, or a large quantity of myocardium should be supplied by the stenotic coronary artery. Patients experiencing acute MI such as ST segment elevation MI (Chapter 58) represent an important subgroup in whom PCI has proved beneficial compared with medical therapy (Fig. 59-6). In ST segment elevation MI, randomized trials have consistently shown a reduction in mortality, stroke, subsequent MI, and recurrent ischemia with immediate PCI compared with thrombolytic therapy or with initial thrombolytic therapy followed by rescue PCI as needed even if immediate PCI requires transfer to another hospital. For non–ST segment elevation MI and many patients with unstable angina, an early aggressive approach that includes either PCI or CABG in angiographically suitable patients is generally preferable to a conservative strategy except in lower risk patients (Chapter 57).[12]

CORONARY ARTERY SURGERY

Coronary artery bypass graft surgery is based on the premise that the morbidity and mortality associated with coronary atherosclerosis are largely related to atherosclerotic coronary stenoses that can be demonstrated by coronary angiography and that if grafts are constructed to route blood flow around these stenoses, myocardial blood supply can be improved or preserved, cardiac symptoms relieved, cardiac events diminished, and survival prolonged.

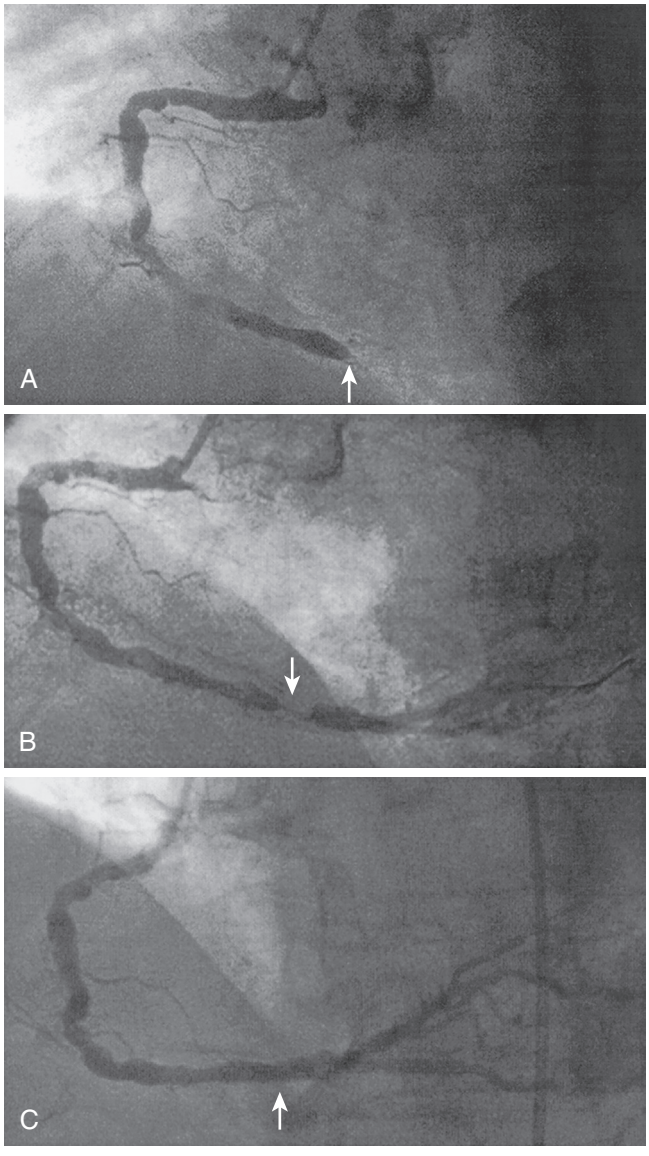

FIGURE 59-6. Primary coronary angioplasty for acute myocardial infarction. This 50-year-old man presented at midnight with 70 minutes of crushing substernal chest pressure accompanied by inferior ST segment elevation. Emergency angiography performed 45 minutes after arrival found 100% occlusion of the right coronary artery (**A**, *arrow*). Within 10 minutes, a guidewire was negotiated through the obstruction (presumably caused by fresh thrombus), allowing perfusion into the distal vessel and uncovering a high-grade stenotic lesion (**B**, *arrow*). After deployment of a coronary stent (**C**, *arrow*), the stenosis was abolished and significant myocardial damage aborted.

The most common types of grafts for coronary artery bypass have been reversed segments of saphenous vein and the internal thoracic arteries. Saphenous vein grafts are anastomosed to the aorta (proximal anastomosis) and to the coronary artery distal to the major obstruction (Fig. 59-7). Saphenous vein grafts have the advantages of availability, larger size than most coronary arteries, and favorable handling characteristics. With time, however, saphenous vein grafts may develop intrinsic pathologic changes, intimal fibroplasia, and vein graft atherosclerosis, each of which may lead to narrowing or occlusions. Modern treatment with platelet inhibitors and statins (Chapter 190) decreases the risk of vein graft failure but cannot eliminate it. Internal thoracic artery grafts, on the other hand, are resistant to the development of late atherosclerosis. When used as an in situ (subclavian origin intact) graft to the left anterior descending (LAD) coronary artery, the left internal thoracic artery graft has a more than 90% patency rate up to 20 years after operation. As a result, patients who receive a left internal thoracic artery to LAD graft, with or without saphenous vein grafts, have a better long-term survival rate, fewer reoperations, and fewer cardiac events compared with

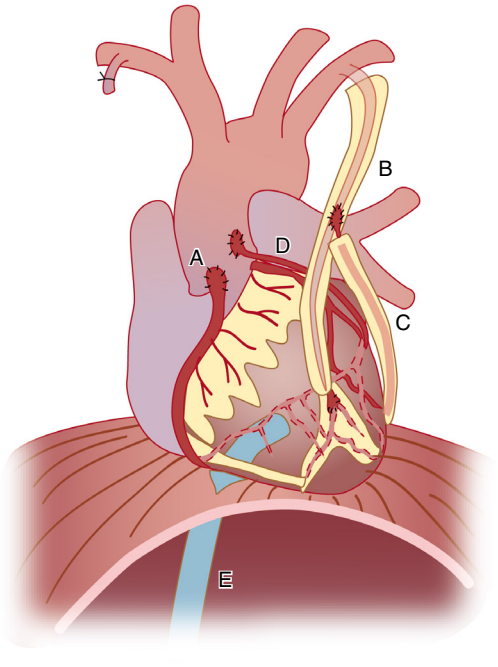

FIGURE 59-7. Types of bypass grafts. Bypass grafts include reversed saphenous vein graft from the aorta to the right coronary artery (**A**), in situ left internal mammary artery graft to the anterior descending coronary artery (**B**), Y graft of the right internal mammary artery from the left internal mammary artery to the circumflex coronary artery (**C**), radial artery graft from the aorta to the circumflex coronary artery (**D**), and in situ gastroepiploic graft to the posterior descending branch of the right coronary artery (**E**).

patients receiving only saphenous vein grafts. The right internal thoracic artery also may be used for revascularization as an in situ graft, as an aorta to coronary artery graft, or as a composite arterial graft from the left internal thoracic artery to a coronary artery. Despite its theoretical appeal, use of both internal thoracic arteries as grafts has not been proven to provide benefit over a single internal thoracic artery graft strategy and is associated with a higher rate of sternal infections and complications.[A23,A24] For the second graft, using the radial artery as another arterial conduit is preferred over a saphenous vein graft.[A25]

Most CABG operations are performed with a full median sternotomy incision, historically with the aid of cardiopulmonary bypass, aortic cross-clamping, and cardioplegic solution—techniques that allow exposure and arrest of the heart such that detailed microsurgical anastomoses can be constructed while myocardial function is effectively protected. By comparison, operations performed through smaller incisions (minimally invasive surgery) can be more challenging to perform without specialized training and have had limited application for coronary revascularizations. In randomized trials, beating heart ("off-pump") surgery without cardiopulmonary bypass has not consistently reduced morbidity, often has been associated with a lower rate of long-term graft patency, and does not provide better outcomes;[A26] as a result, it is usually reserved for carefully selected patients.

PERIOPERATIVE RISKS

The risk of mortality associated with CABG correlates with the extent of ischemia at the time of operation, left ventricular function, extent of coronary stenoses, noncardiac atherosclerosis, and comorbid conditions, as well as with the experience, skill, and judgment of the surgeon. Effective myocardial protection has diminished much of the incremental risk based on the severity of cardiac disease. For patients younger than 70 years without serious comorbid conditions, the mortality risk of primary CABG surgery is less than 1% in experienced hands. Nevertheless, CABG surgery in the presence of ongoing myocardial ischemia caused by acute MI, unstable angina, or acute vessel closure after PCI is still associated with increased risk. Noncardiac comorbid conditions (aortic atherosclerosis, renal function, chronic obstructive pulmonary disease, and coagulation system disorders) increase perioperative risk when these conditions are severe.

Aside from mortality, the most serious postoperative morbidity after CABG is stroke, often related to aortic or cerebrovascular atherosclerosis and atherosclerotic embolization. Heightened awareness of the importance of aortic and carotid atherosclerosis and improved management strategies appear to have decreased the risk of focal stroke in patients previously at high risk. Serious wound complications of median sternotomy are uncommon (1 to 2%).

INDICATIONS FOR BYPASS SURGERY

The goals of CABG are to relieve symptoms and to prolong life expectancy. On the basis of randomized trials and the emergence of alternative medical treatments and PCI, the surgical population has evolved toward patients who benefit most from CABG relative to other treatments: patients with complex conditions, often involving left main or triple-vessel disease, diffuse coronary stenoses, totally obstructed vessels, abnormal left ventricular function, and diabetes. Surgically treated patients with single-vessel disease usually have LAD stenoses or have failed alternative treatments, such as developing recurrent restenosis after PCI.

Relief of Symptoms

If patients who experience angina have severe stenoses in graftable coronary arteries that supply areas of myocardium ischemia at rest or with stress, CABG will reliably relieve angina. Randomized trials have shown that the relief of angina after CABG is more consistent than that achieved with alternative treatments. When intermittent heart failure symptoms represent an "anginal equivalent" that is also caused by ischemia, such symptoms also respond well to relief of that ischemia by CABG. For patients with symptoms of heart failure at rest, dobutamine echocardiography (Chapter 43), positron emission tomography (Chapter 44), and cardiac magnetic resonance imaging (Chapter 44) can identify segments of viable but hibernating myocardium (ischemic at rest) that may improve with bypass grafting, thus reducing symptoms of heart failure.

Survival

Chronic Stable Angina

In randomized trials of patients with mild to moderate chronic stable angina, an improved survival rate has been documented for patients treated with initial CABG compared with those treated with initial medical treatment in the presence of a left main stenosis of more than 50% of the diameter, triple-vessel disease, double-vessel disease with a proximal LAD lesion, abnormal left ventricular function, or a strongly abnormal exercise test result (Chapter 56). Meta-analysis of these randomized trials also suggests a survival benefit of CABG for any patient with a proximal LAD lesion and myocardial ischemia. These are subgroups of patients for whom bypass surgery should be strongly considered even in the absence of severe symptoms. During these trials, patients with severe angina were not randomized but were included in observational studies that noted improved survival rates with CABG for patients with double- and triple-vessel disease and normal or abnormal left ventricular function. Medical, interventional, and surgical treatments have all advanced substantially since these trials were completed.

Acute Coronary Syndrome and Ischemic Cardiomyopathy

Current data suggest an aggressive strategy, including CABG when indicated, in patients who have an acute coronary syndrome (unstable angina or non–ST segment elevation acute MI; Chapter 57). Patients who have coronary artery disease, heart failure, and severe left ventricular systolic dysfunction often can be controlled symptomatically with medications (Chapter 46). However, CABG added to guideline-directed medical therapy significantly reduces all-cause death, death from cardiovascular causes, and death from any cause or hospitalization for cardiovascular causes at 10 years,[A27] irrespective of whether it improves left ventricular function.[A28]

Other Ischemic Syndromes

ST Segment Elevation Acute Myocardial Infarction

For patients with ST segment elevation acute MI, CABG may be indicated in the acute setting when thrombolytic therapy or PCI has not been effective, ischemia is ongoing, and large areas of myocardium remain jeopardized. CABG after a completed MI may be indicated in patients in whom persistent ischemia in noninfarcted areas of myocardium produces post-infarction angina or hemodynamic instability. Mechanical complications of myocardial necrosis, including papillary muscle rupture, ventricular septal rupture, and myocardial free wall rupture, are acute life-threatening situations that usually require urgent operation for repair of the defect, often combined with CABG (Chapter 58).

Failed Percutaneous Coronary Intervention

Drug-eluting stents have decreased the need for emergency CABG to treat acute failure of PCIs. Current indications for emergency CABG include closure or threatened closure of a vessel supplying a significant amount of myocardium or recurrent restenosis despite several PCIs.

Coronary Bypass Reoperations

Patients in whom new stenoses develop in native arteries or in bypass grafts may have recurrent ischemic syndromes. Severe vein graft atherosclerosis is an unstable lesion that often leads to serious cardiac events, particularly if the LAD or multiple vessels are jeopardized; reoperation appears to improve the survival rate of these patients. Conversely, if the LAD coronary artery is supplied by a patent internal thoracic artery graft, reoperation does not appear to improve survival, although it may improve symptoms. Reoperations are more difficult and dangerous than primary procedures, but the risk now approaches that for primary procedures in institutions performing a large number of reoperations. PCI is often less-invasive and potentially a lower-risk alternative for the treatment of vein graft disease.

Late Outcomes

The late outcomes after CABG are related to age, severity of cardiac disease before operation, noncardiac comorbid conditions, progression of atherosclerosis, and the operation itself. For patients with severe coronary artery disease, CABG prolongs life expectancy. The achievement of complete revascularization (bypass grafts to all stenotic coronary vessels) and the use of internal thoracic artery grafts improve long-term survival rates and symptomatic status.

More than 80% of patients are alive more than 10 years after operation. Over the long term, control of the progression of atherosclerosis by lifestyle modifications, pharmacologic treatment of hypertension (Chapter 64) and lipids (Chapter 190), and platelet inhibitors (Chapter 70) appear to extend the benefits of CABG.[13]

COEXISTING CARDIAC DISEASE

During cardiac operations performed for valvular (Chapter 60) or aortic (Chapter 63) disease, the standard treatment is to perform bypass grafts to major coronary arteries with angiographic stenoses of more than 50% of the luminal diameter. No randomized trials have addressed this issue, and these indications, although logical given the natural history of atherosclerosis, remain practice patterns based on consensus but not on definitive data.

PERCUTANEOUS CORONARY INTERVENTION VERSUS CORONARY ARTERY BYPASS GRAFTING

The decision between PCI and CABG surgery is largely determined by clinical status and anatomic features, but some areas remain controversial. For patients with acute coronary syndromes, PCI is the preferred initial approach and has been shown to improve the survival rate of patients with ST segment elevation MI.[14] CABG is reserved for patients with failed acute PCI or residual myocardial ischemia. For patients who have chronic coronary syndromes, no data confirm that PCI prolongs life regardless of anatomy.

By comparison, randomized trials, albeit older trials, demonstrate that CABG prolongs the life expectancy of patients with severe coronary artery disease, particularly patients with left ventricular dysfunction or severe ischemia. Patients with more complex, multivessel coronary artery disease benefit most from CABG, including a clear improvement in survival rate, but patients with more limited coronary disease have equivalent survival outcomes with drug-eluting PCI.[A29] For patients with left main coronary artery disease[15] without extensive additional disease, PCI appears to be similar to CABG in terms of subsequent death, superior with respect to stroke, but inferior with respect to the need for repeat revascularization and out-of hospital myocardial infarction, and perhaps all-cause mortality.[A30-A33] Randomized trials also show that diabetic patients with multivessel coronary artery disease have better survival rates with CABG compared with PCI.[A34]

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60 VALVULAR HEART DISEASE

BLASE A. CARABELLO AND SUSHEEL KODALI

APPROACH TO THE PATIENT WITH VALVULAR HEART DISEASE

The cardiac valves permit unobstructed forward blood flow through the heart when they are open while preventing backward flow when they are closed. Most valvular heart diseases cause either valvular stenosis with obstruction to forward flow or valvular regurgitation with backward flow. Valvular stenosis imparts a pressure overload on the left or right ventricle because these chambers must generate higher than normal pressure to overcome the obstruction to pump blood forward. Valvular regurgitation imparts a volume overload on the heart, which now must pump additional volume to compensate for what is regurgitated. When valve disease is severe, these hemodynamic burdens can lead to ventricular dysfunction, heart failure, and sudden death (Table 60-1). In almost every instance, definitive therapy for severe valvular heart disease is mechanical restoration of valve function.

A careful history and physical examination are key to the evaluation of a patient with suspected or known valvular heart disease. Because the presence or absence of symptoms dramatically affects prognosis and hence the proper therapy in most valvular diseases, an intense effort must focus on the patient's symptomatic status. The physical examination should include not only careful auscultation but also a detailed assessment for evidence of heart failure (Chapter 45). Transthoracic echocardiography (Chapter 43), which is the mainstay of diagnosis, provides both anatomic and physiologic information regarding the lesion's type, cause, and severity. In cases in which transthoracic echocardiography fails to provide adequate information, transesophageal echocardiography, cardiac magnetic resonance imaging (MRI; Chapter 44), and cardiac computed tomography (CT) usually provide the additional needed information, but invasive hemodynamic measurements are still occasionally required.[1,2]

AORTIC STENOSIS

EPIDEMIOLOGY

Bicuspid and Other Congenitally Abnormal Aortic Valves

Approximately 0.8% of the population is born with a bicuspid aortic valve,[3] with a male preponderance (Chapter 55). Although this abnormality does not usually cause a hemodynamic disturbance at birth, bicuspid aortic valves tend to deteriorate with age. Approximately one third of these valves become stenotic, another third become regurgitant, and the remainder cause only minor hemodynamic abnormalities. A murmur is typically noted in childhood or adolescence, and congenital aortic stenosis from a bicuspid tricuspid valve can cause symptoms during childhood and require correction by adolescence (Chapter 55). However, bicuspid valves more commonly become symptomatic when patients are in their 40s, 50s, and 60s. Aortic aneurysms develop in nearly one-third of patients with bicuspid aortic valves, so careful screening is warranted, even in asymptomatic patients.

Tricuspid Aortic Valve Stenosis

The most common form of aortic stenosis is a calcific process that results from the deposition of calcium and the thickening of valve leaflets in patients with apparently normal tricuspid aortic valves. This disease process typically develops in the seventh to eighth decade of life. This type of aortic stenosis is not a degenerative process but rather arises from an active inflammatory process similar to that of coronary heart disease (Chapter 41), with hypertension and hyperlipidemia as risk factors.

Rheumatic Valvular Heart Disease

Rheumatic valve disease is now a rare cause of aortic stenosis in developed countries, but rheumatic fever and its sequelae remain an important issue in many developing countries (Chapter 269). In virtually every case, the mitral valve is also involved in the disease process.

PATHOBIOLOGY

The normal aortic valve area is 3 to 4 cm^2, and little hemodynamic disturbance occurs until the orifice is reduced to about half of normal, at which point a systolic gradient develops between the left ventricle and aorta. Typically left ventricular and aortic pressures are nearly equal during systole (E-Fig. 60-1A). In aortic stenosis, however, intracavitary left ventricular pressure must increase above aortic pressure to produce forward flow across the stenotic valve and to achieve acceptable downstream pressure (E-Fig. 60-1B). Each of the processes that cause aortic stenosis has a typical pathoanatomic configuration (Fig. 60-1). There is a geometric progression in the magnitude of the gradient as the valve area narrows. Given a normal cardiac output, the gradient rises rapidly from 10 to 15 mm Hg at valve areas of 1.5 to 1.3 cm^2 to about 25 mm Hg at 1.0 cm^2, 50 mm Hg at 0.8 cm^2, 70 mm Hg at 0.6 cm^2, and 100 mm Hg at 0.5 cm^2. The rate of progression of aortic stenosis varies widely from patient to patient; it may remain stable for many years or increase by more than 15 mm Hg per year.

A major compensatory response to the increased left ventricular pressure associated with aortic stenosis is the development of concentric left ventricular hypertrophy. The Laplace equation—Stress (s) = Pressure (p) × Radius (r)/2 Thickness (th)—indicates that the stress on the left ventricle (afterload) varies directly with intracavitary pressure and radius but inversely with wall thickness. As left ventricular pressure increases with increasing severity of aortic stenosis, it can be offset by increased left ventricular wall thickness (concentric hypertrophy). The determinants of the left ventricular ejection fraction are contractility, preload, and afterload. By normalizing afterload, the development of concentric hypertrophy helps preserve ejection fraction and cardiac output despite the pressure overload. Although hypertrophy may serve as a compensatory function, it also has a pathologic role and is in part responsible for the classic symptoms and the poor outcome of untreated symptomatic aortic stenosis.

Angina

In general, angina (Chapter 56) results from ischemia when myocardial oxygen (and other nutrient) demand exceeds supply, which is predicated on coronary blood flow. In normal subjects, coronary blood flow can increase five- to eight-fold under maximum metabolic demand, but in patients with aortic stenosis, this reserve is limited. Reduced coronary blood flow reserve may be caused by a relative diminution in capillary ingrowth to serve the needs of the hypertrophied left ventricle or by a reduced transcoronary gradient for coronary blood flow because of the elevated left ventricular end-diastolic pressure. Restricted coronary blood flow reserve is in part responsible for angina in many patients who have aortic stenosis despite normal epicardial coronary arteries, but angina also may be caused by increased oxygen demand when inadequate hypertrophy allows wall stress, a key determinant of myocardial oxygen consumption, to increase.

Syncope

Syncope (Chapters 39 and 49) generally occurs because of inadequate cerebral perfusion. In aortic stenosis, syncope is often related to exertion. It may result when exertion causes a fall in total peripheral resistance that cannot be offset by increased cardiac output because output is limited by the obstruction to outflow across the stenotic valve. Furthermore, patients with small left ventricular cavity size are more prone to syncope because of lower stroke volume. In addition, high left ventricular pressure during exercise may trigger a systemic vasodepressor response that lowers blood pressure and produces syncope. Any sudden drop in preload may precipitate syncope because the left ventricle is unable to maintain cardiac output. Finally, cardiac arrhythmias, often related to a dilated left atrium, can also result in hypotension and syncope.

Heart Failure

In aortic stenosis, contractile dysfunction (systolic failure) and failure of normal relaxation (diastolic failure) result in symptoms of heart failure (Chapter 45). The extent of ventricular contraction is governed by contractility and afterload. In aortic stenosis, contractility (the ability to generate force) is often reduced. The mechanisms of contractile dysfunction may include abnormal calcium handling, microtubular hyperpolymerization causing an internal viscous load on the myocyte, and myocardial ischemia (Chapter 41). In some cases, contractile function is normal, but the hypertrophy is inadequate to normalize wall stress and excessive afterload results. Excessive afterload inhibits ejection, reduces forward output, and leads to heart failure.

The increased wall thickness that helps normalize stress increases diastolic stiffness. Even if muscle properties remain normal, higher filling pressure is required to distend a thicker ventricle. As aortic stenosis advances, collagen deposition also stiffens the myocardium and adds to the diastolic dysfunction. These processes eventually result in elevated left atrial and pulmonary artery pressures.

ABSTRACT

The heart valves are mechanical structures that control one-way circulation through the heart. Valve malfunction is manifest either by stenosis, which creates obstruction to flow, or by regurgitation, which allows backward flow. When severe, valve disease is almost universally fatal, but when treated properly, the outcome is excellent. In most cases, mechanical problems created by valve disease require mechanical solutions for proper management. The advent of transcatheter valve repair and replacement has broadened applicability of these solutions to a wide range of previously untreatable patients. Increased therapeutic options also increase the need for an understanding of their place in the valve disease armamentarium. This chapter describes the etiology and diagnosis of valvular heart disease, with a special emphasis on the proper timing and appropriate use of the therapeutic options.

KEYWORDS

valvular heart disease
aortic stenosis
aortic regurgitation
mitral stenosis
mitral regurgitation
tricuspid valve disease
pulmonic valve disease

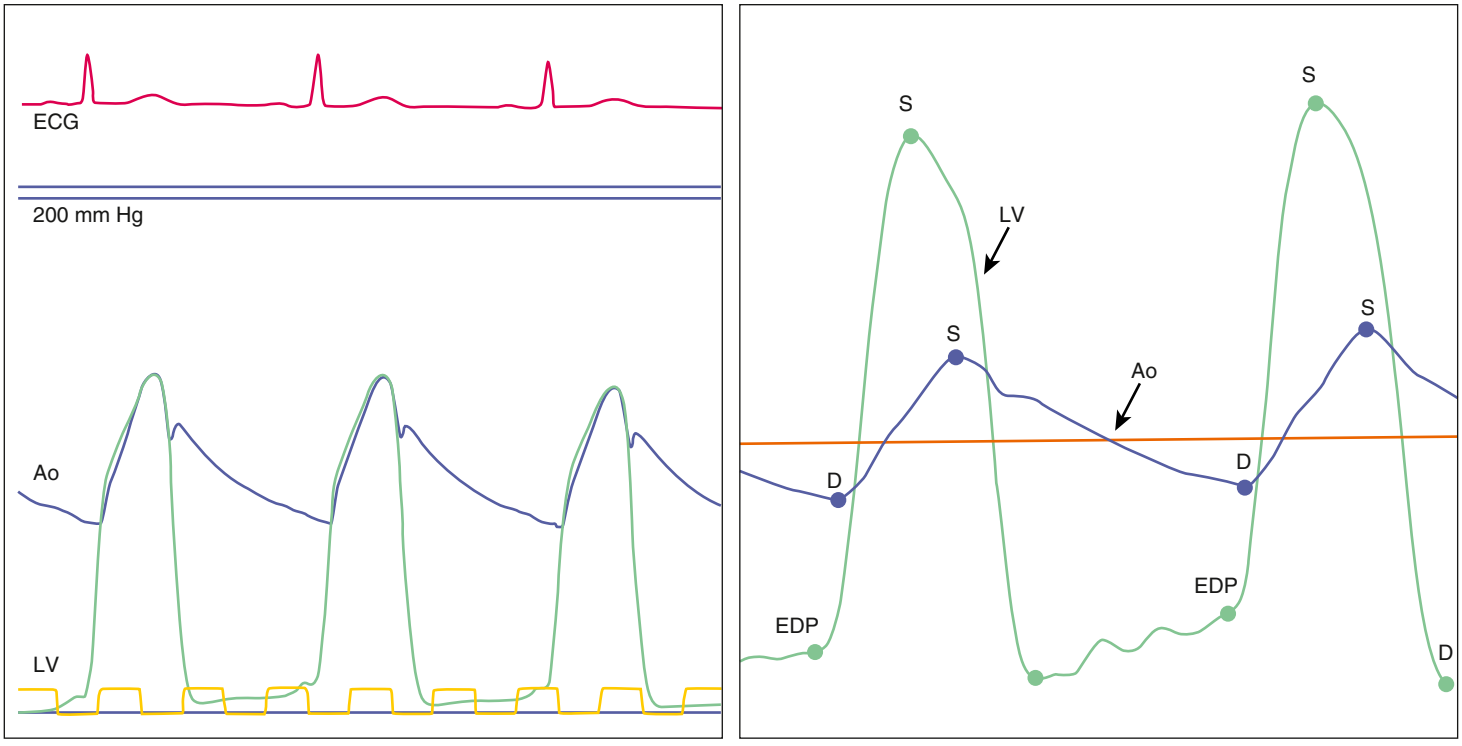

E-FIGURE 60-1. **The pressure gradient between the left ventricle (*LV* green) and aorta (*Ao* blue) in (A) a normal patient and (B) a patient with severe aortic stenosis.** The end-diastolic pressure (EDP) is slightly elevated.

TABLE 60-1 SUMMARY OF SEVERE VALVULAR HEART DISEASE

	AORTIC STENOSIS	MITRAL STENOSIS	MITRAL REGURGITATION	AORTIC REGURGITATION
Etiology	Idiopathic calcification of a bicuspid or tricuspid valve Congenital Rheumatic	Rheumatic fever Annular and leaflet calcification	Mitral valve prolapse Ruptured chordae Endocarditis Ischemic papillary muscle dysfunction or rupture Collagen vascular diseases and syndromes Secondary to LV myocardial diseases	Annuloaortic ectasia Hypertension Endocarditis Marfan syndrome Ankylosing spondylitis Aortic dissection Syphilis Collagen vascular disease
Pathophysiology	Pressure overload on the LV with compensation by LVH. As disease advances, reduced coronary flow reserve predisposes to angina. Hypertrophy and afterload excess lead to systolic and diastolic LV dysfunction.	Obstruction to LV inflow increases LA pressure and limits cardiac output, thus mimicking LV failure. Mitral valve obstruction increases the pressure work of the RV. Right ventricular pressure overload is augmented further when pulmonary hypertension develops.	Places volume overload on the LV. Ventricle responds with eccentric hypertrophy and dilation, which allow increased ventricular stroke volume. Eventually, however, LV dysfunction develops if volume overload is uncorrected.	*Chronic:* Total stroke volume causes hyperdynamic circulation, induces systolic hypertension, and causes pressure and volume overload. Compensation is by concentric and eccentric hypertrophy. *Acute:* Because cardiac dilation has not developed, hyperdynamic findings are absent. High diastolic LV pressure causes mitral valve preclosure and potentiates LV ischemia and failure.
Symptoms	Angina Syncope Dyspnea Heart failure	Dyspnea Orthopnea PND Hemoptysis Hoarseness Edema Ascites	Dyspnea Orthopnea PND	Dyspnea Orthopnea PND Angina
Signs	Systolic ejection murmur radiating to the neck Delayed carotid upstroke S_4, soft or paradoxical S_2	Diastolic rumble after an opening snap Loud S_1 RV lift Loud P_2	Holosystolic apical murmur radiating to the axilla, S_3 Displaced PMI	*Chronic:* Diastolic blowing murmur Hyperdynamic circulation Displaced PMI Quincke pulse de Musset sign Austin Flint murmur *Acute:* Short diastolic blowing murmur Soft S_1
Electrocardiogram	LAA LVH	LAA RVH	LAA LVH	LAA LVH
Chest radiograph	Boot-shaped heart Aortic valve calcification on lateral view	Straightening of left heart border Double density at right heart border Kerley B lines Enlarged pulmonary arteries	Cardiac enlargement	*Chronic:* Cardiac enlargement Uncoiling of the aorta *Acute:* Pulmonary congestion with normal heart size
Echocardiographic findings	Concentric LVH Reduced aortic valve cusp separation Doppler shows mean gradient ≥40 mm Hg in most severe cases	Restricted mitral leaflet motion Valve area ≤1.5 cm^2 LA enlargement Tricuspid Doppler may reveal pulmonary hypertension	LA enlargement LV enlargement and LV dysfunction in severe cases Doppler: large regurgitant jet	*Chronic:* LV enlargement Large Doppler jet with PHT <400 msec *Acute:* Small LV Mitral valve preclosure
Catheterization findings	Increased LVEDP Transaortic gradient 40 mm Hg AVA ≤0.8 in most severe cases	Elevated pulmonary capillary wedge pressure Transmitral gradient usually >5 mm Hg in severe cases MVA <1.5 cm^2	Elevated pulmonary capillary wedge pressure with prominent V waves Ventriculography shows regurgitation of dye into LA	Wide pulse pressure Aortography shows regurgitation of dye into LV
Medical therapy	Avoid vasodilators Avoid a decline in venous return (preload) Diuretics for symptom control in inoperable cases	Diuretics for mild symptoms Anticoagulation in atrial fibrillation Digitalis, β-blockers, verapamil, or diltiazem for rate control	Afterload reduction in acute MR—primarily with ACE inhibitors Blood pressure control	*Chronic:* Vasodilators in chronic asymptomatic disease with hypertension even if LV function is normal *Acute:* Vasodilators
Indications for surgery	Appearance of symptoms in patients with severe disease (see text) or asymptomatic LV dysfunction	Appearance of more than mild symptoms Development of pulmonary hypertension Appearance of persistent atrial fibrillation	Appearance of symptoms EF <0.60 ESD ≥40 mm	*Chronic:* Appearance of symptoms EF <0.50 ESD ≥50 mm *Acute:* Even mild heart failure Mitral valve preclosure

ACE = angiotensin-converting enzyme; AVA = aortic valve area; EF = ejection fraction; ESD = end-systolic diameter; LA = left atrial; LAA = left atrial abnormality; LV = left ventricle or left ventricular; LVEDP = left ventricular end-diastolic pressure; LVH = left ventricular hypertrophy; MR = mitral regurgitation; MVA = mitral valve area; PHT = pressure half-time; PMI = point of maximal impulse; PND = paroxysmal nocturnal dyspnea; RV = right ventricle or right ventricular; RVH = right ventricular hypertrophy.

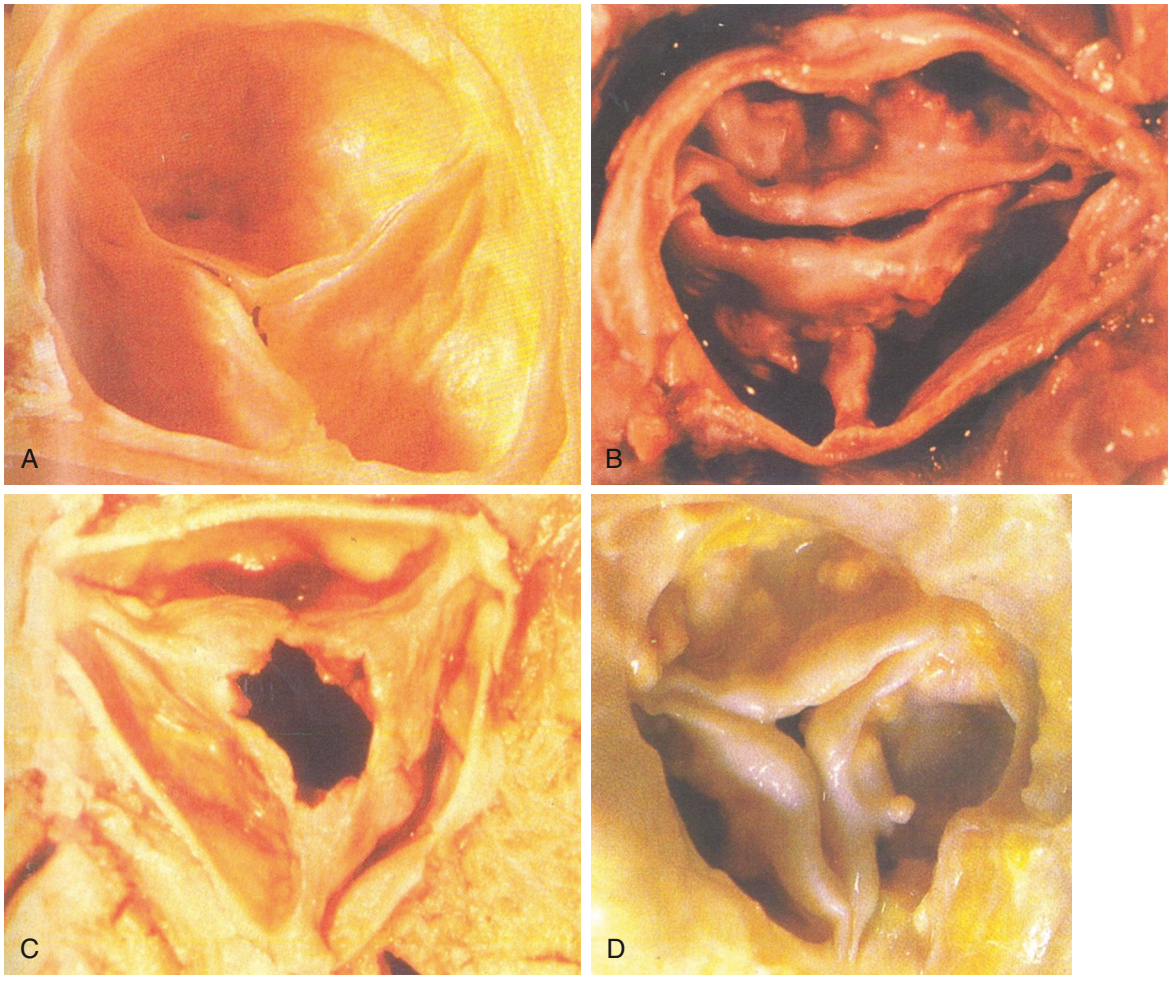

FIGURE 60-1. Pathology of aortic stenosis. A, A normal aortic valve. **B,** A stenotic congenital bicuspid valve. **C,** Rheumatic aortic stenosis. **D,** A stenotic calcified tricuspid aortic valve. (From Bonow RO, Braunwald E. Valvular heart disease. In: Zipes DP, Libby P, Bonow RO, Braunwald E, eds. *Heart Disease: A Textbook of Cardiovascular Medicine*. 7th ed. Philadelphia: WB Saunders; 2005:1583.)

CLINICAL MANIFESTATIONS

The diagnosis of aortic stenosis is usually first suspected when the classic systolic ejection murmur is heard during physical examination (Chapter 39) in an often asymptomatic individual. The murmur is loudest in the aortic area and radiates to the neck. In some cases, the murmur may disappear over the sternum and reappear over the left ventricular apex, thereby giving the false impression that a murmur of mitral regurgitation is also present (Gallavardin phenomenon). The intensity of the murmur increases with cycle length because longer cycles are associated with greater aortic flow. In mild disease, the murmur peaks in intensity in early systole or mid systole. As the severity of stenosis worsens, the murmur peaks progressively later in systole. Perhaps the most helpful clue to the severity of aortic stenosis by physical examination is the characteristic delay in the carotid pulse with a diminution in its volume (see Fig. 39-4 in Chapter 39); in elderly patients, however, increasing carotid stiffness may pseudonormalize the carotid upstrokes. The left ventricular apical impulse in aortic stenosis is not displaced but is enlarged and forceful. The simultaneous palpation of a forceful left ventricular apex beat and a delayed and weakened carotid pulse is a persuasive clue that severe aortic stenosis is present. S_1 in aortic stenosis is generally normal. In congenital aortic stenosis when the valve is not calcified, S_1 may be followed by a systolic ejection click. In calcific disease, S_2 may be single and soft when the aortic component is lost because the valve neither opens nor closes well. In some cases, delayed left ventricular emptying may create paradoxical splitting of S_2. An S_4 gallop is common. In advanced disease, pulmonary hypertension and signs of right-sided failure are common.

Because of the dire consequences of missing the diagnosis of aortic stenosis, the physician must have a low threshold for obtaining an echocardiogram whenever aortic stenosis cannot be excluded by physical examination, especially in patients with a history of angina, syncope, or heart failure. In asymptomatic patients with suspicious murmurs, early diagnosis allows the patient and physician to be more vigilant regarding possible early signs and symptoms.

Although exercise testing is contraindicated in symptomatic patients with aortic stenosis because of the high risk for complications, cautious exercise testing is reasonable in asymptomatic patients to detect latent symptoms or hemodynamic instability that is otherwise unrecognized. Exercise-induced hypotension (>10 mm Hg drop in systolic blood pressure from baseline) or symptoms are indications for aortic valve replacement in patients who have severe aortic stenosis; in patients who have only mild to moderate aortic stenosis, another source of exercise limitation should be sought.

DIAGNOSIS

Echocardiography (Chapter 43) performed in multiple views by an experienced sonographer is the primary modality for confirming the diagnosis of aortic stenosis (Fig. 60-2). Although the visual appearance of the valve leaflets is useful, the assessment of the severity of aortic stenosis relies on Doppler interrogation of the aortic valve. As blood flows from the body of the left ventricle across the stenotic valve, the flow rate must accelerate for the volume to remain constant. Doppler interrogation of the valve can be performed to detect this increase in velocity. If the peak aortic flow velocity is 3.0 m/second or less, symptoms are unlikely to develop in the next 5 years; by comparison, in patients with a flow velocity of 4.0 m/second or greater, symptoms usually develop within 2 years, and when the velocity exceeds 5 m/second, symptoms are likely to develop within 1 year. The modified Bernoulli equation (gradient = $4 \times \text{velocity}^2$) can calculate the peak gradient across the valve and estimate the aortic valve area (Chapter 43). In patients in whom there is discrepancy between the visual appearance of the aortic valve and the calculated valve area, transesophageal echocardiography can measure the valve area directly by tracing its opening, although the measured orifice area should not replace other ways to assess the severity of aortic stenosis.

When echocardiography shows severe aortic stenosis and the patient has one or more of the classic symptoms of the disease, cardiac catheterization to document the severity of the stenosis is not recommended. However, when the

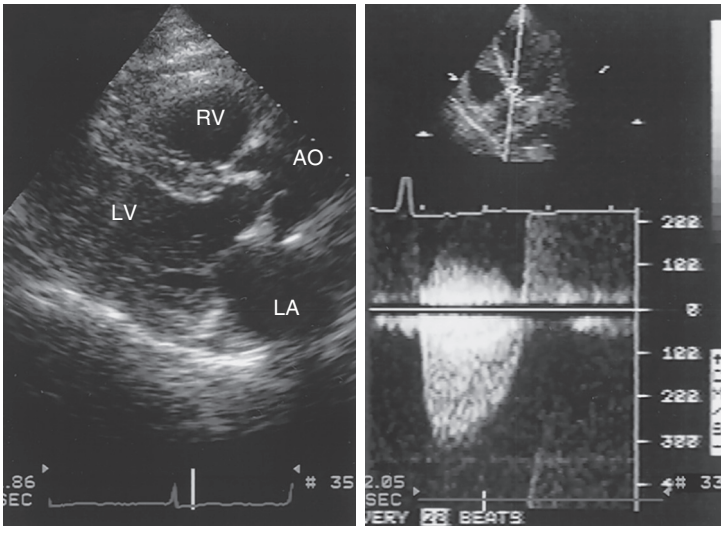

FIGURE 60-2. Doppler echocardiogram from a patient with aortic stenosis. The *left panel* shows thickened aortic valve leaflets that dome into the aorta with restricted opening in systole. The *top right panel* shows a miniaturized apical four-chamber view at the top with a Doppler cursor through the aorta, and the *bottom right panel* shows a continuous-wave spectral Doppler signal with a peak velocity of 3 m/second. The peak valve gradient can be calculated as 4×3^2, or 36 mm Hg. AO = aorta; LA = left atrium; LV = left ventricle; RV = right ventricle. (Courtesy of Dr. Anthony DeMaria.)

hemodynamic diagnosis is unclear, right- and left-sided heart catheterization should be performed to determine the transaortic valvular pressure gradient and cardiac output, which are used to calculate the aortic valve area by the Gorlin formula:

$$A = \frac{CO/SEP \times HR}{44.3\sqrt{h}}$$

where *CO* is the cardiac output (mL/minute), *SEP* is the systolic ejection period (seconds), *HR* is the heart rate, and *h* is the mean gradient. Coronary arteriography is commonly recommended before aortic valve surgery because most patients with aortic stenosis are of the age at which coronary disease is common.

The extent of valve calcification correlates with the severity of aortic stenosis, so quantification of valve calcification by CT scanning can occasionally be helpful. A calcium score greater than 1300 in women or greater than 2000 in men is consistent with severe aortic stenosis.

Brain natriuretic peptide levels may be higher in patients who will become symptomatic in a short time span and also have prognostic importance. Levels exceeding three to four times the normal value portend a poor prognosis and may be a criterion for referral for valve replacement.

The electrocardiogram (ECG) in patients with aortic stenosis usually shows left ventricular hypertrophy (Chapter 48). In some cases of even severe aortic stenosis, however, left ventricular hypertrophy is absent on the ECG, possibly because of the lack of left ventricular dilation. Left atrial abnormality is common because the stiff left ventricle increases left atrial afterload and causes the left atrium to dilate.

The chest radiograph in aortic stenosis is generally nondiagnostic. The cardiac silhouette is not usually enlarged but may assume a boot-shaped configuration. In advanced cases, there may be signs of cardiomegaly and pulmonary congestion; severe aortic valve calcification may be seen in the lateral view.

Low Flow, Low Gradient Aortic Stenosis

Two types of pathophysiology can reduce cardiac output and reduce the aortic gradient, thereby misleading the clinician into underestimating the severity and clinical gravity of aortic stenosis. The first type occurs in patients who have developed systolic dysfunction, typically from valvular heart disease or coronary artery disease. In such patients, the ejection fraction and stroke volume are reduced, as is the transvalvular gradient. Although these patients have a poorer prognosis than do patients with preserved left ventricular function, many still benefit from aortic valve replacement. The second type is patients who have severe left ventricular hypertrophy, which reduces left ventricular volume. Although the ejection fraction is normal, stroke volume and the valve gradient are reduced. Such patients also usually benefit from valve replacement.

In general, the diagnosis of severe aortic stenosis should not rely on a single diagnostic value or test, and current guidelines deemphasize valve area as the single gold standard of severity. Rather, the findings of the physical examination, jet velocity, transvalvular gradient, valve area, biomarkers, and valve calcium should be viewed in their totality.

Mixed Moderate Aortic Stenosis and Regurgitation

Some patients have combined moderate aortic stenosis and regurgitation, with neither condition by itself mandating therapy. However, symptomatic patients with combined moderate stenosis and moderate regurgitation have a prognosis similar to that of patients with pure severe aortic stenosis if their peak aortic jet velocity is 4.0 m/sec or greater. As a result, they should undergo aortic valve replacement.[4]

TREATMENT

Asymptomatic Patients

In asymptomatic patients, no medical treatment has been shown to delay the progression of stenosis, but careful blood pressure control (Chapter 64) is recommended to minimize pressure overload on the left ventricle. Close follow-up is very important to detect early symptoms, especially in elderly patients who may have other reasons to limit their exercise. In patients with severe asymptomatic aortic stenosis, the prognosis is poor, and data suggest that early aortic valve replacement improves outcomes.[A1,A2] For example, valve replacement may be considered in asymptomatic patients who have left ventricular dysfunction with very high jet velocities (>5 m/second), brain natriuretic peptide values three to four times normal, or positive exercise tolerance test results.

Symptomatic Patients

No accepted effective medical therapy is available for symptomatic aortic stenosis, and valve replacement should be performed as expeditiously as possible.[5] In patients who are awaiting surgery, diuretics can be used cautiously to relieve pulmonary congestion and nitrates may be used very cautiously to treat angina pectoris. However, vasodilation reduces pressure distal to the obstruction, often without increasing cardiac output, and may cause syncope. In rare situations in which surgery is impossible, diuretics can improve symptoms but will not improve life expectancy.

Aortic Valve Procedures

Balloon Aortic Valvuloplasty

Percutaneous balloon aortic valvuloplasty, by which a balloon is inserted via the femoral artery and inflated across the aortic valve to increase its mobility, can provide a temporary reduction in the aortic valve gradient for perhaps 6 to 12 months. This palliation may be useful in inoperable patients and is sometimes used in very advanced patients who have low flow and a low left ventricular ejection fraction to determine whether aortic valve replacement may be of benefit.

Valve Replacement Surgery

Surgical aortic valve replacement, which nearly always requires either a mechanical or bioprosthetic valve, is a proven effective therapy for symptomatic aortic stenosis and for selected asymptomatic patients (see earlier). The one exception is young patients with bicuspid valves, in whom the Ross procedure (an autograft by which the patient's own pulmonic valve is transplanted to the aortic portion and a prosthetic pulmonic valve is implanted) is the preferred operation.[6] Even octogenarians benefit from valve replacement unless other comorbid factors preclude surgery, so aortic valve replacement should not be denied simply on the basis of age. Class I indications for aortic valve replacement include the presence of symptoms or severe disease in patients who are undergoing another cardiac operation. Valve replacement also should not be denied because the ejection fraction is reduced, because the excess afterload imposed by the stenotic valve is relieved with valve replacement, and a depressed ejection fraction usually improves dramatically after surgery. The exception to this rule is a patient who has a severely reduced ejection fraction (<20%) and a low aortic valve gradient (<20 mm Hg); in this case, the severity of the aortic stenosis may be overestimated because the failing left ventricle has difficulty opening a mildly to moderately stenotic valve. In such patients, left ventricular dysfunction either has another cause or is often so severe that it does not recover after valve replacement. Even in this situation, however, patients who demonstrate increased cardiac output during dobutamine infusion may benefit from aortic valve replacement.

Transcatheter Aortic Valve Replacement

Percutaneous transcatheter aortic valve implantation[7] reduces the 1-year mortality rate by 45% (from 51 to 31%) in patients who have severe aortic stenosis and are too ill to undergo open surgery. In addition, outcomes, including mortality at up to 5 years, are as good as or better than standard surgical valve replacement in high-risk, intermediate-risk, and low-risk adults,[A3–A7] using either a balloon-expandable or self-expanding prosthesis. In intermediate-risk patients with noncomplex coronary artery disease, a percutaneous valve replacement with coronary stenting is as good as open valve replacement and coronary artery bypass surgery.[A8]

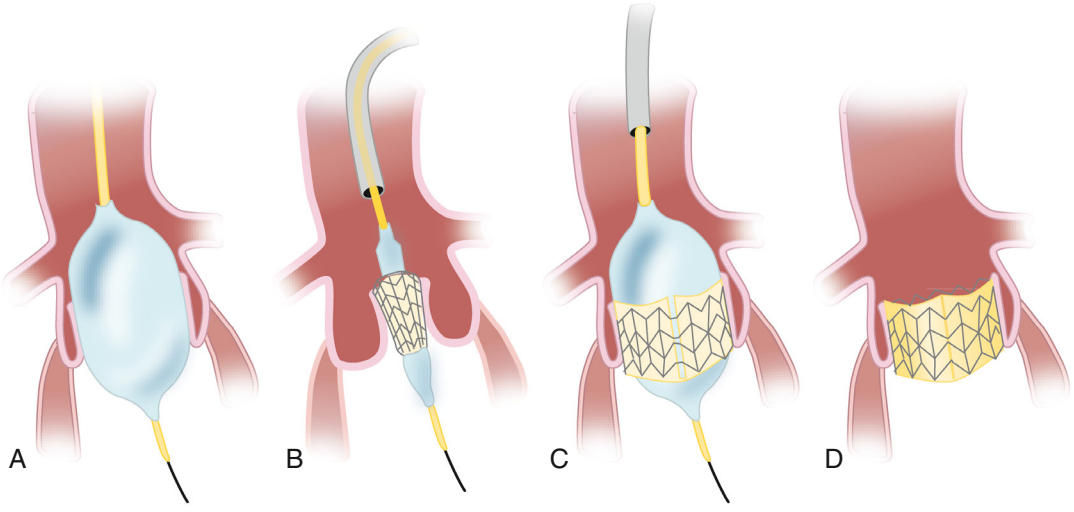

FIGURE 60-3. Steps for transcatheter aortic valve replacement. A, Dilation of the native stenotic valve. **B,** A crimped stented valve has been inserted over a guidewire into the aortic annulus. **C,** Inflation of the balloon deploys the valve. **D,** The balloon is deflated and removed with the aortic valve replaced. (Modified from Cleveland Clinic. Heart valve disease—percutaneous interventions. http://my.clevelandclinic.org/heart/percutaneous/percutaneousValve.aspx.)

It is important to note that major randomized trials of transcatheter aortic valve replacement have been limited to patients who have degenerated tricuspid aortic valves. Emerging data on current devices suggest equivalent outcomes in patients with bicuspid valves or rheumatic aortic disease,[8] but data are limited.

Two types of valves are available throughout much of the world, including the United States. One is a balloon-expandable, a bioprosthetic, stented valve that is crimped onto a balloon catheter, which is advanced across the aortic annulus (Fig. 60-3). The balloon is then inflated to expand the prosthesis and secure it in the native annulus while excluding the diseased valve. In the second type, the tissue valve is sewn into a self-expanding frame and crimped within a delivery catheter, which is advanced across the aortic valve and slowly withdrawn, thereby allowing the prothesis to expand and exclude the diseased valve.

The success of transcatheter aortic valve replacement has resulted in an estimated 100,000 such procedures being performed annually in the United States and exceeding the volume of surgical aortic valve replacement. Rates of stroke are lower with transcatheter aortic valve replacement than with surgical valve replacement; paravalvular regurgitation now occurs rarely. Finally, the rate of structural deterioration of newer transcatheter valves appears to be similar to that of surgical tissue valves, at least in the mid-term. After implantation, 3 months of aspirin alone is preferred over 3 months of dual-antiplatelet therapy in patients who do not have an indication for ongoing anticoagulation.[A9]

PROGNOSIS

In asymptomatic patients with normally functioning or minimally dysfunctional aortic valves, the survival rate is reasonably similar to age-matched control participants, and sudden death is rare, occurring in fewer than 1% of asymptomatic patients. However, mortality is increased with a valve gradient above 20 mm Hg, and about 25% of patients require surgery by 20 years after diagnosis. In adults with asymptomatic but hemodynamically significant aortic stenosis, symptoms typically develop within 5 years. A higher peak aortic jet velocity, heavy valve calcification, a positive exercise test result, severe left ventricular dysfunction, and high brain natriuretic peptide levels predict a worse prognosis and may warrant consideration of valve replacement in asymptomatic patients with severe disease.

The progression of mild to moderate aortic stenosis to severe disease is the key to the natural history of the disease and is quite variable. Aortic stenosis may remain mild for a decade or more in some patients, but it may progress to severe disease in as little as 5 years in other patients.

When symptoms develop, survival declines precipitously. Approximately 35% of patients with aortic stenosis are initially evaluated for angina. Of these, 50% are dead in 5 years unless aortic valve replacement is performed. Approximately 15% have syncope; of these, 50% are dead in only 3 years unless the aortic valve is replaced. Of the 50% with symptoms of heart failure, 50% are dead in 2 years without aortic valve replacement. In all, only 25% of patients with symptomatic aortic stenosis survive 3 years in the absence of valve replacement, and the annual risk for sudden death ranges from 10% in patients with angina to 15% with syncope to 25% with heart failure. After valve replacement surgery, prognosis improves to near normal, especially for patients older than 65 years at the time of valve implantation, presumably because older patients have fewer years at risk for valve-related complications.

MITRAL STENOSIS

EPIDEMIOLOGY

Traditionally the cause of acquired mitral stenosis has been rheumatic heart disease. Although it has become rare in developed countries because of the waning incidence of rheumatic fever, rheumatic mitral stenosis is still prevalent in developing nations, where rheumatic fever is common (Chapter 269). Rheumatic disease is three times more common in women and usually develops in their 40s and 50s. Although the vast majority of mitral stenosis worldwide still results from rheumatic disease, severe age-associated calcification of the mitral annulus and leaflet bases is an increasingly common cause of mitral stenosis in the absence of rheumatic involvement.[9]

PATHOBIOLOGY

At the beginning of diastole, a transient gradient between the left atrium and left ventricle normally initiates left ventricular filling. After early filling, left atrial and left ventricular pressures equilibrate. In mitral stenosis, obstruction to left ventricular filling increases left atrial pressure and produces a persistent gradient between the two chambers (E-Fig. 60-2). The combination of elevated left atrial pressure (and pulmonary venous pressure) and restriction of inflow into the left ventricle limits cardiac output. Although myocardial involvement from the rheumatic process occasionally affects left ventricular muscle function, the muscle itself is normal in most patients with mitral stenosis. However, in approximately one third of patients with mitral stenosis, left ventricular ejection performance is reduced despite normal muscle function because of reduced preload (from inflow obstruction) and increased afterload as a result of reflex vasoconstriction caused by reduced cardiac output.

Because the right ventricle generates most of the force that propels flow across the mitral valve, the right ventricle incurs the pressure overload of the transmitral gradient. In addition, secondary but reversible pulmonary vasoconstriction develops, thus further increasing pulmonary artery pressure and the burden on the right ventricle. As mitral stenosis worsens, right ventricular failure develops.

CLINICAL MANIFESTATIONS

Patients with mitral stenosis usually remain asymptomatic until the valve area is reduced to about one third its normal size of 4 to 5 cm^2. Then the symptoms typical of left-sided failure—dyspnea on exertion, orthopnea, and paroxysmal nocturnal dyspnea—develop. As the disease progresses and right ventricular failure occurs, ascites and edema are common. Hemoptysis, which is common in mitral stenosis but uncommon in other causes of left atrial hypertension, develops when high left atrial pressure ruptures the anastomoses of small bronchial veins. In some cases, a large left atrium may impinge on the left recurrent laryngeal nerve and cause hoarseness (Ortner syndrome) or may impinge on the esophagus and cause dysphagia.

Physical Examination

Although mitral stenosis produces typical and diagnostic findings on physical examination, the diagnosis is missed frequently because the auscultatory

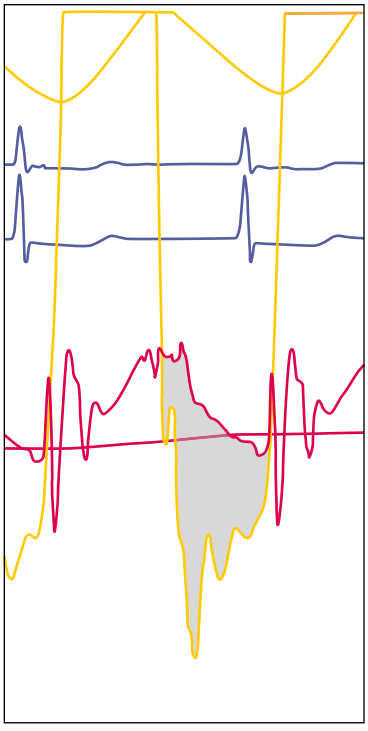

E-FIGURE 60-2. **The gradient (gray area) between left atrial pressure *(red tracing)* and left ventricular pressure *(yellow tracing)* in a patient with severe mitral stenosis.**

findings may be subtle. Palpation of the precordium finds a quiet apical impulse. If pulmonary hypertension and right ventricular hypertrophy have developed, the examiner notes a parasternal lift. S_1 is typically loud and may be the most prominent physical finding of the disease. A loud S_1 is present because the transmitral gradient holds the mitral valve open throughout diastole until ventricular systole closes the fully opened valve with a loud closing sound. In far-advanced disease, the mitral valve may be so damaged, however, that it neither opens nor closes well, so S_1 may become soft. S_2 is normally split; the pulmonic component is increased in intensity if pulmonary hypertension has developed. Left-sided S_3 and S_4 gallop sounds, which represent the ventricular and atrial components of rapid left ventricular filling, are exceedingly rare in mitral stenosis because obstruction at the mitral valve prevents rapid filling. S_2 is usually followed by an opening snap. The distance between S_2 and the opening snap provides a reasonable estimation of left atrial pressure and the severity of the mitral stenosis. The higher the left atrial pressure, the sooner the left atrial pressure and the falling left ventricular pressure of early ventricular relaxation equilibrate. At this equilibration point, the mitral valve opens, and the opening snap occurs. When left atrial pressure is high, the opening snap closely (0.06 second) follows S_2. Conversely, when left atrial pressure is relatively normal, the snap occurs later (0.12 second) and may mimic the cadence of an S_3 gallop. The opening snap is followed by the classic low-pitched early diastolic mitral stenosis rumble, which increases in length as the mitral stenosis worsens. This murmur may be inaudible if the patient has a relatively low resting cardiac output. Modest exercise, such as isometric handgrip, may accentuate the murmur's intensity. If the patient is in sinus rhythm, atrial systole may produce a presystolic accentuation of the murmur. If pulmonary hypertension has developed, the pulmonic component of S_2 increases in intensity to become as loud as or louder than the aortic component. With pulmonary hypertension, a diastolic blowing murmur of pulmonary insufficiency (Graham Steell murmur) is often heard, although in many cases, a coexistent murmur of mild aortic insufficiency is mistaken for this murmur. Neck vein elevation, ascites, and edema are present if right ventricular failure has developed.

DIAGNOSIS

Similar to other valvular lesions, an echocardiogram is the most important diagnostic tool in confirming the diagnosis (Fig. 60-4). Transthoracic echocardiography or, if necessary, transesophageal echocardiography makes the diagnosis in nearly 100% of cases and accurately assesses severity. Mitral stenosis, similar to aortic stenosis, can be quantified by assessing the transvalvular gradient with the modified Bernoulli principle. The stenosis is considered severe when the area is smaller than 1.5 cm^2 and very severe when the valve area is smaller than 1.0 cm^2. It is important to keep in mind that gradients are rate dependent. In patients with poorly controlled atrial fibrillation, gradients will be increased owing to decreased diastolic filling time. Therefore, it is important to assess multiple heart beats or obtain better rate control to assess mitral stenosis properly.

During echocardiography, the suitability of the valve for percutaneous balloon mitral valvotomy also can be assessed. Patients with pliable valves, minimal valvular calcification, limited involvement of the subvalvular apparatus, and less than moderate mitral regurgitation are ideal candidates.

In addition to evaluating the mitral valve, echocardiography can be used to evaluate pulmonary artery pressures by measuring the systolic gradient across the tricuspid valve. The elevation of pulmonary pressures is a poor prognostic sign in mitral stenosis and may drive treatment decisions.

Atrial fibrillation is common, especially in patients older than 50 years of age, but left atrial abnormality is generally present on the ECG if the patient is in sinus rhythm. If pulmonary hypertension has developed, there is often evidence of right ventricular hypertrophy.

On the chest radiograph, left atrial enlargement produces straightening of the left heart border and a double density at the right heart border as a result of the combined silhouettes of the right and left atria. Pulmonary venous hypertension produces increased vascularity. Kerley B lines, which represent thickening of the pulmonary septa secondary to chronic venous engorgement, also may be seen.

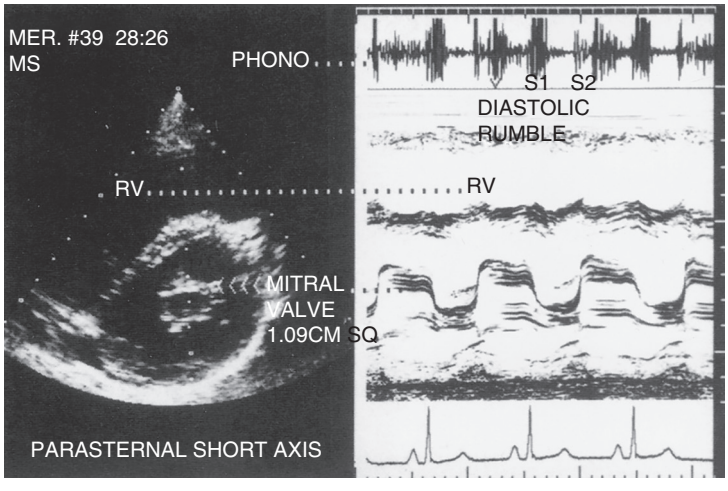

FIGURE 60-4. Mitral stenosis. An *en face* view of a stenotic mitral valve in the short-axis view of the left ventricle is shown on the *left*. Planimetry for the mitral valve orifice yielded an area of 1.09 cm^2. The M-mode echocardiogram on the *right* has been aligned with the appropriate structures on the *left*. It shows the restricted opening of the mitral valve in diastole associated with the classic diastolic rumbling murmur. RV = right ventricle. (From Assey ME, Usher BW, Carabello BA. The patient with valvular heart disease. In: Pepine CJ, Hill JA, Lambert CR, eds. *Diagnostic and Therapeutic Cardiac Catheterization*. 3rd ed. Baltimore: Williams & Wilkins; 1998:709.)

Invasive Evaluation

Cardiac Catheterization

Cardiac catheterization is usually unnecessary to assess the severity of mitral stenosis. Because many patients with mitral stenosis are of an age when coronary disease might be present, however, coronary arteriography is generally performed if cardiac surgery is anticipated or if the patient has coexistent angina. In these cases, it is common to perform left- and right-sided heart catheterization to confirm the transmitral gradient and to calculate the valve area from the Gorlin formula (see earlier).

PREVENTION, TREATMENT, AND PROGNOSIS

Mitral stenosis can be prevented by appropriate antibiotic treatment of β-hemolytic streptococcal infections (Chapter 269).

Medical Therapy

Asymptomatic patients with mitral stenosis and sinus rhythm require no therapy. Symptoms of mild dyspnea and orthopnea can be treated with diuretics alone. When symptoms worsen to more than mild or if pulmonary hypertension develops (resting pulmonary artery systolic pressure > 50 mm Hg), mechanical correction of the stenosis is preferable to medical therapy because it improves longevity in severely symptomatic patients. In patients in whom symptoms are not consistent with resting hemodynamics, exercise testing with either echocardiography or invasive hemodynamic monitoring is reasonable to assess exercise tolerance as well as the expected increases in gradients and pulmonary pressures with exercise.

Patients with mitral stenosis in whom atrial fibrillation develops usually decompensate because the rapid heart rate reduces diastolic filling time, increases left atrial pressure, and decreases cardiac output. The heart rate must be controlled promptly, preferably with an infusion of diltiazem, amiodarone, or esmolol for acute atrial fibrillation or with a β-blocker, a calcium-channel blocker, or oral digoxin in chronic atrial fibrillation (Chapter 52).

Conversion to sinus rhythm is routinely recommended either pharmacologically or with direct-current countershock (Chapter 52) after anticoagulation is therapeutic. It should be noted that patients with rheumatic atrial fibrillation have been excluded from trials of echocardiogram-guided cardioversion without anticoagulation and from trials of rate control versus rhythm control for the chronic management of atrial fibrillation. If sinus rhythm cannot be maintained, mechanical therapy for the mitral stenosis is generally recommended in the hope that sinus rhythm can be restored after the obstruction to atrial outflow is corrected. However, the cause of atrial fibrillation in patients with mitral stenosis probably includes atrial rheumatic inflammation, so restoration of sinus rhythm is unpredictable even after mechanical intervention.

Because patients with concomitant mitral stenosis and atrial fibrillation have an extraordinarily high risk for systemic embolism, they should undergo chronic anticoagulation with warfarin at an international normalized ratio (INR) target of 2.5 to 3.5 unless there is a serious contraindication to its use. It should be noted that atrial fibrillation with rheumatic mitral stenosis or a mechanical heart valve requires vitamin K antagonist anticoagulation instead of direct-acting oral anticoagulants (Chapter 70).

Mechanical Therapy

When symptoms occur with ordinary activity or if pulmonary hypertension develops, prognosis is worse unless the mitral stenosis is relieved. In contrast to aortic stenosis, the valve leaflets are fused at the commissures in mitral stenosis.

As a result, percutaneous balloon dilation produces a commissurotomy, thereby substantially increasing the valve area, and provides improvement comparable to that of open surgical commissurotomy for at least a decade in suitable patients. Even at 20 years, 30% of patients have durable functional benefit. In patients whose anatomy is not suitable for balloon dilation, usually because of significant mitral regurgitation, open surgery with placement of a bioprosthetic or mechanical valve is preferred.

Nonrheumatic mitral stenosis caused by mitral annular calcification does not respond to balloon valvotomy. The only effective mechanical therapy for this condition is surgical debridement of the mitral annulus followed by mitral valve replacement. Because this procedure carries up to a 30% risk, it should be reserved for highly symptomatic patients with an otherwise good life expectancy and performed only by surgeons with experience performing this operation. Clinical trials are ongoing to evaluate the role of transcatheter valve replacement as an option to open surgical therapy in this population.[10]

PRIMARY (ORGANIC) MITRAL REGURGITATION

EPIDEMIOLOGY

The mitral valve is composed of the mitral annulus, the leaflets, the chordae tendineae, and the papillary muscles. Abnormalities in any of these structures may lead to mitral regurgitation. In primary mitral regurgitation, valvular abnormalities cause the valve to leak; the resulting hemodynamic overload, if prolonged and severe, causes left ventricular damage, heart failure, and eventual death if untreated. This condition must be distinguished from secondary or functional mitral regurgitation, wherein disease of the left ventricle causes the valve to leak; this secondary mitral regurgitation is discussed later in this chapter.

The most common cause of primary mitral regurgitation in the United States is mitral valve prolapse, which is responsible for approximately 90% of all cases and comprises many diseases, including myxomatous degeneration of the valve (E-Fig. 60-3). Annular calcification, endocarditis, papillary muscle dysfunction or infarction, collagen vascular disease, and rheumatic heart disease are less common causes. Dopamine receptor agonists such as pergolide, cabergoline and ergot derivatives and serotonin receptor agonists such as fenfluramine when used in high doses and for prolonged periods of time may lead to mitral regurgitation.

Primary mitral regurgitation can be subdivided on the basis of chronicity. Common causes of severe acute mitral regurgitation include ruptured chordae tendineae and infective endocarditis. Chronic severe mitral regurgitation is more likely to be caused by myxomatous degeneration of the valve, rheumatic heart disease, or annular calcification.[11]

PATHOBIOLOGY

The pathophysiology of mitral regurgitation can be divided into three phases (Fig. 60-5). In acute mitral regurgitation of any cause, the sudden option for ejection of blood into the left atrium "wastes" a portion of the left ventricular stroke volume as backward rather than forward flow. The combined regurgitant and forward flow causes volume overload of the left ventricle and stretches the existing sarcomeres toward their maximum length. Use of the Frank-Starling mechanism is maximized, and end-diastolic volume increases concomitantly. The regurgitant pathway unloads the left ventricle in systole because it allows ejection into the relatively low-impedance left atrium and thereby reduces end-systolic volume. Although increased end-diastolic volume and decreased end-systolic volume act in concert to increase total stroke volume, forward stroke volume is subnormal because a large portion of the total stroke volume is regurgitated into the left atrium. This regurgitant volume increases left atrial pressure, so the patient experiences heart failure with low cardiac output and pulmonary congestion despite normal left ventricular contractile function.

In many cases, severe acute mitral regurgitation necessitates emergency surgical correction. By comparison, patients who can be managed through the acute phase or in whom the valve abnormalities develop more slowly may enter the phase of hemodynamic compensation. In this phase, eccentric left ventricular hypertrophy and increased end-diastolic volume, combined with normal contractile function, allow ejection of a sufficient total stroke volume to permit forward flow to return toward normal. At the same time, left atrial enlargement allows accommodation of the regurgitant volume while maintaining a lower left atrial pressure. In this phase, the patient may be relatively asymptomatic even during strenuous exercise. Although mitral regurgitation is often thought to reduce left ventricular afterload, reduced afterload occurs only in acute, severe, primary mitral regurgitation. In the chronic phase, the increased left ventricular radius returns afterload (wall stress) to normal, and impedance is decreased only in the most severe cases.

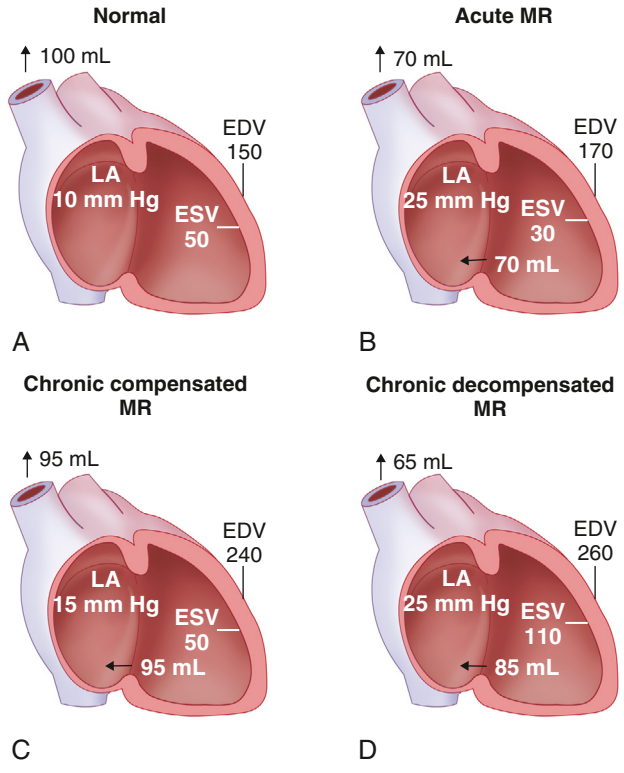

	Preload SL (μ)	Afterload ESS (kdyne/cm^2)	CF	EF	RF	FSV (mL)
N	2.07	90	N	.67	.0	100
AMR	2.25	60	N	.82	.50	70
CCMR	2.19	90	N	.79	.5	95
CDMR	2.19	120	↓	.58	.57	65

FIGURE 60-5. Mitral regurgitation (MR). Normal physiology (N) **(A)** is compared with the physiology of acute mitral regurgitation (AMR) **(B)**. Acutely, the volume overload increases preload (sarcomere length [SL]), and end-diastolic volume (EDV) increases from 150 to 170 mL. Unloading of the left ventricle (LV) by the presence of the regurgitant pathway decreases afterload (end-systolic stress [ESS]), and end-systolic volume (ESV) falls from 50 to 30 mL. These changes result in an increase in the ejection fraction (EF). Because 50% of the total LV stroke volume (regurgitant fraction [RF]) is ejected into the left atrium (LA), however, forward stroke volume (FSV) falls from 100 to 70 mL. At this stage, contractile function (CF) is normal. **C,** Chronic compensated mitral regurgitation (CCMR). In CCMR, eccentric cardiac hypertrophy has developed, and EDV has increased substantially. Increased EDV, combined with normal contractile function, permits ejection of a larger total stroke volume and a larger forward stroke volume than in the acute phase. Left atrial enlargement permits lower left atrial pressure. Because the radius term in the Laplace equation has increased with increasing LV volume, afterload and ESV return to normal. **D,** Chronic decompensated mitral regurgitation (CDMR). In this stage, contractile dysfunction causes a large increase in ESV with a fall in total and forward stroke volume. Additional LV enlargement leads to worsening mitral regurgitation. The relatively favorable loading conditions in this phase still permit a normal EF, however, despite contractile dysfunction. (From Carabello BA. Mitral regurgitation: basic pathophysiologic principles. *Mod Concepts Cardiovasc Dis*. 1988;57:53-57.)

Although severe mitral regurgitation may be tolerated for many years, the lesion often causes left ventricular dysfunction, atrial fibrillation, or heart failure within 5 years of the detection of severe mitral regurgitation. The now damaged ventricle has impaired ejection performance, and end-systolic volume increases. Greater left ventricular residual volume at end systole increases end-diastolic volume and end-diastolic pressure, and the symptoms of pulmonary congestion may reappear. Additionally, left ventricular dilation may worsen the amount of regurgitation by causing further enlargement of the mitral annulus and displacement of the papillary muscles, thereby leading to malcoaptation of the mitral leaflets. Although there is substantial contractile dysfunction, the increased preload and the presence of the regurgitant pathway, which mitigates the increased afterload expected from ventricular enlargement, augment the ejection fraction and may maintain it in a relatively normal range.

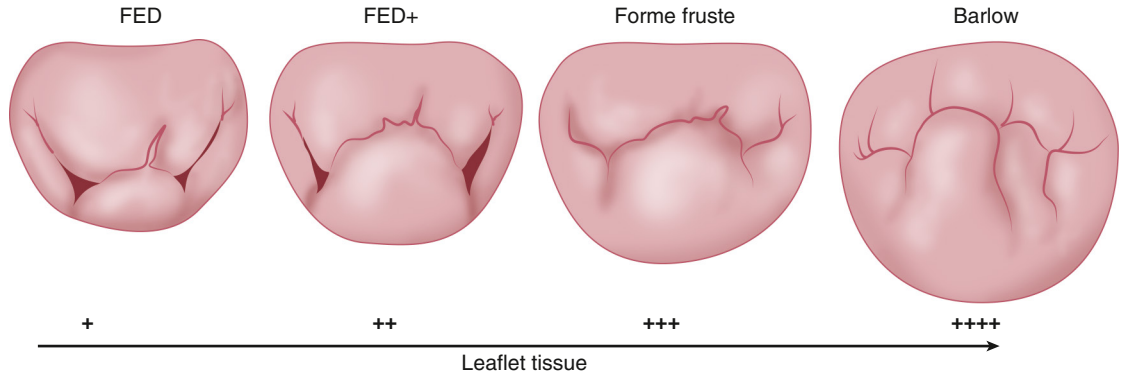

E-FIGURE 60-3. **Pathology specimens of myxomatous degeneration of the mitral valve showing the progression of disease from its simplest form (fibroelastic deficiency [FED]) to more extensive FED (FED+) to the early stages of a Barlow-type valve (forme fruste) to the highly redundant Barlow type valve.** (From Adams DH, Rosenhek R, Falk V. Degenerative mitral valve regurgitation: best practice revolution. *Eur Heart J*. 2010;31:1958-1966.)

The causes of left ventricular contractile dysfunction in patients with mitral regurgitation may relate to loss of contractile proteins and abnormalities in calcium handling. In at least some cases, contractile dysfunction is reversible by timely mitral valve surgery.

CLINICAL MANIFESTATIONS

In the medical history, the standard symptoms of left-sided heart failure should be sought (Chapter 45). An attempt to discover potential causes should be made by questioning for a history of a heart murmur or abnormal findings on cardiac examination (Chapter 39), rheumatic heart disease, endocarditis (Chapter 61), or the use of anorexigenic drugs.

Volume overload of the left ventricle displaces the apical impulse downward and to the left. S_1 may be reduced in intensity, whereas S_2 is usually physiologically split. In severe mitral regurgitation, S_2 is followed by S_3, which may not indicate heart failure but reflects rapid filling of the left ventricle by the large volume of blood stored in the left atrium during systole. The typical murmur of mitral regurgitation is a holosystolic apical murmur that often radiates toward the axilla (Chapter 39). There is a rough correlation between the intensity of the murmur and the severity of the disease, but this correlation is too weak to use in clinical decision making because the murmur may be soft when cardiac output is low. In contrast to aortic stenosis, murmur intensity does not usually vary with the RR interval. In acute mitral regurgitation, the presence of a large v wave may produce rapid equilibration of left atrial and left ventricular pressure, thereby reducing the driving gradient and shortening the murmur. Pulmonary hypertension may develop and produce right-sided signs, including an right ventricular lift, an increased P_2, and, if right ventricular dysfunction has developed, signs of right-sided heart failure.

DIAGNOSIS

The ECG usually shows left ventricular hypertrophy and left atrial abnormality. The chest radiograph typically shows cardiomegaly; the absence of cardiomegaly indicates either that the mitral regurgitation is mild or that it has not been chronic enough to allow cardiac dilation to occur.

Echocardiography shows the extent of left atrial and left ventricular enlargement (Chapter 43). Ultrasonic imaging of the mitral valve is excellent and offers clues to the mitral valve abnormalities responsible for the regurgitation. In some patients, three-dimensional echocardiography can add pathoanatomic information of potential use in aiding surgical repair of the valve. Color-flow Doppler interrogation of the valve (Fig. 60-6) helps assess the severity of regurgitation, but because this technique images flow velocity rather than actual flow, it is subject to errors in interpretation. The Doppler technique is excellent for excluding the presence of mitral regurgitation and for distinguishing between mild and severe degrees. Newer techniques may quantify regurgitation more precisely but are not applicable in every patient,

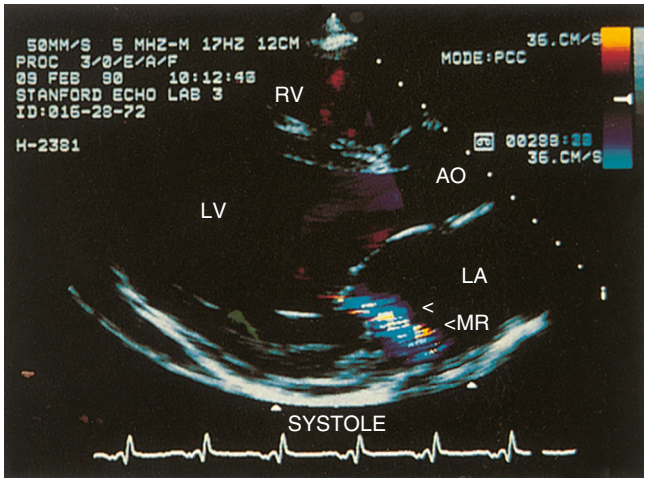

FIGURE 60-6. Two-dimensional echocardiogram of mitral regurgitation with Doppler flow mapping superimposed on a portion of the image. The color information is represented in the sector of the imaging plane extending from the apex of the triangular plane to the two small *arrowheads* at the *bottom* of the image plane. Mitral regurgitation (MR) is indicated *(open arrows)* and extends from the mitral valve leaflets toward the posterior aspect of the left atrium (LA) during systole. The mosaic of colors representing the mitral regurgitant signal is typical of high-velocity turbulent flow. The low-intensity *orange-brown* signal represents flow directed away from the transducer on the chest wall, and the *blue* shades represent blood in the left ventricular outflow tract moving toward the transducer. AO = aorta; LV = left ventricle; RV = right ventricle.

and standard color-flow Doppler examination may not be sufficient for exact quantification of mitral regurgitation or to determine whether the severity of the lesion is sufficient to cause eventual left ventricular dysfunction. Cardiac MRI (Chapter 44), when available, can more precisely quantify the severity of the regurgitation. When the severity of mitral regurgitation is in doubt or if mitral valve surgery is being contemplated, cardiac catheterization (Chapter 59) can be helpful in resolving the severity of the lesion; coronary arteriography should be included in patients older than 40 years or with symptoms suggesting coronary disease (Chapter 56).

TREATMENT AND PROGNOSIS

Medical Therapy

Severe Acute Mitral Regurgitation

In severe acute mitral regurgitation, the patient is usually symptomatic with heart failure or even shock. The goal of medical therapy is to increase forward cardiac output while concomitantly reducing regurgitant volume (Chapter 46). Arterial vasodilators reduce systemic resistance to flow and preferentially increase aortic outflow and simultaneously decrease the amount of mitral regurgitation and left atrial hypertension. If hypotension already exists, vasodilators such as nitroprusside lower blood pressure further and cannot be used. In these cases, intra-aortic balloon counterpulsation (Chapter 93) is preferred if the aortic valve is competent. Counterpulsation increases forward cardiac output by lowering ventricular afterload while augmenting systemic diastolic pressure.

Chronic Symptomatic Mitral Regurgitation

In patients with *symptomatic* mitral regurgitation, angiotensin-converting enzyme (ACE) inhibitors (e.g., lisinopril, 20 mg/day) reduce left ventricular volume and improve symptoms but do not alter outcome and are reserved for inoperable patients. Observational evidence suggests that such patients may benefit from administration of β-blockers. Mitral valve surgery rather than medical therapy is indicated in most symptomatic patients with mitral regurgitation. When atrial fibrillation is present, anticoagulation is indicated.

Chronic Asymptomatic Mitral Regurgitation

Vasodilators have had little effect in reducing left ventricular volume or improving normal exercise tolerance in patients with mitral regurgitation, perhaps because afterload is not usually increased in chronic asymptomatic mitral regurgitation, so there is no definitive indication to begin afterload reduction before symptoms appear. However, hypertension, if present, should be treated with standard guideline-directed therapy (Chapter 64).

Surgical Therapy

The timing of mitral valve surgery must weigh the risks of the operation and placement of a prosthesis, if one is inserted, against the risk for irreversible LV dysfunction if surgery is delayed unwisely. In patients with mitral regurgitation, the native valve often can be repaired, and this option may influence the patient and physician towards earlier surgery.

Types of Mitral Valve Surgery

Mitral Valve Repair

When feasible, mitral valve repair (Fig. 60-7) is the preferred operation.[12] Repair restores valve competence, maintains the functional aspects of the apparatus, and avoids the insertion of a prosthesis. Repair is most applicable in cases of posterior chordal rupture; anterior involvement and rheumatic involvement make repair more difficult. Currently, the percentage of mitral valve surgeries that are valve repair average about 70% across the United States overall, with outcomes that are highly dependent on the skill and experience of the operating physician.

Percutaneous mitral valve repair, with implantation of a clip device via the femoral vein and a transseptal puncture, is less invasive than conventional mitral valve repair but is also less effective than open surgery for eliminating mitral regurgitation.[A10] Percutaneous repair, which is approved in the United States for primary mitral regurgitation in symptomatic patients who are at high risk for surgery, usually leaves the patient with mild to moderate residual regurgitation that does not usually worsen over time.[13]

Mitral Valve Replacement with Preservation of the Mitral Apparatus

In this procedure, a prosthetic valve is inserted, but continuity between the native leaflets and the papillary muscles is maintained. This procedure has the advantage of ensuring mitral valve competence while preserving the functional aspects of the mitral apparatus in the left ventricle. Even if only the posterior leaflets and chordae are preserved, the patient benefits from improved postoperative ventricular function and possibly better survival. Although the patient benefits from restored mitral valve competence and maintenance of left ventricular function, insertion of a prosthesis still carries all prosthesis-associated risks. Operative mortality with all mitral valve replacement operations is at least twice as high as with mitral valve repair.

Mitral Valve Replacement without Preservation of the Mitral Apparatus

When the native valve cannot be repaired or the chordae preserved, such as in severe rheumatic deformity, the mitral valve leaflets and its apparatus are

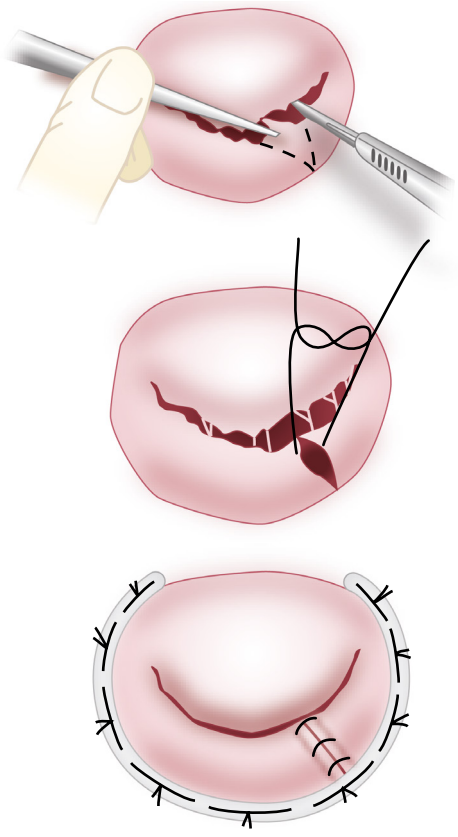

FIGURE 60-7. The stages of mitral valve repair. (Modified from Cleveland Clinic. Mitral valve repair. http://my.clevelandclinic.org/heart/disorders/valve/mvrepair.aspx.)

removed and a prosthetic valve is inserted. Although this operation almost guarantees mitral valve competence, the mitral valve apparatus is responsible for coordinating left ventricular contraction and for helping maintain the efficient prolate ellipsoid shape of the left ventricle. Destruction of the apparatus leads to a sudden fall in left ventricular function and a decline in postoperative ejection fraction that is often permanent.

Transcatheter Mitral Valve Replacement

Transcatheter mitral valve replacement has been used especially in patients who are unsuitable for repair, such as patients who have severe mitral annular calcification and have an extremely high operative risk.[14] Although the technical success rate has been promising, the procedure is still experimental.

Timing of Surgery

Symptomatic Patients

Most patients with symptoms of dyspnea, orthopnea, or fatigue should undergo surgery regardless of which operation is performed because they already have lifestyle limitations from their disease. The mere presence of symptoms worsens the prognosis despite relatively well-preserved left ventricular function. The onset or worsening of symptoms is a summary of the patient's pathophysiology and may give a broader view of cardiovascular integrity than possible with any single measurement of pressure or function. For patients with acute mitral regurgitation owing to flail mitral valve leaflets, earlier surgery appears to be better than prolonged medical management, but randomized trials have not been performed.

Asymptomatic Patients with Normal Left Ventricular Function

Surgery has increasingly been considered in asymptomatic patients who have normal left ventricular function but echocardiographic findings indicating that valve repair is likely to be successful. Although these patients are at low risk with continued medical therapy, early surgery reduces the risks of subsequent left ventricular dysfunction or atrial fibrillation and should be considered if the risk associated with valve repair is less than 1% because lifespan can be normal if successful repair is performed before left ventricular dysfunction has developed. This approach is sensible, however, only if it is certain that valve repair can be performed, because insertion of a prosthesis carries unacceptable risk in this low-risk group.

Asymptomatic Patients with Left Ventricular Dysfunction

The onset of left ventricular dysfunction in patients with mitral regurgitation may occur without causing symptoms. Early surgery is warranted to prevent the muscle dysfunction from becoming severe or irreversible. Regardless of whether valve repair or replacement is eventually performed, survival is prolonged if surgery is performed before the ejection fraction declines to less than 60% or the left ventricular end-systolic dimension increases beyond 40 mm. Elevated brain natriuretic peptide levels and deterioration of global longitudinal strain also may be considered as adjuncts to the decision for surgery. Patients with severe mitral regurgitation should be monitored yearly with a history, physical examination, and echocardiographic evaluation of left ventricular function. When the patient reports symptoms or echocardiography shows the onset of left ventricular dysfunction, surgery should be undertaken. However, it is not necessary to wait until these thresholds are reached to recommend surgery. If it is clear that valve repair is highly likely and the patient is approaching these indications for intervention, surgery should be considered at that time.

Asymptomatic Elderly Patients

Among Medicare recipients, the operative mortality rate is 4% for patients undergoing mitral valve repair and 9% for patients undergoing replacement. Even in patients who have no comorbid conditions, the mortality rates are 2% for repair and 4% for replacement. Patients older than 75 years of age may have poorer surgical results than younger patients, especially if coronary disease is present or if mitral valve replacement rather than repair must be performed. As a result, there is little compelling reason to commit elderly asymptomatic patients to a mitral valve operation.

MITRAL VALVE PROLAPSE

DEFINITION

Mitral valve prolapse occurs when one or both of the mitral valve leaflets prolapse during systole beyond the mitral valve annular plane and into the left atrium. The importance of mitral valve prolapse varies from patient to patient. In some cases, prolapse is simply a consequence of normal left ventricular physiology without significant medical impact, such as in situations that produce a small left ventricle (e.g., the Valsalva maneuver or an atrial septal defect), in which reduction of ventricular volume causes relative lengthening of the chordae tendineae and subsequent mitral valve prolapse. At the other end of the spectrum, severe redundancy and deformity of the valve, which occur in myxomatous valve degeneration, increase the risk for stroke, arrhythmia, endocarditis, and progression to severe mitral regurgitation.[15]

DIAGNOSIS

History

Most patients with mitral valve prolapse are asymptomatic. In some cases, however, mitral valve prolapse is associated with symptoms, including palpitations, syncope, and chest pain. In some cases, chest pain indicates true myocardial ischemia despite normal epicardial coronary arteries, perhaps because excessive tension on the papillary muscles increases oxygen consumption. Palpitations, syncope, and presyncope, when present, are linked to autonomic dysfunction (Chapters 39, 49, and 386), which appears to be more prevalent in patients with mitral valve prolapse.

Physical Examination

On physical examination, the mitral valve prolapse syndrome produces the characteristic findings of a midsystolic click and a late systolic murmur. The click occurs when the chordae tendineae are stretched taut by the prolapsing mitral valve in mid-systole. As prolapse occurs, the mitral leaflets move past their coaptation point, permit mitral regurgitation, and cause the late systolic murmur (see Table 39-7 in Chapter 39). Maneuvers that make the left ventricle smaller, such as the Valsalva maneuver, cause the click to appear earlier and the murmur to be more holosystolic and often louder (see Table 39-8 in Chapter 39). In some cases of echocardiographically proven mitral valve prolapse, neither the click nor the murmur is present; in other cases, only one of these findings is present.

Noninvasive Evaluation

Echocardiography is useful to prove that prolapse is present, to image the amount of regurgitation and its physiologic effects, and to discern the pathoanatomy of the mitral valve. Although an echocardiogram is not necessary to diagnose prolapse in patients with the classic physical findings, the echocardiogram adds significant prognostic information because it can detect patients who have specifically abnormal valve morphology and in whom most of the complications of the disease occur.

TREATMENT

Because most cases of mitral valve prolapse are asymptomatic, therapy is usually unnecessary and prophylaxis against infective endocarditis is not recommended (Chapter 61). In patients with palpitations and autonomic dysfunction, β-blockers are often effective in relieving symptoms. If severe mitral regurgitation or a flail mitral leaflet develops, the therapy is the same as for other causes of mitral regurgitation. If surgical valve repair is chosen, leaflet preservation and leaflet resection provide equivalent results.[A11]

PROGNOSIS

Most patients with mitral valve prolapse, even patients with redundant and misshapen mitral leaflets, have a benign clinical course. Approximately 10% of patients with thickened leaflets experience infective endocarditis, stroke, progression to severe mitral regurgitation, or sudden death. The progression to severe mitral regurgitation varies with gender and age, and men are approximately twice as likely to progress as women. By 50 years of age, only approximately 1 in 200 men requires surgery to correct mitral regurgitation. By the age of 70 years, the risk increases to approximately 3%.

SECONDARY (FUNCTIONAL) MITRAL REGURGITATION

DEFINITION

Secondary or functional mitral regurgitation is a very different disease than primary mitral regurgitation. In primary mitral regurgitation, treating the mitral regurgitation cures the patient. Conversely, secondary mitral regurgitation is typically a consequence of left ventricular myocardial dysfunction, usually caused by myocardial infarction or dilated cardiomyopathy,[16] but sometimes occurs when atrial fibrillation results in annular dilatation and leaflet malcoaptation.[17] Because treating secondary mitral regurgitation cannot reverse those entities, the role of valve therapy is often unclear.

EPIDEMIOLOGY

An estimated 6 million Americans have heart failure (Chapters 45 and 46), and about half of them have heart failure with a reduced ejection fraction. About 75% of these latter patients also have some degree of secondary mitral regurgitation, which is severe in about 20% of them.

PATHOBIOLOGY

In secondary mitral regurgitation, the valve itself is normal. Regurgitation occurs because of leaflet malcoaptation that results from either displacement of the papillary muscles in patients with left ventricular dysfunction or annular dilatation in patients with atrial fibrillation. Mitral closing is further impaired by mitral annular dilation and reduced closing force from the weakened myocardium.

CLINICAL MANIFESTATIONS

Because virtually all patients with secondary mitral regurgitation have heart failure, almost all complain of the symptoms of heart failure. Some may note a worsening of symptoms when more than mild secondary mitral regurgitation develops. Probably because the mitral valve itself is normal, as well as because of the weakened force of contraction, the murmur of functional mitral regurgitation may be unimpressive or even inaudible.

DIAGNOSIS

Echocardiography is the mainstay of the diagnosis. In addition to evaluating the severity of the mitral regurgitation itself, the echocardiogram is helpful in establishing the extent of the dilated cardiomyopathy or of the prior myocardial infarction that is responsible for causing the secondary mitral regurgitation.

TREATMENT AND PROGNOSIS

The presence of mitral regurgitation in patients with systolic dysfunction is associated with worsened prognosis, which in turn probably reflects both poorer left ventricular function and the imposition of an extra volume overload on an already weakened left ventricle.

Because almost all patients with secondary mitral regurgitation have heart failure, the primary treatment is standard treatment for heart failure (Chapter 46). For secondary functional mitral regurgitation owing to heart failure with left ventricular dilation, the combination of sacubitril/valsartan (49/51 mg twice daily, titrated as tolerated at 4-week intervals to a maximum dose of 97/103 mg twice daily) is better than valsartan alone for reducing regurgitation.[A12] Many patients with secondary mitral regurgitation also have conducting system abnormalities, and patients with left bundle branch block may benefit from cardiac resynchronization therapy (Chapters 46 and 54), which improves systolic function while often reducing secondary mitral regurgitation, sometimes even eliminating it. When these therapies fail to relieve symptoms, surgical treatment can be considered.[18]

For severe *ischemic mitral regurgitation*, mitral valve repair and chordal-sparing mitral valve replacement provide equivalent clinical outcomes at 1 and 2 years, although replacement results in less residual mitral regurgitation and is associated with less severe heart failure, fewer heart failure–related adverse events, and fewer cardiovascular admissions.[A13] For moderate ischemic mitral regurgitation, mitral valve repair does not clearly add benefit above and beyond the benefits of coronary artery bypass surgery.[A14]

For *mitral regurgitation secondary to heart failure*, several studies have shown percutaneous mitral repair to be no better than optimal medical therapy[A15] or open surgery,[A16] but one trial demonstrated better survival than medical therapy.[A17] However, the average survival rate at 5 years is about 50%, and this figure has not changed much over the past several decades.

AORTIC REGURGITATION

DEFINITION

Aortic regurgitation is caused either by abnormalities of the aortic leaflets or by abnormalities of the proximal aortic root. Leaflet abnormalities causing aortic regurgitation include a bicuspid aortic valve, infective endocarditis, and rheumatic heart disease. Dopamine receptor agonists and serotonin receptor agonists have also been implicated. Common aortic root abnormalities that cause aortic regurgitation include Marfan syndrome (Chapter 239), hypertension-induced annuloaortic ectasia, aortic dissection (Chapter 63), syphilis (Chapter 295), ankylosing spondylitis (Chapter 244), and psoriatic arthritis (Chapter 244). Acute aortic regurgitation is usually caused by infective endocarditis (Chapter 61) or aortic dissection.

PATHOBIOLOGY

As with mitral regurgitation, aortic regurgitation imparts a volume overload on the left ventricle because it must pump the forward flow entering from the left atrium and the regurgitant volume returning through the incompetent aortic valve. Also as with mitral regurgitation, the volume overload is compensated for by the development of eccentric cardiac hypertrophy, which increases chamber size and allows the ventricle to pump a greater total stroke volume and a greater forward stroke volume. Ventricular enlargement also accommodates the volume overload at a lower filling pressure. Because pulse pressure is proportional to stroke volume and elastance of the aorta, the increased stroke volume increases systolic pressure. Systolic hypertension leads to afterload excess, which does not generally occur in mitral regurgitation. Accordingly, ventricular geometry also differs between mitral and aortic regurgitation because the afterload excess in aortic regurgitation causes a modest element of concentric hypertrophy, as well as severe eccentric hypertrophy.

In acute aortic insufficiency, such as might occur in infective endocarditis, severe volume overload of the previously unprepared left ventricle results in a sudden fall in forward output while precipitously increasing left ventricular filling pressure. It is probably this combination of pathophysiologic factors that leads to rapid decompensation, presumably because the severely diminished gradient for coronary blood flow causes ischemia and progressive deterioration in left ventricular function. In acute aortic insufficiency, reflex vasoconstriction increases peripheral vascular resistance. In compensated chronic aortic insufficiency, vasoconstriction is absent, and vascular resistance may be reduced and contribute to the hyperdynamic circulation observed in these patients.

CLINICAL MANIFESTATIONS

The most common symptoms from chronic aortic regurgitation are those of left-sided heart failure (Chapter 45); that is, dyspnea on exertion, orthopnea, and fatigue. In acute aortic regurgitation, cardiac output and shock may develop rapidly. The onset of symptoms in patients with chronic aortic regurgitation usually heralds the onset of left ventricular systolic dysfunction. Some patients with symptoms have apparently normal systolic function, however, and the symptoms may be attributed to diastolic dysfunction. Other patients may have ventricular dysfunction yet remain asymptomatic.

Angina may also occur in patients with aortic insufficiency but less commonly than in patients with aortic stenosis. Coronary blood flow reserve is reduced in some patients because diastolic runoff into the left ventricle lowers aortic diastolic pressure while increasing left ventricular diastolic pressure; these two influences lower the driving pressure gradient for flow across the coronary

bed. When angina occurs in aortic regurgitation, it may be accompanied by flushing. Other symptoms include carotid artery pain and an unpleasant awareness of the heartbeat.

DIAGNOSIS

Physical Examination

Chronic aortic regurgitation produces a myriad of signs because a hyperdynamic, enlarged left ventricle ejects a large stroke volume at high pressure into the systemic circulation. Palpation of the precordium finds a hyperactive apical impulse displaced downward and to the left. S_1 and S_2 are usually normal. S_2 is followed by a diastolic blowing murmur heard best along the left sternal border with the patient sitting upright. In mild disease, the murmur may be short and heard only in the beginning of diastole when the gradient between the aorta and the left ventricle is highest. As the disease worsens, the murmur may persist throughout diastole. A second murmur, a mitral valve rumble, is heard at the left ventricular apex in patients with severe aortic insufficiency. Although the cause is still debated, this Austin Flint murmur is probably produced as the regurgitant jet impinges on the mitral valve and causes it to vibrate.

In chronic aortic regurgitation, the high stroke volume and reduced systemic arterial resistance result in a wide pulse pressure, which may generate a number of signs, including Corrigan pulse (sharp upstroke and rapid decline of the carotid pulse), de Musset sign (head bobbing), Duroziez sign (combined systolic and diastolic bruits created by compression of the femoral artery with the stethoscope), and Quincke pulse (systolic plethora and diastolic blanching in the nail bed when gentle traction is placed on the nail). Perhaps the most reliable of physical signs indicating severe aortic regurgitation is Hill sign, an increase in femoral systolic pressure of 40 mm Hg or more compared with systolic pressure in the brachial artery.

In contrast to chronic aortic insufficiency with its myriad clinical signs, acute aortic insufficiency may have a subtle manifestation. The eccentric hypertrophy, which compensates for chronic aortic insufficiency, has not yet had time to develop, and the large total stroke volume responsible for most of the signs of chronic aortic insufficiency is absent. The only clues to the presence of acute aortic insufficiency may be a short diastolic blowing murmur and reduced intensity of S_1. This latter sign occurs because high diastolic left ventricular pressure closes the mitral valve early in diastole (mitral valve preclosure) so that when ventricular systole occurs, only the tricuspid component of S_1 is heard.

Noninvasive Evaluation

The ECG in patients with aortic insufficiency is nonspecific but almost always demonstrates left ventricular hypertrophy. The chest radiograph shows an enlarged heart, often with uncoiling and enlargement of the aortic root.

Echocardiography (Chapter 43) is the most important noninvasive tool for assessing the severity of aortic insufficiency and its impact on left ventricular geometry and function (Fig. 60-8). During echocardiography, the left ventricular end-diastolic dimension, end-systolic dimension, and fractional shortening are determined. Aortic valve anatomy and aortic root anatomy can be assessed, and the cause of the aortic regurgitation often can be determined. Color-flow Doppler examination of the aortic valve helps quantify the severity of aortic regurgitation by assessing the depth and width to which the diastolic jet penetrates the left ventricle. Another way to assess the severity of aortic regurgitation is the pressure half-time method: continuous-wave Doppler interrogation of the aortic valve displays the decay of the velocity of retrograde flow across the valve. In mild aortic insufficiency, the gradient across the valve is high throughout diastole, and its rate of decay is slow, with production of a long Doppler half-time (the time that it takes the velocity to decay from its peak to that value divided by the square root of 2). In severe aortic regurgitation, pressure in the aorta and pressure in the left ventricle equilibrate rapidly, and the Doppler half-time is short. In cases in which the severity of aortic insufficiency is in doubt, MRI can quantify regurgitant flow or catheterization with aortography can visualize regurgitant flow to resolve the issue.

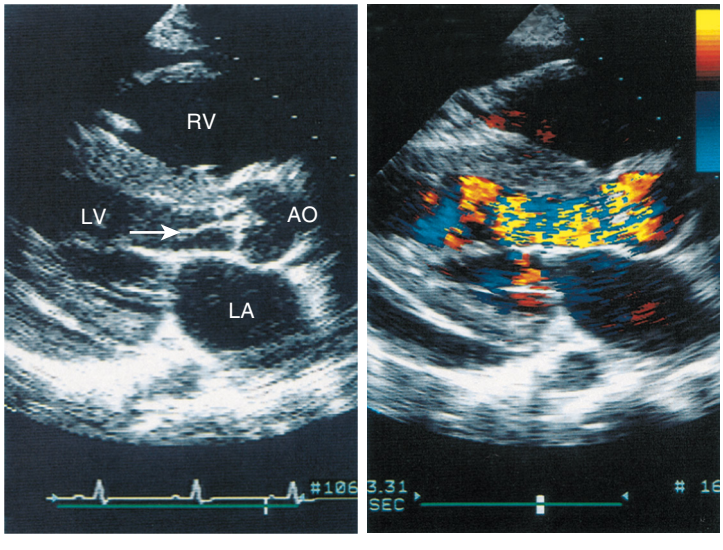

FIGURE 60-8. Echocardiogram of a patient with aortic regurgitation caused by infective endocarditis. The *left panel* shows a linear vegetation *(arrow)* prolapsing into the left ventricular (LV) outflow tract from the aortic valve leaflet in diastole. The *right panel* is a color-flow Doppler image exhibiting turbulent blood flow filling the LV tract during diastole. AO = aorta; LA = left atrium; RV = right ventricle. (Courtesy of Dr. Anthony DeMaria.)

TREATMENT AND PROGNOSIS

Acute Aortic Regurgitation

When any of the symptoms or signs of heart failure develop, even if mild, the medical mortality rate is high and approaches 75%. Echocardiographic evidence of preclosure of the mitral valve from high diastolic intracavitary left ventricular pressure is an especially ominous sign and an indication for urgent surgery. Therapy with vasodilators, such as nitroprusside, may temporarily improve the patient's condition before surgery but is never a substitute for surgery. In patients with acute aortic regurgitation caused by bacterial endocarditis (Chapter 61), surgery may be delayed to permit a full or partial course of antibiotics, but persistent, severe aortic regurgitation requires emergency valve replacement. Even when blood cultures have been positive recently and antibiotic therapy has been of brief duration, the valve reinfection rate is low, 0 to 10%, with valve replacement or valve repair. Emergency surgery should not be withheld simply because the duration of antibiotic therapy has been brief.

Chronic Aortic Regurgitation

Asymptomatic Patients

Because aortic regurgitation increases left ventricular afterload, which decreases cardiac efficiency, afterload reduction with nifedipine and other vasodilators, including ACE inhibitors, improves hemodynamics in the short term but does not reliably delay or reduce the need for aortic valve surgery. When hypertension accompanies aortic regurgitation, it should be treated according to standard guidelines (Chapter 64).

Asymptomatic patients who manifest evidence of left ventricular dysfunction benefit from surgery. When the left ventricular ejection fraction is less than 50% or the end-systolic dimension is greater than 50 mm, postoperative outcome is impaired, presumably because these markers indicate that left ventricular dysfunction has developed. Data suggest that surgery should be timed even before an end-systolic dimension of 45 mm has been reached.[19] A calculated regurgitant orifice above 30 mm^2 portends a poorer prognosis and may warrant surgery.

Symptomatic Patients or Patients with Left Ventricular Dysfunction

Patients who have symptoms or manifest left ventricular dysfunction should not be treated medically, except for short-term stabilization, but should undergo aortic valve surgery as soon as feasible before symptoms compromise their lifestyle. Although some patients may be able to undergo successful aortic valve repair to restore aortic valve competence, most patients require insertion of an aortic valve prosthesis.

TRICUSPID REGURGITATION

DEFINITION

As the population ages, the prevalence of tricuspid regurgitation has increased. Tricuspid regurgitation is usually caused by the hemodynamic load on the right ventricle, owing to pulmonary hypertension, an intracardiac shunt, left ventricular dysfunction, or mitral or aortic valve disease, rather than by a structural valve deformity. Because most of the force that is needed to fill the left ventricle is provided by the right ventricle, left ventricular dysfunction leading to elevated left ventricular filling pressure also places the right ventricle under a hemodynamic load and can eventually lead to right ventricular failure and tricuspid regurgitation. Another frequent cause of tricuspid regurgitation is atrial fibrillation, which can lead to annular dilatation and regurgitation on the right side similar to what happens on the left side with the mitral valve.[20] Less commonly, tricuspid regurgitation may be caused by pathology of the

valve itself, usually from infective endocarditis, typically stemming from intravenous drug abuse and unsterile injections (Chapter 61). Other causes include trauma (especially from hitting the steering wheel or dashboard in motor vehicle accidents), carcinoid syndrome (Chapter 213), rheumatic involvement of the tricuspid valve, myxomatous degeneration, and right ventricular infarction. Pacemaker leads placed across the tricuspid valve can also lead to significant tricuspid regurgitation by tethering the leaflets and preventing leaflet coaptation.[21]

DIAGNOSIS

The traditional symptoms of tricuspid regurgitation are those of right-sided heart failure (Chapter 45), including ascites, edema, and occasionally right upper quadrant pain. However, some patients may present with atypical symptoms of low cardiac output such as fatigue and dyspnea. In elderly patients, these symptoms often can be difficult to attribute solely to the tricuspid valve because they often have other comorbid conditions that could be responsible.

On physical examination, tricuspid regurgitation produces jugular venous distention accentuated by a large v wave as blood is regurgitated into the right atrium during systole. Regurgitation into the hepatic veins causes hepatic enlargement and liver pulsation. Right ventricular enlargement is detected as a parasternal lift. Ascites and edema are common. The murmur of tricuspid regurgitation is a holosystolic murmur heard along the left sternal border, often increasing with inspiration. The murmur may be faint, and it usually can be heard only under the best auscultatory conditions.

The definitive diagnosis of tricuspid regurgitation is made by echocardiography. Doppler interrogation of the tricuspid valve shows systolic disturbance of the right atrial blood pool. Echocardiography (Chapter 43) also can be used to determine the severity of pulmonary hypertension, measure right ventricular dilation and function, and assess whether the valve itself is intrinsically normal or abnormal.

TREATMENT AND PROGNOSIS

Therapy for secondary tricuspid regurgitation is generally aimed at the cause of the lesion. If left ventricular failure has been responsible for right ventricular failure and tricuspid regurgitation, the standard therapy for improving left ventricular failure (Chapter 46) lowers left ventricular filling pressure, reduces secondary pulmonary hypertension, relieves some of the hemodynamic burden of the right ventricle, and partially restores tricuspid valve competence. If pulmonary disease is the primary cause, therapy is directed toward improving lung function. Medical therapy directed at tricuspid regurgitation is usually limited to diuretics because the vasodilators that are so useful in the treatment of left-sided heart failure are often ineffective in treating pulmonary hypertension. However, a number of options can improve late-stage symptoms that are primarily caused by the pulmonary hypertension itself (Chapter 69).

Transcatheter repair[22] of severe tricuspid regurgitation can improve quality of life.[A18] Open surgical intervention for the tricuspid valve is rarely entertained in isolation. However, if other cardiac surgery is planned in a patient with severe tricuspid regurgitation, concomitant ring annuloplasty or tricuspid valve repair is frequently attempted to ensure postoperative tricuspid competence. Because a second operation to address residual tricuspid regurgitation after successful left-sided valve surgery carries an unacceptably high mortality rate, concomitant tricuspid annuloplasty is now entertained for even mild to moderate tricuspid regurgitation during left-sided valve surgery if annular dilatation is present. For example, concurrent tricuspid valve repair at the time of mitral valve surgery for mitral regurgitation reduces the likelihood of progressive tricuspid regurgitation but has not been shown to reduce subsequent all-cause mortality.[A19,A20] Tricuspid valve replacement is often not well tolerated and is rarely performed except when severe deformity, as is often seen in endocarditis or carcinoid disease, precludes valve repair.

PULMONIC STENOSIS

DEFINITION

Pulmonic stenosis is a congenital disease resulting from fusion of the pulmonic valve cusps (Chapter 55). It is usually detected and corrected during childhood, but occasionally cases are diagnosed for the first time in adulthood. Symptoms of pulmonic stenosis include angina and syncope. Occasionally, symptoms of right-sided heart failure develop. During physical examination, the uncalcified valve in pulmonic stenosis produces an early systolic ejection click on opening. During inspiration, the click diminishes or disappears because increased flow into the right side of the heart during inspiration partially opens the pulmonic valve in diastole so that systole causes less of an opening sound. The click is followed by a systolic ejection murmur that radiates to the base of the heart. If the transvalvular gradient is severe, right ventricular hypertrophy develops and produces a parasternal lift.

The diagnosis of pulmonic stenosis is confirmed by echocardiography, which quantifies the transvalvular gradient and the degree of right ventricular hypertrophy and dysfunction.

TREATMENT AND PROGNOSIS

In asymptomatic patients with a gradient less than 25 mm Hg, no therapy is required. If symptoms develop or the gradient exceeds 50 mm Hg, balloon commissurotomy is effective in reducing the gradient, improving right ventricular function, and relieving symptoms.[23] Although long-term prognosis is not yet established, 90% of patients do not require reintervention 10 years after balloon therapy. If pulmonary valve replacement is required, the transcatheter approach generally provides excellent outcomes.[24]

CHOICES AMONG PROSTHETIC VALVES

Different types of prosthetic valves (Fig. 60-9) have different advantages and disadvantages (Table 60-2). At long-term follow-up, primary valve failure with resulting need for reoperation is much more common with bioprosthetic valves, and bleeding is generally more common with mechanical valves. For mitral valves, long-term survival is similar with bioprosthetic and mechanical valves. Survival after aortic valve replacement is probably better with mechanical valves, except for young patients with congenital bicuspid aortic stenosis, in whom the Ross procedure is preferred.[25]

In general, a tissue valve is recommended in patients who have a life expectancy of less than 15 years or who are unable or unwilling to maintain warfarin anticoagulation. The choice of tissue valve is left to the implanting surgeon because no randomized trials have compared tissue valves to each other. A mechanical valve is preferred in patients who already have another indication for anticoagulation or who have a longer life expectancy and want to minimize the risk of reoperation. Because many patients prefer the risk of reoperation to that of anticoagulation, the age at which bioprostheses are implanted has steadily declined, and many 60-year-old patients now request and receive a bioprosthetic valve.

Reoperations to replace prosthetic valves are required when the valve becomes stenotic or regurgitant. Prosthetic valve failure is much more common in bioprosthetic valves compared with mechanical valves. For unclear reasons, bioprosthetic failure occurs more rapidly in younger patients, especially patients younger than age 50 years. Transcatheter aortic valve replacement is an alternative to open surgery in patients with an uninfected, nonthrombosed prior aortic bioprosthesis that now needs replacement.[26] Emerging data also support the use of transcatheter mitral valve insertion in patients who have a dysfunctional but noninfected or thrombosed mitral bioprosthesis and are at high risk for repeat open surgery.[27]

POSTOPERATIVE CARE OF PATIENTS WITH SUBSTITUTE HEART VALVES

After a prosthetic valve has been inserted, a baseline echocardiogram should be obtained to provide a reference point in the event that valve dysfunction is suspected at a later date. Echocardiography does not need to be repeated unless the patient's clinical status or physical findings change. The major causes of mechanical valve dysfunction are infective endocarditis and thrombus formation. For bioprostheses, endocarditis is also a risk, but valve degeneration, which can cause either stenosis or regurgitation, is a major concern.

Whenever a patient with a prosthetic heart valve has a temperature higher than 100° F, endocarditis must be excluded by blood culture; for fever with signs of sepsis, broad-spectrum antibiotics must be begun while awaiting culture results. For patients with bioprosthetic valves, mechanical prostheses, and homografts, endocarditis prophylaxis should be instituted at the time of procedures that are associated with a high risk for bacteremia (Chapter 61). Whether prophylaxis is necessary for a pulmonary autograft after the Ross procedure is currently unclear, but physicians usually prescribe prophylaxis for these patients.

All patients with a mechanical heart valve require warfarin anticoagulation. Recommended INR values range from 2.0 (1.5 for the On-X aortic valve) for a young normotensive patient in sinus rhythm with an aortic valve prosthesis to 3.5 for a patient with atrial fibrillation and a mitral valve prosthesis. Aspirin 75 to 100 mg/day added to warfarin may be beneficial in patients who have a separate indication for antiplatelet therapy. Direct-acting anticoagulants such as dabigatran are associated with more thrombosis and bleeding in patients with mechanical prosthetic valves[A21] and should not be used. Direct-acting oral anticoagulants are, however, appropriate for patients who have atrial fibrillation in the setting of a bioprosthetic valve.[A22] When thrombosis occurs on a prosthetic

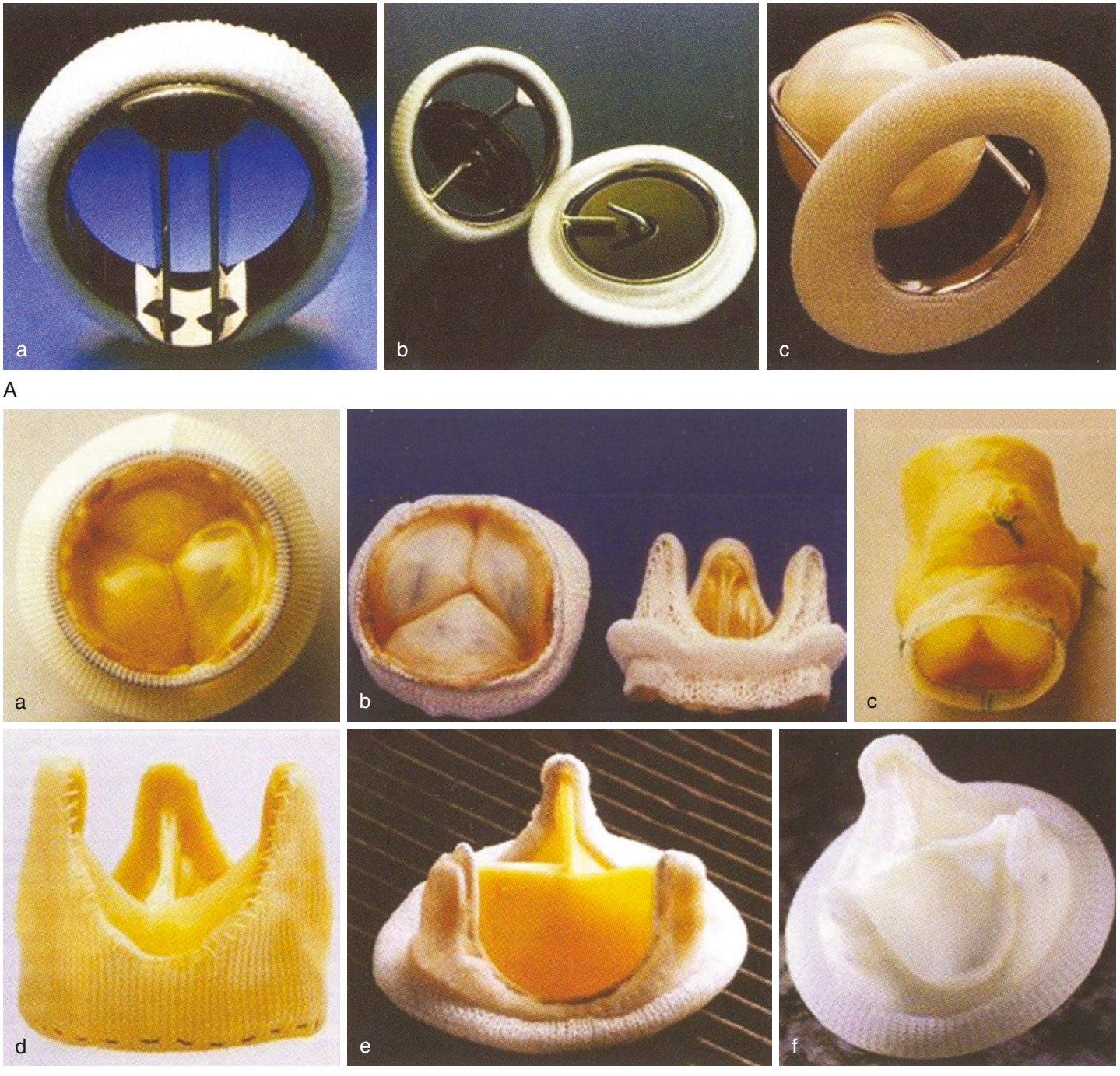

FIGURE 60-9. Prosthetic aortic valves. A, Common mechanical valves: *a,* a bileaflet St. Jude Medical valve; *b,* a Medtronic-Hall tilting disc valve; *c,* a Starr-Edwards ball cage valve (no longer manufactured but still in use). (From Antunes MJ, Burke AP, Carabello B. Valvular heart disease. In: Braunwald E, Rahimtoola SH, eds. *Essential Atlas of Heart Diseases*. 3rd ed. Philadelphia: Current Medicine Group; 2005:296-297.) **B,** Common bioprostheses: *a,* Hancock modified orifice stented valve; Carpentier-Edwards stented porcine valve; Medtronic Freestyle Stentless Valve; *d,* St. Jude Medical Toronto SPV stentless valve; *e,* Carpentier-Edwards pericardial valve; *f,* Autologous pericardial valve. (From Grunkemeier GL, Rahimtoola SH, Starr A. Prosthetic heart valves. In: Rahimtoola SH, ed. *Valvular Heart Disease*. Philadelphia: Current Medicine Group; 1997:13.9-13.11.)

TABLE 60-2 ADVANTAGES AND DISADVANTAGES OF SUBSTITUTE CARDIAC VALVES

TYPE OF VALVE	ADVANTAGES	DISADVANTAGES
Bioprosthesis (Carpentier-Edwards, Hancock)	Avoids anticoagulation in patients with sinus rhythm	Durability limited to 10-15 yr Relatively stenotic
Mechanical valves (St. Jude)	Good flow characteristics in small sizes	Require anticoagulation
Homografts and autografts	Anticoagulation not required Durability increased over that of bioprostheses	Surgical implantation technically demanding

valve, about 60% of patients can have restored valve function after intravenous infusion of a thrombolytic agent. In patients with periprosthetic paravalvular leaks, a percutaneous procedure can successfully close about 85% of the leaks.

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61 INFECTIVE ENDOCARDITIS

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DEFINITION

Infective endocarditis is defined as an infection, usually bacterial, of the endocardial surface of the heart. Infective endocarditis affects primarily the cardiac valves, although in some cases the septa between the chambers, the mural endocardium, or cardiovascular implantable electronic devices (e.g., pacemakers) may be involved. In the past, infective endocarditis was categorized as "acute" or "subacute," based on the duration of symptoms before presentation. However, these strict categories have proven to be unreliable, so clinical classification considers the causative organism, the involved valve, and the "pace" of clinical disease.

EPIDEMIOLOGY

The true incidence of infective endocarditis is difficult to determine because of the different criteria for diagnosis and methods of reporting. An analysis based on strict case definitions reveals that only a relatively small proportion (≈20%) of clinically diagnosed cases are categorized as "definite." In 10 large surveys, infective endocarditis accounted for approximately one case per 1000 U.S. hospital admissions, with a range of 0.16 to 5.4 cases per 1000 admissions. Estimates from the American Heart Association (AHA) place the incidence of infective endocarditis in the United States at 10,000 to 20,000 new cases per year. Recent data also suggest that rates of *Staphylococcus aureus* infective endocarditis have increased significantly, in part due to an increase in injection drug use (Chapter 365) as part of the current opioid epidemic, as well as the increasing use of implantable cardiac devices.[1]

Men are more commonly affected than women (mean male : female ratio, 1.7 : 1 in 18 large series). However, in patients younger than 35 years, more cases occur in women. More than 50% of patients with infective endocarditis in the United States are now older than 50 years of age, due in part to the low incidence of acute rheumatic heart disease (Chapter 269) and a simultaneous rise in the prevalence of degenerative valvular heart disease in the aging population.

Although some patients have no clearly definable risk factors for endocarditis, cardiac conditions that cause turbulent flow at the endocardial surface or across a valve (Chapter 60) predispose patients to infective endocarditis (Table 61-1). The most commonly affected valves in descending order of prevalence are the mitral valve only, the aortic valve only, the mitral and aortic valves together, the tricuspid valve, mixed right- and left-sided infection, and the pulmonic valve.

Historically, rheumatic heart disease with valvular dysfunction was the most common underlying condition, although its contribution has diminished in the antibiotic era, especially in developed countries. Degenerative valvular disease is also associated with infective endocarditis, particularly in elderly patients; the increasing relevance of senile calcification as a risk factor is reflected in the increasing proportion of aortic valve involvement in infective endocarditis (e.g., calcific aortic stenosis). Most significant congenital heart defects (Chapter 55) confer an increased risk of infective endocarditis, particularly complex cyanotic disease such as single-ventricle states, transposition of the great vessels, and tetralogy of Fallot. Similarly, surgically constructed pulmonary–systemic shunts and ventricular septal defects are risk factors associated with infective endocarditis.

Mitral valve prolapse is currently the most common underlying cardiac condition in patients with infective endocarditis, a statistic that reflects its prevalence in the general population (4%). Notably, mitral valve prolapse is a risk only in patients with thickened mitral leaflets or significant regurgitation, in which case the risk of endocarditis increases by about 10-fold over that of the general population. In addition, patients with hypertrophic cardiomyopathy are at increased risk of infective endocarditis, particularly in the presence of outflow obstruction. Finally, previous endocarditis is among the highest risk factors for subsequent infective endocarditis cases.

Prosthetic cardiac valves represent an important risk factor for infective endocarditis. More than 150,000 heart valves are implanted annually worldwide, and prosthetic valve infective endocarditis develops in 1 to 4% of prosthetic valve recipients in the first year after valve replacement and in approximately 0.8% of recipients annually thereafter. Mechanical prosthetic valves may initially be more susceptible to infective endocarditis, but bioprosthetic valves are more likely to develop infective endocarditis after 1 year; overall, the rate is similar with either type of valve. Bioprosthetic valve endocarditis can also involve transcatheter-placed aortic, mitral, or pulmonic valve prostheses.

The incidence of infective endocarditis in injection drug users (Chapter 365) may be 30 times higher than in the general population and four times higher than in adults with rheumatic heart disease.[2] In some areas of the United States, injection drug use is the most common predisposing cause of infective endocarditis in patients younger than 40 years. *S. aureus* is the predominant organism, and tricuspid valve involvement is noted in 78% of cases, mitral involvement in 24%, and aortic involvement in 8%. More than

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Prosthetic valves*	Coarctation of the aorta
Congenital (valvular heart disease or ventricular [especially uncorrected] septal defect)	Complex cyanotic congenital heart disease*
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*Indicates conditions with highest risk for endocarditis.
†Still common in developing countries.

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61 INFECTIVE ENDOCARDITIS

VANCE G. FOWLER, JR., ARNOLD S. BAYER, AND LARRY M. BADDOUR

DEFINITION

Infective endocarditis is defined as an infection, usually bacterial, of the endocardial surface of the heart. Infective endocarditis affects primarily the cardiac valves, although in some cases the septa between the chambers, the mural endocardium, or cardiovascular implantable electronic devices (e.g., pacemakers) may be involved. In the past, infective endocarditis was categorized as "acute" or "subacute," based on the duration of symptoms before presentation. However, these strict categories have proven to be unreliable, so clinical classification considers the causative organism, the involved valve, and the "pace" of clinical disease.

EPIDEMIOLOGY

The true incidence of infective endocarditis is difficult to determine because of the different criteria for diagnosis and methods of reporting. An analysis based on strict case definitions reveals that only a relatively small proportion (≈20%) of clinically diagnosed cases are categorized as "definite." In 10 large surveys, infective endocarditis accounted for approximately one case per 1000 U.S. hospital admissions, with a range of 0.16 to 5.4 cases per 1000 admissions. Estimates from the American Heart Association (AHA) place the incidence of infective endocarditis in the United States at 10,000 to 20,000 new cases per year. Recent data also suggest that rates of *Staphylococcus aureus* infective endocarditis have increased significantly, in part due to an increase in injection drug use (Chapter 365) as part of the current opioid epidemic, as well as the increasing use of implantable cardiac devices.[1]

Men are more commonly affected than women (mean male : female ratio, 1.7 : 1 in 18 large series). However, in patients younger than 35 years, more cases occur in women. More than 50% of patients with infective endocarditis in the United States are now older than 50 years of age, due in part to the low incidence of acute rheumatic heart disease (Chapter 269) and a simultaneous rise in the prevalence of degenerative valvular heart disease in the aging population.

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Historically, rheumatic heart disease with valvular dysfunction was the most common underlying condition, although its contribution has diminished in the antibiotic era, especially in developed countries. Degenerative valvular disease is also associated with infective endocarditis, particularly in elderly patients; the increasing relevance of senile calcification as a risk factor is reflected in the increasing proportion of aortic valve involvement in infective endocarditis (e.g., calcific aortic stenosis). Most significant congenital heart defects (Chapter 55) confer an increased risk of infective endocarditis, particularly complex cyanotic disease such as single-ventricle states, transposition of the great vessels, and tetralogy of Fallot. Similarly, surgically constructed pulmonary–systemic shunts and ventricular septal defects are risk factors associated with infective endocarditis.

Mitral valve prolapse is currently the most common underlying cardiac condition in patients with infective endocarditis, a statistic that reflects its prevalence in the general population (4%). Notably, mitral valve prolapse is a risk only in patients with thickened mitral leaflets or significant regurgitation, in which case the risk of endocarditis increases by about 10-fold over that of the general population. In addition, patients with hypertrophic cardiomyopathy are at increased risk of infective endocarditis, particularly in the presence of outflow obstruction. Finally, previous endocarditis is among the highest risk factors for subsequent infective endocarditis cases.

Prosthetic cardiac valves represent an important risk factor for infective endocarditis. More than 150,000 heart valves are implanted annually worldwide, and prosthetic valve infective endocarditis develops in 1 to 4% of prosthetic valve recipients in the first year after valve replacement and in approximately 0.8% of recipients annually thereafter. Mechanical prosthetic valves may initially be more susceptible to infective endocarditis, but bioprosthetic valves are more likely to develop infective endocarditis after 1 year; overall, the rate is similar with either type of valve. Bioprosthetic valve endocarditis can also involve transcatheter-placed aortic, mitral, or pulmonic valve prostheses.

The incidence of infective endocarditis in injection drug users (Chapter 365) may be 30 times higher than in the general population and four times higher than in adults with rheumatic heart disease.[2] In some areas of the United States, injection drug use is the most common predisposing cause of infective endocarditis in patients younger than 40 years. *S. aureus* is the predominant organism, and tricuspid valve involvement is noted in 78% of cases, mitral involvement in 24%, and aortic involvement in 8%. More than

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ABSTRACT

Infective endocarditis is an uncommon illness associated with increased morbidity and mortality. The patient's presentation can sometimes present diagnostic challenges. Management of patients with infective endocarditis includes antimicrobial therapy and, often, valve surgery. Timing of and indications for surgery can be challenging, so a multispecialty team with expertise in the care of patients with infective endocarditis is advisable.

KEYWORDS

endocarditis
infective endocarditis
bacterial endocarditis

one valve is infected in approximately 20% of cases, and some of these infections are polymicrobial.

Health care–associated infective endocarditis arises primarily as a consequence of invasive therapies, including intravenous (IV) catheters, hyperalimentation lines, pacemakers, other cardiovascular implantable electronic devices,[3] and hemodialysis devices.[4] In a recent prospective, multinational cohort study of more than 1600 non–drug-using patients with native valve endocarditis, more than one third of patients had health care–associated endocarditis, many cases of which originated in the community (e.g., in patients on outpatient hemodialysis). The emerging importance of health care–associated infective endocarditis in industrialized nations has also influenced the microbiology of the disease, with an increasing prevalence of *S. aureus* and a decreasing prevalence of viridans group streptococci in much of the industrialized world.

Implantable cardiovascular electronic devices can become infected at the time they are implanted, particularly if patients develop local pocket site complications, such as a hematoma, at the incision site or need the device to be revised or replaced. Other factors that increase the risk of device infection include older age, comorbid conditions (particularly dialysis-dependent renal failure), and a larger number of device leads.

Systemic medical conditions can predispose patients to the development of infective endocarditis. For example, HIV infection is an independent risk factor for the development of infective endocarditis in injection drug users, with the risk increasing as the CD4 count decreases. Vascular catheter–related bacteremia is an important risk factor for nosocomial infective endocarditis. Patients with end-stage renal disease, particularly those receiving long-term hemodialysis, and patients with diabetes mellitus are also at increased risk, presumably because of the recurrent vascular access–site infections associated with the former and the low-level immunosuppression associated with both conditions.

PATHOBIOLOGY

Experimental models of infective endocarditis have demonstrated that the disease follows a predictable sequence: endocardial damage; aggregation of platelets, fibrin, and other coagulation molecules to create a "sterile vegetation" *(nonbacterial thrombotic endocarditis);* transient bacteremia resulting in seeding of the vegetation; microbial proliferation on and invasion of the endocardial surface; and metastatic infection to organs receiving high blood flow (e.g., kidneys, spleen, and brain). Such sterile vegetations can occur either on previously damaged native valves or at the sewing ring following prosthetic valve placement. Nonbacterial thrombotic endocarditis may also occur spontaneously in patients with systemic illnesses (e.g., the marantic endocarditis of malignancy [Chapter 47] or other wasting diseases or the Libman-Sacks marantic endocarditis of systemic lupus erythematosus [Chapter 245]).

When transient bacteremia occurs—for example, as a result of distant infection or gingival manipulations—the previously sterile vegetation may be seeded. Some bacterial species, such as staphylococci and streptococci, are more avidly adherent to vegetations, better able to evade innate endovascular host defenses, and, as a result, more frequently cause endocarditis. The bacteria then proliferate within the vegetation and may ultimately achieve an organism load of 10^9 to 10^{11} colony-forming units per gram of tissue. Lastly, the surfaces of cardiac valves and vegetations are avascular, thereby making antibiotic therapy and healing difficult. Implantable cardiac devices disrupt the endothelial surface and predispose to infection and the formation of biofilms, particularly early after their placement and before endothelialization and fibrosis occur.

CLINICAL MANIFESTATIONS

History

The initial presentation of infective endocarditis varies enormously from patient to patient. Some cases develop acutely, with symptoms progressing rapidly over days. Other cases develop insidiously and present with progressive but nonspecific symptoms for weeks to months. In patients suspected of having infective endocarditis, the initial history should include a complete review of systems, a travel history, exposures to pets or other animals, illicit drug use, and sexual activity. Most patients complain of fever and nonspecific constitutional symptoms such as fatigue, malaise, or weight loss. Nearly 50% of patients complain of musculoskeletal symptoms ranging from frank arthritis to diffuse myalgias. In about 5 to 10% of patients, low back pain is the chief complaint, even in the absence of osteomyelitis or epidural abscess. In IV drug users with tricuspid valve infective endocarditis and patients with venous or right heart implantable devices, endocarditis can present as pleuritic chest pain and multilobar pneumonia. Health care–associated infective endocarditis is more likely to be clinically occult and requires a high index of suspicion.

Physical Examination

A thorough physical examination should include a search for the prototypic stigmata of endocarditis (Table 61-2), which are very helpful when present but are less frequent than in the past, now that patients are diagnosed and treated more expeditiously. Although fever is present in up to 90% of patients, it is less common in elderly patients and in patients with renal or heart failure. A widened pulse pressure should alert the clinician to the possibility of acute aortic insufficiency (Chapter 60). The skin and nails should be carefully examined for evidence suggestive of embolic phenomena, such as petechiae (Fig. 61-1), Osler nodes, Janeway lesions, and splinter hemorrhages. Petechiae are most often found on the conjunctiva, palate, and extremities. Osler nodes are small, painful nodules found most often on the palmar surfaces of the fingers and toes; they frequently wax and wane (Fig. 61-2). Classically considered to be an immunologic phenomenon, Osler nodes may have an immune complex–mediated component but are most likely initiated by microemboli. Janeway

TABLE 61-2 PHYSICAL EXAMINATION AND LABORATORY FINDINGS IN INFECTIVE ENDOCARDITIS

FINDING	% OF CASES
Fever	96
Worsening of previous murmur	20
New murmur	48
Vascular embolic event	17
Splenomegaly	11
Splinter hemorrhages	8
Osler nodes	3
Janeway lesions	5
Roth spots	2
Elevated ESR	61
Hematuria	26
Positive rheumatoid factor	5
Abnormal chest radiography findings (effusion, infiltrate, septic emboli)	67-85 (right-sided infective endocarditis)

ESR = erythrocyte sedimentation rate.
Adapted from Murdoch DR, Corey GR, Hoen B, et al. Clinical presentation, etiology, and outcome of infective endocarditis in the 21st century: International Collaboration on Endocarditis—Prospective Cohort Study. *Arch Intern Med.* 2009;169:463-473.

FIGURE 61-1. Petechiae in infective endocarditis.

FIGURE 61-2. Osler node in infective endocarditis.

lesions (Fig. 39-10 in Chapter 39) are hemorrhagic, nonpainful macules also found primarily on the palms and soles; they are embolic in origin and are less frequently noted than the other cutaneous stigmata. Splinter hemorrhages (see Fig. 39-10 in Chapter 39) are nonblanching, linear, brownish red lesions in the nail beds parallel to the direction of nail growth; they are nonspecific and may also be found in a significant percentage of hospitalized patients without infective endocarditis.

Funduscopic examination should be performed to look for Roth spots (see Fig. 391-26 in Chapter 391), chorioretinitis, or endophthalmitis; the latter two are present in a substantial proportion of cases of fungal endocarditis (e.g., *Candida*). A careful cardiac examination (Chapter 39) should be performed to detect any murmurs, especially new-onset or worsening murmurs, as well as any evidence of heart failure, which is an ominous sign. Of note, patients with health care–associated infective endocarditis are less likely than others to have a pathologic murmur on initial presentation. The abdomen should be examined for evidence of splenomegaly (Chapter 154), which is more common in patients with subacute endocarditis. Finally, a thorough neurologic examination should be performed, both to assess for any focal neurologic deficits and to serve as a baseline during the patient's hospital stay. The neurologic examination may demonstrate evidence of major vessel embolism, cranial nerve palsies, visual field defects, or generalized toxic-metabolic encephalopathy with altered mental status. Up to 15 to 20% of patients with endocarditis initially have or develop a stroke or stroke-like symptoms (Chapter 375). Patients with device-related infective endocarditis often have local signs and symptoms of infection at the site of implantation.

DIAGNOSIS

The "gold standard" for the diagnosis of infective endocarditis is culture of a pathologic organism from a valve or other endocardial surface. However, unless the patient undergoes valve surgery or postmortem examination, the diagnosis is usually made clinically.[5] The most widely accepted clinical criteria are the modified Duke criteria (Table 61-3), which rely heavily on blood culture results and echocardiographic data and have an estimated 76 to 100% sensitivity and 88 to 100% specificity, with a negative predictive value of at least 92%.

Microbiology

When bacteremia is suspected,[6] at least three sets of blood cultures, each set consisting of one aerobic and one anaerobic bottle, should be obtained from separate sites, with careful attention to aseptic technique. Because some bacteria may not be eliminated by skin surface disinfection, the likelihood of a contaminant can be reduced by 50% if the blood culture is obtained after another tube of blood is collected with the same venipuncture.[A1] Starting antibiotics before blood cultures are drawn will reduce their sensitivity by about one third.[7] Ideally, blood cultures should be collected at least 1 hour apart to document continuous bacteremia, which is a characteristic of infective endocarditis and is not seen in many other infectious syndromes; however, when patients are critically ill, this approach, which requires that antimicrobial therapy be delayed, may not be feasible. In this latter circumstance, the three sets of blood cultures should be drawn without interim time delays.

Causative Organisms

About 90% of community-acquired, native valve infective endocarditis is caused by staphylococci, streptococci, or enterococci, which are normal inhabitants of the skin, oropharynx, urogenital, and gastrointestinal tracts, respectively. These organisms express specific receptors for attachment and adherence to damaged endothelial surfaces. Streptococcal species (Chapter 269) are the most common cause of community-acquired infective endocarditis in patients with no history of injection drug use or health care contact. In patients with either of these latter epidemiologic risk factors, *S. aureus* (Chapter 267) is the predominant cause of infective endocarditis. Because of the emergence of health care contact as the predominant risk factor for blood stream infections, *S. aureus* is now the most common cause of infective endocarditis in most industrialized regions of the world.

Viridans group streptococci (Chapter 269) are the most common streptococci implicated in native valve endocarditis. This group of organisms, which normally inhabit the oropharynx, includes species such as *Streptococcus sanguinis, Streptococcus mutans,* and *Streptococcus mitis/oralis*. Group B streptococci (β-hemolytic organisms that are normal oropharyngeal and urogenital flora, as well as skin flora in patients with diabetes) most frequently cause infective endocarditis in patients with cirrhosis or diabetes mellitus, as well as in injection drug users. In contrast, group A streptococci, although also β-hemolytic, rarely cause infective endocarditis. Among streptococcal species, the risk of developing endocarditis after blood stream infection is highest with *Streptococcus mutans, Streptococcus gordonii, Streptococcus sanguinis, Streptococcus gallolyticus* (previously known as *Streptococcus bovis*), and *Streptococcus mitis/oralis*, and it is lowest with *Streptococcus pneumoniae*.[8] *Streptococcus gallolyticus* is now a leading cause of infective endocarditis in some parts of the world; for example,

TABLE 61-3 MODIFIED DUKE CRITERIA FOR THE DIAGNOSIS OF INFECTIVE ENDOCARDITIS

MAJOR CRITERIA

1. Blood culture positive (a *OR* b)
   a. Typical organism (α-hemolytic streptococcus, *Streptococcus gallolyticus,* HACEK organisms, or *Staphylococcus aureus,* or community-acquired *Enterococcus* species, without a primary focus) from two separate blood cultures *OR*
   b. Persistent bacteremia with any organism (two positive cultures >12 hr apart or three positive cultures or a majority of ≥4 cultures positive >1 hr apart)
2. Evidence of endocardial involvement (a *OR* b)
   a. Echocardiographic findings: mobile mass attached to valve or valve apparatus, abscess, or new partial dehiscence of prosthetic valve *OR*
   b. New valvular regurgitation
3. Serology: single positive blood culture for *Coxiella burnetii* or anti–phase 1 *C. burnetii* IgG antibody titer ≥1 : 800

MINOR CRITERIA

1. Predisposing condition: IV drug use or predisposing cardiac condition
2. Fever ≥38° C
3. Vascular phenomena: arterial embolism, septic pulmonary emboli, mycotic aneurysm, intracranial hemorrhage, conjunctival hemorrhages, Janeway lesions
4. Immunologic phenomena: glomerulonephritis, Osler nodes, Roth spots, rheumatoid factor
5. Echocardiogram findings consistent with endocarditis but not meeting major criteria
6. Microbiologic evidence: positive blood cultures not meeting major criteria or serologic evidence of active infection consistent with endocarditis

DEFINITE INFECTIVE ENDOCARDITIS (1 *OR* 2)

1. Pathologically proven infective endocarditis *OR*
2. Clinical diagnosis defined by
   a. Two major criteria *OR*
   b. One major and three minor criteria *OR*
   c. Five minor criteria

POSSIBLE INFECTIVE ENDOCARDITIS (1 *OR* 2)

1. One major criterion and one minor criterion *OR*
2. Three minor criteria

REJECTED INFECTIVE ENDOCARDITIS

1. Firm alternative diagnosis *OR*
2. Resolution of infective endocarditis syndrome with antibiotic therapy for ≤4 days *OR*
3. No pathologic evidence of infective endocarditis at surgery or autopsy with antibiotic therapy for ≤4 days *OR*
4. Does not meet criteria for possible infective endocarditis, as above

HACEK = *Haemophilus* spp, *Aggregatibacter* spp (formerly *Actinobacillus actinomycetemcomitans*), *Cardiobacterium hominis, Eikenella corrodens,* and *Kingella* spp; IgG = immunoglobulin G; IV = intravenous.

Adapted from Li JS, Sexton DJ, Mick N, et al. Proposed modifications to the Duke criteria for the diagnosis of infective endocarditis. *Clin Infect Dis*. 2000;30:633-638.

its incidence in France has increased significantly in recent years. Its presence in blood cultures should prompt endoscopic evaluation for adenocarcinoma of the colon or other malignant lesions of the gastrointestinal tract.

S. aureus (Chapter 267) is the predominate pathogen among injection drug users and patients with health care contact. The clinical course of *S. aureus* endocarditis is typically acute, with a rapid progression over the course of days. Because about 10 to 15% of patients with *S. aureus* bacteremia have echocardiographic evidence of endocarditis even in the absence of classic stigmata, possible cardiac involvement should always be considered in any patient with *S. aureus* bacteremia but especially in patients with relapsing or persistent bacteremia or fever, community-acquired infection, or an implantable cardiac device. Coagulase-negative staphylococci are an uncommon cause of native valve endocarditis but are important pathogens in the setting of prosthetic valves or other intracardiac devices.

Enterococci are responsible for a significant number of cases of both community-acquired and nosocomial endocarditis, and the bulk (>90%) are due to *Enterococcus faecalis*. In most cases, the source of bacteremia is thought to be the genitourinary tract, and the presentation is usually subacute. Endocarditis, which develops in about 25% of patients with *E. faecalis* bacteremia, is suggested by community acquisition of infection, the absence of a clear source of infection, preexistent valvular heart disease, and the absence of polymicrobial bacteremia. As with *S. gallolyticus* endocarditis, gastrointestinal screening for colonic neoplasms is recommended.[9]

The HACEK group of gram-negative organisms (*Haemophilus* spp, *Aggregatibacter* spp [formerly *Actinobacillus actinomycetemcomitans*], *Cardiobacterium hominis, Eikenella corrodens,* and *Kingella* spp) accounts for about 5% of endocarditis cases. Because these fastidious organisms usually grow in blood cultures within 7 days using current methods, prolonged incubation is no longer required to isolate HACEK strains. Many other gram-negative bacilli can cause infective endocarditis but are even more unusual. Traditionally, injection drug use has been the primary risk factor for enteric aerobic gram-negative bacillary bacterial endocarditis. However, recent experience from large multinational studies shows that nosocomial health care contact, not injection drug use, is currently the most common risk factor for enteric gram-negative endocarditis.

Fungal endocarditis is often difficult to diagnose and treat; it is most commonly found in patients with a history of injection drug use, recent cardiac valve surgery, or prolonged use of indwelling vascular catheters, especially those used for total parenteral nutrition. The most common fungi found in infective endocarditis are *Aspergillus* and *Candida* spp. *Aspergillus* (Chapter 311) rarely grows in blood cultures and usually must be cultured from a pathologic specimen (either an embolic site or vegetation). Serodiagnostic strategies for antigen detection are often useful to diagnose *Aspergillus* endocarditis. By contrast, *Candida* spp (Chapter 310) frequently grow in blood cultures. Mortality is very high, and valve replacement surgery is usually necessary for fungal endocarditis.

Prosthetic valve endocarditis can be classified into one of two groups based on the time between valve surgery and disease onset: *early* (<2 months after surgery) and *late* (>2 months) (Table 61-4). Staphylococci, particularly *S. aureus,* predominate during the early postsurgery period, when most episodes of infective endocarditis are thought to be related to perioperative infection. In the late postsurgery period, the spectrum of organisms becomes more akin to that of community-acquired native valve endocarditis, in which *S. aureus* and viridans group streptococci predominate. Of note, among the coagulase-negative staphylococci, oxacillin resistance is frequently seen in these late cases. A transcatheter prosthetic valve placement (aortic, mitral, or pulmonic) procedure also can be complicated by endocarditis, with enterococci, *S. aureus,* and coagulase-negative staphylococci as the most common pathogens in the aortic valve position and *S. aureus* predominating in the pulmonic valve position.

Staphylococcal species account for the large majority (≥70%) of implantable cardiac device infections. The prevalence of oxacillin resistance among *S. aureus* strains varies but is generally in the 30 to 50% range; such resistance is even higher among coagulase-negative staphylococci.

TABLE 61-4 CAUSES OF PROSTHETIC VALVE ENDOCARDITIS*

EARLY (<2 mo POSTOPERATIVELY)	LATE (>2 mo POSTOPERATIVELY)
Staphylococcus aureus	Coagulase-negative staphylococci
Coagulase-negative staphylococci	*Staphylococcus aureus*
Gram-negative bacilli	Viridans group streptococci
Enterococci	Enterococci
Fungi	*Mycobacterium chimaera*†
Diphtheroids	

*Listed in order of relative frequency.
†May occur up to 4-5 years after valve replacement.
Adapted from Wang A, Athan E, Pappas PA, et al. Contemporary clinical profile and outcome of prosthetic valve endocarditis. *JAMA*. 2007; 297:1354-1361.

Endocarditis with Negative Blood Cultures

In most patients who have infective endocarditis and who have not received previous antibiotic therapy, every blood culture is positive. Blood cultures are truly negative in less than 5% of cases of endocarditis; however, prior antibiotic administration may decrease the yield of blood cultures by up to 35%. Accordingly, the large majority of "culture-negative" cases of endocarditis occur in patients who have recently received antimicrobial agents. These cases are probably caused by the same organisms responsible for most native valve endocarditis; viridans group streptococci and the HACEK organisms are the most "likely suspects" because they are much more fastidious than staphylococci and enterococci and are therefore more likely to be affected by previous antibiotic administration. Ultimately, however, when blood cultures are negative and endocarditis is suspected, especially when a history of recent antimicrobial treatment is lacking, consideration should be given to fastidious bacterial organisms, fungi, and noncultivatable organisms (Table 61-5), particularly when the patient's history suggests exposure to farm animals or unpasteurized milk (*Coxiella burnetii, Brucella* spp), cats (*Bartonella henselae*), body lice (*Bartonella quintana*), or pet birds (*Chlamydophila psittaci*). It is important to notify the microbiology laboratory that endocarditis is suspected because special culture techniques, including prolonged (>5 days) incubation of blood cultures, can occasionally increase the yield for nutritionally variant streptococci (*Abiotrophia* and *Granulicatella* spp), *Brucella* spp, *Legionella* spp, *Cutibacterium acnes,* and some fungi. Specific serologic tests can diagnose endocarditis related to *C. burnetii* (the agent of Q fever; Chapter 302), *Brucella* spp (Chapter 286), *Bartonella* spp (Chapter 291), and *C. psittaci* (Chapter 294). *Tropheryma whippelii,* the etiologic agent in Whipple disease (Chapter 305), and multiple other organisms may be diagnosed by broad-range polymerase chain reaction testing in plasma or especially on resected cardiac tissue.[10] Histopathologic features of resected tissue also can provide clues in the etiologic diagnosis of culture-negative endocarditis. If the search for a causative organism is fruitless, noninfectious causes such as marantic or Libman-Sacks endocarditis and atrial myxoma (Chapter 47) should be considered.

Laboratory Findings

Initial laboratory tests should include a complete blood count with differential, serum electrolytes, measurement of renal function, and urinalysis. Most patients with subacute infective endocarditis have the serum iron profile of "anemia of chronic disease" (Chapter 145). The peripheral white blood cell count is frequently elevated in acute infective endocarditis, particularly if *S. aureus* is the causative organism, but may not be elevated in more subacute forms. Microscopic hematuria is common, as is proteinuria.

Rheumatoid factor, which is an ancillary test that has been included in the modified Duke criteria as a "minor criterion" in the category of "immunologic phenomenon," may be positive in subacute or chronic endocarditis. Other ancillary tests, such as the erythrocyte sedimentation rate, the C-reactive protein level, and the procalcitonin level, are generally not helpful in establishing the diagnosis of endocarditis.

Imaging, Including Echocardiography

The chest radiograph is abnormal—demonstrating consolidation, atelectasis, pleural effusion, or clear septic emboli—in the overwhelming majority of patients with right-sided endocarditis. In others, it may show evidence of heart failure. The electrocardiogram (ECG) should be carefully examined for evidence of atrioventricular conduction blocks, especially a prolonged PR interval (see Figs. 51-4 through 51-9 in Chapter 51), suggestive of an aortic ring abscess or frank myocardial infarction (see Figs. 58-1 and 58-2 in Chapter 58).

Both transthoracic echocardiography and transesophageal echocardiography (Chapter 43) are highly specific tests for defining valvular vegetations (≈98%) when used as part of the diagnostic evaluation of suspected endocarditis. By contrast, transesophageal echocardiography has a much

TABLE 61-5 ORGANISMS CAUSING "CULTURE-NEGATIVE" ENDOCARDITIS*

ORGANISM	EPIDEMIOLOGY	DIAGNOSTIC TESTS
HACEK spp	Mostly oral flora, so often history of periodontal disease	May require up to 7 days to grow
Nutritionally variant streptococci	Slow and indolent course	Supplemented culture media or growth as satellite colonies around *Staphylococcus aureus* streak
Coxiella burnetii (Q fever)	Worldwide; exposure to raw milk, farm environment, or rural areas	Serologic tests (high titers of antibody to both phase 1 and phase 2 antigens); also PCR on blood or valve tissue
Brucella spp	Ingestion of contaminated milk or milk products; close contact with infected livestock	Bulky vegetations usually seen on echocardiography; blood cultures positive in 80% of cases with incubation time of 4-6 wk; lysis-centrifugation technique may expedite growth; serologic tests are available
Bartonella spp	*Bartonella henselae:* transmitted by cat scratch or bite or by cat fleas; *Bartonella quintana:* transmitted by human body louse; predisposing factors include homelessness and alcohol abuse	Serologic testing (may cross-react with *Chlamydophila psittaci*); PCR of valve or emboli is best test; lysis-centrifugation technique may be useful
Chlamydophila psittaci	Exposure to birds	Serologic tests available, but must exclude *Bartonella* spp because of cross-reactivity; monoclonal antibody direct stains on tissue may be useful; PCR now available
Tropheryma whippelii (Whipple disease)	Systemic symptoms include arthralgias, diarrhea, abdominal pain, lymphadenopathy, weight loss, CNS involvement; however, endocarditis may be present without systemic symptoms	Histologic examination of valve with PAS stain; valve cultures may be done using fibroblast cell lines; PCR on vegetation material
Legionella spp	Contaminated water distribution systems; often nosocomial outbreaks; usually prosthetic valves	Lysis-centrifugation technique; also periodic subcultures onto buffered charcoal yeast extract medium; serologic tests and PCR available
Aspergillus and other noncandidal fungi	Prosthetic valve	Lysis-centrifugation technique; also culture and direct examination of any emboli; serodiagnostic test for *Aspergillus* antigen
Mycobacterium chimaera	Following cardiac surgery with contaminated heater/cooler units used for cardiopulmonary bypass; often delayed months-years	PCR and mycobacterial cultures of blood and other sterile body sites

*Listed in approximate order of relative frequency.
CNS = central nervous system; HACEK = *Haemophilus* spp, *Aggregatibacter* spp, *Cardiobacterium hominis, Eikenella corrodens,* and *Kingella* spp; PAS = periodic acid–Schiff; PCR = polymerase chain reaction.

higher sensitivity (90 to 95%) in this setting than transthoracic echocardiography (48 to 63%). In most cases in which endocarditis is a serious diagnostic consideration, the evaluation should begin with initial transthoracic echocardiography followed by transesophageal echocardiography as soon as possible because both studies provide complementary information (Fig. 61-3). Because transesophageal echocardiography is a relatively noninvasive means of detecting perivalvular extension of infection, any patient with a new conduction system abnormality or persistent fever—clinical predictors of perivalvular extension—should be evaluated with it. Likewise, transesophageal echocardiography is strongly preferred in the evaluation of suspected prosthetic valve– or device–related endocarditis. Of note is that bland clots can occur on the leads of 5 to 10% of patients with intracardiac devices, and the finding of a "vegetation" on a lead is not specific for infection. The high sensitivity of transesophageal echocardiography in detecting valvular vegetations on native valves also may be used in combination with clinical parameters (e.g., prompt resolution of bacteremia and defervescence) to support the clinical decision to abbreviate therapy in patients with vascular catheter–associated *S. aureus* bacteremia. A vegetation greater than 10 mm is a significant predictor of an increased risk of peripheral embolization and mortality.[11]

A negative transesophageal echocardiography result has a negative predictive value of about 95%. Nevertheless, when clinical suspicion of endocarditis is high (e.g., persistent fever or embolic events) and the initial transesophageal echocardiography is negative, repeat transesophageal echocardiography in 3 to 5 days may reveal the diagnosis.

When echocardiographic results are negative or indeterminant, multislice computed tomography with or without angiography can be helpful in patients with possible prosthetic valve endocarditis or with a perivalvular extension of infection.[12] Positron emission tomography with computed tomography (PET/CT) scanning may be useful for identifying prosthetic valve endocarditis [13] and may sometimes identify a noncardiac primary source of infection, a metastatic site that requires a change in the therapeutic approach, or evidence of undiagnosed tumors. However, these tests should not be obtained routinely but rather should be reserved for difficult diagnostic situations.

The diagnosis of infective endocarditis complicating transcatheter aortic or pulmonic valve replacements can be difficult. Vegetations may not be detected with echocardiography, but leaflet thickening and an increased transvalvular gradient are often seen.

TREATMENT

Definitive antibiotic treatment of infective endocarditis (Table 61-6) is guided by antimicrobial susceptibility testing of the responsible pathogen isolated from clinical cultures.[14–16] Although it is often advisable to begin empiric treatment before definitive culture results are available, not all patients who are admitted because of possible endocarditis necessarily need to be treated empirically.[17] Patients who are clinically stable, with a subacute presentation syndrome and without evidence of heart failure or other end-organ complications, can be closely observed without antibiotics so that serial blood cultures can be obtained. Likewise, such stable patients who were started on empiric antibiotics before hospitalization and before blood was drawn for cultures can discontinue antibiotics so that blood cultures can be obtained, preferably as long as possible after stopping the antibiotics. A normal procalcitonin level does not exclude endocarditis, but procalcitonin-guided treatment may help reduce the duration of antibiotic treatment in patients with positive blood cultures.[A2] By contrast, acutely ill patients, patients with evidence of complications of endocarditis, and patients who are at high risk for endocarditis (e.g., prosthetic valve recipients)[18] should be treated empirically with antibiotics pending culture results. An infectious diseases specialist, as part of an multidisciplinary endocarditis team, is critical in guiding the diagnostic evaluation and designing an appropriate initial empiric (and subsequent definitive) antibiotic regimen. This consultation may guide molecular diagnostic testing by the hospital's microbiology laboratory or a reference laboratory to secure a specific etiologic diagnosis.

Empiric Therapy

Either of two regimens provides appropriate empirical coverage for patients with suspected native valve endocarditis when cultures have not revealed a specific organism: nafcillin (or oxacillin)–penicillin–gentamicin or vancomycin–gentamicin (Table 61-7). Some experts recommend a regimen of nafcillin–ceftriaxone–penicillin–gentamicin to cover for HACEK isolates that produce β-lactamase. If methicillin-resistant *S. aureus* (MRSA) is an important consideration, as in injection drug users and patients with health care contact, empirical therapy should consist of vancomycin–ceftriaxone–gentamicin. Patients with prosthetic valves should be empirically treated with vancomycin–gentamicin–rifampin for adequate coverage of the most important pathogens in this setting (MRSA, methicillin-sensitive staphylococci, and coagulase-negative staphylococci).

Treatment of Specific Organisms

When the organism is definitively identified, the antibiotic treatment must be narrowed accordingly, and validated regimens should be followed (see Table 61-6). Infectious disease consultation should be obtained in all cases of infective endocarditis as part of an "Endocarditis Team" approach, which has been shown to improve outcomes.

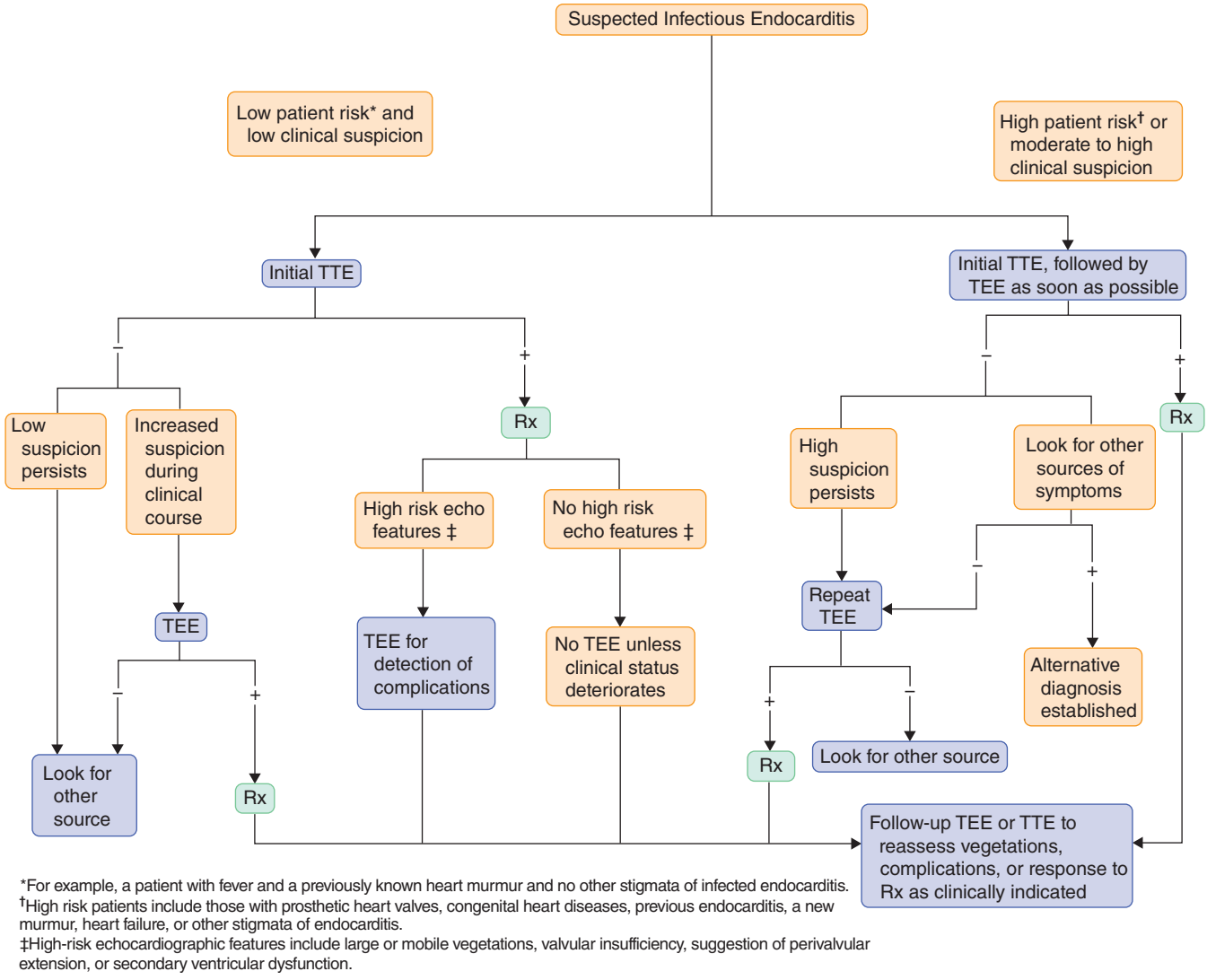

*For example, a patient with fever and a previously known heart murmur and no other stigmata of infected endocarditis.
†High risk patients include those with prosthetic heart valves, congenital heart diseases, previous endocarditis, a new murmur, heart failure, or other stigmata of endocarditis.
‡High-risk echocardiographic features include large or mobile vegetations, valvular insufficiency, suggestion of perivalvular extension, or secondary ventricular dysfunction.

FIGURE 61-3. Approach to the diagnostic use of echocardiography (Echo). Rx = treatment, TEE = transesophageal echocardiography, TTE = transthoracic echocardiography. (Adapted from Baddour LM, Wilson WR, Bayer AS, et al. Infective endocarditis in adults: diagnosis, antimicrobial therapy, and management of complications: a scientific statement for healthcare professionals from the American Heart Association. *Circulation*. 2015;132:1435-1486.)

Many regimens recommend consideration of low-dose gentamicin to provide antibacterial synergy with a low risk of toxicity. However, aminoglycoside toxicity is a significant risk in elderly patients and in patients with preexisting renal disease or hearing impairment; even low-dose gentamicin increases the likelihood of a decrease in creatinine clearance by about three-fold. Among the organisms listed in Table 61-6, added gentamicin is critical for cure only in enterococcal endocarditis (when combined with penicillin). As a result of these risks and the minimal data supporting its benefit, initial low-dose gentamicin should not be routinely used.

In uncomplicated viridans group streptococcal endocarditis, outpatient therapy with once-daily ceftriaxone is as effective as more complex regimens, provided the patient has been observed in the hospital for the development of complications. The decision to administer antimicrobial therapy in the outpatient setting must, of course, take into account the patient's social situation, likelihood of compliance, and other risks involved with either an indwelling IV line or recurrent peripheral IV line placements.

Traditional therapy for infective endocarditis caused by fully susceptible enterococci includes penicillin or ampicillin plus gentamicin. Although gentamicin is preferred over streptomycin, the choice of a specific aminoglycoside should be based on in vitro susceptibility testing. Nonrandomized data suggest that the duration of aminoglycoside therapy can be limited to 2 to 3 weeks in combination with either penicillin, ampicillin, or vancomycin; an aminoglycoside can be avoided in favor of combination therapy with ampicillin plus high-dose (2 g IV every 12 hours) ceftriaxone in endocarditis that is due to *Enterococcus faecalis*. Optimal therapy for enterococci that are resistant to aminoglycosides or vancomycin is not well defined. Endocarditis caused by vancomycin-resistant enterococci may be treated with daptomycin, quinupristin–dalfopristin (7.5 mg/kg IV every 8 hours), or linezolid (600 mg orally or IV twice daily); however, clinical experience with these agents is limited. In this situation, relapse or failure rates are likely to be high, and many cases require surgical intervention (discussed later).

Semisynthetic penicillins, such as nafcillin, are advocated for endocarditis caused by methicillin-susceptible *S. aureus*. Cefazolin represents an alternative to semisynthetic penicillins in patients in whom the latter are not tolerated or feasible to administer. Although vancomycin is recommended in patients who are allergic to β-lactams, the microbiologic and clinical cure rates are less than those of β-lactam therapy. Because of this lower cure rate and the fact that over 90% of patients who report a history of penicillin allergy do not have it when skin tested, an allergy expert should be consulted. Daptomycin (6 mg/kg/day for 10 to 42 days, depending on the severity of infection) is as effective as either a semisynthetic antistaphylococcal penicillin or vancomycin for the treatment of *S. aureus* bacteremia and right-sided infective endocarditis caused by methicillin-susceptible *S. aureus* and MRSA; the combination of daptomycin plus fosfomycin may be slightly better than daptomycin alone.[A3] Non-randomized data suggest that higher-dose daptomycin regimens (8-10 mg/kg/d) are safe and may be superior for clearing bacteremia in *S. aureus* endocarditis. Ceftaroline, a fifth-generation cephalosporin, can be successful in patients with MRSA bacteremia and endocarditis, especially when combined with daptomycin.

Data suggest that after about 2 weeks of successful IV therapy, patients with stable left-sided endocarditis due to streptococcus, *Enterococcus faecalis*, *Staphylococcus aureus*, or coagulase-negative staphylococci have been safely switched from IV to oral antibiotics for the duration of their treatment,[A4] although experience with *S. aureus* endocarditis, especially MRSA, is relatively limited.

Rifampin or gentamicin can be added to either nafcillin or vancomycin for the treatment of prosthetic valve infection caused by methicillin-susceptible *S. aureus* or to MRSA, respectively. Gentamicin is administered for 2 weeks, and rifampin is given for the duration of either nafcillin or vancomycin therapy.

TABLE 61-6 DEFINITIVE THERAPY OF BACTERIAL ENDOCARDITIS

ORGANISM AND REGIMEN*	COMMENTS
PCN-SUSCEPTIBLE VIRIDANS STREPTOCOCCI (MIC ≤0.1 μg/mL) AND *STREPTOCOCCUS GALLOLYTICUS (formerly S. bovis)*	
1. Aqueous crystalline PCN G 2-3 million units IV q4h × 4 wk; 6 wk for prosthetic valve endocarditis	1. Also effective for other PCN-susceptible nonviridans streptococci
2. Ceftriaxone 2 g IV qd × 4 wk; 6 wk for prosthetic valve endocarditis	2. Useful in outpatient therapy and in patients with non-IgE-mediated PCN allergy
3. Aqueous crystalline PCN G 2-3 million units IV q4h × 2 wk plus gentamicin 3 mg/kg IV per 24 h in 1 dose × 2 wk	3. Uncomplicated infection with none of the following features: renal insufficiency, eighth cranial nerve deficit, prosthetic valve infection, CNS complications, severe heart failure, age >65 yr; also not acceptable for nutritionally variant streptococci; this option is not commonly used
4. Vancomycin 15-20 mg/kg IV q8-12h × 4 wk	4. For IgE-mediated PCN allergy; goal trough level of 15-20 mg/L
RELATIVELY PCN-RESISTANT VIRIDANS STREPTOCOCCI (MIC 0.12-<0.5 μg/mL)	
1. Aqueous crystalline PCN G 4 million units IV q4h × 4 wk plus gentamicin 3 mg/kg IV q24h × 2 wk	—
2. Vancomycin 15-20 mg/kg IV q8-12h × 4 wk	For IgE-mediated PCN allergy or to avoid gentamicin; goal trough level of 15-20 mg/L
ENTEROCOCCI† *ABIOTROPHIA*, AND *GRANULICATELLA* SPECIES, AND PCN-RESISTANT VIRIDANS STREPTOCOCCI (PCN MIC ≥0.5 μg/mL)	
1. Penicillin‡ 18-30 million units IV per day in divided doses × 4-6 wk or ampicillin 12 g/24 hr IV in 6 equally divided plus gentamicin 3 mg/kg IV q24h × 4-6 wk	1. Increase duration of both drugs to 6 wk for prosthetic valve endocarditis or symptoms >3 mo in enterococcal infection
2. Vancomycin 15-20 mg/kg IV q8-12h × 6 wk plus gentamicin 1 mg/kg q8h × 6 wk§	2. For IgE-mediated PCN allergy; high risk of nephrotoxicity with this regimen
3. Ampicillin 12 g/24 h IV in 6 equally divided doses plus ceftriaxone 2 g IV q12h × 6 wk	3. An alternative to aminoglycoside-containing regimens in infective endocarditis due to *Enterococcus faecalis*, especially in patients with pre existing renal disease
STAPHYLOCOCCUS AUREUS	
1. Nafcillin 2 g IV q4h × 6 wk	1. Methicillin-susceptible strain; gentamicin discouraged for native valve endocarditis
2. Vancomycin 15-20 mg/kg IV q8-12h × 6 wk	2. PCN allergy (immediate hypersensitivity or anaphylaxis) or MRSA
3. Nafcillin 2 g IV q4h × 2 wk	3. Methicillin-susceptible strain; 2-wk regimen for use only in people who inject drugs and have uncomplicated tricuspid valve endocarditis
4. Nafcillin 2 g IV q4h × ≥6 wk plus gentamicin 1 mg/kg IV q8h × 2 wk plus rifampin 300 mg PO/IV q8h × ≥6 wk	4. Prosthetic valve endocarditis with methicillin-susceptible strain; use vancomycin instead of nafcillin for MRSA
5. Cefazolin 2 g IV q8h × 4-6 wk	5. Non-IgE-mediated PCN allergy
6. Daptomycin 6 mg/kg IV qd × 14-42 days	6. Daptomycin is FDA-approved for treatment of right-sided *S. aureus* infective endocarditis; for adults; some experts recommend up to 10 mg/kg IV qd
COAGULASE-NEGATIVE STAPHYLOCOCCI, PROSTHETIC VALVE INFECTION	
Vancomycin 15-20 mg/kg IV q8-12h × ≥6 wk plus gentamicin 1 mg/kg IV q8h × 2 wk plus rifampin 300 mg PO/IV q8h × ≥6 wk	Can substitute nafcillin in above listed doses for vancomycin if isolate is sensitive to methicillin
HACEK STRAINS	
1. Ceftriaxone 2 g IV qd × 4 wk; 6 wk for prosthetic valve endocarditis	This regimen is used in most patients
2. Ampicillin–sulbactam 3 g IV q6h × 4 wk; 6 wk for prosthetic valves	HACEK strains increasingly may produce β-lactamase
NON-HACEK GRAM-NEGATIVE BACILLI	
Enterobacteriaceae	
Extended-spectrum PCN or cephalosporin plus aminoglycosides for susceptible strains	Treat for a minimum of 6-8 wk; some species exhibit inducible resistance to third-generation cephalosporins; valve surgery is required for most patients with left-sided endocarditis caused by gram-negative bacilli
Pseudomonas aeruginosa	
High-dose tobramycin (8 mg/kg/day IV or IM in once-daily doses) with maintenance of peak and trough concentrations of 15 to 20 μg/mL and ≤2 μg/mL, respectively, in combination with an extended-spectrum PCN (e.g., ticarcillin, piperacillin, azlocillin); ceftazidime, cefepime, or imipenem in full doses; or imipenem	Treat for a minimum of 6-8 wk; early valve surgery usually required for left-sided *Pseudomonas* endocarditis
Fungi	
Treatment with a parenteral antifungal agent (usually a lipid-containing amphotericin B product, 3-5 mg/kg/day IV for at least 6 weeks) with or without flucytosine (25 mg/kg PO four times daily in patients with normal renal function) in patients with *Candida* infections; fluconazole, 400 mg daily PO is an alternative for susceptible yeasts; other azoles, such as voriconazole, may be required for resistant yeasts or molds	Combined with valve replacement and subsequent lifelong suppressive therapy with oral antifungal agents; for patients who are not candidates for surgery, lifelong oral suppressive therapy should follow completion of initial IV therapy.

‡Ampicillin 12 g/day can be used instead of PCN.

§The need to add an aminoglycoside has not been demonstrated for PCN-resistant streptococci.

*Dosages are for patients with normal renal function; for those with renal insufficiency, adjustments must be made for all drugs except nafcillin, rifampin, and ceftriaxone. Gentamicin doses should be adjusted to achieve a peak serum concentration of approximately 3 μg/mL 30 min after dosing and a trough gentamicin level of <1 μg/mL.

†Enterococci must be tested for antimicrobial susceptibility. These recommendations are for enterococci sensitive to PCN, gentamicin, and vancomycin.

HACEK = *Haemophilus* spp, *Aggregatibacter* spp (formerly *Actinobacillus actinomycetemcomitans*), *Cardiobacterium hominis, Eikenella corrodens*, and *Kingella* spp; ID = infectious diseases; IM = intramuscular; IV = intravenous; MIC = minimum inhibitory concentration; MRSA = methicillin-resistant *Staphylococcus aureus;* PCN = penicillin; PO = oral; q = every; qd = every day.

Consultation with an infectious diseases specialist is recommended in all cases of infective endocarditis.

Adapted from Baddour LM, Wilson WR, Bayer AS, et al. Infective endocarditis in adults. *Circulation*. 2015;132:1435-1486.

TABLE 61-7 EMPIRICAL TREATMENT OF ENDOCARDITIS

CHARACTERISTICS OF PATIENTS	TREATMENT REGIMEN*
Native valve, community-acquired infection, MRSA unlikely	Nafcillin 2 g IV q4h plus penicillin 4 million units IV q4h plus gentamicin 1 mg/kg IV q8h
Any of the following: health care–associated infection or other reason to suspect MRSA; severe penicillin allergy	Vancomycin 15-20 mg/kg IV q8-12h† plus gentamicin 1 mg/kg IV q8h
Prosthetic valve	Vancomycin 15-20 mg/kg IV q8-12h† plus gentamicin 1 mg/kg IV q8h plus rifampin 300 mg PO/IV q8h

*Dosages are for patients with normal renal function; for those with renal insufficiency, adjustments must be made for all drugs except nafcillin.
†Goal is trough level of 15-20 mg/L.
IV = intravenous; MRSA = methicillin-resistant *Staphylococcus aureus;* PO = oral; q = every.

Rifampin is never used as monotherapy because of the rapid development of resistance.

Fungal endocarditis is usually a consequence of extensive health care contact. Traditionally, fungal endocarditis was regarded as a primary indication for valvular surgery, and intravenous amphotericin B was considered the adjunctive treatment of choice (Chapter 307). However, selected patients with *Candida* endocarditis have been successfully treated medically (with azole-containing antimicrobial agents, with or without amphotericin B), particularly patients who have been deemed not to be surgical candidates. Importantly, the management of fungal endocarditis should always involve the collaboration of an experienced infectious diseases specialist.

Zoonotic endocarditis is usually culture-negative and most commonly caused by *Bartonella* spp (Chapter 291), *C. burnetii* (Chapter 302), or *Brucella* spp (Chapter 286). The treatments of choice for these fastidious pathogens are based on limited data, but documented *Bartonella* endocarditis is treated with doxycycline for 6 weeks plus gentamicin for the first 2 weeks.

In cases of presumed culture-negative endocarditis in which unusual organisms (see Table 61-5) and other infections have been reasonably excluded, an empirical course of treatment may be undertaken. The choice of antimicrobial therapy should be influenced by the specifics of the patient's presentation, and an infectious diseases consultation is recommended.

Continuing Care of the Patient with Endocarditis

In addition to antibiotics, appropriate inpatient care includes attention to other chronic medical issues. For endocarditis in people who inject drugs, early inpatient consultation with an addiction medicine specialist is strongly advised to optimize adherence to completion of antimicrobial therapy as well as to implement strategies to mitigate subsequent drug use and reduce harm in this high-risk population that is at risk of a variety of serious infectious diseases, including recurrent endocarditis (Chapter 365).[19,20]

Regular surveillance should assess the potential development of complications. A careful cardiac examination should be performed on a daily basis to assess for new regurgitant murmurs. Widening of the pulse pressure should alert the clinician to the possible development of acute aortic insufficiency (Chapter 60). New conduction delays on the ECG suggest a possible myocardial abscess.

Repeat echocardiography is recommended during therapy for patients with persistent fever, recurrent embolic events, a new murmur, widening of the pulse pressure, or signs or symptoms of heart failure. Repeat echocardiography is also recommended to look for periannular complications in prosthetic valve endocarditis. Although end-of-therapy echocardiography is not routinely recommended if patients respond adequately to antimicrobial therapy, serial echocardiography is usually suggested over the ensuing years to screen for long-term valvular dysfunction.

Routine serial ECGs are not recommended. ECG-documented conduction abnormalities are a late sign of perivalvular infections in patients with endocarditis; transesophageal echocardiography (TEE) is the screening method of choice if this complication is suspected.

Any new neurologic findings should prompt a search for evidence of central nervous system (CNS) complications such as embolic events, cerebral hemorrhage, mycotic aneurysm, or brain abscess. Renal function should be closely monitored so that antibiotic doses can be adjusted if necessary. If gentamicin is used for more than a few days, the patient should be alerted to watch for the signs and symptoms of vestibular or ototoxicity. Audiometric testing at baseline and periodically thereafter should be considered in patients at high risk for aminoglycoside-induced ototoxicity, including elderly patients, patients with preexisting renal dysfunction or hearing damage, patients receiving prolonged courses of gentamicin, and patients who also receive other potentially nephrotoxic agents. Serum gentamicin trough concentrations should also be assayed at regular intervals (e.g., twice weekly and more often if renal function is changing) and should be targeted for 1 to 3 μg/mL or less; higher concentrations should prompt either lower or less frequent dosing or both.

Serial blood cultures, especially early in the treatment course, are indicated in patients whose infective endocarditis is caused by virulent organisms that commonly fail first-line treatment, such as *S. aureus* or aerobic gram-negative bacilli. Positive follow-up blood cultures in this setting might suggest the need to change therapy, search for metastatic abscesses, or repeat echocardiography. Infectious disease consultation is highly recommended in this scenario.

Patients with infective endocarditis may continue to be febrile for some time after the institution of appropriate antibiotic treatment. About 50% of patients defervesce within 3 days of starting antibiotics, 75% by 1 week, and 90% by 2 weeks. Patients whose endocarditis is caused by *S. aureus*, aerobic gram-negative organisms, or fungi tend to defervesce more slowly than patients infected with other organisms. Prolonged fever (>1 week after the institution of appropriate antibiotics) should prompt repeat blood cultures. If such cultures are negative, several possibilities should be considered: myocardial abscess, extracardiac infection (e.g., mycotic aneurysm, psoas or splenic abscess, vertebral osteomyelitis, septic arthritis), immune complex–mediated tissue damage, or a complication of hospitalization and therapy (e.g., drug fever, nosocomial superinfection, pulmonary embolism). Appropriate studies might include TEE, CT scan of the abdomen, bone scan, and urinalysis with microscopy (to elicit evidence of interstitial nephritis). IV line sites should be carefully examined for evidence of infection, and indwelling central lines should be changed according to published guidelines.

Anticoagulation in individuals with infective endocarditis is controversial. Although new anticoagulation in the setting of native valve endocarditis does not appear to provide a benefit, continuing ongoing anticoagulation may be advisable. Some authorities recommend continuing anticoagulation in patients with mechanical prosthetic valve endocarditis. However, discontinuation of all anticoagulation for at least the first 2 weeks of antibiotic therapy is generally advised in patients who have *S. aureus* prosthetic valve endocarditis and who have experienced a recent CNS embolic event. This approach allows any CNS thrombus to organize and potentially prevents the acute hemorrhagic transformation of such embolic lesions. Reintroduction of anticoagulation in these patients must be cautious, and the international normalized ratio must be monitored carefully. The best option for patients with other indications for anticoagulation, such as deep vein thrombosis, major vessel embolization, or atrial fibrillation, is less clear and should be decided in a multidisciplinary fashion that balances the risks and benefits for each individual patient.

Initiation of high-dose (325 mg/day) aspirin in patients with infective endocarditis does not prevent subsequent embolic events and tends to increase the incidence of bleeding. Whether patients should remain on chronic, low-dose (81 mg) prophylactic aspirin if they develop subsequent infective endocarditis is uncertain, although nonrandomized data suggest such an approach is safe and may even reduce the risk of embolization from the infected valve.

Complications

The complications of infective endocarditis can be divided into four groups for ease of classification: direct valvular damage and consequences of local microbial invasion, embolic complications, metastatic infections from bacteremia, and immunologic phenomena. Local damage to the endocardium or myocardium may directly erode through the involved cardiac valve or adjacent myocardial wall, resulting in hemodynamically significant valvular perforations or intracardiac or extracardiac fistulae. Such local complications typically present clinically with the acute onset of heart failure and carry a poor prognosis, even with prompt cardiac surgery. Valve ring abscesses also require surgical intervention and are more frequent in patients with prosthetic valves. Although a conduction defect on ECG may suggest the diagnosis, TEE is the diagnostic technique of choice for detecting paravalvular abscess, valve perforation, or intracardiac fistulae. Frank myocardial abscesses are found in up to 20% of cases on autopsy, and *Aspergillus* endocarditis invades the myocardium in more than 50% of cases. Purulent pericarditis is rare and is usually associated with a concomitant myocardial abscess. Myocardial infarction (MI), thought to be caused by embolism of vegetative material into the coronary arteries, is seen in 40 to 60% of cases on autopsy, although most cases are clinically silent and lack characteristic ECG changes. However, up to 15% of elderly patients may present with clinical evidence of acute MI, with potentially disastrous complications if the MI is thought to be the primary event and the patient is given thrombolytic therapy. Heart failure is the leading cause of death in infective endocarditis, usually related to direct valvular damage.

About 35% of patients have at least one clinically evident embolic event. In fungal endocarditis, the majority of patients have at least one embolic event, frequently with a large embolus. The presence of large (>10 mm), mobile vegetations on the echocardiogram, particularly when the anterior mitral valve leaflet is involved, predicts a high risk of embolic complications. Systemic emboli most commonly lodge in the kidneys, spleen, large peripheral blood vessels, or especially in the CNS. Vegetations in right-sided endocarditis usually embolize to the lungs and cause abnormalities on the chest radiograph, although occasionally such emboli reach the left-sided circulation via a patent foramen ovale.

Renal abscesses are rare in infective endocarditis; however, bland renal infarction is a frequent, asymptomatic finding on abdominal CT scanning (about 50%

of cases at autopsy). Similarly, splenic infarction occurs in up to 44% of autopsy-confirmed cases. Such emboli may be asymptomatic but also can cause left upper quadrant pain radiating to the left shoulder, sometimes as the presenting symptom of infective endocarditis. A splenic infarction that progresses to form an abscess can cause persistent fever or bacteremia, so such patients should undergo abdominal CT to search for this complication.

Mycotic vascular aneurysms, which frequently occur at bifurcation points, are found in about 10 to 15% of cases at autopsy but may be clinically silent until they rupture (which may be months to years after apparently successful antibiotic treatment of infective endocarditis). Whereas peripheral mycotic aneurysms require surgical resection, intracerebral aneurysms can be resected or managed with intravascular techniques (e.g., coils) if they bleed, increase in size, and/or cause a mass effect (Chapter 377). For mycotic aneurysms of the abdominal aorta, endovascular repair may be preferable, but long-term antibiotics are generally recommended.

Many patients may have evidence of cerebrovascular emboli, which have a predilection for the middle cerebral artery distribution. Most emboli to the CNS occur early in the course of the disease, and are evident at the time of presentation or shortly thereafter. Embolic strokes may undergo hemorrhagic transformation, with a sudden worsening of the patient's neurologic status. Many patients with fungal endocarditis present with an embolic stroke or large emboli that occlude major vessels.

Some complications of infective endocarditis result when bacteremic seeding causes metastatic infection at a distant site. Patients may present with or develop osteomyelitis, septic arthritis, or epidural abscess. Purulent meningitis (Chapter 381) is a rare complication except in pneumococcal endocarditis, although many patients with *S. aureus* infective endocarditis who undergo lumbar puncture have a pleocytosis, without frank meningitis. Importantly, the finding of one metastatic complication of infective endocarditis does not exclude the possibility of additional sites of hematogenous infection, particularly in *S. aureus* endocarditis. Thus, the need for additional diagnostic evaluations should be guided by the patient's clinical course.

Immunologic phenomena complicating infective endocarditis are often directly related to high levels of circulating immune complexes. Renal biopsy results are usually abnormal in the setting of active infective endocarditis, especially in patients with renal impairment and abnormal urinalyses. Endocarditis classically causes a hypocomplementemia-related glomerulonephritis (Chapter 107). Histopathologically, the glomerular changes may be focal, diffuse, or membranoproliferative, or they may be akin to the immune complex disease found in systemic lupus erythematosus. In addition, many of the musculoskeletal conditions associated with infective endocarditis, including monoarticular and oligoarticular arthritides, are probably mediated by immune complexes. These immunologic phenomena usually abate with successful antimicrobial therapy.

Surgery

Some patients with infective endocarditis require surgical treatment, either to cure the infection or to address its complications (Table 61-8).[21] Most patients with evidence of direct extension of infection to myocardial structures, prosthetic valve dysfunction, or heart failure from endocarditis-induced valvular damage should undergo surgery. In addition, many cases of endocarditis caused by fungi, aerobic gram-negative bacilli, or multidrug-resistant organisms (e.g., vancomycin- or gentamicin-resistant enterococci) require surgical management. Progression of disease or persistence of fever and bacteremia for more than 7 to 10 days in the presence of appropriate antibiotic therapy also may indicate the need for valve surgery, although a thorough search must first be conducted to exclude other primary or metastatic foci of infection. In a randomized trial of patients with left-sided infective endocarditis, severe valve disease, and large vegetations (>10 mm), early valve surgery did not significantly reduce all-cause mortality at 6 months, but it markedly decreased the risk of systemic embolism, including stroke and MI. Surgical management also should be considered for patients who have recurrent (two or more) embolic events on appropriate antibiotic therapy and sometimes in patients who have large vegetations (>10 mm) on echocardiography plus one embolic event. The presence of *S. aureus* endocarditis involving the anterior mitral valve leaflet and large vegetations (>10 mm) may be a special circumstance calling for early surgical intervention to reduce the high risk of CNS emboli, especially when mitral valve repair, rather than valve replacement, can be accomplished. Unfortunately, only about 15 to 20% of these latter patients are judged to be candidates for valve repair at the time of valve surgery.

After 7 days of preoperative antibiotics, the risk of infection on a newly implanted valve is low.[22] Delaying surgery in patients with deteriorating cardiac function in an attempt to sterilize the affected valve is ill advised because the risk of progressive heart failure or further complications usually outweighs the relatively small risk of recurrent infective endocarditis after prosthetic valve implantation. Relative contraindications to valve replacement include recent large CNS emboli (>2 cm) or bleed (because of the risk of CNS bleeding in the perioperative period, when systemic anticoagulation is required), multiple prior valve replacements (because of the difficulty of sewing a new valve into tissue already weakened from previous surgeries), and ongoing injection drug use. On occasion, patients have both a compelling indication for valve replacement (e.g., acute heart failure) and a recent CNS embolic event. The risk of hemorrhagic transformation of such lesions during cardiac bypass–associated anticoagulation is controversial, but the greatest risk of such transformation is with larger (>2 cm) emboli, especially those that have exhibited a hemorrhagic component. In these latter scenarios, it is prudent to try to delay surgery for at least 2 to 4 weeks to allow organization and resolution of such emboli. However, there appears to be no survival benefit in delaying indicated valve replacement surgery (>7 days) after an ischemic stroke, especially in patients who have smaller CNS lesions.

After definitive surgical treatment, most patients should receive further antibiotic therapy unless a full course of antibiotics was administered before surgery and there is no evidence of ongoing infection. If the patient received antibiotics for less than 1 week before surgery or the culture from the operative site is positive, the patient should receive the equivalent of a full initial course of antibiotics appropriate for the organism. If the patient received antibiotics for 2 weeks or more and the culture result from the operative site is negative (regardless of whether valve histopathology shows inflammation or a positive Gram stain result), the patient should receive whatever remains of the originally planned course of appropriate antibiotic therapy.

In patients with infective endocarditis related to implanted cardiovascular devices, complete device removal is usually mandatory, regardless of the pathogen, if the goal is to cure the infection.[23] In patients who truly cannot tolerate device removal, chronic antibiotic therapy, sometimes delivered regionally in situ,[24] is the best alternative. If a replacement device needs to be implanted, the optimal timing for such a procedure is unclear. However, blood culture results should be negative, and any concomitant local or pocket site infection should be completely resolved.

The duration of antimicrobial therapy after device extraction depends on the device and the infection. For lead-related infective endocarditis, which is usually

TABLE 61-8 INDICATIONS FOR VALVE SURGERY IN ENDOCARDITIS

INDICATION	CLASS*
NATIVE VALVE ENDOCARDITIS	
Acute aortic insufficiency or mitral regurgitation with heart failure	I
Acute aortic insufficiency with tachycardia and pre-closure of the mitral valve on echocardiogram	I
Fungal endocarditis	I
Evidence of annular or aortic abscess, sinus or aortic true or false aneurysm, valvular dehiscence, rupture, perforation, or fistula	I
Evidence of valve dysfunction and persistent infection after a prolonged period (7-10 days) of appropriate therapy, provided there are no noncardiac causes of infection	I
Recurrent emboli after appropriate antibiotic therapy	I
Infection with enteric gram-negative organisms or organisms with a poor response to antibiotics in patients with evidence of valve dysfunction	I
Anterior mitral leaflet vegetation (especially with size >10 mm) or persistent vegetation after systemic embolization	IIa
Increase in vegetation size despite appropriate antimicrobial therapy	IIb
Early infections of the mitral valve that probably can be repaired, especially in the presence of large vegetations and/or recurrent emboli	III
Persistent fever and leukocytosis with negative blood cultures	III
PROSTHETIC VALVE ENDOCARDITIS	
Early prosthetic valve endocarditis (<2 mo after surgery)	I
Heart failure with prosthetic valve dysfunction	I
Nonstreptococcal/non-HACEK endocarditis	I
Evidence of perivalvular leak, annular or aortic abscess, sinus or aortic true or false aneurysm, fistula formation, or new-onset conduction disturbances	I
Persistent bacteremia after 7-10 days of appropriate antibiotic therapy, with noncardiac causes for bacteremia excluded	IIa
Recurrent peripheral embolus despite therapy	IIa

*Class I = conditions for which there is evidence or general agreement that a given procedure or treatment is useful and effective; class II = conditions for which there is conflicting evidence or a divergence of opinion about the usefulness or efficacy of a procedure or treatment; class IIa = weight of evidence or opinion is in favor of usefulness or efficacy; class IIb = usefulness or efficacy is less well established by evidence or opinion; class III = conditions for which there is evidence or general agreement that the procedure or treatment is not useful and in some cases may be harmful.
HACEK = *Haemophilus, Aggregatibacter, Cardiobacterium, Eikenella,* and *Kingella* spp.
Adapted from Otto CM, Nishimura RA, Bonow RO, et al. 2020 ACC/AHA guideline for the management of patients with valvular heart disease: a report of the American College of Cardiology/American Heart Association Joint Committee on Clinical Practice Guidelines. *Circulation.* 2021;143:e72-e227.

associated with blood stream infection, 2 weeks of therapy is recommended if there are no infection complications. For infection caused by *S. aureus*, therapy should be extended for up to 4 weeks.

Nearly 40% of patients with infective endocarditis related to implantable cardiovascular electronic devices have concomitant valve involvement, predominantly tricuspid valve infection, with in-hospital and 1-year mortality rates of 15% and 23%, respectively. Removal of the device appears to reduce the mortality rate by about 50% (from about 40% to about 20%). In such patients, 4 to 6 weeks of concomitant antibiotic therapy is recommended after complete removal of the device.

PREVENTION

No randomized clinical trials have addressed whether dental procedures predispose to infective endocarditis and whether antibiotic prophylaxis prevents it. However, data support a temporal association between invasive dental procedures and the subsequent development of infective endocarditis in high-risk patients,[25] and antibiotic prophylaxis is associated with reduced incidence of endocarditis following these procedures.[26] Based on these observational data, antibiotic prophylaxis is recommended by the American Heart Association (Table 61-9) when patients with the highest risk of endocarditis-related adverse outcomes undergo dental procedures that involve manipulation of the gingival tissue, the periapical region of teeth, or perforation of the oral mucosa.[27] Antibiotic prophylaxis is also recommended when high-risk patients undergo an invasive procedure of the respiratory tract, with incision or biopsy of the respiratory mucosa, such as tonsillectomy and adenoidectomy; or invasive procedures involving infected skin, skin structures, or musculoskeletal tissue (Table 61-10). Other consensus guidelines have also narrowed the indications for antibiotic prophylaxis with dental procedures. For example, guidelines from the European Society of Cardiology are largely consistent with American Heart Association guidelines. In contrast, guidelines in the United Kingdom state that no prophylaxis is routinely advised for any dental patient, regardless of underlying cardiac valvular conditions, while still giving dentists the latitude to prescribe antibiotic prophylaxis for selected patients. Since the recent publications of these more limited recommendations, follow-up surveys in these countries have generated mixed results without definitive evidence of cause-and-effect between reduction in the use of dental prophylaxis and any increased incidence of endocarditis due to viridans group streptococci.[28]

Amoxicillin is the usual first choice for prophylaxis of infective endocarditis in patients undergoing invasive dental procedures, but other options are likely equally given (Table 61-11). More than 90% of patients labeled as being "penicillin allergic" are not truly allergic by skin testing. If such patients require ongoing antibiotic prophylaxis, allergy evaluation (Chapter 234) is warranted so that appropriate patients can be "de-labeled" and receive amoxicillin in the future.

Patients with implanted electronic cardiovascular devices do not require antibiotic prophylaxis for dental or other invasive procedures, but such patients do require surgical site prophylaxis at the time of device placement. The recommended regimens for this latter scenario generally include a β-lactam (commonly cefazolin, 2 g IV 1 hour before device placement), regardless of whether a new device is being placed or a device is being revised. More aggressive prophylaxis with vancomycin, intraprocedural bacitracin pocket wash, and 2 days of postprocedural oral cephalexin does not significantly reduce infection rates.[A5] However, one randomized trial showed that use of an absorbable antibiotic-eluting envelope at the time

TABLE 61-9 UNDERLYING CONDITIONS FOR WHICH ANTIBIOTIC PROPHYLAXIS IS AND IS NOT SUGGESTED FOR DENTAL PROCEDURES

ANTIBIOTIC PROPHYLAXIS GENERALLY RECOMMENDED
Prosthetic cardiac valve or material
Presence of cardiac prosthetic valve
Transcatheter prosthetic valves
Cardiac valve repair with devices, including annuloplasty, rings, or clips
Left ventricular assist devices or implantable heart
Previous, relapsed, or recurrent infectious endocarditis
Congenital heart disease
Unrepaired cyanotic congenital congenital heart disease, including palliative shunts and conduits
Completely repaired congenital heart defect with prosthetic material or device, whether placed by surgery or by transcatheter during the first 6 mo after the procedure
Repaired congenital heart disease with residual defects at the site of or adjacent to the site of a prosthetic patch or prosthetic device
Surgical or transcatheter pulmonary artery valve or conduit placement
Cardiac transplant recipients who develop cardiac valvulopathy
ANTIBIOTIC PROPHYLAXIS NOT RECOMMENDED
Implantable electronic devices such as a pacemaker or similar devices
Septal defect closure devices when complete closure is achieved
Peripheral vascular grafts and patches, including those used for hemodialysis
Coronary artery stents or other vascular stents
Central nervous system ventriculoatrial shunts
Vena cava filters

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TABLE 61-10 PROCEDURES FOR WHICH ENDOCARDITIS PROPHYLAXIS IS AND IS NOT RECOMMENDED

PROPHYLAXIS IS RECOMMENDED*
Dental: all dental procedures involving manipulation of gingival tissue, the periapical region of teeth, or perforation of the oral mucosa
Respiratory: procedures involving incision or biopsy of the respiratory mucosa, such as tonsillectomy and adenoidectomy
Other: procedures involving infected skin, skin structures, or musculoskeletal tissue prior to incision and drainage
PROPHYLAXIS IS NOT RECOMMENDED
Dental: routine anesthetic injections through noninfected tissue, dental radiographs, placement of removable prosthodontic or orthodontic appliances, adjustment of orthodontic appliances, placement of orthodontic brackets, shedding of deciduous teeth, bleeding from trauma to the lips or oral mucosa
Respiratory: procedures not involving incision or biopsy of the respiratory mucosa, including bronchoscopy (unless the procedure involves incision of the respiratory tract mucosa)
Genitourinary: antibiotic prophylaxis solely to prevent infective endocarditis is not recommended
Gastrointestinal: antibiotic prophylaxis solely to prevent infective endocarditis is not recommended

*Only in patients with underlying cardiac conditions associated with the highest risk for adverse outcome from endocarditis (listed in Table 61-9).

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TABLE 61-11 ANTIBIOTIC REGIMENS FOR AN ADULT UNDERGOING A DENTAL PROCEDURE: SINGLE DOSE 30 TO 60 MINUTES BEFORE PROCEDURE*†

PATIENT CHARACTERISTICS	REGIMEN‡
Able to take oral medications	Amoxicillin 2 g PO
Unable to take oral medications	Ampicillin 2 g IV or IM; or cefazolin or ceftriaxone 1 g IM or IV
Allergic to penicillin or ampicillin and able to take oral medications	Cephalexin 2 g PO (or other first- or second-generation oral cephalosporin in equivalent adult doses); azithromycin 500 mg PO; or clarithromycin 500 mg PO; or doxycycline 100 mg PO
Allergic to penicillin or ampicillin and unable to take oral medications	Cefazolin or ceftriaxone 1 g IM or IV

*For the applicable procedures, see Table 61-10.

†For the applicable conditions, see Table 61-9.

‡Cephalosporins should not be used in an individual with a history of anaphylaxis, angioedema, or urticaria with penicillin or ampicillin.

Clindamycin is no longer recommended for antibiotic prophylaxis for a dental procedure.

IM = intramuscular; IV = intravenous; PO = oral.

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of device placement, replacement, or pocket revision could significantly reduce infections without adverse effects.[A6]

PROGNOSIS

Untreated infective endocarditis is uniformly fatal. Aggressive medical and surgical management dramatically improves the outcome. The overall mortality rate from both native and prosthetic valve endocarditis remains fairly high, ranging from 17 to 36%. Whereas certain subgroups, such as patients with viridans group streptococcal endocarditis, have a lower risk of death, patients with *S. aureus,* fungal, aerobic gram-negative bacillary, and zoonotic endocarditis have higher mortality rates. Heart failure and CNS events are the most frequent causes of death.

Endocarditis recurs in about 12 to 16% of patients and is more common in injection drug users, elderly people, and patients with prosthetic valves. The rate of relapse also varies depending on the causative organism. Easily treated infections, such as those with viridans group streptococci, have a low rate of relapse (5%), but more difficult-to-eradicate organisms may have significantly higher rates.

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62 PERICARDIAL DISEASES

BRIAN D. HOIT AND JAE K. OH

The pericardium is a two-layered sac composed of visceral and parietal components. The visceral pericardium is a serosal cell monolayer that adheres firmly to the epicardium, reflects over the origin of the great vessels, and, together with a tough, fibrous parietal layer encases the heart. The pericardial space enclosed between the two serosal layers normally contains up to 50 mL of plasma ultrafiltrate. The pericardium is well innervated, so pericardial inflammation may produce severe pain and trigger vagally mediated reflexes.

As a result of its relatively inelastic physical properties, the pericardium limits acute cardiac dilation and enhances mechanical interactions of the cardiac chambers.[1] In response to chronic stretch, the pericardium dilates to allow a slowly accumulating pericardial effusion to become quite large without compressing the cardiac chambers and to allow left ventricular remodeling to occur without excessive pericardial restraint. Conversely, a scarred or thickened pericardium can limit the filling of the heart, resulting in pericardial constriction. Despite the important functions of the normal pericardium, congenital absence or surgical resection of the pericardium does not appear to have any major untoward effects.

ACUTE PERICARDITIS

EPIDEMIOLOGY AND PATHOBIOLOGY

Acute inflammation of the pericardium, with or without an associated pericardial effusion, can occur as an isolated clinical problem or as a manifestation of systemic disease. Although about 85% of isolated cases of acute pericarditis are idiopathic or viral, the list of other potential causes is quite extensive (Table 62-1). Viral causes include echoviruses, group B coxsackieviruses, and, recently, severe acute respiratory syndrome coronavirus 2 (Chapter 336),[2] but obtaining specific viral titers does not alter patient management. About 6% of cases are neoplastic in origin, about 4% are caused by tuberculosis, about 3% are caused by other bacterial or fungal infections, and about 2% are caused by collagen vascular disease. Patients with fever greater than 38° C or a subacute course or who fail to respond promptly to therapy are most likely to have pericarditis caused by a systemic autoimmune disease, malignancy, drugs (including checkpoint inhibitors [Chapter 164]),[3] or bacterial infection.

CLINICAL MANIFESTATIONS

Most patients with acute pericarditis experience sharp retrosternal chest pain (see Table 39-2 in Chapter 39), which can be quite severe and debilitating. In some cases, however, pericarditis is asymptomatic, such as when it accompanies rheumatoid arthritis. Pericardial pain is usually worse with inspiration and when supine, and it is generally relieved by sitting and leaning forward. Typically, pericardial pain is referred to the scapular ridge, presumably owing to irritation of the phrenic nerves, which provide sensory innervation to the pericardium. The chest pain of acute pericarditis must be differentiated from pulmonary embolism and myocardial ischemia or infarction (Table 62-2).

The pericardial friction rub is the classic finding in patients with acute pericarditis. A friction rub is a high-pitched, scratchy sound that can have one, two, or three components corresponding to ventricular ejection, rapid ventricular filling in early diastole, and atrial systole. A pericardial rub, which is differentiated from a murmur by its scratchy quality, is sometimes localized to a small area on the chest wall and may come and go spontaneously or with changes in position. To hear a rub, it may be necessary to auscultate the heart with the patient in multiple positions, especially using the diaphragm with the patient learning forward and not breathing after full expiration. The pericardial friction rub must be differentiated from a pleural rub, which is absent during suspended respiration, but the pericardial rub is unaffected.

DIAGNOSIS

A targeted evaluation (Table 62-3) can help distinguish pericarditis from other conditions as well as help establish the cause of true pericarditis (Table 62-4).[4] The diagnosis of acute pericarditis can be made with two of the following criteria: typical chest pain, pericardial friction rub, characteristic electrocardiogram (ECG) changes, and pericardial effusion. Early in the course of acute pericarditis, the ECG typically displays diffuse ST elevation in association with PR depression (Fig. 62-1). The ST elevation is usually present in all leads except for aVR, but the changes may be atypical in post–myocardial infarction (MI) pericarditis. Classically, the ECG changes of acute pericarditis evolve over several days; resolution of the ST elevation is followed by widespread T wave inversion that subsequently normalizes, although the temporal evolution of ECG changes is highly variable. Uremic pericarditis usually occurs without the typical ECG abnormalities.

Patients with acute pericarditis usually have evidence of systemic inflammation, including leukocytosis, an elevated erythrocyte sedimentation rate (ESR), and increased C-reactive protein (CRP) level. A low-grade fever is common, but a temperature greater than 38° C is unusual and suggests the possibility of bacterial pericarditis.

Troponin levels typically are minimally elevated in acute pericarditis owing to some involvement of the epicardium by the inflammatory process. An elevated troponin level in acute pericarditis usually returns to normal within 1 to 2 weeks and is not associated with a worse prognosis. Although the elevated troponin level may lead to the misdiagnosis of an ST elevation MI (Chapter 58), most patients with elevated troponin levels and acute pericarditis have normal coronary angiograms. An echocardiogram (Chapter 43) can help avoid a misdiagnosis of MI.

Echocardiography may demonstrate a small pericardial effusion in the presence of acute pericarditis, but a normal echocardiogram does not exclude the diagnosis of acute pericarditis. An echocardiogram is critical, however, in excluding the diagnosis of cardiac tamponade (see later). When the diagnosis of acute pericarditis is unclear, cardiac magnetic resonance imaging (MRI) can demonstrate pericardial inflammation as delayed enhancement of the pericardium (Fig. 62-2). Diagnostic pericardiocentesis is indicated in suspected purulent tuberculosis or malignant pericarditis or if the patient has cardiac tamponade.

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of device placement, replacement, or pocket revision could significantly reduce infections without adverse effects.[A6]

PROGNOSIS

Untreated infective endocarditis is uniformly fatal. Aggressive medical and surgical management dramatically improves the outcome. The overall mortality rate from both native and prosthetic valve endocarditis remains fairly high, ranging from 17 to 36%. Whereas certain subgroups, such as patients with viridans group streptococcal endocarditis, have a lower risk of death, patients with *S. aureus,* fungal, aerobic gram-negative bacillary, and zoonotic endocarditis have higher mortality rates. Heart failure and CNS events are the most frequent causes of death.

Endocarditis recurs in about 12 to 16% of patients and is more common in injection drug users, elderly people, and patients with prosthetic valves. The rate of relapse also varies depending on the causative organism. Easily treated infections, such as those with viridans group streptococci, have a low rate of relapse (5%), but more difficult-to-eradicate organisms may have significantly higher rates.

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62 PERICARDIAL DISEASES

BRIAN D. HOIT AND JAE K. OH

The pericardium is a two-layered sac composed of visceral and parietal components. The visceral pericardium is a serosal cell monolayer that adheres firmly to the epicardium, reflects over the origin of the great vessels, and, together with a tough, fibrous parietal layer encases the heart. The pericardial space enclosed between the two serosal layers normally contains up to 50 mL of plasma ultrafiltrate. The pericardium is well innervated, so pericardial inflammation may produce severe pain and trigger vagally mediated reflexes.

As a result of its relatively inelastic physical properties, the pericardium limits acute cardiac dilation and enhances mechanical interactions of the cardiac chambers.[1] In response to chronic stretch, the pericardium dilates to allow a slowly accumulating pericardial effusion to become quite large without compressing the cardiac chambers and to allow left ventricular remodeling to occur without excessive pericardial restraint. Conversely, a scarred or thickened pericardium can limit the filling of the heart, resulting in pericardial constriction. Despite the important functions of the normal pericardium, congenital absence or surgical resection of the pericardium does not appear to have any major untoward effects.

ACUTE PERICARDITIS

EPIDEMIOLOGY AND PATHOBIOLOGY

Acute inflammation of the pericardium, with or without an associated pericardial effusion, can occur as an isolated clinical problem or as a manifestation of systemic disease. Although about 85% of isolated cases of acute pericarditis are idiopathic or viral, the list of other potential causes is quite extensive (Table 62-1). Viral causes include echoviruses, group B coxsackieviruses, and, recently, severe acute respiratory syndrome coronavirus 2 (Chapter 336),[2] but obtaining specific viral titers does not alter patient management. About 6% of cases are neoplastic in origin, about 4% are caused by tuberculosis, about 3% are caused by other bacterial or fungal infections, and about 2% are caused by collagen vascular disease. Patients with fever greater than 38° C or a subacute course or who fail to respond promptly to therapy are most likely to have pericarditis caused by a systemic autoimmune disease, malignancy, drugs (including checkpoint inhibitors [Chapter 164]),[3] or bacterial infection.

CLINICAL MANIFESTATIONS

Most patients with acute pericarditis experience sharp retrosternal chest pain (see Table 39-2 in Chapter 39), which can be quite severe and debilitating. In some cases, however, pericarditis is asymptomatic, such as when it accompanies rheumatoid arthritis. Pericardial pain is usually worse with inspiration and when supine, and it is generally relieved by sitting and leaning forward. Typically, pericardial pain is referred to the scapular ridge, presumably owing to irritation of the phrenic nerves, which provide sensory innervation to the pericardium. The chest pain of acute pericarditis must be differentiated from pulmonary embolism and myocardial ischemia or infarction (Table 62-2).

The pericardial friction rub is the classic finding in patients with acute pericarditis. A friction rub is a high-pitched, scratchy sound that can have one, two, or three components corresponding to ventricular ejection, rapid ventricular filling in early diastole, and atrial systole. A pericardial rub, which is differentiated from a murmur by its scratchy quality, is sometimes localized to a small area on the chest wall and may come and go spontaneously or with changes in position. To hear a rub, it may be necessary to auscultate the heart with the patient in multiple positions, especially using the diaphragm with the patient learning forward and not breathing after full expiration. The pericardial friction rub must be differentiated from a pleural rub, which is absent during suspended respiration, but the pericardial rub is unaffected.

DIAGNOSIS

A targeted evaluation (Table 62-3) can help distinguish pericarditis from other conditions as well as help establish the cause of true pericarditis (Table 62-4).[4] The diagnosis of acute pericarditis can be made with two of the following criteria: typical chest pain, pericardial friction rub, characteristic electrocardiogram (ECG) changes, and pericardial effusion. Early in the course of acute pericarditis, the ECG typically displays diffuse ST elevation in association with PR depression (Fig. 62-1). The ST elevation is usually present in all leads except for aVR, but the changes may be atypical in post–myocardial infarction (MI) pericarditis. Classically, the ECG changes of acute pericarditis evolve over several days; resolution of the ST elevation is followed by widespread T wave inversion that subsequently normalizes, although the temporal evolution of ECG changes is highly variable. Uremic pericarditis usually occurs without the typical ECG abnormalities.

Patients with acute pericarditis usually have evidence of systemic inflammation, including leukocytosis, an elevated erythrocyte sedimentation rate (ESR), and increased C-reactive protein (CRP) level. A low-grade fever is common, but a temperature greater than 38° C is unusual and suggests the possibility of bacterial pericarditis.

Troponin levels typically are minimally elevated in acute pericarditis owing to some involvement of the epicardium by the inflammatory process. An elevated troponin level in acute pericarditis usually returns to normal within 1 to 2 weeks and is not associated with a worse prognosis. Although the elevated troponin level may lead to the misdiagnosis of an ST elevation MI (Chapter 58), most patients with elevated troponin levels and acute pericarditis have normal coronary angiograms. An echocardiogram (Chapter 43) can help avoid a misdiagnosis of MI.

Echocardiography may demonstrate a small pericardial effusion in the presence of acute pericarditis, but a normal echocardiogram does not exclude the diagnosis of acute pericarditis. An echocardiogram is critical, however, in excluding the diagnosis of cardiac tamponade (see later). When the diagnosis of acute pericarditis is unclear, cardiac magnetic resonance imaging (MRI) can demonstrate pericardial inflammation as delayed enhancement of the pericardium (Fig. 62-2). Diagnostic pericardiocentesis is indicated in suspected purulent tuberculosis or malignant pericarditis or if the patient has cardiac tamponade.

ABSTRACT

The pericardium is a two-layered sac that encases the heart and constrains its filling. The pericardium can be affected by virtually every category of disease, including infectious, neoplastic, immune-inflammatory, metabolic, iatrogenic, traumatic, and congenital causes. Pericardial heart disease includes pericarditis, cardiac tamponade, constrictive pericarditis, and cysts. Pericarditis is an acute inflammatory condition, typically as a result of viral infection. Such cases usually resolve, occasionally recur, and infrequently progress to pericardial tamponade. Pericarditis caused by acute bacterial infection requires urgent drainage. Tuberculous pericarditis can progress to chronic constriction. The primary abnormality of cardiac tamponade is pan-cyclic compression of the cardiac chambers by increased pericardial fluid, so that all four cardiac chambers compete for a fixed intrapericardial volume. Features responsible for the pathophysiology include transmission of thoracic pressure through the pericardium and heightened ventricular interdependence. In constrictive pericarditis, the pericardium limits diastolic filling, causes dissociation of intracardiac and intrathoracic pressures, and heightens ventricular interdependence. Both conditions result in diastolic dysfunction, elevated and equal venous and ventricular diastolic pressure, respiratory variation in ventricular filling, and, ultimately, reduced cardiac output.

KEYWORDS

pericardium
pericarditis
pericardial effusion
cardiac tamponade
pericardial constriction
effusive-constrictive
imaging

TABLE 62-1 CAUSES OF PERICARDITIS: INFECTIOUS AND NONINFECTIOUS

INFECTIOUS PERICARDITIS (⅔ OF CASES)

Viral (most common): echovirus and coxsackievirus (usual), influenza, EBV, CMV, adenovirus, varicella, rubella, mumps, SARS-CoV-2, HBV, HCV, HIV, parvovirus B19, human herpesvirus 6
Bacterial: tuberculosis (4-5%)* and *Coxiella burnetii* (most common); other bacterial causes (rare) include pneumococcosis, meningococcosis, gonococcosis, *Haemophilus,* staphylococci, *Chlamydia, Mycoplasma, Legionella, Leptospira, Listeria*
Fungal (rare): histoplasmosis more likely in immunocompetent patients; aspergillosis, blastomycosis, candidiasis more likely in immunosuppressed patients
Parasitic (very rare): *Echinococcus, Toxoplasma*

NONINFECTIOUS PERICARDITIS (⅓ OF CASES)

Autoimmune Pericarditis (<10%)*
Pericardial injury syndromes: post–myocardial infarction syndrome; postpericardiotomy syndrome; posttraumatic pericarditis, including iatrogenic pericarditis (e.g., after percutaneous coronary interventions, pacemaker insertion, ablation)
Pericarditis in systemic autoimmune and autoinflammatory diseases: more common in systemic lupus erythematosus, Sjögren syndrome, rheumatoid arthritis, systemic sclerosis, systemic vasculitides, Behçet syndrome, sarcoidosis, familial Mediterranean fever
Autoreactive pericarditis†
Neoplastic Pericarditis (5-7%)*
Primary tumors (rare): pericardial mesothelioma
Secondary metastatic tumors (common): lung and breast cancer, lymphoma
Metabolic Pericarditis: Uremia, Myxedema (common); others rare
Traumatic Pericarditis (rare)
Direct injury: penetrating thoracic injury, esophageal perforation, iatrogenic
Indirect injury: nonpenetrating thoracic injury, radiation injury
Drug-related pericarditis (rare): procainamide, hydralazine, isoniazid, and phenytoin (lupus-like syndrome), penicillins (hypersensitivity pericarditis with eosinophilia), doxorubicin, and daunorubicin (often associated with cardiomyopathy; may cause pericardiopathy), immune checkpoint inhibitors (e.g., ipilimumab, pembrolizumab)

*Percentages refer to unselected cases.
†The diagnosis of autoreactive pericarditis is established using the following criteria: (1) increased number of lymphocytes and mononuclear cells >5000/μL (autoreactive lymphocytic) or the presence of antibodies against heart muscle tissue (antisarcolemmal) in the pericardial fluid (autoreactive antibody mediated), (2) signs of myocarditis on epicardial or endomyocardial biopsies by ≥14 cells/mm^2, and (3) exclusion of infections, neoplasia, and systemic and metabolic disorders.
CMV = cytomegalovirus; EBV = Epstein-Barr virus; HBV = hepatitis B virus; HCV = hepatitis C virus; HIV = human immunodeficiency virus; SARS-CoV-2 = severe acute respiratory syndrome coronavirus 2.
From Imazio M, Spodick DH, Brucato A, et al. Controversial issues in the management of pericardial diseases. *Circulation*. 2010;121:916-928.

TABLE 62-2 DIFFERENTIATION OF PERICARDITIS FROM MYOCARDIAL ISCHEMIA OR INFARCTION AND PULMONARY EMBOLISM

FINDINGS	MYOCARDIAL ISCHEMIA OR INFARCTION	PERICARDITIS	PULMONARY EMBOLISM
CHEST PAIN			
Character	Pressure-like heavy, squeezing	Sharp, stabbing, occasionally dull	Sharp, stabbing
Change with respiration	No	Worsened with inspiration	In phase with respiration (absent when the patient is apneic)
Change with position	No	Worse when supine; improved when sitting up or leaning forward	No
Duration	Minutes (ischemia); hours (infarction)	Hours to days	Hours to days
Response to nitroglycerin	Improved	No change	No change
PHYSICAL EXAMINATION			
Friction rub	Absent (unless pericarditis is present)	Present in most patients	Pleural friction rub may occur
ELECTROCARDIOGRAM			
ST segment elevation	Localized convex	Widespread concave	Limited to leads III, aVF, and V_1
PR segment depression	Rare	Frequent	None

Modified from Little WC, Freeman GL. Pericardial disease. *Circulation*. 2006;113:1622-1632.

TREATMENT

Patients who have manifestations of an underlying systemic process, such as an inflammatory disease, have high-risk features (i.e., fever >38° C, subacute course, failure to respond to treatment, an elevated troponin level with evidence of concomitant left ventricular dysfunction, a large pericardial effusion, incipient or established pericardial tamponade), or have suspected acute MI (Chapter 58) warrant hospitalization and further evaluation. Patients without these features can usually be followed as outpatients (Fig. 62-3).

If acute pericarditis is a manifestation of an underlying disease, such as a systemic rheumatologic condition, it often responds to treatment of the primary condition. Most cases of acute idiopathic or viral pericarditis are self-limited and respond to treatment with aspirin (650 mg every 6 hours) or another nonsteroidal anti-inflammatory drug (NSAID) such as ibuprofen (300 to 800 mg every 6 to 8 hours).[5] The dose of NSAID should be tapered after symptoms and any pericardial effusion have resolved, but the medication should be taken for at least 3 to 4 weeks to minimize the risk of recurrent pericarditis.

In addition, colchicine (0.6 to 1.2 mg/day for 3 months) should be started in all patients with acute pericarditis[6] to reduce the rate of persistent symptoms at 72 hours, reduce the likelihood of recurrent pericarditis from 55 to 24% at 18 months, and reduce the rate of subsequent hospitalization.[A1] The major side effect of colchicine is diarrhea. The lower dose of colchicine should be used in patients who weigh less than 70 kg or who have side effects with the higher dose. Colchicine should be avoided in patients with abnormal renal or hepatic function and in patients being treated with macrolide antibiotics, which alter its metabolism.

A proton pump inhibitor, such as omeprazole (20 mg/day), should be considered to improve the gastric tolerability of NSAIDs. Warfarin and heparin should be avoided to minimize the risk of hemopericardium, but anticoagulation may be required if the patient is in atrial fibrillation or has a prosthetic heart valve. It is prudent to avoid exercise until after the chest pain completely resolves. If pericarditis recurs, the patient can be reloaded with colchicine and intramuscular ketorolac (15 to 30 mg, once) and then continued on an oral NSAID and colchicine for at least 3 months.

TABLE 62-3 SELECTED DIAGNOSTIC TESTS IN ACUTE PERICARDITIS

IN ALL PATIENTS
Tuberculin skin test (plus control skin test to exclude anergy)
BUN and creatinine to exclude uremia
Erythrocyte sedimentation rate
Electrocardiogram
Chest radiograph
Echocardiogram
IN SELECTED PATIENTS
Cardiac magnetic resonance imaging
ANA and rheumatoid factor to exclude SLE or rheumatoid arthritis in patients with acute arthritis or pleural effusion
TSH and T_4 to exclude hypothyroidism in patients with clinical findings suggestive of hypothyroidism and in asymptomatic patients with unexplained pericardial effusion
HIV test to exclude AIDS in patients with risk factors for HIV disease or a compatible clinical syndrome
Blood cultures in febrile patients to exclude infective endocarditis and bacteremia
Fungal serologic tests in patients from endemic areas or in immunocompromised patients
ASO titer in children or teenagers with suspected rheumatic fever
Heterophil antibody test to exclude mononucleosis in young or middle-aged patients with a compatible clinical syndrome or acute fever, weakness, and lymphadenopathy

AIDS = acquired immunodeficiency virus; ANA = antinuclear antibody; ASO = antistreptolysin O; BUN = blood urea nitrogen; HIV = human immunodeficiency virus; SLE = systemic lupus erythematosus; T_4 = thyroxine; TSH = thyroid-stimulating hormone.

Modified from Nishimura RA, Kidd KR. Recognition and management of patients with pericardial disease. In: Braunwald E, Goldman L, eds. *Primary Cardiology*. 2nd ed. Philadelphia: WB Saunders; 2003:625.

Although acute pericarditis usually responds dramatically to systemic corticosteroids, observational studies strongly suggest that the use of steroids increases the probability of relapse in patients treated with colchicine. Except when needed to treat an underlying inflammatory disease, every effort should be made to avoid the use of steroids, reserving low-dose steroids for patients who cannot tolerate aspirin and other NSAIDs or whose recurrence is not responsive to colchicine and intravenous NSAIDs. If steroids are used, low-dose prednisone (0.2 to 0.5 mg/kg) appears to be as effective as higher doses and is less likely to be associated with recurrence. Steroids should be continued for at least 1 month before slow tapering, which can be guided by return of the CRP level to the normal range. Pericardiocentesis is not recommended unless purulent or tuberculous pericarditis is clinically suspected or the patient fails to respond to 2 to 3 weeks of NSAID therapy.

PROGNOSIS

The course of viral and idiopathic pericarditis is usually self-limited. Although most patients recover completely, the 5-year mortality after hospitalization for pericarditis is about 30% higher than in age-matched controls.

About 25% of patients, however, have recurrent pericarditis weeks to months later, probably caused by an immune response, and some patients may have multiple debilitating episodes.[7] Interestingly, in patients whose acute pericarditis is accompanied by myocarditis, as evidenced by elevation of serum troponin levels, the recurrence rate is closer to 10%. Recurrent pericarditis is more common in patients treated with steroids for the acute episode, especially during a rapid steroid taper. Prolonged high-dose NSAID treatment (e.g., ibuprofen 300 to 600 mg three times a day) plus colchicine (0.5 to 0.6 mg twice daily, reducing to once daily after 3 to 6 months) is effective for recurrent pericarditis.[A2] In patients who cannot tolerate colchicine or who have recurrent episodes despite colchicine and high-dose NSAID treatment (e.g., indomethacin 50 mg three times a day or ibuprofen 800 mg four times a day), oral steroids (e.g., prednisone 0.2 to 0.5 mg/kg/day for 2 to 4 weeks and then slowly tapered over several months) are generally recommended. The addition of an anti–interleukin 1 drug, such as rilonacept[A3] (after a 320-mg load, 160 mg subcutaneously once weekly) or anakinra[A4] (100 mg subcutaneously once daily), lowers the risk of recurrent pericarditis by over 90%.[A5] In patients with refractory, recurrent pericarditis, surgical pericardiectomy can be considered. Patients who have tuberculous or purulent pericarditis have the highest risk for progression to constrictive pericarditis (see later).

PERICARDIAL EFFUSION AND TAMPONADE

EPIDEMIOLOGY

A pericardial effusion can be caused by any disease that causes acute pericarditis (see Table 62-1), but a majority of cases are caused by conditions other than viral or idiopathic pericarditis (Table 62-5). For example, tamponade occurs in about 10 to 15% of patients with idiopathic pericarditis, but it develops in more than 50% of patients with malignant, tuberculous, or purulent pericarditis. Tuberculosis and neoplastic disease are typically associated with serosanguineous effusions, but such effusions also can be seen with typical viral or idiopathic pericarditis, with uremia, and after mediastinal irradiation. Hemopericardium is seen most commonly with trauma, myocardial rupture after MI, catheter-induced myocardial or epicardial coronary artery rupture, aortic dissection with rupture into the pericardial space, or primary hemorrhage in patients receiving anticoagulant therapy, often after cardiac valve surgery. Chylopericardium is rare and usually results from traumatic or surgical injury to, or neoplastic obstruction of, the thoracic duct.

PATHOBIOLOGY

Under normal conditions, the space between the parietal and visceral pericardium can accommodate only a small amount of fluid before the development of tamponade physiology. The clinical consequences of a pericardial effusion depend on the rate of increase. A rapidly accumulating effusion, as in hemopericardium caused by trauma or aortic dissection, may result in tamponade physiology with just 100 to 200 mL of fluid. It is not surprising, therefore, that cardiac perforation quickly results in tamponade. By comparison, a more slowly developing effusion gradually stretches the pericardium and shifts the normally steep pericardial pressure-volume relation to the right; this explains why large but slowly developing effusions may not produce tamponade.

Tamponade physiology occurs when fluid accumulation in the intrapericardial space is sufficient to compress the heart, resulting in impaired cardiac filling. The increased pericardial pressure in cardiac tamponade accentuates the interdependence among the cardiac chambers as the total cardiac volume is limited by the pericardial effusion. With normal inspiration, right ventricular filling is enhanced, the intraventricular septum is displaced toward the left ventricle, and left ventricular filling and the resulting stroke volume are reduced; these changes are reversed during expiration. In tamponade, these physiologic variations are enhanced and are responsible for the clinical finding of "paradoxical pulse." A small (<10 mm Hg) pulsus paradoxus, which is a decline in systemic blood pressure during inspiration, is normal and is related to the ventricles being confined within the pericardium and sharing a common septum. In cardiac tamponade, this phenomenon is exaggerated, and systemic blood pressure falls by more than 10 mm Hg during inspiration. A pulsus paradoxus also may be present with hypovolemic shock, chronic obstructive pulmonary disease, and bronchospasm.

CLINICAL MANIFESTATIONS

A slowly accumulating, isolated pericardial effusion is often completely asymptomatic. The physical examination results may be normal, but the heart sounds may be muffled. The diagnosis is usually suggested by a chest radiograph that shows cardiomegaly with a globular heart (Fig. 62-4; see also Fig. 44-5) or by an echocardiogram, computed tomography (CT) scan, or MRI performed for another indication. Patients with hypothyroidism, uremia, or collagen vascular disease may have asymptomatic effusions discovered during comprehensive evaluations.

Patients with tamponade are usually anxious and tachycardic, and they may complain of dyspnea, orthopnea, and chest pain. The increased venous pressure is usually apparent as jugular venous distention.[8] The x descent (during ventricular systole) is typically the dominant jugular venous wave, with little or no y descent (during early diastole) (Chapter 39). The heart sounds are classically soft or muffled, especially if there is a large pericardial effusion. In rapidly developing cardiac tamponade, especially hemorrhagic cardiac tamponade, the jugular veins may not be distended because the time course has been insufficient for a compensatory increase in venous pressure. Such "low-pressure" tamponade may also occur in volume-depleted patients. The patient may have signs of right heart failure, with peripheral edema, right upper quadrant pain caused by hepatic congestion, or abnormal liver enzymes and serum bilirubin level.

TABLE 62-4 PRESENTATION AND TREATMENT OF THE MOST COMMON CAUSES OF PERICARDITIS

TYPE	PATHOGENESIS OR ETIOLOGY	DIAGNOSIS	TREATMENT	COMPLICATIONS	COMMENTS
Viral	Coxsackievirus B Echovirus type 8 Epstein-Barr virus	Leukocytosis Elevated ESR Mild cardiac biomarker elevation	Symptomatic relief, NSAIDs, colchicine	Tamponade Relapsing pericarditis	Peaks in spring and fall
Tuberculous	*Mycobacterium tuberculosis*	Isolation of organism from biopsy fluid Granulomas not specific	Triple-drug antituberculosis regimen Pericardial drainage followed by early (4-6 wk) pericardiectomy if signs of tamponade or constriction develop	Tamponade Constrictive pericarditis	1-8% of patients with tuberculosis pneumonia; rule out HIV infection
Bacterial	Group A streptococcus *Staphylococcus aureus* *Streptococcus pneumoniae*	Leukocytosis with marked left shift Purulent pericardial fluid	Pericardial drainage by catheter or surgery Systemic antibiotics Pericardiectomy if constrictive physiology develops	Tamponade in one third of patients	Very high mortality rate if not recognized early
Post–myocardial infarction	12 hr–10 days after infarction	Fever Pericardial friction rub Echo: effusion	Aspirin Prednisone	Tamponade rare	More frequent in large Q wave infarctions Anterior > inferior
Uremic	Untreated renal failure: 50% Chronic dialysis: 20%	Pericardial rub: 90%	Intensive dialysis Indomethacin: probably ineffective Catheter drainage Surgical drainage	Tamponade Hemodynamic instability on dialysis	Avoid NSAIDs ≈50% respond to intensive dialysis
Neoplastic	In order of frequency: lung cancer, breast cancer, leukemia and lymphoma, others	Chest pain, dyspnea Echo: effusion CT, MRI: tumor metastases to pericardium Cytologic examination of fluid positive in 85%	Catheter drainage Subxiphoid pericardiectomy Chemotherapy directed at underlying malignant neoplasm	Tamponade Constriction	

CT = computed tomography; Echo = echocardiogram; ESR = erythrocyte sedimentation rate; HIV = human immunodeficiency virus; MRI = magnetic resonance imaging; NSAIDs = nonsteroidal anti-inflammatory drugs.

Modified from Malik F, Foster E. Pericardial disease. In: Wachter RM, Goldman L, Hollander H, eds. *Hospital Medicine*. 2nd ed. Philadelphia: Lippincott Williams & Wilkins; 2005:449.

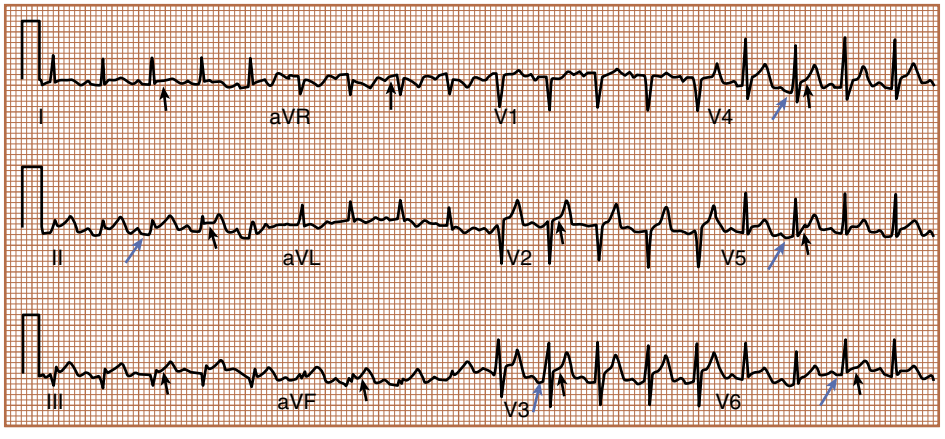

FIGURE 62-1. Electrocardiogram demonstrating typical features of acute pericarditis on presentation. There is diffuse ST elevation and PR depression, except in aVR, in which there is ST depression and PR elevation.

The hallmark of cardiac tamponade is a paradoxical pulse, which is defined as a drop of more than 10 mm Hg in inspiratory systolic arterial pressure (usually measured with a sphygmomanometer during slow inspiration). When severe, the paradoxical pulse may be apparent as the absence of a palpable brachial or radial pulse during inspiration. A paradoxical pulse can also occur when there are wide swings in intrathoracic pressure, pulmonary embolism (Chapter 68), or hypovolemic shock (Chapter 92). A paradoxical pulse may be difficult to recognize in the presence of severe shock.

DIAGNOSIS

Cardiac tamponade, which is a treatable cause of shock (Chapter 93), can be rapidly fatal if unrecognized. As such, cardiac tamponade should be considered in the differential diagnosis of any patient with shock or pulseless electrical activity.

Cardiac tamponade is usually suspected based on jugular venous distention, sinus tachycardia with hypotension, narrow pulse pressure, elevated (>10 mm Hg) pulsus paradoxus, and distant heart sounds.

The ECG often shows low voltage and sometimes electrical alternans (Fig. 62-5) when the heart swings within a large pericardial effusion. The chest radiograph shows a globular, enlarged cardiac shadow (see Fig. 44-5 and Fig. 62-6) without pulmonary venous congestion.

Echocardiography, which is the key diagnostic test for cardiac tamponade, must be performed without delay in any patient suspected of having this condition. Echocardiography detects pericardial effusions as an echo-free space around the heart (Fig. 62-4), demonstrates the size and distribution of the pericardial effusion, and reflects its hemodynamic consequences. The inferior vena cava is almost always enlarged, right atrial and right ventricular collapse indicates cardiac compression, and enhanced respiratory variation of ventricular filling is a manifestation of increased ventricular interdependence.

FIGURE 62-2. Cardiac magnetic resonance image of a patient with acute pericarditis shows late gadolinium hyperenhancement of the pericardium and epicardium.

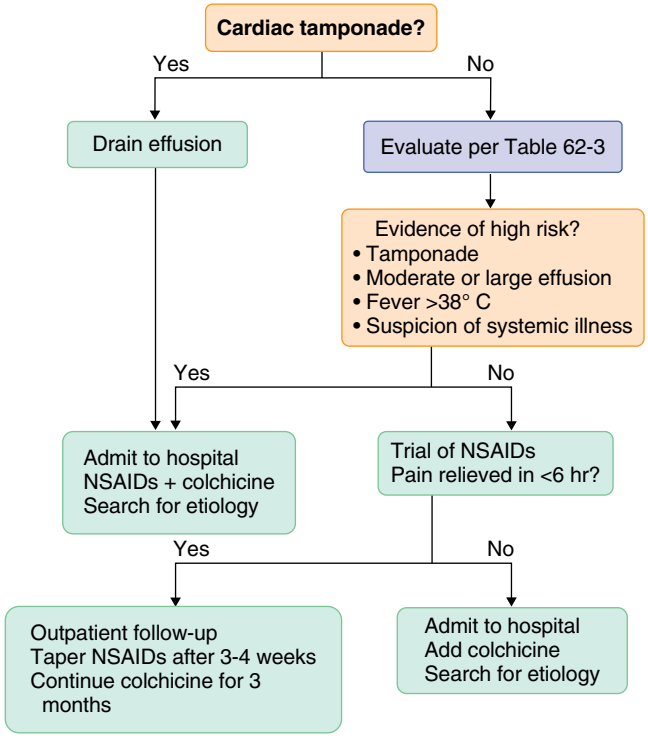

FIGURE 62-3. Initial management of patients with pericarditis. NSAID = nonsteroidal anti-inflammatory drug.

Right ventricular collapse is more specific for tamponade than is right atrial collapse, but the right-sided chambers may not collapse when tamponade occurs in patients with pulmonary hypertension. Cardiac tamponade can result from a loculated pericardial effusion after cardiac surgery or trauma and may present atypically. A loculated effusion may not be apparent on transthoracic echocardiography, but transesophageal echocardiography and thoracic CT or MRI can delineate loculated pericardial effusions.

On Doppler study, mitral inflow velocity (especially early diastolic velocity, designated as E velocity) normally increases with expiration and decreases with inspiration; the opposite respiratory variation is seen in tricuspid inflow velocity. Doppler findings for tamponade, which are more sensitive than two-dimensional echocardiography, include augmented respiratory variation of mitral and tricuspid inflow E velocities as a function of ventricular interdependence. These changes may be seen even before frank hemodynamic compromise caused by pericardial effusion. Although Doppler echocardiography provides important information, it must be emphasized that cardiac tamponade is ultimately a clinical diagnosis.

TABLE 62-5 CAUSES OF MODERATE TO LARGE ASYMPTOMATIC PERICARDIAL EFFUSIONS

CAUSE	CASES (%)
Idiopathic or viral	37
Neoplastic	19
Iatrogenic or trauma	13
Tuberculous or purulent	6
Acute myocardial infarction	6
Collagen vascular disease	4
Heart failure	4
Uremia	4
Radiation induced	2
Aortic dissection	2
Hypothyroidism	1
Other	2

Modified from Nishimura RA, Kidd KR. Recognition and management of patients with pericardial disease. In: Braunwald E, Goldman L, eds. *Primary Cardiology*. 2nd ed. Philadelphia: WB Saunders; 2003:625.

The routine evaluation should include an assessment of renal function, a thyroid-stimulating hormone level, a complete blood count with differential, a platelet count, coagulation parameters, and a tuberculin skin test. Common medications that can cause a pericardial effusion include cromolyn, isoniazid, phenytoin, hydralazine, and procainamide. Blood cultures are indicated if an infectious cause is suspected. Complement levels, antinuclear antibodies, and the ESR can suggest systemic lupus erythematosus (Chapter 245), which may initially present as an isolated pericardial effusion.

TREATMENT

Pericardial Effusion without Tamponade

Acute pericarditis is often accompanied by a small pericardial effusion that does not produce tamponade. If there is no hemodynamic compromise and the diagnosis can be established by other means, pericardiocentesis is not necessary (Fig. 62-7). Even small pericardial effusions may be related to underlying systemic illnesses such as systemic lupus erythematosus (Chapter 245), cardiac amyloid (Chapter 174), scleroderma (Chapter 246), hypothyroidism (Chapter 207), or AIDS, so it is important to consider and treat associated illnesses. Chylous pericardial effusion, which is usually related to obstruction of the thoracic duct, may require a surgical procedure for relief.

For suspected pericardial effusion, transthoracic echocardiography is the initial test of choice, although loculated effusions may be identified better by CT or MRI. If a small (0.5 to 1 cm) echolucent or "organized" pericardial effusion is observed, a follow-up echocardiogram in 1 to 2 weeks, or sooner if the patient deteriorates, is recommended. If the effusion is getting smaller, subsequent echocardiograms are not necessary unless the patient's clinical condition changes.

For moderate (1 to 2 cm) or large (>2 cm) effusions in patients who are hemodynamically stable and in whom tamponade is not suspected, a follow-up echocardiogram should be performed in 7 days and then every month until the effusion is minimal. If bacterial or malignant pericarditis is suspected, diagnostic pericardiocentesis should be performed immediately even in the absence of clinical instability or suggestion of tamponade; tuberculous pericarditis is diagnosed best by pericardial biopsy. Anticoagulation with heparin or warfarin should be discontinued unless the patient has a mechanical heart valve or atrial fibrillation.

In hypothyroidism (Chapter 207), the effusion and the coexistent cardiomyopathy respond to hormone replacement, sometimes over several months. Uremic pericardial effusions often respond to initiation of dialysis or more intensive dialysis (Chapter 117).

Cardiac Tamponade

The treatment of cardiac tamponade is urgent drainage of the pericardial effusion, especially when there is hemodynamic compromise. Fluid resuscitation may be of transient benefit if the patient is volume depleted (hypovolemic cardiac tamponade), but inotropic agents are usually ineffective because there is already intense endogenous adrenergic stimulation. The initiation of mechanical ventilation in a patient with tamponade may produce a sudden drop in blood pressure because the positive intrathoracic pressure further impairs cardiac filling.

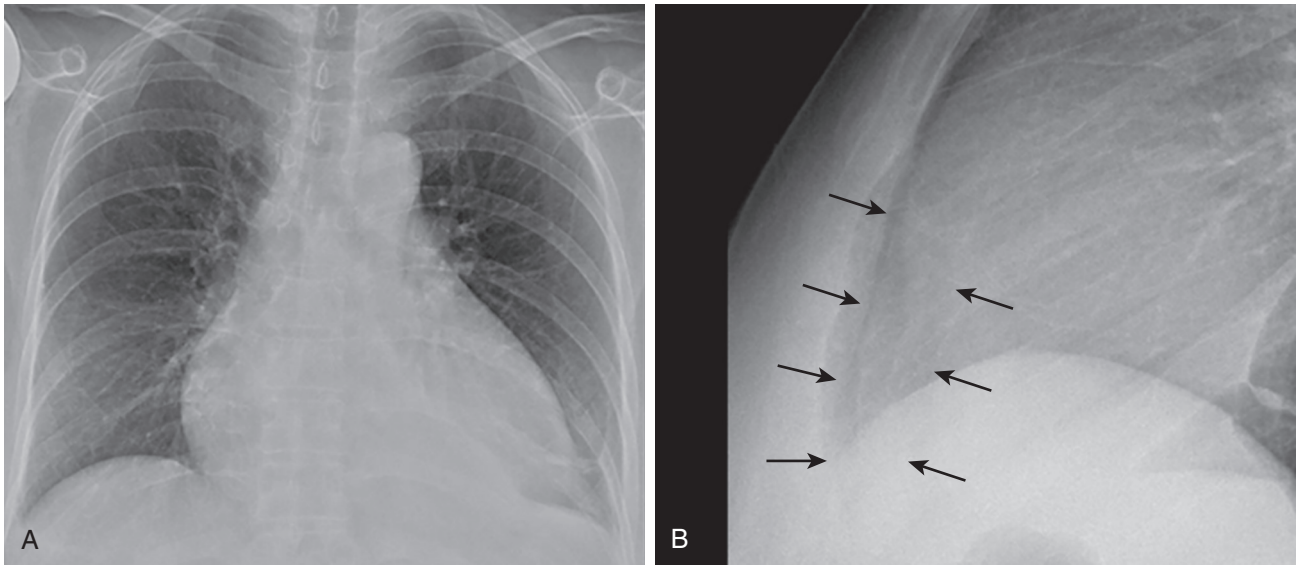

FIGURE 62-4. Chest radiographs in a patient with a large pericardial effusion. The cardiac silhouette on the posteroanterior view (**A**) is enlarged with a "water bag" configuration. The lateral view (**B**) shows a separation between the pericardial and epicardial fat stripes *(arrows)*.

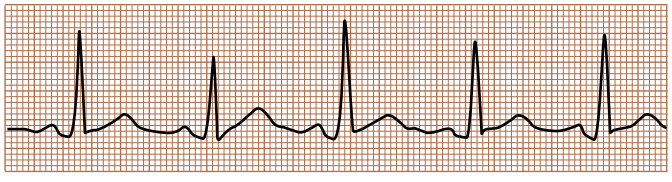

FIGURE 62-5. Electrical alternans. Lead V_5 rhythm strip from a patient with a large pericardial effusion and tamponade physiology. Note the relatively low voltage and electrical alternans.

Echocardiographic-guided percutaneous pericardiocentesis, which can be performed at the bedside by experienced operators (Fig. 62-8), is indicated if a patient is in dire circumstances and at least 1 cm of fluid is seen anterior to the mid-right ventricular free wall throughout diastole. The ideal entry site (usually near the apex) is defined using echocardiography as the minimal distance from the skin to pericardial fluid without intervening structures. The pericardial space is entered with a needle and then drained through a catheter. Although clinical and epidemiologic clues should tailor the extent of the diagnostic evaluation, pericardial fluid should be analyzed for lactate dehydrogenase, protein, cell count, cytology, polymerase chain reaction for tuberculosis, and culture for bacteria and tuberculosis. Continued drainage of the pericardial fluid through an indwelling catheter minimizes the risk of recurrent effusion. For hemodynamically significant effusions of less than 1 cm, organized or multiloculated effusions, and focal effusions, a limited thoracotomy-mediastinoscopy and creation of a pericardial window are advised.

Surgical drainage may be the preferred treatment if pericardial tissue is required for diagnosis or in the case of recurrent effusions or bacterial pericarditis. Malignant pericardial effusions frequently recur and, similar to other recurrent pericardial effusions, may necessitate the surgical creation of a pericardial window that allows the effusion to drain into the pleural space, preventing recurrence of cardiac tamponade. An attractive alternative in these patients, especially if their overall prognosis is poor from the malignancy, is the percutaneous creation of a pericardial window by balloon dilation. Hemorrhagic effusions related to cardiac trauma or aortic dissection are best managed by emergency surgery.

PROGNOSIS

A pericardial effusion may recur or persist. Symptoms are usually weight loss, fatigue, dyspnea on exertion, and whatever symptoms are associated with the specific cause. Treatment of chronic or recurrent idiopathic effusions is similar to the treatment of recurrent pericarditis. If medical therapy is unsuccessful, creation of a pericardial window is indicated.

A large idiopathic, asymptomatic effusion that persists for 6 months or longer can unpredictably result in tamponade in as many as 30% of patients over long-term follow-up; diagnostic pericardiocentesis occasionally detects a neoplastic or tuberculous cause. Pericardiocentesis with prolonged drainage resolves many chronic large pericardial effusions, but pericardiectomy is often required. The long-term prognosis depends on the cause of the effusion. With pericardial tamponade, the in-hospital mortality rate is less than 10%, but the subsequent mortality rate is about 75% with a malignant effusion compared with only a 3 to 5% subsequent annual mortality rate for other causes.

PERICARDIAL CONSTRICTION

EPIDEMIOLOGY AND PATHOBIOLOGY

Pericardial constriction, which is usually the result of pericardial inflammation and subsequent scarring, occurs when a scarred and usually thickened pericardium impairs cardiac filling, thereby limiting the total cardiac volume and causing venous congestion. As the pericardium thickens from its normal 2 mm or less, it may also calcify and adhere to the adjacent epicardium.

The most frequent causes in the developed world are previous cardiac surgery, chronic idiopathic or viral pericarditis, and mediastinal radiation. Constriction may follow cardiac surgery by several weeks to months and may occur decades after chest wall irradiation. In developing countries, tuberculous pericarditis remains a more common cause of constrictive pericarditis. Other less common causes include malignant disease, especially lung cancer, breast cancer, or lymphoma; histoplasmosis; rheumatoid arthritis; and uremia. However, a specific cause may not be identified in many patients.

Fibrous scarring and adhesions of both pericardial layers obliterate the pericardial cavity. The ventricles are unable to fill beyond the rapid filling period because of physical constraints imposed by a thickened, rigid, and sometimes calcified pericardium. In a subset of patients with constriction, especially patients with superimposed myocardial diseases after previous cardiac surgery or radiation therapy, the pericardium may be only minimally thickened and less calcified. The pathophysiologic hallmarks of pericardial constriction are exaggerated interventricular dependence and the dissociation of intracardiac and intrathoracic pressures.

CLINICAL MANIFESTATIONS

Patients with pericardial constriction typically present with manifestations of elevated systemic venous pressures and low cardiac output. Because there is equalization of all cardiac pressures (including right and left atrial pressures), systemic congestion is much more marked than pulmonary congestion. Typically, patients develop marked jugular venous distention, hepatic congestion, ascites, and peripheral edema, but their lungs usually remain clear, and patients with pericardial constriction are much more likely to have left-sided or bilateral pleural effusions than the right-sided effusions that are typically seen in heart failure (Chapter 45). The limited cardiac output typically presents as exercise intolerance and may progress to cardiac cachexia with muscle wasting. In long-standing pericardial constriction, lower extremity edema, ascites, and hepatic dysfunction may be prominent clinical features. Because of the prominent clinical symptoms of ascites and liver enzyme abnormalities, patients may be evaluated for hepatic disease before constrictive pericarditis

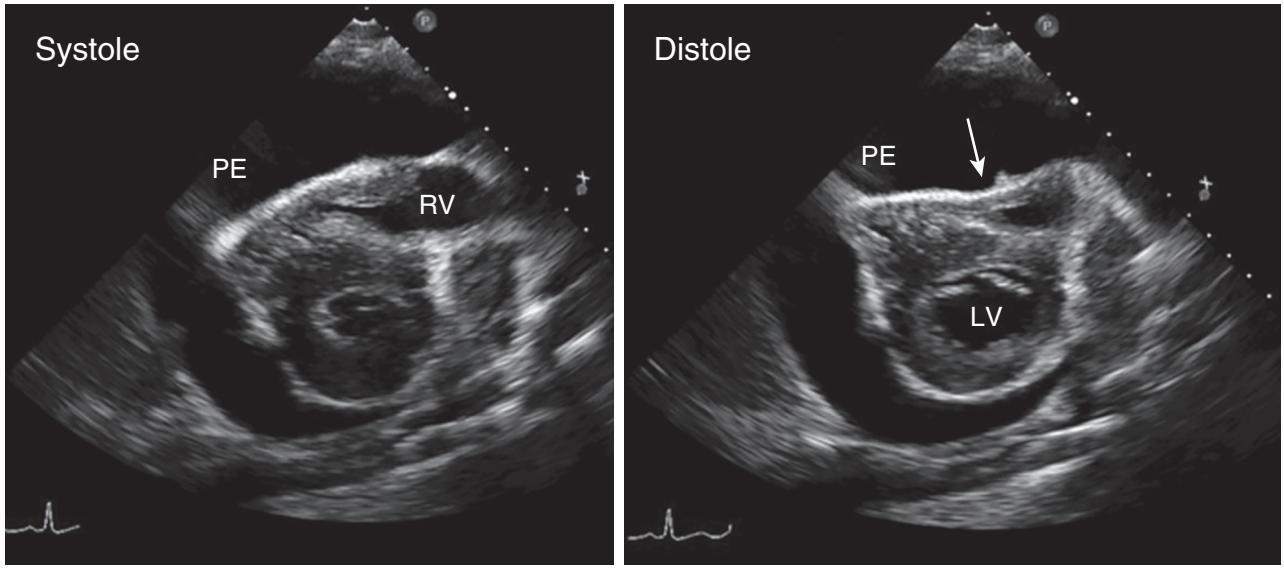

FIGURE 62-6. Two-dimensional echocardiogram from a patient with cardiac tamponade. A large pericardial effusion (PE) is apparent as an echo-free space surrounding the left ventricle (LV) and right ventricle (RV). In diastole, there is collapse of the right ventricle *(arrow)*.

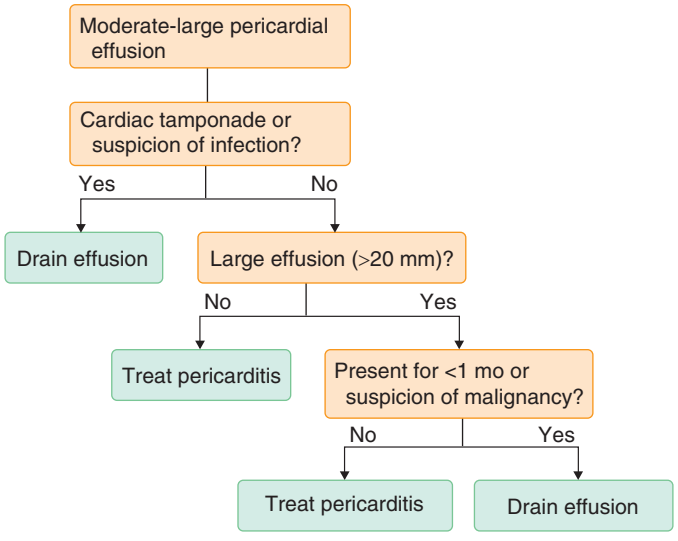

FIGURE 62-7. Algorithm for managing patients with moderate to large pericardial effusions. (Modified from Little WC, Freeman GL. Pericardial disease. *Circulation*. 2006;113:1622-1632.)

is recognized. If a patient has patent foramen ovale, hypoxemia from right to left shunting with increased right atrial pressure may be a presenting symptom of constrictive pericarditis.

The jugular veins are distended with prominent y descent. The normal inspiratory drop in jugular venous distention may be replaced by a rise in venous pressure (Kussmaul sign). The y descent, which is when rapid diastolic ventricular filling suddenly ceases, coincides with the timing of the classic auscultatory finding of pericardial constriction, which is an audible pericardial knock (Fig. 39-5)—a high-pitched sound early in diastole.

DIAGNOSIS

Pericardial constriction should be considered in any patient with unexplained systemic venous congestion or a low cardiac output syndrome. Pericardial calcification, seen best on the lateral plain chest radiograph, is a classic finding but is present in only 25% of patients with constrictive pericarditis, mostly in those with long-standing constriction.

Transthoracic echocardiography, which is usually the initial diagnostic tool, classically shows paradoxical interventricular dependence, with ventricular septal motion during inspiration; restrictive mitral inflow velocity, often with respiratory variation; normal or increased (≥8 cm/sec) medial mitral annulus e′ velocity; and reversal of diastolic flow in the hepatic vein during expiration (E-Fig. 62-1). In addition, the hepatic veins are plethoric, and cardiac morphology may be pear shaped, with the narrowest dimension at the atrioventricular grooves. Echocardiography also differentiates pericardial constriction from right heart failure caused by tricuspid valve disease or associated pulmonary hypertension (see later).

Most patients with pericardial constriction have a thickened pericardium (>2 mm) that can be imaged by echocardiography (better by transesophageal than transthoracic echocardiography), CT, and MRI (Fig. 62-9). It is important to recognize, however, that most patients with pericardial constriction present without pericardial calcification and, in about 20% of patients, without any obvious pericardial thickening.[9]

At cardiac catheterization, both cardiac tamponade and pericardial constriction impair diastolic ventricular filling and elevate venous pressure. However, the impairment in ventricular filling with constriction is minimal in early diastole until cardiac volume reaches the anatomic limit set by the noncompliant pericardium, at which time diastolic pressure rises abruptly and remains elevated until the onset of systole. The result is a prominent "y" descent with an elevated plateau of ventricular pressure, which has been termed the "square root" sign (E-Fig. 62-2) and which differentiates constriction from tamponade, in which the y descent is absent.

The pulmonary artery systolic pressure is typically less than 50 mm Hg, and the end-diastolic pressures of both ventricles are equalized. However, the best way to distinguish constrictive pericarditis from a restrictive cardiomyopathy (Chapter 47) is a discordant change in the systolic pressure of the left and right ventricles with respiration compared with a concordant change seen in restrictive cardiomyopathy. In restrictive pericarditis, the left ventricular systolic pressure decreases with inspiration, whereas the right ventricular systolic pressure increases; the opposite change occurs with expiration (E-Fig. 62-3). Stroke volume and cardiac output are reduced because of impaired filling, but the intrinsic systolic function of the ventricles is usually normal.

Differential Diagnosis

The most difficult differentiation is between pericardial constriction and restrictive cardiomyopathy (Chapter 47) (Fig. 62-10), the clinical manifestations of which may be very similar to those of pericardial constriction (Table 62-6).[10] Doppler echocardiography is the most useful method to distinguish constriction from restriction. Whereas patients with pericardial constriction usually have pronounced respiratory variation (>25%) of mitral inflow E velocity, patients with restrictive cardiomyopathies do not. In some patients with pericardial constriction and markedly elevated venous pressures, the respiratory variation may not be present unless preload can be decreased; for example, with head-up tilt. The tissue Doppler measurement of early diastolic septal mitral annular velocity (e′) is almost always reduced in patients with myocardial restriction due to abnormal myocardial relaxation, but it remains normal or increased in patients with

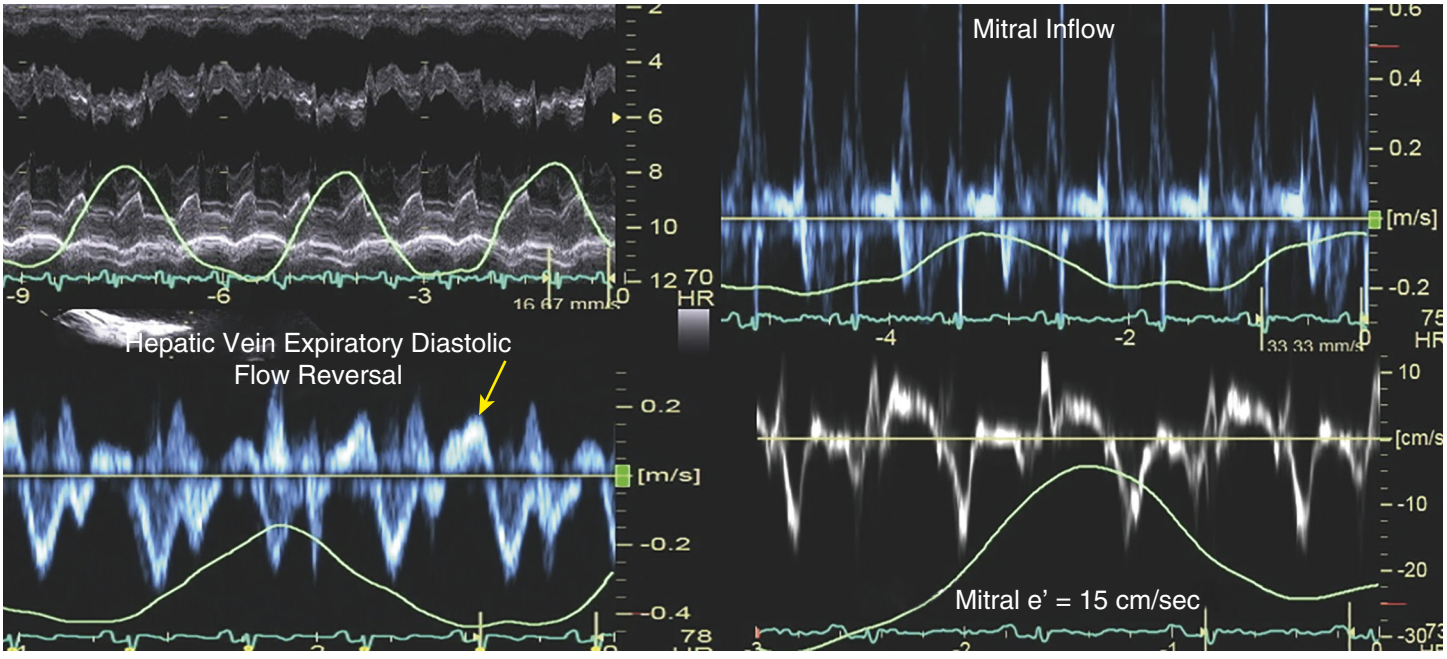

E-FIGURE 62-1. **A composite of echocardiographic features diagnostic for constrictive pericarditis.** *Upper left,* M-mode echocardiogram of left ventricle showing respiratory variation of ventricular septum due to interventricular dependence. *Upper right,* Variation in mitral inflow velocity with respiration. Mitral E velocity decreases with inspiration and increases with expiration. It is also restrictive because of increased filling pressure. *Lower* left, Hepatic vein Doppler velocity showing diastolic flow reversal with expiration. *Lower right,* Medial mitral annulus early diastolic velocity (e') is increased to 15 cm/sec.

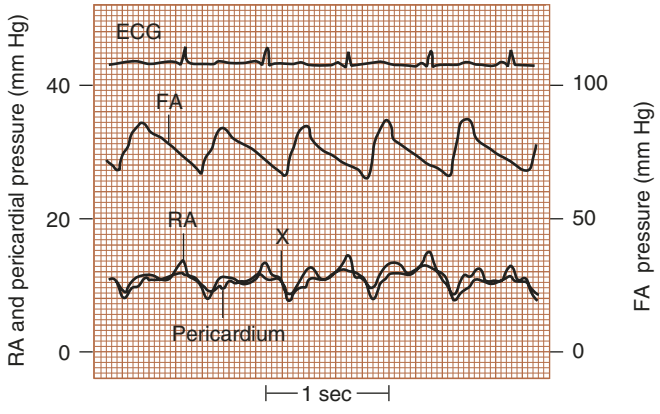

E-FIGURE 62-2. **Right atrial (RA) pressure recording from a patient with constrictive pericarditis.** Note the elevation in pressure and the prominent y descent, corresponding to rapid, early diastolic right atrial emptying. ECG = electrocardiogram; FA = femoral artery. (From Lorell BH. Profiles in constriction, restriction and tamponade. In: Baim DS, Grossman W, eds. *Cardiac Catheterization, Angiography, and Intervention*. 6th ed. Philadelphia: Williams Wilkins; 2000:832.)

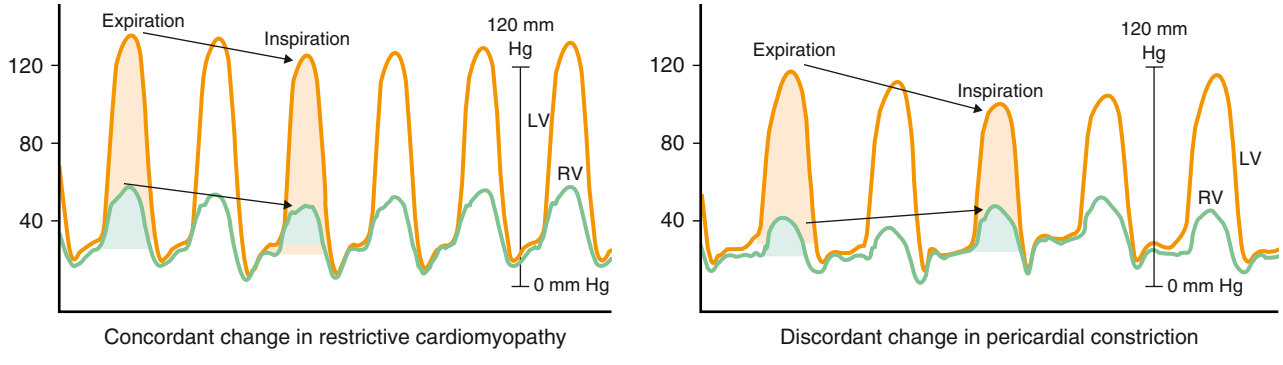

E-FIGURE 62-3. **Simultaneous left ventricular (LV) and right ventricular (RV) pressure tracing in patients with a restrictive cardiomyopathy *(left)* and constrictive pericarditis (right). In restrictive cardiomyopathy, LV and RV systolic pressures appropriately decrease with inspiration and increase with expiration, concordantly.** In contrast, LV and RV pressures move discordantly in constrictive pericarditis.

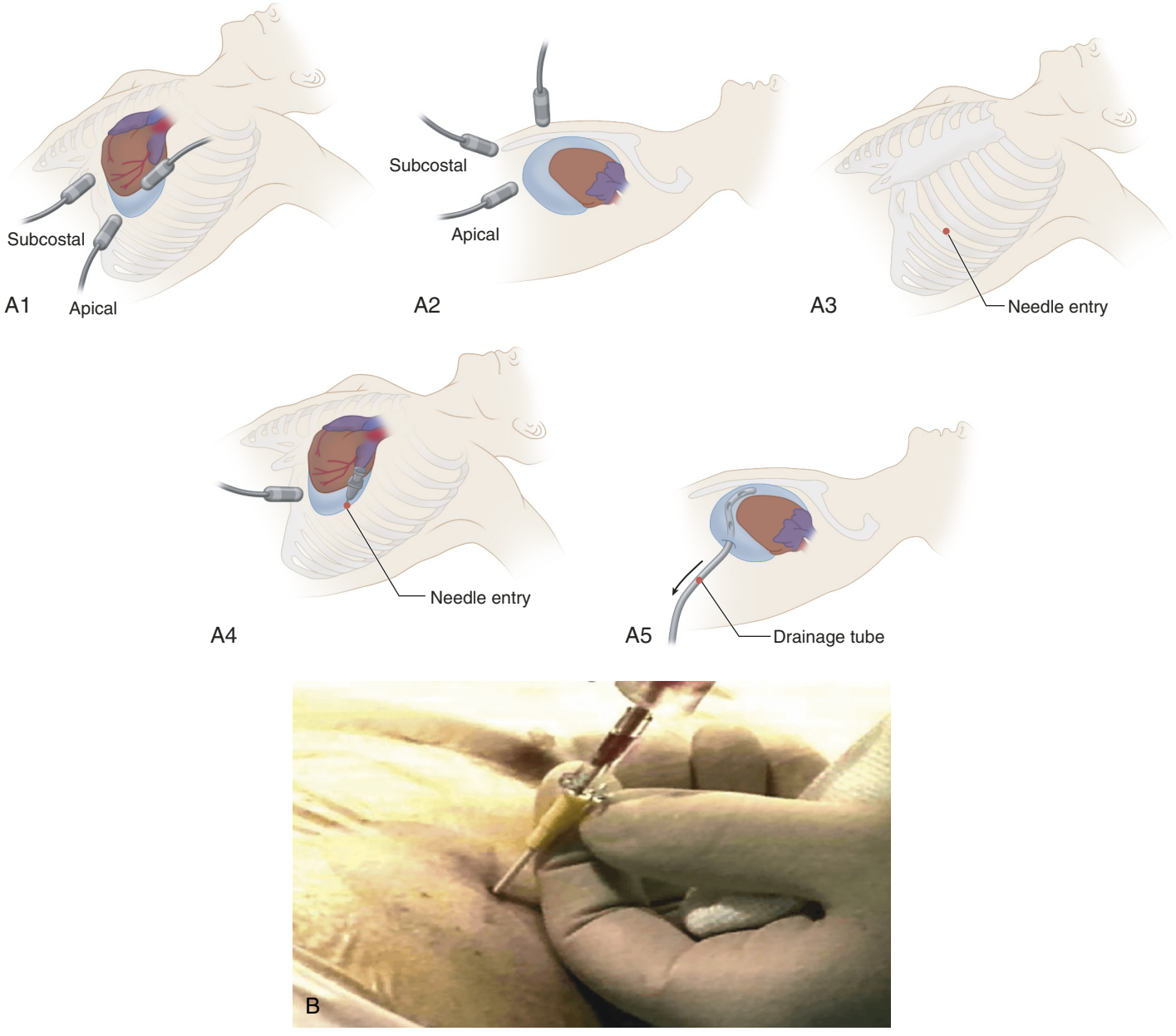

FIGURE 62-8. **Pericardiocentesis. A,** Schematic diagrams demonstrate steps of echocardiography-guided pericardiocentesis.
Step 1. Locate an area on the chest or subcostal region from which the largest amount of pericardial effusion can be visualized and mark it (A1-A3).
Step 2. Determine the depth of effusion and the optimal angulation from the marked position.
Step 3. After sterile preparation and local anesthesia, perform pericardiocentesis (A4).
Step 4. When in doubt about the location of the needle, inject saline solution through the needle and image it from a remote site to locate the bubbles.
Step 5. Monitor the completeness of the pericardiocentesis with repeat echocardiography.
Step 6. Place a 6 F or 7 F pigtail catheter in the pericardial space to minimize the reaccumulation of fluid (A5).
Step 7. Drain any residual fluid or fluid that has reaccumulated via the pigtail catheter every 4 to 6 hours. If after 2 to 3 days pericardial fluid has not reaccumulated by echocardiography, the pigtail catheter may be removed. Always have the pericardial fluid analyzed for cell counts, glucose and protein measurements, culture, and cytology. (Modified from Callahan JA, Seward JB, Tajik AJ, et al. Pericardiocentesis assisted by two-dimensional echocardiography. *J Thorac Cardiovasc Surg*. 1983:85:877-879. Used with permission.)
B, A photo of actual pericardiocentesis. Echocardiography determined the site and the angulation of needle insertion as well as anticipated depth of needle insertion. In this case, bloody fluid is being drained.

pericardial constriction. In addition, lateral e′, which is higher than septal or medial e′ velocity in normal and restrictive cardiomyopathy, is lower than septal e′ in most patients with constrictive pericarditis ("Annulus Reversus"). Whereas a prominent diastolic reversal of hepatic vein flow velocity during expiration is characteristic of constriction, the reversal flow velocity occurs during inspiration in patients with right heart failure from other causes. Patients with pericardial constriction usually have only minimally elevated (<200 pg/mL) brain natriuretic peptide (BNP), but BNP levels are typically markedly increased (<600 pg/mL) in patients with restrictive cardiomyopathy.

Confirmation of the diagnosis of constriction may require cardiac catheterization in patients whose noninvasive evaluation is not clear-cut. Traditional invasive hemodynamic findings of equalized end-diastolic pressures in the right and left ventricles and the "dip and plateau" pattern of left ventricular diastolic pressure do not reliably differentiate constriction from restrictive cardiomyopathy. More specific invasive hemodynamic features of constriction and restriction are based on the respiratory variation in ventricular filling; the simultaneous measurement of left and right ventricular pressures demonstrates discordant changes in their systolic pressures with respiration in constrictive pericarditis. By comparison, the direction of these pressures is concordant (both left and right sides increase with expiration and decrease with inspiration) in restrictive cardiomyopathy.

All patients with documented but otherwise unexplained pericardial constriction should be evaluated for potential tuberculosis.

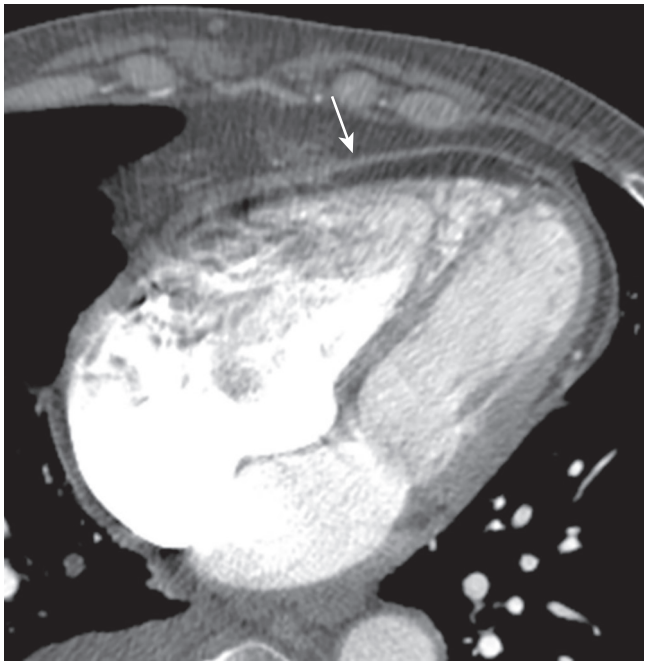

FIGURE 62-9. **Computed tomography in a patient with constrictive pericarditis shows a thickened pericardium *(arrow)*.**

TREATMENT AND PROGNOSIS

In some patients with pericardial constriction of less than 3 months' duration, the symptoms and constriction may resolve over several weeks with medical therapy consisting of NSAIDs (e.g., ibuprofen 300-800 mg every 6-8 hours), colchicine (0.6 mg once or twice daily), and the cautious use of diuretics. If the patient is severely compromised hemodynamically, steroid therapy (e.g., 0.5 to 1.0 mg/kg up to a maximum dose of 60 mg tapered slowly over 3 months as guided by the clinical response and normalization of the CRP) can be very effective. Patients with constriction who respond to medical therapy usually have high inflammatory biomarkers (ESR and CRP) and intense inflammation of the pericardium on cardiac MRI. For more chronic pericardial constriction or cases that do not respond to medical therapy, the definitive treatment is surgical pericardial decortication, with a wide resection of both the visceral and parietal pericardium. This operation is a major undertaking, but it can be undertaken with acceptable risk (about a 5% mortality rate in the most experienced centers).[11] In many patients, surgery does not immediately restore normal cardiac function; it may take weeks after removal of the constricting pericardium to return to normal. Empirical treatment of tuberculosis (Chapter 299) may be required in patients with constriction and a high suspicion of tuberculosis, even without a definitive diagnosis.

EFFUSIVE-CONSTRICTIVE PERICARDITIS

In about 10 to 20% of patients who present with cardiac tamponade, the elevated right atrial pressure and jugular venous distention do not resolve after removal of the pericardial fluid. In these patients, pericardiocentesis converts the hemodynamics from those typical of tamponade to those of constriction.[12] Thus, the restriction of cardiac filling is not only attributable to pericardial effusion but also to pericardial constriction, predominantly involving the visceral pericardium. Effusive-constrictive pericarditis[13] most likely represents an intermediate transition from acute pericarditis with pericardial effusion to pericardial constriction. Restrictive mitral inflow and plethora of the hepatic veins on echocardiography may be early predictors of which patients will progress to constriction.[14] Frequently, the symptoms resolve after several weeks of treatment with an NSAID (e.g., ibuprofen 300 to 800 mg every 6 to 8 hours). Pericardiectomy may be necessary if constrictive pericarditis persists.

SPECIFIC FORMS OF PERICARDIAL DISEASE

POSTPERICARDIOTOMY SYNDROME

The postcardiac injury syndromes comprise the postpericardiotomy syndrome, post–myocardial infarction pericarditis (Dressler syndrome), and post-traumatic pericarditis. The postpericardiotomy syndrome, like all of the post–cardiac injury syndromes, is initiated by the combination of damage to mesothelial pericardial cells and blood in the pericardial space, which releases cardiac antigens and stimulates an immune response. An inflammatory response is later generated by immune complexes that deposit in the pericardium, pleura, and lungs. This syndrome occurs several days to weeks after cardiothoracic surgery. It most commonly occurs after surgery involving the pericardium, but it can also occur after pacemaker lead implantation, coronary stenting, and other therapeutic misadventures. Patients have typical symptoms of acute pericarditis, which is associated with antimyocardial antibodies. Leukocytosis and elevated inflammatory markers are common laboratory findings. Pericardial effusions are commonly seen, but tamponade physiology is rare. Pleural effusions or pulmonary infiltrates may also be seen.

Treatment of postcardiotomy syndrome is similar to the treatment of acute pericarditis. One month of colchicine therapy (0.5 mg twice daily for patients weighing 70 kg or more; half that dose for smaller patients or patients with side effects) started 48 to 72 hours prior to cardiac surgery appears to reduce the rate of the postcardiotomy syndrome from about 30% to less than 20% but does not reduce the occurrence of atrial fibrillation.

Some patients who have undergone cardiac surgery develop late pericardial constriction without preceding acute pericarditis owing to bleeding in and around the open pericardium followed by inflammation, scarring, and fibrosis. If active inflammation is present, a trial of anti-inflammatory agents may be instituted; however, surgical removal of the blood clot, usually accompanied by more extensive pericardiectomy, is typically required.

UREMIC PERICARDITIS

Pericardial effusions develop in patients with severe renal failure, especially those on dialysis (Chapter 117). Aggressive dialysis may decrease the pericardial effusion, but sometimes the effusion persists and requires drainage or even pericardiectomy.

INFECTIOUS PERICARDITIS

BACTERIAL PERICARDITIS

Purulent bacterial pericarditis may result from direct extension of bacterial pneumonia, direct extension of pleural empyema, or, rarely, peritonitis or a subphrenic abscess. Most patients are acutely ill with systemic sepsis and develop acute tamponade. The most common organisms are streptococci, pneumococci, and staphylococci. Urgent pericardiocentesis, which is required for both diagnosis and therapy, shows leukocytosis and frank pus, and the fluid glucose level is markedly depressed. Persistent or recurrent drainage with an indwelling catheter or repeated taps combined with antimicrobial therapy leads to a high survival rate, but late constrictive pericarditis requiring pericardiectomy develops in 30 to 40% of patients.

TUBERCULOUS PERICARDITIS

Tuberculous pericarditis is common in developing countries but accounts for less than 5% of cases of acute pericarditis in developed countries, usually in patients who are immunosuppressed, including patients infected with the human immunodeficiency virus. Symptoms are often nonspecific, and acute painful pericarditis is rare. Most patients have an effusive-constrictive physiology or pericardial constriction. The chest radiograph suggests active pulmonary tuberculosis in about 30% of cases, and a pleural effusion is present in 40 to 60% of cases. The echocardiogram typically shows fibrinous strands in the pericardial effusion, with multiple echo densities adherent to the pericardial surface. Pericardiocentesis is mandatory if tuberculous pericarditis is suspected. About 75% of patients have a positive culture, and a pericardial fluid adenosine deaminase level of 40 U/L or greater is seen in 75% of patients. Polymerase chain reaction testing and pericardial biopsy are recommended when tuberculous pericarditis is strongly suspected but not otherwise confirmed.

Aggressive antituberculosis therapy (Chapter 299) yields a cure rate of about 85 to 90%. Neither corticosteroids nor adjunctive immunotherapy improves outcome.[A6] Empirical treatment may be required in patients with a consistent clinical picture but without a confirmed diagnosis.

Even with prompt treatment, 30 to 60% of patients develop constrictive pericarditis, for which surgical pericardiectomy is the treatment of choice. In cases of suspected tuberculous constriction, antituberculosis therapy (Chapter 299) should be administered before and after pericardial surgery.

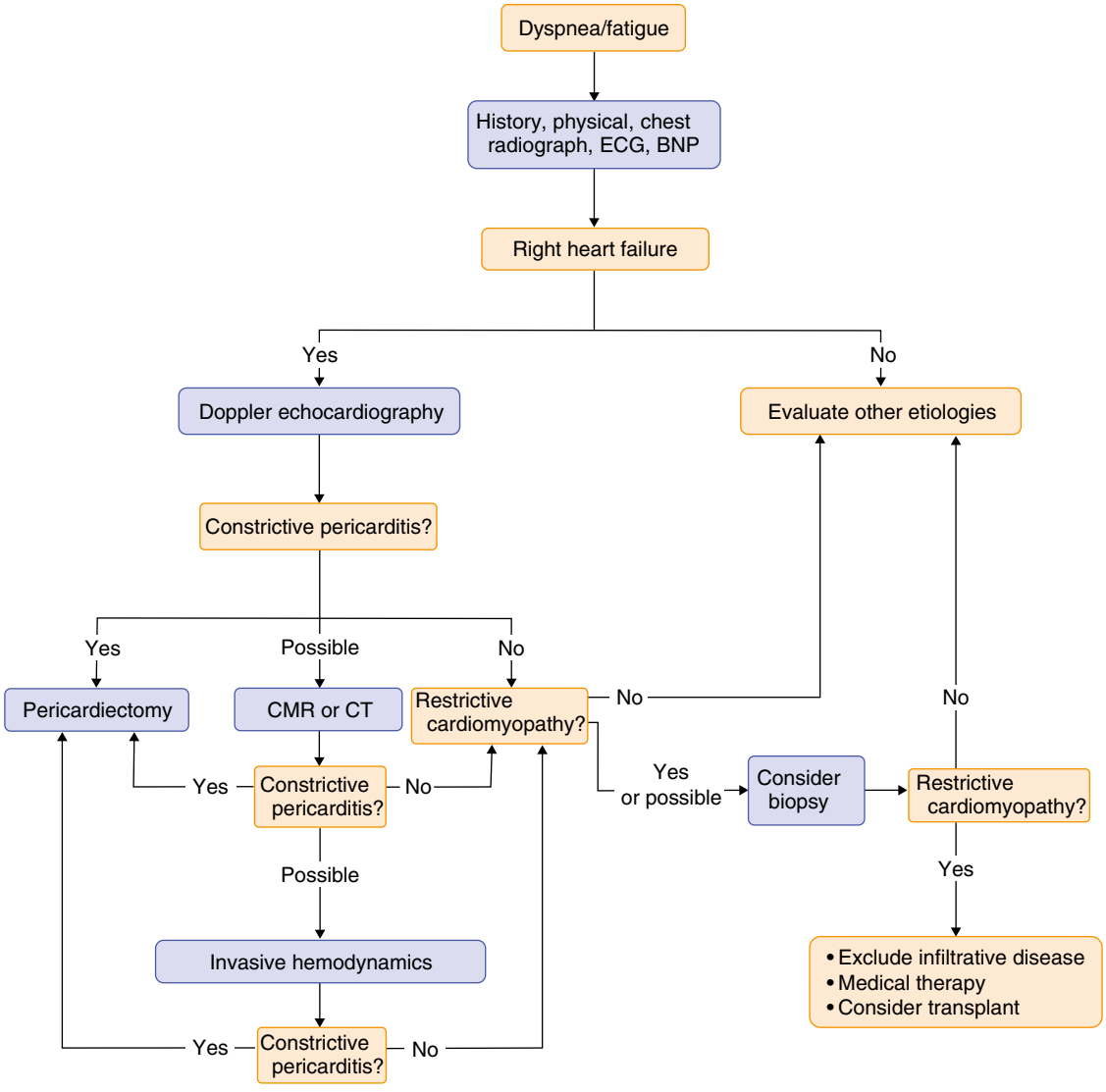

FIGURE 62-10. Approach to the differentiation of constrictive pericarditis vs. restrictive cardiomyopathy. BNP = brain natriuretic peptide; CMR = cardiovascular magnetic resonance; CT = computed tomography; ECG = electrocardiogram.

FUNGAL PERICARDITIS

The most common fungal pericarditis is histoplasmosis, which usually resolves in several weeks and can be treated successfully with NSAIDs. Specific antifungal therapy (Chapter 307) is recommended only in patients with disseminated histoplasmosis (Chapter 308).

MALIGNANT PERICARDITIS

About 6% of cases of acute pericarditis that initially have no obvious cause, and about 20% of cases of moderate to large pericardial effusions are related to malignant diseases; in patients with cardiac tamponade, the percentage is even higher. About 80% of malignant pericarditis is linked to breast cancer (Chapter 183), lymphoma (Chapters 171 and 172), and leukemia (Chapters 168, 169, and 170). Melanoma (Chapter 188) is an uncommon cause of malignant pericarditis, but a large proportion of patients with melanoma have pericardial involvement.

Most patients have direct tumor extension from an adjacent malignant lesion or a tumor from hematogenous or lymphatic spread.[15] Pericardial effusions also may be caused by pericardial irritation or compromised lymphatic drainage in patients with mediastinal lymphoma.

Pericardiocentesis is key to diagnosis and management. Fluid cytology results are positive in about 85% of patients. Complete drainage with an indwelling catheter for 2 or 3 days is the treatment of choice. Colchicine (0.6 mg twice daily for 6 months) may be useful,[16] and cancer chemotherapy may sometimes be helpful.[17] If the effusion does not resolve, pericardiectomy is generally recommended, but extended catheter drainage is also an option.[18]

The prognosis depends on the treatment of the underlying malignancy. The 1-year mortality rate is 80% or higher, but patients with breast cancer may have 1-year survival rates as high as 40%.

POSTRADIATION PERICARDITIS

Postradiation pericarditis develops in about 2% of patients after mantle radiation for Hodgkin disease (Chapter 172) and in 0.4 to 5% of patients after irradiation for breast cancer. Pericardial injury occasionally manifests during treatment, but it more commonly appears months or even a decade later. The initial pericarditis and effusion may resolve spontaneously, but constrictive pericarditis, adjacent myocarditis, and even coronary artery damage can develop. Pericardiocentesis is critical to distinguish postradiation pericarditis from malignant pericardial disease. Pericardiectomy is recommended for recurrent pericarditis and for large recurrent pericardial effusions.

AUTOIMMUNE PERICARDITIS

Pericarditis, often with an effusion, can complicate systemic rheumatologic conditions.[19] Up to 50% of patients with systemic lupus erythematosus (Chapter 245) have pericarditis, usually during an acute flare.[20] Patients usually present with acute pericarditis or an asymptomatic effusion; cardiac tamponade is uncommon, and constrictive pericarditis is rare. If purulent pericarditis is not suspected, pericardiocentesis is not usually required. The underlying disease should be treated aggressively.

Acute pericarditis or asymptomatic pericardial effusions also can develop in patients with advanced rheumatoid arthritis (Chapter 243), scleroderma

TABLE 62-6 DIFFERENTIATION OF PERICARDIAL CONSTRICTION FROM RESTRICTIVE CARDIOMYOPATHY

FINDINGS	PERICARDIAL CONSTRICTION	RESTRICTIVE CARDIOMYOPATHY
PHYSICAL EXAMINATION		
Pulmonary congestion	Usually absent	Usually present
Early diastolic sound	Pericardial knock	S_3 (low pitched)
ECHO/DOPPLER		
Respiratory variation in E wave (%)	>25	<20
Mitral septal annular early diastolic velocity (cm/sec)	>7	<7
CT/MRI		
Pericardial thickness	>2 mm (but <2 mm in 20%)	<2 mm
BIOMARKER		
B-type natriuretic peptide (pg/mL)	<200	>600
HEMODYNAMICS		
PA systolic pressure (mm Hg)	<60	>60
PCW-LV diastolic pressure	Respiratory variation with reduction in inspiration	No variation
Respiratory variation in RV/LV peak systolic pressure	Discordant	Concordant

CT = computed tomography; LV = left ventricular; MRI = magnetic resonance imaging; PA = pulmonary artery; PCW = pulmonary capillary wedge; RV = right ventricular.
Modified from Little WC, Freeman GL. Pericardial disease. *Circulation*. 2006;113:1622-1632.

(Chapter 246), or mixed connective tissue disease (Chapter 246). The process is usually self-limited or responds to aggressive treatment of the underlying disease, although cardiac tamponade can develop.

A wide variety of drugs and toxins may cause pericardial heart disease (see Table 62-1) by producing either drug-induced lupus, a hypersensitivity or idiosyncratic reaction, pericardial irritation, or hemorrhage. Immune checkpoint inhibitors are monoclonal antibodies that target a critical mechanism of immune evasion and thereby activate immune responses against tumor cells; cases of pericarditis, pericardial effusion, and cardiac tamponade can complicate cancer treatment with these drugs.

MYOPERICARDITIS

Concomitant myopericarditis (Chapter 47) may develop in patients with pericarditis, probably owing to direct extension of the inflammatory process. It is often manifested by ECG conduction delays, ventricular arrhythmias, and elevated troponin levels. No specific treatment is available.

Acute ventricular dilation and sudden or progressive heart failure develop in some patients after pericardiectomy for constrictive pericarditis or even after drainage of a large pericardial effusion. The syndrome may be due to an underlying myocarditis.

CONGENITAL ABNORMALITIES

Congenital total absence of the pericardium is asymptomatic and clinically unimportant. However, partial or localized absence of the pericardium around the left atrium can cause focal herniation and lead to strangulation. CT or MRI can establish the diagnosis. Patients may present with atypical chest pain or sudden death. Surgical repair is often recommended for a partial pericardial defect.

BENIGN CYSTS

Benign pericardial cysts are rare and are usually asymptomatic, but they can be associated with chest pain. They are typically seen as rounded or lobulated structures adjacent to the heart on the chest radiograph or adjacent to the right atrium on transthoracic echocardiography (Chapter 43). Thoracic CT and MRI are useful for the diagnosis. Cysts rarely rupture and do not require treatment unless they become symptomatic with chest pain. In this situation, the cyst can be removed surgically or drained percutaneously or with a thoracoscope.[21]

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63 DISEASES OF THE AORTA

JOSHUA A. BECKMAN

The aorta, which is the singular vascular recipient of cardiac output, facilitates the distribution of blood throughout the body. Anatomic landmarks that define its segments (Fig. 63-1A) include the aortic root, which arises from the aortic valve annulus; the ascending aorta, which extends to the branching of the innominate artery; the transverse aorta or arch segment, which begins at the innominate artery and ends at the left subclavian artery; the descending thoracic aorta, which extends from beyond the left subclavian artery to the diaphragm; and the abdominal aorta, which begins at the diaphragm and terminates at the iliac bifurcation.

The aorta comprises three layers: the intima, media, and adventitia. The intima is a single layer of endothelial cells delimited by the internal elastic lamina. The media, which represents approximately 80% of the aortic wall, is composed of vascular smooth muscle cells, collagen fibers, elastin fibers, and fibroblasts. The presence of elastin defines the aorta as an elastic artery and permits the compliance needed to absorb and distribute cardiac output and modulate vascular tone. The adventitia, which contains collagen fibers and fibroblasts, contains the aortic vascular supply (the vaso vasorum). Three pathologic processes comprise the majority of aortic disease encountered by the medical clinician: aneurysm, acute aortic syndromes, and vasculitis.

AORTIC ANEURYSM

DEFINITION

The normal aorta is at its largest at takeoff from the aortic annulus and decreases in size to reach its nadir in the distal abdominal aorta prior to its bifurcation. The normal diameter of the aorta varies by sex (Table 63-1). The normal diameter also increases directly in association with older age, heavier weight, taller height, and greater body surface area, especially for the thoracic aorta.

All segments of the aorta are at risk for the formation of aneurysms, which are defined as enlargement of a segment by more than 50% when compared with a more proximal segment. Below this amount, an increase in size is described as ectasia. Aneurysms may occur in two different morphologies: fusiform, which is a generalized expansion of the entire aortic segment, and saccular, which is a focal area of expansion or outpouching.

EPIDEMIOLOGY

Based on screening with computed tomographic (CT) scanning, the estimated prevalences of aortic aneurysms of the ascending aorta, aortic arch, descending aorta, and abdominal aorta at an average age of 68 years are 0.1%, <0.1%, 0.1%, and 3.7% in men and 0.1%, 0.0%, 0.1%, and 0.4% in women, respectively.[1] Other studies have shown similar results using abdominal ultrasound screening, with data showing abdominal aortic aneurysms above 3 cm in 3.6% of men and above 4 cm in 1.2% of men ages 50 to 79 years but above 3 cm in only 1.3% of women in this age range.

Risk Factors

Abdominal Aortic Aneurysm

The risk of an abdominal aortic aneurysm is largely determined by four risk factors: age, sex, cigarette smoking, and a family history. Abdominal aortic aneurysms are very uncommon in individuals under age 60 years, but the prevalence increases to 6% for persons ages 55 to 64 years and 18.5% for persons ages 75 to 84 years.

The prevalence of abdominal aortic aneurysms is significantly higher among men. Furthermore, about 75% of the abdominal aortic aneurysms found in women are small, between 3 and 3.9 cm.

The presence of an abdominal aortic aneurysm in a first-degree relative is a particularly powerful risk factor, with the increased risk ranging from three- to five-fold. Genome-wide association studies have identified multiple loci for the development of abdominal aortic aneurysm,[2] including a polygenic risk score that appears to be able to explain this familial tendency.

Among acquired risk factors, cigarette smoking (Chapter 363) increases the risk of all aneurysms by 2.7-fold and large abdominal aortic aneurysms by 5.6-fold; the risk is about 2.5-fold higher in current smokers compared with former smokers. Other cardiovascular risk factors, including hypertension (Chapter 64) and dyslipidemia (Chapter 190), also increase the risk of abdominal aortic aneurysm, albeit more modestly than smoking.

Thoracic Aortic Aneurysm

The factors that enhance the risk of abdominal aortic aneurysm are similar in thoracic aortic aneurysm, including hypertension (Chapter 64) and smoking (Chapter 363). The prevalence of thoracic aortic aneurysms in the general population is about 2.7%, and the presence of an aneurysm in one aortic segment is also strongly associated with aortic dilation in another segment. Predisposing conditions include heritable thoracic aortic diseases (Marfan syndrome [Chapter 239], vascular Ehlers-Danlos syndrome [Chapter 239], and familial bicuspid aortic valve syndrome) and inflammatory diseases (e.g., giant cell arteritis, Takayasu arteritis). Thoracic aortic dilatation, especially of the ascending segment, is also seen in Turner syndrome (Chapter 214), tertiary syphilis (Chapter 295), and rheumatoid vasculitis (Chapter 243). About 10% of thoracic aneurysms extend below the diaphragm and are designated as thoracoabdominal aortic aneurysms.

PATHOBIOLOGY

The mesoderm is the source of smooth muscle cells in the distal abdominal aorta, whereas neural crest cells give rise to smooth muscle cells in the thoracic aorta. Both thoracic and abdominal aortic aneurysms are associated with a reduction in the density of this medial smooth muscle cell layer, with evidence of apoptosis or reductions in structural proteins such as elastin, collagen, and glycosaminoglycans.

Four major interconnected processes have been identified in abdominal aortic aneurysm: dysregulation of matrix metalloproteinase, inflammation, activation of the renin-angiotensin pathway, and the increased elaboration of reactive oxygen species. Matrix metalloproteinases are enzymes that degrade extracellular matrix proteins and participate in cell proliferation, differentiation, and apoptosis. Multiple matrix metalloproteinases, including 1, 3 (stromelysin-1), 9, and 13 (collagenase-3), are elevated in the aorta and blood of patients with abdominal aortic aneurysms.[3] The normal source of these enzymes includes endothelial cells, smooth muscle cells, and adventitial fibroblasts, but inflammation may play an important role in the adverse expression of matrix metalloproteinases. Inflammatory cells serve as important additional sources of matrix metalloproteinases. Most major components of cellular immunity, including neutrophils, T cells, B cells, and macrophages, are thought to participate in the inflammatory process. The inflammation underlying the formation of an aneurysm may be coordinated by the production of adverse cytokines that infiltrate the aortic wall.

Oxidative stress increases many components of aneurysmal formation, including induction of proinflammatory genes, activation of matrix metalloproteinases, and apoptosis. Superoxide anion, which is a potent oxygen-derived free radical, is found in excess in the smooth muscle and inflammatory cells of abdominal aortic aneurysm specimens. Important enzymatic sources of oxidants include nicotinamide adenine dinucleotide phosphate (NADPH) oxidase and uncoupled endothelial nitric oxide synthase.

In contrast to the formation of aneurysms in the abdomen, thoracic aortic aneurysms may have a more varied explanation. Among patients with Marfan syndrome, for example, 92% of males and 84% of females have aortic root dilatation. In addition to systemic genetic syndromes (e.g., Marfan, Turner syndrome), familial nonsyndromic conditions (e.g., bicuspid aortic valve), infections (e.g., syphilis, mycotic aneurysm), or inflammatory conditions (e.g., rheumatoid vasculitis), about 20 genetic abnormalities that predispose to heritable causes of thoracic aortic aneurysms have been identified.[4]

CLINICAL MANIFESTATIONS

The hallmark of aneurysms, both in the thorax and abdomen, is asymptomatic clinical silence until dissection or rupture.

Abdominal Aortic Aneurysms

Abdominal aortic aneurysms are almost always asymptomatic and are discovered incidentally on routine abdominal palpation, on an imaging study obtained for another purpose, or as part of a screening program. Slowly progressive enlargement can very rarely cause nerve compression or vertebral erosion. When an abdominal aortic aneurysm begins to leak or rupture, however, patients may complain of hypogastric, flank, lower back, or hip pain associated with tenderness on physical examination. An expanding hematoma can compress or impair the blood supply to the bowel or the urinary tract, thereby causing constipation, bloating, or urinary retention for hours to a few days. Acute rupture and cardiovascular collapse may occur unless the aneurysm is repaired.

ABSTRACT

Aortic diseases include aneurysms of the abdominal and thoracic aorta, acute aortic syndromes (intramural aortic hematomas, penetrating aortic ulcers, and aortic dissections), and arteritis of the aorta and aortic arch (e.g., Takayasu and giant cell arteritis). In men ages 65 to 75 years, one-time screening, especially of ever-smokers, can detect asymptomatic abdominal aortic aneurysms, which should undergo endovascular or open repair if they reach 5.5 cm in diameter. Thoracic aneurysms should be repaired if they reach 5 cm in patients with congenital syndromes such as Marfan disease or 5.5 to 6 cm otherwise. For a symptomatic penetrating aortic ulcer, intramural aortic hematoma, and aortic dissection, urgent surgical repair is recommended when the aortic arch is involved, but aggressive medical therapy is first-line treatment when it is not. Takayasu arteritis, which is a panarteritis of unknown cause, is treated with corticosteroids, often combined with methotrexate. Giant cell arteritis, which often is associated with polymyalgia rheumatica, headaches, visual disturbances, and a markedly elevated erythrocyte sedimentation rate, is initially treated with high-dose corticosteroids and then with tocilizumab maintenance therapy.

KEYWORDS

abdominal aortic aneurysm
thoracic aortic aneurysm
intramural hematoma
aortic dissection
Takayasu arteritis
giant cell arteritis

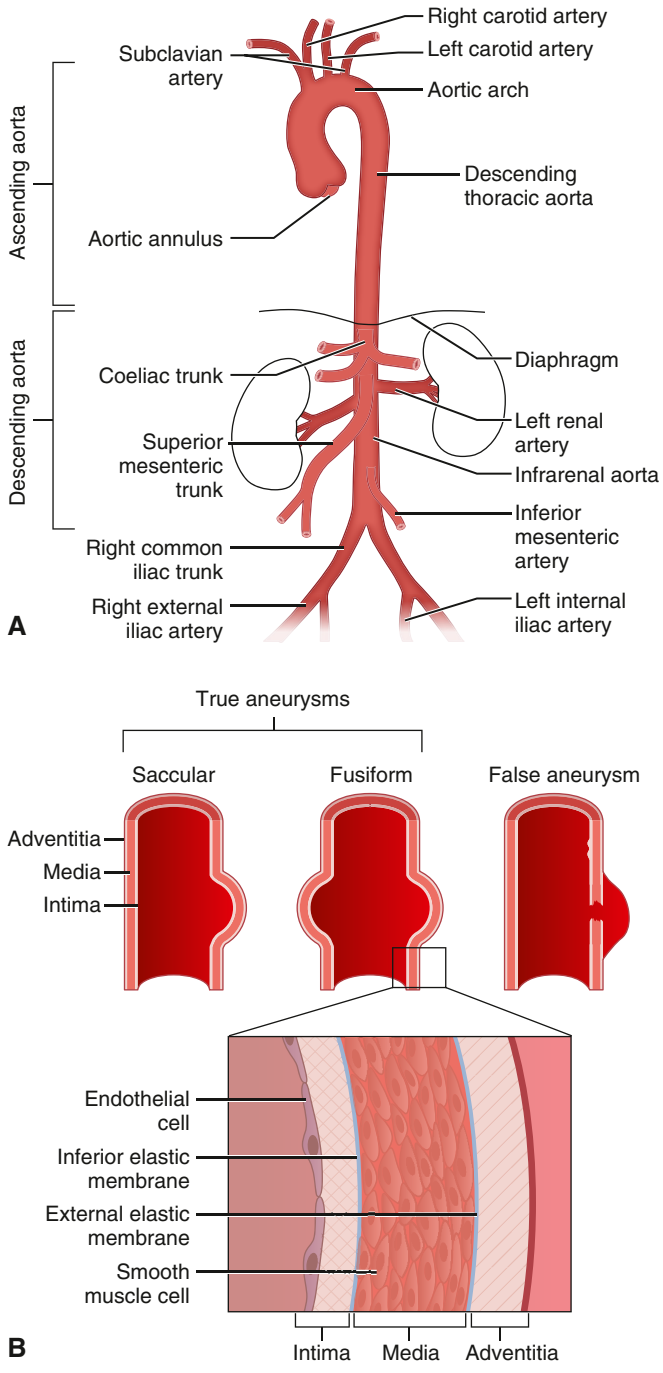

FIGURE 63-1. Schematic of the anatomy of the aorta. A, The aorta, which is divided into segments in the thorax and abdomen. **B,** The aorta has three layers: the intima, media, and adventitia. The formation of an aneurysm may occur in any segment. Fusiform aneurysms are a generalized expansion of the vessel, whereas saccular aneurysms represent a focal outpouching. (Reproduced from Sakalihasan N, Michel JB, Katsargyris A, et al. Abdominal aortic aneurysms. *Nat Rev Dis Primers*. 2018;4:34.)

TABLE 63-1 MEAN AORTIC DIMENSIONS FROM 15,000 NONCONTRAST CT SCANS

	MEN (N = 14,235)	WOMEN (N = 754)
Ascending aorta, mm	37.5 ± 4.1	34.1 ± 3.6
Aortic arch, mm	30.7 ± 2.9	28.1 ± 2.6
Descending aorta, mm	28.5 ± 2.7	25.2 ± 2.4
Abdominal aorta, mm	20.5 ± 4.8	16.6 ± 2.2

Adapted from Obel LM, Diederichsen AC, Steffensen FH, et al. Population-based risk factors for ascending, arch, descending, and abdominal aortic dilations for 60-74-year-old individuals. *J Am Coll Cardiol*. 2021;78:201-211.

Thoracic Aortic Aneurysms

As with abdominal aortic aneurysms, thoracic or thoracoabdominal aneurysms usually expand asymptomatically and are either discovered incidentally by echocardiography or thoracic imaging obtained for other reasons or are found on routine screening of patients with congenital causes. However, expanding thoracic aortic aneurysms, especially from systemic conditions such as syphilis, can sometimes compress adjacent mediastinal structures to cause chest pain, back pain, hoarseness, wheezing, coughing, and dysphagia. Rupture may present with chest or back pain, aortic valve insufficiency, and cardiovascular collapse.

DIAGNOSIS

Abdominal Aortic Aneurysms

An abdominal aortic aneurysm can often be palpated as a pulsatile mass a few centimeters cephalad from the umbilicus, which is at the level of the aortic bifurcation. By placing both hands with the palms down on the abdomen and an index finger at each side of the pulsation, the examiner can palpate the aneurysm and estimate its width. Any pulsatile abdominal mass that exceeds 2.5 to 3.0 cm by this method requires prompt abdominal ultrasonography for a more accurate measurement. An aortic diameter of 3 cm or more establishes the diagnosis of an aneurysm that requires ongoing surveillance.

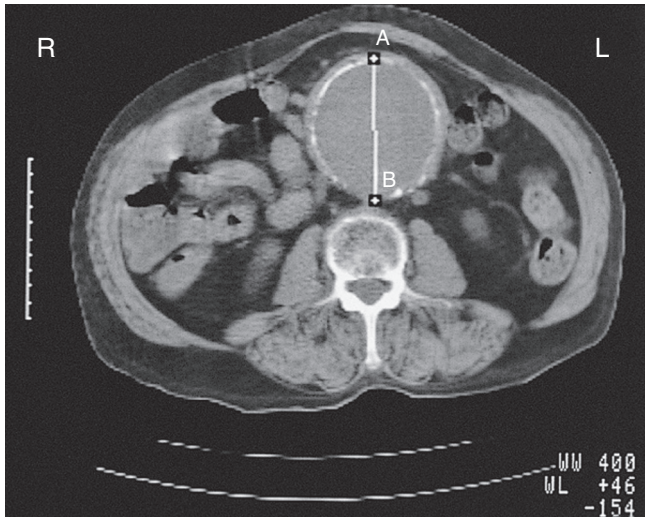

FIGURE 63-2. Abdominal aortic aneurysm on computed tomography. This sensitive imaging method allows precise measurement of size (*point A* to *point B*) and demonstrates the thickened wall of the aneurysm. (From Forbes CD, Jackson WF. *Color Atlas and Text of Clinical Medicine*. 3rd ed. London: Mosby; 2003.)

The diagnosis of a leaking or rupturing abdominal aortic aneurysm is a medical emergency. The classic findings of abdominal pain, hypotension, and a palpable pulsatile abdominal mass is insensitive, and any one of the three should be considered a warning sign, especially in older men with a history of smoking or in a patient with known aortic enlargement. An abdominal aortic aneurysm can be detected and measured by abdominal ultrasonography or by a CT scan (Fig. 63-2), but urgent CT is required when leaking or rupture is being considered.[5]

Because of the usual lack of symptoms, screening abdominal ultrasonography is uniformly recommended to assess for an abdominal aortic aneurysm in men ages 65 to 75 years with any history of smoking, and some guidelines recommend screening for men and women ages 65 to 75 years who have ever smoked or who have a first-degree relative with an abdominal aortic aneurysm. Such screening strategies can detect an abdominal aortic aneurysm in about 5.5% of examinations and reduce aneurysm-related mortality by 45%,[A1] although overall reductions in mortality are less dramatic because of associated comorbid conditions.[6]

Once the diagnosis is made, periodic follow-up ultrasonographic surveillance imaging is generally recommended every 2 to 3 years if the aneurysm is 3 to 3.9 cm, every 12 months if the aneurysm is 4.0 to 4.9 cm, and every 6 months if it is ≥5 cm. Such follow-up permits repair to be performed when an abdominal aortic aneurysm reaches the threshold of 5.5 cm, which is as safe as earlier repair.

Thoracic Aortic Aneurysms

Thoracic aortic aneurysms rarely can be palpated or detected on physical examination even when very large, so they are either found incidentally by a widened mediastinal silhouette or enlarged aortic knob on a chest radiograph or incidentally on an echocardiogram or a CT scan (Fig. 63-3) obtained for other indications.[7] Because of its low prevalence in the general population, routine screening is not recommended.

However, about 20% of thoracic aortic aneurysms are a result of genetic disorders, and screening transthoracic echocardiography is generally recommended in patients who have syndromes such as Marfan (Chapter 239), Loeys-Dietz, or vascular Ehlers-Danlos (Chapter 239), as well as in individuals who have a family history of aneurysmal disease or a first- or second-degree relative with a history of sudden or unexplained death at a young age. Screening should be repeated every 2 to 3 years if the size is normal.

Subsequent surveillance once an aneurysm is detected commonly requires CT imaging if the aorta is involved beyond the routine scanning range of echocardiography. A follow-up scan may be performed in 6 months and then every 6 to 24 months thereafter, based on the size of the aorta and the underlying condition. Surveillance imaging seeks to identify one of two criteria that would lead to referral for surgery: rapid growth or attainment of a specific size (see Treatment).

TREATMENT

Abdominal Aortic Aneurysm

The presence of an abdominal aortic aneurysm mandates aggressive risk modification (Chapter 40), including smoking cessation (Chapter 363), aggressive lowering of blood pressure (Chapter 64), and treatment of dyslipidemia (Chapter 190). Smoking cessation and treatment with high-intensity statins (Table 190-2), which may have some anti-inflammatory as well as hypolipidemic effects, have been associated with a reduced rate of aneurysmal growth and rupture in observational studies. No medical therapy has been proven to reduce the expansion of aneurysms.

Once an abdominal aortic aneurysm reaches the threshold for repair, intervention, whether by open surgical repair or endovascular repair,[8,9] reduces aneurysm-related mortality.[A2] The endovascular approach is preferable for reducing early morbidity and mortality, but both treatments are associated with similar survival after about 2 years and probably extending for at least a decade.[A3-A5] Unfortunately, endovascular repair is not worthwhile in patients whose overall surgical risk would exclude them from open repair because their all-cause mortality rate offsets any potential benefit from repair of the abdominal aortic aneurysm itself.[A6]

After open surgical repair, follow-up surveillance imaging is not needed. In contrast, the risk of late aortic rupture after endovascular repair is >5% over 8 years of follow-up, and current recommendations are for surveillance at 1 month, 12 months, and annually thereafter to delineate any potential endoleaks, stent migration, fracture, and noncontiguous aneurysms. Duplex ultrasound is recommended for surveillance if the first CT angiogram at 1 month does not demonstrate any endoleaks. Endoleaks may result in an abdominal aortic aneurysmal sac that is not depressurized by the placement of a graft. The two most worrisome are type 1 leaks, which occur as a result of an inadequate seal at the graft end, and type 2 leaks, in which the aneurysmal sac fills by a branch vessel (E-Fig. 63-1). Enlargement is a sign that the aneurysmal sac remains under increased or systemic pressure and may require repair.

Thoracic Aortic Aneurysm

Although data regarding medical therapies to reduce the rate of expansion, dissection, or rupture are limited, hypertension increases the risk of aortic dissection and rupture 2.7-fold. Patients with thoracic aortic aneurysm, regardless of cause, should be treated to a heart rate of 60 to 70 beats per minute, systolic blood pressure of ≤120 mm Hg, and diastolic pressure of ≤80 mm Hg by titrating a β-blocking agent (e.g., atenolol starting at 25 to 50 mg twice daily) and using angiotensin receptor blockers (e.g., irbesartan 150 mg daily increased to 300 mg daily as tolerated), or a combination of the two, based on data for the treatment of aortic enlargement in patients with Marfan syndrome.[A7] Isometric exercises, which can acutely increase peripheral arterial resistance and intrathoracic pressure, generally should be avoided.

In contrast to the standard size at which repair is recommended for abdominal aortic aneurysms, surgical recommendations vary depending on the cause of a thoracic aortic aneurysm. Upon diagnosis, a transthoracic echocardiogram is recommended to assess aortic diameters and aortic valvular function. In addition, the entire thoracic aorta should be imaged by CT scan because an aneurysm in one segment is a strong predictor of aneurysmal dilatation in another. Standard surveillance, with echocardiography if it can visualize the aneurysm, should be performed at 6 months after diagnosis and then annually. If the thoracic aortic aneurysm enlarges to within 0.5 cm of the size recommended for surgical referral, the frequency of surveillance imaging should increase to twice yearly.

Surgical repair of the aortic root or ascending aorta with resection of the aneurysm and an interposition graft replacement is recommended when an ascending or aortic root aneurysm reaches a diameter of 5.5 cm or greater or grows ≥5 mm in a single year in a nonsyndromic patient. In patients with a heritable cause of thoracic abdominal aneurysm (e.g., Marfan syndrome), the recommended size for repair is usually 5 cm, but it is 4.5 cm in patients who have high-risk features, including a family history of sudden death, rapid growth, or significant aortic valve regurgitation. In addition to size, the presence of symptoms arising from an aneurysm is an indication for repair. Urgent repair is required for severe pain or hemodynamic collapse.

For rare mycotic aortic aneurysms in patients who have survived bacterial endocarditis (Chapter 61), either open surgery or endovascular repair can be recommended. If endovascular repair is selected, long-term antibiotic treatment is recommended to prevent late recrudescence of infection.

PROGNOSIS

Aneurysms typically expand slowly over time, with an average growth in diameter of about 0.17 cm per year for abdominal aortic aneurysms,[10] and the risk of rupture increases accordingly. An abdominal aortic aneurysm below 5.5 cm in diameter has a 1% or lower annual rupture risk. For nonsyndromic thoracic aortic aneurysms, the 5-year rupture risk is essentially 0% if the aneurysm is below 4.0 cm in diameter but rises to about 15% for aneurysms 4.0 to 6.0 cm in diameter and about 30% if the aneurysm is larger than 6.0 cm in diameter in patients without inherited connective tissue disorders.[11]

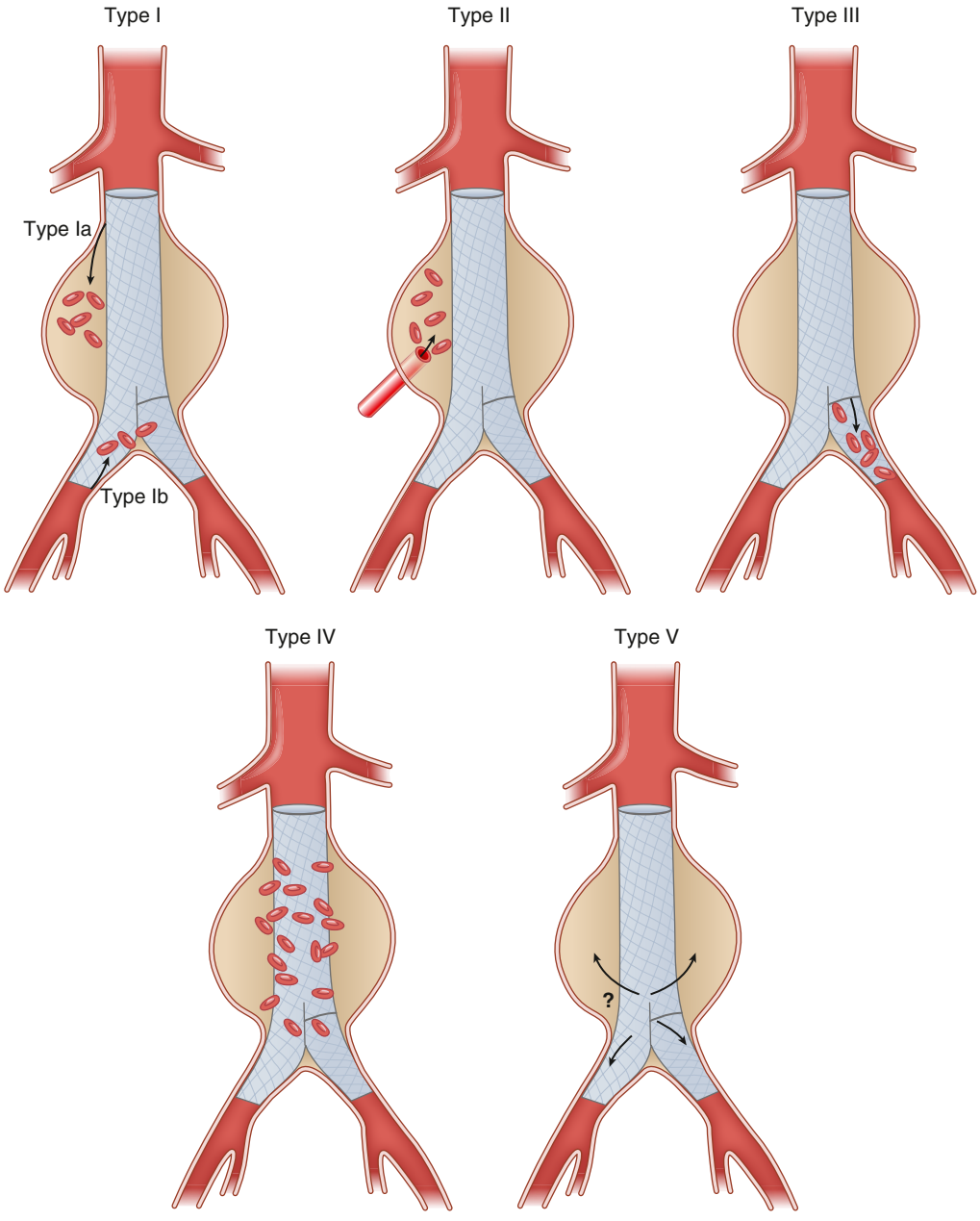

E-FIGURE 63-1. Endoleaks. The five varieties of endoleaks are demonstrated here. Types 1 and 2 are the ones to most commonly preserve a pressurized aortic aneurysm sac and require revision. (From Erbel R, Aboyans V, Boileau C, et al. 2014 ESC guidelines on the diagnosis and treatment of aortic diseases: document covering acute and chronic aortic diseases of the thoracic and abdominal aorta of the adult. The Task Force for the Diagnosis and Treatment of Aortic Diseases of the European Society of Cardiology (ESC). *Eur Heart J*. 2014;35:2873-2926.)

FIGURE 63-3. Sagittal plane computed tomographic image of a tortuous proximal descending aortic aneurysm.

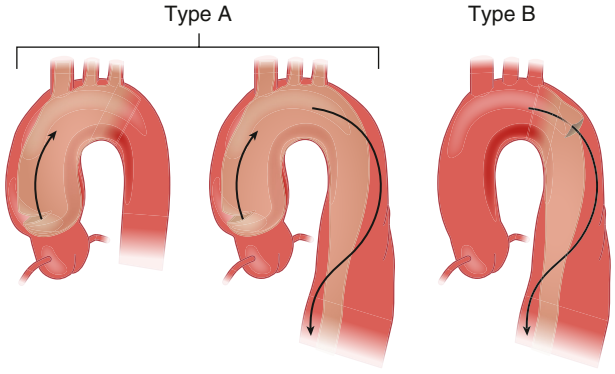

FIGURE 63-4. Schematic representation of types of aortic dissections by location.

The impact of an unruptured aneurysm, per se, on survival is modest, and there is no variation in survival whether an aneurysm is repaired at or below the recommended threshold size of 5.5 cm. However, life expectancy is reduced in patients who have an abdominal aortic aneurysm because of their higher rates of cardiovascular disease and cancer. In one study, for example, overall mortality was about 30% at 5 years and about 65% at 12 years.

When an aortic aneurysm leaks or ruptures, the mortality rate is about 75%, with about a 35% mortality rate even after emergent intervention. After endovascular repair, lifelong surveillance imaging is recommended, probably annually. The patient's prognosis is determined largely by risk factors and comorbid conditions rather than the aneurysm itself. Careful attention to blood pressure (Chapter 64) and lipid levels (Chapter 190) is indicated.

Survival in all-comers after repair of an ascending aortic aneurysm is 93% at 3 years and 80% at 8 years.[12] In patients with Marfan syndrome, results are similar after elective aortic root replacement.

ACUTE AORTIC SYNDROMES

DEFINITION

Acute aortic syndromes are an uncommon but life-threatening emergency. The three types of acute aortic syndrome are penetrating aortic ulceration, intramural hematoma, and aortic dissection.[13] Aortic dissection represents about 75% of all acute aortic syndromes.

EPIDEMIOLOGY

The incidence of acute aortic syndromes is likely underappreciated because as many as 1 in 15 out-of-hospital arrests may be due to aortic dissection, and an estimated 20 to 50% of patients die before the diagnosis can be made. In emergency departments, the incidence is about 5 to 8 cases per 100,000 patients per year.[14]

The peak age of incidence is between 50 and 70 years, and about two thirds of cases occur in men.[15] Key predisposing features include genetic abnormalities of the aorta (e.g., Marfan syndrome [Chapter 239]), arterial hypertension, a bicuspid aortic valve, advanced atherosclerosis, use of cocaine or methamphetamines, pregnancy,[16] prior known aortic aneurysm, aortitis, blunt trauma to the chest, heart surgery, and intraaortic catheter-based procedures.

PATHOBIOLOGY

Each of the acute aortic syndromes is characterized by a different mechanism of rupture in the aortic wall. The location of an acute aortic syndrome typically is defined by whether or not the site of dissection, origin of intramural hematoma, or penetrating aortic ulceration involves the ascending aorta (Fig. 63-4), because the initial lesion may propagate proximally as well as distally.

Aortic dissection is defined by the presence of an intimal tear that facilitates entry of the fully pressurized circulation into the media, thereby dividing it into two layers. The most common site of intimal tear is just beyond the level of the aortic valve for dissections that involve the ascending and/or transverse aorta (called type A dissections regardless of whether or not they extend into the descending aorta; see Fig. 63-5) and just beyond the insertion of the ligamentum arteriosum (where the mobile arch meets the fixed descending aorta) for dissections that are limited to the descending aorta (called type B dissections). The pulsatile blood flow propagates this separation, both distally and proximally, to create a false lumen or channel for blood flow. The false lumen may continue to extend, rupture back into the aortic true lumen, or rupture outward.

The complications of aortic dissection include rupture and end-organ malperfusion. Common sites of rupture include the pericardial space, thereby leading to cardiac tamponade in type A dissection and the left pleural space in type B dissection. Compromised blood flow to viscera or limbs may be the result of compression of the branch vessels by the hematoma within the false lumen, extension of the dissection within a branch vessel, or swinging movement of the dissection flap over the branch vessel.

Intramural hematoma, which is the second most common form of acute aortic syndrome, is usually found in 20 to 25% of cases in Western populations and as high as 40% of cases in Asian populations. In contrast to a dissection, the intramural hematoma is collection of blood in the wall of the aorta as a result of rupture of the vaso vasorum or an unappreciated intimal microtear. Unlike the linear tear seen on imaging with a dissection, an intramural hematoma appears as a round or crescent-shaped thickening without connection to the active circulation in the lumen. In Western populations, almost 50% of intramural hematomas progress to frank intimal tear and dissection, but intramural hematoma appears to carry a lower risk of morbidity and mortality than aortic dissection in East Asian populations.

A penetrating aortic ulcer, which probably represents about 5% of acute aortic syndromes, is initiated by ulceration of an atherosclerotic plaque. Disruption of the internal elastic lamina permits penetration of blood through the intima into the medial layers but, at least initially, no further. Because aortic atherosclerosis is most common in the descending aorta, this portion of the aorta is the most common segment for a penetrating aortic ulcer.

CLINICAL MANIFESTATIONS

For type A aortic dissections, which involve the ascending aorta, the vast majority of patients present as an acute aortic syndrome, with the sudden onset of severe anterior chest pain that is described as the most severe or worst pain ever experienced. Pain often radiates to the neck or jaw with an ascending aortic dissection and to the back and sometimes to the abdomen if the dissection extends to the descending aorta (Table 63-2). Tearing or ripping pain, once thought to be common, is reported in fewer than half of patients. In up to 20% of patients, however, syncope is the presenting symptom.

For type B dissection, severe pain is reported by more than 90% of patients. Back pain is reported in 55 to 80% of patients, but chest or abdominal pain is also common. Syncope is present in less than 5% of patients.

Other symptoms and signs can indicate compromise of aortic branch blood vessels and malperfusion or impingement on adjacent structures. For example, the presence of abdominal pain may indicate mesenteric ischemia (Chapter 129). Severe dyspnea or collapse may arise when retrograde extension causes aortic valve regurgitation or when rupture into the pericardial space causes cardiac tamponade. Paraplegia may be a result of spinal vascular malperfusion. Oliguria or hematuria can be the direct result of involvement of the renal arteries. Cerebral malperfusion, sometimes with a stroke, occurs in 6

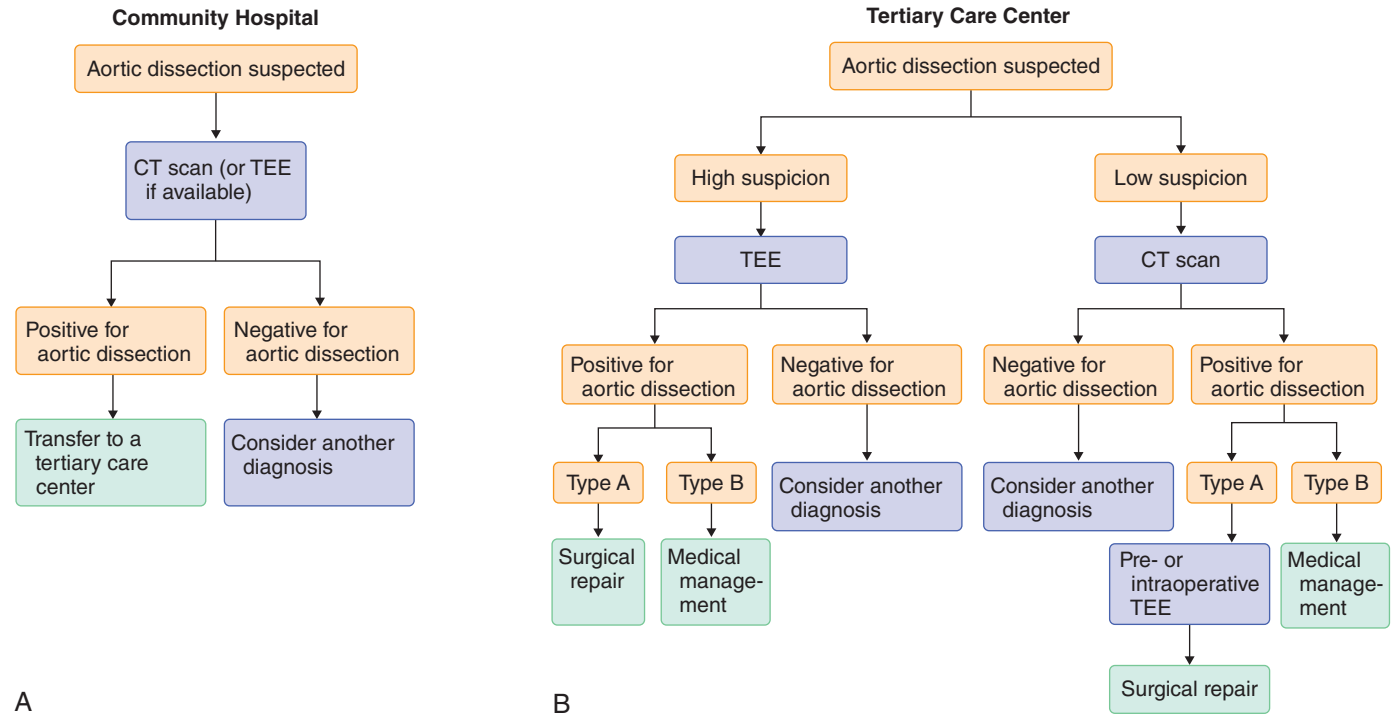

FIGURE 63-5. **Algorithms for the evaluation of suspected acute aortic dissection. A,** This approach is used in many community hospitals where cardiac surgery is not performed. **B,** This approach is used in many tertiary care centers where transesophageal echocardiography (TEE) and cardiac surgery are available. CT = computed tomography. (Courtesy of Eric M. Isselbacher, MD.)

TABLE 63-2 HIGH-RISK CHARACTERISTICS FOR ACUTE AORTIC DISSECTION

High-Risk Predisposing Conditions • Marfan syndrome • Family history of aortic disease • Known aortic valve disease • Recent aortic manipulation • Known thoracic aortic aneurysm
High-Risk Pain Chest, back, or abdominal pain described as the following: • Abrupt in onset • Severe in intensity • Ripping or tearing

High-Risk Physical Examination
• Evidence of perfusion deficit
  • Pulse deficit
  • Systolic blood pressure differential
  • Focal neurologic deficit (in conjunction with pain)
• Murmur of aortic insufficiency (new or not known to be old and in conjunction with pain)
• Hypotension or shock state

Adapted from Rogers AM, Hermann LK, Booher AM, et al. Sensitivity of the aortic dissection detection risk score, a novel guideline-based tool for identification of acute aortic dissection at initial presentation: results from the international registry of acute aortic dissection. *Circulation.* 2011;123:2213-2218.

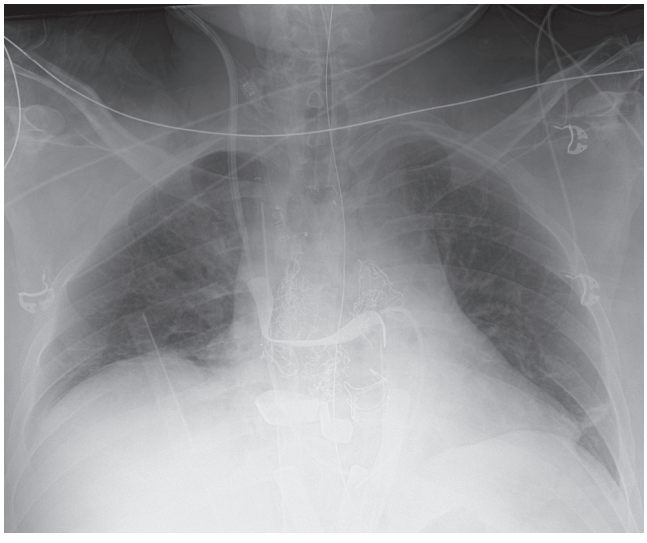

FIGURE 63-6. **Chest radiograph in ascending aortic dissection.** Note the widened mediastinum.

to 14% of proximal aortic dissection patients because of a partial or complete occlusion of the great vessels.

DIAGNOSIS

The significant early mortality associated with acute aortic syndromes can be reduced with rapid clinical evaluation and imaging (Fig. 63-5). The physical examination should include a complete cardiac and vascular inspection. Key high-risk findings include pulse deficits, a murmur of aortic valvular insufficiency, hypotension, and a focal neurologic deficit (particularly with pain). If patients have two of three high-risk characteristics (predisposing conditions, typical pain, suspicious findings on physical examination; see Table 63-2), emergent aortic imaging is required. If patients have one of the features, any chest pain syndrome (see Table 39-2) without clear evidence of an alternative diagnosis should prompt consideration of urgent imaging, especially if the chest radiograph shows any evidence of aortic widening.

Chest radiographs show a widened mediastinum (Fig. 63-6) in about 50% of type A dissections but are rarely diagnostic. Electrocardiography is also commonly abnormal and can show an inferior or anterior wall myocardial infarction if retrograde dissection compromises the ostium of the right or left coronary artery, respectively; in large series each of the two coronary ostia is equally likely to be compromised.[17] Transthoracic echocardiography has an 85 to 90% sensitivity for diagnosing aneurysms of the ascending aorta and can provide additional information about ventricular and valvular function, but it is not accurate for type B dissection. Transesophageal echocardiography (Fig. 63-7) raises the sensitivity for detecting a type A dissection to about 98% and may show the luminal tear but again is not very accurate for type B dissection. As a result, CT angiography, which is available in many emergency departments, is usually the test of choice for detecting proximal (Fig. 63-8) or distal (Fig. 63-9) aortic dissection, intramural hematoma (Fig. 63-10), or penetrating

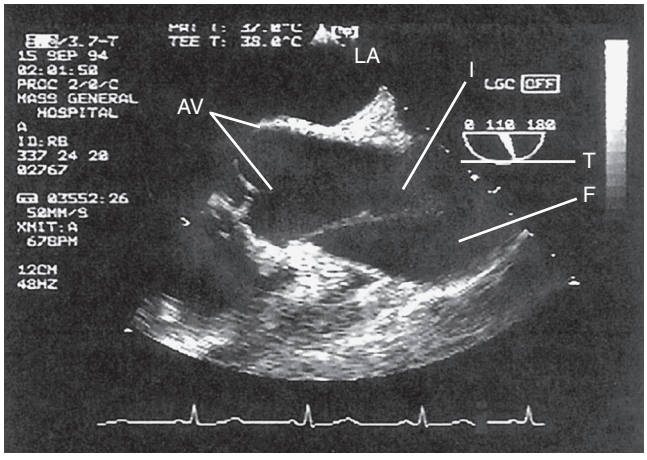

FIGURE 63-7. Transesophageal echocardiogram of the ascending aorta in the long axis in a patient with type A aortic dissection. The aortic valve (AV) is on the *left*, and the ascending aorta extends to the *right*. Within the aorta is an intimal flap (I) that originates at the level of the sinotubular junction. The true (T) and the false (F) lumens are separated by the intimal flap. LA = left atrium. (From Isselbacher EM. Diseases of the aorta. In: Braunwald E, Zipes DP, Libby P, Bonow RO, eds. *Braunwald's Heart Disease: A Textbook of Cardiovascular Medicine*. 7th ed. Philadelphia: Saunders; 2004:1423.)

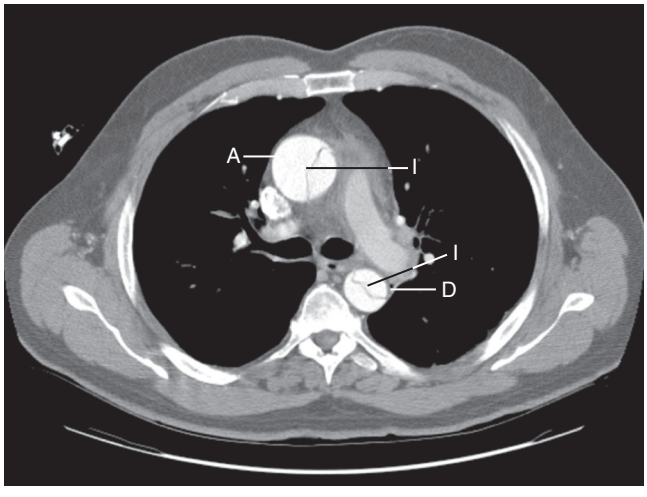

FIGURE 63-8. Aortic dissection. Contrast-enhanced computed tomography scan of the chest at the level of the pulmonary artery shows an intimal flap (I) separating the two lumens of the ascending (A) and descending (D) thoracic aorta in a type A aortic dissection. (Courtesy of Eric M. Isselbacher, MD.)

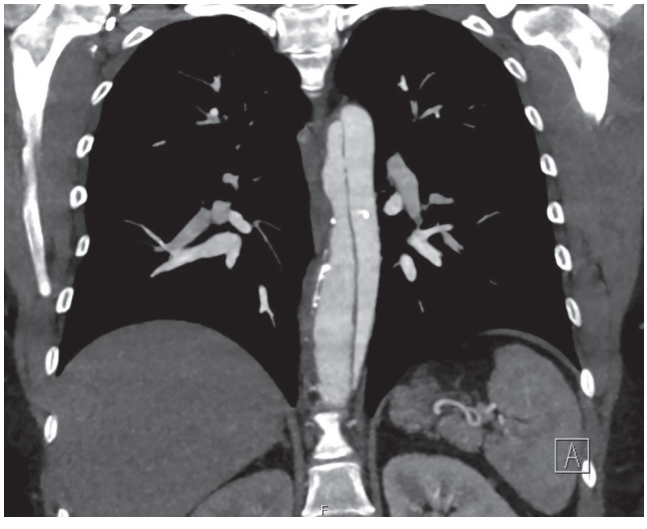

FIGURE 63-9. Coronal plane computed tomography angiogram of a type B aortic dissection.

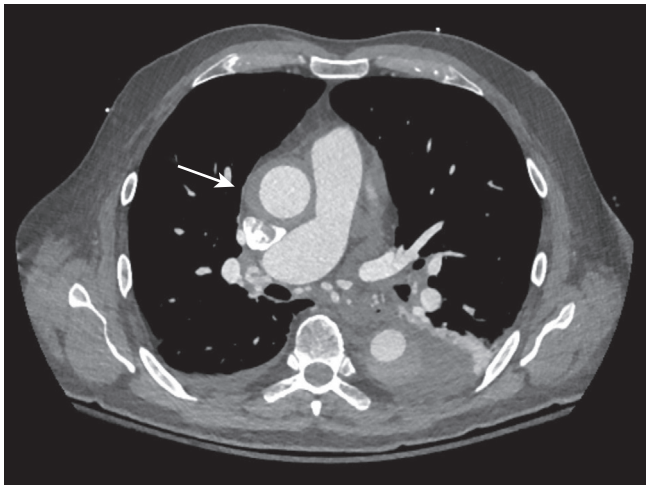

FIGURE 63-10. Axial plane computed tomography angiographic of an ascending aorta intramural hematoma. The *arrow* identifies the crescenteric wall thickening.

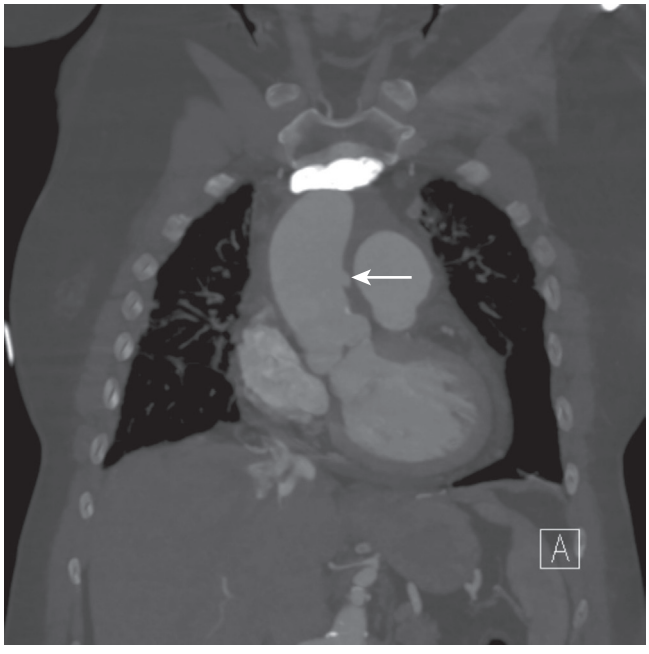

FIGURE 63-11. Computed tomographic angiogram showing a penetrating aortic ulcer. Coronal plane computed tomography angiographic image of an ascending aorta penetrating ulcer. The *arrow* identifies the outpouching of the ulceration.

aortic ulcer (Fig. 63-11). Magnetic resonance (MR) angiography is equally accurate but typically requires significantly more time in a poorly supervised setting for a critically ill patient. As a result, it is more commonly used as a second-line examination when clinical suspicion requires additional testing.

TREATMENT

Acute Type A Aortic Dissection and Intramural Hematoma

As soon as the diagnosis of a type A aortic dissection or intramural hematoma is made, surgical consultation should be obtained and arrangements should be made to transfer the patient to a high-volume facility if possible. In the meantime, acute medical management requires aggressive blood pressure control with agents that also decrease cardiac inotropy (Fig. 63-12). The goal of medical therapy is a systolic blood pressure of 100 to 120 mm Hg with a heart rate of 60 to 70 beats per minute. The first line of therapy is an intravenous β-adrenergic blocker, such as esmolol, labetalol, or metoprolol (Table 63-3). Should blood pressure control not be achieved despite realizing heart rates ≤60 beats per minute, intravenous vasodilators should be administered as second-line therapy. In addition to hemodynamic therapy, narcotic analgesia (Table 26-6) should be provided for treatment of pain. In the setting of spontaneous hypotension, pseudohypotension resulting from limb vascular compromise must be excluded, the cause must be ascertained, and hemodynamic support should be provided en route to emergency surgery (Chapter 93).

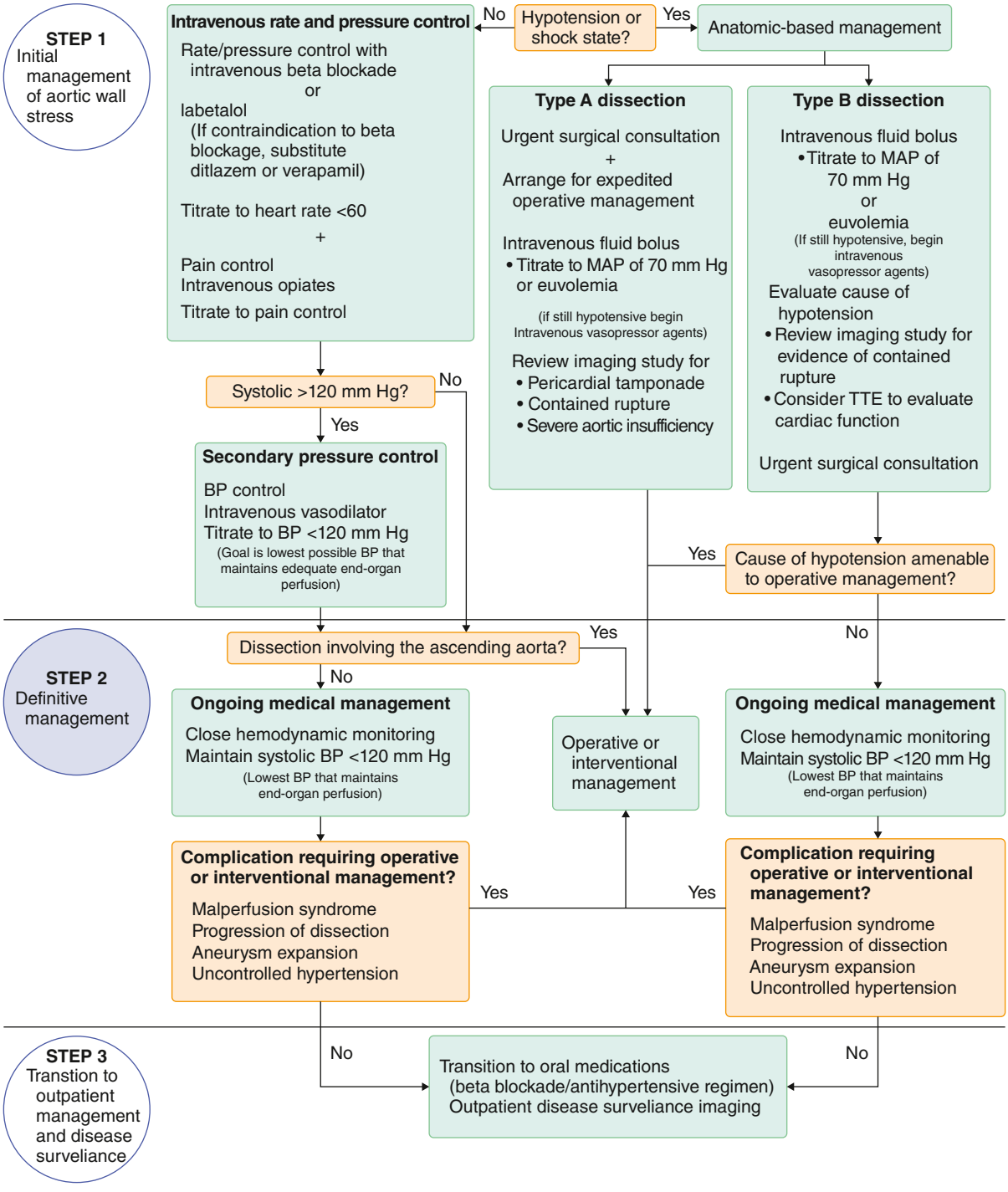

FIGURE 63-12. Management pathway for acute aortic dissection. AoD = aortic dissection; BP = blood pressure; MAP = mean arterial pressure. (Adapted from Hiratzka LF, Bakris GL, Beckman JA, et al. 2010 ACCF/AHA/AATS/ACR/ASA/SCA/SCAI/SIR/STS/SVM guidelines for the diagnosis and management of patients with thoracic aortic disease: executive summary. A report of the American College of Cardiology Foundation/American Heart Association Task Force on Practice Guidelines, American Association for Thoracic Surgery, American College of Radiology, American Stroke Association, Society of Cardiovascular Anesthesiologists, Society for Cardiovascular Angiography and Interventions, Society of Interventional Radiology, Society of Thoracic Surgeons, and Society for Vascular Medicine. *J Am Coll Cardiol*. 2010;55:e27-e129.)

For type A aortic dissection or intramural hematoma, prompt surgical repair of the ascending aorta is indicated, if possible, even in the setting of complications such as cardiac tamponade, aortic rupture, or stroke. For type A aneurysms, urgent surgical repair reduces death by more than 50% compared with medical therapy alone.[18,19] In patients who have malperfusion syndromes of the abdomen or lower extremity, repair of the ascending aorta should be performed first.

Acute Type B Aortic Dissection or Intramural Hematoma

The acute treatment of aortic dissections that do not involve the ascending aorta and of intramural hematomas is more nuanced. In the absence of ongoing pain, malperfusion syndromes, or rupture, type B aortic dissections usually should be treated medically, initially with an approach similar to the approach for type A lesions (Table 63-3). Interventional treatment is recommended, however, for type B aortic dissections with complications such as rupture, ongoing extension of the dissection, unremitting pain, or a visceral or peripheral malperfusion. For type B aortic dissection, endovascular stent grafting, including the placement of stent grafts or the creation of a channel through the dissection flap to decompress a hypertensive false lumen, is preferred over surgical repair.

Once blood pressure and pulse have been acutely controlled, the patient should be weaned from intravenous medications and switched to an oral regimen. The oral regimen should emphasize β-blockers[20] with adjunctive angiotensin-converting enzyme inhibitors or angiotensin receptor blockers (see Table 64-7).

Penetrating Aortic Ulcers

The acute medical management of a symptomatic penetrating aortic ulcer mirrors that of type A aortic dissection (Table 63-3). Ascending aortic penetrating atherosclerotic aortic ulcers should be repaired when they are associated with symptoms. Symptomatic penetrating aortic ulcers of the descending aorta are usually managed medically as for type B dissections. However, stable penetrating ulcers of the descending aorta and isolated asymptomatic penetrating aortic ulcers identified on CT angiographic scanning have a low (<4%) risk of progressing and should be managed medically as for a stable type B dissection.[21]

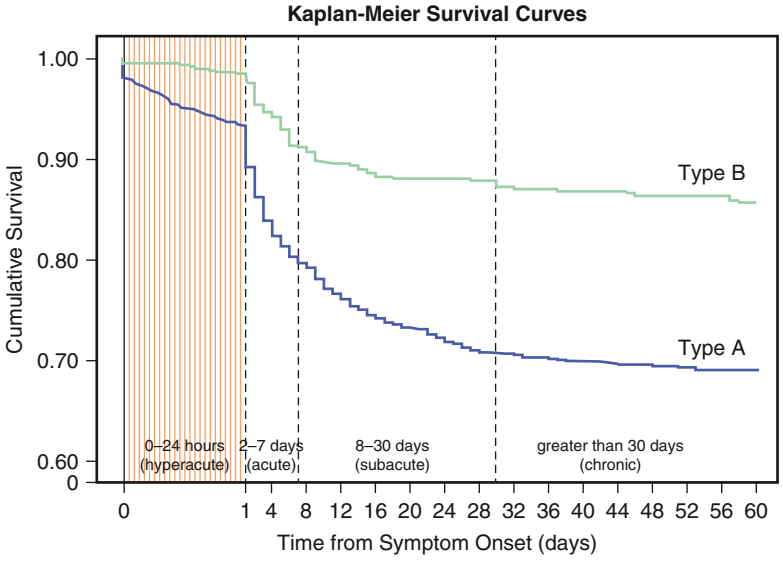

E-FIGURE 63-2. Survival curves by type of aortic dissection. The incidence of death is at its peak early after dissection. (From Booher AM, Isselbacher EM, Nienaber CA, et al. The IRAD classification system for characterizing survival after aortic dissection. *Am J Med*. 2013;126:730 e719-724.)

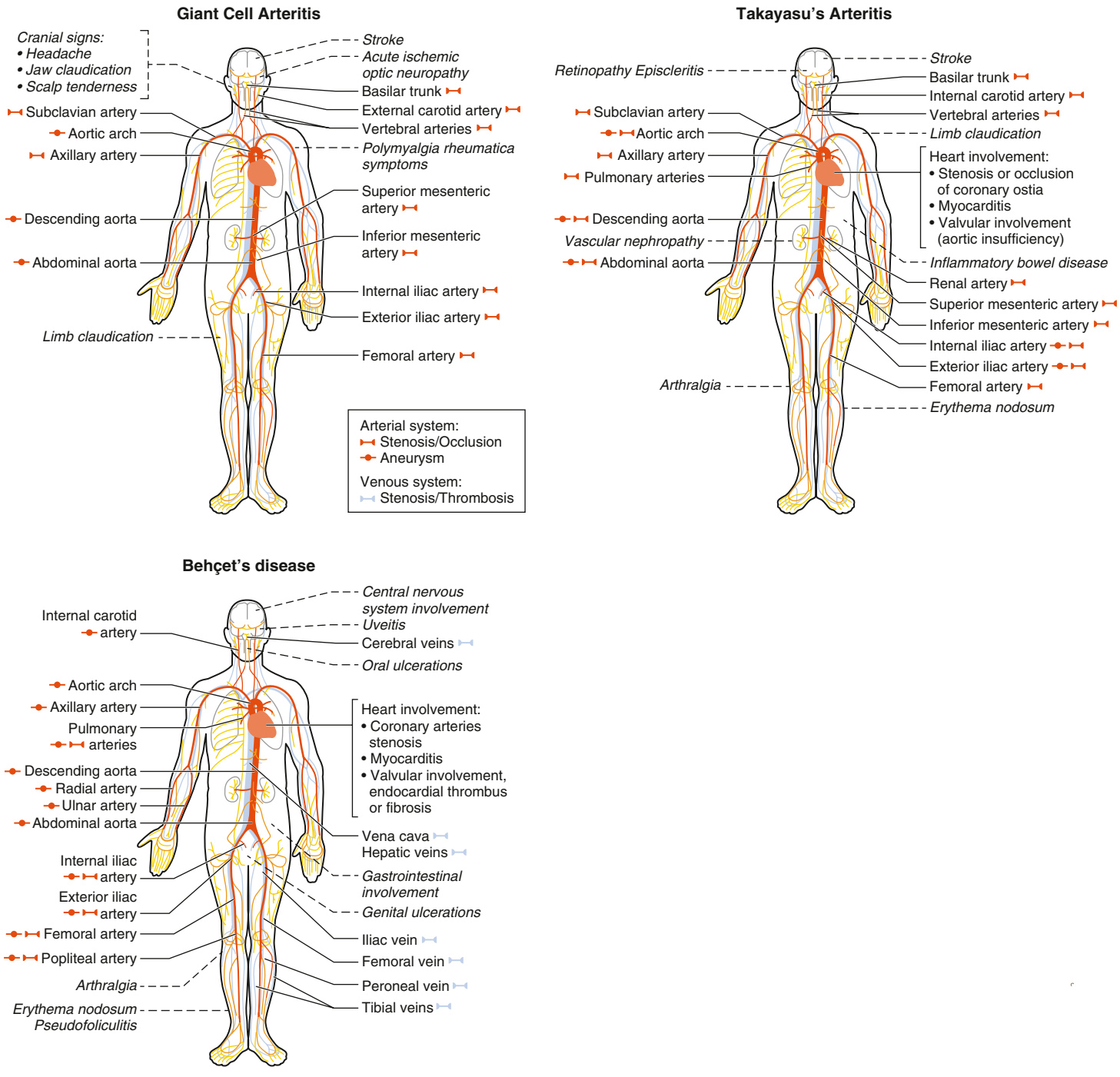

E-FIGURE 63-3. Schematic representation of vascular and organ involvement in giant cell and Takayasu arteritis. (From Saadoun D, Vautier M, Cacoub P. Medium- and large-vessel vasculitis. *Circulation*. 2021;143:267-282.)

TABLE 63-3 ACUTE MEDICAL THERAPY FOR AORTIC DISSECTION*

Intravenous β-Blocker (Preferred Negative Inotrope)
- Esmolol: 250-500 μg/kg IV bolus followed by a 50-200 μg/kg/min infusion, titrated to effect
- Labetalol: 20 mg IV bolus over 2 min, followed by 20-80 mg IV every 10 min, then 0.5-2 mg/min IV fusion
- Metoprolol: 2.5-15 mg IV bolus followed by 2.5-15 mg IV every 3-6 hr

Intravenous Vasodilator (After Initiation of Negative Inotrope)
- Clevidipine: Start at 1-2 mg/hr, up to maximum of 16-32 mg/hr
- Sodium nitroprusside: Start at 0.25-0.5 μg/kg/min, up to a maximum of 8-10 μg/min (only in presence of β-blockers to avoid tachycardia and with careful observation to avoid thiocyanate toxicity with prolonged perfusion, especially in patients with renal impairment)
- Nicardipine: 2.5-5 mg/hr (to a maximum of 15 mg/hr)
- Nitroglycerin: 5 μg/min infusion (to a maximum 200 μg/min)
- Enalaprilat: 1.25 mg, then 1.25-5 mg IV every 6 hr
- Fenoldopam: Start at 0.1 μg/kg/min and titrate up to a maximum of 1.6 μg/kg/min

*Goal of therapy is heart rate less than 70 beats/min and blood pressure 100-120 mm Hg or as low as possible without compromising organ perfusion.

Adapted from Braverman AC, Schermerhorn M. Diseases of the aorta. In: Libby P, Bonow RO, Mann DL, Tomaselli GF, Bhatt D, Solomon SD, Braunwald E, eds. *Braunwald's Heart Disease: A Textbook of Cardiovascular Medicine*, 12th ed. Philadelphia: Elsevier; 2022.

PROGNOSIS

Mortality for type A dissections and intramural hematoma is 1 to 2% per hour in untreated patients, peaks within the first 24 hours, remains quite high from days 2 to 7 but is lower from days 8 to 30 and chronically thereafter (E-Fig. 63-2). Despite the delay, however, interfacility transfer from a low-volume hospital to a high-volume hospital is associated with a better short- and long-term outcome. For type B dissections, the acute mortality is lower, but the time pattern of mortality is similar.

The unadjusted 1-year survival for type A aortic dissection is 96% after repair compared with 89% with medical therapy, and the mortality curves continue to separate over time, with deaths about 2.5-fold more likely in patients who are treated medically. Predictors of death included older age, a history of atherosclerosis, prior cardiac surgery, and poorer control of blood pressure.

The survival for patients with type B aortic dissection is about 80% at 3 years. Predictors of mortality include older age, female sex, a history of prior aortic aneurysm, a history of atherosclerosis, in-hospital renal failure, and hypotension or shock. Surveillance imaging after hospitalization is recommended at 1, 6, and 12 months and annually thereafter. Adherence to careful follow-up and good control of blood pressure is associated with better outcomes.[22]

AORTIC VASCULITIS

Two large-vessel inflammatory diseases involve the aorta—giant cell arteritis and Takayasu arteritis (E-Fig. 63-3).[23]

GIANT CELL ARTERITIS

Giant cell arteritis, which is the most common vasculitis in the United States (Chapter 250), has an age-adjusted prevalence of 204 per 100,000 among persons older than age 50 years, with similar frequencies in White and Black patients. Giant cell arteritis commonly involves aortic branch vessels but may involve the aorta itself in up to 30% of cases. Markers of inflammation, such as the erythrocyte sedimentation rate (ESR) and C-reactive protein level, are increased in the vast majority of patients. The primary risk for adverse outcomes is the development of aortic aneurysm or dissection, with these risks about double that of unaffected individuals.

CLINICAL MANIFESTATIONS AND DIAGNOSIS

The hallmark clinical manifestations of aortic involvement are related to vascular insufficiency, commonly including fatigue and claudication of the upper extremities and sometimes of the lower extremities. Patients may complain of headache, fatigue, muscle aches, jaw claudication, and amaurosis fugax. On physical examination, diminished or absent pulses and diminished blood pressure are noted in the upper extremities. The temporal artery may also be tender and tortuous. Bruits may be audible over the involved arteries, and vigorous exercise of the involved extremity may reveal pallor from diminished circulation.

The diagnosis of giant cell arteritis is based on the presence of three of five criteria including age over 50 years, ESR ≥50 mm/hour, a temporal artery abnormality (tenderness), new-onset headache, and/or temporal artery biopsy showing mononuclear or granulomatous inflammation, commonly with giant cell infiltrates (see Chapter 250).[24] Ultrasonographic imaging of the temporal artery or one of its branches[25] with a hypoechoic halo sign around the lumen is also a useful diagnostic sign.[26] The extent of aortic involvement can be determined by CT angiography or MR angiography.

TREATMENT

In patients with visual symptoms, treatment should be started even while awaiting biopsy results. Otherwise, medical therapy with 40 to 60 mg per day of prednisone (or its equivalent) should be started as soon as the diagnosis is established. The dose can be tapered based on clinical response and normalization of the ESR.[27] After the patient is stabilized, tocilizumab (an anti-interleukin 6 receptor antibody at 162 mg subcutaneously weekly) should be started, and corticosteroids usually can be tapered or discontinued within about 6 months.[A8] Methotrexate (15 to 25 mg per week) also has modest benefit.[A9] Adding abatacept (10 mg/kg on days 1, 15, and 29 and week 8) to prednisone also can reduce the risk of relapse.[A10]

Endovascular intervention may be required for severe stenoses. Should a large aneurysm be diagnosed and surgical repair deemed necessary, surgery should be delayed, if possible, until remission of the active inflammatory state has been achieved to avoid surgical complications.

TAKAYASU ARTERITIS

Takayasu arteritis, which is the most common cause of aortitis in persons under age 40 years, is more common in women than in men. It occurs in 2 to 3 persons per million in the United States, is most prevalent in East Asia, but is seen worldwide. Takayasu arteritis typically affects the major aorta branch vessels, including the innominate, carotid, and subclavian arteries, but it also can affect the thoracic and abdominal aorta.[28]

Takayasu arteritis is a panarteritis in which all layers of the artery are involved. In its early stages, the aorta and its branches show active inflammation. As the disease progresses, a sclerotic stage with intimal hyperplasia, medial degeneration, and obliterative changes is common. Takayasu arteritis also can occasionally involve the pulmonary artery. Most arterial lesions are stenotic, but aneurysms may also be seen.

CLINICAL MANIFESTATIONS AND DIAGNOSIS

The presentation of Takayasu arteritis may include constitutional symptoms (e.g., fevers, night sweats, weight loss, myalgias, arthralgias), but arterial occlusive disease is the predominant manifestation, with aortic symptoms and signs similar to giant cell arteritis. Aneurysms form in less than 5% of patients.

Pulses may be diminished or absent in the upper extremities, and blood pressure may be different in the two arms. Bruits may be audible over affected arteries. More than 50% of patients are hypertensive because of renal artery involvement, but hypertension may be obscured on routine examination because of the diminished pulses. Involvement of the proximal aorta can cause aortic valve insufficiency. Involvement of the coronary ostia can cause angina or myocardial infarction. Cerebral ischemia or stroke may result from involvement of the carotid artery, and compromise of the mesenteric circulation may cause abdominal angina.

Laboratory abnormalities include an elevated C-reactive protein level, an elevated ESR, anemia, mild leukocytosis, and elevated immunoglobulin levels. Diagnostic criteria include age <40 years at onset, claudication of extremities, a decreased brachial artery pulse, a systolic blood pressure difference >10 mm Hg between arms, a bruit over subclavian arteries or aorta, and an arteriographic abnormality on CT or MR angiography or contrast aortography. On imaging, Takayasu arteritis can be diffuse or patchy, and it is usually most prominent at aorta branch points and in the abdominal aorta.

TREATMENT

Corticosteroid therapy (e.g., prednisone 40 to 60 mg daily or the equivalent) is the foundation of therapy to reduce the inflammation and arrest the inflammatory process. Methotrexate (15 to 25 mg/week) is commonly given as an adjunct to corticosteroid therapy. Tofacitinib 5 mg twice daily may be as good as or better than methotrexate.[29] Tocilizumab is also used, but the supporting data are not as strong as in giant cell arteritis.[A11] Routine follow-up with monitoring of disease activity, both by blood-based markers and imaging, is recommended. Percutaneous stent-based treatments are effective and can be repeated if needed.[30] As with giant cell arteritis, endovascular and surgical procedures have better outcomes when performed in periods of disease remission.

PROGNOSIS

About 50% of patients relapse within 10 years. The 15-year survival rate is about 95% in patients without major complications but only about 65% in patients with major complications. The predominant causes of morbidity and mortality are cardiovascular, including myocardial infarction, heart failure, pulmonary hypertension, and aortic aneurysm rupture.

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For the General References and other additional features, please visit Elsevier eBooks+ at https://ebooks.health.elsevier.com.

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64 ARTERIAL HYPERTENSION

JOHN M. FLACK

DEFINITION

Obtaining accurate blood pressure readings in any setting requires observer training, use of validated and calibrated devices, and adherence to a rigorous measurement protocol. The current threshold for diagnosing arterial hypertension is 130/80 mm Hg or greater.[1] The diagnosis should be confirmed by averaging multiple blood pressure readings over several temporally spaced visits, with confirmation by home measurements or by ambulatory blood pressure readings.

However, the cardiovascular risk associated with blood pressure begins at a systolic blood pressure of 100 mm Hg, and every increase of 10 mm Hg above that level is associated with about a 50% higher risk for atherosclerotic vascular disease.[2] Since risk rises at blood pressure levels that are well below the threshold for initiating pharmacologic therapies or the goals of therapy, primordial prevention of hypertension is key for mitigating the risk for pressure-related complications in the nonhypertensive population. In clinical trials, a treatment target of less than 120 mm Hg systolic is the most beneficial, but an office blood pressure target of 130/80 mm Hg or less is reasonable because blood pressures that are measured without standard protocols in most clinical settings are systematically higher than blood pressure readings obtained in clinical trials or on home monitoring.

EPIDEMIOLOGY

Aging and Pulse Pressure

In industrialized societies, systolic blood pressure rises with advancing age, whereas diastolic blood pressure plateaus in the sixth decade of life and declines thereafter (Fig. 64-1). Both systolic and diastolic blood pressure are important cardiovascular risk factors, but systolic blood pressure accounts for most of the pressure-related cardiovascular risk after middle age.

Arterial hypertension, defined at a threshold of 140/90 mm Hg, affects nearly 1.4 billion adults worldwide, with approximately three-quarters of all hypertensive individuals living in low- and middle-income countries, where the incidence of hypertension is rising much faster than in high-income countries.[3] Worldwide, hypertension is the leading cause of preventable death and is the number one reason for ambulatory office visits. In the United States, the prevalence of hypertension at the 140/90 mm Hg threshold has been declining since 2000, but its prevalence at the 130/80 mm Hg threshold is 45%, thereby affecting more than 115 million U.S. adults aged 20 years and older. In the United States, the prevalence of hypertension is higher in men (49%) than women (43%), but women have a higher prevalence than men after age 65 years.

The worldwide prevalence of hypertension varies considerably by geography. It is highest in Eastern Europe and Central Asia and lowest in South Asia. In high-income countries, hypertension is more prevalent in rural than in urban areas, but its prevalence is greater in urban than in rural areas in low- and middle-income countries. In the United States, the prevalence of hypertension is inversely related to educational attainment.

The relationship between blood pressure and cardiovascular risk begins at systolic blood pressure levels greater than 100 mm Hg, and most incident cardiovascular disease events occur in adults whose blood pressures are less than 140/90 mm Hg, whether naturally or while taking antihypertensive medications. Systolic blood pressure is a more important determinant of cardiovascular risk than diastolic blood pressure, at least for persons who are middle-aged and older.

In recent years, U.S. rates of control of hypertension to less than 140/90 mm Hg has begun to worsen after many decades of incrementally better control.[4] Since most blood pressure–related cardiovascular events occur in adults whose blood pressure levels are lower than levels that qualify for initial pharmacologic treatment (140/90 mm Hg), pharmacologic therapy of preexisting hypertension will never suffice to ameliorate the population burden of pressure-related complications.

Sex, Race, and Ethnicity

The prevalence of hypertension varies by race and ethnicity. In the United States, the prevalence is higher in non-Hispanic Blacks (59% of men, 56% of women) than in non-Hispanic Whites (48% of men, 41% of women), Asians (46% of men, 36% of women), and Hispanics (47% of men, 41% of women).[5] Not only is hypertension more prevalent in non-Hispanic Black adults relative to any other race-ethnicity group, it is also more severe and is preceded by higher blood pressure levels beginning in childhood. The prevalence of hypertension is higher in Black Americans who reside in the southeastern United States than in those living outside of that geographic region. A southern U.S.

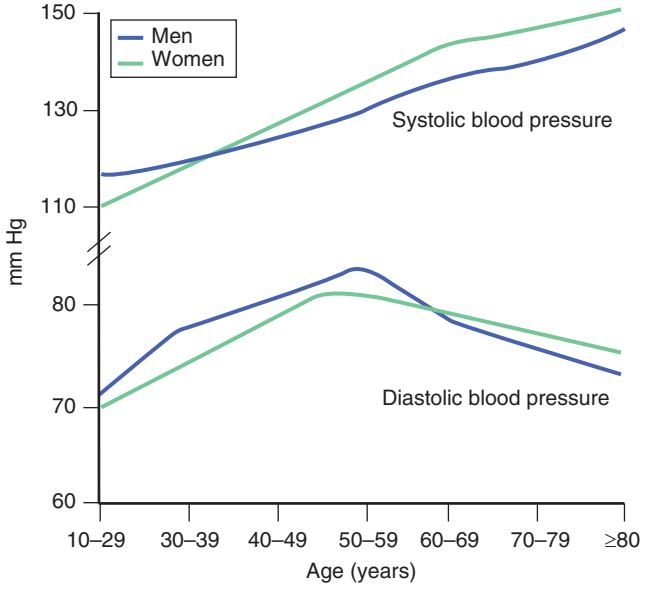

FIGURE 64-1. Aging and blood pressure. Age-dependent changes in systolic and diastolic blood pressure in the United States. (From Burt V, Whelton P, Rocella EJ, et al. Prevalence of hypertension in the U.S. adult population: results from the Third National Health and Nutrition Examination Survey, 1988-1991. *Hypertension*. 1995;25:305-313.)

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PROGNOSIS

About 50% of patients relapse within 10 years. The 15-year survival rate is about 95% in patients without major complications but only about 65% in patients with major complications. The predominant causes of morbidity and mortality are cardiovascular, including myocardial infarction, heart failure, pulmonary hypertension, and aortic aneurysm rupture.

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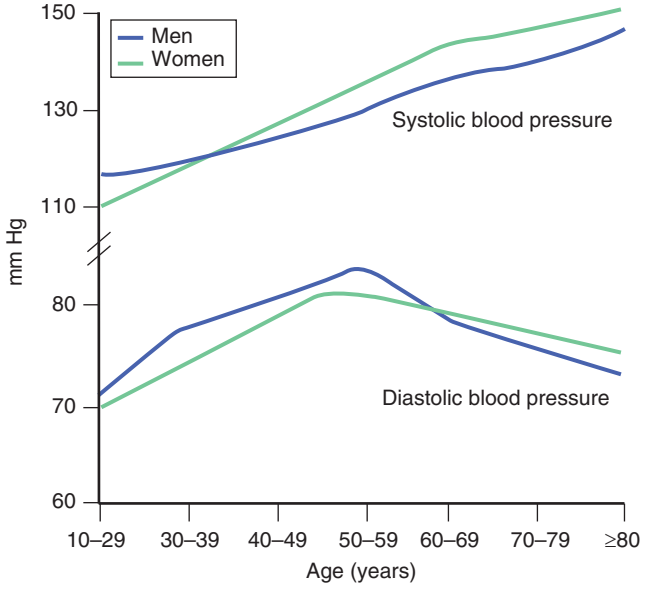

FIGURE 64-1. Aging and blood pressure. Age-dependent changes in systolic and diastolic blood pressure in the United States. (From Burt V, Whelton P, Rocella EJ, et al. Prevalence of hypertension in the U.S. adult population: results from the Third National Health and Nutrition Examination Survey, 1988-1991. *Hypertension*. 1995;25:305-313.)

ABSTRACT

Arterial hypertension is a major risk factor for premature mortality as well as for morbid and fatal cardiovascular events, renal disease, and dementia. The optimal strategy for reducing the growing worldwide incidence of hypertension is primordial prevention by dietary moderation, physical activity, and maintenance of ideal body weight. Accurate ascertainment of blood pressure requires that devices to measure blood pressure are validated and calibrated and that the measurement is taken by a well-trained clinician. The preferred diagnosis of hypertension depends on blood pressure measurement both in the office as well as either at home or by an ambulatory device. Secondary causes of hypertension (e.g., primary aldosteronism, obstructive sleep apnea, critical renal artery obstruction, Cushing disease, and pheochromocytoma) should be excluded in selected patients. Treatment should combine diet and lifestyle modification with evidence-based drug therapies initiated at the appropriate blood pressure threshold. Contemporary medical treatment has shifted from monotherapy toward combination therapy with thiazide diuretics, calcium-channel antagonists, angiotensin receptor blockers, and angiotensin-converting enzyme inhibitors, with specific medications chosen based on the patient's characteristics and comorbid conditions. Suboptimal blood pressure control is typically related to poor adherence, inadequate intensity of drug therapy, ineffective drug regimens, co-use of drugs that raise blood pressure, high dietary salt intake, and secondary causes of hypertension. Hypertensive emergencies are severe blood pressure elevations (≥180/110 mm Hg) with new or worsening blood pressure–related target-organ injury that requires immediate blood pressure lowering with intravenous drugs in critical care settings. The long-term prognosis of hypertension is excellent if blood pressure can be maintained at persistently nonhypertensive levels while avoiding the sequelae of overtreatment, such as symptomatic hypotension.

KEYWORDS

hypertension
arterial hypertension
secondary hypertension
primary aldosteronism
hypertensive emergency

dietary pattern appears to account for nearly one third (women) to half (men) of the excess risk of developing hypertension in Black compared with White Americans.[6] Pressure-related complications, such as stroke and heart failure, also occur disproportionately in non-Hispanic Black Americans, and their age-adjusted death rates are approximately two-fold higher compared with those of non-Hispanic White Americans. Black Americans who move from high to low segregation census tracts have significantly lower blood pressures than do those who remain in highly segregated areas.

Black populations do not invariably have higher blood pressure than White populations. The prevalence of hypertension is higher in several predominantly White European countries than in non-Hispanic Black Americans or Black Africans (E-Fig. 64-1). The prevalence of hypertension is similar in Black and non-Black Hispanic Cuban adults.

PATHOBIOLOGY

Normal Circulatory Physiology

Systole accounts for about one third of the cardiac cycle, and the cardiac stroke volume (the amount of blood propelled forward from the left ventricle with each heartbeat) is primarily ejected during the first half of systole (Chapter 41). However, blood flow is continuous throughout the cardiac cycle. A compliant aorta readily expands during systole and partially stores stroke volume. After the conclusion of active cardiac systole, the elastic recoil of the aorta provides a mechanical advantage to the pumping heart by propelling the stored blood volume forward, thereby damping the fall in blood pressure during diastole. Reflected pressure waveforms from the peripheral resistance arterioles normally arrive back at the aorta during diastole, thereby augmenting coronary artery perfusion, which occurs exclusively during diastole. Pulse pressure (systolic blood pressure minus diastolic blood pressure) is determined by the rise in pressure inside the arterial vasculature in response to the stroke volume that was ejected during systole.

Age-Related Changes

The development of hypertension is not an invariable consequence of normal aging. Age-related pathologic changes (e.g., vascular remodeling, endothelial dysfunction, atherosclerosis) reduce compliance and stiffen the aorta and large capacitance vessels, thereby resulting in less storage of the stroke volume in the aorta (E-Fig. 64-2). This change causes the forward pressure wave to travel faster and reflect back more quickly from the peripheral resistance arterioles, where it merges with the forward pressure wave, thereby augmenting systolic blood pressure. Accordingly, systolic blood pressure rises, diastolic blood pressure falls, and pulse pressure widens. The net result of wide pulse pressure hypertension is for cardiac systole to prolong, thereby increasing the work of the myocardium and its requirements for oxygen and blood supply. Because myocardial perfusion occurs during diastole, cardiovascular risk is greater in isolated systolic (e.g., 160/70 mm Hg) hypertension than in combined systolic/diastolic hypertension (e.g., 160/95 mm Hg) or isolated diastolic hypertension (e.g., 125/95 mm Hg).

Essential Hypertension

Approximately 85 to 90% of adults with hypertension have primary or essential hypertension for which no single reversible cause can be readily identified. At least 10% of hypertensive patients will, however, have an identifiable or secondary cause of their elevated blood pressure. Furthermore, essential and secondary hypertension are not mutually exclusive, and some patients who initially have essential hypertension may subsequently develop superimposed secondary hypertension. Risk factors for essential hypertension include multiple behaviors, such as lower levels of physical activity, high consumption of dietary sodium, low consumption of dietary potassium, and high caloric intake. The prevalence of hypertension parallels obesity as measured by body mass index. The primary vascular abnormality in essential hypertension is elevated systemic vascular resistance.

Behavioral Determinants of Human Blood Pressure Variation

Obesity, especially visceral fat, is linked to multiple physiologic derangements—augmented sympathetic nervous system activity, activation of the renin–angiotensin–aldosterone system, secretion of cytokines, insulin resistance, hyperinsulinemia, and the compression of the renal medulla—all of which impair renal-pressure natriuresis, thereby resulting in enhanced renal tubular absorption of sodium. Furthermore, obesity causes intrarenal vasodilation and hyperfiltration, which can injure the glomerulus. Obesity is also a risk factor for obstructive sleep apnea (Chapter 374), which contributes to nocturnal hypertension via repetitive arousals that further contribute to sympathetic nervous system activation.

Human hypertension is rare when the dietary sodium intake is less than 50 mmol per day, and virtually no age-related rise in blood pressure is seen in societies with very low dietary sodium intake. In patients with resistant hypertension, dietary sodium restriction promptly lowers blood pressure to a degree similar to the best single-drug add-on therapies.

People who smoke cigarettes (Chapter 363) tend to have lower blood pressures than nonsmokers, but cigarette smoking transiently raises blood pressure by 10 to 15 mm Hg for each cigarette smoked, and people who smoke a pack or more per day may have higher out-of-office than in-office blood pressures. Moderate alcohol consumption (Chapter 364) does not raise blood pressure, but heavy alcohol consumption (≥3 drinks per day; Chapter 364) results in the activation of the sympathetic nervous system in response to the withdrawal of alcohol. A polymorphism linked to increased enzymatic activity in the alcohol dehydrogenase gene is common in East Asians and raises systolic and diastolic blood pressure by 3/1 mm Hg per one drink per day in men but not women.

Genetic Determinants of Human Blood Pressure Variation

The concordance of blood pressure within a family is greater than that observed among unrelated individuals, and identical twins show greater blood pressure concordance than nonidentical twins. Adopted siblings have some, though less, blood pressure concordance than biologically related siblings, thereby suggesting that genetics is more important than shared environment.

The genetics of essential hypertension are complex, with multiple genetic alleles producing very small effects on blood pressure in the general population. However, several uncommon forms of hypertension caused by metabolic perturbations in salt metabolism are inherited as mendelian traits. For example, autosomal dominant Liddle syndrome, caused by a gain-of-function mutation in the *SCNN1A*, *SCNN1B*, or *SCNN1G* genes, causes hypertension by upregulation of the epithelial sodium channels (ENaCs) in the kidney. In autosomal dominant Gordon syndrome, disordered sodium metabolism is caused by increased activity of the sodium chloride transporter in the renal distal tubule. The autosomal recessive syndrome of apparent mineralocorticoid excess is caused by an inactivating mutation of the 11β-hydroxysteroid dehydrogenase type 2 enzyme that permits cortisol to bind to and activate the mineralocorticoid receptor. These uncommon forms of inherited hypertension highlight the important role of sodium metabolism in the genesis of hypertension.

CLINICAL MANIFESTATIONS

The vast majority of hypertensive individuals do not have symptoms that are attributable to hypertension per se. However, some patients may experience symptoms such as sleep disturbances and poor exercise tolerance.

The earliest sign of hypertension on physical examination is usually hypertensive retinopathy (Fig. 391-24). Cardiac (atrial and ventricular) enlargement on an electrocardiogram (ECG) or chest radiograph or an elevated serum creatinine level will often precede more serious end-organ damage such as stroke (Chapters 376 and 377), ischemic heart disease (Chapters 56, 57, and 58), heart failure (Chapters 45 and 46), or kidney damage (Chapters 116 and 117). Since the advent of effective antihypertensive drug therapies, hypertensive emergencies, defined as severe blood pressure elevations typically at least 180/110 mm Hg in conjunction with new or worsening pressure-related end-organ injury (see later), has become an uncommon initial clinical presentation in industrialized societies.

DIAGNOSIS

The three major goals for the initial evaluation of individuals with known or suspected hypertension are: an accurate determination of blood pressure levels; identification of non-blood-pressure cardiovascular risk factors so as to estimate global cardiovascular risk; and in selected patients, a screen for secondary forms of hypertension (Fig. 64-2). If blood pressure is elevated, the clinician must screen for orthostatic hypotension and identify any behavioral, lifestyle, or social determinants that will influence the choice of drug therapies.

GOAL 1: ACCURATE MEASUREMENT OF BLOOD PRESSURE

Blood pressure can be measured in the office by auscultation or by an oscillometric device, or outside of the office, either intermittently (typically by an oscillometric device) or continuously (by an ambulatory monitor). Potential hypertension is almost always first suspected by an office measurement but then should be confirmed by measurement outside of the office. The blood pressure thresholds for diagnosing hypertension in each of these settings (Table 64-1)

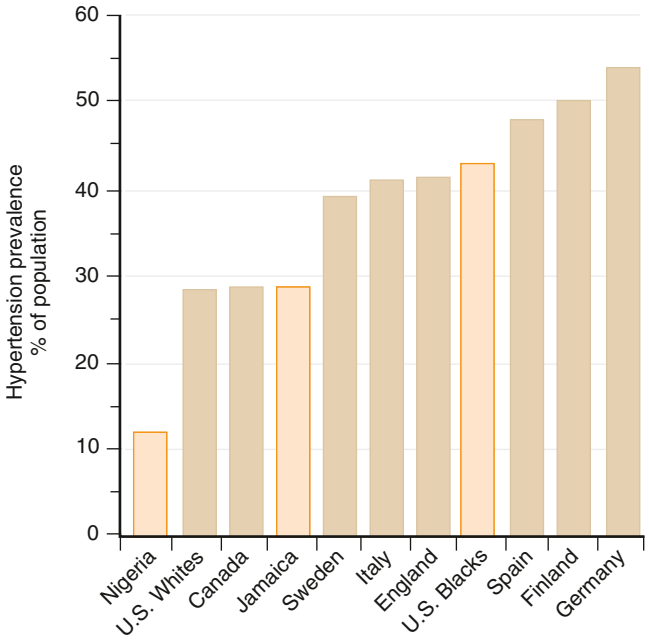

E-FIGURE 64-1. Geographic variation in hypertension prevalence in populations of African and European ancestries. (From Cooper RS, Wolf-Maier K, Luke A, et al. An international comparative study of blood pressure in populations of European vs. African descent. *BMC Med*. 2005;3:2.)

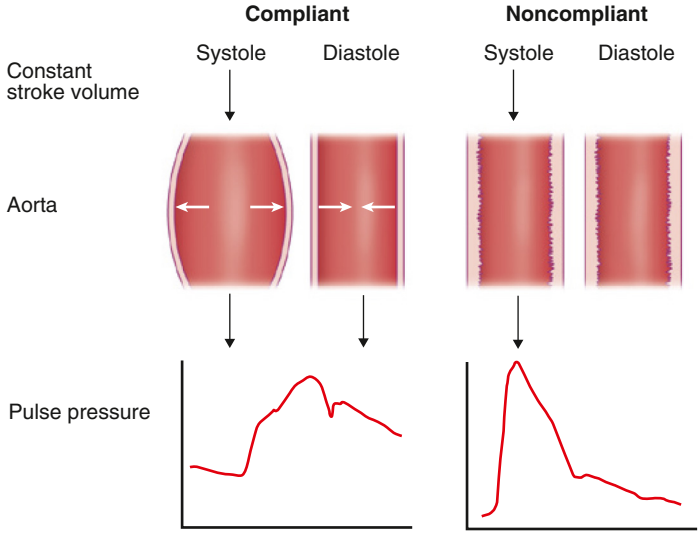

E-FIGURE 64-2. Aging and pulse pressure. Schematic diagram showing the relation between aortic compliance and pulse pressure. (Courtesy of Dr. Stanley Franklin, University of California at Irvine.)

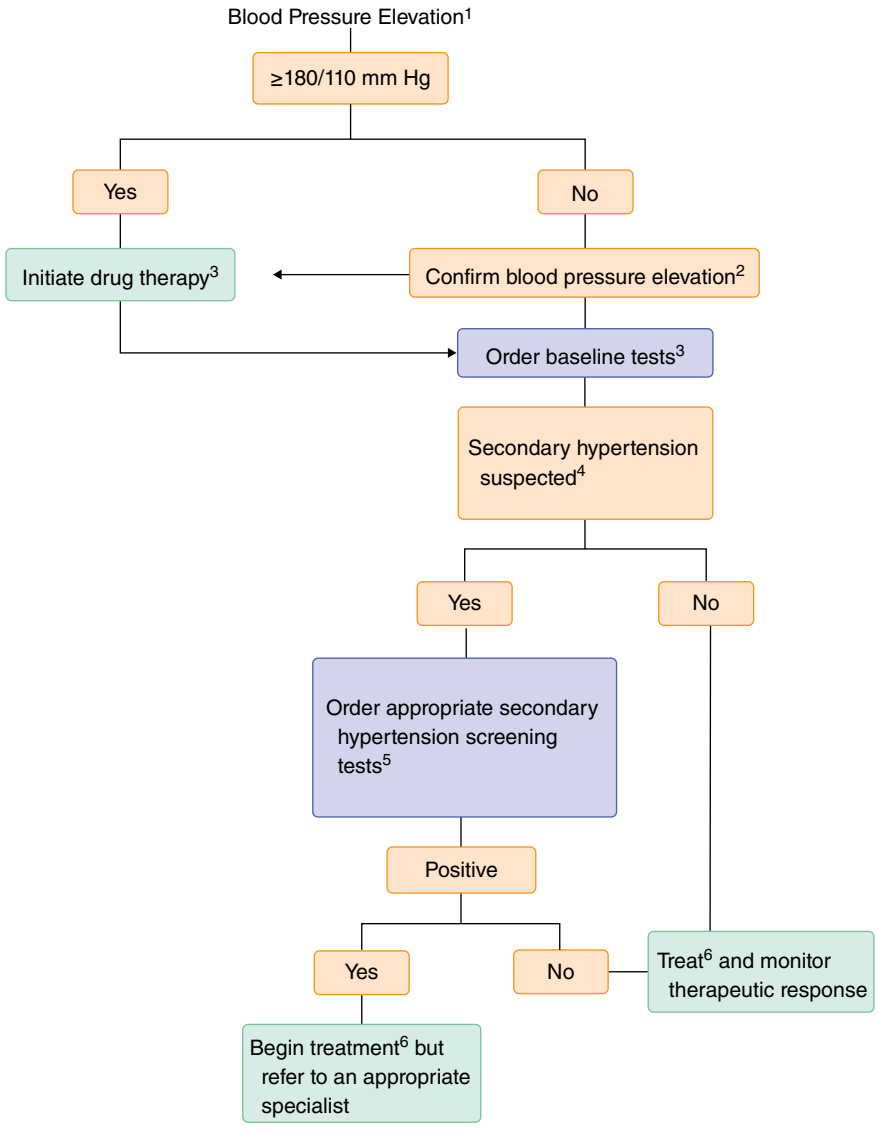

FIGURE 64-2. Evaluation of new-onset elevated blood pressure. [1]Obtain multiple (≥2) blood pressure readings using a standard protocol with validated/calibrated devices. [2]Blood pressure elevation should be confirmed by repeat office blood pressure measurement as well as by home blood pressure or ambulatory monitor readings. [3]Fasting glucose, hemoglobin A_{1C}, serum creatinine ratio, urinalysis, urine albumin: creatinine ratio, electrolyte panel, electrocardiogram test. [4]Abrupt hypertension onset of worsening of previously controlled blood pressure, resistant or refractory hypertension, hypertension in <25-yr-old, diastolic hypertension in ≥60-yr-old individuals, spontaneous hypokalemia or excessive hypokalemia in diuretic treated patients. [5]See text. Primary aldosteronism (AM plasma renin activity and aldosterone), renovascular (renal artery duplex scan), Cushing syndrome (overnight dexamethasone suppression test), pheochromocytoma (serum metanephrine levels). [6]Diet and lifestyle modifications should be used in all patients, to the degree possible, who initiate antihypertensive drug therapy (see Tables 64-6, 64-7, and 64-8).

TABLE 64-1 DEFINITIONS OF HYPERTENSION

CATEGORY	SYSTOLIC (mm Hg)		DIASTOLIC (mm Hg)
Auscultatory office blood pressure	≥130	and/or	≥80
Automated oscillometric blood pressure*	≥130	and/or	≥80
Home blood pressure	≥130	and/or	≥80
Ambulatory blood pressure			
• Daytime (awake)	≥130	and/or	≥80
• Nighttime (asleep)	≥110	and/or	≥65
• 24-hour	≥125	and/or	≥75

*Can be attended or unattended.

Adapted from Whelton PK, Carey RM, Aronow WS, et al. 2017 ACC/AHA/AAPA/ABC/ACPM/AGS/APhA/ASH/ASPC/NMA/PCNA guideline for the prevention, detection, evaluation, and management of high blood pressure in adults. *J Am Coll Cardiol*. 2018;71:e127-e248.

requires a careful approach that yields accurate readings.[7,8] For each modality, a standardized protocol should be followed by trained individuals.

AUSCULATORY OFFICE BLOOD PRESSURE

Ausculatory office blood pressure measurement is still a method commonly used by medical personnel, unfortunately with varying degrees of training and standardization. As a result, this method is the least accurate relative to average daytime ambulatory blood pressure measurements. The patient should be instructed to empty their bladder and should rest in a quiet room with no distractions for at least 5 minutes before the initial blood pressure measurement. Caffeine and tobacco should not be consumed within 30 minutes of measurement. An appropriately sized cuff should be placed on a bare arm. While in the seated position, the back and measurement arm (at heart level) should be supported, and the legs should be uncrossed and supported on the floor. Two to three blood pressure readings should be taken, with 30 seconds to 1 minute of rest between readings, then averaged; a set of averaged blood pressure readings will typically be lower than a solitary reading. At the initial visit, blood pressure should be measured in both arms as well as in both the seated and upright positions (after 1 minute standing). Most patients with orthostatic hypotension do not have symptoms, and

most patients with orthostatic dizziness do not have orthostatic hypotension. Differences in blood pressure levels between arms can be caused by coarctation of the aorta (Chapter 55), upper extremity arterial occlusion (Chapters 63 and 65), or possibly by external compression of the aorta. Subsequent blood pressure determinations should always be obtained from the arm with the higher reading at the initial visit. To make the diagnosis of hypertension, the readings taken on at least two temporally spaced visits should be averaged.

OSCILLOMETRIC OFFICE BLOOD PRESSURE

Oscillometric office blood pressure readings, obtained with a standard measurement protocol on validated and calibrated devices by trained observers, are the most accurate way to measure blood pressure in the office setting. These devices typically can be programmed to allow a 5-minute rest period before the initial measurement, as well for 1-minute intervals between the subsequent measurements. Unattended automated office blood pressure measurement (without medical personnel in the room) minimizes but does not completely eliminate the white coat reaction and is considered ideal; however, attended office blood pressure measurement is a reasonable alternative. Hypertension is diagnosed when oscillometric blood pressure is 130/80 mm Hg or higher.

HOME BLOOD PRESSURE

Home blood pressure measurement, typically with semi-automated oscillometric devices, is a reasonable alternative to the less widely available and less well-tolerated 24-hour ambulatory blood pressure monitoring. Home blood pressure readings, which may be either self-measured by the patient or obtained by another observer, are typically lower than office blood pressure readings. However, when office and home blood pressure readings are obtained using standard protocols with validated and calibrated devices, their difference will be minimized. The patient or observer should be instructed on a standard protocol for blood pressure measurement. Multiple readings should be obtained before any diagnostic or therapeutic decisions are made. A suggested approach is to obtain blood pressure readings over at least 3 days, both in the morning and the evening, with two readings at each time of measurement made 1 minute apart that are averaged.[9] Carefully obtained home blood pressure readings are at least as good, if not better, than ambulatory monitoring blood pressures. For example, 1 week of averaged home blood pressure readings better correlates with left ventricular mass than either three averaged office blood pressure measurements or two averaged 24-hour ambulatory blood pressure recordings. Newer devices have the capability of storing blood pressure measurements as well as for measuring blood pressure at night. Home blood pressure readings should be used to confirm office readings when diagnosing hypertension as well as for monitoring its therapeutics. Hypertension is diagnosed when home blood pressure is 130/80 mm Hg or higher.

AMBULATORY BLOOD PRESSURE MONITORING

Ambulatory blood pressure monitoring, which is the gold standard for noninvasive blood pressure measurement, provides multiple blood pressure readings through the day and night, typically over a 24- to 48-hour recording period (E-Fig. 64-3). However, this approach is less widely available and less well tolerated than is home blood pressure measurement. Ambulatory blood pressure monitoring predicts pressure-related cardiovascular events as accurately as home measurements predict such events and better than usual office blood pressure readings predict them.[10] Normally, the ambulatory blood pressure and pulse rate are 10 to 20% lower at night than during the daytime. When the nocturnal decline in blood pressure is less than 10% of the daytime level, this "non-dipping" phenomenon is often associated with obstructive sleep apnea (Chapter 374), disturbed sleep patterns, diabetes mellitus (Chapter 210), or autonomic dysfunction (Chapter 386). Non-dipping occurs in 10 to 30% of White Americans and in at least twice as many Black Americans. This aberrant ambulatory blood pressure phenotype is also associated with a greater risk for pressure-related end-organ damage and cardiovascular events. Hyper-dipping, which is defined as a nocturnal decline in blood pressure to a level that is more than 20% lower than daytime levels, is also seen in patients with autonomic dysfunction (Chapter 386). Hypertension is diagnosed when the average ambulatory blood pressure level is 125/75 mm Hg or greater.

WHITE COAT AND MASKED HYPERTENSION

Patients who have an elevated office blood pressure (≥130/80 mm Hg) with normal home (<130/80 mm Hg) or ambulatory blood pressure (<125/75 mm Hg) have white coat hypertension if they are not taking antihypertensive medication or white coat effect if they are taking drug therapy. White coat hypertension or effect is the result of a short-lived adrenergic response to blood pressure measurement in the office. The prevalence of white coat hypertension among patients with an elevated office blood pressure is 15 to 30% when 24-hour ambulatory blood pressure is used to confirm out of office blood pressure levels; an even higher percentage of drug-treated hypertensive patients will manifest white coat effect. Also, the prevalence of white coat hypertension/effect rises dramatically with age. The use of a standard blood pressure measurement protocol in conjunction with unattended automated oscillometric office blood pressure measurements minimizes the likelihood of white coat hypertension/effect. Patients who have white coat hypertension have minimal, if any, excess cardiovascular risk. However, 1 to 5% of individuals with white coat hypertension progress annually to sustained hypertension.

Patients who have normal office blood pressure measurements (<130/80 mm Hg) but elevated home (≥130/80 mm Hg) or ambulatory blood pressure (≥125/75 mm Hg) have masked hypertension if they are not taking antihypertensive medication or masked uncontrolled hypertension if they are taking antihypertensive drug therapy. This phenomenon occurs when frequently encountered daily stressors evoke hyperactivity of the sympathetic nervous system, but these stressors actually decrease when the individual is in the clinical setting. However, a potential cause of erroneously diagnosed masked hypertension is when measurements are obtained under nonstandard conditions and/or with inaccurate devices, thereby resulting in inflated home blood pressure readings. The prevalence of masked hypertension among persons with an office blood pressure more than 140/90 mm Hg ranges between 15 and 30%. Masked hypertension, which occurs more often in older persons and in patients who have diabetes mellitus, chronic kidney disease, and/or obstructive sleep apnea (E-Fig. 64-4), portends a similar risk for cardiovascular events as does sustained hypertension. However, no randomized control trial data have, as of yet, demonstrated benefit from drug therapy in patients who have masked hypertension or masked uncontrolled hypertension.

STAGING HYPERTENSION

The degree of confirmed blood pressure elevation by validated methods permits blood pressure to be categorized into one of four stages (Table 64-2). For nearly 70% of hypertensive individuals, the drug treatment threshold is 140/90 mm Hg, whereas higher risk and older hypertensive individuals qualify for treatment at 130/80 mm Hg.

GOAL 2: CARDIOVASCULAR RISK STRATIFICATION

Cardiovascular disease risk increases incrementally at higher levels of blood pressure, beginning well within the normal range, but the absolute level of cardiovascular risk also depends on the presence of other modifiable and nonmodifiable risk factors (Table 64-3). Initial diagnostic testing (Table 64-4) allows the clinician to estimate global cardiovascular risk in hypertensive patients (see http://tools.acc.org/ASCVD-Risk-Estimator).

GOAL 3: IDENTIFICATION AND TREATMENT OF SECONDARY (IDENTIFIABLE) CAUSES OF HYPERTENSION

Although a detailed search for secondary causes is neither prudent or cost-effective in all hypertensive patients, screening (Table 64-5) is important in younger patients and in patients who have suggestive findings on the history, physical examination, laboratory parameters, or imaging, regardless of the severity of their hypertension.

PRIMARY ALDOSTERONISM

Primary aldosteronism, which is the most common form of surgically curable secondary hypertension, has a prevalence that ranges from approximately 11%

TABLE 64-2 STAGES OF BLOOD PRESSURE

	SYSTOLIC (mm Hg)	DIASTOLIC (mm Hg)
Normal	<120	<80
Slightly elevated systolic	120-129	<80
Stage 1	130-139	80-89
Stage 2	≥140	≥90
Hypertensive urgency	≥180	>120

Adapted from Whelton PK, Carey RM, Aronow WS, et al. 2017 ACC/AHA/AAPA/ABC/ACPM/AGS/APhA/ASH/ASPC/NMA/PCNA guideline for the prevention, detection, evaluation, and management of high blood pressure in adults. *J Am Coll Cardiol.* 2018;71:e127-e248.

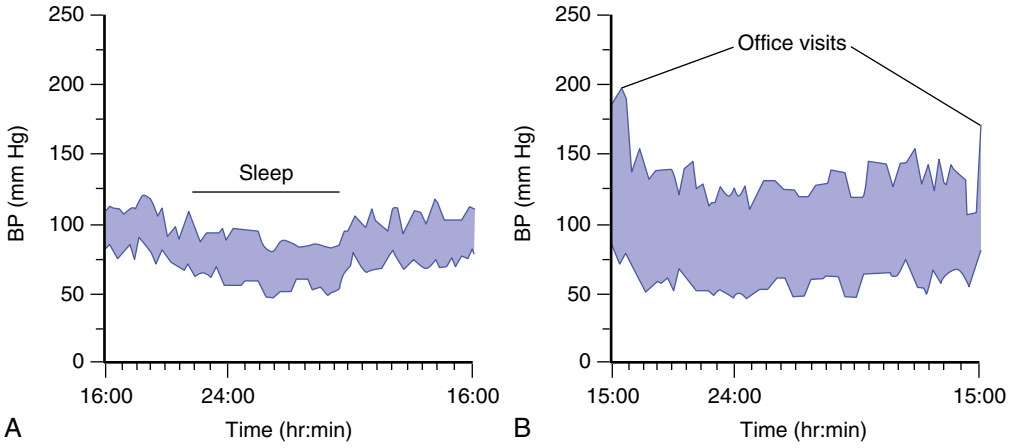

E-FIGURE 64-3. **The 24-hour ambulatory blood pressure (BP) monitor tracings of two different patients. A,** Optimal blood pressure in a healthy 37-year-old woman. Note the normal variability in blood pressure, the nocturnal dip in blood pressure during sleep, and the sharp increase in blood pressure on awakening. **B,** Pronounced white coat effect in an 80-year-old woman referred for evaluation of medically refractory hypertension. Documentation of the white coat effect prevented overtreatment of the patient's isolated systolic hypertension. (A, Courtesy of the late Ronald G. Victor, MD. B, Courtesy of Wanpen Vongpatanasin, MD, Hypertension Division, Department of Internal Medicine, University of Texas Southwestern Medical Center, Dallas, Texas.)

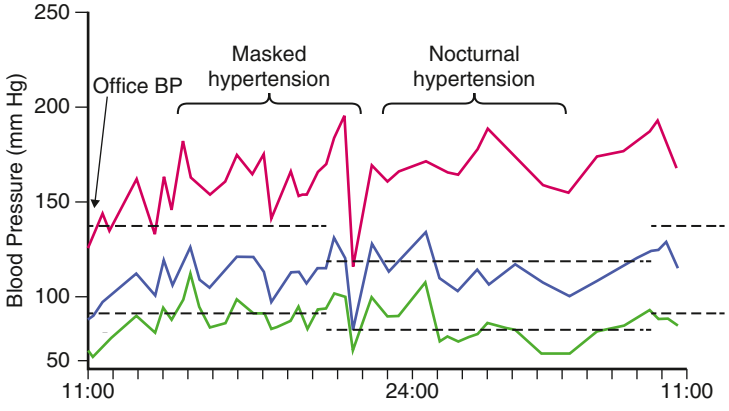

E-FIGURE 64-4. **The 24-hour ambulatory blood pressure (BP) recording of a patient with apparently normal office blood pressure but with masked hypertension and nocturnal hypertension.** The patient had left ventricular hypertrophy by electrocardiogram and nondiabetic chronic kidney disease, which is a common cause of masked and nocturnal hypertension. Antihypertensive medication was intensified to manage the out-of-office blood pressure. (Courtesy of the late Ronald G. Victor, MD.)

in normotensive individuals to 22% of patients who have either stage 2 or resistant/refractory hypertension.[11] Fewer than 40% of patients with primary aldosteronism are hypokalemic, so a serum potassium level alone is not adequate for screening. Approximately 60% of cases of primary aldosteronism result from bilateral adrenal gland hypersecretion. The aldosterone and epithelial sodium channel (ENaC) receptors in the distal nephron/collecting duct are stimulated by aldosterone, thereby resulting in sodium retention, kaliuresis, and expansion of the plasma volume. In many cases, hypertension can be severe and accompanied by extensive hypertension-related target-organ injury.

This diagnosis should be considered in patients who have refractory or resistant hypertension and especially patients in whom the plasma renin activity is suppressed (<1 μg/L), because the prevalence of primary aldosteronism in such patients is approximately 50%. Primary aldosteronism should also be suspected in the setting of a hypertensive emergency, sleep apnea, severe hypertension-related target-organ injury, a family history of primary aldosteronism, an incidentally detected adrenal adenoma, unprovoked (i.e., not associated with a diuretic) hypokalemia, or excessive hypokalemia (i.e., <3.0 mmol/L) when treated with a diuretic.

TABLE 64-3 COMMON CARDIOVASCULAR DISEASE RISK FACTORS IN PATIENTS WITH HYPERTENSION

MODIFIABLE RISK FACTORS	RELATIVELY FIXED RISK FACTORS
• Cigarette smoking, secondhand smoke • Pre-diabetes/diabetes mellitus • Dyslipidemia/hypercholesterolemia • Overweight/obesity • Physical inactivity/low fitness • Unhealthy diet	• Low socioeconomic status/educational attainment • Male sex • Obstructive sleep apnea • Known cardiovascular disease • Psychosocial stress • Chronic kidney disease • Family history • Increased age

Adapted from Whelton PK, Carey RM, Aronow WS, et al. 2017 ACC/AHA/AAPA/ABC/ACPM/AGS/APhA/ASH/ASPC/NMA/PCNA guideline for the prevention, detection, evaluation, and management of high blood pressure in adults. *J Am Coll Cardiol*. 2018;71:e127-e248.

TABLE 64-4 DIAGNOSTIC TESTING FOR ESSENTIAL HYPERTENSION

Fasting blood glucose level
Hemoglobin A_{1C}
Serum creatinine level with estimated glomerular filtration rate
Serum levels of sodium, potassium, and calcium
Complete blood count
Lipid profile
Thyroid-stimulating hormone
Urine albumin to creatinine ratio (spot morning urine)
Urinalysis
Electrocardiogram
OPTIONAL
Serum uric acid
Echocardiogram

Adapted from Arnett DK, Blumenthal RS, Albert MA, et al. 2019 ACA/AHA guideline on the primary prevention of cardiovascular disease: executive summary. *Circulation*. 2019;140:e563-595.

DIAGNOSIS

Serum aldosterone levels and a plasma renin activity level should be measured in a potassium replete state (a concentration of at least 3.5 Eq/L and preferably 4.0 mEq/L) in the early morning hours when aldosterone levels are at their highest. Although a usually defined upper limit of normal for a single serum aldosterone level is 15 ng/dL, about 25% of patients with primary aldosteronism have a serum aldosterone level less than 10 ng/dL. However, most patients with primary aldosteronism have suppressed renin activity, so patients should be further evaluated if their serum aldosterone level is greater than 10 ng/dL, if their renin level is low, or if they have other suggestive characteristics. The diagnostic hallmark of primary aldosteronism is excessive autonomous aldosterone secretion that does not suppress adequately (<12 μg/24 hour) during high levels (>150 mmol/day) of dietary sodium intake.[12] If the patient is at least willing to consider laparoscopic adrenalectomy, they should undergo adrenal computed tomographic scanning, with subsequent referral to an experienced interventional radiologist for bilateral adrenal vein sampling.

Most incidentally discovered adrenal adenomas, often termed incidentalomas (Chapter 208), do not secrete any detectable hormones, so they cannot be assumed to contribute to a patient's hypertension. Nevertheless, when an adenoma is discovered in hypertensive patients, the absence of hormone secretion (e.g., cortisol, catecholamines, and aldosterone) should be confirmed. However, an extensive diagnostic evaluation need not be performed prior to adrenalectomy in young (age <35 years) patients who have unprovoked hypokalemia and a typical appearing unilateral adenoma (<10 Hounsfield units of attenuation) on a computed tomographic (CT) scan.

TREATMENT

If adrenal vein sampling shows unilateral hypersecretion of aldosterone, laparoscopic adrenalectomy is the treatment of choice even if thin-slice CT scans of the affected adrenal gland show no detectable adenoma. Adrenalectomy cures the hypertension in just over 50% of cases. Catheter-based adrenal ablation is another alternative but is less likely to result in complete biochemical remission.[13] However, an appreciable percentage of patients with diagnosed primary aldosteronism likely also have underlying essential hypertension.

In patients who have bilateral adrenal gland hypersecretion or who choose to forego adrenalectomy for unilateral hypersecretion, dietary restriction, especially reductions in dietary sodium intake to less than 1500 mg per day, and intensive medical therapy are essential (see later). Aldosterone antagonists (e.g., spironolactone and eplerenone), an ENaC inhibitor (e.g., amiloride), and a thiazide-like diuretic (e.g., chlorthalidone and indapamide) should be combined with an angiotensin-converting enzyme (ACE) inhibitor or an angiotensin receptor blocker, a calcium-channel antagonist, and occasionally β-blockers. Nonrandomized data suggest better clinical outcomes in medically managed patients with primary aldosteronism when medical therapies and restriction of dietary sodium result in a rise in plasma renin activity to greater than 1 μg/L.

TABLE 64-5 GUIDE TO EVALUATION OF SECONDARY CAUSES OF HYPERTENSION

SUSPECTED DIAGNOSIS	CLINICAL CLUES	DIAGNOSTIC TESTING
Primary aldosteronism (Chapter 208)	Resistant or refractory hypertension, hypertensive emergency, severe hypertensive target-organ injury, hypokalemia, adrenal adenoma	Plasma renin and serum aldosterone, 24-hour urinary aldosterone excretion, adrenal vein sampling
Chronic kidney disease (Chapter 116)	Estimate GFR <60 mL/min/1.73 m^2 and/or urine albumin:creatinine ratio ≥300 mg/g	Serum creatinine, urine albumin : creatinine ratio
Renovascular disease (Chapter 110)	Azotemia, transient rise in creatinine when BP is lowered and/or with ACE or ARB therapy, flash pulmonary edema, abdominal/flank bruit	Renal artery duplex scan, CT or MR or invasive angiography, CO_2 angiography
Coarctation of the aorta (Chapter 55)	Arm pulses > leg pulses, arm BP > leg BP, chest bruits, rib notching on chest radiography	MR angiography, TEE, invasive angiography
Cushing syndrome (Chapter 208)	Adrenal adenoma, central obesity, pigmented abdominal striae, easy bruising, muscle weakness, cervical buffalo hump	Overnight dexamethasone suppression test, adrenal CT
Pheochromocytoma (Chapter 209)	Adrenal mass, paroxysms of hypertension, palpitations, sweating, pallor, orthostatic hypotension	Serum metanephrines, 24-hour fractionated urinary metanephrines, abdominal CT or MR imaging

ACE = angiotensin-converting enzyme; ARB = angiotensin receptor blocker; BP = blood pressure; CT = computed tomography; CO_2 = carbon dioxide; GFR = glomerular filtration rate; MR = magnetic resonance imaging; TEE = transesophageal echocardiography.

From Victor RG. Arterial hypertension. In: Goldman L, Schafer AI, eds., *Goldman-Cecil Medicine*. Philadelphia: Elsevier; 2020:443-456.

RENAL PARENCHYMAL HYPERTENSION

Hypertension affects at least 85% of patients who have chronic kidney disease (Chapter 116). Cardiovascular events, not kidney failure, are the predominant cause of morbidity and mortality, thereby highlighting the need for good blood pressure control. Mechanisms responsible for blood pressure elevations in these patients include impaired natriuresis, expansion of plasma volume, endothelial dysfunction, impaired arterial vasodilation, and arterial vasoconstriction as a consequence of activation of the sympathetic nervous system and renin–angiotensin system.

The serum creatinine level alone is not an adequate marker of kidney function but should be measured for inclusion in equations used to generate the estimated glomerular filtration rate (see Table 100-1 and Fig. 100-2). An estimated glomerular filtration rate below 60 mL/min/1.73 m^2 is considered reduced kidney function or chronic kidney disease. A spot urinary protein or, preferably, urinary albumin excretion should be measured, because chronic kidney disease is diagnosed when the urine albumin : creatinine ratio is greater than 300 mg/g irrespective of the estimated glomerular filtration rate. Quantification of protein or albumin excretion over 24 hours is not recommended.

TREATMENT

Patients who have chronic kidney disease typically have relatively resistant hypertension and require intensive multidrug therapy to slow the progressive decline in kidney function and also to lower the risk of nonrenal cardiovascular complications. An ACE inhibitor or angiotensin receptor blocker should be preferentially included in the treatment regimen, especially if the urine albumin : creatinine ratio is greater than 300 mg/g, because these agents most prominently slow the progressive decline in kidney function in patients who have significant proteinuria. If a thiazide-like diuretic is being used, indapamide maintains effectiveness down to an estimated glomerular filtrate rate of 30 mL/min/1.73 m^2 whereas chlorthalidone effectively lowers blood pressure in patients with an average estimated glomerular filtration rate in the low 20s. Nevertheless, loop diuretics (e.g., furosemide) are generally preferred if the estimated glomerular filtration rate is less than 40 mL/min/1.73 m^2. When patients develop end-stage renal disease and require dialysis (Chapter 117), tight blood pressure control is not warranted and may be dangerous, especially if blood pressure is too low pre-dialysis. An inter-dialytic systolic blood pressure less than 90 mm Hg or low enough to evoke symptoms should be avoided.[14]

RENOVASCULAR HYPERTENSION

Among patients with renovascular hypertension (Chapter 110), the cause is atherosclerotic renal artery obstruction in approximately 85% of cases, with fibromuscular dysplasia accounting for nearly all of the remainder. Atherosclerotic renal artery obstruction typically affects middle-aged to older patients, more commonly men who usually have evidence of advanced atherosclerosis, whereas fibromuscular dysplasia typically presents at a younger age and is more common in women. Atherosclerotic renal artery obstruction, which can be unilateral or bilateral, can raise blood pressure and cause ischemic nephropathy. Bilateral critical renal artery stenosis is a volume-dependent form of hypertension that, unlike unilateral renal artery stenosis, can cause azotemia.

CLINICAL MANIFESTATIONS

Critical atherosclerotic renal artery stenosis can present clinically with accelerating, resistant, or refractory hypertension and, especially if bilateral, with flash pulmonary edema, recurrent heart failure, and/or ischemic nephropathy.

DIAGNOSIS

When renal artery stenosis is suspected, its diagnosis should be pursued in patients who have characteristics that predict the failure of medical therapy and responsiveness to renal artery revascularization. Such patients have refractory hypertension, ischemic nephropathy, flash pulmonary edema, or recurrent heart failure. Young to middle-aged women with signs or symptoms suggestive of fibromuscular dysplasia should be screened. The most commonly used screening test is renal artery duplex scanning, but this test is highly operator-dependent and is technically difficult in obese patients. A positive duplex scan can be confirmed by direct renal angiography or by CT, MRI, or carbon dioxide angiography. Gadolinium-enhanced MRI should be avoided in patients who have acute kidney injury, an estimated glomerular filtration rate less than 30 mL/min/1.73 m^2, or are on dialysis because of the risk of a systemic fibrotic reaction (Chapter 246).

Fibromuscular dysplasia classically causes a "string of beads" sign in the midportion of the renal artery (see Fig. 64-3A), although it may occasionally present as a focal lesion. Atherosclerotic renal artery obstruction is more discrete, with a predilection for the proximal renal artery near the ostia (see Fig. 64-3B). However, simply documenting critical renal artery stenosis does not invariably prove that it is substantively affecting the blood pressure level.

TREATMENT

Angioplasty without stenting is the treatment of choice for fibromuscular dysplasia, and it resolves hypertension in about 45% of cases (Chapter 110). For atherosclerotic renal artery stenosis, however, renal artery revascularization may reduce the intensity of required medical therapy but does not lead to better control.[A1] Accordingly, medical therapy is preferred for most hypertensive patients with atherosclerotic renal artery obstruction, except it is reasonable to consider renal artery revascularization in patients who have refractory hypertension, ischemic nephropathy, heart failure, or recurrent episodes of pulmonary edema.

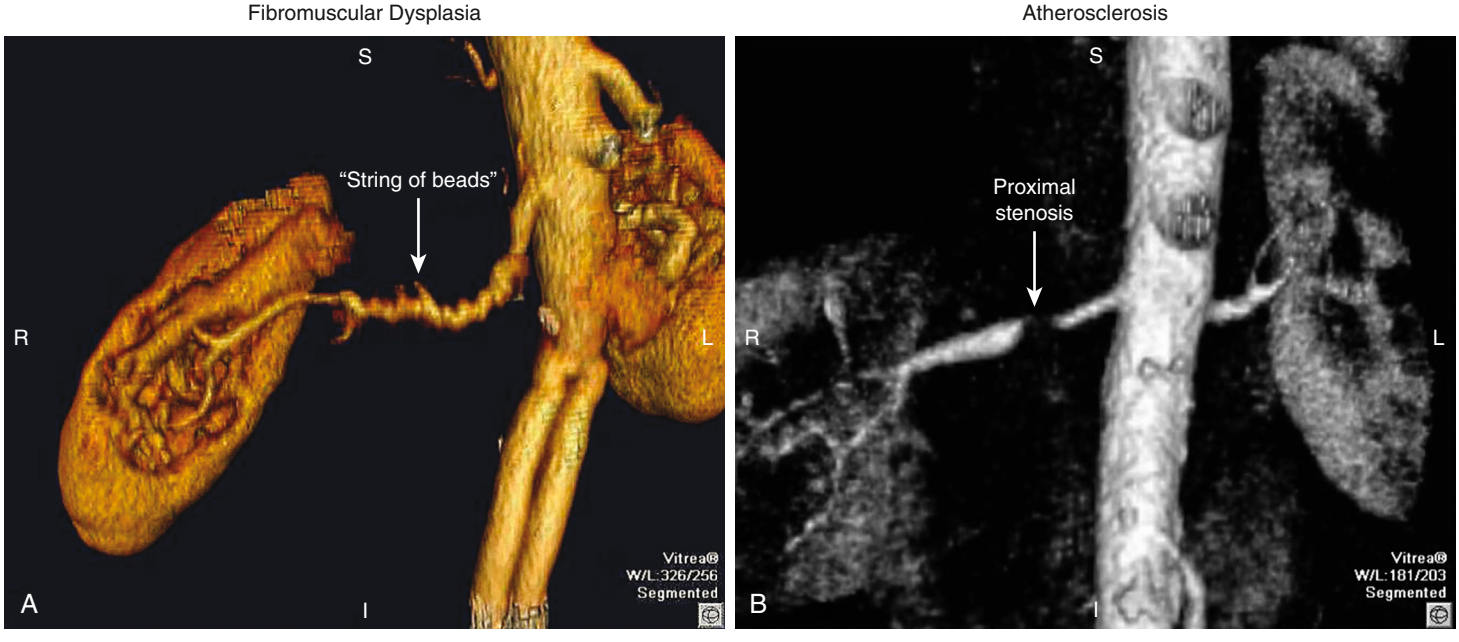

FIGURE 64-3. Computed tomographic angiogram with three-dimensional reconstruction. A, The classic "string of beads" lesion of fibromuscular dysplasia (bilateral in this patient). **B,** A severe proximal atherosclerotic stenosis of the right renal artery and mild stenosis of the left renal artery. (Images courtesy of Bart Domatch, MD, Radiology Department, University of Texas Southwestern Medical Center, Dallas, Texas.)

PHEOCHROMOCYTOMA AND PARAGANGLIOMA

Pheochromocytoma and paraganglioma are rare, histologically indistinguishable catecholamine-producing neuroendocrine tumors that are differentiated solely on the basis of their anatomic location (Chapter 209). This diagnosis should be suspected in patients who have suggestive symptoms, such as often paroxysmal headache, palpitations, profuse sweating, and anxiety, as well as weight loss. Patients who have proven pheochromocytoma can sometimes be misdiagnosed as having neuroses, anxiety, or panic disorders. Most (98%) of pheochromocytomas are intra-abdominal, with the majority occurring in the adrenal gland; the remaining 2% are paragangliomas that are found in the neck and thorax. Some pheochromocytomas are part of multiple endocrine neoplasia syndromes (Chapter 212). The best screening test is plasma fractionated metanephrines. Because these catecholamine-secreting tumors are exceedingly rare, most positive metanephrine tests are false-positive results, but elevations greater than 3 times the upper limit of normal rarely represent false-positive elevations. The diagnosis can be confirmed by measurement of fractionated metanephrines and catecholamines in a 24-hour urine specimen, followed by localization studies (Chapter 209).

TREATMENT

See Chapter 209.

OTHER SECONDARY CAUSES OF HYPERTENSION

Causes of neurogenic hypertension that can mimic pheochromocytoma include the use of sympathomimetic substances (cocaine, methamphetamine; Chapter 365), untreated obstructive sleep apnea (Chapter 374) and baroreflex failure. A history of surgery and/or radiation for head and neck tumors (Chapter 176) can damage baroreceptor reflexes and cause widely fluctuating blood pressure levels. Snoring and daytime sleepiness are suggestive of sleep apnea. Continuous positive airway pressure can modestly lower blood pressure in patients with sleep apnea.

In coarctation of the aorta (Chapter 63), which occurs in 0.4% of live births, an anatomic narrowing of the left subclavian artery distal to its origin results in paradoxically weaker pulses and lower blood pressure in the lower than the upper extremities. Intercostal collateral arteries can result in audible bruits on physical examination as well as notching of the ribs on a chest radiograph.

Hyperthyroidism (Chapter 207) can cause systolic hypertension with a wide pulse pressure, whereas hypothyroidism is associated with isolated diastolic hypertension. Hyperparathyroidism (Chapter 227) also has been linked to hypertension. Calcineurin inhibitors (cyclosporine more than tacrolimus), which are used predominantly to reduce rejection after solid organ transplantation, raise blood pressure, presumably by increasing sympathetic nervous system activity. Multiple oncologic drugs raise blood pressure, including vascular endothelial growth factor (VEGF) inhibitors (salt-sensitive hypertension), poly-ADP ribose polymerase inhibitors (niraparib), Bruton tyrosine kinase inhibitors, mammalian target of rapamycin (mTOR) inhibitors, inhibitors of androgen synthesis (mineralocorticoid effect), proteosome inhibitors, and rearranged during transfection (REF) inhibitors. Mendelian forms of salt-sensitive hypertension (Chapter 113) are typically uncovered when screening for primary aldosteronism shows suppressed levels of urinary renin (<1 μg/L/hour) and plasma level aldosterone (<5 ng/dL).

TREATMENT OF ESSENTIAL HYPERTENSION

Optimal management of hypertension is ideally undertaken by an experienced team of health care professionals, often though not always led by a knowledgeable physician, who accurately measure blood pressure, diligently diagnose hypertension, prescribe adequate evidence-based medical therapies, avoid therapeutic inertia, and build effective rapport with patients and their families.

LIFESTYLE MODIFICATION

Diet and lifestyle modifications (Table 64-6) are core strategies for primordial prevention of hypertension as well as for treating adults with elevated blood pressure or established hypertension. Lifestyle modifications can lower systolic blood pressure by 7 to up to 15 mm Hg and can be tried before embarking on drug therapy. However, lifestyle changes are more effective for delaying the need for drug therapy or reducing the intensity of drug therapy than for avoiding it altogether.

TABLE 64-6 DIET AND LIFESTYLE RECOMMENDATIONS TO LOWER BLOOD PRESSURE IN ADULTS WITH ELEVATED BLOOD PRESSURE OR HYPERTENSION

DIET
1. Recommended dietary patterns (see Fig. 13-1 and Table 13-4): High in fresh fruits, vegetables, legumes, fish, low-fat dairy products, nuts, and whole grains Low in energy-dense foods such as refined carbohydrates and sugar-sweetened beverages, total and saturated fats Reduce dietary sodium intake to <1500 mg per day or at least a reduction of 1000 mg per day
PHYSICAL ACTIVITY
2. Increased physical activity as part of a structured exercise program Aerobic or dynamic resistance 90 to 150 min/wk
ALCOHOL INTAKE
3. ≤2 drinks per day (men) or ≤1 drink per day (women)

Adapted from Whelton PK, Carey RM, Aronow WS, et al. 2017 ACC/AHA/AAPA/ABC/ACPM/AGS/APhA/ASH/ASPC/NMA/PCNA guideline for the prevention, detection, evaluation, and management of high blood pressure in adults. *J Am Coll Cardiol*. 2018;71:e127-e248.

The Mediterranean diet (Fig. 13-1; fresh fruit, vegetables, fatty fish, canola/olive oil) and the Dietary Approaches to Stop Hypertension diet (Table 13-4; fresh fruits, vegetables, low-fat dairy products) can effectively lower blood pressure by about 6 mm Hg systolic without limiting the intake of calories or sodium. The average U.S. adult consumes about 3400 mg of sodium per day (148 mmol). Reduction of dietary sodium intake minimally to less than 2000 mg/day (87 mmol) and preferably to less than 1500 mg/day (65 mmol) is advisable because reductions in dietary sodium lower blood pressure[A2] and cardiovascular risk.[A3] Approximately 70% of dietary sodium intake is from processed food, so most adults cannot achieve sodium targets just by eliminating the discretionary addition of salt to their food.

Moderate intensity regular physical activity (Chapter 14), consisting of aerobic and/or dynamic resistance, will lower blood pressure approximately 4 to 8 mm Hg in hypertensive patients. Stress management techniques, such as meditation, biofeedback, and breathing exercises, can also lower blood pressure, but the durability and magnitude of their effect has not been firmly established (Chapter 30). People who smoke cigarettes should be counseled to quit (Chapter 363). Alcohol should be limited to no more than the equivalent of two drinks per day in men and one drink per day in women.

MEDICAL THERAPY

Pharmacologic treatment of hypertension can lower risk for cardiovascular disease (e.g., stroke [Chapters 375, 376, and 377], heart failure [Chapters 45 and 46], myocardial infarction [Chapters 57 and 58], chronic kidney disease [Chapters 116 and 117], atrial fibrillation [Chapter 52], peripheral vascular disease [Chapter 65]), with each 5–mm Hg reduction in systolic blood pressure corresponding to about a 10% reduction in events,[A4] as well as the risks of dementia (Chapter 371)[A5] and premature mortality, even in elderly persons.[A6] Nevertheless, successfully treated hypertensive patients have residual cardiovascular risk, with an absolute risk that remains higher than the risk of untreated patients with the same blood pressure level. As a result, reduction of global cardiovascular disease risk requires identification and treatment of non–blood-pressure risk factors, such as dyslipidemia (Chapter 190) and diabetes (Chapter 210).

In most patients, effective antihypertensive drug therapy requires two or more drugs, ideally with complementary mechanisms of action.[15] The overwhelming majority of patients with established hypertension require lifelong drug therapy.[16] Desirable antihypertensive drug combinations not only effectively lower blood pressure but they also mitigate the potential side effects of high-dose monotherapy.[17]

Clinicians should tailor and simplify drug regimens, often by using single-pill, preferably once-daily, combinations that patients can afford and tolerate. Adherence to prescribed drug therapies is problematic, however, as reflected by the reality that approximately 20% of new prescriptions for antihypertensive medications in the United States are never filled and, even when filled initially, up to 50% of prescriptions are no longer filled by 1 year.

CLASSES OF ORAL ANTIHYPERTENSIVE MEDICATIONS

More than 100 drugs from multiple classes are approved for the treatment of hypertension (Table 64-7). Each has contraindications and potential side effects, and many have preferred indications for certain subsets of patients (Tables 64-8 and 64-9).

First-Line Drugs for Hypertension

Guidelines recommend initiating antihypertensive drug therapy with two or more of three groups of antihypertensive medication: calcium-channel blockers, ACE inhibitors or angiotensin receptor blockers or thiazide or thiazide-like diuretics.

TABLE 64-7 SELECTED ORAL ANTIHYPERTENSIVE MEDICATIONS

DRUG	TYPICAL DOSE RANGE (mg/day)	DOSING FREQUENCY
PRIMARY AGENTS		
Thiazide or Thiazide-like Diuretics		
Chlorthalidone	12.5-25	1
Hydrochlorothiazide	25-50	1
Indapamide	1.25-2.5	1
Metolazone	2.5-5	1
ACE Inhibitors		
Benazepril	10-40	1 or 2
Captopril	12.5-150	2 or 3
Enalapril	5-40	1 or 2
Fosinopril	10-40	1
Lisinopril	10-40	1
Moexipril	7.5-30	1 or 2
Perindopril	4-16	1
Quinapril	10-80	1 or 2
Ramipril	2.5-20	1 or 2
Trandolapril	1-4	1
Angiotensin Receptor Blockers		
Azilsartan	40-80	1
Candesartan	8-32	1
Eprosartan	600-800	1 or 2
Irbesartan	150-300	1
Losartan	50-100	1 or 2
Olmesartan	20-40	1
Telmisartan	20-80	1
Valsartan	80-320	1
CCB—Dihydropyridines		
Amlodipine	2.5-10	1
Felodipine	2.5-10	1
Isradipine	5-10	2
Nicardipine SR	60-120	2
Nifedipine LA	30-90	1
Nisoldipine	17-34	1
CCB—Nondihydropyridines		
Diltiazem ER	120-360	1
Verapamil IR	120-360	3
Verapamil SR	120-480	1 or 2
Verapamil—delayed-onset ER	100-300	1 (in the evening)
SECONDARY AGENTS		
Diuretics—Loop		
Bumetanide	0.5-2	2
Ethacrynic acid	25-80	2
Furosemide	20-80	2
Torsemide	5-10	1
Diuretics—Potassium Sparing (ENaC Channel Inhibitors)		
Amiloride	5-10	1 or 2
Triamterene	50-100	1 or 2
Diuretic—Aldosterone Antagonists		
Eplerenone	50-100	1 or 2
Spironolactone	12.5-100	1
β-Blockers—Cardioselective		
Atenolol	25-100	2
Betaxolol	5-20	1
Bisoprolol	2.5-10	1
Metoprolol tartrate	100-200	2
Metoprolol succinate	50-200	1
β-Blockers—Cardioselective and Vasodilatory		
Nebivolol	5-40	1
β-Blockers—Noncardioselective		
Nadolol	40-120	1
Propranolol IR	80-160	2
Propranolol LA	80-160	1
Timolol	10-20	2
β-Blockers—Intrinsic Sympathomimetic Activity		
Acebutolol	200-800	2
Carteolol*	2.5-10	2.5
Penbutolol	10-40	1
Pindolol	10-60	2
β-Blockers—Combined α- and β-Receptor		
Carvedilol	12.5-50	2
Carvedilol phosphate	20-80	1
Labetalol	200-800	2
Direct Renin Inhibitor		
Aliskiren	150-300	1
α-1 Blockers		
Doxazosin	1-16	1
Prazosin	2-20	2 or 3
Terazosin	1-20	1 or 2
α-1 and 2 Blockers		
Phenoxybenzamine	20-120	2 or 3
Central α_2-Agonist and Other Centrally Acting Drugs		
Clonidine oral	0.1-0.8	2
Clonidine patch	0.1-0.3	1 weekly
Guanabenz	8-32	2
Guanfacine	0.5-2	1
Methyldopa	250-1000	2
Reserpine	0.1-0.25 0.05-0.125†	1 1
Hydralazine	100-200	2 or 3
Minoxidil	5-100	1-3
Angiotensin–Neprilysin Inhibitor		
Sacubitril/valsartan	Initial dose‡ 24/26 Initial dose§ 49/51 Maintenance dose‖ 97/103	2 2 2
Fixed-Dose Combinations		
Aliskiren/HCTZ	75-300/12.5-25	1
Amiloride/HCTZ	5/50	1
Amlodipine/benazepril	2.5-5/10-20	1
Amlodipine/olmesartan	5-10/20-40	1
Amlodipine/perindopril	3.5/2.5	1
Amlodipine/telmisartan	5/20-10/80	1

TABLE 64-7 SELECTED ORAL ANTIHYPERTENSIVE MEDICATIONS—cont'd

DRUG	TYPICAL DOSE RANGE (mg/day)	DOSING FREQUENCY
Amlodipine/valsartan	5-10/160-320	1
Atenolol/chlorthalidone	20-100/25	1
Azilsartan/chlorthalidone	40-80/12.5-25	1
Benazepril/HCTZ	5-20/6.25-25	1
Bisoprolol/HCTZ	2.5-10/6.25	1
Candesartan/HCTZ	16-32/12.5-25	1
Captopril/HCTZ	25/15	1
Enalapril/HCTZ	5-10/25	1
Eprosartan/HCTZ	600/12.5-25	1
Fosinopril/HCTZ	10-20/12.5	1
Irbesartan/HCTZ	150-300/12.5-25	1
Lisinopril/HCTZ	10-20/12.5	1
Losartan/HCTZ	50-100/12.5-25	1
Metoprolol succinate/HCTZ	25-200/12.5-25	1
Metoprolol tartrate/HCTZ	100-200/25-50	1 or 2
Moexipril/HCTZ	7.5-15/12.5-25	1
Olmesartan/HCTZ	20-40/12.5	1
Olmesartan/amlodipine/HCTZ	20-40/5-10/12.5-25	1
Quinapril/HCTZ	10-20/12.5	1
Spironolactone/HCTZ	25/25	½
Telmisartan/HCTZ	40-80/12.5-25	1
Trandolapril/verapamil	2-4/180-240	1
Triamterene/HCTZ	37.5/25	½
Valsartan/HCTZ	80-160/12.5-25	1
Valsartan/amlodipine/HCTZ	80-160/5-10/12.5-25	1

*No longer commercially available in the United States.
†This dose range is indicated when given with a diuretic.
‡In patients taking a high-dose of an ACE-I or ARB.
§In patients previously not taking or taking a low dose of an ACE-I or ARB.
‖Double initial dose every 2 to 4 weeks as tolerated to reach the maintenance dose.
ACE = angiotensin-converting enzyme; CCB = calcium-channel blocker; ER = extended release; HCTZ = hydrochlorothiazide; IR = immediate release; LA = long-acting; SR = sustained release.
Adapted from the Whelton PK, Carey RM, Aronow WS, et al. 2017 ACC/AHA/AAPA/ABC/ACPM/AGS/APhA/ASH/ASPC/NMA/PCNA guideline for the prevention, detection, evaluation, and management of high blood pressure in adults: a report of the American College of Cardiology/American Heart Association Task Force on clinical practice guidelines. *J Am Coll Cardiol*. 2018;71:e127-e248.

Calcium-Channel Blockers

Mechanism of Action

Dihydropyridine and non-dihydropyridine calcium-channel blockers inhibit opening of voltage-gated calcium channels in vascular smooth muscle and the myocardium, thereby resulting in arterial dilatation. The dihydropyridine calcium-channel blockers (e.g., amlodipine) more potently lower blood pressure than do the non-dihydropyridine calcium-channel blockers (e.g., diltiazem, verapamil).

Clinical Use

Calcium-channel blockers effectively lower blood pressure when used alone or in combination with other antihypertensive drugs, especially ACE inhibitors, angiotensin receptor blockers, and thiazide diuretics. These agents are useful for the treatment of angina pectoris, are the most effective drug class for the primary prevention of stroke, and are equally useful in Black patients and other ethnic groups. Amlodipine, which is the prototype dihydropyridine calcium-channel blocker to treat hypertension, is comparable to chlorthalidone for reducing cardiovascular events other than heart failure. Unlike the other first-line antihypertensive drug classes, the antihypertensive effects of calcium-channel blockers are independent of dietary sodium intake and of concurrent use of nonsteroidal anti-inflammatory drugs. In patients with chronic kidney disease, dihydropyridine calcium-channel blockers should be prescribed only after the initiation of either an ACE inhibitor or an angiotensin receptor blocker. Non-dihydropyridine calcium-channel blockers typically should be avoided when β-blockers are concurrently prescribed because both drug classes share negative inotropic and chronotropic effects. Short-acting calcium-channel blockers (e.g., nifedipine) are effective to reduce blood pressure rapidly in a hypertensive urgency but should not be used chronically because it causes prominent, precipitous, and short-lived arterial vasodilation (and blood pressure lowering) that reflexively activates the sympathetic nervous system.

Side Effects

A common dose-dependent side effect of dihydropyridine calcium-channel blockers, especially in women, is lower extremity edema, which typically is worse later in the day after hours of upright posture. ACE inhibitors are the best antidote for this dose-dependent edema, whereas diuretics should not be used for this purpose. Gingival hyperplasia, which is an uncommon but serious side effect with both dihydropyridine and non-dihydropyridine calcium-channel blockers, occurs more often with dihydropyridines and diltiazem than with verapamil. The signature side effect for verapamil is constipation. All calcium channel antagonists can depress the sinoatrial node, so they should be avoided in patients who have the sick sinus syndrome (Chapter 51) unless they have a functioning ventricular pacemaker.

Renin–Angiotensin System Inhibitors: ACE Inhibitors, Angiotensin Receptor Blockers, and Direct Renin Inhibitors

Mechanisms of Action

ACE inhibitors inhibit the conversion of angiotensin 1 by angiotensin-converting enzyme (ACE) to its vasoactive form, angiotensin 2, while also inhibiting the degradation of bradykinin. Angiotensin receptor blockers antagonize the action of angiotensin 2 by blocking the angiotensin 1 receptor, thereby allowing angiotensin 2 to bind preferentially to the angiotensin 2 receptor instead. Direct renin inhibitors block conversion of pro-renin to renin, thereby inhibiting the renin–angiotensin system at its first metabolic step.

Clinical Use

All inhibitors of the renin–angiotensin system have relatively flat dose–response curves. ACE inhibitors and angiotensin receptor blockers lower blood pressure to a similar degree. Although both agents are less effective as monotherapy in Black compared with White patients, the efficacy of combination therapy, which is now routinely recommended with these drugs, appears to be equivalent in Black and White patients. ACE inhibitors provide equal protection against coronary events, lesser protection against stroke, and better protection against heart failure compared with calcium-channel blockers.

Angiotensin receptor blockers do not cause dose-related side effects and generally are the best tolerated of all hypertensive drug classes. Unlike ACE inhibitors, angiotensin receptor blockers do not cause cough or angioedema. Azilsartan is the most potent angiotensin receptor blocker for blood pressure reduction, and several long-acting agents (e.g., olmesartan, telmisartan, and irbesartan) lower blood pressure more effectively than does losartan.[A7]

Either an ACE inhibitor or an angiotensin receptor blocker is indicated in patients with chronic kidney disease, especially when the urine albumin : creatinine ratio is greater than 300 mg/g, because they slow the progressive loss of kidney function, particularly in patients who have significant proteinuria. ACE inhibitors and angiotensin receptor blockers should not be used concurrently, nor should either drug class be used concurrently with aliskirin because of the heightened risk of renal injury and hyperkalemia.

Side Effects

Because of the risk of fetal injury, all renin–angiotensin system inhibitors are contraindicated in women who are of childbearing age and who are not using an effective form of contraception, in women who are planning to become pregnant, or in women who are pregnant (Chapter 221). ACE inhibitors inhibit kininase II, thereby resulting in the accumulation of bradykinin, which stimulates bradykinin 2 receptors that lead to vasodilation, extravasation of plasma into the interstitial space, and release of substance P. These physiologic

derangements appear to underly both the dry cough (seen in 10 to 15% of patients) and angioedema (<1% of patients) that are associated with their use. However, angioedema is more common in women, Black patients, patients who smoke, and patients who are older than age 65 years, have seasonal allergies, have a history of drug rashes or drug allergies, or are taking immunosuppressive drugs. In patients who experience angioedema during treatment with an ACE inhibitor, the ACE inhibitor should be discontinued and an angiotensin receptor blocker can be substituted if patients have a clear indication for blockade of the renin–angiotensin system.

Hyperkalemia is a potential complication of all of these agents, especially in patients who have chronic kidney disease (Chapter 116), diabetes (Chapter 210), or hyporeninemic hypoaldosteronism (type IV renal tubular acidosis; Chapter 104). Although these agents are reno-protective, some patients have an increase in the serum creatinine level that may require their discontinuation, most likely related to sluggish renal autoregulation but also associated with bilateral renal artery stenosis. The serum creatinine level and serum electrolytes should be measured within 1 to 2 weeks after initiating therapy with these agents.

TABLE 64-8 MAJOR CONTRAINDIATIONS AND SIDE EFFECTS OF ANTIHYPERTENSIVE DRUGS

DRUG CLASS	MAJOR CONTRAINDICATIONS	SIDE EFFECTS
DIURETICS		
Thiazides	Gout	Insulin resistance, new-onset type 2 diabetes Hypokalemia, hyponatremia, hypomagnesemia Triglyceride increase Hyperuricemia, precipitation of gout Erectile dysfunction Potentiates nondepolarizing muscle relaxants Photosensitivity dermatitis Skin cancer (mostly squamous cell)
Loop diuretics	Hepatic coma	Interstitial nephritis Hypokalemia Potentiate succinylcholine Potentiate aminoglycoside ototoxicity
Potassium-sparing diuretics	Serum potassium concentration >5.5 mEq/L GFR <45 mL/min, but may be used in patients with heart failure down to eGFR ~30 mL/min/1.73 m^2	Hyperkalemia
ACE inhibitors	Pregnancy Bilateral renal artery stenosis Hyperkalemia History of angioedema	Cough Hyperkalemia Angioedema Leukopenia Fetal toxicity Cholestatic jaundice (rare fulminant hepatic necrosis if the drug is not discontinued)
Dihydropyridine CCBs	As monotherapy in CKD with proteinuria Sick sinus syndrome	Headaches (vascular) Flushing Ankle edema Heart failure Gingival hyperplasia Esophageal reflux
Nondihydropyridine CCBs	Heart block Systolic heart failure Sick sinus syndrome Bradycardia	Bradycardia, AV block (especially with verapamil) Constipation (with verapamil) Worsening of systolic function, heart failure Gingival edema or hypertrophy Increase cyclosporine and tacrolimus blood levels Esophageal reflux
Angiotensin receptor blockers, direct renin inhibitors	Pregnancy Bilateral renal artery stenosis Hyperkalemia	Hyperkalemia Angioedema Fetal toxicity
β-Adrenergic blockers	Heart block Asthma Depression Cocaine and methamphetamine abuse	New-onset type 2 diabetes (especially in combination with a thiazide) Erectile dysfunction Heart block, acute decompensated heart failure Bronchospasm Depression, nightmares, fatigue Cold extremities, claudication (β_2 effect) Stevens-Johnson syndrome Rebound hypertension with abrupt cessation Weight gain
α-Adrenergic blockers	Orthostatic hypotension Systolic heart failure Left ventricular dysfunction	Orthostatic hypotension Drug tolerance (in the absence of diuretic therapy) Fluid retention Heart failure First-dose effect (hypotension) Potentiate hypotension with PDE-5 inhibitors (e.g., sildenafil)
Central sympatholytics	Orthostatic hypotension Bradycardia	Depression, dry mouth, lethargy Rebound hypertension with abrupt cessation Coombs test–positive hemolytic anemia and elevated liver enzymes with α-methyldopa
Direct vasodilators	Use prior to late add-on therapy	Reflex tachycardia Fluid retention Hirsutism, pericardial effusion with minoxidil Lupus with hydralazine

ACE = angiotensin-converting enzyme; AV = atrioventricular; CCBs = calcium-channel blocker; CKD = chronic kidney disease; GFR = glomerular filtration rate; NSAIDs = nonsteroidal anti-inflammatory drugs; PDE-5 = phosphodiesterase-5.

From Victor RG. Arterial hypertension. In: Goldman L, Schafer AI, eds. *Goldman-Cecil Medicine*. Philadelphia: Elsevier; 2020:443-456.

TABLE 64-9 PREFERRED ANTIHYPERTENSIVE DRUG CLASSES FOR SPECIFIC CONDITIONS

CONDITION	DRUG CLASSES
Hypertension (general)	ACE inhibitor or angiotensin receptor blocker and/or calcium-channel blocker or diuretic
Diabetes mellitus	ACE inhibitor or angiotensin receptor blocker and/or calcium-channel blocker or diuretic
Diabetes mellitus with nephropathy*	ACE inhibitor or angiotensin receptor blocker and calcium-channel blocker or diuretic
Chronic kidney disease	ACE inhibitor or angiotensin receptor blocker and calcium-channel blocker or diuretic
Kidney transplantation	Calcium-channel blocker
Heart failure (reduced ejection fraction)	β-Blocker, aldosterone antagonist, angiotensin receptor–neprilysin inhibitor, and diuretic† (congestive symptoms)
Heart failure (preserved ejection fraction)	Angiotensin receptor–neprilysin inhibitor and diuretic† (congestive symptoms)
Stable ischemic heart disease	GDMT β-blocker and ACE inhibitor or angiotensin receptor blocker plus dihydropyridine calcium-channel blocker for persistent angina or thiazide diuretic and/or mineralocorticoid receptor for blood pressure control
Aortic disease	β-Blocker
Atrial fibrillation	ACE inhibitor or angiotensin receptor blocker plus β-blocker or nondihydropyridine calcium-channel blocker (rate control)
Pregnancy	Methyldopa, β-blocker (labetalol), calcium-channel blocker (nifedipine)

*Urine albumin : creatinine >300 mg/g.
†Diuretics should be added to control volume overload and/or for additional blood pressure lowering.
ACE = angiotensin-converting enzyme; β-blockers = carvedilol, metoprolol tartrate, metoprolol succinate, nadolol, bisoprolol, propranolol, timolol; GDMT = guideline directed medical therapy.
Adapted from Whelton PK, Carey RM, Aronow WS, et al. 2017 ACC/AHA/AAPA/ABC/ACPM/AGS/APhA/ASH/ASPC/NMA/PCNA guideline for the prevention, detection, evaluation, and management of high blood pressure in adults: a report of the American College of Cardiology/American Heart Association Task Force on clinical practice guidelines. *J Am Coll Cardiol*. 2018;71:e127-e248; Tomson CRV, Cheung AK, Mann JFE, et al. Management of blood pressure in patients with chronic kidney disease not receiving dialysis: synopsis of the 2021 KDIGO clinical practice guideline. *Ann Intern Med*. 2021;174:1270-1281.

Diuretics

Mechanism of Action

During diuretic therapy, the circulating blood volume falls initially, but gradually returns toward baseline over the ensuing weeks. Over time, the predominant effect of thiazide or thiazide-like diuretics is to reduce systematic vascular resistance. Loop diuretics are more potent diuretics than thiazide or thiazide-like diuretics, but the latter are preferred to treat hypertension until the estimated glomerular filtration rate is significantly reduced (<40 mL/min/1.73 m^2).

Clinical Use

Hydrochlorothiazide (HCTZ) is by far the most common thiazide diuretic used to treat hypertension and may be equivalent to chlorthalidone , which is a thiazide-like diuretic, for reducing cardiovascular risk with less hypokalemia.[A8] Kidney function is an important determinant of which diuretics are likely to be effective options. Thiazide diuretics must cause an effective natriuresis to lower blood pressure. HCTZ does not predictably cause a natriuresis when the estimated glomerular filtrate rate is less than 45 mL/min/1.73 m^2, whereas indapamide, which is also a thiazide-like diuretic, effectively evokes a diuresis at an estimated glomerular filtration rate as low as 30 mL/min/1.73 m^2 and chlorthalidone is effective down to an average estimated glomerular filtration rate in the low 20s.[A9] HCTZ has a clear dose-response curve between 6.25 to 50 mg per day, whereas thiazide-like diuretics tend to have a flat dose-response curve. Chlorthalidone has a 1.5- to 2.5-day duration of action, which is a beneficial characteristic for the chronic treatment of hypertension.

Side Effects

Thiazide diuretics can cause dose-related hypokalemia (Chapter 103), worsened glucose tolerance (Chapter 210), hypomagnesemia (Chapter 105), hyperuricemia (Chapter 252), raised serum lipid levels, photosensitivity skin reactions, skin cancer (mostly squamous cell carcinoma), and erectile dysfunction. These agents can also cause serious hyponatremia (Chapter 102), particularly in older patients, by impairing free water clearance both with and without volume depletion. Over-diuresis is more likely with the more potent diuretic chlorthalidone than with HCTZ.

Add-On Drugs for Difficult-to-Treat Hypertension

Potassium-Sparing Diuretics

Mechanism of Action

Spironolactone and eplerenone, both of which are aldosterone receptor antagonists, prevent aldosterone and glucocorticoids from binding and subsequently activating the mineralocorticoid receptor in the distal nephron and collecting duct (as well as in the heart and vascular endothelium) and thereby inhibit the activation of ENaC channels. Increased reabsorption of sodium proximal to the collecting duct reduces the urinary secretion of potassium and, as a result, raises the serum potassium level because less sodium is presented to the collecting duct for exchange with potassium. Baxdrostat, which inhibits aldosterone synthase, is an experimental drug that has shown promise for resistant hypertension.[A10]

Clinical Use and Side Effects

These agents are very effective adjuncts in patients on complex drug regimens for resistant hypertension. Potassium-sparing diuretics should generally be avoided when the estimated glomerular filtration rate is less than 45 mL/min/1.73 m^2 to prevent potentially dangerous hyperkalemia. Eplerenone is a more specific inhibitor of the mineralocorticoid receptor than is spironolactone, so it less frequently activates sex hormone receptors and causes less gynecomastia, menstrual irregularities, and erectile dysfunction. However, spironolactone lowers blood pressure more effectively than eplerenone. Amiloride, which is a direct inhibitor of the ENaC channel, is at least as, if not more, potent than spironolactone. The risk of hyperkalemia is higher in patients who are treated concurrently with ACE inhibitors or angiotensin receptor blockers.

β-Adrenergic Blockers

Mechanism of Action

A heterogenous variety of β-blockers lower blood pressure to a relatively similar degree. When β-blocker therapy is initiated, the reduction in cardiac output is countered by an increase in systemic vascular resistance, but this reaction wanes over time, thereby allowing blood pressure to fall. The reduction of blood pressure is due to a reduction in cardiac output, decreased release of renin, and a decreased release of norepinephrine. Cardioselective β_1-blockers (which include metoprolol, atenolol, acebutolol, and bisoprolol) tend to lose some of their cardioselectivity at higher doses. Propranolol is a nonselective β-blocker that occupies both β_1 and β_2 receptor sites. Labetalol and carvedilol, which are combined α- and β-blockers, and nebivolol, which is a β-blocker that stimulates the endogenous production of nitric oxide, are collectively known as vasodilating β-blockers.

Clinical Use and Side Effects

β-Blockers are no longer recommended as part of the initial drug regimen for hypertension because they are generally less effective for lowering blood pressure and are less protective against stroke compared with first-line antihypertensive agents. β-Blockers can, however, be useful adjunctive antihypertensive agents and are part of evidence-based treatment in patients with heart failure or ischemic heart disease. Vasodilating β-blockers may cause fewer side effects, such as cold extremities and claudication.

Fatigue and reduced exercise tolerance are common side effects that contribute to the poor overall tolerability of β-blockers. Weight gain and acute bronchospasm can occur in patients with underlying lung disease, and these agents are the antihypertensive drug class most likely to cause erectile dysfunction. β-Blockers should be gradually tapered over several weeks when being discontinued, and they should be avoided in patients with suspected or known nonadherence because their abrupt cessation can result in rebound hypertension.

α-Adrenergic Blockers

Mechanism of Action

α-Adrenergic blockers block the effect of norepinephrine on vascular adrenergic receptors, thereby resulting in vasodilation and lowering of blood pressure. α-Adrenergic blockers improve both insulin sensitivity (by augmenting skeletal muscle blood flow; Chapter 210) and symptoms of bladder outlet obstruction (dilatation of urethral smooth muscle; Chapter 114). Prazosin, doxazosin, terazosin, and phentolamine block α-1 adrenergic receptors, whereas phenoxybenzamine blocks α-1 and α-2 adrenergic receptors.

Clinical Use and Side Effects

Phenoxybenzamine is very useful for the preoperative management of pheochromocytoma (Chapter 209), for which blockade of α-adrenergic receptors should be undertaken before administering β-blockers so as to prevent

unopposed stimulation of the α-adrenergic receptor. α-1 Adrenergic receptor inhibitors are not recommended for first-line therapy because they do not lower blood pressure nor do they reduce the risk for cardiovascular events as well as first-line drugs, and they also can precipitate heart failure. α-Adrenergic agents are usually limited to late add-on therapy in men who have hypertension and symptoms of bladder outlet obstruction (Chapter 114), preferably combined with a diuretic to block their salt- and water-retaining properties. Orthostatic hypotension is a frequent adverse effect, and these agents must be used cautiously with phosphodiesterase-5 (PDE) inhibitors because of the risk of precipitous and profound drops in blood pressure.

Central Sympatholytics

Mechanism of Action

Central sympatholytic drugs stimulate the postsynaptic α-2 adrenergic or imidazoline receptors in the brain, thereby reducing the release of norepinephrine from peripheral sympathetic nerves, lowering sympathetic nervous system activity, and, as a result, lowering blood pressure.

Clinical Use and Side Effects

These drugs are limited to late add-on therapy for the treatment of resistant hypertension, in part because of their sedating side effects. These agents also cause orthostatic hypotension, which may go undetected if blood pressure is not measured in both the seated and standing positions. Clonidine is a rapidly acting oral agent, but it does not appear to have any discernable clinical benefit for acutely lowering blood pressure in patients who have a hypertensive urgency. Central sympatholytic drugs should be avoided in patients who have suspected or known nonadherence to prescribed drug therapy because of the possibility of rebound hypertension after their abrupt cessation. When these drugs are discontinued, they should be gradually tapered over several weeks.

Other Vasodilators

Mechanism of Action

Minoxidil and hydralazine work primarily by opening ATP-sensitive potassium channels in the resistance arterioles.

Clinical Use and Side Effects

These drugs are reserved for very late add-on therapy in the treatment of resistant hypertension. They cause profound arterial vasodilation that reflexively activates the sympathetic nervous system, thereby causing tachycardia. The use of either minoxidil or hydralazine necessitates the concurrent use of a potent diuretic to prevent the retention of salt and water, as well as a β-blocker to prevent reflex tachycardia. Hydralazine has also been linked to a lupus-like syndrome. Hirsutism, which is a common side effect of minoxidil therapy, can be particularly troubling in women. Endothelin antagonists, which are widely used for pulmonary hypertension (Chapter 69), are an experimental option for drug resistant hypertension.[A11]

ANTIHYPERTENSIVE DRUG INTERACTIONS

Nonsteroidal anti-inflammatory drugs (NSAIDs; Table 26-4) raise blood pressure and negatively affect kidney function. Of currently available NSAIDs, sulindac and celecoxib appear to have minimal, if any, effect on blood pressure levels in patients with hypertension. Acetaminophen can also raise blood pressure[A12] via unknown mechanisms. Grapefruit can cause excessive vasodilation for up to 24 hours in patients who are taking dihydropyridine calcium-channel blockers other than amlodipine by inactivating intestinal cytochrome P-450 3A4 (CYP34A) and possibly by inhibiting intestinal/hepatic p-glycoprotein (P-gp), thereby resulting in increased drug bioavailability. Verapamil and diltiazem are potent CYP3A4 inhibitors and can significantly raise the exposure to drugs such as simvastatin, atorvastatin, and fluvastatin that are all metabolized via CYP3A4; as a result, these drugs should be used at lower than the usually recommended reduced doses (Table 190-2), for both the initiation and maintenance of therapy, when patients are treated with verapamil or diltiazem. By comparison, amlodipine has more modest effects, but the dose of simvastatin still should not exceed 20 mg daily in amlodipine-treated patients. Rosuvastatin is a potent statin that does not inhibit CYP3A4 and can be used in its usual doses (Table 190-2). Cyclosporine and tacrolimus are also potent inhibitors of the CYP3A4 enzyme system and can significantly raise the blood levels of several statins that are metabolized via this pathway. Patients who are prescribed rivaroxaban, which is significantly metabolized via CYP3A4, should be monitored closely for bleeding. A lower than usual dose (see Table 70-6) is often preferred in patients who are treated with verapamil or diltiazem, particularly in the setting of renal impairment. In pregnant women requiring drug treatment for hypertension, iron supplementation reduces the absorption of methyldopa by 50%.

EVIDENCE-BASED MANAGEMENT OF HYPERTENSION

HOW FAR TO LOWER BLOOD PRESSURE?

U.S. guidelines recommended a blood pressure target of less than 130/80 mm Hg for most hypertensive patients, including less than 130 mm Hg systolic for patients ages 65 years and older (E-Table 64-1). However, published data demonstrate a mortality and cardiovascular benefit when middle-aged and older high-risk hypertensive patients are treated to a blood pressure target of less than 120 mm Hg systolic, including persons ages 75 years and older, even if they are frail, provided that they are not institutionalized.[A13,A14] The apparent contradiction is because clinical trials utilize rigorous standard protocols to measure blood pressure, and these protocols yield systolic blood pressure readings that, on average, are at least 10 mm Hg lower than are measurements that are obtained in routine clinical practice. In settings that use standard protocols to measure blood pressure, the recommended target blood pressure should be less than 120 mm Hg systolic.[18] In patients with diabetes, the currently recommended blood pressure target is less than 130/80 mm Hg, although guidelines suggest considering a goal of less than 120/80 mm Hg for patients who are at higher risk for complications of hypertension but at low risk for adverse effects from medications to lower blood pressure.[19]

WHICH DRUGS FOR WHICH PATIENTS?

Preferred antihypertensive drugs should be prescribed to patients who have specific indications (Table 64-9) because of their proven clinical benefit and safety. However, preferred antihypertensive agents often will be insufficient to control blood pressure without additional drugs.

Hypertensive Patients in General

The modern hypertension treatment paradigm emphasizes carefully selected combinations of antihypertensive drugs to control blood pressure. The selection of drugs should be guided by patient's clinical characteristics using combinations that have complementary efficacy and do not share adverse effects. Effective combinations include an ACE inhibitor or angiotensin receptor blocker combined with either a calcium-channel blocker (e.g., amlodipine) or a thiazide-like diuretic (e.g., chlorthalidone or indapamide). A single pill with quarter-doses of four medications (irbesartan 37.5 mg, amlodipine 1.25 mg, indapamide 0.625 mg, and bisoprolol 2.5 mg) is a potential simple alternative.[A15] However, β-blockers are not recommended for initial therapy in uncomplicated hypertension because they do not lower blood pressure nor protect against stroke as well as other first-line drugs. The combined use of any two renin–angiotensin system inhibitors (e.g., an ACE inhibitor, an angiotensin receptor blocker, or a dopamine reuptake inhibitor) should be avoided because of minimal incremental blood pressure lowering as well as a high risk of renal impairment and hyperkalemia.

Systolic Hypertension in Elderly Patients

Isolated systolic hypertension is the predominant phenotype in hypertensive patients ages 65 years and older. Randomized controlled trials have unequivocally proven that pharmacologic blood pressure lowering reduces premature mortality, morbid and fatal cardiovascular events, and dementia in such patients, even after age 80 years and even in the frail elderly. One caveat in such patients is a higher risk of orthostatic hypotension. Fortunately, intensive treatment to low blood pressure targets does not specifically cause orthostatic hypotension.[20] Older patients may not tolerate reductions in blood pressure as well as younger patients, so drug therapy should start with low doses of medications. Older patients are also more likely to have white coat hypertension or effect as well as masked or masked uncontrolled hypertension, thereby highlighting the need for home and/or ambulatory blood pressure measurements to assist therapeutic decision-making to prevent overtreatment as well as undertreatment. Older patients, particularly patients who have orthostatic hypotension, are also prone to developing postprandial hypotension (E-Fig. 64-5) because their splanchnic circulation dilates, thereby resulting in the pooling of blood. Postprandial home blood pressure measurements and/or ambulatory blood pressure monitoring is the best way to confirm this condition, which can be managed by consuming smaller and more frequent meals with a low glycemic index, drinking coffee with meals, and avoiding alcohol as well as hot showers.

Other potential problems in older persons include their higher risk for thiazide-induced hyponatremia, poorer adherence to medications, and polypharmacy with a greater probability of deleterious drug-drug interactions. The antihypertensive drug regimen should be simplified as much as possible, and medication refills should be synchronized with their pharmacy to the greatest degree possible.

E-TABLE 64-1 DIFFERENCES AMONG CURRENT TREATMENT GUIDELINES FOR ADULTS WITH HYPERTENSION

GUIDELINE	POPULATION	THRESHOLD OFFICE BP (mm Hg) TO START OR INTENSIFY THERAPY	TARGET BP (mm Hg)	INITIAL DRUG OPTIONS
2021 KDIGO*	Chronic kidney disease		SBP <120†	ACE-I or ARB‡
2020 ISH§	CAD	≥140/90	<130/80 <140/80 in elderly	ACE-I or ARB; BB, CCB
	Previous stroke	≥140/90	<130/80 <140/80 in elderly	ACE-I or ARB; CCB, diuretic
	Heart failure	≥140/90	<130/80 but >120/70	ARNI‖ or ACE-I or ARB; BB, MRA
	Chronic kidney disease	≥140/90	<130/80 <140/80 in elderly	ACE-I or ARB
	COPD	≥140/90	<130/80 <140/80 in elderly	ARB and CCB and/or diuretic, BB¶
	Diabetes	≥140/90	<130/80 <140/80 in elderly	ACE-I or ARB and/or CCB or thiazide-like diuretic
2020 ACCE/ACE**	Diabetes	≥130/80	<130/80 <120/80††	ACE-I or ARB or if BP >150/100, ACE-I or ARB plus CCB, BB‡‡ or thiazide
2020 ADA§§	Diabetes (general)	≥140/90	<140/90‖‖	ACE-1, ARB, thiazide-like diuretic¶¶ or DHP-CCB
	Albuminuria***	≥140/90	<140/90	ACE-I or ARB
	CVD or 10-year ASCVD risk ≥15%	≥140/90	<130/80	ACE-I or ARB
2020 Hypertension Canada's CHEP†††	Low risk (no target organ damage or CV risk factors)	≥160/100	<140/90	ACE-I, ARB, CCB, thiazide-like diuretics, BB‡‡‡
	High risk of cardiovascular disease	SBP ≥130	SBP <120	ACE-I or ARB; BB or CCB for patients with stable angina
	Diabetes mellitus	≥130/80	<130/80	ACE-I or ARB
	All others	≥140/90	<140/90	ACE-I, ARB, CCB, thiazide-like diuretics, BB§§§
2018 ESC/ESH Guideline‖‖‖,¶¶¶	**Hypertension**			
	Age 18-65 yr	≥140/90	120-129/<80 if tolerated	ACE-1, ARB, diuretic,**** CCB or BB
	Age 65-79 yr	≥140/90	130-139/<80	
	Age ≥80 yr	≥160/90	130-139/<80	
	Chronic Kidney Disease			
	Age 18-65 yr	≥140/90	120-129/<80 if tolerated	ACE-I or ARB plus CCB
	Age 65-79 yr	≥140/90	130-139/<80 if tolerated	or
	Age ≥80 yr	≥160/90	130-139/≤80 if tolerated	ACE-I or ARB plus diuretic (or loop diuretic)
	Diabetes			
	Age 18-65 yr	≥140/90	120-129/<80 if tolerated	ACE-I or ARB plus CCB or diuretic
	Age 65-79 yr	≥140/90	130-139/<80 if tolerated	
	Age ≥80 yr	≥160/90	130-139/<80 if tolerated	
2017 ACP/AAFP††††	≥60 yr:			Thiazide-type diuretic, ACE-I, ARB, CCB, BB
	General	SBP ≥150	SBP <150	
	Stroke or TIA	SBP ≥140	SBP <140	
	High CV risk	SBP ≥140	SBP <140	
2017 AHA/ACC/ASH‡‡‡‡	Uncomplicated hypertension—no clinical CVD, 10-yr ASCVD risk <10% and age <65 yr	≥140/90	<130/80	ACE-I, ARB, thiazide diuretic, CCB
	Clinical CVD or 10-yr ASCVD risk ≥10%	≥130/80	<130/80	ACE-I, ARB, thiazide diuretic, CCB
	Older persons (≥65 yr of age: noninstitutionalized, ambulatory, community-living adults)	SBP ≥130	SBP <130	ACE-I, ARB, thiazide diuretic, CCB
	Diabetes mellitus	≥130/80	<130/80	ACE-I, ARB, diuretics, CCB
	albuminuria§§§§	≥130/80	<130/80	ACE-I or ARB
	no albuminuria	≥130/80	<130/80	ACE-I, ARB, diuretics, CCB
	Chronic kidney disease	≥130/80	<130/80	ACE-I or ARB‖‖‖
	albuminuria	≥130/80	<130/80	ACE-I or ARB
	no albuminuria	≥130/80	<130/80	ACE-I, ARB diuretics, CCB

E-TABLE 64-1 DIFFERENCES AMONG CURRENT TREATMENT GUIDELINES FOR ADULTS WITH HYPERTENSION—cont'd

*Tomson CRV, Cheung AK, Mann JFE, et al. Management of blood pressure in patients with chronic kidney disease not receiving dialysis: synopsis of the 2021 KDIGO clinical practice guideline. *Ann Intern Med*. 2021;174:1270-1281.
†BP needs to be measured according to a standard measurement protocol. The BP target should not be applied to routine office BP measurement.
‡In diabetes and CKD, albuminuria category >30 mg/g; in person without diabetes, albuminuria >300 mg/g.
§Unger T, Borghi C, Charchar F, et al. 2020 International Society of Hypertension global hypertension practice guidelines. *Hypertension*. 2020;75:1334-1357.
‖Both reduced and preserved ejection fraction heart failure.
¶May be used in patients with coronary artery disease or heart failure.
**Garber AJ, Handelsman Y, Grunberger G, et al. Consensus statement by the American Association of Clinical Endocrinologists and American College of Endocrinology on the comprehensive type 2 diabetes management algorithm: 2020 executive summary. *Endocr Pract*. 2020;26:107-139.
††Consider this target for patients unlikely to have medication/BP-lowering adverse effects.
‡‡Cardioselective β_1-blockers in selected patients (HF + CAD).
§§American Diabetes Association. 10. Cardiovascular disease and risk management: standards of medical care in diabetes, 2021. *Diabetes Care*. 2021;44:S125-S150.
‖‖Target for those at lower risk for CV disease (10-yr ASCVD risk <15%).
¶¶Long-acting agents shown to reduce cardiovascular events, such as chlorthalidone and indapamide, are preferred.
***Urine to albumin : creatinine ratio ≥30-299 mg/g.
†††Rabi DM, McBrien KA, Sapir-Pichhadze R, et al. Hypertension Canada's 2020 comprehensive guidelines for the prevention, diagnosis, risk assessment, and treatment of hypertension in adults and children. *Can J Cardiol*. 2020;36:596-624.
‡‡‡Can safely be used as first-line therapy in younger patients only with uncomplicated hypertension.
§§§Can safely be used as first-line therapy in younger patients only with uncomplicated hypertension.
‖‖‖Williams B, Mancia G, Spiering W, et al. 2018 ESC/ESH guidelines for the management of arterial hypertension. *Eur Heart J*. 2018;39:3021-3104.
¶¶¶All initial target blood pressures are <140/90 mm Hg.
****Thiazide/thiazide-like diuretic.
††††Qaseem A, Wilt TJ, Rich R, et al. Pharmacologic treatment of hypertension in adults aged 60 years or older to higher versus lower blood pressure targets: a clinical practice guideline from the American College of Physicians and the American Academy of Family Physicians. *Ann Intern Med*. 2017;166:430-437.
‡‡‡‡Whelton PK, Carey RM, Aronow WS, et al. 2017 ACC/AHA/AAPA/ABC/ACPM/AGS/APhA/ASH/ASPC/NMA/PCNA guideline for the prevention, detection, evaluation, and management of high blood pressure in adults: a report of the American College of Cardiology/American Heart Association Task Force on Clinical Practice Guidelines. *J Am Coll Cardiol*. 2018;71:e127-e248.
§§§§Albuminuria = ≥300 mg/day, or ≥300 mg/g albumin : creatinine ratio or the equivalent in the first morning void.
‖‖‖‖If ACE-I is not tolerated.
ACE-I = angiotensin-converting enzyme inhibitor; ARB = angiotensin receptor blocker; ARNI = angiotensin receptor-neprilysin inhibitor; ASCVD = atherosclerotic cardiovascular disease; BB = β-blocker; BP = blood pressure; CAD = coronary artery disease; CCB = calcium-channel blocker; CKD = chronic kidney disease; COPD; chronic obstructive pulmonary disease; CVD = cardiovascular disease; DHP-CCB = dihydropyridine calcium-channel blocker; MRA = mineralocorticoid receptor antagonist; SBP = systolic blood pressure; TIA = transient ischemic attack.
Combination drug therapy is favored in most hypertensive patients as initial treatment except the frail elderly and low-risk hypertensives with SBP <150.

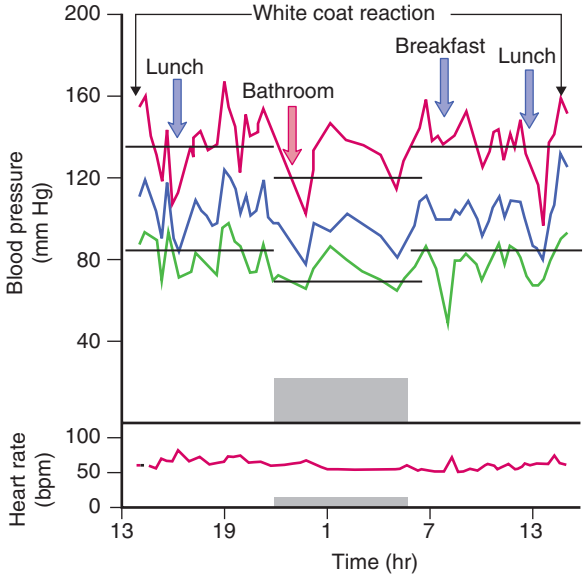

E-FIGURE 64-5. The 24-hour blood pressure monitor tracing of a patient with postprandial and orthostatic hypotension. This frail 70-year-old woman was referred for evaluation of labile hypertension and dizziness. *Blue arrows* show repeated episodes of postprandial hypotension. The *red arrow* shows an episode of orthostatic hypotension when the patient walked to the bathroom 90 minutes after going to sleep. White coat reactions are also seen when the patient came to the clinic, both to have the monitor placed and then to have it removed. (Courtesy of the late Ronald G. Victor, MD.)

Patients with Hypertensive Heart Disease

Left ventricular hypertrophy, which is an undesirable maladaptive myocardial response to uncontrolled blood pressure (Chapter 41), is a risk factor for atrial fibrillation, heart failure, ventricular arrhythmias, sudden death, and stroke. Most antihypertensive drug classes that successfully lower blood pressure will also lead to some degree of regression of left ventricular hypertrophy, but angiotensin receptor blockers and ACE inhibitors may be the best for this purpose. For patients who have a reduced left ventricular ejection fraction, guideline-directed medical therapy emphasizes β-blockers, aldosterone antagonists, and combination angiotensin receptor neprilysin inhibitors.

In patients with stable ischemic heart disease, a β-blocker combined with an ACE inhibitor or an angiotensin receptor blocker is first-line therapy. If such patients require further medication to control angina (Chapter 56), a dihydropyridine calcium-channel blocker should be added. If, however, the medical issue is resistant blood pressure, then an aldosterone antagonist or a thiazide-like diuretic is first-line add-on therapy.

Diabetes and Normal Renal Function

Approximately 80% of patients with type 2 diabetes (Chapter 210) have hypertension. Although no compelling evidence suggests that any particular first-line medications are preferred, treatment usually begins with an ACE inhibitor or angiotensin receptor blocker plus a calcium-channel blocker, or perhaps a thiazide-like diuretic.

Chronic Diabetic Kidney Disease

Diabetic nephropathy (Chapter 109) is characterized by albuminuria (≥300 mg/g), dysfunctional renal autoregulation, depressed glomerular filtration capacity, elevated blood pressure, and a high risk for cardiovascular–renal events. ACE inhibitors and angiotensin receptor blockers are indicated for patients who have chronic diabetic kidney disease to slow the progressive loss of kidney function. In addition to sodium–glucose cotransporter-2 inhibitors, combination drug therapy should be initiated with an ACE inhibitor or angiotensin receptor blocker plus a calcium-channel blocker, often with a thiazide-like diuretic, preferably chlorthalidone. However, a loop diuretic may be substituted for a thiazide-like diuretic when the estimated glomerular filtration rate is less than 25 mL/mm/1.73 m^2.

Secondary Stroke Prevention

Prior stroke (Chapters 376 and 377) is a major risk factor for recurrent stroke, disability, mortality, and cardiovascular events. In patients who have survived a stroke or a transient ischemic attack, oral medications should be started or restarted a few days post-stroke if possible. The blood pressure threshold for starting antihypertensive drug therapy is uncertain, but drug therapy is usually initiated when the blood pressure exceeds 140/90 mm Hg. Preferred drugs in this high-risk group include thiazide-like diuretics (especially indapamide), ACE inhibitors, and angiotensin receptor blockers. The magnitude of cardiovascular protection likely relates to the degree of blood pressure reduction. For example, lowering blood pressure to less than 130/80 mm Hg after a lacunar infarction reduces the risk for subsequent hemorrhagic stroke (Chapter 377).

Hypertension In Black Americans

Hypertension in Black Americans, relative to White Americans, has an earlier onset, is more prevalent and severe, and is accompanied by a greater risk for pressure-related target-organ injury, including left ventricular hypertrophy, heart failure, stroke, and death. Reductions in dietary sodium intake not only lower blood pressure but also reduce the intensity of antihypertensive drug therapy required to control blood pressure. However, hypertensive Black Americans have higher prevalences of several characteristics that confer resistance to antihypertensive drug therapy, including obesity, chronic kidney disease, and diabetes mellitus. As a result, more intense pharmacotherapy is typical required. Nevertheless, excellent responses can be provided by carefully selected combination drug therapy (anchored by either an ACE inhibitor or angiotensin receptor blocker plus a thiazide or thiazide-like diuretic or a calcium-channel blocker). Pharmacist-led treatment programs in barbershops are a useful strategy for controlling blood pressure in Black men with previously uncontrolled hypertension.[A16]

Hypertension Associated with Oral Contraceptives and Estrogen Replacement

Hypertension occurs in up to 8.5% of women who use oral contraception, especially with higher-dose ethinyl estradiol preparations (>50 mcg; see Table 220-2), and is directly related to the duration of therapy. By comparison, progestin-only contraceptives do not appear to raise blood pressure. Risk factors for oral contraceptive–associated hypertension include prior hypertensive disorders of pregnancy, smoking, older age, obesity, diabetes mellitus, chronic kidney disease, and Black race. Hormonal contraception (e.g., estrogen and estrogen/progestin combinations) is best avoided in women who have poorly controlled blood pressure, whereas progestin-only preparations are acceptable. If hypertension develops during use of estrogen-containing hormonal contraception, it should be discontinued and replaced with a nonhormonal or progestin-only form of contraception. Data are inconclusive as to whether postmenopausal estrogen therapy (Chapter 222) modestly raises or reduces blood pressure.

Hypertension in Pregnancy

Hypertension during pregnancy is an important cause of maternal and fetal morbidity. It is discussed in detail in Chapter 221.

Drug-Resistant Hypertension

Many patients with hypertension are treated with two or fewer antihypertensive drugs, so most patients who have persistent hypertension despite treatment have not been treated intensively enough to be categorized as having resistant or refractory hypertension. Many of these patients have pseudo-resistance (Table 64-10), and most will be effectively treated with appropriate multidrug regimens (Fig. 64-4). Among patients who are treated with multiple antihypertensive drugs, poor control may be a result of suboptimal or ineffective treatment regimens rather than true resistance.

Resistant hypertension is defined as persistent hypertension (≥130/80 mm Hg) despite prescribing three or four antihypertensive medications, one of which is a diuretic, or controlled blood pressure (<130/80 mm Hg) that requires four or more antihypertensive drugs, one of which is a diuretic. The prevalence of resistant hypertension in U.S. adults is about 15%. Refractory hypertension is defined as uncontrolled blood pressure despite five or more antihypertensive medications, one of which is a diuretic. The prevalence of refractory hypertension in U.S. drug-treated adults is 0.8%. Resistant and refractory hypertension are more common in Black Americans, older persons, and persons with chronic kidney disease, primary aldosteronism (Chapter 208), renal artery stenosis, pheochromocytoma, diabetes, known cardiovascular disease, obesity, high sodium intake, low levels of physical activity,[21] and low household income.

Among patients who have apparent treatment-resistant hypertension, nonadherence to medication is highly prevalent.[22] Long-acting antihypertensive agents (e.g., chlorthalidone, amlodipine) should be favored because they will provide better efficacy if some doses are missed.[23] Other strategies to maximize the effectiveness of antihypertensive drug regimens include using thiazide-like diuretics (e.g., indapamide or chlorthalidone) rather than HCTZ and adding an aldosterone antagonist (spironolactone, eplerenone) or an ENaC channel inhibitor (amiloride) in patients who have adequate kidney function (eGFR ≥ 45 mL/min/1.73 m^2). Counseling that successfully reduces dietary sodium intake rapidly lowers blood pressure in resistant or refractory hypertension

TABLE 64-10 CAUSES OF PSEUDORESISTANT AND TRULY RESISTANT HYPERTENSION

PSEUDORESISTANT HYPERTENSION	TRULY RESISTANT HYPERTENSION

• Ineffective medical regimen
• Heavy arterial calcification
• Medication nonadherence
• Pressor substances
  • Most nonsteroidal anti-inflammatory drugs
  • Calcineurin inhibitors (e.g., cyclosporine, tacrolimus)
  • Glucocorticoids
  • Herbs (e.g., yohimbine, St. John's wort)
  • Sympathomimetics (e.g., phenylephrine, sibutramine, methylphenidate)
  • Antipsychotic agents (e.g., clozapine, thioridazine)
  • Antidepressant agents (e.g., venlafaxine, fluoxetine)
  • Anxiolytic agents (e.g., buspirone)
	• Primary aldosteronism
	• Chronic kidney disease
	• Obesity
	• Obstructive sleep apnea
	• Other causes of secondary hypertension
	  • Pheochromocytoma
	  • Cushing syndrome
	  • Atherosclerotic renal artery stenosis
	  • Fibromuscular dysplasia
	  • Coarctation of the aorta
	  • Hyperthyroidism
	  • Hypothyroidism
	  • Hyperparathyroidism
	  • Severe essential hypertension

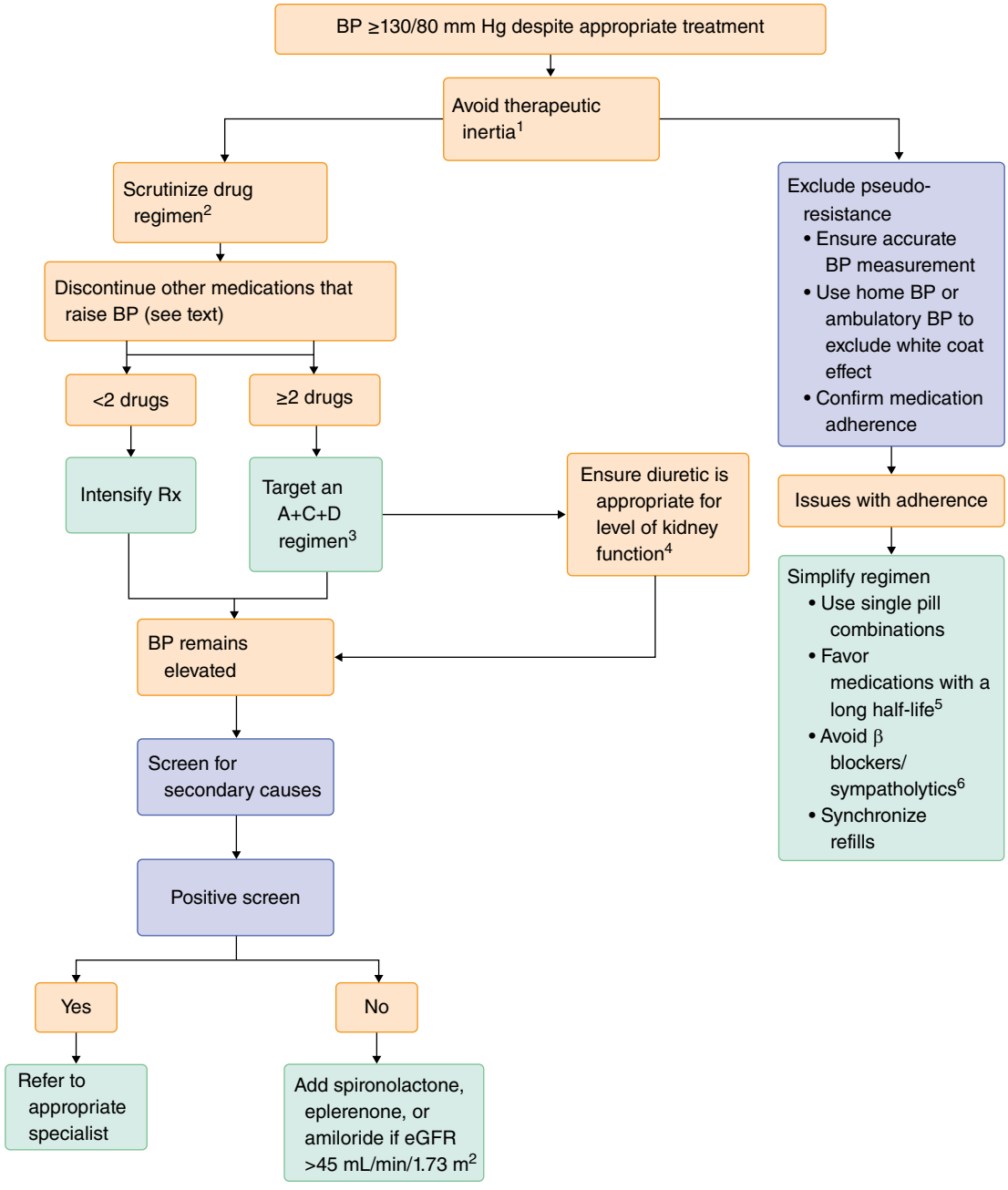

FIGURE 64-4. Algorithm for evaluating and treating residual hypertension. A = angiotensin-converting enzyme inhibitor or angiotensin receptor blocker; BP = blood pressure; C = calcium-channel blocker; D = diuretic; eGFR = estimated glomerular filtration rate; Rx = treatment. [1]Regimen should include comorbidity-indicated drugs (see Table 64-8). [2]Documenting office blood pressure elevations but taking no action(s) to intensify drug treatment or initiate treatment if unmediated. [3]3-Drug treatment with A: an angiotensin-converting enzyme inhibitor or an angiotensin receptor blocker, C: a calcium-channel blocker, and D: a diuretic (see Table 64-7). [4]eGFR ≥45 mL/min/1.73 m² (chlorthalidone, indapamide, hydrochlorothiazide); eGFR 30-45 (chlorthalidone, indapamide, loop diuretics); and eGFR <30 (loop diuretics or metolazone). [5]Drugs such as chlorthalidone, amlodipine, azilsartan, olmesartan. [6]Because their abrupt discontinuation can lead to rebound hypertension.

to a degree that exceeds the blood pressure reductions with most add-on single drug therapies.

Second-generation catheter-based electrode renal denervation modestly lowers blood pressure, whereas first-generation attempted treatments did not.[A17] Ultrasound renal denervation is another experimental option.[A18] To date, however, renal artery denervation has not received FDA approval for widespread use in the United States, and its future role remains unclear.

PREVENTION

Effective primordial prevention of hypertension is not principally dependent on medical care but rather on the widespread adoption of a prudent diet (Chapter 13) and lifestyle changes to reduce the intake of excess calories, sodium, and alcohol (Chapter 364), as well as to increase physical activity (Chapter 14) and prevent obesity (Chapter 201). Although these issues represent individual choices, societal barriers to the adoption of these guidelines include the limited availability and higher cost of healthy foods and safety concerns that limit outdoor physical activity in some geographic areas. Primary prevention depends on screening,[A19] which should be performed at least every 2 years or so in adults.[24]

Acute Severe Hypertension

Hypertensive urgencies and emergencies occur in approximately 1% and 0.3%, respectively, of all emergency department visits.[25] Most patients have an exacerbation of previously diagnosed but typically poorly controlled hypertension, but new-onset hypertension also can present as an urgency or emergency, especially in vulnerable populations and in middle- and low-income countries.[26]

A hypertensive urgency is defined as a blood pressure level of 180/110 mm Hg or greater without new or worsening pressure-related target-organ injury, such as myocardial or cerebral ischemia, aortic dissection,[27] or acute heart

failure. A hypertensive emergency is defined by the new onset of end-organ damage with a blood pressure level that usually exceeds 180/110 mm Hg but may be substantially higher.

Nonadherence to prescribed antihypertensive medications is a commonly encountered cause of precipitous rises in blood pressure. Hypertensive emergencies also can occur after ingestion of sympathomimetic substances (Chapter 365), eclampsia (Chapter 221), traumatic head injuries (Chapter 368), extensive body burns (Chapter 97), and postoperatively.

CLINICAL MANIFESTATIONS AND DIAGNOSIS

Patients with a hypertensive urgency are typically asymptomatic. However, some patients with hypertensive urgency present with minimal vague symptoms but striking high blood pressure elevations (e.g., 220/120 mm Hg). The most common hypertensive emergencies include heart failure/acute pulmonary edema (Chapters 45 and 46), acute coronary syndromes/myocardial infarction (Chapters 57 and 58), and severe blood pressure elevations after surgery.

Patients should be closely questioned regarding their adherence to prescribed antihypertensive medications. In patients who may have abruptly stopped taking either β-blockers or other sympatholytic drugs, rebound hypertension should be considered, especially in the presence of tachycardia and other signs of sympathetic nervous system activation. Patients also must be carefully questioned about the use of illicit sympathomimetic substances, including cocaine (Chapter 365).

In patients who have central nervous system manifestations of a hypertensive emergency, the specific causes (Table 64-11; e.g., hypertensive encephalopathy, acute ischemic stroke, hemorrhagic stroke, and subarachnoid hemorrhage [Chapter 377; see Table 64-10]) must be determined because the recommended treatment approaches vary significantly. All patients who present with hypertensive emergencies should be screened for secondary forms of hypertension (see Table 64-4) while hospitalized, if possible.

Hypertensive encephalopathy is characterized by severe blood pressure elevations, obtundation, visual disturbances, altered sensorium, seizures, and marked hypertensive retinopathy (with or without papilledema; see Fig. 391-25), but an absence of focal neurologic findings. Brain imaging with CT or MRI is useful to exclude intracranial hemorrhage and acute ischemic stroke. An important subset of patients with hypertensive encephalopathy have the posterior leukoencephalopathy syndrome, which is characterized by symmetrical vasogenic edema in the posterior occipital regions of the brain, most readily visualized on MRI. Such patients can have focal neurologic signs that can be difficult to distinguish from an evolving stroke (Chapter 376).

TREATMENT

Patients who have hypertensive urgencies are often initially seen in ambulatory settings and are then subsequently referred to an emergency department, despite little evidence that such transfer is beneficial or that hospital admission should be required. Patients who present with severe blood pressure elevations above the threshold for diagnosing hypertensive urgency should have any discontinued blood pressure medications restarted or be switched to longer-acting drugs that do not cause rebound hypertension if they are abruptly discontinued. Previously untreated patients typically should be started on routine oral therapy and scheduled for prompt follow-up. However, rapid blood pressure reductions via either the oral or intravenous route run the short-term risk of precipitating target-organ ischemia. Patients should be observed long enough to be confident that they do not have any new or worsening target-organ injury that requires urgent therapy.

No precise blood elevation in the setting of new and worsening pressure-related target-organ injury (e.g., obtundation, confusion, focal neurologic signs, seizures, heart failure, pulmonary edema, blurred vision, severe retinopathy) confirms the diagnosis of hypertensive emergency. Nevertheless, when blood pressure is approximately 180/110 mm Hg or greater, the blood pressure is high enough to be the likely cause of the new/worsening target-organ injury and the patient should be diagnosed with hypertensive emergency and be treated in a closely monitored critical care settings with intravenous medications (Fig. 64-5; Tables 64-11 and 64-12).

When blood pressure lowering is undertaken, however, rapid reductions to achieve normalization or near normalization of blood pressure is not recommended except in patients who have aortic dissection (Chapter 63), cardiogenic pulmonary edema (Chapter 46), an acute coronary syndrome (Chapter 57), or hemorrhagic stroke (Chapter 377). Immediate blood pressure lowering is also indicated in postoperative patients to prevent bleeding, particularly from vascular suture lines.

Immediate blood pressure lowering can be accomplished with rapid-onset intravenous drugs such as clevidipine and nicardipine outside of the intensive care setting. In other hypertensive emergencies that do not necessitate a more immediate reduction in blood pressure, a prudent approach is to reduce blood pressure by 10 to 15% over the first 1 to 2 hours, then by another 10 to 15% over the ensuing 12 to 24 hours. The rationale for allowing blood pressure to remain in the hypertensive range is to prevent iatrogenic hypoperfusion and ischemia of pressure-sensitive target organs. For example, in severely hypertensive patients with acute ischemic stroke (Chapter 376), care must be taken to avoid overzealous blood pressure lowering because the cerebral autoregulation of blood flow is disrupted in the ischemic penumbra and is entirely dependent on the difference between systemic and intracranial pressures to sustain blood flow to vulnerable brain tissue in watershed areas.

Oral Medications for Hypertensive Urgencies

The overwhelming majority of patients with blood pressure levels above the threshold of 180/110 mm Hg will not require immediate blood pressure lowering with oral medications in the office nor in the hospital setting and do not require

TABLE 64-11 HYPERTENSIVE EMERGENCIES REQUIRING IMMEDIATE LOWERING OF BLOOD PRESSURE

CLINICAL PRESENTATION	TIMELINE AND TARGET BLOOD PRESSURE	PREFERRED TREATMENT	ALTERNATIVE
Malignant hypertension with or without thrombotic microangiopathy or acute renal failure	Several hours, MAP –20 to –25%	Labetalol OR nicardipine	Nitroprusside Urapidil
Hypertensive encephalopathy	Immediate, MAP –20 to –25%	Labetalol OR nicardipine	Nitroprusside
Acute ischemic stroke and BP >220 mm Hg systolic or >120 mm Hg diastolic (Chapter 376)	1 hour, MAP –15%	Labetalol OR nicardipine	Nitroprusside
Acute ischemic stroke with indication for thrombolytic therapy and BP >185 mm Hg systolic or >110 mm Hg diastolic (Chapter 376)	1 hour, MAP –15%	Labetalol OR nicardipine	Nitroprusside
Acute hemorrhagic stroke and systolic BP >180 mm Hg (Chapter 377)	Immediate, systolic BP 130 to 180 mm Hg	Labetalol OR nicardipine	Urapidil
Acute coronary event (Chapters 57 and 58)	Immediate, systolic BP <140 mm Hg	Nitroglycerin OR labetalol	Urapidil
Acute cardiogenic pulmonary edema (Chapter 46)	Immediate, systolic BP <140 mm Hg	Nitroprusside OR nitroglycerin (with a loop diuretic)	Urapidil (with loop diuretic)
Acute aortic disease (Chapter 63)	Immediate, systolic BP <120 mm Hg and heart rate <60 beats per minute	Esmolol PLUS nitroprusside OR nitroglycerin plus nicardipine	Labetalol OR metoprolol
Eclampsia and severe preeclampsia/HELLP (Chapter 221)	Immediate, systolic BP <160 mm Hg and diastolic BP <105 mm Hg	Magnesium sulfate PLUS labetalol OR nicardipine	

BP = blood pressure; HELLP = hemolysis, elevated liver enzymes and low platelets; MAP = mean arterial pressure.

Adapted from van den Born BH, Lip GYH, Brguljan-Hitij J, et al. ESC Council on hypertension position document on the management of hypertensive emergencies. *Eur Heart J Cardiovasc Pharmacother*. 2019;5:37-46; Victor RG. Arterial hypertension. In: Goldman L, Schafer AI eds. *Goldman-Cecil Medicine*. Philadelphia: Elsevier; 2020:443-456.

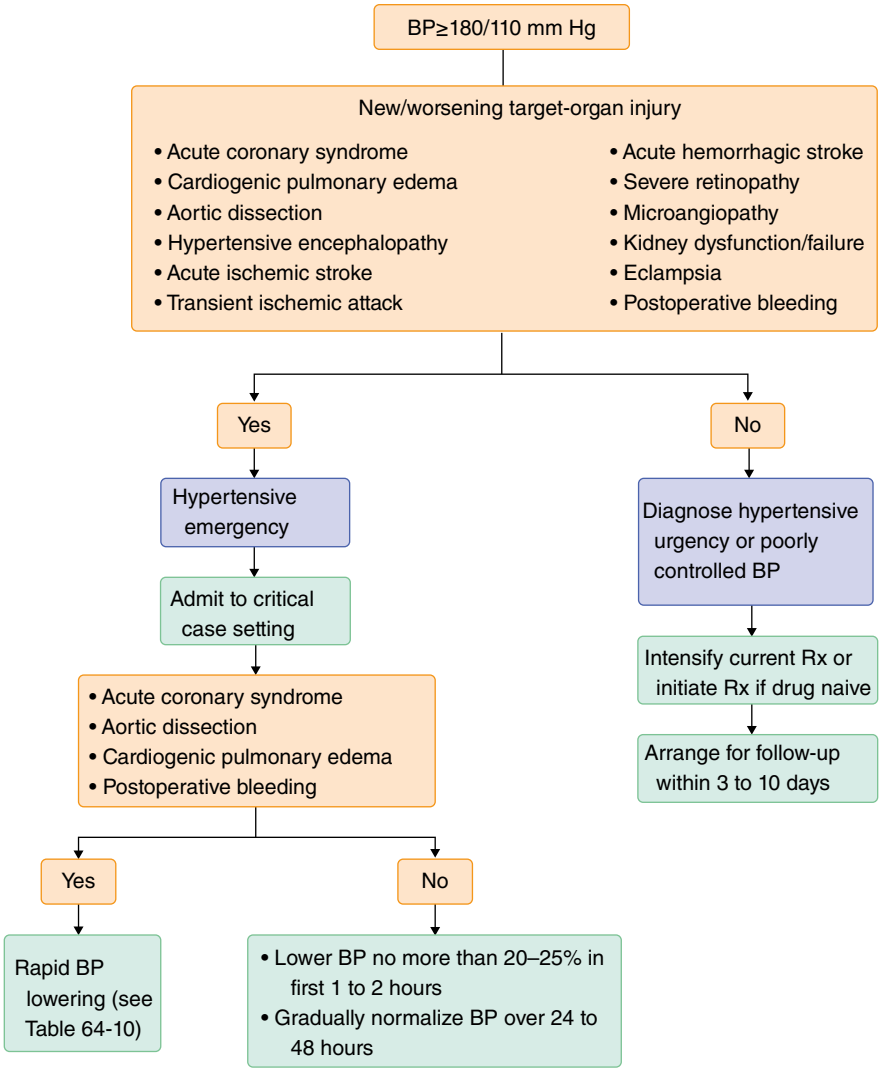

FIGURE 64-5. **Algorithm for diagnosing and treating hypertensive emergency.** BP = blood pressure; Rx = treatment.

referral to an emergency department. The one important exception, however, is patients who have abruptly discontinued β-blockers or sympatholytic drugs and who present with rebound hypertension with overt signs of sympathetic nervous system activation (e.g., tachycardia). Initiating intravenous labetalol (e.g., 20 mg initially then 20 mg to 80 mg every 10 minutes until the clinical manifestations of sympathetic nervous system hyperactivity have lessened) or oral clonidine (0.1 to 0.2 mg initially, then up to 0.1 mg hourly up to 0.7 mg total dose) to diminish sympathetic nervous system activity is reasonable in this situation. Other patients should have their discontinued medications restarted or their prescribed regimen intensified. If patients have not previously been treated, treatment should be initiated with two-drug therapy consisting of either a thiazide-like diuretic or calcium antagonist plus either an ACE inhibitor or an angiotensin receptor blocker.

Intravenous Medications for Hypertensive Emergencies

For a hypertensive emergency, labetalol (Table 64-12) is usually the favored drug, especially when treating severe blood pressure elevations in patients who have an acute ischemic stroke, because it has a reasonably quick onset of action and minimally reduces cerebral blood flow. However, labetalol has a delayed offset of action, thereby making it harder to titrate the blood pressure response, particularly if blood pressure falls too rapidly during the infusion. Conversely, nitroprusside has a near-immediate onset and offset of action, so near-instantaneous blood pressure titration can be obtained. A disadvantage of nitroprusside is that it does not preserve cerebral blood flow as well as labetalol as blood pressure is lowered. Nicardipine has a nearly identical onset of action as labetalol, but, importantly, has a much faster offset of action.

After gradual reduction of blood pressure into the target ranges for the various types of hypertensive emergencies, patients must be weaned from intravenous medications and transitioned to oral antihypertensive drugs so they can be transferred out of the intensive care unit. Patients should be transitioned to carefully selected combination drug therapies (e.g., calcium-channel blocker or thiazide-like diuretic plus an ACE inhibitor or angiotensin receptor blocker, depending on their comorbid conditions; see Tables 64-5 and 64-7). However, immediate blood pressure normalization is not the goal. A 20- to 40-mg dose of intravenous furosemide (repeated, if needed no sooner than 2 hours later) can enhance the blood pressure response to oral medications, especially because saline-containing intravenous fluid infusions and the profound vasodilation from intravenous antihypertensive drugs can expand the plasma volume and extracellular fluid volume, and thereby attenuate the response to antihypertensive drugs.

INCIDENTAL BLOOD PRESSURE ELEVATIONS IN THE EMERGENCY DEPARTMENT

Blood pressure elevations are commonly encountered in patients who present to emergency departments for a variety of complaints and conditions. The vast majority of these patients truly do have hypertension, but its severity is often overestimated because of pain, stress, and poor blood pressure measurement

TABLE 64-12 INTRAVENOUS DRUGS FOR HYPERTENSIVE EMERGENCIES

DRUG	ONSET OF ACTION	DURATION OF ACTION	DOSE	CONTRAINDICATIONS	ADVERSE EFFECTS
Clevidipine	2-3 min	5-15 min	2 mg/h IV infusion, increase every 2 min with 2 mg/h until goal BP		Headache and reflex-tachycardia
Enalaprilat	5-15 min	4-6 h	0.625-1.25 mg IV	History of angioedema	
Esmolol	1-2 min	10-30 min	500 μg/kg IV bolus over 1 min; 50-300 μg/kg/min as continuous IV infusion	History of 2nd- or 3rd-degree AV block (in the absence of rhythm support), systolic heart failure, asthma, and bradycardia	Bradycardia
Fenoldopam	5-15 min	30-60 min	0.1 μg/kg/min IV infusion, increase every 15 min until goal BP is reached with 0.05-0.1 μg/kg/min increments		
Labetalol	5-10 min	3-6 h	0.25-0.5 mg/kg IV bolus; 2-4 mg/min continuous infusion until goal BP is reached, thereafter 5-20 mg/h	History of 2nd- or 3rd-degree AV block, systolic heart failure, asthma, and bradycardia	Bronchoconstriction and fetal bradycardia
Metoprolol	1-2 min	5-8 h	2.5-5 mg IV bolus over 1 min; may repeat every 5 min to a maximum dose of 15 mg	History of 2nd- or 3rd-degree AV block, systolic heart failure, asthma and bradycardia	Bradycardia
Nicardipine	5-15 min	30-40 min	5-15 mg/h as continuous IV infusion, starting dose 5 mg/h, increase every 15-30 min with 2.5 mg until goal BP, thereafter decrease to 3 mg/h	Liver failure	Headache and reflex-tachycardia
Nitroglycerin	1-5 min	3-5 min	5-200 μg/min, 5 μg/min increase every 5 min		Headache and reflex-tachycardia
Nitroprusside	Immediate	1-2 min	0.3-10 μg/kg/min, increase by 0.5 μg/kg/min every 5 min until goal BP	Liver/kidney failure (relative)	Cyanide intoxication
Phentolamine	1-2 min	10-30 min	500-1000 μg/kg IV bolus OR 50-300 μg/kg/min as continuous IV infusion		Tachyarrhythmias and chest pain
Urapidil	3-5 min	4-6 h	12.5-25 mg IV bolus, 5-40 mg/h as continuous infusion		

1000 μg = 1 mg; AV = atrioventricular; BP = blood pressure; IV = intravenous.
Adapted from van den Born BH, Lip GYH, Brguljan-Hitij J, et al. ESC Council on hypertension position document on the management of hypertensive emergencies. *Eur Heart J Cardiovasc Pharmacother*. 2019;5:37-46.

techniques. Even in a busy emergency department, a careful review of medical records, clinical examination, and review of the ECG can yield signs of prior chronic blood pressure elevations. To the degree possible, patients should receive referral to a medical physician for follow-up and further evaluation. In patients who have severe blood pressure elevations and evidence of target-organ injury, consideration should be given to referral to a hypertension specialist.

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65

ATHEROSCLEROTIC PERIPHERAL ARTERIAL DISEASE

CHRISTOPHER J. WHITE

DEFINITION

Lower extremity atherosclerotic peripheral arterial disease is one subset of a larger group of peripheral vascular diseases that includes all noncoronary vascular disorders that may affect the arterial, venous (Chapters 66 and 68), or lymphatic circulation. Atherosclerotic arterial diseases are characterized by arterial narrowing or occlusion caused by the accumulation of atherosclerotic plaque elements in the vessel wall. Atherosclerotic vascular disease can also lead to aneurysm formation, which is the pathologic enlargement of arterial segments, and may result in rupture, dissection, or thromboembolism (Chapter 63).

EPIDEMIOLOGY

The prevalence of lower extremity peripheral arterial disease in the United States, Europe, and Asia continues to increase as the population ages and is exposed to atherosclerotic risk factors (Chapter 40). The presence of peripheral arterial disease is defined as an ankle-brachial index (ABI)—the ratio of the highest systolic blood pressure in the ankle divided by the highest systolic blood pressure in the arm (Fig. 65-1)—less than 0.90. Among individuals age 40 years and older, the prevalence is 4.3% (95% confidence interval [CI], 3.1 to 5.5%), but the prevalence in individuals with diabetes ranges from 20 to 30%.[1]

Risk factors for atherosclerosis (Chapter 40) increase the likelihood of developing lower extremity peripheral arterial disease (Table 65-1). More than 95% of individuals with peripheral arterial disease have at least one traditional cardiovascular risk factor, and most have multiple risk factors. More than one third of patients with peripheral arterial disease have significant coronary disease, and up to one quarter have carotid artery disease. As a result, the risk of heart attack, stroke, and death are increased several-fold in patients with peripheral arterial disease.

Among conventional atherosclerotic risk factors, cigarette smoking is two to three times more likely to cause lower extremity peripheral arterial disease than to cause coronary artery disease. Hypertension is also associated with lower extremity peripheral arterial disease. The development of peripheral arterial disease is more likely in patients with lipid abnormalities (elevated total and low-density lipoprotein [LDL] cholesterol, decreased high-density lipoprotein [HDL] cholesterol, and hypertriglyceridemia), and the risk increases by 5 to 10% for each 10 mg/dL increase in total cholesterol. Increased homocysteine levels are associated with a two- to three-fold increased risk for developing atherosclerotic peripheral arterial disease. Diabetes mellitus increases the risk of lower extremity peripheral arterial disease by two- to four-fold, and the risk of developing lower extremity peripheral arterial disease is proportional to the severity and duration of diabetes. Tight control of diabetes is important because the risk of developing peripheral arterial disease increases by 28% for every 1% increase in glycosylated hemoglobin (Chapter 210). Patients with diabetes who have lower extremity peripheral arterial disease are seven- to 15-fold more likely to undergo a major amputation than nondiabetics with lower extremity peripheral arterial disease.

Peripheral arterial disease disproportionately affects older individuals, non-Hispanic Blacks, current smokers, individuals with diabetes, and those with abnormal renal function. The overall prevalence of peripheral arterial disease in the United States among persons age 70 years and older is 14.5% (95% CI, 10.8 to 18.2%), which corresponds to approximately 4 million individuals.

TABLE 65-1 PATIENTS AT RISK FOR PERIPHERAL ARTERIAL DISEASE

- Age ≥65 yr
- Age 50-64 yr with risk factors for atherosclerosis (e.g., diabetes mellitus, history of smoking, hyperlipidemia, hypertension; see Chapter 40) or family history of peripheral arterial disease
- Age <50 yr with diabetes mellitus and 1 additional risk factor for atherosclerosis
- Known atherosclerotic disease in another vascular bed (e.g., coronary, carotid, subclavian, renal, mesenteric artery stenosis, or abdominal aortic aneurysm)

Adapted from Gerhard-Herman MD, Gornik HL, Barrett C, et al. 2016 AHA/ACC guideline on the management of patients with lower extremity peripheral artery disease: executive summary: a report of the American College of Cardiology/American Heart Association Task Force on Clinical Practice Guidelines. *J Am Coll Cardiol*. 2017;69:1465-1508.

PATHOBIOLOGY

Acute Limb Ischemia

Acute limb ischemia occurs when blood flow to an extremity is abruptly halted or markedly diminished, resulting in hypoperfusion that threatens the viability of the limb. Acute limb ischemia is most commonly caused by either thrombosis

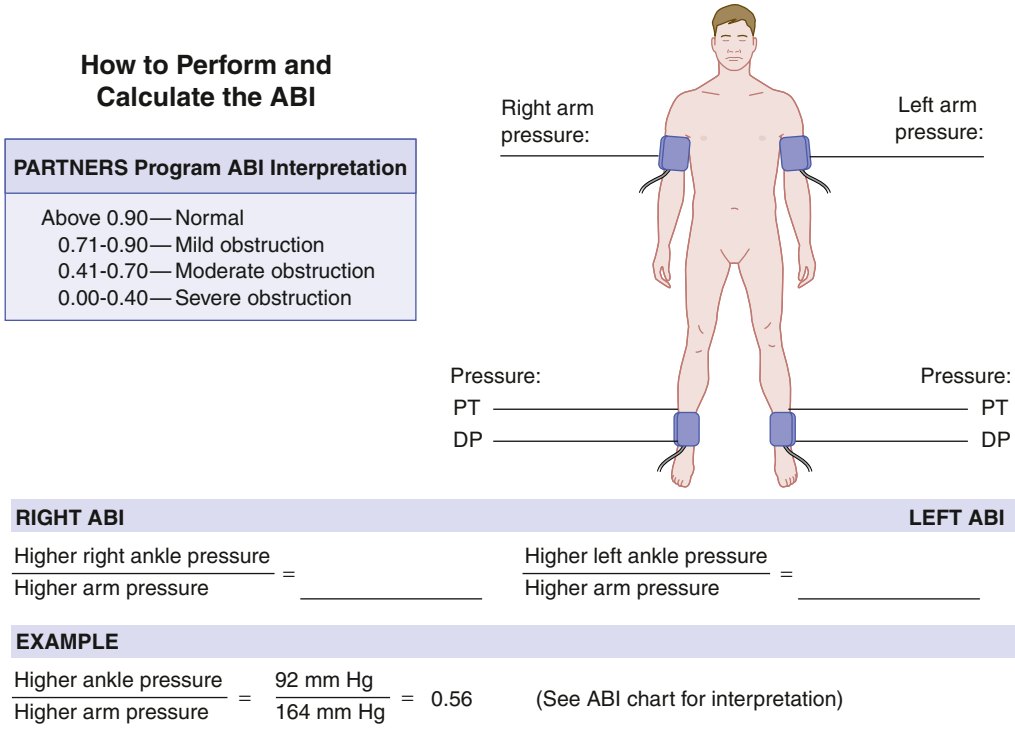

FIGURE 65-1. Performing pressure measurements and calculating the ankle-brachial index (ABI). To calculate the ABI, systolic pressures are determined in both arms and both ankles with the use of a handheld Doppler instrument. The higher reading in either the dorsalis pedis (DP) or the posterior tibial (PT) arteries of the right foot and the left foot is divided by the higher systolic blood pressure reading in either the right or left arm to calculate the index. PARTNERS = PAD (peripheral arterial disease) Awareness, Risk, and Treatment: New Resources for Survival.

ABSTRACT

Atherosclerotic lower extremity arterial diseases are characterized by arterial narrowing or occlusion caused by the accumulation of atherosclerotic plaque. The risks of heart attack, stroke, and death are increased several-fold in patients with peripheral arterial disease. The overall prevalence of peripheral arterial disease in the United States among persons age 70 years and older is 14.5% (95% confidence interval [CI], 10.8 to 18.2%), which corresponds to approximately 4 million individuals. Individuals who have diabetes are 15 times more likely to have an amputation than are patients without diabetes, whose annual amputation rate is less than 1%. Peripheral arterial disease manifests as three clinical syndromes: chronic stable ischemia (claudication); chronic critical limb-threatening ischemia; and acute limb ischemia. The primary treatment of patients with peripheral arterial disease is medical therapy directed at reducing the patient's risk for life-threatening cardiovascular complications of atherosclerosis. Structured exercise therapy, with or without revascularization, improves functional status such as walking distance.

KEYWORDS

atherosclerotic lower extremity arterial disease
claudication
critical limb-threatening ischemia
amputation

or embolism. Most emboli originate from the heart as a mural thrombus from a recent myocardial infarction (MI; Chapter 58) or from the atrial appendage in a patient with atrial fibrillation (Chapter 52). A less common cause of lower extremity emboli is an abdominal aortic aneurysm (Chapter 63) that serves as the source of cholesterol emboli (Chapter 66).

Arterial in situ thrombosis as a result of plaque rupture usually represents the final stage of a chronically diseased artery, most commonly the femoral or popliteal artery. If native artery thrombosis occurs in the absence of a preexisting stenosis, a thorough search for a hypercoagulable state or undetected atrial fibrillation should be undertaken. A vascular ultrasound may reveal thrombosis of a popliteal aneurysm presenting as acute limb ischemia.

Chronic Limb Ischemia

Lower extremity peripheral artery disease may be manifest as either chronic stable disease[2] or as critical limb ischemia.[3] Peripheral arterial disease is most commonly caused by atherosclerosis, but it also may be caused by thromboembolism, inflammatory disease, trauma, aneurysmal disease, adventitial cysts, entrapment syndromes, or congenital abnormalities. Aneurysms may be associated with atherosclerosis, or they may be caused by underlying hereditary (familial) or acquired (e.g., smoking or trauma) causes.

Patients with critical limb ischemia have inadequate blood flow to sustain viability in the distal tissue bed. Critical limb ischemia is most often caused by atherosclerosis, but it also can be caused by atheroembolic or thromboembolic disease, vasculitis, in situ thrombosis related to hypercoagulable states, thromboangiitis obliterans, cystic adventitial disease, popliteal entrapment, or trauma. Patients presenting with critical limb ischemia typically have multisegment disease along the length of the limb.

Inflammation plays a fundamental role in the development and progression of atherosclerosis. Elevated levels of C-reactive protein (CRP) are strongly associated with the development of peripheral arterial disease. Markers of inflammation such as interleukin-6, tumor necrosis factor-α, CRP, and platelet activation are increased compared with normal subjects.

No specific genetic markers have been confirmed for peripheral arterial disease, although one study identified a linkage on chromosome 1p. The proportion of low ABIs attributable to heritability is estimated at 20%. Concordance rates among twins are about 33% for monozygotic pairs and about 31% for dizygotic pairs, suggesting a limited role for heritability. Taken together, these data suggest a modest but significant heritability factor for peripheral arterial disease.

CLINICAL MANIFESTATIONS

Acute Limb Ischemia

A patient with acute limb ischemia presents with a cool, painful extremity (Table 65-2). Typically, the major muscle groups below the level of obstruction are symptomatic. The absence of a pulse may help localize the site of occlusion, but pulses may be normal in cases of microemboli or cholesterol emboli (Chapter 66). Venous and capillary filling is an indicator of the severity of acute limb ischemia. The leg should be carefully examined for color and temperature abnormalities. Pallor is seen early on, but with time, cyanosis is common. Poikilothermia, or coolness, is an important finding, particularly if the opposite limb is warm. A transition level for color and temperature changes, which is often clinically obvious, should be correlated with the pulses and denoted as a baseline reference at the initial examination for comparison with subsequent examinations.

Sensory changes include numbness and paresthesias. Paralysis indicates that ischemia had advanced to jeopardize the survival of the limb unless the patient undergoes urgent revascularization. Any motor deficit indicates tissue anoxia and implies a very poor prognosis. Motor deficits progress from distal to more proximal muscle groups, so early motor weakness is seen in the intrinsic foot muscles. Complete motor paralysis is a late symptom that suggests irreversible injury. With irreversible ischemia, paralysis progresses to rigor.

TABLE 65-3 FONTAINE'S AND RUTHERFORD'S CLINICAL CLASSIFICATIONS OF CHRONIC LOWER LIMB ISCHEMIA

FONTAINE		*RUTHERFORD*		
STAGE	**CLINICAL**	**GRADE**	**CATEGORY**	**CLINICAL**
I	Asymptomatic	0	0	Asymptomatic
IIa	Mild claudication	I	1	Mild claudication
IIb	Moderate to severe claudication	I	2	Moderate claudication
		I	3	Severe claudication
III	Rest pain	II	4	Rest pain
IV	Ulceration or gangrene	III	5	Minor tissue loss
		IV	6	Ulceration or gangrene

Adapted from Norgren L, Hiatt WR, Dormandy JA, et al. Inter-society consensus for the management of peripheral arterial disease (TASC II). *Eur J Vasc Endovasc Surg.* 2007;33(Suppl):S1-S75.

Chronic Stable Lower Limb Ischemia

Among patients with chronic stable lower extremity peripheral arterial disease, 50% of patients are asymptomatic despite abnormal pulse examinations, the presence of a vascular bruit, or an abnormal ABI (see Fig. 65-1). About 40% of patients have atypical symptoms (e.g., leg tiredness or fatigue), and only about 10% of patients have classic symptoms of intermittent claudication.

Claudication is defined as exertional discomfort, relieved with rest, in specific muscle groups at risk for ischemia during exercise (Table 65-3). Symptoms usually begin one segment below the level of the arterial narrowing. For example, whereas vascular obstructions (occlusions or stenoses) of the iliac vessels typically cause hip, thigh, and calf pain, femoral and popliteal artery obstructions typically cause symptoms in the calf and foot muscles. Claudication, which is a specific vascular syndrome, must be distinguished from other conditions that cause exertional leg pain, which have been termed *pseudoclaudication* (Table 65-4).

Symptoms in individual patients are remarkably variable despite similar degrees of vascular stenosis, in part owing to collateral vessel formation. A patient with superficial femoral artery occlusion but robust collateral formation via the deep femoral artery and geniculate collaterals, which supply blood to the infrapopliteal vessels, may have minimal or no symptoms. Another patient with similar anatomy but poor collaterals may have severe functional limitation.

Chronic Critical Lower Limb Ischemia

Critical limb ischemia, which develops in about 10% of all patients with peripheral arterial disease, presents as resting limb pain, nonhealing lower extremity ulcers, or gangrene (see Table 65-3). These patients' limbs are in jeopardy, and even the most minor trauma from a poorly fitting shoe or a carelessly clipped toenail may cause a nonhealing wound or infection that leads to amputation. Critical limb ischemia can be exacerbated by conditions that reduce blood flow to the microvascular bed, such as diabetes; severe low cardiac output states; and, rarely, vasospastic diseases.

DIAGNOSIS

Acute Limb Ischemia

In patients with acute limb ischemia, the history and physical examination are the most important steps, not only for assessing the cause and severity of ischemia but also for determining the diagnostic and therapeutic path. Upon

TABLE 65-2 CLINICAL CATEGORIES OF ACUTE LIMB ISCHEMIA

CATEGORY	DESCRIPTION	SENSORY LOSS	MUSCLE WEAKNESS	ARTERIAL DOPPLER	VENOUS DOPPLER
I. Viable	Not immediately threatened	None	None	Audible	Audible
IIa. Threatened marginally	Salvageable if promptly treated	Minimal or none	None	Inaudible	Audible
IIb. Threatened immediately	Salvageable if immediately treated	More than toes, associated with rest pain	Mild to moderate	Inaudible	Audible
III. Irreversible	Major tissue loss inevitable	Profound, anesthetic	Profound, paralysis, rigor	Inaudible	Inaudible

Adapted from Rutherford RB, Baker JD, Ernst C, et al. Recommended standards for reports dealing with lower extremity ischemia: revised version. *J Vasc Surg.* 1997;26:517-538.

TABLE 65-4 DIFFERENTIATION OF TRUE CLAUDICATION FROM PSEUDOCLAUDICATION

	INTERMITTENT CLAUDICATION	SPINAL STENOSIS	ARTHRITIS	VENOUS CONGESTION	COMPARTMENT SYNDROME
Character of discomfort	Cramping, tightness, or tiredness	Same as claudication or tingling, weakness, clumsiness	Aching	Tightness, bursting pain	Tightness, bursting pain
Location of discomfort	Buttock, hip, thigh, calf, foot	Buttock, hip, thigh	Hip, knee	Groin, thigh	Calf
Exercise-induced discomfort	Yes	Variable	Variable	After walking	Excessive exercise
Walking distance to discomfort	Reproducible	Variable	Variable	Variable	Excessive exercise
Occurs with standing	No	Yes	Yes, but positional	Yes, but positional	Yes, but positional
Relief of discomfort	Rapid relief with rest	Relief with sitting or changing position	Slow relief with avoidance of weight bearing	Slow relief with leg elevation	Slow relief with leg elevation
Other	Associated with atherosclerosis and decreased pulses	History of lower back problems	Discomfort at joint	History of deep vein thrombosis, signs of venous congestion	Typical in athletes

From White C. Intermittent claudication. *N Engl J Med*. 2007;356:1241-1250.

completion of the history and physical examination, the physician should be able to answer the following questions about the severity of acute limb ischemia: Is the limb viable? Is the limb's viability immediately threatened? Are there already irreversible changes that may preclude salvage of the limb? Three findings that help differentiate "threatened" from "viable" extremities are the presence of persistent pain, sensory loss, and muscle weakness.

Chronic Limb Ischemia

The clinical severity of chronic stable and chronic critical limb ischemia can be semiquantitatively assessed using either the Fontaine or the Rutherford classification (see Table 65-3). The clinician must distinguish intermittent claudication from nonvascular causes that may mimic claudication (i.e., pseudoclaudication), such as neurogenic pain from spinal stenosis or nerve root compression (Chapter 369), musculoskeletal or arthritic pain, or discomfort from venous congestion or a compartment syndrome (see Table 65-4). A typical history of claudication has a low sensitivity but a high specificity for peripheral arterial disease.

Patients presenting with peripheral arterial disease should be assessed for atherosclerotic risk factors (blood pressure, serum lipid and glucose levels, renal function) and undergo a complete vascular physical examination with their shoes and socks removed. A diminished palpable peripheral pulse is insufficiently sensitive to exclude the diagnosis, so measurement of the ABI (see Fig. 65-1) is required.[4] ABI results should be uniformly reported, with noncompressible values defined as greater than 1.40, normal values defined as 1.00 to 1.40, borderline values as 0.91 to 0.99, and abnormal values as 0.90 or less.[5]

Imaging

Duplex imaging combines ultrasound imaging and Doppler blood velocity measurements to localize vascular obstructions and estimate lesion severity. The sensitivity and specificity of duplex ultrasonography for the diagnosis of a 50% stenosis or greater in the lower extremity is 90% or higher.

Computed tomography angiography (CTA) and magnetic resonance angiography (MRA) offer cross-sectional images that can be reconstructed into a three-dimensional angiogram (Fig. 65-2). Whereas CTA requires iodinated intravenous contrast material and ionizing radiation, MRA uses gadolinium contrast and does not expose the patient to ionizing radiation but cannot be used in patients with ferromagnetic metallic implants such as pacemakers or defibrillators. The major toxicity of gadolinium is a rare but potentially debilitating systemic disorder called nephrogenic systemic fibrosis or nephrogenic sclerosing dermopathy (Chapter 246); a glomerular filtration rate of 60 mL/minute or less is a risk factor.

An advantage of CTA over MRA is its ability to visualize metallic stents and stent grafts (Fig. 65-3). CTA requires only about one-fourth the radiation required for invasive digital angiography, and it can be performed more quickly and with less pretreatment planning than MRA. Vascular calcification may be a source of artifact with CTA but is inconsequential with MRA. MRA tends to overestimate lesions at the ostia of arteries owing to turbulent flow.

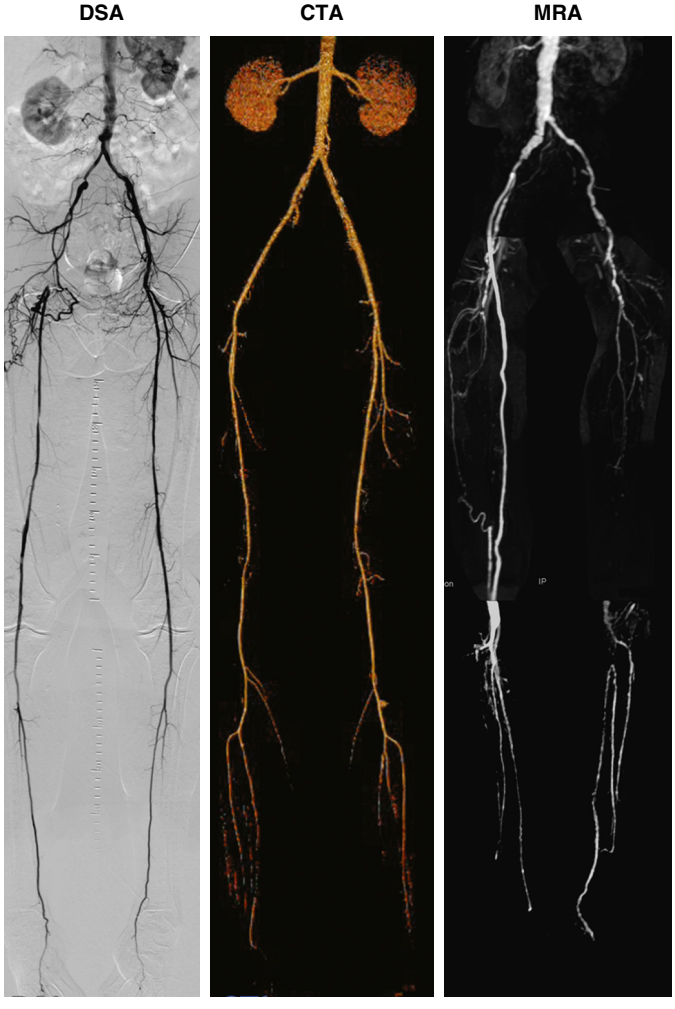

FIGURE 65-2. **Aortography with distal run-off in three different patients by three different methods: digital subtraction angiography (DSA), computed tomography angiography (CTA), and magnetic resonance angiography (MRA).** (From White C. Intermittent claudication. *N Engl J Med*. 2007;356:1241-1250.)

Invasive digital subtraction angiography remains the "gold standard" for the diagnosis and evaluation of peripheral arterial disease despite the need for iodinated contrast material and the exposure to ionizing radiation. Invasive angiographic procedures (Chapter 59) are associated with a relatively small but nontrivial rate of complications, including severe contrast allergy in 0.1%, access-related bleeding complications, and contrast-induced nephropathy.

FIGURE 65-3. Pre- and postprocedural angiograms in a patient with peripheral arterial disease. A, Baseline angiogram of left leg showing occlusion (arrowheads) of the femoral-popliteal segment. B, Post-treatment angiogram after balloon angioplasty and stent placement. C, More than 5 years later, the patient returns with claudication and a reduced ankle-brachial index. Follow-up computed tomography angiogram shows narrowing of the superficial femoral artery between the two stents. D, Final angiogram following balloon angioplasty and stent placement.

TREATMENT

The primary treatment of patients with atherosclerotic lower extremity peripheral arterial disease is guideline-directed medical therapy to reduce the patient's risk for life-threatening cardiovascular complications of atherosclerosis.[6,7] Structured exercise therapy with or without revascularization strategies improves functional status such as walking distance.[A1] Revascularization strategies to improve walking distance and avoid amputation have shifted from open surgical approaches to percutaneous, catheter-based endovascular treatments because of the relative safety, success, and durability of stenting and drug-coated balloons.

Acute Limb Ischemia

Patients with irreversible limb ischemia (nonviable limb) should not undergo angiography and should be scheduled for amputation (Fig. 65-4). All other patients with acute limb ischemia should undergo emergent angiography to define the culprit lesion and to treat it endovascularly if possible.

The options for prompt revascularization include (1) endovascular therapies, with intra-arterial thrombolysis (e.g., recombinant tissue plasminogen activator 0.05 to 0.1 mg/kg/hr intra-arterially) and/or catheter-based thrombectomy and stenting, or (2) open surgical thrombectomy with or without arterial bypass. In general, endovascular therapy is recommended for patients with an onset of acute symptoms less than 14 days earlier, and surgical revascularization is recommended for patients with a duration of symptoms longer than 14 days.

Chronic Lower Limb Ischemia

The approach to patients with claudication is directed at both the limb disease itself (preserving the limb and improving walking distance), as well as to reducing the patient's risk for life-threatening cardiovascular complications of atherosclerosis (Fig. 65-5). Risk factor modification (e.g., aggressive treatment of elevated LDL cholesterol levels [Chapter 190] and blood pressure [Chapter 64], as well as smoking cessation [Chapter 363]), an exercise prescription, antiplatelet agents (Chapter 70), and medical therapy to reduce claudication are the basic elements of treating chronic stable peripheral arterial disease[8] (Fig. 65-5).

Risk Factor Modification

Patients with known peripheral arterial disease should be encouraged to modify or eliminate atherosclerotic risk factors such as diabetes (Chapter 210), tobacco use (Chapter 363), hyperlipidemia (Chapter 190), and hypertension (Chapter 64) and to exercise regularly (Chapter 14).[9]

Patients who are smokers or former smokers should be asked about their status of tobacco use at every visit. Smokers should receive counseling, usually be offered pharmacotherapy (e.g., nicotine replacement therapy, sometimes with varenicline or bupropion), and be considered for referral to a smoking cessation program (Chapter 363). For patients with severe peripheral arterial disease and elevated CRP levels, statin therapy, and especially high-intensity therapy to reduce LDL cholesterol levels to 70 mg/dl or lower, reduces the risk of both amputation and death. In patients who have peripheral arterial disease and are already on statin therapy, the proprotein convertase subtilisin/kexin type 9 (PCSK9) inhibitors further reduce LDL cholesterol levels, cardiovascular events, and the risk of major adverse limb events.[A2] Blood pressure control is very important, especially in patients with coexisting diabetes. β-Blockers are effective antihypertensive therapy and are not contraindicated in peripheral arterial disease.

Exercise Therapy

Patients should be reassured that exercising, even though it may precipitate their claudication symptoms, is not harmful and is the preferred initial treatment.[10] A meta-analysis comparing supervised with unsupervised exercise therapy demonstrated superior improvement in claudication with supervised exercise,[A3] but home-based exercise does not appear to be as useful even if combined with a wearable activity monitor and telephone coaching.[A4,A5] Improvement in walking distance often can be achieved with pharmacologic management; discontinuation of tobacco use; and a regular, supervised exercise program. For example, a randomized trial of patients with aortoiliac peripheral arterial disease who underwent a supervised exercise program showed greater improvement in walking performance compared with those who underwent primary stent therapy or home walking with cilostazol.

Antiplatelet and Antithrombotic Therapy

Antiplatelet therapy with aspirin (usually 75 to 325 mg/day) has an established role in the secondary prevention of cardiovascular events in all patients with peripheral arterial disease because they are at high risk of MI, stroke, and vascular death, whether they are being managed medically, have had prior endovascular or surgical revascularization, or have had prior amputation. The addition of low-dose rivaroxaban (2.5 mg twice daily) to aspirin (100 mg daily) can further reduce major cardiovascular events, limb events,[A6] and all-cause mortality,[A7,A8] despite an increase in bleeding events.[A9]

The thienopyridines, such as clopidogrel (usually 75 mg/day), are indicated only if aspirin is not tolerated, based on clopidogrel's efficacy compared with aspirin among patients with peripheral arterial disease. Recent evidence suggests that another thienopyridine, ticagrelor (usually 90 or 60 mg twice daily), is not more effective than clopidogrel as monotherapy for reducing cardiovascular events,[A10] but ticagrelor on a background of low-dose aspirin therapy does reduce major cardiac events compared with aspirin alone in patients who have also had an MI.[A11] A promising novel protease-activated receptor-1 antagonist, vorapaxar, may significantly reduce the incidence acute limb ischemia and the need for revascularization in patients with peripheral arterial disease.[A12]

Pharmacology

Cilostazol, a phosphodiesterase inhibitor, at 50 to 100 mg twice daily, improves maximal walking distance by 40 to 50% compared with placebo[A13] and has been shown to reduce restenosis after femoral artery revascularization.[A14] Cilostazol is contraindicated in patients with heart failure. Oral vasodilating prostaglandins, vitamin E, and chelation therapy with ethylenediaminetetraacetic acid (EDTA) have not been effective in improving either symptoms or walking distance.

Revascularization

The decision to perform an endovascular or surgical revascularization procedure for the relief of claudication in a patient with chronic stable lower limb ischemia is based upon a risk-to-benefit assessment that weighs the patient's disability and discomfort against the estimated short- and long-term benefits and risks of the procedure. Because very few patients with claudication are in danger of losing their limbs, the primary goal of revascularization is durable functional improvement, not limb salvage. Patients selected for revascularization to relieve symptoms of intermittent claudication should have significant lifestyle limitation or be unable to work and should have failed to respond to medications and to a structured exercise program.[11,12]

Superficial femoral and popliteal artery stenoses or occlusions (E-Fig. 65-1) are commonly associated with calf claudication. Revascularization with endovascular techniques or surgery is indicated for the relief of vocational or lifestyle-limiting claudication in patients who have failed to respond to exercise and pharmacologic therapy.

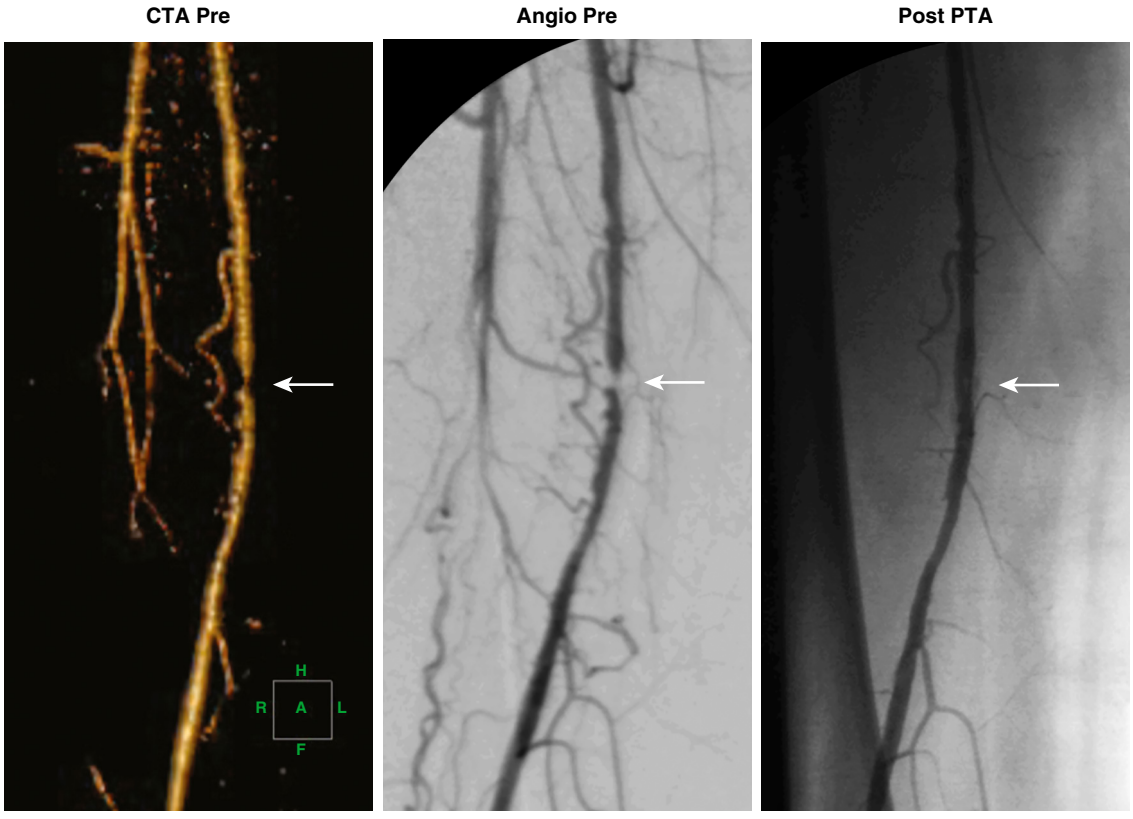

E-FIGURE 65-1. **Discrete stenosis *(arrows)* of the left superficial femoral artery seen on computed tomography angiography (CTA Pre; *left*), digital subtraction angiography (Angio Pre; *middle*), and digital angiography after percutaneous transluminal angioplasty (Post PTA; *right*).** (From White C. Intermittent claudication. *N Engl J Med*. 2007;356:1241-1250.)

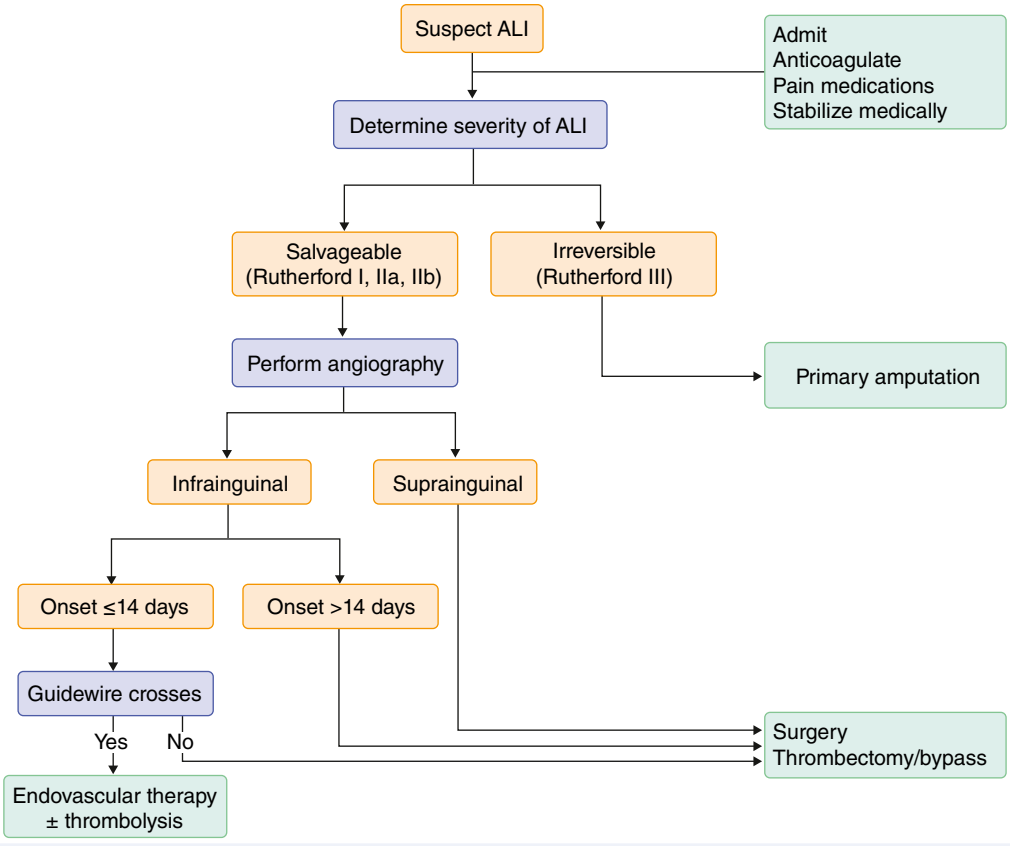

FIGURE 65-4. Treatment algorithm for acute limb ischemia (ALI). (Modified from Gray BH, Conte MS, Dake MD, et al. Atherosclerotic Peripheral Vascular Disease Symposium II: lower-extremity revascularization: state of the art. *Circulation*. 2008;118:2864-2872.)

In patients with claudication, the combination of a structured exercise program plus balloon angioplasty is superior to supervised exercise therapy alone for improving the ABI, walking distance and quality of life.[A15] Randomized trials comparing surgery with angioplasty show similar rates of mortality, amputation, and patency at 4 years in patients with lower extremity ischemia.[A16] Percutaneous therapy is preferred in amenable lesions because of its lower periprocedural mortality and morbidity. Angioplasty is more cost effective than surgery if the expected 5-year patency rate of the treated vessel is 30% or greater.

Drug-eluting stents and drug-coated balloons,[13] which appear to be equivalent to each other,[A17] safely provide a superior and more durable benefit for claudication caused by femoral-popliteal disease than do angioplasty and stenting alone.[A18,A19] Adjunctive angioplasty devices such as atherectomy, cryotherapy, and the cutting balloon have not been meaningfully tested in any population, and there are few data to support their use.

For chronic critical lower limb ischemia, the therapeutic goal is urgent revascularization to reestablish pulsatile, straight-line flow to the distal extremity and to reduce the rate of amputation. Surgical bypass using the great saphenous vein provides the best outcomes, but endovascular therapy is as good as open surgery if an adequate saphenous vein is not available. It also is reasonable to attempt a percutaneous therapy first if a patient is a candidate for either surgery or angioplasty, particularly if the patient's life expectancy is less than 2 years. In tibial arteries, coronary drug-eluting stents and drug-coated balloons are superior to conventional therapies,[A20,A21] but the two approaches may produce similar results for the treatment of critical limb ischemia in below-the-knee arteries.[A22]

Nevertheless, primary amputation is indicated in patients who have extensive necrosis or infectious gangrene with rest pain, are not ambulatory, and are not candidates for revascularization. Cellular therapies and growth factor therapy are being investigated for limb salvage, but none have yet proven clinically effective.

PROGNOSIS

Peripheral arterial disease is a major cause of acute and chronic illness associated with impaired functional capacity, reduced quality of life, limb loss, and increased risk of death (E-Fig. 65-2). About 18% of patients who undergo peripheral arterial revascularization have an unplanned readmission within 30 days.[14]

Approximately two thirds of patients with peripheral arterial disease have at least one severely diseased coronary artery, and up to one quarter of patients have significant carotid artery stenosis. Consequently, patients with peripheral arterial disease face an increased risk of cardiovascular ischemic events such as MI, ischemic stroke, and death. It is estimated that coronary and cerebrovascular adverse events occur two- to four-fold more commonly than do limb adverse events in patients with peripheral arterial disease. Outcomes are improved when guideline-recommended therapy is followed.

The annual mortality rate for patients with peripheral arterial disease is about 5%, but it is higher for patients with severe disease. For example, the estimated 1-year mortality rate for patients with critical limb ischemia is 25%, but this can climb to 45% for patients requiring amputation; in contrast, the annual mortality rate for patients with intermittent claudication is only 1 to 2%. For patients presenting with acute limb ischemia, the 30-day amputation rate is as high as 40%, and mortality rates up to 30% have been reported.

Patients with lower extremity claudication should be reassured that the risk of limb loss is low. Moreover, a history of claudication by itself only slightly increases the risk of amputation after 10 years. However, a reduced ABI and diabetes mellitus are associated with the development of ischemic rest pain and ischemic ulceration, which may lead to limb loss. Among patients with peripheral arterial disease, those who have diabetes are 15 times more likely to have an amputation than are patients without diabetes, whose annual amputation rate is less than 1%.

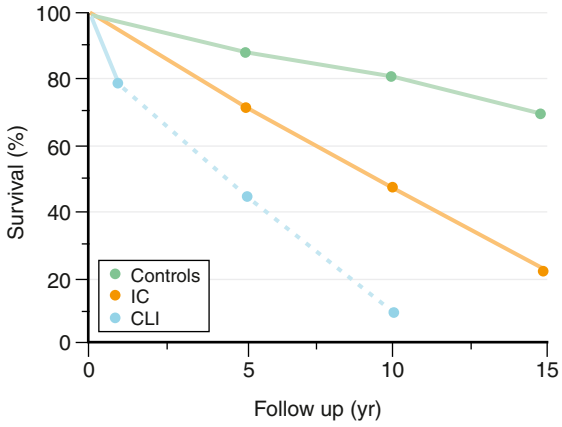

E-FIGURE 65-2. Survival curve of patients with intermittent claudication (IC) versus critical limb ischemia (CLI). (Modified from Norgren L, Hiatt WR, Dormandy JA, et al. Inter-society consensus for the management of peripheral arterial disease [TASC II]. *Eur J Vasc Endovasc Surg*. 2007;33[Suppl]:S1-S75.)

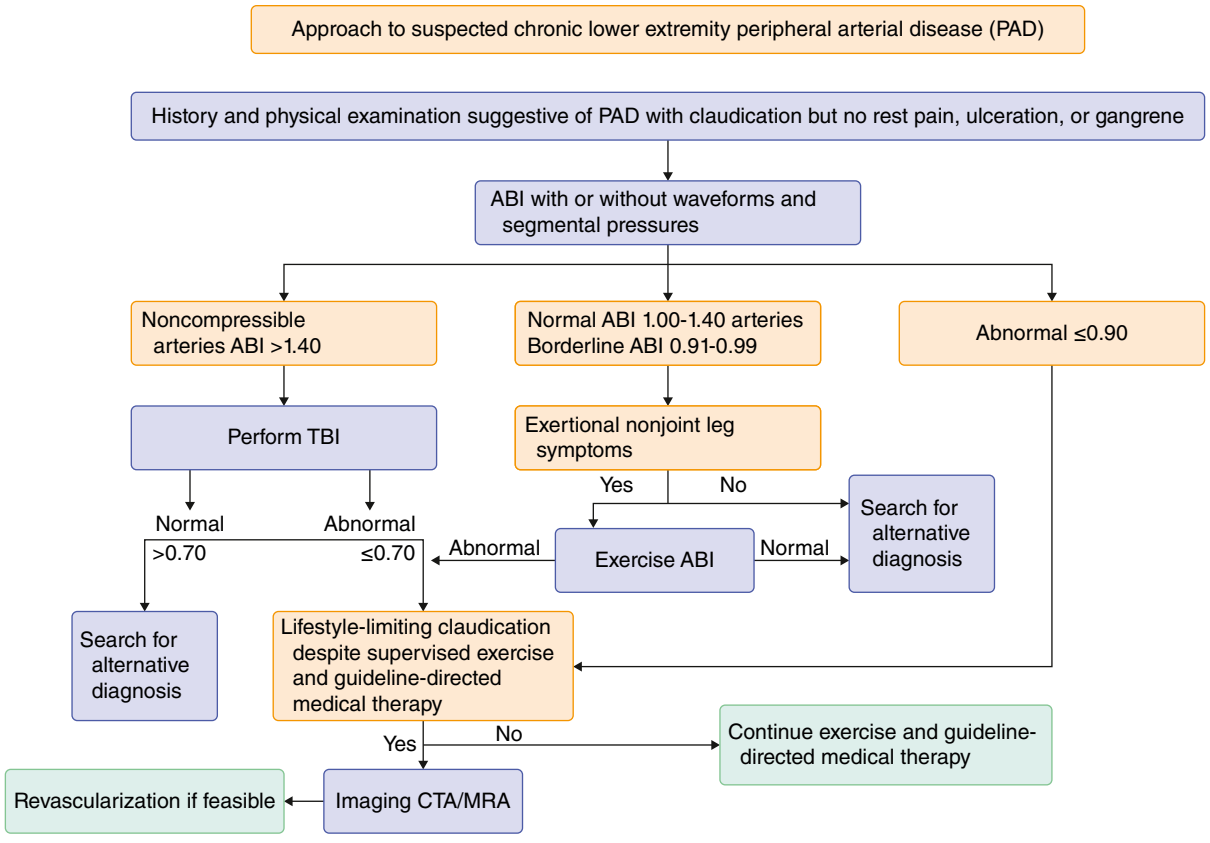

FIGURE 65-5. Approach to suspected chronic lower extremity peripheral arterial disease. ABI = ankle brachial index; CTA = computed tomographic angiography; MRA = magnetic resonance angiography; TBI = toe brachial index.

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66 OTHER PERIPHERAL ARTERIAL DISEASES

JOHN R. BARTHOLOMEW

POPLITEAL ARTERY ENTRAPMENT SYNDROME

Popliteal artery entrapment syndrome, which is a cause of intermittent claudication in young and often athletic patients, can be anatomic or functional. Anatomic popliteal artery entrapment syndrome results from extrinsic compression on the popliteal artery by muscles or ligaments within or surrounding the popliteal fossa. In a functional version of popliteal artery entrapment, the medial head of the gastrocnemius, plantaris, or soleus muscle becomes hypertrophied and occludes the popliteal artery without a true fixed anatomic abnormality.[1] The popliteal vein and nerve can also can be involved.

Anatomic evidence of entrapment can be found on physical examination or imaging performed for unrelated reasons in up to 4% of apparently normal individuals and imaging evidence for popliteal artery compression with provocative maneuvers in as many of 80% of asymptomatic individuals. Clinically evident popliteal artery entrapment syndrome is rare, with one study showing a prevalence of approximately 0.16% among military recruits.

CLINICAL MANIFESTATIONS AND DIAGNOSIS

Symptoms of popliteal artery entrapment syndrome include exertional limb pain, cold feet after exercise, ischemic rest pain, and even tissue necrosis if undiagnosed cases progress to arterial degeneration with thromboembolization. Entrapment of the popliteal vein results in swelling and discoloration of the calf, heaviness, varicosities, nocturnal or exertional calf cramping, and even deep vein thrombosis (Chapter 68). Nerve involvement can cause paresthesias.

The diagnosis of popliteal artery entrapment syndrome is suggested by demonstration of popliteal artery compression on active pedal plantar flexion against resistance. This compression is manifested by a decrease in the intensity of the pedal arterial pulse on physical examination and loss of the continuous-wave Doppler signal over the pedal arteries. Pulse volume recordings and segmental limb pressures should be measured at rest with the knee extended and the ankle in the neutral, dorsiflexed, and plantar-flexed positions. Exercise treadmill studies also may demonstrate diminished limb arterial pressure after exercise in the symptomatic limb. Arterial duplex ultrasonography, dynamic computed tomographic (CT) arteriography, or magnetic resonance (MR) arteriography may confirm the diagnosis, whereas CT or MR arteriography also define the structure that causes the entrapment. The differential diagnosis includes compartment syndrome, stress fracture, cystic adventitial disease, and arterial embolism.

TREATMENT AND PROGNOSIS

Treatment of structural popliteal artery entrapment is largely surgical, with relief of the entrapment by resection or translocation of the compressing elements. If popliteal artery entrapment syndrome is not identified until after the artery has been injured, arterial reconstruction or surgical bypass, ideally with a venous autologous graft, may be required. In functional popliteal artery entrapment, exertional symptoms may respond to injection of botulinum toxin A into the popliteal space. In patients whose functional entrapment symptoms persist, resection or translocation of the medial head of the gastrocnemius muscle is recommended. If therapy is offered early in the course of the syndrome, patients may expect full recovery with complete resolution of symptoms.

CYSTIC ADVENTITIAL DISEASE OF THE LOWER EXTREMITY ARTERIES

In cystic adventitial disease, a mucinous cyst develops within the adventitial layers of the arterial wall and encroaches on the arterial lumen.[2] Cystic adventitial disease most commonly affects the popliteal artery, thereby resulting in intermittent claudication, classically in middle-aged men. However, the external iliac, femoral, axillary, brachial radial, and ulnar arteries can be involved. The exact cause of cystic adventitial disease is unknown.

CLINICAL MANIFESTATIONS AND DIAGNOSIS

Intermittent claudication is the most common symptom of cystic adventitial disease. However, limb discomfort may persist for up to 20 minutes after the cessation of activity, unlike the classic relief of limb pain on cessation of activity in atherosclerotic peripheral artery disease (Chapter 65). The limb symptoms of cystic adventitial disease also tend to be inconsistent, often reappearing without obvious precipitants and resolving without an obvious explanation. Acute limb ischemia (Chapter 65) secondary to arterial compression and thrombosis also can occur.

The diagnosis is suspected when pedal pulses disappear with passive knee flexion and occasionally with exercise. However, cystic adventitial disease is most often confirmed with MR angiography. By comparison, arteriography may demonstrate only compression of the arterial lumen without identifying the cyst. The finding of eccentric compression of the popliteal arterial lumen, known as the scimitar sign, is considered pathognomonic for cystic adventitial disease (Fig. 66-1).

TREATMENT AND PROGNOSIS

Image-guided aspiration of the cyst may be attempted, but recurrence is likely. Balloon angioplasty is unlikely to be an effective and durable therapy and is not advised. Surgical resection of the cyst, potentially with placement of a venous interposition graft, is the primary therapy. When this condition is identified early, patients may anticipate complete resolution of claudication after resection of the cyst.

ENDOFIBROSIS OF THE ILIAC ARTERY

Endofibrosis of the iliac artery represents stenosis of the external iliac artery, thought to be due to repetitive trauma in highly functioning and competitive athletes.[3] This condition, which is increasingly being diagnosed, commonly occurs in cyclists, football players, or long-distance runners 30 to 50 years of age.

Endofibrosis results from intimal hyperplasia and fibrosis of the arterial wall. Smooth muscle cell proliferation and medial and intimal proliferation also may occur.

CLINICAL MANIFESTATIONS AND DIAGNOSIS

Symptoms include exercise-interfering, intermittent thigh claudication and leg weakness accompanied by a sensation of swelling or paresthesia in the proximal lower limb at the time of maximal exercise. Physical examination may be normal at rest, although a bruit may be heard over the ipsilateral pelvic fossa or inguinal region.

Diagnostic imaging includes preexercise and postexercise Doppler ankle pressure measurements at the time of maximal, symptom-limiting treadmill exercise. Ultrasound imaging and contrast angiography, preferably when the leg is flexed at the hip in the cycling position, will reveal concentric stenosis, often with lengthening of the affected iliac artery. Intravascular ultrasound and intra-arterial translesional pressure gradients may be helpful.

FIGURE 66-1. The finding of eccentric compression of the popliteal artery lumen known as the scimitar sign is considered pathognomonic for cystic adventitial disease.

ABSTRACT

Nonatherosclerotic peripheral arterial diseases are uncommon, often affecting patients who appear otherwise healthy and lack the traditional risk factors for peripheral arterial disease. The manifestations may be subtle and related to environmental factors, thermal factors, other systemic disorders, or medications. Prompt identification of these vascular syndromes will prevent more serious outcomes.

KEYWORDS

peripheral artery entrapment syndrome
cystic adventitial disease
external iliac endofibrosis
thromboangiitis obliterans
fibromuscular dysplasia
atheromatous embolization
livedo reticularis
erythromelalgia
erythema ab igne
Raynaud phenomenon
pernio
frostbite
acrocyanosis

TREATMENT AND PROGNOSIS

The first line of treatment is to avoid activities that aggravate the symptoms. If intervention is required, angioplasty results in high restenosis rates, and endovascular stenting is complicated by the risk of stent fracture. As a result, surgical revascularization with vein patch angioplasty or interposition grafts is the recommended treatment and usually ameliorates the symptoms. With continued trauma to the arterial segment, however, careful surveillance for recurrence is warranted.

FIBROMUSCULAR DYSPLASIA

Fibromuscular dysplasia (Chapter 110) is a noninflammatory, nonatherosclerotic arterial disease that most commonly involves the medial layer of the artery wall and can affect any artery in the body.[4] It is most commonly seen in women 20 to 60 years of age, with a mean age at onset of 52 years but a range of 5 to 83 years. Its true prevalence is unknown, but a series of potential renal donors showed a prevalence as high as almost 4%.

Fibromuscular dysplasia is multifocal in 90% of cases and focal in 10% of cases. Multifocal fibromuscular dysplasia results in the classic "string of beads" appearance on contrast arteriography (Fig. 66-2). Pathology shows alternating segments of thinning and thickening of the arterial media, but the adventitia or intima may be predominantly affected, thereby resulting in an angiographic appearance different from that for medial fibroplasia. Other types of fibromuscular dysplasia include an intimal variant that causes a single focal, weblike stenosis within the affected artery.

CLINICAL MANIFESTATIONS AND DIAGNOSIS

The clinical presentation of patients with fibromuscular dysplasia depends on the arteries involved, and sometimes it may be incidentally discovered without any symptoms when imaging is performed for other reasons. Although most symptoms are related to stenoses, about 20% of patients develop aneurysms, about 25% develop dissections, and rare patients develop occlusions.

The renal arteries are affected in almost 60% of cases (Chapter 110), and the extracranial carotid and vertebral arteries are involved in almost 40% of cases. Not surprisingly, hypertension (Chapter 64) and recurrent headaches (especially migraine type; Chapter 367) represent the two most common signs and symptoms. Less common symptoms and signs include dizziness, pulsatile tinnitus, and cervical bruits. Additional clinical clues include a transient ischemic attack or stroke in a patient under 60 years of age, an aneurysm in an intracranial vessel, subarachnoid hemorrhage, or renal infarction.[5] Fibromuscular dysplasia may occasionally affect the brachial, iliac, femoral, or popliteal arteries, and it also can be associated with spontaneous coronary artery dissection (Chapter 58).[6]

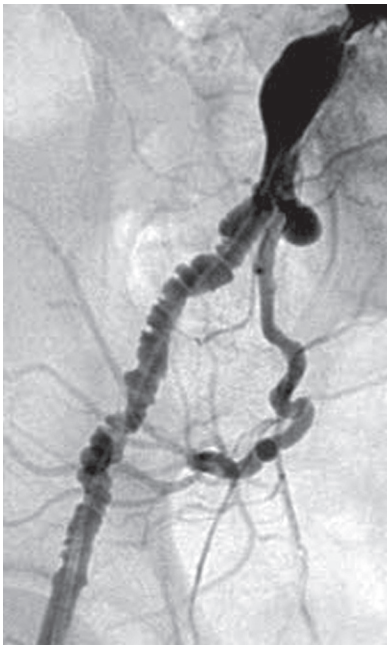

FIGURE 66-2. Angiogram showing a typical "string of beads" pattern, typical of the medial type in fibromuscular dysplasia, in the external iliac artery. Also note the aneurysm proximal to the area of dysplasia. (Courtesy Dr. Jeffrey W. Olin.)

The diagnosis of fibromuscular dysplasia relies on a combination of clinical and imaging findings. Duplex ultrasound, MR angiography, and CT angiography can identify fibromuscular dysplasia and assess possible aneurysms, but contrast angiography and intravascular ultrasound are the best diagnostic tests. Because fibromuscular dysplasia may involve several vascular beds, patients should initially undergo comprehensive MR or CT imaging of their intracranial arteries, the extracranial carotid arteries, the thoracic and abdominal aorta and its branches, and the renal arteries. Nearly 13% of patients have intracranial aneurysms detectable by imaging. If arterial aneurysms or dissections are identified without clear evidence of fibromuscular dysplasia, a genetic collagen disorder should be considered.

TREATMENT AND PROGNOSIS

Treatment of fibromuscular dysplasia depends on the clinical presentation and extent of arterial involvement.[7] Asymptomatic patients are empirically prescribed aspirin. In young patients with sudden onset of hypertension and renal artery fibromuscular dysplasia, percutaneous transluminal angioplasty can cure the hypertension that is often found (Chapter 110). Renal and intracranial artery aneurysms should be followed closely for expansion and may require surgery. The decision about repair is often based on the size of the aneurysm, its rate of expansion, and the presence of associated symptoms. Carotid artery fibromuscular dysplasia is generally treated with antiplatelet therapy (e.g., aspirin 81 to 325 mg/day) or 3 to 6 months of warfarin anticoagulation in the case of carotid artery dissection. Percutaneous transluminal angioplasty is reserved for patients with hemispheric cerebral ischemic symptoms and progressive dissection. Peripheral artery percutaneous transluminal angioplasty is recommended only for patients with symptoms of intermittent claudication.

In general, patients with fibromuscular dysplasia have an excellent outcome. After percutaneous transluminal angioplasty of the renal arteries, approximately one third of patients with hypertension will have normal blood pressures and most others will have substantial improvement. Optimal antiplatelet therapy (e.g., aspirin 81 to 325 mg/day) is recommended for the majority of patients with fibromuscular dysplasia. The most feared complications, which occur in less than 5% of patients, are stroke owing to progressive carotid dissection, rupture of an intracranial arterial aneurysm, or rupture of a visceral artery aneurysm.

THROMBOANGIITIS OBLITERANS (BUERGER DISEASE)

Thromboangiitis obliterans is a nonatherosclerotic, segmental inflammatory disorder that affects small and medium-sized arteries, veins, and nerves, most often but not exclusively of the lower extremities.[8] Thromboangiitis obliterans is typically found in men who are under the age of 50 years and who smoke, chew tobacco, or use cannabis.

Although rarely performed, biopsy of affected digits demonstrates highly cellular inflammatory thrombi with sparing of the artery wall. Thromboangiitis obliterans is one of the few vascular disorders that affects both arteries and veins, so superficial thrombophlebitis can also develop.

CLINICAL MANIFESTATIONS AND DIAGNOSIS

Patients classically present with digital or extremity pain with digital ischemia, distal limb claudication (such as in the arch of the foot or arm), and digital ulcerations (Fig. 66-3). More than 40% of patients have Raynaud phenomenon.

Clinicians must maintain a high degree of clinical suspicion in young smokers with distal extremity ischemia and pain without evidence of atherosclerosis. Many patients will demonstrate an abnormal Allen test, in which one of two of the major arteries to the hand (radial or ulnar) does not fill after the examiner compresses the other artery, as well as absent peripheral arterial pulses. The ankle-brachial index (Chapter 65) is classically abnormal, even though plethysmographic studies demonstrate essentially normal proximal artery circulation. Serologic results show no evidence for inflammatory vasculitis (Chapter 249), and proximal sources of arterial emboli are not found. Contrast arteriography is often needed to demonstrate distal arterial involvement with the absence of atherosclerosis. Segmental arterial occlusions with corkscrew collaterals are commonly found but are not pathognomonic.

TREATMENT AND PROGNOSIS

The cornerstone of treatment is complete abstinence from tobacco (preferably confirmed by urinary testing for cotinine) and cannabis.[9] Patients who cannot abstain commonly have unremitting pain, recurrent tissue necrosis, and the need for progressive limb amputation.

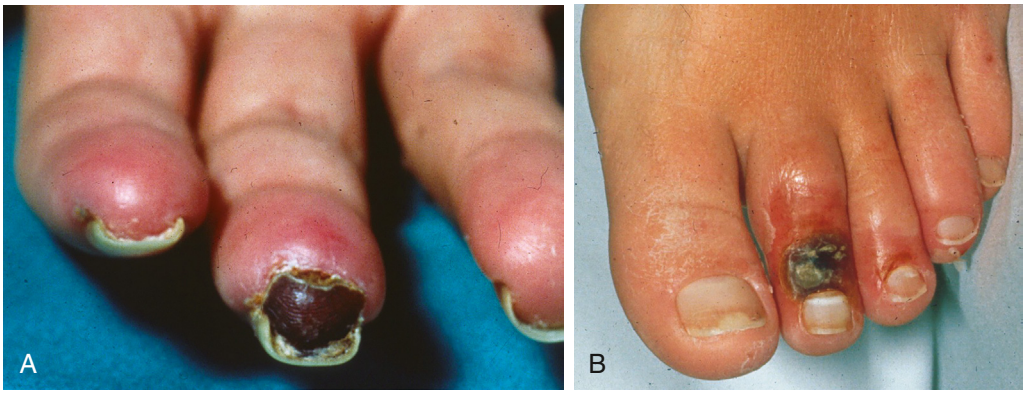

FIGURE 66-3. Buerger disease. Ischemic finger of a young male patient (**A**) and ischemic toe of a 28-year-old woman (**B**) with Buerger disease. (Courtesy Dr. Jeffrey W. Olin.)

Antiplatelet therapy (e.g., aspirin 81 to 325/day) is commonly prescribed, though usually with no more than modest benefit. A 28-day course of the prostacyclin analogue iloprost (1 ng/kg/minute intravenously for 6 hours daily) may be tried off-label by experts to improve pain and accelerate wound healing compared with aspirin or lumbar sympathectomy.[A1] There are no data demonstrating benefit with vasodilators such as calcium-channel antagonists, peripheral α-blockers, or sildenafil. Digital sympathectomy, bosentan, spinal cord stimulators, and intermittent pneumatic compression have all been tried with variable success. Angioplasty may be effective in preserving the limb and preventing amputation,[10,11] with stenting generally reserved for bail-out procedures or for more proximal disease.

LIVEDO RETICULARIS AND LIVEDO RACEMOSA

Livedo reticularis, which typically involves the lower extremities, is an ischemic dermopathy caused by an increased prominence of venous beds owing to obstruction of arterial inflow, venous dilation, or blockage of venous outflow. It is a vasospastic disorder that appears as a violaceous or reddish-blue netlike or mottled discoloration surrounding a pale central area of skin (Fig 66-4).

Primary livedo reticularis is a benign condition exacerbated by cold temperatures, tobacco, or emotional upset, whereas the secondary form, referred to as livedo racemosa (Fig. 66-5), is a pathologic variant seen in association with a number of disorders (Table 66-1). Primary livedo reticularis is commonly found in healthy women during their second to fifth decade of life. The secondary form may be associated with antiphospholipid antibodies (Chapter 67). Livedo reticularis is rare in males, in whom its presence warrants investigation for possible secondary causes such as antiphospholipid syndrome (Chapter 160), other hypercoagulable syndromes (Chapter 67), vasculitis (Chapter 249), and infections.

Livedo reticularis and livedo racemosa have been reported in patients with coronavirus disease 2019 (Chapter 336). In such patients, livedo reticularis lesions are frequently mild and transient, whereas the racemosa form can be associated with an acute coagulopathy.[12]

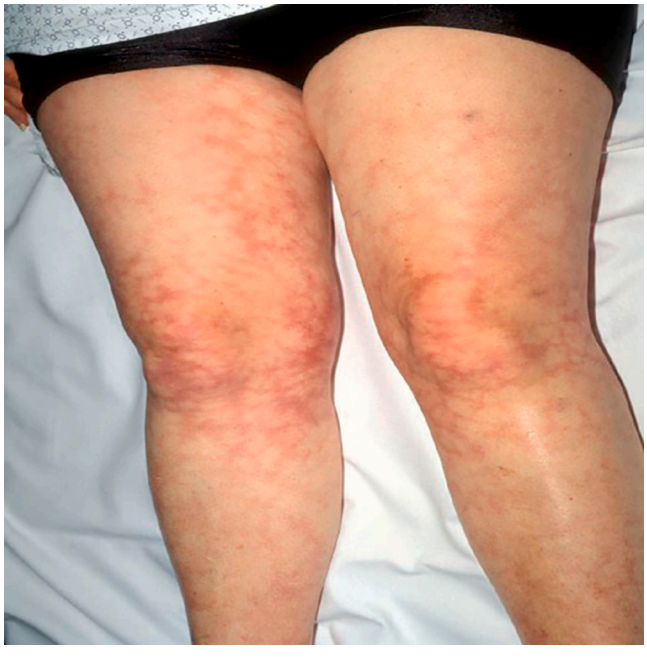

FIGURE 66-4. Livedo reticularis. Livedo reticularis appearing as a violaceous or reddish-blue netlike or mottled discoloration surrounding a pale central area of skin.

FIGURE 66-5. Livedo racemosa. Livedo racemosa with ischemic ulcerations and violaceous, netlike, and broken patterns in a patient who developed atheromatous embolization after cardiac catheterization on the buttocks.

TABLE 66-1 DISORDERS ASSOCIATED WITH LIVEDO RACEMOSA

Polyarteritis nodosa, systemic lupus erythematosus, rheumatoid arthritis, Sjögren syndrome, scleroderma
Atheromatous embolization, atrial myxoma
Antiphospholipid syndrome, Sneddon syndrome
Infections
Polycythemia vera, essential thrombocythemia, cryoglobulinemia, cryofibrinogenemia, cold agglutinin disease
Calciphylaxis, hyperoxaluria
Medications: Amantadine, amphetamines, ergotamines, vasopressors (epinephrine, norepinephrine, dopamine), heparin, minocycline, gemcitabine

CLINICAL MANIFESTATIONS AND DIAGNOSIS

The legs and, to a lesser extent, arms are most commonly involved in primary livedo reticularis, whereas the face, trunk, buttocks, and extremities may be involved with livedo racemosa. The discoloration of livedo reticularis is worsened by dependency and improves with elevation, but livedo racemosa does

not show such postural changes. It is important to differentiate the usually painless, symmetrical, unbroken vessel network of primary livedo reticularis from the frequently painful, irregular, asymmetrical, and broken pattern observed in livedo racemosa.

A thorough history should focus on exacerbating conditions. Laboratory investigation is usually not necessary for the primary form, but specific testing for antiphospholipid antibodies should be performed to diagnose the secondary forms (i.e., circulating lupus anticoagulant, anticardiolipin antibodies) and P and C antineutrophil cytoplasmic antibodies. A skin biopsy may be necessary when serologies are indeterminate and the diagnosis remains unclear. The differential diagnosis includes erythema ab igne, retiform purpura, livedoid vasculopathy (a rare subtype of livedo racemosa), and acrocyanosis.

TREATMENT AND PROGNOSIS

Cold temperatures, tobacco, and stressful conditions should be avoided. Primary livedo reticularis does not require treatment, although calcium-channel blockers (e.g., nifedipine 10 to 20 mg PO every 6 hours or amlodipine 2.5 to 10 mg/day PO) may be beneficial for patients who are uncomfortable with their appearance. Treatment for livedo racemosa should focus on the underlying disorder. Anticoagulants, including warfarin to provide an international normalized ratio of 2.0 to 3.0, antiplatelet therapy (e.g., aspirin 81 to 325 mg/day), or both are recommended for livedo racemosa associated with antiphospholipid syndrome, cerebrovascular disease (Sneddon syndrome), or both. The prognosis is excellent for primary livedo reticularis but depends on the underlying disorder for patients with livedo racemosa.

ATHEROMATOUS EMBOLIZATION

Atheromatous embolization, also known as cholesterol crystal embolization, atheroembolic renal disease, or blue or purple toe syndrome, refers to the showering of multiple small cholesterol crystals or fibrin-platelet aggregates to the extremities or any organ. The exact incidence of atheromatous embolization is unknown, in part because it is often poorly recognized. In unselected autopsy series, the prevalence ranges from 0.18 to 2%, although it is reported to be much higher in individuals who have undergone aortic manipulation, arteriography, or cardiac or vascular procedures. As many as 5 to 10% of all cases of acute renal failure may result from atheroembolism (Chapter 110). Atheromatous embolization is more common in elderly individuals with advanced atherosclerosis but is less commonly diagnosed in Blacks, largely owing to a failure to recognize the classic dermatologic feature because of their skin pigmentation.

Atheromatous embolization usually originates from ulcerated or stenotic atherosclerotic plaques or aneurysms of both large and small arteries. Precipitating factors include arteriography, endovascular procedures (cerebral, coronary, or peripheral), surgery, trauma, or anticoagulation.[13] The risk after a cardiovascular interventional procedure is about 4 per 10,000 patients.[14] Atheroembolism also may occur spontaneously. Light microscopy demonstrates multiple biconvex, needle-shaped cholesterol crystals that lodge in arterioles and result in a foreign body inflammatory response in which polymorphonuclear leukocytes, macrophages, and multinucleated giant cells are observed days to weeks after the initiating event. This process eventually leads to end-organ damage owing to intraluminal obliteration, ischemia, and even often infarction.

CLINICAL MANIFESTATIONS AND DIAGNOSIS

Dermatologic findings involving the lower extremities are the most common clinical presentation (see Fig. 66-5), but atheromatous embolization may be seen in any organ (Table 66-2). Atheromatous embolization is frequently overlooked or misdiagnosed because the signs and symptoms are nonspecific and diverse. Once suspected, the diagnosis usually can be made on clinical grounds alone. The clinical triad of a history of a precipitating event, acute renal failure, and cutaneous or retinal findings should raise suspicion for the diagnosis. In some cases, the definitive diagnosis may require biopsy of the skin, kidney, or gastrointestinal tract. Patients may have elevated markers of inflammation (erythrocyte sedimentation rate, C-reactive protein) or transient eosinophilia. Elevations in amylase, hepatic aminotransferase, blood urea nitrogen, serum creatinine, or serum creatinine kinase levels may be seen with involvement of the pancreas, liver, kidney, or muscle, respectively. The urine is generally nonspecific, but eosinophiluria can be seen.

Invasive diagnostic angiographic procedures should be avoided. Noninvasive procedures, including multidetector CT angiography, MR angiography, or transesophageal echocardiography, may be helpful if they reveal a markedly irregular and shaggy aorta.

TABLE 66-2 CLINICAL MANIFESTATIONS OF ATHEROMATOUS EMBOLIZATION

Skin	Purple or blue toes Gangrenous digits Livedo reticularis or livedo racemosa Petechiae Ulcers, nodules Splinter hemorrhages
Kidney	Uncontrolled hypertension Advanced renal disease End-stage renal disease
Neurologic	Amaurosis fugax Hollenhorst plaque Transient ischemic attack or stroke Confusion, organic brain syndrome Spinal cord infarction
Gastrointestinal	Abdominal pain Diarrhea Gastrointestinal bleeding Ischemic bowel Acute pancreatitis Acute gangrenous cholecystitis
Cardiac	Angina pectoris Myocardial infarction
Constitutional symptoms	Fever Weight loss Malaise, myalgias Anorexia, nausea, vomiting

The differential diagnosis, which depends on the end organ involved, includes contrast-induced nephropathy (Chapters 59 and 106), polyarteritis nodosa (Chapter 249), leukocytoclastic vasculitis (Chapters 249 and 406), cryoglobulinemia (Chapter 173), antiphospholipid syndrome (Chapter 67), and thrombotic thrombocytopenia purpura (Chapter 158). An underlying malignancy must be considered in patients who present with constitutional symptoms such as anorexia and weight loss. Cardiac sources such as nonbacterial thrombotic endocarditis (Chapter 61), infective endocarditis (Chapter 61), or atrial myxoma (Chapter 47) should be excluded.

TREATMENT AND PROGNOSIS

The most important aspect of treatment is prevention and avoidance of recurrent atheroembolism. Smoking cessation (Chapter 363) and aggressive control of hypertension (Chapter 64), diabetes (Chapter 210), and hyperlipidemia (Chapter 190) should be instituted to prevent progression of the disease. In the absence of data from randomized trials, therapy is directed toward prescribing aggressive lipid-lowering treatment, avoiding recurrent embolization, removing the source of the atheroemboli, and providing symptomatic care of the end organ(s) involved.

Patients with ischemic ulcers require pain control and local wound care. Statins (e.g., atorvastatin 10 to 80 mg/day or rosuvastatin 10 to 40 mg/day to obtain optimal low-density lipoprotein cholesterol levels [Chapter 190]) may provide plaque-stabilizing activity. Evolocumab, a human monoclonal antibody that targets anti-protein convertase subtilisin/kexin type 9 (PCSK9) antibody, may be helpful.[15] Other pharmacologic approaches—including antiplatelet agents (aspirin or clopidogrel), calcium-channel blockers (e.g., nifedipine 10 to 20 mg PO every 6 hours or amlodipine 2.5 to 10 mg/day PO), angiotensin-converting enzyme inhibitors (e.g., lisinopril 20 to 30 mg per day or enalapril 10 to 40 mg per day), or angiotensin receptor blockers (e.g., valsartan 80 to 160 mg daily or losartan 50 mg per day), cilostazol (100 mg PO every 12 hours), pentoxifylline (400 mg PO every 8 hours), and intravenous prostaglandins—have been tried with varying degrees of success. The use of anticoagulants is controversial because of concerns that they may lead to plaque instability, and data do not support the use of corticosteroids.

Nonpharmacologic approaches, including chemical or surgical sympathectomy, a spinal cord stimulator, and arterial flow pumps, may help control pain. Endovascular therapies (angioplasty, stent placement, atherectomy, or covered stent grafts and the use of embolic protective devices) may help prevent future embolic events, but studies are limited and further clinical evaluation is needed. Surgical therapies, including thromboendarterectomy, aortobiiliac or aortobifemoral bypass grafting, or extra-anatomic reconstruction, may be necessary to eliminate the embolic source and reduce further embolization.

Patients with advanced atherosclerosis and atheromatous embolization have a poor prognosis. The estimated 1-year mortality rate is approximately 15% even with optimal medical care.

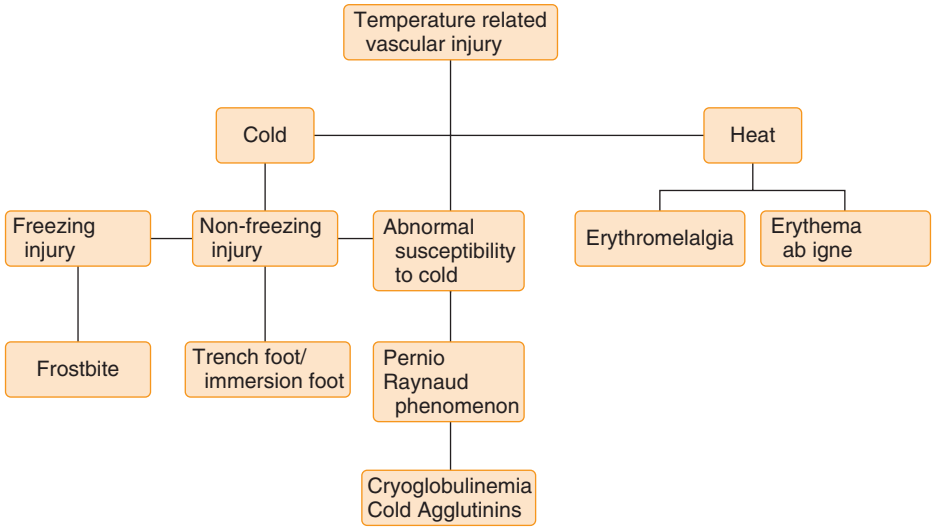

FIGURE 66-6. **Clinical syndromes caused by heat or cold.**

THERMAL DISORDERS

A variety of clinical syndromes can be caused by heat or cold (Fig. 66-6).

ERYTHROMELALGIA

The term *erythromelalgia* is derived from the Greek words *erythros* ("red"), *melos* ("extremities"), and *algos* ("pain"). It is characterized by episodic periods of erythema, increased warmth, and intense burning pain of the extremities.

Erythromelalgia is an uncommon disorder that affects younger to middle-aged women, adolescents, and children. The exact incidence is not known but has been reported at 1.3 per 100,000 living in Olmsted County, Minnesota. Erythromelalgia has been reported to occur in nearly 30% of patients with polycythemia vera (Chapter 152).

Both primary (familial and sporadic/idiopathic) and secondary forms occur. The primary trigger is heat exposure or increased ambient temperature. The familial form is autosomal dominant, with symptoms most often beginning in childhood. The pathophysiology is believed to be due to a small and large fiber neuropathy and vasculopathy. Although the exact cause of primary erythromelalgia is unknown, it is a neuropathic disorder with neuronal hyperexcitability owing to sodium-channel abnormalities because of a mutation of the gene (*SCN9A*) that encodes the Nav1.7v sodium channel (located on 2q). The causes of secondary erythromelalgia (Table 66-3) are not as well understood but are thought to be due to neuropathologic and microvascular functional changes caused by the underlying condition.

CLINICAL MANIFESTATIONS AND DIAGNOSIS

A triad of clinical findings including erythema, increased warmth, and intense burning pain of the extremities is usually observed (Fig. 66-7). The lower limbs (soles or entire foot) are more often affected than the hands. Involvement of the knees, elbows, ears, and face has been reported. Symptoms are generally bilateral and paroxysmal. An attack, which may last for several minutes or hours to days, is generally aggravated by dependency, alcohol, warm rooms, summer heat, exercise, or simply wearing shoes and socks or gloves. Attacks may also be more frequent at night. Erythromelalgia is often a disabling condition, and ulceration or even gangrene can occur in secondary forms.

TABLE 66-3 CAUSES OF SECONDARY ERYTHROMELALGIA

Myeloproliferative neoplasms: Essential thrombocythemia, polycythemia vera, chronic myelogenous leukemia, myelodysplastic syndrome
Drugs: Calcium-channel blockers, cyclosporine, bromocriptine, pergolide
Infectious diseases: Human immunodeficiency virus, hepatitis B vaccine, influenza vaccine, infectious mononucleosis, varicella virus
Connective tissue diseases: Systemic lupus erythematosus, rheumatoid arthritis
Neuropathic: Diabetic neuropathy, peripheral neuropathies, neurofibromatosis, Riley-Day syndrome, multiple sclerosis, spinal cord disease
Neoplastic: Paraneoplastic syndrome, astrocytoma, malignant thymoma, colorectal cancer, lung cancer, and thyroid cancer
Others: Mushroom ingestion, mercury poisoning

FIGURE 66-7. **Erythromelalgia.** Note the erythema of the feet. The patient also had pain and increased warmth on physical examination.

The history and physical examination are keys to the diagnosis. The physical examination is usually normal unless the patient is examined during an attack. A thorough vascular and neurologic examination should include demonstration of color changes and measurement of elevated skin temperatures during an attack. In between attacks, the affected area may be purple or cyanotic when dependent, consistent with acrocyanosis. A complete blood count is essential to exclude an underlying myeloproliferative disorder, and periodic blood counts are recommended because a myeloproliferative disorder (Chapter 152) may develop several years after the onset of symptoms. Electromyography and nerve conduction studies, autonomic and small fiber nerve testing, and vascular studies may help exclude other disorders. The quantitative sudomotor axon reflex test is useful to assess for small fiber neuropathy. Genetic testing is helpful for diagnosing primary erythromelalgia.

The differential diagnosis includes complex regional pain syndrome (Chapter 26), cellulitis (Chapter 408), peripheral neuropathy (Chapter 388), osteomyelitis (Chapter 251), Raynaud syndrome, acrocyanosis, peripheral arterial disease (Chapter 65), and gout (Chapter 252).

TREATMENT AND PROGNOSIS

Patients must avoid aggravating conditions, such as warm environments, exercise, tight shoes, and alcohol intake, as well as learn to cool their involved areas without causing tissue damage.[16] Patients seek relief by cooling the affected area with a fan, cold towels, cooling blankets, or immersion in ice water for short periods of time. These approaches may be helpful, but care must be taken not to overuse these methods. Elevation of the feet may help. Medications aimed at treatment of both the neuropathy and vasculopathy are often tried. Intravenous iloprost (at varying doses for up to 6 hours per day on 3 consecutive days) can

significantly reduce symptoms and sympathetic dysfunction in about 60% of patients. In the genetic form, a small trial showed benefit from orally administered XEN402 (an inhibitor of Nav1.7 that is designated as an orphan drug by the U.S. Food and Drug Administration). Patients with an infectious, traumatic, or surgical precipitant may respond to varying doses of glucocorticoids if given early in their course. Aspirin may be helpful for patients with an underlying myeloproliferative disorder (Chapter 152). Tricyclic antidepressants (e.g., nortriptyline 25 to 100 mg/day PO), anticonvulsants (e.g., pregabalin 50 to 100 mg PO three times daily), mexiletine (10 mg/kg/day PO), topical lidocaine patches, and opioids (e.g., hydromorphone 2 to 8 mg PO every 4 to 6 hours as needed) have been used with benefit in some patients. Topical options without systemic side effects include lidocaine patches, a gel of 1% amitriptyline and 0.5% ketamine, capsaicin, and 1% diclofenac. Small case series have reported some success with the peripheral acting alpha-1 agonist midodrine (0.2% applied topically in a moisturizing cream three times daily) and with local injection of botulinum toxin.

Other methods, including a pain rehabilitation program, biofeedback, sympathectomy, spinal cord stimulator, and epidural blocks, have been tried with varying degrees of success. Patients have a reduced quality of life, and life expectancy is also reduced, primarily owing to suicide.

ERYTHEMA AB IGNE

Erythema ab igne is a hyperpigmented skin condition that results from repeated or chronic exposure to a heating source or infrared radiation that is not warm enough to burn the skin. Women are about twice as frequently affected as men.[17]

Skin manifestations result from damage to the dermis and venous plexus system. Dysplastic changes can predispose the patient to actinic keratosis and squamous cell carcinomas (Chapter 188). Erythema ab igne is an occupational hazard for persons whose arms are repeatedly exposed to fire in bakeries, foundries, or kitchens. It can also result from repeated application of a hot water bottle, heating pads, or electric blankets for the treatment of chronic pain. It also may be seen in persons who sit on heated seats or too close to space heaters, wood burning stoves, or car heaters, and it has been reported to involve the anterior thighs of persons using laptop computers.

CLINICAL MANIFESTATIONS AND DIAGNOSIS

Patients may report a slight burning or itching sensation but generally have no symptoms. The skin discoloration is described as reticular, erythematous, or brownish (Fig. 66-8 and E-Fig. 66-1). Ulceration and bullous lesions have been reported in chronic cases.

The diagnosis is made clinically based solely on dermatologic findings and on the history of exposure to a heating source or infrared radiation, so laboratory tests should be avoided. A biopsy must be obtained if signs such as hyperkeratotic, hyperpigmented papular or nodular lesions suggest a malignant transformation. The differential diagnosis includes livedo reticularis and livedo racemosa.

FIGURE 66-8. Erythema ab igne. Note the hyperpigmentation and livedo reticularis pattern.

TREATMENT AND PROGNOSIS

Removing the offending heat source is essential for treatment, and patients should be advised to avoid prolonged exposure to any form of infrared heat. Topical therapies, including topical tretinoin (0.05% cream) or hydroquinone, have been used to reduce the hyperpigmentation.

The prognosis is favorable once the source is removed, but the condition can be chronic and progressive if prolonged and repeated exposure continues. Follow-up examinations are recommended because of the potential for malignant conversion.

RAYNAUD PHENOMENON

Raynaud phenomenon is defined as episodic attacks of discoloration (white or blue) of the digits brought on by cold or emotional stimuli and resulting in a characteristic triphasic color change from white to blue to red. Raynaud phenomenon affects 3 to 5% of the U.S. population and is seen more often in young women, in whom it is reported to have a prevalence as high as 5 to 15%. The prevalence is higher in cooler northern climates and in smokers. Family history (as many as 30 to 50% of patients with primary Raynaud have a first-degree relative with this condition), estrogen exposure, and emotional stress are commonly associated with Raynaud phenomenon in women.

The pathophysiology of the vasoconstriction in Raynaud phenomenon is not well understood. It includes abnormalities of the blood vessel wall, neural control mechanisms, and intravascular factors, including platelet activation and oxidative stress. As the arterial vasoconstriction subsides, postcapillary venular constriction leads to deoxygenation of the blood and the cyanotic appearance. On rewarming, blood flow increases as a result of vasodilation, which leads to the red or hyperemic appearance of the digits.

Primary Raynaud phenomenon is a benign vasospastic disorder, whereas a number of conditions are associated with the secondary form (Table 66-4). Several clinical features can help distinguish between these two forms (Table 66-5).

TABLE 66-4 UNDERLYING CONDITIONS ASSOCIATED WITH SECONDARY RAYNAUD PHENOMENON

Rheumatologic: Scleroderma, systemic lupus erythematosus, rheumatoid arthritis, Sjögren syndrome, mixed connective tissue disorders
Obstructive arterial disease: Atherosclerosis, thromboangiitis obliterans, arterial embolism
Occupational/environmental disorders: Hypothenar hammer syndrome, hand-arm vibration syndrome, frostbite
Endocrine: Hypothyroidism
Hematologic: Polycythemia vera, multiple myeloma, cryoglobulinemia, cryofibrinogenemia, cold agglutinins
Drugs: Amphetamines, cocaine, β-blockers, clonidine, ergot preparations, oral contraceptives, cyclosporine, certain antineoplastic agents
Infections: Hepatitis B and C antigenemia
Thoracic outlet syndrome, subclavian artery aneurysm
Complex regional pain syndrome
Arteriovenous fistula
Lead and arsenic poisoning

TABLE 66-5 FEATURES SUGGESTIVE OF PRIMARY OR SECONDARY RAYNAUD PHENOMENON

CLINICAL FEATURE	PRIMARY	SECONDARY
Sex	Female	Female or male
Age	<40 yr	≥40 yr
Involvement	Bilateral	Unilateral or bilateral
Ischemic digits or ulcerations	Absent	±
Underlying cause	Absent	Present
Systemic complaints	Absent	±

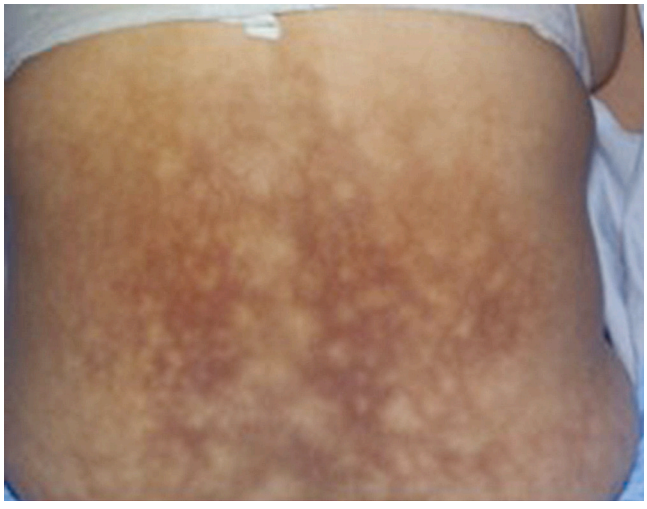

E-FIGURE 66-1. Erythema ab igne. Hyperpigmentation and livedo reticularis pattern in a patient who used a heating pad for back pain.

FIGURE 66-9. Unilateral Raynaud phenomenon. (From Forbes CD, Jackson WF. *Color Atlas and Text of Clinical Medicine*, 3rd ed. London: Mosby; 2003.)

CLINICAL MANIFESTATIONS AND DIAGNOSIS

Raynaud phenomenon is characterized by triphasic color change of the digits, pallor, cyanosis, and rubor after exposure to cold or stressful stimuli (Fig. 66-9 and E-Fig. 66-2). All three color changes are not seen in most individuals, and pallor may be the only finding. The middle and ring fingers are most commonly involved, whereas the thumb may be entirely spared. Raynaud phenomenon also can affect the toes, nose, ears, tongue, knees, or nipples. Patients may experience paresthesias and clumsiness of the hand during an attack.

A thorough history and physical examination is essential, but it may be normal in primary Raynaud phenomenon unless there is an ongoing attack. Secondary Raynaud findings may include ulceration or necrosis of the fingertips. Raynaud phenomenon is often the presenting symptom of an underlying connective tissue disorder, especially systemic sclerosis (Chapter 246).[18]

Routine laboratory testing should include a complete blood count, erythrocyte sedimentation rate, C-reactive protein level, thyroid function tests, antinuclear antibody, serum protein electrophoresis, urinalysis, and chest radiograph to evaluate for secondary causes. If the antinuclear antibody is positive or if the patient's history and physical examination indicate an underlying rheumatologic disorder, specific autoantibodies should be ordered (Chapter 237). Other tests including cryoglobulin levels, cryofibrinogen, and cold agglutinins may be helpful, depending on the clinical presentation (Chapter 236).

A number of noninvasive tests may help differentiate primary and secondary Raynaud phenomenon and evaluate the extent of vasospasm, including photoplethysmography, pulse volume recordings, laser Doppler flux, duplex ultrasonography, and nail-fold capillary microscopy. The presence of abnormal nail-fold capillaries on capillaroscopy (or video capillaroscopy) is useful for distinguishing patients with primary Raynaud phenomenon from those with secondary causes, and it can be an early predictor of systemic sclerosis. MR angiography or contrast angiography may be necessary, and the latter can help determine the cause of ischemia.

TREATMENT AND PROGNOSIS

Lifestyle modifications, including avoidance of cold exposure (such as when moving from a warm to an air-conditioned environment) and known stressful stimuli (with an emphasis on keeping the body core temperature and extremities warm), are essential for preventing attacks.[19] Raynaud phenomenon can be treated with both pharmacologic and nonpharmacologic approaches (Table 66-6). Topical nitroglycerin is effective for both primary and secondary Raynaud phenomenon.[A2]

For primary Raynaud phenomenon, calcium-channel blockers (e.g., nifedipine 10 to 20 mg orally every 6 hours or amlodipine 2.5 to 10 mg/day) can reduce attacks and the severity of symptoms.[A3] For patients with secondary Raynaud phenomenon, aggressive treatment of the underlying condition is essential, and the addition of calcium-channel blockers also may be beneficial. If the symptoms of ischemia persist or side effects are not tolerable, the addition of phosphodiesterase type 5 inhibitors (e.g., sildenafil 20 mg orally up to three times daily or tadalafil 5 mg orally daily) may help.[A4] Additional options include an endothelin-1 inhibitor (e.g., bosentan 62.5 to 125 mg orally twice daily) or a prostanoid infusion (e.g., iloprost 1 ng/kg/minute for 6 hours intravenously daily). Pain control with narcotics, chemical or surgical sympathectomy, and spinal cord stimulation may be necessary in the most severe cases, particularly in situations of nonhealing digital ulceration and tissue loss.

The prognosis for primary Raynaud phenomenon is excellent, whereas the prognosis for secondary Raynaud phenomenon depends on the underlying condition.

TABLE 66-6 PHARMACOLOGIC AND NONPHARMACOLOGIC THERAPIES FOR RAYNAUD PHENOMENON

NONPHARMACOLOGIC THERAPIES
Educate and reassure patients about their condition
Avoid cold exposure or other triggering factors
Use warm clothing to maintain core body temperature (cover the entire body and wear a hat and scarf)
Teach how to terminate attacks: Exit from cold, warming techniques
Avoid nicotine
Biofeedback
PHARMACOLOGIC THERAPIES
Nitroglycerin topical 1 inch q6h
Calcium channel blockers (nifedipine 10-20 mg q6h or amlodipine 2.5-10 mg q24h
Phosphodiesterase-5 inhibitors (sildenafil 25-50 mg three times daily, tadalafil 5-20 mg three times daily) and phosphodiesterase-3 inhibitors (cilostazol 100 mg twice daily)
Angiotensin-converting enzyme inhibitors/angiotensin-receptor blockers (especially for scleroderma-associated Raynaud phenomenon)
Others: Hydralazine 10-50 mg four times daily; reserpine 0.1-0.25 mg/day PO; bosentan 125 mg PO twice daily
Prostaglandins: Iloprost, epoprostenol, alprostadil, beraprost
Antithrombotics/anticoagulants: (aspirin 81-325 mg/day, dipyridamole 75 mg three times daily, heparin [via weight-based nomogram; see Table 68-6 in Chapter 68], low-molecular-weight heparin [e.g., enoxaparin 1 mg/kg q12h; see Table 70-3 in Chapter 70])
Botulinum toxin A

PERNIO

Pernio, also known as chilblains, is a cold-induced vasospastic inflammatory process that affects the skin after exposure to nonfreezing temperatures or damp climates. Pernio is seen more commonly in the northern United States and northwestern Europe. It is most common in individuals with a low body mass and in young women between the ages of 15 and 30 years, although it also can occur in children and in the elderly.

The cause is unknown but is likely a result of cold-induced vasoconstriction that induces inflammation and ischemia of vessels and surrounding tissue. It has been seen as a complication of coronavirus disease 2019 (COVID-19; Chapter 336), often with elevated D-dimer levels and significantly increased levels of interferon-alpha after in vitro stimulation.[20] The histopathologic findings include dermal edema, keratinocyte necrosis, a deep dermal lymphocytic infiltrate, thickening of venule walls, and pericyte hyperplasia.

Pernio can be classified as acute or chronic. Acute pernio develops a few hours after exposure, whereas chronic pernio develops after repeated exposures to nonfreezing cold or damp conditions.

CLINICAL MANIFESTATIONS AND DIAGNOSIS

Pernio occurs most frequently in late fall to early spring in wet or nonfreezing cold environments. Acute pernio is characterized by intense itching, numbness, or a burning sensation that develops shortly after exposure to cold or damp conditions and disappears within a few weeks.

Pernio is generally symmetrical. It usually involves the toes and fingers and less commonly involves the nose, ears, or cheeks. Pernio may also affect the thighs of horse riders, young women wearing tight slacks, motorcycle riders, or people who frequently apply ice packs. Pernio is associated with single or multiple erythematous, brownish or red, purple-blue skin lesions (macules, papules, or plaques) that may progress to blisters or ulcers (Fig. 66-10 and E-Fig. 66-3).

Chronic pernio develops after repeated cold exposure and results in cyanotic papules, macules, or nodules. Patients often report a history of similar episodes that develop each year during the cold months and typically resolve with warmer temperatures.

The diagnosis is based on the history and physical examination (Table 66-7). Patients generally have a normal arterial examination. Pulse volume recordings may reveal vasoconstriction, but capillaroscopy is usually normal. A skin biopsy may be necessary to differentiate pernio from other disorders, such as Raynaud phenomenon, frostbite, acrocyanosis, atheromatous embolization, erythema nodosum (Chapter 407), erythema induratum (Chapter 407), lupus erythematosus (Chapter 245), sarcoidosis (Chapter 83), or atherosclerosis (Chapter 65). Laboratory testing is important to exclude an underlying collagen vascular disease. Up to 35 to 40% of patients may have cold agglutinins as a precipitating cause (Chapter 236).

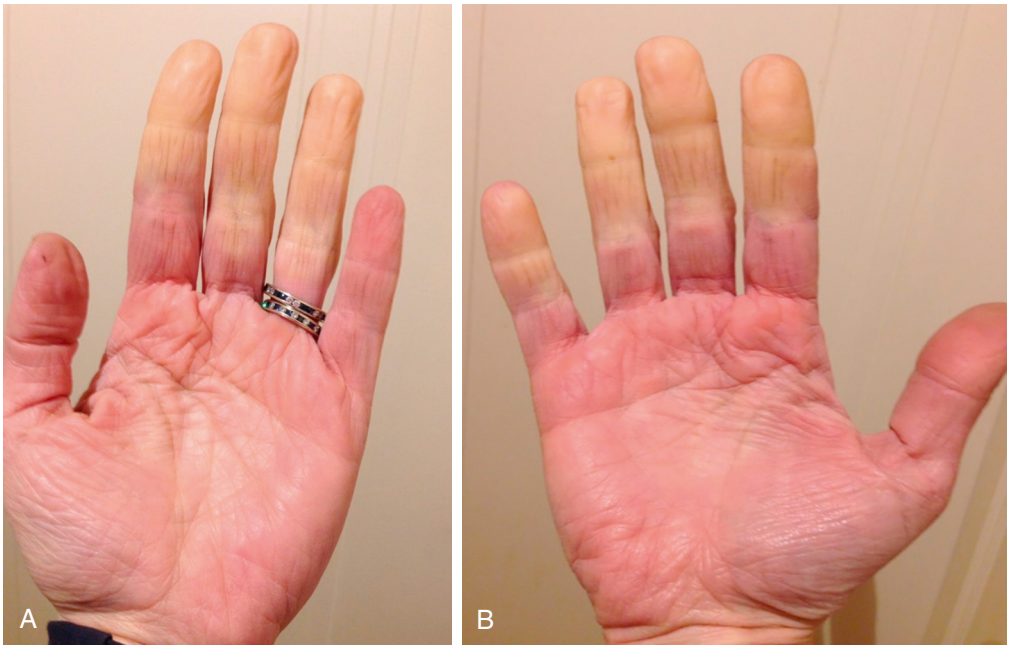

E-FIGURE 66-2. **Bilateral Raynaud phenomenon.**

E-FIGURE 66-3. **Pernio on the fingers.** Note the papules and small blisters.

PREVENTION

Patients susceptible to pernio should be advised to avoid cold exposure. If they must go outside in cold or damp weather, they should dress appropriately with layered outdoor clothing, insulated footgear, gloves, scarf, and hat.

Pernio is usually self-limiting in the acute state. Chronic pernio can lead to scarring, atrophy, and chronic occlusive vascular disease.

TREATMENT AND PROGNOSIS

Treatment begins by warming and drying the affected areas. Topical corticosteroids (e.g., 0.025% fluocinolone acetonide) may be tried, and oral calcium-channel blockers (nifedipine 20 to 60 mg/day or amlodipine 2.5 to 10 mg/day) may reduce symptoms. Nifedipine may also be given in a topical gel form. Pentoxifylline (400 mg three times daily)[A5] and capsaicin have also been reported to be helpful. Tissue loss is uncommon.

FIGURE 66-10. Pernio on the toes of the right foot. The lesions on the second, third, and fourth toes are the typical red, brown, and yellow scaling lesions. The lesion on the fifth toe can be confused with atheromatous embolization.

TABLE 66-7 PROPOSED DIAGNOSTIC CRITERIA OF PERNIO

MAJOR CRITERIA
Localized erythema and swelling involving acral sites and persisting for >24 hours
MINOR CRITERIA
Onset and/or worsening in cooler months (between November and March)
Skin biopsy consistent with pernio (dermal edema with superficial and deep perivascular lymphocytic infiltrate) without findings of lupus erythematosus.
Response to conservative treatments (warming and drying of affected areas)

FROSTBITE

Frostbite is a local cold-induced injury (Chapter 95) that occurs when persons are exposed to temperatures below the freezing point of intact skin or in above-freezing temperatures in association with wet environments, high altitudes, and strong winds.

Frostbite is more common in individuals 30 to 49 years who participate in winter outdoor sports and in individuals who are homeless, have psychiatric illnesses (Chapter 362), survive outdoor trauma (Chapter 97), consume excess alcohol (Chapter 364), or use illegal drugs (Chapter 365). Patients with peripheral arterial disease (Chapter 65), a smoking history (Chapter 363), younger or older age, or diabetes (Chapter 210) are also at increased risk. Frostbite injury involves three pathophysiologic components: tissue injury from extracellular and intracellular ice crystal formation, intracellular dehydration, and ischemia.

CLINICAL MANIFESTATIONS AND DIAGNOSIS

The severity of frostbite relates to the absolute temperature and to the duration of exposure. The digits of the hands and feet account for most injuries, although the ears, nose, and cheeks may be affected. Patients complain of numbness or paresthesias and report clumsiness and lack of fine coordination if the hands are involved. The numbness may persist even after rewarming. The skin may be pale, waxy, and cool to touch, and the patient may have mild to extensive swelling depending on the severity of the frostbite. Large, clear or hemorrhagic blisters often appear (Fig. 66-11), followed by black scabs. Damage to the muscles, tendons, cartilage, joints, and bones occur in severe frostbite. Pain is often severe during the rewarming process.

FIGURE 66-11. Blisters in a patient with frostbite.

The diagnosis of frostbite is made by the exposure history and physical examination. The differential diagnosis includes peripheral arterial disease, pernio, trench foot, or thermal burns.

TREATMENT AND PROGNOSIS

Proper recognition of frostbite and removal from cold exposure is essential. Local rewarming should begin only if refreezing will not occur while the patient is being transferred to a hospital. Uninterrupted rapid rewarming in a water bath of between 40 and 42° C for 15 to 30 minutes is critical to help minimize tissue loss. Removal of wet or damp clothing and jewelry is important, but rubbing or massage should be avoided. Splinting and elevation of the affected limb can help minimize swelling and improve perfusion. Patients should receive tetanus toxoid and analgesics (e.g., hydromorphone 2 to 8 mg either orally or parenterally every 3 to 4 hours as needed) for pain. Ibuprofen (12 mg/kg) divided in twice-daily doses to inhibit the release of harmful prostaglandins should also be administered unless contraindicated.[21,22] Broad-spectrum antibiotics should be given only to patients with significant trauma, other potential infectious sources, or signs and symptoms of cellulitis or sepsis. Daily cleansing in a warm whirlpool bath and physical therapy are important. Clear blisters should be left alone, but ruptured blisters should be covered with a topical antibiotic, such as neomycin/bacitracin/polymyxin B ointment.

For severe frostbite, the combination of intravenous iloprost (not available in the United States) plus aspirin is superior to the combination of aspirin plus buflomedil (an α-blocker) or the combination of aspirin plus iloprost plus tissue plasminogen activator (tPA) for reducing the amputation rate. The Wilderness Medical Society Clinical Practice guidelines for the prevention and treatment of frostbite recommend tPA (intravenous or intra-arterial) be initiated within 24 hours of injury if appropriate monitoring capabilities are available and iloprost cannot be obtained promptly. If possible, surgical débridement and amputation should be avoided until complete demarcation occurs.

Patients subjected to frostbite are more susceptible to future cold injuries, including frostbite arthritis of the small joints of the hands or feet. They also are susceptible to chronic pain, complex regional pain syndrome (Chapter 26), cold hypersensitivity, and a reduced sensitivity to touch.

ACROCYANOSIS

DEFINITION

Acrocyanosis is a poorly defined and often misunderstood clinical condition that manifests as painless, symmetrical, bluish or cyanotic discoloration affecting the hands, the feet, or both.[23] Acrocyanosis occurs in primary and secondary forms. Primary acrocyanosis is generally a benign condition seen most often in young women during their second to fourth decades of life. It may be more common in cooler temperatures, and a familial predisposition has been reported. The overall incidence is not known, but its prevalence has been reported to be approximately 20 to 40% in persons with anorexia nervosa (Chapter 200) and up to 25% of all patients with cancer.

Acrocyanosis was originally thought to be a vasospastic disorder that develops when small cutaneous arteries and arterioles constrict and reduce blood flow, dilation, and oxygen desaturation in the venules. More recent data suggest that low pressures and sluggish flow result in capillary constriction.

FIGURE 66-12. Acrocyanosis. Persistent, painless, symmetrical bluish discoloration (of different shades) in a patient with acrocyanosis.

The underlying cause of primary acrocyanosis is unknown, but a role for estrogen is suggested. Some of the secondary causes of acrocyanosis can be associated with a number of conditions, including Ehlers-Danlos syndrome (Chapter 239), hypoxemia (Chapter 90), cryoglobulins (Chapter 173), cryofibrinogens, cold agglutinins, antiphospholipid antibodies (Chapter 160), malignancy, spinal cord injury (Chapter 368), arsenic poisoning (Chapter 20), eating disorders (including anorexia nervosa [Chapter 200] and chronic starvation), and some medications (vasopressors and tricyclic antidepressants). It is also seen with "puffy hand syndrome," a finding unique to injection drug users (Chapter 365) who inject into their hands or fingers.

CLINICAL MANIFESTATIONS AND DIAGNOSIS

Persistent, painless, symmetrical bluish discoloration (of different shades) (Fig 66-12) involves the hands and feet but also can affect the forearms, nose, ears, and even nipples. Acrocyanosis may be exacerbated by cold exposure, emotional stress, or dependency of the limbs. It improves with elevation. Patients also report clamminess and hyperhidrosis of their hands and feet. Secondary acrocyanosis may be asymmetrical and associated with pain, ulceration, or tissue loss or gangrene.

The diagnosis of acrocyanosis is based on the history and physical examination. Laboratory evaluation should include a complete blood count, metabolic profile, and levels of antiphospholipid antibodies, cold agglutinins, cryofibrinogens, and cryoglobulins, as well as testing for connective tissue disorders (Chapter 236).

The differential diagnosis includes Raynaud phenomenon, pernio, erythromelalgia, and peripheral cyanosis. Acrocyanosis can be differentiated from peripheral cyanosis by the presence of cyanosis on the mucous membranes and hypoxia on an arterial blood sample.

TREATMENT AND PROGNOSIS

No treatment is necessary for primary acrocyanosis other than reassurance and avoidance of cold and damp exposures. Wearing gloves and avoiding tobacco may be helpful. A trial of α-adrenergic blocking agents such as prazosin (3 mg/daily) may be considered. Calcium-channel blockers, including amlodipine or nifedipine, are generally not helpful. Bioflavonoids and nicotinic acid derivatives have been reported beneficial in some cases, and sympathetic nerve block and sympathectomy may be tried for more severe cases. Treatment for secondary acrocyanosis depends on the underlying cause.

The prognosis of primary acrocyanosis is excellent. The prognosis of secondary acrocyanosis depends on the underlying cause.

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67 THROMBOTIC DISORDERS: HYPERCOAGULABLE STATES

ANDREW I. SCHAFER

The hypercoagulable states, also referred to as thrombophilias, encompass a group of inherited or acquired conditions that are associated with an increased risk for thrombosis. The primary hypercoagulable states are quantitative or qualitative prothrombotic abnormalities in specific coagulation proteins. Most of these disorders involve inherited mutations and polymorphisms that lead to either a deficiency of a physiologic antithrombotic factor (typically associated with a loss-of-function mutation) or an increased level of a prothrombotic factor (typically associated with a gain-of-function mutation) (Table 67-1).[1] Particularly when they are combined with other inherited prothrombotic mutations (multigene interactions), these primary hypercoagulable states are associated with a lifelong predisposition to thrombosis.

The secondary hypercoagulable states, which are a diverse group of mostly acquired conditions, cause a thrombotic tendency by more complex, often multifactorial mechanisms. The trigger for a discrete, clinical thrombotic event is often of one of the acquired secondary hypercoagulable states superimposed on an inherited state of hypercoagulability (E-Fig. 67-1).[2]

PRIMARY HYPERCOAGULABLE STATES

Antithrombin III Deficiency

EPIDEMIOLOGY AND PATHOBIOLOGY

Inherited quantitative or qualitative deficiency of antithrombin III leads to increased accumulation of fibrin and a lifelong propensity to thrombosis (Chapter 157). Antithrombin is the major physiologic inhibitor of thrombin and other activated coagulation factors, so its deficiency leads to the increased formation of fibrin.[3]

The frequency of asymptomatic heterozygous antithrombin deficiency in the general population is 1 in 350 (Table 67-2). Most of these individuals have clinically silent mutations and never have thrombotic manifestations. The frequency of symptomatic antithrombin deficiency in the general population has been estimated to be between 1 in 2000 and 1 in 3000. Among all patients seen with venous thromboembolism (VTE), antithrombin deficiency is detected in only about 1 to 2%, but it is found in approximately 2.5% of selected patients with recurrent thrombosis or the onset of thrombosis at a younger age (<45 years).

Patients with type I antithrombin deficiency have proportionately reduced plasma levels of antigenic and functional antithrombin because of a quantitative deficiency of the normal protein. Impaired synthesis, defective secretion, or instability of antithrombin in type I antithrombin-deficient individuals is caused by major gene deletions, single nucleotide changes, or short insertions or deletions in the antithrombin gene. Patients with type II antithrombin deficiency have normal or nearly normal plasma antigen levels but low activity

TABLE 67-1 PRIMARY HYPERCOAGULABLE STATES

DEFICIENCY OF ANTITHROMBOTIC FACTORS
Antithrombin (III) deficiency
Protein C deficiency
Protein S deficiency
INCREASED PROTHROMBOTIC FACTORS
Factor Va (activated protein C resistance; factor V Leiden)
Prothrombin (prothrombin G20210A mutation)
Factor IX Padua (factor IX R338L mutation)
Factors VII, XI, IX, VIII; von Willebrand factor; fibrinogen (epidemiologic data; molecular mechanisms unknown)

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Factors VII, XI, IX, VIII; von Willebrand factor; fibrinogen (epidemiologic data; molecular mechanisms unknown)

ABSTRACT

The hypercoagulable states, also referred to as thrombophilias, encompass a group of inherited or acquired conditions that are associated with an increased risk of thrombosis. Many patients who have a venous thromboembolic event, including deep vein thrombosis and pulmonary embolism, have an underlying inherited molecular abnormality that creates a lifelong hypercoagulable state. By contrast, patients who have arterial thrombotic events, such as myocardial infarction, stroke, or peripheral vascular occlusion, are much less likely to have an inherited clotting abnormality. The primary hypercoagulable states that can be diagnosed in the clinical laboratory include inherited deficiencies of physiologic anticoagulant factors (prototypically antithrombin III, protein C, or protein S deficiency) or increased levels of prothrombotic factors (prototypically factor V Leiden or the prothrombin gene G20210A mutation). The precipitating event that actually triggers a discrete thromboembolic event is usually an acquired or a secondary hypercoagulable state, such as pregnancy, cancer, the postoperative period, the use of estrogens, trauma, immobilization, or an inflammatory condition. When the precipitating event is clinically overt, the venous thromboembolism has been termed "provoked" and requires only 3 to 6 months of prophylactic anticoagulation after the provoking factor has been eliminated. If the patient does not have a clinically overt precipitating condition, it is termed an "unprovoked" thromboembolic event and traditionally requires an indefinite duration of prophylactic anticoagulation. It is increasingly recognized, however, that the etiology of venous thromboembolism is not simply binary but rather a spectrum of clinically overt to clinically occult provoking factors, usually superimposed on an inherited tendency to thrombosis.

KEYWORDS

hypercoagulable state
thrombophilia
venous thromboembolism
provoked thrombosis
unprovoked thrombosis
anticoagulation

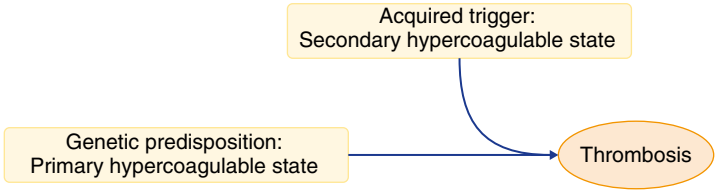

E-FIGURE 67-1. General scheme of thrombosis pathogenesis. A clinical episode of thrombosis is triggered by an acquired trigger, often one of the secondary hypercoagulable states, superimposed on a genetic predisposition caused by a primary hypercoagulable state. The magnitude of the acquired trigger varies from major (e.g., knee or hip surgery) to minor (e.g., lengthy air travel) to subclinical (not overt and identifiable). Likewise, the magnitude of the lifelong genetic predisposition varies from major (e.g., heterozygous antithrombin III, protein C, or protein S deficiency; homozygous factor V Leiden or prothrombin gene mutation; or two or more primary hypercoagulable states) to minor (e.g., heterozygous factor V Leiden or prothrombin gene mutation).

levels, thereby indicating a functionally defective molecule. Type II deficiency is usually caused when specific point mutations lead to single amino acid substitutions that produce a dysfunctional protein.

The pattern of inheritance of antithrombin deficiency is autosomal dominant. Most affected individuals are heterozygotes whose antithrombin activity levels are typically about 40 to 60% of normal. These individuals may have the full clinical manifestations of lifelong hypercoagulability. Rare homozygous antithrombin-deficient patients generally have type II deficiency with reduced heparin affinity (and consequently heparin resistance), a variant that is associated with a low risk for thrombosis in its heterozygous form. Other forms of homozygous antithrombin deficiency, however, are probably incompatible with life due to thrombosis-related intrauterine demise.

PROTEIN C DEFICIENCY

Protein C deficiency leads to the unregulated generation of fibrin because of impaired inactivation of factors VIIIa and Va, two essential cofactors in the coagulation cascade.[4]

EPIDEMIOLOGY AND PATHOBIOLOGY

The prevalence of heterozygous protein C deficiency in the general population is about 1 per 200 to 500. Protein C deficiency is found in 2 to 5% of all patients with VTE (Table 67-2).

As with antithrombin deficiency, two general forms of protein C deficiency are recognized: type I, in which quantitative deficiency of the protein is associated with a proportionate decrease in protein C antigen and activity, and type II, in which qualitative defects in protein C are associated with disproportionately reduced protein C activity relative to antigen. In the more common type I deficiency, frameshift, nonsense, or missense mutations cause premature termination of synthesis or loss of protein C stability. In type II deficiency, different mutations can cause abnormalities in the activation or function of protein C. The mode of inheritance of protein C deficiency is autosomal dominant. As in antithrombin deficiency, most affected individuals are heterozygotes. Neonatal purpura fulminans, a very rare complication involving widespread and sometimes fatal thrombosis, occurs in homozygous protein C– or protein S–deficient individuals.

PROTEIN S DEFICIENCY

Protein S is the principal cofactor of activated protein C, and its deficiency mimics that of protein C deficiency in causing loss of regulation of fibrin generation because of impaired inactivation of factors VIIIa and Va.[5] Reduced levels of free protein S and total protein S only marginally increase the risk for venous thrombosis; only levels far below the normal range cause increase thrombosis risk two-fold to five-fold.

EPIDEMIOLOGY AND PATHOBIOLOGY

Protein S deficiency is estimated to occur in about 1 in 500 in the general population. Its frequency in all patients evaluated for VTE (1 to 3%) is comparable to that of protein C deficiency.

Protein S circulates in plasma partly in complex with C4b-binding protein; only free protein S, which normally constitutes about 35 to 40% of total protein S, can function as a cofactor of activated protein C. As in deficiencies of antithrombin and protein C, quantitative (type I) and qualitative (type II) forms of inherited protein S deficiency are known. In addition, type III protein S deficiency is characterized by normal plasma levels of total protein S but low levels of free protein S. Most mutations involve frameshift, nonsense, or missense point variants.

ACTIVATED PROTEIN C RESISTANCE (FACTOR V LEIDEN)

EPIDEMIOLOGY AND PATHOBIOLOGY

The factor V Leiden mutation is remarkably frequent (3 to 8%) in healthy White populations of European ancestry but is far less prevalent in certain Black and Asian populations. The factor V Leiden mutation causes activated protein C resistance and an increased risk of VTE.[6] In various studies, activated protein C resistance has been found in a wide range of frequencies (10 to 64%) in patients with VTE.

Almost all subjects with functional activated protein C resistance have a single specific point mutation in the gene for factor V, which is a critical target of the physiologic anticoagulant action of activated protein C. In this mutation, termed factor V Leiden, guanine is replaced with adenine at nucleotide 1691 (G1691A), and this mutation leads to the amino acid substitution of Arg504 by Gln and renders factor Va incapable of being inactivated by activated protein C. Heterozygosity factor V Leiden mutation increases the risk for thrombosis by a factor of 5 to 10, whereas homozygosity increases the risk by a factor of 50 to 100.

TABLE 67-2 MOST COMMON INHERITED HYPERCOAGULABLE STATES (THROMBOPHILIAS): EPIDEMIOLOGY AND RISK OF VENOUS THROMBOEMBOLISM (VTE)

	PREVALENCE (%)		*RELATIVE RISK*	
THROMBOPHILIA	***General Population****	***Unselected VTE***	***First VTE***	***Recurrent VTE***
Antithrombin deficiency	0.02-0.3	1-2	5-8	2.5
Protein C deficiency	0.2-0.5	2-5	5-8	2.5
Protein S deficiency	0.5	1-3	1.7-8	2.5
Factor V Leiden	3-8	10-65	5-10†	1.3
Factor II G20210A	1-6	3-8	1.5-3.8	1.4
Factor V Leiden and factor II G20210A	0.01	—	20-60	2.5

*Data refer to White populations. The prevalence of factor V Leiden and factor II G20210A is much lower in African, African American, and Asian populations.

†Relative risk of first VTE with homozygous factor V Leiden is up to 10-fold higher (50-100).

Modified from Coppola A, Tufano A, Cerbone AM, et al. Inherited thrombophilia: implications for prevention and treatment of venous thromboembolism. *Semin Thromb Hemost*. 2009;35:683-694.

PROTHROMBIN GENE MUTATION (PROTHROMBIN G20210A)

The substitution of G for A at nucleotide 20210 of the prothrombin gene is associated with elevated plasma levels of prothrombin and an increased risk for venous thrombosis. The allele frequency for this gain-of-function mutation is 1 to 6% in White populations, but it is much less prevalent in other racial groups. The prothrombin G20210A mutation is found in 3 to 8% of all patients with VTE.

OTHER PRIMARY HYPERCOAGULABLE STATES

X-linked thrombophilia is caused by a gain-of-function mutation in the gene for coagulation factor IX (factor IX Padua). Hereditary thrombosis can be caused by a missense mutation in the prothrombin gene (prothrombin Yukuhashi) that results in impaired inhibition of its mutant thrombin product by antithrombin. Elevated levels of factor VIII coagulant activity are a significant risk factor for venous thrombosis and its recurrence, and family studies suggest that high factor VIII levels are often genetically determined. Increased levels of factor VII, factor IX, factor XI, fibrinogen, von Willebrand factor, and thrombin-activatable fibrinolysis inhibitor, as well as very low levels of tissue factor pathway inhibitor, may also confer increased risk. Mutations in *STAB2*, which codes for stabilin-2, may raise levels of procoagulant von Willebrand factor.[7]

Many other inherited abnormalities of specific physiologic antithrombotic systems may be associated with a thrombotic tendency. Most of these conditions are limited to case reports or family studies, their molecular genetic bases are less well defined, and their prevalence rates are unknown but are probably much lower than those of the disorders described earlier. These uncommon hereditary disorders include heparin cofactor II deficiency, dysfunctional thrombomodulin, and many fibrinolytic disorders that lead to impaired fibrin degradation, including hypoplasminogenemia, dysplasminogenemia, plasminogen activator deficiency, and certain dysfibrinogenemias that cause a thrombotic rather than a bleeding diathesis.

CLINICAL MANIFESTATIONS

The primary hypercoagulable states are associated with predominantly venous thromboembolic complications (see Table 157-3). Deep venous thrombosis (DVT) of the lower extremities and pulmonary embolism (Chapter 68) are the most frequent clinical manifestations. Venous thromboses occurring in more unusual sites include superficial thrombophlebitis and splanchnic and cerebral venous thrombosis (see Table 157-3). Arterial thrombosis involving the coronary, cerebrovascular, and peripheral circulations is not generally linked to any of the primary hypercoagulable states.[8] However, venous thrombosis can result in arterial occlusion by paradoxical embolism across a patent foramen ovale. Also, epidemiologic studies have revealed increased overall risk of arterial thrombotic and atherosclerotic vascular disease in patients with a history of VTE and vice versa. Recurrent pregnancy loss is probably increased in primary hypercoagulable states, but this association is not as strongly established as it is in antiphospholipid syndrome (see later under Secondary Hypercoagulable States).

The initial episode of VTE can occur at any age in patients with primary hypercoagulable states, but it typically is seen in early adulthood. Positive family histories of thrombosis can frequently be elicited. Recurrent VTE, especially at a young age, and VTE in unusual sites (e.g., splanchnic or cerebral veins) are also suggestive of an underlying primary hypercoagulable state. The risk for thrombosis varies among the individual primary hypercoagulable states and is highest in patients with deficiencies of antithrombotic factors (Table 67-2); it is also markedly increased with the coexistence of multiple prothrombotic mutations. Patients with homozygous deficiency states tend to have more severe thrombotic complications.

In most patients with primary hypercoagulable states, discrete clinical thrombotic complications appear to be provoked by acquired prothrombotic events (e.g., pregnancy, use of oral contraceptives, surgery, trauma, immobilization), many of which are the secondary hypercoagulable states (see E-Fig. 67-1). For example, thrombosis complicates pregnancy, especially during the puerperium, in about 30 to 60% of women with antithrombin deficiency, 10 to 20% with protein C or protein S deficiency, and almost 30% with activated protein C resistance (factor V Leiden) unless prophylactic anticoagulation is administered during this period.

Whether or not an episode of VTE has been "provoked" by a precipitating event is presently considered pivotal in determining the recommended duration of anticoagulation and possibly even the extent of the required evaluation for an underlying thrombophilia. Whereas active cancer, immobilization, oral contraceptives or hormone replacement therapy, pregnancy, and the postoperative state at the time of VTE are clearly "provoking" factors, many weak transient risk factors for thrombosis (e.g., minor soft tissue injury to a leg) or risk factors that preceded VTE by some length of time are less certainly related events. Furthermore, many acquired triggers for VTE are subclinical or undisclosed by the patient. Therefore, the notion of a straightforward binary distinction between "provoked" versus "unprovoked" VTE can be challenged as a primary determinant of diagnostic testing or the duration of anticoagulant therapy.

DIAGNOSIS

Who to Test

The diagnostic approach to a patient with a documented episode of VTE includes a thorough history (including inquiry about changes in activity or medications, trauma, immobility, surgical procedures, use of oral contraceptive agents or hormone replacement therapy in the months leading up to the VTE and family history of thrombosis), physical examination (especially signs that suggest an occult malignancy), and basic laboratory tests to search for possible precipitating conditions or triggers for the acute event and to exclude underlying acquired causes of hypercoagulability. No randomized trial data are available to determine whether testing for a primary hypercoagulable state is worthwhile after a first episode of thrombosis. Guidelines commonly recommend against detailed testing for inherited thrombophilia after a first VTE in adults if the VTE occurred in the presence of major transient risk factors (Fig. 67-1).[9]

A reasonable diagnostic approach is to screen patients after an initial episode of VTE with a documented event before 40 years of age, a positive family history, or unprovoked or recurrent VTE. However, thrombophilia testing is not routinely recommended indiscriminately in all patients after a first VTE episode or in patients with overt provoking factors. Although indefinite anticoagulation is recommended for patients who have had two or more VTE events, regardless of whether a primary hypercoagulable state is found, testing of these individuals for thrombophilia can still be useful to guide family screening strategies (see Fig. 67-1).

Individuals with arterial thrombosis generally should not be tested for any of these disorders because primary hypercoagulable states are not clearly associated with an increased risk for arterial thrombosis. In contrast, some of the secondary hypercoagulable states, including hyperhomocysteinemia and antiphospholipid syndrome (see later), are associated with an increased risk for arterial as well as venous thrombosis (Table 67-3).

When to Test

In general, testing for primary hypercoagulable states is not recommended immediately after a major thrombotic event, particularly because these test results are very unlikely to alter initial management. Testing ideally should be performed in clinically stable patients after completion of oral anticoagulation at least 3 to 6 months after a thrombotic episode because active thrombosis may transiently consume and deplete some of the antithrombotic proteins in plasma and lead to the erroneous diagnosis of inherited antithrombin, protein C, or protein S deficiency. In addition to acute thrombosis, pregnancy, estrogen use, liver disease, and disseminated intravascular coagulation may cause acquired deficiencies of antithrombin, protein C, or protein S.

Anticoagulation may also interfere with some of the functional tests for primary hypercoagulable states. Heparin treatment can cause a decline in antithrombin levels to the deficiency range even in normal individuals. In contrast, warfarin can elevate antithrombin levels into the normal range in patients who do have an inherited deficiency state. Warfarin therapy, by its very mode of action, also predictably reduces the functional levels and, less prominently, the immunologic levels of protein C and protein S. Active warfarin treatment thereby potentially leads to a misdiagnosis of inherited deficiency. The direct oral anticoagulants can interfere with testing for lupus anticoagulant (see later). To avoid interference of oral anticoagulants with functional tests of hypercoagulable states or interpretation of their results, blood should be

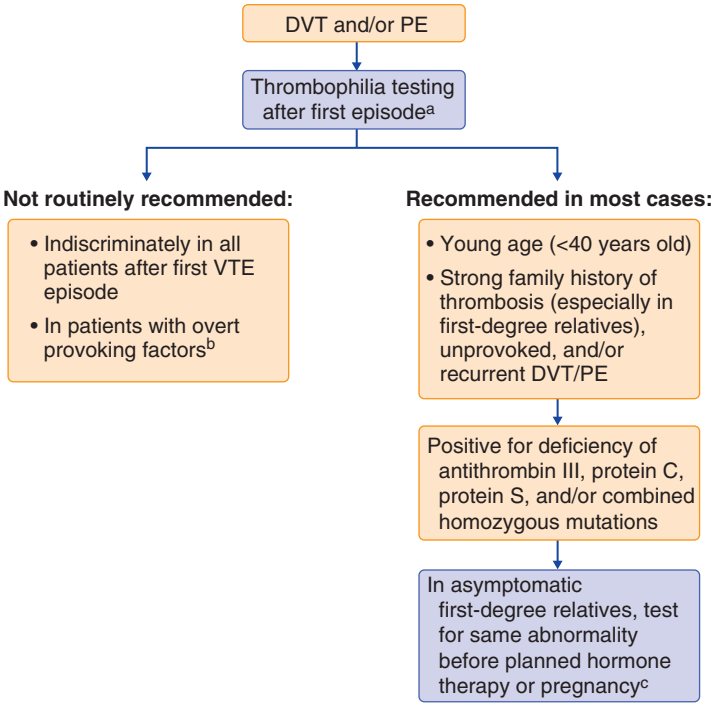

FIGURE 67-1. Algorithm for thrombophilia testing after a first episode of deep venous thrombosis (DVT) or pulmonary embolism (PE) and in asymptomatic, first-degree relatives. In the absence of strong evidence-based guidelines (see text), decisions about thrombophilia testing should be individualized, ranging from "not routinely recommended" to "recommended in most cases." VTE = venous thromboembolism. [a]Thrombophilia testing to include antithrombin III, protein C, protein S, factor V Leiden, prothrombin 20210A gene mutation, and lupus anticoagulant/antiphospholipid antibodies. [b]Provoking factors include active malignant disease, postoperative state, immobilization, trauma, active chronic inflammatory disease (e.g., extensive psoriasis), myeloproliferative neoplasm, pregnancy, oral contraceptives, and hormone replacement therapy. [c]In asymptomatic first-degree relatives of such individuals, avoidance is an alternative to testing.

TABLE 67-3 LONG-TERM MANAGEMENT OF PATIENTS WITH PRIMARY HYPERCOAGULABLE STATES*

RISK CLASSIFICATION	MANAGEMENT
High risk ≥2 spontaneous thromboses 1 spontaneous life-threatening thrombosis 1 spontaneous thrombosis at an unusual site (e.g., mesenteric, cerebral venous) 1 spontaneous thrombosis in the presence of antiphospholipid syndrome, antithrombin deficiency, or more than a single hypercoagulable state	Indefinite or lifelong anticoagulation
Moderate risk 1 thrombosis with an acquired prothrombotic stimulus	Vigorous prophylaxis during high-risk situations
Asymptomatic	

*Beyond initial period of thromboprophylaxis.

Modified from Bauer K. Approach to thrombosis. In: Loscalzo J, Schafer AI, eds. *Thrombosis and Hemorrhage*. 3rd ed. Philadelphia: Lippincott Williams & Wilkins; 2003:330-342.

drawn at least 2 weeks after stopping warfarin and at least 48 to 72 hours after stopping a direct oral anticoagulant.

How to Test

Laboratory diagnosis (Chapter 157) of the primary hypercoagulable states requires testing for each of the disorders individually because no general screening test is currently available to determine whether a patient may have such a condition.[10] Factor V Leiden can be diagnosed by a DNA-based assay or by a functional test for activated protein C resistance; the DNA-based assay is required to distinguish between heterozygous and homozygous states. A DNA-based assay is also required to identify the prothrombin G20210A mutation.

In contrast, many different mutations have been found in the genes for antithrombin, protein C, and protein S, so DNA-based tests are not practical for the diagnosis of these inherited deficiency states. Functional activity assays are preferred for antithrombin, protein C, and protein S because they detect both quantitative and qualitative defects; antigenic (immunologic) assays detect only quantitative deficiencies of these proteins. Functional coagulation assays for protein C and protein S may yield spuriously low values, however, if activated protein C resistance is present. Activated protein C resistance can be diagnosed by newer high-sensitivity and high-specificity coagulation assays or by DNA analysis of peripheral blood for the factor V Leiden mutation.

FIGURE 67-2. Acute skin necrosis in a patient with previously not known protein C deficiency who was given prophylactic warfarin for prevention of deep venous thrombosis after elective hip surgery. Warfarin treatment was withdrawn and anticoagulation continued with heparin. Skin grafting of the affected area was required. (From Forbes CD, Jackson WF. *Color Atlas and Text of Clinical Medicine*. 3rd ed. London: Mosby; 2003.)

TREATMENT

Initial Therapy

The initial treatment of acute deep venous thrombosis or pulmonary embolism in patients with primary hypercoagulable states is not different from that in patients without genetic defects (Chapter 68). As in patients without known thrombophilia, thrombolytic therapy should be considered after massive venous thrombosis or pulmonary embolism.

In most patients, direct oral anticoagulants (e.g., rivaroxaban, edoxaban, apixaban, and dabigatran) can be used for both acute treatment (at higher doses) and long-term prophylaxis against recurrence of venous thromboembolism (see Table 70-6). In addition to the convenience of fixed dosing, these medications are at least as effective and safer in terms of bleeding complications compared with warfarin. Even in patients who have cerebral venous thrombosis, anticoagulation with a direct-acting anticoagulant leads to similar clinical and imaging outcomes and has a more favorable safety profile when compared with warfarin.[A1]

However, warfarin is still preferred in some special circumstances. In patients who have prosthetic heart valves or high-risk antiphospholipid syndrome, however, treatment with heparin followed by warfarin is superior to direct oral anticoagulants[11] (Chapters 68 and 70). Acute management is initiated with at least 5 days of unfractionated or low-molecular-weight heparin or fondaparinux (see Tables 70-1 and 70-3). Oral anticoagulation with warfarin can be started on the first day of parenteral anticoagulation use (see Table 70-4) and continued for at least 6 months in patients with a first episode of VTE in the absence of triggering factors (e.g., postoperative state), with regulation of the dose to maintain an international normalized ratio of the prothrombin time between 2.0 and 3.0. This approach is especially preferred for secondary prevention of VTE in the antiphospholipid syndrome, particularly for patients who are "triple positive" (two positive IgG antiphospholipid antibodies plus lupus anticoagulant).[A2]

Warfarin-induced skin necrosis (Fig. 67-2) infrequently complicates the initiation of the anticoagulant in patients with heterozygous protein C or protein S deficiency. Because both these proteins depend on vitamin K for normal function, their plasma levels in patients with inherited deficiency states may drop to nearly zero within a few days of starting therapy with warfarin (which is a vitamin K antagonist) and lead to a transient prothrombotic imbalance and skin necrosis caused by dermal vascular thrombosis, especially in patients who are started on higher doses of warfarin without concurrent heparin. Acutely, the patient can be switched to heparin, but case reports suggest that switching to a direct-acting anticoagulant such as rivaroxaban is safe and effective for long-term antithrombotic prophylaxis in these individuals.

Duration of Therapy

Continuing oral anticoagulant prophylaxis beyond the initial 6 to 12 months after an acute episode of VTE must weigh the risk of bleeding with continued treatment against the significant risk of recurrent VTE after stopping anticoagulant prophylaxis. The risk of recurrence after an unprovoked episode of VTE following discontinuation of anticoagulation is greatest during the first 6 months and then decreases linearly by 4 to 5% per year, whereas the risk of major bleeding with continued anticoagulation is low and decreases linearly by less than 2% per year. Among patients with a first episode of unprovoked pulmonary embolism who received 6 months of anticoagulation, an additional 18 months of treatment with warfarin reduced the rate of recurrent VTE compared with placebo, although that benefit was not maintained after discontinuation of anticoagulation prophylaxis. These findings, which are consistent with earlier studies, highlight the fact that unprovoked VTE is a chronic, often recurrent, disease in the absence of prophylaxis. Patients with primary hypercoagulable states who have had two or more thrombotic events should receive indefinite or lifelong prophylactic oral anticoagulation (Chapter 70). Indefinite or lifelong anticoagulation is probably also indicated for individuals with recurrent thrombosis even in the absence of an identifiable primary hypercoagulable state (Table 67-3).

Asymptomatic Individuals

Asymptomatic individuals who have known thrombophilia but who have not had previous thrombotic complications do not require prophylactic anticoagulation except during periods of high risk for thrombosis. Because about half of the first-degree relatives of a patient with a primary hypercoagulable state should be affected, these individuals should be counseled about the implications of testing and potentially making a diagnosis.

Pregnancy

Management of pregnancy in women with primary hypercoagulable states requires special consideration because of the high risk for thrombosis, particularly during the puerperium. Women who have thrombophilia and who have previously had thrombosis—and probably also asymptomatic women with thrombophilia—should receive prophylactic anticoagulation throughout pregnancy and for at least the high-risk 6 weeks postpartum. Coumarin derivatives cross the placenta and have the potential to cause both bleeding and teratogenic effects in the fetus. The safety to the fetus of the direct oral anticoagulants has not yet been established. Therefore, oral anticoagulants should not be used during pregnancy. Heparin does not cross the placenta and does not cause these fetal complications. Fixed-dose, low-molecular-weight heparin (Table 70-3) is the anticoagulant of choice during pregnancy. Neither warfarin nor heparin induces an anticoagulant effect in a breast-fed infant when the drug is given to a nursing mother, so either can be given safely when indicated in the postpartum period. The same is not yet established for the direct oral anticoagulants.

Heparin Resistance

Antithrombin concentrate purified from normal human plasma or human recombinant antithrombin may be a useful adjunct to anticoagulation in "heparin-resistant" patients, who represent unusual cases of type II antithrombin deficiency, and in antithrombin-deficient patients with recurrent thrombosis despite adequate anticoagulation. Infusion of antithrombin concentrate can also be considered in some perioperative or obstetric settings in which anticoagulation poses an unacceptable bleeding risk.

SECONDARY HYPERCOAGULABLE STATES

DEFINITION

The secondary hypercoagulable states are diverse, mostly acquired disorders that predispose patients to thrombosis by complex, multifactorial pathophysiologic mechanisms. Many of these conditions also represent the acquired provocative stimuli for clinical thrombotic events in individuals with a genetic predisposition (primary hypercoagulable states; Table 67-4). Although each disorder causes thrombosis primarily through abnormalities in blood flow (rheology), the composition of blood (coagulation factors and platelet function), or the vessel wall, multiple overlapping mechanisms are operative in many of them.

TABLE 67-4 CAUSES OF SECONDARY HYPERCOAGULABLE STATES (PROVOKING FACTORS FOR VENOUS THROMBOEMBOLISM)

Immobilization
Surgery (postoperative state)*
Trauma*
Estrogen-mediated medications
Oral contraceptives*
Hormone replacement therapy*
Tamoxifen
Pregnancy (including early postpartum period)
Assisted reproductive technologies*
Ovarian hyperstimulation syndrome
Malignancy*
Myeloproliferative neoplasms*
Polycythemia vera
Essential thrombocythemia
Paroxysmal nocturnal hemoglobinuria*
Hyperviscosity states
Sickle cell disease and trait
Other hemolytic anemias
Corticosteroid excess
Therapeutic corticosteroids
Cushing syndrome
Nephrotic syndrome
Drugs
Lenalidomide, thalidomide*
L-asparaginase*
Cisplatin*
Bevacizumab*
Anabolic steroids (testosterone derivatives)*
Heparin (heparin-induced thrombocytopenia and thrombosis)*
Erythropoiesis-stimulating agents*
Intravenous immunoglobulin
Antifibrinolytics
Cocaine*
Systemic inflammatory states* (see Table 67-5)

*In these disorders there is also increased risk of arterial thrombosis.

HYPERHOMOCYSTEINEMIA

Hyperhomocysteinemia (Chapter 193) is an elevated blood level of homocysteine, a sulfhydryl amino acid derived from methionine by a transmethylation pathway (E-Fig. 67-2). Homocysteine is remethylated to methionine or catabolized to cystathionine. The major remethylation pathway requires folate and cobalamin (vitamin B_{12}) and involves the action of methylenetetrahydrofolate reductase (MTHFR); a minor remethylation pathway is mediated by betaine–homocysteine methyltransferase. Alternatively, homocysteine is converted to cystathionine in a trans-sulfuration pathway catalyzed by cystathionine β-synthase, with pyridoxine used as a cofactor.

Homozygous cystathionine β-synthase deficiency states that lead to severe hyperhomocysteinemia (homocystinuria) (Chapter 193) cause premature arterial atherosclerotic disease and VTE as well as mental retardation, neurologic defects, lens ectopy, and skeletal abnormalities. By comparison, adults with heterozygous cystathionine β-synthase deficiency have only mild to moderate hyperhomocysteinemia but still are at risk for venous or arterial thrombotic manifestations. Hyperhomocysteinemia resulting from inherited remethylation pathway defects usually involves reduced activity of MTHFR. In some homozygous individuals with the autosomal recessive C677T mutation of the *MTHFR* gene, which occurs in 15% of certain populations, moderate hyperhomocysteinemia may occur, but the mutation by itself does not appear to be related to the risk of venous thrombosis in the absence of coexisting hyperhomocysteinemia. Acquired causes of hyperhomocysteinemia in adults most commonly involve nutritional deficiencies of the cofactors required for homocysteine metabolism, including pyridoxine, cobalamin, and folate. Hyperhomocysteinemia is correctable with folic acid, pyridoxine, and cobalamin (Chapter 193), but treatment of nonhomozygous adults has not proven beneficial in reducing serious adverse events or death.[A3]

MALIGNANT DISEASE

Multiple abnormalities of hemostasis are involved in the hypercoagulable state in cancer patients, many of which initiate a systemic process of chronic disseminated intravascular coagulation (Chapter 161). The thrombotic tendency of patients with cancer may also be related to mechanical factors, such as immobility, indwelling central venous catheters, or a bulky tumor mass compressing vessels, and to comorbid conditions, such as sepsis, surgery, liver dysfunction secondary to metastases, and the prothrombotic effects of certain antineoplastic agents

The incidence of thrombotic complications in cancer patients depends in part on the type of malignant disease. Hypercoagulability is most prominent in patients with pancreatic cancer (Chapter 180), adenocarcinoma of the gastrointestinal tract (Chapters 178 and 179), lung cancer (Chapter 177), ovarian cancer (Chapter 184), prostate cancer (Chapter 186), and hematologic malignant neoplasms. The presence of underlying malignant disease compounds the independent risk for thrombosis in the postoperative state. There is a two-fold increase in the risk of postoperative thrombosis (see later section, Postoperative State, Immobilization, and Trauma) in cancer patients compared with noncancer patients. Thrombosis most commonly occurs in patients with established or concurrently diagnosed malignant disease. In these patients, the risk of venous thrombosis has been found to be highest in the first few months after the diagnosis of malignant disease, then decreases progressively during the subsequent 15 years.

The increased risk of harboring an occult malignant neoplasm in patients who present with VTE is now well established. The overall prevalence of undiagnosed cancer in patients with unprovoked VTE is approximately 3.5 to 6% at the time of thrombosis and 5 to 10% within the first year after thrombosis.[12] Because of the relatively low prevalence of occult cancer among adults with a first unprovoked VTE, routine screening with computed tomography (CT) of the abdomen and pelvis[A4] or with F-fluorodeoxyglucose positron emission tomography/CT[A5] is generally not recommended. However, focused screening with a complete blood count, serum electrolytes, tests of renal and liver function, and a chest radiograph are indicated (Fig. 67-3). A mammogram should be obtained in women, and a prostate-specific antigen level should be checked in men. Suspicious results on these basic tests should be pursued with CT scans or other appropriate diagnostic tests. In the absence of suggestive findings on these basic tests, decisions about screening must be individualized based on factors such as age or family history.

The most frequent thrombotic manifestations in patients with neoplasms are DVT and pulmonary embolism, but more unusual and distinctive thrombotic complications are also found. Trousseau syndrome (Chapter 68), characterized by migratory superficial thrombophlebitis of the upper or lower extremities, is strongly linked to cancer. Of patients with nonbacterial thrombotic endocarditis (Chapter 61), 75% have underlying malignant neoplasms at autopsy. Trousseau syndrome and nonbacterial thrombotic endocarditis are highly associated with adenocarcinomas. The occurrence of either syndrome in patients without known cancer demands a more vigorous search for occult malignant disease than in other patients with DVT or pulmonary embolism. Thrombotic microangiopathy (Chapter 158) occurs in about 5% of patients with metastatic carcinomas, most commonly patients with gastric (Chapter 178), lung (Chapter 177), and breast (Chapter 183) primary sites.

Some antineoplastic agents themselves increase the risk of thrombosis in cancer patients. For example, the antiangiogenic agents thalidomide and lenalidomide increase the risk of VTE, whereas bevacizumab, sunitinib, and sorafenib increase the risk of arterial thrombosis. Newly diagnosed, treatment-naïve patients with multiple myeloma are at significant risk of thrombosis, and therapy with immunomodulatory agents such as lenalidomide and thalidomide markedly increases that risk (Chapter 173).[13] Other thrombogenic chemotherapeutic agents include all-*trans*-retinoic acid and arsenic trioxide, particularly when used as induction chemotherapy for acute promyelocytic leukemia (Chapter 168); cis-platin (causing both venous and arterial thrombosis); L-asparaginase (which can also cause bleeding); and methotrexate (Table 67-3).

TREATMENT

Treatment of acute VTE in cancer patients should be initiated as in other patients, but subsequent prophylactic anticoagulation generally should be continued while active malignant disease is present.[14,15] In some patients, however, complete resolution of the VTE may allow treatment to be stopped safely.

Anticoagulation can be challenging in many cancer patients because of nausea, vomiting, low platelet counts, and bleeding into tumors. Long-term treatment of cancer patients with edoxaban (60 mg daily) or other direct-acting oral anticoagulants is as good as low-molecular-weight heparin (LMWH) overall, with insignificantly lower rates of recurrent VTE balanced against insignificantly higher rates of bleeding, without differences in overall mortality.[A6,A7] If direct-acting oral anticoagulants cannot be tolerated, LMWH is preferred over warfarin.

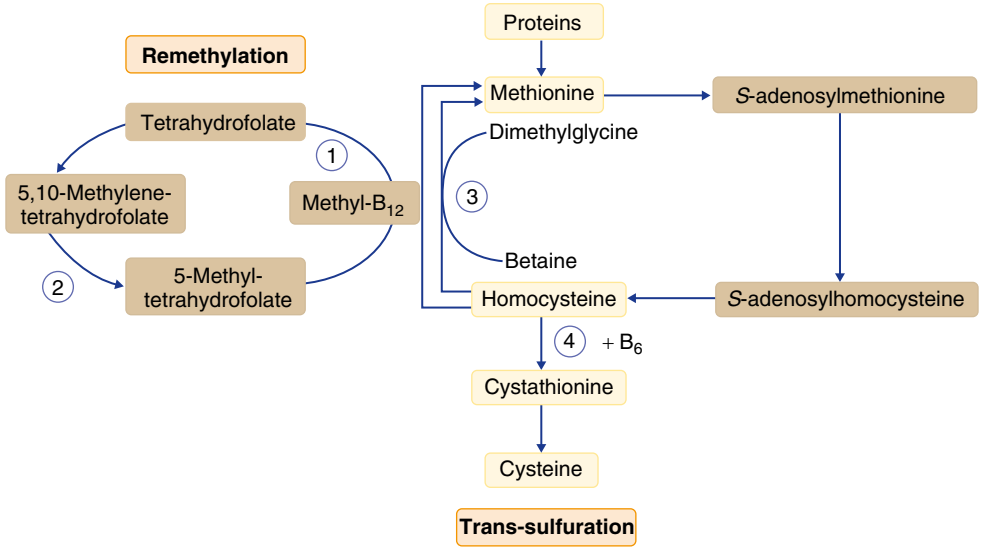

E-FIGURE 67-2. Intracellular metabolism of homocysteine occurs through remethylation to methionine or trans-sulfuration to cysteine. Numbered circles indicate the principal enzymes involved: (1) methionine synthase; (2) 5,10-methylenetetrahydrofolate reductase; (3) betaine–homocysteine methyltransferase; (4) cystathionine β-synthase. (Modified from De Stefano V, Finazzi G, Mannucci PM. Inherited thrombophilia: pathogenesis, clinical syndromes, and management. *Blood*. 1996;87:3531-3544.)

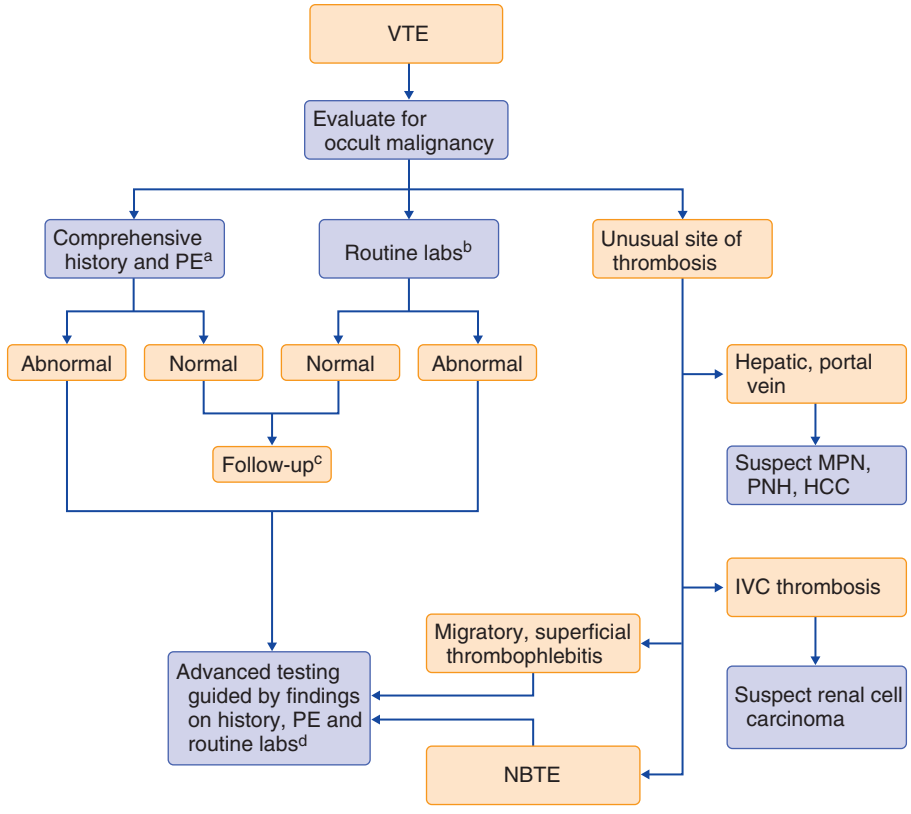

FIGURE 67-3. **Algorithm for evaluating a patient for occult malignant neoplasm after an unprovoked episode of deep venous thrombosis or pulmonary embolism or thrombosis at an unusual site.** HCC = hepatocellular carcinoma; IVC = inferior vena cava; MPN = myeloproliferative neoplasm; NBTE = nonbacterial thrombotic endocarditis; PE = physical examination; PNH = paroxysmal nocturnal hemoglobinuria; VTE = venous thromboembolism. [a]Physical examination to include rectal (with stool sample for occult blood) and breast and pelvic examinations for women. [b]Routine laboratory evaluations to include chest radiography, complete blood count, basic chemistries, calcium concentration, tests of liver and renal function, and a mammogram in women and a prostate-specific antigen level in men. [c]Follow-up suggested at 6 to 12 months. [d]Advanced testing could include advanced imaging, endoscopies, cytologies, and the like.

PREVENTION

For primary prevention of venous thrombosis in patients with cancer, rivaroxaban (10 mg daily) and apixaban (2.5 mg twice daily) are safe and effective as prophylaxis against a first VTE in patients who are at very high risk (pancreas, gastric, brain malignancies) or high risk (gynecologic and genitourinary cancers and lymphoma), especially in patients who have advanced disease.[A8–A10] LMWH is also an option if a direct-acting oral anticoagulant cannot be tolerated or is unsuccessful.[A11] However, prophylaxis is not recommended in low-risk patients.[16]

PROGNOSIS

Although treatment of cancer-associated thrombosis is usually successful, thrombosis generally portends poor prognosis. Venous thromboembolism is associated with increased mortality in cancer patients, especially within the first year after the thrombotic event.

MYELOPROLIFERATIVE NEOPLASMS AND PAROXYSMAL NOCTURNAL HEMOGLOBINURIA

Thrombosis and, apparently paradoxically, bleeding are major causes of morbidity and mortality in patients with chronic myeloproliferative neoplasms (Chapter 152)[17,18] and the related bone marrow stem cell disorder paroxysmal nocturnal hemoglobinuria (Chapter 146). In uncontrolled polycythemia vera, increased whole blood viscosity contributes to the thrombotic tendency. Thrombocytosis, abnormal platelet function, and other less well-understood factors are also probably involved in the hemostatic defect of myeloproliferative neoplasms and paroxysmal nocturnal hemoglobinuria.

In addition to DVT and pulmonary embolism, some distinctive thrombotic manifestations are seen. Hepatic vein thrombosis (Budd-Chiari syndrome) and portal and other intra-abdominal venous thromboses (Chapter 129) are associated with myeloproliferative neoplasms and paroxysmal nocturnal hemoglobinuria (Chapter 146) and may be the initial manifestations of the disease. Myeloproliferative neoplasms, particularly polycythemia vera (Chapter 152) and essential thrombocythemia (Chapter 152), may cause erythromelalgia (Chapter 66). Erythromelalgia is a syndrome of microvascular thrombosis manifested by intense pain accompanied by warmth, duskiness, and mottled erythema, sometimes resembling livedo reticularis. It is seen in a patchy distribution on the extremities, most prominently in the feet, and digital microvascular ischemia can progress to vascular insufficiency and gangrene (Chapter 66). A wide spectrum of neurologic manifestations may be caused by cerebrovascular ischemia, especially in patients with essential thrombocythemia.

TREATMENT

Treatment of VTE in patients with myeloproliferative neoplasms and paroxysmal nocturnal hemoglobinuria should be initiated as in patients without these hematologic disorders. In patients with thrombosis associated with polycythemia vera (Chapter 152), the hematocrit should be maintained in the normal range with phlebotomies or chemotherapy, or with both. Patients maintained at a hematocrit target of less than 45% have a significantly lower rate of cardiovascular death and major thrombosis than do those with hematocrit targets of 45 to 50%. Low-dose aspirin (100 mg daily) can prevent thrombotic complications without increasing the incidence of major bleeding in patients who have polycythemia vera and no contraindications to such treatment. In patients with essential thrombocythemia and high risk or previous history of thrombosis, cytoreduction of the elevated platelet count should be achieved with chemotherapy.

Patients with paroxysmal nocturnal hemoglobinuria (Chapter 146) benefit from treatment with a complement inhibitor that targets terminal complement. Options include eculizumab (600 mg IV weekly as the initial dose, followed by maintenance dosing with expert consultation) and ravulizumab (single loading dose of 2400 to 3000 mg depending on weight, followed by maintenance dosing with expert consultation).[A12] These drugs also reduce the risk of thrombosis.[A13,A14]

ANTIPHOSPHOLIPID SYNDROME

Antiphospholipid syndrome (Chapter 160) is characterized by venous and arterial thrombosis, recurrent spontaneous pregnancy loss (which may also be due to thrombosis), thrombocytopenia, and a variety of neuropsychiatric manifestations.[19] The syndrome is associated with a heterogeneous group of autoantibodies that bind to anionic phospholipid-protein complexes, a protein cofactor of which is β_2-glycoprotein I. Patients with this syndrome have any combination of positive tests for different plasma antiphospholipid-protein antibodies (e.g.,

anticardiolipin, beta-2-glycoprotein I antibodies) and phospholipid-based clotting tests (lupus anticoagulants; Chapter 245).[20] The predominant prothrombotic effects of these antibodies are probably directed to the vessel wall.

DVT and pulmonary embolism are the most frequent venous thrombotic events in these patients. Cerebrovascular events, which are the most common arterial thrombotic complications, are manifested as stroke, transient ischemic attacks (Chapter 376), multi-infarct dementia (Chapter 371), or retinal artery occlusion (see Fig. 391-27). Peripheral and intra-abdominal vascular occlusion is encountered more rarely. About one third of these patients have nonbacterial heart valve vegetations (Libman-Sacks endocarditis; Chapter 61). The most prominent obstetric complications are recurrent spontaneous pregnancy loss and fetal growth retardation, which are probably due to thrombosis of placental vessels. Patients are occasionally seen with "catastrophic" antiphospholipid syndrome involving a series of acute and sometimes fatal vascular occlusive events, or "thrombotic storm." Thrombotic complications are limited largely to patients with primary antiphospholipid syndrome and patients in whom the antibodies are associated with collagen vascular disease, not with drugs or infections.

TREATMENT AND PREVENTION

Acute management of thrombosis in patients with antiphospholipid syndrome is essentially the same as in other individuals with thrombosis. Monitoring of heparin anticoagulation is difficult in patients with a lupus anticoagulant because they already have a prolonged activated partial thromboplastin time at baseline; the use of low-molecular-weight heparin, which does not require monitoring, can circumvent this problem. Warfarin is effective in preventing recurrent thrombosis but usually requires prolonged or indefinite therapy with doses to achieve an international normalized ratio of 2.0 to 3.0. Unlike most other situations, direct oral anticoagulants are not as effective as warfarin in patients with the antiphospholipid syndrome.[A15,21] Whereas laboratory evidence of antiphospholipid antibodies in patients with a first episode of VTE is still usually considered an indication for indefinite anticoagulant therapy, the data supporting this strategy are limited. No established treatment of women with the antiphospholipid syndrome has been shown to prevent recurrent fetal loss.

PROGNOSIS

Patients with the lupus anticoagulant have a six-fold higher risk of future thrombosis, a two- to four-fold increased risk of recurrent thrombosis, and 12% increased 10-year mortality.[22]

PREGNANCY, ASSISTED REPRODUCTIVE TECHNOLOGIES, ORAL CONTRACEPTIVES, AND HORMONE REPLACEMENT THERAPY

Activation of the coagulation system is initiated locally in the maternal uteroplacental circulation, where the placenta is the source of increased generation of thrombin. Platelet activation and increased platelet turnover also occur during normal pregnancy, and about 8% of healthy women have mild thrombocytopenia at term. Simultaneously, the fibrinolytic system is progressively blunted throughout pregnancy because of the action of placental plasminogen activator inhibitor type 2. The net effect of these coagulation changes is creation of a state of hypercoagulability. These systemic alterations are compounded by prothrombotic mechanical and rheologic factors in pregnancy, including venous stasis in the legs (especially the left lower extremity) caused by the gravid uterus, pelvic vein injury during labor, and the trauma of cesarean section. Increasing age, increasing parity, cesarean delivery, prolonged bedrest or immobilization, obesity, and previous thromboembolism are additional prothrombotic risk factors in pregnant women. Most thrombotic events associated with pregnancy occur in the peripartum period, especially after delivery. Special considerations for anticoagulation in the setting of pregnancy are noted in the section on treatment of primary hypercoagulable states.

Assisted reproductive technologies, mainly in vitro fertilization (IVF), confer an increased risk of venous thromboembolism, although the absolute magnitude is quite low. With IVF, the incidence of VTE is approximately 0.1 to 0.5% per treatment cycle. Ovarian hyperstimulation syndrome (Chapter 218), which is an iatrogenic and potentially fatal complication of IVF, represents an important risk factor for thrombosis.

Oral contraceptives induce a prothrombotic state by increasing procoagulant effects and decreasing physiologic anticoagulant effects. The use of oral contraceptives is associated with an increased risk for venous thrombosis, myocardial infarction, stroke, and peripheral arterial disease, particularly during the first year of use (Chapter 220). Unexpectedly, third-generation oral contraceptives, which contain less estrogen and a different progestin, double the risk for VTE in comparison to second-generation preparations. Postmenopausal hormone replacement increases the risk for deep VTE by a factor of 2 to 3.5, at least during the first year. Combined hormone replacement therapy with an estrogen and a progestin has no beneficial effect and possibly even a detrimental effect on the risk for arterial disease (Chapter 222),[A16] but low-dose estrogen monotherapy may reduce the risk of arterial thrombosis.[A17]

DVT and pulmonary embolism are the most common thrombotic complications of pregnancy and of the use of oral contraceptives or hormone replacement therapy. Coexisting primary hypercoagulable states are an at least additive risk factor in all these settings. In the absence of a clear family history of clinical VTE or a strongly thrombophilic mutation in a first-degree relative, there is little justification, however, to screen for prothrombotic mutations with pregnancy or before starting hormone replacement therapy or oral contraceptives.

TABLE 67-5 SOME PROTOTYPICAL SYSTEMIC INFLAMMATORY STATES THAT ARE ASSOCIATED WITH INCREASED THROMBOSIS RISK

Immune-mediated rheumatic and cutaneous inflammatory states
Rheumatoid arthritis
Systemic lupus erythematosus
Ankylosing spondylitis
ANCA-associated vasculitis
Psoriasis
Infections
Human immunodeficiency virus (HIV)
Cytomegalovirus
COVID-19
Acute pneumonia or urinary tract infection
Autoinflammatory disorders
Familial Mediterranean fever
Behçet disease
Systemic-onset juvenile idiopathic arthritis
Obesity
Sarcoidosis
Autoimmune gastrointestinal diseases
Ulcerative colitis
Crohn disease
Celiac disease
Pancreatitis

ANCA = anti-neutrophil cytoplasmic antibody; COVID-19 = coronavirus disease-2019.

SYSTEMIC INFLAMMATION

Diseases that cause systemic inflammation (Table 67-5) may be involved in the pathogenesis of VTE because of inflammation and damage to vessel walls as well as systemic hypercoagulability. Patients with autoimmune connective tissue diseases, particularly rheumatoid arthritis (Chapter 243), juvenile rheumatoid arthritis, and systemic lupus erythematosus (Chapter 245), are at increased risk of VTE. Psoriasis (Chapter 405), an immunoinflammatory disease that is associated with cardiovascular risk and atherothrombotic events, carries an increased risk of VTE, especially in younger patients with severe psoriasis. Other autoimmune skin diseases have not been associated with VTE.

In hospitalized patients with severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) and coronavirus disease 2019 (COVID-19) infection (Chapter 336), the overall thrombosis rate has been reported to be 9.5%.[23] About 20% of patients with SARS-CoV-2 and COVID-19 have a prolonged aPTT, of which about 90% are caused by a lupus anticoagulant. This finding should not, however, be considered a barrier to anticoagulation when it is otherwise appropriate (see Chapter 337). Intermediate-dose (enoxaparin 1 mg/kg daily) anticoagulation does not reduce venous or arterial thrombosis compared with standard-dose (enoxaparin 40 mg daily) prophylactic anticoagulation.[A18]

POSTOPERATIVE STATE, IMMOBILIZATION, AND TRAUMA

Postoperative thrombosis (Chapter 401) is caused by a combination of local mechanical factors, including decreased venous blood flow in the lower extremities, as well as systemic changes in coagulation. The level of risk for postoperative thrombosis depends largely on the type of surgery performed. However, the risk is increased in the presence of coexisting risk factors, such as an underlying inherited primary hypercoagulable state or malignant disease (see earlier sections), advanced age, and prolonged procedures. Postoperative

DVT and pulmonary embolism, which are the most common thrombotic complications, are often asymptomatic and detectable only by imaging. The incidence of DVT after general surgical procedures is about 20 to 25%, with almost 2% of these patients having clinically significant pulmonary embolism. Without prophylaxis, the risk for DVT after hip surgery and knee reconstruction ranges from 45 to 70%, and clinically significant pulmonary embolism occurs in 20% of patients undergoing hip surgery. Although the process of thrombosis generally begins intraoperatively or within a few days of surgery, the risk for this complication can extend to at least 6 weeks beyond the time of discharge from the hospital, particularly in hip replacement patients.

Patients who are bedridden or experiencing prolonged air travel (Chapter 265) are at increased risk for VTE. VTE is also one of the most common causes of morbidity and mortality in survivors of major trauma (Chapter 97), and asymptomatic DVT of the lower extremities has been detected by venography in more than 50% of hospitalized trauma patients. The risk for venous thrombosis after trauma is increased by advanced age, need for surgery or transfusions, and the presence of lower extremity fractures or spinal cord injury.

PREVENTION

Mechanical methods of prophylaxis against VTE are recommended in high-risk postoperative patients and bedridden patients with medical conditions (see Chapter 68).[24] Such methods include graduated compression stockings, intermittent pneumatic compression devices, and venous foot pumps. In-hospital anticoagulant prophylaxis is recommended for 10 to 14 days after major hip or limb surgery and in medical inpatients whose mobility is likely to be reduced for 72 hours or longer (see Chapter 68).[25] When anticoagulation is contraindicated in a severely injured patient, prophylactic placement of an inferior vena cava (IVC) filter does not reduce the incidence of symptomatic pulmonary embolism or 90-day mortality.[A19]

For long-distance travelers at increased risk of VTE (Chapter 265), including individuals with previous VTE or hypercoagulable states, current recommendations include frequent ambulation, nonalcoholic hydration, calf muscle exercises, and the use of properly fitted, below-knee graduated compression stockings providing 15 to 30 mm Hg of pressure at the ankle during travel; compression stockings are not recommended for other long-distance travelers. Aspirin or anticoagulants to prevent VTE are often used but not recommended for long-distance travelers at increased risk of VTE.

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68 VENOUS THROMBOSIS AND EMBOLISM

JEFFREY I. WEITZ AND JOHN W. EIKELBOOM

DEFINITIONS

Venous thromboembolism (VTE) includes deep vein thrombosis (DVT) and pulmonary embolism. DVT usually involves the deep veins of the legs or arms, but it can occur in other sites. Occlusion of the deep veins in a limb by thrombus impairs drainage of blood, thereby leading to pain and swelling distal to the obstruction. Pulmonary embolism refers to an obstruction of a pulmonary artery by thrombus that has traveled from elsewhere in the body, through the blood stream, and to the lungs. DVT in the legs or, less commonly, the arms is by far the leading source of pulmonary embolism.

Chronic complications of DVT and pulmonary embolism include post-thrombotic syndrome and chronic thromboembolic pulmonary hypertension, respectively. Post-thrombotic syndrome, which occurs in up to 40% of patients with extensive DVT, is characterized by dependent swelling and discomfort in the affected limb and in severe cases can lead to venous ulcers. The syndrome is caused by venous hypertension because of venous obstruction by residual thrombus and reflux of blood because of incompetent venous valves. Chronic thromboembolic pulmonary hypertension, which complicates up to 4% of cases of pulmonary embolism, occurs when emboli in the major pulmonary arteries fail to resolve and are replaced by fibrous tissue that becomes incorporated into the vessel walls, thereby narrowing or obstructing them. Obstruction of the pulmonary vascular bed increases pulmonary arterial resistance and can lead to right heart failure.

Thrombosis also can occur in superficial veins. Although benign and self-limiting when veins in the hand or antecubital fossa are involved as a complication of blood collection, intravenous catheters, or drug delivery, superficial vein thrombosis in the lower extremities can extend into the deep veins, thereby leading to DVT and pulmonary embolism.

EPIDEMIOLOGY

A first episode of VTE occurs in about 1 to 2 persons per 1000 each year in the United States. The incidence rises with age, with 5 to 10 cases per 1000 persons per year by the age of 80 years. Although men and women are affected equally, the incidence is four times higher in high-income than low-income countries.

Approximately one third of patients with symptomatic VTE present with pulmonary embolism, whereas the remainder present with DVT. Pulmonary embolism accounts for an estimated 15% of deaths in hospitalized patients and is responsible for about 150,000 deaths each year in the United States. As a result, VTE is the third most common cause of vascular death after myocardial infarction and stroke.

PATHOBIOLOGY

Heritable and acquired risk factors determine the intrinsic risk of VTE (E-Fig. 68-1).[1] Heritable risk factors include abnormalities associated with hypercoagulability of the blood (Chapter 67), the most common of which are factor V Leiden and the prothrombin G20210A gene mutation. Acquired risk factors include advanced age, history of previous VTE, obesity, and active cancer, which limit mobility and may be associated with hypercoagulability. Superimposed on this background risk, VTE often occurs in the presence of triggering factors, which increase the risk above a critical threshold. Triggering factors such as surgery, trauma, and pregnancy or estrogen therapy lead to endothelial cell activation, stasis, and hypercoagulability, which are the components of the Virchow triad.

Up to half of patients with a first episode of VTE have no identifiable risk factors and are described as having unprovoked or idiopathic VTE. The

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Patients who are bedridden or experiencing prolonged air travel (Chapter 265) are at increased risk for VTE. VTE is also one of the most common causes of morbidity and mortality in survivors of major trauma (Chapter 97), and asymptomatic DVT of the lower extremities has been detected by venography in more than 50% of hospitalized trauma patients. The risk for venous thrombosis after trauma is increased by advanced age, need for surgery or transfusions, and the presence of lower extremity fractures or spinal cord injury.

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Mechanical methods of prophylaxis against VTE are recommended in high-risk postoperative patients and bedridden patients with medical conditions (see Chapter 68).[24] Such methods include graduated compression stockings, intermittent pneumatic compression devices, and venous foot pumps. In-hospital anticoagulant prophylaxis is recommended for 10 to 14 days after major hip or limb surgery and in medical inpatients whose mobility is likely to be reduced for 72 hours or longer (see Chapter 68).[25] When anticoagulation is contraindicated in a severely injured patient, prophylactic placement of an inferior vena cava (IVC) filter does not reduce the incidence of symptomatic pulmonary embolism or 90-day mortality.[A19]

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68 VENOUS THROMBOSIS AND EMBOLISM

JEFFREY I. WEITZ AND JOHN W. EIKELBOOM

DEFINITIONS

Venous thromboembolism (VTE) includes deep vein thrombosis (DVT) and pulmonary embolism. DVT usually involves the deep veins of the legs or arms, but it can occur in other sites. Occlusion of the deep veins in a limb by thrombus impairs drainage of blood, thereby leading to pain and swelling distal to the obstruction. Pulmonary embolism refers to an obstruction of a pulmonary artery by thrombus that has traveled from elsewhere in the body, through the blood stream, and to the lungs. DVT in the legs or, less commonly, the arms is by far the leading source of pulmonary embolism.

Chronic complications of DVT and pulmonary embolism include post-thrombotic syndrome and chronic thromboembolic pulmonary hypertension, respectively. Post-thrombotic syndrome, which occurs in up to 40% of patients with extensive DVT, is characterized by dependent swelling and discomfort in the affected limb and in severe cases can lead to venous ulcers. The syndrome is caused by venous hypertension because of venous obstruction by residual thrombus and reflux of blood because of incompetent venous valves. Chronic thromboembolic pulmonary hypertension, which complicates up to 4% of cases of pulmonary embolism, occurs when emboli in the major pulmonary arteries fail to resolve and are replaced by fibrous tissue that becomes incorporated into the vessel walls, thereby narrowing or obstructing them. Obstruction of the pulmonary vascular bed increases pulmonary arterial resistance and can lead to right heart failure.

Thrombosis also can occur in superficial veins. Although benign and self-limiting when veins in the hand or antecubital fossa are involved as a complication of blood collection, intravenous catheters, or drug delivery, superficial vein thrombosis in the lower extremities can extend into the deep veins, thereby leading to DVT and pulmonary embolism.

EPIDEMIOLOGY

A first episode of VTE occurs in about 1 to 2 persons per 1000 each year in the United States. The incidence rises with age, with 5 to 10 cases per 1000 persons per year by the age of 80 years. Although men and women are affected equally, the incidence is four times higher in high-income than low-income countries.

Approximately one third of patients with symptomatic VTE present with pulmonary embolism, whereas the remainder present with DVT. Pulmonary embolism accounts for an estimated 15% of deaths in hospitalized patients and is responsible for about 150,000 deaths each year in the United States. As a result, VTE is the third most common cause of vascular death after myocardial infarction and stroke.

PATHOBIOLOGY

Heritable and acquired risk factors determine the intrinsic risk of VTE (E-Fig. 68-1).[1] Heritable risk factors include abnormalities associated with hypercoagulability of the blood (Chapter 67), the most common of which are factor V Leiden and the prothrombin G20210A gene mutation. Acquired risk factors include advanced age, history of previous VTE, obesity, and active cancer, which limit mobility and may be associated with hypercoagulability. Superimposed on this background risk, VTE often occurs in the presence of triggering factors, which increase the risk above a critical threshold. Triggering factors such as surgery, trauma, and pregnancy or estrogen therapy lead to endothelial cell activation, stasis, and hypercoagulability, which are the components of the Virchow triad.

Up to half of patients with a first episode of VTE have no identifiable risk factors and are described as having unprovoked or idiopathic VTE. The

ABSTRACT

Venous thromboembolism (VTE), which includes deep vein thrombosis (DVT) and pulmonary embolism, is the third most common cause of vascular death after myocardial infarction and stroke. In patients with suspected VTE, the diagnosis can be readily established with noninvasive testing: compression ultrasonography for the diagnosis of DVT and computed tomographic pulmonary angiography for the diagnosis of pulmonary embolism. Many patients with VTE have well-known risk factors such as a personal or family history of VTE, recent surgery, or hospitalization for medical illness or cancer. However, up to half have no readily identifiable risk factors and are said to have unprovoked VTE. Anticoagulation therapy is the mainstay for treatment of VTE. Adjunctive measures such as thrombectomy, thrombolytic therapy, or inferior vena cava filters are reserved for selected patients. The duration of anticoagulant therapy varies depending on whether the VTE is provoked or unprovoked and whether the provoking factors are transient or persistent. Direct oral anticoagulants, such as apixaban, dabigatran, edoxaban, and rivaroxaban, have essentially replaced warfarin for the treatment of VTE and are increasingly being used in place of low-molecular-weight heparin for the treatment of VTE in selected cancer patients.

KEYWORDS

deep vein thrombosis
pulmonary embolism
venous thromboembolism
anticoagulants

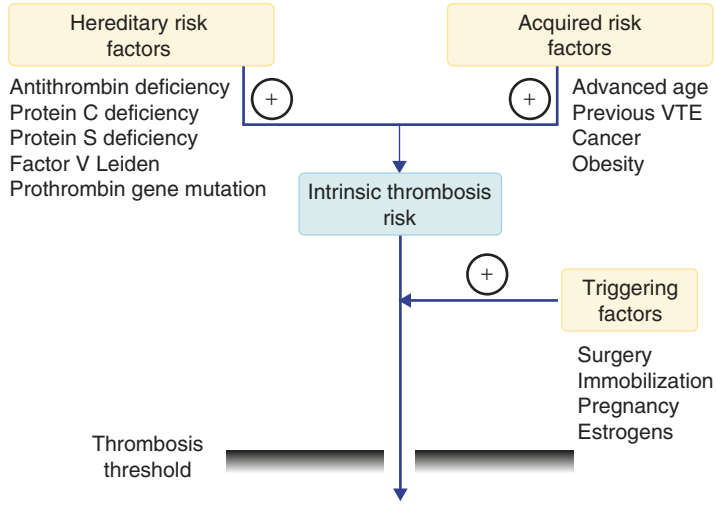

E-FIGURE 68-1. Thrombosis threshold. Hereditary and acquired risk factors combine to create an intrinsic risk of thrombosis. This risk is increased by extrinsic triggering factors. If the intrinsic and extrinsic forces exceed a critical threshold at which thrombin generation overwhelms protective mechanisms, thrombosis occurs. VTE = venous thromboembolism.

TABLE 68-1 ALTERNATIVE DIAGNOSES IN 87 CONSECUTIVE PATIENTS WITH CLINICALLY SUSPECTED DEEP VEIN THROMBOSIS AND NORMAL VENOGRAMS

DIAGNOSIS	PATIENTS (%)
Muscle strain	24
Direct twisting injury to the leg	10
Leg swelling in paralyzed limb	9
Lymphangitis, lymphatic obstruction	7
Venous reflux	7
Muscle tear	6
Baker cyst	5
Cellulitis	3
Internal abnormality of the knee	2
Unknown	26

remainder develop VTE secondary to risk factors; these episodes are considered provoked. Risk factors for VTE can be classified according to their magnitude and duration as major or minor and transient or persistent, respectively. Major transient risk factors include surgery or trauma, whereas active cancer is an example of a major persistent risk factor. Minor transient risk factors include estrogen therapy or prolonged travel, whereas obesity, a past or family history of VTE, and thrombophilic defects such as the factor V Leiden or prothrombin gene mutation are examples of minor persistent risk factors (Chapter 67).

Coronavirus disease 2019 (COVID-19) caused by the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) is a major transient risk factor for VTE and other thrombotic events (Chapter 336). The risk of VTE is greatest in patients who are hospitalized with moderate or severe COVID-19 disease and who develop a hypercoagulable state characterized by marked elevation of D-dimer levels. Symptomatic VTE occurs in about 10% of patients hospitalized with COVID-19, and its incidence is four-fold higher in patients who are in intensive care units compared with non–intensive care settings.[2]

DVT can occur in either leg. However, DVT in pregnancy involves the ileofemoral veins of the left leg in 90% of cases and typically spares the calf and popliteal veins. Localization to this site reflects compression of the left iliac vein by the enlarging uterus, an exaggeration of the so-called May-Thurner syndrome, in which venous webs and compression of the left iliac vein by the overlying right iliac artery reduce blood flow and can lead to DVT.

Most pulmonary emboli originate from DVT in the lower limbs, and pulmonary embolism can be detected in about 40% of patients with proximal DVT. Likewise, at least 50% of patients with proven pulmonary embolism have demonstrable DVT. Upper extremity DVT involving the axillary or subclavian veins also can give rise to pulmonary embolism but only in 10 to 15% of such patients. Upper extremity DVT most often occurs in patients with cancer (Chapter 164), particularly patients with indwelling central venous catheters. Spontaneous upper extremity DVT, usually involving the dominant arm, can occur with strenuous effort—the so-called Paget-Schroetter syndrome.

CLINICAL MANIFESTATIONS

Patients with DVT typically present with swelling, pain, warmth, and redness in the involved extremity (Fig. 68-1).[3] However, some patients may have minimal symptoms. The differential diagnosis includes trauma, infection, a ruptured Baker cyst (Chapter 243; Table 68-1), peripheral artery disease (Chapter 65), and other venous diseases such as chronic venous insufficiency; DVT may coexist with these disorders.

DVT usually starts in the calf veins, where it remains isolated in about 15% of such patients. Most cases of isolated calf DVT resolve spontaneously, but in about 20% of such patients the thrombus extends into the proximal veins, usually within a week after the onset of symptoms. Once thrombi extend into the proximal veins of the leg, they can dislodge and cause pulmonary embolism.

The most common symptoms and signs of pulmonary embolism include dyspnea on exertion,[4] often pleuritic chest pain, tachypnea, and cough. Many patients with pulmonary emboli have concomitant symptoms and signs of DVT. Less common symptoms and signs include fever, hemoptysis, cyanosis, hypotension, and shock. Other nonspecific symptoms include palpitations, anxiety, and light-headedness.

Patients with extensive pulmonary emboli often have dyspnea at rest and hypotension, and they may present with syncope (Chapters 39 and 49) because

FIGURE 68-1. **Deep vein thrombosis (DVT) manifesting as an acutely swollen left leg.** Note the dilation of the superficial veins. The leg was hot to the touch, and there was tenderness along the course of the left popliteal and femoral veins. Fewer than 50% of patients with DVT present with these findings, and other conditions may mimic DVT, so further investigation is always indicated. Note the coincidental psoriatic lesion below the right knee. (From Forbes CD, Jackson WF. *Color Atlas and Text of Clinical Medicine*, 3rd ed. London: Mosby; 2003.)

of hypoxemia and low cardiac output. Central and peripheral cyanosis can occur, and a gallop rhythm may develop as a consequence of heart failure. The jugular veins may be distended if right heart failure develops. The second heart sound can be widely split, and the pulmonic component may be loud because of delayed emptying of the right ventricle. A right ventricular heave may be present with massive pulmonary embolism and acute pulmonary hypertension. The combination of hypotension, hypoxemia, and increased cardiac workload may trigger angina (Chapter 56) or overt myocardial infarction (Chapters 57 and 58).

When patients present with chest symptoms suggestive of pulmonary embolism, the differential diagnosis includes pulmonary disorders, such as pneumonia (Chapter 85), an exacerbation of chronic obstructive lung disease (Chapter 76), or asthma (Chapter 75); pleurisy secondary to connective tissue disease (Chapter 86); cardiac disorders, such as heart failure (Chapter 45), acute coronary syndrome (Chapter 57), or pericarditis (Chapter 62); and musculoskeletal disorders, such as rib fracture.

DIAGNOSIS

By itself, the clinical diagnosis of DVT or pulmonary embolism is inaccurate because no individual symptom or sign is sufficiently predictive for confirming or excluding the diagnosis. In patients with symptoms suggestive of DVT, the diagnosis is confirmed in up to 25%.

Therefore, diagnosis starts with determination of the pretest probability using validated risk assessment models for DVT (Table 68-2) or pulmonary embolism (Table 68-3).[5] Although these clinical assessment tools categorize patients according to their pretest probability of VTE with reasonable accuracy, they should not be used in isolation. Instead, risk assessment models should be combined with laboratory testing such as the D-dimer, which, if normal, can be used to exclude the diagnosis of VTE in patients with low to moderate pretest probability. If the D-dimer test is positive or if the pretest probability is high, the diagnosis of DVT or pulmonary embolism should be confirmed using venous compression ultrasonography or computed tomography pulmonary angiography (CTPA), respectively (Fig. 68-2).

Laboratory Tests

D-Dimer

A plasmin-derived degradation product of cross-linked fibrin, D-dimer can be measured in whole blood or plasma and is a biomarker that reflects ongoing activation of the coagulation system. D-dimer assays vary in their sensitivity and specificity for the diagnosis of VTE. Enzyme-linked immunosorbent and advanced turbidimetric D-dimer assays have sensitivities over 95%, but they are not specific for the diagnosis of VTE. D-dimer levels can be elevated with

TABLE 68-2 PREDICTION RULE FOR LIKELIHOOD OF DEEP VEIN THROMBOSIS

CLINICAL CHARACTERISTIC	SCORE*
Active cancer (treatment ongoing within previous 6 months or receiving palliative care)*	1
Paralysis, paresis, or recent plaster immobilization of the lower extremities	1
Recent bedrest of >3 days or major surgery within 3 months requiring anesthesia	1
Localized tenderness of the deep veins of the leg	1
Entire leg swollen	1
Calf swelling of >3 cm larger than asymptomatic side measured 10 cm below tibial tuberosity	1
Pitting edema confined to the symptomatic leg	1
Collateral superficial veins (not varicose)	1
Previously documented deep vein thrombosis	1
Alternative diagnosis as likely as or more likely than deep vein thrombosis	−2

*A score of 0 or less indicates low probability, 1 or 2 indicates moderate probability, and 3 or more indicates high probability. Non-melanoma skin cancer is not a risk factor.

Modified from Wells PS, Anderson DR, Bormanis J, et al. Value of assessment of pretest probability of deep-vein thrombosis in clinical management. *Lancet*. 1997;350:1795-1798.

TABLE 68-3 PREDICTION RULE FOR LIKELIHOOD OF PULMONARY EMBOLISM

VARIABLE	POINTS
PREDISPOSING FACTORS	
Previous VTE	1.5
Recent surgery or immobilization	1.5
Cancer	1
SYMPTOMS	
Hemoptysis	1
SIGNS	
Heart rate >100 beats/min	1.5
Clinical signs of DVT	3
CLINICAL JUDGMENT	
Alternative diagnosis less likely than PE	3
CLINICAL PROBABILITY	**TOTAL POINTS***
Low	<2
Moderate	2-6
High	>6

*This rule also can be used to classify patients into two groups in which a score of 4 or less indicates low probability and a score of more than 4 indicates high probability. When this approach is used, D-dimer testing should be considered in those with low probability.

DVT = deep vein thrombosis; PE = pulmonary embolism; VTE = venous thromboembolism.

Adapted from Wells PS, Ginsberg JS, Anderson DR, et al. Use of a clinical model for safe management of patients with suspected pulmonary embolism. *Ann Intern Med*. 1998;129:997-1005.

advanced age, chronic inflammatory conditions, and malignancy. In addition, hospitalized patients are more likely to have elevated D-dimer levels than outpatients. Because of this lack of specificity, the value of the D-dimer assay resides with its high negative predictive value. A normal D-dimer level in a patient with a low or moderate pretest probability of DVT or pulmonary embolism essentially excludes the diagnosis, thereby obviating the need for further diagnostic testing[6] without increasing the risk of a missed VTE.[A1]

Compression Ultrasonography

Compression ultrasonography with or without Doppler imaging is the most widely used noninvasive test for diagnosis of DVT because of its accuracy for detecting thrombus involving the popliteal or more proximal veins. Noncompressibility (Fig. 68-3) of the proximal leg veins on ultrasonography is diagnostic of DVT in symptomatic patients and is an indication for treatment. The sensitivity of ultrasonography for detecting calf DVT is lower than for detecting proximal DVT; consequently, some centers examine only the veins above the trifurcation in the calf, whereas others examine both the proximal and calf veins. A normal whole-leg ultrasound excludes the diagnosis of DVT. If only the proximal veins are examined, the ultrasound should be repeated in 1 week to identify the 20% of patients who initially have isolated calf vein thrombosis but whose thrombus subsequently extends into the proximal veins.

Contrast Venography

Although ascending contrast venography remains the gold standard for diagnosis of DVT, the test is rarely performed because of its expense, discomfort to the patient, and potential for complications. A constant intraluminal filling defect is diagnostic of acute thrombosis (Fig. 68-4), and DVT can be excluded in patients who have a normal, adequately performed venogram. Minor side effects, including local pain, nausea, and vomiting, are not uncommon, whereas more serious adverse reactions, such as anaphylaxis or other allergic manifestations, are rare.

Computed Tomographic Pulmonary Angiography

Multidetector CT pulmonary angiography has largely replaced ventilation-perfusion lung scanning for diagnosing pulmonary embolism because of its wide availability, the rapidity of its results, and a sensitivity and specificity sufficient for its use as a stand-alone test. In contrast to lung scanning, CT pulmonary angiography not only permits direct visualization of thrombi in the pulmonary arteries of patients with pulmonary embolism (Fig. 68-5) but also provides an alternative diagnosis in many of those who prove not to have pulmonary embolism. A CT pulmonary angiogram showing thrombus in pulmonary arteries up to the segmental level provides evidence of pulmonary embolism, whereas a negative CT pulmonary angiogram excludes pulmonary embolism and is associated with subsequent clinical outcomes that are at least as good as those in patients with negative lung scans. Compared with lung scanning, CT pulmonary angiography detects more isolated subsegmental thrombi in about 1 to 5% of patients, but it is unclear whether isolated subsegmental defects are benign or associated with outcomes like those of more proximal thrombi. A normal bilateral venous compression ultrasound examination of the lower extremities to exclude DVT in this setting may help to identify patients with a low thrombus burden who do not require anticoagulation.

CT pulmonary angiography can be combined with CT venography so that the diagnosis of pulmonary embolism and DVT can be established with a single test and only one injection of contrast dye. Compared with CT pulmonary angiography alone, combining it with CT venography increases the sensitivity for diagnosing pulmonary embolism from 83 to 90%, but the specificity remains unchanged, thereby resulting in only a modest increase in negative predictive value. CT venography adds significant radiation exposure and only marginally increases the overall detection rate. Therefore, venous compression ultrasonography is preferred over CT venography for the diagnosis of DVT because it provides the same information without exposing patients to ionizing radiation.

Ventilation-Perfusion Lung Scanning

This two-part test consists of a ventilation phase and a perfusion phase. The ventilation phase involves inhalation of an aerosol form of radioactive isotopes of xenon or technetium to assess air delivery to the various parts of the lung. In contrast, the perfusion phase involves the intravenous injection of technetium-labeled macroaggregates of albumin, which enables assessment of blood flow within the lungs once the aggregates lodge in the pulmonary microcirculation. Images for both parts of the test are acquired using a gamma counter. Areas of lung affected by pulmonary embolism do not light up on the perfusion scan because the macroaggregates of albumin fail to reach sites where the pulmonary arteries are occluded (Fig. 68-6). By comparison, areas with abnormal perfusion because of pulmonary embolism will ventilate normally, yielding a ventilation-perfusion mismatch.

A normal ventilation-perfusion lung scan effectively excludes the diagnosis of pulmonary embolism, but only 25% of patients with suspected pulmonary embolism have a normal scan. One or more segmental or larger perfusion defects that ventilate normally characterize a high-probability lung scan, which establishes the diagnosis of pulmonary embolism. However, even with single-photon emission CT technology, only about 10% of patients with suspected pulmonary emboli have a high-probability lung scan. The remaining 65% of lung scans exhibit smaller areas of mismatch or matched defects and fall within the non–high-probability category. Because up to 40% of patients with non–high-probability scans have pulmonary emboli, such patients require additional investigations to exclude the diagnosis.

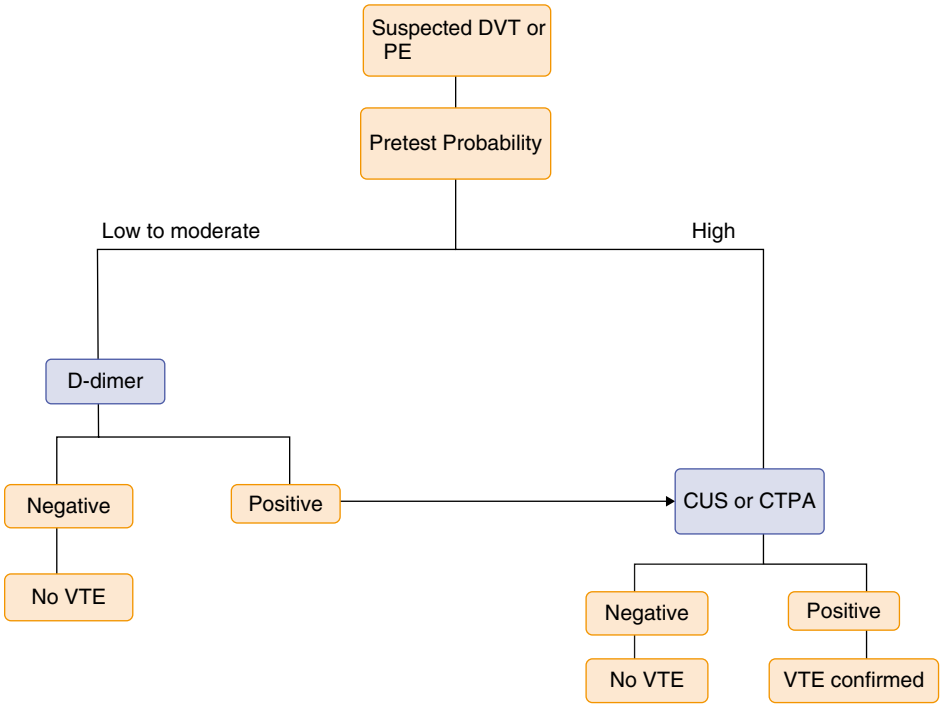

FIGURE 68-2. **Clinical approach in patients with suspected deep vein thrombosis (DVT) or pulmonary embolism (PE).** CTPA = computed tomographic pulmonary angiogram; CUS = compression ultrasound; VTE = venous thromboembolism.

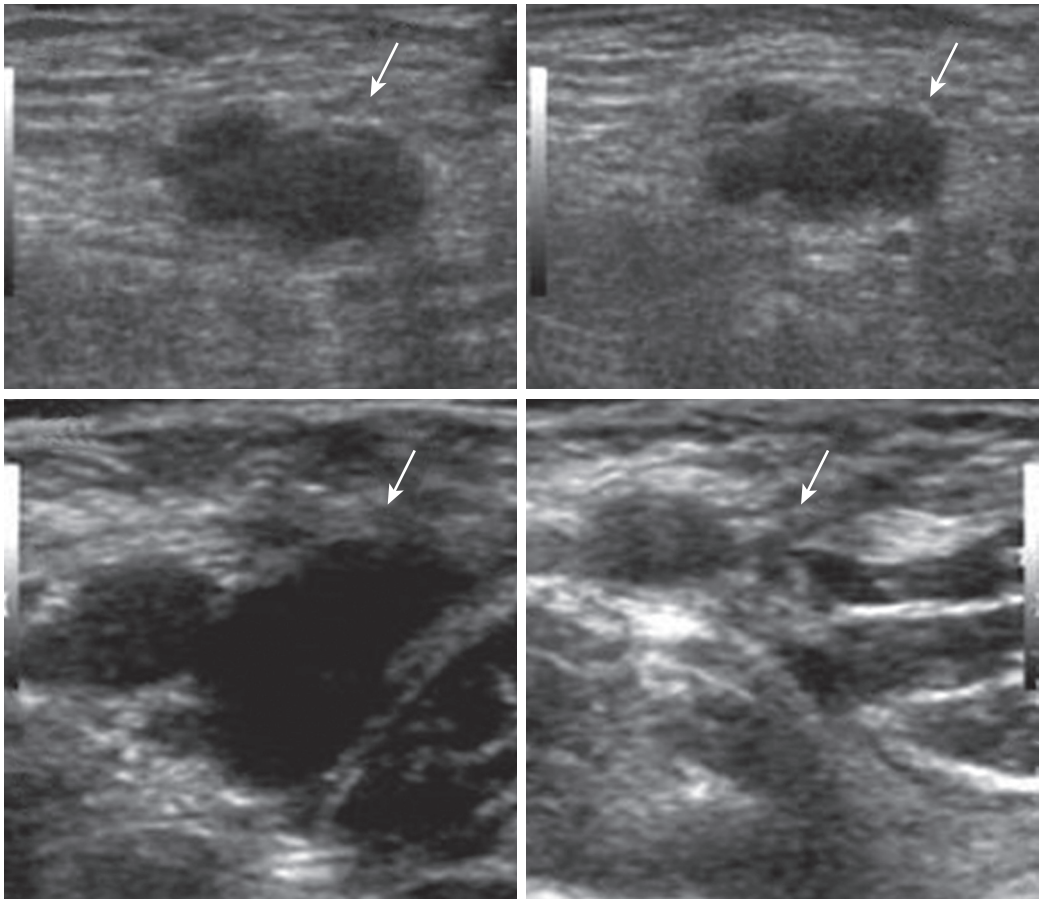

FIGURE 68-3. **Compression ultrasonography demonstrates thrombosis in the popliteal vein.** The sonograms in the *top row* demonstrate examination without *(left side)* and with *(right side)* probe compression of the skin overlying the popliteal vein. The lack of compressibility is diagnostic of deep vein thrombosis. The *bottom row* shows analogous views of the femoral vein, which shows partial compressibility.

Although CT pulmonary angiography has largely replaced lung scanning for the diagnosis of pulmonary embolism, the lung scan is the diagnostic test of choice for patients with renal impairment or a history of allergy to angiographic contrast media and for women younger than 40 years to reduce radiation exposure to the breasts. For the diagnosis of pulmonary embolism in pregnancy, lung scanning produces less maternal and fetal radiation exposure and is sometimes preferred over CT pulmonary angiography. However, the incremental value of a ventilation-perfusion scan is low in patients with a nondiagnostic CT pulmonary angiogram.

Magnetic Resonance Imaging

In contrast to CT pulmonary angiography, gadolinium-enhanced magnetic resonance imaging (MRI) does not subject patients to ionizing radiation, and gadolinium can safely be given to patients with a history of allergy to contrast dye but not to patients with renal impairment. The combination of MR pulmonary angiography with MR venography has a higher sensitivity than MR pulmonary angiography alone for the diagnosis of pulmonary embolism, and MRI can be especially useful for diagnosing recurrent ipsilateral DVT.[7] However, MR angiography and venography protocols are technically

FIGURE 68-4. Ascending venography. The venogram demonstrates a persistent (two or more different views) intraluminal filling defect in the popliteal vein.

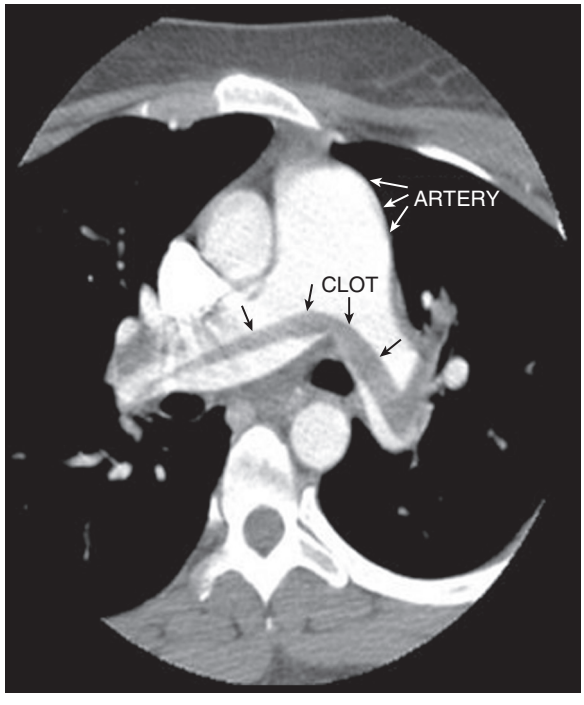

FIGURE 68-5. Computed tomographic pulmonary angiography. The scan demonstrates a saddle pulmonary embolus in the main pulmonary artery.

demanding, so MRI should be used to diagnose pulmonary embolism only in experienced centers and in patients for whom standard tests are contraindicated.

Interventional Contrast Pulmonary Angiography

Pulmonary angiography requires direct contrast injection into the pulmonary arteries, followed by imaging using digital subtraction technology. Presence of a thrombus, which appears as a filling defect or as a sudden cutoff of blood flow in a pulmonary arterial branch, establishes the diagnosis of pulmonary embolism. Although direct angiography allows visualization of small thrombi in subsegmental pulmonary arteries, high interobserver variability in the interpretation of isolated filling defects at this level limits the specificity of this finding. As an invasive test, the mortality rate associated with pulmonary angiography is 0.2%, with deaths usually occurring in patients with hemodynamic compromise or respiratory failure.

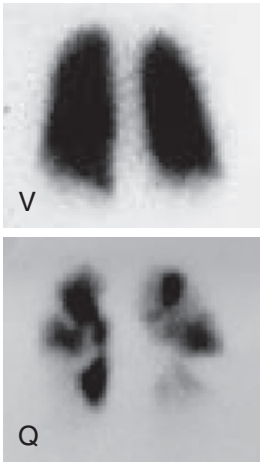

FIGURE 68-6. Ventilation-perfusion lung scan. The ventilation scan (V) is normal, whereas the perfusion scan (Q) shows multiple defects. This combination is diagnostic of pulmonary embolism.

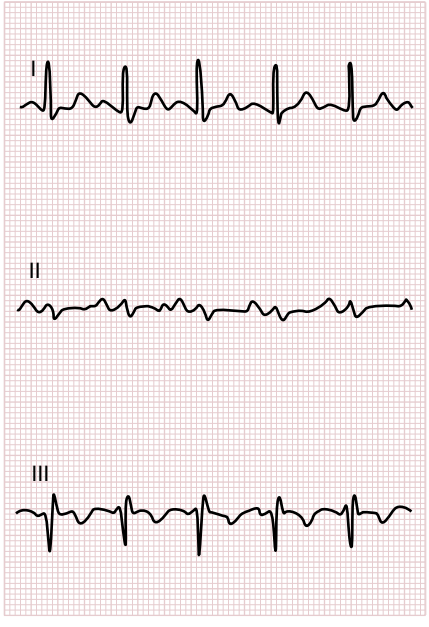

FIGURE 68-7. Classic electrocardiogram findings with pulmonary embolism. Note the S waves in lead I and the Q waves and inverted T waves in lead III, findings that comprise the S_1, Q_3, and T_3 pattern.

Because of its associated risks and because CT pulmonary angiography offers similar or better information, direct pulmonary angiography is rarely performed.

Other Tests

Routine blood tests in patients with suspected or diagnosed VTE should include a complete blood count, including a platelet count, and a baseline international normalized ratio (INR) and activated partial thromboplastin time (aPTT). Serum creatinine and blood urea nitrogen levels are needed to help guide the choice of anticoagulant therapy and the suitability for diagnostic testing using angiographic dyes; serum electrolytes and liver enzymes also may provide useful information.

Blood markers of right ventricular dysfunction, which occurs with extensive pulmonary embolism, include brain natriuretic peptide (BNP) or its precursor, N-terminal pro-BNP, which are released in response to myocardial stretching (Chapter 45). Elevated levels of troponin I or T provide evidence of myocardial injury (Chapter 57). Although these markers are associated with a worse prognosis in patients with pulmonary embolism, their positive predictive value for making the diagnosis is low.

The ECG may show new changes suggestive of right ventricular strain, such as T wave inversion in leads V_1 to V_4; the classic S_1, Q_3, and T_3 pattern (Fig. 68-7); and complete or incomplete right bundle branch block. However, these ECG changes have limited sensitivity and are mainly found in patients with more extensive pulmonary emboli.

Echocardiographic findings suggestive of right ventricular dysfunction include right ventricular dilation or hypokinesis, increased right ventricular diameter relative to that of the left ventricle, and increased velocity of the jet of tricuspid regurgitation. Echocardiography may also detect a right-to-left shunt through a patent foramen ovale (Chapter 55) and may provide evidence of right ventricular thrombus, both of which are associated with increased mortality in patients with pulmonary embolism. With no universal criteria for the diagnosis of right ventricular dysfunction, however, the utility of routine echocardiography remains uncertain. In general, routine echocardiography is recommended only in patients with severe hypoxemia or other evidence to suggest hemodynamic compromise.

TREATMENT

Outpatient treatment is as safe as routine inpatient treatment for most patients with DVT and for low-risk patients with acute pulmonary embolism.[8,9] In pulmonary embolism patients at intermediate risk, such as patients with right ventricular enlargement, outpatient management can be considered, but brief admission to hospital may be a safer approach. Therefore, rapid risk stratification is crucial to help guide treatment. Patients who have contraindications to anticoagulant therapy may require insertion of a retrievable inferior vena cava filter.

Anticoagulation is the cornerstone of treatment for VTE and should be initiated immediately in patients with suspected pulmonary embolism or DVT even while awaiting the results of confirmatory tests. Although anticoagulant therapy remains the main treatment for pulmonary embolism, patients with severe hemodynamic compromise may benefit from reperfusion therapy or surgical thrombectomy to restore blood flow rapidly to the pulmonary arteries and to reduce pulmonary artery pressure.

The risk of recurrent VTE is highest in the first few weeks after diagnosis and progressively decreases thereafter. Consequently, VTE treatment has been divided into three stages: initial therapy for the first 1 to 3 weeks, the goals of which are to prevent thrombus extension and fatal pulmonary embolism; therapy for the subsequent 3 months, which is often termed long-term therapy and is given to treat the VTE and to reduce the risk of complications, such as post-thrombotic syndrome and chronic thromboembolic pulmonary hypertension; and extended therapy beyond 3 months, which is administered when the risk of recurrent VTE without anticoagulant therapy is high and exceeds the risk of major bleeding with continued anticoagulant therapy.[10]

High-Risk Pulmonary Embolism

High-risk patients can be identified at the bedside based on the presence of hemodynamic compromise. Such patients also may have right ventricular dysfunction and elevated levels of biomarkers (i.e., troponin and BNP). The most common cause of death in patients with severe pulmonary embolism is acute right ventricular failure, which causes low systemic output. To prevent this complication, patients who present with hemodynamic compromise require circulatory and respiratory support. Patients with right ventricular failure often require modest fluid expansion and may need inotropic agents, such as dobutamine, dopamine, or norepinephrine, for severe hypotension or shock (Chapter 93). Emerging data raise the possibility that endothelin antagonists and phosphodiesterase-5 inhibitors may attenuate the pulmonary hypertension in patients with severe pulmonary embolism (Chapter 69).

Patients with pulmonary embolism frequently have hypoxemia and hypocapnia. Hypoxemia can usually be reversed with nasal oxygen. Measures to reduce fever and agitation with acetaminophen and mild sedation may help minimize oxygen consumption. In patients who have severe pulmonary embolism and who require mechanical ventilation, low tidal volumes should be used, and positive end-expiratory pressure should be applied with caution because it can reduce venous return and worsen right ventricular failure (Chapter 91).

Patients with pulmonary embolism associated with hypotension or shock also may benefit from pharmacologic, mechanical, or surgical reperfusion therapy. Pharmacologic reperfusion therapy involves the systemic administration of a fibrinolytic agent (Table 68-4), preferably within 48 hours of the onset of symptoms, but later treatment still may be of benefit. Up to 13% of patients who receive fibrinolytic therapy experience a major bleed, and the rate of intracranial or fatal bleeding can reach 1.8%. Consequently, fibrinolytic therapy currently is justified only in patients who have severe pulmonary embolism and no contraindications (Table 68-5). In patients at intermediate risk, fibrinolytic therapy prevents hemodynamic deterioration but increases bleeding and stroke. If patients with severe pulmonary embolism are not treated with reperfusion therapy, they should generally be treated with heparin (Table 68-6) or low-molecular-weight heparin (LMWH) (Table 68-7). LMWH is preferred in the majority of patients, including patients with a creatinine clearance of 15 to 30 mL/min, whereas heparin remains the treatment of choice in patients who have end-stage renal disease (creatine clearance <15 mL/min) and patients who are on dialysis.

TABLE 68-4 APPROVED REGIMENS FOR INTRAVENOUS FIBRINOLYTIC THERAPY FOR TREATMENT OF SEVERE PULMONARY EMBOLISM

AGENTS	RECOMMENDED REGIMENS
Streptokinase	250,000 IU as a loading dose over 30 min, followed by 100,000 IU/hr over 12 to 24 hr
Tissue plasminogen activator	100 mg over 2 hr or 0.6 mg/kg over 10 to 15 min (maximal dose of 50 mg)

TABLE 68-5 CONTRAINDICATIONS TO FIBRINOLYTIC THERAPY

ABSOLUTE CONTRAINDICATIONS
Any hemorrhagic stroke or stroke of unknown origin
Central nervous system damage or neoplasm
Major trauma, surgery, or head injury in past 3 weeks
Gastrointestinal bleeding in past month
Significant ongoing bleeding
RELATIVE CONTRAINDICATIONS
Ischemic stroke or transient ischemic attack in past 6 months
Treatment with a direct oral anticoagulant or a vitamin K antagonist
Pregnancy or within 1 week of delivery
Noncompressible puncture site
Traumatic resuscitation
Advanced liver disease
Infective endocarditis
Active peptic ulcer disease

TABLE 68-6 WEIGHT-BASED NOMOGRAM FOR INITIAL INTRAVENOUS HEPARIN THERAPY

aPTT	DOSE (IU/kg)
Initial dose	80 bolus, then 18/hr
<35 sec (<1.2×)*	80 bolus, then 4/hr
35-45 sec (1.2-1.5×)	40 bolus, then 2/hr
46-70 sec (1.5-2.3×)	No change
71-90 sec (2.3-3×)	Decrease infusion rate by 2/hr
>90 sec (>3×)	Hold infusion 1 hr, then decrease infusion rate by 3/hr

*Figures in parentheses show comparison with control.

aPTT = activated partial thromboplastin time. In general, with contemporary aPTT reagents, the target therapeutic range is two to three times control.

Modified from Raschke RA, Reilly BM, Guidry JR, et al. The weight-based heparin dosing nomogram compared with a "standard care" nomogram: a randomized controlled trial. *Ann Intern Med.* 1993;119:874-881.

TABLE 68-7 SUBCUTANEOUS DOSING REGIMENS FOR VARIOUS LOW-MOLECULAR-WEIGHT HEPARIN PREPARATIONS

AGENT	DOSE	INTERVAL
Enoxaparin	1 mg/kg 1.5 mg/kg	Twice daily Once daily
Dalteparin	100 IU/kg 200 IU/kg	Twice daily Once daily
Tinzaparin	175 IU/kg	Once daily

IU = international unit (note that 1 mg of enoxaparin = 100 IU).

Mechanical reperfusion includes percutaneous catheter thrombectomy, an approach that avoids the need for fibrinolytic drugs altogether, or catheter-directed fibrinolytic therapy (without or with ultrasound assistance), which requires lower doses of fibrinolytic agents than are used for systemic administration. In some centers, surgical pulmonary embolectomy may be an option for patients who have severe pulmonary embolism, such as a saddle embolus

occluding the main pulmonary artery (see Fig. 68-5), and who are at high risk for bleeding with systemic fibrinolytic therapy or who have failed such treatment. Mechanical and surgical techniques require skilled operators and should only be performed in high-volume centers.

DVT and Low-Risk Pulmonary Embolism

Most patients with DVT and low-risk patients with pulmonary embolism are treated as outpatients.[11] The principal indications for admission include clinical instability, the inability to adhere to outpatient therapy, or the need for interventions to treat massive pulmonary embolism or extensive iliofemoral DVT.

Guidelines favor direct oral anticoagulants (Table 70-6) for the treatment of VTE based on their efficacy and safety, as well as the ease of fixed dosing without the need for monitoring. Treatment typically starts with an oral factor Xa inhibitor (e.g., rivaroxaban 15 mg twice daily or apixaban 10 mg twice daily).[12] Four direct oral anticoagulants are licensed for VTE treatment: dabigatran, which inhibits thrombin, and rivaroxaban, apixaban, and edoxaban, which inhibit factor Xa (Chapter 70). These agents are as effective as LMWH followed by warfarin but are associated with less bleeding.[A2]

In patients suitable for treatment with direct oral anticoagulants, apixaban (begin at 10 mg twice daily for 7 days followed by 5 mg twice daily thereafter) and rivaroxaban (begin at 15 mg twice daily for 21 days followed by 20 mg once daily thereafter) can be started as soon as the diagnosis is established.[13] If dabigatran or edoxaban is chosen, a minimum 5-day course of treatment with a parenteral anticoagulant (see below) is needed before their initiation because these agents have not yet been evaluated for the initial treatment of VTE. Dabigatran is given at a dose of 150 mg twice daily, whereas edoxaban is given at a dose of 60 mg once daily. The dose of edoxaban is reduced to 30 mg once daily in patients who have a creatinine clearance of 15 to 50 mL/min, weigh 60 kg or less, or are taking potent P-glycoprotein inhibitors.

Patients who require thrombolytic therapy for massive pulmonary embolism or pharmacomechanical treatment for extensive DVT are usually started on heparin or LMWH but can be switched to a direct oral anticoagulant (see later) when their condition stabilizes. Direct oral anticoagulants should be avoided in patients with renal impairment (creatinine clearance <15 mL/min for rivaroxaban, apixaban, and edoxaban and <30 mL/min for dabigatran), in patients with severe hepatic impairment associated with coagulopathy, and in women who are pregnant or breast-feeding.

Parenteral Anticoagulation Followed by Warfarin

Direct oral anticoagulants should be used with caution in patients who weigh more than 150 kg because data on their efficacy in such patients are limited. The recommended role for warfarin is now limited to situations in which direct oral anticoagulants are contraindicated. Direct oral anticoagulants should be avoided if the patient is taking multiple medications that may interact with the direct oral anticoagulants (including strong inhibitors of P-glycoprotein, such as verapamil or dronedarone, or potent inducers or inhibitors of both P-glycoprotein and cytochrome P450 A34 isoenzymes, such as carbamazepine, phenytoin, rifampin, itraconazole, or ketoconazole). Warfarin also is the treatment of choice for VTE patients with a creatinine clearance less than 15 mL/min and for patients with antiphospholipid syndrome (Chapter 67).[A3] When warfarin is chosen, it must be combined with parenteral anticoagulant therapy such as unfractionated heparin, LMWH, or fondaparinux, given for at least 5 days and overlapped with warfarin.

Unfractionated heparin is the parenteral agent of choice for patients with a creatinine clearance less than 30 mL/min because LMWH and fondaparinux are cleared by the kidneys. Heparin should be administered by continuous intravenous infusion and dosed using a weight-based nomogram (see Table 68-6). Typically, a heparin bolus is followed by an infusion, and subsequent doses are adjusted based on the results of the activated partial thromboplastin time (aPTT). The aPTT is determined 6 hours after starting heparin or after changing the infusion rate. Once-daily aPTT determination is sufficient after a therapeutic value is achieved. Rapid achievement and maintenance of therapeutic aPTT values are important to reduce the risk for recurrent VTE.

Up to 25% of patients with acute VTE have resistance to unfractionated heparin, which is defined as a requirement for higher-than-expected doses (e.g., >40,000 units in 24 hours) to achieve a therapeutic aPTT.[14] If available, anti–factor Xa monitoring is recommended in place of aPTT monitoring in such patients. In addition to coagulation monitoring, the platelet count should be measured at least two or three times per week because of the risk for heparin-induced thrombocytopenia (Chapter 158).

LMWH is administered using weight-based dosing, and the use of prefilled syringes simplifies its delivery. Dosage regimens differ for the various LMWH formulations (see Table 68-7), but once-daily LMWH administration appears to be as safe and effective as twice-daily administration. Anti–factor Xa monitoring should be considered for three types of patients: patients with severe renal impairment (creatinine clearance 15 to 30 mL/min), patients with morbid obesity (e.g., BMI >40 or weight >150 kg) because the volume of distribution of LMWH in such patients might render weight-adjusted dosing inappropriate, and pregnant women because the dose may require adjustment as their weight changes. Anti–factor Xa levels are usually determined on blood samples drawn 4 hours after subcutaneous injection; therapeutic ranges of 0.5 to 1.0 IU/mL for twice-daily dosing and 1.0 to 1.8 IU/mL for once-daily dosing have been proposed.

Fondaparinux is a synthetic analogue of the pentasaccharide sequence required for the binding of heparin to antithrombin. The drug is given subcutaneously once daily in a weight-adjusted manner: 5 mg for a body weight below 50 kg, 7.5 mg for body weights of 50 to 100 kg, and 10 mg for body weights greater than 100 kg.

Warfarin can be started on the same day that parenteral anticoagulant therapy is initiated. Parenteral anticoagulant therapy should be continued for at least 5 days and should be stopped only when the INR has been within the therapeutic range of 2 to 3 for at least 48 hours. Initiation of warfarin therapy should be delayed in patients with massive pulmonary embolism or extensive DVT; such patients should receive only a parenteral anticoagulant until they have stabilized. Pharmacogenetic factors influence the relatively wide range of warfarin dose requirements among different populations, but their ability to guide warfarin dosing and increase the percentage of time that patients have INR values within the therapeutic range is limited. Warfarin requirements also vary over time in individual patients (Chapter 70), and it is unclear whether dosing algorithms enhance the efficacy or safety of warfarin therapy.

Although LMWH and fondaparinux are effective and safe, they require daily subcutaneous injection, which is difficult for some patients. Warfarin also is problematic because it requires frequent monitoring and dose adjustments, which are cumbersome for patients and physicians and costly for health care systems. The use of direct oral anticoagulants circumvents these problems.

Thrombolytic Therapy for DVT

Although catheter-directed thrombolytic therapy with or without mechanical intervention can increase early patency rates in patients with proximal DVT, such therapy has not been shown to reduce the subsequent rate of post-thrombotic syndrome. Therefore, thrombolysis is recommended only for patients whose proximal DVT is associated with extensive leg swelling or incipient venous gangrene.

Evaluation for Underlying Malignancy

Once treatment is underway, the possibility of an underlying malignancy must be considered, especially in patients with apparently unprovoked VTE. Age- and sex-specific cancer screening tests (e.g., colonoscopy and mammography) can be considered to exclude a previously undiagnosed malignancy as the precipitant. If these tests are negative and a comprehensive history, physical examination, and routine testing (blood counts, serum chemistries, chest radiography, urine analysis, stool for blood) are unrevealing or if their abnormalities are evaluated further without pathologic findings, the likelihood of finding occult cancer within a year of diagnosis is about 5%.[15] Therefore, routine abdominal and pelvic CT scanning or positron emission tomography is not recommended because such testing is expensive and does not increase the rate of cancer diagnosis or improve outcome.[A4,A5]

Long-Term Anticoagulant Therapy

All VTE patients require anticoagulant therapy for at least 3 months, when a decision should be made as to whether to stop or to extend it based on the balance between the risk of recurrence if treatment is discontinued and the risk of bleeding if it is not.[16] Patient preference also is an important factor to consider.

A 3-month course of treatment is sufficient for patients whose VTE was provoked by major transient and reversible risk factors, such as surgery or trauma, provided that these risk factors have resolved. The risk of recurrence after stopping anticoagulation treatment in such patients is about 1% at 1 year and 5% at 5 years. Women who develop VTE with estrogen therapy also can be treated for 3 months if hormonal treatment is withdrawn.

Patients who have an unprovoked VTE or persistent major risk factors, such as active cancer, are at higher risk for recurrence if anticoagulant therapy is stopped and therefore are expected to benefit from extended treatment unless they are at high risk for bleeding. Patients with pulmonary embolism are more likely to have recurrent pulmonary emboli, which are associated with a two-fold higher case-fatality rate than is DVT. Patients with a history of prior VTE have a 1.5-fold higher risk of recurrence than after a first VTE. Patients with recurrent DVT also are at higher risk for the post-thrombotic syndrome and may benefit from extended anticoagulation.

An elevated D-dimer level 1 month after stopping anticoagulant therapy identifies patients at higher risk for recurrence. Even with a normal D-dimer level, however, men have a 1-year risk of recurrence of about 9%, which typically is too high to justify stopping anticoagulation. The risk of recurrence in women with a normal D-dimer level 1 month after stopping anticoagulant therapy is about 5%, but the only women who probably should stop treatment are those who are younger than age 65 years, are not obese, have no evidence of post-thrombotic syndrome, and have either a normal D-dimer level 1 month after stopping anticoagulant therapy or a D-dimer level <250 μg/L while still on anticoagulant therapy.

For anticoagulation therapy extended beyond 6 months, the dose of apixaban can be reduced from 5 mg twice daily to 2.5 mg twice daily and the dose of rivaroxaban can be reduced from 20 mg once daily to 10 mg once daily without compromising efficacy and with the potential of reducing the risk of bleeding. Anticoagulation therapy is superior to aspirin for secondary VTE prevention and is not associated with an increased risk of major bleeding.[A6] It remains unclear whether the lower-dose regimens of apixaban or rivaroxaban are as effective as the higher-dose regimens for prevention of recurrent VTE in patients with

active cancer. The higher-dose regimens should be resumed if patients develop recurrent VTE when the dose is lowered.

If warfarin is used for extended anticoagulation therapy, the target INR remains between 2.0 and 3.0. For patients with erratic INR values, consideration should be given to switching to a direct oral anticoagulant. Switching also can be considered for patients who find INR testing and warfarin dose adjustment burdensome, such as patients who have limited mobility or travel frequently.

Side Effects of Anticoagulants

Bleeding is the most common side effect of anticoagulant therapy.[17] Factors such as recent surgery, trauma, and concurrent aspirin or thrombolytic therapy increase the risk for bleeding.

Major bleeding—such as intracranial (Chapter 377), gastrointestinal (Chapter 121), or retroperitoneal bleeding—leads to transfusion or death in approximately 2% of patients treated with intravenous unfractionated heparin for acute VTE. The risk for major bleeding with direct oral anticoagulants is about 40% lower than the 1 to 3% per year risk of adjusted-dose warfarin targeted to an INR of 2.0 to 3.0. The risk for major bleeding increases with older age, the presence of comorbid conditions (e.g., diabetes, hypertension, renal insufficiency, previous gastrointestinal bleeding, or cancer), and the use of concomitant drugs, particularly antiplatelet agents.

Dabigatran can be rapidly reversed with idarucizumab (Chapter 70), a monoclonal antibody fragment that binds it with high affinity. Andexanet alfa, a recombinant variant of factor Xa that competes with native factor Xa for binding these drugs, can reverse apixaban and rivaroxaban (Chapter 70). If these drugs are unavailable, four-factor prothrombin complex concentrate is suggested for life-threatening bleeding[18] (Chapter 70). If serious bleeding occurs with heparin or LMWH, protamine sulfate (Chapter 70) completely reverses the anticoagulant effect of heparin but only partially reverses that of LMWH because protamine fails to bind to shorter LMWH chains. For serious bleeding with warfarin, vitamin K should be given by slow intravenous infusion along with four-factor prothrombin complex concentrate to replenish the missing vitamin K–dependent clotting factors (Chapter 70).

Heparin-induced thrombocytopenia (Chapter 158), which is a relatively common nonhemorrhagic complication of unfractionated heparin but a very uncommon complication with LMWH or fondaparinux, typically presents with thrombocytopenia and new thrombosis (Chapter 158). Monitoring of the platelet count is recommended at least two to three times per week in patients who receive therapeutic unfractionated heparin but is not routinely recommended with LMWH or fondaparinux.

When Medications Fail or Are Contraindicated

Therapeutic strategies to manage patients in whom symptomatic VTE recurs while they are receiving direct oral anticoagulants or conventional-intensity warfarin include LMWH, higher direct oral anticoagulant doses, higher-intensity warfarin (INR range of 3.0 to 4.0), or insertion of a vena cava filter. However, the optimal management of such patients is unknown because few randomized studies have been performed.

Inferior vena cava filters, which are inserted percutaneously, are usually placed below the level of the renal veins but can be placed higher if thrombus extends higher into the inferior vena cava. Both permanent and retrievable filters reduce the risk of recurrent pulmonary embolism[19] but do not reduce mortality, in part because permanent filters can be associated with long-term complications, including inferior vena cava occlusion because of thrombus, recurrent DVT, and post-thrombotic syndrome.[A7] Retrievable filters, designed to be removed within 2 to 4 weeks of implantation, can circumvent these long-term complications, but device migration or thrombosis occurs in up to 10% of patients with such filters because many are not removed. Because of these potential problems, vena cava filters should be used only in patients who are at high risk for pulmonary embolism and who have an absolute contraindication for anticoagulation therapy, such as patients who develop extensive DVT after major surgery, patients who experience major bleeding with anticoagulant therapy, and pregnant women who suffer a DVT shortly before delivery. Retrievable filters should be used in these cases, and the devices should be removed as soon as anticoagulant therapy safely can be administered. Laser-assisted removal may be useful in difficult cases. Permanent filters are suitable for patients who have ongoing contraindications to anticoagulation.

Specific Patient Subgroups

Patients with VTE in the setting of active cancer and women who suffer a VTE during pregnancy require special treatment.

Cancer-Associated VTE

Active cancer (Chapter 67) and its treatment with chemotherapy, radiation therapy, growth factors or other biologic agents, or immunotherapy increase the risk for VTE (Chapter 164). Patients with advanced cancer often have limited mobility, and venous compression by tumor adds to their risk for VTE. In addition, central venous access catheters or ports can trigger upper extremity DVT, which can lead to pulmonary embolism. Therefore, the index of suspicion should be high in cancer patients who present with symptoms and signs suggestive of VTE. With advances in diagnostic imaging, incidental pulmonary emboli may be discovered on CT scans performed for staging purposes or for monitoring response to treatment. Incidental pulmonary emboli or calf DVTs involving segmental or more proximal veins should be treated because of the risk of recurrence or extension.

In patients with active cancer, apixaban, edoxaban, and rivaroxaban are associated with similar or lower risks of recurrent VTE compared with subcutaneous LMWH, but edoxaban and rivaroxaban have been associated with more bleeding.[A8–A10] Most of the excess bleeding with edoxaban and rivaroxaban is from the gastrointestinal tract and occurs in patients with gastrointestinal cancers, particularly unresectable tumors of the upper gastrointestinal tract such as esophageal or gastric cancers. Warfarin is less effective in these patients and is not recommended.[20] As a result, apixaban, edoxaban, and rivaroxaban are suitable alternatives to LMWH for treatment of cancer-associated VTE, but they should be used with caution in patients with intact cancers involving the gastrointestinal or genitourinary tract and should be avoided in patients with a platelet count below 50,000/μL.

Apixaban (2.5 mg twice daily) and rivaroxaban (10 mg daily) are also effective for preventing a first VTE in intermediate and high-risk cancer patients, but they are associated with about a two-fold increase in major bleeding.[A11–A13] Therefore, when used for primary thromboprophylaxis, careful patient selection is important.[21]

VTE in Pregnancy

The management of pregnant women with VTE (Chapter 221) is problematic because direct oral anticoagulants and warfarin cross the placenta. Consequently, LMWH or unfractionated heparin, which do not cross the placenta and are safe for the fetus, are the agents of choice for treatment of VTE in pregnancy. The easiest approach is to initiate therapy with weight-adjusted treatment doses of LMWH (see Table 68-7), which is continued for the duration of the pregnancy. As pregnancy progresses, women gain weight and generally require higher doses of LMWH to achieve an anti–factor Xa level like that achieved at the time of diagnosis. The adequacy of the dose can be assessed by measuring the anti–factor Xa level 4 hours after injection and adjusting the dose to achieve a level of 0.5 to 1.0 IU/mL for twice-daily LMWH and 0.8 to 1.5 IU/mL for once-daily LMWH. Alternatively, the dose of LMWH can simply be adjusted based on weight.

Subcutaneous unfractionated heparin is less attractive than LMWH because it must be given twice daily and is associated with a greater reduction in bone density and a higher risk of heparin-induced thrombocytopenia than LMWH. Unfractionated heparin can be initiated by continuous intravenous infusion in doses adjusted to maintain an aPTT in the therapeutic range (see Table 68-6) or simply with 12-hourly subcutaneous injections throughout the course of pregnancy. The subcutaneous dose should be adjusted to achieve a therapeutic aPTT 6 hours after its injection.

Pregnant women with VTE should be treated for the duration of pregnancy and for at least 6 weeks postpartum. If the VTE occurs early in pregnancy, elective induction of delivery at approximately 37 weeks with discontinuation of the heparin 24 hours earlier is recommended. If the VTE occurs in the latter part of the third trimester, intravenous heparin should be administered by continuous infusion until approximately 6 hours before the expected time of delivery.

Subcutaneous LMWH should be started postpartum as soon as hemostasis has been achieved. Warfarin is safe for nursing mothers because neither the parent drug nor its metabolites are secreted into breast milk. Consequently, warfarin can be started after delivery, with bridging using LMWH or unfractionated heparin for a minimum of 5 days and until the INR is 2.0 or higher. Direct oral anticoagulants should not be used in nursing mothers because small amounts may pass into the breast milk and it is uncertain whether this may cause harm.

PROGNOSIS

At 30 days, the mortality rates in patients with DVT and pulmonary embolism are about 6% and 12%, respectively. Many of these deaths are due to concomitant diseases rather than to the VTE. Death rates are about 75% higher if the pulmonary embolism was associated with syncope.[22] If anticoagulation therapy is stopped after 3 months, patients whose VTE was provoked by a major transient risk factor such as surgery or trauma have the lowest risk of recurrence (about 1% at 1 year and 5% at 5 years), whereas those with unprovoked VTE are at higher risk (about 10% at 1 year and 25% at 5 years).[23] Patients whose VTE was provoked by minor nonsurgical risk factors such as prolonged travel or short-term immobility are at intermediate risk for recurrent VTE (about 5% at 1 year and 15% at 5 years), whereas those with major persistent risk factors such as active cancer (particularly brain, pancreatic, or colorectal cancer) are at highest risk of recurrence (at least 15 to 20% at 1 year). Therefore, when evaluating patients with VTE, it is important to determine whether the episode was unprovoked and, if provoked, whether the provoking factor was major or minor and transient or persistent.

LONG-TERM COMPLICATIONS OF VTE

The post-thrombotic syndrome, recurrent VTE, and chronic thromboembolic pulmonary hypertension are potential long-term complications of VTE.

POST-THROMBOTIC SYNDROME

The initial pain and swelling in patients with DVT are caused by venous obstruction and the inflammation that accompany venous thrombosis. After anticoagulant therapy is initiated, the acute obstruction usually resolves as recanalization occurs and collateral venous channels develop, thereby leading to a reduction in the pain and swelling. However, venous hypertension can occur if there is residual venous obstruction and incompetence of the venous valves. Venous hypertension is the hallmark of post-thrombotic syndrome, which develops in up to 50% of patients with proximal DVT, usually 6 months to 2 years after the event. The syndrome is characterized by dependent pain and swelling that is worse at the end of the day and is relieved with elevation of the legs.

Evidence regarding compression stockings to prevent post-thrombotic syndrome is conflicting,[24] and they are not routinely recommended. Lifestyle alterations such as frequent leg elevation, avoidance of prolonged standing or sitting, and occasional use of analgesics relieve symptoms of the post-thrombotic syndrome in many patients. If symptoms are severe, a lightweight stocking (e.g., support hose) can be helpful until the edema improves. A stocking that applies 30 to 40 mm Hg of pressure at the ankle can be prescribed if symptoms persist or worsen despite these measures. However, if symptoms subside or have little or no impact on quality of life, most patients opt to avoid the use of stockings.

Venous ulcers, which are the most severe complication of post-thrombotic syndrome, typically occur in the perimalleolar area of the leg. The best management is prevention by application of graduated compression stockings if skin changes develop in association with leg swelling. Treatment of ulcers consists of an emollient cream such as a moisturizer, with or without a low-dose topical corticosteroid (Table 404-2), and regular leg wrapping. After the ulcer heals, graduated compression stockings should be prescribed. Surgical closure or removal of the incompetent saphenous veins does not accelerate healing time in patients with chronic venous ulcers compared with dressing management alone, but surgery can significantly reduce the rate of recurrent ulceration.[A14]

SUSPECTED RECURRENT VTE

Approximately 10% of patients with unprovoked VTE will experience a recurrent thromboembolic event in the first year after stopping anticoagulant therapy. The diagnosis of recurrent DVT is complicated by the fact that many patients with prior DVT have positional leg swelling and pain because of the post-thrombotic syndrome. This syndrome and other venous disorders such as chronic venous insufficiency can produce symptoms that are similar to those of acute DVT, so accurate diagnostic testing to confirm recurrence is mandatory. Residual venous abnormalities on ultrasound are common in patients with a history of proximal DVT and are found in approximately 80% of patients at 3 months and in 50% of patients at 1 year after the event. Therefore, comparison with previous ultrasound images is required in patients with suspected recurrence. Although an increase in vein diameter of 4 mm or more in the compressed vein segment suggests recurrent DVT, a new noncompressible proximal venous segment is the most reliable criterion for the diagnosis of recurrence. A normal D-dimer test result helps to exclude recurrent DVT.

For patients with suspected recurrent pulmonary embolism, the diagnosis is confirmed by finding new thrombi on CT pulmonary angiography. Comparison with previous tests is important, particularly if ventilation-perfusion lung scanning is performed because residual perfusion defects are common in patients with a history of pulmonary embolism. As with suspected recurrent DVT, a normal D-dimer test helps to exclude the diagnosis. The treatment of recurrent VTE is the same as for a first event, except that most patients with recurrent VTE that is either unprovoked or provoked by minor risk factors require extended anticoagulation therapy.

CHRONIC THROMBOEMBOLIC PULMONARY HYPERTENSION

A rare complication of pulmonary embolism, chronic thromboembolic pulmonary hypertension develops in 0.5 to 5% of patients over the course of months or years when emboli in major pulmonary arteries are replaced by fibrous tissue that becomes incorporated into the vessel walls, thereby narrowing or obstructing them.[25] Chronic obstruction of the pulmonary vascular bed increases pulmonary arterial resistance and can lead to right heart failure. Although patients initially may be asymptomatic, they experience increasing dyspnea on exertion and hypoxemia as the disease progresses. Chronic thromboembolic pulmonary hypertension[26] should be suspected in patients who have pulmonary hypertension (Chapter 69), and the diagnosis can be established with a combination of echocardiography and lung scanning or CT pulmonary angiography.

Medical therapy focuses on treatment of right heart failure and the use of vasodilating agents (Chapter 69). Riociguat, a soluble guanylate cyclase stimulator (starting at 0.5 to 1 mg three times daily and titrated up to 2.5 mg three times per day as tolerated) is the only licensed medication for medical treatment of chronic thromboembolic pulmonary hypertension.[A15] A lower starting riociguat dose of 0.5 mg three times daily is suggested for patients at risk for hypotension. Riociguat may be of limited utility, however, because of the fibrotic nature of the obstructing material. Therefore, definitive treatment involves surgical thromboendarterectomy to remove the occluding material from the pulmonary arteries. For patients who are too sick for surgery, balloon pulmonary angioplasty can be effective and, in selected patients, provides excellent outcomes. This procedure is associated with a perioperative mortality rate that can be as high as 4%, depending on the severity of the disease, and a 3-year survival rate of about 80%. In patients with residual pulmonary hypertension after endarterectomy, pulmonary artery denervation is a potential option to reduce the pressure and improve functional capacity.[27]

VENOUS THROMBOSIS OF THE UPPER EXTREMITIES

DVT of the upper extremities (including the axillary, subclavian, and internal jugular veins, as well as the superior vena cava) is much less common than DVT of the legs, but it is not rare, especially among critically ill adults in intensive care units.[28] Factors associated with upper extremity DVT include central venous catheters, pacemakers, acquired or hereditary thrombophilias (Chapter 67), and anatomic (cervical rib) and physiologic (muscular individuals) impingement of the vein. The incidence of clinically important post-thrombotic syndrome is not high if patients receive anticoagulant therapy.

Contrast venography is the gold standard for the diagnosis of upper extremity DVT, but venous ultrasonography is accurate and less invasive. Because it is not feasible to test for compression of the subclavian vein, a diagnosis of subclavian DVT by ultrasonography is based on flow abnormalities or direct visualization of thrombus by B-mode ultrasonography. Upper extremity DVT can cause pulmonary emboli, although the exact frequency is unknown. Controversy exists about the management of patients in whom DVT develops in association with a central venous catheter. If the line is no longer required or is nonfunctional, some experts recommend removing the line without subsequent anticoagulant therapy, whereas most recommend full-dose anticoagulant therapy. If the line is functional and is needed for drug delivery or venous access, full-dose anticoagulant therapy should be given. Such therapy should be given to all patients whose upper extremity DVT was not triggered by a central venous catheter or port. The medications, doses, regimens, and treatment durations generally are identical to those for treatment of DVT of the leg.[29]

SUPERFICIAL VEIN THROMBOSIS

Superficial vein thrombosis usually manifests with pain, swelling, redness, and tenderness of superficial veins. Thrombosed varicose veins (Fig. 68-8) can be red, warm, and clustered in a circumscribed area. When superficial vein thrombosis involves the greater or lesser saphenous veins, a tender cord often follows the course of the involved vein in the thigh or medial aspect of calf, respectively. Superficial vein thrombosis also can occur at the insertion site of intravenous catheters. Approximately 25% of patients with superficial vein thrombosis in the lower extremity have concurrent DVT at the time of presentation, and approximately 3% of the others will subsequently develop DVT or pulmonary embolism in the next 3 months, with a subsequent risk of about 1% per year thereafter.[30] Therefore, compression ultrasonography should be performed to exclude DVT in patients with superficial vein thrombosis in the lower extremity.

Treatment with nonsteroidal anti-inflammatory drugs (NSAIDs), moderate or full doses of LMWH, fondaparinux, or rivaroxaban is approximately 70% more effective than placebo for treating superficial vein thrombosis. LMWH relieves symptoms more quickly and prevents thrombotic extension more effectively than do NSAIDs. Fondaparinux, 2.5 mg/day for 45 days, reduces the risk of DVT or pulmonary embolism from approximately 1.3 to 0.2% without notable adverse effects. A 45-day course of rivaroxaban (10 mg once daily) is as effective and safe as fondaparinux.[A16] Thus, it is reasonable to use these moderate doses of rivaroxaban, fondaparinux, or LMWH to treat symptomatic superficial vein thrombosis, particularly

FIGURE 68-8. Varicose veins. Varicose veins are a risk factor for superficial and deep vein thrombosis. (From Forbes CD, Jackson WF. *Color Atlas and Text of Clinical Medicine*, 3rd ed. London: Mosby; 2003.)

in patients with severe symptoms, proximal saphenous vein thrombosis, recurrent disease, or underlying cancer or thrombophilia. For less severe cases, topical or systemic NSAIDs can be prescribed. For treatment of varicose veins, laser and surgical treatments appear to be superior to liquid or foam sclerotherapy.[A17]

PREVENTION OF VTE

At least half of all outpatients with newly diagnosed VTE have a history of recent hospitalization, and many failed to receive thromboprophylaxis during their hospital stay. Consequently, pulmonary embolism is thought to be a common preventable cause of death in hospitalized patients in the United States. Therefore, every patient admitted to hospital should be assessed for their risk of VTE and, if indicated, appropriate thromboprophylaxis should be administered.

Despite the plethora of large, randomized trials demonstrating the efficacy and safety of mechanical and pharmacologic measures in reducing the risk for VTE in a wide range of hospitalized populations of patients, prophylaxis remains underused. Factors that increase the risk for DVT include surgery (particularly major orthopedic surgery and neurosurgery [Chapters 255 and 399]), major trauma (Chapter 97), prolonged bedrest or immobilization, history of VTE, presence of malignant disease, paralysis or paresis, morbid obesity, chronic heart failure, and advanced age. Interestingly, statins and inhibition of proprotein convertase subtilisin/kexin type 9 (PCSK9) to lower low-density lipoprotein levels also reduce the risk of venous thromboembolism, perhaps owing to their effects on lowering Lp(a).[A18,A19]

In general, mechanical prophylaxis (graded compression stockings and intermittent pneumatic compression) should be used as a stand-alone prophylaxis in patients at high risk for bleeding. Pneumatic compression or stockings are often added to pharmacologic thromboprophylaxis, but a randomized trial showed no increased value of adding pneumatic compression to such medications in critically ill patients.[A20] Early prophylactic placement of a vena cava filter is of no benefit in severely injured patients who have a contraindication to pharmacologic thromboprophylaxis.[A21]

For general medical patients admitted to the hospital with a major illness and in whom mobility is likely to be reduced for 72 hours or longer, a 45-day course of rivaroxaban (10 mg once daily) can reduce the risk of symptomatic VTE after hospital discharge without a significant increase in major bleeding.[A22]

For patients hospitalized with COVID-19 (Chapter 337), standard-dose prophylaxis (e.g., enoxaparin 40 mg daily or rivaroxaban 15 to 20 mg daily) is preferred over intermediate therapeutic doses,[A23,A24] but therapeutic-dose heparin may be better than prophylaxis in non–critically ill hospitalized patients.[A25]

In patients who undergo major hip or knee surgery, oral rivaroxaban (10 mg once daily), apixaban (2.5 mg twice daily), warfarin (dose-adjusted to achieve an INR of 2.0 to 3.0), subcutaneous LMWH, or subcutaneous fondaparinux (2.5 mg/day) should generally be administered for 10 to 14 days postoperatively. In lower risk patients undergoing knee or hip arthroplasty, a 5-day course of rivaroxaban (10 mg once daily) followed by a 9- or 30-day course of aspirin (81 mg daily) appears to be as effective and safe as an extended course of rivaroxaban.[A26] In patients with continued immobility, prophylaxis should be extended until full mobility is regained.

Compared with inhibition of factor Xa, less is known about the clinical utility of inhibiting factor XIa. However, a single postoperative dose of intravenous monoclonal antibody against factor XIa appears to be as effective as enoxaparin or apixaban for preventing venous thromboembolism after knee arthroplasty.[A27,A28] The oral factor XIa inhibitor milvexian (50 mg twice daily) appears to be as safe and more effective compared with enoxaparin (40 mg once daily) to prevent VTE in patients undergoing knee arthroplasty.[A29] Whether this approach will be widely applicable, however, must await further studies.

NONTHROMBOTIC PULMONARY EMBOLISM

DEFINITION

Nonthrombotic material that can embolize to the lungs includes fat, air, amniotic fluid, tumor cells, talc in intravenous drug abusers, and medical devices.

FAT EMBOLISM SYNDROME

EPIDEMIOLOGY

Fat embolism syndrome usually occurs in the setting of trauma, particularly after fracture of long bones or the pelvis. The risk increases with the number of fractured bones, and the syndrome occurs more often with closed fractures than with open ones. Fat embolism also can complicate orthopedic surgery or trauma to tissues rich in fat, such as may occur with liposuction.

PATHOBIOLOGY

Characterized by a combination of respiratory, neurologic, hematologic, and cutaneous manifestations, fat embolism syndrome reflects a combination of vascular obstruction by fat globules (E-Fig. 68-2) as well as the deleterious effects of free fatty acids released from these fat globules by the action of lipoprotein lipases. These free fatty acids increase vascular permeability, induce a capillary leak syndrome, and can trigger platelet aggregation.

CLINICAL MANIFESTATIONS

Symptoms typically develop 24 to 72 hours after trauma or surgery. Patients often complain of vague chest pain and shortness of breath. Tachypnea and fever associated with disproportionate tachycardia are common. The syndrome can rapidly progress to severe hypoxemia that requires mechanical ventilation. Neurologic manifestations, which often start after the respiratory distress, include drowsiness, confusion, decreased level of consciousness, and seizures. Patients may have petechiae, particularly involving the conjunctiva, oral mucosa, and upper half of the body.

DIAGNOSIS

Fat embolism syndrome should be suspected when respiratory distress occurs a day or more after major trauma or orthopedic surgery, particularly when there are associated neurologic defects and petechiae.[31] The chest radiograph may reveal diffuse alveolar infiltrates. Although fat droplets may be found in bronchoalveolar lavage fluid (Chapter 73), this finding lacks specificity for the fat embolism syndrome.

PREVENTION, TREATMENT, AND PROGNOSIS

Early stabilization of long bone fractures reduces the risk for fat embolization. Supportive treatment should be provided, including oxygen and mechanical ventilation. The utility of corticosteroids remains controversial.

Although mortality rates as high as 10% have been reported, most patients fully recover without residual deficits.

VENOUS AIR EMBOLISM

EPIDEMIOLOGY

Venous air embolism, which involves entrapment of environmental air or exogenous gas in the venous system, requires direct communication between the air and a vein, as well as a pressure gradient that favors entry of the air into the vein. Air can be introduced through indwelling central venous catheters as a consequence of invasive surgical or medical procedures or after barotrauma.

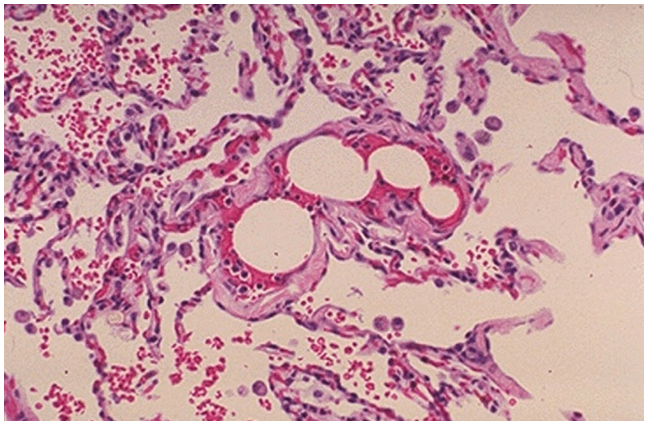

E-FIGURE 68-2. Fat embolism. Fat globules in small vessels of the lung in a patient who died 2 days after traumatic fracture of the femur.

PATHOBIOLOGY

Large venous air emboli obstruct the right ventricular pulmonary outflow tract, whereas mixtures of air bubbles and fibrin thrombi can obstruct pulmonary arterioles. In either case, right ventricular failure can result. With a patent foramen ovale (Chapter 55), venous air emboli can enter the coronary, cerebral, or systemic circulation.

CLINICAL MANIFESTATIONS

Symptoms and signs depend on the volume of air and the rapidity of its entry into the circulation. Large, rapid boluses of air are tolerated less well than slow entry of smaller amounts. Small air emboli may be asymptomatic. With larger emboli, patients often complain of dyspnea and retrosternal chest discomfort, and they may feel lightheaded. Physical findings include tachypnea, tachycardia, and evidence of respiratory distress. Patients may have signs of right heart failure. A continuous, drum-like, mill-wheel murmur, which reflects air in the right ventricle, may be heard.

PREVENTION AND TREATMENT

All catheters should be removed using techniques that minimize air embolism, air should be removed from syringes before injection, and care should be taken during surgery to ensure that air bubbles do not form in blood vessels. To avoid air embolism associated with barotrauma, divers require training in how to dive and surface safely (Chapter 82).

The source of any air embolism should be identified so that further embolism can be prevented. Left lateral decubitus positioning may benefit patients who have a large air bubble trapped in the right ventricular outflow tract; such positioning places the outflow tract below the right ventricular cavity, thereby allowing the air bubble to migrate into a nonobstructing position. Aspiration of the right ventricle through a central venous catheter also may be of benefit. Patients should receive high-flow supplemental oxygen, and hyperbaric oxygenation should be considered for patients with cardiac or neurologic dysfunction.

DIAGNOSIS

Patients may present with ECG evidence of right ventricular dysfunction associated with elevated levels of troponin, indicative of myocardial injury. Echocardiography or chest CT may reveal air in the right ventricle. Patients may have hypoxemia and hypercapnia, and the platelet count may be low.

PROGNOSIS

The outcome depends on the extent of air embolism. With good supportive care, the mortality rate can be less than 10%, even in patients with major air emboli. However, residual neurologic defects often persist.

AMNIOTIC FLUID EMBOLISM

EPIDEMIOLOGY AND PATHOBIOLOGY

Amniotic fluid embolism is a rare but catastrophic complication of pregnancy, occurring in about 1 in 8000 to 1 in 80,000 pregnancies.[32] The syndrome develops when amniotic fluid and fetal cells enter the maternal blood stream through small tears in the uterine veins during labor. Emboli to the heart and lungs (E-Fig. 68-3) cause cardiac dysfunction and respiratory distress. In addition, amniotic fluid and other debris activate the coagulation system, and the resultant thrombin then triggers fibrin formation and platelet activation to induce disseminated intravascular coagulation (Chapter 161).

CLINICAL MANIFESTATIONS AND DIAGNOSIS

The syndrome often starts with the abrupt onset of dyspnea, cyanosis, and hypotension that can rapidly progress to cardiovascular collapse and death. Patients who survive this stage often develop manifestations of disseminated intravascular coagulation (Chapter 161) characterized by diffuse bleeding, petechiae, and ecchymoses.

The diagnosis should be suspected in women late in pregnancy, often in labor, who present with sudden onset of respiratory distress followed by cyanosis, hypotension, and shock. These findings are often associated with confusion or reduced level of consciousness, seizures, and evidence of a consumptive coagulopathy.

TREATMENT

Supportive measures include oxygen, mechanical ventilation, and hemodynamic support. Fresh-frozen plasma, cryoprecipitate, and platelets transfusion can be given to replace consumed clotting factors and platelets. Heparin, often in low therapeutic doses, may be useful in some cases. If amniotic fluid embolism occurs before or during delivery, the fetus often has a poor outcome. As soon as the mother stabilizes, therefore, every attempt should be made to deliver the fetus.

PROGNOSIS

Although rare, amniotic fluid embolism remains the leading cause of maternal death during labor and the first few hours after delivery. Despite advances in critical care management, maternal and fetal mortality rates continue to be about 60% and 20%, respectively, with up to half of the survivors, both mother and baby, suffering from permanent hypoxia-induced neurologic dysfunction.

OTHER EMBOLIC MATERIAL

Many substances, such as talc, starch, and cellulose, are used as fillers in the manufacture of illicit drugs. Some of these drugs are ground up by drug users (Chapter 365), mixed in liquids, and then injected intravenously. The filler particles can then be trapped in the pulmonary vasculature, where they can induce granuloma formation.

Tumor emboli[33] in the lung can mimic pneumonia, tuberculosis, or interstitial lung disease on the chest radiograph. Cancers of the prostate and breast are the most common sources of such emboli, followed by hepatocellular cancer and cancers of the stomach and pancreas. Although found in up to 26% of autopsies in patients with advanced cancer, tumor emboli are infrequently identified before death.

Various types of intravascular devices can embolize to the lungs, including vena cava filters, broken catheter tips, guidewires, stent fragments, and coils used for embolization. Many of these devices lodge in the right atrium, right ventricle, or pulmonary arteries. Intravascular retrieval can recover most of these devices; open surgery may be required for the remainder.

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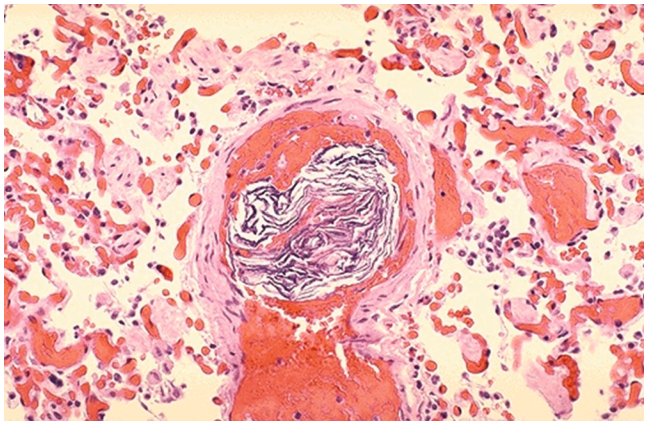

E-FIGURE 68-3. Amniotic fluid embolism. Fetal squamous cells, hair, and mucin in the pulmonary vasculature of a woman who developed acute shortness of breath, circulatory collapse, and coagulopathy shortly after delivery.

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69 PULMONARY HYPERTENSION

MARIUS M. HOEPER AND VALLERIE MCLAUGHLIN

DEFINITION

The normal pulmonary vasculature is a low-pressure system, with less than one tenth the resistance to flow observed in the systemic vasculature. Pulmonary hypertension refers to the hemodynamic state in which the pressure in the pulmonary artery is elevated above a mean of 20 mm Hg.[1] A specific type of pulmonary hypertension, pulmonary arterial hypertension, also requires that the left-sided heart filling pressure (pulmonary capillary wedge pressure, left ventricular end-diastolic pressure, or left atrial pressure) be 15 mm Hg or less and that the calculated pulmonary vascular resistance be greater than 2 Wood units (Wood unit = [pulmonary artery pressure minus mean pulmonary capillary wedge pressure] divided by cardiac output). The syndrome of pulmonary arterial hypertension (Table 69-1) results when blood flow through the pulmonary circulation is restricted, thereby leading to pathologic increases in pulmonary vascular resistance and, ultimately, to right ventricular failure. Pulmonary hypertension may also be a consequence of many other chronic diseases, including left-sided heart failure (Chapter 45), a variety of parenchymal lung diseases, and thromboembolic disease (Chapter 68).

TABLE 69-1 CLINICAL CLASSIFICATION OF PULMONARY HYPERTENSION

GROUP 1
Pulmonary arterial hypertension
Idiopathic pulmonary arterial hypertension
Heritable pulmonary arterial hypertension
Mutations in *BMPR2*, *BMPR1B*, *ALK1*, endoglin, *SMAD9*, *CAV1*, *KCNK3*
Unknown
Drug- and toxin-induced pulmonary hypertension
Associated with
Connective tissue diseases
HIV infection
Portal hypertension
Congenital heart diseases
Schistosomiasis
Pulmonary veno-occlusive disease
Pulmonary capillary hemangiomatosis
GROUP 2
Pulmonary hypertension due to left heart disease
Heart failure with preserved LVEF
Heart failure with reduced LVEF
Valvular heart disease
Congenital/acquired cardiovascular conditions leading to postcapillary pulmonary hypertension
GROUP 3
Pulmonary hypertension due to lung diseases and/or hypoxia
Obstructive lung disease
Restrictive lung disease
Other lung diseases with mixed restrictive/obstructive pattern
Hypoxia without lung disease
Developmental lung disorders
GROUP 4
Chronic thromboembolic pulmonary hypertension
Other pulmonary artery obstructions
GROUP 5
Pulmonary hypertension with unclear and/or multifactorial mechanisms
Hematologic disorders
Systemic and metabolic disorders
Complex congenital heart disease

ALK1 = activin receptor-like kinase type 1; *BMPR1B* = bone morphogenetic protein receptor type 1B; *BMPR2* = bone morphogenetic protein receptor type 2; *CAV1* = caveolin-1; HIV = human immunodeficiency virus; *KCNK3* = potassium two pore domain channel subfamily K member 3; LVEF = left ventricular ejection fraction.

Adapted from Simonneau G, Montani D, Celermajer DS, et al. Haemodynamic definitions and updated clinical classification of pulmonary hypertension. *Eur Resp J*. 2019;53:1801913.

EPIDEMIOLOGY

Normal pulmonary blood pressure is 20/10 (mean, 15) mm Hg at rest at sea level, rising to 30/13 (mean, 20) mm Hg with mild exercise. Pressures rise with altitude, and at an altitude of about 15,000 feet, normal resting pulmonary artery pressures are about 38/14 (mean, 20) mm Hg. Pulmonary arterial systolic pressure rises gradually with age, and each increase of 10 mm Hg is associated with a 2.7-fold greater risk for mortality.

Idiopathic pulmonary arterial hypertension, formerly called primary pulmonary hypertension, is the prototype of group 1 pulmonary arterial hypertension. This disease affects women more than men in a 1.5 : 1 ratio. It may be manifested at any age, with a mean age at onset in the fourth to sixth decade of life. The prevalence of pulmonary arterial hypertension is between 15 and 50 per million persons. Heritable pulmonary arterial hypertension occurs in a familial context, most often (70%) due to a mutation in the bone morphogenetic protein receptor type 2. (See Pathobiology.)

Drug- and toxin-induced pulmonary arterial hypertension has been most clearly linked to anorexigens, including aminorex, fenfluramine, and dexfenfluramine. Although these agents are no longer used, observational studies link amphetamines, methamphetamines, interferons, and L-tryptophan to pulmonary arterial hypertension. Tyrosine kinase inhibitors (dasatinib and bosutinib) also have been associated with the development of pulmonary arterial hypertension.

One of the most common types of group 1 pulmonary arterial hypertension occurs in the setting of connective tissue diseases.[2] In patients with systemic sclerosis (Chapter 246),[3] for example, the prevalence of pulmonary arterial hypertension is in the range of 7 to 12%. It is less common in systemic lupus erythematosus (Chapter 245), rheumatoid arthritis (Chapter 243), and other systemic vasculitides (Chapter 249). Pulmonary arterial hypertension is a rare but well-established complication of human immunodeficiency virus (HIV) infection (Chapter 359), and its prevalence of 0.5% in such patients has not changed with the widespread use of highly active antiretroviral therapy. Prospective hemodynamic studies show that 2 to 6% of patients with portal hypertension (Chapter 139) develop pulmonary arterial hypertension, although the reason for the association is not clear.

A significant proportion of patients with untreated systemic-to-pulmonary shunts, commonly due to congenital heart disease (Chapter 55), develop pulmonary arterial hypertension. Persistent exposure of the pulmonary vasculature to increased blood flow and pressure leads to an elevated pulmonary vascular resistance. In some cases, Eisenmenger syndrome (Chapter 55), with a reversal of flow across the defect, results in right-to-left shunting. Pulmonary veno-occlusive disease (Chapter 68) and pulmonary capillary hemangiomatosis[4] are rare disorders that directly affect the pulmonary vasculature. The presentation of each is often similar to pulmonary arterial hypertension, but the prognosis is particularly poor.

Pulmonary hypertension due to left-sided heart disease (group 2) probably represents the most frequent cause of pulmonary hypertension seen in practice (group 2 patients).[5] Left-sided ventricular (Chapter 45) or valvular (Chapter 60) disease may increase left atrial pressure, which then is transmitted back to the pulmonary vasculature. The pulmonary vascular resistance is often normal (isolated postcapillary pulmonary hypertension). In such cases, optimal treatment of the left-sided heart disease may result in reduction of the left-sided heart filling pressures and, consequently, a reduction in the pulmonary artery pressures. However, some patients have a pulmonary vascular resistance greater than 3 Wood units in the setting of left-sided heart disease (combined post- and

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69 PULMONARY HYPERTENSION

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DEFINITION

The normal pulmonary vasculature is a low-pressure system, with less than one tenth the resistance to flow observed in the systemic vasculature. Pulmonary hypertension refers to the hemodynamic state in which the pressure in the pulmonary artery is elevated above a mean of 20 mm Hg.[1] A specific type of pulmonary hypertension, pulmonary arterial hypertension, also requires that the left-sided heart filling pressure (pulmonary capillary wedge pressure, left ventricular end-diastolic pressure, or left atrial pressure) be 15 mm Hg or less and that the calculated pulmonary vascular resistance be greater than 2 Wood units (Wood unit = [pulmonary artery pressure minus mean pulmonary capillary wedge pressure] divided by cardiac output). The syndrome of pulmonary arterial hypertension (Table 69-1) results when blood flow through the pulmonary circulation is restricted, thereby leading to pathologic increases in pulmonary vascular resistance and, ultimately, to right ventricular failure. Pulmonary hypertension may also be a consequence of many other chronic diseases, including left-sided heart failure (Chapter 45), a variety of parenchymal lung diseases, and thromboembolic disease (Chapter 68).

TABLE 69-1 CLINICAL CLASSIFICATION OF PULMONARY HYPERTENSION

GROUP 1
Pulmonary arterial hypertension
Idiopathic pulmonary arterial hypertension
Heritable pulmonary arterial hypertension
Mutations in *BMPR2*, *BMPR1B*, *ALK1*, endoglin, *SMAD9*, *CAV1*, *KCNK3*
Unknown
Drug- and toxin-induced pulmonary hypertension
Associated with
Connective tissue diseases
HIV infection
Portal hypertension
Congenital heart diseases
Schistosomiasis
Pulmonary veno-occlusive disease
Pulmonary capillary hemangiomatosis
GROUP 2
Pulmonary hypertension due to left heart disease
Heart failure with preserved LVEF
Heart failure with reduced LVEF
Valvular heart disease
Congenital/acquired cardiovascular conditions leading to postcapillary pulmonary hypertension
GROUP 3
Pulmonary hypertension due to lung diseases and/or hypoxia
Obstructive lung disease
Restrictive lung disease
Other lung diseases with mixed restrictive/obstructive pattern
Hypoxia without lung disease
Developmental lung disorders
GROUP 4
Chronic thromboembolic pulmonary hypertension
Other pulmonary artery obstructions
GROUP 5
Pulmonary hypertension with unclear and/or multifactorial mechanisms
Hematologic disorders
Systemic and metabolic disorders
Complex congenital heart disease

ALK1 = activin receptor-like kinase type 1; *BMPR1B* = bone morphogenetic protein receptor type 1B; *BMPR2* = bone morphogenetic protein receptor type 2; *CAV1* = caveolin-1; HIV = human immunodeficiency virus; *KCNK3* = potassium two pore domain channel subfamily K member 3; LVEF = left ventricular ejection fraction.

Adapted from Simonneau G, Montani D, Celermajer DS, et al. Haemodynamic definitions and updated clinical classification of pulmonary hypertension. *Eur Resp J*. 2019;53:1801913.

EPIDEMIOLOGY

Normal pulmonary blood pressure is 20/10 (mean, 15) mm Hg at rest at sea level, rising to 30/13 (mean, 20) mm Hg with mild exercise. Pressures rise with altitude, and at an altitude of about 15,000 feet, normal resting pulmonary artery pressures are about 38/14 (mean, 20) mm Hg. Pulmonary arterial systolic pressure rises gradually with age, and each increase of 10 mm Hg is associated with a 2.7-fold greater risk for mortality.

Idiopathic pulmonary arterial hypertension, formerly called primary pulmonary hypertension, is the prototype of group 1 pulmonary arterial hypertension. This disease affects women more than men in a 1.5 : 1 ratio. It may be manifested at any age, with a mean age at onset in the fourth to sixth decade of life. The prevalence of pulmonary arterial hypertension is between 15 and 50 per million persons. Heritable pulmonary arterial hypertension occurs in a familial context, most often (70%) due to a mutation in the bone morphogenetic protein receptor type 2. (See Pathobiology.)

Drug- and toxin-induced pulmonary arterial hypertension has been most clearly linked to anorexigens, including aminorex, fenfluramine, and dexfenfluramine. Although these agents are no longer used, observational studies link amphetamines, methamphetamines, interferons, and L-tryptophan to pulmonary arterial hypertension. Tyrosine kinase inhibitors (dasatinib and bosutinib) also have been associated with the development of pulmonary arterial hypertension.

One of the most common types of group 1 pulmonary arterial hypertension occurs in the setting of connective tissue diseases.[2] In patients with systemic sclerosis (Chapter 246),[3] for example, the prevalence of pulmonary arterial hypertension is in the range of 7 to 12%. It is less common in systemic lupus erythematosus (Chapter 245), rheumatoid arthritis (Chapter 243), and other systemic vasculitides (Chapter 249). Pulmonary arterial hypertension is a rare but well-established complication of human immunodeficiency virus (HIV) infection (Chapter 359), and its prevalence of 0.5% in such patients has not changed with the widespread use of highly active antiretroviral therapy. Prospective hemodynamic studies show that 2 to 6% of patients with portal hypertension (Chapter 139) develop pulmonary arterial hypertension, although the reason for the association is not clear.

A significant proportion of patients with untreated systemic-to-pulmonary shunts, commonly due to congenital heart disease (Chapter 55), develop pulmonary arterial hypertension. Persistent exposure of the pulmonary vasculature to increased blood flow and pressure leads to an elevated pulmonary vascular resistance. In some cases, Eisenmenger syndrome (Chapter 55), with a reversal of flow across the defect, results in right-to-left shunting. Pulmonary veno-occlusive disease (Chapter 68) and pulmonary capillary hemangiomatosis[4] are rare disorders that directly affect the pulmonary vasculature. The presentation of each is often similar to pulmonary arterial hypertension, but the prognosis is particularly poor.

Pulmonary hypertension due to left-sided heart disease (group 2) probably represents the most frequent cause of pulmonary hypertension seen in practice (group 2 patients).[5] Left-sided ventricular (Chapter 45) or valvular (Chapter 60) disease may increase left atrial pressure, which then is transmitted back to the pulmonary vasculature. The pulmonary vascular resistance is often normal (isolated postcapillary pulmonary hypertension). In such cases, optimal treatment of the left-sided heart disease may result in reduction of the left-sided heart filling pressures and, consequently, a reduction in the pulmonary artery pressures. However, some patients have a pulmonary vascular resistance greater than 3 Wood units in the setting of left-sided heart disease (combined post- and

ABSTRACT

Pulmonary hypertension affects about 1% of the adult population and is most commonly associated with left heart disease or lung disease. However, pulmonary hypertension can also be idiopathic, inherited, induced by drugs or toxins, associated with a variety of systemic diseases, or caused by chronic pulmonary thromboembolism. Exertional dyspnea is the most common presenting symptom, but patients can also have dyspnea while bending forward (bendopnea), chest pain, palpitations, lightheadedness, or syncope. On physical examination, jugular venous distension, tricuspid valve regurgitation, pulmonary valve insufficiency, and peripheral edema are common. Treatment emphasizes medications that reduce pulmonary arterial resistance, but most forms of pulmonary hypertension are associated with a reduced life expectancy.

KEYWORDS

chronic pulmonary embolism
pulmonary arterial hypertension
jugular venous distension
right heart failure

precapillary pulmonary hypertension); such patients may have pulmonary vascular remodeling owing to persistently elevated left-sided filling pressures.

Group 3 patients have pulmonary hypertension due to lung diseases or hypoxia.[6] The most common underlying conditions are chronic obstructive lung disease (Chapter 76), interstitial lung disease (Chapter 80), and chronic hypoventilation syndromes (Chapters 74 and 374). Echocardiography-based observations have suggested that up to 80% of patients with advanced chronic obstructive lung disease and idiopathic pulmonary fibrosis have elevated pulmonary artery pressures. Most often, the elevations in pulmonary artery pressures are modest, but a small proportion of patients develop severe pulmonary hypertension, defined by a pulmonary vascular resistance greater than 3 Wood units.

Group 4 patients have chronic thromboembolic pulmonary hypertension (Chapter 68),[7] which must be differentiated from the other groups because the treatment is different. Approximately 2 to 3% of patients who have suffered an acute pulmonary embolism progress to development of chronic thromboembolic pulmonary hypertension. About one third of patients who are ultimately diagnosed with chronic thromboembolic pulmonary hypertension do not have a known history of an acute pulmonary embolism.

PATHOBIOLOGY

The pathobiology of pulmonary arterial hypertension is complex and incompletely elucidated (E-Fig. 69-1). The pulmonary arterial hypertension phenotype is characterized by endothelial dysfunction, a decreased ratio of apoptosis to proliferation in pulmonary artery endothelial and smooth muscle cells, and a thickened, disordered adventitia in which adventitial metalloproteases are excessively activated. The evolution of pulmonary vascular disease frequently originates with the interaction of a predisposing state and one or more inciting stimuli, a concept referred to as the multiple-hit hypothesis.

In group 1 pulmonary arterial hypertension, patients have a vasculopathy that predominantly affects the small pulmonary arterioles. It is characterized by a variety of arterial abnormalities, including intimal hyperplasia, medial hypertrophy, adventitial proliferation, thrombosis in situ, varying degrees of inflammation, and plexiform lesions. An individual patient may manifest all or some of these lesions, and the distribution of the lesions may be diffuse or focal.

The genetic defect best characterized in heritable pulmonary arterial hypertension is that of the bone morphogenetic protein receptor type 2, a member of the transforming growth factor-β (TGF-β) signaling family.[8] Less commonly, mutations in activin receptor–like kinase type 1, or endoglin, have been identified in patients with pulmonary arterial hypertension, predominantly with coexistent hereditary hemorrhagic telangiectasia (Chapter 159). Mutations in other genes (i.e., *BMPR1B*, *CAV1*, and *SMAD9*), all of which are involved in the TGF-β signaling pathway, are considerably less common. A novel channelopathy of KCNK3, which has been identified in familial and idiopathic cases of pulmonary arterial hypertension, is the first indication that the disease may involve factors apparently independent of the TGF-β signaling pathway.

The imbalance in the production or metabolism of vasoactive mediators in the pulmonary vasculature includes a reduction in prostacyclin and nitric oxide, which have vasodilator and antiproliferative properties, and an increase in thromboxane and endothelin, which are vasoconstrictors as well as mitogens. The reduction in nitric oxide synthase in pulmonary arterial hypertension diminishes nitric oxide and, subsequently, cyclic guanosine monophosphate production. Upregulation of phosphodiesterase-5 further diminishes the intracellular concentration of cyclic guanosine monophosphate. Endothelin-1 is a potent vasoconstrictor and smooth muscle mitogen that may contribute to the development of pulmonary arterial hypertension. Prostacyclin synthase is reduced in pulmonary arterial hypertension, resulting in an inadequate production of prostacyclin, which is a vasodilator with potent antiproliferative effects. Other aberrations include those of the voltage-dependent potassium channels and serotonin pathways. Disorders of inflammatory and coagulation pathways have also been described.

Chronic changes in the pulmonary vasculature also occur as a result of other types of pulmonary hypertension. Chronic elevation of left-sided heart filling pressures causes a backward transmission of pressure to the pulmonary venous system and triggers vasoconstriction in the pulmonary arterial bed. On histologic evaluation, the veins are thickened abnormally, and a neointima is formed. As secondary features, medial hypertrophy and thickening of the neointima on the arterial side of the pulmonary circulation occur. These changes can be partly reversed with therapies that result in chronic reduction of left-sided heart filling pressures.

In parenchymal lung disease, changes in the distal pulmonary arterial vessels consist of muscularization of the distal vessels and medial hypertrophy of the more proximal vessels. Neither neointima formation nor the development of plexiform lesions is observed.

The pathologic process of chronic thromboembolic pulmonary hypertension is distinct from idiopathic pulmonary arterial hypertension. The lesions are more variable, with some arterial pathways that appear relatively unaffected and others that show recanalized vascular thromboses. However, the involvement of distal microvessels, particularly when thromboses have occurred in subsegmental arteries, can resemble idiopathic pulmonary arterial hypertension, even with the formation of plexiform lesions.

Pathophysiology

The normal pulmonary vasculature bed has a remarkable capacity to dilate and recruit unused vasculature to accommodate increases in pulmonary blood flow. In pulmonary hypertension, the pulmonary artery pressure and pulmonary vascular resistance are increased at rest and further increase with exertion. In response to this increased afterload, the normally very thin right ventricle hypertrophies and eventually dilates. Early in the process, the right ventricle may be capable of maintaining normal cardiac output at rest, although it may fail to augment cardiac output with exercise, thereby leading to exertional dyspnea. As the disease progresses, the right ventricular dysfunction may progress to the point that resting cardiac output is impaired. Right ventricular function is a major determinant of functional capacity and prognosis in pulmonary arterial hypertension. Although the left ventricle is not directly affected by pulmonary vascular disease itself, progressive right ventricular dilation can impair left ventricular filling and lead to left-sided diastolic dysfunction. The pathophysiologic mechanism of pulmonary hypertension related to left-sided heart and lung disease is further complicated by those underlying disorders.

Right ventricular failure, as evidenced by elevated jugular venous pressure, lower extremity edema, and occasionally ascites, may also be accompanied by evidence of poor forward flow due to inadequate filling of the left ventricle. Hypotension, hypoperfusion, and renal insufficiency may result.

CLINICAL MANIFESTATIONS

History

Dyspnea, which is the most common symptom of pulmonary hypertension, typically is insidious in onset and gradually progressive. Dyspnea is classified by the World Health Organization (WHO) system, which is similar to the New York Heart Association classification system for angina and heart failure (see Table 39-5), and may progress to dyspnea with minimal physical activity.

Other common symptoms of pulmonary hypertension include fatigue, lightheadedness, chest pain (Chapter 39), and palpitations (Chapters 39 and 49). Syncope (Chapter 49), which may be an ominous finding, is often exertional in nature; it signifies the inability of the right ventricle to augment cardiac output as needed for physical activity. Symptoms of right-sided heart failure, including extended jugular veins, edema, and ascites, signify advanced disease.

The nonspecific symptoms of pulmonary hypertension often explain its delayed recognition. In various reviews, the delay from onset of symptoms to diagnosis can be as long as 2 years.

Patients with group 2 pulmonary hypertension may also exhibit paroxysmal nocturnal dyspnea and orthopnea. Patients with group 3 disease may have cough, sputum production, or wheezing. Patients with group 4 chronic thromboembolic pulmonary hypertension may have a history of venous thromboembolism, edema, and hemoptysis.

Physical Examination

Distention of jugular veins (see Fig. 39-2) may signify right ventricular failure, and prominent *v* waves (see Fig. 39-3) may be a result of tricuspid regurgitation.[9] The amplitude of the carotid upstroke may give some insight into the cardiac output. The classic physical examination finding in pulmonary hypertension is a loud pulmonic component to the second heart sound, which reflects high pulmonary pressures that increase the force of the pulmonic valve closure. A palpable left parasternal heave may be caused by the hypertrophied, pressure-overloaded right ventricle. A right ventricular fourth heart sound reflects diastolic filling of the hypertrophied, noncompliant right ventricle, akin to the left-sided fourth heart sound in a patient with systemic hypertension and left ventricular hypertrophy. The murmur of tricuspid regurgitation, which is holosystolic, located at the left lower sternal border, and augments with inspiration, is common in patients with moderate to severe pulmonary hypertension. Other findings on auscultation may include an early systolic click and the murmur of pulmonic regurgitation. A right ventricular third heart sound often signifies advanced disease and right-sided heart failure. Other signs consistent with right ventricular failure include hepatomegaly, peripheral edema (see Fig. 39-6), ascites, hypotension, diminished pulse pressure, and cool extremities.

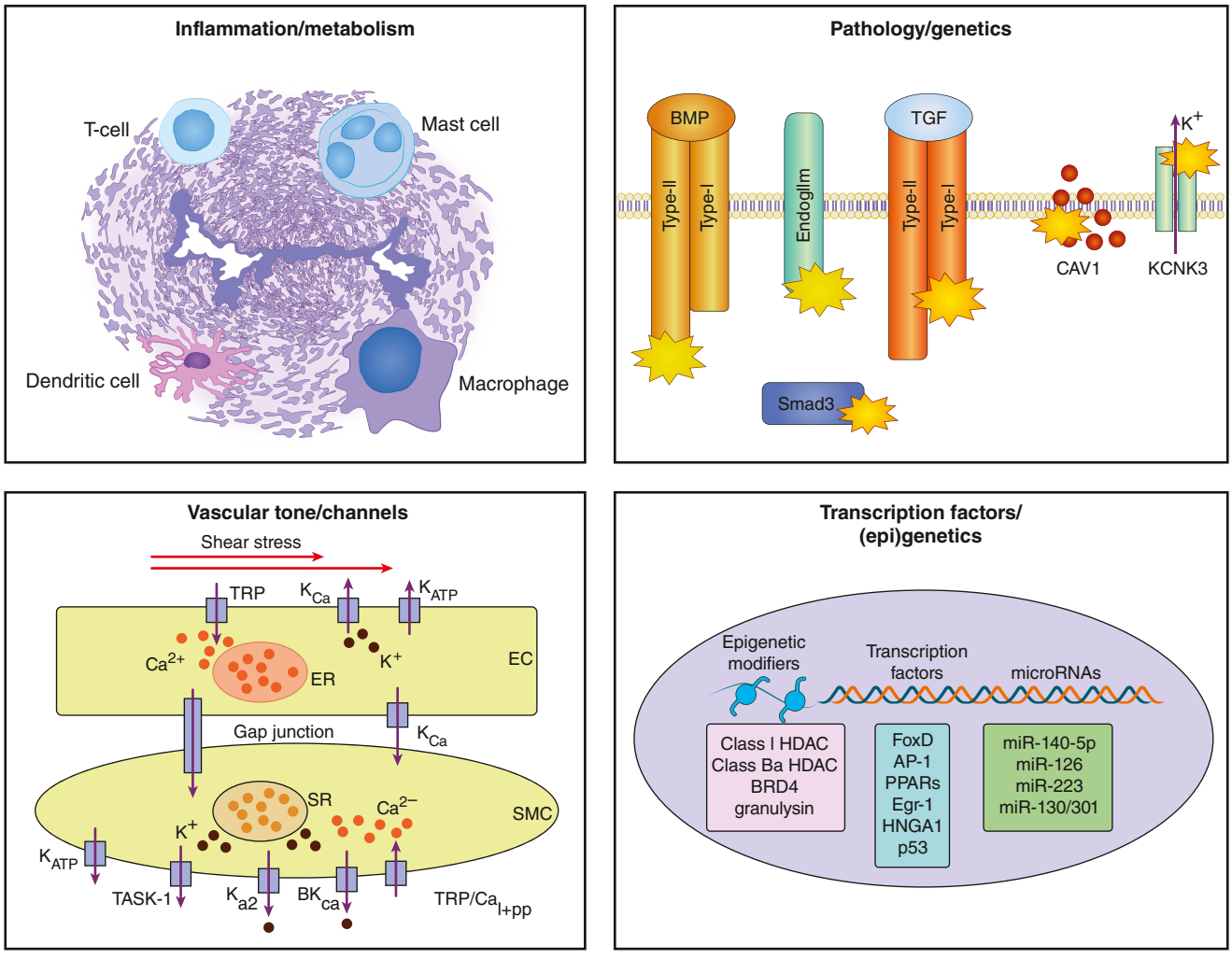

E-FIGURE 69-1. Processes involved in the development of pulmonary hypertension. Current studies are investigating the different signal transduction pathways shown. BKCa = calcium-sensitive potassium channels; BMP = bone morphogenetic protein; CaL type = L-type calcium channels; CAV1 = caveolin-1; EC = endothelial cells; ER = endoplasmic reticulum; HDAC = histone deacetylases; KATP = ATP-sensitive potassium channels; KCNK3 = TASK-1 potassium channels; KV = voltage-dependent potassium channels; SMC = smooth muscle cells; SR = sarcoplasmic reticulum; TGF = transforming growth factor; TRP = transient receptor potential (channels). (From Olschewski A, Berghausen EM, Eichstaedt CA, et al. Pathobiology, pathology and genetics of pulmonary hypertension: update from the Cologne Consensus Conference 2018. *Int J Cardiol*. 2018;272S:4-10.)

Other physical examination findings may give some insight into the etiology of the pulmonary hypertension. For example, central cyanosis and clubbing may suggest an intracardiac shunt and Eisenmenger physiology. Sclerodactyly, digital ischemia (see Fig. 246-2), telangiectasias (see Fig. 159-3), arthritis, Raynaud phenomenon (see Fig. 66-9), and rashes may increase the suspicion of an underlying connective tissue disease. Splenomegaly, spider angioma, palmar erythema (see Fig. 132-2), icterus (see Fig. 132-1), and caput medusae may suggest portal hypertension as an etiology. Signs of left-sided heart disease, such as pulmonary congestion, left-sided third heart sound, or findings of mitral or aortic valve disease on auscultation, may signify pulmonary hypertension as a result of left-sided heart disease. Fine rales, crackles, accessory muscle use, wheezing, protracted expiration, and productive cough may denote group 3 pulmonary hypertension as a result of lung disease.

DIAGNOSIS

Initial assessments should include measurement of serum N-terminal fragment of pro–brain natriuretic peptide (NT-proBNP), an electrocardiogram, and chest radiograph.[10] NT-proBNP is frequently elevated in patients who have pulmonary hypertension, but normal values do not exclude its presence. The electrocardiogram may show right axis deviation, right ventricular enlargement, right atrial enlargement, and ST- and T-wave changes across the anterior precordium that reflect right ventricular strain (Fig. 69-1). The chest radiograph may demonstrate enlarged proximal pulmonary arteries (see Fig. 44-4) with peripheral tapering or pruning of the pulmonary vasculature (Fig. 69-2A). The lateral radiograph may reveal the reduction in retrosternal air space as a result of right ventricular enlargement (Fig. 69-2B). Notably, normal electrocardiographic and radiographic findings do not exclude the presence of pulmonary hypertension.

If pulmonary hypertension is suspected, a series of diagnostic evaluations should follow (Fig. 69-3), usually beginning with an echocardiogram and with further testing guided by the patient's subtype.[11,12] The echocardiogram gives insight not only into the presence of pulmonary hypertension but also into the presence of common disorders of the left side of the heart that may result in pulmonary hypertension. Two-dimensional echocardiographic findings reflective of elevated pulmonary artery pressures include right atrial enlargement, right ventricular enlargement, flattening of the intraventricular septum, and underfilled left ventricle (Fig. 69-4). The right ventricular systolic pressure may be estimated on the basis of the velocity of the tricuspid regurgitant jet by the modified Bernoulli equation (Chapter 43) (Fig. 69-5), although a reliable estimate of right ventricular systolic pressure is not always obtainable, and this measurement is prone to error, particularly in patients with parenchymal lung disease.

The echocardiogram is also useful to assess for left-sided heart causes of pulmonary hypertension, such as systolic dysfunction, diastolic dysfunction, and valvular heart disease. On occasion, a previously unknown congenital heart defect is discovered during this evaluation. In approximately 25% of patients, a previously trivial patent foramen ovale may shunt blood from the right atrium to the left atrium because of the high pulmonary vascular resistance and thereby worsen systemic oxygenation.

In a patient with unexplained dyspnea and evidence of pulmonary hypertension on echocardiography, chronic thromboembolic pulmonary hypertension must be excluded. The study of choice for this assessment is the ventilation-perfusion (V/Q) scan (see Fig. 68-6), which often shows multiple perfusion defects that are not matched on ventilation. Although computed tomography is excellent for the assessment of acute pulmonary embolus, it sometimes fails to detect chronic thromboembolic disease. If either of these studies detects an abnormality, further evaluation with pulmonary angiography may be required to determine whether chronic thromboembolic disease is the diagnosis and, if so, whether it is surgically accessible.

Pulmonary function tests in patients with pulmonary arterial hypertension may show a mild restrictive or obstructive pattern and (usually) a mildly reduced diffusing capacity for carbon monoxide. Pulmonary function tests may disclose evidence of obstructive or restrictive lung disease; further evaluation with chest computed tomography may be necessary. Polysomnography may be required to evaluate for obstructive sleep apnea (Chapter 374).

Recommended serologic testing includes an antinuclear antibody test and HIV serology in addition to liver function tests. A study of functional capacity, most commonly the 6-minute walk test, is useful to assess the severity of disease and to establish a baseline against which to assess subsequent changes in exercise capacity as a result of medical interventions. The high prevalence of pulmonary arterial hypertension in patients with scleroderma (Chapter 246) serves as an opportunity for screening of this high-risk population using pulmonary function testing, biomarkers, and echocardiography to make an early diagnosis.

If pulmonary arterial hypertension is suspected on the basis of the noninvasive evaluation, the diagnosis must be confirmed with a right-sided heart catheterization that measures right atrial pressure, right ventricular pressure, pulmonary artery (systolic, diastolic, and mean) pressures, pulmonary arterial wedge pressure (reflective of left ventricular end-diastolic pressure or left atrial pressure), cardiac output and index, heart rate, systemic blood pressure, and oxygen saturations in the superior vena cava, inferior vena cava, pulmonary artery, and a systemic artery. From this information, pulmonary vascular resistance and systemic vascular resistance may be calculated, right ventricular

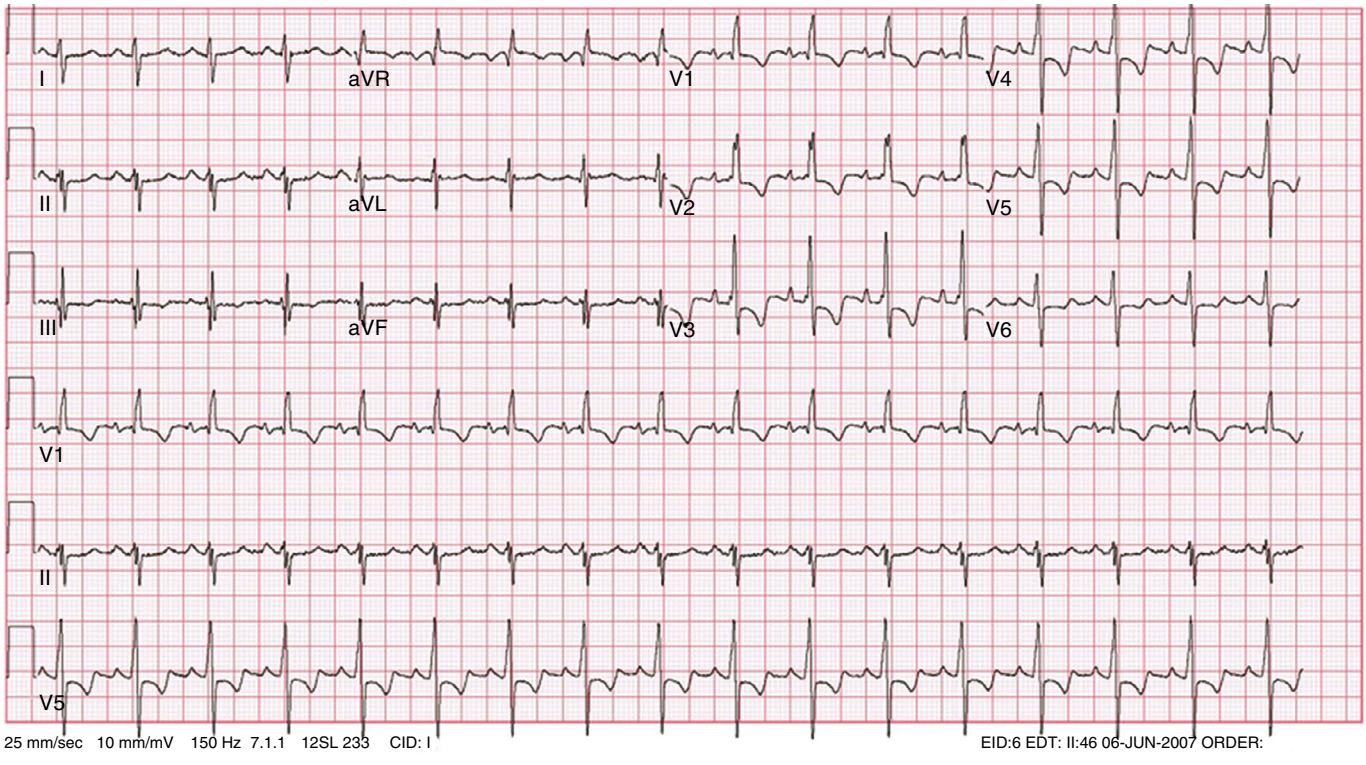

FIGURE 69-1. Electrocardiogram demonstrating sinus rhythm, right axis deviation, and right ventricular hypertrophy with a strain pattern.

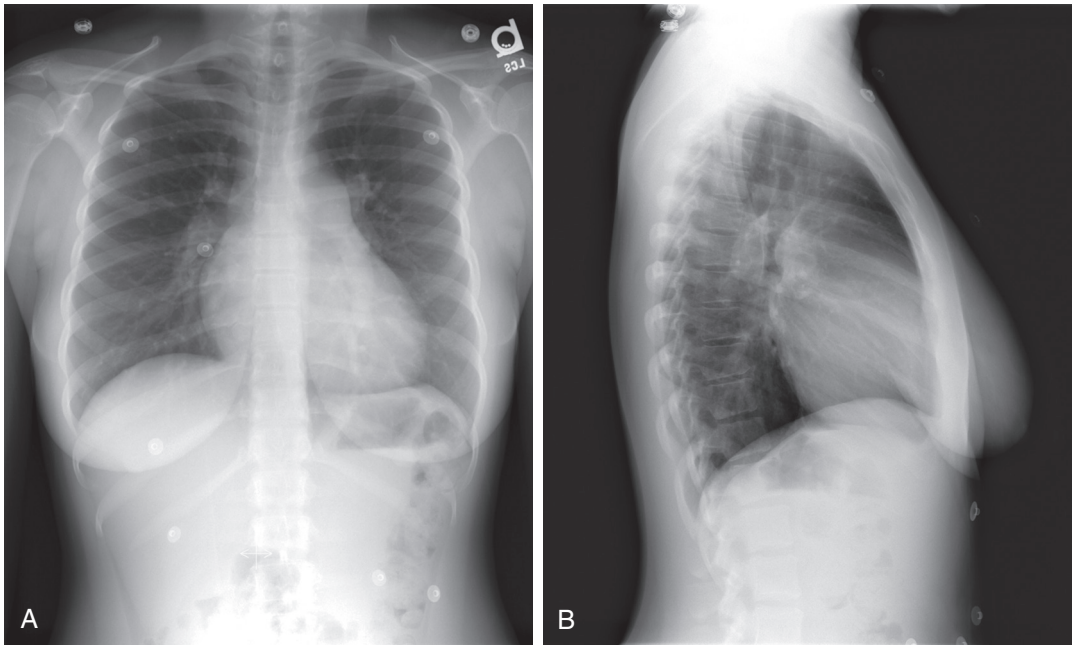

FIGURE 69-2. Posterior-anterior (A) and lateral (B) chest radiographs demonstrating enlarged proximal pulmonary arteries and right ventricular enlargement.

performance can be ensured, and an intracardiac or intrapulmonary shunt can be confirmed or excluded.

Measurement of the wedge pressure, a surrogate for left atrial pressure in the absence of pulmonary vein obstruction, is useful to exclude pulmonary hypertension caused by left-sided heart disease. If an optimal wedge pressure tracing cannot be obtained, or if there is any question about the accuracy of the wedge pressure tracing, a left ventricular end-diastolic pressure should be obtained. At the time of the initial right-sided heart catheterization, acute vasodilator testing is recommended in patients with idiopathic pulmonary arterial hypertension to identify patients who might be candidates for therapy with calcium-channel blockers.

The three agents most commonly used for acute vasodilator testing in the cardiac catheterization laboratory are inhaled nitric oxide, intravenous epoprostenol, and inhaled iloprost. A positive response to an acute vasodilator is a decrease in mean pulmonary artery pressure by at least 10 mm Hg to a mean pulmonary artery pressure of less than 40 mm Hg, without a decrease in cardiac output. If a patient meets these criteria, it is reasonable to administer a trial of oral calcium-channel blockers.

TREATMENT

General Measures

Patients with pulmonary arterial hypertension should always be treated at or in collaboration with a pulmonary hypertension center. Basic counseling and education are important components in the care of patients with pulmonary arterial hypertension. Patients are encouraged to avoid strenuous activities but to engage in low-level graded aerobic exercise, such as walking, as tolerated, and to enroll in specialized pulmonary rehabilitation programs, which can improve hemodynamic metrics and exercise tolerance.[A1] Exposure to high altitudes should be avoided because it may aggravate hypoxemia and cause hypoxic pulmonary vasoconstriction. A sodium-restricted diet (<2400 mg/day) and restricted fluid intake are advised in patients with right ventricular failure. Routine immunizations, such as for influenza (Chapter 332), pneumococcal pneumonia (Chapter 268), and severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2; Chapter 337), are advised. In patients with persistent oxygen saturations below 90%, supplemental oxygen is recommended. In patients with intracardiac shunting and Eisenmenger physiology (Chapter 55), supplementary oxygen is recommended only if it produces a consistent increase in oxygen saturations and relief of symptoms.

Women with pulmonary arterial hypertension are advised to avoid pregnancy because the hemodynamic changes during pregnancy, labor, delivery, and the postpartum period are potentially life-threatening. Women of childbearing potential should be counseled on contraception options (Chapter 220) at the time of diagnosis. If women with pulmonary arterial hypertension consider pregnancy or become pregnant, prompt counseling by an experienced center is recommended.

Background Therapy

Diuretics (e.g., furosemide, initiated at 20 mg and titrated as needed, optionally in combination with other diuretics, such as spironolactone 25 mg; Table 102-4) are indicated to manage right ventricular volume overload; serum electrolytes and renal function must be closely monitored. Anticoagulation is not recommended in patients with pulmonary arterial hypertension unless other indications for anticoagulation are present.

Medical Therapy

Medical therapy for pulmonary arterial hypertension (Fig. 69-6) is based on the patient's characteristics and a comprehensive risk assessment (Table 69-2).[13,14] Reaching and maintaining a low-risk profile (determined by a 6-minute walking distance >440 meters, functional class I or II, and normal or near-normal NT-proBNP) is a key objective when treating a patient with pulmonary arterial hypertension. Unfortunately, this goal is not always achievable, especially in older patients with comorbid conditions.

Calcium-Channel Blockers

Approximately 7% of adult patients with idiopathic pulmonary arterial hypertension have a favorable response to acute vasodilator testing and an excellent prognosis with calcium-channel blockers. Long-acting nifedipine (90 to 180 mg daily), diltiazem (360 to 720 mg daily), and amlodipine (10 to 20 mg daily) are the most commonly used calcium-channel blockers. Because of its potential negative inotropic effects, verapamil should be avoided. Patients must be observed closely for both the safety and efficacy of this therapy. If a patient who meets the definition of an acute response does not improve to functional class I or II with calcium-channel blocker therapy, alternative or additional therapies should be instituted (see later).

Targeted Therapies

Targeted therapies for pulmonary arterial hypertension can be directed against endothelin or the pathways for nitric oxide, cyclic guanosine monophosphate (GMP), and prostacyclin.

Endothelin Receptor Antagonists

The endothelin receptor antagonist bosentan (initiated orally at 62.5 mg twice daily and titrated up to 125 mg twice daily after 1 month) improves hemodynamic measurements, exercise capacity, and the clinical course of pulmonary arterial hypertension.[A2] Liver enzymes must be monitored on a monthly basis; the dose should be reduced if liver enzymes rise to more than three to five times the upper limits of normal and discontinued if they rise to five times the upper limit of normal. Ambrisentan (administered orally at doses of either 5 mg or 10 mg once daily) has similar benefits, but liver function monitoring is not mandated.[A3] Other side effects include lower extremity edema, headache, and nasal congestion. Macitentan, a dual endothelin receptor antagonist (10 mg once daily), improves exercise capacity and delays disease progression in patients with pulmonary arterial hypertension.[A4] The most frequent adverse events are headache, nasopharyngitis, and anemia, without an increased rate of peripheral edema or elevated liver enzymes.

Phosphodiesterase Type 5 Antagonists

The phosphodiesterase type 5 antagonists sildenafil (20 mg three times daily) and tadalafil (40 mg once daily) improve hemodynamic measurements and

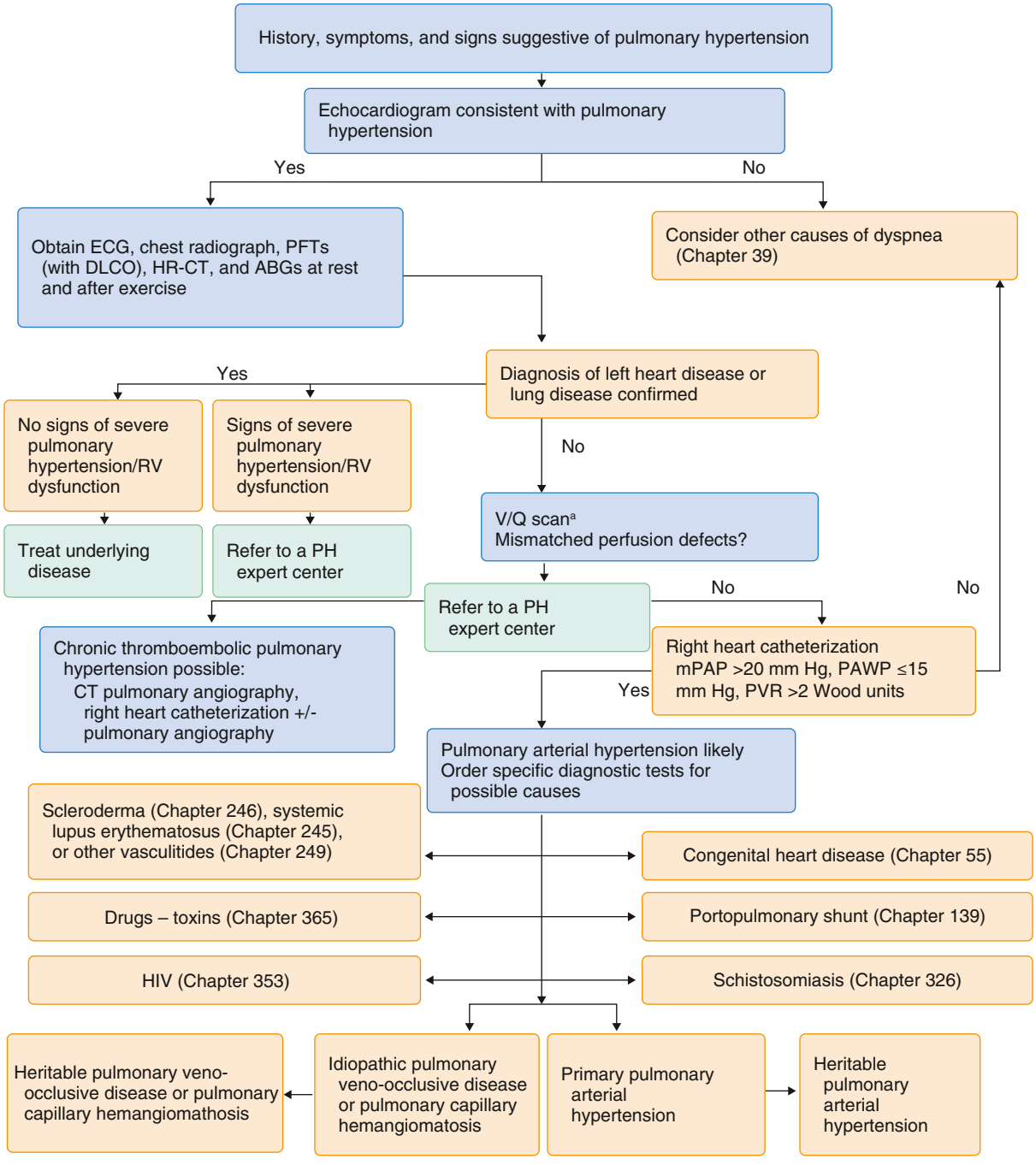

FIGURE 69-3. Diagnostic algorithm for pulmonary hypertension. [a]CT pulmonary angiography alone may miss diagnosis of chronic thromboembolic pulmonary hypertension. ABG = arterial blood gas; CT = computed tomography; DLCO = carbon monoxide diffusing capacity; ECG = electrocardiogram; HIV = human immunodeficiency virus; HR-CT = high resolution CT; mPAP = mean pulmonary arterial pressure; PAWP = pulmonary artery wedge pressure; PFT = pulmonary function test; PH = pulmonary hypertension; PVR = pulmonary vascular resistance; RV = right ventricular; V/Q = ventilation/perfusion. (Adapted from Galie N, Humbert M, Vachiery JL, et al. 2015 ESC/ERS guidelines for the diagnosis and treatment of pulmonary hypertension: the Joint Task Force for the Diagnosis and Treatment of Pulmonary Hypertension of the European Society of Cardiology [ESC] and the European Respiratory Society [ERS]: endorsed by: Association for European Paediatric and Congenital Cardiology [AEPC], International Society for Heart and Lung Transplantation [ISHLT]. *Eur Heart J*. 2016;37:67-119.)

exercise capacity in patients with pulmonary arterial hypertension.[A5] The most common side effects of these medications are headache, back pain, flushing, dyspepsia, and epistaxis.

Guanylate Cyclase Stimulation

Riociguat, which is a soluble guanylate cyclase stimulator, directly stimulates soluble guanylate cyclase independent of nitric oxide and thereby increases the sensitivity of soluble guanylate cyclase to nitric oxide. Riociguat (1.0 mg up to 2.5 mg three times daily) significantly improves 6-minute walking distance as well as pulmonary vascular resistance, brain natriuretic peptide levels, functional class, and time to clinical worsening, including in patients who were previously treated with endothelin receptor antagonists or nonparenteral prostanoids.[A6] The most common adverse events include headache, dyspepsia, peripheral edema, and hypotension. Riociguat should not be used concurrently with a phosphodiesterase type 5 inhibitor.

Prostanoids

Intravenous epoprostenol improves functional class, exercise endurance, hemodynamics, and survival in patients with idiopathic pulmonary arterial hypertension,[A7] and it also improves exercise tolerance and hemodynamics in patients with pulmonary arterial hypertension related to the scleroderma spectrum of diseases. Epoprostenol must be delivered by continuous intravenous infusion, commonly initiated in the hospital at a dose of 2 ng/kg/minute, with the dose titrated up on the basis of symptoms of pulmonary arterial hypertension and side effects of the therapy. Each patient must learn the techniques of sterile preparation of the medication, operation of the ambulatory infusion pump, and care of the central venous catheter. Although dosing must be highly individualized, maintenance doses in the range of 25 to 40 ng/kg/minute are typically needed. Common side effects include headache, jaw pain, flushing, nausea, diarrhea, rash, and musculoskeletal pain. Infections and infusion interruption can be life-threatening.

Subcutaneous treprostinil provides a modest but statistically significant improvement in exercise tolerance. Subcutaneous treprostinil is often started in the home, with the dose titrated on the basis of symptoms and side effects. Treprostinil is less potent than epoprostenol, and higher doses are required to achieve the desired efficacy. The main limitation of this therapy is pain and erythema at the site of the subcutaneous infusion, a complication that occurs in 85% of patients. Treprostinil may also be delivered as a continuous intravenous infusion via a fully implantable pump.[15] Oral treprostinil

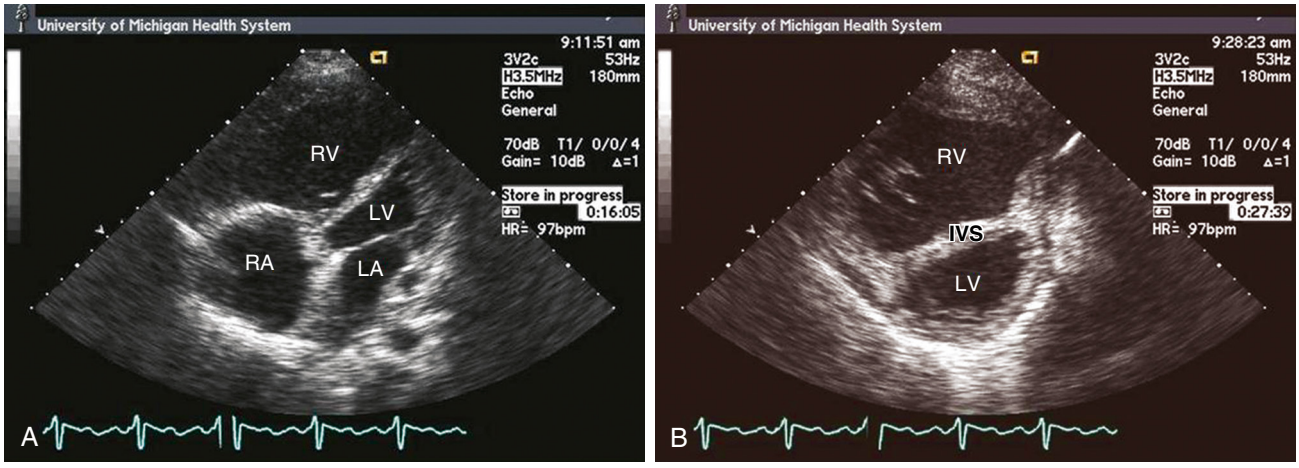

FIGURE 69-4. Echocardiographic images of the heart. A, Four-chamber view. Right atrial (RA) enlargement, right ventricular (RV) enlargement. The left atrium (LA) and left ventricle (LV) are small and underfilled. **B,** Short-axis view. RV enlargement is present. Flattening of the intraventricular septum (IVS) results from pressure and volume overload of the RV.

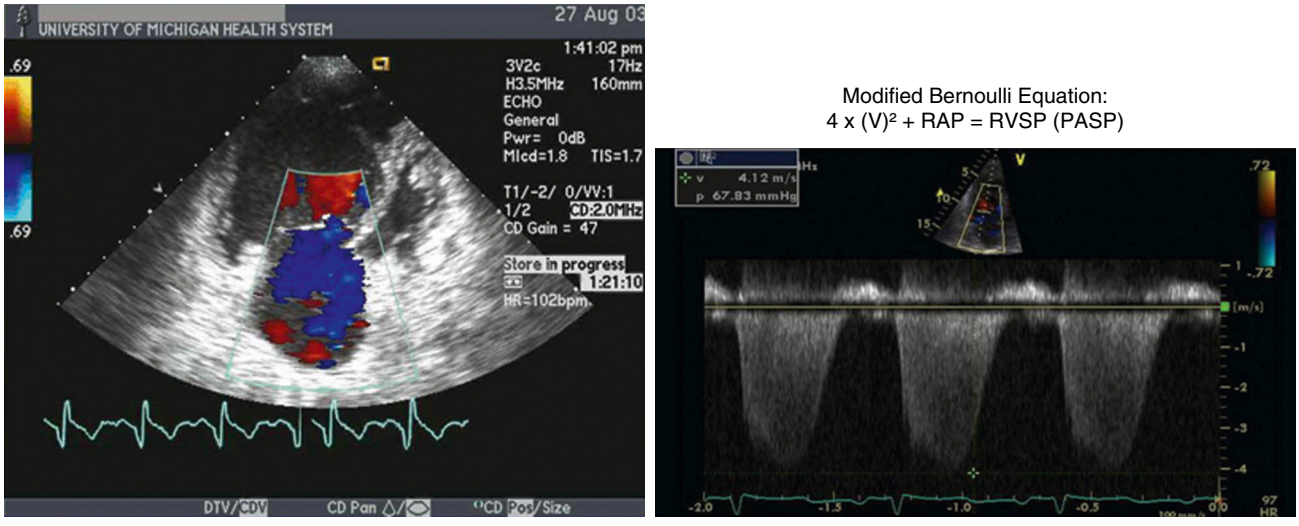

FIGURE 69-5. Calculation of estimated pulmonary artery pressure based on the velocity of the tricuspid regurgitant jet. PASP = pulmonary artery systolic pressure; RAP = right atrial pressure; RVSP = right ventricular systolic pressure; V = tricuspid jet velocity (m/sec).

(starting at 0.25 mg with meals two to three times daily and increased to as high as 12 mg two to three times daily as tolerated) delays the progression of disease when added to other medications.[A8] For subcutaneous or oral therapy, other prostanoid-type side effects, including headache, diarrhea, rash, and nausea, also occur.

Inhaled treprostinil four times daily and inhaled iloprost six to nine times daily also provide modest improvements in exercise capacity, including in patients with pulmonary hypertension owing to interstitial lung disease.[A9] Cough is an additional side effect with this method of administration.

Another option is selexipag, which is a selective prostacyclin receptor agonist, at a maximum dose of 1600 μg orally twice daily. Selexipag can significantly reduce the risk of the composite end point of death from any cause or a complication related to pulmonary arterial hypertension, but it has not been shown to reduce mortality per se significantly.[A10]

Targeting BMP

Sotatercept (a fusion protein designed to help regulate bone morphogenetic protein pathway signaling, given as 0.3 to 0.7 mg/kg subcutaneously every 3 weeks) also can reduce pulmonary vascular resistance in patients already on other therapies for pulmonary arterial hypertension.[A11,A12] It also reduces brain natriuretic peptide levels and increases walking distance.

Combination Therapy

Combination therapy[16] targeting different pathways is increasingly used in patients with pulmonary arterial hypertension. For example, initial combination therapy[A13] with ambrisentan plus tadalafil is more effective in improving exercise and preventing disease progression than monotherapy with either drug alone.[A14] In newly diagnosed patients whose pulmonary arterial hypertension is not associated with comorbid conditions, initial combination therapy with a phosphodiesterase-5 inhibitor plus an endothelin receptor antagonist has become the preferred treatment. Initial oral triple therapy has not been shown to be superior to double therapy.[A15] In contrast, in newly diagnosed patients who have other cardiopulmonary comorbid conditions, oral monotherapy is preferred, and initial therapy with a phosphodiesterase-5 inhibitor is often the most commonly used class of medications (Fig 69-6).

Invasive Therapies

Despite advances in medical therapies for pulmonary arterial hypertension, many patients experience progressive functional decline, largely related to worsening right-sided heart failure. In carefully selected patients, atrial septostomy may improve symptoms. Atrial septostomy creates a right-to-left interatrial shunt, thereby decreasing right-sided heart filling pressures and improving right-sided heart function and left-sided heart filling. Although the right-to-left shunting decreases systemic arterial oxygen saturation, the anticipated improvement in cardiac output will result in overall augmentation in systemic oxygen delivery. Because of its high morbidity and mortality as well as its limited benefit, atrial septostomy is rarely performed in the United States and should be considered only by experienced operators in specialized centers.

Bilateral lung (Chapter 87) or heart-lung (Chapter 46) transplantation remains an option for selected patients with pulmonary arterial hypertension when medical therapy fails. Transplantation should be discussed with selected patients at the time of diagnosis, although timing of referral is challenging. The International Society for Heart and Lung Transplantation recommends that patients with pulmonary arterial hypertension be referred for transplantation evaluation if they have persistent functional class III or IV symptoms despite optimized medical therapy, including prostanoids. Patients who are otherwise good transplant candidates should be referred when they have an unsatisfactory response to medical therapies. In some instances, advanced circulatory support may be required as a bridge to transplantation.

Special Populations

Group 2: Pulmonary Venous Hypertension

No specific therapy is currently approved for the treatment of pulmonary hypertension caused by left heart disease. Treatment should focus on the treatment of the heart failure itself (Chapter 46), with the goal of lowering pulmonary venous pressure and, as a result, pulmonary arterial pressure as well.

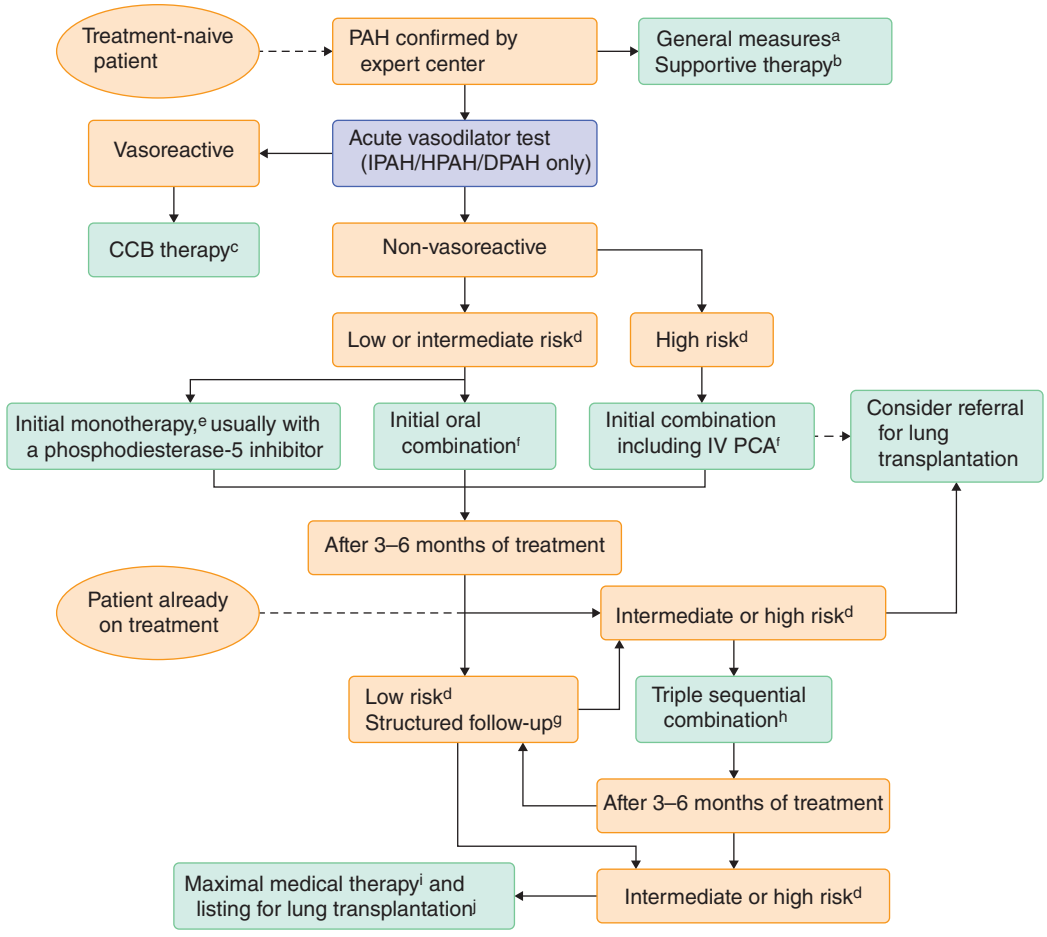

FIGURE 69-6. Pulmonary hypertension treatment algorithm. CCB = calcium channel blocker; DPAH = drug-induced pulmonary arterial hypertension; HIV = human immunodeficiency virus; HPAH = hereditary pulmonary arterial hypertension; IPAH = idiopathic pulmonary arterial hypertension; IV = intravenous; PAH = pulmonary arterial hypertension; PCA = prostacyclin analogues.

a. General measures include psychosocial support, supervised rehabilitation, and avoidance of excessive physical activity.
b. Supportive therapy includes the use of diuretics and oxygen as needed.
c. Calcium-channel blocker treatment is recommended for patients with idiopathic, hereditary, or drug-induced pulmonary arterial hypertension who have a positive vasoreactivity test.
d. Risk assessment should be done using established and validated risk stratification tools.
e. Initial monotherapy is recommended for patients with pulmonary arterial hypertension and cardiopulmonary comorbid conditions and for patients with distinct forms of pulmonary arterial hypertension (portopulmonary hypertension, pulmonary arterial hypertension associated with congenital heart disease, and human immunodeficiency virus–associated pulmonary arterial hypertension).
f. In patients with idiopathic, hereditary, or drug-induced pulmonary arterial hypertension and pulmonary arterial hypertension associated with connective tissue disease without cardiopulmonary comorbid conditions who present at a low or intermediate risk of death, initial oral combination therapy with an endothelin receptor antagonist and a phosphodiesterase type 5 inhibitor is recommended; if such patients present at a high risk of death, initial combination therapy with an endothelin receptor antagonist, a phosphodiesterase type 5 inhibitor, and an intravenous or subcutaneous prostacyclin analogue is recommended.
g. Regular follow-up at a pulmonary hypertension center, including risk assessment, is advised.
h. Addition of oral or parenteral prostacyclin pathway agents as determined by risk assessment and other clinical variables, such as comorbid conditions and patients' preferences, is recommended.
i. Optimized medical therapy, usually including an endothelin receptor antagonist, a phosphodiesterase type 5 inhibitor, and/or a soluble guanylate cyclase stimulator, plus an intravenous or subcutaneous prostacyclin analogue, is recommended.
j. Potentially eligible patients who do not reach a low-risk profile with optimized medical therapy should be referred for transplant evaluation; active listing should be considered if these patients present with a high risk profile. (Adapted from Galiè N, Channick RN, Frantz RP, et al. Risk stratification and medical therapy of pulmonary arterial hypertension. *Eur Resp J*. 2019;53:1801889.)

Group 3: Primary Lung Disease

For primary lung disease, treatment of the underlying disorder is indicated. Inhaled treprostinil can be effective in patients with interstitial lung disease (Chapter 80) and pulmonary hypertension, but other medications that are helpful for pulmonary arterial hypertension are usually not recommended for the treatment of pulmonary hypertension due to lung disease. However, in patients who have severe pulmonary hypertension but only mild lung disease, individualized decisions should be made in consultation with a specialized pulmonary hypertension center.

Group 4: Chronic Thromboembolic Hypertension

For patients with chronic thromboembolic pulmonary hypertension, pulmonary endarterectomy (E-Fig. 69-2) is the treatment of choice and is a potentially curative procedure.[17] Balloon pulmonary angioplasty is an option for patients who are not surgical candidates owing to distal disease.[18] Riociguat (1.0 up to 2.5 mg three times daily) improves 6-minute walking distance, pulmonary vascular resistance, NT-proBNP level, and functional class[A16] in patients with either inoperable chronic thromboembolic pulmonary hypertension or persistent pulmonary hypertension after pulmonary endarterectomy. If these options fail, pulmonary artery denervation may be helpful.[19] Indefinite anticoagulation is also recommended.

Group 5: Other Causes

Group 5 pulmonary hypertension consists of several forms for which the cause is unclear or multifactorial. Among these conditions are a number of hematologic, systemic, and metabolic disorders (see Table 69-1). No treatments are of proven value, but patients who have evidence of severe pulmonary hypertension should be referred to a pulmonary hypertension center for individualized treatment.

Assessing Response to Therapy

Given the complexity of the disease, the variable response to therapy, and the goal of optimizing and individualizing care, patients with pulmonary arterial hypertension must be observed closely (Table 69-3). Consensus recommendations rely on the routine assessment of important prognostic indicators, such as WHO functional class, 6-minute walking distance, NT-proBNP, and echocardiographic and hemodynamic parameters (Table 69-2).

Collaborative Care

Due to the rare and complex nature of pulmonary arterial hypertension, optimal care requires collaboration among multiple disciplines. At pulmonary hypertension centers, this collaboration helps patients receive high-quality specialty care for a rare disease while also coordinating with the patient's local primary care doctor and specialists.

E-FIGURE 69-2. **Chronic thromboembolic material endarterectomized from a patient.** (Image courtesy Dr. Jonathan Haft.)

TABLE 69-2 RISK ASSESSMENT IN PULMONARY ARTERIAL HYPERTENSION

DETERMINANTS OF PROGNOSIS* (ESTIMATED 1-YEAR MORTALITY)	LOW RISK <5%	INTERMEDIATE RISK 5-10%	HIGH RISK >10%
Clinical signs of right heart failure	Absent	Absent	Present
Progression of symptoms	No	Slow	Rapid
Syncope	No	Occasional syncope†	Repeated syncope‡
WHO functional class	I, II	III	IV
6MWD	>440 m	165-440 m	<165 m
Cardiopulmonary exercise testing	Peak VO_2 > 15 mL/min/kg (>65% pred.) VE/VCO_2 slope < 36	Peak VO_2 > 11-15 mL/min/kg (35-65% pred.) VE/VCO_2 slope 36-44.9	Peak VO_2 > 11 mL/min/kg (<35% pred.) VE/VCO_2 slope > 45
BNP or NT-proBNP plasma levels	BNP < 50 ng/L NT-proBNP < 300 ng/L	BNP 50-300 ng/L NT-proBNP 300-1400 ng/L	BNP > 300 ng/L NT-proBNP < 300 ng/L
Imaging (echocardiography, CMR imaging)	RA area < 18 cm^2 No pericardial effusion	RA area 18-26 cm^2 No or minimal pericardial effusion	RA area > 26 cm^2 Pericardial effusion
Hemodynamics	RAP < 8 mm Hg CI ≥ 2.5 L/min/m^2 SvO_2 > 65%	RAP 8-14 mm Hg CI 2.0-2.4 L/min/m^2 SvO_2 60-65%	RAP > 14 mm Hg CI < 2.0 L/min/m^2 SvO_2 < 60%

*Most of the proposed variables and cutoff values are based on expert opinion. They may provide prognostic information and may be used to guide therapeutic decisions, but application to individual patients must be done carefully. Most of these factors have been validated primarily for idiopathic pulmonary arterial hypertension, and the cutoff levels used above may not necessarily apply to other forms of pulmonary arterial hypertension. Furthermore, the use of approved therapies and their influence on the variables should be considered in the evaluation of the risk.

†Occasional syncope during brisk or heavy exercise, or occasional orthostatic syncope in an otherwise stable patient.

‡Repeated episodes of syncope, even with little or regular physical activity.

6MWD = 6-minute walking distance; BNP = brain natriuretic peptide; CI = cardiac index; CMR = cardiac magnetic resonance; NT-proBNP = N-terminal pro-brain natriuretic peptide; pred. = predicted; RA = right atrium; RAP = right atrial pressure; SvO_2 = mixed venous oxygen saturation; VE/VCO_2 = ventilatory equivalents for carbon dioxide; VO_2 = oxygen consumption; WHO = World Health Organization.

Adapted from Galie N, Humbert M, Vachiery JL, et al. 2015 ESC/ERS guidelines for the diagnosis and treatment of pulmonary hypertension: the Joint Task Force for the Diagnosis and Treatment of Pulmonary Hypertension of the European Society of Cardiology (ESC) and the European Respiratory Society (ERS): endorsed by: Association for European Paediatric and Congenital Cardiology (AEPC), International Society for Heart and Lung Transplantation (ISHLT). *Eur Heart J*. 2016;37:67-119.

TABLE 69-3 SUGGESTED ASSESSMENT AND TIMING FOR THE FOLLOW-UP OF PATIENTS WITH PULMONARY ARTERIAL HYPERTENSION

	AT BASELINE	EVERY 3-6 MONTHS*	EVERY 6-12 MONTHS*	3-6 MONTHS AFTER CHANGES IN THERAPY*	IN CASE OF CLINICAL WORSENING
Medical assessment and determination of functional class	+	+	+	+	+
Electrocardiogram	+	+	+	+	+
6MWT/Borg dyspnea score	+	+	+	+	+
Cardiopulmonary exercise testing	+		+		+‖
Echocardiography	+		+	+	+
Basic laboratory tests†	+	+	+	+	+
Extended laboratory tests‡	+		+		+
Blood gas analysis§	+		+	+	+
Right heart catheterization	+		+¶	+‖	+‖

*Intervals to be adjusted according to patient needs.

†Basic lab includes blood count, INR (in patients receiving vitamin K antagonists), serum creatinine, sodium, potassium, ASAT/ALAT (in patients receiving ERAs), bilirubin, and BNP/NT-proBNP.

‡Extended lab includes TSH, troponin, uric acid, iron status (iron, ferritin, soluble transferrin receptor), and other variables according to individual patient needs.

§From arterial or arterialized capillary blood; may be replaced by peripheral oxygen saturation in stable patients or if BGA is not available.

‖Should be considered.

¶Some centers perform RHCs at regular intervals during follow-up.

6MWT = 6-minute walking test; ALAT = alanine aminotransferase; ASAT = aspartate aminotransferase; BGA = blood gas analysis; BNP = brain natriuretic peptide; ERAs = endothelin receptor antagonists; FC = functional class; INR = international normalized ratio; lab = laboratory assessment; NT-proBNP = N-terminal pro–brain natriuretic peptide; RHC = right heart catheterization; TSH = thyroid-stimulating hormone.

Adapted from Galie N, Humbert M, Vachiery JL, et al. 2015 ESC/ERS guidelines for the diagnosis and treatment of pulmonary hypertension: the Joint Task Force for the Diagnosis and Treatment of Pulmonary Hypertension of the European Society of Cardiology (ESC) and the European Respiratory Society (ERS): endorsed by: Association for European Paediatric and Congenital Cardiology (AEPC), International Society for Heart and Lung Transplantation (ISHLT). *Eur Heart J*. 2016;37:67-119.

PROGNOSIS

Even mild pulmonary hypertension on echocardiography, as evidenced by an estimated pulmonary artery systolic pressure of 27 to 39 mm Hg, is associated with a significant increase in mortality.[20] The natural history of symptomatic idiopathic pulmonary arterial hypertension is a median survival of 2.8 years with 1-, 3-, and 5-year survival rates of 68%, 48%, and 34%, respectively. In the era of targeted therapies, survival has improved but remains suboptimal, with 1-, 2-, and 3-year survival of approximately 90%, 70%, and 55%, respectively, for incident cases. The most frequent cause of death in patients with advanced pulmonary hypertension is progressive right ventricular failure.

Several clinical factors are correlated with prognosis (see Table 69-2). Patients who have better functional, echocardiographic, and hemodynamic parameters or who improve on these parameters with treatment have a better prognosis than patients who do not achieve these goals or who experience pulmonary hypertension–related morbidities.[21,22] For example, achieving a 6-minute walk of more than 440 meters, functional class I or II symptoms, and a normal brain natriuretic peptide level is associated with excellent survival.[23]

Patients with pulmonary arterial hypertension related to the scleroderma spectrum of diseases tend to have a poorer prognosis than that of patients with idiopathic pulmonary arterial hypertension, whereas patients with pulmonary

arterial hypertension related to congenital heart disease tend to have a better prognosis, perhaps because they have better right ventricular function. The natural history of patients with groups 2, 3, and 4 pulmonary hypertension is influenced by their left-sided heart and lung disease. In most cases, the presence of pulmonary hypertension in addition to the underlying disease portends a poor prognosis.

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70 ANTITHROMBOTIC AND ANTIPLATELET THERAPY

RICHARD C. BECKER AND THOMAS L. ORTEL

Antithrombotic therapy is a key component of the prevention and treatment of cardiovascular, cerebrovascular, and peripheral vascular diseases. These therapies include anticoagulation, which targets secondary hemostasis; antiplatelet agents, which target primary hemostasis; and fibrinolysis, which enhances natural fibrinolytic mechanisms. The therapies may be used individually or in combination, depending on the clinical setting.

ANTICOAGULANT THERAPY

Anticoagulant therapies are used for the prevention and treatment of venous and arterial thromboembolic events. Parenteral agents include heparin and related compounds, as well as two direct thrombin inhibitors (Table 70-1). Oral therapies include the vitamin K antagonists and direct oral anticoagulants (DOACs; Table 70-2).

PARENTERAL ANTICOAGULANTS

Parenteral anticoagulants include heparin, low-molecular-weight heparins, and fondaparinux.

Heparin

Unfractionated heparin, which is prepared from porcine intestine or bovine lung, is a heterogeneous mixture of negatively charged polysulfated glycosaminoglycans that range in size from 3000 to 30,000 daltons. Anticoagulant activity depends on a specific sequence of five sugar residues within the polysaccharide chain. Up to two thirds of the chains lack this sequence, however, and have minimal to no anticoagulant effect.

Heparin binds to the natural anticoagulant antithrombin through the pentasaccharide sequence, thereby inducing a conformational change that markedly enhances antithrombin's ability to inhibit thrombin, factor Xa, and other hemostatic proteinases. Factor Xa inhibition requires the pentasaccharide sequence only. In contrast, thrombin inactivation requires the pentasaccharide sequence and a minimal chain length of 18 sugar units to provide an essential docking surface for both inhibitor and enzyme. Unfractionated heparin binds

TABLE 70-1 PARENTERAL ANTICOAGULANT THERAPIES

	UNFRACTIONATED HEPARIN	LOW-MOLECULAR-WEIGHT HEPARIN*	FONDAPARINUX	BIVALIRUDIN	ARGATROBAN
Mechanism of action	Enhances AT-mediated inactivation of thrombin, factor Xa, and other serine proteinases	Primarily enhances AT-mediated inactivation of factor Xa with less effect on thrombin	Enhances AT-mediated inactivation of factor Xa with no effect on thrombin	Direct inhibition of thrombin	Direct inhibition of thrombin
Typical dosing	Treatment: 80 U/kg IV bolus then 15-18 u/kg/hr (see Table 68-6) Prophylaxis: 5000 U SQ 2 to 3 times daily	See Table 70-3	Treatment: 7.5 mg SQ daily (5 mg if <50 kg, 10 mg if >100 kg) Prophylaxis: 2.5 mg SQ daily (avoid if <50 kg)	Treatment: 0.75 mg/kg IV bolus, then 1.75 mg/kg/hr (for PCI)	Treatment: For heparin-induced thrombocytopenia, start at 2 μg/kg/min IV
Laboratory monitoring	aPTT, anti-factor Xa activity; ACT for selected indications	Usually not necessary, but can use anti-factor Xa activity	Usually not necessary, but can use anti-factor Xa activity	aPTT; dilute thrombin time	aPTT; dilute thrombin time
Plasma half-life	1-2 hr	See Table 70-3	17 hr	25 min	45 min
Reversal therapy	Protamine	Protamine partially effective	Protamine ineffective; factor VIIa can be used to treat the hemorrhagic event	Discontinue anticoagulant; no specific reversal agent available	Discontinue anticoagulant; no specific reversal agent available

*Includes enoxaparin and dalteparin.
ACT = activated clotting time; aPTT = activated partial thromboplastin time; AT= antithrombin; IV = intravenous; PCI = percutaneous coronary intervention; SQ = subcutaneous.

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70 ANTITHROMBOTIC AND ANTIPLATELET THERAPY

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Antithrombotic therapy is a key component of the prevention and treatment of cardiovascular, cerebrovascular, and peripheral vascular diseases. These therapies include anticoagulation, which targets secondary hemostasis; antiplatelet agents, which target primary hemostasis; and fibrinolysis, which enhances natural fibrinolytic mechanisms. The therapies may be used individually or in combination, depending on the clinical setting.

ANTICOAGULANT THERAPY

Anticoagulant therapies are used for the prevention and treatment of venous and arterial thromboembolic events. Parenteral agents include heparin and related compounds, as well as two direct thrombin inhibitors (Table 70-1). Oral therapies include the vitamin K antagonists and direct oral anticoagulants (DOACs; Table 70-2).

PARENTERAL ANTICOAGULANTS

Parenteral anticoagulants include heparin, low-molecular-weight heparins, and fondaparinux.

Heparin

Unfractionated heparin, which is prepared from porcine intestine or bovine lung, is a heterogeneous mixture of negatively charged polysulfated glycosaminoglycans that range in size from 3000 to 30,000 daltons. Anticoagulant activity depends on a specific sequence of five sugar residues within the polysaccharide chain. Up to two thirds of the chains lack this sequence, however, and have minimal to no anticoagulant effect.

Heparin binds to the natural anticoagulant antithrombin through the pentasaccharide sequence, thereby inducing a conformational change that markedly enhances antithrombin's ability to inhibit thrombin, factor Xa, and other hemostatic proteinases. Factor Xa inhibition requires the pentasaccharide sequence only. In contrast, thrombin inactivation requires the pentasaccharide sequence and a minimal chain length of 18 sugar units to provide an essential docking surface for both inhibitor and enzyme. Unfractionated heparin binds

TABLE 70-1 PARENTERAL ANTICOAGULANT THERAPIES

	UNFRACTIONATED HEPARIN	LOW-MOLECULAR-WEIGHT HEPARIN*	FONDAPARINUX	BIVALIRUDIN	ARGATROBAN
Mechanism of action	Enhances AT-mediated inactivation of thrombin, factor Xa, and other serine proteinases	Primarily enhances AT-mediated inactivation of factor Xa with less effect on thrombin	Enhances AT-mediated inactivation of factor Xa with no effect on thrombin	Direct inhibition of thrombin	Direct inhibition of thrombin
Typical dosing	Treatment: 80 U/kg IV bolus then 15-18 u/kg/hr (see Table 68-6) Prophylaxis: 5000 U SQ 2 to 3 times daily	See Table 70-3	Treatment: 7.5 mg SQ daily (5 mg if <50 kg, 10 mg if >100 kg) Prophylaxis: 2.5 mg SQ daily (avoid if <50 kg)	Treatment: 0.75 mg/kg IV bolus, then 1.75 mg/kg/hr (for PCI)	Treatment: For heparin-induced thrombocytopenia, start at 2 μg/kg/min IV
Laboratory monitoring	aPTT, anti-factor Xa activity; ACT for selected indications	Usually not necessary, but can use anti-factor Xa activity	Usually not necessary, but can use anti-factor Xa activity	aPTT; dilute thrombin time	aPTT; dilute thrombin time
Plasma half-life	1-2 hr	See Table 70-3	17 hr	25 min	45 min
Reversal therapy	Protamine	Protamine partially effective	Protamine ineffective; factor VIIa can be used to treat the hemorrhagic event	Discontinue anticoagulant; no specific reversal agent available	Discontinue anticoagulant; no specific reversal agent available

*Includes enoxaparin and dalteparin.
ACT = activated clotting time; aPTT = activated partial thromboplastin time; AT= antithrombin; IV = intravenous; PCI = percutaneous coronary intervention; SQ = subcutaneous.

ABSTRACT

Parenteral anticoagulant therapies include heparin and related compounds, as well as the direct thrombin inhibitors argatroban and bivalirudin. Commonly used fibrinolytic therapies include alteplase, reteplase, and tenecteplase. Oral anticoagulant therapies include the vitamin K antagonists and the direct oral anticoagulants (DOACs). DOACs are as effective and safe as warfarin for many indications, including prevention of stroke and peripheral arterial thromboembolism in patients who have atrial fibrillation as well as the prevention and treatment of venous thromboembolism. Warfarin remains the drug of choice for patients with prosthetic cardiac valves and high-risk antiphospholipid syndrome. Antiplatelet therapies include aspirin, the irreversible (clopidogrel, prasugrel) and reversible (ticagrelor, cangrelor) P2Y12 inhibitors, cilostazol, vorapaxar, and the platelet glycoprotein IIb/IIIa inhibitors. Aspirin is used most broadly, both as monotherapy and sometimes as dual antiplatelet therapy, typically with one of the P2Y12 inhibitors. All the P2Y12 inhibitors are oral except for cangrelor, which is an intravenous agent with a rapid onset and a half-life of several minutes. No FDA-approved reversal agents are available for platelet antagonists.

KEYWORDS

anticoagulation
antiplatelet
fibrinolysis
thromboembolism
bleeding
reversal

TABLE 70-2 ORAL ANTICOAGULANT THERAPIES

	WARFARIN	DABIGATRAN	RIVAROXABAN	APIXABAN	EDOXABAN
Mechanism of action	Vitamin K antagonist	Direct thrombin inhibition	Direct factor Xa inhibition	Direct factor Xa inhibition	Direct factor Xa inhibition
Bioavailability	Essentially 100%	6%	80%	50%	55%
Plasma half-life	~40 hr	14-17 hr	7-11 hr	8-14 hr	8-10 hr
Plasma protein binding (%)	99%	35%	92-95%	87%	40-59%
Clearance	Hepatic, primarily through CYP2C9	80% renal	~2/3 renal (half as unchanged drug and half metabolized by CYP 3A4); ~1/3 fecal	25% renal; remainder metabolized by CYP 3A4	50% renal (primarily unchanged)
Laboratory monitoring	Regular monitoring of the PT/INR required	Not necessary, but can check for drug with a modified thrombin time	Not necessary, but can check for drug with an anti-factor Xa assay	Not necessary, but can check for drug with an anti-factor Xa assay	Not necessary, but can check for drug with an anti-factor Xa assay
Drug interactions	Multiple*	Inducers/inhibitors of P-gp	Inducers/inhibitors of P-gp or CYP3A4	Inducers/inhibitors of P-gp or CYP3A4	Inducers/inhibitors of P-gp
Reversal therapy	Vitamin K, PCC, FFP	Idarucizumab	Andexanet-alfa	Andexanet-alfa	Andexanet-alfa

*Drugs associated with an increase in the INR, listed by class: antibiotics (azithromycin, clarithromycin, erythromycin, ciprofloxacin, levofloxacin, moxifloxacin, metronidazole, sulfamethoxazole, isoniazid); antifungal agents (fluconazole, itraconazole, voriconazole, miconazole); cardiovascular drugs (amiodarone, propafenone, propranolol, diltiazem, simvastatin, fluvastatin, fenofibrate, gemfibrozil, fish oil); central nervous system agents (sertraline, paroxetine, fluoxetine, fluvoxamine, citalopram, escitalopram, venlafaxine, desvenlafaxine, duloxetine, ropinirole, phenytoin); gastrointestinal medications (cimetidine, omeprazole); pain medications (aspirin, diclofenac, etodolac, ibuprofen, indomethacin, ketoprofen, naproxen, piroxicam, sulindac, nabumetone, celecoxib, acetaminophen); other agents (e.g., tamoxifen, testosterone, methotrexate); and herbal supplements (e.g., gingko biloba, garlic). Drugs associated with a decrease in the INR, listed by class: antibiotics (nafcillin, rifampin); central nervous system agents (carbamazepine, trazodone, phenobarbital, phenytoin); and herbal supplements (e.g., ginseng, St. John wort).

FFP = fresh frozen plasma; INR = international normalized ratio; PCC = prothrombin complex concentrate; P-gp = P-glycoprotein; PT = prothrombin time.

to multiple other circulating proteins and cell surfaces, thereby contributing to its variable anticoagulant effect.

DOSAGE AND MONITORING. Heparin is an effective anticoagulant for the prevention and initial treatment of venous thromboembolism (Chapter 68) and for the treatment of the acute coronary syndrome (Chapter 57) and myocardial infarction (Chapter 58). Prophylactic unfractionated heparin uses a fixed dose, typically 5000 units, administered subcutaneously two or three times a day, without laboratory monitoring. In contrast, therapeutic anticoagulation is administered intravenously using a weight-based algorithm, with an initial bolus of 80 units/kg followed by an infusion of 15 to 18 units/kg/hour. Therapeutic unfractionated heparin requires monitoring, typically with an activated partial thromboplastin time (aPTT) range of approximately 50 to 70 seconds for patients with the acute coronary syndrome or acute myocardial infarction but determined in each clinical laboratory to correlate with 0.3 to 0.7 anti-factor Xa units/mL in an assay specific for heparin for venous thromboembolism.

Heparin is also an effective anticoagulant for patients undergoing surgical procedures that require cardiopulmonary bypass, during vascular surgery, during extracorporeal membrane oxygenation (ECMO), with intra-aortic balloon pumps, and with coronary angioplasty and placement of a coronary stent. In these settings, the activated clot time is the best way to monitor heparin therapy.

ADVERSE EFFECTS. The most common complication associated with unfractionated heparin is bleeding, which is influenced by the dose and duration of therapy as well as by any additional risk factors specific to the patient (e.g., concomitant thrombocytopenia or coagulopathy, recent surgery, presence of ex vivo circuits such as ECMO). Major bleeding is rarely encountered in patients who receive prophylactic unfractionated heparin, but it occurs in up to 3% of patients who receive therapeutic unfractionated heparin.

Less common complications associated with unfractionated heparin are heparin-induced thrombocytopenia and osteopenia. Heparin-induced thrombocytopenia (Chapter 158), which is an immune complication that develops in response to circulating complexes of heparin and platelet factor 4, is associated with the development of thrombotic complications despite the thrombocytopenia. Osteoporosis can develop in patients who receive unfractionated heparin over a prolonged period of time, such as women during the course of a pregnancy.

REVERSING THE ANTICOAGULANT EFFECT. Protamine sulfate is a positively charged protein that forms a complex with heparin, thereby neutralizing its anticoagulant effect. Protamine sulfate (1 mg per 100 units of unfractionated heparin, with a maximum dose of 50 mg) has a short half-life (about 7 minutes), and repeated doses may be necessary for complete reversal. Protamine sulfate can be associated with a hypersensitivity reaction, including anaphylaxis, in patients with recurrent exposures, fish allergies, or prior exposure to protamine-containing drugs (e.g., NPH insulin).

Low-Molecular-Weight Heparins

The low-molecular-weight heparins (LMWHs) are smaller fragments produced by chemical or enzymatic depolymerization of unfractionated heparin. Chain lengths range from 4 to 22 monosaccharide units, so these agents primarily inhibit factor Xa and have less effect on thrombin. The LMWHs also exhibit reduced binding to plasma proteins and endothelial surfaces, thereby resulting in increased bioavailability compared with unfractionated heparin. The LMWHs are administered subcutaneously, have a half-life of 3 to 5 hours, and are primarily excreted by the kidney (Table 70-3).

The LMWHs are safe and effective for the prevention and treatment of venous thromboembolism (Chapter 68). For cancer-associated venous thromboembolism (Chapters 67 and 68), they are safer and more effective compared with warfarin and are somewhat less effective but safer than direct oral anticoagulants.[A1,A2] They also have been used in patients with acute coronary syndrome and acute myocardial infarction (Chapter 57). LMWHs do not cross the placenta and are therefore safe and effective during pregnancy. Patients who receive LMWHs are significantly less likely to develop heparin-induced thrombocytopenia than are patients who receive unfractionated heparin, but LMWH should not be used in patients who have acutely developed heparin-induced thrombocytopenia while receiving unfractionated heparin because of the risk of cross-reactive antiplatelet factor 4/heparin antibodies.

Laboratory monitoring is typically not necessary for patients treated with LMWHs, although anti-factor Xa testing may be useful in select situations (e.g., patients with renal insufficiency or to confirm adherence). Protamine sulfate partially reverses the anticoagulant effect of LMWH, but protamine sulfate is less effective in reversing the anticoagulant effect of LMWH compared with unfractionated heparin.

Fondaparinux

Fondaparinux is a synthetic pentasaccharide designed for the binding sequence of antithrombin. Fondaparinux binds antithrombin with high affinity and inactivates factor Xa; because of its short chain length, it has no inhibitory activity against thrombin. Fondaparinux is administered once daily subcutaneously (7.5 mg for a 50- to 100-kg patient; 5 mg if lighter, 10 mg if heavier), has a

TABLE 70-3 ANTICOAGULANT PROFILES, MOLECULAR WEIGHTS, PLASMA HALF-LIVES, AND RECOMMENDED DOSES OF COMMERCIAL LOW-MOLECULAR-WEIGHT HEPARINS AND HEPARINOID

		RECOMMENDED DOSE (INTERNATIONAL ANTI-XA UNITS)[§]		
AGENT	**PLASMA HALF-LIFE (MIN)**	**GENERAL SURGERY PROPHYLAXIS**	**ORTHOPEDIC SURGERY PROPHYLAXIS**	**ACUTE TREATMENT**
Enoxaparin	130-180	4000 U SQ daily	4000 U SQ daily or 3000 U SQ bid	7000 U SQ bid*† or 10,500 U SQ daily*
Dalteparin	120-139	5000 U SQ daily	2500 U SQ bid or 5000 U SQ daily	8400 U SQ bid for acute coronary syndromes or 7000 U SQ bid or 14,000 U SQ daily for venous thromboembolism*
Nadroparin	130-162	2850 U SQ daily	2700 U SQ daily,* 4000 U SQ daily* from day 4	13,300 U SQ daily*
Tinzaparin	110	3500 U SQ daily	3500 U SQ daily* or 4500 U SQ daily*	12,250 U daily*
Ardeparin	200	50 U/kg SQ bid		
Danaparoid‡	1100	750 U SQ bid	750 U SQ bid	2500 U IV, then 4 hr each of 400 U/hr and 300 U/hr, then 200 U/hr; or 2000 U SQ bid

*Weight-adjusted dose; stated dose for 70-kg patient.
†The twice-daily dose is for acute coronary syndromes; either twice-daily (preferred) or once-daily dosing is for venous thromboembolism.
‡Danaparoid sodium is a heparinoid.
§Dosing of low-molecular-weight heparins and heparinoid is based on international units (IU or U), representing anti-Xa activity. In the case of enoxaparin only, the conversion of U to mg is simple: 1 mg inhibits 100 anti-Xa units, so dosing of enoxaparin can be prescribed as either 1 mg or 100 U, for example.
bid = twice daily; IV = intravenously; SQ = subcutaneously.
From Schulman S, Levin GN. Antithrombotic and antiplatelet therapy. In: Goldman L, Schafer AI, eds. *Goldman-Cecil Medicine*. 26th ed. Philadelphia: Elsevier; 2020:496.

bioavailability of 100%, has a long terminal half-life (17-21 hours), and is primarily excreted by the kidney (see Table 70-1).

Fondaparinux is approved for the prevention of venous thromboembolism in surgical patients and treatment of acute deep venous thrombosis and pulmonary embolus (Chapter 68).[A3] Off-label, it can be used in patients with heparin-induced thrombocytopenia,[1] although rare cases of fondaparinux-induced thrombocytopenia have been described. Laboratory monitoring is typically not necessary, but an anti-factor Xa assay can be used to detect circulating drug. Protamine sulfate is not effective in reversing the anti-factor Xa effect of fondaparinux. Recombinant factor VIIa has been used in patients with fondaparinux-related bleeding, but there is an increased risk for thromboembolic complications with this approach.

PARENTERAL DIRECT THROMBIN INHIBITORS

The direct thrombin inhibitors inhibit thrombin without the need for antithrombin (see Table 70-1). Argatroban, which is a synthetic molecule derived from the amino acid L-arginine, reversibly inhibits thrombin by binding to the enzyme's active site. Argatroban is useful for prophylaxis or treatment of thrombosis in patients who have developed heparin-induced thrombocytopenia.[2] It is administered intravenously (starting at 2 μg/kg/min for heparin-induced thrombocytopenia) and monitored by the aPTT. The drug is primarily cleared by the liver and should be used with caution, or avoided, in patients with hepatic insufficiency. Argatroban can be used in patients with renal failure.

Bivalirudin is an analog of hirudin, which is a thrombin inhibitor isolated from leeches. Bivalirudin binds to both the active and fibrin-binding sites of thrombin in patients undergoing percutaneous coronary intervention who have, or are at risk for, heparin-induced thrombocytopenia. Bivalirudin has also been used as an alternative to heparin in patients who require mechanical circulatory support. It is administered intravenously (typically starting with an intravenous bolus of 0.75 mg/kg followed by 1.75 mg/kg/hour for percutaneous coronary intervention) and monitored by an aPTT targeted to a ratio of 1.5 to 2.5 times the patient's baseline or the upper boundary of the reference range. Bivalirudin is primarily cleared by the kidneys and by enzymatic degradation; it can be used in patients with hepatic insufficiency.

Argatroban and bivalirudin have short half-lives, and their anticoagulant effects resolve quickly once the infusion is discontinued. No specific reversal agents are available.

ORAL ANTICOAGULANTS

Vitamin K Antagonists

Vitamin K is an essential cofactor for post-translational γ-carboxylation of glutamate residues that are located within the vitamin K–dependent proteins. This post-translational modification is necessary for normal function of coagulation factors II, VII, IX, and X, as well as proteins C, S, and Z. The vitamin K antagonists interfere with the cyclic conversion of vitamin K and its 2,3-epoxide by vitamin K epoxide reductase, thereby inhibiting the regeneration of the reduced form of vitamin K and blocking post-translational γ-carboxylation. The resulting coagulation factors are dysfunctional, thereby resulting in the observed anticoagulant effect.

Warfarin, which is the most commonly used vitamin K antagonist, is rapidly absorbed in the proximal gastrointestinal tract and has a circulating half-life of about 40 hours. The duration of its anticoagulant effect depends on the synthesis of new coagulation proteins. Factor VII has the shortest half-life (about 4 to 6 hours), so its level drops first after the initiation of warfarin. In contrast, factor II (also called prothrombin), has a half-life of 2 to 3 days, and its level does not begin to decrease until after several days of therapy. Since decreased factor II levels are most important for clinical efficacy, warfarin's benefits are delayed for several days after it is initiated.

Warfarin is an effective anticoagulant for the prevention and treatment of thromboembolism for multiple clinical indications, including venous thromboembolism and thromboembolic events originating from atrial fibrillation or cardiac valve replacement. However, the direct oral anticoagulants (DOACs) have largely replaced warfarin, except for patients who have prosthetic cardiac valves or conditions such as high-risk antiphospholipid syndrome, for which vitamin K antagonists are still the anticoagulant of choice.

DOSAGE AND MONITORING. Warfarin has a narrow therapeutic index, and its effects must be monitored to prevent recurrent thromboembolism if subtherapeutic or bleeding if supratherapeutic. Monitoring is performed with the prothrombin time (PT), reported as an international normalized ratio (INR). The target INR for most clinical indications is 2.5 (range, 2 to 3), but the target INR is 3.0 (range, 2.5 to 3.5) for patients with a mechanical prosthetic heart valve in the mitral position. The PT can be checked on a blood sample drawn by phlebotomy or on a capillary specimen obtained by fingerstick. A typical starting dose would be 5 mg daily with an initial INR level checked at 3 days after initiation of therapy, then daily depending on the result until the INR is in range (with dose modifications as needed; Table 70-4), then in 1 to 2 weeks, and then every 4 weeks when a stable dose is reached. Polymorphisms in the genes encoding for vitamin K epoxide reductase complex 1 (*vitamin K epoxide reductase C1*) and the CYP2C9 enzyme are associated with lower dosage requirements, but dosing based on such data has been no better than standard therapy.[A4]

The INR, which is most sensitive to the level of factor VII, usually can reach its therapeutic range before the level of factor II, which is most important for efficacy, has declined sufficiently for true therapeutic efficacy. As a result, 4 to 5 days of therapy are typically required to achieve a full therapeutic effect. Patients who are started on warfarin for the treatment of acute thromboembolism must be started concomitantly on heparin, which should be continued until the INR is in the target therapeutic range for 2 days.

Factors that can adversely impact the INR include adherence, changes in the intake of vitamin K, other medications (see Table 70-2, footnote), and comorbid conditions. Accurate point-of-care testing using capillary blood obtained by fingerstick has enabled more frequent self-testing, more time in therapeutic range, and likely better clinical outcomes.

ADVERSE EFFECTS. The median rate of major bleeding for patients who are taking a vitamin K antagonist for atrial fibrillation therapy is about 2.51 bleeds per 100 patient years, and the most common bleeding site is the gastrointestinal tract. The risk of bleeding associated with the use of a vitamin K antagonist increases as the INR becomes increasingly supratherapeutic. The risk of bleeding also increases in patients whose INR results are difficult to manage, patients who concomitantly take aspirin or other antiplatelet therapies, older patients, and patients with comorbid conditions such as liver disease or thrombocytopenia.

REVERSING THE ANTICOAGULANT EFFECT. For asymptomatic patients with an isolated elevated INR, simply decreasing the dose or withholding the vitamin K antagonist for 1 to 2 days is appropriate (Table 70-5). Since this approach depends on the synthesis of new factors, it takes a few days to have an impact on the INR. For INR results that are markedly elevated, reversal can be augmented by supplementation with vitamin K (2.5 to 5.0 mg orally). For patients with hemorrhagic complications, urgent normalization can be achieved by augmenting vitamin K therapy with 4-factor prothrombin complex concentrates (pretreatment INR 2 to <4, 25 units/kg, not to exceed 2500 units; pretreatment INR 4 to 6, 35 units/kg, not to exceed 3500 units; pretreatment INR >6, 50 units/kg, not to exceed 5000 units), which contain factors VII, IX, X, and II, and which are more effective than fresh frozen plasma for this purpose.

TABLE 70-4 WARFARIN DOSE PROTOCOL

1. ACHIEVING A THERAPEUTIC RANGE		
DAY	**INR**	**RECOMMENDED DOSE (MG)**
1		5
2		5
3	<1.5 1.5-1.9 2.0-3.0 >3.0	10 5 2.5 0
4	<1.5 1.5-1.9 2.0-3.0 3.0-4.0 >4.0	10 7.5 5 2.5 0
5	<1.5 1.5-1.9 2.0-3.0 3.0-4.0 >4.0	10 7.5 5 2.5 0
6	<1.5 1.5-1.9 2.0-3.0 3.0-4.0 >4.0	12.5 10 5 2.5 0
2. INR-INTERNATIONAL NORMALIZED RATIO GOAL		
2 to 3	target 2.5	Venous thromboembolism (treatment and prevention), atrial fibrillation, bioprosthetic heart valve
2.5 to 3.5	target 3.0	Mechanical prosthetic heart valve (except low-risk patients with bileaflet aortic valves) Anti-phospholipid syndrome with recurrent thromboembolism

INR = international normalized ratio.

Direct Oral Anticoagulants

The direct oral anticoagulants (DOACs) are small molecules that specifically inhibit either thrombin or factor Xa (Table 70-2). Because of their efficacy, safety, and ease of use, direct oral anticoagulants, often with dose adjustments, have largely replaced warfarin for most clinical indications.[3,4]

Direct Thrombin Inhibitors

Dabigatran etexilate is an oral prodrug that is rapidly converted by serum esterases to dabigatran, which is a potent, reversible, direct thrombin inhibitor (Table 70-6). It has a rapid onset of action, a 14- to 17-hour half-life, and is predominantly cleared by the kidney. Dabigatran's serum concentration may be affected by drugs that induce or inhibit the P-glycoprotein transporter (e.g., dronedarone, systemic ketoconazole), but the interactions are generally minor.

Dabigatran is non-inferior to warfarin for the prevention of stroke and systemic thromboembolism in patients with non-valvular atrial fibrillation,[5] with less bleeding at the 110-mg daily dose. Dabigatran is as effective as warfarin for the treatment of acute venous thromboembolism. In this setting, treatment should start with a parenteral anticoagulant (e.g., unfractionated heparin or LMWH) for 5 days prior to starting therapy with dabigatran (see Table 70-6). Dabigatran is also effective for extended prevention of recurrent venous thromboembolism, and it is as effective as enoxaparin for the prevention of venous thromboembolism in patients undergoing total hip arthroplasty or total knee arthroplasty, with a similar safety profile. As with other direct oral anticoagulants, however, dabigatran cannot substitute for warfarin in patients with prosthetic cardiac valves. Dabigatran should generally be avoided in patients who have atrial fibrillation and renal insufficiency (creatinine clearance <30 mL/minute), although a lower dose (75 mg twice daily) is available for patients with a creatinine clearance of 15-30 mL/minute.

DOSAGE AND MONITORING. Dabigatran is taken twice daily without regard to food, but the dose varies by indication. Dabigatran is primarily absorbed in the lower stomach and duodenum, and bariatric gastric bypass procedures may decrease absorption.[6] Laboratory monitoring is not necessary. The INR and aPTT may be prolonged, but the degree of prolongation correlates poorly with the drug concentration. The thrombin time is the most useful screening assay for detection of an anticoagulant effect (e.g., suspected drug overdose, acute trauma, need for emergent surgery).

ADVERSE EFFECTS. Dyspepsia, which is a frequent side effect, can be decreased by taking the drug with food. The risk for major bleeding, particularly for intracranial bleeding, is less than with warfarin and is comparable to the bleeding risk associated with the other direct oral anticoagulants. Gastrointestinal bleeding occurs more frequently with dabigatran, possibly related to the pill's tartaric acid content, which is designed to increase absorption.

REVERSAL OF THE ANTICOAGULANT EFFECT. Idarucizumab, which is a humanized monoclonal antibody fragment developed to specifically reverse

TABLE 70-5 REVERSAL STRATEGIES FOR ANTICOAGULANT THERAPY WITH VITAMIN K ANTAGONISTS

INR	CLINICAL MANIFESTATIONS	INTERVENTION
<5.0	None	Decrease or withhold 1 dose, recheck INR within 1-2 weeks
5.0-9.9	None	Decrease or withhold 1-2 doses, recheck INR within 1-2 weeks
≥10	None	Withhold VKA, consider oral vitamin K (2.5 to 5.0 mg), and recheck INR within 2-3 days; resume VKA when INR in therapeutic range with an appropriate dose adjustment
Any	Serious bleeding	Withhold VKA, give vitamin K (10 mg IV or orally), and consider supplementation with 4-factor PCCs (pretreatment INR 2 to <4, 25 units/kg, not to exceed 2500 units; pretreatment INR 4 to 6, 35 units/kg, not to exceed 3500 units; pretreatment INR >6, 50 units/kg, not to exceed 5000 units), FFP, or recombinant factor VIIa*; recheck INR within 24 hours
Any	Life-threatening bleeding	Withhold VKA, administer 4-factor PCCs (same as above), FFP (1-2 units), or recombinant factor VIIa (approximately 16 µg/kg),* supplemented with vitamin K (10 mg IV or orally)

*Recombinant factor VIIa can be associated with thromboembolic events when used in this setting and should be used only when PCCs or FFP are not available.
FFP = fresh frozen plasma; INR = international normalized ratio; IV = intravenously; PCCs = prothrombin complex concentrates; VKA = vitamin K antagonist.
Adapted from Ansell J, Hirsh J, Hylek E, et al. Pharmacology and management of the vitamin K antagonists: American College of Chest Physicians Evidence-Based Clinical Practice Guidelines (8th edition). *Chest*. 2008;133:160S-198S.

TABLE 70-6 DIRECT-ACTING ORAL ANTICOAGULANTS

	DABIGATRAN	RIVAROXABAN	APIXABAN	EDOXABAN
Mechanism of action	Direct factor IIa (thrombin) inhibitor	Direct factor Xa inhibitor	Direct Xa inhibitor	Direct factor Xa inhibitor
DOSING				
Acute phase (within the first 1-3 weeks of diagnosis)	Initial therapy with a parenteral anticoagulant for at least 5 days	Initial therapy is 15 mg twice daily for 21 days	Initial therapy is 10 mg twice daily for 7 days	Initial therapy with a parenteral anticoagulant for 5-10 days
Treatment phase (following acute phase, and continuing for 3-6 months from diagnosis	150 mg twice daily	20 mg daily	5 mg twice daily	60 mg once daily (30 mg once daily if weight ≤60 kg)
Extended thromboprophylaxis (following treatment phase and typically lasting indefinitely)	Same as for treatment phase	10 or 20 mg daily	2.5 or 5 mg twice daily	Same as for treatment phase
Atrial fibrillation (indefinite duration)	150 mg or 110 mg twice daily	20 mg daily	5 mg twice daily	60 mg or 30 mg daily
VTE prevention after knee or hip replacement surgery (14-30 days)	110 mg (initial dose) then 220 mg daily	10 mg daily	2.5 mg twice daily	Not applicable
RENAL ADJUSTMENT				
Creatinine clearance in mL/min				
>95	No dose adjustment	No dose adjustment	No dose adjustment	Avoid
50-95	"	"	"	No dose adjustment
30-49	"	"	2.5 mg twice daily for AF	"
15-29	Avoid	Avoid	"	30 mg
<15	"	"	"	Avoid
KEY DRUG INTERACTIONS				
Increase levels	Amiodarone, quinidine, azole antifungals (e.g., ketoconazole), ritonavir	Azole antifungals (e.g., ketoconazole), ritonavir, clarithromycin		
Decrease levels	Rifampin	Anticonvulsants (e.g., phenytoin, carbamazepine), rifampin		
Antidote	Idarucizumab (5 gm intravenously)	Andexanet alfa (see Table 70-7)		
Laboratory monitoring	Not necessary, but can check for drug with a modified thrombin time	Not necessary, but can check for drug with an anti-factor Xa assay		

the effect of dabigatran,[7] irreversibly binds dabigatran, with an affinity about 350-fold higher than the affinity of dabigatran for thrombin. Administration of idarucizumab (5 g intravenously, provided as two separate vials of 2.5 g/50 mL infused consecutively) normalizes dabigatran-induced prolongation of the thrombin time within minutes in a dose-dependent fashion.

Direct Factor Xa Inhibitors

Several direct oral anticoagulants that specifically target factor Xa include rivaroxaban, apixaban, and edoxaban (see Table 70-6). Although these agents share some characteristics, each also has unique characteristics that may make one more attractive than the others in certain situations.

Each of the factor Xa inhibitors is as effective as warfarin for the treatment of acute venous thromboembolism, with a risk for bleeding that ranges from similar to slightly lower than with warfarin.[8] These agents are also effective for the treatment and secondary prophylaxis of venous thromboembolism in patients with cancer, in which they are more effective than LMWH but associated with somewhat more bleeding.[A5,9] The factor Xa inhibitors also are noninferior or superior to warfarin for the prevention of ischemic stroke and systemic thromboembolism in patients with non-valvular atrial fibrillation,[10] except edoxaban is not as good as warfarin for patients with a creatinine clearance greater than 95 mL/min.

Rivaroxaban (10 or 20 mg daily) and apixaban (2.5 or 5.0 mg twice daily) are effective for extended thromboprophylaxis in patients with venous thromboembolism. Rivaroxaban (10 mg daily) and apixaban (2.5 mg twice daily) are effective for thromboprophylaxis following total hip or total knee arthroplasty (duration for a minimum of 10 to 14 days, extending up to 35 days). In patients with stable coronary artery disease, rivaroxaban (2.5 mg twice daily) combined with aspirin can decrease the frequency of major vascular events compared to aspirin alone, although it is associated with an increased risk for major bleeding,[A6] and this combination also is better than aspirin alone in preventing adverse limb events in patients with lower extremity peripheral arterial disease (Chapter 65).[A7] For hospitalized medically ill patients, an extended post-discharge course of rivaroxaban (10mg daily for 45 days) decreases the risk for fatal and major thromboembolic events without significantly increasing major bleeding.[A8] Rivaroxaban, apixaban, and dabigatran have all been used off-label as an alternative anticoagulant for patients with heparin-induced thrombocytopenia. Rivaroxaban is less effective than warfarin in high-risk patients with antiphospholipid syndrome, however.[A9]

DOSAGE AND MONITORING. Rivaroxaban is administered once daily for all indications, except during the first 21 days of treatment of acute venous thromboembolism and for patients with coronary artery disease or peripheral arterial disease, in whom it is administered twice daily. The drug is rapidly absorbed, primarily in the stomach and small intestine, with a time to peak effect of 2 to 4 hours. It is best absorbed when taken with food. It is metabolized by CYP3A4 and should be avoided in patients being treated with strong inducers or inhibitors of P-glycoprotein or CYP3A4, such as carbamazepine, phenytoin, rifampin, systemic ketoconazole, or ritonavir. Approximately two thirds of the drug is excreted in the urine (half unchanged and half as inactive metabolites), so it should be avoided in patients with severe renal insufficiency (creatinine clearance <15-30 mL/min). Rivaroxaban is highly protein-bound in the circulation and is not removed by hemodialysis.

Apixaban is administered twice daily for all clinical indications and can be taken with or without food. It is rapidly absorbed, primarily in the upper gastrointestinal tract, with a time to peak effect of 3 to 4 hours. It is primarily eliminated by metabolism by CYP3A4 and other cytochromes to inactive metabolites, and it should be avoided in patients being treated with strong inhibitors or inducers of the P450 system. Approximately 25% of the drug is excreted in the urine, the remainder in the feces. For the prevention and treatment of venous thromboembolism, no dose adjustment is necessary for renal insufficiency. For the treatment of atrial fibrillation,

TABLE 70-7 DOSING AND ADMINISTRATION OF ANDEXANET ALFA*

FACTOR XA INHIBITOR	LAST DOSE OF FACTOR XA INHIBITOR	TIME FROM LAST DOSE OF FACTOR XA INHIBITOR	
		<8 HOURS OR UNKNOWN	≥8 HOURS
Apixaban	≤5 mg >5 mg or unknown	Low-dose andexanet alfa High-dose andexanet alfa	Low-dose andexanet alfa
Rivaroxaban	≤10 mg >10 mg or unknown	Low-dose andexanet alfa High-dose andexanet alfa	

*Low-dose andexanet alfa: initial 400 mg IV bolus administered at a target rate of about 30 mg/min, followed within 2 minutes by continuous IV infusion of 4 mg/min for up to 120 minutes.
High-dose andexanet alfa: initial 800 mg IV bolus administered at a target rate of about 30 mg/min, followed within 2 minutes by continuous IV infusion of 8 mg/min for up to 120 minutes.
For patients receiving edoxaban, enoxaparin, or other low-molecular-weight heparins, the high-dose andexanet alfa dosing has been used.

TABLE 70-8 ANTIPLATELET AGENTS

DRUG	CLOPIDOGREL	PRASUGREL	TICAGRELOR	CANGRELOR	TIROFIBAN	EPTIFIBATIDE	VORAPAXAR
Prodrug	Yes	Yes	No	No	No	No	No
Route	Oral	Oral	Oral	Intravenous	Intravenous	Intravenous	Oral
Mechanism of action	$P2Y_{12}$ inhibition	$P2Y_{12}$ inhibition	$P2Y_{12}$ inhibition	$P2Y_{12}$ inhibition	GPIIb/IIIa inhibition	GPIIb/IIIa inhibition	PAR -1 inhibition
Onset of action	2–6 hr	30 min	30 min	2 min	<15 min	<15 min	1–2 hr
Duration of action	3-10 days	7-10 days	3-5 days	1-2 hr	4-8 hr	4-8 hr	2-3 wk
Withdrawal before surgery	5 days	7 days	5 days	1 hr	8 hr	8 hr	12 hr
Loading dose	300-600 mg	60 mg	180 mg	30 μg/kg	25 μg/kg	180 μg/kg	NA
Regular dose	75 mg daily	10 mg daily	90 mg twice daily	4 μg/kg/min infusion	0.15 μg/kg/min infusion	2 μg/kg/min infusion	2.5 mg twice daily

GP = glycoprotein.

the dose should be reduced to 2.5 mg twice daily for patients with a serum creatinine ≥1.5 mg/dL and either age ≥80 years or body weight ≤60 kg. As with rivaroxaban, apixaban is highly protein-bound and not removed by hemodialysis.

Edoxaban is administered once daily and can be taken with or without food. It is rapidly absorbed, primarily in the proximal small intestine, with a time to peak effect of 1 to 2 hours. Absorption is dependent on acidic solubility. Edoxaban has negligible CYP450 metabolism, but inducers or inhibitors of P-glycoprotein (e.g., rifampin, systemic ketoconazole, and clarithromycin) can affect serum concentrations. Approximately 50% of the drug is excreted by the kidney, primarily unchanged. The dose should be reduced in patients with moderate renal insufficiency (creatinine clearance 15 to 50 mL/minute), and edoxaban should be avoided in patients with severe renal insufficiency (creatinine clearance <15 mL/minute).

Several notable differences must be noted among these three direct oral anticoagulants when initiating therapy. As for dabigatran, edoxaban requires an initial lead-in phase with heparin or a LMWH before starting it for an acute indication. In contrast, rivaroxaban and apixaban do not require co-therapy with LMWH or heparin if started at a higher dose for 7 days (apixaban) or 21 days (rivaroxaban).

ADVERSE EFFECTS. Other than bleeding, the direct factor Xa inhibitors are associated with relatively few adverse events. Compared with warfarin, the risk for major bleeding is less, particularly for intracranial bleeding, but the risk of gastrointestinal hemorrhage is increased with rivaroxaban[11] and the risk of menstrual bleeding is increased, particularly with rivaroxaban.[12]

REVERSAL OF THE ANTICOAGULANT EFFECT. For most patients who have bleeding complications with the factor Xa inhibitors, simply withholding the drug and providing supportive measures is sufficient. For severe hemorrhagic complications, however, andexanet alfa (a modified recombinant form of factor Xa that is enzymatically inactive but binds to and rapidly neutralizes the factor Xa inhibitors) is effective within 12 hours against the oral factor Xa inhibitors as well as against enoxaparin and fondaparinux (Table 70-7).[13] If andexanet alfa is not available, 4-factor prothrombin complex concentrates (2000 units once, or 25 to 50 units/kg once) can be used as a nonspecific pro-hemostatic alternative.[14]

Anticoagulant Strategies in Development

Several promising strategies that target factor XI are in development based on the concept that factor XI is important for thrombosis but not hemostasis.[15] Decreasing factor XI levels with an antisense oligonucleotide provides effective prophylaxis against postoperative venous thromboembolism in patients undergoing elective primary unilateral total knee arthroplasty.[A10] Direct inhibition of factor Xia with a fully human monoclonal antibody[A11] or with a small molecule inhibitor[A12] also can prevent postoperative venous thromboembolism in patients undergoing total knee arthroplasty.

ANTIPLATELET THERAPY

The development of antiplatelet drugs for clinical use has closely followed an understanding of platelet surface receptors that, under specific conditions, are activated, thereby resulting in platelet adhesion and aggregation, assembly of coagulation proteins, and the formation of thrombus encased in a fibrin meshwork (Table 70-8). No direct antagonist can reverse their effects, so treatment of bleeding relies on platelet transfusions (usually 1 U platelets, except 2 U for P2Y12 inhibitors and glycoprotein [GP] IIb/IIIa inhibitors) and desmopressin (0.3 μg/kg every 12 hours). Cryoprecipitate (1 unit per 10 kg body weight) also can be administered in GP IIb/IIIa-related bleeding.

Aspirin

Aspirin represents a mainstay for the prevention and treatment of atherosclerotic vascular events, including ischemic stroke (Chapter 376), acute coronary syndrome (Chapter 57), chronic coronary disease (Chapter 56), and peripheral arterial disease (Chapter 65).

PHARMACOLOGY. Aspirin irreversibly acetylates cyclooxygenase (COX), thereby impairing the metabolism of prostaglandin and the synthesis of thromboxane A_2. Aspirin is rapidly absorbed in the stomach and duodenum, and it achieves peak levels within 15 to 20 minutes and platelet inhibition within 40 to 60 minutes after administration. Despite the drug's rapid clearance (20 minutes), platelet inhibition persists for the platelet's life span (7 ± 2 days) owing to aspirin's irreversible inactivation of COX-1. For cardiovascular protection, 81 mg per day[A13] is as effective as higher doses and is associated with less bleeding.

USES. Although all patients may achieve reasonably similar relative benefits from aspirin for preventing vascular events, the risks of bleeding increase with age. Aspirin's net beneficial effect is determined by the patient's absolute risk of vascular events and of bleeding based on patient-specific underlying conditions. Patients who have a low absolute risk derive minimal absolute benefit, whereas patients at high risk (e.g., with acute coronary syndrome, chronic

coronary syndrome, percutaneous coronary intervention, or ischemic stroke) derive greater benefit. Aspirin (81 mg) is also useful to reduce the likelihood of developing colorectal cancer (Chapter 179).[A14]

PRIMARY PREVENTION OF VASCULAR EVENTS. The benefit-to-risk ratio for aspirin at a dose of 75 to 100 mg daily becomes favorable when the 10-year atherosclerotic cardiovascular disease risk ≥10%, despite the increased risk of bleeding.[16] As a result, aspirin may be beneficial for the primary prevention of MI and stroke in persons who have not achieved optimal control of risk factors for atherosclerotic cardiovascular disease. However, prophylactic aspirin is not recommended for primary prevention in adults over age 70 years because of the risks of bleeding.[A15]

SECONDARY PREVENTION OF VASCULAR EVENTS. Aspirin is a first-line antiplatelet agent for secondary presentation and a routine component of dual antiplatelet regimens that are useful after an acute coronary syndrome (Chapter 57), with or without percutaneous coronary intervention (Chapter 59).[A16]

Acute Coronary Syndrome. The duration of dual antiplatelet therapy after an acute coronary syndrome (Chapter 57) is based on the risk of ischemic compared with the risk of bleeding.[17] In general, patients who are at low and intermediate risk for bleeding are often treated up to 12 months, whereas patients at high or very high risk for bleeding may be treated for 1 to 3 months. Extended dual antiplatelet therapy beyond 1 year should be considered for patients at high risk for ischemic and thrombotic events, including patients with diabetes mellitus, recurrent myocardial infarction, concomitant inflammatory or autoimmune disease, chronic kidney disease, left main coronary artery disease, bifurcating stents, or a history of stent thrombosis.

Chronic Coronary Artery Syndrome. Aspirin can reduce vascular events in a wide variety of high-risk patients. Antiplatelet therapy (predominantly aspirin) reduces nonfatal myocardial infarction and non-fatal stroke by approximately one-third and vascular death by about 25%.

Coronary Artery Bypass Grafting and Percutaneous Coronary Intervention. Aspirin is recommended after internal thoracic and other coronary arterial bypass grafting. Dual antiplatelet therapy is recommended after off-pump CABG.[18] Recommendations for percutaneous coronary intervention include aspirin prior to and after the procedure. For patients unable to tolerate aspirin, pretreatment with clopidogrel (600 mg oral loading dose followed by 75 mg daily) is suggested. Dual antiplatelet therapy with aspirin and a P2Y12 receptor agonist is now usually recommended for only 1 to 3 months after insertion of a polymer-free drug-eluting stent.

Peripheral Artery Disease. Although proven to reduce cardiovascular mortality in atherosclerotic cardiovascular disease, the data for aspirin in peripheral arterial disease (Chapter 65) are less robust. Current recommendations are antiplatelet therapy with aspirin alone (75 to 325 mg per day) or clopidogrel alone (75 mg per day) to reduce MI, stroke, and vascular death in patients with symptomatic peripheral arterial disease.

ADVERSE EFFECTS. The principal adverse effect of aspirin is bleeding, especially upper gastrointestinal bleeding. These risks are lower with lower doses of aspirin (75 to 100 mg daily) and with aspirin monotherapy compared with dual antiplatelet therapy. Bleeding risks are higher in patients who have a prior history of acid-peptic disease or gastrointestinal bleeding or who have a coagulopathy, thrombocytopenia, chronic kidney or liver disease, or poorly controlled hypertension. Salicylate toxicity (Chapter 96), whether an intentional overdose or unintentional, is a life-threatening emergency.

Platelet $P2Y_{12}$ Receptor Antagonists

The density of $P2Y_{12}$ receptors on the platelet surface, coupled with their active role in platelet activation and aggregation makes this receptor an attractive target for pharmacologic inhibition. Clopidogrel (75 mg once daily), prasugrel (10 mg once daily), and ticagrelor (90 mg twice daily) are oral inhibitors of the platelet-stimulatory ADP receptor ($P2Y_{12}$), whereas cangrelor is administered intravenously. Clopidogrel and prasugrel bind irreversibly to platelet $P2Y_{12}$ receptor, whereas ticagrelor and cangrelor bind to it reversibly.

PHARMACOLOGY. Clopidogrel is rapidly absorbed following oral administration with peak levels of the predominant circulating metabolite occurring 60 minutes later. As a pro-drug, it is extensively metabolized in the liver to an active compound with a plasma elimination half-life of 7.7 ± 2.3 hours. Dose-dependent inhibition of ADP-mediated platelet aggregation is observed several hours after a single oral dose of clopidogrel.

Prasugrel is a prodrug that undergoes rapid de-esterification to an intermediate thiolactone, which is then converted to the active metabolite via a single CYP-dependent step. Maximal concentrations of prasugrel's active metabolite are reached within 0.5 hours after oral administration. After discontinuation, platelet aggregation returns to pretreatment levels within 7 to 10 days.

Ticagrelor, unlike clopidogrel and prasugrel, does not require metabolic activation or conversion for platelet inhibition. It is rapidly absorbed, and 60 to 80% inhibition of ADP-induced platelet aggregation is achieved 2 to 4 hours after a 180 mg loading dose. Its plasma half-life is 6 to 13 hours, so twice-daily administration is required.

Cangrelor intravenously acts within 20 minutes to achieve high-level inhibition of ADP-induced platelet aggregation. Cangrelor occupies the platelet $P2Y_{12}$ binding site, thereby precluding the binding and pharmacodynamic effect of clopidogrel and prasugrel but not of ticagrelor. Following rapid dephosphorylation, it is excreted in urine (58%) and feces (35%), with an average half-life of 3 to 6 minutes.

CLINICAL USES. Monotherapy with $P2Y_{12}$ inhibition provides essentially the same benefit and risks as aspirin monotherapy. As a result, $P2Y_{12}$ monotherapy is generally limited to patients who have an aspirin allergy or situations in which dual antiplatelet therapy is indicated for secondary prevention in patients with established cardiovascular disease. Ticagrelor and prasugrel are more potent antiplatelet inhibitors than clopidogrel, so they tend to provide more antithrombotic protection but at a higher risk of bleeding. Clopidogrel is therefore generally preferred in patients who have a high underlying bleeding risk.

SECONDARY PREVENTION

Acute Myocardial Infarction and Stent. Clopidogrel or ticagrelor added to aspirin for up to 12 months improves outcomes in patients who have survived an ST-elevation myocardial infarction compared with aspirin alone. Ticagrelor plus aspirin for 30 days is also more effective than aspirin alone in patients who have had an ischemic stroke or transient ischemic attack.[A17,A18]

Acute Coronary Syndrome and Post–Percutaneous Coronary Intervention. Aspirin plus clopidogrel is superior compared with aspirin alone in patients who have an acute coronary syndrome, despite carrying a higher risk of bleeding.[19] Prasugrel is even (about 20%) more effective than clopidogrel but with yet a higher risk of bleeding.

Cangrelor is used as an adjunct to percutaneous coronary intervention to reduce the risk of periprocedural MI, repeat coronary revascularization, and stent thrombosis in patients who have not been treated with a GPIIb/IIIa antagonist.[20] When transitioning from cangrelor to an oral $P2Y_{12}$ receptor antagonist, ticagrelor can be administered during cangrelor administration, but clopidogrel should be administered after cessation of cangrelor and prasugrel.

After percutaneous coronary intervention, 12 months of dual treatment with aspirin plus either clopidogrel or prasugrel reduces the risk of in-stent thrombosis and major adverse cardiovascular events, but at the expense of an increased risk of bleeding. By comparison, in patients with an acute coronary syndrome, ticagrelor monotherapy (180 mg loading dose, 90mg twice daily thereafter) is preferred over clopidogrel monotherapy to reduce subsequent coronary events. Aspirin plus ticagrelor may reduce the incidence of ischemic events in patients with diabetes and known coronary artery disease but without a history of MI or stroke, especially after prior percutaneous coronary intervention,[A19] but the modest benefit (absolute reduction <1%) comes with an increased risk of major bleeding (absolute increase 2.2%). Clopidogrel and ticagrelor are equivalent in patients with peripheral arterial disease.[A20]

Dual antiplatelet therapy after percutaneous coronary intervention reduces the risk of ischemic events compared with monotherapy but increases the risk of bleeding.[A21] With modern polymer-free drug-eluting stents, one to at most 3 months of dual antiplatelet therapy followed by continual treatment with aspirin or clopidogrel appears to be the preferred option. Clopidogrel may be favored over aspirin for monotherapy.

Intracardiac Procedures. Current guidelines recommend the use of dual antiplatelet therapy with aspirin and clopidogrel for 3 to 6 months in patients who have undergone transcatheter aortic valve replacement (Chapter 60),[21] although the incremental benefit of dual antiplatelet therapy over single antiplatelet therapy is unproven. After transcutaneous mitral valve replacement or insertion of a mitral valve clip, monotherapy with aspirin 81 to 325 mg daily for 6 months is reasonable (Chapter 60).[A22] For edge-to-edge mitral repair, either a short course (30 days) of dual antiplatelet therapy followed by aspirin or monotherapy (aspirin or clopidogrel) for about 6 months is recommended. In patients undergoing percutaneous closure of an atrial

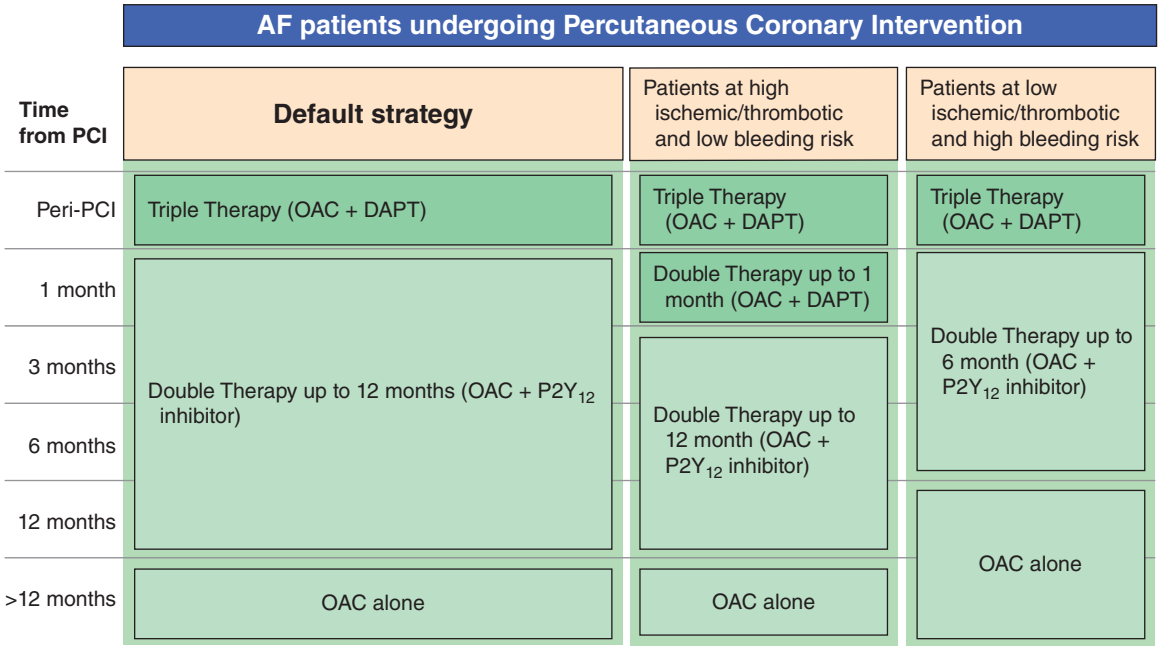

FIGURE 70-1. Management of antiplatelet therapy in patients with atrial fibrillation (AF) undergoing percutaneous coronary intervention (PCI) treated with an oral anticoagulant: 2018 North American Consensus Update. A double-therapy regimen, consisting of oral anticoagulant therapy plus a $P2Y_{12}$ inhibitor, should be considered for most patients immediately after the peri-PCI period (default strategy). Aspirin should be used during the peri-PCI period, defined as inpatient stay until time of discharge, generally 1 to 2 days after PCI, and in some patients continued for 1 week after PCI. A non–vitamin K antagonist direct-acting oral anticoagulant (DOAC) should be preferred over a vitamin K antagonist unless contraindicated. Clopidogrel is the $P2Y_{12}$ inhibitor of choice; ticagrelor may be an alternative in patients with high thrombotic and acceptable bleeding risk; prasugrel should be avoided. It is reasonable to continue aspirin for up to 1 month after PCI (i.e., triple therapy) in patients at high thrombotic risk and who have an acceptable risk of bleeding. Extending aspirin therapy beyond 1 month after PCI is not recommended. $P2Y_{12}$-inhibiting therapy should be discontinued at 1 year in most patients; earlier discontinuation (e.g., 6 months) can be considered in patients at low ischemic or high bleeding risk; continuation of antiplatelet therapy beyond 1 year should be considered only in select patients with high risk for ischemic recurrences and low bleeding risk. DAPT = dual antiplatelet therapy; OAC = oral anticoagulant. (From Angiolillo DJ, Bhatt DL, Cannon CP, et al. Antithrombotic therapy in patients with atrial fibrillation treated with oral anticoagulation undergoing percutaneous coronary intervention: a North American perspective: 2021 update. *Circulation*. 2021;143:583-596. With permission.)

septal defect or patent foramen ovale (Chapter 55), the post-procedural antithrombotic therapy regimen typically includes a combination of aspirin 75 to 325 mg daily plus clopidogrel 75 mg daily for 1 to 3 months followed by aspirin monotherapy for an additional 3 to 5 months. After closure (or exclusion) of a left atrial appendage, up to 6 months of dual antiplatelet therapy is generally administered after the procedure, followed by long-term aspirin monotherapy.

ADVERSE EFFECTS. Idiopathic thrombocytopenic purpura and thrombotic thrombocytopenic purpura (Chapter 158) have rarely been reported with clopidogrel. Prasugrel causes more major bleeding, life-threatening bleeding, and fatal bleeding compared with clopidogrel. Prasugrel is contraindicated in patients who have a history of transient ischemic attacks or stroke and generally is not recommended in patients age 75 years or older. Ticagrelor can be reversed with the monoclonal antibody bentracimab under expert oversight.

COMBINATION ANTICOAGULANT AND ANTIPLATELET THERAPY. In patients with stable cardiovascular disease (Chapter 56), the combination of rivaroxaban plus aspirin can reduce the composite end point of cardiovascular death, stroke, or myocardial infarction, but at a cost of a higher rate of major bleeding. In patients who have atrial fibrillation and who have an acute coronary syndrome, evidence supports the safety and benefit of dual therapy,[A23] although monotherapy with an oral anticoagulant may be sufficient 1 year after percutaneous coronary intervention in some patients[A24] (Fig. 70-1).

Patients with stable ischemic coronary artery disease and a clinical indication for time-limited anticoagulation, such as a venous thromboembolism, should receive triple therapy for up to 3 months, at which time the anticoagulant therapy can be discontinued. Aspirin should be continued in combination with clopidogrel for another 3 to 6 months, followed by aspirin monotherapy. In patients with acute coronary syndrome, the same strategy for anticoagulant therapy and aspirin is recommended, but clopidogrel is recommended for 12 months unless there is a high-to-very-high risk for bleeding. For patients who have an indefinite indication for anticoagulant therapy, anticoagulation with a reduced prophylactic dose (see Table 70-6) is recommended in combination with a $P2Y_{12}$ receptor inhibitor (clopidogrel is preferred) for 3 to 6 months followed by either a $P2Y_{12}$ receptor inhibitor or aspirin for 6 to 12 months; antiplatelet therapy can be stopped at 12 months.[22]

Intravenous Platelet GPIIb/IIIa Receptor Antagonists

The two intravenous GPIIb/IIIa receptor antagonists are tirofiban and eptifibatide. These agents are generally used only by interventional cardiologists in situations of no-reflow (patency without perfusion) or a thrombotic complication after a percutaneous coronary intervention. The duration of platelet inhibition with these agents is about 4 hours following cessation of tirofiban and eptifibatide.

Phosphodiesterase Inhibition: Cilostazol

PHARMACOLOGY. Cilostazol, a quinolinone derivative, and several of its metabolites inhibit phosphodiesterase III activity and suppress the degradation of cyclic adenosine monophosphate. The resultant increase in cyclic adenosine monophosphate in platelets and blood vessels leads to inhibition of platelet aggregation and vasodilation, respectively.

Metabolism occurs via the hepatic cytochrome P-450 enzymes, and most of the metabolites are excreted in the urine (75% of overall clearance). Cilostazol and its active metabolites have elimination half-lives of about 11 to 13 hours. Short-term coadministration of aspirin with cilostazol inhibits ADP- and arachidonic acid-induced platelet aggregation by about 30% and 25%, respectively, compared with cilostazol alone.

CLINICAL USES

Peripheral Artery Disease. Cilostazol is approved for the treatment of intermittent claudication (Chapter 65). Cilostazol should not be considered a substitute for aspirin or clopidogrel in patients with acute coronary syndrome and concomitant peripheral arterial disease.

ADVERSE EFFECTS. The most common adverse effect associated with cilostazol is headache. Other relatively frequent causes of drug discontinuation include palpitations, ventricular tachycardia, and diarrhea. Cilostazol is contraindicated in patients with heart failure of any severity.

Direct Thrombin Inhibition: Vorapaxar

PHARMACOLOGY. Vorapaxar, which is a tricyclic himbacine-derived selective inhibitor of the thrombin receptor, inhibits platelet aggregation through reversible antagonism. Vorapaxar is rapidly absorbed after oral administration, with peak concentrations at about 1 hour. Vorapaxar is primarily eliminated as its metabolite M19 through the feces (91.5%), and partially eliminated in

the urine (8.5%). It has an effective half-life of 3 to 4 days and an apparent terminal half-life of 8 days.

CLINICAL USES. Vorapaxar is indicated for reducing the incidence of thrombotic cardiovascular events in patients with a history of MI or with peripheral arterial disease.

ADVERSE EFFECTS. Vorapaxar is associated with an increased risk of major bleeding, including intracranial hemorrhage. It should not be used in patients with prior intercranial hemorrhage.

FIBRINOLYTIC AND ANTITHROMBIN AGENTS

Fibrinolytic Therapy

Fibrinolytic agents directly or indirectly activate plasminogen to plasmin, which then degrades fibrin to soluble fragments, thereby lysing a thrombus. Both streptokinase, which indirectly activates plasminogen by binding to the zymogen and triggering a conformational change that leads to its activation, and urokinase, which directly activates plasminogen, degrade fibrinogen as well as fibrin.

These first-generation plasminogen activators have been largely replaced by newer agents, particularly alteplase, which is a second-generation plasminogen activator that possesses greater fibrin specificity, is not allergenic or antigenic, and has a short half-life of about 3.5 minutes. Third generation plasminogen activators, such as reteplase and tenecteplase, have been engineered to improve various structural and functional properties, thereby resulting in a longer half-life, resistance to inhibitors, improved safety profiles, and/or enhanced fibrin specificity.

CLINICAL USES. For acute ischemic stroke (Chapter 376), alteplase has been the mainstay of treatment,[23] but tenecteplase[A25] provides better recanalization rates and early neurologic improvement than alteplase. Fibrinolytic therapy is recommended for patients within 12 hours of an ST-elevation myocardial infarction (Chapter 58) when primary percutaneous coronary intervention is not available. Intra-arterial, catheter-directed fibrinolytic therapy is an effective treatment for acute limb ischemia within 14 days of the acute onset of symptoms (Chapter 65). Fibrinolytic therapy followed by anticoagulant therapy is recommended over anticoagulant therapy alone when a pulmonary embolism causes acute hemodynamic compromise (Chapter 68).[24] Dosing of the fibrinolytic agents varies for the different clinical indications. Laboratory monitoring is not necessary for most patients.

Reversal of fibrinolytic therapy is most directly achieved by discontinuing the fibrinolytic agent, and if the fibrinogen level is low, replacing fibrinogen, either with cryoprecipitate or fibrinogen concentrate. For patients with significant bleeding complications, antifibrinolytic agents, such as aminocaproic acid (4 to 5 g loading dose, oral or intravenous, followed by 1 g/hour for 8 hours or until bleeding is controlled) or tranexamic acid (1 g [or 10 to 15 mg/kg] once intravenously, not to exceed 100 mg/minute), can inhibit the fibrinolytic effect.

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71 APPROACH TO THE PATIENT WITH RESPIRATORY DISEASE

MONICA KRAFT

Respiratory symptoms, which are among the most common reasons why patients seek medical care, are responsible for approximately 20% of office visits to a primary care physician. In addition to a careful history, a systematic physical examination is critical for accurate diagnosis. Even in young adults, persistent respiratory symptoms are associated with a greater likelihood of developing chronic lung disease.[1]

A careful pulmonary examination complements the cardiac physical examination (Chapter 39). Inspection may reveal an elevated jugular pressure, indicative of right heart failure owing to cor pulmonale (Chapter 69). Cervical or supraclavicular adenopathy (Chapter 154) may be the first clue to suggest a thoracic malignancy (Chapter 177) or mycobacterial infection (Chapter 299). Unilateral arm swelling can be caused by venous thrombosis (Chapter 68), whereas venous engorgement of the head and neck can be caused by a tumor that results in superior vena cava syndrome (see Fig. 86-8 in Chapter 86). On the cardiac examination, a loud pulmonic second heart sound is suggestive of pulmonary hypertension, which also can result in a murmur of tricuspid (see Table 39-7 in Chapter 39) or pulmonic valve insufficiency.

Inspection of the chest may show hyperinflation and reduced diaphragmatic excursion, typical of chronic obstructive pulmonary disease (COPD; Chapter 76), chest wall abnormalities such as kyphoscoliosis (Chapter 86), or diaphragmatic muscle wall weakness as in many hypoventilation syndromes (Chapter 74). Percussion may reveal dullness in patients with pleural effusions or with lung that has been consolidated by pneumonia.

Auscultation of the lungs includes listening at both apices and over both upper and lower lobes, anteriorly and posteriorly, and during inspiration and expiration. Normal lung sounds are heard during inspiration and early expiration as soft and non-musical sounds (Table 71-1).[2,3] *Bronchial breath sounds*, which sound similar to but often somewhat harsher than normal lung sounds, are heard throughout expiration as well as inspiration, similar to what would be heard by placing a stethoscope over the trachea.

The term *rales* is no longer used and has been replaced by the term *crackles*. Fine crackles are non-musical and heard typically in late inspiration; they are most commonly a sign of heart failure (Chapter 45) or interstitial lung disease (Chapter 80). By comparison, coarse crackles, which, unlike fine crackles, tend to be transmitted through the mouth and cleared by coughing, are typical of bronchitis (Chapter 84) and COPD (Chapter 76). *Wheezes* are high-pitched, musical sounds heard during expiration and sometimes inspiration, most commonly in asthma (Chapter 75) and sometimes in COPD (Chapter 76). When these diseases are severe, however, the degree of airflow may be insufficient to produce wheezes. A *rhonchus* is a musical, low-pitched sound typically heard in expiration and sometimes during inspiration; it often resolves with coughing. Like coarse crackles, rhonchi are common in bronchitis (Chapter 84) and COPD (Chapter 76). A *pleural friction rub,* which classically occurs during inspiration but sometimes also during expiration, is heard in a fraction of patients with inflammatory diseases or malignancies involving the pleura (Chapters 86 and 177). *Stridor* is a musical, high-pitched sound that may be audible without a stethoscope and that indicates upper airway obstruction, such as found with acute inflammatory or chronic degenerative diseases of the larynx (Chapter 397) or obstruction of the trachea, as may be caused by intrathoracic malignant diseases (Chapter 177). An absence of breath sounds would be noted if the lung is not ventilated because of a complete bronchial obstruction or if it is displaced by a pleural effusion.

Tactile fremitus, which is a vibratory sensation noted during breathing, is increased in patients who have consolidated lung from pneumonia, because the vibratory sensation conducts better through such lung tissue and is diminished in patients with pleural effusion. *Egophony*, by which a patient's recitation of the long E sound is heard on auscultation as a long A sound, is another indication of consolidation typical of pneumonia.

Evaluation of the abdomen may show a readily palpable liver, sometimes mistaken for hepatomegaly, in patients with COPD whose pulmonary hyperinflation results in a low diaphragm. Examination of the extremities may reveal cyanosis in patients who are hypoxemic, usually with a partial pressure of oxygen less than 55 mm Hg, although it also may be observed in patients with methemoglobinemia (Chapter 144). Clubbing (Chapter 39) is indicative of chronic hypoxemia, as seen in patients with chronic right-to-left-shunting from congenital heart disease (Chapter 55) or other causes of long-standing hypoxemia (Chapters 76 and 80), but it also may be indicative of pleural-based diseases (Chapter 86) as part of the syndrome of hypertrophic pulmonary osteoarthropathy (Chapters 164 and 254).

In patients with suspected hypoxemia, careful analyses of arterial blood gases can help determine its severity and guide therapy (Chapter 89). In patients in whom it is difficult to distinguish heart failure from a pulmonary cause of hypoxemia, an elevated brain natriuretic peptide level may point to a cardiac cause (Chapter 45). Chest imaging (Chapter 72) is a crucial part of the evaluation of many potential pulmonary complaints, and pulmonary function testing (Chapter 73) can be extremely helpful in distinguishing among causes of acute and chronic lung disease.

Among the most common respiratory complaints are cough, wheezing, dyspnea, and hemoptysis. Each can and should be approached in a systematic way.

TABLE 71-1 DIAGNOSTIC UTILITY OF LUNG AUSCULTATION

AUSCULTATORY FINDING	CLINICAL CORRELATION
Bronchial breathing	Pneumonia or interstitial lung disease
Fine crackle	Heart failure, interstitial lung disease, alveolar filling disorders
Coarse crackle	Bronchitis
Wheeze	Asthma, COPD, bronchomalacia
Rhonchus	Bronchitis, COPD
Stridor	Upper-airway obstruction from laryngeal or tracheal inflammation, mass lesions, or external compression
Pleural friction rub	Pleural inflammation or tumors

COPD = chronic obstructive pulmonary disease.

APPROACH TO THE PATIENT WITH COUGH

Cough is the single most common respiratory complaint for which patients seek care. Referrals of patients with persistently troublesome chronic cough of unknown cause account for 10 to 38% of outpatient visits to respiratory specialists.

For acute cough, defined as coughing that has been present for less than 8 weeks, a careful medical history and physical examination will usually reveal the diagnosis[4] (Table 71-2). Although most acute coughs are of minor consequence,[5] cough occasionally can be a sign of a potentially life-threatening illness, such as pulmonary embolism (Chapter 68), pneumonia (Chapter 85), or heart failure (Chapter 46).

Up to 98% of all cases of chronic cough, defined as a cough that persists for more than 8 weeks, in immunocompetent adults are caused by eight common conditions: postnasal drip syndrome from a variety of rhinosinus conditions often termed the "upper airway cough syndrome" (asthma; Chapter 75), gastroesophageal reflux disease (GERD; Chapter 124), chronic bronchitis (Chapter 76), eosinophilic bronchitis, bronchiectasis (Chapter 78), use of angiotensin-converting enzyme (ACE) inhibitors, and postinfectious cough. Postinfectious cough is usually nonproductive and generally persists for 3 to 8 weeks after an upper respiratory tract infection; patients have a normal chest radiograph. Environmental and occupational factors can also contribute to chronic cough and should be assessed. Cough in athletes is usually due to reactive airway disease, exercise-induced asthma, rhinitis, respiratory tract infections, and environmental exposures. Uncommon causes of chronic cough include bronchogenic carcinoma (Chapter 177), chronic interstitial pneumonia (Chapter 80), sarcoidosis (Chapter 83), left ventricular failure (Chapter 45), and aspiration (Chapter 82).[6] Cough itself also can cause complications, sometimes life-threatening, involving many organ systems, thereby providing further rationale for its diagnosis and treatment.[7]

DIAGNOSIS

In chronic cough (Fig. 71-1), the character and timing are not of diagnostic help. A chest radiograph should be obtained in all patients, but other tests should not be ordered in current smokers or patients taking ACE inhibitors

ABSTRACT

Respiratory symptoms, which are among the most common reasons why patients seek medical care, are responsible for approximately 20% of office visits to a primary care physician. In addition to a careful history, a systematic physical examination is critical for accurate diagnosis and subsequent evaluation. Among the most common respiratory complaints are cough, wheezing, dyspnea, and hemoptysis. Each can and should be approached in a systematic way. This chapter discusses the necessary history, differential diagnosis, and evaluation to determine a diagnosis and guide therapy for these very common complaints.

KEYWORDS

cough
wheeze
dyspnea
hemoptysis

TABLE 71-2 SPECTRUM OF CAUSES AND FREQUENCIES OF COUGH IN IMMUNOCOMPETENT ADULTS

COMMON	LESS COMMON
ACUTE COUGH	
Common cold	Asthma exacerbation
Acute bacterial sinusitis	Pneumonia
Pertussis	Heart failure
Exacerbations of COPD	Aspiration syndromes
Allergic rhinitis	Pulmonary embolism
Environmental irritant rhinitis	Exacerbation of bronchiectasis
SUBACUTE COUGH	
Postinfectious cough	
Pertussis	
CHRONIC COUGH	
Rhinosinus conditions/UACS	Bronchiolitis
Asthma	Occupational and environmental
Non-asthma eosinophilic bronchitis	Aspiration Bronchogenic carcinoma
Bronchiectasis	Drug-induced cough
Gastroesophageal reflux	Tuberculosis
Chronic bronchitis/COPD	Interstitial lung disease

COPD = chronic obstructive pulmonary disease; UACS = upper airway cough syndrome.

until the response to smoking cessation or discontinuation of the drug for at least 4 weeks can be assessed.[8] Sinus radiographs, barium esophagography, methacholine challenge, esophageal pH, and bronchoscopy can be ordered as part of the initial evaluation, depending on the history and physical examination (Table 71-3; see Fig. 71-1). If a test points toward a possible diagnosis, a trial of treatment for that condition is needed to confirm the diagnosis. The diagnosis of psychogenic cough is often a diagnosis of exclusion.

TREATMENT

The specific cause of cough can be diagnosed and treated successfully 84 to 98% of the time, so nonspecific therapy aimed to suppress the cough per se is rarely indicated.[9,10] There is no strong evidence that nonspecific therapies such as antitussives, mucolytics, decongestants, or antihistamine-decongestant combinations are efficacious for acute cough in the setting of an upper respiratory tract infection. For nonspecific persistent cough, effective treatment of chronic gastroesophageal reflux disease with a proton pump inhibitor (Chapter 124) provides no more than modest benefit, with approximately one in five patients improving. Inhaled corticosteroids can reduce cough but should be used only after evaluation by chest radiography and often spirometry.[A1] Dextromethorphan and codeine-containing cough suppressants can reduce chronic cough by approximately 40%. In adults with refractory chronic cough without active respiratory disease or infection, gabapentin (up to a maximum daily dose of 1800 mg) or pregabalin (300 mg daily) significantly improves cough-specific quality of life compared with placebo.[A2] For chronic refractory cough despite comprehensive evaluation and opioid therapy, a combination of education, speech and language intervention, which includes cough suppression techniques, and counseling can significantly reduce cough and its negative impact on quality of life.[A3] Gefapixant, a P2X3 inhibitor that has shown promise in improving unexplained or chronic cough in randomized trials,[A4,A5] is currently undergoing FDA review.

APPROACH TO THE PATIENT WITH WHEEZING

Wheeze is a continuous musical sound that lasts longer than 80 to 100 msec, likely generated by flow through critically narrowed collapsible bronchi. Although expiratory wheezing is a common physical finding in asthma (Chapter 75), the many causes of wheezing (Table 71-4) (e.g., COPD [Chapter 76], pulmonary edema [Chapter 45], bronchiolitis [Chapter 80], bronchiectasis [Chapter 78], and less common entities such as carcinoid [Chapter 213] and

TABLE 71-3 TESTING CHARACTERISTICS OF DIAGNOSTIC PROTOCOL FOR EVALUATION OF CHRONIC COUGH

TESTS	DIAGNOSIS	POSITIVE PREDICTIVE VALUE, %	NEGATIVE PREDICTIVE VALUE, %
Sinus radiograph	Sinusitis	57-81	95-100
Methacholine inhalation challenge	Asthma	60-82	100
Modified barium esophagography	GERD, esophageal stricture	38-63	63-93
Esophageal pH*	GERD	89-100	
Bronchoscopy	Endobronchial mass/lesion	50-89	100

*24-Hour esophageal pH monitoring.
GERD = gastroesophageal reflux disease.

parasitic infections) often can be distinguished based on the history, physical examination, and pulmonary function testing (Chapter 73).[11]

DIAGNOSIS

On pulmonary function testing, the shape of inspiratory and expiratory flow-volume loops provides key information about the presence of airway obstruction and whether the obstruction is extrathoracic or intrathoracic (E-Fig. 71-1). An important cause of extrathoracic obstruction is vocal cord lesions (Chapter 176). Variable intrathoracic obstruction can be caused by tracheomalacia, whereas fixed upper airway obstruction can be caused by a proximal tracheal tumor.

TREATMENT

Treatment of the specific cause will usually lead to complete or at least partial resolution of wheezing. However, treatment of associated asymptomatic or minimally symptomatic gastroesophageal reflux disease is not beneficial.

APPROACH TO THE PATIENT WITH DYSPNEA

Dyspnea is the sensation of difficult, labored, or unpleasant breathing. The word *unpleasant* is very important to this definition because the labored or difficult breathing encountered by healthy individuals while exercising does not qualify as dyspnea because it is at the level expected for the degree of exertion. The sensation of dyspnea is often poorly or vaguely described by the patient. The physiology of dyspnea remains unclear, but multiple neural pathways can be involved in processes that lead to dyspnea.

In acute dyspnea, or shortness of breath of sudden onset, the history, physical examination, and laboratory testing must first focus on potential life-threatening conditions, including pulmonary embolism (Chapter 68), pulmonary edema (Chapters 45 and 46), acute airway obstruction from anaphylaxis or foreign bodies, pneumothorax (Chapter 86), or pneumonia (Chapter 85). For chronic dyspnea, specific conditions to consider include COPD (Chapter 76), asthma (Chapter 75), interstitial lung disease (Chapter 80), heart failure (Chapter 45), cardiomyopathy (Chapter 47), GERD (Chapter 124), other respiratory diseases, or hyperventilation syndrome (Table 71-5).[12]

DIAGNOSIS

Dyspnea is often underdiagnosed unless patients are specifically questioned, especially in critical care settings. In addition to an appropriate history and physical examination, a chest radiograph, electrocardiogram (ECG), pulmonary function testing, and an exercise test with electrocardiographic monitoring and pulse oximetry at rest and during exercise[13] are key tests to assess patients with unexplained dyspnea (Fig. 71-2). For acute dyspnea, B-type natriuretic peptide testing can be extremely helpful in distinguishing heart failure from other causes.[14] Point-of-care ultrasound[15] by appropriately trained clinicians can improve the sensitivities of standard diagnostic pathways to detect heart failure, pneumonia, pulmonary embolism, pleural effusion, or pneumothorax.[A6] The utility of more detailed pulmonary testing with maximal inspiratory and

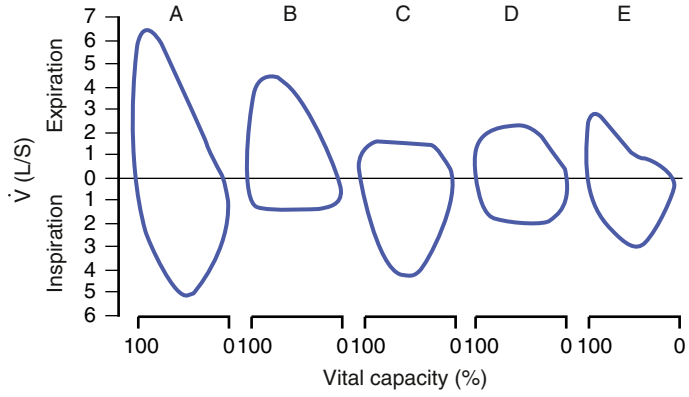

E-FIGURE 71-1. Schematic flow-volume loop configurations in a spectrum of airway lesions. *A* is normal; *B* is variable extrathoracic upper airway obstruction; *C* is variable intrathoracic large airway lesion; *D* is fixed upper airway obstruction; and *E* is small airway obstruction. L/S = liters per second; V̇ = ventilation.

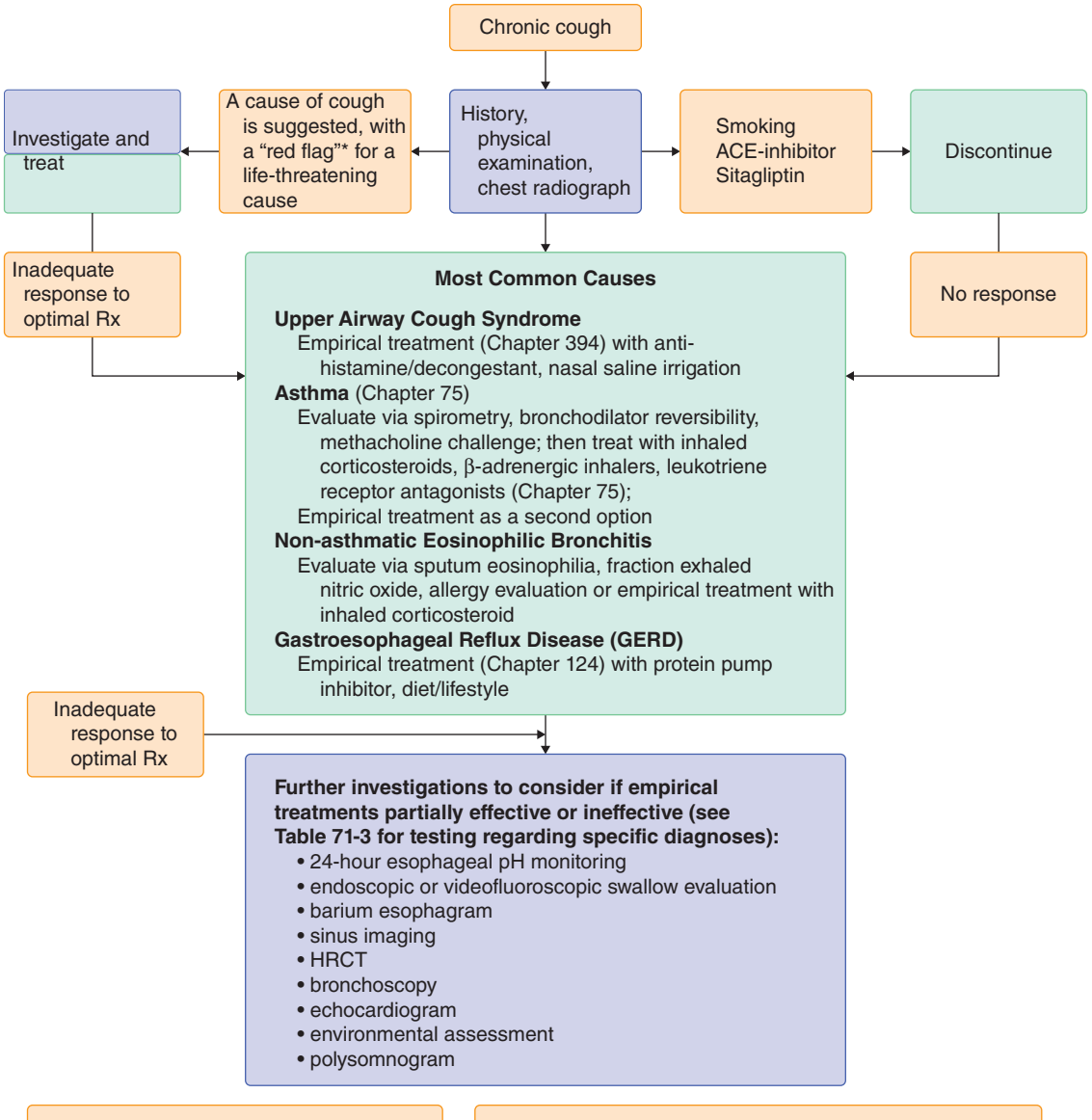

FIGURE 71-1. Algorithm for the management of selected causes of chronic cough that persists for longer than 8 weeks. ACE = angiotensin-converting enzyme; HRCT = high-resolution computed tomography; Rx = prescription. (Based on recommendations in Irwin RS, French CL, Chang AB, et al. Classification of cough as a symptom in adults and management algorithms: CHEST guideline and expert panel report. *Chest*. 2018;153:196-209.)

expiratory pressures; flow-volume loops, with or without methacholine challenge (Chapter 73); computed tomographic screening of the chest; and echocardiography depends on history and physical examination and the results of these tests. When GERD is a suspected cause of dyspnea, a modified barium esophagogram or 24-hour esophageal pH monitoring, or both, should be considered (Chapter 124). Other more invasive tests such as cardiac catheterization or lung biopsy may be indicated when the results of less invasive tests have not been conclusive.

TREATMENT AND PROGNOSIS

Whenever possible, the final determination of the cause of dyspnea is made by observing which specific therapy eliminates it. Dyspnea may be simultaneously the result of more than one condition, each of which may need to be treated. In patients with chronic exertional dyspnea, exercise-induced pulmonary hypertension is a predictor of a worse outcome.[16] In cases of refractory dyspnea despite maximally treated chronic heart and lung disease, judicious use of opioids can curb air hunger.[17]

APPROACH TO THE PATIENT WITH HEMOPTYSIS

Hemoptysis is the expectoration of blood from the lung parenchyma or airways. Hemoptysis may be scant, with just the appearance of streaks of bright red blood in the sputum, or massive, with the expectoration of a large volume of blood. Massive hemoptysis, which is defined as the expectoration of at least 600 mL of blood in 24 to 48 hours, may occur in 3 to 10% of patients with hemoptysis. Dark red clots also may be expectorated when the blood has been present in the lungs for days.

Pseudohemoptysis, which is the expectoration of blood from a source other than the lower respiratory tract, may cause diagnostic confusion when patients cannot clearly describe the source of the bleeding. Pseudohemoptysis can occur when blood from the oral cavity, nares, pharynx, or tongue clings to the back of the throat and initiates the cough reflex or when patients who have hematemesis aspirate into the lower respiratory tract. When the oropharynx is colonized with *Serratia marcescens*, a red pigment–producing aerobic gram-negative rod, the sputum also can be red and can be confused with hemoptysis.

TABLE 71-4 DIAGNOSIS OF SELECTED WHEEZING ILLNESSES OTHER THAN ASTHMA

DISEASES	DISTINGUISHING FEATURES
UPPER AIRWAY DISEASES	
Postnasal drip syndrome	History of postnasal drip, throat clearing, nasal discharge; physical examination shows oropharyngeal secretions or cobblestone appearance to mucosa.
Epiglottitis	History of sore throat out of proportion to pharyngitis. Evidence of supraglottitis on endoscopy or lateral neck radiographs.
Vocal cord dysfunction syndrome/ paradoxical vocal fold movement	Lack of symptomatic response to bronchodilators, presence of stridor plus wheeze in absence of increased $P(A\text{-}a)O_2$; extrathoracic variable obstruction on flow-volume loops; paradoxical inspiratory and/or early expiratory adduction of vocal cords on laryngoscopy during wheezing. This syndrome can masquerade as asthma, be provoked by exercise, and often coexists with asthma.
Retropharyngeal abscess	History of stiff neck, sore throat, fever, trauma to posterior pharynx; swelling noted by lateral neck or CT radiographs.
Laryngotracheal injury due to tracheal cannulation	History of cannulation of the trachea by endotracheal or tracheostomy tube; evidence of intrathoracic or extrathoracic variable obstruction on flow-volume loops, neck and chest radiographs, laryngoscopy, or bronchoscopy.
Neoplasms	Bronchogenic carcinoma, adenoma, or carcinoid tumor is suspected when there is hemoptysis, unilateral wheeze, or evidence of lobar collapse on chest radiograph or combinations of these; diagnosis is confirmed by bronchoscopy.
Anaphylaxis	Abrupt onset of wheezing with urticaria, angioedema, nausea, diarrhea, and hypotension, especially after insect bite, in association with other signs of anaphylaxis such as hypotension or hives, or administration of drug or IV contrast, or family history.
LOWER AIRWAY DISEASES	
COPD	History of dyspnea on exertion and productive cough in cigarette smoker. Because productive cough is nonspecific, it should only be ascribed to COPD when other cough-phlegm syndromes have been excluded, forced expiratory time to empty more than 80% of vital capacity is >4 sec, and there is decreased breath sound intensity, unforced wheezing during auscultation, and irreversible, expiratory airflow obstruction on spirometry.
Pulmonary edema	History and physical examination consistent with passive congestion of the lungs, ARDS, impaired lung lymphatics; abnormal chest radiograph, echocardiogram, radionuclide ventriculography, cardiac catheterization, or combinations of these.
Aspiration	History of risk for pharyngeal dysfunction or gastroesophageal reflux disease; abnormal modified barium swallow, 24-hr esophageal pH monitoring, or both.
Pulmonary embolism	History of risk for thromboembolic disease, positive confirmatory tests.
Bronchiolitis	History of respiratory infection, connective tissue disease, transplantation, ulcerative colitis, development of chronic airway obstruction over months to a few years rather than over many years in a nonsmoker; mixed obstructive and restrictive pattern on PFTs and hyperinflation; may be accompanied by fine nodular infiltrates on chest radiograph.
Cystic fibrosis	Combination of productive cough, digital clubbing, bronchiectasis, progressive COPD with *Pseudomonas* sp colonization and infection, obstructive azoospermia, family history, pancreatic insufficiency, and two sweat chloride determinations of >60 mEq/L; some patients are not diagnosed until adulthood, in one instance as late as age 69 yr; when sweat test is occasionally normal, definitive diagnosis may require nasal transepithelial voltage measurements and genotyping.
Carcinoid syndrome	History of episodes of flushing and watery diarrhea; elevated 5-hydroxyindoleactic acid level in 24-hr urine specimen.
Bronchiectasis	History of episodes of productive cough, fever, or recurrent pneumonias; suggestive chest radiographs or typical chest CT findings; ABPA should be considered when bronchiectasis is central.
Endobronchial sarcoidosis	Consider in patient with history of sarcoidosis with bilateral lymphadenopathy on chest radiography with wheezing and dyspnea out of proportion to findings on imaging. Confirmation required by bronchoscopy with biopsies.
Lymphangitic carcinomatosis	History of dyspnea or prior malignancy; reticulonodular infiltrates with or without pleural effusions; suggestive high-resolution chest CT scan; confirmed by bronchoscopy with biopsies.
Parasitic infections	Consider in a nonasthmatic patient who has traveled to an endemic area and complains of fatigue, weight loss, fever; peripheral blood eosinophilia; infiltrates on chest radiograph; stools for ova and parasites for nonfilarial causes; blood serologic studies for filarial causes.

ABPA = allergic bronchopulmonary aspergillosis; ARDS = acute respiratory distress syndrome; COPD = chronic obstructive pulmonary disease; CT = computed tomography; IV = intravenous; $P(A\text{-}a)O_2$ = alveolar-arterial oxygen tension gradient; PFTs = pulmonary function tests.

TABLE 71-5 DISEASES THAT CAUSE DYSPNEA GROUPED BY PHYSIOLOGIC MECHANISMS OF ACTION*

INCREASED RESPIRATORY DRIVE
Stimulation of Chemoreceptors
Conditions leading to acute hypoxemia
Impaired gas exchanger (e.g., asthma, pulmonary embolism, pneumonia, congestive heart failure†)
Environmental hypoxia (e.g., altitude, contained space with fire)
Conditions leading to increased dead space, acute hypercapnia
Impaired gas exchanger (e.g., acute, severe asthma; exacerbation of COPD; severe pulmonary edema)
Impaired ventilator pump (e.g., muscle weakness, airflow obstruction)
Metabolic acidosis
Renal disease (e.g., renal failure, renal tubular acidosis)
Decreased oxygen carrying capacity (e.g., anemia)
Decreased release of oxygen to tissues (e.g., hemoglobinopathy)
Decreased cardiac output
Stimulation of Pulmonary Receptors (Irritant, Mechanical, Vascular)‡
Interstitial lung disease
Pleural effusion (compression atelectasis)
Pulmonary vascular disease (e.g., thromboembolism, idiopathic pulmonary hypertension)
Heart failure
Mild asthma
Behavioral Factors
Hyperventilation syndrome, anxiety disorders, panic attacks
VENTILATORY PUMP: INCREASED EFFORT OR WORK OF BREATHING
Muscle Weakness
Myasthenia gravis, Guillain-Barré syndrome, spinal cord injury, myopathy, postpoliomyelitis syndrome
Decreased Compliance of the Chest Wall
Severe kyphoscoliosis, obesity, pleural effusion
Airflow Obstruction (including increased resistive load from narrowing of the airways and increased elastic load from hyperinflation)
Asthma, COPD, laryngospasm, aspiration of foreign body, bronchitis

*Some diseases appear in more than one category, because they act via several physiologic mechanisms.
†Heart failure includes both systolic and diastolic dysfunction. Systolic dysfunction may produce dyspnea at rest and with activity. Diastolic dysfunction typically leads to symptoms primarily with exercise. In addition to the mechanisms noted above, systolic heart failure may produce dyspnea via metaboreceptors, which are postulated to exist in muscles and be stimulated by changes in the metabolic milieu when oxygen delivery does not meet oxygen demand.
‡These conditions probably produce dyspnea by a combination of increased ventilator drive and primary sensory input from the receptors.
COPD = chronic obstructive pulmonary disease.

Hemoptysis can be caused by a wide variety of disorders. Virtually all causes of hemoptysis (Table 71-6) may result in massive hemoptysis, but massive hemoptysis is most frequently caused by infection (e.g., tuberculosis [Chapter 299], bronchiectasis [Chapter 78], lung abscess [Chapter 78], and cancer [Chapter 177]).[18] Infections with aspergilloma (Chapter 311) and in patients with cystic fibrosis (Chapter 77) also are associated with massive hemoptysis. Iatrogenic causes of massive hemoptysis include rupture of a pulmonary artery after less than 0.2% of cases of balloon-guided flotation catheterization and tracheal artery fistula as a complication of tracheostomy.

In nonmassive hemoptysis, the cause is bronchitis in more than one third of cases (Chapter 84), bronchogenic carcinoma (Chapter 177) in one fifth of cases, tuberculosis (Chapter 299) in 7%, pneumonia (Chapter 85) in 5%, and bronchiectasis in 1% (Chapter 78). Using a systematic diagnostic approach (see later), the cause of hemoptysis can be found in 68 to 98% of cases. The remaining 2 to 32% have idiopathic or central hemoptysis, which occurs most commonly in men between 30 and 50 years of age. Prolonged follow-up of idiopathic hemoptysis almost always fails to reveal the source of bleeding, even though 10% continue to have occasional episodes of hemoptysis.

DIAGNOSIS

The diagnostic evaluation for hemoptysis begins with a detailed medical history and a complete physical examination.[19] Information on the amount of bleeding should be obtained, as well as details about the frequency, timing, and duration of hemoptysis. For example, repeated episodes of hemoptysis occurring over a period of months to years suggest a bronchial adenoma or bronchiectasis as the cause, whereas small amounts of hemoptysis occurring every day for weeks are more likely to be caused by bronchogenic carcinoma. A travel history can suggest coccidioidomycosis (Chapter 308) and histoplasmosis (Chapter 308) in the United States, paragonimiasis and ascariasis (Chapter 327) in the Far East, and schistosomiasis (Chapter 326) in South America. Orthopnea and paroxysmal nocturnal dyspnea suggest heart failure (Chapter 45), especially from mitral stenosis (Chapter 60). In patients who have occupational exposure to trimellitic anhydride, which occurs when heated metal surfaces are sprayed with a corrosion-resistant epoxy resin, hemoptysis can be part of the postexposure syndrome, sometimes referred to as reactive airways dysfunction syndrome (Chapter 81). In a patient with the triad of upper airway disease, lower airway disease, and renal disease, granulomatosis with polyangiitis (Chapter 249) should be suspected. Pulmonary hemorrhage also may be a presenting manifestation of systemic lupus erythematosus (Chapter 245). Goodpasture syndrome, which typically occurs in young men, is also associated with renal disease (Chapter 107). Diffuse alveolar hemorrhage occurs in 20% of cases during autologous bone marrow transplantation (Chapter 163) and should be suspected in patients who have undergone recent bone marrow transplantation when they present with cough, dyspnea, hypoxemia, and diffuse pulmonary infiltrates.

On physical examination, inspection of the skin and mucous membranes may show telangiectasias suggesting hereditary hemorrhagic telangiectasia (Chapter 159) or ecchymoses and petechiae, suggesting a hematologic abnormality (Chapter 158). Pulsations transmitted to a tracheostomy cannula should heighten suspicion of a tracheal artery fistula. Inspection of the thorax should show evidence of recent or old chest trauma, and unilateral wheeze or crackles may herald localized disease such as a bronchial adenoma or carcinoma. Although pulmonary embolism (Chapter 68) cannot be definitively diagnosed on physical examination, tachypnea, phlebitis, and pleural friction rub suggest this disorder. If crackles are heard on the chest examination, heart failure as well as other diseases causing diffuse pulmonary hemorrhage (see earlier) or idiopathic pulmonary hemosiderosis (Chapter 80) should be considered. Careful cardiovascular examination may help diagnose mitral stenosis (Chapter 60), pulmonary artery fistulas, or pulmonary hypertension (Chapter 69).

Routine laboratory studies should include a complete blood count, urinalysis, and coagulation studies. The complete blood count may suggest an infection, hematologic disorder, or chronic blood loss. Urinalysis may reveal hematuria and suggest the presence of a systemic disease (e.g., Wegener granulomatosis, Goodpasture syndrome, systemic lupus erythematosus) associated

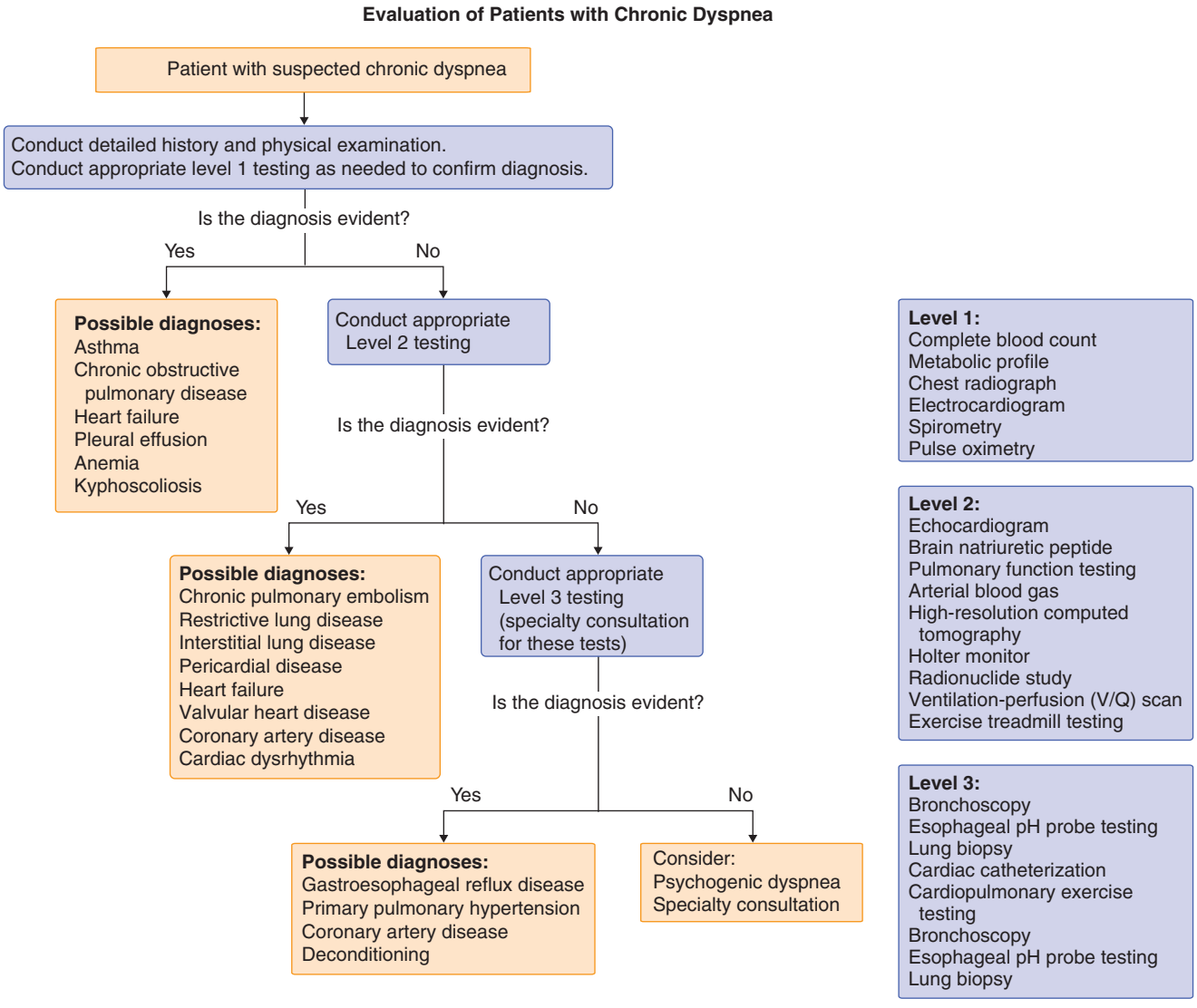

FIGURE 71-2. Algorithm outlining the approach to selected causes of chronic dyspnea. (Modified from Karnani NG, Reisfield GM, Wilson GR. Evaluation of chronic dyspnea. *Am Fam Phys*. 2005;71:1529-1537.)

with renal disease. Coagulation studies may uncover a hematologic disorder that is primarily responsible for hemoptysis or that contributes to excessive bleeding from another disease. The ECG may help suggest the presence of a cardiovascular disorder. Although as many as 30% of patients with hemoptysis have a normal chest radiograph, a routine chest radiograph is the beginning of the diagnostic process (Fig. 71-3).

Bronchoscopy can localize the bleeding site in up to 93% of patients by fiberoptic bronchoscopy and in up to 86% with rigid bronchoscopy. It may establish sites of bleeding different from those suggested by the chest radiograph. The best results are obtained when bronchoscopy is performed during or within 24 hours of active bleeding, and rates of diagnosis fall to approximately 50% by 48 hours after bleeding. When there is no active bleeding, bronchoscopy with bronchoalveolar lavage can be helpful in patients thought to have diffuse intrapulmonary hemorrhage. Typical findings include bright red or blood-tinged lavage fluid from multiple lobes in both lungs or a substantial number of hemosiderin-laden macrophages (i.e., at least 20% of the total number of alveolar macrophages).

Depending on the results of the initial evaluation and the likely categories of hemoptysis, additional diagnostic tests can be helpful (Table 71-7). Bronchoscopy may not be needed in patients who have stable chronic bronchitis (Chapter 76) with one episode of blood streaking or who have acute tracheobronchitis (Chapter 76). Bronchoscopy also may not be needed with obvious cardiovascular causes of hemoptysis, such as heart failure and pulmonary embolism.

TABLE 71-6 COMMON CAUSES OF HEMOPTYSIS

- Cardiovascular
  - Arteriovenous malformation
  - Congenital heart disease
  - Pulmonary embolism (fat, septic, thrombotic)
  - Heart failure, especially from mitral stenosis
- Pulmonary Vascular Disease
  - Pulmonary veno-occlusive disease
  - Pulmonary artery rupture following catheterization
  - Tricuspid endocarditis
- Pulmonary Infection
  - Anthrax
  - Lung abscess
  - Mycetoma/fungal infection
  - Necrotizing pneumonia
  - Parasitic (e.g., *Paragonimus westermani*)
  - Tuberculosis or nontuberculous mycobacterial disease
  - Tularemia
  - Viral (e.g., herpes simplex)
  - *Yersinia pestis* (plague)
- Rheumatic Disease
  - Amyloid
  - Anti–glomerular basement membrane disease (Goodpasture)
  - Behçet disease
  - Genetic collagen defect (Ehlers-Danlos)
  - Granulomatosis with polyangiitis
  - Idiopathic pulmonary hemosiderosis
  - Primary antiphospholipid syndrome
  - Systemic lupus erythematosus
- Tracheobronchial/Airway Diseases
  - Bronchogenic carcinoma
  - Bronchiectasis, including cystic fibrosis
  - Bronchitis, acute and chronic
  - Bullous emphysema
  - Broncholithiasis
  - Bronchovascular fistula
  - Dieulafoy disease (subepithelial bronchial artery)
  - Foreign body
  - Metastatic cancer to bronchus or trachea
- Drugs and Toxins
  - Anticoagulants
  - Anti-platelet medications
  - Argemone alkaloid (e.g., contaminated cooking oil)
  - Bevacizumab
  - Cocaine use
  - Nitrogen dioxide toxicity
  - Trimellitic anhydride
- Trauma
  - Blunt chest trauma (bronchial rupture, lung contusion)
  - Penetrating lung injury
- Iatrogenic
  - Airway stent
  - Aortobronchial fistula due to aortic graft or stent
  - Erosion of tracheal tube into innominate artery
  - Erosion of airway stent
  - Lung transplantation
  - Pulmonary laceration from chest tube placement or thoracentesis
  - Pulmonary vein stenosis after radiofrequency ablation of the AV node
  - Thrombolytic therapy
  - Transbronchial biopsy or cryobiopsy
  - Transthoracic needle aspiration
  - Vascular injury from pulmonary artery catheter
- Miscellaneous and Rare Causes
  - Systemic coagulopathy or thrombolytic agents
  - Platelet dysfunction/antiplatelet medications/thrombocytopenia
  - von Willebrand disease
  - Catamenial hemoptysis (pulmonary endometriosis)
  - Leukemia/bone marrow transplant

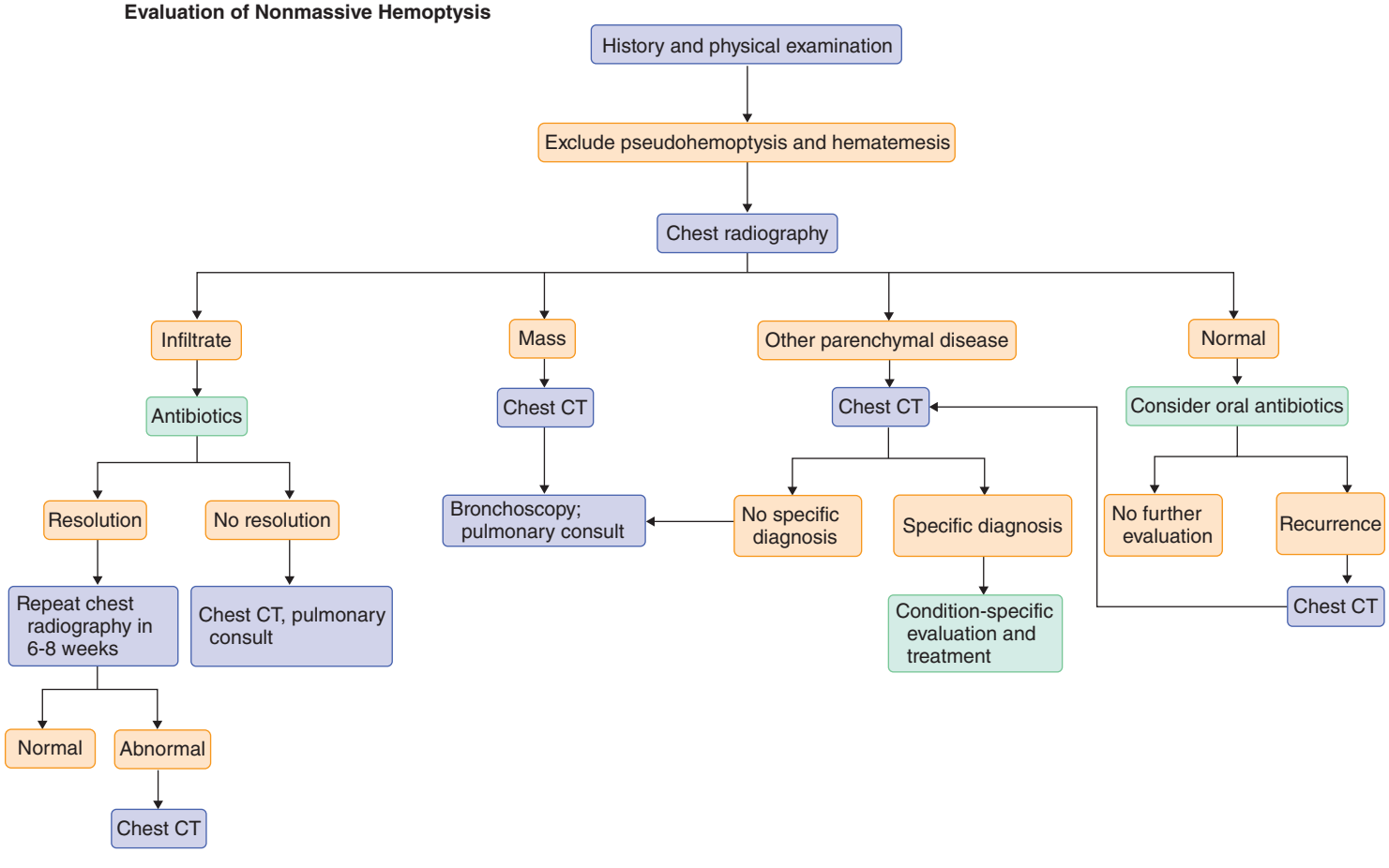

FIGURE 71-3. Algorithm for evaluation of nonmassive hemoptysis. CT = computed tomographic scan. (Adapted from Earwood JS, Thompson TD. Hemoptysis: evaluation and management. *Am Acad Fam Physicians*. 2015;91:243-249.)

TABLE 71-7 EXAMPLES OF SPECIAL EVALUATIONS FOR HEMOPTYSIS ACCORDING TO CATEGORY OF DISEASE*

TRACHEOBRONCHIAL DISORDERS
Expectorated sputum for TB, parasites, fungi, and cytology Bronchoscopy (if not done previously) High-resolution chest CT scan
LOCALIZED PARENCHYMAL DISEASES
Expectorated sputum for TB, parasites, fungi, and cytology Chest CT scan Lung biopsy with special stains
DIFFUSE PARENCHYMAL DISEASES
Expectorated sputum for cytology Blood for BUN, creatinine, ANA, RF, complement, cryoglobulins, ANCA, anti-GBM antibody High-resolution chest CT scan Lung or kidney biopsy with special stains
CARDIOVASCULAR DISORDERS
Echocardiogram Arterial blood gas on 21% and 100% oxygen Ventilation-perfusion scans Chest CT with contrast Aortogram
HEMATOLOGIC DISORDERS
Coagulation studies Bone marrow

*This table is not meant to be all-inclusive.

ANA = antinuclear antibody; ANCA = antineutrophil cytoplasmic antibody; BUN = blood urea nitrogen; CT = computed tomography; GBM = glomerular basement membrane; RF = rheumatoid factor; TB = tuberculosis.

TREATMENT

Treatment is targeted toward the cause of hemoptysis. Bronchoscopic approaches (Chapter 87) are increasingly used for endobronchial lesions, as is bronchial artery embolization[20] for the emergency treatment of hemoptysis and the treatment of hemoptysis associated with bronchiectasis.[21] In nonmassive hemoptysis, inhaled tranexamic acid (500 mg by nebulizer, three times daily) can safely and effectively control bleeding.[A7]

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72 IMAGING IN PULMONARY DISEASE

PAUL STARK

IMAGING OF THE LUNGS, MEDIASTINUM, AND CHEST WALL

EPIDEMIOLOGY

Worldwide, chest radiography is the most commonly performed imaging procedure; more than 75 million chest radiographs are performed every year in the United States alone. Chest radiographs provide useful information about the patient's anatomy and disease at a minimal monetary cost and with radiation exposure that most experts agree is negligible (0.05 to 0.1 mSv; Chapter 18). Although many novel imaging techniques are available, the conventional chest radiograph remains invaluable in the initial assessment of disorders of the lung, pleura, mediastinum, and chest wall.

IMAGING TECHNIQUES

The standard chest radiograph is performed at 2 m from the x-ray tube focal spot to the image detector, in frontal and lateral projections. If possible, the radiographs should be obtained with the patient inhaling to total lung capacity. These images, which provide views of the lungs, mediastinum, and chest wall simultaneously, are typically acquired, stored, and distributed digitally.

Bedside Radiography

Although bedside radiography accounts for a large number of chest radiographs, especially in the intensive care unit (ICU), the images obtained are generally of lower technical quality, cost more, and are more difficult to interpret. Lung volumes are low, thereby leading to crowding of vascular structures, and the low kilovoltage technique required for the mobile equipment yields radiographs with overexposed lungs and an underpenetrated mediastinum. The anteroposterior projection and the slightly lordotic angulation of the x-ray beam combine to distort the basal lung structures and magnify the cardiac silhouette. Recumbent studies also make recognition of pleural effusions or pneumothoraces more difficult. In the ICU, chest radiography can be ordered selectively rather than as a daily routine, without compromising care.

Computed Tomography

Computed tomography (CT) has multiple advantages over conventional radiography. It displays cross-sectional anatomy free of superimposition, with a 10-fold higher contrast resolution. Multislice CT scanners acquire a continuous, volumetric, near-isotropic data set with possibilities for high-quality two-dimensional or three-dimensional reformatting (volume rendering) in any plane. High-resolution CT of the lung parenchyma is an important application; narrow collimation of the beam combined with an edge-enhancing high spatial frequency algorithm results in exquisite detail of normal and abnormal lungs, and correlation with pathologic anatomy is high. CT angiography is also a key component of the evaluation of suspected pulmonary embolism (Chapter 68) and coronavirus disease 2019 (COVID-19).[1]

Magnetic Resonance Imaging

Magnetic resonance imaging (MRI) depends on the magnetic properties of hydrogen atoms. Magnetic coils and radio frequency coils lead to induction, excitation, relaxation, and eventual readout of magnetized protons. The molecular environment of hydrogen atoms will affect the rate at which they release energy; this energy yields a spatial distribution of signals that is converted into an image by computer algorithms, similar to CT. Because of its soft tissue specificity, MRI has applications in the assessment of chest wall invasion, mediastinal infiltration, and diaphragmatic involvement by lung cancer or malignant mesothelioma.

Positron Emission Tomography

Fluorodeoxyglucose positron emission tomography (FDG-PET) uses labeled fluorodeoxyglucose to image the glycolytic pathway of tumor cells or other metabolically active tissues with affinity for glucose. This technique has proved helpful in studying intrathoracic tumors and has facilitated the work-up of solitary pulmonary nodules. Integrated PET-CT scans have improved the diagnosis and staging of intrathoracic tumors.

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ABSTRACT

Thoracic imaging relies primarily on chest radiography and computed tomography. Important radiologic features that allow for detection and localization of abnormalities on chest radiographs include the following signs:

1. Silhouette sign indicates obscuration of a contour or soft tissue border normally outlined by aerated lung owing to adjacent pulmonary or pleural opacification.
2. Spine sign relies on an increase in basal opacification over the lower thoracic spine as seen on the lateral chest radiograph, thereby raising the possibility of a subtle pulmonary opacity in the lower lobes.
3. Incomplete border sign in the context of an intrathoracic nodule or mass indicates that the opacity is not located in the lung parenchyma but rather represents a pleural, mediastinal, or chest wall lesion. It can also be described as a "one-edged" lesion; it can form obtuse angles of interface with the chest wall or the mediastinum and can display tapered borders.
4. Hilum overlay sign distinguishes a mediastinal mass from a hilar mass; only a hilar mass obscures the ipsilateral pulmonary artery.
5. Mach bands or Mach effect relies on retinal illusions due to edge enhancement and facilitates visualization of contours on chest radiographs but can also mimic pathologic findings such as a pneumothorax.

The task of a thoracic radiologist consists of detection and description of abnormal findings followed by a differential diagnosis, most likely diagnosis, and discussion, which include comparison with prior imaging studies, recommendations for further imaging, pertinent negatives, and follow-up. In this way, the radiologist aims to decrease diagnostic uncertainty and increase the overall probability of a correct diagnosis.

KEYWORDS

chest radiograph
CT scanning
lung
pleura
mediastinum

Ultrasonography

Outside the heart, ultrasonography traditionally has played only a limited role in thoracic imaging. Its primary use has been to localize pleural effusions and guide their drainage (Chapter 86). However, some data suggest that lung ultrasound can be used as a preliminary screen for pneumonia (Chapter 85), pulmonary edema (Chapter 45),[2] or pneumothorax (Chapter 86). In the intensive care setting, ultrasound also may help with the diagnosis of ventilator-associated pneumonia (Chapter 85), pneumothorax (Chapter 86), and diffuse alveolar damage (Chapter 79).

EVALUATION OF CHEST IMAGES

Images of the chest are best evaluated by examining regions of the lung for specific findings and relating these findings to known diagnostic groups.[3] A number of critical radiographic features should be considered, with an appreciation for the known causes of these changes. Artificial intelligence is a promising method to aid in the clinical interpretation of chest images.

Diffuse Lung Disease

Diffuse lung disease is an overall term for a number of related abnormal parenchymal radiographic patterns. Although radiologists have attempted to separate alveolar (Chapter 79) from interstitial lung disease (Chapter 80) radiographically, this distinction is no longer recommended because the correlation between the radiographic localization to a compartment and the actual histopathologic findings is relatively poor. For example, nodular patterns can be produced by either interstitial or alveolar disease. Conversely, so-called alveolar disease processes can induce an interstitial reaction. Ground-glass opacities can be induced by either alveolar or interstitial disease. Air bronchograms, the presumed paradigm of air space disease, can be identified in a small percentage of patients with predominantly interstitial lung disease (Chapter 80), such as sarcoidosis, pulmonary lymphoma, and pulmonary calcinosis.

Because of such limitations, a graphically descriptive approach that combines analysis of predominant opacities, assessment of lung expansion, and distribution and profusion of disease yields a differential diagnosis. The term *infiltrate* should be avoided; instead, the term *pulmonary opacities* should be used, with opacities further classified as large (i.e., >1 cm in the largest dimension) or small (i.e., <1 cm in diameter).

Large Opacities

Large opacities (Table 72-1) are characterized according to their distribution. Diffuse homogeneous opacities are typical for diffuse alveolar damage (Fig. 72-1); increased permeability (noncardiogenic) pulmonary edema; diffuse viral pneumonia (see Fig. 72-1B), including COVID-19 (E-Fig 72-1; see Chapter 336)[4,5]; or *Pneumocystis jirovecii* pneumonia. Multifocal patchy opacities (see Fig. 72-1C) are found in bacterial multifocal bronchopneumonia, recurrent aspiration with multifocal pneumonia or abscesses (Chapter 78), COVID-19 pneumonia in the organizing phase (E-Figs. 72-2 to 72-6), and vasculitis (E-Fig. 72-7). Lobar opacities without atelectasis are typically seen in lobar pneumonia (Fig. 72-2, E-Figs. 72-8 and 72-9). Lobar opacities with atelectasis often result from obstruction of a lobar bronchus by foreign bodies, tumors, or mucous plugs. Perihilar opacities are seen in hydrostatic pulmonary

TABLE 72-1 CLASSIFICATION OF LARGE PULMONARY OPACITIES

Diffuse homogeneous
Multifocal patchy
Lobar without atelectasis
Lobar with atelectasis
Perihilar
Peripheral

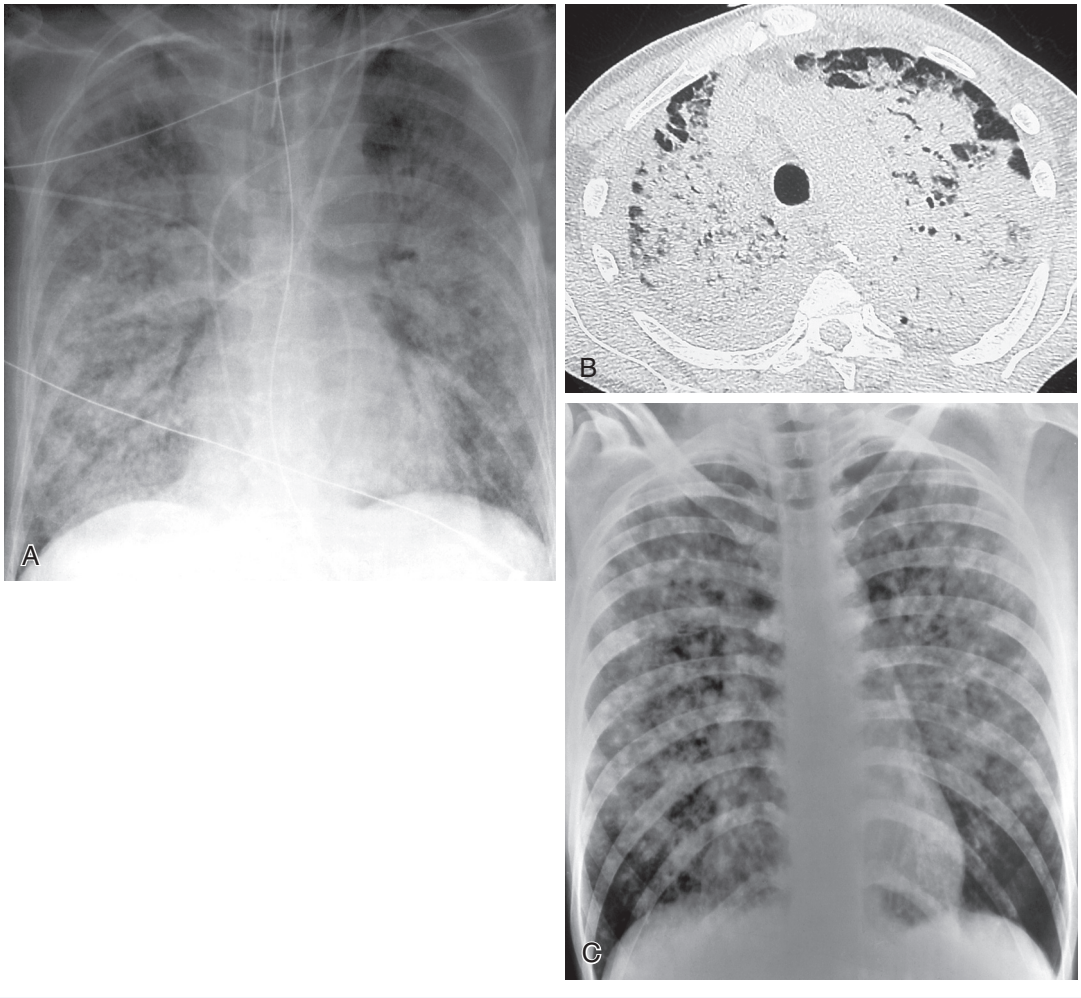

FIGURE 72-1. Diffuse alveolar damage. A, Chest radiograph shows diffuse homogeneous opacification of both lungs with clearly visible air bronchograms. **B,** Computed tomographic scan demonstrates diffuse consolidation with air bronchograms extending to the periphery of both lungs in a patient with community-acquired pneumonia. **C,** Patient with acute varicella pneumonia. Chest radiograph demonstrates multiple acinar nodules with tendency for confluence, yielding multifocal, patchy parenchymal opacification.

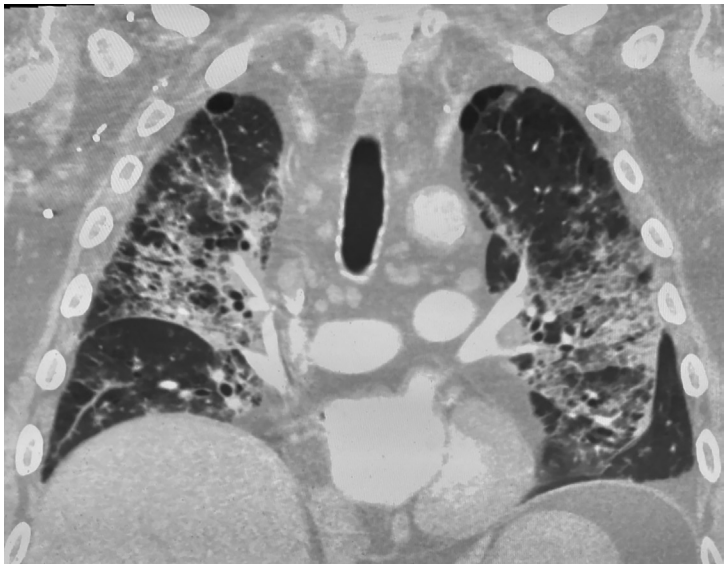

E-FIGURE 72-1. Computed tomographic chest scan in a patient with COVID-19 pneumonia. Coronal reformation of a computed tomographic scan of this thorax shows extensive confluent consolidation with ground-glass opacification and reticular opacities suggestive of "crazy paving" pattern with traction bronchiectasis indicative of advanced organizing COVID-19 pneumonia with pulmonary fibrosis. A small left pleural effusion and paraseptal emphysema are visible.

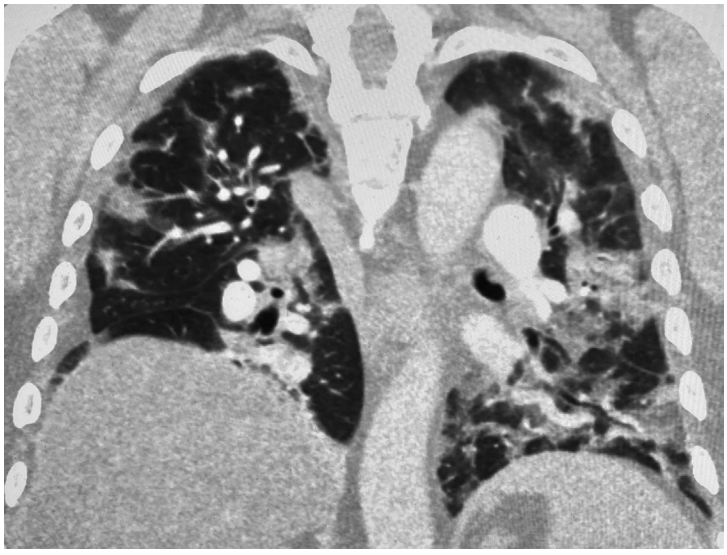

E-FIGURE 72-3. Computed tomographic scan in a patient with COVID-19 pneumonia. Coronal reformation of a computed tomographic scan of this thorax shows multifocal, rounded, predominantly peripheral foci of consolidation and ground-glass opacification compatible with the exudative phase and early organizing phase of COVID-19 pneumonia.

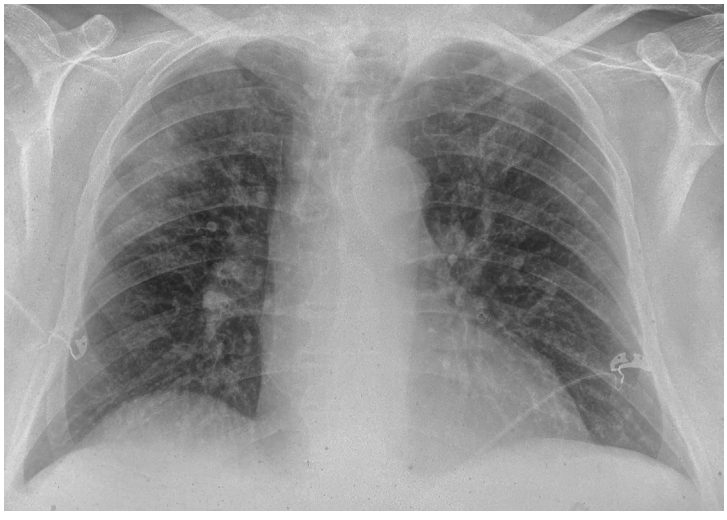

E-FIGURE 72-2. Chest radiograph in a patient with COVID-19 pneumonia. Frontal chest radiograph shows bilateral peripheral upper lobe rounded ground-glass opacities compatible with early exudative phase of COVID-19 pneumonia.

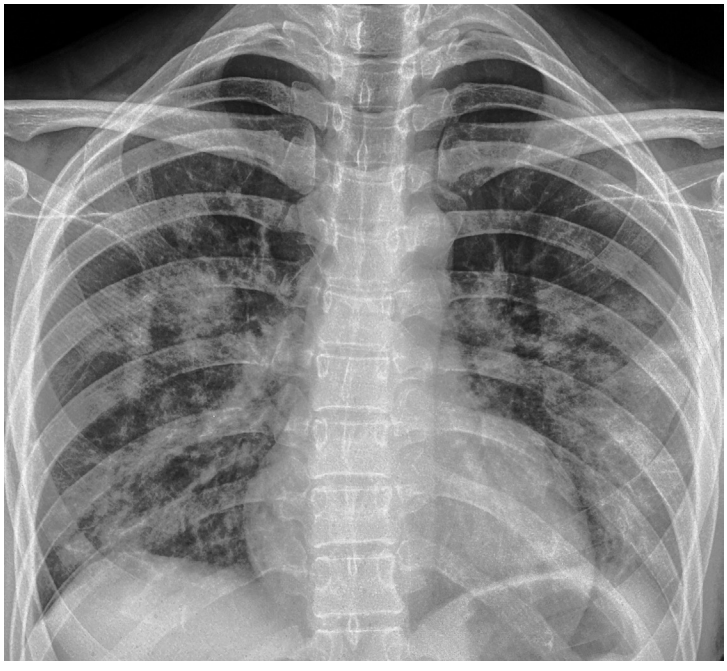

E-FIGURE 72-4. Chest radiograph in a patient with COVID-19 pneumonia. Frontal chest radiograph shows multifocal rounded, confluent areas of consolidation and ground-glass opacities compatible with the organizing phase of COVID-19 pneumonia. A small left pleural effusion is blunting the left lateral costophrenic sulcus.

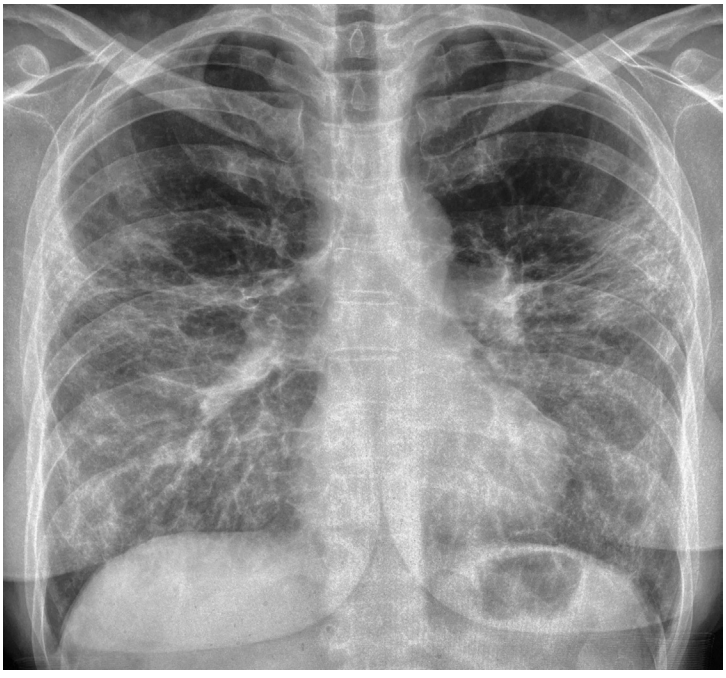

E-FIGURE 72-5. Chest radiograph in a patient with COVID-19 pneumonia. The image shows bilateral extensive confluent ground-glass opacities, heterogeneous consolidation, and linear opacities compatible with the organizing stage of pneumonia.

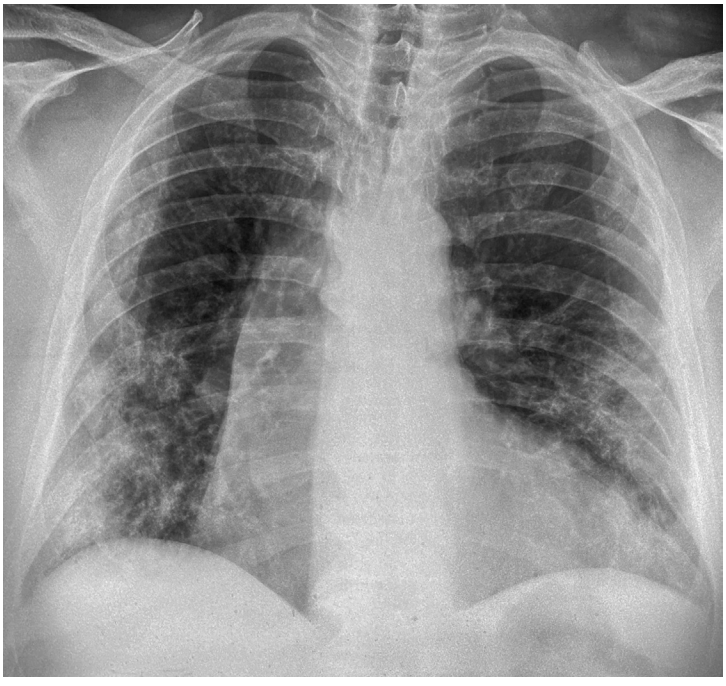

E-FIGURE 72-6. Imaging in COVID-19 pneumonia. A chest radiograph in a patient with COVID-19 shows bilateral peripheral, subpleural ground-glass opacities compatible with the exudative stage of pneumonia.

E-FIGURE 72-7. Microscopic polyangiitis with pulmonary hemorrhage. Computed tomographic scan shows heterogenous ground-glass opacification with mosaic attenuation.

E-FIGURE 72-8. Primary coccidioidomycosis pneumonia. Computed tomographic scan shows segmental consolidation of the medial basal segment of the right lower lobe.

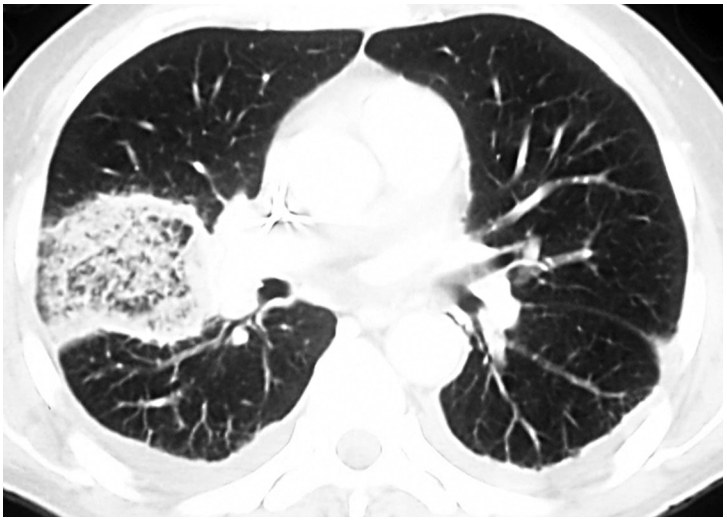

E-FIGURE 72-9. Mucormycosis in an immunocompromised patient. Computed tomographic scan shows a focal right upper lobe opacity with a "reversed halo sign," typically with a central ground-glass opacity surrounded by a circular or crescentic rind of homogeneous consolidation. This finding is characteristic of focal cryptogenic pneumonia, mucormycosis, or bland pulmonary infarction.

edema as a result of left-sided heart failure (Figs. 72-3A and B), renal failure, volume overload, or pulmonary hemorrhage. Subacute or chronic peripheral opacities are described in eosinophilic lung disease. Acute, rounded, large, ground-glass peripheral, subpleural opacities are characteristic of the acute, exudative, and early organizing phase of COVID-19 pneumonia (Fig. 72-4). Similar patterns may also be seen in e-cigarette or vaping use–associated lung disease (Chapter 82).

Small Opacities

In contrast to the large pulmonary opacities, a number of radiographic patterns characterize small pulmonary opacities in diffuse lung disease. It is helpful to differentiate small nodular, linear, reticular, or combined patterns (Table 72-2).

Nodular Patterns

Micronodular opacities, which include nodules 1 mm and smaller in diameter, can result from talc granulomatosis (excipient lung disease) in intravenous drug abusers (Chapter 365), alveolar microlithiasis, rare cases of silicosis, talcosis, coal workers' pneumoconiosis (Chapter 81), and beryllium-induced lung diseases (Chapter 81), as well as from occasional cases of sarcoidosis (Chapter 83) or hemosiderosis. The nodular pattern includes nodules up to 1 cm in diameter. Frequent causes include infections or inflammatory granulomata such as miliary tuberculosis (Chapter 299), sarcoidosis (Chapter 83), fungal diseases, hypersensitivity pneumonitis (Chapter 82), and Langerhans cell histiocytosis (Chapter 80).[6]

Linear Patterns

Linear patterns, also called Kerley lines, are mostly a reflection of thickened interlobular septa. Kerley A lines, which radiate 2 to 4 cm from the hilum toward the pulmonary periphery and particularly toward the upper lobes (Fig. 72-5), reflect thickening of the axial interstitial compartment and can be a feature of left ventricular failure or allergic reactions. Kerley B lines, which reflect thickening of the subpleural interstitial compartment, typically are approximately 1 cm in length and 1 mm in thickness and usually found in the periphery of the lower lobes, abutting the pleura. The B lines are characteristic of subacute and chronic left ventricular failure (Chapter 45), mitral valve disease (Chapter 60), lymphangitic carcinomatosis, viral pneumonia, and pulmonary fibrosis (Chapter 80). Kerley C lines, which are rarely diagnosed by radiologists, result from thickening of the lung parenchymal interstitium and form a reticular pattern on chest radiographs.

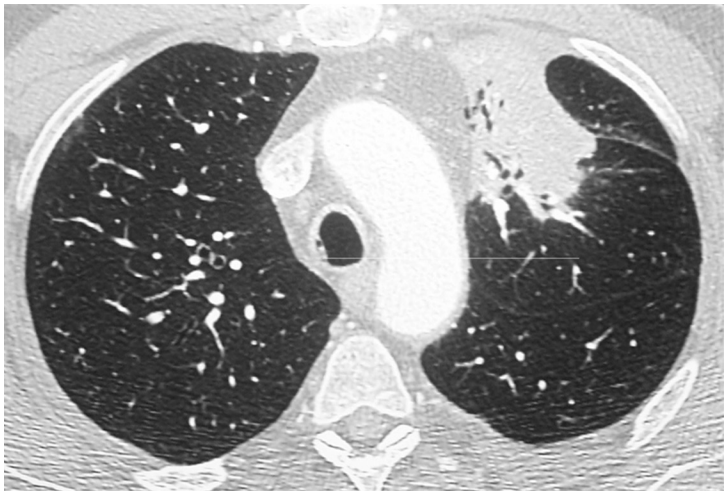

FIGURE 72-2. Bacterial pneumonia in the left upper lobe. Computed tomographic scan demonstrates segmental consolidation of the anterior segment of the left upper lobe with air bronchograms.

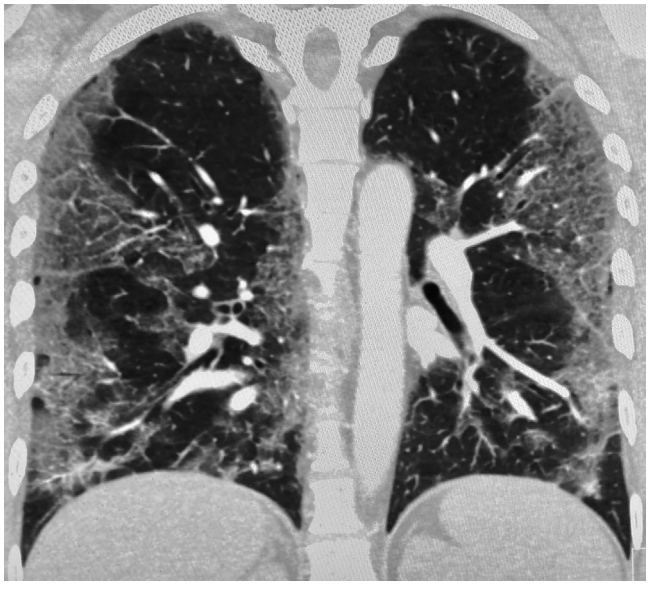

FIGURE 72-4. Computed tomographic scan in a patient with COVID-19 pneumonia. Image with coronal reformation shows extensive bilateral subpleural, peripheral ground-glass opacification with interlobular and intralobular septal thickening forming a "crazy pattern" indicative of organizing pneumonia.

TABLE 72-2 PATTERNS OF SMALL PULMONARY OPACITIES

Micronodular
Acinar
Linear
Reticular
Bronchial
Arterial
Destructive

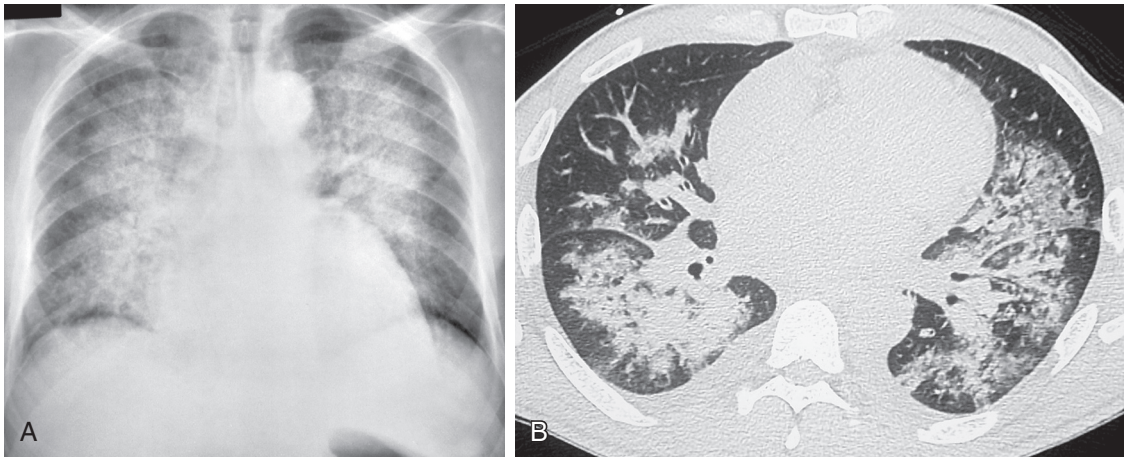

FIGURE 72-3. A, Pulmonary edema. Chest frontal radiograph demonstrates classic "batwing" distribution of hydrostatic pulmonary edema. **B,** Computed tomographic scan shows bilateral perihilar consolidations and a small right pleural effusion in a patient with pulmonary edema.

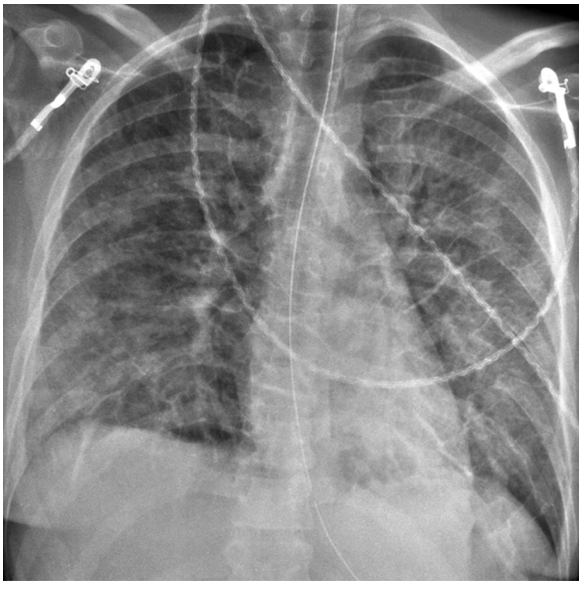

FIGURE 72-5. Patient with known transfusion reaction. Chest radiograph displays ground-glass opacification of both lungs and bilateral Kerley A lines, presenting as long linear structures extending from the hilar regions into the pulmonary periphery.

FIGURE 72-6. Diffuse reticular lung disease. Chest radiograph in a 94-year-old patient with diffuse reticular opacities (due to idiopathic pulmonary fibrosis with honeycombing) and multiple areas with traction bronchiectasis. The lung volumes are typically reduced by a decreased pulmonary compliance.

Reticular Patterns

Reticular patterns are small polygonal, irregular, or curvilinear opacities on chest radiographs (Fig. 72-6). The differential diagnosis varies according to the timeline of the pathologic change. Acute onset of a reticular pattern can occur in interstitial pulmonary edema (e.g., due to left-sided heart failure), atypical pneumonias (e.g., viral or mycoplasmal pneumonia), early exudative changes in a connective tissue disorder (e.g., systemic lupus erythematosus; Chapter 245), and acute allergic reactions (e.g., transfusion reactions [Chapter 162] or reactions to *Hymenoptera* stings). The common chronic processes resulting in a reticular pattern are idiopathic interstitial pneumonias (Chapter 80), connective tissue diseases (particularly scleroderma and rheumatoid lung), asbestosis (Chapter 81), radiation fibrosis (Chapter 80), end-stage hypersensitivity pneumonitis (Chapters 81 and 82), drug reactions, lymphangitic spread of cancer, end-stage granulomatous infection, lymphoma in its bronchovascular form, Kaposi sarcoma in its bronchovascular manifestation, and sarcoidosis.

Honeycombing

Honeycombing, which is an indication of end-stage interstitial lung disease (Chapter 80), reflects a restructuring of pulmonary anatomy with subpleural cysts, accompanied by bronchiolectasis. Honeycombs (Fig. 72-7) form a multilayer of small subpleural spaces between 3 and 10 mm in diameter. They can be distinguished from paraseptal emphysema by their thicker wall and multiple layers.

FIGURE 72-7. Honeycombing in a patient with idiopathic pulmonary fibrosis and usual interstitial pneumonia. Computed tomographic scan shows multiple bibasal reticular opacities with honeycombing and traction bronchiectases.

Alveolar Pattern

An alveolar (Chapter 79) or air space pattern is characterized by acinar nodules, 0.6 to 1 cm in diameter. These nodules encompass more than the acinus, in the strict anatomic sense, with surrounding peribronchiolar lung tissue. Other patterns include ground-glass opacities (a reflection of incomplete alveolar filling), coalescent large opacities, consolidation involving whole lobes or segments, opacification in a bronchocentric distribution, air bronchograms, and air alveolograms. These radiographic features are helpful in placing a disease into a particular radiologic category, but the radiographic pattern called *alveolar* does not simply correspond to exclusive histologic alveolar filling because the interstitial compartment is involved as well in most cases. A more accurate description is parenchymal rather than alveolar opacification or consolidation.

Bronchial Patterns

Bronchial patterns, as best depicted by diffuse bronchiectasis (Chapter 78), are seen on conventional radiographs as linear, tubular, or cystic lucencies and opacities that follow the expected path of bronchi, so-called tramlines because they resemble tram tracks. Mucoid impaction, as seen in patients with asthma, allergic bronchopulmonary aspergillosis, or plastic bronchitis,[7] leads to opacities described as toothpaste, cluster of grapes, or finger-in-glove. The "dirty lung" pattern seen in smokers with chronic bronchitis (Chapter 76) results from bronchial wall thickening, peribronchial fibrosis, respiratory bronchiolitis, and pulmonary arterial hypertension.

Vascular Patterns

Arterial patterns reflect changes in pulmonary perfusion. The term *caudalization* reflects the normal blood flow distribution pattern in an upright person in which the basal pulmonary vessels are two to three times wider than the upper lobe vasculature. *Cephalization*, in which the ratios of diameters of vessels are reversed, is frequently seen in recumbent persons, in whom it may be considered normal; however, when it is present in individuals imaged in the upright position, it indicates left ventricular failure (Fig. 72-8), mitral valve disease, or basal emphysema. Equalization or balanced flow with well-demonstrated vessels to upper and lower lung zones is found in hyperkinetic circulation due to anemia, obesity, pregnancy, hyperthyroidism, or left-to-right shunts. Equalization or balanced flow with oligemia can be seen in hypovolemia, diffuse emphysema, or right-to-left shunts. Centralization reflects dilation of central pulmonary arteries, with accompanying normal or diminished peripheral circulation. Typically, it is seen in pulmonary arterial hypertension (Fig. 72-9). Lateralization of flow, favoring one lung over the other, also called *asymmetrical perfusion*, is visible with unilateral emphysema, unilateral bronchiolitis obliterans (Swyer-James-McLeod syndrome), or unilateral obstruction of the pulmonary artery. Locally dilated pulmonary vessels occur adjacent to affected oligemic lung regions in patchy emphysema, multiple pulmonary emboli,

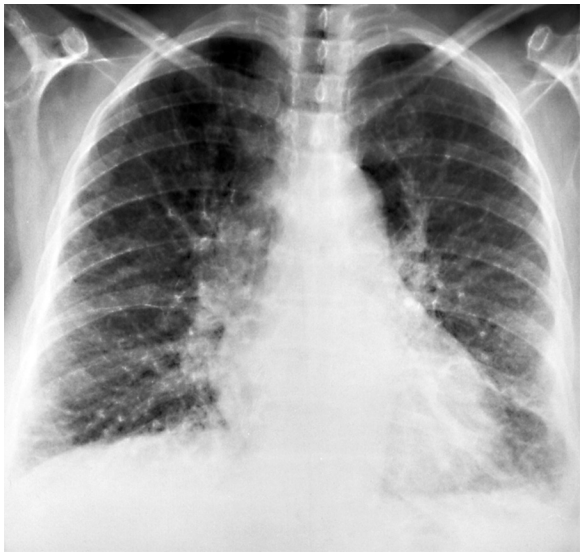

FIGURE 72-8. Patient with left ventricular failure. Chest frontal radiograph shows cephalization of pulmonary blood flow.

FIGURE 72-9. Patient with primary pulmonary arterial hypertension. Chest frontal radiograph shows centralization of flow with pulmonary artery aneurysms and peripheral pulmonary oligemia.

arteriovenous malformations, and nonuniform bronchiolitis obliterans. This pattern produces mosaic attenuation on high-resolution CT scanning. Focal oligemia with vascular deficiency is characteristically seen in emphysema but also can occur after pulmonary embolism (Westermark sign). Centrilobular emphysema (Chapter 76), paraseptal emphysema, and bullous lung disease have a predilection for the upper lung regions, whereas panlobular emphysema induces basal oligemia with vascular deficiency.

Lung Volume

Conventional radiographs and CT scans are performed during a breath hold at full inspiration and total lung capacity. Low lung volumes are inferred by the high position of the diaphragm and the crowding of basal vascular structures (Table 72-3). Lung volumes larger than expected are commonly found in patients with diffuse emphysema (Fig. 72-10; Chapter 76), chronic or severe acute asthma (Chapter 75), or diffuse bronchiolitis obliterans and in highly trained athletes. With a few rare exceptions, chronic diffuse infiltrative lung diseases (Chapter 80) lead to loss of volume.

Anatomic Distribution

The anatomic distribution of disease can often guide the approach to diagnosis (Table 72-4 and Fig. 72-11). Upper zone lung disease predominates in

TABLE 72-3 CONDITIONS ASSOCIATED WITH VARIOUS LUNG VOLUMES IN PATIENTS WITH AN UNDERLYING DIFFUSE LUNG DISEASE PATTERN

LARGE LUNG VOLUMES
Emphysema
Chronic or severe asthma
Diffuse bronchiolitis obliterans
Highly trained athletes
Lymphangioleiomyomatosis
SMALL LUNG VOLUMES
End-stage lung fibrosis
Bilateral diaphragmatic paralysis
Massive ascites
NORMAL LUNG VOLUMES
Sarcoidosis
Langerhans cell histiocytosis
Neurofibromatosis
Combined pulmonary fibrosis and emphysema

FIGURE 72-10. Patient with severe emphysema. Chest radiograph shows hyperexpansion of both lungs with bullous changes at the right lung base and leftward mediastinal shift.

TABLE 72-4 CONDITIONS ASSOCIATED WITH DISEASE DISTRIBUTION PATTERNS

UPPER ZONE LUNG DISEASE
Bullous lung disease
Centrilobular and paraseptal emphysema
Tuberculosis
Fungal disease
Sarcoidosis
Pneumoconiosis
Langerhans cell histiocytosis
Cystic fibrosis
End-stage hypersensitivity pneumonitis
Ankylosing spondylitis
Radiation pneumonitis
BASAL LUNG DISEASE
Panlobular emphysema
Bronchiectasis
Aspiration
Drug reactions
Interstitial pulmonary fibrosis, nonspecific interstitial pneumonia, desquamative interstitial pneumonia, cryptogenic organizing pneumonia (also called bronchiolitis obliterans with organizing pneumonia)
Asbestosis
Scleroderma

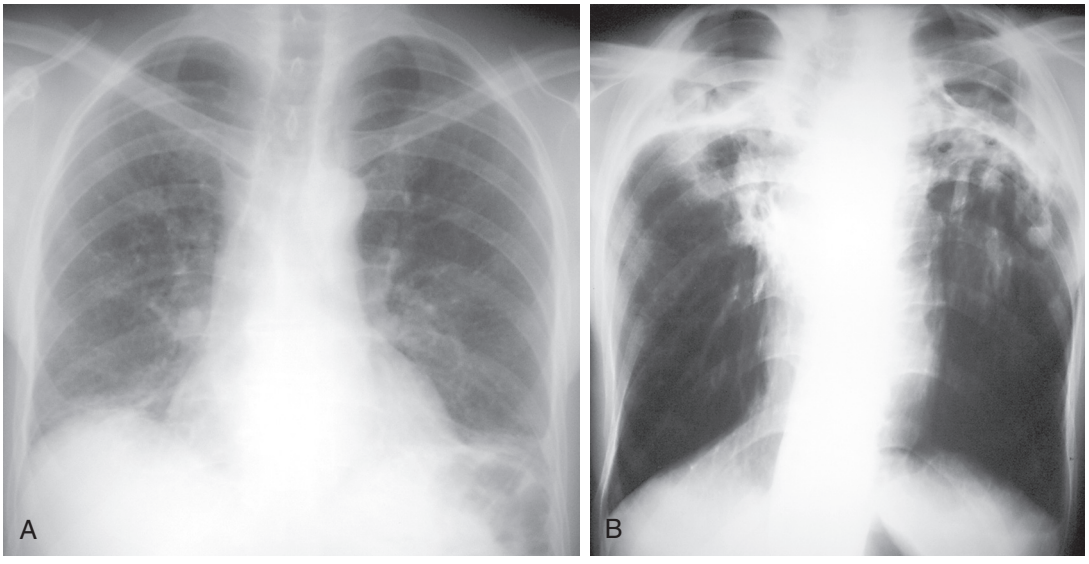

FIGURE 72-11. **A, Basal pulmonary disease. Chest radiograph in a 48-year-old patient with known scleroderma. Bibasal fine reticular opacities and parenchymal bands are visible in both lower lobes. B, Apical lung disease. Chest radiograph in a 42-year-old patient with ankylosing spondylitis. Severe architectural distortion with cicatrizing atelectasis of both upper lobes, retraction of both pulmonary arteries cephalad, and bilateral bulla formation containing fungus balls are evident.**

TABLE 72-5 DISEASES AFFECTING THE LUNG PERIPHERY

Chronic eosinophilic pneumonia
Cryptogenic organizing pneumonia
Idiopathic interstitial fibrosis (usual interstitial pneumonia)
Bronchioloalveolar cell carcinoma (rare)
Pseudo-alveolar sarcoidosis (rare)
COVID-19 pneumonia
E-cigarette or vaping product use-associated lung injury

TABLE 72-6 CONDITIONS ASSOCIATED WITH HILAR AND MEDIASTINAL LYMPH NODE ENLARGEMENT

Sarcoidosis
Lymphoma
Fungal disease
Tuberculosis
Metastatic cancer
Silicosis, coal worker's pneumoconiosis, beryllium lung

tuberculosis, fungal disease, sarcoidosis, pneumoconiosis (except asbestosis), Langerhans cell histiocytosis, ankylosing spondylitis, cystic fibrosis, cystic *P. jirovecii* pneumonia, radiation pneumonitis, and end-stage hypersensitivity pneumonitis. Basal lung disease is preferentially found in bronchiectasis (Chapter 78), aspiration pneumonia, desquamative interstitial pneumonia, nonspecific interstitial pneumonia, usual interstitial pneumonia (Chapter 80), drug reactions, asbestosis, scleroderma (Chapter 246), and rheumatoid arthritis (Chapter 243). Peripheral lung disease is seen in the initial exudative and early organizing phase of COVID-19 pneumonia (Chapter 336)[8]; in eosinophilic pneumonia, cryptogenic organizing pneumonia, usual interstitial pneumonia, bronchioloalveolar cell carcinoma, adenocarcinoma in situ or minimally invasive adenocarcinoma (Chapter 177); and in occasional patients with so-called alveolar sarcoidosis (Table 72-5). However, any diffuse lung process will eventually progress to involve both lungs irrespective of zonal boundaries.

Lymph Nodes

Enlarged lymph nodes that are visible on chest CT scans and, when larger, on chest radiographs can provide diagnostic information (Table 72-6). The following entities can be associated with diffuse lung disease and concurrent enlarged lymph nodes: sarcoidosis (Chapter 83); lymphoma; fungal disease; tuberculosis (Chapter 299); pneumoconiosis (Chapter 81), particularly silicosis and beryllium-associated lung disease; lung cancer; and metastatic malignant disease other than lung cancer.

FIGURE 72-12. **Multifocal pulmonary opacities. Chest radiograph in a 70-year-old patient with known carcinoma of the thyroid gland shows widening of the superior mediastinum, displacing the cervical trachea to the right. Bilateral large and small pulmonary nodules and masses due to metastatic tumor are present.**

Pulmonary Nodules

Deep-learning models are increasingly being pilot-tested to help determine whether pulmonary nodules are likely to be benign or malignant.[9] The detailed approach to evaluating solitary pulmonary nodules is covered in Chapter 177.

Most patients with multiple pulmonary nodules larger than 1 cm in diameter have metastatic disease from primary cancers either within or outside the lung (Fig. 72-12). These lesions have a predilection for subpleural lung regions, including the lung subtending the interlobar fissures. In patients with human immunodeficiency virus infection, Kaposi sarcoma and lymphoma can induce the formation of such nodules. Infectious processes that present with multiple nodules include multiple abscesses from recurrent aspiration (Chapter 82) or septic emboli (Chapter 61); tuberculous and nontuberculous mycobacterial granulomata (Chapters 299 and 300); fungal processes, including histoplasmosis (Chapter 308), coccidioidomycosis (Chapter 308), and cryptococcosis (Chapter 309); and infestation with flukes, such as *Paragonimus westermani* (Chapter 326). Noninfectious inflammatory conditions that can present with multiple pulmonary nodules include granulomatosis with polyangiitis (Chapter 249), rheumatoid nodules (Chapter 243), sarcoidosis (Chapter 83), and amyloidosis (Chapter 174).

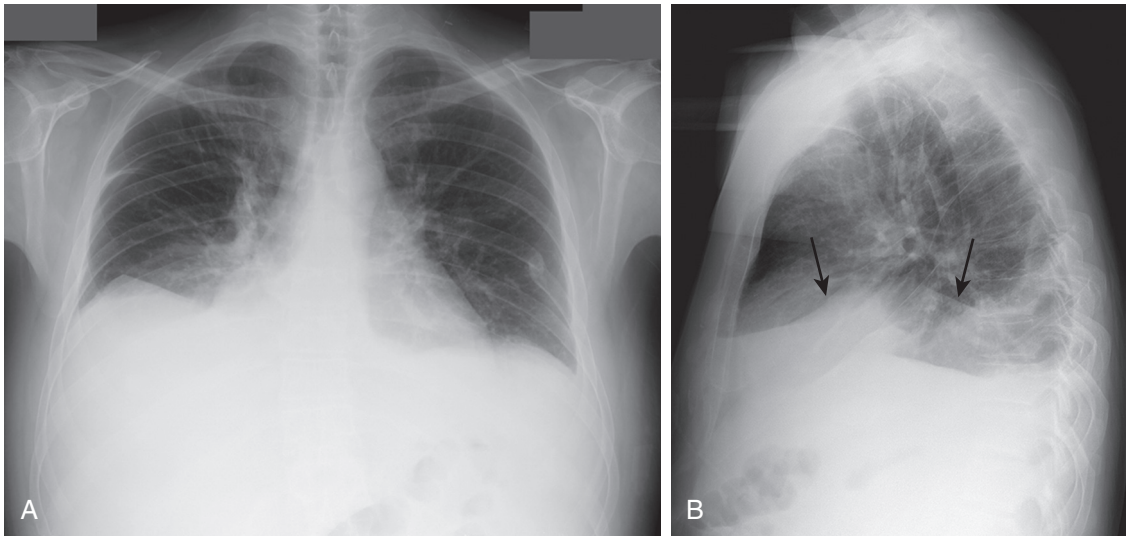

FIGURE 72-13. Bilateral subpulmonic pleural effusions. Chest frontal (**A**) and lateral (**B**) views. Both lung bases are elevated, with lateralization of the lung base curvature that mimics an elevated diaphragm. In the lateral projection, the configuration of the interface between the effusion and the aerated lung mimics the shape of the Rock of Gibraltar (*arrows*).

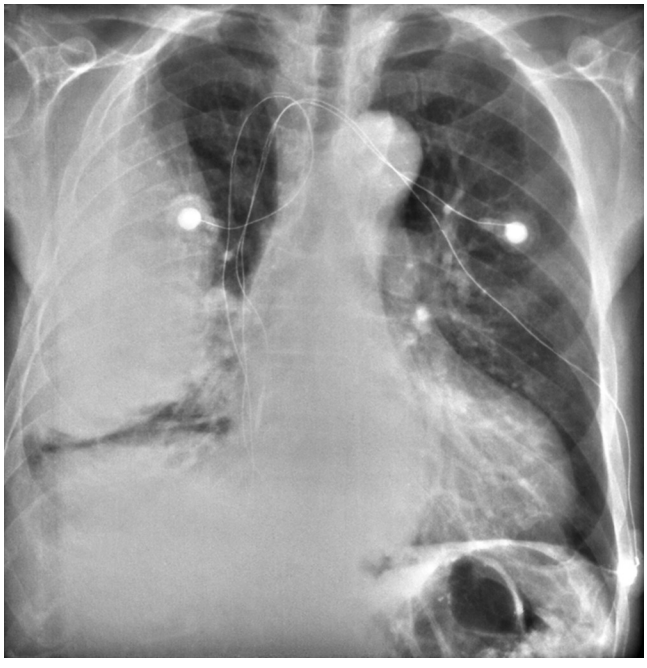

FIGURE 72-14. Loculated right-sided pleural effusion. Chest frontal view. A right-sided peripheral pleural mass is seen with characteristic obtuse angles of interface toward the chest wall, with tapered borders and sharp contour toward the lung. These findings localize the mass to the pleural or extrapleural compartment and not to the lung parenchyma. This loculated effusion proved to be an empyema.

FIGURE 72-15. Patient with known prior occupational asbestos exposure. Chest radiograph shows extensive bilateral calcified pleural plaques seen en face, in profile, and along the diaphragmatic contour.

Pleural Disease

Abnormalities of the pleural space (Chapter 86) can be displayed effectively by conventional radiographic methods supplemented by CT scanning. The volume of a pleural effusion (see Figs. 86-3 and 86-4 in Chapter 86) can be reliably estimated on standard frontal upright chest radiograph: 75 mL obscures the posterior costophrenic sulcus, 150 mL obscures the lateral costophrenic sulcus, 200 mL produces a rind of 1 cm in thickness on decubitus radiographs, 500 mL obscures the diaphragm and is visible on supine radiographs, and 1000-mL effusions reach the level of the fourth anterior rib on upright chest radiographs. An effusion of 200 mL or more can be sampled by thoracentesis. The smallest amount visible on decubitus radiographs is 10 mL. With care, as little as 175 mL of effusion can be detected on supine images. Free-layering pleural effusions produce a veil of opacity or filter effect superimposed on the aerated lung; pulmonary vessels are clearly visible through the added opacity generated by the effusion, and air bronchograms are absent.

Subpulmonic and Loculated Pleural Effusions

Subpulmonic pleural effusions elevate the lung base, mimicking a high-riding hemidiaphragm. The highest curvature point of the pseudodiaphragm is shifted laterally with an abrupt lateral descent, the so-called Rock of Gibraltar sign; it also can be seen in the lateral projection (Fig. 72-13). Large pleural effusions can lead to diaphragmatic inversion. Separation of the lung base from the gas-containing stomach is indicative of a subpulmonic effusion, particularly when the stomach gas bubble is displaced inferomedially.

Loculated pleural effusions suggest the presence of pleural adhesions or indicate an underlying parenchymal lung abnormality with a focal decrease in adjacent pleural pressure. Such encapsulated collections have obtuse angles of interface with the chest wall, tapered borders that are incomplete toward the chest wall, and a sharply defined contour with the adjacent lung (Fig. 72-14).

Pleural Plaques

Pleural plaques result from parietal pleural accumulation of hyalinized collagen fibers (Fig. 72-15); their presence suggests asbestos exposure (Chapter 81). Plaques preferentially involve the parietal pleura adjacent to ribs six through nine and the diaphragm. They are less pronounced in the intercostal spaces and spare the costophrenic sulci as well as the apices. Calcifications are visible on chest radiographs in 20% and on CT scans in 50% of individuals with pleural plaques. Imaged in

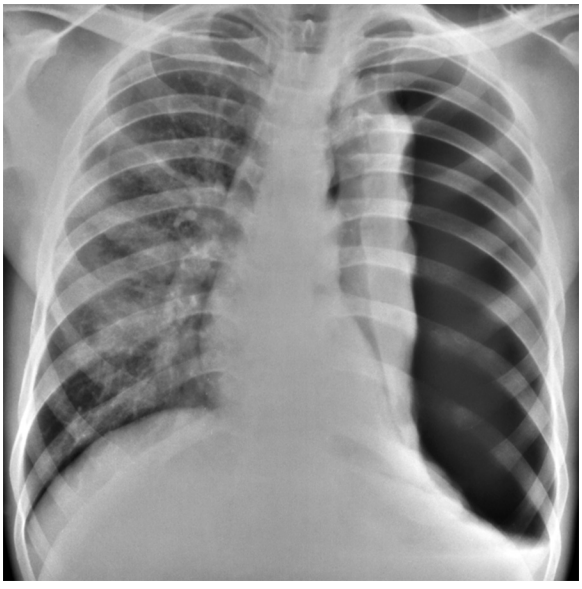

FIGURE 72-16. Patient with spontaneous tension hydropneumothorax. Chest radiograph shows complete atelectasis of the left lung with a large pneumothorax and a left basal gas-liquid level. The patient had primary tuberculosis.

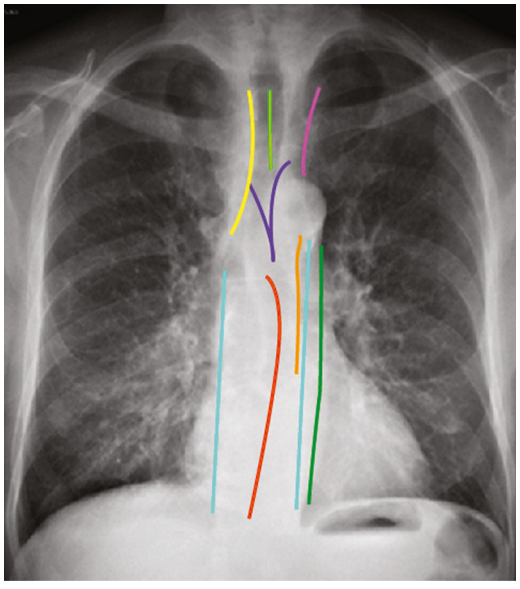

FIGURE 72-17. Chest radiograph with superimposed mediastinal stripes. *Yellow:* Right paratracheal stripe. *Light blue:* Right and left paraspinal stripes. *Red:* Azygoesophageal stripe. *Brown:* Pleuroesophageal stripe. *Purple:* Anterior junction line complex. *Pink:* Left subclavian artery border. *Light green:* Posterior-superior junction line. *Dark green:* Para-aortic line.

TABLE 72-7 CLASSIFICATION OF MEDIASTINAL COMPARTMENTS

ANTERIOR MEDIASTINUM
Retrosternal: Prevascular compartment
MIDDLE MEDIASTINUM: VISCERAL COMPARTMENT
Subcarinal space Paratracheal region Retrotracheal space Aortopulmonic window Retrocardiac space
POSTERIOR MEDIASTINUM: PARAVERTEBRAL COMPARTMENT
Paraspinal region

profile, pleural plaques produce focal areas of apparent pleural thickening. Over the diaphragm, they appear as curvilinear calcifications or scalloping. Pleural plaques viewed en face can simulate lung disease. Their appearance has been likened to holly leaves, sunburst patterns, or geographic patterns and, when calcified, to a dripping candle, rolled margins, or stippled or irregular structures. Rare visceral pleural plaques that occur in interlobar fissures can mimic pulmonary nodules.

Diffuse Pleural Thickening

Diffuse thickening of the parietal and visceral pleurae is a response observed after exposure to any of a number of stimuli, including infection, inflammation, trauma, tumor, thromboembolism, radiation, and asbestos. Severe involvement results in formation of a generalized pleural peel with smooth margins, usually less than 2 cm in thickness. Radiologically diffuse pleural thickening is characterized by a smooth, noninterrupted pleural opacity involving at least one fourth of the chest wall circumference, obliterating the costophrenic sulci and encompassing also the apices. The CT criteria for diffuse pleural thickening include a thickness of at least 3 mm.

Pleural Tumors

Malignant tumors of the pleura are more common than benign ones, and metastatic disease is more frequent than primary pleural mesothelioma. Primary tumors originate from pleural membranes. Pleural invasion by lung cancer, subpleural plaques in lymphoma, hematogenous dissemination to the pleura, and direct pleural seeding are other mechanisms of pleural involvement by tumor. Benign pleural tumors include lipomas, fibrous tumors, and neurogenic tumors. Lipomas are most common; their diagnosis is facilitated by CT scanning. Fibrous tumors of the pleura originate from pluripotent mesenchymal cells found in the visceral pleura or, less commonly, in the parietal pleura. Fibrous tumors can induce paraneoplastic syndromes, such as hypertrophic osteoarthropathy (Chapter 164) or hypoglycemia (Doege-Potter syndrome), but they rarely invade or metastasize. In nearly half of affected patients, the tumor can be on a pedicle and be mobile as a patient changes position. Torsion of this pedicle can, on rare occasions, lead to tumor necrosis with accumulation of gas in the mass. Post-traumatic splenosis can lead to multiple pleural masses, particularly in the left hemithorax.

Pneumothorax

Pneumothorax, which means gas in the pleural space (Chapter 86), can be open or closed. An open pneumothorax results when a penetrating injury of the chest wall allows atmospheric air to enter the pleural space, whereas a closed pneumothorax is the accumulation of air that originated in the respiratory system within the pleural space. A closed pneumothorax can be simple, where the air pressure within the pneumothorax is similar to that in the adjacent alveolar space, or under tension, where the air pressure within the pneumothorax is substantially above the air pressure in the adjacent alveolar space and can compress lung tissue and great vessels (Chapter 86). The most important radiologic feature of a pneumothorax is a visceral pleural line or edge that is convex or straight toward the chest wall and produces a lucent separation of the visceral and parietal pleura (Fig. 72-16). In most cases, no pulmonary vascular structures are visible beyond the visceral pleura. On upright chest radiographs, gas is primarily found in the apicolateral pleural space. Expiratory chest radiographs are not necessary for the detection of small pneumothoraces because all pneumothoraces are visible on inspiratory studies. On supine chest radiographs, pleural gas accumulates in a subpulmonic location; it outlines the costophrenic sulcus, forming the deep sulcus sign. A tension pneumothorax leads to a marked shift of the mediastinum to the contralateral side and to flattening or inversion of the ipsilateral hemidiaphragm. In supine patients with a hydropneumothorax, a veil of opacity can be seen with a gradient of decreasing attenuation toward the apex of the affected hemithorax. Post-traumatic, open pneumothorax can lead to mediastinal flutter with wide respiratory excursions. After evacuation of a pneumothorax, unilateral pulmonary edema can occur in the re-expanded lung (E-Fig. 72-10).

IMAGING OF THE MEDIASTINUM

The mediastinum encompasses midline thoracic structures that are delineated by mediastinal pleura, the diaphragm, the sternum, the spine, and the thoracic inlet. The mediastinum is commonly divided into an anterior prevascular compartment, a visceral middle compartment, and a paraspinal, posterior mediastinal compartment (Table 72-7). Each compartment contains specific pathologic entities.

IMAGING TECHNIQUES

On well-penetrated chest radiographs, the anterior junction line, the posterior-superior junction line, the azygoesophageal stripe, the pleuroesophageal stripe, the paratracheal stripe, and the para-aortic and the paraspinal stripes or lines should be assessed (Fig. 72-17). Mediastinal masses need to be detected and

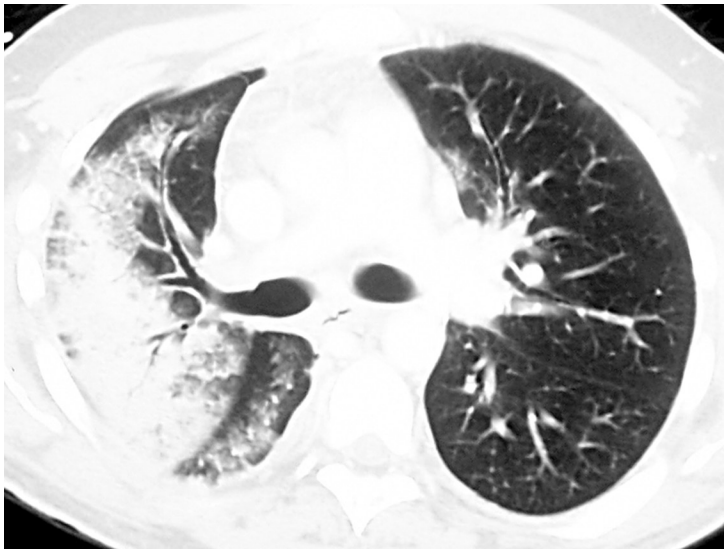

E-FIGURE 72-10. Unilateral reexpansion pulmonary edema after evacuation of right pneumothorax. Computed tomographic scan shows unilateral right-sided consolidation.

FIGURE 72-18. Mediastinal findings on chest radiographs. A, Patient with anterior mediastinal teratoma. Chest radiograph shows a mediastinal contour abnormality due to projection of the mass into the right hemithorax. Note the obtuse angle of interface formed by the pleura covering the mass with the mediastinum. The right descending pulmonary artery is visible through the mass, thereby proving that the mass is mediastinal and not hilar. This finding is called the hilum overlay sign. **B**, Patient with Castleman giant lymph node hyperplasia. Chest frontal radiograph shows large subcarinal middle mediastinal mass that projects lateral to the right atrium. **C**, Patient with paraspinal ganglioneuroma. Chest radiograph shows right lower paraspinal contour abnormality widening the right paraspinal region and encompassing the height of three thoracic vertebrae.

localized first. Their obtuse angles of interface with the mediastinal pleura, incomplete border toward the mediastinum, sharp contour toward the lung, and extension into both hemithoraces indicate the mediastinal origin of such lesions.

CT facilitates localization of a mass to a specific mediastinal compartment. When it is known whether the mass is predominantly fatty or cystic, contains soft tissue, or is calcified, the differential diagnosis can be limited. MRI of the mediastinum has a role in diagnosis of vertebral disease or neurogenic tumors with extension into the spinal canal. It is equivalent to CT in diagnosis of aortic aneurysms and dissections (Chapter 63).

MEDIASTINAL COMPARTMENTS

The anterior mediastinum or prevascular compartment is actually a potential space that may contain the fatty replaced thymus and small normal lymph nodes. Space-occupying lesions in this compartment typically include thymomas, lymphomas, teratomas, and other germ cell tumors; substernal thyroid goiters; lipomas; and other connective tissue tumors, as well as hemangiomas or lymphangiomas (Fig. 72-18).

The middle mediastinum or visceral compartment is subdivided into the subcarinal space, paratracheal region, retrotracheal region, aortopulmonic window region, cardiac space, and retrocardiac space. Characteristic lesions are enlarged lymph nodes and bronchopulmonary foregut malformations (see Fig. 72-18B).

In the retrotracheal region, aberrant right subclavian arteries, posterior descending goiters, esophageal tumors, diverticula, or thoracic duct cysts can be found. In the aortopulmonic window, enlarged lymph nodes, ductus diverticula, bronchopulmonary foregut malformations, and aortic or pulmonic artery aneurysms can form compartment-specific space-occupying lesions. Pericardial cysts, pericardial tumors, and cardiac masses are the common space-occupying lesions in the cardiac space. Hiatal hernias are common masses in the retrocardiac region.

The paraspinal region or paravertebral compartment is considered radiologically to belong to the posterior mediastinum. Important masses in that space include neurogenic tumors that originate from the sympathetic chain or from segmental nerve roots (see Fig. 72-18C). Extramedullary hematopoiesis in patients with severe anemia can result in paravertebral masses formed by hypertrophied bone marrow that extrudes from ribs or vertebral bodies. Enlarged lymph nodes due to lymphoma or metastatic disease are occasionally seen in a paraspinal location. Vertebral disease, including bacterial or tuberculous spondylitis, tumors, and post-traumatic hematomas, can widen the paraspinal region and produce contour abnormalities.

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73 RESPIRATORY TESTING AND FUNCTION

PAUL D. SCANLON AND ALEXANDER S. NIVEN

Pulmonary function testing has been used in the medical evaluation of patients with respiratory issues since Hutchinson's 1846 demonstration that vital capacity, the largest volume of air that can be exhaled, is an important measure of health. Lung function is one of the most important predictors of all-cause mortality. Environmental exposures, especially exposure to tobacco smoke, and diseases affect pulmonary function, as do genetic and socioeconomic factors, especially during periods of lung growth. Pulmonary function is central to our understanding of pulmonary disorders; many are classified as "obstructive" or "restrictive" disorders in acknowledgement of their pulmonary function pattern. Change or stability of pulmonary function is a key outcome in many clinical trials of respiratory medications.

Pulmonary function can also be an important outcome after an acute respiratory infection. For example, about 70% of survivors of moderate to severe, but not critical, coronavirus-2019 (COVID-19; Chapter 336) pneumonia have pulmonary diffusion abnormalities on pulmonary function testing 6 weeks after discharge, about 25% have obstructive findings, and about 20% have restrictive findings.[1]

Measures of lung function include assessments of respiratory mechanics, for example, the volume of gas that is contained by the lung in various circumstances, the inspiratory and expiratory flow rates across the vital capacity, the pressures that can be generated by inspiratory and expiratory efforts, and the resistance to airflow, as well as calculations of gas exchange. Exertional symptoms often correlate poorly with resting physiologic measurements, and cardiopulmonary exercise testing can be a valuable tool to measure the degree of functional impairment.[2] The analysis of bronchoalveolar lavage fluid, obtained by bronchoscopy, can also provide important insights into pulmonary disease.

SPIROMETRY

The simplest, most commonly performed pulmonary function test is spirometry (Table 73-1).[3,4] This test measures the forced vital capacity (FVC), which is the amount of air that can be forcefully expelled from the lungs, beginning at maximal inhalation (termed total lung capacity [TLC]) and ending with the lungs emptied to their minimal volume (residual volume [RV]). Many secondary measures are derived from the FVC maneuver, including volume exhaled in a given time, termed the forced expiratory volume (FEV), with a subscript indicating the number of seconds during which this measurement is made (e.g., FEV_1, FEV_3). The ratio of the FEV_1/FVC is the proportion of the total vital capacity that can be expelled in the first second of a maximal expiratory effort; a low (<70%) FEV_1/FVC ratio (below the predicted lower limit of normal) indicates obstructive lung disease. In patients with asthma (Chapter 75), the FEV_1 and FEV_1/FVC ratio will often vary based on the degree of airway inflammation. By comparison, a fixed low ratio is consistent with chronic obstructive pulmonary disease (COPD; see Chapter 76) and is associated with an increased risk for future hospitalization or mortality.[5] In addition, expiratory flow can be measured at specific portions of exhaled vital capacity, termed forced expiratory flow (FEF), followed by a number to represent the percentage of the FVC at which the flow was measured (e.g., FEF_{75}, FEF_{50}, FEF_{25}). Expiratory flow can also be measured over a volume range (e.g., FEF_{25-75}). With appropriate coaching and modest patient effort, spirometry results are reproducible between test sessions, thereby allowing comparisons over time.

The data from a maximal exhalation can be displayed using a spirogram (volume-time tracing) or a flow-volume curve (Fig. 73-1A), which depicts exhaled flow at any given volume as a function of exhaled volume. The flow-volume curve has a unique shape for any individual at any given time. It can reflect airflow obstruction (Fig. 73-1B and C), such as is seen in asthma (Chapter 75) and chronic obstructive lung disease (COPD; Chapter 76), or lung restriction (Fig. 73-1D and E), such as is seen in many interstitial lung diseases (Chapter 80). A restrictive disorder may be indicated by a decreased FEV_1 and FVC but a preserved or even an increased FEV_1/FVC ratio. It also may demonstrate less common abnormalities, including variable extrathoracic (Fig. 73-1F) or intrathoracic (Fig. 73-1G) obstruction, fixed central airway obstruction (Fig. 73-1H), or severe muscle weakness (Chapter 74; Fig. 73-1I).

The FVC, FEV_1, FEV_1/FVC ratio, and shape of the flow-volume curves are highly reproducible measures of lung function if the tested individual makes an expiratory effort above a certain, easy-to-obtain level in a pulmonary function laboratory with modern spirometry equipment and trained staff. In the absence of quality assurance, however, measurements of lung function are often neither accurate nor reproducible; poor-quality pulmonary function testing results are biased to lower values, thereby giving an incorrect impression of disease where none may exist. In many but not all cases, poor performance can be identified from inspection of the flow-volume curve (Fig. 73-1L).[6] Poor performance should be noted by the interpreter to avoid erroneous diagnoses.

Spirometry is recommended for the diagnosis of respiratory symptoms, for monitoring lung function in response to a therapeutic intervention or potentially harmful drug exposure, for objective quantification of physiologic impairment, for disability evaluations, and for preemployment and lung health monitoring for at-risk occupations. Use of spirometry as a screening test for asymptomatic persons thought to be at risk for development of lung disease, such as current or former smokers, should be used with caution. Unfortunately, an abnormal spirometry result has not been shown to improve the likelihood that such at-risk individuals will quit smoking, and a normal screening spirometry test result might be misinterpreted to indicate that an individual may continue smoking without risk.

Spirometry is often performed before and after administration of an inhaled bronchodilator, either a selective β_2-agonist (e.g., albuterol/salbutamol), a muscarinic antagonist (e.g., ipratropium), or both, especially if it shows changes consistent with airflow obstruction. The degree of improvement after administration of a bronchodilator indicates the degree of airflow responsiveness, which is generally more in asthma (Chapter 75) and less in COPD (Chapter 76). Unfortunately, the measured response to a bronchodilator on spirometry varies with the dose of drug used in the test, is poorly repeatable from test to test, and is not a good predictor of the clinical response to bronchodilator therapy in an individual patient.

TABLE 73-1 PULMONARY FUNCTION TESTS

LUNG VOLUMES	
TLC	Total lung capacity (volume of gas in lungs at the end of maximal inspiration)
FRC	Functional residual capacity (volume of gas in the lungs at relaxation, when the inward pull of lungs is balanced by the outward pull of the relaxed chest wall)
RV	Residual volume (FRC – ERV, volume of gas left in lungs after maximal exhalation)
IC	Inspiratory capacity (volume of gas inspired from FRC to TLC)
EXPIRATORY FLOW	
FEV_1	Forced expiratory volume (in 1 second)
FVC	Forced vital capacity
FEV_1/FVC	FEV_1/FVC ratio (can be expressed as a ratio or as a percentage)
DIFFUSING CAPACITY	
D_{LCO}	Diffusing capacity of lungs for carbon monoxide
ARTERIAL BLOOD GASES	
Pa_{O_2}	Partial pressure of oxygen in arterial blood
Pa_{CO_2}	Partial pressure of carbon dioxide in arterial blood
pH	Negative log of hydrogen ion concentration in a solution

OTHER TESTS OF VENTILATION

Maximal voluntary ventilation (MVV) is an indication of the maximal ventilation a patient can perform, expressed in liters per minute. MVV estimates a person's upper limit of ventilatory capacity. Reductions in MVV may be due to central airway obstruction, muscle weakness, or poor performance. Because MVV is effort dependent, it may be a better predictor of postoperative respiratory complications (Chapter 401) than is FEV_1. Concomitant measurement of inspiratory flows can be useful for patients in whom there is a suspicion of upper airway disease, such as a patient who has stridor or a patient whose MVV is reduced out of proportion to the FEV_1.

ABSTRACT

Pulmonary function testing (PFT) is essential to the evaluation and treatment of many disorders of the respiratory system, and is central to the definition of obstructive and restrictive disorders. This chapter briefly summarizes methods for lung function testing, well-illustrated with "real" flow volume curves and guided by a detailed algorithm. Bronchoalveolar lavage is also succinctly reviewed. Supplementary online materials include a more complete discussion of complex pulmonary function disorders (mixed, nonspecific, and complex restrictive), the effects of obesity on PFTs, and a series of review questions.

KEYWORDS

pulmonary function testing
cardiopulmonary exercise testing
bronchoalveolar lavage
interpretation
obstruction
restriction
nonspecific pattern
complex restriction

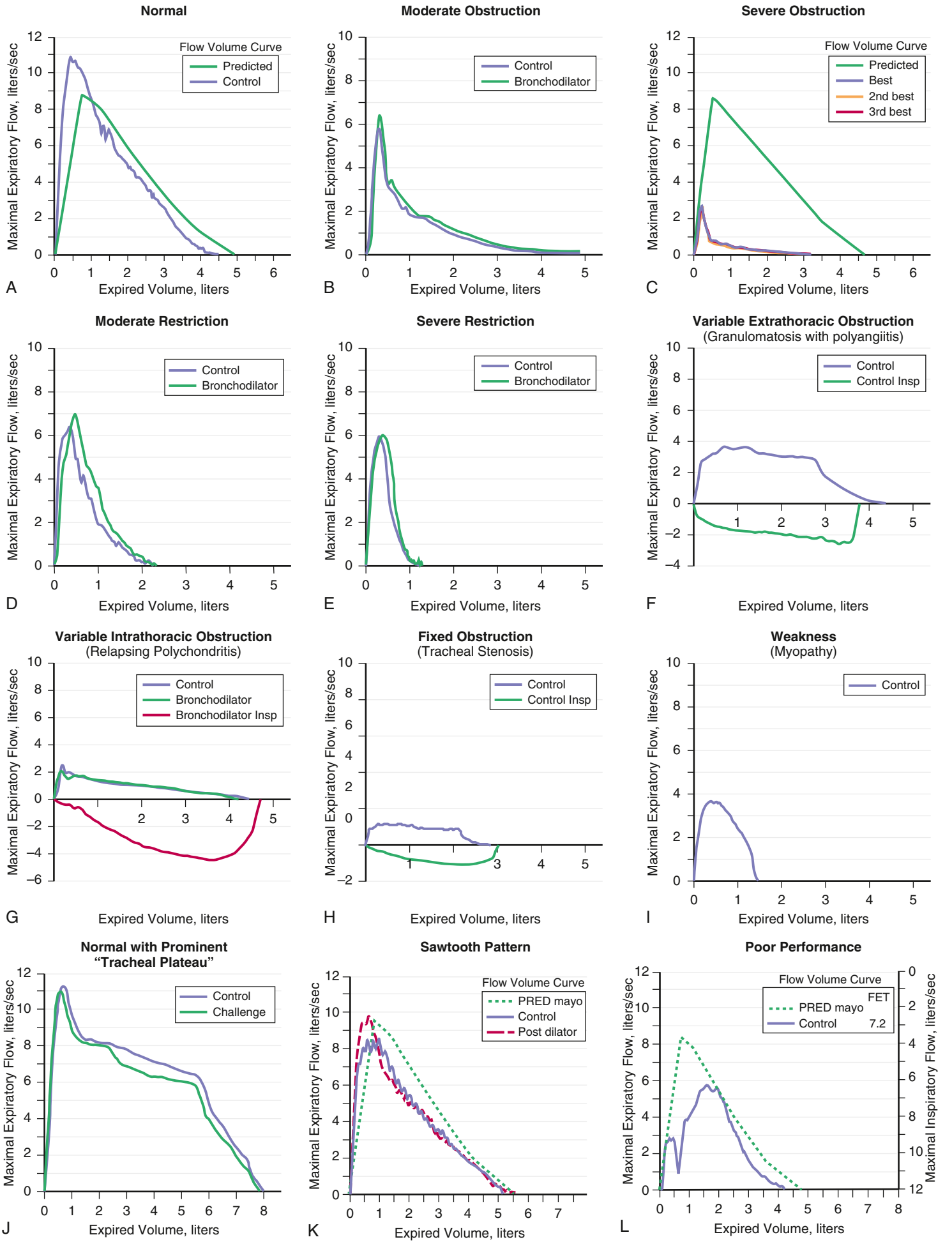

FIGURE 73-1. **Common patterns of flow-volume curve. A**, Normal. **B**, Moderate obstruction. **C**, Severe obstruction. **D**, Moderate restriction. **E**, Severe restriction. **F**, Variable extrathoracic obstruction (granulomatosis with polyangiitis). **G**, Variable intrathoracic obstruction (relapsing polychondritis). **H**, Fixed obstruction (tracheal stenosis). **I**, Weak effort (myopathy). **J**, Normal but with a prominent tracheal plateau. **K**, Sawtooth curve associated with obstructive sleep apnea. **L**, Poor-quality maneuver with both delay in peak flow and cough within the first second. Challenge = methacholine challenge; Control = patient's baseline performance; Insp = inspiration.

REFERENCE EQUATIONS

Normal lung size varies from person to person as a function of height, age, sex, and a wide variety of environmental and socioeconomic factors that impact lung development and function over time. Differences historically attributed to ethnic origin have been replaced by race-neutral equations.[7,8] Therefore, values obtained from pulmonary function testing are compared with those of normal individuals with similar characteristics. Results are expressed as a percentage of a reference value calculated with those factors.

LUNG VOLUMES

The volume of air in the lung at any given time can be partitioned (Fig. 73-2). The air that remains in the lung after a maximal expiratory effort is the residual volume. The difference between functional residual capacity (FRC) and residual volume is the expiratory reserve volume (ERV). The volume exhaled in a normal breath is the tidal volume (TV). The volume that can be inhaled above tidal volume is the inspiratory reserve volume (IRV).

A series of *capacities* consist of the sum of two or more different volumes. FRC, which is the sum of expiratory reserve volume plus residual volume, represents the resting level at which the opposing forces of lung and chest wall elastic recoil are equal in the absence of volitional inspiratory or expiratory efforts. Inspiratory capacity (IC) is the sum of tidal volume plus inspiratory reserve volume. A low IC is strongly associated with chronic dyspnea, reduced exercise capacity, and increased mortality in patients with COPD. Vital capacity (VC) is the sum of tidal volume plus inspiratory reserve volume plus expiratory reserve volume. Total lung capacity is the sum of residual volume plus expiratory reserve volume plus tidal volume plus inspiratory reserve volume.

Three volumes (tidal volume, inspiratory reserve volume, expiratory reserve volume) can be measured with a spirometer. Measurement of residual volume or any of the capacities that include it (so-called *absolute lung volumes*) requires more sophisticated methods, such as body plethysmography, the inert gas dilution technique, or the nitrogen washout technique.

BODY PLETHYSMOGRAPHY

Body plethysmography, the preferred method for measuring lung volumes, is based on Boyle's law: at a given temperature, the product of the pressure and volume of a quantity of gas at one time will be equal to the product of the pressure and volume of the gas at another time ($P1 \times V1 = P2 \times V2$). The body plethysmograph, which is a sealed box in which the patient sits, measures FRC while the patient pants against a closed shutter to compress and to rarify gas in the chest. During panting, the pressure measured at the mouth represents the pressure changes within the lung during these volume changes. A similar panting maneuver with the shutter open is used to calculate airway resistance, which is another method used to measure airway function Although body plethysmography is generally the most accurate method for measurement of lung volumes, particularly in patients with airway obstruction, it can overestimate lung volumes if panting is too rapid. A plethysmographic total lung capacity greater than 150% of the reference value should be viewed with suspicion.

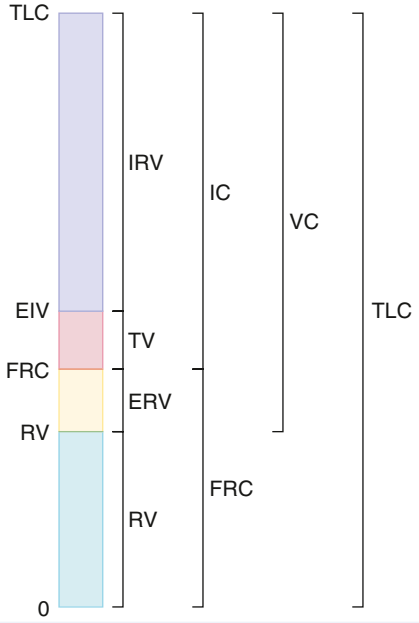

FIGURE 73-2. A schematic diagram showing lung volume partitions as measured in lung function tests. EIV = end-inspiratory volume; ERV = expiratory reserve volume; FRC = functional residual capacity; IC = inspiratory capacity; IRV = inspiratory reserve volume; RV = residual volume; TLC = total lung capacity; TV = tidal volume; VC = vital capacity.

INERT GAS DILUTION TECHNIQUE

Lung volumes also can be measured by having the patient breathe from a device containing a known volume and concentration of an inert gas (e.g., helium, neon, argon, or methane), which does not react with elements in the blood or tissues, until equilibrium is achieved. The final concentration of inert gas equals the initial inert gas concentration times the initial gas volume of the device divided by the final volume of the lungs plus the device, adjusting for oxygen consumption and carbon dioxide production during the test. This equation can be solved for lung volume. This method underestimates lung volumes when portions of the lung communicate poorly with the central airways, particularly in patients who have severe obstructive lung disease and emphysematous bullae.

NITROGEN WASHOUT TECHNIQUE

The air that we breathe consists of approximately 21% oxygen, 1% argon, 0.04% carbon dioxide, and a variable amount of water vapor. The remainder is nitrogen. Exhaled air contains a lower concentration of oxygen, usually 14 to 16%, plus 3 to 5% carbon dioxide and water. For the nitrogen washout technique, the individual being tested inhales 100% oxygen beginning at FRC. As the subject breathes, exhaled gas is collected until the concentration of nitrogen reaches a plateau. Knowing that the initial concentration of exhaled nitrogen is approximately 75% and measuring the final concentration and volume of gases collected, the initial volume of gas in the lungs at FRC can be calculated. As with the inert gas dilution technique, this method also underestimates lung volumes in patients with poorly communicating air spaces.

Absolute lung volumes, as determined by body plethysmography, inert gas dilution, or nitrogen washout, can refine the spirometric evaluation of both obstructive and restrictive disorders. In obstructive disorders, air trapping or hyperinflation can be inferred when a residual volume, total lung capacity, or residual volume/total lung capacity (RV/TLC) ratio is above the upper limit of normal.[9] However, in patients who have chest wall limitations or neuromuscular weakness, residual volume may be increased—not because of true airway trapping, but because of limitation to expiratory chest wall movement, so the term *air trapping* should be used with caution.

A restrictive disorder can be inferred from a spirometry pattern that shows a reduced FVC with a normal or increased FEV_1/FVC ratio. To confirm the presence of true restriction, lung volumes are required to demonstrate a TLC less than the lower limit of normal. If TLC is normal, these findings are called a nonspecific pattern (see online supplement).

DIFFUSING CAPACITY

The single-breath diffusing capacity for carbon monoxide (DLCO, also referred to as transfer factor or TLCO) measures the capacity of the lungs to exchange gas.[10] The maneuver for measurement of DLCO requires breathing out to residual volume and then quickly inhaling a mixture of known concentrations of an inert gas (e.g., helium or methane) and of carbon monoxide. After inhaling to total lung capacity, patients hold their breath for 10 seconds. During this time, the tracer gases mix with other gases occupying the lungs, and a portion of the carbon monoxide diffuses across the alveolar-capillary membrane and binds to hemoglobin with strong affinity. After the 10-second breath-hold, the remaining gas mixture is exhaled. The concentration of inert gas is used to calculate the volume of the lungs (alveolar volume); the concentration of carbon monoxide is used to calculate the absorption of carbon monoxide, expressed in volume per minute per unit of pressure (mL/min per mm Hg).

A normal value for DLCO indicates relatively normal gas exchange, which requires a normal pulmonary gas-exchange surface, normal capillary blood volume, and relatively homogeneous ventilation-perfusion relationships. A low DLCO is indicative of impaired gas exchange. Among patients with obstructive disorders (Chapters 75 and 76), impaired gas exchange occurs most commonly in patients with COPD as opposed to asthma. In restrictive disorders, impaired gas exchange is seen most commonly in patients with interstitial disease rather than patients with chest wall disorders. Patients with pulmonary vascular disorders typically have a low DLCO and may have restriction or normal lung mechanics (Chapter 80). An isolated reduction in DLCO (i.e., in association with normal total lung capacity, vital capacity, and FEV_1) can indicate a pulmonary vascular disorder, but is more commonly seen in association with emphysema (Chapter 76), interstitial disease (Chapter 80), or a combination of the two.

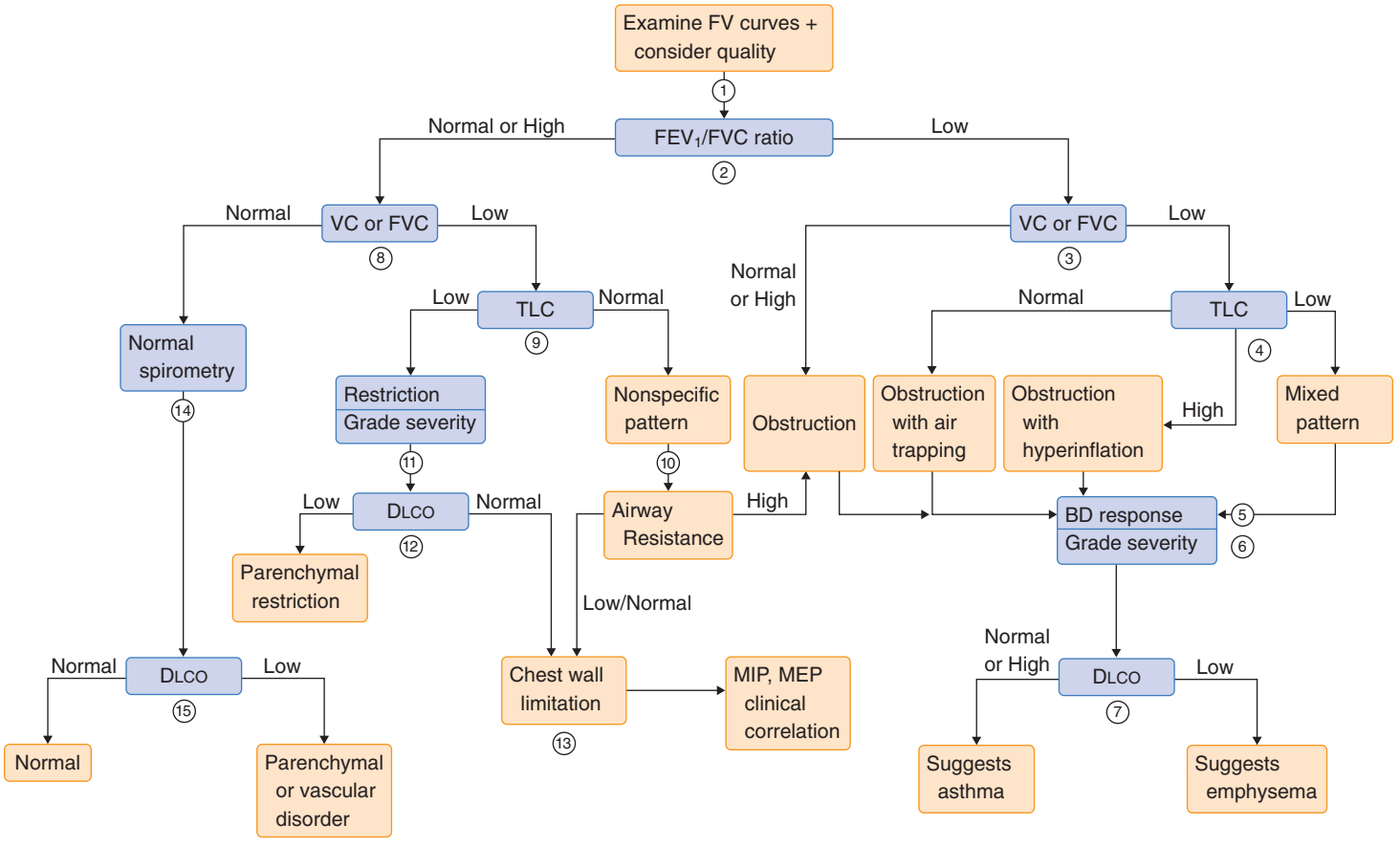

FIGURE 73-3. An algorithm for interpreting pulmonary function tests in which spirometry, lung volumes, and D_{LCO} are measured. If only spirometry is available, interpretation is more limited. The legend keys refer to numbered branch points in the algorithm. BD = bronchodilator; D_{LCO} = diffusing capacity of the lung for carbon monoxide; FEV_1 = forced expiratory volume in one second; FVC = forced vital capacity; MEP = maximal expiratory pressure; MIP = maximal inspiratory pressure; TLC = total lung capacity; VC = vital capacity.

1. Inspect the data and flow-volume (FV) curve to assess test quality and then consider the basic type of abnormality (e.g., obstruction vs. restriction).
2. A reduced FEV_1/FVC ratio suggests obstruction, and the obstruction algorithm on the right side should be followed. If the FEV_1/FVC ratio is normal or high, the restriction side (left side) of the algorithm should be followed.
3. If FEV_1/FVC is low and the VC or FVC is normal or high, simple obstruction is present. If VC or FVC is low, TLC should be measured.
4. If TLC is normal, simple obstruction is present. If TLC is high, obstruction with hyperinflation is present. If TLC is low, a mixed obstructive/restrictive pattern is present. (Note that the inert gas dilution and nitrogen washout methods commonly underestimate TLC in the presence of obstruction and can give a false impression of a mixed disorder.)
5. Bronchodilator responsiveness (BD) may be assessed to determine whether the change in FEV_1 or FVC is significant (i.e., a ≥12% improvement and at least a 200 mL absolute increase) and to determine the degree of positivity.
6. The severity of obstruction should be graded based on the FEV_1 percentage predicted. Some algorithms grade severity based on post-bronchodilator values.
7. In current or former smokers with obstruction, a low D_{LCO} suggests emphysema or other pulmonary parenchymal or vascular disorders. A normal D_{LCO} may suggest asthma or chronic bronchitis.
8. If FEV_1/FVC is normal or high, the restriction (left) side of the algorithm is followed. If VC or FVC is normal, spirometry is generally normal (occasional patients have an isolated abnormality of FEV_1 of uncertain significance). If VC or FVC is low, TLC should be checked.
9. If TLC is low, a restrictive disorder is present. If TLC is normal, the "nonspecific pattern" is present.
10. If the nonspecific pattern is identified, airway resistance (Raw) can be measured. An increased Raw suggests obstruction. A normal Raw suggests an alternative cause (see #13).
11. If true restriction is present, grade severity on the basis of the reduction in TLC percentage predicted.
12. If restriction is demonstrated, D_{LCO} should be measured next. If abnormal, it indicates a pulmonary parenchymal restrictive process. If normal, it suggests an extraparenchymal or nonpulmonary cause of restriction.
13. Restriction with a normal D_{LCO} or a nonspecific pattern with normal Raw suggests an alternative cause (chest wall limitation, weakness, heart failure, poor performance). Consider measurement of maximal respiratory pressures and review the study for test performance.
14. If spirometry is normal, lung volumes are rarely useful, but D_{LCO} is sometimes helpful.
15. If D_{LCO} is normal, gas exchange can be considered normal. An isolated reduction in D_{LCO} is seen most often in patients with emphysema, pulmonary fibrosis, or both. It less commonly indicates a pulmonary vascular disorder, such as primary pulmonary hypertension, or an obliterative vasculopathy, as is sometimes seen in systemic sclerosis.

An increased D_{LCO} is relatively uncommon and is most often seen in individuals with asthma (Chapter 75) or obesity (Chapter 201). It can also be seen in association with polycythemia (Chapter 152), left-to-right intracardiac shunt (Chapter 55), or acute pulmonary hemorrhage (Chapter 79). It can also be seen during or after exercise or when the patient is in the supine position.

MAXIMAL RESPIRATORY PRESSURES

Maximal respiratory pressures help identify muscle weakness, which can cause a restrictive disorder, a nonspecific pattern, or an isolated reduction in MVV relative to FEV_1. Maximal respiratory pressures do not distinguish muscle weakness from poor test performance (Fig. 73-3).

INTERPRETATION OF LUNG FUNCTION TESTS

Interpretation of pulmonary function tests uses the data obtained to infer a physiologic diagnosis and to categorize the nature and magnitude of the impairment of lung function (Table 73-2).[11] The four broad categories of physiologic abnormalities include obstructive disorders, such as asthma and COPD (Chapters 75 and 76); restrictive disorders of the lung, such as pulmonary fibrosis (Chapter 80) or restriction due to factors outside the lung, such as chest wall limitation due to obesity, pleural disease, or musculoskeletal disorders,[12] or weak chest wall (Chapter 86), such as Guillain-Barré syndrome (Chapter 388); and disorders resulting in impaired gas exchange, which are often associated with an obstructive or restrictive disorder, but in some cases can be found in patients who have normal mechanical function of the lungs, such as pulmonary embolism (Chapter 68). Some patients have mixed physiologic defects, such as a combined restrictive and obstructive defect (see Fig. 73-3), or more than one cause of restriction (e.g., pulmonary fibrosis plus obesity or heart failure).

Spirometry screening of the U.S. adult population shows evidence of airflow obstruction in about 13.5% of individuals and evidence of restriction in about 6.5%. Of individuals with spirometric evidence of restriction, about 50% have true restriction when lung volumes are measured, whereas the other 50% have a nonspecific pattern.

TABLE 73-2 COMMON CHANGES ASSOCIATED WITH PATTERNS OF LUNG FUNCTION ABNORMALITY

	FORCED EXPIRATORY VOLUME IN 1 SECOND (FEV_1)	FORCED VITAL CAPACITY (FVC)	FEV_1/FVC RATIO	RESIDUAL VOLUME	TOTAL LUNG CAPACITY	MAXIMAL RESPIRATORY PRESSURES
Normal	Normal*	Normal	Normal	Normal	Normal	Normal
Obstructive	↓	Normal to ↓	↓	↑ to ↑↑	Normal to ↑↑	Normal
Restrictive	↓	↓ to ↓↓	Normal or ↑	Normal or ↓	↓ to ↓↓	Normal
Weak chest wall	↓	↓ to ↓↓	Normal or ↑	↑	Normal or ↓	↓

*Normal or abnormal values are determined by comparing the measured values with those predicted from regression equations based on the patient's sex, age, height, and race. The normal range for FEV_1/FVC also varies, mainly with age, ranging from 0.70 to 0.80 among 25-year-olds to 0.63 to 0.68 among 65-year-olds.

The first step in interpretation of a set of pulmonary function measurements is to inspect the numeric data, the spirogram, and the flow-volume curve to assess the quality of the test. A poor-quality test result, whether it is due to poor performance by the patient or poor coaching by the technician, may have an irregular flow-volume curve (see Fig. 73-1L) or poor reproducibility of results from one effort to another. Once good quality is affirmed, the presence of an abnormal pattern (e.g., obstruction or restriction) can be determined. If so, attention then turns to assessing the severity, subtleties of the flow-volume curve, and other physiologic data (e.g., total lung capacity, residual volume, MVV, and D_{LCO}) that either support or supplement the initial impression.

The normal flow-volume curve is roughly triangular (see Fig. 73-1A). A *tracheal plateau*, which is a normal variant (see Fig. 73-1J) usually seen in younger subjects, is caused by normal flow limitation in the trachea in the absence of peripheral airway obstruction.

In obstructive diseases, the degree of pulmonary functional impairment can be classified on the basis of the FEV_1. Patients with obstructive disorders typically have a reduced FEV_1/FVC ratio and a flow-volume curve with a "scooped" appearance (see Fig. 73-1B and C). Atypical patients may have unusually shaped flow-volume curves or unusual patterns of obstruction (e.g., abnormal airway resistance despite a normally shaped flow-volume curve and normal FEV_1/FVC ratio). If a patient has what appears to be obstruction, the next step is to determine the degree to which the obstruction can be reversed by administration of a bronchodilator. Hyperinflation or air trapping can be identified by an increase in total lung capacity, residual volume, or the RV/TLC ratio. The adequacy of gas exchange can be assessed by measuring D_{LCO} and oximetry. For individuals with normal spirometry and alveolar volume (from the D_{LCO}), measurement of total lung capacity can be avoided to save unnecessary expense.

Patients with restrictive disorders have reduced lung volumes and typically have a flow-volume curve with a "witch's hat" shape—a tall peaked curve (see Figs. 73-1D and E). Restriction may be due to either reduced lung compliance or mechanical changes to the chest wall and tissues surrounding the lungs (e.g., obesity, muscle weakness, chest wall deformity, pregnancy, pleural effusion, or heart failure). For many restrictive diseases, the severity can be graded with use of the total lung capacity as a percentage of the predicted value, and changes in VC and TLC measured over time are helpful in predicting prognosis.

In patients with restriction caused by interstitial lung disease, the total lung capacity and the vital capacity or FVC are usually reduced by a similar proportion. In some patients with restriction, however, the total lung capacity and the vital capacity percentages of predicted values are quite different (>10% difference). The usual cause is the presence of more than one restrictive process, such as a parenchymal restrictive disorder plus obesity, respiratory muscle weakness, atelectasis, or occult obstruction.

Some patients have a mixed disorder with evidence of both obstruction and restriction. Common causes include cystic fibrosis (Chapter 77), sarcoidosis (Chapter 83), and heart failure (Chapters 45 and 46) as well as cases in which the causes of the obstructive disorder and the restrictive disorder are unrelated.

Disorders of the central airways can cause characteristic patterns of abnormality. In a "fixed airway obstruction" such as tracheal stenosis (see Fig. 73-1H), flows are typically reduced on both inspiration and expiration. In contrast, in a variable extrathoracic (upper) airway obstruction (see Fig. 73-1F), inspiratory flow is disproportionately reduced; expiration is often abnormal, but merely less so. Likewise, in variable intrathoracic obstruction (e.g., relapsing polychondritis, tracheomalacia, or a dynamic intrathoracic tracheal tumor), the expiratory flow-volume curve is reduced but often in a pattern unlike that seen in asthma or COPD (see Fig. 73-1G). These central airway obstructive patterns are often mistaken for COPD but may signify a localized, treatable cause of obstruction.

In patients with heart disease, a decline in FEV_1/FVC ratio is associated with underfilling of the left heart and low cardiac output. By comparison, a decline in FVC with preserved FEV_1/FVC ratio is associated with left ventricular hypertrophy and diastolic dysfunction.

PROVOCATIVE TESTING

ASSESSING AIRWAY RESPONSIVENESS

Hyperresponsiveness of airways to the smooth muscle–contracting effect of pharmacologic agents (such as methacholine, mannitol, hypertonic saline), cold air, dry air, and other physical stimuli is characteristic of asthma (Chapter 75). Hyperresponsiveness is also less commonly observed in COPD and other obstructive airway diseases. Bronchoprovocation studies, in which graded doses of a stimulus are used to elicit airway constriction, are performed to measure airway responsiveness. A responsive airway (i.e., one in which a small stimulus leads to a fall in FEV_1 to 15 to 20% below starting values) may be used to confirm the diagnosis of asthma (Chapter 75). Fractional concentration of exhaled nitric oxide (F_{ENO}), which is a marker of eosinophilic airway inflammation, also can be used to predict the likelihood that airflow obstruction will improve with corticosteroid treatment.

CARDIOPULMONARY EXERCISE TESTS

Some patients have dyspnea (Chapter 71) or exercise limitation that is not adequately explained by the clinical examination, standard pulmonary function testing, and chest imaging. For such patients, laboratory testing of physiologic performance during exercise can be enlightening.

Cardiopulmonary exercise testing, which is usually performed on a cycle ergometer or treadmill, includes monitoring of the heart rate, electrocardiography, and pulse oximetry as well as breath-by-breath measurement of tidal volume, breathing rate, oxygen consumption, and carbon dioxide production. Optional measurements include but are not limited to arterial blood gases and noninvasive cardiac output. Outcomes include peak oxygen uptake, maximal workload, maximal heart rate, ventilation parameters during exercise, and measurements of gas exchange. Results are analyzed to determine if anaerobic metabolism occurs when the study subject reaches maximal effort and to determine what limits the ability of a patient to exercise—a gas exchange abnormality, ventilatory limitation, cardiac limitation, or deconditioning.

Simple tests of exercise performance, such as the 6-minute walk test, can quantify and serially assess exercise performance. This test measures the maximum distance that a patient can walk at their own pace in an indoor corridor 30 meters long during a 6-minute interval. The result, which provides a global assessment of functional capacity, is commonly used to monitor responses to therapeutic interventions and pulmonary rehabilitation in patients with significant functional impairment. The 6-minute walk test also has prognostic significance in cardiac and pulmonary diseases.[13]

BRONCHOALVEOLAR LAVAGE

Bronchoalveolar lavage is most commonly used to diagnose opportunistic infections in immunocompromised hosts (Chapter 260), ventilator-associated pneumonia (Chapters 85 and 261), diffuse alveolar hemorrhage (Chapter 79), atypical pulmonary infections in immunocompetent individuals, or peripheral malignancies. Bronchoalveolar lavage also can be useful in patients with acute

respiratory failure,[14] but its utility in the evaluation of interstitial lung disease (Chapter 80) is less clear.[15]

The differential cell count on a normal bronchoalveolar lavage specimen includes 85% macrophages or more, 10 to 15% lymphocytes, 3% neutrophils or less, 1% eosinophils or less, 1% mast cells or less, and less than 5% squamous epithelial cells (which are an indicator of contamination from the upper airway). Individuals who smoke may have higher cell counts and a higher percentage of neutrophils. Increased lymphocyte counts are seen in sarcoidosis (Chapter 83), hypersensitivity pneumonitis (Chapter 82), nonspecific interstitial pneumonitis (Chapter 80), collagen vascular diseases (Chapter 80), radiation pneumonitis (Chapter 82), cryptogenic organizing pneumonia (Chapter 80), and lymphoproliferative disorders. Increased neutrophil counts are seen in idiopathic pulmonary fibrosis (Chapter 80), collagen vascular diseases (Chapter 80), infectious pneumonia (Chapter 85), aspiration pneumonia (Chapter 85), acute respiratory distress syndrome (Chapter 90), diffuse alveolar damage (Chapter 79), acute interstitial pneumonia (Chapter 80), and asbestosis (Chapter 81). Increased eosinophils can be seen in asthma (Chapter 75), bronchitis (Chapter 84), allergic bronchopulmonary aspergillosis (Chapter 311), eosinophilic granulomatosis with polyangiitis (Chapter 249), Hodgkin lymphoma (Chapter 172), and drug-induced lung disease (Chapter 82). If eosinophils are more than 25%, eosinophilic pneumonia is likely (Chapter 156). If lymphocytes are increased and the clinical differential diagnosis includes sarcoidosis (Chapter 83) or hypersensitivity pneumonitis (Chapter 82), analysis of T-cell populations may be helpful; the CD4:CD8 ratio is typically increased in sarcoidosis but reduced in hypersensitivity pneumonitis. If more than 20% of macrophages stain positive for hemosiderin, diffuse alveolar hemorrhage is considered likely (Chapter 79), particularly if lavage fluid is progressively bloody in successive aliquots.

Cellular constituents of bronchoalveolar lavage are usually stained for cytologic analysis for malignant cells and viral inclusions. If Langerhans cell histiocytosis (Chapter 80) is considered possible, 5% or more CD1a–positive cells support the diagnosis. If chronic beryllium disease or beryllium sensitization is possible, a lymphocyte proliferation test in response to exposure to beryllium salts can be helpful (Chapter 81). Staining of solid material from the bronchoalveolar lavage with periodic acid–Schiff (PAS) stain for the presence of PAS-positive material is essential to the diagnosis of pulmonary alveolar proteinosis (Chapter 79). A diagnosis of lipoid pneumonia (Chapter 82), caused by the aspiration of oil, can be confirmed by an excess of lipid-laden macrophages from bronchoalveolar lavage. The presence of asbestos bodies or silica is not diagnostic of lung disease related to these substances (Chapter 81) but does indicate significant exposure.

COMPLEX DISORDERS

Approximately 3 to 5% of pulmonary function tests have more than one physiologic defect, such as a combination of restriction plus obstruction, or more than one cause of restriction (e.g., pulmonary fibrosis plus obesity or heart failure). These cases do not fit neatly into standard interpretive patterns of typical obstruction or restriction, yet they can be described, and their patterns suggest a differential diagnosis.

A *mixed disorder* is a combination of both restriction, as indicated by a reduced TLC, plus obstruction, as indicated by a reduced FEV_1/FVC ratio. Although it is widely recognized, it only occurs in 1 to 2% of pulmonary function tests. A mixed disorder may be due to a combination of a restrictive disorder plus an unrelated obstructive disorder, such as an interstitial disease plus COPD, but several disorders typically produce a mixed pattern, including cystic fibrosis (Chapter 77), sarcoidosis (Chapter 83), Langerhans cell histiocytosis (Chapter 155), and heart failure (Chapters 45 and 46). In a mixed pattern, the degree of severity of restriction can be determined from the TLC percent predicted. The overall impairment can be determined from the FEV_1 percent predicted. The severity of the obstructive component can be inferred from the FEV_1 percent predicted divided by the TLC percent predicted.

Reduced lung volumes are the sine qua non of the diagnosis of restriction. However, about half of patients whose spirometry suggests restriction (reduced vital capacity with normal FEV_1/FVC ratio, also called preserved ratio impaired spirometry or PRISM) have a normal total lung capacity, so they do not have true restriction, but rather what is called the *nonspecific pattern*. The nonspecific pattern is very common, occurring in 9 to 10% of all complete pulmonary function tests. It is approximately as frequent as true restriction. Patients with the nonspecific pattern commonly have evidence of an obstructive disorder, not restriction, as indicated either by increased airway resistance, a response to a bronchodilator, or other clinical indicator of obstruction. It can be argued that the clinical utility of the measurement of airway resistance is limited to patients with the nonspecific pattern of whom about half have an increased airway resistance. Some patients with a nonspecific pattern do not have evidence of airway obstruction but are obese or have other chest wall limitations, neuromuscular weakness, poor performance, heart failure, pleural effusion, or a variety of other conditions.

In typical cases of restrictive lung disease, including most cases of interstitial lung disease, lung volumes are reduced in proportion to the severity of the interstitial disease. For example, TLC might be reduced to 60% of the predicted value and FVC would be similarly reduced to about 60% of the predicted value. In such a case, grading the severity of restriction is easy. One should be cautious not to overlook the fact that the gas exchange abnormality may be more or less severe, depending on the underlying pathology. In contrast, about one third of patients with restrictive diseases have reductions in FEV_1 and FVC that are disproportionate (lower by >10% of predicted value) to the reduction in TLC. The discrepancy may be large; for example, TLC may be 70% predicted while FVC is only 25% predicted. Interpreting physicians sometimes disagree whether to grade severity of restriction based on TLC percent predicted or FVC percent predicted. In such a case, the impairment might be called either mild or very severe. Cases of "typical restriction" are seen in association with interstitial lung disease, and hence weighted toward older men, whereas patients with "complex restriction" are more often women; younger; either underweight or obese; have slightly less severe reductions in D_{LCO}; and more often have atelectasis, a mosaic pattern on computed tomography, diaphragmatic dysfunction, or neuromuscular disease.

PULMONARY FUNCTION IN OBESITY

The epidemic of obesity is manifested in many organ systems, including the respiratory system. Dyspnea, exercise limitation, and respiratory failure are more common in obese persons than in the nonobese. Asthma is more common and more severe in obese patients. The effects of obesity on lung function are usually relatively modest among ambulatory patients with a body mass index (BMI) less than 40. The most commonly observed effect of obesity on lung function is a reduction in expiratory reserve volume (the amount of air exhaled between FRC and residual volume), which is substantially reduced even in persons who are overweight (BMI 25 to 30) or mildly obese (BMI 30 to 35). Vital capacity is reduced in obesity, but the effect is modest, usually within the normal range, and highly variable. In large studies, vital capacity or FVC is reduced on average by 0.5 to 0.8% for each unit increase in BMI above 25. Effects of obesity on total lung capacity and FEV_1 are somewhat smaller. The FEV_1/FVC ratio and D_{LCO} actually increase slightly with increasing BMI.

In exercise studies, the effects of obesity among ambulatory outpatients are likewise modest. Such patients have an increased work of breathing and decreased external work efficiency related to the work of moving their own body mass, but peak oxygen uptake is often normal.

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74 DISORDERS OF VENTILATORY CONTROL

ATUL MALHOTRA AND FRANK POWELL

DEFINITIONS AND PATHOGENESIS

Ventilatory Control

Ventilation is controlled by complex interactions between central chemoreceptors, which respond mainly to arterial carbon dioxide tensions, and peripheral chemoreceptors, which respond to arterial carbon dioxide and oxygen tensions. These reflexes modulate the underlying respiratory rhythm, and disorders of ventilatory control are caused by derangements in these control systems.

HYPOVENTILATION SYNDROMES

Hypoventilation syndromes are defined by a lack of adequate alveolar ventilation to maintain a normal arterial carbon dioxide tension of 40 mm Hg. The two most common clinical settings that result in chronic hypoventilation are severe chronic obstructive pulmonary disease (COPD; Chapter 76) and morbid obesity (Chapters 374 and 201); less common causes are chronic opiate therapy, neuromuscular weakness (Chapters 389 and 390), and severe kyphoscoliosis (Chapter 86). The epidemiology of these hypoventilation syndromes is poorly studied, but about 15 to 30% of patients with severe COPD or morbid obesity have an elevated $Paco_2$. Regardless of the cause, patients with hypoventilation frequently have further worsening of their ventilation at the onset of sleep due to loss of the wakefulness stimulus, which is the normal drive to breathe while awake, and some degree of upper airway collapse after the onset of sleep (Chapter 374).

Patients with central sleep apnea (Chapter 374), which is a group of conditions in which cessation of airflow occurs because of a lack of respiratory effort, are classified into those with inadequate ventilatory drive and those with excessive drive (Table 74-1).[1] The apparent paradox of how excessive drive leads to central apnea is explained by the concept of loop gain. A negative feedback control system with a high loop gain is prone to instability that leads to periods of excessive breathing followed by periods of apnea. The prototype of a condition with high loop gain is periodic breathing or Cheyne-Stokes breathing (Fig. 74-1). Hypercapnic diseases include acquired diseases and the central congenital hyperventilation syndrome (Table 74-2).

CHEYNE-STOKES BREATHING

Cheyne-Stokes breathing is a waxing and waning pattern of breathing, which is classically described as crescendo-decrescendo and often includes periods of central apnea. Cheyne-Stokes is seen most commonly during sleep in patients with heart failure.

EPIDEMIOLOGY

Cheyne-Stokes breathing is a form of ventilatory instability that occurs in 20 to 40% of patients with left ventricular systolic dysfunction.[2] Male sex, advanced age, low baseline $Paco_2$, and atrial fibrillation are risk factors for Cheyne-Stokes breathing among patients with heart failure. Controversy remains regarding whether this breathing pattern itself is deleterious or whether it is simply a marker of the underlying severity of cardiac disease. Cheyne-Stokes breathing represents about 5 to 10% of all cases of sleep apnea (Chapter 374) and is uncommon among patients who do not have heart failure.

PATHOBIOLOGY

Individuals with Cheyne-Stokes breathing have robust chemosensitivity, as evidenced by marked increases in ventilation with small increases in $Paco_2$. The drive to breathe may be further increased by neural reflexes that are triggered by extravascular lung fluid and an elevated left atrial pressure. Intermittent hypoxemia and catecholamine surges, which are frequent in these patients, contribute to oxidative stress and neuroendocrine activation, both of which are thought to contribute to worsening of the underlying heart failure.

CLINICAL MANIFESTATIONS AND DIAGNOSIS

Patients with Cheyne-Stokes breathing can sometimes be diagnosed at the bedside by careful observation of their breathing pattern. During sleep or exercise, breathing becomes dependent primarily on metabolic stimuli. Patients may complain of fatigue or sleepiness because arousals from sleep tend to occur during the hyperpneic phase. Paroxysmal nocturnal dyspnea, a classic symptom of heart failure (Chapter 45), most commonly reflects underlying Cheyne-Stokes breathing. Patients often are diagnosed in the sleep laboratory while undergoing investigation for possible obstructive sleep apnea. However, in contrast to obstructive sleep apnea, Cheyne-Stokes breathing usually resolves during rapid eye movement (REM) sleep, and arousals on the electroencephalogram typically occur during the hyperpneic phase. Furthermore, Cheyne-Stokes breathing generally does not resolve immediately when nasal continuous positive airway pressure (CPAP) is applied.

TREATMENT

Medical management of Cheyne-Stokes breathing most often is treatment of the underlying heart failure (Chapter 46). After optimization of medical management, the Cheyne-Stokes breathing pattern frequently resolves. CPAP can improve breathing indices but is no better than standard medical therapy from the standpoint of mortality. Results have been similar with other ventilator techniques.[A1,3] An implantable phrenic nerve stimulator has been approved by the U.S. Food and Drug Administration, but definitive outcome data are still lacking.[4]

CENTRAL CONGENITAL HYPOVENTILATION SYNDROME

DEFINITION AND EPIDEMIOLOGY

Central congenital hypoventilation syndrome is a rare congenital condition, previously referred to as Ondine's curse, characterized by a diminished ventilatory response to carbon dioxide. The central congenital hypoventilation syndrome was traditionally diagnosed in neonates, but more subtle forms of disease are increasingly noted in older children and adults.

PATHOBIOLOGY

The syndrome is now defined by a mutation in the *PHOX2B* gene, located on chromosome 4p12. The *PHOX2B* gene is a highly conserved homeobox gene

TABLE 74-1 CLASSIFICATION OF CENTRAL SLEEP APNEA

CENTRAL SLEEP APNEA SYNDROME	MECHANISM	THERAPY
Sleep transition apneas	Carbon dioxide fluctuations during transitions from sleep to wake to sleep	Reassurance, occasionally hypnotics or oxygen
Chronic narcotic therapy	Lack of central drive	Reduce narcotic dose Consider positive-pressure device
Cheyne-Stokes breathing	High loop gain from robust chemosensitivity and ventilatory drive	Optimize medical therapy for heart failure; consider PAP device
Idiopathic central apnea	Unknown	Supportive, bilevel PAP; consider ventilatory stimulants
Treatment of emergent central apnea or "complex apnea"	Lowering upper airway resistance at CPAP initiation improves efficiency of carbon dioxide excretion	Reassurance, generally resolves spontaneously
Sleep hypoventilation syndromes	Fall in drive with loss of wakefulness stimulus, loss of accessory muscle activity during REM sleep	Noninvasive ventilation

CPAP = continuous positive airway pressure; PAP = positive airway pressure; REM = rapid eye movement.

ABSTRACT

Ventilation is controlled by complex interactions between central chemoreceptors, which respond mainly to arterial carbon dioxide tensions, and peripheral chemoreceptors, which respond to arterial carbon dioxide and oxygen tensions. Disorders of ventilatory control are caused by derangements in this control system. Hypoventilation syndromes, defined by a lack of adequate alveolar ventilation to maintain a normal arterial carbon dioxide tension of 40 mm Hg, are observed with morbid obesity, opiate overdoses, muscular weakness, and in some cases of severe chronic obstructive pulmonary disease (COPD). Central apneas can occur when the "loop gain" in the negative feedback ventilatory control system is too high and becomes prone to instability, thereby leading to periods of excessive breathing followed by apnea. The prototype of this condition is Cheyne-Stokes breathing, which is common during sleep in patients with heart failure. Treatment of Cheyne-Stokes breathing is controversial but starts with addressing any underlying medical causes such as optimizing medical therapy for heart failure. Finally, central congenital hypoventilation syndrome is a rare condition that is defined by a mutation in the *PHOX2B* gene on chromosome 4p12 and characterized by a diminished ventilatory response to carbon dioxide and sleep apnea.

KEYWORDS

arterial chemoreceptor
central chemoreceptor
central apnea
central congenital hypoventilation syndrome
Cheyne-Stokes breathing
loop gain

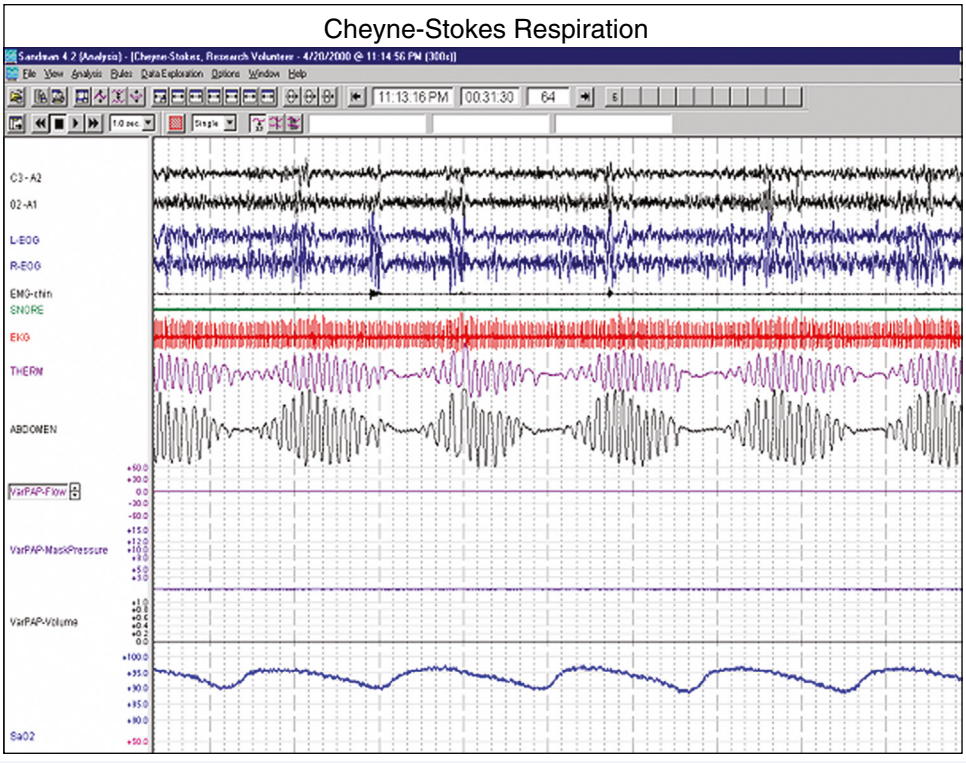

FIGURE 74-1. Cheyne-Stokes breathing with crescendo-decrescendo pattern of breathing. The thermistor detects air temperature changes at the mouth and nose. Note absences in airflow without respiratory effort seen in the abdominal belts. This breathing pattern leads to intermittent desaturations, arousals from sleep, and bursts of tachycardia. The loop gain concept can be understood by considering the thermostat analogy in which a control system is working to regulate a stable room temperature (e.g., 20° C). By analogy, the respiratory control system is working primarily to maintain a stable $Paco_2$ of 40 mm Hg and stable pH. Situations in which marked fluctuations in room temperature might occur would include one in which the thermostat is excessively sensitive (i.e., furnace turns on if room temperature falls to 19.999° C); if the furnace is too powerful, a marked overshoot in room temperature will be followed by a prolonged period when the furnace does not run. In the analogy to Cheyne-Stokes breathing, carbon dioxide is equated to room temperature and would be predicted to be unstable if chemosensitivity (i.e., the thermostat) were excessively robust (i.e., a marked increase in ventilation for a small change in carbon dioxide) or if the efficiency of carbon dioxide excretion were high (i.e., marked fall in $Paco_2$ with increased ventilation). Situations that increase the propensity for carbon dioxide fluctuations lead to elevated loop gain and thus increase the risk for Cheyne-Stokes breathing. C3-A2 and O2-A1 = leads for electroencephalogram; EKG = electrocardiogram; EMG = electromyogram; EtCO2 = end-tidal carbon dioxide; L and R-EOG = left and right electrooculogram; SaO2 = oxygen saturation; Therm = thermistor.

TABLE 74-2 CLASSIFICATION OF HYPERCAPNIC DISEASES

HYPERCAPNIC DISEASES	MECHANISM	DIAGNOSIS	TREATMENT
ACQUIRED DISEASE			
Narcotic overdose	Reduced central drive	History, narcotized pupils, toxicology	Supportive care, naloxone
Acute severe asthma (Chapter 75)	Severe airflow obstruction, high dead space	Typical history, wheezing on examination, low FEV_1/FVC	Bronchodilators, anti-inflammatories, mechanical ventilation (usually invasive)
Acute exacerbation of COPD (Chapter 76)	Airflow obstruction, high dead space	History, cigarette smoking, low FEV_1/FVC, infectious etiology	Bronchodilators, anti-inflammatories, noninvasive ventilation
Obesity-hypoventilation syndrome	Low respiratory system compliance, high upper airway resistance, low central drive	High BMI, lack of other diagnoses; blunted carbon dioxide response	Weight loss, nocturnal bilevel positive airway pressure
Neuromuscular disease (e.g., myasthenia gravis, polymyositis, GBS/AIDP, ALS; Chapters 248, 387, and 390)	Lack of respiratory muscle force	Immediate orthopnea, low VC, low MIPs/MEPs	Underlying cause, nocturnal noninvasive ventilation, supportive care
Severe parenchymal lung disease (e.g., COPD)	Lack of alveolar surface area; high pulmonary dead space and work of breathing	Typical history, smoking, low FEV_1 and FEV_1/FVC	Bronchodilator, anti-inflammatory therapy, possible nocturnal noninvasive ventilation, smoking cessation
Kyphoscoliosis (Chapter 86)	Low respiratory system compliance	Physical examination	Supportive care, noninvasive ventilation
CONGENITAL DISEASE			
Central congenital hypoventilation syndrome	*PHOX2B* mutation, lack of central drive	Genetic testing	Supportive care, mechanical ventilation (usually noninvasive)

AIDP = acute inflammatory demyelinating polyneuropathy; ALS = amyotrophic lateral sclerosis; BMI = body mass index; COPD = chronic obstructive pulmonary disease; FEV_1 = forced expiratory volume in 1 second; FVC = forced vital capacity; GBS = Guillain-Barré syndrome; MEPs = maximal expiratory pressures; MIPs = maximal inspiratory pressures; VC = vital capacity.

that is expressed in cardiopulmonary reflex pathways, including central CO_2-sensitive chemoreceptors that are located in the retrotrapezoid nucleus and that provide excitatory input to the respiratory pattern generator. Abnormalities in *PHOX2B* genes have also been associated with Hirschsprung disease (Chapter 122), neural crest tumors, cardiac asystole (Chapter 50), and other abnormalities of the autonomic nervous system (Chapter 386).

Because most parents of affected children with central congenital hypoventilation syndrome do not carry a *PHOX2B* mutation, the mutations are de novo. About 90% of patients are heterozygous for a polyalanine repeat expansion mutation, in which the affected allele has 24 to 33 alanines rather than the normal 20 alanines. The remaining 10% of central congenital hypoventilation syndrome patients have missense, nonsense, or frameshift mutations in the *PHOX2B* gene.[5]

CLINICAL MANIFESTATIONS AND DIAGNOSIS

Neonates can present with cyanosis at birth, recurrent central apneas, or both. Adults can present with idiopathic central sleep apnea, unexplained hypercapnia, or autonomic abnormalities (Chapter 386).[6] The degree of oxygen desaturation during ventilatory and orthostatic challenges correlates with measures of neurocognition.[7] Confirmation of the diagnosis requires the demonstration of an abnormality in the *PHOX2B* gene.

TREATMENT

There are currently no specific therapies for central congenital hypoventilation syndrome beyond supportive care. Genetic counseling is required for afflicted individuals and their families, given the autosomal dominant pattern of inheritance. Patients must be cautioned against the use of sedatives, which could precipitate respiratory failure. Mechanical ventilation during sleep either invasively (through tracheostomy) or noninvasively (through bilevel positive airway pressure support [Chapter 374]) is required in most patients. Some patients remain fully ventilator dependent. Diaphragmatic pacing can sometimes be effective, but ventilatory stimulants are generally ineffective.

ACQUIRED HYPOVENTILATION SYNDROMES

DEFINITION AND EPIDEMIOLOGY

Patients with hypoventilation syndromes cannot maintain adequate minute ventilation to keep their $Paco_2$ at 40 mm Hg. Patients can be classified into those who lack central ventilatory drive and those who have a pulmonary mechanical or neuromuscular abnormality that prevents adequate gas exchange (see Table 74-2). The case frequency is unknown, but hypercapnic respiratory failure is one of the more common admission diagnoses in intensive care units.

PATHOBIOLOGY

Patients with conditions characterized by the lack of central drive have reasonably normal lungs and respiratory muscle function but lack adequate response to carbon dioxide and hypoxia. In contrast, most patients with mechanical or neuromuscular abnormalities have a larger work of breathing compared with normal individuals; the most common underlying conditions are severe COPD (Chapter 76) and morbid obesity (Chapter 201) with obesity-hypoventilation syndrome. Such individuals have diminished but not absent chemoresponsiveness, which may be an acquired trait or may relate to an as yet unknown genetic predisposition. Another cause of inadequate gas exchange is neuromuscular disease; common causes include disorders of neuromuscular transmission (Chapter 390), severe muscle weakness (Chapter 389), the residua from poliovirus infection (Chapter 349), Guillain-Barré syndrome (Chapter 388), and acute poisoning (Chapter 96). Although coronavirus disease 2019 (COVID-19) was thought to involve impaired hypoxic sensing, data now suggest chemosensitivity is not systematically impaired in afflicted patients (Chapter 336).[8,9]

CLINICAL MANIFESTATIONS AND DIAGNOSIS

Patients with hypoventilation have myriad presentations ranging from asymptomatic abnormalities in laboratory testing (e.g., elevated $Paco_2$, unexplained low Sao_2, or elevated serum bicarbonate level) to respiratory failure in the intensive care unit (e.g., respiratory infection with laboratory evidence of chronic abnormalities, such as acute-on-chronic respiratory acidosis). Patients who acutely overdose on sedative-hypnotic or narcotic agents may present with acute respiratory acidosis and loss of consciousness. Patients who take chronic narcotics may present with central sleep apnea-hypopnea or otherwise unexplained oxygen desaturation at night.

Once it is suspected, the diagnosis of hypoventilation is confirmed by the finding of $Paco_2$ higher than 42 mm Hg on analysis of an arterial blood sample. If the increase in $Paco_2$ is of short duration so that renal compensation has not yet occurred (Chapter 104), the serum bicarbonate level is increased by 1 mEq/L for every rise of 10 mm Hg in $Paco_2$. By comparison, if the respiratory acidosis is of sufficient duration for renal compensation to occur, the serum bicarbonate level will usually be increased by 4 mEq for every rise of 10 mm Hg in $Paco_2$ (Fig. 74-2).

Once an elevated $Paco_2$ is established, it is appropriate to distinguish patients who "can't breathe" from those who "won't breathe." "Can't breathe" implies that a respiratory mechanical problem or neuromuscular weakness is causing the elevation in $Paco_2$. Abnormalities in pulmonary function testing (e.g., a very low vital capacity) suggest a parenchymal or chest wall disorder. Ultrasound can identify phrenic neuropathy causing diaphragmatic dysfunction. Patients who "won't breathe" have central nervous system abnormalities that affect central drive, chemosensitivity, or both.

TREATMENT AND PROGNOSIS

The treatment of hypoventilation should focus on the underlying cause. Acute poisonings can be managed supportively or, in some cases, with specific antidotes (Chapter 96). Chronic conditions can be treated by addressing the underlying cause, such as weight loss in obesity-hypoventilation syndrome[10] or cholinesterase inhibitors in myasthenia gravis (Chapter 390). For parenchymal lung disease, treatment is directed at the underlying cause, if possible (Chapters 76 and 80).

Sedative medications should be used cautiously because they can occasionally precipitate acute respiratory failure.[11] Although profound hypoxemia can clearly be deleterious, oxygen occasionally can precipitate severe acute respiratory acidosis, particularly in patients with acute exacerbations of COPD (Chapter 76). As a result, hypoventilating patients with COPD require cautious management, including the careful administration of supplemental oxygen, which should be titrated to an arterial oxygen saturation of 90% or an arterial oxygen tension of 60 mm Hg.

Severe hypoventilation requires mechanical ventilation (Chapter 91), such as noninvasive ventilation for an acute exacerbation of COPD. For other presentations in which the $Paco_2$ is believed to be acutely elevated, endotracheal intubation and mechanical ventilation are frequently used, especially in patients with impaired consciousness.

For chronic hypoventilation in hypercapnic COPD, noninvasive bilevel positive airway pressure through a face mask during sleep can maintain alveolar ventilation, but there is no definitive evidence that noninvasive positive-pressure ventilation can prolong life or reduce hospitalizations in patients with COPD and chronic respiratory failure. In addition, the considerable difficulty of adhering to nocturnal bilevel therapy in COPD emphasizes the need for discussions with patients and families regarding its risks and benefits. For obesity hypoventilation syndrome without severe obstructive sleep apnea, noninvasive ventilation improves $Paco_2$ and reduces daytime sleepiness, as well as improving health-related quality of life.[A2] If such patients also have severe obstructive sleep apnea, noninvasive ventilation and continuous positive airway pressure (CPAP) are equally effective,[A3,A4] but CPAP is easier and less expensive to implement. If noninvasive ventilation is chosen, nasal and oronasal masks are equally effective and tolerated.[A5] In patients with central sleep apnea and heart failure, adaptive servo-ventilation, which provides inspiratory pressure support in addition to expiratory positive airway, was not helpful.[A6]

Other chronic hypoventilation syndromes are also commonly treated with bilevel positive airway pressure, although data are not compelling. In some chronic conditions, such as motor neuron disease (Chapter 387), tracheostomy should be discussed, although the impact of such interventions on quality of life should be carefully considered. Regardless of the underlying cause, an elevation in the $Paco_2$ level is considered a poor prognostic sign. End-of-life discussions are also important in such cases because the prognosis of patients with chronic respiratory failure is generally poor.

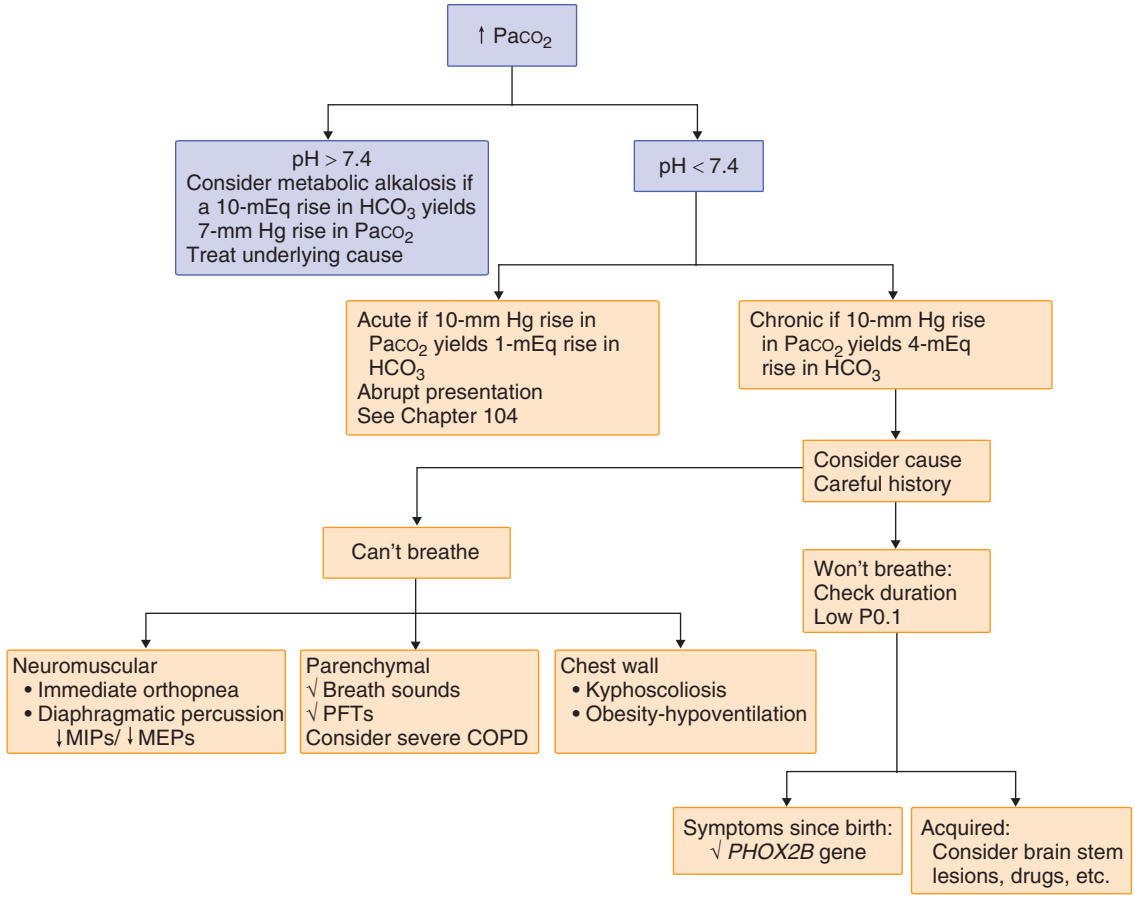

FIGURE 74-2. A flowchart of a systematic approach to hypercapnia and various causes of hypoventilation. The change in pH can help determine the cause and chronicity. A careful history and physical examination, coupled with pulmonary function testing, can help classify patients into those who "can't breathe" because of neuromuscular or mechanical abnormalities of the respiratory system compared with those who "won't breathe" because of central nervous system disease. COPD = chronic obstructive pulmonary disease; MEPs = maximal expiratory pressures; MIPs = maximal inspiratory pressures; P0.1 = the negative mouth pressure generated during the first 100 msec of an occluded inspiration; PFTs = pulmonary function tests.

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75 ASTHMA

JEFFREY M. DRAZEN AND ELISABETH H. BEL

DEFINITION

Asthma is a clinical syndrome of unknown etiology characterized by recurrent episodes of airway obstruction that resolve spontaneously or as a result of treatment. These changes occur in the setting of various types of airway inflammation that are thought to reflect specific endotypes of this clinical syndrome. Although airway obstruction is largely reversible, some changes that lead to obstruction in the asthmatic airway may be irreversible.

EPIDEMIOLOGY

Asthma is an extremely common disorder affecting boys more commonly than girls and, after puberty, women more commonly than men (rate ratio

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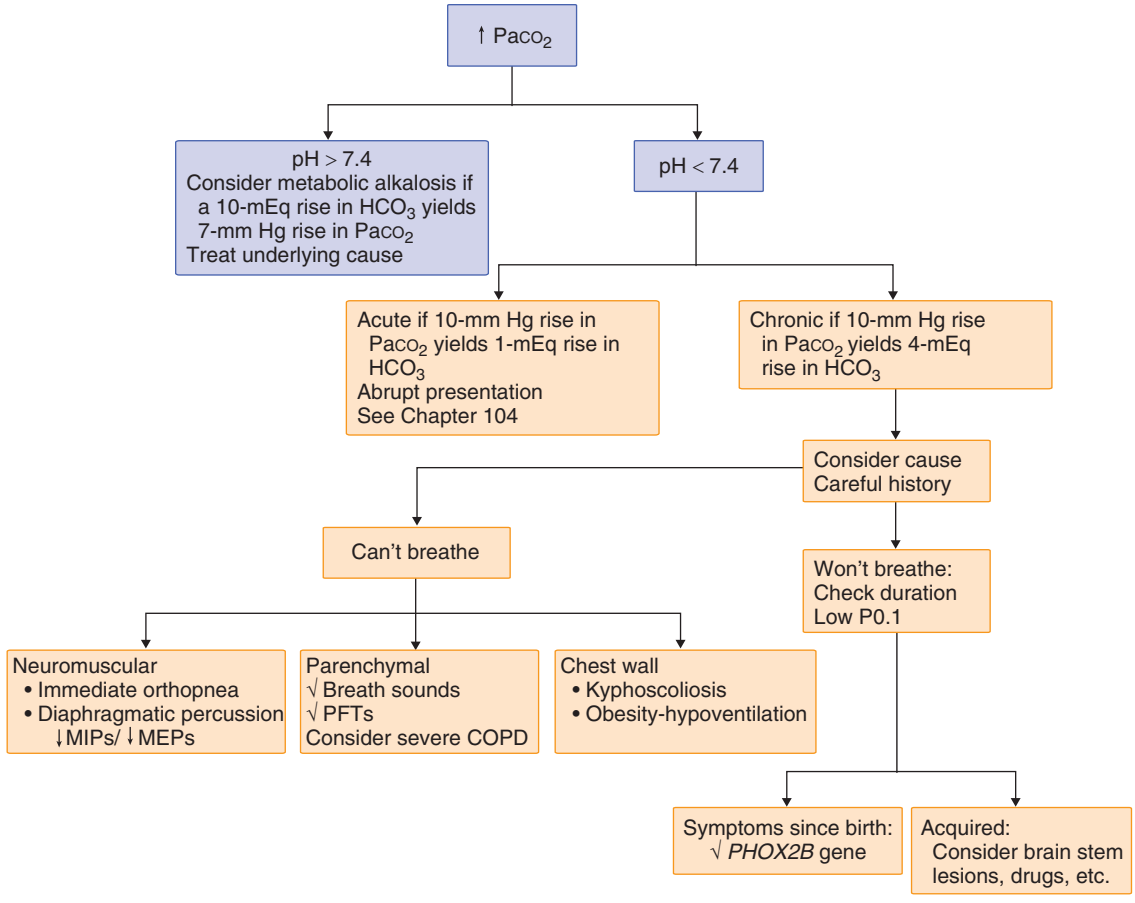

FIGURE 74-2. A flowchart of a systematic approach to hypercapnia and various causes of hypoventilation. The change in pH can help determine the cause and chronicity. A careful history and physical examination, coupled with pulmonary function testing, can help classify patients into those who "can't breathe" because of neuromuscular or mechanical abnormalities of the respiratory system compared with those who "won't breathe" because of central nervous system disease. COPD = chronic obstructive pulmonary disease; MEPs = maximal expiratory pressures; MIPs = maximal inspiratory pressures; P0.1 = the negative mouth pressure generated during the first 100 msec of an occluded inspiration; PFTs = pulmonary function tests.

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75 ASTHMA

JEFFREY M. DRAZEN AND ELISABETH H. BEL

DEFINITION

Asthma is a clinical syndrome of unknown etiology characterized by recurrent episodes of airway obstruction that resolve spontaneously or as a result of treatment. These changes occur in the setting of various types of airway inflammation that are thought to reflect specific endotypes of this clinical syndrome. Although airway obstruction is largely reversible, some changes that lead to obstruction in the asthmatic airway may be irreversible.

EPIDEMIOLOGY

Asthma is an extremely common disorder affecting boys more commonly than girls and, after puberty, women more commonly than men (rate ratio

ABSTRACT

Asthma is the most common chronic lung disease in the world. This chapter reviews the epidemiology, pathobiology, and treatment of asthma. Specific treatment scenarios are reviewed based on the severity of asthma symptoms and airflow derangements manifested by the patient.

KEYWORDS

asthma
reversible airway obstruction
β-agonist inhalers
mild persistent asthma
severe asthma
asthma emergencies
asthma in pregnancy
status asthmaticus

women : men is 1.8); approximately 8% of the adult population of the United States has signs and symptoms consistent with a diagnosis of asthma. Although most cases begin before the age of 25 years, new-onset asthma may develop at any time throughout life. An estimated 340 million people worldwide suffer from asthma, with 420,000 annual deaths attributed to the disease.[1]

The worldwide prevalence of asthma increased more than 50% in the latter half of the 20th century. During that period, the greatest increases in the prevalence of asthma occurred in countries that adopted an "industrialized" lifestyle without contact with farm animals. In contrast, being raised in a farming environment in close contact with cows is associated with a much lower risk of asthma, independent of genetic factors. By comparison, the prevalence of wheezing in children increased by only about 0.1% per year in the first decade of the 21st century, and the prevalence seems to have plateaued by 2015 and stabilized since then.

PATHOBIOLOGY

Genetics

In twin studies, asthma has about 60% heritability, thereby indicating that both genetic and environmental factors are important in its etiology. Multiple genome-wide association studies have identified multiple genetic loci associated with asthma; the common theme appears to be genes related to immune mechanisms.[2]

Pathology

The asthma syndrome is characterized by marked heterogeneity in clinical expression, environmental triggers, and immunopathologic mechanisms. Traditionally, clinicians identified only two forms of asthma, atopic and nonatopic asthma, but this division is an oversimplification. Multiple underlying pathobiologic mechanisms, also known as endotypes, underlie the classic signs and symptoms that typify asthma.

Atopic or allergic asthma represents the most common and most studied subtype of asthma. It is characterized by the presence of immunoglobulin E (IgE)-mediated sensitization to environmental allergens and can be observed in almost all school-aged children with asthma and about half of adult asthmatics. Inflammation and remodeling of the airways are characteristic pathologic features of atopic asthma. Remodeling changes include epithelial fragility, edema, and hyperemia of the mucosa, as well as thickening of the subepithelial reticular basement due to deposition of collagen types III and IV. In more severe chronic asthma, the airway wall thickens as a result of hyperplasia of airway smooth muscle, hypertrophy of mucus secreting glands, and subepithelial angiogenesis. Infiltration of the airway wall with inflammatory cells including adaptive T helper-2 (T_H2) cells, mast cells, and eosinophils is a general finding, and occurs even in the mildest cases of atopic asthma.

T_H2 cells initiate and propagate the inflammatory cascade associated with allergy by producing a variety of cytokines, including interleukin (IL)-4, IL-5, and IL-13. IL-4 induces B-cell proliferation and is capable of stimulating these cells to produce IgE. IL-13 has similar effects of those to IL-4 with respect to B-cell stimulation and IgE production but, in addition, induces airway hyperresponsiveness, goblet cell metaplasia, and mucus hypersecretion. IL-5 plays a major role in the regulation of eosinophil formation, maturation, recruitment, and survival. Increased production of IL-5 may be related to the pathogenesis of severe eosinophilic asthma.

Mast cells are found in close association with airway smooth muscle cells and are classically activated by allergens when IgE is bound to the high-affinity IgE receptor. IgE-mediated mast cell degranulation and activation results in the release of histamine and in the generation of cysteinyl leukotrienes and prostaglandins, which contribute to bronchoconstriction and airway hyperresponsiveness.

Eosinophils accumulate in the airways after sensitized persons are exposed to allergens. Elevated numbers of circulating eosinophils are now considered a key biomarker indicating that a patient has a form of asthma that is likely to respond to inhaled glucocorticoids and, in more severe cases, to treatment with antibodies against aspects of the *T_H2* inflammatory pathway. Upon activation, eosinophils release toxic granule products (e.g., major basic protein and eosinophil cationic protein) that damage airway epithelium and nerves. These cells also produce lipid mediators such as leukotrienes and platelet activating factor, as well as a range of cytokines, growth factors, and chemokines.

Nonatopic or intrinsic asthma develops in adulthood and accounts for less than 5% of cases of asthma. It is not associated with allergies, is often accompanied by chronic rhinosinusitis and nasal polyposis, and is poorly responsive to inhaled glucocorticoids. The eosinophilic airway inflammation observed in this type of asthma is not dependent on adaptive immunity but is likely caused by type 2 innate lymphoid cells (ILC2) that produce high amounts of IL-5 and IL-13. The growth and maturation of ILC2 cells are stimulated by epithelial cytokines ("alarmins"), which are induced by chronic exposure to pollutants, viruses, or fungi. ILC2 cells produce little IL-4, so there is no associated IgE response from B cells. Patients with intrinsic asthma often have a severe form of asthma with elevated eosinophil counts in peripheral blood, and generally require high doses of systemic glucocorticoids or biologics aimed at IL-5 or IL-13 to keep their asthma under control.

Both atopic and intrinsic asthma are so called "type-2-high" asthma phenotypes. However, cluster analyses of large cohorts of adult patients with asthma have identified at least three subtypes of asthma that are not characterized by the presence of type 2 cytokines or eosinophilic airway inflammation. These "type-2-low" subtypes of asthma are characterized by increased numbers of neutrophils in the airway or by no airway inflammation at all. One increasingly recognized "type-2-low" asthma phenotype is obesity-associated asthma. This type of asthma occurs later in life, usually in female patients without prior airway disease. The mechanism of obesity-associated asthma is not well understood. Other "type-2-low" phenotypes of asthma include certain forms of occupational asthma (Chapter 81) (e.g., isocyanate-induced asthma), neutrophilic asthma with subclinical microbial infection, and asthma in athletes (e.g., in endurance aquatic sports). In clinical practice in adults, different asthma phenotypes can coexist and interact within the same patient, thereby underscoring the need for a personalized and targeted approach to diagnosis and management.

Physiological Changes in Asthma

Increased resistance to airflow is the physiological hallmark of asthma; it is due to airway obstruction that results from smooth muscle constriction, thickening of the airway epithelium, and free secretions within the airway lumen. Obstruction to airflow is manifested by increased airway resistance and decreased flow rates throughout the vital capacity. At the onset of an exacerbation of asthma, obstruction occurs at all airway levels; as the exacerbation resolves, these changes are reversed—first in the large airways (i.e., mainstem, lobar, segmental, and subsegmental bronchi) and then in the more peripheral airways. This anatomic sequence of onset and reversal is reflected in the physiological changes observed during resolution of an asthmatic episode. Specifically, as an exacerbation of asthma resolves, flow rates first normalize at volumes high in the vital capacity and only later at volumes low in the vital capacity. Because asthma is largely an airway disease rather than an air space disease, no primary changes occur in the static pressure-volume curve of the lungs. However, during an acute exacerbation of asthma, airway narrowing may be so severe as to result in airway closure, with individual lung units closing at a volume that is near their maximal volume. This closure results in a change of the pressure-volume curve such that for a given contained gas volume within the thorax, elastic recoil is decreased, which in turn further depresses expiratory flow rates.

Exercise-induced bronchoconstriction, which is the transient narrowing of the airways after exercise, occurs frequently among athletes who may not have asthma or even have any respiratory symptoms. The mechanism is uncertain, but the key stimulus is probably airway dehydration because of increased ventilation.

Additional factors influence the mechanical behavior of the lungs during an exacerbation of asthma. During inspiration in this setting, the maximal inspiratory pleural pressure becomes more negative than the subatmospheric pressure of 4 to 6 cm H_2O usually required for tidal airflow. The expiratory phase of respiration also becomes active as the patient tries to force air from the lungs. As a consequence, expiratory peak pleural pressures, which normally are, at most, only a few centimeters of water above atmospheric pressure, may be as high as 20 to 30 cm H_2O above atmospheric pressure. The low pleural pressures during inspiration tend to dilate airways, whereas the high pleural pressures during expiration tend to narrow airways. During an exacerbation of asthma, the wide pressure swings, coupled with alterations in the mechanical properties of the airway wall, lead to a much higher resistance to expiratory airflow than to inspiratory airflow.

The respiratory rate is usually rapid during an acute exacerbation. This tachypnea is driven not by abnormalities in arterial blood gas composition but rather by stimulation of intrapulmonary receptors with subsequent effects on central respiratory centers. One consequence of the combination of airway narrowing and rapid airflow rates is a heightened mechanical load on the ventilatory pump. During a severe exacerbation, the load can increase the work of breathing by a factor of 10 or more and can predispose to fatigue of the ventilatory muscles. With respect to gas exchange, the patchy nature of asthmatic airway narrowing results in a maldistribution of ventilation $(\dot{V})$ relative to pulmonary perfusion (Q). A shift occurs from the normal preponderance of $(\dot{V}/Q)$ units, with a ratio of near unity, to a distribution with a large number of alveolar-capillary units, with a $(\dot{V}/Q)$ ratio of less than unity. The net effect is to induce modest arterial hypoxemia with Pa_{O_2} values commonly in the 60 mm Hg range while the patient is respiring ambient air at sea level. In addition, the hyperpnea of asthma is reflected as hyperventilation with a low arterial P_{CO_2}.

CLINICAL MANIFESTATIONS

History

During an acute exacerbation of asthma, often referred to as an asthma exacerbation, patients seek medical attention for shortness of breath accompanied by cough, wheezing, and anxiety. The degree of breathlessness experienced by the patient is not closely related to the degree of airflow obstruction but is often influenced by the acuteness of the exacerbation. Dyspnea may occur only with exercise (exercise-induced asthma), after treatment with agents inhibiting the actions of cyclooxygenase 1 (aspirin-exacerbated respiratory disease),[3] after exposure to a specific known allergen (extrinsic asthma), or for no identifiable reason (intrinsic asthma). Variants of asthma exist in which cough, hoarseness, or inability to sleep through the night is the presenting symptom. Identification of a provoking stimulus through careful questioning helps establish the diagnosis of asthma and may be therapeutically useful if the stimulus can be avoided. Most patients with asthma complain of shortness of breath when they are exposed to rapid changes in the temperature and humidity of inspired air. For example, during the winter months in less temperate climates, patients commonly become short of breath on leaving a heated house; in warm humid climates, patients may complain of shortness of breath on entering a cold dry room, such as an air-conditioned theater.

An important factor to consider in taking a history from a patient with asthma is the potential for occupational exposures (Chapter 81). Asthma that is triggered by occupational exposures is termed occupational asthma; preexisting asthma that is exacerbated by workplace exposures is termed workplace-exacerbated asthma. In reactive airway dysfunction syndrome, a single large exposure leads to a persistent asthma-like phenotype in a previously normal individual.

Physical Examination

Vital Signs

Common features noted during an exacerbation of asthma include a rapid respiratory rate (often 25 to 40 breaths per minute), tachycardia, and pulsus paradoxus (an exaggerated inspiratory decrease in the systolic pressure). The magnitude of the pulsus is related to the severity of the exacerbation; a value greater than 15 mm Hg indicates an exacerbation of moderate severity. Pulse oximetry, with the patient respiring ambient air at sea level, commonly reveals an oxygen saturation near 90%.

Thoracic Examination

Inspection may reveal that patients experiencing acute asthma exacerbations are using their accessory muscles of ventilation; if so, the skin over the thorax may be retracted into the intercostal spaces during inspiration. The chest is usually hyperinflated, and the expiratory phase is prolonged relative to the inspiratory phase. Percussion of the thorax demonstrates hyperresonance, with loss of the normal variation in dullness due to diaphragmatic movement; tactile fremitus is diminished. Auscultation reveals wheezing, which is the cardinal physical finding in asthma but does not establish the diagnosis (Chapter 71). Wheezing, commonly louder during expiration but heard during inspiration as well, is characterized as polyphonic in that more than one pitch may be heard simultaneously (Video 75-1). Accompanying adventitious sounds may include rhonchi, which are suggestive of free secretions in the airway lumen, or rales, which should raise the suspicion of an alternative diagnosis and are indicative of localized infection or heart failure. The loss of intensity or the absence of breath sounds in a patient with asthma, the so-called quiet chest, is an indication of severe airflow obstruction.

DIAGNOSIS

Laboratory Findings

Pulmonary Function Findings

A decrease in airflow rates throughout the vital capacity is the cardinal pulmonary function abnormality during an asthmatic episode.[4] The peak expiratory flow rate (PEFR), the forced expiratory volume in the first second (FEV_1), and the maximal mid-expiratory flow rate (MMEFR) are all decreased in asthma (Chapter 73). In severe asthma, dyspnea may be so severe as to prevent the patient from performing a complete spirogram. In this case, if 2 seconds of forced expiration can be recorded, reasonable estimates for PEFR and FEV_1 can be obtained. Gradation of the severity of the exacerbation (Table 75-1) must be assessed by objective measures of airflow; no other methods yield accurate and reproducible results. As the exacerbation resolves, the PEFR and the FEV_1 increase toward normal together while the MMEFR remains substantially depressed; as the episode resolves further, the FEV_1 and the PEFR may normalize while the MMEFR remains depressed (Fig. 75-1). Even when the exacerbation has fully resolved clinically, residual depression of the MMEFR is not uncommon; this depression may resolve during a prolonged course of treatment. If the patient is able to cooperate such that more complete measurements of lung function can be made, lung volume measurements made during an exacerbation demonstrate an increase in both total lung capacity and residual volume; the changes in total lung capacity and residual volume often, but not always, resolve with treatment. Because of the extra cooperation needed for this testing, it is not advised during an acute asthma exacerbation but is indicated before discharge in a patient hospitalized for such treatment or between exacerbations.

Pulmonary function testing obtained when the patient is relatively stable, for example, a month or more after a clinical exacerbation,[5] usually demonstrates airway obstruction, as indicated by low FEV_1 (as a percentage of the patient's predicted value), low forced vital capacity, and slightly elevated total lung capacity and residual volume values. These results may fully normalize after administration of a bronchodilator. In a patient with suspected asthma, a "bronchodilator response" is canonically defined as a 12% increase in the FEV_1, provided it is at least 200 mL (Fig. 75-2).

Exhaled NO•

The fraction of NO• in the exhaled air ($F_{E_{NO}}$) is elevated in patients with asthma. Although the exact concentration considered "elevated" will vary with the details of the technique used to obtain the gas sample, a concentration of 20 to 25 parts per billion is a convenient and reliable

TABLE 75-1 RELATIVE SEVERITY OF AN ASTHMATIC EXACERBATION AS INDICATED BY PEFR, FEV_1, AND MMEFR

TEST	PREDICTED VALUE (%)	SEVERITY OF ASTHMA
PEFR	>80	
FEV_1	>80	No spirometric abnormalities
MMEFR	>80	
PEFR	>80	
FEV_1	>70	Mild asthma
MMEFR	55-75	
PEFR	>60	
FEV_1	45-70	Moderate asthma
MMEFR	30-50	
PEFR	<50	
FEV_1	<50	Severe asthma
MMEFR	10-30	

FEV_1 = forced expiratory volume in the first second; MMEFR = maximal mid-expiratory flow rate; PEFR = peak expiratory flow rate.

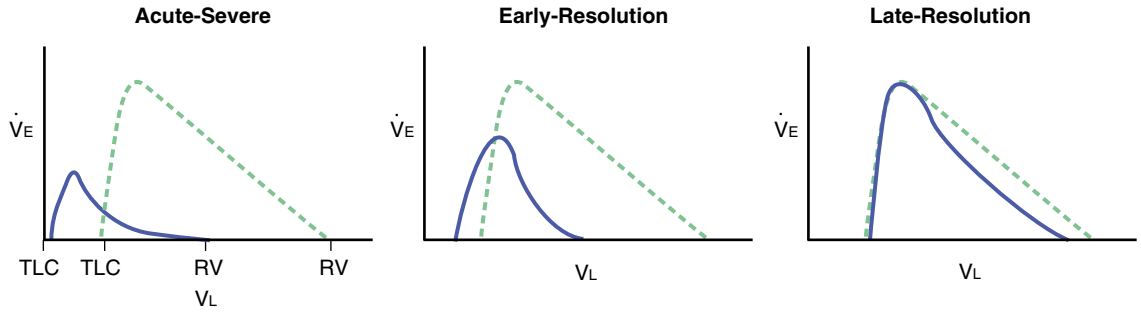

FIGURE 75-1. Schematic flow-volume curves in various stages of asthma. In each figure, the *dashed line* depicts the normal flow-volume curve. Predicted and observed total lung capacity (TLC) and residual volume (RV) are shown at the extremes of each curve. $\dot{V}_E$ = expiratory flow rate; V_L = lung volume.

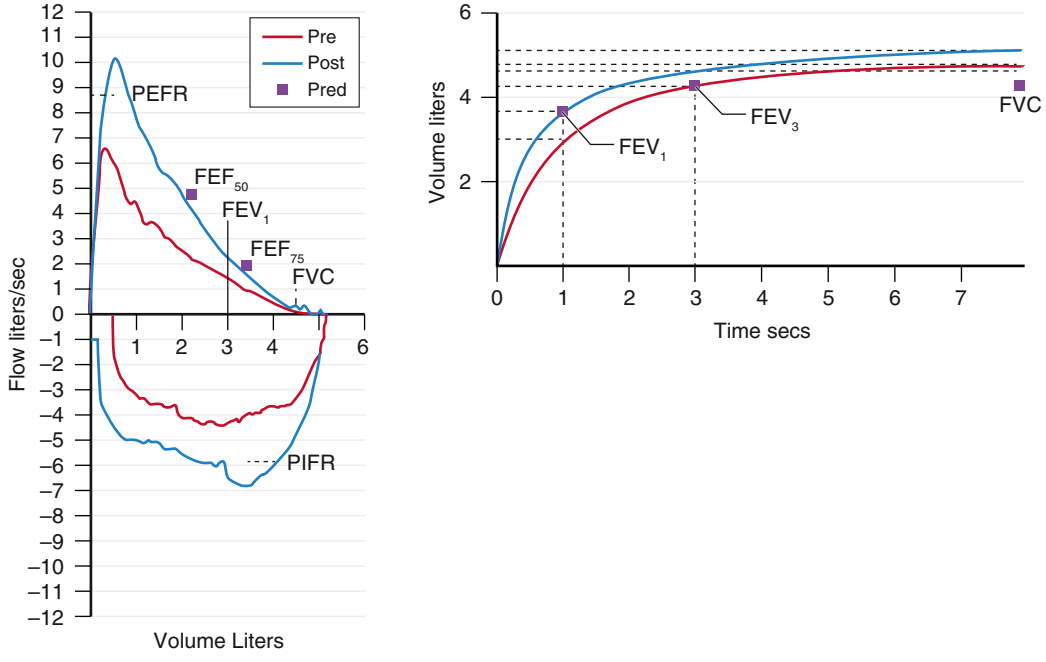

Spirometry (BTPS)

		Pre Bronchodilator			*Predicted Range*		Post Bronchodilator	*Percent*
		Actual	%Pred	Mean	95% CI	Actual	%Pred	Change
FVC	(L)	4.78	105	4.51	3.46	5.12	113	7
FEV_1	(L)	3.01	80	3.75	2.89	3.70	98	22
FEV_1/FVC	(%)	63.00	75	83.00	75.00	72.00	86	14
FEF_{25-75}	(L/s)	1.87	46	4.03		2.64	65	41
PEFR	(L/s)	6.64	75	8.74		10.17	116	53
FET	(sec)	7.89				7.89		

FIGURE 75-2. Lung function test results of a patient with asthma before (*red line*) and after (*blue line*) treatment with inhaled albuterol. BTPS = body temperature, pressure, water vapor saturated; FEF_{25-75} = forced expiratory flow rate of the middle 50% of expiration; FET = forced expiratory time; FEV_1 = forced expiratory volume in the first second; FVC = forced vital capacity; PEFR = peak expiratory flow rate; PIFR = optimal peak inspiratory flow rate; Pred = predicted.

level that can be used to distinguish people without asthma from patients with untreated asthma.

Arterial Blood Gases

Blood gas analysis need not be undertaken in individuals with mild asthma. If the asthma is of sufficient severity to merit prolonged observation, however, blood gas analysis is indicated[6]; in such cases, hypoxemia and hypocapnia are the rule. With the patient breathing ambient air near sea level, the Pa_{O_2} is usually between 55 and 70 mm Hg and the Pa_{CO_2} between 25 and 35 mm Hg. At the onset of the exacerbation, an appropriate pure respiratory alkalemia is usually evident; with exacerbations of prolonged duration, the pH returns toward normal as a result of a compensatory metabolic acidemia. A normal Pa_{CO_2} in a patient with a history of several days of moderate to severe airflow obstruction is reason for concern because it may indicate that the mechanical load on the respiratory system is greater than can be sustained by the ventilatory muscles and that respiratory failure is imminent. When the Pa_{CO_2} increases in such settings, the pH decreases quickly because the bicarbonate stores have become depleted as a result of renal compensation for the prolonged preceding respiratory alkalemia. Because this chain of events can take place rapidly, close observation is indicated for asthmatic patients with "normal" Pa_{CO_2} levels and a history of several days of moderate to severe airflow obstruction.

Other Blood Findings

Patients with asthma are frequently of the "type-2-high" phenotype; thus, blood eosinophilia is common but not universal. The number of eosinophils in a microliter of blood has been used as a method to forecast a given patient's response to anti-cytokine treatment in asthma (see later). In addition, elevated serum levels of immunoglobulin E (IgE) are often documented and are part of the indication for treatment with anti-IgE monoclonal antibodies. If indicated by the patient's history, specific immunosorbent tests, which measure IgE directed against specific offending antigens, can be conducted. Epidemiologic studies indicate that asthma is unusual in subjects with low IgE levels, but some patients with severe asthma have high blood eosinophil levels with low IgE levels.

Radiographic Findings

The chest radiograph of a patient with asthma is often normal. Severe asthma is associated with hyperinflation, as indicated by depression of the diaphragm and abnormally lucent lung fields. Complications of severe asthma, including

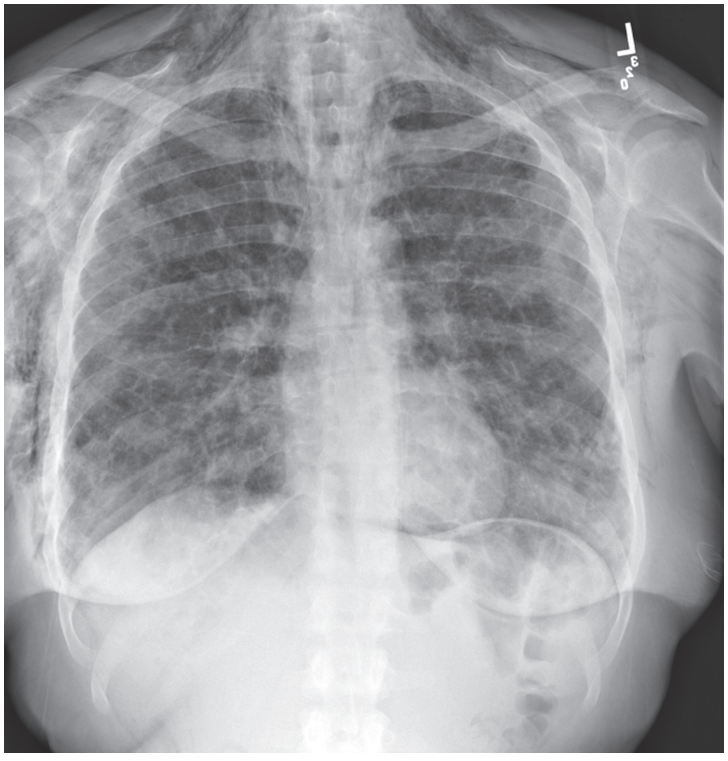

FIGURE 75-3. Chest radiograph showing substantial subcutaneous emphysema and pneumomediastinum in a patient with a severe asthma exacerbation. (Radiograph courtesy Christopher Fanta, MD.)

subcutaneous emphysema, pneumomediastinum (Fig. 75-3), and pneumothorax, may be detected radiographically. In mild to moderate asthma without adventitious sounds other than wheezing, a chest radiograph need not be obtained; if the asthma is of sufficient severity to merit hospital admission, a chest radiograph is advised.

Electrocardiographic Findings

The electrocardiogram, except for sinus tachycardia, is usually normal in acute asthma. However, right axis deviation, right bundle branch block, "P pulmonale," or even ST-T wave abnormalities may arise during severe asthma and resolve as the exacerbation resolves.

Sputum Findings

The sputum of the asthmatic patient may be either clear or opaque with a green or yellow tinge. The presence of color does not invariably indicate infection, and examination of a Gram-stained and Wright-stained sputum smear is indicated. The sputum often contains eosinophils, Charcot-Leyden crystals (crystallized eosinophil lysophospholipase), Curschmann spirals (bronchiolar casts composed of mucus and cells), or Creola bodies (clusters of airway epithelial cells with identifiable cilia that, in fresh samples, often can be seen to beat), which can affect color without the presence of infection. Asthma specialists may examine induced sputum samples to help identify specific asthma endotypes.

DIAGNOSIS

Differential Diagnosis

Asthma is easy to recognize in a young patient without comorbid medical conditions who has exacerbating and remitting airway obstruction accompanied by blood eosinophilia. A rapid symptomatic and laboratory response to bronchodilator treatment is usually all that is needed to establish the diagnosis. However, in the patient with cryptic episodic shortness of breath, an elevated F_{ENO} can help establish a diagnosis of asthma. However, in the absence of an elevated F_{ENO}, other causes of wheezing (see Table 71-4 in Chapter 71) should be investigated. It is important to note that cigarette smoking and the use of inhaled glucocorticoids can lower measured F_{ENO} values, and this information should be used when interpreting this laboratory test. Epidemiologic studies show that up to one-third of patients who have physician-diagnosed asthma may not actually have asthma when they are studied systematically.[7]

TREATMENT

The treatment of asthma is directed at two distinct facets of the disease: the control of symptoms and the prevention of exacerbations.

Symptomatic control is graded by the severity and frequency of asthmatic symptoms during the day, including limitations of activities of daily life, the need to use "rescue" inhaler treatments, and asthmatic symptoms that wake the patient from sleep. The prevention of exacerbations is less linked to symptoms than to levels of lung function, so management must include objective measures of lung function. The best measure is FEV_1, but measures of PEFR can be substituted, especially because inexpensive and easy-to-use peak flowmeters make this measurement feasible in virtually all cases.

Treatment of asthma has two components. The first is the use of acute treatments when the patient has symptoms consistent with airway obstruction; these are known as *rescue treatments*. The second is the use of *controller treatments*, which modify the asthmatic airway environment so that acute exacerbations occur less frequently.[8]

In a given individual, the intensity of asthma treatment is adjusted, for the most part, to achieve five goals:

1. to allow the patient to pursue the activities of her or his daily life without excessive interference from asthma,
2. to allow the patient to sleep without awakening because of asthmatic symptoms,
3. to minimize the use of rescue treatments,
4. to prevent the need for unscheduled medical care, and
5. to maintain lung function reasonably near normal.

The treatment of asthma is divided into five steps ranging from step 1 with minimal treatment to step 5 with very intensive treatment. Based on a patient's history and lung function values, the clinician must decide if the patient's asthma is "in control" or not and note the current treatment step. A patient who is "in control" should stay at their current step or can attempt to step down after about 3 months of stability at a given treatment step. By comparison, a patient whose disease is "out of control" should have their treatment stepped up (Fig. 75-4).

Asthma Medications

Although some chronic asthma treatments are oral, the core of treatment relies on inhaled medications to provide effects directly on the airways and thereby to avoid systemic toxicity.

Using an Inhaler

With all pressurized propellant-driven inhalers (Fig. 75-5), patients should be instructed to exhale to a comfortable volume and to actuate the inhaler as they breathe in very slowly (such as they would when sipping hot soup). Inspiration to near total lung capacity is followed by holding the breath for 10 seconds to allow the deposition of smaller aerosol particles in more peripheral airways (Video 75-2). Patients should be asked to demonstrate their ability to use inhalers correctly and instructed if they are not. Aerosol "spacers" can help patients who have difficulty in coordinating their inspiratory effort and inhaler actuation. For dry-powder inhalers, the manufacturer's directions must be followed because each inhaler differs. With nebulized treatments, patients fill the nebulizer reservoir with the appropriate medication and breathe the generated aerosol quietly until the reservoir is empty.

Inhaled Glucocorticoids

Inhaled glucocorticoids, which have less systemic impact than systemic steroids for a given level of therapeutic effect, are effective controller treatments for improving lung function and preventing asthmatic exacerbations in patients with persistent asthma; inhaled glucocorticoids do not change the long-term natural history of asthma.[9] Inhaled glucocorticoids are combined with inhaled β-agonists for the treatment of acute asthmatic symptoms controller and reliever treatment in which the immediate benefits of bronchodilation with inhaled β-agonists are accompanied by the disease-controlling effects of inhaled glucocorticoids.

All available inhaled glucocorticoids (Table 75-2) are effective treatments for asthma but differ in terms of cost, the magnitude of adrenal suppression, and the potential for systemic effects, including loss of bone mineralization, cataracts, and glaucoma. Overall, no convincing data are available to suggest that there is reason to prefer one glucocorticoid to the others. Adverse effects common to all inhaled glucocorticoids are oral thrush and hoarseness (attributed to myopathy of the laryngeal muscles); the risk and severity can be reduced by aerosol spacers and good oropharyngeal hygiene (i.e., rinsing out the mouth by gargling with drinking water after dosing).

Patients whose disease can be categorized as being in control most of the time without any regularly scheduled treatment are categorized as mild asthma and represent the largest number of asthmatic patients. They are on step 1 of the treatment staircase, and they should use controller and reliever therapy only when they have asthmatic symptoms.[A1-A3]

β_2-Adrenergic Agents

β_2-Adrenergic agonists (Table 75-3) can be classified as short-acting or long-acting. Therapy with β_2-adrenergic agonists always must be accompanied by an inhaled glucocorticoid. Short-acting agonists are used to treat an acute asthmatic exacerbation in patients who are on step 4 or 5 of the treatment staircase and who are already using inhaled glucocorticoids. By comparison, either short

Asthma Treatment Staircase. See legend to understand how to apply		STEP 2	STEP 3	STEP 4	STEP 5
CONTROLLER MEDICATIONS to prevent exacerbations: Primary options	STEP 1 No controller except as needed for symptoms using controller and reliever therapy*	Daily low-dose IGC	Daily low-dose IGC-LABA	Daily high-dose IGC-LABA	Daily high-dose IGC-LABA plus seek expert consultation for anti-cytokine Rx or anti-IgE Rx
Secondary options		LTRA	Daily medium-dose IGC	Daily high-dose IGC, add-on tiotropium	Add oral glucocorticoids at as low a dose as possible
RELIEVER MEDICATIONS to treat symptoms	Controller and reliever therapy*			SABA	

FIGURE 75-4. Asthma treatment algorithm. To use this staircase, determine what treatment your patient is receiving and then if their asthma is "in control" as noted in the text. If the patient's asthma is in control (e.g., with all five stability indicators noted in the text for 2 to 3 months), leave the patient at the current treatment level or decrease one step as indicated in the figure. If the patient's asthma is not in control, increase it from the current level of treatment by one or two steps depending on overall control. If it is not possible to get the patient's asthma in control while using step 4 treatment, it is prudent to refer the patient to a specialty asthma center for evaluation by an asthma expert. Treatments such as asthma biologics (monoclonal antibodies) or daily oral glucocorticoids should be monitored by such a specialist. At steps 1-3, the patient should be instructed to use controller and reliever therapy (termed CART) in which a patient uses an inhaled glucocorticoid and a β_2 selective bronchodilator (either in separate inhalers or as a combined product) to treat bothersome asthmatic symptoms at step 1 or "breakthrough" symptoms in steps 2 and 3. See text for more details of controller and reliever therapy. Ig = immunoglobulin; IGC = inhaled glucocorticoid; IL4r = interleukin-4 receptor; IL5/5r = interleukin-5 or its receptor; LABA = long-acting β_2-agonist; LTRA = leukotriene receptor antagonist; Rx = prescription; SABA = short-acting β_2-agonist. *See legend for an explanation of controller and reliever therapy. (Modified from National Asthma Education and Prevention Program, Update December 2020. https://www.nhlbi.nih.gov/health-topics/all-publications-and-resources/2020-focused-updates-asthma-management-guidelines.)

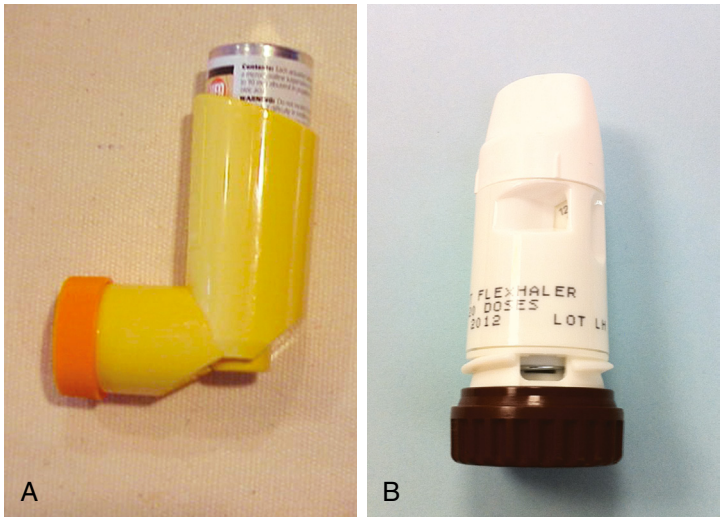

FIGURE 75-5. Commonly used inhalers. A, A pressurized metered-dose inhaler for a branded form of albuterol. Such inhalers propel the medication by means of a pressurized gas; many inhalers use propellants that do not harm the ozone layer, but recent concerns have arisen about greenhouse effects of such gases. **B**, One of many types of dry powder inhalers; the one shown is a Flexhaler and dispenses budesonide. When this type of inhaler is activated, the active agent is released as a dry powder into a chamber. The patient creates the energy for airflow by means of an inspiratory effort that is directed through the device and that entrains medication into the inhaled airway. As a result, effectiveness can be impaired in patients whose airflow is extremely limited.

or long-acting β_2-adrenergic agonists can be used with an inhaled glucocorticoid as part of controller and reliever therapy (see below) when patients are on step 1, 2, or 3 of the treatment staircase.

Short-Acting β-Adrenergic Agents (SABA)

These agents, given by inhalation, are an important part of treatment for asthma. Constricted airway smooth muscle relaxes in response to stimulation of β_2-adrenergic receptors. Short-acting β-adrenergic agonists with varying degrees of β_2-selectivity, onset of action, and duration of response are available for routine use in inhaled (or oral preparations, only in parts of the world where cost or availability limits the use of inhalers) and for emergent use as parenteral preparations.

Long-Acting β-Agonists (LABA)

Long-acting β-agonists should not be used in patients with asthma unless they are given as concomitant treatment with an inhaled glucocorticoid. To avoid inappropriate monotherapy, patients should be prescribed a dual inhaler that contains both an inhaled glucocorticoid and a long-acting β-agonist together so that the treatments with these two agents cannot be separated. Triple inhalers contain an inhaled glucocorticoid, a long-acting β_2-agonist, and a long-acting muscarinic antagonist (see later) in the same aerosol device. Although the combination inhalers are convenient and effective,[A4] they generally are not recommended because of their expense and the problem that "stepping down" treatment requires the patient to switch to entirely different inhalers. When choosing among the many dual combination (i.e., a β_2-agonist and an inhaled glucocorticoid) inhalers available, the selection should be driven by the lowest inhaled dose of glucocorticoid (fluticasone, budesonide, beclomethasone, mometasone, or others) that the patient requires and then identifying a combination product that will also deliver the long-acting β_2-agonist when given as 2 puffs twice per day or less. Prescribing physicians also must consider cost and availability.

Randomized trials demonstrate that, when used with inhaled glucocorticoids, long-acting β_2-agonists do not result in a higher frequency of severe asthmatic events compared with inhaled glucocorticoids alone.[A5]

Antimuscarinic Agents

Agents that inhibit the effects of acetylcholine, which is released from the intrapulmonary motor nerves that run in the vagus nerve and innervate airway smooth muscle, are useful as add-on asthma treatment in step 5. Ipratropium bromide is available in a metered-dose inhaler; the recommended dose is 2 puffs from a metered-dose inhaler every 4 to 6 hours. In adults, inhaled tiotropium (2.5 μg by metered dose inhaler every morning) can be added to an inhaled glucocorticoid as a controller treatment. In patients who have asthma and a low sputum eosinophil level, treatment with tiotropium bromide, 5 μg once-daily, can provide a salutary effect that is equivalent to an inhaled glucocorticoid.[A6] Although other antimuscarinic agents have also been used in the treatment of chronic obstructive pulmonary disease (see Chapter 76), their use in asthma is not evidence based and not recommended.

Antileukotrienes

Agents with the capacity to inhibit the synthesis of the leukotrienes (zileuton, 600 mg four times a day, or controlled-release [Zyflo CR], 1200 mg twice daily) or the action of leukotrienes at the $CysLT_1$ receptor (montelukast [Singulair], 10 mg once a day; pranlukast [Onon, Ultair], 225 mg twice a day, not available in the United States; and zafirlukast [Accolate], 20 mg twice a day) are effective oral controller medications for some patients with mild or moderate persistent asthma. In older patients with asthma, leukotriene inhibitors are equivalent to low-dose inhaled glucocorticoids.[A7] In patients treated with zileuton, alanine aminotransferase levels should be monitored for the first 3 to 6 months; if levels rise to more than three times the upper limit of normal, the drug should be stopped. Theophylline metabolism is slowed by zileuton, so monitoring of levels is indicated if both are prescribed. These treatments can be used on their own for mild persistent asthma or in combination with inhaled glucocorticoids for more severe asthma.

Systemic Glucocorticoids

Systemic glucocorticoids are effective for the treatment of moderate to severe persistent asthma as well as for occasional severe exacerbations of asthma in a patient with otherwise mild asthma. No consensus has been reached on the specific type, dose, or duration of glucocorticoid to be used in the treatment of asthma. In non-hospitalized patients with asthma refractory to standard therapy, a steroid "pulse" of prednisone (40 mg/day for 5 days without a taper)

TABLE 75-2 GLUCOCORTICOID INHALERS USED FOR THE TREATMENT OF ASTHMA

AGENT	COMMON BRAND NAMES*	INHALER TYPES	LOW DOSE	HIGH DOSE	COMMENTS
Beclomethasone dipropionate Standard particle size For extrafine particle size-use half the standard particle size dose	Beclovent, Clenil, Qvar, Asmabec	Comes in both MDI and DPI inhalers with amounts per puff varying from 40-400 µg	1-2 puffs twice a day of low strength	5-6 puffs twice a day of high strength	Inhaled glucocorticoid with the longest use record. Although medication is generic, the inhaler type and propellant may be proprietary. Dose adjustments for patients in renal or hepatic failure are not needed
Budesonide	Budelin, Pulmicort	Inhalers are all DPIs with amounts per dose 100-400 µg. Solution for nebulization is also available with amount of drug per treatment varying between 0.5 and 1.0 mg	1-2 puffs twice a day of the 100 µg strength	1-2 puffs twice a day of the 400-µg strength The maximum DPI dose is two puffs twice daily of the 400-µg strength. The maximum nebulized dose is 4 mg/day.	Dose adjustments for patients in renal or hepatic failure are not needed
Ciclesonide	Alvesco	MDIs delivering 80 or 160 µg	1 puff of the 80-µg strength twice daily	2 puffs of the 160-µg strength twice daily. The maximum dose is 2 puffs twice daily of the highest strength	Dose adjustments for patients in renal or hepatic failure are not needed
Fluticasone propionate	Flovent, Flixotide	MDIs with 50, 125, 250 µg dose strengths; DPIs 50, 100, 250 µg; packets for nebulization at 0.25 and 1.0 mg/mL	1-2 puffs twice/day of 50 µg/puff dose strength With nebulizer, 1 mL of 0.25 mg/mL twice a day	1-2 puffs twice/day of 250-µg/puff dose strength-the maximum dose is two puffs twice daily of the 250 µg/puff dose With nebulizer, 1 mL of 1.0 mg/mL twice a day, which is the maximum dose	Dose labels vary depending on whether it is the amount loaded in the metering chamber (outside of United States [U.S.]) vs. the dose leaving the inhaler (U.S.). The three strengths are generally equal to low, medium, and high doses Dose adjustments for patients in renal failure not needed. In patients with hepatic failure, patients should be carefully monitored for steroid side effects and dose adjusted appropriately
Fluticasone furoate (DPI)	Arnuity Ellipta	DPIs with strengths of 50, 100 and 200 µg/dose	1 puff daily of the 50-µg/dose	1 puff daily of the 200-µg/dose The above is the maximum recommended dose	Once-daily dosing
Mometasone furoate	Asmanex	MDI with strengths of 100 and 200-µg/dose DPIs with strengths of 100 and 200 µg/dose	1 puff low strength daily	2 puffs high strength twice a day	Dose adjustments for patients in renal failure not needed. In patients with hepatic failure, patients should be carefully monitored for steroid side effects and dose adjusted appropriately

*Not all products marketing each medication are listed.
DPI = dry powder inhaler; MDI = metered dose inhaler.

TABLE 75-3 SELECTED SHORT-ACTING INHALED β-ADRENERGIC AGONISTS FOR ASTHMA[†]

GENERIC NAME	TRADE NAME*	DOSE/PUFF	DOSE AS PUFFS	COMMENTS
Albuterol-MDI[‡]	AccuNeb, Proair HFA, Proventil HFA, Ventolin HFA, Airomir HFA, Salamol HFA	Varies from 90-200 µg	2 puffs as needed for asthma symptoms. Can be repeated every 4 hr. 10-12 puffs in 24 hr is the maximum dose. Use of more than 6 puffs/day should prompt medical consultation for asthma control.	All are metered-dose inhalers that deliver a fixed amount of medication per puff
Albuterol-DPI	Ventolin, Asmasal, Salbulin	100 or 200 µg	1 puff as needed, otherwise same as albuterol MDI	All are dry powder inhalers that deliver a fixed amount of medication per inhalation
Albuterol solution	—	Varies from 0.63 mg/mL to 5 mg/mL	Inhale while breathing till solution consumed. Need for more than 6 home treatments/day should prompt medical consultation.	This solution is for use with a liquid nebulizer driven by compressed gas. Mix the dose with a volume of sterile normal saline to achieve a nebulizer concentration of 0.63 mg/mL
Levalbuterol-MDI	Xopenex HFA		Same as albuterol-MDI	The isolated R-isomer of albuterol. Some studies show superiority to the racemic albuterol found in the MDIs listed above
Levalbuterol-solution	Xopenex inhalation solution	0.63 mg/mL	Same as albuterol solution	Nebulizer solution as noted for albuterol above
Terbutaline-DPI	Bricanyl	250 or 500 µg	Same as albuterol-MDI	Dry powder inhaler, uses patient-generated effort to achieve airflow to disperse and deposit medication
Terbutaline solution	Bricanyl inhalation solution	2.5 mg/mL	Same as albuterol	The per dose amount is 2 mL with sterile saline added to achieve the requisite volume for the nebulizer used

*Not all products marketing each medication are listed.
[†]All have onset of effect 5 to 10 minutes and duration of effect 4 to 8 hours. All patients with asthma should have a short-acting bronchodilator as a rescue inhaler to use for rescue from signs of airway obstruction.
[‡]The generic names albuterol and salbutamol are synonyms. Albuterol is used in the United States and salbutamol in many other countries.
DPI = dry powder inhale; HFA = hydrofluoroalkane; MDI = metered dose inhaler.

is recommended.[A8] When patients cannot stop taking steroids without having recurrent uncontrolled bronchospasm, referral to an asthma specialist for biologic treatment is indicated. For patients whose asthma requires in-hospital treatment but is not considered life-threatening, an initial intravenous bolus of 2 mg/kg of hydrocortisone, followed by continuous infusion of 0.5 mg/kg/hour, has been shown to be beneficial within 12 hours. In exacerbations of asthma that are considered life-threatening, the use of intravenous methylprednisolone (125 mg every 6 hours) has been advocated. As the patient improves, oral steroids are substituted for intravenous steroids, and the oral dose is tapered during 1 to 3 weeks; addition of inhaled steroids is strongly recommended when oral steroids are started. Patients whose asthma requires oral glucocorticoid treatment to maintain control are prime candidates for monoclonal antibody treatment.

Monoclonal Antibody Treatment

Monoclonal antibodies are effective in carefully selected patients under expert guidance,[10-12] but they are quite expensive. Most insurance companies require specific clearance before these drugs can be administered, and they should be prescribed only by an asthma specialist who is familiar with their use.

Omalizumab (Xolair), a humanized murine monoclonal antibody that binds circulating IgE, is associated with decreased serum free (not total) IgE levels. In patients who have moderate to severe allergic asthma with elevated levels of serum IgE and who are receiving inhaled glucocorticoids, omalizumab treatment improves asthma control even as doses of inhaled steroids are decreased.[13] Dosing is guided by weight and by pretreatment IgE levels: a monthly subcutaneous dose of 0.016 mg × body weight (kg) × IgE level (IU/mL). Dosing calculators can be found online (e.g., https://www.xolairhcp.com/starting-treatment/dosing.html). Treatment with anti-IgE antibodies can reduce asthma exacerbations and improve quality of life in patients with severe allergic asthma; it is also useful in patients with aspirin-exacerbated respiratory disease (see later), but omalizumab's place in treatment schema has not been fully established. Because of the potential for anaphylaxis, all patients need to be monitored for 30 to 60 minutes after injection.

Mepolizumab (Nucala) is a humanized monoclonal antibody directed against IL-5. In randomized trials, it reduces asthma exacerbations by about 50% among patients who have severe asthma and who still have blood eosinophils greater than 150 cells/µL despite treatment with oral or high-dose inhaled glucocorticoids. In patients requiring daily oral glucocorticoid therapy to maintain asthma control, mepolizumab has a significant glucocorticoid-sparing effect.[A9] The dose is 100 mg subcutaneously every 4 weeks.

Reslizumab (Cinqair), which is another humanized monoclonal antibody against circulating IL-5 for patients with severe eosinophilic asthma, has benefits similar to mepolizumab. At 3 mg/kg intravenously every 4 weeks, it can reduce the frequency of exacerbations by about 50% in patients who had asthma and elevated blood eosinophil counts and who were inadequately controlled on inhaled glucocorticoid-based therapy.[A10]

Benralizumab (Fasenra) is a humanized monoclonal antibody against the α subunit of the IL-5 receptor that induces near-complete depletion of eosinophils and basophils in the circulation and lung tissue. In randomized trials, benralizumab (30 mg subcutaneously every 4 to 8 weeks) reduced exacerbations by 50% and improved lung function in patients with severe eosinophilic asthma, often despite a reduced dose of oral glucocorticoids.[A11]

Dupilumab (Dupixent), a monoclonal antibody against the α subunit of the shared interleukin-4 and interleukin-13 receptor (at 300 mg subcutaneously every 2 weeks), can improve the control of moderate to severe asthma and allow the dose of inhaled and oral glucocorticoids to be reduced, oftentimes with an improvement in lung function as well.[A12]

Tezepelumab, a human monoclonal antibody specific for the epithelial-cell-derived cytokine thymic stromal lymphopoietin (at 210 mg given subcutaneously every 4 weeks), reduces asthma exacerbations among patients treated with medium-to-high doses of inhaled glucocorticoids and at least one additional controller medication with or without oral glucocorticoids,[A13] regardless of their blood eosinophil level, although efficacy is greater when patients have a higher percentage of eosinophils in their peripheral blood.

Theophylline

Theophylline, and its more water-soluble congener aminophylline, are moderately potent bronchodilators. Because of potential toxicity and the availability of other regimens, they are not recommended for routine outpatient treatment. An exception is that aminophylline, given intravenously, can be helpful for the treatment of status asthmaticus.

Other Medical and Procedural Options

Vaccination for Seasonal Influenza, Pneumococcal Disease, and COVID-19

Vaccination (Chapter 15) for seasonal influenza (Chapter 332), pneumococcal disease (Chapter 268), and COVID-19 (Chapter 337) is recommended because all are efficacious, safe, and not associated with enhanced risk of asthmatic exacerbations. No worsening of any component of asthma has been identified with any of the vaccines.

Antibiotics

Azithromycin (500 mg 3 times a week for 48 weeks) added to standard step 4 treatment (Fig. 75-4) in patients with persistent symptomatic asthma can reduce exacerbations and improve quality of life in patients with persistent symptoms but at the expense of more diarrhea and an unknown risk of selecting resistant organisms.[A14] The electrocardiographic QT-C interval should be monitored to detect a risk of potentially serious cardiac arrythmias.

Suppression of Gastric Acid

Proton-pump inhibitor treatment had been advocated based on the concern that asthma could be caused by silent gastroesophageal reflux disease, even in

the absence of gastrointestinal symptoms. Adequately powered clinical studies suggest that this approach provides no benefit for asthma control.

Radio Frequency Ablation of Airway Smooth Muscle

A proprietary system to ablate airway smooth muscle by delivery of radio frequency energy through a bronchoscopically placed probe has reduced exacerbations of asthma in sham-controlled trials among patients whose asthma remained out of control despite the use of multiple controller medications. Although a device for such treatment has been approved by the FDA, specific recommendations with respect to its use are not available, and it should be considered only at specialized centers.

Treatment of Specific Clinical Scenarios

Consensus guidelines recommend a stepped approach to the treatment of asthma (Fig. 75-4).

Minimally Symptomatic Patients

At the mild end of the spectrum (i.e., step 1 of the staircase), a patient who has rare limitations in activities of daily life, has nearly normal lung function, and sleeps without interruption from asthma can be prescribed a combination inhaler with a rapid-onset, long-acting β-agonist (e.g., formoterol plus a glucocorticoid; see Table 75-4) to use as a rescue inhaler on an as-needed basis or be prescribed a combination inhaler with a short-acting β-agonist plus a glucocorticoid (e.g., 180 μg albuterol/160 μg budesonide, with 2 puffs given up to 6 times a day). If a combination inhaler is not available or is cost prohibitive, the patient should use their short-acting β-agonist inhaler and their glucocorticoid inhaler one after the other up to 6 times per day.[A15-A18] Alternatively, for the patient who uses nebulized treatment on an intermittent basis, treatment with a short-acting β-agonist should ALWAYS be accompanied a treatment with an inhaled glucocorticoid. If a patient has a requirement for such rescue treatment more than twice weekly (excluding events brought on by exercise), they should progress to step 2 of the staircase with maintenance controller treatment with an inhaled glucocorticoid (see Table 75-2) or an anti-leukotriene (should be added, starting at the lowest dose recommended for the particular drug). For inhaled glucocorticoids, treatment can be escalated either by increasing the number of puffs or the strength per puff until control is achieved—this approach cycles the patient through low-, medium-, and high-dose inhaled glucocorticoid therapy (see Fig. 75-4) and will move the patient "up the staircase" to steps 3 and 4.

Rescue for Acute Exacerbations

All patients who have asthma should be prescribed a rescue treatment to be used if they develop symptoms consistent with acute asthmatic airway obstruction.[14] Rescue treatment should always include a rapid-acting inhaled β-agonist (Table 75-4). If appropriate dual-medication inhalers containing both drugs are not available, patients should be instructed to use sequential separate inhalers or nebulizer treatments, one containing a short-acting β_2-selective agonist and another containing an inhaled glucocorticoid, taken one after the other. For the patient who is already using low to medium doses of inhaled glucocorticoids (i.e., those on step 2 or 3 of therapy; see Fig. 75-4) and who then develops an exacerbation, a self-directed quadrupling of the inhaled glucocorticoid can abort the exacerbation and reduce the number of severe exacerbations by about 30%.[A19]

Patients Not on Chronic Asthma Medication

Most patients with mild asthma do not require regularly scheduled treatment, but should be treated with controller and reliever therapy when they develop asthmatic symptoms. Controller and reliever therapy with formoterol plus budesonide or albuterol plus budesonide (see Table 75-4) can potentially be used as up to 12 inhalations (6 treatments of 2 puffs each) from a combination inhaler per day without toxicity, although most patients use this combination at much lower frequencies. (This use of combination formoterol-inhaled glucocorticoid for "as-needed" asthma treatment is approved in many other countries around the world but is *off-label* for budesonide-formoterol in the United States. An albuterol plus budesonide combination inhaler is approved in the United States.)

For all IGC-containing inhalers after inhalation, the patient should rinse his/her mouth with water without swallowing to help reduce the risk of oropharyngeal candidiasis.

Concurrent Pulmonary Infection

In some patients, acute exacerbations of asthma may be due to concurrent infection, which requires targeted therapy (Chapters 76, 78, and 85). In patients with suspected or known infection with severe acute respiratory syndrome coronavirus-2 (Chapter 336), all asthma treatments should be continued as prescribed, including inhaled or systemic glucocorticoids.

Aspirin-Exacerbated Respiratory Disease (Previously Termed Aspirin-Induced Asthma)

Approximately 5% of patients with moderate to severe persistent asthma develop asthma when they ingest agents that inhibit cyclooxygenase, such as aspirin and other nonsteroidal anti-inflammatory drugs.[15] Inhibitors of cyclooxygenase 2 are less likely to cause these reactions, but aspirin-type reactions have been reported in sensitive patients treated with selective cyclooxygenase 2 inhibitors. The physiological manifestations of a laboratory-based aspirin challenge can be blocked by inhibitors of the leukotriene pathway and by omalizumab, but only omalizumab has been shown to prevent clinical disease.[A20] For most patients with this disorder, avoidance of aspirin and other nonsteroidal anti-inflammatory drugs is the first-line therapy, but omalizumab (see Monoclonal Antibody Treatment above for dosing) is indicated if that approach is not successful.

Exercise-Induced Asthma

Patients who develop asthmatic symptoms most prominently with exercise are said to have exercise-induced asthma.[16] In such patients preexercise treatment is recommended. Although 2 puffs of an inhaler containing a short-acting β-agonist had been the standard of care, expert opinion now suggests using a combination formoterol-budesonide inhaler before exercise for this purpose.

Allergic Bronchopulmonary Aspergillosis

Some patients with asthma as well as some patients with cystic fibrosis (Chapter 77), develop a phenotype characterized by wheezing, sputum containing brown sputum plugs, intermittent hemoptysis, fleeting pulmonary infiltrates, high levels of serum IgE, (often >1000 IU/mL), positive skin test reactions to *Aspergillus fumigatus* (Chapter 311), and positive IgG titers to *A. fumigatus*. When this combination of findings is present, the diagnosis is allergic of bronchopulmonary is established.[17]

Treatment with oral prednisone at (0.5 mg/kg a day for 4 weeks, then reducing the dose by 50% for 4 weeks, and finally reducing the dose by 50% for another 4 weeks before discontinuing it). Monotherapy with voriconazole (200 mg twice daily for 4 months) is usually successful and is as effective as prednisolone (dosed as noted earlier) for preventing exacerbations.[A21]

Occupational Asthma

Occupational asthma is discussed in Chapter 81.

Asthma in the Emergency Department

When a patient with asthma presents for acute emergency care, objective measures of the severity of the exacerbation, including quantification of pulsus paradoxus and, if the patient's dyspnea allows it, measurement of airflow rates (PEFR or FEV_1), should be evaluated in addition to the usual vital signs. If the exacerbation has been prolonged and failed to respond to treatment with bronchodilators (e.g., albuterol by metered-dose inhaler, two puffs every 2 to 3 hours) and high-dose inhaled glucocorticoids (see Table 75-2) before arrival at the emergency department, high-dose inhaled glucocorticoids should be continued[A22] and intravenous glucocorticoids (40 to 60 mg of methylprednisolone or its equivalent) should be administered. If the patient has not been receiving treatment with a leukotriene receptor antagonist, such agents should be administered (10 mg of montelukast or 20 mg of zafirlukast) as soon as possible. Treatment with inhaled β-agonists (either nebulized albuterol, 0.5 mL of a 0.5% solution repeated at 20- to 30-minute intervals, or albuterol by metered-dose inhaler, 2 puffs every 30 minutes) should be used until the PEFR or FEV_1 increases to greater than 40% of the predicted values or the patient shows obvious signs of clinical improvement, such as a slowed respiratory rate, a decrease in the magnitude of pulsus paradoxus, or less use of accessory muscles of ventilation. If this point is not reached within 2 hours, admission to the hospital for further treatment is strongly advocated.

When patients have PEFR and FEV_1 values that are greater than 60% of their predicted value on arrival in the emergency department, treatment with inhaled β_2-agonists alone, albuterol (0.5 mL of an albuterol 0.083% solution) or equivalent, is likely to result in an objective improvement in airflow rates. If significant improvement takes place in the emergency department, such patients can usually be treated as outpatients with inhaled β_2-agonists and a controller agent (see Fig. 75-4). A good strategy is to add inhaled glucocorticoids if the patient has not been receiving this treatment or has been using a single controller therapy.

For patients whose PEFR and FEV_1 values are between 40 and 60% of the values predicted at the time of initial evaluation in the emergency care setting, a plan of treatment varying in intensity between these two plans is indicated. Failure to respond to treatment by objective criteria (e.g., respiratory rate, PEFR or FEV_1) within 2 hours of arrival at the emergency department is an indication for the use of systemic glucocorticoids.

Status Asthmaticus

Status asthmaticus is defined as a PEFR or FEV_1 that does not increase to greater than 40% of the predicted value with treatment, an increasing $Paco_2$ without improvement of indices of airflow obstruction, or the development of a major complication, such as pneumothorax, pneumomediastinum, acute myocardial ischemia (Chapter 57), or a cardiac tachyarrhythmia other than sinus tachycardia (Chapter 52). Patients who have status asthmaticus should be admitted to the hospital for close monitoring. Frequent treatments with inhaled β-agonists (0.5 mL of an albuterol 0.083% solution every 2 hours), intravenous aminophylline (at doses to yield maximal acceptable plasma levels, that is, 15 to 20 μg/mL; 500- to 1000-mg loading dose given during an hour followed by an infusion of 30 to 60 mg/hour), and high-dose intravenous steroids (methylprednisolone, 40 to 60 mg every 4 to 6 hours) are indicated. Oxygen should be administered by face mask or nasal cannula in amounts sufficient to achieve Spo_2 values between

TABLE 75-4 SELECTED COMBINED INHALED FDA-APPROVED INHALED MEDICATIONS FOR MAINTENANCE TREATMENT OF ASTHMA

GENERIC NAME	TRADE NAME*	DOSE/PUFF	DOSE AS PUFFS	COMMENTS
COMBINATION INHALERS THAT CAN BE USED AT ALL ASTHMA STEPS				
IGC = budesonide LABA = formoterol	Symbicort, Generic	Available only as MDIs. Each strength contains the same fixed dose of LABA with varying amounts of IGC. Exact amounts vary by inhaler type.	Start with one puff twice daily at the lowest dose of IGC that is effective for asthma control. Titrate up and down as symptom control requires. Max dose is 4 puffs of highest strength per day.	Dose adjustments for patients in renal or hepatic failure are not needed. When used as both regular maintenance and controller and reliever therapy, which is not FDA approved, the maximum dose is 12 puffs a day. This is the only LABA-IGC combination that can be used with this frequency.
IGC = budesonide SABA = albuterol	Airsupra	MDI containing 180 µg of albuterol and 160 µg of budesonide	FDA approved for use when asthma symptoms require treatment as 2 puffs per treatment; 6 treatments (12 puffs) is the maximum daily dose.	If available a formoterol/IGC combination is preferred. Dosing is not adjusted for renal or hepatic failure.
IGC = fluticasone propionate LABA = salmeterol	Advair Diskus, Advair HFA, AirDuo Digihaler, AirDuo RespiClick, Wixela Inhub, Generic	Available as MDIs or DPIs. Each type contains the same fixed dose of LABA with varying amounts of IGC. Exact amounts vary by inhaler type.	Start with one puff twice daily at the lowest dose of IGC that is effective for asthma control. Titrate up and down as symptom control requires. Max dose is 4 puffs of highest strength per day.	Dose adjustments for patients in renal failure not needed. In patients with hepatic failure, patients should be carefully monitored for steroid side effects and dose adjusted appropriately.
IGC = mometasone LABA = formoterol	Dulera	Available only as MDIs. Each strength contains a 5-µg dose of formoterol with 50, 100, or 200 µg doses of mometasone.	Start with one puff twice daily at the lowest dose of IGC that is effective for asthma control. Titrate up and down as symptom control requires. Max dose is 4 puffs of highest strength per day.	Dose adjustments for patients in renal or hepatic failure are not needed.
IGC = fluticasone furoate LABA = vilanterol	Breo Ellipta	All forms contain 25 µg of vilanterol with 100 (low strength) or 200 µg (high strength) of fluticasone furoate-once daily dosing.	Adjust IGC dose to achieve asthma control with a dose of 1 puff once/day.	Bronchodilator effect of vilanterol onsets in about 15 min. Maximum dose is 1 puff of high strength per day. Dose adjustments for patients in renal failure not needed. In patients with hepatic failure, patients should be carefully monitored for steroid side effects and dose adjusted appropriately.
TRIPLE COMBINATION INHALERS CONTAINING AN IGC, A LABA, AND A LONG-ACTING MUSCARINIC ANTAGONIST (LAMA)*				
IGC = fluticasone furoate LABA = vilanterol trifenatate LAMA = umeclidinium bromide	Trelegy Ellipta†	Products are DPIs. All inhalers contain per puff 62.5 µg of umeclidinium bromide and 25 µg of vilanterol trifenatate with either 100 or 200 µg of fluticasone furoate with once-daily dosing.	Adjust IGC dose to achieve asthma control with a dose of 1 puff once/day.	Bronchodilator effect of vilanterol onsets in about 15 min. Maximum dose is 1 puff of high strength per day. Dose adjustments for patients in renal failure not needed. In patients with hepatic failure, patients should be carefully monitored for steroid side effects and dose adjusted appropriately. Urinary retention may occur. Close monitoring for glaucoma and cataracts is warranted; use in patients with patients with narrow angle glaucoma may require ophthalmologic consultation.
IGC = budesonide LABA = formoterol fumarate LAMA = glycopyrrolate	Breztri Aerosphere‡	Product is an MDI containing a combination 160 µg of budesonide, 9 µg of glycopyrrolate and 4.8 µg of formoterol fumarate per inhalation.	Adjust dose to achieve asthma control using 1-2 puffs twice daily. Maximum dose is 2 puffs twice daily.	Dose adjustments for patients in renal or hepatic failure are not needed. Urinary retention may occur. Close monitoring for glaucoma and cataracts is warranted; use in patients with patients with narrow-angle glaucoma may require ophthalmologic consultation.

*Not all products marketing each medication are listed. Only products containing formoterol as the LABA should be used for rescue treatment.

†FDA approved for asthma.

‡Not FDA approved for asthma—thus use is off label. This is a scheduled maintenance treatment; acute symptoms should be treated with a SABA + IGC or LABA + formoterol at steps 1 and 2 and a SABA alone at steps 4 and 5.

DPI = dry powder inhaler; FDA = U.S. Food and Drug Administration; HFA = hydrofluoroalkane; IGC = inhaled glucocorticoid; LABA = long-acting β-agonist; LAMA = long-acting muscarinic antagonist; MDI = metered dose inhaler; SABA = short-acting β-agonist.

92% and 94%; a higher F_{IO_2} promotes absorption atelectasis and provides no therapeutic benefit. If objective evidence of an infection is present, appropriate treatment should be given for that infection. If no improvement is seen with treatment and if respiratory failure appears imminent, bronchodilator treatment should be intensified to the maximum tolerated by the patient as indicated by the maximum tolerated heart rate, usually 130 to 140 beats per minute. If indicated, intubation of the trachea and mechanical ventilation can be instituted; in this case, the goal should be to provide a level of ventilation just adequate to sustain life but *not sufficient to normalize arterial blood gases*. For example, a P_{aCO_2} of 60 to 70 mm Hg, or even higher, is acceptable for a patient in status asthmaticus.

Asthma in Pregnancy

Asthma may be exacerbated, remain unchanged, or remit during pregnancy (Chapter 221), and the ordinary management of asthma need not be changed during pregnancy.[18] The only potential difference is that one randomized trial suggests that, unlike in other settings, measurement of the fraction of exhaled nitric oxide can improve the management of asthma during pregnancy.

Good asthma control is beneficial to both the mother and the fetus, and key medications (inhaled glucocorticoids, β_2-agonists, montelukast, and theophylline) are not associated with an increased incidence of fetal abnormalities, but long-acting muscarinic antagonists should be avoided to prevent fetal tachycardia. Most importantly, no unnecessary medications should be administered; systemic steroids should be used sparingly to avert fetal complications, and certain drugs should be avoided: ipratropium bromide and tiotropium, which may cause fetal tachycardia; terbutaline, which is contraindicated during active labor because of its tocolytic effects; and tetracycline, which should not be used as a treatment of intercurrent infection. Biologic therapies for asthma have not been assigned a pregnancy risk category, so the risks and benefits of treatment should be weighed under expert care, and such agents should be used only if their benefit outweighs the risk to the fetus. Conversely, use of prostaglandin $F_{2\alpha}$ as an abortifacient should be avoided in asthmatic patients because of the potential for bronchoconstriction due to these agents.

PROGNOSIS

Asthma is a chronic relapsing disorder. Most patients have recurrent exacerbations without a major loss in lung function for many years. A minority of patients experience a significant irreversible loss in lung function over and above the normal pulmonary senescence. Risk factors for death from asthma include the need for emergent intensive care in the prior year, overuse of short-acting β-adrenergic agonists, poor adherence to medications, and comorbid conditions such as diabetes, cardiac arrhythmias, and psychiatric disease.

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76 CHRONIC OBSTRUCTIVE PULMONARY DISEASE

JOHN REILLY

DEFINITION

Chronic obstructive pulmonary disease (COPD) is an umbrella term for a number of conditions that result in fixed airway obstruction and dyspnea on exertion. COPD is characterized by persistent respiratory symptoms and airflow limitation that is due to airway or alveolar abnormalities usually caused by significant exposure to noxious particles or gases. Nearly all patients have both the air space destruction associated with emphysema as well as the pathologic airway changes that are consistent with chronic bronchitis. However, subsets of the COPD population can differ in terms of natural history and response to therapeutic intervention. Daily cough and sputum for 3 months for 2 or more years is the qualifying definition for chronic bronchitis.

Airflow limitation is defined as a ratio of forced expiratory volume in 1 second (FEV_1) and the forced vital capacity (FVC) of less than 0.7 ($FEV_1/FVC < 0.7$) (Chapter 73). Classification systems can also incorporate other characteristics that are independent predictors of symptoms and mortality (Fig. 76-1).

EPIDEMIOLOGY

COPD is a disease of adults, typically presenting in the sixth decade of life or later, with an estimated global prevalence of 175 million. The estimated annual 3.2 million deaths from COPD make it the third leading cause of death worldwide.[1] Given the lag time between the initiation of smoking and the development of clinical disease, the global prevalence of cigarette smoking and the aging of the population imply that the number of cases will continue to increase. In the United States, the costs associated with COPD are estimated to be about $50 billion annually: $30 billion in direct medical costs and $20 billion in indirect costs.

Epidemiologic data support the concept that habitual cigarette smoking is the major risk factor for the development of COPD.[2] At the population level, the smoking "dose," as measured in pack-years (the product of the number of packs of cigarettes smoked per day and the number of years with the habit at this intensity), is inversely related to FEV_1. Factors that impair full lung growth, including childhood respiratory infections, result in lower peak lung function in adulthood; subsequent decline, whether accelerated or not, can result in the development of COPD (E-Fig. 76-1). Cigarette smoking is by far the major contributor to the development of COPD, but other implicated exposures include combustion of biomass fuels, especially in poorly ventilated spaces where such materials are used for cooking food and heating.[3] The role of environmental air pollution is less clear. Cough, sputum, and permanent loss of lung function may also occur among individuals who are exposed to workplace dust in mines, grain-handling facilities, and cotton mills. Although data show that increased pollution levels are temporally associated with increased mortality in patients with established COPD, it is less clear whether air pollution alone

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76 CHRONIC OBSTRUCTIVE PULMONARY DISEASE

JOHN REILLY

DEFINITION

Chronic obstructive pulmonary disease (COPD) is an umbrella term for a number of conditions that result in fixed airway obstruction and dyspnea on exertion. COPD is characterized by persistent respiratory symptoms and airflow limitation that is due to airway or alveolar abnormalities usually caused by significant exposure to noxious particles or gases. Nearly all patients have both the air space destruction associated with emphysema as well as the pathologic airway changes that are consistent with chronic bronchitis. However, subsets of the COPD population can differ in terms of natural history and response to therapeutic intervention. Daily cough and sputum for 3 months for 2 or more years is the qualifying definition for chronic bronchitis.

Airflow limitation is defined as a ratio of forced expiratory volume in 1 second (FEV_1) and the forced vital capacity (FVC) of less than 0.7 ($FEV_1/FVC < 0.7$) (Chapter 73). Classification systems can also incorporate other characteristics that are independent predictors of symptoms and mortality (Fig. 76-1).

EPIDEMIOLOGY

COPD is a disease of adults, typically presenting in the sixth decade of life or later, with an estimated global prevalence of 175 million. The estimated annual 3.2 million deaths from COPD make it the third leading cause of death worldwide.[1] Given the lag time between the initiation of smoking and the development of clinical disease, the global prevalence of cigarette smoking and the aging of the population imply that the number of cases will continue to increase. In the United States, the costs associated with COPD are estimated to be about $50 billion annually: $30 billion in direct medical costs and $20 billion in indirect costs.

Epidemiologic data support the concept that habitual cigarette smoking is the major risk factor for the development of COPD.[2] At the population level, the smoking "dose," as measured in pack-years (the product of the number of packs of cigarettes smoked per day and the number of years with the habit at this intensity), is inversely related to FEV_1. Factors that impair full lung growth, including childhood respiratory infections, result in lower peak lung function in adulthood; subsequent decline, whether accelerated or not, can result in the development of COPD (E-Fig. 76-1). Cigarette smoking is by far the major contributor to the development of COPD, but other implicated exposures include combustion of biomass fuels, especially in poorly ventilated spaces where such materials are used for cooking food and heating.[3] The role of environmental air pollution is less clear. Cough, sputum, and permanent loss of lung function may also occur among individuals who are exposed to workplace dust in mines, grain-handling facilities, and cotton mills. Although data show that increased pollution levels are temporally associated with increased mortality in patients with established COPD, it is less clear whether air pollution alone

ABSTRACT

Chronic obstructive pulmonary disease (COPD) is a syndrome that encompasses a number of conditions that share the property of expiratory airflow obstruction that does not fully reverse with bronchodilator therapy. These syndromes include chronic bronchitis and emphysema. COPD is common and a major source of health care expenditures, morbidity, and mortality. It results in exercise limitation due to dyspnea, cough, sputum production, and, in a subset of patients, recurrent exacerbations. It most often results from habitual cigarette smoking, but other exposures have been implicated, as have genetic factors. The inflammatory response engendered by inhalational exposure disrupts protease/antiprotease balance and can also affect vascular and apoptotic pathways and trigger an autoimmune response. A major source of morbidity and expense for this condition includes acute exacerbations, characterized by increased dyspnea, increased cough, and an increase and/or change in character of sputum. Exacerbations are often accompanied by fever and systemic symptoms suggestive of infection. Current therapeutic strategies focus on prevention, primarily smoking cessation; symptom control; exacerbation prevention; and, in selected cases, the use of supplemental oxygen, pulmonary rehabilitation, surgical intervention, or lung transplantation. Current pharmacotherapy is delivered primarily by the inhalational route, and the three most common classes of agents are β-agonists, anticholinergics, and inhaled corticosteroids. The first two are bronchodilators, whereas inhaled corticosteroids are primarily anti-inflammatory. All have been shown to improve symptoms, produce modest improvements in measured lung function, and reduce the frequency of exacerbations. There is some additive benefit to using more than one class of agent. Exacerbations are treated with systemic corticosteroids, inhaled bronchodilators, oxygen when indicated, and, in most cases, antibiotics.

KEYWORDS

emphysema
chronic bronchitis
chronic obstructive pulmonary disease
COPD
inhaled corticosteroids
oxygen therapy
lung volume reduction surgery

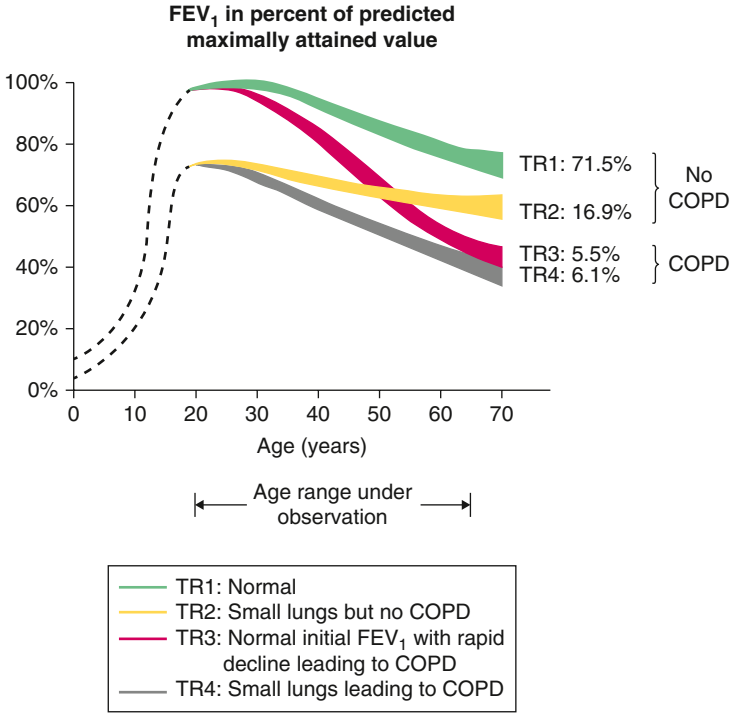

E-FIGURE 76-1. Decline in lung function with age. COPD = chronic obstructive pulmonary disease; FEV_1 = forced expiratory volume in 1 second; TR = hypothetical trajectories. (Adapted from Global Initiative for Chronic Obstructive Lung Disease [GOLD]. Global strategy for the diagnosis, management and prevention of COPD. http://goldcopd.org. Accessed March 20, 2018. Based on Lange P, Celli B, Agusti A, et al. Lung-function trajectories leading to chronic obstructive pulmonary disease. *N Engl J Med*. 2015;373:111-122.)

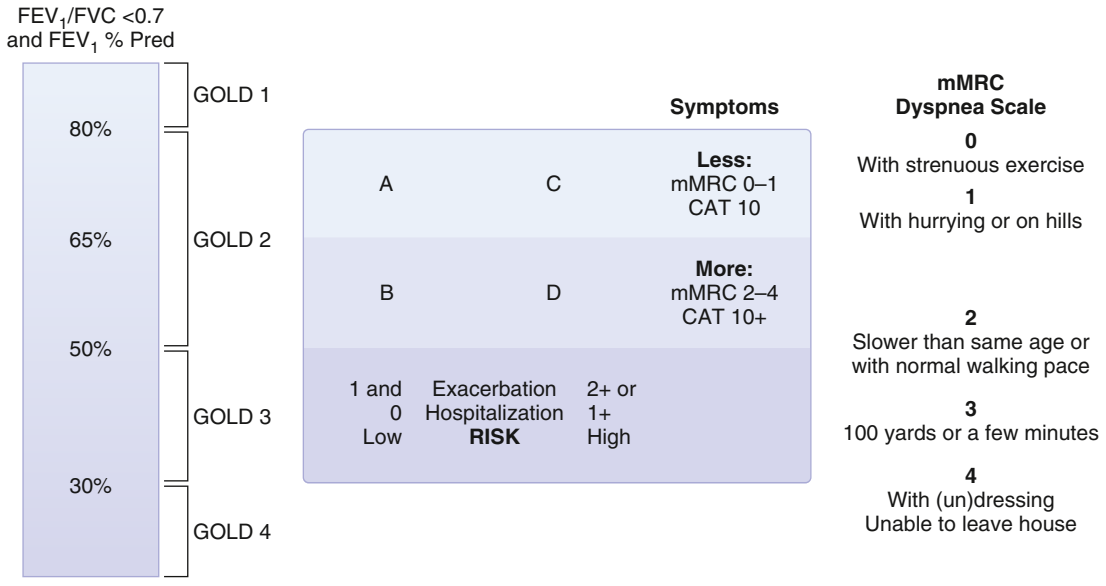

FIGURE 76-1. GOLD Classification System for COPD. In addition to airflow obstruction, as defined by an FEV_1/FVC ratio of less than 0.7 and quantified by the FEV_1 as a percent of the predicted value *(box on the left)*, it incorporates symptoms and risk of exacerbation to create four categories: GOLD 1, GOLD 2, GOLD 3, and GOLD 4. These in turn are used to recommend therapy and estimate prognosis. CAT = COPD Assessment Test (scores range from 0-40, with higher numbers more severe dyspnea); FEV_1 = forced expiratory volume in 1 second; FVC, forced vital capacity; mMRC = modified Medical Research Council Dyspnea Score (scores range 0-4, with higher numbers more severe dyspnea); Pred = predicted.

is a substantial risk factor for the disease. Whether prior respiratory infections produce residual effects on adult lung function is unclear.

PATHOBIOLOGY

Pathology

The pathology of COPD includes parenchymal destruction characteristic of emphysema as well as inflammation and fibrosis in the small airways. The relative contributions of these distinct components vary from individual to individual. The parenchymal destruction, which is characterized by a loss of alveolar walls and their associated capillary beds, can be demonstrated by a reduction in the diffusing capacity for carbon monoxide (D_{LCO}) on pulmonary function testing (Chapter 73) and by areas of reduced tissue density on computed tomographic (CT) scanning of the lung.

Pathogenesis

Data suggest important roles for the airways, the lung parenchyma, and the pulmonary vasculature in patients with COPD. The relative importance of these mechanisms varies among patients and contributes to the heterogeneity of disease presentation and response to therapy.[4]

The most widely accepted paradigm for the development of emphysema is the protease-antiprotease theory. This theory postulates that emphysema develops when elastolytic protease activity is in excess compared with antiprotease levels. The prototype for this theory is that individuals deficient in α_1-antiprotease are at higher risk for developing emphysema. α_1-Antiprotease is a member of the serpin (serine protease inhibitor) superfamily and is the major inhibitor of neutrophil elastase. Proteases that degrade elastin can produce emphysema. In addition to neutrophil elastase, macrophage elastases can produce emphysema. Cigarette smoking induces an influx of inflammatory cells into the lung, including neutrophils and macrophages. Quantitatively, macrophages are the largest component of this response. Experimental data also support the hypotheses that vascular mechanisms and apoptosis may contribute to the development of emphysema.

Small airway inflammation with the presence of pigmented macrophages is a consistent finding in cigarette smokers. CD8+ lymphocytes and neutrophils also are important components of the inflammatory response. In COPD, in contrast to many patients with asthma, eosinophils are a relatively small component of the inflammatory response, but a subpopulation of patients with COPD manifest sputum and peripheral eosinophilia. The signaling that promotes this inflammatory response may involve oxidative stress and the production of reactive oxygen species. However, attempts to block various inflammatory pathways with monoclonal antibodies have generally been disappointing.

In patients with COPD, the inflammatory response in the lung persists after smoking cessation. This observation, coupled with documented changes in the microbiome and the demonstration of autoimmunity in subjects with COPD, provides a potential mechanism for the clinical observation of the continued progression of disease despite smoking cessation.

In patients with emphysema, cigarette smoking induces intimal thickening and smooth muscle proliferation in the endothelium of the pulmonary vasculature, with decreased expression of vascular endothelial growth factor (VEGF) and apoptosis of endothelial cells in septal vessels. Manipulating VEGF expression in animal models can produce emphysema, thereby suggesting that pulmonary vascular changes may be a primary driving event in some patients with COPD. Data also suggest that inhibiting the expression of transforming growth factor-beta by blocking the angiotensin pathway may slow the loss of lung tissue that is characteristic of emphysema.[5] In addition, chronic hypoxemia produces pulmonary vascular constriction that leads to the development of pulmonary hypertension (Chapter 69). Hypertrophied bronchial mucous glands, an expanded epithelial goblet cell population, and increased airway mucin concentration all correlate with symptoms of cough and excess sputum production in chronic bronchitis but do not correlate with airflow obstruction.

Pathophysiology

By definition, COPD is characterized by obstruction of expiratory airflow. The anatomic site of this flow limitation is in the small airways (<2 mm). Obstruction may result from a variety of mechanisms: airway smooth muscle constriction; small airway inflammation, wall thickening, and scarring; loss of small airways owing to parenchymal destruction; and dynamic airway collapse owing to the loss of parenchymal tethering secondary to the parenchymal destruction that is characteristic of emphysema. A concomitant alteration may be a decreased driving force owing to loss of elastic recoil in the setting of parenchymal destruction. This airflow obstruction results in a prolonged expiratory time, which can be measured as lower flow rates over time on a spirogram and which produces a characteristic "coving" of the expiratory portion of the flow volume loop. When the expiratory time is shortened owing to an increased respiratory rate, the previous tidal volume is incompletely exhaled prior to the initiation of the next inspiration. This phenomenon, termed dynamic hyperinflation, results in an increase in end-expiratory lung volume to a level at which expiratory flow rates increase enough to achieve complete exhalation of the prior tidal volume. The increase in end-expiratory lung volume can produce a sensation of dyspnea independent of hypoxemia.

In its pure form, emphysema results in dynamic expiratory airway collapse owing to a loss of tethering, a loss of small airways because of parenchymal destruction, and a loss of alveolar gas exchange surface. Chronic bronchitis, in contrast, is characterized by airway inflammation, increased airway reactivity with resultant dynamic airway smooth muscle constriction, mucous gland hypertrophy, and hypersecretion. The result of this is airflow obstruction and a chronic productive cough with sputum. Clinical observation, pathologic studies, physiologic measurements, and imaging studies have shown neither of these entities typically exist in isolation; almost all patients with COPD have elements of both emphysema and chronic bronchitis, although the relative contributions of each process vary from patient to patient.

Genetics

The most common monogenic trait associated with COPD is α_1-antitrypsin deficiency.[6] α_1-Antitrypsin is encoded by the *SERPINA1* gene; the gene product is a serine protease inhibitor synthesized and secreted by the liver. The most common mutations associated with deficiency result in polymerization of α_1-antitrypsin in the liver and the inability to secrete a functional protein product. Circulating levels of α_1-antitrypsin are decreased to about 15% of normal, a level that is associated with an increased incidence of emphysema and bronchiectasis (Chapter 78), as well as liver disease (Chapter 132) in some individuals. Very uncommon in non-White populations, the allele frequency of mutations in the White population is as high as 4 to 5%. Because fewer patients are diagnosed with COPD and α_1-antitrypsin deficiency than would be expected based on mathematical calculations, other factors, especially cigarette smoking,[7] presumably influence whether clinically significant organ damage results from these mutations. Whether patients who are heterozygous for a mutant allele are at increased risk for lung disease is controversial.

Several other genetic syndromes include emphysema or airflow obstruction. Among these genes are cutis laxa (*ATP7A*, *elastin*, *fibulin 4*, and *fibulin 5*), Ehlers-Danlos syndrome (Chapter 239; collagen type 3 α_1), and Marfan syndrome (Chapter 239; fibrillin 1).

The observations that COPD clusters in families and that many smokers do not develop COPD have led to the hypothesis that genetic factors explain the differential response to cigarette smoke. A number of genes have been implicated, including *MMP-12*, *Serpin E2*, and the interleukin-33 pathway, which is also implicated in asthma, but such findings have been inconsistent. Ongoing longitudinal studies may potentially provide more evidence concerning genetic contributions to COPD.[8]

CLINICAL MANIFESTATIONS

The hallmark symptom of COPD is breathlessness with exertion. Because maximal exertion typically is not limited by ventilatory capacity, individuals can develop significant COPD before becoming symptomatic. The gradual progression of disease, coupled with the fact that other factors such as cardiac disease, obesity, and deconditioning can also result in dyspnea on exertion, often results in patients being symptomatic for months to years before the diagnosis of COPD is made.[9]

In many instances, the diagnosis of COPD is made when a patient presents with an exacerbation manifested by increased dyspnea, increased cough, and an increase or change in character of sputum production; it may or may not be accompanied by fever and constitutional symptoms suggestive of infection. The development of these symptoms may prompt the patient to seek medical evaluation, at which time the history may reveal exposure(s) that increase the risk of COPD (typically chronic cigarette smoking) and antecedent dyspnea on exertion. In a subset of patients, an important component of the natural history of COPD is recurrent exacerbations.

By definition, COPD with chronic bronchitis includes chronic cough and sputum. Hemoptysis may occur in patients with chronic bronchitis, particularly in the context of an exacerbation. Clubbing (Fig. 39-9) is not a manifestation in COPD, and its presence should prompt an evaluation for other conditions, notably lung cancer (Chapter 177) or pulmonary fibrosis (Chapter 80).

Patients with more advanced disease may develop hypoxemia or hypercarbia. Hypoxemia, which is usually documented by pulse oximetry, can produce cyanosis. Hypercarbia, which may be suggested by an elevated serum bicarbonate level, requires an arterial blood gas measurement for confirmation.

COPD also can have systemic manifestations, including arrhythmias such as atrial fibrillation.[10] Patients with emphysema lose body mass and may develop sarcopenia. Pulmonary hypertension (Chapter 69) may develop and be associated with a significant limitation in exercise. Depression (Chapter 362) is a frequent comorbidity with COPD.

DIAGNOSIS

History and Physical Examination

Elements of the history relevant to establishing the diagnosis include a history of cigarette smoking, other inhalational or environmental exposures, a childhood history of recurrent lung infections or premature birth, cough (chronicity, frequency), and sputum production. Particular emphasis should be placed on the degree to which limitations are caused by dyspnea because patients may gradually restrict activity over time to avoid the uncomfortable sensation of being out of breath and may not report dyspnea during their daily activities. Patients should be asked about any family history of lung disease and about the presence of comorbid conditions.

The physical findings seen in COPD include whether or not the patients have evidence of cyanosis, use of pursed lip breathing, use of accessory muscles of respiration, or other signs of respiratory distress. The chronic hyperinflation associated with COPD may result in a large anteroposterior thoracic dimension (barrel chest), use of the arms to fix the shoulder girdle to allow the use of accessory muscles of respiration (tripod position, history of less dyspnea when pushing a cart than when walking), and, in advanced cases, retraction of the lower rib cage with inspiration owing to the altered biomechanics of flattened diaphragms (Hoover sign). The presence of paradoxical abdominal wall motion with inspiration suggests respiratory muscle fatigue. Percussion of the chest may reveal increased resonance. Auscultation may reveal decreased breath sounds in patients who primarily have emphysema; asymmetry raises the possibility of a pneumothorax. Patients with airway disease may exhibit rhonchi with inspiration and wheezing with forced exhalation.

Cardiac findings related to COPD mainly relate to chest wall geometry and right heart function. Heart sounds may be diminished owing to increased retrosternal airspace. Elevated jugular venous pressure (Fig. 39-2), an accentuated pulmonic valve closure sound (P2), a right ventricular heave, hepatic congestion, and peripheral edema all raise the possibility of pulmonary hypertension (cor pulmonale; Chapter 69). Given that cigarette smoking is also a risk factor for lung cancer and that patients with COPD have about a twofold increased risk of lung cancer compared with smokers without COPD, hemoptysis should prompt an evaluation to determine whether the patient has lung cancer. Patients whose COPD is manifested primarily as emphysema may develop weight loss and sarcopenia, evident on physical examination.

Diagnostic Testing

Spirometry demonstrating airflow obstruction (Fig. 76-2) establishes the diagnosis (Chapter 73). The hallmark of obstruction on spirometry is a reduction in the FEV_1/FVC ratio to less than 0.7, with lower ratios commonly expressed as a percent of predicted calculated from reference data gathered for a normal population (standardized by age, sex, height, and ethnic background), indicating greater severity (Table 76-1). Lung volumes may demonstrate an elevated residual volume (RV) and total lung capacity (TLC). In patients with emphysema or pulmonary hypertension, the D_{LCO} may be reduced, consistent with the degree of loss of pulmonary capillary vessels participating in gas exchange.

All adults with COPD or bronchiectasis should be tested for alpha-1 antitrypsin deficiency, although the patients most at risk have a family history of COPD, lower lobe predominant emphysema, or presentation at a relatively young age. The evidence for screening family members of patients with α_1-antitrypsin is not as strong, although the case can be made that such screening

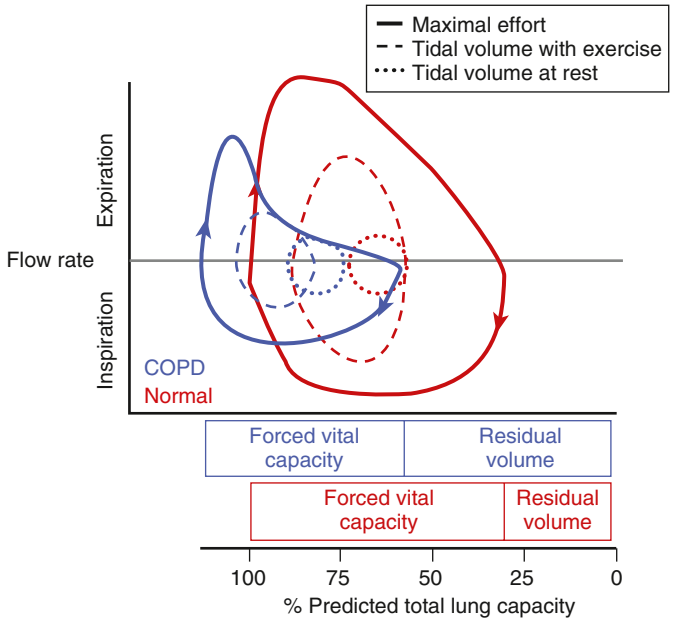

FIGURE 76-2. Representative flow-volume loops in normal subjects *(red)* and COPD *(blue)*. Flow-volume tracings are shown at rest, with exercise (*dashed lines*), and with maximal effort. The normal tracings demonstrate that the metabolic demands generated by exercise can be met with increased tidal volumes and frequency without reaching flow limitation and that lung volumes do not change. In contrast, the patient with COPD has flow limitation during tidal breathing. Increasing tidal volumes and frequency limit expiratory time, and the flow limitation results in a failure to reach resting end-expiratory lung volume. The resulting increases in lung volumes, termed dynamic hyperinflation, are associated with an increased work of breathing and, hence, dyspnea. COPD = chronic obstructive pulmonary disease.

allows for an intensified focus on avoiding inhalational exposures, including smoking, and careful observation for the development of early signs of disease so that replacement therapy can be considered.

In patients for whom pharmacotherapy is being considered, a peripheral blood eosinophil count may help guide decisions regarding inhaled glucocorticoids.

Imaging

Chest radiographs may demonstrate hyperinflation as evidenced by a flattened diaphragmatic silhouette, increased retrosternal air space on the lateral image, decreased parenchymal markings, and bullae in patients with emphysema (Fig. 76-3). In patients with a suspected COPD exacerbation, the chest radiograph may show an infiltrate suggestive of pneumonia (Chapter 85).

Chest CT (Fig. 76-4) provides a more detailed assessment of parenchymal characteristics and is more sensitive than plain chest radiographs for demonstrating parenchymal loss consistent with emphysema, bullae, and pulmonary vascular changes suggestive of pulmonary hypertension. It is now the tool of choice for screening for lung cancer (Chapter 177) in an at-risk population that includes most patients with COPD and a significant smoking history. Although CT scanning provides information about the presence and extent of emphysema and airway abnormalities, most available therapeutic options are prescribed regardless of the relative contributions of emphysema and chronic bronchitis. Hence, CT scanning has little role in guiding therapy in COPD, with the exception of instances in which surgical intervention (discussed later) or replacement therapy for alpha-1 antitrypsin deficiency is being considered.

TABLE 76-1 SEVERITY OF AIRFLOW OBSTRUCTION IN COPD ACCORDING TO POSTBRONCHODILATOR SPIROMETRY

STAGE AND SEVERITY	DEFINITION
I: Mild	$FEV_1/FVC < 0.70$, $FEV_1 \geq 80\%$ of predicted
II: Moderate	$FEV_1/FVC < 0.70$, $50\% \leq FEV_1 < 80\%$ of predicted
III: Severe	$FEV_1/FVC < 0.70$, $30\% \leq FEV_1 < 50\%$ of predicted
IV: Very severe	$FEV_1/FVC < 0.70$, $FEV_1 < 30\%$ of predicted or $FEV_1 < 50\%$ of predicted plus chronic respiratory failure

COPD = chronic obstructive pulmonary disease; FEV_1 = forced expiratory volume in the first second; FVC = forced vital capacity.

MRI has little clinical role in the assessment of COPD because the presence of air adversely impacts the ability to generate detailed images of lung parenchyma. Echocardiography can noninvasively quantify pulmonary artery pressures by assessing the velocity of any tricuspid regurgitant jet (Chapter 43), but imaging may be compromised by retrosternal hyperinflation between the ultrasound probe and the heart. Transthoracic ultrasound is primarily used to assess for the presence of pleural effusion (Chapter 86) and to guide thoracentesis.

Arterial Blood Gases and Oximetry

Hypoxemia can be assessed by oximetry or arterial blood gases, whereas the diagnosis of hypercarbia requires an arterial blood gas sample. Chronic hypercarbia is typically accompanied by a respiratory acidosis with a compensatory elevation in the serum pH and the serum bicarbonate level that incompletely corrects the acidemia (Chapter 89).

Differential Diagnosis

The differentiation of COPD from asthma (Chapter 75) has become less important as the treatments for the two conditions have become more similar. Clinical manifestations suggestive of asthma rather than COPD include the onset of symptoms at a young age, atopy, no history of smoking, varying symptoms over time, and airflow obstruction that is largely reversible. However, elderly people can develop new-onset asthma, some patients with asthma smoke, many asthmatics do not have a history of atopy, and long-standing, severe asthma may result in some degree of fixed airflow obstruction. Furthermore, many COPD patients have asthma-like features.[11]

In bronchiectasis (Chapter 78), which is characterized by chronic inflammation and results in abnormal airway dilation, clinical manifestations are dominated by cough and purulent sputum. Bronchiectasis can be distinguished from COPD by high-resolution chest CT imaging that demonstrates abnormally widened and thickened airways that have irregular walls and do not taper in the periphery of the lung.[12]

In bronchiolitis obliterans, cicatricial narrowing of distal airways is associated with severe and irreversible airflow obstruction. Bronchiolitis obliterans can develop in patients with collagen vascular diseases (Chapters 243 and 245), and it is common after lung transplantation (Chapter 87). A similar disorder can be caused by industrial inhalants, such as diacetyl, which is a butter-like flavoring used with microwavable popcorn (Chapter 81). In nonsmokers, bronchiolitis obliterans can be reliably diagnosed based on a careful history and the presence of irreversible airflow obstruction in the absence of emphysema or other explanations on a chest CT. In smokers, however, the diagnosis is more difficult to make because exposure to diacetyl produces abnormalities similar to those caused by cigarette smoke.

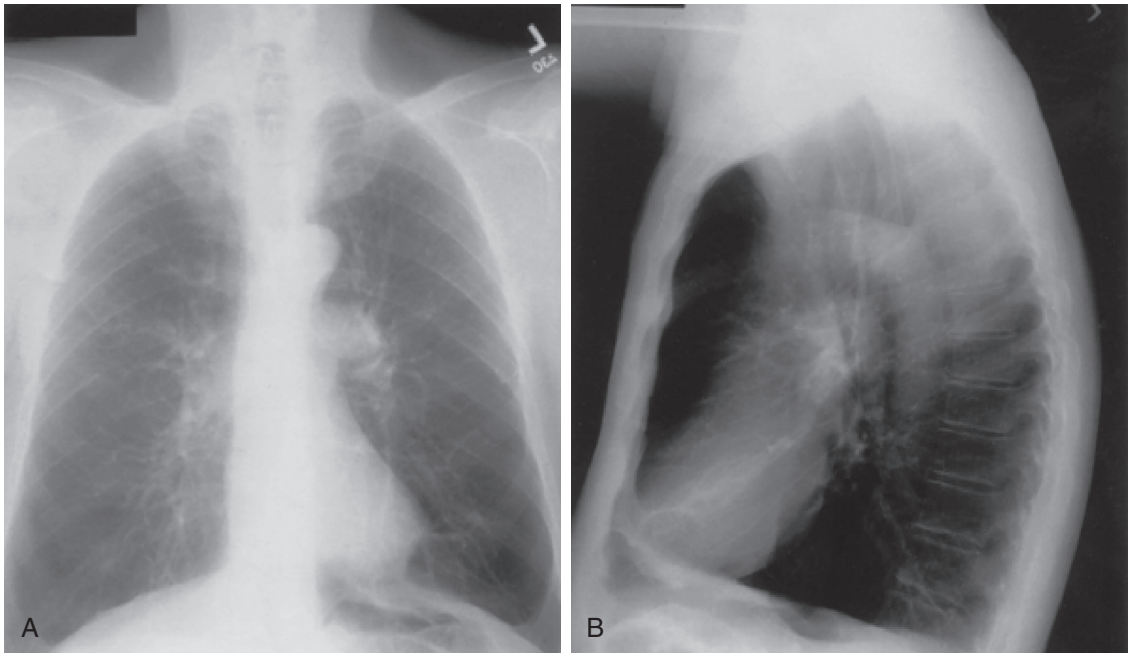

FIGURE 76-3. Posteroanterior (A) and lateral (B) radiographs of the thorax in a patient with emphysema. The most obvious abnormalities are those associated with increased lung volume. The lungs appear dark because of their increased air relative to tissue. The diaphragms are caudal to their normal position and appear flatter than normal. The heart is oriented more vertically than normal because of caudal displacement of the diaphragm, and the transverse diameter of the rib cage is increased; as a result, the width of the heart relative to the rib cage on the posteroanterior view is decreased. The space between the sternum and heart and great vessels is increased on the lateral view.

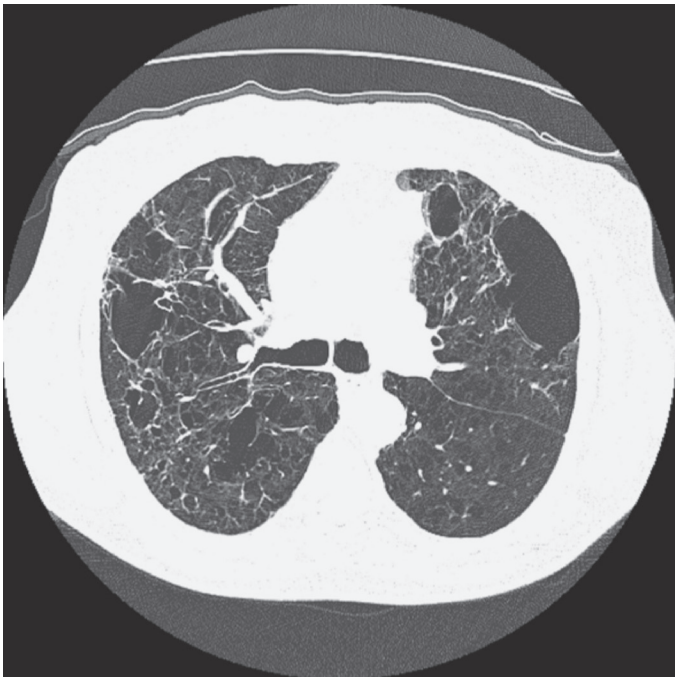

FIGURE 76-4. Computed tomographic (CT) scan demonstrating emphysema. High-resolution CT scan of the thorax at the level of the tracheal carina in a patient with emphysema. The left lung is seen on the right. There are multiple areas of confluent parenchymal loss (bullae) that appear as black areas with no parenchymal markings. There are additional small areas of parenchymal loss consistent with emphysema. The right upper lobe bronchus is seen entering the lung; its walls are thickened, thereby suggesting chronic inflammation. (Courtesy Bruce Maycher, MD.)

TREATMENT

No intervention other than lung transplantation can reverse or cure COPD, so treatment focuses on modifying its natural history, improving symptoms, minimizing complications, and reducing mortality.[13,14]

Modifying the Natural History of COPD

Smoking cessation reduces the rate of decline in FEV_1 and overall long-term mortality, including mortality attributable to lung cancer and cardiovascular disease. By comparison, pharmacotherapy has not been conclusively demonstrated to alter the rate of decline of FEV_1. An inhaled anticholinergic, ipratropium bromide, can provide a small initial increase in FEV_1, but it does not impact the subsequent rate of decline. Inhaled tiotropium, another anticholinergic agent, can modestly reduce the rate of decline in post-bronchodilator FEV_1 when used regularly in patients with early-stage COPD.[A1] Multiple other studies of inhaled β-agonists, anticholinergic agents, and glucocorticoids have not consistently demonstrated an impact on the rate of decline in FEV_1. Based on these disappointing results, the United States Preventative Services Task Force has reinforced their recommendation against screening of asymptomatic individuals for COPD because of the lack of data to support a substantial beneficial effect of intervention in such individuals.[15] Nevertheless, emerging data suggest that aggressive combination therapy can prolong survival in well-established disease (see Combined Treatment).

Oxygen Therapy

For patients with serious resting hypoxemia, defined as an arterial oxygen saturation less than 88% or a PaO_2 less than 56 mm, continuous supplemental oxygen for 24 hours/day can significantly reduce mortality. In patients with persistent stable hypercapnia, home high-flow nasal cannula oxygen[A2] or adding noninvasive ventilation to oxygen therapy can reduce future hospital admissions and delay death.[A3,16] The oxygen flow rate should be titrated in 1-L/minute increments every 15-minute interval to provide a resting oxygen saturation that is consistently above 90%. Long-term oxygen may decrease polycythemia and pulmonary hypertension, and it also can improve neuropsychiatric function.

For patients with COPD and moderate resting hypoxemia (SaO_2 88 to 93%) accompanied by exertional desaturation or nocturnal desaturation that does not fall below an SaO_2 of 80%, however, oxygen supplementation does not alter the time to first hospitalization or mortality.[A4] In patients who are normoxemic or minimally hypoxemic at rest while breathing ambient air but develop oxygen desaturation with exercise, ambulatory oxygen can modestly improve dyspnea, lactic acidosis with exercise, and dynamic hyperinflation, but activities of daily living are rarely improved,[A5] so these benefits do not routinely justify the expense and inconvenience of chronic supplemental oxygen therapy.[17]

Improving Symptoms

Interventions directed at improving COPD symptoms include pharmacotherapy, rehabilitation, and surgery.

Pharmacotherapy

For chronic symptoms, the mainstay of therapy is inhaled medications (Fig. 76-5), which fall into three classes: β-agonists, muscarinic antagonists, and glucocorticoids (Table 76-2). Within each of these three classes, medications differ primarily by their pharmacokinetics and dosing intervals.

Each class of long-acting bronchodilators is about 15 to 20% more effective than placebo for reducing exacerbations, and only about six patients need to be treated to prevent one exacerbation per year. The adverse events of long-acting bronchodilators are generally minor in patients with COPD.

Inhaled β-agonists

Although COPD is defined by airflow obstruction that is not completely reversible, many patients have a measurable increase in expiratory flow rates in response to inhaled β-agonists. *Short-acting β-agonists* have a rapid onset of action and a duration of action of 4 to 6 hours. The most commonly prescribed is albuterol (salbutamol), which produces modest increases in FEV_1 and reduces symptoms in patients with moderate to severe COPD. Side effects include tachycardia and tremor. These agents require frequent dosing, so they are typically used to relieve acute symptoms and to treat exacerbations.

Long-acting β-agonists, including salmeterol and formoterol, have a duration of action of about 12 hours, whereas indacaterol has a 24-hour duration of action. These agents modestly increase FEV_1 and improve quality of life, with indacaterol perhaps having the largest improvement on quality of life. These agents also reduce the frequency of exacerbations by about 20%, although this benefit may be muted in patients who are also taking inhaled glucocorticoids. These agents can cause tachycardia and tremor. Whether they may increase the risk of cardiovascular events in patients with COPD remains unresolved.[18]

Muscarinic Antagonists

Muscarinic antagonists, which are used in the same way as β-agonists in patients with COPD, produce modest improvements in FEV_1 and significant improvements in health-related quality of life and also reduce the risk of exacerbations. The primary short-acting muscarinic antagonist is ipratropium bromide, which can be used both acutely and chronically in symptomatic patients with COPD. However, its chronic use has largely been supplanted by the long-acting muscarinic antagonists, which have a more convenient dosing schedule. Muscarinic antagonists are useful in patients with chronic symptoms and/or a history of recurrent exacerbations. These agents are generally well tolerated, with the most common side effects being related to anticholinergic activity: dry mouth, urinary retention, and constipation, without any significant increase in cardiac risk.

Inhaled Glucocorticoids

Inhaled glucocorticoids reduce COPD exacerbations and the rate of decline in quality of life. However, they do not reliably improve measured lung function, reduce the rate of decline in FEV_1, or decrease mortality. They are best prescribed in addition to a long-acting adrenergic agonist or muscarinic antagonist rather than as the sole treatment for COPD (see Table 76-2). Inhaled corticosteroids produce marginal improvements in lung function and respiratory health status in COPD patients, and they reduce COPD exacerbation rates by about 15 to 20% in relative terms.[19] Retrospective analyses of interventional studies suggest that the benefit of inhaled corticosteroids for reducing exacerbations is higher when the peripheral blood eosinophil count is ≥300 cells/μL.

Side effects are oropharyngeal candidiasis and dysphonia, as well as an apparent increase in the risk of pneumonia. Therefore, the decision to use inhaled corticosteroids in COPD should weigh the anticipated benefit against the small but significant risk of side effects.

Combined Treatment

Inhaled corticosteroids combined with an inhaled long-acting β_2-agonist (e.g., vilanterol, formoterol, fumarate, or indacaterol) safely provide incremental benefit compared with either monotherapy.[A6] The combination of a long-acting β_2-adrenergic agonist inhaler plus a long-acting anticholinergic inhaler or the combination of a once-daily inhaled glycopyrronium (a long-acting antimuscarinic agent at 50 μg) plus long-acting indacaterol (110 μg) is also more effective than single-agent treatment.[A7] Furthermore, once- or twice-daily triple therapy, which combines a long-acting muscarinic antagonist with a long-acting β-agonist and a corticosteroid (e.g., adding umeclidinium [62.5 μg] to vilanterol [25 μg] plus fluticasone furoate [100 μg] or adding glycopyrrolate [18 μg] to formoterol [9.6 μg] plus budesonide [160 or 320 μg]) is even more effective for preventing COPD exacerbations and hospitalizations than double therapy[A8–A10] and can reduce all-cause mortality.[A11,A12]

Phosphodiesterase 4 (PDE4) Inhibitors

Roflumilast and cilomilast are oral phosphodiesterase-4 inhibitors that reduce COPD exacerbations and result in modest improvements in lung function and quality of life, with benefits similar to those seen with inhaled corticosteroids. Oral roflumilast (500 μg once daily) can increase FEV_1 by about 50 mL and can reduce both exacerbations and hospital admissions in patients who have severe COPD and who have had severe or frequent exacerbations despite using inhaled corticosteroids and long-acting β_2-agonists, even in combination with tiotropium.[A13] However, these agents generally have more side effects than inhaled corticosteroids, including nausea,

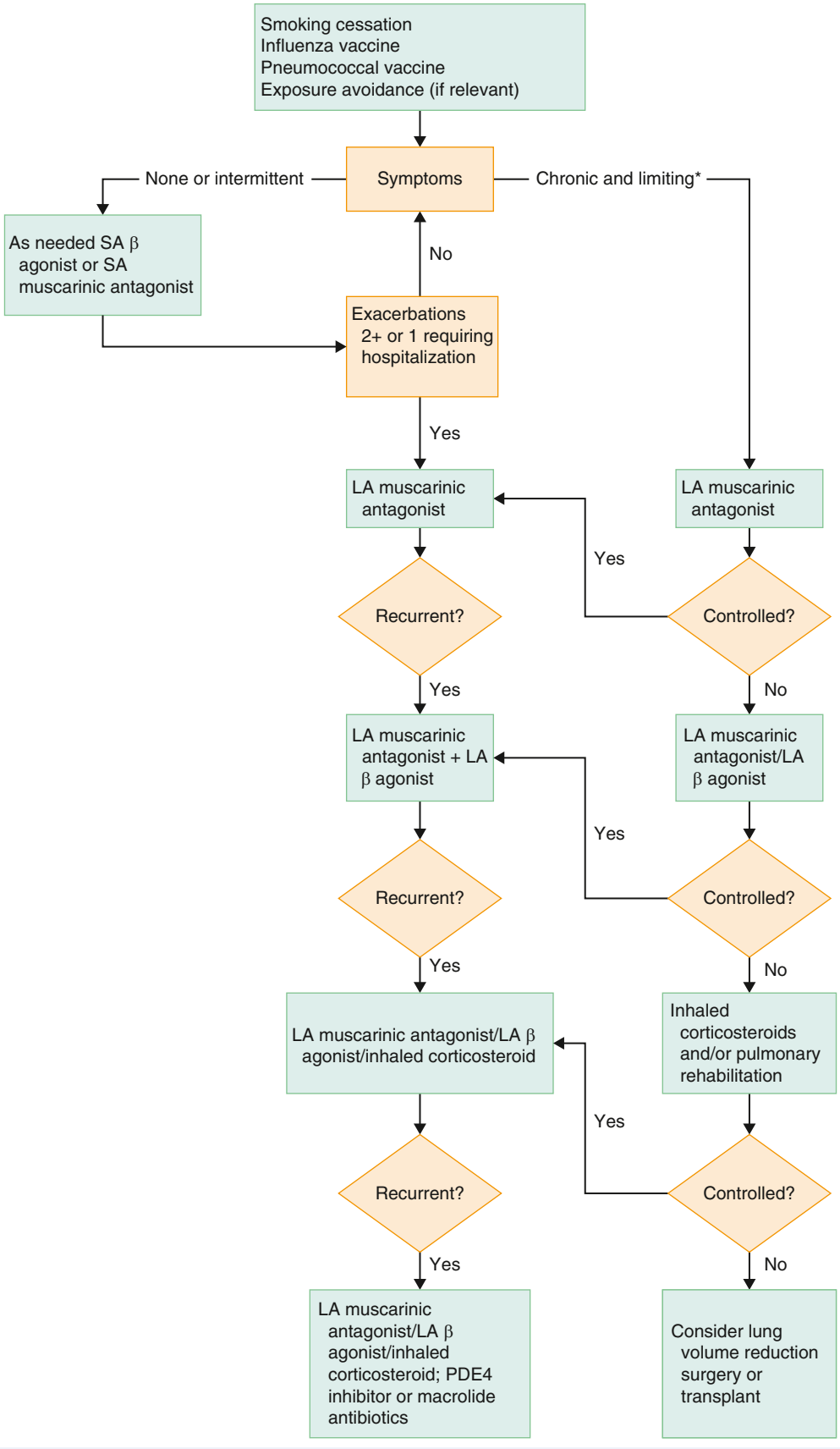

FIGURE 76-5. Approach to the patient with chronic obstructive pulmonary disease. *Dyspnea causes the patient to walk slower than patients of the same age or to stop to catch their breath when walking at their own pace; patient stops for breath after walking 100 yards or less or after a few minutes; or patient is breathless when dressing or housebound due to dyspnea. COPD = chronic obstructive pulmonary disease; LA = long acting; PDE = phosphodiesterase; SA = short acting.

TABLE 76-2 MEDICATIONS FOR CHRONIC OBSTRUCTIVE PULMONARY DISEASE

DRUG(S)	FREQUENCY/FORMULATION	DOSAGE	SIDE EFFECTS OF EACH CLASS OF DRUGS
β-AGONISTS			
Salmeterol	bid/DPI	50 μg	Palpitations, hypokalemia
Formoterol	bid/nebulizer	20 μg	
Indacaterol	qd/DPI	75 μg	
Olodaterol	qd/MDI	5 μg (2.5 μg/puff)	
MUSCARINIC ANTAGONISTS			
Aclidinium bromide	bid/DPI	400 μg	Dry mouth, constipation, aggravation of narrow angle glaucoma
Tiotropium bromide	qd/MDI or DPI	5 μg (MDI), 18 μg (DPI)	
Glycopyrronium	bid/DPI	15.6 μg	
Umeclidinium	qd/DPI	62.5 μg	
Ipratropium bromide	qid/MDI	34 μg (17 μg/puff)	
INHALED CORTICOSTEROIDS			
Fluticasone	bid/DPI	88-500 μg	Oropharyngeal candidiasis and hoarseness, and risk of pneumonia
Budesonide	bid or qd/nebulizer	360-1600 μg daily total	
Beclomethasone	bid/MDI	40-320 μg bid	
Mometasone	qd/DPI bid/MDI	220-440 μg 200-800 μg	
Flunisolide	bid/MDI	160-320 μg bid	
PHOSPHODIESTERASE-4 INHIBITORS			
Roflumilast	qd/pill	500 μg	Diarrhea, nausea, and weight loss
COMBINATION INHALERS			
*Combination Long-acting β-Agonist/Long-acting Muscarinic Antagonist**			
Formoterol/glycopyrrolate	bid/MDI	9.6 μg formoterol/18 μg glycopyrrolate	Side effects of each constituent
Indacaterol/glycopyrrolate	bid/DPI	27.5 μg indacaterol/15.6 μg glycopyrrolate	
Olodaterol/tiotropium	qd/MDI	5 μg of each (2 puffs)	
Vilanterol/umeclidinium	qd/DPI	25 μg vilanterol/62.5 μg umeclidinium	
Combination Short-acting β-Agonist/Short-acting Muscarinic Antagonist			
Albuterol/ipratropium	q4-6h/MDI or nebulizer	100 μg albuterol/20 μg ipratropium	Side effects of each constituent
Combination Long-acting β-Agonist/Inhaled Corticosteroids			
Salmeterol/fluticasone	bid/MDI	25 μg salmeterol/115 μg fluticasone; 2 inhalations bid	Side effects of each constituent
	bid/DPI	50 μg salmeterol/250 μg fluticasone; 1 inhalation bid	
Formoterol/budesonide	bid/MDI	9 μg formoterol/160-320 μg budesonide (two strengths available)	
Formoterol/mometasone	bid/MDI	5 μg formoterol/100 or 200 μg mometasone; 2 inhalations per administration	
Vilanterol/fluticasone	qd/DPI	25 μg vilanterol/100 μg fluticasone; 1 inhalation	
Combination Long-acting β-Agonist/Long-acting Muscarinic Antagonist/Inhaled Corticosteroids			
Vilanterol/umeclidinium/fluticasone	qd/DPI	25 μg vilanterol/62.5 μg umeclidinium/100 μg fluticasone	Side effects of each constituent
Formoterol/glycopyrrolate/budesonide	bid/MDI	9 μg formoterol/4.8 μg glycopyrrolate/160 μg budesonide; 2 inhalations bid	Side effects of each constituent

* = dose labeling (i.e., the amount of drug per puff varies across the world but the doses, either loaded in the dosing chamber or delivered from the inhaler, are generally within 10% of each other).
bid = twice daily; DPI = dry powder inhaler; MDI = metered dose inhaler; qd = once daily; qid = four times daily.

diarrhea, and weight loss. Although these side effects tend to abate over time, patients often discontinue these drugs shortly after starting therapy. As a result, phosphodiesterase-4 inhibitors are recommended only in COPD patients who experience persistent symptoms or recurrent exacerbations despite treatment with long-acting muscarinic antagonists, long-acting β-agonists, and inhaled corticosteroids.

Eosinophilic COPD

Some patients have substantial eosinophilia in their sputum or blood. In such patients, treatment with mepolizumab, a monoclonal antibody directed against interleukin-5, as 100 mg subcutaneously every 4 weeks for 1 year can reduce exacerbations.[A14]

Alpha-1 Antitrypsin Replacement Therapy

Patients with α_1-antitrypsin deficiency and signs of lung disease may benefit from replacement therapy, with weekly infusion of Prolastin (a proprietary mix of protease inhibitors) at 60 mg/kg.[20] Replacement therapy is not recommended for heterozygous patients.

Pulmonary Rehabilitation

Rehabilitation does not demonstrably change lung function, but education and exercise training can significantly improve quality of life, patients' sense of mastery of their disease, and exercise performance as assessed by ergometry and the 6-minute walk. In all patients with COPD, these effects are, on average, comparable to or greater than the benefit achievable with pharmacotherapy.[A15]

Surgical Therapy

Three principal surgical interventions have been used in selected patients with COPD: bullectomy, lung volume reduction, and lung transplantation (Chapter 87).

Bullectomy

A bulla is defined as a contiguous air space measuring more than 1 cm, and a giant bulla is defined as occupying more than 30% of a hemithorax. Bullectomy is a consideration in patients who have a giant bulla and who have persistent symptoms or exercise limitations despite medical therapy and rehabilitation. The likelihood of benefit and magnitude of risk for surgical intervention are largely dictated by an assessment of the characteristics of the parenchyma in the nonbullous lung. Patients with diffuse emphysema in addition to bullous disease are at higher risk for perioperative mortality and are less likely to experience substantial benefit than are those with relatively normal surrounding lung that is underexpanded due to the volume occupied by the giant bulla.

Lung Volume Reduction

Lung volume reduction is based on the premise that reducing the increase in lung volume that develops in patients with emphysema would help promote better diaphragmatic mechanics, reduce dyspnea associated with thoracic hyperinflation, and improve parenchymal tethering of airways during exhalation, thereby leading to improved expiratory flow rates. Two general interventions attempt to achieve these goals: lung volume reduction surgery and bronchoscopic interventions designed to produce regional volume loss (Chapter 87). Lung volume reduction surgery, most typically performed via a thoracoscopic approach, can reduce mortality in patients with predominantly upper lobe disease but not in patients with non–upper-lobe–predominant emphysema. Patients with FEV_1 less than 20% predicted and either low exercise capacity or a D_{LCO} less than 20% are at high risk for perioperative mortality and should not be offered surgery.

The bronchoscopic approach eliminates the need for a chest wall incision. Emphysematous lung regions can be deflated by endoscopic placement of one-way bronchial valves, endobronchial coils, or transbronchial stents. Such procedures can provide modest benefit, primarily in patients with heterogeneous emphysema, intact interlobar fissures, and no collateral interlobar ventilation (Chapter 87).[A16] These procedures also may benefit patients with homogeneous emphysema but no collateral ventilation. Other devices, including airway bypass conduits, are under evaluation.

Lung Transplantation

Lung transplantation (Chapter 87) is an option for a broad variety of advanced lung diseases, including COPD. Initially, single-lung transplantation was recommended for patients with COPD, but emerging data suggest better long-term survival in those receiving bilateral lung transplants, so about 75% of transplants are currently bilateral procedures. COPD now accounts for about 25% of the lung transplants done in the United States. Median survival after lung transplant for COPD is 5.8 years.

PREVENTION

Given that the vast majority of those with COPD develop it as the result of inhalational exposures, avoiding such exposures will reduce the incidence of the disease.[21] The most commonly identified inhalational exposure associated with COPD is cigarette smoking, and smoking cessation, which slows the rate of decline in measured lung function, is critical (Chapter 363).

ACUTE EXACERBATIONS OF COPD

An acute exacerbation of COPD is defined as an increase in dyspnea over the patient's usual state, an increase in cough, or increase and change in character of mucus production. Acute exacerbations of COPD carry a short-term mortality of about 10%, have an independent detrimental effect on quality of life, and are responsible for about 60% of the direct medical costs of COPD.

EPIDEMIOLOGY

The risk of acute exacerbation of COPD increases with increasing chronic airflow obstruction, but there is substantial heterogeneity in the frequency of exacerbations at any degree of airflow obstruction. The best predictor of patients likely to have recurrent exacerbations is a history of recurrent exacerbations. Exacerbations exhibit a seasonality, with the highest frequency being during the winter months.

PATHOBIOLOGY

The final common pathway for an exacerbation, regardless of the initial stimulus, is an inflammatory response characterized by airway inflammation, mucus hypersecretion, and airway smooth muscle constriction that combine to produce the classic triad of dyspnea, cough, and sputum. Viral or bacterial pathogens can be implicated in 75 to 80% of acute exacerbations of COPD. The most frequently implicated viruses are rhinovirus (Chapter 329), influenza (Chapter 332), parainfluenza (Chapter 331), respiratory syncytial virus (Chapter 330), coronaviruses (Chapter 334), and adenovirus (Chapter 333). Many patients with chronic bronchitis are chronically colonized with bacterial species that have also been implicated in exacerbations, notably *Streptococcus pneumoniae* (Chapter 268), *Haemophilus influenza* (Chapter 277), *Moraxella catarrhalis* (Chapter 277), and, to a lesser extent, *Pseudomonas aeruginosa* (Chapter 282). In cohort studies of patients with chronic colonization, acquisition of a new genotype of these species is associated with an increased risk of exacerbation and the development of new strain-specific antibodies that contribute to the inflammatory response characteristic of an exacerbation. Additional support for the hypothesis that exposure to infectious agents is a likely source of exacerbations of COPD comes from the observation that such exacerbations decreased in frequency during social distancing and widespread use of face masks to help control the spread of illness during the severe acute respiratory syndrome coronavirus 2 pandemic.

Other environmental exposures also likely contribute, particularly in the 20 to 25% for which no pathogen or infectious exposure is identified. For example, emergency department visits for respiratory symptoms in patients with COPD increase during times of higher ambient air pollution.

CLINICAL MANIFESTATIONS AND DIAGNOSIS

Because acute exacerbations of COPD are often accompanied by fever or occur after contact with other sick individuals, the symptoms are generally similar to those of acute bronchitis (Chapter 84). The patient should be questioned about acute symptoms, prior history of exacerbations, presence of comorbidities such as heart disease, any infectious exposures, baseline functional status, past response to therapy (if any), and the presence of somnolence or confusion that may suggest hypercarbia. In addition to acute exacerbations of COPD, other possibilities that should be considered include decompensated heart failure (Chapter 45), pneumonia (Chapter 85), pulmonary embolism (Chapter 68), and pneumothorax (Chapter 86). Less likely is a tumor of the large airways.[22]

The physical examination should include assessment of vital signs and signs of respiratory distress (i.e., use of accessory muscles, intercostal retractions, tachypnea, and the inability to speak in complete sentences). The cardiac examination should assess the presence of tachycardia, irregular rhythm, and signs of left or right heart failure, including bibasilar rales, an elevated jugular venous pressure, hepatic congestion, peripheral edema, and an S3 gallop. Abnormal mental status should raise concerns for hypercarbia.

Laboratory evaluation should include oximetry and, in patients in respiratory distress or other reasons to suspect hypercarbia, an arterial blood gas. Given that tachycardia, elevated jugular venous pressure, and peripheral edema can be seen in both left and right heart failure, measurement of the circulating level of brain natriuretic peptide in patients may help identify patients with significant left heart failure (Chapter 45). Point-of-care testing of C-reactive protein to guide the prescribing of antibiotics can reduce antibiotic prescriptions with no evidence of harm.[A17]

A chest radiograph will demonstrate abnormalities in about 15% of patients but likely alter therapy in only about 5% of cases. A chest radiograph should always be obtained in any patient with chest pain, leukocytosis, a history of heart disease, or other complicating comorbidity. A chest CT scan is not routinely indicated, but a contrast-enhanced CT scan is the preferred mode of evaluation for patients in whom pulmonary embolism (Chapter 68) is a serious consideration. In most circumstances, a sputum culture is unlikely to influence therapy.

TREATMENT

Antibiotics and corticosteroids are beneficial for patients with an acute exacerbation of COPD.[A18] Indications for hospitalization include hypercarbia, acidemia, or significant respiratory distress despite bronchodilator therapy. In other cases, the decision is subjective and requires consideration of the patient's living situation, social support, transportation, reliability, and ability to perform activities of daily living. Similarly, in patients who are admitted for inpatient treatment, the timing of discharge depends on these same considerations.

Bacterial infection is involved in about 50% of cases of acute exacerbations of COPD. Antibiotics, which should be selected based on the need to cover the most common pathogens (i.e., *Streptococcus pneumoniae, Haemophilus influenza*, and *Moraxella catarrhalis*) reduce the duration of symptoms, particularly in patients with the triad of cough, increased dyspnea, and sputum (Table 76-3). In patients with severe COPD, a history of recent hospitalization or prior colonization with *Pseudomonas aeruginosa*, an antibiotic with anti-pseudomonal activity should be considered, such as levofloxacin 750 mg orally daily for 7 to 10 days. The specific choice of agent should take into account the local antibiotic resistance patterns of these species, but examples include azithromycin (500 mg orally daily) or amoxicillin-clavulanate (875 mg/125 mg orally twice daily) for 5 days. Continuing low-dose azithromycin (250 mg every 2 days) for 3 months after an infection can significantly reduce the likelihood of treatment failure.[A19]

Glucocorticoids (e.g., 40 mg daily by mouth for 5 days) should be administered to patients with symptoms severe enough to present for emergency

TABLE 76-3 HOSPITAL MANAGEMENT OF EXACERBATIONS OF COPD*

Diagnostic testing	Chest radiograph, oximetry, ABGs, and ECG Other testing as warranted by clinical indication
Bronchodilator therapy	Inhaled short-acting β_2-agonist Consider ipratropium if inadequate clinical response
Antibiotics	Recommended if (1) increases in dyspnea, sputum volume, and sputum purulence all are present; (2) increase in sputum purulence along with increase in either dyspnea or sputum volume; or (3) need for assisted ventilation Initial empirical therapy with amoxicillin plus clavulanic acid (875 mg/125 mg orally twice daily for 5 to 7 days), a macrolide antibiotic (e.g., azithromycin 500 mg orally daily for 5 days), or doxycycline (100 mg orally twice daily for 5 to 7 days) based on local bacterial resistance patterns Subsequent therapy based on sputum and blood cultures
Systemic corticosteroids	Daily oral prednisolone 30-40 mg (or its equivalent) for 5 days
Supplemental oxygen	Maintain oxygen saturation 88-92% Monitor ABGs for hypercapnia and acidosis
Assisted ventilation	Indications for NPPV include respiratory acidemia (arterial pH ≤7.35) or severe dyspnea with clinical signs of respiratory muscle fatigue or increased work of breathing

*Data from http://goldcopd.com.
ABGs = arterial blood gases; COPD = chronic obstructive pulmonary disease; ECG = electrocardiogram; ICU = intensive care unit; NPPV = noninvasive positive-pressure ventilation.

care, and parenteral corticosteroids are no more effective and are associated with potential complications and morbidity.[A20] Patients should be treated with a short-acting bronchodilator to help alleviate their dyspnea; β-agonists and antimuscarinics are equally efficacious in this setting. Methylxanthines are not recommended.

Patients with hypoxemia should be treated with supplemental oxygen at a dose sufficient to maintain an SaO_2 of above 90%. Some patients may experience a modest increase in P_{CO_2} owing to changes in their respiratory pattern and V/Q matching, but this phenomenon should not be a reason to withhold supplemental oxygen. In patients with persistent respiratory distress, acute hypercarbia, or acidemia, noninvasive positive-pressure ventilation (NIPPV) (Chapter 91) can improve these parameters and reduce the need for invasive mechanical ventilation, the number of ICU days, and mortality.[A21] For patients who have refractory hypoxemia, progressive hypercarbia, or acidemia despite NIPPV, endotracheal intubation and mechanical ventilator support (Chapter 91) are indicated if such an intervention is consistent with the patient's wishes. Care should be used to prescribe a relatively low respiratory rate to avoid dynamic hyperinflation ("auto-PEEP") in the setting of expiratory airflow obstruction. If evaluation demonstrates the presence of auto-PEEP, exogenous PEEP can be used to reduce the chest wall muscle work associated with initiating inspiration.

PREVENTION

Annual influenza vaccination (Chapter 332) reduces COPD-related hospitalization. Data are less clear for polyvalent pneumococcal vaccination (Chapter 15), but recommendations are to administer it in patients over 65 years of age, patients with heart disease or other comorbidities, and patients with severe COPD.

Patients who have an exacerbation requiring corticosteroid therapy are at increased risk for additional exacerbations in the year following the initial episode. Consideration should be given to the interventions demonstrated to decrease this risk.

The commonly prescribed inhaled agents (i.e., long-acting β-agonists, long-acting muscarinic antagonists, inhaled corticosteroids) reduce exacerbations by about 20% in patients with a history of exacerbations. There is modest additive benefit, and recommendations are to add inhaled corticosteroids to single or double inhaled bronchodilator therapy in patients who are still experiencing exacerbations. For patients who continue to have exacerbations on this regimen, a phosphodiesterase-4 inhibitor (roflumilast in patients with chronic bronchitis and recurrent exacerbations) or azithromycin (250 mg orally daily) can be added to reduce the risk of exacerbations by about 25% in patients with a history of COPD exacerbation.[A22] Patients who receive chronic azithromycin require assessment of their electrocardiographic QT interval and have a low (about 5%) but appreciable risk of reversible hearing loss on therapy. Unfortunately, other prophylactic antibiotics have generally failed to reduce exacerbations.[A23] Oral glucocorticoid therapy, with or without concomitant theophylline, is also ineffective.[A24]

PROGNOSIS

In patients with COPD, post-bronchodilator spirometry (see Table 76-1 and Fig. 76-1), typically assessed as FEV_1 (% predicted), predicts mortality and other important health outcomes. The body mass index, airflow obstruction, dyspnea, and exercise capacity index (BODE) index has more predictive value for mortality than the FEV_1 percent predicted alone. It incorporates patient-reported dyspnea, spirometry results, 6-minute walk distance, and body mass index to generate a score ranging between 0 and 10, with higher scores indicating a higher risk of death and scores ranging from 7 to 10 having a 48-month mortality of about 80%.

Exacerbations are independent determinants of health-related quality of life and are associated with an increase in short-term mortality (about 10% for patients hospitalized with an exacerbation) and longer-term mortality (43% at 1 year, 49% at 2 years). Resting hypoxemia, weight loss, a low body mass index, more severe dyspnea, and low exercise tolerance are independent predictors of mortality in patients with COPD.[23] A diagnosis of COPD is also a risk factor for lung cancer (Chapter 177). Given that most patients with COPD have a significant smoking history, the prevalence of cardiovascular disease (Chapter 40) is also increased. If β-blocking agents are indicated for cardiovascular disease, they can be used safely in patients with COPD while reducing cardiovascular risk.[24]

Pharmacotherapy can blunt the usual annual reduction in FEV_1 by about 5 mL per year.[A25] For patients with resting hypoxemia, supplemental oxygen therapy reduces mortality. For patients with significant exercise limitation in the setting of upper-lobe predominant emphysema, lung volume reduction surgery (Chapter 87) reduces mortality. End-of-life care for advanced COPD includes palliative care and the judicious use of opioids for dyspnea (Chapter 3).[25]

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77

CYSTIC FIBROSIS

HARTMUT GRASEMANN

DEFINITION

Cystic fibrosis, which is among the most common life-shortening autosomal recessive genetic diseases in White populations, is caused by absent or reduced function of the cystic fibrosis transmembrane conductance regulator (CFTR) protein. CFTR, which is expressed at the mucosal surfaces of the aerodigestive tract, sweat glands, and vas deferens, conducts the flow of chloride, bicarbonate, and thiocyanate ions across cell membranes. The loss of CFTR function in the airways of patients with cystic fibrosis leads to progressive lung disease.

EPIDEMIOLOGY

In Northern Europe and the Americas, the incidence of cystic fibrosis is approximately 1 : 2500 to 1 : 3000 live births. The worldwide prevalence of cystic fibrosis is about 1 in 60,000, with about 100,000 total cases, but the prevalence in the United States is about 1 : 10,000 (resulting in about 35,000 cases). Although most patients are of European ancestry, the disease is also seen in Hispanic Americans (about 1 : 7000), African Americans (about 1 : 12,000), and infrequently in Native Americans. The disease is rarely diagnosed in Africa or Asia. With improved treatment and prognosis, affected adults now outnumber children and adolescents.[1]

PATHOBIOLOGY

Absent or deficient CFTR function causes dehydration of mucosal surfaces and viscous secretions that obstruct the impacted luminal compartments and ducts.

Sweat Glands

Sweat gland sodium chloride (NaCl) concentrations are initially isotonic with plasma, but CFTR function normally reclaims NaCl to minimize salt loss as the sweat travels to the skin surface. In cystic fibrosis, sweat chloride concentrations are 60 mEq/L or more, a level that is used in the case definition, compared with sweat chloride concentrations that are almost always less than 20 mEq/L in nonaffected individuals. Because the sweat of individuals with cystic fibrosis is almost isotonic with plasma, patients become dehydrated in conditions that cause substantial sweating. However, because their plasma sodium levels do not rise, they perceive less of a sense of thirst compared with when normal individuals sweat heavily.

Sinuses and Lungs

CFTR dysfunction in the airways results in reduced chloride and bicarbonate secretion by the respiratory epithelium into the airway lumen. In addition, sodium absorption by the airway epithelial cells is increased. This imbalance in ion transport leads to airway surface dehydration. Reduction in height of the airway surface liquid layer causes impaired mucociliary clearance and, subsequently, mucus plugging of airways.

For reasons that are not entirely clear, cystic fibrosis airways represent an ecologic niche that favors infections with pathogens such as *Staphylococcus* and *Pseudomonas* species. The infection is often characterized by the formation of biofilms, in which cells are mostly nondividing; as a result, antibiotics are less effective than they would be for traditional infections. These microorganisms activate both innate and adaptive immune responses in the airway mucosa (E-Fig. 77-1). Unfortunately, chronic polymorphonuclear neutrophils cannot obliterate the biofilm, but their enzymes (especially neutrophil elastase) do cause collateral damage that leads to inflammation, destruction of the airway wall, and bronchiectasis (Chapter 78).

Exacerbations of cystic fibrosis lung disease are believed to occur when the increased metabolic activity in the biofilm results in the recruitment of more neutrophils into the airway. These neutrophils do not rapidly apoptose but instead disintegrate and form neutrophilic extracellular traps that activate local macrophages that then increase the inflammatory response. This process leads to more airway obstruction and a measurable decrease in the forced expiratory volume in one second (FEV_1) on pulmonary function testing.

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In classic cystic fibrosis, the inability of the exocrine pancreatic ducts to secrete bicarbonate and chloride leads to pancreatic autodigestion. Whereas the normal pancreas secretes about 1 to 1.5 L of bicarbonate- and chloride-rich fluid daily, patients with cystic fibrosis secrete less than half of that volume because the exocrine pancreas is replaced by fatty infiltration and chronic inflammation. In many cases, this inflammation also leads to loss of pancreatic endocrine function, thereby resulting in cystic fibrosis–related diabetes mellitus.

Liver

In the biliary tract, the absence of CFTR-mediated hydration leads to obstruction of the biliary canaliculi, which can then cause cirrhosis (Chapter 139) and its complications. In many patients with cystic fibrosis, mildly elevated aminotransferase levels are the only hepatic abnormality, but about 5% of patients progress to hepatic failure that requires transplantation (Chapter 140). Liver disease often presents in childhood, and the SERPINA1 Z allele may lead to genetic predisposition.

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The small intestine secretes about 1.8 L of fluid each day (per 70 kg body mass). Abnormal CFTR-mediated secretion leads to inadequate hydration of small bowel contents, which in turn can lead to obstipation and intussusception, principally in the ileum and appendix.

Other associated conditions include short stature, delayed sexual maturation, clubbing of the digits (see Fig. 39-9 in Chapter 39), wrinkling of the hands and feet, hypochloremic hypokalemic alkalosis (Chapter 104), gastric reflux (Chapter 124), and esophagitis (Chapter 124).

Genetics

Although over 2000 CFTR variants have been described, about 70% of all patients with cystic fibrosis have at least one copy of F508del—the gene that encodes CFTR is missing the codon for phenylalanine at position 508. The origin is thought to be a founder mutation about 52,000 years ago in the Middle East.

The various cystic fibrosis–causing CFTR variants can interfere with virtually every aspect of protein expression (Tables 77-1 and 77-2). A limitation of the current classification system is that some mutations—including W1282X,

TABLE 77-1 CLASSIFICATION OF CYSTIC FIBROSIS–CAUSING VARIANTS

	CFTR DYSFUNCTION	COMMON VARIANTS
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Class II	Protein misfolding, premature degradation	F508del, N1303K
Class III	Disordered regulation, ATP binding, and hydrolysis	G551D, G551S, G1349D
Class IV	Defective chloride conductance or gating	R117H, R334W, R347P
Class V	Reduced transcripts, promoter or splicing	2789 +5 G>A, A445E
Class VI	Accelerated turnover from cell surface	120del23, rescued F508del, N287Y

CFTR = cystic fibrosis transmembrane conductance regulator.

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77

CYSTIC FIBROSIS

HARTMUT GRASEMANN

DEFINITION

Cystic fibrosis, which is among the most common life-shortening autosomal recessive genetic diseases in White populations, is caused by absent or reduced function of the cystic fibrosis transmembrane conductance regulator (CFTR) protein. CFTR, which is expressed at the mucosal surfaces of the aerodigestive tract, sweat glands, and vas deferens, conducts the flow of chloride, bicarbonate, and thiocyanate ions across cell membranes. The loss of CFTR function in the airways of patients with cystic fibrosis leads to progressive lung disease.

EPIDEMIOLOGY

In Northern Europe and the Americas, the incidence of cystic fibrosis is approximately 1 : 2500 to 1 : 3000 live births. The worldwide prevalence of cystic fibrosis is about 1 in 60,000, with about 100,000 total cases, but the prevalence in the United States is about 1 : 10,000 (resulting in about 35,000 cases). Although most patients are of European ancestry, the disease is also seen in Hispanic Americans (about 1 : 7000), African Americans (about 1 : 12,000), and infrequently in Native Americans. The disease is rarely diagnosed in Africa or Asia. With improved treatment and prognosis, affected adults now outnumber children and adolescents.[1]

PATHOBIOLOGY

Absent or deficient CFTR function causes dehydration of mucosal surfaces and viscous secretions that obstruct the impacted luminal compartments and ducts.

Sweat Glands

Sweat gland sodium chloride (NaCl) concentrations are initially isotonic with plasma, but CFTR function normally reclaims NaCl to minimize salt loss as the sweat travels to the skin surface. In cystic fibrosis, sweat chloride concentrations are 60 mEq/L or more, a level that is used in the case definition, compared with sweat chloride concentrations that are almost always less than 20 mEq/L in nonaffected individuals. Because the sweat of individuals with cystic fibrosis is almost isotonic with plasma, patients become dehydrated in conditions that cause substantial sweating. However, because their plasma sodium levels do not rise, they perceive less of a sense of thirst compared with when normal individuals sweat heavily.

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For reasons that are not entirely clear, cystic fibrosis airways represent an ecologic niche that favors infections with pathogens such as *Staphylococcus* and *Pseudomonas* species. The infection is often characterized by the formation of biofilms, in which cells are mostly nondividing; as a result, antibiotics are less effective than they would be for traditional infections. These microorganisms activate both innate and adaptive immune responses in the airway mucosa (E-Fig. 77-1). Unfortunately, chronic polymorphonuclear neutrophils cannot obliterate the biofilm, but their enzymes (especially neutrophil elastase) do cause collateral damage that leads to inflammation, destruction of the airway wall, and bronchiectasis (Chapter 78).

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Although over 2000 CFTR variants have been described, about 70% of all patients with cystic fibrosis have at least one copy of F508del—the gene that encodes CFTR is missing the codon for phenylalanine at position 508. The origin is thought to be a founder mutation about 52,000 years ago in the Middle East.

The various cystic fibrosis–causing CFTR variants can interfere with virtually every aspect of protein expression (Tables 77-1 and 77-2). A limitation of the current classification system is that some mutations—including W1282X,

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Class VI	Accelerated turnover from cell surface	120del23, rescued F508del, N287Y

CFTR = cystic fibrosis transmembrane conductance regulator.

ABSTRACT

Cystic fibrosis, which is among the most common genetic diseases in people of European descent, is caused by mutations in the cystic fibrosis transmembrane conductance regulator (CFTR). This gene codes for a transmembrane protein channel that conducts chloride, bicarbonate, and thiocyanate ions across the epithelium of the lung, mucus membranes, and sweat glands and also impacts the release of digestive enzymes. Among the hundreds of identified mutations, about a dozen account for most clinical disease worldwide. The most common variant, deletion of the codon for phenylalanine at position 508 of the protein, termed F508del, is responsible for the largest fraction of cases. Clinically, cystic fibrosis has its biggest impact on the lungs, the digestive system, and the reproductive system, with the onset of bronchiectasis and chronic lung infection at an early age. Specific, highly effective CFTR modulator therapy is now available for patients with one or two copies of the most common mutation, F508del, as well as some relatively uncommon variants.

KEYWORDS

bronchiectasis
pancreatic insufficiency
airway obstruction
male sterility

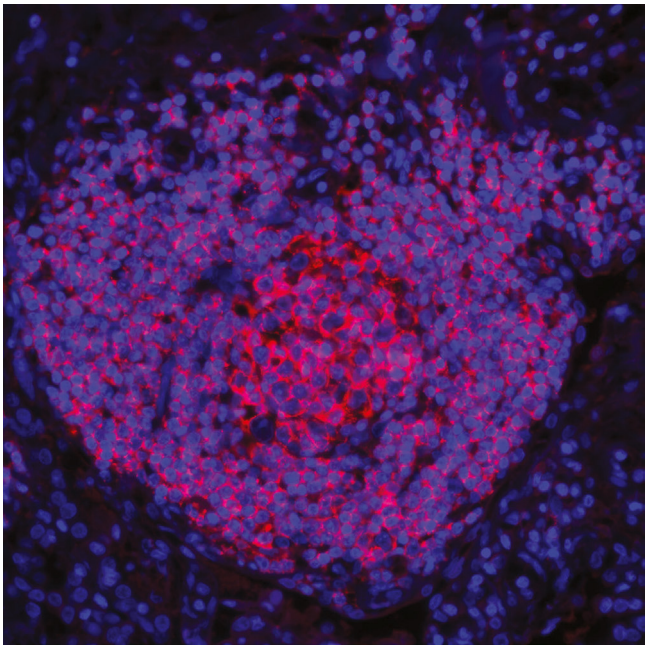

E-FIGURE 77-1. Lymphoid follicle from airway submucosa from lung explant prior to transplant. The B-cell marker CD20 is stained red, and the DAPI nuclear counterstain is stained blue.

TABLE 77-2 CYSTIC FIBROSIS–ASSOCIATED VARIANTS WITH A FREQUENCY OF >1%

VARIANT (>1%)	PERCENTAGE OF ALL VARIANTS	ORIGIN
F508del	66%	Middle East
G542X	2.4%	Spain
G551D	1.6%	England
N1303K	1.3%	Italy
W1282X	1.2%	Ashkenazi Jewish

Data from http://www.genet.sickkids.on.ca/resource/Table1.html.

F508del, and R117H—display combinatorial molecular defects, which may explain some of the variability seen in response to CFTR modulator therapies.

Patients with the most severe CFTR variants (Class I to III) usually develop pancreatic insufficiency, but other patients may retain some pancreatic function. Genome-wide association studies suggest that variants in genes encoding mucin and alternative ion channels could explain some of the variation in lung, sinus, pancreatic, and hepatobiliary diseases. For example, patients who are homozygotic for the F508del mutation but who nevertheless have stable lung function into the fifth or sixth decade of life often have variants in the epithelial sodium channel.

CLINICAL MANIFESTATIONS

Lung Disease

Pulmonary manifestations include chronic productive cough and crackles on auscultation. Mucus retention and airway inflammation may cause chronic wheezing. Even in children diagnosed by newborn screening, bronchiectasis (Chapter 78) can be detected on chest computed tomography imaging in up to 30% of infants at 3 months of age, increasing to about 60% at 3 years of age even in the absence of clinically apparent lung disease.

As in asthma (Chapter 75) and chronic obstructive pulmonary disease (Chapter 76), an exacerbation of cystic fibrosis lung disease is frequently preceded by a viral respiratory infection. Exacerbations are characterized by increased cough, dyspnea, and often changes in sputum color and viscosity. Fever is uncommon, but hypoxemia may develop. During the social isolation imposed by the severe acute respiratory syndrome coronavirus 2 pandemic, rates of pulmonary exacerbations of cystic fibrosis actually decreased, thereby suggesting that an underlying exogenous infectious cause is responsible for a substantial fraction of exacerbations.

In cystic fibrosis, secondary polymicrobial endobronchial colonization is dominated by *Staphylococcus aureus* (including multidrug-resistant *Staphylococcus aureus*) and *Pseudomonas aeruginosa*. *Burkholderia* species, *Stenotrophomonas*, and anaerobes are less common but can be associated with a greater inflammatory response. *Aspergillus* and *Candida* infections also can develop.

During an exacerbation, the FEV_1 usually decreases by at least 10% from the previous baseline. Pulmonary function testing also typically shows a decreased mid-expiratory flow rate (MEFR 25 to 75) or an increase in the lung clearance index (Chapter 73). Over time, repeated exacerbations lead to a progressive loss in pulmonary function and to bronchiectasis (Chapter 78), predominantly in the upper lobes (Fig. 77-1). Radiographic evidence of sinusitis is common, as are nasal polyps, but only a minority of patients with cystic fibrosis have chronic sinus disease (Chapter 394) manifested with pain, anosmia, congestion, and discharge.

Gastrointestinal Disease

Infants with cystic fibrosis are susceptible to meconium ileus and small bowel obstruction that may necessitate life-saving surgery at birth. In many patients, inadequate hydration leads to distal intestinal obstruction syndrome, which may result in ileo-ileal intussusception (Chapter 128) that can require emergent surgery. Bulky, inadequately hydrated stools may also cause chronic obstipation, abdominal pain, hemorrhoids, and rectal prolapse.

Up to 90% of patients with cystic fibrosis develop pancreatic insufficiency (Chapter 130) with resulting fat malabsorption that leads to deficiencies in fat-soluble vitamins D, A, K, and E. Osteopenia and coagulopathies are common sequelae of these deficiencies.[2] The minority of patients who initially retain pancreatic sufficiency usually have milder Class IV or V mutations but still are subject to chronic pancreatitis (Chapter 130) that may lead to eventual pancreatic insufficiency. Many patients with cystic fibrosis suffer from reflux esophagitis (Chapter 124). Portal hypertension owing to liver involvement[3] increases the risk for esophageal varices.

FIGURE 77-1. Cystic fibrosis. Chest radiograph shows cystic bronchiectasis preferentially involving both upper lobes with accompanying bilateral apical bullae. Bilateral upper lobe loss of volume with retraction of the hilar regions cephalad. (Courtesy of Paul Stark, MD.)

Reproductive Issues

Some men are diagnosed with cystic fibrosis after evaluation for infertility (Chapter 216). Sperm production is normal, but virtually all men with cystic fibrosis have congenital bilateral absence of the vas deferens. Many females with cystic fibrosis may have difficulty conceiving due to blockage of the cervix with viscid mucus.

Additional Manifestations

By 30 years of age, approximately one third of patients have cystic fibrosis–related diabetes (Chapter 210). Although ketoacidosis rarely develops, the microvascular and macrovascular complications of diabetes mellitus can occur. The risks of osteoporosis (Chapter 225), osteopenia, and fracture also increase in frequency with age.

Patients who have cystic fibrosis are also predisposed to short stature, developmental delay, atypical mycobacterial infections (Chapter 300), obstructive sleep apnea (Chapter 374), pulmonary hypertension (Chapter 69), gallstones (Chapter 141), amenorrhea (Chapter 218), cystic fibrosis–related rheumatoid arthritis (Chapter 243), erythema nodosum (Chapter 407), renal calculi (Chapter 111), and chronic renal insufficiency (Chapter 116).

DIAGNOSIS

In the United States, routine newborn screening for cystic fibrosis is performed by measuring immunoreactive trypsinogen from a heel stick at birth. This test is highly sensitive but relatively less specific. For babies who have initially positive results, most hospitals perform genetic mutation analysis as the next step. For patients whose genetic testing is negative using a panel of the 40 or so most common CFTR mutations, sequencing of the gene, which may not be available in all centers, is required. In patients who are suspected of having cystic fibrosis but who have only a single identified mutation, sweat testing is required to establish the diagnosis. Even if patients have two CFTR mutations, pilocarpine iontophoresis sweat testing is the gold-standard diagnostic test. Chloride values equal to or greater than 60 mEq/L are diagnostic of cystic fibrosis, and values lower than 30 mEq/L are normal. Borderline results

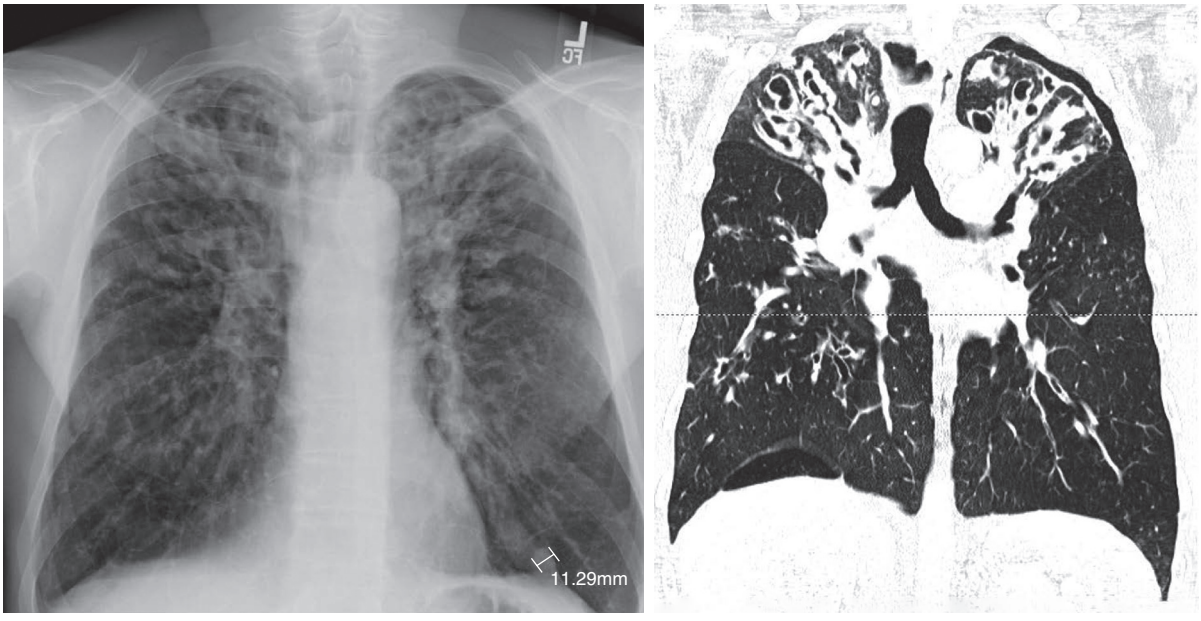

FIGURE 77-2. Chest radiograph and computed tomographic scan show bronchiectasis in a patient with cystic fibrosis.

(between 30 and 59 mEq/L) may be associated with milder CFTR variants and *forme fruste* cystic fibrosis.

In infants with steatorrhea or failure to thrive, CFTR variant genetic analyses should supplement standard testing. The sweat test can be falsely positive in patients who have nephrogenic diabetes insipidus (Chapter 206), malnutrition (Chapter 197), Addison disease (Chapter 208), or hypoparathyroidism (Chapter 227).

In an occasional patient, cystic fibrosis can present in adulthood. Nearly all such patients have chronic rhinosinusitis (Chapter 394), and many have recurrent respiratory infections (including bronchitis [Chapter 84] and bronchiectasis [Chapter 78]), abdominal pain, and pancreatitis (Chapter 130).[4] If the sputum culture reveals *Pseudomonas*, *S. aureus*, atypical mycobacteria, or fungi, the physician should suspect possible cystic fibrosis. The clinical evaluation should include spirometry, computed tomographic scanning of the sinuses and chest, and sweat testing. The chest radiograph typically shows evidence of cystic bronchiectasis, especially involving the upper lobes (see Fig. 77-1), most evident in a computed tomographic scan (Fig. 77-2). In advanced cases, pulmonary hypertension can also develop (E-Fig. 77-2).

DIFFERENTIAL DIAGNOSIS

Conditions that can mimic cystic fibrosis include bronchiectasis (Chapter 78), chronic aspiration, tuberculosis (Chapter 299), primary or secondary immunodeficiencies (Chapter 231), Crohn disease (Chapter 127), and connective tissue diseases (such as rheumatoid arthritis [Chapter 243] and Sjögren syndrome [Chapter 247]), primary ciliary dyskinesia (Chapter 78), and Shwachman-Diamond syndrome (Chapter 231).

In some patients who have a clinical phenotype that suggests cystic fibrosis, the diagnosis cannot be established, either because their sweat test is normal or because two genetic mutations cannot be identified. Such patients have what is now termed CFTR-related disorder. In some such patients, comprehensive analysis of the CFTR coding and flanking regions may help establish the diagnosis of cystic fibrosis.

TREATMENT

In the United States, nearly every patient with cystic fibrosis receives care by a highly specialized multidisciplinary care team at a Cystic Fibrosis Foundation–accredited center, where better outcomes are achieved compared with treatment in other settings.[5] Standard supportive therapy involves airway clearance, mucolytic drugs, bronchodilators, treatment of infections, anti-inflammatory therapy, pancreatic enzyme replacement, and bowel clearance. CFTR potentiators and correctors can substantially benefit patients with certain CFTR mutations.[6]

Airway Clearance

The clearance of viscid mucus from the airways is facilitated by exercise[A1] as well as chest physical therapy, including postural drainage, percussion, and external vests that utilize vibration. Chest physical therapy is optimally performed two to three times a day. A positive-pressure expiratory mask, autogenic drainage, and the forced expiratory technique are also useful. Airway clearance can be improved by using mucolytics, including human recombinant DNase (dornase alfa, 2.5 mg once daily by inhalation),[A2] N-acetyl cysteine (10% solution, 10 to 30 mL every 6 hours), and osmotic drugs (e.g., 7% hypertonic saline solution, 4 mL nebulized twice daily) immediately prior to these airway clearance techniques.

For nasal sinus symptoms, nasal saline irrigation with or without xylitol (12 mg dissolved into 240 mL water in a sinus irrigation bottle for 10 days) and topical corticosteroids (e.g., betamethasone 100 μg twice daily for 6 weeks) are efficacious. Nasal polyposis and sinus ostia blockage can also be treated surgically (Chapter 394).

Treatment of Infection

Antibiotic therapy should focus on the microorganisms identified in the sputum or on throat swab. Typical organisms include *Staphylococcus* sp. (Chapter 267), *Pseudomonas aeruginosa* (Chapter 282), and atypical mycobacteria (Chapter 300). Multidrug-resistant *Staphylococcus aureus* are increasingly observed, and multidrug-resistant *Burkholderia* species (Chapter 282) are associated with high morbidity and mortality.

Outpatient therapies for chronic *Pseudomonas* infection include nebulized tobramycin solution (300 mg twice daily for 28 days on-off cycles), inhaled tobramycin powder (112 mg twice daily for 28 days on-off cycles), aerosolized colistin (1 to 2 million units twice daily), or inhaled aztreonam (75 mg inhaled every 8 hours for 28 days).[A3] For *Staphylococcus aureus* infections, by comparison, there is insufficient evidence for chronic antimicrobial therapy.

For exacerbation of lung disease, oral antibiotics are usually prescribed for 2- to 3-week courses.[7] Depending on culture and sensitivity results, options include ciprofloxacin (500 to 750 mg twice daily), trimethoprim/sulfamethoxazole (1 double-strength tablet twice daily), amoxicillin (1 gram three times daily), linezolid (600 mg twice daily), erythromycin (500 mg four times a day), and clarithromycin (500 mg twice daily) (Chapters 78 and 266).[8] Other options include doxycycline, tetracycline, minocycline, and tigecycline (Chapter 266).

For severe exacerbations, patients may require intravenous antibiotics: options include penicillins, cephalosporins, aminoglycosides, macrolides, vancomycin, carbapenems, aztreonam, colistin, sulfa drugs, and quinolones (Chapter 266). For atypical mycobacterial infections, combination therapy is required (Chapter 300).

Unfortunately, many of these antimicrobial agents have significant side effects, including nephrotoxicity; dosing must be tailored to renal function. Antibiotic resistance is frequent and can complicate choices among antibiotic options.

Bronchodilators

Clinically important airway hyperresponsiveness, presumably caused by chronic airway inflammation, is nearly universal among patients with cystic fibrosis (Chapter 75). Treatment with inhaled β-adrenergic bronchodilators may include albuterol (aerosol or dry powder 90 to 180 μg every 4 to 6 hours, or 3 mL of a 0.083% solution [2.5 mg] nebulized three to four times daily) and salmeterol (50 μg inhalation twice daily). A β-adrenergic agent is typically combined with an anticholinergic agent, such as ipratropium bromide (17 μg two puffs twice daily) or tiotropium (1.25 μg inhaled daily). Combination inhalers (such as ipratropium bromide 20 μg/albuterol sulfate 120 μg [Combivent Respimat], 1 inhalation four

E-FIGURE 77-2. **Cystic fibrosis with pulmonary hypertension and cor pulmonale.** Chest radiograph shows hyperinflation, bilateral dilated central pulmonary arteries, bilateral upper lobe tubular and cystic bronchiectatic areas, mucoid impactions, and right apical bulla. (Courtesy of Paul Stark, MD.)

times daily or ipratropium bromide 0.5 mg/albuterol sulfate 3.0 mg [DuoNeb], 3-mL vial nebulized four times daily) may be easier for patients to use.

Anti-Inflammatory Agents

Macrolide antibiotics have antimicrobial and immunomodulatory properties. Azithromycin in subinhibitory doses (250 to 500 mg three times weekly) can improve lung function and weight gain and is often recommended regardless of whether patients have chronic *Pseudomonas aeruginosa* infection.[9] Because chronic azithromycin may result in bacterial resistance, patients should be screened for nontuberculous mycobacterium (Chapter 300) before starting it and then at 6- or 12-month intervals; azithromycin should be withheld in the presence of active nontuberculous mycobacterial infection.

High-dose ibuprofen (800-mg tablets titrated to achieve serum concentrations between 50 and 100 μg/mL) can slow the rate of decline in FEV_1 and is recommended for patients who are under 18 years of age and who have an FEV_1 lower than 60% of predicted. The narrow therapeutic window and side effects limit the clinical utility of this treatment.

Corticosteroids, both inhaled (e.g., beclomethasone, fluticasone, budesonide; see Chapter 75) and oral (e.g., prednisone up to 1 mg/kg on alternate days with close attention to adverse effects), are recommended for patients who have asthma or allergic bronchopulmonary aspergillosis (Chapter 311). Allergic bronchopulmonary aspergillosis should be treated with prednisone (0.5 to 2.0 mg/kg/day for 1 to 2 weeks, then hopefully tapered over 1 to 3 months). Itraconazole (5 mg/kg/day, up to a maximum of 400 mg per day, for 3 to 6 months) can be added if patients with bronchopulmonary aspergillus have a slow or poor response to corticosteroids or if they relapse; it is also recommended if patients develop steroid toxicity.

CFTR Correctors and Potentiators

In patients who have gating mutations (including G551D, which affect about 4% of the cystic fibrosis population), ivacaftor (a CFTR potentiator at 150 mg twice daily) can increase FEV_1, as well as decrease the sweat chloride concentration, increase weight, and decrease the rate of hospitalization.[10,11] Ivacaftor is currently approved for patients with at least 1 of 38 CFTR gating or splice mutations.

For the nearly 50% of cystic fibrosis patients who are homozygous for F508del alleles, a combination of a CFTR corrector (lumacaftor 400 mg daily) plus ivacaftor (250 mg twice daily) can modestly improve FEV_1 and increase the interval between hospitalizations.[A4,A5] The combination of tezacaftor (100 mg once daily) plus ivacaftor (150 mg twice daily) also improves FEV_1 and reduces pulmonary exacerbation rates with an acceptable side effect profile in patients who are homozygous for F508del.[A6,A7] The three-drug combination of the CFTR corrector elexacaftor (200 mg once daily) plus tezacaftor (100 mg once daily) and ivacaftor (150 mg twice daily) can improve FEV_1 in patients homozygous for F508del by 10% compared to tezacaftor plus ivacaftor and by 14% in patients who are heterozygous for F508del and a minimal function mutation, thus extending such therapy to about 90% of patients.[A8-A11] However, CFTR modifier treatment can cause serious side effects, and dosing must be reduced in patients who have hepatic failure or who are taking CYP3A inhibitors such as itraconazole or clarithromycin.

Improving CFTR function can benefit even patients with advanced lung disease,[11] but it may not halt the ongoing inflammatory response in chronically infected and bronchiectatic airways. Ion channel modulator agents may therefore need to be started as early as perinatally to prevent lung disease and potentially other organ manifestations, including exocrine pancreatic insufficiency and cystic fibrosis–related diabetes.

Despite more than two decades of research since the discovery of CFTR, gene therapy is not currently an effective therapeutic option. Whether nucleic acid technologies, antisense oligonucleotides, CRISPR/Cas9, or induced pluripotent stem cell therapy will become clinically useful is currently unknown.

Pancreatic Enzyme Replacement Therapy

The replacement of pancreatic enzymes (Chapter 130) is an essential component of the treatment of patients with cystic fibrosis. Dosing (see Table 130-5 in Chapter 130) should aim for the near elimination of steatorrhea. Oral pancreatic enzymes are inactivated by stomach acid. Enteric-coated capsules or acid-resistant microspheres are preferred over acid suppression with H_2 blockers or proton pump inhibitors (see Table 124-1 in Chapter 124), in part because protein pump inhibitors may increase the risk of pneumonia. The absorption of fat-soluble vitamins (D, A, K, and E) may be inadequate despite pancreatic enzyme therapy, so the blood levels of these vitamins should be monitored, and vitamins should be supplemented as needed.[12]

Gastrointestinal Agents

Virtually all patients with cystic fibrosis should receive an empiric bowel regimen to avoid obstipation. Mineral oil (e.g., 15 to 45 mL/day depending on the product), senna (17.2 to 34.4 mg per day), and osmotic stool softeners (e.g., polyethylene glycol 3350 at 0.5 to 1 g/kg/day to a maximum of 40 g/day) are routinely used. Lactulose is another alternative, but it may cause flatulence or abdominal pain in high doses.

A more serious complication is distal intestinal obstructive syndrome, which may occur with dehydration or the use of opioid analgesics. This complication usually requires hospitalization, intravenous rehydration, and administration via a nasogastric tube of iso-osmotic polyethylene glycol 3350 plus an electrolyte solution (20 to 40 mL/kg/h up to a maximum of 1 L/h over 8 hours) or diatrizoate (Gastrografin). Surgical consultation is often required if small bowel obstruction persists.

Other Organ Systems

Sweating may cause excessive salt loss with resulting dehydration and hypotension. Adolescents and adults with cystic fibrosis require about 6000 mg (3 teaspoons) of salt per day. Foods naturally high in salt are recommended, but prophylactic sodium chloride tablets are often added.

Because pancreatic damage can lead to cystic fibrosis–related diabetes, annual glucose tolerance testing is recommended beginning at age 10 years for all patients who do not have diagnosed diabetes. Treatment is similar to type 1 diabetes (Chapter 210). The need for insulin therapy may be delayed by diet and exercise.

Women with cystic fibrosis can have children, but intrauterine insemination may be required if the cervix is blocked with viscid mucus. In men, epididymal sperm aspiration is needed because of the ubiquitous absence of the vas deferens. Patients with cystic fibrosis should be routinely screened for depression and anxiety (Chapter 362) and referred to mental health professionals as appropriate.

Lung Transplantation

Lung transplantation (Chapter 87), which is a life-saving therapy in patients with end-stage lung disease, results in improved quality of life because of better lung function, even though disease progresses in other organs.[13] Current survival rates for adult lung transplant recipients with cystic fibrosis are about 75% at 5 years and 50% at 10 years. In recipients with risk factors such as *Burkholderia cepacia* complex infection or retransplantation, however, outcomes are less favorable. Long-term (>5 years) survival is limited by chronic lung allograft dysfunction (bronchiolitis obliterans and restrictive allograft syndrome) and by reinfection of donor lungs with opportunistic pathogens.

PREVENTION

Genetic counseling should be offered to all at-risk couples prior to pregnancy. Antenatal screening, especially if a previous child was diagnosed with cystic fibrosis, can identify whether future offspring may be affected as well. Prenatal screening can make the diagnosis in utero. Parents also can choose to undergo in vitro fertilization with an embryo that has undergone preimplantation screening for cystic fibrosis.

PROGNOSIS

Factors that influence the outcome of patients with cystic fibrosis include the initiation of effective treatment early in life, the number of hours per day each patient spends in physical therapy, adherence to an often-complicated medical regimen, transition from parental care to self-care, insurance, and psychosocial coping. Although life expectancy for people born with cystic fibrosis has increased over recent years, respiratory failure and death still often occur before the fourth decade of life.

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For the General References and other additional features, please visit Elsevier eBooks+ at https://ebooks.health.elsevier.com.

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78 BRONCHIECTASIS, ATELECTASIS, AND CAVITARY OR CYSTIC LUNG DISEASES

ANNE E. O'DONNELL

BRONCHIECTASIS

DEFINITION

Bronchiectasis is an abnormal permanent dilation of the bronchi and bronchioles caused by repeated cycles of airway infection and inflammation. The distal airways become thickened; the mucosal surfaces develop edema, inflammation, and suppuration; and ultimately there is neovascularization of the adjacent bronchial arterioles. Bronchiectasis, which can be focal or diffuse, is triggered by a variety of genetic, anatomic, and systemic processes. Abnormalities of cilia, mucus clearance, mucus rheology, airway drainage, and host defenses can result in bronchiectasis.[1] Regardless of the cause, patients with bronchiectasis develop chronic infections, which may lead to progressive lung destruction.

EPIDEMIOLOGY

Based on insurance claims reviews, an estimated 110,000 or more patients in the United States are receiving treatment for bronchiectasis that is not related to cystic fibrosis (Chapter 77), and these numbers appear to be increasing.[2] Similar findings have been reported in the United Kingdom and in other parts of the world. Recent U.S. data showed a prevalence of 4.2 per 100,000 persons aged 18 to 34 years and 272 per 100,000 among those older than 75 years. In the older age category, women are disproportionally represented. Other epidemiologic surveys suggest that there is increased risk for the development of bronchiectasis in individuals with reduced access to health care and higher rates of pulmonary infection in childhood.

PATHOBIOLOGY

In up to one third of cases, the cause of bronchiectasis is not identified. Other cases are related to pulmonary infections, genetic causes, anatomic abnormalities, and immune and autoimmune diseases.[3] Hyperconcentrated airway mucous is a characteristic pathogenic abnormality.

Pulmonary Infections

Approximately one third of patients with bronchiectasis have an infectious trigger, usually years before the onset of the disease. Childhood viral infections, such as pertussis (Chapter 289) and bacterial infection, can cause permanent damage to the airways, leading to bronchiectasis years after the initial infection. Mycobacterial tuberculosis with its resultant granulomatous inflammation of the airway, lung parenchyma, and lymph nodes can cause subsequent bronchiectasis (Chapter 299), and nontuberculous mycobacterial infections have been recognized as an increasing cause and complication of bronchiectasis, particularly in White women older than 55 years (Chapter 300). Nontuberculous mycobacterial–related bronchiectasis typically involves the right middle lobe and lingula and can be associated with the "tree-in-bud" pattern of bronchiolar involvement on computed tomography (CT) scans (see later section on imaging).

Genetics

Cystic fibrosis (Chapter 77) is characterized by bilateral diffuse bronchiectasis. Although many cystic fibrosis patients are diagnosed in childhood with multisystem disease, older patients may present with only pulmonary or pulmonary and sinus manifestations. Some patients with bronchiectasis may have subtle defects in the cystic fibrosis transmembrane conductance regulator channel without a clear-cut diagnosis of cystic fibrosis.

In primary ciliary dyskinesia, abnormalities in the dynein arms prevent normal ciliary beating. Patients with primary ciliary dyskinesia generally have significant sinopulmonary disease and infertility, and approximately half of these patients have Kartagener syndrome with situs inversus (Chapter 55). Patients with α_1-antitrypsin deficiency also may develop bronchiectasis.

Anatomic Causes

Patients with chronic abnormalities of their swallowing mechanism or with esophageal dysfunction may develop focal or diffuse bronchiectasis with lower lobe predominance (Chapter 124). Direct lung injury caused by acid or particulate matter aspiration or recurrent pneumonia may lead to bronchiectasis.

Severe asthma (Chapter 75) and chronic obstructive pulmonary disease (COPD; Chapter 76) are sometimes complicated by bronchiectasis.[3] Allergic bronchopulmonary aspergillosis (Chapter 311) can cause a distinct "finger-in-glove" central bronchiectasis observed on CT scans owing to chronic inflammation and mucous plugging. Airway abnormalities such as endobronchial tumors (Chapter 177), extrinsic compression by lymph nodes (right middle lobe syndrome), and foreign bodies are also rare causes of focal bronchiectasis. Tracheobronchomegaly (Mounier-Kuhn syndrome) is associated with distal bronchiectasis.

Immune and Autoimmune Diseases

Primary hypogammaglobulinemia (Chapter 231) leads to recurrent pulmonary infections that may result in bronchiectasis. Patients with immunoglobulin G subclass deficiencies may develop bronchiectasis if the deficiency leads to reduction in antibody production. Defects of neutrophil adhesion and chemotaxis (Chapter 153) have been found to cause bronchiectasis. Patients with human immunodeficiency virus infection (Chapter 359) have a higher prevalence of bronchiectasis than individuals with a normally functioning immune system.

Bronchiectasis is an increasingly recognized complication of collagen vascular diseases, particularly rheumatoid arthritis (Chapter 243) and Sjögren syndrome (Chapter 247). The airway injury is likely attributable to chronic inflammation or esophageal dysfunction. Inflammatory bowel disease (Chapter 127) also causes bronchiectasis by undetermined mechanisms.

CLINICAL MANIFESTATIONS

Patients present with chronic cough and usually have mucopurulent or purulent sputum production. Occasionally, a dry nonproductive cough is the primary manifestation. Other symptoms include dyspnea, intermittent hemoptysis, and pleuritic chest pain. Weight loss, malaise, and fatigue sometimes develop. When patients have infectious exacerbations, they may develop fever as well as an increase in their baseline symptoms. Physical findings in patients with bronchiectasis are nonspecific and include an abnormal chest examination with wheezing, crackles, or both. Clubbing of the digits is rare.

The clinical course of patients with bronchiectasis is variable. Some patients have few to no symptoms, others have daily cough with sputum production, and some patients have occasional to frequent exacerbations. A slow decline in pulmonary function is seen with bronchiectasis; the decline is more rapid in patients infected with *Pseudomonas aeruginosa* (Chapter 282) and in patients who have more frequent exacerbations.

DIAGNOSIS

Imaging Studies

Although the diagnosis may be suspected by plain chest radiography, high-resolution computed tomography (HRCT) is the current "gold standard" for confirming bronchiectasis. The characteristic CT findings are lack of bronchial tapering, bronchi visible in the peripheral 1 cm of the lungs, and an internal bronchial diameter greater than the diameter of the accompanying bronchial artery.[4] Other associated HRCT findings are cysts off the end of a bronchus, tree-in-bud irregular branching lines (E-Fig. 78-1) indicating mucus impaction (E-Figs. 78-2 and 78-3), volume loss (E-Fig. 78-4), and occasionally associated consolidation (Fig. 78-1). The location of the bronchiectatic airways may suggest the cause: upper lobe predominance is seen in cystic fibrosis and lower lobe predominance in aspiration syndromes (E-Fig. 78-5). Whereas right middle lobe and lingula involvement suggests the presence of nontuberculous mycobacterial infection (Fig. 78-2 and E-Figs. 78-6A and 78-6B), central bronchiectasis is seen with allergic bronchopulmonary aspergillosis (Fig. 78-3).

Pulmonary function testing, which should be performed on all patients with suspected bronchiectasis, usually shows airflow obstruction as measured by the ratio between the forced expiratory volume in 1 second (FEV_1) and forced vital capacity (FVC) (Chapter 73). The severity of the airflow obstruction and the rate of decline correlate with radiographic extent of disease and frequency of exacerbation. Bronchoscopy will detect airway abnormalities, including tumors, structural deformities, and foreign bodies, and hence should be considered in the evaluation of localized bronchiectasis.

Cultures of sputum and of bronchoalveolar lavage when expectorated sputum is not available have an important role in assessing the infectious complications of bronchiectasis. Molecular techniques have recently demonstrated diverse polymicrobial communities in the lungs of patients with bronchiectasis, both when they are clinically stable and also during an exacerbation.[5]

ABSTRACT

Non–cystic fibrosis bronchiectasis, acquired and congenital lung cysts, lung abscesses, and other focal lung disorders, other than atelectasis, are uncommon but potentially serious conditions that require specific treatments. Atelectasis is very common, occasionally transitory, but potentially a warning sign of a serious underlying disease.

KEYWORDS

bronchiectasis
primary ciliary dyskinesia
atelectasis
lung cysts
pulmonary infections

E-FIGURE 78-1. A thin-slice high-resolution computed tomography image showing bronchiectasis and volume loss on the left and areas of mild cylindrical bronchiectasis and "tree-in-bud" bronchiolitis in the right lower lobe.

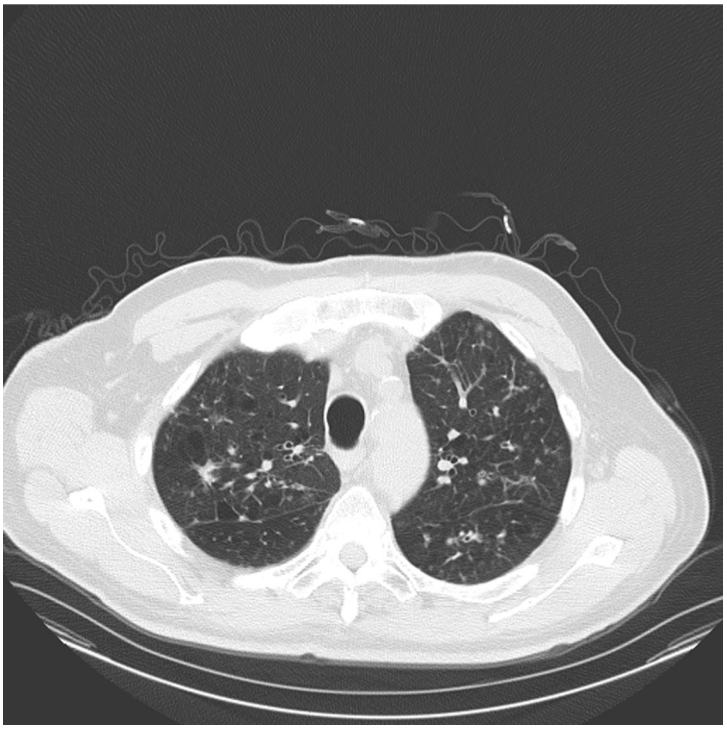

E-FIGURE 78-3. Bronchiectatic changes and mucous plugging superimposed on diffuse emphysematous changes in the lungs.

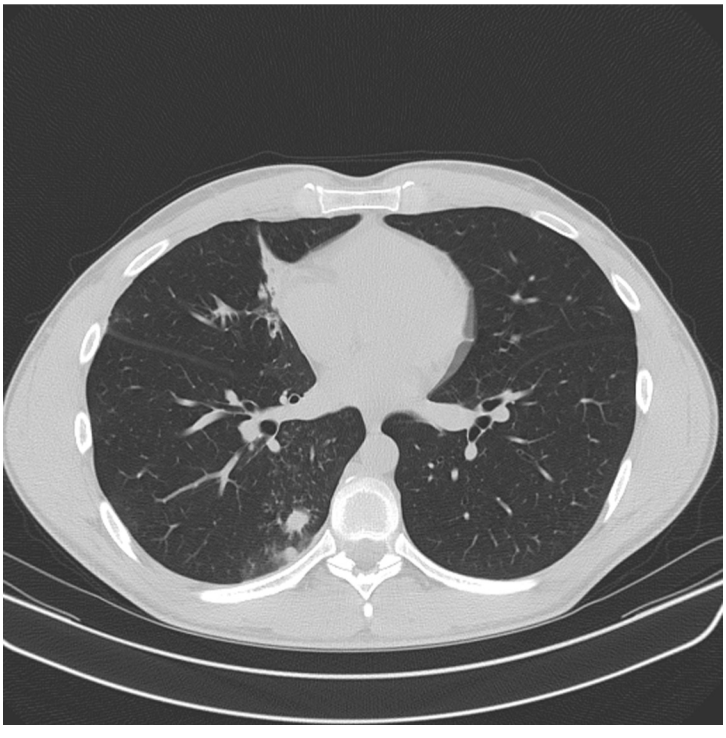

E-FIGURE 78-2. A thin-slice high-resolution computed tomography image through the middle chest; there are mild bronchiectasis in the right middle lobe adjacent to the heart and mucous plugging in areas of bronchiectasis at the right base.

E-FIGURE 78-4. Extensive bronchiectasis in lower cuts of the left lung with associated volume loss.

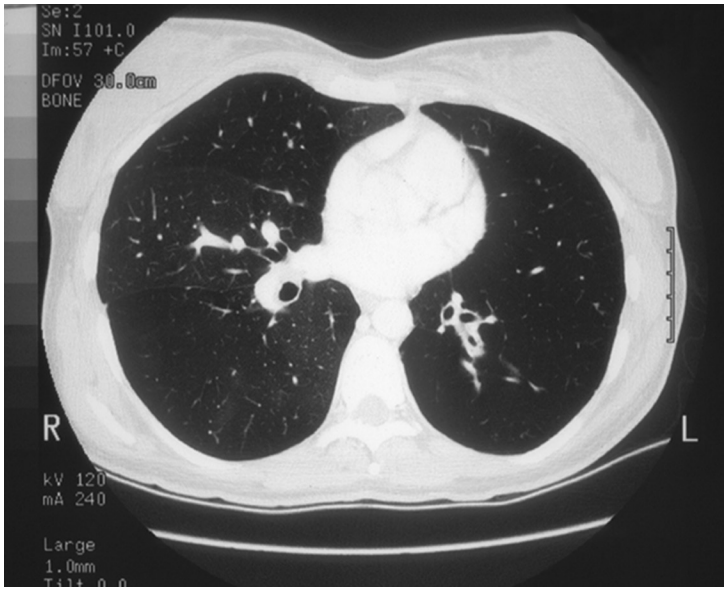

E-FIGURE 78-5. **Computed tomography slice showing a "signet ring" abnormality consistent with a localized area of bronchiectasis in the right lower lobe.**

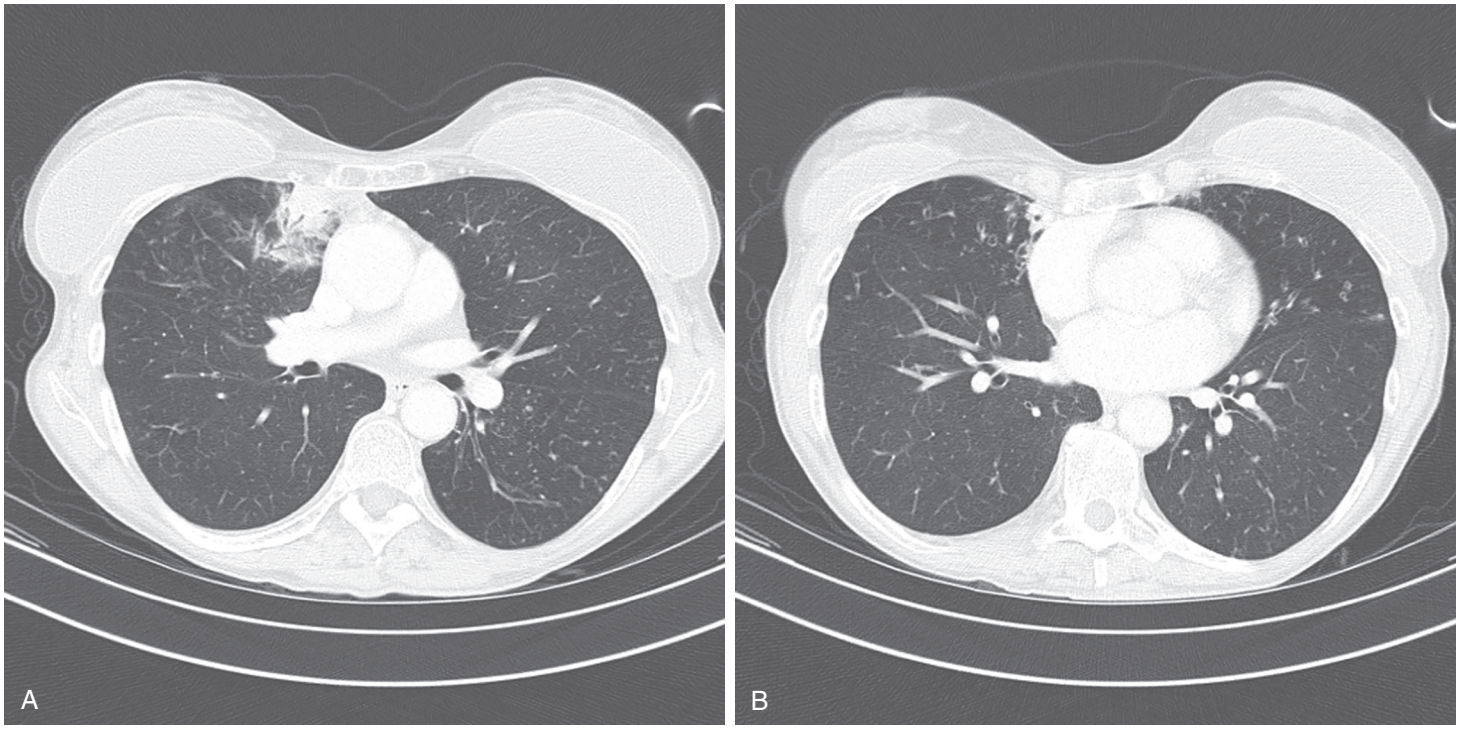

E-FIGURE 78-6. **Mycobacterial infection. A,** A pneumonic infiltrate superimposed on an area of bronchiectasis in the right middle lobe. Bilateral breast implants are also visible. The patient had a history of chronic mycobacterial infection but was acutely ill with a superimposed bacterial pneumonia when this study was performed. **B,** Follow-up imaging after treatment of the acute infection. A residual minor area of right middle lobe bronchiectasis is seen.

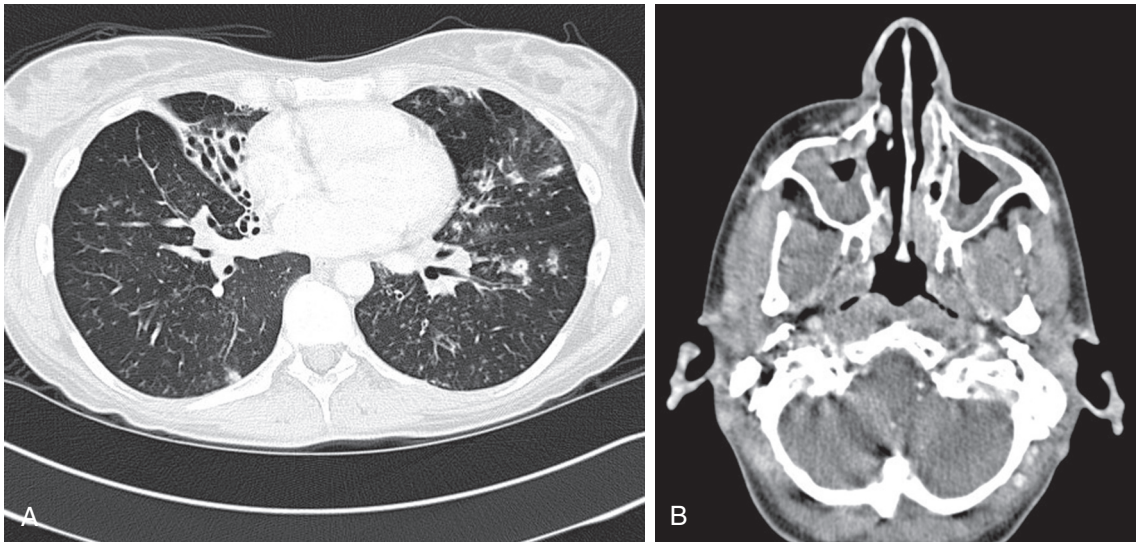

FIGURE 78-1. Bilateral bronchiectasis. A and B, High-resolution computed tomography images of bilateral bronchiectasis in a patient with primary ciliary dyskinesia.

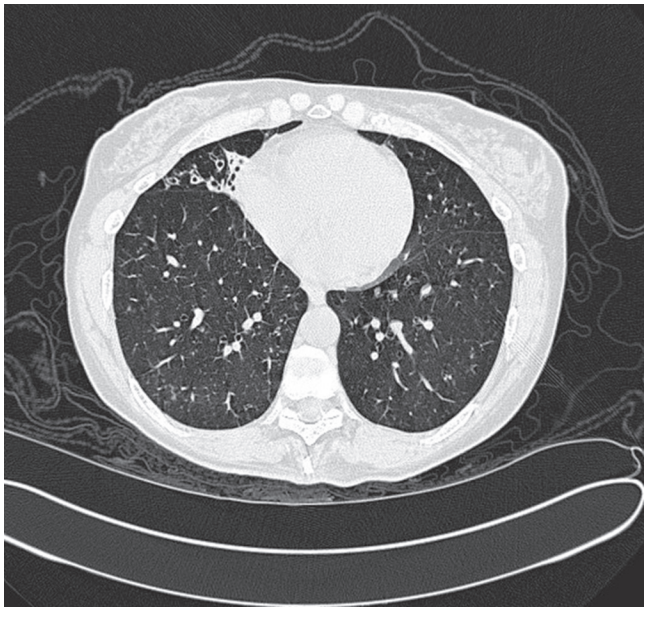

FIGURE 78-2. High-resolution computed tomography image of nodular bronchiectasis caused by a nontuberculous mycobacterium infection.

The dominant organisms are *P. aeruginosa* and *Haemophilus influenzae,* but anaerobic organisms also may be detected. The presence of *P. aeruginosa* portends a worse prognosis and more frequent exacerbations. Patients with no identifiable pathogens have the mildest disease. *Staphylococcus aureus* in the airway may suggest cystic fibrosis as the cause of the bronchiectasis. Nocardia and fungi, particularly aspergillus and candida, are sometimes cultured from bronchiectasis patients but do not always require treatment. Nontuberculous mycobacteria are found with increasing frequency in the airways of patients with bronchiectasis, usually as a complication of preexisting bronchiectasis but occasionally as its primary cause. The laboratory evaluation of patients with bronchiectasis should be individualized. All patients should have sputum cultures for bacterial, fungal, and mycobacterial testing. Other tests that should be considered include measurement of serum immunoglobulin levels and screening for genetic diseases, particularly in patients with diffuse bronchiectasis. Cystic fibrosis (Chapter 77) is diagnosed by elevated sweat chloride levels and by genetic testing. Primary ciliary dyskinesia can be evaluated by measurement of nasal nitric oxide levels, ciliary beat frequency and pattern testing, and electron microscopy studies. α_1-Antitrypsin deficiency is diagnosed by measuring levels and performing phenotyping (Chapter 76). Screening for rheumatoid arthritis (Chapter 243) or Sjögren syndrome (Chapter 247) also may be reasonable in patients with diffuse bronchiectasis.

TREATMENT

The goals of treatment are to reduce the frequency of exacerbations and potentially to improve quality of life, reduce symptoms, and alter the natural history of the disease (Table 78-1).[6–8] Multimodality maintenance treatment for patients with more advanced or symptomatic disease may include airway clearance and anti-inflammatory therapies. Long-term antibiotic therapy, which reduces markers of airways and systemic inflammation, should be considered in patients who have two to three or more exacerbations per year. Pulmonary rehabilitation also is efficacious. Exacerbations are treated based on clinical acuity. Because patients are heterogeneous and therapeutic trials are few, therapy is commonly individualized, especially because no therapies are currently approved by the U.S. Food and Drug Administration for non–cystic fibrosis bronchiectasis and because the proven treatments for cystic fibrosis are often not effective in this patient population.

Preventing Exacerbations

The 23-valent pneumococcal vaccination (Chapter 15) is recommended for patients with bronchiectasis. Routine seasonal influenza vaccination is also standard. At present, no vaccines are available for prevention of the other infectious complications of bronchiectasis. Of note, is that infectious exacerbations appear to have decreased during the coronavirus-19 (COVID-19) pandemic, presumably attributed to social distancing and masking.[9]

Treatment of the Underlying Etiology

For treatable conditions, such as immunoglobulin deficiency or α_1-antitrypsin deficiency (Chapter 76), replacement therapy (Chapter 231) should be considered even though there are few data on whether those therapies alter the natural history of the bronchiectasis and resultant infections. Patients with allergic bronchopulmonary aspergillosis (Chapter 311) should be treated with steroids to mitigate the inflammatory process that leads to the bronchiectasis.

Airway Clearance

Chest physiotherapy and the use of devices to aid mucociliary clearance appear to be beneficial in non–cystic fibrosis bronchiectasis. Patients should be taught airway clearance maneuvers that they can perform independently.[10] Twice-daily use of an oscillatory positive expiratory pressure device (Acapella) can improve sputum volume and quality of life. Other techniques that also may have a role for airway clearance include traditional chest physical therapy with postural drainage and high-frequency chest wall oscillator vests. Formal pulmonary rehabilitation and exercise likely benefit patients with bronchiectasis. Personalizing the treatment yields the best compliance and results.

Inhaled therapy with nebulized hypertonic saline (3 to 7%) may enhance airway clearance, decrease exacerbations, and improve lung function as well as quality of life.[A1] A novel neutrophil elastase inhibitor, brensocatib (10 to 25 mg orally daily), can improve clinical outcomes, including prolonging the time to first exacerbation, in patients who have non–cystic fibrosis bronchiectasis and who have had two or more exacerbations in the prior year.[A2] Although recombinant human DNase is efficacious in cystic fibrosis bronchiectasis, a large clinical trial showed it had deleterious effects when given as maintenance therapy in patients with non–cystic fibrosis bronchiectasis, so it should not be used. Other mucolytic agents are of unproven benefit.

No randomized trials support the use of routine short-acting β-agonist or anticholinergic bronchodilators in bronchiectasis. However, a subset of patients with airway reactivity likely benefits from use of these agents (Chapter 75).

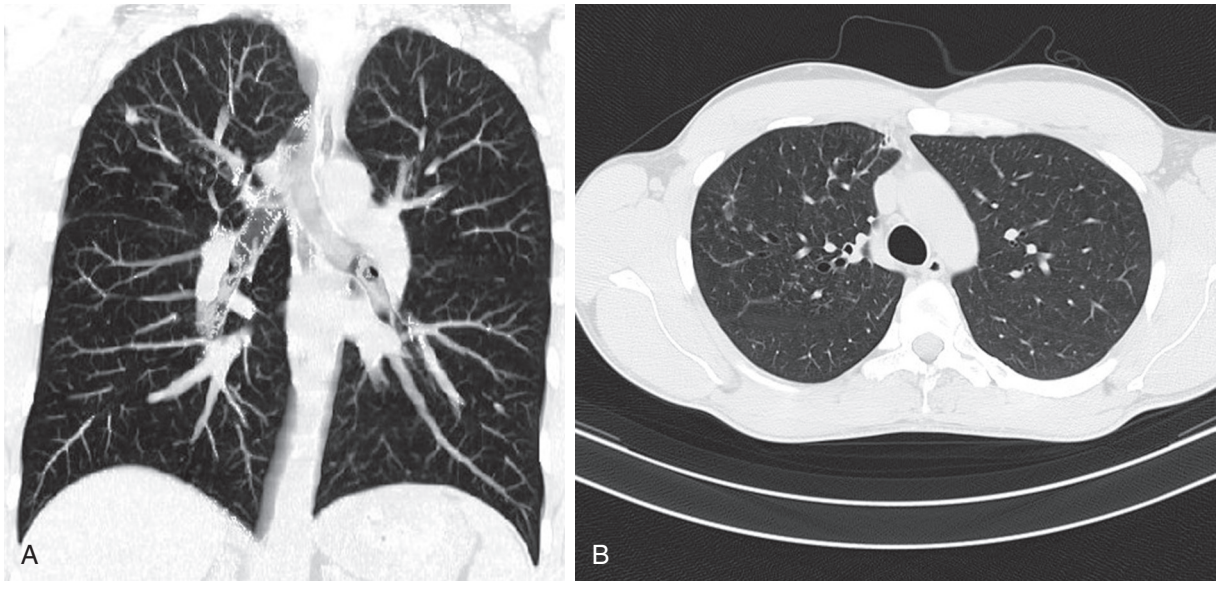

FIGURE 78-3. A and B, High-resolution computed tomography images of finger-in-glove central bronchiectasis caused by allergic bronchopulmonary aspergillosis; best shown in the coronal display of panel A.

TABLE 78-1 POTENTIAL THERAPIES FOR BRONCHIECTASIS

Treatment of underlying condition, if possible
Mobilization of secretions
Pharmacologic
Mechanical
Anti-inflammatory therapy
Inhaled steroids
Macrolides
Antimicrobial therapy
Pathogen specific
Surgery
Localized or refractory disease
Transplantation
End-stage disease

Adapted from O'Donnell A. Bronchiectasis. *Chest*. 2008;134:815-823.

Reduction of Airway Inflammation

Inhaled medium-dose budesonide, when combined with formoterol, is safe and more effective than high-dose budesonide in treating patients with non–cystic fibrosis bronchiectasis. Oral steroids, although occasionally used in patients with bronchiectasis, have never been evaluated in a clinical trial. A small case series suggested potential benefit from mepolizumab in patients who have severe uncontrolled asthma complicated by bronchiectasis.[11]

Antimicrobial Therapy

At present, there is no firm evidence to support the use of routine maintenance antibiotics, although such therapy may be considered in patients with frequent exacerbations and progressive lung destruction. When mycobacterial species are cultured from patients with bronchiectasis, decisions regarding whether to treat and which antimicrobial agents to use are based on published guidelines (Chapters 299 and 300).[12]

Chronic low-dose oral macrolide therapy (e.g., azithromycin 500 mg three times per week or 250 mg/day or erythromycin ethylsuccinate 400 mg twice daily) can reduce exacerbations in patients with non–cystic fibrosis bronchiectasis.[A3] Whether patients will develop resistant organisms is of concern, and the respiratory microbiota is clearly changed by the chronic use of macrolides. Macrolide monotherapy should not be used in patients coinfected with nontuberculous mycobacteria.

Targeted inhaled antimicrobial therapies are also an option, particularly in patients infected with *Pseudomonas* spp. For example, nebulized gentamicin (80 mg twice daily) for 12 months can provide sustained bacteriologic and clinical benefit. Inhaled tobramycin can reduce bacterial colony forming units, but adverse respiratory side effects limit its use.[A4] Inhaled colistin, 1 million IU twice daily delivered by nebulizer, also is safe and possibly effective in adherent patients with bronchiectasis and *P. aeruginosa* infection. Two large trials of inhaled aztreonam lysine showed no clinical improvement, but there may be a benefit in patients with the most severe baseline symptoms. Randomized controlled trials of dry powder ciprofloxacin and nebulized liposomal ciprofloxacin have shown mixed results.[A5] Other off-label antibiotic strategies include prolonged intravenous antibiotics targeted at the specific cultured pathogens.

Surgery and Transplantation

Resectional surgery may have a role for patients who have focal disease or for patients who have hemoptysis that cannot be controlled by embolization of the bleeding vessels (Chapter 87). Surgical resection can also benefit some patients who have diffuse bronchiectasis unresponsive to conventional therapy and some patients infected with nontuberculous mycobacteria. Double-lung transplantation (Chapter 87) has been successfully performed in patients with end-stage lung disease caused by non–cystic fibrosis bronchiectasis, and the clinical outcomes parallel those seen with transplantation for other end-stage lung diseases.

Treatment of Acute Exacerbations of Bronchiectasis

When a patient with bronchiectasis experiences an acute exacerbation, antimicrobial treatments should be aimed at the chronic infecting organisms.[13] Mild to moderate exacerbations can be treated with oral antibiotics, targeted to the results of the sputum culture, for 2 to 3 weeks. Viruses, including coronavirus, rhinovirus, and influenza A and B viruses also cause exacerbations. More severe exacerbations or exacerbations caused by resistant organisms generally require intravenous antibiotics administered in the hospital or at home. No benefit has yet been demonstrated by adding an inhaled antibiotic to systemic therapy for an acute exacerbation. Patients experiencing an acute exacerbation likely benefit from airway clearance modalities and the other nonantibiotic therapies discussed previously.

PROGNOSIS

Non–cystic fibrosis bronchiectasis is a heterogeneous disease with a widely variable prognosis. Patients with more severe obstructive and restrictive findings on pulmonary function tests, poor gas transfer, and chronic pseudomonal infection have the worst prognosis. Independent predictors of future hospitalization include prior hospital admissions, advanced dyspnea, FEV_1 less than 30% predicted, *P. aeruginosa* colonization, colonization with other pathogenic organisms, and three or more lobes involved on HRCT. Comorbidities, including COPD and rheumatoid arthritis, increase the risk for mortality. Radiographic extent of disease, hypoxemia, hypercapnia, and evidence of right heart failure are also predictors of outcome. Bronchiectasis patients who are admitted to an intensive care unit for respiratory failure have been reported to have a 60% 4-year survival rate.

ATELECTASIS

DEFINITION

Atelectasis, or collapse, is caused by hypoventilation of lung units. Atelectasis may involve an entire lung or a lobe, segment, or subsegment. Atelectasis

can be caused by intrinsic obstruction of an airway or external compression from lymph nodes, parenchymal masses, or other entities. When lung units are atelectatic, ventilation-perfusion mismatch leads to hypoxemia. Infection may result from sustained atelectasis.

EPIDEMIOLOGY AND PATHOBIOLOGY

The lung bases and posterior segments are vulnerable to dependent atelectasis, which is caused by inadequate ventilation, particularly in an immobilized or postoperative patient. Patchy atelectasis is caused by alveolar filling processes, such as hemorrhage and edema (Chapter 79). Passive, relaxation, or compression atelectasis occurs when the lung recoils to a smaller volume because of fluid or air in the adjacent pleural space.

Obstructive or resorptive atelectasis is caused by bronchial block to the entry of air, with resultant retractile consolidation. Intrinsic airway obstruction may be caused by mucous plugs, foreign bodies, or tumors in the airway. Extrinsic airway obstruction results from compression of the airway owing to peribronchial lymph node enlargement or other masses impinging on the airway.

Rounded atelectasis is caused by pleural thickening that invaginates and traps adjacent lung. Any chronic pleural disease can cause rounded atelectasis, particularly asbestos-related pleural disease.

CLINICAL MANIFESTATIONS AND DIAGNOSIS

Atelectasis is typically asymptomatic and diagnosed on chest imaging or bedside ultrasound; it may cause dyspnea and tachypnea and result in hypoxemia.[14] In postoperative patients, atelectasis may be a cause of low-grade fever. An arterial oxygen saturation of 96% or less after breathing oxygen through a Venturi mask for 30 minutes is a moderately sensitive and specific test for diagnosing postoperative atelectasis.

Plain chest radiography shows loss of lung volume and the displacement of the lobar fissure, mediastinum, or diaphragm toward the involved lung unit (Fig. 78-4). Platelike or discoid atelectasis manifests as horizontal or curvilinear lines on plain chest radiography. Rounded atelectasis (Fig. 78-5) is an ovoid masslike density abutting the pleura. Secondary atelectasis can be seen in association with a mass lesion (E-Figs. 78-7A and 78-7B). The type and cause of atelectasis can sometimes be elucidated by CT or ultrasonography. Bronchoscopy is required to confirm intrinsic versus extrinsic compression in obstructive-resorptive atelectasis and to determine the exact pathology of the obstruction.

At the bedside, a measurement of arterial oxygen saturation can help assess the severity of the atelectasis and overall lung dysfunction.

PREVENTION AND TREATMENT

Incentive spirometry is commonly prescribed to prevent or treat atelectasis in patients with limited mobility because of recent surgery, neuromuscular weakness, or any prolonged immobilization, but no randomized controlled trials have proved its effectiveness. Preoperative inspiratory muscle training and recruitment maneuvers may reduce atelectasis in patients undergoing upper abdominal or cardiac surgery,[A6] and prophylactic use of noninvasive ventilation may reduce pulmonary dysfunction after lung resection surgery. Other modalities such as positive expiratory pressure devices, high-frequency chest wall oscillation airway clearance, and pharmacologic agents are of no proven benefit.

Patchy atelectasis is treated by addressing the underlying disease process in the lung parenchyma. Compression atelectasis is treated by alleviating the pleural space process.

Obstructive or resorptive atelectasis often requires bronchoscopy for diagnosis and treatment. In patients with obstruction owing to retained secretions, multiple bronchoscopies are sometimes required, but the mucus often rapidly reaccumulates and will resolve only when the patient's overall status improves.

Rounded atelectasis does not require treatment. CT is helpful in distinguishing rounded atelectasis from parenchymal tumor.

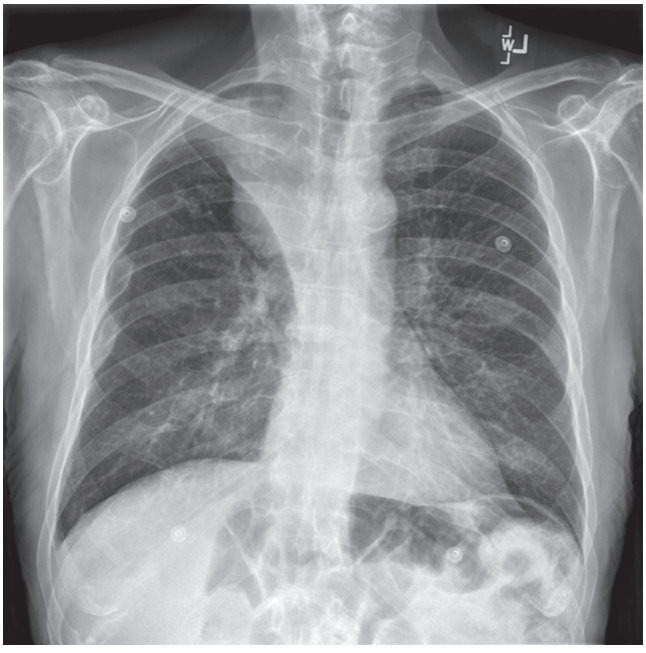

FIGURE 78-4. Plain chest radiograph demonstrating right upper lobe atelectasis (caused by an endobronchial tumor).

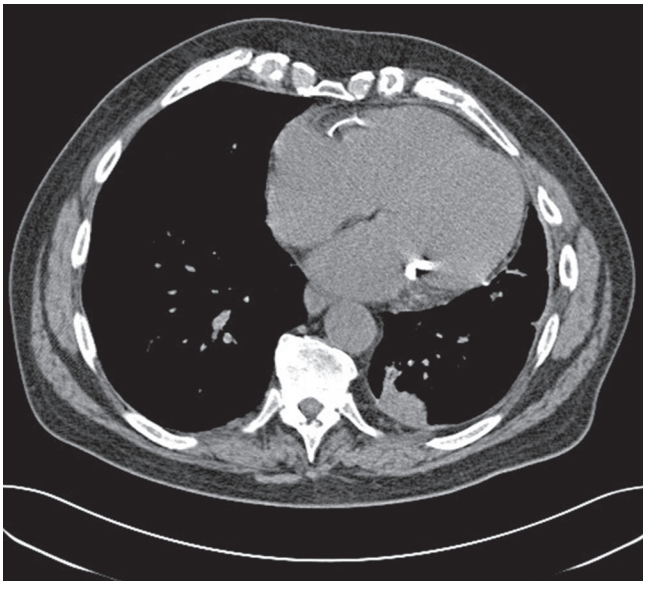

FIGURE 78-5. Computed tomography image of rounded atelectasis.

CAVITARY LUNG DISEASES

DEFINITION

A lung cavity is a gas-filled space with a well-defined wall (greater than 4 mm thick) within a nodule, mass, or area of parenchymal consolidation. Cavities can be acute or subacute, and they may be solitary or multiple. A cavity that is more than 2 cm in largest diameter, is caused by liquefactive necrosis of the lung tissue, and that contains necrotic debris or fluid as a result of microbial infection is a lung abscess.[15]

EPIDEMIOLOGY

The incidence and prevalence of cavitary lung disease is unknown. Lung cavitation can occur across a wide range of underlying diseases, including pulmonary infection, vascular pulmonary disease, malignancy, and autoimmune disorders (Table 78-2).

PATHOBIOLOGY

A lung cavity forms when necrosis and subsequent liquefaction of lung tissue is followed by removal of that debris via the bronchial tree. Bacterial, fungal, mycobacterial, and parasitic infections can cause cavitation. Bacterial infections also can result from aspiration of oral bacteria, especially in patients who have chronic aspiration but also in healthy immunocompetent individuals as a result of dental procedures. Infections that spread hematogenously (septic pulmonary emboli; Chapter 61) may result in multiple areas of cavitation. Organisms associated with lung necrosis include gram-negative and anaerobic bacteria, *Staphylococcus aureus* (Chapter 267), aspergillus (Chapter 311), tuberculous and nontuberculous mycobacteria (Chapters 299 and 300), paragonimus

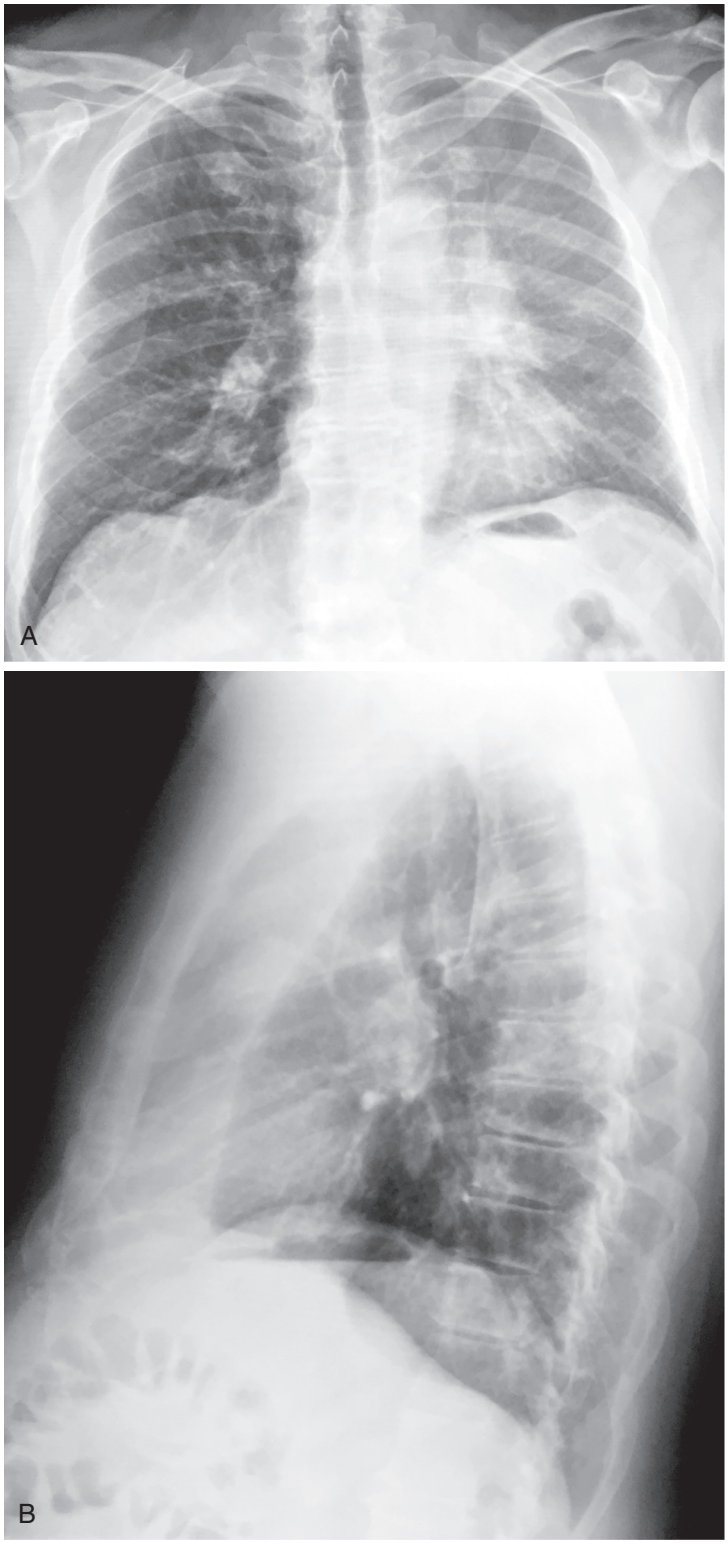

E-FIGURE 78-7. **Left upper lobe atelectasis due to left central bronchogenic carcinoma. A,** Frontal chest radiograph shows veil of opacity over the left upper hemithorax with tracheal deviation to the left and horizontal reorientation of the left mainstem bronchus. **B,** Lateral chest radiograph shows hyperexpansion of the left lower lobe with anterior displacement of the left major fissure. The collapsed left upper lobe and the lingula form an anterior, retrosternal band of opacity. (Courtesy of Paul Stark, MD.)

(Chapter 326), and echinococcus (Chapter 325). Lung abscesses also have been reported as a complication of severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2) pneumonia. Noninfectious causes of lung cavities include autoimmune diseases such as rheumatoid arthritis (Chapter 243) and granulomatosis with polyangiitis (Chapter 249), as well as malignancy (e.g., carcinoma or lymphoma). Sometimes lung cavitation is a consequence of cancer treatment, especially radiation therapy.

CLINICAL MANIFESTATIONS

Patients with cavitary lung disease generally have a productive cough, often with purulent or bloody sputum. Chest pain is occasionally present, particularly if the lung abscess has resulted in pleural effusion or empyema (Chapter 86). Other manifestations include systemic symptoms such as fever, rigors, and weight loss. Subacute presentations (3 months or less of symptoms) are more typical of bacterial infection, whereas more chronic symptoms suggest fungal, mycobacterial, vasculitic, or neoplastic causes.

Cavitary lung disease due to noninfectious causes may be less likely to present with these symptoms, but patients often have constitutional complaints as well as extrapulmonary manifestations of the systemic disease. Untreated cavitary lung disease may lead to local complications, including pleural infection, and may also cause sepsis or even sepsis shock. Rarely, life-threatening hemoptysis (Chapter 71) can occur as a complication of lung cavitation.

DIAGNOSIS

Cavitary lung disease is diagnosed by chest imaging (Fig. 78-6). Plain chest radiographs may demonstrate areas of cavitation; whereas CT imaging is often helpful in documenting the extent of disease and detecting features that may suggest the etiology of the cavities.[16] If prior imaging studies are available, they may also provide clues as to the cause of the cavitation. Further diagnostic evaluation includes cultures of sputum and blood. If septic emboli are suspected, echocardiography may be helpful to assess for valvular vegetations indicative of endocarditis. Inflammatory markers and testing for autoimmune diseases may also provide clues, especially when there are no clinical signs to suggest infection. When malignancy is suspected, positron emission tomography (PET) scanning may be helpful to look for evidence of extrathoracic disease. Image-guided aspiration for culture or needle biopsy[17] is often required to make a definitive diagnosis.

TABLE 78-2 CAUSES OF CAVITARY LUNG LESIONS

INFECTIOUS
Bacterial aspiration/pneumonia
Anaerobic bacteria
Aerobic bacteria
Bacterial embolic
Especially *Staphylococcus aureus*
Mycobacteria
Often multifocal
Fungi
Parasites
Especially *Echinococcus* or *Paragonimus westermani*
VASCULITIS
Especially rheumatoid arthritis or granulomatosis with polyangiitis
MALIGNANT
Necrotizing carcinoma
Lymphoma

TREATMENT

Treatment of cavitary lung disease must be aimed at the underlying cause. Necrotizing pneumonia due to bacterial, mycobacterial, fungal, and parasitic infections often responds to prolonged (6 weeks) systemic antibiotic therapy,[18] targeted against the pathogen diagnosed by cultures of blood, bronchoalveolar lavage fluid, or needle aspiration. Percutaneous tube drainage of a lung abscess can speed the resolution of infection and decrease hospital length-of-stay.[A7] Occasionally, salvage surgery is needed to remove areas of persistent necrosis. Patients who have lung cavitation owing to autoimmune disease or malignancy generally resolve the cavities with successful systemic treatment of the underlying process.

PREVENTION

Infectious cavitary lung disease can be prevented in some patients by improving oral hygiene and preventing aspiration of oral and gastric contents. Prompt treatment of endocarditis and removal of infected intravascular devices may also prevent cavitary infections owing to septic pulmonary emboli.

PROGNOSIS

The prognosis of cavitary lung disease depends upon the cause. Successful treatment of primary infections will often cure the areas of cavitation. Likewise, cavitary lung disease caused by autoimmune disease and malignancy may resolve if those underlying diseases are successfully treated.

CONGENITAL CYSTIC DISEASES OF THE THORAX

Thoracic cysts,[19] which are exceedingly rare, develop because of abnormal development or branching of the foregut. Cysts may develop in the mediastinum at an early stage of gestation or in the lung parenchyma at a later stage. Abnormalities include bronchogenic cysts (mediastinal and parenchymal), congenital pulmonary airway malformation, and pulmonary sequestrations. The cysts are lined with airway and alveolar epithelium but do not communicate in a normal fashion with the airways or lung tissue. Congenital lung malformations may be due to disruptions in Ras or phosphatidylinositol 3-kinase-AKT-mammalian target of rapamycin signaling pathways.

Most patients with thoracic cysts present in childhood, but the cysts can remain asymptomatic and unnoticed until adulthood. In the absence of symptoms, these cystic lesions sometimes present as an incidental finding on chest imaging performed for another indication. Congenital cystic diseases can cause recurrent pneumonia, hemoptysis, or compression of normal structures.

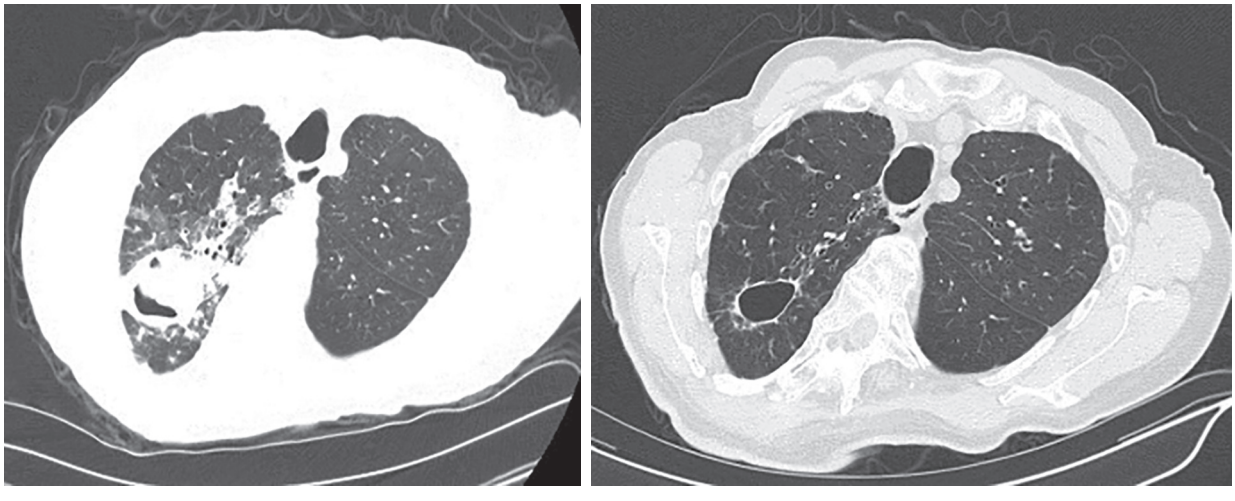

FIGURE 78-6. Cavitary pneumonia due to *Mycobacterium* abscess (left slice pre-treatment; right slice post-treatment).

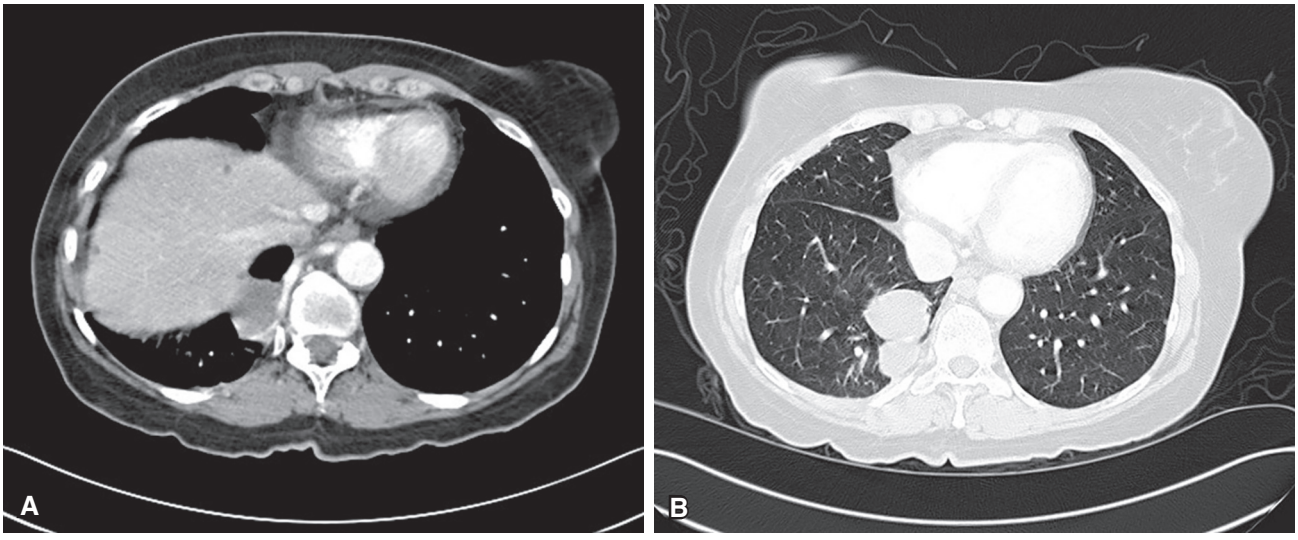

FIGURE 78-7. Pulmonary sequestration. A, Computed tomography image of pulmonary sequestration in right lower lobe. **B,** Feeding vessel visible arising from the aorta.

CT angiography can usually detect congenital cystic lesions of the thorax, but pulmonary or bronchial angiography is sometimes necessary to define the blood flow to the lesion.

Bronchogenic cysts are usually found in the right paratracheal or subcarinal areas of the mediastinum but are occasionally seen in the lung parenchyma. These cysts are often asymptomatic, but they can cause wheezing, dyspnea, and cough when they compress adjacent structures. Secondary infection may develop in the cysts, and there are a few case reports of malignant transformation. Complete surgical resection is generally recommended, but partial excision with de-epithelization of the cysts also has been performed. Observation is also an option when the cysts are asymptomatic.

Congenital pulmonary airway malformation, previously called *congenital cystic adenomatoid malformation of the lung,* is an exceedingly rare abnormality with reported incidence of 1 in every 25,000 to 35,000 pregnancies. The abnormality is caused by arrested development of the bronchial tree. Most patients are diagnosed prenatally by ultrasonography, but the condition may rarely first present in adulthood with complications, including pneumothorax and air embolism. Treatment is anatomic surgical resection.

Pulmonary sequestrations are areas of nonfunctioning pulmonary parenchyma with no communication to the tracheobronchial tree and abnormal arterial supply and venous drainage (Fig. 78-7). Intralobar sequestration, which accounts for about 75% of cases, does not have visceral pleura and is generally found in a lower lobe, the left more frequently than the right. Extralobar sequestrations have their own visceral pleura, are separate from the normal lobes, and even may be found below the diaphragms. Sequestrations usually have a feeding vessel that arises from the aorta. Sequestrations may be asymptomatic, but patients sometimes develop recurrent infections and/or hemoptysis. Surgical excision with special care for the management of the feeding vessel is curative. Embolization of the feeding vessel is sometimes a successful treatment option.

Hyperlucent lungs are diagnosed by a paucity of vascular and interstitial markings noted on chest imaging. Lung parenchymal air collections can be caused by congenital parenchymal cysts, congenital lobar emphysema (almost exclusively diagnosed in infancy), giant bullous emphysema (vanishing lung syndrome), or Swyer-James syndrome. Lung parenchymal cysts may be a bullous alveolar type or may contain bronchial wall elements such as cartilage, smooth muscle, and glands. They may become infected and may rupture to cause pneumothorax. Surgical resection is generally recommended unless the lesions are small. Congenital lobar emphysema, otherwise known as *congenital large hyperlucent lobe,* may cause severe respiratory distress in infants owing to compression of surrounding lung tissue. Giant bullous emphysema is a rare condition that usually affects the upper lobes of young male smokers. Compression of normal lung parenchyma from these overdistended lobes may require surgical resection.

Birt-Hogg-Dubé syndrome is caused by an autosomal dominant condition of germline mutations in the folliculin gene. It is characterized by pulmonary cysts, recurrent pneumothoraces, renal cell carcinomas, and skin fibrofolliculomas.

Swyer-James-Macleod syndrome, which is characterized by unilateral lucency of an entire lung, is caused by childhood bronchiolitis obliterans owing to viral or bacterial infection or toxic inhalation. CT shows air trapping and hyperlucency of the affected lung, with a normal contralateral lung. No therapy is required.

ACQUIRED CYSTIC LUNG DISEASES

High-resolution CT scans can detect a variety of acquired cystic lung diseases.[20] Cysts typically represent as subpleural emphysema or bullae in the lung parenchyma. Causes of multifocal cysts include lymphocytic interstitial pneumonia (Chapter 80), Birt-Hogg-Dubé syndrome, tracheobronchial papillomatosis, and primary and metastatic cancers. Multifocal cysts with associated nodules are seen in lymphocytic interstitial pneumonia (Chapter 80), light chain deposition disease (Chapter 173), amyloidosis (Chapter 174), and Langerhans cell histiocytosis (Chapter 155) and are associated with ground-glass opacities in *Pneumocystis jiroveci* pneumonia (Chapter 313) and desquamative interstitial pneumonia (Chapter 80). Emphysema (Chapter 76) and cystic bronchiectasis also can mimic cystic disease. A careful noninvasive evaluation can usually determine the cause, but bronchoalveolar lavage or even lung biopsy may be required.

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79 ALVEOLAR FILLING DISORDERS

STEPHANIE M. LEVINE

DEFINITION

Alveolar filling disorders (Table 79-1) are characterized by chest radiographic findings of alveolar involvement ranging from a ground-glass appearance to consolidation; the pathologic process shows primary involvement of the alveolar air spaces distal to the terminal bronchioles. For example, in pulmonary alveolar proteinosis, the alveoli are filled by proteinaceous fluid. By comparison, the alveolar walls are lined by adenocarcinoma cells in invasive mucinous adenocarcinoma and lepidic predominant nonmucinous adenocarcinoma, formerly called bronchioloalveolar cell cancer. In acute interstitial pneumonia, exudative organizing fibroproliferative infiltrates fill the alveolar space; in the alveolar hemorrhage disorders, blood fills the alveolar space. Alveolar spaces filled with acute inflammatory cells, as in bacterial pneumonia (Chapter 85); water, as in cardiogenic or hydrostatic pulmonary edema (Chapter 45); or high-protein fluid, as in noncardiogenic or increased permeability pulmonary edema (Chapter 90), are also part of the radiographic differential diagnosis of alveolar filling disorders and must be excluded.

A general approach to these suspected alveolar filling diseases (Fig. 79-1) can be stratified by the time elapsed since the onset of symptoms. The typical patient may present with the onset of cough (usually dry) and dyspnea of variable duration, depending on the disease process. Hemoptysis is a frequent presenting symptom in the alveolar hemorrhagic disorders. With the exception of acute interstitial pneumonia, symptoms suggesting an acute infectious process such as fever, leukocytosis, and productive cough are usually absent. If the initial chest radiograph or chest computed tomography (CT) is consistent with a possible alveolar filling process (Chapter 72) and acute pneumonia and pulmonary edema are excluded, bronchoscopy with bronchoalveolar lavage (Chapter 73) and transbronchial biopsy should be performed, particularly if pulmonary alveolar proteinosis, invasive mucinous adenocarcinoma, lepidic predominant nonmucinous adenocarcinoma (Chapter 177), or alveolar hemorrhage is suspected. When these tests are nondiagnostic, and in many cases of suspected acute interstitial pneumonia, a surgical lung biopsy obtained by thoracoscopy or an open surgical procedure may be indicated to establish a firm diagnosis.

TABLE 79-1 ALVEOLAR FILLING DISORDERS

DISEASES	PATHOPHYSIOLOGY	RADIOGRAPHIC FINDINGS
Pulmonary alveolar proteinosis	Impaired processing of surfactant by alveolar macrophages caused by defects in GM-CSF signaling	Bilateral alveolar opacities with "crazy paving" and diffuse areas of ground-glass attenuation on CT scan
Acute interstitial pneumonia	Diffuse alveolar damage with temporal uniformity	Diffuse alveolar filling process similar to acute respiratory distress syndrome
Diffuse alveolar hemorrhage	Bleeding from the pulmonary microcirculation, usually from the capillaries	Acute development of bilateral alveolar opacities
Invasive mucinous adenocarcinoma and lepidic predominant nonmucinous adenocarcinoma (formerly called bronchioloalveolar cell carcinoma)	Cancer cells growing along the alveolar septa	Pneumonic opacities, consolidation with air bronchograms, ground-glass opacities (either solitary or multiple)

CT = computed tomography; GM-CSF = granulocyte-macrophage colony-stimulating factor.

PULMONARY ALVEOLAR PROTEINOSIS

EPIDEMIOLOGY

Pulmonary alveolar proteinosis is a rare alveolar filling disease caused by the accumulation of phospholipoproteinaceous surfactant material in the alveoli. The incidence is estimated to be 3.7 cases per million people. Pulmonary alveolar proteinosis is a primary acquired, autoimmune disorder in more than 90% of cases,[1] but similar histopathologic features may be found with identifiable secondary causes, such as acute silicosis (silicoproteinosis; Chapter 81), aluminum dust exposure (Chapter 81), indium dust exposure, immunodeficiency disorders (e.g., immunoglobulin G monoclonal gammopathy and severe combined immunodeficiency syndrome), hematologic malignant neoplasms (particularly myeloid leukemias; Chapters 168 and 170), and certain infections (e.g., *Pneumocystis jiroveci* pneumonia and severe acute respiratory syndrome coronavirus 2 [Chapter 336]).[2] Pulmonary alveolar proteinosis has also been described after bone marrow transplantation (Chapter 163). A congenital form also usually presents in infancy.

PATHOBIOLOGY

The pathogenesis of pulmonary alveolar proteinosis is related to impaired processing of surfactant by alveolar macrophages caused by defects in granulocyte-macrophage colony-stimulating factor (GM-CSF) signaling. This impairment

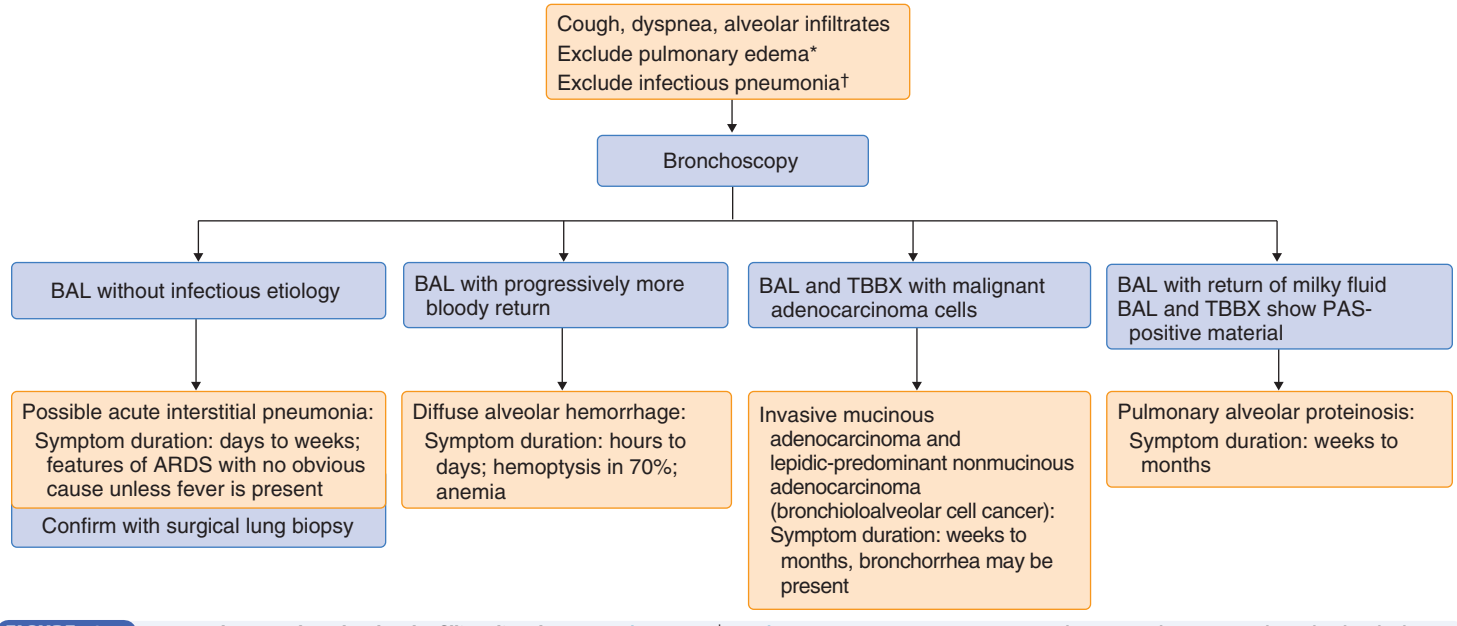

FIGURE 79-1. A general approach to the alveolar filling disorders. *See Chapter 45. †See Chapter 85. ARDS = acute respiratory distress syndrome; BAL = bronchoalveolar lavage; PAS = periodic acid–Schiff; TBBX = transbronchial biopsy.

ABSTRACT

Alveolar filling disorders are characterized by chest radiographic findings of alveolar involvement ranging from a ground-glass appearance to consolidation. In pulmonary alveolar proteinosis, the alveoli are filled by proteinaceous fluid. In acute interstitial pneumonia, exudative organizing fibroproliferative infiltrates fill the alveolar space. In the alveolar hemorrhagic disorders, blood fills the alveolar space. In invasive mucinous adenocarcinoma and lepidic predominant nonmucinous adenocarcinoma, formerly called bronchioloalveolar cell cancer, the alveolar walls are lined by adenocarcinoma cells. This chapter reviews the definition, epidemiology, pathobiology, clinical manifestations, diagnosis, treatment, and prognosis for each of these disorders.

KEYWORDS

pulmonary alveolar proteinosis
acute interstitial pneumonia
diffuse alveolar hemorrhage
invasive mucinous adenocarcinoma
lepidic predominant nonmucinous adenocarcinoma
alveolar filling disorders

may be caused by autoantibodies against GM-CSF or GM-CSF receptor gene mutations, which are found in 90% of cases. The secondary forms are caused by a relative GM-CSF deficiency, leading to macrophage dysfunction and reduced surfactant clearance. The autosomal recessive congenital form of pulmonary alveolar proteinosis, caused by a mutation in the genes encoding surfactant protein B or C, or the GM-CSF receptor results in abnormal surfactant function and severe respiratory distress in homozygous infants. The result of this impairment is accumulation of surfactant-rich material and progressive dysfunction in phagocytosis caused by excessive production or diminished clearance of surfactant by alveolar macrophages.

Histologic examination in pulmonary alveolar proteinosis reveals alveoli filled with lipoproteinaceous material that stains pink (positive reaction) with periodic acid–Schiff stain. Classically, there is no destruction of alveolar architecture. Electron microscopy reveals lamellar (phospholipid-containing) myelin bodies.

CLINICAL MANIFESTATIONS

Pulmonary alveolar proteinosis presents in patients in the third to fourth decade of life with a 2 : 1 male predominance. Most patients (72%) are smokers. Patients present with the insidious onset of dyspnea and cough, which may be dry or occasionally productive of grayish material.[3] The duration of symptoms before diagnosis is typically 6 weeks to 6 to 8 months. Low-grade fevers, malaise, and weight loss may also be present. Hemoptysis is unusual. On physical examination, rales are present in 50% of cases. Clubbing is an unusual finding until later stages of disease.

DIAGNOSIS

Mildly elevated leukocyte counts and mildly to moderately elevated lactate dehydrogenase (LDH) levels may be found in the blood in more than 80% of patients; LDH levels may correlate with the severity of disease. Polycythemia and hypergammaglobulinemia may also be present. The chest radiograph (Fig. 79-2) and chest CT scans demonstrate a diffuse symmetrical alveolar filling process with predominance in the lower two thirds of the lung fields; the radiographic appearance may mimic pulmonary edema. The characteristic CT pattern is often described as "crazy paving," which is attributable to scattered or diffuse areas of ground-glass attenuation with thickening of intralobular structures and interlobular septa in polygonal shapes (Fig. 79-3 and E-Fig. 79-1), sometimes with a subpleural sparing pattern.[4] This radiographic pattern is not specific for this disorder and can be seen in a variety of pulmonary disorders, including but not limited to acute respiratory distress syndrome (ARDS; Chapter 90), *P. jiroveci* pneumonia (Chapter 313), adenocarcinomas formerly described as bronchioloalveolar carcinoma (Chapter 177), lipoid pneumonia (Chapter 82), sarcoidosis (Chapter 83), organizing pneumonia, drug reactions, pulmonary hemorrhage, cardiogenic pulmonary edema (Chapter 46), and acute interstitial pneumonias. Pulmonary function tests often, but not always, show a restrictive pattern with a reduced diffusing capacity. Arterial blood gas analyses reveal hypoxemia.

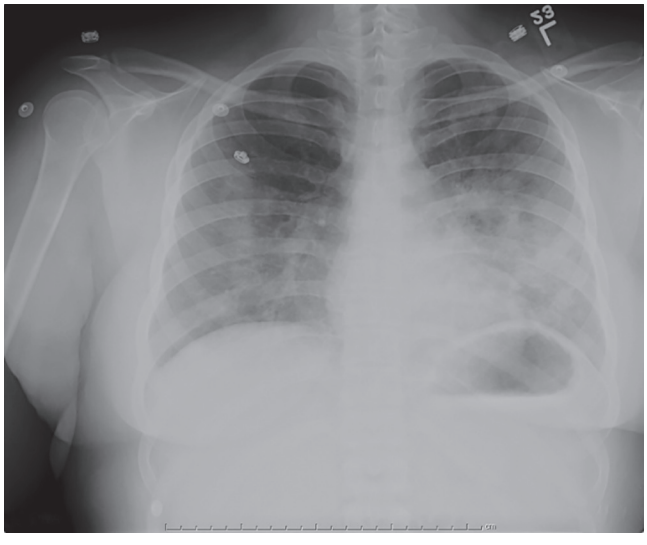

FIGURE 79-2. A chest radiograph showing bilateral alveolar opacities in a patient with pulmonary alveolar proteinosis.

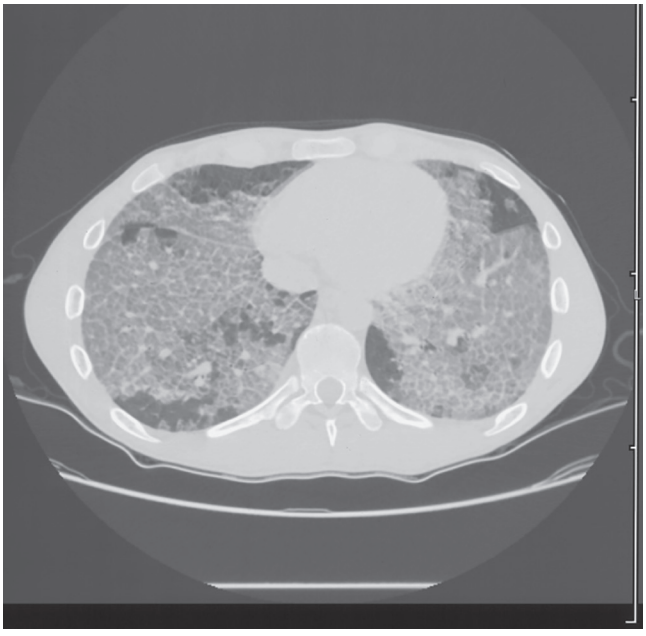

FIGURE 79-3. A chest computed tomography scan showing the "crazy paving" pattern characteristic of pulmonary alveolar proteinosis.

Bronchoscopy should be the initial procedure when pulmonary alveolar proteinosis is suspected. The diagnosis of pulmonary alveolar proteinosis can be established in most cases by the recovery of milky white to sandy-colored or light brown fluid on bronchoalveolar lavage. When it is subjected to cytologic analysis, the lavage fluid has a positive reaction on periodic acid–Schiff staining and reveals alveolar macrophages filled with positive staining material. Transbronchial biopsy or thoracoscopic biopsy can confirm the diagnosis by providing tissue that has similar staining characteristics. Serologic analysis for GM-CSF antibodies is now often performed to support the diagnosis. GM-CSF autoantibody levels may be obtained and are thought to be 100% sensitive and specific for the autoimmune form of pulmonary alveolar proteinosis. There does not appear to be a correlation between antibody levels and the severity of disease.

TREATMENT

About 8 to 30% of cases of pulmonary alveolar proteinosis resolve spontaneously, and smoking cessation may contribute to spontaneous resolution. A second group of patients will progress to respiratory failure. The remainder will have stable disease. Superinfection with *Nocardia* spp, atypical mycobacteria, fungi, and other opportunistic organisms can occur in more than 15% of patients as a result of macrocyte phagocytic dysfunction.

Therapy depends on the severity of symptoms. Corticosteroids are ineffective and may be deleterious. Treatment of severely symptomatic patients with dyspnea and hypoxemia[5] begins with multistage or sequential whole-lung lavage performed under general anesthesia with a double-lumen endotracheal tube. The recovered fluid initially has an opaque, sandy-colored appearance (E-Fig. 79-2). This procedure may have to be repeated at variable intervals. Asymptomatic patients should be observed and followed closely. Mildly symptomatic patients should receive supportive therapy with supplemental oxygen as needed. Case reports suggest that inhaled GM-CSF can improve quality of life, oxygenation, pulmonary function, and exercise capacity in about half of treated patients who cannot undergo whole-lung lavage or who have failed standard treatment with whole-lung lavage. One randomized trial of this experimental therapy in patients with mild to moderate disease showed no clinical benefits despite modest improvements in arterial saturation and chest radiography,[A1] but another showed improvement in clinical symptoms as well as in arterial saturation, especially with continuous daily therapy.[A2] Isolated case series have reported variable responses to CD-20 monoclonal antibody, rituximab, or plasmapheresis. Corticosteroids are not routinely used. Lung transplantation can be performed, but recurrent pulmonary alveolar proteinosis has been reported.

Survival rates at 5 years approach 75%.

ACUTE INTERSTITIAL PNEUMONIA

DEFINITION

Acute interstitial pneumonia, also referred to as *Hamman-Rich syndrome*, is a rare and often fatal disease that mimics ARDS (Chapter 90). The etiology

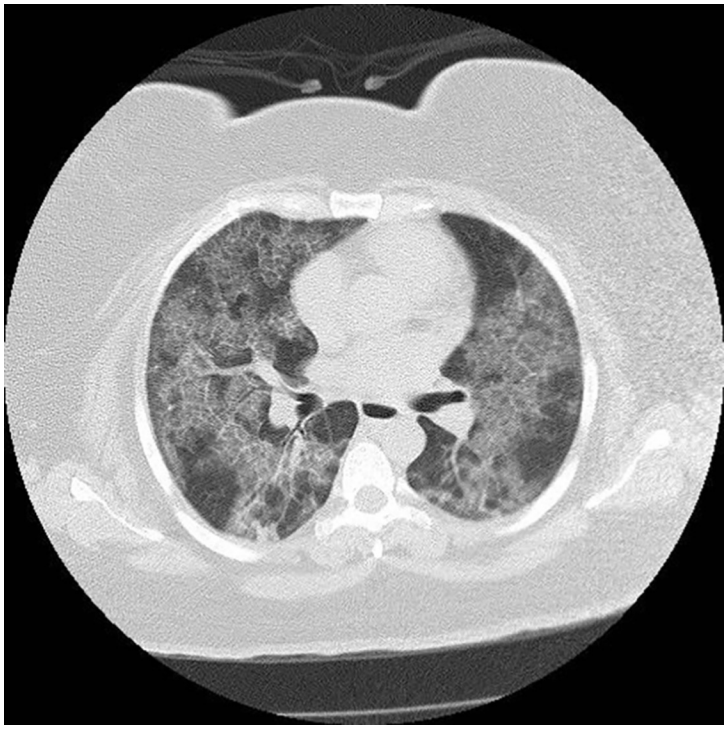

E-FIGURE 79-1. A chest computed tomography scan showing the "crazy paving" pattern characteristic of pulmonary alveolar proteinosis.

E-FIGURE 79-2. Whole-lung lavage from a patient with pulmonary alveolar proteinosis revealing sandy-colored fluid.

is unknown, and acute interstitial pneumonia is sometimes defined as the development of ARDS in the absence of known triggers. A similar acute presentation may be seen in patients with an acute exacerbation of idiopathic pulmonary fibrosis (Chapter 80), but most investigators believe that acute interstitial pneumonia is a separate disease process with no histologic evidence of underlying usual interstitial pneumonia.

PATHOBIOLOGY

The pathogenesis of acute interstitial pneumonia is damage to the epithelium of the alveolar membranes by a neutrophil-mediated mechanism; the result is pouring of exudate into the air space in the initial exudative phase of disease. Histologic examination reveals diffuse alveolar damage with intra-alveolar hyaline membrane formation, interstitial and intra-alveolar edema, acute inflammation, and epithelial cell necrosis with a nonspecific distribution and temporal uniformity. This process progresses to the organizing phase, characterized by alveolar septal thickening, type II pneumocyte hyperplasia, and fibroblast proliferation along the interstitium and alveolar spaces. In situ thrombi of small pulmonary arteries may be present. Finally, a fibrotic phase occurs with alveolar septal thickening from organizing fibrosis. One of the key pathologic findings in acute interstitial pneumonia is the temporal uniformity of the diffuse alveolar damage and of organizing and proliferating connective tissue. This uniformity supports a single acute injury at a particular point in time. Long-standing fibrosis is not a typical pathologic finding in acute interstitial pneumonia.

CLINICAL MANIFESTATIONS

Acute interstitial pneumonia manifests with equal frequency in men and women, typically in previously healthy individuals in the 50- to 55-year age range. It develops acutely to subacutely during a few days to a few weeks. The mean duration of symptoms is 7 to 15 days. Dry cough, shortness of breath, malaise, and fever (in 75% of patients) are typical clinical findings. A virus-like prodrome period has been described. Pulmonary rales are heard on physical examination, and hypoxemia is characteristic. Clubbing is rare. Leukocytosis may be present. Acute interstitial pneumonia often progresses to hypoxemic respiratory failure, and intensive care unit admission with mechanical ventilation is usually required. Early mortality rates are high. Radiographic features of acute interstitial pneumonia are diffuse alveolar opacities and air space consolidation similar to the appearance of ARDS (Fig. 79-4 and E-Fig. 79-3); CT scans reveal bilateral air space consolidation with areas of ground-glass opacities with little honeycombing. Septal thickening and a subpleural distribution of the opacities may also be present.

DIAGNOSIS

The diagnosis of acute interstitial pneumonia is made in the appropriate clinical setting in a patient who has a clinical presentation compatible with ARDS but without a clear etiology. The differential diagnosis histologically and clinically includes other causes of ARDS (Chapter 90), such as severe infection, trauma, and sepsis, as well as other causes of acute lung injury (Chapter 82), such as drug toxicity, inhalation injury, and collagen vascular diseases. The presentation is clinically and radiographically similar to that of diffuse alveolar hemorrhage, acute hypersensitivity pneumonitis, acute exacerbation of pulmonary fibrosis, acute eosinophilic pneumonia, and cryptogenic organizing pneumonia. Bronchoscopy with bronchoalveolar lavage is often performed to exclude alveolar hemorrhage, eosinophilic pneumonias, and infectious causes of lung injury. In a small number of cases, transbronchial biopsy may yield the diagnosis, but definitive diagnosis in most cases of acute interstitial pneumonia requires a surgical lung biopsy revealing diffuse alveolar damage.

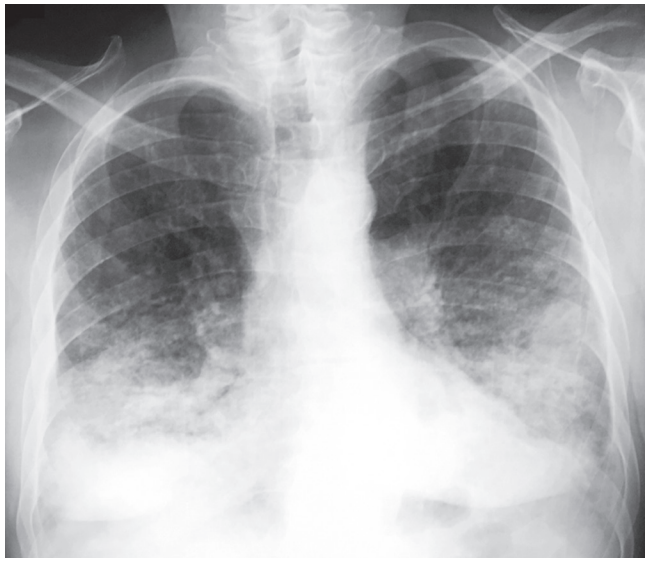

FIGURE 79-4. Acute interstitial pneumonia (AIP), also called idiopathic ARDS. Chest radiograph shows perihilar, right middle lobe, and bibasal consolidations with air bronchograms. (From Dr. Stark with courtesy of Paul Stark, MD.)

TREATMENT

Treatment includes supportive intensive care unit management. In small case series, corticosteroids (up to 1 g of methylprednisolone in divided doses intravenously per day for 3 consecutive days, followed by prednisone or the equivalent at 1 mg/kg/day with a taper over several weeks to months, with or without cyclophosphamide) may be of benefit, but the mortality rate remains higher than 70%. Patients also can have recurrences in months to years. Some cases of acute interstitial pneumonia may resolve without sequelae, but in some series, more than 50% of survivors may be left with residual fibrosis.

DIFFUSE ALVEOLAR HEMORRHAGE

DEFINITION

The alveolar hemorrhage syndromes cause alveolar filling disease, usually with an acute onset and often with life-threatening severity. They can be associated with antineutrophil cytoplasmic antibody (ANCA)–associated vasculitides such as microscopic polyangiitis (Chapter 249) and granulomatosis with polyangiitis (Chapter 249)[6]; immunologic diseases, such as Goodpasture syndrome (anti–glomerular basement membrane antibody disease; Chapter 107)[7]; collagen vascular diseases,[8] such as systemic lupus erythematosus (Chapter 245); cocaine inhalation (Chapter 365); drugs (including penicillamine, mitomycin C, trimellitic anhydride inhalation, all-*trans* retinoic acid, propylthiouracil, and isocyanates); hematopoietic cell transplantation[9] (Chapter 163); coagulopathy (Chapter 160); and mitral stenosis (Chapter 60). A small percentage of idiopathic and recurrent cases are termed idiopathic pulmonary hemosiderosis.[10] In Goodpasture syndrome, there is a strong association with tobacco use and a male predominance, with young men most frequently affected. A viral syndrome and exposure to hydrocarbons may simulate Goodpasture disease. Idiopathic pulmonary hemosiderosis most often occurs in children and young adults.

PATHOBIOLOGY

Alveolar hemorrhage is caused by bleeding from the pulmonary microcirculation, including the capillaries, arterioles, and venules. It may be associated with injury or neutrophilic inflammation of the alveolar walls and adjacent interstitial capillaries (i.e., a capillaritis), usually when it is associated with collagen vascular or vasculitic processes. In Goodpasture syndrome, for example, the circulating anti–glomerular basement membrane antibodies are directed against the α_3 chain of type IV collagen in the glomerular basement membrane, where they cause glomerulonephritis; these core antibodies can cross-react with the alveolar capillary basement membranes, resulting in alveolar hemorrhage. Alternatively, alveolar hemorrhage may be associated with relatively bland pathologic changes with red blood cells in the alveolar spaces. Idiopathic pulmonary hemosiderosis can be an example of bland hemorrhage.

CLINICAL MANIFESTATIONS

Patients present acutely (usually in hours to a week) with dyspnea, shortness of breath, hemoptysis (which may be absent in up to one third of patients), and cough. Some patients also have low-grade fever. Lung examination reveals rales.

Laboratory examination may reveal anemia, and arterial blood gases reveal hypoxemia. In Goodpasture syndrome and the ANCA-associated vasculitides, hematuria and renal insufficiency caused by glomerulonephritis are typically present.

Radiographic features[11] include the acute development of bilateral alveolar filling disease similar to pulmonary edema but without cardiomegaly or pleural effusions (E-Fig. 79-4), sometimes with a subpleural sparing pattern. Rapid remission and recurrences are seen with repeated episodes of bleeding, which also may result in chronic interstitial changes on the chest radiograph. Pulmonary function testing may reveal an increase in the diffusion capacity for carbon monoxide because of the presence of hemoglobin in the alveolar spaces.

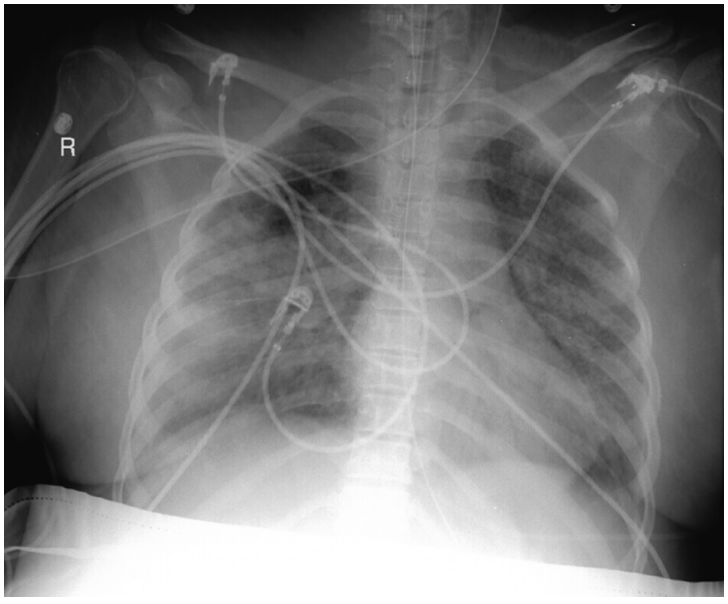

E-FIGURE 79-3. A chest radiograph showing bilateral alveolar opacities in an intubated patient with acute interstitial pneumonia.

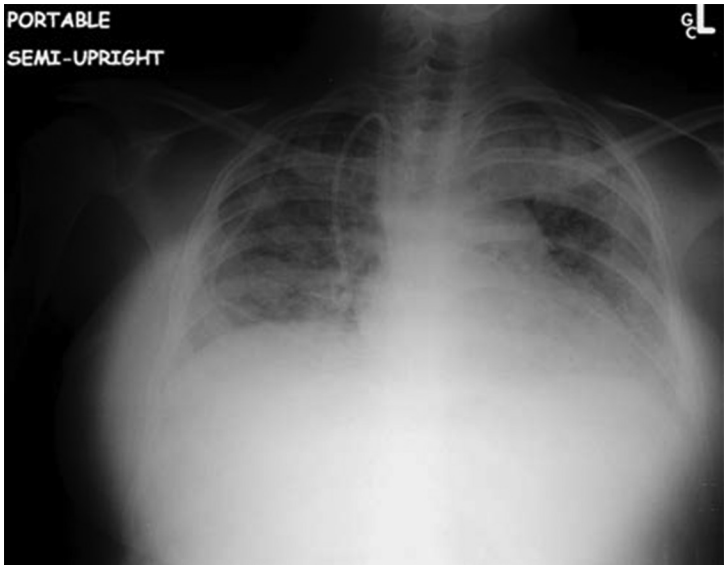

E-FIGURE 79-4. A chest radiograph showing bilateral alveolar opacities in a patient with diffuse alveolar hemorrhage.

DIAGNOSIS

The diagnosis of alveolar hemorrhage is usually made in the appropriate clinical setting by the triad of diffuse alveolar opacities (Fig. 79-5), hemoptysis (in two thirds of patients), and anemia. In immunosuppressed patients, the most frequent causes of diffuse alveolar hemorrhage are hematologic neoplasms, hematopoietic stem cell or solid organ transplantation, drug reaction or infection, and associated HIV infection. Bronchoalveolar lavage typically demonstrates the return of progressively more bloody aliquots of fluid (E-Fig. 79-5), and cytologic analysis reveals that more than 20% of the macrophages are hemosiderin laden. Although rarely recommended, lung biopsy is the gold standard for diagnosing diffuse alveolar hemorrhage and pulmonary capillaritis. Goodpasture syndrome is diagnosed by circulating anti–glomerular basement membrane antibodies, which are present in more than 90% of patients, or by the demonstration of linear deposition of immunoglobulin G antibodies along the alveolar or renal capillary basement membrane tissue when it is viewed by direct immunofluorescence. Cytoplasmic antineutrophil cytoplasmic antibody (c-ANCA)–associated vasculitis causes a focal, segmental, necrotizing glomerulonephritis and is associated with the presence of proteinase 3 antineutrophilic cytoplasmic antibodies in 90% of active cases of granulomatosis with polyangiitis (Chapter 249). Necrotizing granulomatous inflammation is often found in the upper airway in addition to the lungs and kidneys. A perinuclear myeloperoxidase antineutrophilic antibody is often present in association with microscopic polyarteritis (Chapter 249). Patients with systemic lupus erythematosus usually have antinuclear antibodies (Chapter 245). Patients using illicit drugs such as cocaine may have a positive drug screen. Idiopathic pulmonary hemosiderosis is a diagnosis of exclusion after other causes of diffuse alveolar hemorrhage have been eliminated.

TREATMENT

Treatment of alveolar hemorrhage varies according to its underlying cause. Massive hemoptysis (Chapter 71) from any cause of alveolar hemorrhage should be managed as needed. In the case of anticoagulation-, drug-, or toxin-related alveolar hemorrhage, the offending agent should be withdrawn, and supportive care is indicated. In Goodpasture syndrome, the ANCA-associated vasculitides, and other vasculitides (Chapter 249), treatment typically includes immunosuppressant agents such as corticosteroids (methylprednisolone, 500 to 1000 mg/day in divided doses for 3 to 5 days followed by a prednisone taper beginning at 1 mg/kg/day during the next 6 to 9 months) and cyclophosphamide (2 mg/kg/day orally or 0.5 g/m^2 to 0.75 g/m^2 intravenously for one dose) and then, if needed, every 2 weeks or change to oral therapy. Plasmapheresis (3 to 14 exchanges) to remove the offending circulating antibody is a mainstay of therapy for Goodpasture syndrome and may also be used in alveolar hemorrhage caused by systemic lupus erythematosus. However, plasmapheresis is not beneficial for ANCA-associated vasculitis.[A3] In patients with ANCA-associated vasculitis, rituximab (375 mg/m^2 once a week for 4 weeks) is at least as good as cyclophosphamide (2 mg/kg adjusted for renal function) followed by azathioprine (2 mg/kg) for 12 to 15 months for inducing and maintaining remission (≈50% at 12 months and about 40% at 18 months), and rituximab (at 500 mg on days 0 and 14 and at 6, 12, and 18 months) is better than azathioprine for maintaining remission and improving quality of life at 5 years.[A4]

PROGNOSIS

Alveolar hemorrhage can result in acute respiratory failure and death. Recurrent alveolar hemorrhage from any cause, such as idiopathic pulmonary hemosiderosis, can be associated with the development of pulmonary fibrosis. Alveolar hemorrhage related to collagen vascular disease, vasculitides, and idiopathic pulmonary hemosiderosis can have mortality rates ranging from 25 to 50%. With Goodpasture syndrome, renal failure is common, and the degree of renal impairment may correlate with outcome.

INVASIVE MUCINOUS ADENOCARCINOMA AND LEPIDIC PREDOMINANT NONMUCINOUS ADENOCARCINOMA (FORMERLY CALLED BRONCHIOLOALVEOLAR CELL CARCINOMA)

DEFINITION

In 2011, a multidisciplinary committee eliminated the term *bronchioloalveolar cell carcinoma* and divided pulmonary adenocarcinomas into five types: adenocarcinoma in situ, minimally invasive adenocarcinoma, lepidic predominant nonmucinous adenocarcinoma, invasive mucinous adenocarcinoma, and invasive adenocarcinoma and its subtypes. The types that would most likely be correlated with an alveolar filling appearance pathologically and on chest imaging are invasive mucinous adenocarcinoma, in which consolidation and air bronchograms may be present, and lepidic-predominant nonmucinous adenocarcinoma, in which a ground-glass appearance is characteristic. Both of these types of adenocarcinoma are among those formally characterized as bronchioloalveolar cell carcinoma. In general, these tumors are characterized by malignant cells lining the alveolar cell wall (Chapter 177). Among bronchogenic carcinomas, these subtypes are the least associated with tobacco use, and patients with these cancers are more likely to be nonsmokers. Unlike other non–small cell lung cancers, the sex ratio approaches 1:1 or may be slightly female predominant, and younger patients may be affected.

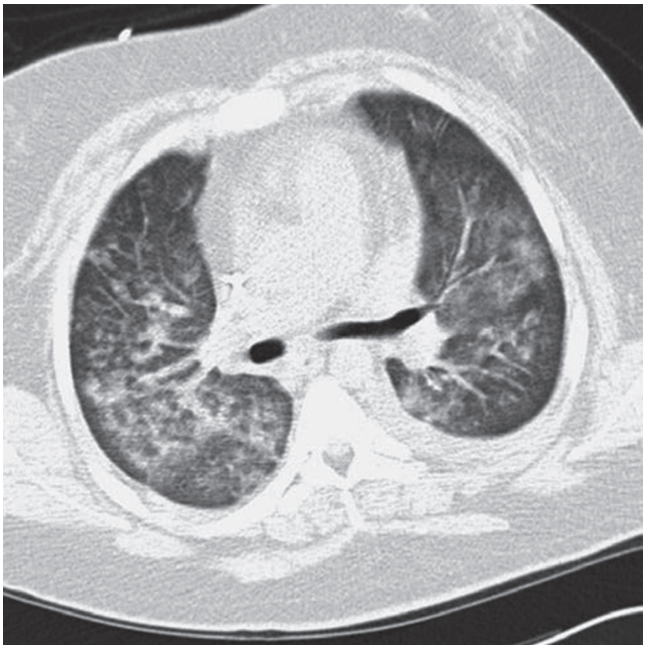

FIGURE 79-5. A chest computed tomography scan showing alveolar opacities in a patient with diffuse alveolar hemorrhage.

PATHOBIOLOGY

These types of adenocarcinoma usually arise in the periphery of the lung and may be characterized by lepidic growth, which means contiguous growth along the intact alveolar septa, with varying degrees of stromal, pleural, vascular, or lymphatic invasion and without a known primary adenocarcinoma elsewhere. The mucinous type is thought to derive from respiratory goblet cells and columnar cells, and the nonmucinous type from type II pneumocytes or Clara cells.

CLINICAL MANIFESTATIONS

Patients present with a gradual onset of shortness of breath and cough. The duration of symptoms is usually several months. Constitutional symptoms such as malaise and weight loss may be present. Hemoptysis may occur. An unusual but unique clinical finding is bronchorrhea, with patients reporting the production of copious amounts of clear sputum daily. This finding is more common in the invasive mucinous form of the disease.

DIAGNOSIS

Radiographic patterns vary and can include localized disease with peripheral solitary or multiple nodules or masses in 60% of cases or a persistent pneumonic pattern in 40% of cases. The radiographic findings of consolidation with air bronchograms are often initially thought to be consistent with acute pneumonia (Fig. 79-6), but the typical clinical presentation is that of a nonresolving peripheral density on chest radiograph (E-Fig. 79-6).[12] In addition, CT may show areas of ground-glass attenuation. Positron emission tomography may be normal because of the low glucose uptake of these tumors. The diagnosis of invasive mucinous adenocarcinoma and lepidic predominant

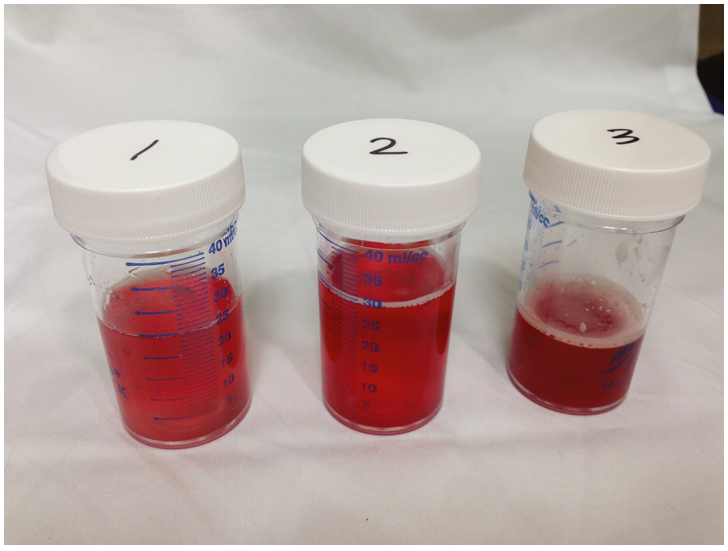

E-FIGURE 79-5. Bronchoalveolar lavage fluid revealing a progressively increasingly bloody lavage consistent with diffuse alveolar hemorrhage.

E-FIGURE 79-6. A chest computed tomography scan in a patient with invasive mucinous adenocarcinoma.

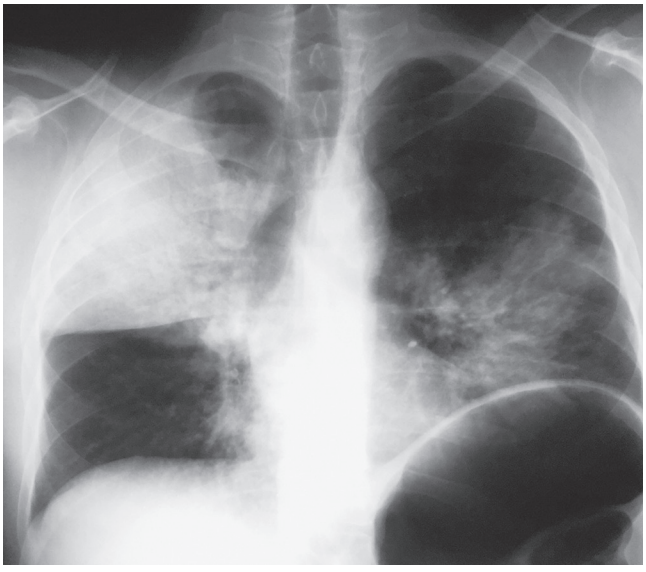

FIGURE 79-6. Mucinous adenocarcinoma (bronchioloalveolar carcinoma). Chest radiograph shows right upper lobe complete consolidation with air bronchograms as well as left lower lobe consolidation. The findings mimic extensive lobar pneumonia. Eventration of the left hemidiaphragm and gastric distention are unrelated. (From Dr. Stark with courtesy of Paul Stark, MD.)

nonmucinous adenocarcinoma is most often made by bronchoscopy with transbronchial biopsy.

TREATMENT

For staging and treatment, these types of adenocarcinoma are approached like other types of non–small cell lung cancers (Chapter 177).[13] Testing for epidermal growth factor receptor (EGFR) mutations should be performed, and chemotherapy planned accordingly. In general, the invasive mucinous adenocarcinomas are KRAS positive and EGFR negative. The lepidic predominant nonmucinous type tends to be EGFR positive. Bilateral lung transplantation has been performed, but recurrence in the transplanted lungs has been reported.

PROGNOSIS

Prognosis correlates with stage, histology, and genetics. Patients who undergo surgical resection for adenocarcinoma in situ or minimally invasive adenocarcinoma with a single focus of disease have a better prognosis than patients with other adenocarcinomas of like stage, with the 5-year survival rate approaching 100%. Lepidic pattern adenocarcinomas generally present at an early stage and have a better prognosis than do solid/micropapillary patterns that usually present at a higher stage with a worse prognosis. More advanced forms likely have a prognosis similar to that of other adenocarcinomas. Mutations in *EGFR*, the epidermal growth factor receptor gene, are a poor prognostic factor.[14]

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For the General References and other additional features, please visit Elsevier eBooks+ at https://ebooks.health.elsevier.com.

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80

INTERSTITIAL LUNG DISEASE

GANESH RAGHU AND FERNANDO J. MARTINEZ

DEFINITION

In an apparently immunocompetent host, *interstitial lung disease* is a clinical term for a heterogenous group of acute and chronic lower respiratory tract disorders with many potential causes.[1] Clinical and physiologic features commonly include cough, exertional dyspnea, absence of pulmonary infection or neoplasm, and abnormal pulmonary physiology, including a restrictive pattern on pulmonary function testing (Chapter 73), coexistent airflow obstruction, decreased diffusing capacity (DLCO), and increased alveolar-arterial oxygen difference (P_{AO_2}-P_{aO_2}) (Chapter 89) at rest or during exertion. Interstitial lung diseases include acute and chronic lung disorders with variable degrees of pulmonary inflammation and/or fibrosis (Table 80-1). The term *interstitial* is a misnomer because the pathologic processes are not restricted to the interstitium, which is the microscopic space bounded by the basement membranes of epithelial and endothelial cells. All of the cellular and soluble constituents that make up the gas exchange units (alveolar wall, capillaries, alveolar space, and acini) and the bronchiolar lumen, terminal bronchioles, and pulmonary parenchyma beyond the gas exchange units (as well as the pleura and lymphatics and sometimes the lymph nodes) may be involved in the pathogenesis and manifestations of interstitial lung disease.

EPIDEMIOLOGY

Among persons 18 years or older, the prevalence of all interstitial lung diseases in the United States is about 80 per 100,000 men and 70 per 100,000 women. The overall incidence is higher in men (31.5 per 100,000 per year) than in women (26.1 per 100,000 per year).[2] Moreover, the prevalence of undiagnosed or early interstitial lung disease is estimated to be 10 times that of clinically recognized disease; as physicians' awareness of these entities increases, it is expected that the frequency of the diagnosis will rise. Among the interstitial lung diseases, the two most common are idiopathic pulmonary fibrosis and connective tissue–associated disease. In the United States, the annual incidence of idiopathic pulmonary fibrosis is 94 per 100,000 in the Medicare population, with a mean age of onset of 79 years. Recent data suggest that more than 5000 new cases are diagnosed each year in the United Kingdom.

Although idiopathic pulmonary fibrosis is the prototypical progressive interstitial lung disease, up to one third of patients with interstitial lung diseases other than idiopathic pulmonary fibrosis (e.g., interstitial lung disease associated with systemic sclerosis or associated with hypersensitivity pneumonitis) also develop the progressive phenotype. This clinical phenotype, which is agnostic to etiology, is now termed progressive pulmonary fibrosis, and its prevalence is estimated to be 70.3 per 100,000 patients.

PATHOBIOLOGY

Interstitial lung diseases are thought to result from an unknown tissue injury and attempted repair in the lung of a genetically predisposed person. Numerous genetic variants have been associated with subsets of familial pulmonary fibrosis and with some sporadic cases. These variants include the *MUC5B* gene, genes related to immune function (*TOLLIP*, *TLR3*, *IL1RN*, *IL8*, *TGFβ1*), epithelial cell function (*DSP*, *DPP9*), the maintenance of telomeres (*TERT*, *TERC*, *OBFC1*, *TINF2*, *DKC1*, *RTEL1*, *PARN*), the production of surfactant (SFTPC, SFTPA1, ABCA3), and cell cycle regulation (*KIF15*, *MAD1L1*, *CDKN1A*).[3] About 3 to 4% of patients treated with programmed cell death-1 inhibitors can develop interstitial lung diseases.[4]

In *idiopathic pulmonary fibrosis*, varying degrees of acute, subacute, and chronic fibrinous proliferation are present in the lungs. Ultimately, progressive fibrosis results in honeycombing, an end-stage finding that is often associated with increased pulmonary vascular resistance and secondary pulmonary hypertension. As a reflection of these dynamic processes, histopathologic examination of lung tissue often reveals highly heterogeneous findings within the same biopsy specimen.

CLINICAL MANIFESTATIONS

Interstitial lung diseases are typically characterized by cough and progressive dyspnea. Pleuritic chest pain may occur with certain connective tissue or

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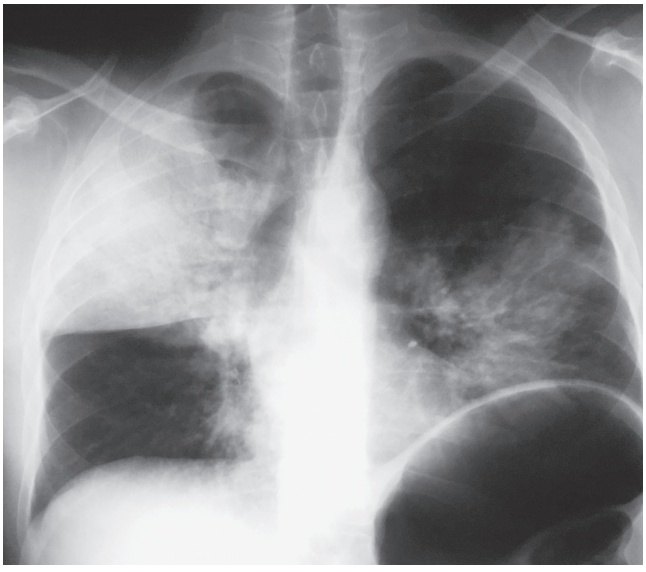

FIGURE 79-6. Mucinous adenocarcinoma (bronchioloalveolar carcinoma). Chest radiograph shows right upper lobe complete consolidation with air bronchograms as well as left lower lobe consolidation. The findings mimic extensive lobar pneumonia. Eventration of the left hemidiaphragm and gastric distention are unrelated. (From Dr. Stark with courtesy of Paul Stark, MD.)

nonmucinous adenocarcinoma is most often made by bronchoscopy with transbronchial biopsy.

TREATMENT

For staging and treatment, these types of adenocarcinoma are approached like other types of non–small cell lung cancers (Chapter 177).[13] Testing for epidermal growth factor receptor (EGFR) mutations should be performed, and chemotherapy planned accordingly. In general, the invasive mucinous adenocarcinomas are KRAS positive and EGFR negative. The lepidic predominant nonmucinous type tends to be EGFR positive. Bilateral lung transplantation has been performed, but recurrence in the transplanted lungs has been reported.

PROGNOSIS

Prognosis correlates with stage, histology, and genetics. Patients who undergo surgical resection for adenocarcinoma in situ or minimally invasive adenocarcinoma with a single focus of disease have a better prognosis than patients with other adenocarcinomas of like stage, with the 5-year survival rate approaching 100%. Lepidic pattern adenocarcinomas generally present at an early stage and have a better prognosis than do solid/micropapillary patterns that usually present at a higher stage with a worse prognosis. More advanced forms likely have a prognosis similar to that of other adenocarcinomas. Mutations in *EGFR*, the epidermal growth factor receptor gene, are a poor prognostic factor.[14]

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For the General References and other additional features, please visit Elsevier eBooks+ at https://ebooks.health.elsevier.com.

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80

INTERSTITIAL LUNG DISEASE

GANESH RAGHU AND FERNANDO J. MARTINEZ

DEFINITION

In an apparently immunocompetent host, *interstitial lung disease* is a clinical term for a heterogenous group of acute and chronic lower respiratory tract disorders with many potential causes.[1] Clinical and physiologic features commonly include cough, exertional dyspnea, absence of pulmonary infection or neoplasm, and abnormal pulmonary physiology, including a restrictive pattern on pulmonary function testing (Chapter 73), coexistent airflow obstruction, decreased diffusing capacity (DLCO), and increased alveolar-arterial oxygen difference (P_{AO_2}-P_{aO_2}) (Chapter 89) at rest or during exertion. Interstitial lung diseases include acute and chronic lung disorders with variable degrees of pulmonary inflammation and/or fibrosis (Table 80-1). The term *interstitial* is a misnomer because the pathologic processes are not restricted to the interstitium, which is the microscopic space bounded by the basement membranes of epithelial and endothelial cells. All of the cellular and soluble constituents that make up the gas exchange units (alveolar wall, capillaries, alveolar space, and acini) and the bronchiolar lumen, terminal bronchioles, and pulmonary parenchyma beyond the gas exchange units (as well as the pleura and lymphatics and sometimes the lymph nodes) may be involved in the pathogenesis and manifestations of interstitial lung disease.

EPIDEMIOLOGY

Among persons 18 years or older, the prevalence of all interstitial lung diseases in the United States is about 80 per 100,000 men and 70 per 100,000 women. The overall incidence is higher in men (31.5 per 100,000 per year) than in women (26.1 per 100,000 per year).[2] Moreover, the prevalence of undiagnosed or early interstitial lung disease is estimated to be 10 times that of clinically recognized disease; as physicians' awareness of these entities increases, it is expected that the frequency of the diagnosis will rise. Among the interstitial lung diseases, the two most common are idiopathic pulmonary fibrosis and connective tissue–associated disease. In the United States, the annual incidence of idiopathic pulmonary fibrosis is 94 per 100,000 in the Medicare population, with a mean age of onset of 79 years. Recent data suggest that more than 5000 new cases are diagnosed each year in the United Kingdom.

Although idiopathic pulmonary fibrosis is the prototypical progressive interstitial lung disease, up to one third of patients with interstitial lung diseases other than idiopathic pulmonary fibrosis (e.g., interstitial lung disease associated with systemic sclerosis or associated with hypersensitivity pneumonitis) also develop the progressive phenotype. This clinical phenotype, which is agnostic to etiology, is now termed progressive pulmonary fibrosis, and its prevalence is estimated to be 70.3 per 100,000 patients.

PATHOBIOLOGY

Interstitial lung diseases are thought to result from an unknown tissue injury and attempted repair in the lung of a genetically predisposed person. Numerous genetic variants have been associated with subsets of familial pulmonary fibrosis and with some sporadic cases. These variants include the *MUC5B* gene, genes related to immune function (*TOLLIP*, *TLR3*, *IL1RN*, *IL8*, *TGFβ1*), epithelial cell function (*DSP*, *DPP9*), the maintenance of telomeres (*TERT*, *TERC*, *OBFC1*, *TINF2*, *DKC1*, *RTEL1*, *PARN*), the production of surfactant (SFTPC, SFTPA1, ABCA3), and cell cycle regulation (*KIF15*, *MAD1L1*, *CDKN1A*).[3] About 3 to 4% of patients treated with programmed cell death-1 inhibitors can develop interstitial lung diseases.[4]

In *idiopathic pulmonary fibrosis*, varying degrees of acute, subacute, and chronic fibrinous proliferation are present in the lungs. Ultimately, progressive fibrosis results in honeycombing, an end-stage finding that is often associated with increased pulmonary vascular resistance and secondary pulmonary hypertension. As a reflection of these dynamic processes, histopathologic examination of lung tissue often reveals highly heterogeneous findings within the same biopsy specimen.

CLINICAL MANIFESTATIONS

Interstitial lung diseases are typically characterized by cough and progressive dyspnea. Pleuritic chest pain may occur with certain connective tissue or

ABSTRACT

Interstitial lung diseases are heterogeneous lower respiratory tract disorders. They present with respiratory symptoms and abnormal pulmonary physiology in the absence of pulmonary infection or neoplasm. Interstitial lung diseases include acute and chronic disorders with variable degrees of pulmonary inflammation and/or fibrosis. The idiopathic interstitial pneumonias include chronic fibrosing disorders such as idiopathic pulmonary fibrosis and nonspecific interstitial pneumonias. Smoking-related disorders include respiratory bronchiolitis, interstitial lung disease, and desquamative interstitial pneumonia. Acute or subacute interstitial pneumonias include cryptogenic organizing pneumonia, acute interstitial pneumonia, and lymphoid interstitial pneumonia. Demographic features, smoking/family history, and a careful assessment of environmental/occupational/drug exposures are vital. The onset and duration of symptoms, the rate of disease progression, and association with hemoptysis or extrathoracic symptoms are of diagnostic value. Extrapulmonary manifestations on the physical examination suggest a coexisting systemic disease, especially a connective tissue disorder. Routine laboratory testing and serologic studies may prove valuable. High-resolution computed tomography has become the essential diagnostic study, although some patients may require video-assisted thoracoscopic biopsy or open lung biopsy. The key to management is an accurate diagnosis. When the cause is clear, avoidance of the inciting agent is essential. Antifibrotic agents are helpful for the treatment of idiopathic pulmonary fibrosis. For other interstitial lung diseases, immunosuppressive agents are typically recommended, but their optimal dose and duration are unclear. Selected patients may benefit from lung transplantation.

KEYWORDS

interstitial lung diseases
idiopathic interstitial pneumonias
idiopathic pulmonary fibrosis
connective tissue–associated interstitial lung disease
hypersensitivity pneumonitis

TABLE 80-1 CLINICAL CLASSIFICATION OF INTERSTITIAL LUNG DISEASE

IDIOPATHIC INTERSTITIAL PNEUMONIAS
Chronic Fibrosing Interstitial Pneumonias
Idiopathic pulmonary fibrosis
Nonspecific interstitial pneumonia
Smoking-Related Interstitial Pneumonias
Respiratory bronchiolitis–interstitial lung disease
Desquamative interstitial pneumonia
Acute or Subacute Idiopathic Interstitial Pneumonias
Cryptogenic organizing pneumonia
Acute interstitial pneumonia
Lymphoid and lymphocytic interstitial pneumonia
Rare Interstitial Pneumonias
Histologic pattern of acute fibrinous and organizing pneumonia
Histologic pattern of interstitial pneumonias with a bronchiolocentric distribution
Pleuroparenchymal fibroelastosis
INTERSTITIAL LUNG DISEASE ASSOCIATED WITH CONNECTIVE TISSUE DISEASE
Progressive systemic sclerosis
Rheumatoid arthritis
Systemic lupus erythematosus
Dermatomyositis and polymyositis
Sjögren syndrome
Mixed connective tissue disease
Ankylosing spondylitis
HYPERSENSITIVITY PNEUMONITIS
Occupational and environmental factors (e.g., farmer's lung, bird fancier's lung)
Iatrogenic
DRUG-INDUCED AND IATROGENIC INTERSTITIAL LUNG DISEASE
See Table 80-2
ALVEOLAR FILLING DISORDERS (Chapter 79)
Goodpasture syndrome
Pulmonary alveolar proteinosis
Pulmonary hemosiderosis
Alveolar hemorrhage syndromes
Chronic eosinophilic pneumonia
INTERSTITIAL LUNG DISEASE ASSOCIATED WITH PULMONARY VASCULITIS
Pulmonary capillaritis
Granulomatosis with polyangiitis (formerly known as Wegener granulomatosis)
Churg-Strauss syndrome
OTHER SPECIFIC FORMS OF INTERSTITIAL LUNG DISEASE
Sarcoidosis
Langerhans cell histiocytosis (histiocytosis X)
Lymphangioleiomyomatosis
Coronavirus-19 disease associated
INHERITED FORMS OF INTERSTITIAL LUNG DISEASE
Familial idiopathic pulmonary fibrosis
Familial pulmonary fibrosis or interstitial pneumonia
Tuberous sclerosis
Neurofibromatosis
Gaucher disease
Niemann-Pick disease
Hermansky-Pudlak syndrome

drug-induced forms; acute pleuritic chest pain with dyspnea may represent a spontaneous pneumothorax (Chapter 86) in association with lymphangioleiomyomatosis, tuberous sclerosis (Chapter 385), neurofibromatosis, or Langerhans cell histiocytosis. Hemoptysis suggests a diffuse alveolar hemorrhagic syndrome, systemic lupus erythematosus (SLE) (Chapter 245), lymphangioleiomyomatosis, granulomatosis with polyangiitis (Chapter 249), or Goodpasture syndrome (Chapter 107); it is rare in other interstitial lung diseases. In patients with existing disease, new hemoptysis should prompt consideration of a superimposed malignancy, pulmonary embolus, or infection such as aspergillosis.

In some patients, the first and the only clue to the presence of an interstitial lung disease may be the incidental finding of parenchymal abnormalities in computed tomography (CT) images of the chest or rales (crackles) on lung auscultation. A history of wheezing suggests the coexistence of occult hyperactive airways and airflow obstruction, thereby raising the possibility of allergic bronchopulmonary aspergillosis (Chapter 311), eosinophilic granulomatosis with polyangiitis (Chapter 249), chronic eosinophilic pneumonia (see later), or parasitic infection (Chapter 315). In some patients, the initial presentation may be with peripheral cyanosis, clubbing, or the signs and symptoms of an underlying systemic disease (see later).

DIAGNOSIS

The first key in patients is to establish the syndromic diagnosis and then pursue the differential diagnosis of its specific cause (Fig. 80-1). However, a conclusive cause often may not be identified despite an exhaustive medical history and invasive diagnostic interventions, including bronchoalveolar lavage and bronchoscopic or surgical lung biopsy specimens. Thus, the cause of several of the interstitial lung diseases, even when diagnosed as specific entities, remains unknown.

History

The patient's age, sex, and cigarette smoking history may provide useful clues to the diagnosis. Idiopathic pulmonary fibrosis is an adult disorder that usually occurs in patients older than 50 years. Pulmonary sarcoidosis (Chapter 83), in contrast, is more common in young and middle-aged adults. Whereas pulmonary Langerhans cell histiocytosis (Chapter 155) characteristically occurs in young cigarette-smoking men, lymphangioleiomyomatosis occurs exclusively in women of childbearing age. Respiratory bronchiolitis–associated interstitial lung disease is seen almost exclusively in cigarette smokers but occurs in both men and women of all ages.

The medical history should include a careful assessment of environmental and occupational exposures, as well as medication and drug use (Chapters 81 and 82). A family medical history should address possible familial disease. Environmental risk factors that may suggest the diagnosis of hypersensitivity pneumonitis include farming or exposure to overt or occult avian antigens at or in the close vicinity of home; bird droppings or feather duvets; visible molds; unkempt recreational hot tubs; dusty homes; unchanged filters in furnaces; unkempt ventilatory systems at home, in the workplace, other frequently visited places or in automobiles; water leaks or humidifiers in the domestic and/or work environment; and changes in environmental exposures (hypersensitivity to thermophilic actinomycetes, *Aureobasidium pullulans*). At-risk occupations include mining (pneumoconioses), machine tool grinding, sandblasting and working with granite (silicosis), welding, as well as working in a shipyard (asbestosis) or the aerospace or electronic industries (berylliosis) (Chapters 81 and 82). Because of the long interval between the exposure and the onset of symptoms in many occupations, it is important to take a detailed, lifelong occupational history (Chapter 16) as well as to establish the interval between exposure and the onset of symptoms. Because the list of medications known to cause interstitial lung disease is long and continues to grow (Table 80-2), a careful history regarding recent use of prescription and over-the-counter products is essential. Risk factors for immunosuppression, including infection with human immunodeficiency virus, raise the possibility of opportunistic lung infections (Chapter 359), neoplasm (Chapter 177), and transplant-related pulmonary complications. Infection with severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2; Chapter 336) can result in a clinical syndrome (COVID-19) that includes diffuse parenchymal damage with features of organizing pneumonia, interstitial pneumonitis, and fibrosing interstitial lung disease.

Particular attention should be paid to the onset and duration of symptoms, the rate of disease progression, and association with hemoptysis, fever, or extrathoracic symptoms. Symptoms that persist 4 weeks or less and the presence of fever suggest infection, cryptogenic organizing pneumonia, drug-induced pulmonary injury, or acute hypersensitivity pneumonitis. Idiopathic pulmonary fibrosis, interstitial lung disease associated with connective tissue diseases, and Langerhans cell histiocytosis tend to have a more subacute onset. Extrapulmonary symptoms suggest that the interstitial lung disease may be associated with systemic disorders (e.g., sarcoidosis; Chapter 83), and symptoms such as dysphagia, dry eyes or mouth, skin rash, or arthritis may suggest a connective tissue disorder (Chapters 245 to 249). Proximal muscle aches or weakness suggests the possibility of polymyositis or dermatomyositis (Chapter 248), and recurrent sinusitis suggests granulomatosis with polyangiitis (Chapter 249). Extrathoracic manifestations present in tuberous sclerosis (Chapter 385) include hematuria, epilepsy, and developmental delay.

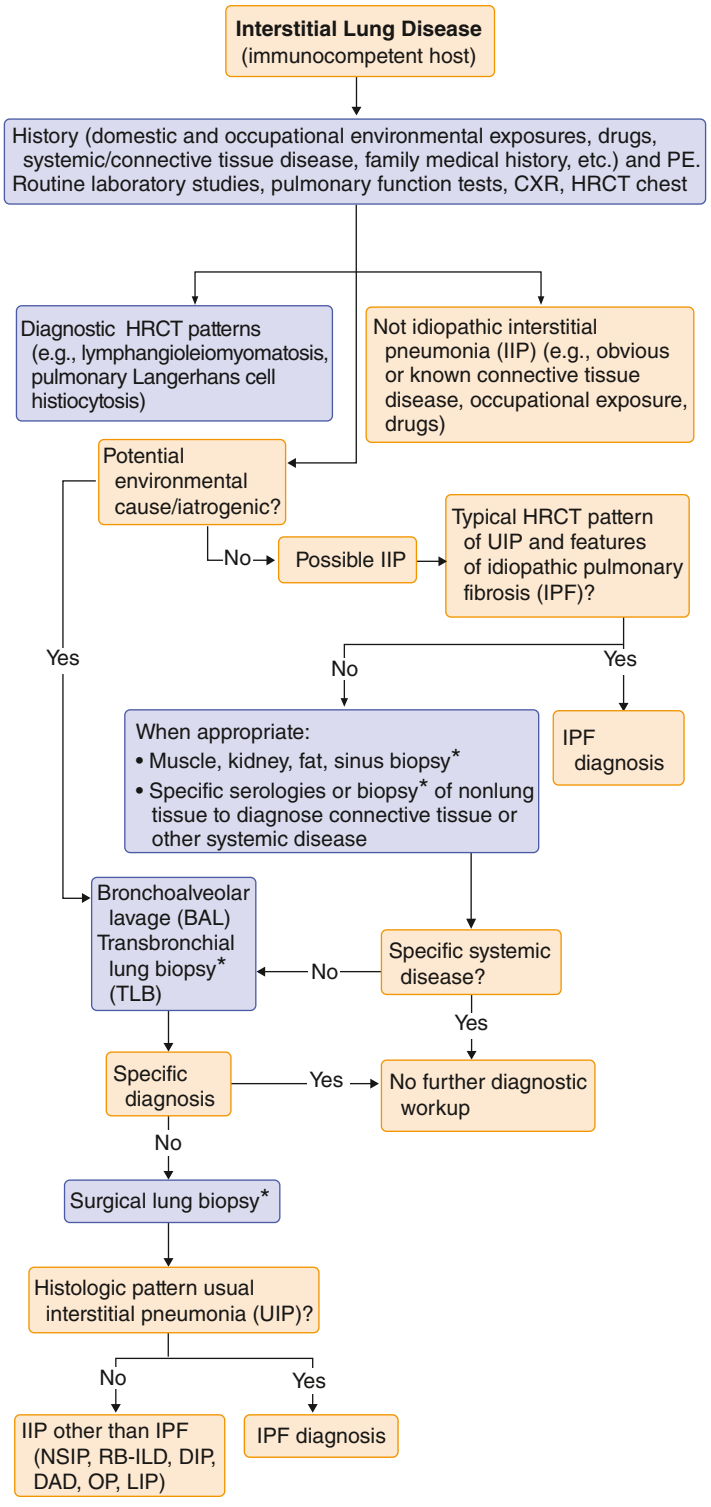

FIGURE 80-1. A diagnostic approach to interstitial lung disease. The evaluation commonly should include multidisciplinary discussions with experts in interstitial lung disease, including a pulmonologist, chest radiologist, thoracic surgeon, pathologist, and rheumatologist. *Surgical lung biopsy is not indicated in patients with a probable UIP pattern on HRCT if all other features of IPF are typical, and lung biopsy is considered a last resort in patients who have a significant risk of surgical complications; CXR = chest radiograph; DAD = diffuse alveolar damage; DIP = desquamative interstitial pneumonia; HRCT = high-resolution computed tomography; IIP = idiopathic interstitial pneumonia; IPF = idiopathic pulmonary fibrosis; LIP = lymphoid interstitial pneumonia; NSIP = nonspecific interstitial pneumonia; OP = organizing pneumonia; PE = physical examination; RB-ILD = respiratory bronchiolitis–associated interstitial lung disease; TLB = transbronchial lung biopsy; UIP = usual interstitial pneumonia. (Adapted from American Thoracic Society/European Respiratory Society: International multidisciplinary consensus classification of idiopathic interstitial pneumonias. *Am J Respir Crit Care Med*. 2002;165:277-304; Raghu G, Collard HR, Egan JJ, et al. Diagnosis of idiopathic pulmonary fibrosis. An official ATS/ERS/JRS/ALAT clinical practice guideline. *Am J Respir Crit Care Med*. 2018;198:e44-e68.)

TABLE 80-2 DRUG-INDUCED AND IATROGENIC INTERSTITIAL LUNG DISEASE*

ANTIMICROBIAL AGENTS
Cephalosporins
Isoniazid
Nitrofurantoin
Penicillins
Sulfonamides
ANTI-INFLAMMATORY AGENTS
Aspirin
Everolimus
Gold
Methotrexate
Nonsteroidal anti-inflammatory agents
D-Penicillamine
Phenylbutazone
Sirolimus
Tensirolimus
Zafirlukast
CARDIOVASCULAR DRUGS
Amiodarone
Angiotensin-converting enzyme inhibitors
β-Blockers
Hydralazine
Hydrochlorothiazide
Procainamide
Protamine sulfate
Tocainide
IMMUNE MODULATING, ANTINEOPLASTIC, AND CHEMOTHERAPEUTIC AGENTS
Atezolizumab
Bleomycin
Busulfan
Chlorambucil
Cyclophosphamide
Durvalumab
Erlotinib
Gefitinib
Gemcitabine
Imatinib
Ipilimumab
Melphalan
Mercaptopurine
Methotrexate
Mitomycin
Nitrosoureas
Nivolumab
Pembrolizumab
Procarbazine
Tumor necrosis factor-α–modulating agents
CENTRAL NERVOUS SYSTEM DRUGS
Carbamazepine
Chlorpromazine
Imipramine
Phenytoin
ORAL HYPOGLYCEMIC AGENTS
Chlorpropamide
Tolazamide
Tolbutamide
ILLICIT DRUGS
Cocaine
Heroin
Methadone
Propoxyphene
OTHER AGENTS
Antithymocyte globulin
All-*trans*-retinoic acid
Colony-stimulating factors
Interferon-α and -β
Irradiation
Mycophenolate mofetil
High fraction of inspired oxygen (F_{IO_2}) with mechanical ventilation

*This list contains examples only and is not meant to be inclusive. An exhaustive list is available at www.pneumotox.com.

TABLE 80-3 CHARACTERISTIC CHEST RADIOGRAPHIC PATTERNS IN PATIENTS WITH INTERSTITIAL LUNG DISEASE

PATTERN	SUGGESTED DIAGNOSES*
Decreased lung volumes	Idiopathic pulmonary fibrosis, nonspecific interstitial pneumonia, desquamative interstitial pneumonia, connective tissue disease, chronic eosinophilic pneumonia, asbestosis, chronic hypersensitivity pneumonitis, or drug-induced interstitial lung disease (ILD)
Increased or preserved lung volumes	Idiopathic pulmonary fibrosis with emphysema, respiratory bronchiolitis–associated ILD, cryptogenic organizing pneumonia, hypersensitivity pneumonitis, lymphangioleiomyomatosis, Langerhans cell histiocytosis, sarcoidosis, neurofibromatosis, tuberous sclerosis
Micronodules	Infection, hypersensitivity pneumonitis, sarcoidosis, respiratory bronchiolitis–associated ILD
Septal thickening	Malignancy, infection, chronic congestive heart failure, pulmonary veno-occlusive disease
Honeycombing	Idiopathic pulmonary fibrosis, fibrotic nonspecific interstitial pneumonia, connective tissue disease, asbestosis, chronic hypersensitivity pneumonitis, sarcoidosis
Recurrent infiltrates	Cryptogenic organizing pneumonia, chronic eosinophilic pneumonia, drug- or radiation-induced ILD
Migratory or fleeting infiltrates	Cryptogenic organizing pneumonia, hypersensitivity pneumonitis, eosinophilic granulomatosis with polyangiitis, Löffler syndrome, allergic bronchopulmonary aspergillosis
Pleural disease	Connective tissue disease, asbestosis, malignancy, radiation-induced ILD, amyloidosis, sarcoidosis, lymphangioleiomyomatosis, nitrofurantoin-induced ILD
Pneumothorax	Langerhans cell histiocytosis, lymphangioleiomyomatosis, tuberous sclerosis, neurofibromatosis
Mediastinal or hilar adenopathy	Lymphocytic interstitial pneumonia, connective tissue disease, silicosis, chronic berylliosis, malignancy, infection, sarcoidosis, amyloidosis, Gaucher disease
Normal (rare)	Cellular nonspecific interstitial pneumonia, respiratory bronchiolitis–associated interstitial lung disease, connective tissue disease, hypersensitivity pneumonitis, sarcoidosis
LOCATION OF RADIOGRAPHIC ABNORMALITY	**SUGGESTED DIAGNOSES***
Mid to upper lung zone	Hypersensitivity pneumonitis, chronic berylliosis, ankylosing spondylitis, silicosis, Langerhans cell histiocytosis, sarcoidosis, pleuroparenchymal fibroelastosis, cystic fibrosis
Lower lung zone	Idiopathic pulmonary fibrosis, nonspecific interstitial pneumonia (fibrotic), connective tissue disease, asbestosis, chronic hypersensitivity pneumonitis
Peripheral	Idiopathic pulmonary fibrosis, nonspecific interstitial pneumonia (fibrotic), cryptogenic organizing pneumonia, chronic eosinophilic pneumonia

*This list is not intended to be comprehensive.
Adapted from Raghu G, Brown K. Clinical issues: patient evaluation. In: Baughman RP, du Bois RM, eds. *Diffuse Lung Disease: A Practical Approach*. New York: Oxford University Press; 2004.

Physical Examination

Physical examination of the respiratory system is rarely helpful in the diagnostic evaluation because findings such as rhonchi and rales on auscultation and digital clubbing are nonspecific. An accentuated P_2, a right ventricular heave, or tricuspid insufficiency on the cardiac examination suggest pulmonary hypertension (Chapter 69) and cor pulmonale in patients with advanced lung disease. However, extrathoracic findings such as skin abnormalities, peripheral lymphadenopathy, and hepatosplenomegaly may be more specifically associated with underlying sarcoidosis (Chapter 83); muscle tenderness and proximal muscle weakness may point to coexisting polymyositis (Chapter 248); and signs of arthritis may indicate connective tissue disease (Chapters 243, 245, and 249) or sarcoidosis (Chapter 83). Characteristic rashes occur in several connective tissue diseases, disseminated Langerhans cell histiocytosis, tuberous sclerosis, and neurofibromatosis. Ophthalmologic findings (Chapter 391) such as iridocyclitis, uveitis, or conjunctivitis may be a clue to the diagnosis of sarcoidosis or a connective tissue disease. Central nervous system abnormalities may be present in sarcoidosis, SLE, Langerhans cell histiocytosis, or tuberous sclerosis.

Laboratory Testing

Routine laboratory testing should include a complete blood count, leukocyte differential, erythrocyte sedimentation rate, C-reactive protein, chemistry panel (calcium, liver enzymes, electrolytes, creatinine), serologies for connective tissue disease, and urinalysis. Although these data rarely yield a specific diagnosis, they may provide helpful clues. Routine serology for occult connective tissue diseases (Chapter 237) may reveal typical findings of SLE (e.g., antinuclear antibodies), rheumatoid arthritis (rheumatoid factor, anti–citrullinated peptide antibody), scleroderma (ScL 70), dermatomyositis or polymyositis (creatine kinase, aldolase, myositis panel [Chapter 248], and anti–Jo-1 antibody), granulomatosis with polyangiitis (antineutrophil cytoplasmic antibodies), Sjögren syndrome, and Goodpasture syndrome (anti-basement membrane antibodies).

Mild hypoxemia is typically present on arterial blood gas analysis because of abnormal ventilation-perfusion ratios, especially in moderate to severe cases. However, carbon dioxide retention is rare and suggests possible coexisting emphysema (Chapter 76) or a hypoventilatory disorder (Chapter 74).

Noninvasive Evaluation

Chest Radiograph

The distribution and appearance of radiographic abnormalities (Chapter 72) may prove useful in differentiating among the clinicopathologic syndromes in patients with interstitial lung disease (Table 80-3). Comparison of previous chest radiographs with the current one is important in establishing the rate of progression of the patient's disease. A diffuse ground-glass pattern is often observed early in the course of disease followed by progression to reticular (linear) infiltrates with nodules (reticulonodular infiltrates) or, in the case of alveolar filling disorders, ill-defined nodules (acinar rosettes) with air bronchograms. Most interstitial lung diseases cause infiltrates in the lower lung zones, but upper lobe predominance is typically present in sarcoidosis, berylliosis, Langerhans cell histiocytosis, silicosis, chronic hypersensitivity pneumonitis, cystic fibrosis, and ankylosing spondylitis. The middle and lower lung zones show the most prominent abnormalities in lymphangitic carcinomatosis, idiopathic pulmonary fibrosis, subacute eosinophilic pneumonia, asbestosis, and pulmonary fibrosis caused by rheumatoid arthritis or progressive systemic sclerosis. Hilar adenopathy and mediastinal adenopathy are not common; their presence should suggest sarcoidosis, berylliosis, silicosis, lymphocytic interstitial pneumonia, amyloidosis, or Gaucher disease. A pattern of peripherally located pulmonary infiltrates in the upper and middle lung zones with relatively clear perihilar and central zones is a clue to chronic eosinophilic pneumonia. Recurrent infiltrates raise the possibility of cryptogenic organizing pneumonia, chronic eosinophilic pneumonia, or drug- or radiation-induced pneumonitis, and fleeting or migratory infiltrates may occur in eosinophilic granulomatosis with polyangiitis, cryptogenic organizing pneumonia, allergic bronchopulmonary aspergillosis, tropical eosinophilic pneumonia, or Löffler syndrome. Whereas localized pleural plaques may indicate asbestosis, diffuse pleural thickening can result from asbestosis, rheumatoid arthritis, progressive

TABLE 80-4 RADIOGRAPHIC FEATURES OF IDIOPATHIC INTERSTITIAL PNEUMONIAS

CLINICAL DIAGNOSIS	USUAL RADIOGRAPHIC FEATURES	TYPICAL FINDINGS ON HRCT
Idiopathic pulmonary fibrosis	Basal-predominant abnormality with volume loss	Pattern of usual interstitial pneumonia—peripheral, basal, subpleural reticulation; honeycombing, traction bronchiectasis
Nonspecific interstitial pneumonia	Ground-glass and reticular opacification	Peripheral, basal, subpleural, symmetrical ground-glass attenuation with irregular lines and consolidation; occasional subpleural sparing
Cryptogenic organizing pneumonia	Patchy bilateral consolidation	Subpleural or peribronchial patchy consolidation or nodules
Acute interstitial pneumonia	Diffuse ground-glass density or consolidation	Diffuse consolidation and ground-glass opacification, often with lobular sparing and late traction bronchiectasis
Desquamative interstitial pneumonia	Ground-glass opacity	Peripheral, lower lung zone ground-glass attenuation with reticulation and/or small cysts
Respiratory bronchiolitis–associated interstitial lung disease	Bronchial wall thickening, ground-glass opacification	Diffuse bronchial wall thickening with poorly defined centrilobular nodules and patchy ground-glass opacification
Lymphocytic interstitial pneumonia	Reticular opacities and nodules	Diffuse centrilobular nodules, ground-glass attenuation, septal and bronchovascular wall thickening, and thin-walled cysts

HRCT = high-resolution computed tomography.

Adapted from American Thoracic Society/European Respiratory Society. International multidisciplinary revised classification of the idiopathic interstitial pneumonias. *Am J Respir Crit Care Med*. 2002;165:277-304; Travis WD, Costabel U, Hansell DM, et al. An official American Thoracic Society/European Respiratory Society statement: update of the international multidisciplinary classification of the idiopathic interstitial pneumonias. *Am J Respir Crit Care Med*. 2013;188:733-748; Raghu G, Remy-Jardin M, Myers JL, et al. Diagnosis of idiopathic pulmonary fibrosis. An official ATS/ERS/JRS/ALAT clinical practice guideline. *Am J Respir Crit Care Med*. 2018;198:e44-e68.

systemic sclerosis, radiation pneumonitis, nitrofurantoin, or malignancy. In the absence of left ventricular failure, the presence of a pleural effusion (Chapter 86) raises the possibility of rheumatoid arthritis, SLE, acute hypersensitivity pneumonitis, sarcoidosis, asbestosis, amyloidosis, lymphangioleiomyomatosis, or lymphangitic carcinomatosis. A reduction of lung volumes is typical in most interstitial lung diseases; the presence of preserved lung volumes or hyperinflation should raise suspicion for chronic hypersensitivity pneumonitis, Langerhans cell histiocytosis, lymphangioleiomyomatosis, neurofibromatosis, sarcoidosis, the combination of idiopathic pulmonary fibrosis and emphysema, or tuberous sclerosis. However, plain chest radiographs may be normal in about 10% of patients with interstitial lung disease.

High-Resolution Computed Tomography

Because of its increased sensitivity and ability to distinguish ground-glass changes, which are generally considered to be reversible areas of lung disease, from irreversible fibrotic and honeycomb changes, high-resolution computed tomography (HRCT) is essential in both the diagnosis and staging of interstitial lung disease. Although microscopic interstitial lung disease cannot be excluded by a normal HRCT result, HRCT allows recognition of abnormalities not apparent in plain chest radiographs and may lead to an earlier diagnosis, help narrow the differential diagnosis patterns (Table 80-4), aid in selecting the site or sites for bronchoalveolar lavage and lung biopsy, assist in choosing among therapeutic options, and allow monitoring the response to treatment. Whereas a normal HRCT excludes the diagnosis of pulmonary fibrosis, the presence of patchy subpleural reticular and basilar septal fibrosis, traction bronchiectasis, and honeycombing increases the level of diagnostic confidence for the pattern of usual interstitial pattern, which is characteristic of idiopathic pulmonary fibrosis. The finding of lung cysts, including their size, configuration, distribution, and appearance, helps differentiate among lymphangioleiomyomatosis, tuberous sclerosis, pulmonary Langerhans cell histiocytosis, Birt-Hogg-Dube syndrome, Erdheim-Chester disease, and lymphocytic interstitial pneumonia. HRCT can detect interstitial lung disease despite normal chest radiographs in patients with asbestosis, silicosis, sarcoidosis, and scleroderma. Patients with respiratory bronchiolitis–associated interstitial lung disease typically have patchy ground-glass attenuation on HRCT in concert with bilateral interstitial prominence, fine nodular radiographic opacities, and normal lung volumes. Images obtained in the supine and prone positions help to differentiate fibrosis from atelectasis. Images obtained on deep inspiration and exhalation sometimes aid in identifying areas of air trapping, which reflect airway abnormalities.

Pulmonary Function Tests

The most characteristic physiologic abnormalities in patients with interstitial lung disease, regardless of etiology, are a restrictive lung defect and decreased D_{LCO} (see Table 73-1 in Chapter 73). Forced expiratory volume in 1 second (FEV_1) and forced vital capacity (FVC) are decreased proportionally such that the ratio of the two remains normal or may even be increased. Both total lung capacity (TLC) and lung volumes measured by body plethysmography are reduced. Pulmonary function tests (PFTs) may be useful in monitoring the progression of disease, assessing the response to therapy, and estimating prognosis; significant changes in FVC or D_{LCO} (corrected to hemoglobin) at 1 year after diagnosis portend a worse survival in patients with idiopathic pulmonary fibrosis.

Certain PFT findings may also aid in the differential diagnosis. A mixed obstructive–restrictive pattern occurs in patients with eosinophilic granulomatosis with polyangiitis syndrome, allergic bronchopulmonary aspergillosis, endobronchial sarcoidosis, hypersensitivity pneumonitis, cryptogenic organizing pneumonia, tropical pulmonary interstitial eosinophilia, coexisting chronic obstructive pulmonary disease or asthma, or secondary bronchiectasis. Diseases associated with respiratory muscle weakness, such as polymyositis, progressive systemic sclerosis, and SLE, may exhibit a decrease in maximal voluntary ventilation and increased residual volume out of proportion to the decrease in total lung capacity.

Exercise Testing

The magnitude of the increase in P_{AO_2}-P_{aO_2} on exercise correlates well with the severity of disease and the degree of pulmonary fibrosis in patients with idiopathic pulmonary fibrosis. Other exercise-induced physiologic abnormalities in interstitial lung disease include a decrease in work rate and maximal oxygen consumption, abnormally high minute ventilation at submaximal work rates, decreased peak minute ventilation, and failure of tidal volumes to increase at submaximal levels of work while the respiratory rate increases disproportionately. The 6-minute walk test, performed on a flat surface, can provide quantitative data on exercise capacity and on oxygen desaturation with exercise and can justify use of supplemental oxygen based on clinical and physiologic needs. It also provides prognostic information in patients with idiopathic pulmonary fibrosis.

Invasive Evaluation

A collegial interaction and multidisciplinary discussions among the clinician, chest radiologist, thoracic surgeon, pathologist, and rheumatologist can help determine the best diagnostic approach for an individual patient (see Fig. 80-1). Findings on bronchoalveolar lavage can be diagnostic in some patients and can narrow the differential diagnosis in others (Chapter 73). For example, a lymphocyte-predominant cellular pattern raises the possibility of sarcoidosis or hypersensitivity pneumonitis in the appropriate clinical setting. Eosinophils may be seen in pulmonary Langerhans cell granulomatosis or eosinophilic pneumonia, an asbestos body count greater than 1 fiber per milliliter of bronchoalveolar lavage fluid may be seen in asbestosis, and specially staining surfactant material may be seen in pulmonary alveolar proteinosis. A transbronchial lung biopsy may reveal noncaseating granulomas in sarcoidosis, "loose" noncaseating granulomas in hypersensitivity pneumonitis, giant cell granulomas in hard metal

pneumoconiosis, or smooth muscle proliferation in lymphangioleiomyomatosis. However, failure to establish a diagnosis despite bronchoalveolar lavage and transbronchial lung biopsy does not exclude these entities. Transbronchial cryobiopsy, a procedure which requires highly specific training, can yield diagnostic histopathology in about 80% of cases.[5] In cases in which the imaging pattern suggests usual interstitial pneumonia, a genomic classifier has proven valuable in identifying a pattern of usual interstitial pneumonia regardless of HRCT imaging features.[6]

Video-assisted thoracoscopic biopsy (Chapter 87) or open lung biopsy may be required to obtain an adequate sample for histologic evaluation of a patient with unexplained signs and symptoms when other studies have failed to establish a diagnosis. The mortality rate is generally less than 2% when the procedure is performed electively.

TREATMENT

When the cause of the interstitial lung disease is clearly known (e.g., acute or subacute hypersensitivity pneumonitis, occupational interstitial lung disease, iatrogenic), further avoidance of the inciting agent or agents is essential (Chapter 81). Although systemic corticosteroids are generally indicated and are associated with a favorable response in some interstitial lung diseases, the dosage and duration are unclear and essentially based on anecdotal experience (Table 80-5).

Supportive oxygen supplementation is dictated by clinical needs. For selected patients with end-stage interstitial lung diseases, such as those associated with significant pulmonary fibrosis and pulmonary hypertension, lung transplantation (Chapter 87) may be a viable option. Treatments for pulmonary hypertension associated with interstitial lung diseases (Chapter 69) are indicated in patients with connective tissue diseases, but their clinical benefit for patients with other interstitial lung diseases has been disappointing.

TABLE 80-5 INTERSTITIAL LUNG DISEASE: CLINICAL RESPONSE TO SYSTEMIC CORTICOSTEROIDS ALONE*

GENERALLY RESPONSIVE	UNRESPONSIVE†
Sarcoidosis	Idiopathic interstitial pneumonia
Acute hypersensitivity pneumonitis	Idiopathic pulmonary fibrosis (usual interstitial pneumonia)
Drug induced	Desquamative interstitial pneumonia (subset)
Environmental causes (some)	Chronic secondary and advanced pulmonary fibrosis
Idiopathic interstitial pneumonia	Fibrotic hypersensitivity pneumonitis (subset)
Cryptogenic organizing pneumonia	Chronic radiation fibrosis
Nonspecific interstitial pneumonia (cellular)	Cryptogenic organizing pneumonia (subset)
Respiratory bronchiolitis–associated ILD	Acute interstitial pneumonia (?)
Lymphocytic interstitial pneumonia	Chronic pulmonary hemorrhage syndromes
Desquamative interstitial pneumonia (subset)	Pulmonary veno-occlusive disease
Acute interstitial pneumonia (some)	Environmental (e.g., asbestosis, pneumoconiosis)
Acute pulmonary capillaritis	End-stage ILDs, pulmonary fibrosis coexisting or associated with pulmonary hypertension
Eosinophilic pneumonia (acute and chronic)	Pulmonary Langerhans cell granulomatosis
Acute radiation pneumonitis‡	Lymphangioleiomyomatosis
Organizing pneumonia associated with connective tissue diseases	ILD in inherited disorders (?)

*The dosage plus duration of corticosteroids used is variable and based on anecdotal experience, individual expert opinion, clinical judgment, and response as judged by objective measurements (clinical, radiologic, or physiologic). Oral prednisone or prednisolone is the most common corticosteroid used. Most patients who respond during the first few weeks of 20 to 60 mg of prednisone per day require maintenance low-dose oral prednisone at 5 to 10 mg/day beyond 6 months. Some patients who require maintenance of oral prednisone doses higher than 20 mg/day beyond 4 to 6 months may tolerate lower doses of prednisone if other immune-modulating agents (e.g., azathioprine, mycophenolate) are used in combination. There is no evidence to recommend a specific regimen. Patients should be monitored carefully and regularly for known side effects of corticosteroid use (e.g., osteoporosis, glucose intolerance), and preventive and therapeutic measures must be undertaken appropriately.

†Some patients unresponsive to oral corticosteroids alone may respond to combined treatment with corticosteroids and other immune-modulating drugs (e.g., azathioprine, mycophenolate).

‡Although most patients respond to modest doses of oral prednisone (initially, 40-60 mg/day), it is important to taper the prednisone very slowly to reach a maintenance dose of 5 to 10 mg/day beyond 6 months; rapid taper of oral prednisone has been associated with "rebound," which is an exaggerated lung injury beyond the irradiated segment of the lung and in the contralateral lung.

ILD = interstitial lung disease.

SPECIFIC TYPES OF INTERSTITIAL LUNG DISEASE

IDIOPATHIC INTERSTITIAL PNEUMONIAS

Idiopathic interstitial pneumonias, which are a subset of acute or chronic interstitial lung diseases of unknown etiology, are characterized by the presence of varying degrees of interstitial and alveolar inflammation and fibrosis. Distinct clinicopathologic forms of idiopathic interstitial pneumonia include chronic fibrosing interstitial pneumonias (idiopathic pulmonary fibrosis and nonspecific interstitial pneumonia), smoking-related interstitial pneumonias (respiratory bronchiolitis–interstitial lung disease and desquamative interstitial pneumonia), and acute or subacute idiopathic interstitial pneumonias (cryptogenic organizing pneumonia and acute interstitial pneumonia). Rare histologic patterns of acute fibrinous and organizing pneumonia and interstitial pneumonias with a bronchiolocentric distribution and pleuroparenchymal fibroelastosis have been recently recognized. In some patients, mixed histopathologic features are evident in different segments of the same lung. When the distinct pathologic forms are not evident, the diagnosis of unclassifiable interstitial pneumonia has been recently recognized. The accuracy of the diagnosis of idiopathic interstitial pneumonias is increased by multidisciplinary discussions among expert pulmonologists, radiologists, and pathologists familiar with interstitial lung diseases and idiopathic interstitial pneumonias.

Although the clinical severity may vary, the idiopathic interstitial pneumonias tend to manifest as an insidious onset of exertional dyspnea and a nonproductive cough. Chest pain and systemic symptoms such as weight loss and fatigue may be present. Bibasilar end-inspiratory crackles are often heard on auscultation. Clubbing, although not specific, is found in 25 to 50% of patients with idiopathic pulmonary fibrosis. Findings on the chest radiograph are most often nonspecific, and the presence of normal lung markings on the chest radiograph does not exclude interstitial lung disease. On HRCT, many pathologic entities have characteristic image patterns that have greatly aided diagnosis (see Table 80-4). The clinical course of idiopathic pulmonary fibrosis is heterogeneous.

CHRONIC FIBROSING INTERSTITIAL PNEUMONIA

Idiopathic Pulmonary Fibrosis

Idiopathic pulmonary fibrosis accounts for 50 to 60% of all idiopathic interstitial pneumonias. Idiopathic pulmonary fibrosis occurs in adult men and women with a mean age at onset of 62 years. Some patients have familial disease, likely autosomal dominant with variable penetrance. Numerous genes have been associated with familial disease as well as some sporadic disease. Examples include the *MUC5B* gene, genes related to immune function, epithelial cell function, maintenance of telomeres, surfactant production, and cell cycle regulation.

Idiopathic pulmonary fibrosis is limited to the lungs in adults, usually older than 60 years, and generally occurs in men with a history of cigarette smoking. Most often patients have otherwise been in good health and have no known connective tissue disease or exposure to drugs or environmental factors known to cause pulmonary fibrosis, although patients with significant cigarette smoking history may have coexisting emphysema. Typical clinical manifestations include a gradual onset and progression of exertional dyspnea, restrictive abnormalities on PFTs (Chapter 73), and a distinct pattern of bilateral pulmonary fibrosis on HRCT.[7]

DIAGNOSIS

Chest radiographs typically show basal-predominant reticular abnormalities with low lung volumes (Fig. 80-2). Compared with the other idiopathic interstitial pneumonias, the HRCT appearance of idiopathic pulmonary fibrosis is distinguished by the presence of fibrotic abnormalities, predominantly in the bases of the lower lobes (E-Fig. 80-1), by subpleural reticulations (E-Fig. 80-2), and by its hallmark honeycombing (E-Fig. 80-3) and traction bronchiectasis (E-Fig. 80-4). These features on HRCT are diagnostic in the appropriate clinical setting (Fig. 80-3A). Radiographs are notable for the absence of extensive ground-glass opacification, micronodules, cysts, consolidation, significant air trapping in multiple lobes, pleural plaques, pleural effusion, and extensive mediastinal adenopathy, all of which are inconsistent with the radiographic pattern of usual interstitial pneumonia.

PFTs usually show a progressive restrictive pattern. However, patients with milder disease may have normal lung volumes and a decreased D_{LCO}; rarely, PFT results may be normal.

The cellular pattern in bronchoalveolar lavage fluid, which is nonspecific, is marked by an excess of neutrophils in proportion to the extent of reticular change on HRCT; the percentage of eosinophils may be mildly increased. The histopathologic pattern of usual interstitial pneumonia consists of patchy interstitial

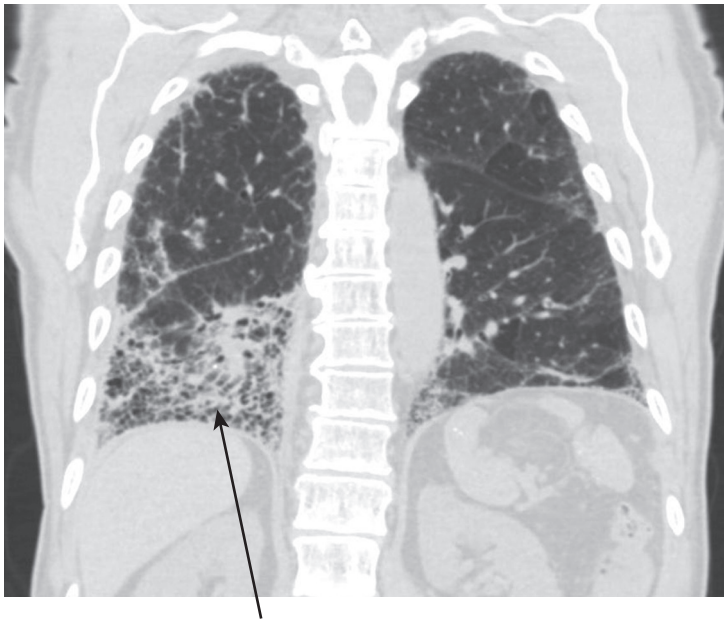

E-FIGURE 80-1. Computed tomography scan demonstrating lower lobe predominant fibrosis in a patient with idiopathic pulmonary fibrosis.

E-FIGURE 80-2. Computed tomography scan showing subpleural reticulations *(arrows)* in a patient with idiopathic pulmonary fibrosis.

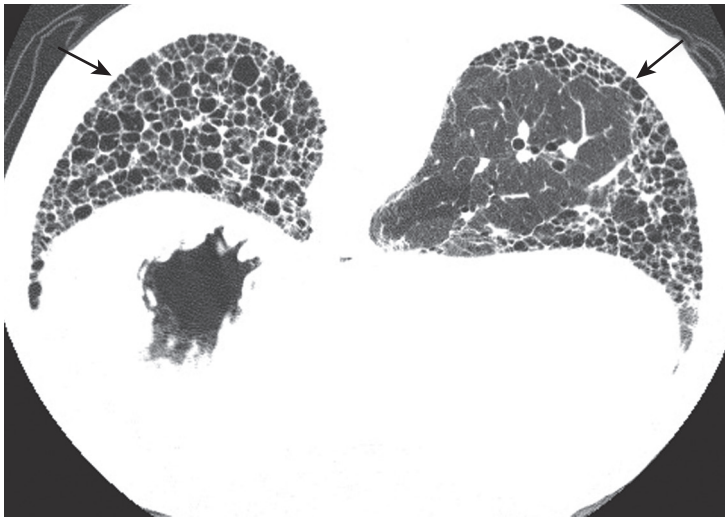

E-FIGURE 80-3. Computed tomography scan showing honeycombing *(arrows)* in a patient with idiopathic pulmonary fibrosis.

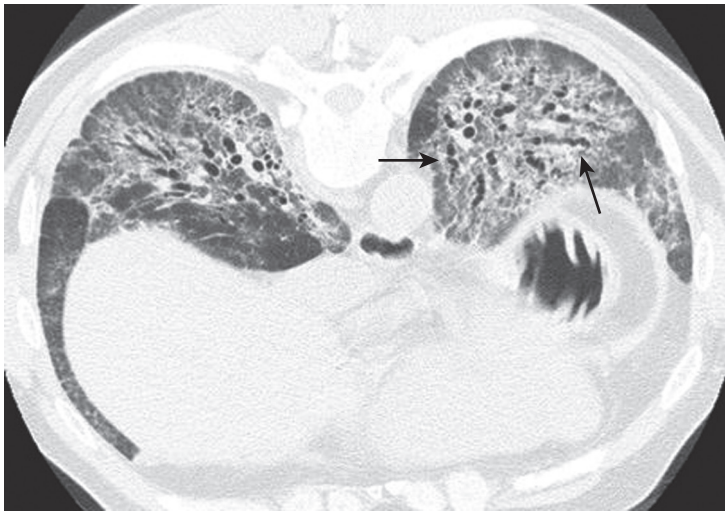

E-FIGURE 80-4. Computed tomography scan showing traction bronchiectasis *(arrows)*.

changes alternating with zones of honeycombing, fibrosis, minimal inflammatory cells, collagen deposition, and normal lung (Fig. 80-3B). Subepithelial fibroblastic foci, small aggregates of myofibroblasts, and fibroblasts within myxoid matrix are invariably present and represent areas of active fibrosis. The presence of temporal heterogeneity, or areas at different stages of fibrosis transitioning with normal areas and honeycomb cysts, along with fibrotic foci within the lung, is an essential feature of usual interstitial pneumonia that distinguishes it from other processes such as nonspecific interstitial pneumonia. Interstitial cellular inflammation is minimal in usual interstitial pneumonia. Although usual interstitial pneumonia characterizes the microscopic abnormality in idiopathic pulmonary fibrosis, the same histologic and radiologic pattern also can be seen in patients with rheumatologic lung diseases, chronic hypersensitivity pneumonitis, and asbestosis (Chapter 81). In the appropriate clinical setting (and after definitive exclusion of other known clinical conditions associated with interstitial lung disease) (see later), a definitive diagnosis of idiopathic pulmonary fibrosis is based on the presence of a pattern of usual interstitial pneumonia on HRCT or surgical lung biopsy (Table 80-6).

FIGURE 80-2. Idiopathic pulmonary fibrosis. Chest radiograph shows low lung volumes with coarse diffuse bilateral reticular opacities and honeycombing. Traction tracheomegaly is also present. (Courtesy of Paul Stark, MD.)

TREATMENT

Antifibrotic therapy[8,9] with pirfenidone (up to 2403 mg per day) slows the rate of decline in forced vital capacity[A1] and the number of respiratory-related hospitalizations[A2] in patients who have idiopathic pulmonary fibrosis and mild to moderate impairment in pulmonary function, with pooled data suggesting an improvement in survival.[A3] Treatment with nintedanib (a tyrosine kinase inhibitor) at 150 mg orally twice daily also reduces the decline in FVC in patients with idiopathic pulmonary fibrosis and mild to moderate impairment in pulmonary function by a similar amount.[A4] Data suggest that both pirfenidone and nintedanib reduce mortality to a similar extent.[10]

Abnormal acid gastroesophageal reflux (Chapter 124) is very common in patients with idiopathic pulmonary fibrosis. Treatment with standard doses of proton pump inhibitors, H_2 receptor antagonists, or both as used for gastroesophageal reflux disease (Chapter 124) may alleviate symptoms, but observational data do not suggest a benefit for survival[11] and their routine use is not recommended.[12]

Warfarin increases respiratory hospitalizations and death in patients with idiopathic pulmonary fibrosis. Prophylactic antibiotics,[A5] interferon-γ1b, cyclophosphamide, colchicine, D-penicillamine, simtuzumab, dual endothelin receptor antagonists (bosentan and macitentan), *N*-acetylcysteine, oral corticosteroids as monotherapy or in combination with azathioprine or cyclophosphamide, sildenafil alone or in combination with nintedanib or pirfenidone[A6] are not beneficial.

Despite the absence of data, patients who require hospitalization and intensive care for an acute exacerbation with loss of respiratory function in the absence of infection or other complications are often treated with empirical intravenous corticosteroids (e.g., methylprednisolone 1.0 g intravenously as a pulse dose once a day for 3 days and followed by hydrocortisone, 125 mg every 6 hours for another 3 to 5 days), with further dosing dependent on the clinical response. Ancillary treatment measures, including supplemental oxygen (based on clinical and physiologic needs), prompt detection and treatment of respiratory tract infections and pulmonary embolism (Chapter 68), pulmonary rehabilitation,[A7] and immunization for influenza, herpes zoster, and pneumococcus, are all appropriate. Treatment of acute exacerbations of idiopathic pulmonary fibrosis with pulse cyclophosphamide is not beneficial.[A8]

Pulmonary hypertension, if present, may be treated (Chapter 69) with inhaled treprostonil (72 mg four times daily), which can significantly improve exercise capacity.[A9] However, endothelin receptor antagonists (e.g., ambrisentan, bosentan, or macitentan) should not be used because of clear data that ambrisentan is harmful in all patients with idiopathic pulmonary fibrosis, even those who have pulmonary hypertension.

Lung transplantation (Chapter 87) is indicated in selected patients, but most patients with idiopathic pulmonary fibrosis are older than age 65 years, an age that is a relative contraindication to lung transplantation. Nevertheless, lung transplantation should be considered in selected patients who are younger than 70 years of age. Palliative care measures should be discussed and instituted before patients reach the terminal stages of the disease.

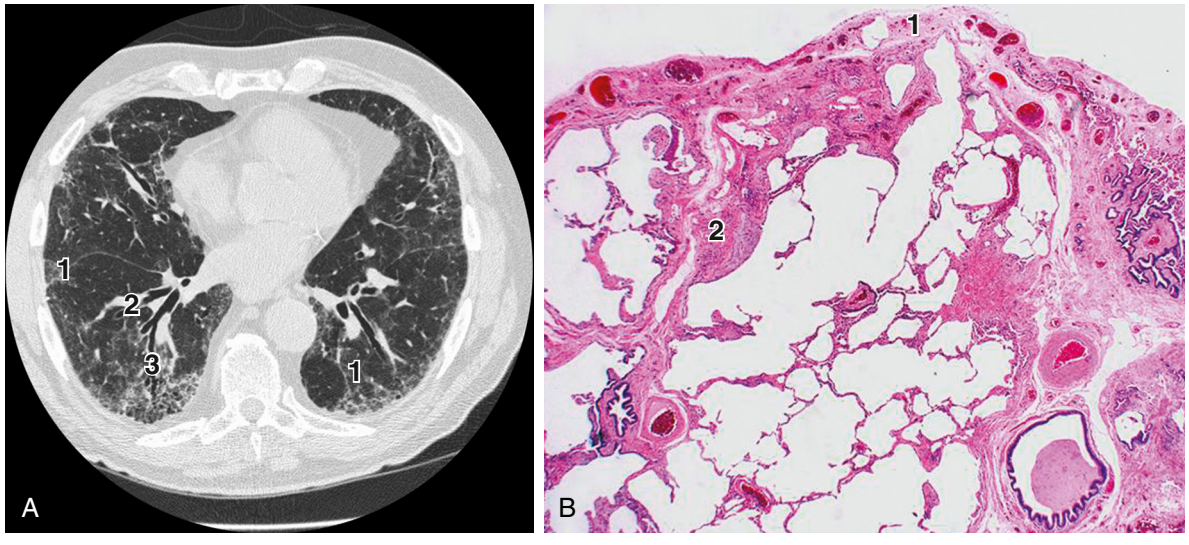

FIGURE 80-3. Diagnosis of idiopathic pulmonary fibrosis. A, The usual interstitial pneumonia pattern of idiopathic pulmonary fibrosis in the lower lobes on high-resolution computed tomography consists of (1) subpleural fibrotic changes with (2) traction bronchiectasis and (3) honeycomb cysts in the lower lobes. **B,** Usual interstitial pneumonia pattern of idiopathic pulmonary fibrosis. Note the presence of (1) subpleural fibrosis with (2) fibroblastic foci and temporal heterogeneity of microscopic abnormalities at low magnification. (Courtesy of Dr. Kevin Leslie.)

TABLE 80-6 DIAGNOSIS CRITERIA FOR IDIOPATHIC PULMONARY FIBROSIS

The diagnosis of idiopathic pulmonary fibrosis requires the exclusion of other known causes of interstitial lung disease (e.g., domestic, occupational, and environmental exposures; connective tissue disease; and drug toxicity) AND either #1 or #2:

1. the presence of HRCT pattern of usual interstitial pneumonia (UIP)
2. specific combinations of HRCT patterns and histopathology patterns of UIP in patients subjected to lung tissue sampling†

HRCT FEATURES OF UIP	HISTOPATHOLOGIC FEATURES OF UIP
• Subpleural, basal predominance • Reticular abnormality • Distribution is often heterogeneous • Honeycombing with or without peripheral traction bronchiectasis or bronchiolectasis • Absence of peribronchovascular predominance, extensive ground-glass abnormality, diffuse micronodules, discrete cysts, diffuse mosaic attenuation, or consolidation	• Marked fibrosis/architectural distortion, +/− honeycombing in a predominantly subpleural/paraseptal distribution • Patchy parenchymal lung fibrosis • Fibroblast foci • No features suggesting an alternative diagnosis*

*Based on data from Raghu G, Remy-Jardin M, Myers JL, et al. Diagnosis of idiopathic pulmonary fibrosis. An official ATS/ERS/JRS/ALAT clinical practice guideline. *Am J Respir Crit Care Med*. 2018;198:e44-e68.

†See above article by Raghu G et al. for specific criteria for patterns of probable UIP, indeterminate for UIP, and alternate diagnosis and combinations.

HRCT = high-resolution computed tomography.

FIGURE 80-4. Nonspecific interstitial pneumonia. Computed tomography scan showing characteristic subpleural sparing (*arrow*).

PROGNOSIS

The natural course of idiopathic pulmonary fibrosis is heterogeneous. Most patients exhibit a slow and steady decline, as measured by FVC (at a rate 150 to 200 mL at the end of first year of follow-up), with a mortality rate of about 7% at 1 year and 14% at 2 years after diagnosis. Treatment with antifibrotic agents appears to reduce mortality by up to 50% at 1 year, but its long-term benefit remains to be determined.

A small subset of patients declines rapidly over several months, but another subset of patients remains stable over several years before declining. Progressive impairment of lung function and gas exchange ultimately is fatal unless the patient undergoes lung transplantation. Patients who survive longer generally have less fibrosis on HRCT, less functional impairment, no evidence of pulmonary hypertension, and no significant oxygen desaturation during a modified version of the 6-minute walk test. Patients with coexisting emphysema, pulmonary hypertension, or episodes of acute exacerbation have even shorter survival times.

Nonspecific Interstitial Pneumonia

Nonspecific interstitial pneumonia is often associated with connective tissue diseases, but idiopathic nonspecific interstitial pneumonia is also recognized as a distinct clinical entity. It typically occurs in middle-aged, nonsmoking women with an average age at diagnosis of about 50 years. The prevalence of nonspecific interstitial pneumonia has been estimated at 1 to 9 per 100,000.

Two subgroups have been described, cellular and fibrotic. Because the average age at onset is about 10 years earlier in nonspecific interstitial pneumonia than in idiopathic pulmonary fibrosis and because the clinical features of idiopathic fibrotic nonspecific interstitial pneumonia are very similar to early cases of idiopathic pulmonary fibrosis, questions persist as to whether idiopathic fibrotic nonspecific interstitial pneumonia is a separate clinical entity or represents an early form of idiopathic pulmonary fibrosis.

DIAGNOSIS

Chest radiographs show bilateral patchy pulmonary infiltrates with lower lung zone predominance. HRCT reveals a predominant ground-glass pattern of attenuation, usually bilateral and often associated with reticulation and subpleural sparing (Fig. 80-4), and loss of volume in the lower lobe. In cellular nonspecific interstitial pneumonia, HRCT shows ground-glass opacification, consolidation, or both, but the biopsy shows mild to moderate lymphoplasmacytic interstitial chronic inflammation. The major differential diagnosis to consider as an alternative to cellular nonspecific interstitial pneumonia is acute or subacute hypersensitivity pneumonitis, so a thorough history regarding environmental exposures is crucial. In contrast, fibrotic nonspecific interstitial pneumonia has a bilateral lower lobe distribution with architectural derangement on HRCT; histopathologically, it has uniformly dense interstitial fibrosis and may sometimes be difficult to distinguish from idiopathic pulmonary fibrosis and usual interstitial pneumonia in the early clinical stages. In these circumstances, the diagnosis of fibrotic nonspecific interstitial pneumonia can be ascertained only by the histologic features in a surgical lung biopsy specimen.

TREATMENT AND PROGNOSIS

Patients with cellular nonspecific interstitial pneumonia usually respond to treatment with corticosteroids (see Table 80-5), and their prognosis is generally better than that of patients with idiopathic pulmonary fibrosis. Nonetheless, some patients progress over several years, and some manifest acute exacerbations similar to patients with idiopathic pulmonary fibrosis. Nintedanib (150 mg orally twice daily) can attenuate the loss of lung function in patients with progressive nonspecific interstitial pneumonia.[A10,A11] Immune-modulating drugs, including prednisone, azathioprine, and mycophenolate, have been used empirically, with their doses based on clinical response as assessed by clinicians and not on evidence with randomized clinical trials.

SMOKING-RELATED INTERSTITIAL PNEUMONIAS

Respiratory Bronchiolitis–Associated Interstitial Lung Disease

This interstitial lung disease is almost invariably associated with cigarette smoking and usually manifests clinically during the fourth or fifth decade of life. However, it also may be detected incidentally on radiographs in relatively younger and asymptomatic persons with a previous history of cigarette smoking or in people passively exposed to chronic cigarette smoke.

DIAGNOSIS

Pulmonary function tests show varying degrees of airway obstruction, mildly decreased or preserved TLC, and decreased D_{LCO}. The chest radiograph typically reveals bronchial wall thickening and areas of ground-glass attenuation. HRCT reveals centrilobular nodules with an upper lobe predominance, patchy ground-glass attenuation, and peribronchial alveolar septal thickening (Fig. 80-5A). Areas of hypoattenuation (mosaic attenuation) represent air trapping as a result of small airways disease. The characteristic finding on bronchoalveolar lavage is numerous brown-pigmented alveolar macrophages,

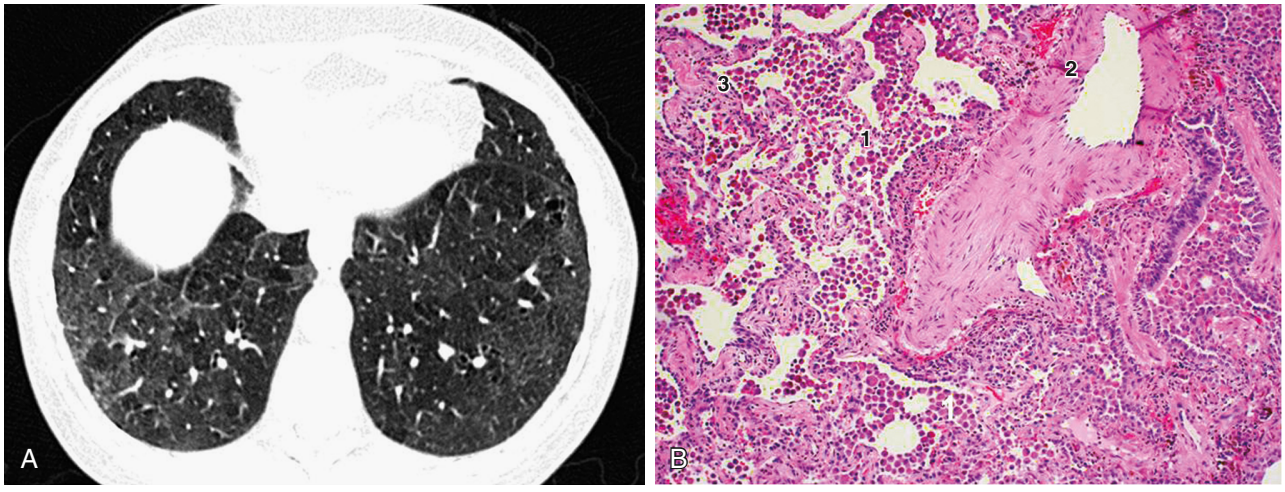

FIGURE 80-5. Respiratory bronchiolitis–associated interstitial lung disease. A, Ground-glass attenuation with a mosaic pattern on high-resolution computed tomography. **B**, Note the dense aggregates of (1) pigmented macrophages present in the air spaces around the terminal airways with (2) variable bronchiolar metaplasia and (3) interstitial fibrosis.

often with a modest increase in neutrophils. Lung biopsy is rarely needed, but its hallmark histopathologic feature is the accumulation of pigmented alveolar macrophages with glassy eosinophilic cytoplasm and granular pigmentation within respiratory bronchioles, typically with a chronic inflammatory cell infiltrate in the bronchioles and surrounding alveolar walls (Fig. 80-5B). Fibroblastic foci and honeycomb change are not present, but centrilobular emphysema is frequent.

TREATMENT AND PROGNOSIS

Progression to honeycomb lung and end-stage fibrosis seldom occurs if patients completely cease smoking. Total discontinuation of cigarette smoking is essential, and the prognosis is good. Patients who discontinue cigarette smoking may benefit from low-dose corticosteroids (e.g., prednisone, 10 to 20 mg/day) for a few months.

Desquamative Interstitial Pneumonia

Desquamative interstitial pneumonia is a rare entity (<3% of all interstitial lung diseases) that may represent a form of respiratory bronchiolitis–associated interstitial lung diseases extending into the alveolar spaces and alveolar walls. Although most affected individuals are cigarette smokers, the histologic pattern of desquamative interstitial pneumonia may also occur in pneumoconiosis, rheumatologic disease, and drug-associated interstitial lung disease. Patients are often initially seen with advanced disease and striking hypoxemia. The histopathology features of desquamative interstitial pneumonia are characterized by accumulation of pigmented alveolar macrophages within the alveoli. Histologic changes within the respiratory bronchioles and within the alveolar spaces can coexist and represent a histopathologic spectrum of alveolar macrophage accumulation, with a variable degree of interstitial fibrosis.[13]

DIAGNOSIS

PFTs reveal a restrictive lung defect and decreased DLCO with or without coexisting airway obstruction. The chest radiograph shows patchy basal consolidation with a lower lobe and peripheral predominance (Fig. 80-6). HRCT shows bilateral symmetrical ground-glass opacities with a predominantly basal and peripheral distribution as well as diffuse alveolar septal thickening (Fig. 80-7A). Irregular linear opacities, typically associated with traction bronchiectasis, may be noted. The finding of small discrete cysts, believed to represent trapped air in dilated bronchioles, within areas of ground-glass changes (E-Fig. 80-5) and intervening normal lung parenchyma is highly suggestive of desquamative interstitial pneumonia. Fluid recovered from bronchoalveolar lavage quite often shows increased numbers of pigmented alveolar macrophages, frequently with increased neutrophils. Histopathologic findings on biopsy include diffuse alveolar septal thickening, hyperplasia of type II pneumocytes, and intense accumulation of intra-alveolar granular pigmented macrophages in a uniform manner (Fig. 80-7B); fibrosis is minimal.

FIGURE 80-6. Desquamative interstitial pneumonia (DIP). Chest radiograph shows homogeneous bilateral perihilar ground-glass opacification and basal predominant consolidation. (Courtesy of Paul Stark, MD.)

TREATMENT AND PROGNOSIS

With total cessation of smoking and administration of oral corticosteroid therapy (see Table 80-5), outcomes are generally good, with an estimated overall survival rate of 70% at 10 years. However, a subset of patients may progress despite cessation of cigarette smoking, and a trial of corticosteroid therapy with or without immune-modulating agents and lung transplantation is an appropriate consideration for selected patients.

ACUTE OR SUBACUTE IDIOPATHIC INTERSTITIAL PNEUMONIA

Acute Interstitial Pneumonia

Acute interstitial pneumonia is seen in otherwise healthy persons usually after an apparent acute viral upper respiratory infection (Fig. 80-8). The syndrome, historically known as Hamman-Rich syndrome (Chapter 79), mimics acute respiratory distress syndrome (Chapter 90). Acute interstitial pneumonia is a rare and fulminant idiopathic interstitial pneumonia that presents with acute symptoms and leads to respiratory distress or failure.

Cryptogenic Organizing Pneumonia

Cryptogenic organizing pneumonia,[14] previously referred to as bronchiolitis obliterans organizing pneumonia (BOOP) of unknown cause, is an idiopathic form of organizing pneumonia. Organizing pneumonia affects the small airways, including the distal bronchioles, respiratory bronchioles, alveolar ducts, and

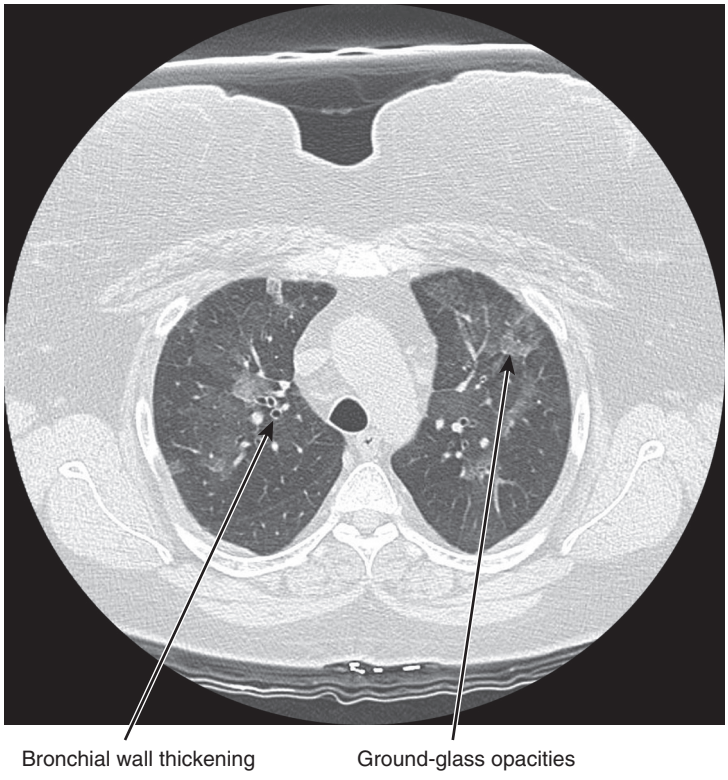

E-FIGURE 80-5. **Computed tomography scan showing ground-glass opacities and bronchial wall thickening in a patient with desquamative interstitial pneumonia.**

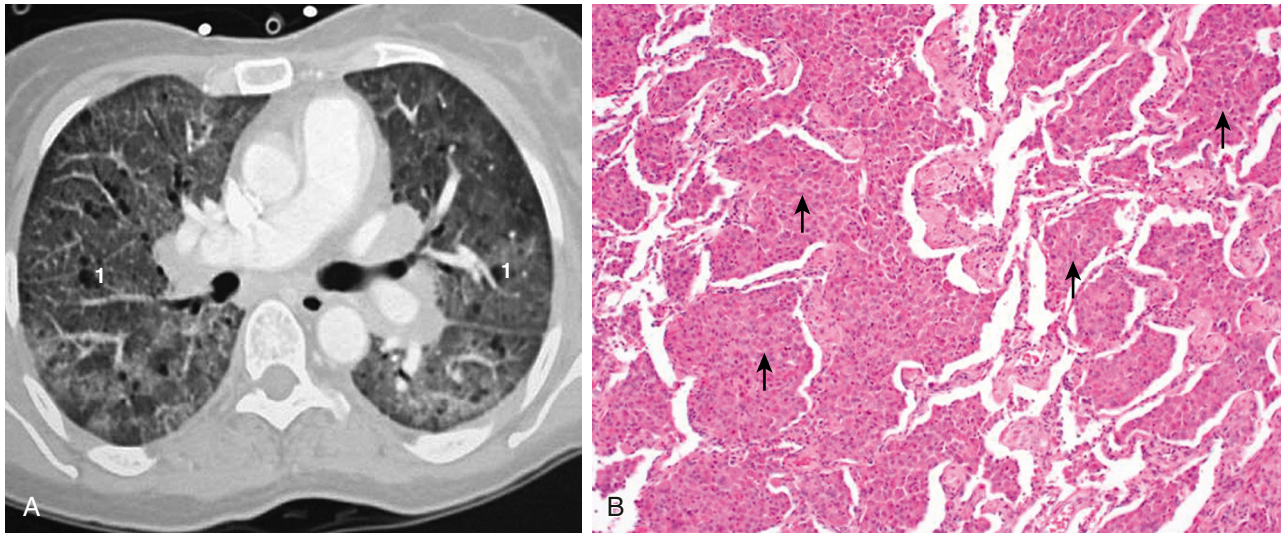

FIGURE 80-7. Desquamative interstitial pneumonia. A, Ground-glass attenuation with cystic spaces on high-resolution computed tomography. **B,** Note that the alveolar spaces are densely filled with macrophages *(arrowheads)*.

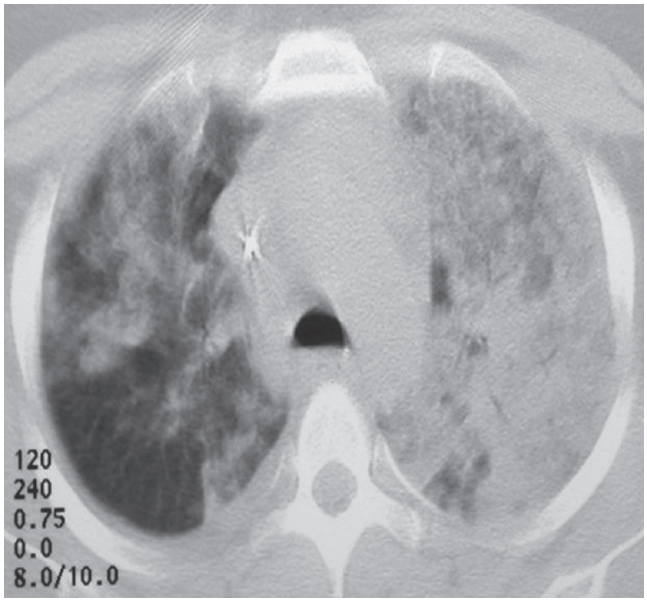

FIGURE 80-8. Acute interstitial pneumonia with diffuse alveolar damage histologically. Note the dense air space consolidation.

FIGURE 80-9. Chest radiograph showing cryptogenic organizing pneumonia. Note the bilateral patchy air space opacities.

alveolar walls. Although the incidence and prevalence of cryptogenic organizing pneumonia are unknown, the estimated annual incidence in the United States is 6 to 7 cases per 100,000. The mean age at presentation is about 60 years, and there is no sex predominance.

DIAGNOSIS

Cryptogenic organizing pneumonia most commonly manifests as a flulike illness with a nonproductive cough followed by exertional dyspnea. This scenario has been reported to occur following SARS-CoV-2 infection. PFTs show a restrictive defect, but 20% of patients, most of whom are current or past smokers, also have an obstructive defect. Chest radiography reveals patchy unilateral or bilateral alveolar opacities that may be peripheral or migratory; small nodular opacities are seen in 10 to 50% of cases (Fig. 80-9). In about 90% of patients, HRCT shows areas of air space consolidation with lower lung zone predominance, frequently in a subpleural or peribronchial distribution (Fig. 80-10); other features include small nodules along bronchovascular bundles and ground-glass attenuation. Bronchoalveolar lavage is nonspecific; increased lymphocytes, neutrophils, and eosinophils may be seen. On biopsy, key histologic features are excessive proliferation of granulation tissue within the small airways and alveolar ducts as well as chronic inflammation in the surrounding alveoli.

TREATMENT AND PROGNOSIS

Most patients recover rapidly and completely when treated with oral corticosteroids (see Table 80-5) for 6 months but may relapse after discontinuation and require oral corticosteroids for longer periods and sometimes indefinitely, often with adjunct immunomodulating agents such as azathioprine or mycophenolate. Some data suggest that clarithromycin (250 to 500 mg daily) is an alternative for patients whose PFTs are reasonably normal (forced vital capacity >80% of predicted). A small subset of patients in whom pulmonary fibrosis develops despite corticosteroids and immune-modulating agents progress to pulmonary fibrosis and behave similarly to patients with idiopathic pulmonary fibrosis. Spontaneous remissions are known to occur.

Lymphoid and Lymphocytic Interstitial Pneumonia

This condition is more common in women, especially in the fifth decade of life, but it may occur at any age. Patients should be evaluated for concurrent connective tissue disease, an autoimmune disorder (especially Sjögren syndrome; Chapter 247), or common variable immunoglobulin deficiency (Chapter 231) because idiopathic LIP is very rare. Symptoms are nonspecific and include a gradual onset of cough and exertional dyspnea. Lymphoid and LIP is within the spectrum of benign lymphoproliferative

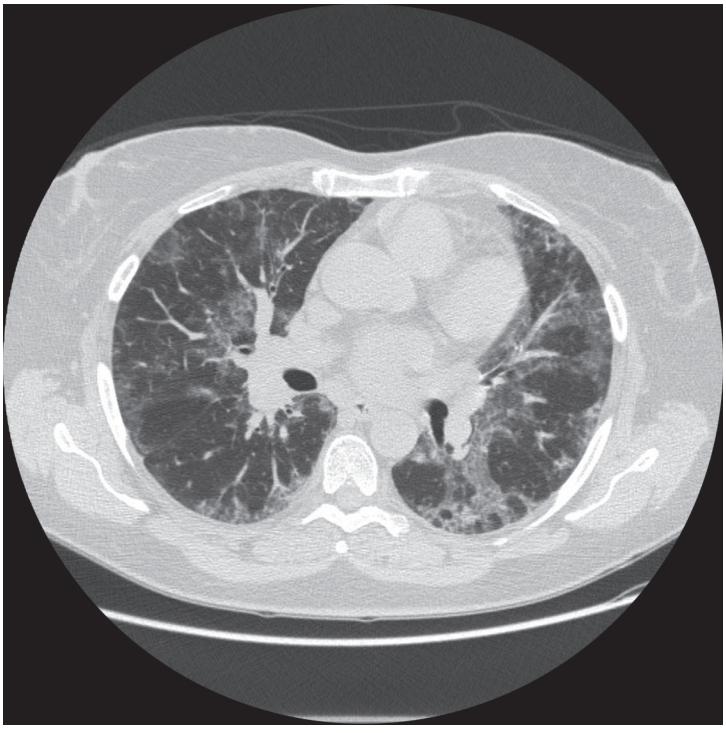

FIGURE 80-10. Peripheral ground-glass opacities in a patient with cryptogenic organizing pneumonia.

disorders, and some patients manifest pseudolymphoma or lymphoma as a complication.

DIAGNOSIS

Chest radiographs show a reticular or reticulonodular pattern predominantly involving the lower lung zones. HRCT reveals bilateral ground-glass attenuation, small or large nodules, and scattered cysts; perivascular honeycombing and reticular abnormalities also may be seen (E-Fig. 80-6). Increased numbers of lymphocytes are found on bronchoalveolar lavage, and biopsy reveals a dense interstitial lymphocytic infiltrate.

TREATMENT AND PROGNOSIS

Some patients respond to or stabilize with oral corticosteroids (see Table 80-5). The prognosis is variable, with more than one third of patients progressing to diffuse pulmonary fibrosis.

INTERSTITIAL LUNG DISEASE ASSOCIATED WITH CONNECTIVE TISSUE DISEASE

Many of the connective tissue diseases, including progressive systemic sclerosis (Chapter 246), rheumatoid arthritis (Chapter 243), SLE (Chapter 245), dermatomyositis and polymyositis (Chapter 248), Sjögren syndrome (Chapter 247), and mixed connective tissue disorder (Chapter 246), may have interstitial lung disease as one of their manifestations.[15] In fact, up to 20% of patients with connective tissue diseases may initially be thought to have an interstitial lung disease alone. Therefore these diagnoses must be considered in patients with interstitial lung disease, even in the absence of extrathoracic findings. Conversely, because pulmonary involvement is a major cause of death in patients with connective tissue diseases, the presence of interstitial lung disease should be carefully sought in affected patients.[16] All forms of interstitial pneumonia can occur in patients with connective tissue diseases. The natural history of interstitial lung disease complicating connective tissue diseases is variable, especially because coexisting pulmonary vascular disease or nonparenchymal pulmonary involvement may be present.

PROGRESSIVE SYSTEMIC SCLEROSIS

Of the connective tissue diseases, progressive systemic sclerosis is most frequently associated with interstitial lung disease.[17] Pulmonary symptoms may antedate cutaneous or digital manifestations of the disease by several years. Most patients affected have nonspecific interstitial pneumonia, with a minority having a usual interstitial pneumonia pattern. DLCO levels correlate with mortality. Pulmonary hypertension, which can occur in the absence of pulmonary fibrosis, may result in cor pulmonale. Patients with chronic pulmonary fibrosis also have an increased risk for bronchogenic carcinoma, usually either bronchoalveolar cell carcinoma or adenocarcinoma. For scleroderma-associated interstitial lung disease, mycophenolate (target dose 1500 mg twice daily) provides similar physiologic improvement and stabilization of pulmonary function compared with cyclophosphamide (2.0 mg/kg/day) with fewer side effects,[A12] so mycophenolate is now considered first-line therapy. Rituximab (two cycles of a 1000 mg intravenous infusion, 2 weeks apart) has been used as an alternate immunosuppressive regimen of interstitial lung disease associated with systemic sclerosis.[18] Nintedanib (150 mg orally twice daily) can attenuate the loss of lung function when administered alone or in addition to mycophenolate.[A13] Tocilizumab, an IL-6 receptor blocker (162 mg weekly subcutaneously), also can mitigate decline in lung function in patients with elevated systemic inflammatory markers and a short duration of systemic disease.[A14]

FIGURE 80-11. Rheumatoid interstitial lung disease with usual interstitial pneumonia pattern. Chest radiograph shows low lung volumes, diffuse reticular opacities, and honeycombing with basal predominance. (Courtesy of Paul Stark, MD.)

RHEUMATOID ARTHRITIS

Although rheumatoid arthritis is more common in women (2 : 1 to 4 : 1 ratio), interstitial lung disease associated with rheumatoid arthritis is more common in men (3 : 1 ratio). Most cases occur at 50 to 60 years of age, and pulmonary symptoms follow the onset of arthritis in about 75% of cases.[19] Lung involvement in rheumatoid arthritis may take many forms, but bronchiectasis, bronchiolitis, idiopathic interstitial pneumonias (Fig. 80-11), and pleural effusions or pleural thickening are some of the most common. Early in the course, the histologic changes are similar to those of idiopathic interstitial pneumonias, including pulmonary fibrosis, but are distinguished by a prominent lymphocytic infiltrate that may contain germinal follicles adjacent to vessels and airways. As the disease progresses, the infiltration becomes less pronounced and is replaced by fibrous tissue, honeycomb changes, or both. Other pulmonary manifestations include pulmonary nodules, vasculitis, pulmonary hypertension, and Caplan syndrome (progressive upper lobe nodular pulmonary fibrosis in a coal miner with rheumatoid arthritis) but are relatively rare. Patients with usual interstitial pneumonia pattern on HRCT have worse prognosis than those with a nonspecific interstitial pneumonia pattern. Treatment is directed at the underlying rheumatoid arthritis (Chapter 243), but methotrexate therapy is generally avoided since one of its potential toxicities is the development of interstitial lung disease. Nintedanib (150 mg orally twice daily) can attenuate the decline in lung function in patients with progressive inherited lung disease.

SYSTEMIC LUPUS ERYTHEMATOSUS

Pulmonary abnormalities complicating SLE (Chapter 245) may vary greatly. Pleural disease or pleural effusions (or both) are commonly present in lung disease that complicates SLE. Acute lupus pneumonitis may mimic acute interstitial pneumonia, with widespread ground-glass attenuation admixed with consolidation, or it may manifest as diffuse alveolar hemorrhage.

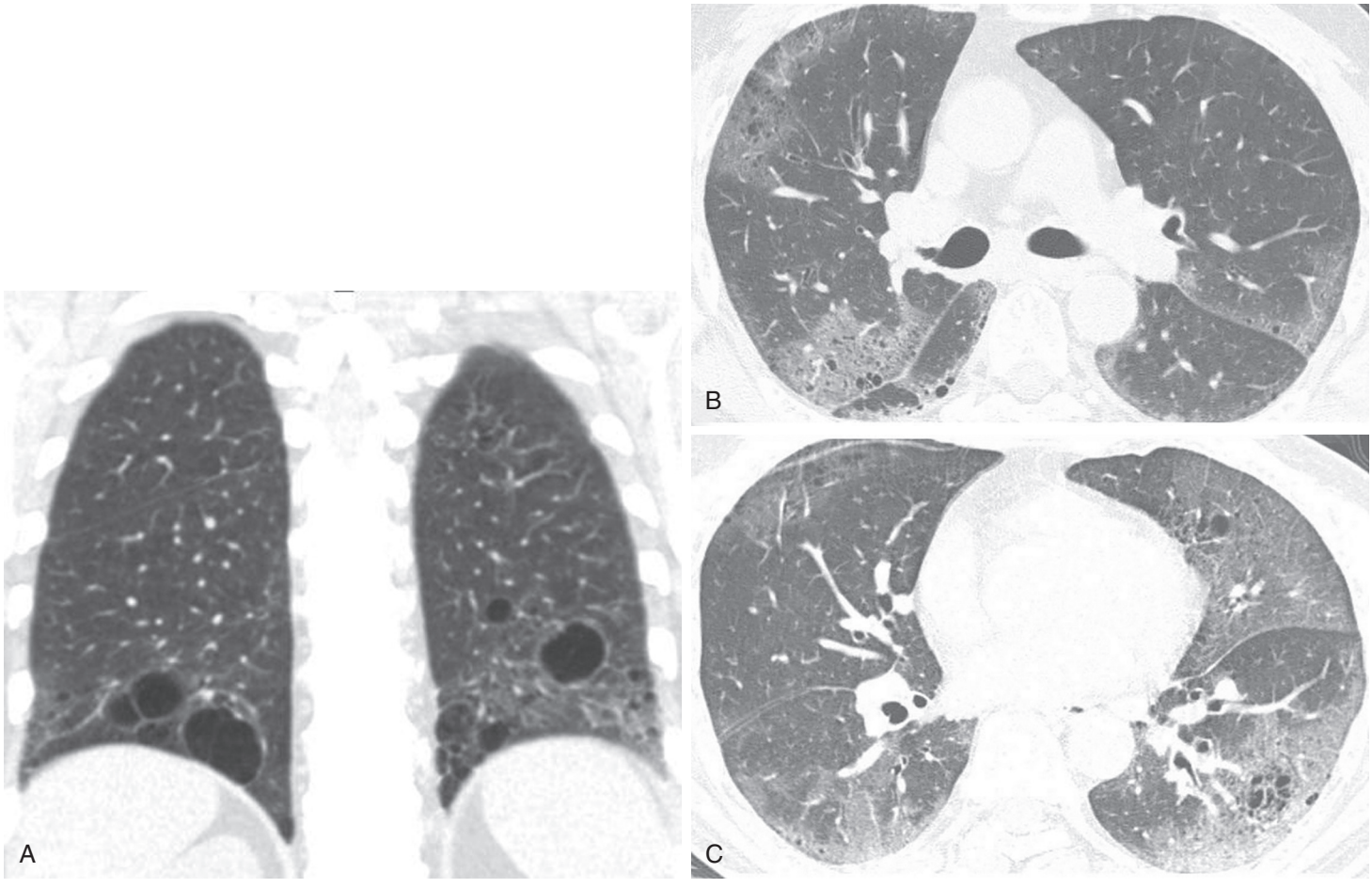

E-FIGURE 80-6. Lymphoid interstitial pneumonia. Note the cysts within the patchy ground-glass attenuation in lower lobes (**A**). The cysts are interspersed within areas of ground-glass attenuation (**B** and **C**).

Chronic interstitial lung disease may also occur. Infection must always be considered in acutely ill patients who have received steroids or other immunosuppressive therapy. Rarely, the restrictive lung defect, which may be predominantly a result of diaphragmatic weakness, leads to a chest radiographic pattern of small-appearing lungs that may look progressively smaller over time. This so-called "shrinking lung" is generally resistant to corticosteroids or other immunosuppressive agents used to treat SLE. Otherwise, treatment of the interstitial lung disease is similar to treatment of the underlying SLE.

DERMATOMYOSITIS AND POLYMYOSITIS

In contrast to progressive systemic sclerosis, the pattern of lung involvement in dermatomyositis and polymyositis is more heterogeneous. Usual interstitial pneumonia, nonspecific interstitial pneumonia, and organizing pneumonia have all been reported. Most patients have an anti–Jo-1 antibody or anti-PL-7 antibody, and the disease is typically progressive over time.[20] An acute interstitial pneumonia–like syndrome occurs in a subset of patients and is associated with high mortality rate despite aggressive immunosuppressive agents and high-dose corticosteroids. Interstitial lung disease may precede the muscular manifestations by months to years or be superimposed on established muscle disease. The severity of the muscular disease does not correlate with that of the interstitial lung disease. Treatment is directed at the underlying disease (Chapter 248).

SJÖGREN SYNDROME

Interstitial lung disease is seen in patients with Sjögren syndrome, particularly those with the primary form of the disease. LIP is the most frequent subtype, but cryptogenic organizing pneumonia also may be present. Respiratory infections and bronchiectasis are common in advanced stages, perhaps because of inspissated mucus. Response to corticosteroid or immunosuppressive therapy is usually good (Chapter 247).

MIXED CONNECTIVE TISSUE DISEASE

This overlap syndrome (Chapter 246) combines features of progressive systemic sclerosis, SLE, rheumatoid arthritis, and polymyositis or dermatomyositis. Pulmonary disease is common, but it is most often subclinical and identified only radiographically. Treatment includes corticosteroids and other immune-modulating agents for the underlying disease.

ANKYLOSING SPONDYLITIS

The most common pulmonary manifestation of ankylosing spondylitis (Chapter 244) is upper lobe bilateral reticulonodular infiltrates with cyst formation as a result of parenchymal destruction. There is no known effective therapy for this apical fibrobullous disease.

HYPERSENSITIVITY PNEUMONITIS

PATHOBIOLOGY

Hypersensitivity pneumonitis, which is an inflammatory and/or fibrotic disease affecting the lung parenchyma and small airways, is a syndrome caused when sensitized individuals repeatedly inhale specific antigens from occupational or environmental exposure (Chapters 81 and 82). Within a short period after inhalation of an inciting agent, patients develop a nonspecific diffuse pneumonitis with inflammatory cell infiltration of the bronchioles, alveoli, and interstitium, sometimes associated with a pleural effusion. Loosely formed, noncaseating, epithelioid cell granulomas and a mononuclear infiltrate may be dispersed in the interstitium. Hypersensitivity pneumonitis can occur with exposure to a wide range of inhaled antigens (Chapters 81 and 82). Some of the more common exposures are farmer's lung, bird fancier's lung, parakeet keeper's lung, and pigeon breeder's lung. The avian antigen may be related to overt exposure to birds, bird droppings, or bird nests or to occult exposures to bird feeders or bird feather components used in beddings, down comforters, duvets, or jackets. Despite a thorough evaluation, the source and/or the inciting agent/antigen may not be identified in a substantial number of patients who meet the diagnostic criteria for HP. Hobbies (woodworker's lung) and recreational activities (sauna taker's lung; hot tub) may be implicated as well as occupations.

CLINICAL MANIFESTATIONS

The clinical features and severity of symptoms vary according to the frequency and intensity of exposure. The index of clinical suspicion for hypersensitivity pneumonitis should be high in every patient with new-onset interstitial lung disease. This should prompt a detailed history of exposure to potential agents or changes in the domestic and other environments (or both) (Chapters 16 and 81). The interval between exposure to the antigen and the clinical manifestations of lung disease is unknown, although symptoms can occur as soon as 4 to 12 hours after exposure. In such cases, fever and chills are common symptoms, are often temporally related to the workplace or to hobbies, and may actually disappear on vacations or during absence from the site of exposure, only to recur when exposure is resumed. In more chronic and low-level exposures, however, the onset is insidious. Some patients with fibrotic hypersensitivity pneumonitis owing to many years of exposure may manifest clinical features similar to those of patients with idiopathic pulmonary fibrosis.

DIAGNOSIS

Findings on chest radiography are diverse, with focal patchy consolidation or a diffuse ground-glass appearance in nonfibrotic hypersensitivity pneumonitis (E-Fig. 80-7), micronodular and reticular shadowing, and diffuse, predominantly upper lung zone reticulation with honeycombing in the fibrotic form. Chest radiograph results may be normal in up to 30% of patients with significant physiologic abnormalities.

On HRCT, small centrilobular ill-defined nodules of ground-glass densities are seen, along with evidence of mosaic attenuation (trapped air) as a result of concomitant bronchiolitis and upper lobe predominance of the parenchymal abnormalities (E-Fig. 80-8). Chronically, findings of lung fibrosis may be indistinguishable from the patterns seen in usual interstitial pneumonia and idiopathic pulmonary fibrosis (E-Fig. 80-9).

Precipitating serum antibodies for potential causes of hypersensitivity pneumonitis confirm exposure but not cause and effect. The absence of antibodies does not exclude hypersensitivity pneumonitis. In some cases, a thorough investigation of the patient's home and workplace by an industrial hygienist may reveal occult molds, spores, *Thermoactinomycetes* spp, *Aureobasidium pullulans*, and other precipitating causes. When such exposures are evident and suspected to be the cause of the manifested interstitial lung disease, further diagnostic interventions such as bronchoalveolar lavage may be quite helpful by showing the most marked increase in T lymphocytes and an increased number of plasma cells. The characteristic histologic triad in hypersensitivity pneumonitis is cellular nonspecific interstitial pneumonia, cellular bronchiolitis, and granulomatous inflammation; however, this triad is seen in no more than 75% of affected patients. Differentiation from cellular nonspecific interstitial pneumonia may be challenging. Prompted by an elicited history of environmental exposure for an attributable antigen, bronchochallenge testing with the suspected antigen in experienced laboratories may provide further clues for the diagnosis of hypersensitivity pneumonitis in a patient otherwise suspected to have idiopathic pulmonary fibrosis. A subset of patients who meet the diagnostic criteria for idiopathic pulmonary fibrosis may be subsequently diagnosed as having fibrotic hypersensitivity pneumonitis after careful evaluation by experts who are familiar with hypersensitivity pneumonitis. Hypersensitivity pneumonitis can be diagnosed with high confidence in patients in whom an exposure has been identified by history or by serum IgG antibodies against associated antigens or a specific inhalation challenge, a typical pattern on HRCT imaging, and lymphocytosis on bronchoalveolar lavage.[21]

TREATMENT AND PROGNOSIS

A thorough investigation must be undertaken to identify the antigen in the patient's environment. Sometimes an industrial hygienist is needed to obtain samples for culture from potential sources in the patient's domestic or workplace environment. The identified antigen must be eradicated from the patient's environment. Avoidance of exposure to the identified antigen or antigens and treatment with corticosteroids (see Table 80-5) are important if improvement is to be obtained. However, despite thorough searches, the antigen may remain undetected in a substantial number of patients who have hypersensitivity pneumonitis confirmed by lung biopsy. Corticosteroids (0.5 to 1 mg/kg daily) and immune-modulating agents (e.g., mycophenolate usually at 1000 to 1500 mg bid and azathioprine usually at 100 to 150 mg daily) are useful for patients with nonfibrotic hypersensitivity pneumonitis. Continued exposure to the unidentifiable antigens, prolonged exposure to antigens, or both can lead to chronic pneumonitis and irreversible fibrosis that may not respond to any treatment regimen. In the fibrotic stages, the prognosis and clinical course may be similar to those of idiopathic pulmonary fibrosis, and antifibrotic agents used for idiopathic pulmonary fibrosis may slow the progression of the disease.

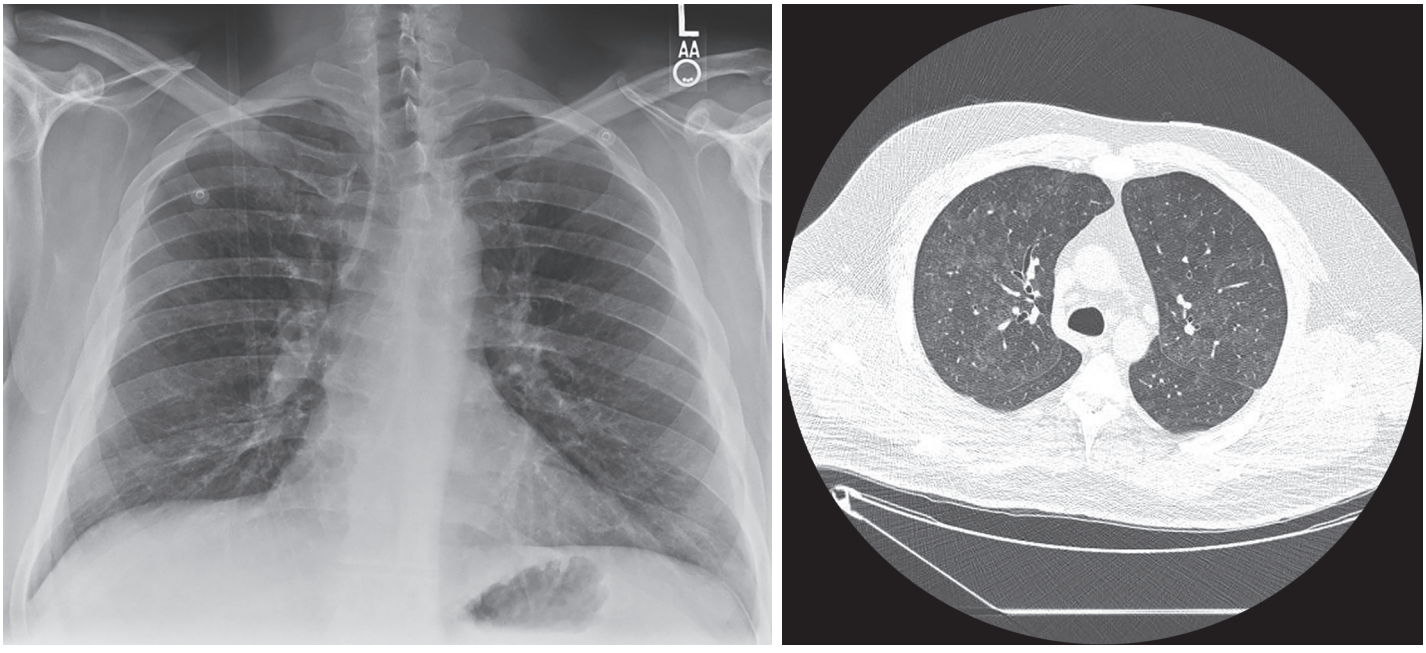

E-FIGURE 80-7. Chest radiograph *(left)* and computed tomography scan *(right)* on the same patient with hypersensitivity pneumonitis. Note the centrilobular nodules and ground-glass opacities on the computed tomography scan.

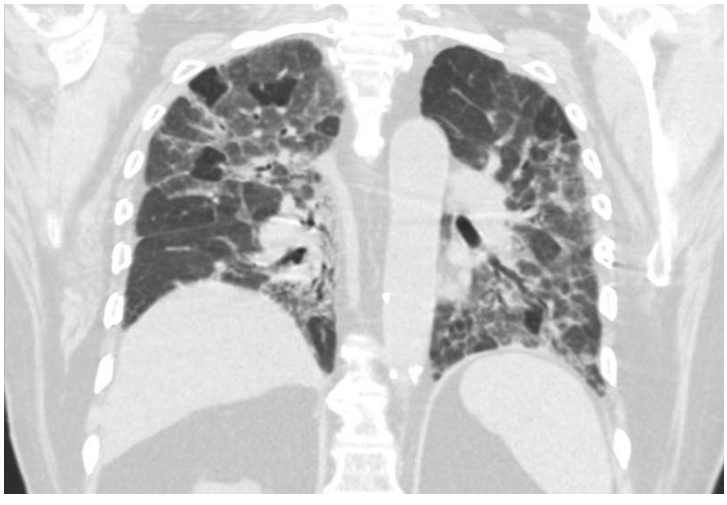

E-FIGURE 80-8. Upper lobe air trapping and mosaic attenuation in a patient with hypersensitivity pneumonitis.

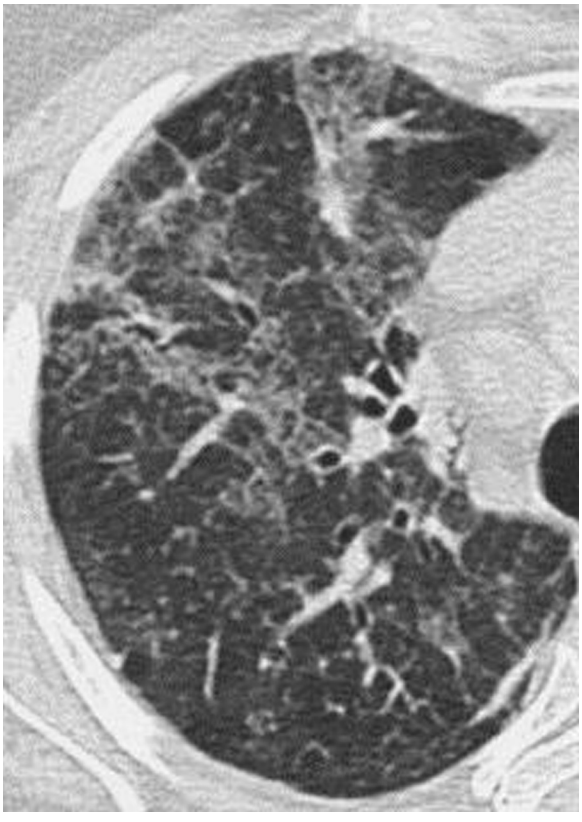

E-FIGURE 80-9. Upper lobe nodular and patchy fibrosis in a patient with chronic hypersensitivity pneumonitis.

OCCUPATIONAL INTERSTITIAL LUNG DISEASES

Interstitial lung diseases associated with specific occupations generally involve the inhalation and deposition of dust in the lungs followed by a tissue reaction that ultimately results in fibrosis. Examples include silicosis (inhalation of silica in crystalline form or silicon dioxide as quartz, cristobalite, or tridymite; at-risk occupations include sandblasting and working with granite), coal workers' pneumoconiosis (inhalation of coal dust), asbestosis (deposition of fibers during mining, milling, or other handling of asbestos; welding and working in a shipyard are two at-risk occupations), berylliosis (seen in aerospace workers and in electronic industries), and hard metal disease (Chapter 81). Radiographic features vary depending on the inciting inhalant. Cessation of the exposure is important, but the fibrosis is generally irreversible.

DRUG-INDUCED INTERSTITIAL LUNG DISEASE

More than 300 drugs, biomolecules, or homeopathic remedies (see Table 80-2) can cause acute, subacute, or chronic interstitial lung disease, and the list continues to increase as new medications are introduced (https://www.pneumotox.com). The clinical and radiographic manifestations are quite varied. Examples of known syndromes include chronic nitrofurantoin-induced interstitial lung disease that mimics idiopathic pulmonary fibrosis (and is fatal in ≈8% of cases), granulomatous pneumonitis secondary to methotrexate (<5%), sarcoid-like granulomatous interstitial lung disease induced by interferon-α and tumor necrosis factor–modulating agents, nonspecific bilateral alveolar and interstitial inflammatory and fibrotic abnormalities caused by bleomycin, immune-modulating agents and other chemotherapeutic agents, and alveolar and interstitial abnormalities and nodular densities in acute and chronic amiodarone pulmonary toxicity. Most drug-induced interstitial lung disease is reversible if recognized early and if use of the responsible drug is discontinued. In addition to discontinuing the implicated drug, treatment with corticosteroids (see Table 80-5) is indicated in patients with moderate to severe functional impairment.

ALVEOLAR FILLING DISORDERS

In alveolar filling disorders (Chapter 79), air spaces distal to the terminal bronchioles are filled with blood, lipid, protein, water, or inflammatory cells. The radiographic appearance is that of an alveolar infiltrate with small nodular densities and ill-defined margins; hence, the radiographic picture is similar to an interstitial lung disease, and virtually all the alveolar filling disorders may result in interstitial lung disease, including Goodpasture syndrome, pulmonary alveolar proteinosis (primary and secondary), alveolar hemorrhage syndromes (Chapter 79), acute interstitial pneumonia, and bronchoalveolar cell carcinoma (Chapter 177).

IDIOPATHIC PULMONARY HEMOSIDEROSIS

This rare disorder of children and young adults (Chapter 79) is characterized by intermittent, diffuse alveolar hemorrhage without evidence of vasculitis, inflammation, granulomas, or necrosis. The etiology is poorly understood. Anemia and hepatosplenomegaly may be present. Hemosiderin-laden macrophages in bronchoalveolar lavage fluid and lung tissue are part of the diagnostic picture. The chest radiograph reveals diffuse, bilateral alveolar infiltrates. A chronic interstitial infiltrate may develop after repeated episodes, infrequently with hilar and mediastinal adenopathy. Systemic corticosteroids (see Table 80-5) may be beneficial in treating acute disease.

CHRONIC EOSINOPHILIC PNEUMONIA

The clinical manifestation of chronic eosinophilic pneumonia varies over a wide spectrum, from asymptomatic to respiratory failure. The disease often occurs in women in the second to fourth decades of life; such women often manifest constitutional symptoms of fevers, sweats, weight loss, fatigue, dyspnea, and cough. Peripheral blood eosinophilia (Chapter 156), usually at levels of 10 to 40%, is common but may be absent in up to one third of affected patients at initial evaluation. On chest radiography and HRCT, the cardinal feature is peripheral multifocal consolidation, predominantly in the upper and mid lung zones. These dense peripheral infiltrates, which have sometimes been called the "photographic negative of pulmonary edema," often resolve dramatically after treatment with corticosteroids. Ground-glass attenuation commonly accompanies the consolidation. Bronchoalveolar lavage fluid may show greater than 40% eosinophils during exacerbations. Treatment with corticosteroids (see Table 80-5) results in a rapid response, frequently within hours; in fact, such a dramatic resolution of symptoms with radiographic clearance of infiltrates shortly after initiation of corticosteroid therapy is considered "diagnostic." However, the rate of relapse is high, so most patients require prolonged treatment with low-dose corticosteroids (prednisone, 5 to 10 mg/day) to stay in remission.

INTERSTITIAL LUNG DISEASE ASSOCIATED WITH PULMONARY VASCULITIDES

GRANULOMATOSIS WITH POLYANGIITIS

Granulomatosis with polyangiitis (Chapter 249) is the most common form of vasculitis that involves the lung. The systemic necrotizing granulomatous inflammation and small-vessel vasculitis are often manifested first in the upper respiratory tract as chronic rhinitis or sinusitis (or both), epistaxis, oropharyngeal ulcerations, gingival hyperplasia with clefting, or serous otitis media. Destruction of the nasal cartilage may lead to septal perforation or a saddle nose deformity. Ulcerative lesions of the tracheobronchial tree, cavitating nodules within the lung parenchyma, and diffuse alveolar hemorrhage caused by pulmonary capillaritis are lower respiratory tract manifestations. Focal segmental necrotizing glomerulonephritis is the most common extrathoracic manifestation, although pulmonary involvement may occur without renal disease. Chest radiography usually reveals multiple nodular or cavitating infiltrates, but single nodules may be found as well. The diagnosis is most commonly made serologically, with demonstration of antineutrophil cytoplasmic antibodies, although a negative test result does not exclude the disease. Treatment is usually with cyclophosphamide (50 to 100 mg/day or 2 mg/kg of ideal body weight per day but not more than 150 mg/day) in conjunction with oral corticosteroids (prednisone, 10 to 40 mg/day). Initial remission occurs in more than 90% of patients, but most patients require treatment for several years. Relapses may occur in up to 30% of patients, especially when treatment is tapered; such patients may need treatment indefinitely. Rituximab has become a first-line therapy for anti-neutrophil cytoplasma antibody (ANCA) associated vasculitis (remission-induction dose of 375 mg/m^2 body-surface area typically infused once a week for 4 weeks) (Chapter 249). Prophylaxis for *Pneumocystis jiroveci* infection is indicated in patients receiving chronic treatment.

EOSINOPHILIC GRANULOMATOSIS WITH POLYANGIITIS

This systemic necrotizing vasculitis, previously known as Churg-Strauss syndrome (Chapter 249), affects both the upper and lower respiratory tracts and is almost invariably preceded by allergic disorders such as asthma, allergic rhinitis, sinusitis, or a drug reaction. Peripheral and lung eosinophilia, bronchospasm, increased immunoglobulin E levels, and rashes are common manifestations. The pulmonary radiographic findings are bilateral patchy, fleeting infiltrates; diffuse nodular infiltrates; or diffuse reticulonodular disease. Histopathologic examination of lung tissue is generally diagnostic with features of granulomatous angiitis or vasculitis. Although treatment with corticosteroids is indicated, the dosage and duration are unclear (see Table 80-5). Response rates are high when mepolizumab (an anti-IL-5 monoclonal antibody at a dose of 300 mg administered subcutaneously every 4 weeks) is added to standard care.[A15] Additional immunosuppression, usually with cyclophosphamide (2 mg/kg/day orally or an initial intravenous pulse dose of 15 mg/kg or 0.6 g/m^2 to maximum dose of 1.2 g), is often used to achieve disease control particularly in severe disease.

IDIOPATHIC PULMONARY CAPILLARITIS

Idiopathic pulmonary capillaritis may involve the pulmonary vasculature within the alveolar walls and be manifested as interstitial lung disease. Patients may also have subclinical alveolar hemorrhage, often associated with the presence of perinuclear antineutrophilic cytoplasmic antibodies. Corticosteroids are the mainstay of treatment, but the doses and duration of treatment are unclear. Frequently, patients need adjunctive treatment with cyclophosphamide or rituximab, similar to patients with vasculitis and granulomatosis with polyangiitis (Chapter 249).

OTHER FORMS OF INTERSTITIAL LUNG DISEASE

SARCOIDOSIS

See Chapter 83.

PULMONARY LANGERHANS CELL HISTIOCYTOSIS

Langerhans cell histiocytosis is an idiopathic, granulomatous interstitial lung disease that typically occurs in the second or third decade of life, with a male preponderance (Chapter 155). The currently accepted term is pulmonary Langerhans cell histiocytosis. It is rare, with an estimated incidence of two to five cases per million population. The large majority (about 90%) of affected individuals are male smokers, and current evidence suggests that the disorder results from an abnormal immune response to a component or derivative of cigarette smoke. The disease is thought to be a myeloid neoplasm, with a high

proportion of cells carrying somatic mutations in the *BRAF* gene and/or in the *NRAS*, *KRAS*, and *MAP2K1* genes.

CLINICAL MANIFESTATIONS

The clinical findings are variable and range from an abnormal chest radiograph in an asymptomatic patient to progressive dyspnea with a nonproductive cough. Systemic symptoms of malaise, fever, and weight loss may be present. Hemoptysis is rare. Spontaneous pneumothorax, which occurs in approximately 25% of patients and is caused by rupture of subpleural cysts, may be an initial finding. Langerhans cell histiocytosis may be confined to the lung or may be a component of a multisystem disease that includes painful cystic bone lesions and diabetes insipidus (Chapter 206).

DIAGNOSIS

The chest radiograph shows diffuse symmetrical reticulonodular opacities superimposed on multiple small cysts in the upper and mid lung zones. HRCT reveals subpleural nodules, scattered ground-glass densities, and irregular cysts of varying number, size, and configuration in both lungs, with sparing of the lung bases (E-Fig. 80-10). In the appropriate clinical setting, this pattern may be pathognomonic.[22] As the disease progresses, the increase in fibrosis and cysts may lead to honeycombing of the lung. PFTs are characterized by a mixed restrictive and obstructive pattern, including a reduction in diffusing capacity. Vital capacity is disproportionately reduced compared with TLC because of air trapping within the cysts; the result is an increased residual volume. Bronchoalveolar lavage reveals Langerhans cells (atypical histiocytes) that have the characteristic "x body" (i.e., Birbeck granule) on electron microscopy; immunostaining shows CD1 antigen on the cell surface and S-100 protein in the cytoplasm. However, the absence of these findings does not exclude the diagnosis. The diagnosis is usually made by transbronchial biopsy or surgical lung biopsy, which reveals interstitial and peribronchiolar collections of histiocytes, eosinophils, and lymphocytes; peribronchiolar nodules; and cysts with areas of central stellate fibrosis.

TREATMENT AND PROGNOSIS

Although definitive regression after discontinuation of smoking has not been proved, small series report improvement, so patients should be encouraged to discontinue smoking.[23] The prognosis in pulmonary Langerhans cell histiocytosis is usually favorable, with approximately 75% of patients improving or stabilizing, especially with cessation of smoking; some patients, however, may progress to end-stage lung disease. In patients with progressive disease, corticosteroids (see Table 80-5) with or without vincristine, vemurafenib in patients with *BRAF* V600 mutations, arabinoside, cyclosporine, cyclophosphamide, and azathioprine have been used with some anecdotal reports of success. Lung transplantation has been performed, but recurrent disease has been reported in the allograft.

LYMPHANGIOLEIOMYOMATOSIS

This rare interstitial lung disease is limited to women, primarily of childbearing age. The two clinical forms are sporadic disease and tuberous sclerosis complex–associated disease (Chapter 385).[24] The disorder is thought to reflect tuberous sclerosis complex 1 or 2 mutations that regulate the mammalian target of rapamycin (mTOR) pathway. Proliferation of abnormal smooth muscle around bronchioles leads to bilateral small cysts (E-Fig. 80-11), which give an appearance of interstitial lung disease on chest radiographs, and progressive impairment of lung function. Hemoptysis, pneumothorax (from rupture of subpleural cysts), and chylothorax (from lymphatic obstruction) may be initial symptoms that distinguish this disorder from other diffuse lung diseases. Although lymphangioleiomyomatosis is usually limited to the lungs, angiomyolipomas of the mediastinal and retroperitoneal lymph nodes and kidney can mimic the manifestations of tuberous sclerosis (Chapter 385). Coarse reticulonodular infiltrates, often with cysts or bullae, are typically seen on chest radiographs. In contrast to most other interstitial lung diseases, increased lung volumes may be present and should prompt consideration of this diagnosis in a nonsmoking woman of reproductive age. HRCT shows characteristic diffuse thin-walled cysts, generally less than 2 cm in diameter. For women who have cystic changes on HRCT of the chest but have no additional clinical, radiologic, or serologic features of lymphangioleiomyomatosis, a clinical diagnosis is based on a combination of characteristic HRCT features plus one or more of the following: presence of tuberous sclerosis complex, angiomyolipomas, chylous effusions, lymphangioleiomyomas, or an elevated serum vascular endothelial growth factor-D (VEGF-D) level of 800 pg/mL or higher. When a definitive diagnosis is required in patients who have characteristic parenchymal cysts on HRCT but no additional confirmatory features, transbronchial lung biopsy should be considered before a surgical lung biopsy.

Bronchoalveolar lavage may show occult alveolar hemorrhage. Lung biopsy reveals abnormal smooth muscle cells lining the airways, lymphatics, and blood vessels, with concurrent airflow obstruction and replacement of the lung parenchyma with cysts.

TREATMENT AND PROGNOSIS

Sirolimus, an inhibitor of rapamycin signaling, initially at 2 mg/day and titrated to maintain trough levels between 5 and 15 ng/mL, can safely stabilize lung function. Treatment with progesterone or tamoxifen has been tried, but no randomized trials support the use of interventions to alter the estrogen–progesterone balance. Although lung transplantation is indicated as the patient reaches severe functional impairment, the disease may recur in the transplanted lung. Most patients currently die of respiratory failure about 10 years after the onset of symptoms.

INHERITED DISORDERS

Several rare genetic disorders are associated with interstitial lung disease and pulmonary fibrosis. Inheritance is autosomal dominant with variable penetrance for most cases of familial idiopathic pulmonary fibrosis and familial idiopathic interstitial pneumonia and for tuberous sclerosis (Chapter 385), neurofibromatosis (Chapter 385), and familial hypocalciuric hypercalcemia (Chapter 227). Inheritance is autosomal recessive for Gaucher disease (Chapter 192), Niemann-Pick disease (Chapter 192), and Hermansky-Pudlak syndrome (Chapter 192). The congenital form of the alveolar filling disorder pulmonary alveolar proteinosis also is inherited in an autosomal recessive manner.

Tuberous sclerosis (Chapter 385), an autosomal dominant disease of variable penetrance, is characterized pathologically by the presence of hamartomas in multiple organs. The most well-known clinical manifestations include epilepsy, developmental delay, adenoma sebaceum, and renal angiomyolipomas. Interstitial lung disease occurs in only 1% of patients with tuberous sclerosis, usually in women older than 30 years with little or no mental retardation. The pulmonary involvement, which is indistinguishable from lymphangioleiomyomatosis both radiographically and histopathologically, may be manifested as exertional dyspnea, recurrent pneumothorax, and hemoptysis. HRCT reveals thin-walled cysts and a diffuse reticulonodular infiltrate. Recurrent parenchymal hemorrhage may lead to hemosiderin deposition and interstitial pulmonary fibrosis. There is no cure, and treatment is supportive.

Neurofibromatosis (Chapter 385) may affect all age groups and both sexes. Type 1 (von Recklinghausen disease) is characterized by café au lait spots, neurofibromas, optic glioma, and bony lesions; the rarer type 2 is associated with bilateral acoustic neuromas. Diffuse interstitial lung disease is manifested as bilateral lower lobe fibrosis as well as bullae or cystic changes. Interstitial fibrosis and alveolitis with thickening of the alveolar septa, accompanied by a cellular infiltrate, are seen on lung biopsy. Management is as for idiopathic pulmonary fibrosis.

Gaucher disease (Chapter 192), a lysosomal glycolipid storage disorder, has a predilection for the Ashkenazi Jewish population. Pulmonary manifestations, which occur most frequently in type 2 disease, may be a result of interstitial infiltration by Gaucher cells with fibrosis, alveolar consolidation, and filling of alveolar spaces; capillary plugging by Gaucher cells may cause secondary pulmonary hypertension. Treatment is as for the systemic disease, and the general approaches for idiopathic interstitial pneumonias and pulmonary arterial hypertension may be followed for these patients.

Niemann-Pick disease (Chapter 192) is a rare lipid storage disease that may cause infiltration of the characteristic "foam cell" throughout the pulmonary lymphatics, the pulmonary arteries, and the pulmonary alveoli. Patients with type B may survive into adulthood. Treatment is as for the systemic disease.

Hermansky-Pudlak syndrome (Chapter 192) is characterized by oculocutaneous albinism, a bleeding diathesis, and ceroid inclusions in macrophages. Most patients are of Puerto Rican ancestry, and women are affected more frequently than men. Pulmonary fibrosis, with onset in the third or fourth decade, is slowly progressive. Treatment principles and interventions are largely supportive and extrapolated from other related conditions, especially idiopathic pulmonary fibrosis.

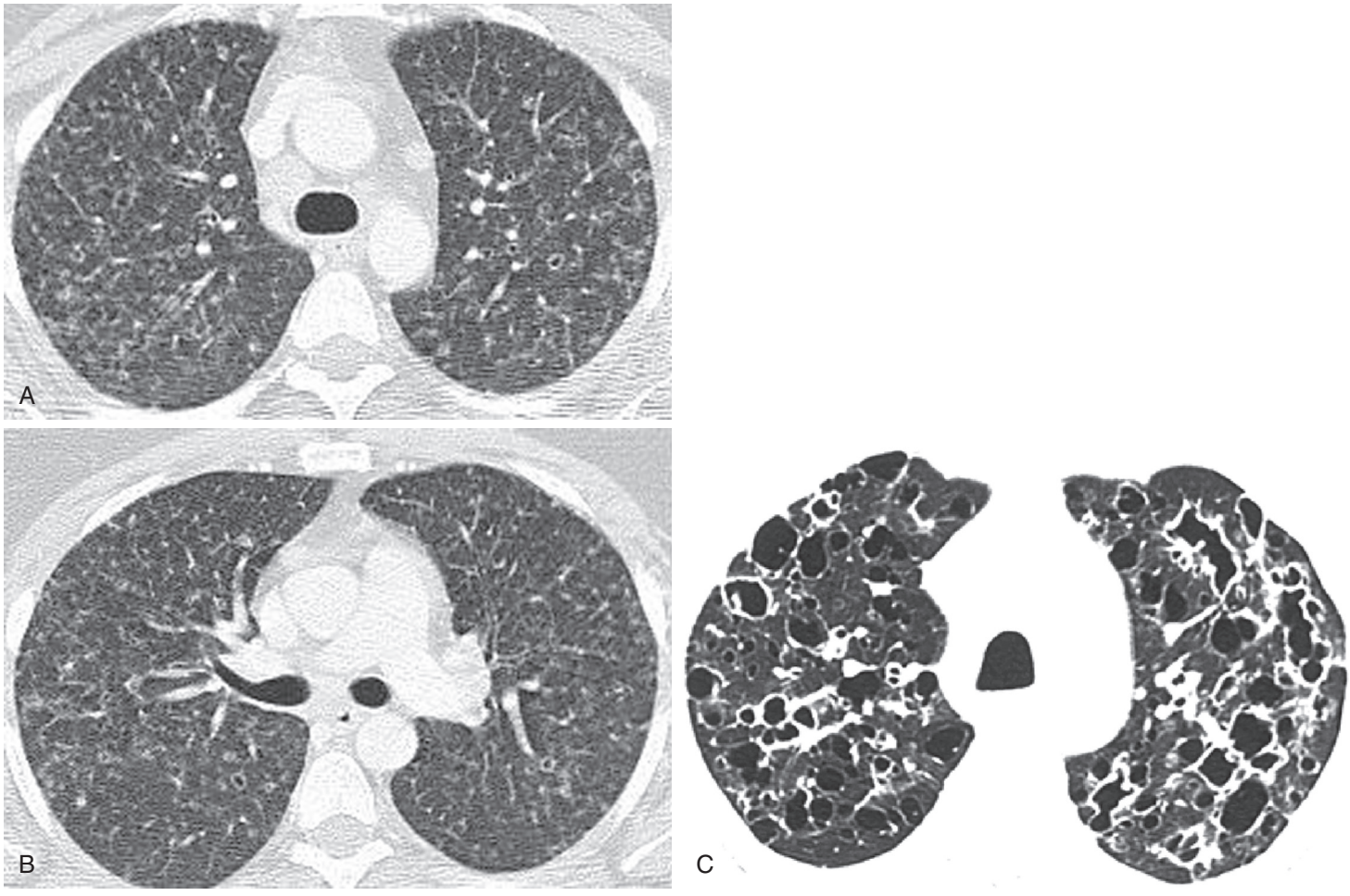

E-FIGURE 80-10. Pulmonary Langerhans cell histiocytosis. High-resolution computed tomography reveals subpleural nodules, scattered ground-glass densities (**A** and **B**), and irregular cysts of varying number and size (**C**).

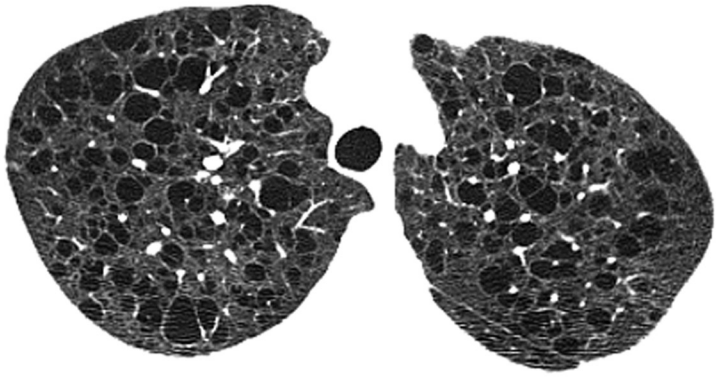

E-FIGURE 80-11. Bilateral thin wall cysts in a patient with lymphangioleiomyomatosis.

Short telomere syndromes are a group of rare genetic disorders that are caused by mutations of the telomere complex, including the telomerase reverse transcriptase *(TERT)*, the telomerase RNA component *(TERC)*, poly(A)-specific ribonuclease *(PARN)*, regulator of telomere elongation helicase 1 *(RTEL1)*, and TERF1 interacting nuclear factor 2 *(TINF2)*.[25] The prevalence of telomerase mutations in lung disease makes the short telomere syndromes the most-common premature aging disorders, with an estimated 10,000 affected adult individuals in the United States alone. The most common short telomere syndromes are interstitial lung diseases, including idiopathic pulmonary fibrosis. Approximate 10 to 25% of patients with familial pulmonary fibrosis have mutations in a telomerase enzyme gene, as do a smaller percentage of sporadic cases. Although specific criteria are evolving, genetic testing for telomere variants has been suggested in patients with a family history of interstitial lung disease, patients with early-onset idiopathic pulmonary fibrosis (<50 years), and patients who have extrapulmonary features suggesting a telemeropathy.[26]

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81 OCCUPATIONAL LUNG DISEASE

SUSAN M. TARLO AND CARRIE A. REDLICH

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When evaluating any respiratory disease, the clinician should consider the possibility of an occupational cause or contribution (see E-Fig. 16-1; see Table 81-1).[2] The onset of disease after an occupational exposure may occur with a short latency period, as for an acute toxic inhalation injury, or over a period of months to years, as for occupational asthma or hypersensitivity pneumonitis. Latency can be 20 years or more for pneumoconioses such as asbestosis or silicosis, for chronic beryllium disease, or for lung cancer from asbestos or other carcinogens. The most relevant job and occupational exposure history will therefore depend in part on the type of lung disease: for acute syndromes, the recent job exposure is most relevant; for asthma or hypersensitivity pneumonitis, the exposures at the onset of symptoms and ongoing exposures are most relevant; but for chronic diseases or diseases that may result from a long latency exposure, a full working history is essential. Consideration also should be given to potentially relevant exposures that may be related to a patient's hobbies or avocations (e.g., woodworking, model building, or insect collecting).

The clinical relevance of a correct occupational attribution is most apparent for diseases with a close temporal relationship between exposure and the onset of symptoms because intervention to reduce or remove exposure may reverse the disease or prevent progression. In addition, interventions in the workplace may reduce or prevent disease in other workers. However, even for diseases with a potential long latency, such as chronic beryllium disease, identification of disease in one worker should be regarded as a sentinel event that can lead to investigation of the workplace exposures and introduction of preventive measures. The implementation of occupational health interventions can reduce adverse pulmonary events.[3] With the assistance of their physicians, workers with occupational lung diseases also often can qualify for workers' compensation.

EPIDEMIOLOGY

Work-related lung diseases frequently go unrecognized and unreported, so no reliable figures exist for the total incidence or prevalence of occupational lung diseases. Furthermore, regional variations in occupations and exposures are substantial. Nevertheless, work-related asthma has become the most common chronic occupational lung disease in developed countries, where occupational asthma (asthma caused by work) accounts for about 15% of all adult-onset asthma, and work-exacerbated asthma occurs in 25 to 52% of asthmatic workers. The occupational contribution of workplace dusts, fumes, and gases to chronic obstructive pulmonary disease (COPD) is estimated at 15%.[4]

Pneumoconiosis from silica or coal dust, although more important in developing countries,[5] still persists in developed countries. For example, although the total number of cases of coal miners with pneumoconiosis has fallen in the United States substantially since the 1970s, since about 2000 the prevalence of coal workers pneumoconiosis has risen from approximately 5% to over 10% nationally and to over 20% in some regions, especially among long-tenured (>25 years) underground coal miners. In some regions, mortality rates have also started to rise again, especially in smaller mines, and silicosis continues to occur in industries such as construction and sandblasting where exposures can be more challenging to monitor and control. Newer work settings that can cause silicosis include the textile industry's use of jet silica blasting of denim jeans, the use of artificial stone for kitchen counters, and hydraulic fracturing (fracking) to extract oil and gas from subterranean deposits. Because of the persistence of silicosis in the United States, standards were implemented in 2018[6] to lower the permissible exposure limit and to mandate medical surveillance of workers who have exposures above this limit.

Newly recognized asbestos-related cases continue to occur, owing to the long latency period between exposure and clinical disease, despite the declining exposure to asbestos in developed countries. Although annual deaths from asbestosis have now reached a plateau in North America and will likely decline, asbestosis continues to increase worldwide,[7] and new cases of mesothelioma, which has a latency of up to 35 years or more, are expected to plateau in the next few years.

SPECIFIC OCCUPATIONAL LUNG DISORDERS

Occupational lung diseases are often misdiagnosed as other common nonoccupational diseases, but a careful history and appropriate investigations can lead to a correct diagnosis. For many occupational lung diseases, the diagnosis

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Short telomere syndromes are a group of rare genetic disorders that are caused by mutations of the telomere complex, including the telomerase reverse transcriptase *(TERT)*, the telomerase RNA component *(TERC)*, poly(A)-specific ribonuclease *(PARN)*, regulator of telomere elongation helicase 1 *(RTEL1)*, and TERF1 interacting nuclear factor 2 *(TINF2)*.[25] The prevalence of telomerase mutations in lung disease makes the short telomere syndromes the most-common premature aging disorders, with an estimated 10,000 affected adult individuals in the United States alone. The most common short telomere syndromes are interstitial lung diseases, including idiopathic pulmonary fibrosis. Approximate 10 to 25% of patients with familial pulmonary fibrosis have mutations in a telomerase enzyme gene, as do a smaller percentage of sporadic cases. Although specific criteria are evolving, genetic testing for telomere variants has been suggested in patients with a family history of interstitial lung disease, patients with early-onset idiopathic pulmonary fibrosis (<50 years), and patients who have extrapulmonary features suggesting a telemeropathy.[26]

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EPIDEMIOLOGY

Work-related lung diseases frequently go unrecognized and unreported, so no reliable figures exist for the total incidence or prevalence of occupational lung diseases. Furthermore, regional variations in occupations and exposures are substantial. Nevertheless, work-related asthma has become the most common chronic occupational lung disease in developed countries, where occupational asthma (asthma caused by work) accounts for about 15% of all adult-onset asthma, and work-exacerbated asthma occurs in 25 to 52% of asthmatic workers. The occupational contribution of workplace dusts, fumes, and gases to chronic obstructive pulmonary disease (COPD) is estimated at 15%.[4]

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SPECIFIC OCCUPATIONAL LUNG DISORDERS

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ABSTRACT

Occupational lung diseases include a wide spectrum of respiratory disorders with symptoms, signs, and diagnostic test results that often present with features similar to nonoccupational diseases. For example, adult-onset asthma may be occupational asthma, presumed sarcoidosis may actually be chronic beryllium disease, apparent idiopathic pulmonary fibrosis may be asbestosis, or a suspected viral pneumonia may be hypersensitivity pneumonitis from an occupational cause such as contaminated metal-working fluid. Therefore, when evaluating any respiratory disease, the clinician should consider the possibility of an occupational cause or contribution that should be further suspected and investigated with an appropriate work history. The onset of disease after an occupational exposure may occur with a short latency period, as for an acute toxic inhalation injury, or over a period of months to years, as for occupational asthma or hypersensitivity pneumonitis. Conversely, the latency period between exposure and the clinical presentation of disease can be 20 years or more in chronic beryllium disease or lung cancer from chromium, asbestos, or other carcinogens. The most relevant job and occupational exposure history will therefore depend in part on the type of lung disease. For acute syndromes, the recent job exposure is most relevant, but for asthma or hypersensitivity pneumonitis, the exposures at the onset of symptoms and ongoing exposures are most relevant. For chronic diseases or diseases that may develop after a long latency period after exposure, a full working history is essential. Consideration also should be given to potentially relevant exposures that may be related to a patient's hobbies or avocations (e.g., woodworking, model building, or insect collecting) or home environment (e.g., mold, dampness, pets).

KEYWORDS

occupational lung disease
work-related asthma
chronic beryllium disease
occupational COPD
occupational hypersensitivity pneumonitis

TABLE 81-1 EXAMPLES OF OCCUPATIONAL RESPIRATORY DISEASES THAT COULD BE MISDIAGNOSED AS COMMON NONOCCUPATIONAL RESPIRATORY DISEASE

DISEASE THAT IS MIMICKED	POSSIBLE OCCUPATIONAL DISEASE	EXAMPLES OF FEATURES THAT SUPPORT AN OCCUPATIONAL DIAGNOSIS
Asthma	Occupational asthma from a work sensitizer	Asthma symptoms begin and are worse during a working period, with some improvement on days or weeks off work. Exposure to a workplace sensitizer
	Occupational asthma—irritant induced, including reactive airways dysfunction syndrome	Asthma begins within days after a high-level (accidental) workplace exposure or begins months to years after repeated more moderate levels of exposures (less definitive)
	Work-exacerbated asthma	History of prior asthma. Severity is worse at work and/or improves away from work and work exposures
COPD	Occupational COPD	Prolonged exposure at work to dusts, fumes, or gases regardless of smoking status
Pneumonia	Acute hypersensitivity pneumonitis	Symptoms typically resolve within days and recur on re-exposure to the same work trigger (e.g., metal-working fluid, moldy hay, humidifiers)
Acute viral respiratory illness or pneumonia	Humidifier fever, organic dust toxic syndrome, metal fume fever, polymer fume fever, cotton dust fever	Work exposures trigger the episodes
Sarcoidosis	Chronic beryllium disease	History of exposure to beryllium dust or fumes up to 30 years or more before onset of disease
	Silicosis	History of exposure; typical radiographic findings of rounded opacities with upper lobe predominance and/or progressive massive fibrosis
Idiopathic pulmonary fibrosis	Asbestosis	History of moderate or high asbestos exposure and appropriate latency period, often with pleural plaques
	Chronic hypersensitivity pneumonitis	± Work exposure to a known trigger, ± improvement during periods away from exposure
	Hard metal disease	History of exposure to hard metal (e.g., tungsten, cobalt), with giant cell pneumonitis noted on lung biopsy
	Flock-worker's lung	Lymphocytic bronchiolitis and interstitial lung disease from nylon/synthetic textile microfibers
Pulmonary fibrosis or alveolar proteinosis	Silicoproteinosis, indium lung	Exposure to silica, exposure to indium–tin oxide in making of flat screens
Pulmonary chest infections	Occupational causes of chest infections (e.g., SARS-CoV-2 or TB in health care workers, TB in miners, histoplasmosis in construction workers, anthrax in wool workers or farmers)	History of relevant occupation and/or work exposures
Pleural effusion	Asbestos-related benign pleural effusion	History of previous asbestos exposure with appropriate latency; pleural plaques may be present
Incidental pulmonary nodule	Rounded atelectasis from asbestos	History of previous asbestos exposure with appropriate latency; pleural plaques commonly present
Multiple nodules	Silicosis or pneumoconiosis	History of silica or other causative dust exposure, distribution of nodules, presence of progressive massive fibrosis
Lung cancer	Occupational lung cancer	History of work exposure to lung carcinogens (e.g., asbestos, radon, chromium, diesel exhaust fumes) with an appropriate latency period
Bronchiolitis obliterans	Popcorn lung; bronchiolitis in military personnel	History of working with microwave popcorn or flavorings; history of deployment in Southeast Asia with exposure to burn pits and other irritants

COPD = chronic obstructive pulmonary disease; SARS-CoV-2 = severe acute respiratory syndrome coronavirus 2; TB = tuberculosis.

can significantly improve prognosis and lead to measures to prevent illness in other workers.

WORK-RELATED ASTHMA

Work-related asthma includes both occupational asthma that is caused by work and asthma that is not caused by work but is exacerbated by work exposures.

SENSITIZER-INDUCED OCCUPATIONAL ASTHMA

EPIDEMIOLOGY

Occupational asthma is most commonly associated with a specific immune response to a high- or low-molecular-weight sensitizer[8] (Table 81-2). Sensitizer-induced occupational asthma usually affects no more than 5 to 20% of workers exposed to the sensitizing agent, but exposure to complex platinum salts or detergent enzymes may result in symptoms in about 50% of highly exposed workers. In most studies, higher levels of exposure are associated with higher rates of sensitization in the exposed populations, but there is no clear threshold exposure below which all workers are protected from the risk for sensitization. Overall, work exposures may cause or worsen about 10 to 15% of cases of adult asthma.[9]

PATHOBIOLOGY

Genetic factors increase the risk for sensitization, but the risks appear to be polygenic and may differ for different allergens and sensitizers. Underlying atopy, as exemplified by a history of allergy or positive skin tests to common environmental allergens (Chapter 230), carries an increased risk for sensitization to the high-molecular-weight allergens, and smoking (Chapter 363) has been reported as a risk factor for sensitization to complex platinum salts. Currently, no host factors are sufficiently specific to justify exclusion of workers from settings with exposure to potential sensitizers. Occupational asthma from a high-molecular-weight allergen is associated with specific immunoglobulin E (IgE) antibody production. Low-molecular-weight sensitizers may act as haptens or may induce neoantigens by reacting with proteins in vivo, but specific IgE antibodies have been demonstrated with only a few low-molecular-weight sensitizers, such as complex platinum salts, acid anhydrides used in epoxy compounds, and sometimes with isocyanates used to make polyurethane coatings, foam, and adhesives.[10]

CLINICAL MANIFESTATIONS

Sensitizer-induced occupational asthma has a latency period ranging from weeks to several years before it develops, but most patients develop symptoms within the first few years of exposure. After a patient has become sensitized

TABLE 81-2 COMMON OCCUPATIONS AT RISK FOR WORK-RELATED ASTHMA AND CAUSATIVE EXPOSURES

SELECTED OCCUPATIONS AT RISK	
SENSITIZER-INDUCED OCCUPATIONAL ASTHMA	**ALLERGEN, SENSITIZER**
Bakers	Wheat, rye, fungal amylase in flour
Laboratory workers	Animal allergens (e.g., proteins in rat urine, mouse or rabbit dander), chemical sensitizers (e.g., glutaraldehyde, anhydrides, diamines)
Detergent making, medical instrument cleaning, pharmaceuticals	Enzymes (e.g., *Bacillus subtilis,* pancreatic enzymes)
Farmers	Grains, plant, and animal allergens; mites, fungi
Greenhouse workers, florists, woodworkers	Pollen, fungi, mites, wood dusts
Food workers	Airborne food allergens (e.g., powdered milk or eggs and vegetables)
Health care workers	Cleaning products (e.g., quaternary ammonium compounds, glutaraldehyde), latex, aerosolized medications
Factory or other industrial workers	Chemical sensitizers (e.g., isocyanates, epoxies) in spray paints, glues, polyurethane, coatings, spray foam insulation, and adhesives
Electronic workers, machinists	Soldering flux with colophony, metal-working fluids
WORK-EXACERBATED ASTHMA	**TRIGGERS**
Any occupation with exposure to asthma triggers at work (e.g., office workers, teachers, factory workers, construction workers, transportation workers)	Typical asthma triggers (irritants and allergens), including dusts, fumes, smoke, mold, dampness, common environmental allergens, cleaning products, perfumed products, extreme temperatures

and has developed asthma, even very small subsequent exposures can trigger asthma, sometimes including exposures that may be below the limit of measurable detection. Pulmonary function and histologic changes are similar to those in nonoccupational asthma (Chapter 75). Sensitizer-induced occupational asthma from a high-molecular-weight agent sensitizer typically causes a prompt asthmatic response within minutes after exposure with or without a late asthmatic response starting 4 to 6 hours after exposure. By comparison, responses to low-molecular-weight sensitizers typically start 4 to 6 hours after exposure.

DIAGNOSIS

The diagnosis of sensitizer-induced occupational asthma is clinically suspected by history and should be considered in all cases of new-onset asthma in patients who work.[11] Supportive features include symptomatic improvement when away from work, such as weekends off work or holidays but not necessarily in the evenings after a work shift, when symptoms from a late asthmatic response may occur. In patients who are exposed to high-molecular-weight sensitizers, allergic rhinitis or conjunctivitis associated with work frequently appears before the development of asthma. A detailed occupational history (Chapter 16) or review of Material Safety Data Sheets or occupational hygiene reports may reveal a known occupational sensitizer. However, more than 300 occupational respiratory sensitizers are currently known, and new agents or exposures are reported each year; as a result, the absence of a recognized sensitizer does not exclude occupational asthma.

Although the history can be very helpful, the evaluation should also include objective pulmonary function testing (Chapter 73) to confirm asthma, either when the patient has symptoms or within 24 hours of the typical suspected work exposure (Fig. 81-1). Allergy skin-prick tests, blood samples, or both should be obtained to test for specific IgE antibodies to any relevant sensitizer if feasible. Serial monitoring of peak expiratory flow rates, symptom diaries, or use of rescue inhalers can provide supportive information. The results of a methacholine challenge test (Chapter 75) toward the end of a typical work week can help when compared with results after 10 days or more without exposure. A comparison of eosinophil counts in induced sputum at work and after a period away from exposure, showing higher levels when exposed, provides supportive diagnostic information. If the diagnosis is still in doubt, a carefully controlled specific inhalation challenge with the suspected workplace sensitizer can be performed in a specialized referral center. Each investigation can be falsely positive or negative, so a combination of investigations is advised while the patient continues to work until the diagnosis is confirmed. Given the specialized nature of many of these studies, consultation with a specialist is recommended. The main differential diagnosis for patients with confirmed asthma is the coincidental onset of asthma with subsequent work-exacerbated asthma. Other conditions, such as vocal cord dysfunction, may explain symptoms or may coexist with asthma and confound the diagnosis.

TREATMENT AND PREVENTION

The optimal management of patients with sensitizer-induced occupational asthma includes complete removal from further exposure to the sensitizer and cross-reacting agents combined with the usual pharmacologic approach to the treatment of asthma (Chapter 75) and advocacy for appropriate workers' compensation. Consideration of the other exposed workers typically includes communication with the workplace or public health officials, in the hope that measures may be instituted to protect other workers from similar exposures and symptoms. Recommendations for primary prevention have been to reduce exposures to occupational sensitizers as far as possible, removing unnecessary sensitizing agents (e.g., removing high-powdered and high-protein latex gloves), and limiting exposures to sensitizers with occupational hygiene measures.[12,13] Ongoing medical surveillance measures in the workplace also may be of value.

PROGNOSIS

Outcome is best if an early diagnosis results in removal from further exposure while asthma is relatively mild. Improvement may continue to occur up to 10 years after removal from exposure, but asthma does not completely resolve in most patients. For patients with occupational asthma from natural rubber latex, use of powder-free, low-protein latex gloves by coworkers and direct avoidance of natural rubber products by the sensitized worker usually result in improvement that is similar to the improvement in patients who are completely removed from work.

WORK-EXACERBATED ASTHMA

EPIDEMIOLOGY AND CLINICAL MANIFESTATIONS

Work-exacerbated asthma is defined as asthma that is not caused by work but is aggravated or exacerbated by work conditions. Asthma may have been present before starting employment or may begin coincidentally during employment, but it is not caused by work. Work exposures that commonly exacerbate asthma include extreme temperature or humidity, exertion, dusts, fumes, and gases. Patients may be exposed at work to common environmental allergens (e.g., fungal allergens in an office setting or dust mites or animals in domestic settings) that exacerbate asthma in patients who are sensitized to these allergens. Symptoms of work-exacerbated asthma may occur transiently with an unusual work exposure (e.g., during renovation in a work building) or may occur on a daily basis (e.g., daily exposure to fumes while performing physical exertion in an industrial setting).

DIAGNOSIS AND TREATMENT

Work-exacerbated asthma is commonly diagnosed on the basis of the history of work exposures and the associated increase in asthmatic symptoms, medication requirements, or unscheduled physician visits. The recommended evaluation of patients with daily or frequent work exacerbations of asthma is similar to that for patients with suspected occupational asthma. Work-related changes in serial peak flow recordings can mimic those seen in occupational asthma, but sputum eosinophil counts typically show less of a work-related increase than is observed with occupational asthma. If the workplace exposure includes a potential work sensitizer, immunologic testing or a controlled challenge exposure may confirm whether respiratory sensitization has occurred.

Management includes the same pharmacologic measures as for non–work-related exacerbations, including the optimization of pharmacologic asthma management (Chapter 75) and, when needed, adjusting the work exposures to avoid ongoing exacerbations. Occupational hygiene measures can reduce exposures, but some patients require a change in job description or work area. Workers' compensation may be available for some patients who have work-related exacerbations of their asthma.

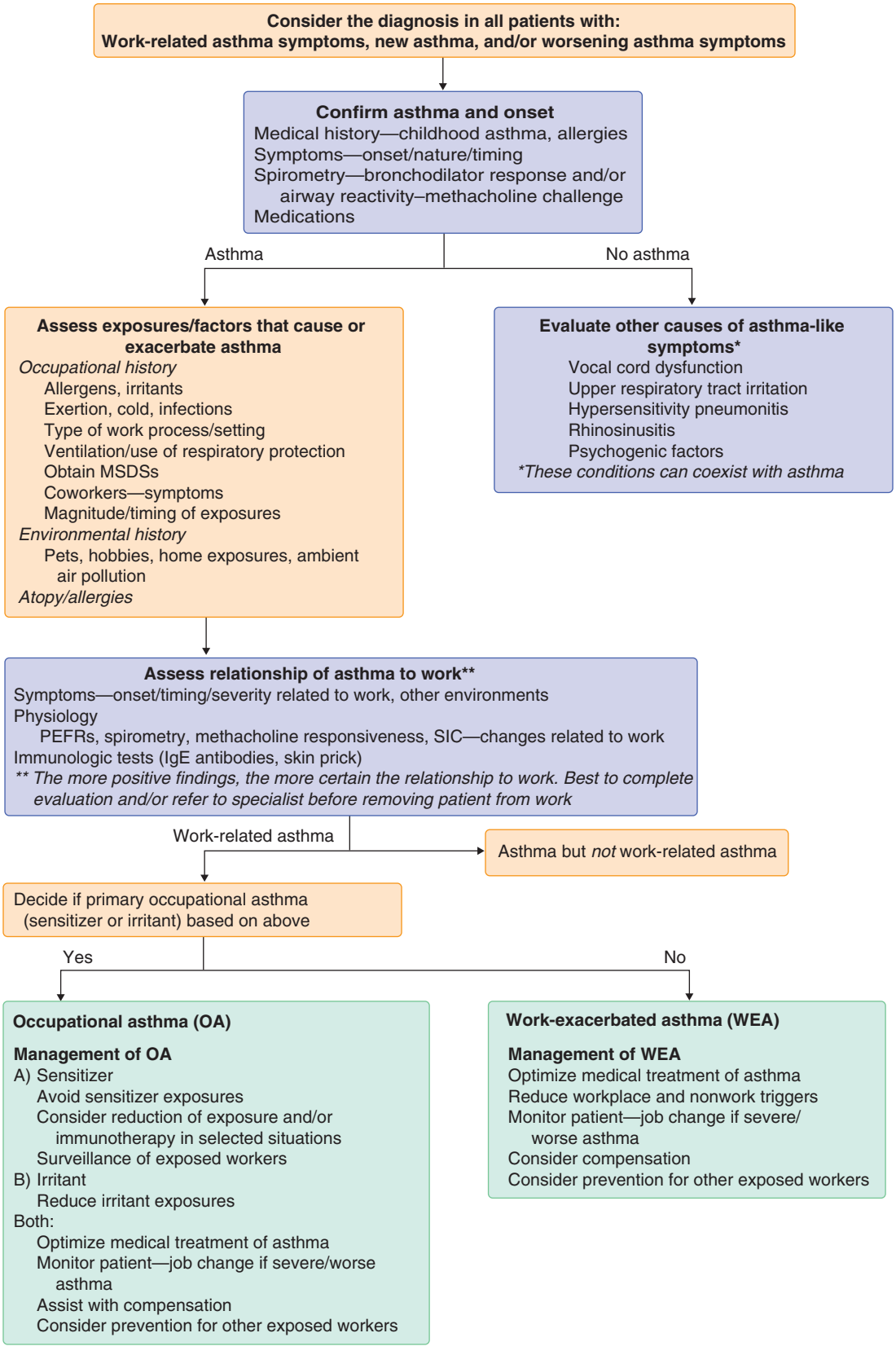

FIGURE 81-1. Clinical evaluation and management of work-related asthma. IgE = immunoglobulin E; MSDS = Material Safety Data Sheet; PEFR = peak expiratory flow rates; SIC = specific inhalation challenge. (From American College of Chest Physicians. Consensus statement: diagnosis and management of work-related asthma. *Chest*. 2008;134:1S-41S.)

Irritant Exposure and Reactive Airways Dysfunction Syndrome

A high level of usually accidental exposure to an irritant agent can cause asthma. Although the clinical manifestations can be dramatic, irritant-induced occupational asthma represents a relatively small proportion of all occupational asthma. The most definitive criteria for this condition are those applied to the term *reactive airways dysfunction syndrome:* the onset of asthma symptoms within 24 hours of the exposure, generally severe enough to lead to an unscheduled physician visit; exposure to a single high-level irritant; asthma symptoms that persist for at least 3 months; pulmonary function testing that confirms asthma with a significant beneficial response to bronchodilators or a bronchoconstrictor response to a methacholine challenge; and the lack of preexisting lung disease or other conditions to explain the symptoms.

When these criteria are not completely met (e.g., symptoms start later than 24 hours after exposure or resolve within weeks after exposure), the term *irritant-induced asthma* is commonly applied, recognizing that this diagnosis is less certain than reactive airways dysfunction syndrome. Chronic low-level exposures to cleaning products and other irritants also may precipitate asthma.

Irritant-induced asthma and reactive airways dysfunction syndrome may clear after weeks or months. Management is the same as for other causes of asthma (Chapter 75), although these patients are often less responsive to the usual pharmacologic treatment.

Occupational hygiene measures at the workplace should be improved to prevent similar future exposures. Affected patients may need a modified work environment to prevent subsequent exacerbations of asthma.

OCCUPATIONAL CHRONIC OBSTRUCTIVE PULMONARY DISEASE

Chronic exposure to dusts, vapors, fumes, and gases can cause occupationally induced COPD, with pathophysiologic changes essentially identical to those seen in COPD that is related to smoking (Chapter 76). Symptoms of chronic bronchitis, including chronic cough and sputum production, may occur with or without changes on pulmonary function testing, perhaps more commonly in individuals with a genetic susceptibility. Causes include mineral dusts such as silica and organic dust exposures such as those of farmers and woodworkers, particulate matter in diesel exhaust fumes, and nitrogen oxides, ozone, and ultrafine particles in welding fumes.[14,15] Occupational exposures such as diacetyl in artificial flavorings and styrene can cause constrictive bronchiolitis.

No specific diagnostic tests distinguish an occupational from a nonoccupational cause of COPD. The diagnosis is based on the history of exposure, consideration of nonoccupational exposures such as smoking, and objective documentation of lung function. The absence of a smoking history can assist in determining probability of an occupational cause, but a positive smoking history does not exclude an occupational contribution because the two can be synergistic.

Management is the same as for patients with nonoccupational COPD (Chapter 76). In addition, however, further exposure to dusts, vapors, fumes, and gases that are likely to worsen disease should be minimized.

HYPERSENSITIVITY PNEUMONITIS

Many exposures that lead to hypersensitivity pneumonitis (Chapters 80 and 82) occur in the workplace, and several bear the name of the occupation or job associated with them: farmer's lung, maple bark stripper's lung, cheese washer's lung, thatcher's lung, mushroom worker's lung, and metal-working fluid hypersensitivity pneumonitis (Table 81-3).[16] Occupational causes also include exposure to contaminated humidifiers (with protozoa or fungi) in factories or office buildings (humidifier lung), as well as lifeguards exposed to sprays of water from pool fountains contaminated with microorganisms. One of the most common current causes of occupational hypersensitivity pneumonitis occurs when workers or machinists develop hypersensitivity pneumonitis from recirculated coolants that can become contaminated with gram-negative bacteria or atypical mycobacteria, which then are aerosolized in the coolant mist and inhaled.[17]

TABLE 81-3 EXAMPLES OF OCCUPATIONAL CAUSES OF HYPERSENSITIVITY PNEUMONITIS

OCCUPATION	CAUSE
Farmer	Thermophilic actinomycetes in moldy hay
Metal worker	Contamination of metal-working fluids with microorganisms such as *Mycobacteria immunogens* or fungi
Worker exposed to humidifiers	Contamination with microorganisms such as protozoa or fungi
Sugarcane worker	Moldy sugarcane (bagassosis)
Maple bark stripper	Fungi
Chicken or turkey worker	Avian proteins
Pharmaceutical worker	Penicillin
Food handler	Soybeans
Office worker	Microorganisms contaminating air conditioners or humidifiers
Swimming pool attendant	Fungal contamination in sprays around pool area
Animal worker	Rat proteins
Mushroom worker	Fungi
Wheat farmer or handler	Weevil-infested flour
Greenhouse worker	Fungi
Workers spraying urethane paint or adhesives/sealants (or less often, other workers using diisocyanate)	Methylene diphenyl diisocyanate, hexamethylene diisocyanate, toluene diisocyanate
Chemical worker using plastics, resins, paints	Trimellitic anhydride

PATHOBIOLOGY

Most antigenic exposures that lead to hypersensitivity pneumonitis are organic, especially thermophilic actinomycetes (Chapter 304), fungi, atypical mycobacteria (Chapter 300), and protozoa. Other common antigens include avian and rat proteins. Less commonly, hypersensitivity pneumonitis can be induced by low-molecular-weight chemical antigens, such as penicillin or methylene diphenyl diisocyanate (MDI), which is used as a sealant or binder. Small particles, commonly 3 to 5 μm in mass median aerodynamic diameter, reach the small airways and alveoli, where the immune response leads to hypersensitivity pneumonitis. This immune response is associated with specific IgG antibodies and T lymphocytes, and it recurs with repeated exposures.

CLINICAL MANIFESTATIONS AND DIAGNOSIS

The acute form of disease manifests as cough, dyspnea, chills, and malaise, typically occurring 4 to 8 hours after exposure and clearing by 12 to 24 hours. On examination, patients typically are febrile and tachypneic, with reduced chest expansion and basal crackles. An elevated blood neutrophil count is common, and the chest radiograph shows acute infiltrates. Pulmonary function testing may show a restrictive pattern, with a reduced diffusing capacity, and arterial blood gases may show hypoxemia owing to ventilation-perfusion mismatch.

Chronic hypersensitivity pneumonitis may follow repeat acute episodes or start de novo. It causes a chronic dry cough, progressive dyspnea, and, often, significant weight loss. The physical examination typically reveals reduced chest expansion and basal crackles. Results on pulmonary function testing and radiographic findings may be similar to nonspecific idiopathic pulmonary fibrosis (Chapter 80), and ground-glass opacities are often seen on a computed tomography (CT) scan of the chest. Bronchoalveolar fluid typically shows an increase in the lymphocyte count, and there may be a predominance of $CD8^+$ T lymphocytes (Chapter 73).

The specific occupational cause for hypersensitivity pneumonitis may be suspected from a temporal relationship to work exposures. The differential diagnosis in the chronic form includes idiopathic pulmonary fibrosis, although clubbing is less common in hypersensitivity pneumonitis. Radiographic and pulmonary function test findings may also mimic idiopathic pulmonary fibrosis, but a distinguishing finding is often a bronchoalveolar lavage that shows lymphocytes as high as 60 to 80% of the cells, usually with a predominance of $CD8^+$ T lymphocytes but sometimes with $CD4^+$ cells in chronic forms of disease.

Laboratory investigations include determining the presence of serum IgG antibodies to the suspected antigen. However, IgG antibodies also may be present in exposed individuals who do not have disease and are therefore not specific to the diagnosis. Conversely, failure to demonstrate specific antibodies is not uncommon in hypersensitivity pneumonitis because the limited number of antigens used for testing may not include the relevant occupational antigen. Specific challenge with the suspected antigen in a specialized laboratory setting is occasionally needed if the diagnosis is in doubt.

Some patients can safely undergo a work challenge that monitors changes in symptoms, fever, blood neutrophil count, radiographic findings, and pulmonary function with and without exposure to the suspected agent, but such testing is not readily available and rarely performed. Lung biopsy, if performed, may show granulomas and foreign body giant cells. If other findings are supportive of hypersensitivity pneumonitis, however, open biopsy usually is not needed.

TREATMENT AND PROGNOSIS

Treatment principles are the same as for nonoccupational hypersensitivity pneumonitis (Chapter 82).[18] Removal from exposure to the causative agent is the primary treatment measure. As with occupational asthma from a sensitizer, the removal must be complete and often requires a change in work if the causative agent cannot be removed. Reduction of exposure by use of respiratory protective devices is generally not practical and not effective, with the exception of air-supplied respirators for occasional short-term exposures. Patients with acute (nonfibrotic) hypersensitivity pneumonitis may not require any medications in addition to removal from antigen exposure, but if acute episodes are severe, they may need supportive measures, including corticosteroids (e.g., 20 to 60 mg of prednisone orally per day), supplemental oxygen, and, rarely, intensive care (Chapter 82). Chronic hypersensitivity pneumonitis, also termed fibrotic or nonfibrotic hypersensitivity pneumonitis (Chapter 80), may require additional oral corticosteroid treatment (e.g., 60 mg of prednisone orally per day, tapering down to <20 mg per day) similar to what is recommended for nonoccupational chronic hypersensitivity pneumonitis. Immunosuppressive agents of potential use to reduce the required dose of corticosteroids include azathioprine (e.g., 125 mg per day orally) or mycophenolate mofetil (e.g., 1000 mg orally twice daily), with doses dependent on the patient's weight, response to and duration of prior treatment and response to the new agent. However, more evidence is needed to guide the use of these medications and for antifibrotic agents (e.g., pirfenidone or nintedanib) that are used for idiopathic pulmonary fibrosis (Chapter 80).

Prognosis is better with early diagnosis and complete removal from exposure to the causative agent. Despite treatment, severe end-stage fibrosis may require lung transplantation. Preventive measures include occupational hygiene to reduce inhalational allergen exposures and use of appropriate protective respiratory devices.

CHRONIC BERYLLIUM DISEASE

EPIDEMIOLOGY AND PATHOBIOLOGY

Acute toxic pneumonitis, first described in workers who had high exposure to beryllium in the manufacture of fluorescent light bulbs, is now rare, but chronic beryllium disease remains a problem in many countries (Table 81-4). Chronic hypersensitivity beryllium disease has a strong genetic association with *HLA-DPB1* gene variants that code for Glu69. *HLA-DPB1* genotyping for the number of E69-containing alleles and the calculated surface electronegativity of the *HLA-DPB1* allele has predictive value, but the utility of using this information in future job selection is not known.[19]

CLINICAL MANIFESTATIONS

The pulmonary clinical features of chronic beryllium disease are similar to those of sarcoidosis (Chapter 83), ranging from asymptomatic histologic or imaging findings, to potential progression, to severe granulomatous restrictive lung disease. Onset can occur up to 20 years or more after exposure to beryllium, even if the patient no longer is exposed. The clinical history in all patients with apparent sarcoidosis must include inquiry about possible beryllium exposure, even many years ago.

DIAGNOSIS AND TREATMENT

The chest radiograph shows changes that appear identical to sarcoidosis with enlarged hilar or mediastinal lymph nodes or multiple lung nodules or both (Fig. 81-2). Sensitization to beryllium can be detected by a beryllium lymphocyte proliferation test that demonstrates the presence of sensitized lymphocytes in blood or bronchoalveolar lavage fluid. This test also can detect sensitization to beryllium among asymptomatic exposed workers, who can then be evaluated to assess possible chronic beryllium disease and provided with advice for reducing or eliminating further work exposures.

After disease develops, removal from exposure is advised, but the disease may still worsen. Progressive deterioration in lung function is treated similarly to sarcoidosis (Chapter 83), with oral corticosteroids and supportive measures.

ASBESTOS-RELATED DISEASES

Although the use of asbestos has declined and better protective equipment has been mandated, asbestos-related disease has continued to occur owing to the long latency between exposure and disease. Chrysotile asbestos has less effect on the lungs than other forms of asbestos; that is, amphiboles. Effects of exposure include benign and malignant disease.[20]

Benign asbestos disease is often asymptomatic and identified on chest imaging. Pleural thickening and pleural plaques, commonly with calcification, can occur 20 to 30 years after first exposure and may initially appear on the chest radiograph as calcified linear opacities over the hemidiaphragms and cardiac border (see Fig. 72-15 in Chapter 72). If extensive, it may be difficult to exclude intrapulmonary opacities except by CT scan. Pleural plaques are a marker of asbestos exposure but do not occur in all workers with significant asbestos exposure. Plaques generally do not cause significant changes in

TABLE 81-4 POTENTIAL OCCUPATIONAL EXPOSURES TO BERYLLIUM

Metal and alloy production (alloys of aluminum, copper, and nickel; recently includes golf clubs and metal pen clips)
Ceramic manufacturing
Metal casting, including dental technicians (crowns, bridges)
Electronics, including computer components, transistors, microwave and x-ray windows, heat sinks, telecommunications
Aerospace and atomic engineering (rocket fuels, heat shields, nose cones, and metal parts)
Aircraft manufacture and repair
Nuclear reactors, nuclear weapons, and defense industry
Coating of cathode ray tubes for radar and similar installations
Laboratories
Extraction of beryllium from ore
Metal reclamation and recycling

From Tarlo SM, Rhee K, Powell E, et al. Marked tachypnoea in siblings with chronic beryllium disease due to copper-beryllium alloy. *Chest*. 2001;119:647-650.

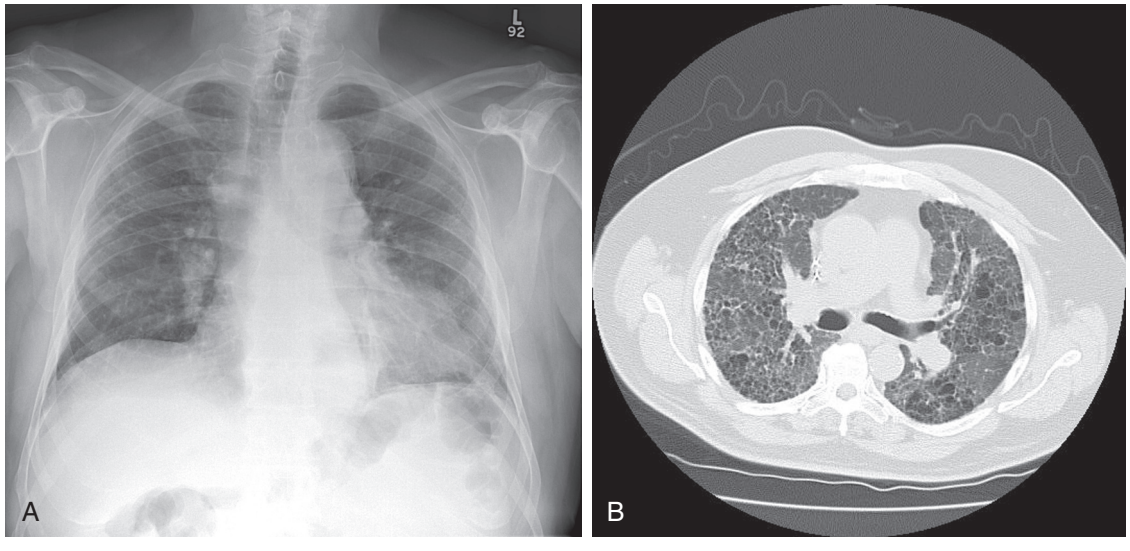

FIGURE 81-2. Posteroanterior chest radiograph (A) and high-resolution computed tomography scan (B) from patients with chronic beryllium disease. The chest radiograph demonstrates hilar adenopathy and infiltrates, and the scan shows air space destruction and infiltrates.

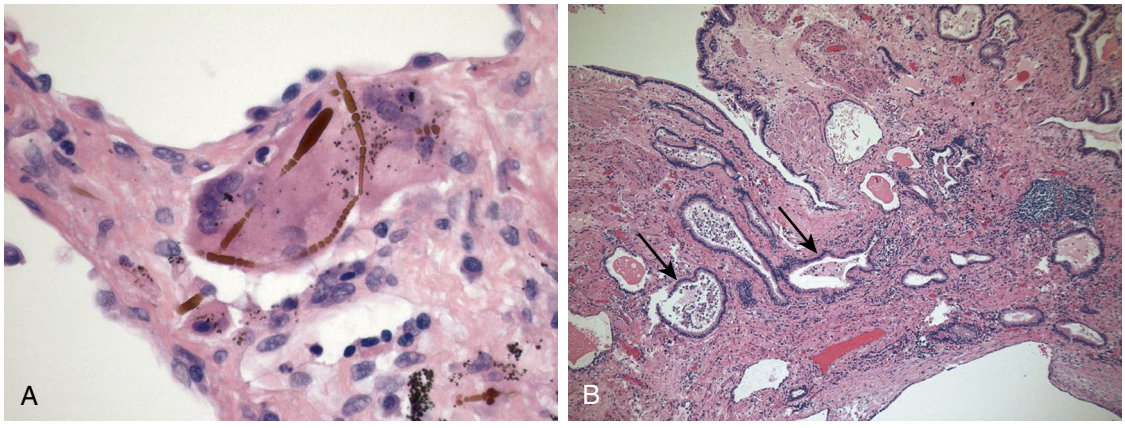

FIGURE 81-3. Histology from a lung biopsy showing asbestos bodies. (A, higher power, B, low power) Ferruginous bodies consisting of asbestos fibers coated by iron-protein-mucopolysaccharide material with typical golden-brown, beaded appearance. The two longest asbestos bodies, at the center of figure A, are present within a multinucleated giant cell. (Hematoxylin and eosin stain, ×400.) (Courtesy of Dr. David Hwang, Toronto General Hospital.)

lung function, except that diffuse pleural thickening may result in exertional dyspnea and extrapulmonary restrictive lung disease. Pleural thickening may cause rounded atelectasis (Chapter 78) when encasement of a portion of the peripheral lung tissue by thickened pleura causes an apparent lung nodule, typically with a "comet sign" showing the thickened pleura. Benign pleural effusion can develop, usually about 10 to 15 years after asbestos exposure. It requires further investigation because the differential diagnosis includes malignant pleural effusion (Chapter 86).

Asbestosis is the term for interstitial lung disease caused by asbestos. The clinical presentation is usually with dry cough and dyspnea on exertion. Physical examination usually reveals digital clubbing and basal crackles on lung auscultation. Chest imaging shows basal interstitial lung disease, with or without additional pleural changes as described earlier. Pulmonary function testing shows restrictive lung disease (Chapter 73), and histologic findings are the same as in usual interstitial pneumonia (Chapter 80). Findings supporting the diagnosis of asbestosis rather than usual interstitial pneumonia include a significant duration and level of exposure to asbestos, an appropriate latency of usually 20 to 40 years after first exposure, and/or the finding of ferruginous asbestos bodies in sputum, bronchoalveolar fluid, or lung tissue (Fig. 81-3).[21] Unfortunately, pharmacologic treatment is not effective, and the lung disease may progress to end-stage fibrosis. Management is supportive, including supplemental oxygen and consideration for lung transplantation (Chapter 87). As with the other diseases of long latency, preventing exposure is paramount.

Mesothelioma (Chapter 177), a malignant tumor of the pleura, peritoneum, or both, is the one complication of asbestos exposure that can occur after even relatively minor exposure, such as second-hand exposure from dust on clothing in the families of those working with exposure. It typically occurs 30 to 40 years after exposure to asbestos and may present incidentally on chest imaging or with chest pain or weight loss. Radiographs show pleural thickening, and a pleural effusion may be present. Mesothelioma often is difficult to distinguish from benign pleural thickening without a biopsy. No treatment has proved effective (Chapter 177), so routine screening to detect mesothelioma in exposed persons is not currently recommended. The risk for lung cancer (Chapter 177) increases after significant exposure to asbestos, with a usual latency period of 20 to 30 years. Smoking and asbestos exposure have additive effects, and smoking and asbestosis have even greater effects on the risk for lung cancer.

SILICOSIS AND OTHER PNEUMOCONIOSES

The incidences of silicosis[22] and other inorganic dust diseases of the lungs (Table 81-5) have declined substantially in recent decades, in part owing to better worksite protection in mines, sandblasting, and other settings, but silicosis remains an important preventable pneumoconiosis worldwide.[23] Silicosis is associated with the development of mycobacterial infection[24] and of collagen vascular disease, especially rheumatoid arthritis. Patients with pneumoconiosis and rheumatoid arthritis may be at higher risk for developing rheumatoid nodules in the lung, so-called Caplan syndrome, and mycobacterial infections.

TABLE 81-5 JOBS THAT CAN LEAD TO SILICOSIS

Mining: surface or underground mining (tunneling)
Milling: ground silica for abrasives and filler
Quarrying
Sandblasting: e.g., of buildings, preparing steel for painting
Pottery: ceramic or clay work
Grinding and polishing using silica wheels
Stone work
Foundry work: grinding, molding, chipping
Refractory brick work
Glass making: to polish and as an abrasive
Boiler work: cleaning boilers
Manufacture of abrasives

Patients may initially be identified incidentally during a medical surveillance program or by a chest radiograph that shows multiple small lung nodules, often with enlarged mediastinal lymph nodes that can mimic sarcoidosis (Fig. 81-4).[24] Nodules can coalesce and lead to progressive massive fibrosis, especially in the upper lungs, sometimes mimicking malignancy, and can be positive on positron emission tomography scanning owing to their metabolic activity. There can be compensatory emphysema in the lower lung fields. On chest imaging, mediastinal lymph nodes may have a characteristic "eggshell" calcification in silicosis. Treatment is supportive. Patients with exposure to silica or coal dust may develop COPD from the dust exposure or dust-related diffuse fibrosis. Patients who develop end-stage lung disease may be considered for lung transplantation.

ACUTE FEBRILE SYNDROMES

A variety of occupational exposures can cause acute febrile respiratory syndromes that may mimic acute viral respiratory illnesses (Table 81-6). The mechanism of these syndromes is incompletely understood, but they are associated with systemic neutrophilia and cytokine activation, often with increased interleukin-6 (IL-6) and IL-8.

CLINICAL MANIFESTATIONS AND DIAGNOSIS

Typically, chills, fever, malaise, dry cough, and chest tightness start about 6 to 8 hours after onset of an exposure at work and generally resolve by the next day. Occasionally, shortness of breath and other respiratory symptoms are severe enough for patients to seek emergency medical attention. Infiltrates on the chest radiograph can occur with neutrophilia and hypoxemia that can mimic acute pneumonia or acute hypersensitivity pneumonitis. Symptoms and signs usually resolve in 24 to 48 hours without antibiotics and recur with further exposures, although the clinical manifestations generally become milder with repeated daily exposures (e.g., Monday morning fever in cotton mill workers). Workers are often familiar with the syndrome because it commonly affects up to 30% of exposed workers. If the diagnosis is not provided by the patient, however, careful elicitation of potential work exposures is needed.

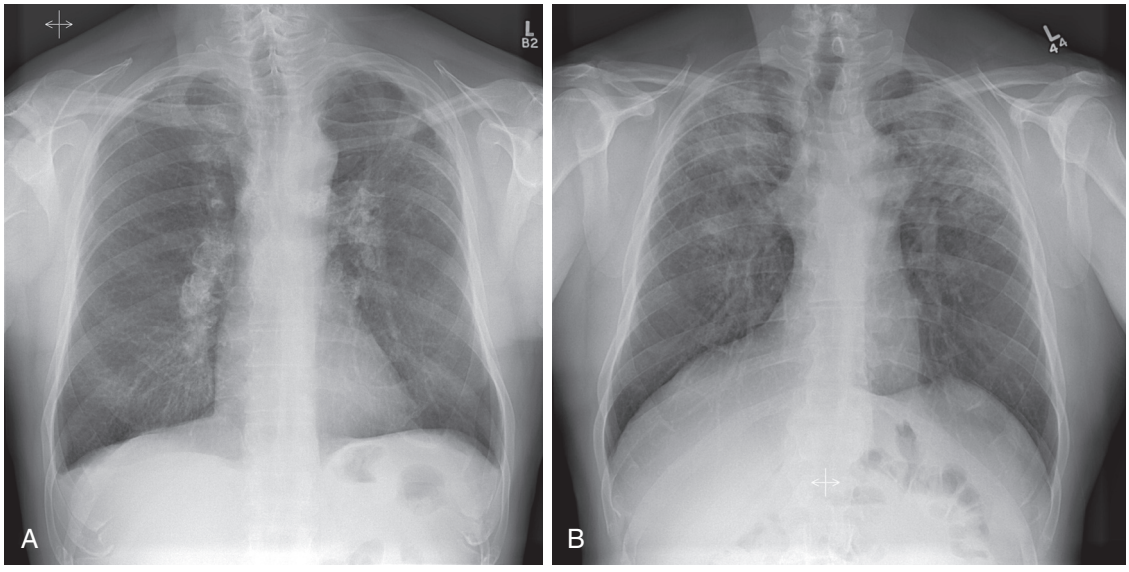

FIGURE 81-4. **Posteroanterior chest radiographs from two patients with silicosis. A,** Small nodules and eggshell calcification of hilar lymph nodes. **B,** Progressive massive fibrosis of the upper lung zones with compensatory emphysema.

TABLE 81-6 OCCUPATIONAL CAUSES OF AN ACUTE FEBRILE SYNDROME

SYNDROME	CAUSE
Polymer fume fever or Teflon fever	Polytetrafluoroethylene and other fluorocarbon polymer fumes
Metal fume fever	Zinc fumes from welding of galvanized steel, less commonly other metal fumes
Cotton mill fever	Dust and endotoxins from bacterial contamination of unprocessed cotton, flax, and hemp
Humidifier fever	Microorganisms found in reservoirs (e.g., humidifiers, air conditioners, aquariums); the differential diagnosis includes acute hypersensitivity pneumonitis
Organic dust toxic syndrome	Grain dust, moldy wood chips; the differential diagnosis includes acute hypersensitivity pneumonitis

TREATMENT

Treatment is supportive. If the causative exposure can be removed (e.g., cleaning a contaminated humidifier), symptoms can be prevented. If the cause cannot be removed and symptoms are severe, the patient may need reduction or change of the work exposure.

OCCUPATIONAL LUNG CANCER

A significant duration and level of exposure to a recognized carcinogen such as asbestos, hexavalent chromium (as in chromate production and the pigment industry), soluble radon compounds or radon gas, polycyclic aromatic hydrocarbons, chloromethyl ethers, arsenic, diesel exhaust, or silica[25,26] can increase the risk for lung cancer (Chapter 177). Such a history should be elicited in all patients, and exposure to these agents represents a risk factor when considering whether to recommend patients for CT screening for lung cancer (Chapter 177).[27]

GENERAL REFERENCES

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82 PHYSICAL AND CHEMICAL INJURIES OF THE LUNG

DAVID C. CHRISTIANI AND LISA A. MAIER

SUBMERSION INCIDENTS: DROWNING

DEFINITION

Drowning is defined as the process of experiencing respiratory impairment from submersion/immersion in liquid. The term *near-drowning* was previously used to describe individuals who survived a submersion incident, at least temporarily, but it has been abandoned on the basis of recommendations of the First World Congress of Drowning in Amsterdam in 2002.

EPIDEMIOLOGY

The estimated annual number of deaths worldwide due to drowning is about 400,000, mostly in low- and middle-income countries. About 4200 persons are treated per year for nonfatal drowning in U.S. emergency departments, and about another 3400 suffer fatal drowning. Alcohol use, age younger than 4 years, and male gender are associated with increased rates of both nonfatal and fatal drowning.

PATHOBIOLOGY

The physiology of drowning is complex and relates to two different events: immersion (upper airway above water) and submersion (upper airway under water). Immersion involves integrated cardiorespiratory responses to skin and deep body temperature, including cold shock, physical incapacitation, and hypovolemia, as precursors of collapse and submersion. The initial response to submersion/immersion is apnea, followed almost invariably by aspiration. Laryngospasm may result in aspiration of a variable quantity of liquid medium into the lungs. Hypoxemia, hypercapnia, and acidemia develop acutely. Aspiration of either fresh or salt water results in occlusion of the airway, reduced surfactant activity, direct alveolar injury, and bronchospasm. Acute lung injury or acute respiratory distress syndrome (ARDS)—associated with noncardiogenic pulmonary edema, respiratory failure, and severe hypoxemia—may develop hours or days after the incident. Acute renal failure may also occur. Alcohol consumption also increases the risk for hypothermia. Changes to serum electrolytes with drowning in either fresh water or salt water are not clinically significant.

The most serious secondary consequence of hypoxemia is anoxic brain injury. Fortunately, a reduction of brain temperature by 10°C during drowning decreases adenosine triphosphate (ATP) consumption by approximately 50%,

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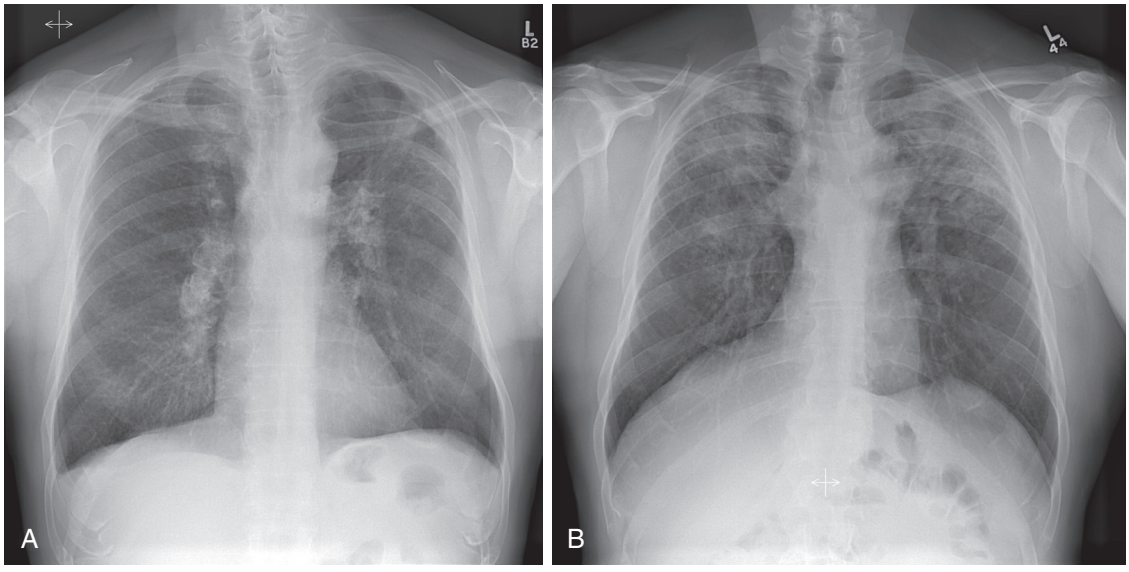

FIGURE 81-4. **Posteroanterior chest radiographs from two patients with silicosis. A,** Small nodules and eggshell calcification of hilar lymph nodes. **B,** Progressive massive fibrosis of the upper lung zones with compensatory emphysema.

TABLE 81-6 OCCUPATIONAL CAUSES OF AN ACUTE FEBRILE SYNDROME

SYNDROME	CAUSE
Polymer fume fever or Teflon fever	Polytetrafluoroethylene and other fluorocarbon polymer fumes
Metal fume fever	Zinc fumes from welding of galvanized steel, less commonly other metal fumes
Cotton mill fever	Dust and endotoxins from bacterial contamination of unprocessed cotton, flax, and hemp
Humidifier fever	Microorganisms found in reservoirs (e.g., humidifiers, air conditioners, aquariums); the differential diagnosis includes acute hypersensitivity pneumonitis
Organic dust toxic syndrome	Grain dust, moldy wood chips; the differential diagnosis includes acute hypersensitivity pneumonitis

TREATMENT

Treatment is supportive. If the causative exposure can be removed (e.g., cleaning a contaminated humidifier), symptoms can be prevented. If the cause cannot be removed and symptoms are severe, the patient may need reduction or change of the work exposure.

OCCUPATIONAL LUNG CANCER

A significant duration and level of exposure to a recognized carcinogen such as asbestos, hexavalent chromium (as in chromate production and the pigment industry), soluble radon compounds or radon gas, polycyclic aromatic hydrocarbons, chloromethyl ethers, arsenic, diesel exhaust, or silica[25,26] can increase the risk for lung cancer (Chapter 177). Such a history should be elicited in all patients, and exposure to these agents represents a risk factor when considering whether to recommend patients for CT screening for lung cancer (Chapter 177).[27]

GENERAL REFERENCES

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82 PHYSICAL AND CHEMICAL INJURIES OF THE LUNG

DAVID C. CHRISTIANI AND LISA A. MAIER

SUBMERSION INCIDENTS: DROWNING

DEFINITION

Drowning is defined as the process of experiencing respiratory impairment from submersion/immersion in liquid. The term *near-drowning* was previously used to describe individuals who survived a submersion incident, at least temporarily, but it has been abandoned on the basis of recommendations of the First World Congress of Drowning in Amsterdam in 2002.

EPIDEMIOLOGY

The estimated annual number of deaths worldwide due to drowning is about 400,000, mostly in low- and middle-income countries. About 4200 persons are treated per year for nonfatal drowning in U.S. emergency departments, and about another 3400 suffer fatal drowning. Alcohol use, age younger than 4 years, and male gender are associated with increased rates of both nonfatal and fatal drowning.

PATHOBIOLOGY

The physiology of drowning is complex and relates to two different events: immersion (upper airway above water) and submersion (upper airway under water). Immersion involves integrated cardiorespiratory responses to skin and deep body temperature, including cold shock, physical incapacitation, and hypovolemia, as precursors of collapse and submersion. The initial response to submersion/immersion is apnea, followed almost invariably by aspiration. Laryngospasm may result in aspiration of a variable quantity of liquid medium into the lungs. Hypoxemia, hypercapnia, and acidemia develop acutely. Aspiration of either fresh or salt water results in occlusion of the airway, reduced surfactant activity, direct alveolar injury, and bronchospasm. Acute lung injury or acute respiratory distress syndrome (ARDS)—associated with noncardiogenic pulmonary edema, respiratory failure, and severe hypoxemia—may develop hours or days after the incident. Acute renal failure may also occur. Alcohol consumption also increases the risk for hypothermia. Changes to serum electrolytes with drowning in either fresh water or salt water are not clinically significant.

The most serious secondary consequence of hypoxemia is anoxic brain injury. Fortunately, a reduction of brain temperature by 10°C during drowning decreases adenosine triphosphate (ATP) consumption by approximately 50%,

ABSTRACT

Physical and chemical injuries to the lung constitute important health problems globally. These disorders include drowning, high-altitude pulmonary edema, decompression syndromes, carbon monoxide poisoning, smoke inhalation and thermal injury, toxic gas inhalation, lipoid pneumonia, and radiation injury. In the clinical setting, oxygen toxicity may be encountered, and aspiration pneumonitis is common. This chapter describes these conditions and the latest approaches to their management.

KEYWORDS

environmental lung diseases
physical hazards
chemical hazards
high-altitude lung disorders
decompression illness
aspiration pneumonia

thereby doubling the duration of time that the brain can survive. Mortality is primarily due to the cardiovascular sequelae of severe early or late hypoxemia.

CLINICAL MANIFESTATIONS

The initial presentation of a drowning victim varies widely. Hypothermia, which is common in drowning victims, may be associated with bradycardia or cardiac arrest due to asystole or ventricular fibrillation. Tachypnea, tachycardia, and low-grade fever are typical in nonhypothermic patients. Cyanosis may be present, and a coughing patient may produce pink frothy sputum. Neurologic evaluation may reveal agitation with or without intoxication or coma. The patient should be examined carefully for signs of associated trauma.

Expected laboratory findings include mild electrolyte abnormalities independent of whether submersion occurs in salt water or fresh water, moderate leukocytosis, and slight decrease in hematocrit in the first 24 hours or slight increase in free hemoglobin with a stable hematocrit in fresh water submersion due to hemolysis, severe hypoxemia, and metabolic acidosis. Evidence of disseminated intravascular coagulation (DIC) may occur. Initial electrocardiographic changes include sinus tachycardia and nonspecific ST segment and T wave changes, which revert to normal within hours. Life-threatening ventricular arrhythmias, complete heart block, or evidence of myocardial infarction can occur early or late in the course. Chest radiographs may initially be normal, despite severe respiratory impairment. Bilateral patchy alveolar infiltrates, which indicate progression to ARDS, may develop.

DIAGNOSIS

The diagnosis of drowning is made on clinical history of submersion in liquid medium with resulting respiratory impairment. Patients with unusual presenting circumstances should be carefully examined for evidence of trauma or assault.

PREVENTION

Drowning incidents are largely preventable, particularly in children. Pool fencing is a proven, effective strategy to prevent drowning. The primary cause of drowning of infants and toddlers is lack of adult supervision, and supervision of all young children near any form of water is strongly recommended. The role of alcohol in teenage and adult drowning incidents is substantial, and all individuals participating in water-based activities should restrict alcohol intake. The use of personal flotation devices is recommended for children and adults.

TREATMENT

When the victim has been recovered from submersion, treatment should focus on basic life support, including notification of emergency response personnel, establishment of an adequate airway, and cardiopulmonary resuscitation,[1] if necessary (Chapter 50). If the victim is apneic, rescue breathing should occur immediately, even before removal from the water. Cervical spine stabilization is needed if there is a history of diving, use of a water slide, signs of injury, or signs of alcohol intoxication. Spinal cord injury (Chapter 368) is otherwise unlikely, and cervical spine stabilization techniques and equipment may impede timely and effective treatment. Attempts to remove water from the airway are unnecessary. Cardiac arrhythmias should be treated with Advanced Cardiac Life Support protocols, including the use of automated external defibrillators when appropriate (Chapter 50). A majority of drowning victims who receive cardiopulmonary resuscitation or rescue breathing will vomit; if vomiting occurs, the head should be turned to the side, and any visible vomitus remaining in the oral cavity should be removed with a finger. When vomiting occurs in patients who may have spinal cord injury, log-rolling techniques are recommended for turning the patient to the side.

All victims of a submersion incident should be transported to a hospital for further evaluation, treatment of potential respiratory failure (Chapter 90), and monitoring for up to 24 hours. Bronchoscopy may be required to evaluate localized wheezing or persistent atelectasis. Prophylactic antibiotics are not useful, but evidence of pneumonia (Chapter 85) should be treated with appropriate antibiotics. Because unusual microorganisms may be isolated from the lower airways, efforts should be made to identify specific microbial flora pertinent to the locus of the drowning incident. Randomized controlled trials of specific ventilator strategies have not been conducted, but lung-protective ventilation (i.e., a tidal volume of 4 to 6 mL/kg ideal body weight) with sufficient positive end expiratory pressure of 5 to 10 cm H_2O to avoid atelectasis is commonly recommended.

Treatment of neurologic injury is focused on supportive care while the extent of cerebral edema is minimized. To decrease cerebral edema and intracranial pressure, intravenous hypertonic saline (7.5 to 23% to target serum sodium values of 145 to 155 mmol/L) or mannitol (1-g/kg bolus of 20% mannitol, with repeat dosing every 6 to 8 hours as necessary to target serum osmolality of less than 300 to 320 mOsm/kg) may be used, although their benefit in this setting is unproved. Hyperventilation to a $Paco_2$ of 34 to 36 mm Hg may be helpful. Intracranial pressure may increase in response to shivering or purposeless movements, which should be reduced. Maintaining targeted normothermia (temperature < 37.8°C)[A1] improves neurologic outcome after cardiac arrest (Chapter 50). Hyperthermia should be avoided at all times.

PROGNOSIS

Most drownings are fatal. The mortality rate for drowning victims who present alive to an emergency department is about 25%. Long-term neurologic deficits persist in approximately 6% of nonfatal drowning victims. Prolonged duration of submersion is associated with a worse prognosis, and the risk for death or severe permanent neurologic deficits increases from 10% after less than 5 minutes of submersion, to about 55% with 6 to 10 minutes of submersion, nearly 90% with 11 to 25 minutes of submersion, and nearly 150% with more than 25 minutes of submersion. However, young children who are hypothermic when they are rescued after submersion times of up to 60 minutes have recovered without neurologic damage. Other factors associated with poor prognosis include hypotension, persistent apnea, coma, more than a 10-minute delay in receiving basic life support, and duration of resuscitation of more than 25 minutes.

DISEASES OF HIGH ALTITUDE

DEFINITION

Neurologic and pulmonary disturbances, primarily due to direct tissue effects of hypoxia, occur in individuals who either ascend to or reside at altitudes of 7000 feet (2133 meters) or more (Table 82-1).

EPIDEMIOLOGY

Acute mountain sickness is the most common high-altitude syndrome. It occurs in approximately 20% of individuals who ascend to altitudes of 7000 to 9000 feet, 40% at 10,000 to 14,000 feet, and more than 50% above 14,000 feet.[2] The incidence of chronic mountain sickness, also known as Monge disease, is thought to be between 5 and 18%. More severe neurologic disturbances due to high-altitude cerebral edema are rare, occurring in approximately 1 to 2% of individuals who ascend to altitudes above 15,000 feet. High-altitude pulmonary edema occurs in approximately 2 to 6% of otherwise healthy individuals who ascend to altitudes of 8000 to 15,000 feet. However, the incidence in individuals with a prior history of high-altitude pulmonary edema may be as high as 60%, or higher during rapid ascents. The occurrence of high-altitude retinal hemorrhage is approximately 33% among individuals who ascend to very high altitudes (up to 19,000 feet) and is thought to be common at lower altitudes as well. High-altitude retinal hemorrhage is not associated with high-altitude cerebral edema or long-term visual consequences.

PATHOBIOLOGY

Clinically significant hypoxemia is the underlying factor in all high-altitude diseases. The decrease in barometric pressure during an ascent to altitude causes a decrease in the alveolar pressure of oxygen (Pao_2). For example, Pao_2 drops from 105 mm Hg at sea level to 60 mm Hg at 10,000 feet and to 40 mm Hg at 18,000 feet. Below 60 mm Hg, oxygen dissociates from hemoglobin more readily (see Fig. 144-1 in Chapter 144), thereby decreasing oxygen saturation and oxygen delivery to tissues. The effect is even more noticeable in patients with impaired diffusion capacity, such as occurs in emphysema, interstitial lung diseases, or heart failure. Furthermore, increased ventilatory drive induces an acute respiratory alkalosis. In the brain, tissue hypoxia causes cerebral vasodilation, whereas hypobaria causes cerebral vasoconstriction. In severe hypoxemia, vasodilation is the likely cause of cerebral edema in susceptible individuals. The response to hypoxemia in the lungs is primarily increased pulmonary

TABLE 82-1 HIGH-ALTITUDE SYNDROMES

SYNDROME	CLINICAL DESCRIPTION
Acute mountain sickness	Common after recent ascent to altitudes above 7000 feet; symptoms include headache, anorexia, and malaise
Chronic mountain sickness	Occurs in 5-18% of people dwelling above 10,000 feet; symptoms include headache, fatigue, dyspnea, and digestive disturbances
High-altitude pulmonary edema	Occurs in 2-6% of people above 9500 feet; symptoms include dyspnea, cough, and tachycardia
High-altitude retinal hemorrhage	Common above 15,000 feet; asymptomatic or reversible vision changes
High-altitude cerebral edema	Occurs in 1-2% of people above 15,000 feet; symptoms include confusion, ataxia, hallucinations, coma, or death

arterial pressures due to hypoxic pulmonary vasoconstriction, which results in reversible injury to pulmonary capillaries, increased capillary permeability, and eventually pulmonary edema. Reduced oxygen consumption also occurs, perhaps because of impaired mitochondrial function. Sleep disordered breathing has also been noted but has minimal, if any, clinical significance.

CLINICAL MANIFESTATIONS

Symptoms of acute mountain sickness begin 2 to 3 hours after ascent and include breathlessness, lightheadedness, fatigue, nausea, anorexia, headache, and insomnia. Most symptoms resolve within 2 to 3 days, although insomnia may persist. Chronic symptoms of headache, fatigue, sleep disturbances, dyspnea, and digestive complaints are seen with chronic mountain sickness in individuals residing at higher elevations. Chronic mountain sickness may be associated with polycythemia (hemoglobin concentrations above 21 g/dL). Severe neurologic symptoms with high-altitude cerebral edema include ataxia and confusion that may progress to coma or death. Symptoms of high-altitude pulmonary edema that usually begin 2 to 4 days after ascent to higher altitudes include dyspnea, cough, and tachycardia. Funduscopic changes of flame-shaped hemorrhages are seen with high-altitude retinal hemorrhage.

DIAGNOSIS

Diagnosis of most high-altitude disease is made on the basis of clinical manifestations at high altitude. Diagnosis of chronic mountain sickness, and a milder form often termed subacute mountain sickness, is more challenging because it may mimic other cardiopulmonary, neurologic, or psychiatric disease. Individuals with chronic mountain sickness typically have higher hemoglobin concentrations, higher serum erythropoietin levels, higher nocturnal heart rates, lower nocturnal oxygen saturation, and higher systolic and diastolic arterial pressure than do normal individuals living at similar altitude.

PREVENTION

Prevention of high-altitude disease can be achieved by avoidance in high-risk individuals, such as young children and persons with a history of high-altitude disease. Gradual ascent and acclimatization are crucial to prevention of high-altitude illness, particularly at extreme altitudes. At altitudes up to 10,000 feet, 2 to 3 days or more may be needed for adjustment to the effects of hypoxemia. For mountaineers, current recommendations are to ascend no more than approximately 984 feet (300 meters) per day at altitudes higher than 9843 feet (3000 meters).

When rapid ascent is unavoidable, such as flights to high-altitude locales, the carbonic anhydrase inhibitor acetazolamide (125 mg orally twice daily)[2] provides effective prophylaxis of acute mountain sickness,[A2,A3] and 125 mg at night may improve sleep[A4] (Table 82-2). Other medications shown to be effective in the prevention of acute mountain sickness in randomized, controlled trials include dexamethasone (2 mg every 6 hours or 4 mg every 12 hours), prednisolone (20 mg daily), ibuprofen (600 mg three times daily), and sumatriptan (50 mg orally once after ascent), although a head-to-head comparison showed that ibuprofen was not as effective as acetazolamide.[A5] Inhaled budesonide (200 µg inhaled twice daily) may be useful for prevention of mild but not severe acute mountain sickness if acetazolamide or oral corticosteroids cannot be used.[A6] For prevention of high-altitude pulmonary edema in susceptible individuals, options include the long-acting β-adrenergic agonist salmeterol (125 µg inhaled twice daily), the phosphodiesterase inhibitor tadalafil (10 mg twice daily), the calcium-channel blocker nifedipine (20 mg of slow-release formulation every 8 hours, or 30 mg of slow-release formulation every 12 hours), and dexamethasone (8 mg twice daily).

TREATMENT

For acute, life-threatening symptoms such as high-altitude pulmonary edema and high-altitude cerebral edema, the best treatment is immediate descent, if possible, combined with supplemental oxygen therapy and, if needed, use of a portable hyperbaric chamber. For individuals who develop less severe symptoms, acetazolamide (250 mg twice daily) or dexamethasone (4 mg every 6 hours) is useful.[A7,A8] Sildenafil (50 mg, one-time dose) can increase exercise capacity at altitude by 10 to 35%. Increasing inspired oxygen concentrations in high-altitude working facilities also improves productivity and quality of sleep. Sustained-release theophylline (300 mg daily) significantly reduces the symptoms of acute mountain sickness compared with placebo. Milder forms of acute mountain sickness, such as headache, can be treated with typical doses of nonsteroidal anti-inflammatory medications, including aspirin or acetaminophen.

TABLE 82-2 RECOMMENDED MEDICATION FOR THE PREVENTION AND TREATMENT OF ALTITUDE SICKNESS

MEDICATION	INDICATION	ROUTE	DOSE
Acetazolamide	Prevention of AMS, HACE	Oral	62.5 mg or 125 mg twice per day Pediatrics: 2.5 mg/kg every 12 hr
	Treatment of AMS*	Oral	250 mg twice per day Pediatrics: 2.5 mg/kg every 12 hr
Dexamethasone	Prevention of AMS, HACE	Oral	2 mg every 6 hr or 4 mg every 12 hr Pediatrics: should not be used for prophylaxis
	Treatment of AMS, HACE	Oral, IV, IM	AMS: 4 mg every 6 hr HACE: 8 mg once then 4 mg every 6 hr Pediatrics: 0.15 mg/kg/dose every 6 hr
Nifedipine	Prevention of HAPE	Oral	30 mg SR version every 12 hr, *or* 20 mg of SR version every 8 hr
	Treatment of HAPE	Oral	30 mg SR version every 12 hr, *or* 20 mg of SR version every 8 hr
Tadalafil	Prevention of HAPE	Oral	10 mg twice per day
Salmeterol	Prevention of HAPE	Inhaled	125 µg twice per day†

*Acetazolamide can also be used at this dose as an adjunct to dexamethasone in HACE treatment, but dexamethasone remains the primary treatment for that disorder.
†Should not be used as monotherapy and should only be used in conjunction with oral medications.
AMS = acute mountain sickness; HACE = high-altitude cerebral edema; HAPE = high-altitude pulmonary edema; IM = intramuscular; IV = intravenous; SR = sustained release.

PROGNOSIS

Symptoms of high-altitude disease respond rapidly to immediate descent. However, high-altitude cerebral edema and high-altitude pulmonary edema can be fatal, particularly at extreme altitudes and weather when descent may be impossible.

DECOMPRESSION ILLNESS: DECOMPRESSION SICKNESS, BAROTRAUMA, AND ARTERIAL GAS EMBOLISM

DEFINITION

Exposures to changes in ambient pressure cause a spectrum of illness, either by increasing or decreasing the volume of gas in air-filled body cavities or by causing the release of inert gas bubbles from solution in tissues or blood vessels. Symptoms associated with decreasing ambient pressure, which occur most commonly with ascent from depth during recreational or occupational diving, are known as decompression illness. The most common form of decompression illness is decompression sickness, which is classified as either type I (mild symptoms, such as general fatigue or joint pain) or type II (more severe neurologic or cardiopulmonary disturbances). Life-threatening forms of decompression illness include pulmonary barotrauma and arterial gas embolism syndromes. During the descent of a dive, increasing ambient pressure may cause mild symptoms of facial or sinus pain, often called "the squeezes."

EPIDEMIOLOGY

In addition to the approximately 9 million recreational divers in the United States, aviators, astronauts, and compressed air workers are also exposed to changes in ambient pressure that may cause decompression illness. Among recreational divers, the annual incidence rate for either type I or type II decompression sickness is estimated at 1 case per 5000 to 10,000 dives. Approximately 1000 episodes of decompression illness severe enough to warrant recompression therapy occur each year, up to 10% of which are fatal. Well-recognized risk factors for decompression illness include long duration of dives, deep dives, repetitive dives, heavy exertion at depth, cold water, and rapid ascent. Additional risk occurs in individuals who experience further decreases in ambient pressure after the dive, such as on commercial or private aircraft or driving over mountainous areas.

PATHOBIOLOGY

The principles of Boyle's law and Henry's law describe the properties of gases during changes in ambient pressure. Boyle's law states that the volume of a gas varies inversely to changes in pressure, $P_1V_1 = P_2V_2$. During the descent of a dive, pain due to the "squeezes" is caused by increasing ambient pressures that are not equalized by a compensatory increase in gas volume. The resulting negative pressure causes a vacuum effect in the mask associated with engorgement of the blood vessels in adjacent tissues, such as periorbital and ocular vessels, and may result in swelling, pain, and subconjunctival hemorrhages. Facial sinuses, the middle ear, and the external auditory canals may also be affected.

Barotrauma in sinus, otic, or pulmonary tissues may be due to changes in ambient pressures and the resulting increase or decrease in the volume of gas. During descent, the decreasing volume of gas causes vascular engorgement in the sinuses and otic compartments and may result in rupture of the tympanic or inner ear membranes. During ascent, breath holding, particularly with compressed air devices (SCUBA diving), and the presence of obstructive lung disease with delayed exhalation times and air trapping impair equilibration and increase the risk for pulmonary barotrauma (E-Fig. 82-1). If the expanding volume of gas causes a pressure gradient between the alveoli and pulmonary interstitium that exceeds the compliance of the lung, alveolar rupture will lead to pulmonary interstitial emphysema. Further extension of gas along pulmonary tissues may cause additional barotrauma, leading to pneumothorax, mediastinal emphysema, pneumopericardium, and soft tissue emphysema.

Arterial gas embolism, which is a serious consequence of pulmonary barotrauma, results in the development of free gas in the pulmonary arterial circulation. The resulting bubbles may then enter the systemic circulation by overwhelming the filtering mechanism of the pulmonary capillaries or through a right-to-left intracardiac shunt (Chapter 55), such as a patent foramen ovale. Bubbles may then migrate to the brain, spinal cord, heart, lung, or kidney and lead to tissue ischemia or infarct.

Henry's law states that the solubility of a gas in liquid is proportional to the partial pressure of that gas above the liquid. An increase in partial pressure of gases during descent will therefore cause the amount of gas dissolved in the pulmonary capillaries to increase. Dissolved oxygen is used during normal body metabolism; however, inert nitrogen, which is abundant in inspired air, becomes dissolved in the blood and tissues, particularly in fat, where it is five-fold more soluble than in water. During ascent, decreasing ambient pressure causes tissues to become supersaturated with nitrogen, and nitrogen is subsequently released into blood vessels and tissues as gas bubbles. Decompression-induced gas bubbles cause decompression illness by either mechanical compression of tissues or embolization through blood vessels to end organs. Bubbles that obstruct capillaries or venules damage the endothelium and cause tissue ischemia, which leads to activation of inflammatory mediators or tissue reperfusion injury. Although not well understood, toxic effects due to increased partial pressure of gases also are likely to contribute to symptoms of decompression illness, possibly by denaturing proteins and releasing fatty acids from cell membranes.

CLINICAL MANIFESTATIONS AND DIAGNOSIS

Symptoms of decompression illness can occur within minutes and up to 24 hours or more after exposure to changes in ambient pressure associated with dives of 20 feet in depth or more. The severity of symptoms depends on the rate and the magnitude of the change of ambient pressure and can vary among individuals. Diagnosis is based on clinical manifestations, which can be classified according to whether they are caused by formation of inert nitrogen gas bubbles or the localized toxic effects of gas (associated with decompression sickness), barotrauma associated with descent (sinus or otic barotrauma), barotrauma associated with ascent (pulmonary barotrauma), or more severe arterial gas embolism syndromes.

Symptoms vary according to location of bubble formation. For example, type I decompression sickness, also known as the bends or caisson disease, is typically associated with pain in the joints, from mild to severe, and numbness of the extremities. Rashes and lymphedema may also occur. Symptoms of type II decompression sickness may be systemic (fatigue, hypovolemic shock), cardiopulmonary (cough, substernal chest pain, tachypnea, asphyxia), otic (vertigo, hearing loss), or neurologic (ataxia, aphasia, speech disturbances, incontinence, confusion, personality changes, depression, paralysis, and loss of consciousness).

Otic barotrauma, which typically occurs during descent, can affect the external, middle, or inner ear (Chapter 394). External ear symptoms, such as a sensation of ear fullness or otalgia, are caused by a blockage of the canal, for example, with the use of ear plugs or presence of cerumen. Middle ear symptoms of otalgia, vertigo, tinnitus, transient conductive hearing loss, and facial nerve palsy occur when inadequate equalization of pressures results from blocked eustachian tubes, typically in association with allergic rhinitis or upper respiratory infections. Inner ear barotrauma, which is a more serious form of otic barotrauma, is associated with elevated intracranial pressure and rupture of the inner ear membrane. Inner ear barotrauma causes symptoms of sensorineural deafness, tinnitus, vertigo, nausea, and vomiting. Sinus barotrauma typically occurs during descent, is associated with facial pain and epistaxis, and occurs more frequently in individuals with mucosal inflammation from allergies or infection.

Pulmonary barotrauma, which is the second leading cause of death among divers, should be suspected in postdive individuals, particularly at-risk individuals, with symptoms of sudden pleuritic pain, dyspnea, or coughing. Physical examination findings include tachypnea, subcutaneous emphysema, and dullness to percussion or decreased breath sounds over a pneumothorax. Development of tension pneumothorax (Chapter 86) or severe pneumomediastinum may lead to decreased venous return of systemic blood and reduced cardiac preload, a situation that is characterized by hypotension and may lead to refractory shock or cardiac arrest. Chest and neck radiographs are recommended for diagnosis, particularly because pneumothoraces must be treated with chest tube thoracostomy before recompression therapy.

Because arterial gas embolism syndromes are caused by pulmonary barotrauma, careful neurologic assessment is critical. The neurologic findings are similar to those of an acute stroke (Chapter 376), with manifestations of focal or unilateral motor deficits, visual disturbances, sensory deficits, speech difficulties, and cognitive disturbances, including loss of consciousness. Symptoms typically occur within 10 minutes after ascent. Delayed neurologic symptoms are more likely to be due to type II decompression sickness.

PREVENTION

Education is the most effective method of preventing decompression illness.[3] Before participation in diving-related activities, all individuals should undergo a thorough and intensive training program. Instruction of proper pressure equalization techniques is critical in the prevention of decompression illness. Persons with asthma who wish to dive should be assessed by a physician (preferably knowledgeable in the field of diving medicine), have no wheezing on physical examination, and have normal spirometry before and after exercise. The presence of structural lung disease (e.g., lung cysts or bullae) is associated with a significant increase in the risk for pneumothorax and is a contraindication to diving. Presence of a known right-to-left intracardiac shunt, such as a patent foramen ovale, is not an absolute contraindication to diving, although conservative diving is recommended, and patients should be cautioned that they are at increased risk for decompression illness.

TREATMENT

Symptoms of decompression illness at altitude should be treated with supplemental oxygen and return to the lowest attainable altitude. Serious decompression illness associated with diving requires immediate medical evaluation by emergency personnel, including basic and advanced life support (Chapter 50) when hemodynamic instability is present. Pneumothorax (Chapter 86) should be treated immediately with needle decompression or chest tube thoracostomy. Symptoms that persist for more than 2 hours or increase in intensity require recompression therapy, preferably with 100% oxygen or transfer to a facility with a hyperbaric chamber,[4] where standard protocols should be followed. The only two randomized controlled trials to evaluate recompression therapy found that the addition of tenoxicam (20 mg daily, not available in the United States) or a helium-oxygen mixture (rather than pure oxygen) decreases the number of recompression treatments needed in divers with decompression illness, but neither improved the overall effectiveness of recompression treatment.

PROGNOSIS

Survival of patients with decompression illness depends on prompt medical evaluation and treatment. Immediate hyperbaric oxygen therapy per standard protocols is associated with resolution of symptoms in 95% of cases. However, symptoms of decompression illness, even neurologic deficits, may respond to recompression therapy after delays of 24 hours or more.

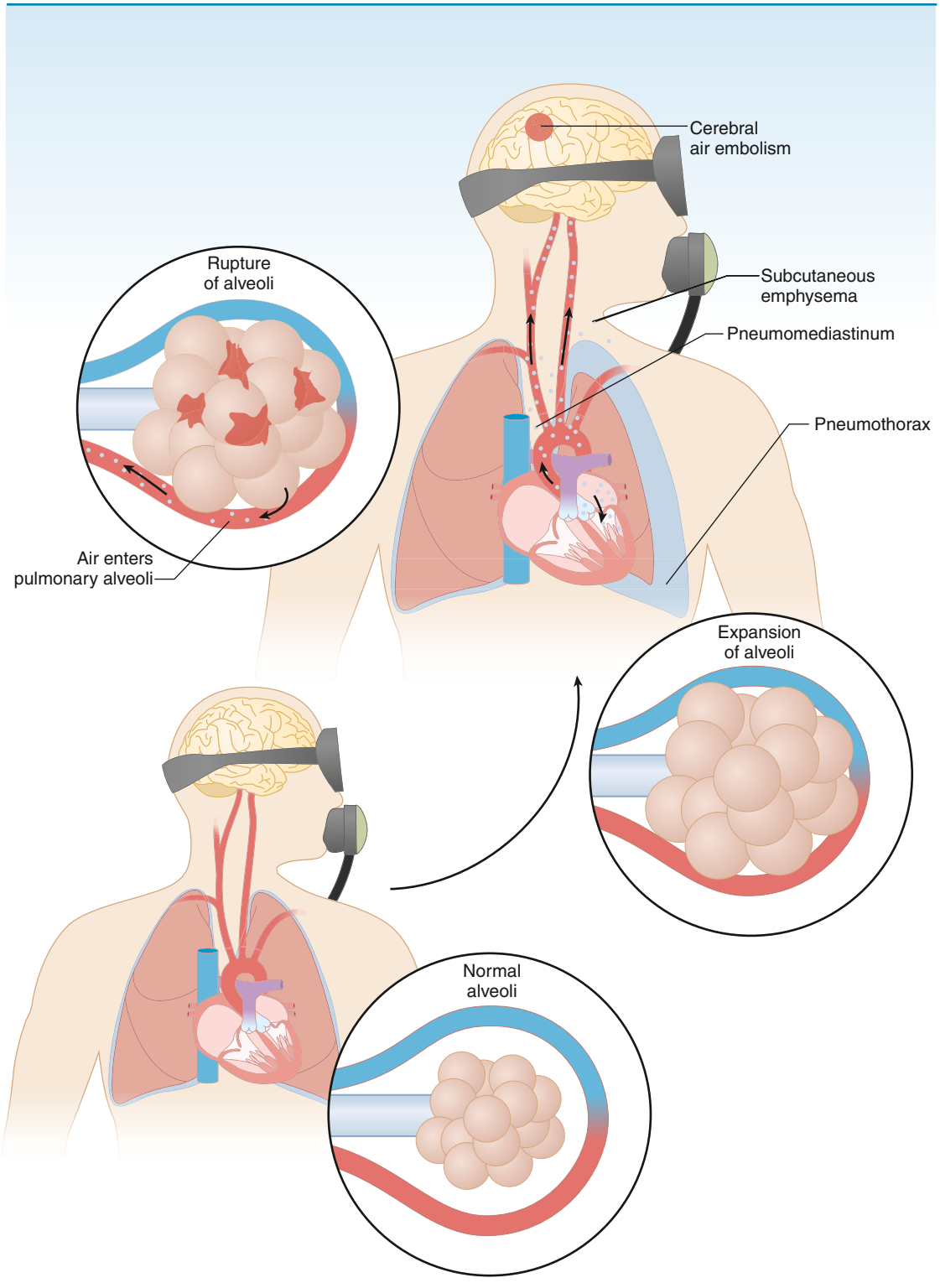

E-FIGURE 82-1. Pulmonary barotrauma in a diver during breath-holding ascent. (From Vann RD, Butler FK, Mitchell SJ, et al. Decompression illness. *Lancet*. 2011;377:153-164, Fig. 1, p. 154.)

INHALATION INJURIES

Smoke Inhalation and Thermal Injury

DEFINITION

Pulmonary complications, largely caused by smoke inhalation, occur in a large proportion of burn victims (Chapter 97) and account for a substantial number of deaths in these patients. Even patients who do not sustain surface burns in a fire can inhale sufficient smoke to result in injury to the lungs or airways.

EPIDEMIOLOGY

Modern building codes and the widespread presence of firefighting personnel in communities have decreased the importance of fire as a cause of death in the United States. However, fire continues to cause several thousand deaths annually. Also, larger-scale fires with mass casualties and wildfires that affect large geographic areas still occur occasionally.

PATHOGENESIS

Smoke loses heat rapidly as it traverses the upper airway, so direct thermal injury is often limited to the mucosa of the supraglottic airway. A notable exception is steam inhalation, which can produce thermal injury throughout the airways. Smoke inhalation injury affects the entire respiratory tract. The pathogenesis of smoke inhalation is complicated by the wide variety of pulmonary irritants in smoke, many of which are directly toxic to respiratory epithelial or alveolar cells: aldehydes such as acrolein, acetaldehyde, and formaldehyde; acids such as hydrochloric, hydrofluoric, and hydrocyanic acid; and ammonia, nitrogen oxides, and phosgene.

Irritants can rapidly induce intense neutrophilic inflammation, which evolves during 12 to 24 hours after injury and is characterized by mucosal edema and ulceration; abnormally increased permeability of pulmonary capillaries with resultant capillary leak; and epithelial, alveolar, and immune cellular dysfunction. Bronchospasm or bronchorrhea may occur, and the processes may result in ARDS. In addition, because oxygen is consumed in fires, breathing of hypoxic air for prolonged periods may potentiate other injuries or cause clinically significant hypoxemia in its own right.

CLINICAL MANIFESTATIONS

Thermal injury to upper airway mucosa can cause airway compromise, particularly due to laryngeal edema, sometimes rapidly and sometimes over the first 12 to 24 hours. Burns to the face, mouth, and neck can externally damage and distort structures of the upper airway and cause airway compromise, both subacutely and late in the course. Inhalation injury manifests primarily with bronchospasm and bronchorrhea, which cause cough, dyspnea, or wheezing and may progress rapidly to respiratory failure. Accumulation of secretions, failure of mucociliary clearance and immune mechanisms, and epithelial necrosis predispose to pulmonary infection, particularly 3 to 5 days after injury. Late pulmonary complications can also be caused indirectly by eschar formation and restriction of thoracic motion.

DIAGNOSIS

Patients with apparent or suspected burn injuries (Chapter 97) should be assessed emergently for airway patency. Head or neck burns, respiratory distress, stridor, or visibly erythematous or edematous oral mucosa should prompt immediate laryngoscopic evaluation of the oropharynx and supraglottic airway. Hypoxemia may develop and may be severe enough to meet criteria for ARDS. Chest radiography should be performed serially to detect the evolution of lung injury or superinfection.

TREATMENT

All patients should receive supplemental oxygen, with the goal of providing a high fractional concentration of inspired oxygen (F_{IO_2}) to reverse the effects of hypoxemia and carbon monoxide inhalation (see later). If airway patency is threatened, endotracheal intubation should be performed immediately.[5] Delay can result in increased edema and greater technical difficulty of intubation. Patients who cannot be intubated should have emergent tracheostomy performed surgically. Because of the risk for ARDS, mechanical ventilation with a goal tidal volume of 4 to 6 mL/kg of ideal body weight should be considered. Extracorporeal membrane oxygenation may occasionally be life saving.[6] Whether inhaled anticoagulants mitigate the development of acute lung injury is unproven. Pulmonary toilet is essential to clear secretions in the face of bronchorrhea and epithelial sloughing. Because of the risk for superinfection, surveillance for infection should be vigilant, including diagnostic bronchoscopy if ventilator-associated pneumonia is suspected.

PROGNOSIS

Patients who survive burns and recover generally do not have long-term pulmonary sequelae. Tracheostomies placed at the time of injury can usually be removed later, unless airway structures are damaged or distorted. Impaired pulmonary function is uncommon but may be manifested as airway hyperresponsiveness that has been termed reactive airway dysfunction syndrome.

E-CIGARETTES/VAPING

Electronic nicotine delivery systems (ENDSs; see Chapter 363) include an e-liquid cartridge, a heating element, and a battery. The e-liquid solution can have variable amounts of nicotine (0 to 26 mg/mL) mixed with flavoring agents. The inhaled e-liquid can irritate the mouth and throat and cause dry coughing. Most concerning, however, is vaping-associated acute lung disease (E-VALI), in which cough, fever, and sometimes severe acute lung injury are typically associated with constitutional and gastrointestinal symptoms.[7-9] Vitamin E acetate, which was commonly added to vaping products that contained tetrahydrocannabinol or cannabidiol, or its breakdown products appears to be a primary cause. E-VALI is now very uncommon since the removal of vitamin E acetate from vaping products, although illicit formulations may still contain it, and cases have been reported since the original outbreak.

Chest radiographs usually show bilateral infiltrates, consistent with ARDS.[9] Bronchoalveolar lavage shows lipid-laden macrophages.

After excluding infection, cessation of exposure and systemic corticosteroids usually lead to clinical improvement, but the steroid dose is uncertain in the absence of clinical trials. However, a substantial proportion of patients have residual abnormalities on their chest radiographs or pulmonary function tests, and the mortality rate is about 2%.[10]

CARBON MONOXIDE POISONING

DEFINITION AND EPIDEMIOLOGY

Carbon monoxide is a colorless, odorless gas produced by the combustion of carbon-based fuels. Because of the ubiquity of these substances, carbon monoxide inhalation is often coincident with smoke inhalation in fires or may occur accidentally in association with malfunctioning equipment or improper venting of emissions from heaters, stoves, combustion motors, or other similar devices. In addition, intentional inhalation of carbon monoxide is a method commonly used in suicide attempts. Carbon monoxide inhalation is the leading cause of death from poisoning (Chapter 96) worldwide.

PATHOBIOLOGY

Carbon monoxide readily diffuses across the alveolar-capillary interface and binds to hemoglobin with extremely high affinity. When the resulting carboxyhemoglobin molecule undergoes an allosteric change at oxygen-binding sites, the ability of bound oxygen to dissociate and to be delivered to peripheral tissues is greatly reduced. This tissue hypoxia can cause severe functional impairment and ischemic injury of oxygen-sensitive tissues, particularly in the brain and heart.

CLINICAL MANIFESTATIONS

Mild carbon monoxide intoxication may go unrecognized because the symptoms are nonspecific and may include headache, nausea, malaise, fatigue, and dizziness. With more severe intoxications, neuropsychiatric symptoms may range from minor disturbances in attention and cognition to agitation, confusion, hallucination, or, in the worst intoxications, seizures or frank coma. Physical findings, which are generally nonspecific, can include tachycardia or hyperthermia. The classic "cherry-red" skin thought to be associated with carbon monoxide intoxication is rarely seen. Other manifestations of severe intoxications may include lactic acidosis, cardiac dysfunction with arrhythmia or ischemia, pulmonary edema, and rhabdomyolysis.

DIAGNOSIS

A high index of suspicion is required for diagnosis because clinical findings are nonspecific. All patients known to have been involved in fires, suicide attempts, or other scenarios compatible with exposures should have arterial carboxyhemoglobin levels checked by co-oximetry. Although levels do not correlate well with clinical findings or risk for complications, symptoms generally occur at carboxyhemoglobin concentrations of 10% or higher.

TREATMENT

All patients should be treated with 100% supplemental oxygen, which competes with carbon monoxide for hemoglobin-binding sites and gradually eliminates it from the blood. If patients require mechanical ventilation because of a depressed neurologic status or respiratory problems, 100% oxygen should be administered by endotracheal tube. Rigorously conducted randomized controlled trials are lacking, but most expert guidelines endorse treatment with hyperbaric oxygen at a pressure of 2.5 to 3.0 atm, which can increase the dissolved oxygen content of blood by more than 10-fold.[11] At least one treatment of approximately 2 hours should be considered in severe cases to reverse the effects of acute intoxication; three hyperbaric oxygen treatments within 24 hours of diagnosis reduce neurocognitive sequelae.

PROGNOSIS

The mortality rate is highly variable according to the severity of intoxication but can approach 30% in severe cases. Approximately two thirds of patients who survive acute intoxication will recover without sequelae. However, the presence of acute brain abnormalities in magnetic resonance imaging portends long-term neuropsychiatric symptoms,[12] including cognitive dysfunction, abnormal mood or affect, memory disturbances, and other motor or sensory abnormalities, which can often occur within the first month but may be delayed for up to 6 to 9 months.

CYANIDE AND OTHER GASES

PATHOBIOLOGY

In addition to carbon monoxide and pulmonary irritants, cyanide gas may be formed when a number of commonly found substances, particularly plastics and textiles, are combusted. This gas is highly toxic and can rapidly cause morbidity and death by binding to cytochrome enzymes and inhibiting cellular respiration.

Other inhaled gases that can injure the lungs in occupational settings include ammonia, chlorine, nitrogen dioxide, organic dust, paraquat, phosgene (which has also been used as a chemical weapon), sulfur dioxide, and toxic metal fumes such as cadmium and mercury.

CLINICAL MANIFESTATIONS AND DIAGNOSIS

Cyanide intoxication typically includes shock, lactic acidosis, and coma; it can rapidly lead to death before results of laboratory studies are available. In the setting of possible exposure, an elevated venous oxygen saturation indicates that cyanide is preventing cells from extracting oxygen from arterial blood.

Other inhaled gases that can produce potent irritant responses include ammonia, chlorine, and nitrogen dioxide ("silo-filler's lung"). Phosgene is notable for its propensity to cause delayed symptoms up to 24 hours after exposure. Other inhalants may produce an acute chemical pneumonitis with respiratory distress (Chapter 81). A diverse group of inhaled toxins can cause syndromes of inhalational fever, including heavy metal fumes, polymer fumes, and organic dust aerosols that contain thermophilic bacteria, gram-negative bacteria and their associated endotoxins, and fungal elements. These inhalations are characterized by fever and malaise with mild respiratory symptoms and are also notable for tachyphylaxis with repeated exposure (and thus are referred to as Monday morning fever in some occupational settings).

TREATMENT

Cyanide intoxication preferably is treated using hydroxocobalamin intravenously (usually 5 mg once, can be repeated for a total of 10 mg) to bind cyanide directly. If no clinical improvement is noted, sodium thiosulfate (12.5 g one-time dose) can be added via a separate intravenous line to detoxify cyanide to less harmful thiocyanate ions.

If hydroxocobalamin is not available, induction of methemoglobinemia, usually with intravenous sodium nitrate (300 mg to induce 15 to 20% methemoglobinemia) is another strategy. Nithiodote, which contains both sodium nitrite and sodium thiosulfate, is a cyanide antidote kit available in the United States. If carboxyhemoglobinemia is present (e.g., due to carbon monoxide poisoning) or the patient has heart disease or lung disease, sodium nitrate is contraindicated because of the additive toxicity of methemoglobinemia.

The mainstay for treatment of other irritating inhalations is to remove the patient immediately from the toxic environment and to provide supportive care for respiratory injury. Depending on the intensity and duration of exposure, most patients will recover completely without sequelae.

OXYGEN TOXICITY

DEFINITION

Hypoxemic respiratory failure often requires treatment with supplemental oxygen to maintain tissue oxygenation. In some settings, such as ARDS, patients may require high F_{IO_2} for prolonged periods to combat severe hypoxia. However, it has long been recognized that oxygen may be toxic to the lungs when it is present in concentrations higher than those found in ambient air.

PATHOBIOLOGY

When the concentration of oxygen in the airways is high, formation of reactive oxygen species and free radicals is increased. Under normal circumstances, innate antioxidant mechanisms in airway epithelia and alveoli are sufficient to abrogate the effect of these molecules. However, under conditions of critical illness, prolonged exposure to increased concentrations of these toxins may overwhelm these defenses. Superoxide, hydrogen peroxide, and hydroxyl radicals may directly oxidize cellular components. Cellular damage potentiates inflammation and may be synergistic with inflammatory processes already underway in the diseased lung; the result can be alveolar edema, formation of hyaline membranes, hypoxemia, and progression to fibrosis and obliteration of alveolar and capillary structures. In addition, washout of nitrogen from air spaces can result in absorptive atelectasis if oxygen is removed by the circulation faster than it can be replenished by ventilation (especially in the setting of ventilation-perfusion mismatch). Hyperoxia can also worsen hypercapnia through multiple mechanisms, as occurs in patients with chronic obstructive pulmonary disease who suffer from carbon dioxide retention.

CLINICAL MANIFESTATIONS AND DIAGNOSIS

Although the exact levels of hyperoxia that cause lung injury are unclear, injury appears to occur with exposure to F_{IO_2} of 50 to 60% after exposures as short as 6 hours in duration.[13] Because of the high flow of supplemental oxygen required to deliver this F_{IO_2}, oxygen toxicity is observed primarily in mechanically ventilated patients who are being treated for hypoxemic respiratory failure. This level of exposure can cause a clinically detectable tracheobronchitis, demonstrable by symptoms of cough and dyspnea, as well as airway erythema that is visible macroscopically on bronchoscopy. This syndrome may impair mucociliary clearance and result in impaction of secretions, especially in conjunction with absorptive atelectasis.

Patients who may be susceptible to oxygen toxicity generally already have a significant degree of parenchymal injury from other processes. Thus, although some patients may appear to display a syndrome of worsening air space disease, atelectasis, consolidation, hypoxemia, and diffuse alveolar damage, it is not clear when these changes are related to oxygen therapy or merely occur as part of the acute lung injury from other causes.

TREATMENT

Because the threshold level for oxygen toxicity is unknown, a general guideline for treatment of hypoxemic respiratory failure (Chapter 90) is that patients be ventilated with the lowest possible F_{IO_2} that is required to restore an acceptable oxygen saturation. An Sa_{O_2} of 90%, which corresponds to Pa_{O_2} of 55 to 60 mm Hg, is generally considered the minimum acceptable level, and targeting a Pa_{O_2} of 60 mm Hg is as safe and efficacious as targeting a Pa_{O_2} of 90 mm Hg in intensive care unit patients who require an inspired oxygen concentration of at least 50%.[A9] Unfortunately, under conditions of severe hypoxemia, such as ARDS, patients often require an F_{IO_2} approaching 100% to achieve this oxygen level. Maneuvers to improve oxygenation without increasing F_{IO_2} include paralysis with continuous infusions of neuromuscular blocking agents; inhaled pulmonary vasodilators; red blood cell transfusions to improve the delivery of oxygen; alternative ventilatory strategies, such as high-frequency oscillatory ventilation, airway pressure-release ventilation, inverse-ratio ventilation, and prone positioning; and alveolar recruitment maneuvers using positive end-expiratory pressure or transiently increased inflation pressures (Chapter 91).

PROGNOSIS

Patients who sustain oxygen toxicity in the setting of prior bleomycin exposure may be left with residual pulmonary fibrosis. In other patients, the incremental impact of oxygen toxicity on prognosis is unknown.

LUNG INJURY

Radiation Lung Injury

DEFINITION

Accidental or occupational radiation exposures (Chapter 18) are generally characterized by systemic toxicity that outweighs any injury to the lungs. As such, radiation lung injury refers to a pneumonitis that can progress to pulmonary fibrosis and that results from therapeutic use of ionizing radiation, usually in the treatment of malignant neoplasms.

EPIDEMIOLOGY

As many as 50% of patients receiving thoracic radiation will display radiographic abnormalities after treatment; duration and dose of therapy affect the odds for development of lung injury. However, most of these patients will never have clinically significant radiation lung injury. For unclear reasons, the incidence of lung injury appears to vary by the type of underlying malignant disease and modality of treatment, with lung cancer carrying the greatest risk. The highest frequency is in lung cancer (10 to 20%).

PATHOBIOLOGY AND CLINICAL MANIFESTATIONS

The pathogenesis of radiation lung injury is often divided into three or four phases on the basis of time course. Typically, the early phase occurs immediately after exposure and is characterized by injury to alveolar cells, resulting in mild alveolitis, recruitment of inflammatory cells, capillary leak, and pulmonary edema. These changes are usually asymptomatic; patients do not usually come to clinical attention, although the chest radiograph will be abnormal if it is performed. In most patients, these changes resolve without progression within 1 to 3 months.

A minority of patients will progress to the next phase, in which alveolar cells desquamate and the air spaces fill with protein-rich fluid. In this phase, referred to as radiation pneumonitis, patients will complain of cough, dyspnea, and occasionally fever or pleuritic chest pain. Severe cases may present with hypoxemic respiratory failure. This phase generally resolves within 3 to 6 months after exposure and is followed by an organizing phase, in which alveolar edema resolves and the damaged alveoli heal. Clinically, patients generally show improvement in symptoms during this period. However, this phase is also characterized by fibroblast proliferation and deposition of collagen in the lung. In a minority of patients, this process will proceed unchecked and result in clinically significant fibrosis, with progressive loss of alveolar-capillary surface and development of restrictive lung disease.

DIAGNOSIS

Clinical history and radiographic evaluation are often sufficient for diagnosis of radiation lung injury, because patients typically present with respiratory symptoms and opacities on chest radiography after undergoing radiation therapy. Radiography may show air space disease with alveolar filling or consolidation during the pneumonitis phase, which may progress to an interstitial pattern and eventual honeycombing with parenchymal distortion in the chronic phase.[14] Because radiation characteristically causes injury only within directly affected lung tissue, radiography may show opacities that are well delineated and form straight lines that cross anatomically distinct regions of lung. This finding is rarely, if ever, seen in other conditions.

The differential diagnosis may include pneumonia, recurrence, and metastatic malignant disease. On occasion, invasive evaluation with bronchoalveolar lavage or even biopsy is required to exclude these possibilities if the clinical history and imaging do not provide a diagnosis.

TREATMENT AND PREVENTION

Corticosteroids, such as prednisone 1 mg/kg body weight per day for 2 to 4 weeks followed by a slow taper over several weeks or months, are the mainstay of therapy for radiation pneumonitis.[15] Patients often show a dramatic response to treatment, and symptoms may recur after treatment is discontinued. Other immunosuppressive agents have been used successfully in case reports of patients who failed to respond to corticosteroids. No treatments are currently available for radiation fibrosis.

Reduction in radiation dose and volumes are the best approach to reduce incidence and severity of radiation-induced lung injury. Prophylactic amifostine, a cytoprotective agent, at 340 mg/m^2 IV daily prior to irradiation significantly reduces the risk for radiation pneumonitis but does not improve survival in patients who receive radiation treatment for lung cancer. Side effects, including hypotension, nausea, and vomiting, limit its use.

PROGNOSIS

Within 2 years after initial exposure, progression will usually slow, and symptoms and lung function will stabilize or improve. After this time, further improvement or worsening is uncommon. In severe cases that become chronic, patients may develop features of advanced interstitial lung disease, including pulmonary hypertension and hypoxic respiratory failure.

ASPIRATION INJURY

DEFINITION AND EPIDEMIOLOGY

Aspiration, which is defined as the inhalation of any nongaseous foreign substance into the lungs, generally refers specifically to the inhalation of gastric contents or secretions from the oropharynx. Aspiration is a common occurrence, and in most cases it resolves spontaneously without clinical manifestations. Clinically significant aspiration can range from acute pneumonitis and respiratory failure caused by a single massive aspiration to chronic symptoms of respiratory disease caused by recurrent small-scale aspiration. These syndromes may overlap with pneumonia that occurs when the lungs are exposed to bacteria from the gastrointestinal tract (Chapter 85).

PATHOBIOLOGY

The common element of clinically significant aspiration is impairment of normal airway protective mechanisms. Under normal circumstances, the airway is protected by the normal swallowing mechanism, the cough reflex, and the anatomy of the supraglottic airway. However, even healthy individuals experience microaspiration despite having functional protective mechanisms. These secretions are handled by normal pulmonary clearance mechanisms.

Any disturbance of these protective mechanisms can result in aspiration injury to the lungs. An altered level of consciousness can impair normal swallowing and suppress the cough reflex. Even in patients who are alert, neurologic injury can result in dysphagia and concomitant aspiration, as in patients who have bulbar neurologic deficits in association with ischemic stroke. Patients with altered airway or oropharyngeal anatomy, such as patients who have received surgical or radiation therapy for head and neck malignant neoplasms, may also be highly susceptible to aspiration of oral secretions.

The nature of the aspirated material is also important in determining whether an injury occurs. Materials with a pH lower than 2.5, such as acidic gastric contents, are much more likely to cause a significant chemical pneumonitis. Particulate matter also increases the likelihood for development of clinically significant inflammation. A large-volume aspiration with distribution throughout the lungs is more likely to produce an acute, severe pneumonitis.

When material has been aspirated into the lungs, the injury that occurs is similar to a chemical burn. Acid rapidly injures airway epithelial and alveolar cells; within hours, cells become dysfunctional and capillary leak occurs, resulting in profound noncardiogenic pulmonary edema. In severe cases, diffuse alveolar damage may result.

CLINICAL MANIFESTATIONS

The classic eponym applied to aspiration pneumonia is Mendelsohn syndrome, which refers to a single, large-volume aspiration of gastric contents followed by rapidly progressive hypoxemic respiratory failure that develops within hours. Patients may suffer from cough, dyspnea, fever, and respiratory distress. Physical examination may reveal diffuse crackles, wheezing, cyanosis, and hypotension. Chest radiography may show a pattern of alveolar filling with diffuse bilateral involvement or involvement of dependent regions, particularly the right lower lobe if the patient is upright at the time of aspiration. In many patients, this period of acute deterioration is followed by stabilization and resolution within 2 or 3 days. In other patients, deterioration may continue, and patients may meet clinical criteria for ARDS. If the volume of aspirated material is large enough, the initial aspiration may be sufficient to cause tracheal obstruction and asphyxiation.

In patients who initially improve, a small percentage will show further deterioration after 2 or 3 days. This deterioration should prompt an investigation for bacterial superinfection.

DIAGNOSIS

The clinical history and presentation are generally sufficient for diagnosis of aspiration pneumonitis. Bacterial pneumonia and other causes of ARDS also should be considered, as should cardiogenic pulmonary edema. Airway erythema and edema on bronchoscopy can be suggestive of aspiration. Bronchoalveolar lavage may help evaluate for the presence of bacterial infection.

PREVENTION

Prevention should focus on identification of patients who are at risk for aspiration[16] and then use of strategies to minimize the risk. Patients with swallowing dysfunction or airway abnormalities can work with speech pathologists to learn effective strategies for swallowing. Patients who are unsuccessful or not suitable for this approach may benefit from tracheostomy or enteral tube feedings, which do not prevent microaspiration but can prevent large-volume aspiration. However, the risk for aspiration pneumonia is no different among patients with nasogastric tubes compared with patients who have percutaneous endoscopy gastrostomy tubes. In hospitalized patients, particularly patients with an altered mental status due to illness or sedation, simple strategies such as avoidance of oral feeding and semirecumbent positioning can effectively reduce the risk for aspiration. Use of histamine-2 blockers or proton pump inhibitors (Chapter 125) can alter gastric pH to reduce the risk for injury from acidic secretions.

TREATMENT

Because of the acuity and severity of aspiration pneumonitis, immediate attention should be paid to maintaining a patent airway. The oropharynx and trachea should be suctioned to clear any potentially obstructing material, and endotracheal intubation should be performed if necessary (Chapter 91). Bronchoscopy is often performed to clear residual particulate or solid matter, but it cannot remove acidic secretions, which damage airways and parenchyma quickly and then are rendered neutral. Oxygen supplementation should be provided as needed for hypoxia. Corticosteroids have not been shown to be beneficial. Antibiotics should be reserved for patients who appear to have developed bacterial superinfection (Chapter 85).

PROGNOSIS

For patients with severe respiratory failure or ARDS, mortality can be high. In others, improvement should be expected within days. If the underlying factor that led to aspiration is irreversible, patients have an increased likelihood of recurrent episodes.

LIPOID PNEUMONIA

DEFINITION

Lipoid pneumonia is a chronic inflammatory reaction of the lungs to the presence of lipid substances. Exogenous lipoid pneumonia results from the aspiration of vegetable, animal, or (most commonly) mineral oils.

PATHOBIOLOGY

The most frequently implicated agent is mineral oil used as a laxative and to reduce dysphagia, either in clear liquid form or as petroleum jelly. Mineral oil is bland and, when introduced into the pharynx, can enter the bronchial tree without eliciting the cough reflex. It also mechanically impedes the ciliary action of the airway epithelium. The risk for mineral oil aspiration is increased in debilitated or senile patients, in those with neurologic disease that interferes with deglutition, and in patients with esophageal disease. Mineral oil taken as nose drops to relieve nasal dryness can also cause lipoid pneumonia. Inhalation of mineral oil mist by airplane and automobile mechanics has also been implicated as a cause.

Mineral oils, which cannot be hydrolyzed in the body, provoke a chronic inflammatory reaction that may not become clinically overt until years later. In the alveolar spaces, macrophages accumulate and phagocytose the emulsified oil. Some macrophages disintegrate, releasing their lysosomal enzymes and oil. The alveolar septa become thickened and edematous, containing lymphocytes and lipid-laden macrophages. Oil droplets are seen in the pulmonary lymphatics and hilar nodes. Later, fibrosis develops, and the normal lung architecture is effaced. A single pathologic specimen may include both the early inflammatory and the later fibrotic picture, in keeping with repetitive aspirations during many months or years. Nodular lesions may grossly resemble tumor and be called paraffinomas.

CLINICAL MANIFESTATIONS

Most patients are asymptomatic and come to the physician's attention because of an abnormal chest radiograph. When patients are symptomatic, cough and exertional dyspnea are the most frequent complaints. Chest pain (sometimes pleuritic), hemoptysis, fever (usually low grade), chills, night sweats, and weight loss may occur. Findings on physical examination may be completely normal, but fever, tachypnea, dullness on percussion of the chest, bronchial or bronchovesicular breath sounds, rales, and rhonchi may be found. Clubbing and cor pulmonale are rare.

DIAGNOSIS

In mild lipoid pneumonia, arterial blood gas values may be normal with the patient at rest but may show hypoxemia after exercise. In more severe disease, resting hypoxemia, hypocapnia, and mild respiratory alkalosis develop. Pulmonary function testing reveals a restrictive ventilatory defect; lung compliance is decreased. The only specific laboratory finding is the presence in sputum of macrophages with clusters of vacuoles that are 5 to 50 μm in diameter and that stain deep orange with Sudan IV; extracellular droplets may stain similarly.

On radiographic examination, the earliest abnormalities are air space infiltrates, most often in the dependent portions of the lung.[17] The infiltrates may be unilateral or bilateral, localized or diffuse. Air bronchograms may be seen. Hilar adenopathy and pleural reaction are rare. As fibrosis develops, volume loss occurs, and linear and nodular infiltrates appear. A solid lesion that closely resembles bronchogenic carcinoma may develop. High-resolution computed tomography usually shows consolidated areas of low attenuation and "crazy paving" (Fig. 82-1).

The differential diagnosis is extensive, particularly in the late phase, when multiple other causes of pulmonary fibrosis must be considered. The key to the correct diagnosis before biopsy is the history of chronic oral or intranasal use of an oil- or a lipid-based product or an occupational exposure to oil mists. The presence of lipid-laden macrophages in sputum or bronchoalveolar lavage fluid also can be used to confirm the diagnosis, particularly in conjunction with typical findings on high-resolution computed tomography.

TRANSFUSION-RELATED ACUTE LUNG INJURY

DEFINITION

The syndrome of transfusion-related acute lung injury (TRALI; Chapter 162) involves the rapid onset of respiratory distress within minutes to hours after the transfusion of blood products (fresh-frozen plasma, platelets, and red blood cells). The initial clinical picture is indistinguishable from acute lung injury or ARDS due to other causes, such as sepsis, multiple trauma, and lung injury. TRALI may similarly be confused with pulmonary edema due to volume overload (Chapter 45).

TREATMENT AND PREVENTION

When the diagnosis has been made and the aspiration stopped, the subsequent course is variable. Because the only way the lung can dispose of mineral oil is by expectoration, the patient should be instructed in coughing exercises to be performed many times each day for months. Expectorants have not been shown to help. In some uncontrolled case reports, systemic corticosteroids have been used successfully at varying doses and length, but the literature suggests that they cannot be routinely recommended for treatment.

FIGURE 82-1. Lipoid pneumonia on a computed tomographic scan.

EPIDEMIOLOGY

The true incidence of TRALI is unknown; incidence rates are underestimated because of the difficulty in distinguishing TRALI from other causes of acute respiratory failure and the labor-intensive and costly diagnostic evaluation required. Reported incidences range from 1 in 1000 to 1 in 100,000 units of blood products transfused. The risk for TRALI varies according to the volume and type of blood product transfused, with pooled products associated with a higher incidence. In fact, risk factors for TRALI (pre-existing positive fluid balance, shock, severe multisystem disease) are the same as for noncardiogenic pulmonary edema (Chapter 90).[18] Only 8 to 21 TRALI-related deaths are reported to the U.S. Food and Drug Administration annually, and even liberal estimates accounting for underreporting suggest the number may be only as high as 300 per year of an estimated 25 million transfusions in the United States.

PATHOBIOLOGY

The physiologic manifestations of TRALI are caused by alveolar filling with fluid and protein.[19] This alveolar process is the result of increased microvascular permeability due to pulmonary endothelial damage mediated by either leukocyte antibodies or the priming and activation of neutrophils in the pulmonary circulation by bioactive substances.

TRALI most commonly occurs when human leukocyte antigen (HLA) type I or II or neutrophil-specific antigen antibodies from the donor attach to the recipient's leukocytes, leading to the release of injurious oxidative and nonoxidative products. Development of HLA antibodies occurs commonly in women during pregnancy, and increasing parity in female blood donors is associated with an increased risk for TRALI.

Episodes of TRALI occurring in patients without HLA or neutrophil-specific antigen antibodies in either the donor or recipient are thought to be caused by a two-hit process of neutrophil priming and activation. Neutrophils are primed and sequestered in the lung by conditions that often occur in patients requiring blood products, such as multiple trauma, surgery, or sepsis. Primed neutrophils are then activated by bioactive lipids and cytokines stored in the blood products, thereby leading to lung injury and alveolar damage. Levels of these bioactive lipids or cytokines may increase after prolonged storage of blood products.

CLINICAL MANIFESTATIONS

Although most cases of TRALI present within 1 to 2 hours after the transfusion of blood products, tachypnea, hypoxemia, cyanosis, dyspnea, and fever can develop during the transfusion or up to 6 hours later. Hypertension or hypotension commonly occurs, depending on the severity of the reaction. Copious amounts of pink, frothy edema fluid may be present. Lung auscultation generally reveals bilateral crackles and decreased breath sounds in dependent lung zones.

DIAGNOSIS

Bilateral patchy infiltrates consistent with alveolar edema are found on plain chest radiographs, typically without effusions. Arterial blood gas analysis demonstrates reduced P_{O_2}, and further laboratory testing may reveal thrombocytopenia or a transient leukopenia. Diagnosis of TRALI type I requires the presence of the following: acute onset of hypoxemia with P_{aO_2}/F_{IO_2} of less than 300 mm Hg or room air oxygen saturation of less than 90% during or within 6 hours after a transfusion, bilateral infiltrates on the chest radiograph, no evidence of left atrial hypertension, no preexisting acute lung injury before transfusion, and no temporal relationship to an alternative risk factor for acute lung injury.

The diagnosis of TRALI type II (formerly known as possible TRALI) is made in patients who had an acute lung injury within 6 hours of transfusion, had a stable respiratory status for 12 hours before transfusion, but also had either another concurrent risk factor for acute lung injury or a pre-existing mild acute lung injury.[20] In these situations, a prior inflammatory lung condition may predispose the patient to develop TRALI.

TREATMENT

Most cases are self-limited and resolve within hours to days with supplemental oxygen and supportive care. Volume resuscitation, with or without vasopressors, is required for hypotension. Mechanical ventilation should be managed as for any other case of acute lung injury, with the implementation of a low tidal volume ventilation strategy to prevent further ventilator-induced lung injury. Diuresis should be attempted cautiously and may even be detrimental because intravascular filling pressures are often low.

PROGNOSIS

The mortality of TRALI is approximately 5%. If an implicated donor can be identified, the recipient should not receive any further transfusions from that donor, but patients are not at increased risk for further episodes of TRALI from nonimplicated donor transfusions.

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83 SARCOIDOSIS

MICHAEL C. IANNUZZI

DEFINITION

Sarcoidosis, a systemic granulomatous disease of unknown cause, is characterized by a variable clinical presentation and course. More than 90% of patients exhibit thoracic involvement with mediastinal and hilar lymph node enlargement or parenchymal lung disease, but any organ may be involved. The presentation and course vary from asymptomatic disease with spontaneous resolution to organ system failure and even death.

EPIDEMIOLOGY

Sarcoidosis occurs worldwide, affects people of all racial and ethnic groups, and may present at any age. Sarcoidosis usually develops before the age of 50 years, with the incidence peaking at 20 to 39 years. The incidence of sarcoidosis fluctuates throughout the world, most likely because of differences in the disease presentation and the surveillance methods used. The annual incidence of sarcoidosis is highest in Northern European countries, where it is 5 to 40 cases per 100,000 people. The incidence in Japan is about 1 to 2 cases per 100,000 people. In the United States, the adjusted annual incidence among Black Americans is about 3.5 times higher than among White Americans (35.5 cases per 100,000 compared with 10.9 per 100,000). Regardless of ethnic or racial group, sarcoidosis affects women more often. The reportedly low incidence in certain regions such as Africa, China, India, and Russia may be due to decreased access to health care, minimal surveillance, and misdiagnosis of sarcoidosis as tuberculosis or leprosy.

Black women in the United States have the highest lifetime risk for developing sarcoidosis (2.7%). In both Black men and women, sarcoidosis occurs later in life, peaks in the fourth decade, and is more likely to be chronic and fatal. Socioeconomic status does not affect the incidence of sarcoidosis, but low income and other financial barriers to care are associated with more severe sarcoidosis, even after adjustment for age, sex, and race or ethnic group.

Sarcoidosis clusters in families.[1] A Scandinavian registry study of 210 twin pairs identified an 80-fold increased risk for sarcoidosis in monozygotic

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EPIDEMIOLOGY

The true incidence of TRALI is unknown; incidence rates are underestimated because of the difficulty in distinguishing TRALI from other causes of acute respiratory failure and the labor-intensive and costly diagnostic evaluation required. Reported incidences range from 1 in 1000 to 1 in 100,000 units of blood products transfused. The risk for TRALI varies according to the volume and type of blood product transfused, with pooled products associated with a higher incidence. In fact, risk factors for TRALI (pre-existing positive fluid balance, shock, severe multisystem disease) are the same as for noncardiogenic pulmonary edema (Chapter 90).[18] Only 8 to 21 TRALI-related deaths are reported to the U.S. Food and Drug Administration annually, and even liberal estimates accounting for underreporting suggest the number may be only as high as 300 per year of an estimated 25 million transfusions in the United States.

PATHOBIOLOGY

The physiologic manifestations of TRALI are caused by alveolar filling with fluid and protein.[19] This alveolar process is the result of increased microvascular permeability due to pulmonary endothelial damage mediated by either leukocyte antibodies or the priming and activation of neutrophils in the pulmonary circulation by bioactive substances.

TRALI most commonly occurs when human leukocyte antigen (HLA) type I or II or neutrophil-specific antigen antibodies from the donor attach to the recipient's leukocytes, leading to the release of injurious oxidative and nonoxidative products. Development of HLA antibodies occurs commonly in women during pregnancy, and increasing parity in female blood donors is associated with an increased risk for TRALI.

Episodes of TRALI occurring in patients without HLA or neutrophil-specific antigen antibodies in either the donor or recipient are thought to be caused by a two-hit process of neutrophil priming and activation. Neutrophils are primed and sequestered in the lung by conditions that often occur in patients requiring blood products, such as multiple trauma, surgery, or sepsis. Primed neutrophils are then activated by bioactive lipids and cytokines stored in the blood products, thereby leading to lung injury and alveolar damage. Levels of these bioactive lipids or cytokines may increase after prolonged storage of blood products.

CLINICAL MANIFESTATIONS

Although most cases of TRALI present within 1 to 2 hours after the transfusion of blood products, tachypnea, hypoxemia, cyanosis, dyspnea, and fever can develop during the transfusion or up to 6 hours later. Hypertension or hypotension commonly occurs, depending on the severity of the reaction. Copious amounts of pink, frothy edema fluid may be present. Lung auscultation generally reveals bilateral crackles and decreased breath sounds in dependent lung zones.

DIAGNOSIS

Bilateral patchy infiltrates consistent with alveolar edema are found on plain chest radiographs, typically without effusions. Arterial blood gas analysis demonstrates reduced P_{O_2}, and further laboratory testing may reveal thrombocytopenia or a transient leukopenia. Diagnosis of TRALI type I requires the presence of the following: acute onset of hypoxemia with P_{aO_2}/F_{IO_2} of less than 300 mm Hg or room air oxygen saturation of less than 90% during or within 6 hours after a transfusion, bilateral infiltrates on the chest radiograph, no evidence of left atrial hypertension, no preexisting acute lung injury before transfusion, and no temporal relationship to an alternative risk factor for acute lung injury.

The diagnosis of TRALI type II (formerly known as possible TRALI) is made in patients who had an acute lung injury within 6 hours of transfusion, had a stable respiratory status for 12 hours before transfusion, but also had either another concurrent risk factor for acute lung injury or a pre-existing mild acute lung injury.[20] In these situations, a prior inflammatory lung condition may predispose the patient to develop TRALI.

TREATMENT

Most cases are self-limited and resolve within hours to days with supplemental oxygen and supportive care. Volume resuscitation, with or without vasopressors, is required for hypotension. Mechanical ventilation should be managed as for any other case of acute lung injury, with the implementation of a low tidal volume ventilation strategy to prevent further ventilator-induced lung injury. Diuresis should be attempted cautiously and may even be detrimental because intravascular filling pressures are often low.

PROGNOSIS

The mortality of TRALI is approximately 5%. If an implicated donor can be identified, the recipient should not receive any further transfusions from that donor, but patients are not at increased risk for further episodes of TRALI from nonimplicated donor transfusions.

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For the General References and other additional features, please visit Elsevier eBooks+ at https://ebooks.health.elsevier.com.

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83 SARCOIDOSIS

MICHAEL C. IANNUZZI

DEFINITION

Sarcoidosis, a systemic granulomatous disease of unknown cause, is characterized by a variable clinical presentation and course. More than 90% of patients exhibit thoracic involvement with mediastinal and hilar lymph node enlargement or parenchymal lung disease, but any organ may be involved. The presentation and course vary from asymptomatic disease with spontaneous resolution to organ system failure and even death.

EPIDEMIOLOGY

Sarcoidosis occurs worldwide, affects people of all racial and ethnic groups, and may present at any age. Sarcoidosis usually develops before the age of 50 years, with the incidence peaking at 20 to 39 years. The incidence of sarcoidosis fluctuates throughout the world, most likely because of differences in the disease presentation and the surveillance methods used. The annual incidence of sarcoidosis is highest in Northern European countries, where it is 5 to 40 cases per 100,000 people. The incidence in Japan is about 1 to 2 cases per 100,000 people. In the United States, the adjusted annual incidence among Black Americans is about 3.5 times higher than among White Americans (35.5 cases per 100,000 compared with 10.9 per 100,000). Regardless of ethnic or racial group, sarcoidosis affects women more often. The reportedly low incidence in certain regions such as Africa, China, India, and Russia may be due to decreased access to health care, minimal surveillance, and misdiagnosis of sarcoidosis as tuberculosis or leprosy.

Black women in the United States have the highest lifetime risk for developing sarcoidosis (2.7%). In both Black men and women, sarcoidosis occurs later in life, peaks in the fourth decade, and is more likely to be chronic and fatal. Socioeconomic status does not affect the incidence of sarcoidosis, but low income and other financial barriers to care are associated with more severe sarcoidosis, even after adjustment for age, sex, and race or ethnic group.

Sarcoidosis clusters in families.[1] A Scandinavian registry study of 210 twin pairs identified an 80-fold increased risk for sarcoidosis in monozygotic

ABSTRACT

Sarcoidosis affects people of all racial and ethnic groups at any age, with an incidence peaking at 20 to 39 years. Sarcoidosis is immunologically mediated, with the accumulation of granulomas representing the basic pathologic abnormality. Multiple inciting infectious or environmental agents rather than a single pathogen likely cause sarcoidosis. Sarcoidosis clusters in families. Major histocompatibility complex (MHC) genes and non-MHC genes have been implicated as genetic risk factors. Any organ may be involved. Intrathoracic involvement occurs in up to 90% of patients. Clinical presentation varies, with as many as 30 to 50% of patients without symptoms at the time of diagnosis. Symptomatic sarcoidosis may present insidiously or acutely. Symptomatic individuals commonly experience night sweats, weight loss, and fatigue. With respiratory tract involvement, symptoms include dry cough, dyspnea, and vague chest pain. The most common radiographic finding is intrathoracic lymph node enlargement, with or without parenchymal lung involvement. Skin involvement occurs in 25 to 35% of patients. Erythema nodosum occurs in about 10% of patients, usually as part of Löfgren syndrome. Any part of the eye and adnexa may be involved, with uveitis sometimes preceding the diagnosis of sarcoidosis by decades. Magnetic resonance imaging (MRI) and positron emission tomography (PET) scans detect cardiac sarcoidosis in 25 to 30% of patients in the United States and up to 60% in Japan. The diagnosis of sarcoidosis should be based on compatible clinical and radiographic findings supported by histologic evidence of noncaseating granulomas. Corticosteroids and other immunosuppressant drugs may be necessary for treating symptomatic patients or patients who develop organ dysfunction.

KEYWORDS

sarcoidosis
granuloma
Löfgren
neurosarcoidosis
uveitis

compared with a 7-fold increase in dizygotic twins. Familial sarcoidosis occurs in 10% of cases from the Netherlands, 7.5% from Germany, 6% from the United Kingdom, 4.7% from Finland, and 0.8% from Spain. In the United States, sarcoidosis patients are five times as likely to have siblings or parents with sarcoidosis as control subjects. However, less than 1% of the first-degree relatives of patients with sarcoidosis are affected, so screening for disease in asymptomatic relatives is ineffective.

PATHOBIOLOGY

The development and accumulation of granulomas represent the basic pathologic abnormality in sarcoidosis (E-Fig. 83-1). Sarcoidal granulomas are tightly organized collections of macrophages and macrophage-derived epithelioid cells encircled by lymphocytes. Fused epithelioid cells, which become multinucleated giant cells, are often found scattered throughout the granuloma. This structural appearance suggests that the granuloma is assembled to contain an inciting agent.

Granuloma formation begins with HLA-mediated processing of antigens by macrophages. T-cell activation follows, with oligoclonal expansion of $CD4^+$ (helper-inducer) lymphocytes. These $CD4^+$ cells, primarily of the T_H1 phenotype, produce interleukin-2 (IL-2) and interferon-γ (IFN-γ). A complex interplay of cytokines, along with macrophage-derived tumor necrosis factor-α, organizes the inflammatory cells into granulomas. Additional T-cell phenotypes, T_H17 and T-regulatory cells (Treg), help to orchestrate the formation, perpetuation, and resolution of sarcoidal granulomas.[2] Treg cell activity, which can abolish IL-2 production and inhibit T-cell proliferation, is likely responsible for the immune paradox that exists in sarcoidosis. Patients often develop anergy, as indicated by a suppressed response to tuberculin, despite active granulomatous inflammation. Although sarcoidosis is predominantly a T-cell–driven disease, the presence of polyclonal hyperglobulinemia, increased numbers of circulating B cells, and a clinical response to anti–B-cell therapies indicates that B lymphocytes also play a role.

In some cases, likely due to unbridled inflammation, fibroblasts and collagen encase the granulomas and lead to fibrosis, which in part may be due to a noninflammatory healing response to epithelial injury. The fibrotic process irreversibly alters organ architecture and function.

Multiple inciting agents rather than a single pathogen are likely to cause sarcoidosis. Airborne antigens are suspected because the lungs, followed by the eyes and skin, are the most commonly involved organs. A microbial origin of the antigens is favored because sarcoidosis occurs sporadically in clusters and is worldwide. Sarcoidosis may recur in transplanted organs and can develop in recipients of tissues from donors with sarcoidosis. Several environmental exposures are modestly associated with the risk for sarcoidosis, each with odds ratios of about 1.5: mold or mildew, musty odors at work, agricultural employment, and pesticide-using industries. Epidemiologic studies suggest a potential causal association between sarcoidosis and occupational exposure to specific agents.[3] Mycobacteria and propionibacteria have long been candidates as causative sarcoidal antigens,[4] but an infectious cause for sarcoidosis remains to be firmly demonstrated.

Major histocompatibility complex (MHC) genes and non-MHC genes located on the short arm of chromosome 6p have been implicated as genetic risk factors for sarcoidosis HLA-DQB1*0201, and HLA-DRB1*0301 alleles are strongly associated with acute disease and good prognosis. The HLA-DRB1*1501/DQB1*0602 haplotype predicts a chronic course and severe pulmonary sarcoidosis.[5] Genome-wide scans and whole-genome sequencing have identified several gene candidates including *ANXA11* (annexin A11), *BTNL2* (butryophillin-like 2 gene), *Notch 4* (neurogenic locus notch homolog protein 4), *Rab-23* (Ras-related protein), *XIAP*-associated factor (*XAF1*), Janus kinase 2 (*Jak2*), BTB domain and CNC homology 2 (*BACH2*), and neutrophil cytosolic factor 1 (*NCF1*).[6]

CLINICAL MANIFESTATIONS

Patients may present with any organ involved, with or without concomitant intrathoracic involvement. The severity of symptoms and organ dysfunction also varies, and as many as 30 to 50% of patients have no symptoms at the time of diagnosis. Clinical manifestations also vary by ethnicity, race, and sex, as well as by the particular organ system predominantly affected.

Sarcoidosis often first comes to attention during routine screening when enlarged mediastinal and hilar lymph nodes are detected on a chest radiograph (Figs. 83-1 and 83-2). Symptomatic individuals commonly experience night sweats and weight loss. Fatigue, which may be related to inflammation, depression, small fiber neuropathy, and corticosteroid use, often remains a prominent problem and can lead to impaired quality of life.

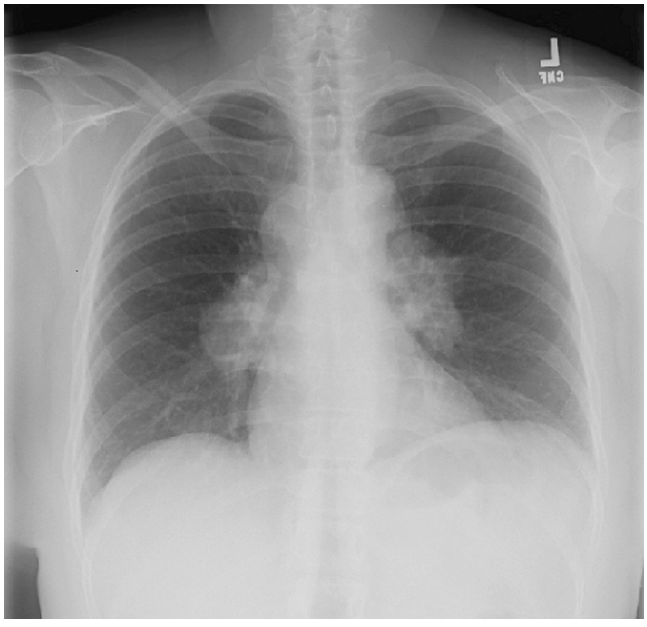

FIGURE 83-1. Chest radiograph demonstrating a stage 1 disease with enlarged mediastinal and hilar lymph nodes.

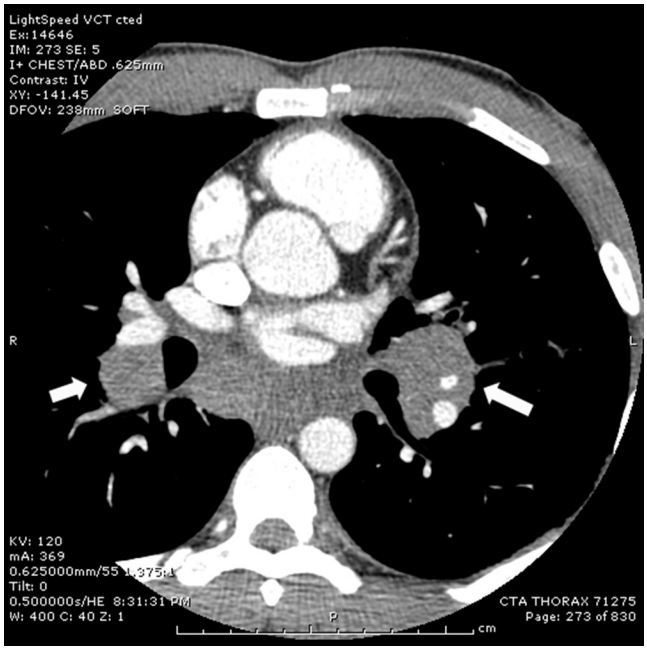

FIGURE 83-2. Chest computed tomographic scan showing typical hilar adenopathy *(arrows)*, which correlates with stage 1.

Symptomatic sarcoidosis may present insidiously or as an acute illness. Löfgren syndrome, an acute form of the disease, consists of erythema nodosum (see Fig. 407-24), arthritis, and bilateral hilar adenopathy. Fever and uveitis may also accompany Löfgren syndrome. Erythema nodosum occurs predominantly in women, whereas arthritis predominates in men.

Respiratory System Disease

More than 90% of patients have respiratory tract involvement, sometimes with symptoms and sometimes with asymptomatic radiographic abnormalities. The most common respiratory symptoms are dry cough and dyspnea. Chest pain, when present, is vague and nonspecific.

Upper respiratory tract involvement occurs in 2 to 6% of patients, with most having nasal mucosal involvement. Severe upper respiratory tract disease may lead to anosmia, erosion of septal cartilage, and nasal deformity. Supraglottic and glottic involvement can lead to stridor, dysphonia, cough, and dysphagia.

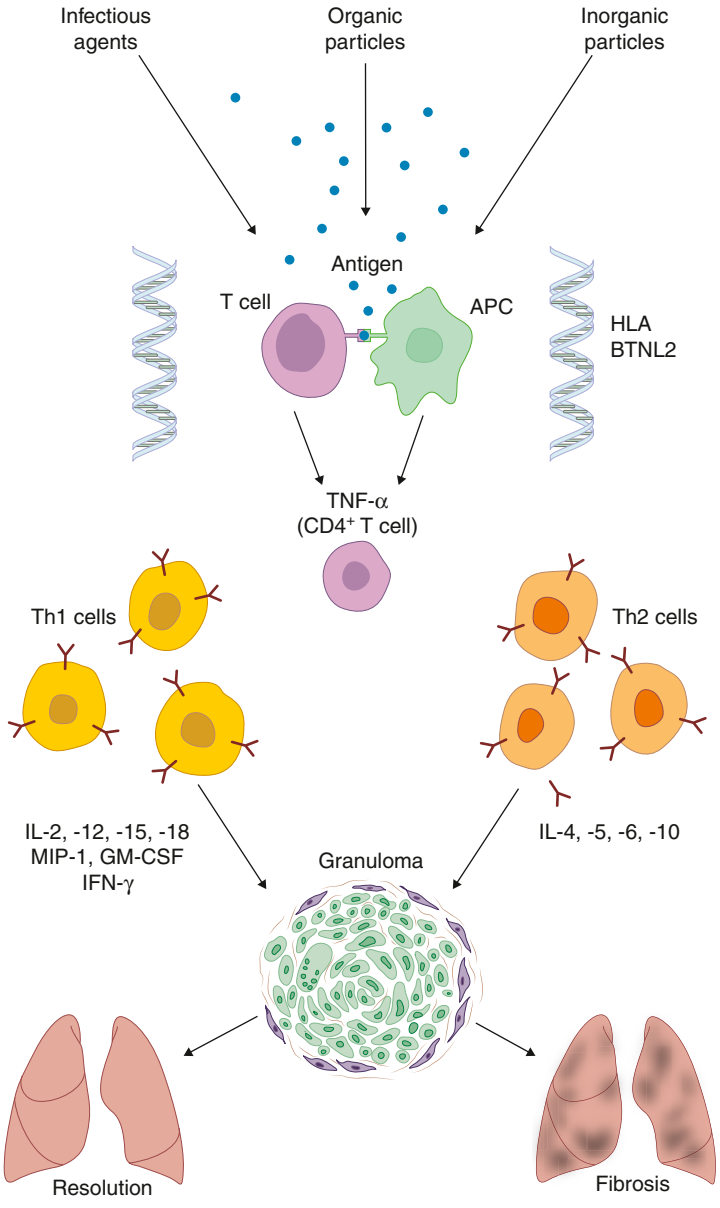

E-FIGURE 83-1. Immunopathogenesis of sarcoidosis. APC = antigen-presenting cell; BTNL2 = butyrophilin-like protein 2; GM-CSF = granulocyte-macrophage colony-stimulating factor; HLA = human leukocyte antigen; IFN-γ = interferon-γ; IL = interleukin; MIP-1 = macrophage inflammatory protein-1; TNF-α = tumor necrosis factor-α.

TABLE 83-1 CHEST RADIOGRAPHIC STAGING

Stage 0: Normal
Stage 1: Bilateral hilar adenopathy, often with right paratracheal adenopathy
Stage 2: Bilateral hilar adenopathy and parenchymal infiltration
Stage 3: Parenchymal infiltration without lymphadenopathy
Stage 4: Advanced parenchymal disease demonstrating fibrosis and possibly including honeycombing, cysts, bullae, and traction bronchiectasis

Examination of the chest often reveals few or no findings. Localized wheezing suggests endobronchial granulomatous disease, whereas diffuse wheezing suggests hyperreactive airways disease. Crackles may be heard when bronchiectasis and fibrosis are present. Hemoptysis may occur with bronchiectasis or cavitary disease.

The most common radiographic finding is intrathoracic lymph node enlargement with or without parenchymal lung involvement. Mediastinal lymphadenopathy without hilar adenopathy is extremely rare. Hilar lymph node enlargement is usually symmetrical, and less than 3% of patients have unilateral enlargement. Concurrent enlargement of right paratracheal and aortic-pulmonary window lymph nodes is common.

The chest radiograph is traditionally categorized into five stages (Table 83-1), but these stages do not necessarily denote the severity or chronologic progression of disease, particularly when extrathoracic involvement is present. Furthermore, 50 to 94% of patients will have hilar or mediastinal lymphadenopathy on computed tomography (CT) scans irrespective of their stage on a plain chest radiograph.

Chest CT may demonstrate nodules, ground-glass opacities, bronchiectasis, cysts, and thickening of the pleural surface (Fig. 83-3). In more advanced cases, patients develop fibrotic changes (Fig. 83-4) and evidence of pulmonary hypertension (Fig. 83-5). CT, however, generally adds little to diagnosis and management, particularly for those with a stage 1 chest radiograph. No evidence exists that CT changes help to guide therapy. CT can be justified when atypical clinical and chest radiographic findings are present, a normal chest radiograph is found during the evaluation of suspected extrathoracic disease, or complications are suspected.

Endobronchial sarcoidosis may lead to bronchial stenosis and recurrent obstructive pneumonias. Pleural effusions on plain radiography are uncommon (1 to 3% of patients). Pulmonary hypertension (Chapter 69) may complicate sarcoidosis, particularly when pulmonary fibrosis is present.

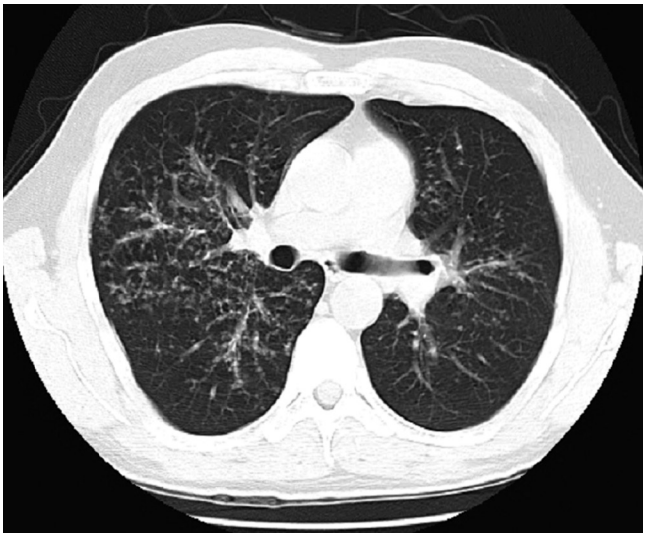

FIGURE 83-3. High-resolution chest computed tomographic scan demonstrating numerous small nodules in a predominantly bronchovascular distribution.

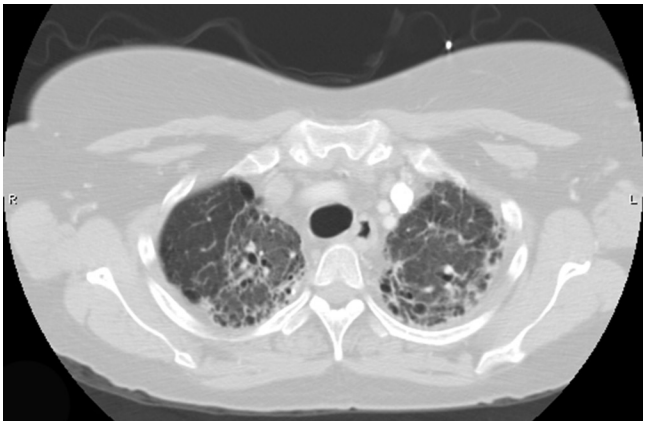

FIGURE 83-4. Chest computed tomographic scan showing fibrotic changes in the upper lobes with bronchiectasis.

FIGURE 83-5. Chest computed tomographic scan showing diffuse bilateral fibrosis along with severe pulmonary artery enlargement consistent with pulmonary hypertension.

Skin Disease

Skin involvement occurs in 25 to 35% of patients, but lesions are commonly misdiagnosed because they can present as macules, papules, plaques, subcutaneous lesions, areas of increased or decreased pigmentation, and ulcerations.[7] Lesions are commonly found on the upper back, the nape of the neck, and extremities (Fig. 83-6) and have a predilection for scars and tattoos. The most common skin manifestation is a maculopapular eruption, consisting of firm, flesh-colored to violaceous lesions that have a predilection for the eyelids and perioral area. Scalp involvement with alopecia may occur. Skin lesions in Black American patients frequently leave hyperpigmented scars and pale or depigmented areas.

Erythema nodosum occurs in about 10% of patients and commonly occurs as part of Löfgren syndrome. It presents as raised, red, hot, tender subcutaneous nodular lesions, most commonly on the shins but sometimes also on the arms and buttocks (see Fig. 407-24). Lesions persist for 1 to 3 weeks and may recur. The lesions of erythema nodosum typically show nonspecific septal panniculitis without sarcoidal granulomas, so biopsy is not usually helpful. Erythema nodosum portends a good prognosis, with up to 85% of patients resolving their sarcoidosis within 2 years.

Lupus pernio (Fig. 83-7) consists of chronic, lumpy, violaceous, indurated plaques and nodules distributed around the nose, cheeks, lips, and ears; it is specific to sarcoidosis. Patients with lupus pernio more commonly have a chronic course, fibrotic lung disease, and upper respiratory tract involvement.

Eye Disease

More than 25% of patients have ocular involvement (Chapter 391), and any part of the eye and adnexa may be involved. Women are more likely to develop ocular involvement. Dry eyes, the most common ocular manifestation, usually do not affect vision. Lacrimal gland enlargement and conjunctival involvement are common. Conjunctival involvement consists of pale yellow nodules, which demonstrate granulomas on biopsy. Corneal involvement is rare. Acute anterior uveitis presents with pain, photophobia, lacrimation, and redness. Chronic anterior uveitis, which is more common than acute uveitis, may have minimal symptoms. Posterior uveitis, which occurs in about 30% of patients with ocular sarcoidosis, is frequently accompanied by central nervous system involvement. Choroidal lesions may occur anywhere in the fundus and may be multifocal. In 10 to 15% of patients with uveitis, both the anterior and posterior segments are affected.

Uveitis can herald the nonocular signs of sarcoidosis and may precede the diagnosis of sarcoidosis by decades. Chronic anterior uveitis may lead

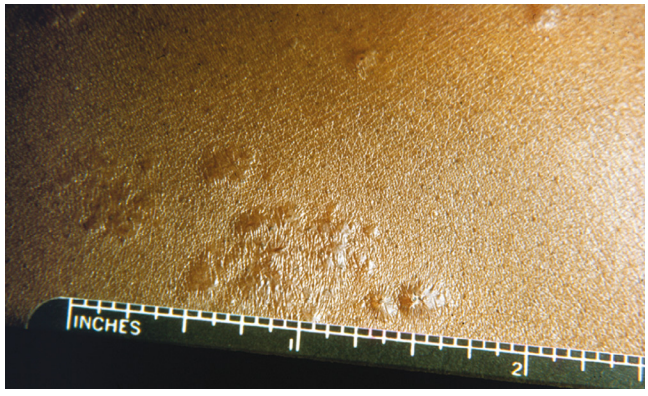

FIGURE 83-6. Skin lesions of sarcoidosis. Sarcoidal lesions may occur at any site. This patient's papules have a waxy appearance and are located on the upper part of the back.

FIGURE 83-7. ***Lupus pernio*** **is the term used to describe infiltrative skin lesions affecting the nose, cheeks, and ears in chronic sarcoidosis.**

to cataracts and glaucoma. Heerfordt syndrome consists of anterior uveitis accompanied by parotid gland enlargement and fever.

Cardiac Disease

Cardiac granulomas are found in about 25% of sarcoidosis patients who are examined at autopsy, and cardiac magnetic resonance imaging (MRI) and positron emission tomography (PET) scans reveal cardiac sarcoidosis in 25 to 30% of patients with systemic sarcoidosis in the United States and nearly 60% in Japan. Cardiac sarcoidosis may be the only manifestation of sarcoidosis in about 25% of patients. In cardiac sarcoidosis (Chapter 47), granulomas most often infiltrate the left ventricular free wall. Next most frequently, sarcoidal granulomas infiltrate the intraventricular septum, where they often involve the conduction system. Cardiac manifestations include atrioventricular block, ventricular arrhythmias, left ventricular dysfunction, and sudden death.[8]

Neurologic Disease

Nervous system granulomas are found in up to 25% of sarcoidosis patients who undergo autopsy, but only 10% of patients present with neurologic symptoms (Table 83-2). In patients with neurologic involvement, the neurologic signs or symptoms precede the diagnosis of sarcoidosis in up to 75% of patients and may be the only manifestation of sarcoidosis.[9]

Neurosarcoidosis has a predilection for the base of the brain, hypothalamus, and pituitary gland. When the pituitary gland is involved, the most common abnormalities are deficiencies in gonadotropins (Chapter 205) and thyroid-stimulating hormone, as well as hyperprolactinemia. Myelopathy may occur anywhere in the spinal cord and carries a poor prognosis. Peripheral neuropathy (Chapter 388) may manifest as mononeuropathy or polyneuropathy.

TABLE 83-2 NEUROSARCOIDOSIS

Cranial neuropathies
VII—Facial nerve palsy (unilateral, bilateral)
II—Optic nerve (unilateral and bilateral)
VIII—Hearing loss
Other cranial neuropathies
Myelopathy (sensory and motor)
Seizure
Basilar meningitis
Central diabetes insipidus
Panhypopituitarism
Intraparenchymal mass
Hydrocephalus
Peripheral neuropathy

Liver and Spleen

Liver involvement is twice as common in Black Americans as in White Americans.[10] Symptoms due to liver disease are infrequent, but abdominal pain and pruritus are the most common symptoms. Fever, weight loss, and jaundice are present in less than 5% of those with liver involvement. About 20% of patients will have hepatomegaly on physical examination, and 35% will have an elevated serum aminotransferase or alkaline phosphatase level. Sarcoidosis can rarely (<1%) cause progressive liver disease that leads to portal hypertension with variceal bleeding; hepatopulmonary syndrome, with refractory hypoxemia, cirrhosis, and liver failure, may also occur.

Splenomegaly is found on physical examination in 5 to 15% of patients with sarcoidosis. Massive splenomegaly is rare.

Bone and Joint

Most patients complain of arthralgias, but only about 35% develop arthritis. Acute sarcoid arthritis (Chapter 254) consists of large joint periarthritis, particularly involving the ankles and knees, and commonly occurs with Löfgren syndrome.[11] These patients often report difficulty walking related to joint pain. Acute sarcoid arthritis usually persists for up to 3 months but is self-limited. Chronic sarcoid arthritis with direct granulomatous synovial infiltration is rare. Osseous sarcoidosis occurs in 3 to 13% of patients and usually does not produce symptoms.

Calcium Metabolism

Increased 1-α hydroxylase activity in macrophages within granulomas and the alveoli converts 25-hydroxyvitamin D to the biologically active form, 1,25-dihydroxyvitamin D (calcitriol), resulting in increased intestinal absorption of calcium in up to 50% of patients and may result in renal stones (Chapter 111), nephrocalcinosis with renal insufficiency, and hypercalciuria (urine calcium > 300 mg/24 hours) with or without hypercalcemia (Chapter 227). In chronic sarcoidosis, 10 to 14% of patients have at least one symptomatic renal stone.

Renal Involvement

Renal involvement, other than as a result of dysregulated calcium metabolism, occurs in less than 1% of patients. Renal disease may include granulomatous interstitial nephritis, glomerular disease, renal tubular dysfunction, renal vascular disease, and obstructive uropathy. Granulomatous interstitial nephritis is more common in White men.

DIAGNOSIS

The diagnosis of sarcoidosis is often delayed because it can be confused with infections, tumors, or autoimmune conditions.[12] The diagnosis should be based on compatible clinical and radiographic findings supported by histologic evidence of noncaseating granulomas in one or more organs in the absence of any foreign particles or organisms.[13] An occupational history consistent with beryllium exposure (Chapter 81), such as employment in the aerospace, automotive, ceramic, or computer industries, requires further investigation because chronic beryllium disease cannot be clinically or histologically distinguished from sarcoidosis.

A diagnosis of sarcoidosis is reasonably certain even without histologic confirmation in patients who present with Löfgren syndrome.[14] In all other cases, a biopsy specimen from an involved organ should be obtained. The organ for which biopsy is safest, such as the skin, peripheral lymph nodes, lacrimal glands, or conjunctiva, should be sampled.

Up to 65% of patients will have granulomas on liver biopsy, but hepatic granulomas (Chapter 137) occur commonly with other disorders such as infection and drug-induced hepatitis. As a result, the diagnosis of sarcoidosis should not be based solely on detection of hepatic granulomas.

If diagnosis requires intrathoracic sampling, fine-needle aspiration of enlarged intrathoracic lymph nodes guided by endobronchial ultrasound has become the preferred procedure, with a diagnostic yield of 80% or higher. Endobronchial ultrasound visualizes mediastinal structures, including the subcarinal region, the paraesophageal space, and the aortopulmonary window. Wherever available, rapid-onsite cytologic evaluation should be performed to assess the adequacy of the sample and guide the need for additional needle aspirates or endobronchial or transbronchial biopsies. Bronchoscopy and endobronchial ultrasound-guided fine-needle aspiration have generally replaced more invasive approaches, such as mediastinoscopy or video-assisted thoracoscopic surgical biopsies.

Bronchoalveolar lavage sampling demonstrates lymphocytosis with normal or low granulocyte counts in more than 85% of patients (Chapter 73). The CD4/CD8 ratio is increased in bronchoalveolar lavage in about 50% of patients with sarcoidosis, but bronchoalveolar lavage findings are nonspecific and should not be used to diagnose sarcoidosis. Bronchoalveolar lavage findings cannot predict prognosis or responsiveness to corticosteroid therapy.

Sarcoidal granulomas produce angiotensin-converting enzyme (ACE). Although serum ACE levels are elevated in 60% of patients with sarcoidosis, the value of a serum ACE level in diagnosing sarcoidosis remains limited because positive and negative predictive values are only about 84% and 74%, respectively.

Patients should routinely undergo pulmonary function testing, which often does not correlate with the chest radiographic stage. For example, pulmonary function tests may be abnormal even in patients with a normal chest radiograph. Diffusion capacity for carbon monoxide (DLCO) is usually the first abnormality detected and the last to normalize on remission. A DLCO of less than 50% of predicted is associated with exercise-induced oxygen desaturation and should prompt formal oxygen saturation testing with exercise.

About two thirds of patients have airflow limitation at presentation. Spirometry usually indicates restrictive ventilatory dysfunction with a reduced forced vital capacity (FVC) and reduced forced expiratory volume in 1 second (FEV_1). At least 50% of patients have concurrent obstructive airway disease. Airway hyperreactivity, as measured by increased responsiveness to methacholine, occurs in up to 83% of patients. In patients with abnormal spirometric findings at diagnosis, spirometry returns to normal in 80%. Alterations in cardiopulmonary exercise testing have been reported in nearly 50% of patients with sarcoidosis. Abnormalities, including a ventilatory limitation with exercise and a widened alveolar-arterial O_2 gradient, may be present. FVC is the single best test for following respiratory involvement and correlates well with FEV_1, total lung capacity, and DLCO.

Because ocular involvement is common and vision loss may occur, complete ocular evaluation with slit lamp and funduscopic examinations should be routinely performed during the initial evaluation and then annually in patients with active systemic disease.

An electrocardiogram (ECG) should be performed at the initial encounter. Screening for cardiac symptoms (palpitations, dizziness, and syncope) should be performed during the initial evaluation and routinely during follow-up visits if the disease is active. Any cardiac symptoms or abnormalities on the ECG should prompt further cardiac event monitoring (Chapter 49) and testing by echocardiography (Chapter 43).

PET with use of the marker ^{18}F-FDG combined with CT (PET/CT) may demonstrate uptake in metabolically active macrophages within granulomas. This approach has proven to be highly sensitive for diagnosing sarcoidosis, and it can demonstrate active granulomas in patients who have stage 0 chest radiographs, as well as in patients with marked fibrosis.[15]

If cardiac involvement is suspected, PET scanning (see E-Fig. 44-3) or cardiac MRI with contrast should be performed, separately or simultaneously.[16] Endomyocardial biopsy, which can be considered in highly suspected cases with nondiagnostic imaging results, has less than 20% diagnostic yield because cardiac involvement is patchy and is usually most dense in the left ventricle and basal ventricular septum where endomyocardial biopsies are avoided. Targeted endomyocardial biopsy guided by real-time cardiovascular MRI may reduce sampling error.

A definite diagnosis of neurosarcoidosis requires histologic confirmation of noncaseating granulomas in affected tissue. A probable diagnosis of neurosarcoidosis requires compatible MRI findings and clinical presentation, exclusion of other neurologic disease, and histologic confirmation of sarcoidosis elsewhere. Histologic confirmation of disease elsewhere, which may be detected by PET scan, supports the diagnosis of neurosarcoidosis. Cerebrospinal fluid (CSF) analysis typically demonstrates nonspecific lymphocytic inflammation (Chapter 381). The CSF glucose can be as low as 14 mg/dL, with a white blood cell count as high as 350 cells/μL and a protein concentration as high as 670 mg/dL. CSF ACE levels are neither sensitive nor specific. CSF oligoclonal immunoglobulin bands are elevated in one third of patients, thereby making it difficult to differentiate sarcoidosis from multiple sclerosis (Chapter 380).

On plain radiographic images, most skeletal lesions of sarcoidosis are seen in the small bones of the hands and feet. MRI and PET scanning show much greater involvement of the axial skeleton and long bones, and osseous sarcoidosis may appear similar to metastatic disease on a PET scan.

Drug-Induced Sarcoidosis and Sarcoidosis-like Reaction

Type 1 interferons, IFN-α and IFN-β, used to treat viral hepatitis (Chapter 135), multiple sclerosis (Chapter 380), and autoimmune and malignant disease, may increase the T_H1 cytokines, IFN-γ, and IL-2 and rarely (<1 to 5%) result in sarcoidosis.[17] Most reported cases of interferon-induced sarcoidosis occur within 6 months of therapy and manifest primarily with lung and skin involvement. Paradoxically, patients receiving anti-TNF-α biologics for various autoimmune diseases also have developed sarcoidosis. Sarcoidosis-like syndrome has also been reported with monoclonal immunomodulators such as tocilizumab and adalimumab, as well as with the use of checkpoint inhibitors (antiprogrammed cell death [PD-1]) to treat metastatic melanoma.[18]

TREATMENT

Because the inciting agent has not yet been identified nor genetic risk factors firmly established, no means exist to prevent sarcoidosis. Most patients with sarcoidosis are not disabled by their illness, so the decision to recommend treatment should weigh the risks of using corticosteroids (Chapter 28), which are the most common treatment, against potential benefits (Table 83-3).[19,20] Hypercalcemia, cardiac disease, and neurologic disease are indications for treatment, and immediate treatment is appropriate whenever organ function is threatened or when symptoms are severe. Detection of granulomatous inflammation on physical examination, biopsy, or imaging or the presence of an elevated serum ACE level is not a mandate to provide treatment.

Pulmonary Sarcoidosis

Treatment is recommended for patients who have a progressive decline in their pulmonary function, which sometimes is accompanied by progressive changes on chest imaging. Oral prednisone at a dose of 20 to 40 mg per day for 3 months is usually the initial recommended therapy. Response to treatment is indicated by improvement in symptoms or objective measures, such as decreased size and number of skin lesions, increased FVC, or a reduction of detectable cardiac or brain lesions. For pulmonary involvement, steroids improve symptoms, pulmonary function test results, and chest radiographic findings. If a response is noted at 3 months, the prednisone dose should be tapered to 10 to 15 mg per day for an additional 6 to 9 months and then tapered off.

Fatigue and poor quality of life often accompany active sarcoidosis. A small randomized trial found that low-dose dexamethasone (1mg once daily) may improve fatigue and quality of life.[A1] Inhaled corticosteroids should be used only in patients with bronchial hyperreactivity or persistent cough. As with other chronic respiratory diseases, pulmonary rehabilitation should be considered, particularly for patients with pulmonary fibrosis (stage 4 chest imaging).[A2]

Because recurrence after discontinuing therapy may occur in from 30 to 80% of patients, patients should be followed closely for 1 to 2 years after discontinuing treatment. The indications for restarting treatment are the same as those used to begin treatment. When treatment or retreatment is indicated, short courses of high-dose steroids (burst and taper over a few weeks) are unlikely to result in sustained benefit. Lack of response after a 3-month trial suggests nonadherence to therapy, an inadequate dose of prednisone, or irreversible fibrotic disease. Repository drugs may help mitigate poor adherence. One potential option is repository corticotropin, 40 units injected subcutaneously twice weekly; in a small study, this approach was prednisone-sparing and associated

with improvement in lung function, PET scan parameters, and patient-reported outcomes. However, cost and limited availability may restrict the use of parenteral corticotropin. In a small randomized trial of patients with fibrotic sarcoidosis, roflumilast (a phosphodiesterase-4 inhibitor at 500 μg orally daily) reduced the risk of exacerbations, but further studies are needed to determine its role in sarcoidosis.[A3] Treatment of advanced pulmonary sarcoidosis is mostly based on expert consensus, because of limited evidence-based data.[21]

Hypercalcemia

Moderate doses of corticosteroids (15 to 20 mg prednisone) reduce elevated serum and urinary calcium levels within a few days of starting treatment. Failure of serum calcium to normalize within 2 weeks should alert the clinician to an alternative diagnosis such as hyperparathyroidism or malignancy (Chapter 227). With treatment, most patients with granulomatous interstitial nephritis regain renal function but are often left with chronic kidney disease of varying severity.

Neurosarcoidosis

Neurologic disease generally requires much higher doses (80 to 100 mg prednisone a day). If neurosarcoidosis is not sufficiently responsive to corticosteroids alone, early immunosuppressive treatment with azathioprine, methotrexate, or infliximab (see Table 83-3) may improve clinical outcomes.[22]

Despite the absence of definitive randomized trials, cytotoxic and immunosuppressive drugs have been used to treat patients who do not respond to corticosteroid therapy or who cannot tolerate it (see Table 83-3), and both methotrexate and azathioprine appear to have significant steroid-sparing effects. Corticosteroids should be continued for at least 1 month after the addition of immunosuppressive agents. Generally, 3 to 6 months of cytotoxic and immunosuppressive treatment are required to determine whether a response has occurred. For patients who respond, the duration of treatment should be 9 to 12 months.

Cardiac Sarcoidosis

For cardiac sarcoidosis, corticosteroid doses of 30 to 40 mg per day are as good as higher doses. In patients who have arrhythmias, decreased ventricular function, or septal involvement detected on MRI or PET, electrophysiologic studies should be considered, and the need for an automatic implantable cardioverter-defibrillator (ICD) should be evaluated (Chapters 53 and 54).[23] For patients with pulmonary hypertension, bosentan (up to 125 mg daily) can reduce pulmonary arterial pressure[24] but has not been shown to improve exercise tolerance in patients with sarcoidosis.

Steroid-Dependent Sarcoidosis

In patients who are steroid dependent but have ongoing disease, TNF-α antagonists may be useful despite their potential side effects. The addition of infliximab (3 to 5 mg/kg for 24 weeks) can be efficacious for extrapulmonary disease.[25] Other options include adalimumab 40 mg subcutaneously once a week for 6 to 12 months, especially for uveitis and for skin lesions.

Transplantation

Less than 1% of heart and liver and about 3% of lung transplantations are performed in patients with sarcoidosis. The 1- and 5-year graft survival rates for lung, liver, and heart transplantations in patients with sarcoidosis compare favorably with the results obtained for patients with other disorders.

TABLE 83-3 TREATMENT

ORGAN	CLINICAL FINDINGS	TREATMENT
Respiratory	Dyspnea, persistent cough, FVC < 70%	Prednisone, 20-40 mg/day
	Mild cough, wheezing	Inhaled corticosteroid
Skin	Lupus pernio	Prednisone, 20-40 mg/day Hydroxychloroquine, 400 mg/day Methotrexate, 10-15 mg/wk Infliximab, 3-5 mg/kg every 2-4 wk
	Maculopapular eruptions	Topical corticosteroid Hydroxychloroquine, 400 mg/day Prednisone, 20-40 mg/day
	Erythema nodosum	NSAID*
Eyes	Anterior uveitis	Topical corticosteroid
	Posterior uveitis	Prednisone, 20-40 mg/day
Cardiac	Complete heart block, ventricular arrhythmias	AICD, prednisone, 20-40 mg/day
	Decreased LVEF (<35%)	AICD, prednisone, 20-40 mg/day
Central nervous system	Cranial nerve palsies	Prednisone, 20-40 mg/day
	Myelopathy	Prednisone, 40-60 mg/day, and azathioprine, 150 mg/day (or methotrexate 10-15 mg/wk or mycophenolate mofetil, 1000-2000 mg/day, or cyclophosphamide, 1-5 mg/kg/day)
	Intracerebral involvement	Prednisone, 40-60 mg/day, and azathioprine, 150 mg/day (or methotrexate 10-15 mg/wk or mycophenolate mofetil, 1000-2000 mg/day, or cyclophosphamide, 1-5 mg/kg/day)
Liver	Cholestatic hepatitis	Prednisone, 20-40 mg/day
Bone and joint	Arthralgias	NSAID
	Granulomatous arthritis	Prednisone, 20-40 mg/day Methotrexate, 10-15 mg/wk
	Bone destruction/pain	Prednisone, 20-40 mg/day Methotrexate, 10-15 mg/wk
Hypercalciuria and hypercalcemia	Kidney stones	Prednisone, 20-40 mg/day Hydroxychloroquine, 400 mg/day

*For example, ibuprofen, 200-800 mg three times a day.

AICD = automatic implantable cardioverter-defibrillator; FVC = forced vital capacity; LVEF = left ventricular ejection fraction; NSAID = nonsteroidal anti-inflammatory drug.

PROGNOSIS

Patients with Löfgren syndrome have a good prognosis characterized by spontaneous resolution with few consequences. Overall, spontaneous remission with few or no consequences occurs in more than 50% of patients within 3 years of diagnosis and in two thirds of patients within a decade. After 1 or more years of remission without treatment, recurrence occurs in less than 5% of patients. Up to one third of patients have unrelenting disease that leads to significant organ impairment, but less than 5% of patients die from sarcoidosis. Black Americans tend to have a worse prognosis with more chronic disease and more extrathoracic involvement of the eyes, liver, bone marrow, extrathoracic lymph nodes, and skin. In the absence of extrathoracic disease, patients with stage 1 radiographs generally have the best prognosis. Pulmonary function testing is more reliable in determining prognosis than is radiograph staging. Patients with neurologic and cardiac involvement have a poorer prognosis. Sarcoidosis-associated pulmonary hypertension is a harbinger for poor prognosis. For cardiac sarcoidosis, for example, estimates for 1-, 5-, and 10-year transplantation-free cardiac survival are 97%, 90%, and 83%, respectively, but heart failure at presentation predicts a poorer outcome, with a 10-year transplantation-free cardiac survival of only 53%.

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84 ACUTE BRONCHITIS AND TRACHEITIS

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DEFINITION

The term *acute bronchitis and tracheitis* defines a self-limited (1 to 3 weeks) inflammation of the large airways of the lung that extends to the tertiary bronchi (E-Fig. 84-1). In patients with a primary symptom of cough (Chapter 71), the diagnosis is made if there is no clinical or imaging evidence of pneumonia. At the bedside, the absence of criteria for systemic inflammatory response syndrome (Chapter 94) suggests bronchitis and tracheitis and makes a diagnosis of pneumonia (Chapter 85) unlikely. The criteria for the systemic inflammatory response syndrome are met if the patient has more than two of the following: temperature lower than 36° C or higher than 38° C, pulse greater than 90 beats per minute, respiratory rate higher than 20 breaths per minute, or white blood cell count less than 4000 cells/μL or higher than 12,000 cells/μL or with greater than 10% bands.

The definition of acute bronchitis and tracheitis also seeks to differentiate the illness from acute inflammation of the small airways (bronchiolitis), even though the accompanying symptoms with the former may include sputum production, wheezing, and shortness of breath. Among patients with primarily small airways disease, some might be expected to have prominently decreased breath sounds in the areas involved. Acute bronchitis and tracheitis is also different from bronchiectasis (Chapter 78), which is associated with permanent dilation of bronchi and a chronic cough. Furthermore, a diagnosis of chronic bronchitis (Chapter 76) is reserved for patients who have prolonged cough and sputum production: at least 3 months of the year for 2 consecutive years.

EPIDEMIOLOGY

Occurring at a rate of 44 per 1000 adults per year, acute bronchitis and tracheitis affects approximately 5% of adults annually. A higher incidence is observed in the winter and fall than in the summer and spring. In the United States, acute bronchitis and tracheitis is the ninth most common illness in outpatients as reported by physicians.

The disorder is thought to be viral in origin almost all the time. However, viruses have been isolated in only 8 to 37% of patients. Thus, the true causes of the illness are unknown in most cases. Nevertheless, at least 70% of patients with acute bronchitis and tracheitis in the United States receive antibacterial antibiotics after visiting a physician. Importantly, although the same bacteria that are commonly implicated in community-acquired pneumonia are also isolated from the sputum in half the patients, their role in the pathobiology of acute bronchitis and tracheitis or its attendant symptoms is unclear, and bronchial biopsies have not shown bacterial invasion.

PATHOBIOLOGY

Infections of the epithelium of the bronchi and trachea are thought to incite an inflammatory response. Pathologically, there is an accompanying microscopic thickening of bronchial and tracheal mucosa corresponding to the inflamed areas. Such pathologic findings are also consistent with the occasional case report of upper airway inflammation confined to the bronchi and trachea detected by ^{18}F-labeled fluorodeoxyglucose positron emission tomography (FDG-PET).

In various studies, specific pathogens have been found in more than half of patients with acute bronchitis. These pathogens include common respiratory viruses, typical respiratory bacteria, and atypical bacteria. At least three variables can influence the yield of specific pathogens: the presence of epidemics, the season of the year, and the population's influenza vaccination status. Furthermore, there are probably wide variations in the anatomic distribution of all pathogens causing acute bronchitis and tracheitis, extending from the nasal mucosa to the bronchiolar epithelium.

The viruses implicated in acute bronchitis and tracheitis include influenza A and B (Chapter 332), parainfluenza (Chapter 331), respiratory syncytial virus (Chapter 330), coronavirus (Chapters 334 and 335), adenovirus (Chapter 333), and rhinoviruses (Chapter 329), usually in this order from the most to the least common, with the pandemic spread of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2; Chapter 336) as a striking anomaly. Human metapneumovirus (Chapter 329) also has been identified as an etiologic agent. In children, bronchiolitis has been associated with respiratory syncytial virus, influenza virus, parainfluenza virus, and metapneumovirus.

Typical bacteria implicated in acute bronchitis include *Haemophilus influenzae* (Chapter 277) and *Moraxella catarrhalis* (Chapter 277). Severe bronchiolitis has also been reported with *Mycoplasma pneumoniae* (Chapter 293), even though this pathogen is usually associated with either pneumonia or acute bronchitis and tracheitis in adults. Up to 25% of cases of acute bronchitis and tracheitis may be due to "atypical" bacteria: *Bordetella pertussis* (Chapter 289), *Chlamydophila (Chlamydia) pneumoniae* (Chapter 294), and *Mycoplasma pneumoniae* (Chapter 293).

CLINICAL MANIFESTATIONS

The cardinal clinical symptom is cough (Chapter 71) of recent onset. Because most upper respiratory infections resolve within 1 week, a more extended period of cough is useful for considering the diagnosis of acute bronchitis. Patients usually seek care from their physician after 4 to 7 days of coughing that is not resolving. With acute bronchitis, there is often a continued cough and sometimes a worsened cough that lasts an initial 1 to 3 weeks. Associated symptoms vary and include sputum production, fever, malaise, wheezing, and dyspnea. Adults with pertussis may exhibit paroxysms of coughing, whooping, or vomiting, although less commonly than seen in children with this infection. Pertussis can infrequently lead to a cough lasting months, but data are lacking on the prevalence of pertussis among adults with chronic cough.

DIAGNOSIS

Acutely ill patients may not be able to distinguish their early symptoms from those accompanying very mild upper respiratory infections. However, with acute bronchitis and tracheitis, a protracted phase of coughing persists beyond 1 to 5 days, during which time a substantial proportion of patients will have significant declines in forced expiratory volume in 1 second (FEV_1) (Chapter 73).

When "atypical" bacteria are identified by culture or serology, patients tend to be seen later in the course of their illness than patients with viral causes and more often have wheezing. In some studies, 12 to 32% of patients with coughing that persists for longer than 1 week have pertussis. In other studies, however, pertussis has been confirmed in only 1% of such patients.

Because a major issue is whether symptoms are caused by an organism that could be responsive to antibiotics, the differentiation between bacterial infection compared with viral infection is often more important than determining the precise organism primarily responsible for the infection.

Rapid molecular diagnostic tests can identify specific bacteria or viruses linked to acute bronchitis and tracheitis. However, their major value lies in identifying a virus for which there is therapy or avoiding antibacterial antibiotics if a pathogenic virus is identified.[1]

Measurement of serum levels of procalcitonin, which is the prohormone of calcitonin and an inflammatory marker suggesting bacterial infection, also can help guide the initiation or discontinuation of antibacterial antibiotics.[2] A level lower than 0.1 ng/L makes bacterial infection highly unlikely, and limiting treatment to patients with levels higher than 0.25ng/L can markedly reduce the use of antibiotics without adverse clinical outcomes[A1] in some settings but not in emergency departments of U.S. hospitals with high adherence rates to pneumonia guidelines.[A2,A3] If the test is available, the finding of very low levels may help the clinician decide against prescribing antibiotics.

For diagnosing specific bacterial causes, polymerase chain reaction (PCR) testing of nasopharyngeal swabs or aspirates is the easiest and most sensitive way to diagnose infections by *B. pertussis, M. pneumoniae*, and *C. pneumoniae;* most experts recommend calcium alginate swabs for pertussis because cotton inhibits growth. Dacron swabs with aluminum handles are preferred for specimens used to diagnose *Chlamydophila* because cotton, calcium alginate, and the wooden shaft can all inhibit growth of the organism. Cultures for *M. pneumoniae* are slow and insensitive. In general, testing for atypical organisms should not be done because of the cost of PCR and both the insensitivity and slowness of cultures. However, if the clinician suspects an outbreak in the community or the likelihood of pertussis, rapid testing with PCR may be quite beneficial.

ABSTRACT

Acute bronchitis and tracheitis affect 5% of adults annually, are caused by bacteria in fewer than 50% of cases, and are characterized by a cough that persists for an average of 10 to 14 days. The viruses implicated include influenza A and B, respiratory syncytial virus, coronavirus, human metapneumovirus, and rhinovirus. A substantial portion of patients have a decline in FEV_1. Antibiotics lead to an approximately half-day less of fever, productive cough, and feeling ill, but adverse effects, in aggregate, offset the mild improvement in these outcomes.

KEYWORDS

bronchitis
tracheitis
cough
respiratory infections
influenza
pertussis

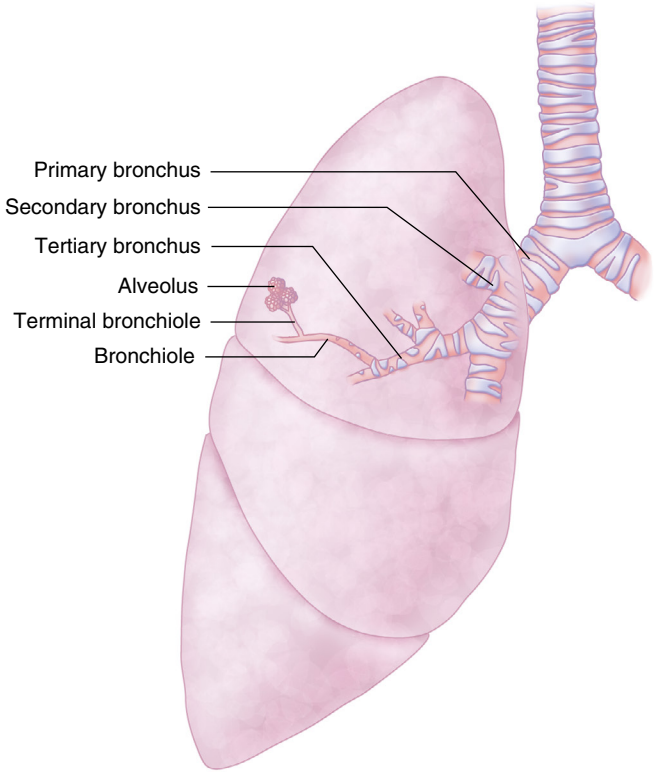

E-FIGURE 84-1. Many infecting agents that cause bronchitis and tracheitis can infect both large and small airways of the lung and occasionally the alveoli. Drawing is provided to show anatomic elements and is not to scale. Not surprisingly, a wide spectrum of signs and symptoms are associated with bronchitis, including cough, wheezing, and shortness of breath.

TREATMENT

For acute cough thought to be caused by acute bronchitis in an immunocompetent adult, no further tests or treatments are routinely recommended.[3] Nevertheless, although fewer than 50% of cases of acute bronchitis are probably caused by bacterial pathogens, antibiotics are used in 50 to 85% of cases worldwide and in about 45% of elderly patients with nonbacterial upper respiratory infections in the United States.[4] In a meta-analysis of randomized trials of antibacterial antibiotics for acute bronchitis, patients receiving antibiotics were significantly less likely to have a cough, but their 0.58 fewer days with cough, 0.46 fewer days of productive cough, and 0.64 fewer days of feeling ill were not statistically significant and were generally offset by the adverse effects of the antibiotics themselves.[A4] Electronic feedback, integrated into clinical practice workflow, can reduce antibiotic prescribing without adverse consequences.[A5]

When antibiotics are prescribed, azithromycin (500 mg daily for 3 days) is probably better than other alternatives. Another option is to delay the initiation of antibiotics and to use them only in patients with persistent symptoms. This strategy substantially reduces antibiotic use, slightly reduces patient satisfaction, but has had no detectable adverse clinical implications.[A6] Of note is that discolored sputum per se does not appear to predict responsiveness to antibiotics. Based on such data, guidelines suggest that antibiotics generally should be reserved for patients with suspected pneumonia.

Antibiotics may be used in patients with known atypical pathogens, but even then their effect on outcomes is not clear except to limit the spread of pertussis, especially during a defined outbreak. In adults suspected of having pertussis, erythromycin, 500 mg four times a day for 14 days, is thought to be most effective. However, many patients cannot tolerate erythromycin, and either doxycycline, 100 mg every 12 hours, or a newer macrolide such as azithromycin, 500 mg on day 1 and 250 mg/day thereafter, is effective. The latter two drugs are also active against *C. pneumoniae* and *M. pneumoniae*, although the optimal duration of therapy for acute bronchitis is unknown. A useful range is 5 to 14 days.

During influenza season, anti-influenza agents may be useful in decreasing symptoms by approximately 1 day and may lead to a 0.5-day earlier return to normal activity in patients with influenza. The first-generation drugs amantadine and rimantadine are ineffective against H3N2 influenza A viruses and are not recommended. Second-generation drugs such as zanamivir (two inhalations of 5 mg each, twice a day) or oseltamivir (75 mg twice a day) can be given for 5 days. Up to 20% of patients given oseltamivir will have nausea or vomiting.

Antihistamines and over-the-counter antitussives and expectorants have no apparent value. Although some subsets of patients with bronchial hyperresponsiveness may benefit from inhaled selective β_2-agonists at doses commonly used to treat asthma (see Chapter 75), overall they appear to confer no benefit. No data support the routine use of inhaled steroids. Mucolytic agents may be of small benefit.

In experimental rhinovirus colds, nonsteroidal drugs, alone or in combination with antihistamines, reduce the severity of symptoms, including cough. However, the widespread use of either type of drug alone or as a combination in naturally occurring, community-acquired bronchitis and tracheitis has not been evaluated.

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Because antibiotics are overused and probably lead to community-wide alterations in antibiotic resistance,[6] interventions to reduce overuse can potentially have substantial long-term benefits while also reducing health care costs.[7] The increasing availability of multiplex PCR testing, which commonly includes detection of SARS-CoV-2, should help decrease the use of empiric antibiotics in the emergency department setting. Antibiotic use also can be safely reduced by physician education, peer review, and feedback,[A10] and the combination of education plus feedback is better than education alone.[A11]

PROGNOSIS

Coughing usually lasts 10 to 14 days, during which time the illness causes significant transient decrements in vitality and social functioning. Limited data on short- and long-term outcomes show that up to 20% of patients have persistent or recurrent symptoms for a month. Antibiotics may reduce symptoms by a fraction of a day, but they do not reduce return visits to the emergency department.[8] Furthermore, side effects, the emergence of antibiotic resistance, and cost must be weighed against their modest benefits.

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85 OVERVIEW OF PNEUMONIA

LINDSEY R. BADEN, MARIE R. GRIFFIN, AND MICHAEL KLOMPAS

Hospital-acquired pneumonia and ventilator-acquired pneumonia are more frequently caused by *Staphylococcus aureus* or gram-negative bacilli. Pneumonia in immunocompromised hosts can be caused by a wide range of pathogens depending on the nature of the immune impairment, so early diagnosis and treatment are critical.

DEFINITION

Pneumonia is an acute infection of the lung parenchyma associated with at least one respiratory symptom (e.g., cough, dyspnea, chest pain) and abnormal opacities on lung imaging, with or without fever, in the absence of an alternative diagnosis. Pneumonia may be community-acquired pneumonia (CAP) or hospital-acquired pneumonia (HAP). In patients with immunocompromising conditions (e.g., inherited or acquired immunodeficiencies, neutropenia, human immunodeficiency virus (HIV) infection with a suppressed CD4 count, a solid organ or hematopoietic stem cell transplant, or conditions that require immunosuppressive agents), the causes of pneumonia include common organisms but also a number of organisms that are uncommon in hosts who have normal immunity.

COMMUNITY-ACQUIRED PNEUMONIA

EPIDEMIOLOGY

Community-acquired pneumonia is one of the most common serious health conditions and the most common infectious cause of hospitalization and death in the United States. It accounts for about 7 annual health care visits per 1000 young adults but 96 health care visits per 1000 adults ages 85 years and older. Hospitalization rates increase exponentially with age, from about 1 to 2 per 1000 in young adults to about 15 to 20 per 1000 individuals ages 65 to 84 years and almost 40 per 1000 among persons ages 85 years and older. About 35% of hospitalizations for community-acquired pneumonia among U.S. adults[1] occur in patients with recent exposures to health care settings, and about 25% occur in patients with immunocompromising conditions.

In the United States, pneumonia hospitalizations and deaths increase in November through March, coincident with the seasonal increases in influenza (Chapter 332) and other respiratory viruses, with the degree of excess morbidity and mortality depending on the circulating viral strains. Respiratory

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TREATMENT

For acute cough thought to be caused by acute bronchitis in an immunocompetent adult, no further tests or treatments are routinely recommended.[3] Nevertheless, although fewer than 50% of cases of acute bronchitis are probably caused by bacterial pathogens, antibiotics are used in 50 to 85% of cases worldwide and in about 45% of elderly patients with nonbacterial upper respiratory infections in the United States.[4] In a meta-analysis of randomized trials of antibacterial antibiotics for acute bronchitis, patients receiving antibiotics were significantly less likely to have a cough, but their 0.58 fewer days with cough, 0.46 fewer days of productive cough, and 0.64 fewer days of feeling ill were not statistically significant and were generally offset by the adverse effects of the antibiotics themselves.[A4] Electronic feedback, integrated into clinical practice workflow, can reduce antibiotic prescribing without adverse consequences.[A5]

When antibiotics are prescribed, azithromycin (500 mg daily for 3 days) is probably better than other alternatives. Another option is to delay the initiation of antibiotics and to use them only in patients with persistent symptoms. This strategy substantially reduces antibiotic use, slightly reduces patient satisfaction, but has had no detectable adverse clinical implications.[A6] Of note is that discolored sputum per se does not appear to predict responsiveness to antibiotics. Based on such data, guidelines suggest that antibiotics generally should be reserved for patients with suspected pneumonia.

Antibiotics may be used in patients with known atypical pathogens, but even then their effect on outcomes is not clear except to limit the spread of pertussis, especially during a defined outbreak. In adults suspected of having pertussis, erythromycin, 500 mg four times a day for 14 days, is thought to be most effective. However, many patients cannot tolerate erythromycin, and either doxycycline, 100 mg every 12 hours, or a newer macrolide such as azithromycin, 500 mg on day 1 and 250 mg/day thereafter, is effective. The latter two drugs are also active against *C. pneumoniae* and *M. pneumoniae*, although the optimal duration of therapy for acute bronchitis is unknown. A useful range is 5 to 14 days.

During influenza season, anti-influenza agents may be useful in decreasing symptoms by approximately 1 day and may lead to a 0.5-day earlier return to normal activity in patients with influenza. The first-generation drugs amantadine and rimantadine are ineffective against H3N2 influenza A viruses and are not recommended. Second-generation drugs such as zanamivir (two inhalations of 5 mg each, twice a day) or oseltamivir (75 mg twice a day) can be given for 5 days. Up to 20% of patients given oseltamivir will have nausea or vomiting.

Antihistamines and over-the-counter antitussives and expectorants have no apparent value. Although some subsets of patients with bronchial hyperresponsiveness may benefit from inhaled selective β_2-agonists at doses commonly used to treat asthma (see Chapter 75), overall they appear to confer no benefit. No data support the routine use of inhaled steroids. Mucolytic agents may be of small benefit.

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ABSTRACT

Pneumonia is a lung infection associated with fever, cough, sputum, pleuritic chest pain, and a pulmonary infiltrate. Pneumococcus, *Haemophilus influenzae, Staphylococcus aureus,* and gram-negative bacilli cause up to 30% of cases, and less than 5% of cases are caused by *Mycoplasma, Chlamydia,* or *Legionella* species. Respiratory viruses typically have caused about 20 to 30% of cases, but this percentage has increased dramatically during the coronavirus-19 (COVID-19) pandemic. In over 50% of cases, no clear pathogen is confirmed. Empirical antibiotic treatment should be started promptly if bacterial pneumonia is suspected but then narrowed if possible based on microbiologic studies. The most common pulmonary complication is empyema, which develops in about 3 to 5% of cases. Acute cardiac events such as atrial fibrillation, new or worsening heart failure, or myocardial ischemia develop in about 20 to 25% of patients who are hospitalized with pneumonia. The mortality rate for community-acquired pneumonia requiring hospitalization is about 6% during hospitalization and about 15% by 1 month. Recovery may be slow, especially in older adults. Prevention focuses on vaccination for pneumococcus, influenza, and the severe acute respiratory syndrome coronavirus-2.

KEYWORDS

pneumonia
immunocompromised
hospital-acquired pneumonia
community-acquired pneumonia
treatment of pneumonia
diagnosis of pneumonia

illness associated with influenza, human metapneumovirus (Chapter 330), respiratory syncytial virus (Chapter 330), *Staphylococcus aureus* (Chapter 267), and *Streptococcus pneumoniae* (Chapter 268) also peak during winter months. The seasonality of the novel pandemic severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2; Chapter 336) has yet to be determined, but during the pandemic it became the leading cause of death owing in large part to pneumonia and respiratory failure.

Risk factors for developing pneumonia include male sex, smoking (Chapter 363), poor dental hygiene, crowded living conditions (including institutional settings), and more underlying comorbid conditions, especially malnutrition (Chapter 198), alcohol use disorder (Chapter 364), chronic immunosuppression, chronic lung disease, and neurologic disease, particularly dementia or conditions that compromise the normal gag reflex.[2] Medications associated with an increased risk of pneumonia include opioids, proton pump inhibitors,[3] corticosteroids, and other immunosuppressive drugs. Both inherited and acquired genetic disorders also can result in an increased frequency and/or severity of pneumonia. Examples include disorders of white cell production or function (Chapter 153), common variable immunodeficiency (Chapter 231), multiple myeloma (Chapter 173), and cystic fibrosis (Chapter 77).

PATHOBIOLOGY

Even in healthy adults, the lungs receive a continuous barrage of diverse microbes from inhaled air and from subclinical microaspiration of microbes that colonize the oropharynx. In healthy lungs, dominant bacteria, which most closely resemble those in the mouth, include *Prevotella, Veillonella,* and *Streptococcus* species. The lung microbiome includes both microbial elements (bacteria, viruses, phages, and fungi) and the normal host response. The mucosa of the upper respiratory tract is in direct communication with that of the lungs, so no region of the respiratory tract can be considered sterile.

Because bacterial pathogens can be found in low quantities in the healthy lung, pneumonia can be viewed as an alteration of homeostasis such that one (or more) pathogens can become dominant in the microbiome and stimulate a host response that results in inflammation (inflammatory markers and migration of cells into the lung), thereby resulting in the clinical picture of pneumonia. Infectious agents also can reach the lungs by hematogenous spread.

The total microbial burden and the frequency of specific types of bacteria in the lung depend on three factors: immigration, elimination, and relative reproduction rates. Lipid-rich and bacteriostatic surfactant, which lines the alveoli, other local conditions (e.g., pH, oxygen tension, temperature, microbial competition), and host defenses limit reproduction of pathogenic bacteria in the healthy lung. Inhaled and aspirated bacteria are eliminated by ciliated epithelial cells, which propel microbes entrapped in the mucous layer toward the upper airway, coughing, and both innate and adaptive immune defenses. Factors that increase microbial immigration (e.g., increased oropharyngeal colonization, supine position, more frequent mini-aspiration events, or gastrointestinal reflux), decrease the elimination of microbes (e.g., decreased cough, impaired ciliary function, obstructing lesions in the airways), or change the micro-environment (e.g., immunosuppression, destruction of lung surface area) contribute to infection.

Aging is the strongest risk factor for both the incidence and severity of pneumonia. Even among healthy adults, aging is associated with loss of adult stem cell reservoirs, mitochondrial dysfunction, oxidative stress, and shortening of telomeres, all of which interfere with the regeneration and repair needed to maintain homeostatic balance in the lung.[4] Chronic cumulative damage from exposure to atmospheric pollution, cigarette smoke, and other airborne substances are amplified by these changes. Chronic inflammation upregulates epithelial cell surface receptors that may increase bacterial adhesion in the aging lung and increase susceptibility to pneumonia. Decreased clearance mechanisms, including cough and mucociliary dysfunction, and structural lung changes may also increase susceptibility. Patients who have chronic lung conditions (e.g., chronic obstructive pulmonary disease [Chapter 76], cystic fibrosis [Chapter 77], or bronchiectasis [Chapter 78]) commonly have exacerbations that are triggered by bacterial or viral infections that cause inflammation and reduce lung function.

Whereas microaspiration is the presumed primary mechanism for most bacterial pneumonias, bacterial infections such as *Mycobacterium tuberculosis* (Chapter 299) and *Bacillus anthracis* (Chapter 272) are typically acquired by the direct inhalation of aerosols. Some bacteria, such as *Staphylococcus aureus* and *Escherichia coli,* can infect the lung via hematogenous spread. Any organism that causes vascular infection, especially right-sided endocarditis, also can seed the lungs and cause pneumonia.

Viruses are not typically part of the normal oropharyngeal flora but rather tend to be transmitted from infected persons by aerosols or by fomites. Viruses then replicate and spread through respiratory epithelial cells. Although viruses can cause pneumonia in the absence of bacterial infection,[5] some viruses (e.g., influenza, parainfluenza, respiratory syncytial virus) also may facilitate bacterial coinfection.

CLINICAL MANIFESTATIONS

Most patients with bacterial, COVID-19, or influenza pneumonia are acutely ill, but patients with *Mycoplasma, Chlamydia* pneumonia, or other viral pneumonias may not appear very ill. Pulmonary symptoms associated with pneumonia include cough (with or without purulent sputum), tachypnea, shortness of breath (dyspnea), and chest pain, which may be pleuritic. The classic triad of fever, dyspnea, and productive cough is absent in more than 40% of older adults with community-acquired pneumonia.[6] Instead, older adults and frail individuals often have atypical presentations, including malaise, changes in mental status, general fatigue, a decrease in functional status, urinary incontinence, and falls. Hypoxemia can cause confusion, but any neurologic symptoms should raise suspicion for meningitis.

DIAGNOSIS

The diagnosis of pneumonia requires compatible clinical manifestations combined with new opacities detected on chest imaging. Clinical judgement is paramount to avoid overtreatment that may result from the lack of an alternative diagnoses as well as the fear of potential negative consequences of withholding antibiotics from a patient with a bacterial pneumonia.

Physical Examination

Systemic signs include fever or hypothermia and tachycardia; hypotension suggests sepsis (Chapter 94). The respiratory rate may be increased, and a rate above 25 breaths per minute or an oxygen saturation below 92% suggests respiratory compromise. On the pulmonary examination, crackles are generally heard over the affected area (in bacterial pneumonia). Bronchial breath sounds and egophony (the patient says "a" but the clinician hears "e" on auscultation over the affected area) strongly suggest pneumonia with lobar consolidations but often are not heard. Dullness to percussion is consistent with consolidation or a pleural effusion. Increased tactile fremitus (a feeling of vibration over the affected area when the patient speaks) may be noted in an area with a pulmonary infiltrate but not over a pleural effusion. If the diaphragm does not move by percussion, an effusion is likely. Unfortunately, none of these findings on physical examination is sufficiently sensitive or specific to avoid the need for imaging for radiographic validation.

Radiology

The diagnosis of pneumonia requires a chest radiograph; thus, the first decision in the outpatient setting is often whether someone with cough or other respiratory symptoms needs an imaging study to confirm the diagnosis. Normal vital signs, especially if accompanied by lack of abnormal findings on physical examination of the chest, identify patients who have a sufficiently low risk of pneumonia such that imaging will likely not be useful. Rhinorrhea and sore throat suggest an upper respiratory process rather than pneumonia.

Chest radiographic abnormalities (Chapter 72) associated with community-acquired pneumonia include lobar consolidation, cavitation, and/or interstitial infiltrates (Fig. 85-1). Although consolidation or cavitation make a bacterial (or mycobacterial if cavitation is seen in the upper lobes) cause more likely, the radiographic presentation cannot reliably differentiate among pathogens. Parapneumonic effusions (Chapter 86) occur in up to 60% of patients with community-acquired pneumonia. Lung ultrasound is an attractive point-of-care option in experienced hands,[7] but standardized ultrasonographic criteria do not exist, and ultrasound does not avoid the need for a chest radiograph.

Chest computed tomography (CT) scanning (see Figs. 72-2 and 72-4) has higher sensitivity and specificity than a chest radiograph but is not ideal as an initial test because of its limited availability, cost, and radiation exposure. CT also can help distinguish whether an abnormal chest radiograph is being caused by an exacerbation of COPD or heart failure (see Fig. 72-3). Other conditions that should be included in the differential diagnosis in patients who have abnormalities on chest imaging include interstitial lung diseases (Chapter 80), lung cancer (Chapter 177), vasculitis (Chapter 249), pulmonary embolus (Chapter 69), or pulmonary hemorrhage (Chapter 69). In a patient who has symptoms and signs consistent with pneumonia, the absence of an infiltrate suggests an acute exacerbation of chronic obstructive pulmonary disease (Chapter 76), asthma (Chapter 75), or bronchitis (Chapter 84), or a viral infection such as pertussis (Chapter 289).

Radiographic abnormalities unfortunately are not particularly helpful in determining the cause of the pneumonia. Dense consolidation of a segment or lobe (see Fig. 85-1A1-1A3) suggests a bacterial cause, especially *S. pneumoniae, Klebsiella,* and often *Legionella.* Viral pneumonias other than COVID-19 usually cause diffuse

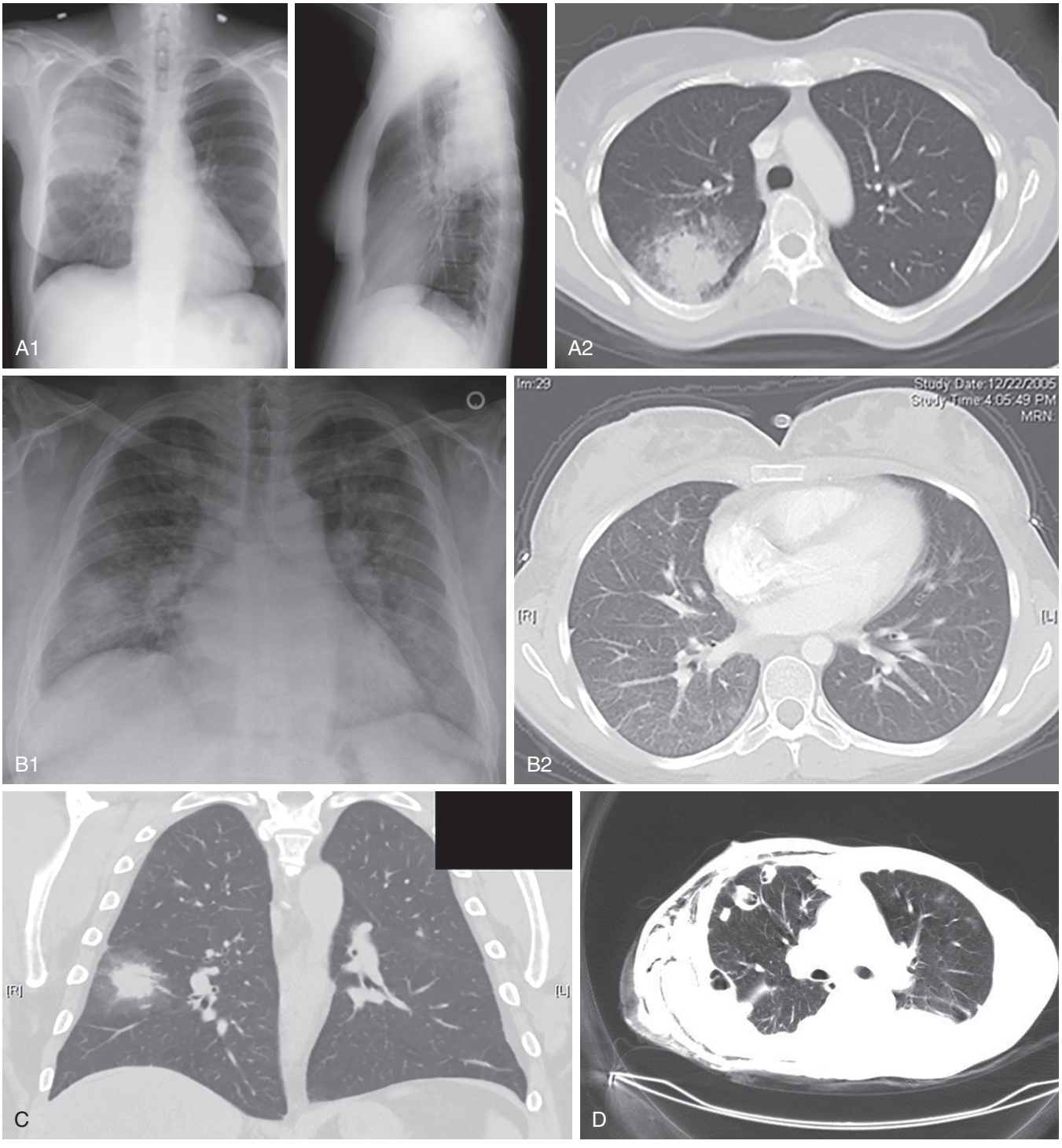

FIGURE 85-1. Chest radiographic findings in pneumonia. A, Lobar Infiltrate: Right upper lobe infiltrate in patient with pneumococcal pneumonia. 1. Anteroposterior chest radiograph. 2. Lateral chest radiograph. **B,** Diffuse or "patchy" interstitial infiltrates. 1. Anteroposterior chest radiograph. Bilateral patchy infiltrates in a patient with coronavirus pneumonia. 2. Computed tomographic scan. Diffuse interstitial infiltrates in a patient with *Pneumocystis jiroveci* pneumonia. **C,** Nodular Infiltrates. Computed tomographic scan. **D,** Cavitation. Computed tomographic scan. Cavitation in a patient with staphylococcal pneumonia. (From Musher DM. Overview of pneumonia. In: Goldman L, Schafer AI, eds. *Goldman-Cecil Medicine*. 26th ed. Philadelphia: Elsevier; 2020.)

infiltration (see Fig. 85-1B1) but may present with segmental or lobar consolidation, particularly when complicated by bacterial superinfection.[8] Subsegmental infiltration (see Fig. 85-1B2) can be seen with *Mycoplasma, Chlamydia,* and viruses. Hematogenous spread of *S. aureus* typically causes 1- to 3-cm round lesions that frequently cavitate (see Fig. 85-1D). A cavitary upper lobe lesion without a fluid level is typical of tuberculosis (Chapter 299), nontuberculous *Mycobacterium* (Chapter 300), or nocardiosis (Chapter 306). *Aspergillus* (Chapter 311) can cause a cavity with a distinctive intracavitary mycetoma (fungus ball; Fig. 311-2).

Diagnosing the Causative Agent

Polymerase chain reaction (PCR) testing of a nasopharyngeal swab is the best and most sensitive method for detecting viral pneumonias, which tend to have a presentation similar to that of atypical bacterial pneumonia. The SARS-CoV-2 (Chapter 336) and the disease it causes (COVID-19) have been the dominant causes of pneumonia worldwide during the recent pandemic, but other viruses such as rhinovirus (Chapter 329), influenza virus (Chapter 332), parainfluenza virus (Chapter 331), respiratory syncytial virus (Chapter 330), human metapneumovirus (Chapter 330), pre-2019 coronavirus (Chapter 334), and adenovirus (Chapter 333) also must be considered. Although a positive result may reflect colonization rather than infection, PCR is sensitive and specific for organisms that do not normally colonize the upper airways (e.g., *Chlamydia, Mycoplasma,* SARS-CoV-2, other coronaviruses, influenza, parainfluenza, respiratory syncytial virus, human metapneumovirus, and adenovirus). PCR testing should be done routinely for both SARS-CoV-2 and influenza when these viruses are circulating in the community, at least for patients who are eligible for antiviral treatment and for patients who will be hospitalized.

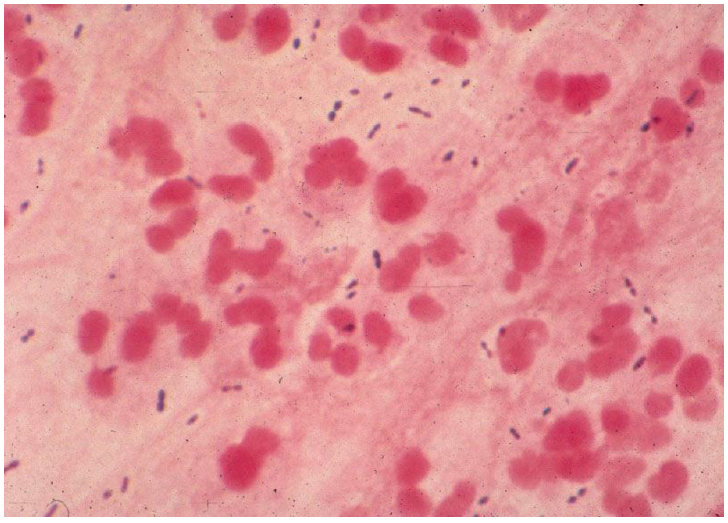

FIGURE 85-2. **Gram stain of sputum from a patient with pneumococcal pneumonia shows large numbers of polymorphonuclear leukocytes and many lancet-shaped gram-positive cocci with no epithelial cells, indicating that this specimen originated in the lower airways. Such a specimen is diagnostic of pneumococcal pneumonia, although it cannot exclude coinfection by an organism such as a virus that is not seen by Gram stain. (From Musher DM. Overview of pneumonia. In: Goldman L, Schafer AI, eds. *Goldman-Cecil Medicine*. 26th ed. Philadelphia: Elsevier; 2020.)**

Guidelines recommend against obtaining a sputum Gram stain (Fig. 85-2) and culture in most adults with community-acquired pneumonia because of their low sensitivity, the difficulty in obtaining adequate specimens, and the low likelihood that the results will change the choice of antibiotic treatment.[9] However, pretreatment Gram stain and culture of respiratory samples should be obtained in patients who are hospitalized with disease that meets the definition of severe pneumonia (Table 85-5, later) or who have risk factors for methicillin-resistant *Staphylococcus aureus* (MRSA) or *Pseudomonas aeruginosa*.[10] Blood cultures have a low yield and are not recommended, except in patients who meet criteria for severe pneumonia (Table 85-5, later) or who have risk factors for methicillin-resistant *Staphylococcus aureus* (MRSA) or *Pseudomonas aeruginosa*.[11]

In the recent pre-coronavirus-2019 (COVID-19) era, more than 50% of adults diagnosed and hospitalized with community-acquired pneumonia had no identifiable pathogen despite PCR testing of respiratory samples for viruses and atypical bacteria; culture of blood, sputum, and pleural fluid; and urinary assays for antigens (*Legionella* and *Streptococcus pneumoniae*). Bacteria were identified in 15 to 30% of cases, with *Streptococcus pneumoniae* (5 to 16%; Chapter 268), *Haemophilus influenzae* (<1 to 7%; Chapter 277), *Staphylococcus aureus* (2 to 5%; Chapter 267) and *Pseudomonas* (<1 to 3%; Chapter 282) being the most frequent (Table 85-1). Atypical bacteria each were responsible for less than 3%, even when routinely included in the testing protocol. In the pre-coronavirus-19 (COVID-19) era, routine multiplex PCR detected respiratory viruses in 20 to 27% of patients, with rhinoviruses (5 to 13%; Chapter 329) and influenza viruses (1 to 9%; Chapter 332) being the most common and all other viruses accounting for only 1 to 4% of cases. Other rare pathogens included mycobacteria (Chapter 300), nocardia (Chapter 306), and fungi.

Laboratory Testing

Many patients with community-acquired pneumonia do not require additional diagnostic testing other than a chest radiograph to confirm the diagnosis of pneumonia, a pulse oximetry measurement (with a saturation of 95% or higher indicating normal oxygenation), plus PCR testing for SARS-CoV-2 and, during flu season, for influenza. Additional routine testing for hospitalized patients to assess clinical stability should include a complete blood count, glucose level, and a measure of renal function. If the patient is tachypneic, an arterial blood gas should be obtained.

Laboratory findings include an elevated white blood cell count with neutrophilia in bacterial pneumonia, but viral infections and overwhelming bacterial infections can present with leukopenia. Inflammatory markers (e.g., the erythrocyte sedimentation rate, the C-reactive protein level, and, in bacterial infections, the procalcitonin level) may be elevated, especially with more severe bacterial pneumonias. Specific additional diagnostic testing is recommended for patients in whom admission is being contemplated (see Fig. 85-4) or in whom MRSA or *Pseudomonas aeruginosa* is suspected. Guidelines recommend against routine testing of urine for pneumococcal or *Legionella* antigens except in patients who have severe community-acquired pneumonia, or during *Legionella* outbreaks. If a *Legionella* outbreak is suspected, culture of respiratory secretions on selective media is also recommended.

TABLE 85-1 BACTERIAL AND VIRAL PATHOGENS IN COMMUNITY-ACQUIRED PNEUMONIA IN THE PRE-SARS-COV-2 ERA

PATHOGEN	PERCENT*
TYPICAL BACTERIA	**15-30**
Streptococcus pneumoniae	5-16
Staphylococcus aureus	3-5
Haemophilus influenzae	<1-7
Pseudomonas aeruginosa	<1-3
Escherichia coli	<1
Klebsiella pneumoniae	<1
Moraxella catarrhalis	<1
Other streptococci	<1
Acinetobacter baumannii	<1
ATYPICAL BACTERIA	**4**
Mycoplasma pneumoniae	1-2
Legionella spp	1
Chlamydia pneumoniae	1-2
VIRUSES	**20-27**
Human rhinoviruses	9-13
Influenza A and B viruses	1-6
Human metapneumovirus	2-4
Respiratory syncytial virus	2-3
Parainfluenza viruses 1-3	2-3
Other coronaviruses (229E, HKU1, NL63, and OC43)	2-3
NO PATHOGEN IDENTIFIED	**55-66**

*Percents based on various studies since 2010.
SARS-CoV-2 = severe acute respiratory syndrome coronavirus-2.

Unusual Causes of Pneumonia

Epidemiologic clues may be useful, especially for prompt consideration of unusual causes of pneumonia (Table 85-2), including *Coccidioides immitis* (southwest United States; Chapter 308), *Histoplasma capsulatum* (Midwest and South-Central United States; Chapter 308), *Francisella tularensis* (exposure to rabbits; Chapter 287), *Chlamydia psittaci* (exposure to parrots and parakeets; Chapter 294), *Cryptococcus neoformans* (exposure to pigeons; Chapter 302), and *Coxiella burnetii* (exposure to farm animals; Q fever; Chapter 302). Tuberculosis (Chapter 299) and nontuberculous mycobacterial infection (Chapter 300) must be considered in patients who have lived in endemic areas, have been incarcerated or homeless, have bronchitis (Chapter 78), or have extensive lung scarring owing to emphysema (Chapter 76).

Differential Diagnosis

Fever, cough, sputum production in the absence of infiltrate or a chest radiograph is consistent with acute bronchitis (Chapter 84). Persistent cough for several weeks in the absence of a fever or sputum should raise suspicion for pertussis (Chapter 289) but is also seen after a viral infection such as adenovirus (Chapter 333) or respiratory syncytial virus (Chapter 330).

About 15 to 20% of patients who are admitted to the hospital for suspected pneumonia have noninfectious causes for their symptoms. Acute heart failure (Chapter 45), which is the most likely noninfectious cause in older patients, may be suspected based on the history, physical examination, and radiographic findings, and it often can be confirmed by an elevated B-natriuretic peptide level. Pulmonary emboli with infarction (Chapter 68) can cause pleuritic chest pain and pulmonary infiltrates. Lung cancer (Chapter 177) can present with fever and a pulmonary infiltrate from a postobstructive pneumonia. The acute respiratory distress syndrome (Chapter 90), which can be the result of

TABLE 85-2 CONDITIONS SUGGESTING VARIOUS CAUSES OF PNEUMONIA

UNDERLYING CONDITION	ASSOCIATED MICROORGANISM
Pandemic condition	SARS-CoV-2
Aspiration/poor dentition	Microaerophilic and anaerobic mouth flora; *Candida* spp
Gross aspiration, bedridden person	*Staphylococcus aureus*, gram-negative rods
Travel to southwestern United States	*Coccidioides immitis*
Residence in Mississippi River basins, exposure to bats	*Histoplasma capsulatum*
Exposure to birds	Cryptococcus neoformans, *H. capsulatum*
Exposure to sick psittacine birds	*Chlamydia psittaci*
Exposure to rabbits	*Francisella tularensis*
Exposure to farm animals	*Coxiella burnetii* (Q fever)
Influenza active in community	Influenza virus, *S. aureus, S. pneumoniae, H. influenzae, Streptococcus pyogenes*
Bronchiectasis, cystic fibrosis	*Pseudomonas aeruginosa, Burkholderia cepacia, S. aureus, Aspergillus* spp, nontuberculous mycobacteria
Cavitary lung lesion	Microaerophilic and anaerobic mouth flora, *S. aureus*, tuberculous and nontuberculous mycobacteria, endemic fungi
Intravenous drug use	*S. aureus, Mycobacteria tuberculosis, S. pneumoniae*
Endobronchial obstruction	Microaerophilic and anaerobic mouth flora, gram-negative bacilli, *S. aureus*
Recent antibiotic therapy	Antibiotic-resistant *S. pneumoniae*
HIV (early)	*S. pneumoniae, H. influenzae, M. tuberculosis*
HIV/AIDS	Pathogens listed for early HIV infection, plus *Pneumocystis jiroveci, Cryptococcus, Histoplasma, Aspergillus, Mycobacterium kansasii, Mycobacterium avium* complex, *P. aeruginosa*
Travel to Middle East	Middle East respiratory syndrome (MERS) coronavirus
Bioterrorism	*Bacillus anthracis* (anthrax), *Yersinia pestis* (plague), *Francisella tularensis* (tularemia)

AIDS = acquired immunodeficiency syndrome; HIV = human immunodeficiency virus; SARS-CoV-2 = severe acute respiratory syndrome coronavirus 2; spp = species.

Data from Infectious Diseases Society of America/American Thoracic Society. Consensus guidelines on the management of community-acquired pneumonia in adults. *Clin Infect Dis*. 2007;44:S27-S72. From Musher DM. Overview of pneumonia. In: Goldman L, Schafer AI, eds. *Goldman-Cecil Medicine*. 26th ed. Philadelphia: Elsevier; 2020;592-603.

a serious nonpulmonary infection, may have clinical manifestations that are difficult to distinguish from pneumonia. Noninfectious interstitial pneumonia (Chapter 80), especially cryptogenic organizing pneumonia, eosinophilic pneumonia, and sarcoidosis (Chapter 83), are frequently initially misdiagnosed as community-acquired pneumonia.

TREATMENT

Initial Treatment

If SARS-CoV-2 is identified by point-of-care PCR testing, antibacterial agents should not be given unless bacterial coinfection is suspected, but antiviral agents and/or antibody treatments should be used in higher risk patients (see Chapter 337). When PCR testing documents influenza infection, antiviral treatment (see Chapter 332 and Table 85-6, later) is recommended in addition to empirical treatment for community-acquired pneumonia, due to possible coinfection with a bacterial pathogen.

Otherwise, empirical treatment (Table 85-6, later) for community-acquired pneumonia often begins before a specific etiologic diagnosis is established because the early administration of antibiotics improves outcomes for patients who have bacterial pneumonia. Antibiotic treatment can then be tailored if and when a pathogen is identified.[12] Despite some promising data, professional societies recommend against the use of procalcitonin levels to determine whether to administer antibiotics.

The Admission Decision

The severity of pneumonia guides the key decision of whether hospitalization is required and, if so, what level of care is most appropriate. The decision regarding hospital admission can be guided by validated approaches such as the pneumonia severity index along with clinical judgement. A score of 90 or fewer points (Fig. 85-3 and Table 85-3), which corresponds to classes I to III, indicates that outpatient management is likely to be safe in nonhypoxemic patients. Higher scores should alert clinicians to increasingly grave prognoses and the need for higher levels of care, as well as communication of such prognoses to patients and their designees when appropriate. If laboratory testing is not readily available to make the decision about admission, another severity index, the CURB-65 (Table 85-4), is a less preferred alternative. In patients who have more than 130 points on the pneumonia severity score (Fig. 85-3), more than 3 points on the CURB-65 score, or meet criteria for severe pneumonia (Table 85-5), admission to an intermediate care unit or intensive care unit is usually appropriate.

Choices among Antibiotics for Syndromes Suggesting Bacterial Pneumonia

Antibiotic treatments depend on the site of care (see Fig. 85-4 and Table 85-3),[13,14] the presence or absence of comorbid conditions (see Fig. 85-4), and epidemiologic clues (see Table 85-2).

Treatment should be altered as appropriate when a specific organism and its antimicrobial sensitivities are identified. Patients must be reevaluated if clinical stability is not achieved, and treatment must be discontinued in a timely and appropriate way.

Outpatient Antimicrobial Therapy

For otherwise healthy adults with community-acquired pneumonia in the outpatient setting, monotherapy is recommended for 5 days[15] with amoxicillin, doxycycline, or azithromycin (see Table 85-6). For outpatient adults who have chronic conditions that may both increase the risk of acquiring a drug-resistant organism, as well as the consequences of insufficient antibiotic coverage, the recommended antibiotic regimens include monotherapy with a respiratory fluoroquinolone or the combination of one of amoxicillin/clavulanate, cefpodoxime, or cefuroxime plus azithromycin, clarithromycin, or doxycycline (see Table 85-6). For patients who will not be hospitalized, there is no evidence for or against an initial dose of a parenteral antibiotic before sending the patient home.[16]

Inpatient Antimicrobial Therapy

For inpatients who have nonsevere community-acquired pneumonia without risk factors for MRSA or *P. aeruginosa,* antibiotic choices include monotherapy with a respiratory fluoroquinolone or the combination of a β-lactam plus either a macrolide or doxycycline (see Table 85-6).[A1,A2] In clinically stable patients (temperature 37.8°C or less, heart rate less than 100 beats per minute, respiratory rate less than 24 breaths per minute, oxygen saturation 90% or higher, systolic blood pressure 90 mm Hg or higher, and normal mental status), 3 days of intravenous treatment need not be followed by oral treatment.[A3] Newer options found noninferior to fluoroquinolone monotherapy are omadacycline monotherapy[A4] and lefamulin monotherapy[A5,A6] (see Table 85-6). Alternatives to fluoroquinolones should be strongly considered because of the association of fluoroquinolones with the development of *Clostridioides difficile* infection, tendinopathy/tendon rupture, mental status changes, and peripheral neuropathy. Fluoroquinolones are contraindicated in patients who have a prolonged QT interval, and lefamulin is contraindicated in patients who have a prolonged QT interval as well as in patients who have moderate to severe liver disease.

Patients who are hospitalized with severe community-acquired pneumonia should receive dual therapy with a β-lactam and either a macrolide or a respiratory fluoroquinolone[17] (see Table 85-6). The risk of infection with MRSA or *Pseudomonas* is increased in patients who have received parenteral antibiotics in the prior 90 days and who have had infection with these organisms previously. If treatment is being considered to cover MRSA, a rapid negative nasal PCR test has high predictive value and suggests a different etiology; a positive test has a low predictive value but warrants empirical treatment in patients who have severe community-acquired pneumonia or who are at high risk for MRSA in the absence of other etiology. Anaerobic coverage such as with clindamycin is not routinely recommended unless a lung abscess or empyema is suspected.

Antibiotics generally should be continued for a minimum of 5 days for most patients, for 7 days for patients with suspected MRSA or *Pseudomonas,* but longer if needed to achieve clinical stability (i.e., resolution of vital sign abnormalities, toleration of oral intake, and normal mentation). In patients whose community-acquired pneumonia does not require an intensive care unit (ICU); however, 3 days of intravenous treatment that includes a β-lactam can be adequate if they are clinically stable.

All hospitalized patients who test positive for influenza should receive antiinfluenza treatment regardless of the duration of illness before diagnosis. Such patients also should receive adjunctive antibiotic treatment given the high prevalence of bacterial coinfection.

Adjunctive Therapy and Supportive Care

Guidelines recommend against the use of corticosteroids in most adults with community-acquired pneumonia, except in patients who have refractory septic shock (Chapter 94). However, corticosteroids (e.g., hydrocortisone 200 mg for 4 or 8 days

Sex

- ○ M (0 points)
- ○ F (–10 points)

Demographic factors

- ▭ Age
- ☐ Nursing home resident (10 points)

Comorbid illnesses

- ☐ Cancer, not of skin (30 points)
- ☐ Active chronic liver disease (20 points)
- ☐ Heart failure (10 points)
- ☐ Cerebrovascular disease (10 points)
- ☐ Renal disease (10)

Physical examination findings

- ☐ Altered mental status (20 points)
- ☐ Respiratory rate ≥30/minute (20 points)
- ☐ Temperature <35° C or ≥40° C (15 points)
- ☐ Pulse ≥125/minute (10 points)

Laboratory and radiographic findings

- ☐ Arterial pH <7.35 (30 points)
- ☐ Blood urea nitrogen ≥30 mg/dL (11 mmol/L) (20 points)
- ☐ Serum sodium <130 mEq/L (20 points)
- ☐ Serum glucose ≥250 mg/dL (14 mmol/L) (10 points)
- ☐ Hematocrit <30 percent (10 points)
- ☐ Partial pressure of arterial oxygen <60 mmHg or oxygen saturation <90% (10 points)
- ☐ Pleural effusion on chest radiograph (10 points)

FIGURE 85-3. Community-Acquired Pneumonia Severity Index for Adults. Compute total point score (see Table 85-3).

TABLE 85-3 MORTALITY AT 30 DAYS BASED ON THE SCORE ON THE COMMUNITY-ACQUIRED PNEUMONIA SEVERITY INDEX (SEE FIG. 85-3)

POINT SCORE	CLASS	APPROXIMATE 30-DAY MORTALITY
≤70	II	<1-3%
71-90	III	3-4%
91-130	IV	8%
>130	V	25%

From Fine MJ, Auble TE, Yealy DM, et al. A prediction rule to identify low-risk patients with community-acquired pneumonia. *N Engl J Med*. 1997;336:243-250; and Musher DM, Roig IL, Cazares G, et al. Can an etiologic agent be identified in adults who are hospitalized for community-acquired pneumonia: results of a one-year study. *J Infect*. 2013;67:11-18.

TABLE 85-4 CURB-65 SCORING SYSTEM FOR PNEUMONIA

CLINICAL FACTOR	POINTS
Confusion	1
Blood urea nitrogen ≥ 20 mg/dL	1
Respiratory rate ≥ 30 breaths per minute	1
Systolic blood pressure < 90 mm Hg or Diastolic blood pressure ≤ 60 mmHg	1
Age ≥ 65 years	1
Total points:	

One point given for the presence of each of the factors. Higher scores indicate a greater risk of death. A score of >2 points generally suggests that hospital admission is required, and a score of >3 points suggests that admission to an intensive care unit is advisable.
Data from Eccles S, Pincus C, Higgins B, et al. Diagnosis and management of community and hospital acquired pneumonia in adults: summary of NICE guidance. *BMJ*. 2014;349:g6722.

depending on clinical improvement, then tapered for a total of 8 or 14 days) improve outcomes in severe community-acquired pneumonia,[A7] and corticosteroids (e.g., dexamethasone) also benefit severely ill patients who have COVID-19 and who are receiving supplemental oxygen or are on ventilatory support (Chapter 337).

Supportive Care

Supportive care will depend on severity of pneumonia and site of care. Patients should remain active as tolerated, but hospitalized patients may require assistance to ambulate safely. Frequent monitoring of vital signs and oxygenation should alert clinicians to important clinical deterioration in a timely way. At discharge, some patients may require supplemental oxygen, but often only temporarily. Patients should be warned of the cardiovascular complications that frequently accompany or follow pneumonia (including arrhythmias, heart failure, and acute coronary syndrome) and seek care if they do not continue to improve or develop new symptoms.

Failure to Improve

A follow-up chest radiograph is not routinely recommended to ensure resolution because radiograph clearance may require weeks. However, failure to achieve clinical stability within 5 to 7 days should prompt consideration of empyema (Chapter 86), lung abscess (Chapter 78), or an alternative diagnosis that requires repeat imaging and merits alternative specific management (Table 85-7).

Most parapneumonic effusions (Chapter 86) resolve with resolution of the pneumonia and do not require drainage. If appropriate antibiotic treatment is not timely; however, an uncomplicated parapneumonic effusion may progress to a fibrinopurulent stage (complicated pleural effusion or empyema), which carries significant morbidity. In patients with a complicated parapneumonic effusion, bacteria are identified in fewer than 20% of cases by culture, but by PCR testing in 93% of cases. When bacteria are identified, viridans streptococci are the most frequent pathogens, followed by *Fusobacterium* and *Streptococcus pneumoniae*.

TABLE 85-5 INFECTIOUS DISEASES SOCIETY OF AMERICA/AMERICAN THORACIC SOCIETY CRITERIA FOR DEFINING SEVERE COMMUNITY-ACQUIRED PNEUMONIA*

Major criteria
Septic shock with need for vasopressors
Respiratory failure requiring mechanical ventilation
Minor criteria
Hypotension requiring aggressive fluid resuscitation
Hypothermia (core temperature <36° C)
Respiratory rate ≥30 breaths/min
PaO_2/FiO_2 ratio ≤250
Confusion/disorientation
Multilobar infiltrates
White blood cell count <4000 cells/μL†
Thrombocytopenia (platelet count <100,000/μL)
Renal impairment (blood urea nitrogen level ≥20 mg/dL)

*Validated definition includes either one major criterion or three or more minor criteria.
†Due to infection alone (i.e., not chemotherapy-induced).
Reprinted with permission of the American Thoracic Society. Copyright © 2023 American Thoracic Society. All rights reserved. Metlay JP, Waterer GW, Long AC, et al. 2019, Diagnosis and treatment of adults with community-acquired pneumonia. An official clinical practice guideline of the American Thoracic Society and Infectious Diseases Society of America. *Am J Respir Crit Care Med.* 2019;200:e45-e67.

PREVENTION

Smoking cessation, avoidance of drugs known to increase the risk of pneumonia (e.g., opioids, proton pump inhibitors, corticosteroids, and other immunosuppressive agents) and control of the blood sugar in patients with diabetes can help prevent pneumonia and its morbidity. Masks, social distancing, and good ventilation have a substantial benefit for preventing SARS-CoV-2 (Chapter 336) and may also decrease rates of infection with influenza and respiratory syncytial virus. Individuals who have acute respiratory symptoms should avoid close contact with others, practice good hand hygiene, and may consider using appropriate face masks while symptomatic.

Influenza vaccine is recommended annually for all persons age 6 months and older (Chapter 15) and is especially important for individuals who have chronic health conditions, pregnant women, and older adults. SARS-CoV-2 vaccines (Chapter 15) are currently recommended for all adults and children ages 6 months and older. Pneumococcal conjugate vaccines protect against pneumonia, bacteremia, and meningitis caused by pneumococcal serotypes 15 (PCV15) and 20 (PCV20). Either of these vaccines is recommended for all adults ages 65 years and older and for adults age 19 through 64 years with certain medical conditions or risk factors (e.g., chronic heart; liver, lung, or kidney disease; diabetes mellitus; alcohol use disorder; cigarette smoking; cerebrospinal fluid leak; cochlear implant; or an immunocompromising

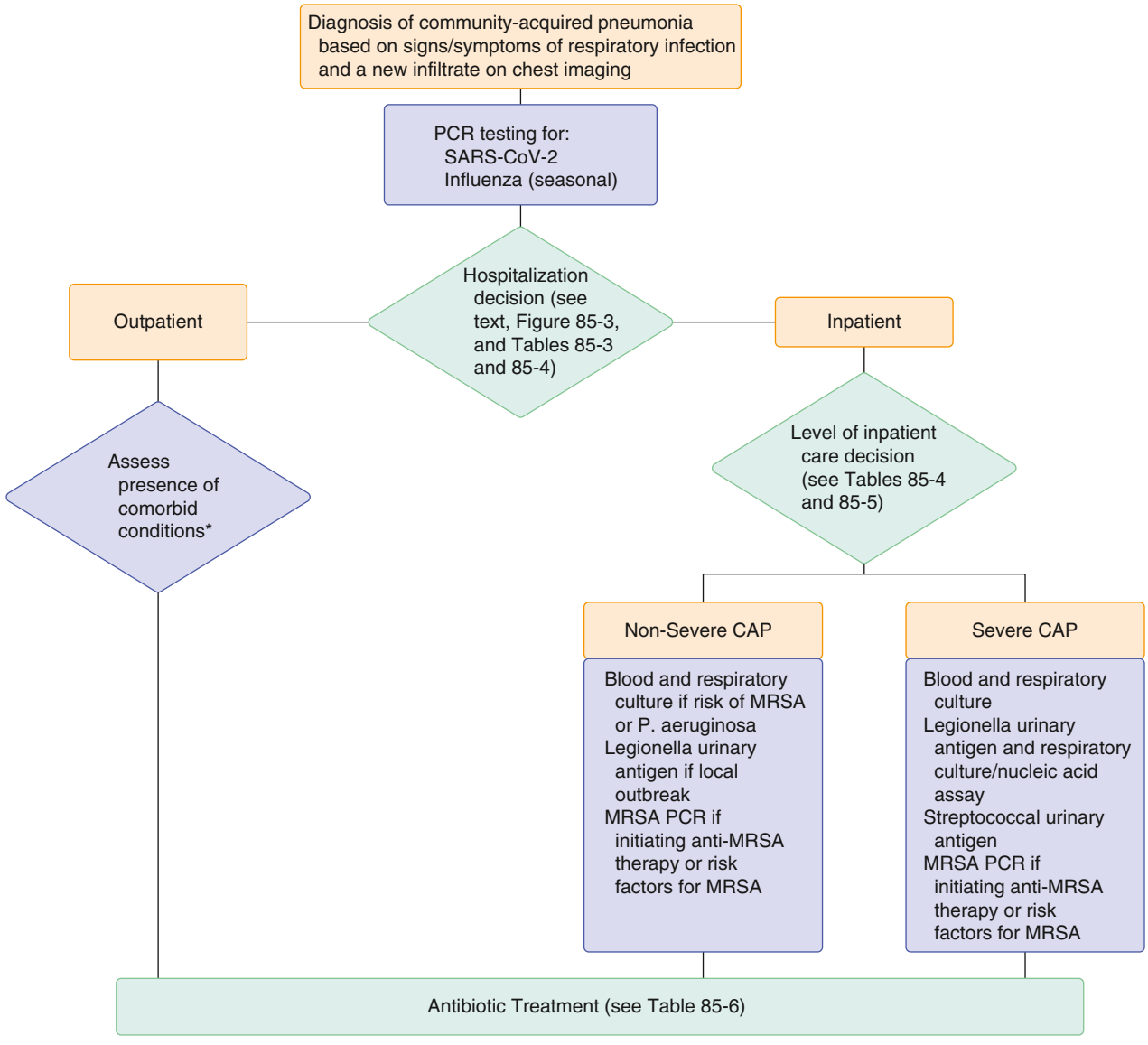

FIGURE 85-4. Diagnostic approach to community-acquired pneumonia management pathway for community-acquired pneumonia (CAP). *Comorbid conditions: chronic heart, lung, liver or renal disease; diabetes mellitus, alcoholism, malignancy; or asplenia. MRSA = methicillin-resistant *Staphylococcus aureus; P. aeruginosa = Pseudomonas aeruginosa;* PCR = polymerase chain reaction; SARS-CoV-2 = severe acute respiratory syndrome coronavirus-2. (Data from Jones BE, Herman DD, Dela Cruz CS, et al. Summary for clinicians: clinical practice guideline for the diagnosis and treatment of community-acquired pneumonia. *Ann Am Thorac Soc.* 2020;17:133-138.)

TABLE 85-6 RECOMMENDED ANTIMICROBIAL REGIMENS AND DOSING (ORAL FOR OUTPATIENTS, INTRAVENOUS FOR INPATIENTS)

I. FOR OUTPATIENT SYNDROMES SUGGESTING BACTERIAL PNEUMONIA
  A. Healthy outpatient adults with no comorbid conditions or risk factors for MRSA or *P. aeruginosa:*
    1. Amoxicillin 1 g three times daily
    2. Or doxycycline 100 mg twice daily),
    3. Or a macrolide (azithromycin 500 mg on first day then 250 mg daily or clarithromycin 500 mg twice daily or clarithromycin extended-release 1000 mg daily)
  B. Outpatient adults with comorbid conditions (e.g., chronic heart, lung, liver, or renal disease; diabetes mellitus; alcohol use disorder; malignancy; or asplenia)
    1. Combination therapy: amoxicillin/clavulanate (500 mg/125 mg three times daily or 875 mg/125 mg twice daily, or 2000 mg/125 mg twice daily) or a cephalosporin (cefpodoxime 200 mg twice daily or cefuroxime 500 mg twice daily); PLUS a macrolide (azithromycin 500 mg daily, or clarithromycin 500 mg daily or extended-release 1000 mg once daily), or doxycycline (100 mg twice daily)
    2. OR: Monotherapy: respiratory fluoroquinolone (levofloxacin 750 mg daily, or moxifloxacin 400 mg daily, or gemifloxacin 320 mg daily)

II. FOR OUTPATIENT SYNDROMES SUGGESTING VIRAL PNEUMONIA
  A. For SARS-CoV-2 (see Chapter 337)
  B. For syndromes suggesting influenza pneumonia:
    1. Oseltamivir (75 mg twice daily for 5 days)
    2. Treat as above for possibility of bacterial coinfection

III. FOR SYNDROMES SUGGESTING VIRAL PNEUMONIA OTHER THAN INFLUENZA, treat for possibility of bacterial coinfection

IV. FOR INPATIENT SYNDROMES SUGGESTING BACTERIAL PNEUMONIA
  A. Inpatient adults with nonsevere community-acquired pneumonia without risk factors for MRSA or *P. aeruginosa*:
    1. Combination therapy: a β-lactam (ampicillin 1 sulbactam 1.5-3 g every 6 hr, cefotaxime 1-2 g every 8 hr, ceftriaxone 1-2 g daily, or ceftaroline 600 mg every 12 hr) plus a macrolide (azithromycin 500 mg daily or clarithromycin 500 mg twice daily)
    2. Monotherapy: a respiratory quinolone (levofloxacin 750 mg daily, moxifloxacin 400 mg daily, or gemifloxacin 320 mg daily)
    3. For adults hospitalized with community-acquired pneumonia and contraindications to both macrolides and fluoroquinolones: combination therapy with a β-lactam (ampicillin sulbactam, cefotaxime, ceftaroline, or ceftriaxone; doses as earlier) plus doxycycline (100 mg twice daily)
    4. New monotherapies: omadacycline (100 mg every 12 hours × 2 then every 24 hours, substituting 300 mg by oral route on or after 3 days); lefamulin (150 mg every 12 hours, substituting 600 mg by oral route on or after 3 days)
  B. Adults hospitalized with severe community-acquired pneumonia (specific agents and doses are the same as earlier):
    1. A β-lactam plus a macrolide or a β-lactam plus a respiratory fluoroquinolone
    2. If MRSA is a consideration (see text): vancomycin (15 mg/kg every 12 hr, adjust based on levels) or linezolid (600 mg every 12 hr).
    3. If *P. aeruginosa* is a consideration: piperacillin-tazobactam (4.5 g every 6 hr), cefepime (2 g every 8 hr), ceftazidime (2 g every 8 hr), aztreonam (2 g every 8 hr), meropenem (1 g every 8 hr), or imipenem (500 mg every 6 hr)

V. FOR INPATIENT SYNDROMES SUGGESTING VIRAL PNEUMONIA
  A. If SARS-CoV-2:
    1. (See Chapter 337)
  B. If influenza is likely, bacterial coinfection may coexist:
    1. Oseltamivir (75 mg twice daily for 5 days) PLUS
    2. As per IV A and B
  C. For other viral pneumonias, bacterial coinfection may coexist, so patients should be treated as per IV A and B

MRSA = methicillin-resistant *Staphylococcus aureus; P. aeruginosa = Pseudomonas aeruginosa.*

Data from Jones BE, Herman DD, Dela Cruz CS, et al. Summary for clinicians: clinical practice guideline for the diagnosis and treatment of community-acquired pneumonia. *Ann Am Thorac Soc.* 2020;17:133-138.

TABLE 85-7 REASONS FOR FAILURE OF ANTIMICROBIAL THERAPY IN TREATING PNEUMONIA

Correct organism, but inappropriate antibiotic choice or dose
Organism not susceptible
Wrong dosage (e.g., morbidly obese or fluid-overloaded patient)
Correct organism and antibiotic, but infection is loculated
Empyema (the most common)
Obstruction (e.g., lung cancer, foreign body)
Causative organism not susceptible to chosen antibiotics
Noninfectious condition
Pulmonary embolism
Malignancy
Inflammatory noninfectious lung disease (see text)
Heart failure

Adapted from Musher DM. Overview of pneumonia. In: Goldman L, Schafer AI, eds. *Goldman-Cecil Medicine*. 26th ed. Philadelphia: Elsevier; 2020;592-603.

condition). Pneumococcal polysaccharide vaccine (PPSV23), which protects against serious pneumococcal disease from 23 serotypes of the pneumococcus, is recommended for all adults ages 19 years and older who receive PCV15 but is unnecessary for people who receive PCV20 (Chapter 15). When both vaccines are given, the conjugate vaccine should be given first, followed by the polysaccharide vaccine 1 year later. Vaccines for RSV may be available soon.[18]

PROGNOSIS

For patients who are treated as outpatients, the prognosis for full recovery is excellent. However, close follow-up is required to ensure that clinical stability is achieved and maintained.

About 85% of hospitalized patients respond within 7 days in terms of improved cough and shortness of breath, becoming afebrile, and tolerating of oral intake; such patients have only a 1% in-hospital mortality and 5% 30-day mortality. Characteristics associated with a failure to improve include the need for initial intensive care, obesity, diabetes, and an active malignancy. Overall, all-cause mortality is about 6% for hospitalized patients during their acute hospital stay and is about 13% at 30 days, 23% at 6 months, and 30% at 1 year, partly owing to the pneumonia itself and partly as a reflection of comorbid conditions and underlying frailty. For example, nearly 25% of patients experience at least one new cardiovascular event, including decompensated heart failure, atrial fibrillation or flutter, an acute coronary syndrome or stroke,[19] within the first 3 days of hospitalization. Mortality depends to a large degree on achievement of clinical stability.

Among hospitalized patients, about 70% are ultimately discharged home (including one-third of whom require home health follow-up), whereas about 30% are discharged to a nursing home or rehabilitation care facility. The overall readmission rate is about 15% at 30 days but is higher among patients who are discharged with a need for home health care.

HOSPITAL-ACQUIRED PNEUMONIA IN THE IMMUNOCOMPETENT HOST

Hospital-acquired pneumonia, which is defined as pneumonia that develops 48 hours or more after hospital admission, is typically divided into ventilator-associated pneumonia (VAP) and nonventilator hospital-acquired pneumonia (NV-HAP) depending on whether or not the patient was treated with mechanical ventilation in the 48 hours preceding the onset of pneumonia.

EPIDEMIOLOGY

Hospital-acquired pneumonia, which is the most common and morbid health care–associated infection (Chapter 261), affects approximately 1 in every 100 hospitalized patients. Incidence rates differ markedly, however, in different

populations: about 3.5% of ventilated patients (Chapter 91) develop pneumonia compared with about 0.5% of nonventilated patients.[20] Nonetheless, many more hospitalized are nonventilated, so most hospital-acquired pneumonia is not ventilator-associated. The incidence of hospital-acquired pneumonia rises with age and most commonly affects patients on medical, surgical, oncology, and neurology services. Key risk factors include impaired consciousness, dysphagia, and feeding by an oral or nasogastric tube.

PATHOBIOLOGY

Hospital-acquired pneumonia, like community-acquired pneumonia, is thought to be due largely to microaspiration or macroaspiration events when perturbations of the oral microbiome permit pathogenic organisms to proliferate. Microscopic and microbial evaluations of material obtained at autopsy note scattered, heterogenous areas of inflammation at various stages of injury and recovery, some with microorganisms and some without. Chemical analyses of tracheal aspirates and bronchoalveolar lavage specimens identify gastrin and/or pepsin in up to two thirds of intubated patients. These findings collectively suggest that patients routinely aspirate oral and gastric secretions, thereby leading to scattered local areas of inflammation of various degrees of severity throughout the lungs. Some affected areas remain subclinical and resolve spontaneously, whereas others progress to frank infection and clinically overt pneumonia.

CLINICAL MANIFESTATIONS

After a median interval from hospital admission until the onset of pneumonia of 4 to 7 days,[21] the cardinal symptoms and signs of hospital-acquired pneumonia are fever, tachypnea, increased respiratory secretions, leukocytosis, a decline in oxygen saturation, measured by pulse oximetry, new radiographic infiltrates, and positive lower respiratory tract cultures. However, none of these findings is particularly sensitive or specific for hospital-acquired pneumonia[22] (Table 85-8). For example, the combination of a radiographic infiltrate and any two of fever, purulent secretions, and leukocytosis has a sensitivity and specificity of 69 and 75%, respectively, for histologically confirmed ventilator-associated pneumonia. The combination of a radiographic infiltrate plus fever, purulent secretions, and leukocytosis, increases the specificity to 92% but decreases sensitivity to 23%.

DIAGNOSIS

The diagnosis of hospital-acquired pneumonia is subjective because of the limited accuracy of clinical manifestations, and experienced clinicians often disagree. Furthermore, bacteria and viruses can colonize the respiratory tract without causing an invasive infection, so a positive PCR assay, Gram stain, or culture does not necessarily mean that the identified organism is the cause of the patient's respiratory syndrome. Procalcitonin, which is the most frequently used biomarker, has a sensitivity that ranges from 60 to 70% and a specificity that ranges from 24 to 80%, but current guidelines recommend against its routine use to diagnose hospital-acquired pneumonia and ventilator-associated pneumonia. Bronchoalveolar lavage cultures are positive in only about one third of patients with clinically suspected ventilator-associated pneumonia. Blood cultures can be positive in up to 10% of hospital or ventilator associated pneumonia, depending on its severity, and should be obtained.

The organisms that are typically associated with ventilator-associated pneumonia (Table 85-9) and nonventilator hospital-acquired pneumonia are similar.[23] *Staphylococcus aureus* (Chapter 267) predominates and accounts for approximately 30 to 40% of pneumonias in which an organism is recovered. Fortunately, the incidence of staphylococcal infections that are resistant to methicillin has declined by 50% in recent years. *Pseudomonas* (Chapter 282), which is the second

TABLE 85-8 ACCURACY OF CLINICAL SIGNS TO DIAGNOSE VENTILATOR-ASSOCIATED PNEUMONIA, DERIVED FROM A META-ANALYSIS OF 25 STUDIES, INCLUDING 1639 PATIENTS*

SIGN	SENSITIVITY	SPECIFICITY	POSITIVE LIKELIHOOD RATIO	NEGATIVE LIKELIHOOD RATIO	DIAGNOSTIC ODDS RATIO
Fever	66%	54%	1.4	0.6	2.3
Purulent secretions	77%	39%	1.3	0.6	2.1
Leukocytosis	64%	59%	1.6	0.6	2.6
Infiltrate on chest radiograph	89%	26%	1.2	0.4	2.8
Endotracheal aspirate culture ($\geq 10^5$ CFU/mL)	76%	68%	2.4	0.4	6.6
Bronchoalveolar lavage culture ($\geq 10^4$ CFU/mL)	71%	80%	3.5	0.4	9.6

*Histopathology is used as reference standard.
CFU = colony-forming units.
From Fernando SM, Tran A, Cheng W, et al. Diagnosis of ventilator-associated pneumonia in critically ill adult patients—a systematic review and meta-analysis. *Intensive Care Med*. 2020;46:1170-1179.

TABLE 85-9 ORGANISMS AND ANTIBIOTIC SUSCEPTIBILITY RATES ASSOCIATED WITH 6131 CULTURE-POSITIVE EPISODES OF VENTILATOR-ASSOCIATED PNEUMONIA IN THE UNITED STATES, 2015-2017

	APPROXIMATE FREQUENCY	SUSCEPTIBILITY RATES TO COMMON ANTIBIOTICS
Staphylococcus aureus (Chapter 267)	30-40%	Methicillin or oxacillin 63%
Pseudomonas aeruginosa (Chapter 282)	15-20%	Aminoglycosides 86% Antipseudomonal cephalosporins 74% Fluoroquinolones 73% Carbapenems 73% Piperacillin-tazobactam 78%
Klebsiella pneumoniae (Chapter 281)	10%	Antipseudomonal cephalosporins 85% Carbapenems 94%
Escherichia coli (Chapter 280)	5-10%	Antipseudomonal cephalosporins 77% Carbapenems 99% Fluoroquinolones 67%
Enterobacter spp (Chapter 281)	5-10%	Cefepime 93% Carbapenems 96%
Acinetobacter baumannii (Chapter 283)	3%	Carbapenems 58%

spp = species.
From Weiner-Lastinger LM, Abner S, Edwards JR, et al. Antimicrobial-resistant pathogens associated with adult healthcare-associated infections: summary of data reported to the National Healthcare Safety Network, 2015-2017. *Infect Control Hosp Epidemiol*. 2020;41:1-18.

most common organism, accounts for 15 to 20% of culture-positive hospital acquired pneumonias. Other organisms include *Klebsiella* species (10%; Chapter 281), *Enterobacter* species (5 to 10%; Chapter 281), *Escherichia coli* (5 to 10%; Chapter 280), *Haemophilus influenzae* (5%; Chapter 277), *Streptococcus* species (5%; Chapter 268), and *Acinetobacter* species (3%; Chapter 283).

A substantial proportion, perhaps 20 to 25%, of hospital-acquired pneumonia may be attributable solely to respiratory viruses, including rhinovirus (Chapter 329), influenza (Chapter 332), parainfluenza (Chapter 331), metapneumovirus (Chapter 330), and non–SARS-CoV-2 coronaviruses (Chapter 334). Another 15% or so may be caused by coinfection with both a virus and a bacterium. Large nosocomial clusters of hospital-onset respiratory viral infections, including SARS-CoV-2 and influenza, also have been reported.

The clinical signs associated with pneumonia are also common in hospitalized patients who have pulmonary edema (Chapter 45), exacerbations of chronic obstructive lung disease (Chapter 76), thromboembolic disease (Chapter 68), mucous plugging, and atelectasis (Chapter 78). As a result, clinicians should aggressively search for these alternative explanations for patients' clinical manifestations. CT scanning, especially with contrast, can help differentiate among atelectasis, pulmonary edema, pneumonitis, and pneumonic consolidation. An elevated BNP level is suggestive of heart failure.

TREATMENT

Antibiotics can generally be withheld in clinically stable patients unless and until the diagnosis is confirmed.[24] Conversely, immediate treatment is mandatory in clinically unstable patients whose oxygenation is rapidly deteriorating (Chapter 90) or who are hypotensive.

Despite the popular perception that antibiotic-resistant organisms are common in hospital-associated pneumonia, the majority of culture-positive hospital-onset bacterial pneumonias are caused by organisms susceptible to common first-line agents (see Table 85-9),[25] and antimicrobial susceptibility rates have generally been increasing in the United States.

Guidelines recommend tailoring treatment regimens to each individual patient's risk factors for potentially drug-resistant pathogens, including both individual risk factors (e.g., recent exposure to intravenous antibiotics, prior history of resistant organisms) and the local distribution and antibiotic resistance profiles of organisms associated with hospital or ventilator associated pneumonia. Initial empirical treatment (Table 85-10) typically includes an agent active against methicillin-resistant *Staphylococcus aureus* (MRSA) (e.g., linezolid or vancomycin) plus one or two agents active against *Pseudomonas aeruginosa* and other gram-negative organisms (e.g., cefepime, ceftazidime, piperacillin-tazobactam, imipenem, meropenem, imipenem-relebactam, ceftolozane-tazobactam, ceftazidime-avibactam, ciprofloxacin, levofloxacin, aztreonam, colistin, cefidorocol). Key risk factors for drug-resistant pathogens include a prior history of infection or colonization with drug-resistant organisms and a history of receiving intravenous antibiotics within the preceding 90 days. If PCR on a nasal swab or bronchoalveolar lavage is negative for MRSA, specific coverage for MRSA can be withheld in patients who do not have a history of drug-resistant organisms and in patients who are admitted to hospitals with a low prevalence of MRSA (typically <20% of *Staphylococcus aureus* isolates). In such cases, the regimen should still include coverage active against MSSA (e.g., cefazolin, ceftriaxone, cefepime, piperacillin-tazobactam, imipenem, meropenem, or levofloxacin. Similarly, one gram-negative agent may be adequate for patients who do not have risk factors for multidrug-resistant pathogens and who are receiving care in hospitals with a low prevalence of such organisms. For gram-negative nosocomial pneumonia, adding cefiderocol (2 g every 8 hours for 7 to 10 days) to linezolid (600 mg every 12 hours for at least 5 days) is as good as adding meropenem (also 2 g every 8 hours for 7 to 10 days) to linezolid.[A8]

Once the causative pathogen and its antibiotic susceptibilities have been established, the antibiotic regimen should immediately be narrowed to a single active agent so as to reduce the risk of adverse effects. Treatment is usually for 7 to 8 days. If patients fail to improve clinically after several days of therapy, additional diagnostic studies (e.g., computed tomography or bronchoalveolar lavage) are advised to identify possible causes, such as the development of pyogenic complications that require drainage or prolonged treatment (e.g., empyema [Chapter 86] or abscess [Chapter 78]), superinfection with a drug-resistant pathogen, and/or a noninfectious diagnosis (e.g., pulmonary edema, pulmonary embolism, atelectasis, pneumothorax, etc.). Serial measurement of procalcitonin values every day or every other day can help decrease treatment courses to less than 7 days in patients who are clinically improving. Antibiotics can generally be safely discontinued when the procalcitonin value drops to normal or 20% or less of its peak value.[A9]

PREVENTION

The most important step to prevent ventilator-associated pneumonia is to try to avoid tracheal intubation, whenever safe and possible, and to minimize time spent on mechanical ventilation when tracheal intubation is required. Potential strategies to avoid tracheal intubation include the use of high-flow oxygen by nasal cannula or noninvasive positive pressure ventilation (Chapters 90 and 261). Strategies to reduce exposure to mechanical ventilation include minimizing sedation by using propofol or dexmedetomidine rather than benzodiazepine, trials of spontaneous breathing (Chapter 91), and mobilization.

For nonventilated patients, bundling interventions such as oral care, having patients sit up in a chair to eat, compulsive care of feeding tubes, and patient education may decrease the use of antibiotics and the rate of hospital-acquired pneumonia (Chapter 261).[26] Prevention of hospital acquired pneumonia should also focus on preventing aspiration by elevating the head of the bed, exercising dysphagia precautions when feeding patients with impaired swallowing or impaired attention, and mobilizing patients to prevent deconditioning and delirium. Enhancing the frequency and rigor of oral care may also decrease hospital-acquired pneumonia and ventilator-associated pneumonia by decreasing the microbial burden in the mouth and in aspirated secretions. Toothbrushing twice a day is recommended. Oral care with antiseptics, by contrast, is discouraged because aspiration may lead to pneumonitis.[A10] The combination of oral and digestive decontamination with a slurry of oral antibiotics (typically a combination of an aminoglycoside, polymyxin, and amphotericin) plus a 4-day course of intravenous cefotaxime has been associated with lower mortality rates in the Netherlands but has not been widely adopted because it has not been proven to be beneficial in settings with higher baseline rates of antibiotic utilization and drug-resistant pathogens (Chapter 261).[A11] Probiotics are not helpful for prevention.[A12]

Modifications to endotracheal tubes and cuffs can reduce microbial colonization, prevent the formation of biofilm, and decrease aspiration around the cuff. Unfortunately, none of these innovations has consistently led to earlier extubation or lower mortality rates.

PROGNOSIS

Crude mortality rates for patients with ventilation-associated pneumonia and nonventilation hospital-acquired pneumonia range from 15 to 30%. Mortality rates appear to be similar regardless of whether the infection was viral, bacterial, or both. The median length-of-stay for patients who develop hospital-acquired pneumonia is 15 to 30 days compared with approximately 5 days for hospitalized patients who do not develop hospital-acquired pneumonia.

The extent to which these adverse events reflect patients' underlying conditions and baseline severity of illness as compared with incremental morbidity from pneumonia itself is uncertain, especially for ventilator-associated pneumonia. For example, some estimates suggest that eliminating ventilator-associated pneumonia would reduce overall ICU mortality by only about 2%.[27] Non–ventilator-associated hospital-acquired pneumonia, however, may increase mortality rates by two-fold or more compared with similar patients who do not develop it.

ASPIRATION PNEUMONIA

EPIDEMIOLOGY AND PATHOBIOLOGY

Although microaspiration is the most common cause of all pneumonias, gross aspiration of oropharyngeal contents is a different clinical syndrome. Predisposing factors include alcohol use disorder, poor dental hygiene, dental procedures, homelessness, drug overdose, seizures, an inadequate gag reflex, acute or chronic changes in mental status, poststroke paralysis, neuromuscular diseases, esophageal obstruction, and severe esophageal reflux. Oftentimes the pneumonia is not infectious but rather a chemical response to gastric acid or gastric contents.

CLINICAL MANIFESTATIONS

Gross aspiration pneumonia usually presents acutely[28] and then leads to progressive fever, dyspnea, purulent sputum, and leukocytosis. Hypoxemia may evolve over several days. A common complication is a lung abscess (Chapter 78), which often causes sputum with a foul taste and odor. Lung abscesses (Chapter 78), which most often results from a large volume aspiration, are typically associated with impaired consciousness.

Physical examination generally reveals evidence of the underlying precipitating condition as well as coarse rhonchi in the lower lobes or dependent lung regions.

DIAGNOSIS

Aspiration pneumonia commonly causes a parenchymal bronchopneumonia process, typically in areas of the lung that are dependent when the patient is supine: the superior segment of the right lower lobe and the posterior segment of the upper lobes.[29] However, aspiration can involve any part of the lung except the apices depending on the patient's position during aspiration. A thick-walled abscess with a fluid level (Chapter 78) can confirm the diagnosis.

TABLE 85-10 EMPIRICAL ANTIBIOTIC TREATMENT OF HOSPITAL-ACQUIRED PNEUMONIA, VENTILATOR-ASSOCIATED PNEUMONIA, AND HEALTH CARE–ASSOCIATED PNEUMONIA

GROUP A: PATIENTS WITH EITHER HOSPITAL-ACQUIRED PNEUMONIA OR VENTILATOR-ASSOCIATED PNEUMONIA, WITHOUT RISK FACTORS FOR MULTIDRUG-RESISTANT PATHOGENS, AND WITH EARLY-ONSET PNEUMONIA

POTENTIAL PATHOGENS	RECOMMENDED THERAPY
Streptococcus pneumoniae *Haemophilus influenzae* Methicillin-sensitive *Staphylococcus aureus* Antibiotic-sensitive enteric gram-negative bacilli *Escherichia coli* *Klebsiella pneumoniae* *Enterobacter* spp *Proteus* spp *Serratia marcescens*	Ceftriaxone, 1-2 g IV/IM every 12-24 hr, maximum of 2 g/day* *Or* Levofloxacin, 750 mg IV every day, or ciprofloxacin, 400 mg IV every 8 hr, or moxifloxacin, 400 mg IV or orally every 24 hr* *Or* Ampicillin-sulbactam, 1.5-3 g (1-2 g ampicillin and 0.5-1 g sulbactam) IV/IM every 6 hr, maximum of 4 g/day sulbactam, depending on type and severity of infection* Ertapenem, 1 g IV/IM once a day*

GROUP B: HOSPITALIZED PATIENTS WITH LATE-ONSET PNEUMONIA OR WITH RISK FACTORS FOR MULTIDRUG-RESISTANT PATHOGENS

ORGANISMS	THERAPY (SELECT TWO AGENTS IF >20% OF LOCAL PSEUDOMONAS ISOLATES ARE RESISTANT TO PROPOSED MONOTHERAPY)
S. pneumoniae *H. influenzae* Methicillin-sensitive *S. aureus* Antibiotic-sensitive enteric gram-negative bacilli *E. coli* *K. pneumoniae* *Enterobacter* spp *Proteus* spp *S. marcescens* Multidrug-resistant pathogens *Pseudomonas aeruginosa* *K. pneumoniae* (extended spectrum β-lactamase producing) *Acinetobacter* spp Methicillin-resistant *S. aureus* *Legionella pneumophila*	Antipseudomonal cephalosporin (ceftazidime, 2 g IV every 8 hr; cefepime, 1-2 g every 8-12 hr; ceftazidime/avibactam [2.5 g IV every 8 hr], ceftolozane/tazobactam [3 g IV every 8 hr]; or cefiderocol [3 g IV every 8 hr] depending on renal function)* *Or* Antipseudomonal carbapenems (meropenem, 1 g every 8 hr; imipenem, 500 mg every 6 hr or 1 g every 8 hr; or imipenem-relebactam 1.25 g every 6 hr)* *Or* β-Lactam/β-lactamase inhibitor (piperacillin-tazobactam, 4.5 g IV every 6 hr)* *Or* Antipseudomonal fluoroquinolone (levofloxacin, 750 mg IV every day, or ciprofloxacin, 400 mg IV every 8 hr).* This choice is increasingly limited by antibiotic resistance. *Plus* Vancomycin (15 mg/kg IV every 12 hr, with monitoring to maintain trough at 10-15 μg/mL and duration dependent on clinical response and individualized) or linezolid (600 mg IV every 12 hr)*

*Dosing requires modification if renal function impaired. Duration of treatment typically 7 days but should be individualized depending on the clinical response.

IM = intramuscular; IV = intravenous; spp = species.

Data from American Thoracic Society. Guidelines modified from Kalil AC, Metersky ML, Klompas M, et al. Executive summary: management of adults with hospital-acquired and ventilator-associated pneumonia: 2016 clinical practice guidelines by the Infectious Diseases Society of America and the American Thoracic Society. *Clin Infect Dis*. 2016;63:575-582. From Musher DM. Overview of pneumonia. In: Goldman L, Schafer AI, eds. *Goldman-Cecil Medicine*. 26th ed. Philadelphia: Elsevier; 2020.

Lung abscesses are polymicrobial infections that reflect oral flora and often include anaerobic bacteria.

Aspiration can cause a purely chemical pneumonia without infection that is often self-resolving but occasionally leads to ARDS. Some aspiration episodes, however, lead to a polymicrobial infection with purulent sputum and mixed bacteria. Cultures usually show normal respiratory flora, and lung abscesses typically show mouth organisms (e.g., microaerophilic streptococci and staphylococci, *Bacteroides* species, *Fusobacterium* species, and *Prevotella* species). However, aspiration in hospitalized patients and residents of long-term care facilities often involves gram-negative bacteria, *P. aeruginosa,* and *S. aureus*.

TREATMENT

Community-acquired aspiration pneumonia should be treated empirically with parenteral ampicillin-sulbactam (1.5 to 3 g intravenously every 6 hours) or clindamycin (600 mg intravenously every 8 hours) for at least 5 days. If cultures reveal organisms not sensitive to this regimen, other antibiotics should be added based on sensitivity results while continuing to provide anaerobic coverage. When the patient is stable, oral therapy (e.g., clindamycin 600 mg three times daily or ampicillin-sulbactam 750 mg three times daily) can be used to complete a 7 to 10 day course. In patients with a lung abscess (Chapter 78), however, therapy typically must be continued until the cavity is no longer detectable.

For health care–acquired aspiration pneumonia, the initial therapy should be ceftriaxone (1 to 2 g IV every 12 hours),[30] intravenous piperacillin-tazobactam (3.375 g intravenously every 6 hours), meropenem (1 g intravenously every 8 hours), or imipenem (1 g intravenously every 6 to 8 hours). If the clinical syndrome resolves within 24 hours, then antibiotics typically can be stopped. Otherwise, antibiotics should be continued for at least 5 to 7 days.

For a lung abscess, clindamycin (600 mg every 8 hours if hospitalized followed by 150 to 300 mg orally 4 times daily) typically results in improvement within 7 to 10 days. Treatment is usually continued for 3 weeks or until substantial resolution. Drainage may be necessary in 20% of cases.

Cultures are critical in patients who fail to improve rapidly so as to identify potentially resistant organisms that may require expanded or alternative treatment regimens (e.g., coverage for MRSA or *Pseudomonas*). Therapy can be modified based on microbiologic results.

The most common serious complication of anaerobic pneumonia or a lung abscess is the development of an empyema (Chapter 86). In patients with otherwise untreatable recurrent aspiration, a gastrostomy or jejunostomy feeding tube (Chapter 198) can provide palliative nutrition, fluids, and medications.

PROGNOSIS

The mortality rate for hospitalized aspiration pneumonia is 15 to 30%, including about 20% for a lung abscess. Prognosis is largely determined by precipitating underlying conditions rather than by the aspiration itself.

PNEUMONIA IN IMMUNOCOMPROMISED HOSTS

EPIDEMIOLOGY

Patients with weakened immune systems are at risk for pneumonic routine community acquired organisms, geographically restricted (e.g., coccidiomycosis and histoplasmosis [Chapter 308] organisms), and nosocomial (Chapter 261) infections. In such patients, a lower inoculum of any given organism may be sufficient to establish infection. In addition, however, immunocompromised patients are at risk for a variety of opportunistic pathogens (e.g., *Pneumocystis jiroveci* [Chapter 313], cryptococcus [Chapter 309], legionella [Chapter 290], and nocardia [Chapter 306]) and geographically restricted organisms (e.g., coccidiomycosis, talaromycosis [Chapter 308]) (Table 85-11).[31] The risk for various lower virulence organisms is a function of the overall net-state of immunosuppression, which changes based on time from immunosuppressive events, and the interval since the receipt of cancer chemotherapy, or a hematopoietic stem cell or solid organ transplant. Latent

TABLE 85-11 RESPIRATORY PATHOGENS THAT MAY CAUSE COMMUNITY-ACQUIRED PNEUMONIA IN IMMUNOCOMPROMISED HOSTS

GRAM-POSITIVE BACTERIA	GRAM-NEGATIVE BACTERIA	"ATYPICAL" BACTERIA	RESPIRATORY VIRUSES	MYCOBACTERIA	FUNGI	PARASITES
Streptococcus pneumoniae (Chapter 268) *Staphylococcus aureus* (MRSA and MSSA) (Chapter 267) *Streptococcus pyogenes* (Chapter 269) Other streptococci (Chapter 269) *Rhodococcus equi* (Chapter 272)	*Haemophilus influenzae* (Chapter 277) Nonfermenting gram-negative bacilli (e.g., *Pseudomonas* or *Acinetobacter*) (Chapter 282) *Moraxella catarrhalis* (Chapter 277) Enterobacteriaceae (e.g., *Klebsiella* spp [Chapter 281], *Escherichia coli* [Chapter 280])	*Legionella pneumophila* (Chapter 290) *Chlamydophila pneumoniae* (Chapter 294) *Mycoplasma pneumoniae* (Chapter 293) *Coxiella burnetii* (Chapter 302)	Influenza virus (Chapter 332) Parainfluenza virus (Chapter 331) Coronavirus (Chapter 334) Respiratory syncytial virus (Chapter 330) Rhinovirus (Chapter 329) Adenovirus (Chapter 333) Human metapneumovirus (Chapter 330) Cytomegalovirus (Chapter 347) Herpes simplex virus (Chapter 345) Varicella-zoster virus (Chapter 346)	*Mycobacterium tuberculosis* (Chapter 299) Nontuberculous mycobacteria (Chapter 300)	*Pneumocystis jiroveci* (Chapter 313) *Aspergillus* spp (Chapter 311) *Mucorales* spp (Chapter 312) *Histoplasma* spp (Chapter 308) *Cryptococcus* spp (Chapter 309) *Blastomyces* spp (Chapter 308) *Coccidioides* spp (Chapter 308) *Talaromycosis* spp [Chapter 308])	*Toxoplasma gondii* (Chapter 320) *Strongyloides stercoralis* (Chapter 327)

MRSA = methicillin-susceptible *Staphylococcus aureus;* MSSA = methicillin-resistant *Staphylococcus aureus*; spp = species.
Adapted from Ramirez JA, Musher DM, Evans SE, et al. Treatment of community-acquired pneumonia in immunocompromised adults: a consensus statement regarding initial strategies. *Chest.* 2020; 158:1896-1911.

organisms, which may have been previously controlled, may reactivate (e.g., *Mycobacteria tuberculosis* [Chapter 299], coccidiomycosis, and herpes group viruses [Chapters 345 to 348]), or patients may develop hyperinfection from a previous low-level infection (e.g., *Strongyloides stercoralis;* Chapter 327). In patients undergoing an organ transplant, donor-derived infection also should be considered.

PATHOBIOLOGY

The nature of the immunocompromising process or processes substantially affects the risk for pneumonia. Risk factors include impairments of T cells (e.g., advanced HIV infection; use of medications such as calcineurin inhibitors, glucocorticoids, and T cell–depleting agents), of B cells (e.g., lymphomas and medications such as anti-CD19 and 20 agents), neutrophils (e.g., chronic granulomatous disease and severe neutropenia), and of mucosal integrity (e.g., cytotoxic chemotherapy). In patients who are receiving B cell–depleting agents, such as anti-CD19 or 20 agents, the ability to form antibodies to neopathogens is significantly impaired for months after treatment, so encapsulated organisms such as pneumococcus become greater concerns.

CLINICAL MANIFESTATIONS

In immunocompromised hosts, many of the typical symptoms and signs of inflammation may be attenuated or absent (Chapter 260) and may not readily localize to the chest. For example, classic physical examination findings of pneumonia may be absent. However, cough, fever, and dyspnea are often noted and associated with hypoxemia and pulmonary infiltrates.

DIAGNOSIS

Although a chest radiograph can show abnormal pulmonary opacities, a chest CT scan is often required to detect lobar, interstitial, and nodular or cavitary abnormalities (see Fig. 85-1).[32] Lobar infiltrates often indicate bacterial infections, sometimes postobstructive in etiology. Interstitial patterns are suggestive of pneumocystis, viral, and atypical bacterial pathogens. Nodular or cavitary images are consistent with bacterial, fungal, or hematogenous processes. However, the many noninfectious conditions that can mimic pneumonia include hypersensitivity reactions, cardiogenic or non-cardiogenic pulmonary edema, medication reactions, or lung injury due to the primary underlying diagnosis.

Given the broad differential diagnosis of potential pathogens that cause pneumonia in immunocompromised patients, a specific etiologic diagnosis is critical to minimize unnecessary toxicity from empirical therapy (Fig. 85-5). Blood cultures and samples collected via fine needle aspirate, biopsy, or bronchoscopy are more likely to represent the infecting pathogens than is examination of expectorated sputum.

Multiple molecular technologies (e.g., PCR and nucleic acid testing) of nasopharyngeal swabs can aid in the identification of suspected pathogens. Serum markers (e.g., antigen testing for cryptococcus, aspergillus, and other fungi) may be helpful to avoid more invasive diagnostic testing. Serology is of very limited value because many immunocompromised patients may have a limited ability to generate antibody responses.

TREATMENT

Treatment requires not only the correct antimicrobial agent for the infecting organism but also, if possible, efforts to improve the host's immunity by lowering the dose of any immunosuppressive agents. In patients who are seriously ill or at risk of rapid deterioration, prompt antibiotic therapy targeting the likely infecting pathogen(s), if known, are warranted. However, antibiotic therapy typically must be initiated as an urgent diagnostic evaluation is begun.[33] When no obvious pathogen is evident, the radiographic pattern and the nature of the host's immunodeficiency will further inform the diagnostic evaluation and empirical therapy. For an interstitial pattern, broad-spectrum antibacterial agents (e.g., a carbapenem or respiratory fluoroquinolone) are recommended, along with consideration of treatment for *Pneumocystis jiroveci* (Chapter 313). For a nodular or cavitary process, broad-spectrum antibacterial agents are recommended, with consideration for nocardia (Chapter 306), and antifungal treatment (Chapter 307).

In appropriate circumstances, other bacteria (e.g., mycobacteria), parasites (e.g., *Toxoplasma, Strongyloides*), and fungal pathogens (e.g., *Cryptococcus, Aspergillus,* and *Mucorales* sp.) must be considered. For certain infections, such as severe *Pneumocystis jiroveci* pneumonia with hypoxemia, adjunctive glucocorticoids may be warranted. As soon as the infecting organism is identified, antibiotics should be narrowed to reduce the risk of adverse effects, or the acquisition of antimicrobial-resistant organisms.

PREVENTION

Principles of prevention include minimizing exposure to pathogens of concern, augmenting immunity, and pharmacologic prophylaxis. Immunosuppressive treatments should be limited to the lowest dose for the shortest duration possible. Vaccinations (Chapter 15) to measles, *Streptococcus pneumoniae*, SARS-CoV-2, and influenza should be updated before the initiation of immunosuppression or at a time when immunosuppression is the lowest to allow the strongest possible immune response.

Antimicrobials should be used to prevent infections associated with immunosuppression. Effective prophylaxis against *Pneumocystis jiroveci* includes trimethoprim-sulfamethoxazole (either a single-strength tablet once a day or a double-strength tablet 3 times a week), atovaquone (1500 mg orally once daily), pentamidine (aerosolized or intravenous), and dapsone (100 mg orally once daily). Of these regimens trimethoprim-sulfamethoxazole, is the most efficacious and preferred. Prophylaxis should be continued until immunosuppression is decreased, such as lowering the prednisone dose to less than 20 mg per day. When possible, treatment for latent tuberculosis (e.g., isoniazid) is warranted in patients with prior exposure to tuberculosis before initiating immunosuppression when possible (Chapter 299). In patients who have potential exposure to geographically

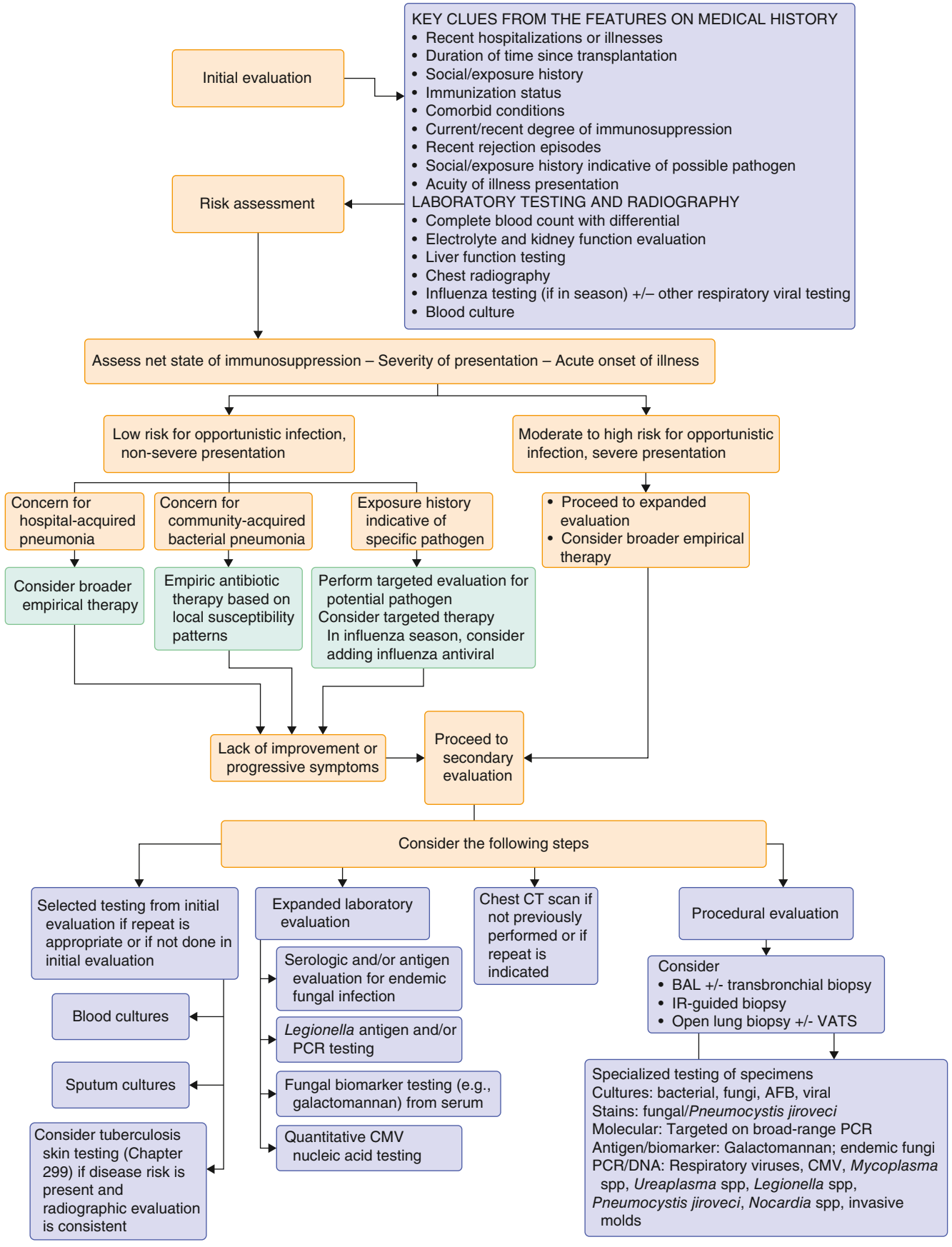

FIGURE 85-5. Evaluation of pneumonia in the immunocompromised host. AFB = acid fast bacillus; BAL = bronchoalveolar lavage; CMV = cytomegalovirus; CT = computed tomography; IR = interventional radiology; PCR = polymerase chain reaction; spp = species; VATS = video-assisted thoracic surgery. (Adapted from Dulek DE, Mueller NJ; AST Infectious Diseases Community of Practice. Pneumonia in solid organ transplantation: guidelines from the American Society of Transplantation Infectious Diseases Community of Practice. *Clin Transplant*. 2019;33:e13545.)

restricted organisms, consideration for the assessment of their presence and secondary prophylaxis is warranted (e.g., ivermectin for strongyloides [Chapter 327], fluconazole for *Coccidioides immitis* or *Coccidioides posadasii* [Chapter 308]).

PROGNOSIS

The response to treatment depends on diagnosing the etiologic pathogen as early as possible, before more serious complications develop. With targeted antimicrobial therapy, drug-drug interactions and significant perturbations in healthy microbial flora can be minimized.

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For the General References and other additional features, please visit Elsevier eBooks+ at https://ebooks.health.elsevier.com.

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86 DISEASES OF THE DIAPHRAGM, CHEST WALL, PLEURA, AND MEDIASTINUM

F. DENNIS MCCOOL

DIAPHRAGM

The diaphragm is the major muscle of ventilation. It is a dome-shaped structure that separates the thorax from the abdomen. It consists of a central tendon and a muscular component that inserts into the rib cage laterally along the inner surface of the lower six ribs, anteromedially along the costal cartilages, and posteriorly along the upper three lumbar vertebral bodies. The diaphragm is innervated by the phrenic nerve, which originates from cervical nerve roots 3 through 5.

DIAPHRAGMATIC WEAKNESS AND PARALYSIS

EPIDEMIOLOGY AND PATHOBIOLOGY

When activated, the diaphragm contracts and descends caudally. The downward descent of the diaphragm expands the anterior abdominal wall and lower rib cage, lowers pleural pressure, and thereby promotes lung inflation. It is the major muscle of inspiration, and its action accounts for approximately 70% of the inspired tidal volume in the normal individual. Diaphragm function can be impaired by disorders that affect the brain (Chapter 368), spinal cord, and peripheral nerves (Chapter 388), neuromuscular junction (Chapter 390), and muscle itself (Chapter 389). The incidence and prevalence of diaphragmatic paralysis and weakness are unknown.

CLINICAL MANIFESTATIONS

Diaphragmatic weakness or paralysis can involve either one or both hemidiaphragms.[1] With unilateral diaphragmatic paralysis, patients are generally asymptomatic at rest but may have dyspnea with exertion or when supine, especially with comorbid conditions such as obesity. If they are asymptomatic, the abnormality may be discovered as an incidental finding of an elevated hemidiaphragm on chest radiography.

Bilateral diaphragmatic paralysis is less common than unilateral paralysis. The disability with bilateral paralysis is more dramatic than with unilateral paralysis, and orthopnea is an especially prominent symptom.[2] Other symptoms include dyspnea with exertion or when bending and lifting objects. These individuals also are at an increased risk of hypoventilation during sleep, especially during rapid eye movement (REM) sleep. Occasionally patients may present with symptoms related to nocturnal hypoventilation, including frequent nocturnal awakenings, nocturia, vivid nightmares, night sweats, daytime hypersomnolence, depression, and morning headaches.

The physical examination is remarkable for use of accessory muscles of inspiration and paradoxical inward motion of the abdominal wall during inspiration, particularly in patients with bilateral diaphragmatic paralysis. This finding is especially noticeable when these individuals are supine. Chest wall percussion during inspiration and expiration can detect the absence of diaphragmatic movement.

DIAGNOSIS

Disorders that can cause unilateral diaphragmatic weakness or paralysis (Table 86-1) include traumatic phrenic nerve injury, neuropathies such as neuralgic amyotrophy (Chapter 388), herpes zoster (Chapter 346), cervical spinal

TABLE 86-1 CAUSES OF DIAPHRAGMATIC WEAKNESS AND PARALYSIS

TRAUMA
Cardiac surgery with cold cardioplegia
Blunt trauma
Spinal cord injury
Cervical manipulation
Scalene and brachial nerve block
TUMOR COMPRESSION
Lung cancer
Metastatic mediastinal tumor
METABOLIC
Diabetes
Vitamin deficiency (B_6, B_{12}, folate)
Hypothyroidism
Acid maltase deficiency
INFLAMMATORY NEURITIS
Neuralgic amyotrophy (Parsonage-Turner syndrome)
Mononeuritis multiplex
Vasculitis
Paraneoplastic
MUSCULAR DYSTROPHIES
Limb-girdle
Duchenne and Becker
MISCELLANEOUS
Amyloidosis
Malnutrition
Radiation injury
Cervical spondylosis
Poliomyelitis
Amyotrophic lateral sclerosis
IDIOPATHIC

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restricted organisms, consideration for the assessment of their presence and secondary prophylaxis is warranted (e.g., ivermectin for strongyloides [Chapter 327], fluconazole for *Coccidioides immitis* or *Coccidioides posadasii* [Chapter 308]).

PROGNOSIS

The response to treatment depends on diagnosing the etiologic pathogen as early as possible, before more serious complications develop. With targeted antimicrobial therapy, drug-drug interactions and significant perturbations in healthy microbial flora can be minimized.

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For the General References and other additional features, please visit Elsevier eBooks+ at https://ebooks.health.elsevier.com.

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DIAPHRAGMATIC WEAKNESS AND PARALYSIS

EPIDEMIOLOGY AND PATHOBIOLOGY

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Diaphragmatic weakness or paralysis can involve either one or both hemidiaphragms.[1] With unilateral diaphragmatic paralysis, patients are generally asymptomatic at rest but may have dyspnea with exertion or when supine, especially with comorbid conditions such as obesity. If they are asymptomatic, the abnormality may be discovered as an incidental finding of an elevated hemidiaphragm on chest radiography.

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TABLE 86-1 CAUSES OF DIAPHRAGMATIC WEAKNESS AND PARALYSIS

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Vasculitis
Paraneoplastic
MUSCULAR DYSTROPHIES
Limb-girdle
Duchenne and Becker
MISCELLANEOUS
Amyloidosis
Malnutrition
Radiation injury
Cervical spondylosis
Poliomyelitis
Amyotrophic lateral sclerosis
IDIOPATHIC

ABSTRACT

Diseases affecting the diaphragm and chest wall can produce severe lung volume restriction that results in hypoventilation, dyspnea, impaired cough, and increased risk of respiratory complications. A broad array of diseases can involve the pleura and cause pleural effusions, which can be classified as transudates (protein-poor effusions) or exudates (protein-rich effusions). Large effusions can impair breathing, and malignant effusions are typically associated with a poor prognosis. Mediastinal masses can be located in the anterior, middle, or posterior mediastinum; they may affect breathing by compressing airways and can cause pleural effusions by blocking lymphatic drainage. Treatment options include noninvasive positive pressure ventilation for diseases involving the diaphragm or chest wall, management of recurrent pleural effusions and malignant effusions, procedures directed toward correcting chest wall abnormalities, and management of mediastinal masses.

KEYWORDS

diaphragm paralysis
kyphoscoliosis
pectus excavatum
pleural effusion
mediastinal mass
ankylosing spondylitis

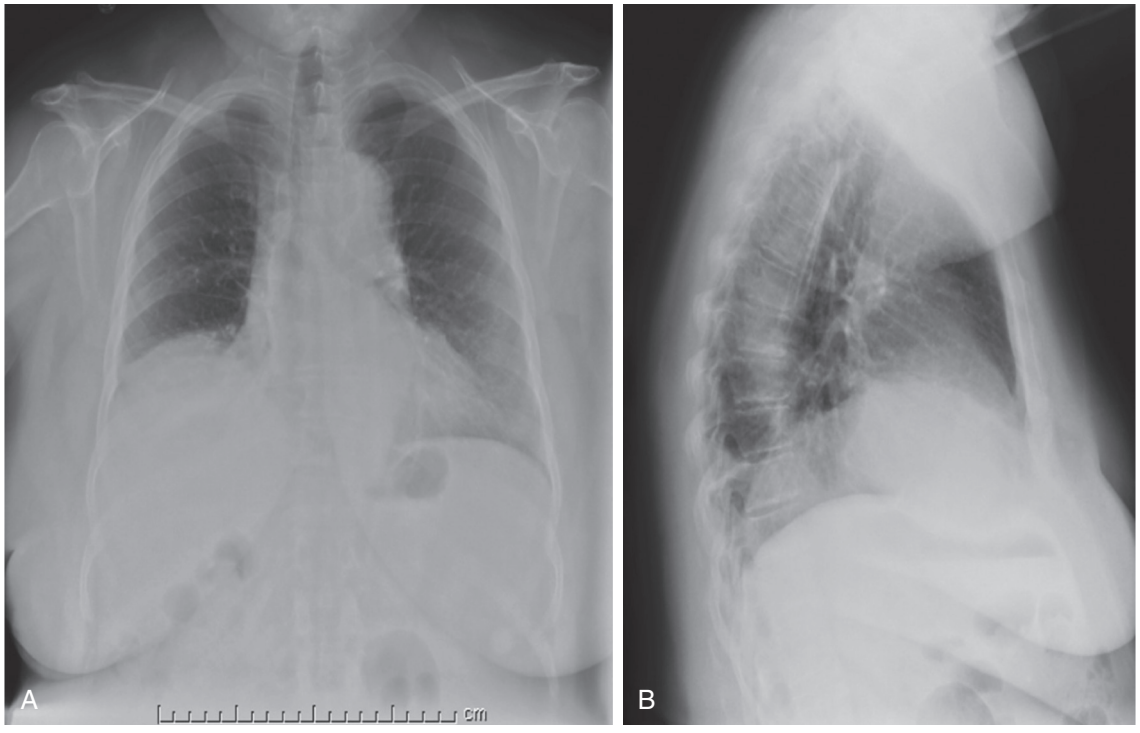

FIGURE 86-1. Paralysis of the right hemidiaphragm. Patient with paralysis of the right hemidiaphragm as seen on the posteroanterior radiograph of the chest (A) and lateral radiograph of the chest (B).

disease (Chapter 369), compressive tumors, and phrenic nerve injury related to cardiac or thoracic surgery or prolonged mechanical ventilation. Neuralgic amyotrophy has been linked to the *SEPT9* gene and may occasionally be an extrahepatic manifestation of hepatitis E (Chapter 135). Diagnosis of diaphragmatic dysfunction is often suggested by elevation of a hemidiaphragm on a chest radiograph (Fig. 86-1). The diagnosis of unilateral paralysis can be confirmed by performing a "sniff test" using fluoroscopy or ultrasound, in which paradoxical (cephalad) movement of the hemidiaphragmatic dome occurs during a sniff maneuver.

Bilateral diaphragmatic paralysis is more difficult to diagnose than unilateral paralysis. Chest radiography typically shows elevation of both hemidiaphragms. This finding may be interpreted as a "poor inspiratory effort" or "low lung volumes." Routine pulmonary function testing (Chapter 73) is nonspecific; it typically demonstrates moderate to severe restriction, with both the vital capacity and total lung capacity reduced to 30 to 60% of predicted. A more specific test for diaphragmatic paralysis is the measurement of supine vital capacity. A decline of 20% or greater when supine is consistent with diaphragmatic paralysis. Maximal static inspiratory pressure measured at the airway opening ($P_{I_{max}}$) is reduced to 20 to 30% of predicted in individuals with bilateral diaphragmatic paralysis, but maximal static expiratory pressure may be preserved in individuals with isolated diaphragm paralysis.[3]

The diagnosis of unilateral or bilateral diaphragmatic paralysis can be confirmed using ultrasound. Absence of diaphragmatic thickening during inspiration indicates paralysis. A more invasive test is the measurement of transdiaphragmatic pressure (the pressure difference between the thoracic and abdominal cavity), which requires the patient to swallow a balloon for manometry. With diaphragmatic paralysis, there is no increase in transdiaphragmatic pressure during inspiration. Diaphragm electromyography and phrenic nerve conduction studies may be useful to distinguish neuropathy or myopathy. If the diagnosis of bilateral diaphragmatic paralysis is confirmed, the patient should be evaluated for nocturnal hypoventilation (Chapter 374). Computed tomography (CT) of the chest may be needed to exclude a mediastinal mass, and magnetic resonance imaging (MRI) of the neck may be necessary to evaluate the spinal cord and nerve roots (E-Fig. 86-1).

TREATMENT AND PROGNOSIS

Bilateral diaphragmatic paralysis may not be reversible unless the underlying cause is treatable. For example, myopathies (Chapter 389) related to metabolic disturbances may be improved by correcting electrolyte imbalances or replacing thyroid hormone. Toxic or metabolic disturbances related to diabetes, alcohol, or viral infections may resolve with treatment of the underlying disease. Idiopathic diaphragmatic paralysis or paralysis due to neuralgic amyotrophy may spontaneously improve or resolve completely in approximately 60% of individuals, but recovery can take 18 months to 3 years. Phrenic nerve damage related to cardiac surgery usually resolves spontaneously but may persist if the phrenic nerve is transected. For a high spinal cord injury, in which the phrenic nerve roots remain intact (injury above C3), phrenic nerve pacing can provide ventilation.

Noninvasive positive-pressure ventilation (NPPV) is the preferred method of treatment for patients with diaphragmatic paralysis because it can improve both symptoms and physiologic derangements related to nocturnal hypoventilation (E-Table 86-1 and Chapter 374). NPPV also may reverse the brain's adaptation to high levels of CO_2 by "resetting" chemoreceptors in the medulla toward normal. When patients with unilateral paralysis have severe symptoms, surgical plication of the paralyzed hemidiaphragm may improve vital capacity, but this intervention has no role in bilateral diaphragmatic paralysis. Phrenic nerve reconstruction is a promising treatment that has been associated with symptomatic relief and improved respiratory function at 1- to 2-year follow-up.[4]

MISCELLANEOUS DIAPHRAGMATIC DISORDERS

Diaphragmatic eventration results from localized atrophy of the diaphragm muscle or from part of the diaphragm being replaced with fibroelastic tissue. Eventration most often results in an elevation of the right anteromedial portion of the diaphragm. Metastatic tumors to the diaphragm usually are related to direct extension of lung cancer. Primary tumors of the diaphragm are very rare. Lipomas are the most common benign tumor, and fibrosarcomas are the most common malignant neoplasm.

CHEST WALL

The chest wall is a key component of the "inspiratory pump" and allows for maintenance of normal alveolar ventilation. It consists of the bony structures of the rib cage, the articulations between the ribs and the vertebrae, the diaphragm, intercostal muscles, and abdomen. Disorders that affect any of the components of the chest wall can impair breathing.

KYPHOSCOLIOSIS

EPIDEMIOLOGY AND PATHOBIOLOGY

Kyphoscoliosis is a common spinal disorder that affects approximately 1 in 1000 individuals, about 1 in 10,000 of whom has a severe spinal deformity. Deformities include excessive spinal curvature in the coronal (scoliosis) and sagittal (kyphosis) planes as well as rotation of the spinal axis. The most common form is idiopathic, but kyphoscoliosis also can be caused by congenital vertebral malformations or be secondary to neuromuscular disorders

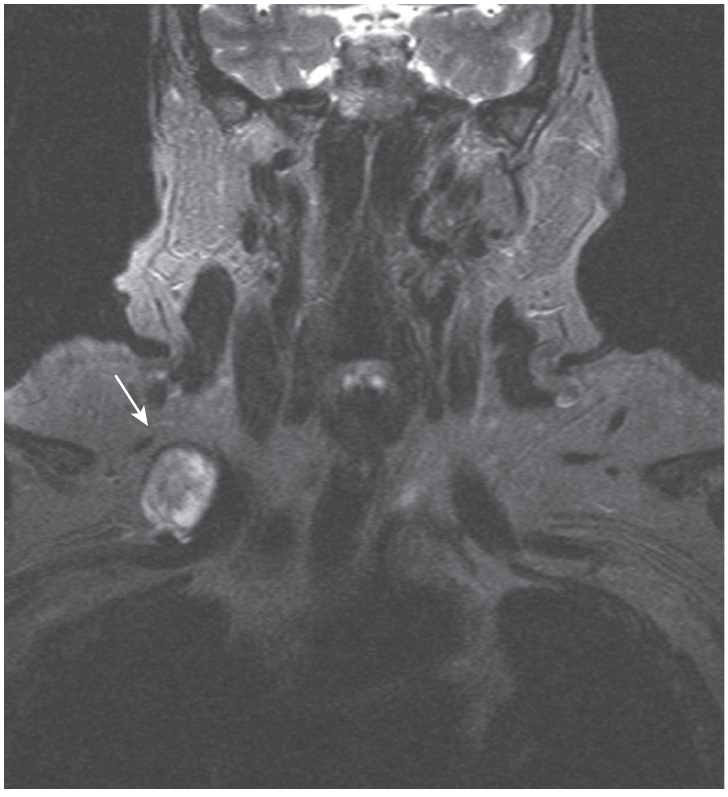

E-FIGURE 86-1. **Magnetic resonance imaging of the neck in the same patient as in Fig. 86-1. There is a hypervascular mass at the apex of the right axilla and right supraclavicular fossa that was a schwannoma. The right phrenic nerve was involved, resulting in right hemidiaphragm paralysis.**

E-TABLE 86-1 THERAPEUTIC BENEFITS OF NONINVASIVE MECHANICAL VENTILATION IN PATIENTS WITH CHEST WALL AND NEUROMUSCULAR DISORDERS*

GAS EXCHANGE INDICES	
Pa_{O_2}	Increase
Pa_{CO_2}	Decrease
Bicarbonate	Decrease
RESPIRATORY MECHANICS	
MIP, MEP	No change or slight increase
HEMODYNAMIC PARAMETERS	
PAP	Decrease
VENTILATORY CONTROL	
Hypercapnic ventilatory response	Increase
SLEEP	
Epworth sleepiness score	Decrease
OTHER PARAMETERS	
Quality of life	Improvement
Survival	Increase

*Efficacy data derived from mostly nonrandomized, noncontrolled studies.
MEP = maximal expiratory pressure; MIP = maximal inspiratory pressure; PAP = pulmonary artery pressure.

(Chapter 390). Adult degenerative scoliosis is an increasing affliction as the population ages.[5]

A familial predilection may be related to the chromatin-remodeling gene family *(CHD7)*. Kyphoscoliosis typically becomes more prominent in late childhood or early adolescence, with a female-to-male ratio of 4 : 1.

CLINICAL MANIFESTATIONS

Kyphoscoliosis may be classified as mild, moderate, or severe based on the angle of spinal deformity. In younger individuals with milder spinal deformities, the physical findings may be subtle. Individuals with mild to moderate kyphoscoliosis may have complaints of back pain and have psychosocial problems related to the spinal deformity. Adolescents with mild idiopathic kyphoscoliosis usually have normal exercise capacity, whereas those with moderate idiopathic kyphoscoliosis have reduced exercise capacity with additional exercise limitations owing to deconditioning. With severe deformities, patients may experience dyspnea with minimal exertion or at rest.

Typical findings of severe kyphoscoliosis are the dorsal hump, which is due to the angulated ribs and shoulder asymmetry and the presence of tilted hips. With severe kyphoscoliosis, signs of right heart failure (Chapter 45) may be present.

DIAGNOSIS

Severe kyphoscoliosis can be readily diagnosed on physical examination, whereas mild or moderate degrees of kyphoscoliosis may be noted only on chest radiographs. The Adams forward bend test, in which the examiner observes for thoracic or lumbar region asymmetry while the patient bends forward at the waist until the spine becomes parallel to the floor, can help detect minor deformities. The degree of spinal deformity should be calculated based on the angle of spinal curvature (the Cobb angle) from radiographs (E-Fig. 86-2). Angles more than 100 degrees are severe and are usually associated with respiratory symptoms such as dyspnea.

Kyphoscoliosis reduces the internal volume and mobility of the rib cage, thereby producing a restrictive respiratory impairment, with total lung capacity and vital capacity reduced to as low as 30% of predicted values. As the degree of spinal angulation increases, the degree of restriction worsens. The patient's age, sex, degree of spinal rotation, presence of respiratory muscle weakness, and involvement of the thoracic vertebrae are all factors that promote the restrictive process.

TREATMENT

Patients should be encouraged to remain physically active to improve quality of life.[A1] In addition, general supportive measures, including immunizations against influenza and pneumococci (Chapter 15), smoking cessation (Chapter 363), maintenance of a normal body weight (Chapter 201), and treatment of respiratory infections in a timely fashion should be instituted. Patients with severe kyphoscoliosis and Cobb angles of more than 100 degrees should be monitored closely for respiratory complications and nocturnal hypoventilation.

Because sleep-related abnormalities and their effects on cardiorespiratory function are potentially treatable, individuals with kyphoscoliosis should be evaluated for nocturnal hypoventilation (Chapter 374), which typically precedes findings of daytime hypercapnia and hypoxemia. Indications for instituting NPPV include symptoms of nocturnal hypoventilation or signs of cor pulmonale (Chapter 45), with either an elevated daytime $Paco_2$ (≥45 mm Hg) or nocturnal oxygen saturation of 88% or less for 5 consecutive minutes while breathing ambient air. Supplemental oxygen is needed if hypoxemia persists despite correction of hypoventilation. NPPV can reduce the number and duration of hospitalizations and improve gas exchange, daytime blood gases, quality of life, and survival (see E-Table 86-1).

Surgical and nonsurgical (back-brace) treatments are useful in growing children and adolescents with Cobb angles between 25 and 40 degrees,[6] whereas surgery has been used for adolescents with a Cobb angle of more than 45 degrees. Although screening radiographs can detect otherwise asymptomatic scoliosis, there is no evidence to support screening for scoliosis in adults.[7]

PROGNOSIS

Individuals with mild kyphoscoliosis have an overall benign course. Patients with moderate or severe deformities are at higher risk for developing respiratory complications. Cobb angles more than 120 degrees can be associated with respiratory failure. Factors associated with progression of the spinal deformity include inspiratory muscle weakness, a large spinal curvature at the time of presentation, skeletal immaturity, and a thoracic location of the curve apex. For a given degree of spinal deformity, individuals with inspiratory muscle weakness and kyphoscoliosis are more prone to develop respiratory failure than those with kyphoscoliosis and normal inspiratory muscle strength. Treatment with NPPV improves prognosis compared to treatment with oxygen alone.

In secondary kyphoscoliosis, early age of onset, rapid curve progression during growth, progression of scoliosis after skeletal maturity, large curves at the time of presentation, and a thoracic rather than a thoracolumbar or lumbar location of the curve apex are risk factors for respiratory complications. When cor pulmonale develops (Chapter 45), the prognosis is poor, and death may occur within 1 year without therapy.

PECTUS EXCAVATUM

EPIDEMIOLOGY AND PATHOBIOLOGY

Pectus excavatum (funnel chest) is a common congenital chest wall deformity that occurs in approximately 0.5 to 2% of the population. It is characterized by excessive depression of the sternum and its adjacent costal cartilages. It affects males more than females (4 : 1), and a family history is common.

CLINICAL MANIFESTATIONS AND DIAGNOSIS

Cosmetic concerns are the usual reason for seeking medical attention. Pectus excavatum typically produces minimal respiratory impairment, and it is occasionally associated with mild reductions in vital capacity and total lung capacity. Individuals with the most severe pectus deformities may exhibit a mild reduction in maximal exercise capacity. On physical examination, sternal depression is readily apparent. Rib cage excursion is normal during inspiration. A mild degree of scoliosis may be present in 40 to 60% of individuals.

Pectus excavatum is readily diagnosed by inspecting the rib cage. On the chest radiograph, the anteroposterior diameter is reduced (Fig. 86-2). The severity of the deformity is best assessed with a chest CT. A transverse-to-anteroposterior diameter ratio greater than 3.5 signifies a significant pectus deformity.

TREATMENT AND PROGNOSIS

Surgical correction of the deformity is considered for patients with a transverse to anteroposterior rib cage ratio of more than 3.0 to 3.5 in conjunction with symptoms of dyspnea or laboratory evidence of cardiac or pulmonary restriction. However, there is no convincing evidence that correction of the deformity improves either cardiopulmonary function or exercise capacity. Minimally invasive approaches use rods to force the sternum outward gradually. The overall prognosis is excellent in individuals who have mild deformities and in patients whose more severe deformities have been corrected. A multidisciplinary team composed of thoracic surgeons, radiologists, and cardiologists can provide recommendations for surgery by not only assessing the severity of chest wall deformity by CT scan but also by assessing echocardiographic findings such as interventricular dependence, compression of the tricuspid annulus, and exercise-related systolic and diastolic function.[8] The risk of complications is similar following either open or minimally invasive repair of the pectus excavatum.[9]

FLAIL CHEST

EPIDEMIOLOGY AND PATHOBIOLOGY

Flail chest occurs following chest trauma (Chapter 97) in which there have been either double fractures of three or more contiguous ribs or combined sternal and rib fractures. The result is an unstable segment of the chest wall, which moves paradoxically inward with inspiration and outward with expiration. In adults, flail chest is most commonly a consequence of blunt chest wall trauma owing to automobile accidents or falls. Pulmonary contusion may be present and contribute to hypoxemia.

CLINICAL MANIFESTATIONS

The vital capacity may be acutely reduced by 50% or more. Flail-related changes in respiratory muscle function can lead to acute respiratory failure (E-Fig. 86-3). The causes are an increase in the work of breathing (owing to excessive diaphragmatic shortening) in concert with reduced oxygen supply to the diaphragm (owing to pulmonary contusion or hypoventilation) and impaired cough (owing to pain associated with the rib fractures as well as paradoxical motion of the flail segment). Appropriate diagnostic studies should be undertaken to determine if the patient has a concomitant pneumothorax or hemothorax.

DIAGNOSIS

Bedside inspection looking for paradoxical motion of the flail segment is key to the diagnosis. Gentle palpation of the rib cage and abdomen may reveal the characteristic paradoxical movement of the flail segment. Chest radiographs will confirm the presence of multiple rib fractures, but a three-dimensional reconstruction of a thoracic CT can provide better visualization of thoracic injuries, including lung contusion. The diagnosis may be less apparent in a sedated mechanically ventilated patient, in whom paradoxical motion of a segment of the rib cage may not occur because the positive alveolar and pleural pressures act as a "pneumatic splint" and allow for uniform inflation of the chest wall.

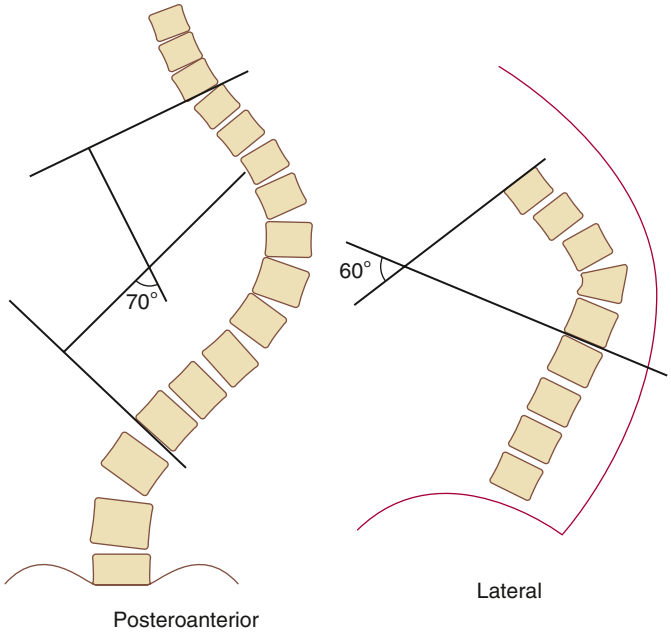

E-FIGURE 86-2. Schematic drawings of the spine illustrating the lines constructed to measure the Cobb angle of scoliosis and kyphosis. The angle can be calculated either from the intersection of the lines parallel to the vertebrae (as shown for kyphosis, on the *right*) or from the intersection of lines perpendicular to these lines (as shown for scoliosis, on the *left*).

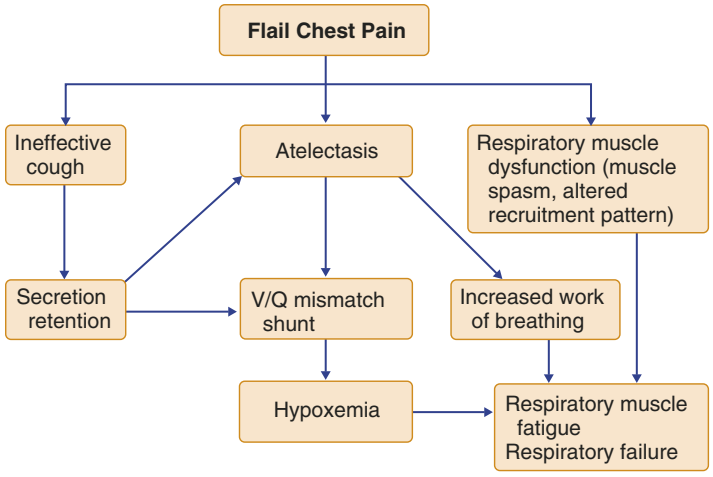

E-FIGURE 86-3. Factors involved in the pathophysiology of respiratory failure in flail chest. V/Q = ventilation/perfusion.

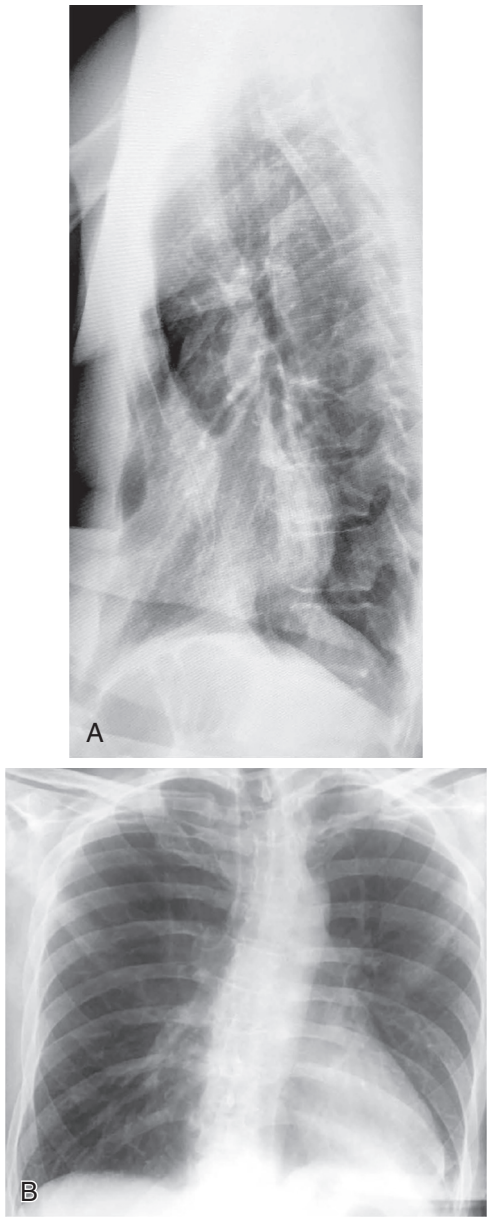

FIGURE 86-2. **Pectus excavatum deformity. A,** Chest lateral radiograph. The pectus excavatum deformity is marked by dorsal displacement of the cardiac structures and a narrow anterior-posterior diameter of the chest measuring less than 8 cm from the posterior cortex of the sternal body to the anterior cortex of the lower thoracic vertebrae. **B,** Chest frontal radiograph. The right heart border is obscured, mimicking right middle lobe disease. The cardiac silhouette is slightly rotated and shifted into the left hemithorax. (Courtesy of Paul Stark, MD.)

TREATMENT

Nonsurgical management of flail chest consists of adequate analgesia, clearance of bronchial secretions, and mechanical ventilatory assistance if needed. Pain relief (Chapter 26), which is crucial for averting atelectasis and achieving an effective cough, can be accomplished by oral medications (Table 26-4), patient-controlled analgesic pumps, intercostal nerve blocks, or epidural anesthesia. NPPV delivered by a nasal or face mask to patients who are spontaneously breathing improves gas exchange, can stabilize the flail segment, and may allow for early mobilization and access to physical therapy. If respiratory failure ensues despite NPPV, intubation and positive-pressure ventilation will stabilize the flail segment and enhance gas exchange. Surgical fixation of the flail segment may be needed for patients who are unable to wean from mechanical ventilation, patients with significant chest wall deformities, and patients who are undergoing thoracotomy for concomitant injuries. Surgical stabilization of flail chest may reduce the incidence of pneumonia as well as length-of-stay in the intensive care unit and hospital. Surgical stabilization of non-flail rib fractures reduces the need for narcotic medications to control pain but does not have other proven benefits.[A2]

PROGNOSIS

A flail chest is a marker of increased mortality, both in patients with isolated chest wall trauma and in patients with multiple sites of trauma, with an overall mortality ranging from 7 to 16%. Mortality from rib fractures increases after age 45 years, and 60% of patients over age 60 years who die from chest trauma have at least one rib fracture. Patients who have flail chest without a concomitant lung contusion may have restrictive impairment that typically resolves, with the vital capacity returning to baseline values within 6 months. By contrast, patients who have both flail chest and a concomitant lung contusion often have impairment of pulmonary function that may persist for up to 4 years after injury. If concomitant lung contusion and flail chest are present, the mortality rate increases further and may be as high as 70%, in part due to the coexistence of other injuries.

ANKYLOSING SPONDYLITIS

EPIDEMIOLOGY AND PATHOBIOLOGY

Ankylosing spondylitis (Chapter 244) is a chronic progressive inflammatory disease that involves the ligamentous structures of the spine, sacroiliac, and large peripheral joints. It affects men more than women, with the most common age of onset between 15 and 25 years. There is a genetic predisposition, with the HLA-B27 antigen present in 95% of Whites with ankylosing spondylitis. Chronic inflammation of the spine and peripheral joints may cause fibrosis and ossification of structures adjacent to the spine. Fusion of the costovertebral and sternoclavicular joints produces relative fixation of the rib cage in an inspiratory position. This limited motion may produce mild restrictive respiratory impairment with the degree of restriction proportional to disease duration and activity, as well as to the degree of spinal and rib cage immobility. Concomitant kyphosis, which may occur in advanced disease or be secondary to osteoporosis, will further impair respiratory function. Because the rib cage is less distensible, the diaphragm shortens to a greater degree for a given tidal volume, thereby increasing the work performed by the diaphragm. Intercostal muscle atrophy secondary to decreased rib cage mobility may cause inspiratory muscle weakness.

Fibrobullous upper lobe disease, which is one of the extra-articular manifestations of ankylosing spondylitis (Chapter 244), occurs in roughly 1 to 4% of patients. The cause of this apical disease is unknown, but its presence may impair gas exchange. Occasionally, individuals with ankylosing spondylitis develop nonapical interstitial lung disease (Chapter 80). When these complications occur, lung compliance, which otherwise is usually normal despite a pronounced reduction in rib cage mobility, may be reduced.

CLINICAL MANIFESTATIONS AND DIAGNOSIS

Ankylosing spondylitis is diagnosed when there is a history of low back pain and stiffness for more than 3 months, limited chest wall expansion (<2.5 cm at the fourth intercostal space), limited lumbar spine motion in the sagittal and frontal planes, and radiographic evidence of sacroiliitis. Radiographic findings include calcifications and ossifications of the vertebrae and paravertebral tissues. Low back pain and spinal stiffness are the most common presenting symptoms. Dyspnea may be present as the disease progresses and chest wall expansion becomes more restricted. Physical examination may reveal loss of lateral flexion of the lumbar spine, tenderness over the sacroiliac joints, and kyphosis. Respiratory function may be further impaired and kyphosis worsened by fractures involving the rigid spine. Endotracheal intubation should be performed with caution because hyperextension of a rigid cervical spine may lead to fracture because of frequent involvement of the cricoarytenoid joint.

TREATMENT AND PROGNOSIS

Exercise and physiotherapy programs can enhance cardiorespiratory fitness and spinal mobility.[A3] When ankylosing spondylitis is treated with nonsteroidal anti-inflammatory agents and biologic agents, such as tumor necrosis factor antagonists (Chapter 29), rib cage expansion can also improve. A high index of suspicion for possible reactivation of latent tuberculosis is required for patients treated with anti–tumor necrosis factor-α (anti-TNF-α) agents. Corticosteroids do not prevent the progression of fibrobullous disease, which can be complicated by major hemoptysis. Thoracic surgery may be indicated for hemoptysis, but surgical intervention carries major risk, with 50 to 60% of patients developing bronchopleural fistulas. Ankylosing spondylitis rarely leads to pulmonary disability unless individuals develop fibrobullous disease.

OBESITY

Obesity (Chapter 201) can be accompanied by changes in pulmonary function or alterations in respiratory control. Obesity characteristically reduces functional reserve capacity and expiratory reserve volume. Total lung capacity and vital capacity may be normal or only mildly reduced, except in the most severe cases. Obesity-hypoventilation is characterized by alterations in respiratory control, thereby resulting in elevated levels of $Paco_2$ (Chapter 74).

Dyspnea and exercise intolerance, which are the most frequent respiratory complaints of obese individuals, may be related to disordered chest wall mechanics, altered respiratory control, or the presence of inflammatory mediators, such as those linking obesity to airway hyper-responsiveness. The increase in intra-abdominal pressure when supine will further reduce functional residual capacity, impair lung emptying, increase auto–positive end-expiratory pressure, and contribute to orthopnea. The worsening of respiratory mechanics in the supine position must be considered when evaluating the risk for general anesthesia in obese patients. Weight loss (Chapter 201) is the optimal therapy, and it improves lung volumes, respiratory muscle performance, gas exchange, dyspnea, and sleep apnea.[10] In individuals with obesity-hypoventilation syndrome (Chapter 74), NPPV can reverse abnormalities in gas exchange.

PLEURA

The pleura is a thin membrane that covers the inner surfaces of the thoracic cavity. It consists of a layer of mesothelial cells supported by a network of connective and fibroelastic tissue. The visceral pleura lines the lung, whereas the parietal pleura lines the rib cage, diaphragm, and mediastinal structures. The closed space between the visceral and parietal pleura is referred to as the pleural space. The vascular supply of the parietal pleural surface is from the systemic circulation, and it contains sensory nerves and lymphatics. By contrast, the visceral pleura is supplied with blood vessels from the pulmonary circulation and has no sensory nerves.

PLEURAL EFFUSION

EPIDEMIOLOGY AND PATHOBIOLOGY

The overall frequency of pleural effusion on a chest radiograph ranges from 0.3 to 1% but varies widely depending on the underlying disease. Pleural effusions can be caused by a vast number of disease processes and are most frequently seen in patients with pneumonia (Chapter 85) and heart failure (Chapter 45).[11]

Normally, a small amount of fluid in the pleural space forms a thin layer between the visceral and parietal pleural surfaces and acts as a lubricant to minimize friction between the chest wall and lung as they move against each other during inspiration and expiration. There is continual movement of fluid into and out of the pleural space. This flux of fluid depends on the oncotic and hydrostatic pressures within the parietal and visceral pleura as well as the pressure within the pleural space itself. Hydrostatic pressure in the parietal pleura is similar to systemic circulation (30 cm H_2O), whereas that of the visceral pleura is similar to the pulmonary circulation (10 cm H_2O). Accordingly, most fluid in the pleural space is filtered from the higher pressure vascular structures in the parietal pleura. Because the pressure within the pleural space itself is more subatmospheric at the apex than at the base, most of the fluid filters in from the upper lung zones. Fluid is drained out primarily through lymphatic stomas on the surface of the parietal pleura. The normal turnover of fluid within the pleural space is 10 to 20 mL/day, with only 0.2 to 1 mL remaining in the pleural space. Excess fluid can accumulate in the pleural space because of decreased removal (owing to obstruction of pleural lymphatics) or increased production (owing to an increase in hydrostatic pressure, a decrease in oncotic pressure, decreased pressure in the pleural space, or increased pleural membrane permeability; Table 86-2).

An increase in hydrostatic pressure or decrease in oncotic pressure will result in a low-protein collection of pleural fluid characterized as *transudates* (Table 86-3). Heart failure (Chapter 45) can produce transudates by increasing hydrostatic pressure in the pulmonary venous system, atelectasis (Chapter 78) can promote transudates by making pleural pressure more subatmospheric, and occasionally, oncotic pressure may be sufficiently reduced to cause transudates (e.g., with hypoalbuminemia). Changes in pleural membrane permeability can produce high-protein effusions, which are characterized as *exudates* and can be seen in malignancy or inflammatory states such as pneumonia, tuberculosis, or rheumatoid arthritis. Tumors can disrupt the integrity of the mesothelial layer or the integrity of the capillary epithelium, thereby resulting in exudative effusions, or they may block

TABLE 86-2 MECHANISMS PROMOTING PLEURAL FLUID ACCUMULATION

MICROVASCULAR CIRCULATION
Increased hydrostatic pressure (heart failure)
Decreased oncotic pressure (severe hypoalbuminemia)
Increased permeability (pneumonia)
PLEURAL SPACE
Decreased pressure (lung collapse)
LYMPHATICS
Impaired lymphatic drainage (malignant effusion)
DIAPHRAGM
Movement of fluid from the peritoneal space (hepatic hydrothorax)

TABLE 86-3 CONDITIONS THAT CAUSE PLEURAL EFFUSION

TRANSUDATES
Heart failure
Nephrotic syndrome
Hepatic hydrothorax
Superior vena cava syndrome
Peritoneal dialysis
Atelectasis
Urinothorax
EXUDATES
Parapneumonic effusions
Simple
Complicated
Empyema
Infections
Tuberculosis
Fungal
Parasites
Nocardia
Esophageal rupture
Malignancy
Carcinoma
Lymphoma
Mesothelioma
Metastatic disease
INFLAMMATORY DISORDERS
Connective tissue disease
Rheumatoid arthritis
Systemic lupus erythematosus
Churg-Strauss syndrome (now termed eosinophilic granulomatosis with polyangiitis)
Wegener granulomatosis (now termed granulomatosis with polyangiitis)
Familial Mediterranean fever
Abdominal disease
Subdiaphragmatic abscess (hepatic, splenic)
Pancreatitis, pancreatic pseudocyst
Postoperative
Iatrogenic
Drug induced
Misplacement of enteral feeding tube
Esophageal endoscopic interventions
Miscellaneous
Asbestos exposure
Atelectasis
Cholesterol effusion
Chylothorax
Dressler syndrome
Meigs syndrome
Pulmonary embolus
Radiation
Sarcoidosis
Trapped lung
Uremia
Yellow nail syndrome

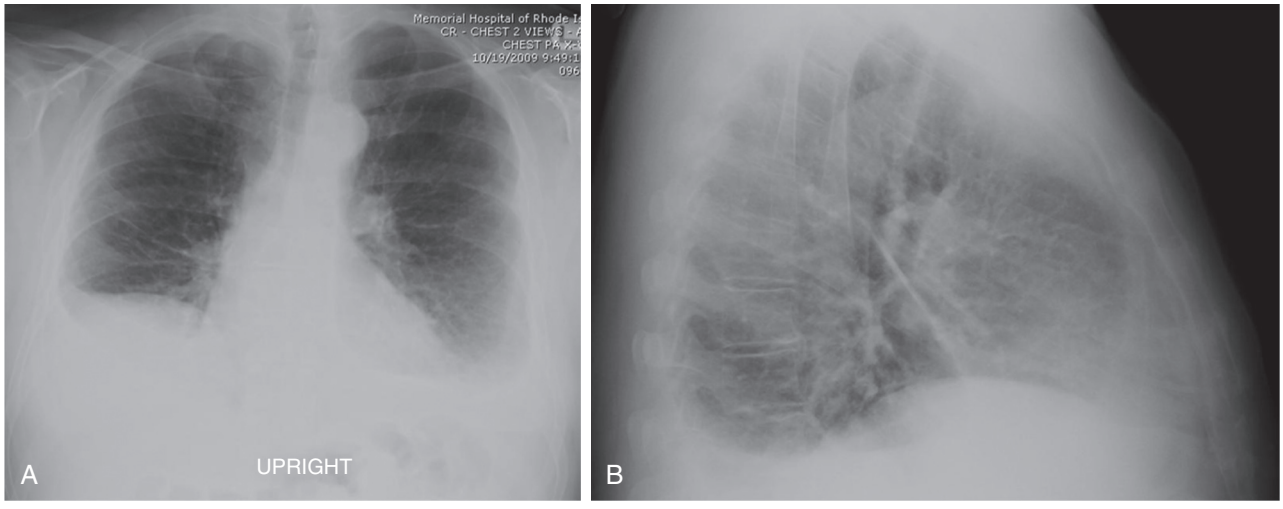

FIGURE 86-3. Patient with bilateral pleural effusions as seen on the posteroanterior radiograph of the chest (A) and lateral radiograph of the chest (B).

lymphatic drainage either through interference with stomal openings into the pleural space or obstruction of lymphatic channels. Pleural effusions also may be caused from transdiaphragmatic movement of intra-abdominal fluid related to hepatic or pancreatic disease.

CLINICAL MANIFESTATIONS

Patients with pleural effusions may be asymptomatic, experience dyspnea, or have pleuritic chest pain that is generally unilateral and sharp. At times, effusions may be sufficiently large to contribute to respiratory failure. Physical findings include dullness to percussion in the area of the effusion, along with diminished breath sounds and absent tactile fremitus.

DIAGNOSIS

Chest radiography (Chapter 72) is often the first imaging method used to detect an effusion (Fig. 86-3). The volume of fluid in the pleural space needs to exceed 250 mL to be visualized on a standing posteroanterior chest radiograph. When an effusion is present, there is blunting of the costophrenic angle on the posteroanterior chest radiograph (see Fig. 86-3), and a meniscus can be seen posteriorly on the lateral chest radiograph (see Fig. 86-3B). Fluid may also collect in either the minor or major fissures. Occasionally, pleural fluid collections in the major or minor fissures may appear as a pulmonary mass and are referred to as *pseudotumors*. Apparent elevation or changes in the contour of the diaphragm on a posteroanterior chest radiograph may signify a subpulmonic effusion, which does not distort the general shape of the diaphragm but will be evident on the lateral film. A lateral decubitus chest radiograph can determine whether fluid is free flowing or loculated. Chest CT can detect much smaller amounts of pleural fluid and determine if an effusion is loculated. It also can identify pleural and parenchymal abnormalities that may be causing the effusion, differentiate between atelectatic lung and fluid, and distinguish a loculated effusion from lung abscess (Fig. 86-4). Ultrasound can detect as little as 5 to 10 mL of fluid and is usually used to guide needle placement when performing a thoracentesis (Fig. 86-5). Positron emission tomography (PET) CT demonstrating pleura uptake of fluorodeoxyglucose is suggestive of pleural malignancy.

Pleurocentesis is required to determine whether an effusion is a transudate or exudate, as well as to determine its specific cause. The tests needed to diagnose the cause of the effusion require a relatively small amount of fluid (30 to 50 mL). Larger volumes of fluid (1 to 1.5 L) can be removed in an attempt to alleviate symptoms. Removing volumes greater than 1.5 L may result in re-expansion pulmonary edema. Relative contraindications to a diagnostic thoracentesis include a bleeding diathesis, a very small volume of pleural fluid, and a low benefit-to-risk ratio.

The fluid can be classified as either a transudate or exudate (Table 86-4).[12,13] Pleural fluid is an exudate if one of the following criteria is met: the pleural fluid–to–serum protein ratio is greater than 0.5, the pleural fluid–to–serum lactate dehydrogenase (LDH) ratio is greater than 0.6, or the pleural fluid LDH level is greater than two-thirds the normal serum LDH level. When all three criteria are met, the sensitivity, specificity, and positive predictive value exceed 98% for defining an exudative effusion. An exudate also can be defined if the pleural fluid cholesterol level is greater than 45 mg/dL in conjunction with a pleural fluid protein level greater than 2.9 g/dL and LDH level greater than 0.45 the upper limit of normal.

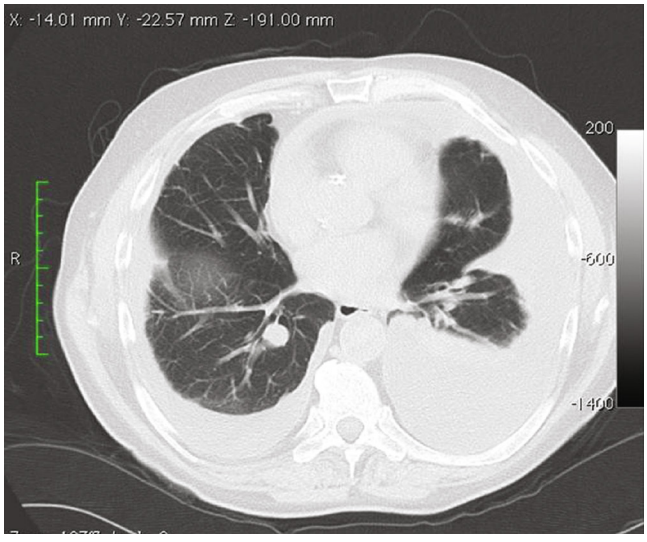

FIGURE 86-4. Chest computed tomography showing pleural effusion in the same patient as in Fig. 86-3.

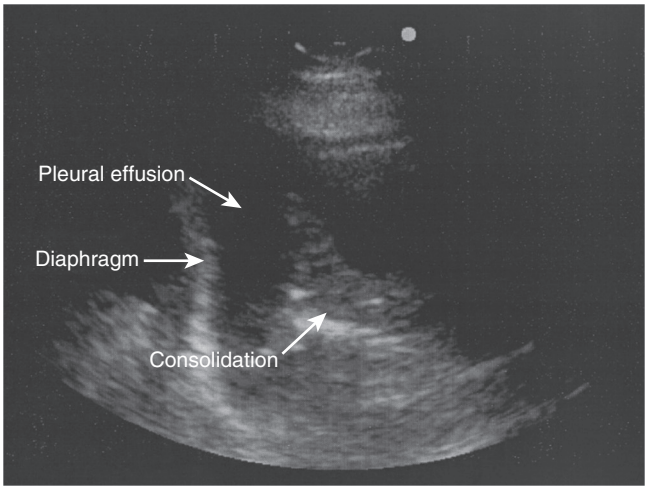

FIGURE 86-5. A right-sided pleural effusion as seen on ultrasound. The ultrasound can be performed at the bedside to aid in needle placement for thoracentesis.

Transudates

Effusions that accumulate owing to changes in osmotic and hydrostatic forces usually form transudates. Transudative effusions are most commonly due to heart failure, in which the effusions are often bilateral or, if unilateral, preferentially involve the right hemithorax. Effusions caused by heart failure are usually related to elevated

TABLE 86-4 PLEURAL FLUID CHARACTERISTICS OF EXUDATES

LIGHT CRITERIA	
Protein	>0.5 pleural fluid/serum value
LDH	>0.6 pleural fluid/serum value
LDH	>⅔ upper limit of normal serum value

LDH = lactate dehydrogenase.

TABLE 86-5 CORRELATION OF THE CHARACTERISTICS OF PLEURAL EXUDATES WITH SPECIFIC DISEASE

TEST	DISEASE
pH < 7.2	Empyema, malignancy, esophageal rupture; rheumatoid, lupus, and tuberculous pleuritis
Glucose (<60 mg/dL)	Infection, rheumatoid pleurisy, tuberculous and lupus effusions, esophageal rupture
Amylase (>200 µg/dL)	Pancreatic disease, esophageal rupture, malignancy, ruptured ectopic pregnancy
RF, ANA, LE cells	Collagen vascular disease
↓ Complement	SLE, RA
RBCs (>5000/µL)	Trauma, malignancy, pulmonary embolus
Chylous effusion (triglycerides > 110 mg/dL)	Tuberculosis, disruption of thoracic duct (trauma, malignancy)
Cytology or biopsy (+)	Malignancy
ADA (>50 µg/L)	Tuberculosis

ADA = adenosine deaminase; ANA = antinuclear antibody; RA = rheumatoid arthritis; RBC = red blood cell; RF, rheumatoid factor; SLE = systemic lupus erythematosus.

left and right heart pressures (Chapter 45), although right heart failure alone (such as seen in advanced pulmonary arterial hypertension) may rarely cause an effusion. Transudates also may be seen in cirrhosis (Chapter 139), nephrotic syndrome (Chapter 107), myxedema (Chapter 207), pulmonary embolism (Chapter 68), superior vena caval obstruction, and peritoneal dialysis (Chapter 117). With cirrhosis, ascites may cross from the peritoneum into the pleural space through small defects in the diaphragm (hepatic hydrothorax; see Table 86-3). Unusual causes of transudates include peritoneal dialysis and atelectasis. Although malignancy typically causes an exudate, it can occasionally produce a transudate.

Urinothorax, which is a rare cause of transudate, results from obstruction of the urinary system. Urinothorax typically has a pleural fluid/serum creatinine ratio greater than 1.0 and may be associated with a pleural fluid pH less than 7.40. Occasionally, aggressive diuresis for heart failure may elevate the pleural fluid protein level sufficiently for the effusion to be classified as an exudate; in such cases, an N-terminal pro–brain natriuretic peptide (BNP) level should be greater than 1500 pg/mL.

Exudates

Exudative effusions, which occur because of an alteration in vascular permeability and/or pleural fluid resorption, can be seen in inflammatory states, infection, or neoplasm. Pleural fluid analysis helps distinguish among the causes of pleural exudates (Table 86-5). In some cases, however, definitive diagnosis may require the procurement of pleural tissue via a CT-guided needle biopsy or a video-assisted thoracoscopic pleural biopsy.

TREATMENT

Treatment should be directed at the underlying cause of the effusion. Unless the effusion is clearly related to heart failure, the first step is thoracentesis to identify whether the effusion is a transudate or exudate and whether it is infected or malignant. Nonmalignant effusions may be treated with thoracentesis if the patient is symptomatic. If the fluid reaccumulates, repeat thoracentesis may be needed. However, thoracentesis must be performed carefully if the lung is nonexpandable (trapped lung); in this circumstance, pleural pressure may become excessively negative as the fluid is withdrawn, thereby resulting in complications such as chest discomfort and re-expansion pulmonary edema. Pleural manometry does not appear to safeguard against these complications.[A4] For a refractory effusion, an indwelling pleural catheter may provide relief of dyspnea but may be associated with complications in patients with hepatic hydrothorax.[14] Other options for refractory effusion include talc or chemical pleurodesis.

SPECIFIC CAUSES OF PLEURAL EFFUSIONS

Parapneumonic Effusions and Empyemas

Parapneumonic effusions, which are the most common type of exudative pleural effusion, occur in up to 40% of patients with pneumonia, typically in patients with bacterial pneumonia (Chapter 85). In an uncomplicated parapneumonic effusion, the pH is generally greater than 7.3, the glucose content greater than 60 mg/dL, and the pleural fluid LDH less than 1000 IU/L. Complicated effusions are characterized by a pH less than 7.2 and often have a glucose content less than 60 mg/dL.

An empyema is present when frank pus is aspirated from the pleural space, when the Gram stain of the fluid is positive for bacteria, or when bacteria are cultured from the fluid. Patients with empyema often report pleuritic chest pain and have refractory fevers several days or more into the course of their pneumonia. Immunocompromised patients may develop empyema sooner and more rapidly. Pneumonia caused by *Streptococcus pneumoniae* (Chapter 268) or *Staphylococcus aureus* (Chapter 267) infection can cause empyema. Patients who aspirate are at high risk for empyema caused by anaerobic organisms, and patients with tuberculosis (Chapter 299) can develop a tuberculous empyema. Methicillin-resistant staphylococci, *Klebsiella* species pneumonia, and *Pseudomonas* species infections may cause an empyema that is difficult to treat. Uncommon infectious causes of effusions include *Actinomyces* species (Chapter 304), *Nocardia* species (Chapter 306), amebiasis (Chapter 323), *Echinococcus* species (Chapter 325), and paragonimiasis (Chapter 326).

TREATMENT

Uncomplicated parapneumonic effusions are usually free flowing, do not require drainage, and will respond to the same antibiotic therapy as the pneumonia itself (Chapter 85). However, in comparison, uncomplicated effusions can transition rapidly to complicated effusions, sometimes within 24 hours. Complicated parapneumonic effusions and empyemas require not only appropriate antibiotics for the particular infection (see Chapter 85) but also prompt drainage by tube thoracostomy to cure the infection as well as prevent cutaneous fistulas, bronchopleural fistulas, or a thick pleural peel (fibrothorax).[A5]

The combination of intrapleural t-PA (10 mg) and DNase (5 mg) therapy can improve chest tube drainage in patients with parapneumonic pleural infections and emyema.[A6] These agents may reduce treatment failure but do not significantly change mortality.[A7] If chest tube drainage is unsuccessful, video-assisted thoracic surgery (Chapter 87) is preferred.[A8] Occasionally, empyema requires thoracotomy and decortication.

MALIGNANT EFFUSION

Malignant effusions, which may account for up to 35% of exudative pleural effusions,[15] may be due to seeding of the parietal or visceral pleura with malignant cells that change vascular permeability and/or impede resorption. Tumor cells also may amplify the production of mediators that promote leakage of fluid into the pleural space. Rarely, a malignant effusion may be transudative. Lung cancer (Chapter 177) is the most frequent cause of malignant pleural effusion, and other malignancies that can involve the pleural space include breast cancer (Chapter 183), ovarian cancer (Chapter 184), gastric cancer (Chapter 178), and lymphoma (Chapters 171 and 172). When malignancy involves the pleural space, the prognosis is poor. However, the finding of a pleural effusion in an individual with underlying malignancy does not necessarily imply that there is a metastatic malignant process involving the pleural space, because effusions in patients with underlying malignancy also may be due to atelectasis, postobstructive pneumonia, hypoalbuminemia, pulmonary emboli (Chapter 68), lymphatic obstruction, and complications from radiation (Chapter 18) or chemotherapy. For this reason, it is critical to obtain a sample of pleural fluid in these individuals. The diagnosis of malignant pleural effusion is established by demonstrating malignant cells in the pleural fluid. Approximately 60% of malignant pleural effusions can be diagnosed with one thoracentesis, and the yield increases to 80% with repeat thoracenteses. A chest CT may show a pleural mass, and pleural biopsy, obtained either by medical or surgical thoracoscopy (Chapter 87), may be helpful in difficult cases.

TREATMENT

Treatment options for malignant pleural effusion include observation and treatment of the underlying malignancy.[16–18] Malignant effusions with a tendency to respond to generalized chemotherapy include those related to breast cancer (Chapter 183), small cell carcinoma of the lung (Chapter 177), and lymphomas (Chapters 171 and 172) with obstruction of lymphatic drainage of the pleural

space. The other options are chemical pleurodesis (with tetracycline derivatives, talc poudrage, or talc slurry[A9]) and placement of an indwelling pleural catheter. These two options are equivalent initial options for relieving patient-reported dyspnea, with catheter-based treatment shortening hospital length of stay[A10] but also producing more adverse effects. A complete response occurs in perhaps 50% of patients, but a low pleural fluid pH (<7.2) portends a poorer response to chemical pleurodesis. For patients with recurrent malignant effusions, symptom-guided drainage is generally as good as more aggressive approaches.[A11] The tunneled placement of an indwelling pleural catheter can permit outpatient talc administration, which increases the likelihood of successful resolution of the effusion,[A12] as well as a way to perform intermittent drainage to relieve symptoms. Daily drainage via an indwelling catheter is more effective than every-other-day drainage.[A13] Indwelling pleural catheters can be left in place for several weeks and can induce spontaneous pleurodesis in about 40% of patients.[19] The value of injecting intrapleural urokinase to facilitate treatment of a nondraining malignant pleural effusion is uncertain.

Tuberculous Effusions

Tuberculosis (Chapter 299) can cause pleural effusion in up to 30% of patients who reside in locations endemic for tuberculosis. The pleural effusion typically is not due to direct mycobacterial infection but rather to increased vascular permeability of the pleural membrane because of a hypersensitivity reaction to mycobacterial proteins. The pleural fluid is generally lymphocyte predominant and culture negative for acid-fast bacilli. Adenosine deaminase levels greater than 50 U/L may be helpful in identifying tuberculous pleural effusions, especially when the effusion is lymphocytic. A tuberculous empyema, which is distinct from a tuberculous effusion, is characterized by direct extension of the infection from thoracic lymph nodes or hematogenous spread of tuberculosis into the pleural space.

TREATMENT

Tuberculous effusions typically respond to initial drainage followed by appropriate antitubercular therapies (Chapter 299), whereas tuberculous empyemas require treatment as noted earlier for other bacterial empyemas.

Systemic Inflammatory Disorders

Effusions may be seen in as many as 15% of patients with rheumatoid arthritis (Chapter 243), with a male preponderance. Effusions typically appear after the onset of disease but may precede joint disease. Rheumatoid factor in the pleural fluid is often greater than 1 : 320, and pleural fluid glucose is low (<60 mg/dL, or the pleural fluid–to–serum glucose ratio is <0.5). Other causes of low pleural fluid glucose levels include complicated parapneumonic effusions or empyema, malignant effusions, tuberculous pleurisy, lupus pleuritis, and esophageal rupture, with the lowest concentrations typically seen in rheumatoid arthritis and empyema. Pleural effusions can be seen in 15 to 50% of patients with systemic lupus erythematosus (Chapter 245) and may be characterized by the presence of lupus erythematosus cells, low levels of complement (C3 and C4), and a pleural fluid antinuclear antibody titer greater than 1 : 160. Pleural fluid ANA titers ≥1 : 160 in patients with systemic lupus erythematosus generally indicates that the fluid is a result of lupus pleuritis rather than from other causes. Granulomatosis with polyangiitis (Chapter 249), Sjögren syndrome (Chapter 247), and sarcoidosis (Chapter 83) are less common causes of pleural effusions.

TREATMENT

For inflammatory effusion, treatment of the underlying disease is key, with anti-inflammatory agents and corticosteroids as needed (Chapters 243 and 245).[20] Thoracentesis is useful for symptomatic control, but local measures cannot be expected to resolve the effusion.

PANCREATITIS

Patients with pancreatitis or pancreatic pseudocysts (Chapter 130) may develop exudative pleural effusions that often involve the left hemithorax. A pleural fluid amylase concentration that is greater than the upper limit of normal for serum amylase is consistent with the diagnosis. Extremely high amylase levels have been reported in effusions due to pancreaticopleural fistulas. Amylase also may be seen in the pleural fluid with an esophageal rupture or malignancy. Pancreatic disease is associated with pancreatic isoenzyme amylase, whereas malignancy and esophageal rupture are characterized by a predominance of salivary amylase isoenzymes.

TREATMENT

Large pleural effusions secondary to pancreatitis (Chapter 130) may be evacuated by thoracentesis. General measures to reduce pancreatic stimulation, including the use of octreotide (100 µg subcutaneously three times daily for 7 days) may prevent further fluid accumulation. For chronic effusions, endoscopic or surgical procedures to correct a pancreaticopleural fistula may be required.

Chylous Effusions

A chylothorax has a milky-white appearance and is characterized by high levels of triglycerides (>110 mg/dL) and chylomicrons. A chylothorax is caused by leakage of lymph from the thoracic duct into the pleural space, most commonly related to mediastinal malignancy but also occurring after trauma to the thoracic duct. Major complications from a chylothorax are malnutrition and immunologic compromise when fat, protein, and lymphocytes are depleted by repeated thoracentesis or chest tube drainage. Chylous effusions must be distinguished from pseudochylous effusions, which have a white appearance but are devoid of chylomicrons, and are indicative of a chronic long-standing effusion.

TREATMENT

For chylous effusions, transpedal interstitial magnetic resonance lymphangiography can visualize the central lymphatic system and help guide interventional radiologic or surgical approaches to correct chylous leaks.[21] Treatment of chylothorax includes tube thoracostomy or repeated thoracentesis, combined with dietary restriction of fat intake, although fat malnutrition may ensue. Attempts to decrease chyle formation can be accomplished by intravenous hyperalimentation, and the intake of medium- and light-chain fatty acids, which are absorbed directly into the portal circulation. Ligation of the thoracic duct should be considered for traumatic chylous effusions.[22] Thoracic duct embolization has been performed successfully for nontraumatic chylous effusion.

Hemothorax

A hemothorax has a pleural fluid hematocrit that is at least half that of the circulating hematocrit. By contrast, a bloody pleural effusion will appear red but have a lower hematocrit. A bloody effusion often suggests a malignant process. Other causes include trauma, pulmonary infarction (Chapter 68), tuberculosis (Chapter 299), collagen vascular disease (Chapters 243 and 245), and hematologic disorders. Generally, blood removed from the pleural space does not clot, whereas blood resulting from the trauma of the thoracentesis itself will clot when collected. Because blood in the pleural space does not clot, it can be removed by lymphatics if the volume is small. Larger hemothoraces that impair ventilatory function may require chest tube drainage.

Asbestos Exposure

Pleural effusion may occur after exposure to asbestos. The effusion is often small, unilateral, and serosanguineous, and it generally contains less than 6000 cells/mL. The effusion tends to resolve within a year, resulting in pleural plaques that may calcify over time. Malignant mesothelioma (see later) should be excluded in these individuals.

Other Causes of Pleural Exudates

Meigs syndrome is the triad of ovarian tumor (Chapter 184), ascites, and pleural effusion. The effusion, which is usually large and on the right side, is formed when fluid moves from the abdomen to the pleural space through diaphragmatic defects. Meigs syndrome usually occurs in postmenopausal women and resolves following removal of the tumor.[23] Dressler syndrome may occur from 3 to 30 days after open heart surgery or myocardial infarction. The patient usually experiences pleuritic pain and has a small to moderate left-sided effusion. Pleural effusions that accompany acute idiopathic pericarditis are exudates, typically left-sided, usually occupy less than one third of the hemithorax, and have a predominance of lymphocytes. Treatment is as for the accompanying pericardial effusion (Chapter 62).

Uremia (Chapter 116), which can cause a polyserositis with effusion, must be distinguished from the transudate that commonly is seen in the nephrotic syndrome. Treatment is intensified dialysis, but repeated drainage may sometimes be required (Chapter 117).

Subdiaphragmatic processes, such as hepatic or splenic abscesses (Chapter 137), may cause effusions that typically resolve with resolution of the underlying cause. Trapped lung occurs when a lobe or segment is unable to re-expand owing to a restrictive visceral pleural peel or an endobronchial mass. Increased negative intrapleural pressures associated with trapped lung promote the formation of an effusion.

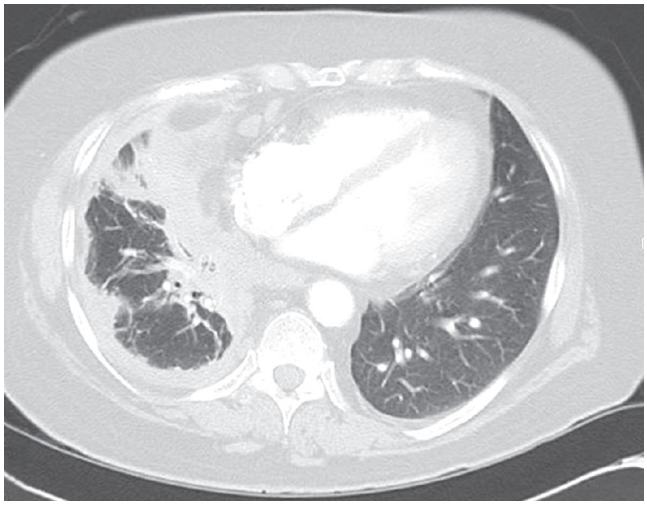

FIGURE 86-6. Computed tomographic angiogram of the chest in a patient with mesothelioma. There is diffuse thickening of the pleura and pericardium on the right with a rind-like appearance.

A number of drugs, including amiodarone, bleomycin, dantrolene, hydralazine, isoniazid, methotrexate, methysergide, mitomycin, procainamide, and procarbazine, can cause pleural effusions. Treatment consists of discontinuing the offending agent, although treatment with oral corticosteroids may be needed (Chapter 234).

MESOTHELIOMA

EPIDEMIOLOGY AND PATHOBIOLOGY

Malignant mesotheliomas arise from the serosal membrane of body cavities and usually originate in the pleural space. Patients are typically male, older than age 60 years, and have a distant history (30 to 40 years) of air- or waterborne exposure to asbestos. Smoking is not a risk factor for developing mesothelioma, but smoking in concert with asbestos exposure increases the risk for lung cancer. Mesothelioma is rare, with approximately 3000 cases annually in the United States. The annual incidence in the United States peaked in the early 1990s at 1.5 cases per 100,000 and has been decreasing as a result of better control of occupational exposure. However, the incidence may still be increasing in other countries that have fewer occupational regulations.

CLINICAL MANIFESTATIONS AND DIAGNOSIS

Patients with mesothelioma may complain of dyspnea, loss of appetite, night sweats, weight loss, and chest pain. CT findings of malignant mesothelioma may include localized or circumferential pleural thickening, various amounts of calcified pleural plaque, a pleural based mass, and varying degrees of pleural effusion (Fig. 86-6). The diaphragm or the lung parenchyma also may be involved. The pleural fluid level of hyaluronic acid may be elevated, but pleural fluid cytology frequently is insufficient for diagnosis; as a result, a CT-guided video-assisted thoracoscopic biopsy is commonly needed. A PET-CT can assess mediastinal nodes for staging purposes. Pleural fluid biomarkers such as fibulin-3 and soluble mesothelin-related peptides may help detect mesothelioma at an earlier stage and distinguish it from other malignancies involving the pleura.

A fraction of mesotheliomas are benign. Benign mesotheliomas are usually large and often pedunculated at the time of diagnosis.

TREATMENT AND PROGNOSIS

Benign mesotheliomas should be surgically resected. In highly selected patients with localized malignant disease and no comorbid illnesses, surgical resection or radical extrapleural pneumonectomy may be attempted, although the benefits are uncertain. With more extensive disease, pleural decortication may be preferred over radical extrapleural pneumonectomy.[24,25] Radiation therapy can provide symptom palliation and has been used following attempts at curative surgery. Combination checkpoint inhibitor immunotherapy,[26] such as nivolumab plus ipilimumab, can provide an additional 4 months of median survival compared with standard platinum-based chemotherapy.[A14] Gemcitabine plus ramucirumab is a potentially useful second-line option.[A15] Palliative therapy includes pleurodesis with talc or pleurectomy. Even with the addition of chemotherapy, the prognosis is poor, with a median survival of only 8 to 12 months. However, the presence of tissue biomarkers ERCC1 and RRM1 predict better patient outcomes.[27]

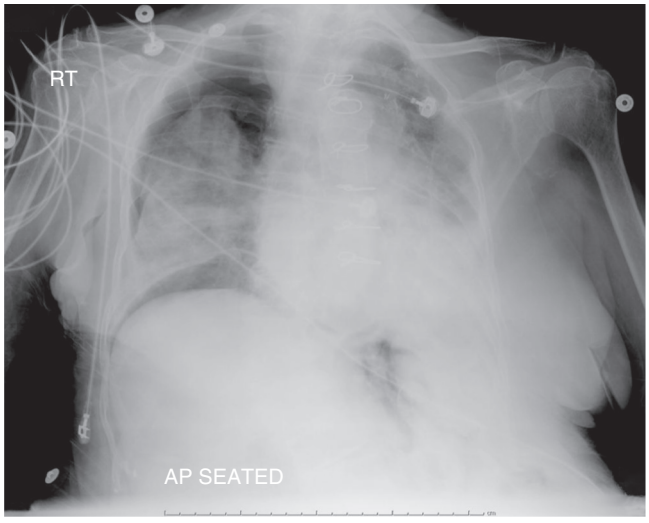

FIGURE 86-7. A portable anteroposterior chest radiograph demonstrating a right-sided pneumothorax. Note that the right lung has collapsed to less than half the size of the right hemithorax. In addition, there is a pneumoperitoneum best seen as a collection of air under the right hemidiaphragm.

PNEUMOTHORAX

Pneumothorax refers to the accumulation of air in the pleural space between the parietal pleura lining the rib cage and visceral pleura lining the lung (see Fig. 72-16). Normally, the pressure within the pleural space is slightly subatmospheric, but more than a very small amount of air within the pleural space causes positive pressure that compresses the underlying lung. A primary spontaneous pneumothorax occurs with no precipitating event in a person without underlying lung disease, whereas a secondary pneumothorax is a complication of underlying lung disease or trauma.[28]

EPIDEMIOLOGY AND PATHOBIOLOGY

Spontaneous primary pneumothorax is more common in tall, young, thin men, presumably as a result of rupture of preexisting apical blebs. It is associated with Marfan syndrome (Chapter 239) and Birt-Hogg-Dube syndrome. Secondary pneumothorax may be associated with a number of lung diseases, including but not limited to emphysema (Chapter 76), cystic fibrosis (Chapter 77), granulomatous inflammation, necrotizing pneumonia, pulmonary fibrosis (Chapter 80), eosinophilic granulomatous disease (Chapter 156), sarcoidosis (Chapter 83), necrotizing pneumonia, and lung cancer (Chapter 177). Patients with underlying lung disease undergoing mechanical ventilation (Chapter 91) may acutely develop a pneumothorax when high local pressures disrupt lung tissue, thereby leading to a leak. Blunt or penetrating trauma (Chapter 97) can cause pneumothorax. Catamenial pneumothorax occurs in patients who have subpleural and diaphragmatic endometriosis (Chapter 218); rupture of the endometrial nodules at the time of menstruation causes pneumothorax.

CLINICAL MANIFESTATIONS AND DIAGNOSIS

Symptoms typically include acute shortness of breath and sharp chest pain. Physical examination is characterized by tachycardia, tachypnea, decreased breath sounds, decreased tactile fremitus, a pleural friction rub, subcutaneous emphysema, hyper-resonance to percussion, and a tracheal shift toward the uninvolved hemithorax.

Diagnosis can be made by obtaining an upright chest radiograph, and rapid assessment with point-of-care ultrasound can be used as well. Air within the pleural space appears as an area of lucency on the chest radiograph (Fig. 86-7). With a small pneumothorax, the lucency is best appreciated at the lung apex when the patient is upright. An end-expiratory radiograph is particularly helpful in diagnosing a small pneumothorax. When a portable chest radiograph is obtained with the patient in the supine position, such as a patient in an intensive care unit, the lucent area may be most noticeable over the lower rib cage (superior sulcus sign). Ultrasound may be more sensitive than the chest radiograph for detecting a small pneumothorax, especially in the intensive care unit setting.

A *tension pneumothorax* is associated with a contralateral mediastinal shift and hemodynamic compromise, usually because high intrathoracic pressures compress the vena cava and atrium. This physiology implies an ongoing leak of air into the pleural space.

TREATMENT AND PROGNOSIS

Small unilateral pneumothoraces (<3 cm of air between the lung and chest wall on the chest radiograph) and pneumothoraces that are not associated with physiologic impairments typically resolve on their own. Analgesics, preferably nonopioid (see Table 26-4) but opioids if required (see Table 26-6), may be given for pain control. Moderate to large unilateral pneumothoraces without physiologic impairment also can be managed initially with careful observation (with pain medication and supplemental oxygen if the oxygen saturation is <92%), with interventional therapy reserved for patients who develop a systolic blood pressure less than 90 mm Hg, a pulse rate greater than their systolic blood pressure, a respiratory rate above 30 breaths per minute, or an oxygen saturation below 90%. Such a strategy provides good radiologic and symptomatic resolution at 8 weeks with less risk of later recurrence or adverse events, including just a 1% risk of subsequent pneumothorax.[A16] Another option is to place a device with a one-way valve, which can decrease hospitalizations at the expense of more short-term but usually manageable complications.[A17] Supplemental oxygen may help the pleural air resorb more quickly.

For a tension pneumothorax or pneumothorax with initial physiologic impairment or intractable pain, the pleural air must be evacuated, preferably by inserting a thoracentesis catheter into the pleural space and evacuating the air with a syringe. If the pneumothorax occupies more than 50% of the hemithorax or a tension pneumothorax develops, management requires insertion of a thoracostomy tube, suction, and water-seal drainage.[A18,A19]

If a leak continues despite tube thoracostomy, a bronchopleural fistula may be suspected. In this instance, chemical pleurodesis or surgical correction, usually by video-assisted thoracoscopic surgery, may be necessary (Chapter 87). For recurrent pneumothorax, which may occur in up to 50% of patients with primary spontaneous pneumothorax, pleurodesis is safe and effective.

MEDIASTINUM

The mediastinum, which is the central part of the thoracic cavity, lies between the right and left lungs. It contains the heart and aorta, esophagus, trachea, lymph nodes, thymus, and great vessels. It is bordered by the two pleural cavities laterally, the diaphragm inferiorly, and the thoracic inlet superiorly.

MEDIASTINAL MASSES

PATHOBIOLOGY

The mediastinum can be divided into three compartments: anterior, middle, and posterior (E-Fig. 86-4). The anterior compartment contains the thymus, substernal extensions of the thyroid, blood vessels, pericardium, and lymph nodes. The middle compartment contains the heart, great vessels, trachea, main bronchi, lymph nodes, and the phrenic and vagal nerves. The posterior compartment contains the vertebrae, descending aorta, esophagus, thoracic duct, azygous and hemizygous veins, lower portion of the vagus, sympathetic chain, and lymph nodes.

CLINICAL MANIFESTATIONS

Mediastinal masses usually are not accompanied by symptoms, and most masses are incidentally found on either a chest radiograph or a chest CT scan. If present, however, symptoms may be related to compression of normal mediastinal structures or to systemic effects. Symptoms include chest pain, cough, hoarseness, stridor, dysphasia, dyspnea, fever, and night sweats. One third of patients with a mediastinal thymoma have symptoms or weakness owing to myasthenia gravis (Chapter 390), and individuals with mediastinal lymphoma (Chapters 171 and 172) may have systemic symptoms such as fever, night sweats, and weight loss. Occasionally, a mass may compress the superior vena cava, causing partial obstruction and resulting in facial edema and dilated neck and chest veins (Fig. 86-8).

DIAGNOSIS

When a mass is identified by chest radiography or chest CT, further evaluation is mandatory. Chest CT can usually provide resolution sufficient to determine the tissue composition of the mass and the presence of fluid, fat, or calcifications.[29] If a benign process is suspected, follow-up CT may be indicated. If a malignant process is suspected, radiologic evaluation may include angiography, PET scan, or MRI. A technetium scan may be useful if a goiter is suspected. Biopsies can be obtained by mediastinotomy, ultrasound-guided transbronchial needle aspiration biopsy, or transthoracic CT-guided needle aspiration. Biopsy should be avoided if thymoma is suspected because of potential seeding of tumor cells.

The evaluation and differential diagnosis of mediastinal masses are guided by the compartment in which they arise (Table 86-6). The *anterior mediastinal compartment* includes lesions such as thymomas, germ cell tumors (teratomas), lymphomas, and intrathoracic thyroid tissue. Thymomas make up about 30% of mediastinal neoplasms in adults, in whom they are the most common anterior mediastinal primary neoplasm. Patients with systemic lymphoma often have involvement of the mediastinum, but only 5 to 10% of patients with lymphoma present with primary mediastinal lesions. Teratomas, which account for most mediastinal germ cell tumors, are benign but may undergo malignant transformation. They may contain squamous cells, hair follicles, sweat glands, cartilage, and linear calcifications; about one third are malignant. Intrathoracic goiters (Chapter 207) (Fig. 86-9) may compress the trachea and cause stridor, cough, dyspnea, and, occasionally, superior vena

FIGURE 86-8. Superior vena cava obstruction in bronchial carcinoma. Note the swelling of the face and neck and the development of collateral circulation in the veins of the chest wall.

TABLE 86-6 CAUSES OF MEDIASTINAL MASSES

ANTERIOR	MIDDLE	POSTERIOR
Teratoma	Pericardial cyst	Neurogenic tumor
Thymoma	Lymph node hyperplasia	Esophageal tumor
Thyroid tumor	Bronchogenic tumor	Bronchogenic tumor
Goiter	Bronchogenic cyst	Bronchogenic cyst
Aneurysm	Aneurysm	Aneurysm
Lymphoma	Lymphoma	Lymphoma
Parathyroid tumor		Meningocele
Lipoma		Enteric cyst
Morgagni diaphragm hernia		Esophageal diverticula
		Bochdalek diaphragm hernia

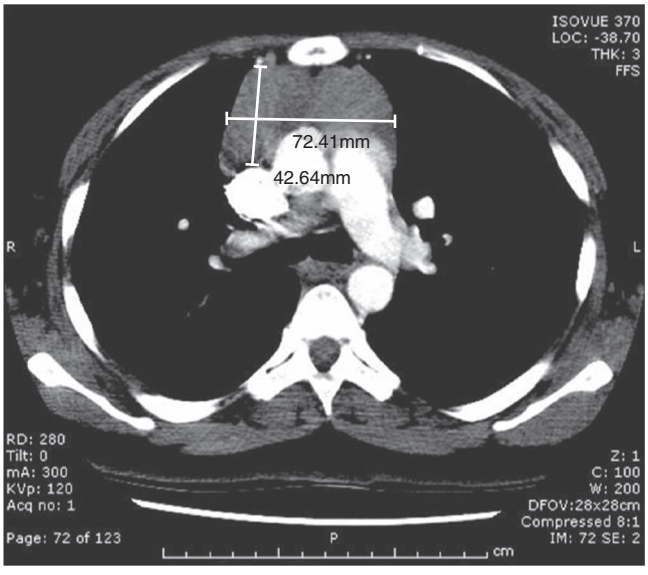

FIGURE 86-9. Chest computed tomography of a patient with an anterior mediastinal mass that proved to be a substernal goiter.

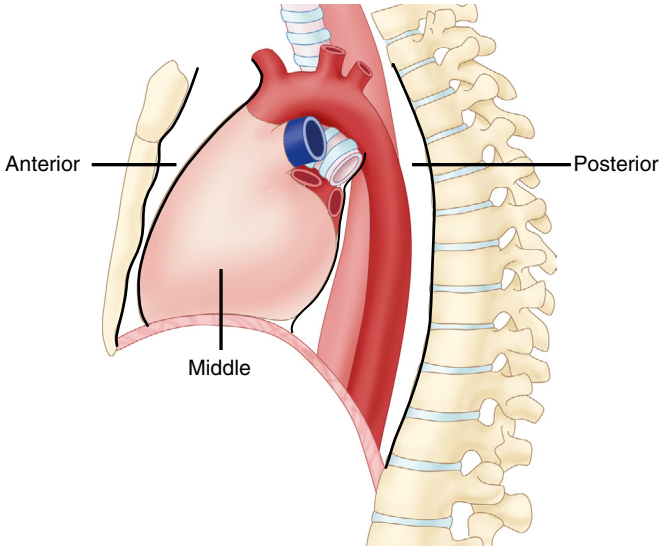

E-FIGURE 86-4. Depiction of the mediastinal compartments. The anterior compartment is bounded posteriorly by the pericardium, ascending aorta, and brachiocephalic vessels and anteriorly by the sternum. The middle compartment extends from the posterior limits of the anterior compartment to the posterior pericardial line. The posterior compartment extends from the pericardial line to the dorsal chest wall.

cava obstruction. Anterior masses in the right cardiophrenic angle, which are rare and may be associated with pericardial defects or obesity, may be due to herniation of liver or intestinal contents through the foramina of Morgagni. Lymphadenopathy related to sarcoid, lung cancer, or lymphoma accounts for most middle mediastinal masses.

Neurogenic tumors are the most common lesions that cause posterior mediastinal masses. CT or MRI can help distinguish schwannomas greater than 10 cm, which often show cystic degeneration, from other neoplasms.[30] Many of these tumors are benign and originate in the nerve sheath or sympathetic ganglion cells (schwannoma or ganglioneuroma). Posterior mediastinal masses also include cysts, meningoceles, and lymphomas (Chapters 171 and 172). Aortic aneurysm (Chapter 63) and esophageal disorders (Chapter 124) such as diverticula and neoplasm may be seen in the middle or posterior mediastinum. Herniation of abdominal contents into the thorax can result in posterior mediastinal masses. Herniation of abdominal contents through the foramina of Bochdalek results in a mass in the posterolateral area of the diaphragm, usually on the left side; it is the most common congenital hernia and may contain spleen or kidney. Herniation of the stomach through the esophageal hiatus (Chapter 124), which is the most common type of diaphragmatic herniation, produces a mass posterior to the heart, often with an air-liquid level.

Benign cysts can occur in the anterior, middle, or posterior compartments. They can arise in the pericardium, bronchi, thymus, thoracic duct, esophagus, and stomach and can produce compressive symptoms. Pericardial cysts, which are often located in the cardiophrenic angle, contain clear liquid. Bronchogenic cysts occur in the middle or posterior compartments and are filled with liquid and lined with respiratory epithelium; they often develop around the paratracheal area or carina and do not communicate with the tracheal bronchial tree.

TREATMENT

The treatment of a mediastinal mass depends on the underlying pathology. Some lesions, such as thymomas, teratomas, cysts, neurogenic tumors, and hernias, require surgical resection. Others, such as lymphoma, are treated with radiation or chemotherapy.

MEDIASTINITIS

Acute mediastinal infections, which are uncommon, are usually complications after oropharyngeal and odontogenic infections, cardiothoracic or other thoracic surgical procedures (e.g., sternotomy), or procedures involving the esophagus or tracheobronchial tree. Rupture of the esophagus or trachea from trauma or tissue necrosis can cause mediastinitis.[31] Treatment of acute mediastinitis requires antibiotics, pleural drainage, and evacuation of necrotic tissue.[32] Fibrosing mediastinitis is a rare, progressive illness that may be idiopathic or can be caused by chronic granulomatous infection (histoplasmosis), radiotherapy, autoimmune disease, immunoglobulin (Ig)G4–related diseases, or drugs (e.g., methysergide). Patients with fibrosing mediastinitis remain asymptomatic until vascular or neurologic structures are affected. When respiratory structures are involved, tracheobronchial narrowing is the most common presentation. The diagnosis and treatment often require surgical exploration. In patients with fibrosing mediastinitis, catheter-based treatment of pulmonary vein stenosis may sometimes provide relief. The prognosis is poor and treatment ineffective unless it is related to tuberculosis (Chapter 299) or autoimmune disease.

PNEUMOMEDIASTINUM

Pneumomediastinum occurs when air infiltrates the mediastinal structures. Air leaks owing to alveolar rupture or less commonly esophageal tears will dissect into the hilum and mediastinal space because the pressure in the mediastinum is more negative than the pulmonary parenchymal pressure. Loss of esophageal or tracheal integrity often results from trauma, whereas leaks from alveoli may result from trauma, occur spontaneously, or can be a complication of mechanical ventilation (Chapter 91). Pneumomediastinum rarely is seen as a complication of an exacerbation of asthma (Chapter 75), violent coughing, or emesis. Pneumomediastinum may present as a sore throat, neck pain, or shortness of breath. A chest radiograph or CT scan will reveal thin columns of hyperlucency between mediastinal structures. Mediastinal air can dissect into the subcutaneous tissues of the neck and chest wall, where it results in subcutaneous emphysema with characteristic palpable crepitus. Spontaneous pneumomediastinum generally resolves without treatment. When more severe collections of subcutaneous air occur, surgical decompression may be warranted.

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87 INTERVENTIONAL AND SURGICAL APPROACHES TO LUNG DISEASE

DAVID J. FELLER-KOPMAN AND MALCOLM M. DECAMP

Interventional pulmonology and minimally invasive thoracic surgery have drastically changed the approach to the diagnosis and staging of lung cancer, the management of central airway obstruction, and the treatment of patients with pleural disease.

BRONCHOSCOPIC PROCEDURES

Flexible bronchoscopy and endobronchial ultrasound have revolutionized the evaluation of airway and parenchymal diseases, the approach to hilar and mediastinal adenopathy, and the staging of lung cancer. New technologies offer bronchoscopic treatment for patients with severe asthma and emphysema.

ENDOBRONCHIAL ULTRASOUND

Bronchoscopy is a standard component of the evaluation and staging of patients with thoracic tumors. Convex-probe endobronchial ultrasound uses a curvilinear ultrasound probe (E-Fig. 87-1), which is incorporated into the tip of the bronchoscope, to visualize structures outside of the airway and sample hilar and mediastinal lymph nodes under direct, real-time imaging. This approach has largely replaced mediastinoscopy in the staging of patients with lung cancer and in the diagnosis of sarcoidosis (Chapter 83) and mediastinal lymphomas. Adding endobronchial ultrasound to surgical staging improves the sensitivity for finding nodal metastases and can reduce the unnecessary thoracotomy rate from 18 to 7%. Additionally, endobronchial ultrasound–guided biopsies can provide adequate tissue for identification of "tumor markers," which are now required to guide lung cancer treatment. It also reduces complications as well as the need for additional procedures for molecular marker analysis compared with computed tomography (CT)-guided transthoracic needle aspiration. It is important to note, however, that the sensitivity of endobronchial ultrasound is not 100%, so nondiagnostic samples must be confirmed as true negatives with either surgical staging or clinical and radiologic follow-up.

In radial-probe endobronchial ultrasound, an ultrasound probe is passed through the working channel of the bronchoscope to visualize parenchymal lesions as well as to discriminate tumor invasion compared with compression of the central airways. When used with smaller bronchoscopes and advanced navigational technologies, such as electromagnetic navigation or virtual bronchoscopic navigation, this technique can improve the diagnostic yield when sampling pulmonary nodules.

BRONCHIAL THERMOPLASTY

Bronchial thermoplasty uses radio frequency energy to ablate airway smooth muscle in patients whose severe asthma (Chapter 75) remains symptomatic despite medical therapy. The patient must undergo three bronchoscopic procedures to treat all of the visible airways. The right lower lobe is treated during the first procedure, the left lower lobe in the second, and both upper lobes in the third (the right middle lobe is not treated). Although asthma may be exacerbated in the immediate peritreatment period, this approach can significantly improve asthma-related quality of life, days lost from work or school, and emergency department visits in carefully selected patients.[A1]

BRONCHOSCOPY FOR CENTRAL AIRWAY OBSTRUCTION

A variety of malignant and nonmalignant diseases can obstruct the central airways (Table 87-1). Malignant causes include bronchogenic carcinoma (Chapter 177) or metastatic malignancy to the airways, as well as extrinsic compression from adenopathy. Nonmalignant causes include granulation tissue arising after an intubation or tracheostomy, adenopathy from sarcoidosis (Chapter 83), inflammatory conditions such as relapsing polychondritis (Chapter 254), amyloidosis (Chapter 174), and infectious causes such as tuberculosis (Chapter 299) and respiratory papillomatosis.

CLINICAL MANIFESTATIONS AND DIAGNOSIS

A high index of suspicion is essential because significant airway obstruction can be present before the development of symptoms or the characteristic abnormalities on the inspiratory and expiratory flow-volume curves (Chapter 73). Patients with central airway obstruction often develop exertional dyspnea when the tracheal lumen is less than 8 mm in diameter (normal is about 18 to 20 mm) but do not develop stridor, which usually is a sign of impending respiratory failure and the need for urgent intervention, until the tracheal diameter is less than 5 mm.

Hemoptysis (Chapter 71) may be present in patients with malignancies but is also seen in infectious and inflammatory conditions. Some patients may present with a postobstructive pneumonia that responds poorly to antibiotic treatment. Most patients, however, present with nonspecific symptoms including dyspnea and cough.

Patients who have risk factors for chronic airway obstruction and present with symptoms consistent with obstruction unresponsive to conventional therapy should undergo airway imaging by CT (Fig. 87-1) and flexible bronchoscopy (Fig. 87-2). Because loss of airway patency can be lethal, evaluation of these patients should be performed by individuals experienced in the management of critical airway disorders.

TABLE 87-1 CAUSES OF CENTRAL AIRWAY OBSTRUCTION

NONMALIGNANT	MALIGNANT
Congenital vascular sling	Primary airway tumors (e.g., bronchogenic, mucoepidermoid, adenoid cystic carcinoid)
Cartilage	Tumors metastatic to the airway (e.g., bronchogenic, renal cell, breast, melanoma, thyroid, colon, esophageal)
Relapsing polychondritis	External compression
Tracheobronchomalacia	Lymphadenopathy from any malignancy
Lymphadenopathy	Mediastinal tumors (e.g., thyroid, thymus, germ cell, lymphoma)
Infectious (e.g., histoplasmosis, tuberculosis)	
Sarcoidosis	
Granulation tissue associated with artificial airways, airway stenosis, aspirated foreign bodies, surgical anastomosis	
Inflammatory lesions (e.g., granulomatosis with polyangiitis, amyloidosis, papillomatosis)	
External compression (e.g., goiter)	
Internal	
Secretions	
Blood clot	

Adapted from Feller-Kopman D, Shojaee S. Therapeutic bronchoscopy: interventional techniques. In: Mason RJ, Broaddus VC, Martin T, et al, eds. *Murray and Nadel's Textbook of Respiratory Medicine*. 7th ed. Philadelphia, PA: Elsevier; 2022.

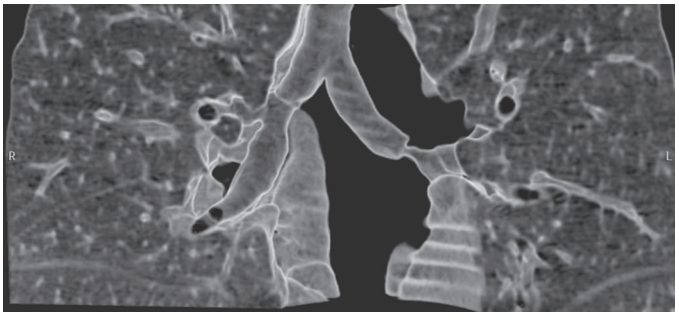

FIGURE 87-1. Three-dimensional reconstruction of a computed tomographic scan in a 20-year-old woman after bilateral lung transplantation. The image clearly shows the high-grade stenosis at the level of the left mainstem anastomosis. The right-sided airways are normal.

TREATMENT

Relief of airway obstruction requires a multidisciplinary approach by expert physicians. Techniques for achieving a patent airway include coring out the tissue with the barrel of the rigid bronchoscope; laser treatment to vaporize the tissue; electrocautery or argon plasma coagulation to carbonize the tissue, so it will later slough; cryotherapy; and mechanical débridement with forceps or a microdebrider. In the absence of definitive randomized trials, the choice of modality is often left to the expertise and resources of the bronchoscopist.

In contrast to endobronchial disease, airway stenting, preferably with silicone stents,[1] is the primary treatment for airway obstruction caused by extrinsic compression. Because airway stents can be associated with long-term complications, including stent fractures, the formation of granulation tissue, infection, and migration, they are primarily a palliative approach for malignant diseases and should be used sparingly in patients with nonmalignant airway obstruction.

ABSTRACT

Interventional approaches to lung disease include bronchoscopy, thoracoscopy, and surgery. Endobronchial stenting is the primary treatment for airway obstruction caused by external compression, whereas laser treatment, electrocautery, or argon plasma coagulation can be used for intrabronchial obstruction. Pulmonary resection, which can be performed by a minimally invasive approach or with open surgery, is central to most curative approaches to lung cancer. Lung reduction surgery is useful for predominantly upper lobe emphysema, but newer endoscopic approaches are less invasive and can significantly improve lung function and symptoms with severe emphysema. Lung transplantation is indicated for end-stage lung disease, usually as bilateral rather than unilateral transplantation. Post-transplant challenges include infection, acute rejection, chronic rejection, and the side effects of immunosuppressive therapy.

KEYWORDS

bronchoscopy
thoracoscopy
lung reduction surgery
lung transplantation

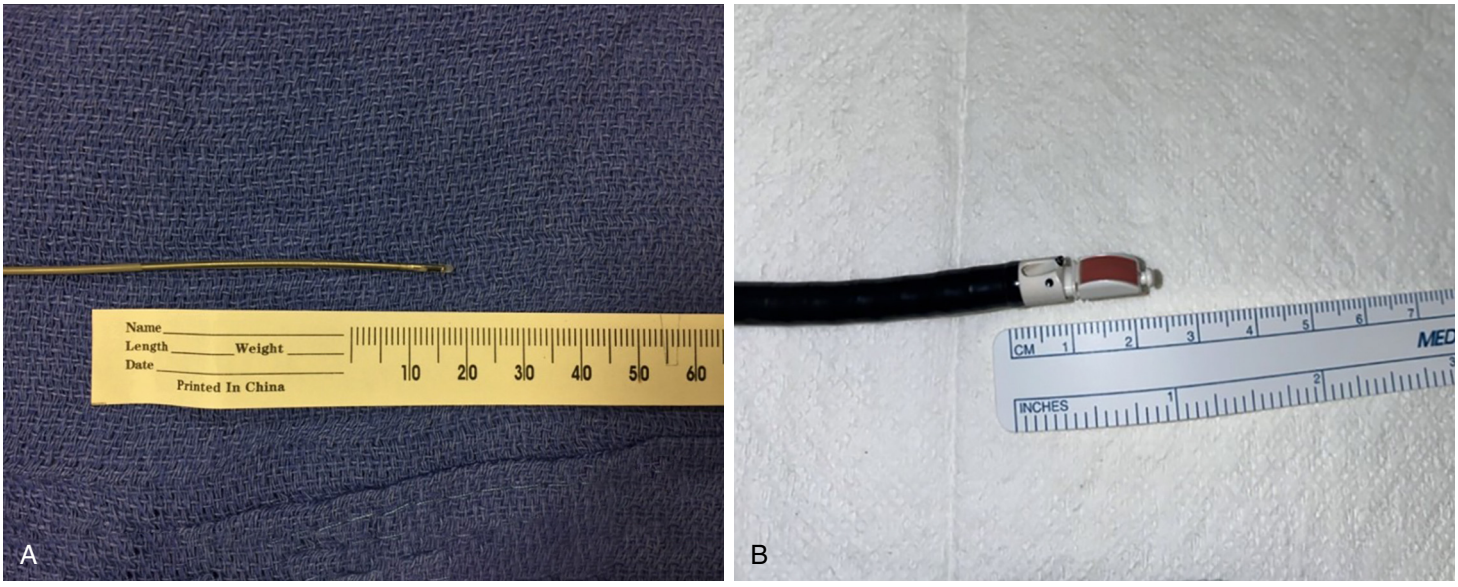

E-FIGURE 87-1. Probes for endobronchial ultrasound. Left = a radial probe; Right = a convex probe.

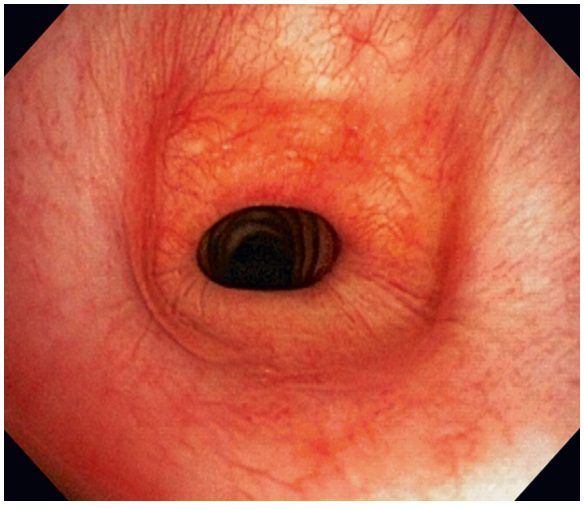

FIGURE 87-2. Bronchoscopic view of the proximal trachea in a 54-year-old man with shortness of breath and stridor. Significant circumferential narrowing is noted in the subglottic space, consistent with gastric reflux–induced subglottic stenosis.

PROGNOSIS

Successful endoscopic treatment can significantly improve the quality of life of patients with malignant airway obstruction and improve their survival rates to be the equivalent of similar stage patients without airway obstruction. Patients with nonmalignant disease similarly experience significant improvements in physiology (pulmonary function), exercise capacity, and quality of life.

SURGICAL PROCEDURES

Open Approaches

Thoracotomy has been the standard approach to evaluate the contents of the pleural space, lung parenchyma, pulmonary hilum, and ipsilateral mediastinum and diaphragm. Selective lung ventilation, achieved by use of a double-lumen endotracheal tube or mainstem bronchial blocker, allows one lung to be collapsed and visualized. The precision and accuracy of preprocedure CT and magnetic resonance imaging (MRI) now allow many procedures to be performed using smaller targeted incisions, with a muscle-sparing technique that allows specific access to regional pathology.

Minimally Invasive Approaches

Point-of-care ultrasound can guide catheter drainage of an effusion, hemothorax, empyema, or pneumothorax with persistent air leak. Thoracoscopy or video-assisted thoracoscopic surgery (VATS) and robotic-assisted thoracic surgery require between two and four port incisions to place a camera, light source, and instruments in almost any intercostal space. With a VATS or robotic approach, recovery is shorter than after an open thoracotomy because little if any muscle is divided and no mechanical rib spreading retractors are used.

A variety of benign lung diseases present as focal parenchymal lesions or diffuse processes that require a tissue biopsy for diagnosis. Thoracoscopy has essentially replaced a limited thoracotomy and wedge resection for this purpose. VATS provides a more complete view of the ipsilateral hemithorax, including the visceral, parietal, and mediastinal pleura, as well as access to all lung lobes. In addition, nodules within 1 to 2 cm of the pleura can be identified so that representative excisional biopsies can be performed.

SPONTANEOUS PNEUMOTHORAX

Although most spontaneous pneumothoraces (Chapter 86) are uncomplicated, up to 20% of patients with pneumothoraces experience complications such as tension pneumothorax, persistent air leak despite tube drainage, or recurrent pneumothoraces either ipsilaterally or contralaterally. If the patient is clinically stable and has an oxygen saturation of 92% or higher on room air or supplemental oxygen, a spontaneous pneumothorax can be managed with observation, a single aspiration, or an ambulatory device with a one-way valve alone.[A2,A3] Such conservative therapy can safely reduce invasive procedures and the duration of hospitalization. More complicated patients typically require continuous in-hospital drainage. Patients in whom a second pneumothorax develops have a 70 to 80% chance of a third recurrence within 2 years. The current surgical approach to the treatment of recurrent pneumothoraces is VATS resection of the subpleural blebs responsible for the pneumothorax, usually combined with mechanical abrasion of the parietal pleura, a parietal pleurectomy, or chemical pleurodesis (e.g., with 300 mg of minocycline or with insufflated talc) to induce an inflammatory reaction that will cause the visceral and parietal pleural surfaces to fuse, thereby preventing subsequent recurrence.

MALIGNANT LUNG DISEASE

Solitary Pulmonary Nodules

Most small pulmonary nodules (see Fig. 177-2 in Chapter 177) present in the periphery of the lung beyond the reach of diagnostic bronchoscopy. Nevertheless, advanced techniques such as electromagnetic navigation[2] and robotic bronchoscopy[3] can significantly increase the diagnostic yield to about 75% even for nodules smaller than 2 cm. If peripheral nodules are not amenable to a bronchoscopic approach, VATS excisional biopsy (Video 87-1) of a small pulmonary nodule leads to a definitive diagnosis in almost all cases and is generally preferred over transthoracic needle biopsy. Furthermore, thoracoscopy can allow concurrent nodal staging should a primary malignancy (Chapter 177) be confirmed. In the absence of regional adenopathy, patients with primary malignant lesions can undergo definitive resection at the same time.

Primary Lung Cancer

In patients with node-negative primary lung cancer and adequate pulmonary reserve, lobectomy or pneumonectomy is indicated to obtain optimal survival and to decrease the risk for local recurrence. Similar oncologic outcomes can be achieved by performing an open thoracotomy via VATS or robotic assistance, and either of these minimally invasive approaches generally is associated with fewer complications, less pain, a shorter hospitalization, and a speedier recovery.[4] Lobectomy is preferred because sublobar resection (segmentectomy or wedge) for stage I lung cancers is historically associated with a two- to three-fold higher incidence of locoregional recurrence.

Metastatic Cancer

The lung is a frequent site of metastatic recurrence. Common histologies include colorectal cancer (Chapter 179), renal cell carcinoma (Chapter 182), sarcoma (Chapter 187), melanoma (Chapter 188), breast cancer (Chapter 183), and head and neck cancer (Chapter 176). VATS is often the diagnostic procedure of choice to locate and excise nodules that are too small for reliable percutaneous biopsy.

The role of pulmonary metastectomy as therapy for advanced disease remains controversial. Five-year survival rates of 20 to 30% have been reported for selected patients, especially if the disease-free interval from original diagnosis to lung metastasis is greater than 2 to 3 years.

PROCEDURES FOR EMPHYSEMA

LUNG VOLUME REDUCTION SURGERY

Emphysema (Chapter 76) is the most common chronic progressive disabling lung disease treated by pulmonologists and thoracic surgeons. In eligible patients (Table 87-2), lung volume reduction surgery confers durable symptomatic, physiologic, and survival benefits compared with medical therapy (E-Fig. 87-2) for patients who have severe emphysema but who do not have a forced expiratory volume in 1 second (FEV_1) measure of less than 20% of predicted with either a homogeneous distribution of emphysema on CT or a diffusing capacity of less than 20% of predicted.[A4] However, subgroup analyses suggest that the benefit is mainly in patients with upper lobe predominant disease.

For eligible patients, most programs require a 6- to 10-week period of preoperative pulmonary rehabilitation followed by a cardiopulmonary exercise test to assess the risks and benefits of surgery. Patients with upper lobe predominant emphysema and a low preoperative exercise capacity have a nearly 50% lower risk for death after lung volume reduction surgery compared with continued medical therapy. Lung volume reduction surgery also can reduce systemic blood pressure, allow for weight gain, and reduce exacerbations of chronic obstructive pulmonary disease (COPD). In experienced centers, bilateral stapled resection approaches yield nearly twice the physiologic benefit of unilateral lung volume reduction surgery without adversely affecting operative morbidity or mortality. High-risk patients with severe airflow obstruction ($FEV_1 < 20\%$) should be assessed for lung transplantation unless their disease is localized to the upper lobes and their gas exchange as defined by diffusing capacity is preserved (Table 87-3).

Most patients with COPD have diffuse parenchymal disease, but a small number of patients with COPD have dominant or giant bullae that may occupy 50% or more of the volume of the hemithorax and that compress relatively preserved lung parenchyma. The indications for bullectomy include progressive symptoms with demonstrated disability, obstructive spirometry (Chapter 73),

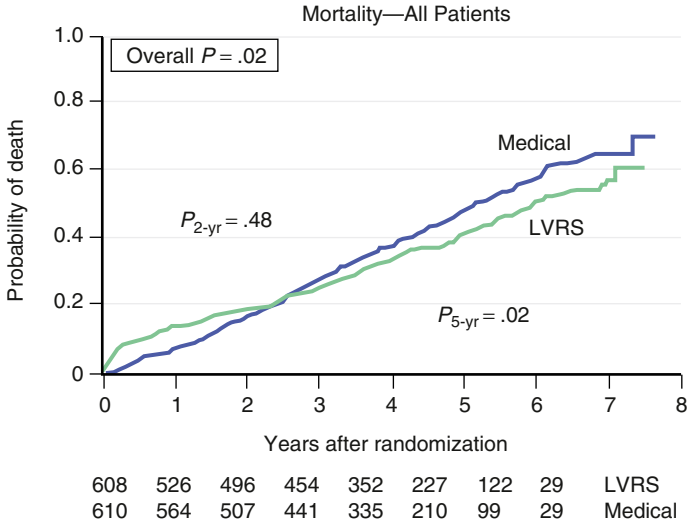

E-FIGURE 87-2. Long-term mortality of all patients treated with lung volume reduction surgery (LVRS) versus maximal medical therapy in the National Emphysema Treatment Trial. Note the statistically significant ($P = .02$) reduction in relative risk for death (RR = 0.85) in the surgical cohort. (Adapted from Naunheim KS, Wood DE, Mohsenifar Z, et al., for the National Emphysema Treatment Trial Research Group. Long-term follow-up of patients receiving lung-volume-reduction surgery versus medical therapy for severe emphysema in the National Emphysema Treatment Trial. *Ann Thorac Surg*. 2006;82:431-443.)

TABLE 87-2 INCLUSION AND EXCLUSION CRITERIA FOR LUNG VOLUME REDUCTION SURGERY

INCLUSION CRITERIA
Radiographic evidence of emphysema, especially involving upper lobes
Hyperinflation evidenced by TLC > 100% predicted and RV > 150% predicted
FEV_1 > 20 and <45% predicted (after bronchodilator)
D_{LCO} > 20% predicted
Severe dyspnea
Restricted activities of daily living
Decreased quality of life
Abstinence from tobacco
EXCLUSION CRITERIA
Active smoking
Bronchiectasis
Pulmonary nodule requiring evaluation
Excessive daily sputum production
Previous thoracotomy
Obvious pleural disease
Active or inducible coronary ischemia
Pulmonary hypertension
Depressed LVEF (<45%)
Obesity (BMI > 32)
Unable or unwilling to participate in pulmonary rehabilitation
Systemic steroids, ≥20 mg prednisone/day

BMI = body mass index; D_{LCO} = diffusion capacity for carbon monoxide; FEV_1 = first second forced expiratory volume; LVEF = left ventricular ejection fraction; RV = residual capacity; TLC = total lung capacity.

Adapted from DeCamp MM Jr, McKenna RJ Jr, Deschamps CC, et al. Lung volume reduction surgery: technique, operative mortality and morbidity. *Proc Am Thorac Soc*. 2008;5:442-446; and DeCamp MM Jr, Lipson D, Krasna M, et al. The evaluation and preparation of the patient for lung volume reduction surgery. *Proc Am Thorac Soc*. 2008;5:427-431.

TABLE 87-3 DECISION GUIDE FOR SELECTION OF LUNG VOLUME REDUCTION SURGERY VERSUS TRANSPLANTATION FOR SEVERE CHRONIC OBSTRUCTIVE PULMONARY DISEASE

FACTORS FAVORING LVRS	FACTORS FAVORING TRANSPLANTATION
Age > 65 yr	FEV_1 ≤ 20% predicted
Upper lobe predominant disease	D_{LCO} ≤ 20% predicted
Chronic medical conditions	Homogeneous or lower lobe distribution of disease
Hepatitis B and/or C	TLC < 100% predicted
HIV infection	RV < 150% predicted
Renal insufficiency	$PaCO_2$ > 60 mm Hg
Cirrhosis	PaO_2 < 45 mm Hg
Neuropathy	6 MWD < 140 m or <3 min unloaded pedaling cycle ergometer
Poorly controlled diabetes	Pulmonary hypertension
Osteoporosis	Bronchiectasis
Severe GERD	Recurrent pulmonary infections
Poor esophageal motility	
Malignancy	
Unable to maintain long-term follow-up	
Psychiatric issues limiting compliance	
Insufficient social support	

6 MWD = 6-minute walk distance; D_{LCO} = diffusion capacity of carbon monoxide; FEV_1 = first second forced expired volume; GERD = gastroesophageal reflux disease; HIV = human immunodeficiency virus; LVRS = lung volume reduction surgery; RV = residual volume; TLC = total lung capacity.

Adapted from Patel N, DeCamp M, Criner GJ. Lung transplantation and lung volume reduction surgery versus transplantation in chronic obstructive pulmonary disease. *Proc Am Thorac Soc*. 2008;5:447-453.

and a single or dominant bullous lesion with radiographic demonstration of compression of surrounding preserved lung parenchyma. Either excision or plication can remove the bullous lesion.

ENDOSCOPIC MANAGEMENT OF EMPHYSEMA

Endoscopic approaches to lung volume reduction may offer a less invasive way to achieve some of the benefits of surgical lung volume reduction for patients with severe emphysema.[5,6] As with surgical lung volume reduction, the goals of these technologies are to reduce the magnitude of overdistended and poorly perfused lung tissue, thereby increasing elastic recoil, diminishing dynamic hyperinflation, and redistributing airflow to better perfused areas of the lung. Unilateral lobar occlusion with endobronchial valves can significantly improve lung function, exercise capacity, and quality of life in patients who have heterogeneous emphysema with intact interlobar fissures and no interlobar collateral ventilation,[A5,A6] as well as in patients who have homogeneous emphysema without collateral ventilation.[A7,A8] Overall, the preponderance of evidence from randomized trials supports meaningful 1-year symptomatic benefit[A9-A11] but uncertain mortality benefit.[A12]

TABLE 87-4 INDICATIONS AND CONTRAINDICATIONS FOR LUNG TRANSPLANTATION

SINGLE-LUNG TRANSPLANT	PATIENTS (%)	DOUBLE-LUNG TRANSPLANT	PATIENTS (%)
INDICATIONS			
COPD	39	CF, bronchiectasis	26
Pulmonary fibrosis, sarcoid	46	Emphysema	26
α_1-Antitrypsin deficiency	4	α_1-Antitrypsin deficiency	5
PPH, Eisenmenger	1.2	PPH, Eisenmenger	6
CF, bronchiectasis	1.5	Pulmonary fibrosis, sarcoid	30
Retransplantation	5	Retransplantation	3.6
ABSOLUTE CONTRAINDICATIONS			
Untreatable advanced extrapulmonary organ dysfunction (e.g., heart, liver, kidney)			
CAD not amenable to PCI or bypass			
Poor LV function (could consider heart-lung transplantation)			
Malignancy within 2 years (excludes cutaneous squamous or basal cell carcinoma)			
5-year disease-free interval preferred			
Noncurable extrapulmonary infection			
Infection with human immunodeficiency virus			
Hepatitis B antigen positivity			
Hepatitis C with histologic evidence of active liver disease			
Active substance abuse (including cigarettes)			
Severe musculoskeletal disease affecting the thorax			
Documented noncompliance			
Untreatable psychiatric condition that impairs compliance			
Absence of consistent and reliable social support			
RELATIVE CONTRAINDICATIONS			
Physiologic age > 65 yr			
Poor nutritional status (BMI < 18 kg/m^2)			
Severe obesity (BMI > 30 kg/m^2)			
Symptomatic osteoporosis			
Colonization with highly virulent and/or highly resistant fungi, mycobacteria, or bacteria			
Requirement for invasive ventilation and/or circulatory support			
Uncontrolled chronic medical conditions (e.g., diabetes, hypertension, GERD)			
Severely limited functional status with poor rehabilitation potential			
Psychosocial problems likely to affect the outcome adversely			
High-dose (>20 mg of prednisone daily) corticosteroid use			

BMI = body mass index; CAD = coronary artery disease; CF = cystic fibrosis; COPD = chronic obstructive pulmonary disease; GERD = gastroesophageal reflux disease; LV = left ventricle; PCI = percutaneous coronary intervention; PPH = primary pulmonary hypertension.

Adapted from Weill D, Benden C, Corris PA, et al. A consensus document for the selection of lung transplant candidates: 2014—an update from the Pulmonary Transplantation Council of the International Society for Heart and Lung Transplantation. *J Heart Lung Transplant*. 2015;34:1-15.

LUNG TRANSPLANTATION

More than 160 worldwide lung transplant centers perform nearly 4500 transplantations per year.[7] Lung transplantation is now an accepted therapy for all forms of advanced lung disease.[8] The use of ex vivo perfusion to resuscitate lungs considered unsuitable for transplant by traditional procurement criteria appears to be expanding the availability of donor organs.

The most common indications for transplantation (Table 87-4) are diseases or conditions that share the following features: they produce extreme disability in affected patients, they are unresponsive to medical therapy, and they are responsible for limited life expectancy in affected patients. With the exception of a small number of cases of sarcoidosis and lymphangioleiomyomatosis, the original lung disease does not usually recur after lung transplantation.

TYPES OF PROCEDURES

Currently, four types of lung transplantation procedures are performed. *Bilateral lung transplantation* is performed in a sequential fashion that is functionally

equivalent to two single-lung transplantations completed during a single operation, most commonly through a transverse bilateral sternothoracotomy ("clamshell") incision. It is the procedure of choice for patients with bilaterally infected lungs and is also performed in certain patients with emphysema, primary pulmonary hypertension, and other diseases (see Table 87-4). Bilateral transplantation is preferred for nearly all indications because a double-lung recipient can expect a 7.4-year 50% survival compared with 4.6 years for a single-lung recipient. As a result, about 80% of the world's reported lung transplants are now bilateral.

Single-lung transplantation is typically performed through a posterolateral thoracotomy incision. The contralateral lung is not removed, so single-lung transplantation is not appropriate for patients with bilaterally infected lungs (e.g., patients with cystic fibrosis or bronchiectasis) (see Table 87-4).

Heart-lung transplantation is now performed in only about 60 cases per year. It is performed in patients with advanced lung disease and coexistent irreparable cardiac disease, usually associated with fixed pulmonary hypertension, and in those with Eisenmenger syndrome (Chapter 55).

Living donor lobar transplantation involves the removal of a lower lobe from each of two living donors. One is implanted into each hemithorax of the recipient in a manner similar to bilateral lung transplantation.

EVALUATION OF POTENTIAL TRANSPLANT RECIPIENTS

The ideal candidate for lung transplantation has lung disease unresponsive to medical therapy but is in otherwise good health. Patients who experience critical illness as a result of lung disease often have poor nutritional status, coexistent major organ dysfunction, refractory infection, or other contraindications to transplantation. The specific evidence-based recommendations for referral for transplant evaluation vary with the underlying disease.

In the United States, the lung allocation score system is based on expected disease-specific and patient-specific survival during the waiting period and after engraftment, thereby reflecting net transplant benefit. Evaluations of the lung allocation score system, which was introduced in 2005, indicate shorter waiting times, an increase in the total number of transplants performed, a decreased waitlist mortality, and unchanged overall survival after transplantation.

POST-TRANSPLANTATION ISSUES

Most of the medical issues that patients and physicians face after lung transplantation are the consequence of the transplanted lung(s) and post-transplantation medication rather than the underlying disease for which the transplantation was performed. Examples include toxicities of immunosuppression, infections and their prophylaxis, acute allograft rejection, chronic allograft rejection, and nonpulmonary complications of transplantation.

Immunosuppression

The standard chemotherapeutic regimen for immunosuppression after lung transplantation consists of a calcineurin inhibitor such as cyclosporine or tacrolimus, an antimetabolite such as azathioprine or mycophenolate mofetil, and corticosteroids (Chapter 28). More than 50% of centers add a monoclonal or polyclonal antilymphocyte antibody preparation in the first days after transplantation, and this practice has led to a small but statistically significant improvement in long-term survival.

Infections and Prophylaxis after Lung Transplantation

Lung transplant recipients are at high risk for bacterial, viral, fungal, and protozoal infections; infections are the leading causes of death during the early post-transplantation period. In the first 3 months after transplantation, bacterial infections are responsible for most deaths. In approximately one third of patients, pneumonia is diagnosed in the first weeks after transplantation, with gram-negative organisms as the cause in 75% of cases. Colonization and recurrent infections, usually with *Pseudomonas* species, often develop in patients with chronic rejection.

Among potential viral pathogens, *cytomegalovirus* (CMV; Chapter 347) is the most important in lung transplant recipients. Seronegative patients who receive an allograft from a seropositive donor are at particularly high risk for the development of a clinically significant CMV infection. Seronegative patients who have a seronegative donor are at low risk for infection if they are treated with seronegative blood products. Epstein-Barr virus (EBV) has been associated with the development of post-transplantation lymphoproliferative disorder.

Aspergillus species are the most common cause of invasive fungal infection (Chapter 311). Colonized patients and those deemed at risk may receive prophylactic inhaled amphotericin B.

Because of the nature of the immunosuppressive chemotherapeutic regimen used, patients are at high risk for infection by the protozoan *Pneumocystis jirovecii* (Chapter 313). The use of trimethoprim-sulfamethoxazole prophylaxis (typically 1 double-strength tablet three times weekly indefinitely) has virtually eliminated *Pneumocystis* pneumonia.

Acute Rejection

Histologically, the initial manifestation of acute rejection is a lymphocyte-predominant inflammatory response, usually centered on blood vessels, airways, or both. By convention, acute rejection is graded histologically from 0 (normal) to 4 (severe), with subclasses defined by the presence or absence of airway inflammation.

The risk for acute allograft rejection is highest in the early months after transplantation and declines with time. Multiple episodes of acute rejection are the major risk factor for the subsequent development of chronic rejection.

Clinically, patients may have fever, cough, and exertional dyspnea. Evaluation may demonstrate crackles or rhonchi on chest examination, a decline in pulmonary function by spirometry, leukocytosis, opacities on chest radiography, and exertional desaturation. The clinical manifestation is often indistinguishable from infectious pneumonia, and the clinical impression is accurate in only 50% of cases. Histologic confirmation by a transbronchial biopsy is mandatory.

Treatment of acute rejection most often consists of high-dose corticosteroids (typically 500 to 1000 mg/day of methylprednisolone administered intravenously for 3 days).

CHRONIC REJECTION

PATHOBIOLOGY

The bronchiolitis obliterans syndrome, also termed chronic lung allograft dysfunction, is thought to be a manifestation of chronic rejection. Risk factors include the number of acute rejection episodes and, in some series, previous symptomatic CMV infection. Pathologically, "early" lesions demonstrate inflammation and disruption of the epithelium of small airways, followed by growth of granulation tissue into the airway lumen and subsequent complete or partial obstruction. The granulation tissue then organizes in a stereotypical pattern with resultant fibrosis that obliterates the lumen of the airway.

CLINICAL MANIFESTATIONS

Clinically, bronchiolitis obliterans is accompanied by nonspecific symptoms. Progressive exertional breathlessness typically develops, and pulmonary function testing usually demonstrates evidence of progressive airflow obstruction (Chapter 73). Bronchiolitis obliterans is classified according to the FEV_1: 0 (no significant abnormality) if FEV_1 is greater than 80% of baseline, 1 (mild) if FEV_1 is 65 to 80% of baseline, 2 (moderate) if FEV_1 is 50 to 65% of baseline, and 3 (severe) if FEV_1 is 50% or less of baseline. Later stages of bronchiolitis obliterans may include a syndrome of bronchiectasis with chronic productive cough and airway colonization with *Pseudomonas* species.

DIAGNOSIS

The diagnosis of bronchiolitis obliterans or chronic lung allograft dysfunction is made on both clinical and pathologic grounds. Transbronchial biopsy has a low yield for demonstrating histologic evidence of bronchiolitis obliterans, but when such evidence is seen, it is diagnostic. In patients with a compatible clinical syndrome, exclusion of anastomotic stenosis and occult pulmonary infection is sufficient to establish the diagnosis.

TREATMENT

A variety of therapies have been tried for chronic rejection, including pulse corticosteroids, antilymphocyte antibodies, total lymphoid irradiation, photopheresis, and nebulized cyclosporine, but none has been clearly established as effective. Most patients with bronchiolitis obliterans experience a progressive decline in pulmonary function despite immunosuppression.

PROGNOSIS

Bronchiolitis obliterans is the leading cause of late mortality after lung transplantation. Half of lung transplant recipients surviving to 5 years will have either clinically diagnosed or biopsy-proven bronchiolitis obliterans.

Nonpulmonary Medical Complications of Lung Transplantation

Most of the nonpulmonary medical complications that arise in patients after lung transplantation are the result of immunosuppressive therapy.[9] One or more of these complications develop in virtually all lung transplant recipients.

Osteoporosis (Chapter 225) is common because of the long-term use of corticosteroids and cyclosporine. Bone density should be monitored periodically, and pharmacologic therapy should be instituted if excessive bone loss is identified.

Chronic renal insufficiency (Chapter 116) is common and is the result of therapy with the calcineurin inhibitors cyclosporine or tacrolimus, both of which affect afferent vascular tone in the kidneys and result in an average 50% drop in the glomerular filtration rate in the first 12 months after lung transplantation. Systemic arterial hypertension is also common and is caused by corticosteroids and cyclosporine. Calcium-channel blockers, which are often used to treat hypertension, raise serum cyclosporine levels; appropriate monitoring and dose adjustment are needed when starting such therapy. Both corticosteroids and tacrolimus contribute to the development of diabetes mellitus and hyperlipidemia.

Solid organ transplantation is associated with an increased incidence of malignancy, thought to be due to pharmacologic immunosuppression and alteration in immune surveillance. Patients are at increased risk for lymphoproliferative malignancies and other types of cancers. Post-transplantation lymphoproliferative disorders occur in about 4% of patients after organ transplantation; most are associated with EBV. These syndromes can be polyclonal or monoclonal. Reduction in immunosuppression is sometimes therapeutic in those with polyclonal disease. The prognosis in patients with monoclonal disease is poor, with little response to modification of immunosuppression or antineoplastic chemotherapy. Patients are also at increased risk for skin, bladder, lung, cervical, and hepatobiliary malignancy after solid organ transplantation.

Currently, the annual mortality rate following lung transplantation is 7 to 10% per year, largely owing to the bronchiolitis obliterans syndrome. The median survival after lung transplantation averages 6.2 years but varies between 4.8 to 7.8 years[10] depending on both the type of operation performed and the indication for transplant (E-Fig. 87-3).

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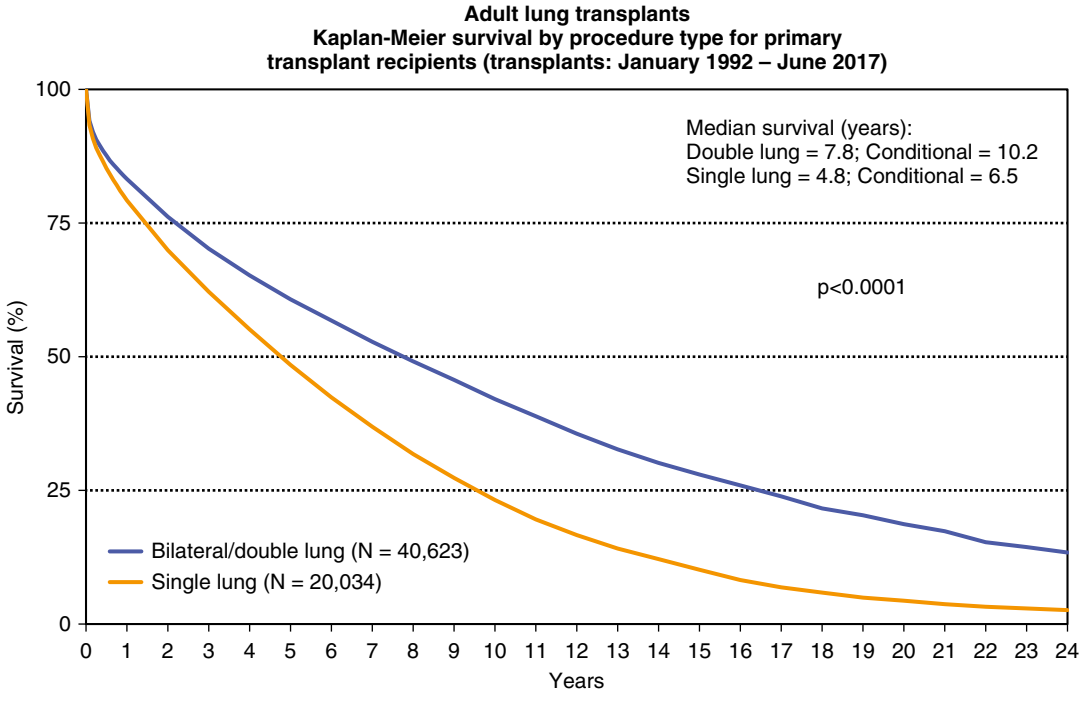

E-FIGURE 87-3. **Kaplan-Meier survival estimates for all adult lung transplantations reported to the International Registry for Heart and Lung Transplantation from 1992 to 2017. Note the highly statistically significant survival advantage conferred by double lung grafts. Because the decline in survival is greatest during the first year after transplantation, the conditional survival (i.e., when 50% of the recipients who survive to at least 1 year have died) provides a more realistic expectation of survival time for recipients who survive the early post-transplant period. (From International Thoracic Organ Transplant Registry of the International Society for Heart and Lung Transplantation. 2019 Data Slides. https://ishltregistries.org/registries/slides.asp?yearToDisplay=2019. Accessed December 11, 2020.)**

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88 APPROACH TO THE PATIENT IN A CRITICAL CARE SETTING

DEBORAH J. COOK

THE INTENSIVIST-LED INTERPROFESSIONAL TEAM

Unlike many other specialties, critical care medicine is not limited to a particular population, disease, diagnosis, or organ system. Patients with critical illness in the intensive care unit (ICU) usually require advanced life support, such as invasive or noninvasive mechanical ventilation, vasopressors, inotropic agents, or renal replacement therapy. Morbidity associated with critical illness includes complications of both acute and chronic diseases, nosocomial and iatrogenic consequences, slow recovery, and impaired quality of life among survivors. Patients who are critically ill are at a higher risk of death than any other hospital population. Accordingly, the goals of critical care are to reduce morbidity and mortality, to maintain organ function, and to restore health. The care of surviving critically ill patients often follows a trajectory of resuscitation, stabilization, improvement, and rehabilitation.

One model for staffing of ICUs uses critical care physicians, who are often referred to as *intensivists*, who provide mandatory consultations or principal ongoing care. Specialist care by intensivists is associated with a significantly reduced ICU and hospital mortality and reduced ICU and hospital lengths of stay compared with other staffing models. The addition of nighttime intensivist staffing appears to reduce mortality by about 40% in ICUs with low-intensity daytime staffing but not in centers with high-intensity daytime staffing, such as academic ICUs. These findings emphasize the value of the on-site availability of trained physicians who are dedicated to appropriate triaging, diagnosis, monitoring, treatment, and palliation of critically ill patients.

Daily rounds by an ICU physician who leads the coordinated work of nurses, pharmacists, respiratory therapists, physiotherapists, dietitians, chaplains, and other physicians appear to improve outcomes. Observational studies suggest that a standardized, goal-oriented approach to care delivered by multidisciplinary clinicians, with explicitly defined roles, an interprofessional perspective, and best practices checklists, can help improve the quality of ICU rounds. Critical care can be optimized by interprofessional leadership, communication, and a positive organizational culture.[1] However, although processes of care may be improved by multifaceted quality improvement interventions with explicit-goal setting and daily checklists, such approaches have not been shown to reduce hospital mortality.[A1] Furthermore, ICU admission is not beneficial for all seriously ill patients, and attempts to increase the use of ICUs for frail elderly patients do not necessarily improve outcomes.[A2]

FLUID RESUSCITATION AND ACUTE KIDNEY INJURY

Intravenous fluids to maintain or to restore intravascular volume are an important component of ICU therapy. Both crystalloid and colloid solutions are in widespread use. Crystalloids are readily available and inexpensive, whereas colloids generally require less volume to achieve a specific physiologic goal.[2]

Fluid replacement with either normal saline or 4% albumin results in similar rates of death, organ failure, and other clinical outcomes, but crystalloids may lower mortality for patients with traumatic brain injury (Chapter 368). Fluid management with hydroxyethyl starch increases the need for renal replacement therapy and increases mortality compared with crystalloid infusions. On the basis of these data, either crystalloid- or albumin-based colloid fluid resuscitation is recommended for most critically ill patients, crystalloids are recommended for head-injured patients, and starches are not recommended.

However, crystalloids differ regarding their pH, tonicity, and osmolality. Hypertonic saline is not recommended for general ICU patients. The most commonly used isotonic crystalloid is 0.9% (normal) saline, which contains a supraphysiologic concentration of chloride. Other isotonic crystalloids, referred to as balanced crystalloids, contain an organic anion (e.g., lactate as in Ringer lactate) and, because their lower chloride content resembles that in human plasma, result in lower chloride concentrations and higher base excess. Data from various randomized trials have not shown a significantly lower all-cause mortality, reduction in ventilator-free days, or decrease in the need for renal replacement therapy with the use of balanced crystalloids.[A3-A5]

The early initiation of renal replacement therapy in critically ill patients with acute kidney injury does not reduce mortality compared with standard therapy.[A6,A7] Furthermore, intensive dialytic renal support therapy is no better than standard dialytic therapy, and intermittent hemodialysis and continuous renal replacement therapy lead to similar clinical outcomes in acute renal failure. It also is important to verify that the prescribed dialysis is received and that standardized measures of the intensity of dialysis are achieved. Some patients—especially patients in an increased catabolic state, trauma patients, and patients receiving glucocorticoids—may require dialysis more than three times per week to achieve adequate therapy (Chapter 117). Neither furosemide nor low-dose dopamine infusions improve outcome, even though low-dose dopamine may temporarily improve metrics of renal physiology.

OXYGEN INTUBATION, SEDATION, ANALGESIA

Critically ill patients commonly require high-flow oxygen, noninvasive mechanical ventilation, or invasive mechanical ventilation. In patients with hypoxemic respiratory failure (Chapter 90), high-flow nasal oxygen by cannula is associated with a lower risk of requiring escalation of oxygen therapy or endotracheal intubation compared with conventional oxygen therapy. However, using high-flow nasal oxygen does not reduce length of stay in the ICU or mortality.[A8]

Among critically ill general medical inpatients, oxygen to maintain a median oxyhemoglobin saturation of 96% is preferred to a median saturation below 94% and is associated with lower rates of mortality, shock, liver failure, and bacteremia than values between 97% and 100%.[A9] In patients with acute respiratory failure requiring at least 10 L of oxygen per minute, a target Pao_2 of 60 mm Hg is as good as a target of 90 mm Hg.[A10] In patients with septic shock (Chapter 94), hyperoxia achieved by administration of Fio_2 of 1.0 also may increase the risk of death.[A11]

Endotracheal intubation, central venous catheterization, postoperative pain management, and other ICU procedures typically require that most patients receive sedation, analgesia, or both. Sedatives (e.g., propofol 5 to 50 μg titrated to effect) and analgesics (e.g., hydromorphone, 0.5 to 2 mg loading dose followed by 0.5 to 3 mg/hour titrated to effect) are used to ensure ongoing tolerance to invasive mechanical ventilation, particularly in patients with shock or severe acute respiratory distress syndrome (ARDS). If pain[3] and anxiety can be well treated, bolus injections are preferred to continuous infusions because of emerging concerns about drug accumulation drug-induced delirium and delayed weaning from the ventilator. Co-analgesics (e.g., acetaminophen up to 3 g/day assuming normal hepatic function) can provide cost-effective pain control and decrease exposure to opiates in critically ill patients.[A12] If patients are receiving drug infusions, daily interruption of sedatives and analgesics, by protocols that provide an opportunity for the patient to be observed safely in a less sedated state, are associated with a shorter duration of mechanical ventilation and ICU length of stay than continuous infusions. A second key component of managing sedation and analgesia is to use a drug titration protocol and nurse-led sedation scale; in these situations, daily interruption of sedation infusions may confer no additional benefit.

Discontinuation of ventilation is affected by sedation and analgesic infusions and vice versa. A daily sedation vacation followed by a spontaneous breathing test increases the days of breathing without assistance and shortens ICU stay and hospital stay compared with usual sedation management plus a daily spontaneous breathing test. In the year after enrollment, patients who were treated with a "wake up and breathe" protocol, which linked daily sedation vacation periods with daily spontaneous breathing trials, had a 32% better survival rate. On the basis of these data, a nurse-implemented sedation and analgesic management scale with daily drug interruption and daily spontaneous breathing trials is recommended for mechanically ventilated critically ill patients.

Following endotracheal extubation, high-flow oxygen via a nasal cannula decreases the risk of reintubation and postextubation respiratory failure compared with conventional oxygen therapy, but it does not decrease ICU length of stay or mortality.[A13]

LONG-TERM OUTCOMES FOR SURVIVORS

Biomarkers of inflammation, residual organ dysfunction, and functional disabilities persist in most ICU survivors even after transfer out of the ICU. Treatments administered in the ICU also have serious sequelae. For example, neuromuscular blockers and corticosteroids may contribute to critical illness polyneuropathy. These problems have particularly serious adverse consequences for frail patients who are deconditioned before hospitalization.

ABSTRACT

Intensive care has become a mainstay of the care of critically ill patients. Challenges associated with intensive care include adequate fluid resuscitation (balanced intravenous solutions are not necessarily better), minimal sedation individualized to the goal for each patient, adequate (but not excessive) oxygen supplementation, low tidal volume ventilation, individualized minimal sedation, a restrictive red blood cell transfusion threshold, early enteral small bowel nutrition, thromboprophylaxis with low-molecular-weight heparin, and insulin therapy to avoid marked hyperglycemia but not targeting normoglycemia. Early renal replacement therapy does not reduce mortality, and intensive dialytic renal support is no better than standard dialysis. Survivors often face a variety of psychological and physical challenges. When patients are unable to make decisions, surrogate decision-makers must be consulted. Patients, family members, and physicians often face difficult decisions about end-of-life care to ensure death with dignity.

KEYWORDS

critical care
intensive care unit
palliative care
death with dignity
complications of critical illness

Although highly selected patients may be discharged home directly from intensive care,[4] the large majority of patients require further hospital care. Although ICU discharge and hospital discharge are milestones in a patient's trajectory, sequelae of critical illness have rarely resolved completely when patients are on the regular hospital unit. For example, over 50% of survivors have new physical, mental, or cognitive problems 1 year after admission,[5] and their caregivers are at risk for anxiety and mood disorders. Residual muscle weakness is common, even 5 years after ICU discharge.

APPLYING EVIDENCE TO PREVENT COMPLICATIONS OF CRITICAL ILLNESS

About 50% of ICU patients have suspected or proven infection. An ICU-acquired infection increases mortality rates by about 30% compared with community-acquired infection.[6] The Surviving Sepsis Campaign has developed evidence-based guidelines that are periodically updated to incorporate recent literature.[7] The proactive implementation of these performance-based improvement strategies at the systems level is associated with better outcomes and lower costs. Evidence-based initial management of a patient with sepsis (Chapter 94) and ARDS (Chapter 90) includes rapid administration of antimicrobial agents when infection is suspected, a target mean arterial pressure of greater than 65 mm Hg,[A14] initial resuscitation with crystalloids, avoidance of starches for resuscitation, initial inotrope infusion of norepinephrine, and corticosteroids for refractory shock.[A15] For patients who are endotracheally intubated, other proven management strategies include low tidal volume ventilation, targeting low plateau pressures below 30 mm H_2O (Chapter 91), head of bed elevation, early enteral small bowel nutrition (Chapter 198), oral antisepsis with chlorhexidine (Chapter 261), thromboprophylaxis with low-molecular-weight heparin (Table 70-3), and insulin therapy aimed at avoiding marked hyperglycemia but not achieving normoglycemia (Chapters 90 and 91). Treatment should avoid early high-frequency oscillation, high positive end-expiratory pressure (unless patients have ARDS), routine use of paralytic agents (Chapter 90),[A16] and antioxidants. Stress ulcer prophylaxis (e.g., pantoprazole 40 mg intravenously daily) can reduce the risk of gastrointestinal bleeding but not overall complications or mortality.[A17] Antimicrobial stewardship is important to reduce the risk of nosocomial infection (Chapter 261) and renal injury.[8]

In mechanically ventilated adults, a strategy of obtaining chest radiographs based on clinical need provides clinical outcomes equivalent to a strategy of routine radiographs, despite about one-third fewer radiographs. Later during the stabilization and recovery phase of critical illness, evidence-based management includes targeted protocol-driven sedation, daily interruption of sedation infusions, and daily spontaneous breathing trials. Low-dose (starting at 0.2 μg/kg/hour and titrated to sedation and agitation) nocturnal intravenous dexmedetomidine can help prevent ICU delirium.[A18]

Neuromuscular weakness is a common complication of ICU care.[9] Physical rehabilitation interventions delivered in the ICU can hasten and improve overall recovery in some patients but have not been shown to reduce mortality. Active mobilization and rehabilitation improves muscle strength at ICU discharge, the probability of walking without assistance at hospital discharge, and the number of days alive and out of the hospital; however, it does not improve quality of life, reduce the duration of mechanical ventilation or length of stay in the ICU or hospital, or change the discharge destination.[A19]

Potential barriers to applying evidence in fast-paced ICUs include a perceived lack of responsibility, unclear decisional authority, and errors of omission. Passive dissemination of information, whether written or verbal, is generally ineffective in modifying physicians' behaviors. More effective strategies to encourage the implementation of evidence-based recommendations are interactive education, audit and feedback, reminders (written or computerized), involvement of local opinion leaders, and multifaceted approaches. In the high-acuity ICU setting, preprinted physician orders may help guide (but not dictate) management (Table 88-1). For example, a statewide intervention coached local safety teams to lead multidisciplinary education about central venous catheter management strategies known to decrease infection risk, including a procedural checklist that incorporated handwashing, full barrier precautions for catheter insertion, chlorhexidine skin cleansing, avoidance of the femoral site, and removal of unnecessary catheters. A multimethod approach including video conferencing, education, provision of algorithms, audit, and feedback can increase adoption of beneficial management strategies in community ICUs.

TABLE 88-1 ICU ADMISSION ORDERS: EXAMPLE FOR A PATIENT WITH UROSEPSIS AND ARDS

MANAGEMENT STRATEGY	ORDERS	REEVALUATE
ACUTE PHASE		
Mechanical ventilation	Target TV 5-7 mL/kg of ideal body weight, PC 16 cm, rate 12, F_{IO_2} 0.7, PEEP 16 cm, plateau pressure <35 cm	PRN
Maintenance fluid	Lactated Ringer 75 mL/hr IV	PRN
Norepinephrine	Titrate to mean arterial pressure >65 mm Hg	PRN
Corticosteroids	Hydrocortisone 50 mg IV q6h while vasopressor dependent	Daily
Sedation	Midazolam 2-8 mg/hr IV, bolus 2-4 mg PRN	PRN
Analgesia	Morphine 1-4 mg IV PRN	PRN
Red blood cell transfusion	Transfuse 1 unit of packed red blood cells if hemoglobin <70 g/L	PRN
Antibiotics	Ampicillin 2 g IV q6h	Daily
Head of bed	45-Degree elevation from horizontal	PRN
Oral antisepsis	Chlorhexidine 15 mL q6h	Daily
Enteral nutrition	10 mL/hr of a commercial balanced feed containing about 1 kcal/mL; increase by 20 mL q4h to 70 mL/hr as tolerated	Daily
Bowel protocol	Individualized for constipation management	PRN
Stress ulcer prophylaxis	Pantoprazole 40 mg IV daily	Daily
Thromboprophylaxis	Dalteparin 5000 U SQ daily	Daily
Intensive insulin therapy if blood glucose >180 mg/dL	50 U insulin in 50 mL NS; start at 0.5 U/hour, repeat glucose q1h for 4 hours, and reassess; target 110-150 mg/dL	Daily
Glucometer calibration	Calibrate glucose from glucometer and central laboratory every morning	Daily
Tests	Glucose q4h when stable, ABG with each ventilator change, other tests as per ICU team	PRN
Monitoring	Arterial catheter for systolic blood pressure, central venous catheter for central venous pressure and mixed venous oxygen saturation, ECG, oximetry, ABGs, sedation scale, Foley catheter, others as per ICU monitoring protocols	PRN
STABILIZATION AND RECOVERY PHASES		
Sedation vacation	Daily interruption of sedation from 7 AM until 9 AM; restart at half prior infusion rate at 9 AM if necessary; aim to discontinue infusion as soon as possible	Daily
Spontaneous breathing trials	Spontaneous breathing trial when weaning readiness criteria met	Daily
Early mobility	Individualized, graduated physiotherapy and occupational therapy	Daily

ABG = arterial blood gas; ARDS = acute respiratory distress syndrome; ECG = electrocardiogram; F_{IO_2} = fraction of inspired oxygen; ICU = intensive care unit; IV = intravenous; NS = normal saline; PC = pressure control; PEEP = positive end-expiratory pressure; PRN = as needed; SQ = subcutaneous; TV = tidal volume.

PREDICTIONS, PREFERENCES, AND PALLIATIVE CARE

The prognosis of many critically ill patients improves once they are in the ICU. For others, treatment responsiveness is delayed or not realized, organ dysfunction evolves but does not resolve, and complications arise. Despite best efforts of the multidisciplinary ICU team, critical illness proves fatal to between 5% and 40% of adults. Approximately 2% of ICU patients discharged to a general inpatient service are readmitted to an ICU within 48 hours and about 4% within 120 hours. When a therapeutic trial of critical care is started, and particularly when it is failing, it is crucial to discuss prognosis openly with families (Chapter 3). Among medical ICU patients older than 80 years at one tertiary care university hospital, ICU mortality was 46%, hospital mortality was 55%, and mortality among hospital survivors was 53% at 2 years. About 15% of patients who are admitted to an ICU have clinical courses that probably should generate discussion about palliative care. Families bring key information about the patient's prior function and preferences.

In the shared decision-making model dominant in many settings today, these exchanges often result in plans to withhold or to withdraw basic or advanced life support. Physicians and the entire health care team must be well trained to discuss prognosis with surrogate decision-makers, to address requests for potentially inappropriate therapies, and to manage any resulting discordance. Mechanical ventilation is the most frequent life support administered to and withdrawn from critically ill patients. Ventilator withdrawal very often precedes death in the ICU. Patients undergoing ventilator withdrawal or who die while mechanically ventilated have a shorter ICU stay than patients successfully weaned from the ventilator. When life support modalities are withdrawn because their further use would be futile, each can be discontinued or weaned, with attendant considerations and cautions (Table 88-2 and E-Table 88-1).

Withdrawal may be guided by the severity of the illness and other physiological characteristics, but it is more heavily influenced by the contemporary life support model that is attentive to a patient's values and the physician's predictions about future quality of life. A patient's status at ICU discharge, particularly orders to limit subsequent medical therapy, is the major predictor of hospital survival. This complexity underscores the need for ICU teams to be expert communicators, sensitive in eliciting patients' preferences (often through family members), timely in relieving suffering, and compassionate in providing dignity to the dying. In today's pluralistic society, administering culturally competent, patient-centered, and family-centered end-of-life care, including respect and expressions of spirituality, is paramount. During the coronavirus disease 2019 (COVID-19) pandemic, this holistic approach to family-centered end-of-life care was particularly challenged by severe restrictions on visitors. Family-support interventions also can reduce ICU length of stay.[A20] A death with dignity in the ICU infers that whereas some treatments may be foregone, care can be enhanced as death ensues. Fundamental to maintaining dignity is the need to understand a patient's unique perspectives on what gives life meaning in a setting replete with depersonalizing devices. The goal is caring for patients in a manner consistent with their age,[10] comorbid conditions, and values at a time of incomparable vulnerability, when they cannot speak for themselves.[11] For patients who are unrepresented (i.e., they lack capacity, do not have an advance directive, do not have an available surrogate decision-maker), a multidisciplinary committee rather than the treating physicians should guide end-of-life care.[12]

TABLE 88-2 CONSIDERATIONS AND CAUTIONS IN THE WITHDRAWAL OF LIFE SUPPORT

ISSUE	RISKS	OTHER CONSIDERATIONS
Weaning from inotropes or vasopressors	No risk of physical distress	May prolong the dying process, particularly if patient requires low doses and this is the only life support withdrawn
Discontinuation of inotropes or vasopressors	No risk of physical distress	Death may not occur quickly if the patient requires low doses, particularly if mechanical ventilation is ongoing Death may occur quickly if the patient requires high doses, with or without withdrawal of mechanical ventilation
Weaning from mechanical ventilation	Low risk of dyspnea	May prolong the dying process, particularly if the patient requires low pressure settings or low oxygen levels and this is the only life support withdrawn
Discontinuation of mechanical ventilation	Risk of dyspnea	Death may not occur quickly if the patient requires low pressure settings or low oxygen levels Death may occur quickly if the patient requires high pressure settings or high oxygen levels Preemptive sedation is typically needed to blunt air hunger due to rapid changes in mechanical ventilation
Extubation	Risk of dyspnea Risk of stridor (steroids) Risk of airway obstruction (jaw thrust) Risk of noisy breathing (glycopyrrolate)	Avoids discomfort and suctioning of endotracheal tube Can facilitate oral communication Informing families about possible physical signs after extubation can prepare and reassure them Allows for the most natural appearance Not advised if the patient has hemoptysis
Discontinuation of renal replacement therapy	Low risk of physical distress	Death may take several days if this is the only advanced life support withdrawn

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E-TABLE 88-1 PROCEDURES TO ENSURE PATIENT DIGNITY BEFORE WITHDRAWAL OF LIFE SUPPORT

Prepare staff members

- Review the planned procedures in detail with all relevant staff members.
- Ensure that the referring physician is aware of the plans, if not already engaged.
- Ensure that spiritual care is offered, if not already engaged.
- Remind staff members that all their actions should respect the dignity of the patient.
- Remind staff members that the patient and family are the unit of care.
- Alert the charge nurse to the planned withdrawal of life support.
- Schedule staff to maximize continuity of care during the dying process, if possible.
- Ensure that the bedside nurse is not also assigned to another acutely ill patient, if possible.
- Ensure that the bedside nurse is experienced in palliative care; if not, change the assignment or arrange for supervision by a nurse experienced in palliative care.
- Ensure that the respiratory therapist is experienced in palliative care; if not, arrange for supervision by a respiratory therapist experienced in palliative care.
- Introduce the relevant house staff members to the patient and family.
- Introduce the respiratory therapist to the patient and family, when applicable.
- Ensure that physicians are readily available and do not abandon the patient or family.
- Ensure that staff members minimize unnecessary noise immediately outside the room.

Prepare the patient's room

- Consider the comfort of the patient and family (e.g., lighting, temperature, personal items).
- Liberalize visiting restrictions (e.g., timing, duration, number of visitors).
- Minimize unnecessary routine tasks (e.g., bathing, turning).
- Remove unnecessary equipment from the room.
- Bring additional chairs into the room, if necessary.
- Lower guard rails above the bed, if they are up.
- Humanize and personalize the room as much as possible.
- Secure a quiet room for the family away from the bedside.

Prepare the patient

- Position the patient as comfortably as possible.
- Honor requests for cultural, spiritual, and religious rituals.
- Discontinue unnecessary monitoring (e.g., oximetry), devices (e.g., feeding tubes), tests (e.g., blood work), and treatments (e.g., enteral nutrition).
- Change remaining monitoring to remote and dim the screen lighting (e.g., ECG tracing).
- Discontinue medications that do not provide comfort and provide those that do.
- Ensure that the patient is as calm and distress-free as possible before proceeding to withdraw life support.

Prepare the family

- Following the prior compassionate conversations with the family, remind them of what they may observe during the dying process (e.g., unusual sounds; changes in skin color; continued, agonal, or noisy breathing).

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89 RESPIRATORY MONITORING IN CRITICAL CARE

JAMES K. STOLLER AND NICHOLAS S. HILL

PHYSICAL EXAMINATION

The physical examination can provide important information about the patient's ventilation and oxygenation. Ventilation can be assessed by recording the respiratory rate (normally 12 to 20 breaths/minute in adults) as well as by closely inspecting the pattern of chest wall movement during inspiration and by noting the use of accessory inspiratory muscles (e.g., the scalene, trapezius, and sternocleidomastoid muscles). Hypopnea (shallow or slow breathing) or a slowed respiratory rate (bradypnea) can indicate decreased ventilation. Shallow breathing may relate to muscle weakness (Chapter 389) or increased lung stiffness, which is commonly accompanied by a compensatory increase in the respiratory rate to maintain ventilation. Bradypnea may relate to a suppressed respiratory drive (e.g., excessive use of narcotics, slowing the respiratory rate). Conversely, sustained tachypnea (e.g., >35 breaths/minute in an adult) can indicate ongoing increased work of breathing, impending respiratory failure, and the need for mechanical assistance, such as noninvasive ventilation or intubation and mechanical ventilation, depending on the etiology of the respiratory failure.

Contraction of the sternocleidomastoid muscles or scalene muscles, often with a seated, bent posture, is called the tripod sign (E-Fig. 89-1). This response indicates inadequate diaphragmatic function, most commonly in the setting of emphysema with associated diaphragmatic flattening, which causes a mechanical disadvantage of diaphragmatic contraction. In this circumstance, patients may demonstrate Hoover sign, which is inspiratory retraction of the rib cage at the level of the zone of apposition, where the diaphragm inserts on the chest wall.

The physical examination of the nail beds and lips may also reveal cyanosis, which suggests hypoxemia. Cyanosis occurs when saturation falls, but it requires the presence of 5 g of desaturated hemoglobin. As such, polycythemic patients may show cyanosis with relatively high oxyhemoglobin saturation values, whereas patients with profound anemia may not demonstrate cyanosis even in the face of low values of oxyhemoglobin saturation.

SYSTEMIC ARTERIAL BLOOD GAS ANALYSIS

Sampling of arterial blood, either through a percutaneous arterial puncture or by withdrawal of blood from an indwelling arterial catheter, provides important information about the patient's oxygenation and ventilation status as well as the acuity of and compensation for derangements. The partial pressure of carbon dioxide ($Paco_2$) reflects ventilation, the elimination of carbon dioxide. In many but not all cases, $Paco_2$ is close to the mixed alveolar $Paco_2$. The $Paco_2$ in the arterial blood is closely related to the ratio of metabolic carbon dioxide production to alveolar ventilation:

$$Paco_2 = (K)(CO_2 \text{ production rate})/(\text{alveolar ventilation } [V_A]) \quad (1)$$

The partial pressure of oxygen (Pao_2) reflects the level of oxygenation. Normal levels of oxygenation are defined by the alveolar-arterial oxygen gradient, $P(A\text{-}a)o_2$, which is calculated as

$$P(A\text{-}a)o_2 = Fio_2(P_B - P_{H_2O} \text{ at standard pressure and body temperature}) - (Pao_2 + Paco_2/\text{respiratory quotient}) \quad (2)$$

where the respiratory quotient equals the number of moles of carbon dioxide produced for each mole of oxygen consumed (generally ~0.8 under normal metabolic conditions at rest but variable with dietary intake and metabolic rate). The normal value of the alveolar-arterial oxygen gradient varies with age and position and can be approximated by the simple equation

$$P(A\text{-}a)o_2 = (\text{age}/4) + 4 \quad (3)$$

Normal age-related values of Pao_2 in the sitting position can be determined by the equation

$$Pao_2 \text{ sitting} = 104.2 - (0.27 \times \text{age in years}) \quad (4)$$

Normal values of Pao_2 are generally in the range of 70 to 95 mm Hg, depending on the patient's age. Nevertheless, a goal of a Pao_2 of 60 mm Hg is as good as a goal of 90 mm Hg in intensive care unit (ICU) patients who have acute hypoxemic respiratory failure that requires at least 10 liters of oxygen per minute.[A1]

The $Paco_2$ helps assess the adequacy of the patient's ventilation. At sea level, normal values of $Paco_2$ range from 35 to 45 mm Hg. Values of $Paco_2$ below 35 mm Hg indicate hyperventilation, either as a primary respiratory event (e.g., with anxiety) or in response to another insult (e.g., hypoxemia, sepsis, liver disease). Similarly, values of $Paco_2$ exceeding 45 mm Hg indicate hypoventilation, hypercapnia, and respiratory acidosis, which may result either from suppression of the ventilatory drive (Chapter 74) (e.g., excess narcotics; Chapter 365) or from respiratory insufficiency (e.g., respiratory muscle weakness; Chapter 389).

Assessment of the patient's bicarbonate level (HCO_3^-) helps define the chronicity of changes in the patient's $Paco_2$, where the value of bicarbonate is defined by the Henderson-Hasselbalch equation:

$$pH = 6.1 + \log_{10}[HCO_3^-]/0.003\, Paco_2 \quad (5)$$

Acute increases in $Paco_2$ drive the normal kidney to retain bicarbonate (Chapter 104), whereas acute decreases in $Paco_2$, as in hyperventilation from anxiety or liver disease, would be expected to cause the normal kidney to waste bicarbonate to preserve the body's pH (normally 7.35 to 7.45).

The clinician can also assess whether the patient's ventilatory response to metabolic acidosis is appropriate or inadequate by the Winter equation, which predicts the expected $Paco_2$ in the face of a decreased bicarbonate from a metabolic acidosis (Eq. 6). Specifically, a measured $Paco_2$ above the expected value indicates an inadequate ventilatory response, whereas a value of $Paco_2$ that falls within the expected range indicates an expected, appropriate ventilatory response to the metabolic derangement (i.e., the acidosis).

$$Paco_2 = (1.5[HCO_3^-] + 8) \pm 2 \quad (6)$$

When the patient is hypercapnic and hypoxemic, a useful step is to calculate the ambient air $P(A\text{-}a)o_2$ and to determine whether it is normal or increased for the patient's age. Of the six mechanisms of hypoxemia, only two (hypoventilation and breathing decreased ambient oxygen, as at altitude or from a hypoxic gas mixture) are associated with a preserved $P(A\text{-}a)o_2$ (Table 89-1). Under clinical circumstances at sea level, hypoxemia in the face of a normal $P(A\text{-}a)o_2$ indicates that the patient's hypoxemia is caused by hypoventilation and should prompt the clinician to consider the various causes of suppressed respiratory drive (Chapter 74) or respiratory insufficiency that interferes with a normal ventilatory response (e.g., respiratory muscle weakness; Chapter 389).[1]

Increasingly, venous blood gases (VBGs) are being used instead of arterial blood gases (ABGs) because they are easier and safer to obtain.[2] Peripheral venous blood may be used, but central VBGs are considered more accurate. The correlation with arterial pH has been good, with venous pH averaging about 0.03 lower; $Pvco_2$ and $Paco_2$ correlate less well, with $Pvco_2$ averaging 3 to 8 mm Hg higher and not being reliably comparable to $Paco_2$. VBGs are considered unacceptably inaccurate in hypotensive patients and patients with severe hypercapnia, but a normal $Pvco_2$ may be used to exclude hypercapnia.

TABLE 89-1 PHYSIOLOGIC MECHANISMS OF HYPOXEMIA AND ACCOMPANYING VALUES OF THE ALVEOLAR-ARTERIAL OXYGEN GRADIENT ON BREATHING OF ROOM AIR

MECHANISM/ PHYSIOLOGIC PROCESS	EXAMPLE	ALVEOLAR-ARTERIAL OXYGEN GRADIENT ON ROOM AIR
Ventilation-perfusion mismatch	Pneumonia	Increased
Diffusion impairment	Interstitial lung disease	Increased
Anatomic right-to-left shunt	Pulmonary arteriovenous malformation	Increased
Hypoventilation	Neuromuscular weakness	Normal
Breathing decreased ambient oxygen (from either hypobaric conditions [e.g., altitude] or breathing a gas mixture with decreased inspired oxygen fraction)	Altitude exposure	Normal
Diffusion-perfusion impairment	Hepatopulmonary syndrome	Increased

ABSTRACT

Monitoring of the respiratory system involves a broad array of assessment techniques, ranging from low-technology approaches such as a careful physical examination, to sophisticated technologies to monitor oxygenation and ventilation.

KEYWORDS

respiratory monitoring
blood gases
carbon dioxide production
hypoxemia
hypercapnia
respiratory compliance
work of breathing

E-FIGURE 89-1. This patient with chronic obstructive pulmonary disease (COPD) demonstrates the posture referred to as the tripod sign. The patient is sitting forward with his hands on his knees to provide a mechanical advantage to the accessory muscles of ventilation, such as the sternocleidomastoid and trapezius. Diaphragmatic flattening accompanying COPD lessens the diaphragm's ability to generate pressure, thereby resulting in increased dependence on the accessory muscles of respiration and leading to this posture.

PULSE OXIMETRY

Pulse oximetry is a noninvasive method to assess arterial blood oxygenation.[3] The percentage of hemoglobin that is oxygenated is measured by passing light of two different wavelengths (660 nm [for deoxyhemoglobin] and 940 nm [for oxyhemoglobin]) through a blood-carrying tissue (e.g., finger, earlobe, forehead), identifying the pulsatile component (which contains arterial blood and background tissue elements), and subtracting the nonpulsatile component to isolate the arterial component. The device can estimate the percentage of oxygenated hemoglobin over the range of 100% to about 75%. By comparison smart phone pulse oximeters have, to date, been unreliable.[4]

Clinicians must be aware of the diagnostic accuracy of pulse oximetry in assessing hypoxemia and, in particular, the risk that pulse oximetry measurements may overestimate true arterial oxygenation. In one large series of over 48,000 paired measurements of pulse oximetry and arterial blood gases, the prevalence of "occult hypoxemia" (i.e., a pulse oximetry measurement of 92% to 96% with a paired arterial oxygen saturation of <88%) was more frequent among Black individuals (12% to 17%) than among White individuals (3.6% to 6.2%), apparently because darker skin affects the accuracy of the devices. Blue or green nail polish may have the same effect.[5,6] Thus, clinicians must remain vigilant for hypoxemia even when pulse oximetry measurements appear acceptable, especially in Black patients. Concern about occult hypoxemia should prompt obtaining an arterial blood gas.

Most clinicians also regard the output of pulse oximeters to be inaccurate for percentage saturation values of less than 70%, although the probability of a low saturation should not be discounted (Fig. 89-1). Pulse oximetry measurements may help identify significant drops in Pa_{O_2} below 60 to 65 mm Hg but are relatively insensitive to changes in Pa_{O_2} from 90 to 65 mm Hg.

Prolonged hypoxemic episodes are common in postoperative patients after noncardiac surgery, but it is not clear whether routine continuous monitoring will improve clinical outcomes. Similarly, the true value of pulse oximetry for decision making in the emergency department setting remains uncertain, although even asymptomatic hypoxemia by pulse oximetry appears to be a poor prognostic sign in patients with coronavirus disease 2019 (COVID-19).[7] When patients are markedly tachypneic, a reasonably normal pulse oximetry should not be reassuring because of the patient's difficulty in maintaining oxygenation.

CARBON DIOXIDE MONITORING: CAPNOMETRY AND TRANSCUTANEOUS CARBON DIOXIDE MEASUREMENT

The fraction of carbon dioxide in exhaled air can be measured in real time by infrared capnometry.[8] Partial pressures can then be calculated on the basis of knowledge of atmospheric pressure. The expiratory capnogram (E-Fig. 89-2) represents a continuous plot of exhaled P_{CO_2} versus time or exhaled volume and reflects the sequential appearance of gas from various compartments (e.g., the endotracheal tube, central airways, and finally the alveoli, where the P_{CO_2} is in equilibrium with end-capillary blood). The shape of the capnogram provides clues to the presence of chronic obstructive pulmonary disease, in that emptying of areas of lung with increased dead space (see later) can cause the capnogram to have a rising contour (E-Fig. 89-2A), whereas the attainment of a so-called alveolar plateau on the normal capnogram (E-Fig. 89-2B) indicates that alveolar gas is composed of a mix with a relatively small contribution from areas of increased dead space. The value of P_{ECO_2} measured at the end of expiration on the capnometer (i.e., the highest value recorded) represents the end-tidal P_{ETCO_2}. Notably, the value of P_{ETCO_2} is always below the Pa_{CO_2} because there is a normal component of dead space ventilation (V_D/V_T) related to the anatomic dead space of the conducting airways (i.e., the trachea and airways to the level of gas-exchanging alveolar ducts and alveoli). The numeric difference between the Pa_{CO_2} and the mixed exhaled carbon dioxide tension (P_{ECO_2}, defined as the partial pressure of carbon dioxide that would be measured in a balloon in which the entire exhaled volume is gathered) is related to the magnitude of dead space ventilation (i.e., areas of the lung that are ventilated without accompanying blood flow, normally ~0.3 to 0.4) as defined by the Bohr equation:

$$V_D/V_T = (Pa_{CO_2} - P_{ECO_2})/Pa_{CO_2} \quad (7)$$

The difference between Pa_{CO_2} and P_{ECO_2} may be as low as several millimeters of mercury, but changing conditions of ventilation-perfusion matching (e.g., with pulmonary embolism [Chapter 68], atelectasis [Chapter 78]) may change the gradient over time. Measurement of the P_{ETCO_2} can be clinically useful to assess trends, to help detect esophageal intubation, to detect disconnection from the ventilator, and to detect perfusion during cardiopulmonary resuscitation, but it is not a reliable surrogate for Pa_{CO_2}. Furthermore, measurement of the dead space fraction has prognostic value in patients with early acute respiratory distress syndrome (Chapter 90), in whom rising dead space is linearly related to increased mortality risk. Measurement of transcutaneous P_{CO_2} by heated probes applied to the skin is an alternative noninvasive method for estimating P_{CO_2}, especially during anesthesia or sleep studies. However, these measures are not reliable for determining absolute values or trends in ICU settings, where patients are unstable hemodynamically or have respiratory failure owing to parenchymal lung disease.

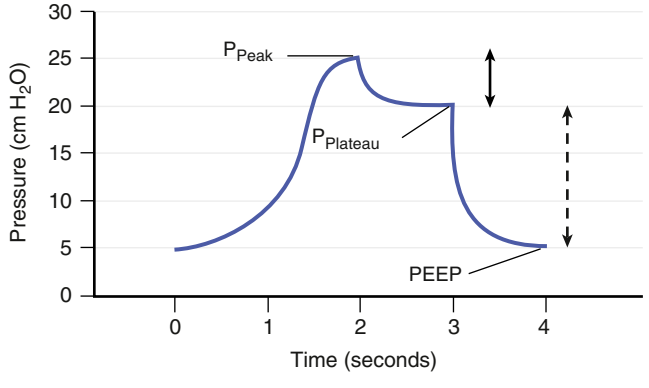

FIGURE 89-1. Illustration of inspiratory hold maneuver to determine plateau pressure ($P_{plateau}$). Airway pressure during volume-targeted mechanical ventilation rises as the tidal volume is delivered and reaches a peak. An inspiratory hold is initiated at peak pressure that prevents exhalation, so pressure falls to a "plateau" of about 20 cm H_2O. The drop in pressure reflects the pressure needed to overcome airway resistance. After slightly more than 1 second, the inspiratory hold is released, and airway pressure falls to positive end-expiratory pressure (PEEP). The difference between $P_{plateau}$ and PEEP is used to calculate static compliance by dividing the difference into the tidal volume.

ARTERIAL OXYGEN CONTENT AND SYSTEMIC OXYGEN DELIVERY

Arterial (Ca_{O_2}) and venous oxygen content (Cv_{O_2}) are used to calculate cardiac output by the Fick equation (Eq. 8), which is an alternative to determining cardiac output by the thermodilution method with a flow-directed pulmonary artery (Swan-Ganz) catheter (Chapter 59). The Fick equation is

$$\text{Oxygen consumption}\,(\text{mL } O_2/\text{min}) = \text{cardiac output} \times (Ca_{O_2} - Cv_{O_2}) \quad (8)$$

where oxygen content (C) has the units of milliliters of oxygen per 100 mL of blood and hemoglobin units are grams per 100 mL of blood, and is calculated as:

$$\text{Oxygen content} = 1.34\,(\text{hemoglobin})(\%\ \text{saturation}) + 0.0031(Pa_{O_2}) \quad (9)$$

Under normal conditions (with, for example, an arterial percentage saturation of 95% and a hemoglobin level of 15 g/100 mL and an oxygen consumption of 250 mL/minute), arterial oxygen content is about 20 mL/100 mL, and because mixed venous oxygen saturation is about 75%, central venous oxygen content is about 15 mL/100 mL, making the normal arteriovenous oxygen content difference with a normal cardiac output about 5 mL/100 mL.

Systemic oxygen transport defines the amount of oxygen delivered to the tissues and multiplies the arterial oxygen content by the cardiac output:

$$\text{Systemic oxygen transport}\,(\text{mL/min}) = \text{cardiac output} \times Ca_{O_2} \quad (10)$$

where the normal value is about 1000 mL/minute.

MEASURING VENTILATION: MINUTE VENTILATION AND ALVEOLAR VENTILATION

Minute ventilation ($\dot{V}_E$), which is the amount of gas exhaled from the airway per minute, is the product of the respiratory rate times the exhaled tidal volume, measured at body temperature and standardized to barometric pressure at sea level, saturated with water vapor (BTPS). The BTPS is a standard condition under which many measurements for most pulmonary function equipment and mechanical ventilators are made. These devices use an airflow meter to measure exhaled airflow and integrate the signal to derive tidal volume. An alternative way to measure tidal volume in an intensive care setting is respiratory impedance plethysmography, which uses calibrated magnetic coils in belts strapped around the chest and abdomen to monitor respiratory frequency and changes in thoracic volume.

Alveolar ventilation is the rate of gas delivery in liters per minute to gas-exchanging areas of the lung (i.e., the alveoli and alveolar ducts). The portion of minute ventilation that fails to undergo gas exchange is dead space ventilation ($\dot{V}_D$) and is determined by Eq. 7. Minute, alveolar ($\dot{V}_A$), and dead space ventilation are related as follows:

$$\dot{V}_E = \dot{V}_A + \dot{V}_D \quad (11)$$

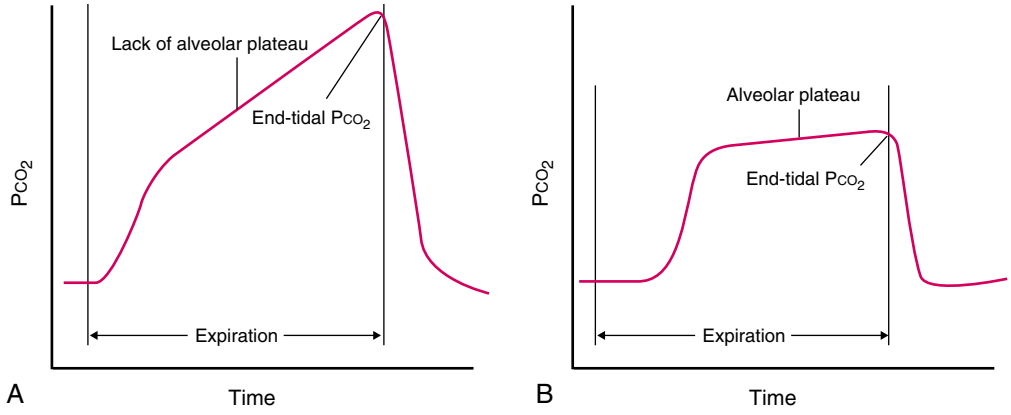

E-FIGURE 89-2. **Abnormal and normal end-tidal capnograms. A,** Illustration of a capnogram from a patient with chronic obstructive pulmonary disease in which the end-tidal P_{CO_2} rises throughout expiration as carbon dioxide excretion varies from different parts of the lung. **B,** Illustration of a normal capnogram in which the end-tidal P_{CO_2} reaches a plateau with more uniform carbon dioxide excretion. The end-tidal P_{CO_2} is the highest point of the alveolar plateau.

It follows that conditions such as acute lung injury and acute respiratory distress syndrome (ARDS; Chapter 90) that are associated with very high dead space ratios require high V_E to achieve a sufficient V_A. Conversely, conditions that cause neuromuscular weakness (Chapter 389) are associated with small tidal volumes and have a high V_D/V_T ratio because the anatomic dead space is fixed and constitutes a higher fraction of the diminished tidal volume.

MEASURING CARBON DIOXIDE PRODUCTION

Measurement of carbon dioxide production is sometimes referred to as indirect calorimetry because it provides an index of metabolic rate and permits estimation of calorie requirements. Metabolic "carts" that simultaneously measure not only carbon dioxide production but also oxygen consumption and respiratory quotient are commonly used clinically to estimate metabolic needs to prescribe nutritional repletion (Chapter 198). The normal baseline carbon dioxide production is in the range of 200 mL/minute but is subject to wide variation because of hypermetabolic states commonly encountered in critically ill patients, such as sepsis and systemic inflammatory response syndrome.

The respiratory quotient also gives insight into the composition of feedings because carbohydrates yield a respiratory quotient of 1, whereas fatty acids yield a ratio of 0.8 and amino acids a ratio of 0.7. Thus, balanced nutrition should yield a respiratory quotient of approximately 0.85. A respiratory quotient of 1 in combination with a high carbon dioxide production suggests that the dietary proportion of carbohydrates is excessive.

MEASURING RESPIRATORY COMPLIANCE

Respiratory compliance is the change in respiratory system volume induced by a change in applied pressure (i.e., inspiratory pressure) and is the mathematical inverse of elastance. Compliance diminishes in conditions like lung injury and ARDS (Chapter 90) or pulmonary fibrosis (Chapter 80), in which diffuse inflammation and scarring alter lung structure and contribute to increased lung "stiffness." Static respiratory compliance is measured in patients receiving volume-limited mechanical ventilation by imposing a brief inspiratory hold at end inspiration. Assuming the patient has no spontaneous breathing effort, the airway pressure measured when airflow ceases is referred to as the plateau pressure ($P_{plateau}$). The difference between this pressure and the positive end-expiratory pressure (PEEP) is taken as the driving pressure required to deliver the tidal volume (see Fig. 89-1). Static respiratory system compliance (C_{RS}) is then calculated as

$$C_{RS} = \Delta V(\text{exhaled tidal volume})/\Delta P\,(P_{plateau} - \text{PEEP}) \qquad (12)$$

This compliance not only reflects the status of the lung but also includes contributions of the chest wall and abdomen. Thus, patients with chest wall deformities or morbid obesity have lower values of respiratory compliance even in the absence of lung abnormalities (Chapter 86). The normal respiratory compliance is in the range of 50 to 70 mL/cm H_2O, and patients with ARDS usually have values of C_{RS} of less than 30 cm H_2O. If respiratory compliance is below 20 to 25 cm H_2O, weaning from mechanical ventilation (Chapter 91) is difficult or impossible because of the high work of breathing requirements (see later).

MEASURING RESPIRATORY DRIVE

The respiratory center, located in the pons and medulla, regulates respiratory drive.[9] Hypercapnia is a strong stimulus to ventilation (Chapter 74). This response may be blunted by chronic carbon dioxide retention or by drugs like narcotics. Hypoxemia is a weaker ventilatory stimulus that is potentiated by hypercapnia and blunted by hypocapnia.

Thus, respiratory drive can be assessed as the response to carbon dioxide in the blood in the hypercapnic ventilatory response. In one technique to measure respiratory drive, the patient rebreathes his or her exhaled air while minute ventilation and P_{ETCO_2} are monitored; a graph relating P_{ETCO_2} with minute ventilation is used to measure respiratory drive. However, this technique is impractical in an ICU setting. Another technique is to measure the negative swing in airway pressure during the first 100 msec of inspiration (P_{100}). This technique avoids the problem of diminished ventilatory response due to airway obstruction, but it is still subject to blunting by some drugs and still underestimates drive in patients with respiratory muscle weakness, a common problem in the ICU. In patients who are failing to be weaned from mechanical ventilation, a practical way to assess the integrity of respiratory drive is to determine whether the respiratory rate increases, usually into the range of 30 to 40 breaths/minute, as P_{ACO_2} rises after the patient is removed from ventilatory support.

MEASURING RESPIRATORY MUSCLE STRENGTH

Respiratory muscle weakness has long been recognized as a contributor to respiratory failure and failure to be weaned from mechanical ventilation in the ICU (Chapter 91). This recognition has intensified in recent years with the increased awareness of ICU-acquired weakness after critical illness. However, measurement of respiratory muscle strength remains challenging because of the need to differentiate between actual weakness and reduced muscle performance due to inability to cooperate or to exert a full inspiratory effort.

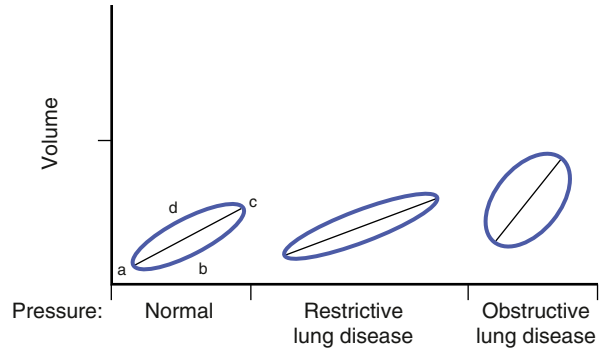

FIGURE 89-2. Pressure-volume curves illustrating components of work in a normal subject and in patients with restrictive or obstructive disease. The line between *a* and *c* represents elastic work as the lung expands, but this work is a net zero because static forces return the lung to its neutral position. The restrictive curve is flatter than normal because the lung is stiffer and volume changes less for a given unit change in pressure. The obstructive curve has a greater slope because (e.g., in emphysema) the lung is more compliant and starts inhalation from a higher volume. The *abc* curve represents resistive work during inspiration, and *cda* represents resistive work during exhalation. Resistive work during exhalation is greater in patients with obstructive lung disease.

The most commonly used measures of respiratory muscle strength are the maximal inspiratory and expiratory pressures (P_{I}max or MIP and P_{E}max or MEP). These values are obtained by measuring the pressure change with a manometer when the patient inhales with maximal force from residual volume and exhales with maximal force from total lung capacity. Normal MIP is usually more negative than −75 cm H_2O, and normal MEP is usually more positive than 125 cm H_2O. When the value for MIP is less negative than −20 or −30 cm H_2O, weaning from mechanical ventilation may be difficult, and values less positive than 60 cm H_2O suggest cough insufficiency. However, these values have poor predictive value for weaning of mechanically ventilated patients because many of these patients are unable to cooperate. This problem may be addressed by attaching a one-way valve to the end of an endotracheal tube that permits exhalation but not inhalation and then measuring the inspiratory pressure efforts for 20 to 25 seconds.

MEASURING WORK OF BREATHING

Work of breathing is the product of pressure and volume for each breath (Fig. 89-2). The components include work needed to overcome elastic recoil of the lung and to displace the chest wall and abdomen as well as work needed to overcome airway resistance and lung viscosity and work needed to overcome inertia. With restrictive lung diseases, the inspiratory work of breathing is increased because of the decreased lung elasticity. With obstructive diseases, the work of breathing is increased because of increased airway resistance.

In clinical settings, a more practical way to assess the inspiratory work of breathing is to calculate the pressure-time product (in cm H_2O-seconds). The pressure-time product can be calculated by the decrease in airway pressure during inspiration, esophageal pressure (measured with an esophageal balloon manometer), or transdiaphragmatic pressure (measured with esophageal and gastric balloon manometers) as an index of diaphragmatic work. The work can be calculated as work of breathing per breath or as work of breathing per minute by multiplying the work per breath by the respiratory frequency. Commercially available devices using esophageal manometry automatically calculate the inspiratory work of breathing, which may be of some value in assessing the likelihood of weaning from mechanical ventilation. If the drop in inspiratory pressure necessary to achieve an adequate tidal volume is too large, the calculated work of breathing will be high, and the likelihood of successful weaning will be reduced.

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90 ACUTE RESPIRATORY FAILURE

MICHAEL A. MATTHAY AND LORRAINE B. WARE

DEFINITION

Acute respiratory failure occurs when dysfunction of the respiratory system results in abnormal gas exchange that is potentially life-threatening. Each element of this definition is important to understand. The term *acute* implies a relatively sudden onset (from hours to days) and a substantial change from the patient's baseline condition. *Dysfunction* indicates that the abnormal gas exchange may be caused by abnormalities in any element of the respiratory system (e.g., a central nervous system abnormality affecting the regulation of breathing or a musculoskeletal thoracic abnormality affecting ventilation [Chapter 71]) in addition to abnormalities of the lung itself. The term *respiration* refers, in a broad sense, to the delivery of oxygen (O_2) to metabolically active tissues for energy use and the removal of carbon dioxide (CO_2) from these tissues (Table 90-1). Respiratory failure is a failure of the process of delivery of O_2 to the tissues or removal of CO_2 from the tissues.[1] Abnormalities in the periphery (e.g., cyanide poisoning, circulatory shock, pathologic distribution of organ blood flow in sepsis) can lead to tissue hypoxia; although these conditions represent forms of respiratory failure in the broadest terms, this chapter focuses on respiratory failure resulting from dysfunction of the lungs, chest wall, and control of respiration.

PATHOBIOLOGY

Abnormal gas exchange is the physiologic hallmark of acute respiratory failure, which can be classified in several ways (Table 90-2). Although gas exchange can be abnormal for either oxygenation or CO_2 removal, significant hypoxemia is nearly always present when patients with acute respiratory failure breathe ambient air. If CO_2 is retained at a potentially life-threatening level under these conditions, it will be accompanied by significant hypoxemia (see later). The *life-threatening* aspect of the condition places the degree of abnormal gas exchange in a clinical context and calls for urgent treatment.

The diagnosis of acute respiratory failure requires a significant change in arterial blood gases or arterial oxygen saturation from baseline. Many patients with chronic respiratory problems can function with blood gas tensions that would be alarming in a physiologically normal individual. Over time, patients with so-called chronic respiratory failure or chronic respiratory insufficiency develop mechanisms to compensate for inadequate gas exchange. Conversely, chronic respiratory failure makes patients vulnerable to respiratory insults (e.g., pneumonia, heart failure) that could be easily tolerated by a previously healthy individual.

In acute respiratory failure, the O_2 content in the blood (available for tissue use) is reduced to a level at which the possibility of end-organ dysfunction, as a result of inadequate oxygen delivery, increases. The value of the partial pressure of O_2 in the arterial blood (Pa_{O_2}) that demarcates this vulnerable zone is often considered to be the point of the oxyhemoglobin dissociation relationship at which any further decrease in the Pa_{O_2} results in sharp decreases in the amount of hemoglobin saturated with O_2 (Sa_{O_2}) and in the arterial blood O_2 content (Ca_{O_2}). Thus, acute respiratory failure is often defined in practice as occurring when the Pa_{O_2} is less than about 55 to 60 mm Hg (Fig. 90-1). However, it is important to note that the oxyhemoglobin dissociation curve of whole blood, which governs the partial pressure at which O_2 is unloaded to the tissues, is a critical determinant of how much O_2 is available for the cells and their mitochondria at a given Pa_{O_2}. Conditions such as fever or acidosis can shift the curve rightward. Other than under conditions of an extremely hypoxic environment (e.g., in utero or on the summit of Mt. Everest), however, the enhanced ability to unload O_2 at the tissue level more than compensates for small decreases in the amount of O_2 picked up in the lungs when the oxyhemoglobin dissociation curve is shifted rightward. With a leftward shift in the curve, O_2 is bound more tightly to hemoglobin, so less O_2 is available for tissue delivery.

These physiologic and clinical considerations imply that any definition of acute respiratory failure based on an absolute level of Pa_{O_2} is arbitrary. A healthy, young, conditioned individual climbing at high altitude may have a Pa_{O_2} of less than 50 mm Hg because of the reduction in inspired O_2 pressure. This individual is not in acute respiratory failure, even though the Pa_{O_2} may be in the low 40s. A patient who has chronic obstructive pulmonary disease (COPD) and whose usual range of Pa_{O_2} is 50 to 55 mm Hg would not be considered to be in acute respiratory failure if the Pa_{O_2} was 50 mm Hg. However, if a patient's usual Pa_{O_2} is 80 mm Hg, a sudden drop to a Pa_{O_2} of 50 to 55 mm Hg could be associated with a substantial risk for a further life-threatening reduction in oxygenation; this patient should be considered to have acute respiratory failure.

Traditionally, the level of arterial CO_2 partial pressure (Pa_{CO_2}) that defines acute respiratory failure has been 45 mm Hg or greater, if it is accompanied by arterial acidosis with a pH of less than about 7.35. The Pa_{CO_2} is linked to

TABLE 90-1 ABBREVIATIONS COMMONLY USED IN ACUTE RESPIRATORY FUNCTION

ABG	Arterial blood gas or arterial blood gas analysis
ARDS	Acute respiratory distress syndrome
ARF	Acute respiratory failure
cm H_2O	Centimeters of water
Ca_{O_2}	Content of oxygen in arterial blood
Cc_{O_2}	Content of oxygen in end-capillary blood
CO_2	Carbon dioxide
COPD	Chronic obstructive pulmonary disease
CPAP	Continuous positive airway pressure (used when positive pressure during exhalation is applied with spontaneous ventilation)
Cv_{O_2}	Content of oxygen in mixed venous blood
F_{IO_2}	Fraction of inspired oxygen
g/dL	Grams per deciliter
HbO_2	Saturation of hemoglobin by oxygen
L/min	Liters per minute
mL/kg	Milliliters per kilogram
mL/min	Milliliters per minute
mm Hg	Millimeters of mercury
NIPPV	Noninvasive positive-pressure ventilation
O_2	Oxygen
$P(A\text{-}a)o_2$	Difference of partial pressure of oxygen between mean alveolar gas and arterial blood (alveolar-to-arterial oxygen difference)
P_{ACO_2}	Partial pressure of carbon dioxide in alveolar gas
Pa_{CO_2}	Partial pressure of carbon dioxide in arterial blood
P_{AO_2}	Partial pressure of oxygen in alveolar gas
Pa_{O_2}	Partial pressure of oxygen in arterial blood
Pa_{O_2}/F_{IO_2}	Ratio of partial pressure of oxygen in arterial blood to fraction of inspired oxygen
PBW	Predicted body weight
Pc_{co2}	Partial pressure of carbon dioxide in end-capillary blood
P_{CO_2}	Partial pressure of carbon dioxide
Pc_{o2}	Partial pressure of oxygen in end-capillary blood
PEEP	Positive end-expiratory pressure (used when positive pressure during exhalation is applied with mechanical ventilation)
P/F	Pa_{O_2}/F_{IO_2} ratio
P_{IO_2}	Partial pressure of oxygen in inspired gas
P_{O_2}	Partial pressure of oxygen
Pv_{CO_2}	Partial pressure of carbon dioxide in mixed venous blood
Pv_{O_2}	Partial pressure of oxygen in mixed venous blood
$\dot{Q}$	Blood flow or perfusion
RR	Respiratory rate
Sa_{O_2}	Percentage of saturation of hemoglobin by oxygen in arterial blood
$\dot{V}$	Ventilation
$\dot{V}/\dot{Q}$	Ventilation-perfusion ratio
Vt	Tidal volume

ABSTRACT

This chapter discusses the physiological and clinical basis for the diagnosis and management of the clinical disorders that lead to acute respiratory failure. Acute respiratory failure is defined by abnormal gas exchange that leads to life-threatening hypoxemia or hypercapnia. Acute hypercapnia with respiratory acidosis is caused by ventilation-perfusion mismatch in the lungs, abnormal neuromuscular function, or a decrease in central respiratory drive. The most common clinical causes are COPD, asthma, neuromuscular diseases such as Guillain-Barre, and drug overdoses. Severe hypoxemia is most commonly caused by ventilation-perfusion mismatch and intrapulmonary shunting. Clinically, life-threatening hypoxemia is commonly caused by pneumonia, ARDS, cardiogenic pulmonary edema, and pulmonary thromboembolism. Clinical assessment guided by the history, physical examination, and laboratory data (including chest radiographic imaging and arterial blood gas results) establishes the clinical disorder responsible for the patient's respiratory failure. The first treatment objective is to improve oxygenation. In the spontaneously breathing patient, supplemental oxygen may be supplied with low-flow oxygen by nasal cannula (2 to 6 liters/min), a face mask, or a non-rebreathing face mask. In more severely ill patients, oxygen may be delivered with continuous positive airway pressure (CPAP) or with humidified high-flow nasal oxygen (10 to 60 liters/minute). In spontaneously breathing patients with severe hypercapnia, a trial of noninvasive positive-pressure ventilation (NIPPV) is often indicated. Endotracheal intubation with positive-pressure ventilation is required if the patient's hypoxemia or hypercapnia cannot be managed with the previous interventions. For ARDS, patients should be ventilated with a low tidal volume (6 mL/kg predicted body weight [PBW]) and a plateau airway pressure <30 cm H_2O.

KEYWORDS

acute respiratory distress syndrome
pulmonary edema
acute exacerbation of chronic obstructive lung disease
mechanical ventilation
oxygen therapy
sepsis

TABLE 90-2 SYSTEMS TO CLASSIFY HYPOXEMIC VERSUS HYPERCAPNIC ACUTE RESPIRATORY FAILURE

Common Causes of Primary Hypoxemic Acute Respiratory Failure	Mechanisms of Hypoxemia
ARDS Pneumonia Acute lobar atelectasis Cardiogenic pulmonary edema Pulmonary embolism Lung contusion	**Normal $P(A\text{-}a)O_2$*** ↓P_{IO_2} High altitude; inadvertent administration of low F_{IO_2} gas mixture Hypoventilation See causes of hypercapnic-hypoxemic acute respiratory failure earlier
Common Causes of Primary Hypercapnic Acute Respiratory Failure	**Increased $P(A\text{-}a)O_2$***
Pulmonary disease COPD Asthma: advanced, acute, severe asthma Drugs causing respiratory depression Neuromuscular Guillain-Barré syndrome Acute myasthenia gravis Metabolic derangements causing weakness (including hypophosphatemia, hypomagnesemia) Obesity hypoventilation syndrome (with additional acute, superimposed abnormality as cause of acute respiratory failure)	Ventilation-perfusion ($\dot{V}/\dot{Q}$) mismatch (in severe disease $\dot{V}/\dot{Q}$ mismatch can act like a shunt) Airway disease Vascular disease, including pulmonary thromboembolism ARDS Cardiogenic pulmonary edema Pneumonia Parenchymal lung disease Pulmonary infarction Shunt Intracardiac right to left shunt Intrapulmonary shunt (e.g., A-V malformation/trauma) Decreased mixed venous oxygen concentration (P_{VO_2}) (e.g., heart failure or hypovolemia)

*Calculated by the alveolar-air equation; see text for description.

ARDS = acute respiratory distress syndrome; A-V = arteriovenous; COPD = chronic obstructive pulmonary disease; F_{IO_2} = fraction of inspired oxygen; $P(A\text{-}a)O_2$ = alveolar-to-arterial oxygen difference; P_{IO_2} = partial pressure of inspired oxygen: $\dot{V}/\dot{Q}$ = ventilation-perfusion ratio.

pH in this definition because of the general belief that acidosis is what leads to tissue dysfunction and symptoms. Patients with severe COPD may have chronic CO_2 retention, but renal compensation for the respiratory acidosis protects them against acidosis related to the elevation in CO_2. A further acute rise in P_{ACO_2} can precipitate symptoms and other organ dysfunction; however, even severe respiratory acidosis (pH 7.1) seems to be better tolerated than metabolic acidosis of the same pH in most previously healthy individuals if arterial and tissue oxygenation is adequate.

Pathophysiology

Six mechanisms can lead to a reduction in P_{AO_2}: (1) decreased inspired partial pressure of O_2 (P_{IO_2}) (e.g., at high altitude or when breathing a reduced percentage O_2 mixture); (2) hypoventilation; (3) ventilation-perfusion mismatch; (4) shunting of blood from the pulmonary to systemic circulation, thereby bypassing the alveoli anatomically or functionally; in essence, a shunt is an extreme $\dot{V}/\dot{Q}$ mismatch in which blood perfuses alveoli with *no* ventilation, and it is differentiated clinically from other $\dot{V}/\dot{Q}$ mismatching by the response to breathing supplemental O_2 (see later); (5) any barrier for diffusion of O_2 from the alveoli into the capillary blood; and (6) a decrease in the concentration of oxygen in the mixed venous blood in the pulmonary artery.

If only hypoventilation is present, the resulting hypoxemia is associated with a normal difference between the calculated alveolar and the measured arterial oxygenation levels [$P(A\text{-}a)O_2$]. In this setting, an elevated P_{ACO_2} suggests disease processes that affect nonpulmonary respiratory function (e.g., central respiratory depression resulting from drug overdose, neuromuscular diseases such as Guillain-Barré syndrome, or chest wall disease such as flail chest; Chapter 74). In contrast, $\dot{V}/\dot{Q}$ mismatch and shunting are associated with an elevated $P(A\text{-}a)O_2$, which may or may not coexist with hypoventilation. The normal value for $P(A\text{-}a)O_2$ varies as a function of the fraction of inspired O_2 (F_{IO_2}), increasing as F_{IO_2} increases.

When $\dot{V}/\dot{Q}$ mismatch or shunting is the cause of hypoxemia, some alveolar regions have increased levels of P_{CO_2} and associated reduced levels of P_{O_2}; the blood in the vessels perfusing these alveoli reflects these abnormal gas tensions. The resulting increased arterial P_{CO_2} (P_{ACO_2}) usually can be reversed by increasing overall ventilation, but this increased ventilation usually does not correct the decreased arterial P_{O_2} (P_{AO_2}).

$\dot{V}/\dot{Q}$ mismatch is distinguished from shunting by assessing the P_{AO_2} response to enhanced O_2 administration. Hypoxemia caused by $\dot{V}/\dot{Q}$ mismatch can be corrected to a nearly complete O_2 saturation of the hemoglobin in most patients by a relatively small increase in F_{IO_2}, such as from 0.24 to 0.28 by face mask or 1 to 2 L/minute O_2 by nasal prongs, in patients with acute exacerbations of COPD. If the airways to poorly ventilated alveoli remain open and the enriched O_2 mixture is administered for an adequate length of time (ranging from a few minutes to about 20 minutes, depending on the degree of $\dot{V}/\dot{Q}$ inequality), the increased P_{IO_2} is reflected by an increased P_{AO_2} and an increased P_{aO_2}. When a shunt is present (no ventilation but continued perfusion), a relatively small increase in the F_{IO_2} has little or no effect on the P_{aO_2}, and even large increases in F_{IO_2} up to 1.0 result in only modest increases in P_{aO_2} (Fig. 90-2).

For clinical purposes, diffusion abnormalities are not usually important causes of hypoxemia at sea level because there is sufficient time for adequate diffusion of O_2 during the transit of a red blood cell through the pulmonary capillary bed, even in the presence of severe lung disease. When diffusion

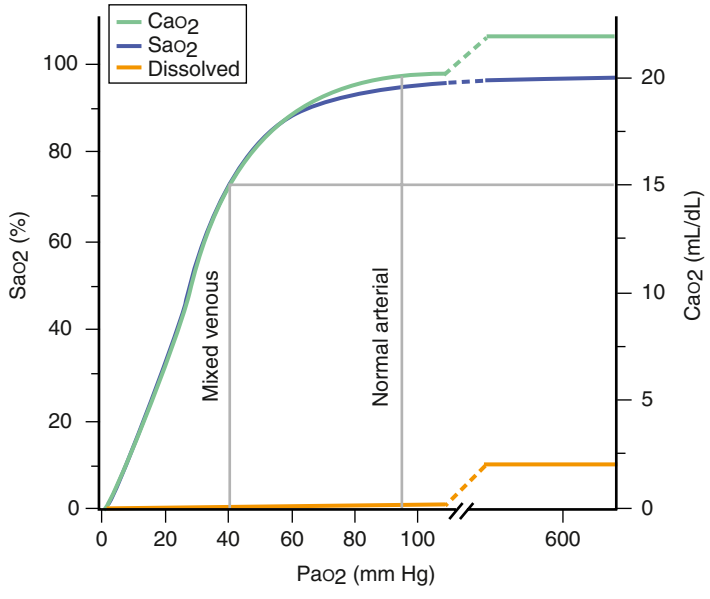

FIGURE 90-1. Oxyhemoglobin association-dissociation curve. The axis for oxygen saturation in the arterial blood (Sao_2) is on the left, and the axis for arterial content of oxygen (Cao_2) is on the right. Cao_2 is the sum of the oxygen dissolved in plasma (denoted as "Dissolved" in the figure) plus the oxygen bound to hemoglobin. With a normal hemoglobin, most of the oxygen is carried bound to hemoglobin, with only a relatively small amount of oxygen dissolved in plasma. When the value of the arterial partial pressure of oxygen (Pao_2) is on the "flat" portion of the curve ($Pao_2 \geq 60$ to 65 mm Hg, normal partial pressure of arterial carbon dioxide [$Paco_2$], and normal pH), raising the Pao_2 further has relatively little effect on total oxygen content. Increases in temperature, Pco_2, hydrogen ion concentration, or 2,3-diphosphoglycerate cause a rightward shift in the oxyhemoglobin association-dissociation curve.

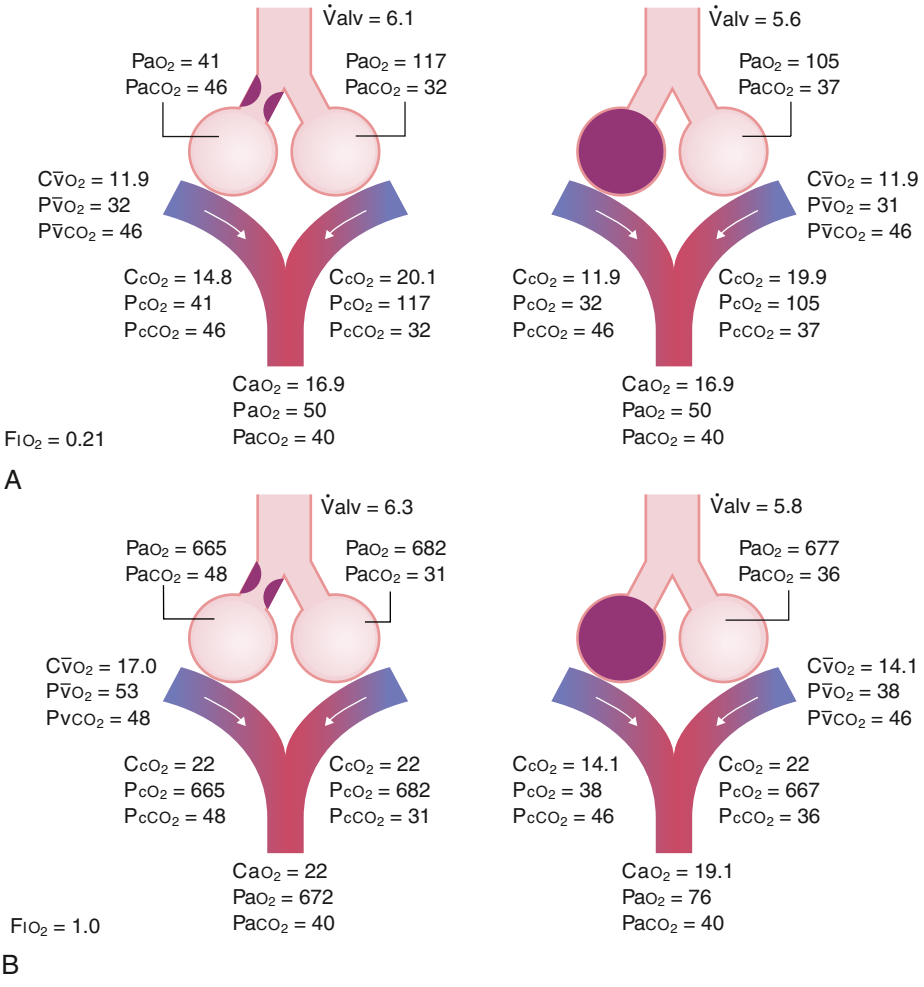

FIGURE 90-2. Arterial oxygenation. Comparison of the effect on arterial oxygenation of increasing the fraction of inspired oxygen (F_{IO_2}) from breathing of ambient air ($F_{IO_2} = 0.21$) (**A**) to breathing of 100% oxygen ($F_{IO_2} = 1.0$) (**B**) with a low ventilation-perfusion ratio ($\dot{V}/\dot{Q}$) (*left*) and a shunt (*right*), using a two-compartment lung model. Shunting and decreased $\dot{V}/\dot{Q}$ can lead to identical arterial blood gases (partial pressure of oxygen in arterial blood [P_{aO_2}] = 50 mm Hg; partial pressure of carbon dioxide in arterial blood [P_{aCO_2}] = 40 mm Hg). The response to supplemental oxygen administration is markedly different. Hypoxemia is only partially corrected by breathing of 100% oxygen when a shunt is present because arterial oxygenation represents an average of the end-capillary oxygen content (C_{cO_2}) from various parts of the lung, not an average of the partial pressures of oxygen (partial pressure of carbon dioxide in the end-capillary blood [P_{cCO_2}]). When the C_{cO_2} values are mixed, the P_{aO_2} is determined from the resultant content of oxygen in the arterial blood (C_{aO_2}) by the oxyhemoglobin association-dissociation relationship (see Fig. 90-1). With low $\dot{V}/\dot{Q}$ (as is often the case in patients with chronic obstructive pulmonary disease), an increase in F_{IO_2} increases the alveolar partial pressure of oxygen (P_{O_2}) of the low $\dot{V}/\dot{Q}$ unit and leads to a marked increase in arterial P_{O_2}. The values in this figure were generated from modeling to result in the same P_{aCO_2} (40 mm Hg) for all four situations shown; this is the reason for slight changes in alveolar ventilation (V) for some of the conditions. Several assumptions are made: no diffusion limitation is present; oxygen consumption = 300 mL/minute, and CO_2 production = 240 mL/minute; cardiac output = 6.0 L/minute; the low $\dot{V}/\dot{Q}$ regions in the left panels represent 60% of the cardiac output perfusing alveoli with a $\dot{V}/\dot{Q}$ 25% of normal; and the shunts in the right panels represent a 37% shunt (i.e., 37% of the cardiac output is perfusing alveoli with no ventilation).

abnormalities are present and contribute to hypoxemia, $\dot{V}/\dot{Q}$ mismatch nearly always coexists with the shunting, and this mismatch is an important cause of hypoxemia. Except at high altitude or when a person is breathing a gas mixture low in O_2, hypoventilation, $\dot{V}/\dot{Q}$ mismatch, and shunting are the dominant causes of hypoxemia.

The sixth cause of arterial hypoxemia, a reduced mixed venous oxygen concentration, usually reflects a reduction in cardiac output, with increased oxygen extraction from the blood in the periphery leading to a decrease in oxygen content of blood returning to the heart. The most common causes are heart failure (Chapter 45) or hypovolemia, but it is also a common cause of arterial hypoxemia immediately after resuscitation from cardiac arrest (Chapter 50).

CLINICAL MANIFESTATIONS

The hallmark of acute respiratory failure is the inability to maintain adequate oxygenation or the inability to maintain an appropriate P_{aCO_2}. Patients are typically dyspneic and tachypneic, unless progressive respiratory failure causes fatigue—sometimes leading to respiratory arrest—or a drug overdose or neuromuscular condition prevents an appropriate respiratory response to hypoxemia or hypercapnic acidosis. Neurologic function may deteriorate, and myocardial ischemia (Chapter 57) or even infarction (Chapter 58) may be precipitated by hypoxemia; other organ dysfunction such as acute kidney injury (Chapter 106) may also occur. In addition, each cause has its own specific manifestations (see later).

DIAGNOSIS

As part of the diagnosis of acute respiratory failure, the physician has three objectives: (1) to confirm the clinical suspicion that acute respiratory failure is present; (2) to classify the type of acute respiratory failure as primary hypoxemia or primary hypercapnia (Table 90-2) (e.g., hypoxemia caused by $\dot{V}/\dot{Q}$ mismatch or shunting, as compared with hypoxemia caused by hypoventilation); and (3) to determine the specific cause. Defining the type of acute respiratory failure and determining the specific cause are prerequisites to optimal management.

The initial approach to diagnosis consists of considering information from four sources: (1) clinical history and physical examination; (2) physiologic abnormalities, particularly arterial blood gas derangements, which help establish the mechanisms of hypoxemia; (3) chest radiographic findings; and (4) other tests aimed at elucidating specific causes. In many cases, the clinical picture from the history is so clear that the presumptive type of acute respiratory failure (and sometimes the cause) is obvious, so treatment can be started while confirmatory laboratory studies are ordered. In other cases, a clinician may be asked to see a patient because of an abnormal chest radiograph, abnormal oxygen saturation, or abnormal arterial blood gases ordered by someone else and may elicit the pertinent history based on these clues. When the degree of hypoxemia is life-threatening, therapeutic decisions must be made quickly, even if data are limited. The clinician must obtain updated information continually and should view most therapeutic decisions as therapeutic trials, with careful monitoring to assess for benefits and possible detrimental effects.

TABLE 90-3 CLINICAL MANIFESTATIONS OF HYPOXEMIA AND HYPERCAPNIA

HYPOXEMIA	HYPERCAPNIA
Tachycardia	Somnolence
Tachypnea	Lethargy
Anxiety	Restlessness
Diaphoresis	Tremor
Altered mental status	Slurred speech
Confusion	Headache
Cyanosis	Asterixis
Hypertension	Papilledema
Hypotension	Coma
Bradycardia	Diaphoresis
Seizures	
Coma	
Lactic acidosis*	

*Usually indicates additional reduction in oxygen delivery because of inadequate cardiac output, severe anemia, or redistribution of blood flow.

Clinical Evaluation

The presentation often reflects one of three clinical scenarios: (1) the systemic effects of hypoxemia or respiratory acidosis, (2) the local effects of primary (e.g., pneumonia) or secondary (e.g., heart failure) diseases on the lungs, and (3) the nonpulmonary effects of the underlying disease process (e.g., shock from sepsis). The clinical effects of hypoxemia and respiratory acidosis are manifested mainly in the central nervous system (e.g., irritability, agitation, anxiety, changes in personality, depressed level of consciousness, coma) and the cardiovascular system (e.g., arrhythmias, hypotension, hypertension) (Table 90-3). In patients with underlying COPD (Chapter 76) with a gradual onset of acute respiratory failure, central nervous system abnormalities may be the major presenting findings. Cyanosis, which requires at least 5 g/dL of unsaturated hemoglobin to be detectable, may not be present before serious tissue hypoxia develops, especially in patients with underlying anemia.

Pulmonary symptoms and signs often reflect the respiratory disease causing the acute respiratory failure. Examples include cough and sputum with pneumonia (Chapter 85) or pleuritic chest pain from pulmonary thromboembolism with infarction (Chapter 68). Dyspnea and respiratory distress are nonspecific reflections of the respiratory system's difficulty in meeting the increased demands from both pulmonary and nonpulmonary diseases.

Physical findings may be associated with a particular pathologic lung process, such as pneumonia (Chapter 85), which often results in bronchial breath sounds, egophony, and crackles on auscultation, or cardiogenic pulmonary edema (Chapter 45), which commonly is associated with crackles (rales) or an S_3 heart sound. Abnormal findings may be minimal or absent in patients with ARDS or pulmonary thromboembolism (Chapter 68).

In some patients, the clinical picture is dominated by the underlying disease process, particularly with diseases that cause ARDS, such as sepsis (Chapter 94), severe pneumonia (Chapter 85), aspiration of gastric contents (Chapter 82), and trauma. In these conditions, the physical examination findings are often nonspecific, with no obvious clues except, for example, fever with sepsis or pneumonia and hypotension with septic shock.

Assessment of Physiologic Abnormalities

The clinical suspicion of acute respiratory failure must be addressed by arterial blood gas analysis to answer several questions.

Is hypoxemia present? The answer is based largely on the F_{IO_2} and the Pa_{O_2} or Sa_{O_2}. The degree of the hypoxemia not only confirms the diagnosis of acute respiratory failure but also helps define its severity.

Is hypoventilation present? If the Pa_{CO_2} is elevated, alveolar hypoventilation is present.

Does the degree of hypoventilation fully explain the hypoxemia? If the $P(A\text{-}a)O_2$ is normal, hypoventilation fully explains the presence and degree of hypoxemia. When this is the case, the most likely causes of acute respiratory failure are central nervous system abnormalities or a chest wall abnormality. If the $P(A\text{-}a)O_2$ is increased such that hypoventilation does not fully explain the hypoxemia, another condition must be present; common diagnoses include COPD (Chapter 76), severe asthma (Chapter 75), pneumonia (Chapter 85), and early stages of ARDS.

If hypoxemia exists without hypoventilation, an elevated $P(A\text{-}a)O_2$ should be confirmed, and the response to breathing of an enhanced O_2 mixture would answer this question: *Is the increase in $P(A\text{-}a)O_2$ primarily the result of a $\dot{V}/\dot{Q}$ abnormality or of shunting?* If hypoxemia is primarily the result of a $\dot{V}/\dot{Q}$ abnormality, the likely cause is an airway disease, either COPD or acute severe asthma, or a vascular disease, such as pulmonary thromboembolism. If effective shunting (lung units with very low but not zero $\dot{V}/\dot{Q}$ values) is the major explanation for the hypoxemia, processes that fill the air spaces (e.g., cardiogenic pulmonary edema, noncardiogenic pulmonary edema or severe ARDS, or purulent pulmonary secretions in acute pneumonia) or, less commonly, an intracardiac or anatomic intrapulmonary shunt is the likely cause. In the setting of pulmonary edema of any cause, $\dot{V}/\dot{Q}$ mismatch and intrapulmonary shunting usually coexist. Conditions that fill air spaces should be confirmed by abnormal findings on a chest radiograph; if the radiograph is normal, the possibility of intracardiac shunt (Chapter 55) or thromboembolism (Chapter 68) should be evaluated. If there is a reduction in the mixed venous oxygen saturation, causes of a reduced cardiac output should be considered, including acute or chronic heart failure or hypovolemia.

Chest Radiography

The chest radiograph in acute respiratory failure is likely to show one of three patterns (Fig. 90-3): (1) normal (or relatively normal), (2) localized alveolar filling opacities, or (3) diffuse alveolar filling opacities. Diffuse interstitial opacities are also possible, but diseases that cause this pattern usually have a more gradual onset and are associated with chronic respiratory failure. If the chest radiograph is normal (i.e., it is clear or relatively clear), airway diseases, such as COPD and asthma, or pulmonary vascular diseases, such as thromboembolism, are more likely. If a localized alveolar filling abnormality is present, pneumonia is the major consideration, but pulmonary embolism with infarction should also be considered. When diffuse (bilateral) alveolar filling abnormalities (E-Fig. 90-1) are present, cardiogenic pulmonary edema and ARDS (e.g., as seen after sepsis, trauma, and pneumonia, including coronavirus disease 2019 [COVID-19] pneumonia [Chapter 336], or aspiration of gastric contents) are the major considerations. The combination of the chest radiograph and the arterial blood gas interpretation can be helpful. The finding of a significant shunt may suggest ARDS in a patient in whom this diagnosis was not clinically obvious; the chest radiograph should help confirm that possibility.

Other Evaluations

All patients with acute respiratory failure should have a complete blood count including a platelet count, routine blood chemistry tests, prothrombin time, and urinalysis to screen for possible underlying causes and comorbid conditions. Other blood tests should be guided by the clinical picture. Examples include a serum lipase level if pancreatitis is a possible cause of ARDS and thyroid indices if severe hypothyroidism is a possible cause of hypoventilation. Blood cultures are recommended when an infectious cause such as sepsis is suspected. Sputum Gram stain and cultures can be useful if bacterial pneumonia is suspected, but nucleic acid testing for viruses is recommended when severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2; Chapter 337), influenza, and other respiratory viruses are suspected. A urine toxicology screen is recommended if drug overdose is a possibility. Any abnormal fluid collections, especially pleural effusion (Chapter 86), should usually be aspirated for diagnostic purposes.

Other specific tests should be directed by the history, physical examinations, arterial blood gas levels, and chest radiograph. An abdominal computed tomography (CT) scan may be indicated to search for the source of infection in a patient with sepsis and ARDS. A chest CT scan may help define pulmonary disease if the chest radiograph is not definitive. CT arteriography of the pulmonary circulation may diagnose pulmonary thromboembolism (Chapter 68). An electrocardiogram should be obtained routinely and be supplemented by cardiac troponin levels and echocardiography if a primary cardiac cause of pulmonary edema (Chapter 45) is suspected. A head CT scan may be indicated if a stroke involving the respiratory center is suspected. Routine blood chemistry studies can detect diabetic ketoacidosis (Chapter 210) or renal failure (Chapter 106) as contributing causes.

E-FIGURE 90-1. Diffuse alveolar damage in a patient with the acute respiratory distress syndrome. Chest radiograph shows diffuse bilateral ground-glass opacification and consolidation in a patient with acute respiratory failure from ARDS and subsequent intubation. (Courtesy of Paul Stark.)

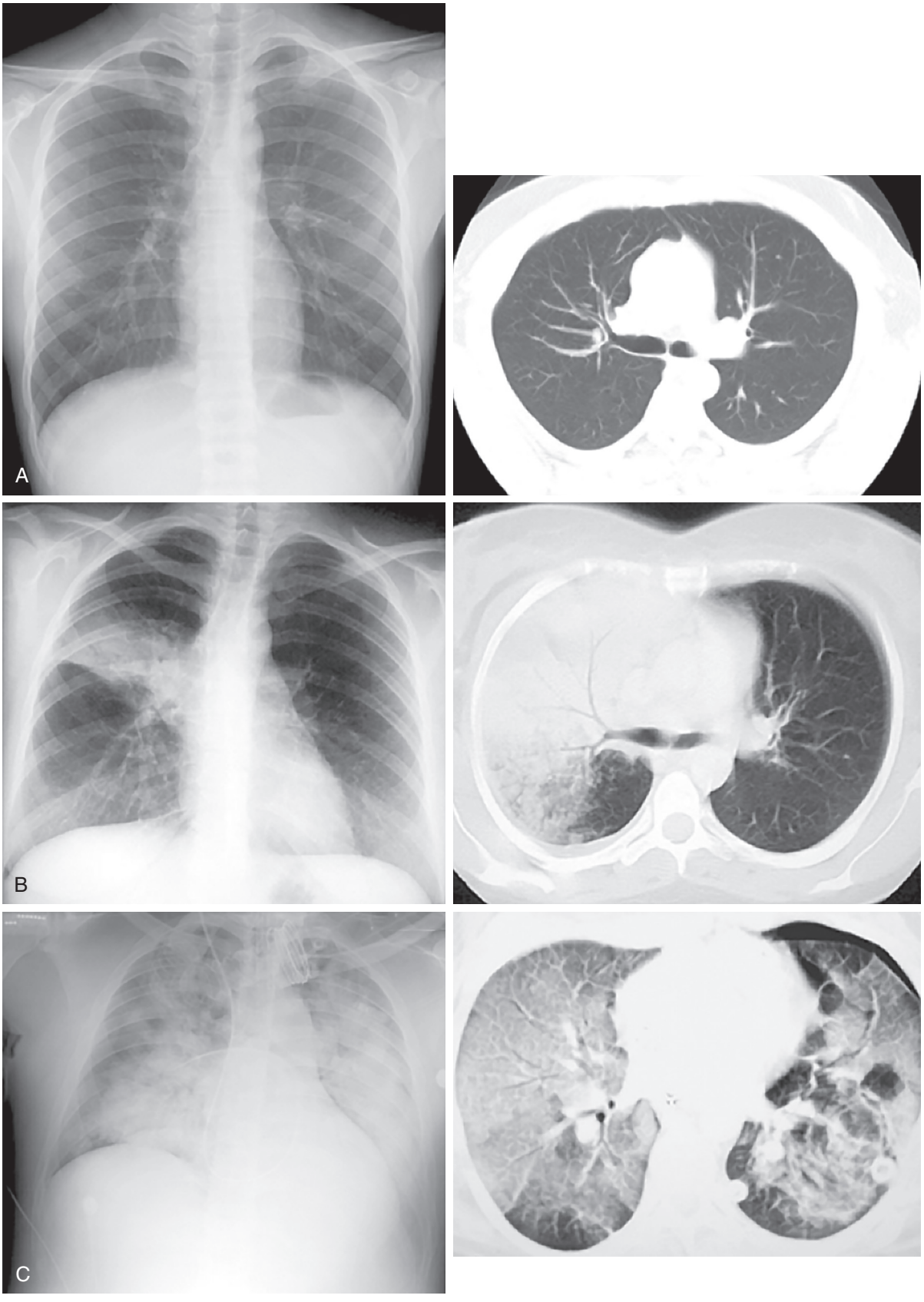

FIGURE 90-3. **Chest radiographs (*left*) and computed tomography scans (*right*) of the three most common findings in diseases causing acute respiratory failure. A,** Relatively clear chest, consistent with an acute exacerbation of airway disease (e.g., asthma, chronic obstructive pulmonary disease) or a central nervous system or neuromuscular disease as the cause of acute respiratory failure. **B,** Localized alveolar filling opacity, most commonly seen with acute pneumonia. **C,** Diffuse bilateral alveolar filling opacities consistent with acute respiratory distress syndrome or cardiogenic pulmonary edema. The computed tomography scan in C shows a small left pneumothorax and cavities or cysts that are not apparent on the anteroposterior chest radiograph.

TREATMENT

General Measures

The management of acute respiratory failure depends on its cause, its clinical manifestations, and the patient's underlying status.[2] Certain goals apply to all patients: improvement of the hypoxemia to eliminate or markedly reduce the acute threat to life; improvement of the acidosis if it is considered life-threatening; maintenance of cardiac output or improvement if cardiac output is compromised; treatment of the underlying disease process; and avoidance of predictable complications.

The precise methods for improving hypoxemia depend on the cause of the acute respiratory failure. However, an increase in the inspired O_2 concentration is a cornerstone of treatment for nearly all patients, even though it may not produce a marked increase in Pao_2 in patients whose underlying pathophysiologic process involves a significant amount of lung with low ventilation-perfusion ratios or true shunting. Earlier treatment is preferred. For example, continuous positive airway pressure (CPAP) begun in the prehospital setting can reduce subsequent intubation rates and mortality. Often, however, initial oxygen therapy alone is as good as early noninvasive ventilation. Conservative oxygen therapy is as good as more liberal therapy, and the peripheral Sao_2 goal should not be above 94 to 96%.[A1,A2]

The level of acidosis that requires treatment other than for the underlying disease process is a matter of debate. Although normalization of the arterial pH was suggested in the past, respiratory acidosis seems to be well tolerated in many patients with severe ARDS, so a patient with a pH of 7.15 or higher may not require bicarbonate therapy. If the acidemia coexists with clinical complications, such as cardiac arrhythmias or a decreased level of consciousness, that have no other obvious cause, treatments to increase pH should be considered. The therapeutic goal is alleviation or reduction of the accompanying complications by improving the level of acidosis; normalization of the pH usually is not indicated (Chapter 104).

The maintenance of cardiac output is crucial for O_2 delivery in acute respiratory failure, especially because mechanical ventilation and positive end-expiratory pressure (PEEP) may compromise cardiac output. Placement of a pulmonary artery catheter allows measurement of cardiac output and filling pressures, but most patients who have these catheters do no better than similar patients managed without them. Nevertheless, selective use of diagnostic pulmonary artery catheterization can help determine the cause of the pulmonary edema (cardiogenic vs. noncardiogenic) and the physiologic basis for shock (sepsis, hypovolemia, or decreased cardiac output from impaired cardiac function) in selected patients in whom the diagnosis is not clear.

Many therapeutic interventions that improve short-term physiologic measures may worsen long-term, clinically important outcomes. For example, transfusing all patients to maintain a hemoglobin greater than 10 g/dL *increases* mortality in critically ill patients who have not had an acute myocardial infarction and do not have unstable angina, even though the O_2-carrying capacity of the blood is acutely increased. Use of a relatively large tidal volume (e.g., 12 mL/kg predicted body weight, which is equivalent to approximately 10 to 10.5 mL/kg measured body weight in patients who are somewhat overweight) *increases* mortality in patients with ARDS compared with a lower tidal volume (6 mg/kg predicted body weight), even though it raises Pao_2 more in the short term than does a lower tidal volume. When vasopressors are no longer required to support the systemic blood pressure in ARDS, liberal use of fluids to optimize organ perfusion is usually detrimental to lung function and increases the duration of mechanical ventilation and intensive care.

Improvements in oxygenation, acid-base status, and cardiac output are of no more than temporary benefit unless the underlying disease processes are diagnosed and treated properly. In patients with ARDS, untreated or suboptimally treated sepsis may worsen injury to the lung and other organs despite optimal supportive care, so careful attention should be given to control the source of any infectious process. Similarly, if the precipitating cause of acute respiratory failure in a patient with COPD is not identified and treated, supportive care is likely to be futile. Complications may arise from the physiologic effects of the gas exchange abnormality, from the disease processes causing the acute respiratory failure, from being critically ill and its associated incursions on homeostasis (e.g., sleep deprivation), from limited mobility (critical illness myopathy and/or neuropathy), or from iatrogenic complications of therapy.

Therapy to Improve Oxygenation

The preferred approach to providing adequate oxygenation depends on the severity of disease and the patient's response to progressive intensification of therapy (Fig. 90-4). An initial step-wise approach begins with low-flow nasal oxygen (starting with 2 L/min and advancing to 6 L/min). If hypoxemia persists, therapy should be advanced to high-flow nasal oxygen (initially at 15 to 20 L/min but can be increased to higher flow rates of 40 to 60 L/min). The fraction of oxygen can be adjusted between 50% and 100% as well to achieve an arterial oxygen saturation of approximately 90 to 97%. If adequate oxygenation cannot be achieved with nasal oxygen, then therapy can be advanced to CPAP or NIPPV, if possible, before proceeding to endotracheal intubation and mechanical ventilation.

A Pao_2 greater than 60 mm Hg is usually adequate to produce an Sao_2 in the low to middle 90s and to provide an adequate oxygen content of the blood for tissue oxygenation. The Pao_2 can be increased by the administration of supplemental O_2, by pharmacologic manipulations (e.g., diuretics to reduce pulmonary edema [see Fig. 46-2]), by CPAP, by mechanical ventilation with or without maneuvers such as PEEP, and by the prone position. PEEP, pharmacologic manipulations, and prone positioning are used primarily in patients with ARDS (see later).

The initial choice of the concentration and amount of supplemental O_2 is based on the severity of the hypoxemia, the clinical diagnosis, the likely mechanism causing the hypoxemia, and the O_2 delivery systems available. For the tracheal F_{IO_2} to be the same as the delivered F_{IO_2}, the O_2 delivery system must deliver a flow that matches the patient's peak inspiratory flow rate with gas of a known F_{IO_2}.

Simple face masks, non-rebreather masks, and partial rebreather masks use a simple regulator that mixes room air with O_2 from a wall unit or tank, with resulting flows that are frequently unable to match the patient's peak inspiratory flow rate. The patient entrains more air from the environment, and the resulting tracheal F_{IO_2} or partial pressure of oxygen in inspired gas (Pao_2) is unknown. The amount of air entrained depends on the patient's inspiratory pattern and minute ventilation. Although the resulting F_{IO_2} is unknown, these systems are satisfactory if the delivery is constant and if they result in adequate arterial O_2 saturation, as monitored by arterial blood gases or oximetry.

Nasal and Face Mask Oxygen

Standard nasal prongs can deliver a tracheal F_{IO_2} of approximately 0.50, and non-rebreather masks can deliver 50 to 100% O_2; in both cases, this concentration depends on the inspiratory pattern and flow rate. If only hypoventilation or $\dot{V}/\dot{Q}$ mismatch is present, a small increment in F_{IO_2} (e.g., an F_{IO_2} of 0.24 or 0.28 delivered by a Venturi principle face mask or by mechanical ventilation; or 1 to 2 L/minute O_2 delivered by nasal prongs) is likely to be sufficient to restore normoxia. By comparison, if marked shunting or many lung units with low but not zero $\dot{V}/\dot{Q}$ are the cause of hypoxemia, a considerably higher F_{IO_2} (e.g., >0.7) may be required, and even this high F_{IO_2} may not reverse the hypoxemia. A common practice when a significant shunt is suspected is to give an F_{IO_2} of 1.0, then adjust the F_{IO_2} downward as guided by the resulting Pao_2 or Sao_2.

A low concentration of supplemental O_2 can be administered by nasal prongs or nasal cannula, which most patients find comfortable and allows them to cough, speak, eat, and drink while receiving O_2. When the nasal passages are open, the P_{IO_2} does not depend too much on whether the patient breathes through the nose or the mouth because O_2 is entrained from the posterior nasal pharynx during a breath taken through the mouth. The level of O_2 can be adjusted by the flow rate to the nasal prongs. In patients with COPD, flows as low as 0.5 to 2 L/minute are usually adequate unless an intrapulmonary shunt is contributing to the hypoxemia, as usually occurs in acute pneumonia. At flows greater than approximately 6 L/minute, only a small further augmentation in the P_{IO_2} can be achieved.

Because gas flow through the nose has a drying and irritating effect, a face mask should be considered at high flow rates. O_2 face masks using the Venturi principle allow the regulation of F_{IO_2} and can be particularly useful when COPD is suspected, and it is important to avoid the CO_2 retention that can be associated with the unregulated administration of O_2. A higher F_{IO_2} of 0.5 to nearly 1.0 can be administered through a non-rebreathing face mask with an O_2 reservoir.

High-Flow Nasal Oxygen

High-flow O_2 blenders deliver humidified nasal oxygen at rates as high as 60 L/minute or more to a nonintubated spontaneously breathing patient. These systems require a large flow of O_2 (from a wall unit or tank), however, and are not universally available.

This method of oxygen delivery provides a low level of positive end-expiratory airway pressure (about 2 to 3 cm H_2O) and a modest increase in the elimination of carbon dioxide.[3] High-flow nasal oxygen may reduce subsequent rates of intubation compared with conventional oxygen delivery with a face mask[A3] but not in comparison with noninvasive ventilation,[A4] except in immunocompromised patients with acute hypoxemic respiratory failure.[A5]

The O_2 concentration that is toxic to the lungs in critically ill patients is not known, but prior injury may provide tolerance to O_2 toxicity, whereas prior exposure to conditioning agents, such as bleomycin, may enhance oxidative

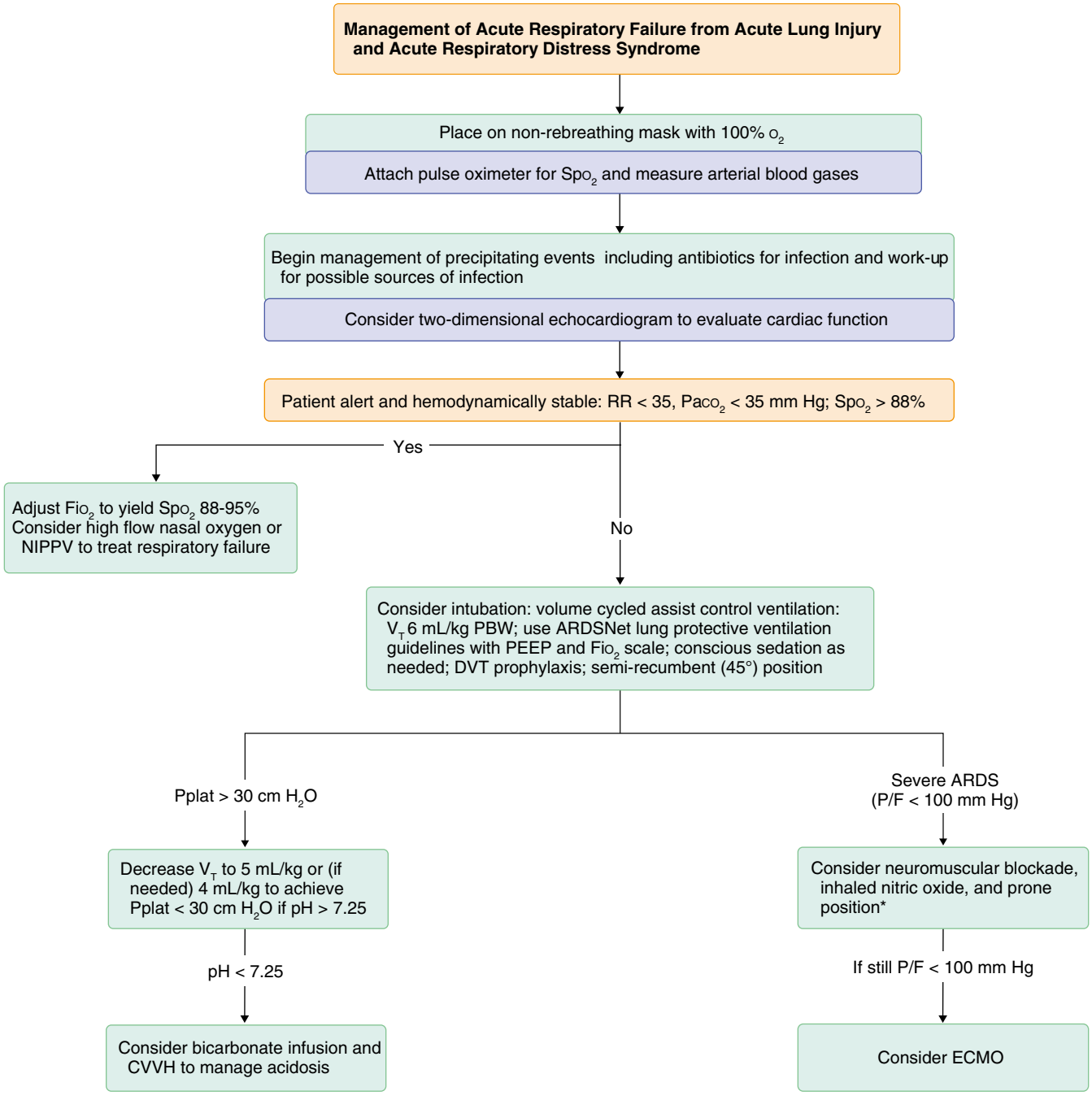

FIGURE 90-4. Management of acute respiratory failure from acute lung injury and acute respiratory distress syndrome. *Prone positioning can be considered when P/F < 150 mm Hg if clinically indicated. ARDS = acute respiratory distress syndrome; CVVH = continuous veno-venous hemofiltration; DVT = deep venous thrombosis; ECMO = extracorporeal membrane oxygenation; Fio_2 = fraction of inspired oxygen; NIPPV = noninvasive positive pressure ventilation; PBW = predicted body weight; PEEP = positive end-expiration pressure; P/F = Pao_2/Fio_2; Pplat = plateau airway pressure; RR = respiratory rate; Spo_2 = arterial oxygen saturation; V_T = tidal volume.

injury. An Fio_2 of 0.7 or higher is generally considered potentially injurious to the normal human lung. Because it is unknown what lower concentration is safe, however, patients should be given the lowest Fio_2 that provides an adequate Sao_2 (≥90%). If an Fio_2 equal to or greater than 0.5 to 0.7 is required for adequate oxygenation, other measures, especially PEEP or CPAP, should be considered. Even a lower Fio_2 of about 0.5 may be associated with impaired ciliary action in the airways and impaired bacterial killing by alveolar macrophages, but the clinical importance of these effects is not known.

Pressure-Assisted Ventilation

CPAP refers to the maintenance of positive pressure during the respiratory cycle while breathing spontaneously.[4] PEEP refers to the maintenance of positive pressure throughout the expiratory cycle when it is applied together with mechanical ventilation (Chapter 91). CPAP and PEEP can result in recruitment of microatelectatic regions of the lung that are perfused but were not previously ventilated, thus contributing substantially to hypoxemia. CPAP and PEEP have the theoretical advantage of keeping some of these regions open during exhalation, thus preventing cyclic closure and reopening of lung units, which may result in alveolar wall stress and injury.

Ventilatory maneuvers that may increase arterial oxygenation include mechanical ventilation itself and the administration of PEEP or CPAP, all of which allow ventilation of areas of the lung that were previously poorly ventilated or unventilated. Although large tidal volumes with mechanical ventilation may open areas of atelectasis and may improve oxygenation initially, these higher tidal volumes can cause ventilator-induced lung injury, particularly if the lung has already been injured (Chapter 91).

If the patient has refractory hypoxemia, acidosis, or a high work of breathing, then endotracheal intubation should be considered to provide positive-pressure ventilation. Indications for placement of an artificial airway in a patient with acute respiratory failure are to protect the airway against aspiration of gastric contents, to deliver an increased F_{IO_2}, to facilitate ventilation, and possibly to aid in the control of respiratory secretions (Chapter 91).

Supportive Measures

Every patient with acute respiratory failure is at risk for deep venous thrombosis, pulmonary thromboembolism, gastric stress ulceration, acute delirium, and deconditioning/weakness. Prophylactic anticoagulation to prevent venous thrombosis (Chapter 68) is recommended in patients who are not at high risk for bleeding complications; sequential leg compression therapy may be preferred for high-risk patients. Nutrition is important to maintain strength needed for weaning. In patients with ARDS, limited enteral feeding for up to 6 days is as good as full enteral feeding in terms of ventilator-free days, 60-day mortality, and infectious complications, and limited feedings induce less gastrointestinal intolerance.

The best means of preventing gastric stress ulceration is not known, but current evidence indicates that the use of an H_2-receptor blocker is superior to the gastric administration of sucralfate on the basis of a large randomized, controlled trial that found a higher incidence of significant bleeding in patients receiving sucralfate than in those receiving ranitidine. Evidence also indicates that proton pump inhibitors may be useful in the acute care setting, although there is concern that more complete acid suppression with these agents may lead to a higher incidence of ventilator-associated pneumonia (Chapter 85) and *Clostridium difficile* infection (Chapter 271).

Current evidence supports maintaining the head of the bed at a 45-degree angle to reduce aspiration and the risk of ventilator-associated pneumonia in critically ill patients. Attempts should be made to ensure a normal day-night sleep pattern, including minimizing activity and reducing direct lighting at night. The patient should change position frequently, including sitting in a chair and walking short distances if possible, even while receiving mechanical ventilatory support. Mobilization can enhance the removal of secretions, help maintain musculoskeletal function, reduce the risk of deep venous thrombosis, and provide psychological benefits.

To facilitate early mobilization and weaning from the ventilator, sedating agents should be minimized and benzodiazepines should be avoided because of their potential to induce or exacerbate delirium in critical illness. Daily awakening and spontaneous breathing trials in mechanically ventilated patients facilitate weaning, reduce time on the ventilator, and improve survival (Chapter 91).

SPECIFIC ACUTE RESPIRATORY FAILURE SYNDROMES

Chronic Obstructive Pulmonary Disease

EPIDEMIOLOGY AND PATHOBIOLOGY

The epidemiology and pathobiology of COPD are discussed in Chapter 76.

CLINICAL MANIFESTATIONS

When patients with COPD develop acute respiratory failure, they commonly have a history of increasing dyspnea and sputum production. Acute respiratory failure may also present with a change in mental status, arrhythmias, or other cardiovascular abnormalities. Acute respiratory failure must be considered whenever patients with COPD have significant nonspecific clinical changes.

DIAGNOSIS

The diagnosis can be confirmed by an arterial blood gas that reveals alveolar hypoventilation with an elevated $Paco_2$ and an acidemic pH. The pH is helpful in assessing whether the hypoventilation is partly or exclusively acute. The pH declines by approximately 0.08 for each rise of 10 mm Hg in the $Paco_2$ in acute respiratory acidosis without renal compensation. By comparison, in chronic respiratory acidosis with normal renal compensation, the pH declines by only about 0.03 for each 10 mm Hg rise in the $Paco_2$.

TREATMENT

General Care

As soon as acute respiratory failure is confirmed in a patient with COPD, attention must focus on identifying the precipitating events (Table 90-4), including increased airway resistance, caused by bronchospasm or increased secretions, often associated with an upper respiratory viral infection; atelectasis, pneumonia, or pulmonary edema; decreased ventilatory drive, secondary to oversedation; decreased muscle strength or function, often related to electrolyte abnormalities, including hypophosphatemia and hypomagnesemia; decreased chest wall elasticity, possibly related to rib fracture, pleural effusion, ileus, or ascites; or increased metabolic O_2 requirements that may be associated with a systemic infection. Some of these abnormalities can impair the cough mechanism and diminish the clearance of airway secretions.

TABLE 90-4 PRINCIPLES IN THE MANAGEMENT OF CHRONIC OBSTRUCTIVE PULMONARY DISEASE PATIENTS WITH ACUTE RESPIRATORY FAILURE

1. Monitor and treat life-threatening hypoxemia (these measures should be performed simultaneously)
   a. Assess the patient clinically, and measure oxygenation by arterial blood gases and/or oximetry
      (1) If the patient is hypoxemic, initiate supplemental oxygen therapy with nasal prongs (low flows [1to 2 L/min] are usually sufficient) or by Venturi face mask (24 or 28% oxygen delivered)
      (2) If the patient needs ventilatory support, consider noninvasive ventilation
      (3) Determine whether the patient needs to be intubated; this is almost always a clinical decision. Immediate action is required if the patient is comatose or severely obtunded
   b. A reasonable goal in most patients is a Pao_2 of 55 to 60 mm Hg or Sao_2 of 88 to 90%
   c. After changes in F_{IO_2}, check blood gases and check regularly for signs of carbon dioxide retention and worsening respiratory acidosis
2. Start to correct life-threatening acidosis
   a. The most effective approach is to correct the underlying cause of acute respiratory failure (e.g., bronchospasm, infection, heart failure)
   b. Consider ventilatory support, based largely on clinical considerations
   c. With severe acidosis, the use of bicarbonate is often ineffective, and there is little evidence of a clinical benefit
3. If ventilatory support is required, consider noninvasive mechanical ventilation.
   a. The patient must have intact upper airway reflexes and be alert, cooperative, and hemodynamically stable
   b. Careful monitoring is required; if the patient does not tolerate the mask, becomes hemodynamically unstable, or has a deteriorating mental status or worsening acidosis, consider intubation
4. Treat airway obstruction and the underlying disease process that triggered the episode of acute respiratory failure
   a. Treat airway obstruction with pharmacologic agents: systemic corticosteroids and bronchodilators (ipratropium and β-adrenergic agents)
   b. Improve secretion clearance: encourage the patient to cough; administer chest physical therapy if cough is impaired and a trial appears effective
   c. Treat the underlying disease process (e.g., antibiotics, diuretics)
5. Prevent complications of the disease process and minimize iatrogenic complications
   a. Pulmonary thromboembolism prophylaxis: use intermittent pneumatic compression or use subcutaneous low-dose unfractionated heparin or low-molecular-weight heparin if no contraindications exist
   b. Gastrointestinal complications: administer prophylaxis for gastrointestinal bleeding in patients requiring mechanical ventilation
   c. Hemodynamics: if the patient is ventilated, monitor and minimize auto-PEEP, which can cause hypotension and barotrauma
      (1) Treat the underlying airway obstruction
      (2) Decrease the respiratory rate to allow adequate expiratory time; may require sedation and controlled hypoventilation
      (3) Use small tidal volumes (6 to 8 mL/kg/PBW); increase the inspiratory flow rate to decrease the inspiratory time and lengthen the expiratory time
   d. Cardiac arrhythmias: maintain oxygenation and normalize electrolytes

F_{IO_2} = fraction of inspired oxygen; Pao_2 = partial pressure of oxygen in arterial blood; PBW = predicted body weight; PEEP = positive end-expiratory pressure; Sao_2 = oxygen saturation.

Infection

The most common specific precipitating event is airway infection, especially acute bronchitis. The role played by viral agents, *Mycoplasma pneumoniae*, chronic colonizers of the lower airway such as *Haemophilus influenzae* and *Streptococcus pneumoniae*, and other acute pathogens is difficult to determine. Acute exacerbations of COPD commonly result from new infections rather than from reemergence of an infection by preexisting colonization. Antibiotics modestly shorten the duration of the exacerbation, with no significant increase in toxicity, compared with placebo; the impact of antibiotics on the subsequent emergence of resistant organisms is not known. It is standard practice to use antibiotics to treat a patient with COPD who has an exacerbation severe enough to cause acute respiratory failure and who has evidence consistent with acute tracheobronchitis (Chapters 76 and 84). Pneumonia may account for 10 to 20% of cases of acute respiratory failure in patients with COPD. Compared with the physiologically normal population, patients with COPD who have community-acquired pneumonia are more likely to have gram-negative enteric bacteria or *Legionella* infections and are more likely to have antibiotic-resistant organisms.

Other Precipitating Causes

Other common precipitating causes of acute respiratory failure include heart failure and worsening of the underlying COPD, often related to noncompliance with medications. Pulmonary thromboembolism must also be considered, particularly if no other cause of acute respiratory failure is identified.

Mechanical Ventilation

The decision to institute mechanical ventilation in patients with COPD and acute respiratory failure must be made on clinical grounds and is not dictated by any particular arterial blood gas values. In general, if the patient is alert and is able to cooperate with treatment, mechanical ventilation often is not necessary. If ventilatory support is required (Chapter 91), the decision is whether to use NIPPV therapy (i.e., ventilatory support through a mask without endotracheal intubation) or endotracheal intubation with positive-pressure ventilation. A number of clinical trials have demonstrated that NIPPV is preferred for patients with COPD and can decrease mortality if it is applied in appropriate patients with no characteristics that are likely to lead to complications, such as a markedly decreased mental status, hypotension, or an inability to tolerate the tight-fitting face mask that is required for NIPPV. A trial of therapy with NIPPV requires close monitoring. If the patient develops worsening acidosis (pH < 7.25), a decline in mental status, or worsening oxygenation, then endotracheal intubation is indicated. In most patients, improvement in the pH and the $Paco_2$ within 30 minutes to 2 hours predicts success. Most patients with acute respiratory failure caused by an exacerbation of COPD require treatment in an intensive care unit where appropriate physician, nursing, and respiratory care are available (Chapter 76).

PROGNOSIS

Acute respiratory failure in patients with severe COPD is associated with an in-hospital mortality rate of 6 to 20%. The severity of the underlying disease and the severity of the acute precipitating illness are important determinants of hospital survival. Hospital mortality is higher if the respiratory failure is associated with a pH lower than 7.25 and if the patient requires invasive mechanical ventilation. However, the pH, the $Paco_2$, and other clinical characteristics are not reliable in predicting a particular patient's chances of survival to hospital discharge.

ACUTE RESPIRATORY DISTRESS SYNDROME

DEFINITION

ARDS is the abrupt onset of diffuse lung injury characterized by severe hypoxemia (shunting) and bilateral pulmonary infiltrates not explained by left-sided cardiac failure (Table 90-5).[4] The severity of ARDS is determined on the basis of the Pao_2 divided by the Fio_2 (Pao_2/Fio_2, also called the P/F ratio). These oxygenation categories require positive-pressure ventilation with at least 5 cm H_2O positive end-expiratory pressure.

One limitation of this definition is that it does not include patients who have ARDS-like acute respiratory failure but who are not receiving positive-pressure ventilation, including patients who initially are profoundly hypoxemic but can be sufficiently oxygenated with high-flow nasal oxygen.[5] Such early acute lung injury can be diagnosed in spontaneously breathing patients who have bilateral pulmonary infiltrates and in whom the inspired Fio_2 can be estimated and the Pao_2 measured.[6,7] In addition, pulse oximetric oxygen saturation (Spo_2) can be substituted for the directly measured Pao_2 in most patients to estimate the P/F ratio. If patients with early acute lung injury can be identified prior to the need for positive-pressure ventilation, they can be treated with strategies, such as high-flow nasal oxygen, that might reduce the progression of their acute respiratory failure.

EPIDEMIOLOGY

ARDS is a clinical syndrome triggered most commonly by pulmonary or nonpulmonary infections, aspiration of gastric contents, or severe trauma (Table 90-6). The annual incidence of ARDS is about 80 cases per 100,000 in the U.S. adult population, with a high frequency in intensive care units worldwide. These numbers have increased dramatically with the SARS-CoV-2 (Chapter 336) COVID-19 pandemic.[8,9] The underlying precipitating factor may affect and injure the lungs directly, such as in diffuse pneumonia or aspiration of gastric contents, or it may affect the lungs indirectly, as in severe sepsis from a nonpulmonary source (Chapter 94) or severe nonthoracic trauma associated with shock (Chapter 97). Sepsis is the most common precipitating cause of ARDS worldwide. The organisms vary widely, ranging from gram-negative and gram-positive bacteria and viruses (e.g., H1N1 influenza [Chapter 332] in 2009; SARS-CoV-2 infection [Chapter 337] in 2020-2021) to leptospiral infections (Chapter 298) or malaria (Chapter 316).

TABLE 90-5 BERLIN DEFINITION OF THE ACUTE RESPIRATORY DISTRESS SYNDROME

CRITERIA			
Timing	Within 1 week of a known clinical insult or new/worsening respiratory symptoms		
Chest imaging	Bilateral opacities—not fully explained by effusions, lobar/lung collapse, or nodules		
Origin of edema	Respiratory failure not fully explained by cardiac failure or fluid overload Need objective assessment (e.g., echocardiography) to exclude hydrostatic edema		
	MILD	**MODERATE**	**SEVERE**
Oxygenation	$200 < Pao_2/Fio_2 \leq 300$ with PEEP or CPAP ≥ 5 cm H_2O	$100 < Pao_2/Fio_2 \leq 200$ with PEEP ≥ 5 cm H_2O	$Pao_2/Fio_2 \leq 100$ with PEEP ≥ 5 cm H_2O

CPAP = continuous positive airway pressure; Fio_2 = fraction of inspired oxygen; Pao_2 = partial pressure of oxygen in arterial blood; PEEP = positive end-expiratory pressure.
Ranieri VM, Rubenfeld GD, Thompson BT, et al. Acute respiratory distress syndrome: the Berlin Definition. *JAMA*. 2012;307:2526-2533.

TABLE 90-6 DISORDERS ASSOCIATED WITH ACUTE RESPIRATORY DISTRESS SYNDROME

COMMON
Sepsis (gram-positive or gram-negative bacterial, viral, fungal, or parasitic infection; Chapter 94)
Diffuse pneumonia (bacterial, viral, or fungal; Chapters 85, 336)
Aspiration of gastric contents
Trauma (usually severe; Chapter 97)
LESS COMMON
Drowning (fresh or salt water; Chapter 82)
Drug overdose
Acetylsalicylic acid (Chapter 96)
Heroin and other narcotic drugs (Chapter 365)
Transfusion-associated lung injury (Chapter 162)
Massive blood transfusion (likely a marker of severe trauma, but also seen with severe gastrointestinal bleeding, especially in patients with severe liver disease; Chapter 162)
Inhalation of smoke or corrosive gases (usually requires high concentrations; Chapter 82)
Acute pancreatitis (Chapter 130)
Fat embolism (Chapter 68)
Cardiopulmonary bypass (Chapter 59)

PATHOBIOLOGY

Pathology

Despite the variety of underlying disease processes leading to ARDS, the lung's response to these insults results in similar clinical findings, physiologic changes, and morphologic abnormalities. The pathologic abnormalities in ARDS are nonspecific and are described as *diffuse alveolar damage* by pathologists. Ultrastructural studies with electron microscopy usually show endothelial and alveolar epithelial injury. Routine histology shows acute inflammation, usually with neutrophils predominating in the alveolar edema fluid. Hyaline membranes are present in some, but not all, patients, similar to those seen in premature infants with infant respiratory distress syndrome, presumably related to a procoagulant environment in the injured alveoli. Large-molecular-weight plasma proteins, including fibrinogen, accumulate, and inflammatory factors lead to fibrin deposition. Alveolar flooding impairs surfactant, which is abnormal in quantity and quality. The result is microatelectasis, which may be associated with impaired immune function. The resolution of ARDS depends in part on restoration of a functional alveolar epithelial barrier that is capable of removing alveolar edema fluid by sodium-dependent vectorial fluid transport. Pulmonary fibrosis may occur, particularly in the setting of injurious mechanical ventilation (Chapter 91). However, lung function tends to improve over time in survivors of ARDS, and the fibrosis is often reversible.

Pathophysiology

The physiologic abnormalities are dominated by severe hypoxemia with shunting, decreased lung compliance, decreased functional residual capacity, increased pulmonary dead space, and increased work of breathing. Initially, the $Paco_2$ is low or normal, usually associated with increased minute ventilation. The initial abnormalities in oxygenation are thought to be related to alveolar flooding and collapse, which create a physiologic shunt. As the lung injury progresses, especially in patients who require ventilatory support, fibroproliferation may develop; the lungs (including alveoli, blood vessels, and small airways) remodel and scar, with a loss of microvasculature. Pulmonary microvascular thrombosis may also occur. In some patients, these changes may lead to pulmonary hypertension and increased pulmonary dead space; marked elevations in minute ventilation are sometimes required to achieve a normal $Paco_2$, even as oxygenation abnormalities are improving.

CLINICAL MANIFESTATIONS

In most cases of ARDS, the onset either coincides with or occurs within 72 hours of the onset of the underlying disease process; the mean time from onset of the underlying cause to onset of ARDS is 12 to 24 hours. The onset may be more protracted in patients with viral pneumonia, such as COVID-19 pneumonia due to SARS-CoV-2 infection (Chapter 337). The presenting clinical picture is dominated by respiratory distress and the accompanying findings of severe hypoxemia, tachypnea, an increase in minute ventilation, and generalized alveolar infiltrates or opacities on the chest radiograph. The clinical presentation may also reflect manifestations of the underlying disease process, such as severe sepsis with hypotension and other manifestations of systemic infection.

DIAGNOSIS

The key to diagnosis is to distinguish ARDS from pure cardiogenic pulmonary edema (Table 90-7). No specific blood test or bronchoalveolar lavage finding (Chapter 73) is sufficiently specific to be useful for diagnosing ARDS. Furthermore, ARDS may coexist with left ventricular failure or intravascular volume overload, and as many as 30% of ARDS patients can have an elevated pulmonary arterial wedge pressure at some point during their clinical course (Table 90-7).

TABLE 90-7 FEATURES ASSOCIATED WITH NONCARDIOGENIC AND CARDIOGENIC PULMONARY EDEMA*

NONCARDIOGENIC PULMONARY EDEMA (ARDS)	CARDIOGENIC PULMONARY EDEMA/VOLUME OVERLOAD
PRIOR HISTORY	
No history of heart disease	Prior history of heart disease
Appropriate fluid balance (difficult to assess after resuscitation from shock or trauma)	Hypertension, chest pain, new-onset palpitations; positive fluid balance
PHYSICAL EXAMINATION	
Flat neck veins	Elevated neck veins
Hyperdynamic pulses	Left ventricular enlargement, lift, heave, dyskinesis
Early diastolic gallop	S_3 and S_4; gallops
Absence of edema	Edema: flank, presacral, legs
ELECTROCARDIOGRAM	
Sinus tachycardia, nonspecific ST-T wave changes	Evidence of prior or ongoing ischemia, supraventricular tachycardia, left ventricular hypertrophy
CHEST RADIOGRAPH	
Normal heart size	Cardiomegaly
Peripheral distribution of abnormal opacities	Central or basilar abnormal opacities peribronchial and vascular congestion Cephalization of great vessels
Air bronchograms common (80%)	Septal lines (Kerley lines), air bronchograms (25%), pleural effusion
HEMODYNAMIC MEASUREMENTS	
Pulmonary artery wedge pressure < 15 mm Hg, cardiac index > 3.5 L/min/m^2	Pulmonary capillary wedge pressure > 18 mm Hg, cardiac index < 3.5 L/min/m^2 with ischemia, may be >3.5 L/min/m^2 with volume overload
ECHOCARDIOGRAM	
Transthoracic echocardiogram showing a left ventricular ejection fraction >50%	Transthoracic echocardiogram showing a decreased left ventricular ejection fraction
LABORATORY VALUES	
B-type natriuretic peptide < 100 pg/mL	B-type natriuretic peptide > 500 pg/mL

*These features are neither highly sensitive nor specific. Although the findings are more commonly associated with the type of pulmonary edema as listed, they do not have high positive or negative predictive value.
ARDS = acute respiratory distress syndrome.

TREATMENT

Treatment of ARDS consists predominantly of respiratory support and treatment of the underlying disorder (see Fig. 90-4).[10–12] Sepsis, which is a common predisposing condition for the development of ARDS, must be treated promptly (Chapter 94).

Because infection is the most common cause of ARDS, it is very important to identify the pulmonary or extrapulmonary source of infection. The differential diagnosis of pneumonia (Chapter 85) should be carefully considered, including determining whether the patient is immunosuppressed and, as a result, susceptible to a wider variety of infectious agents. Viral pneumonia from influenza (Chapter 332), respiratory syncytial virus (Chapter 330), or other viruses should be considered. A recent travel history should inform the patient's exposure to malaria (Chapter 316), leptospirosis (Chapter 298), ehrlichiosis (Chapter 302), or fungal infections such as coccidiomycosis (Chapter 308) or blastomycosis (Chapter 308). If the patient has an abdominal source of infection, then appropriate diagnostic imaging and surgical approaches are needed to establish a diagnosis and drain the infection. Any coexisting left heart failure or intravascular volume overload should be treated promptly (Chapter 46).

Current recommendations for lung-protective mechanical ventilation by endotracheal intubation in ARDS (Table 90-8) emphasize lower tidal volumes based on the patient's predicted body weight (Chapter 91).[A6] This approach also includes achieving a plateau airway pressure less than 30 cm H_2O. PEEP is a mainstay in the ventilatory strategy for ARDS. Although the method for determining the optimal level of PEEP has not been established, moderately high PEEP levels in the range of 12 to 20 cm H_2O may be beneficial compared with lower levels, but routine use of very high PEEP levels (greater than 20 cm H_2O) and large recruitment maneuvers is potentially detrimental.[A7] PEEP may allow a lower Fio_2 to provide adequate oxygenation, thereby reducing the risk of O_2 toxicity. It also may prevent the cyclic collapse and reopening of lung units, a process that is thought to be a major cause of ventilator-induced lung injury, even when adequate oxygenation can be obtained at relatively low levels of Fio_2. Routine early neuromuscular blockade does not appear to be beneficial,[A8] but it can be used to obtain patient-ventilator synchrony if deep sedation is not sufficient. In patients with severe ARDS who do not respond to standard therapy but otherwise have a reasonable life expectancy and do not have multiorgan failure, extracorporeal membrane oxygenation is an acceptable rescue therapy[13,14] that can be reserved for patients who require it for severe refractory hypoxemia.[A9] Data also indicate that prone positioning[15] reduces mortality in patients with moderate to severe ARDS (initial P/F < 150 mm Hg).[A10]

In patients with ARDS, a conservative fluid strategy decreases the duration of positive-pressure ventilation[A11] and can be instituted if a patient is not in shock, as defined by the need for vasopressors to support systemic blood pressure. The primary principle of a conservative fluid strategy is to achieve a daily net negative fluid balance of 0.5 to 2 liters, usually by limiting intravenous fluids and administering diuretics at least twice daily, though more frequent dosing may be required. Measurement of pulmonary artery or central venous pressure is not of major value for guiding fluid balance in most cases.

PROGNOSIS

Case-fatality rates are 30 to 50% and are highly dependent on disease severity, the underlying predisposing condition, and the presence of comorbid diseases. Based on the degree of hypoxemia (mild, 200 mm Hg < Pao_2/Fio_2 < 300 mm Hg; moderate, 100 mm Hg < Pao_2/Fio_2 < 200 mm Hg; and severe, Pao_2/Fio_2 < 100 mm Hg), inpatient mortality rates are about 27%, 32%, and 45%, respectively, not including patients with severe underlying conditions, such as end-stage cancer. Patients who require higher driving pressures while intubated

TABLE 90-8 ARDS NETWORK VENTILATORY MANAGEMENT PROTOCOL FOR TIDAL VOLUME AND PLATEAU AIRWAY PRESSURE

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- Female PBW: 45.5 + 2.3 (height in inches − 60) or 45.5 + 0.91 (height in centimeters − 152.4)

Select assist control mode
Set initial Vt at 8 mL/kg PBW
Reduce Vt by 1 mL/kg at intervals <2 hr until Vt = 6 mL/kg PBW
Set initial RR to approximate baseline minute ventilation (maximum RR = 35/min)
Set inspiratory flow rate higher than patient's demand (usually >80 L/min)
Adjust Vt and RR further to achieve P_{plat} and pH goals
- If P_{plat} >30 cm H_2O: decrease Vt by 1 mL/kg PBW (minimum = 4 mL/kg PBW)
- If pH ≤7.30, increase RR (maximum = 35)
- If pH <7.15, increase RR to 35; consider sodium bicarbonate administration or increase Vt

ARDS = acute respiratory distress syndrome; PBW = predicted body weight; P_{plat} = plateau pressure (airway pressure at the end of delivery of a tidal volume breath during a condition of no airflow); RR = respiratory rate; Vt = tidal volume.
See the ARDSNet website (http://www.ardsnet.org) for further details about the protocol, including the approach for setting positive end-expiratory pressure and fraction of inspired oxygen.

also have a worse prognosis. Memory, verbal fluency, and executive function are impaired in about 13%, 16%, and 49% of long-term survivors after ARDS.

ACUTE RESPIRATORY FAILURE WITHOUT LUNG DISEASE

Acute respiratory failure without pulmonary abnormalities (see Table 90-2) develops in patients with depressed ventilatory drive secondary to central nervous system dysfunction and in patients with severe neuromuscular disease. The prototypical patient with suppressed ventilatory drive has taken an overdose of a sedative or tranquilizing medication (Chapter 96). The prototypical patient with neuromuscular disease has Guillain-Barré syndrome (Chapter 388). The treatment for both types of patients is supportive. In the case of a patient with a sedative overdose, the threshold for intubation with mechanical ventilatory support should be low because this temporary condition is quickly reversible when the responsible drug is eliminated. In addition, such a patient may require intubation for airway protection against aspiration of gastric contents regardless of whether acute respiratory failure has developed.

Patients with Guillain-Barré syndrome (Chapter 388) or other forms of progressive neuromuscular disease should be monitored with serial measurements of vital capacity and of their ability to cough and swallow. In general, when the vital capacity decreases to less than 10 to 15 mL/kg body weight and the patient's normal upper airway reflexes are impaired for protection against aspiration of oropharyngeal or gastric contents, then intubation and mechanical ventilatory support should be considered without regard to the patient's $Paco_2$.

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91 MECHANICAL VENTILATION

LAURENT BROCHARD AND ARTHUR S. SLUTSKY

Mechanical ventilation is a life-sustaining therapy in which a mechanical device (the ventilator) provides partial or full support for patients with respiratory failure (Chapter 90). The main goals of ventilatory support are to maintain adequate gas exchange, to rest the respiratory muscles, and to decrease the oxygen cost of breathing, while minimizing iatrogenic consequences of ventilation. To achieve these goals, the clinician can use a variety of modes of ventilation and can alter the inspired oxygen fraction, the pressure at the end of a breath, and other facets of the volume or pressure time pattern generated by the ventilator.

Modern ventilation strategies focus on minimizing its iatrogenic consequences, such as hyperinflation (from endogenously derived positive pressure at the end of a breath; i.e., auto-PEEP), infection, oxygen toxicity, injury to the respiratory muscles (e.g., disuse atrophy or injury due to excessive loading), and ventilator-induced lung injury. A major goal of current ventilatory strategies is to protect the ventilated aerated lung and, to some extent, to protect the respiratory muscles. In some patients, the physician should be willing to accept arterial blood gases that are not in the normal range to avoid these complications, by using lower levels of minute ventilation or smaller tidal volumes than those required to normalize gas exchange.[1] As a result, targeting normal values of blood gases is not always preferred for critically ill patients in the intensive care unit (ICU). For example, a conservative protocol for oxygen therapy (e.g., a goal Pao_2 between 70 and 100 mm Hg or arterial oxyhemoglobin saturation between 94% and 98%) is at least as good as more aggressive or liberal oxygen therapy (e.g., Pao_2 up to 150 mm Hg or arterial oxyhemoglobin saturation between 97% and 100%).[A1,A2] However, further reducing the target Pao_2 to 55 to 75 mm Hg or an oxyhemoglobin saturation goal of 90% is not beneficial.[A3,A4] Other trade-offs include the acceptable level of $Paco_2$ and pH versus the minute ventilation and the risks related to excessive energy delivered to the lungs, and the degree of spontaneous breathing versus the risks of injury to the respiratory muscles from disuse atrophy or excessive loading.[2]

POSITIVE-PRESSURE VENTILATION

Modern mechanical ventilation delivers gas to the lung with positive-pressure ventilation applied through an endotracheal tube, a tracheostomy, or a tight-fitting mask. The approach using a mask is termed noninvasive ventilation (NIV).[3]

The most basic positive pressure mode is controlled ventilation, in which a pre-set tidal volume (volume-controlled) or a pre-set inspiratory pressure (pressure-controlled) is delivered at a predetermined rate and insufflation time, regardless of the patient's effort. This form of ventilation is used in patients who cannot initiate spontaneous breaths (e.g., heavily sedated or paralyzed patients) and/or in patients who need full ventilatory support because of extremely severe pulmonary (e.g., severe acute respiratory distress syndrome [ARDS]) or cardiovascular disease (e.g., severe shock).

A disadvantage of this approach is that respiratory muscle atrophy can occur relatively rapidly, since there is no respiratory muscle contraction. Another disadvantage is that gas exchange may not be optimal because the distribution of ventilation is altered compared with spontaneous breathing. This altered

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ABSTRACT

Mechanical ventilation is a life-sustaining therapy that is used to treat respiratory failure. The main goals of mechanical ventilation are to maintain adequate gas exchange, to rest the respiratory muscles, and to decrease the oxygen cost of breathing, while at the same time minimizing iatrogenic consequences. These consequences include complications of intubation and sedation, hyperinflation (i.e., auto-positive end expiratory pressure [PEEP]), hemodynamic compromise, disuse atrophy of respiratory muscles or other forms of muscle injury, and ventilator-induced lung injury. To mitigate complications, discontinuation of ventilatory support should be considered as early as possible, and the weaning process should be attempted expeditiously. This chapter summarizes the different types of ventilators, the various modes of ventilation, the physiology that underpins these modes, the complications of mechanical ventilation, and ventilatory strategies for specific disease entities, including acute respiratory distress syndrome (ARDS) and chronic obstructive pulmonary disease (COPD).

KEYWORDS

respiratory failure
gas exchange
artificial ventilation
ventilator-induced lung injury
ARDS
COPD

ventilation is an indirect effect of deep sedation, with or without paralysis, and the patient's supine position, both of which promote atelectasis in the dorsal regions of the lungs. For these reasons, it is best to limit the time that a patient is paralyzed and receiving controlled ventilation.

Assisted ventilation is a general term that describes mechanical ventilation in which the patient's spontaneous ventilatory effort triggers the ventilator to deliver a breath, rather than having the breaths delivered by the ventilator at a fixed rate. Assist-control ventilation (in pressure or volume control mode) uses settings similar to controlled ventilation for the delivery of each breath, but breaths can be triggered by the patient's spontaneous ventilatory effort; it will provide a baseline ventilatory rate if the patient fails to trigger the ventilator. The back-up rate is set to allow the patient to breathe at a faster rate than set on the ventilator. Assist-control is the most frequently used mode of ventilation at the early phase of mechanical ventilation.

Positive End-Expiratory Pressure

A key characteristic that can be combined with most ventilatory modes is the pressure level at end expiration. Positive end-expiratory pressure (PEEP) is used in patients with diffuse pulmonary diseases (e.g., pulmonary edema or ARDS) to prevent atelectasis, to reopen collapsed lung units or closed airways, or, more precisely, to help ensure that collapsed alveolar regions opened during inspiration remain open during expiration, so as to redistribute ventilation to dependent, atelectatic lung regions. All these changes can increase end-expiratory lung volume above the natural functional residual capacity and improve the matching of ventilation to perfusion, thereby frequently improving oxygenation and allowing the fractional inspiratory concentration of oxygen (F_{IO_2}) to be reduced. In addition, when PEEP is able to keep part of the lung reopened, the tidal volume can be delivered into a larger lung volume, thereby potentially reducing the risk of injury. PEEP does not usually improve alveolar ventilation and, in fact, it may increase dead space by overdistending alveoli, with a concomitant decrease in alveolar capillary blood flow in certain regions of the lung. The major risks of PEEP are overdistention of the lung (or regions of the lung) and hemodynamic consequences, such as decreasing cardiac output by decreasing venous return or increasing right ventricular afterload. The main limitation of titrating PEEP as a single pressure delivered to the whole lung is that the distribution of lung injury and collapse in patients with hypoxemia is influenced by gravity. Therefore, a certain level of positive pressure may effectively reopen the dorsal (dependent) lung region but excessively distend the ventral (nondependent lung).

Volume- and Pressure-Controlled Ventilation

Volume-controlled ventilation (or volume-limited ventilation) refers to mechanical ventilation in which the tidal volume (and usually the peak flow) is pre-set. The major advantage is that the delivered tidal volume is maintained even if lung mechanics change, thereby ensuring a more constant partial pressure of arterial carbon dioxide ($Paco_2$). If respiratory mechanics deteriorate, higher pressures may be required to achieve the tidal volume goal. In volume-controlled ventilation, an upper limit to applied airway pressure is commonly used for safety reasons.

With pressure-controlled ventilation, the ventilator delivers pressure-limited breaths to the patient. The delivered volume is variable and depends on the pre-set pressure, the ventilatory rate, the inspiratory time, and the patient's respiratory mechanics (resistance, compliance, and auto-PEEP). The ventilation resulting from volume and pressure-controlled ventilation is very similar in passive conditions.

Assist-control ventilation can accompany either volume-limited ventilation or pressure-limited ventilation. Pressure-controlled breaths are often considered more comfortable for the patient because they do not limit the flow or delivered volume in response to patient's demand. The disadvantage is that tidal volume is more difficult to control because it is greatly influenced by patient effort. With volume assist-control, the volume is strictly controlled, but local overdistention can still occur when the patient is breathing with high intensity and a high respiratory drive. In this latter case, high inspiratory peak flows are required to allow the ventilator to meet the patient's volume demands to minimize the work of breathing required by the patient.

Intermittent Mandatory Ventilation

Intermittent mandatory ventilation (IMV) is a mode in which the patient receives some pre-set (and thus mandatory) volume or pressure-limited breaths from the ventilator but in which the patient also breathes spontaneously with different or no support above a certain rate. The so-called mandatory breaths are triggered by the patient and are synchronized (synchronized IMV), and spontaneous breaths are often aided by pressure-support ventilation. This mode has fallen into disfavor, based on clinical studies showing that it leads to longer durations of ventilation.

Pressure-Support Ventilation

Pressure-support ventilation is a pressure-limited, patient-triggered form of assisted ventilation. The patient triggers each ventilator breath by creating either a small negative pressure or a low inspiratory flow at the airway opening, and the ventilator switches to inspiratory mode and provides the airflow needed to maintain a pre-set level of pressure. In contrast to pressure-controlled ventilation, the inspiratory time is not fixed and terminates when the inspiratory airflow decreases to a threshold level (a level that is often adjustable by the person responsible for the ventilator). This mode provides flexibility for the patient with respect to tidal volume, inspiratory flow, respiratory rate, and ratio of time allowed for inspiration compared with expiration. Tidal volume depends on the patient's effort, respiratory system mechanics, and the level of pressure set for support. It is considered to be comfortable for the patient.

The disadvantage of pressure-support ventilation is that it is easy to over-assist the patient because a minimal ventilation (determined by pressure and compliance) is always delivered regardless of the patient's effort.[4] It can thereby deliver breaths that exceed a patient's needs, both in terms of volume and inspiratory duration, and often result in patient-ventilator asynchrony. Pressure-support ventilation has been used to help wean patients because it provides a simple way of reducing the magnitude of mechanical support as the patient assumes a larger fraction of the ventilatory work. It also has become the most frequently used mode of ventilation when the patient begins to stabilize.

High-Frequency Ventilation

High-frequency ventilation refers to modes of ventilation delivered at frequencies that are substantially greater than those used during normal breathing. During high-frequency ventilation, tidal volumes may be less than the dead space, so adequate gas transport takes place by various convective and diffusive mechanisms. Interest in these modes of ventilation has waned for adult patients because it appears to be no better or even worse than conventional ventilation for adults with ARDS.

Proportional Assist Ventilation and Neurally Adjusted Ventilatory Assist

Two major difficulties in providing assisted ventilation are ensuring adequate synchrony between the patient's respiratory pattern and the delivery of the ventilator's breaths and adapting to the patient's variable demand over time. The first point is particularly of concern for patients with markedly abnormal respiratory mechanics, including significant auto-PEEP. Two modes of ventilation, proportional assist ventilation and neurally adjusted ventilatory assist, can partly address these concerns. Both modes deliver ventilation (and pressure) in direct proportion to the instantaneous effort of the patient. However, neither approach is in widespread use because they are not available on all ventilators and because of limited clinical data. Nevertheless, some evidence suggests that these modes may reduce the time spent on the ventilator.[A5]

Noninvasive Positive-Pressure Ventilatory Support

Positive-pressure ventilation can be provided through a mask rather than through an endotracheal tube. This method, which has been termed noninvasive because the patient is not intubated, is conceptually simple but requires appropriate implementation and monitoring for successful application. Of particular importance are patient selection and training of hospital personnel. Patients must be alert, cooperative, and hemodynamically stable. Patients must also have intact upper airway reflexes to prevent aspiration, and they must not have facial trauma that precludes the use of a mask. Once patients are started on noninvasive ventilation, they should be carefully monitored, and noninvasive ventilation should be discontinued if the patient's clinical condition deteriorates, if the patient develops cardiovascular instability, or if it appears that the patient is likely to aspirate. Noninvasive ventilation also can be delivered through a "helmet," thereby avoiding some of the problems associated with use of face masks.[A6]

Noninvasive ventilation offers advantages compared with invasive ventilation because it can avoid many complications associated with intubation and sedation; patients are able to speak and to eat if they are sufficiently stable to remove the mask for short periods, and they are probably able to sleep better. Noninvasive ventilation is also relatively simple to apply, and it can be used for short intervals because it can be started and stopped easily.

However, noninvasive ventilation has limitations and risks. Adequate implementation can be labor intensive, and the time course of correction of blood gases is slower than usually occurs if patients are intubated and ventilated. Data strongly support the use of noninvasive ventilation for patients with chronic obstructive pulmonary disease (COPD; see Chapter 76) or cardiogenic pulmonary edema with elevated CO_2. It is uncertain whether noninvasive ventilation improves outcomes or unduly delays intubation in patients who have hypoxemic respiratory failure and who do not also have concomitant ventilatory failure (i.e., hypoxemic, nonhypercapnic, respiratory failure).

PEEP also can be administered to spontaneously breathing patients by a technique termed continuous positive airway pressure (CPAP). In patients with exacerbations of COPD, PEEP and CPAP can overcome some of the negative mechanical consequences of auto-PEEP (see later) and minimize the work of breathing, provided that the magnitude of the PEEP is sufficiently low that it does not cause additional hyperinflation. CPAP is very effective for relieving the respiratory distress associated with cardiogenic pulmonary edema, in which it has clinical benefits similar to those of noninvasive ventilation. Both noninvasive ventilation and CPAP also can be useful in the postoperative period after thoracic or abdominal surgery to prevent reintubation.

High-flow nasal oxygen (HFNO) therapy offers an attractive alternative for supporting patients who have hypoxemic respiratory failure.[A7] Heated and fully humidified gas at adjustable levels of oxygen concentration is delivered through the nose to the upper airways. This technique generates low levels of positive pressure, washes out the upper airway dead space, and is associated with reduced mortality in patients with acute hypoxemic respiratory failure.[A8]

COMPLICATIONS OF MECHANICAL VENTILATION

INTUBATION, SEDATION, AND BED IMMOBILIZATION

Endotracheal intubation can act as a conduit to deliver gas from the ventilator to the patient, secure a patient's airway, prevent aspiration, and help with pulmonary toilet. However, intubation can be associated with complications, including a risk of aspiration or hypoxemia during insertion of the endotracheal tube, difficulty in swallowing and communicating, disruption of normal host defense mechanisms, and upper airway trauma. Pressure from the cuff of the endotracheal tube that provides a pneumatic seal between the tube and trachea can lead to tracheal ischemia and may eventually cause tracheal stenosis. Bag-mask ventilation during tracheal intubation can maintain better oxygen saturation concentrations and reduce the risk of severe hypoxemia.[A9]

The upper airway is normally an effective means of heating and humidifying inspiratory gases. This natural system is bypassed by an endotracheal tube; inadequately humidified inspiratory gases reduce mucociliary clearance and can lead to inspissation of tracheal secretions and occlusion of the endotracheal tube.

Intubation increases the likelihood of nosocomial pneumonia (Chapters 85 and 261) by a number of mechanisms. Cough involves an increase in airway pressure as respiratory muscles contract against a closed glottis; this mechanism is impaired in the presence of the tube. A cuffed endotracheal tube helps prevent gross aspiration, but pharyngeal secretions that pool at the top of the cuff often seep into the lungs. Endotracheal tubes often become colonized with the microorganisms that cause ventilator-associated pneumonia (Chapter 85). Silver-coated tubes may reduce this risk in selected patients but are considerably more expensive than conventional endotracheal tubes and are unlikely to be used routinely for initial intubation. Endotracheal tubes with a port that allows suctioning of secretions above the cuff may also reduce the incidence of ventilator-associated pneumonia, although results of studies have been mixed.

Endotracheal intubation is often not well tolerated in awake patients, in whom the tube is more likely to be inadvertently dislodged—a complication that can have tragic consequences. Sedation reduces these problems and also prevents or treats dyssynchronies between the patient's respiratory drive and the delivery of gas from the ventilator. Modern strategies focus on reducing sedation as much as possible, thereby facilitating early mobilization of the patient even while ventilated but still allowing for patient-ventilator synchrony. Daily interruption of sedation, light sedation, or no sedation have all been tested with various results in terms of ICU length of stay and mortality.[A10] Studies suggest that adjunctive dexmedetomidine can reduce the time on the ventilator and decrease the incidence of delirium[A11] compared with benzodiazepines, but it has not been shown to impact mortality, and patients may require more supplemental sedation.[A12] Endotracheal intubation, sedation, and paralysis can lead to atelectasis and can reduce functional residual capacity by at least 20%, even in patients with normal lungs.

To decrease sedation, enhance patient mobilization, and improve oral care and feeding, a tracheostomy can be performed. However, tracheostomy is associated with its own complications, and performing a tracheostomy in the first week is frequently no better than waiting until the patient has been ventilated for about 10 to 15 days, in part because clinicians cannot accurately predict which patients will require prolonged ventilatory support. As a result, a common practice is to consider tracheostomy when a patient has been intubated for at least 2 weeks.

HEMODYNAMIC COMPROMISE

Cardiovascular instability, which is the most common peri-intubation complication, may occur in up to 40% of emergency intubations.[5] The subsequent major mechanical determinants of cardiovascular hemodynamics during mechanical ventilation are intrathoracic pressure, changes in lung volume, and the patient's circulatory volume status. An increase in lung volume can be beneficial if it opens lung units that had been closed (thereby leading to a decrease in pulmonary vascular resistance), or it can be detrimental if the resulting pulmonary overdistention leads to compression of alveolar vessels and increased pulmonary vascular resistance. One complication of mechanical ventilation with high pressures is therefore excessive right ventricular loading and acute cor pulmonale.

Positive pressure can affect cardiovascular hemodynamics through its effect on pleural pressure, an effect that is related to changes in lung volume and chest wall stiffness but not necessarily directly reflected in measurements of airway pressure. For example, in a patient with low lung compliance (e.g., ARDS), a given increase in airway pressure will lead to a much lower increase in lung volume than in a patient with COPD, so the increase in pleural pressure will be much lower. As a result, patients with ARDS tolerate relatively higher PEEP levels compared with patients with COPD. At high lung volumes, a direct effect of the pressure of the lung on the heart can increase pericardial pressure and can thereby decrease cardiac filling. Obese patients can tolerate PEEP levels on average 8 cm H_2O above those used in non-obese patients because obese patients have higher intrathoracic pressures generated by the load of the chest wall and abdomen.[6]

AUTO-PEEP, DYNAMIC HYPERINFLATION, AND AIRWAY CLOSURE

A key factor that affects cardiovascular hemodynamics and other physiologic variables is the development of auto-PEEP, defined as the difference between alveolar pressure and airway opening pressure at end expiration. The auto-PEEP is associated with dynamic hyperinflation, which is an increase in the end-expiratory lung volume above the value that would be obtained if there was complete exhalation to the static functional residual capacity. This phenomenon occurs whenever time is insufficient for complete exhalation to occur. The major determinants of auto-PEEP and hence dynamic hyperinflation are high minute ventilation, increased expiratory airway resistance, increased respiratory system compliance, and decreased expiratory time. In addition, expiratory flow limitation may further aggravate hyperinflation in patients with small airway pathology. The auto-PEEP phenomenon is a reason to reduce the tidal volume delivered to patients' lungs.

Auto-PEEP is not detected at the airway opening during the ventilator cycle, because the pressure drop occurs across the airways upstream of where the airway pressure is measured in the ventilatory circuit. When patients are not making spontaneous breathing efforts, auto-PEEP can be easily assessed as the difference in pressure between the set PEEP and the pressure obtained when the airway opening is occluded at the end of expiration (E-Fig. 91-1). If it is considered safe for the patient, a rapid estimate of the effect of auto-PEEP on cardiovascular hemodynamics can be obtained by a prolonged expiration to atmosphere. Matching the alveolar pressure, referred to as total PEEP, is especially important when the patient triggers the ventilator. Reliable measurements of auto-PEEP, however, are more difficult to obtain in spontaneously breathing patients.

If auto-PEEP is not considered in the interpretation of respiratory mechanics, measurements of respiratory system compliance can be falsely low. Dynamic hyperinflation can be measured as the volume of gas that is released during a prolonged expiration (20 to 30 seconds).

Auto-PEEP should be suspected whenever flow at end expiration remains detectable or when a patient fails to trigger the ventilator consistently with inspiratory efforts. This failure to trigger the ventilator occurs because the patient must generate sufficient pressure to overcome the level of auto-PEEP before a negative deflection of pressure or generation of inspiratory flow (either of which may be used by the ventilator to detect the onset of inspiration) is sensed at the airway opening. These failed attempts are referred to as ineffective efforts, and they occur in more than 10% of breathing efforts in about 25% of patients who receive pressure support ventilation, usually because the patients receive ventilatory volume in excess of the expiratory capacity of the

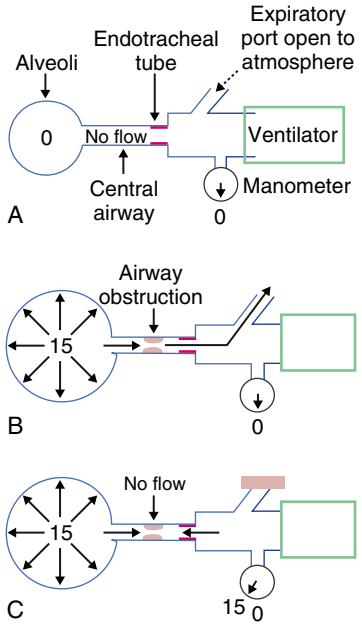

E-FIGURE 91-1. **The relationships among alveolar, central airway, and ventilator circuit pressure at the end of exhalation under the following conditions: A**, Normal conditions (no auto-positive end-expiratory pressure [auto-PEEP]). **B**, Severe dynamic airway obstruction with the expiratory port open. **C**, Severe dynamic airway obstruction with the expiratory port occluded at the end of exhalation. The auto-PEEP level is identified by creating an end-expiratory hold, thereby allowing the alveolar, central airway, and ventilator circuit pressures to equilibrate because there is no flow in the circuit. During equilibration, the level of auto-PEEP can be read on the manometer in the ventilator circuit. (Modified from Pepe PE, Marini JJ. Occult positive end-expiratory pressure in mechanically ventilated patients with airflow obstruction: the auto-PEEP effect. *Am Rev Respir Dis*. 1982;126:166-170.)

patient's respiratory system. As a result, the respiratory rate of the ventilator may be considerably lower than the patient's real respiratory rate.

Auto-PEEP and the attendant dynamic hyperinflation have detrimental consequences. In a patient who is not breathing spontaneously, dynamic hyperinflation increases pleural pressure and right atrial pressure, thereby leading to a decrease in the driving pressure for venous return. This effect can be magnified immediately after intubation and initiation of mechanical ventilation because compensatory mechanisms to enhance venous return are impaired by pharmacologic agents used for intubation, which itself also reduces venous and arterial tone.

Auto-PEEP is more likely to occur in patients with airway obstruction, especially when expiratory flow limitation is present. Minimizing auto-PEEP, which is a fundamental principle in ventilating patients who have severe airway obstruction, can best be achieved by decreasing minute ventilation, increasing expiratory time, and decreasing airway resistance (e.g., using bronchodilators, when appropriate).

Another phenomenon that can affect ventilation, especially in patients with ARDS or obesity, is referred to as airway closure, in which some airways are either continuously closed or cyclically open and close during ventilation. Although an airway is closed, the lung distal to the closure still may be inflated. The pressure needed to reopen the airways during each insufflation may reach more than 20 cm H_2O. Airway closure, which occurs in 30 to 60% of patients with ARDS,[7] can be visualized by performing a low-flow inflation pressure-time (or pressure-volume) maneuver.[8]

VENTILATOR-INDUCED LUNG INJURY

The forces generated during mechanical ventilation can cause lung injury (E-Fig. 91-2). High levels of inspired oxygen concentrations can cause oxygen toxicity.

Barotrauma refers to pulmonary air leaks, such as pneumothorax and pneumomediastinum. Other forms of pressure injury include diffuse alveolar damage presenting as pulmonary edema and biotrauma. For these types of injury, the critical factor is the degree of overdistention of the lung, which is related to the transpulmonary pressure, defined as airway pressure minus pleural pressure, when airway flow is zero. Esophageal pressure (Pes), measured with an esophageal balloon, is used clinically to estimate pleural pressure.

A high peak pressure does not necessarily indicate an increased propensity to overdistention. For example, use of a smaller endotracheal tube will increase peak pressure, but the danger of pulmonary overdistention is no greater than would be present if the patient was ventilated with a larger-bore tube and a lower peak pressure, provided there is no auto-PEEP. The plateau pressure, which is the airway pressure at the end of an end-inspiratory pause (usually after 0.2 to 0.5 seconds), is an easy-to-measure direct estimate of peak alveolar pressure. As a first approach in patients with ARDS, the plateau pressure should be kept below 30 cm H_2O to minimize the risks of distention. If the patient is breathing spontaneously, however, pleural pressure will be negative, and overdistention may occur even with a plateau pressure much lower than 30 cm H_2O because the transpulmonary pressure distending the lung could be high during the patient's inspiratory effort. Conversely, in a patient who is not making ventilatory efforts and who has a stiff chest wall (e.g., owing to obesity, ascites, abdominal compartment syndrome, pregnancy), much of the pressure increase will be dissipated across the chest wall, and a high plateau pressure may not be indicative of lung distention.

An even better prediction of risk of ventilator-induced lung injury may be the driving pressure, termed δP, which is equal to plateau pressure minus PEEP (or total PEEP). Values above 15 cm H_2O are associated with increased mortality.

During mechanical ventilation, some areas of the lung may undergo cyclic recruitment and de-recruitment, a process termed atelectrauma. Prevention of this type of injury provides part of the rationale for the use of PEEP to maintain recruitment of lung units during tidal ventilation (Video 91-1).

Ventilatory strategies that promote overdistention and atelectrauma can lead to an inflammatory response in the lung, a mechanism of injury termed biotrauma. The release of proinflammatory cytokines and chemokines and can potentially lead to dysfunction of other organs (E-Fig. 91-3), thereby suggesting that optimal ventilatory strategies are important not only to maintain lung function but also to prevent the development of multiple-organ dysfunction (Chapter 90). This hypothesis may explain the lower mortality when patients with ARDS are treated with a strategy designed to minimize ventilator-induced lung injury.

Lung injury also can occur in patients who have high respiratory drive. This drive can translate into large negative intrathoracic pressures that lead to injury that has been termed "patient self-inflicted lung injury," which can occur whether the patient is being ventilated or not. An increased respiratory rate can also contribute to ventilator-induced lung injury, albeit to a lesser degree.[9]

TABLE 91-1 STEPS AND GUIDELINES FOR INITIATION OF MECHANICAL VENTILATION*

1. Ventilatory mode
   Unintubated patients
   - NIV for patients with COPD and acute hypercapnic respiratory failure, if patient is cooperative and hemodynamically stable
   - NIV not routinely recommended for acute hypoxemic respiratory failure; high-flow oxygen therapy may be initiated in these patients, or the patients may be intubated

   Intubated patients
   - Assist/control volume-limited ventilation or PCV as initial mode
   - PSV: consider as soon as patient's effort are reasonable, respiratory mechanics are such that pressure support levels of 10-15 can be used, ventilatory needs are moderate to low, and the patient is more comfortable during PSV trial than while receiving full ventilatory support
   - Oxygenation:
     - If there are infiltrates on chest radiograph, begin with F_{IO_2} 0.8 (avoid 1.0 if possible), reduce rapidly according to Spo_2; PEEP: begin with 5 cm H_2O, but use rapidly higher levels if oxygenation is poor and Pplat high (i.e., up to 15 cm H_2O in severe ARDS). Adapt according to Pao_2 or Spo_2, F_{IO_2} requirements, and hemodynamic effects; consider PEEP/F_{IO_2} "ladder" or estimate of recruitability (recruitment to inflation ratio; see Fig. 91-1); goal of Spo_2 >90% and ≤96% (except in the case of acute myocardial infarction), F_{IO_2} adapted to Spo_2
     - If no infiltrates on chest radiograph (COPD, asthma, PTE), start at F_{IO_2} 0.4 and adjust according to Spo_2 (consider starting higher if pulmonary embolism is strongly suspected)
     - Tidal volume: begin with 8 mL/kg PBW (see Fig. 91-1 for formulas); decrease to 6 mL/kg PBW over a few hours if ARDS present (see Fig. 91-1); inspiratory flow rate of 50-60 L/min
     - Rate: begin with 10-20 breaths/min (10-15 if not acidotic; 20-30 if acidotic or ARDS and small volumes); adjust for pH; goal pH > 7.3 with maximal rate of 35; may accept higher $Paco_2$ and lower pH goal if minute ventilation high
2. Secondary modifications
   - Triggering: in assisted modes, minimize diaphragm inactivity
   - Assessment of auto-PEEP, especially in patients with increased airways obstruction (e.g., asthma, COPD)
3. Monitoring
   - Clinical: blood pressure, ECG, observation of ventilatory pattern including assessment of dyssynchrony, minimal effort or work by the patient (as measured by the pressure at the airway opening of 2-4 cm H_2O or less when flow is occluded for 100 msec), assessment of airflow throughout the expiratory cycle
   - Ventilator: tidal volume, minute ventilation, airway pressures (including auto-PEEP), total compliance
   - Arterial blood gases, pulse oximetry

*Decisions within this algorithm will be influenced by the specific conditions of the individual patient.

ARDS = acute respiratory distress syndrome; COPD = chronic obstructive pulmonary disease; ECG = electrocardiogram; F_{IO_2} = fraction of inspired oxygen; HFOV = high-frequency oscillatory ventilation; I/E ratio = inspiratory-to-expiratory ratio; NIV = noninvasive ventilation; $Paco_2$ = arterial partial pressure of carbon dioxide; Pao_2 = partial pressure of oxygen in arterial blood; PBW = predicted body weight; PCV = pressure-controlled ventilation; PEEP = positive end-expiratory pressure; Pplat = plateau pressure; PSV = pressure-support ventilation; PTE = pulmonary thromboembolism; Spo_2 = arterial oxygen saturation by pulse oximetry.

Finally, mechanical ventilation can also lead to diaphragmatic weakness and dysfunction after a few days of mechanical ventilation. Respiratory muscle weakness is strongly associated with difficulties in weaning the patient from ventilator support.[10]

SPECIFIC COMMON TREATMENT SCENARIOS

INITIATION OF MECHANICAL VENTILATION

The initiation of mechanical ventilation involves several steps in clinical decision making (Table 91-1). Each patient must be evaluated for specific factors that could modify the recommendation or mandate an alternative.

ACUTE RESPIRATORY DISTRESS SYNDROME

Patients with ARDS (Chapter 90) have noncardiogenic pulmonary edema, with a reduced functional residual capacity and a mortality rate that commonly exceeds 30%. Although therapy may be available for the underlying disease process that led to the development of ARDS (e.g., antibiotics for a predisposing pneumonia), and corticosteroids may reduce subsequent damage, no therapy directly reverses diffuse alveolar damage. These patients require mechanical ventilation as a life-supportive therapy to improve oxygenation decrease the work of breathing and reduce the associated oxygen cost of breathing until their lungs recover from the primary insult that led to the alveolar damage. The

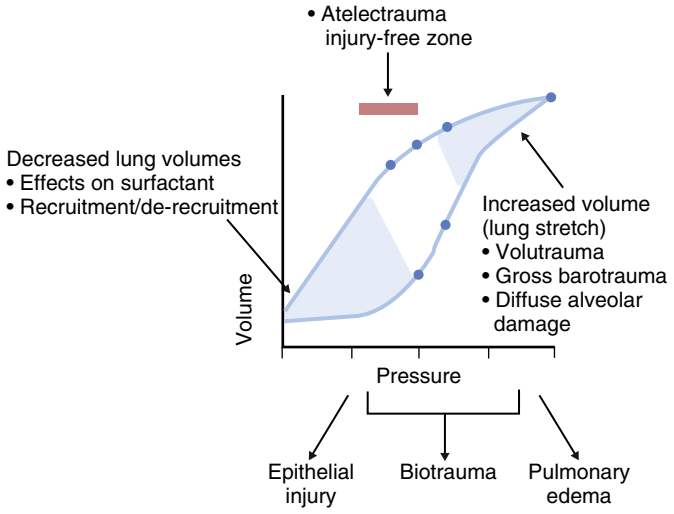

E-FIGURE 91-2. Schematic representation of the pressure-volume curve of a lung with diffuse alveolar edema. Mechanical ventilation can induce or worsen lung injury by numerous mechanisms when ventilation occurs at high lung volumes or when ventilation occurs at low lung volumes. Lung-protective strategies during ventilation of patients with acute respiratory distress syndrome should try to keep the ventilatory pattern in the injury-free zone. Data in patients confirm the benefit of limiting overdistention.

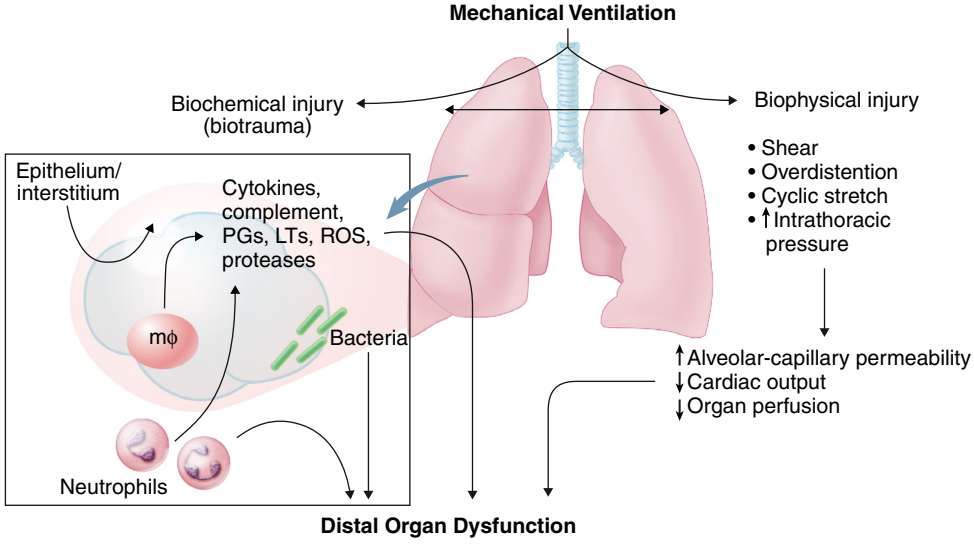

E-FIGURE 91-3. Mechanisms by which mechanical ventilation may lead to distal organ dysfunction. LTs = leukotrienes; mϕ = macrophages; PGs = prostaglandins; ROS = reactive oxygen species. (Modified from Slutsky AS, Tremblay LN. Multiple system organ failure: is mechanical ventilation a contributing factor? *Am J Respir Crit Care Med*. 1998;157:1721-1725.)

Ventilatory Strategy for Patients with ARDS*

Goal 1: Low Vt /P_{plat}

Initiation:
Calculate PBW
—Male:
50 + 2. 3 (height [inches] – 60)
—Female:
45.5 + 2.3 (height [inches] – 60)

Initiate volume assist control
—start with 8 mL/kg, and to
6 mL/kg over a few hours

↓

Keep P_{plat} (based on 0.5-sec pause) < 35 cm H_2O
If P_{plat} > 30 cm H_2O, Vt by 1 mL/kg to 5 or 4 mL/kg
If P_{plat} < 25 AND Vt < 6 mL/kg, Vt by 1 mL/kg until P_{plat} > 25 cm H_2O OR Vt = 6 mL/kg
If patient severely distressed and/or breath stacking, consider Vt to 7 or 8 mL/kg, as long as P_{plat} ≤ 30 cm H_2O†

Goal 2: Adequate Oxygenation

Specific goal:
Pao_2 55-80 mm Hg
or
Spo_2 88-95%

Use only FIO_2 /PEEP combinations shown below to achieve this target
- if oxygenation is low, choose FIO_2 /PEEP combination (from FIO_2 /PEEP table) to the right
- if oxygenation is high, choose FIO_2 /PEEP combination to the left

Goal 3: Arterial pH

Goal:
pH: 7.30–7.45

Acidosis algorithm
If pH 7.15–7.30
- set rate until pH > 7.30 or $Paco_2$ < 25 mm Hg (max RR = 35)
- if RR = 35 & pH < 7.30 $NaHCO_3$ may be given

If pH < 7.15
- set RR to 35
- if set RR = 35 & pH < 7.15, Vt may be in 1 mL/kg steps until pH > 7.15

(P_{plat} target may be exceeded)

Alkalosis algorithm
If pH > 7.45
- set RR until patient RR > set RR

(minimum set RR = 6/min)

FIO_2/PEEP Table

FIO_2	0.3	0.4	0.4	0.5	0.5	0.6	0.7	0.7	0.7	0.8	0.9	0.9	0.9	1.0
PEEP	5	5	8	8	10	10	10	12	14	14	14	16	18	18–24

*Based on ARDS Network Algorithm
†If compliance of the chest wall is markedly decreased (e.g., massive ascites), it may be reasonable or necessary (if the patient is very hypoxemic) to allow a P_{plat} >30 cm H_2O.

FIGURE 91-1. Ventilatory strategy for patients with the acute respiratory distress syndrome (ARDS) as proposed by the ARDSNetwork. FIO_2 = fraction of inspired oxygen; $Paco_2$ = arterial partial pressure of carbon dioxide; Pao_2 = arterial partial pressure of oxygen; PBW = predicted body weight; Pplat = plateau pressure; RR = respiratory rate; Spo_2 = oxygen saturation based on pulse oximeter; Vt = tidal volume.

major therapeutic goal is to provide adequate gas exchange while ensuring that damaged lungs are not further injured by the ventilatory strategy and/or by spontaneous breathing. The ventilatory approaches used to achieve this goal are termed lung-protective ventilation or lung-protective strategies.

Lung-Protective Ventilation Strategies

Because the heavy, edematous lung in ARDS behaves like a sponge, the distribution of lesions is influenced by gravity: most patients have a dependent zone that is either consolidated and fluid filled or atelectatic and recruitable; a nondependent, often small zone that looks normal; and a middle zone with poorly aerated regions that can be recruited to resemble the nondependent regions. Alveolar recruitment, which can occur during ventilation, is facilitated by PEEP or by transient high levels of airway pressure. Gas exchange can often be improved by high tidal volumes but at the expense of regional overdistention of lung units that were not affected by the disease process itself—a treatment strategy that can lead to worse lung injury and poorer clinical outcomes.

Ventilator-induced lung injury can be minimized by strategies that avoid or diminish regional lung overdistention. For example, the use of lower tidal volumes (6 mL/kg predicted body weight) along with plateau pressure less than 30 cm H_2O can decrease mortality by about 20% (from an absolute value of about 40% to about 30%) compared with 12 mL/kg predicted body weight, even though larger tidal volumes provide higher values of Pao_2 (see Fig. 91-1). Lung-protective strategies also may be useful in ventilated patients who are intubated for reasons other than ARDS (e.g., intubated ICU patients, patients undergoing major abdominal surgery, and patients with brain death whose lungs may subsequently be donated for transplantation).

Several caveats should be considered in using the low tidal volume strategy. First, the protocols mandate a tidal volume of 6 mL/kg or less of predicted body weight if the plateau pressure is greater than 30 cm H_2O and allow small increases in tidal volume if the patient is severely distressed and develops breath stacking (i.e., unintended high tidal volumes that occur as a consequence of incomplete exhalation between consecutive inspiratory cycles delivered by the ventilator). Driving pressure may better reflect the risk of injury, and larger tidal volumes may be used safely in patients with higher compliance,[I1] so as to avoid the detrimental consequences of low tidal volumes (e.g., respiratory acidosis, further atelectasis, lower Pao_2, poor patient-ventilator synchrony, and increased need for sedation). Second, respiratory acidosis can be treated with increasingly aggressive strategies depending on the arterial pH. Third, in specific patients with a stiff chest wall or with elevated intrathoracic pressures owing to obesity, it is reasonable for the plateau pressure to increase to greater than 30 cm H_2O.

Positive End-Expiratory Pressure

Some level of PEEP is necessary to reduce lung injury by recruiting lung units and keeping them open. PEEP also may be used to keep airways open in cases of airway closure.[I2] The critical issue, however, is how to set the optimum PEEP level in an individual patient and to determine whether procedures to recruit lung units and keep them open are more harmful than allowing the lung units to remain de-recruited. A bedside index of lung recruitability, termed the recruitment-to-inflation ratio, measures the change in expired volume when PEEP is abruptly reduced from 15 to 5 cm H_2O and calculates the compliance of the recruited lung by dividing the change in volume by the effective pressure change.[I3]

Data suggest that higher PEEP levels (about 12 to 13 cm H_2O) may be better than lower levels (about 8 cm H_2O),[A13,A14] and PEEP levels are often individualized on the basis of the relationship of PEEP to FIO_2 (see Fig. 91-1). Higher PEEP levels are probably associated with decreased mortality in severe and moderate ARDS (Pao_2/FIO_2 <200 mm Hg) but not in patients with mild ARDS with higher Pao_2/FIO_2 ratios; very high PEEP associated with recruitment maneuvers and an open-lung strategy can be harmful.[A15] PEEP guided by esophageal pressures has not been shown to improve outcomes when used in all patients, but possible benefits have been suggested in less severe disease and in obese patients.[A16]

Adjunctive Approaches for Ventilating ARDS Patients

The routine use of neuromuscular blockers is not recommended in patients with moderate-severe ARDS,[A17] but the judicious use of these agents may be beneficial in selected patients (e.g., patients with patient-ventilator asynchrony that leads to breath stacking or patients with very large inspiratory efforts). Use of prone rather than the supine position in patients with ARDS improves oxygenation, permits a more even distribution of pleural pressure and distribution of ventilation, reduces ventilator-induced lung injury because of a more optimal distribution of ventilation, and decreases mortality by about 15% in ARDS patients with Pao_2/FIO_2 less than 150 mm Hg.[A18] This life-saving procedure should be used irrespective of its effect on oxygenation in any given patient.

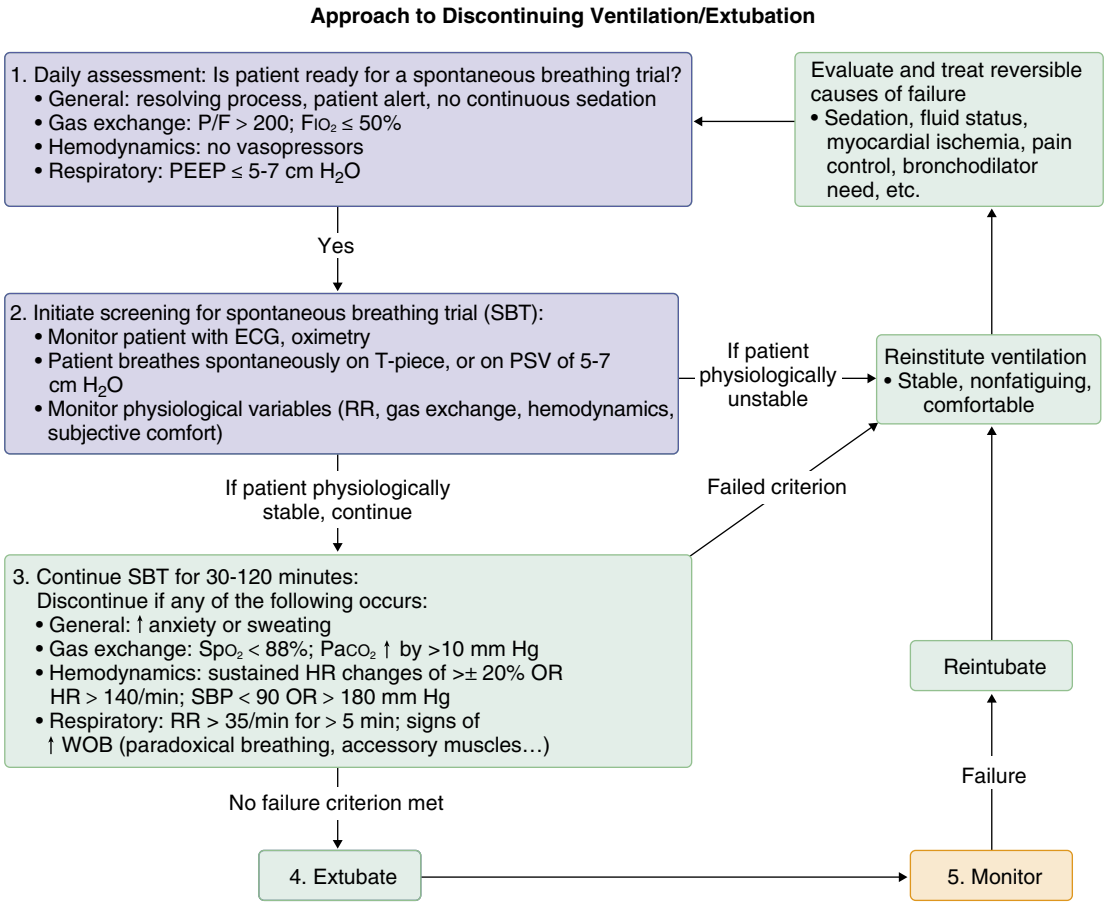

FIGURE 91-2. Algorithm for assessing whether a patient is ready to be liberated from mechanical ventilation and extubated. ECG = electrocardiogram; HR = heart rate; $Paco_2$ = arterial partial pressure of carbon dioxide; PEEP = positive end-expiratory pressure; P/F = Pao_2/Fio_2 ratio; PSV = pressure support ventilation; RR = respiratory rate; SBP = systolic blood pressure; Spo_2 = oxygen saturation based on pulse oximeter; WOB = work of breathing.

OBSTRUCTIVE AIRWAYS DISEASES

The major physiologic abnormality in patients with obstructive airways diseases (e.g., COPD, asthma) is an increase in airway resistance with limitation in tidal expiratory airflow. The result is dynamic hyperinflation, which is associated with numerous complications. The first goal in the ventilatory support of these patients is to avoid intubation by using noninvasive ventilation. If the patient is hemodynamically stable and does not need to be intubated to protect the airway, this strategy is usually applied using pressure support and positive end-expiratory airway pressure.

OTHER CONDITIONS

If patients require intubation, it is important to minimize auto-PEEP, maintain reasonable ventilation (normalizing pH more than $Paco_2$), and rest the respiratory muscles to decrease the oxygen cost of breathing, while simultaneously minimizing the iatrogenic complications of mechanical ventilation. These strategies allow time for the diagnosis and treatment of the primary cause of the exacerbation (Chapters 75 and 76). When the patient is being assisted by the ventilator and the patient has an intrinsic PEEP higher than the external PEEP, adding external PEEP to match the patient's intrinsic PEEP is essential to reduce the work of breathing.

Intubation and Ventilation

The key goal after intubation of patients with airway obstruction is to minimize the detrimental effects of dynamic hyperinflation. The most effective approach is to minimize the delivered minute ventilation, even if this strategy does not normalize $Paco_2$. Judicious use of sedation may decrease the production of carbon dioxide and improve patient-ventilator synchrony, but the avoidance of sedation can reduce the duration of ventilation and hospitalization.

In patients who have COPD and who are spontaneously breathing, the addition of external (set) PEEP at a level that is just less than what is necessary to overcome the auto-PEEP will not increase hyperinflation and may decrease the inspiratory effort that the patient needs to generate to initiate inspiratory airflow. This strategy does not appear to be as effective in patients with status asthmaticus, however.

Noninvasive ventilation or even simple CPAP is extremely useful for patients with respiratory distress related to cardiogenic pulmonary edema. Patients who are obese or have sleep disorders may require higher PEEP levels.

DISCONTINUATION OF MECHANICAL VENTILATION

From the moment that mechanical ventilation is instituted, it is important to start planning for its eventual discontinuation. A key aspect of this approach is serial evaluation, with aggressive treatment of the factors that contribute to the patient's ventilator dependence.

Readiness for extubation requires clinical stability (e.g., hemodynamic stability with no or minimal need for vasopressors and oxygen requirements that can be met by face mask after extubation)[14] (Fig. 91-2). One way to assess whether the patient is ready to be extubated is the use of the rapid shallow breathing index, which is the ratio of tidal volume in liters to the respiratory rate in breaths per minute, measured after 2 minutes of spontaneous breathing. If this ratio is not elevated (<105 breaths/min/L), a spontaneous breathing trial is recommended (see Fig. 91-2).

Spontaneous breathing trials assess the ability of the patient to be separated from the ventilator, but they do not accurately predict the outcomes of extubation,[A19] which are often related to a weak cough, abundant secretions, microaspirations, and limited wakefulness. For example, a strategy that pairs spontaneous awakening, based on the daily interruption of sedatives, with spontaneous breathing trials can improve extubation rates, reduce ICU length of stay, and decrease mortality at 1 year. However, early active physiotherapy is not beneficial in intubated patients.[A20] The advantages of early discontinuation must be balanced against the detrimental consequences if patients require urgent reintubation. Within 3 to 5 days, approximately 15% of patients require reintubation, which is associated with a higher mortality rate that may be partly precipitated by the failed extubation itself. A majority of patients (between 60 and 75%) will be successfully extubated after the first spontaneous breathing trial, whereas others will need repeated attempts. Patients with a high pre-test probability of success (e.g., postoperative patients) may not need a formal spontaneous breathing trial and may

be extubated as soon as they are awake. Noninvasive ventilation,[15] especially in obese patients,[16] or high-flow nasal oxygen after extubation can reduce the risk of reintubation within 72 hours, and a combination of the two is even better.[A21]

Apart from new complications or persistence of the initial insult, three factors that contribute to inability to wean and prolong the time on the ventilator include general muscle weakness and, more specifically, respiratory muscle dysfunction, which in part may be caused by the ventilatory process; cardiovascular factors and volume status that may lead to weaning-induced pulmonary edema via diastolic dysfunction or ischemia; and neurologic factors including residual sedation or inability of patients to protect their airways. A fluid management strategy based on measurement of brain natriuretic peptide may reduce the duration of weaning.

Gradual weaning is not necessary. Patients should be assessed on a daily basis regarding their suitability for removal from ventilatory support. If they are not ready, a comfortable, nonfatiguing form of mechanical ventilation should be used between assessments.

Despite repeated trials of spontaneous breathing, about 10 to 15% of patients will continue to be ventilator-dependent even after one week of weaning attempts. In these patients, a global approach including mobilization, nutrition, and therapies focused on psychological factors can be crucial,[17] respiratory muscle rehabilitation may be of potential benefit, and specialized weaning centers may be useful.[18] For patients who have a tracheostomy, trials of simple tracheostomy masks, during which patients breathe unassisted through their tracheostomy for varying periods of time before being reconnected to the ventilator, may be the preferred approach for weaning.

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92 APPROACH TO THE PATIENT WITH SHOCK

DEREK C. ANGUS

DEFINITION

Shock, which is an acute circulatory dysfunction that results in inadequate tissue perfusion, is a medical emergency requiring prompt diagnosis and intervention to prevent circulatory collapse, multisystem organ failure, and death. The four major categories of shock are cardiogenic, distributive, hypovolemic, and obstructive (Fig. 92-1).

Cardiogenic shock (Chapter 93) is due to pump failure caused most commonly by acute myocardial ischemia but also by acute valvular dysfunction, arrhythmias, myocarditis, or ventricular wall rupture. Distributive shock is caused by loss of peripheral vasomotor tone, most commonly due to sepsis (Chapter 94). Rarer causes of distributive shock include neurogenic shock, typically following major spinal cord injury (Chapter 368), and anaphylaxis (Chapter 233). Hypovolemic shock is caused by loss of circulating volume from dehydration, profound vascular leakage (e.g., secondary to the toxin-mediated endothelial leak of dengue fever), or hemorrhage (e.g., secondary to trauma, perioperative, or gastrointestinal bleeding, or rupture of an aortic aneurysm). Obstructive shock, which is less common, is caused by intrinsic blockage of a major vessel, such as saddle pulmonary embolus (Chapter 68), or extrinsic compression, such as cardiac tamponade (Chapter 62), status asthmaticus (Chapter 75), or tension pneumothorax.

Patients also can present with combined forms of shock. For example, septic shock can include loss of autonomic tone (distributive), myocardial depression (cardiogenic), and loss of vascular volume (hypovolemic) owing to dehydration and vascular leak.

EPIDEMIOLOGY

In the United States, an estimated 500,000 incident cases of shock occur each year. Septic shock, which is the most common cause, accounts for more than 250,000 cases per year. Hemorrhagic shock accounts for 60,000 deaths each year in the United States, predominantly owing to trauma.[1] Of the 650,000 cases per year of acute myocardial infarction, about 25,000 (4%) develop cardiogenic shock (Chapter 93).[2] Of the 200,000 or so patients who suffer a clinically significant pulmonary embolus each year, about 25,000 (13%) present in shock (or cardiac arrest). Thus, over half of all shock is due to sepsis (primarily distributive), one fifth is due to trauma (primarily hypovolemic),[3] one tenth is due to coronary artery disease (cardiogenic), and the remaining (approximately 20%) is due to other causes. Shock occurs in both sexes, all age groups, and all racial and ethnic groups, with its incidence depending on the frequency of precipitating conditions within these populations.

PATHOBIOLOGY

Shock is classically described in terms of cardiovascular pathophysiology when oxygen delivery to tissues is inadequate because of reduced cardiac output (hypovolemic, cardiogenic, or obstructive) or impaired vasomotor tone (distributive). However, these macrocirculatory changes are often accompanied by important pathobiologic changes in the cells and tissue beds of vital organs.

Cardiovascular Pathophysiology

In *hypovolemic shock* a decrease in circulating blood volume decreases venous return and thus cardiac preload. As preload decreases, the heart shifts left on the

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ABSTRACT

Shock, which is acute circulatory dysfunction that results in inadequate tissue perfusion, is a medical emergency requiring prompt diagnosis and intervention to prevent circulatory collapse, multisystem organ failure, and death. The four major, not mutually exclusive, categories of shock are cardiogenic, distributive, hypovolemic, and obstructive. Cardiogenic, hypovolemic, and obstructive shock are a result of reduced cardiac output, whereas distributive shock is caused by loss of vasomotor tone. Septic shock, which is predominantly distributive, accounts for over half of the 500,000 or so cases of shock per year in the United States. A presumptive diagnosis is based on hypotension, signs of hypoperfusion, and lactic acidosis. A rapid history, clinical examination, and bedside ultrasound help establish the probable type of shock, which can guide therapy as well as help identify the inciting cause and any concomitant problems. Respiratory support is provided with supplemental oxygen and mechanical ventilation. Obstructive shock requires specific procedures to relieve obstruction, such as needle thoracostomy for tension pneumothorax. Rapid intravenous fluid resuscitation with crystalloids, accompanied by vasopressors as necessary, is key for all forms of shock except cardiogenic shock. In cardiogenic shock, a small fluid bolus may still be necessary, but inotropic support is the primary strategy. The adequacy of resuscitation is determined by ensuring adequate cardiac preload via dynamic measures, such as straight leg raises, and monitoring blood pressure, lactate clearance, and clinical signs of hypoperfusion. Even when the initial resuscitation is successful, patients often will develop multisystem organ dysfunction that requires admission to intensive care for ongoing management.

KEYWORDS

shock
hypotension
hypoperfusion
cardiac output
vasomotor tone
sepsis
trauma

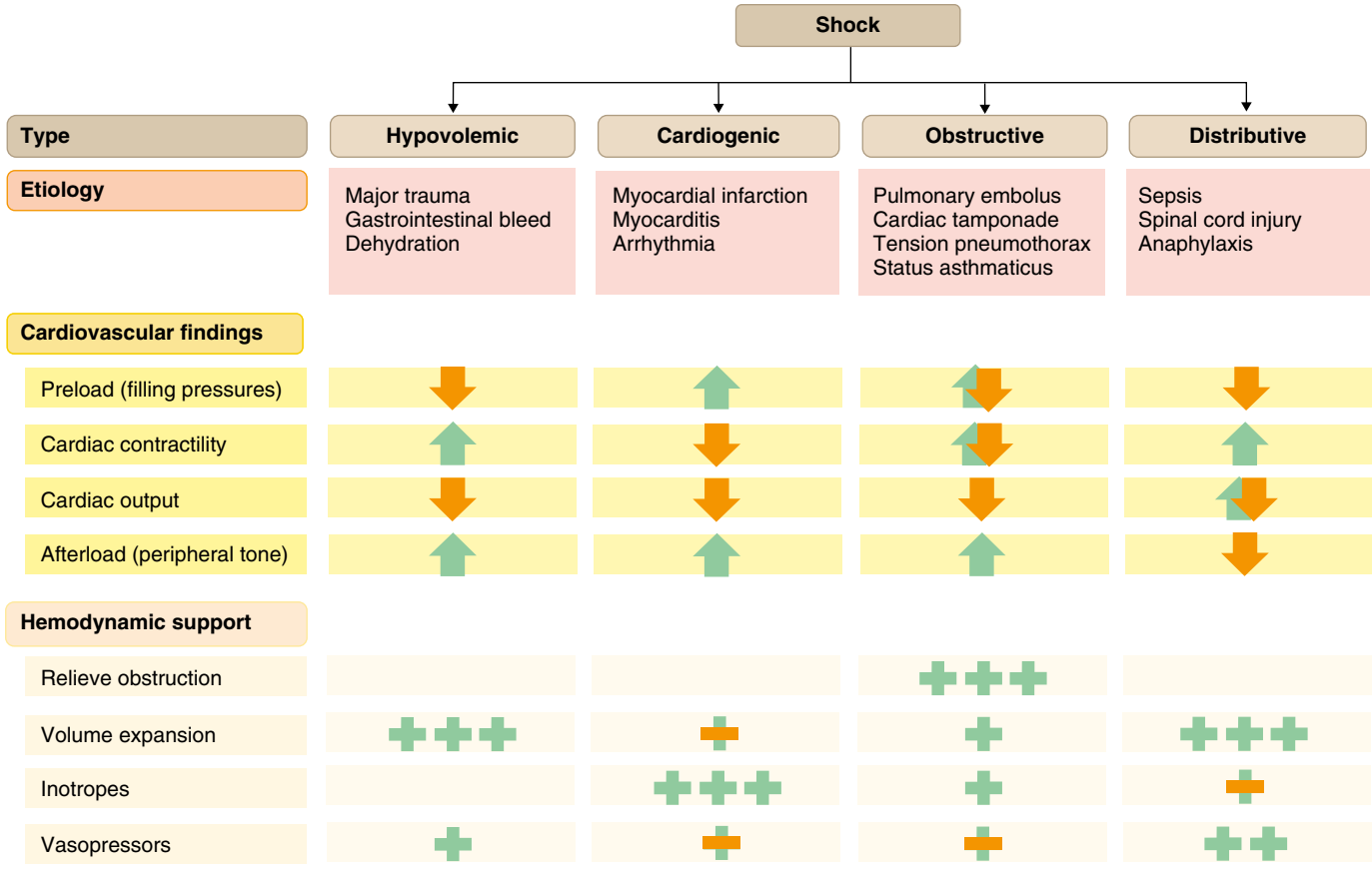

FIGURE 92-1. The causes, cardiovascular findings, and hemodynamic support for different types of shock. Under cardiovascular findings, bidirectional *arrows* indicate variation in findings among patients with the particular type. Under hemodynamic support, the number of + signs indicate the importance of therapy. A combined + and − indicates that the intervention could help some patients but must be used with caution.

Starling curve to the point that stroke volume and, hence, both cardiac output and oxygen delivery fall. Decreases in cardiac output and oxygen delivery are detected by a complex system of baroreceptors and chemoreceptors that stimulate autonomic and endocrine-mediated compensatory changes in the heart and vasculature. Peripheral vasomotor tone is increased in arterial and venous capacitance vessels, thereby reducing total capacitance and effectively increasing the circulating volume, venous return, and preload. Selective autoregulatory changes also redistribute blood flow preferentially to vital organs (e.g., heart and brain) at the expense of the splanchnic, muscle, and skin vascular beds. In addition, sympathetic stimulation of the heart generates tachycardia and increases inotropy to increase cardiac output. The tradeoff initially sustains effective oxygen delivery. However, as blood volume decreases, compensation fails, and tissue hypoperfusion of vital organs ensues.

In *cardiogenic shock* (Chapter 93), cardiac output falls because of primary pump failure rather than reduced preload. When left ventricular failure predominates, accompanying pulmonary edema (Chapter 46) can lead to arterial hypoxemia, which further compromises oxygen delivery. Peripheral and central compensatory mechanisms are similar to those in hypovolemic shock, with the caveat that increasing sympathetic drive to increase myocardial contractility has limited effect.

In *obstructive shock*, the mechanism that reduces cardiac output depends on the cause: massive pulmonary embolus (Chapter 68) increases right ventricular afterload but reduces left ventricular preload, whereas tension pneumothorax (Chapter 86) and cardiac tamponade (Chapter 62) principally reduce cardiac output via reduced preload, akin to hypovolemic shock. As with cardiogenic shock, obstructive shock can be accompanied by impaired oxygenation, thereby further compromising oxygen delivery.

In *distributive shock*, the autoregulation of peripheral vasomotor tone is impaired. For example, neurogenic shock following acute spinal cord injury (Chapter 368) arises owing to loss of sympathetic tone, thereby leading to dilatation of capacitance vessels, increased arterial-venous shunting, and loss of selective autoregulation. Preload is reduced, but afterload is also reduced. Compensatory mechanisms, such as reflex tachycardia, will depend on the level of the cord injury. Thus, the effects on cardiac output are variable (and cardiac output can even be increased), but effective oxygen delivery to vital organs can still be compromised. Septic shock (Chapter 94) is primarily a form of distributive shock triggered initially by the release of circulating mediators that have local effects on peripheral vessels, thereby causing both vasodilation and vascular leak. These effects impair autoregulation, increase capacitance, and reduce the absolute and effective circulating blood volume, thereby reducing preload and afterload, with variable effects on cardiac output. Inflammatory mediators released in sepsis also have direct myocardial depressant effects. Importantly, because of both impaired redistribution of flow and impaired tissue oxygen extraction (discussed later), distributive shock can persist despite a seemingly adequate oxygen delivery, and blood returning from the peripheral beds can have a normal or elevated oxygen content.

Cellular and Organ Pathobiology

As oxygen delivery falls, hypoperfused tissue beds increase oxygen extraction, which decreases venous oxygen content but preserves aerobic metabolism. With further reduction in oxygen delivery, cells switch to glycolysis, thereby generating lactic acid and a base deficit. An acid environment helps oxygen dissociate from hemoglobin, partially offsetting the consequences of reduced oxygen delivery. Cells also decrease mitochondrial activity, a form of protective hypometabolism to decrease oxygen demand. However, these compensatory mechanisms can be overwhelmed, thereby resulting in deepening ischemia and acidosis.

When cells are stressed or injured by ischemia, they release molecules that signal via damage-associated molecular pattern (DAMP) receptors, which stimulate innate immune cells (Chapters 35 and 36) to release a cascade of inflammatory mediators that alter endothelial function and permeability, coagulation and fibrinolysis, and leukocyte recruitment and activity. These changes disrupt microvascular flow and increase tissue edema and hypoxia. Tissue hypoxia also directly stimulates release of vasoactive mediators, such as nitric oxide and adenosine, thereby further contributing to vasomotor dysregulation. Reduced mitochondrial activity can also be maladaptive, with impaired oxygen utilization exacerbating cellular injury. After prolonged ischemia, reperfusion can aggravate these effects via reactive oxygen species, which induces local tissue ischemia-reperfusion injury. Thus, regardless of the initial cause of shock, prolonged tissue ischemia generates local changes characteristic of distributive shock, and these changes can persist for hours or days after resuscitation.

Untreated, prolonged ischemia eventually exhausts stores of adenosine triphosphate (ATP); as a result, tissue cells undergo bioenergetic failure, which triggers widespread apoptotic and necrotic cell death.

Genetic Susceptibility

Many conditions that predispose to shock have a multifactorial etiology that includes a genetic component. For example, genetic variants at over 243 loci (especially the 9p21 locus) are associated with coronary artery disease, the principal cause of cardiogenic shock. Individuals with a high genetic risk score for coronary artery disease (a composite measure of over 300 genetic variants) have an increased risk of serious coronary events, such as acute myocardial infarction, heart failure, or premature death. Susceptibility and outcome of septic shock have also been linked to genetic variations, such as variable number tandem repeats in genes involved in the detection of microbial products (e.g., mannose binding lectin-2 and toll-like receptor [TLR]-4), activation of the inflammatory cascade (e.g., tumor necrosis factor-alpha), and downstream events, such as leukocyte recruitment (e.g., macrophage migration inhibitory factor-1) and coagulation activation (e.g., plasminogen activator inhibitor-1). For example, these relationships are well-documented in sibling and familial studies of meningococcal disease (Chapter 274). Genetic variation has also been described in other components of the host response to shock, such as the sympathetic receptors in the peripheral vasculature that are responsible for regulating vasomotor tone (e.g., alpha 1B adrenergic receptor gene) and a broad set of innate immune cell functions.[4] These variations may affect the trajectory and outcome of shock, as well as the therapeutic response to various agents, such as adrenergic vasopressors, used to treat shock. However, none of the described variations have yet led to a specific clinical approach for the management of shock.

CLINICAL MANIFESTATIONS

Early Manifestations

Before the overt expression of shock, the dominant clinical features are those of the inciting event, such as the chest pain of an acute myocardial infarction (Chapter 58) or the fever, cough, and purulent sputum production of a worsening pneumonia (Chapter 85). During these early phases, the body's compensatory mechanisms to ensure adequate oxygen delivery will produce only subtle nonspecific signs and symptoms (Chapter 7). For example, the respiratory rate will typically rise to generate a compensatory respiratory alkalosis to the incipient metabolic acidosis. Sympathetic autonomic responses to absolute or relative hypovolemia include tachycardia, sometimes a temporary increase in blood pressure, and peripheral vasoconstriction, which can result in cool skin, peripheral cyanosis, and sluggish capillary refill. However, in patients with impending distributive shock, impaired vasomotor control may paradoxically present as warm, flushed peripheries.

Overt Shock

The cardinal features of overt shock are hypotension together with evidence of inadequate perfusion (Table 92-1). Typically, a systolic blood pressure lower than 90 mm Hg or mean blood pressure lower than 60 mm Hg overwhelms autoregulatory mechanisms so that selective vasoconstriction no longer can preserve adequate blood flow to vital organs. With decreased cerebral perfusion, confusion, disorientation, altered consciousness, or coma develop; focal or localizing signs are atypical and suggest an alternative diagnosis or preexisting cerebrovascular disease (Chapter 375) sensitive to low-flow states. Oliguria develops but may not be noted immediately. Skin changes will be more apparent, and the patient will typically appear cold, clammy, and cyanotic, with loss or diminution of peripheral pulses (Chapter 7). Hypothermia is common, even in septic shock.

Reliance of hypoperfused tissue beds on anaerobic metabolism leads to hyperlactatemic metabolic acidosis (Chapter 104), which stimulates increased respiratory effort; as the patient fatigues or mental status worsens, however, air hunger may give way to agonal breathing. Similarly, although tachycardia is typical, worsening hypotension and myocardial ischemia in advanced shock can result in paroxysmal bradycardia. Although peripheral cyanosis is a common early feature, central cyanosis is also common in cardiogenic and obstructive shock. Even in hypotensive or septic shock, profound oxygen extraction coupled with compromised respiration may promote central cyanosis. All organs are compromised, even if not clinically evident. For example, splanchnic and hepatic flow is severely diminished, often resulting in ileus and hepatic ischemia (Chapter 129).

TABLE 92-1 PHYSICAL EXAMINATION AND SELECTED LABORATORY SIGNS IN SHOCK

Central nervous system	Acute delirium, restlessness, disorientation, confusion, and coma, which may be secondary to decreased cerebral perfusion pressure (mean arterial pressure minus intracranial pressure). Patients with chronic hypertension or increased intracranial pressure may be symptomatic at normal blood pressures. Cheyne-Stokes respirations may be seen with severe decompensated heart failure. Blindness can be a presenting complaint or complication.
Temperature	Hyperthermia results in excess tissue respiration and greater systemic oxygen delivery requirements. Hypothermia can occur when decreased systemic oxygen delivery or impaired cellular respiration decreases heat generation.
Skin	Cool distal extremities (combined low serum bicarbonate and high arterial lactate levels) aid in identifying patients with hypoperfusion. Pallor, cyanosis, sweating, and decreased capillary refill and pale, dusky, clammy, or mottled extremities indicate systemic hypoperfusion. Dry mucous membranes and decreased skin turgor indicate low vascular volume. Low toe temperature correlates with the severity of shock.
General cardiovascular	Neck vein distention (e.g., heart failure, pulmonary embolus, pericardial tamponade) or flattening (e.g., hypovolemia), tachycardia, and arrhythmias. Decreased coronary perfusion pressures can lead to ischemia, decreased ventricular compliance, and increased left ventricular diastolic pressure. A "mill wheel" heart murmur may be heard with an air embolus.
Heart rate	Usually elevated. However, paradoxical bradycardia can be seen in patients with preexisting cardiac disease and severe hemorrhage. Heart rate variability is associated with poor outcomes.
Systolic blood pressure	May actually increase slightly when cardiac contractility increases in early shock and then fall as shock advances. A single episode of undifferentiated hypotension with a systolic blood pressure <80 mm Hg carries an in-hospital mortality of 18%.
Diastolic blood pressure	Correlates with arteriolar vasoconstriction and may rise early in shock and then fall when cardiovascular compensation fails.
Pulse pressure	Defined as systolic minus diastolic pressure and related to stroke volume and the rigidity of the aorta. Increases early in shock and decreases before systolic pressure decreases.
Pulsus paradoxus	An exaggerated change in systolic blood pressure with respiration (systolic blood pressure declines >10 mm Hg with inspiration) seen in asthma, cardiac tamponade, and air embolus.
Mean arterial blood pressure	Diastolic blood pressure + [pulse pressure/3]
Shock index	Heart rate/systolic blood pressure. Normal = 0.5 to 0.7. A persistent elevation of the shock index (>1.0) indicates impaired left ventricular function (as a result of blood loss or cardiac depression) and is associated with increased mortality.
Respiratory	Tachypnea, increased minute ventilation, increased dead space, bronchospasm, hypocapnia with progression to respiratory failure, acute lung injury, and adult respiratory distress syndrome.
Abdomen	Low-flow states may result in abdominal pain, ileus, gastrointestinal bleeding, pancreatitis, acalculous cholecystitis, mesenteric ischemia, and shock liver.
Renal	Because the kidney receives 20% of cardiac output, low cardiac output reduces the glomerular filtration rate and redistributes renal blood flow from the renal cortex toward the renal medulla, thereby leading to oliguria. Paradoxical polyuria in early sepsis may be confused with adequate hydration.
Metabolic	Respiratory alkalosis is the first acid-base abnormality, but metabolic acidosis occurs as shock progresses. Hyperglycemia, hypoglycemia, and hyperkalemia may develop.

Courtesy of Emanuel P. Rivers, MD.

Cryptic Shock

In some patients, signs of hypoperfusion and hyperlactatemia develop despite blood pressure that is temporarily normal, either because of pronounced vasoconstriction at the expense of compromised flow and hypoperfusion or because the patient's preexisting hypertension is masking an important decline relative to baseline blood pressure.

Untreated Shock

The length of time that a patient can survive in shock before diagnosis and intervention depends on the patient's underlying fitness and the magnitude of the inciting event. For example, a patient with shock from major arterial hemorrhage may only survive minutes. A patient who suffers a massive acute myocardial infarction with ensuing cardiogenic shock may survive only a few hours. Similarly, gram-negative septic shock in patients with chemotherapy-induced neutropenia may also be fatal within hours. However, other patients may survive for several days with altered mental status, borderline hypotension, and oliguria. Regardless of the rate of decline, untreated shock progresses to catastrophic ischemia, acidemia, vital organ failure, and death. The patient will lapse into coma, potentially with seizures typical of anoxic brain injury; worsening myocardial ischemia will accelerate pump failure and potentially cause fatal arrhythmias; and ventilation will degenerate to agonal breaths or apnea.

Typical Progression of Treated or Partially Treated Shock

A period of prolonged tissue hypoperfusion can compromise the function of any vital organ or tissue bed. Thus, even if the patient is resuscitated, sequelae that may blossom over the following hours and days include acute kidney injury (Chapter 106), shock liver (Chapters 133 and 140), intestinal ileus and ischemia (Chapter 129), anoxic brain injury (Chapter 373), and acute respiratory distress syndrome (Chapter 90).

DIAGNOSIS

Discerning That the Patient Is in Shock

Shock, which is a syndrome with multiple causes, lacks unambiguous diagnostic criteria. Instead, the diagnosis is based on a constellation of features not otherwise explained by other causes (see Table 92-1). Three principles dominate the diagnosis of shock. First, the clinical context is critical to inform the index of suspicion, especially regarding the inciting event. Second, because shock requires immediate treatment, the emphasis must focus on establishing a presumptive diagnosis; if in doubt, the patient should be presumed to be in shock until proven otherwise. Third, other conditions (e.g., an acute cerebrovascular accident [Chapter 376], drug overdose or poisoning [Chapter 96], or diabetic ketoacidosis [Chapters 104 and 210]) can mimic shock yet be present concomitantly; their presence should not be inferred as evidence that shock is absent.

Shock is diagnosed when the patient is hypotensive (systolic blood pressure <90 mm Hg or mean arterial pressure <60 mm Hg) with signs of hypoperfusion not otherwise explained by another diagnosis. Even if other conditions could explain the clinical features, shock must be presumed to be present until definitively excluded, given its gravity and need for immediate intervention. These blood pressure cut-points reflect population norms and are somewhat arbitrary. Thus, borderline values should be interpreted in light of other findings. If blood pressure is normal despite signs suggestive of hypoperfusion, a serum lactate level should be checked immediately[5]; values above 2 mmol/L are clearly consistent with hypoperfusion and shock. In the appropriate clinical setting, however, any patient who has elevated serum lactate levels not explained by another cause (e.g., metformin-induced hyperlactatemia or recent seizure) should be presumed to have shock. Although the magnitude of hypoperfusion broadly correlates with the serum lactate level and although even a minor elevation within the normal range (typically <2 mmol/L) can portend an increased risk of death, a mild elevation in the lactate level is not specific for shock. A sensitive but nonspecific cut-point for suspected shock is any value greater than 1 or greater than 1.5 mmol/L, though a less sensitive but more specific cut-point of 4 mmol/L also can be used to establish the diagnosis.

Differential Diagnosis

Acute emergencies that resemble shock include altered mental status owing to a variety of intoxications and drug overdoses (Chapter 96), acute metabolic derangements (e.g., hypoglycemia or diabetic ketoacidosis; Chapter 210), seizures (Chapter 372), or nonlocalizing stroke or intracranial hemorrhage (Chapters 376 and 377). Similarly, acute hypoxemic respiratory failure (Chapter 90) due to any cause may present as respiratory distress, tachycardia, and cyanosis and thus mimic shock.

Shock is caused by inadequate oxygen delivery owing to cardiovascular compromise, so conditions that impair the oxygen delivery/oxygen demand relationship via other mechanisms are not shock. For example, acute hypoxemic respiratory failure (Chapter 90) or severe anemia (Chapter 144) can cause tissue hypoxia, but they are not shock states. Rare conditions, such as cyanide poisoning (Chapters 82 and 96), in which oxygen is unavailable to the tissues because it cannot be released from hemoglobin, or carbon monoxide poisoning (Chapter 82), in which carbon monoxide competitively blocks the binding of oxygen to hemoglobin, are not examples of true shock.

Discerning the Type of Shock

The history and physical examination provide strong clues to the type of shock. If the patient arrives following trauma (Chapter 97), gastrointestinal bleeding (Chapter 121), or several days of severe diarrhea (Chapter 126), hypovolemic shock will be most likely. If the presentation suggests an acute myocardial infarction (Chapter 58), then cardiogenic shock (Chapter 93) is most likely, and so on. In addition to a physical examination focused on features of potential inciting events, attention should be paid to the skin color and turgor, peripheral pulses, and signs suggestive of obstruction or pump failure, such as jugular venous distension, tachypnea, cyanosis, and late inspiratory basilar crackles (Chapters 39 and 71). A chest radiograph may help by demonstrating evidence of cardiomegaly and pulmonary edema (see Fig. 44-2 in Chapter 44) in cardiogenic shock or oligemic lung fields in massive pulmonary embolus or status asthmaticus. However, the most useful rapid imaging study is bedside ultrasound (Chapter 44) to assess the size, filling, and contractility of cardiac chambers to suggest cardiogenic shock (Chapter 93); the presence of a pericardial effusion (Chapter 62) to suggest obstructive shock; and the collapsibility of the inferior vena cava to suggest hypovolemic shock (Table 92-2).

TABLE 92-2 RAPID ULTRASOUND IN SHOCK (RUSH) PROTOCOL*

RUSH EVALUATION	HYPOVOLEMIC SHOCK	CARDIOGENIC SHOCK	OBSTRUCTIVE SHOCK	DISTRIBUTIVE SHOCK
Heart	Hypercontractile LV Small LV chamber size	Hypocontractile or dilated LV	Hypercontractile LV Pericardial effusion Cardiac tamponade RV strain Cardiac thrombus	Hypercontractile LV in early sepsis, hypocontractile LV in late sepsis
Fluid status	Flat IVC Flat jugular veins Peritoneal fluid (fluid loss) Pleural fluid (fluid loss)	Distended IVC Distended jugular veins Pulmonary edema Pleural or peritoneal fluid (fluid loss)	Distended IVC Distended jugular veins Pneumothorax	Normal or small IVC in early sepsis Peritoneal or pleural fluid (fluid loss)
Extracardiac circulatory system	Abdominal aneurysm Aortic dissection	Normal	DVT	Normal

*Data from Perera P, Mailhot T, Riley D, et al. The RUSH exam: Rapid Ultrasound in SHock in the evaluation of the critically ill. *Emerg Med Clin North Am*. 2010;28:29-56.
DVT = deep venous thrombosis; IVC = inferior vena cava; LV = left ventricle; RV = right ventricle.

TREATMENT

The First Hour

When resuscitating a patient with shock, the goal is to restore adequate tissue perfusion as quickly as possible—a task that usually requires initiation of treatment before a definitive diagnosis and cause are established (Fig. 92-2). The first steps focus on establishing adequate oxygen delivery by ensuring adequate preload, cardiac output, and arterial oxygenation. Therefore, resuscitation begins with intravenous access to administer fluids (including blood products when indicated) and vasoactive agents (typically vasopressors), as well as the institution of ventilatory support (supplemental oxygen or mechanical ventilation [Chapter 91]). Optimal body positioning (e.g., the Trendelenburg position—elevation of the legs and feet to increase venous pressure) and other emergency procedures (e.g., needle thoracostomy to relieve a tension pneumothorax) are also recommended, depending on the clinical situation.

APPROACH TO THE PATIENT WITH SUSPECTED SHOCK

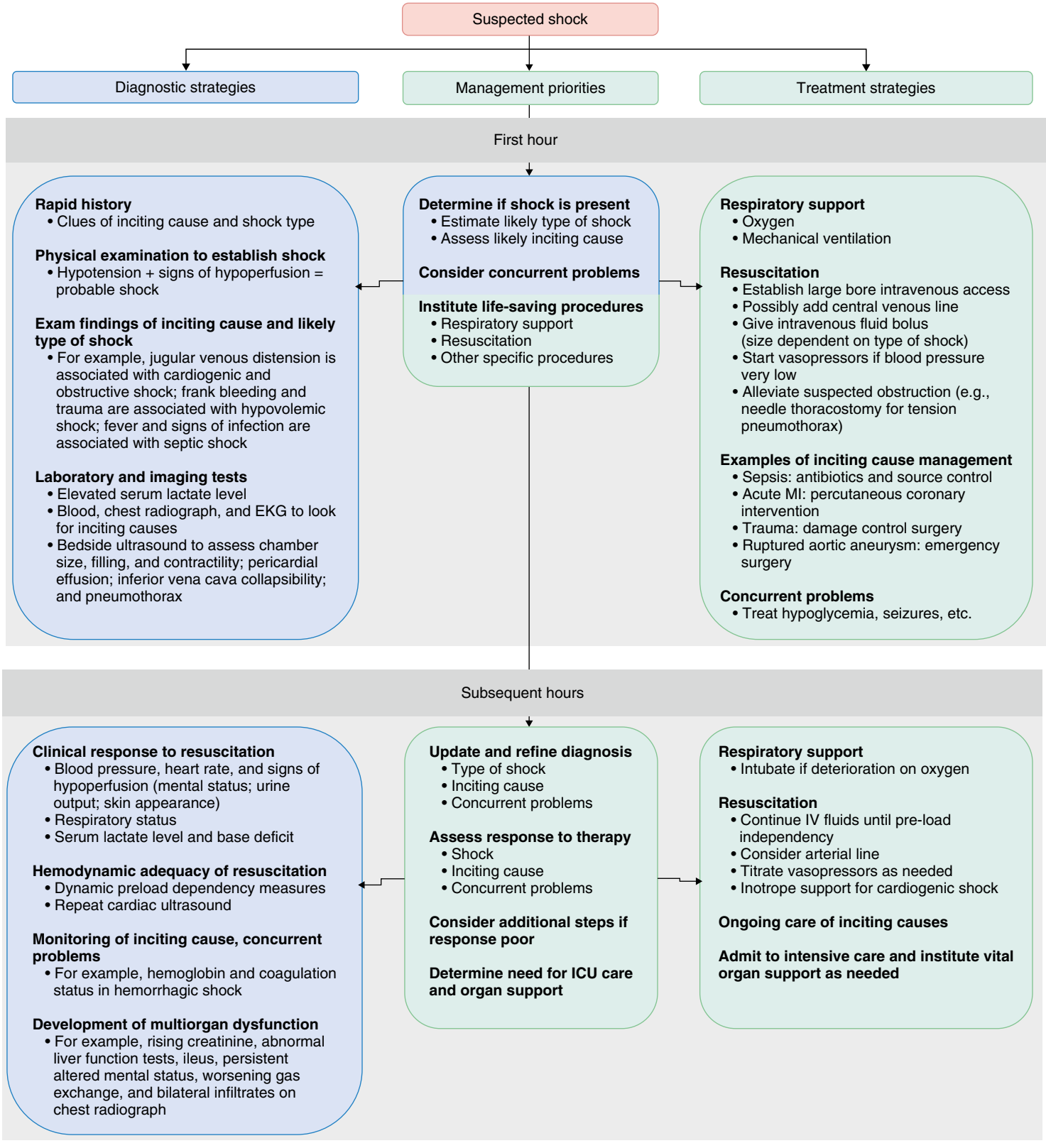

FIGURE 92-2. Management principles for the diagnosis and treatment of shock. Examples are intended to be representative. Further detail is provided in the corresponding text. BP = blood pressure; EKG = electrocardiogram; ICU = intensive care unit; IV = intravenous; MI = myocardial infarction.

Intravenous Access

Because all key treatment interventions are administered intravenously, intravenous access is a priority. If large-volume resuscitation is anticipated (hypovolemic or distributive shock), large-bore intravenous access (e.g., two #16 gauge peripheral catheters in case one malfunctions) will facilitate rapid resuscitation. Central venous catheterization, typically into a subclavian or internal jugular vein and ideally using ultrasound guidance,[A1,A2] is preferred for the administration of vasopressors. Of note, central access does not necessarily facilitate more rapid fluid infusion, because central lines are longer and infusion rates are a function of both diameter and length. If a central line is inserted for rapid infusion, a short #8.5 French catheter is ideal. Central venous access should be obtained with appropriate attention to sterile technique; a femoral vein can be used, albeit with a higher risk of infection.

Intravenous Fluids

Intravenous fluids are the primary method to ensure adequate preload—the point on the Starling curve (see Fig. 41-3 in Chapter 41) where further increases in preload do not increase output (preload independence). Intravenous fluids should ideally be given until the heart is preload independent but not to the point that the heart is overfilled and pushed too far to the right on the Starling curve, with subsequent cardiac decompensation, pulmonary edema, and worsening oxygen delivery.[6] The volume chosen for the initial bolus of fluids must be made somewhat empirically, but a challenge dose of 500 mL of crystalloids (e.g., normal saline, lactated Ringer solution) over 20 to 30 minutes is typically used, and infusion rates of 333 mL/hour and 1 L/hour produce equivalent outcomes.[A3] Of note, even in cardiogenic shock, where a patient typically has high preload pressures, a small bolus of intravenous fluid (e.g., 125 to 250 mL) can sometimes improve cardiac output and oxygen delivery.

When the clinician can be confident that the ventricles are underfilled (e.g., major hemorrhage, severe dehydration, or septic shock), resuscitation begins with a large volume of fluid—20 to 30 mL/kg administered as a bolus.[7] However, when pulmonary edema or cardiogenic shock is evident, a smaller amount (e.g., a 250-mL bolus) is more prudent.

Broadly speaking, there is no clear advantage of colloid over crystalloid solutions,[A4] so crystalloids, which are less expensive, are preferred. Crystalloids have a greater volume of distribution than colloids, so the effective intravascular volume expansion is less once fluid redistributes. However, there is no evidence that use of colloids during the initial resuscitation improves patient outcomes. "Balanced" crystalloids, such as PlasmaLyte or lactated Ringer solution, have a lower chloride content than normal saline, but their potential advantage over saline for improving outcomes is uncertain.[A5–A7] Hetastarches are never recommended because they are associated with worse outcomes.

Blood and Blood Products

Hemorrhagic shock can be classified by the degree of blood loss (Table 92-3). In trauma-induced hemorrhagic shock (Chapter 97), guidelines suggest commencing with 1 to 2 L of intravenous crystalloid but augmenting resuscitation of patients with massive hemorrhage by also administering plasma, platelets, and packed red blood cells in a ratio of 1 : 1 : 1 until bleeding is controlled.[8] Some advocate a similar approach for massive nontraumatic hemorrhage, such as from upper gastrointestinal bleeding (Chapter 121), though data to support this approach are scant.

TABLE 92-3 CLASSIFICATION OF HEMORRHAGIC SHOCK*

	CLASS I	CLASS II	CLASS III	CLASS IV
Blood loss (mL)	Up to 750	750-1500	1500-2000	>2000
% Volume	Up to 15	15-30	30-40	>40
Pulse rate (per minute)	<100	>100	>120	>140
Blood pressure	Normal	Normal	Decreased	Decreased
Pulse pressure	Normal or increased	Decreased	Decreased	Decreased
Respiratory rate (per minute)	14-20	20-30	30-40	>35
Urine output (mL/hr)	>30	20-30	5-15	Negligible
Mental status	Slightly anxious	Mildly anxious	Anxious, confused	Confused, lethargic
Fluid replacement	Crystalloid	Crystalloid	Crystalloid and blood	Crystalloid and blood

*Estimates based on a 70-kg patient.

From Committee on Trauma of the American College of Surgeons. *Advanced Trauma Life Support for Doctors*. Chicago: American College of Surgeons; 1997:108.

In septic shock, patients frequently become anemic—primarily because the considerable volume expansion with intravenous fluids leads to dilutional anemia, although hemolysis, coagulopathy-induced bleeding, and marrow suppression can all contribute over time. Anemia can compromise oxygen delivery, but transfusion of packed red blood cells beginning at a hemoglobin level of 7 g/dL is as good as beginning at a level of 9 g/dL.[A8] Unlike hemorrhagic shock, there is no role for the routine use of platelets or other blood products in the resuscitation of septic shock.

Transfusion of blood products in cardiogenic shock (Chapter 93) runs the risk of exacerbating pulmonary edema and worsening heart failure. For patients with acute myocardial infarction, a transfusion threshold of 8 g/dL is as safe as 10 g/dL,[A9] but maintaining myocardial oxygen supply is critical. When transfusing a patient with cardiac ischemia and cardiogenic shock, the patient must be monitored carefully for signs of worsening failure. Blood and blood products are not typically required in obstructive shock.

Vasopressors

Because fluid alone may be inadequate to restore blood pressure, especially in distributive shock, vasopressors (Table 92-4) are often required.[9–11] Vasopressors increase afterload, so adequate hydration is important to optimize their effects. Vasopressors may have to be started concomitantly with fluid resuscitation, and they often can be reduced after adequate fluid resuscitation. In patients with vasodilatory shock, such as with sepsis, postresuscitation strategies that restrict fluids, so as to rely more on vasopressors, yield similar outcomes to those that restrict vasopressors, so as to rely more on fluid administration.[A10,A11] In vasodilatory shock, permissive hypotension to a target mean arterial pressure of 60 to 65 mmHg by reducing vasopressor doses does not appear to be preferable to standard care.[A12]

The preferred vasopressor for distributive shock is norepinephrine,[8] because it is a strong vasoconstrictor with enough beta-adrenergic effects to increase myocardial contractibility and to protect the heart against the increased afterload posed by vasoconstriction. Dopamine offers the theoretical advantage of selective vasodilation of the renal and splanchnic beds, but it has not provided renal protection in clinical practice; dopamine also had more side effects than norepinephrine in a large study of septic shock.

Vasopressin is not superior to norepinephrine as a single agent for septic shock[A13] but is useful as a second-line vasopressor when blood pressure remains inadequate despite high doses of norepinephrine. Vasopressin may also be a useful alternative to norepinephrine in nonseptic distributive shock.[A14] A synthetic angiotensin II pharmacologic agent has adrenergic vasopressor-sparing effects in distributive shock and may prove to be a useful alternative, but it cannot be recommended now based on available data.

Vasopressors play less of a role in cardiogenic shock (Chapter 93) but may be required temporarily in hypovolemic or obstructive shock until adequate cardiac output and blood pressure are restored. All vasopressors increase afterload, thereby potentially worsening cardiac failure, and can cause severe vasoconstriction, thereby leading to worsening acidosis and ischemia of the gut or limb.

Other Vasoactive Agents

Adrenergic (e.g., dobutamine) and nonadrenergic (e.g., milrinone) inotropic agents are used in cardiogenic shock (Chapter 93) but are not useful as routine agents in other forms of shock. Vasodilator therapy may be useful in cardiogenic shock, where it can increase cardiac output by reducing afterload without increasing myocardial oxygen demand (Chapter 93). However, the risk is worsened by hypotension, so it is not a routine treatment for other forms of shock. Some data suggest that beta-blockade might be useful in some patients in whom overstimulation by synthetic agents causes myocardial dysfunction akin to what is seen in patients with pheochromocytoma, but the clinical utility of such an approach is speculative at this time.

Respiratory Support

Although the primary cause of inadequate oxygen delivery is cardiovascular failure, supplemental oxygen can raise arterial oxygen content, thereby ameliorating tissue hypoxia. Supplemental oxygen by face mask is encouraged for all patients in suspected shock, with a greater emphasis placed on invasive mechanical ventilation (Chapter 91) via endotracheal intubation for patients with significant respiratory distress or severe hypotension or acidosis. A patient who is in shock and who is struggling to breathe despite supplemental oxygen should be intubated without a trial of noninvasive ventilation because it can be difficult to implement effectively, does not provide airway protection, and is less effective than invasive ventilation at reducing the work of breathing, facilitating gas exchange, and recruiting alveoli (Chapter 90). Invasive mechanical ventilation (Chapter 91) protects the airway, reduces the risk of aspiration, decreases the work of breathing (and therefore decreases oxygen demand), and improves gas exchange (to increase oxygen delivery and facilitate compensatory respiratory alkalosis). In cardiogenic shock (Chapter 93), mechanical ventilation provides the added benefit of improving alveolar recruitment and increasing transmural pressure on the heart, thereby reducing cardiac afterload and facilitating ventricular function.

The major complication of initiating mechanical ventilation in patients with shock is inadvertent worsening of cardiac output and hypotension because the positive intrathoracic pressure associated with mechanical ventilation retards

TABLE 92-4 VASOPRESSOR AGENTS

		PERIPHERAL VASCULATURE		*CARDIAC EFFECTS*			
AGENT	**IV DOSE RANGE**	**VASOCONSTRICTION**	**VASODILATION**	**HEART RATE**	**CONTRACTILITY**	**DYSRHYTHMIAS**	**TYPICAL USE**
Dopamine	1-4 μg/kg/min	0	1+	1+	1+	1+	"Renal dose" does not improve renal function; may be used with bradycardia and hypotension
	5-10 μg/kg/min	1-2+	1+	2+	2+	2+	
	11-20 μg/kg/min	2-3+	1+	2+	2+	3+	Vasopressor range
Vasopressin	0.04-0.1 units/min	3-4+	0	0	0	1+	Septic shock, post–cardiopulmonary bypass shock state, no outcome benefit in sepsis
Phenylephrine	20-200 μg/min	4+	0	0	0	1+	Vasodilatory shock; best for supraventricular tachycardia
Norepinephrine	1-20 μg/min	4+	0	2+	2+	2+	First-line vasopressor for septic shock, vasodilatory shock
Epinephrine	1-20 μg/min	4+	0	4+	4+	4+	Refractory shock, shock with bradycardia, anaphylactic shock
Dobutamine	1-20 μg/kg/min	1+	2+	1-2+	3+	3+	Cardiogenic shock, septic shock
Milrinone	37.5-75 μg/kg bolus followed by 0.375-0.75 μg/min	0	2+	1+	3+	2+	Cardiogenic shock, right-sided heart failure, dilates pulmonary artery; caution in renal failure

IV = intravenous.
Courtesy of Emanuel P. Rivers, MD.

right ventricular filling. This complication is most likely in patients with hypovolemic shock (who are most dependent on preload), but distributive shock, obstructive shock due to extrinsic compression, and some instances of cardiogenic shock can all be preload-dependent. Many sedation agents typically used during intubation, such as etomidate or short-acting benzodiazepines, cause vasodilation and hypotension, thereby potentially exacerbating this problem. A bolus of intravenous fluids (e.g., 500 mL normal saline) before or during intubation will frequently be necessary, together with judicious use of sedation agents, avoidance of excessive positive-pressure ventilation, and a potential increase in the dose of vasopressors.

Body Positioning

If the patient is very hypotensive, cardiac filling and cerebral perfusion can be augmented by having the patient lie flat or with the legs elevated (Trendelenburg position), especially patients in hypovolemic or distributive shock. Intubation and central line access are also facilitated by these positions. However, patients in severe respiratory distress, especially owing to pulmonary edema, usually cannot tolerate lying flat, and their hypoxemia may worsen. Similarly, until the airway is secured, a patient at risk of vomiting blood or gastric contents will be at higher risk of aspiration when managed flat. Furthermore, if a patient is suspected of having increased intracranial pressure (e.g., following major intracranial hemorrhage [Chapter 377], fulminant hepatic failure [Chapter 140], or traumatic brain injury [Chapter 368]), lying flat or in the Trendelenburg position could paradoxically worsen cerebral perfusion.

Other Emergency Procedures

A variety of other procedures must be initiated immediately in specific situations. For example, obstructive shock owing to cardiac tamponade (Chapter 62) will require emergency pericardial drainage, and a tension pneumothorax will require emergent drainage of the air. A trauma patient (Chapter 97) may require a pelvic binder or other tourniquet, a bedside ultrasound to evaluate possible intra-abdominal bleeding, and an emergency computed tomographic scan or exploratory laparotomy, depending on the findings. Similarly, a patient with an obvious major upper gastrointestinal bleed (Chapter 121) requires emergent endoscopy. Patients with septic shock and right upper quadrant pain require intravenous antibiotics and an urgent ultrasound followed by endoscopic retrograde cholangiopancreatography if dilated biliary ducts or stones are seen (Chapter 141). Patients with cardiogenic shock (Chapter 93) may require emergent percutaneous coronary intervention (Chapter 59). In addition, problems that can frequently co-occur with shock, such as generalized seizures (Chapter 372), acute alcohol intoxication (Chapter 364), drug overdose (Chapter 96), and hyperglycemia (Chapter 210), require emergency evaluation and treatment.

Monitoring the Adequacy of Resuscitation

After the initial appraisal and management, the subsequent hours are crucial to confirm the diagnosis and cause of shock, as well as to monitor the effectiveness of resuscitation. Simple measures of the adequacy of resuscitation include restoration of normal blood pressure, improvement in the clinical signs of hypoperfusion (e.g., sustained production of urine output and improved mental status), and improvement in base deficit and hyperlactatemia.

Although blood pressure can be measured by cuff manometry, the unreliability of this method in patients who are in profound shock commonly requires placement of an arterial line if the patient does not improve rapidly. However, restoration of blood pressure does not mean that oxygen delivery has improved or that tissue perfusion has been restored. Clinical and biochemical improvement may lag improvement in oxygen delivery by hours, or it may be obfuscated either by medical treatment, such as the need for sedating agents, or the blossoming of acute organ dysfunction despite successful resuscitation.

A pulmonary artery catheter can monitor right and pulmonary capillary wedge pressures, stroke volume, cardiac output, and mixed venous oxygen saturation. In shock states, inadequate oxygen delivery leads to increased peripheral oxygen extraction and low venous oxygen saturation for venous blood returning to the right heart. However, multiple clinical trials failed to demonstrate better outcomes based on therapy guided by a pulmonary artery catheter, and it is no longer recommended in the routine management of shock.[12]

One way to assess the adequacy of fluid resuscitation is to determine the responses to maneuvers that increase preload. Examples include passive leg raising or administering a fluid challenge (e.g., 500 mL of 0.9% saline or Ringer lactate solution) over 30 minutes.

Several multicenter trials of early goal-directed therapy, which specifically tries to improve measures of hemoglobin and oxygenation, have failed to demonstrate benefit beyond standard care. For example, a low central venous pressure suggests hypovolemia, but treatment of septic shock based on central venous pressure readings and blood pressure targets does not improve outcomes.[A15] Current recommendations therefore emphasize an early suspicion for shock, a low threshold to check a serum lactate level, prompt antibiotics if sepsis is a possible cause (Chapter 94), and an initial bolus of 20 to 30 mL/kg of intravenous fluids, followed by close monitoring of the adequacy of resuscitation using the

clinical examination, serial blood lactate assessments, or measures of preload dependency, such as a passive leg raise test.

Ongoing Supportive Care

Unless a patient has advanced directives to limit care, shock should be treated with the goal of saving the patient's life. Patients who do not rapidly improve are typically admitted to an intensive care unit, where vital organ function can be monitored and appropriate support can be instituted.

As soon as the patient is able or family members are available, conversations to understand preferences for cardiopulmonary resuscitation (Chapter 7), mechanical ventilation (Chapter 91), and other aspects of intensive care are extremely important (Chapter 3). The physician should provide the best possible information about the diagnosis, potential course, and prognosis.

PREVENTION

Shock can be prevented by preventing the events that cause it (e.g., trauma, sepsis, myocardial infarction) or intervening promptly in sick patients to prevent their progression to shock. Many hospitals have instituted early warning systems to deploy rapid response teams for patients with abnormal vital signs (Chapter 7). Such programs can facilitate early assessment and treatment, and they may also improve outcomes.

PROGNOSIS

Mortality from shock is now about 25%. The degree to which blood pressure, cardiac output, and measures of hypoperfusion, such as serum lactate, are responding to resuscitation is prognostic, and early evidence of multiorgan dysfunction is predictive of the need for prolonged intensive care and higher mortality. For patients who survive, the long-term prognosis is variable but is a function of age, chronic health, the natural history of the inciting event, and the duration and intensity of the hospital course. Interestingly, acute features of the shock itself (e.g., degree of hypotension) predict short-term mortality but are less predictive of long-term outcomes.

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93

CARDIOGENIC SHOCK

STEVEN M. HOLLENBERG AND CLYDE W. YANCY

DEFINITION

Cardiogenic shock occurs when the heart is unable to deliver enough blood to maintain adequate tissue perfusion. Cardiogenic shock is a hemodynamic syndrome defined by sustained systemic hypotension (systolic BP less than 90 mm Hg), high pulmonary capillary wedge pressure (PCWP greater than 18 mm Hg), and low cardiac index (less than 2.2 L/minute/m^2) (Table 93-1). The diagnosis of cardiogenic shock is often made on clinical grounds—hypotension combined with signs of poor tissue perfusion, including oliguria, clouded sensorium, and cool extremities, all in the setting of myocardial dysfunction. To make the diagnosis, it is important to document myocardial dysfunction and to exclude or correct factors such as hypovolemia, hypoxemia, and acidosis.

EPIDEMIOLOGY

The classic cause of cardiogenic shock (Fig. 93-1) is left ventricular failure secondary to an extensive acute myocardial infarction (MI), often with a mechanical complication of MI (Chapter 58).[1] However, recent data suggest the epidemiology is shifting, with an increased proportion of cases related to acute decompensated chronic heart failure (Chapter 46).[2] Other causes include arrhythmia, valvular heart disease, and prolonged cardiopulmonary bypass (Table 93-2).[3] Fulminant myocarditis and stress-induced (takotsubo) cardiomyopathy may also present with cardiogenic shock (Chapter 47). Cardiac tamponade (Chapter 62) and massive pulmonary embolism (Chapter 68) with acute right ventricular failure can cause shock without pulmonary edema. An important consideration is that some cardiogenic shock may have an iatrogenic component. Early diagnosis of impending shock and identification of patients at high risk for development of shock is essential, both to speed intervention and to avoid therapies that may worsen hemodynamics.

After a decline over the past two decades, the incidence of cardiogenic shock complicating various acute clinical syndromes appears to be increasing, albeit for unclear reasons. The mortality associated with cardiogenic shock continues to decline, because effective early treatment and more widespread adoption of early revascularization have improved outcomes.

Only about 25% of patients who develop cardiogenic shock in the setting of an MI are in shock at initial presentation; in the others, shock usually evolves over several hours, thereby suggesting that early treatment may prevent shock. Patients with early and late shock show similar demographic, historical, clinical, and hemodynamic characteristics.

Risk factors for the development of cardiogenic shock in MI parallel those for LV dysfunction and the severity of coronary artery disease (CAD). Patient characteristics include older age, anterior MI, diabetes, hypertension, multivessel CAD, previous MI, and peripheral vascular or cerebrovascular disease. Clinical risk factors include decreased ejection fraction, larger infarctions, and lack of compensatory hyperkinesis in myocardial territories remote from the infarction. Clinical harbingers of impending shock include the degree of hypotension and tachycardia at hospital presentation. The factors that predict

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Pulmonary capillary wedge pressure > 18 mm Hg
OTHER
Documented myocardial dysfunction
Exclusion of hypovolemia, hypoxemia, and acidosis

ABSTRACT

Cardiogenic shock is the syndrome that ensues when the heart is unable to deliver enough blood to maintain adequate tissue perfusion. Acute myocardial infarction is the leading cause, but other potential etiologies need to be considered. The pathogenesis of cardiogenic shock is a "downward spiral" in which myocardial dysfunction reduces stroke volume, cardiac output, and blood pressure; these changes compromise myocardial perfusion, exacerbate ischemia, and further depress myocardial function, cardiac output, and systemic perfusion. Evaluation and therapy must begin simultaneously. Echocardiography should be performed promptly to assess overall and regional systolic function and to exclude mechanical causes of shock. Invasive hemodynamic monitoring is often useful in patients who do not respond to initial therapy because clinical estimates of filling pressures can be unreliable, hemodynamic status can change precipitously, and concomitant right ventricular dysfunction is often under-recognized. Vasopressor support may be needed to break the vicious circle of progressive hypotension and further myocardial ischemia. Patients who do not respond rapidly to inotropic agents may be considered for mechanical support. Routine use of an intra-aortic balloon pump (IABP) is not effective. Percutaneous cardiac assist devices provide better hemodynamics compared with IABPs but have not been shown to improve mortality. Nevertheless, survival rates are improving as advances in supportive therapy and reperfusion are applied in clinical practice.

KEYWORDS

cardiogenic shock
coronary revascularization
vasopressors
inotropic therapy
hemodynamic monitoring
IABP
mechanical circulatory support

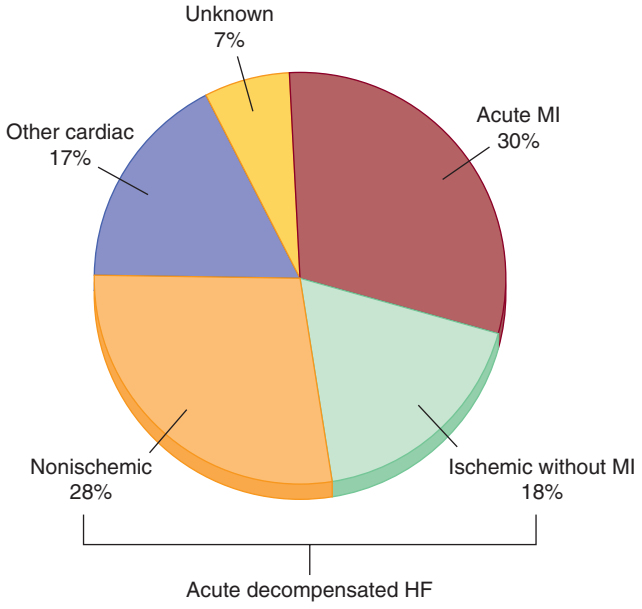

FIGURE 93-1. **Causes of cardiogenic shock from the Critical Care Trial Network registry. HF = heart failure; MI = myocardial infarction. (Berg DD, Bohula EA, van Diepen S, et al. Epidemiology of shock in contemporary cardiac intensive care units. *Circ Cardiovasc Qual Outcomes*. 2019;12:e005618.)**

TABLE 93-2 CAUSES OF CARDIOGENIC SHOCK

ACUTE MYOCARDIAL INFARCTION
Pump failure
Large infarction
Smaller infarction with preexisting left ventricular dysfunction
Infarct extension
Reinfarction
Infarct expansion
Mechanical complications
Acute mitral regurgitation due to papillary muscle rupture
Ventricular septal defect
Free wall rupture
Pericardial tamponade
Right ventricular infarction
CARDIOMYOPATHY
Myocarditis
Peripartum cardiomyopathy
End-stage low-output heart failure
Hypertrophic cardiomyopathy with outflow tract obstruction
Stress cardiomyopathy
VALVULAR HEART DISEASE
Acute mitral regurgitation (chordal rupture)
Acute aortic regurgitation
Aortic or mitral stenosis with tachyarrhythmia or other comorbid condition causing decompensation
Prosthetic valve dysfunction
TACHYARRHYTHMIA
OTHER CONDITIONS
Prolonged cardiopulmonary bypass
Septic shock with severe myocardial depression
Penetrating or blunt cardiac trauma
Orthotopic transplant rejection
Massive pulmonary embolism
Pericardial tamponade

mortality after cardiogenic shock reflect the severity of the acute insult as well as comorbid conditions.

Coronary angiography most often demonstrates multivessel CAD, with left main stenosis in 30% of patients and three-vessel coronary disease in 60%. Multivessel CAD may help explain failure to develop compensatory hyperkinesis in remote myocardial segments.

PATHOBIOLOGY

Cardiogenic shock is characterized by a downward cascade in which myocardial dysfunction reduces stroke volume, cardiac output, and blood pressure; these changes compromise myocardial perfusion, exacerbate ischemia, and further depress myocardial function, cardiac output, and systemic perfusion. Concomitant diastolic dysfunction increases left atrial pressure, which leads to pulmonary congestion and hypoxemia that can exacerbate myocardial ischemia and impair ventricular performance.

Compensatory mechanisms include sympathetic stimulation, which increases heart rate and contractility, thereby raising cardiac output but also increasing myocardial oxygen demand. Compensatory vasoconstriction can increase blood pressure, but it also increases myocardial afterload, further impairing cardiac performance and increasing myocardial oxygen demand. In the face of inadequate perfusion, this increased demand can worsen ischemia and perpetuate a vicious circle that, if unbroken, may culminate in death. Interruption of this circle of myocardial dysfunction and ischemia is the basis for therapeutic regimens for cardiogenic shock.

Patients with cardiogenic shock do not always have severe left ventricular dysfunction, so mechanisms other than primary pump failure are often operative. Furthermore, systemic vascular resistance is not always elevated, suggesting that compensatory vasoconstriction is not universal. Inflammatory responses may contribute to vasodilation and myocardial dysfunction in cardiogenic shock.

Patients in cardiogenic shock may have areas of nonfunctional but viable myocardium because of myocardial stunning, or postischemic dysfunction that persists despite restoration of normal blood flow. Some patients have hibernating myocardial segments with persistently impaired function at rest owing to severely reduced coronary blood flow. Although conceptually distinct, the two conditions may overlap; repetitive episodes of myocardial stunning can occur in areas of viable myocardium subtended by a critical coronary stenosis. Contractile function of hibernating myocardium improves with revascularization, and the severity of the antecedent ischemic insult determines the intensity of stunning, thereby providing a rationale for the early reestablishment of coronary patency in cardiogenic shock. The notion that some myocardial tissue may recover function emphasizes the importance of measures to provide hemodynamic support and minimize myocardial necrosis in patients with shock.

CLINICAL MANIFESTATIONS

The physical examination should be geared toward characterizing the patient's hemodynamic profile by evaluating congestion ("wet" or "dry") and systemic perfusion ("cold" or "warm") (Table 93-3). Signs of left-sided congestion (Chapter 45) include pulmonary rales, whereas jugular venous distention (see Fig. 39-1), peripheral edema, and ascites may indicate right-sided congestion.

Most patients with cardiogenic shock present "wet" and "cold," but a mixed shock profile, with congestion and vasodilation ("wet" and "warm") also occasionally can be seen. Patients with shock are usually ashen or cyanotic, and they have faint pulses, cool skin, and mottled extremities. Cerebral hypoperfusion may cloud the sensorium. Jugular venous distention and pulmonary rales are usually present, although their absence does not exclude the diagnosis. A precordial heave resulting from left ventricular dyskinesis may be palpable. The heart sounds may be distant, and third and/or fourth heart sounds are usually present. A systolic murmur of mitral regurgitation or a ventricular septal defect may be heard, but either complication can occur without an audible murmur (Chapter 58). Signs or symptoms of kidney, liver, intestinal, and cognitive dysfunction may be observed.

DIAGNOSIS

After recognizing the clinical manifestations of apparent cardiogenic shock, the clinician must confirm its presence and assess its cause while simultaneously initiating supportive therapy before irreversible organ damage ensues. The clinician must balance overzealous pursuit of an etiologic diagnosis before achieving stabilization with overzealous empirical treatment without adequate characterization of the underlying pathophysiologic process.

An electrocardiogram (ECG) should be performed immediately. In cardiogenic shock caused by acute MI, the ECG most commonly shows ST elevation, but ST depression or nonspecific changes are found in 25% of cases. If RV infarction is suspected, ST elevation in modified right-sided leads may be diagnostic (Chapter 58). An ECG showing Q waves or bundle branch block may suggest extensive disease.

Other initial diagnostic tests include a chest radiograph, complete blood count, and measurement of arterial blood gases, electrolytes, and cardiac biomarkers. Metabolic acidosis with elevated serum lactate levels may indicate

TABLE 93-3 SIGNS AND SYMPTOMS OF VOLUME STATUS AND PERFUSION

SIGNS AND SYMPTOMS OF CONGESTION
Orthopnea, paroxysmal nocturnal dyspnea
Jugular venous distention
Abdominojugular reflux
Rales
Hepatomegaly
Edema
Right upper quadrant tenderness
POSSIBLE EVIDENCE OF LOW PERFUSION
Hypotension
Narrow pulse pressure
Obtundation
Cool extremities
Cachexia, muscle loss
Decreased exercise tolerance
Renal/hepatic dysfunction

global hypoperfusion. A point-of-care ultrasound examination[4] or chest radiograph may demonstrate pulmonary edema and or suggest an alternative diagnosis, as when a widened mediastinum indicates aortic dissection (Chapter 63).

Echocardiography

Echocardiography is an indispensable tool for confirming the diagnosis of cardiogenic shock[5] and should be performed as early as possible, preferably with Doppler (Chapter 43). Echocardiography provides information about overall and regional systolic function, diastolic function, and valvular disease, and it can rapidly diagnose mechanical causes of shock, such as papillary muscle rupture, acute ventricular septal defect, and free wall rupture, and tamponade (Chapter 58).

Right Heart Catheterization

If the history, physical examination, chest radiograph, and echocardiogram demonstrate systemic hypoperfusion, low cardiac output, and elevation of venous pressures, right heart catheterization may not be necessary for diagnosis. If there is any uncertainty, however, invasive hemodynamic monitoring can be quite useful to characterize hemodynamics and to exclude volume depletion, right ventricular infarction, and mechanical complications.

Right heart catheterization is most useful, however, to optimize therapy in unstable patients. In such patients, clinical estimates of filling pressures can be unreliable, and optimal filling pressures may be higher than expected in individual patients with left ventricular diastolic dysfunction. Changes in myocardial performance or therapeutic interventions, including revascularization, can change cardiac output and filling pressures precipitously. Concomitant right ventricular dysfunction is often underrecognized in patients with cardiogenic shock, and its importance underappreciated; right heart catheterization is the best and most expeditious way to assess right-sided hemodynamics in these patients. Measurement of cardiac output and mixed venous oxygen saturation can assess cardiac performance and help select patients for inotropic and/or mechanical circulatory support. Some data suggest that, in contrast to patients with other forms of shock or with straightforward heart failure, the use of hemodynamic monitoring is associated with improved outcomes in patients with cardiogenic shock.[6]

TREATMENT

Initial Management

Initial stabilization of the patient with suspected cardiogenic shock includes venous access, supplemental oxygen, and continuous ECG monitoring (Fig. 93-2).[7,8] Management by a dedicated shock team is associated with better outcomes.[9] Many patients require endotracheal intubation and mechanical ventilation (Chapter 91), not only to improve gas exchange but also to reduce the work of breathing and facilitate sedation. Electrolyte abnormalities should be corrected. Relief of pain and anxiety with opiates (Chapter 58) can reduce excessive sympathetic activity, as well as decrease oxygen demand, preload, and afterload. Arrhythmias (Chapter 52) can reduce cardiac output and should be corrected promptly with antiarrhythmic drugs (see Table 52-2 in Chapter 52), cardioversion, or pacing (Chapter 54).

If the cause is likely an acute MI, aspirin and heparin should be given immediately (Chapter 58). Some therapies routinely used in acute MI (e.g., nitrates, β-blockers, renin-angiotensin system blockers) have the potential to exacerbate hypotension in cardiogenic shock and have been associated with poorer outcomes in hypotensive patients. Consequently, these agents should be avoided in patients with tenuous hemodynamic status until they stabilize.[10]

An initial assessment of fluid status and systemic perfusion should be performed.[11] Ischemia produces diastolic dysfunction, so high filling pressures may be necessary to maintain stroke volume in some patients. Some patients may benefit from rapid bolus infusions of 100 to 200 mL of crystalloid titrated to clinical end points. Patients who do not respond rapidly to initial treatment should be considered for invasive hemodynamic monitoring to identify the filling pressure at which cardiac output is maximized. Maintenance of adequate preload is particularly important in patients with right ventricular infarction.

Following initial stabilization and restoration of adequate blood pressure, tissue perfusion should be assessed. If tissue perfusion is adequate but significant pulmonary congestion remains, diuretics (e.g., intravenous furosemide as a 20 to 40 mg bolus) may be employed. If tissue perfusion remains inadequate, inotropic support and/or mechanical support should be initiated.

Vasopressors and Inotropes

Maintenance of adequate blood pressure is essential to break the vicious circle of progressive hypotension and further myocardial ischemia. When arterial pressure remains inadequate, therapy with vasopressor agents, titrated not only to blood pressure but also to clinical indices of perfusion and mixed venous oxygen saturation, may be required.[12] Norepinephrine (0.02 to 1.0 μg/kg/minute) acts primarily as a vasoconstrictor, has only a relatively mild inotropic effect, and increases coronary flow. It is preferable to dopamine,[A1,A2] which acts as both an inotrope (at 3 to 10 μg/kg/minute) and vasopressor (at 10 to 20 μg/kg/minute). Epinephrine (at 0.05 to 2 μg/kg/minute) increases both vascular tone and cardiac output, but it is associated with more refractory shock and more metabolic derangement when compared to norepinephrine.[A3] Vasopressin (at 0.02 to 0.04 U/min) may raise blood pressure in patients who are refractory to catecholamines. Vasopressor infusions must be titrated carefully in patients with cardiogenic shock to maximize coronary perfusion pressure with the least possible increase in myocardial oxygen demand. Invasive hemodynamic monitoring with an arterial line and temporary right heart catheterization are advisable during the initial titration of vasoactive agents.

If tissue perfusion remains inadequate despite norepinephrine, inotropic therapy should be initiated. Dobutamine (2.5 to 20 μg/kg/minute), a selective β1-adrenergic receptor agonist, can improve myocardial contractility and increase cardiac output. Dobutamine is the initial agent of choice in patients with systolic blood pressures greater than 90 mm Hg, but it may exacerbate hypotension in some patients, and can precipitate tachyarrhythmias. Milrinone (a phosphodiesterase inhibitor at 0.125 to 0.75 μg/kg/minute without a loading dose) has fewer chronotropic and arrhythmogenic effects than catecholamine but also has a long half-life and can cause hypotension. Milrinone is equivalent to dobutamine in patients who are in cardiogenic shock.[A4]

Intra-Aortic Balloon Pumps

Intra-aortic balloon pumps reduce systolic afterload and augment diastolic perfusion pressure without increasing oxygen demand, but do not significantly improve blood flow distal to a critical coronary stenosis. Despite a hemodynamic rationale for their use, randomized trials have shown no improvement in 30-day, 1-year, or 6-year mortality with intra-aortic balloon pump insertion in patients who have cardiogenic shock and who undergo early revascularization for acute MI.[A5] Whether intra-aortic balloon insertion may still be reasonable to support occasional patients through a critical period of shock until definitive therapy undertaken is not known. Failure of an intra-aortic balloon to reverse hypoperfusion, however, is a poor prognostic sign, and such patients should be considered for more aggressive mechanical support, e.g., a left ventricular assist device.

Cardiogenic Shock Complicating Acute MI

Reperfusion

Supportive therapy may improve blood pressure and cardiac output in cardiogenic shock, but rapid restoration of myocardial blood flow is the cornerstone of therapy for patients with cardiogenic shock due to MI (Chapter 58). Prompt revascularization is the only intervention that consistently reduces mortality rates in patients with cardiogenic shock that complicates an acute MI,[13] and randomized trials suggest that about 13 patients will be saved at 1 year for each 100 patients treated. Furthermore, most survivors will have good functional status.

Outcomes are best when PCI is performed within 6 hours after the onset of symptoms, but survival benefits are still demonstrable up to 18 hours after the onset of shock. In patients with multivessel disease, data suggest that stenting of the culprit lesion only is as good as immediate multivessel PCI, with a lower risk that the patient will require renal replacement therapy.[A6] Patients over 75 years of age who are suitable for aggressive therapy also appear to benefit.[14]

CABG surgery is more likely to provide complete revascularization and achieves long-term survival rates comparable to PCI, often despite worse coronary anatomy and a higher prevalence of diabetes. In practice, however, emergency CABG is performed less than 10% of the time.

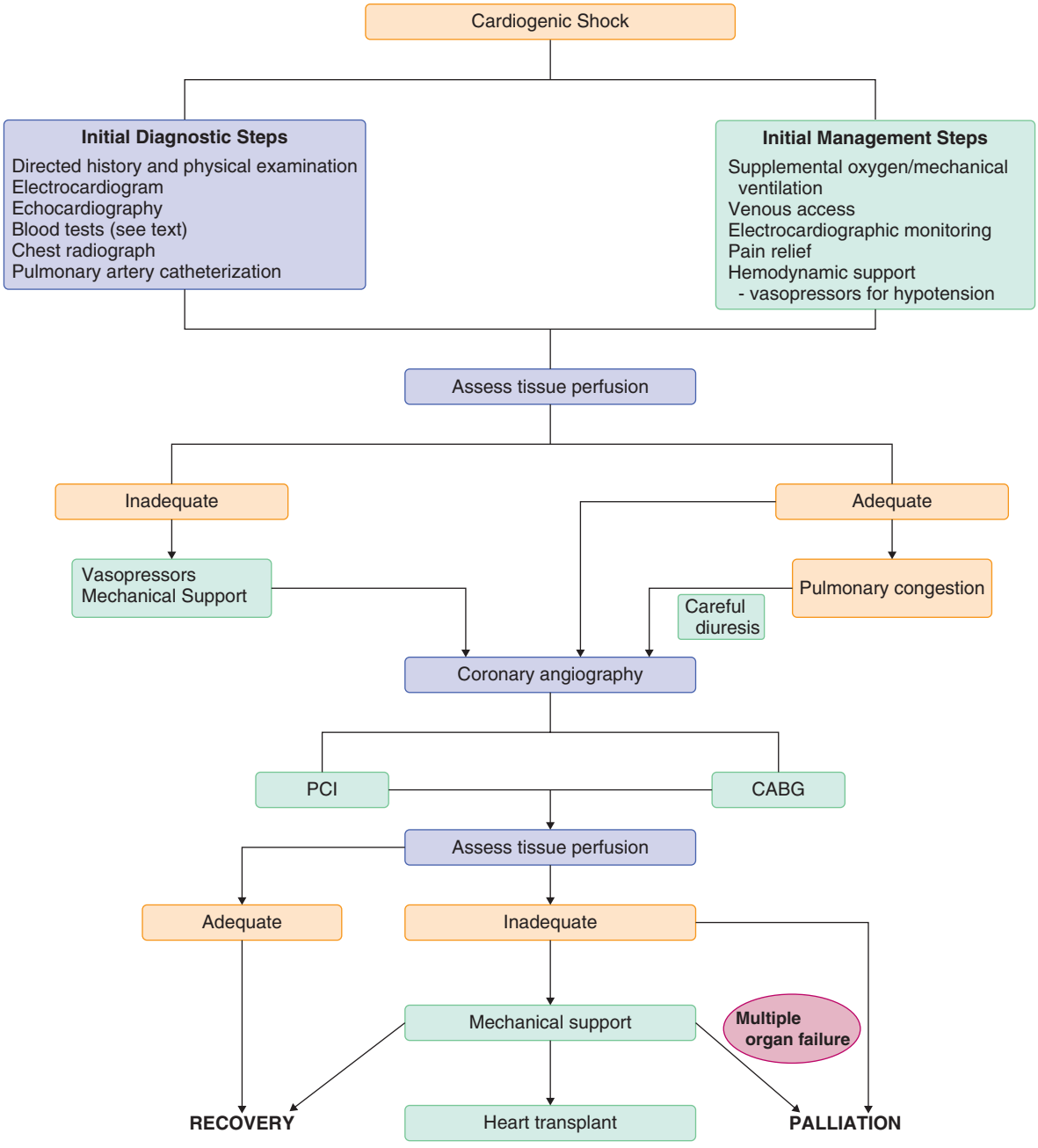

FIGURE 93-2. Approach to the diagnosis and treatment of cardiogenic shock caused by myocardial infarction. Right ventricular infarction and mechanical complications are discussed in the text. CABG = coronary artery bypass graft; LVAD = left ventricular assist device; PCI = percutaneous coronary intervention.

When cardiogenic shock results from mechanical complications of MI (Chapter 58), surgery is recommended when feasible. For acute mitral regurgitation owing to papillary muscle rupture, vasoactive and mechanical support are temporizing measures; definitive therapy requires expeditious surgical valve repair or replacement (Chapter 60). Although mortality is 20 to 40%, surgical results are improving, and both survival and ventricular function are improved compared with medical therapy.

Timely surgery is also critical in patients whose cardiogenic shock results from ventricular septal or free wall rupture. Because perforations are exposed to shear forces, the rupture site can expand abruptly. Repair can be technically difficult owing to the need to suture in areas of necrosis. Surgical mortality is 20 to 50% and is especially high for serpiginous inferoposterior ruptures, which are typically less well circumscribed than anteroapical ruptures. Right ventricular function is an important determinant of outcome in this setting. Timing of surgery has been controversial, but guidelines now recommend that operative repair be undertaken early, within 48 hours of the rupture. Placement of a septal occluding device may be helpful in selected patients.

Mechanical Circulatory Support

Percutaneous mechanical circulatory support devices can potentially interrupt the downward spiral of myocardial dysfunction, hypoperfusion, and ischemia in cardiogenic shock, thereby allowing time for myocardial recovery.[15] These devices, to different extents, increase arterial pressure and cardiac output, reduce left ventricular filling pressures and afterload, and support coronary perfusion. They can provide short-term support as a bridge to recovery or to transplantation,[16] and they are sometimes used as destination therapy when transplantation cannot be performed.[17] For cardiogenic shock in acute MI, however, these devices improve hemodynamic function but have not been shown to reduce morbidity.[A7]

Extracorporeal membrane oxygenation (ECMO) provides cardiopulmonary support for both heart and lungs using a membrane oxygenator and an arterial return catheter. ECMO reduces right ventricular and left ventricular preload but increases left ventricular afterload, and it can be useful for refractory cardiogenic shock,[18,19] including otherwise-refractory sepsis-induced cardiogenic shock, although its optimal timing and use remain uncertain.[A8,20]

A key issue in choosing among mechanical support options is right ventricular function. Some patients with both right and left heart failure might benefit from initial biventricular support with addition of right ventricular support. The left ventricle rarely fails alone for long, and assessment of right ventricular hemodynamics with invasive hemodynamic monitoring can be important to optimize mechanical support strategies.

Cardiogenic Shock Not Related to Acute MI

At the end stage of a dilated or restrictive cardiomyopathy (Chapter 47), low cardiac output can result in cardiogenic shock.[21] A search for reversible precipitating causes should be undertaken. Some patients will respond to inotropic therapy and will have a brief period of relative improvement. Appropriate candidates should be referred for evaluation for possible cardiac transplantation (Chapter 46) or mechanical support. A fully magnetically levitated circulatory pump can provide an 85% survival rate free of device surgery or disabling stroke in appropriately selected patients at 6 months.[A9] Left ventricular assist devices can be used either as a bridge to transplantation or as destination therapy. A discussion about end-of-life care is also warranted.

Acute myocarditis (Chapter 47) can take a fulminant course leading to shock in 10 to 15% of cases. Patients with acute myocarditis are typically younger than those with cardiogenic shock due to MI, and more commonly present with dyspnea rather than chest pain. Echocardiography usually shows global left ventricular dysfunction. Supportive therapy is indicated; some patients may require circulatory support and even consideration of cardiac transplantation. Immunosuppressive therapy has not been shown to improve outcome in fulminant myocarditis.

Patients with hypertrophic cardiomyopathy (Chapter 47) may sometimes present with severe outflow tract obstruction and shock. In such patients, diuretic and inotropic therapy typically worsen the obstruction. Careful volume resuscitation and use of a pure α-agonist, such as phenylephrine (0.1 to 0.3 mg/kg/minute), can reduce obstruction by increasing afterload and cavity size.

Stress (takotsubo) cardiomyopathy (Chapter 47) presents with chest pain and ECG changes similar to acute MI; exclusion of significant coronary obstruction and characteristic apical hypokinesis with basal sparing establish the diagnosis. Some patients may have left ventricular dysfunction severe enough to produce shock. Treatment is supportive. Most patients recover left ventricular function within days to weeks, and long-term prognosis is excellent.

Acute mitral regurgitation (Chapter 60) presents with pulmonary edema and decreased forward cardiac output. Causes include posterior papillary muscle rupture in acute MI, spontaneous chordal rupture, infective endocarditis (Chapter 61), and trauma (Chapter 97). The diagnosis is best made by echocardiography. Immediate stabilization may include inotropic or vasopressor therapy or mechanical support to support cardiac output and blood pressure. Definitive therapy, however, entails surgical valve repair or replacement (Chapter 60).

Acute aortic regurgitation most commonly results from infective endocarditis (Chapter 61) with leaflet destruction, but it may also be due to traumatic injury (Chapter 97) or acute aortic dissection (Chapter 63). The pulse pressure is usually narrow, indicating decreased forward stroke volume, and the bounding pulsations seen with chronic aortic regurgitation are typically absent. Temporizing measures include afterload reduction, with vasopressor and inotropic support as needed. Intra-aortic balloon pump is contraindicated, and excessive slowing of the heart rate may worsen hemodynamics by prolonging diastole. Definitive therapy is surgical.

PROGNOSIS

Cardiogenic shock is still the most common cause of death in acute MI. Survival rates are improving as advances in supportive therapy and reperfusion are used in appropriately selected patients. Lower systolic blood pressure, acidosis, and higher serum lactate and alanine aminotransferase levels are associated with a poorer prognosis.[22] Age and time to revascularization independently predict survival, but the benefits of revascularization are seen at every level of risk. Better myocardial perfusion at the capillary level, as determined by postrevascularization angiography, predicts better prognosis.[23] Average 1-year survival after early revascularization is 50 to 55%, and the survival benefit is maintained at follow-up, with 5-year survival approaching 45%. The quality of life in survivors is usually excellent; 83% of patients are either asymptomatic or have only mildly symptomatic heart failure. For patients with end-stage nonischemic myocardial disease, the prognosis is very poor in the absence of heart transplantation or long-term mechanical support.[24]

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94 SHOCK SYNDROMES RELATED TO SEPSIS

ANTHONY C. GORDON AND JAMES A. RUSSELL

DEFINITION

Sepsis is life-threatening organ dysfunction caused by a dysregulated host response to infection. Organ dysfunction is defined as an acute change of two or more points in the total Sequential Organ Failure Assessment (SOFA) score[1] (Table 94-1). In addition to the full SOFA, a briefer quick SOFA—defined by respiratory rate of 22/min or more, altered mentation, and systolic blood pressure lower than 100 mm Hg—provides simple bedside criteria to screen quickly for sepsis. *Bacteremia* is defined as the growth of bacteria in blood cultures, but infection does not have to be proved to diagnose sepsis at the onset. *Septic shock* was also redefined in 2016 as a subset of sepsis with persisting hypotension requiring vasopressors to maintain a mean arterial pressure of 65 mm Hg or higher accompanied by a serum lactate level greater than 18 mg/dL (2 mmol/L), despite adequate volume resuscitation.[2]

EPIDEMIOLOGY

More than 750,000 cases of severe sepsis or septic shock occur every year in the United States, and more than 48 million cases are estimated to occur globally each year. Sepsis, which is diagnosed in 6% of adult U.S. hospitalizations, causes as many deaths as acute myocardial infarction, and septic shock and its complications are the most common causes of death in noncoronary intensive care units (ICUs). Worldwide, the age-standardized incidence and mortality rates of sepsis have been declining substantially over the past three decades, although less so in sub-Saharan Africa.[3] The medical care costs associated with sepsis are approximately $20 billion a year in the United States alone. The incidence of septic shock is increasing as physicians perform more aggressive surgery, as more resistant microorganisms are present in the environment, and as the prevalence of immune compromise resulting from disease and immunosuppressive drugs increases. Risk factors for septic shock include age, underlying chronic conditions (e.g., chronic obstructive pulmonary disease, cancer), and immunosuppressive drugs. Studies suggest that African Americans have a higher incidence of sepsis than Whites (6.0 vs. 3.6 per 1000 population) and a higher mortality in ICUs (32% vs. 29%) even after adjusting for poverty levels. The mechanisms of this apparent difference in risk for and mortality from sepsis are not known.

Gram-positive or gram-negative bacteria, fungi, and, very rarely, protozoa or rickettsia can cause septic shock. Increasingly common causes of septic shock are antibiotic-resistant gram-positive bacteria, especially methicillin-resistant *Staphylococcus aureus*, vancomycin-resistant enterococci, and penicillin-resistant *Streptococcus pneumoniae*, as well as sometimes multidrug-resistant gram-negative bacilli.

The most common infections causing septic shock are pneumonia (about half of cases), peritonitis, pyelonephritis, abscess (especially intra-abdominal), primary bacteremia, cholangitis, cellulitis, necrotizing fasciitis, and meningitis. Nosocomial pneumonia is the most common cause of death from nosocomial infection. Blood cultures are positive in only about one third of patients with septic shock, and 20 to 30% of cases are culture negative from all sites.

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EPIDEMIOLOGY

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The most common infections causing septic shock are pneumonia (about half of cases), peritonitis, pyelonephritis, abscess (especially intra-abdominal), primary bacteremia, cholangitis, cellulitis, necrotizing fasciitis, and meningitis. Nosocomial pneumonia is the most common cause of death from nosocomial infection. Blood cultures are positive in only about one third of patients with septic shock, and 20 to 30% of cases are culture negative from all sites.

ABSTRACT

The definition of septic shock is life-threatening organ dysfunction with underlying circulatory and cellular/metabolic abnormalities caused by a dysregulated host response to infection. Endotoxins bind to innate immune receptors or can be shuttled from HDL to LDL and be cleared by the liver via the LDL receptor. Widespread endothelial injury increases endothelial permeability. Septic shock activates the coagulation system and causes sepsis-associated coagulopathy. An immunosuppressed state, which can exceed the pro-inflammatory response, can be fatal. Cardiovascular features include vasodilation, hypovolemia, decreased ventricular contractility, and increased vascular permeability. Management includes oxygen (many patients require mechanical ventilation), early antibiotics (within 1 hour), fluid resuscitation (30 mL/kg crystalloid over first 3 hours followed by additional fluids), vasopressors (e.g., norepinephrine, 1 to 50 μg/minute if the mean arterial pressure is less than 65 mm Hg despite adequate fluid resuscitation), consideration of vasopressin and hydrocortisone if the response to vasopressors is inadequate, transfusion if the hemoglobin level is less than 7 g/dL, and dobutamine if there is ventricular dysfunction. Early goal-directed therapy is no better than usual care. Continuous renal replacement therapy may be preferable to intermittent hemodialysis in patients with hemodynamic instability. The 28-day mortality is about 20 to 25%. Early deaths are usually due to refractory septic shock. Later deaths (after day 3) are usually due to multiple organ dysfunction, nosocomial infection, or both.

KEYWORDS

septic shock
antibiotics
fluids
norepinephrine
vasopressin
corticosteroids
dobutamine

TABLE 94-1 SCREENING FOR SEPSIS AND SEPTIC SHOCK

Step 1. Screen for sepsis using Quick SOFA (Sepsis-related Organ Failure Assessment): One point is given for each adverse finding as follows:
1. Respiratory rate ≥22/minute
2. Altered mentation—Glasgow Coma Score less than 15
3. Systolic blood pressure ≤100 mm Hg

Step 2. Diagnose sepsis as a 2-point increase in SOFA as follows:
Sequential SOFA
Step 3. Diagnose septic shock by the following:
Use of vasopressors (e.g., norepinephrine, epinephrine, phenylephrine) to maintain a mean arterial pressure ≥65 mm Hg
PLUS
Serum lactate >18 mg/dL (2 mmol/L) despite adequate volume resuscitation

SEQUENTIAL (SEPSIS-RELATED) ORGAN FAILURE ASSESSMENT (SOFA) SCORE

	SCORE				
SYSTEM	**0**	**1**	**2**	**3**	**4**
Respiratory (PaO_2/FIO_2)	≥400	<400	<300	<200	<100
Coagulation (platelet count × $10^3/\mu L$)	≥150	<150	<100	<50	<20
Liver (bilirubin mg/dL [μmol/L])	<1.2 (20)	1.2-1.9 (20-32)	2.0-5.9 (33-101)	6.0-11.9 (102-204)	>12 (204)
Cardiovascular	MAP ≥70 mm Hg	MAP <70 mm Hg	Dopa <5 (or any dose dob*)	Dopa 5.1-15 or epi ≤0.1 or norepi ≤0.1	Dopa >15 or epi >0.1 or norepi >0.1
CNS (Glasgow Coma Scale)†	15	13-14	10-12	6-9	<6
Renal (creat mg/dL [μmol/L])	<1.2 (100)	1.2-1.9 (110-170)	2.0-3.4 (171-299)	3.5-4.9 (300-400)	>5 (440)
Urine output, mL/d				<500	<200

*Catecholamine doses are given as μg/kg/minute for at least 1 hour.
†Glasgow Coma Scale scores range from 3 to 15; higher score indicates better neurological function.
CNS = central nervous system; Dob = dobutamine; Dopa = dopamine; epi = epinephrine; FIO_2 = fraction of inspired oxygen; MAP = mean arterial pressure; norepi = norepinephrine; PaO_2 = partial pressure oxygen.
Adapted from Singer M, Deutschman CS, Seymour CW, et al. The third international consensus definitions for sepsis and septic shock (Sepsis-3). *JAMA*. 2016;315:801-810.

Septic shock occurs in about 20 to 30% of patients hospitalized with coronavirus disease 2019 (COVID-19; Chapter 336), likely with a similar pathophysiology as other causes of septic shock. In addition, however, severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), which is the causative agent of COVID-19, binds and downregulates angiotensin-converting enzyme 2, which normally degrades angiotensin II (a very potent vasoconstrictor and permeability-inducing agent) to angiotensin 1-7 (a vasodilator). This effect appears to enhance lung damage (Chapter 335) and increase the risk of septic shock.

PATHOBIOLOGY

At its onset, septic shock activates inflammation, as evidenced by neutrophilia and a shift to immature neutrophils and a procoagulant phenotype (detected by an increased international normalized ratio and thrombocytopenia) owing to enhanced coagulation, activated platelets, and diminished fibrinolysis. An immunosuppressed state may emerge and may contribute to death. Several pathways amplify one another: inflammation triggers coagulation, coagulation triggers inflammation, and tissue hypoxia amplifies both inflammation and coagulation, thereby resulting in positive pro-inflammatory and procoagulant feedback loops. Many mediators critical to homeostatic control of infection are also injurious to the host (e.g., tumor necrosis factor-α [TNF-α], interleukin-1 [IL-1]), perhaps in part explaining why therapies that neutralize such mediators have generally been ineffective to date.

Widespread endothelial injury is an important feature of septic shock; an injured endothelium is more permeable. Consequently, protein-rich edema fluid fluxes into tissues such as the lung, where it leads to acute respiratory distress syndrome (ARDS). In septic shock, injured endothelial cells release nitric oxide, a potent vasodilator. Septic shock also injures epithelial cells of the lung and intestine. Intestinal epithelial injury increases intestinal permeability and the epithelial translocation of intestinal bacteria and endotoxin, thereby further augmenting the inflammatory phenotype of septic shock.

Early Infection, the Innate Immune Response, Inflammation, and the Endothelium

Bacteria have cell surface endotoxins (lipopolysaccharide [LPS] and lipoteichoic acid [LTA] of gram-negative and gram-positive bacteria, respectively) that are major ligands for innate immune receptors, mainly on various immune cells that launch the septic inflammatory response. Endotoxins are shuttled from high-density lipoprotein (HDL) to low-density lipoprotein (LDL) (E-Fig. 94-1) and are cleared mainly by the liver via the LDL receptor—the same receptor that clears LDL cholesterol—and then are excreted harmlessly in bile (E-Fig. 94-2). Endotoxin clearance is modulated by proprotein convertase subtilisin/kexin type 9 (PCSK9); lower PCSK9 activity increases recycling of the LDL receptor to the hepatocyte cell surface, thereby increasing hepatic endotoxin clearance.

Host defense is organized into innate and adaptive immune responses. The innate immune system uses pattern recognition receptors (e.g., toll-like receptors [TLRs], C-type lectin receptors, retinoic acid inducible gene 1–like receptors, and nucleotide-binding oligomerization domain–like receptors) to bind pathogen-associated molecular patterns, which are extremely well-conserved molecules of microorganisms. LPS and LTA of gram-negative and gram-positive bacteria, respectively, bind to TLR-4 and TLR-2, respectively (see E-Fig. 94-2; E-Fig. 94-3). TLR-4 and TLR-2 binding initiates an intracellular signaling cascade that causes nuclear transport of the transcription factor nuclear factor κB (NF-κB), which in turn initiates transcription of cytokines such as TNF-α and IL-6. Nucleotide-binding oligomerization domain–like receptors are important in the inflammasome response to sepsis. IL-3 also amplifies acute inflammation and is a potential therapeutic target in sepsis.

Cytokines upregulate adhesion molecules of neutrophils and endothelial cells, and neutrophil activation leads to bacterial killing. However, cytokines also directly injure host endothelial cells, as do activated neutrophils, monocytes, and platelets. Inhibition of early cytokine mediators of sepsis, such as TNF-α and IL-1β, has not proved successful, probably because TNF-α and IL-1β peak and then decline quickly, before these antagonist therapies can be applied clinically.

After the early cytokine inflammatory response, immune cells, including macrophages and neutrophils, release later mediators, such as high-mobility group box 1 (HMGB-1). HMGB-1 activates neutrophils, monocytes, and endothelium. Unlike TNF-α antagonists, inhibitors of HMGB-1 decrease mortality even when they are given 24 hours after the induction of experimental peritonitis.

Autophagy is a self-degradative housekeeping cellular process in many tissues and is increased in sepsis in immune cells, heart, lung, kidney, and liver. Autophagy removes damaged mitochondria in hepatocytes, regulates

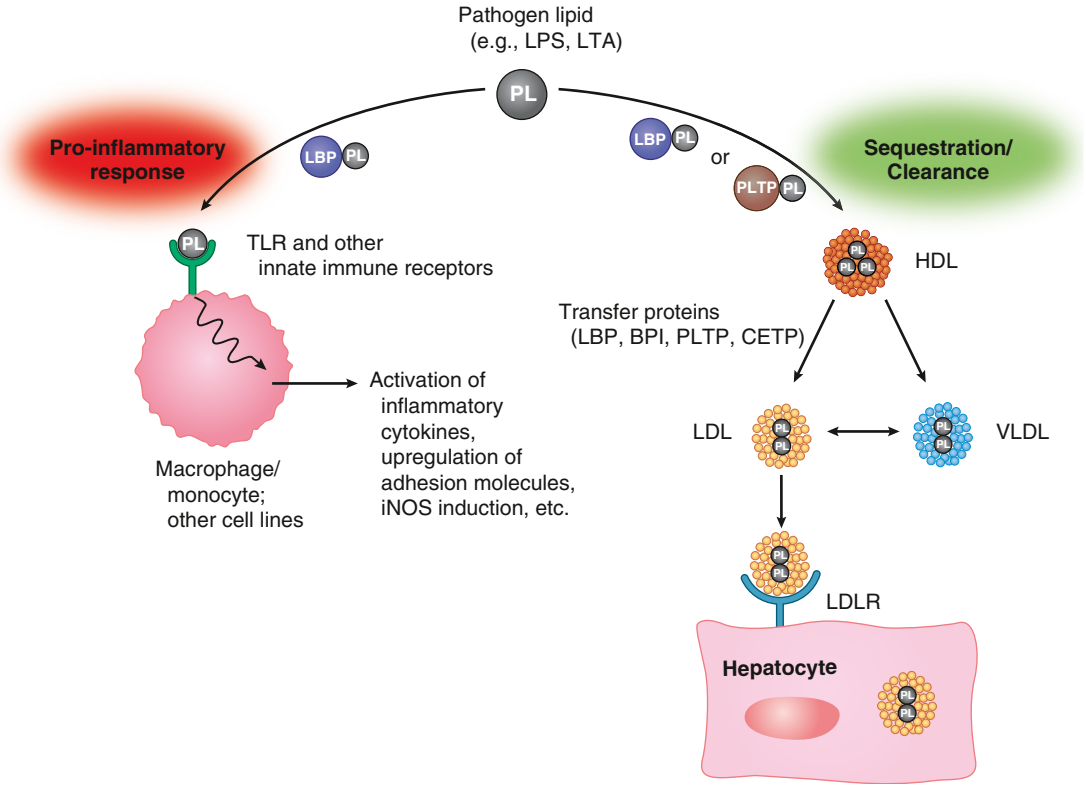

E-FIGURE 94-1. **Pathogen lipid shuttling and clearance.** Pathogen lipids (PL) such as lipopolysaccharide (LPS) and lipoteichoic acid (LTA) can induce a pro-inflammatory response *(left side of figure)* via innate immune receptors (toll-like receptor [TLR]) that induce the inflammatory response, upregulate adhesion molecules, and increase inducible nitric oxide (iNOS) or, alternatively, can be sequestered and cleared from the circulation *(right side of figure)*. Steps in this pathway include binding by transfer proteins (LPS binding protein [LBP]); bactericidal/ permeability increasing protein (BPI); phospholipid transfer protein (PLTP); and cholesterol ester transfer protein [CETP]) incorporation into lipoprotein particles with shuttling from high-density lipoprotein (HDL) to low-density lipoprotein (LDL) and very-low-density lipoprotein (VLDL), binding to LDL receptor (LDLR) and possibly other receptors, and clearance, primarily by the liver. (Reproduced from Walley KR, Thain KR, Russell JA, et al. PCSK9 is a critical regulator of the innate immune response and septic shock outcome. *Sci Transl Med*. 2014;6:258ra143.)

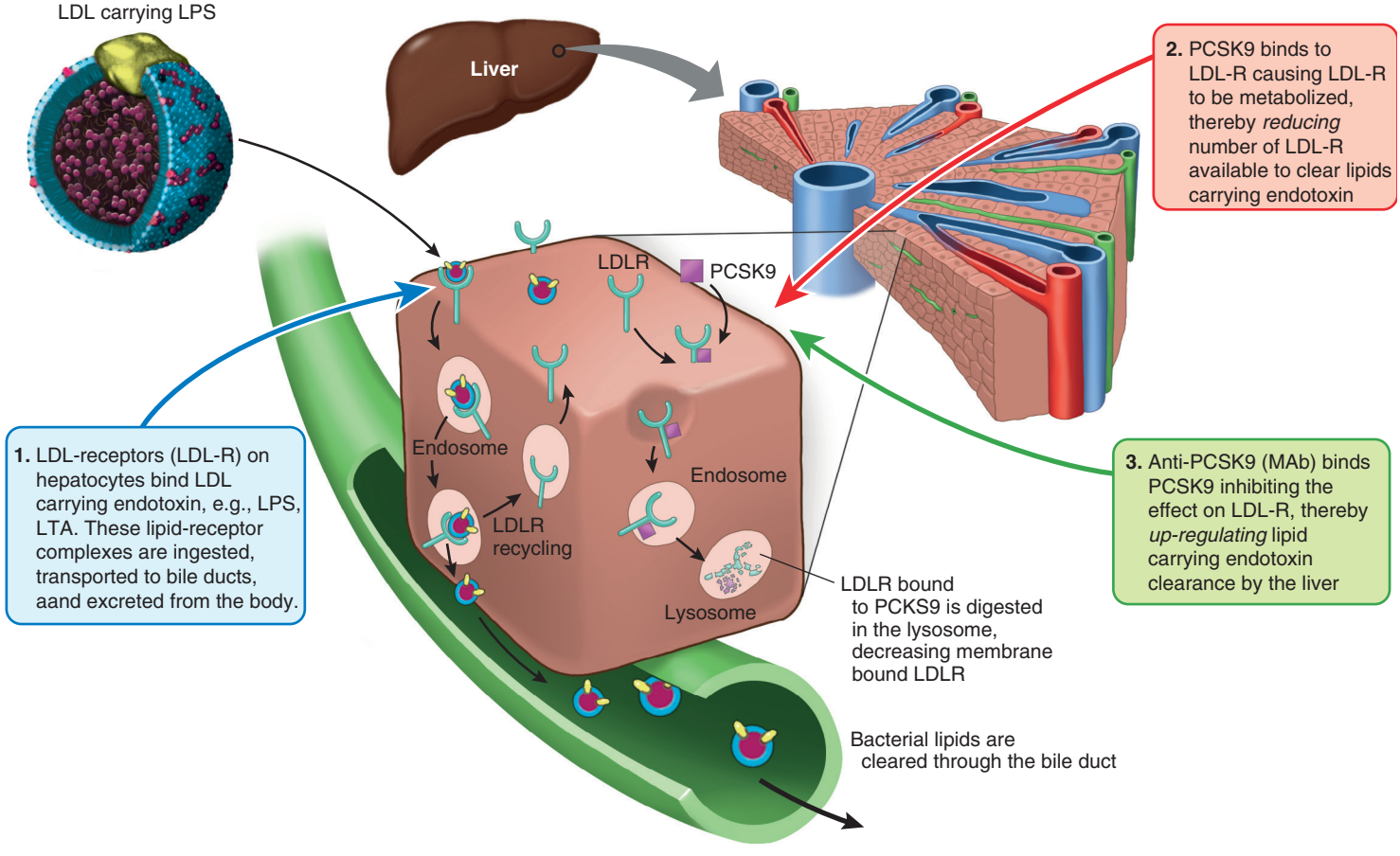

E-FIGURE 94-2. **Clearance of endotoxin by the liver via the LDL receptor pathway.** Schematic view of hepatocytes within the liver. Free proprotein convertase subtilisin/kexin type 9 (PCSK9) in plasma binds to an extracellular portion near the N terminus of the LDL receptor (LDLR) and triggers endosomal internalization. The C-terminus portion of PCSK9, now complexed to LDLR, mediates PCSK9 and LDLR degradation. The net result of increased PCSK9 activity is lower levels of membrane-associated LDLR. Bacterial lipids, such as endotoxin and lipoteichoic acid, are carried within LDL and other lipoproteins. Decreased PCSK9 increases clearance of LDL and associated pathogen lipids, thereby reducing the harmful effects of the pathogen lipids.

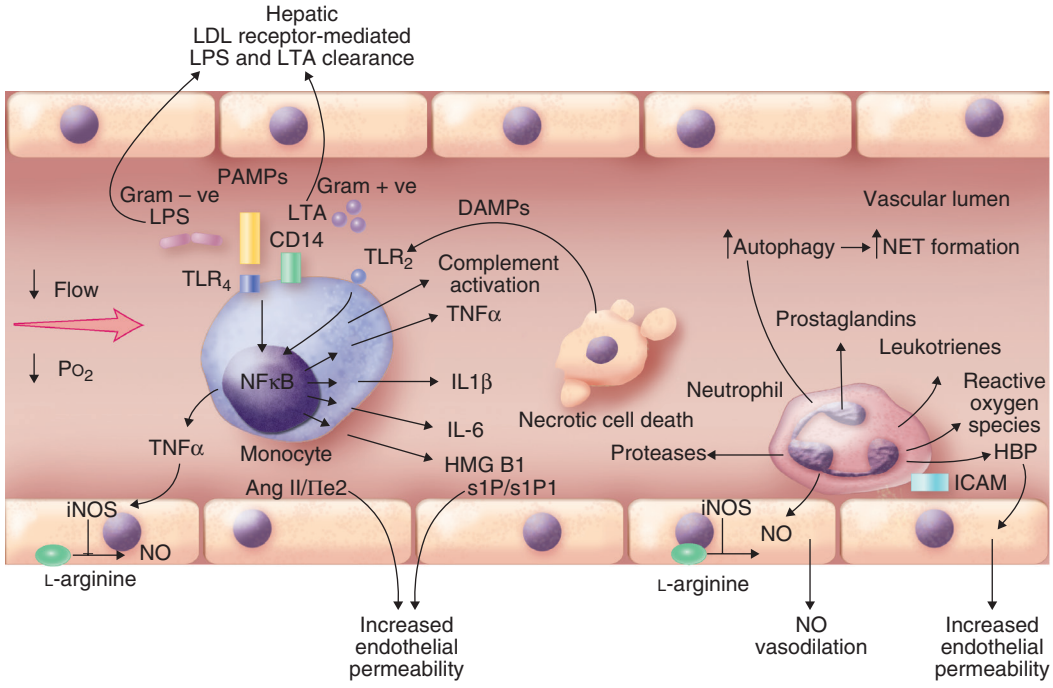

E-FIGURE 94-3. **Inflammatory responses to sepsis.** Gram-positive and gram-negative bacteria, viruses, and fungi have unique cell wall molecules called pathogen-associated molecular patterns (PAMPs) that bind to pattern recognition receptors (called toll-like receptors [TLRs]) on the surface of immune cells as well as C-type lectin receptors, retinoic acid inducible gene 1–like receptors, and nucleotide-binding oligomerization domain–like receptors. Nucleotide-binding oligomerization domain–like receptors alter protein complexes in the inflammasome. The lipopolysaccharide (LPS) of gram-negative bacilli binds to the LPS-binding protein–CD14 complex. The lipoteichoic acid (LTA) of gram-positive bacteria and the LPS of gram-negative bacteria bind to TLR-2 and TLR-4, respectively. TLR-2 and TLR-4 binding activates intracellular signal transduction pathways that lead to the activation of the cytosolic transcription factor nuclear factor κB (NF-κB). Activated NF-κB moves from the cytoplasm to the nucleus, binds to transcription start sites, and increases the transcription of pro-inflammatory cytokines such as tumor necrosis factor-α (TNF-α), interleukin-1β (IL-1β), and interleukin-6 (IL-6). Increased necrotic cell death releases damage-associated molecular patterns (DAMPs or alarmins) that bind to TLRs and thus feed back to further amplify the pro-inflammatory response. TNF-α, IL-1β, and IL-6 are pro-inflammatory cytokines that activate the adaptive immune response but also cause both direct and indirect host injury (e.g., by complement activation). LPS and LTA activation of inflammation is offset by hepatic low-density-lipoprotein receptor (LDLR)–mediated LPS and LTA clearance. Sepsis increases the activity of inducible nitric oxide synthase (iNOS), which increases the synthesis of nitric oxide (NO), a potent vasodilator. Cytokines activate endothelial cells by upregulating adhesion receptors such as intercellular adhesion molecule (ICAM), and they injure endothelial cells by the activation and binding of neutrophils, monocytes, macrophages, and platelets to endothelial cells. These effector cells release mediators such as proteases, reactive oxygen species, prostaglandins, and leukotrienes. Cytokines also activate the coagulation cascade. Autophagy increases in neutrophils, thereby leading to increased neutrophil extracellular trap (NET) formation. Dysregulated autophagy in sepsis impairs NET formation and is associated with decreased survival. Endothelial permeability is increased by injurious agents such as heparin-binding protein (HBP) that is released by neutrophils, angiopoietin 2/Tie 2 receptor interaction, and sphingosine 1-phosphate (S1P) ligation to its G protein–coupled receptor S1P1.

inflammasome activation of immune cells (see E-Fig. 94-3), and is a pro-survival mechanism of cardiomyocytes. Dysregulated autophagy is associated with decreased survival in septic models. Autophagy research suggests that modulation of autophagy in sepsis may prove beneficial. The inflammatory response to septic shock varies according to the organism load, host genotype, underlying conditions, and prior immunosuppressing drugs.

Endothelial Injury

In septic shock, widespread endothelial injury is common and leads to increased endothelial permeability with loss of protein and fluid to the interstitial space. Endothelial permeability is a final common pathway for widespread tissue injury. Cytokines and other inflammatory mediators induce intercellular endothelial cell gaps by disrupting intercellular junctions, by changing cytoskeletal structure, or by direct damage to endothelial cells. Several pathways of altered endothelial permeability have been implicated in sepsis, including protease-activated receptor 1 (PAR-1) and disruption of the intercellular VE-cadherin, β-catenin, and p120-catenin complex. PAR-1 binding by activated protein C and low-dose thrombin is cytoprotective, whereas PAR-1 stimulation by high-dose thrombin increases endothelial permeability. Binding of Slit to Robo4 maintains the integrity of the intercellular VE-cadherin, β-catenin, and p120-catenin complexes and thus maintains healthy endothelial permeability. Mediators of increased permeability in sepsis include heparin-binding protein, soluble thrombomodulin, angiopoietin-2, sphingosine-1 phosphate, and natriuretic peptides.

Adaptive Immunity Adds Specificity and Amplifies the Immune Response

Microorganisms stimulate specific humoral and cell-mediated adaptive immune responses that amplify innate immunity. B cells release immunoglobulins that bind to microorganisms and thereby facilitate delivery of microorganisms to natural killer cells and neutrophils. In sepsis, type 1 helper T (T_H1) cells generally secrete pro-inflammatory cytokines (TNF-α, IL-1β), and type 2 helper T (T_H2) cells secrete anti-inflammatory cytokines (IL-4, IL-10).

Coagulation Response to Infection

Septic shock activates the coagulation system, thereby causing sepsis-associated coagulopathy (E-Fig. 94-4), and ultimately converts fibrinogen to fibrin, which binds to platelets to form microvascular thrombi. A marked or sustained procoagulant response to septic shock can lead to disseminated intravascular coagulation (DIC; Chapter 161) and widespread tissue injury, including loss of digits and limbs. The three main features of sepsis-associated coagulopathy are increased procoagulant activity and decreased anticoagulant and fibrinolytic activity. Microvascular thrombi amplify endothelial injury by the release of inflammatory mediators and by tissue hypoxia because of obstruction to blood flow.

Normally, natural anticoagulants (protein C, protein S, antithrombin, and tissue factor pathway inhibitor) dampen coagulation, enhance fibrinolysis, and remove microthrombi. Thrombin-α binds to thrombomodulin, which activates protein C when protein C is bound to the endothelial protein C receptor (EPCR). Activated protein C dampens the procoagulant phenotype because it inactivates factors Va and VIIIa and inhibits the synthesis of plasminogen activator inhibitor 1 (PAI-1). Activated protein C also decreases apoptosis, leukocyte activation and adhesion, and production of cytokines. Endothelial thrombomodulin expression is decreased in meningococcemia (Chapter 274), thereby explaining in part the profound DIC characteristic of meningococcemic shock.

Septic shock decreases the levels of the natural anticoagulants protein C, protein S, antithrombin, and tissue factor pathway inhibitor. Furthermore, lipopolysaccharide and TNF-α decrease the expression of thrombomodulin and EPCR, thereby further limiting the activation of protein C. Lipopolysaccharide and TNF-α also increase levels of PAI-1, inhibiting fibrinolysis. The coagulation system is linked to the inflammatory response by protease activated receptors (PARs), especially PAR-1.

Tissue Hypoxia in Septic Shock

Tissue hypoxia independently activates inflammation (by activation of NF-κB and cytokines, synthesis of nitric oxide, and activation of HMGB-1); induces coagulation (through tissue factor and PAI-1); and activates neutrophils, monocytes, and platelets. Hypoxia disinhibits hypoxia-inducible factor-1α (HIF-1α), which upregulates erythropoietin, and vascular endothelial growth factor (VEGF). Erythropoietin is protective to brain and other tissues. VEGF inhibits fibrinolysis and increases inducible nitric oxide synthase, thereby increasing nitric oxide–induced vasodilation. Nitric oxide's other injurious effects include inhibiting the beneficial actions of HIF-1α (e.g., upregulating synthesis of erythropoietin) during hypoxia. Tissue hypoxia also causes release of damage-associated molecular patterns (alarmins), which are ligands for the pattern recognition receptors described earlier, thereby increasing the inflammation in septic shock.

Endocrine Responses Relevant to Cardiovascular Support

Complex interactions of several endocrine systems modulate vascular tone, heart rate, and other noncardiovascular functions such as immune function. The main axes stimulated to increase hormone production are the adrenal medullary release of norepinephrine and epinephrine (Chapter 209), hypothalamic-posterior pituitary release of vasopressin (Chapter 204), the hypothalamic-anterior pituitary-adrenal cortex release of corticosteroids (such as cortisone) (Chapter 208), and the renin-angiotensin-aldosterone (RAAS) release of angiotensin II (E-Fig. 94-5). Norepinephrine binds to α1 receptors, vasopressin binds to V1a receptors, and angiotensin II similarly binds to angiotensin II receptors on smooth muscle to stimulate calcium-mediated vasoconstriction. Cortisone modulates α1 receptor density. Deficiencies in each of these hormone levels and the downregulation of relevant receptors (such as V1a) in part explain the need for vasopressor(s)—such as first-line norepinephrine, and second-line epinephrine, vasopressin, and possibly angiotensin II—to increase vascular tone by producing vasoconstriction in patients who do not respond to volume resuscitation.

Immunosuppression and Apoptosis of Immune and Epithelial Cells

Septic shock can initiate an immunosuppressed state that can exceed the pro-inflammatory response starting soon after the onset of septic shock and can be fatal. Patients move through the balance of pro- versus anti-inflammatory/immunosuppressed states at different rates, likely accounting for the wide variability in the clinical progression and recovery from septic shock. Immunodepression occurs in the humoral, cellular, and neural regulation of immunity. Immunosuppression is suggested by anergy, lymphopenia, a decreased CD-4 level, hypothermia, and nosocomial infection (E-Fig. 94-6). Multiple organ dysfunction may be an immunodepressed phenotype because of the apoptosis of immune (B and T cells as well as dendritic cells), epithelial, and endothelial cells. Activated $CD4^+$ T cells evolve into either a T_H1 pro-inflammatory (TNF-α, IL-1β) or a T_H2 anti-inflammatory (IL-4, IL-10) phenotype. Sepsis leads to migration from a T_H1 to a T_H2 phenotype; for example, persistent elevation of IL-10 is associated with an increased risk of death. Immunosuppression also develops because of apoptosis of lymphocytes. Pro-inflammatory cytokines, activated B and T cells, and glucocorticoids induce lymphocyte apoptosis, whereas TNF-α and endotoxin induce apoptosis of lung and intestinal epithelial cells. Other late features of septic shock include expansion of regulatory T cells and myeloid suppressor cells, decreasing inflammation, but impaired phagocytosis. The vagus nerve activates the splenic nerve, thereby causing CD4+ T cells to release acetylcholine, which further attenuates inflammation.

Septic patients can be divided into subgroups based on transcriptomic signatures in blood and the key differences in gene expression related to immunosuppression.[4] These subgroups may respond differently to treatment such as corticosteroids, thereby paving the way for personalized medicine approaches in septic shock.

Death from infectious disease appears to be highly heritable. Sepsis is a prime example of a polygenic disease related to the interaction of multiple genes and an environmental insult (infection). Single-nucleotide polymorphisms of cytokines (TNF-α, IL-6, IL-10), coagulation factors (protein C, fibrinogen-β), the catecholamine pathway (β-adrenergic receptor), and innate immunity genes (CD14, TLR-1, TLR-2) have been variably associated with an increased risk of death from sepsis. To date, none of these findings have evolved into actionable diagnostic or prognostic biomarkers for clinical use.

Cardiovascular Dysfunction

The main features of cardiovascular dysfunction in septic shock are vasodilation, hypovolemia, decreased ventricular contractility, and increased vascular permeability. Inadequate tissue perfusion and tissue hypoxia are the cardinal features of all types of shock. Peripheral levels of catecholamines are dramatically increased in septic shock, but peripheral vasodilation indicates decreased responsiveness to these endogenous vasoconstrictors. Vasodilation in sepsis is mediated mainly by increased synthesis of nitric oxide and prostacyclin. Nitric oxide is increased by a calcium-independent nitric oxide synthase induced by

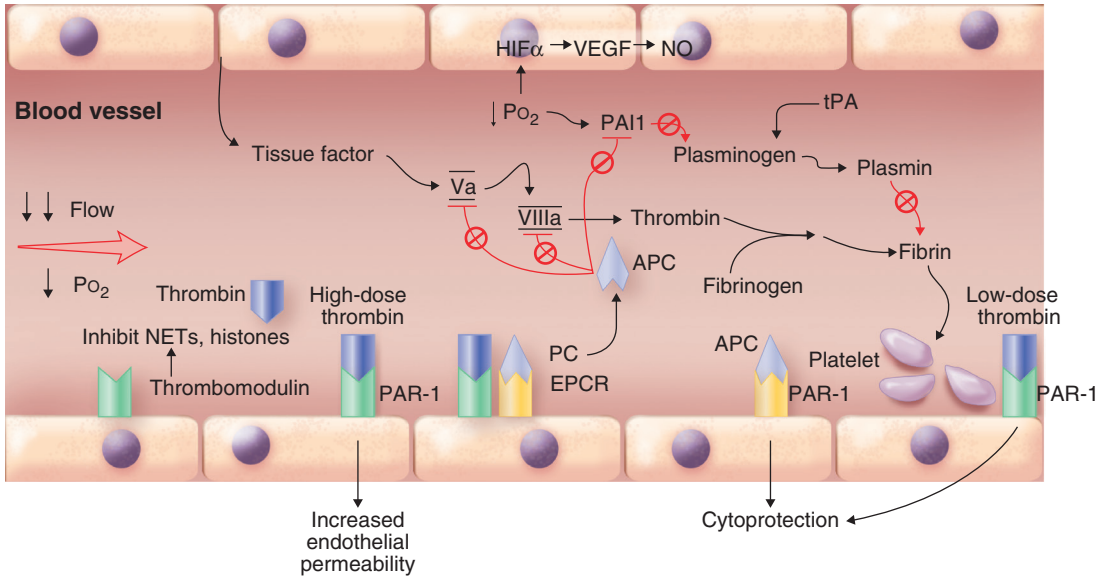

E-FIGURE 94-4. **Procoagulant response in sepsis.** Sepsis initiates coagulation by activating the endothelium to increase tissue factor. Protease-activated receptors (PARs), especially PAR-1, link the inflammatory and coagulation responses to sepsis. Activation of factors Va and VIIIa leads to the formation of thrombin-α, which converts fibrinogen to fibrin. Fibrin binds to platelets that adhere to endothelial cells, forming microvascular thrombi. Microvascular thrombi amplify injury by the release of mediators and by microvascular obstruction, which causes distal ischemia and tissue hypoxia. Normally, natural anticoagulants—protein C (PC), protein S (PS), antithrombin, and tissue factor pathway inhibitor (TFPI)—dampen coagulation, enhance fibrinolysis, and remove microthrombi. Thrombin-α binds to thrombomodulin on endothelial cells and thus activates the binding of PC to endothelial PC receptor (EPCR). PC forms a complex with its cofactor PS. PC binding to EPCR increases the activation of PC to activated PC (APC). APC proteolytically inactivates factors Va and VIIIa and decreases the synthesis of plasminogen activator inhibitor 1 (PAI-1). Sepsis decreases levels of PC, PS, antithrombin, and TFPI. Lipopolysaccharide and tumor necrosis factor-α (TNF-α) decrease thrombomodulin and EPCR, thus decreasing the activation of PC. PAR-1 binding by activated protein C and low-dose thrombin is cytoprotective, whereas PAR-1 stimulation by high-dose thrombin increases endothelial permeability. Lipopolysaccharide and TNF-α also inhibit PAI-1, so fibrinolysis is inhibited. HIFα = hypoxia-inducible factor-α; NO = nitric oxide; tPA = tissue plasminogen activator; VEGF = vascular endothelial growth factor.

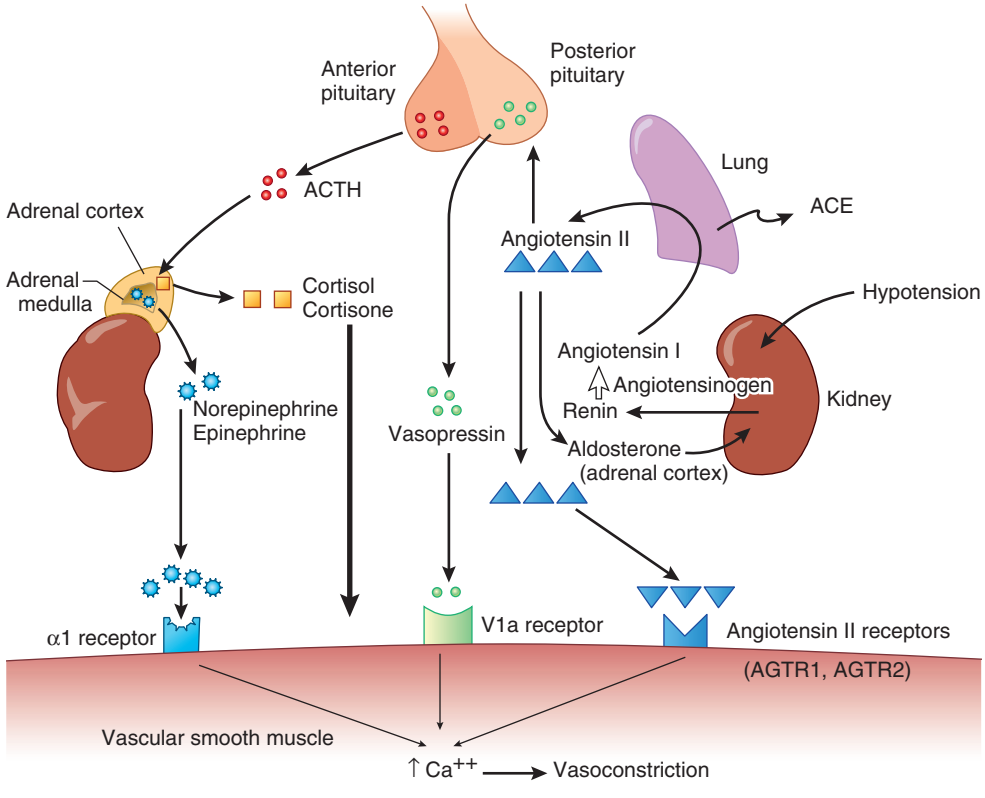

E-FIGURE 94-5. **Endocrine response and therapies in septic shock.** The complex interplay of several key endocrine axes in septic shock includes (1) release of norepinephrine and epinephrine from the adrenal medulla; (2) release of adrenocorticotropic hormone (ACTH) from the anterior pituitary, then stimulating synthesis and release of cortisone and cortisol from the adrenal cortex; (3) release of vasopressin from the posterior pituitary; and (4) release of renin (in response to hypotension) from the kidney. Renin is converted to angiotensin I by angiotensinogen (that was released from the liver), and then angiotensin I is converted to angiotensin II by angiotensin-converting enzyme (ACE) in the lung. Angiotensin II increases aldosterone synthesis and release from the adrenal cortex, and aldosterone increases sodium retention in the kidney. Angiotensin II also increases release of vasopressin. Norepinephrine and epinephrine bind to alpha-1 adrenergic receptors, vasopressin binds to V1a receptors, and angiotensin II binds to angiotensin II receptors (AGTR1 and AGTR2), all on vascular smooth muscle. After ligand binding, intracellular signal transduction increases intracellular calcium, thereby causing vascular smooth muscle contraction and vasoconstriction. Corticosteroids have complex cardiovascular effects that are incompletely understood but include modulation of α-1 receptor density and other actions that quickly increase responsiveness to catecholamines, such as norepinephrine. Thus, much of the management of septic shock—such as infusions of norepinephrine, vasopressin, and possibly angiotensin II, as well as administration of hydrocortisone, have foundations in the endocrine axes and pathophysiologic effects of septic shock on endocrine function.

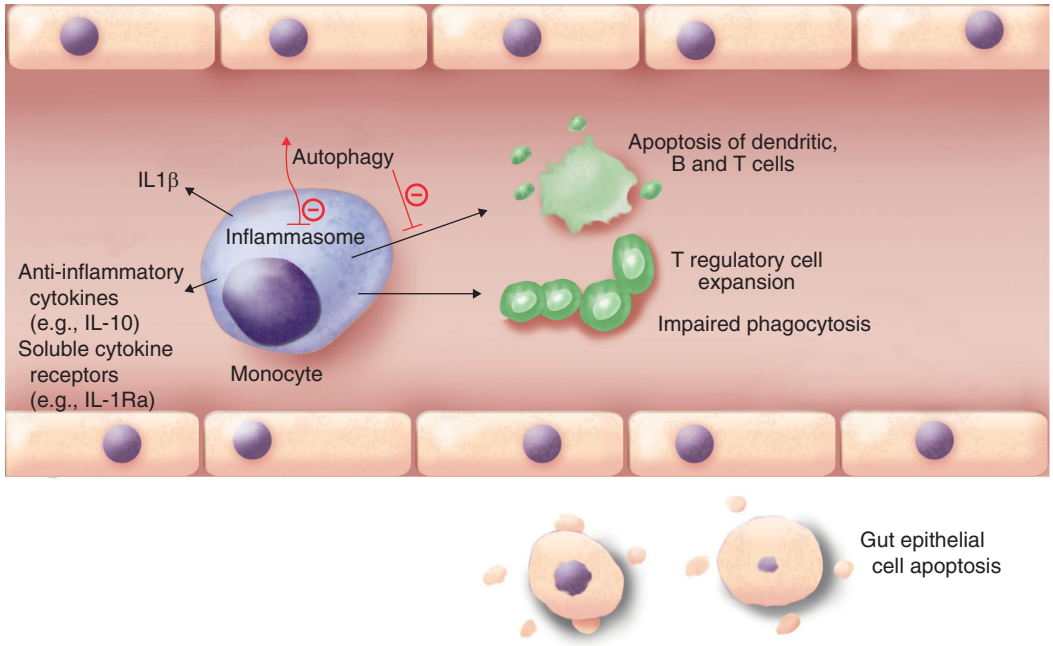

E-FIGURE 94-6. Immunodepression in sepsis. Monocytes release anti-inflammatory cytokines, such as IL-10, and anti-inflammatory soluble cytokine receptors, such as IL-1Ra. Monocytes also induce apoptosis of dendritic, B, and T cells and also induce T regulatory cell expansion as well as impaired phagocytosis. Induction of autophagy is critical for survival and differentiation of monocytes, and it also inhibits apoptosis of monocytes and other cells. Monocytes and macrophages also use autophagy to inhibit the activation of the inflammasome and so limit mature IL-1β synthesis and release. IL = interleukin; IL-1Ra = interleukin 1 receptor antagonist.

endotoxin interaction with vascular endothelial cells. Prostacyclin is released by endothelial cells in response to both endotoxin and inflammatory cytokines. Adrenomedullin, which is a pleiotropic vasodilating hormone and cardiac depressant, is increased in septic shock. Early in septic shock, most patients have sinus tachycardia and, by definition, a need for vasopressor(s) because of decreased blood pressure (<90 mm Hg systolic, a decrease of ≥40 mm Hg from baseline systolic pressure, or mean arterial pressure <65 mm Hg; see Table 94-1). Septic shock is the classic form of distributive shock (Chapter 92), characterized by increased pulse pressure (bounding pulses), decreased systemic vascular resistance (warm, flushed skin), and functional hypovolemia (low jugular venous pressure). Distributive shock means that the distribution of systemic blood flow is abnormal, with areas of low flow (and low venous oxygen saturation) and high flow (and high venous oxygen saturation) present. Nevertheless, about one third of patients with septic shock initially present with findings more typical of hypovolemic shock (low central venous pressure, low central venous oxygen saturation, and cold, poorly perfused limbs) because the clinical features depend on the stage and severity of septic shock as well as on the degree of fluid resuscitation that has occurred. After fluid resuscitation, patients typically develop the characteristic clinical and hemodynamic features of classic distributive shock.

Vascular volume and ventricular preload are commonly decreased in early septic shock for several reasons. First, patients may be volume depleted because of decreased fluid intake and because of increased fluid losses due to fever, vomiting, and diarrhea if gastrointestinal disease is present. Second, fluid loss from the intravascular to the interstitial space (capillary leak) is caused by mediators that induce widespread endothelial injury, which increases capillary permeability. Increased capillary permeability leads to loss of protein-rich edema fluid into the interstitial space. The increased vascular permeability exacerbates transmural vascular leak at any given transmural hydrostatic pressure, thereby creating a vicious cycle. Sicker patients have greater increases in endothelial permeability, yet sicker patients have greater third-space fluid losses, so they need more fluid input. If, however, fluid input increases transmural hydrostatic pressure even modestly, then sicker patients will have greater fluid leakage into tissues, with increasing organ edema, organ dysfunction, and mortality.

In the lung, increased capillary permeability is a key component of ARDS (Chapter 90). Ventricular preload is also decreased in septic shock because of venodilation induced by mediators such as nitric oxide. Venodilation increases venous capacitance and relative volume depletion, thereby compounding absolute volume depletion. Ventricular afterload is decreased because of excessive release of potent vasodilators such as nitric oxide, prostaglandin I_2, adenosine diphosphate, and other vasodilators.

In addition to abnormal vasodilation, patients have concurrent microvascular vasoconstriction. Microvascular vasoconstriction may not be apparent clinically but can cause tissue hypoxia, detected by increased arterial lactate concentrations. Microvascular vasoconstriction is caused by increased norepinephrine, thromboxanes, and other local vasoconstrictors. Microvascular vasoconstriction-induced focal hypoxia is exacerbated by microvascular obstruction by platelets and leukocytes.

The abnormal mismatch of oxygen delivery to oxygen demand disturbs the global relationship of oxygen delivery to oxygen consumption. Normally, oxygen consumption is independent of oxygen delivery over a wide range. When oxygen delivery decreases to less than the critical oxygen delivery level, oxygen consumption decreases and leads to a state in which oxygen consumption depends on oxygen delivery. At levels lower than the critical oxygen delivery level, blood lactate increases as a result of tissue hypoxia, explaining in part why an elevated serum lactate level is a component of the diagnosis of septic shock. The clinical implication is that oxygen delivery should be increased (e.g., by increasing cardiac output by volume resuscitation, infusion of dobutamine, or transfusion of erythrocytes) to more than the critical level.

Cardiovascular function is further compromised in septic shock because of decreased ventricular contractility.[5] Within minutes of recognizing bacteria, cardiomyocytes secrete pro-inflammatory cytokines and chemokines that recruit inflammatory cells. Cardiomyocytes concurrently express cell-surface-adhesion molecule ICAM-1, which interacts with actin filaments within the cell to reduce contractile efficiency. Decreased ventricular contractility may be difficult to detect clinically and may be diagnosed only by hemodynamic or echocardiographic assessment. Numerous circulating mediators of sepsis, including endotoxin, cytokines (e.g., IL-6, TNF-α), and nitric oxide (locally released into the coronary circulation), decrease contractility. Endotoxin signals through TLRs to upregulate the expression of proteins such as two small calcium-regulated molecules (S110A8 and S100A9) to cause a receptor for advanced glycation end products (RAGE)–dependent decrease in calcium flux, thereby decreasing the ejection fraction. Coronary ischemia resulting from microvascular obstruction is another mechanism of decreased contractility.

Early in septic shock, patients who ultimately survive have increased left ventricular end-diastolic volume to help maintain cardiac output despite decreased contractility. In contrast, nonsurvivors do not increase their left ventricular end-diastolic volume, so cardiac output is compromised. In some patients with septic shock, concurrent ARDS causes secondary pulmonary hypertension, which increases right ventricular afterload and shifts the interventricular septum from right to left. This septal shift decreases left ventricular end-diastolic volume, thereby further limiting cardiac output.

CLINICAL MANIFESTATIONS

Patients in septic shock have a systolic pressure of 100 mm Hg or less, often accompanied by an elevated respiratory rate (>22/minute) or altered mental status. About 80% of patients are febrile, but patients can be normothermic or even hypothermic (in about 20% of cases). On initial presentation, the source of infection may be obvious, especially if patients have previous evidence of a specific site of infection such as pneumonia or a surgical site infection, or can be occult.

The cardiovascular dysfunction in septic shock is characterized by decreased preload (because of decreased intake, fluid losses, third spacing resulting from increased permeability, and venodilation), decreased afterload, and often decreased ventricular contractility. Decreased ventricular volume is detected clinically by low jugular venous pressure and hemodynamically by decreased central venous pressure. Left ventricular resistance, or afterload, is also commonly decreased and is detected clinically by warm, flushed skin and hemodynamically by decreased systemic vascular resistance.

DIAGNOSIS

The initial assessment of a critically ill patient must focus on the airway (need for intubation), breathing (respiratory rate, respiratory distress, pulse oximetry), circulation (heart rate, blood pressure, jugular venous pressure, skin perfusion), and the rapid initiation of warranted resuscitation (Fig. 94-1).[6] Arterial blood gases and lactate levels are useful especially since an elevated lactate level is a component of the clinical diagnosis of septic shock.

A secondary survey is designed to determine the source of infection and the status of organ function. Pneumonia (Chapter 85) is suggested by cough, sputum, and respiratory distress; empyema (Chapter 86) is suggested by pleuritic chest pain. Signs of peritonitis (Chapter 128), an abdominal mass (Chapter 118), and tenderness (Chapter 141) suggest abdominal sepsis (Chapter 118). Pyelonephritis (Chapter 263) is likely in patients with dysuria and costovertebral angle tenderness. Integumentary assessment for erythema (cellulitis), erythema at the vascular access site (line sepsis), tenderness (necrotizing fasciitis; Chapter 271), crepitus (anaerobic myonecrosis), and petechiae and purpura (meningococcemia; Chapter 274) can be illuminating. Headache, stiff neck, and signs of meningismus raise the suspicion of meningitis (Chapter 381). Focal neurologic signs suggest brain abscess (Chapter 382).

Laboratory investigations that are helpful to identify the source of infection include appropriate cultures and Gram stains (blood, sputum, urine, fluids, and cerebrospinal fluid). Blood cultures are positive in about 30 to 40% of patients with septic shock, but they are positive one-third less often if antibiotics were administered before the cultures were drawn.[7] In patients with negative cultures, RNA gene-targeted metagenomic sequencing can find a likely pathogenic organism in about 40% of cases.[8] The chest radiograph aids in the diagnosis of pneumonia, empyema, and the acute respiratory distress syndrome.

Direct visualization of the heart by transthoracic bedside echocardiography can immediately estimate the left ventricular ejection fraction. It can also be used to assess intravascular volume status (diagnosed by collapse of the inferior vena cava) and valvular dysfunction. Echocardiographic features of decreased ventricular contractility include decreased right and left ventricular ejection fractions and increased end-diastolic and end-systolic volumes. Early in septic shock, the left ventricular ejection fraction is decreased, and it remains low in nonsurvivors. In survivors, the left ventricular ejection fraction usually returns to normal during 5 to 10 days.

In early septic shock, central venous pressure is usually low and increases in response to volume resuscitation. Central venous oxygen saturation, cardiac output, and ventricular filling pressures may be determined. Central venous pressure measurement is recommended in patients who require vasopressors because their hypotension is not responsive to fluids alone. Pulmonary artery pressure is usually normal but may be increased because septic shock can cause pulmonary hypertension. Pulmonary artery occlusion (or wedge) pressure is

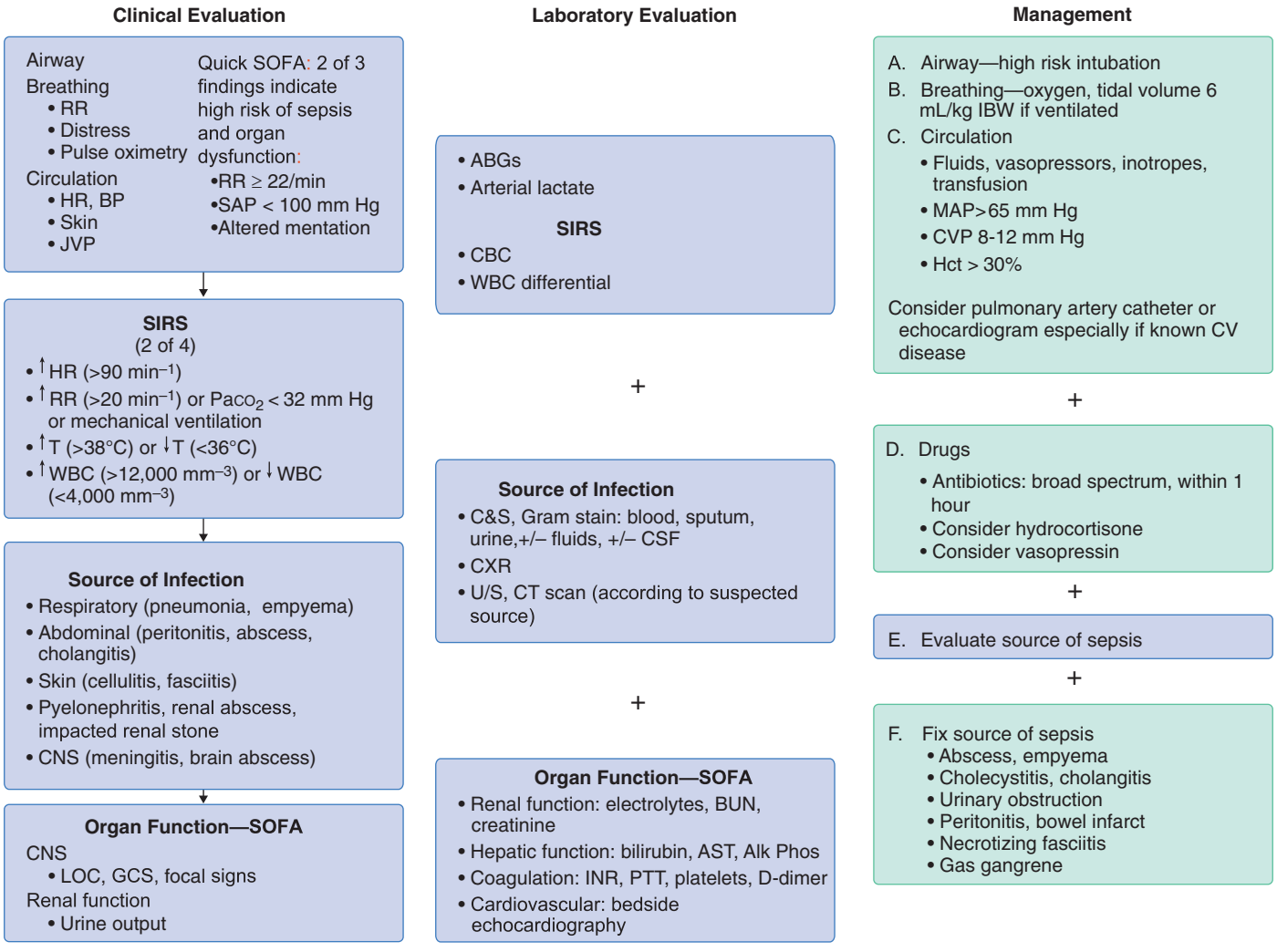

FIGURE 94-1. Algorithm for the clinical and laboratory evaluation and management of septic shock. ABGs = arterial blood gases; Alk Phos = alkaline phosphatase; AST = aspartate aminotransferase; BP = blood pressure; BUN = blood urea nitrogen; C&S = culture and sensitivity; CBC = complete blood count; CNS = central nervous system; CSF = cerebrospinal fluid; CT = computed tomography; CV = cardiovascular; CVP = central venous pressure; CXR = chest radiograph; GCS = Glasgow Coma Scale; Hct = hematocrit; HR = heart rate; IBW = ideal body weight; INR = international normalized ratio; JVP = jugular venous pressure; LOC = level of consciousness; MAP = mean arterial pressure; $Paco_2$ = partial pressure of carbon dioxide; PTT = partial thromboplastin time; RR = respiratory rate; SAS = systolic arterial pressure; $Scvo_2$ = central venous oxygen saturation; SIRS = systemic inflammatory response syndrome; SOFA = Sequential Organ Failure Assessment; T = temperature; U/S = ultrasound; WBC = white blood cell count.

usually low before resuscitation, but it may be normal or increased if the patient has underlying preexisting heart disease (e.g., heart failure, prior myocardial infarction) or if left ventricular contractility is decreased by sepsis. Cardiac output may be low or normal before fluid resuscitation and typically increases to higher than normal after fluid resuscitation. If fluid resuscitation increases central venous pressure and pulmonary artery occlusion pressure but cardiac output does not increase, left ventricular dysfunction is presumably present.

Vital signs and the leukocyte count quickly establish whether the patient has the systemic inflammatory response syndrome (SIRS). Abdominal ultrasound and computed tomography are indicated if abdominal sepsis is suspected. Renal, hepatic, and coagulation function tests are helpful to evaluate acute kidney injury, hepatic dysfunction, and sepsis-associated coagulopathy, respectively. After determining the source of sepsis, the clinician must address source control by draining abscesses and empyemas; using image-directed procedures or open surgery to correct urinary tract obstruction; and surgically managing peritonitis, bowel infarction, cholecystitis, cholangitis, necrotizing fasciitis, and gas gangrene.

Differential Diagnosis

The major differential diagnoses of septic shock are acute pancreatitis (Chapter 130), the acute respiratory distress syndrome (Chapter 90), aspiration pneumonitis (Chapter 82), multiple trauma (Chapter 97), cytokine storm,[9] and recent major surgery without infection (Chapter 401). Other causes of distributive shock to consider are anaphylactic shock (suggested by angioedema and hives; Chapter 407), spinal shock (recent trauma and paraplegia; Chapter 368), acute adrenal insufficiency ("tanned skin," hyperkalemia, metabolic alkalosis; Chapter 208), and acute or acute-on-chronic hepatic failure (jaundice, ascites, encephalopathy; Chapter 139).

The differential diagnosis of septic shock must include the other causes of shock: hypovolemic, cardiogenic, and obstructive shock (Chapters 92 and 93). Patients with hypovolemic shock (e.g., from internal or external fluid losses or hemorrhage) present with a suggestive history and signs of hypovolemia (low jugular venous pressure) and skin hypoperfusion (cool and clammy skin, peripheral cyanosis, slow capillary refill). Cardiogenic shock (e.g., owing to myocardial infarction, heart failure, or post–cardiovascular surgery) is suggested by the history, signs of increased filling pressure (increased jugular venous pressure, crackles, S_3, pulmonary edema, cardiomegaly), and skin hypoperfusion (Chapter 93). Some patients who have acute myocardial infarction and cardiogenic shock have features of SIRS, with excessive vasodilation in the absence of infection. Obstructive shock (e.g., pulmonary thromboembolism [Chapter 68], cardiac tamponade [Chapter 62], pneumothorax [Chapter 86]) manifests similarly to cardiogenic shock.

TREATMENT

Respiratory Therapy

All patients in septic shock require oxygen initially, and many require mechanical ventilation because acute respiratory distress syndrome (ARDS) is the most common complication of septic shock.[10] Endotracheal intubation of the patient in septic shock can be complicated by worsening hypotension, but a 500 mL intravenous bolus of normal saline prior to intubation does not improve

outcomes in critically ill patients undergoing intubation.[A1] Lung-protective ventilation (mechanical ventilation that minimizes lung injury by using a combination of strategies, including a set tidal volume, such as 6 to 8 mL/kg of predicted body weight [when using volume-cycled ventilatory assist]) decreases mortality from ARDS (Chapter 91).

Patients on mechanical ventilation need adequate, but not excessive, sedation because excessive sedation worsens hemodynamic instability, prolongs the need for mechanical ventilation, and increases the risk for development of nosocomial pneumonia. Sedation should be titrated by objective assessment. Daily interruption of sedation decreases the duration of mechanical ventilation and intensive care. The use of dexmedetomidine to induce sedation does not improve outcomes, including delirium, compared with propofol.[A2] Weaning from mechanical ventilation is often associated with fluid overload from prior fluid resuscitation and from the reduction in intrathoracic pressure. Patients whose weaning is guided by brain natriuretic peptide levels are weaned more quickly and have more ventilator-free days because they receive more aggressive diuretic therapy.

Circulatory Therapy

Early therapy is the cornerstone of emergency management, but such therapy need not achieve specific central hemodynamic or oxygen-delivery targets, or require the placement of a central venous catheter or the administration of inotropic agents or blood transfusions.[A3] Standard therapies aim to increase perfusion and tissue oxygen delivery by increasing profoundly low blood pressure, increasing inadequate cardiac output, and increasing low arterial oxygen saturation.

The overall goal is to achieve adequate mean arterial pressure (>65 mm Hg) and other indices of perfusion such as urine output (>0.5 mL/kg/hour), blood lactate levels (<2 mmol/L), mental status, and skin perfusion. To assess the adequacy of early resuscitation of septic shock and to guide ongoing therapy, a central venous oxygen saturation goal greater than 70% or a lactate clearance of at least 10% is equivalent.[11]

A mean arterial blood pressure target of 65 to 70 mm Hg generally is as effective as a target of 80 to 85 mm Hg[A4] or compared with usual care.[A5] In patients who have ARDS, no difference in outcomes is seen with management using a pulmonary artery catheter versus a central venous catheter, so measurement and monitoring of central venous pressure (CVP) is recommended in patients who require vasopressor infusion. Patients whose ARDS is managed after 24 to 48 hours with a conservative fluid strategy (compared with a liberal fluid strategy) have shorter durations of mechanical ventilatory assist and ICU stay.

Fluids must be administered in an adequate but not excessive volume. Restrictive and liberal fluid strategies result in similar mortality rates for patients in septic shock,[A6,A7] but the restrictive fluid approach requires strict protocols for identifying and treating hypovolemia to avoid more prevalent and longer duration vasopressor support. Fluids (30 mL/kg of intravenous crystalloid, either 0.9% saline or a balanced solution such as lactated Ringer solution) should be given over the first 3 hours followed by additional fluids to achieve and maintain central venous pressure at 8 to 12 mm Hg and adequate tissue perfusion (e.g., mentation, urine output). In critically ill adults, balanced crystalloids are often used instead of sodium chloride because of lower rates of acute kidney injury, less need for renal replacement therapy, and fewer deaths,[A8] but a recent double-blind trial comparing a balanced solution with saline found no difference in outcomes in a diverse group of ICU patients, including the subgroup who had sepsis.[A9] There are no convincing data indicating that albumin is better than crystalloid solutions.[A10] Hetastarch should not be used in septic shock. Excess fluid resuscitation is associated with increased mortality from septic shock, and an increased CVP may indicate fluid overload and a higher risk of developing pulmonary edema. Heart failure with a decreased ejection fraction is common in patients with sepsis,[12] and lesser amounts of fluid administration (i.e., below guideline recommended volumes) are safer and associated with no difference in risk-adjusted mortality compared with patients with normal ejection fractions.[13]

Vasopressors (e.g., first-line: norepinephrine, 1 to 50 μg/minute; alternative: epinephrine, 1 to 30 μg/minute) should be added if the mean arterial pressure is less than 65 mm Hg despite adequate fluid resuscitation,[14] and earlier administration concomitant with fluid resuscitation appears to improve the early control of septic shock but not clearly reduce septic shock mortality.[A11] Norepinephrine is slightly, but not significantly, better than dopamine for reducing mortality when used as the first-line vasopressor for patients with septic shock; however, norepinephrine is associated with a lower rate of arrhythmias, especially atrial fibrillation. Norepinephrine and vasopressin are similar for preventing acute kidney failure in patients with septic shock.[A12] These accumulated data suggest that norepinephrine is the preferred first-line vasopressor in septic shock.

Although vasopressin deficiency and downregulation of vasopressin receptors are common findings in septic shock, a low-dose vasopressin infusion added to norepinephrine is not significantly better than a norepinephrine infusion alone in septic shock. Vasopressin (up to 0.03 U/min) may be added in patients not responding adequately to norepinephrine to increase mean arterial pressure and to decrease norepinephrine dose, but selepressin (a vasopressin agonist) has no incremental value when added to norepinephrine.[A13] Whether vasopressin infusion may be beneficial in patients with less severe shock is uncertain.

Angiotensin II infusion (20 ng/kg/minute initially, adjusted upward to a maximum of 200 ng/kg/minute) can decrease early norepinephrine requirements and improve the cardiovascular component of the SOFA score. However, it does not significantly reduce mortality. Levosimendan, which is an inotropic agent and mild vasodilator with anti-inflammatory properties, is not of added benefit in patients with septic shock.

Some patients, especially younger patients, have excessive tachycardia that limits diastolic filling time. Short-acting intravenous β-blockers (e.g., esmolol started at about 0.2 μg/kg/minute and titrated to a targeted heart rate of 80 to 90 beats per minute) have shown encouraging results,[A14] but more evidence is required before recommending this approach for routine clinical use.

In some patients in septic shock, the cardiac index is inadequate, as reflected by a low mixed venous oxygen saturation despite a high central venous pressure (>12 mm Hg) because of underlying cardiovascular dysfunction or because of acute left ventricular dysfunction resulting from sepsis. In such patients, clinicians can consider use of an inotropic agent (e.g., dobutamine, initially 2 to 5 μg/kg/minute and increasing to 20 μg/kg/minute) to increase left ventricular contractility and raise cardiac output. In patients with septic shock, however, the combination of norepinephrine plus dobutamine results in a mortality similar to that with epinephrine alone, with no differences in organ dysfunction.

Fever is common in septic shock and may have beneficial effects for resisting infection but also increases oxygen demand. Reducing fever can decrease the need for vasopressors and possibly the risk of septic encephalopathy. External cooling for 48 hours to maintain core body temperature between 36.5°C and 37°C is safe and can decrease the need for vasopressors and 14-day mortality rates. Cooling to reduce fever to normothermia is especially promising for febrile septic shock patients who are receiving high doses of vasopressors or inotropic agents, or who have marked tachycardia.

Transfusion of Red Blood Cells

Anemia is common in septic shock, but red cell transfusion can increase risk of nosocomial infection and other complications, so the appropriate hemoglobin level for resuscitation has been controversial. A transfusion threshold of a hemoglobin level of 7 g/dL is equivalent to a threshold of 9 to 10 g/dL in terms of the need for life support, or death, and such a goal can decrease the need for transfusion.[A15] The freshest available, compatible red blood cells are no better than standard-issue red blood cells for patients with septic shock.[A16]

Drugs

Antibiotics

Early antibiotic administration, ideally within 1 hour, is highly recommended and allows the duration of antibiotic administration to be shortened without increasing resistance or the subsequent need for additional antibiotics.[15] Meropenem alone is equivalent to the combination of meropenem and moxifloxacin in terms of mortality rates and organ dysfunction. Adding empirical fluconazole treatment does not result in better outcomes in critically ill, non-neutropenic patients. Continuous infusion of beta-lactam antibiotics results in higher clinical cure rates 14 days after cessation of antibiotics, better pharmacokinetic/pharmacodynamic target attainment, and more ventilator-free days compared with an intermittent bolus of antibiotics but does not improve 30-day survival.[A17]

The infected site and infecting organisms of septic shock are often not known initially, and clinicians often must select an empirical antibiotic regimen before knowing culture results. After appropriate culture specimens are obtained, intravenous broad-spectrum antibiotics as guided by an infectious disease consultation should be administered within 1 hour (while considering host factors such as immune and allergic status) complemented by control of the infectious source based on an anatomic diagnosis, which may require radiologic investigations (Chapters 259 and 260; see Fig. 94-1). Emergency, empirical antibiotic therapy (Table 94-2) should be guided by the greater frequency of gram-positive bacteria, the possibility of resistant organisms, and the local bacteriologic features. In a meta-analysis, the efficacies of empirical antibiotic monotherapies and combination antibiotic therapy appear to be equivalent for the treatment of sepsis.[A18]

Broad-spectrum antibiotics should be used for as short a time as possible. If a causative organism is identified, the antibiotic regimen should be quickly narrowed within 3 to 5 days to decrease the emergence of resistant organisms. The duration of antibiotics should be guided by the cause of septic shock, reviewed regularly, but patients generally require 7 to 10 days of therapy. Compared with usual care, procalcitonin-guided use of antibiotics (e.g., a ≥80% reduction in the procalcitonin level or a level ≤0.5 μg/L on day 5 or later) in critically ill patients can decrease the duration of antibiotic therapy and hospitalization, but its effect on more important outcomes is less clear.[A19,A20]

Corticosteroids

Corticosteroids administered before antibiotics can decrease the neurologic sequelae of bacterial (especially pneumococcal) meningitis (Chapter 381). Although corticosteroids are not effective for preventing septic shock in patients who have sepsis but are not in shock, the combination of 50 mg intravenous hydrocortisone every 6 hours (200 mg daily) plus 50 μg fludrocortisone (orally

via a nasogastric tube) once daily for 7 days can improve 90-day all-cause mortality in patients with septic shock.[A21] By comparison, hydrocortisone (200 mg intravenously daily) treatment alone is associated with a shorter duration of shock but no reduction in 90-day mortality,[A22] and no benefit from the combination of hydrocortisone, vitamin C, and thiamine has been seen in randomized clinical trials.[A23,A24] Current sepsis guidelines suggest that corticosteroids not be used if fluid resuscitation and vasopressors can restore hemodynamic stability, but low-dose corticosteroids (200 mg hydrocortisone per day) or the combination of hydrocortisone plus fludrocortisone may be added if hemodynamic stability cannot be achieved. The one exception is COVID-19 (Chapter 337), for which corticosteroids (e.g., dexamethasone 6 mg intravenously once daily) decrease the need for ventilation and mortality by about 30% in patients who require oxygen.[A25] Enthusiasm for steroid therapy must be tempered by the risk of complications such as superinfection, neuromyopathy, hyperglycemia, immune suppression, and impaired wound healing.

Hyperglycemia and Intensive Insulin Therapy

Hyperglycemia and insulin resistance are common in septic shock, but intensive insulin therapy to control blood glucose levels tightly is not beneficial in patients in medical ICUs because of significantly higher rates of hypoglycemia and perhaps increased mortality. Aggressive insulin therapy to address the hyperglycemia that often accompanies corticosteroid treatment is no better than usual glucose control.

Renal Dysfunction and Dialysis

Acute kidney injury is an important complication of septic shock because of its associated morbidity, mortality, and resource use (Fig. 94-2). In critically ill patients who have acute kidney injury, hemodialysis six times per week is no better than conventional hemodialysis, and intensive renal replacement therapy is no better than standard therapy overall or in patients who have sepsis.

Continuous renal replacement therapy may be preferable to intermittent hemodialysis in patients with septic shock who remain hemodynamically unstable. The use of regional citrate for anticoagulation increases the filter's life span during renal replacement therapy and reduces the risk of bleeding.[A26]

The timing for initiation of renal replacement therapy in the critically ill remains uncertain. The largest trials have not shown any benefit in mortality when renal replacement therapy is started earlier than with standard criteria.[A27] Venoarterial extracorporeal membrane oxygenation may be beneficial for patients with sepsis-induced cardiogenic shock (Chapter 93).

Low-dose dopamine (2 to 4 μg/kg/minute) does not decrease the need for renal support, does not improve outcomes, and is not recommended. Lactic acidosis is a common complication of septic shock, but administration of sodium bicarbonate for lactic acidosis does not improve hemodynamics or the response to vasopressors.

Other Therapies

Deep venous thrombosis prophylaxis with low-molecular-weight heparin (LMWH) may be superior to low-dose unfractionated heparin because it may decrease the risk of pulmonary emboli in the critically ill. LMWH is recommended for patients who do not have active bleeding, coagulopathy, or a contraindication to heparin (see Fig. 94-2). Stress ulcer prophylaxis with proton pump inhibitors or H_2-receptor antagonists decreases the risk of gastrointestinal hemorrhage.

Adding vitamin C and thiamine does not add benefit to corticosteroids alone,[A28] and, as noted earlier, the three-drug combination may be no better than placebo. Enteral nutrition is generally safer and more effective than total parenteral nutrition (Chapter 198), but total parenteral nutrition is sometimes required in patients with abdominal sepsis, surgery, or trauma. Initial trophic feeding, which provides about 25% of normal calorie requirements, is comparable to full enteral feeding after stabilization of patients in septic shock. The use of sedation, neuromuscular blocking agents, and corticosteroids should be minimized because they can exacerbate septic encephalopathy and the polyneuropathy or myopathy of sepsis. Neutropenic patients may benefit from granulocyte colony-stimulating factor (Chapter 153). The risk of nosocomial infection is decreased by narrow-spectrum antibiotics, early weaning from ventilation, and periodic removal and replacement of catheters (Chapter 261).

TABLE 94-2 POTENTIAL ANTIBIOTIC REGIMENS FOR PATIENTS WITH SEPTIC SHOCK*

SOURCE OF SEPSIS	INITIAL ANTIBIOTIC REGIMEN	ALTERNATIVE ANTIBIOTIC REGIMEN
Community-acquired pneumonia	Third-generation cephalosporin (e.g., cefotaxime 2 g IV q6h; ceftriaxone 2 g IV q12h; ceftizoxime 2 g IV q8h) *plus* fluoroquinolone (e.g., ciprofloxacin 400 mg IV q12h, levofloxacin 750 mg IV q24h, moxifloxacin 400 mg IV q24h) *or* macrolide (azithromycin 500 mg IV q24h)	Piperacillin-tazobactam (3.375 g IV q6h) *plus* fluoroquinolone (e.g., ciprofloxacin 400 mg IV q12h, levofloxacin 750 mg IV q24h, moxifloxacin 400 mg IV q24h) *or* macrolide (azithromycin 500 mg IV q24h)
Hospital-acquired pneumonia	Vancomycin (15 mg/kg IV q 8-12h, if increased risk of MRSA) *or* linezolid (600 mg IV q12h, if increased risk of MRSA) *plus* carbapenem (e.g., imipenem 0.5 g IV q6h *or* meropenem 1 g IV q8h) *plus* fluoroquinolone (e.g., ciprofloxacin 400 mg IV q12h, levofloxacin 750 mg IV q24h)	Fluoroquinolone (e.g., ciprofloxacin 400 mg IV q12h, levofloxacin 750 mg IV q24h) *plus* vancomycin (1.5 g IV q12h) *plus* piperacillin-tazobactam (3.375 g IV q6h) *or* ceftazidime (2 g IV q8h) *or* aztreonam (2 g IV q8h)
Spontaneous bacterial peritonitis	Ceftriaxone (1 g IV q12h)	Moxifloxacin (400 mg IV q24h)
Gastrointestinal perforation	Piperacillin-tazobactam (3.375 g IV q6h) *or* carbapenem (e.g., imipenem 0.5 g IV q6h, meropenem 1 g IV q8h)	Cefepime (1 g IV q8h) *plus* metronidazole (500 mg IV q8h) *or* Metronidazole (500 mg IV q8h) *plus* fluoroquinolone (e.g., ciprofloxacin 400 mg IV q12h)
Urinary tract	Third-generation cephalosporin (e.g., cefotaxime 2 g IV q6h, ceftriaxone 2 g IV q12h, or ceftizoxime 2 g IV q8h)	Ampicillin (2 g IV q4h) *plus* gentamicin (1.5 mg/kg IV q8h) *or* ertapenem (1 g IV q24h, if ESBL)
Necrotizing fasciitis	Vancomycin (15 mg/kg IV q8-12h) *plus* piperacillin-tazobactam (3.375 g IV q6h) *plus* clindamycin (600 mg IV q8h)	Vancomycin (15 mg/kg IV q8-12h) *plus* ciprofloxacin (400 mg IV q12h) *plus* clindamycin (600 mg IV q8h)
Primary bacteremia (normal host)	Piperacillin-tazobactam (3.375 g IV q6h) *plus* vancomycin (1.5 g IV q12h)	Carbapenem (e.g., imipenem 0.5 g IV q6h, meropenem 1 g IV q8h) *plus* vancomycin (1.5 g IV q12h)
Primary bacteremia (intravenous drug user)	Vancomycin (1.5 g IV q12h) *plus* fluoroquinolone (e.g., ciprofloxacin 400 mg IV q12h)	Piperacillin-tazobactam (3.375 g IV q6h) *plus* vancomycin (1.5 g IV q12h)

TABLE 94-2 POTENTIAL ANTIBIOTIC REGIMENS FOR PATIENTS WITH SEPTIC SHOCK*—cont'd

SOURCE OF SEPSIS	INITIAL ANTIBIOTIC REGIMEN	ALTERNATIVE ANTIBIOTIC REGIMEN
Catheter-related bloodstream infection (CR-BSI)	Vancomycin (1.5 g IV q12h) +/− cefepime (2 g IV q8h)	Vancomycin (1.5 g IV q12h) +/− carbapenem (e.g., imipenem 0.5 g IV q6h, meropenem 1 g IV q8h)
If gram-positive cocci in clusters ≥2 blood cultures	Vancomycin (1.5 g IV q12h)	Piperacillin-tazobactam (3.375 g IV q6h) *or* ceftazidime (2 g IV q8h) *or* aztreonam (2 g IV q8h)
Febrile neutropenia	Cefepime (2 g IV q8h) *plus* vancomycin (1.5 g IV q12h)	Aztreonam (2 g IV q8h) *plus* gentamicin (1.5 mg/kg q8h) *or* Cefepime (2 g IV q8h) *plus* gentamicin (1.5 mg/kg q8h) *or* Piperacillin-tazobactam (3.375 g IV q6h) *plus* gentamicin (1.5 mg/kg q8h) *or* Carbapenem (e.g., imipenem 0.5 g IV q6h, meropenem 1 g IV q8h) *plus* gentamicin (1.5 mg/kg q8h) If beta-lactam allergy: Vancomycin (1.5 g IV q12h) *plus* gentamicin (1.5 mg/kg q8h) *plus* ciprofloxacin (400 mg IV q12h)
Bacterial meningitis	Ceftriaxone (2 g IV q12h) *plus* ampicillin (3 g IV q6h) *plus* vancomycin (1.5 g IV q12h) *plus* dexamethasone (0.15 mg/kg IV q6h for 2-4 days)	Gram-positive cocci: vancomycin (1.5 g IV q12h) *plus* ceftriaxone (2 g IV q12h) Gram-negative diplococci: cefotaxime (2 g IV q4-6h) *or* ceftriaxone (2 g IV q12h) Gram-positive bacilli: ampicillin (3 g IV q6h) *plus* gentamicin (1.5 mg/kg IV q8h) Gram-negative bacilli: ceftazidime (2 g IV q8h) *plus* gentamicin (1.5 mg/kg IV q8h) *or* cefepime (1 g IV q8h) All above *plus* dexamethasone (0.15 mg/kg IV q6h for 2-4 days)
Cellulitis†	Severe: Vancomycin (1.5 g IV q12h) *plus* piperacillin-tazobactam (3.375 g IV q6h)	Moderate: Cefazolin (1-2 g IV q8h) *or* ceftriaxone (2 g IV q12h) *or* clindamycin (600 mg IV q8h)

*Most antibiotic doses must be adjusted if there is hepatic or renal dysfunction. Some antibiotics require adjustment based on levels (e.g., gentamicin). In selecting a drug, carefully consider the patient's history of antibiotic (especially penicillin) allergy.
†Assess for necrotizing fasciitis and consider surgical consultation; raise extremity.
ESBL = gram-negative organisms including those that produce extended spectrum β-lactamases (ESBL); IV = intravenous; MRSA = methicillin-resistant *S. aureus*.

PREVENTION

Measures to prevent sepsis include caregiver handwashing before and after patient contact, elevation of the head of the bed to help prevent aspiration, sterile techniques for the insertion of catheters, and possibly the use of antibiotic-impregnated catheters. New catheter insertion sites for catheter changes, isolation of patients who have resistant organisms, and isolation of significantly immunocompromised patients may also prevent infection.

Preventing the progression from sepsis to septic shock requires early diagnosis and aggressive resuscitation.[16] Early intravenous antibiotics (within 1 hour),[17] fluid resuscitation, and lung-protective ventilation are critical therapies in early septic shock (Table 94-3). In patients with severe community-acquired pneumonia (Chapter 85), hydrocortisone (200 mg intravenously daily for 4 to 8 days) can reduce the need for vasopressors.[A29]

PROGNOSIS

The survival and quality of life after hospital discharge after septic shock remain poorer than expected for at least the next 10 years. For example, the 28-day mortality of septic shock is about 20% in academic centers, where early initiation of appropriate therapies, especially antibiotics, is routine.[18] Deaths in the first 72 hours are usually due to refractory septic shock despite increasing life support. Later deaths (after day 3) are usually due to multiple organ dysfunction, nosocomial infection, or both. The number of dysfunctional organs is a marker of poor prognosis, especially in patients who do not improve or have progressive organ dysfunction. Other markers of poor prognosis include delays in achieving adequate resuscitation and antibiotics, increased age, underlying chronic comorbidities, more severe critical illness, increased arterial lactate, and the need for high doses of vasopressors. Patients who have an episode of acute kidney injury during septic shock also have a significantly decreased long-term survival than patients without it.

The increasing numbers of septic shock survivors highlight the importance of long-term sequelae, such as depression, cognitive dysfunction, and post-traumatic stress disorder. Septic shock survivors have about a 35% risk of hospital readmission within 6 months, higher than that of patients who are discharged after an acute myocardial infarction, heart failure, or chronic obstructive pulmonary disease.

Quality of life is frequently impaired in survivors of septic shock. For example, survivors of septic shock accompanied by ARDS (Chapter 90) can have neuromuscular dysfunction (weakness) and dyspnea on exertion or other persistent organ dysfunction. Unfortunately, a trial of more intensive postdischarge therapy compared with usual care found no difference in mental health–related quality of life.[A30]

B. Breathing—Oxygen, with a tidal volume 6 mL/kg IBW if ventilated. Wean according to ARDSNet protocol (Chapters 90 and 91)

C. Circulation
- Fluids, vasopressors, inotropes, transfusion; goals include:
  - MAP >65 mm Hg
  - CVP 8-12 mm Hg
  - Hgb 7.0-9.0 g/L

Consider pulmonary artery catheter or echocardiogram especially if known cardiovascular disease; goals include:
- Wedge pressure 8-15 mm Hg
- Cardiac index: normal or increased

D. Drugs:
- Antibiotics: Narrow spectrum to cause of infection

Consider:
- Hydrocortisone (see text): hydrocortisone 50 mg intravenously every 6 hours daily for 7 days
- Vasopressin 0.01–0.03 units/minute intravenously

Other Organ Support
- Renal function: Continuous renal replacement
- DVT prophylaxis: (e.g., low molecular weight heparin [e.g., dalteparin 5000 IU subcutaneously daily])
- Stress ulcer prophylaxis: PPI (e.g., pantoprazole 40 to 80 mg intravenously once or twice daily) or H_2-receptor antagonist (e.g., ranitidine 50 mg intravenously every 8 hours)
- Nutrition: Enteral preferred
- Sedation: Intermittent with daily awakening

FIGURE 94-2. Ongoing critical care support and management in septic shock. ARDSNet = The US National Institute of Health Acute Respiratory Distress Syndrome; CVP = central venous pressure; DVT = deep venous thrombosis; Hgb = hemoglobin; IBW = ideal body weight; MAP = mean arterial pressure; NG = nasogastric; PPI = proton pump inhibitor; $Scvo_2$ = central venous oxygen saturation.

TABLE 94-3 HEMODYNAMIC VARIABLES, ABBREVIATIONS, AND NORMAL VALUES

Arterial pressure: systolic pressure (SAP) (>100 mm Hg), diastolic pressure, pulse pressure, mean arterial pressure (MAP) (>65 mm Hg)
Central venous pressure (CVP): normal, 6-12 mm Hg
Pulmonary artery pressure (PAP): normal, 25/15 mm Hg
Pulmonary vascular resistance (PVR): normal, 150-250 dynes*sec/cm^5

$$\left(= \frac{\text{PAP} - \text{PAOP}}{\text{CO}} \times 80\right)$$

Pulmonary artery occlusion pressure (PAOP) or pulmonary artery wedge pressure (PAWP): normal, 8-15 mm Hg
Systemic vascular resistance (SVR): normal, 900-1400 dynes*sec/cm^5

$$\left(= \frac{\text{PAP} - \text{CVP}}{\text{CO}} \times 80\right)$$

Cardiac output (CO): normal, 5 L/min
Left ventricular stroke work index (LVSWI): normal, (60-100 grams × meters/beats) = (SV × [MAP − PAWP] × 0.0136)
Oxygen delivery (Do_2): normal, 1 L/min (= CO × [Hb × 1.38 × Sao_2] + [0.003 × Po_2])
Oxygen consumption ($\dot{V}o_2$): normal, 250 mL/min (= CO × Hb × 1.38 × [Sao_2 − Svo_2] + [0.003 × (Pao_2 − Pvo_2)])
Oxygen extraction ratio: normal, 0.23-0.32 (= $\dot{V}o_2/Do_2$)
Hemodynamic variables are often normalized to account for different body mass by dividing by body surface area (BSA)
Pulmonary vascular resistance index (PVRI): normal (= PVR/BSA)
Systemic vascular resistance index (SVRI): normal (= SVR/BSA)
Cardiac index (CI): normal, 2.5-4.2 L/min/m^2 (= CO/BSA)
Left ventricular stroke work index (LVSWI): normal (= LVSW/BSA)
Oxygen delivery index (Do_2I): normal, 460-650 mL/min/m^2 (= Do_2/BSA)
Oxygen consumption index ($\dot{V}o_2I$): normal, 95-170 mL/min/m^2 (= $\dot{V}o_2$/BSA)
Hb = hemoglobin concentration in grams/liter: Normal value is 12 to 15 mg/dL in females and about 10% higher in males.

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95 DISORDERS DUE TO HEAT AND COLD

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TEMPERATURE REGULATION

Body temperature is regulated through two parallel processes that modify body heat balance: behavioral (clothing, shelter, physical activity) and physiologic (skin blood flow, sweating, shivering). Both peripheral (skin) and central (core) thermal receptors provide afferent input to a central nervous system integrator (hypothalamic thermoregulatory center), and any deviation between the controlled variable (body temperature) and a theoretical reference variable ("set point" temperature) results in a heat loss or conservation response.

Humans normally regulate body (core) temperature at about 37° C (98.6° F), and fluctuations within the narrow range of 35° to 41° C (95° to 105.8° F) can be tolerated by healthy acclimatized persons; core temperatures outside this range can induce morbidity and mortality. By one estimate, about 8% of worldwide mortality can be attributed to high or low ambient environmental temperatures, with cold-attributable mortality exceeding heat-attributable mortality by a wide margin worldwide.[1]

There is no single core temperature because it varies at different deep body sites, during rest and physical exercise, and with different measurement techniques.[2] Arterial blood temperature, which provides the best invasive measurement of core temperature, is slightly lower than brain temperature. The most accurate noninvasive index of core temperature is esophageal temperature, followed in order of preference by rectal, gastrointestinal tract (telemetry pill), and oral temperature. Ear (tympanic and auditory meatus) or scanned temporal artery temperature should not be relied on for clinical judgment. Rectal temperatures are most commonly recommended because they are easy to measure and are not biased by environmental conditions.

HEAT ILLNESS

DEFINITION

Minor heat-related illnesses include miliaria rubra, heat syncope, and heat cramps. Serious heat illness represents a spectrum from heat exhaustion to heat injury and heatstroke.

EPIDEMIOLOGY

Heat illness, which is increasing because of global warming, accounts for considerable morbidity and mortality in the world today.[3] Serious heat illness is associated with a variety of individual factors, health conditions, drugs, and environmental factors (Table 95-1). Exertional heat illness is among the leading causes of death in young athletes, and its incidence appears to be increasing in the United States, particularly in vulnerable (e.g., homeless) populations.[4] Classic heat illness caused by high environmental temperatures remains a problem, especially in homebound elderly persons without air conditioning.[5] Anticholinergic and sympathomimetic poisoning (Chapter 96) can induce hyperthermia. Malignant hyperthermia (Chapter 400) is a rare disorder occurring in genetically predisposed individuals. Rapid and massive skeletal muscle contraction from exposure to certain volatile anesthetic agents (most commonly halothane, sevoflurane, desflurane, isoflurane, or enflurane) or depolarizing muscle agent relaxants (e.g., succinylcholine) can trigger core temperature elevations well above 43° C (110° F). However, some speculate that heat disorders with extreme exercise may represent a similar syndrome. Neuroleptic malignant syndrome (Chapter 402) is an idiosyncratic hyperthermic reaction caused by skeletal muscle rigidity from treatment with neuroleptic medications (e.g., antipsychotics, antidepressants, antiemetics, and L-dopa. Both malignant hyperthermia and neuroleptic malignant syndrome are potentially fatal without prompt recognition and early intervention.

Heat illness can also occur in low-risk individuals who have taken appropriate precautions relative to situations to which they have been exposed in the past. Historically, such unexpected cases were attributed to dehydration (which impairs thermoregulation and increases hyperthermia and cardiovascular strain), but it is now suspected that a previous heat exposure or a concurrent event (e.g., sickness or injury) might make these individuals more susceptible to serious heat illness. One theory is that previous heat injury or illness primes the acute phase response and augments the hyperthermia of exercise, inducing unexpected serious heat illness. Another theory is that previous infection produces proinflammatory cytokines that deactivate the cells' ability to protect against heat shock.

TABLE 95-1 FACTORS PREDISPOSING TO SERIOUS HEAT ILLNESS

INDIVIDUAL FACTORS
Lack of acclimatization
Low physical fitness
Excessive body weight
Dehydration
Advanced age
Young age
Toll-like receptor-4 polymorphisms
HEALTH CONDITIONS
Inflammation and fever
Viral or bacterial infection
Cardiovascular disease
Diabetes mellitus
Gastroenteritis
Rash, sunburn, and previous burns to large areas of skin
Seizures
Thyroid storm
Neuroleptic malignant syndrome
Malignant hyperthermia
Sickle cell trait
Cystic fibrosis
DRUGS
Anticholinergic properties (atropine)
Antiepileptic (topiramate)
Antihistamines
Anti-Parkinsonian medications
Glutethimide
Phenothiazines
Tricyclic antidepressants
Amphetamines, cocaine, ecstasy [3,4-methylenedioxy-methamphetamine (MDMA)]
Ergogenic stimulants (e.g., ephedrine, ephedra)
Lithium
Diuretics
β-Blockers
Ethanol
Nonsteroidal anti-inflammatory drugs
ENVIRONMENTAL FACTORS
High temperature
High humidity
Little air motion
Lack of shade
Heat wave
Physical exercise
Heavy clothing
Prior compromised heat exposures

PATHOBIOLOGY

Body temperature can increase from a number of mechanisms: exposure to environmental heat (impeded heat dissipation), physical exercise (increased heat production), fever from systemic illness (elevated set point with subsequent activation of shivering), and medications (neuroleptic malignant syndrome and malignant hyperthermia). In addition, febrile persons have accentuated elevations in core temperature when they are exposed to high ambient temperature, physical exercise, or both. Environmental temperature and humidity, medications, and exercise heat stress in turn challenge the cardiovascular system to provide high blood flow to the skin, where blood pools in warm, compliant vessels such as those found in the extremities. When blood flow is diverted to the skin, reduced perfusion of the intestines and other viscera can result in ischemia, endotoxemia, and oxidative stress. Several common mutations in toll-like receptor 4 are associated with endotoxin hypo-responsiveness. In addition, excessively high tissue temperatures (heat shock: >41° C [105.8° F]) can produce direct tissue injury; the magnitude and duration of the heat shock influence whether cells respond by adaptation (acquired thermal tolerance), injury, or death (apoptotic or necrotic). Heat shock, ischemia, and systemic inflammatory responses can result in cellular dysfunction, disseminated intravascular coagulation, and multiorgan dysfunction syndrome (E-Fig. 95-1). Furthermore, reduced cerebral blood flow, combined with abnormal local metabolism and coagulopathy, can lead to dysfunction of the central nervous system.

ABSTRACT

Humans normally regulate body (core) temperature at about 37° C (98.6° F), and fluctuations within the narrow range of 35° to 41° C can be tolerated by healthy acclimatized persons. Rectal, esophageal, and oral measures of core temperature can be used for clinical judgment but not ear or scanned temporal artery temperature. Serious heat illness includes heat exhaustion, heat injury, and heatstroke. Heat illness accounts for substantial morbidity and mortality in the world and appears to be increasing in the United States. With global climate change, the resultant warming has led to severe heat waves that put vulnerable populations at particular risk. Management of serious heat illness should stress early and aggressive whole-body cooling (e.g., cool/cold water immersion or skin soaking with accelerated evaporation), rehydration, and monitoring. Cold injuries are classified as hypothermia (mild, moderate, and profound) and peripheral cold injuries (nonfreezing and freezing), which often occur simultaneously. Moderate (core temperature < 32° C) and profound (core temperature < 26° C) cold require active rewarming with common complications including ventricular fibrillation. Frostbitten tissues should be protected from trauma and not thawed until confident that warmth can be maintained because refreezing causes additional injury. Gentle rewarming in a water-bath (38° to 43° C) with ibuprofen administration is recommended. Imaging can help predict likelihood of tissue viability, and surgical consultation is recommended. Therapeutic hyperthermia and hypothermia are experimental.

KEYWORDS

temperature regulation
heatstroke
heat exhaustion
hypothermia
freezing and nonfreezing peripheral cold injuries
frostbite
therapeutic hypothermia and hyperthermia

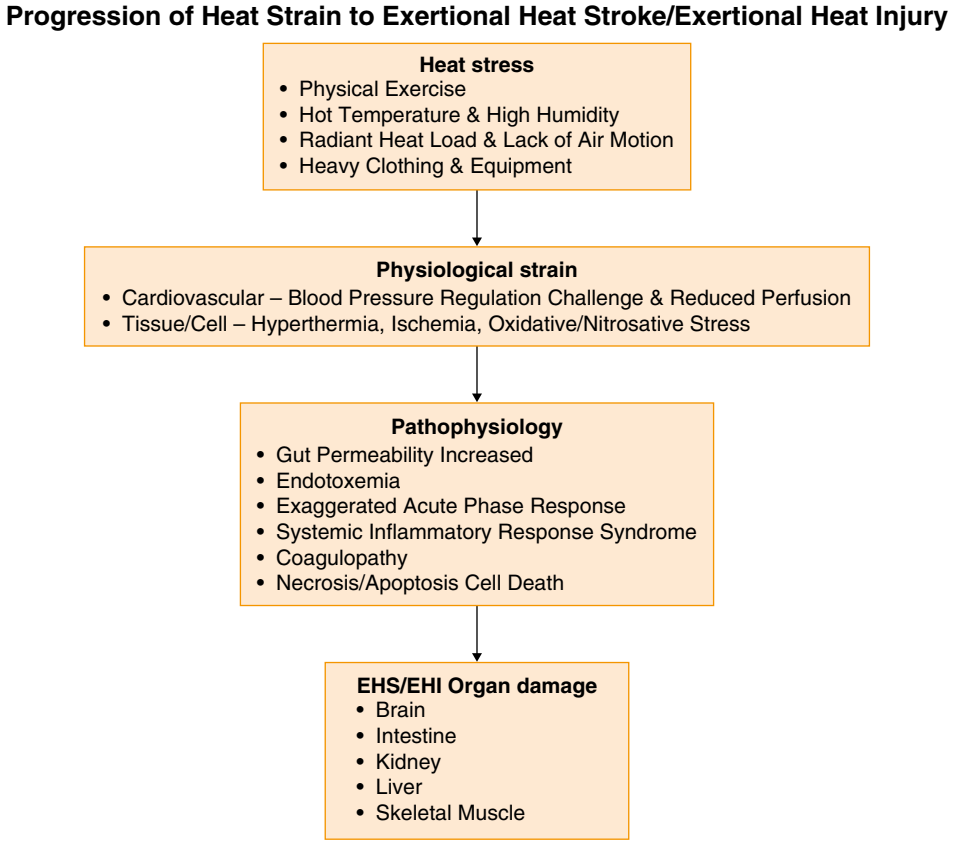

E-FIGURE 95-1. Progression of heat strain to exertional heat injury/exertional heat stroke. EHI = exertional heat injury; EHS = exertional heat stroke.

CLINICAL MANIFESTATIONS AND DIAGNOSIS

Minor heat illness is common and can be recognized by its clinical features. Miliaria rubra (heat rash) results from the occlusion of eccrine sweat gland ducts and can be complicated by secondary staphylococcal infection. Heat syncope (fainting) is caused by temporary circulatory insufficiency as a result of blood pooling in the peripheral veins, especially the cutaneous and lower extremity veins. Skeletal muscle cramps most commonly occur during and after intense exercise and are probably related to dehydration, loss of sodium or potassium, and neurogenic fatigue rather than to overheating itself.

Serious heat illness includes heat exhaustion, heat injury, and heatstroke, with some individuals progressing along this spectrum. Patients who exhibit symptoms (e.g., dizziness, unsteady gait, ataxia, headache, confusion, weakness, fatigue, nausea, vomiting, diarrhea) should have an immediate assessment of their mental status, core (rectal) temperature, and other vital signs. The most common heat-related causes of hospital admission are fluid and electrolyte disorders (Chapters 102 and 103), acute kidney injury (Chapter 106), urinary tract infection (Chapter 263), and heatstroke. Until proven otherwise, heatstroke should be the initial working diagnosis in anyone who is a heat casualty and has an altered mental status.

Heat exhaustion is defined as a syndrome of hyperthermia (temperature at time of event usually ≤40° C or 104° F) and debilitation that occurs during or immediately after exertion in the heat, accompanied by no more than minor central nervous system dysfunction (headache, dizziness, mild confusion), which resolves rapidly with intervention. It is primarily a cardiovascular event (insufficient cardiac output) frequently accompanied by sweaty hot skin, dehydration, and collapse.

Heat injury is a moderate to severe illness characterized by evidence of damage to end organs (e.g., liver, renal, gut) and tissues (e.g., rhabdomyolysis) without sufficient neurologic symptoms to be diagnosed as heatstroke. It is usually associated with body temperatures above 40° C (104° F).

Heatstroke is a severe illness characterized by profound mental status changes with high body temperatures usually, but not always, higher than 40.5° C (104.9° F).[6] However, patients with a core temperature higher than 40.5° C do not universally have a heat injury or heatstroke, and core temperatures this high can be seen transiently after stressful exercise in the heat. To establish the diagnosis of heatstroke, the entire clinical picture, including mental status and laboratory results, must be considered. Heatstroke is often categorized as classic or exertional; classic heatstroke is observed primarily in otherwise sick and compromised individuals, and exertional heatstroke is observed during or after vigorous exercise (Table 95-2).

Severe heatstroke evolves clinically through three distinct phases, more commonly seen in exertional heatstroke than in classic heatstroke: a hyperthermic-neurologic acute phase, a hematologic-enzymatic phase, and a late renal-hepatic phase. In the hyperthermic-neurologic acute phase, the marked elevation in tissue and organ temperatures is associated with gastrointestinal and central nervous system dysfunction. In the hematologic-enzymatic phase, manifestations range from mild activation of coagulation and fibrinolysis to severe disseminated intravascular coagulation with elevated aminotransferase and creatine kinase levels. The late renal-hepatic phase is characterized by diffuse end-organ failure. In fulminant heatstroke, patients have the full spectrum of abnormalities associated with the systemic inflammatory response syndrome (Chapter 94).

TREATMENT AND PREVENTION

Heat illness can be prevented by heat acclimatization and acquired thermal tolerance, maintenance of adequate hydration, and avoidance of overwhelming heat exposure.[7] Adequate fluid intake is critical, and oral rehydration solutions should contain sodium and other electrolytes to restore both intracellular and extracellular fluid.

Management of serious heat illness, which should begin in the field setting, includes cooling, rehydration, and monitoring (Table 95-3).[8] The first priority should be immediately to initiate whole-body cooling and to continue cooling until the core temperature falls below 38.8° C (102° F). Body cooling lowers skin temperatures, thereby facilitating conduction and convection from the core to the shell, and reduces cardiovascular stress by causing arterial and venous constriction that redirects blood back to the heart. Immersion or soaking of the skin in cool or ice water with skin massage is the most effective method,[9] but other effective methods include soaking of the skin followed by accelerated evaporation with fans or the use of ice sheets and ice packs. These noninvasive treatments can be supplemented with the infusion of chilled (≈4° C) normal saline. Cooling can induce shivering, which is usually not sufficient to increase body temperature, so shivering need not be treated.

Hospital care of exertional heat stroke, while largely supportive, can rapidly escalate to the complex management of fulminant multiorgan failure.[10] The highest priority for patient care remains urgent cooling, including cold intravascular fluid. Cooling is usually discontinued at a core temperature of 38° to 39° C to avoid overcooling, but this practice is not based on data from controlled trials.[11]

Patients who are unconscious are at risk of poor airway control and may require endotracheal intubation to prevent aspiration. Fluid and electrolyte deficits should be corrected; restoration of plasma volume with isotonic fluids (e.g., normal saline) sufficient to sustain adequate perfusion, as judged by carefully monitored urine output, is also a priority. Rapid overcorrection of serum electrolytes (e.g., sodium) should be avoided. If rhabdomyolysis (Chapter 99) and myoglobinuria are present, maintaining urine flow helps minimize renal injury.

TABLE 95-2 COMPARISON OF CLASSIC AND EXERTIONAL HEATSTROKE

PATIENT CHARACTERISTICS	CLASSIC	EXERTIONAL
Age	Young children or elderly	15-55 years
Health	Chronic illness	Usually healthy
Fever	Unusual	Common
Prevailing weather	Frequent in heat waves	Variable
Activity	Sedentary	Strenuous exercise
Drug use	Diuretics, antidepressants, anticholinergics, phenothiazines	Ergogenic stimulants or cocaine
Sweating	Often absent	Common
Acid-base disturbances	Respiratory alkalosis	Lactic acidosis
Acute renal failure	Uncommon	Common (≈15%)
Rhabdomyolysis	Uncommon	Common (≈25%)
CK	Mildly elevated	Markedly elevated (500-1000 U/L)
ALT, AST	Mildly elevated	Markedly elevated
Hyperkalemia	Uncommon	Common
Hypocalcemia	Uncommon	Common
DIC	Mild	Marked
Hypoglycemia	Uncommon	Common

ALT = alanine aminotransferase; AST = aspartate aminotransferase; CK = creatine kinase; DIC = disseminated intravascular coagulation.

TABLE 95-3 MANAGEMENT OF HEAT ILLNESS

HEAT EXHAUSTION
Rest and shade
Loosen and remove clothing
Supine position and elevate legs
Actively cool skin
Fluids by mouth
Monitor core temperature
Monitor mental status
HYPERTHERMIA
Protect the airway
Insert at least two large-bore intravenous lines
Monitor core temperature; options include rectal, pulmonary artery, esophageal probe
Actively cool the skin until core temperature reaches <39° C (<102.2° F)
Ice baths or cool water (≈22° C [71.6° F]) immersion
Wetting with water (avoid alcohol rubs)
Continuous fanning
Exposure to cool environment
Axillary or perineal ice packs and ice sheets
Infusion of room-temperature saline
Gastric or colonic iced saline lavage
Peritoneal lavage with iced normal saline
Monitor electrocardiogram for arrhythmia
Obtain serial diagnostic studies*

*Electrocardiogram, chest radiograph, complete blood count with differential, platelet count, urinalysis, aminotransferases, alkaline phosphatase, bilirubin, creatine kinase, blood urea nitrogen, creatinine, phosphate, calcium, glucose, electrolytes, uric acid, prothrombin time and partial thromboplastin time, D-dimer, fibrinogen, arterial blood gases, toxicology screen.

The hematologic-enzymatic and renal-hepatic phases should be anticipated, because they may require appropriate subspecialty care. Patients should be carefully monitored to detect possible metabolic abnormalities (e.g., hyperkalemia; Chapter 103), renal or hepatic failure (Chapters 116 and 140), disseminated intravascular coagulation (Chapter 161), cardiac arrhythmias (Chapters 51 to 53), and acute respiratory failure (Chapter 90). Management of these complications is largely supportive, with specific therapies as indicated for any critically ill patient. Medications to be avoided include antipyretics and sedatives with hepatic toxicities. Lorazepam (1 to 2 mg administered intravenously during a 2- to 5-minute period, repeated if necessary), which is a safe sedative because of its low hepatotoxicity and rapid metabolism, may be indicated in patients who are combative or exhibit seizure activity.

For exercise-induced and environmental heat illness, no pharmacologic interventions have been proved to augment cooling. For patients with malignant hyperthermia, however, dantrolene should be administered as a loading bolus of 2.5 mg/kg intravenously, with subsequent bolus doses of 1 to 2.5 mg/kg every 5 minutes intravenously as needed (up to a maximum total loading dose of 10 mg/kg) until the signs have abated.

PROGNOSIS

A single episode of heat exhaustion does not imply a predisposition to heat illness, and most patients recover within several hours after cooling and rehydration. For patients who present to a hospital with heatstroke, however, mortality rates can range from 26 to 63%. Mortality in both classic and exertional heatstroke correlates directly with the magnitude and duration of temperature elevation, the delay in time to initiation of cooling, and the number of organ systems affected. The likelihood of survival to discharge can be estimated based on prehospital severity as determined by a respiratory rate 22/minute or higher, a Glasgow coma score (Table 368-1) below 15, a systolic blood pressure below 100 mm Hg, a heart rate above 100/minute, a body temperature of 38° C or higher, and age 65 years or above.[12] Although most patients who survive a heatstroke event will have a full recovery, some can sustain permanent organ damage.[13] Neurologic injury with cerebellar dysfunction is the most common clinical picture. Patients who have recovered from heatstroke with organ damage have a higher long-term mortality from cardiovascular, liver, and digestive diseases.

Patients who have suffered heat injury or heatstroke should not be re-exposed to heat until recovery is complete, which can be many weeks or months, and about 10% of heatstroke patients remain intolerant of heat. Return to physical activity should be a gradual process of increased physical activity without heat exposure and then combined with heat exposure.[14]

COLD INJURY

DEFINITION

Cold injuries are classified as hypothermia and peripheral cold injuries. Hypothermia is whole-body cooling, whereas peripheral cold injuries are localized to the extremities and exposed skin. Hypothermia is further divided into three categories: mild (≈33° C to ≈35° C), moderate (≈27° C to ≈32° C), and profound (<27° C). Peripheral cold injuries can be divided into nonfreezing (chilblain, trench foot) and freezing (frostbite). Both hypothermia and peripheral cold injuries often occur simultaneously, and treatment priority should be given to rewarming in moderate and profound hypothermia.

EPIDEMIOLOGY

Accidental hypothermia can occur in most climates, but exposure to cold, wet conditions pose the greatest risk.[15] A variety of individual factors, health conditions, medications, and environmental factors are associated with a predisposition to cold injury (Table 95-4). Homeless persons are at increased risk owing to climatic exposure, which is often exacerbated by the concomitant use of alcohol and other intoxicating substances. In trauma patients (Chapter 97), hypothermia is associated with increased morbidity and mortality. Unwarmed anesthetized patients (Chapter 400) typically become 1° to 2° C hypothermic because of an internal redistribution of body heat from the core to the periphery, so warming should be considered to maintain normothermia

PATHOBIOLOGY

Cold exposure elicits peripheral vasoconstriction to reduce heat transfer between the body's core and shell (skin, subcutaneous fat). If sufficiently cold, the underlying tissues (e.g., muscle) constrict to thicken the isolative shell while reducing the body's core area. This vasoconstrictor response defends core temperature but at the expense of declining peripheral tissue temperatures, which contribute to peripheral cold injuries. Hypothermia depresses enzymatic activity, interferes with physiologic functions (e.g., clotting, respiration, cardiac conduction and rhythm), impairs the expression of cytokines, and can induce cellular injury and death.

TABLE 95-4 FACTORS PREDISPOSING TO COLD INJURY

INDIVIDUAL FACTORS
Inadequate clothing and shelter
Lean and low body fat
Low physical fitness
Prior exhaustive physical exercise
Advanced age
Young age
Black race (men and women)
HEALTH CONDITIONS
Burns
Diabetes mellitus
Hypoglycemia
Neurologic lesions
Dementia
Hypoadrenalism, hypopituitarism, hypothyroidism
Prior frostbite or trench foot
Raynaud phenomenon
Sickle cell trait
Trauma
Spinal cord injury
DRUGS
Alcohol
Anesthetics
Antidepressants
Antipsychotics
Antithyroid agents
Sedatives and narcotics
ENVIRONMENTAL FACTORS
Cold temperatures
High air motion
Rain and immersion
Skin contact with metal and fuels
Repeated cold exposure
Physical fatigue
Immobility
High-altitude and low-oxygen-tension environments

The pathophysiologic mechanism of frostbite includes four overlapping pathologic phases: prefreeze, freeze-thaw, vascular stasis, and late ischemic. The prefreeze phase consists of tissue cooling with accompanying vasoconstriction and ischemia but does not involve actual ice crystal formation. In the freeze-thaw phase, intracellular ice crystals form, thereby causing protein and lipid derangement, cellular electrolyte shifts, cellular dehydration, cell membrane lysis, and subsequent cell death. In the vascular stasis phase, vessels may fluctuate between constriction and dilation; blood may leak from vessels or coagulate within them. The late ischemic phase results from progressive tissue ischemia and infarction due to a cascade of inflammatory cytokines and prostaglandins, intermittent vasoconstriction with continued thrombus formation, and secondary reperfusion injury.

CLINICAL MANIFESTATIONS AND DIAGNOSIS

Hypothermia is a core temperature below 35° C (95° F), and clinical manifestations are related to the core temperature achieved (Table 95-5). The classic J wave on the electrocardiogram (Fig. 95-1) appears at a core temperature below about 33.8° C (93° F).

Chilblain (Chapter 66) appears as localized inflammatory lesions of the skin, most often involving the dorsal surface of fingers but also involving the ears, face, and exposed shins. Trench foot is caused by prolonged cold, wet exposure (e.g., wet socks or gloves), which can cause skin breakdown and nerve damage. Trench foot is often accompanied by infection and increased sensitivity to pain.

Frostbite (Chapter 66),[16] which is actual freezing of tissues, has traditionally been categorized as first degree (superficial, "frostnip"), second degree (full skin) with superficial skin vesiculation, third degree (subcutaneous tissue) with hemorrhagic blisters, and fourth degree (extensive tissue and bone). For patients with frostbite, early surgical consultation is advised.

TABLE 95-5 HYPOTHERMIA: STAGES AND ASSOCIATED CLINICAL MANIFESTATIONS

STAGE	CORE TEMPERATURE °F	CORE TEMPERATURE °C	CLINICAL MANIFESTATIONS
Normothermia	98.6	37.0	
Mild hypothermia	95.0	35.0	Cold diuresis, maximal shivering
	93.0	33.8	Ataxia, poor judgment, ECG J wave
	91.0	32.7	Amnesia, blood pressure difficult to measure
Moderate hypothermia	89.0	31.6	Stupor, pupils dilated
	87.0	30.5	Shivering ceases
	85.0	30.0	Cardiac arrhythmias, insulin inactive
	82.0	27.8	Unconsciousness, ventricular fibrillation likely
	80.0	26.6	No muscle reflexes
Profound hypothermia	78.0	25.5	Acid-base disturbances, no response to pain
	75.0	23.8	Pulmonary edema, hypotension
	73.0	22.7	No corneal reflexes
	66.0	18.8	Heart standstill
	62.0	16.6	Isoelectric electrocardiogram
	57.6	14.2	Lowest infant survival from accidental hypothermia
	48.2	9.0	Lowest adult survival from accidental hypothermia

ECG = electrocardiogram.

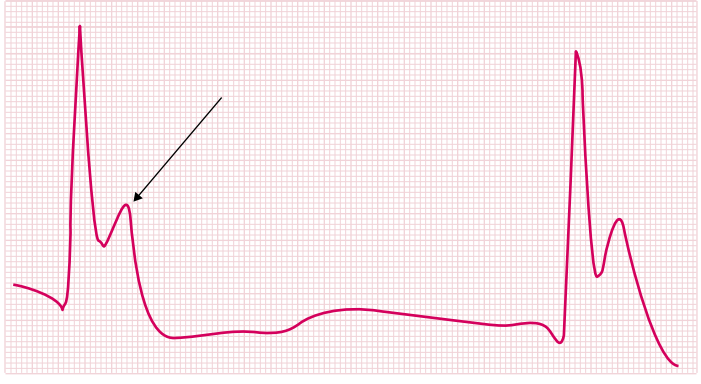

FIGURE 95-1. J (Osborne) wave.

PREVENTION AND TREATMENT

Humans demonstrate minimal cold acclimatization, so prevention depends primarily on avoiding cold exposure and having adequate protection and calorie intake to support metabolism.[17,18] Management of hypothermia depends on the core temperature (Table 95-6). Patients' wet clothing should be removed, and they should be provided with dry insulation. Shivering is an effective physiologic rewarming mechanism and should not be pharmacologically suppressed.

Moderately and profoundly hypothermic patients require active rewarming. Rewarming of the hypothermic patient includes both passive (insulation of the patient to prevent further heat loss) and active core (e.g., warmed saline and warmed humidified oxygen) and external (e.g., warmed water bottles, electric blankets) techniques. Rewarming at a rate of 0.5° to 1.0° C (0.9° to 1.8° F) per hour is acceptable in most cases, except that aggressive rewarming is warranted in patients with significant trauma (because coagulation is hindered by hypothermia) or cardiac arrest.

Complications commonly associated with rewarming of the hypothermic individual include both afterdrop (reduction of core temperature by cold blood returning to the circulation from the periphery) and aftershock (hypotension caused by peripheral vasodilation). Another potential complication of rewarming is ventricular fibrillation, which is more difficult to treat in the presence of moderate or profound hypothermia. If ventricular tachycardia or ventricular fibrillation develops, defibrillation should be attempted (Chapter 50). If ventricular tachycardia or ventricular fibrillation persists after a single shock, additional defibrillation attempts should be made, concurrent with rewarming but without waiting for the patient to warm to a particular target body temperature. Standard resuscitation approaches generally should be followed (Chapter 50). Extracorporeal life support is an option for refractory hypothermia-induced cardiac arrest.[19]

Body cooling induces cold diuresis, so plasma volume must be reestablished to support adequate perfusion. Patients should receive an intravenous infusion of 250 to 1000 mL of heated (40° to 42° C [104° to 108° F]) 5% dextrose in normal saline. Lactated Ringer solution should be avoided because the liver cannot metabolize lactate efficiently during hypothermia. Patients should be monitored for disturbances in potassium and glucose. If hypoglycemia, alcohol, or opiate intoxication is contributing to hypothermia, intravenous glucose (50 to 100 mL of 50% dextrose), thiamine (100 mg), or naloxone (0.4 to 2 mg intramuscularly or intravenously), respectively, may be indicated.

The treatment of frostbite is detailed in Chapter 66.

TABLE 95-6 TREATMENT OF HYPOTHERMIA

STAGE	MANAGEMENT	BODY REWARMING
Mild hypothermia	Monitor vital signs Warm intravenous saline Oxygen Monitor electrocardiogram for arrhythmia	Insulate Shivering Warm bath Active warming blanket
Moderate hypothermia	Diagnostic studies* Intensive care Anticipate infection and multiorgan dysfunction	Prevent extra heat loss by supplementing with airway rewarming Colonic irrigation Peritoneal dialysis
Profound hypothermia	Diagnostic studies*	Central rewarming

*See Table 95-3. Also lactate dehydrogenase, serum lactate, cortisol, thyroid-stimulating hormone, T3, and T4.

PROGNOSIS

Although noninvasive imaging with technetium pyrophosphate or magnetic resonance imaging can often predict the likelihood of tissue viability, it may take weeks to determine the precise demarcation of tissue that will require amputation. As morbidity may result from premature or unnecessary surgical intervention, consultation with a surgeon with experience evaluating and treating frostbite should be obtained to assess the need for and the timing of any amputations.

HYPOTHERMIC SYNDROMES

Exercise-induced bronchospasm (Chapter 75) can be triggered by exercise in cold air, particularly in patients with asthma. Livedo reticularis is patchy mottling of the limbs with cold exposure. Cryoglobulinemia (Chapter 173) occurs when immunoglobulins (IgM, IgG) reversibly precipitate after being cooled and contribute to impaired capillary blood flow in hypothermic tissues. Cold urticaria (Chapters 232 and 407) is the development of localized and general erythema and wheals in skin exposed to cold. Paroxysmal hypothermia is periodic lowering of the thermoregulatory set point and is often associated with hypothalamic abnormalities. Raynaud phenomenon (see Fig. 66-9 in Chapter 66) is intense vasoconstriction with sensitivity to pain in limbs exposed to cold.

TRAUMA HYPOTHERMIA

In trauma patients (Chapter 97), unintended hypothermia (<34° C [93° F]) is associated with increased morbidity and mortality due to impaired coagulation, peripheral vasoconstriction, respiratory depression, and increased risk for cardiac arrhythmias. Shivering aggravates perfusion problems by requiring blood flow to support increased metabolism in contracting muscles. Trauma patients become hypothermic because of heat loss from exposed cavities, environmental exposure, infusion of cool fluids, and ischemia, which depletes cell energy stores. Body temperature should be measured, and appropriate actions, as noted earlier, should be taken to restore normothermia during the early treatment of trauma patients.

THERAPEUTIC HYPOTHERMIA AND HYPERTHERMIA

THERAPEUTIC HYPOTHERMIA

For adults after an out-of-hospital cardiac arrest (Chapter 50), therapeutic cooling (a goal of 36° C for 24 to 48 hours) to prevent the usual hyperthermia

can improve survival and neurologic outcomes[A1,A2] but is no better than therapeutic normothermia (<37.8° C).[A3] However, in-hospital hypothermia does not improve outcomes for patients after brain trauma, patients with intracranial hypertension,[A4] patients after an in-hospital arrest, patients who have undergone decompressive hemicraniectomy for malignant middle cerebral artery stroke,[A5] or patients with convulsive status epilepticus (Chapter 372).[A6]

THERAPEUTIC HYPERTHERMIA

Hyperthermia treatment (whole body or regional) is an experimental technique used as an adjunct to chemotherapy or radiation therapy in patients with advanced cancer. Hyperthermia (40° to 43° C [104° to 109° F]) alone can damage or kill cancer cells but, more important, hyperthermia might potentiate the effectiveness of chemotherapy and radiation by softening the tumor tissue, thus reducing its interstitial pressure.

Externally applied radiant heat, microwaves, or extracorporeal circulation usually induces local, regional, or whole-body hyperthermia. Target tissue temperatures are achieved and maintained based upon the specific cancer protocol, then followed by a passive cooling phase. Patients are usually sedated while core and skin temperatures are monitored. In regional hyperthermia, the part of the body where the tumor is located is heated while being perfused or bathed by a warmed solution containing anticancer drugs. The potential benefit of regional hyperthermia as an adjunct treatment of advanced prostate cancers is currently under investigation.

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96 ACUTE POISONING

LEWIS S. NELSON AND DIANE P. CALELLO

EPIDEMIOLOGY

Each year, more than 4 million poisoning cases, suspected or verified, and 300,000 related hospital admissions occur in the United States. Poison centers provide support and collect data on more than 2 million of these exposures annually.[1] Poisoning-related deaths now total about 10,000 annually, and the number of opioid-related deaths has tripled since 2000. Poisonings are the leading cause of injury-related death in the United States, where approximately 90% of these deaths involve drugs, predominantly opioids (75%), such as heroin, fentanyl, and prescription analgesics.[2] Worldwide, however, pesticides, insecticides, caustics, and snakebites (Chapter 98) are also common causes. The incidence of recurrent, purposeful self-poisoning is 12 to 18%, with most events occurring within 3 months of the original attempt. To reduce fatalities and repeated attempts, an emphasis must be placed on measures to improve the safety of prescription drugs, including appropriate prescribing and aggressive treatment of poisoned patients with early psychiatric intervention for suicidal behavior (Chapter 362).

DIAGNOSIS

Despite the vast array of toxins to which a patient may be exposed, the clinical manifestations of poisoning are fairly limited. In most cases, it is less important to predict exactly which toxin is responsible for the acute poisoning than it is to create a differential diagnosis based on a careful history and physical examination as well as basic laboratory assays. The recognition of the specific toxic syndrome, or *toxidrome*, guides the clinician toward the likely diagnosis based on reasonably solid evidence. On this basis, treatment, including initial stabilization, critical care, decontamination, and even the empirical administration of antidotes, can be guided by an understanding of the pharmacology and physiology of the patient's toxidrome. More advanced care, such as methods to enhance the elimination of specific toxicants, commonly requires serial examinations, additional history, and subsequent laboratory testing. Even then, however, the clinical picture is often clouded by exposures to multiple toxicants and an ill-defined time course since the initial exposure.

History

Details elicited about toxic exposures should include the involved drugs and other toxicants, their estimated or known amounts, the time and routes of exposure, the patient's symptoms and signs, and any treatment already administered. Poisoning may result from acute, chronic, or acute-on-chronic exposure. A *toxicant* is defined as a chemical capable of harming a biologic organism; this definition encompasses toxins, which are derived from living organisms (such as plants, bacteria, and venoms), as well as synthetic substances, such as medications, drugs of abuse, and industrial and other chemicals.[3] Determination of chronicity is important because signs and symptoms of chronic exposure (Chapter 20) can differ from those of acute and acute-on-chronic exposure. For example, a history of acute multisystem organ failure narrows the toxicant possibilities to a few gases, chemicals, and drugs. A listing of available medications (e.g., those of the patient, spouse, relatives, or friends), nonprescription medications and herbals, dietary supplements, or ethnic remedies and occupational and avocational activities should be obtained. Occupational and avocational histories should include present and all past jobs and hobbies, with a focus on chemicals, metals, and gases. Known medical conditions may suggest classes of medications available to the patient. The patient's history, which may be incomplete or inaccurate if the patient is confused or suicidal, should be correlated with the clinical manifestations and course. Corroborative history from relatives and friends and findings from the scene as reported by the transporting emergency medical services personnel may be relevant.

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The physical examination should focus on vital signs; the eye, ear, nose, and throat examination; and the neurologic, cardiopulmonary, gastrointestinal, and dermatologic systems. Findings can suggest certain toxidromes, which are clusters of signs and symptoms typical of a specific class of poison. Among the dozens of toxidromes that assist in patient assessment and guide management, those due to adrenergic, anticholinergic, cholinomimetic, opioid, and sedative-hypnotic agents are most relevant to the emergency management of poisoned patients (Table 96-1). Patients may have some or all of these signs and symptoms; an incomplete clinical picture does not exclude a particular toxidrome, and it can still assist the clinician in identifying the correct category of toxicant involved.

Vital Signs

Tachycardia, which can occur with numerous toxicants, is most prominent in patients with anticholinergic and sympathomimetic toxidromes. However, because tachycardia also may occur with anxiety and other nontoxicologic conditions, it is not generally a helpful finding. The differential diagnosis for toxicant-induced *bradycardia* is more limited and includes β-adrenergic receptor antagonists, L-type calcium-channel antagonists (diltiazem or verapamil), cardioactive steroids, peripheral α-adrenergic receptor agonists (e.g., phenylephrine, whose effects are mediated by baroreceptor reflexes), central α_2-agonists such as clonidine, γ-hydroxybutyric acid, opioids, sedative-hypnotics, baclofen, organophosphorus and carbamate pesticides, muscarine-containing mushrooms (*Clitocybe, Inocybe* sp), plant- and animal-derived toxins (e.g., aconitine, andromedotoxin, ciguatoxin, and veratridine, all of which open sodium channels in the myocardium), therapeutic cholinesterase inhibitors (e.g., physostigmine), and some antiarrhythmic drugs (e.g., procainamide, flecainide, and other class IA, IC, and III drugs, such as amiodarone and sotalol). Bradycardia also is a preterminal sign for many highly lethal toxicants, such as cyclic antidepressants and cyanide.

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ABSTRACT

Although there are thousands of potentially toxic substances to which humans can be exposed, the majority of patients who are clinically evaluated can be managed with readily available clinical information. Historical information, including potential home and workplace toxins, plus a brief physical examination generally allow identification of one of the various toxicologic syndromes that expedites the decision making regarding treatment. For some patients, the use of routine or specialized clinical laboratory testing or imaging may be needed to confirm a diagnostic suspicion. More advanced testing is occasionally required for certain patients but is generally not available in a clinically relevant time frame, highlighting the need for empiric therapy in these cases. Some patients with toxic exposures may benefit from specific antidotal therapy or elimination techniques, but many require little more supportive and symptomatic care.

KEYWORDS

poisoning
overdose
toxicology
poison
toxin
antidote

TABLE 96-1 TOXIDROMES AND ASSOCIATED DRUGS AND TOXICANTS

	SYNDROME FEATURES		
TOXIDROME	**VITAL SIGNS**	**END ORGAN**	**REPRESENTATIVE DRUGS AND TOXICANTS**
Adrenergic	Hypertension, hyperthermia, tachycardia, tachypnea	Agitation, dysrhythmias, diaphoresis, mydriasis, seizures	Amphetamines, caffeine, cathinone derivatives, cocaine, ephedrine, pseudoephedrine, *Ephedra* sp, phenylephrine,* synthetic cannabinoids, theophylline
Anticholinergic	Hyperthermia, tachycardia, blood pressure generally normal	Agitation, delirium, decreased or absent bowel sounds, dry flushed skin and mucous membranes, mydriasis or blurred vision, seizures, urinary retention	First-generation H_1-receptor antagonists (e.g., diphenhydramine), belladonna alkaloids (e.g., scopolamine, atropine) from plants (e.g., *Datura* sp—deadly nightshade, henbane), benztropine, cyclic antidepressants, dicyclomine, muscle relaxants (e.g., orphenadrine, cyclobenzaprine), trihexyphenidyl
Cholinomimetic	Tachycardia or bradycardia†	Agitation, delirium, coma; bronchorrhea, bronchospasm; diaphoresis; fasciculations; lacrimation; miosis; urination; diarrhea, vomiting; seizures	Carbamate cholinesterase inhibitors (e.g., physostigmine, neostigmine), organophosphorus compounds including pesticides (e.g., diazinon, malathion) and nerve agents (e.g., soman, sarin, VX, novichok), *Inocybe* or *Clitocybe* mushroom spp
Opioid	Bradypnea or apnea, bradycardia, hypotension (late), hypothermia	CNS depression; hypotonia; miosis	Fentanyl, fentanyl analogs, heroin, hydrocodone, oxycodone, morphine, buprenorphine, central α_2-agonists (e.g., clonidine, guanfacine)
Sedative-hypnotic	Generally near normal with benzodiazepines, but bradypnea or apnea, mild hypotension, and mild hypothermia can occur	Ataxia, CNS depression, hyporeflexia, slurred speech, stupor, or coma	Barbiturates, benzodiazepines, bromides, ethanol, gamma-hydroxybutyrate and its precursors, meprobamate, propofol, zolpidem

*Reflex bradycardia can occur as a result of a pure α-adrenergic agonist effect.
†Depending on the specific toxicant, tachycardia can occur early as a result of a preganglionic nicotinic effect; as toxicity progresses, postganglionic muscarinic effects may predominate, and bradycardia develops.
CNS = central nervous system.

Many toxicants cause *hypotension* (Chapter 7). The primary mechanisms are decreased peripheral vascular resistance, decreased myocardial contractility, hypovolemia secondary to gastrointestinal or dermal loss of intravascular volume, and, occasionally, dysrhythmias. Common causes of *hypertension* (Chapter 64), which is generally due to vasoconstriction with or without enhanced inotropy, include amphetamines, cocaine, ephedrine and similar agents, ergots, phencyclidine, nicotine, phenylephrine, thyroid hormones, yohimbine, and chronic lead toxicity. Blood pressure can rise early in poisoning with central α_2-adrenergic agonists and monoamine oxidase inhibitors, but subsequent hypotension should be expected and is more concerning.

Hyperthermia (Chapter 95) occurs with toxicants that cause agitation or excessive psychomotor activity (e.g., cocaine, phencyclidine, monoamine oxidase inhibitors, strychnine), uncouple oxidative phosphorylation (e.g., salicylates, 2,4-dinitrophenol), increase the metabolic rate (e.g., thyroid hormones), impair sweating (e.g., first-generation antihistamines, anticholinergics, phenothiazines), cause vasoconstriction (e.g., amphetamines, cocaine, ephedrine), or alter perception of heat (e.g., cocaine). Other toxicant-induced states associated with hyperthermia include malignant hyperthermia, neuroleptic malignant syndrome, serotonin syndrome, metal fume fever, and aspiration pneumonitis. Toxicant-induced *hypothermia* is typically due to sedative-hypnotics, opioids, barbiturates, ethanol, phenothiazines, or hypoglycemic agents (such as insulin, sulfonylureas, and meglitinides) or rarely to unripe ackee fruit. Oxygen saturation (see Fig. 90-1 in Chapter 90), as measured by *pulse oximetry,* decreases with true hypoxemia (see Table 90-3 in Chapter 90) or methemoglobinemia (not proportionally to concentration) (Chapter 144) but remains normal or may be increased in patients with carbon monoxide or cyanide poisoning (Chapter 82).

Eyes, Ears, Nose, and Throat

Toxicant-induced bilateral miosis (Fig. 96-1) has a limited differential diagnosis that includes central α_2-agonists such as clonidine, guanfacine, and the imidazolines; olanzapine; opioids; organophosphorus compounds or carbamates; therapeutic cholinesterase inhibitors (e.g., pyridostigmine); topical miotic ophthalmic drugs (e.g., pilocarpine, carbachol); and, variably, phencyclidine, phenothiazines, ethanol, and some sedative-hypnotics (Chapter 392). Pontine hemorrhage is a major nontoxicologic diagnosis to consider in a comatose patient with miotic pupils (Chapter 377). Mydriasis is a nonspecific finding. A unilateral dilated pupil may be due to topical ocular application of sympathomimetics (e.g., phenylephrine), antihistamines, or anticholinergic agents (e.g., inhaled anticholinergics such as ipratropium or tiotropium, dust or sap from *Datura* sp) and can be caused by a postauricular scopolamine patch. Failure of topical 4% pilocarpine ophthalmic drops to constrict the pupil supports the diagnosis of pupillary dilation from a topical mydriatic agent. Visual disturbances, including partial or total blindness as a result of systemic toxicity, have been reported with anticholinergic agents, carbon monoxide, digitalis, ethambutol, methanol, methyl bromide, quinine, and agents that are associated with pseudotumor cerebri, including antimicrobials (e.g., ampicillin, metronidazole, nalidixic acid, nitrofurantoin, sulfa drugs, tetracycline), glucocorticosteroids, lead, lithium, oral contraceptives, phenothiazines, phenytoin, and vitamin A. Nonarteritic anterior ischemic optic neuropathy has developed after the use of sildenafil and other related drugs (Chapter 216); the causal relationship is unknown.

Neurologic Signs

Many toxicants affect the central nervous system (CNS) and can produce agitated delirium,[4] decreased level of consciousness,[5] or seizures (Table 96-2). Distinguishing features of various toxicants may assist in making the correct diagnosis. Patients who are withdrawing from opioids because of abstinence (as opposed to after being administered naloxone) are alert and oriented, whereas patients withdrawing from alcohol, barbiturates, benzodiazepines, and other sedative-hypnotics are often disoriented. Initial CNS depression can also develop with large ingestions of acetaminophen or ibuprofen. Isoniazid and theophylline are noted for producing seizures refractory to the usual doses of benzodiazepines and barbiturates. Pyridoxine treats isoniazid-induced seizures by increasing CNS γ-aminobutyric acid, synthesis of which is inhibited by isoniazid. Bupropion can cause seizures at both therapeutic doses and overdoses. Phenytoin is relatively ineffective for the majority of toxicant-induced seizures, perhaps because of the absence of a discrete seizure focus in most poisoned patients. Plant or mushroom ingestion can also produce CNS depression (e.g., *Rhododendron* sp, *Solanum* [bittersweet], *Taxus* [yew], *Sophora* [mescal bean]), CNS stimulation (e.g., *Catha edulis* [khat], *Strychnos nux-vomica* [contains strychnine], *Cicuta* sp [water hemlock], *Ephedra* [Mormon tea]), atropine-like effects (e.g., *Atropa belladonna* [deadly nightshade], *Datura* sp [jimsonweed]), and cholinomimetic effects (e.g., *Nicotiana* genus [tobacco], *Conium maculatum* [poison hemlock], *Inocybe* and *Clitocybe* mushrooms). Seizures can also occur with many of these plants and with mushrooms that contain gyromitrins (e.g., false morel, *Gyromitra* sp) and muscimol (e.g., *Amanita muscaria, Amanita pantherina*).

Distal axonopathy, a primary degeneration of peripheral nervous system axons with secondary degeneration of the myelin sheath, is the predominant type of toxicant-induced peripheral neuropathy. It usually is insidious in onset

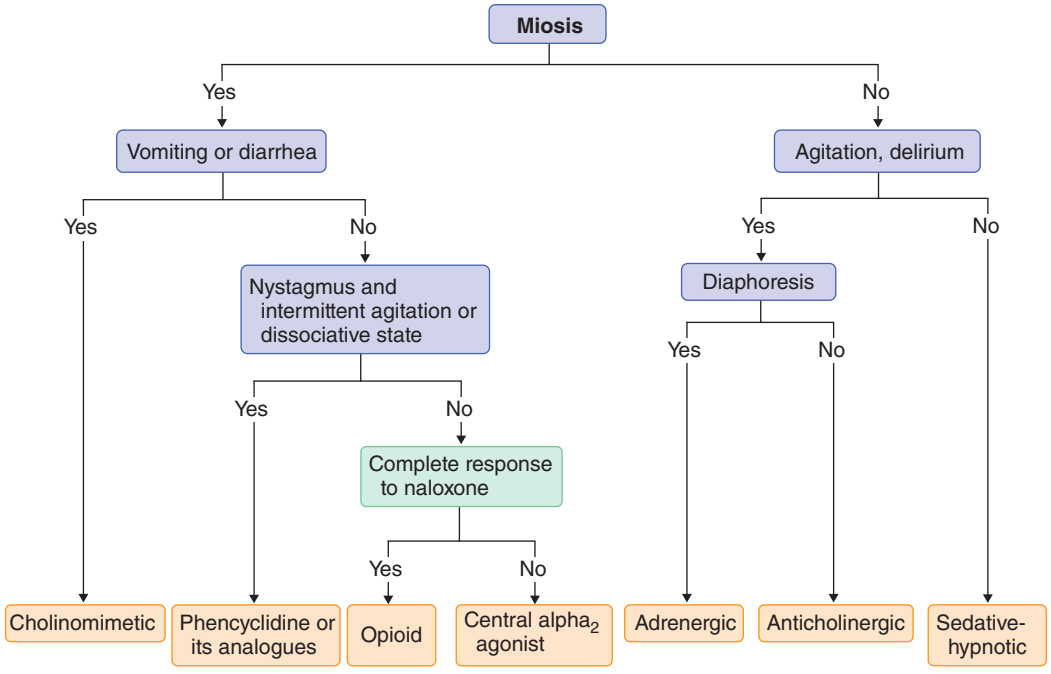

FIGURE 96-1. Diagnostic algorithm for assessing toxicant-induced bilateral miosis. Note that atypical toxidromes are common because of mixed toxicant exposures, so the examiner can be misled if relying only on this sign.

and follows chronic exposure; there is often slow recovery following termination of exposure, but, depending on the exposure and extent of neuronal damage, the clinical effects may be permanent. Neuropathy may be sensory, motor, or mixed. Common causative agents include acrylamide monomer, allyl chloride, arsenic (inorganic), capsaicin, carbon disulfide, chloramphenicol, cisplatin, colchicine, cyanate, dapsone, dideoxycytidine, dideoxyinosine, disulfiram, ethambutol, ethanol, ethylene oxide, gold salts, hexachlorophene, *n*-hexane, hydralazine, interferon, isoniazid, lead, linezolid, mercury, methyl bromide, methyl *n*-butyl ketone, metronidazole, nitrofurantoin, nitrous oxide, some organophosphorus compounds, phenol, platinum, podophyllotoxin, polychlorinated biphenyls, pyridoxine, tacrolimus, taxoids, thalidomide, thallium, vidarabine, vinca alkaloids, and vinyl chloride. Amiodarone, arsenic, and trichloroethylene can produce a demyelinating neuropathy, whereas pyridoxine can produce a sensory, sometimes painful, neuropathy. In addition, the neuropathy may be multifactorial in nature, such as vitamin deficiency associated with chronic ethanol consumption (Chapter 384). Neuronal transmission can be altered by aminoglycosides; the venom of *Latrodectus* species (widow spiders; see also Chapter 98 on envenomation and related injuries), scorpions (only the bark scorpion, *Centruroides sculpturatus*, in the United States), and crotaline (e.g., rattlesnakes) and elapid snakes; brevetoxin (shellfish) and ciguatoxin (various fish); neuromuscular blocking drugs; nicotine and related alkaloids; paralytic shellfish toxins; saxitoxin (shellfish); organophosphorus compounds and carbamates; tetrodotoxin (puffer fish [fugu], blue-ringed octopus, salamanders, newts, and others); and veratridine (e.g., false hellebore). Cranial nerves can be affected by carbon disulfide, ciguatoxin, domoic acid (shellfish), elapid venom, ethylene glycol metabolites, paralytic shellfish toxins, bark scorpion, saxitoxin, tetrodotoxin, thallium, and trichloroethylene. Mononeuropathies and vasculitic neuropathies are unlikely to be induced by toxicants (Chapter 98).

Cardiopulmonary Effects

The examination should focus on blood pressure, heart rate, electrocardiographic abnormalities (e.g., rhythm, conduction, depolarization, repolarization), and pulmonary findings, including pulse oximetry. Drugs and other toxicants that can cause dysrhythmias or conduction abnormalities include β-adrenergic receptor antagonists, butyrophenones (e.g., haloperidol), L-type calcium-channel antagonists, cardioactive steroids (e.g., bufadienolides, found in toxic toad venom and incorporated into some illicit aphrodisiacs; cardenolides, such as digoxin,[6] found in plants such as foxglove, oleander, and lily of the valley), halogenated hydrocarbons, chloroquine, cocaine, cyclic antidepressants, ethanol, halogenated hydrocarbons (e.g., halothane, trichloroethylene), magnesium salts, potassium salts, propoxyphene, thioridazine or mesoridazine, bupropion, and antiarrhythmics and other agents that affect the myocardial voltage-gated sodium channels (e.g., bupivacaine, chloroquine, cocaine, cyclic antidepressants, flecainide, mexiletine, quinidine, procainamide, propafenone) and potassium channels (e.g., typical and atypical antipsychotics, citalopram/escitalopram, erythromycin [especially when taken concomitantly with cytochrome P-450 A inhibitors; Chapter 25], quinidine, sotalol, terfenadine). Bedside echocardiography may reveal depressed myocardial contractility as a result of agents that block the myocardial voltage-gated sodium channel, β-adrenergic receptor antagonists, calcium-channel antagonists, cyclic antidepressants, magnesium salts, arsenic salts, ciguatoxin, cyanide, ethanol, iron salts, and scorpion venom.

Toxicants can produce myriad pulmonary effects, including airway irritation, parenchymal and pleural diseases, vascular diseases, and barotrauma. Typical syndromes and etiologic agents include pulmonary edema (β-adrenergic receptor antagonists, calcium-channel antagonists, antiarrhythmics, daunorubicin, doxorubicin), acute respiratory distress syndrome (Chapter 90) (amphetamines, cadmium, chlorine, cocaine, ethchlorvynol, methotrexate, opioids, heroin, paraquat, salicylates; inhalation of smoke, zinc chloride, methyl bromide, methyl chloride, and hydrocarbons), and rapidly developing pulmonary fibrosis or bronchiolitis obliterans (oxides of nitrogen, paraquat). For organophosphorous nerve agent and insecticide poisoning, acute respiratory failure is the most common primary cause of death, but some patients develop delayed neuromuscular junction dysfunction (i.e., intermediate syndrome), aspiration pneumonia, and acute respiratory distress syndrome.[7]

Gastrointestinal Effects

Symptoms of nausea, vomiting, diarrhea, and abdominal pain are nonspecific and must be interpreted in the context of other findings. Agents that produce severe or life-threatening toxicity with early gastrointestinal findings include acid or large alkali ingestions; cardioactive steroids; colchicine and other microtubular toxicants (e.g., podophyllin, vincristine); metal salts such as arsenic, iron, mercury salts, and thallium; mushrooms containing amanitin (*Amanita phalloides, Amanita virosa, Amanita verna, Lepiota chlorophyllum*), gyromitrins (*Gyromitra esculenta*), orellanines (*Cortinarius orellanus*), or allenic norleucine (*Amanita smithiana*); nicotine; organophosphorus compounds; and theophylline. Caustic damage is found with ingestion of alkalis (e.g., ammonium hydroxide, sodium hydroxide, potassium hydroxide, or sodium hypochlorite), acids (e.g., acetic acid, hydrochloric acid, oxalic acid, phosphoric acid, selenous acid, sulfuric acid, or hydrofluoric acid), and other agents (e.g., benzalkonium chloride, hydrogen peroxide, phenol, and zinc chloride).[8] Severe abdominal pain and rigidity can occur with lower extremity envenomation by *Latrodectus* species (widow spiders), unrelated to any direct organ injury. Hepatotoxicity can occur as an adverse effect of the therapeutic use of many drugs; in the United States, acetaminophen and ethanol are the most common causes of toxicant-induced hepatotoxicity (Chapter 136). For acetaminophen overdose,

TABLE 96-2 CENTRAL NERVOUS SYSTEM EFFECTS OF TOXICANTS

	CNS EFFECTS		
TOXICANT CATEGORIES AND AGENTS	**AGITATED DELIRIUM**	**DECREASED LEVEL OF CONSCIOUSNESS**	**SEIZURES**
CLASSES			
Anticholinergic agents	+	+	+
Anticonvulsants	+	+	+ (paradoxical with some agents)
Antipsychotic drugs		+	+
β-Adrenergic receptor antagonists	+	+	+ (theophylline/caffeine)
Hallucinogenic agents	+	+	+ (MDMA, substituted amphetamines)
Monoamine oxidase inhibitors	+	+	+
Opioids	+ (withdrawal, tramadol)	+	+ (meperidine, tramadol, dextromethorphan)
Sedative-hypnotics	+ (rare, paradoxical)	+	
Antidepressants	+ (serotonin syndrome)	+	+ (bupropion, venlafaxine)
AGENTS			
Amphetamines, cocaine	+	+ (following binge use)	+
Antidepressants (non SSRI)	+ (MAOI)	+	+
Antihistamines (first generation, e.g., diphenhydramine)	+	+	+
Barbiturates		+	
Benzodiazepines	+ (rare, paradoxical)	+	
Cytochrome oxidase inhibitors (e.g., carbon monoxide, cyanide, hydrogen sulfide, azides)		+	+
Ephedra alkaloids and similar agents	+	+	+
Ethylene glycol, methanol		+	+
γ-Hydroxybutyrate and precursors	+ (paradoxical, withdrawal)	+	+ (vs. myoclonus, withdrawal)
Lithium	+	+	+ (rare)
Organophosphorus compounds (e.g., diazinon, malathion, nerve agents) and carbamates (e.g., carbaryl, physostigmine)	+	+	+
Salicylates	+ (delirium)	+	+ (often pre-terminal)
SSRIs/SRIs/SNRI antidepressants	+ (serotonin syndrome)	+	+
Withdrawal from alcohol, barbiturates, benzodiazepines, other sedative-hypnotics	+		+
Withdrawal from opioids	+		+ (only in neonates)

CNS = central nervous system; MAOI = monamine oxidase inhibitor; MDMA = 3,4,-Methylenedioxymethamphetamine, also known as ecstasy or Molly; SNRIs = serotonin and norepinephrine re-uptake inhibitors; SRIs = serotonin re-uptake inhibitors; SSRIs = selective serotonin re-uptake inhibitors.

early measurement of the concentration of acetaminophen-protein adducts can predict the likelihood of hepatotoxicity.[9] Other notable hepatotoxicants include aflatoxins (in food contaminated with *Aspergillus flavus*), anabolic steroids, arsenicals, carbon tetrachloride, copper sulfate, cyclopeptide mushrooms (e.g., *Amanita phalloides*),[10] *Ephedra* species (e.g., ma huang), iron salts, methamphetamine, pennyroyal oil, pyrrolizidine alkaloids (various plant species used in herbal teas), and vitamin A in chronic excessive doses.

Dermatologic Signs

The skin, hair, nails, and mucous membranes should be examined for evidence of intravenous drug use; the presence or absence of skin and mucous membrane moisture; abnormal skin coloration, including erythema and cyanosis; alopecia; and nail abnormalities. Bullous skin lesions have been reported with chronic barbiturate use, glutethimide, carbon monoxide, meprobamate, methadone, and valproic acid. Sulfur mustard gas produces large yellow bullae on affected skin. Bluish discoloration may be dermal in origin (as with argyria from excessive exposure to colloidal silver) or due to cyanosis. Cyanosis may reflect hypoxemia or methemoglobinemia. Commonly used agents that can cause methemoglobinemia include aniline dyes, benzocaine and other amide anesthetics, dapsone, naphthalene, nitrates, nitrites, phenazopyridine, rifampin, and sulfonamides. Skin erythema or flushing occurs with anticholinergic agents, boric acid ingestion, monosodium glutamate, niacin, scombroid toxicity as a result of the ingestion of inadequately refrigerated fish with a high histidine content (e.g., tuna, mahi-mahi, amberjack), vancomycin, and interactions between ethanol and numerous agents that produce disulfiram or disulfiram-like reactions (e.g., carbon disulfide, some cephalosporins, *Coprinus atramentarius* mushroom, disulfiram, griseofulvin, metronidazole, thiuram herbicides, trichloroethylene).

Specific Toxicants

Some common toxicants can be suspected from their characteristic manifestations (Table 96-3). These suspicions should guide specific diagnostic and therapeutic strategies that complement general decontamination and supportive treatments.

Diagnostic Tests

Drug testing should be guided by the history and physical examination, with emphasis on tests that can influence management. Rapid qualitative urine drug screening tests are readily available in most hospitals, but their clinical value is limited by the number of drugs that can be tested and the reliability of the tests themselves. Although such testing may be valuable for subsequent psychiatric evaluation, it is less reliable for urgent diagnosis and therapy. For example, a positive test result may be unrelated to the patient's condition because drug analytes may be detectable for days after drug use, depending on the drug, dose, and frequency of use. In addition, both false-positive and false-negative results occur (Table 96-4), so the screening result must be verified with a

TABLE 96-3 PATHOPHYSIOLOGY, CLINICAL EFFECTS, AND MANAGEMENT OF SPECIFIC DRUGS AND TOXICANTS

DRUG OR TOXICANT	PATHOPHYSIOLOGY	TOXIC EFFECTS	LABORATORY	SPECIFIC THERAPY
Acetaminophen	NAPQI (toxic metabolite) binds hepatic and renal tubular cells, where it causes oxidant tissue damage; acetaminophen itself induces transient decrease in functional coagulation factor VII and can increase INR	Initial: nausea, vomiting, coma, lactic acidosis in severe cases Days 1-3: elevated INR, aminotransferase levels; RUQ tenderness; increased creatinine level in severe cases Days 4-14: gradual recovery or continued increase in INR and creatinine, lactic acidosis, coma, cerebral edema, death	Potentially toxic level ≥150 μg/mL 4 hours after single acute ingestion* INR may be transiently elevated in first 24 hours because of decrease in functional factor VII, and further increases indicate hepatic necrosis; elevated serum lactate levels and acidosis correlate with severity, but elevated aminotransferase and bilirubin levels are not predictive of hepatic failure Creatinine elevated in severe cases	N-acetylcysteine (see dosing guidelines in Table 96-6); NAC can increase INR but not aPTT†
Amphetamines (also cathinones, which are a class of keto substituted amphetamines)	Increased release of presynaptic norepinephrine and dopamine Increased serotonin release (especially MDMA, cathinones, other novel psychoactive drugs)	Mild: euphoria, decreased appetite, repetitive behavior, hallucinations Moderate: vomiting, agitation, hypertension, tachycardia, mydriasis, bruxism, diaphoresis Severe: hypertension or hypotension, dysrhythmias, hyperthermia, seizures, coma, multisystem organ failure, hyponatremia (SIADH), cerebral infarction or hemorrhage	Not helpful; many false-positives and false-negatives on screening tests (see Table 96-4)	IV crystalloids External cooling Benzodiazepines to control agitation or seizures Benzodiazepines for hypertension See SSRIs/SRIs for features and treatment of serotonin syndrome
β-Adrenergic receptor antagonists[11]	Blocks catecholamines from β-adrenergic receptors Additional actions: • α- and β-adrenergic receptor antagonism: carvedilol, labetalol • Delayed rectifier potassium-channel blockade: sotalol	Bradydysrhythmias (with high doses), decreased myocardial contractility, hypotension, respiratory depression, decreased consciousness with seizures or coma (lipophilic agents, e.g., propranolol), prolonged QT interval (sotalol)	ECG No specific tests	Regular insulin, 1 U/kg by IV bolus followed by 1 U/kg/hr (plus dextrose, usually needed within 20-30 min to maintain euglycemia), with upward titration every 10 min to max of 10 U/kg/hr. Other options include (1) IV glucagon (3-5 mg over 2-minute period; if no increase in BP or HR, can repeat up to 10 mg); if effective, immediately start continuous infusion at 2-10 mg/hr; or (2) norepinephrine infusion titrated to desirable BP and HR (less predictable) Electrical pacing, IABP, or intravenous lipid emulsion therapy in refractory cases
Calcium-channel antagonists	Blocks L-type voltage-sensitive calcium channels, thereby decreasing calcium entry into myocardial (verapamil, diltiazem) and vascular smooth muscle cells (all, but predominant effect of dihydropyridines) Decreases pancreatic insulin release and increases insulin resistance	Bradydysrhythmias (verapamil, diltiazem), hypotension, hyperglycemia Tachycardia and hypotension (dihydropyridines such as amlodipine, nifedipine)	ECG No specific tests	3 g (30 mL of 10% calcium gluconate solution) over 10 minutes (60 seconds if in extremis). Repeat in 10-20 minutes up to three times as needed. Alternative preferably via a central line: calcium chloride 10%, 10 mL (1 g) over 10 minutes (60 seconds if in extremis). Ionized Ca^{2+} levels should not exceed 2× normal (severe cases will be refractory to calcium therapy). Glucagon, high-dose insulin and dextrose, catecholamines, and milrinone (as for β-adrenergic antagonists). Intravenous lipid emulsion therapy for verapamil and diltiazem, unclear for dihydropyridines; indicated only for moribund patients.

TABLE 96-3 PATHOPHYSIOLOGY, CLINICAL EFFECTS, AND MANAGEMENT OF SPECIFIC DRUGS AND TOXICANTS—cont'd

DRUG OR TOXICANT	PATHOPHYSIOLOGY	TOXIC EFFECTS	LABORATORY	SPECIFIC THERAPY
Cardioactive steroids, including digoxin, bufadienolides (toxic toad venom), and cardenolides (e.g., oleander, lily of the valley, dogbane)	Inhibits Na^+,K^+-ATPase Decreased CNS sympathetic output Decreased baroreceptor sensitivity Increased vagal acetylcholine discharge	Bradydysrhythmias, including second- and third-degree AV block and asystole Ventricular ectopy, tachycardia, fibrillation Junctional tachycardia, paroxysmal atrial tachycardia with block Weakness, visual disturbances, nausea, vomiting	ECG Serum digoxin level Serum potassium (hyperkalemia occurs in acute poisoning and is prognostic for poor outcome without Fab; hypokalemia may be present in chronic poisoning due to concomitant medications such as furosemide), magnesium, and creatinine levels	Digoxin-specific antibody fragments (Fab) indicated if patient has rhythm disturbances such as sinus bradycardia, Mobitz II, or third-degree AV block, ventricular ectopy, serum potassium ≥5 mEq/L if acute overdose, ingestion of bufadienolide- or cardenolide-containing agents, or renal insufficiency Empiric dose: Acute: 10-20 vials Chronic: 3-6 vials Calculated dose: Acute: number of vials = 2 × oral digoxin dose (mg) × 0.8. Correcting the hyperkalemia with standard interventions is not helpful. Do not give calcium salts. If hypokalemic (generally chronic overdose), replete serum potassium. Chronic: number of vials = serum digoxin level (ng/mL) × wt (kg)/100
Cyclic antidepressants	Myocardial sodium- and potassium-channel blockade Blockade of α-adrenergic and cholinergic muscarinic receptors Inhibition of norepinephrine re-uptake	Decreased level of consciousness (can develop rapidly), myoclonus, seizures, coma Anticholinergic toxidrome (see Table 96-1) Sinus tachycardia, ventricular conduction delays, ventricular dysrhythmias, asystole Hypotension	Serum levels not helpful in management	Intermittent IV boluses of $NaHCO_3$ (1 mEq/kg) to narrow QRS to <100 msec; infusion of $NaHCO_3$ is less effective; maintain arterial pH at 7.5 because alkalemia and sodium ions can improve cardiovascular performance Contraindicated drugs: types IA and IC antiarrhythmic agents, physostigmine, flumazenil
Ethylene glycol, methanol (e.g., antifreeze, window cleaners, camping stove fuels)[12]	Ethylene glycol: toxic metabolites (glycolate and oxalate) produce cytotoxicity in CNS, kidneys, lungs, heart, liver, muscles; metabolic acidosis is due to glycolate accumulation; oxalate complexes with calcium, so hypocalcemia can develop Methanol: metabolized to formic acid, which is responsible for metabolic acidosis and inhibition of cytochrome aa_3; target organs include retina, optic nerve, CNS	Ethylene glycol: CNS depression, cerebral edema, seizures, anion gap metabolic acidosis, renal failure with acute tubular necrosis, pulmonary edema, myositis Methanol: nausea, vomiting; cerebral edema, hemorrhage, infarcts; necrosis of thalamus and putamen; anion gap metabolic acidosis; visual disturbances, papilledema, hyperemic optic disc, nonreactive pupils	Serum ethylene glycol and methanol levels; levels may be low or undetectable if significant metabolism has occurred Osmolar gap must be interpreted with caution, but a very high value (>50) more likely indicates the presence of a toxic alcohol Ethylene glycol: serum calcium, creatinine, BUN levels; examine urine for calcium oxalate crystals; false hyperlactatemia occurs with certain analyzers using L-lactate oxidase, which cross-reacts with glycolic and glyoxylic acid metabolites	For both: fomepizole[13] (inhibits alcohol dehydrogenase and blocks formation of toxic metabolites), 15 mg/kg IV loading dose, then 10 mg/kg IV every 12 hours for four doses during the next 48 hours, then 15 mg/kg for subsequent doses; interval dosing is q12h (q4h during hemodialysis, with dosing interval adjustments at start and finish); continue until ethylene glycol or methanol is no longer detectable Treatment with ethanol is no longer recommended Hemodialysis: initiate if level is ≥25 mg/dL or metabolic acidosis with end-organ toxicity; continue until acidosis resolves and serum level of ethylene glycol or methanol is undetectable (if available) Monitor for cerebral edema with possible herniation Ethylene glycol: IV calcium for symptomatic hypocalcemia Methanol: folic acid 1-2 mg/kg (50-75 mg) IV q4h × 24 h; extra dose at completion of hemodialysis; continue until methanol not detectable and acidosis cleared
γ-Hydroxybutyrate (GHB) and its precursors (γ-butyrolactone and 1,4-butanediol)	Agonist effect on CNS GHB receptors; indirect action with opioid receptors (may increase proenkephalins); metabolized to GABA, interacts with $GABA_B$ receptors; decreases dopamine release	CNS: rapid loss of consciousness, myoclonus/seizure, with recovery typical within 2-4 hours Respiratory depression; bradycardia; nausea, vomiting	No specific tests for acute management. Forensic testing available	Supportive care, including respiratory support as needed Withdrawal resembles sedative-hypnotic withdrawal and can be treated with benzodiazepines or phenobarbital

TABLE 96-3 PATHOPHYSIOLOGY, CLINICAL EFFECTS, AND MANAGEMENT OF SPECIFIC DRUGS AND TOXICANTS—cont'd

DRUG OR TOXICANT	PATHOPHYSIOLOGY	TOXIC EFFECTS	LABORATORY	SPECIFIC THERAPY
Lithium	Decreases brain inositol; alters CNS serotonin, dopamine, and norepinephrine; inhibits adenylate cyclases, including those that mediate vasopressin-induced renal concentration and thyroid function	Chronic toxicity usually more severe than acute toxicity: tremor, hyperreflexia, drowsiness, incoordination, clonus, confusion, ataxia; in severe cases, seizures (rare), coma, death (very rare); recovery may take weeks, and CNS deficits may persist (common) Sinus node dysfunction, QT prolongation, T wave abnormalities, U waves Nephrogenic diabetes insipidus, hypothyroidism, hyperthyroidism, hypercalcemia, pseudotumor cerebri Acute toxicity: nausea, vomiting, diarrhea, and milder neurologic findings	Peak serum levels: Normal dose, 2-3 hours; up to 5 hours for sustained-release lithium Acute overdose: peak may be delayed ≥4-12 hours	Replenish intravascular volume, maintain urinary output at 1-2 mL/kg/hr Consider gastrointestinal decontamination with oral or NG polyethylene glycol electrolyte solution within 1-2 hours after acute overdose of sustained-release drug Hemodialysis[‡] in patients with altered mental status, ataxia, seizures, or coma or in patients with mild symptoms in the setting of acute overdose or renal insufficiency Ineffective or contraindicated therapies include oral activated charcoal, diuretics
Opioids (e.g., opiate [natural]: morphine, codeine; semisynthetic: heroin, oxycodone, hydrocodone; synthetic: methadone, fentanyl and fentanyl analogs such as carfentanil and acetylfentanyl)	Agonist effect at CNS μ, κ, and δ opioid receptors; result is cell hyperpolarization and decreased neurotransmitter release	CNS depression, respiratory depression, miosis (see Table 96-1) Nearly all fatalities due to respiratory depression, highlighting the importance of assessing and managing based on oxygenation and ventilation Seizure risk with tramadol, meperidine QTc prolongation and torsades de pointes with methadone	Rapid urine drug screens detect morphine, poorly detect semisynthetic opioids, and do not detect synthetic opioids at all; some interferents/irrelevants (see Table 96-4)	Ventilate and oxygenate IV naloxone, 0.04 mg initial dose and titrate every 2-3 minutes in patients with likely opioid dependence; in patients known to be naïve, start 0.4 mg; repeat in frequent, escalating doses up to 10 mg if no response Continuous infusion for recurrent symptoms or sustained-release opioid ingestion; give 50% of dose that produces desired effect 15 minutes after initial effect is obtained, then infuse two thirds of this dose every hour; infusion rate can be increased or decreased to maintain normal ventilation and to avoid withdrawal symptoms Contraindicated therapies: naltrexone should not be used for acute opioid reversal Intranasal naloxone (2-4 mg) can be given if IM/IV not possible
Organophosphorus compounds and carbamates (e.g., diazinon, mevinphos, fenthion, aldicarb); nerve agents (e.g., sarin); medicinals (pyridostigmine for myasthenia gravis and donepezil for Alzheimer disease)	Inhibits acetylcholinesterase, resulting in excessive acetylcholine stimulation of nicotinic and muscarinic receptors in autonomic and somatic motor nervous systems and CNS	Nicotinic-mediated effects: tachycardia, mydriasis, hypertension, delirium, coma, seizures, muscle weakness, fasciculations Muscarinic-mediated effects: salivation, lacrimation, urination, vomiting, defecation, miosis, bronchorrhea, bronchospasm, bradycardia Muscarinic or nicotinic effects may be mixed and unpredictable in an individual patient	Plasma (butyrylcholinesterase) or RBC (acetylcholinesterase) activity <50% of normal (see Table 96-6) Clinical recovery occurs before plasma cholinesterase levels normalize	Atropine, 1-2 mg by initial IV bolus; double the dose every 5 minutes (2 mg, 4 mg, 8 mg, 16 mg, and so on) until drying of bronchial secretions and adequate oxygenation is achieved or progress ceases; continuous infusion at 10-20% of total stabilizing dose per hour; stop infusion when patient develops concerning signs or symptoms of anticholinergic toxidrome (see Table 96-1); restart infusion at lower rate when signs or symptoms abate Pralidoxime chloride 30 mg/kg (maximum 2 g) IV over 30 minutes, then 8-10 mg/kg/hr (maximum 650 mg/hr) continuous infusion; administer as soon as possible after poisoning; continue 12-24 hours after atropine no longer required and symptoms resolve[§] Benzodiazepines for agitation or seizures Magnesium sulfate (4 g IV over 30minutes upon ICU admission) can decrease the need for atropine, the need for intubation, and the length of ICU stay[A1] Treatment not generally needed for overdose of Alzheimer medications

TABLE 96-3 PATHOPHYSIOLOGY, CLINICAL EFFECTS, AND MANAGEMENT OF SPECIFIC DRUGS AND TOXICANTS—cont'd

DRUG OR TOXICANT	PATHOPHYSIOLOGY	TOXIC EFFECTS	LABORATORY	SPECIFIC THERAPY
Salicylates[14]	Inhibit cyclooxygenase; decrease formation of prostaglandins and thromboxane A_2; stimulate CNS medullary respiratory center and chemoreceptor trigger zone; impair platelet function; disrupt carbohydrate metabolism; uncouple oxidative phosphorylation; increase vascular permeability	Acute toxicity Mild: nausea, vomiting, diaphoresis, tinnitus, decreased hearing, hyperpnea, tachypnea Moderate-severe: confusion, delirium, coma, seizures, hyperthermia, ARDS; death can occur within hours of overdose Chronic toxicity: same as acute, but may not have diaphoresis or vomiting Consider diagnosis in patients with new-onset confusion, anion gap metabolic acidosis, or acute lung injury	Serum salicylate level: acute: toxic ≥30 mg/dL; level ≥100 mg/dL indicates life-threatening toxicity with possible sudden, rapid clinical deterioration; in chronic toxicity, levels may be minimally elevated (>30 mg/dL), and clinical evaluation is more reliable for gauging degree of toxicity Arterial blood gases: respiratory alkalosis with metabolic acidosis Anion gap metabolic acidosis Prolonged PT and PTT, ketonuria, ketonemia	Multidose activated charcoal q2-3h in acute overdose Frequent monitoring of salicylate level and acid-base status Alkalinization of serum and urine with IV $NaHCO_3$ Hemodialysis with progressive clinical findings, particularly neurologic, hyperthermia, renal failure, ARDS, with any moderately elevated salicylate level or salicylate level >100 even with minor clinical findings
SSRIs/SRIs	Inhibit re-uptake of serotonin SRIs have additional effects (e.g., duloxetine inhibits norepinephrine re-uptake, nefazodone inhibits serotonergic 5-HT_2 receptors, trazodone inhibits peripheral α-adrenergic receptors, venlafaxine inhibits norepinephrine and dopamine re-uptake)	Vomiting, blurred vision, CNS depression, tachycardia Seizures and coma rare except with bupropion Torsades de pointes reported with citalopram Serotonin syndrome: clonus, agitation, tremor, diaphoresis, hyperreflexia; hyperthermia and hypertonicity in severe cases	No specific tests If serotonin syndrome suspected: electrolytes, BUN, glucose, liver enzymes, coagulation panel, blood gases, chest radiograph	Respiratory support as needed Benzodiazepines for agitation or seizures Serotonin syndrome: consider cyproheptadine, 4-12 mg PO initial dose, then 2 mg PO q2h (to a maximum of 32 mg/day) until symptoms resolve Critical therapies for hyperthermia, rhabdomyolysis, DIC, ARDS, renal and hepatic dysfunction, torsades de pointes; dantrolene not indicated

*A nomogram to evaluate the potential toxicity of levels drawn more than 4 hours after ingestion is available at: https://en.wikipedia.org/wiki/Rumack–Matthew_nomogram.

†Intravenous *N*-acetylcysteine (NAC) has generally replaced oral NAC for the majority of cases, largely because of convenience, not efficacy. The full 21-hour course of intravenous NAC should be administered in most situations in which it is used. Oral NAC, which remains an acceptable alternative, can be discontinued in patients with uncomplicated disease after a loading dose plus six maintenance doses if hepatic aminotransferase levels are normal and acetaminophen is not detected; otherwise, the full regimen should be administered.

‡Continue hemodialysis until the serum lithium level is less than 1 mEq/L. Recheck the level 4 to 8 hours after dialysis, and restart hemodialysis if the level rebounds significantly or if clinical findings of lithium toxicity are present. Repeat this cycle until the serum lithium level remains low or the patient remains clinically well.

§Randomized, placebo-controlled trials of pralidoxime in acute organophosphorus poisoning have not found a significant difference in mortality rates or need for intubation.

aPTT = activated partial thromboplastin time; ARDS = acute respiratory distress syndrome; AV = atrioventricular; BP = blood pressure; BUN = blood urea nitrogen; CNS = central nervous system; DIC = disseminated intravascular coagulation; DOB = 4-bromo-2,5-dimethoxyamphetamine; ECG = electrocardiogram; GABA = γ-aminobutyric acid; HR = heart rate; IABP = intra-aortic balloon counterpulsation; ICU = intensive care unit; INR = international normalized ratio; IV = intravenous, MDMA = 3,4-methylenedioxymethamphetamine, also known as ecstasy or Molly; Na^+,K^+-ATPase = sodium, potassium adenosine triphosphatase; NAC = *N*-acetylcysteine; NAPQI = *N*-acetyl-*p*-benzoquinone imine; NG = nasogastric; NMDA = *N*-methyl-D-aspartate; PMA = paramethoxyamphetamine; PO = orally; PT = prothrombin time; PTT = partial thromboplastin time; QT = QT interval from an electrocardiogram, QTc = rate-corrected QT interval from an electrocardiogram; RBC = red blood cell; RUQ = right upper quadrant (abdomen); SIADH = syndrome of inappropriate antidiuretic secretion; SRIs = serotonin re-uptake inhibitors; SSRIs = selective serotonin re-uptake inhibitors.

TABLE 96-4 QUALITATIVE URINE DRUG SCREENS: CAUSES OF ERRONEOUS RESULTS*

DRUG/TOXICANT	INTERFERENTS/CROSS-REACTIONS†	COMMENTS
Amphetamines	Amantadine, bupropion, chlorpromazine, ephedrine, pseudoephedrine, desoxyephedrine, ephedra alkaloids (from *Ephedra* sp), mexiletine, phenylephrine, phenylpropanolamine, selegiline, trazodone	Many false-positives from medicinal sympathomimetics or true positives from prescribed stimulants; nasal inhaler (desoxyephedrine) and selegiline cause positive GC-MS findings; chiral confirmation is required; newer immunoassays have reduced false rates but also lower sensitivity for the class of amphetamines
Benzodiazepines	Oxaprozin, sertraline	Most assays directed against oxazepam; poor detection of benzodiazepines without the oxazepam metabolite (e.g., alprazolam, lorazepam, triazolam)
Cocaine	Coca leaf teas (clinical false-positive; still considered illicit use)	Few analytical false-positives; urine is reliable for detecting true positives
Opioids	Poppy seeds (contain morphine)	Assay directed against morphine; poorly detects semisynthetic opioids and does not detect synthetic opioids (e.g., fentanyl, meperidine, methadone, propoxyphene, oxycodone, buprenorphine)
Phencyclidine	Dextromethorphan, diphenhydramine, doxylamine, ibuprofen, ketamine, tramadol, venlafaxine	Can be used, although not reliably, to identify dextromethorphan or ketamine
Tetrahydrocannabinol	Dronabinol, efavirenz, proton pump inhibitors	Positive result is seldom clinically relevant and does not indicate recent use; synthetic cannabinomimetics (e.g., spice, K2) are not reliably detected
Tricyclic antidepressants	Carbamazepine, cyclobenzaprine, cyproheptadine, diphenhydramine, phenothiazines, quetiapine	

*Advances in drug screening and variability in immunoassay results should be considered by the clinician when interpreting qualitative drug screening results. There are many marketed assays, so consultation with the testing laboratory is advised. Positive screening results are considered presumptive and should be verified by GC-MS or another advanced analytical methodology.

†Cross-reactants are agents causing true-positive but clinically irrelevant results on laboratory screening tests; they vary, depending on the screening method.

GC-MS = gas chromatography–mass spectrometry.

TABLE 96-5 CLINICALLY IMPORTANT QUANTITATIVE DRUG LEVELS

DRUG OR TOXICANT	LEVELS: THERAPEUTIC	LEVELS: TOXIC*
SOURCE: BLOOD OR SERUM		
Acetaminophen†	10-30 µg/mL	≥150 µg/mL 4 hours after ingestion‡
Carbamazepine	4-12 µg/mL	>15 µg/mL
Carboxyhemoglobin	Nonsmoker: 0.5-1.5% Smoker: 4-9%	>20%§
Cholinesterase|		
Serum (butyrylcholinesterase)	3100-6500 U/L	<50% of normal value
Red blood cell (acetylcholinesterase)	26.7-49.2 U/g of hemoglobin	<50% of normal value
Digoxin (≥6 hours after oral dose for long-term therapy)	0.8-2.0 ng/mL¶	>2.0 ng/mL
Ethanol	None measured	>80 mg/dL**
Ethylene glycol	None measured	>25 mg/dL
Iron	50-175 µg/dL	>350 g/dL
Lead	<5 µg/dL	>25 µg /dL
Lithium	0.6-1.2 mEq/L	>1.2 mEq/L††
Methanol	None measured	>25 mg/dL
Methemoglobin	1-2%	>15%
Phenobarbital	15-40 µg/mL	>40 g/mL
Phenytoin	10-20 µg/mL	>20 g/mL
Salicylate	≤30 mg/dL	>30 mg/dL
Theophylline	8-20 µg/mL	>20 g/mL
Valproic acid	50-100 µg/mL	>100 g/mL
	NORMAL	**TOXIC***
SOURCE: URINE		
Arsenic	<50 µg/day	>100 g/24-hr urine††
Mercury	<20 µg/L	>20 g/L††
Thallium	<5.0 µg/L	>200 g/L††

*The "toxic" level is provided for perspective. For many toxicants, simply being above this value does not imply a specific need for therapy or a necessarily poor prognosis. It does, however, generally suggest a need for additional evaluation, observation, or monitoring. Similarly, depending on the clinical context, levels below the "toxic" range may still be consequential.

†False-positive levels of 16 to 28 µg/mL have been reported in patients with bilirubin levels greater than 17 mg/dL.

‡Levels drawn more than 4 hours after ingestion should be plotted on the nomogram provided by Rumack and Matthew (Rumack BH, Matthew H. Acetaminophen poisoning and toxicity. *Pediatrics*. 1975;55:871-876) to assess the potential for toxicity.

§Lower levels may be toxic in pregnant patients and in those with prolonged exposure to carbon monoxide.

|Consult a reference laboratory for normal values; results are assay dependent.

¶Some patients may require levels above the therapeutic range to control symptoms.

**The value of 80 mg/dL (0.08 g/dL) for ethanol is the statutory limit for operating a motor vehicle, but not for other activities. Consequential clinical effects other than inebriation are uncommon with concentrations below 200 mg/dL, even in ethanol-naïve patients.

††Lower values may indicate toxicity if appropriate clinical findings are present. For mercury and arsenic, both inorganic and organic levels should be measured when total levels are elevated.

second method, such as gas chromatography–mass spectrometry. The type of drug use in a population should be considered in determining the drugs to be screened to decrease the incidence of false-positive results. A test with 99% specificity for a drug with a prevalence of 0.1% in a population would produce 10 false-positive results for every true-positive result. Clinically irrelevant true-positive findings also occur, such as when poppy seeds produce a positive opiate assay result. Failure to consider these limitations of drug screens can result in misdiagnosis.

For a limited number of drugs and toxicants, levels in blood or urine are useful for diagnosis, therapy, or monitoring (Table 96-5). Threshold levels of certain toxicants indicate the need for specific therapies: acetaminophen (*N*-acetylcysteine), ethylene glycol (fomepizole and hemodialysis), iron (deferoxamine), methanol (fomepizole and hemodialysis), methemoglobin (methylene blue), and salicylates (urine alkalinization and hemodialysis). In chronic poisoning with some drugs, such as salicylates or theophylline, these therapies may be indicated at lower drug levels. In general, any end-organ toxicity that is evident or anticipated (on the basis of the toxicant, amount ingested, and time required to produce toxic effects) is more important than a specific level in determining the need for treatment.

Occult acetaminophen ingestion with toxic serum levels occurs in 0.3 to 1.9% of intentional ingestions. Given that these patients may be asymptomatic until hepatotoxicity develops and that administration of an antidote can prevent this hepatotoxicity, the current recommendation is to test the serum for acetaminophen in all patients with intentional self-harm ingestions.

Other Blood Tests

Anion gap metabolic acidosis resulting from primary lactic acidosis can be caused by cyanide, hydrogen sulfide, iron, isoniazid, metformin, nucleoside reverse transcriptase inhibitors, phenformin, sodium azide, and, rarely, acetaminophen with high serum levels. Anion gap metabolic acidosis not related to lactic acidosis occurs with diethylene glycol, ethylene glycol, nonsteroidal anti-inflammatory drugs, methanol, salicylates, and toluene. In poisonings resulting from ibuprofen, methanol, propylene glycol, and salicylates, lactic acid can also be produced, but the level is insufficient to account for the anion gap. Anion gap metabolic acidosis can also develop in patients with ongoing agitation, hyperthermia, and muscle rigidity, such as in neuroleptic malignant syndrome (Chapter 402), or in some cases of rhabdomyolysis (Chapter 99) secondary to toxicants such as doxylamine, phencyclidine, strychnine, cocaine, and amphetamines. Elevated serum creatinine and blood urea nitrogen levels indicative of declining renal function may be seen with numerous toxicants. Direct renal toxicity occurs with acetaminophen, aminoglycosides, cadmium, Chinese weight-loss botanicals containing *Stephania tetrandra* or *Magnolia officinalis*, chromium, *Crotalus durissus* venom, diethylene glycol, diquat, ethylene glycol, fluorinated anesthetics, gold, heroin, lithium (diabetes insipidus), mercury salts, mushrooms (*Amanita smithiana* and *Cortinarius* sp), paraquat, radiocontrast agents, solvents (e.g., carbon tetrachloride, trichloroethylene, tetrachloroethylene, toluene), and sulfonamides. Agents that decrease glomerular perfusion by reducing renal blood flow include amphotericin, angiotensin-converting enzyme inhibitors, angiotensin receptor blockers, cocaine,

cyclosporine, mannitol (excessive chronic doses), methotrexate, and nonsteroidal anti-inflammatory drugs.

Imaging

A computed tomographic scan of the head can detect life-threatening cerebral edema secondary to toxicant-induced hepatic failure, ethylene glycol, and methanol. It also detects intracranial bleeding caused by anticoagulants, scorpion venom, and sympathomimetics (e.g., amphetamines, cocaine, phenylpropanolamine). An abdominal radiograph can reveal radiopaque ferrous sulfate tablets, drug-filled packets in illicit drug smugglers (body packers), or metals such as arsenic, lead, mercury, and thallium.

Diagnostic Syndromes

Given the myriad combinations of signs, symptoms, and laboratory findings, making the correct diagnosis in a noncommunicative patient can be daunting. A thorough history from bystanders, friends, and prehospital medical personnel may yield crucial information. In addition, the diagnostic possibilities can be narrowed by findings that can narrow the differential diagnosis with modest certainty. For example, consider a patient with sudden loss of consciousness, anion gap metabolic acidosis, and bradycardia without hypoxemia. Among the relevant possible causes from the list of toxicants that cause an anion gap metabolic acidosis (see earlier) along with sudden loss of consciousness are hydrogen sulfide, cyanide, and sodium azide.

TREATMENT

Initial Stabilization

Intubation and Respiratory Support

Appropriate airway management should be instituted to correct hypoxemia and respiratory acidosis and to protect against pulmonary aspiration (Fig. 96-2); intubation should be considered if the patient has depressed consciousness and a decreased gag reflex.[15] Rapid-sequence intubation facilitates airway management. Anatomic difficulties should be anticipated in patients with caustic ingestions (e.g., hypopharyngeal burns that may perforate); angioedema caused by angiotensin-converting enzyme inhibitor therapy or envenomation by some rattlesnakes, such as the canebrake (*Crotalus horridus atricaudatus*) and eastern diamondback (*Crotalus adamanteus;* Chapter 98); and swelling secondary to direct tissue injury (e.g., huffing compressed hydrocarbons, smoking crack) or secondary to anaphylactoid and anaphylactic reactions. Endotracheal intubation by flexible fiberoptic nasopharyngoscopy may be indicated in these cases. Hypoxemia can occur with toxicants that produce CNS depression, such as opioids, antidepressants, barbiturates, sedative-hypnotics, and central α_2-adrenergic receptor agonists (clonidine), or agents causing peripheral neuromuscular impairment, such as nicotine, organophosphorus compounds, tetrodotoxin (puffer fish, blue-ringed octopus), botulinum, or envenomation from elapids (coral snake), Mojave rattlesnakes, or certain coelenterates (box jellyfish; Chapter 98).

Respiratory acidosis can rapidly worsen the toxicities of cyclic antidepressants and salicylates; sedation of these patients should be accompanied by immediate airway placement and ventilatory support to match the patient's intrinsic minute ventilation. Intoxicated patients may have an increased risk for pulmonary aspiration because of concomitant CNS depression, attenuated airway reflexes, full stomachs, and delayed gastric emptying.

Succinylcholine can cause prolonged paralysis in patients with organophosphorus poisoning and can exacerbate hyperkalemia from cardioactive steroids (e.g., digoxin), hydrofluoric acid, or rhabdomyolysis (Chapter 99). Rhabdomyolysis has been reported with adrenergic agents, doxylamine, phencyclidine, heroin, carbon monoxide, *Tricholoma equestre* mushrooms, and envenomation by crotaline snakes, scorpions, or widow spiders (*Latrodectus* sp); short-acting nondepolarizing agents, such as vecuronium and rocuronium, are preferable in these cases.

Advanced Life Support

Standard emergency cardiovascular care algorithms (Chapter 50) must be modified for effects caused by specific poisons. Atropine often does not reverse bradycardia secondary to β-adrenergic receptor antagonists, L-type calcium-channel antagonists, or cardioactive steroids, and it may actually impair the ability to perform adequate gastrointestinal decontamination. In these cases, more specific therapy with intravenous calcium (calcium-channel antagonists), high doses of glucagon (β-adrenergic receptor antagonists, calcium-channel antagonists), or digoxin-specific Fab antibody (cardiac glycosides) is indicated. High-dose insulin-glucose therapy can successfully reverse myocardial depression and conduction abnormalities in humans poisoned with β-adrenergic receptor antagonists and calcium-channel antagonists (Table 96-6). Intravenous sodium bicarbonate may reverse cardiac conduction delays caused by antiarrhythmic drugs with sodium-channel blockade recovery rates of greater than 1 second (Vaughn-Williams classification IA and IC), cocaine, cyclic antidepressants, diphenhydramine, and quinine. β-Adrenergic receptor antagonists are relatively contraindicated in patients with acute cocaine-induced myocardial ischemia because they can result in unopposed α-adrenergic–mediated vasoconstriction, but phentolamine can reverse the agonistic effects of cocaine on α-adrenergic receptors (see Table 96-6). Benzodiazepines can reverse the significant sinus tachycardia seen with sympathomimetic agents by reducing autonomic outflow from the CNS. Calcium may also be life-saving in systemic hydrofluoric acid poisoning and severe hypermagnesemia, and it is indicated for symptomatic hypocalcemia caused by ethylene glycol toxicity (see Table 96-6). Drug-induced hypertension may be transitory; nitroprusside, phentolamine, or labetalol should be used if treatment is clinically indicated. (See Table 96-6.) Conversely, vasopressor infusions may be indicated in drug-induced hypotension (Chapter 92). In patients with toxicant-induced circulatory collapse refractory to maximal therapy, intravenous lipid emulsion therapy should be administered to those poisoned by lipophilic toxicants (e.g., calcium-channel blockers), and circulatory assist devices may support the patient until sufficient toxicant is eliminated (see Table 96-6 for dosing details) (Chapter 93).

Decontamination

Activated Charcoal

Activated charcoal consists of pyrolysis products that have been specially cleaned to produce an internal pore structure to which substances can adsorb, thereby limiting their systemic absorption. Single-dose activated charcoal without prior gastric emptying has been the preferred method of treatment for the ingestion of substances that have the potential to cause moderate to life-threatening toxicity and are known to adsorb to activated charcoal. The decision to administer activated charcoal should be based on a risk/benefit assessment that includes nature of the exposure, clinical effects displayed during evaluation, and abilities of the medical facility and staff. For patients likely to have a good outcome without decontamination, charcoal administration introduces unnecessary inconvenience and risk. Its use is justified in patients who present early (1 to 2 hours) after exposures to a large amount of a concerning toxin that is likely to be adsorbed to charcoal or to an unknown toxin that has presented with a concerning clinical picture. However, the documented efficacy of activated charcoal for reducing toxicant blood levels has not translated into a reduction in mortality.[A2]

The oral dose is approximately 1 g/kg body weight, with a maximum single dose of 100 g. Activated charcoal can be administered with antiemetic drugs or given through a nasogastric tube, when necessary. Efficacy in preventing toxicant absorption declines with time, so activated charcoal should be given as soon as possible after ingestion.

Activated charcoal should not be used in patients at risk for aspiration until the airway is secure to minimize aspiration; the patient's head should also be elevated unless it is contraindicated. Activated charcoal is contraindicated in patients with a perforated bowel, functional or mechanical bowel obstruction, ingestion of a pure aliphatic hydrocarbon such as gasoline or kerosene (no benefit and increased risk for aspiration), and ingestion of caustic acid and alkali (no benefit and obscures endoscopy). Certain agents, such as lithium, iron, and metal salts and ethanol, do not adsorb significantly to activated charcoal, but its use is not precluded if the patient has ingested other toxicants that do adsorb to activated charcoal. Pulmonary aspiration and bowel obstruction from inspissated activated charcoal are the most common complications; both occur more frequently when multidose activated charcoal is administered, but they can be avoided by withholding treatment in patients who have suboptimal bowel function or decreased fecal elimination.

Gastric Emptying

Two methods of gastric emptying, syrup of ipecac and orogastric lavage through a large-bore tube, are no longer routinely used; both are relatively ineffective therapies that potentially increase the risk for aspiration. Syrup of ipecac is no longer recommended, and no well-designed study has documented any benefit of gastric lavage compared with the use of activated charcoal alone. Nevertheless, gastric emptying may be of benefit in patients who have ingested toxicants that do not adsorb to activated charcoal and are known to produce significant morbidity or for which aggressive decontamination may offer the best chance for survival (e.g., colchicine, sodium azide, sodium fluoroacetate). Removal of a liquid toxicant, such as ethylene glycol, may be accomplished by simple aspiration of gastric contents (without lavage) through a nasogastric tube. Contraindications to gastric emptying include those for activated charcoal, a bleeding diathesis, and the ingestion of sharp objects. Placement of a cuffed endotracheal tube before gastric lavage may be necessary to protect the airway in patients who have a decreased level of consciousness and impaired gag reflex, but it is not required in all cases. Major complications of gastric emptying include pulmonary aspiration, esophageal tears and perforations, and laryngospasm (with lavage).

Whole Bowel Irrigation

Whole bowel irrigation with a nonabsorbable polyethylene glycol solution has been recommended for iron and sustained-release medications, for agents not

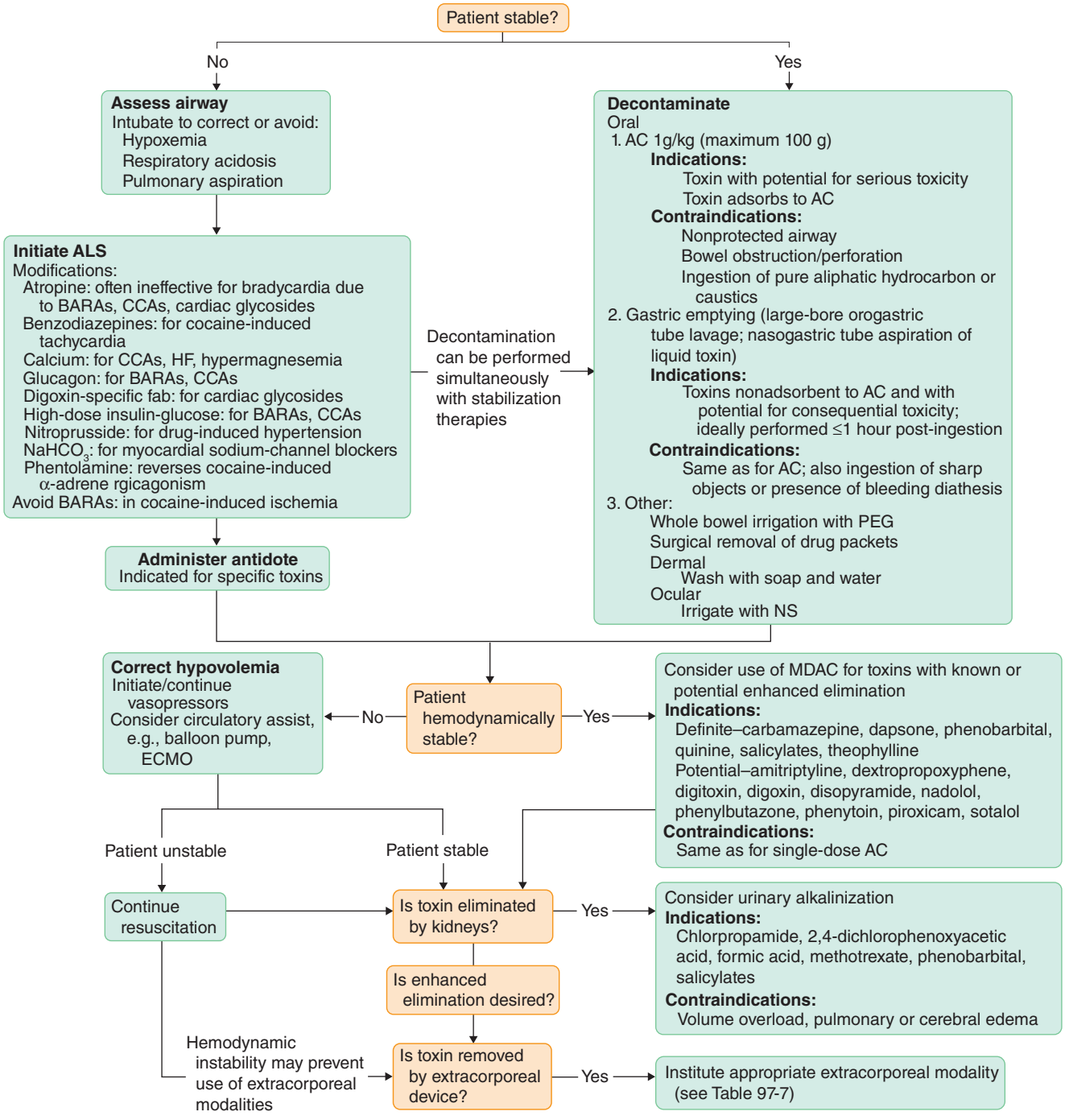

FIGURE 96-2. Algorithm for the management of acute poisoning. AC = activated charcoal; ALS = advanced life support; BARAs = β-adrenergic receptor antagonists; CCAs = L-type calcium-channel antagonists; ECMO = extracorporeal membrane oxygenation; HF = hydrofluoric acid; MDAC = multidose activated charcoal; NS = 0.9% saline solution; PEG = nonabsorbable polyethylene glycol solution.

adsorbed to activated charcoal, and for body packers (smugglers who swallow packets of illicit drugs, usually heroin or cocaine). The most common complication is vomiting, and whole bowel irrigation is contraindicated in patients with bowel perforation, obstruction, hemorrhage, or hemodynamic or respiratory instability. The initial recommended dose is 500 mL/hour given orally or by nasogastric tube, with titration to 2000 mL/hour as tolerated; treatment continues until the rectal effluent clears. Rarely, surgery may be necessary to remove packets in smugglers who have symptoms of cocaine toxicity or are obstructed; heroin toxicity is usually adequately managed with naloxone. Endoscopic removal of cocaine packets should never be attempted because of the risk of packet rupture.

Antidotes

Few toxicants have specific therapies (see Table 96-6). Although antidotes may be essential in treating patients exposed to certain toxicants, their use does not preclude the need for ongoing supportive care and, in some cases, extracorporeal elimination.

Enhanced Elimination

Methods to accelerate the elimination of toxicants or drugs from the body include multiple doses of activated charcoal, urinary alkalinization, and extracorporeal removal. Another method, using the oral ion exchange resins sodium polystyrene sulfonate and cholestyramine, has experimentally enhanced the elimination of lithium, digoxin, digitoxin, and organochlorines but has limited clinical usefulness.

Multiple Doses of Oral Activated Charcoal

The rationale for administering multiple doses of oral activated charcoal includes the adsorption of any toxic agent remaining in the gastrointestinal tract (e.g., sustained-release drugs or drugs that retard their absorption, such as anticholinergics), interference with the enterohepatic and enteroenteric recirculation of toxicants, and enhancement of the elimination of drugs with a long half-life, a volume of distribution less than 1 L/kg body weight, and low protein binding (termed gastrointestinal dialysis). The existing evidence shows enhanced elimination of carbamazepine, dapsone, phenobarbital, quinine, salicylates, and

theophylline, but multiple doses of activated charcoal may also be effective for amitriptyline, dextropropoxyphene, digitoxin, digoxin, disopyramide, nadolol, phenytoin, piroxicam, and sotalol. Whether enhanced elimination provided by repeated doses of activated charcoal translates into decreased morbidity and mortality has not been adequately examined in large controlled clinical trials, except for yellow oleander and organophosphate ingestion, for which it has shown no benefit. The usual recommendations are an average dose of 12.5 g of activated charcoal (after the initial dose of 1 g/kg body weight, with a maximum single dose of 100 g) administered every 4 to 6 hours after the previous dose. The contraindications to single-dose activated charcoal also apply to multidose activated charcoal. Reported complications include pulmonary aspiration, bowel obstruction from inspissated charcoal, and fluid and electrolyte imbalance from multiple doses of a simultaneously administered cathartic.

Urinary Alkalinization

Alkalinization of the urine, which increases the renal elimination of weak acids, is used primarily to enhance the elimination of salicylates, but the elimination of chlorpropamide, 2,4-dichlorophenoxyacetic acid, formic acid, methotrexate, and phenobarbital may be increased with this method. Urinary alkalinization is accomplished by an intravenous bolus of 1 to 2 mEq of sodium bicarbonate per kilogram body weight, followed by three ampules (150 mL) of sodium bicarbonate (44 mEq/50 mL) in 850 mL of 5% dextrose in water infused at two to three times the normal maintenance fluid rate. Urinary pH should be checked hourly, and the infusion should be adjusted to maintain a urine pH of 7.5 to 8.0. Potassium should be administered simultaneously to avoid hypokalemia, which prevents urinary alkalinization because the distal tubule excretes hydrogen ion in exchange for potassium (Chapters 103 and 104). Serum pH should be monitored and kept below 7.55 to avoid excessive alkalemia. Contraindications to this therapy include volume overload and cerebral or pulmonary edema. Urinary acidification is not recommended to enhance the elimination of weak bases, such as amphetamines, because of the danger of precipitating tubular myoglobin in patients with rhabdomyolysis.

Extracorporeal Removal

Extracorporeal techniques enhance the elimination of a few drugs and toxicants, especially those that exist in the blood and are otherwise poorly eliminated.[17,18] Such drugs generally have single-compartment kinetics, a volume of distribution less than 1 L/kg, and endogenous clearance of less than 4 mL/minute/kg (Table 96-7). For hemodialysis, the toxicant must be water soluble, have a small molecular weight, and exhibit low protein binding. For continuous renal replacement therapy, the toxicant must have a molecular weight less than the permeability limit of the filter membrane. As a group, these latter forms of elimination are slow and likely to be of limited benefit to most patients with acute poisoning. Rarely, extracorporeal removal has been used for aminoglycosides, atenolol, bromide, carbamazepine, diethylene glycol, isopropanol, magnesium, metformin, methotrexate, *N*-acetylprocainamide, phenobarbital, procainamide, sotalol, and trichloroethanol (chloral hydrate).

TABLE 96-6 ANTIDOTES AND INDICATIONS FOR USE[§]

ANTIDOTE	INDICATION FOR USE	DOSE*	TREATMENT END POINT	COMMENTS
Antivenom, *Crotalidae* (Fab)[†¶A3]	Crotaline snake (e.g., rattlesnakes, copperhead; see Chapter 98)	Variable (several products available); initial dose followed by repeated doses as needed	Halt in progression of circumferential and proximal swelling Resolving systemic effects	Better safety profile than historical equine-derived antivenom Repetitive dosing indicated for recurrent soft tissue swelling Less effective at correcting hematologic (i.e., coagulation and platelet) disorders
Antivenom, *Latrodectus* (equine)[†,¶]	Black widow spider (*Latrodectus* sp)	1 vial diluted in 50-100 mL NS, infused over 1 hour; can repeat	Resolution of symptoms, vital signs normal	Dilution and slow infusion rate are **critical** to avoid anaphylactoid reaction Indications include severe pain unresponsive to opioids and severe hypertension Serum sickness can occur IV calcium is ineffective
Atropine	Carbamates Nerve agents Organophosphorus compounds	2 mg IV; double the dose every 5 minutes to achieve atropinization and hemodynamic stability; then start continuous infusion of 10-20% of total stabilizing dose per hour	Cessation of excessive oral and pulmonary secretions, >80 beats/min, systolic blood pressure >80 mm Hg	Doubling of the dose every 5 minutes (e.g., 2 mg, 4 mg, 8 mg, 16 mg) estimated to achieve atropinization within 30 minutes Stop infusion when patient develops concerning signs or symptoms of anticholinergic toxidrome (see Table 96-1); restart infusion at lower rate when signs or symptoms abate
Calcium salt[‡]	Calcium-channel antagonists	Calcium gluconate 10%, 30 mL (3 g) over 10 minutes; can be given in 1 minute if critically ill Calcium chloride 10%, 10 mL (1 g) over 10 minutes; can be given in 1 minute if critically ill	Reversal of hypotension; may not reverse bradycardia	*All indications:* Monitor ionized calcium levels IV extravasation causes tissue necrosis, especially with calcium chloride Can administer at faster than stated rates for immediate life-threatening conditions (i.e., in 1 minute) Calcium chloride contains three times more elemental calcium than calcium gluconate does
	Hydrofluoric acid	Systemic toxicity: calcium gluconate 10%, 1-3 g (10-30 mL) per dose IV over 10-minute period; repeat as needed every 5-10 minutes Topical toxicity: calcium chloride 10%, 1 g (10 mL) mixed into water-soluble lubricant	Reversal of life-threatening manifestations of hypocalcemia and hyperkalemia Topical: reversal of severe neuropathic pain from dermal exposure	Can dilute and give intra-arterially or IV with a Bier block for extremity exposures and burns Topical: apply to skin under occlusive dressing
	Hyperkalemia (except due to cardiac glycosides)	Calcium gluconate 10%, 1 g (10 mL) per dose IV over 10-minute period; repeat as needed every 5-10 minutes	Reversal of myocardial depression and conduction delays	May precipitate ventricular dysrhythmias
	Hypermagnesemia	Calcium gluconate 10%, 1-2 g (10-20 mL) per dose IV over 10-minute period; repeat as needed every 5-10 minutes	Reversal of respiratory depression, hypotension, and cardiac conduction blocks	Simultaneous therapies to increase magnesium elimination should be instituted
	Hypocalcemia (e.g., ethylene glycol)	Calcium gluconate 10%, 0.5-1.0 g (5-10 mL) per dose over 10-minute period; repeat as needed every 10 minutes	Reversal of tetany	Correct symptomatic hypocalcemia; avoid excessive administration that may increase production of calcium oxalate crystals in ethylene glycol poisoning

TABLE 96-6 ANTIDOTES AND INDICATIONS FOR USE[§]—cont'd

ANTIDOTE	INDICATION FOR USE	DOSE*	TREATMENT END POINT	COMMENTS
L-Carnitine	Valproate-induced hyperammonemia or hepatotoxicity	100 mg/kg (maximum 6 g) IV over 30 minutes, then 15 mg/kg IV over 30-minute period q4h (maximum 6 g/day)	Treat until clinical improvement occurs	Levocarnitine is active form Adjust dose for end-stage renal disease
Cyanide antidote kit Hydroxocobalamin (preferred) Sodium thiosulfate	Cyanide	Hydroxocobalamin 5 g IV over 5 minutes (15 mL/min); second dose of 5 g if needed; the entire cyanide antidote kit is rarely indicated if hydroxocobalamin is available. Sodium thiosulfate 25%: 50 mL (12.5 g) IV over 10-minute period	Resolution of lactic acidosis and moderate to severe clinical signs and symptoms: seizures, coma, dyspnea, apnea, hypotension, bradycardia	Hydroxocobalamin causes red discoloration of urine and blood, may interfere with laboratory testing for carbon monoxide and lactate Sodium thiosulfate dosing can be repeated (the other components of the "cyanide antidote kit" cause methemoglobinemia and should not be administered to patients with possible carbon monoxide poisoning; e.g., fire exposure)
Deferoxamine	Iron salts	Initiate at 5 mg/kg/hr, titrate to 15 mg/kg/hr IV (maximum 8 g/day) Mild to moderate: administer for 6-12 hours Severe toxicity: administer for 24 hours	Resolution of clinical signs and symptoms Urine may appear rose-colored but is not a reliable marker for iron clearance Laboratory testing is unreliable while antidote is being received	Indications: symptomatic patients with lethargy, severe abdominal pain, hypovolemia, acidosis, shock; any symptomatic patient with peak serum iron level >350 g/dL Rate-related hypotension may occur Prolonged therapy can cause pulmonary toxicity
Digoxin-specific antibody fragments (Fab)	Digoxin Digitalis and related plants (e.g., oleander, lily of the valley) Other cardiac glycosides (e.g., bufadienolides [Bufo toads])	Unknown digoxin dose or serum level acute toxicity—10 vials; chronic toxicity—3-6 vials Digoxin dose known: number of vials = 2 × oral digoxin dose (mg) × 0.8 Digoxin serum level known: number of vials = [serum level (ng/mL) × weight (kg)] ÷ 100 Infuse dose over 30 minutes Plant or toad source of cardioactive steroid; 10-20 vials	Resolution of hyperkalemia, symptomatic bradydysrhythmias, ventricular dysrhythmias, Mobitz II or third-degree heart block	Each vial binds 0.5 mg of digoxin or digitoxin Monitor ECG and potassium levels Digoxin serum levels unreliable after antidote administered unless test is specific for free serum digoxin
Dimercaprol (BAL)	Arsenic salts Lead salts Mercury, elemental and inorganic salts	Inorganic arsenic: 3-5 mg/kg IM q4h for 48 hours and then q12h for 7 to 10 days Lead: 75 mg/m^2 (4 mg/kg) IM q4h for 5 days Inorganic mercury: 5 mg/kg IM, then 2.5 mg/kg IM q12h for 10 days or until patient is clinically improved	Arsenic: 24-hour urinary arsenic <50 µg/L Lead: encephalopathy resolved, blood lead level <100 µg/dL, and succimer therapy can be started Mercury, elemental and inorganic: 24-hour urinary mercury <20 µg/L	Formulated in peanut oil; painful IM injection is painful and is contraindicated in patients with peanut allergy Maximum adult dose is 3 g/day BAL started 4 hours before initiation of concomitant $CaNa_2EDTA$ for lead encephalopathy Dosing not well established for arsenic and elemental or inorganic mercury toxicity; not used for organic mercury poisoning Adverse effects: painful injections, fever, diaphoresis, agitation, headache, salivation, nausea and vomiting, hemolysis in G6PD-deficient patients, chelation of essential metals Check essential metal levels if chelation is prolonged Succimer is replacing BAL for many indications except lead encephalopathy Treatment end points for arsenic and mercury include improving clinical condition
Edetate calcium disodium ($CaNa_2EDTA$)	Lead	1500 mg/m^2/24 hr (maximum 3 g) by continuous infusion	Treat for 5 days, followed by 2-day hiatus; repeat until encephalopathy resolved, lead level <100 µg/dL, and succimer therapy can be started	Use in patients with lead encephalopathy or lead level >100 g/dL Administer BAL 4 hours before initiating $CaNa_2EDTA$ Hydrate patient and establish good urinary output before starting therapy Avoid thrombophlebitis by diluting in NS or D_5W to a concentration ≤0.5% Substitution of Na_2EDTA can cause fatal hypocalcemia

TABLE 96-6 ANTIDOTES AND INDICATIONS FOR USE[§]—cont'd

ANTIDOTE	INDICATION FOR USE	DOSE*	TREATMENT END POINT	COMMENTS
Flumazenil[A4]	Benzodiazepines	0.1 mg/min IV to a total dose of 1 mg Alternative: 0.2 mg IV over 2 min; repeat with 0.3 mg, then 0.5 mg. Total dose remains at 1.0 mg	Reversal of coma	Limit use to reversal of inadequate ventilation in benzodiazepine-toxic patients Acute benzodiazepine withdrawal may occur in patients dependent on benzodiazepines Increases intracranial pressure and risk for seizures in presence of underlying seizure disorder or ingestion of seizure-producing toxicants Monitor for resedation up to 2 hours after last dose
Folinic acid (tetrahydrofolic acid [leucovorin])	Methanol Methotrexate	Methanol intoxication: 50 mg IV q4h Methotrexate overdose: 100 mg/m^2 IV over 15-30 minutes q3-6h; dosing lower when used as "rescue" in chemotherapy	Methanol: methanol undetectable, metabolic acidosis cleared Methotrexate: serum level $<1 \times 10^{-8}$ mol/L	Essential therapy for both toxicants Little concern with excessive dosing when used for methotrexate overdose Methotrexate: large overdoses may require increased dose If indicated, glucarpidase administered 2-4 hours before or after folinic acid
Fomepizole	Ethylene glycol Methanol	Initial dose: 15 mg/kg IV bolus 10 mg/kg IV q12h for four doses (48 hr) All subsequent doses: 15 mg/kg IV q12h When hemodialysis (HD) performed: HD initiation: additional dose if >6 hours since last dose HD ongoing: q4h End of HD (based on time of last dose): <1 hour, no dose until next scheduled dose immediately after HD completion; 1-3 hours, 50% dose; >3 hours, 100% dose	For both: serum level <25 mg/dL and metabolic acidosis resolved	Start immediately if toxic alcohol suspected, without waiting for confirmatory levels Dose amount is not affected by interval timing of doses
Glucagon	β-Adrenergic receptor antagonists Calcium-channel antagonists	Bolus of 3-5 mg IV; can repeat to achieve clinical effect, then infusion of 2-10 mg/hr	Reversal of hypotension and bradycardia; taper infusion	Can precipitate vomiting; be prepared to protect airway Mild hyperglycemia occurs Maximum dosing amounts unknown; bolus doses up to 30 mg reported Duration of effect is 15 minutes; thus, infusion must be started immediately
Hydroxocobalamin	Cyanide	Initial: 5 g IV over 15-minute period Second dose: 5 g IV over 15 minutes to 2 hours; maximum total dose is 10 g Follow each hydroxocobalamin dose with sodium thiosulfate 25%: 50 mL (12.5 g) IV over 10-minute period	Resolution of lactic acidosis and moderate to severe clinical signs and symptoms: seizures, coma, dyspnea, apnea, hypotension, bradycardia	Can be administered IV push if patient is in cardiac arrest Do not give hydroxocobalamin and sodium thiosulfate through the same IV line Adverse effects: red discoloration of plasma, urine, mucous membranes, skin; transient hypertension Interference with laboratory colorimetric assays: Levels increased: bilirubin; creatinine; glucose; hemoglobin; magnesium; co-oximetry total Hb, COHb%, MetHb% Levels decreased: AST, ALT, creatinine, co-oximetry O_2Hb%
Hyperbaric oxygen (HBO)	Carbon monoxide COHb >25% independent of symptoms, 15% if pregnant Serious symptoms or findings with any elevated COHb concentration	3.0 atm pressure for 60 minutes (25 minutes O_2, 5 minutes air, 25 minutes O_2, 5 minutes air), then 2.0 atm for 65 minutes (30 minutes O_2, 5 minutes air, 30 minutes O_2), then "surface" to 1.0 atm	One treatment Repeated treatment controversial	Carbon monoxide: treatment protocols may vary HBO indicated for loss of consciousness; seizures; cerebellar dysfunction; impaired cognition; headache, nausea/vomiting persisting after 4 hours of O_2 therapy regardless of repeat carboxyhemoglobin level
Insulin-glucose (hyperinsulinemic euglycemic therapy)	Calcium-channel antagonists β-Adrenergic receptor antagonists	Regular insulin, 1 U/kg IV bolus, followed by 0.5-1 U/kg/hr; titrate up to 10 U/kg/hr as needed Titrate 50% dextrose IV to avoid hypoglycemia and replete serum potassium as needed	Reversal of myocardial depression	Initiate early to reverse myocardial depression Monitor glucose and potassium; hypoglycemia can occur during and after therapy Hyperglycemia results from calcium-channel antagonist–induced insulin resistance, and initial dextrose requirements may be less than anticipated Recovery may be heralded by normalization of glucose levels, with increased dextrose required to avoid hypoglycemia

TABLE 96-6 ANTIDOTES AND INDICATIONS FOR USE[§]—cont'd

ANTIDOTE	INDICATION FOR USE	DOSE*	TREATMENT END POINT	COMMENTS
Lipid emulsion	Cardiac toxicity from local anesthetics (e.g., bupivacaine, ropivacaine) and other lipophilic toxicants Provisional: verapamil, diltiazem, tricyclic antidepressants, bupropion, propranolol and other lipophilic toxicants	Use 20% formulation Initial bolus: 1.5 mL/kg IV during 1 minute, followed immediately by infusion of 0.25 mL/kg/min for 30-60 minutes Can repeat bolus for asystole	Return of hemodynamic stability	Use for other than bupivacaine based on animal experiments and human case reports Use if advanced life support measures fail and generally only if the patient is moribund; continue CPR as needed during drug administration
Methylene blue	Methemoglobin-producing agents	1-2 mg/kg body weight (0.1-0.2 mL/kg of 1%) methylene blue IV over 5-minute period; repeat dose for persistent or recurrent symptoms or signs	Resolution of dyspnea and altered mental status	Use if patient is symptomatic (i.e., dyspneic, altered mental status) Maximum dose should not exceed 7 mg/kg (0.7 mL/kg) Contraindicated in G6PD-deficient patients; may cause hemolysis Some toxicants (e.g., dapsone) may require prolonged therapy
N-Acetylcysteine (NAC)	Acetaminophen[A5] Other hepatotoxins: carbon tetrachloride, chloroform, pennyroyal oil, amatoxin[16]	Intravenous (preferred) Load: 150 mg/kg over 1-hour period Maintenance infusion: 12.5 mg/kg/hr over 4-hour period, then 6.25 mg/kg/hr over 16 hours as continuous infusion Oral (total 72 hours) Load: 140 mg/kg Maintenance (starting 4 hours after load): 70 mg/kg q4h × 17 doses IV (total 21 hours)	At the end of therapy, repeat AST and APAP levels: if AST normal and APAP not detected, treatment complete; if AST normal and APAP detected, continue NAC; if AST elevated, continue NAC After patient has received full course of NAC therapy, if INR ≥2.0 or severe hepatotoxicity present (AST > 1000 U/L), continue NAC until INR <2.0 and aminotransferases normalize	Most effective if initiated within 8 hours after acetaminophen ingestion; may be started any time after ingestion and is beneficial in patients with severe hepatotoxicity Longer duration of treatment may be required in patients with persistently elevated acetaminophen levels or ongoing hepatotoxicity Treatment end points simplified for ease of use INR result not valid indicator if fresh frozen plasma recently administered
Naloxone	Opioids	Possible opioid dependence: 40-50 µg (0.04-0.05 mg) IV titrated upward to reverse symptoms while providing respiratory support if needed and cautiously avoiding withdrawal Opioid dependence not likely: 0.4 mg by any route and titrate up to 10 mg Intranasal naloxone (2-4 mg) may be given if IM/IV not possible Continuous infusion: establish bolus dose required to reverse respiratory depression; begin infusing two thirds of reversal dose every hour and titrate to maintain adequate respirations; repeated bolus with half of reversal dose 15 minutes after reversal of respiratory depression	Initial: reversal of respiratory depression with resolution of hypoxemia and hypercapnia Final: resolution of CNS and respiratory depression Avoid rapid and full awakening in opioid-dependent patients to avoid precipitating opioid withdrawal Since the duration of naloxone is shorter than most opioids, re-sedation may occur—so several hours of observation is optimal	Pre-ventilate patients with respiratory depression by bag-valve-mask or intubation before administration Use smaller doses in opioid-dependent patients Some opioids (e.g., buprenorphine) may require larger doses of naloxone (fentanyl does not) Use continuous infusion for recurrent symptoms and prolonged action of some formulations (e.g., sustained-release morphine, methadone) Re-sedation can occur Do not use naltrexone to reverse acute toxicity
Octreotide	Sulfonylurea-induced hypoglycemia	50 µg SQ q6h	Resolution of hypoglycemia and dextrose no longer required to maintain euglycemia	Maintain dextrose infusion as needed Not for insulin-induced hypoglycemia
Physostigmine	Anticholinergic agents (e.g., diphenhydramine, jimsonweed [*Datura* sp], scopolamine)	1-2 mg IV during 5-minute period; can repeat in 5 minutes if no effect and cholinergic effects do not occur	Reversal of anticholinergic effects	Duration of effect is 60-90 minutes Benzodiazepine used for subsequent treatment of agitation and seizures; additional physostigmine used rarely (e.g., refractory seizures or agitation) Adverse effects include seizures, excessive oral secretions, bradydysrhythmias; contraindicated in cyclic antidepressant toxicity

TABLE 96-6 ANTIDOTES AND INDICATIONS FOR USE[§]—cont'd

ANTIDOTE	INDICATION FOR USE	DOSE*	TREATMENT END POINT	COMMENTS
Pralidoxime chloride	Organophosphorus compounds Nerve agents: sarin, VX	30 mg/kg IV bolus (maximum 2 g) over 30 minutes, followed by continuous infusion of 8-10 mg/kg/hr (maximum 650 mg/hr)	Resolution of signs and symptoms, atropine no longer required	Can give initial dose over 2-minute period for life-threatening clinical events Administer early when diagnosis known or strongly suspected Efficacy variable, depending on the organophosphate Fat-soluble organophosphates may require prolonged treatment
Pyridoxine	Ethylene glycol Isoniazid Monomethylhydrazine (*Gyromitra esculenta* mushrooms)	100 mg IV (ethylene glycol) 5 g IV, repeat for refractory seizures	One dose Resolution of seizures	Efficacy theoretical for ethylene glycol to enhance elimination of toxic metabolites Pyridoxine may be required even with benzodiazepines to stop seizures, but patient can remain comatose (isoniazid, *Gyromitra* mushrooms) Excessive dosing can cause neuropathy
Sodium bicarbonate ($NaHCO_3$)	Reversal of myocardial sodium-channel blockers (e.g., cyclic antidepressants, cocaine, sodium-channel–blocking antiarrhythmics with $\tau_{recovery}$ >1 second, piperidine phenothiazines (thioridazine, mesoridazine)	1-2 mEq $NaHCO_3$/kg by intermittent IV bolus; repeat as needed	Narrowing of prolonged QRS, resolution of ventricular dysrhythmias, reversal of hypotension	Monitor blood pH (optimal pH approximately 7.50); avoid pH > 7.55
	Altered tissue distribution or enhanced elimination of salicylates; may be used for chlorophenoxy herbicides, formic acid, methotrexate, phenobarbital	1-2 mEq $NaHCO_3$/kg, followed by 3 ampules (150 mL) $NaHCO_3$ (44 mEq per 50 mL) in 850 mL of D_5W, infused at two to three times normal maintenance fluid rate	Serum salicylate <30 mg/dL and patient clinically stable	Target blood pH: 7.50-7.55 Monitor urinary pH hourly; adjust infusion to maintain urine pH of 7.5-8.0 (avoid blood pH >7.55) Monitor ABGs Maintain normokalemia to allow urinary alkalinization
Succimer (DMSA)	Arsenic Lead Mercury, all forms	10 mg/kg/dose q8h for 5 days, followed by q12h for 14 days Drug holiday for 2 weeks; repeat if treatment end point not reached	Arsenic: 24-hour urinary arsenic <50 µg/L Lead: resolution of encephalopathy, gastrointestinal symptoms, neuropathy, nephropathy, arthralgias, myalgias, and blood lead level <70 µg/dL Mercury, elemental and inorganic: 24-hour urinary mercury <20 µg/L Mercury, organic: end point not well established	Oral chelator; adverse effects include rash, transient AST and alkaline phosphatase elevations, and gastrointestinal distress; minimal chelation of essential metals occurs Dosing for arsenic and mercury not well established Therapeutic end point for organic mercury not established; neurotoxicity not responsive to chelation therapy; suggest chelation until blood mercury level within normal value range for reference laboratory
Vitamin K	Vitamin K antagonist anticoagulants (e.g., warfarin, long-acting anticoagulant rodenticides [LAARs]) (note this is not for normalizing a supratherapeutic INR in patients prescribed warfarin)	Subcutaneous: phytonadione (K_1), 10-25 mg, repeat every 6-12 hours until oral vitamin K_1 started Oral: 25-50 mg q6h; larger doses may be required	INR is normal 48-72 hours after stopping vitamin K_1 therapy Can also monitor factor VII activity	Anaphylactoid reaction can occur with rapid IV administration Severe bleeding may also require FFP, prothrombin protein concentrate (off-label), or factor concentrates Base decision to treat on finding of elevated INR; do not administer prophylactic vitamin K_1 Oral therapy may be required for months with LAAR poisoning because of lipophilicity of toxicant, with slow body clearance

*Dose concentrations and infusion times are not given. Drug dosages may require adjustment in patients with renal or hepatic failure.

†Administer antivenom in a monitored setting; antivenom must be reconstituted and then diluted; initially infuse at a rate of 2 to 5 mL/hr, and double the infusion rate every 5 minutes as tolerated to administer antivenom during a 1-hour period.

‡Ten percent calcium chloride solution = 100 mg/mL (27.2 mg/mL elemental calcium); 10% calcium gluconate solution = 100 mg/mL (9 mg/mL elemental calcium).

§See also Chapter 98.

¶Given the relative infrequency of use of these antidotes, it is prudent that, when possible, the indications, alternatives, and doses for these antidotes should be confirmed if possible with a poison control center or medical toxicologist.

ABGs = arterial blood gases; ALT = alanine aminotransferase; APAP = acetyl-*p*-aminophenol (acetaminophen); AST = aspartate aminotransferase; BAL = British antilewisite; CNS = central nervous system; COHb% = percentage carboxyhemoglobin; CPR, cardiopulmonary resuscitation; D_5W = 5% dextrose in water; DMSA = 2,3-dimercaptosuccinic acid; ECG = electrocardiogram; FFP = fresh-frozen plasma; G6PD = glucose-6-phosphate dehydrogenase; Hb = hemoglobin; HD = hemodialysis; INR = international normalized ratio; IV = intravenous; MetHb% = percentage methemoglobinemia; NS = normal saline; O_2Hb% = percentage oxyhemoglobin; SQ = subcutaneous; $\tau_{recovery}$ = drug blockade recovery rate.

TABLE 96-7 COMMON TOXICANTS REMOVED BY HEMODIALYSIS

TOXICANT	INDICATIONS	COMMENTS
Ethylene glycol	Serum level ≥50 mg/dL, or lower levels with concomitant metabolic acidosis and evidence of end-organ toxicity, or if fomepizole not available	Not routinely required in a patient with normal creatinine clearance and acid-base status who is receiving fomepizole
Lithium*	Clinical indications, primarily CNS toxicity (e.g., decreased level of consciousness, ataxia, coma, seizures) in patients with an elevated blood lithium concentration	Use dialysate containing bicarbonate to decrease Na^+/K^+ antiporter intracellular sequestration of lithium
Methanol	Serum level ≥50 mg/dL, or lower levels with concomitant metabolic acidosis and evidence of end-organ toxicity, or if fomepizole not available	Usually required because of slow elimination half-life in presence of fomepizole (mean, 52 hours; range, 22-87 hours), even in patients with no metabolic acidosis or evidence of end-organ toxicity
Phenobarbital	Clinical indications (e.g., deep coma)	Rarely necessary except when a patient is hemodynamically unstable despite aggressive support
Salicylates	Acute toxicity: serum level ≥100 mg/dL without clinical abnormality or <100 mg/dL in the presence of a clinical indication. Chronic toxicity: any clinical indication, typically altered mental status	Serum protein binding decreases with increasing toxic levels, increasing the amount of free salicylate available for HD removal; clinical indications are one or more of the following: impaired kidney function, altered mental status, seizures, pulmonary edema, intractable acidosis
Valproic acid	Severe intoxication with serum concentration >900 mg/L	Clinical indications include hepatic dysfunction; coma, especially with hyperammonemia; deteriorating clinical status despite aggressive support

*Hemodiafiltration removes lithium; the clinical benefit of this technique is unknown.
CNS = central nervous system; HD = hemodialysis.

PROGNOSIS

Almost all patients who reach the hospital alive survive with appropriate care. Inpatient mortality rates are 0.2 to 0.5%.

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97 MEDICAL ASPECTS OF TRAUMA AND BURNS

ROBERT L. SHERIDAN

Injured or burned patients are complex to manage not only because of the vast number of potential anatomic derangements but also because of the complex physiologic cascades triggered by injury. Although most intense after extensive burns, stereotypical physiologic derangements are a characteristic of all injuries. As a result, needed interventions are often predictable regardless of the mechanism of injury.

EPIDEMIOLOGY

In the United States alone each year, about 2.5 million people are injured and about 35,000 to 40,000 are killed in automobile crashes, whereas about 120,000 are injured and about 40,000 are killed by gunshots. Burns and falls follow in frequency. Worldwide, injury by trauma and burns is the leading cause of death in children and young adults.[1] In the United States, injury follows only cancer and heart disease as a cause of death. Many long-term survivors of trauma and burns have high degrees of disability, which creates a particularly difficult and expensive problem given the young age of many victims.

The time of death after injury has a trimodal distribution. At least 50% of fatalities occur within minutes of the injury as a result of massive hemorrhage or nonsurvivable brain injury. Approximately one third of deaths occur within a few hours of injury, usually by hemorrhage, anoxia, or progressive brain trauma. This interval provides an opportunity for emergent intervention. Later fatalities are usually the result of multisystem organ dysfunction or overwhelming infection in the days and weeks after the injury. The likelihood of surviving a severe injury is better in communities that are closer to major trauma centers.[2]

PATHOBIOLOGY

Early Local Response to Injury

The local response to blunt, penetrating, electrical, crush, thermal, blast, or other injury varies with the energy transferred. All are associated with some degree of secondary injury by progressive microvascular thrombosis, progressive edema, and secondary compromise of perfusion. The most common preventable mechanisms are related to progressive edema beneath an inelastic eschar or fascial compartments or direct injury to vascular inflow or outflow.

Early Systemic Response to Injury

The early systemic response to burns and local trauma is driven by fluid loss and release of vasoactive mediators from injured tissue. In more severe injuries, including surface burns greater than about 20% of the body surface, interstitial edema develops in unburned skin as well as in distant organs and soft tissues. These distant microvascular effects, which can compromise the function of organs that were not directly injured, explain the frequent occurrence of pulmonary and other organ dysfunctions in patients with large burns.

The capillary leak syndrome, in which the leak is typically proportional to the scope of the injury, is caused by the release of vasoactive substances from the injured and reperfused tissue. As a result, during the first 18 to 24 hours after a serious burn, both electrolytes and large colloid molecules freely diffuse into the interstitial space.

Late Local Response to Injury

At about 72 hours after the initial trauma, local wound issues are particularly important in patients who have extensive soft tissue damage, especially after burns or crush injury with extensive volumes of devitalized tissue. Tissue that has been crushed or suffered reduced blood flow is subject to progressive necrosis. As bacteria multiply in the avascular tissue during the succeeding days, proteases liquefy the eschar and necrotic tissue, which then separates and leaves a bed of granulation tissue. In healthy patients with

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Injured or burned patients are complex to manage not only because of the vast number of potential anatomic derangements but also because of the complex physiologic cascades triggered by injury. Although most intense after extensive burns, stereotypical physiologic derangements are a characteristic of all injuries. As a result, needed interventions are often predictable regardless of the mechanism of injury.

EPIDEMIOLOGY

In the United States alone each year, about 2.5 million people are injured and about 35,000 to 40,000 are killed in automobile crashes, whereas about 120,000 are injured and about 40,000 are killed by gunshots. Burns and falls follow in frequency. Worldwide, injury by trauma and burns is the leading cause of death in children and young adults.[1] In the United States, injury follows only cancer and heart disease as a cause of death. Many long-term survivors of trauma and burns have high degrees of disability, which creates a particularly difficult and expensive problem given the young age of many victims.

The time of death after injury has a trimodal distribution. At least 50% of fatalities occur within minutes of the injury as a result of massive hemorrhage or nonsurvivable brain injury. Approximately one third of deaths occur within a few hours of injury, usually by hemorrhage, anoxia, or progressive brain trauma. This interval provides an opportunity for emergent intervention. Later fatalities are usually the result of multisystem organ dysfunction or overwhelming infection in the days and weeks after the injury. The likelihood of surviving a severe injury is better in communities that are closer to major trauma centers.[2]

PATHOBIOLOGY

Early Local Response to Injury

The local response to blunt, penetrating, electrical, crush, thermal, blast, or other injury varies with the energy transferred. All are associated with some degree of secondary injury by progressive microvascular thrombosis, progressive edema, and secondary compromise of perfusion. The most common preventable mechanisms are related to progressive edema beneath an inelastic eschar or fascial compartments or direct injury to vascular inflow or outflow.

Early Systemic Response to Injury

The early systemic response to burns and local trauma is driven by fluid loss and release of vasoactive mediators from injured tissue. In more severe injuries, including surface burns greater than about 20% of the body surface, interstitial edema develops in unburned skin as well as in distant organs and soft tissues. These distant microvascular effects, which can compromise the function of organs that were not directly injured, explain the frequent occurrence of pulmonary and other organ dysfunctions in patients with large burns.

The capillary leak syndrome, in which the leak is typically proportional to the scope of the injury, is caused by the release of vasoactive substances from the injured and reperfused tissue. As a result, during the first 18 to 24 hours after a serious burn, both electrolytes and large colloid molecules freely diffuse into the interstitial space.

Late Local Response to Injury

At about 72 hours after the initial trauma, local wound issues are particularly important in patients who have extensive soft tissue damage, especially after burns or crush injury with extensive volumes of devitalized tissue. Tissue that has been crushed or suffered reduced blood flow is subject to progressive necrosis. As bacteria multiply in the avascular tissue during the succeeding days, proteases liquefy the eschar and necrotic tissue, which then separates and leaves a bed of granulation tissue. In healthy patients with

ABSTRACT

Injured or burned patients are complex to manage not only because of the vast number of potential anatomic derangements but also because of the complex physiologic changes triggered by injury. Proper support and management of these derangements is an essential component of successful care, regardless of the mechanism of injury. Practical care and long-term outcomes can be further complicated by the emotional impact of the injuries.

KEYWORDS

burns
injury
trauma
physiology
critical care

TABLE 97-1 INJURY CLASSES

INJURY CLASS	CLINICAL IMPLICATIONS	COMMON ERRORS
Blunt	Graded soft tissue and bone injury, edema Occult vascular or visceral injury	Delayed consequences of edema Missed visceral injury and secondary consequences
Penetrating	Soft tissue and bone injuries vary with energy of injuring object (e.g., knife vs. fragment vs. bullet) Occult vascular or visceral injury	Missed vascular or visceral injury Secondary consequences of missed vascular injury
Thermal	Graded soft tissue injury (first- to fourth-degree burns) Capillary leak phenomenon	Inadequate appreciation of capillary leak phenomenon and consequent under-resuscitation Inaccurate wound evaluation and over-resuscitation Unanticipated local injury progression
Electrical	Range of soft tissue injury with increasing voltage and contact duration and quality	Occult cardiac and muscle injury Secondary compartment syndrome complications
Crush	Graded soft tissue, bone, and visceral injury with secondary consequences of edema and of reperfusion	Underappreciation of injury severity Missed muscle ischemia due to primary ischemia and to reperfusion edema
Blast	Graded injury severity (primary to quaternary injury patterns) Occult visceral injury	Underappreciation of secondary, tertiary, and quaternary components of injury Missed associated visceral injury
Fragmentation injury	Multiple unpredictable penetrations with associated visceral and vascular injury	Missed visceral and vascular injury Associated blast trauma

smaller wounds and burns (<20% of the body surface), this septic process is usually tolerated. When injuries are larger, however, systemic infection results and explains the rare survival of patients who have burns in excess of 40% of body surface area or who have massive soft tissue injuries with incomplete early wound excision.

Late Hypermetabolic Systemic Response to Injury

Successfully resuscitated patients with large burns or major non-burn trauma demonstrate an initial decrease in cardiac output and metabolic rate. After successful resuscitation, a hypermetabolic response occurs, with a near doubling of cardiac output and resting energy expenditure during the next 24 to 72 hours. The magnitude of the response, which becomes greater with larger burns and more severe injuries, peaks at up to twice the normal metabolic rate in otherwise healthy patients with burn involving 60% or more of the body surface area. This hypermetabolic response is characterized by enhanced gluconeogenesis, insulin resistance, and increased protein catabolism. Although the causes of these physiologic changes are not well understood, they seem to involve the systemic release of bacterial products, the breakdown of gastrointestinal barrier dysfunction with translocation of bacteria and their byproducts into the circulation, and increases in the secretion of glucagon, cortisol, and catecholamines.

CLINICAL MANIFESTATIONS

Common mechanisms of injury include blunt, penetrating, electrical, thermal, blast, and crush (Table 97-1), often in combination. For example, patients crushed in building collapses frequently suffer a concomitant penetrating component, and patients who suffer high-voltage injury frequently fall from a height, such as a utility pole. In all mechanisms, edema or vascular injury can compromise perfusion and lead to secondary injury.

Blunt injury is commonly seen in motor vehicle accidents and falls. Injuries are often multisystem. Penetrating soft tissue injuries vary widely (Fig. 97-1), but the overarching concern is the possibility of occult injury to vascular, bone, or visceral structures. The degree of trauma is directly related to the energy of the injury. For example, high-velocity gunshots cause greater injury than lower velocity rounds because they create a local blast effect, called cavitation, along their trajectory.

Thermal injury (Fig. 97-2) by whatever mechanism (flame, scald, contact) is associated with a graded soft tissue injury described in degrees. As thermal injuries increase beyond about 15% of the body surface, a diffuse capillary leak phenomenon occurs that continues for 18 to 24 hours after injury and involves both burned and unburned tissue. This phenomenon can result in cardiovascular collapse and is the key physiologic derangement underlying the shock state accompanying burns.[3]

The severity of electrical injuries (Fig. 97-3) varies with voltage, current flow, and contact quality. Low-voltage injuries are rarely associated with distant sequelae, whereas high-voltage injuries are commonly associated with compartment syndromes, cardiac complications, pigmenturia, and other trauma.

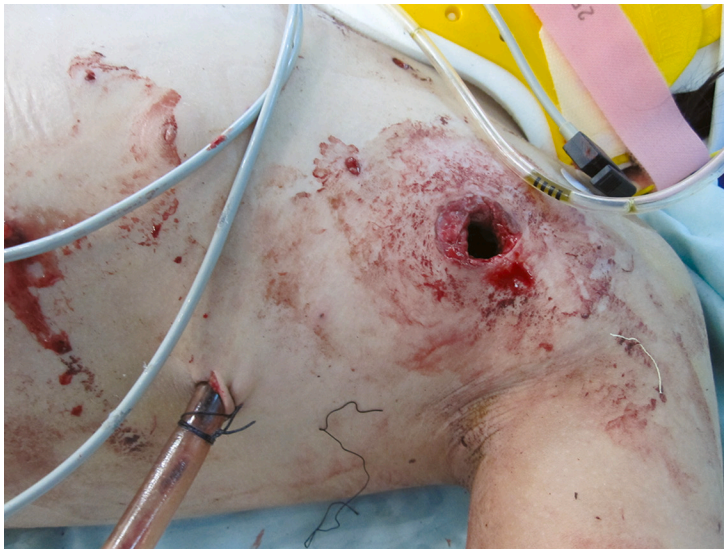

FIGURE 97-1. Penetrating injury often is associated with visceral and bone trauma.

FIGURE 97-2. Thermal injury is of variable depth. Initial evaluation usually underestimates this depth.

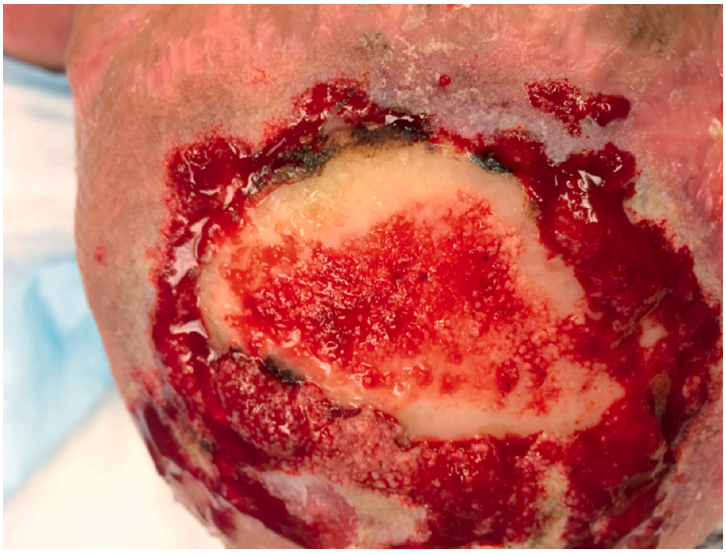

FIGURE 97-3. Electrical injury can be associated with a number of systemic sequelae, depending on current strength and pattern of flow.

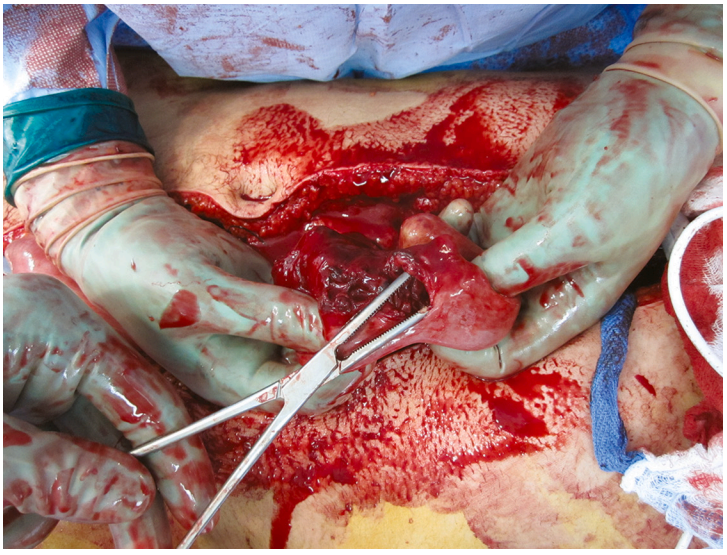

FIGURE 97-5. Blast injury is a complex of four injury subtypes. Missed injuries are common.

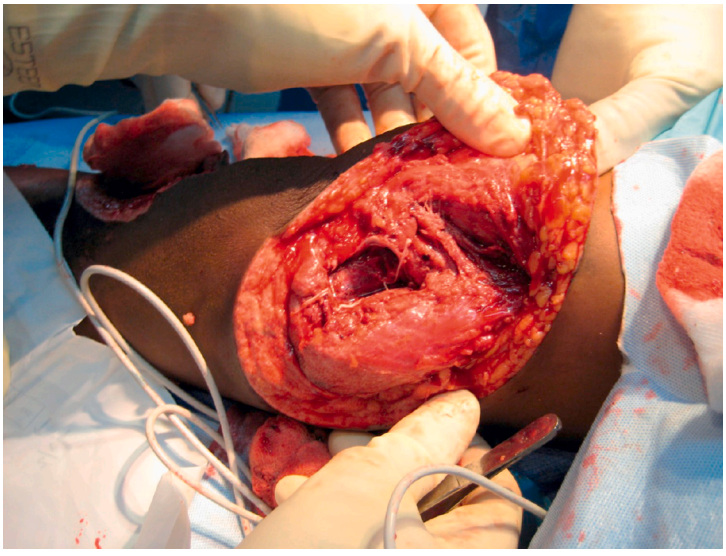

FIGURE 97-4. Crush injury is often associated with underappreciated deep muscle injury.

FIGURE 97-6. Fragmentation injury is a particular form of penetrating injury frequently associated with missed injuries.

Crush injuries (Fig. 97-4) include direct soft tissue injuries as well as secondary ischemic damage due to a compartment syndrome or ischemia-reperfusion. Associated bone, visceral, and vascular injuries are common. Major septic complications are common when necrotic soft tissues are left unexcised.

Blast injuries (Fig. 97-5) are graded complex injuries with four characteristics: primary injury to air-filled structures and the central nervous system, secondary injury from flying debris, tertiary injury from collisions with stationary objects, and quaternary injury from associated crush or other trauma. Blast injuries of all types can be subtle or have a delayed clinical presentation, and visceral injuries often are not diagnosed promptly.

Fragmentation injuries (Fig. 97-6) are penetrating injuries characterized by multiple foreign bodies of variable size and energy as well as unpredictable trajectories. As with blast injuries, the full extent of injury is often underestimated initially.

DIAGNOSIS AND TREATMENT

Complex burns and trauma are most successfully and cost-effectively managed in high-volume programs.[4] Trauma and burn center programs emphasize the comprehensive nature of injury care, including community involvement with injury prevention programs, thorough prehospital care, early resuscitation and surgery, and long-term rehabilitation and reconstruction. Most programs include embedded specialty intensive care units and operating rooms. Multidisciplinary staff include physicians, physician assistants, nurse practitioners, nurses, physical and occupational therapists, respiratory therapists, psychiatrists, social workers, and nurse administrators. Coordination and scheduled communication are essential.

Care of individual patients with serious multisystem injury is complex and requires a longitudinal four-phase approach.[5] Phase One, which describes the initial evaluation and resuscitation, generally is completed in the first 24 hours. Phase Two includes initial wound excision for burn patients and initial resuscitative surgery and fracture stabilization for non-burn trauma patients. This phase frequently overlaps with Phase One but is usually completed within 72 hours. Phase Three involves definitive wound closure for burns and the completion of surgery for trauma patients. The duration of this phase varies greatly with injury but is usually complete at the time of discharge. Phase Four describes the sometimes long process of reconstruction, rehabilitation, and reintegration. This phase of care commonly spans the later part of the acute hospitalization, inpatient rehabilitation, and variable amounts of time in the home-based setting.

Prehospital Care and Interhospital Transport

When prehospital and interhospital transfers are being arranged, key issues include control of the airway, secure venous access, placement of bladder and nasogastric catheters, maintenance of body temperature, fluid administration if transport time will be more than 1 hour, documentation of the events of the injury from personnel who will not be available to the receiving facility, efforts to notify family members, and clear documentation of all interventions.

Hypothermia (Chapter 95) is a particular problem in burn patients because of their evaporative heat losses. Transporting vehicles and emergency department receiving areas should be heated before the patient's arrival. Initial burn dressings should be dry, clean sheets rather than wetted dressings. Cooling of a wound involving less than 15% of the body surface within minutes of injury may help limit burn depth without causing systemic hypothermia, whereas cooling after a few minutes is generally unhelpful.

Phase One: Initial Evaluation and Resuscitation

Primary Survey

The organized approach to the initial evaluation of injured patients requires primary and subsequent patient surveys. The primary survey is an initial look for major aberrations in airway, circulatory, or neurologic status that justify emergent intervention. The airway is controlled with intubation if needed. Clinically obvious pneumothoraces (Chapter 86) should be decompressed, and hemothoraces must be diagnosed and drained. In suspicious cases, pericardial tamponade (Chapter 62) can usually be documented or excluded by handheld bedside ultrasonography. Vascular access is obtained and fluid resuscitation started. A very brief neurologic assessment (Chapter 366), including use of the Glasgow Coma Scale, is critical.

Secondary Survey

The secondary survey includes a much more detailed head-to-toe physical examination after the patient has a reliable airway and has been hemodynamically stabilized. The physical examination should assess for evidence of closed head injury, skull and facial fractures, and eye and ear injuries, with a low threshold for a head computed tomography (CT) scan. The neck must be stabilized and assessed for possible injury. Burns should be categorized as first-degree burns, involving only the epidermis; second-degree burns, involving variable amounts of dermis; third-degree burns, involving the entire dermis; and fourth-degree burns, involving fat, muscle, and bone.

A constant concern is the potentially missed injury. In the chaos of initial care, major issues can be missed if they do not have a dramatic initial presentation. Unfortunately, many injuries, such as epidural hematoma and small bowel perforations, are initially subtle and become catastrophic hours or days later. The best way to deal with this difficult reality is to have a highly organized approach that includes both a detailed initial evaluation and subsequent reevaluation so that all potential injuries are considered and reasonably excluded.

Projectiles often follow an unpredictable course through tissue and bone, thereby increasing the likelihood of missed injury. Missed visceral injury is also common with fragmentation injuries, especially because surgical exploration of all potential sites of injury is often impractical. Selected exploration is guided by initial and serial examination and by imaging when available.

Appropriate laboratory and imaging studies should be obtained. The fundamental goal is to consider carefully the injury mechanism and to exclude all potential occult injuries to a reasonable level of confidence. High-energy injuries, such as electrical burns, motor vehicle crashes, and blasts, are notorious for generating significant injuries that are missed during the initial evaluation. Bedside ultrasonography has emerged as a routine, rapid, and repeatable method to assess for abdominal fluid, usually blood. CT scanning of the head, chest, abdomen, and pelvis is justified if the mechanism of injury is consistent with head or abdominal trauma, and conventional imaging with selective CT scanning is as good as immediate total-body CT scanning.[A1] Rapid imaging has largely supplanted operative exploration for diagnostic purposes, except in unstable patients, in whom immediate operative exploration is performed for ongoing hemorrhage.

Chest Injuries

Tension pneumothorax (Chapter 86), hemothorax, cardiac tamponade (Chapter 62), flail chest, open pneumothorax, and disruption of the thoracic aorta (Chapter 63) are among the life-threatening injuries that should be considered during the primary and secondary surveys. All trauma patients should have a supine chest radiograph to examine the lung fields, mediastinal contour, and chest wall. Thoracic aortic injury is usually an immediately fatal complication of severe acceleration-deceleration injury, but some patients may have a contained mediastinal hematoma that requires urgent diagnosis and medical or surgical management.

Myocardial contusion should be suspected in patients with blunt trauma, especially if they have a sternal fracture or anterior rib fractures. Such blunt cardiac injuries can result in electrocardiographic abnormalities, ventricular arrhythmias, and cardiogenic shock. Coronary artery injuries are uncommon, although lacerations and dissections can occur and require emergent percutaneous coronary intervention similar to a typical ST elevation myocardial infarction (Chapter 58).

Commotio cordis is sudden cardiac arrest (Chapter 50) after acute blunt chest trauma from softballs, baseballs, hockey pucks, or collisions. The trauma presumably occurs during an electrically vulnerable period between 30 and 15 msec before the T-wave peak and produces ventricular fibrillation. Death is essentially universal unless the victim receives immediate cardiopulmonary resuscitation.

Abdominal Injuries

The liver and spleen are the most frequently injured intra-abdominal organs. Suggested findings on physical examination include lower rib fractures, upper quadrant pain or tenderness, and pain referred to the shoulder secondary to diaphragmatic irritation. CT scanning is the test of choice. High-grade injuries require surgery, but most lesser injuries can be managed nonoperatively. Focused abdominal sonography has a sensitivity of 95% for detection of free blood in the abdomen (Fig. 97-7) but is not usually able to identify the source. An alternative in unstable patients or in austere environments is diagnostic peritoneal aspiration or lavage. Abdominal CT is a reliable determinant of both intraperitoneal and retroperitoneal injury (Fig. 97-8) and is preferable to diagnostic aspiration or lavage in stable patients. For selected stable patients whose blunt liver or spleen injury is originally treated nonoperatively, discharge on day 3 may be as safe as discharge on day 5, provided that the patient is stable and does not have other indications for continued hospitalization.[A2]

Head and Spine Injuries

Neurologic issues often dominate the quality of long-term outcome. The initial evaluation of the neurotrauma patient focuses on detection of reversible causes of elevated intracranial pressure or reduced perfusion (Chapter 368), but routine

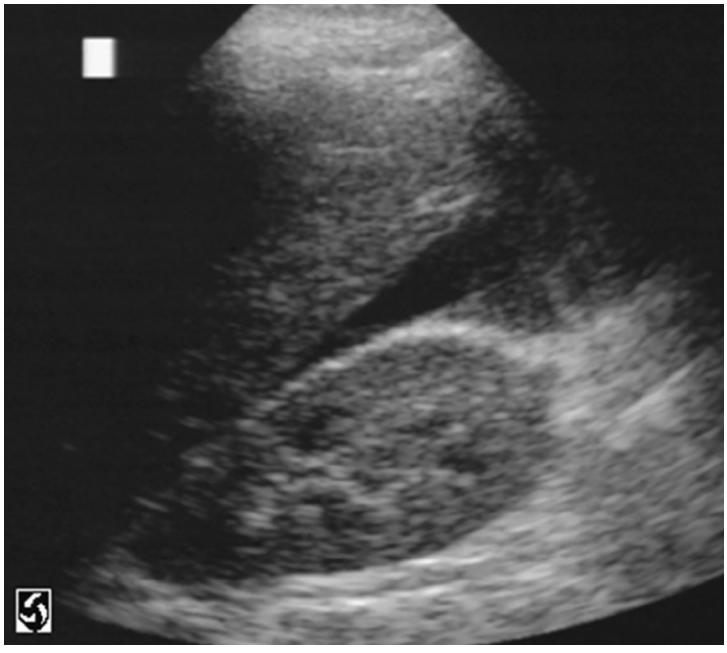

FIGURE 97-7. Positive focal abdominal sonography in trauma (FAST) study. There is a collection of fluid that shows up as a black strip between the liver and kidney. The white appearance is fat around the kidney. These findings are consistent with a fluid collection in the Morison pouch. (Courtesy Robert H. Demling, MD.)

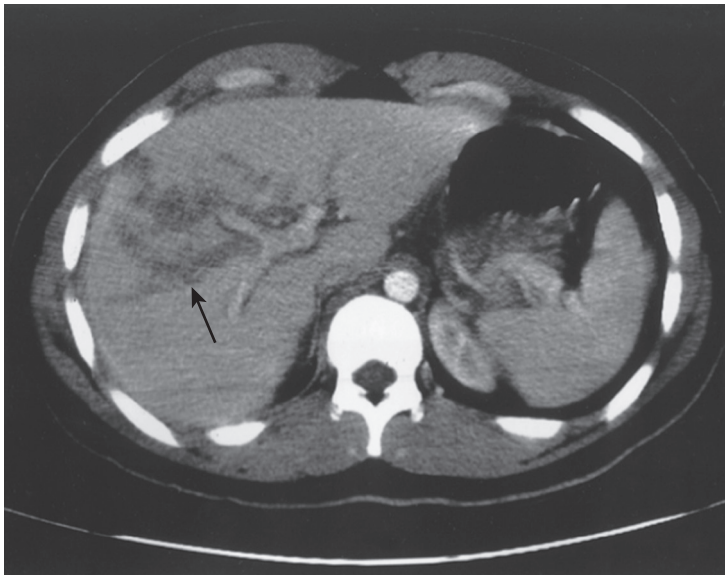

FIGURE 97-8. Abdominal injury. An abdominal computed tomography scan shows an injury to the right lobe of the liver (*arrow*). (Courtesy Robert H. Demling, MD.)

measurement of intracranial pressures does not improve outcome.[6] Although many outcomes are fixed from the time of injury, opportunities for early intervention should not be missed. It is particularly important to avoid secondary neurologic injury, most commonly due to reduced perfusion from hypotension and cerebral edema.

Prevention of spinal cord injury (Chapter 368) and evaluation of the spine for bone and ligamentous disruption are also important components of the early evaluation. Multidetector CT images can be obtained quickly to detect occult spinal injuries, and routine magnetic resonance imaging is rarely clinically indicated.[7]

A multidisciplinary approach to the evaluation and management of pain and anxiety in injured patients has important short- and long-term benefits. An organized approach facilitates dealing with the inevitable pain and anxiety in an organized and consistent manner and allows the unit to determine the effectiveness of new interventions.

Tertiary Survey

The tertiary survey is a planned repeat physical examination, usually 1 or 2 days after admission, often accompanied by focused imaging tests.[8] The goal is to exclude missed subtle injuries that might otherwise cause significant long-term morbidity. Examples include minor fractures of the wrist or foot, small deep lacerations of the scalp, subtle eye injuries, and some abdominal injuries, particularly retroperitoneal duodenal or colonic perforations. Such injuries can become the patient's dominant source of long-term morbidity if they are missed during initial evaluation and treatment.

Key Management Issues

Fluid Resuscitation and Transfusion

The clinical goal is to administer adequate, but not excessive, fluid[9] while ensuring that soft tissues are not rendered ischemic by increasing pressure beneath inelastic eschar or tense muscle compartments. The severity of hemorrhagic shock should be assessed and treated appropriately (Table 97-2).

For burn patients, several formulas based on weight, surface area, and burn size have been developed over the years. These are general guides, and physiologic monitoring is needed with individual titration of infusions to meet set resuscitation end points, such as urine output, base deficit, and vital signs (E-Table 97-1).[10]

In well-resuscitated trauma and burn patients, capillary integrity generally returns at 18 to 24 hours, and fluid requirements decrease to approximately 1.5-fold maintenance in most patients. With the reduction in the infusion rate of isotonic crystalloid, topical care of large wounds will have a major impact on serum electrolytes. Wounds treated with nonaqueous topical antimicrobials, such as silver sulfadiazine cream or mafenide acetate cream, promote transeschar water loss and generate a free water requirement. By comparison, wounds treated with aqueous topical agents are associated with electrolyte leaching and secondary hyponatremia (Chapter 102). Serum levels of potassium, calcium, and magnesium (Chapters 103-105 and 227) should be monitored frequently and replaced as needed. In most patients, enteral feedings (Chapter 198) can be started.

Current fluid resuscitation practices in trauma patients emphasize initial "permissive hypotension" to reduce early bleeding (Chapters 90 and 92). Patients with mean systemic arterial pressures in the range of 60 to 80 mm Hg are resuscitated initially to modest hypotension (i.e., the range of 80 to 90 mm Hg) if they are otherwise alert and well perfused. They are then taken expeditiously to the operating room for surgical control before targeting a normotensive state. Early use of blood products such as fresh-frozen plasma and red cells rather than crystalloid can minimize the coagulopathy and improve outcomes in rapidly hemorrhaging patients. Among patients with severe trauma and major bleeding, early administration of plasma, platelets, and red blood cells in a 1 : 1:1 ratio of infusion units is better than a 1 : 1:2 ratio for achieving hemostasis and reduces early death due to exsanguination.[A3] Liberal use of tourniquets and compressive dressings before surgery further improves outcome by reducing blood loss. Among the various crystalloids, none seem to have any obvious advantages or disadvantages for treatment of hemorrhage. Tranexamic acid (e.g., loading dose of 1g during 10 minutes, then infusion of 1 g during 8 hours), which inhibits thrombolysis, beginning within 8 hours of injury may reduce bleeding and improve survival in selected patients who require massive transfusion.[A4]

Pigmented urine is commonly seen in the setting of high-voltage, crush, blast, or very deep thermal injury. Myoglobin and hemoglobin that are liberated from lysed muscle (Chapter 99) and red cells cause the pigmentation. To avoid renal tubular injury (Chapter 106), crystalloids should be administered to achieve a urine output of 2 mL/kg/hour (Chapter 99).

Decompression Procedures

An important component of the initial evaluation of the trauma and burn patient is to find and to rectify compartment syndromes before irreversible tissue ischemia occurs.[11] Perfusion of the extremities can be compromised by inelastic near-circumferential burns, and the normal fascial envelopes of major muscle groups can cause high soft tissue pressure if muscles are injured by crush, thermal, or electrical injury or in association with major fractures. Extremities at risk should be dressed simply to facilitate frequent assessment for temperature, pliability, voluntary motion, pain with passive motion, detectable pulsations, and low-pressure flow by capillary refill and Doppler signals in the digital vessels and digital pulp. In assessing capillary refill, it is important to elevate the extremity, as even a mottled nonperfused extremity will demonstrate venous refill when it is dependent. Measurement of compartment pressures may be valuable in selected patients, with decompression recommended when measured pressures are above 30 cm H_2O. In most situations, serial clinical examination is sufficient to determine the need for escharotomy or fasciotomy, thereby avoiding the risk of bacterial seeding posed by passing pressure-monitoring catheters through contaminated wounds. Compromised extremities should be promptly decompressed by escharotomy or fasciotomy before the development of irreversible tissue necrosis (E-Fig. 97-1).

Abdominal Compartment Syndrome

If abdominal viscera become extremely edematous, abdominal compartment syndrome may result.[12] This syndrome, which is usually caused by edema of the bowel wall, occurs after abdominal trauma or after the gut is reperfused by resuscitative therapies. When intra-abdominal pressures exceed 25 mm Hg (34 cm H_2O), renal blood flow, inferior vena cava blood return, and diaphragmatic excursion are impaired. This syndrome typically is manifested with oliguria, hypotension, and difficult ventilation. Diagnosis is by physical examination and measurement of bladder pressure. Treatment is by laparotomy with temporary abdominal closure.

Phase Two: Initial Surgical Care

Phase Two includes initial wound excision for burn patients and initial resuscitative surgery and fracture stabilization for non-burn trauma patients. This phase frequently overlaps with Phase One but is usually completed within 72 hours. Multiple subspecialty surgical teams may need to be coordinated by a trauma surgeon who directs overall care and reconciles conflicting priorities.

Early Wound Excision

Excisional débridement of nonviable soft tissues or deep burns during the first days following injury, before heavy microbial colonization occurs, will reduce the incidence and severity of sepsis from burns, crush, or other soft tissue trauma.

TABLE 97-2 CATEGORIZATION AND INITIAL TREATMENT OF HEMORRHAGIC SHOCK*

	CLASS I	CLASS II	CLASS III	CLASS IV
Blood loss (mL)	≤750	750-1500	1500-2000	≥2000
Blood loss (% of blood volume)	≤15	15-30	30-40	≥40
Pulse rate	<100	>100	>120	≥140
Blood pressure	Normal	Normal	Decreased	Decreased
Capillary refill test	Normal	Positive	Positive	Positive
Respiratory rate	14-20	20-30	30-40	>35
Urine output (mL/hr)	≥30	20-30	5-15	Negligible
Mental status	Slightly anxious	Mildly anxious	Anxious and confused	Confused and lethargic
IV fluid replacement (3 : 1 rule)	Crystalloid	Crystalloid	Crystalloid + blood	Crystalloid + blood

*Based on a 70-kg adult.
IV = intravenous.
From Demling RH, Gates JD. Medical aspects of trauma and burn care. In: Goldman L, Schafer AI, eds. *Goldman's Cecil Medicine*. 24th ed. Philadelphia: Saunders-Elsevier; 2012.

E-TABLE 97-1 BURN INTRAVENOUS RESUSCITATION FORMULA

FIRST 24 HOURS

Adults and Children >20 kg

- Lactated Ringer solution: 2-4 mL/kg per percentage of total body surface area (TBSA) burned per 24 hours (first half in first 8 hours)
- Colloid: in many patients, particularly those with small injuries, no colloid is advised in the first 24 hours. However, colloid, generally as 5% albumin solution, is increasingly used early in resuscitation of patients with large burn injuries. This is program specific and should ideally be discussed with the unit to which the child with a large injury will be referred.

SECOND 24 HOURS—ALL PATIENTS

- Crystalloid: to maintain urine output. If silver nitrate is used, sodium leaching will mandate continued isotonic crystalloid. If other topical agents are used, then free water requirement is significant. Serum sodium should be monitored closely.
- Nutritional support should begin, ideally by the enteral route.
- Colloid (5% albumin):
  - 0-30% burn: none
  - 30-50% burn: 0.3 mL/kg per percentage of TBSA burned per 24 hours
  - 50-70% burn: 0.4 mL/kg per percentage of TBSA burned per 24 hours
  - 70-100% burn: 0.5 mL/kg per percentage of TBSA burned per 24 hours

E-FIGURE 97-1. **Tight extremities should be promptly decompressed by escharotomy or fasciotomy before the development of irreversible tissue necrosis.**

Damage Control Surgery

Damage control surgery identifies the most important surgical tasks that must be done to save the patient's life, and only these tasks are performed initially, thereby allowing a more stable patient to return to the operating room later for a subsequent definitive and often time-consuming operation. The prototypical example is for abdominal trauma, when bleeding and gastrointestinal contamination are addressed initially but the abdomen is left open so a warmed and more stable patient can return to the operating room in 12 to 36 hours for a definitive bowel anastomosis and abdominal closure. This concept can also be applied to the trauma care system. If multiple patients need to share limited operating room resources, truncating individual operations allows more patients to be treated urgently.

Early Fracture Fixation

Early surgical fixation of long bone fractures benefits injured patients by reducing the complications of immobilization, enhancing rehabilitation, and likely reducing the systemic inflammatory state and proclivity to thromboembolic complications.

Prophylaxis for Thromboembolic Complications, Gastrointestinal Hemorrhage, and Infection

Trauma incites a hypercoagulable state, and seriously injured patients are prone to deep venous thrombosis and pulmonary embolism. Prophylaxis using low-molecular-weight heparin and/or automatic compression stockings has become routine in most trauma programs.

During the early hypodynamic phase with reduced splanchnic blood flow, gastrointestinal hemorrhage may occur in the seriously injured or burned patient. This complication can be sharply reduced with routine pharmacologic prophylaxis, including proton pump inhibitors or histamine-2 receptor blockers.

Prophylactic antibiotics are not recommended[A5] except perhaps in patients who have severe burns and require mechanical ventilation or who have undergone split-thickness skin grafting, because they can promote the growth of resistant organisms.[13] However, careful observation and prompt cultures in febrile patients are critical for optimal management.

Critical Care of the Injured or Burned

Many injured patients require transient intubation and mechanical ventilation (Chapter 91) to facilitate resuscitation, evaluation, and initial care. Some will go on to develop respiratory failure (Chapter 90) requiring protracted ventilator support.

Multiple mechanical and injury factors contribute to respiratory insufficiency in trauma patients, including chest wall trauma and pulmonary contusion. In patients with more severe injuries, including flail chest, rib fixation is a useful intervention.

In burn patients, inhalation injury (Chapter 82) is an important cause of respiratory failure. The diagnosis of inhalation injury is best made by history and clinical examination revealing singed nasal vibrissae and carbonaceous debris in the mouth and pharynx (E-Fig. 97-2). Chest radiographs are usually normal initially. Airway management is challenging but generally is similar to non-burn patients.[14] Carbon monoxide poisoning (Chapter 82) can be seen in conjunction with inhalation injury; the standard of care is 100% oxygen at the prevailing atmospheric pressure for 6 hours, with hyperbaric oxygen reserved for patients with a carboxyhemoglobin level above 30% or neurologic changes.

Pneumonia (Chapter 85) or tracheobronchitis (Chapter 84) occurs in about 30% of burn patients with inhalation injury. Acute respiratory distress syndrome (Chapter 90) also is common in burn and trauma patients, particularly those who go on to develop sepsis, pneumonia, and multiple organ failure. Antibiotic therapy is directed by sputum Gram stain and cultures and should not be prolonged beyond a 7- to 10-day therapeutic course. Vigorous pulmonary toilet, with directed bronchoscopy to clear secretions in selected patients, is an important component of therapy.

Post-Resuscitation Metabolic Issues

In the days that follow successful resuscitation, a hyperdynamic state predictably occurs, characterized by a high cardiac output and low peripheral resistance. Excision of necrotic tissue, prevention of tissue ischemia by repair of vascular injuries, and prompt management of compartment syndromes will minimize the burden of necrotic tissue and reduce post-injury infection and hypermetabolism (E-Fig. 97-3).

Several formulas have been devised to predict non-protein calorie needs (E-Table 97-2). A very rough estimate of calorie needs is a range of 25 to 35 kcal/kg/day, with the lower number applying to more stable and older patients and the upper number applying to more seriously injured and younger patients. Protein administration of 2 to 3 g per kilogram per day will adequately support the needs of most injured patients.

The route of nutritional support is ideally enteral (Chapter 198), with tube feeding beginning during resuscitation. However, some patients, particularly those with very severe and abdominal injuries or those with intervening sepsis, will not tolerate enteral feedings at goal rates and will require supplemental parenteral nutrition to ensure delivery of all needed nutrients (Chapter 198).

Safe and reliable modification of adverse components of the hypermetabolic response, particularly protein catabolism, has proved an elusive goal. Anabolic agents such as recombinant human growth hormone and anabolic steroids may help restore positive nitrogen balance but are not universally used because of their complications, expense, and conflicting data regarding the efficacy. Other attempted interventions, such as enteral glutamine,[A6] antipyretics, β-adrenergic blockade, β-adrenergic supplementation, nonsteroidal anti-inflammatory agents, recombinant growth hormone, insulin-like growth factor-I, and anabolic steroids, have been tried, but available data are inadequate to support any of these therapies as standard care.

Septic Complications and Multiple Organ Failure

Injured patients are at elevated risk for a multitude of infectious complications (Chapter 261). Multiple organ dysfunction and septic shock (Chapter 94) are manifestations of uncontrolled systemic inflammation for severe infection.

Phase Three: Definitive Surgical Care

Phase Three involves definitive wound closure for burns and completion surgery for trauma patients. In non-burn trauma patients, this phase may involve removal of vacuum wound dressings and definitive closure, closure of fasciotomy sites, and fixation of facial fractures. The duration of this phase varies greatly with injury, but it is usually complete at the time of acute hospital discharge. For example, in burn patients, this phase of care is defined by replacement of temporary membranes with permanent grafts and the important but time-consuming grafting of hands and face.

Phase Four: Rehabilitation and Reintegration

Phase Four describes the sometimes long process of reconstruction, rehabilitation, and reintegration.[15] This phase of care may begin in an inpatient rehabilitation setting and progress into the home environment. Depending on the specifics of the injury, the process may be a few weeks to months or years. Daily passive range-of-motion movements, splinting, anti-deformity positioning, and strengthening can reduce the frequency of these complications.

The environment of recovery is an important therapeutic consideration. Data suggest that specific qualities of the family have a major impact on multiple aspects of recovery, some that can potentially be modified. Community resources can be used to enhance recovery and are an important part of discharge planning. Attempts to reduce opiod use during the acute phase may reduce overall opiod use during the hospital course and afterwards.[A7]

REHABILITATION OF THE INJURED PATIENT

REHABILITATION IN THE CRITICALLY ILL PATIENT

Passive range-of-motion movement, splinting, and anti-deformity positioning will minimize the capsular contraction and shortening of tendon and muscle groups that otherwise occur with protracted immobilization.

Emotional recovery after severe trauma can be limited by neurologic injury and post-traumatic stress. These issues can be anticipated and their adverse effects blunted by early and continuous involvement of emotional supports for the family and patient. Ideally, psychiatric, social service, and psychological resources are available.

SPECIAL CONSIDERATIONS

Electrical Injury

Cardiopulmonary arrest can be caused by low-voltage electrical injury but is more common with high-voltage electrical injury. Extensive tissue necrosis may also liberate enough potassium to cause cardiac dysfunction. Because cardiac arrhythmias may recur after resuscitation or develop 24 to 48 hours after injury, all patients who have sustained high-voltage electrical injury should undergo continuous electrocardiographic monitoring for at least 24 to 48 hours after the last documented arrhythmia.

Deep muscle necrosis can be initially inapparent, so many patients benefit from serial operative evaluation and débridement. Recovery of function after direct electrical nerve damage is rare. Conversely, the nerves that are not injured directly commonly recover. Rarely, a polyneuritic syndrome of relatively late onset can cause deficits in the function of peripheral nerves far removed from the points of contact. Among patients hospitalized with serious high-voltage electrical injuries, about 8% die and another 22% have permanent neurologic deficits despite optimal care. Most patients with low-voltage injuries, such as can be caused by electrical flash burns, also develop long-term sequelae, including neurologic (memory loss, numbness, headache, chronic pain, weakness) and musculoskeletal (pain, reduced range of motion, contracture) symptoms.

E-FIGURE 97-2. Inhalation injury is predicted by history and physical findings, including soot in the mouth and teeth as shown here.

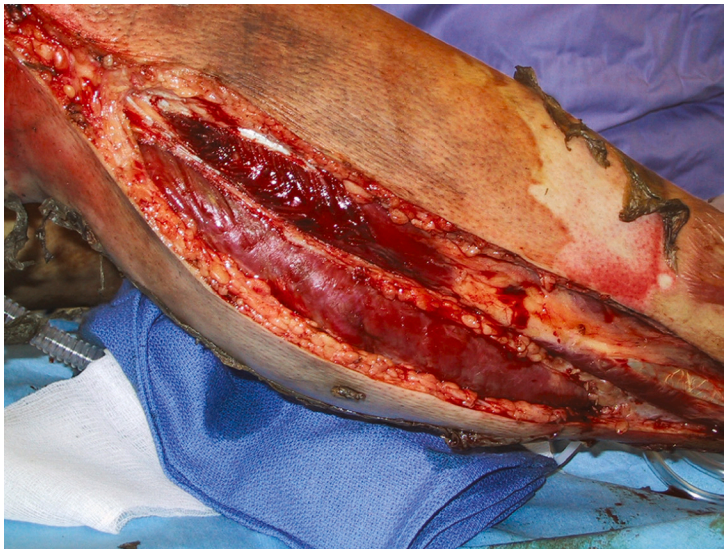

E-FIGURE 97-3. Prevention of tissue ischemia of edematous limbs by escharotomy or fasciotomy will minimize the burden of necrotic tissue.

E-TABLE 97-2 MODIFIED HARRIS-BENEDICT EQUATION

MALE PATIENTS
BMR = 88.362 + (13.397 × weight in kg) + (4.799 × height in cm) − (5.677 × age in years)
FEMALE PATIENTS
BMR = 447.593 + (9.247 × weight in kg) + (3.098 × height in cm) − (4.330 × age in years)

BMR = basal metabolic rate.

From Roza AM, Shizgal HM. The Harris Benedict equation reevaluated: resting energy requirements and the body cell mass. *Am J Clin Nutr*. 1984;40:168-182.

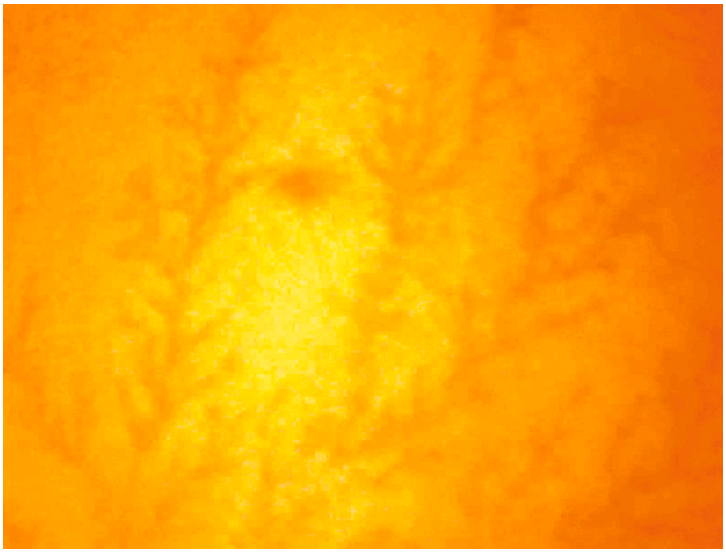

FIGURE 97-9. The "flowers of Lichtenberg" is an evanescent cutaneous phenomenon commonly seen in lightning-struck patients.

Lightning Injury

Cardiopulmonary arrest is common in patients struck by lightning.[16] The "flowers of Lichtenberg" is an evanescent cutaneous phenomenon commonly seen in lightning-struck patients (Fig. 97-9). Coma is also common acutely but typically resolves in a few hours. Keraunoparalysis, which is lightning-induced paralysis, is characterized by usually transient paresthesias and paralysis that develop during several days and typically involve the lower limbs. Ruptured tympanic membranes and hearing loss may also occur. With immediate cardiopulmonary resuscitation, about two thirds of lightning victims survive, and persistent neurologic deficits are relatively uncommon.

Considerations at the Extremes of Age

Injured patients at the extremes of age bring with them a number of important physiologic and psychosocial issues that directly affect their care (E-Table 97-3). Older adults do not have the depth of physiologic reserve of the young (Chapter 24). Cardiopulmonary function may be compromised, and peripheral vascular disease is common. Muscle mass and respiratory muscle strength are often reduced. Reduced renal reserve increases sensitivity to nephrotoxic drugs. The skin is relatively atrophic and consequently tolerates burning and donor harvest poorly. Nutritional needs are not well predicted by standard equations.

As a result, a major injury is often the event that changes the subsequent living condition of an elderly person. Injuries are often the result of cognitive or functional changes (Chapter 361) and may be associated with syncopal episodes (Chapter 49) that need to be concurrently evaluated. Resuscitation should be carefully considered if burns are very large or trauma is severe. Data suggest that mortality is nearly 90% in patients who are older than 60 years, have burns of more than 40% of their body surface, and have concomitant inhalation injury. Patients may have advanced directives, interested families, or health care proxies who should be consulted as early as possible in the care of such patients (Chapter 3).

Older adults bring unique psychosocial issues to the trauma and burn center. They may live alone or have a spouse who cannot meet their discharge care needs for wound care, transportation, or general support. Children may live far away and be unable to support them. Discharge planning can be very involved, requiring orchestration of many community resources, and must be started early.

Emotional Consequences of Injury

Most patients who suffer significant injury will develop some degree of acute stress disorder characterized by anxiety, hypervigilance, fear, and re-experiencing the event.[17] This normal reaction can become pathologic and debilitating as post-traumatic stress disorder (Chapter 362). Early recognition and emotional support can blunt this progression and enhance both short-term rehabilitation and long-term recovery.

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98 ENVENOMATION, BITES, AND STINGS

STEVEN A. SEIFERT†, RICHARD C. DART, AND JULIAN WHITE

EPIDEMIOLOGY

Envenomation (e.g., snakebite, spider bite, scorpion stings, jellyfish stings) may seem to be a rare medical problem, but envenomation affects millions of humans annually and results in hundreds of thousands of deaths (Table 98-1). For example, the annual number of venomous snakebites is estimated to be in excess of 2.5 million per year, with more than 100,000 fatalities and hence a case fatality rate of about 1 : 25. Another common envenomation, jellyfish stings, affects more than 1 million people per year, with a case fatality rate of about 1 : 10,000. The epidemiology of envenomations will differ by region. In Australia, for example, spider bites cause nearly twice as many hospital visits as compared with snakebites. In the United States, spider bites reported to poison centers are roughly equal to the number of venomous snakebites (about 5000 to 10,000 per year),[1] whereas reports of scorpion envenomations are nearly double that number.

PATHOBIOLOGY

Envenomation occurs when a venomous animal, usually via a bite or sting, injects a physiologically impactful quantity of venom into a target animal. A venomous animal may bite or sting without injecting enough venom to cause effects (a "dry bite"),[2] so signs of envenomation will not always develop. The rate of dry bites will vary by species and other circumstances. In the United States, for example, viperid bites have about a 20% dry bite rate, whereas elapid bites have about a 50% rate. Some snake species lack the capacity to envenomate because they have no venom apparatus.

Venom is an often complex mixture of a number of substances, including toxins. Venoms can be produced in specialized glands (e.g., venomous snakes, scorpions, spiders, cone snails, venomous stinging fish, stingrays) or cell structures (e.g., jellyfish nematocysts), or they can be acquired from the environment and concentrated in specific glands/organs (e.g., venomous octopuses). The function of venom is to assist the animal as a predator and/or in defense against predation.

CLINICAL MANIFESTATIONS AND DIAGNOSIS

Most envenomations are accompanied by dermatologic findings, commonly at the site of the bite or sting (Fig. 98-1), starting with the puncture mark(s) of

†Deceased.

E-TABLE 97-3 PSYCHOSOCIAL AND PHYSIOLOGIC CONSIDERATIONS IN GERIATRICS

- Injury mechanisms more often involve compromised mobility or dexterity.
- Injuries may reflect an inability to safely live alone.
- Injuries occur during syncopal episodes.
- Resuscitation should be carefully considered if burns are very large, particularly in the presence of inhalation injury.
- Patients may have advanced directives, interested families, or health care proxies who should be consulted as early as possible in their care.
- Older adults often do not have the physiologic reserve of the young.
- Pulmonary function may be compromised by years of smoking.
- Occult or overt coronary artery or peripheral vascular disease may exist.
- Muscle strength, including respiratory muscles, may be reduced.
- Renal function may be reduced with resulting greater sensitivity to nephrotoxic drugs or hypotensive insults.
- Nutritional needs of the elderly are poorly predicted by standard predictive equations.
- The skin of the elderly person is thin and therefore sustains full-thickness injury more readily and tolerates repeated donor harvest less well.
- Older adults may live alone or have a spouse who cannot reasonably meet post-discharge needs.
- Discharge planning may be very involved and must be started early.

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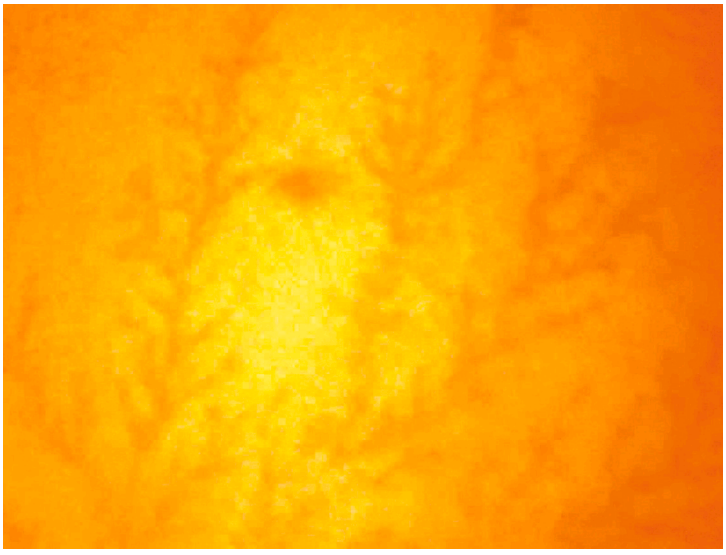

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STEVEN A. SEIFERT†, RICHARD C. DART, AND JULIAN WHITE

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CLINICAL MANIFESTATIONS AND DIAGNOSIS

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ABSTRACT

Envenomation (e.g., snakebite, spider bite, scorpion stings, jellyfish stings) may seem to be a rare medical problem, but envenomation affects millions of humans annually and results in hundreds of thousands of deaths. For example, the annual number of venomous snakebites is estimated to be in excess of 2.5 million per year, with more than 100,000 fatalities (and hence a case fatality rate of about 1 : 25). Another common envenomation, jellyfish stings, affects more than 1 million people per year, with a case fatality rate of about 1 : 10,000. Envenomation by arthropods is also a substantial worldwide problem. Dangerous scorpions, limited to mainly the Buthidae family, are distributed worldwide. Ticks, mites, hymenoptera, and various other insects also produce a wide array of envenomation syndromes. Finally, marine animals not only produce envenomations but also are a major source of foodborne illness.

KEYWORDS

envenomation
snakes
spiders
scorpions
arthropods
insects
venom
toxin
antivenom
marine
foodborne
bite
sting

TABLE 98-1 ESTIMATED ANNUAL GLOBAL IMPACT OF SOME SELECTED MAJOR GROUPS OF VENOMOUS ANIMALS AFFECTING HUMANS

VENOMOUS ANIMAL GROUP	ESTIMATED NUMBER OF NEW CASES PER YEAR	ESTIMATED NUMBER OF FATAL CASES PER YEAR
Venomous snakes	>2.5 million	>100,000
Scorpions	>1 million	<5000
Stinging insects	>1 million	>1000 (mostly due to anaphylactic reaction to venom in sting)
Jellyfish	>1 million	<100
Spiders	>100,000	<100
Venomous spiny fish and stingrays	>100,000	<10
Paralysis ticks	>1000	<10
Venomous mollusks (blue-ringed octopus, cone snails)	<1000	<10

the biting or stinging apparatus. Local tissue injury might result from mechanical effects and/or cytotoxic venom components that produce tissue edema, which may remain local, spread, or progress to necrosis. Snakes, scorpions, spiders, and jellyfish commonly have venoms that can injure tissue.

Systemic effects may include nausea and vomiting, bleeding, thrombosis, renal impairment, neurotoxicity, and even pituitary abnormalities or more specific end-organ effects, such as hematologic derangements, vascular toxicity, nephrotoxicity,[3] or neurotoxicity. For example, some snake, scorpion, and caterpillar venoms can produce thrombosis or uncontrolled bleeding. Snake, tick, blue-ringed octopus, and cone snail venoms are all capable of impairing transmission at the neuromuscular junction and causing paralysis (Table 98-2). Some scorpions, spiders, and jellyfish have venoms that can cause excitatory neurotoxicity, with pain, sweating, autonomic effects, cardiotoxicity, and pulmonary edema.

Key points of the history include time, place, and circumstances of the bite or sting; whether the patient was bitten/stung once or multiple times; a description of the offending animal if witnessed; the type and timing of first aid application; the type and time of onset of any symptoms; relevant past medical history; and any medications used. Some envenomation scenarios (e.g., attempting to capture or kill an offending animal, collections of venomous animals, multiple stings by a colony of marine animals) may include multiple bites or stings and may include multiple envenomating animals. Any symptoms of specific toxic effects (e.g., symptoms of progressive paralysis, neuroexcitation, myolysis, coagulopathy, cardiotoxicity, acute kidney injury, allergy) and systemic effects (e.g., headache, nausea/vomiting, abdominal pain, collapse, convulsions) should be sought. Examination should similarly target specific venom effects, including careful examination of the bite or sting site and a careful neurologic examination (Chapter 366).

Laboratory tests will vary depending on the likely animal and the consequent likely risks (e.g., a coagulation profile for venomous snakes). Clinical venom identity testing is available only for Australian snakebites. Hematologic tests typically should include a complete blood and platelet count, a fibrinogen level, and an international normalized ratio (INR). In some locations, the 20-minute whole-blood clotting test may be useful.

TREATMENT

Envenomation may be an obvious diagnosis or a cryptic presentation in which a bite/sting may not be suspected. Many cases of venomous bites/stings result in only mild effects, but clinical events can progress rapidly and require similarly time-sensitive treatment. The best approach is to assume every case may develop into severe envenomation and to ensure urgent and context-sensitive initial assessment, followed by ongoing reassessment over the major at-risk period. It is often very important to reassess all patients at 10- to 15-minute intervals for 8 to 12 hours to detect any developing symptoms, signs, and laboratory abnormalities.

The first aid provided to an envenomated patient before reaching definitive medical care may significantly impact final outcome. Bites and stings are traumatic wounds and should undergo thorough cleansing, evaluation for retained foreign bodies (e.g., teeth, fangs), and tetanus prophylaxis as for any contaminated wound (Chapter 15). In general, prophylactic antibiotics are not effective at preventing infection, and there is no role for glucocorticoids, antihistamines, or other allergy treatments unless the patient is having an acute allergic reaction. In addition, many commonly used first-aid methods, such as tourniquets, incisions, suction devices, electric shock, and snake stones, are ineffective or dangerous and should not be used. Key worthwhile first aid includes immobilizing the bitten limb and the patient if possible; anticipation of swelling with removal of jewelry and loosening or removal of tight-fitting clothing; support of airway, breathing, and circulation (Chapters 7, 50, 90, 92) as needed; and rapid transport to medical care. Local cryotherapy reduces the local inflammatory response and may reduce the needed dose of antivenom therapy and length of hospitalization.[A1] For snakebites by species that do not cause significant local tissue damage (e.g., Australian snakes, sea snakes, coral snakes, kraits, non-necrotic cobras, and South American rattlesnakes) and for Australian funnel web spider bites, the Australian pressure bandage and immobilization technique (E-Fig. 98-1)—which involves wrapping the entire extremity with a bandage, achieving lymphatic obstructive pressures of 40 to 70 mm Hg in the upper extremity and 55 to 70 mm Hg in the lower extremity, followed by immobilization to retard venom absorption—obstructs lymphatic flow but requires substantial training to apply effectively. Box jellyfish stings should be copiously irrigated with distilled ("white") vinegar (5 to 8% acetic acid), whereas all other jellyfish stings and fish/stingray stings respond to immersion in hot water (up to 45° C).

Some types of envenomation are associated with acute coagulopathy, so potentially problematic cannulations and injections should be avoided until any coagulopathy has been corrected. Hemolysis may result in insufficient oxygen-carrying capacity. The risk of spontaneous hemorrhage increases with platelet counts below 50,000/μL, and uncontrolled hemorrhage or thrombosis may occur with complete or near-complete consumption of fibrinogen. Consumption of clotting factors in the coagulation cascade may also increase the risk of spontaneous hemorrhage with an INR greater than 3.

In many cases of suspected envenomation, an intravenous fluid bolus (e.g., normal saline or a balanced salt solution, 10 to 20 mL/kg in the first hour of treatment) may be helpful, particularly in patients with fluid losses from subcutaneous edema, diarrhea, or decreased intake.

A swollen limb should be elevated with frequent monitoring to exclude severe rhabdomyolysis or an acute compartment syndrome (Chapter 97). Other than for bites by snakes with particularly long fangs, such as Gaboon vipers, tissue compartments bounded by rigid fascia are generally deeper than most venomous animals' fangs can reach. An exception is the anterior tibial compartment, which is relatively close to the surface. Nevertheless, elevated tissue pressures may result from subcutaneous deposition of venom and local fluid accumulation that extends to the elastic limits of the skin. Surgical intervention may be considered for patients with directly measured increases in tissue pressures despite adequate antivenom, elevation, and 20% mannitol (1 to 2 g/kg, IV over 1 to 2 hours), but animal studies have shown superior outcomes with antivenom alone. Similarly, dèbridement of necrotic tissue should generally be delayed until after acute envenomation problems have resolved, and it should be delayed for weeks for recluse spider bites.

In patients with evidence for neurotoxic paralysis, intubation and mechanical ventilation may be required (Chapter 91). Antivenom may reverse postsynaptic paralytic neurotoxicity, but an anticholinesterase (neostigmine, 35 μg/kg IV) may also be useful as adjunctive treatment. Patients who respond convincingly to the initial dose of neostigmine may receive repeated doses (up to 35 μg/kg every 1 to 3 hours, and up to 140 μg/kg per 24 hours), together with atropine as needed to block its muscarinic side effects. However, antivenom may not reverse established respiratory paralysis caused by presynaptic neurotoxins. Acute kidney injury may require dialysis (Chapter 117) for days to weeks, but renal function usually recovers. For important venomous animals without a corresponding effective antivenom, non-antivenom treatments must be used.

Antivenom

Antivenom is made by hyperimmunizing an animal (most commonly a horse, but also sheep, goats, dogs, and rabbits) against the venom, harvesting the antibody, and refining it into the final product.[4] The product may be whole IgG, or its $F(ab')_2$ or Fab fractions, and these products may further undergo purification by various methods to reduce adverse effects.

If the identity of the venomous animal is known, a monovalent genus- and/or species-specific antivenom should be administered. If the identity of the animal is uncertain, a polyvalent antivenom or mixture of antivenoms is preferred. Geographically appropriate, species-specific antivenom should be sought, but a paraspecific antivenom, which was produced for a different genus or species, occasionally may be effective. Antivenoms are typically dosed by the vial, as specified in the products' package inserts, because their neutralizing power varies from product to product. Since the amount of venom to be neutralized is not based on the victim's size, children may require the same or even higher doses of antivenom and may also require that the antivenom be reconstituted in a smaller volume to help manage the fluid load.

Adverse effects of antivenom include type 1 hypersensitivity reactions, with immediate or early onset of pruritus, urticarial rash, wheezing, laryngeal edema, hypotension, and other signs of an anaphylactoid reaction

E-FIGURE 98-1. Pressure bandage with immobilization. (This technique is to delay central progression of venom via lymphatics until definitive therapy (antivenom) can be administered. It was developed for Australian Elapid snakes and other snakes that do not routinely produce significant local tissue injury, including sea snakes, coral snakes, kraits, mambas, and some nonspitting cobras. This technique is considered inappropriate for most viperid envenomations (e.g., U.S. rattlesnakes, copperheads, cottonmouths) in which local tissue injury is a major effect. **Upper image:** A clean broad bandage (crepe or elastic) is bound over the bite site at about the same pressure as for a sprain. For bites to digits, the bandage should be applied proximally to the hand or foot, then over all digits together, rather than binding up the bitten digit alone, because this may potentially cause significant vascular impairment if local swelling develops, thereby increasing the likelihood of tissue injury to the affected digit. **Central image:** An elastic bandage is wrapped from the toes to the groin at about the same pressure as for a sprain. Ideally, obtain a constant under-bandage pressure of 50 to 70 mm Hg, ensuring there is no vascular compromise of the limb. **Bottom image:** The extremity is loosely splinted to ensure immobility. It also is important to keep the patient immobile, as far as practical.)

FIGURE 98-1. Clinical signs of envenomation. A, Snake biting thumb (brown snake, *Pseudonaja affinis*). **B,** Bite and scratch marks on thumb, with minimal local reaction (brown snake, *Pseudonaja textilis*). **C,** Python bite with large number of teeth marks (nonvenomous). **D,** Reaction in the first few hours to a bite from a Russell viper (*Daboia siamensis*). Blue discoloration from early hemorrhagic blister formation. **E,** Local oozing and ecchymosis (puff adder, *Bitis arietans*). **F,** Local swelling of bitten hand (mulga snake, *Pseudechis australis*). **G,** Developing skin damage around bite site (jararaca, *Bothrops jararaca*). **H,** Developing skin necrosis around bite site (Russell viper, *Daboia siamensis*), with blue discoloration from bruising/bleeding into the soft tissues. **I,** Extensive full-thickness necrosis days post-bite (Russell viper, *Daboia siamensis*). **J,** Blood ooze from around IV site indicative of active coagulopathy (inland taipan, *Oxyuranus microlepidotus*). **K,** Extensive bruising in bitten limb indicative of coagulopathy (green pit viper, *Trimeresurus albolabris*). **L,** Massive bruising distant from bite site indicative of severe coagulopathy (Russell viper, *Daboia siamensis*). **M,** Chemosis indicative of developing capillary leak syndrome (Russell viper, *Daboia siamensis*). **N,** Incomplete bilateral ptosis indicative of early developing neurotoxic flaccid paralysis (tiger snake, *Notechis scutatus*). **O,** Incomplete bilateral ptosis plus lateral ophthalmoplegia indicative of progressing neurotoxic flaccid paralysis (death adder, *Acanthophis antarcticus*). **P,** Fixed dilated pupils indicative of progressive neurotoxic flaccid paralysis in snakebite, not intracranial pathology (tiger snake, *Notechis scutatus*). **Q,** Complete snakebite neurotoxic flaccid paralysis requiring intubation and ventilation (taipan, *Oxyuranus scutullatus*). **R,** Myoglobinuria indicative of severe systemic rhabdomyolysis (mulga snake, *Pseudechis australis*). **S,** Widow spider bite with central blanching and surrounding erythema (red back spider, *Latrodectus hasseltii*). **T,** Widespread diaphoresis secondary to widow spider bite (red back spider, *Latrodectus hasseltii*). (All images copyright © Prof. Julian White; reproduced with permission.)

or anaphylaxis (Chapter 233). Skin testing for sensitivity to antivenom, a dangerous and unreliable practice, is no longer recommended in the United States. Non–IgE-mediated reactions, which are nonspecific and related to the rate of infusion, are usually easily managed by slowing or stopping the infusion, treating with H_1 and H_2 receptor antagonists (e.g., diphenhydramine, 25 to 50 mg IV, and ranitidine 25 to 50 mg IV) as needed, and restarting the infusion at a slower rate. IgE-mediated reactions are usually seen in patients who previously have been exposed to antivenom or components from the source animal. IgE-mediated reactions, which are usually more severe, require cessation of the infusion, treatment with H_1 and H_2 receptor antagonists (as noted earlier), and possibly the addition of epinephrine (see Chapter 233).

Type 3 hypersensitivity reactions ("serum sickness"), with rash, fever, myalgia, and arthralgias, may be seen 5 to 21 days following antivenom treatment (Chapter 230). These effects are usually easily managed with H_1 and H_2 receptor antagonists (see earlier for dosing recommendations), analgesia, and temperature control (acetaminophen, 1 g every 6 hours as needed); oral glucocorticoids (e.g., prednisone, 5 to 60 mg per day) are helpful if other treatments do not relieve signs or symptoms.

When the identity of the animal is unknown, particularly for venomous snakes, a characteristic clinical picture may indicate the most likely culprit. This process can be enhanced using diagnostic algorithms, which are available for Australia and parts of Asia (e.g., see http://www.toxinology.com or https://apps.who.int/bloodproducts/snakeantivenoms/database/).

TABLE 98-2 A FUNCTIONAL CLASSIFICATION OF SELECTED MAJOR VENOM EFFECTS IMPACTING HUMANS AND SELECTED ANIMAL GROUPS IN WHICH ACTIVITY MAY BE PRESENT

TOXIN ACTIVITY AND TARGET SITE	CLINICAL EFFECTS	PRINCIPAL CLINICAL MANIFESTATIONS	ANIMAL GROUPS
Paralytic neurotoxicity	Progressive descending or ascending flaccid paralysis (may be presynaptic, postsynaptic, or intrasynaptic [e.g., fasciculins])	Descending type: initial cranial nerve paresis commencing with bilateral ptosis, progressing to limb weakness, loss of upper airway protection, finally respiratory paralysis Ascending type: initial ataxia, progressive paralysis, finally respiratory paralysis	• Some snakes (descending) • Paralysis ticks (ascending) • Blue-ringed octopus (descending) • Some cone snails (descending)
Excitatory neurotoxicity	Rapid development of neuroexcitation	Local pain, sweating, autonomic/catecholamine storm effects, cardiotoxicity, pulmonary edema	• Some scorpions • Some spiders • Some jellyfish
Myotoxicity	Progressive systemic damage of skeletal muscles throughout body OR locally adjacent to bite site	Systemic: muscle pain, weakness, tenderness, grossly elevated blood creatine kinase, myoglobinuria; potential secondary acute kidney injury and hyperkalemic cardiac toxicity Local: local pain, swelling, potential compartment syndrome	• Some snakes
Hemostasis: procoagulant or anticoagulant/antiplatelet	Activation and/or consumption of clotting components, or inhibition of clotting	Varies depending on toxin target: consumption of fibrinogen and/or platelets causing bleeding tendency, *OR* inhibition of hemostasis causing bleeding tendency, *OR* formation of thrombi with embolic infarction	• Some snakes • Iranian scorpion (*Hemiscorpius*) • *Lonomia* caterpillars
Hemorrhagins: blood vessel wall	Direct damage to vessel wall allowing increased vascular permeability	Local swelling, bruising, bleeding Systemic vascular damage, capillary leak syndrome	• Some snakes
Cardiotoxins	Direct or indirect cardiac damage	Acute cardiac collapse or insufficiency	• Some snakes • Some scorpions • Some spiders • Box jellyfish
Nephrotoxins	Direct or indirect renal damage	Acute kidney injury; varies from mild rise in blood creatinine to full anuric renal failure	• Some snakes • Massed bee/wasp stings
Local necrotoxins	Progressive local skin/tissue injury	Skin discoloration, may progress to blister formation *AND/OR* skin necrosis and/or necrosis of underlying tissues	• Some snakes • Iranian scorpion (*Hemiscorpius*) • Recluse spiders • Some jellyfish • Stingrays
Allergy-stimulating toxins	Can induce acute allergic response, usually on subsequent bites/stings	Varies from local immune reaction (swelling, erythema, pruritus) through to full anaphylaxis	• Potentially all venomous animals • Particular problem for bees, wasps, and stinging ants

SPECIFIC ENVENOMATION SYNDROMES

SNAKES

Snakes are the most important global cause of human envenomation.[5] Venom composition varies not only between genera and species but also can vary between individuals of the same species and even within a given individual over time.

CLINICAL MANIFESTATIONS

The rate of dry bites varies among snake species, as do the average fang length, venom volume, venom toxicity, and range of clinical effects seen with envenomation (see www.toxinology.com or https://apps.who.int/bloodproducts/snakeantivenoms/database/ and E-Table 98-1). Some African and Asian cobra species have specially evolved fangs that allow them to spit a tightly direct stream of venom forward up to 2 to 3 m away. They specifically aim for the eyes, where the venom causes instant severe pain, blepharospasm, and temporary blindness, thereby incapacitating the victim and allowing the snake to escape. Venom spit ophthalmia requires prompt, copious irrigation, followed by inspection for corneal injury. Venom spit ophthalmia can result in permanent blindness, but it does not cause systemic envenomation and does not require antivenom.

Neurotoxic Paralysis

Pre- and postsynaptic snake venom neurotoxins target the neuromuscular junction and cause a progressive descending flaccid paralysis. In the United States, neurotoxic snakebite is often associated with coral snake bites (elapids), but some rattlesnake species also cause neurotoxicity. Once damaged by presynaptic neurotoxins, the axon must regrow, a process that can take days to weeks. It is critical that the earliest signs of developing paralysis be detected and antivenom given prior to more extensive damage, which antivenom cannot reverse. In contrast, postsynaptic neurotoxins bind to the acetylcholine receptor on the muscle end plate at the neuromuscular junction, external to the cell, so antivenom may reverse this type of paralysis.

Myotoxicity

Some snake venoms contain myotoxins that target muscle, either systemically (mainly skeletal muscle) or locally in the adjacent bitten limb. The former can cause severe progressive myotoxicity, often peaking more than 24 hours postbite, with muscle pain and rhabdomyolysis, as well as with occasionally massive elevations of serum creatine kinase levels (>100,000 IU/L), and myoglobinuria; acute kidney injury and hyperkalemic cardiotoxicity (see Chapter 99) may ensue. Local myotoxicity contributes to tissue injury in the bitten limb.

Coagulopathy

A consumptive coagulopathy reduces fibrinogen levels and may result in bleeding, but venoms also may inhibit coagulation or interfere with platelet function. Some species also have hemorrhagins that damage blood vessels, thereby allowing extravasation of blood, swelling, and the potential for local necrosis or shock. The Martinique viper and related species of *Bothrops* have procoagulant toxins that cause thrombosis, thereby resulting in embolic infarction (e.g., brain, heart, lungs).

Local Tissue Injury

Many snake venoms cause significant tissue injury at and adjacent to the bite site. The resulting necrosis, fluid shift, and secondary shock can be the most medically important effect of the bite. Secondary infection is mainly from streptococcus and staphylococcus species, but gram-negative organisms, mainly Enterobacteriaceae and enterococci, are common in South Africa. Prophylactic treatment with amoxicillin clavulanate is not effective in preventing secondary infection.

Other Envenomation Effects

Russell viper venom can cause direct nephrotoxicity and acute kidney injury (Chapter 106). The same species may cause hypopituitarism owing to anterior pituitary infarction (Chapter 205) and may also cause severe capillary leak syndrome. A number of other snake species may cause secondary acute

E-TABLE 98-1 SELECTED SNAKES OF MEDICAL SIGNIFICANCE

		CLINICAL EFFECTS							
SCIENTIFIC NAME	COMMON NAME	PRE-SYNAPTIC NEUROTOXICITY	POST-SYNAPTIC NEUROTOXICITY	MYOTOXICITY	COAGULOPATHY	ACUTE KIDNEY INJURY	HYPOTENSION/ SHOCK	LOCAL NECROSIS	REGION
Viperidae (Crotalinae)	**Pit vipers (New World)**								NA, SA, AS
Crotalus spp	rattlesnakes	r	–	–	+	–	+	+	NA
Agkistrodon spp	copperheads and moccasins	–	–	–	+	–	+	+	NA
Sistrurus spp	pygmy rattlesnakes	–	–	–	+	–	–	+	NA
Crotalus spp	rattlesnakes	+	–	+	+	+	–	–	SA
Bothrops spp	lancehead vipers	–	–	–	+	+	+	+	SA
Bothriechis spp	eyelash vipers	–	–	–	+	–	r	+	SA
Lachesis spp	bushmaster	–	–	–	+	+	+	+	SA
Calloselasma rhodostoma	Malayan pit viper	–	–	–	+	+	+	+	AS
Gloydius spp	Mamushis	r	–	–	+	+	r	+	AS
Hypnale spp	humpnose vipers	–	–	–	+	+	+	r	AS
Trimeresurus spp									
Protobothrops spp	green tree pit vipers	–	–	–	+	+	r	+	AS
Deinagkistrodon acutus	habus	–	–	–	+	r	+	+	AS
	hundred pace snake	–	–	–	+	–	+	+	AS
Viperidae (Viperinae)	**Vipers and adders (Old World)**								E, ME, AF, AS
Daboia russelii and *D. siamensis*	Russell viper	r	–	r	+	+	+	+	AS
Echis spp	Saw scaled vipers	–	–	–	+	+	+	+	AF, ME, AS
Bitis spp	Puff adder, Gaboon viper, etc.	r	–	–	+	r	+	+	AF, ME
Causus spp	night adders	–	–	–	–	–	–	–	AF
Atheris spp	bush vipers	–	–	–	+	r	+	r	AF
Vipera spp	adders	r	r	–	+	r	+	+	E, ME, AF, AS
Macrovipera spp									
Cerastes spp	horned vipers	–	–	–	+	r	+	+	AF, ME
Elapidae	**Cobras, kraits, etc.**								G
Micrurus spp	coral snakes	+	+	r	–	–	–	–	NA, SA
Naja spp	cobras	–	+	–	–	–	r	+	AF, ME, AS
Hemachatus haemachatus	rhinkals	–	+	–	–	–	+	+	AF
	king cobra	–	+	–	–	–	+	+	AS
Ophiophagus hannah	kraits	+	+	r	–	r	–	–	AS
	mambas	+	–	–	–	–	r	r	AF
Bungarus spp	death adders	+	+	r	–	–	–	–	AU
Dendroaspis spp	copperheads	+	+	r	r	–	–	–	AU
Acanthophis spp	broad headed snakes	–	–	–	+	–	–	–	AU
Austrelaps spp	tiger snakes	+	+	+	+	+	–	r	AU
Hoplocephalus spp	taipans	+	+	+	+	r	–	–	AU
Notechis scutatus	mulga and black snakes	–	r	+	+	r	–	r	AU
Oxyuranus spp	brown snakes	r	r	–	+	+	–	–	AU
Pseudechis spp	rough scaled snake	+	+	+	+	r	–	–	AU
Pseudonaja spp									
Tropidechis carinatus									
Hydrophiinae	**Sea snakes**								
Various species and genera	Yellow-bellied sea snake, etc.	–	+	+	–	+	–	–	Marine
Colubridae (Colubrinae)	**NFFC snakes**								G
Dispholidus typus	boomslang	–	–	–	+	r	+	–	AF
Thelotornis spp	vine snakes	–	–	–	+	r	+	–	AF
Boiga spp	brown tree snakes, etc.	–	–	–	–	–	–	–	AS, AU
Natricidae	**NFFC snakes**								AS, AU
Rhabdophis spp	keelback snakes	–	–	–	+	r	+	–	AS
Lamprophiidae	**mole vipers**								AF, ME
Atractaspis spp	mole vipers	–	–	–	+	–	+	+	AF, ME

Clinical effects: + = present in many species; – = not generally present; r = rarely present or present in only a few species; NFFC = non–front-fanged colubroid; spp = species. Region: G = global; NA = North America; SA = South and Central America; E = Europe; ME = Middle East; AF = Africa; AS = Asia; AU = Australia, New Guinea, Pacific.

kidney injury (Chapter 106), which is usually reversible, but rarely produces irreversible renal cortical necrosis.

SNAKEBITE TREATMENT IN PARTICULAR REGIONS

NORTH AMERICA

In the United States, an estimated 6000 to 8000 venomous snakebites occur per year. Pit vipers (i.e., Viperidae, subfamily Crotalinae, which includes rattlesnakes of the *Crotalus* and *Sistrurus* genera, and *Agkistrodon* species, which include the copperhead and cottonmouth) comprise the vast majority of bites (E-Fig. 98-2). Coral snakes, the only native elapid (mainly *Micrurus* species), are responsible for fewer than 100 bites per year. Approximately 50 non-native snake envenomations occur per year, primarily in private collections and zoos.

Viperid Bites

Ready availability of species-specific antivenom to viperids native to this region and a highly developed health care system has resulted in fewer than 10 deaths per year. Because the viperid antivenoms (a Fab antivenom, CroFab™ and a F(ab′)$_2$ antivenom, Anavip™) are effective against all North American viperid snake species and because differentiation from coral, nonvenomous, and non-native snakebites is usually clear from description and context, the snake does not need to be identified. In the United States, expert assistance can be obtained through regional poison centers (1-800-222-1222).

CLINICAL MANIFESTATIONS AND DIAGNOSIS

Envenomation occurs in approximately 80% of viperid bites, invariably with tissue injury that manifests as proximal progression of edema, ecchymosis, and occasionally tissue loss.[6] Pain is variable but is often severe. Swelling may be difficult to appreciate in certain areas of the body (e.g., the thigh), and patients should be observed for 8 to 12 hours to be certain that no local signs of envenomation are developing. Subcutaneous, circumferential extremity swelling may reach the elastic limits of the skin, thereby resulting in increased tissue pressures. Extravascular fluid loss from extensive edema may compromise circulating blood volume and cause hypotension or shock.

Hematologic effects, including thrombocytopenia, hypofibrinogenemia, or prolongation of INR and partial thromboplastin time (PTT), may occur, singly or in combination, usually beginning within 1 to 2 hours after the bite and peaking several hours later. Bleeding is more likely to occur and be more severe with rattlesnake bites but can also occur with copperhead and cottonmouth envenomations. Other systemic effects, including nausea, vomiting, diaphoresis, hypotension, and muscle fasciculation, may also occur. Muscle fasciculation and weakness may be seen with Mojave (*C. sculpturatus*), Southern Pacific (*C. helleri*), and other species; they rarely progress to respiratory compromise but may cause increased serum levels of creatine kinase. Rattlesnake envenomations are typically more severe than copperhead or cottonmouth envenomations. Elevation, antivenom, and mannitol (20% mannitol, 1 to 2 g/kg intravenously over 1 to 2 hours) reduce local tissue pressures. Fasciotomy is generally neither indicated nor beneficial.

TREATMENT

Jewelry and tight-fitting clothing should be removed, the bitten body part should be loosely splinted, and standard wound care should be applied. Immobilization of the bitten body part at the level of the heart is recommended. Aggressive but appropriately monitored resuscitation with normal saline infusion may be needed, guided by signs of shock (Chapter 92).

Antivenom treatment is usually initiated for any evidence of local envenomation, especially in patients with worsening significant thrombocytopenia (<100,000/μL) or hypofibrinogenemia (<100 mg/dL). When antivenom is indicated, it should be initiated as soon as possible after the bite. Isolated prolongation of the INR usually does not require antivenom, but significant prolongation (>6) may be a marker for profound hypofibrinogenemia.

Two antivenoms are available in the United States. One is ovine Fab, the other an equine Fab2. Both have been approved for use in all types of crotalid snakebites (rattlesnake, copperhead snake, water moccasin), and both begin with an initial infusion to achieve control followed by additional doses as indicated by signs and symptoms.

For the Fab antivenom, a typical initial dose is 4 to 6 vials, over 1 hour, with additional doses of 4 to 6 vials as needed for progressive or worsening symptoms or signs. Following initial control, maintenance doses of 2 vials over 1 hour (infused slowly over the first 10 minutes) are given every 6 hours for three additional doses. Local effects and coagulation factors should be measured after treatment, predischarge, and about 4 to 8 days later (Table 98-3).[A2]

F(ab′)2 antivenom starts with an initial infusion of 10 vials over 1 hour, followed by 10 additional vials to achieve initial control. If further doses are needed based on signs and symptoms, 4 vial boluses are administered. Maintenance doses are not needed for persistent local control. Late hematologic abnormalities are substantially less with F(ab′)2 than with Fab.[A3] Patients should be monitored for local effects and coagulation factors after treatment, predischarge, and about 4 to 8 days later (Table 98-3).[7]

Complete resolution and return of function may require several weeks or months. Copperhead and water moccasin bites usually do not require additional antivenom after initial control is achieved. Rarely, additional antivenom is required for persistent, recurrent, or late-onset coagulopathy.

Type 1 hypersensitivity reactions to antivenom are uncommon, usually mild, and rate related. When they occur, antivenom should be stopped. H_1 (e.g., starting with diphenhydramine, 25 to 50 mg IV every 4 to 6 hours, maximum daily dose 400 mg) and H_2 receptor antagonists (e.g., starting with cimetidine, 300 mg IV every 6 to 8 hours, maximum daily dose 2400 mg), and beta-adrenergic agents (e.g., albuterol by inhalation) should be titrated for reactive airway symptoms. Epinephrine may be given as needed for symptoms and signs of anaphylaxis. If antivenom is still thought to be needed, it can be tried at an infusion rate between one half and one tenth the initial rate, depending on the speed and severity of the initial reaction. A type 3 hypersensitivity reaction ("serum sickness"), usually mild and managed symptomatically with diphenhydramine (25 to 50 mg orally every 6 hours with or without prednisone, 5 to 60 mg orally daily for 5 days), may develop in 5 to 15% of patients treated with antivenom between 5 and 21 days post-treatment. The F(ab′)$_2$ antivenom has similar rates of hypersensitivity reactions.

Infection is uncommon, and prophylactic antibiotics are not indicated to prevent infection. The inflammatory effects of venom (erythema, warmth, lymphangitic erythema) may mimic infection after the first 24 hours, and antibiotics may reasonably be given at that time or if frank necrosis develops. The spectrum of organisms in snakebite, when infection does occur, appears to be similar to that in other contaminated wounds, mainly streptococcus and staphylococcus, but organisms may vary by geographic location.

Coral Snake Bites

Because of their smaller size and short fangs, coral snakes (Elapid snakes) cause an envenomation in only about 50% of bites. Local effects in coral snake envenomation are variable—pain and swelling occur in less than 50% of cases, so their absence cannot exclude envenomation.

Approximately 40% of patients will have local tissue edema, but necrosis is unusual. Systemic effects may include euphoria, perioral paresthesia, hypersalivation, nausea, and vomiting. Neurologic effects include progressive, descending paralysis, beginning with bulbar muscles (ptosis, diplopia, dysphagia). Respiratory muscles may be involved and cause ventilatory insufficiency and death. Symptoms may be delayed in onset but progress rapidly once bulbar muscle symptoms have begun. No routine laboratory monitoring is needed. An effective antivenom is available for North American coral snake envenomation at https://www.pfizer.com/products/product-detail/north_american_coral_snake_antivenin. Hematologic effects do not occur.

TREATMENT

A pressure-immobilization bandage or blood pressure cuff inflated to impede lymphatic flow (upper extremity: 50 mm Hg; lower extremity: 70 mm Hg) may be considered if the transport time will be long or there will be a considerable delay in administering antivenom. The pressure-immobilization technique is not recommended for North American crotaline snakebites, but it may be useful for North American coral snake bites. Antivenom can be administered in cases with likely envenomation (e.g., evidence of fang penetration and prolonged contact time) before neurologic effects are seen. Alternatively, treatment can be withheld unless and until neurologic signs appear if patients are observed very closely for 24 hours.

MEXICO, CENTRAL AND SOUTH AMERICA

Snake envenomation causes more morbidity and mortality in Mexico, Central America, and South America than in North America. The viperids of major importance include species of the *Bothrops, Crotalus*, and *Lachesis* genera (see E-Table 98-1). *Bothrops* spp, which are the predominant cause of medically significant snakebite throughout most of South and Central America, can cause local tissue swelling, blistering, necrosis, fluid shifts, and systemic effects such as coagulopathy. A number of larger *Micrurus* (coral snake) species can produce neurotoxicity, which manifests as a descending paralysis that can result in respiratory compromise and arrest. Coral snake envenomations are

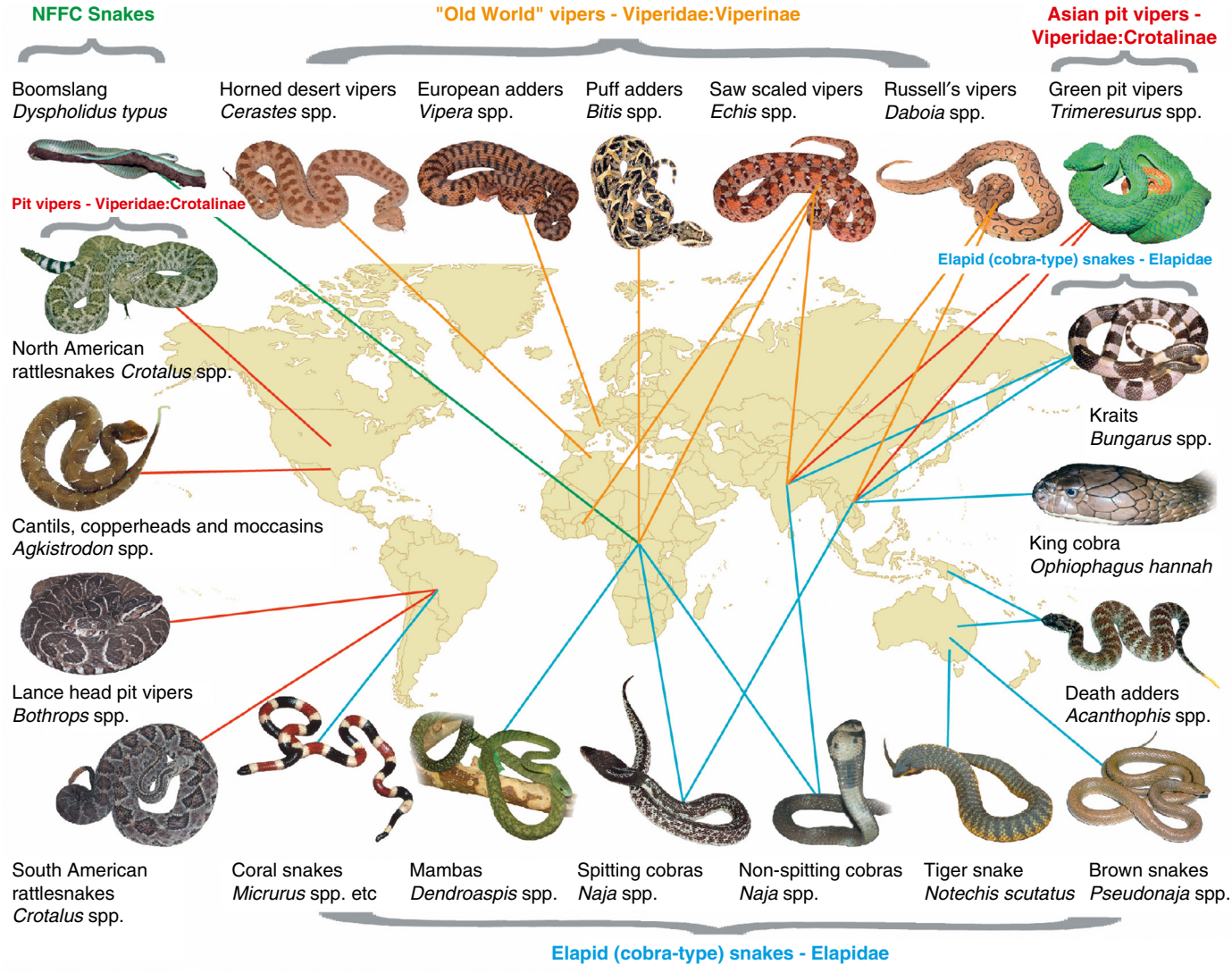

E-FIGURE 98-2. Global representation of venomous snakes. Only a few selected species of medical significance are illustrated. spp = species. (Diagram and all images copyright © Prof. Julian White; reproduced with permission.)

TABLE 98-3 LABORATORY INVESTIGATIONS FOR NORTH AMERICAN CROTALINAE BITES

Baseline tests:
- Platelet count, fibrinogen level, INR, PTT
- CK, if signs of muscle injury, fasciculation, or elevated tissue pressures

Follow-up tests:
- Platelet count, fibrinogen level, INR after the initial dose of antivenom
- Add D-dimer × 1
- Platelet count, fibrinogen level, and INR after each antivenom dose given for hematologic indications
- Predischarge fibrinogen level, INR
- Platelet count, fibrinogen level, INR at 4 and 8 days after envenomation
- Repeat as needed if values severely abnormal or worsening trend

CK = creatine kinase; INR = international normalized ratio; PTT = partial thromboplastin time.

assessed and managed similarly to North American coral snake envenomations. Appropriate antivenoms are available for most species at http://apps.who.int/bloodproducts/snakeantivenoms/database/snakeframeset.html.

Other viperid pit-viper genera (including *Agkistrodon, Atropoides, Bothriechis, Cerrophidion, Ophryacus,* and *Porthidium*), particularly in Central America, can cause significant envenomation similar to *Bothrops* spp. Compared with North American rattlesnakes, South American rattlesnakes (*Crotalus* spp) typically cause less swelling, blistering, and necrosis but more systemic envenomation, particularly neurotoxicity (descending paralysis), systemic rhabdomyolysis with secondary renal damage, and procoagulant coagulopathy.

EUROPE

The medically important European snakes are the native vipers, mostly in Southern Europe and the Balkans, but also in parts of Scandinavia and in the United Kingdom. Several major species can cause severe, even lethal, envenomation, especially in children.

Local swelling can be extensive with fluid shifts and secondary shock, particularly in children. Coagulopathy may develop with bleeding and extensive bruising. Cardiac problems and even acute kidney injury have been reported. The venom of some populations of vipers, particularly *Vipera ammodytes* and *V. aspis*, contains neurotoxins that can cause paralytic effects, primarily to the cranial nerves such as ptosis.

Significant adder/viper bites in Europe warrant antivenom.[8] The dose depends on the type of antivenom, the type of snake, and the degree of severity of envenomation. Acute and ongoing fluid management is important. Poison centers are available in several countries and should be utilized where available.

ASIA

Asia is home to many venomous vipers (including pit vipers) and elapids, with sea snakes in coastal marine waters (see E-Table 98-1). Snakebite and its consequences are more common in Asia than anywhere else in the world, with snakebites predominantly an occupational disease of rural workers. Contributing explanations include the diversity of snake fauna, the size of the human population, and the extent of rural exposure without access to good health care. In India alone, at least 45,000 people die annually following snakebites. In adjacent river delta regions of Bangladesh, snakebites are the second most common cause of death during flooding events—less than drowning but more than all infectious and other diseases. In Myanmar, snakebite accounts for more than 70% of all cases of acute kidney injury. In Sri Lanka, up to 40,000 snakebites are recorded per year.

A variety of different snake envenomation syndromes can help guide diagnosis, which relies on a targeted history and physical examination, as well as simple tests for coagulopathy (20-minute whole-blood clotting test), and kidney damage (dipstick urine test, hourly urine output measurement; E-Table 98-2).

Antivenom is the mainstay of treatment (www.toxinology.com, or https://apps.who.int/bloodproducts/snakeantivenoms/database/), but the availability and quality of the antivenom are often an issue. Because some regional antivenoms have high rates of adverse reactions, including anaphylaxis, premedication with subcutaneous epinephrine (for adults, 0.25 mL of a 1 : 1000 solution, subcutaneously) is recommended to reduce overall risk. Corticosteroids, even intravenously, are not helpful, nor is the administration of fresh frozen plasma for coagulopathy in Russell viper envenomation.[A4] The mortality after snakebites is related to delayed access to treatment and suboptimal care.[9]

AFRICA

Africa is an important global region for snakebite,[10] but epidemiologic statistics are not widely available. Examples of known risks include saw scaled viper bites in West Africa as well as puff adder bites and cobra bites throughout much of sub-Saharan Africa. In the more arid areas of North Africa, scorpion stings may surpass snakebites as the leading cause of envenomation.

Key African snake species include viperids (e.g., puff adders and relatives, saw scaled vipers, night adders, bush vipers, desert horned adders, Persian horned vipers, vipers; there are no pit vipers endemic to Africa) and elapids (e.g., cobras, some of which are spitters; coral snakes; mambas; rhinkals; desert cobras). Unique to Africa and the Middle East are the side fanged burrowing asps. A few non–front-fanged-colubrid African snakes can cause fatal envenomation (e.g., boomslang, vine snakes). Rarely the pelagic sea snake (*Pelamis platurus*) reaches East African coastal waters.

The clinical effects vary with the genus and species (see E-Table 98-1). Puff adders and their close relatives may cause local bleeding but rarely a detectable coagulopathy.

TREATMENT

Treatment principles are similar to other regions, but antivenom is unavailable or unaffordable in most of sub-Saharan Africa. When available, antivenom is useful for saw scaled viper bites, but antivenoms may not be effective for coagulopathy caused by some other *Echis* and *Cerastes* spp. In that setting, clotting replacement factor may be helpful. For the rare cases of severe coagulopathy caused by boomslang and vine snake bites, particularly for vine snake bites for which there is no antivenom, blood products and clotting factor concentrates may be useful.

Spitting cobra venom spat into the eye can cause permanent blindness if inadequately treated. Urgent copious irrigation of the affected eye(s) with water, saline, Ringer solution, buffered commercial eye wash, or other bland fluid is required, with analgesia/anesthesia as needed, followed by assessment for corneal injury and appropriate treatment. Antivenom should not be instilled into the eye. Systemic envenomation is not expected after venom spit into the eye.

AUSTRALIA AND NEW GUINEA

EPIDEMIOLOGY

All venomous snakes of medical significance in Australia and New Guinea are elapids, which account for more than about 1000 annual venomous snakebites in Australia and 3300 in Papua New Guinea.[11] In Australia, up to several hundred patients will require antivenom, and two to four patients typically die each year, primarily from prehospital cardiac collapse. In Papua New Guinea, as many as 900 fatalities occur each year, most outside of the hospital system.

CLINICAL MANIFESTATIONS AND DIAGNOSIS

Each individual snake may have a distinct venom. Significant local effects are uncommon for most species, except for genus *Pseudechis*, whose bites may cause local swelling and pain, without necrosis.

The combination of systemic and local effects can be interpreted using diagnostic algorithms to help determine the type of snake and, therefore, which type of antivenom to use. (See http://www.toxinology.com or https://apps.who.int/bloodproducts/snakeantivenoms/database/.)

The venom detection kit can help determine which type of antivenom to use in a systemically envenomed patient. Laboratory tests should include coagulation studies (INR, PTT, fibrinogen, D-dimer, platelet count, whole-blood clotting time), electrolytes, serum creatinine and blood urea nitrogen levels, and creatinine kinase levels repeated serially in asymptomatic cases for at least 12 hours after the snakebite or after any symptoms or laboratory abnormalities have appeared.

TREATMENT

Antivenom for developing or established systemic envenomation is the mainstay of treatment for Australian and New Guinea snakebites. Monovalent antivenoms are preferred if the type of snake can be determined. Otherwise, a polyvalent antivenom covering all land snake species is available. Sea snakes require sea snake–specific antivenom, but if this is unavailable, tiger snake antivenom may provide some benefit. Antivenom is typically given as one vial diluted and infused intravenously over 20 to 30 minutes.

Although antivenom may neutralize circulating toxins, it cannot replenish consumed clotting factors, which should be replaced only in patients who have potentially life-threatening bleeding despite antivenom. For patients who develop microangiopathic hemolytic anemia (Chapter 146) with intravascular hemolysis, thrombocytopenia, and acute kidney injury, platelet infusions and dialysis may be required. Plasmapheresis is not of proven benefit.

E-TABLE 98-2 WORLD HEALTH ORGANIZATION SYNDROMES FOR SOUTHEAST ASIAN SNAKEBITE

SYNDROME	PRIMARY EFFECT	ADDITIONAL EFFECTS	ADDITIONAL EFFECTS	ADDITIONAL EFFECTS	ADDITIONAL EFFECTS	LIKELY SNAKE
1	Local effects	Coagulopathy/bleeding				Viper bite
2	*Local effects*	*Coagulopathy/bleeding*	*Shock or AKI*			Russell viper
2A	Local effects	Coagulopathy/bleeding	Shock or AKI	Conjunctival edema (chemosis)	Acute pituitary insufficiency)	Russell viper (Myanmar and South India)
2B	Local effects	Coagulopathy/bleeding	Shock or AKI	Minor neurotoxicity (ptosis, external ophthalmoplegia, facial paralysis)	Dark urine (myoglobinuria)	Russell viper (Sri Lanka and South India)
3	Local effects	Neurotoxic paralysis				Cobra or king cobra
4	*Neurotoxic paralysis*	*Minimal or no local effects*				
4A	Neurotoxic paralysis	Minimal or no local effects	Bitten on land, while sleeping on the ground	With or without abdominal pain		Krait
4B	Neurotoxic paralysis	Minimal or no local effect	Bitten in the sea, estuary			Sea snake
4C	Neurotoxic paralysis	Minimal or no local effects	Bitten in Indonesia, Maluku or West Papua	Coagulopathy/ bleeding		Australian elapid
5	Paralysis	Dark urine and AKI				
5A	Paralysis	Dark urine and AKI	Bitten on land	Coagulopathy/ bleeding		Russell viper (Sri Lanka and South India)
5B	Paralysis	Dark urine and AKI	Bitten on land while sleeping indoors			Krait *B. niger, B. candidus, B. multicinctus* (Bangladesh, Thailand)
5C	Paralysis	Dark urine and AKI	Bitten in the sea, estuary	No coagulopathy/ bleeding		Sea snake

AKI = acute kidney injury.

SNAKE HANDLERS AND EXOTIC SNAKEBITE

Any person regularly exposed to venomous snakes, even without being bitten, is at risk of developing allergies to snakes or their venom, a situation accelerated by a history of past bites. Thus, snake keepers and handlers may present with major, even life-threatening anaphylactic reactions that may eclipse the effects of the envenomation itself. Similarly, some may develop allergies to antivenom. Exotic snakebites or snakebites from non-native species[12] should always result in early consultation with experts in this area (e.g., www.toxinology.com), preferably a clinical toxinologist at a regional poison center.

ARTHROPODS

SPIDERS

Data from Australia indicate that spider bites result in nearly twice as many hospital visits as do snakebites, but very few spider species harm humans (E-Fig. 98-3), and fatalities are extremely rare.

Widow spiders, principally of genus *Latrodectus*, are globally distributed and likely cause more significant bites than any other spider group. The venom contains α-latrotoxin, a potent neuroexcitatory toxin. Envenomation results in a classic syndrome, termed latrodectism, characterized by localized pain and sweating, followed in more severe cases by regional and sometimes systemic involvement, with generalized pain, sweating, hypertension, and malaise that can persist for days or longer. Fatalities occur rarely. Treatment of latrodectism is controversial. Specific antivenom was efficacious in one U.S. study but not in an Australian study. Only a minority of patients develop major latrodectism, but pain control may be difficult. An appropriate approach is to use analgesia first and to reserve antivenom for severe symptoms that do not respond adequately to conservative treatment within 2 hours.

Recluse spiders, genus *Loxosceles*, have venomous toxins that cause both local tissue damage and necrosis (necrotic arachnidism), as well as potentially lethal systemic envenoming, with intravascular hemolysis, coagulopathy, and multiorgan failure. The bite is often painless, but local necrosis slowly develops and may become extensive. However, necrotic arachnidism is often overdiagnosed in regions where the spider is not indigenous.[13] Treatment is supportive, with surgical intervention avoided if possible because early dèbridement can spread venomous effects and necrosis. A specific antivenom is available in Brazil, but evidence for its effectiveness is equivocal.

Funnel web and *mouse spiders*, which are limited to Australia, have venom that contains potent neuroexcitatory toxins and can kill humans, but most of their bites are minor. Bites are generally painful and the spider often hangs on. The patient may develop systemic envenomation rapidly (minutes), similar to a catecholamine storm, with death occurring within 60 minutes in some cases. A specific antivenom is very effective, and no known fatalities have been reported since its availability.

Armed or banana spiders, genus *Phoneutria*, are native to South America, especially Brazil, but are occasionally transported accidentally to other regions. They are large (body length of 17 to 48 mm and a leg span of 13 to 18 cm), wandering spiders whose venom contains neuroexcitatory toxins, with effects somewhat similar to latrodectism, though less severe. Pain and autonomic stimulation dominate the clinical picture, with priapism a common finding in boys. A specific antivenom is available in Brazil, where bites by this genus are one of the most common forms of spider bite. Antivenom should be reserved for the most severe cases, with other cases treated with analgesia and, where appropriate, local anesthetic agents.

The goliath tarantula, with a body length of up to 13 cm and a weight of up to 175 g, is found in upland rain forests of northern South America. It can bite humans but, if envenomation occurs, produces only mild effects similar to a wasp sting. Its urticating hairs also may produce intense mucosal irritation.

Other spider species, mostly larger spiders, can occasionally bite humans and cause variable effects such as local pain of limited duration. Treatment is supportive and symptomatic, with no antivenoms available.

SCORPIONS

Scorpions cause more worldwide cases of significant envenomation of humans than any other venomous animal group, except snakes.[14] In Mexico alone, for example, more than 300,000 scorpion stings are treated annually. *Buthid scorpion* venom is rich in peptide neuroexcitatory toxins, particularly ion channel toxins, some of which produce substantial pain. Immediate severe local pain can be followed quickly by autonomic stimulation, including sweating, tachycardia or bradycardia, hypertension, and, for some species, cardiac toxicity and pulmonary edema. A sting can be lethal in children but rarely in adults. North American bark scorpions can cause unusual features such as dystonic eye movements, athetoid limb movements, and reduced consciousness.

A few species can cause lethal effects, particularly in children, but the advent of effective antivenoms, preferably administered intravenously,[A5] has greatly reduced fatality rates. Oral prazosin (30 μg/kg/dose at 3-hour intervals until resolution of the clinical syndrome) is useful as an adjunct therapy in *Hottentotta tamulus* envenomations.[A6] Dobutamine may be helpful when scorpion envenomation leads to pulmonary edema and shock.[15]

Hemiscorpius lepturus is a scorpion found particularly in Iran, where it is responsible for severe and fatal cases. Unlike Buthid scorpions, this species has a cytotoxic venom, similar in clinical effects to *Loxosceles* spider venom. Stings cause minimal local pain, but an initially painless local necrosis develops over subsequent hours to several days, can be extensive, and may be associated with a systemic illness with potentially lethal intravascular hemolysis, coagulopathy, and multiorgan failure. An antivenom is available in Iran.

TICKS

Ticks are parasitic arachnid arthropods that feed on other animals, often with a complex life history involving multiple potential host species. A few tick species produce venom that contains paralytic neurotoxins, but the major medical significance of ticks and mites is as a vector for disease transmission (Chapter 297, 298, 303, and 324) or as a direct cause of disease.

Paralysis ticks, both hard-bodied Ixodid species and soft-bodied Argasid ticks, produce venomous saliva that can cause progressive ascending and potentially fatal flaccid paralysis. The most toxic ticks, genus *Ixodes* from Australia, have caused more fatalities than either funnel web spiders or widow spiders in that country. However, most paralysis ticks cause local irritation, sometimes a local allergic reaction, without detectable neurotoxicity. When neurotoxicity occurs, it usually starts as an ataxic gait and may progress to more generalized paralysis, including ventilatory muscle paralysis. Sometimes the paralysis can be localized, such as a Bell palsy (Chapter 388), after a tick attaches behind the ear near the seventh cranial nerve.

Treatment consists of removing all attached ticks, searching carefully in the scalp, behind and in ears, and in body folds. No antivenom is available. Patients with signs of neurotoxicity should be observed closely for 24 hours (in Australia for at least 48 hours) and provided supportive care, including mechanical ventilation if indicated.

MITES

SCABIES

Human scabies is caused by *Sarcoptes scabiei* variant *hominis*. This mite is an obligate human pathogen. Scabies, which has a worldwide prevalence that ranges from about 0.2% to 71.4%, is most common in Latin America and the Pacific regions, but all regions of the world, except Europe and the Middle East, have populations with prevalences over 10%.[16] In all parts of the world, the infection is seen much more often in children and adolescents than in adults.

PATHOBIOLOGY

After mating on the skin surface, the female mite burrows and lays eggs that hatch over 3 to 4 days. The larvae molt into adults 30 to 60 days later. Mites of all stages can penetrate the skin, and they may reach staggering proportions in immunosuppressed individuals.

CLINICAL MANIFESTATIONS

In immunocompetent adults, the infection causes severe pruritus on both affected and unaffected skin, with a symmetrical erythematous, papulovesicular eruption, especially in the interdigital web spaces, wrists, anterior axillary folds, periumbilical area, the areolae in females, and the penis and scrotum in males. In nodular scabies, patients have intensely pruritic red-brown nodules that range from 2 to 20 mm in the axillary region, groin, buttocks, and genitalia; these nodules represent hypersensitivity to mite products and do not contain mites. The mite burrow—a short serpiginous gray to white keratotic line that is 1 to 4 mm in length—is most common on the hands and feet. Crusted scabies manifests in immunosuppressed individuals as silver to white crusts on any part of the body but especially the hands and ears. Elderly patients may have subtle manifestations with mild pruritus and papules on the trunk and extremities.

DIAGNOSIS

The diagnosis is established by directly identifying mites, mite pellets, or eggs on microscopy (Fig. 98-2). The diagnosis also can be established by videodermoscopy or by using polymerase chain reaction (PCR) and enzyme-linked immunosorbent assay (ELISA) for mite products or specific immunoglobulin E (IgE).

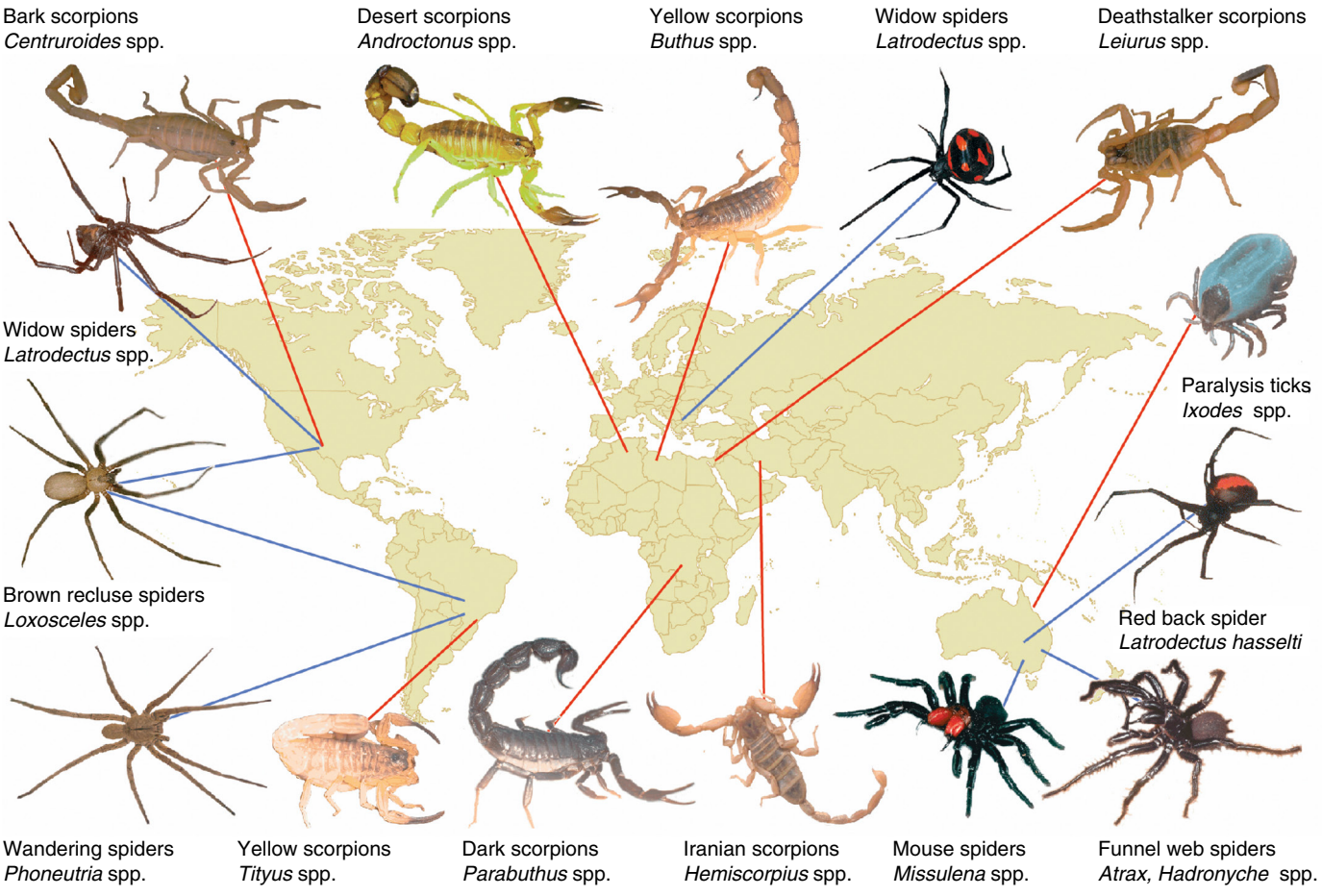

E-FIGURE 98-3. Global representation of venomous arthropods. Only a few selected species of medical significance are illustrated. spp = species. (Diagram and all images copyright © Prof. Julian White; reproduced with permission.)

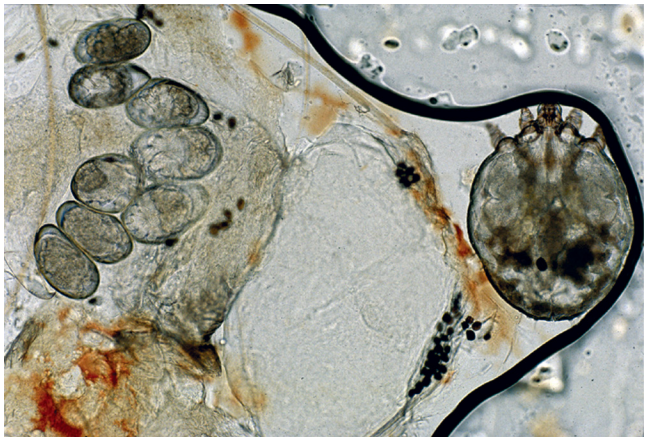

FIGURE 98-2. Scabies preparation demonstrating an adult mite, ova, and feces. (Courtesy of Dirk M. Elston, MD.)

TREATMENT AND PREVENTION

Topical options include permethrin 5% and precipitated sulfur 2 to 10% in petrolatum, benzyl benzoate 10 to 25%, monosulfiram 5 to 25%, malathion 0.5%, and esdepallethrin 0.63%. Topical crotamiton 10% is a weak antiscabic agent but an effective antipruritic; it also has antibacterial activity. Oral ivermectin (200 to 400 μg/kg given as a single dose, then repeated in 10 days) is an effective alternative to topical therapy, and mass administration of ivermectin can control scabies in endemic areas,[A7] with benefits persisting for at least 3 years.[17] Clothes and bed linens should be machine-washed at 60° C or higher followed by heated drying.

OTHER MITES

Mites are ubiquitous and frequently cause a dermatitis that can be a papular, vesicular, urticarial, or morbilliform eruption. Chigger mites, which commonly involve the lower legs, the edges of underwear, and the genitalia, can cause summer penile syndrome with tender to itchy papules of the glans and scrotum resembling a scabies infection. In Asia and South America, chigger mites are vectors for scrub typhus (Chapter 302). In urban areas, house mouse mites can transmit rickettsial pox (Chapter 302). In endemic areas, an eschar in an acutely febrile patient strongly suggests a mite-borne rickettsial infection. Most mite-induced rashes can be treated symptomatically either with topical corticosteroids or with camphor and menthol lotion.

CENTIPEDES

Centipedes are multilegged arthropods that possess pincers with fangs and associated venom glands at their head end. Human bites by some species, especially larger centipedes, can result in a locally painful reaction and sometimes broken skin, which can uncommonly lead to secondary infection. The pain is short-lived, systemic envenomation is unusual, and symptomatic treatment is rarely required, unless a secondary infection develops.

MILLIPEDES

Millipedes are multilegged arthropods that possess venom glands in their body segments. Human skin contact may result in exudation of toxins, thereby resulting in either a local irritant ache, a residual odor, or skin staining. The latter can mimic skin necrosis or bruising. No treatment is available or generally required.

LICE

Lice, which are obligate ectoparasites, cause three syndromes: *Pediculus humanus capitis* (the head louse), *Pediculus humanus* (the body louse), and *Pthirus pubis* (the crab louse).

HEAD LICE

Head lice affect 6 to 12 million people annually in the United States. Worldwide, the prevalence is much higher, especially in children ages 3 to 12 years. Transmission is via direct contact or close contact with scarves and hats.

Head lice should be suspected in a child who has pruritus of the scalp accompanied by cervical adenopathy. Nits can be seen on visual inspection, especially behind the ears. On the scalp, small bites and crusting blood are commonly seen. Definitive diagnosis requires that at least one live louse be found on the scalp.

TREATMENT

Ulesfia lotion contains benzyl alcohol to kill the louse by stunning and occluding its respiratory spiracle. Ivermectin (0.5% lotion in one 10-minute application at home) is 95% effective at 1 day, 85% effective at 7 days, and 74% effective at 14 days after treatment. For refractory infestations in children, oral ivermectin (400 μg/kg, twice at a 7-day interval) is superior to topical malathion 0.5% lotion. In epidemic settings, dimethicone is efficacious,[A8] but two applications of a shampoo-based neem extract is more ovicidal than typical dimethicone.[A9]

BODY LICE

Infestation with body lice is common among homeless people as well as in refugee situations and wars. The louse can serve as a vector for *Bartonella quintana* (which causes trench fever and endocarditis; Chapter 291), *Rickettsia prowazekii* (which causes epidemic typhus; Chapter 302), and *Borrelia recurrentis* (which causes louse-borne relapsing fever; Chapter 297).

Body lice produce a widespread rash that can be confused with allergic contact dermatitis, atopic dermatitis, a viral exanthema, or scabies. The diagnosis is made on physical examination by identifying bluish-hued maculae ceruleae (Fig. 98-3). This finding should then prompt a detailed search for body lice or nits, especially in the seams of clothing.

Lice are killed by washing and hot drying or ironing of the patient's clothing. Permethrin also can be applied to clothing but may not be necessary.

CRAB LICE

Crab louse infestation is a sexually transmitted disease, often concurrently with chlamydial (Chapter 294) or gonorrheal (Chapter 275) infection. Patients present with intense itching. Lice and nits may be found on pubic hairs and chest, abdominal, leg, and head hair. Infestation of the eyelashes can cause phthiriasis palpebrarum infection.

Treatment includes topical agents as used to treat head lice. Oral ivermectin (200 to 400 μg/kg, repeated in 10 days) is an alternative.

HEMIPTERA: BEDBUGS

Bedbugs are increasingly recognized in homes, hotels, and college campuses, and bedbugs can be introduced into buildings by birds, bats, and luggage. They hide in cracks and crevices of beds, particularly along the seams of mattresses. A bedbug is red-brown and about the size of a small tick (Fig. 98-4). Their bites, which characteristically are on the face, neck, and arms, typically present as a string of bites (Fig. 98-5). Symptomatic treatment is with topical corticosteroids (see Table 407-10), but disinfestation requires that all bedding be washed and dried in a hot setting and that the mattress and box spring be placed in a zippered plastic case.[18]

INSECTS

Insects have the largest diversity of species of any animal group, but few are venomous or medically significant. Myiasis, an ectoparasitic infestation by the dipterous larvae of flies, is commonly acquired during travel to areas of animal farming. The larvae must be surgically removed.

VENOMOUS INSECTS

Only two orders of venomous species are of major medical importance: Hymenoptera (ants, including fire ants, bees, wasps) and Lepidoptera (moths and butterflies).

Hymenoptera have a modified ovipositor apparatus that functions as a sting to inject venom produced in an intra-abdominal venom gland. Hymenopteran venom contains highly allergenic peptides, and acute allergy, particularly anaphylaxis (Chapter 233), is the major risk. Fatal anaphylaxis to bee, wasp, or ant stings causes as many or more deaths as true envenomation in most developed countries. Hymenoptera typically cause local effects such as pain, erythema, swelling, blistering, and even minor ulceration. However, massed attacks involving 500 or more stings can cause major envenomation, often characterized by hemolysis, acute renal failure, cardiac complications, and other organ failure. Treatment of systemic hymenopteran envenomation is supportive and symptomatic, commencing with urgent and rapid removal of any remaining embedded stings (honeybee mass attacks only). If an individual has a history of a significant prior type 1 hypersensitivity reaction (e.g., hypotension, airway edema), epinephrine should be carried to environments where exposure may occur. No antivenom is currently available. Any symptoms of anaphylaxis require urgent treatment (Chapter 233).

Lepidoptera larvae (caterpillars) pose a risk to humans because their hairs or spines can cause intense local skin irritation. Hairs may be removed by

FIGURE 98-3. Maculae ceruleae are bluish-red spots that represent sites where body lice have fed. (Courtesy of Dirk M. Elston, MD.)

FIGURE 98-4. Bedbugs are red-brown and about the size of small ticks (~3 mm). (Courtesy of Dirk M. Elston, MD.)

application of duct or masking tape to the exposed area. For pain after envenomation by megalopygidae (moth larvae), local anesthesia alone or combined with oral analgesics is better than analgesics alone.[19] The venom of *Lonomia* caterpillar, found in the greater Amazon basin, includes a potent procoagulant that induces a consumptive coagulopathy and can result in severe and fatal bleeding. A specific anti-*Lonomia* antivenom is available in Brazil.

MARINE ANIMALS

Minor venomous interactions with marine animals probably occur frequently, but major envenomation is far less common, and fatalities are rare.[20] Some marine envenomation-related infections may involve organisms not otherwise commonly encountered, including *Vibrio* spp, *Aeromonas* spp, *Mycobacterium marinum*, *Streptococcus iniae*, and other organisms.

Jellyfish cause envenomation using a stinging organelle (nematocyst) located on its tentacles or main body. When the trigger hair makes contact with a biologic membrane, it fires the stinging tubule, which everts and injects venom into the victim within a fraction of a second.

Fortunately, most jellyfish venom causes local pain, erythema, and mild blistering without systemic effects. However, jellyfish venom can be allergenic in some people, thereby resulting in allergic reactions when stung on a subsequent occasion.

The box jellyfish (*Chironex fleckeri* and *Malo kingi*), so named for their cube-shaped medusae, produce potent venom. Stings are generally very painful and

FIGURE 98-5. Bedbug bites are often arranged in a characteristic "breakfast, lunch, and dinner" pattern. (Courtesy of Dirk M. Elston, MD.)

may be fatal by causing cardiac arrest within 5 minutes of envenomation. Other jellyfish can also produce severe envenomation. A large jellyfish like an Australian or Pacific species may have millions of nematocysts, each able to inject venom in microseconds, with some entering capillaries and causing rapid systemic envenomation. However, most stings have smaller areas of skin contact with insufficient venom injected to cause life-threatening effects. Even small jellyfish such as the Australian irukandji can deliver a potentially lethal dose of venom.

TREATMENT

Treatment of most jellyfish stings is supportive and symptomatic, but application of hot water (no more than 45° C), preferably as a hot shower, will often provide rapid and lasting relief. The bluebottle or Portuguese-man-o-war jellyfish occurs globally. It causes local pain and welt formation and is occasionally associated with allergic reactions. Treatment is supportive and symptomatic (e.g., a hot water shower). No antivenom is available.

For box jellyfish stings, prolonged cardiopulmonary resuscitation (Chapter 50) should be provided for cardiac collapse because cardiotoxicity is likely to resolve within 60 minutes. An antivenom is available, but its effectiveness in severe cases is unclear. For less severe cases, supportive and symptomatic care is indicated. Any local tentacle track necrosis should be treated like a burn injury.

Irukandji syndrome, which is caused by a near-painless sting, is characterized by the onset of severe cramping muscle pains, notably in the back, about 15 to 60 minutes after the sting. Sweating, hypertension, and even cardiac compromise with elevated troponin levels and pulmonary edema may develop. Death is rare. No antivenom is available.

VENOMOUS STINGING FISH AND STINGRAYS

SPINY VENOMOUS FISH

Many fish species have evolved venomous spines that, upon skin puncture, release venom, which causes immediate intense local pain. Systemic effects are unusual. Treatment involves removing any residual spines from the wound. Hot water immersion (not more than 45° C) may provide adequate analgesia, but oral pain medications, including opioids (e.g., oxycodone, 5 to 15 mg orally every 4 to 6 hours) or even nerve block, may be necessary. An effective specific antivenom is available for the Australian stonefish.

VENOMOUS STINGRAYS

The sting of a venomous stingray causes intense local pain but not systemic envenomation. Treatment includes hot water immersion (no more than 45° C),[21] but parenteral analgesia (e.g., morphine, 4 to 10 mg IV every 4 hours) or a regional nerve block may be needed. For extensive wounds, exploration and removal of any residual sting debris, followed by copious irrigation, are appropriate. Stings to the abdomen or chest potentially can result in immediately lethal internal injury or fatal necrosis developing internally over a number of days. Such penetrating injuries warrant careful examination and, where appropriate, exploration and cleaning of the wound track to remove all necrotic tissue.

VENOMOUS MOLLUSKS

A few venomous *octopus species* have a potent paralytic neurotoxin, tetrodotoxin, which causes rapid (5 to 20 minutes) onset of flaccid paralysis, including

respiratory paralysis, that generally persists for a few hours. The actual bite is often painless and thus may go unrecognized. Treatment is supportive and focused on providing respiratory support until the paralysis resolves several hours later. No antivenom is available.

Cone snails can fire tiny venom-inoculated darts into prey. Humans may note instant pain or no significant pain, usually followed by the rapid onset of flaccid paralysis and, in severe cases, ventilatory paralysis. Treatment is supportive. No antivenom is available.

Sea urchins possess numerous sharp spines that can result in both a mechanical injury and a local envenomation. The result is usually intense pain without systemic effects. Retained spines can act as a nidus for secondary infection. Treatment is symptomatic (analgesia; hot water immersion at no more than 45° C), antibiotics if a secondary infection develops, and careful search for and surgical removal of embedded spines.

Many *corals* may cause cuts or abrasions and potentially a local envenomation from coral nematocysts. Fire coral cuts may cause intense immediate pain and later local skin necrosis. Coral wounds may also be contaminated by microorganisms, and coral debris can act as a nidus for infection. Although the initial injury may appear trivial, it can progress to a more significant problem if left untended. Treatment includes standard wound care, analgesia as required, and antibiotics for secondary infection.

Sea anemone stings may cause envenomation with the rapid onset of severe local pain, which may progress to vesiculation and even ulceration or necrosis. The pain may persist for hours to days or even weeks. Treatment is symptomatic and supportive.

POISONING BY MARINE ANIMALS

TETRODOTOXIN POISONING

Tetrodotoxin is a small, highly potent, nonpeptide, paralytic neurotoxin. It is produced by microorganisms and then acquired and accumulated as a venom by certain marine animals for defensive purposes (e.g., fugu fish) or offensive purposes (e.g., blue-ringed octopus). Tetrodotoxin is not destroyed by cooking, so it may remain in contaminated animals prepared as human food. Competent preparation of these fish (i.e., removal of tissues and organs with high concentrations of the toxin) may reduce, but not completely eliminate, the risk of lethal poisoning.

Mild (grade 1) poisoning causes only perioral numbness, paresthesia, and nausea. Grade 2 poisoning includes facial and tongue numbness, mild generalized paresis, incoordination, and slurred speech. More severe poisoning is defined by generalized flaccid paralysis with inability to speak, fixed dilated pupils, and respiratory compromise, often with respiratory paralysis.[22] Progression and death can occur within 60 minutes. Treatment is supportive and focused on cardiopulmonary support until the toxin degrades within a few hours.

CIGUATERA POISONING

Ciguatera is a nonpeptide, small toxin produced by dinoflagellates and concentrated up the food chain. As a result, it accumulates in larger predatory fish, without any apparent effect on them. When the larger fish are eaten by humans, however, ciguatera poisoning may occur. Cooking does not destroy the toxin. Fish such as shark, barracuda, bass, and other predatory species are predominantly involved. Ciguatera poisoning is detected only when an outbreak occurs because the fish appear healthy and taste normal.

Clinical symptoms first appear about 6 to 12 hours after eating. Gastrointestinal effects include nausea, vomiting, diarrhea, and abdominal pain. Systemic symptoms, which can be variable in onset and delayed for hours, may include myalgia, arthralgia, circumoral parasthesiae, fatigue, generalized pruritus, headaches, and abnormal sensitivity to temperature. These effects can persist for days to months and are exacerbated in some patients by consumption of alcohol or any subsequent fish meal.[23] Fatalities are rare and associated with acute-phase dehydration, cardiac failure, or cerebral edema.

Ciguatera is notoriously resistant to treatment, and no specific antidote is available. Mannitol (one dose of 1 g/kg, IV) has been recommended, but trial results are conflicting. Amitriptyline (e.g., 25 mg, orally twice daily) has been used with anecdotal success. Indomethacin (25 mg orally three times daily) may assist with arthralgias.

PALYTOXIN POISONING

Palytoxin poisoning is similar to ciguatera poisoning, except the toxin is produced by zoanthid corals in the Pacific and Mediterranean. A recent problem in the Mediterranean is that massive dinoflagellate blooms can release sea spume (aerosolized palytoxin), which exposes humans onshore, thereby resulting in skin irritation, dyspnea, and airway obstruction. Some beaches and even seaside communities have been closed during intense spume events. Cleaning of tropical aquaria can also result in the aerosolysed release of palytoxin and subsequent poisoning. Treatment is symptomatic and supportive.

SHELLFISH POISONING

Shellfish poisoning can result from the contamination of shellfish fisheries by toxin-producing blooms of dinoflagellates.

Paralytic shellfish toxins are saxitoxin and gonyautoxins. Numbness (of fingertips, lips, tongue), abdominal pain, and nausea develop 30 to 120 minutes after ingestion, followed by progressive flaccid paralysis that may extend to full respiratory paralysis. Patients also may have vertigo, ataxia, transient blindness, headache, and back pain. No specific treatment is available. Management is symptomatic and supportive. Fatalities have occurred.

Neurotoxic shellfish poisoning is caused by brevetoxin, which particularly affects clams and oysters. Clinical manifestations seen several hours after ingestion include gastrointestinal effects (nausea, vomiting, diarrhea, abdominal pain) followed by paresthesias and incoordination but not paralysis. The poisoning is generally a self-limiting nonfatal disease treated with symptomatic and supportive care.

Amnesic shellfish poisoning is caused by domoic acid, which accumulates predominantly in mussels. Gastrointestinal effects begin 6 or more hours after ingestion, but days to weeks later some patients develop encephalopathy, delirium, permanent memory loss, and, less commonly, hypotension, increased pulmonary secretions, cardiac dysrhythmias, hemiplegia, seizures, and coma. Fatalities occur. Treatment is symptomatic and supportive.

Diarrheic shellfish poisoning is caused by polycyclic ethers such as okadaic acid derivatives, which stimulate excessive intraintestinal fluid accumulation. Patients present hours after ingestion with severe gastrointestinal effects, which can persist for days, and dehydration. Symptoms may mimic those of bacterial contaminants (e.g., vibrio parahaemolyticus [Chapter 278] and norovirus [Chapter 350]). Fatalities rarely occur. Treatment is symptomatic and supportive.

Scombroid poisoning is caused by histamine, which is produced by the degradation of histidine in dead fish that are poorly stored. Scombroid is a food processing/storage problem rather than a true toxin-based disease. Clinically it presents within 1 hour of ingestion with a rash, flushing, tachycardia, and, in more severe cases, headache, gastrointestinal symptoms, bronchospasm, hypotension, angioedema, and airway compromise. It usually resolves spontaneously in 6 to 12 hours or, at most, 36 hours. Fatalities have been reported. Treatment includes use of antihistamines (see Table 404-3), beta-2 androgenic inhalers (e.g., albuterol as needed), corticosteroids (see Chapter 28), and intramuscular epinephrine (0.25 mL of a 1 : 1000 solution).

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99 RHABDOMYOLYSIS

FRANCIS G. O'CONNOR AND PATRICIA A. DEUSTER

DEFINITION

Rhabdomyolysis, an acute, potentially fatal clinical syndrome, reflects the dissolution and disintegration of striated muscle, with the release of muscle cell contents into the systemic circulation.[1] Myoglobinemia and myoglobinuria are common sequelae. Other substances released from affected muscle cells (e.g., calcium, potassium) can cause systemic effects. Prerenal azotemia, complicated by the toxicity of free myoglobin on the renal tubules, may lead to acute kidney injury (Chapter 106), which exacerbates other metabolic abnormalities. At the extreme, arrhythmias, caused by the release of intracellular potassium and organic acids, coupled with hypocalcemia may be fatal.

EPIDEMIOLOGY

In the absence of a widely accepted laboratory definition or clinical diagnostic criteria, the true incidence of rhabdomyolysis is unclear, but about 26,000 hospitalized cases are seen each year in the United States. The U.S. military also reports over 500 annual cases of exertional rhabdomyolysis.[2] Among patients with rhabdomyolysis, anywhere from 13 to 67% may develop acute kidney injury, which accounts for 5 to 10% of all cases of acute kidney failure in the United States. Moreover, acute kidney injury secondary to rhabdomyolysis is independently associated with both longer hospitalizations and higher mortality.[3]

Rhabdomyolysis is a complex and multifactorial clinical disorder, with multiple potential inherited and acquired causes (Table 99-1).[4] In urban adults, abuse of alcohol and other drugs, muscle compression, and status epilepticus are common causes of rhabdomyolysis. Various viral infections, including influenza A and B, herpes simplex, adenovirus, echovirus, human immunodeficiency virus, cytomegalovirus, and most recently severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), which causes coronavirus disease 2019 (COVID-19), can cause rhabdomyolysis. In pediatric patients, the most common cause is trauma, followed by nonketotic hyperosmolar coma, viral myositis, dystonia, and malignant hyperthermia. However, exertional rhabdomyolysis from repetitive exercise is also a concern in young athletes. Importantly, children and adolescents with recurrent rhabdomyolysis are increasingly being recognized as possibly having inherited metabolic disorders.

Drugs and Intoxications

Among intoxications, the most frequent illegal drug-associated causes are cocaine and heroin (Chapter 365), with nearly 20% of cocaine overdoses complicated by rhabdomyolysis. Other recreational drugs, such as "bath salts" (of which methylenedioxypyrovalerone is the primary ingredient) and synthetic cannabinoids (or "spice"), have been associated with rhabdomyolysis. Other substances that can induce rhabdomyolysis include ethanol (Chapter 364), amphetamines, phenylalkylamine derivatives, antipsychotics, caffeine, and statins.[5] Up to 10% of patients taking statins (Chapter 190) may experience myalgias, but reported rates of statin-induced rhabdomyolysis range from 0 to 2.2 cases per 1000 person-years,[6] with cerivastatin being associated with the highest rates. Statins can also induce an autoimmune anti-HMG-CoA antibody myopathy with proximal muscle weakness and profound creatine kinase elevations. Dietary supplements, in particular those with combinations of stimulants, have also been associated with exertional rhabdomyolysis. Rhabdomyolysis can also be seen when severe hyponatremia is rapidly corrected.

Exertional Rhabdomyolysis

Rhabdomyolysis can be a consequence of exertion in sports (e.g., baseball, football, track, wrestling, endurance sports[7]), military, and recreational exercise settings, and especially with high-intensity, resistance-exercise training. For example, in one series of patients with rhabdomyolysis (defined as a creatine kinase [CK] level of greater than 25,000 units/L), 35% of patients had exertional rhabdomyolysis, with most of them related to high-intensity resistance training. In another series, 35 of 225,000 emergency department visits to an urban tertiary care center were for exertional rhabdomyolysis; the average CK level was 40,000 U/L, but no patient developed acute kidney injury.

According to data from the military, the incidence rate for exertional rhabdomyolysis is higher among Black, non-Hispanic men (60.0 cases per 100,000 person-years) than for all other ethnic groups. Additionally, individuals with sickle cell trait have a slightly higher risk of exertional rhabdomyolysis than those without sickle cell trait, although their subsequent clinical courses are not different.[8] Consistent risk factors for exertional rhabdomyolysis are low levels of physical fitness and early introduction of high-intensity repetitive exercises (e.g., squats, push-ups, sit-ups). Multiple case reports in athletes and the military identify both over-motivation and leadership (e.g., drill sergeant, coach, trainer) as important risk factors. Although most cases are self-limited, with no long-term evidence of kidney or muscle injury, patients who demonstrate systemic signs, generalized clinical findings, or acute kidney injury may have an underlying metabolic myopathy. Importantly, 25% of all heatstroke cases in the military between 1980 and 2000 were associated with exertional rhabdomyolysis; acute kidney injury developed in 33%.

The extreme exertion characteristics of military service carry over to the population of correctional inmates and civil servant first responders. Unsupervised repetitive exercise in prison populations can lead to exertional rhabdomyolysis. Among New York City firefighters, 32 of 16,506 candidates (0.2%) were hospitalized for exertional rhabdomyolysis after a physical fitness test, with 4 requiring hemodialysis. In a group of 50 prospective police officers from Massachusetts, 13 trainees were hospitalized with exertional rhabdomyolysis and had CK levels higher than 32,000 U/L; 6 required dialysis, and 1 died 44 days later as a result of complications of exertional rhabdomyolysis, heatstroke, and kidney and hepatic failure.

PATHOBIOLOGY

Pathophysiology

The final common pathway for all cases of rhabdomyolysis is from direct or indirect injury or destruction of muscle cells, with displacement of their intracellular contents into extracellular fluid, the circulation, or both (E-Fig. 99-1).

TABLE 99-1 INHERITED AND ACQUIRED CAUSES OF RHABDOMYOLYSIS

INHERITED	ACQUIRED
Glycolytic/glycogenolytic (e.g., McArdle disease [myophosphorylase deficiency])	Exertion (e.g., exercise, status epilepticus, delirium, electrical shock, status asthmaticus, cardiopulmonary resuscitation; see also Table 99-2)
Fatty acid oxidation (e.g., carnitine palmitoyltransferase II deficiency)	Crush (e.g., external weight, prolonged immobility, bariatric surgery)
Krebs cycle (e.g., aconitase deficiency)	Ischemia (e.g., arterial occlusion, compartment syndrome, sickle cell disease, disseminated intravascular coagulation)
Pentose phosphate pathway (e.g., glucose-6-phosphate dehydrogenase deficiency)	Extremes of body temperature (e.g., fever, exertional heatstroke, burns, malignant hyperthermia, hypothermia, lightning)
Purine nucleotide cycle (e.g., myoadenylate deaminase deficiency)	Metabolic (e.g., hypokalemia, hypernatremia or hyponatremia, hypophosphatemia, pancreatitis, diabetic ketoacidosis, renal tubular acidosis, hyperthyroidism or hypothyroidism, nonketotic hyperosmolar states)
Mitochondrial respiratory chain (e.g., succinate dehydrogenase deficiency)	Drugs or toxins (e.g., anticholinergics, amphetamines, antihistamines, arsenic, ethanol, opiates, statins, cocaine, succinylcholine, halothane, corticosteroids, cyclosporine, itraconazole, phenothiazines, bath salts, synthetic cannabinoids)
Malignant hyperthermia susceptibility (e.g., familial malignant hyperthermia [*RYR1*] mutations, myotonic dystrophy, Duchenne and Becker dystrophies)	Infections (e.g., Epstein-Barr virus, human immunodeficiency virus, herpes simplex, influenza A and B, *Borrelia burgdorferi*, tetanus)
Other (e.g., familial recurrent myoglobinuria)	Inflammatory and autoimmune disorders (e.g., polymyositis, dermatomyositis)

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ABSTRACT

Rhabdomyolysis, which is an acute and potentially fatal clinical syndrome, reflects the dissolution and disintegration of striated muscle, with the release of muscle cell contents into the systemic circulation. Myoglobinemia and myoglobinuria are common sequelae. Other substances released from affected muscle cells (e.g., calcium, potassium) can cause systemic effects. Prerenal azotemia, complicated by the toxicity of free myoglobin on the renal tubules, may lead to acute kidney injury, which exacerbates other metabolic abnormalities. At the extreme, arrhythmias, caused by the release of intracellular potassium and organic acids, coupled with hypocalcemia may be fatal.

KEYWORDS

crush injury
rhabdomyolysis
renal failure
exercise induced rhabdomyolysis
striated muscle

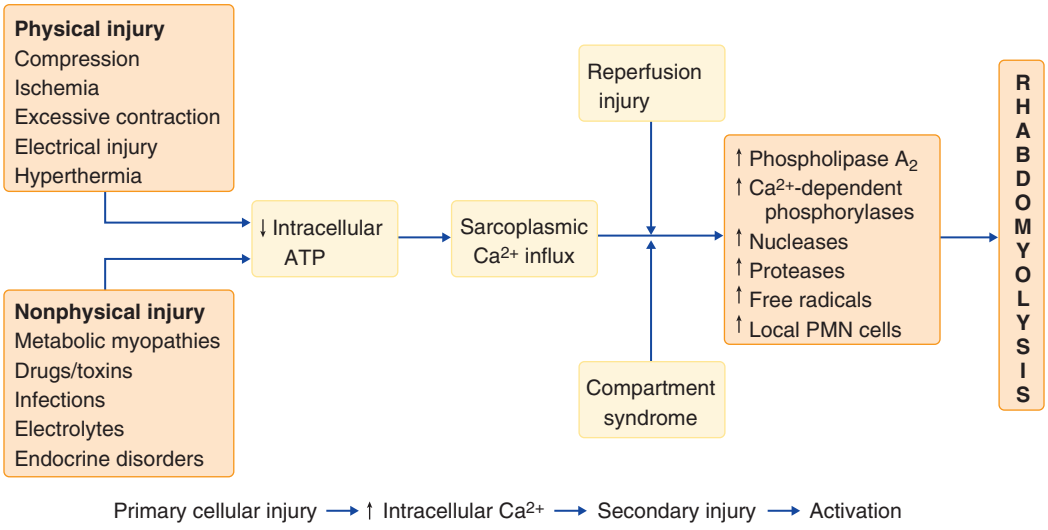

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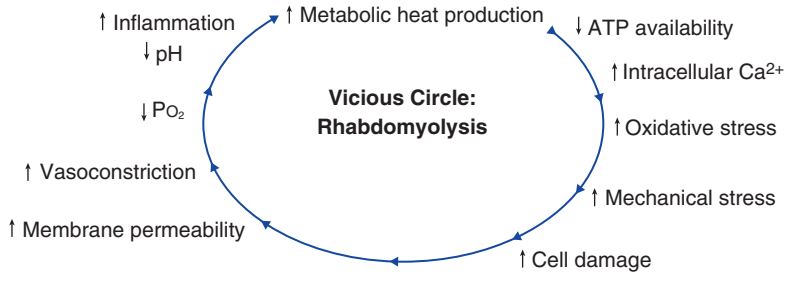

B

E-FIGURE 99-1. **A, Pathogenesis of rhabdomyolysis. B, Vicious circle of rhabdomyolysis. ATP = adenosine triphosphate; PMN = polymorphonuclear.**

Cell function is critically dependent on the relationship between intracellular calcium (Ca^{2+}) and sodium (Na^{+}) concentrations. Sarcolemmal Na^{+},K^{+}-ATPase regulates extracellular Ca^{2+} concentrations by exchanging Na^{+} for Ca^{2+} across the sarcolemma. A low intracellular Na^{+} concentration creates a gradient that actively results in efflux of Ca^{2+} as it is exchanged for Na^{+} ions. This process maintains intracellular Ca^{2+} levels at several orders of magnitude lower than extracellular Ca^{2+}.

When the cell is subjected to mechanical stress, stretch-activated channels in the sarcolemma can open and cause an influx of Na^{+} and Ca^{2+}. With excessive intracellular Ca^{2+}, several pathologic processes begin: persistent contraction of myofibers, depletion of adenosine triphosphate (ATP), production of free radicals, activation of vasoactive molecules, release of proteases, and, ultimately, cell death. Cell death is followed by an invasion of neutrophils, which amplify the damage by further release of proteases and increased production of free radicals. Rather than simple necrosis, a self-sustaining, inflammatory myolytic reaction develops. The activation of complement is a key contributor to the acute kidney injury.[9]

Rhabdomyolysis can be further complicated by reperfusion injury and compartment syndrome. In reperfusion injury, restoration of vascular flow after a prolonged period of ischemia results in the delivery of activated neutrophils in combination with an abundance of oxygen, which contributes to the development of highly reactive free radicals. Because most muscle groups are contained within rigid fascial compartments, rhabdomyolysis can quickly precipitate a secondary acute compartment syndrome. The swelling associated with traumatized tissue can also increase intracompartmental pressure and provoke additional damage by compromising both venous and arterial blood flow. Thus, compartment syndrome can also result in rhabdomyolysis.

Inherited and Acquired Rhabdomyolysis

Rhabdomyolysis can be classified as inherited or acquired (see Table 99-1).

Inherited Rhabdomyolysis

Patients who have recurrent episodes of high levels of CK in the blood triggered by low levels of stress or exertion should be evaluated for a metabolic myopathy. A number of pathways leading to the formation of ATP can be disrupted by genetic defects (e.g., inherited disorders of glycogenolysis, glycolysis, and lipid and purine metabolism).[10] In one series of 77 patients who underwent biopsy for idiopathic myoglobinuria, 47% were found to have enzymatic defects; the most common disorders were deficiencies of carnitine palmitoyltransferase II[11] and myophosphorylase. Mutations in the ryanodine receptor 1 gene also can cause rhabdomyolysis.[12] Carnitine palmitoyltransferase, acid maltase, and lipin deficiencies are other common causes of rhabdomyolysis. Malignant hyperthermia (Chapters 400 and 402) is a potentially fatal, heterogeneous, pharmacogenetic disorder that can be triggered by volatile anesthetics in predisposed individuals. When a susceptible patient is exposed to a triggering anesthetic agent, excessive release of Ca^{2+} into the myoplasm leads to a hypermetabolic state manifested by hypercapnia, tachycardia, and metabolic acidosis. A genetic predisposition to malignant hyperthermia may be linked to a predisposition to exertional rhabdomyolysis and exercise-induced heat injury via mutations in the ryanodine receptor 1 gene, but this association has not been proved.

Acquired Rhabdomyolysis

Drugs and Toxins

Drugs and toxins, also common causes of rhabdomyolysis, operate through a number of mechanisms, including direct membrane toxicity (e.g., herbicides), indirect metabolic derangements (e.g., anticholinergics), ischemia (e.g., cocaine), and agitation (e.g., hemlock). The most commonly cited drugs precipitating rhabdomyolysis are alcohol, statins, cocaine, amphetamines, and antipsychotics (phenothiazines), although new designer street drugs (known as spice and bath salts) are also implicated. Alcohol can induce rhabdomyolysis through a combination of mechanisms, including immobilization, direct myotoxicity, and electrolyte abnormalities. Statins, which inhibit 3-hydroxy-3-methylglutaryl-coenzyme A (HMG-CoA) reductase, can be directly myotoxic and appear to trigger sustained increases in intracellular Ca^{2+}. Although the precise mechanisms underlying statin-induced myopathy are currently incompletely understood, it can be aggravated by the concomitant administration of cytochrome P-450 3A4 inhibitors (e.g., itraconazole, erythromycin, cyclosporine, danazol) and fibrates, as well as by physical exercise, excessive alcohol intake, and preexisting comorbid medical conditions. Amphetamines and phenothiazines may lead to a clinical picture of rhabdomyolysis through the serotonin syndrome (Chapter 402) and the neuroleptic malignant syndrome (Chapter 386), respectively. The mechanism whereby bath salts lead to rhabdomyolysis may be direct muscle toxicity, severe hyperthermia, or electrolyte disorders.

Infections

Both viral and bacterial infections can trigger rhabdomyolysis. Either cellular invasion or generation of various toxins may precipitate infection-induced rhabdomyolysis. Influenza A and B (Chapter 332) are the most common viral causes, followed by human immunodeficiency virus (Chapter 355), coxsackievirus (Chapter 349), and Epstein-Barr virus (Chapter 348). SARS-CoV-2 infection (Chapter 336) also can be associated with myositis and rhabdomyolysis.[14] The most common bacterial organisms that induce rhabdomyolysis are *Legionella* species (Chapter 290), followed by *Francisella tularensis* (Chapter 287) and *Streptococcus pneumoniae* (Chapter 268). Acute kidney injury develops in approximately 57% (33 to 100%) and 34% (0 to 100%) of bacterial and viral cases of rhabdomyolysis, respectively.

Trauma

Trauma is the most common cause of rhabdomyolysis. Wars, natural disasters, and traffic and occupational accidents are frequent causes of trauma-induced "crush injury syndrome" (Chapter 97). Other less frequent causes of trauma- or compression-induced rhabdomyolysis include struggling against restraints, direct blows, child abuse, torture, prolonged immobilization (e.g., anesthesia, coma, drug- or alcohol-induced stupor), and bariatric and other forms of surgery. The primary mechanism of crush syndrome and compression-induced rhabdomyolysis is reperfusion of damaged tissue after a period of ischemia.

Muscle breakdown occurs in response to strenuous exercise in fit and unfit individuals, particularly eccentrically based activities (lengthening contractions, such as lowering a weight). However, it is important to note that muscle breakdown in response to exercise is expected and physiologic, whereas exertional rhabdomyolysis is pathophysiologic. Persons may present with delayed-onset muscle soreness 1 to 3 days after a bout of moderate to strenuous exercise. Key findings distinguishing exertional rhabdomyolysis from physiologic muscle breakdown and/or delayed-onset muscle soreness include (1) pain out of proportion to what one would normally expect; (2) muscle swelling; (3) significant limitation in active and passive range of motion; and (4) the presence of cola-colored urine.

External rhabdomyolysis can be triggered by exertion in combination with prolonged heat exposure (Chapter 95) and altitude, as well as by the use of medications (e.g., anticholinergics) or dietary supplements (e.g., ephedra, caffeine). It can range from a minor clinical event to a catastrophic collapse and death; underlying mechanisms may be mechanical or metabolic in nature, but all are associated with elevated myoplasmic Ca^{2+} concentrations.

A number of underlying genetic polymorphisms and inherited disorders are associated with exertional rhabdomyolysis (Table 99-2). Multiple mutations in the carnitine palmitoyl-transferase II and myophosphorylase genes have been found, and although each mutation has been associated with exercise-induced myoglobinuria, the mutations alone may not explain

TABLE 99-2 GENETIC MUTATIONS/VARIANTS ASSOCIATED WITH EXERTIONAL RHABDOMYOLYSIS

GENE	
Ryanodine receptor 1	*RyR1*
Myoadenylate deaminase	*AMPDA1*
Carnitine palmitoyltransferase II	*CPT2*
Myophosphorylase	*PYGM*
Phosphofructokinase	*PFKM*
Phosphorylase *b* kinase	*PHKA1*
Very long chain acyl–coenzyme A dehydrogenase	*ACAD9*
Phosphoglycerate mutase	*PGAMM*
Phosphoglycerate kinase	*PGK1*
Lactate dehydrogenase	*LDHA*
Cytochrome *c* oxidase	*COX I, II,* and *III*
Cytochrome *b* (complex III)	*CYTB*
Mitochondrial tRNA	*Mt-tRNA*
β-Sarcoglycan	*SGCB*
Mitochondrial DNA	*MT-CO2*

the clinical episodes. Mutations and variants in the ryanodine receptor 1 (*RYR1*) gene, which are common in malignant hyperthermia (Chapter 400), have also been found in persons with external rhabdomyolysis. Other single-nucleotide polymorphisms associated with severe exertional rhabdomyolysis are found in the genes encoding CK muscle isoform (*CKMM* NcoI), α-actinin-3 (*ACTN3* R577X), or myosin light chain kinase (*MYLK* C37885A). However, data are insufficient to use these or other variants to predict an individual's clinical susceptibility to infection-, toxin-, exertion-, or drug-induced rhabdomyolysis.

CLINICAL MANIFESTATIONS

The classic manifestations of rhabdomyolysis include acute myalgia and pigmenturia as a result of myoglobinuria in association with elevated serum muscle enzymes (CK in particular). Many clinical features are nonspecific, and the course and initial signs, symptoms, and laboratory abnormalities are clearly dependent on the underlying cause and severity of the event.[13]

Rhabdomyolysis can be accompanied by both local and systemic features. Local features, generally noted in the area of the traumatized muscle groups, can occur within hours of the trauma and include muscle pain, tenderness, and swelling. Systemic features include tea-colored urine, chills, fever, and malaise. In extreme cases, patients complain of nausea and vomiting and demonstrate confusion, agitation, or delirium. Whenever systemic features such as chills, fever, malaise, or generalized muscle involvement are observed, an underlying metabolic myopathy should be considered.

Clinical findings may also include compartment syndrome, which can occur in muscle groups encased by fascia, especially the lower leg, forearm, and thigh muscle groups. Pain with muscle group passive stretching and sensory abnormalities caused by nerve compression are early manifestations of compartment syndrome; the loss of a pulse as a result of vascular compromise is a later finding. If compartment syndrome is not addressed by surgical decompression within 6 to 8 hours, irreversible ischemic muscle and nerve damage may occur.

Laboratory findings are related to the degree of muscle involvement. Early findings include elevated blood levels of CK, myoglobin, potassium, urea, and phosphorus. CK levels typically peak 2 to 5 days after the initial insult; levels of 15,000 to 20,000 U/L are more likely to be associated with acute kidney injury than lower levels, particularly when it is "crush injury syndrome." Hypocalcemia, caused by the influx and deposition of Ca^{2+} in damaged muscle tissue, may accompany rhabdomyolysis. Also, an anion-gap metabolic acidosis may develop because of the release of organic acids from damaged muscle. With resolution of rhabdomyolysis, sequestered Ca^{2+} may be released back into the circulation and cause hypercalcemia.

DIAGNOSIS

Creatine Kinase Levels

A diagnosis of rhabdomyolysis is made when there is clinical evidence of myonecrosis and release into the systemic circulation of muscle cell contents, including myoglobin, creatinine, CK, organic acids, potassium, aldolase, lactate dehydrogenase, and hydroxybutyrate dehydrogenase. The skeletal muscle subtype CK-MM is abundantly present in skeletal muscle and released as a result of muscle destruction. Serum levels exceeding 100,000 U/L are not uncommon with rhabdomyolysis. Because CK remains in the circulation longer than myoglobin and can be detected easily and efficiently, it is the most frequently used marker to diagnose rhabdomyolysis. No universally accepted clinical or laboratory definition of rhabdomyolysis currently exists, but CK elevations ranging from more than 5 times to more than 50 times the upper limits of normal, as well as varying requirements for serum creatinine elevation, have been proposed. Importantly, sex, ethnicity, and baseline physical activity levels all affect individual baseline CK levels. For example, African American males and young athletic men have the highest baseline CK levels, whereas non–African American women have the lowest. Thus, modifying factors such as sex, ethnicity, and physical fitness must be considered when CK is used for the diagnosis of rhabdomyolysis. In general, CK levels in excess of at least five times normal, in combination with the appropriate clinical presentation, are accepted as evidence of muscle breakdown, which may be consistent with a diagnosis of rhabdomyolysis.

Myoglobin Testing

Because myoglobinuria does not occur in the absence of rhabdomyolysis, myoglobin should be the most specific marker of rhabdomyolysis. However, testing for serum or urine myoglobin is problematic and not always consistent. Because myoglobin is normally bound to plasma globulins, only a small fraction of the myoglobin that is released into the circulation reaches the glomeruli. In the presence of severe muscle damage, blood levels of myoglobin overwhelm the binding capacity of the circulating proteins, so free myoglobin reaches the glomeruli and eventually the renal tubules. Elevations in serum myoglobin occur before the rise in serum CK, but the elimination kinetics of serum myoglobin are more rapid than that of CK, which makes the often evanescent rise in serum myoglobin a less reliable marker of muscle injury. Furthermore, the liver can quickly metabolize myoglobin.

Because most laboratories will perform urine myoglobin testing no more often than once per day, urine myoglobin is neither a timely nor accurate predictor of acute kidney injury. Nevertheless, urine screening for rhabdomyolysis may be performed by dipstick. The orthotoluidine portion of urine dipsticks turns blue in the presence of hemoglobin or myoglobin, so if the urine sediment does not contain erythrocytes, one can assume, in the appropriate clinical setting, that a positive dipstick reading reflects the presence of myoglobin.

Other Laboratory Tests

Other associated laboratory findings in acute rhabdomyolysis can include hypocalcemia, hyperkalemia, hyperphosphatemia, metabolic (lactic) acidosis, thrombocytopenia, and disseminated intravascular coagulation. Muscle biopsy is not required to make a diagnosis of rhabdomyolysis, but it can be confirmatory, especially in cases of recurrent rhabdomyolysis or when the diagnosis is not clear. Histopathologic evaluation usually demonstrates muscle necrosis, loss of the cell nucleus, and muscle stria with the absence of inflammatory cells.

Differential Diagnosis

The clinical findings of acutely swollen muscles or muscle weakness (or both) with reddish-brown urine are not always the result of rhabdomyolysis, and the examining clinician must be careful to scrutinize all information. The differential diagnosis includes disorders that may indirectly affect myocytes, such as Guillain-Barré syndrome and periodic paralysis. Guillain-Barré syndrome (Chapter 388) differs from rhabdomyolysis in that it is characterized as a fulminant polyneuropathy, usually after an antecedent viral infection. Periodic paralysis (Chapter 389) is frequently associated with transient electrolyte disturbances and distinguished from rhabdomyolysis in that most cases follow periods of rest or sleep.

Myoglobinuria causes the urine to be reddish brown, but tea-colored (or cola-colored) urine does not necessarily indicate the presence of myoglobin. Other conditions associated with discoloration of urine include hemoglobinuria from hemolysis, intrinsic renal disease, porphyria, acute glomerulonephritis, "athletic pseudonephritis," and external factors such as ingestion of beets and various drugs (e.g., phenytoin, rifampin) or dietary supplements (riboflavin, or vitamin B_2).

The diagnosis of rhabdomyolysis is complete when the clinician determines the cause. This step, although it is frequently established during the history and physical examination, may require further diagnostic assessment after initiating clinical treatment during the acute phase. Individuals with recurrent rhabdomyolysis, a positive family history of rhabdomyolysis or malignant hyperthermia, low exercise tolerance, no apparent cause, or a fulminant form of rhabdomyolysis appear to warrant further testing.

Testing may include a nonischemic forearm test, which involves isometric exercise at 70% of maximal voluntary contraction for 30 seconds under nonischemic conditions; electromyography; more in-depth blood tests for muscle enzymes (e.g., mitochondrial myopathies [Chapter 389], fatty acid transport defects [Chapter 389], glycogen storage diseases [Chapter 191], diseases associated with myoglobinuria); muscle biopsy to investigate specific metabolic myopathies and other enzyme or genetic defects; or any combination of such testing. The forearm exercise test may help identify metabolic and genetic causes of rhabdomyolysis. Patients who have had an episode of malignant hyperthermia or exertional heat illness may be candidates for a caffeine halothane contracture test, which evaluates the force produced by biopsied muscle samples after separate exposures to caffeine, halothane, and caffeine/halothane in the laboratory (Chapter 400).

PREVENTION

Approaches for preventing rhabdomyolysis induced by infections, medications, and toxins may emerge in the future, but no definitive guidelines currently can be presented. Rhabdomyolysis secondary to heat stress or exercise is best prevented by adhering to recommended guidelines for acclimatization and exercise progression. To prevent further muscle injury, blood flow to ischemic areas must be promptly restored to minimize ischemia-reperfusion damage.

TREATMENT

Treatment of rhabdomyolysis begins with a careful history and physical examination to identify and manage any underlying illness. Vital signs, urine output, and serial electrolyte and CK levels should be obtained as soon as possible. Patients require aggressive early management to preserve renal function (Table 99-3).[15,16] Careful observation and treatment of potential early and late complications are critical, and intensive care monitoring may be required.[17]

Hydration

Hydration is the cornerstone of preserving kidney function in patients with rhabdomyolysis, and delaying fluid administration for more than 6 hours increases the risk for acute kidney injury. Inpatient hydration is indicated for victims of collapse, trauma, or exertional heat injury, as well as for patients who have moderate early symptoms; more than mild elevations in CK; or abnormal serum levels of creatinine, potassium, calcium, phosphate, or bicarbonate. In adults, the target urine output is 300 mL/hr for at least 24 hours to prevent acute kidney injury. Hydration is accomplished by the aggressive administration of isotonic intravenous fluids at a rate that results in a urine output of 200 to 300 mL/hour until CK levels begin to decline. If fluid resuscitation fails to correct intractable hyperkalemia and acidosis, renal replacement therapy should be considered (Chapter 106). By comparison, adults with mild symptoms and serum CK levels less than 3000 U/L are considered to be at low risk and may be treated as outpatients with vigorous oral hydration, limited physical activity, and careful follow-up.

Specific Therapeutic Measures

Alkalinization of the urine decreases cast formation, minimizes the toxic effects of myoglobin on the renal tubules, inhibits lipid peroxidation, and decreases the risk for hyperkalemia. However, bicarbonate therapy can cause calcium to precipitate in the soft tissues and contribute to a hyperosmolar state. Mannitol is an osmotic diuretic, volume expander, and free radical scavenger, but it should be used only after adequate kidney function is established and must be used with great caution in patients with marginal cardiac function. To date, no convincing evidence demonstrates that adding sodium bicarbonate or mannitol is superior to fluid therapy alone.[18] Mannitol should be used only when it is needed to maintain a target urine output.

Sodium bicarbonate should be used only in patients with evidence of systemic acidosis, and mannitol should be used only when it is needed to maintain a urine output of 300 mL/hour (see Table 99-3). Deposition of calcium, which occurs early in rhabdomyolysis, is directly related to the degree of muscle destruction and to the often unnecessary therapeutic administration of calcium given to correct asymptomatic hypocalcemia. Early therapeutic reversal of hypocalcemia can worsen ectopic calcification and exacerbate the exponent hypercalcemia during the resolution phase. Accordingly, hypocalcemia should be treated only when patients develop clinical symptoms, signs of tetany, or severe hyperkalemia.

Management of Compartment Syndrome

Compartment syndrome (Chapter 97) is a well-described late complication as well as a potential cause of rhabdomyolysis. Compartment syndrome can occur as a direct consequence of muscle injury associated with increased vascular permeability, aggressive fluid resuscitation, or restoration of reperfusion. Compartment syndrome should be suspected when the muscles are tense and swollen, previously declining CK levels start to rise, or neurovascular compromise occurs. In these cases, compartment pressures should be measured; if pressures exceed 30 mm Hg, prompt fasciotomy should be considered. However, because late fasciotomy (>12 hours after the onset of symptoms) can convert a closed injury into an open wound and thereby increase the risk of uncontrollable infection, late fasciotomy is relatively contraindicated.

Management of Crush Injury

For victims of crush injury (Chapter 97), aggressive on-site hydration with intravenous normal saline is recommended. For massive damage, amputation of the extremity may be required to protect the patient's overall health. The Mangled Extremity Severity Score can identify nonsalvageable extremities on the basis of the degree of skeletal and soft tissue injury, the patient's blood pressure, the presence of a detectable pulse, and age (see http://www.mdcalc.com/mangled-extremity-severity-score-mess-score/).

Malignant Hyperthermia

Rhabdomyolysis caused by malignant hyperthermia (Chapter 400) requires rapid diagnosis and aggressive management. Anesthetics should be discontinued, and the patient should be treated with dantrolene sodium, 2.5 to 4 mg/kg intravenously, followed by about 1 mg/kg every 4 hours for up to 48 hours to avoid recrudescence.

TABLE 99-3 STEPS IN THE PREVENTION AND TREATMENT OF RHABDOMYOLYSIS-INDUCED ACUTE KIDNEY INJURY

Check for extracellular volume status, central venous pressure, and urine output.*
Measure serum creatine kinase levels. Measurement of other muscle enzymes (myoglobin, aldolase, lactate dehydrogenase, alanine aminotransferase, aspartate aminotransferase) adds little information relevant to diagnosis or management.
Measure levels of plasma and urine creatinine, potassium, and sodium; blood urea nitrogen; total and ionized calcium, magnesium, and phosphorus; and uric acid and albumin. Evaluate acid-base status, blood cell count, and coagulation.
Perform a urine dipstick test and examine the urine sediment.
Identify and discontinue nephrotoxic and myotoxic medications.
Initiate volume repletion with IV normal saline promptly at a rate of approximately 400 mL/hr (200-1000 mL/hr, depending on the patient size, setting, and severity) and monitor the clinical course or central venous pressure.
Target urine output of approximately 3 mL/kg body weight/hr (200-300 mL/hr).
Maintain volume repletion until myoglobinuria is cleared (as evidenced by clear urine or urine dipstick test that is negative for blood).
Consider IV bicarbonate therapy for severe rhabdomyolysis. Check urine pH: if it is <6.5, alternate each liter of normal saline with 1 L 5% dextrose or 0.45% saline plus 100 mmol bicarbonate (2 ampules). Avoid potassium- and lactate-containing solutions.
Consider treatment with IV mannitol only if needed to maintain target urine output. If mannitol is utilized, 50 mL of 20 percent mannitol (1 to 2 g/kg per day [total, 120 g], given at a rate of 5 g per hour) should be added to each liter of fluid. Check for plasma osmolality and calculate the plasma osmolal gap (Chapter 106). Discontinue if diuresis (>20 mL/hr) is not established within a few hours.
Check serum potassium and calcium levels frequently; identify and manage metabolic abnormalities.
Correct hypocalcemia (Chapter 227) only if symptomatic (e.g., tetany, seizures) or severe hyperkalemia occurs.
Hyperkalemia should be treated with standard medical management (Chapter 103). Consider renal replacement therapy for resistant hyperkalemia (>6.5 mmol/L) that is symptomatic (as assessed by electrocardiography), rapidly rising serum potassium levels, oliguria (<0.5 mL of urine/kg/hr for 12 hours), anuria, volume overload, or resistant metabolic acidosis (pH < 7.1).
Investigate and treat the cause of rhabdomyolysis.

*In the case of crush syndrome (e.g., earthquake, building collapse, bariatric surgery), institute aggressive volume repletion promptly before evacuating the patient if creatine kinase level is >15,000 U/L.

IV = intravenous.

Modified from Bosch X, Poch E, Grau JM. Rhabdomyolysis and acute kidney injury. *N Engl J Med.* 2009;361:62-72.

PROGNOSIS

The most serious consequence of rhabdomyolysis is acute kidney injury, which occurs in up to 67% of all cases, regardless of cause. Predictors of the risk of needing renal replacement therapy or death in patients with rhabdomyolysis include age older than 50 years; a higher initial serum potassium level; initial serum creatinine level of 1.4 mg/dL or higher; initial serum calcium level below 7.5 mg/dL; initial serum phosphate level above 4.0 mg/dL[19]; initial serum bicarbonate level below 1 mEq/L; and a cause other than syncope, seizures, exercise, statins, or myositis (E-Table 99-1).

Long-term decline in renal function is best correlated with the serum myoglobin level.[20] A higher initial creatinine level but not a higher initial creatine kinase level also predicts acute kidney injury and mortality. Event rates range from 0% in patients with none of these criteria to 20% or more in patients with four or more criteria. For compartment syndrome, a poor prognosis is associated with an ischemic period lasting longer than 6 hours.

The prognosis of patients with rhabdomyolysis improves markedly when treatment is started soon after the diagnosis is made. With mild episodes, the prognosis is customarily excellent, and the patient can typically resume usual activities within several weeks after CK levels have normalized. However, some patients do not return to normal and continue to experience extreme fatigue and muscle pain on exertion. These patients require additional testing (nonischemic forearm test, electromyography, muscle disease enzyme panel, muscle biopsy; Chapter 389) to determine whether an underlying metabolic myopathy exists. The results of these tests will help determine future recommendations, but the patient's tolerance and response to light and more strenuous exercise are important factors. Most authorities agree that statin-induced rhabdomyolysis is an indication for discontinuation of their use.

GENERAL REFERENCES

For the General References and other additional features, please visit Elsevier eBooks+ at https://ebooks.health.elsevier.com.

E-TABLE 99-1 THE MCMAHON SCORE CALCULATION

- Age in years:
  - <50 = 0 points.
  - 51-70 = 1 point.
  - 71-80 = 2 points.
  - >80 = 3 points.
- Female sex:
  - 1 point.
- Initial serum creatinine level:
  - <1.4 mg/dL (<124 μM/L) = 0 points.
  - 1.4-2.2 mg/dL (124-195 μM/L) = 1.5 points.
  - >2.2 mg/dL (195 μM/L) = 3 points.
- Initial serum calcium level:
  - <7.5 mg/dL (1.88 mM/L) = 2 points.
- Initial serum phosphate level:
  - <4 mg/dL (1 mM/L) = 0 points.
  - 4-5.4 mg/dL (1-1.4 mM/L) = 1.5 points.
  - >5.4 mg/dL (>1.4 mM/L) = 3 points.
- Initial serum bicarbonate level:
  - <19 mM/L = 2 points.
- Initial serum creatine kinase level:
  - >40,000 U/L = 2 points.
- Rhabdomyolysis NOT caused by seizure, syncope, exercise, statins, or myositis:
  - 3 points.

INTERPRETATION

MCMAHON SCORE	RISK GROUP	RECOMMENDATION
<6	Low risk	Usual care (3% risk of death or acute kidney injury requiring renal replacement therapy)
≥6*	Not low risk	Initiate renal protective therapy including high-volume intravenous fluid resuscitation to achieve a urine output of 1-2 mL/kg/hr (about 50% risk of death or acute kidney injury requiring renal replacement therapy at scores ≥10)

*The McMahon score predicts mortality or acute kidney injury in patients with rhabdomyolysis. The score should be used in patients ages 18 years or older with rhabdomyolysis (creatine kinase [CK] level greater than 5000 U/L within 72 hours of admission). The score should not be used in patients with preexisting end-stage renal disease or an elevated CK secondary to a myocardial infarction.

From McMahon GM, Zeng X, Waikar SS. A risk prediction score for kidney failure or mortality in rhabdomyolysis. *JAMA Intern Med*. 2013;173:1821-1828; and Simpson JP, Taylor A, Sudhan N, et al. Rhabdomyolysis and acute kidney injury: creatine kinase as a prognostic marker and validation of the McMahon Score in a 10-year cohort: a retrospective observational evaluation. *Eur J Anaesthesiol*. 2016;33:906-912; and https://www.mdcalc.com/mcmahon-score-rhabdomyolysis.

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100 APPROACH TO THE PATIENT WITH RENAL DISEASE

ALI G. GHARAVI AND DONALD W. LANDRY

The prominent functions of the kidney include the excretion of nitrogenous waste; the regulated excretion of water, sodium, potassium, calcium, magnesium, phosphate, and acid; and the synthesis of a variety of hormones, including 1,25-dihydroxyvitamin D, erythropoietin, and renin. The kidney's elaboration of a protein-free and cell-free ultrafiltrate is uniquely responsible for the excretion of nitrogenous wastes. The approach to the patient with renal disease is largely focused on disordered ultrafiltration and not on defects in the isolated renal tubular processing of individual ions, molecules, water, or acids. A patient may, for example, present with an isolated defect in renal acid excretion (Chapter 104), but in this case the "approach to the patient" is framed for the evaluation of metabolic acidosis, an abnormality for which the kidney is only one among the many causes in a broad differential diagnosis. In contrast, acute kidney injury (Chapter 106) and chronic kidney disease (Chapter 116) refer specifically and exclusively to defects in the filtration function of the kidney. In the context of a diminished magnitude of filtration, many of the other individual functions of the kidney (e.g., hormone synthesis, electrolyte homeostasis) may fail as well.

Primary diseases of the tubules, such as acute tubular necrosis (Chapter 106) and tubulointerstitial disease (Chapter 108), also impair the rate of glomerular filtration and cause acute kidney injury and chronic kidney disease. In contrast, an impairment in ultrafiltration may, in early chronic kidney disease, be reflected solely in a decreased *quality* of glomerular filtration (e.g., the presence of albuminuria) rather than in a decreased *quantity* of filtrate with increased concentrations of nitrogenous waste. Similarly, the glomerular filtration rate (GFR) may be normal in nephrotic syndrome despite ultrafiltration defects that result in massive proteinuria. Defects in the filter can also allow passage of cells, such as red blood cells (RBCs), as is seen in the acute nephritic syndrome (Chapter 107), with or without heavy proteinuria. The paradox of glomerular hematuria without albuminuria is also possible. For example, in mild forms of immunoglobulin A (IgA) nephropathy (Chapter 107), relatively few defects in the glomerular filter will permit a detectable number of RBCs per high-power field in the urine despite a urine albumin level that still remains within normal limits (Fig. 100-1).

In this context, this chapter considers the approach to the patient with acute kidney injury, glomerular syndromes (nephrotic vs. nephritic), tubulointerstitial disease, vasculitis and vascular diseases of the kidney, papillary necrosis, and chronic kidney disease.

PATHOBIOLOGY

The approximately 2 million renal glomeruli normally filter about 180 L/day. The renal glomerulus is not simply a filter but rather a size- and charge-dependent ultrafilter that impedes not only cells but also proteins larger than 60 kD from entering the ultrafiltrate. Smaller proteins are variably filtered at the glomerulus and endocytosed in the proximal tubule so that the protein concentration of the urine is normally low. Kidney disease reflects a failure in the quantity or quality of the glomerular ultrafiltrate.

The normal GFR may decline in hours to days in acute kidney injury or during months to years in chronic kidney disease. An acute decline in glomerular filtration is the necessary and sufficient condition for the diagnosis of acute kidney injury, but abnormal urinary findings can assist with elucidating the etiology of the injury. Proteinuria, ranging from microscopic to nephrotic range (Chapter 107), and urinary findings, from a few cells per microscopic high-power field to gross hematuria or pyuria, may be the only evidence of the earliest stages of chronic kidney disease. As chronic kidney disease advances, the decline in the GFR progresses until dialysis or transplantation (Chapter 117) is required to forestall or to treat the syndrome of uremia.

DIAGNOSIS

Measuring Kidney Function

Although the most accurate method of evaluating kidney function is a formal measurement of GFR with iothalamate, iohexol, or similar markers, these

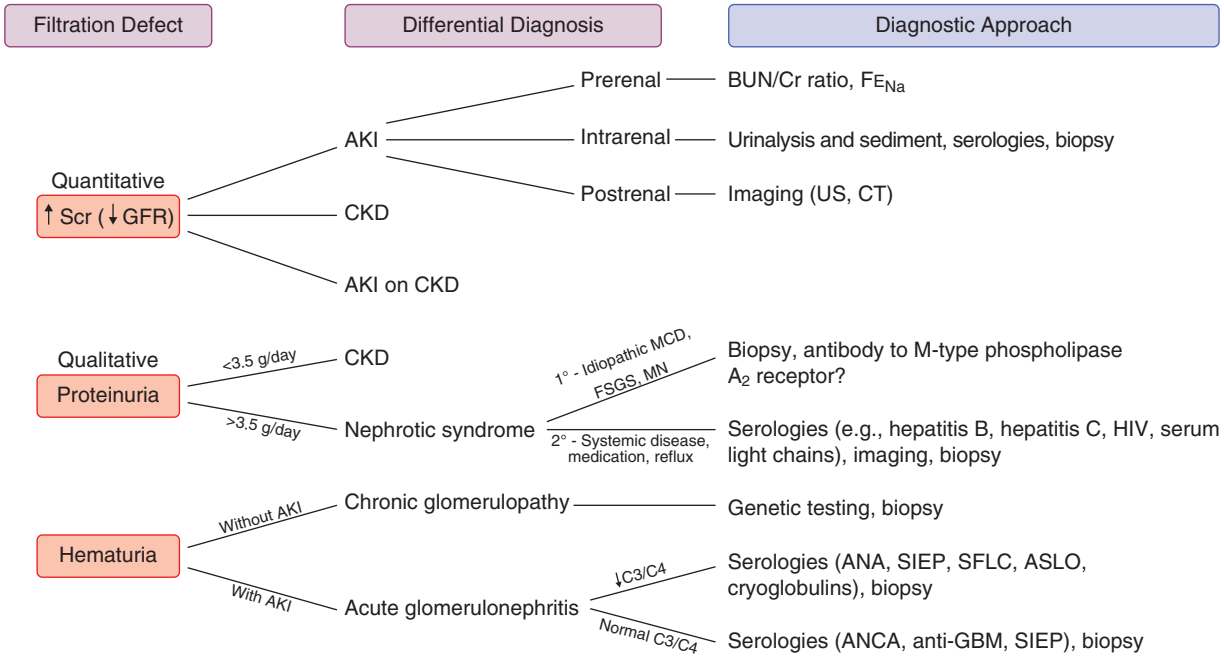

FIGURE 100-1. Overview of approach to kidney disease. Quantitative defects in filtration, manifested by elevated serum creatinine (Scr) and reduced glomerular filtration rate (GFR), should lead to a query into acute kidney injury (AKI) versus chronic kidney disease (CKD). AKI, in turn, is generally divided into prerenal, postrenal, and intrinsic causes. Qualitative defects in filtration, manifested by proteinuria or hematuria, can occur in the absence of changes in GFR and often require biopsy for diagnosis. Proteinuria of more than 3.5 g/day signals nephrotic syndrome, which may be idiopathic or secondary to systemic diseases, such as hepatitis B or C, human immunodeficiency virus (HIV) infection, or diabetes. Glomerular hematuria without AKI is consistent with a chronic glomerulopathy, such as IgA nephropathy, or familial diseases, such as thin basement membranes disease. When hematuria accompanies AKI, acute glomerulonephritis should be suspected and can diagnostically be divided into low-complement glomerulonephritides (immune complex–mediated lesions such as lupus nephritis, postinfectious glomerulonephritis, and cryoglobulinemic glomerulonephritis) and normocomplementemic glomerulonephritides (classically seen in the rapidly progressive glomerulonephropathies due to antineutrophil cytoplasmic antibody [ANCA] and anti–glomerular basement membrane [anti-GBM] antibody). ANA = antinuclear antibody; ASLO = antistreptolysin O; BUN = blood urea nitrogen; Cr = creatinine; CT = computed tomography; MCD = minimal change disease; Fe_{Na} = fractional excretion of sodium; FSGS = focal segmental glomerulosclerosis; MN = membranous nephropathy; SFLC = serum free light chain; SIEP = serum immunoelectrophoresis; US, ultrasonography.

ABSTRACT

The kidneys mediate critical homeostatic functions via excretion of nitrogenous waste and regulated excretion of water, sodium, potassium, calcium, magnesium, phosphate, and acid. The kidney is comprised of about 1 million functional nephrons, and the primary mechanism for excretion is the production of a protein-free and cell-free ultrafiltrate at the vascular origin of the nephron, which is the glomerulus. Renal failure, which refers specifically to a defect in the filtration function, might first be uncovered by abnormalities in blood levels of urea nitrogen, creatinine, and electrolytes. Impaired sodium and water handling in acute kidney injury also may produce symptoms of volume overload, such as edema from decreased urine output. The approach to the patient with renal failure begins by distinguishing acute from chronic processes. Acute renal failure is subdivided into prerenal, intrarenal, and postrenal causes. Prerenal causes include processes that compromise blood flow to the glomerulus. Intrarenal insults (e.g., glomerulonephritis, acute tubular necrosis, and acute interstitial nephritis) affect the kidney's vasculature, tubules, glomeruli, or interstitium. Postrenal causes can obstruct urine flow at any site within the urinary tract. Acute renal failure usually can be distinguished from chronic renal failure by analyzing the urine for protein, infection, and the presence of abnormal cells, as well as by assessing the trajectory of the serum creatinine level over time. Imaging with ultrasound or computerized tomography may identify the presence of postrenal causes, which commonly result in hydronephrosis. Disorders of water and electrolytes may reflect a defect in renal filtration or tubular function, but they may also be caused by primary gastrointestinal, cardiovascular, or endocrine abnormalities.

KEYWORDS

introduction to renal disease
the essentials of ATN
CKD
tubulointerstitial disease
vasculitis
glomerulonephritis

tests are too expensive and time-consuming to be recommended for routine clinical practice. Currently, the most common methods used to estimate GFR are the serum creatinine concentration, the calculated creatinine clearance, and estimation equations based on serum creatinine.

Serum creatinine is, to a first approximation, neither secreted nor reabsorbed, so the amount appearing in the urine per unit time is a measure of the amount that was filtered at the glomerulus during that period. As a result, the rate of creatinine clearance is a reasonably close estimate of the GFR. A decrement in the GFR diminishes creatinine clearance but has no immediate effect on creatinine production by muscle; as a result, the serum creatinine concentration rises. The change in serum creatinine over time indicates the tempo of the renal disease and can distinguish acute injury from chronic kidney disease. The routine use of serum creatinine alone to infer GFR is ill-advised because of the differing rates of creatinine production among individuals, mainly related to variations in muscle mass. Women and the elderly can have deceptively low serum creatinine levels despite significant declines in GFR. In addition, the inverse relationship between GFR and serum creatinine (Fig. 100-2) has important and potentially easily overlooked clinical implications. An initial small absolute rise in creatinine usually reflects a marked fall in GFR, whereas seemingly large changes in the serum creatinine level in patients with more advanced chronic kidney disease (CKD) may reflect minor changes in GFR.

Approach to Diagnosis

The routine screening of asymptomatic adults without risk factors for kidney disease is not recommended. Most patients are diagnosed because other conditions lead to tests of kidney function.

Some kidney diseases may have clinical manifestations in their early stages (e.g., edema in the nephrotic syndrome [Chapter 107] or rash in IgA vasculitis [Chapter 249]). However, because of the kidney's large functional reserve, only significant impairments of kidney function result in clinical manifestations. Advanced renal failure (Chapter 116) is associated with anorexia, abnormal taste, nausea, vomiting, fatigue, sleep difficulties, and shortness of breath from volume overload. Physical examination and laboratory tests reveal malnutrition, hypertension, hypervolemia, anemia, hyperlipidemia, and bone disease. More advanced kidney disease results in the syndrome of uremia, which can manifest as impaired cognition, pericarditis, life threatening hyperkalemia, and acidosis, thereby necessitating renal replacement therapy (Chapter 117).

The serum creatinine level or cystatin C level to estimate and GFR plus additional tests (e.g., a formal 24-hour urine collection to measure creatinine clearance and proteinuria) can confirm the diagnosis of kidney disease. Calculation of creatinine clearance from a 24-hour urine collection can be cumbersome for patients and is prone to error because of inaccurate urine collection. To measure the creatine clearance accurately, the patient must be instructed to discard the first morning urine before initiating the collection and to conclude the collection by including the next morning void. The formula for calculating creatinine clearance is as follows:

$$CCr = (\text{urine Cr} \times V)/(\text{plasma Cr})$$

where *CCr* is creatinine clearance, *urine Cr* is urine creatinine concentration, *V* is urine flow rate, and *plasma Cr* is plasma creatinine. The normal value for GFR ranges from 120 to 140 mL/min/1.73 m^2.

Because of the logistical and practical limitations of a 24-hour urine collection for direct measurement of the GFR, several equations have been developed to estimate GFR based on the serum creatinine or cystatin C level[1–3] and levels of albuminuria (Table 116-2). Although useful for staging CKD, these estimating equations have limitations, particularly in the elderly and at the extremes in the distribution (Chapter 116).[4] For example, physiologic, age-related decline in the GFR in older individuals must be distinguished from a true reduction in the GFR due to kidney disease. All calculations of GFR assume that the patient is in a steady state (Table 100-1), and so values will be inaccurate in situations in which kidney function is changing rapidly (e.g., in acute kidney injury; Chapter 106). The creatinine clearance also overestimates GFR by about 10% owing to tubular secretion of creatinine. The calculations can be further influenced by drugs or conditions (i.e., the nephrotic syndrome or sickle cell disease) that can alter the secretion of creatinine. Cystatin C may provide a more accurate and prognostic measurement of GFR in patients whose creatinine levels are in the upper end of the normal range,[5] but it has not replaced estimated GFR measurements for most clinical purposes.

Urinalysis

Urinalysis can be a very useful test, although it can also be over-ordered in low-risk, asymptomatic individuals. The normal color of the urine is derived from urochromes, which are pigments excreted in the urine. Abnormal color or appearance of the urine may be explained by many conditions (Table 100-2). The basic analysis of the urine sample involves measurements with commercially available dipsticks or microscopic analyses.

Urine Dipstick

The *specific gravity* of the urine generally is related linearly with osmolality. However, it can be raised by the presence of molecules with relatively high molecular weight, such as glucose or contrast dye. A fixed specific gravity of 1.010, so-called isosthenuria, is characteristic of chronic kidney disease (Chapter 117).

Urine pH typically is 5 as a result of daily net acid excretion. An alkaline pH often is noted after meals, when an "alkaline tide" to balance gastric acid excretion increases urine pH. A high urine pH also is seen in patients who are on a vegetarian diet. An exceptionally high urine pH is indicative of an infection with a urea-splitting organism, such as *Proteus* species (Chapter 263). An inappropriately high urine pH in the setting of systemic non–anion gap metabolic acidosis may be seen in certain forms of renal tubular acidosis (Chapter 104). In a proximal renal tubular acidosis, the urine pH is high until the tubular reabsorption threshold for bicarbonate, which is abnormally low, is reached. At this point, the urine pH decreases to 5. In distal renal tubular acidosis, the inability to create a sufficient gradient for hydrogen ions results in a urine pH that is always higher than 5.5. In type 4 renal tubular acidosis, the urine pH is often 5, and the urine net charge is often positive, thereby confirming the

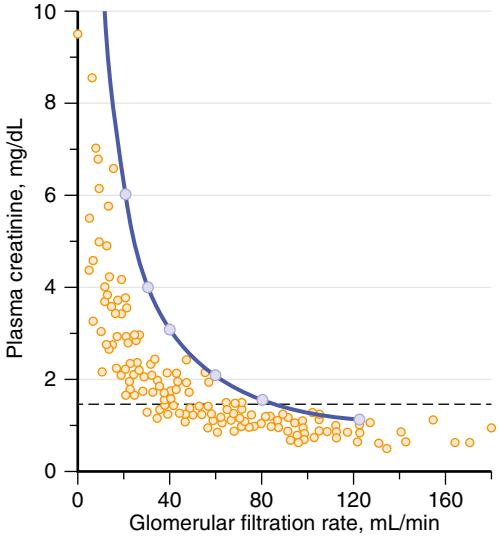

FIGURE 100-2. Relationship between plasma creatinine and glomerular filtration rate measured by inulin clearance in 171 patients (*circles*). The *continuous line* reflects the idealized relationship between these parameters if creatinine were excreted solely by glomerular filtration; the *dashed line* represents an upper limit of "normal" for the creatinine concentration of 1.4 mg/dL. (Redrawn from Shemesh O, Golbetz H, Kriss JP, et al. Limitations of creatinine as a filtration marker in glomerulopathic patients. *Kidney Int.* 1985;28:830-838.)

TABLE 100-1 CONSIDERATIONS FOR INTERPRETATION OF GFR VALUES

ASSUMPTIONS
Assumption of steady state
Assumption of complete 24-hour urine collection
FACTORS THAT ALTER CREATININE PRODUCTION OR SECRETION
Drugs that reduce creatinine secretion (cimetidine, trimethoprim, poly adenosine diphosphate-ribose polymerase inhibitors, tyrosine kinase inhibitors)
Diet (high protein meals can temporarily increase serum creatinine)
Muscle mass (higher muscle mass associated with increased production)
Rhabdomyolysis (increased release due to muscle injury)
Nephrotic syndrome and sickle cell disease (increased secretion)

GFR = glomerular filtration rate.

TABLE 100-2 MACROSCOPIC APPEARANCE OF URINE

APPEARANCE	CAUSE
Milky	Acid urine: urate crystals Alkaline urine: insoluble phosphates Infection: pus Spermatozoa Chyluria
Smoky pink	Hematuria (>0.54 mL blood/L urine)
Foamy	Proteinuria
Blue or green	*Pseudomonas* urinary tract infection Bilirubin Methylene blue
Pink or red	Aniline dyes in sweets Porphyrins (on standing) Blood, hemoglobin, myoglobin Drugs: phenindione, phenolphthalein Anthocyaninuria (beetroot, "beeturia")
Orange	Drugs: anthraquinones (laxatives), rifampicin Urobilinogenuria
Yellow	Mepacrine Conjugated bilirubin Phenacetin Riboflavin
Brown or black	Melanin (on standing) Myoglobin (on standing) Alkaptonuria
Green or black	Phenol Lysol
Brown	Drugs: phenazopyridine, furazolidone, L-dopa, niridazole Hemoglobin and myoglobin (on standing) Bilirubin

From Forbes CD, Jackson WF. *Color Atlas and Text of Clinical Medicine*. 3rd ed. London: Mosby; 2003.

absence of significant amounts of ammonium in the urine; this defect, which is most often present in patients with diabetic kidney disease, is exacerbated by the accompanying hyperkalemia.

Glucose in the urine is detected by an assay using dipsticks impregnated with the enzyme glucose oxidase. Glycosuria, which is seen in diabetes mellitus (Chapter 210), when pregnancy causes the tubular threshold for glucose reabsorption to change, and in tubular diseases that affect the proximal convoluted tubule and cause tubular glycosuria, is an independent risk factor for mortality. Evidence for pan–proximal tubular dysfunction (e.g., glycosuria, aminoaciduria, phosphaturia) indicates that Fanconi syndrome is present.

The dipstick for *protein* is a sensitive assay based on color change induced by the presence of proteins at a given pH. It is most sensitive to the presence of albumin[6] and is much less sensitive to other proteins, such as the light chains of Bence Jones protein (Chapter 173). The presence of 1+ protein correlates with about 30 mg/dL of albuminuria, and 3+ protein correlates with more than 500 mg/dL of proteinuria. Because the dipstick is not a quantitative measurement, small amounts of proteinuria in an oliguric patient may give the false appearance of high-grade proteinuria. The excretion of abnormal quantities of albumin below the level detectable by the urine dipstick is called *microalbuminuria*. Normal albumin excretion, which is less than 30 mg/day, is best detected by radioimmunoassay or enzyme immunoassay. Microalbuminuria is the earliest clinically detectable stage of diabetic nephropathy (Chapter 109). Proteinuria of increasing severity is associated with a more rapid decline in the GFR, regardless of the GFR and even after acute kidney injury,[7] except in minimal change disease (Chapter 107).

The dipstick for *heme* uses the peroxidase-like activity of hemoglobin and myoglobin molecules to detect the presence of heme pigment. The reaction occurs on exposure to hemoglobin, myoglobin, or intact RBCs. Urine dipstick testing is very sensitive (97%) and reasonably specific (75%) for the detection of hematuria. The presence of myoglobin, which is found in patients with rhabdomyolysis (Chapter 99), or free hemoglobin, which is seen in patients with intravascular hemolytic anemias (Chapter 147), is suspected if the heme reaction is intensely positive and there is a paucity of cellular elements in the sediment. Since RBCs lyse rapidly on storage, especially in a hypotonic urine, their absence on routine analysis of the urinary sediment is likely to provide false reassurance in the presence of a positive dipstick. Persistent, isolated, asymptomatic, microscopic hematuria is an independently significant risk factor for the subsequent development of end-stage renal disease (Chapter 116). Although gross asymptomatic hematuria is associated with cancer in 8 to 25% of cases, only about 2.5% of patients with dipstick-positive hematuria have cancer, including less than 0.5% of people under age 50 years.

The dipstick detection of *leukocytes* depends on the presence of leukocyte esterase. Leukocyte esterase is usually present in infections (Chapter 263) and in inflammatory conditions. When positive, it is reasonable to proceed directly to a urine culture without requiring confirmation of leukocytes on a microscopic examination of the urine.[8,9]

Urine Sediment

RBCs, white blood cells (WBCs), tubular cells, transitional cells, and squamous epithelial cells may be seen in the urine.[10] Casts are formed in tubules, may contain cells or cellular debris, or may be acellular.

Hematuria

RBCs may originate from intrarenal vessels, glomeruli, tubules, or anywhere in the urogenital tract (Fig. 100-3). Dysmorphic RBCs are cells that have been deformed by transit through the glomerulus and through the medullary interstitium, as opposed to RBCs from the remainder of the genitourinary tract (Figs. 100-4 and 100-5); these cells are often lysed and less refractile than nonglomerular RBCs. Dysmorphic RBCs often fragment with poikilocytosis and with blebs, forming so-called "Mickey Mouse" RBCs. Phase contrast microscopy aids in the identification of dysmorphic RBCs. The presence of a majority of dysmorphic RBCs in a urine sediment points to a glomerular origin of the hematuria. The presence of RBC casts is often conclusive evidence for the presence of glomerulonephritis.

In asymptomatic individuals with three or more RBCs per high-powered field in a properly collected urine specimen, formal evaluation of the lower and upper urinary tract is commonly indicated, regardless of whether or not patients are taking anticoagulants,[11] if infection, menstruation, and vigorous exercise can be excluded as causes. Lower urinary tract evaluation by cystoscopy should be performed in patients over age 35 years or with risk factors for urinary tract malignancies. Upper tract evaluation usually is performed by computed tomography (CT) or magnetic resonance (MR) imaging urography.[12] Findings suggestive of intrinsic parenchymal renal disease (dysmorphic RBCs, RBC casts, proteinuria, cellular casts) require nephrologic evaluation but do not preclude the need for a urologic evaluation.

Pyuria

WBCs are seen most commonly in bacterial urinary tract infections, but some patients with evident pyuria will have negative urine cultures. Infectious causes of sterile pyuria include tuberculosis (Chapter 299), gonorrhea (Chapter 275), chlamydia (Chapter 294), mycoplasma (Chapter 293) and ureaplasma (Chapter 293, 263, and 264), genital herpes (Chapter 345), trichomoniasis (Chapter 324), fungal infections (Chapter 307), and schistosomiasis (Chapter 326). Even when bacteriuria is confirmed, asymptomatic patients rarely require treatment (Chapter 263).[13,14]

WBCs also can be seen in acute interstitial nephritis, infections with *Legionella* (Chapter 290) and *Leptospira* (Chapter 298) species, allergic interstitial nephritis (Chapter 108), atheroembolic diseases (Chapter 110), granulomatous diseases such as sarcoidosis (Chapter 83), IgG4-related interstitial nephritis, and tubulointerstitial nephritis and uveitis syndrome (Table 100-3). Mononuclear cells often appear with transplant rejection. Tubular cells, which are seen in many conditions involving tubulointerstitial diseases, also are seen in ischemic and nephrotoxic injury, such as with myeloma kidney (Chapter 173) or cast nephropathy. Eosinophils require special stains, with the Giemsa stain being much less sensitive than the Hansel stain (Chapter 108). Urine eosinophils classically are seen in allergic interstitial nephritis (Chapter 108), but they also are seen in atheroembolic disease (Chapter 110), prostatitis (Chapter 114), and vasculitis.

Casts and Crystals

Casts, which are formed in tubules, are characterized by the arrangement of the cells in a clearly formed matrix composed of Tamm-Horsfall protein. Because casts are formed in the renal parenchyma, they may give a clue to the origin of accompanying cellular elements.

Hyaline casts are composed of Tamm-Horsfall proteins that are formed normally and are seen in increased numbers after exercise (Fig. 100-6). *Granular casts* are degenerated tubular cell casts that are seen in the setting of tubular

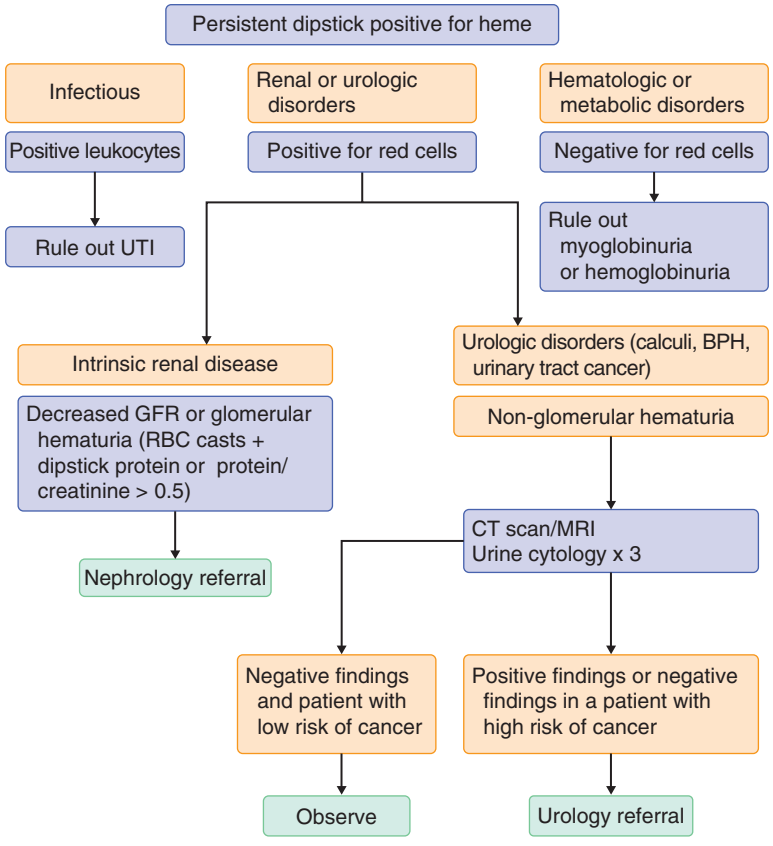

FIGURE 100-3. Algorithm for the evaluation of asymptomatic hematuria. BPH = benign prostatic hyperplasia; CT = computed tomography; GFR = glomerular filtration rate; MRI = magnetic resonance imaging; RBC = red blood cell; UTI = urinary tract infection. (Modified from Cohen RA, Brown RS. Microscopic hematuria. *N Engl J Med*. 2003;348:2330-2338.)

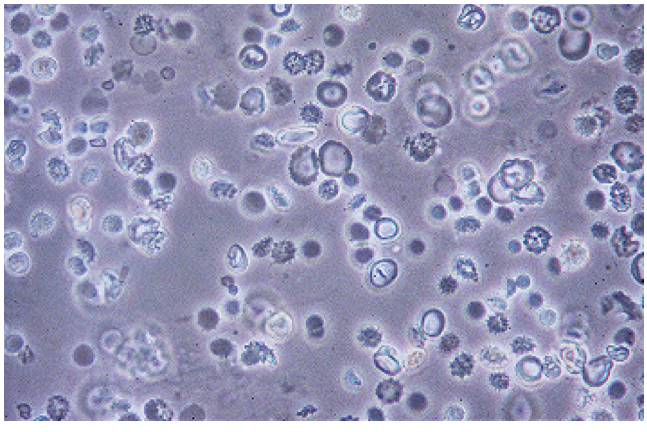

FIGURE 100-4. Dysmorphic erythrocytes. These dysmorphic erythrocytes vary in size, shape, and hemoglobin content and reflect glomerular bleeding. (From Johnson RJ, Feehally J. *Comprehensive Clinical Nephrology*. London: Mosby; 2000.)

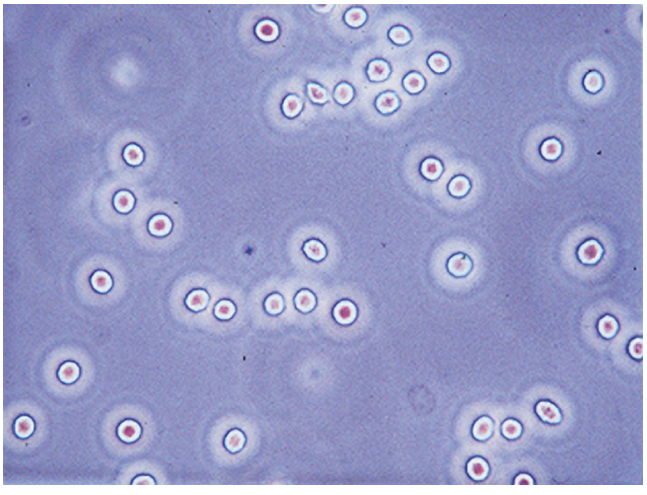

FIGURE 100-5. Isomorphic erythrocytes. These erythrocytes are similar in size, shape, and hemoglobin content. Isomorphic cells reflect nonglomerular bleeding from lesions such as calculi and papillomas or hemorrhage from cysts in polycystic renal disease. (From Johnson RJ, Feehally J. *Comprehensive Clinical Nephrology*. London: Mosby; 2000.)

injury (Fig. 100-7). *Pigmented granular casts* are seen in rhabdomyolysis (Chapter 99) with myoglobinuria or, rarely, hemoglobinuria. *RBC casts* (Fig. 100-8) are rarely seen in allergic interstitial nephritis and diabetic nephropathy, but they are frequently seen in acute glomerulonephritis (Chapter 107). The presence of RBC casts in a patient with microscopic hematuria can narrow the focus of the evaluation to a glomerular lesion. *WBC casts* are seen commonly in pyelonephritis (Chapter 263) and in acute and chronic nonbacterial infections. They also are seen in other conditions in which WBCs are associated with parenchymal renal processes, such as allergic interstitial nephritis (Chapter 108), atheroembolic diseases (Chapter 110), and granulomatous diseases such as sarcoidosis (Chapter 83). Rarely, WBC casts can be a dominant feature of many diseases that traditionally are thought of as glomerular diseases, such as lupus nephritis (Chapter 245) and antineutrophil cytoplasmic antibody (ANCA)–associated glomerulonephritis (Chapter 249). *Tubular cell casts* are seen with any acute tubular injury and are the dominant cellular casts in ischemic acute tubular necrosis (Chapter 106). They also can be seen with nephrotoxic injury, such as with aminoglycosides and cisplatin. Some casts may contain both leukocytes and tubule cells.

Crystals can be a normal finding in the urine or serve as clues to pathophysiologic processes. Certain crystals, such as the hexagonal crystals seen with cystinuria (Chapter 111), are always abnormal (Fig. 100-9). Others, such as the octahedral calcium oxalate crystals (Fig. 100-10), may be a normal finding or may be evidence for ethylene glycol intoxication (Chapter 96). Coffin lid–shaped triple phosphate crystals, which are composed of ammonium magnesium phosphate (Fig. 100-11), are seen in urinary tract infections with urea-splitting organisms (Chapter 263). Uric acid crystals, sodium urate

TABLE 100-3 CAUSES OF STERILE PYURIA

INFECTIOUS
Current use of antibiotics
Past treated urinary tract infection (within past 2 weeks)
Tuberculosis (Chapter 299)
Gonorrhea (Chapter 275) and chlamydia (Chapter 294)
Mycoplasma and ureaplasma (Chapter 293)
Genital herpes (Chapter 345)
Trichomoniasis (Chapter 324)
Fungal infections (Chapter 307)
Schistosomiasis (Chapter 326)
Prostatitis (Chapter 114)
Balanitis
Appendicitis (Chapter 128)
NONINFECTIOUS
Interstitial nephritis (e.g., analgesic nephropathy; Chapter 108)
Urinary tract stones (Chapter 111)
Polycystic kidney (Chapter 112)
Current or recent urinary tract manipulation
Catheter cystoscopy
Endoscopy
Foreign body such as surgical mesh in the urethra or a retained stent
Urinary tract neoplasm (Chapter 182)
Pelvic irradiation
Urinary fistula
Renal transplant rejection (Chapters 38 and 117)
Renal vein thrombosis (Chapter 110)
Papillary necrosis
Interstitial cystitis (Chapter 263)
Inflammatory diseases (e.g., systemic lupus erythematosus [Chapter 245] or Kawasaki disease [Chapter 249])

Adapted from Wise GJ, Schlegel PN. Sterile pyuria. *N Engl J Med*. 2015;372:1048-1054.

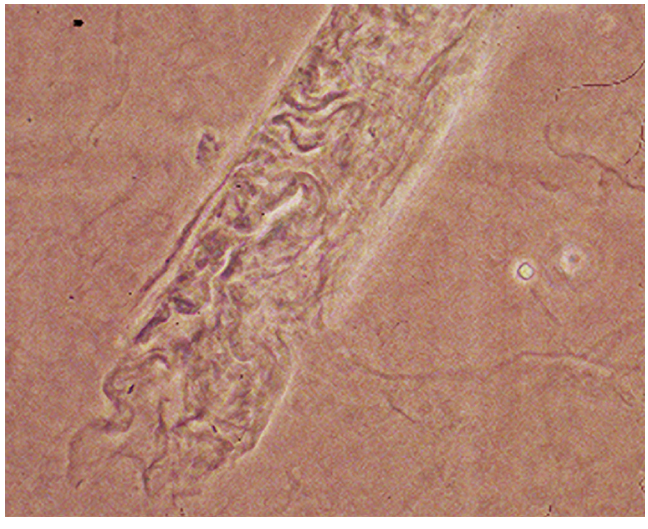

FIGURE 100-6. Hyaline cast of the type seen in small numbers in normal urine. (From Johnson RJ, Feehally J. *Comprehensive Clinical Nephrology*. London: Mosby; 2000.)

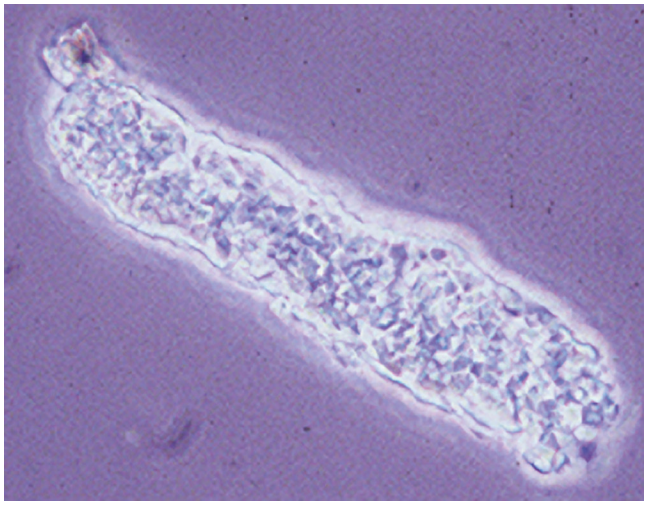

FIGURE 100-7. Number and type of granules and their density in the cast vary in different casts. The presence of erythrocytes in this cast may mean that the granules are derived partly from disrupted erythrocytes. (From Johnson RJ, Feehally J. *Comprehensive Clinical Nephrology*. London: Mosby; 2000.)

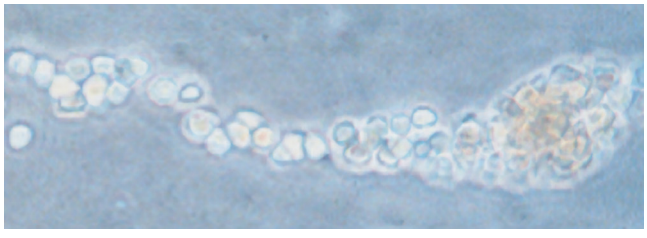

FIGURE 100-8. A cast composed entirely of erythrocytes reflects heavy hematuria and active glomerular disease. Crescentic nephritis is likely to be present if erythrocyte cast density is greater than 100/mL. (From Johnson RJ, Feehally J. *Comprehensive Clinical Nephrology*. London: Mosby; 2000.)

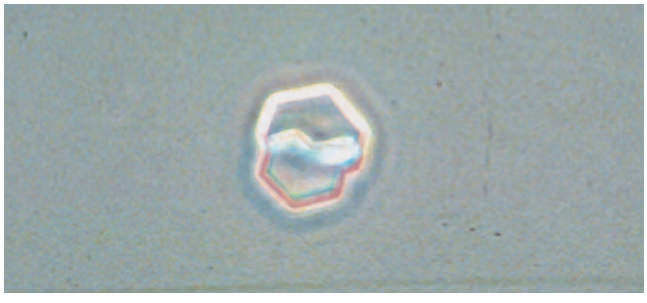

FIGURE 100-9. Typical hexagonal cystine crystal. A single crystal provides a definitive diagnosis of cystinuria. (From Johnson RJ, Feehally J. *Comprehensive Clinical Nephrology*. London: Mosby; 2000.)

crystals (Fig. 100-12), and calcium phosphate amorphous crystals are common and do not usually have pathologic significance.

Other Elements

Bacteria may be seen in the urine sediment. A spun urine sediment may show rods or cocci in chains, but bacteria are identified best by Gram staining of the urine sediment. Budding yeast forms (which are highly refractile), trichomonads, and spermatozoa also may be seen in the urinary sediment.

Disorders of Electrolytes

The kidneys mediate the homeostatic balance of a variety of electrolytes. Electrolyte disorders may accompany renal failure or may reflect isolated defects in tubular function or specific defects in ion transporters. The functional integrity of the renal tubules can be assessed by calculating the fractional excretion of an electrolyte *X*.

$$FE = \frac{(urine_X)/(plasma_X)}{(urine_{Cr})/(plasma_{Cr})} \times 100 = \frac{(urine_X) \times (plasma_{Cr})}{(urine_{Cr}) \times (plasma_X)} \times 100$$

Imbalances in renal sodium and water handling can lead to extracellular volume depletion or to the formation of edema (Chapter 102). Potassium homeostasis is regulated primarily at the distal nephron, but dietary intake, transcellular shifts, and gastrointestinal losses also contribute to balance (Fig. 100-13; Chapter 103). Calcium homeostasis is regulated by the actions of parathyroid hormone, calcitonin, and vitamin D on bone, intestine, kidney, and parathyroid tissue. Although Ca^{++} is also filtered and excreted by the kidney, the important role of these hormones generally places disorders of hypocalcemia and hypercalcemia within endocrinology (Chapter 227). Magnesium deficiency (Chapter 105) may be caused by decreased intake (either orally or by impaired intestinal absorption) or by increased losses via the gastrointestinal tract, kidneys, or skin. Conversely, hypermagnesemia

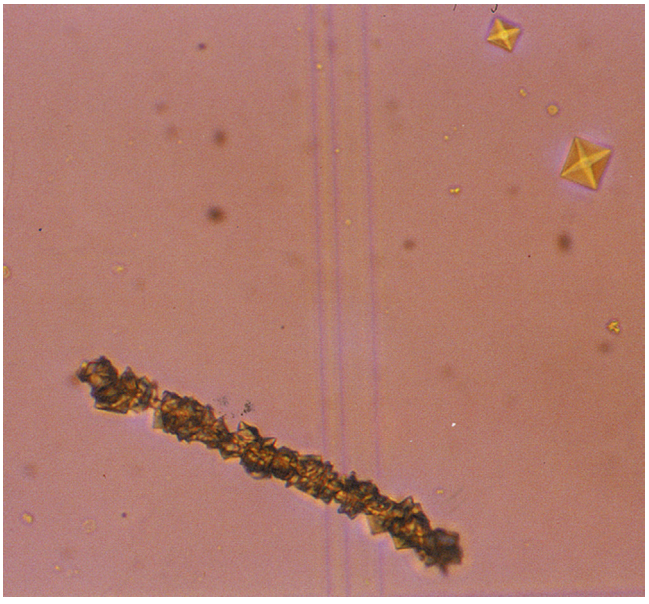

FIGURE 100-10. Oxalate crystals. A pseudocast of calcium oxalate crystals accompanied by crystals of calcium oxalate dehydrate. (From Johnson RJ, Feehally J. *Comprehensive Clinical Nephrology*. London: Mosby; 2000.)

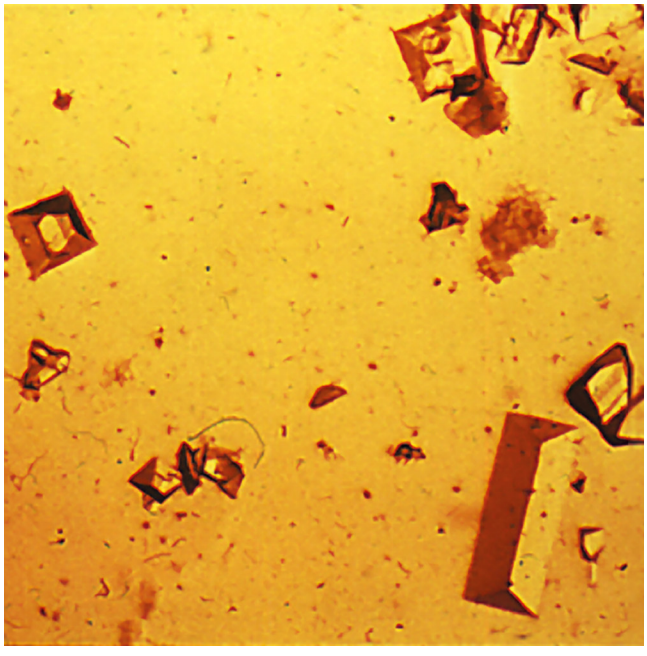

FIGURE 100-11. Coffin lid crystals of magnesium ammonium phosphate (struvite). (From Johnson RJ, Feehally J. *Comprehensive Clinical Nephrology*. London: Mosby; 2000.)

(Chapter 105) can rarely occur in individuals with a normal GFR when the rate of intake exceeds capacity of renal clearance (e.g., excessive use of Mg^{++}-based antacids or large parenteral doses given for preeclampsia). Similar to potassium, hyperphosphatemia (Chapter 105) can arise from reduced excretion (primarily chronic kidney disease), excessive intake, or redistribution of cellular phosphorus. Hypophosphatemia also can be caused by shifts into the intracellular compartment, or may occur from malnutrition or from renal losses. High urine phosphorus in the setting of hypophosphatemia suggests a renal tubule defect, hyperparathyroidism (Chapter 227), or a form of rickets (Chapter 226) and can be assessed by determining the fractional excretion.

SPECIFIC RENAL SYNDROMES

This chapter considers the approach to the patient with acute kidney injury (Chapter 106), glomerular syndromes (nephrotic vs. nephritic; Chapter 107), tubulointerstitial disease (Chapter 108), vasculitis and vascular diseases of the kidney (Chapter 110), papillary necrosis, and chronic kidney disease (Chapter 116).

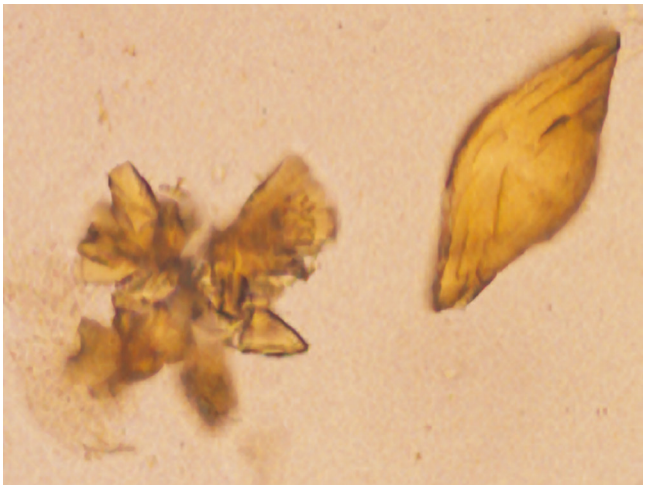

FIGURE 100-12. Urate crystals. Complex crystals suggestive of acute urate nephropathy or urate nephrolithiasis. (From Johnson RJ, Feehally J. *Comprehensive Clinical Nephrology*. London: Mosby; 2000.)

ACUTE KIDNEY INJURY

Acute kidney injury (Chapter 106) is a syndrome in which glomerular filtration declines during a period of hours to days. The serum creatinine level is elevated in both acute and chronic kidney disease, but an actively rising serum creatinine level confirms an acute or acute-on-chronic insult to kidney function. As a blood filtration organ, the kidney is susceptible to an acute compromise of renal arterial perfusion (Chapter 110), such as prerenal kidney injury, or blockage in urine outflow, such as urinary obstruction due to benign prostatic hypertrophy (Chapter 114). Thus, the patient with acute renal failure is best approached by evaluation for prerenal, renal, and postrenal causes. The intrarenal causes of acute kidney injury include acute tubular necrosis (Chapter 106), acute interstitial nephritis (Chapter 108), acute glomerulonephritis (Chapter 107), and acute vasculitis and vascular disease (Chapters 107, 110 and 249). The careful and systematic evaluation of the patient should start with a thorough history and physical examination, which should be followed by selected laboratory tests and often an imaging test, such as renal ultrasonography. Most cases of acute renal failure in the hospital have hemodynamic or toxic causes, so prerenal azotemia and acute tubular necrosis must be considered carefully and distinguished from one another.

DIAGNOSIS

Laboratory Testing

The normal concentration of blood urea nitrogen (BUN), which is a product of protein catabolism, is about 10-fold higher than the creatinine concentration. Because the BUN-to-creatinine ratio commonly rises with arterial underfilling, BUN typically is used as a marker of effective volume status. Classically, the BUN-to-creatinine ratio will be higher than 15 to 20 in prerenal azotemia but 10 or close to it in acute tubular necrosis. However, the BUN concentration (and hence its ratio to creatinine concentration) may be inappropriately high in other circumstances, such as with high protein intake, gastrointestinal bleeding, or the use of steroids or tetracyclines. The BUN concentration and its ratio to creatinine concentration may be low in patients who have a poor dietary intake of protein, malnutrition, or liver disease.

The excretion of sodium in the setting of oliguria and acute kidney injury (Chapter 106) often gives insight into the appropriateness of tubular function. The fractional excretion of sodium (FE_{Na}) is calculated as follows:

$$FE_{Na} = (urine_{Na}/plasma_{Na})/(urine_{Cr}/plasma_{Cr}) \times 100$$

where *Na* is the sodium concentration (in mmol/L) and *Cr* is the creatinine concentration (in mmol/L or mg/dL). In the setting of oliguria, FE_{Na} below 1% often denotes prerenal azotemia, whereas FE_{Na} above 1% suggests intrinsic renal damage. Although this measurement is generally useful, FE_{Na} below 1% may be seen without evidence of a prerenal component, including contrast nephropathy (Chapter 106), hepatorenal syndrome (Chapter 139), obstructive

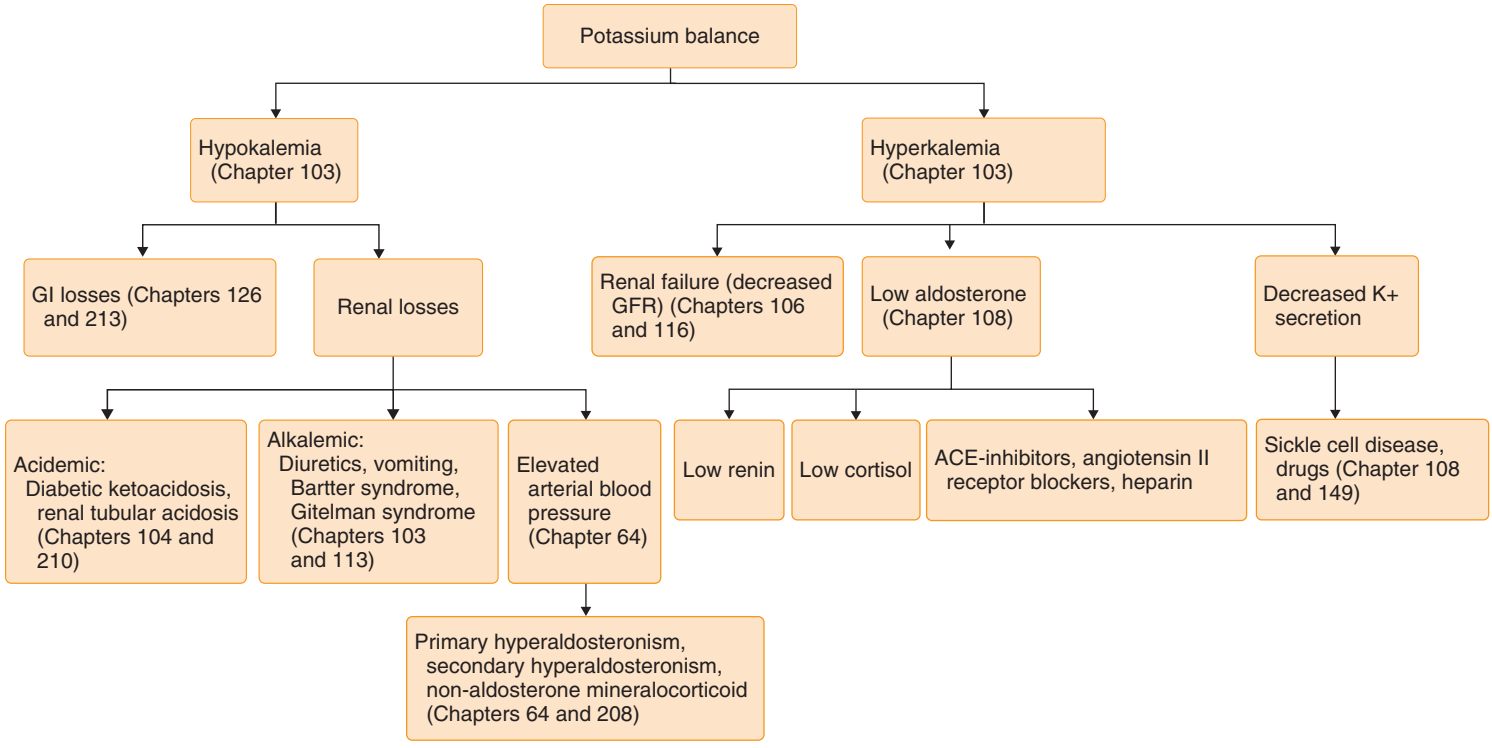

FIGURE 100-13. Regulation of potassium balance. ACE = angiotensin-converting enzyme; AKI = acute kidney injury; GI = gastrointestinal.

uropathy (Chapter 114), interstitial nephritis (Chapter 108), glomerulonephritis (Chapter 107), and rhabdomyolysis (Chapter 99). Conversely, a high FE_{Na} can be seen in cases in which there is a prerenal component, including diuretic use, adrenal insufficiency (Chapter 208), cerebral salt wasting, and salt-wasting nephropathy (Chapter 102). The FE_{Na} must be evaluated in the context of the clinical situation because it can be low or high in a normal patient or in a patient with chronic kidney disease. Ultimately, a patient's volume status is best evaluated at the bedside and should not be deduced solely from a measurement of electrolytes.

Imaging

Ultrasonography, which is the most commonly used renal imaging study (Fig. 100-14),[15] provides reliable information about obstruction, kidney size, presence of masses, and renal echotexture. Ultrasonography has only a 90% sensitivity for the detection of hydronephrosis and hence is not sufficient to exclude obstruction (Chapter 114) with certainty. In addition, its inability to detect stones in the ureters and bladder limits its utility in the evaluation for kidney stones (Chapter 111). Ultrasonography can detect vascular disease, and Doppler imaging permits evaluation of the renal vessels with resistive indices. Resistive indices are crucial in ascribing renal dysfunction to the detected vascular disease (Chapter 110). A high resistive index reflects parenchymal disease with scarring and indicates that intervention on the vascular disease itself is unlikely to improve renal function.

A CT scan stone protocol to assess the kidneys, ureters, and bladder is the study of choice for detecting kidney stones (Chapter 111) because of its ability to detect all types of stones, nonobstructing stones, and stones in the ureters (Fig. 100-15). Masses in the kidney can be evaluated with either contrast CT or a renal ultrasound examination. CT angiography with iodinated contrast material can assess possible renal artery stenosis (Chapter 110) with an accuracy comparable to that of MR angiography.

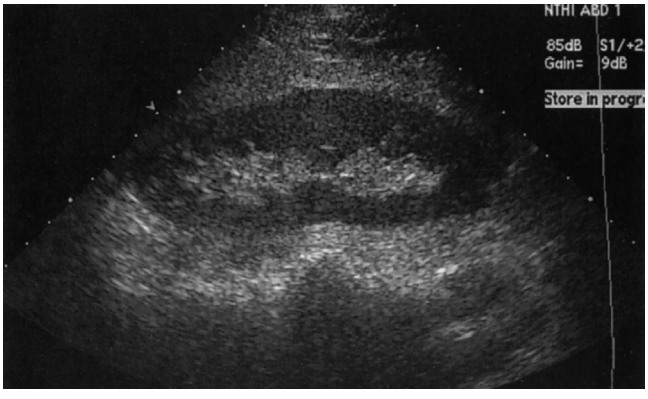

FIGURE 100-14. Normal findings on sagittal renal ultrasound. The cortex is hypoechoic compared with the echogenic fat containing the renal sinus. (From Johnson RJ, Feehally J. *Comprehensive Clinical Nephrology*. London: Mosby; 2000.)

GLOMERULAR SYNDROMES: NEPHROTIC VERSUS NEPHRITIC

The nephrotic syndrome (Chapter 107) is characterized by the presence of proteinuria of more than 3.5 g/day/1.73 m^2, with accompanying edema, hypertension, and hyperlipidemia. Other consequences include a predisposition to infection and hypercoagulability. In general, the diseases associated with nephrotic syndrome do not cause acute kidney injury, although acute kidney injury may be seen with minimal change disease, human immunodeficiency virus (HIV)–associated nephropathy, and bilateral renal vein thrombosis (Chapter 110). The causes of primary idiopathic nephrotic syndrome, in decreasing order of prevalence, are focal and segmental glomerulosclerosis, membranous nephropathy, minimal change disease, and membranoproliferative glomerulonephritis. Membranous nephropathy has been associated with antibodies to the M-type phospholipase A_2 receptor. Secondary causes of the nephrotic syndrome include diabetic nephropathy (Chapter 109), amyloidosis (Chapter 174), and membranous lupus nephritis (Chapters 107 and 245).

The acute nephritic syndrome is an uncommon but dramatic presentation of an acute glomerulonephritis (Chapter 107). The hallmark of the acute nephritic syndrome is the presence of dysmorphic RBCs and RBC casts, but their absence does not exclude the syndrome. The acute nephritic syndrome can be caused by any of the rapidly progressive glomerulonephropathies with ANCA-associated vasculitis (granulomatosis with polyangiitis, microscopic polyangiitis, and eosinophilic granulomatosis with polyangiitis), anti–glomerular basement membrane (anti-GBM) glomerulonephritis, and immune complex–mediated glomerulonephritis (including systemic lupus erythematosus, cryoglobulinemia, postinfectious glomerulonephritis, endocarditis, IgA nephropathy, and IgA vasculitis). The rapid decline in renal function often warrants urgent and usually inpatient evaluation.

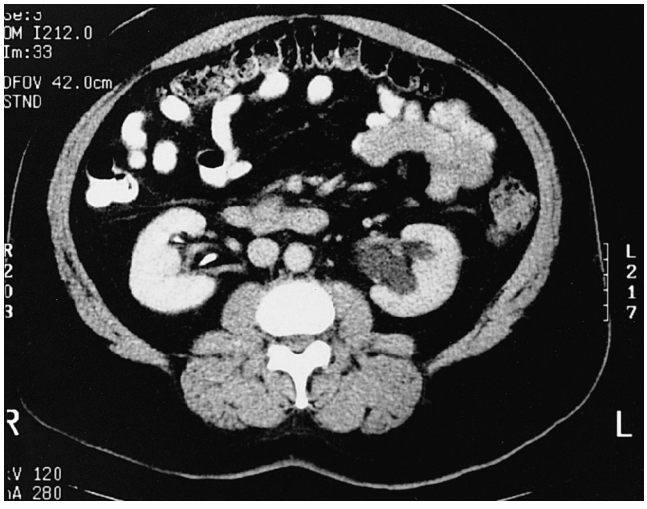

FIGURE 100-15. Delayed excretion in the left kidney secondary to a distal calculus. Contrast-enhanced computed tomography scan shows dilated left renal pelvis. (From Johnson RJ, Feehally J. *Comprehensive Clinical Nephrology*. London: Mosby; 2000.)

DIAGNOSIS

Laboratory Testing

Proteinuria (as albuminuria) of more than 3.5 g in 24 hours generally indicates glomerular disease (Chapter 107). Lesser quantities do not preclude glomerular disease, and electrophoresis gives valuable insight into the composition of the proteinuria (Chapter 173). On occasion, overflow proteinuria of a low-molecular-weight protein, such as light chains in Bence Jones proteinuria, can be higher than 3.5 g/day without any of the manifestations or implications of the nephrotic syndrome; a urine protein electrophoresis study is important in making the distinction. A comparison of the microalbumin-to-creatinine ratio with the protein-to-creatinine ratio will give an insight into the presence of Bence Jones protein because of the absence of albuminuria despite significant proteinuria. Collection must be done by discarding the first morning void and collecting all urine output for the next 24 hours, including the first morning void the next day.

The 24-hour urine collection for protein excretion is cumbersome and subject to inaccuracies. Instead, a spot urine sample for protein and creatinine can be used to estimate the amount of protein excreted. A protein-to-creatinine ratio of 3 translates to a 24-hour protein excretion of about 3 g. The ratio is most accurate when the first morning urine collection is used and may be inaccurate in patients with orthostatic proteinuria.

The evaluation of proteinuric renal dysfunction, particularly when glomerular diseases are suspected, should follow a stepwise progression from noninvasive serologic evaluation to a definitive or confirmatory diagnostic evaluation, such as a renal biopsy. Sometimes an expeditious diagnosis is needed, and a biopsy may be done relatively early in the evaluation.

Serologies

An *antinuclear antibody* (ANA) titer can be useful to evaluate glomerular disease in either nephrotic or nephritic presentations. A high ANA titer (e.g., 1 : 320), especially if it is accompanied by a more specific finding such as anti–double-stranded DNA antibody or anti-Smith antibody, can be highly specific for the diagnosis of lupus nephritis (Chapter 245), which usually requires a renal biopsy. Lower titers (e.g., 1 : 80 or 1 : 40) are nonspecific.

A *rheumatoid factor* titer will usually be elevated in patients with rheumatoid arthritis (Chapter 243), but vasculitis is a relatively late and rare event. Rheumatoid factor can be detected in some forms of cryoglobulinemia (Chapter 173); for example, IgM and occasionally IgG, which is present in type II and type III cryoglobulinemia, has rheumatoid factor activity. Rheumatoid factor also can be seen as a nonspecific finding in bacterial endocarditis (Chapter 61) and systemic vasculitis (Chapter 249).

The levels of *complement* components C3 and C4 and the 50% hemolyzing dose of complement (CH_{50}) usually are measured to evaluate suspected rapidly progressive glomerulonephritis (Chapter 107). Complement levels are usually low in active systemic lupus erythematosus (Chapter 245), post-streptococcal glomerulonephritis (Chapter 107), endocarditis (Chapter 61), membranoproliferative glomerulonephritis, cryoglobulinemia (Chapter 173), shunt nephritis with infection of a ventriculoatrial shunt, and glomerulonephritis associated with visceral abscesses. A particularly depressed C4 compared with C3 should raise the suspicion of cryoglobulinemia.

Serum immunoelectrophoresis will detect elevated polyclonal IgA levels in about 50% of cases of IgA nephropathy (Chapter 107) and IgA vasculitis (Chapter 107). Polyclonal elevation of IgG may occur in a variety of systemic diseases and is a nonspecific finding. The presence of a monoclonal protein in the serum should raise the suspicion for a monoclonal gammopathy–associated disease (Chapter 173). The differential diagnosis includes monoclonal gammopathy of uncertain significance, myeloma kidney, lymphomas (Chapter 171), amyloidosis (Chapter 174), light chain deposition disease, heavy chain deposition disease, immunotactoid glomerulonephritis, and cryoglobulinemia. These conditions, with the exception of monoclonal gammopathy of undetermined significance, have been collectively called monoclonal gammopathy of renal significance when they affect the kidney. The concentration of the monoclonal protein is higher when the diagnosis of multiple myeloma is made, but even small quantities of Bence Jones proteins in the serum can have clinical significance.

A *urine immunoelectrophoresis* always should be obtained if myeloma is suspected. Because a substantial fraction of multiple myelomas can have no heavy chain excretion and small quantities of light chains may be difficult to detect by serum immunoelectrophoresis, a urine immune electrophoresis test for Bence Jones protein should be obtained. In light chain myeloma, patients may have Bence Jones proteinuria even in the absence of an M component in the serum immunoelectrophoresis. Bence Jones proteinuria may be present in myeloma kidney, amyloidosis, light chain deposition disease, lymphoma, or, occasionally, monoclonal gammopathy of uncertain significance. However, some patients with systemic AL (light chain) amyloidosis have a normal serum immunoelectrophoresis and no Bence Jones proteinuria (Chapter 173). More sensitive assays for serum free light chains and an assessment of the ratio of κ to λ lights chains increase the sensitivity for detection of monoclonal gammopathies.

The *antineutrophil cytoplasmic antibody* (ANCA) assay has allowed earlier and more definitive recognition of vasculitic causes of rapidly progressive glomerulonephritis (Chapter 249), especially granulomatosis with polyangiitis, microscopic polyangiitis, and eosinophilic granulomatosis with polyangiitis, when it is confirmed by enzyme-linked immunosorbent assay. The antibodies cause two different patterns of staining: perinuclear staining (p-ANCA) and cytoplasmic staining (c-ANCA). Both antigens actually have a cytoplasmic distribution, and the perinuclear staining pattern is an artifact of the fixation method. In most cases, the antigen for p-ANCA is myeloperoxidase (MPO), whereas the antigen for c-ANCA is proteinase 3 (PR3). Anti-MPO antibodies are associated with microscopic polyangiitis, idiopathic crescentic glomerulonephritis, or Churg-Strauss syndrome (eosinophilic granulomatosis with polyangiitis; Chapter 249). Anti-PR3 antibodies often correlate with the classic disease of granulomatosis with polyangiitis (formerly known as Wegener granulomatosis) (Chapter 249).

Anti–glomerular basement membrane (anti-GBM) antibodies are autoantibodies to the Goodpasture antigen (Chapter 107), which resides in a domain of the α chain of type 4 collagen. An early and accurate diagnosis of Goodpasture syndrome can be made by immunofluorescence and confirmed by Western blot analysis. Anti-GBM antibody staining also may occur in the presence of a positive ANCA. In these cases, the theory is that exposure of the Goodpasture antigen, as a result of the glomerular injury, leads to anti-GBM antibody formation as a secondary process.

Cryoglobulins (Chapter 173) are thermolabile immunoglobulins. They are a single monoclonal type in type I cryoglobulinemia. In type II and type III cryoglobulinemia, however, the mixture of immunoglobulins includes one with rheumatoid factor activity against IgG. Type I and type II cryoglobulins are more likely to be associated with clinical disease, especially at higher titers. Type III cryoglobulinemia is often of less clinical significance. Type I cryoglobulinemia is seen with Waldenström macroglobulinemia and multiple myeloma (Chapter 173); type II with hepatitis C infection (Chapters 134 and 135), Sjögren syndrome (Chapter 247), lymphomas (Chapters 171 and 172), and systemic lupus erythematosus (Chapter 245); and type III with hepatitis C (Chapters 134 and 135), chronic infections, and inflammatory conditions. When cryoglobulinemia is associated with hepatitis C, the hepatitis C virus (HCV) RNA is concentrated in the cryoprecipitate as the antigen; the diagnosis can be made by an RNA assay of the cryoprecipitate at 37° C.

Membranous nephropathy is associated with chronic hepatitis B infection with hepatitis B surface antigenemia (Chapter 135). Classic polyarteritis nodosa (Chapter 249) occasionally is seen with chronic hepatitis B infection, often with surface antigenemia and hepatitis B e antigenemia. M-type phospholipase

A_2 receptor antibodies also have been detected as autoantibodies in about 70% of cases idiopathic membranous nephropathy and have diagnostic value. Antibodies to the thrombospondin type-1 domain-containing 7 A protein are detected in another 5 to 10% of cases.

Hepatitis C serology is associated with a variety of renal diseases, including cryoglobulinemia, membranoproliferative glomerulonephritis, and membranous nephropathy. The evaluation may include the antibody test and an assay for HCV RNA. On occasion, the HCV RNA analysis may have to be conducted on the cryoprecipitate at 37° C.

HIV-associated nephropathy (Chapter 107) is associated with nephrotic syndrome and acute kidney injury. In the appropriate clinical setting, HIV serology and viral titers are warranted tests for both clinical syndromes.

Streptococcal infection can be confirmed as the cause of postinfectious glomerulonephritis (Chapter 107) with an anti-DNase or antistreptolysin O assay. Acute and convalescent serology assays are used to confirm recent infection.

The erythrocyte sedimentation rate (ESR) is a relatively nonspecific test in the evaluation of renal disease. However, a high ESR often points to systemic vasculitis (Chapter 249), multiple myeloma (Chapter 173), or malignant disease as the underlying cause. However, the ESR often is elevated in the nephrotic syndrome (Chapter 107), including diabetic nephropathy (Chapter 109).

Renal Biopsy

No formal guidelines exist for the indications to perform a renal biopsy. Most nephrologists will perform a biopsy for adults with idiopathic nephrotic syndrome and for children with steroid-dependent or steroid-resistant nephrotic syndrome. In addition, acute kidney injury without an identifiable inciting cause is a clear indication for biopsy. Notably, patients with hospital-acquired kidney failure rarely meet this indication. Other abnormal clinical findings, such as gross or microscopic hematuria or subnephrotic proteinuria, often but not always lead to a kidney biopsy. Renal biopsy usually is performed percutaneously with real-time ultrasound or CT guidance. About 1 to 2% of patients without an underlying coagulopathy will develop bleeding that requires a transfusion. The transjugular approach can be used in patients in whom the risks for bleeding are high.

Genetic Testing

Inherited factors play an important role in kidney disease, and 25 to 30% of patients with CKD have a family history of nephropathy. Genetic testing can establish a genetic diagnosis in nearly 10% of patients with CKD and is useful even in patients who have had a renal biopsy.[16,17] The diagnostic yield is higher in patients who have a younger onset of disease, a family history of kidney disease, or multi-organ, syndromic features. The diagnostic yield is highest in patients with cystic kidney disorders (20 to 50%) and patients with nephrotic syndrome (5 to 25%), but full exome sequencing also has a diagnostic yield of about 20% in patients with CKD of unknown cause, thereby leading to the detection of many rare conditions spanning all major clinical categories of kidney disease (E-Fig. 100-1).[18]

TUBULOINTERSTITIAL DISEASES

Tubulointerstitial diseases (Chapter 108) vary in presentation from acute kidney injury to chronic kidney dysfunction that initially is manifested as asymptomatic mild renal insufficiency (Table 100-4). The urine sediment often contains small to moderate amounts of proteinuria, usually less than 1 g/day, as well as WBCs, RBCs, tubule cells, and WBC casts. RBC casts are rare in acute interstitial nephritis and more characteristic of glomerular disease.

TABLE 100-4 MAJOR CAUSES OF TUBULOINTERSTITIAL DISEASE

Ischemic and toxic acute tubular necrosis
Allergic interstitial nephritis
Interstitial nephritis secondary to immune complex–related collagen vascular disease, such as Sjögren disease or systemic lupus erythematosus
Granulomatous diseases: sarcoidosis, tubulointerstitial nephritis with uveitis
IgG4-related interstitial nephritis
Pigment-related tubule injury: myoglobinuria, hemoglobinuria
Hypercalcemia with nephrocalcinosis
Tubular obstruction: drugs such as indinavir, uric acid in tumor lysis syndrome
Myeloma kidney or cast nephropathy
Infection-related interstitial nephritis: *Legionella, Leptospira* species
Infiltrative diseases, such as lymphoma

Ig = immunoglobulin.

VASCULITIS AND VASCULAR DISEASES OF THE KIDNEY

Vascular diseases of the kidney can be divided into large-vessel obstruction and medium- to small-vessel diseases (Chapter 110). Renovascular disease is a common cause of hypertension, heart failure, and renal insufficiency. About 90% of renal artery stenosis is atherosclerotic in origin, with most of the remaining caused by fibromuscular dysplasia, which is more common in women 20 to 50 years of age. Medium-sized arterial vessel diseases include polyarteritis nodosa, which is seen in patients with hepatitis B (Chapters 134 and 135), HIV infection (Chapter 107), or, rarely, hepatitis C (Chapters 134 and 135). Symptoms include abdominal pain, hypertension, and mild renal insufficiency, often with a benign sediment; diagnostic findings include microaneurysms at the bifurcation of medium-sized arteries. Other diseases involving small vessels include atheroembolic disease (Chapter 110), which is seen after arteriography or surgery or, rarely, spontaneously. This syndrome typically affects the kidneys, gastrointestinal tract, and lower extremities, but it can also involve the central nervous system when the aortic arch is affected.

The thrombotic microangiopathies include hemolytic-uremic syndrome and thrombotic thrombocytopenic purpura (Chapter 158). Thrombotic thrombocytopenic purpura is associated with an acquired inhibitor to or the congenital inherited absence of a protease that cleaves large-molecular-weight von Willebrand multimers. The hemolytic-uremic syndrome is caused by endothelial injury. In diarrhea-positive (or typical) hemolytic-uremic syndrome, the endothelial injury is induced by Shiga toxin from *Escherichia coli* O157:H7 infection. In diarrhea-negative (atypical) hemolytic-uremic syndrome, dysregulation of the alternative complement pathway is the underlying cause of endothelial injury. The antiphospholipid antibody syndrome (Chapter 67) can cause large-vessel thrombosis and stenosis as well as a thrombotic microangiopathy with proteinuria, hypertension, and renal insufficiency. Scleroderma renal crisis, which is a manifestation of systemic sclerosis (Chapter 246), often leads to an inexorable progression to end-stage renal insufficiency if untreated.

A systemic vasculitis may be manifested in a variety of ways, including skin manifestations such as petechial rash, purpura, digital gangrene, and splinter hemorrhages. Otitis, sinusitis, epistaxis, hemoptysis, and nasal septal ulcers are common manifestations of granulomatosis with polyangiitis (Chapter 249). Pulmonary hemorrhage can be a catastrophic manifestation of Goodpasture syndrome (Chapter 107), anti-GBM disease, or ANCA-associated vasculitis (Chapter 249). Abdominal pain and tenderness and gastrointestinal hemorrhage may be observed in IgA vasculitis and classic polyarteritis nodosa (Chapter 249). Neurologic symptoms may be a manifestation of vasculitis, such as microscopic polyangiitis (Chapter 249) and cryoglobulinemia (Chapter 173).

DIAGNOSIS

Radiologic Evaluation

Magnetic resonance imaging (MRI) with MR angiography (Fig. 100-16) is highly sensitive for detecting atherosclerotic renovascular disease (Chapter 110), but it tends to overestimate the degree of stenosis. Its accuracy in detecting fibromuscular dysplasia, however, is less well validated. MRI also can be used to evaluate renal masses. MRI does not require iodinated contrast material, but gadolinium-based contrast agents for vascular studies are associated with the syndrome of nephrogenic systemic fibrosis in patients with advanced renal failure (Chapter 246).

Renal arteriography, which is the "gold standard" in the evaluation of renal artery stenosis (Chapter 110), also is used for the evaluation of arteriovenous malformations, polyarteritis nodosa, and other vascular lesions of the kidneys. This invasive study uses iodinated contrast material and incurs a small risk for atheroembolic disease (Chapter 110). Therapeutic angioplasty and stenting can be done at the time of angiography.

PAPILLARY NECROSIS

Acute necrosis of the renal papilla is associated with sickle cell anemia (Chapter 149), analgesic nephropathy (Chapter 108), diabetic nephropathy (Chapter 109), and obstructive pyelonephritis (Chapter 263). In sickle cell disease (Chapter 149), the hypoxic and hypertonic milieu of the inner medulla promotes sickling, and chronic sickling at the vasa recta results in medullary ischemia. Massive and prolonged consumption of analgesics, particularly the combination of aspirin, caffeine, and acetaminophen, is associated with chronic interstitial nephritis and a predisposition to papillary necrosis (Chapter 108); medullary ischemia is thought to be caused by inhibition of synthesis

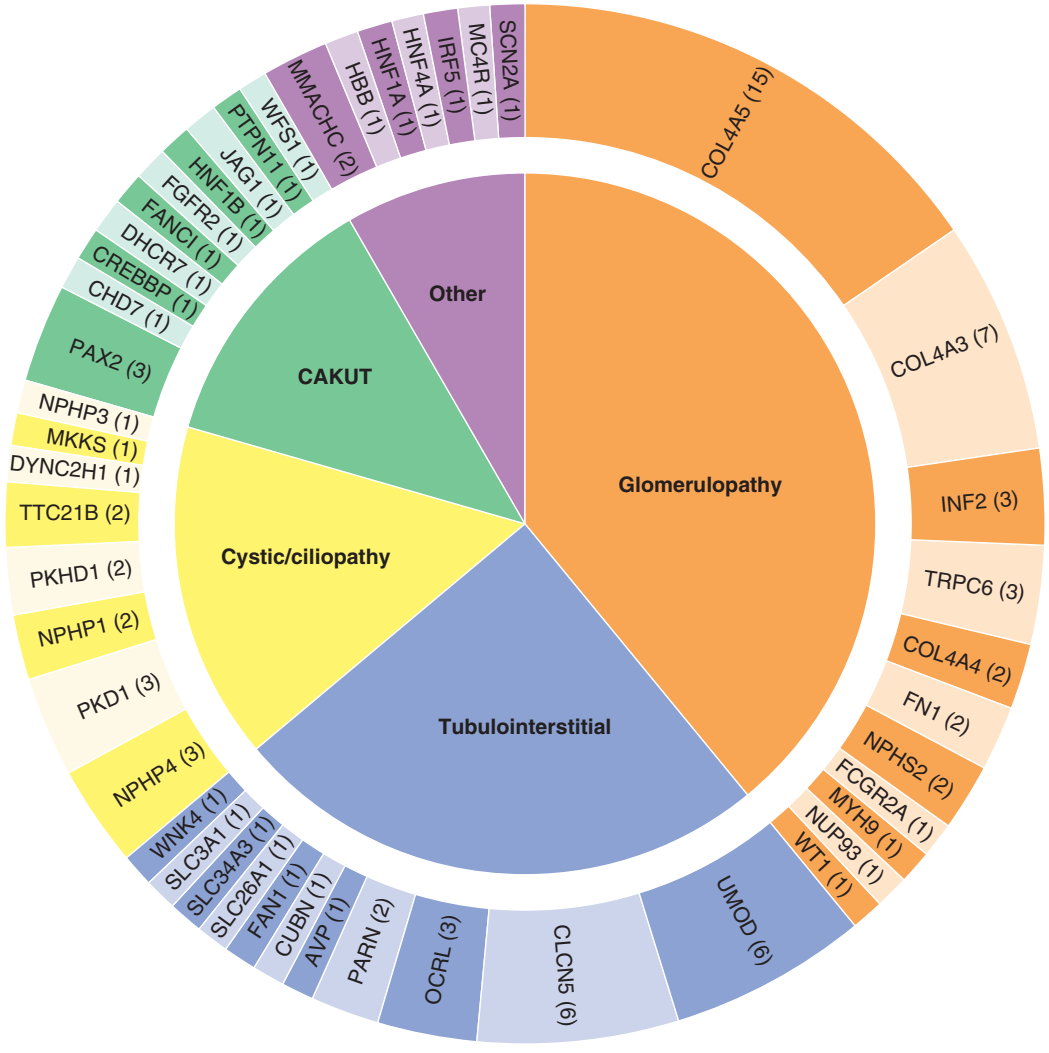

E-FIGURE 100-1. Diagnoses in individuals with kidney disease of unknown etiology. A review of six genome-wide studies identified 47 distinct genetic etiologies corresponding with the categories listed within the inner disc. The genes identified are represented in the outer ring, with the number of patients affected in parentheses. CAKUT = congenital anomalies of the kidneys and urinary tract. (From Hays T, Groopman EE, Gharavi AG. Genetic testing for kidney disease of unknown etiology. *Kidney Int*. 2020;98:590-600.)

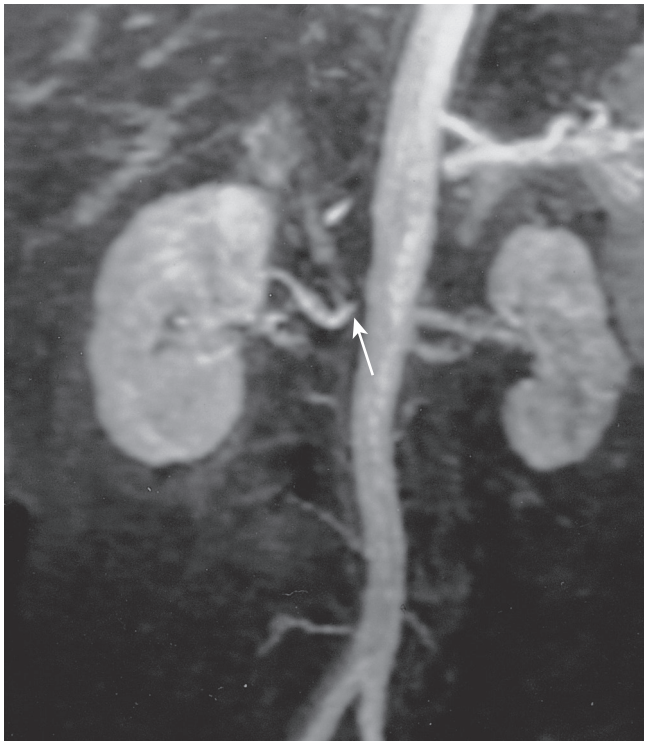

FIGURE 100-16. Magnetic resonance angiography. Coronal three-dimensional image shows right renal artery stenosis (*arrow*). (From Johnson RJ, Feehally J. *Comprehensive Clinical Nephrology*. London: Mosby; 2000.)

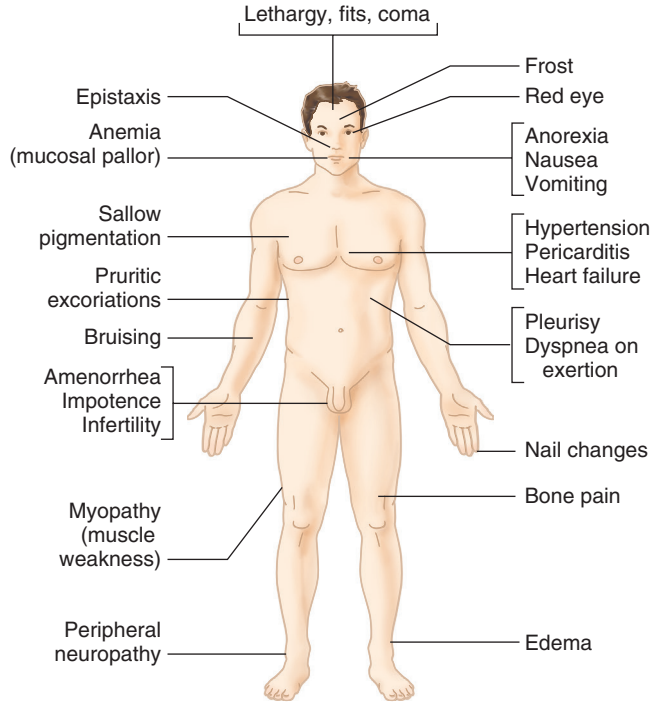

FIGURE 100-17. Common symptoms and signs of chronic renal failure. (Redrawn from Forbes CD, Jackson WF. *Color Atlas and Text of Clinical Medicine*. 3rd ed. London: Mosby; 2003.)

of vasodilatory prostaglandins by aspirin, and direct toxicity is attributed to metabolites of phenacetin. Similarly, medullary perfusion is thought to be compromised in diabetic nephropathy (Chapter 109) and obstructive pyelonephritis (Chapter 114).

The clinical manifestations of papillary necrosis can include flank pain and hematuria. If the papilla is sloughed, obstruction may occur at the renal pelvis or ureter of the affected kidney, with referred pain migrating from the flank to the groin. A sloughed papilla may precipitate frank renal failure if the function of the contralateral kidney is impaired or if obstruction occurs at the level of the bladder or urethra.

Classically, papillary necrosis is diagnosed on an excretory pyelogram as a calyceal defect after sloughing of a papilla, but CT with contrast enhancement is as good for advanced lesions. If the necrotic papilla is retained, however, the defect will be more subtle. Transitional cell carcinoma (Chapter 182) can occur in the setting of papillary necrosis or can mimic its appearance. Obstruction, if present, must be relieved, but treatment otherwise is limited to pain control and hydration.

CHRONIC KIDNEY DISEASE

Chronic kidney disease, which is defined as either kidney damage or a GFR of less than 60 mL/min/1.73 m^2 for longer than 3 months. Kidney damage is defined as pathologic abnormalities or markers of kidney damage, including abnormalities in the composition of blood or urine or abnormalities on imaging tests. The excretion of 30 to 300 mg of albumin in a 24-hour period defines microalbuminuria. CKD is classified according to underlying cause, level of GFR, and level of albuminuria (Fig. 116-2). An estimated 12% of the adult U.S. population has abnormal albumin excretion in the urine, and the frequency increases with age. Kidney failure is defined as either a GFR of less than 15 mL/min/1.73 m^2 that is accompanied by signs and symptoms of uremia or a need for initiation of kidney replacement therapy for treatment of complications of decreased GFR (Fig. 100-17). End-stage renal disease includes all cases requiring treatment by dialysis or transplantation regardless of the level of GFR.

Patients with chronic kidney disease warrant referral to a nephrologist. Care of these patients should focus on efforts to slow disease progression, to optimize medical management, and to make a seamless transition to renal replacement therapy (Chapter 116). The care should include optimal blood pressure control, use of angiotensin-converting enzyme inhibitors and angiotensin receptor blockers if indicated, dietary counseling, careful management of calcium and phosphorus levels, control of the parathyroid hormone level, and management of anemia with the use of erythropoietin and iron supplements. Early referral for placement of access for dialysis and initiation of transplant evaluation (Chapter 117) are important components of the care of patients with chronic kidney disease.

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101 STRUCTURE AND FUNCTION OF THE KIDNEYS

QAIS AL-AWQATI AND JONATHAN BARASCH

The kidney regulates the ionic composition and volume of body fluids, the excretion of nitrogenous waste, the elimination of exogenous molecules (e.g., many drugs), the synthesis of a variety of hormones (e.g., erythropoietin), and the metabolism of low-molecular-weight proteins (e.g., insulin). Befitting such an array of responsibilities, the kidney receives 25% of the cardiac output. The gross anatomy of the kidney is notable for a weight of approximately 150 g and a characteristic bean shape with approximate dimensions of 11 × 6 × 2.5 cm. On bisection, a gross structure is evident with an outer cortex and a more central medulla that narrows to multiple papillae at the apices of so-called pyramids (Fig. 101-1).

Understanding renal physiology, however, requires an appreciation of the intricate microstructure that underlies its complex functions. Although the kidney is an organ, the *nephron* is actually the organ's independent filtration unit. On average, each human kidney is composed of 1 million essentially identical nephrons. All functions of the kidney are performed by each individual nephron, and to a first approximation, all nephrons are independent of each other because they have their own innervation and blood supply.

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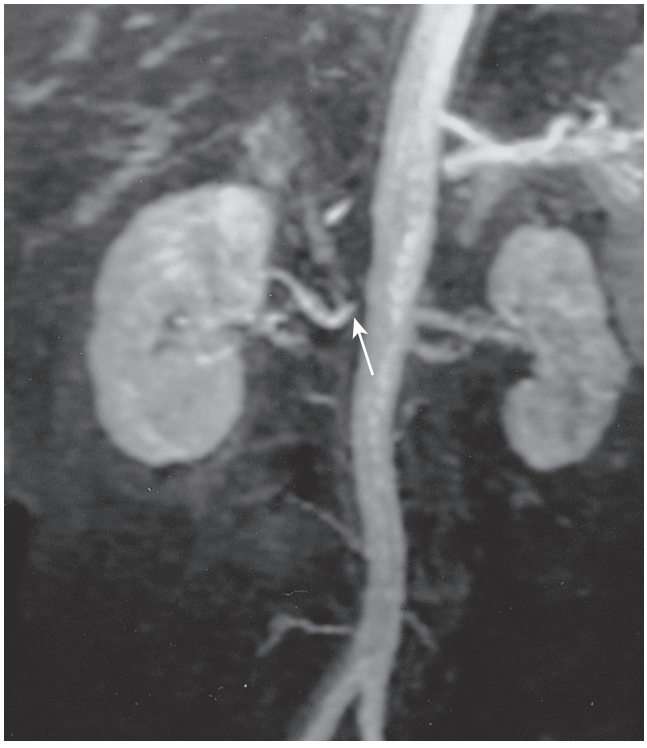

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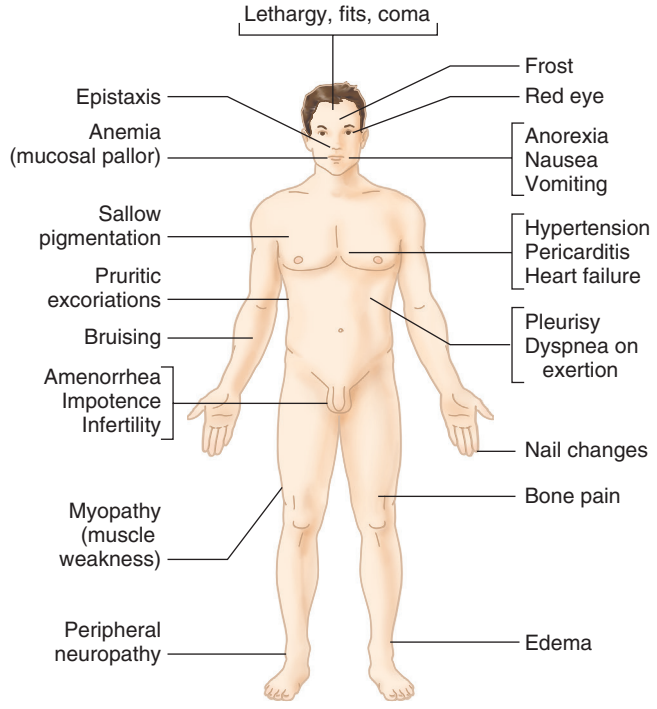

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QAIS AL-AWQATI AND JONATHAN BARASCH

The kidney regulates the ionic composition and volume of body fluids, the excretion of nitrogenous waste, the elimination of exogenous molecules (e.g., many drugs), the synthesis of a variety of hormones (e.g., erythropoietin), and the metabolism of low-molecular-weight proteins (e.g., insulin). Befitting such an array of responsibilities, the kidney receives 25% of the cardiac output. The gross anatomy of the kidney is notable for a weight of approximately 150 g and a characteristic bean shape with approximate dimensions of 11 × 6 × 2.5 cm. On bisection, a gross structure is evident with an outer cortex and a more central medulla that narrows to multiple papillae at the apices of so-called pyramids (Fig. 101-1).

Understanding renal physiology, however, requires an appreciation of the intricate microstructure that underlies its complex functions. Although the kidney is an organ, the *nephron* is actually the organ's independent filtration unit. On average, each human kidney is composed of 1 million essentially identical nephrons. All functions of the kidney are performed by each individual nephron, and to a first approximation, all nephrons are independent of each other because they have their own innervation and blood supply.

ABSTRACT

The kidney is the primary organ that regulates the volume and composition of the body fluids. Each kidney contains about 1 million nephrons, each of which is composed of a filtering unit (the glomerulus) and a reabsorbing unit (the tubule, which is divided into multiple segments, including proximal, loop of Henle, and distal and collecting tubules). Filtration occurs through the interaction of the hydrostatic pressure (controlled by the balance of afferent and efferent arteriolar states of constriction) and the oncotic pressure exerted by plasma albumin. Regulation of volume of the body fluids is mediated by changes in the rates of sodium reabsorption in the tubules as mediated by the renin-angiotensin-aldosterone system and the secretion of atrial natriuretic factor. The osmolarity of the body fluids is controlled by the reabsorption and excretion of water mediated by the effect of the hormone vasopressin on water transport by the collecting tubule. Control of the pH of the body fluids is effected by the reabsorption of filtered HCO_3^- and secretion of H^+ ions into the urine. The kidney also produces two hormones: erythropoietin and $1,2(OH)_2D_3$.

KEYWORDS

glomerulus
tubule
renin
angiotensin
aldosterone
vitamin D
erythropoietin

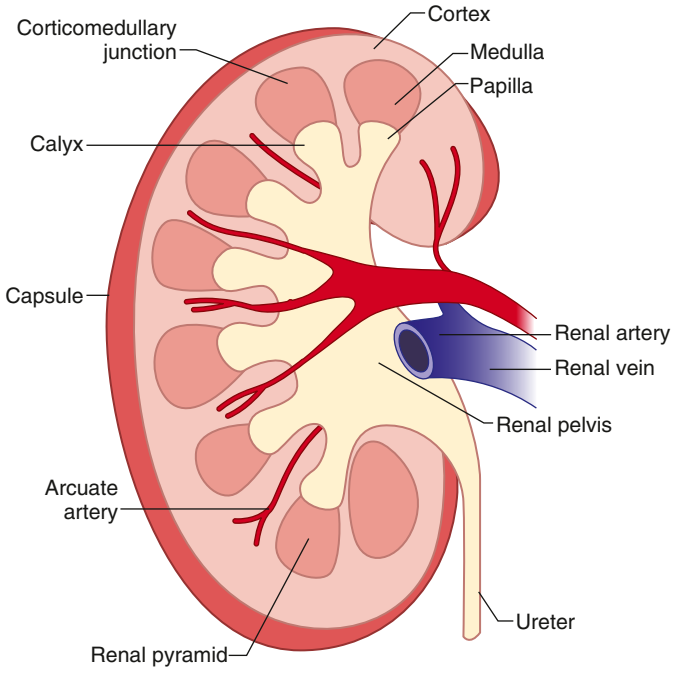

FIGURE 101-1. Sagittal section of the human kidney depicting gross anatomy and organization.

The nephron is made up of two functional subunits, the glomerulus and the tubules and ducts (Fig. 101-2). The glomerulus begins with the branching of the afferent arteriole, an end artery of the corresponding renal artery, into a tuft of capillaries. The glomerular capillaries invaginate an epithelium with the visceral epithelial cells adjacent to the capillary and the parietal epithelial cells outside this tuft. The space between the epithelial layers is the urinary space.[1] The fenestrated glomerular capillary endothelium, the intervening basement membrane, and the foot processes of the visceral epithelium, so-called podocytes, compose the glomerular filtration barrier. The balance of hydrostatic and oncotic pressures drives the extrusion of a protein-free filtrate through this barrier into the urinary space. The urinary space then leads to a series of tubules and ducts: the proximal tubule, the thin limb of the loop of Henle, the thick limb of the loop of Henle, the distal convoluted tubule, the cortical collecting duct, and the medullary collecting duct. The papillary collecting duct empties through the renal papilla into the renal pelvis and then to the ureter. The glomerular capillary bed coalesces to form the efferent arteriole, a vessel that is exquisitely sensitive to angiotensin II, and then the peritubular (proximal) capillaries. This system allows efferent arteriole constriction to regulate proximal tubule reabsorption, as described later.

The nephron regulates homeostasis by three actions. First, in the glomerulus, nephrons collectively produce as much as 120 mL/minute of an ultrafiltrate of blood. Second, different segments of the nephron change the composition of the filtrate by the transfer of nearly 99% of its components (e.g., glucose, NaCl, water) from the lumen to the blood. Third, additional electrolytes (e.g., NH_4^+, K^+, HCO_3^-) are secreted from the blood into the lumen.

To perform these functions, each nephron segment, with the exception of the connecting segment and the collecting ducts, is composed of a single epithelial cell type whose luminal or apical surface (facing the urine) and basolateral surface (facing the blood) differentially express various proteins and lipids. For example, the apical membrane often has microvilli or cilia, whereas the basolateral membrane does not. Polarized endocytosis and exocytosis are often important in the regulation of the number of transport proteins on the apical surface. In addition, epithelia are connected to one another by tight junctions, which confer a characteristic ionic permeability on the epithelial sheet. Transepithelial transport occurs largely through the cell, but transport also can occur through the tight junction (the *paracellular pathway*). For instance, sodium transport begins with entry at the luminal surface down an electrochemical gradient, whereas its exit at the basolateral surface is uphill and requires adenosine triphosphate (ATP) hydrolysis. The Na^+, K^+-ATPase is located at the basolateral surface of all epithelia, and all "active" energy-consuming transport is coupled directly or indirectly to it with the exception of H^+ transport by the H^+ATPase. Each segment has a distinct composition of channels, carriers, and ATPases, and each segment is regulated by different chemical and physical sensors, so the "final urine" contains the components that must be discarded to maintain constancy of body composition.

THE KIDNEY REGULATES EXTRACELLULAR FLUID VOLUME BY REGULATING SODIUM CONTENT

Filtration of 180 L/day of plasma containing 24,000 mEq of sodium is followed by the reabsorption of over 99% of the filtered sodium. Sodium reabsorption accounts for more than 90% of the oxygen consumed by the kidney. It is regulated by volume receptors that are located in the carotid artery and increase β-sympathetic output, which in turn releases renin, an aspartate protease from the granular cells of the juxtaglomerular apparatus, which is located near the afferent arteriole that supplies the glomerulus. Renin cleaves angiotensinogen to angiotensin I, which is then converted locally to angiotensin II. Angiotensin II binds to angiotensin receptors and constricts the efferent arteriole, thereby affecting glomerular hemodynamics. Increased hydrostatic pressure within the glomerular capillaries drives the formation of an ultrafiltrate of plasma. As filtration progresses, a protein-rich, oncotically active solution in the capillary opposes the glomerular capillary hydrostatic pressure until a pressure equilibrium is achieved before the efferent arteriole is reached. Consequently, angiotensin II may not change glomerular filtration rate (GFR) markedly, but it can increase proximal reabsorption by reducing the hydrostatic pressure and increasing the oncotic pressure in the peritubular capillaries that surround the proximal tubule in a plexus, thereby favoring reabsorption of water and solutes such as urea.

The glomerular filtrate next enters the tubules. Na^+ traverses the cell by entering the apical membrane either through a segment-specific cotransporter, counter-transporter, or sodium channel. The apical membrane of the proximal tubule contains an Na^+/H^+ (NHE3) exchanger, Na^+-coupled glucose carrier, and Na^+-coupled amino acid and phosphate cotransporter. Na^+ is then actively transported by the basolateral Na^+, K^+-ATPase into the paracellular space, thereby resulting in local hypertonicity, which causes osmosis through low-resistance tight junctions of the initial segments of the proximal tubule (E-Fig. 101-1).

In the thick ascending limb of Henle, Na^+ is absorbed by an Na-K-2Cl cotransporter. The driving force for this neutral carrier allows Na^+ and Cl^- to enter the cell, but then recycles K^+ across the apical membrane, thereby resulting in depolarization of the transepithelial membrane potential. In the distal convoluted tubule, Na^+ is absorbed by a thiazide-sensitive cotransporter, which conducts Na^+ and Cl^- in a strict 1 : 1 stoichiometry. Na^+ exits as usual by the Na^+, K^+-ATPase, but there is also a basolateral Na/Ca exchanger. In this short segment, the macula densa helps control the GFR by regulating renin release through secretion of adenosine and prostaglandins.

In the principal cells of the collecting duct, aldosterone, derived from the zona glomerulosa of the adrenal cortex, is the final critical regulator of Na^+ balance. Aldosterone increases reabsorption of the final 50 to 100 mEq/day of sodium remaining in the lumen by increasing the number of open sodium channels (ENaC) and by increasing the activity of the basolateral Na^+, K^+-ATPase.[2]

A number of the steps that regulate sodium reabsorption can be counteracted by atrial natriuretic peptide (ANP), which is released from the atria in response to volume overload. ANP increases filtration in the glomerulus by dilating the afferent arteriole, thereby increasing glomerular capillary pressure and lowering the oncotic pressure. In addition, ANP increases sodium excretion by inhibiting the release of renin, the production of aldosterone, and the tubular reabsorption of sodium in the terminal collecting duct.

THE KIDNEY CONTROLS BODY FLUID OSMOLARITY BY REGULATING WATER CONTENT

Water moves freely among all cells and compartments of the body via water-conducting channels called aquaporins. Osmolarity (the concentration of water) is strictly regulated to prevent cells from swelling or contracting via mechanisms that control the intake (thirst) and excretion of fluids, whereby the kidney can vary the osmolarity of urine. Channels in the thick ascending limb, distal tubule, and collecting duct absorb sodium without water to dilute the urine. The absorbed NaCl and urea provide a hyperosmotic region in the medulla, where the limited blood flow maintains an osmotic gradient. To concentrate the urine, water is removed from the filtrate by this osmotic gradient as it passes through the cortical and medullary collecting tubules.

Antidiuretic hormone (ADH), also called *vasopressin,* is a critical component of water reclamation. Changes of less than 1% in osmolarity induce cells in the neurohypophysis to shrink and, via activation of TRPV1 channels, to release ADH. In the kidney, ADH binds to the vasopressin type 2

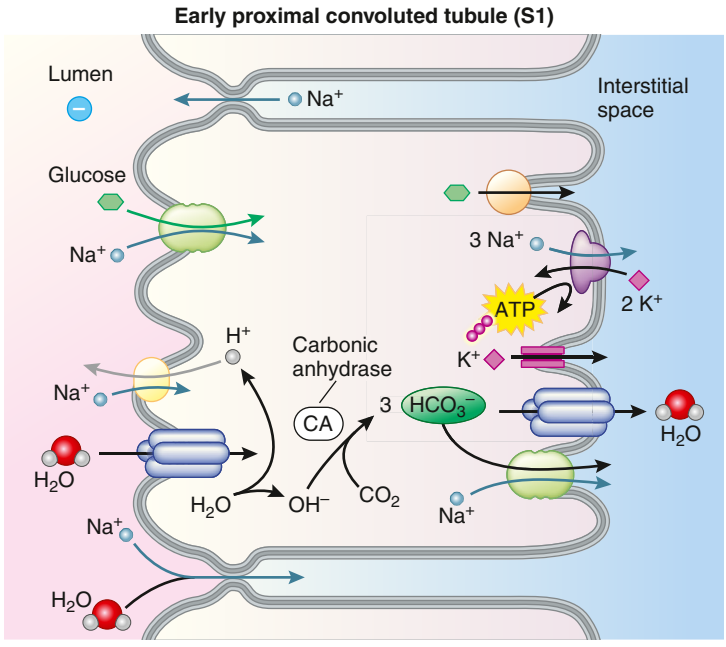

E-FIGURE 101-1. Sodium reabsorption in the proximal tubular cell. (Figure from Boron W, Boulpaep E. *Medical Physiology*, 3rd Edition. Elsevier; 2016. Taken from Figure 35-4A.)

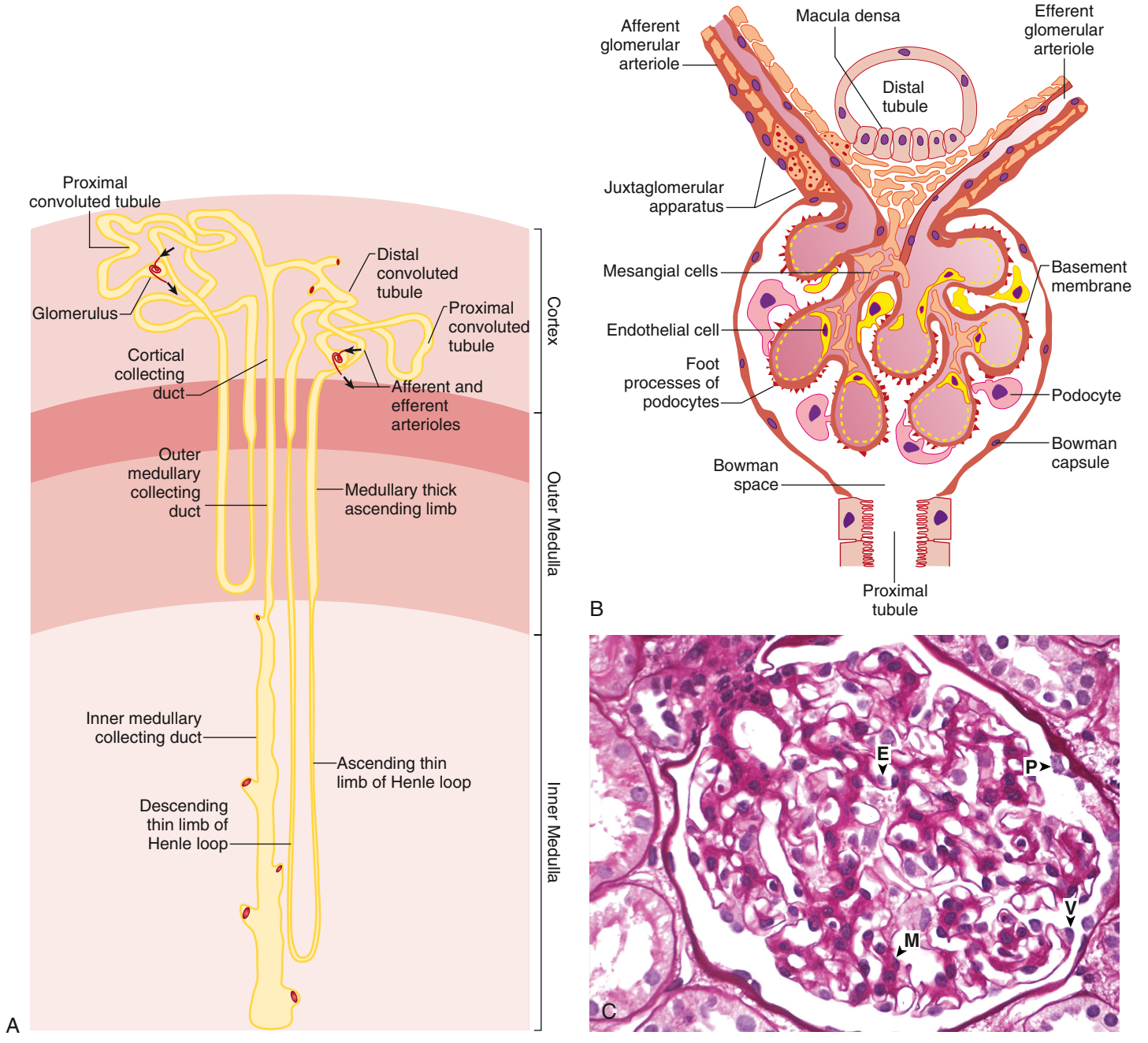

FIGURE 101-2. **Structure of the nephron. A**, Components of the cortical and juxtaglomerular nephrons. **B**, Anatomy of the glomerulus. **C**, Light micrograph of a human glomerulus. E = endothelial cell; M = mesangial cell; P = parietal epithelial cell; V = visceral epithelial cell. (C, Courtesy Dr. Glen Markowitz.)

receptor on collecting tubules and increases water permeability by reversibly inserting a water channel, called *aquaporin 2*, in the apical membrane.[3] During states of water deprivation, the dilute urine generated by the thick ascending limb enters vasopressin-sensitive segments in the cortical collecting tubule, where the bulk of the water is absorbed into the cortex to increase the osmolarity of the urinary filtrate to 300 mOsm, equivalent to plasma osmolarity. When it then travels through the medullary collecting duct, the urine becomes concentrated as it equilibrates with the osmolarity of the medulla (Fig. 101-3).[4]

THE KIDNEY REGULATES PLASMA pH BY REGULATING HCO_3^- CONTENT

The concentration of free H^+ in the intracellular and extracellular fluids is maintained at about 40 nM (pH 7.4) by the daily excretion of acid or base in amounts equal to what is generated by dietary intake and by cellular activity. The complete oxidation of carbohydrates and fats generates approximately 15 to 20 mol/day of the volatile acid CO_2, and nonvolatile acids generated by the metabolism of protein-rich diets account for 60 to 80 mEq/day. HCO_3^- is the most important buffer because it is consumed by metabolic acid, thereby producing CO_2 that can be exhaled, and because it can be regenerated by the kidney. The overall relationship of this buffer system is described by the Henderson-Hasselbalch equation:

$$pH = pK_a + \log[HCO_3^-]/\alpha P_{CO_2}$$

where pK_a is 6.1 and α represents the solubility coefficient of P_{CO_2} (which is 0.03). Because all the body buffers (e.g., bone, intracellular proteins) are in equilibrium, changes in the concentration of HCO_3^- regulate the pH of body fluids.

The kidney reabsorbs about 5000 mEq of HCO_3^- that is filtered daily. Beyond this task, it must replace the HCO_3^- that is lost as a consequence of the production of acid by oxidative metabolism. The proximal tubule reabsorbs luminal HCO_3^- by secreting H^+ through an apical Na^+/H^+ exchanger, which is directly stimulated by angiotensin II to secrete H^+ in strict 1 : 1 exchange for Na^+, thereby mediating both sodium absorption and H^+ secretion. An H^+-ATPase is also present in the apical membrane. H^+ secretion titrates filtered HCO_3 and, catalyzed by carbonic anhydrase, converts it to CO_2 and water, thereby allowing CO_2 reabsorption. H^+ secretion leads to an excess of OH^- in the cell, where it combines with this CO_2 to produce cellular HCO_3^-, which then exits across the basolateral membrane through an Na-HCO_3^- cotransporter (E-Fig. 101-2).

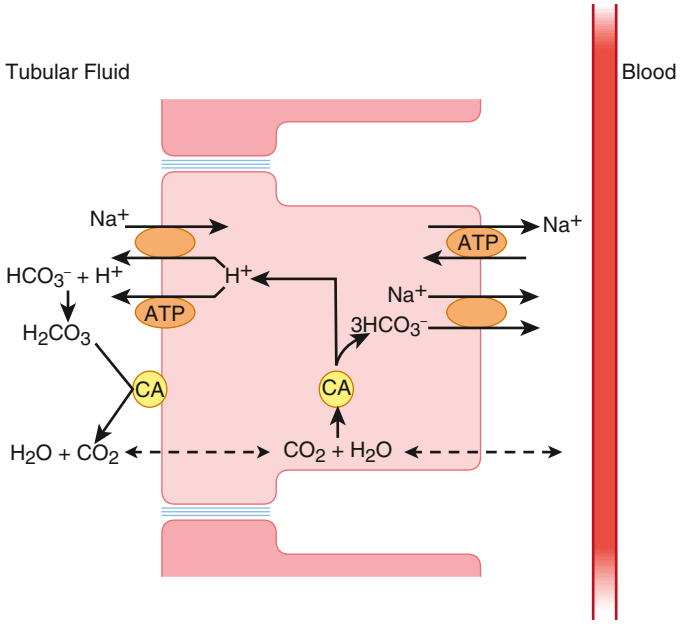

E-FIGURE 101-2. Ion transport in the proximal tubule. ATP = adenosine triphosphate; CA = carbonic anhydrase.

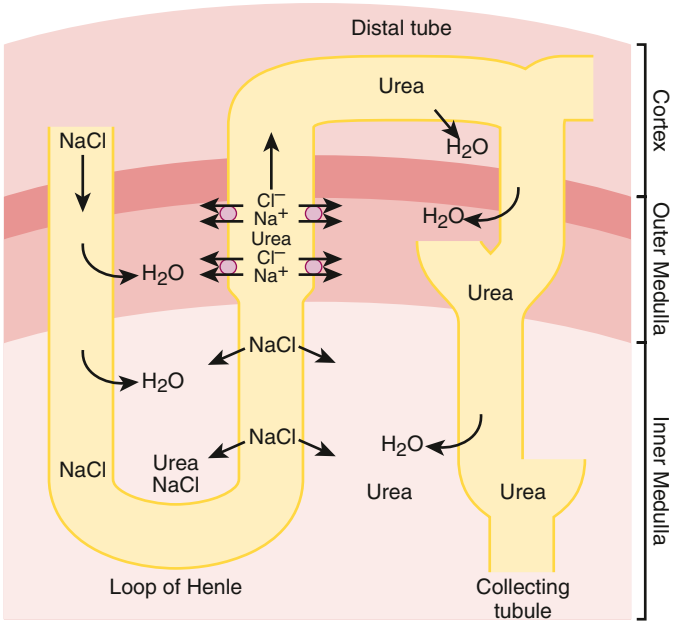

FIGURE 101-3. **Regulation of water content.**

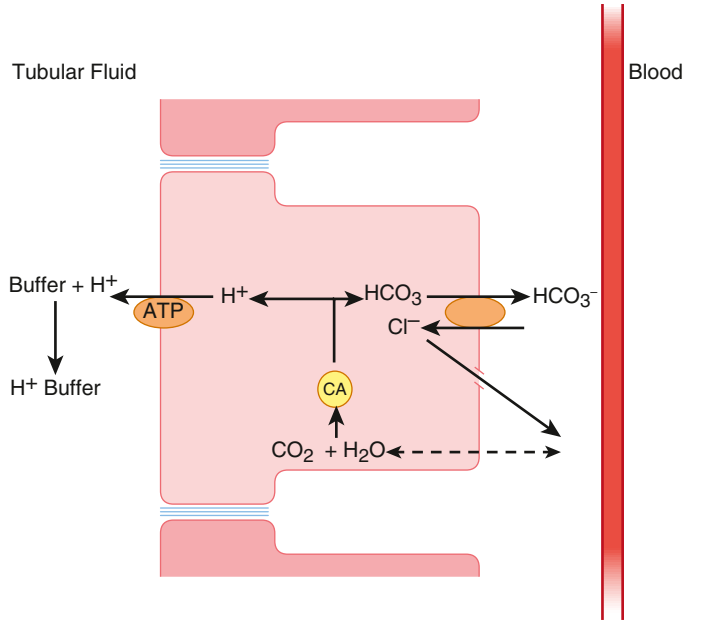

FIGURE 101-4. **Mechanism of acid secretion in the collecting duct.** ATP = adenosine triphosphate; CA = carbonic anhydrase.

Given that the proximal tubule regulates bicarbonate reabsorption, the collecting duct must produce "new" HCO_3 to replace what is lost during titration by nonvolatile acids. The cortical collecting tubules contain intercalated cells that mediate H^+ secretion (α-intercalated cell) and β-cell types that mediate the secretion of HCO_3, whereas only α cells are present in the medulla. In the α-intercalated cell, H^+ secretion is mediated by the H^+-ATPase that is delivered to the apical membrane by fusion of apical vesicles as stimulated by ambient P_{CO_2} (Fig. 101-4).

In a reaction catalyzed by carbonic anhydrase II, the excess OH^- is carboxylated by CO_2 to form HCO_3^-. HCO_3^- is subsequently transported across the basolateral surface in exchange for Cl^- by an alternately spliced form of the red cell anion exchanger (band 3). In contrast, β cells secrete HCO_3^- by an apical Cl/HCO_3 exchanger (pendrin) and a basolateral H^+-ATPase. An H^+, K^+-ATPase in the collecting tubule may also play a role in potassium absorption and perhaps in H^+ secretion.

The collecting tubule is a "tight epithelium" that can maintain electrical and concentration gradients. Secretion of H^+ reduces the pH of the filtrate; the maximal gradient is 3 pH units or 180 mV, but both the size of the pH gradient and its transepithelial membrane potential can be modified to fine-tune H^+ secretion. For example, Na^+ absorption by the principal cell hyperpolarizes the epithelium and can thus drive H^+ secretion. Aldosterone, in addition to regulating Na^+ absorption, independently can stimulate H^+ secretion; hence, it is the major hormone that stimulates acid secretion in the collecting tubule. Finally, chronic metabolic acidosis converts the β-intercalated cells into α-intercalated cells, preferentially increasing the number of acid-secreting cells and reducing the number of HCO_3^- secreting cells in this segment.

The secreted H^+ titrates urinary NH_3 and HPO_4^{2-}. NH_3, which is synthesized by the conversion of glutamine to α-ketoglutarate, is secreted into the proximal lumen. In the loop of Henle and distal segments, the protonated ammonium ion is transferred into the interstitium, from where it re-enters the nephron as ammonia gas. Once in the lumen, ammonia gas becomes reprotonated to ammonium, thus trapping a proton. The amount of NH_3 generated from glutamine increases up to four- to five-fold in the setting of metabolic acidosis. Net acid secretion is consequently urinary NH_4^+ plus titratable weak acids (such as HPO_4^{2-}) minus urinary HCO_3^-. Each of these components is regulated by the kidney.

THE KIDNEY REGULATES PLASMA POTASSIUM BY SECRETION AND THE CONTROL OF EXTRACELLULAR pH

Because the membrane potential of most cells is governed by the ratio of intracellular to extracellular potassium, the plasma potassium concentration must be tightly regulated. Most dietary potassium is pumped into the cell by the Na^+, K^+-ATPase, but about 90% of ingested potassium eventually must be excreted into the urine.[5] K^+ is filtered but is then reabsorbed by the proximal tubule and loop of Henle. K^+ is then secreted by the distal convoluted tubule and the principal cells through apical potassium inwardly rectifying (ROMK) and potassium large conductance calcium-activated (BK) channels. The gradient, in which cellular K^+ is greater than luminal K^+, drives K^+ out of the cell. Secretion is enhanced by the increased entry of K^+ into the principal cell as a result of high extracellular concentration, by metabolic alkalosis, and by aldosterone. Aldosterone increases the synthesis of Na^+, K^+-ATPase and increases the probability that the ROMK channels will be open. Aldosterone also enhances Na^+ reabsorption by ENaC, thereby hyperpolarizing the transepithelial membrane potential, which increases the driving force for potassium secretion. High urinary flow rates deliver a large volume of fluid that is essentially K^+ free, thereby providing a concentration gradient. The flow rate also activates mechanosensory flagella that lead to an increase in cell calcium, which in turn activates BK channels. Potassium reabsorption is not regulated to the same extent as sodium retention, and profound potassium depletion may be required for potassium excretion by the kidneys to be eliminated completely.

THE KIDNEY REGULATES PLASMA PO_4 AND CA^{2+} BY EXCRETION AND BY SYNTHESIZING VITAMIN D_3

The level of PO_4 critically regulates serum Ca^{2+} level. Because their plasma concentrations are close to their saturation product, at which point crystallization occurs, any significant increase in PO_4 results in precipitation of $CaPO_4$.

PO_4 concentration is regulated by glomerular filtration. Initially, about 85% is reabsorbed by the proximal tubule sodium-phosphate cotransporters NaPi-2a and NaPi-2c. Parathyroid hormone and the heteromeric receptor FGFR/Klotho, which binds fibroblast growth factor 23 (FGF23), inhibit the expression of NaPi and hence increase excretion of PO_4. Conversely, the proximal tubule generates vitamin D_3 (1,25-dihydroxycholecalciferol) by capturing 25-hydroxycholecalciferol, bound to its filterable transport protein with brush border megalin (E-Fig. 101-3), after which 1α-hydroxylation is stimulated by low Ca^{2+} and PO_4. 1,25-Vitamin D_3 inhibits parathyroid hormone and stimulates PO_4 reabsorption in gut and kidney, thereby counteracting parathyroid hormone and FGF23-Klotho. Nonetheless, Klotho signaling blocks 1,25-vitamin D_3 synthesis, thereby suggesting that it dominates the control of PO_4.[6]

The level of serum calcium is also regulated by the kidney. Approximately 60% of serum calcium is filtered, after which it is reabsorbed in the proximal tubule through the paracellular pathway. The tight junction protein claudin 2 is critical for calcium selectivity in this segment and mutations in it lead to hypercalciuria. Calcium is also absorbed paracellularly in the thick ascending limb driven by the positive membrane potential generated by the Na-K-2Cl/K recycling transporter. Mutations in the tight junction proteins claudin 14, 16 and 19, have been implicated in monogenic causes of hypercalciuria and nephrolithiasis.[7] In contrast, calcium and sodium are regulated independently in the distal convoluted tubule by parathyroid hormone and Klotho, which increase reabsorption. Phosphate and calcium metabolism is regulated by sodium reclamation, parathyroid hormone, 1,25-dihydroxycholecalciferol, and Klotho in different segments of the nephron.[8]

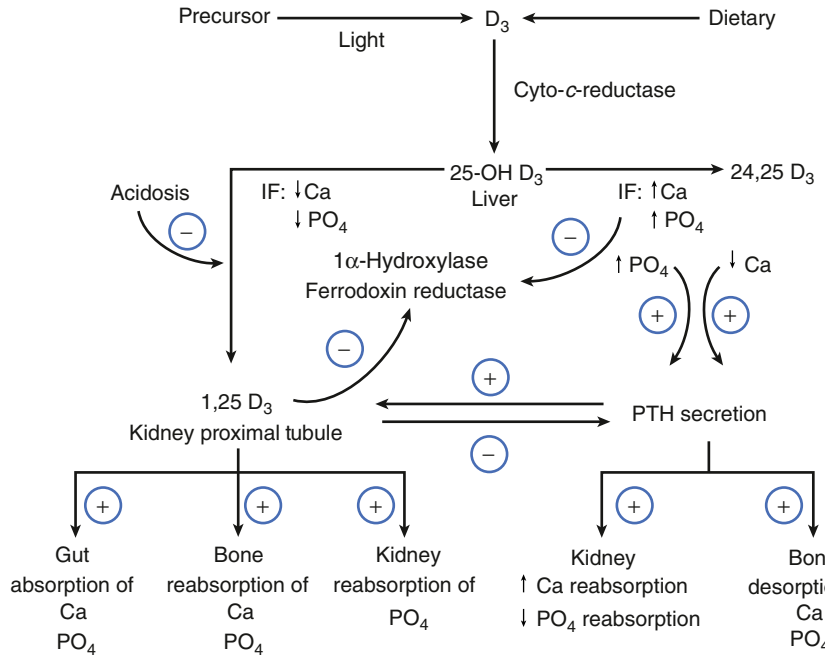

E-FIGURE 101-3. **Calcium and phosphate metabolism.** PTH = parathyroid hormone.

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102 DISORDERS OF SODIUM AND WATER

QAIS AL-AWQATI AND JAI RADHAKRISHNAN

EPIDEMIOLOGY

Disturbances of water and sodium include hypovolemia, hypervolemia, hyponatremia, and hypernatremia.[1] Up to 15 to 20% of hospitalized patients may develop hyponatremia or hypernatremia. Among ambulatory individuals, these abnormalities are more common in the elderly and in patients who are treated with multiple medications. Patients may have combinations of abnormalities in extracellular osmolality and volume (Table 102-1). Hypovolemia, which can be caused by dehydration or bleeding, can cause postural symptoms (Chapter 7) or shock (Chapter 94). Common causes of fluid overload include heart failure (Chapters 45 and 46), renal dysfunction, and liver failure, commonly resulting in edema (Fig. 39-7).[2]

DISORDERS OF EXTRACELLULAR FLUID VOLUME

PATHOBIOLOGY

Control of Extracellular Fluid Volume

The regulation of circulating volume is one of the body's major homeostatic mechanisms, and perturbations in the regulation of volume can cause a number of clinical conditions that carry substantial morbidity and mortality. Water accounts for approximately 60% of body weight (Fig. 102-1). Two thirds of this water resides intracellularly, and the remainder constitutes the extracellular fluid space. The kidney regulates extracellular volume by adjusting the amount of sodium chloride it excretes. Additionally, the kidney's regulated excretion of water maintains serum osmolality within narrow limits. The kidney accomplishes this goal by balancing salt excretion with salt intake, even though the daily intake of salt is highly variable, owing to cultural, social, and personal factors.

In the steady state, the renal excretion of salt is essentially equal to the salt intake because other possible routes of salt loss from the body (e.g., sweat glands and the gastrointestinal tract) do not contribute significantly to the maintenance of salt balance. When the dietary intake of sodium is abruptly increased (Fig. 102-2), only about one half of the increment appears in the urine over the first day. The remainder of the dietary increment is retained as a positive sodium balance. On each successive day of the higher intake of sodium, a smaller fraction of the dietary increment is retained as the excretion of sodium progressively increases over 3 to 5 days to match the new intake. Weight

TABLE 102-1 PATHOGENIC PROCESSES LEADING TO DISORDERS OF BODY SODIUM AND FLUID HOMEOSTASIS

CLINICAL STATE	ECF VOLUME	BODY FLUID TONICITY	PATHOGENIC PROCESS
Normal	↔	↔	NA
Isonatremia			
• Hypovolemia	↓	↔	ECF depletion
• Hypervolemia	↑	↔	ECF overload
Hypernatremia			
• Hypovolemic	↓	↑	ECF depletion Na > H_2O
• Hypervolemic	↑		ECF overload Na > H_2O
Hyponatremia			Net loss of sodium in excess of water
• Normovolemic	↔	↓	
• Hypovolemic	↓		
• Hypervolemic	↑		

ECF = extracellular fluid; H_2O = water; Na = sodium.

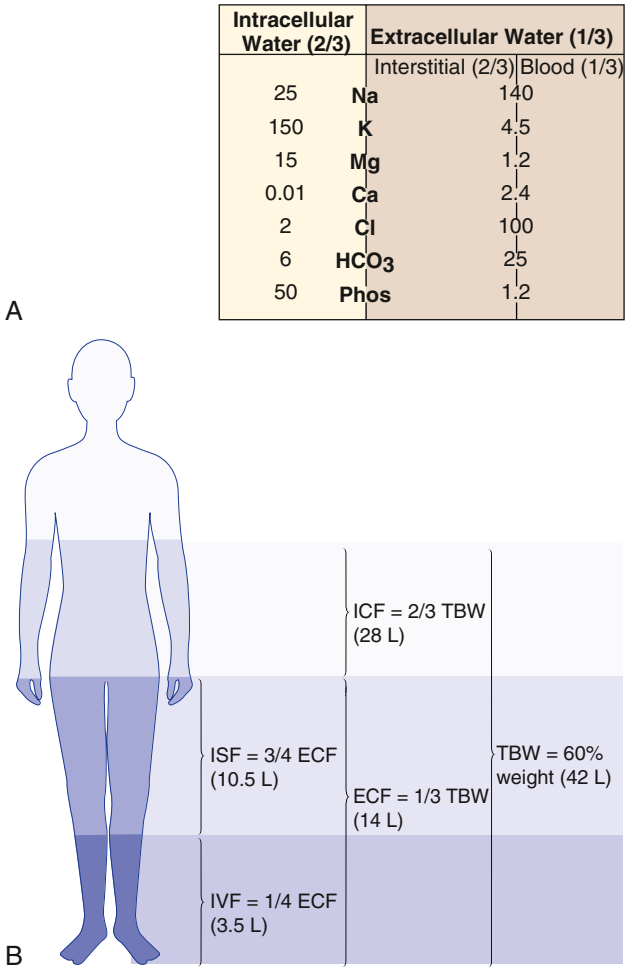

FIGURE 102-1. Composition of body fluid compartments. Schematic representation of (A) electrolyte composition of compartments in humans and (B) body fluid compartments. In A, electrolyte concentrations are in millimoles per liter; intracellular concentrations are typical values obtained from muscle. In B, shaded areas depict the approximate size of each compartment as a function of body weight. In a normally built individual, the total body water content is roughly 60% of body weight. Because adipose tissue has a low concentration of water, the relative water–to–total body weight ratio is lower in obese individuals. Relative volumes of each compartment are shown as fractions; in parentheses are shown approximate absolute volumes of the compartments (in liters) in a 70-kg adult. Ca = calcium; Cl = chloride; ECF = extracellular fluid; HCO_3 = bicarbonate; ICF = intracellular fluid; ISF = interstitial fluid; IVF = intravascular fluid; K = potassium; Mg = magnesium; Na = sodium; Phos = phosphate; TBW = total body water. (B from Verbalis JG. Body water osmolality. In: Wilkinson B, Jamison R, eds. *Textbook of Nephrology*. London: Chapman & Hall; 1997:89-94. Reproduced with permission of Hodder Arnold.)

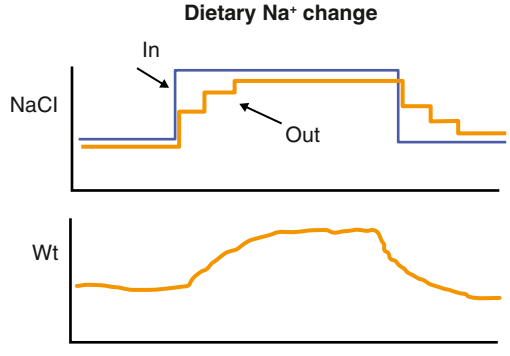

FIGURE 102-2. Time course of sodium excretion and weight change in humans following abrupt changes in daily sodium intake. Positive sodium balance continues for several days after salt intake is increased. As the volume of extracellular fluid increases, sodium excretion increases until the new lower intake of sodium is matched. It is this reduction of body sodium and extracellular fluid that provides the stimulus for diminishing the excretion of sodium. Na^+ = sodium; NaCl = sodium chloride; Wt = weight.

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PATHOBIOLOGY

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The regulation of circulating volume is one of the body's major homeostatic mechanisms, and perturbations in the regulation of volume can cause a number of clinical conditions that carry substantial morbidity and mortality. Water accounts for approximately 60% of body weight (Fig. 102-1). Two thirds of this water resides intracellularly, and the remainder constitutes the extracellular fluid space. The kidney regulates extracellular volume by adjusting the amount of sodium chloride it excretes. Additionally, the kidney's regulated excretion of water maintains serum osmolality within narrow limits. The kidney accomplishes this goal by balancing salt excretion with salt intake, even though the daily intake of salt is highly variable, owing to cultural, social, and personal factors.

In the steady state, the renal excretion of salt is essentially equal to the salt intake because other possible routes of salt loss from the body (e.g., sweat glands and the gastrointestinal tract) do not contribute significantly to the maintenance of salt balance. When the dietary intake of sodium is abruptly increased (Fig. 102-2), only about one half of the increment appears in the urine over the first day. The remainder of the dietary increment is retained as a positive sodium balance. On each successive day of the higher intake of sodium, a smaller fraction of the dietary increment is retained as the excretion of sodium progressively increases over 3 to 5 days to match the new intake. Weight

TABLE 102-1 PATHOGENIC PROCESSES LEADING TO DISORDERS OF BODY SODIUM AND FLUID HOMEOSTASIS

CLINICAL STATE	ECF VOLUME	BODY FLUID TONICITY	PATHOGENIC PROCESS
Normal	↔	↔	NA
Isonatremia			
• Hypovolemia	↓	↔	ECF depletion
• Hypervolemia	↑	↔	ECF overload
Hypernatremia			
• Hypovolemic	↓	↑	ECF depletion Na > H_2O
• Hypervolemic	↑		ECF overload Na > H_2O
Hyponatremia			Net loss of sodium in excess of water
• Normovolemic	↔	↓	
• Hypovolemic	↓		
• Hypervolemic	↑		

ECF = extracellular fluid; H_2O = water; Na = sodium.

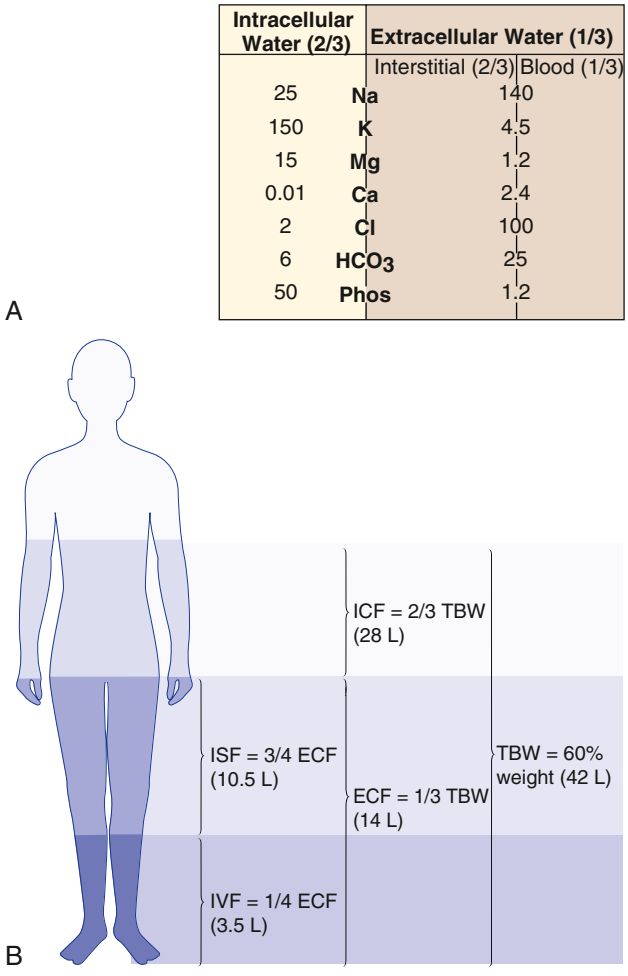

FIGURE 102-1. Composition of body fluid compartments. Schematic representation of (A) electrolyte composition of compartments in humans and (B) body fluid compartments. In A, electrolyte concentrations are in millimoles per liter; intracellular concentrations are typical values obtained from muscle. In B, shaded areas depict the approximate size of each compartment as a function of body weight. In a normally built individual, the total body water content is roughly 60% of body weight. Because adipose tissue has a low concentration of water, the relative water–to–total body weight ratio is lower in obese individuals. Relative volumes of each compartment are shown as fractions; in parentheses are shown approximate absolute volumes of the compartments (in liters) in a 70-kg adult. Ca = calcium; Cl = chloride; ECF = extracellular fluid; HCO_3 = bicarbonate; ICF = intracellular fluid; ISF = interstitial fluid; IVF = intravascular fluid; K = potassium; Mg = magnesium; Na = sodium; Phos = phosphate; TBW = total body water. (B from Verbalis JG. Body water osmolality. In: Wilkinson B, Jamison R, eds. *Textbook of Nephrology*. London: Chapman & Hall; 1997:89-94. Reproduced with permission of Hodder Arnold.)

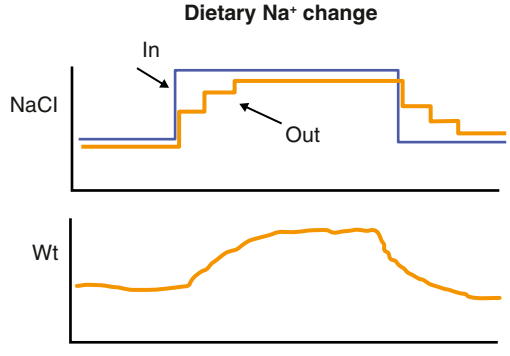

FIGURE 102-2. Time course of sodium excretion and weight change in humans following abrupt changes in daily sodium intake. Positive sodium balance continues for several days after salt intake is increased. As the volume of extracellular fluid increases, sodium excretion increases until the new lower intake of sodium is matched. It is this reduction of body sodium and extracellular fluid that provides the stimulus for diminishing the excretion of sodium. Na^+ = sodium; NaCl = sodium chloride; Wt = weight.

ABSTRACT

The kidney is the major organ that controls the content of salt and water. More than 99% of filtered sodium is reabsorbed in a manner regulated by the renin-angiotensin-aldosterone system as well as by the sympathetic nervous system and by atrial natriuretic peptides. The volume of the extracellular space (and thus the arterial blood pressure) is highly dependent on the amount of sodium reabsorbed by the kidney. Any decrease will lead to hypotension. Sodium retention leading to a large expansion of the extracellular fluid volume is one of the most common problems in medicine and results in the development of edema, which is a characteristic finding in heart failure, liver failure, and kidney diseases. However, the osmolality (tonicity) of the body fluids, as measured by the serum sodium concentration, is regulated by changes in the renal excretion of water. Reabsorption of filtered sodium generates a dilute urine, but vasopressin, which is produced by the hypothalamus, leads to insertion of water channels in the collecting duct and to the formation of concentrated urine by equilibration of urine with the hypertonic medulla. The hypothalamus also senses any decrease in the effective plasma volume, thereby leading to thirst even in the absence of hypernatremia. Clinical syndromes with an inappropriate sensing of the extracellular fluid volume include heart failure, cirrhosis, nephrotic syndrome, and the syndrome of inappropriate secretion of antidiuretic hormone.

KEYWORDS

sodium
renin
angiotensin
angiotensin-converting enzyme
aldosterone
vasopressin

will increase because the retained Na will obligate the retention of an amount of water sufficient to maintain iso-osmolality. This positive balance of sodium and expansion of the extracellular water compartment stimulates a progressive increase in the excretion of sodium until the higher intake is matched by excretion. An abrupt decrease in sodium intake also does not result in an immediate equal reduction in sodium excretion. Negative sodium balance will continue for several days, and extracellular volume will diminish until the new, lower sodium intake is matched by reduced sodium excretion. Similar responses are seen with the introduction of a new salt source (such as intravenous fluids) or the development of new salt losses (such as vomiting or diarrhea).

Afferent Limb Mechanisms

For a change in volume to result in a change in salt excretion, the change in extracellular volume must be sensed. Alterations in extracellular volume stimulate volume and pressure receptors that sense concomitant changes in intravascular volume, blood pressure, or distension of a particular vascular bed. The juxtaglomerular apparatus is a renal volume sensor that releases renin when the perfusion pressure is reduced. In addition to increasing circulating levels of angiotensin II (see later), stimulation of these receptors leads to alterations in the local concentration of angiotensin, which profoundly decreases salt excretion. Volume receptors in the carotid sinus and aorta increase sympathetic output in response to hypotension. The increased sympathetic tone of the renal vasculature decreases salt excretion. Renal sympathetic nerves and catecholamines released from the adrenal medulla also stimulate renin release. The atria contain secretory granules which, in response to an increase in extracellular volume, release atrial natriuretic peptide, which increases salt excretion and causes peripheral vasodilation. Activation of volume receptors located in intrahepatic sinusoids may play a role in sensing changes in volume and salt content.

Efferent Limb Mechanisms

Several of the efferent mechanisms, such as the angiotensin/renin pathway and atrial natriuretic peptide, act in part by altering glomerular hemodynamics, which in turn affects the proximal tubular reabsorption of salt and water. Glomerular filtration is driven by the balance of two opposing forces across the glomerular capillary membrane: the difference in hydrostatic pressure and the difference in colloid osmotic pressure. The normal glomerular filtrate is virtually protein-free. As the plasma courses down the glomerular capillary, the albumin concentration increases, thereby resulting in an oncotic driving force that opposes hydrostatic pressure and decreases the filtration rate. When colloid osmotic pressure increases to match hydrostatic pressure (a condition called filtration pressure equilibrium), filtration ceases.

Because the efferent arteriole is a resistance vessel, the peritubular hydrostatic pressure is lower than the glomerular capillary pressure. Further, the peritubular capillary oncotic pressure is higher than the hydrostatic pressure because protein-free fluid has been removed by filtration. This balance of hydrostatic and oncotic forces in the peritubular capillary favors tubular reabsorption of fluid from the extracellular space of the tubules back into the capillaries. In this way, changes in glomerular hemodynamics can alter tubular reabsorption by changing the peritubular capillary oncotic and hydrostatic pressures.

Changes in glomerular and peritubular hemodynamics can influence the rate of net sodium reabsorption. Reabsorption of the filtered fluid occurs by active transport of sodium from the tubular lumen into the peritubular space. The proximal tubule is quite "leaky," so it cannot maintain large gradients of concentration or electrical potential. Sodium accumulates in the intercellular space, thereby resulting in local hypertonicity. Water is subsequently drawn in by osmosis through the cells and the leaky junctions. Removal of this fluid into the peritubular capillary occurs because the peritubular capillary has a higher protein concentration and a lower hydrostatic pressure than an ordinary capillary; these forces favor reabsorption of fluid from the intercellular space.

Filtered sodium is passively reabsorbed from the tubular lumen into the epithelial cell down a concentration gradient. It is then actively transported into the lateral intercellular channel, which communicates directly with the interstitial space. If the net force for uptake into the capillary is decreased, conductive and/or geometric changes in the tight junction complex may favor increased "back leak" of fluid into the tubular lumen, thereby diminishing net reabsorption. When those forces are in the opposite direction, the leak will decrease, thereby resulting in an increase in net reabsorption.

In principle, sodium excretion could be altered by either a change in the amount filtered or a change in the amount reabsorbed. In practice, both glomerular filtration rate and tubular reabsorption must be considered in analyzing the actions of atrial natriuretic peptide and angiotensin II.

Renin-Angiotensin II—Aldosterone

Renin is released from the juxtaglomerular apparatus in response to hypotension or to extracellular volume depletion in the absence of hypotension. Adrenergic innervation also stimulates renin release in response to the same stimuli. Additionally, prostaglandins, low plasma K^+, and increased Na^+ delivery to the macula densa also stimulate renin release. Circulating renin converts angiotensinogen, which is mainly produced by the liver and secreted into the blood, to angiotensin I. Angiotensin I in turn is converted by a converting enzyme located on the surface of endothelial cells to the active hormone, angiotensin II. Angiotensin II causes peripheral vasoconstriction and decreases salt excretion in the proximal and distal tubules.[3]

Angiotensin II increases the proximal tubule reabsorption of Na^+ by constricting the efferent arteriole, which increases the filtration fraction, which increases the peritubular capillary oncotic pressure, which increases the driving force for Na^+ reabsorption from the interstitial space into the capillary and decreases the backward leak. Increased reabsorption of sodium and water will result in a higher concentration of many solutes, including urea and uric acid, which are reabsorbed at a slower rate than are sodium and water. Based on their ability to be reabsorbed, these solutes will diffuse out of the tubule to a larger extent than normal. Since that diffusion is driven by a difference in concentration, the blood urea nitrogen (BUN) level will increase to a higher level than simply predicted by the reduction in filtration rates. Indeed, the serum ratio of BUN:creatinine is frequently elevated when angiotensin levels are increased. Angiotensin II also stimulates the Na:H exchanger, thereby causing a direct increase in Na reabsorption through the cells in the proximal tubule. Angiotensin II also directly stimulates Na^+ transporters in the thick ascending limb, the distal tubule, and the early collecting tubule.

A major effect of angiotensin II on Na+ reabsorption, however, is to stimulate the release of aldosterone from the zona glomerulosa of the adrenal cortex. In the collecting tubule and late distal tubule, aldosterone leads to an increase in the number of open Na^+ (and also K^+) channels, thereby leading to increased entry of Na^+ into the cell and, consequently, increased exit at the basolateral surface via the Na^+-K^+-ATPase, which is also stimulated by aldosterone. The Na^+ absorbed under the influence of aldosterone is estimated to be 50 to 100 mEq/day, amounting to less than 0.5% of that filtered. However, because it acts on the final 50 to 100 mEq that have escaped absorption, aldosterone has a critical effect on renal salt excretion and total body sodium balance. In the absence of aldosterone, such as in primary adrenal insufficiency (Chapter 209), patients will develop negative salt balance with severe salt depletion and shock unless their intake compensates for this loss of salt.

Interaction of Angiotensin II and Prostaglandins

In the setting of decreased renal perfusion, glomerular filtration is usually preserved. This effect is mediated by two vasoactive factors, angiotensin II and prostaglandins, which have opposing effects on the renal vasculature. Angiotensin II binds to receptor subtypes 1 A in the efferent arteriole and promotes vasoconstriction. Concomitantly, the release of vasodilating prostaglandins mitigates the constriction of the afferent arterioles. This combined effect of efferent arteriolar constriction and afferent arteriolar dilation maintains intraglomerular pressure. These factors also have opposite effects on salt handling: angiotensin II releases aldosterone to promote salt absorption in the distal nephron, whereas prostaglandins inhibit salt absorption in the loop of Henle. Inhibitors of the renin-angiotensin axis and nonsteroidal anti-inflammatory drugs (NSAIDs) may produce acute declines in glomerular filtration in the setting of low renal perfusion pressures (e.g., volume depletion, heart failure, and cirrhosis). Further, NSAIDs may induce salt retention in these circumstances (Chapter 106).

Atrial Natriuretic Peptide

Atrial natriuretic peptide is a 28–amino acid peptide that is released from granule stores of the right and left atria in response to volume overload with atrial distention or after an atrial tachyarrhythmia. Atrial natriuretic peptide inhibits renin release and thus indirectly inhibits the production of angiotensin II. Second, atrial natriuretic peptide inhibits aldosterone production regardless of the presence of angiotensin II, high plasma K^+, or elevated adrenocorticotropic hormone. Third, atrial natriuretic peptide increases the glomerular filtration rate and thus increases the amount of Na^+ available for excretion. Finally, atrial natriuretic peptide directly inhibits the tubular reabsorption of Na^+ in the terminal collecting duct.

Renal Nerves

Renal nerves directly increase afferent and efferent arterial tone, and the resulting decrease in renal plasma flow and glomerular filtration rate will favor Na^+

retention. Stimulation of these nerves also leads to release of renin and angiotensin, which results in salt retention. Sympathetic neurons also are present in apposition to the proximal tubule and thick ascending limb, where their stimulation results in an increase in proximal Na^+ absorption even when the filtration rate, renin, and angiotensin levels are not measurably changed.

HYPOVOLEMIA

Hypovolemia, which is a contraction of intravascular volume, can be caused by renal and nonrenal conditions (Table 102-2).

CLINICAL MANIFESTATIONS AND DIAGNOSIS

The clinical manifestations of hypovolemia depend on its magnitude, the rate at which it developed, and what fluid was lost.[4] A detailed history will usually reveal underlying bleeding, polyuria, gastrointestinal losses, medications, and diaphoresis. However, gradual volume loss with an intravascular volume contraction of less than 5% may be asymptomatic and associated with few physical findings. An intravascular volume contraction of 5 to 15% typically causes symptoms and signs, often including postural lightheadedness and weakness. Thirst is common as the volume loss worsens. Hemodynamic collapse (hypovolemic shock; Chapter 92) can occur with more rapid volume loss.

On physical examination, jugular venous pressure will generally be less than 5 cm H_2O in the absence of confounding factors. Findings such as reduced skin or eyeball turgor and dry mucous membranes are not reliable indicators of hypovolemia.

Relative intravascular hypovolemia also is seen with the vasodilation that typically accompanies sepsis (Chapter 94), even though no fluid has been lost outside of the body. Such patients can be critically ill, but typically they will have warm extremities unlike the cool extremities that are typical of patients in cardiogenic or true hypovolemic shock (Chapter 92). However, the diminished tissue perfusion in sepsis can reduce the level of consciousness and cause oliguria, acute kidney injury, and lactic acidosis.

In addition to oliguria with a high urine osmolality and a low urine sodium concentration (<20 mEq/L), hemoconcentration can raise the hemoglobin level unless the patient is bleeding. The BUN will rise, often out of proportion to the rise in the serum creatinine level. The serum albumin concentration often rises with gastrointestinal, urinary, or skin losses of albumin-free fluids but falls when accompanied by albumin loss (e.g., proteinuria, protein-losing enteropathy, and burns). Loss of hypotonic fluids with inadequate water ingestion or replacement results in hypernatremia. Hypokalemia with metabolic alkalosis frequently accompanies vomiting and hypovolemia induced by thiazide and loop diuretics. By comparison, diarrhea often is associated with a non–anion gap metabolic acidosis. Adrenal insufficiency is typically accompanied by hyperkalemia and mild metabolic acidosis.

An important goal is to assess volume responsiveness (i.e., the probability that the patient with suspected hypovolemia will respond to volume repletion), especially in critically ill patients in whom volume overload is equally, if not as, deleterious as volume depletion. A static assessment of intravascular volume by measuring central venous pressure or pulmonary arterial wedge pressure can be useful but does not provide a reliable measure of volume responsiveness. Dynamic techniques that more predictably indicate volume responsiveness include passive leg raising and respiratory variation in the diameter of the vena cava, pulse pressure, or left ventricular end-diastolic diameter.

TABLE 102-2 CAUSES OF ABSOLUTE AND RELATIVE HYPOVOLEMIA

RENAL
Absolute
Diuretics
Inherited sodium-wasting tubulopathies
Tubulointerstitial diseases
Partial urinary obstruction or postobstruction diuresis
Endocrine disorders (e.g., hypoaldosteronism, adrenal insufficiency)
Relative
Nephrotic syndrome
EXTRARENAL
Absolute
Bleeding
Gastrointestinal fluid loss (e.g., diarrhea, vomiting, ileostomy or colostomy secretions)
Fluid loss from skin (e.g., burns, sweat)
Respiratory fluid loss
Relative
Third space losses (e.g., sepsis, angioedema, pancreatitis, ileus, cirrhosis with ascites)

TREATMENT

Absolute Hypovolemia

The major goal in treating hypovolemia is to restore hemodynamic integrity and tissue perfusion (Chapter 92). The management approach includes treatment of the underlying disease state, assessment and replacement of the volume deficit, treating concomitant electrolyte and acid-base abnormalities, and maintaining volume in the face of continuing losses.[5]

The choice of fluid therapy includes isotonic crystalloids (0.9% and lactated Ringer solution), colloids (albumin), and packed red cells. Generally, crystalloids are used as first-line therapy. Buffered crystalloids (e.g., lactated Ringer solution or Plasmalyte-A) may have an advantage over 0.9% saline in avoiding the dilutional acidosis and the propensity to acute kidney injury that accompanies large-volume resuscitation in critically ill patients,[A1,A2] although data in critically ill patients are less clear.[A3,A4] Using albumin adds no benefit in essentially any situation other than cirrhosis (Chapter 139). Colloids such as hetastarch or dextran should not be used. In hemorrhagic shock, packed red cells are usually required to correct anemia after initial resuscitation with crystalloids.

The rate of fluid repletion depends on the severity of the volume deficit. In patients with hypovolemic shock (Chapter 92), rapid administration of a crystalloid is recommended until hemodynamic parameters are normalized. With lesser degrees of hemodynamic compromise, one or more boluses of crystalloids (e.g., 500 mL of saline followed by an assessment of the response)[A5] may be used. In uncertain situations in which avoidance of fluid overload is critical, dynamic assessment of fluid status (see Clinical Manifestations and Diagnosis) may be helpful.

For an accompanying metabolic acidosis (Chapter 104), hypertonic sodium bicarbonate can be added to half-isotonic saline or 5% dextrose to create an isotonic replacement fluid appropriate for the acid-base abnormality. Similarly, the addition of potassium chloride is indicated in patients with concomitant potassium depletion (Chapter 103).

Relative hypovolemia owing to peripheral vasodilation requires treatment of the underlying cause, such as sepsis (Chapter 94) or anaphylaxis (Chapter 233). While this treatment is being instituted, isotonic crystalloid is the mainstay of treatment until vascular resistance and capacitance are restored to normal. Such patients also may require vasopressors (Chapter 94).

HYPERVOLEMIA

Hypervolemia is an expansion primarily of extracellular volume owing to primary or secondary renal retention of sodium (Table 102-3).

PATHOBIOLOGY

Heart Failure

With heart failure (Chapters 45 and 46), a decrease in cardiac output activates baroreceptors (E-Fig. 102-1). The result is an increase in sympathetic activity, activation of the renin-angiotensin system, and increased levels of angiotensin II. Constriction of the efferent arteriole increases the glomerular capillary hydrostatic pressure but reduces renal plasma flow. In early heart failure, the filtration rate is maintained. In severe heart failure, the filtration rate may be reduced owing to a severe decline in renal plasma flow. However, the filtration fraction is always elevated because the decline in plasma flow is always greater than the decline in the filtration rate.

TABLE 102-3 PRIMARY AND SECONDARY RENAL SODIUM-RETAINING STATES

PRIMARY
Oliguric renal failure
Chronic kidney disease
Glomerular disease, including nephrotic syndrome
Severe bilateral renovascular obstruction
Mineralocorticoid excess
Inherited sodium-retaining tubulopathies
SECONDARY
Cardiac failure
Cirrhosis
Idiopathic edema

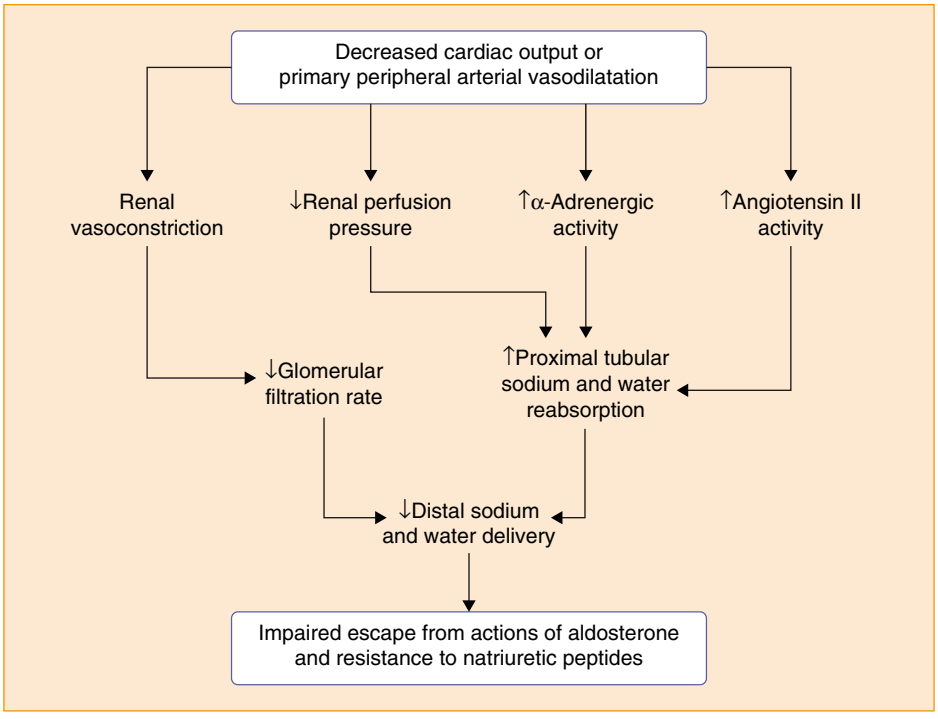

E-FIGURE 102-1. Fluid retention in heart failure. Mechanisms by which arterial underfilling leads to diminished distal tubular sodium and water delivery, impaired aldosterone escape, and resistance to natriuretic peptide hormone. (Reproduced with permission from Schrier RW, Abraham WT. Hormones and hemodynamics in heart failure. *N Engl J Med*. 1999;341:577-585.)

The lower peritubular capillary hydrostatic pressure (owing to reduced glomerular filtration) and elevated albumin concentration (owing to the elevated filtration fraction) favor increased absorption from the proximal tubule, which is the major cause of salt retention in heart failure. Angiotensin II also stimulates aldosterone release, which in turn stimulates Na^+ absorption in the more distal nephron.

Not all patients with heart failure continue to accumulate salt. After the initial salt retention, expansion of the extracellular volume may restore cardiac output to near-normal levels, albeit with a higher-than-normal extracellular volume. In this new state, the initial compensatory mechanisms will be largely deactivated: angiotensin and aldosterone levels will decrease, as will sympathetic tone. In this new steady state, salt excretion will equal salt intake. However, if heart failure worsens, owing, for example, to further myocardial damage, the cycle will be repeated. In severe heart failure, the patient will remain in the salt-retaining, high renin-angiotensin-aldosterone state despite massive extracellular volume expansion. The pathophysiology of heart failure therefore consists of two phases. The first is a salt-retaining, high-renin, high-angiotensin, and high-aldosterone state, in which the extracellular volume will continuously expand. The second phase is characterized by a normal renin-angiotensin-aldosterone axis, a higher-than-normal extracellular fluid volume, and external salt balance.

Cirrhosis

Cirrhosis of the liver (Chapter 139) is uniformly associated with disturbances in salt excretion and the consequent development of edema and ascites. Portal hypertension leads to transudation of fluid into the abdominal cavity, with consequent intravascular volume depletion. Peripheral vasodilation also causes a decrease in the "effective plasma volume," with consequent salt retention.

In general, salt retention appears to precede the development of ascites or portal hypertension. The main stimulus is the activation of volume receptors located in intrahepatic sinusoids. This increase in pressure appears to signal the kidney to retain salt and water, thereby causing volume expansion. At a time when the kidney is retaining Na^+, the glomerular filtration rate and renal plasma flow are normal, as are plasma levels of renin and angiotensin. Although total plasma volume is increased, the capacity of the splanchnic bed is much larger in cirrhotic patients than in normal individuals. If the extra-splanchnic plasma volume is depleted or effectively depleted owing to splanchnic vasodilation and increased capacity, then the mechanism for salt retention is the same as that induced by simple extracellular volume depletion.

Ascites (Chapter 132) is not only due to portal hypertension. As cirrhosis advances, progressive portal hypertension contributes to excessive transudation of fluid into the peritoneal cavity. Further, the albumin secreted by the hepatocytes enters the lymphatic system, which delivers it to the thoracic duct and then to the blood stream. In cirrhosis, however, the disturbed architecture of the hepatic lobules causes much of the albumin to be dumped directly into the ascitic fluid. Thus, although the albumin concentration in ascitic fluid is low enough to be classified as a transudate, it is actually much higher than the albumin concentration in the extravascular fluid elsewhere in the body. In addition, when the synthetic function of the liver deteriorates and the serum albumin concentration falls, the low oncotic pressure results in transudation of fluid into the interstitial space. Volume depletion from any of these causes promotes salt retention through an increase in angiotensin II and aldosterone.

Nephrotic Syndrome and Glomerulonephritis

Immunologic injury to the glomerulus results in proteinuria and, almost uniformly, in salt retention. When the proteinuria is especially severe, nephrotic syndrome (Chapter 107) develops.

In most adults with nephrotic syndrome, the plasma volume appears to be normal or even expanded, likely because of primary salt retention by the kidney. The increased glomerular permeability that causes proteinuria in these diseases also increases the filtration of circulating proteases, which activate the epithelial Na channel (ENaC) in the collecting tubule, thereby increasing Na reabsorption independent of aldosterone. In a minority of patients (usually children), low oncotic pressure leads to intravascular volume depletion and activation of the renin-angiotensin-aldosterone system, which may stimulate sodium retention by the kidney.

In patients with glomerulonephritis, the glomerular filtration rate is reduced; because salt excretion is dependent on the adequacy of the filtered load, the inability to excrete a salt load is common in advanced glomerulonephritis.

CLINICAL MANIFESTATIONS AND DIAGNOSIS

Clinical manifestations depend on the amount and relative distribution of accumulated fluid. Particularly harmful manifestations of hypervolemia include hypertension, pulmonary congestion, pleural effusions with compromised respiratory function, congestive hepatopathy, ascites, and peripheral edema that can be severe enough to compromise skin integrity and predispose the patient to cellulitis (Chapter 408).

On physical examination, left heart failure is associated with pulmonary venous congestion as manifested by pulmonary crackles (Chapter 45), and right heart failure is associated with jugular venous distention (Fig. 39-1), peripheral edema, hepatic congestion, and even ascites (see Fig. 132-4). Pitting peripheral edema (Fig. 39-6) usually does not develop until patients have at least 3 L of excess interstitial volume. Pleural effusions usually are a manifestation of combined right and left heart failure (Chapters 45 and 46). Relative hypotension suggests more severe heart failure or even cardiogenic shock (Chapter 94). When hypotension is caused by portal hypertension (as in cirrhosis) or hypoalbuminemia, the clinical manifestations may be similar to pure right heart failure, except the jugular venous pressure will be low, not high.

Laboratory tests can provide evidence of cardiac, pulmonary, or liver disease. An elevated brain natriuretic peptide (BNP) level is seen in heart failure and other states of central venous overload. Hypoalbuminemia is seen in both cirrhosis and nephrotic syndrome, but the latter is associated with marked proteinuria (Chapter 107). An elevated serum creatinine level suggests acute or chronic renal failure, which can be intrinsic or occur with advanced heart failure (cardiorenal syndrome) or hepatic cirrhosis (hepatorenal failure).

TREATMENT

Treatment must be targeted to the underlying cause to optimize hemodynamic parameters in heart failure (Chapter 46), improve liver function (Chapter 139), or treat nephrotic syndrome (Chapter 107). The reduction of excess volume requires a negative sodium balance, which can be achieved by diuretic therapy in combination with dietary sodium restriction. If these interventions are insufficient, extracorporeal fluid removal by ultrafiltration may be required.

Diuretics

Diuretics (Table 102-4) enhance urinary excretion of sodium by inhibiting its tubular reabsorption (E-Fig. 102-2).[6,7]

Loop Diuretics

Loop diuretics are the most potent diuretics, even in patients who have relatively compromised kidney function. Loop diuretics induce the loss of sodium by inhibiting the coupled entry of Na^+, Cl^-, and K^+ in the thick ascending limb of the loop of Henle, which is responsible for the reabsorption of about 25% of filtered sodium. Loop diuretics also cause hypercalciuria and are useful in some hypercalcemic states (Chapter 227). Side effects include hypokalemia and metabolic alkalosis.

Distal Tubule Diuretics

Distal tubule diuretics generally are used in the same conditions as loop diuretics, except for chronic kidney disease and disorders of calcium metabolism. Distal tubule diuretics block the sodium-chloride cotransport mechanism across apical plasma membranes in the distal tubule. Thiazide diuretics promote calcium retention and are useful in managing hypercalciuric states, including some forms of nephrolithiasis (Chapter 111). As with loop diuretics, thiazide diuretics may cause hypokalemia and metabolic alkalosis.

Collecting Duct Diuretics

Spironolactone and eplerenone compete with aldosterone and inhibit the absorption of sodium in the collecting duct, where they also suppress potassium secretion. Triamterene and amiloride, which directly block sodium uptake by collecting duct cells, also suppress potassium secretion. These collecting duct agents are used in combination with thiazide and loop diuretics to avoid hypokalemia, but hyperkalemia may complicate their injudicious use. Spironolactone and eplerenone are useful in managing disorders characterized by secondary hyperaldosteronism (e.g., cirrhosis with ascites), in promoting natriuresis in hypokalemic patients, and in competitively blocking nonepithelial mineralocorticoid receptors in patients with left ventricular dysfunction (Chapter 46).

Proximal Tubule Diuretics

Proximal tubule diuretics are rarely, if ever, used as primary therapy but are occasionally helpful as supplements to loop diuretics when loop diuretics alone are insufficiently effective. Acetazolamide, which is a carbonic anhydrase inhibitor, blocks the proximal reabsorption of sodium bicarbonate and can lead to hyperchloremic acidosis, in contrast to all other diuretics, which act at loci before the late distal nephron. Used alone, acetazolamide does not produce significant diureses since distal tubular absorption of sodium is maintained. It can, however, produce significant volume loss when used in combination with loop diuretics. Metolazone blocks sodium chloride absorption in the proximal tubule as well as in the early distal tubule, but it can cause phosphaturia.

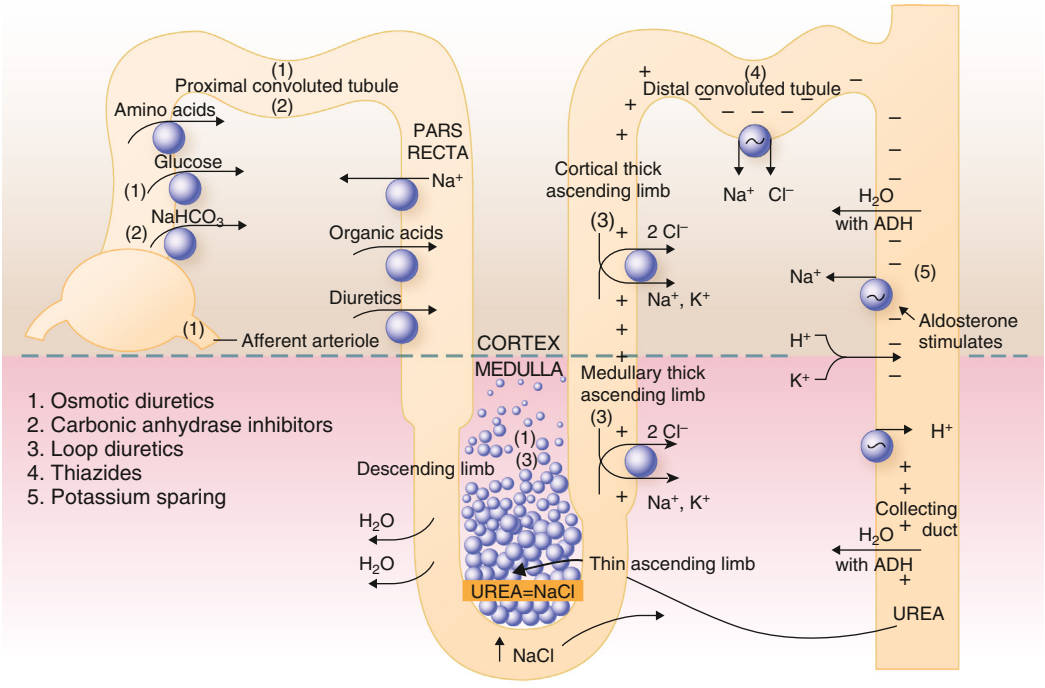

E-FIGURE 102-2. **Major transport processes along the nephron segments and primary sites of action of diuretics.** The site of action of diuretics is shown by numbers in parentheses in each nephron segment; numbers correspond to those next to the diuretics listed in the lower-left section of the figure. ADH = antidiuretic hormone. (From Kokko JP. Diuretics. In: Alexander RW, Schlant RC, Fuster V, eds. *The Heart*. 9th ed. New York: McGraw-Hill; 1998.)

TABLE 102-4 DIURETICS AND OTHER NATRIURETIC MEDICATIONS

CLASSES OF DIURETICS IN COMMON USE	DAILY DOSE RANGE	ADVERSE REACTIONS (CLASS)	COMMENTS (CLASS)
Thiazides (oral)		Rash, neutropenia, thrombocytopenia, hyperglycemia, hyperuricemia.	Usually not effective below GFR of 30-40 mL/mm (metolazone, 20-30 mL/mm)
Hydrochlorothiazide	25-100 mg		
Metolazone	2.5-5 mg		
Chlorthalidone	20-50 mg		
Loop diuretics (oral or iv)		Ototoxicity at high doses. Electrolyte disturbances.	Rapid onset, short duration Split doses in normal renal function; give intravenously in acute situations or if reduced gastrointestinal absorption Can use up to 500 mg furosemide (or equivalent) in severe renal insufficiency
Furosemide	20-320 mg		
Bumetanide	1-8 mg		
Torsemide	20-200 mg		
Potassium-sparing diuretics (oral)		Hyperkalemia	Not very potent
Spironolactone	25-400 mg		
Triamterene	25-100 mg		
Amiloride	5-20 mg		
Eplerenone	25-50 mg		
Vaptans		Constipation, increased thirst, hyperglycemia, hepatotoxicity	Used for hypervolemic hyponatremia
Tolvaptan (oral)	15-60 mg		
Conivaptan (IV)	20-40 mg IV		

GFR = glomerular filtration rate; IV = intravenous.

Combination Diuretic Therapy

Patients with severe degrees of renal sodium avidity can be resistant to conventionally recommended doses of loop diuretics and may require combinations that act at different sites along the nephron. Using various combinations of a loop diuretic with a thiazide diuretic, mineralocorticoid antagonist (e.g., spironolactone), or a proximal tubule diuretic (e.g., acetazolamide) can augment sodium loss as compared with a loop diuretic alone. Plasma concentrations of sodium, potassium, magnesium, calcium, and phosphate must be monitored carefully in such patients.

Sodium restriction does not clearly augment negative fluid balance over what can be achieved by furosemide alone. If dietary sodium is not restricted, however, patients will require higher doses of diuretics and can reaccumulate fluid. Sodium restriction to 50 to 100 mmol/day, which requires abstention from added salt as well as from foods rich in sodium, may be helpful. Sodium substitutes also can be useful, but they must be used with caution to avoid hyperkalemia if the salt substitute contains potassium. Caloric intake and nutrition must be monitored to ensure that a low-salt diet does not cause protein-energy malnutrition. Water restriction is not an appropriate therapy for hypervolemia unless hyponatremia develops. Similarly vasopressin V2-receptor antagonists, which may augment water loss, do not improve symptoms of heart failure but can raise the serum sodium concentration in patients who have hyponatremia (see Hyponatremia).

Extracorporeal Ultrafiltration

A small subset of patients have superimposed renal impairment or extreme resistance to the natriuretic actions of diuretics. Such patients may require the direct removal of excess volume by ultrafiltration, hemodialysis, or peritoneal dialysis (Chapter 117).

DISORDERS OF TONICITY OF BODY FLUIDS: HYPONATREMIA AND HYPERNATREMIA

PATHOBIOLOGY

Regulation of the Tonicity of Body Fluids

Osmotic pressure is a function of the sum of all solutes (in moles or equivalents) in a given volume of body fluids (osmolality). Tonicity is equal to the osmolality minus the concentration of ineffective solutes. Osmolality is a property of a particular solution and is independent of any membrane. Tonicity is a property of a solution in reference to a particular membrane. Tonicity (osmolality) is a highly regulated physiologic human parameter, and reasonable variations in daily water intake do not change osmolality by more than 0.5%. Water is freely permeable via water channels (aquaporins) through most cellular membranes, so no osmotic gradients exist among the body's fluid compartments. In contrast to water, sodium cannot travel freely across cell membranes. Thus, drinking a large volume of water is followed by a reduction in extracellular osmolality, thereby causing water to diffuse into the cell. This exchange causes an acute increase in cell volume, which is usually well tolerated except in cells that are encased in rigid compartments such as in the brain. Over time, compensatory mechanisms will decrease or increase intracellular osmoles in parallel with changes in extracellular osmolality, thereby restoring cell volume towards normal. The opposite phenomenon is seen when extracellular osmolality increases acutely (e.g., after consuming a high-salt diet).

A good approximation of osmolality can be obtained by measuring the serum or plasma sodium concentration, because sodium and its counter-ions (chloride and bicarbonate) comprise 90% of osmolality. With only a few exceptions, a normal Na concentration reflects normal osmolality. Thus, clinical states of low or high osmolality are frequently referred to as hyponatremia and hypernatremia, respectively.

Importantly, the regulation of osmotic pressure is entirely a function of the regulation of water content rather than sodium content. The total sodium *content* of the body fluids is most closely related to the total extracellular volume, whereas the sodium *concentration* is related to osmolality or water content. In hyponatremia, the total body sodium content may be high, low, or normal, but from the perspective of osmolar regulation, the water content is always too high relative to the sodium content.

The balance of water intake and excretion relative to sodium intake and excretion determines serum osmolality. Free water is the volume of electrolyte-free water. For example, 1.0 L of half-normal sodium chloride equals 0.5 L of normal saline and 0.5 L of free water, so infusion of 1.0 L of half-normal saline increases free water content by 0.5 L. When electrolytes other than sodium (e.g., potassium) are added to fluids, they reduce free water by corresponding amounts.

Body fluid tonicity (as measured in the serum) reflects the balance of free water input compared with free water output. Only the renal free water output is regulated; in the steady state, this renal free water output must equal free water input minus nonrenal water losses. Free water input equals oral intake plus intravenous intake. Nonrenal free water losses include cutaneous and respiratory insensible losses, as well as any water lost in the stool.

Oral intake varies with thirst and with habits. Thirst is stimulated by an increase in the osmotic pressure of the body fluids as well as by nonosmotic stimuli, such as hypotension or plasma volume depletion. These latter stimuli can dominate, and thirst, which is quenched only with hypotonic fluids, may be stimulated despite the presence of hypo-osmolarity. Insensible losses increase with increased ambient temperature, fever, or extensive damage to the skin, such as burns (Chapter 97). These variations can be very large; for example, the maximum rate of sweating is about 1 liter per hour.

The renal output of free water is a function of the urine volume and the concentration of the urinary solutes (E-Fig. 102-3). In the proximal tubule,

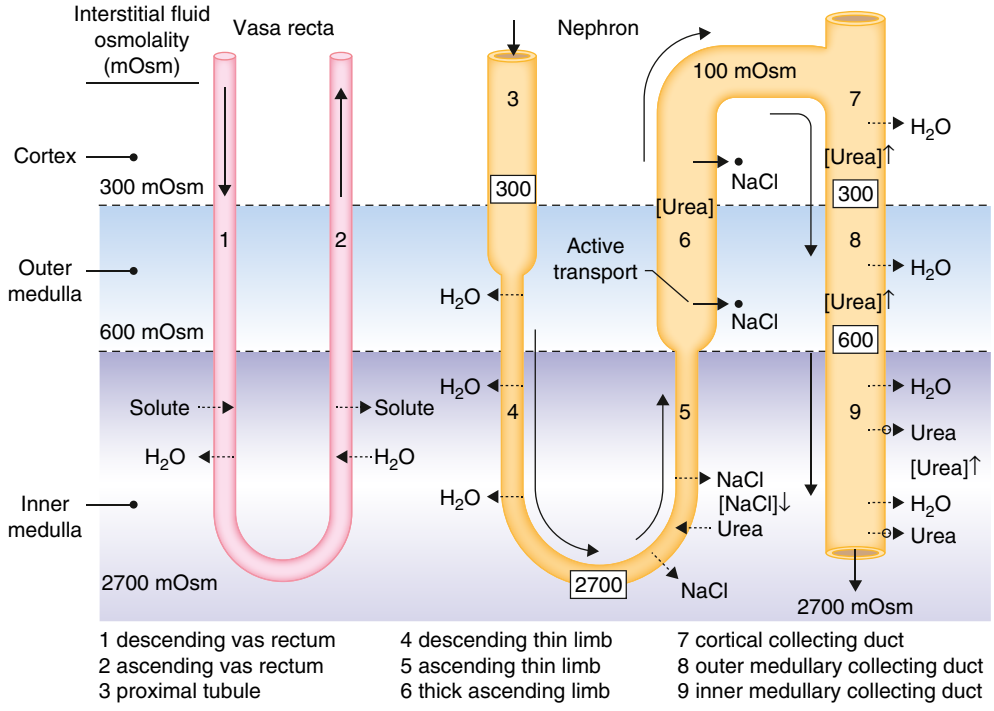

E-FIGURE 102-3. Diagram of a single vas rectum and single long-looped nephron. In the outer medulla, active transport of NaCl out of the water-impermeable thick ascending limb (indicated by *solid arrows* and *black dots*) creates the small osmotic pressure difference between that limb and the descending limb sufficient for classic countercurrent multiplication to generate the osmotic gradient (approximate osmolalities for rat kidney given by numbers in the *black boxes*). For the proposed "passive" mechanism in the inner medulla, urea ([urea]) is concentrated ([urea]↑) in urea-impermeable cortical and outer medullary collecting ducts by reabsorption of NaCl and water (*broken arrows* indicate passive movement). Urea then moves passively out of the inner medullary collecting ducts via vasopressin-regulated urea transporters (UT-A1, UT-A3; *open circles* and *broken lines*) into the surrounding inner medulla interstitium. This increased concentration of urea in the inner medullary interstitium draws water from descending thin limbs (DTLs) and inner medullary collecting ducts (IMCDs), thereby reducing inner medullary interstitial concentration of NaCl ([NaCl]↓). These processes result in a urea concentration in the interstitium that is higher than the urea concentration in the ascending thin limbs (ATLs) and an NaCl concentration in the ATLs that is higher than the NaCl concentration in the interstitium. NaCl will then tend to diffuse out of the ATLs (*broken arrows*) and urea will tend to diffuse into the ATLs (*broken arrows*). If the permeability of the ATLs to NaCl is sufficiently high and to urea sufficiently low, the interstitial fluid will be concentrated (producing the osmotic gradient) as the ATL fluid is being diluted. Countercurrent exchange of solutes and water helping to preserve this gradient is indicated in the vas rectum. Segments are numbered according to the key. (Reproduced with permission from Dantzler WH, Layton AT, Layton HE, et al. Urine-concentrating mechanism in the inner medulla: function of the thin limbs of the loops of Henle. *Clin J Am Soc Nephrol*. 2014;9:1781-1789.)

where more than 60% of the glomerular filtrate is reabsorbed, water permeability is so high that the osmotic pressure at the end of the segment is similar to that of plasma. The volume of glomerular filtrate that reaches the loop of Henle varies with the glomerular filtration rate and the extent of proximal tubule reabsorption. As the fluid courses through the thick ascending limb, active salt reabsorption combined with low water permeability causes dilution of the tubular fluid. The salt that is reabsorbed (without much water) into the medulla establishes a hyperosmolar region. This gradient provides the driving force for water reabsorption from the collecting duct. As the thick ascending limb ends and the distal tubule, which is termed the cortical diluting segment, begins, salt reabsorption in the presence of low water permeability continues to reduce the tonicity of the urine to one third of that of plasma. The volume of hypotonic fluid reaching the collecting duct is about 25 L/day. If the collecting duct is relatively impermeable to water, then much of this volume can be excreted. At the other extreme, if the collecting duct is fully permeable to water and if the medullary concentration gradient is undisturbed, then water is maximally reabsorbed and only a small volume of concentrated urine is excreted (perhaps 0.5 L at 1200 mOsm/L). Arginine vasopressin, which is human antidiuretic hormone (ADH), regulates the collecting duct water permeability.

ADH is synthesized in the supraoptic and paraventricular nuclei and stored in the neurohypophysis. Thirst is mediated by adjacent cells intermingled with cells that synthesize ADH. Hypothalamic osmoreceptors modulate release of ADH in response to very small changes in the plasma osmolality. However, below a certain plasma osmolality, the ADH level does not decrease further. This set point, which is characteristic of each individual, represents the set point of the *osmostat*. ADH is released into the circulation, where it has a short half-life. ADH activates two types of G-protein coupled receptors, V1 that mediates vasoconstriction in vascular smooth muscle and V2 that is expressed in the principal cells of the collecting duct of the kidney. The luminal membrane of these cells is relatively impermeable to water. However, activation of the V2 receptors by ADH causes insertion of a specific water channel, aquaporin 2, into the luminal membrane of the cortical and medullary collecting duct, thereby leading to increased water absorption driven by the osmotic gradient.

Other factors can also stimulate ADH release. Low arterial filling in hypotension (Chapter 64), heart failure (Chapters 45 and 46), cirrhosis (Chapter 139), and intravascular volume depletion stimulate ADH release by activating the carotid sinus and left atrial receptors. Decreases in extracellular volume cause a decrease in the set point but an increase in the steepness of the relation between ADH secretion and osmolality. Compared with a normovolemic person, the same plasma osmolality in a volume-depleted person is associated with a higher ADH level.

HYPONATREMIA

DEFINITION

Hyponatremia is defined as a serum sodium below 135 mmol/L, which corresponds to a serum osmolality <280 mOsm/kg H_2O (Table 102-5). Hyponatremia generally indicates hypo-osmolarity, but with two exceptions. First, in marked hyperlipidemia (Chapter 190) or paraproteinemia (Chapter 173), the aqueous portion of a volume of plasma is reduced. Since Na^+ is present only in the aqueous phase, the Na^+ concentration appears to be low (pseudohyponatremia) even though the measured osmolality is normal. Second, the serum Na^+ concentration may be low in the presence of high concentrations of effective osmoles, such as seen with hyperglycemia (Chapter 210), alcohol ingestions, and mannitol. These molecules do not readily enter cells, but they withdraw water from cells, thereby leading to dilution of the serum Na^+ concentration and initially leading to a normal serum osmolality. However, severe dehydration in the presence of uncontrolled blood glucose elevations can lead to the hyperosmolar hyperglycemic syndrome (Chapter 210), in which the serum is hyperosmolar owing to the elevated concentration of these osmotically active substances.

TABLE 102-5 DEFINITIONS OF HYPONATREMIA

	SERUM SODIUM (mmol/L)	PLASMA OSMOLALITY (mOsm/kg H_2O)	ETIOLOGY
Hypo-osmolar	<135	Low (<280)	Volume depletion (true and effective)
Iso-osmolar	<135	Normal (280-295)	Hyperlipidemia, paraproteinemia, hyperglycemia, alcohols
Hyper-osmolar	<135	High (>295)	Hyperglycemia, alcohols (with severe dehydration)

EPIDEMIOLOGY

The incidence of hyponatremia (serum sodium concentration <135 mmol/L) is as high as 15 to 30% in hospitalized patients. Using a definition of serum sodium concentration <130 to 131 mmol/L, which may represent a more clinically significant threshold, the incidence is about 1 to 4%. In the nonhospitalized general population in the United States, the prevalence of hyponatremia (serum sodium concentration <133 to 136 mmol/L) is estimated to be 1.7%.

PATHOBIOLOGY

In every case of hypo-osmolar hyponatremia, either free water intake minus insensible losses is elevated, renal free water output is decreased, or both. Urine is diluted by the reabsorption of sodium in nephron segments with a low permeability to water. In the absence of antidiuretic hormone, such segments include the thick ascending limb of Henle, the distal tubule, and the collecting tubules. Urine is not diluted in the proximal tubule because reabsorption of sodium is isosmotic to plasma. For the kidney to generate a large volume of dilute urine, a sufficient volume must reach the distal nephron segments. Several mechanisms may impair the kidney's capacity to produce dilute urine, thereby leading to hyponatremia (Table 102-6).

Kidney Failure

In both acute (Chapter 106) and severe chronic renal failure (Chapter 116), a low glomerular filtration rate impairs the delivery of fluid to the distal cortical diluting segment of the nephron. Since the urine volume is relatively fixed, any increase in the intake of free water above the limited urine volume will lead to hyponatremia.

Primary Polydipsia

The capacity of the normal kidney to excrete free water under normal hemodynamic conditions is very large, about 20 L/day. Only rarely, such as in psychogenic polydipsia, can a patient become hyponatremic simply by increasing water intake. The hallmark of psychogenic polydipsia is hyponatremia with a maximally dilute urine (osmolality well below 100 mOsm/kg).[8]

Low Dietary Solute

A diet low in solutes will lead to decreased delivery of urine to the distal diluting segments. When this diet is combined with an increased intake of free water, hyponatremia ensues. For example, beer potomania syndrome occurs when patients consume large volumes of beer (rich in carbohydrates and water but poor in sodium and protein), thereby limiting urinary solutes and hence urinary water excretion. A similar phenomenon is noted with a diet of tea and toast.

Extracellular Volume Depletion

In true volume depletion, the genesis of hyponatremia involves two defects: antidiuretic hormone is secreted despite hypo-osmolarity and, to a lesser extent, inadequate delivery of tubular fluid to the diluting segment. The secretion of antidiuretic hormone is increased owing to the activation of volume receptors. If volume depletion is treated with hypotonic fluids, hyponatremia will ensue.

TABLE 102-6 MECHANISMS OF HYPONATREMIA

MECHANISM	EXAMPLES
Low GFR leading to decreased delivery to distal nephron	Acute or chronic kidney failure
Excessive free water intake exceeding kidney capacity to excrete free water	Primary polydipsia
Low dietary solute	"Beer potomania" and the "tea and toast diet"
True extracellular volume depletion	Diarrhea and vomiting, hypoadrenalism
Effective plasma volume depletion	Heart failure, cirrhosis
Syndrome of inappropriate ADH secretion (SIADH)	See Table 102-7
Multiple mechanisms	Thiazides, NSAIDs

ADH = antidiuretic hormone; GFR = glomerular filtration rate; NSAIDS = nonsteroidal anti-inflammatory drugs.

The urine sodium levels will be low and serum uric acid will be elevated in such conditions, with the exception of active use of diuretics, which will elevate urine sodium levels. Similar findings are seen in patients with a loss of effective intravascular volume (e.g., heart failure), but such patients will have edema.

Thiazide-induced hyponatremia, which is one of the most common causes of drug-induced hyponatremia, occurs in about 9% of treated patients,[9] especially in older female patients. The pathogenesis of hyponatremia is likely multifactorial, owing to an increased intake of water with an impaired capacity to excrete water. Thiazide diuretics reduce the generation of free water because they inhibit Na^+ reabsorption in the diluting segment. In addition, the mild volume depletion caused by thiazides induces a decrease in fluid delivery out of the proximal tubule, thereby further reducing the volume of dilute urine generated by the kidney. Finally, the collecting duct is more permeable to water, likely due in part to an increase in antidiuretic hormone induced by mild volume depletion. Hyponatremia is uncommon with the chronic use of loop diuretics because they abolish the medullary concentration gradient, which is maintained with thiazide diuretics.

Cerebral salt wasting occurs uncommonly after head injury, subarachnoid hemorrhage, and neurosurgical procedures. The pathogenesis is thought to result when proximal tubular salt wasting of unknown etiology leads to volume depletion and subsequent stimulation of antidiuretic hormone. Since uric acid is also lost from the proximal tubule defect, urinary concentrations of sodium and serum uric acid are unreliable markers of volume depletion.

Hypoadrenalism (Chapter 208) is typically associated with hyponatremia, in large part because of the extracellular volume depletion that is a feature of this disease. The volume depletion results from a decrease in salt reabsorption in the collecting duct owing to the absence of aldosterone. In contrast to other patients with extracellular volume depletion, urinary sodium excretion will be high in these patients. Glucocorticoid deficiency may also contribute to the development of hyponatremia (see later).

Effective Volume Depletion

In patients with heart failure (Chapters 45 and 46) and cirrhosis (Chapter 139), the intra-arterial volume is typically low despite total body hypervolemia. The urine sodium concentration is low and serum uric acid elevated, similar to what is seen in volume-depleted patients (in whom the urine sodium may not be low in the presence of diuretics).

Syndrome of Inappropriate Antidiuretic Hormone Secretion (SIADH)

In the presence of high concentrations of antidiuretic hormone, water is avidly reabsorbed in the collecting duct. If water intake is not curtailed, hyponatremia will result. A subclinical increase in the extracellular volume will lead to a decrease in the reabsorption of salt. Urine sodium levels will be high, and, as a result of decreased proximal tubular reabsorption of uric acid, the serum uric acid will be low.

The syndrome of inappropriate antidiuretic hormone (SIADH; Table 102-7)[10] is seen with a number of conditions, including tumors that secrete antidiuretic hormone, various pulmonary abnormalities and CNS disorders, and a number of medications (Table 102-8). Patients with tumor-induced SIADH have high antidiuretic hormone levels regardless of the plasma osmolality. Other patients seem to have a resetting of the osmostat (i.e., they are able to suppress antidiuretic hormone but at a lower plasma sodium concentration than normal). Still others seem to have a continuous low level of antidiuretic hormone secretion regardless of the plasma osmolality, as if there was a continuous leak of antidiuretic hormone from the posterior pituitary. A few others have perfectly normal responses, thereby implying that they might express another antidiuretic hormone.

The nephrogenic syndrome of inappropriate antidiuresis is a very rare condition that is clinically similar to SIADH. In this disorder, gene variants in *V2R* cause constitutive activation of the V2 receptor and result in antidiuresis. Unlike SIADH, plasma vasopressin levels are suppressed.

Isolated glucocorticoid deficiency occurs in association with anterior pituitary disorders (Chapter 205) that impair normal secretion of ACTH, thereby leading to secondary adrenal insufficiency. The deficiency of cortisol leads to failure to suppress vasopressin levels, and the hyponatremia resembles SIADH rather than classic primary adrenal insufficiency in which hypovolemia occurs consequent to a lack of aldosterone.

Other Causes

Hypothyroidism (Chapter 207) is rarely associated with hyponatremia. Patients typically have high antidiuretic hormone levels, perhaps owing to a decrease in cardiac output. However, hypo-osmolality is frequently out of proportion to the clinical signs of decreased cardiac output. Thyroid hormone also appears necessary to maintain the number of sodium pumps in the kidney; because salt reabsorption in the ascending limb of the loop of Henle is dependent on sodium pumping, more Na^+ will be lost in the urine.

Nonsteroidal anti-inflammatory drugs (NSAIDs) inhibit prostaglandin synthesis, and prostaglandins inhibit the effect of antidiuretic hormone on the collecting duct. Thus, NSAIDs increase the sensitivity of the tubule to ADH. This effect will not in and of itself impair free water absorption unless the vasopressin level is increased, as it often is in the setting of volume-depletion or heart failure. In addition, prostaglandins also enhance the effects of angiotensin II. When NSAIDs are administered to volume-depleted patients with elevated angiotensin II, the effect of angiotensin II is potentiated, the filtration fraction is increased, the proximal tubular reabsorption of water is

TABLE 102-7 CRITERIA FOR THE DIAGNOSIS OF THE SYNDROME OF INAPPROPRIATE ANTIDIURETIC HORMONE

Decreased effective osmolality of the extracellular fluid (plasma <275 mOsmol/kg H_2O). Inappropriate urinary concentration (Uosm >100 mOsmol/kg H_2O with normal renal function) at some level of plasma hypo-osmolality.
Clinical euvolemia, as defined by the absence of signs of hypovolemia (orthostasis, tachycardia, decreased skin turgor, dry mucous membranes) or hypervolemia (subcutaneous edema, ascites).
Elevated urinary sodium excretion (>20 to 30 mmol/L) while on normal salt and water intake.
Absence of other potential causes of euvolemic hypo-osmolality (e.g., severe hypothyroidism, hypocortisolism [glucocorticoid insufficiency]).
Normal renal function and absence of diuretic use, particularly thiazide diuretics.

TABLE 102-8 CAUSES OF THE SYNDROME OF INAPPROPRIATE ANTIDIURETIC HORMONE SECRETION

ECTOPIC ADH PRODUCTION FROM TUMORS
Bronchogenic carcinoma (Chapter 177)
Adenocarcinoma of pancreas (Chapter 180)
Adenocarcinoma of duodenum (Chapter 179)
Carcinoma of the ureter (Chapter 182)
Non-Hodgkin lymphoma (Chapter 171)
Hodgkin disease (Chapter 172)
Thymoma (Chapter 390)
PULMONARY DISEASE
Tuberculosis (Chapter 299)
Pneumonia (Chapter 85)
Aspergillosis with cavitation (Chapter 311)
Lung abscess (Chapter 78)
Chronic chest infections (e.g., bronchitis; Chapter 78)
Positive pressure mechanical ventilation (Chapter 91)
CENTRAL NERVOUS SYSTEM DISEASE
Brain tumor (Chapter 175)
Encephalitis (Chapter 383)
Meningitis (Chapter 381)
Brain abscess (Chapter 382)
Head injury (Chapter 368)
Subarachnoid hemorrhage (Chapter 377)
Guillain-Barré syndrome (Chapter 380)
Acute intermittent porphyria (Chapter 194)
In response to stress (Chapter 97)
DRUG-INDUCED
AVP analogs: desmopressin (Chapter 206), oxytocin (Chapter 206)
Alkylating agents/antimetabolites (Chapter 164)
Anticonvulsants (Chapter 372)
Antipsychotic agents (Chapter 362)
Antidepressants (Chapter 362)
Nicotine (Chapter 363)
Opiates (Chapter 365)
3-4-Methylenedioxymethamphetamine (Ecstasy; Chapter 365)

AVP = arginine vasopressin.

increased, and the distal delivery of water is diminished. As a result, free water excretion is decreased.

CLINICAL MANIFESTATIONS AND DIAGNOSIS

Hyponatremia, which is a plasma sodium concentration of less than 136 mmol/L, is often an incidental finding on routine laboratory testing or is found as part of the investigation of other clinical syndromes. Hyponatremia may be hypertonic, isotonic, or hypotonic. Hypertonic hyponatremia is caused by an accumulation of non–sodium-containing effective solutes, such as very high concentrations of glucose in diabetic patients or exogenously administered mannitol or glycerol. Isotonic hyponatremia is not accompanied by any abnormalities in other electrolytes and nearly always reflects pseudohyponatremia from marked hyperlipidemia or hyperglobulinemia.

Hypotonic hyponatremia always reflects an important underlying disorder with abnormal retention of body water (see Table 102-6). Hypotonic hyponatremia can be further classified as hypervolemic (e.g., heart failure [Chapter 45], cirrhosis with ascites [Chapter 139], advanced renal failure [Chapter 116]) or hypovolemic hyponatremia (more sodium than water is lost through the gastrointestinal tract [diarrhea] or in the urine [e.g., thiazide diuretics], or ingested or administered replacement fluid is more hypotonic than the lost fluid).

The symptoms of hypotonic hyponatremia depend on its duration, severity, and rate of development.[11] When it develops over hours to days, acute brain swelling or cerebral edema may be manifested as headache, lethargy, seizures, and decreased levels of consciousness that can lead to coma and death, especially in women between menarche and menopause.[12] By comparison, if the rate of decline in the plasma sodium concentration is more gradual, osmotic adaptation may avoid serious clinical manifestations even with severe hyponatremia (plasma sodium concentration <120 mmol/L).

A careful evaluation, including a review of prior plasma sodium values, will help determine the rate of decline and provide important clues to the cause (Fig. 102-3). The physical examination should assess for hypervolemia (Chapters 7 and 39). Conversely, orthostatic hypotension and tachycardia suggest hypovolemia. The BUN, plasma electrolytes, glucose level, and osmolality should be checked to allow comparison of the measured with the calculated plasma osmolality according to the following equation:

$$\text{Plasma osmolality (mOsm/kg)} = 2\text{Na}^+\text{(mmol/L)} + (\text{blood urea nitrogen[mg/dL]}/2.8) + (\text{glucose[mg/dL]}/18)$$

Other laboratory tests in selected patients should include liver function tests and measurement of plasma creatinine, uric acid, thyroid-stimulating hormone, and cortisol concentrations; if indicated, an adrenocorticotropic hormone stimulation test should be performed (Chapter 209). Symmetrically elevated levels of both BUN and creatinine point to intrinsic renal disease, whereas a disproportionate elevation of BUN over creatinine suggests hypovolemia with a tendency to prerenal azotemia (Chapter 106). In contrast, very low levels of BUN and uric acid are typical of both SIADH and cerebral salt-wasting syndrome (see Normovolemic and Hypovolemic Hyponatremia).

About 85% of inpatients with hyponatremia have true hyponatremia, about 25% of whom are hypovolemic, about 25% of whom have an edematous state, about one third of whom are normovolemic, and the remainder of whom usually have renal failure. Since the plasma sodium concentration declines by approximately 1.6 mmol/L for each increase of 100 mg/dL (5.5 mmol/L) in plasma glucose concentration, marked elevation in the plasma glucose concentration can cause *hypertonic* hyponatremia. In contrast to hyperglycemia, an elevated BUN does not alter the plasma sodium concentration, even though urea contributes to the laboratory measurement of plasma osmolality; thus, a hyponatremic patient with a normal or elevated laboratory measurement of plasma osmolality that can be fully attributed to an increased BUN should be considered as having hypotonic hyponatremia.

A discrepancy in which measured plasma osmolality exceeds calculated plasma osmolality, even after accounting for glucose and urea, indicates the presence of an unidentified small solute (osmolar gap), including alcohols (e.g., ethanol, methanol, ethylene glycol, and isopropyl alcohol) and the organic anions of weak acids, which raise the plasma anion gap. Because these small

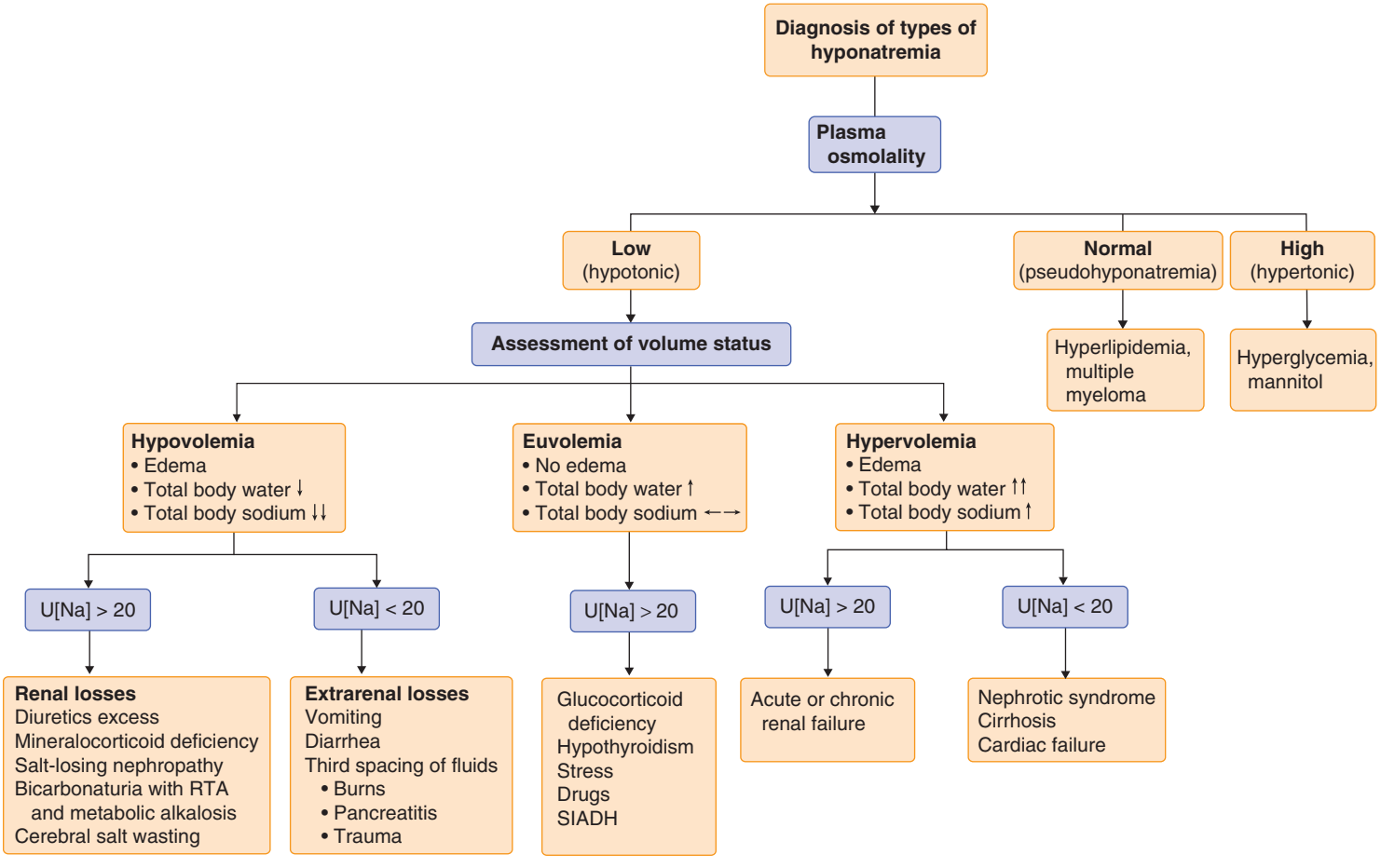

FIGURE 102-3. Diagnostic approach to hyponatremia. RTA = renal tubular acidosis; SIADH = syndrome of inappropriate antidiuretic hormone secretion; U[Na] = urinary sodium concentration. (Modified from Halterman R, Berl T. Therapy of dysnatremic disorders. In: Brady H, Wilcox C, eds. *Therapy in Nephrology and Hypertension*. Philadelphia: Saunders; 1999:256; and data from Cohen DM, Ellison DH. Evaluating hyponatremia. *JAMA*. 2015;313:1260-1261.)

molecules do not affect the movement of water, the patient's water balance is determined by the plasma sodium concentration. However, an osmolar gap should prompt a thorough investigation for poisoning, intoxication, or an organic acidosis (Chapter 104).

As soon as true hypotonic hyponatremia is established, the evaluation aims at classifying the cause into one of three categories based on the patient's volume status (see Fig. 102-3). Abnormal liver function test results can provide adjunctive support for hepatic disease and a hypervolemic hyponatremic state. The diagnosis of heart failure should be made clinically, but it can be assisted by a BNP level, chest radiograph, or echocardiography (Chapter 45).

In the absence of a clinically obvious edema, a low urine sodium concentration (<20 mmol/L) or a low fractional excretion of sodium (<1%) supports the diagnosis of hypovolemic hyponatremia secondary to extrarenal losses or past renal losses that have since abated. In hypovolemia caused by ongoing renal losses, the urine sodium concentration may remain high despite hypovolemia, but the fractional excretion of urea may also be low (<35%). A high urinary concentration of potassium is suggestive of potassium-depleting diuretic use, whereas the urinary potassium concentration of potassium is low (<20 mmol/L) if potassium is being lost because of diarrhea or vomiting.

The combination of hypotonic hyponatremia without hypovolemia, hypervolemia, hypothyroidism, or adrenal insufficiency combined with low plasma urea and uric acid concentrations strongly suggests SIADH. The urine sodium concentration typically is higher than 40 mmol/L, often higher than 100 mmol/L. Lack of sustained improvement after a salt-containing volume challenge further supports the diagnosis of SIADH and should prompt a search for its cause (see Table 102-8). A radiograph or chest computed tomography scan may help identify intrathoracic lesions that are associated with SIADH.

Hypervolemic Hyponatremia

In hypervolemic hyponatremia, both water and sodium are in excess, but the excess of water is greater than the excess of sodium. The most frequent causes are heart failure (Chapter 45), decompensated cirrhosis (Chapter 139) with ascites (Chapter 132), and advanced renal failure (Chapter 117), just as in hypervolemia without hyponatremia. The urine sodium concentration is less than 20 mmol/L and the fractional sodium excretion is less than 1% (despite obvious volume expansion, commonly with edema) unless it is altered by a diuretic-induced natriuresis.

Normovolemic and Hypovolemic Hyponatremia

Normovolemic and hypovolemic hyponatremia may be difficult to distinguish from each other because mild hypovolemia can be difficult to detect on the history and physical examination. A low urine sodium concentration and low fractional excretion of sodium are characteristic of extrarenal hypovolemia, but the urine sodium concentration is usually elevated when hypovolemia is due to urinary loss.

Hypovolemic hyponatremia always signifies past or ongoing sodium loss (often with potassium) accompanied by a lesser degree of water loss, with appropriately elevated ADH levels in response to the hypovolemia. In most cases, loss of sodium results in volume depletion, which activates thirst, thereby inducing the patient to drink water; because volume-mediated release of antidiuretic hormone is retained, hyponatremia develops. Hyponatremia is a common complication of diarrhea (Chapter 126) when the diarrheal fluid is secretory and rich in electrolytes. Sweating-induced hyponatremia occurs when individuals ingest high volumes of hypotonic fluid, often pure water, while losing sodium in sweat.

The renal causes of hypovolemic hyponatremia (see Fig. 102-3) include thiazide-induced hyponatremia and the cerebral salt-wasting syndrome. Thiazide-induced hyponatremia occurs when patients with impaired urinary diluting capacity excrete concentrated urine because thiazides do not affect the ability of the renal medulla to concentrate urine. Thiazide-treated patients are particularly susceptible to hyponatremia when they ingest or receive hypotonic solutions that exceed their maximal capacity to excrete electrolyte-free water in their urine. In cerebral salt wasting, patients who have suffered a head injury or intracranial hemorrhage have inappropriate renal sodium wasting; antidiuretic hormone levels rise and patients develop hyponatremia if hypotonic fluid is then ingested or administered. SIADH also is characterized by a high urine sodium concentration and hyponatremia, but a high fractional excretion of uric acid is found only in cerebral salt wasting.

In normovolemic hypotonic hyponatremia, urine containing sodium concentrations greater than 40 mmol/L usually indicate SIADH (Table 102-8),[13] but hypothyroidism (Chapter 207) and adrenal glucocorticoid insufficiency (Chapter 208) can be associated with hypotonic hyponatremia that mimics SIADH without clinically evident hypovolemia. Pregnancy, which also is associated with thirst as well as a reduction in the osmotic threshold for ADH release, results in mild hyponatremia (Chapter 221).

TREATMENT

Treatment of hyponatremia varies depending on the urgency of the clinical situation, its cause, and the underlying diagnosis (see Fig. 102-3). Some data suggest that a bolus of 3% saline (100 mL repeated up to two more times) may safely correct hyponatremia more rapidly than a continuous infusion. Hyponatremia should be approached from the perspective of free water intake compared with renal free water output.

The first principle is that the rate of correction should be guided by the patient's age, gender, and neurologic status and any information about recent and past plasma sodium concentrations or osmolality values. Delayed correction of hyponatremia can perpetuate cerebral edema and result in irreversible neurologic damage and death, especially in women of reproductive age and in patients whose hyponatremia developed at a pace that outstripped the rate of osmotic adaptation in the brain. In contrast, overly rapid correction or correction to a sodium concentration that is above the level needed to safeguard the patient from the neurologic sequelae of cerebral edema can result in the devastating and often irreversible *osmotic demyelination syndrome* (Chapter 384), which is characterized by fluctuating levels of consciousness, pseudobulbar palsy, ataxia, dysarthria, difficulty in swallowing, and characteristic abnormalities in the region of the brain stem on magnetic resonance imaging (MRI; see Fig. 384-3). Risk factors for the development of osmotic demyelination syndrome include severe hyponatremia (serum sodium concentration <105 mmol/L), hypokalemia, alcohol use disorder, malnutrition, and advanced liver disease.

The second principle is the importance of identifying and treating any underlying disorder, such as the hypervolemia of heart failure (Chapters 45 and 46). In hypovolemic patients, appropriate fluid administration can correct the hyponatremia.

Acute Symptomatic Hyponatremia

Acute symptomatic hyponatremia that requires urgent treatment includes self-induced acute water intoxication (e.g., psychiatric diseases such as acute psychosis or schizophrenia; endurance exercise), known hyponatremia with a duration <24 to 48 hours; hyponatremia from an intracranial cause (includes increased intracranial pressure); or hyponatremia accompanied by seizures or coma, regardless of chronicity. The goal is urgent correction by 4 to 6 mmol/L to prevent brain herniation and neurologic damage from cerebral ischemia.

For severe symptoms, 100 mL of 3% NaCl should be infused intravenously over 10 minutes, repeated twice as needed.[14] This rapid bolus approach is as good as a continuous infusion for correcting hyponatremia with a lower risk of overcorrection.[A6] For mild to moderate symptoms with a low risk of herniation, 3% NaCl should be infused at 0.5 to 2 mL/kg/hour. The rate of correction need not be restricted in patients who have true acute hyponatremia, nor should inadvertent overcorrection be reversed. If, however, the hyponatremia might be chronic rather than acute, the limits for correction of chronic hyponatremia should be followed.

Chronic Hyponatremia

Symptomatic hyponatremia or sodium concentrations below 125 to 130 mmol/L require specific treatment, but mild degrees of asymptomatic hyponatremia can be tolerated for long periods. When deciding treatment strategies in such patients who are known to have developed hyponatremia, the severity of symptoms, risk factors for osmotic demyelination syndrome, and the underlying cause of hyponatremia should be taken into consideration. Frequent monitoring of the plasma sodium concentration and osmolality is crucial. If the safe target rate of correction is exceeded, osmotic demyelination can be prevented by slowing the correction rate, by returning to a lower plasma sodium concentration with the judicious readministration of hypotonic solutions, or by administering vasopressin analogues (see later).

Patients who are at risk for osmotic demyelination syndrome have hyponatremia with serum [Na^+] <120 mmol/L of >48 hours' duration. Examples include outpatients who have been drinking conventional volumes of water, are treated with thiazide diuretics, or have hospital-acquired hyponatremia with a known duration of >48 hours.

To avoid osmotic demyelination syndrome in such patients, the goal of therapy is minimum correction of serum sodium concentration by 4 to 8 mmol/L per day, with a lower goal of 4 to 6 mmol/L per day if the risk of osmotic demyelination syndrome is high. The rate of correction should not exceed 8 mmol/L in any 24-hour period in patients who are at a high risk of osmotic demyelination syndrome, and it should not exceed 10 to 12 mmol/L in any 24-hour period (or 18 mmol/L in any 48-hour period) for patients at normal risk of osmotic demyelination syndrome.

If the correction of chronic hyponatremia has been inadvertently excessive, intervention is probably unnecessary if the starting serum sodium concentration was ≥120 mmol/L. However, if the starting serum sodium concentration was <120 mmol/L, the serum sodium should be lowered to the recommended level

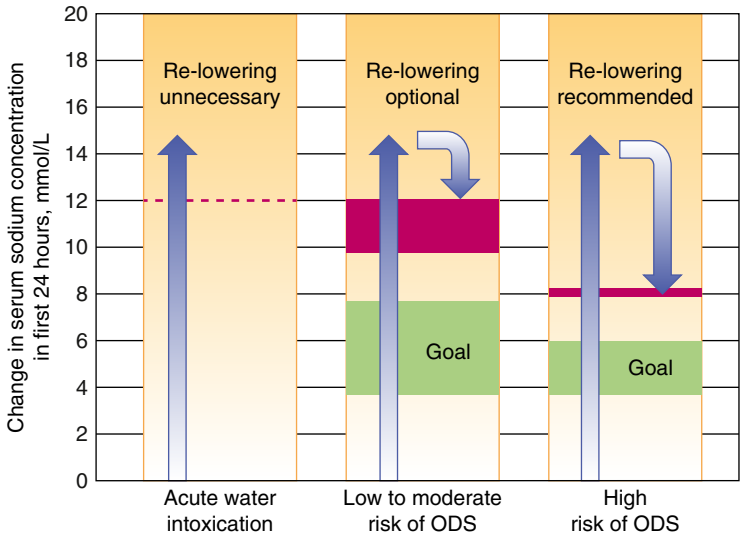

FIGURE 102-4. Recommendations for relowering of serum sodium concentration ([Na]) to goals *(green)* for patients presenting with serum [Na] <120 mmol/L who exceed the recommended limits of correction *(red)* in the first 24 hours. ODS = osmotic demyelination syndrome. (Reproduced with permission from Verbalis JG, Goldsmith SR, Greenberg A, et al. Diagnosis, evaluation, and treatment of hyponatremia: expert panel recommendations. *Am J Med*. 2013;126:S1-S42.)

if overcorrection occurs. To relower the serum sodium concentration (Fig. 102-4), desmopressin (2 to 4 mcg every 8 hours parenterally) should be administered to prevent further water losses, and water losses should be replaced with 5% dextrose in water intravenously at a rate of 3 mL/kg/hour. The next dose of a vasopressin antagonist should be withheld if the correction is >8 mmol/L. The serum sodium concentration should be checked hourly, and water replacement should be continued until the serum sodium concentration is reduced to goal. High-dose glucocorticoids (e.g., dexamethasone, 4 mg every 6 hours) for 24 to 48 hours is recommended if correction has occurred.

Hypervolemic Hyponatremia

In hypervolemic hyponatremia (e.g., heart failure), the goal is to remove salt and water, but relatively more of the latter. Water restriction is helpful but is often inadequate. Treatment with the AVP V_2-receptor antagonist tolvaptan (starting at 15 mg once daily, with a maximal dose of 60 mg once daily) increases the plasma sodium concentration significantly at 30 days in patients with euvolemic or hypervolemic hyponatremia,[A7] but it also increases the risk of overcorrection.[A8] Tolvaptan is not recommended in patients who have cirrhosis because of its potential liver toxicity.

Hypovolemic Hyponatremia

When hypovolemia is clearly evident (appropriate clinical history, orthostatic hypotension, low urine sodium concentration in the setting of extrarenal fluid losses, elevated plasma urea disproportionate to the rise in the serum creatinine level, and elevated uric acid concentrations), isotonic saline is the treatment of choice. However, caution should be exercised in the administration of isotonic saline to these patients because the administration of small volumes of isotonic saline can sometimes induce a brisk and rapid decrease in urine osmolality, an accompanying water diuresis, and an overly rapid correction of hyponatremia. Accordingly, hourly monitoring of urine output, urine osmolality, plasma sodium concentration, and plasma osmolality is required. A rapid drop in urine osmolality accompanied by water diuresis should prompt cessation of volume repletion and, in some cases, administration of hypotonic solutions or even analogues of vasopressin itself (see later) to bring the rise in sodium concentration to within the recommended guidelines. When hypovolemia is not clearly evident but cannot be excluded, a brisk drop in urine osmolality in response to a saline challenge confirms the suspicion of hypovolemia and simultaneously initiates therapy. In contrast, failure to induce such a response lends support to the diagnosis of normovolemic hyponatremia.

Normovolemic Hyponatremia

In patients with normovolemic hyponatremia, the appropriate therapeutic approach is to address the underlying hypothyroidism (Chapter 207), adrenal insufficiency (Chapter 208), or SIADH. If an underlying cause cannot be identified or reversed, treatment aims to generate a gradual net negative water balance. Fluid restriction is usually the first-line strategy.

Fluid restriction should address all intake that is consumed by drinking, not just water, aiming for an intake that is 500 mL/day below the 24-hour urine volume. Neither sodium nor protein intake should be restricted unless the patient has another indication for doing so. Unfortunately, fluid restriction may be insufficient in the setting of a high urine osmolality (e.g., >500 mOsm/kg H_2O), when the sum of the urine sodium and potassium concentrations exceeds the serum sodium concentration, when 24-hour urine volume is <1500 mL/day, or when the increase in serum sodium concentration is <2 mmol/L/day despite fluid restriction below 1 L/day for 24 to 48 hours. In such patients, titrated oral tolvaptan (beginning at 15 mg once daily and increasing to a maximum of 60 mg once daily) is indicated, especially in hospitalized patients, provided that the patient has an intact thirst mechanism to avoid polyuria or hypernatremia. When volume status is in doubt, however, these agents are better avoided.

Vaptans should not be used in patients who have hypovolemic hyponatremia, in conjunction with other treatments for hyponatremia, or immediately after the cessation of other treatments for hyponatremia, particularly 3% NaCl. For the first 24 to 48 hours after initiating treatment, the serum sodium concentration must be monitored every 6 to 8 hours, and ad libitum fluid intake should be maintained. Hyponatremia can correct too quickly if vaptans are given with coincidental fluid restriction in patients who have a defective or impaired thirst mechanism (e.g., intubated or unconscious patients), so sufficient fluid must be provided to prevent overly rapid correction owing to unopposed aquaresis. Vaptans should be discontinued if the patient develops complications that limit their ability to request, access, or ingest fluid. For severe, symptomatic hyponatremia or a serum sodium concentration below <120 mmol/L, treatment should be with 3% NaCl, which provides a quicker and more certain correction of the serum sodium concentration than do vasopressin antagonists. If overcorrection occurs, the serum sodium concentration can be relowered to safe limits as for acute hyponatremia.

Urea (typically starting at 15 g/day diluted in water and divided into two or three daily doses and with the dose increased to 90 g/day based on the patient's response) can increase the excretion of urinary solutes and thereby water excretion in patients with SIADH. Urea is well tolerated and can be used chronically in patients who have SIADH.

PROGNOSIS

Hyponatremia is a marker for worse outcomes among hospitalized patients. A serum sodium level <135 mmol/L is associated with about a 45% relative increased rate of intensive care unit admission.[15]

HYPERNATREMIA

Hypernatremia (a plasma sodium concentration higher than 144 mmol/L) always reflects a state of hypertonicity, with an increased concentration of osmotically active solutes throughout all body fluid compartments. Under normal conditions, the obligate daily loss of water is approximately 500 mL, consisting mostly of the water vapor in expired air and the loss due to insensible sweating. The minimal amount of water needed to keep the urinary solutes in solution is about 500 mL per day. However, sweating in hot, dry environments can lead to massive water losses as high as 1 L/hr. If the daily water intake is less than the obligate water loss, the osmotic pressure of the body fluids will increase.

CLINICAL MANIFESTATIONS AND DIAGNOSIS

Although hypernatremia can be diagnosed as an incidental laboratory abnormality, it most commonly occurs in the setting of a severe underlying disease with other accompanying disturbances to body fluid homeostasis (Table 102-9). Patients with hypovolemic hypernatremia have lost both sodium and water, but the net loss of water is disproportionately greater than the net loss of sodium.

The main clinical consequences of increased body fluid tonicity are confusion, seizures, focal neurologic deficits, and a progressively decreasing level of consciousness that can progress to coma. In the absence of an underlying neurologic problem or disturbance in the thirst mechanism, the patient would be expected to complain of thirst unless the neurologic injury has disturbed consciousness. Failure to replace hypotonic fluid losses generally reflects impairment in thirst, disability or infirmity that prevents the patient from responding to thirst, or failure of the clinician to recognize the need for hypotonic fluid replacement. Rarely, impaired thirst in patients who are awake and alert can be caused by damage to the hypothalamic osmoreceptors that control thirst perception and response, a condition known as *primary hypodipsia*. In patients with hypernatremia of sufficient duration to enable brain cells to undergo osmotic adaptation, few, if any, clinical manifestations are observed.

The causes of hypernatremia include loss of thirst or increased insensible loss of water, diabetes insipidus, or osmotic diuresis. Renal failure (Chapter 116)

TABLE 102-9 CAUSES OF HYPERNATREMIA CLASSIFIED BY EXTRACELLULAR FLUID VOLUME (TOTAL BODY SODIUM CONTENT)

Hypervolemia	Hypertonic saline excess Hypertonic sodium bicarbonate solutions
Hypertonicity with near normovolemia	Diabetes insipidus Febrile fluid loss
Hypovolemia	Gastrointestinal loss (diarrhea, vomiting) Skin fluid loss (burn, sweat) Loop diuretics Osmotic diuresis Impaired thirst perception

and tubulointerstitial disease (Chapter 108) cause relatively mild concentrating defects and tend not to be associated with significant hypernatremia, provided that a normal mechanism can readily compensate for it.

The laboratory diagnosis of hypernatremia should be repeated to confirm its accuracy and should be corroborated by an elevated plasma osmolality. The underlying cause is usually evident from the history and physical examination.

In hypovolemic hypernatremia with extrarenal fluid loss, urine output is usually less than 500 mL/day and urine osmolality is the maximum for age (>1000 mOsm/kg in young adulthood decreasing to >600 mOsm/kg by age 60 years). Polyuria with a submaximal urine osmolality suggests impaired urine-concentrating ability, owing to underlying intrinsic renal disease or diuretic agents. A spot urine osmolality less than 100 to 200 mOsm/kg or polyuria (>3 L/day) combined with 24-hour urine solute excretion less than 600 mOsm/day suggests diabetes insipidus (see later). In contrast, daily solute excretion greater than 800 to 1000 mOsm/day suggests an osmotic diuresis.

Hypervolemic hypernatremia is usually associated with prior administration of sodium-containing solutions, and the findings on physical examination are consistent with volume expansion. In the absence of underlying intrinsic renal disease or diuretic use, urine osmolality is high because the hypertonic stimulus to release vasopressin overrides the effects of hypervolemia.

TABLE 102-10 REASONS FOR POLYURIA

WATER DIURESIS
Diabetes insipidus
Central (neurogenic)
Inherited
Acquired (e.g., tumors, trauma, hypoxia)
Nephrogenic
Hypercalcemia
Amyloidosis
Drugs (e.g., lithium, foscarnet, cidofovir, vaptans)
Sjögren syndrome
Sickle cell disease
Inherited
Polydipsia
Primary (e.g., hypothalamic)
Psychogenic
SOLUTE DIURESIS
Sodium
Excess sodium intake (oral, enteral, parenteral)
Renal sodium wasting (e.g., inherited tubulopathies, interstitial nephritis, natriuretic drugs)
Anion based (sodium is usually the associated cation)
Chloride excretion (e.g., Bartter syndrome, loop diuretic)
Bicarbonate excretion (e.g., exogenous bicarbonate, carbonic anhydrase inhibition)
Glucose/keto acids
Diabetic ketoacidosis
Hyperglycemic-hyperosmolar syndrome
Renal glycosuria
Sugar alcohols
External loading (e.g., mannitol, glycerol)
Urea
Exogenous loading (e.g., urea, protein, amino acids)
Diuretic phase of acute kidney injury
Postobstructive diuresis
Hypercatabolic states
Hemoglobin/myoglobin driven (post-rhabdomyolysis or reabsorption of a hematoma)
Other
Radiocontrast agents

TREATMENT

The management of serious symptomatic hypovolemic hypernatremia is challenging and includes rapid correction of the depleted volume followed by gradual replacement of the water deficit.[16] If volume contraction is severe, isotonic saline is generally the fluid of choice, and the volume and rate of administration should be guided by clinical parameters related to reversal of hypovolemia. After tissue perfusion has been restored, further fluid replacement aims to correct the estimated water deficit:

$$\text{Total body water deficit} = 0.4 \times \text{premorbid weight} \times ([\text{Na}/140] - 1)$$

Unlike the initial isotonic fluid replacement, water replacement should be gradual over hours to days, so the rate of water replacement can match the rate at which brain intracellular solutes can be adaptively extruded or removed, unless the hypernatremia has itself clearly developed over minutes to hours. The estimated water deficit should be replaced at a rate that will lead to a reduction of approximately 0.5 to 1.0 mmol/L in measured plasma sodium concentration per hour and more than 6 mmol/L but no more than 10 to 12 mmol/L in 24 hours. In addition to the estimated water deficit, water replacement should consider estimated ongoing insensible water loss of at least 1 L per 24 hours, supplemented to account for ongoing water losses (renal or gastrointestinal) owing to the underlying disease process. Patients often require large volumes of water, sometimes reaching 5 to 10 L, for the duration of the correction period. This water requirement can be met by the dietary ingestion of tap water or administration of a hypotonic intravenous solution, such as D_5W or half-isotonic saline. The sodium concentration should be monitored at least every 4 hours, and the patient's volume status should be monitored to avoid hypervolemia.

The hypertonic state of uncontrolled diabetes with hyperglycemia (Chapter 210) requires insulin as well as fluid therapy.[17] Some hospitalized patients with hypervolemic hypernatremia require hypotonic solutions combined with a continuous infusion of loop diuretics or even extracorporeal removal of both the sodium and water excess. Once the sodium concentration has normalized, a patient with an intact thirst mechanism will generally correct the hypertonic state by spontaneous oral fluid intake.

PROGNOSIS

Hypernatremia is associated with increased morbidity and mortality, both in the hospital and after discharge. Since hypernatremia in adults is typically associated with serious comorbid conditions, the mortality rates may reflect the severity of the underlying diseases rather than that of hypernatremia itself.

POLYURIA

Polyuria (Table 102-10),[18] which is defined as a urine output of more than 3 L/day, should be distinguished from urinary frequency, which can occur with frequent voiding of small volumes totaling less than this amount per day. Polyuria can be a water diuresis or a solute diuresis.

The evaluation for polyuria centers around the analysis of urine osmolality (Fig. 102-5). Urine osmolality <100 mOsm/kg suggests water diuresis, whereas a urine osmolality >300 mOsm/kg is typically related to solute diuresis.

DIABETES INSIPIDUS

The failure to release antidiuretic hormone is termed central diabetes insipidus (Chapter 206), whereas a lack of responsiveness to antidiuretic hormone is termed nephrogenic diabetes insipidus.[19] In diabetes insipidus, the urine becomes progressively dilute as it ascends in the loop of Henle, reaching osmolalities as low as 100 to 150 mOsm/kg in the distal tubule. In the absence of antidiuretic hormone, urine will be diluted further in the collecting tubules. The daily volume of this dilute urine can be as high as 20 liters.

Central diabetes insipidus (Chapter 206) results from destruction of the hypothalamus by tumor (Chapter 204), head injury (Chapter 368), hemorrhage (Chapter 375), surgical trauma, or congenital causes. If the involved area is extensive, the thirst mechanism will also be impaired. A few patients who manifest partial diabetes insipidus can concentrate their urine, though not to maximal levels.

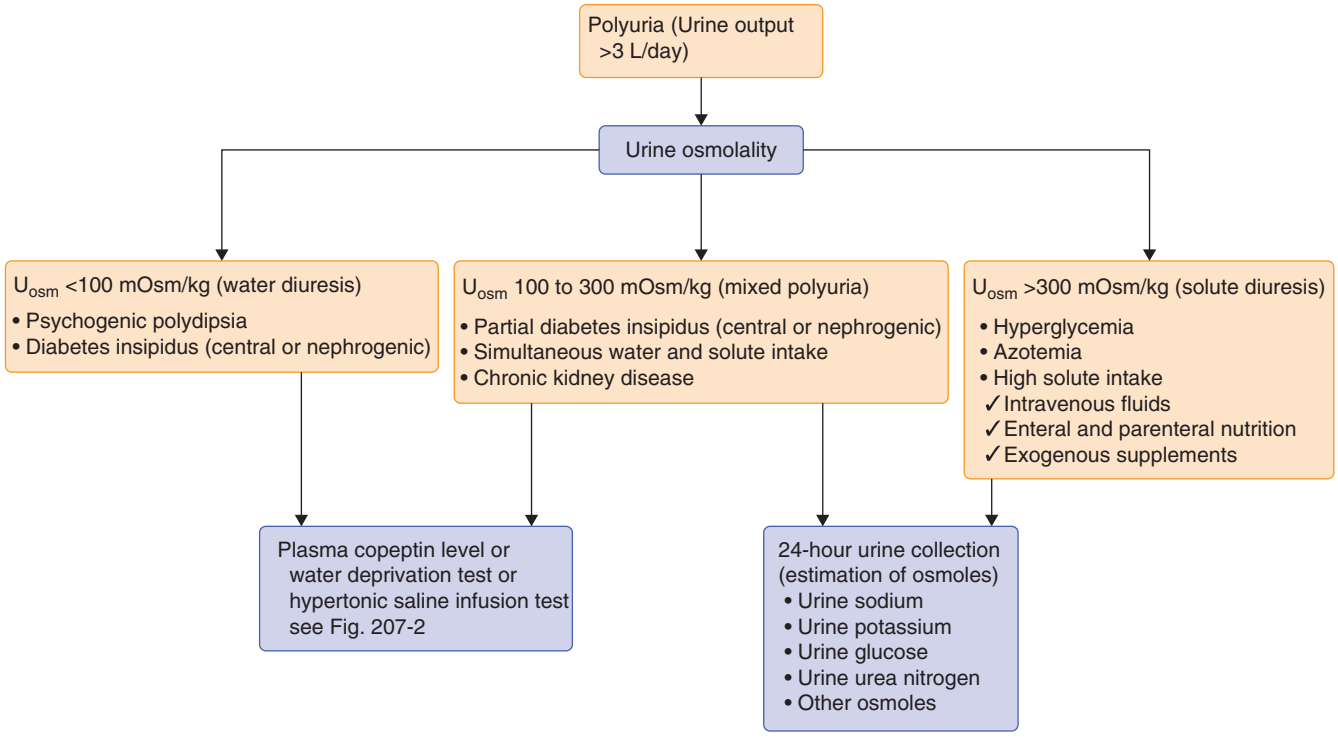

FIGURE 102-5. Diagnostic approach to polyuria. U_{osm} = urinary osmolality. (Adapted with permission from Bhasin B, Velez JCQ. Evaluation of polyuria: the roles of solute loading and water diuresis. *Am J Kidney Dis*. 2016;67:507-511.)

Nephrogenic diabetes insipidus can be caused by a mutation in the vasopressin V2 receptor or the aquaporin 2 water channel.[20] Drugs also can cause nephrogenic diabetes insipidus by interfering with the action of antidiuretic hormone, thereby preventing the insertion of aquaporin water channels into the luminal membrane of the principal cells of the collecting ducts. For example, lithium, used in the treatment of manic-depressive psychosis (Chapter 362), commonly causes polyuria, which can be quite severe. Demeclocycline, a tetracycline now rarely used in dermatologic conditions, also causes nephrogenic diabetes insipidus and is used to treat SIADH that cannot be controlled by water restriction.

Clinically, polyuria, which may be massive, is the hallmark of the disease. Although polyuria itself is not deleterious to health, it is a nuisance if the patient passes more than 6 or 7 liters of urine daily. It can be dangerous, however, if the thirst mechanism is depressed and hyperosmolarity supervenes. Repeated hyperosmolar episodes in such patients frequently lead to irreversible brain damage. If present from childhood, diabetes insipidus frequently leads to massive dilatation of the renal pelvis, ureters, and bladder.

OSMOTIC DIURESIS

Large volumes of urine can be excreted in the presence of large amounts of a poorly reabsorbed solute, most commonly glucose. For example, when the blood sugar concentration rises above the capacity of the kidney to reabsorb all of the filtered glucose, a large volume of glycosuria results. In fact, polyuria and polydipsia are the most common presenting features of diabetes mellitus (Chapter 210).

The more blood that flows through the medulla, the less concentrated it becomes. In some clinical situations, such as intravascular volume expansion and osmotic diuresis, medullary blood flow increases, thereby leading to a washout of the medullary gradient. Osmotic diuretics also impair water reabsorption at the collecting duct.

Osmotic diuresis also occurs after the relief of obstruction to the urinary tract. In this situation, the principal osmotic agent is urea, although other retained solutes also play a role in diuresis.

As the number of functioning nephrons is gradually reduced in renal failure, the amount of solutes added is also reduced; hence the inability to concentrate the urine, manifesting as nocturia and polyuria, is an early sign of renal failure. Direct damage to medullary tubules can also decrease the reabsorption of salt, particularly with tubulointerstitial kidney diseases (Chapter 108), such as analgesic nephropathy and sickle cell disease.

TREATMENT

The clinical manifestations and treatment of polyuria should address its underlying causes (Fig. 206-2). Depending on the nature of fluid intake and medication used at the onset of polyuria, a significant percentage of polyuric patients will have alterations in plasma sodium and volume, so treatment must also address these accompanying fluid and electrolyte abnormalities.

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103 POTASSIUM DISORDERS

JULIAN LAWRENCE SEIFTER

DEFINITION

Maintenance of a normal and narrow range of blood plasma potassium concentration, $[K^+]$, usually on the order of 3.5 to 5.0 mmol/L, is vital for health. *Hyperkalemia* refers to an increased plasma $[K^+]$, and *hypokalemia* to a decreased plasma $[K^+]$. Within the human body, K^+ is not equally distributed in the total body water. Approximately two thirds of body water is intracellular, and K^+ is the major cation within that compartment, reaching concentrations as high as 140 mEq/L. Consequently, more than 98% of K^+ resides within cells. An *excess* of total body K^+ stores is less common than K^+ *depletion* unless renal function is compromised. K^+ *adaptation* defines changes in regulatory mechanisms resulting from K^+ excesses or deficits.

EPIDEMIOLOGY

Because K^+ is widely distributed in both plant and animal dietary sources, avoiding K^+ is difficult in the well-fed state. As a result, a healthy person on a regular diet is likely to require high rates of urinary K^+ losses, primarily by secretion in the cortical distal nephron, to prevent hyperkalemia. The ready availability of potassium in the diet also makes hypokalemia uncommon, unless excessive potassium is lost in gastrointestinal or renal body fluids. The kidney must be able both to eliminate and at other times conserve large amounts of potassium.

Disorders of K^+ balance are common in both inpatient and outpatient settings. Diets high in K^+ and low in Na^+ are associated with lower blood pressure and decrease the risk of cardiovascular disease, including stroke and chronic kidney disease. Mild decreases in plasma $[K^+]$ are seen in healthy well-trained athletes and during normal pregnancy. Patients with chronic kidney disease (Chapter 116) and insulin-deficient diabetes (Chapters 109 and 210) have a tendency to develop hyperkalemia with high-K^+ diets or treatment with medications that interfere with the renin-angiotensin-aldosterone system.[1] Starvation, gastrointestinal disease, commonly used diuretics, and other medications may cause hypokalemia. Some renal disorders, such as tubular interstitial diseases and urinary tract obstruction, may be associated with hyperkalemia, whereas others, particularly if associated with Fanconi syndrome, result in hypokalemia. Some endocrine diseases, including adrenal insufficiency (Chapter 208), characteristically cause hyperkalemia, whereas hypokalemia is a common finding in patients who have hyperaldosteronism or tumors with ectopic secretion of adrenocorticotropic hormone (ACTH; Chapter 208).

Polyuric states may lead to K^+ depletion due to increased urinary flow rates over a period of time. However, chronic hypokalemia is itself a cause of polyuric nephrogenic diabetes insipidus (Chapter 102).

PATHOBIOLOGY

Potassium Balance

Most cells express sodium-potassium adenosine triphosphatase (Na^+, K^+-ATPase) on the cell plasma membranes and thereby use metabolic energy in the form of ATP to develop gradients of Na^+ and K^+. As a result, cellular $[K^+]$ may exceed extracellular concentrations 35-fold. These established electrochemical gradients enable normal muscle and neural function, as well as transcellular solute transport in intestinal and renal epithelia. K^+ entry into cells is balanced by extrusion by K^+ channels and transporters in a regulated and coordinated fashion.

The total body amount of K^+ is usually on the order of 50 mmol/kg of body weight, so a 70-kg individual has a store of about 3500 mmol of K^+, mostly in skeletal muscle. The potassium content of the total extracellular fluid is about 56 mmol, which may approximate the potassium content of a single meal. After a meal containing an 8-ounce steak, baked potato, 1 serving of spinach, and an 8-ounce glass of tomato juice, the plasma $[K^+]$ might rise to 9.25 mmol/L, a likely fatal value, if it were not for the ability of potassium to distribute within minutes from the extracellular space to the intracellular space. The intracellular space, given its large volume and potassium content, can accommodate, or buffer, an extra load of potassium without significant changes in the plasma or cellular $[K^+]$. In contrast without the shift, K^+ would rise greatly in the extracellular fluid, and the large change in ratio would electrically cause serious arrhythmias. Fortunately, carbohydrate and amino acids in a meal increase the secretion of insulin, which increases the shifting of K^+ into cells. Within hours, renal elimination of potassium matches the dietary intake.

Discordance between total body stores and the plasma $[K^+]$, owing to shifts between the intracellular and extracellular compartments, is the reason why total body potassium is poorly reflected by the plasma potassium concentration. Hyperkalemia may occur despite total body K^+ depletion (e.g., diabetic ketoacidosis with an osmotic diuresis causing urinary losses of Na^+ and K^+, a depletion in extracellular volume, and acute kidney injury), and hypokalemia may occur despite total body K^+ excess (e.g., acute diarrhea in a patient who has chronic kidney disease).

The Importance of Potassium

Potassium is essential for a number of critical body functions, including enzymatic reactions that regulate protein and glycogen synthesis, as well as cell growth and division. Within the normal dietary range, a higher intake of potassium and a lower intake of sodium are associated with a lower cardiovascular risk.[2]

The ability of cells to take up or to extrude potassium contributes to the regulation of cell volume during periods of osmotic stress. Because of the relative magnitudes of cellular and extracellular concentrations, larger percentage changes tend to occur in the extracellular potassium concentration, which consequently has the greatest impact on the electrical properties across cell membranes. In excitable cells, such as cardiac myocytes and skeletal muscle, the relationship of intracellular to extracellular potassium concentration contributes to the resting membrane potential. Hypokalemia hyperpolarizes these cells and decreases potassium conductance in some potassium channels required for repolarization (Chapter 48).

The increased potassium conductance in hyperkalemia antagonizes the normal slow depolarization and decrease in potassium conductance of pacemaker tissue, thereby making sinus bradycardia a common first sign of hyperkalemia. Certain muscle-depolarizing anesthetic agents, such as succinylcholine, may potentiate the effects of hyperkalemia.

Potassium is as important a body fluid osmole as sodium. Potassium losses, extracellular volume depletion, increased intake of water, and retained medullary urinary concentrating ability each contribute to thiazide diuretic–induced hyponatremia (Chapter 102). Summative iso-osmotic losses of potassium and sodium salts in watery diarrhea (Chapter 126) may result in isotonic extracellular volume depletion. Similarly, if potassium chloride is added to isotonic saline, the resultant hypertonic solution causes potassium to enter cells as sodium exits, thereby contributing to hypernatremia.

Potassium is also an important local mediator of vascular tone in muscle beds. During exercise, local interstitial fluid potassium concentrations may rise several-fold, thereby causing local vasodilation to allow more blood supply to the exercising muscle, but also resulting in sarcolemmal depolarization that creates muscle fatigue. Very little of that local tissue potassium enters the total extracellular fluid, so severe hyperkalemia does not usually occur with exercise. The trained athlete develops an adaptive increase in Na^+, K^+-ATPase to allow efficient reuptake of potassium into muscle cells but still may have chronically low plasma $[K^+]$ or postexertional hypokalemia. Experienced marathoners know that their diet must provide adequate potassium stores needed for muscle endurance because overexertion during a state of potassium depletion can lead to rhabdomyolysis (Chapter 99).

Potassium excretion follows a circadian rhythm. This rhythm appears to include an intestinal feed-forward sensing mechanism that results in the highest level of urinary potassium excretion coinciding with the anticipated dietary intake of potassium. The relationship likely involves potassium sensing within the gastrointestinal tract or splanchnic or hepatic circulation. In healthy humans, potassium excretion is greatest during the daytime hours but can increase several-fold after a meal without requiring a noticeable change in the blood potassium level. Independent of aldosterone, a direct relationship between increased potassium and sodium excretion may account for the beneficial association of high-potassium diets with lower blood pressures. Additionally, increased dietary potassium may restore a nocturnal dip in blood pressure, thereby potentially reducing cardiac risk in hypertensive patients. The distribution of potassium between the extracellular and intracellular spaces shows a circadian variation that may contribute to the diurnal variance in cardiac arrhythmias and sudden death in patients at risk.

ABSTRACT

Potassium is ubiquitous in animal and plant cells, where it subserves critical electrophysiologic roles in excitable cells and transport functions in epithelial cells. Functions such as growth, protein synthesis, and osmotic survival require adequate potassium. There must be intact food sources of K^+ and a high capacity to eliminate K^+ from the body (external balance). Since more than 98% of K^+ lies within the intracellular space, there must be effective mechanisms to buffer dietary loads of K^+ within cells (internal balance) while the slower excretory processes achieve balance. This chapter discusses the normal pathways of K^+ handling by the renal epithelial cells in states of both depletion and excess of K^+. Mechanisms of reabsorption and secretion are considered, with emphasis given to the distal nephron's regulation of K^+ handling, including the roles of urinary flow rates and of secretory and reabsorptive channels and pumps depending on metabolic energy. Interconnections with acid-base disorders, salt, and osmotic balance are also discussed. Syndromes associated with hypertension or hypotension, acidosis or alkalosis are reviewed, as are hormonal, acquired, toxic, environmental, and genetic disorders. The consequences and physiologic management of hyperkalemia and hypokalemia are also reviewed.

KEYWORDS

hyperkalemia
hypokalemia
alkalosis
acidosis
aldosterone
diabetes mellitus

Renal Potassium Handling

In the kidney, potassium excretion begins with filtration. Because the extracellular concentration of potassium is approximately 4 mmol/L and that of sodium is 140 mmol/L, far less potassium is filtered than sodium. The renal proximal tubule reabsorbs potassium, primarily by the paracellular pathway, in the process of reabsorbing sodium and water. In the thick ascending limb of the loop of Henle, potassium is reabsorbed both by the apical sodium–potassium–2 chloride cotransporter (NKCC2) and, like calcium and magnesium, by paracellular reabsorption of the cation. The latter mechanism is a consequence of the development of an electropositive lumen that is created by the recycling of K^+ to the lumen through renal outer medullary potassium channels (ROMK) in the thick ascending limb of the loop of Henle. Barrter syndrome (Chapter 113) stems from loss-of-function mutations either in the NKCC2, ROMK, or in the chloride channel.

Potassium is neither appreciably reabsorbed nor secreted by the early distal convoluted tubular cells. Potassium that is reabsorbed downstream into the medullary collecting duct interstitium re-enters the tubular fluid by secretion into the thin descending limb in a process known as medullary potassium recycling. This decreased lumen-to-interstitial-fluid gradient facilitates high potassium excretion from the medullary collecting duct when required.

Luminal ammonium (NH_4^+) can substitute for potassium on the thick limb NKCC2; the resulting increase in medullary interstitial fluid NH_4^+ concentrations enhances medullary collecting duct net acid excretion. In hyperkalemic states, less NH_4^+ appears in the urine because the high concentration of luminal potassium competes with NH_4^+ for reabsorption in the thick limb. As a consequence, metabolic acidosis may develop in hyperkalemic states, and lowering of elevated plasma potassium levels helps treat acidosis.

In hypokalemia, whether through proximal tubule intracellular acidosis or other mechanisms, glutaminase enzymes are increased and more ammonia is produced. This ammonia leads to greater medullary interstitial fluid concentrations and therefore to enhanced net acid elimination. Ammonium production in hypokalemia allows potassium reabsorption to continue as cationic NH_4^+ accompanies excreted anions into the urine. The increase in ammonia production may have a deleterious effect in that it may contribute to the chronic tubulointerstitial nephritis of chronic hypokalemia.

By the time the tubular fluid reaches the distal tubule and collecting duct, more than 90% of filtered potassium and sodium has been reabsorbed. The absolute amount of sodium that needs to be reabsorbed far exceeds the amount of potassium that needs to be excreted. Therefore, the basolateral mechanism for potassium reabsorption is required to avoid potassium depletion. In potassium depletion, an increase in the apical membrane hydrogen-potassium ATPase (H^+, K^+-ATPase) of the collecting duct intercalated cell allows additional reabsorption of potassium from the urine. This process may sustain a metabolic alkalosis. It is unusual to see potassium concentrations in the urine lower than 5 to 10 mmol/L. In contrast, when dietary potassium is abundant, the reabsorption of 90% of filtered potassium by the proximal and distal nephron is followed by net potassium secretion in the collecting duct.

The secretion of potassium in the cortical collecting duct (E-Fig. 103-1), which may vary according to need by as much as 400%, is controlled by three major mechanisms: (1) apical membrane depolarization due to Na^+ current through epithelial Na^+ channels (ENaC) supporting K^+ secretion across the apical membrane; (2) regulated apical membrane secretory potassium channels; and (3) tubular fluid flow dependency. The urinary potassium most closely reflects potassium secreted by the distal nephron.

Early Sodium Reabsorption

The traditional view of regulating potassium secretion and therefore excretion has focused on the central role of aldosterone, the steroid hormone synthesized and secreted by the zona glomerulosa of the adrenal cortex. The renal effects of aldosterone show overlap of functions to conserve sodium and to eliminate potassium. Aldosterone is stimulated by angiotensin II in hyperreninemic states and independently by dietary potassium loading. In what has been called the *aldosterone paradox*, undesired losses of potassium are prevented when sodium retention (e.g., via the angiotensin II stimulus) is required to maintain extracellular volume. Conversely, undesired retention of sodium is prevented when potassium loading alone provides the stimulus to aldosterone secretion. The negative feedback that couples aldosterone with serum potassium is fundamental in potassium regulation. Hyperaldosteronism results in potassium loss, whereas hypokalemia reduces aldosterone production. Hyperkalemia stimulates aldosterone release, thereby facilitating urinary potassium.

The major site for potassium secretion resides in the aldosterone-sensitive distal nephron, which is composed primarily of the principal cells of the connecting tubule and the cortical collecting duct. Aldosterone regulates sodium reabsorption by the apical epithelial sodium channel. The reabsorption of sodium is dependent on the low intracellular sodium concentrations that result from the energy-requiring Na^+, K^+-ATPase on the basolateral membrane. Both increased intracellular Na^+ and extracellular K^+ stimulate the Na^+, K^+-ATPase.

To optimize potassium secretion, sodium must be delivered in ample amounts (depending on the flow rate and sodium concentration of the tubular fluid) to result in sodium reabsorption through the apical epithelial sodium channel in the cortical collecting duct cells. If sodium delivery is not limiting, reabsorption of the sodium cation creates a lumen-negative transepithelial potential difference. Aldosterone affects this transepithelial potential difference in several ways. The intracellular mineralocorticoid receptor functions to increase the activity and density of the epithelial sodium channel and of basolateral Na^+, K^+-ATPase enzymes. Cortisol, which is normally present in higher concentrations than aldosterone, has equal affinity for the aldosterone receptor and therefore could lead to increased epithelial sodium channel activity. However, the enzyme 11β-hydroxysteroid dehydrogenase type 2 is present in the principal cells and converts cortisol to inactive cortisone.

Role of Potassium Secretory Channels and Tubular Flow Rate

Potassium secretion requires adequate function of several types of potassium secretory channels on the luminal membranes of distal nephron cells. Two predominant potassium channels are present in the apical membranes of the collecting duct cells. The renal outer medullary potassium channel (ROMK), which is located on the apical membrane of the principal cell in the connecting tubule and cortical collecting duct, is aldosterone sensitive, is increased by dietary potassium loads, and likely subserves constitutive K^+ secretion under basal conditions. ROMK undergoes new synthesis and increased cycling to the apical membrane under the control of aldosterone. The principal cell also mediates vasopressin-responsive water reabsorption. Factors regulating ROMK channels include antidiuretic hormone (ADH) and intracellular pH. The increase in ROMK channel activity in response to ADH, combined with an ADH effect to increase epithelial sodium channel and osmotic water flow, allows the highest possible potassium concentration in the urine with the low tubular flow that accompanies antidiuresis. When ADH is suppressed, luminal potassium concentrations are lower, thereby favoring gradients for potassium secretion, but low ADH levels also suppress ROMK activity, thereby allowing independence of the regulation and the excretion of water and K^+. Cellular acidification inhibits potassium secretion through an effect on ROMK, thereby providing a renal mechanism for decreased electrogenic potassium secretion when proton secretion is necessary during metabolic and respiratory acidoses. In alkalosis, ROMK activity is increased, thereby favoring increased potassium secretion, but the result may be significant potassium loss.

Additional potassium channels, known as maxi-K or big-K channels, are prominent in the principal cells and intercalated cells of the cortical collecting duct, as the intercalated cell also has a role in potassium secretion. The big-K channels are highly regulated by tubular fluid flow rate. One mechanism by which flow rate influences this potassium secretory channel is by the deformation of the primary cilium of the principal cell, which leads to a secondary increase in cellular calcium that has both direct and indirect effects to enhance BK potassium secretion.

Excretion Mechanisms and Normal Function

Thiazide-sensitive NaCl cotransport is independent of aldosterone in the early distal convoluted tubule but is inhibited by sensors in those cells related to high potassium intake, gastrointestinal feed-forward sensing mechanisms, and clock genes associated with the circadian rhythm for potassium excretion. Decreased sodium reabsorption in the early distal convoluted tubule will increase delivery of sodium and water to the downstream aldosterone-sensitive distal nephron. Then, in response to increased plasma potassium-stimulated aldosterone release, the epithelial sodium channel is increased, thereby leading to greater potassium secretion. A network of protein kinases, including the "with no lysine" or WNK kinases, is central to regulated early distal convoluted tubule NaCl cotransporter function and the epithelial sodium channel. When the early aldosterone-insensitive distal convoluted tubule basolateral sensors detect a small drop in blood $[K^+]$ during saline expansion, a regulatory "switch" provides crosstalk to the apical side in the form of phosphorylations, which activate NaCl cotransport and thereby increase the reabsorption of Na^+ in the distal convoluted tubule. The decreased delivery of Na^+ to the common

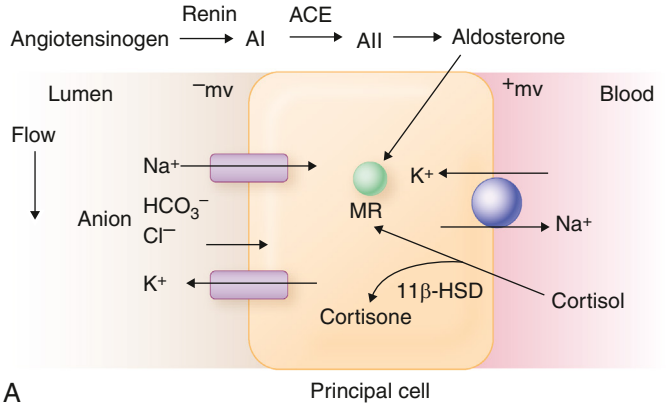

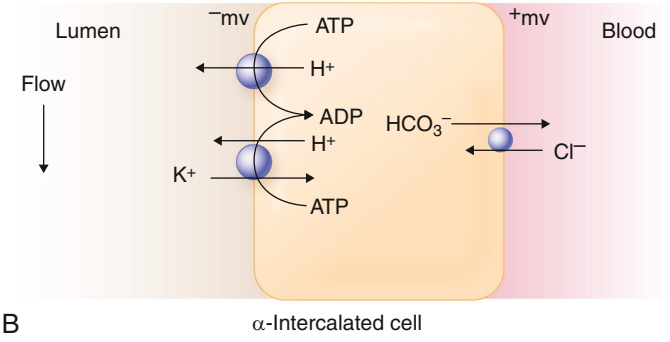

E-FIGURE 103-1. **Two cell types in the cortical collecting duct. A,** The principal cells mediate sodium (Na^+) reabsorption energized by the basolateral Na^+, K^+ pump. Entry from the lumen is through the epithelial Na^+ channel (ENaC), which renders the lumen negatively charged ($^-$mv). This transepithelial voltage stimulates secretion of potassium (K^+) through renal outer medullary potassium (ROMK) channels. Reabsorbable anions such as chloride (Cl^-) lessen the luminal negativity and decrease K^+ secretion. Bicarbonate (HCO_3^-) has an effect to increase K^+ secretion. High flow rates increase net K^+ secretion by activating maxi-K or big-K channels and by preventing development of high K^+ concentrations in the lumen. The effects of the renin-angiotensin-aldosterone axis are shown: increased mineralocorticoid receptor (MR) activation increases ENaC, the Na^+, K^+ pump, and K^+ channels, thereby increasing Na^+ reabsorption and K^+ secretion. Cortisol would also increase MR activity, but it is inactivated by the enzyme 11β-hydroxysteroid dehydrogenase (11β-HSD). AI = angiotensin I; AII = angiotensin II; ACE = angiotensin-converting enzyme; mv = millivolts. **B,** Intercalated cells are carbonic anhydrase–rich cells that secrete acid and reabsorb HCO_3^-. The H^+-ATPase secretes H^+ in a way favored by the negatively charged lumen in conjunction with the aldosterone-stimulated effect on Na^+ reabsorption in neighboring principal cells. The K^+, H^+-ATPase is an electroneutral pump. The K^+/H^+ exchanger, reabsorbing K^+, is important in states of K^+ depletion when urinary K^+ is decreased. Intercalated cells also have apical big-K channels, indicating a role in K^+ secretion. ADP = adenosine diphosphate; ATP = adenosine triphosphate.

collecting duct leads to less K^+ secretion. If the regulation of NaCl cotransport is incremental, the mechanism controlling NaCl reabsorption through the NaCl cotransporter and downstream K^+ secretion performs as a rheostat.

In states of avid sodium reabsorption, including hypovolemic states, hepatorenal syndrome (Chapter 139), and severe heart failure (Chapter 45), sodium delivery from more proximal sites may become the rate-limiting step for potassium secretion. In hypovolemia, sodium reabsorption is increased by angiotensin II in the proximal tubule, the early and late distal convoluted tubule, and the connecting tubule so that very little sodium is delivered to the principal cells of the cortical collecting duct. Potassium losses are diminished because of this decreased delivery of sodium, and an angiotensin II–induced switch involving WNK kinases decreases ROMK activity. Although aldosterone will still activate principal cell epithelial sodium channels, the decrease in sodium delivery and decreased potassium secretion (favoring chloride reabsorption instead) will allow greater NaCl reabsorption while limiting potassium loss. Sodium delivery may be increased by decreased angiotensin II during extracellular volume expansion, but the low aldosterone limits potassium losses.

Internal Potassium Balance and Associated Disorders

Because of the delay in hours before renal excretion matches dietary intake and because potassium first enters the extracellular fluid from the gastrointestinal tract, it is critical that the process of cellular buffering be effective (Table 103-1).[3] Essentially, increases in postprandial blood potassium are minimized before potassium is eliminated from the body. A major factor in this regulation after meals is the feedback loop involving insulin and potassium. An increase in serum potassium stimulates insulin release from the β-cells of the pancreatic islets. Insulin increases potassium uptake into cells, primarily muscle, independent of its effect on glucose uptake. Acutely, potassium uptake is chiefly the result of increased Na^+, K^+-ATPase activity, whereas chronically there is increased abundance in the plasma membranes in these cells.

Another important mechanism of regulating the distribution of potassium between extracellular and cellular spaces involves the sympathoadrenal system. β-Adrenergic activation, particularly through the β_2-receptor, increases potassium uptake into muscle and fat cells. As with insulin, potassium uptake is the consequence of increased Na^+, K^+-ATPase activity associated with increased intracellular cyclic adenosine monophosphate. The adrenergic effect is important in regulating the serum potassium concentration during exercise and is independent of the additional effect that catecholamines may have on blood glucose with the expected increases in insulin. In the trained athlete, a chronic increase in Na^+, K^+-ATPase on cell membranes may cause a transient lowering of the serum potassium concentration after exertion. By the same mechanism, a severe stress may contribute to hypokalemia, through both direct β_2 effects and insulin action secondary to the blood glucose rise.

Phenylephrine, an α-adrenergic agonist, increases serum potassium. Importantly, epinephrine, which also has α-adrenergic effects, is associated with a transient increase in potassium release from the liver before a more prolonged period of decreased serum potassium mediated by the β_2-receptor.

Metabolic acidosis raises the potassium level more than does respiratory acidosis; both metabolic alkalosis and respiratory alkalosis lower the potassium level. Anion gap acidosis does not raise the potassium level, probably because of the movement of the organic anion (e.g., lactate) from cells into the extracellular space with an accompanying proton. In contrast, the ingestion of chloride salts has the most profound effect on the potassium level because chloride concentration increases in the extracellular space. In hyperchloremic acidosis, chloride enters into cells through chloride-bicarbonate exchange and recycles back into the extracellular space in cotransport with potassium. The ingestion of excessive chloride salts of arginine and lysine is associated with hyperkalemic acidosis. ε-Aminocaproic acid has also been associated with hyperkalemia and is hypothesized to exchange for cellular potassium, much like the other cationic amino acids.

Just as a single blood pH measurement can reflect mixed acid-base disturbances, many processes that affect the net potassium concentration can coexist. Metabolic acidosis may be associated with diarrheal or urinary losses of potassium that are sufficient to result in hypokalemia. Metabolic acidosis in diabetes can also be associated with insulin deficiency and renal failure, and it can cause hyperkalemia despite osmotically driven urinary losses of potassium and total body potassium depletion.

Other hormonal effects on potassium include thyroid and growth hormone, but patients with disorders of these hormones do not usually have significant changes in their blood potassium levels. Some patients with hyperthyroidism may have mild hypokalemia, perhaps related to increased sympathetic activity. Growth states are associated with a greater need for potassium; for example, in normal pregnancy, the maternal potassium concentration may fall as the developing fetus grows.

Hypomagnesemia frequently accompanies hypokalemia. Both magnesium and potassium are found predominantly in cells, but the Na^+, K^+-ATPase requires magnesium to function. If magnesium is deficient, potassium distributes more to the extracellular fluid, thereby masking the degree of potassium deficiency. Moreover, magnesium deficiency leads to increased activity of renal potassium secretory channels, so potassium depletion is difficult to correct until magnesium is repleted.

TABLE 103-1 FACTORS REGULATING INTERNAL POTASSIUM BALANCE

Circadian rhythm
Insulin
β-Adrenergic activity
Acid-base balance
Magnesium
Aldosterone
Osmolality
Thyroid hormone
Extracellular potassium
Intracellular sodium

External Potassium Balance and Associated Disorders

Normally, no more than 10 to 20% of total potassium excretion is accomplished by the gastrointestinal tract, but colonic excretion is increased in renal failure, primarily through potassium-induced increases in epithelial Na^+, K^+-ATPase activity and aldosterone. In renal failure, the normal mechanisms to distribute potassium acquire increased importance.

Some conditions that cause the greatest losses of gastrointestinal potassium include secretory diarrheas of the colon, the result of infection or laxative abuse. Disorders of the small intestine, which may lead to large quantities of liquid stool with a low potassium concentration, engender favorable gradients for marked potassium secretion by the colon. A syndrome of watery diarrhea and hypokalemia is associated with neuroendocrine tumors (Chapter 213) that secrete vasoactive intestinal peptide. Rectosigmoid secretion of potassium may result in particularly high potassium losses, and potassium deficiency is seen in patients who have ureterosigmoidostomies. Potassium can be lost from a variety of other sources, including excess sweat or salivation.

Potassium can also be depleted by vomiting or diarrhea. In gastric alkalosis, the loss of potassium is in the urine. In renal tubular disorders, urinary losses may exceed intake when excessive quantities of osmotic or anionic products are excreted in the urine, or in patients who take diuretics.

Patients with pernicious anemia who receive vitamin B_{12} to stimulate erythropoiesis may deplete extracellular potassium and suffer from hypokalemia as a cost of producing new red blood cells. Leukemias with rapid growth rates (Chapter 168) also may cause a drop in the serum potassium level, and some forms of myelogenous leukemia are associated with a high level of lysozyme, which leads to urinary potassium loss.

It is unusual for hyperkalemia to be caused by excessive potassium intake unless the patient has renal dysfunction. However, in patients who have brisk hemolysis, internal hemorrhage, or rhabdomyolysis, particularly if the hemoglobinuria or myoglobinuria also results in acute kidney injury, life-threatening hyperkalemia can quickly develop by the rapid release of cellular potassium stores.

CLINICAL MANIFESTATIONS

Hypokalemia

Clinical manifestations of potassium depletion include hypertension, decreased growth, and muscle symptoms such as weakness, cramps, fasciculations, and even paralysis. In severe cases, the diaphragm may be paralyzed, leading to respiratory failure. Cardiac arrhythmias are a critical component of low potassium states and are usually seen when the serum potassium falls below 3 mmol/L or when ischemia, hypercalcemia, or drugs such as digoxin are simultaneously present. A patient who has a chronically low potassium level (e.g., from diuretic use) may be particularly vulnerable to supraventricular and ventricular tachyarrhythmias during periods of stress, such as head trauma, or during acute coronary syndrome,[4] to which cardiac ischemia also contributes. The prolonged cardiac repolarization phase of hypokalemia accounts for the characteristic electrocardiographic findings of broad, flattened T waves.

U waves are also indicative of this delay in repolarization (Fig. 103-1). In the intestine, hypokalemia may result in paralytic ileus, which may interfere with oral replacement.

In addition to these systemic effects of potassium imbalance, the kidney is particularly sensitive to depletion of potassium. Structural changes in the glomeruli and tubules lead to a decreased glomerular filtration rate, increased proximal tubule ammoniagenesis, increased sodium bicarbonate reabsorption, and net acid excretion, thereby causing and maintaining metabolic alkalosis. A condition of nephrogenic diabetes insipidus results when potassium depletion decreases expression of vasopressin-dependent water channels (aquaporin 2) in the collecting duct luminal plasma membranes. Hypokalemia diminishes insulin secretion and may be associated with glucose intolerance.

Hyperkalemia

Hyperkalemia can be a life-threatening emergency, especially if it develops rapidly. The depolarizing effect on the resting membrane potential and increased potassium channel conductance lead to the classic electrocardiographic changes of hyperacute peaked T waves associated with rapid repolarization (Fig. 103-2). Hyperkalemia commonly results in sinus bradycardia. Heart block, loss of P waves on the electrocardiogram, and prolonged QRS intervals are all seen in cases of severe hyperkalemia, usually in excess of 6 mmol/L. Although deep learning algorithms suggest that the electrocardiogram can be used to screen for hyperkalemia,[5] a standard reading of the electrocardiogram is not a sensitive indicator of severe hyperkalemia, and cardiac arrest may occur without clinical warning. Like hypokalemia, severe hyperkalemia can cause skeletal muscle paralysis; unlike hypokalemic paralysis, it is often ascending in nature.

DIAGNOSIS

The first clue to a disorder in potassium balance usually is an abnormal serum potassium concentration obtained as part of a laboratory evaluation, not because an abnormal potassium level itself is suspected. When the potassium concentration is elevated above normal, it is imperative to exclude common artifacts, known as pseudohyperkalemia. Hemolysis in the test tube is a common artifact; in cases of cold-induced hemolysis (Chapter 147), it is important to collect the blood and to allow it to clot in a warm environment. Some patients have pseudohyperkalemia resulting from high platelet counts, usually in excess of 1 million/μL, or myelogenous leukemia (Chapter 170); in such cases, potassium is released during clot formation in the test tube. Measurement of the plasma potassium level will avoid these artifacts. The serum potassium level may sometimes be elevated because of local ischemia related to application of the tourniquet and clenching of the fist.

A detailed medical history should focus on medications, family history, and sources of potassium excess or loss. The physical examination should pay particular attention to blood pressure, extracellular volume status, heart rate and rhythm, and muscle strength and reflexes.

Laboratory testing should include a complete blood count as well as serum levels of sodium, chloride, bicarbonate, creatinine, and blood urea nitrogen. In more serious cases, arterial blood gases and levels of creatine kinase and magnesium should be obtained. A 12-lead electrocardiogram also should be performed. A urinary potassium excretion rate in a timed urine test is the best measure of K+ excretion. In a hypokalemic patient, a urinary potassium concentration higher than 30 mEq/L suggests renal potassium wasting, whereas extrarenal losses are usually reflected by concentrations lower than 20 mEq/L. In a state of potassium excess, urinary potassium excretion should exceed about 35 mEq/L, unless urinary underexcretion was the cause of the hyperkalemia. A high aldosterone level causes a high urinary potassium-to-sodium ratio, whereas hypoaldosteronism may cause the opposite. Because water reabsorption complicates interpretation of the urinary K^+ concentration, distinguishing urinary loss or retention of K^+ in a hypokalemic or hyperkalemic state can

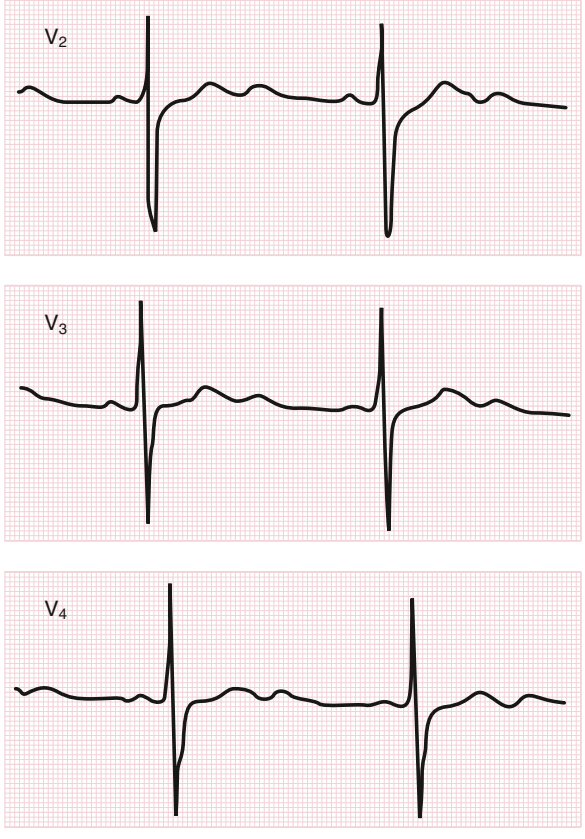

FIGURE 103-1. The electrocardiographic manifestations of hypokalemia. The serum potassium concentration was 2.2 mEq/L. The ST segment is prolonged, primarily because of a U wave following the T wave, and the T wave is flattened.

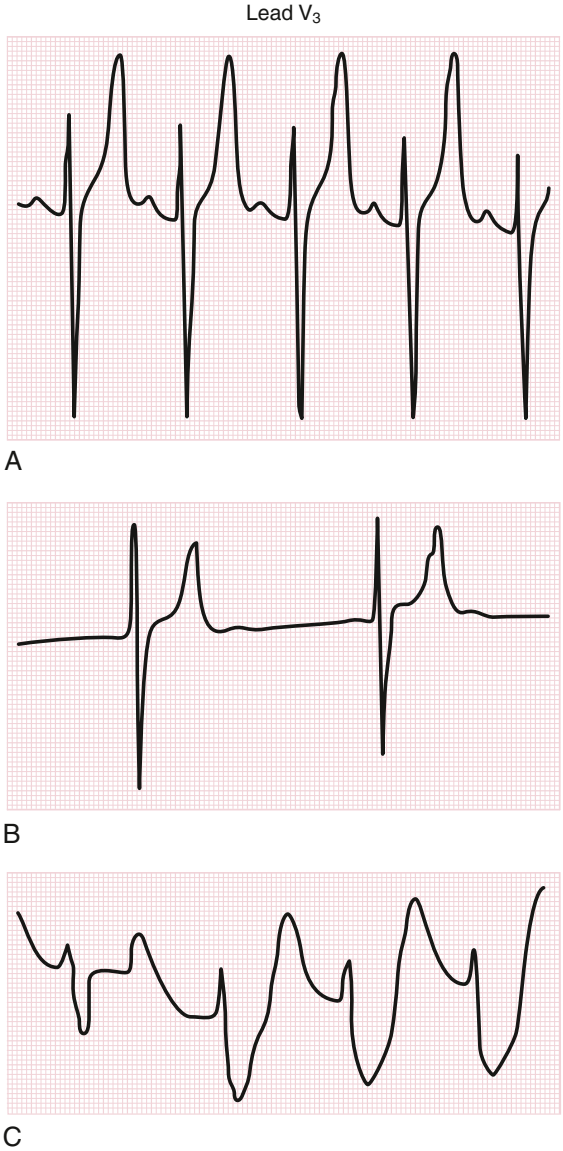

FIGURE 103-2. The effects of progressive hyperkalemia on the electrocardiogram. All of the illustrations are from lead V_3. **A**, Serum potassium concentration ($[K^+]$) = 6.8 mEq/L; note the peaked T waves together with normal sinus rhythm. **B**, Serum $[K^+]$ = 8.9 mEq/L; note the peaked T waves and absent P waves. **C**, Serum $[K^+]$ > 8.9 mEq/L; note the classic sine wave with absent P waves, marked prolongation of the QRS complex, and peaked T waves.

be made by measuring a urine [K^+]:[Cr] ratio using 15 to 20 mEq per gram of creatinine as a cutoff.

Hypokalemic Disorders

The most common cause of hypokalemia (Table 103-2) in medical practice is the use of thiazide or loop diuretics.[6] Patients may have low, normal, or high blood pressures, depending on their volume status and whether the diuretics were prescribed for hypertension or heart failure. The most common acute causes of hypokalemia are diarrhea and vomiting (Fig. 103-3).

Hypokalemic Hypertensive Syndromes

Evaluation of plasma renin and aldosterone levels can help distinguish among specific diagnoses (see Table 103-2). Primary hyperaldosteronism is associated with low renin levels due to volume expansion.[7] If it is corrected for plasma potassium, an aldosterone-to-renin ratio of 30:1 suggests a primary adrenal cortical tumor (aldosteronoma) or hyperplasia (Chapter 208). However, such ratios must be used with caution, and the absolute value of aldosterone is important, especially when the renin and aldosterone levels are both low.

More sensitive measurements of renin have led to the increased recognition of primary hyperaldosteronism (Chapter 208), especially due to microadenomas or increased clusters of adrenal zona glomerulosa cells. At early stages, signs may be absent or manifest only by salt sensitivity and systemic hypertension, whereas more advanced stages typically are associated with a full blown syndrome of hypertension, metabolic alkalosis, hypomagnesemia, and hypokalemia.

The tubular delivery of large amounts of sodium chloride in a setting of volume expansion and nonsuppressible aldosterone results in hypokalemia, which improves after sodium restriction and worsens with the administration of intravenous saline. In congenital adrenal hyperplasia (Chapter 208), such as 11β-hydroxylase deficiency, hypokalemic alkalosis is associated with excessive androgen production. In patients with renin-secreting tumors or unilateral renal artery stenosis, high renin levels stimulate angiotensin II and then aldosterone secretion, with a resulting increase in sodium reabsorption, hypertension, and hypokalemic metabolic alkalosis.

In some patients with overproduction of ACTH, as in ectopic production from lung and other malignant neoplasms (Chapter 164), cortisol may overwhelm the aldosterone receptor and result in hypertensive, hypokalemic alkalosis. The patient may not show signs of Cushing syndrome in the short term. In glucocorticoid-remediable aldosteronism, which is a familial disorder in which episodes of hypokalemia and hypertension develop, a chimeric gene duplication couples the ACTH-responsive 11β-hydroxylase promoter to the coding region of aldosterone synthase.

Glycyrrhizic acid, which is found in licorice and anisette, inhibits the renal enzyme 11β-hydroxysteroid dehydrogenase and thereby causes hypokalemia, metabolic alkalosis, and hypertension. A rare genetic disorder known as apparent mineralocorticoid excess syndrome produces the same effect due to deficiency of 11β-hydroxysteroid dehydrogenase. The syndrome produces a high ratio of cortisol to cortisone; as a result, renin and aldosterone are suppressed by the volume expansion. Hypokalemia may be precipitated by ACTH stimulation of cortisol.

Activating mutations of ENaC cause increased sodium reabsorption (Liddle syndrome; Chapter 113). The syndrome can be distinguished from primary or secondary hyperaldosteronism by suppressed renin and aldosterone levels (see also Fig. 103-3 for an approach to the patient with hypokalemia and metabolic alkalosis).

Hypokalemic Hypotensive Syndromes

In contrast to the hypokalemic hypertensive syndromes, in which increased sodium reabsorption is a primary event, many hypokalemic alkaloses are associated with extracellular volume depletion. With a physiologic response to volume depletion, the potassium losses may be a result of appropriate sodium reabsorption; signs of hypotension or extracellular volume depletion will be observed. Secretory diarrheas, whether associated with hypochloremic alkalosis or hyperchloremic acidosis, lead to extracellular volume depletion and secondary increases in renin and aldosterone; the result is both gastrointestinal and urinary potassium losses. The urinary losses in alkalosis (e.g., vomiting or other chloride-wasting syndromes) result in greater degrees of potassium depletion because of the early bicarbonaturia and volume contraction.

Diuretic use, Bartter syndrome (Chapter 113), and Gitelman syndrome (Chapter 113) are renal tubular causes of extracellular volume depletion, hypotension, and hypokalemic, hypochloremic alkalosis; sodium and chloride are lost in the urine, and secondary rises in renin and aldosterone occur. Increased urinary flow rates are important contributors to the increased potassium losses in each of these examples. Bartter syndrome affects the function of the thick ascending limb through mutations in NKCC2 or in potassium or chloride channels, whereas Gitelman syndrome is characterized by inactivating mutations or dysregulation of the NaCl cotransporter in the distal tubule. The hypokalemia in Gitelman syndrome may be caused by secondary hyperaldosteronism, bicarbonaturia, and hypomagnesemia.

Classic type 1 distal renal tubular acidosis (Chapters 104 and 113) is often associated with hypokalemia, which may improve with correction of the acidemia. In contrast, proximal renal tubular acidosis, when it is corrected with bicarbonate, often results in worsening of the hypokalemia because of greater bicarbonate wasting associated with increases in the filtered bicarbonate load.

Acetazolamide, when it is given to an alkalotic patient, is a particularly potent kaliuretic agent. Volume depletion and hyperaldosteronism contribute to the potassium losses, as does the bicarbonate wasting, which appears to have a direct effect on potassium secretion.

Tubular toxins that may be associated with severe potassium losses include aminoglycosides, cisplatin, and ifosfamide. Amphotericin B results in significant potassium wasting accompanied by renal tubular acidosis. In many of these

TABLE 103-2 CAUSES OF HYPOKALEMIA AND INCREASED POTASSIUM EXCRETION

CAUSES OF INCREASED K^+ EXCRETION AND HYPOKALEMIA	RENIN	ALDOSTERONE	EXTRACELLULAR VOLUME OR BLOOD PRESSURE	ACID-BASE STATUS
Increased ENaC: Liddle syndrome	Low	Low	High	Alkalosis
Decreased β-hydroxysteroid dehydrogenase: apparent mineralocorticoid excess, licorice	Low	Low	High	Alkalosis
Adrenal tumor or hyperplasia	Low	High	High	Alkalosis
Ectopic ACTH: Cushing syndrome	Low	Low	High	Alkalosis
Congenital adrenal hyperplasia	Low	High	High	Alkalosis
Unilateral renal artery stenosis	High	High	High	Alkalosis
Renin-secreting tumor	High	High	High	Alkalosis
Diuretics				
Thiazides	High	High	Low	Alkalosis
Furosemide	High	High	Low	Alkalosis
Acetazolamide	High	High	Variable	Acidosis
Bartter syndrome	High	High	Low	Alkalosis
Gitelman syndrome	High	High	Low	Alkalosis
Fanconi syndrome	High	High	Low	Acidosis
Distal RTA	High	High	Low	Acidosis

ACTH = adrenocorticotropic hormone; ENaC = epithelial Na^+ channel; RTA = renal tubular acidosis.

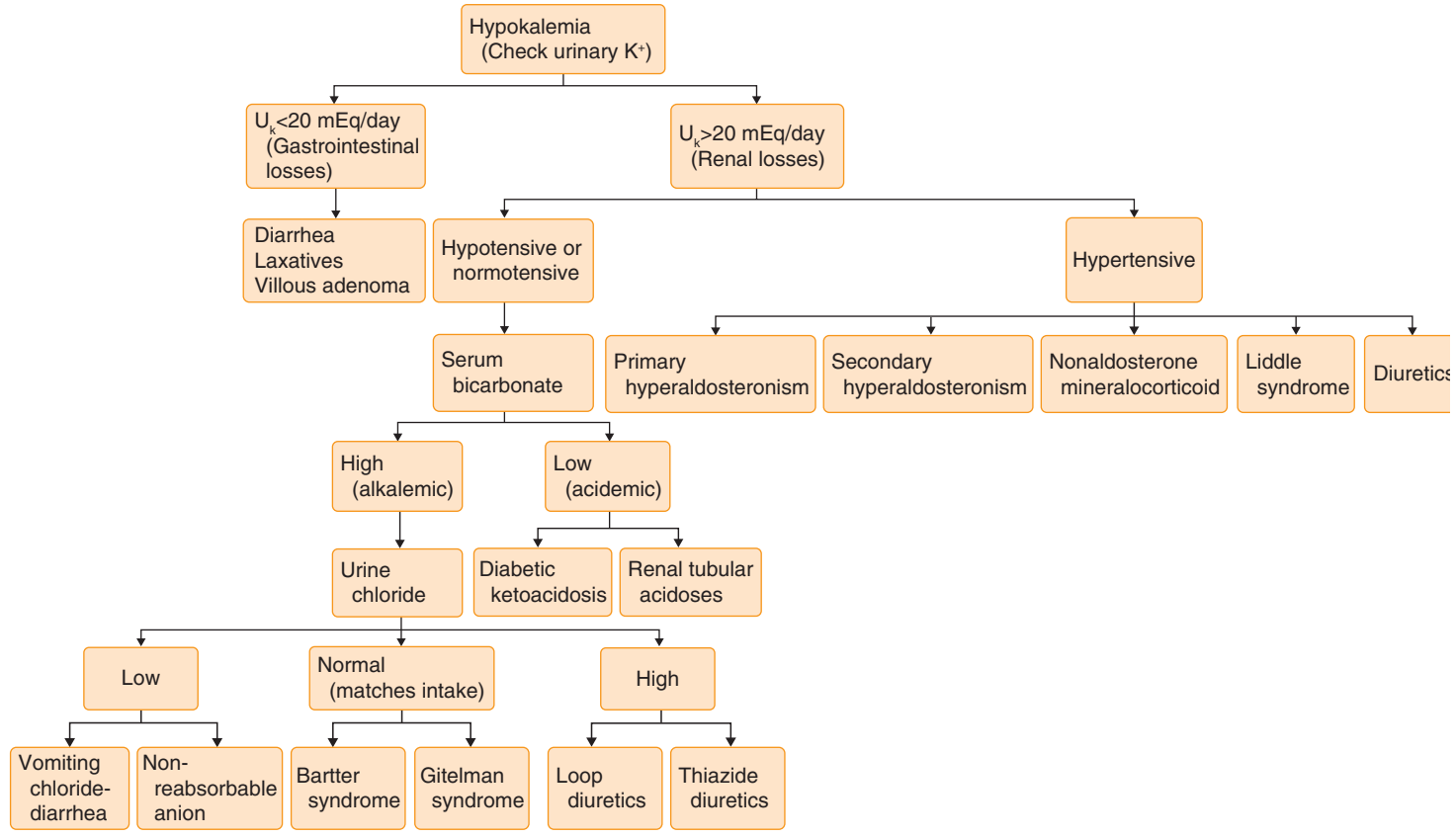

FIGURE 103-3. **Causes of hypokalemia.**

TABLE 103-3 CAUSES OF HYPERKALEMIA AND DECREASED POTASSIUM EXCRETION

CAUSE OF DECREASED K^+ EXCRETION AND HYPERKALEMIA	RENIN	ALDOSTERONE	EXTRACELLULAR VOLUME OR BLOOD PRESSURE	ACID-BASE STATUS
Decreased ENaC Drugs: amiloride, triamterene, trimethoprim, lithium Pseudohypoaldosteronism type 1 autosomal recessive ENaC mutation	High	High	Low or normal	Normal or acidosis
Pseudohypoaldosteronism type 1 autosomal dominant MR mutation	High	High	Low	Acidosis
MR blockade: spironolactone, eplerenone, progesterone	High	High	Low	Acidosis
Hypoaldosteronism: adrenal insufficiency	High	Low	Low	Acidosis
Hyporenin-hypoaldosteronism: NSAIDs, β-blockers, autonomic neuropathy	Low	Low	Low	Acidosis
Pseudohypoaldosteronism type 2	Low	Low	High	Acidosis

ENaC = epithelial Na^+ channel; MR = mineralocorticoid receptor; NSAIDs = nonsteroidal anti-inflammatory drugs.

conditions, simultaneous use of amiloride may diminish potassium losses by as much as 50%.

Patients who present with unexplained hypokalemia and alkalosis with volume depletion should have urinary electrolytes measured to determine whether the urine chloride is low, as with vomiting or laxative abuse. If the urine contains chloride, a diuretic screen should be considered; Gitelman syndrome and Bartter syndrome are other possibilities.

Hyperkalemic Disorders

In clinical practice, acute hyperkalemia is seen most commonly with renal failure (Chapter 117), acidosis (Chapter 104), and acute muscle damage from rhabdomyolysis (Chapter 99) (Table 103-3). Chronic hyperkalemia is most commonly seen with medications that reduce potassium secretion and with renal tubular disorders.[8]

Hyperkalemic Hypotensive or Normotensive Syndromes

When classic type IV renal tubular acidoses (Chapter 104) are due to hypomineralocorticoidism or adrenal insufficiency, the urine will be able to acidify due to a defect in ammonium production. By comparison, type IV renal tubular acidoses that are associated with an inability to excrete sufficient acid in the urine are caused by diseases that disrupt distal nephron function, including systemic lupus erythematosus (Chapter 245), urinary tract obstruction, amyloidosis (Chapter 174), the nephropathy associated with kidney and bone marrow transplantation (Chapters 117 and 163), and sickle cell nephropathy (Chapter 149). Men who present with hyperkalemia and renal insufficiency of unknown cause should be evaluated for possible prostatic obstruction (Chapter 114). Each of these conditions also may be associated with failure to concentrate the urine (nephrogenic diabetes insipidus) or with a hyperchloremic metabolic acidosis caused by abnormalities in acid secretion.

Primary selective hypoaldosteronism or complete adrenal cortical deficiency (Chapter 209) is associated with elevated renin and low aldosterone. Secondary hypoaldosteronism may be seen in hyporenin states caused by β-blockers, renin antagonists, or nonsteroidal anti-inflammatory drugs (NSAIDs). Angiotensin-converting enzyme inhibitors and angiotensin receptor blockers increase renin and decrease aldosterone. Heparin, including low-molecular-weight and fractionated forms (Chapter 70), can lead to hyperkalemia even in small subcutaneous doses.

Disorders that affect the transepithelial potential difference and can result in hyperkalemia, acidosis, and extracellular volume depletion include inactivating mutations of ENaC (autosomal recessive pseudohypoaldosteronism

type 1), which may be accompanied by high renin and aldosterone levels. The ENaC may also be inhibited by the potassium-sparing diuretics (i.e., amiloride and triamterene) and certain medications secreted by the proximal tubule organic cation transporters, such as trimethoprim and pentamidine, as well as by lithium. Inhibition of the aldosterone receptor may be the result of antagonists such as spironolactone and eplerenone.

Hyperkalemic Hypertensive Syndromes

NSAIDs can cause hyperkalemia, particularly in patients with renal disease, by decreasing sodium delivery, increasing water reabsorption, and decreasing renin and aldosterone. Hypertension with the NSAIDs is most likely caused by renal salt and water retention.

Cyclosporine or tacrolimus may produce a hyperkalemic acidosis. The mechanism may involve inhibition of cyclooxygenase-2 and therefore hyporeninhypoaldosteronism. There may also be a decrease in apical potassium secretion in the collecting duct. Familial hyperkalemic hypertension is a genetic disorder (pseudohypoaldosteronism type 2) associated with hyperkalemia, volume expansion, and metabolic acidosis. It is caused by activation of the thiazide-sensitive distal convoluted tubule NaCl cotransporter related to a dysfunction of the WNK kinase regulatory role.

TREATMENT

It may be difficult to determine the exact state of total body potassium stores from the serum potassium level because as much as 100 to 300 mmol of potassium may be lost from the body with a fall in serum potassium of only 1 mmol/L. As a result, therapy must be guided by careful assessment of the patient as well as the serum potassium level.[9,10]

Hypokalemia

The goal of acute therapy for hypokalemia is to prevent or to manage potentially life-threatening arrhythmias or paralysis. Patients at greatest risk are the elderly, patients with known liver disease or cardiac disturbances, and patients who have had an abrupt fall in serum potassium concentration to less than 2.5 mEq/L. Potassium must traverse the extracellular space before repleting intracellular stores, so it is dangerously easy to replete potassium too quickly. Oral potassium should be given, if possible. If the potassium level is greater than 3 mEq/L, an increase in dietary potassium can be considered, along with removal of the underlying cause of hypokalemia. Usual oral replacement is with potassium chloride at a dose of 40 to 100 mmol/day. The chloride salt has the advantage of treating concomitant metabolic alkalosis, but other available forms include potassium citrate (in the acidotic patient) and potassium phosphate (in patients with a phosphate deficit). Giving potassium with a non-reabsorbable anion, such as gluconate, may not replace the potassium deficit adequately. Intravenous potassium is reserved for patients who are unable to take enteral potassium and patients with symptomatic hypokalemia, paralysis, or cardiac arrhythmias. It is usually given as a solution of 20 to 40 mmol of potassium in 1 L of solution at a rate that does not exceed 10 to 20 mmol/hour. If the potassium level is less than 3 mmol/L or if more than 10 mmol/hour is to be delivered, the patient should be in a monitored setting to observe for cardiac complications. A central venous catheter may be required for these higher concentrations, and it is best to consult with a renal specialist and the pharmacy.

In patients who have prerenal azotemia associated with hyperglycemia or severe metabolic alkalosis, volume expansion with sodium chloride solutions alone can result in life-threatening potassium losses, despite improvement in the extracellular volume. Potassium must be given in anticipation of such events.

In a hypokalemic patient, care must be exercised when glucose-containing solutions are given because the resulting increase in insulin may further decrease the blood potassium level. Attention to the urine output and ongoing losses is crucial. If ongoing losses of potassium are severe, it may be necessary to provide a potassium-sparing diuretic (e.g., amiloride 5 to 10 mg orally) and to treat the cause of the ongoing losses (e.g., diarrhea). Magnesium causes further urinary excretion of potassium and should be repleted, if necessary (Chapter 105).

In the inpatient setting, hypokalemia is a common complication of intravenous fluid administration. In patients with normal renal function, a maintenance dose of intravenous potassium can avoid hypokalemia. In the outpatient setting, hypokalemia is a common side effect of diuretic therapy. Serum potassium should be maintained within the normal range (>3.5 mEq/L), especially in high-risk patients. Addition of 40 to 100 mmol of potassium per day as chloride salt is the usual treatment, depending on the patient's response.

Hyperkalemia

Emergent Treatment

If hyperkalemia is severe, concentration must be reduced rapidly by therapies that stabilize cardiac membranes (intravenous calcium) and shift potassium intracellularly (insulin, bicarbonate), while simultaneously instituting treatments that achieve net potassium loss (diuretics, potassium binders or hemodialysis).[11]

Cardiac Arrhythmias

If hyperkalemia is associated with cardiac arrhythmias, treatment in a monitored setting is warranted before the serum potassium level can be expected to decline, even with aggressive therapy. Calcium gluconate, 10 mL of a 10% solution (8.9 mg calcium) over 10 to 20 minutes, is often indicated to stabilize electrical effects on cardiac excitation. Calcium chloride (3 to 4 mL of a 10% solution) is an alternative, but it should be administered through a central access line because extravasation of the chloride salt may result in tissue necrosis. Gastrointestinal losses of potassium can also be achieved by use of potassium-binding drugs.

Lowering the Potassium Level

The administration of calcium does not lower the potassium concentration. Rapid-acting options to lower the potassium level acutely include an inhaled β_2-agonist or the intravenous combination of insulin plus glucose.

β_2-agonists are usually preferred because epinephrine can initially increase the release of K^+ from the liver. Albuterol by nebulizer (10 to 20 mg in 4 mL of saline during 10 minutes) can redistribute potassium acutely but should not be the sole treatment because some patients are not responsive. In some cases, intravenous β-adrenergic agonists (e.g., albuterol, 0.5 mg in 100 mL of 5% dextrose during 15 minutes) have been used to lower the serum potassium level by about 1 mmol/L within minutes to hours.

If insulin plus glucose is chosen, alternatives include 100 mL of 50% glucose alone or in combination with 10 units of regular insulin; the combination will, on average, provide a significantly greater reduction in the serum potassium level (0.8 mmol/L vs. 0.5 mmol/L) at 60 minutes, but about 20% of insulin-treated patients will develop hypoglycemia. Alternatively, 5 units of regular insulin can be given with 10% glucose solution during 1 hour for a total of 30 to 50 g in the normoglycemic patient. The blood glucose level should be monitored because an abrupt increase in plasma osmolality with glucose may worsen hyperkalemia if it causes potassium to leak from cells with osmotic water flow.

Sodium zirconium cyclosilicate (1.25 to 10 g three times a day), an oral crystalline agent with high binding affinity for potassium within the gastrointestinal tract, can reduce the serum potassium concentration within 1 hour, particularly in patients with heart failure.[A1] This potassium binder has been shown to be effective as an adjunct to glucose and insulin therapy.

Sodium bicarbonate, as an isotonic mixture calculated to correct acid-base status, should be reserved for acidemic patients who otherwise require alkalinization, while being careful to avoid hypocalcemia. Complications of sodium bicarbonate infusions include hypernatremia, volume expansion, and decreased ionized calcium, potentially resulting in tetany. Diabetic patients may be potassium depleted even though they present with hyperkalemia; as they are volume repleted, they typically require potassium replacement (Chapter 210).

If hyperkalemia occurs in the setting of volume contraction and oliguria, extracellular volume expansion with saline to achieve a rise in urine output may be adequate. If a patient is hyperkalemic and volume-expanded and not in renal failure, potassium-losing diuretics (e.g., furosemide 10 to 40 mg intravenously) may be effective.

The hyperkalemia of familial hyperkalemic hypertension is highly responsive to thiazide diuretics. In patients who have advanced or end-stage kidney failure, particularly in a volume-expanded hyperkalemic patient, hemodialysis (Chapter 117) will be required to remove potassium effectively from the body. However, patients who are dialyzed against zero K^+ dialysate may become rapidly hypokalemic.

Chronic Treatment

During the longer term, potassium loss may be sustained by use of cation exchange resins and a low-potassium diet.[12] Patiromer (4.2 to 8.4 g twice daily),[A2] a nonabsorbed calcium-potassium exchange resin that works in the colon, can decrease potassium levels for at least a year. It has been used successfully in patients with diabetic renal disease[A3] and in patients receiving potassium-retaining antihypertensive agents.[A4] Its major side effect is constipation, but hypomagnesemia, diarrhea, nausea, abdominal discomfort, and flatulence can also occur. To avoid potential interaction, no other orally administered medication should be taken at least 3 hours before or after patiromer. Zirconium cyclosilicate at 1.25 to 10 g three times daily[A5,A6] is also effective in managing hypokalemia. Sodium polystyrene sulfonate given orally or as an enema (Chapter 116) at a dose of 30 to 50 g can reduce potassium levels over several hours, but its use is limited by its many adverse effects, so it is now rarely used.

If the patient is volume expanded, furosemide (40 to 100 mg), chlorothiazide (500 mg), or, if the patient is also alkalotic, acetazolamide (250 to 500 mg) may enhance renal potassium clearance. If the patient is volume depleted, isotonic saline expansion may improve urine output and, with it, potassium excretion.

SPECIFIC CLINICAL SYNDROMES

Hypokalemic Periodic Paralysis

Familial hypokalemic periodic paralysis is an autosomal dominant disorder usually caused by mutations in certain voltage-gated skeletal muscle sodium channels or L-type calcium channels. Characteristically, periodic attacks of severe hypokalemia are precipitated by stimuli that usually induce mild hypokalemia by distributing potassium into cells. Precipitating factors include the

increase in insulin levels after the ingestion of carbohydrates or postexercise, when the plasma potassium level falls because of ATPase reuptake of potassium. In affected individuals, these stimuli cause progressive and severe hypokalemia, enough to result in muscle paralysis due to hyperpolarization of the sarcolemma. The cause of the syndrome is an imbalance between outwardly directed K^+ current and inwardly directed cation leaks of Na^+ and Ca^{2+}. In the familial mutations, the cation depolarizing influx, normally very small under hyperpolarizing conditions, is instead increased and, when balanced with the outward K^+ current, results in a paradoxical depolarization. In turn, the depolarization inactivates the sodium channel needed for the rapid action potential, so the muscle cell is unexcitable. In nonfamilial hypokalemic periodic paralysis, a loss in function of outwardly directed potassium channels (Kir) accounts for paradoxical depolarization, inactivation of sodium channels, and decreased excitability.

The clinical presentation of hypokalemic periodic paralysis is usually in the teenage years or early adulthood.[13] In some familial cases, a progressive proximal myopathy (Chapter 389) may develop. Asian patients, usually males with hyperthyroidism (Chapter 207), have a decrease-in-function mutation of an outwardly directed potassium channel that causes them to develop episodic paralysis in response to high-carbohydrate meals or resting after exercise. In Anderson syndrome, which is another form of hypokalemic periodic paralysis, cardiac potassium channels are also affected, and serious cardiac arrhythmias may result.

TREATMENT

Hypokalemic periodic paralysis is treated by a high-potassium diet and cautious use of carbonic anhydrase inhibitors such as acetazolamide (125 to 500 mg/day) and dichlorphenamide (50 to 200 mg/day), which can significantly reduce the frequency of attacks. These medications work in part by creating a hyperchloremic acidosis that offsets the urinary potassium wasting they cause. β_2-Blockers (e.g., propranolol 20 to 40 mg twice daily) also may be used.

Insulin Deficiency

The abnormal distribution of potassium between cells and the extracellular space results in the hyperkalemia that is associated with acidosis, insulin-deficient states, and β_2-adrenergic blockade. Although it is not always possible, it is best to know the levels of serum glucose and potassium in an unconscious diabetic patient before infusing concentrated glucose solutions because of the risk of aggravating hyperkalemia.

Hyperkalemic Periodic Paralysis

Familial hyperkalemic periodic paralysis is a myopathy caused by a genetic defect in voltage-gated sodium channels in skeletal muscle. Exercise or dietary increases in plasma potassium result in mild depolarization of skeletal muscle that then unmasks the sodium channel defect, rendering the cells unexcitable. Treatment is frequent meals and acetazolamide (125 to 500 mg).

Digitalis Overdose

Potassium competes with digoxin-binding sites on the Na^+, K^+-ATPase, so that if hypokalemia coexists, digoxin will have an intensified effect and may lead to drug toxicity. In extreme cases of digitalis overdose (Chapter 96), severe hyperkalemia develops as a result of generalized blockade of Na^+, K^+-ATPase.

PROGNOSIS

The prognosis of patients with hypokalemia and hyperkalemia depends on the severity and underlying illness. Hypokalemia is associated with increased mortality, especially in patients with heart disease,[14] and hyperkalemic patients on renal dialysis have a higher cardiovascular mortality. Hypertensive patients with potassium levels either above or below the range of 4.1 to 4.7 mEq/L also appear to have an increased mortality,[15] but modest hyperkalemia (≤5.5 mEq/L) does not appear to have adverse effects on treated patients with heart failure.[16] Most hypokalemic cases are mild (potassium concentration 3 to 3.5 mEq/L). However, mortality of hospitalized patients with hypokalemia is increased 10-fold. Hyperkalemia is reported in 1 to 10% of hospitalized patients, of whom 10% have severe hyperkalemia (potassium concentration > 6.0 mEq/L). Hyperkalemia is associated with increased mortality (14 to 41%), and it accounts for 2 to 5% of deaths in patients with end-stage renal disease. Patients with electrocardiographic abnormalities are at highest risk, especially in the acute period before the serum potassium level is successfully reduced.

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104 ACID-BASE DISORDERS

JULIAN LAWRENCE SEIFTER

DEFINITION

The ability to regulate the H^+ ion concentration, or pH (defined as the negative logarithm of the hydrogen ion concentration), is essential to normal body function. Acid-base balance is assessed by measurements of arterial or venous blood. If arterial pH is below 7.35, *acidemia* is said to exist. If pH is above 7.45, *alkalemia* exists. However, several processes may simultaneously drive the pH upward or downward; these individual processes are known as alkaloses or acidoses, respectively. Because simultaneous alkalosis and acidosis of equal magnitude can coexist, an abnormal pH is not always noted in acid-base disturbances. Also, because pH is a function of the ratio of the blood bicarbonate concentration ($[HCO_3^-]$) to the partial pressure of carbon dioxide (P_{CO_2}), the finding of an abnormal bicarbonate level alone cannot define acidemia or alkalemia.

EPIDEMIOLOGY

An acid-base disturbance should alert the clinician to the possible presence of an important underlying condition. Anion gap acidoses represent serious underlying metabolic disorders, ranging from sepsis (Chapter 94) to uremia (Chapter 116) to diabetic ketoacidosis (Chapter 210) to serious poisonings (Chapter 96). Specific renal abnormalities as well as diarrhea (Chapter 126) can cause hyperchloremic acidosis (Table 104-1). Metabolic alkaloses are commonly caused by diuretics or renal tubular abnormalities or the loss of acid from the stomach due to vomiting or nasogastric suction (Table 104-2). Respiratory acidosis and alkalosis are related to disturbances in ventilation, which is increased by conditions such as sepsis (Chapter 94) and anxiety, and is decreased in many pulmonary conditions and with depression of the central nervous system (CNS) (Chapters 71 and 89).

PATHOBIOLOGY

Growth, cell division, fertilization, and protein and glucose metabolism are examples of pH-sensitive intracellular processes. Acids are generated within cells during metabolism, and each cell must maintain a pH appropriate for its function. For example, cardiac contractility (Chapter 41) is reduced when cardiac myocytes are too acidic. Bone and muscle develop and grow poorly in an acidic environment. Intracellular pH may be lower than extracellular pH because cells are electronegative with respect to extracellular fluid, but they are not as acidic as they would be if H^+ reached electrochemical equilibrium with the extracellular fluid, which means that all cells utilize energy to extrude acid actively. Cells are capable of buffering an acid load, and intracellular vacuoles may use hydrogen adenosine triphosphatases (H^+-ATPases) to sequester excess acid before transport from the cell. The transport processes located on the plasma membranes can protect cells from both acid and alkaline loads. The specific mechanisms may differ from one cell type to another, but they are similar to those used by the excretory organs that finally eliminate the net acid produced by the body into the external world.[1,2]

In severe disease states, arterial pH may fall as low as 6.8 and rise as high as 7.7. Strenuous exercise with the metabolic production of lactic acid may transiently but severely lower pH, even in normal healthy individuals.

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104 ACID-BASE DISORDERS

JULIAN LAWRENCE SEIFTER

DEFINITION

The ability to regulate the H^+ ion concentration, or pH (defined as the negative logarithm of the hydrogen ion concentration), is essential to normal body function. Acid-base balance is assessed by measurements of arterial or venous blood. If arterial pH is below 7.35, *acidemia* is said to exist. If pH is above 7.45, *alkalemia* exists. However, several processes may simultaneously drive the pH upward or downward; these individual processes are known as alkaloses or acidoses, respectively. Because simultaneous alkalosis and acidosis of equal magnitude can coexist, an abnormal pH is not always noted in acid-base disturbances. Also, because pH is a function of the ratio of the blood bicarbonate concentration ($[HCO_3^-]$) to the partial pressure of carbon dioxide (P_{CO_2}), the finding of an abnormal bicarbonate level alone cannot define acidemia or alkalemia.

EPIDEMIOLOGY

An acid-base disturbance should alert the clinician to the possible presence of an important underlying condition. Anion gap acidoses represent serious underlying metabolic disorders, ranging from sepsis (Chapter 94) to uremia (Chapter 116) to diabetic ketoacidosis (Chapter 210) to serious poisonings (Chapter 96). Specific renal abnormalities as well as diarrhea (Chapter 126) can cause hyperchloremic acidosis (Table 104-1). Metabolic alkaloses are commonly caused by diuretics or renal tubular abnormalities or the loss of acid from the stomach due to vomiting or nasogastric suction (Table 104-2). Respiratory acidosis and alkalosis are related to disturbances in ventilation, which is increased by conditions such as sepsis (Chapter 94) and anxiety, and is decreased in many pulmonary conditions and with depression of the central nervous system (CNS) (Chapters 71 and 89).

PATHOBIOLOGY

Growth, cell division, fertilization, and protein and glucose metabolism are examples of pH-sensitive intracellular processes. Acids are generated within cells during metabolism, and each cell must maintain a pH appropriate for its function. For example, cardiac contractility (Chapter 41) is reduced when cardiac myocytes are too acidic. Bone and muscle develop and grow poorly in an acidic environment. Intracellular pH may be lower than extracellular pH because cells are electronegative with respect to extracellular fluid, but they are not as acidic as they would be if H^+ reached electrochemical equilibrium with the extracellular fluid, which means that all cells utilize energy to extrude acid actively. Cells are capable of buffering an acid load, and intracellular vacuoles may use hydrogen adenosine triphosphatases (H^+-ATPases) to sequester excess acid before transport from the cell. The transport processes located on the plasma membranes can protect cells from both acid and alkaline loads. The specific mechanisms may differ from one cell type to another, but they are similar to those used by the excretory organs that finally eliminate the net acid produced by the body into the external world.[1,2]

In severe disease states, arterial pH may fall as low as 6.8 and rise as high as 7.7. Strenuous exercise with the metabolic production of lactic acid may transiently but severely lower pH, even in normal healthy individuals.

ABSTRACT

Measurements of pH, P_{CO_2}, and HCO_3^- in the blood are used in the clinical assessment of acid-base disorders. The constancy of a narrow range of body fluid pH determines many regulatory cellular and extracellular functions. This chapter describes the normal physiologic mechanisms for the metabolic production of volatile carbonic acid, which is eliminated by pulmonary alveolar ventilation, and dietary-derived, nonvolatile acids that require renal mechanisms for urinary excretion. The integrated role of metabolic and renal functions to lessen the severity of or adapt to a specific disorder is known as compensation, and predictable limits exist for both brain-respiratory control and renal responses to achieve these important compensatory responses. Abnormalities in membrane transport, intrinsic diseases of organ function, and hormonal or electrolyte disorders are responsible for the generation and maintenance of simple acid-base disorders. Metabolic acidosis is further characterized as hyperchloremic or anion-gap acidosis depending on the nature of the anion associated with the excessive acid. The consequences and treatments of endogenous acid-base disorders as well as environmental poisonings are emphasized since the prompt recognition, diagnosis, and treatment is often life-saving. The short-term and long-term complications of acid-base disturbances are reviewed, and the integration of pulmonary function, blood pressure, salt, water, potassium, and calcium balance connect intimately to both the initiation and correction of these disorders.

KEYWORDS

respiratory acid-base disorders
metabolic acidosis
metabolic alkalosis
anion gap

TABLE 104-1 EXAMPLES OF HYPERCHLOREMIC ACIDOSIS

TYPE	CAUSE
Renal with hypokalemia	Proximal RTA, type 2 Distal RTA, type 1 Some anion gap acidoses with high anion clearance
Renal with hyperkalemia	Type 4 RTA Hyporenin-hypoaldosteronism
Nonrenal with hypokalemia	Diarrhea Urinary diversions: ureteroileostomy, ureterosigmoidostomy
Nonrenal with hyperkalemia	NaCl, KCl, NH_4Cl, $CaCl_2$, Arg-HCl, Lys-HCl

RTA = renal tubular acidosis.

TABLE 104-2 EXAMPLES OF METABOLIC ALKALOSIS

TYPE	CAUSES
Renal, hypochloremic alkalosis with hypokalemia: chloride responsive with urine chloride concentration >20 mEq/L	Loop and distal tubule diuretics Bartter syndrome Gitelman syndrome Post-hypercapnic status
Nonrenal, hypochloremic alkalosis: chloride responsive with urine chloride concentration <20 mEq/L	Vomiting, nasogastric suction Congenital chloridorrhea Villous adenoma
Renal, alkalosis with extracellular expansion and hypokalemia: chloride unresponsive with urine chloride concentration >20 mEq/L	Hyperaldosteronism, primary and secondary to unilateral renal artery stenosis Liddle syndrome
Nonrenal alkalosis, chloride unresponsive	$NaHCO_3$, acetate, citrate, lactate. Minimal alkalosis will develop unless accompanied by a process such as hypokalemia or hypovolemia
Renal hypokalemic alkalosis	Excessive excretion of non-reabsorbable anions due to excretion of H^+ and K^+
Nonrenal alkalosis with decreased anion gap	Hypoalbuminemia

At a normal arterial blood pH, the hydrogen ion concentration is in the range of 40 nanoequivalents (nEq) per liter, a very small concentration in comparison to a normal plasma sodium concentration of 140 mEq/L. The hydrogen ion concentration of body fluids is in equilibrium with each of multiple weak acids or buffers, such as proteins and phosphate (the isohydric principle), but acid-base equilibria in the body are often described and analyzed by use of the CO_2/HCO_3^- system and the relationship of the proton concentration (thus pH) to the ratio of HCO_3^- to CO_2. The CO_2/HCO_3^- system is quantitatively the largest buffer system in the body, and it is the system whose parameters are most often measured clinically. The Henderson-Hasselbalch equation is a logarithmic expression of the relationship.

$$CO_2 + H_2O \leftrightarrow H_2CO_3 \leftrightarrow H^+ + HCO_3^-$$
$$pH = pK + \log[HCO_3]/0.03(P_{CO_2})$$

In this equation, p*K*, or the negative log of the dissociation constant for the reaction, is 6.1; 0.03 (mM/mm Hg) is the solubility factor for CO_2 in solution. The product of 0.03 × P_{CO_2} represents dissolved CO_2; the "total CO_2" in plasma is the sum of HCO_3^-, normally about 25 mM, and 0.03 × P_{CO_2}, normally about 1.2 mM in arterial blood. It is important to emphasize that pH is a function of the *ratio* of HCO_3^- to P_{CO_2}. The HCO_3^- concentration in the numerator is regulated by the kidney, and P_{CO_2} is regulated by the lung.

Production of Carbonic Acid and the Elimination of Carbon Dioxide by the Lung

Volatile acid is the term used for the approximately 20,000 mmol/day of CO_2 produced, with an equimolar amount of water, by tissue respiration. This CO_2 is carried from tissues to the lung, where it is eliminated by alveolar ventilation. Steady-state arterial P_{CO_2} is normally 38 to 42 mm Hg.

Oxidation of carbohydrates, fat, and the carbon skeleton of amino acids results in the production of water and CO_2. To maintain a steady state, any acid (or base) produced per day must be equivalent to what is eliminated. If tissue CO_2 production exceeds CO_2 elimination by the lungs, respiratory acidosis characterized by a high P_{CO_2} will develop. If the rate of CO_2 eliminated exceeds production, respiratory alkalosis develops. The inverse relationship between alveolar ventilation (the clearance of CO_2) and P_{CO_2} is demonstrated as

$$\text{alveolar ventilation} \approx CO_2 \text{ elimination rate} \div P_{CO_2}$$

The circulation plays a critical role in transporting tissue CO_2 to the lungs. The process depends not only on cellular respiration but also on tissue capillary flow as well as diffusion of CO_2 into the blood and across red blood cell membranes, where it may react with hemoglobin and proteins to form carbamino compounds or combine with water for conversion to H^+ and HCO_3^- in a reaction catalyzed by carbonic anhydrase. The intracellular H^+ can combine with hemoglobin (the Bohr effect) and the HCO_3^- exchanged with plasma Cl^- through red cell anion exchangers. Most tissue CO_2 is brought to the lung as venous plasma HCO_3^-. Compared with arterial blood, venous blood has the characteristics of a respiratory acidosis. Venous pH is normally approximately 0.05 pH units more acid than arterial pH, its P_{CO_2} is 5 to 6 mm Hg higher than that of arterial blood, and its bicarbonate concentrations are normally greater than arterial concentrations.

In disease, changes in P_{CO_2} are most often caused by changes in alveolar ventilation rather than by production of CO_2. Thus, respiratory acidosis is a consequence of decreased pulmonary ventilation because of lung, skeletal muscle, or CNS disease. However, if alveolar ventilation is compromised, increased production of CO_2 will worsen CO_2 retention. Similarly, respiratory alkalosis develops because of hyperventilation rather than decreased CO_2 production. In either case, when the elimination rate of CO_2 (alveolar ventilation × P_{CO_2}) again equals CO_2 production, a new steady-state P_{CO_2} will prevail, with no net retention or loss of carbonic acid.

Production of Acids and Excretion by the Kidney

Nonvolatile or fixed acid describes noncarbonic acids that are formed primarily from protein metabolism. The usual rate of formation is approximately 1 to 2 mEq of H^+ per kilogram of body weight per day. Most diets that contain animal protein metabolically produce a net positive quantity of nonvolatile acids, primarily sulfuric acid from the sulfur-containing amino acids cysteine and methionine. Other acids are produced in the form of phosphoric acid (from phosphoproteins, phospholipids, and phospho-nucleotides) and nonmetabolizable organic acids (e.g., uric acid), and hydrochlorides are produced from metabolism of the cationic amino acids lysine, arginine, and histidine. Conversely, HCO_3^- is generated from metabolism of organic anions absorbed from the diet (e.g., citrate, acetate).

From the Henderson-Hasselbalch equation, consider the addition of metabolic acid HA (where the anion A^- could be Cl^-, lactate$^-$, sulfite, or mono- or dihydrogen phosphate) to blood that contains Na^+ and HCO_3^-:

$$HA + NaHCO_3 \rightarrow Na^+ + A^- + H^+ + HCO_3^-$$

and

$$H^+ + HCO_3^- \leftrightarrow H_2CO_3 \leftrightarrow CO_2 + H_2O$$

The CO_2 produced by this process will not raise the blood P_{CO_2} if the system is well ventilated because the contribution of metabolic acid is a small part of the daily production of CO_2. Note that the addition of protons to body fluids by these acid end products consumes bicarbonate ("lost bicarbonate"), which then must be replenished by the kidney as it eliminates the proton and A^- in the urine. The process of excreting net H^+ and A^- is equivalent to producing a "new" HCO_3^- to restore the HCO_3^- that is lost by the addition of HA, the metabolic acid. The kidney must excrete any nonvolatile acid (or alkali) load to maintain a steady-state serum HCO_3^- concentration in the 22- to 28-mEq/L range.

When the diet requires the excretion of acids, the urine pH will fall to a value as low as 4.5 to 5.0, and the urine will become nominally free of bicarbonate. With an alkaline load, by comparison, the kidney will excrete excess filtered HCO_3^-, and the urine pH may approach a maximal value of 8.0 to 8.5. In most humans, particularly those who eat animal protein or an "acid-ash" diet, the requirement for net acid *excretion* predominates. However, some vegetarians may have an overall "alkaline-ash" diet, for which net alkali must be excreted to match intake.

Bicarbonate and the Kidney in Acid-Base Balance

The first role of the kidney in achieving acid excretion is to reabsorb all filtered HCO_3^- (E-Fig. 104-1). At a normal glomerular filtration rate (e.g., ≈180 L/day in an adult) and plasma HCO_3^- concentration of 25 mEq/L, about 4500 mEq of HCO_3^- is filtered in 1 day. Loss of even a small fraction of that amount would result in metabolic acidosis if not replaced by alkali (HCO_3^-) intake. Just as reabsorption of all filtered glucose does not add glucose to the body, reabsorption of all filtered HCO_3^- will maintain the status quo but will not fulfill the need to generate new HCO_3^-. Therefore, the kidney must perform two functions: reabsorb all filtered HCO_3^- and eliminate enough additional H^+ (producing HCO_3^- in the process) to replace HCO_3^- losses from acid that is generated by cellular metabolism. Urinary buffers are essential because urinary pH alone cannot be lowered enough to excrete the amount of acid needed for this purpose.

The Proximal Tubule

About 80 to 90% of HCO_3^- reabsorption is accomplished in the proximal tubule by a proton secretory process that renders the luminal fluid more acid (pH ≈ 6.5). The brush border membranes facing the lumen of the proximal tubule cell contain transporters known as Na/H exchangers (NHE3), which carry out the greatest proportion of acidification, and vacuolar H^+-ATPases, which provide a smaller contribution. Through the normal function of basolateral membrane Na^+, K^+-ATPase, cell Na^+ is kept at low concentration so that filtered Na^+ in the lumen will be favored to enter the cell in exchange for H^+ secreted into the lumen. This H^+ rapidly combines with filtered HCO_3^- to form H_2CO_3, which then rapidly dehydrates in the lumen to form CO_2 and H_2O. This process is greatly facilitated by the large surface area of microvillous membranes and by luminal carbonic anhydrase (CA_{IV}). The CO_2 enters the proximal cell by diffusion through apical water channels (aquaporin 1). CO_2 within the cell re-forms HCO_3^-, a reaction catalyzed by intracellular carbonic anhydrase (CA_{II}). The cell, more alkaline by apical H^+ secretion, favors the reaction $OH^- + CO_2$ to form HCO_3^- catalyzed by carbonic anhydrase. The HCO_3^- is then transported back toward the blood by an electrogenic sodium bicarbonate cotransporter (NBCel), which couples 1Na and $3HCO_3^-$, thereby completing net Na^+ and HCO_3^- reabsorption. The 1 : 3 net negative charge transport by NBC allows the inside negative membrane potential to drive outward movement of Na^+ and HCO_3^- against an adverse Na gradient in this reabsorptive process. NBC on the basolateral membrane protects the cell from an alkaline load, accomplishes HCO_3^- reabsorption, and mediates a component of Na^+ reabsorption without further direct requirement for adenosine triphosphate (ATP). The entire process requires a mitochondrial source of ATP for the Na^+/K^+ pump, intact NHE3 and NBC, and two isoforms of carbonic anhydrase. In addition, there must be favorable ion gradients for luminal Na^+ entry, H^+ secretion, and basolateral HCO_3^- transport. An inside negative potential depending on outwardly directed K^+ gradients explains how an increase in blood K^+ decreases the proximal reabsorption of HCO_3^- and the production of NH_4^+. Conversely, hypokalemia tends to stimulate the reabsorption of HCO_3^- and the production of ammonium. A disturbance in any of these factors may disrupt proximal HCO_3^- reabsorption and cause loss of HCO_3^- in urine. It is also clear that the acidifying process in the proximal tubule provides a significant mechanism for Na^+ reabsorption, consistent with the finding that HCO_3^- reabsorption is increased by angiotensin II and the sympathetic nervous system in the defense of extracellular volume.

Another 10 to 15% of filtered HCO_3^- is reabsorbed in the thick ascending limb of Henle, so that only small amounts of the filtered HCO_3^- are normally delivered to more distal nephron segments.

The Cortical Collecting Duct

The cortical connecting tubules and collecting ducts reabsorb less than 10% of the filtered HCO_3^-. In principal cells, Na^+ is reabsorbed from lumen to cell by the epithelial sodium channel (ENaC), driven by the inwardly directed Na^+ gradient and favorable electrical potential. With the reabsorption of Na^+, the lumen becomes electronegative, thereby favoring the secretion of both K^+, through potassium channels, and H^+, through vacuolar H^+-ATPases on the luminal surface of neighboring α-intercalated cells, which are acid-secreting cells. The secreted H^+ will combine with the remaining HCO_3^- in the lumen to generate CO_2, with subsequent reabsorption of CO_2, re-formation of cellular HCO_3^- with the help of cellular carbonic anhydrase (CA_{II}), and then exchange of HCO_3^- from cell to blood for entry of extracellular Cl^- through Cl^-/HCO_3^- exchangers, similar to the erythrocytic anion exchangers (AE1) that participate in blood CO_2 transport. The distal nephron, which has a smaller requirement for bicarbonate reabsorption than the proximal tubule, lacks both brush border and luminal carbonic anhydrase. It is at this distal site that tubular fluid pH starts to fall to levels below pH 6.0.

β-Intercalated cells comprise a population of collecting duct cells that have reverse polarity and secrete HCO_3^- into the lumen in exchange for Cl^- entry into the cell. In these, the H^+-ATPase faces the blood side of the cell. An elevated extracellular HCO_3^- concentration, as seen with an alkaline-ash diet or metabolic alkalosis, will increase HCO_3^- secretion by these cells through pendrin, which is the apical Cl^-/HCO_3^- anion exchanger.

The Medullary Collecting Duct

The medullary collecting duct continues to secrete protons into the luminal fluid, where the pH reaches its lowest values of 4.5 to 5.0. The mechanism is based on continued function of H^+-ATPases. In both the cortical and medullary collecting duct there is an additional role of an ATP-dependent K^+/H^+ exchanger, a member of the family of gastric and colonic ATPases.

Once the filtered HCO_3^- is fully reabsorbed, the kidney is still required to eliminate an additional net amount of acid equivalent to that produced in metabolism. Most of this net acid excretion is in the form of ammonium (NH_4^+), which is derived from the metabolism of glutamine in the proximal tubule and the titration of filtered phosphate to acid phosphate (titratable acidity).

$$NH_3 + H^+ \leftrightarrow NH_4^+ \quad pK\ 9.1$$

and

$$HPO_4^{2-} + H^+ \leftrightarrow H_2PO_4^- \quad pK\ 6.8$$

Urinary Buffers

As the collecting duct cells continue to secrete H^+ into urine with a diminishing luminal HCO_3^- concentration and decreasing pH, H^+ is captured by the urinary buffers. The resulting alkalinization of the cells after H^+ secretion results in the formation of cellular HCO_3^- ready for transport into blood. This process generates "new" HCO_3^- that is not a result of the reabsorption of filtered HCO_3^-. The amount of new HCO_3^- matches the amount of net acid eliminated and is also equal to each of the following: the amount of acid produced; the amount of body buffer consumed by that acid; and the amount of fixed acid anions, such as sulfate, phosphate, and Cl^-, that accompanied the H^+. The result is maintenance of normal acid-base equilibrium.

The ability of the kidney to lower urinary pH enables the buffers to capture a proton. Net acid excretion in urine is accomplished not simply by a decrease in urine pH but mostly by titration of these important urinary buffers. For example, a typical daily urine volume of 1 L at pH 5.0 contains only 10^{-5} molar hydrogen ion, or 0.01 mmol, a trivial amount compared with the amount of produced acid (≈1 mmol/kg/day). In chronic kidney disease, the failure to produce sufficient ammonium leads to a poorly buffered urine, thereby causing retention of acid while still consistent with reaching maximal urine acidity with respect to pH.

Regulation of Urinary Acid Secretion

Renal mechanisms of urinary acidification are adaptable. Transport processes such as H^+-ATPases, Na^+/H^+ exchange, and Cl^-/HCO_3^- exchange can increase or decrease their capacity to handle acid-base equivalents, depending on the challenge presented. Renal ammoniagenic mechanisms are also critically regulated to serve the acid-base needs of the individual. Metabolic acidosis and respiratory acidosis increase the capacity to reabsorb HCO_3^-, including increased expression of the transporters involved in acidifying the urine. At the same time, glutamine transport into proximal cells is stimulated, and increased production of ammonium facilitates acid excretion, as well as the generation of new HCO_3^- in the distal nephron. Metabolic alkalosis and respiratory alkalosis have the opposite effects.

Ammoniagenesis, which is a key element in urinary acid excretion, provides the major acceptor for protons. Ammonium is produced predominantly in the proximal tubule cell by mitochondrial glutaminase enzymes. Production is increased by increasing the metabolic acid load in the body, respiratory acidosis, and hypokalemia. NH_4^+ can preserve potassium in the hypokalemic state by serving as a cation needed for anion excretion. In response to metabolic acidosis, the kidney can excrete chloride with ammonium, thereby preserving the ability to retain Na^+.

Metabolic acidosis is a hypercatabolic state with increased cortisol, which increases proteolysis in muscle and increases the release of both glutamine and NH_3 into the circulation. In the liver, acidosis also decreases the activity of the urea cycle, which normally consumes NH_3 and HCO_3^- to form carbamoyl phosphate in the initial regulatory step in ureagenesis. In acidosis, NH_3 is favored to produce hepatic glutamine, which is also delivered to the proximal tubule cell, where mitochondrial enzymes remove NH_4 to assist in urinary net acid excretion. The associated increase in α-ketoglutarate provides

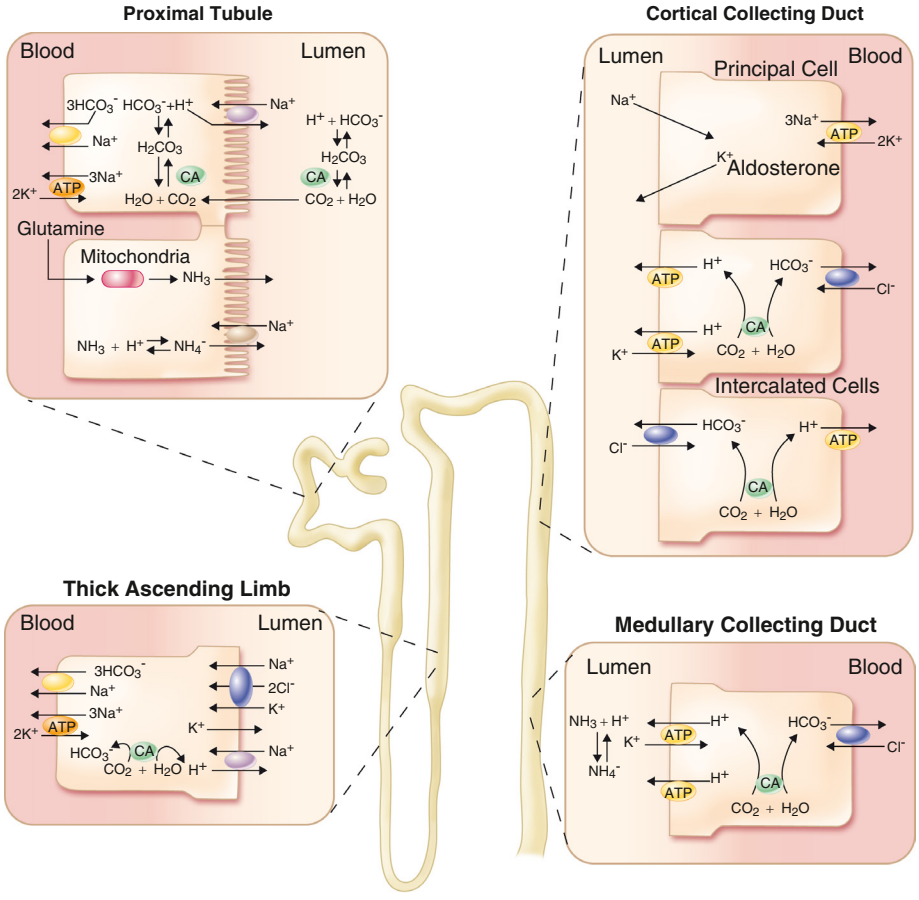

E-FIGURE 104-1. **Renal acidification mechanisms.** As shown, two ammonia molecules are produced per one molecule of glutamine in the mitochondria of the proximal tubule, one each from deamination of glutamine to glutamate (glutaminase) and from the deamidation of glutamate to α-ketoglutarate (glutamate dehydrogenase). HCO_3^- is also generated from metabolism of α-ketoglutarate. ATP = adenosine triphosphate; CA = carbonic anhydrase.

a substrate for gluconeogenesis in the renal proximal tubule and results in the production of HCO_3^-.

Ammonium can be secreted by nonionic diffusion as NH_3 into the proximal fluid, where it will pick up a proton and re-form ammonium (NH_4^+), or it could form ammonium within the proximal tubule cell and be secreted by Na^+/NH_4^+ exchange, a mode of operation of the Na^+/H^+ exchanger. Ammonium is then reabsorbed by the thick ascending limb of Henle on the Na-K-2Cl transporter, where it can substitute for K^+. By countercurrent multiplication, NH_3/NH_4^+ concentrates in the medullary interstitial fluid rather than remaining in the ascending limb fluid as it reaches the highly perfused renal cortex, where it would otherwise dissipate into renal venous blood. The countercurrent mechanism also allows ammonia to diffuse into the medullary interstitium and ultimately the lumen of the medullary collecting duct, where it will be trapped as ammonium in the acid tubular fluid. Diffusion of NH_3 across membranes of collecting duct cells occurs by way of glycoproteins that are in the family of the Rh factor, red blood cell ammonia transporters. The efficient secretion of ammonium in the collecting duct and by acid trapping in the lumen is essential for excretion of acid from the body.

Regulation is accomplished at a number of levels. Hormones such as angiotensin II and catecholamines stimulate Na^+ reabsorption in the proximal tubule by increasing sodium-hydrogen exchange and $NaHCO_3$ cotransport. Aldosterone increases H^+-ATPase in the collecting duct cell and stimulates Na^+ reabsorption, thereby increasing proton secretion. Low extracellular fluid volume increases proximal HCO_3^- reabsorption, as does hypokalemia and high P_{CO_2}. Hyperkalemia (Chapter 103) may limit urinary acidification by decreasing the amount of NH_3 absorbed in the thick limb and, as a result, the amount entering the countercurrent multiplier in the loop of Henle. Hyperkalemia also decreases the secretion of H^+ in the collecting duct as the need to secrete K^+ predominates.

CLINICAL MANIFESTATIONS AND DIAGNOSIS

Assessment of clinical acid-base disturbances usually begins with measurement of arterial blood gases (Fig. 104-1 and Table 104-3). In some situations, venous blood can be used as an alternative.

It is useful to conceptualize acid-base disorders by a mass action shift of the variables to the right or left in the following relationship:

$$H^+ + HCO_3^- \leftrightarrow H_2CO_3 \leftrightarrow CO_2 + H_2O$$

The addition of CO_2, as in respiratory acidosis, will increase the hydrogen and bicarbonate concentrations (left shift). Removal of CO_2, as in respiratory alkalosis, will decrease CO_2, protons, and bicarbonate (shift right). The addition of protons with an anion other than HCO_3^-, as in metabolic acidosis, will lead to increased concentrations of protons and a decreased bicarbonate concentration. Removal of HCO_3^- with a cation such as Na^+, also a cause of metabolic acidosis, will increase the proton concentration and lower the HCO_3^- concentration. Metabolic alkalosis might be caused by the addition of $NaHCO_3$ with a resulting decrease in the proton concentration or by removal of H^+ with chloride, thereby leading to a decreased proton concentration and increased HCO_3^-. Because of the relationship of metabolic acidosis and alkalosis to the gain or loss of fluids and electrolytes, acid-base disorders can be considered a consequence of electrolyte imbalance.[3]

Compensatory Changes

Few patients have an isolated acid-base disturbance. In nearly all cases, a respiratory or renal compensation (or both) occurs in response to counteract a primary acid-base process.[4]

When functioning normally, the lungs may maintain a normal pH and P_{CO_2} during changes in volatile acid production. The kidneys will also maintain normal acid-base balance during changes in fixed acid production. Only excesses beyond the capacity to eliminate an acid or alkali load will lead to clinical disturbances. Patients with renal or lung disease may do less well in response to metabolic and respiratory disorders.

When an acid-base disturbance develops, the initial response to modulate its severity depends on the titration of various body buffer pairs. For example, phosphate, hemoglobin, and albumin change their protonated and unprotonated concentrations. The body will further attempt to correct the extracellular pH toward normal but usually not to normal. For metabolic disturbances caused by increased or decreased nonvolatile acid, the response is respiratory; for primary respiratory acidosis and alkalosis, the compensation is renal (Table 104-4). The direction of change in HCO_3^- and P_{CO_2} is the same when the primary disturbance is compensated; the ratio of HCO_3^- to

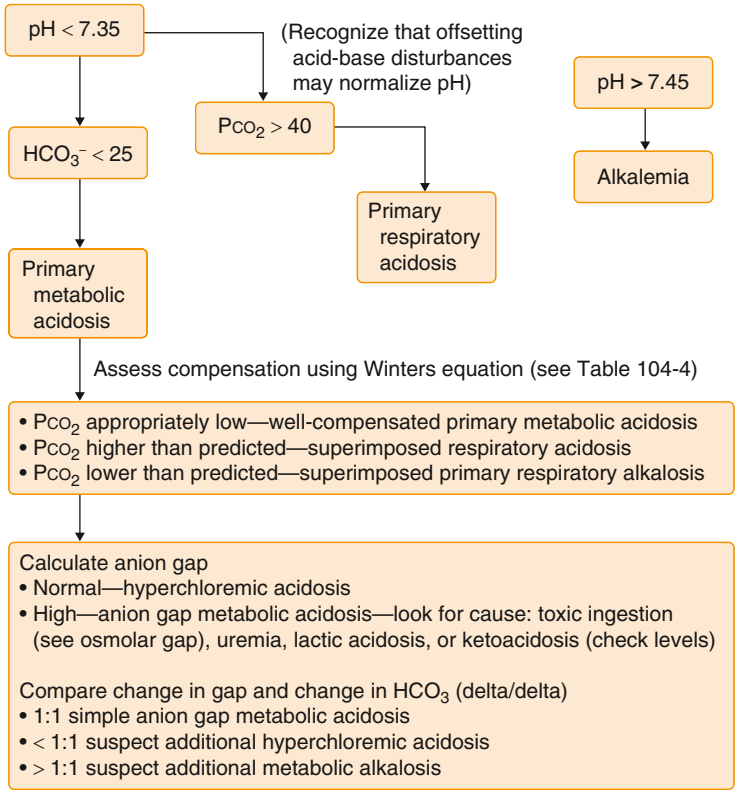

FIGURE 104-1. Evaluation of acidemia. In an anion gap acidosis, a simple 1 : 1 relationship is usually not present because organic anions are variably cleared by organs such as liver and kidney, and because the apparent volume of distribution of organic anions and bicarbonate may differ. In lactic acidosis, a 1 : 1 relationship is usually not present because of clearance of lactic acid from the circulation. In the Cori cycle, muscle lactic acid is taken up by liver cells via monocarboxylic acid transporters, and the lactate goes to re-form glucose via the gluconeogenic pathway. The glucose recycles to the muscle, where it is used for further energy. Another reason the ratio is not 1 : 1 is that lactate anion can be cleared with Na^+ by urinary excretion.

P_{CO_2} and thus pH become closer to normal. These compensations tend to take time, so acid-base disturbances, particularly the respiratory conditions requiring renal compensation, are classified as acute (lasting less than 24 to 48 hours) or chronic.

Peripheral blood does not demonstrate complete compensation for most acid-base disturbances, with the occasional exception of chronic respiratory alkalosis. Full compensation for metabolic acidosis would expend large amounts of respiratory muscle energy, which could limit a prolonged response. Full compensation for metabolic alkalosis would result in excessive hypoventilation and adverse effects on oxygenation. In both situations, the body requires an offset from "normal" to drive continued renal compensation. The degree of offset can be very close, or not that close, to normal. In contrast, the CNS closely regulates its pH, with nearly full correction within 1 to 2 days. Before this compensation occurs, acute alkalemia may be associated with cerebral vasoconstriction and ischemia, whereas acidemia may result in vasodilation and cerebral edema. Rapid changes in blood P_{CO_2} affect the CNS chemosensors more quickly than do changes in HCO_3^- because of more rapid movement of nonionic CO_2 across the blood-brain barrier. Increases in CNS CO_2 lead to acidification of the medullary center interstitial fluid and an increased ventilatory drive. Decreases in CNS CO_2 (alkalinization of the respiratory center) lead to hypoventilation. Acid-base changes are reflected in the composition of the cerebrospinal fluid (CSF).

In metabolic acidosis, peripheral chemosensors in the carotid body stimulate the CNS to increase ventilation to reduce P_{CO_2}. The fall in peripheral P_{CO_2} will lead to dissolved CO_2 leaving the CNS ahead of HCO_3^-; the alkalinization of the medullary center interstitial fluid will then slow the hyperventilatory response until a new steady state of hypocapnia is achieved. Patients may sense dyspnea or air hunger acutely with rapid and shallow respirations. In severe cases of metabolic acidemia, the respirations are deep and gasping, typical of Kussmaul breathing.

When the bicarbonate concentration increases as a result of metabolic alkalosis, a hypoventilatory response, signaled from the peripheral chemosensors, raises P_{CO_2}. As P_{CO_2} rises, the dissolved CO_2 will enter the CSF and acidify

TABLE 104-3 LABORATORY STEPS IN IDENTIFYING ACID-BASE DISORDERS

EVALUATE pH	ACIDEMIC	ALKALEMIC
Elevated P_{CO_2}	Respiratory acidosis	Metabolic alkalosis
Elevated HCO_3	Respiratory acidosis	Metabolic alkalosis
Decreased P_{CO_2}	Metabolic acidosis	Respiratory alkalosis
Decreased HCO_3	Metabolic acidosis	Respiratory alkalosis
EVALUATE FOR EXPECTED COMPENSATION		
Meets expectation: simple disorder with compensation or could be offsetting metabolic alkalosis and acidosis. *Does not meet expectation:* complex disorder, but pH indicates whether acidosis or alkalosis is dominant. *If a metabolic disorder is dominant,* a P_{CO_2} greater than predicted indicates an additional respiratory acidosis. A P_{CO_2} less than predicted indicates an additional respiratory alkalosis. *If a respiratory disorder is dominant,* an HCO_3 concentration greater than predicted indicates additional metabolic alkalosis. An HCO_3 concentration less than predicted indicates an additional metabolic acidosis.		
ASSESS ANION GAP		
Elevated: metabolic acidosis is present whether acidemic or alkalemic. If alkalemic, an additional metabolic or respiratory alkalosis is present. *If the gap is greater than the fall in HCO_3,* consider an additional metabolic alkalosis or respiratory acidosis. *If the gap is less than the fall in HCO_3,* consider an additional nongap acidosis or respiratory alkalosis.		

TABLE 104-4 EXPECTED DEGREES OF COMPENSATION IN ACID-BASE DISORDERS

DISORDER	EXPECTED COMPENSATION
Metabolic acidosis	Steady state in 12-36 hours Expected $P_{CO_2} = 1.5$ (measured HCO_3) + 8 ± 2 (Winters equation)
Metabolic alkalosis	Less predictable Expected P_{CO_2} increases 0.5 – 0.7 mm Hg per 1-mEq/L increase in HCO_3
Respiratory acidosis Acute Chronic, after 24-36 hours	Expected 1-mEq/L increase in HCO_3 per 10-mm Hg rise in P_{CO_2} Expected 3- to 5-mEq/L increase in HCO_3 per 10-mm Hg rise in P_{CO_2}
Respiratory alkalosis Acute Chronic, after 24-36 hours	Expected 1- to 2-mEq/L fall in HCO_3 per 10-mm Hg fall in P_{CO_2} Expected 5-mEq/L fall in HCO_3 per 10-mm Hg fall in P_{CO_2}

the medullary respiratory center. The stimulus to breathe will, in part, antagonize the peripheral signal until a steady state of hypoventilation is reached.

In respiratory acidosis, acute hypoventilation results in hypercapnia, because of the decreased clearance of carbon dioxide. The fall in blood pH and proximal tubular cell acidification results in compensatory ammoniagenesis and increased net renal acid excretion. When the P_{CO_2} reaches a new higher steady-state value, indicating that the production and elimination of carbonic acid have become equal at this low ventilatory rate, no further acid is retained, so further ammoniagenesis and net acid excretion are no longer required. However, the HCO_3^- produced during the period of high acid excretion persists at a high level because the high P_{CO_2} and hypochloremic volume depletion maintain proximal HCO_3^- reabsorption. The hypochloremia, brought about by the compensatory early excretion of NH_4Cl and elevated serum HCO_3^- and then maintained by the high P_{CO_2}, persists until the extracellular volume is replaced with NaCl. An abrupt decrease in P_{CO_2}, such as by mechanical ventilation, cannot correct the high HCO_3^- until chloride returns to its normal level. Reducing the P_{CO_2} before correcting the lost chloride results in post-hypercapnic metabolic alkalosis.

In respiratory alkalosis, the primary event is a fall in P_{CO_2} because of increased alveolar ventilation. On transition from acute to chronic respiratory alkalosis, the compensatory mechanisms that initially maintained a more normal systemic pH are no longer required as CO_2 production and elimination become equal. Thus, the initial compensatory decrease in renal acid excretion brought about by increased loss of filtered $NaHCO_3$ ceases, but low serum HCO_3^- and high serum Cl^- concentrations are maintained because the persistent hypocapnia induces proximal tubule bicarbonaturia. Once a lower steady-state level of HCO_3^- is achieved, net renal acid excretion returns to baseline.

In identifying whether an acid-base disturbance is simple (a single disturbance with its compensation) or complex (multiple primary processes simultaneously present), it is useful to compare the expected compensation for a simple process with the observed parameters of the blood gases (see Table 104-3). For example, if P_{CO_2} is lower than would be predicted by the Winters equation in a patient with a simple, compensated metabolic acidosis, an additional coexistent primary respiratory alkalosis must be driving the P_{CO_2} down. If P_{CO_2} is higher than would be predicted for a low bicarbonate level in a patient with metabolic acidosis, a coexistent respiratory acidosis is present.

METABOLIC ACIDOSIS

EPIDEMIOLOGY AND PATHOBIOLOGY

In metabolic acidosis, the primary change is a fall in serum bicarbonate.[5] The compensatory response is to increase ventilation to reduce P_{CO_2}. Worsening acidosis elicits increasing alveolar ventilation.

Primary metabolic acidosis results from an imbalance between net acid production and net acid excretion in the form of urinary ammonium excretion and acid phosphate excretion. Increased excretion of acid phosphate and other weak acids is called total titratable acidity when measured in the urine. Consider the following relationship, where U_x represents the urinary concentration and the urinary flow rate $\dot{V}$:

$$NAE = (U_{NH4} \times \dot{V}) + (U_{TAphos} \times \dot{V}) - (U_{HCO_3^-} \times \dot{V})$$

In a normal steady-state condition, the rate of excretion of net acid must be equal to the rate of production. The normal production rate depends on diet. If net acid production is normal, metabolic acidosis could occur because of a failure to reabsorb bicarbonate or a failure to secrete adequate net acid, as is the case in renal failure and renal tubular acidosis. An inequality also could develop if net acid production were excessive or if large extrarenal bicarbonate losses were unable to be matched by maximal adaptive increases in net acid excretion. Endogenous sources of acid include ketoacidosis and lactic acidosis, whereas exogenous sources might be acid metabolic products of ingested ethylene glycol or methanol. On occasion, strong inorganic acids may be ingested. When net acid is retained, the serum bicarbonate concentration falls. However, maintenance of a constant low serum HCO_3^- concentration does not guarantee that there is a new steady state in which net acid production is equal to net acid excretion because body buffers such as carbonate salts of bone may become progressively depleted by relentless acid retention, as in chronic kidney disease and distal renal tubular acidosis.

The causes of metabolic acidosis are usually categorized according to the presence of either hyperchloremia or an elevated serum anion gap. The serum anion gap is the net charge difference when the sum of chloride and bicarbonate is subtracted from the serum sodium concentration.

$$\text{Anion gap} = [Na^+] - ([Cl^-] + [HCO_3^-])$$

The normal anion gap is due to the net unmeasured anionic charge associated predominantly with albumin. When acidemia is present, albumin is in a more protonated form, which lowers the normal gap. In alkalemia, the effect of pH is to increase the gap attributed to albumin. Each 1 g/dL of albumin contributes approximately 2.5 mEq/L to the normal anion gap. The anion gap may be low with hypoalbuminemia or with an increase in unmeasured cations, such as immunoglobulin G myeloma paraproteins, calcium, lithium, or magnesium. The anion gap may be high in the presence of unmeasured anions, including sulfates, bromides, iodides, and immunoglobulin A myeloma light

chains. When the anion gap is increased above the normal value of 10 to 12 mEq/L by a non-chloride acid anion, an anion gap metabolic acidosis exists. The accompanying proton is responsible for lowering the serum bicarbonate concentration. The degree of increase in the anion gap, sometimes referred to as the *delta anion gap,* may be estimated by the difference between the observed anion gap and a normal value of 10 to 12 mEq/L. A similar calculation for a change in serum HCO_3^- can be made by subtracting the observed HCO_3^- from the normal value of about 25 mEq/L (the *delta* HCO_3^-). Comparison of the two values (the *delta-delta*) may help identify more complicated acid-base disorders. If the increase in the anion gap is larger than the decrease in serum HCO_3^-, an additional process is raising the HCO_3^- level. The patient may have a coexisting metabolic alkalosis or be compensating for chronic respiratory acidosis. If the decrease in serum HCO_3^- is larger than the increase in the anion gap, it is a sign of another process that raises the Cl^- while lowering the HCO_3^- level, such as an additional hyperchloremic acidosis or respiratory alkalosis. In most anion gap acidoses, the increase in anion gap and the decrease in HCO_3^- is not usually greater than 1 : 1 because the excretion of urinary anions with Na^+ results in a hyperchloremic component to the acidosis. (See Fig. 104-1 and its legend.) Conversely, any buffering of H^+ with non-HCO_3^- buffers will decrease the drop in HCO_3^- compared with the increase in anion gap. In severe cases of anion gap acidosis, Cl^- may be displaced into cells, thereby resulting in a higher anion gap compared with the decrease in HCO_3^-—a hypochloremic anion gap acidosis.

CLINICAL MANIFESTATIONS

The effects of metabolic acidosis depend on its rapidity of onset and severity. Patients often complain of fatigue, nausea, vomiting, shortness of breath, and dyspnea on exertion. Acutely, deep respirations, often labored with the use of accessory muscles, may be detected, but hyperventilation may be less notable with chronic metabolic acidemia. Metabolic acidemia also may be associated with vasodilation, tachycardia, and hypotension (Chapter 92). The negative inotropic effect of acidemia on the heart can exacerbate septic shock (Chapter 94). The stress of an underlying illness or an increase in adrenergic and corticosteroid activity associated with acidemia may elevate the peripheral white blood cell count and cause hyperglycemia. Other findings can include hyperkalemia (Chapter 103), hyperphosphatemia (Chapter 105), and hyperuricemia (Chapter 252) as well as hypocalcemia (Chapter 227) and markers of bone injury as a result of decreased renal synthesis of 1,25-dihydroxyvitamin D.

ANION GAP METABOLIC ACIDOSES

A variety of abnormalities can cause anion gap acidoses.[6] One mnemonic for the common ones is *gold mark,* for *g*lycols (ethylene and propylene), *o*xoproline, L-lactate, D-lactate, *m*ethanol, *a*spirin, *r*enal failure, and *k*etoacidosis. Because some causes are life-threatening, a rapid diagnosis is required. The osmolar gap should be calculated in all cases of anion gap acidosis (Table 104-5) because unmeasured toxic, nonionic alcohols will contribute to body osmolality but not to acidity. Although not acidic themselves, these alcohols oxidize to dangerous unmeasured organic acids with anions that contribute only to the anion gap. The osmolar gap is defined as the difference between the measured and the calculated serum osmolality. The serum osmolality should be measured by a freezing point depression technique and compared with the calculated osmolality.

$$\text{Calculated osmolality} = 2(Na^+) + (\text{Glucose [mg/dL]} \div 18) + (\text{Blood urea nitrogen [mg/dL]} \div 2.8)$$

UREMIC ACIDOSIS

The metabolic acidosis of advanced chronic kidney disease (Chapter 116) may be due to tubular leakage of HCO_3^-, but it is usually present when inadequate production of ammonium is unable to facilitate excretion of the normal metabolic acid load.[7] Because, of the low buffering capacity in the urine, many patients with renal failure maintain the ability to acidify their urine maximally. Many organic and inorganic anions, such as phosphate and sulfates, are retained at glomerular filtration rates of less than 25 mL/minute and constitute an increased anion gap in association with the metabolic acidosis. The magnitude of the gap is usually less than 20 mEq/L consisting of poorly filtered sulfates and phosphates and retention of anions that are suboptimally secreted. The renal patient who is maximally producing NH_3 to stay in balance with daily acid production may be unable to accommodate any further acid production, such as a metabolic or respiratory acidosis, that would require increased ammoniagenesis. The patient with poor glomerular filtration and an alkaline load will retain HCO_3^-, thereby worsening both metabolic and respiratory alkalosis. For example, metabolic alkalosis commonly occurs instead of urinary alkalinization when HCO_3^- is used in the attempt to alkalinize the urine in a patient with kidney failure. The systemic acid-base disturbance in renal diseases with prominent tubular dysfunction is attributable to the kidney's inability to secrete hydrogen and to reabsorb and generate HCO_3^-. It is particularly pronounced in oliguric acute kidney injury and is exacerbated by hypercatabolic states such as infection. A significant metabolic acidosis disproportionate to the severity of chronic kidney disease of unknown cause should raise the possibility of tubular dysfunction due to urinary tract obstruction or chronic tubulointerstitial diseases (Chapter 108), including amyloidosis (Chapter 174), myeloma (Chapter 173), autoimmune disorders (Chapter 236), and analgesic nephropathy (Chapter 108).

It is important to treat the metabolic acidosis of chronic kidney disease.[8] Maintaining the serum HCO_3^- concentration above 20 to 22 mEq/L, by administering $NaHCO_3$ at a rate of 1 mEq HCO_3^-/kg/day, will slow the progression of chronic kidney disease, delay end-stage renal failure, and improve nutritional status.

TABLE 104-5 CAUSES OF INCREASED ANION AND OSMOLAR GAPS

ANION GAP METABOLIC ACIDOSIS	OSMOLAR GAP
Uremia	No
Lactic acidosis	Variable/no
D-Lactic acidosis	No
Diabetic ketoacidosis	No
Starvation ketoacidosis	No
Alcoholic ketoacidosis	If ethanol is present
Ethylene glycol	Yes
Methanol	Yes
Salicylates	No
5-Oxoprolinuria (acetaminophen)	No

PROGNOSIS

In population studies, a low serum bicarbonate level is associated with higher all-cause mortality. The relative risk of death is about 2.6-fold higher in patients with chronic kidney disease and about 1.7-fold higher even without it.

OVERPRODUCTION OF ENDOGENOUS ACIDS

Lactic Acidosis

EPIDEMIOLOGY AND PATHOBIOLOGY

Overproduction of lactic acid may occur with severe exertion, but true lactic acidosis (lactate level >4 mmol/L or >36 mg/dL) is frequently associated with critical illness, multiorgan failure, and increased mortality. Lactic acid, which is the final product in the anaerobic pathway of glucose metabolism, is produced from pyruvate in a reaction catalyzed by lactate dehydrogenase:

$$NADH + \text{pyruvate} + H^+ \rightarrow \text{lactate} + NAD^+$$

A high reduced nicotinamide adenine dinucleotide (NADH)/NAD ratio will favor the formation of lactate. Conversion of ethanol to acetaldehyde and conversion of β-hydroxybutyrate to acetoacetate use NAD and produce NADH. Alcohol metabolism may be associated with excessive β-hydroxybutyrate and lactic acidosis.

Lactic acidosis is caused by an imbalance in the rates of lactate production and its clearance, primarily in the liver. Lactic acidosis, which increases the anion gap, is most often due to circulatory failure, hypoxia, sepsis, and mitochondrial dysfunction that each increase anaerobic glycolysis and the rate of conversion of pyruvate to lactate (Table 104-6).[9] Sepsis (Chapter 94) is associated with an elevated lactate level because of poor clearance and impaired gluconeogenesis.[10] Lactic acidosis can also result from seizure activity (Chapter 372) when lactate is released from muscle cells that have sustained a period of anaerobic metabolism. Other causes include thiamine deficiency (Chapter 199), hypophosphatemia (Chapter 105), isoniazid toxicity (Chapter 96), and hypoglycemic states (Chapter 211). Metformin may cause lactic acidosis, particularly in elderly patients with cardiac, hepatic, or renal dysfunction.

TABLE 104-6 CAUSES OF LACTIC ACIDOSIS

Shock (Chapter 92): septic (Chapter 94), cardiogenic (Chapter 93), or hypovolemic
Advanced heart failure (Chapters 45 and 46)
Severe trauma (Chapter 97)
Severe hypoxemia (Chapter 90) with Pao_2 <30 mm Hg
Carbon monoxide poisoning (Chapter 82)
Severe anemia (Chapter 144) with hemoglobin level <5 g/dL
Vigorous exercise, seizures (Chapter 372), or shivering (Chapter 95)
Diabetes mellitus (Chapter 210), usually in association with ketoacidosis
Cancer (especially lymphomas [Chapters 171 and 172], leukemias [Chapters 168,169 and 170], and solid tumors)
Liver disease with decreased lactate clearance (Chapter 140)
High plasma metformin levels
Nucleoside reverse-transcriptase inhibitors
Cocaine (Chapter 365)
Toxic alcohols, methanol, ethylene glycol, diethylene glycol (Chapter 96)
Propylene glycol (Chapter 96)
Salicylates (Chapter 70)
Cyanide (Chapter 96)
β_2-Agonists (Chapter 75)
Propofol (after prolonged high-dose infusion; Chapter 400)
Thiamine deficiency in children or adults receiving parenteral nutrition or those with fulminant beriberi (Chapters 198 and 199)

Adapted from Kraut JA, Madias NE. Lactic acidosis. *N Engl J Med*. 2014;371:2309-2319.

Nucleoside antivirals (Chapter 357), including zidovudine, may cause lactic acidosis and abnormal liver function as a result of toxic mitochondrial effects. Abnormal mitochondrial function is also a feature of aspirin overdose (Chapter 70) or toxicity with hypoglycin from ingestion of the unripe ackee fruit (Jamaican vomiting sickness). The antibiotic linezolid is another cause of lactic acidosis.

Lactic acidosis also can be caused by the overproduction of the acid, which may occur with severe exertion and malignant neoplasms, particularly with a large tumor burden from lymphoma or widely metastatic cancer. Malignant cells can upregulate glycolytic activity, which may increase their uptake of glucose and decrease their dependence on mitochondrion-derived energy. These tumors can use large amounts of available glucose and inorganic phosphate, thereby leading to a syndrome of hypoglycemia, hypophosphatemia, and lactic acidosis.

CLINICAL MANIFESTATIONS AND DIAGNOSIS

Lactic acidosis typically presents with a blood pH of 7.35 or lower and a serum HCO_3^- 20 mEq/L or lower. To make the diagnosis, however, the serum lactate level should be directly measured in any patient with an anion gap acidosis. Glucose, creatinine, and blood urea nitrogen levels also should be obtained. In cases in which a toxic ingestion is suspected (see Table 104-5), a screen for such toxins in the serum should be performed.

TREATMENT

Treatment of lactic acidosis is aimed at correction of the underlying cause. Central venous oxygen saturation should be increased, with a goal of at least 70%, by restoring tissue perfusion and ventilation. In general, the mean arterial pressure should be maintained at 65 to 70 mm Hg, the heart rate below 100 beats/minute, and the hemoglobin level over 7 g/dL.

Sodium bicarbonate can be considered when the arterial pH is below 7.0 or when acidemia has resulted in decreased cardiac inotropy or systemic vasodilation and shock. It is preferable to give $NaHCO_3$ as an isotonic mixture in 5% dextrose and water rather than as a hypertonic bolus, because the latter carries the risk of pulmonary edema and hypernatremia. The quantity of administered sodium bicarbonate to raise arterial pH to 7.2 should be estimated by multiplying the desired bicarbonate concentration minus the observed bicarbonate concentration by 50% of body weight. The calculated amount in patients with severe acidosis may require continuous dialytic methods to administer adequate amounts of bicarbonate without causing volume overload. Full correction should be avoided.

In patients with a metabolic acidosis after seizures (Chapter 372), the lactate is quickly metabolized to HCO_3^- by the liver and kidneys, and the acidosis often resolves within 60 minutes. The administration of HCO_3^- is usually unnecessary and may precipitate an overshoot metabolic alkalosis as the lactate is metabolized, which lowers the seizure threshold.

In patients with intestinal bacterial overgrowth (Chapter 126), a syndrome of disorientation, ataxia, and anion gap metabolic acidosis may develop after a carbohydrate meal because of bacterial production of D-lactate. This isomer of the mammalian L-lactate can be measured only by a specific D-lactate assay. The condition is treated with oral antibiotics and appropriate diet.

PROGNOSIS

Lactic acidosis, when severe, is associated with a high early mortality. When the pH is less than 7.2, only 17% of patients who are admitted to an intensive care unit are ultimately discharged from the hospital.

Diabetic Ketoacidosis

EPIDEMIOLOGY AND PATHOBIOLOGY

Diabetic ketoacidosis is defined as hyperglycemia with metabolic acidosis resulting from generation of the acids of the anions β-hydroxybutyrate (a hydroxy acid) and acetoacetate (a ketoacid) in response to insulin deficiency and elevated counter-regulatory hormones such as glucagon.[11] It is most commonly seen in cases of type 1 diabetes mellitus but can occasionally be seen in type 2 diabetes mellitus (Chapter 210). Diabetic ketoacidosis is more common in vulnerable populations with less access to quality medical care.

The lack of insulin increases lipolysis in adipose tissue; free fatty acids are transported to the liver, where hepatic mitochondria produce ketoacid anions, including acetoacetate, from acetyl coenzyme A. In the presence of high NADH/NAD ratio, the more reduced form of β-hydroxybutyrate is produced.

CLINICAL MANIFESTATIONS

Symptoms include nausea, vomiting, anorexia, polydipsia, and polyuria. Patients often exhibit Kussmaul respirations and volume depletion. Neurologic symptoms include fatigue and lethargy with depression of the sensorium. CSF exhibits a change in acid-base status with treatment of diabetic ketoacidosis. Even without bicarbonate administration, CSF pH falls as a result of the ventilatory response to the correction of acidosis and the sudden rise in Pco_2. However, no correlation between decreased CSF pH and depression of sensorium has been established. Ketoacidosis is also seen in cases of starvation, in which it is generally mild and not associated with hyperglycemia.

Ketoacid anions in the urine may be accompanied by cations, including sodium and potassium, thereby contributing to an osmotic diuresis with depletion of volume and potassium. The overall electrolyte status in diabetic ketoacidosis may be relative chloride retention, a mixed anion gap, and hyperchloremic acidosis. The delta HCO_3^- may exceed the delta anion gap, especially if the glomerular filtration rate and the filtered load of ketoacid anions are high, thereby facilitating their excretion with sodium and potassium. The serum anion gap in general will be greatest when renal failure is present because the additional anions cannot be cleared from extracellular fluid.

DIAGNOSIS

The urinary dipstick nitroprusside test for ketones may underestimate the degree of ketosis because it does not detect β-hydroxybutyrate; in fact, the ketone test result may become more positive as treatment helps metabolize β-hydroxybutyrate to acetoacetate. This problem should be addressed by direct measurement of serum β-hydroxybutyrate. Diabetic patients also are more prone to lactic acidosis because an increase in NADH favors the formation of lactate from pyruvate, and pyruvate dehydrogenase is inhibited in the absence of insulin.

TREATMENT

Treatment of diabetic ketoacidosis (Chapter 210) consists of volume repletion, insulin administration with dextrose if necessary to avoid hypoglycemia, and potassium replacement (Chapter 103). Bicarbonate administration should be considered only if ketoacidosis is accompanied by shock or if arterial pH is less than 7.0 or 7.1, and bolus infusion should be avoided. The administration of bicarbonate occasionally results in cerebral edema significant enough to lead to loss of consciousness and even death.

PROGNOSIS

Most patients with diabetic ketoacidosis recover. In the less than 0.5% of patients who present with coma from cerebral edema, the mortality rate ranges from 20% to as high as 90%. The cerebral edema may be exacerbated by bicarbonate administration, which is discouraged in this situation.

Salicylate Intoxication

EPIDEMIOLOGY AND PATHOBIOLOGY

Salicylate intoxication can be caused by accidental overdose, therapeutic overdose, or a suicide attempt (Chapters 70 and 96).[12] Salicylate functions as an

uncoupler of oxidative phosphorylation and consequently results in increased oxygen consumption and production of CO_2, as well as production of mixed organic acid, thereby causing an anion gap metabolic acidosis. However, the increase in alveolar ventilation resulting from stimulation of central chemoreceptors overcomes this increase in CO_2.

CLINICAL MANIFESTATIONS AND DIAGNOSIS

The most common clinical manifestation is a combined anion gap metabolic acidosis and respiratory alkalosis, although the condition also can be manifested as either one or the other only. Children are often seen with metabolic acidosis, whereas adults often have predominant respiratory alkalosis. Hypoglycemia, ketoacidosis, and lactic acidosis may result. Other manifestations of intoxication include hemorrhage, fever, nausea and vomiting, hyperventilation, diaphoresis, tinnitus, and occasionally polyuria followed by oliguria. Severe cases may lead to seizures, respiratory depression, and coma. Noncardiogenic pulmonary edema is sometimes seen in adults.

Respiratory alkalosis is the result of a direct stimulatory effect of salicylate on the medullary respiratory control center. Salicylate intoxication also increases the metabolic rate. Diagnosis is suspected by the clinical presentation and confirmed by the salicylate level (Chapters 70 and 96).

Treatment of salicylate intoxication (Chapter 96) is aimed at correction of the metabolic acidosis and removal of salicylate. Bicarbonate as a sodium salt should be administered according to an estimated calculation of the deficit if metabolic acidosis predominates. Salicylates are removed by alkaline diuresis because the less reabsorbable salicylate anion will predominate when the urine pH increases. Urinary alkalinization with acetazolamide should be used cautiously because carbonic anhydrase inhibition may impair CO_2 transport from tissue to blood and potentially worsen acidosis in the respiratory center. In severe intoxication (salicylate concentrations greater than 35 80 mg/dL) or when renal failure is present, dialysis may be required.

PROGNOSIS

The prognosis of salicylate toxicity is better with early diagnosis and prompt management, in which case most patients do well. Patients who ingest oil of wintergreen (methyl salicylate) may have more severe deterioration because of the high lipid solubility of the drug.

Alcoholic Ketoacidosis

EPIDEMIOLOGY AND PATHOBIOLOGY

Alcoholic ketoacidosis occurs in a patient who has been drinking very heavily without eating.[13] The pathophysiologic mechanism is based on the overproduction of the acids of β-hydroxybutyrate and, to a lesser extent, acetoacetate because of an increased production of free fatty acids from adipose tissue. Alcohol inhibits the conversion of lactate to glucose in the liver. The oxidation of ethanol increases the ratio of NADH to NAD^+ and favors the production of β-hydroxybutyrate from acetoacetate. Damage to mitochondria by alcohol can further elevate the ratio of β-hydroxybutyrate to acetoacetate by preventing reoxidation of NADH to NAD. The oxidative metabolism of ethanol favors the reaction of dehydrogenase enzymes to form β-hydroxybutyrate and lactate (opposing glucose production).

CLINICAL MANIFESTATIONS

Alcoholic ketoacidosis usually follows binge drinking and may be associated with withdrawal symptoms (Chapters 364 and 384) and the associated hyperadrenergic state. Alcoholic ketoacidosis is associated with abdominal pain, vomiting, starvation, and volume depletion. In contrast to diabetic ketoacidosis, coma is rare. Blood glucose levels are generally low or normal, and the insulin level is frequently low, with elevated glucagon (favoring ketogenesis) and cortisol levels. Some patients have hyperglycemia because of the increased catecholamine response.

DIAGNOSIS

Initially, patients typically have a high osmolar gap from ethanol or acetone. When serum alcohol or acetone levels become zero, the osmolar gap should disappear. A clue to the diagnosis of toxic alcohol ingestion is the simultaneous presence of an anion gap metabolic acidosis and an osmolar gap. The osmolar gap, if due to ethanol, should equal the ethanol concentration in milligrams per deciliter divided by 4.6. If this calculation does not yield the expected gap based on the ethanol level, ingestion of another alcohol, such as methanol, isopropanol, or ethylene glycol, should be suspected (see Table 104-2).

If possible, ethanol, ethylene glycol, propylene glycol, and methanol levels should be measured directly; each is associated with a metabolic acidosis. In contrast, isopropanol metabolizes to acetone and causes ketosis without acidosis. An osmolar gap may be present.

TREATMENT

Treatment of alcoholic metabolic acidosis consists of volume repletion with normal saline in dextrose; administration of thiamine (50 to 100 mg); treatment of hypoglycemia; and the correction of any hypophosphatemia (Chapter 105), hypokalemia (Chapter 103), and hypomagnesemia (Chapter 105) that may be present. The acid-base disturbance usually resolves after several hours. Both hypophosphatemia and thiamine deficiency, which may not be apparent until 12 to 24 hours after the initiation of treatment in an undernourished patient, are exacerbated by glucose administration and may contribute to an associated lactic acidosis.

PROGNOSIS

The prognosis of alcoholic ketoacidosis is usually favorable. The long-term outlook is more closely tied to other complications of continued alcohol abuse.

5-Oxoprolinuria

5-Oxoprolinuria, which is an acquired form of anion gap metabolic acidosis, is increasingly recognized in patients who have glutathione depletion associated with underlying chronic illness, malnutrition, diabetes, alcoholism, or cancer, especially in the context of a high therapeutic level or overdose of acetaminophen. It has been observed without concomitant hepatic failure. Glutathione, which is a tripeptide consisting of glutamate, cysteine, and glycine, has many functions, including protection from cellular toxins, combating of oxidative stress, and shuttling of amino acids into the cytosol by the γ-glutamyl transpeptidase pathway. Hereditary forms of 5-oxoprolinuria are associated with γ-glutamyl transpeptidase cycle enzyme deficiencies (5-oxoprolinase and glutathione synthase). The usual production of 5-oxoproline is by release of the transported amino acid from the γ-glutamyl–amino acid dipeptide. The enzyme 5-oxoprolinase re-forms glutamate to re-enter the cycle as glutamylcysteine. Acetaminophen causes further depletion of glutathione due to binding of an acetaminophen metabolite, *N*-acetyl-*p*-benzoquinone imine (NAPQI), to glutathione. Treatment with *N*-acetylcysteine, in doses similar to those used for acetaminophen toxicity (Chapter 96), should be considered to decrease further glutathione depletion.

Poisonings

A variety of acute poisonings (Chapter 96) can present as an anion gap acidosis.[14]

Ethylene Glycol

Ethylene glycol (Chapter 96) is commonly found in antifreeze and is used as an industrial solvent. It has a sweet taste, and patients occasionally ingest it as a substitute for ethanol. Although ethylene glycol itself is not particularly damaging, its highly toxic metabolites include the acids of glyoxylate and glycolate, oxalic acid, and ketoaldehydes. Glycolic acid appears to be primarily responsible for the metabolic acidosis observed in this condition. Further, glycolic acid may register as lactic acid in point-of-care measurements of whole blood by the lactic oxidase method, producing an artifactual high lactate level. However if an assay of lactate is performed in the laboratory by lactate dehydrogenase, the true lactate will be significantly less than the value from the lactic acid oxidase method. The difference between these two values, known as the lactate gap, represents glycolic acid.

Intoxication is characterized by profound CNS symptoms, including diplopia, seizures and coma, severe metabolic acidosis, cardiac failure, pulmonary failure, and renal failure. Patients are often dehydrated and hypernatremic because of osmotic diuresis from the renal excretion of the alcohol.

An increased anion gap is attributable to ethylene glycol metabolites. A high osmolar gap also will be present because of the uncharged alcohol. However, an osmolar gap may not be present if all of the alcohol has been converted to the toxic anionic forms. Calcium oxalate crystals in the urine may cause intratubular obstruction and inflammation with acute kidney injury. Treatment is aimed at rehydration with saline and correction of acidosis with $NaHCO_3$ based on an estimate of the bicarbonate deficit. When an osmolar gap exists, competitive inhibition of alcohol dehydrogenase should be initiated with fomepizole at a loading dose of 15 to 20 mg/kg intravenously in 100 mL normal saline

during 30 minutes to 1 hour, followed by a maintenance dose of 10 mg/kg every 12 hours (Chapter 96). If ethanol is used, a solution of 10% ethanol in 5% dextrose can be given as a loading dose of 0.6 g/kg intravenously followed by a maintenance dose of 150 mg/kg per hour in alcoholic patients or 65 mg/kg per hour in nonalcoholic patients. The ethanol level should be maintained at 100 to 200 mg/dL. The goal of therapy is early recognition to prevent metabolism of the uncharged glycol to acidic products. Hemodialysis is required in severe cases. If the diagnosis is made promptly and appropriate therapy is instituted, outcomes are favorable. Renal failure may be reversible.

Methanol

Methanol, wood alcohol, is a component of shellac and windshield wiper fluid and is highly toxic to the CNS after metabolism to formaldehyde and formic acid. Some automotive fluids now contain the less toxic propylene glycol. Optic papillitis may cause blindness. Detection may be made easier if fluorescein has been added to the methanol-containing fluid.

Treatment consists of competitive inhibitors for alcohol dehydrogenase, including ethanol and fomepizole, in similar amounts as for ethylene glycol poisoning, to reduce the formation of acid anions and the anion gap while maintaining a higher level of methanol in the blood (Chapter 96). Hemodialysis may be necessary to increase elimination. Early diagnosis and treatment are associated with a favorable outcome, but visual loss may be permanent. Late presentation is associated with a poor prognosis, particularly if the amount consumed exceeds 30 mL. As with ethylene glycol, the simultaneous presence of ethanol on presentation may help slow the metabolism of methanol and improve outcome.

Isopropyl Alcohol

Toxic ingestion of isopropyl alcohol (Chapter 96), as in rubbing alcohol, does not cause an increased anion gap or ketoacidosis because the metabolite is acetone, but test results for ketones are positive, and a high osmolal gap will be present.

Propylene Glycol

On occasion, patients in the intensive care unit setting are given high doses of intravenous benzodiazepines, such as lorazepam or diazepam, that contain propylene glycol as a diluent. Other intravenous medications that also contain this diluent include phenobarbital, phenytoin, nitroglycerine, and esmolol. Propylene glycol also has been used as a less toxic substitute for methanol in windshield wiper fluid. A high osmolal gap may develop because of the propylene glycol and lead to a clinical picture of sedation, failure to be weaned from the respirator, and an increased lactate level. Propylene glycol can cause a severe lactic acidosis, and patients with this disorder can have a massive osmotic diuresis. Propylene glycol, a 3-carbon glycol, oxidizes to the acids of lactate and pyruvate. Treatment, which consists of early recognition and withdrawal of the offending agent, usually results in a favorable prognosis.

HYPERCHLOREMIC (NORMAL ANION GAP) ACIDOSIS

Hyperchloremic metabolic acidoses (see Table 104-1) can be caused by renal or nonrenal mechanisms and can be associated with an elevated, normal, or low serum potassium level (Fig. 104-2).

HYPERCHLOREMIC METABOLIC ACIDOSIS OF NONRENAL ORIGIN ASSOCIATED WITH NORMAL OR INCREASED POTASSIUM LEVEL

Hyperchloremic metabolic acidoses with a normal or elevated potassium concentration can develop with the administration of chloride salts such as NaCl, KCl, $CaCl_2$, NH_4Cl, arginine and lysine hydrochlorides, or HCl itself. If the quantity of Cl^- introduced exceeds the ability of the kidney to eliminate Cl^- salts in urine, hyperchloremia will develop. Electroneutrality is maintained by a decrease in the serum HCO_3^- concentration, and a hyperchloremic acidosis ensues. Renal production of NH_3 increases in an attempt to improve HCl (NH_4Cl) excretion. Hyperkalemia can occur because the acidemia favors the exit of K^+ from cells. Acidemia also inhibits K^+ secretion in the renal collecting duct.

HYPERCHLOREMIC METABOLIC ACIDOSIS OF NONRENAL ORIGIN ASSOCIATED WITH HYPOKALEMIA

Hypokalemic, hyperchloremic acidosis may result from loss of a body fluid that is low in Cl^- relative to Na^+ and K^+ compared with the ratio of Cl^- to Na^+ in extracellular fluid. For example, stool losses of Na^+, K^+, and HCO_3^- in small bowel diarrhea or organic acid anions of bacterial origin, such as butyrate, in colonic diarrhea lead to hyperchloremic acidosis (Chapter 126). Pancreatic secretions (Chapter 213) or heavy losses from ileostomy sites may lead to loss of bicarbonate-containing fluids. Secretagogues such as vasoactive intestinal peptide (VIP), which is associated with neoplasms of the pancreas or sympathetic chain (Chapter 213), cause large losses of HCO_3^- in stool, with a resulting hypokalemic, hyperchloremic metabolic acidosis. Concomitant gastric achlorhydria is part of the syndrome known as *watery diarrhea, hypokalemic, hypochlorhydric acidosis*. Urinary diversions, such as ureterosigmoidostomies and ileal loops, may increase chloride absorption in exchange for bicarbonate in the intestinal segment and lead to hyperchloremic acidosis. In the presence of urea-splitting bacteria, the net absorption of NH_4Cl can result in both hyperchloremic acidosis and hyperammonemia.

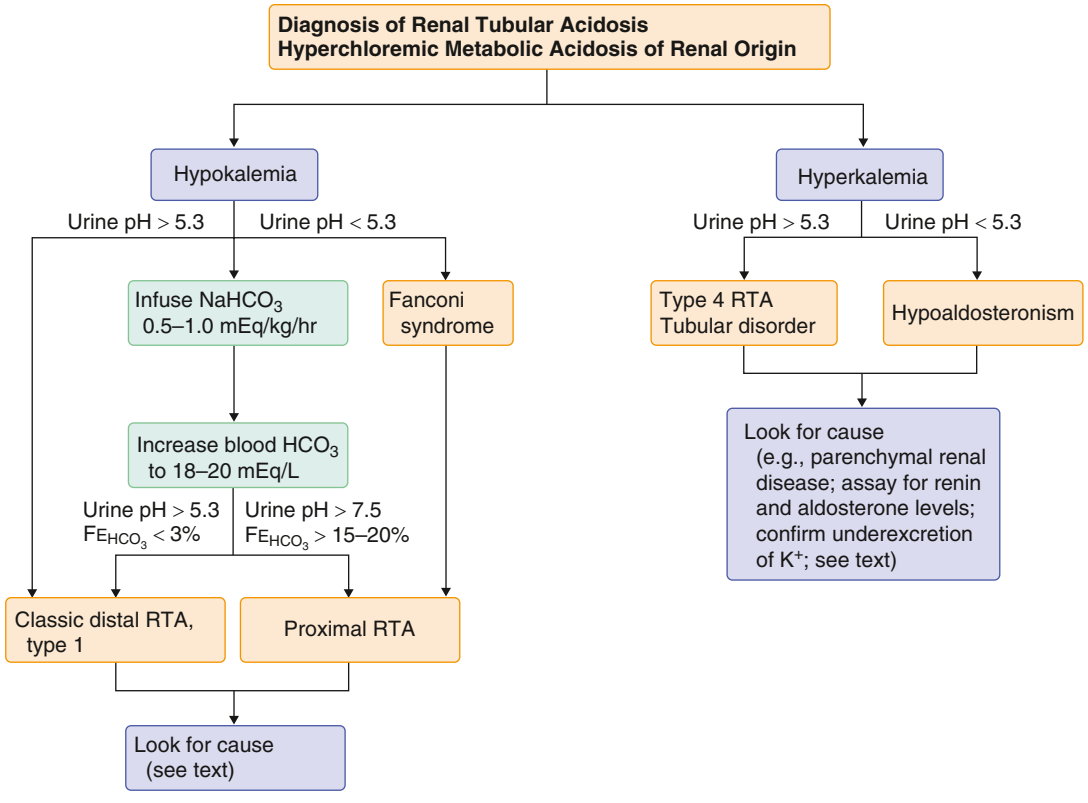

FIGURE 104-2. Evaluation of the patient with suspected renal tubular acidosis, hyperchloremic metabolic acidosis of renal origin. $FeHCO_3$ = fractional excretion of HCO_3^-; RTA = renal tubular acidosis.

RENAL TUBULAR ACIDOSIS TYPES 1 AND 2

Proximal Renal Tubular Acidosis

Renal tubular acidosis causes the cations Na^+ and K^+ to be lost in the urine with HCO_3^- rather than with Cl^-, thereby leading to hyperchloremia.[15] Proximal renal tubular acidosis (type 2) is characterized by a decreased threshold for bicarbonate reabsorption. HCO_3^- wasting and concomitant urinary losses of potassium occur until a lower level of serum bicarbonate reduces the filtered HCO_3^- to a level that the combined function of the dysfunctional proximal tubule and distal nephron can completely reabsorb. At that point, the urine becomes acid (pH < 5.3), and net acid production equals net acid excretion, with a steady-state low plasma HCO_3^-.

Isolated proximal renal tubular acidosis may result from mutations of specific transporters of the proximal tubule, such as the $NaHCO_3$ cotransporter, or from hereditary deficiency of carbonic anhydrase. More commonly, proximal renal tubular acidosis is associated with the Fanconi syndrome or generalized proximal tubule dysfunction. Causes (Table 104-7) include genetic diseases such as glucose-6-phosphatase deficiency (Chapter 147), cystinosis (Chapter 113), hereditary fructose intolerance (Chapter 189), and Wilson disease (Chapter 195). Multiple myeloma (Chapter 173) and Sjögren syndrome (Chapter 247) should be considered in an adult patient. Primary hyperparathyroidism (Chapter 227) results in proximal renal tubular acidosis and hypophosphatemia secondary to inhibition of Na^+/H^+ exchange and sodium phosphate cotransport in the proximal tubule by parathyroid hormone through cyclic adenosine monophosphate. Hyperparathyroidism is one of the few causes of metabolic acidosis with hypercalcemia. The Cl^-/phosphate ratio in plasma may be elevated. Drug toxicity with aminoglycosides, cisplatin, and ifosfamide may cause proximal tubule dysfunction. The antiretroviral drug tenofovir, a nucleotide analogue reverse transcriptase inhibitor, is a cause of the Fanconi syndrome. The syndrome also may be seen after kidney transplantation (Chapter 117).

Distal Renal Tubular Acidosis

In distal renal tubular acidosis (type 1), failure to excrete ammonium leads to an inability to excrete adequate net acid, thereby leading to continuous retention of acid in the body. The degree of acidemia is often severe, with pH reaching values as low as 7.2, whereas urine pH usually exceeds 5.3.[16]

Kindreds have been described in which mutations in genes for the distal vacuolar H^+-ATPase cause an autosomal recessive distal renal tubular acidosis with deafness. Mutations resulting in defective Cl^-/HCO_3^- exchange protein (AE1) have been linked to an autosomal dominant form of distal renal tubular acidosis.[17]

Distal renal tubular acidosis (see Table 104-7) is also associated with autoimmune disorders, including systemic lupus erythematosus (Chapter 245) and Sjögren syndrome (Chapter 247), and genetic diseases, including sickle cell anemia (Chapter 149), Wilson disease (Chapter 195), Fabry disease (Chapter 192), cystic kidney diseases (Chapter 112), and hereditary elliptocytosis (Chapter 147). Hypercalciuria and hyperoxaluria may cause distal renal tubular acidosis; nephrocalcinosis and nephrolithiasis may be present. Increased proximal tubular citrate reabsorption, as a consequence of the chronic acidosis, also leads to hypocitraturia, which is a risk factor for calcium nephrolithiasis (Chapter 111). A chronically alkaline urine is a risk for pure $CaHPO_4$ brushite stones and other calcium phosphate mixtures. Amyloidosis (Chapter 174) may be manifested as severe acidemia and other tubular dysfunction, including nephrogenic diabetes insipidus. Chronic tubulointerstitial diseases of the kidney (Chapter 108), including reflux nephropathy (Chapter 113) and urinary obstruction, may result in renal tubular acidosis with hypokalemia or hyperkalemia. Acute tubulointerstitial nephritis also may result in renal tubular acidosis. Drugs such as amphotericin B can cause hypokalemic distal renal tubular acidosis. Topiramate, used for migraines, is a carbonic anhydrase inhibitor that may cause mixed proximal and distal renal tubular acidosis.

HYPERCHLOREMIC METABOLIC ACIDOSIS OF RENAL ORIGIN ASSOCIATED WITH HYPERKALEMIA

Hyperkalemic, hyperchloremic acidosis (type 4) suggests dysfunction of the cortical collecting duct, where acidification of urine and disorders in potassium secretion may occur. Some patients with high blood potassium and hyperchloremic acidosis can lower urinary pH below 5.3, whereas others appear to have defects in both potassium balance and urinary acidification. Hyperkalemia itself may worsen metabolic acidosis by decreasing NH_3 accumulation by countercurrent multiplication in the medullary interstitium.

Causes include hyporenin-hypoaldosteronism, as seen in diabetic renal disease (Chapter 109); other tubulointerstitial diseases (Chapter 108), usually with some renal impairment; sickle cell anemia (Chapter 149); and the use of drugs such as β-blockers and nonsteroidal anti-inflammatory drugs. Low renin and aldosterone levels also can be found in cases of volume expansion with hypertension. Cyclosporine and tacrolimus may lead to decreased electrical driving forces for K^+ and H^+ secretion. Hyperkalemic acidosis with elevated renin and low aldosterone is found in adrenal insufficiency (Chapter 208), in isolated hypoaldosteronism (Chapter 208), and with the use of angiotensin-converting enzyme inhibitors, renin inhibitors, and angiotensin II receptor blockers. High renin and aldosterone levels are anticipated when the renal collecting duct cell is insensitive to aldosterone, as in urinary tract obstruction, sickle cell anemia, amyloidosis, and systemic lupus erythematosus. Inhibition of aldosterone action with spironolactone or eplerenone may cause hyperkalemic acidosis, as does ENaC inhibition by amiloride, triamterene, trimethoprim, and lithium.

Autosomal recessive pseudohypoaldosteronism type 1 is due to inactivating mutations of the sodium channel ENaC, whereas autosomal dominant pseudohypoaldosteronism type 1 is due to mutations of the mineralocorticoid receptor. Both cause hypovolemia, metabolic acidosis, and hyperkalemia with secondary increases in renin and aldosterone. In Gordon syndrome

TABLE 104-7 CAUSES OF RENAL TUBULAR ACIDOSIS*

HYPOKALEMIC DISTAL (TYPE 1) RTA
Hereditary tubule disorders
Vacuolar H^+-ATPase β-subunit gene mutations
Carbonic anhydrase type II deficiency
Cl^-/HCO_3^- exchanger (AE1) mutations
Genetic causes
Sickle cell anemia
Fabry disease
Wilson disease
Elliptocytosis
Paroxysmal nocturnal hemoglobinuria
Medullary cystic kidneys
Autoimmune disorders
Systemic lupus erythematosus
Sjögren syndrome
Multiple myeloma and amyloidosis
Drugs: amphotericin, cisplatinum, aminoglycosides
Nephrocalcinosis and hypercalcemic disorders
Tubulointerstitial diseases
Acute tubulointerstitial nephritis
Reflux nephropathy
Analgesic nephropathy
PROXIMAL (TYPE 2) RTA
Hereditary tubule disorders
$NaHCO_3$ cotransport (NBC) mutations
Carbonic anhydrase deficiency
Generalized proximal tubular dysfunction
Hereditary Fanconi syndrome
Genetic diseases: cystinosis, glycogen storage disease (glucose-6-phosphatase deficiency), Wilson disease
Hormonal: hyperparathyroidism, vitamin D deficiency
Multiple myeloma
Lysozymuria
Sjögren syndrome
Renal transplantation
Heavy metals: cobalt, mercury, lead
Drugs: ifosfamide, outdated tetracycline, tenofovir, tacrolimus, aminoglycosides
HYPERKALEMIC (TYPE 4) RTA
Renal diseases—aldosterone resistance
Diabetes mellitus
Amyloidosis
Systemic lupus erythematosus
Urinary tract obstruction
Hyporeninism
Autonomic neuropathy (diabetic)
Sickle cell anemia
Primary hypoaldosteronism
Adrenal insufficiency: Addison disease
Genetic disorders: pseudohypoaldosteronism
Drugs: potassium-sparing diuretics, amiloride, triamterene, spironolactone, nonsteroidal anti-inflammatory drugs, lithium, trimethoprim, cyclosporine, tacrolimus, renin inhibitors, angiotensin-converting enzyme inhibitors, angiotensin II receptor antagonists

*Type 3 renal tubular acidosis (RTA) is not listed separately because it is an overlap of proximal and distal dysfunction. Pure aldosterone deficiency will decrease the secretion of H^+ and K^+, thereby causing hyperkalemic acidosis. Also, renal diseases involving tubular cells may result in decreased urinary secretion of acid and potassium.

(pseudohypoaldosteronism type 2), increases in Na^+ and Cl^- reabsorption through increased activity of the distal thiazide-sensitive NaCl transporter lead to hypertension, hyperkalemic acidosis, volume expansion, and consequently low renin and aldosterone.

CLINICAL MANIFESTATIONS AND DIAGNOSIS

The urinary anion, or charge, gap helps distinguish renal tubular acidosis from extrarenal bicarbonate loss (e.g., from diarrhea).[18] Because the normal renal response to metabolic acidosis is an increase in ammoniagenesis, the urine should contain large amounts of NH_4Cl while the kidney retains sodium and potassium; the urinary charge gap, which is $(Na^+ + K^+) - Cl^-$, should be strongly negative because of the unmeasured NH_4^+.

In renal diseases such as distal renal tubular acidosis, however, the urinary anion gap will be zero or positive because of either inadequate excretion of ammonium or the excretion of sodium plus potassium with bicarbonate. With type 2 (proximal) renal tubular acidosis, patients often have Fanconi syndrome with glycosuria, phosphaturia, aminoaciduria, and uricosuria. In proximal renal tubular acidosis, the steady-state urine pH is usually less than 5.3, the acidosis is not severe (i.e., HCO_3^- usually not less than 16), and acid excretion may balance acid production at this new steady state.

In contrast to proximal renal tubular acidosis, distal renal tubular acidosis (type 1) is generally a more severe metabolic disorder that may be accompanied by hypercalciuria, nephrocalcinosis, calcium phosphate kidney stones (Chapter 111), and bone disease that includes rickets in children and osteomalacia in adults. Proximal and distal renal tubular acidoses usually can be distinguished by a careful clinical evaluation (see Fig. 104-2). Helpful findings include the presence of a urine pH greater than 5.3 in distal but not in proximal renal tubular acidosis during acidemia; a fractional excretion of bicarbonate as high as 10 to 15% in proximal renal tubular acidosis treated with alkali supplementation; and the lowering of serum potassium on correction of proximal but not of distal tubular acidosis.

In patients with an elevated serum anion gap, unmeasured anions such as keto acids and lactate, rather than NH_4^+, are present in urine, so a positive urinary anion gap does not indicate renal tubular acidosis. On occasion, the prompt renal excretion of organic anions with sodium and potassium may minimize the increase in the serum anion gap. In the metabolic acidosis of glue sniffers, hippurate, which is a product of toluene, is rapidly excreted, thus giving the appearance of a nongap metabolic acidosis with a positive urinary anion gap and mimicking a renal tubular acidosis. Similarly, if keto acids are completely cleared into the urine, ketoacidosis may be manifested as a hyperchloremic acidosis rather than as an anion gap acidosis.

TREATMENT

If possible, treatment of metabolic acidosis should focus on correction of the underlying cause, such as discontinuation of an offending drug, permitting the body's homeostatic mechanisms to correct the acid-base disturbance.[19]

Patients whose pH is less than 7.2 are typically treated with infusions of sodium bicarbonate,[20] guided by the estimated base deficit in milliequivalents, calculated by the serum HCO_3^- concentration in milliequivalents per liter:

$$\text{Amount of } HCO_3^- = (25 - [HCO_3^-]) \times \text{wt (kg)}/2$$

Such treatment appears to be especially beneficial in patients with acute kidney injury.[A1] In general, the correction of metabolic acidemia should be based on a calculated amount, with not more than 50% of the estimate given before recalculation. Moreover, this equation is used for deficit correction only; the ongoing losses of 1 to 2 mEq/kg per day, equivalent to the daily acid load, should be replaced in distal renal tubular acidosis with $NaHCO_3$ or $KHCO_3$, (depending on whether the patient has hypokalemia or hyperkalemia). Citrate salts (e.g., potassium citrate 60 to 90 mEq/day in divided doses) may be used to achieve a goal serum bicarbonate level of 22 to 24 mEq/L. Hypokalemia may accompany distal renal tubular acidosis and may improve with treatment. Citrate should be avoided as an alkalinizing salt in patients with low glomerular filtration rates because it may increase the gastrointestinal absorption of aluminum.

Proximal renal tubular acidosis in children may affect growth and require large quantities of bicarbonate in excess of 1 to 2 mEq/kg per day to correct the acidosis because ingested alkali is promptly excreted in alkaline urine. In adults, treatment is often deferred because the steady-state acidosis allows a normal acid excretion rate. Hypokalemia may worsen with bicarbonate treatment of proximal tubular acidosis.

In type 4 renal tubular acidosis, treatment of hyperkalemia with a low-potassium diet, thiazide or loop diuretics, or potassium-binding resins often improves urinary acidification without the use of bicarbonate salts. However, base supplements in the form of sodium bicarbonate or sodium citrate (0.5 to 0.8 mEq/kg, or 30 to 60 mEq per day) plus a diuretic aid in the excretion of potassium.

PROGNOSIS

The prognosis of renal tubular acidosis generally depends on the presence of an underlying systemic disease, such as myeloma (Chapter 173). In children, disorders such as medullary cystic kidney disease (Chapter 112) and cystinosis (Chapter 113) usually result in renal failure by the teenage years. These patients are candidates for renal replacement therapy, including transplantation. Chronic metabolic acidosis in children, if not well treated, is associated with rickets (Chapter 226) and short stature.

METABOLIC ALKALOSIS

EPIDEMIOLOGY AND PATHOBIOLOGY

In metabolic alkalosis, the primary event is elevation of the plasma bicarbonate concentration. In response to increased systemic pH, alveolar ventilation is decreased to increase P_{CO_2} and thereby decrease pH.[21] However, respiratory compensation is generally less effective in cases of metabolic alkalosis than in cases of metabolic acidosis. Contributing factors may include the fact that hypoventilation also decreases P_{O_2}, which is a potent stimulus for the peripheral chemoreceptors to increase alveolar ventilation when P_{O_2} falls below about 60 mm Hg. A second mechanism that may blunt respiratory compensation is intracellular acidosis in the brain in the setting of hypokalemia. In acute metabolic alkalosis, an initial paradoxical acidotic shift in CSF pH secondary to a sudden increase in P_{CO_2}, analogous to the alkaline shift in CSF pH in acute metabolic acidosis, may activate central chemoreceptors and increase ventilatory drive despite peripheral stimulation to decrease alveolar ventilation. In chronic metabolic alkalosis, CSF pH may return to normal, so respiratory drive is controlled entirely by the peripheral chemoreceptors. The result is that the ventilatory response to metabolic alkalosis is highly varied: many patients with metabolic alkalosis maintain nearly normal P_{CO_2} levels, and the level rarely rises above 60 mm Hg.

In the normal state, the renal response to metabolic alkalosis is greater filtration of bicarbonate, less proximal reabsorption of bicarbonate, and bicarbonate secretion in exchange for chloride. Metabolic alkalosis requires a generation phase, in which new HCO_3^- is added to the extracellular fluid, and a maintenance phase, in which the new elevated serum HCO_3^- concentration is sustained. Without the maintenance phase, a kidney with normal filtration and tubular function has a high capacity to excrete HCO_3^-, thereby preventing alkalosis. Maintenance of a high HCO_3^- concentration usually occurs because of volume depletion, reduced glomerular filtration rate, hypokalemia, or low chloride levels.

METABOLIC ALKALOSIS OF RENAL ORIGIN ASSOCIATED WITH VOLUME DEPLETION

Generation of metabolic alkalosis by the kidney can result from reduced renal tubular NaCl reabsorption due to diuretics or inherited disorders (e.g., Bartter or Gitelman syndromes). Metabolic alkalosis is usually associated with high urinary chloride levels, especially when diuretics inhibit reabsorption of Cl^- salts. The Cl^- loss results in hypochloremia, with a compensatory increase in plasma HCO_3^- to maintain electroneutrality. Extracellular volume depletion stimulates the renin–angiotensin–aldosterone pathway, and high aldosterone levels superimposed on increased distal Na delivery and urinary flow rates result in increased secretion of K^+, H^+, and $NH4^+$, with hypokalemia and hypokalemic metabolic alkalosis. The volume depletion and hypokalemia enhance proximal reabsorption of HCO_3^-, thereby maintaining the alkalosis, and the prerenal fall in the glomerular filtration rate limits the filtration of HCO_3^-.

Genetic syndromes characterized by urinary sodium chloride wasting include Bartter syndrome and Gitelman syndrome (Chapter 113). Bartter syndrome is an autosomal recessive salt-losing state associated with extracellular volume depletion and excessive urinary chloride loss that results in hypokalemia and hypochloremic metabolic alkalosis. Secondary increases of plasma renin and aldosterone occur, as does renal juxtaglomerular cell hyperplasia. The syndrome resembles the effects of furosemide on the thick ascending limb of Henle; gene mutations in the Na-K-2Cl cotransporter, the renal outer medullary potassium channel (ROMK), and voltage-gated CLC-Kb chloride channels mediating NaCl reabsorption have been described. Because calcium reabsorption occurs in the thick ascending limb of Henle, Bartter syndrome (Chapter 113), like furosemide, causes hypercalciuria and nephrocalcinosis as well as polyuria due to decreased urinary concentrating ability.

Gitelman syndrome is an autosomal recessive cause of extracellular volume depletion, urinary wasting of sodium chloride, and hypokalemic metabolic alkalosis. It is due to inactivating mutations in the *SLC12A3* gene encoding the thiazide-sensitive NaCl cotransporter of the renal distal tubule. Urinary concentrating ability is preserved, and patients are hypocalciuric because decreased

NaCl reabsorption in the distal tubule and volume depletion enhance the reabsorption of Ca^+ in the proximal tubule. Hypomagnesemia also may be severe owing to defective Mg^{2+} reabsorption in the distal convoluted tubule.

METABOLIC ALKALOSIS OF NONRENAL ORIGIN WITH EXTRACELLULAR VOLUME DEPLETION

Metabolic alkalosis may develop as a result of gastrointestinal loss of Cl^- or gain of HCO_3^- owing to vomiting, nasogastric suctioning, or some causes of secretory diarrhea. In such cases, extracellular volume is usually contracted, hypochloremia develops, and the urinary chloride level is usually less than 20 mEq/L.

In Zollinger-Ellison syndrome (Chapter 213), excessive gastrin-induced gastric acid secretion may result in an acidic stool with high chloride content. Diarrhea does not cause metabolic alkalosis unless the electrolyte relationship $[(Na^+ + K^+) - Cl^-]$ in the stool is less than plasma HCO_3^-.

Infectious gastroenteritis, congenital chloridorrhea, and villous adenomas also cause chloride losses in stool. Congenital chloridorrhea is an autosomal recessive disorder of defective intestinal apical Cl^-/HCO_3^- exchange associated with the downregulated adenoma *(DRA)* gene.

With vomiting, the initiating event is loss of HCl. This secretion of HCl into the stomach lumen by the parietal cell is coupled to the absorption of HCO_3^- in exchange for chloride at the basolateral membrane. When gastric acid is normally secreted, a mild increase in serum HCO_3^- spills into urine and causes an "alkaline tide." With vomiting, however, the net loss of HCl generates the alkalosis. With vomiting, the increased HCO_3^- is filtered by the glomeruli and excreted in urine, accompanied by Na^+ and K^+; volume and K^+ begin to be depleted. As vomiting continues, extracellular volume depletion worsens, glomerular filtration falls, HCO_3^- filtration is limited, the renin–angiotensin II–aldosterone system is stimulated, proximal reabsorption of fluid and HCO_3^- increases, distal reabsorption of Na^+ increases under the influence of aldosterone, and greater secretion of H^+ enhances the reabsorption of HCO_3^-. These effects reduce renal Na^+ loss but at the expense of maintaining the metabolic alkalosis. Significant urinary K^+ losses, which occur as a result of the bicarbonaturia and hyperaldosteronism, lead to hypokalemia, which is actually due to renal, not gastrointestinal, losses as a consequence of attempts to maintain extracellular volume. The hypokalemia further increases the proximal reabsorption of $NaHCO_3$, the distal secretion of H^+, and the reabsorption of K^+, all at the expense of further reabsorption of HCO_3^-. In the new steady state after vomiting or nasogastric suctioning ceases, the paradoxical aciduria of metabolic alkalosis develops as the reabsorption of HCO_3^- is complete, and the urine contains low levels of Na^+, K^+, and Cl^-. The patient may be hypovolemic, hypokalemic, and alkalemic, but because Na^+, K^+, and acid-base balance are intrinsically linked, life-threatening volume depletion, potassium depletion, and alkalemia are usually avoided.

Most nonrenal metabolic alkaloses with volume depletion are due to gastrointestinal losses. However, some patients with cystic fibrosis (Chapter 77) may develop hypochloremic alkalosis as a consequence of excessive sweat chloride related to the *CFTR* gene mutation.

The sweat gland, like the principal cell in the kidney, contains the aldosterone-sensitive epithelial sodium channel, so Na^+ absorption from the glandular duct renders the lumen electronegative. When the absorption of Cl^- is decreased in cystic fibrosis (Chapter 77), the lumen becomes more negative, thereby decreasing the absorption of Na^+, Cl^-, and fluid, as well as leading to salty sweat; the proportionally large Cl^- loss generates a hypochloremic metabolic alkalosis.

METABOLIC ALKALOSIS OF RENAL ORIGIN WITH VOLUME EXPANSION AND HYPERTENSION

The renal conditions that cause metabolic alkalosis and volume expansion are due to a proportionately greater increase in Na^+ reabsorption above what is required to maintain a steady state of Na^+ balance, rather than primary loss of the Cl^- anion. As Na^+ is reabsorbed, electroneutrality is maintained by an increase in plasma HCO_3^-. Cl^- appears in urine, but hypochloremia is not present except in cases of significant metabolic alkalosis. In the kidney, the loss of net acid as NH_4Cl in excess of the acid produced generates a metabolic alkalosis, in which the new bicarbonate generated is due to proton secretion by the distal nephron through H^+-ATPases. The H^+ then combines with NH_3 to form NH_4^+ in urine.

Na^+ is reabsorbed independently of Cl^- in the cortical collecting duct through the aldosterone-sensitive cells containing the ENaC. When Na^+ is reabsorbed by the principal cells of the cortical collecting duct, the tubular lumen becomes electronegative and stimulates the secretion of both K^+ and H^+ by the electrogenic H^+-ATPases. To the extent that HCO_3^- remains in the lumen, the secreted protons complete the reabsorption of HCO_3^-. Additional secreted protons combine with NH_3 and phosphates to lead to net acid excretion. Any increase in the distal H^+ secretory mechanism will produce more urinary net acid; more new HCO_3^- will be generated and returned to the now expanded extracellular fluid, and metabolic alkalosis will develop. The increased plasma HCO_3^- will be filtered, but in the absence of a stimulus to increase proximal HCO_3^- reabsorption, the HCO_3^- will flow distally to be reabsorbed by the increased secretion of H^+ in the collecting duct. At first, the alkalosis is mild, but increased Na^+ reabsorption in the cortical collecting duct will also lead to increased K^+ secretion and hypokalemia. Hypokalemia increases the capacity for the proximal reabsorption of HCO_3^-, thereby opposing the effect of volume expansion, so that the distal delivery of HCO_3^- decreases. The higher than normal distal H^+ secretion titrates urinary buffers, so further new HCO_3^- is formed in the presence of the high ENaC activity, thereby allowing the alkalosis to worsen. The alkalosis is maintained at a new steady state only when the distal secretion of H^+ results in the reabsorption of the remaining amount of filtered HCO_3^- in the collecting duct. Metabolic alkalosis in the hypermineralocorticoid syndromes is sustained by hypokalemia. The metabolic alkalosis in these syndromes is only mild if the patient is K^+ replete.

METABOLIC ALKALOSIS OF NONRENAL ORIGIN ASSOCIATED WITH NORMAL OR EXPANDED VOLUME

If an alkalotic patient is not hypochloremic, electroneutrality must be maintained either by depletion of an alternative anion or by an excessive concentration of a cation. An example of a metabolic alkalosis associated with depletion of a non-chloride anion is hypoproteinemic alkalosis, with hypoalbuminemia and a small anion gap. Chloride balance is normal and chloride appears in urine.

Alkalosis also may result from the administration of alkali salts of HCO_3 or metabolizable organic anions. The normal response to the ingestion of $NaHCO_3$ is rapid urinary alkalinization because of an unaltered threshold for the reabsorption of HCO_3^-. However, a marked excess of HCO_3^-, as may be administered in an attempt to alkalinize a patient's urine, expands volume and causes an alkalemia, especially in the presence of volume depletion or low glomerular filtration. Milk-alkali syndrome, usually seen when patients in renal failure ingest milk, excess vitamin D, or calcium antacids, is associated with hypercalcemia and alkalemia. Other situations in which intake of alkali salts results in metabolic alkalosis include infusion of large quantities of sodium salts of metabolizable organic anions, such as acetate, citrate, lactate, or bicarbonate; hyperalimentation with acetate salts; chronic peritoneal dialysis with acetate or lactate dialysate; and excessive transfusions or plasmapheresis, in which large quantities of citrate, used as an anticoagulant, are delivered.

CLINICAL MANIFESTATIONS

Mild metabolic alkalosis up to a pH of 7.50 is usually asymptomatic. When the pH exceeds 7.55, however, the alkalosis itself and the compensatory hypoventilation are frequently associated with metabolic encephalopathy. Symptoms include confusion, obtundation, delirium, and coma. The seizure threshold is lowered. Because more Ca^{2+} is protein-bound and less is ionized Ca^{2+}, tetany, paresthesias, muscle cramping, and other symptoms of low calcium are seen (Chapter 227). In patients with preexisting hypocalcemia, these signs may be seen at pH values above 7.45. Other findings include cardiac tachyarrhythmias and hypotension. The production of lactate increases as a result of the increased anaerobic glycolysis.

DIAGNOSIS

Measurement of urinary Cl can be very helpful in the diagnosis of the cause of metabolic alkalosis, and it is important to distinguish whether the condition is chloride responsive or chloride unresponsive. (See Table 104-2 and Fig. 104-3.) Chloride-responsive metabolic alkalosis with low urinary Cl^- is associated with depletion of extracellular fluid and chloride and is seen with loss of gastric fluid and prior use of diuretics. Chloride-responsive metabolic alkalosis with high urinary Cl^- is associated with Bartter or Gitelman syndrome or ongoing diuretic use. Chloride-unresponsive metabolic alkalosis with high urinary Cl^- is seen in volume-expanded states, such as primary hyperaldosteronism when metabolic alkalosis is primarily maintained by depletion of K^+. A diagnostic clue comes from the serum electrolytes. The HCO_3^- concentration is increased with a corresponding fall in serum chloride (hypochloremic alkalosis). Chloride-unresponsive metabolic alkalosis is seen in patients with extracellular fluid expansion in conditions such as primary aldosteronism and hypokalemia.

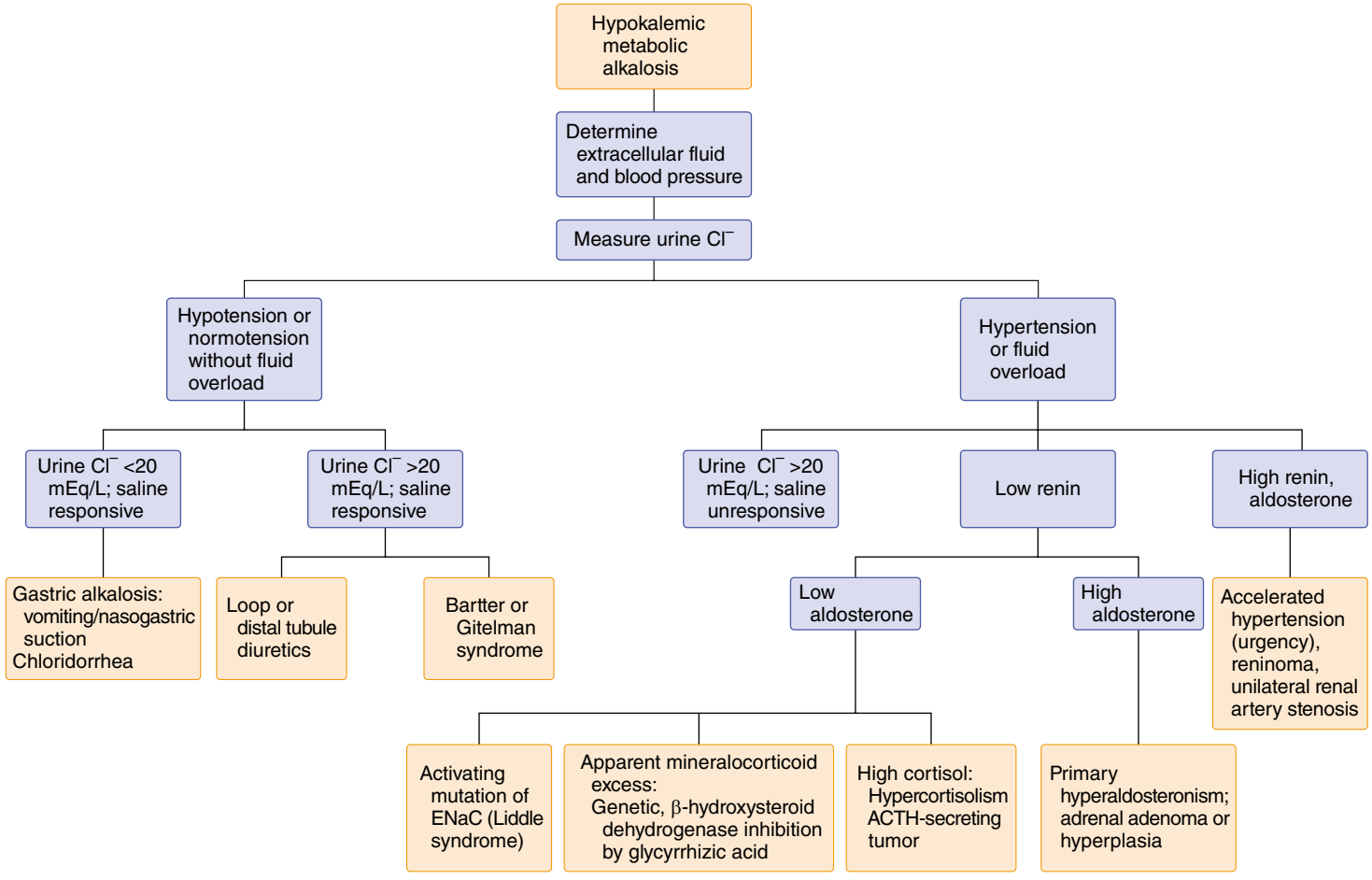

FIGURE 104-3. **Evaluation of the patient with hypokalemic metabolic alkalosis.** ACTH = adrenocorticotropic hormone; Cl = chloride; ENaC = epithelial sodium channel.

Vomiting, nasogastric suction, and diarrhea are usually obvious sources of metabolic alkalosis. However, the Zollinger-Ellison syndrome (Chapter 213), villous adenomas (Chapter 179), and VIPomas (Chapter 213) may be more difficult to diagnose unless the index of suspicion is high.

Patients who present with hypokalemic metabolic alkalosis (Fig. 104-3) with normal or low blood pressure and have urinary chloride concentrations above 25 mEq/L may be taking diuretics such as furosemide or thiazides surreptitiously; a diuretic screen can document the presence of the drug. If the screen is negative, Bartter or Gitelman syndrome (Chapter 113) should be considered. Bartter syndrome is less common, is usually more severe, and presents in young patients. The presence of hypercalciuria favors Bartter syndrome, whereas hypocalciuria and hypomagnesemia suggest Gitelman syndrome.

Specific causes of renal alkalosis with volume expansion and hypertension can be classified according to levels of renin and aldosterone. Primary increases in renin with secondary increases in aldosterone can be seen in patients with unilateral renal artery stenosis (Chapter 110), renin-secreting tumors of the kidney (Chapter 64), and malignant hypertension (Chapter 64). Low renin and elevated aldosterone levels are characteristic of primary hyperaldosteronism from an adrenal adenoma or hyperplasia (Chapter 208). A high cortisol level with volume expansion is seen in hypercortisolism and adrenocorticotropic hormone–secreting tumors (Chapter 208). Inhibition of the intracellular enzyme 11β-hydroxysteroid dehydrogenase type 2 will also result in low renin levels, low aldosterone levels, and hypokalemic alkalosis. Both genetic mutations (the apparent mineralocorticoid excess syndrome) and an excess consumption of glycyrrhizic acid found in licorice and anisette are causes of this enzymatic block. Another cause of hypertension with hypokalemic alkalosis but with low renin and aldosterone levels is Liddle syndrome (Chapter 113), in which an activating mutation in the cortical collecting duct sodium channel (ENaC) leads to increased Na^+ reabsorption.

Metabolic alkalosis may also develop without volume expansion when a non-reabsorbable anion is presented to the cortical collecting duct lumen. Nitrates, sulfates, and certain antibiotics such as nafcillin, carbenicillin, and ticarcillin may obligate the secretion of K^+ and H^+ as Na^+ is reabsorbed. Topical administration of silver nitrate to burn victims may result in alkalosis.

TREATMENT

In chloride-responsive patients who are volume-depleted, chloride-depleted, and most likely potassium-depleted (see Table 104-2), treatment is directed at ameliorating the factors that are maintaining the alkalosis. Providing saline and potassium chloride will increase bicarbonaturia and correct the metabolic alkalosis.[22] In patients with mild to moderate alkalosis, liberalizing NaCl intake and administering potassium chloride (20 to 80 mEq per day in divided doses) is effective in increasing the renal excretion of HCO_3^-. The K^+ deficit, though difficult to estimate from plasma [K^+], is likely to be at least 100 mEq for every 1 mEq/L decrease in plasma [K^+]. Unless potassium deficits are replenished simultaneously with extracellular volume expansion, the combination of increased bicarbonate filtration rate and an ongoing hypokalemia-induced increase in proximal tubular reabsorption of bicarbonate may severely worsen hypokalemia as bicarbonaturia develops and aldosterone's residual effects remain. Complete resolution of alkalosis will not occur until volume is restored and K^+ is normalized.

In a patient with renal failure and vomiting, the elevation in [HCO_3^-] may be more severe because of poor renal filtration of HCO_3^- and may require the administration of HCl or dialysis. If conditions such as volume expansion with decreased effective volume make the administration of NaCl unwise, potassium-sparing diuretics (Chapter 102) may help correct the alkalosis without increasing edema or potassium wasting. In the absence of renal failure, intravenous acetazolamide (250 to 500 mg every 8 hours) may be effective but may greatly increase renal losses of K^+. In patients who have edema and renal failure, acetazolamide treatment may be unsuccessful, so cautious administration of dilute solutions of HCl (0.1 N HCl) may be required. The amount of H^+, in milliequivalents, to be given may be calculated as the product of the desired change in serum HCO_3^- concentration (mEq/L) multiplied by 0.5 of body weight in kilograms. This calculation will likely overestimate the amount of acid needed for correction, so no more than one third of the amount should be given before recalculating to avoid metabolic acidosis. Full correction of HCO_3^- should not be the goal.

Chloride-unresponsive patients (see Table 104-2) include patients who have mineralocorticoid excess. In these patients, the metabolic alkalosis can be lessened by potassium replacement or by blocking Na^+ reabsorption with aldosterone antagonists such as spironolactone (starting with 25 mg orally) or amiloride (beginning with 5 mg orally). Indomethacin (75 mg per day) effectively treats Bartter syndrome (Chapter 113) by interfering with prostaglandin E_2 to allow greater reabsorption of NaCl in the thick ascending limb. Gitelman and Bartter syndromes are best treated with combinations of potassium chloride (40 to 160 mEq per day depending on the severity of the hypokalemia), a potassium-sparing diuretic (e.g., spironolactone 100 to 300 mg per day or eplerenone 150 mg per day), and magnesium if needed.

RESPIRATORY ACIDOSIS

Respiratory acidosis is characterized by a primary elevation in P_{CO_2} as reflected by reduced arterial pH with variable elevations in the HCO_3^- concentration. Respiratory acidosis is most frequently caused by a decrease in alveolar ventilation owing to pulmonary disease (Chapter 90), respiratory muscle fatigue, musculoskeletal abnormalities of the chest wall, or abnormalities in ventilatory control (Chapter 74).

CLINICAL MANIFESTATIONS

Clinical findings in respiratory acidosis are related to the degree and duration of the respiratory acidosis and whether hypoxemia is present. A precipitous rise in P_{CO_2} can lead to confusion, anxiety, psychosis, asterixis, seizures, and myoclonic jerks, with progressive depression of the sensorium and coma at an arterial P_{CO_2} greater than 60 mm Hg (CO_2 narcosis). Hypercapnia, which increases cerebral blood flow and volume, can lead to symptoms and signs of elevated intracranial pressure, including headaches and papilledema. Other findings in acute respiratory acidosis include signs of catecholamine release, such as skin flushing, diaphoresis, and increased cardiac contractility and output. Symptoms of chronic hypercapnia include fatigue, lethargy, and confusion, in addition to the findings seen in acute hypercapnia.

The slow time course of many of these diseases allows the kidney to compensate adequately by increasing its excretion of hydrogen ion as ammonium as well as by generating and reabsorbing bicarbonate to restore systemic pH toward normal values. This compensatory process is not maximal until 3 to 5 days after the onset of respiratory acidosis. Hypoxemia, hypercapnia with resulting chronic $NaHCO_3$ retention, and edema (cor pulmonale) often accompany chronic respiratory acidosis.

DIAGNOSIS

Disorders that cause a respiratory acidosis include central effects of drugs, strokes, and infections; airway obstruction; primary parenchymal processes, such as chronic obstructive pulmonary disease (Chapter 76) and acute respiratory distress syndrome (Chapter 90); disorders of ventilation (Chapter 74); and neuromuscular diseases, such as myasthenia gravis (Chapter 390) and muscular dystrophies (Chapter 389).

TREATMENT

Treatment of both chronic and acute respiratory acidosis aims primarily to correct the underlying cause and to ensure adequate ventilation. In acute respiratory acidosis, measures to relieve severe hypoxemia and acidemia should be instituted immediately, including intubation and assisted mechanical ventilation (Chapter 91) if necessary. Patients with myxedema coma require thyroid replacement (Chapter 207).

In patients with compensated chronic respiratory acidosis, rapid and complete correction of hypercapnia can result in post-hypercapnic metabolic alkalosis. Patients who are chronically hypercapnic and hypoxemic should receive necessary oxygen even though their P_{CO_2} will rise. The rise is not necessarily due to loss of a hypoxic drive to ventilation but may instead be because of release of CO_2 from hemoglobin in the presence of oxygen or because oxygen-induced pulmonary arteriolar vasodilation increases perfusion to poorly ventilated alveoli. Patients recovering from an acute-on-chronic respiratory acidosis should be monitored carefully to correct hypokalemia, hypochloremia, and hypovolemia so that adequate renal excretion of bicarbonate can occur.

Bicarbonate therapy is not indicated for respiratory acidosis unless the pH falls below 7.0 and the patient is about to be intubated.[23] Bicarbonate therapy has no role in patients with renal failure (Chapter 116), in whom adequate compensatory acid excretion cannot occur.

RESPIRATORY ALKALOSIS

EPIDEMIOLOGY AND PATHOBIOLOGY

In respiratory alkalosis, a primary decrease in P_{CO_2} is reflected by increases in the arterial pH and variable decreases in the plasma bicarbonate concentration. The most common cause is alveolar hyperventilation, not underproduction of CO_2.

Acute hypocapnia results in an initial increase in the pH of both the CSF and the brain's intracellular environment. The increased intracellular pH stimulates glycolysis, vasoconstriction, hypoxia, and an increased affinity of hemoglobin for oxygen, thereby offsetting the metabolic alkalosis by producing lactic acid. However, this increase in lactic acid is quickly offset because the renal compensation for decreased bicarbonate reabsorption will result in a lower blood bicarbonate level. The combination of increased oxygen demand and decreased oxygen delivery may contribute to adverse clinical outcomes in hypocapnic alkalosis.

Cerebral blood flow is significantly decreased by hypocapnia, which is a potent vasoconstrictor. As in respiratory acidosis, the CNS is immediately affected because of the blood-brain barrier's permeability to CO_2. In addition, as in respiratory acidosis, CSF and intracellular pH show an initial short-lived response that parallels the systemic increase in pH.

Renal compensation for sustained hypocapnia is complete in 36 to 72 hours. The mechanism rests primarily in the kidney's net reduction of hydrogen ion excretion, which is accomplished largely by decreasing the excretion of ammonium and titratable acid. The threshold for bicarbonate excretion is also lowered, and bicarbonaturia develops. As a result, systemic bicarbonate levels decrease, and arterial pH returns toward normal values.

Acute exposure to high altitude (Chapter 82) results in hypoxia-induced hyperventilation. Compensation requires several days and is characterized by a gradual further increase in hyperventilation, a steadily decreasing P_{CO_2}, and a recovering P_{O_2}. The effect of the hypoxic stimulus to ventilate is initially modulated by the effects of alkalosis, both peripherally and centrally. However, as HCO_3^- falls in the CSF, inhibition of the central stimulus to ventilate decreases. Once a steady state is achieved, the drive to ventilate is determined by the effects of hypoxemia and alkalemia on the peripheral chemoreceptors.

CLINICAL MANIFESTATIONS

The clinical manifestations of respiratory alkalosis depend on the degree and duration of the condition but are primarily those of the underlying disorder. Chronic hypocapnia does not appear to be associated with any significant clinical symptoms.

Symptoms of acute hypocapnia with P_{CO_2} below 30 mm Hg are largely attributable to the alkalemia and include dizziness, perioral or extremity paresthesias, confusion, asterixis, hypotension, seizures, and coma. Shortness of breath and chest wall pain, which frequently accompany hyperventilation because of pain or anxiety, do not appear to be related to hypocapnia itself.

DIAGNOSIS

Alveolar hyperventilation leading to respiratory alkalosis is seen with hypoxemia from pulmonary disease (Chapter 71), heart failure (Chapter 45), high altitudes (Chapter 82), or anemia. Mechanical ventilation (Chapter 91) is also a common cause of respiratory alkalosis. Rarely, patients have chronic hyperventilation syndrome without any detectable underlying disease.[24]

Another common cause of respiratory alkalosis is primary stimulation of the central chemoreceptor, as seen in sepsis (Chapter 94), hepatic cirrhosis (Chapter 139), salicylate intoxication (Chapters 70 and 96), correction of metabolic acidosis, hyperthermia (Chapter 95), and pregnancy, as well as cortical hyperventilation from anxiety and pain. In these situations, central signals override peripheral chemoreceptors until the primary stimulus is removed.

Primary neurologic diseases that can stimulate alveolar hyperventilation include acute stroke, infection, trauma, and tumors. Two patterns of respiration are seen: central hyperventilation and Cheyne-Stokes respiration (Chapter 74). Central hyperventilation, which is associated with lesions at the pontine-midbrain level, is regular but with an increased rate and tidal volume. Cheyne-Stokes breathing, which is characterized by periods of hyperventilation alternating with apnea, is seen in patients with bilateral cortical and upper pontine lesions and in patients with heart failure.

TREATMENT

Treatment of respiratory alkalosis must address the underlying cause of the disturbance. Hyperventilation syndrome is a diagnosis of exclusion, but patients who exhibit symptoms such as tetany and syncope and who do not have more serious causes of hyperventilation can be treated with a rebreathing mask. Hypophosphatemia can be seen, but usually improves with treatment of the alkalosis. Patients with respiratory alkalosis associated with mountain sickness can be pretreated with acetazolamide to induce metabolic acidosis (Chapter 82), thereby preventing extreme elevations in pH, but care must be taken to ensure adequate intake of K^+ to avoid hypokalemia.

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Grade A **Grade A Reference**

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105 DISORDERS OF MAGNESIUM AND PHOSPHORUS

ALAN S.L. YU

MAGNESIUM METABOLISM

Magnesium is an important mineral component of the bony skeleton, a cofactor for many metabolic enzymes, and a regulator of ion channels and transporters in excitable tissues.[1]

NORMAL MAGNESIUM METABOLISM

The majority of total body magnesium is intracellular or in bone, with only 1% in extracellular fluid. The normal serum magnesium concentration is 1.8 to 2.3 mg/dL (1.5 to 1.9 mEq/L). The average daily intake of magnesium is 300 mg, the main sources of which are green vegetables, nuts, whole grain cereals, milk, and seafood. Magnesium is absorbed mainly in the jejunum and ileum. In the kidney, 70 to 80% of serum magnesium is filtered at the glomerulus, with the majority being reabsorbed along the length of the tubule, particularly in the thick ascending limb of Henle. In states of magnesium deficiency or excess, renal tubule reabsorption is tightly regulated so that magnesium excretion is adjusted accordingly.[2]

MAGNESIUM DEFICIENCY

PATHOBIOLOGY

Magnesium deficiency is usually detected when hypomagnesemia becomes evident. However, because magnesium is stored primarily intracellularly, substantial depletion of total body magnesium can occur before serum magnesium levels drop appreciably.

Magnesium deficiency may be due to nutritional deficiency, intestinal malabsorption, redistribution into bone, or losses via cutaneous, lower gastrointestinal, or renal routes (Table 105-1). The recommended daily allowance of magnesium is 420 mg for males and 320 mg for females. Approximately 25% of alcoholics are chronically hypomagnesemic because of a combination of poor nutritional intake and increased renal loss. Magnesium deficiency can occur, rarely, in protein-calorie malnutrition and may be associated with acute hypomagnesemia during refeeding because of rapid cellular magnesium uptake. Fat malabsorption in conditions such as celiac disease, Crohn disease, and small intestinal resection causes magnesium deficiency because free fatty acids accumulate in the intestinal lumen, where they combine with magnesium to form insoluble soaps. Proton pump inhibitors also cause hypomagnesemia by inhibiting intestinal absorption, primarily in patients who are concurrently using diuretics.[3] Lower gastrointestinal tract secretions are rich in magnesium, so diarrhea of colonic origin is a common cause of hypomagnesemia. Sweat contains significant amounts of magnesium, and transient hypomagnesemia can occur after prolonged, intense exercise such as marathon runs. Magnesium is also lost from burned skin surfaces, and 40% of patients with severe burns (Chapter 97) are hypomagnesemic.

In patients with severe hyperparathyroidism (Chapter 227) and high bone turnover, continued sequestration of minerals within bone after parathyroidectomy causes transient hypocalcemia, hypomagnesemia, and hypophosphatemia. Renal magnesium losses can occur in the recovery phase of acute tubular necrosis or urinary tract obstruction. Hypomagnesemia is common in diabetes mellitus (Chapter 210), in which it is thought to be due to a combination of poor intestinal absorption, osmotic diuresis, and decreased renal tubule reabsorption. Inhibition of sodium reabsorption in the thick ascending limb of Henle by loop diuretics and in the distal convoluted tubule by thiazide diuretics inhibits tubular magnesium reabsorption and leads to urinary magnesium wasting. Tubular toxins that are common causes of renal magnesium wasting include cisplatin, carboplatin, amphotericin B, and aminoglycosides, which are often associated with hypokalemia and rarely with renal tubule acidosis, as well as calcineurin inhibitors such as cyclosporine and tacrolimus, which also cause hyperkalemia. Antibodies to the epidermal growth factor receptor, such as cetuximab and panitumumab, which are used to treat metastatic colorectal cancer, downregulate a distal tubule magnesium channel and cause isolated severe hypomagnesemia.

Inherited hypomagnesemia is usually caused by renal magnesium loss and can be subdivided into three main types, depending on the coexistence of other electrolyte disturbances: Bartter and Gitelman syndromes, which are associated with renal salt wasting and hypokalemic metabolic alkalosis; familial hypomagnesemia with hypercalciuria and nephrocalcinosis; and isolated hypomagnesemia, which is usually associated with hypocalcemia.

TABLE 105-1 CAUSES OF MAGNESIUM DEFICIENCY

Nutritional deficiency
Alcoholism*
Malnutrition
Refeeding syndrome
Intestinal malabsorption*
Proton pump inhibitors
Lower gastrointestinal losses
Colonic diarrhea*
Intestinal fistula
Laxative abuse
Cutaneous losses
Burns*
Exercise-induced sweating
Redistribution into bone
Hungry bone syndrome
Renal losses
Polyuria (including diabetes mellitus)*
Volume expansion
Hyperaldosteronism
Bartter and Gitelman syndromes
Hypercalcemia
Loop and thiazide diuretics*
Nephrotoxins (cisplatin, amphotericin, aminoglycosides, pentamidine, foscarnet, cyclosporine, tacrolimus)*
Epidermal growth factor monoclonal antibodies (cetuximab, panitumumab)*

*Common causes.

CLINICAL MANIFESTATIONS

Mild-to-moderate hypomagnesemia or magnesium deficiency is frequently asymptomatic. Manifestations of increased neuronal excitability are the most common symptoms, including paresthesias, tetany, and seizures. These may be associated with Chvostek sign (twitching of the cheek muscles in response to tapping the facial nerve in front of the ear) or Trousseau sign (carpal spasm induced by compressing the upper arm with a tourniquet or blood pressure cuff). Cardiac disturbances range from mild electrocardiographic abnormalities (nonspecific T wave changes, U waves, prolonged QT interval, and repolarization alternans) to ventricular tachycardia, torsades de pointes, and ventricular fibrillation (Chapter 53).

Coexistent hypokalemia is very common for two reasons: many of the causes of hypomagnesemia are also causes of potassium loss, and hypomagnesemia itself causes renal potassium wasting. Severe hypomagnesemia also impairs parathyroid hormone secretion and induces tissue resistance to its actions, thereby leading to hypocalcemia.

DIAGNOSIS

The cause of the magnesium deficiency is often obvious from the history. In difficult diagnostic cases, a random urine sample should be collected and the fractional excretion of magnesium (FE_{Mg}) determined.

$$FE_{Mg} = \frac{\text{Urine magnesium} \times \text{Serum creatinine}}{0.7 \times \text{Serum magnesium} \times \text{Urine creatinine}}$$

With extrarenal magnesium loss (usually diarrhea, malabsorption or laxative abuse), the FE_{Mg} is appropriately suppressed (<4%). Higher FE_{Mg} levels indicate renal magnesium wasting, often secondary to surreptitious diuretic use or one of the familial magnesium-wasting disorders.

TREATMENT

It is unclear whether mild, asymptomatic hypomagnesemia needs to be treated. Magnesium repletion is recommended in hypomagnesemic patients if they are symptomatic, have underlying cardiac or seizure disorders, exhibit concurrent severe hypocalcemia or hypokalemia, or have severe hypomagnesemia (<1.4 mg/dL). In mild cases or in the outpatient setting, oral magnesium salts such as magnesium oxide (250 to 500 mg four times daily) can be used for repletion, but these substances frequently cause diarrhea, particularly at high doses. In the inpatient setting, intravenous magnesium sulfate (1 to 2 g every 6 hours) can be used for repletion. Because the redistribution of magnesium

ABSTRACT

Magnesium and phosphate are important components of bone, but they also play important roles within cells. Disorders of magnesium and phosphate homeostasis—especially hypomagnesemia, hypophosphatemia, and hyperphosphatemia in the setting of kidney disease—are common and most often asymptomatic. This chapter reviews the causes of magnesium and phosphate disorders, tests and algorithms to diagnose the underlying cause, and treatment options, including replacement regimens.

KEYWORDS

magnesium
hypomagnesemia
phosphate
hypophosphatemia
hyperphosphatemia

from extracellular to intracellular compartments is relatively slow, the serum magnesium concentration may normalize before total body magnesium stores are replete. It is therefore prudent to continue intravenous magnesium for an additional 1 to 2 days after restoration of normomagnesemia. In patients with normal renal function, any excess magnesium is simply excreted renally. Adverse effects from intravenous magnesium administration are primarily due to transient hypermagnesemia and include flushing, hypotension, and flaccid paralysis. Amiloride (10 to 20 mg PO once daily) abrogates renal magnesium wasting in some patients.

PROGNOSIS

Hospitalized patients with hypomagnesemia have a higher 1-year mortality, presumably because it is a marker of more severe illness.[4] Low serum magnesium levels (<1.7 mg/dL) are also associated with about a 35% increase in all-cause mortality in the general population.[5] In patients with a self-limited cause of magnesium deficiency, repletion is easily accomplished. However, in patients with persistent magnesium wasting, such as in Gitelman syndrome (Chapter 113), it can be difficult to keep up with the ongoing losses with oral therapy. Fortunately, these individuals tend to adapt to their chronic hypomagnesemia and tolerate it fairly well.

HYPERMAGNESEMIA

Transient hypermagnesemia can occur in patients given large doses of intravenous magnesium, for example, in the setting of preeclampsia. It has also been reported in individuals taking large doses of magnesium-containing antacids or cathartics, particularly in settings in which intestinal absorption is enhanced, such as inflammatory bowel disease and intestinal obstruction. However, the kidney has a very large capacity to excrete excess magnesium. Thus, persistent hypermagnesemia is seen almost exclusively in patients who have a reduced glomerular filtration rate, as in chronic kidney disease (Chapter 116), and who are also taking excessive amounts of magnesium in the form of antacids, cathartics, or enemas.

CLINICAL MANIFESTATIONS

Magnesium toxicity is a serious and potentially fatal condition. Mild hypermagnesemia (serum magnesium level > 4 to 6 mg/dL) causes hypotension, nausea, vomiting, facial flushing, urinary retention, and ileus. Above serum levels of 8 to 12 mg/dL, flaccid skeletal muscle paralysis and hyporeflexia may ensue, along with bradyarrhythmias, respiratory depression, coma, and cardiac arrest. A low or even negative serum anion gap is sometimes seen.

TREATMENT

Mild hypermagnesemia in a patient with good renal function usually requires no treatment because renal clearance is rapid and the normal serum half-life of magnesium is approximately 1 day. In the event of serious toxicity, the effects of magnesium can be temporarily antagonized by the administration of intravenous calcium salts (5 to 10 mL of 10% calcium chloride). Renal magnesium excretion can be enhanced by administering furosemide (20 to 40 mg every 4 hours) together with a saline infusion (0.9% NaCl at 150 mL/hour, titrated to replace urinary losses). In patients with advanced renal insufficiency, the most effective method of magnesium removal is hemodialysis.

PROGNOSIS

Severe hypermagnesemia is potentially fatal. Lesser degrees of hypermagnesemia usually respond well to treatment, but hypermagnesemia at the time of hospital admission is associated with an increased 1-year mortality.[6]

PHOSPHORUS METABOLISM

Phosphorus has many critical roles. It is a major component of bone mineral, of phospholipids in cell membranes, and of nucleic acids. It forms high-energy phosphate bonds in compounds such as adenosine triphosphate (ATP), is post-translationally bound to proteins as an intracellular signal, and acts as a major pH buffer in serum and urine.

NORMAL PHOSPHORUS METABOLISM

Of the total body phosphorus content, 85% is in bone, 14% is in intracellular compartments, and only 1% is in extracellular fluid. The normal concentration of phosphorus in plasma is 3 to 4.5 mg/dL (1 to 1.5 mM). Daily intake of phosphorus is 800 to 1500 mg. Phosphorus is present in many foods, including dairy products, meats, and grains, and it is absorbed in the small intestine. The kidneys excrete excess phosphorus, which is the principal mechanism by which the body regulates extracellular phosphate balance. Ninety percent of serum phosphate is filtered at the glomerulus, of which 80 to 97% is reabsorbed along the nephron, primarily in the proximal tubule. Parathyroid hormone and fibroblast growth factor 23 increase renal phosphate excretion by inhibiting the sodium-phosphate cotransporter in the proximal tubule, whereas vitamin D enhances intestinal phosphate absorption.

HYPOPHOSPHATEMIA

PATHOBIOLOGY

Hypophosphatemia may be caused by decreased intake, impaired intestinal absorption, redistribution into cells or bone, and renal losses (Table 105-2, Fig. 105-1). Phosphate is frequently depleted in alcohol use disorder (Chapter 364) because of the intake of a carbohydrate-rich, phosphate-poor diet, as well as renal phosphate wasting. Divalent cation-containing antacids bind phosphate in the intestinal lumen to form insoluble salts, thereby preventing their absorption. Vitamin D deficiency also leads to decreased intestinal phosphate absorption and hence to hypophosphatemia. Acute respiratory (but not metabolic) alkalosis (Chapter 104), including that due to salicylate intoxication, may cause transient hypophosphatemia. In this disorder, intracellular pH is increased, thereby stimulating glycolysis, which depletes the intracellular inorganic phosphate pool and leads to a shift of phosphate into cells.

Insulin is also a strong stimulus for shifting phosphate into cells. Patients with diabetic ketoacidosis (Chapter 210) are often hyperphosphatemic because of a shift of phosphate out of cells under insulinopenic conditions, but their total body phosphate is actually depleted as a result of urinary losses. Subsequent treatment with insulin may uncover severe hypophosphatemia. Similarly, in malnourished patients (Chapter 197), whose total body phosphate stores may be depleted, overzealous intravenous refeeding with carbohydrate-rich fluids may stimulate insulin release and cause acute hypophosphatemia.[7] The tyrosine kinase inhibitors imatinib, sorafenib, and nilotinib, which are used in the treatment of various cancers (Chapters 164 and 170), can cause profound hypophosphatemia, which appears to be due either to inhibition of bone resorption or a partial Fanconi syndrome.

Renal phosphate wasting is usually due to impaired proximal tubule phosphate reabsorption. In primary hyperparathyroidism (Chapter 227), hypercalcemia is typically associated with hypophosphatemia. Fanconi syndrome is a generalized proximal tubule disorder characterized by hypophosphatemia in association with glycosuria, aminoaciduria, hypokalemia, and type II renal tubular acidosis; it can be caused by a variety of inherited metabolic disorders, multiple myeloma (Chapter 173), heavy metal intoxication (Chapter 20), intravenous iron therapy (Chapter 144),[8] and drugs such as ifosfamide, cidofovir, and tenofovir. Phosphaturia also can occur with diuretics, particularly carbonic anhydrase inhibitors, and with antimicrobial agents such as pentamidine and foscarnet.

TABLE 105-2 CAUSES OF HYPOPHOSPHATEMIA

Nutritional deficiency
Malnutrition/malabsorption
Alcoholism*
Impaired intestinal absorption
Antacids
Chronic diarrhea*
Vitamin D deficiency*
Redistribution into cells
Respiratory alkalosis*
Insulin*
Refeeding syndrome
Burns*
Redistribution into bone
Hungry bone syndrome
Tyrosine kinase inhibitors (imatinib, sorafenib, nilotinib)
Renal losses
Hyperparathyroidism*
Renal tubulopathy
Fanconi syndrome
Drugs (pentamidine, foscarnet, acetazolamide, toluene, acetaminophen overdose, intravenous iron)
Phosphatonin excess syndrome
Oncogenic osteomalacia
Familial hypophosphatemic rickets
Extracorporeal removal
Continuous venovenous hemodiafiltration

*Common causes.

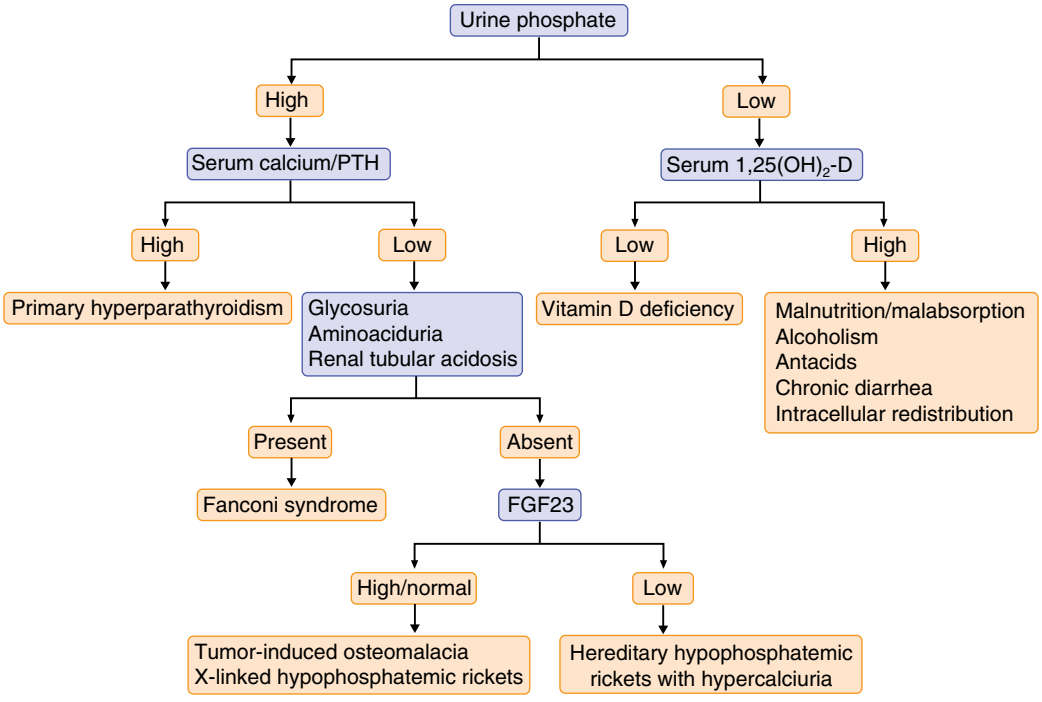

FIGURE 105-1. Diagnostic approach to chronic hypophosphatemia. $1,25(OH)_2$-D = 1,25-Dihydroxyvitamin D; FGF23 = fibroblast growth factor 23; PTH = parathyroid hormone.

Oncogenic osteomalacia is a paraneoplastic syndrome (Chapters 164 and 226) associated primarily with mesenchymal tumors that secrete a variety of phosphaturic factors, including fibroblast growth factor 23, that are collectively known as phosphatonins.[9] A similar phenotype is found in X-linked, autosomal dominant and autosomal recessive hypophosphatemic rickets (Chapter 226), which are inherited disorders that are characterized by an increase in the levels or activity of fibroblast growth factor 23. Fibroblast growth factor 23 inhibits both renal tubular phosphate reabsorption and 1α-hydroxylation of 25-hydroxycholecalciferol, thereby leading to hypophosphatemia, rickets, or osteomalacia (Chapter 226) and inappropriately low serum levels of 1,25-dihydroxycholecalciferol. Finally, patients undergoing renal replacement therapy by continuous venovenous hemodiafiltration (Chapter 117) often become phosphate depleted and need ongoing replacement.

CLINICAL MANIFESTATIONS

Clinical complications, which are usually observed only with severe hypophosphatemia (<1 mg/dL), are thought to be due to the disruption of cell membrane composition, depletion of ATP (which particularly affects high energy–consuming tissues such as skeletal and cardiac muscle), and depletion of 2,3-diphosphoglycerate in erythrocytes, with impaired tissue oxygen delivery. Manifestations of severe hypophosphatemia include encephalopathy, dilated cardiomyopathy, generalized muscle weakness that can lead to respiratory failure, rhabdomyolysis, and hemolysis. Hypophosphatemia also impairs renal ammoniagenesis and reduces the availability of urinary buffer, thereby impairing renal acid excretion and causing metabolic acidosis. Chronic hypophosphatemia leads to resorption of bone and osteomalacia.

DIAGNOSIS

The cause of hypophosphatemia is often evident from the history and physical examination. If not, measurement of either 24-hour urinary phosphate excretion or fractional excretion of phosphate (FE_{PO4}) in a spot urine sample is often helpful.

$$FE_{PO4} = \frac{\text{Urine phosphate} \times \text{Serum creatinine}}{\text{Serum phosphate} \times \text{Urine creatinine}}$$

In the setting of hypophosphatemia, the normal response of the kidney is to reduce urinary phosphate excretion to less than 100 mg/day or to reduce FE_{PO4} to less than 5%. Higher values suggest one of the causes of renal phosphate wasting.

TREATMENT

Patients with asymptomatic mild-to-moderate hypophosphatemia, normal total body phosphorus stores, and minimal ongoing phosphorus losses (e.g., hypophosphatemia caused by acute respiratory alkalosis) do not require treatment. Phosphate should be repleted in patients who are symptomatic, are suspected of having severely depleted intracellular phosphorus stores (malnourished or alcoholic patients), have ongoing gastrointestinal or renal losses, or have severe hypophosphatemia (<1 mg/dL).[10] Oral repletion can be accomplished with sodium or potassium phosphate salts (1 to 2 g/day) or with skim milk. Intravenous phosphorus repletion at a dose of 0.16 to 0.64 mmol/kg over 4 to 8 hours is recommended for severe hypophosphatemia but is contraindicated in patients with renal insufficiency or hypercalcemia. Hypophosphatemia in patients on continuous venovenous hemodiafiltration can also be ameliorated by the use of phosphate-containing dialysate and replacement solutions. Complications of phosphate therapy include hypocalcemia, metastatic calcification, hypotension, acute renal failure, and arrhythmias, as well as concomitant hypernatremia or hyperkalemia, depending on which salt is administered.

PROGNOSIS

Most patients with hypophosphatemia respond well to treatment. However, hypophosphatemia is a marker of the severity of disease in patients who require intensive care.[11]

HYPERPHOSPHATEMIA

PATHOBIOLOGY

Pseudohyperphosphatemia may occur in blood specimens that are hemolyzed or hyperglobulinemic, such as in multiple myeloma (Chapter 173). True hyperphosphatemia is caused by excessive phosphate intake, increased intestinal absorption, redistribution from intracellular stores, or impaired renal excretion (Table 105-3 and Fig. 105-2). Overzealous phosphate repletion also can cause hyperphosphatemia. The phosphorus in some laxatives and enemas may be absorbed and cause hyperphosphatemia. Intoxication with vitamin D or its analogues increases intestinal absorption of both calcium and phosphorus. Conditions associated with massive cell lysis, such as rhabdomyolysis (Chapter 99) and tumor lysis syndrome (Chapter 164), release intracellular phosphate into the extracellular fluid, where it can bind calcium and result in hypocalcemia (Chapter 227). Patients with diabetic ketoacidosis (Chapter 210) are often hyperphosphatemic at initial evaluation because of the redistribution of phosphate out of cells in the insulin-deficient state. Decreased phosphate

TABLE 105-3 CAUSES OF HYPERPHOSPHATEMIA

Phosphate intake
Phosphate repletion
Phosphate-containing laxatives and enemas*
Increased intestinal absorption
Vitamin D toxicity
Redistribution from intracellular stores
Rhabdomyolysis*
Tumor lysis syndrome
Diabetic ketoacidosis
Decreased renal excretion
Renal failure*
Hypoparathyroidism
Pseudohypoparathyroidism
Familial tumoral calcinosis
Inhibitors of fibroblast growth factor receptor (e.g., erdafitinib, infigratinib, pemigatinib)

*Common causes.

TREATMENT

Acute hyperphosphatemia in an asymptomatic patient with normal renal function often resolves spontaneously as excess phosphate is excreted. In symptomatic patients and those with impaired renal function, phosphate can be removed by extracorporeal therapy. Because of the slow rate of phosphate mobilization from intracellular stores, continuous venovenous hemodiafiltration is considerably more effective than intermittent hemodialysis. Chronic hyperphosphatemia (Chapter 116) can be managed by minimizing the dietary intake of phosphorus and administering oral phosphate binders with meals. Current guidelines recommend minimizing the use of calcium salts in chronic kidney disease (Chapter 116), based on evidence that non–calcium-based phosphate binders and especially sevelamer (800 mg three times daily)[A1] may reduce all-cause mortality compared with calcium-based binders.[A2] Tenapanor (starting at 5 mg twice daily and titrating to as high as 30 mg twice daily if needed), which is an inhibitor of the paracellular absorption of phosphorus from the intestine, can lower serum phosphate levels.[A3] Cinacalcet (starting at 30 mg daily and titrated as high as 180 mg daily as needed), which is a calcimimetic used in patients with chronic kidney disease to treat secondary hyperparathyroidism, also reduces the serum phosphate concentration modestly and can be considered in refractory cases.

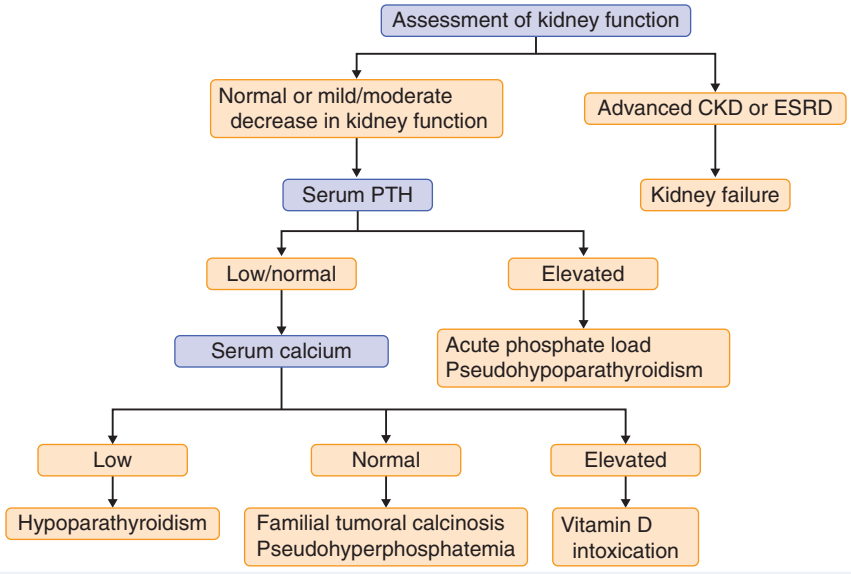

FIGURE 105-2. Diagnostic approach to chronic hyperphosphatemia, a parathyroid hormone (PTH)–based diagnostic algorithm. CKD = chronic kidney disease; ESRD = end-stage renal disease; PTH = parathyroid hormone. (Redrawn from Leaf DE, Wolf M. A physiologic-based approach to the evaluation of a patient with hyperphosphatemia. *Am J Kidney Dis.* 2013;61:330-336.)

excretion is most commonly due to acute or chronic kidney disease (Chapter 116). With a normal diet, serum phosphate levels can be maintained within the normal range until the glomerular filtration rate falls below 25 mL/minute. However, even mild degrees of renal insufficiency may predispose to hyperphosphatemia if there is a concurrent excessive intake of phosphate-containing compounds such as laxatives. Parathyroid hormone stimulates the excretion of phosphate in the proximal tubule, so primary hypoparathyroidism (Chapter 227) is often associated with mild hyperphosphatemia as well as hypocalcemia.[12] Oncologic drugs that inhibit fibroblast growth factor receptors (Chapters 164 and 166) also can cause hyperphosphatemia by antagonizing fibroblast growth factor 23.[13]

CLINICAL MANIFESTATIONS

Acute hyperphosphatemia increases the risk for the precipitation of calcium phosphate and subsequent metastatic calcification in soft tissues, including the kidney, in which it can cause acute kidney injury (Chapter 106).[14] For example, acute hyperphosphatemia is an independent risk factor for acute kidney injury in patients with rhabdomyolysis (Chapter 99).[15] The resultant hypocalcemia (Chapter 227) can cause tetany, hypotension, seizures, and cardiac arrhythmias. Hyperphosphatemia in chronic kidney disease (Chapter 116) is a risk factor for coronary and other vascular calcification and for increased mortality.

PROGNOSIS

Severe acute hyperphosphatemia can be life-threatening owing to metastatic calcification and multiorgan failure, but it generally responds well to prompt therapy. Chronic hyperphosphatemia in patients with chronic kidney disease (Chapter 116) is often fairly resistant to treatment, particularly in poorly compliant individuals, and is associated with increased long-term mortality.

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106 ACUTE KIDNEY INJURY

ANUPAM AGARWAL AND JONATHAN BARASCH

DEFINITION

Acute kidney injury (AKI), which is a clinical syndrome, is defined by a clinically evident defect in the kidney's clearance of waste materials within approximately 1 week after an injurious stimulus. Although formal definitions vary somewhat, the components include an increase in the serum level of the muscle metabolite creatinine by 0.3 mg/dL or greater (within 48 hours), an increase in the creatinine level to 1.5 times higher than a baseline value within 7 days or a fall in urine volume to less than 0.5 mL/kg/hour for 6 hours or longer (Table 106-1). The degree of the rise in serum creatinine or fall in urine output is typically reported in stages that describe progressive functional loss (Table 106-1).

EPIDEMIOLOGY

About 20 to 25% of hospitalized adults have an elevated serum creatinine level. Among patients admitted to the hospital from an emergency department, up to 45% present with an elevated serum creatinine level, and the rate is even higher (55 to 65%) among patients who are admitted to the intensive care unit (ICU). Because the serum creatinine level is insensitive for detecting tubular or vascular damage, the true incidence of acute kidney injury is probably even higher.[1] In contrast, community-acquired acute kidney injury is uncommon and estimated to have an annual incidence of less than 1%. The serum creatinine level can be elevated for a variety of reasons, including prerenal, intrarenal, and postrenal subtypes that are impossible to distinguish on the basis of a single measurement of the serum creatinine level (Fig. 106-1).

Prerenal azotemia, which is the most common cause of an elevated serum creatinine level, is found in 15% of patients admitted from the emergency department. Prerenal azotemia accounts for about 40% of hospital-acquired cases of acute kidney injury and as much as 60 to 70% of community-acquired cases, depending on its precise definition. Intrinsic acute kidney injury, defined as 7 days or longer of azotemia, is present in 5 to 6% of patients who are admitted from the emergency department in the United States and in as many as 60% of patients in the intensive care unit. Acute kidney injury is also common and underdiagnosed in low-resource settings worldwide.[2] Intrinsic acute kidney injury requiring dialysis has increased substantially over the past three decades. For postrenal acute kidney injury, the incidence depends on the patient's age and sex. Prostatic hypertrophy in older men (Chapter 114) is the leading cause.

TABLE 106-1 KIDNEY DISEASE IMPROVING GLOBAL OUTCOMES (KDIGO) ACUTE KIDNEY INJURY DEFINITIONS

STAGE	SERUM CREATININE	URINE OUTPUT
1	1.5-1.9 times baseline OR ≥0.3 mg/dL (≥26.5 µmol/L) increase	<0.5 mL/kg/hour for 6 to 12 hours
2	2.0-2.9 times baseline	<0.5 mL/kg/hour for ≥12 hours
3	3.0 times baseline OR Increase in serum creatinine to ≥4.0 mg/dL (≥353.6 µmol/L) OR Initiation of renal replacement therapy OR In patients <18 years of age, decrease in eGFR to <35 mL/min per 1.73 m^2	<0.3 mL/kg/hour for ≥24 hours OR Anuria for ≥12 hour

eGFR = estimated glomerular filtration rate.
Adapted from Molitoris BA. Acute kidney injury. In: Goldman L, Schafer AI, eds. *Goldman-Cecil Medicine*, 26th ed. Philadelphia: Saunders; 2020.

Prerenal Azotemia/Hypoperfusion

Prerenal azotemia is caused when hypoperfusion of the kidney reduces the clearance of serum creatinine and water, thereby limiting urine output. In prerenal azotemia, kidney function, including the serum creatinine level and urine output, can be corrected within hours of infusing volume, thereby stimulating cardiac output, or withdrawing vasoconstrictors (e.g., nonsteroidal anti-inflammatory drugs [NSAIDs], cyclosporine, radiocontrast agents). Although evidence of tubular injury may be limited, even 1 day of prerenal azotemia can result in hyponatremia, hyperkalemia, acidosis, and hence increased mortality (Fig. 106-2). Urinary biomarkers of acute kidney injury are not particularly elevated.

The causes of prerenal azotemia include true intravascular volume depletion because of limited oral intake, fever and sweating, burns, diarrhea, diuretic agents, and bleeding, as well as effective volume depletion from heart failure (Chapter 45) or liver failure (Chapter 140). In addition, a number of medications potentially reduce glomerular perfusion and raise the serum creatinine level, including NSAIDs, angiotensin-converting enzyme (ACE) inhibitors, and angiotensin receptor blockers. These medications can have a dramatic effect on the serum creatinine level when renal perfusion is compromised by volume depletion or other insults.

Intrinsic Acute Kidney Injury

Intrinsic acute kidney injury can involve any portion of the kidney or its vasculature. Central to the pathobiology is an abrupt decline in kidney function that cannot be restored for a number of days or even weeks owing to slow resolution of intensive vasoconstriction, tubular damage, and cell death, as well as interstitial inflammation with edema. Urinary biomarkers of tubular damage are particularly elevated. In contrast to prerenal azotemia, molecular

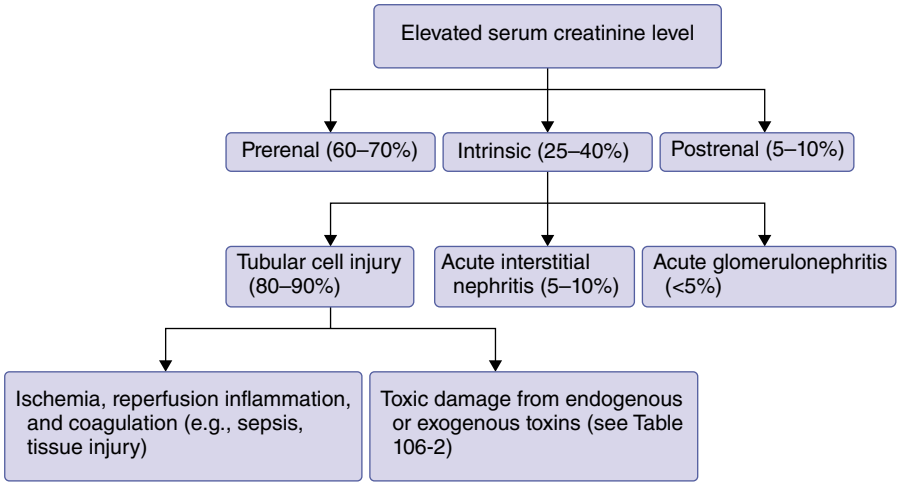

FIGURE 106-1. Categories of acute kidney injury. (Adapted from Molitoris BA. Acute kidney injury. In: Goldman L, Schafer AI, eds. *Goldman-Cecil Medicine*, 26th ed. Philadelphia: Saunders; 2020.)

ABSTRACT

Acute kidney injury, which occurs frequently in hospitalized patients, is defined as a rapid decline in kidney function within 1 week of an injury, such as from a toxin, medication, sepsis, or hemodynamic perturbance. Acute kidney injury includes prerenal, intrarenal, and postrenal subtypes, which differ in their pathogenesis and can be distinguished by imaging studies and by urine and serum biomarkers. Treatments involve removal of offending stimuli, correcting any obstruction, and supportive care to address volume depletion and electrolyte disturbances. Hemodialysis is warranted when prolonged acute kidney injury is associated with volume overload, electrolyte disturbances, or uremic symptoms. Prognosis varies depending on the underlying injury and preexisting comorbid conditions, but acute kidney injury is associated with significant morbidity and mortality. Prevention relies on the identification of high-risk patients and limiting the use of potential nephrotoxins.

KEYWORDS

acute renal failure
chronic kidney disease
proximal tubule
biomarkers
renal replacement therapy
nephrotoxins

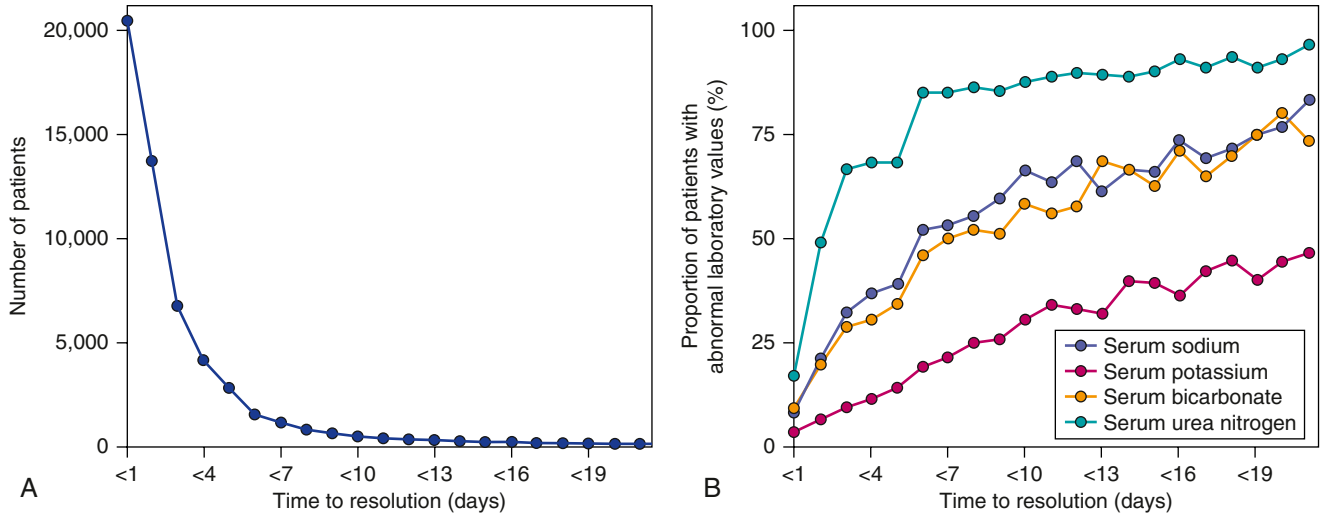

FIGURE 106-2. **Rapid resolution of an elevated serum creatinine in most patients with acute kidney injury. (A)** In about one third of hospitalized patients, the condition resolves within 24 hours, about 60% by 48 hours, and about 70% by 72 hours after meeting criteria for acute kidney injury. **(B)** Electrolyte abnormalities correlate with a sustained elevation in the serum creatinine level. (Data from Xu K, Rosenstiel P, Paragas N, et al. Unique transcriptional programs identify subtypes of AKI. *J Am Soc Nephrol*. 2017;28:1729-1740.)

TABLE 106-2 COMMON RENAL TUBULAR TOXINS

Antimicrobial agents
Acyclovir
Aminoglycosides
Amphotericin B
Foscarnet
Pentamidine
Sulfonamides
Tenofovir
Vancomycin
Calcium oxalate crystals
Cisplatin
Cocaine
Cyclosporine
Metals (e.g., iron, cadmium)
Methotrexate
Myoglobin/hemoglobin
Pancreatic enzymes (endogenous)
Radiocontrast agents
Tacrolimus
Toluene
Uric acid crystals
Ethylene glycol

Adapted from Molitoris BA. Acute kidney injury. In: Goldman L, Schafer AI, eds. *Goldman-Cecil Medicine*, 26th ed. Philadelphia: Saunders; 2020.

TABLE 106-3 MEDICATIONS ASSOCIATED WITH ACUTE INTERSTITIAL NEPHRITIS

ANTIMICROBIAL AGENTS
Acyclovir
Cephalosporins
Ciprofloxacin
Indinavir
Penicillin
Rifampin
Sulfonamides (e.g., trimethoprim-sulfamethoxazole)
Vancomycin
DIURETICS
Furosemide
Hydrochlorothiazide
Triamterene
OTHERS
Allopurinol
Checkpoint inhibitors
Cimetidine
Nonsteroidal anti-inflammatory drugs
Proton pump inhibitors
Salicylates (mesalamine)

Adapted from Molitoris BA. Acute kidney injury. In: Goldman L, Schafer AI, eds. *Goldman-Cecil Medicine*, 26th ed. Philadelphia: Saunders; 2020.

analysis demonstrates the activation of inflammatory, ischemic, and coagulation pathways.

The causes of intrinsic acute kidney injury[3] include ischemic hypoperfusion that results in cellular injury, septic injury,[4] inflammatory injury, and a myriad of renal toxins (Table 106-2), including intrinsic toxins (e.g., myoglobin, hemoglobin, calcium oxalate, uric acid, and endogenous pancreatic enzymes) and exogenous toxins (e.g., radiocontrast agents, antibiotics, and metals). Acute kidney injury does not develop in all patients who are exposed to potentially toxic agents, but patients with prior functional defects, such as elderly patients with chronic kidney disease or volume-depleted patients (e.g., due to diuretics, burns, heart failure, cirrhosis, or hypoalbuminemia), are more likely to suffer toxic tubular injury. For example, the risk of developing antibiotic nephrotoxicity is 10-fold higher in high-risk patients.

Injury to the renal interstitium or acute interstitial nephritis (Chapter 108) is found in about 15% of biopsy samples of patients who have an intrinsic acute kidney injury.[5] Implicated medications include sulfonamides, penicillins, cephalosporins, proton pump inhibitors, and NSAIDs (Table 106-3). In addition, checkpoint inhibitors trigger acute interstitial nephritis in about 5% of treated patients. Bacteria and viruses that can cause interstitial injury include *Legionella,* leptospirosis, *Yersinia,* streptococcus, *Mycobacterium tuberculosis,* Epstein-Barr virus, severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), and cytomegalovirus. Fungal infections, including histoplasmosis and coccidioidomycosis, as well as tuberculosis, are implicated in granulomatous acute interstitial nephritis. Interstitial nephritis also can be seen in patients who have systemic autoimmune diseases, including systemic lupus erythematosus (Chapter 245), Sjögren syndrome (Chapter 247), cryoglobulinemia (Chapter 173), and primary biliary cirrhosis (Chapter 141). Intratubular crystallization of compounds such as uric acid, calcium oxalate, acyclovir, sulfonamides, methotrexate, and myeloma light chains can result in tubular obstruction.

Postrenal Acute Kidney Injury

Postrenal acute kidney injury refers to obstruction of urinary outflow. Both kidneys (or a single solitary kidney) must be obstructed in order to cause postrenal acute kidney injury, because the serum creatinine level is too insensitive to detect kidney damage from partial or unilateral obstruction. Obstruction can occur in the lower tract owing to the constriction of the urethra or the base of the bladder by prostatic hypertrophy (Chapter 114) or cancer of the prostate (Chapter 186), cervix (Chapter 184), or bladder (Chapter 182). Patients with spinal cord disease or diabetes also can develop an elevated serum creatinine

level because of functional obstruction from a neurogenic bladder. Obstruction of both ureters at the bladder trigone or along their course from the kidneys can be seen in retroperitoneal fibrosis (Chapter 246), endometriosis (Chapter 218), metastatic colon cancer (Chapter 179), and lymphomas (Chapters 171 and 172). Intraluminal blockade occurs when renal calculi (Chapter 111), papillary necrosis (Chapter 100), or blood clots obstruct both ureters.

PATHOBIOLOGY

Molecular processes that cause acute kidney injury can be categorized according to the principal site of disease activity. Such processes include decreased kidney perfusion, which can reduce the glomerular filtration rate (GFR) regardless of whether it causes acute cellular injury, a primary glomerular disease, an injury (toxic, septic, ischemic) to the nephron, or inflammation and edema of the tubules or interstitium (Fig. 106-3).

Prerenal Acute Kidney Injury

A reduction in extracellular or intravascular volume, commonly termed effective arterial volume, affects many segments of the kidney by activating the catecholamine–renin–angiotensin–aldosterone–antidiuretic hormone systems. These regulators determine afferent and efferent arteriolar tone in the glomerulus and hence the concentration of albumin and the reabsorption of Na^+ and water in the postglomerular capillary and in the nephron. The hormonal cascade is most active in the inner medulla, where the final capture of salt and water prevents further volume depletion. In addition, Na^+ recovery is a critical pro-inflammatory signal that defends the kidney from urinary infections during periods when urine flow rate is reduced.

In addition to regulating gene transcription via the hormonal axis, volume depletion also regulates oxygen tension in the medulla. Volume depletion reduces and volume expansion increases medullary partial pressure of oxygen (pO_2), without changing cortical pO_2. Severe and prolonged prerenal azotemia can damage the inner medullary tubules by hypoxia (Table 106-4). Conversely, volume resuscitation is needed to protect the kidney when a second insult, such as a nephrotoxic agent or radiologic contrast, may damage the kidney.

Prerenal acute kidney injury may also result from heart failure, called cardiorenal acute kidney injury. Both right-sided congestion, which can involve the renal vein, and left-sided failure with a decreased cardiac output, can reduce the effective arterial volume and, as a result, the filtration of creatinine.

Early in the course of heart failure (Chapter 45) and early in prerenal azotemia, the GFR remains relatively preserved, with only small increases in the serum creatinine level, because kidney hypoperfusion triggers a cascade of hormonal responses that dilate afferent arterioles and constrict efferent arterioles to maintain glomerular perfusion pressure and that stimulate the tubules to retain Na^+ and water. At later stages, however, intravascular volume expansion does not further improve kidney perfusion; rather, removal of volume

TABLE 106-4 CONDITIONS THAT LEAD TO ISCHEMIC ACUTE KIDNEY INJURY

MECHANISM	CONDITION
Severe volume depletion and hypotension	Severe hemorrhage; gastrointestinal, renal, and dermal losses
Severely decreased effective intravascular volume	Severe heart failure and cirrhosis, hepatorenal syndrome, peritonitis
Systemic vasodilation, renal vasoconstriction	Sepsis, hepatorenal syndrome
Large-vessel renal vascular disease	Renal artery thrombosis or embolism, intraoperative arterial cross-clamping, renal artery stenosis, cholesterol emboli
Small-vessel renal vascular disease	Sepsis, vasculitis, atheroembolism, hemolytic-uremic syndrome, malignant hypertension, scleroderma, preeclampsia, sickle cell anemia, hypercalcemia, transplant rejection
Impaired renal blood flow	Cyclosporine, tacrolimus, angiotensin-converting enzyme inhibitors, angiotensin receptor blockers, nonsteroidal anti-inflammatory drugs, radiocontrast agents

Adapted from Molitoris BA. Acute kidney injury. In: Goldman L, Schafer AI, eds. *Goldman-Cecil Medicine*, 26th ed. Philadelphia: Saunders; 2020.

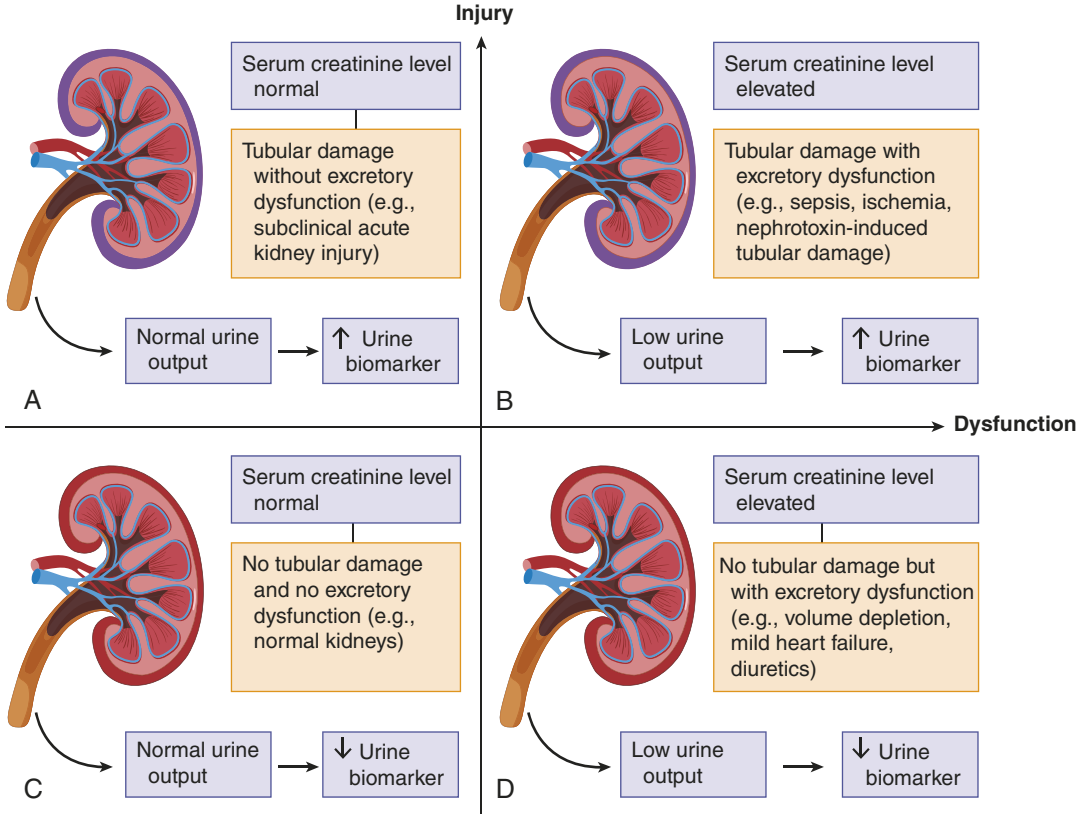

FIGURE 106-3. Three forms of acute kidney injury based on the intersection of an elevated serum creatinine level and urinary biomarkers. (A) Partial damage is detected by biomarkers but not by the serum creatinine level. **(B)** Extensive damage detected by both biomarkers and the serum creatinine level. **(C)** Normal kidney. **(D)** Volume depletion detected by an elevated serum creatinine level without biomarker elevation. (Adapted from Desanti De Oliveira B, Xu K, Shen TH, et al. Molecular nephrology: types of acute tubular injury. *Nat Rev Nephrol*. 2019;15:599-612.)

and reducing congestion in the pulmonary and renal veins is beneficial even as the serum creatinine level rises if tubular damage is not also present.

Progression of Prerenal to Intrinsic Acute Kidney Injury

Prerenal and intrarenal azotemia are distinct conditions, with different molecular pathways, including gluconeogenesis, lipid metabolism, and anti-inflammatory regulators in the prerenal state as compared with coagulation, inflammation, and epithelial remodeling in the intrarenal state. However, when a second insult, such as an inflammatory or toxic stimulus, is superimposed, volume depletion exacerbates the damage.[6] Without early volume repletion, prerenal azotemia may contribute to tubular epithelial injury.

Intrarenal Acute Kidney Injury

Intrinsic acute kidney injury can be classified by the primary site of injury: tubules, interstitium, vasculature, or glomerulus. Renal tubular injury, previously termed *acute tubular necrosis* (ATN) and now *acute tubular injury* (ATI), is typically found in the S3 segment of the proximal tubule and the medullary thick ascending limb of Henle, which are two segments that are located in the outer stripe of the medulla, where oxygen tension is limited. Different forms of ischemia preferentially target these segments: warm ischemia targets the proximal (S3) tubule, whereas cold ischemia, vasoconstrictors, contrast agents, gram-negative sepsis, myoglobinuria, and obstruction target the medullary thick ascending limb of Henle. The balance of injury may depend on the degree of injury-induced hypoxia (the proximal tubule is dependent on aerobic metabolism, whereas the medullary thick ascending limb of Henle can utilize anaerobic metabolisms) and on segmental variations in the activation of mitogen-activated protein kinases.

A very common cause of intrinsic acute kidney injury is sepsis. The initiation stage of sepsis-associated tubular injury is not fully elucidated, but lipopolysaccharide accumulates in proximal tubules and then in distal tubules. The uptake of lipopolysaccharide correlates with broadening of the distribution of toll-like receptors (TLRs), including TLR4, the lipopolysaccharide receptor, and its coreceptor (CD14) from distal tubules to proximal tubules in response to injury.

Tubular toxins initiate damage by binding endocytic receptors (megalin and cubilin) and trafficking to tubular lysosomes in the proximal tubule, similar to the pathway taken by lipopolysaccharide. The many endocytic toxins that may also undergo endocytosis by the megalin pathway include cadmium, aminoglycoside antibiotics, and other medicinal toxins such as intravenous radiocontrast agents and cisplatin (see Table 106-2).[7] The most important endocytic toxin is the endogenous molecule myoglobin (Chapter 99), which contains heme and iron and triggers ferroptosis and necroptosis. Tubular toxins also exacerbate kidney injury by inducing vasoconstriction. This phenomenon is linked to radiocontrast agents, NSAIDs, cyclosporine, and combinations of these agents with renin-angiotensin system inhibitors and diuretics.

In addition to direct cell toxicity and vasoconstriction, many toxins and metabolites can precipitate and thereby block tubular function. Endogenous compounds that can cause crystal nephropathy include calcium oxalate (both the common enteric form and the primary hyperoxaluric form), and uric acid. Exogenous compounds that create intratubular obstruction include acyclovir, sulfonamides (sulfadiazine and sulfamethoxazole), ciprofloxacin, vitamin C, ethylene glycol, methotrexate, protease inhibitors (e.g., indinavir, darunavir), and the light chains of multiple myeloma (Chapter 173).

Cellular Damage

Cellular dysfunction is typical in the proximal tubule, particularly in the S3 segment. In the initiation phase of renal ischemia, the apical membrane with the brush border sheds in blebs from the cells. Subsequently, the polarity of membrane proteins is lost, due to loss of function of cellular tight junctions. Retraction of tight junctions and loss of the epithelial cell barrier allow the back-leak of the glomerular filtrate into the interstitium, thereby reducing clearance of metabolic wastes. As the injury progresses, both live and necrotic proximal cells detach from the basement membrane and enter the tubular lumen, where they ultimately form casts in the distal tubule. Casts contribute to a reduction in GFR by obstructing the tubular flow of urine at the S3-thin limb of Henle junction,[8] thereby preventing further filtration into that nephron. The clearance of casts is necessary for recovery; it is mediated by proteases and by phagocytic proteins that bind intratubular casts. By day 3 after injury, casts are cleared from most of the nephron, but obstructing casts can linger at the S3 segment or descending limb of Henle.

During the phase of cellular death, endothelial dysfunction and an inflammatory endothelial response, particularly in the corticomedullary junction of the kidney, result from extensive signaling between the proximal tubular cells and adjacent endothelial cells. Leukocytes can block blood flow via cellular adhesion and rouleaux formation. Damage to the microvasculature in turn can generate coagulation abnormalities. When proximal tubular cells dedifferentiate, proliferate, and restore the nephron,[9] the kidney recovers and the GFR begins to improve.

In interstitial and vascular acute interstitial nephritis (Chapter 108), interstitial edema comprises an inflammatory infiltrate with T lymphocytes, eosinophils, monocytes, and macrophages invading the tubular basement membrane. In chronic interstitial nephritis, the characteristic findings are interstitial fibrosis and tubular atrophy, but inflammation can persist. Surprisingly, a greater degree of inflammation may portend a higher likelihood of resolution.[10]

Vascular Disease

Microvascular diseases (e.g., sepsis [Chapter 94], the hemolytic-uremic syndrome [Chapter 158], thrombotic thrombocytopenic purpura [Chapter 158], and the HELLP syndrome [*h*emolysis, *e*levated *l*iver enzymes, and *l*ow *p*latelet count; Chapters 132 and 221]) can also cause acute kidney injury by producing fibrin clots in the glomerulus and microvasculature. Acute kidney injury related to macrovascular disease is seen with embolism, including embolism of cholesterol plaques that occur especially after invasive vascular procedures (Chapter 110), and larger thromboembolism as in atrial fibrillation (Chapter 52). Vascular infarcts also can be seen with hypercoagulable states such as the nephrotic syndrome, antiphospholipid syndrome, and homocysteinemia, as well as with the use of oral contraceptive agents. Acute kidney injury also occasionally can be caused by glomerulonephritis (Chapter 107). Sometimes the glomerular injury is part of a systemic disease such as systemic lupus nephritis (Chapter 245), granulomatosis with polyangiitis (Chapter 249), polyarteritis nodosa (Chapter 249), Goodpasture syndrome (Chapter 107), Henoch-Schönlein purpura (Chapters 107 and 249), or the hemolytic-uremic syndrome (Chapter 158).

Postrenal Acute Kidney Injury

Postrenal acute kidney injury is caused by obstruction to luminal flow of the glomerular filtrate. In this condition, the GFR initially remains largely preserved because the glomerular afferent arteriole is dilated. If, however, the obstruction is not rapidly relieved, the release of angiotensin II and thromboxane causes vasoconstriction and reduces the GFR. If the obstruction persists for more than 12 to 24 hours, renal blood flow and intratubular pressure decline, and the GFR declines because of large underperfused areas of renal cortex. Subsequently, the kidney is invaded by macrophages, which stimulate fibrosis.

Acute Kidney Injury in the Setting of SARS-CoV-2

The SARS-CoV-2 virus that causes coronavirus disease 2019 (COVID-19) induces systemic responses, including a cytokine storm, immune and metabolic dysfunction, endothelial injury, coagulopathy, and microangiopathy (Chapter 336).[11] SARS-CoV-2 can directly infect kidney cells, where it causes dedifferentiation and activation of profibrotic pathways in the organoids.[12] Pathology reveals proximal tubular cell injury with loss of apical membrane and intracellular inclusions. In addition, nonviral mechanisms include hemodynamic factors, cardiac dysfunction, high levels of mechanical ventilation, hypovolemia, use of nephrotoxic drugs, and nosocomial sepsis.

CLINICAL MANIFESTATIONS

Acute kidney injury is usually clinically silent, and no specific symptoms are present in early stages of the injury. Some patients will rarely note a change in urine volume or color. Obstructive acute kidney injury due to a stone (Chapter 111) or papillary necrosis (Chapter 100) may result in hematuria and in flank pain radiating to the ipsilateral groin, but they also can be silent. Distal-type renal tubule acidosis (Chapter 104) is a common sequela of obstructive uropathy. In advanced states of acute kidney injury, uremic symptoms (Chapter 116) develop with anorexia, fatigue, nausea and vomiting, pruritus, and reversal of the sleep-wake cycle. Examination of the patient may reveal pulmonary edema and peripheral edema (Chapter 45), inflammatory complications such as a pericardial or pleural friction rub, and neurologic complications of uremia such as myoclonus and asterixis.

DIAGNOSIS

The diagnosis of acute kidney injury is based on a rise in the serum creatinine level and subsequently on elucidating the cause of the injury. Despite the utility of a single measurement of serum creatinine to demonstrate kidney dysfunction, a single elevated serum creatinine level measurement cannot

accurately measure functional loss because it lacks the kinetic properties required to determine function in the absence of steady state. In addition, the serum creatinine level and urine output fail to detect kidney tubule injury in real time, to detect injury that involves less than one entire kidney, or to distinguish different clinical syndromes that elevate serum creatinine levels. Finally, serum creatinine levels are influenced by muscle mass, muscle damage, nutritional status, and medications that block the tubular transport of serum creatinine (e.g., cimetidine, trimethoprim, pyrimethamine, and salicylates), thereby raising serum creatinine in the absence of injury.[13]

All patients with an acutely elevated serum creatinine level should be evaluated with serum measurements of electrolytes, calcium, phosphorus, and a blood urea nitrogen level, as well as a complete blood count with differential. Urine dipstick and microscopy (Table 106-5) can detect blood, cells, and casts that are typical of different forms of intrarenal damage (Chapter 100). The urine and serum Na^+ and serum creatinine levels should be measured simultaneously to determine the fractional excretion of sodium (FE_{Na}), which measures the ability of the tubules to reabsorb Na^+, normalized for water reabsorption by measuring urine creatinine (Table 106-6).

$$FE_{Na} = \frac{\text{Urine Na} \times \text{Plasma Cr}}{\text{Plasma Na} \times \text{Urine Cr}} \times 100$$

In the setting of oliguria, an elevated FE_{Na} suggests tubular damage. Fractional excretion of chloride (FE_{Cl}) can substitute for FE_{Na} because urinary sodium can be elevated by systemic alkalosis when a high urinary bicarbonate level obligates the loss of sodium.

Prerenal azotemia can be diagnosed by evidence of dehydration and by its rapid resolution after a fluid challenge (e.g., 100 mL intravenously in 1 minute or up to 3 to 4 mL/kg over 5 minutes). In early true acute kidney injury, urine output of 100 mL within 1 hour after administering intravenous furosemide (1 or 1.5 mg/kg) can evaluate residual tubular function and can predict the subsequent rise in serum creatinine levels and mortality.[14] A renal ultrasound is key to exclude postrenal azotemia caused by stones, anatomic malformations, and bladder outlet obstruction.

TABLE 106-5 COMMON URINALYSIS FINDINGS IN ACUTE KIDNEY INJURY

CAUSE OF ACUTE KIDNEY INJURY	URINALYSIS
Prerenal	Normal or hyaline casts
Intrarenal	
Tubular cell injury	Muddy-brown, granular, epithelial casts
Interstitial nephritis	Pyuria, hematuria, mild proteinuria, granular and epithelial casts, eosinophils
Glomerulonephritis	Hematuria, marked proteinuria, red blood cell casts, granular casts
Vascular disorders	Normal or hematuria, mild proteinuria
Postrenal	Normal or hematuria, granular casts, pyuria

Adapted from Molitoris BA. Acute kidney injury. In: Goldman L, Schafer AI, eds. *Goldman-Cecil Medicine*, 26th ed. Philadelphia: Saunders; 2020.

TABLE 106-6 FE_{Na} VALUES FOR THE VARIOUS CAUSES OF ACUTE KIDNEY INJURY

CAUSE OF ACUTE KIDNEY INJURY	FE_{Na}	BUN-TO-SERUM CREATININE RATIO
Prerenal	<1%	>20
Intrarenal		<10-15
Tubular necrosis	≥1%	
Interstitial nephritis	≥1%	
Glomerulonephritis (early)	<1%	
Vascular disorders (early)	<1%	
Postrenal	≥1%	>20

FE_{Na} = fractional excretion of sodium.
Adapted from Molitoris BA. Acute kidney injury. In: Goldman L, Schafer AI, eds. *Goldman-Cecil Medicine*, 26th ed. Philadelphia: Saunders; 2020.

When the diagnosis appears to be true acute kidney injury, urine protein measurements for biomarkers (e.g., tissue inhibitor of matrix metalloproteinase 2–insulin-like growth factor–binding protein 7 [TIMP2-IGFBP7], kidney injury molecule 1 [KIM-1], neutrophil gelatinase–associated lipocalin [NGAL], and interleukin 18) can detect cell stress and damage that are typical of tubular injury rather than simple prerenal azotemia, even when the serum creatinine level has just started to rise because of a falling GFR.[15] Based on their sensitivity and specificity for tubular injury, some of these biomarkers may help guide the characterization of acute kidney injury (see Fig. 106-3), but their actual use in clinical practice has been limited.

Prerenal Azotemia

Prerenal azotemia is suggested by history of vomiting, diarrhea, hemorrhage, or poor oral intake. Heart failure indicates hypoperfusion either because of progressive disease or because of volume depletion due to diuretics. Medications such as NSAIDs, ACE inhibitors, and angiotensin-receptor blockers, can cause prerenal azotemia. Physical examination includes findings typical of underperfusion such as systemic or orthostatic hypotension, flat jugular veins, dry mucous membranes, and reflex tachycardia. Laboratory studies in patients with prerenal azotemia demonstrate elevated serum creatinine and blood urea nitrogen (BUN) levels. In prerenal azotemia, patients will typically have a ratio of BUN to serum creatinine of greater than 20 : 1. FE_{Na} is typically less than 1%. The FE_{Na} can provide reliable diagnostic information regarding acute kidney injury only if it is less than 1%, because elevated levels of FE_{Na} are seen in many diseases. In patients who are taking diuretics or in the presence of nonreabsorbable solutes such as glucose, a fractional excretion of urea (FE_{urea}) below 35% suggests prerenal acute kidney injury.

Intrarenal Acute Kidney Injury

In intrarenal acute kidney injury, significant hypotension, sepsis, and exposure to nephrotoxins (see Tables 106-2 and 106-3) are common. Physical examination is usually not revealing except for evidence of hypervolemia (Chapters 39 and 45). The skin examination may reveal embolic phenomenon or a rash consistent with allergic interstitial nephritis.

Laboratory testing will show elevated serum creatinine and BUN levels. Unlike prerenal azotemia, in which the elevation of the serum creatinine level tends to be modest and to plateau below 4 mg/dL, the serum creatinine level in intrarenal acute kidney injury may rise rapidly each day. The FE_{Na} is usually above 1 in acute injury, whereas it typically is below 1 in early sepsis, glomerulonephritis, radiocontrast-induced acute kidney injury, and vascular disorders. The urinalysis also can be helpful in making the diagnostic (see Table 106-6). In rare cases, acute interstitial nephritis may be associated with peripheral and urinary eosinophilia, but eosinophilia can also accompany cholesterol microemboli (Chapter 110). Urinary interleukin (IL)-9 and tumor necrosis factor (TNF)-α may be better markers for acute interstitial nephritis than are urinary findings.[16] Biomarkers can help detect intrarenal tubular injury within hours of the injury, and their levels in the urine can distinguish intrarenal (biomarkers are very elevated) from prerenal (biomarkers are not particularly elevated) forms of acute kidney injury.

Postrenal Acute Kidney Injury

Postrenal acute kidney injury should be suspected in patients who have a history of prostatic hypertrophy (Chapter 114), prostate cancer (Chapter 186), lymphoma (Chapter 171), cervical cancer (Chapter 184), or retroperitoneal disease. However, postrenal acute kidney injury also should be considered when patients have marked oliguria (urine output < 450 mL/day) or anuria (urine output < 100 mL/day). Renal ultrasound can diagnose bladder and upper tract disease, whereas a bladder catheterization showing a large residual is the best way to diagnose lower tract disease.

TREATMENT

Fluids and Supportive Care

The treatment of acute kidney injury initially focuses on optimizing intravascular volume and withdrawing any offending agents. Because the majority of cases of elevated serum creatinine levels result from reversible volume depletion, prompt volume resuscitation during the early phases of acute kidney injury provides the greatest opportunity for minimizing kidney injury (Fig. 106-4) and is critical to avoid progression to tubular damage (Chapter 92). However, aggressive volume resuscitation must be carefully monitored in elderly patients, patients who have a history of heart failure or cirrhosis, or septic patients because of the possibility of precipitating pulmonary and/or peripheral edema. Fluid status can be monitored by an estimation of central venous pressure on physical examination

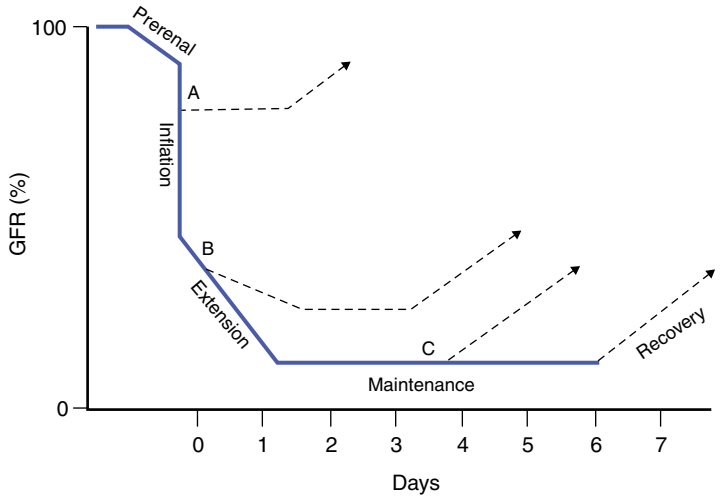

FIGURE 106-4. Phases of acute kidney injury. GFR = glomerular filtration rate. (From Sutton TA, Fisher CJ, Molitoris BA. Microvascular endothelial injury and dysfunction during ischemic acute renal failure. *Kidney Int*. 2002;62:1539-1549.)

(Chapters 39 and 45) as well as by monitoring the return of urine output and echocardiography (Chapter 43).

Postrenal obstructive uropathy from prostatic hypertrophy (Chapter 114) frequently can be corrected by insertion of a catheter into the bladder, often followed by definitive surgery. However, when outlet obstruction is caused by a tumor, a ureteral stent or a percutaneous nephrostomy tube usually is required.

For ischemic or septic tubular damage, no specific therapies are available, but general supportive measures include avoiding nephrotoxins, maintaining fluid balance, treating electrolyte abnormalities (with diets low in sodium, potassium, protein), and treating any comorbid or precipitating conditions aggressively. Volume overload is treated with daily diuretics (e.g., furosemide 40 to 80 mg intravenously) and a low-sodium diet. Hyperkalemia is generally treated with sodium zirconium cyclosilicate/lokelma or patiromer (see Chapter 103) and a low-potassium diet. Hyperphosphatemia is treated with oral binders (Chapter 105), hypocalcemia is treated with calcium tablets (Chapter 227), and acidosis is treated with $NaHCO_3$ tablets (Chapter 104). Intriguing experimental studies suggest that a deficiency of lipid β-oxidation and the production of β-hydroxybutyrate worsen the damage, and that treatment with niacinamide may prove to be beneficial.[17]

Immunosuppression

Intrarenal acute kidney injury resulting from glomerulonephritis (Chapter 107), vasculitis (Chapters 249), or systemic disease typically requires immunosuppressive therapy. For acute interstitial nephritis, an empiric trial of prednisone (often starting with 1 mg/kg for several days, followed by a gradual taper over 1 month) is usually tried (Chapter 108).

Dialysis

Acute hemodialysis is indicated in the setting of marked volume overload, hyperkalemia, acidosis, and uremic symptoms (e.g., changes in mentation, frank encephalopathy, myoclonus, asterixis, seizures, pleuritis, and pericarditis) that are unresponsive to dietary changes and other treatments.[18] Dialysis (Chapter 117) is generally begun when the serum creatinine level reaches about 10 mg/dL in symptomatic patients because starting it sooner is not of incremental benefit[A1,A2] and may result in unnecessary dialysis in some patients.[A3] In fact, delaying dialysis even longer (until the onset of important hyperkalemia, metabolic acidosis, or pulmonary edema) is as safe as initiating dialysis at a blood urea nitrogen level of 112 mg/dL or after 72 hours of oliguria.[A4,A5] The dose and modality of dialysis do not appear to affect the outcomes.

PREVENTION

Prevention begins with recognizing patients who are at the highest risk for developing acute kidney injury because they have known prior kidney disease or predisposing conditions, such as diabetes, atherosclerosis, hypertension, or heart failure. Consultation with a nephrologist before a potentially nephrotoxic exposure can reduce these risks. Key steps include maintaining adequate intravascular volume, avoiding nephrotoxic medications (e.g., NSAIDs and aminoglycosides), minimizing the use of radiocontrast material, and carefully monitoring urinary output and serum creatinine levels after interventions that might cause/induce acute kidney injury.

To prevent contrast-associated acute kidney injury, hydration with intravenous sodium chloride may be helpful, and the use of rosuvastatin (40 mg on admission then 20 mg/day or 10 mg/day for 2 days before and 3 days after the procedure) can reduce the risk of acute kidney injury in patients who have diabetes and chronic kidney disease.[A6] By comparison, neither intravenous sodium bicarbonate nor oral acetylcysteine reduces this risk.[A7-A9] In the intensive care unit, balanced crystalloid therapy (e.g., lactated Ringer solution) reduces the risk of acute kidney injury compared with normal saline[A10] but a similar benefit has not been demonstrated for noncritically ill adults.[A11]

PROGNOSIS

Prerenal acute kidney injury has the best prognosis. If it is diagnosed and treated early, the mortality rate is less than 10%, and most patients fully recover their kidney function. For postrenal acute kidney injury, prompt diagnosis and definitive treatment provide a high likelihood of full recovery of kidney function, but long-term prognosis depends on the cause of the obstruction.

By comparison, intrarenal acute kidney injury has a less favorable outcome, and even a 0.3 mg/dL rise in the serum creatinine level significantly increases risk, with mortality rates ranging from 30 to 80%. Mortality is higher in older patients who have hospital-acquired acute kidney injury and who are admitted to intensive care units. Acute kidney injury accelerates the progression of chronic kidney disease and is often the major reason why it progresses to end-stage kidney disease (Chapter 116). The outcomes of glomerulonephritis (Chapter 107) and vasculitis (Chapter 249) depend on the specific disease. More than 5% of patients who require hemodialysis recover enough renal function to discontinue it, but most patients (and especially patients who have prior underlying kidney disease) require chronic renal replacement therapy (Chapter 117).

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107 GLOMERULAR DISORDERS AND NEPHROTIC SYNDROMES

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GLOMERULAR DISORDERS

DEFINITION

Each *glomerulus,* the basic filtering unit of the kidney, consists of a tuft of anastomosing capillaries formed by the branching of the afferent arteriole. On average, 1 million glomeruli comprise approximately 5% of the weight of each kidney and provide almost 2 m^2 of glomerular capillary filtering surface. The glomerular basement membrane provides both a size- and charge-selective barrier to the passage of circulating macromolecules. Renal pathologic processes involving all glomeruli are called *diffuse* or *generalized;* if only some glomeruli are involved, the process is called *focal*. When dealing with the individual glomerulus, a process is *global* if the whole glomerular tuft is involved and *segmental* if only part of the glomerulus is involved. The descriptive terms *proliferative, sclerosing,* and *necrotizing* are often used (e.g., focal and segmental glomerulosclerosis; diffuse global proliferative lupus nephritis). Extracapillary proliferation or crescent formation is caused by the accumulation of macrophages, fibroblasts, proliferating epithelial cells, and fibrin within Bowman space. Such findings signify aggressive disease and consequently an adverse prognosis. Scarring of the tissue between the tubules and glomeruli, interstitial fibrosis, is also a poor prognostic sign.

EPIDEMIOLOGY

Glomerular disease is an important cause of end-stage kidney disease (Chapter 117), and diabetic kidney damage (Chapter 109) alone affects many millions of persons worldwide. Glomerular diseases associated with infectious agents such as malaria (Chapter 316), schistosomiasis (Chapter 326), human immunodeficiency virus (HIV; Chapter 355), and the hepatitis B and C viruses (Chapter 135) are major worldwide health problems. Manifestations of glomerular injury range from asymptomatic microhematuria and albuminuria to rapidly progressive oliguric kidney failure. Some patients develop massive fluid retention and edema at the onset of their glomerular disease, whereas others present with only the slow insidious signs and symptoms of chronic kidney failure (Chapter 117).

PATHOBIOLOGY

In a normal person, the urine contains no red blood cells (RBCs), the urinary excretion of albumin is less than 30 mg/day, and the total urinary excretion of protein is less than 140 mg/day. Glomerular diseases are characterized by breaks in the glomerular capillary wall, thereby leading to hematuria with proteinuria because of loss of the selective barrier to particles based on size and charge. Although increases in urinary protein excretion may come from the filtration of abnormal circulating proteins (e.g., light chains in multiple myeloma) or from the deficient proximal tubular reabsorption of normal, filtered low-molecular-weight proteins (e.g., β_2-microglobulin), the most common cause of proteinuria, and specifically albuminuria, is glomerular injury.

The nature of the initiating processes varies among different glomerular diseases. The nephrotic syndrome and glomerulonephritis (Table 107-1) are the key forms of glomerular disease. In the nephrotic syndrome (nephrosis), leakage of plasma proteins without inflammation is the primary pathogenic mechanism, whereas glomerulonephritis (nephritis) is characterized by glomerular inflammation that results in the passage of RBCs, white blood cells (WBCs), and plasma proteins into the urine. In some inflammatory diseases (e.g., lupus nephritis), nephrotic levels of proteinuria may be accompanied by cellular elements in a nephrotic-nephritic picture, whereas patients with milder involvement may have only isolated proteinuria or isolated hematuria.

In some conditions, such as diabetes and amyloidosis, structural and biochemical alterations are clearly present in the glomerular capillary wall. In others, immune-mediated kidney injury is caused by deposition of circulating immune complexes, in situ formation of immune complexes, or the localized effects of anti–glomerular basement membrane antibodies. Acquired defects in the glomerular podocytes in an increasingly recognized number of genetic glomerulopathies are also associated with proteinuria and progressive kidney dysfunction.

TABLE 107-1 TYPICAL FINDINGS IN NEPHROTIC SYNDROME VERSUS NEPHRITIS

NEPHROTIC SYNDROME	NEPHRITIS
KIDNEY INSUFFICIENCY ("AZOTEMIA")	
Uncommon at presentation	Common at presentation
PROTEINURIA	
Typically, high grade (>3 g/day)	Variable
Urine RBCs	
Few	Numerous (sometimes with RBC casts)
Urine RBC casts	
Unlikely	Likely

RBCs = red blood cells.

CLINICAL MANIFESTATIONS

Findings indicative of a glomerular origin of kidney disease include erythrocyte casts (Fig. 100-8) and dysmorphic RBCs in the urinary sediment, and abnormal amounts of albuminuria. Persistent urinary excretion of more than 500 to 1000 erythrocytes per milliliter (or more than 5 RBCs per high-power field on microscopy) is abnormal. Dysmorphic RBCs, which are deformed because of their passage through the glomerular capillary wall, as well as RBC casts, which are formed when these erythrocytes become enmeshed in a proteinaceous matrix in the lumen of the tubules, are also indicative of glomerular disease.

Proteinuria associated with glomerular disease may range from several hundred milligrams to more than 30 g daily. In some diseases, such as minimal change nephrotic syndrome, albumin is the predominant protein in the urine. In others, such as focal sclerosing glomerulonephritis and diabetes, the proteinuria, although still largely composed of albumin, is nonselective and contains many higher-molecular-weight proteins.

DIAGNOSIS

Some patients have asymptomatic microhematuria or proteinuria discovered by routine evaluations. Microscopic hematuria associated with deformed (dysmorphic) RBCs or RBC casts is likely to be glomerular in origin. Subnephrotic levels of proteinuria may arise from orthostatic proteinuria, exercise, hypertension, tubular disease, or glomerular damage.

In patients with asymptomatic urinary abnormalities of glomerular origin, the underlying kidney lesion may represent the early phase of a progressive glomerular disease or may be due to a benign, nonprogressive glomerular lesion. In general, if patients have less than 0.5 to 1.0 g of proteinuria daily or only glomerular microhematuria with a normal glomerular filtration rate (GFR) and no evidence of systemic disease, it is not necessary to proceed to a diagnostic kidney biopsy. Most of these patients need no immunosuppressive therapy. The patient can be followed closely, and biopsy need be performed only in patients with progressively increasing proteinuria or evidence of a decreasing GFR.[1]

THE NEPHROTIC SYNDROME

DEFINITION

The nephrotic syndrome (see Table 107-1) is defined by albuminuria of more than 3 to 3.5 g/day (or a ratio of 3.0 to 3.5 mg of protein per mg of creatinine in a random urine specimen) accompanied by hypoalbuminemia, edema, and hyperlipidemia. In practice, many clinicians refer to nephrotic range proteinuria regardless of whether patients have the other manifestations of the full syndrome.

EPIDEMIOLOGY

The annual incidence rate of the nephrotic syndrome in the U.S. is about 2 to 7 per 100,000 in children under age 16 years and about 3 per 100,000 among adults. The nephrotic syndrome may be primary and idiopathic (Table 107-2), or it may be caused by a known underlying condition, such as diabetes, amyloidosis, or systemic lupus erythematosus (Table 107-3). Although minimal change disease is the most common cause of nephrotic syndrome in children, idiopathic membranous nephropathy and focal segmental glomerular sclerosis

ABSTRACT

Glomerular diseases, which are characterized by pathologic alterations in normal glomerular structure and function, may result from systemic disease or from pathologic processes limited to the kidney (primary glomerular disease). The typical clinical signs of patients with glomerular disorders include edema, proteinuria, hematuria, hypertension, decline in kidney function, and abnormal urine sediments. A kidney biopsy is usually needed to make a specific diagnosis. Treatment of glomerular disease is based on the underlying pathogenic mechanism and may include conservative therapy (e.g., renin-angiotensin blockers and control of blood pressure), immunosuppressive therapy (e.g., in many primary glomerular diseases as well as autoimmune diseases such as lupus nephritis), or therapy directed against plasma cells (e.g., amyloidosis).

KEYWORDS

glomerular disease
nephrotic
nephritic
hematuria
proteinuria
glomerulonephritis

TABLE 107-2 SUBTYPES OF IDIOPATHIC NEPHROTIC SYNDROME IN ADULTS

SUBTYPE	INCIDENCE (%)
Minimal change disease	5-10
Focal segmental glomerulosclerosis	20-25
Membranous nephropathy	25-30
Membranoproliferative glomerulonephritis	5
Other proliferative and sclerosing glomerulonephritides	15-30

TABLE 107-3 NEPHROTIC SYNDROME ASSOCIATED WITH SPECIFIC CAUSES (SECONDARY NEPHROTIC SYNDROME)

SYSTEMIC DISEASES
Diabetes mellitus
Systemic lupus erythematosus and other collagen vascular diseases*
Amyloidosis (amyloid AL- or AA-associated)
INFECTIONS
Bacterial (congenital and secondary syphilis)*
Viral (hepatitis B, hepatitis C, HIV infection, infectious mononucleosis, cytomegalovirus infection)*
Parasitic (malaria, toxoplasmosis, schistosomiasis, filariasis)*
MEDICATION RELATED
Gold, mercury, and the heavy metals
Penicillamine
Nonsteroidal anti-inflammatory drugs, including COX2 inhibitors
Lithium
Captopril
"Street" heroin
Others: probenecid, chlorpropamide, rifampin, tolbutamide, phenindione, pamidronate
ALLERGENS, VENOMS, AND IMMUNIZATIONS
NEOPLASMS
Hodgkin lymphoma and leukemias/lymphomas (with minimal change lesion)
Solid tumors (with membranous nephropathy)
HEREDITARY AND METABOLIC DISEASES
Alport syndrome*
Fabry disease
Sickle cell disease
Diseases of the alternative complement pathway (C3 glomerulopathy and dense deposit disease)*
Genetic subtypes resulting from mutations in genes encoding podocyte proteins or mitochondrial proteins (isolated or syndromic)
OTHER
Pregnancy related (includes preeclampsia)
Chronic renal allograft nephropathy
Serum sickness
Accelerated hypertensive nephrosclerosis
Renal artery stenosis
Obesity
Reflux nephropathy

*Indicates disorders that could also present as a nephritic-nephrotic syndrome (RBC, RBC casts with nephrotic-range proteinuria).
COX = cyclooxygenase; HIV = human immunodeficiency virus; RBC = red blood cells.

are the most common causes in adults, with the former being most common in Whites and the latter in Blacks.

PATHOBIOLOGY

Hypoalbuminemia, which is largely a consequence of urinary protein loss, also may be due to proximal tubular catabolism of filtered albumin, the redistribution of albumin within the body, and reduced hepatic synthesis of albumin. As a result, the relationship among urinary protein loss, the level of the serum albumin, and other secondary consequences of heavy albuminuria is inexact.

Salt and volume retention in the nephrotic syndrome may occur via at least two different major mechanisms. In a minority of patients, hypoalbuminemia reduces the oncotic pressure of plasma, the resulting intravascular volume depletion leads to activation of the renin–angiotensin–aldosterone axis, and this activation increases the retention of kidney sodium and fluid. However, primary salt retention in the distal nephron, which occurs independently of the renin–angiotensin–aldosterone axis, is likely the main reason for salt and water retention in nephrosis.

Thromboembolism (Chapters 67 and 68) often occurs in patients with the nephrotic syndrome. Explanations include urinary loss of antithrombin III, protein C, and protein S, which prevent thrombosis, as well as increased synthesis of acute phase reactants that promote thrombosis.

Hyperlipidemia (Chapter 190), sometimes extreme, is common in the nephrotic syndrome, likely because low oncotic pressures upregulate hepatic synthesis of apolipoproteins. Alterations in key regulatory enzymes of lipid synthesis also contribute to the lipid abnormalities. Hyperlipidemia may be absent with some causes of the nephrotic syndrome (e.g., systemic lupus erythematosus, HIV-associated nephropathy, and amyloidosis), either because of hepatic involvement or because of a systemic inflammatory state.

CLINICAL MANIFESTATIONS

Patients may present with weight gain, peripheral edema when sitting or standing, and with periorbital edema on awakening. Hypertension is common, and varying degrees of hematuria may be present. A 24-hour urine sample (or urine protein/creatinine ratio) usually shows more than 3 to 3.5 g of proteinuria. Nephrotic patients often have a hypercoagulable state (Chapter 67) and are predisposed to deep vein thrombosis (Chapter 68), pulmonary emboli (Chapter 68), and renal vein thrombosis (Chapter 110). Patients with nephrotic syndrome have increased risk for atherosclerotic complications because of the hypercoagulability and also because most nephrotic patients have elevated levels of total and low-density lipoprotein (LDL) cholesterol and lipoprotein(a), with low or normal high-density lipoprotein (HDL) cholesterol.

DIAGNOSIS

Initial evaluation of the nephrotic patient includes laboratory tests to define whether the patient has primary or idiopathic nephrotic syndrome (see Table 107-2), or a secondary cause related to a systemic disease, toxin, or medication (see Table 107-3). Common screening tests include fasting blood sugar and glycosylated hemoglobin tests for diabetes, and antinuclear antibody test for collagen vascular disease. In patients with the nephritic or nephrotic-nephritic syndrome, a low serum complement level, suggests an immune complex–mediated disease (Table 107-4). In selected patients, cryoglobulins, hepatitis B and C serologies, HIV testing, antineutrophil cytoplasmic antibodies (ANCAs), anti-GMB antibodies, serum protein and immunofixation, and other tests may be useful.

A kidney biopsy is often required in the adult nephrotic patient. Biopsy results in patients with heavy proteinuria and the nephrotic syndrome are likely to provide a specific diagnosis, determine prognosis, and guide therapy.

TREATMENT

Treatment varies by the specific cause.[2] Elevated lipid levels should be treated (Chapter 190). Chronic oral anticoagulation (Chapter 70) with warfarin is needed if thrombotic complications occur and is commonly recommended in patients with additional risk factors for thrombosis (e.g., a prior idiopathic thromboembolic event, immobilization, severe heart failure, or morbid obesity). Warfarin also may be considered in patients who have membranous nephropathy with hypoalbuminemia (<2.8 g/L) and who are at low risk for bleeding. Data are insufficient regarding the use of the direct-acting oral anticoagulants.

Edema is treated with a low-salt diet and loop diuretics (Table 102-4). Use of maximally tolerated doses of angiotensin-converting enzyme (ACE) inhibitors or angiotensin II receptor blockers (Table 64-7) often reduces proteinuria, increases the serum albumin level, and ameliorates the edema and hyperlipidemia. The combination of loop diuretics with intravenous albumin may be effective in patients with severe edema and signs of volume depletion.

IDIOPATHIC NEPHROTIC SYNDROME

MINIMAL CHANGE DISEASE

Minimal change disease, which is the most common pattern of nephrotic syndrome in children, accounts for only approximately 5 to 10% of cases of idiopathic nephrotic syndrome in adults. A similar histologic pattern may be seen as an adverse reaction to certain medications (e.g., nonsteroidal anti-inflammatory drugs [NSAIDs], lithium) or in association with certain malignancies (e.g., Hodgkin disease). The presence of autoantibodies to the podocyte protein nephrin indicates an autoimmune pathogenesis in at least some cases.[3]

TABLE 107-4 SERUM COMPLEMENT LEVELS IN NEPHRITIC SYNDROME

REDUCED COMPLEMENT LEVEL (TYPICALLY WITH NEPHRITIS)
Infection-related glomerulonephritis (e.g., streptococcal infections, endocarditis, shunt infections)
Systemic lupus erythematosus
Cryoglobulinemia
C3 glomerulopathies
NORMAL SERUM COMPLEMENT LEVEL
Immunoglobulin A nephropathy and Henoch-Schönlein purpura
Anti–glomerular basement membrane disease
Pauci-immune rapidly progressive glomerulonephritis (e.g., granulomatous polyangiitis and microscopic polyangiitis)

CLINICAL MANIFESTATIONS

Patients typically present with weight gain and periorbital and peripheral edema. Proteinuria in adult patients can average as much as 10 g/day, and subnephrotic levels are rare. Approximately 30% of adults are hypertensive and 30% have microscopic hematuria. However, an active urinary sediment with RBC casts is not seen. Many adult patients have mild-to-moderate azotemia, which may be related to hypoalbuminemia and intravascular volume depletion or to a reduction in glomerular permeability and filtration. Complement levels and serologic test results are normal.

DIAGNOSIS

In minimal change disease, histopathology typically reveals no glomerular abnormalities on light microscopy (Fig. 107-1). The tubules may show lipid droplet accumulation from absorbed lipoproteins (hence the older term *lipoid nephrosis*). Immunofluorescence staining and electron microscopy (Fig. 107-2) show no immune-type deposits. By electron microscopy, the glomerular basement membrane is normal and effacement of the visceral epithelial foot processes is noted along virtually the entire distribution of every capillary loop (Fig. 107-2).

TREATMENT

The course of minimal change disease is often one of remissions followed by relapses. About 75 to 85% of adults respond to a regimen of either daily prednisone (1 mg/kg, maximum 80 mg) or alternate-day therapy (2 mg/kg, maximum 120 mg), tapered after 2 months of treatment for a total of 5 to 6 months of therapy.[A1] Adults are not considered steroid-resistant until they have failed to respond to 16 weeks of treatment. Tapering of the steroid dose after remission should be gradual over 1 to 2 months.

Approximately 40% of adults relapse by 1 year. Infrequent relapses can be treated similarly to the initial episode.

However, in adults who have contraindications to corticosteroids, who relapse frequently, or who become corticosteroid-dependent (defined as being unable to decrease the prednisone dose without recurrent proteinuria), equivalently efficacious options include rituximab (1000 mg IV repeated in 2 weeks), cyclosporine (3 to 5 mg/kg/day for 4 months), tacrolimus (0.05 to 0.1 mg/kg/day),[A2] or mycophenolate mofetil (750 to 1000 mg twice daily). Because cyclosporine and tacrolimus are potentially nephrotoxic, trough blood levels must be monitored, and the lowest level that is associated with remission should be maintained. Cyclophosphamide (up to 2 mg/kg/day for 8 weeks) also may be used but is less desirable because of its potential for gonadal toxicity and bone marrow suppression.

PROGNOSIS

The prognosis of minimal change disease is excellent. More than 50% of patients with minimal change disease have relapses, and 10 to 20% may become steroid-dependent. Most patients who have a progressive decline in kidney function exhibit focal segmental glomerulosclerosis rather than minimal change disease on a subsequent kidney biopsy.

FOCAL SEGMENTAL GLOMERULOSCLEROSIS

Approximately 20% of adults with idiopathic nephrotic syndrome are found on biopsy to have focal segmental glomerulosclerosis. The incidence of focal segmental glomerulosclerosis is increasing in all races, but it is especially common in Black Americans.

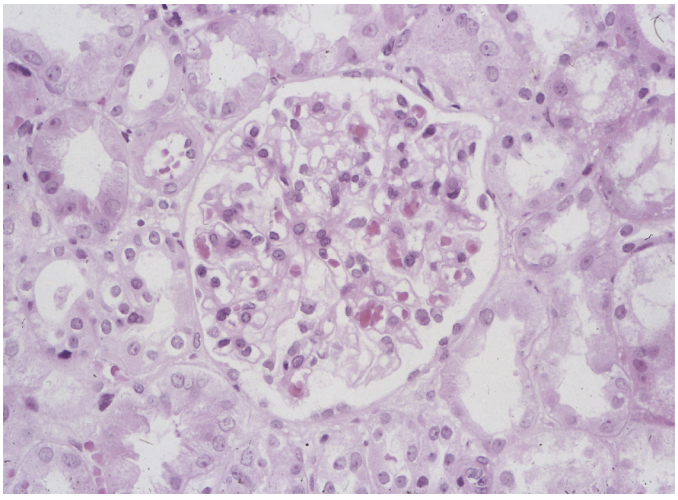

FIGURE 107-1. Unremarkable light microscopic appearance of minimal change disease glomerulopathy. Glomerular capillaries are patent and there is no glomerular hypercellularity.

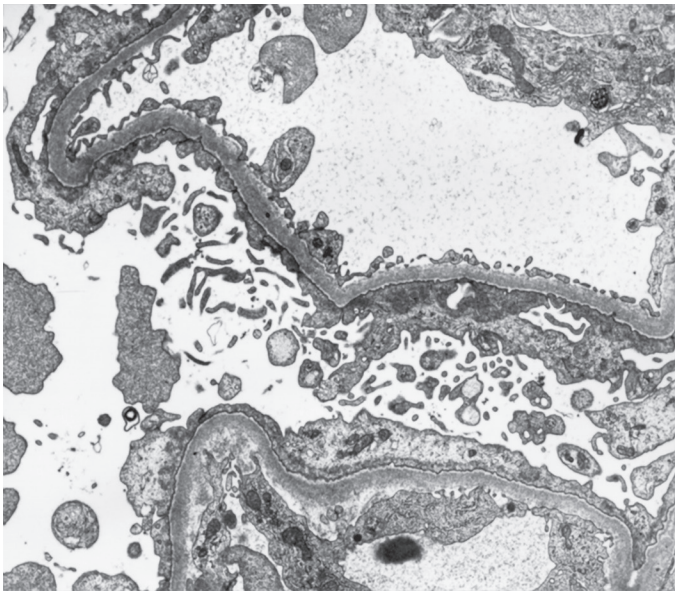

FIGURE 107-2. Minimal change disease. Electron micrograph shows widespread effacement of foot processes with microvillus transformation of the visceral epithelium. No electron-dense deposits are present (uranyl acetate, lead citrate stain; 6000×).

PATHOBIOLOGY

Several mechanisms are thought to underlie focal segmental glomerulosclerosis. In primary focal segmental glomerulosclerosis, glomerular permeability factors may cause direct injury to podocytes. In secondary focal segmental glomerulosclerosis, medications, viral infections,[4] or adaptive changes associated with glomerular hyperfiltration apparently cause the injury (Table 107-5).

Focal segmental glomerulosclerosis also can be associated with genetic variants in podocyte proteins. Pathogenic variants in collagen 4 appear to be emerging as the most common genetic form of focal segmental glomerulosclerosis. Other common defects include an autosomal recessive pattern caused by mutations in the structural protein podocin *(NPHS2)* and autosomal dominant forms caused by mutations in the structural protein α-actinin 4, the *TRPC6* glomerular slit diaphragm–associated channel, or *INF2*, which encodes a formin (actin-regulating protein). The predisposition of Black Americans to focal segmental glomerulosclerosis is partly related to two risk alleles of the apolipoprotein L1 *(APOL1)* gene, which apparently arose in high frequency because heterozygosity confers protection against African trypanosomiasis (Chapter 317), but for which biallelic inheritance increases the risk of focal segmental glomerulosclerosis by 10- to 20-fold. In the setting of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection, the collapsing variant of focal segmental glomerulosclerosis has been associated with high-risk apolipoprotein L1 alleles in Black American patients.[5]

TABLE 107-5 CAUSES OF SECONDARY FOCAL SEGMENTAL GLOMERULOSCLEROSIS

SECONDARY TO ALTERATIONS OF GLOMERULAR EPITHELIAL CELLS	
Viral infections	Human immunodeficiency virus (established) Cytomegalovirus (probably) Parvovirus B19, Epstein-Barr virus, hepatitis C virus (possibly) Hemophagocytic syndrome (possibly) Severe acute respiratory syndrome coronavirus-2 (with *APOL1* risk genotype)
Drug-induced	Direct-acting antiviral therapy mTOR inhibitors Calcineurin inhibitors Anthracyclines Heroin (adulterants) Lithium Interferon Anabolic steroids Nonsteroidal anti-inflammatory drugs
SECONDARY TO ADAPTIVE CHANGES WITH GLOMERULAR HYPERTENSION	
Reduced number of nephrons	Reflux nephropathy Renal dysplasia Oligomeganephronia Sickle cell disease Age-related focal segmental glomerulosclerosis
Normal number of nephrons	Obesity-related glomerulopathy Primary glomerular diseases Systemic diseases (e.g., diabetic nephropathy, hypertensive nephrosclerosis)

APOL1 = apolipoprotein L1; mTOR = mammalian target of rapamycin.

CLINICAL MANIFESTATIONS

Patients with primary focal segmental glomerulosclerosis typically present with proteinuria, hypoalbuminemia, and edema. Absence of hypoalbuminemia is associated with focal segmental glomerulosclerosis secondary to adaptive changes to glomerular hyperfiltration as opposed to primary focal segmental glomerulosclerosis where patients show low serum albumin. Hypertension is found in 30 to 50% of patients, and microscopic hematuria occurs in approximately half of patients. The GFR is decreased at presentation in 20 to 30% of patients. Complement levels and other serologic test results are normal.

DIAGNOSIS

The diagnosis requires kidney biopsy. By light microscopy, only some glomeruli (focal) initially have areas of scarring involving only portions of a glomerulus (segmental) (Fig. 107-3).[6] As kidney function declines, repeat biopsy specimens show more widespread glomerular involvement with segmental sclerosing lesions and increased numbers of globally sclerotic glomeruli. By immunofluorescence staining, immunoglobulin M (IgM) and C3 commonly are trapped in the areas of glomerular sclerosis. Electron microscopy shows no immune-type deposits and only visceral epithelial cell foot process effacement. Typically, primary focal segmental glomerulosclerosis is associated with extensive, diffuse foot process effacement, whereas these findings are segmental in the adaptive type of focal segmental glomerulosclerosis.

TREATMENT

For primary focal segmental glomerulosclerosis, corticosteroids (e.g., prednisone, 1 mg/kg/day, maximum 80 mg, or 2 mg/kg every other day, maximum 120 mg, as tolerated) are used as initial therapy for a minimum of 3 to 4 months and slowly tapered for a total of 6 months of therapy if remission is noted. A complete or partial remission may be seen in up to 40 to 60% of patients, with preservation of long-term kidney function. Patients who do not show any improvement in 4 to 8 weeks are less likely to respond and may be switched to second-line therapy, rather than being continued on high doses of corticosteroids. Patients who do not achieve remission within 4 months are termed steroid-resistant.

In patients who are steroid-resistant, cyclosporine (5 to 6 mg/kg/day) or tacrolimus (0.05 to 0.1mg/kg/day) is recommended.[A3] A minimum duration of 6 months is recommended before declaring resistance to calcineurin inhibitors. If remission occurs, a minimum of 12 months of therapy followed by a slow taper is suggested. Careful monitoring of kidney function and serum drug levels are necessary to avoid nephrotoxicity. Rituximab (e.g., two 1-g doses 1 week apart) has been used successfully in steroid-dependent or frequently relapsing patients,[7] but it is less effective in steroid-resistant patients.

Genetic forms of focal segmental glomerulosclerosis typically do not respond to immunosuppressive therapy. Treatment is conservative using ACE-inhibitors and angiotensin receptor blockers for blood pressure control (Table 64-7).

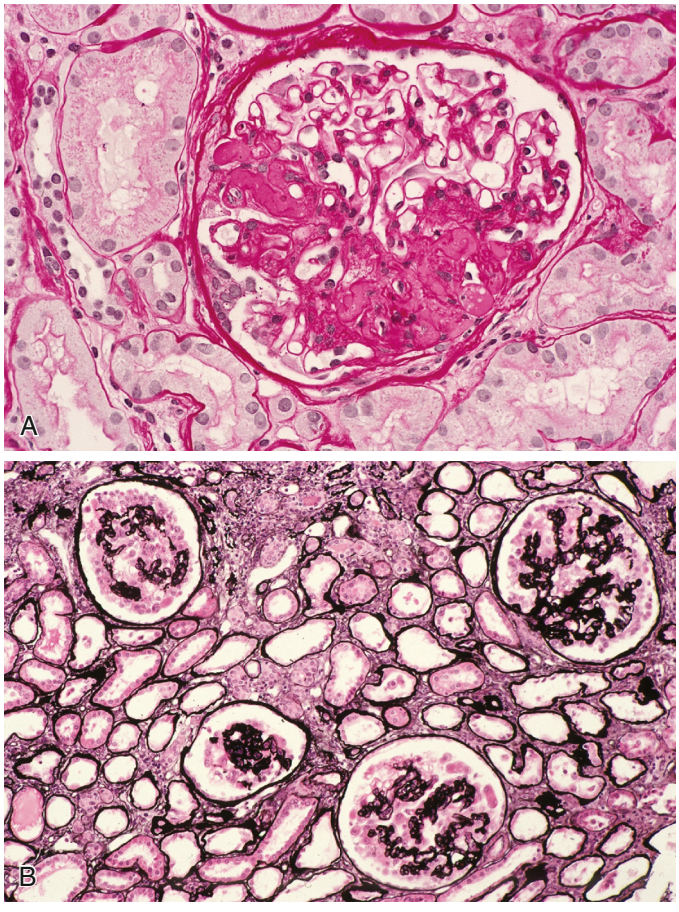

FIGURE 107-3. Focal segmental glomerulosclerosis. A, Segmental obliteration of glomerular capillaries by acellular matrix (sclerosis), which stains red with periodic acid–Schiff (PAS). **B,** Collapsing variant focal segmental glomerulosclerosis showing implosive collapse of the glomerular capillaries and hyperplasia of overlying epithelial cells (silver stain).

PROGNOSIS

The course of untreated focal segmental glomerulosclerosis is usually one of progressive proteinuria and declining GFR. The histopathologic variants of focal segmental glomerulosclerosis are associated with epidemiologic, clinical, and prognostic differences. For example, the "tip" variant has a relatively benign course, whereas the "collapsing" variant progresses more rapidly to kidney failure.

Only a minority of patients experience a spontaneous remission of proteinuria, and most untreated patients who do not remit eventually develop end-stage renal disease within 5 to 20 years. Patients with a sustained remission of their nephrotic syndrome are unlikely to progress to end-stage renal disease.

Most patients with genetic forms of focal segmental glomerulosclerosis are treatment-resistant, have a progressive course, and do not experience recurrences of the focal segmental glomerulosclerosis if they receive a kidney transplant. Primary focal segmental glomerulosclerosis recurs in the transplanted kidney in up to 30% of cases. Younger patients, those with a rapid course to kidney failure, and those with a prior recurrence are more likely to recur in the allograft.

MEMBRANOUS NEPHROPATHY

Membranous nephropathy is the most common pattern of idiopathic nephrotic syndrome in White patients. It also may be associated with infections (syphilis [Chapter 295], hepatitis B and C [Chapter 134]), systemic lupus erythematosus (Chapter 245), medications (gold salts, NSAIDs), and certain tumors (solid tumors and lymphomas). In most patients with primary membranous nephropathy, the antigen in the immune deposits is the M-type phospholipase receptor (PLA2R), which is present in podocytes.[8] Circulating PLA2R antibodies,

which are highly specific for the diagnosis of primary membranous nephropathy, combine with this antigen to form in situ immune complexes on the epithelial side of the basement membrane, thereby leading to proteinuria. Other recently implicated antigens associated with primary membranous nephropathy include exostosin, NCAM-1 (neural cell adhesion molecule 1), NELL-1 (neural epidermal growth factor–like 1 protein), PCDH7 (protocadherin 7), and SEMA3B (semaphoring 3B).[9] About 10% of patients have circulating autoantibodies to the thrombospondin type-1 domain-containing 7 A (THSD7A), which has been associated with malignancy-related membranous nephropathy.

CLINICAL MANIFESTATIONS

Membranous nephropathy typically manifests with proteinuria and edema. Hypertension and microhematuria are not infrequent, but kidney function and GFR are usually preserved at presentation. Despite the finding of complement in the glomerular immune deposits, serum complement levels are normal. Membranous nephropathy is the most common pattern of the nephrotic syndrome to be associated with a hypercoagulable state and renal vein thrombosis (Chapter 110). The presence of sudden flank pain, deterioration of kidney function, or acute pulmonary symptoms in a patient with membranous nephropathy should prompt an investigation for renal vein thrombosis and pulmonary emboli. Conversely, the presence of otherwise unexplained thromboembolism should lead to a search for nephrotic syndrome.

DIAGNOSIS

A kidney biopsy is not required to confirm the diagnosis of membranous nephropathy in patients who have nephrotic syndrome, intact kidney function, absence of systemic disease, and a positive anti-PLA2R antibody test.[10] Otherwise, a kidney biopsy is required to make the diagnosis and to exclude other glomerulopathies.

On light microscopy, the glomerular capillary loops often appear rigid or thickened (Fig. 107-4), but cellular proliferation is not seen. Immunofluorescence staining and electron microscopy show immune deposits along the glomerular capillary loops beneath the visceral epithelial cell layer (Fig. 107-5). The presence of circulating antibodies to the M-type phospholipase A_2 receptor are highly sensitive and specific for idiopathic membranous nephropathy, as is the finding of PLA2R antigen in the immune deposits in the kidney.

In patients who do not have PLA2R or other recently described antibodies, membranous nephropathy may be the result of an underlying condition. In such patients, a search for systemic disease (e.g., systemic lupus erythematosus; Chapter 245), infection (e.g., syphilis [Chapter 295] and hepatitis B and C [Chapter 134]), and occult malignancy should be undertaken.

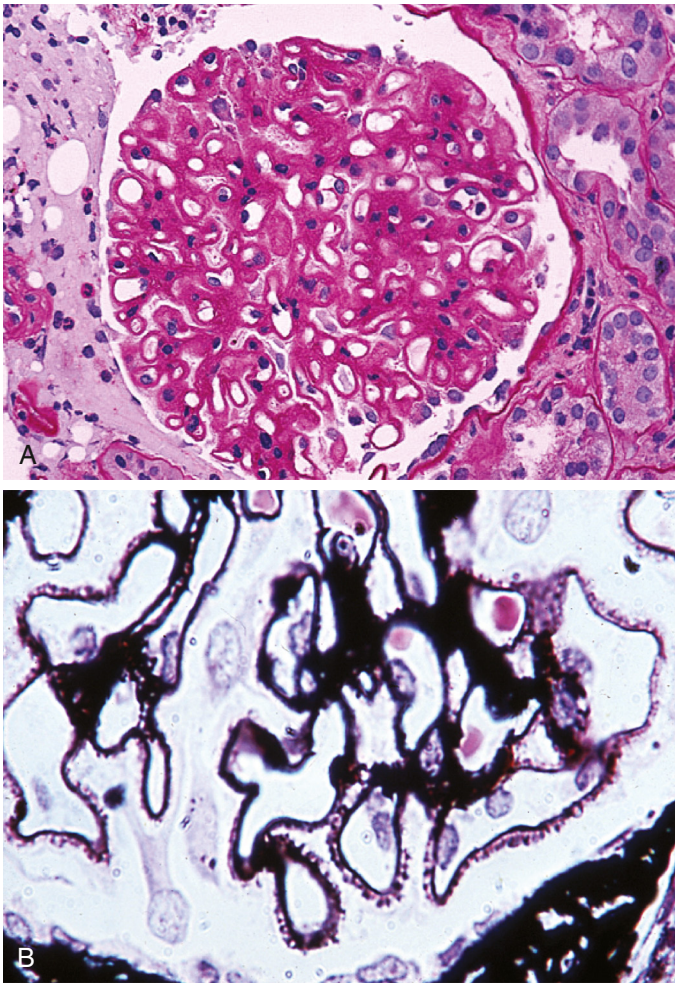

FIGURE 107-4. Membranous nephropathy. A, Light micrograph of membranous nephropathy demonstrating thickening of the glomerular capillary wall but no hypercellularity. **B**, Silver stain of idiopathic membranous nephropathy showing spike formation along the outer aspect of the glomerular basement membrane corresponding to projections of the basement membrane between the epimembranous deposits.

TREATMENT

All patients should receive optimal supportive care including blood pressure control and maximally tolerated doses of renin–angiotensin blockers (Table 64-7). Immunosuppressive therapy should be restricted to patients who are considered at risk for progressive kidney damage (Fig. 107-6).[A4,A5]

Cyclosporine (3.5 mg/kg/day adjusted to serum levels of 125 to 225 µg/L) plus prednisone (0.15 mg/kg/day up to a maximum of 15 mg/day) is the recommended initial therapy. Success with tacrolimus (0.05 to 0.10 mg/kg/day to target trough levels 3 to 8 ng/mL) has been similar to that with cyclosporine. Cyclosporine or tacrolimus should be used for a minimum of 4 months and withdrawn if there is no response. In the event of remission, treatment should be for a minimum of 12 months, usually with slow taper thereafter. Use of the anti-CD20 antibody rituximab (1000 mg IV × 2, 2 weeks apart then repeated at 6 months, if needed) has shown benefit in inducing remission.[A6] In patients at a high risk of progression, addition of rituximab after 6 months of treatment with cyclosporine is one alternative. However, the combination of corticosteroids (e.g., methylprednisolone, 1 g/day intravenously for 3 days, then prednisone, 0.5 mg/kg/day orally for 27 days, in months 1, 3, and 5) plus oral cytotoxic therapy (cyclophosphamide, 2 to 2.5 mg/kg/day, for 30 days in months 2, 4, and 6) is an alternative to rituximab[A7] for high-risk patients and is the suggested therapy for very high-risk patients.

Longitudinal monitoring of anti-PLA2R antibody levels at 6 months after the start of therapy may be useful for evaluating the response to treatment in patients, and can be used to guide adjustments to therapy.[11] Immunologic remission typical precedes proteinuric remission, and disappearance of the PLA2R antibody in patients who were positive allows discontinuation of immunosuppression despite persistent proteinuria.

In patients who do not respond to initial therapy, medications such as mycophenolate mofetil and adrenocorticotropic hormone may be attempted. However, nonresponsive patients should be referred to a specialized center with expertise in managing membranous nephropathy.

PROGNOSIS

In most large series, kidney survival in membranous nephropathy is more than 75% at 10 years, with a spontaneous remission rate of 20 to 30%. Patients with membranous nephropathy are at increased risk for developing renal vein thrombosis (Chapter 110), especially when their serum albumin levels decline.

In general, older patients, males, and those with heavy persistent proteinuria are most likely to progress to kidney failure and hence to benefit from therapy. Patients with primary membranous nephropathy and low levels of anti-*PLA2R* are more likely to have a spontaneous remission than are patients with high levels. Reductions of the circulating level of antibody to *PLA2R* precedes remission in most persons and may be a predictor of remission.

GLOMERULONEPHRITIS AND THE NEPHRITIC SYNDROME

EPIDEMIOLOGY AND PATHOBIOLOGY

The annual incidence of primary glomerulonephritis in U.S. adults is estimated to be between 0.2 to 2.5/100,000/year, with lower rates in children. The pathogenesis of glomerulonephritis includes infectious agents that activate the complement pathway. Glomerulonephritis also can be caused by the deposition of immune complexes in autoimmune diseases such as systemic lupus erythematosus (Chapter 245), IgA nephropathy, and from the effect of circulating antibodies directed against the glomerular basement membrane. Direct damage from activated white blood cells in the presence of antineutrophil cytoplasmic antibodies can also lead to the nephritic syndrome.

Invading neutrophils and monocytes, as well as resident glomerular cells, can damage the glomerulus through a number of mediators, including oxidants, chemoattractant agents, proteases, cytokines, and growth factors. Some

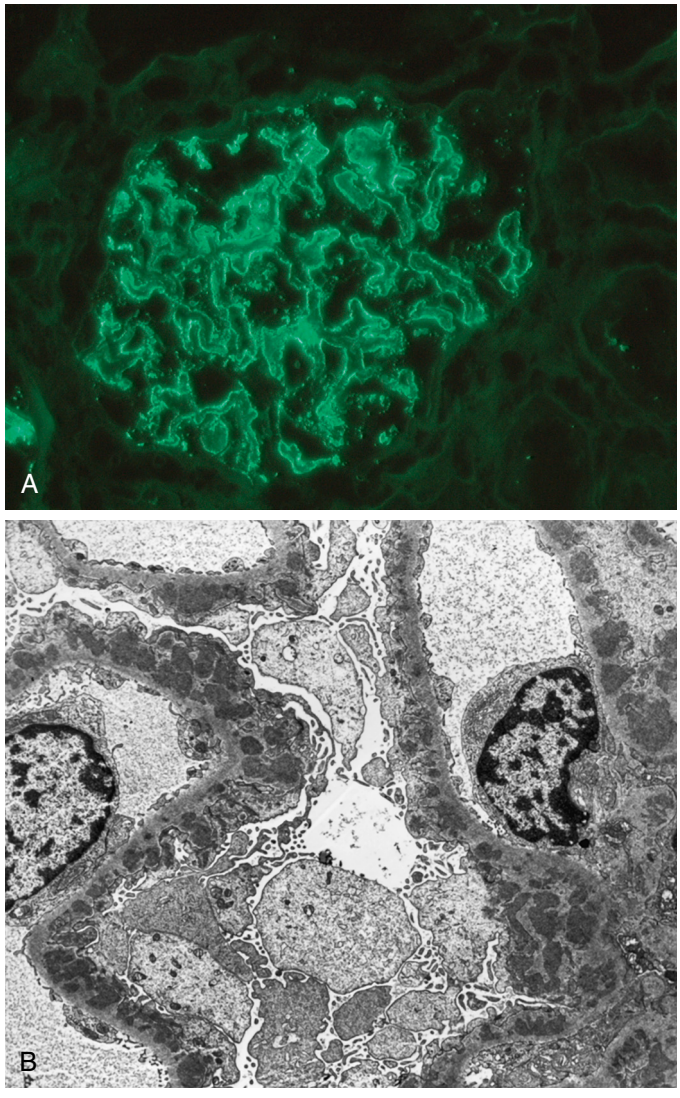

FIGURE 107-5. Membranous glomerulopathy. A. Granular capillary wall deposits of IgG on immunofluorescence microscopy. **B.** On ultrastructural examination, numerous, closely apposed epimembranous electron-dense deposits are separated by basement membrane spikes (uranyl acetate, lead citrate stain; 2500×).

factors, such as transforming growth factor-β, have been related to eventual glomerulosclerosis and chronic glomerular damage.

CLINICAL MANIFESTATIONS AND DIAGNOSIS

Patients with glomerulonephritis present with a nephritic picture characterized by a azotemia, oliguria, hypertension, and an active urinary sediment with hematuria and red blood cell casts (see Fig. 100-8 and Table 107-1).[12] Hypertension is common and is caused by intravascular volume expansion. Patients may note dark, smoky, or cola-colored urine or hematuria, and the urine sediment is typically composed of erythrocytes, leukocytes, and a variety of casts, including red blood cell casts. The degree of proteinuria is variable from subnephrotic to the nephrotic range. An impairment of the GFR is common. Serum complement levels may be low in the immune complex–related cause (Table 107-4). Regardless of the inciting cause, glomerulonephritis is characterized on light microscopy by hypercellularity of the glomerulus, which may be composed of infiltrating inflammatory cells, proliferation of resident glomerular cells, or both. The mechanisms associated with the various forms of glomerulonephritis are based on staining patterns on immunofluorescence microscopy (Fig. 107-7).

IMMUNOGLOBULIN A NEPHROPATHY

EPIDEMIOLOGY AND PATHOBIOLOGY

IgA nephropathy is the most frequent form of idiopathic glomerulonephritis worldwide; it represents 15 to 40% of primary glomerulonephritis in parts of Europe and Asia but is uncommon in people of African ancestry. In the United States, some centers report this diagnosis in up to 20% of all primary glomerulopathies. Males outnumber females, with peak occurrence in the second to third decades of life.

In IgA nephropathy, most patients and many of their direct blood relatives have elevated circulating levels of IgA molecules that are galactose deficient at the hinge region. The predominant form of IgA is composed of polymeric IgA1. Patients, but not relatives, have circulating IgG and IgA autoantibodies against this galactose-deficient IgA. It is thought that a second "hit" phenomenon (e.g., infection, oxidative stress, etc.) stimulates production of these antibodies, and then the resulting immune complexes deposit in the glomeruli, thereby leading to an inflammatory reaction and consequent glomerulosclerosis and interstitial fibrosis.

CLINICAL MANIFESTATIONS AND DIAGNOSIS

IgA nephropathy often presents either as asymptomatic microscopic hematuria with or without proteinuria (the most common presentation in adults) or as episodic gross hematuria after an upper respiratory tract infection or exercise (the most common presentation in children and young adults).[13,14] Approximately 20 to 50% of all patients have hypertension.

IgA nephropathy has no validated diagnostic serum or urine biomarkers. Serum complement levels are typically normal. The diagnosis of IgA nephropathy is established on kidney biopsy by finding dominant or codominant IgA deposits on immunofluorescence microscopy (Fig. 107-8). Deposits of C3 and IgG also are often found. Light microscopy varies from the most common pattern of mild mesangial proliferation to severe crescentic glomerulonephritis. By electron microscopy, immune-type dense deposits are typically found in the mesangial and paramesangial areas.

Secondary causes of IgA nephropathy include viral (HIV [Chapter 359], viral hepatitis [Chapter 135]), inflammatory bowel disease (Chapter 127), autoimmune diseases (Chapter 236), liver cirrhosis (Chapter 139), and IgA-dominant infection-related glomerulonephritis. Variant forms of IgA nephropathy that require specific intervention include IgA deposition with minimal change disease, IgA nephropathy with acute kidney injury, and IgA nephropathy with rapidly progressive glomerulonephritis.

TREATMENT

The main focus of treatment of primary IgA nephropathy is optimized supportive care,[A8] including optimizing blood pressure, with dietary sodium restriction and the use of renin angiotensin blockers at maximally tolerated doses (Table 64-7) for patients whose urine protein is greater than 0.5 g/day, regardless of whether hypertension exists. Patients who present with gross hematuria and acute kidney injury should be treated conservatively because the majority will recover without intervention. No specific dietary intervention has shown to affect progression.

In patients who are at high risk of progression (defined as proteinuria >0.75 to 1g/day despite ≥90 days of optimized supportive care), immunosuppressive treatment should be considered, although its renal benefits are at least partly countered by its side effects.[A9] Corticosteroids are the preferred agents, typically with prednisone (1mg/kg/day for 2 months followed by a tapering schedule over a total of 6 months).[A10] Targeted-release oral budesonide (16 mg/day) to the distal ileum, where mucosal immune dysfunction may be the precipitating cause of the IgA complexes, reduces proteinuria.[A11] Dapagliflozin (10 mg/day) is associated with a reduction in albuminuria and a slower rate of progression of kidney disease.[A12] Omega-3 fish oils are not of proven benefit and are not recommended. Mycophenolate analogs and hydroxychloroquine have shown efficacy in small trials in China.

Nephrotic syndrome with minimal IgA deposits resembles minimal change disease and should be treated as such (see earlier). Rapidly progressive glomerulonephritis with crescents (defined as ≥50% decline in eGFR over <3 months) may rarely occur with IgA nephropathy. Such patients should be treated with corticosteroids and cyclophosphamide, similar to the treatment of antineutrophil cytoplasmic antibody–associated vasculitis (see later).

PROGNOSIS

The course is variable, with some patients showing no decline in GFR over decades and others developing the nephrotic syndrome, hypertension, and kidney failure. The International IgAN Prediction Tool (https://qxmd.com/calculate/calculator_499/international-igan-prediction-tool-at-biopsy-adults?_branch_match_id=656546875419766679) is a valuable resource to quantify the risk of progression and to inform shared decision-making.[15]

Kidney survival rates are estimated at 80 to 85% at 10 years and 65% at 20 years. A significant percentage of transplant recipients have a morphologic recurrence in the allograft, but graft loss is uncommon.

Low risk	Moderate risk	High risk	Very high risk
• Normal eGFR, proteinuria <3.5 g/day, and serum albumin level >3.0 g/dL OR • Normal eGFR and proteinuria <3.5 g/day (or a decrease >50% after 6 months of conservative therapy with an angiotensin converting enzyme inhibitor or an angiotensin receptor blocker)	• Normal eGFR, proteinuria >3.5 g/day (and a failure decrease >50% after 6 months of conservative therapy with an angiotensin converting enzyme inhibitor or an angiotensin receptor blocker) AND • Not fulfilling high-risk criteria	• eGFR <60 mL/min/1.73 m^2 and/or proteinuria >8 g/day for >6 months OR • Normal eGFR, proteinuria >3.5 g/day, and no decrease >50% after 6 months of conservative therapy with an angiotensin converting enzyme inhibitor or an angiotensin receptor blocker AND at least one of the following: • Serum albumin level <2.5 g/dL • PLA2Rab >50 RU/mL • Urinary α_1-microglobulin >40 µg/min • Urinary IgG >1 µg/min • Urinary β_2-microglobulin >250 mg/day • Selectivity index >0.20	• Life-threatening nephrotic syndrome OR • Rapid deterioration of kidney function not otherwise explained
		TREATMENT	
Wait and see	Wait and see OR rituximab OR calcineurin inhibitor ± corticosteroids	Rituximab OR cyclophosphamide + corticosteroids OR calcineurin inhibitor + rituximab	Cyclophosphamide + corticosteroids

FIGURE 107-6. Risk-based treatment of membranous nephropathy. eGFR = estimated glomerular filtration rate (see Table 106-1); PLA2Rab = M-type receptor antibodies. (Based on data from Kidney Disease: Improving Global Outcomes [KDIGO] Glomerular Diseases Work Group. KDIGO 2021 clinical practice guideline for the management of glomerular diseases. *Kidney Int*. 2021;100:S1-S276.)

Immune-complex glomerulonephritis	Anti-glomerular basement membrane disease	Anti-neutrophil cytoplasmic antibody/small vessel vasculitis
Granular deposits	**Linear deposits**	**No deposits**
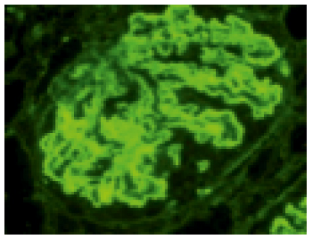	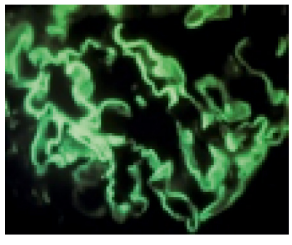	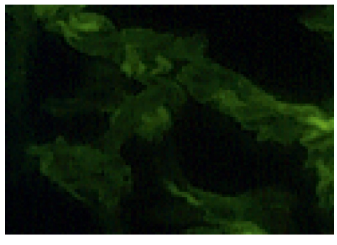
• Infection-related glomerulonephritis • Lupus nephritis • C3 glomerulopathy • IgA nephropathy • Monoclonal gammopathy	• Renal limited • Lung limited • Renal plus lung involvement (Goodpasture syndrome)	• Polyangiitis with granulomatosis • Microscopic polyangiitis • Eosinophilic granulomatosis with polyangiitis

FIGURE 107-7. Mechanisms of glomerulonephritis based on immunostaining patterns.

IgA VASCULITIS (HENOCH-SCHÖNLEIN PURPURA)

IgA vasculitis, also called Henoch-Schönlein purpura (Chapter 249), is characterized by a small-vessel vasculitis with arthralgias, skin purpura, and abdominal symptoms, as well as a proliferative acute glomerulonephritis. IgA vasculitis is predominantly a disease of childhood, although cases occur at all ages.

CLINICAL MANIFESTATIONS AND DIAGNOSIS

The clinical manifestations of IgA vasculitis (Chapter 249) include dermatologic, gastrointestinal, rheumatologic, and renal findings.[16] Skin involvement typically starts with a macular rash that coalesces into purpuric lesions (see Fig. 249-2) on the ankles, legs, and occasionally arms and buttocks. Gastrointestinal symptoms include cramps, diarrhea, nausea, and vomiting, with melena and bloody diarrhea in the most severely involved cases. Although arthralgias of the knees, wrists, and ankles are common, true arthritis is uncommon. Symptoms of different organ system involvement may occur concurrently or separately, and recurrent episodes during the first year are not uncommon.

The clinical presentation resembles small vessel vasculitis and cryoglobulinemic vasculitis. As with IgA nephropathy, patients and their relatives have elevated levels of circulating IgA molecules that are galactose deficient. Kidney biopsies are identical to those seen in IgA nephropathy. Skin biopsies typically show a small-vessel leukocytoclastic angiitis with immune deposition of IgA. The presence of hypertension and degree of proteinuria influences the kidney prognosis especially if persistent over time. Treatment approaches are similar to IgA nephropathy.

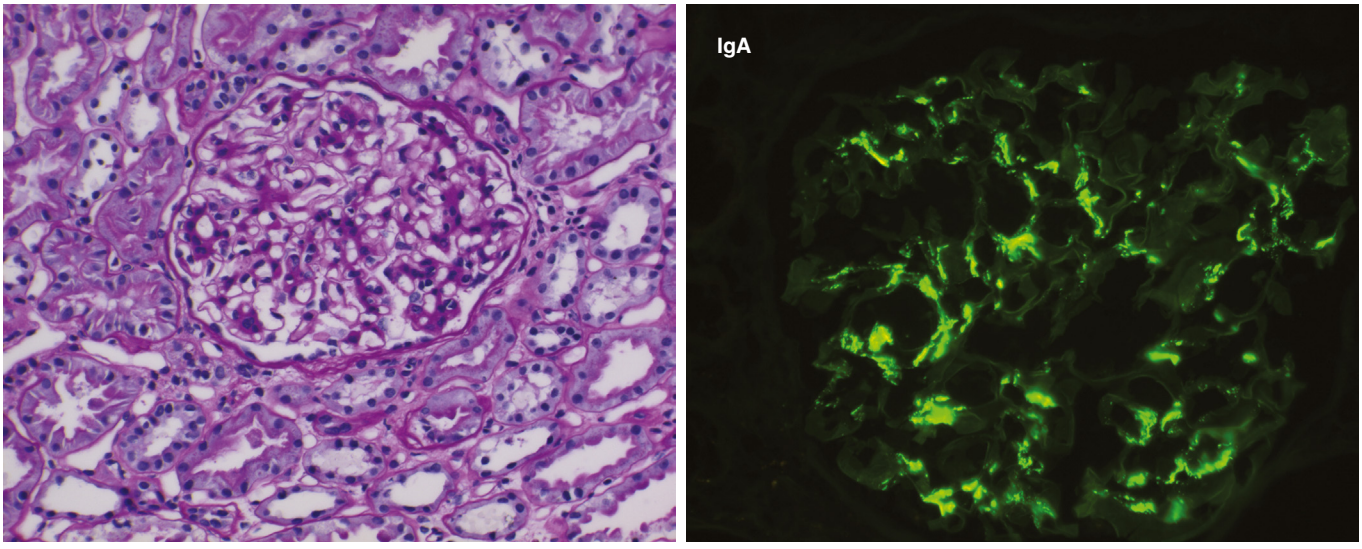

FIGURE 107-8. **Immunoglobulin A (IgA) nephropathy with mesangial cell proliferation by light microscopy and IgA deposition on immunofluorescence.**

POST-STREPTOCOCCAL GLOMERULONEPHRITIS

Acute post-streptococcal glomerulonephritis may occur in either an epidemic form or as sporadic cases after infection with nephritogenic strains of group A β-hemolytic streptococci (Chapter 269). Post-streptococcal glomerulonephritis is largely a disease of childhood, but severe disease in adults is well documented. The disease is most common after episodes of pharyngitis, but it can follow streptococcal infections at any site and subclinical cases greatly outnumber clinical cases. Post-streptococcal glomerulonephritis is an acute immune complex disease characterized by the formation of antibodies against streptococci with the localization of immune complexes and complement in the kidney. With improved socioeconomic conditions, the incidence of post-streptococcal glomerulonephritis has declined in developed nations. In adults, non-streptococcal bacterial infections are more common causes of infection-related glomerulonephritis.

CLINICAL MANIFESTATIONS AND DIAGNOSIS

Most cases manifest with hematuria, proteinuria, hypertension, and the nephritic syndrome (see Table 107-1) 10 days to several weeks after a streptococcal infection. Throat cultures and skin cultures of suspected sites of streptococcal involvement may no longer show group A β-hemolytic streptococci. A variety of antibodies (e.g., antistreptolysin O [ASLO], antihyaluronidase [AHT]) and a panel of antibodies against streptococcal antigens (which includes ASLO, AHT, antistreptokinase, and anti-DNase) often show high titers, but a change in titer over time is more indicative of a recent streptococcal infection. More than 95% of patients with post-streptococcal glomerulonephritis secondary to pharyngitis and 85% of patients with streptococcal skin infections have positive antibody titers. Complement C3 levels are decreased in more than 90% of patients during the episode of acute glomerulonephritis.

In a patient with a classic acute nephritic episode after a documented streptococcal infection, with a change in streptococcal antibody titer and a depressed serum complement level, a kidney biopsy adds little to the diagnosis. In other cases, a biopsy may be necessary to confirm the diagnosis. On light microscopy (Fig. 107-9), glomeruli are markedly enlarged and often fill the Bowman space. Glomeruli exhibit hypercellularity with infiltration of monocytes and polymorphonuclear cells and a proliferation of the glomerular cellular elements. The capillary lumens often are compressed. Some cases demonstrate extracapillary proliferation with crescents. On immunofluorescence microscopy, there is coarse granular deposition of IgG, IgM, and complement, especially C3, along the capillary wall. Electron microscopy shows large dome-shaped, electron-dense subepithelial deposits along the glomerular basement membrane.

TREATMENT AND PROGNOSIS

Therapy is symptomatic and directed at controlling the hypertension (see Table 64-7) and fluid retention with diuretic agents (Table 102-4) as needed. In most patients, this disease is self-limited, with recovery of kidney function and disappearance of hypertension in several weeks.[17] However, the presence of underlying kidney disease, especially diabetic nephropathy, is associated with a worse prognosis. Proteinuria and hematuria may resolve more slowly over months.

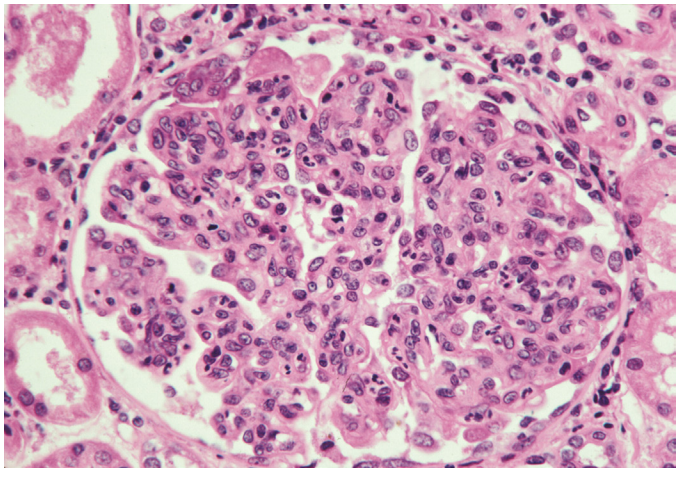

FIGURE 107-9. **Post-streptococcal glomerulonephritis.** A hypercellular glomerulus infiltrated by numerous polymorphonuclear leukocytes.

GLOMERULONEPHRITIS WITH ENDOCARDITIS, VISCERAL ABSCESSES, AND OTHER INFECTIONS

Various glomerular lesions are found in patients with acute and chronic bacterial endocarditis (Chapter 61). Although embolic phenomena can lead to glomerular ischemia and infarcts, a common finding is an immune complex glomerulonephritis. With *Streptococcus viridans* endocarditis, both focal or diffuse proliferative glomerulonephritis may be seen. With the increased incidence of *Staphylococcus aureus* endocarditis, 40 to 80% of patients have clinical evidence of an immune complex proliferative glomerulonephritis. Glomerulonephritis is now more common with acute than subacute bacterial endocarditis.[18]

Patients often have hematuria and urinary RBC casts, proteinuria ranging from less than 1 g/day to nephrotic levels, and progressive kidney failure. Serum complement C3 levels are usually reduced. Antineutrophil cytoplasmic antibodies (ANCA) occasionally may be positive, thereby leading to diagnostic confusion. Kidney insufficiency may be mild and reversible with appropriate antibiotic therapy, or it may be progressive and lead to dialysis and irreversible kidney failure.

A proliferative immune complex glomerulonephritis also can occur in patients with deep visceral bacterial abscesses and infections, such as empyema of the lung (Chapter 86) and osteomyelitis (Chapter 251). Immune complex forms of acute glomerulonephritis also have been noted in patients with bacterial pneumonias, including *Mycoplasma* (Chapter 293), and patients with chronically infected cerebral ventriculoatrial shunts for hydrocephalus. Many of these patients have nephrotic-range proteinuria and only mild kidney dysfunction. With appropriate antibiotic therapy, most glomerular lesions heal and kidney function recovers.

TABLE 107-6 CLASSIFICATION OF RAPIDLY PROGRESSIVE (CRESCENTIC) GLOMERULONEPHRITIS

PRIMARY
Anti–glomerular basement membrane antibody disease, Goodpasture syndrome (with pulmonary disease)
Immune complex–mediated
Pauci-immune (usually antineutrophil cytoplasmic antibody-positive)
SECONDARY
Membranoproliferative glomerulonephritis
IgA nephropathy, Henoch-Schönlein purpura
Post-streptococcal glomerulonephritis
Systemic lupus erythematosus

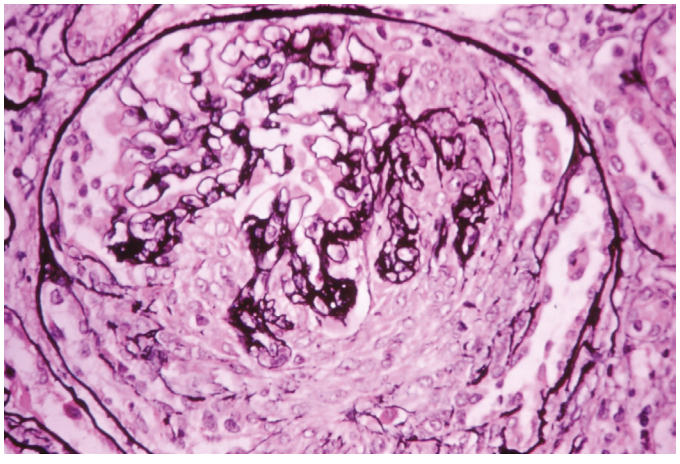

FIGURE 107-10. Rapidly progressive glomerulonephritis. A proliferation of cells in the Bowman space forming a crescent, with compression of the glomerular tuft.

An increased frequency of proliferative glomerulonephritis is also associated with staphylococcal infections in patients with diabetes. This glomerulonephritis is associated with IgA immune deposits (IgA-dominant infection related glomerulonephritis) in the glomeruli and has a poor prognosis.

RAPIDLY PROGRESSIVE GLOMERULONEPHRITIS

Rapidly progressive glomerulonephritis includes glomerular diseases that progress to kidney failure in a matter of weeks to months (Table 107-6).[19] The kidney biopsy shows extensive extracapillary proliferation manifested as crescent formation in the Bowman space (Fig. 107-10). The pathogenic mechanisms include linear anti–glomerular basement membrane antibodies, granular immune complex deposition (e.g., systemic lupus erythematosus, IgA vasculitis, infection-related glomerulonephritis), and pauci-immune, usually ANCA-positive, small vessel vasculitis.

ANTI–GLOMERULAR BASEMENT MEMBRANE DISEASE

Anti–glomerular basement membrane disease has two peaks of occurrence: in the third decade of life, predominantly in men, and after 60 years of age, predominantly in women. Anti–glomerular basement membrane disease (Fig. 107-11) is caused by circulating antibodies that are directed against the noncollagenous domain of the α_3 chain of type IV collagen. These antibodies damage the glomerular basement membrane, thereby resulting in an inflammatory response, breaks in the glomerular basement membrane, and the formation of a proliferative and often crescentic glomerulonephritis. If the anti–glomerular basement membrane antibodies cross-react with and damage the basement membrane of pulmonary capillaries, the patient develops pulmonary hemorrhage and hemoptysis, an association called Goodpasture syndrome and one of several diseases that can present with concomitant kidney and lung disease (Table 107-7).

CLINICAL MANIFESTATIONS AND DIAGNOSIS

Patients present with a nephritic picture (see Table 107-1). Kidney function may deteriorate from normal to dialysis-requiring levels in a matter of days to weeks.[20] Patients with pulmonary involvement may have life-threatening hemoptysis with dyspnea and with diffuse alveolar infiltrates on chest radiograph. The pathology of anti–glomerular basement membrane disease shows a proliferative glomerulonephritis, often with severe crescentic proliferation in the Bowman space (see Fig. 107-10). There is linear deposition of immunoglobulin (usually IgG) along the glomerular basement membrane by immunofluorescence (see Fig. 107-11), but electron microscopy does not show electron-dense deposits.

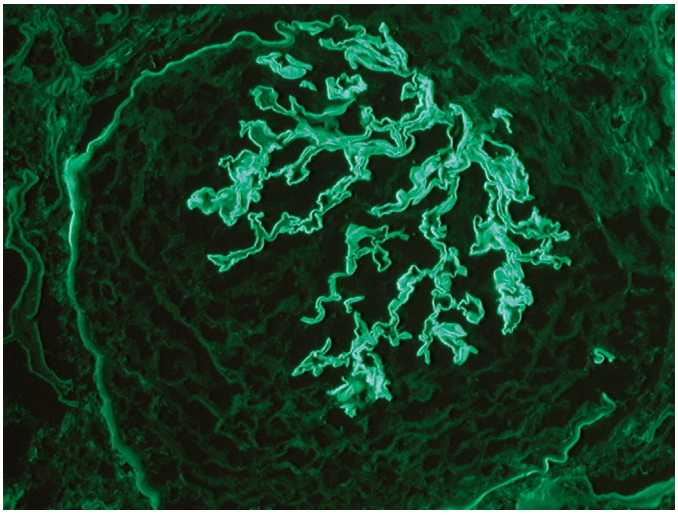

FIGURE 107-11. Anti–glomerular basement membrane glomerulonephritis. An immunofluorescence micrograph of a portion of a glomerulus with anti–glomerular basement membrane glomerulonephritis shows linear staining of glomerular basement membrane for immunoglobulin G (IgG) (fluorescein isothiocyanate anti-IgG stain, ×400).

TABLE 107-7 CLINICAL SYNDROMES OF KIDNEY DISEASES WITH CONCOMITANT PULMONARY DISEASES

DISEASE	MARKER
Goodpasture syndrome	+Anti–glomerular basement membrane antibodies
Small vessel vasculitis (granulomatous polyangiitis and microscopic polyangiitis)	+Antineutrophil cytoplasmic antibodies
Cryoglobulinemic vasculitis	Low C4 complement, +serum cryoglobulins
Systemic lupus erythematosus	+Anti-DNA antibodies, low complement
Nephrotic syndrome, renal vein thrombosis, pulmonary embolus	+Lung scan or +CT angiography
Pneumonia with immune complex glomerulonephritis	Low complement, circulating immune complexes
Uremic lung	Elevated creatinine level

CT = computed tomography.

TREATMENT

Although the treatment of this anti–glomerular basement membrane disease has not been studied in large controlled trials, intensive immunosuppressive therapy is recommended with corticosteroids, cyclophosphamide, and plasmapheresis. Rapid treatment is necessary to prevent irreversible kidney damage and is also needed in patients with pulmonary hemorrhage. The possible exceptions to immunosuppression are patients who have 100% crescents or more than 50% global glomerulosclerosis in an adequate biopsy sample without pulmonary hemorrhage and who are treated with dialysis at presentation, because the prognosis for renal recovery is poor.

Corticosteroids are given as daily pulse methylprednisolone (15 to 30 mg/kg to a maximum dose of 1000 mg/day IV for three doses), followed by prednisone (1 mg/kg/day orally to a maximum of 60 to 80 mg/day), and slowly tapered over 6 months. Cyclophosphamide (2 to 3 mg/kg/day orally, dose adjusted to kidney function, age, and the granulocyte count) for 3 months is also given. Daily plasmapheresis (40 to 50 mL/kg) against albumin is also recommended until anti–glomerular basement membrane antibodies are negative, typically

within 14 days. This combination therapy is effective in 90% of patients with lung hemorrhage. In patients who present with a serum creatinine less than 5.6 mg/dL, kidney survival is about 95% at 5 years. When the creatinine at presentation is greater than 5.6 mg/dL but the patient does not require immediate dialysis, renal survival is about 80% at 1 year and 50% at 5 years. In patients who present with an initial requirement for dialysis, however, renal recovery occurs only in about 8% of patients at 1 year. Relapses and recurrences are very rare after kidney transplantation.

IMMUNE COMPLEX RAPIDLY PROGRESSIVE GLOMERULONEPHRITIS

Rapidly progressive glomerulonephritis-associated immune complex–mediated glomerular damage can be seen with idiopathic glomerulopathies, such as IgA nephropathy, IgA vasculitis, and idiopathic membranoproliferative glomerulonephritis, or with systemic diseases, such as infection-related glomerulonephritis, cryoglobulinemic vasculitis, and systemic lupus erythematosus. Many cases of crescentic postinfectious glomerulonephritis resolve with successful treatment of the underlying infection. The treatments of others are as described elsewhere in this chapter.

PAUCI-IMMUNE AND VASCULITIS-ASSOCIATED RAPIDLY PROGRESSIVE GLOMERULONEPHRITIS

Pauci-immune rapidly progressive glomerulonephritis includes patients with and without evidence of systemic vasculitis. Most patients have circulating antineutrophil cytoplasmic antibodies (ANCAs) that are directed against components of neutrophil primary granules.[21] Clinical syndromes of ANCA-associated vasculitis include granulomatous polyangiitis (Chapter 249), microscopic polyangiitis, and eosinophilic granulomatosis with polyangiitis (Chapter 249).

CLINICAL MANIFESTATIONS AND DIAGNOSIS

Patients with ANCA-associated vasculitis often present with progressive kidney failure and a nephritic picture (see Table 107-1). Patients with microscopic polyangiitis often have circulating perinuclear ANCA (antibodies directed against granulocyte myeloperoxidase) and a systemic clinical picture (Chapter 249) with arthritis, dermal leukocytoclastic vasculitis, pulmonary disease, and constitutional and systemic signs. Patients with granulomatous polyangiitis often have circulating cytoplasmic ANCA (antibodies directed against a granulocyte serine proteinase, anti-PR3), upper and lower respiratory tract involvement by granulomatous angiitis, as well as pauci-immune glomerulonephritis (Chapter 249). However, there is considerable overlap among these groups, and some patients have both ANCA and anti–glomerular basement membrane antibodies. Patients with eosinophilic granulomatosis with polyangiitis usually have a history of asthma, pulmonary infiltrates, and circulating eosinophilia. If they are ANCA positive, they often have associated glomerular disease. Although there is no direct correlation between ANCA titers and disease activity, patients with high titers (especially high anti-PR3 titers) and patients with a major recent increase in titers are more likely to have flares of their disease.

TREATMENT

For induction therapy (Fig. 107-12), corticosteroids in combination with cyclophosphamide or rituximab should be used as initial treatment. Corticosteroids are typically administered as pulse methylprednisolone (10 to 15 mg/kg/day up to a maximum of 500 to 1000 mg/day IV for 3 days, followed by prednisone or equivalent, 1 mg/kg/day orally for the first week). By 6 months, prednisone should be tapered to 5 mg/day in cyclophosphamide-treated patients and withdrawn in rituximab-treated patients. Adjunctive therapy with avacopan (30 mg twice daily for 52 weeks in combination with standard therapy), which is an inhibitor of the C5a complement receptor and which may allow for lower cumulative corticosteroid exposure, is recommended for severe disease.[A13] Cyclophosphamide may be administered intravenously (15 mg/kg IV every 2 to 3 weeks for 6 to 10 doses) or orally (1.5 to 2 mg/kg/day for 3 to 6 months). Rituximab, a monoclonal antibody against CD20-positive B cells (375 mg/m^2 weekly for 4 weeks, or 1 g at 0 and 2 weeks), is effective and as safe as cyclophosphamide at 6 months or more. The role of plasmapheresis is controversial, but it may be considered for patients who have a serum creatinine level greater than 5.7 mg/dL (500 mmol/L), who require dialysis, or who have rapidly worsening renal function, as well as for patients who have diffuse alveolar hemorrhage with hypoxemia. Plasmapheresis is also commonly prescribed in the overlap syndrome of ANCA vasculitis and anti–glomerular basement membrane disease. In patients who have severe ANCA-associated vasculitis, cyclophosphamide may be added to rituximab.

The risk of relapse is significant when ANCA-associated vasculitis is treated with cyclophosphamide induction, so azathioprine (1.5 mg/kg/day) with or without low-dose corticosteroids (e.g., prednisone 5 mg/day) or rituximab (500 mg at months 6, 12, and 18) without corticosteroids should be used to prevent relapse (see Fig. 107-12). Mycophenolate mofetil or methotrexate also have been used in patients intolerant or unable to take rituximab or azathioprine. The optimal duration of maintenance therapy after achieving remission is not known but should be between 18 months and 4 years with azathioprine and 18 months after rituximab. Patients with relapsing disease should preferably be treated with rituximab in addition to corticosteroids.

PROGNOSIS

The prognosis of untreated ANCA-associated vasculitis is poor (Chapter 249), with a 90% mortality at 2 years. Despite treatment, the 5-year mortality is 25%, with infection and active vasculitis being the main causes of death. Fortunately, ANCA-associated vasculitis has a low chance of recurrence in a kidney allograft.

MEMBRANOPROLIFERATIVE GLOMERULONEPHRITIS

Membranoproliferative glomerulonephritis is classified based on immunofluorescence findings into immunoglobulin-mediated, complement-mediated and neither immunoglobulin or complement-mediated categories (Table 107-8).[22]

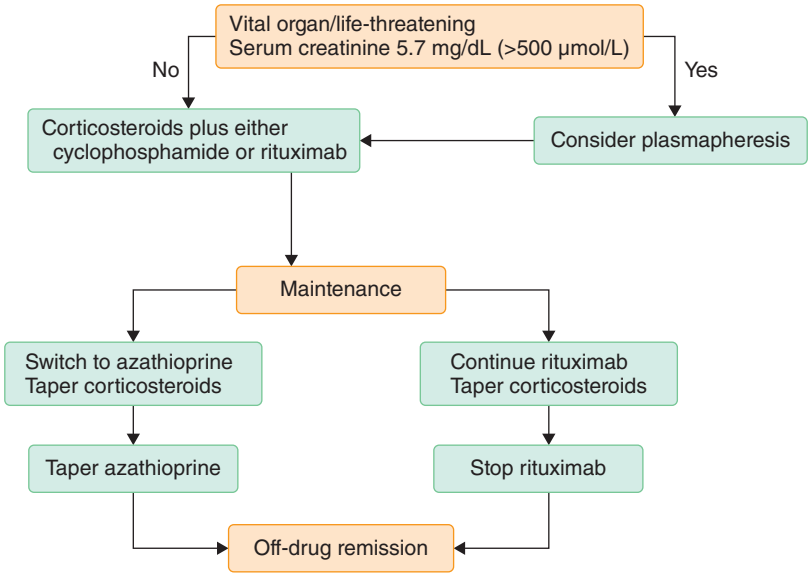

FIGURE 107-12. Treatment regimen for antineutrophil cytoplasmic antibodies–associated vasculitis. (Based on Kidney Disease: Improving Global Outcomes [KDIGO] Glomerular Diseases Work Group. KDIGO 2021 Clinical Practice Guideline for the Management of Glomerular Diseases. *Kidney Int*. 2021;100:S1-S276.)

TABLE 107-8 CAUSES OF A MEMBRANOPROLIFERATIVE PATTERN OF INJURY

Immunoglobulin-/immune complex–mediated	**Deposition of antigen–antibody immune complexes as a result of an infection:** • Viral: hepatitis C (including associated with mixed cryoglobulinemia), hepatitis B • Bacterial: endocarditis, infected ventriculo-atrial shunt, visceral abscesses, leprosy, meningococcal meningitis • Protozoa/other infections: malaria, schistosomiasis, mycoplasma, leishmaniasis, filariasis, histoplasmosis **Deposition of immune complexes as a result of an autoimmune disease:** • Systemic lupus erythematosus • Sjögren syndrome • Rheumatoid arthritis • Mixed connective tissue disease **Deposition of monoclonal Ig as a result of a monoclonal gammopathy due to a plasma cell or B cell disorder** **Fibrillary glomerulonephritis** **Idiopathic:** • None of the conditions above are present
Complement-mediated	**C3 glomerulonephritis and C3 dense deposit disease:** • Mutations in complement regulatory proteins: complement factor H, complement factor I, complement factor H–related protein 5 • Mutations in complement factors: C3 • Antibodies to complement factors: C3, C4, and C5 nephritic factors • Antibodies to complement regulatory proteins: complement factor H, complement factor I, complement factor B **C4 glomerulonephritis and C4 dense deposit disease**
Membranoproliferative pattern without immune complexes or complement	• Healing phase of hemolytic–uremic syndrome/thrombotic thrombocytopenic purpura • Antiphospholipid (anticardiolipin) antibody syndrome • POEMS syndrome • Radiation nephritis • Nephropathy associated with bone marrow transplantation • Drug-associated thrombotic microangiopathies • Sickle cell anemia and polycythemia • Dysfibrinogenemia and other prothrombotic states • Antitrypsin deficiency

POEMS = polyneuropathy, organomegaly, endocrinopathy, monoclonal protein, skin changes.

Common causes of immunoglobulin-mediated membranoproliferative glomerulonephritis include systemic lupus erythematosus (Chapter 245), infections such as hepatitis C (Chapter 134), and monoclonal gammopathy (Chapter 173). Complement-mediated membranoproliferative glomerulonephritis includes dense deposit disease and C3 glomerulonephritis. The membranoproliferative glomerulonephritis pattern also can be seen without either complement or immunoglobulin deposition in chronic thrombotic microangiopathies that are associated with endothelial cell injury. All these stimuli have been proposed to incite the glomerular mesangial cells to grow out along the capillary wall and split the glomerular basement membrane.

C3 glomerulopathies, which include dense deposit disease and C3 glomerulonephritis, are rare glomerular diseases characterized by uncontrolled systemic activation of the alternative complement pathway. Many patients have C3 nephritic factor, an autoantibody that stabilizes the C3 convertase of the alternate complement pathway, whereas others have deficiencies of factor H, factor I, or other inhibitors of the alternative complement pathway. Dense deposit disease may be associated with partial lipodystrophy. Patients who have activation of the alternative complement pathway and who have a proliferative glomerulonephritis with C3 deposits that lack the electron microscopic features of dense deposit disease have C3 glomerulonephritis.

Most patients with membranoproliferative glomerulonephritis present with proteinuria or the nephrotic syndrome.[23] Low serum complement levels (C3 and C4) are found intermittently in immunoglobulin-associated membranoproliferative glomerulonephritis, whereas only the C3 level is usually reduced in dense deposit disease. The diagnosis of dense deposit disease requires a kidney biopsy that shows complement C3 in a characteristic ribbon-like pattern around the capillary loops (Fig. 107-13). All patients with membranoproliferative glomerulonephritis on a biopsy should be evaluated for underlying disease (see Table 107-8). If no cause is found, an evaluation for a complement-related disorder (Chapter 37) should be undertaken if possible.

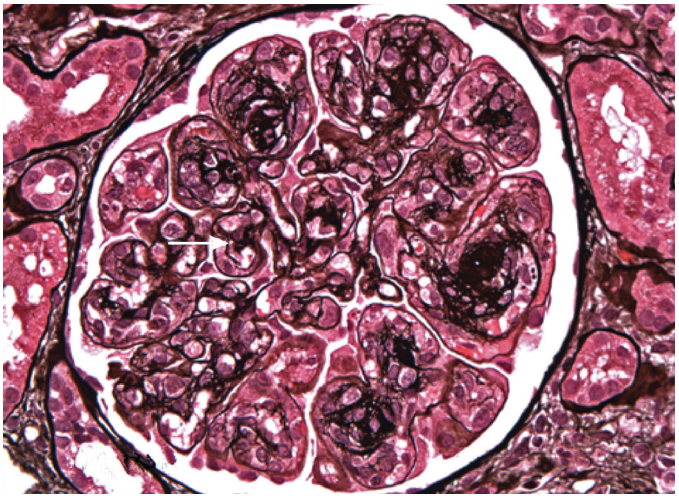

FIGURE 107-13. Membranoproliferative glomerulonephritis. Note lobulation of the glomerular tuft and duplication of the basement membrane as seen by silver stain.

TREATMENT

When the cause of immune complex membranoproliferative glomerulonephritis is determined, the initial approach to treatment should focus on the underlying pathologic process. For idiopathic immune complex membranoproliferative glomerulonephritis with proteinuria 3 g/day or less and normal kidney function, supportive care with blood pressure control, preferably with an ACE-inhibitor or angiotensin receptor blocker (Table 64-7), is adequate. For patients with abnormal kidney function but without crescentic involvements or an active urine sediment, with or without nephrotic-range proteinuria, corticosteroids and immunosuppressive therapy should be prescribed. Prednisone can be initiated at 1 mg/kg/day (maximum dose 60 to 80 mg/day) for 12 to 16 weeks. Mycophenolic acid analogs (e.g., mycophenolate mofetil 2 to 3 g/day) may be added for 6 to 12 months if a suboptimal response is seen after this time, with tapering of prednisone to 20 mg/day. In refractory patients, cyclophosphamide (2 mg/kg/day, maximum 200 mg/day) with prednisone (10 mg/day for 3 to 6 months) or rituximab (1 g × 2 doses 2 weeks apart, followed by a third dose in 6 months) may be given. For patients with rapidly progressive crescentic membranoproliferative glomerulonephritis, treatment with intravenous methylprednisolone (1 to 3 g) followed by oral corticosteroids and oral cyclophosphamide using a regimen similar to that used for patients with ANCA-associated vasculitis is suggested.

Patients who have C3 glomerulopathies (dense deposit disease and C3 glomerulonephritis) with moderate to severe disease (with proteinuria >1 g/day and hematuria or with declining kidney function) may be considered for immunosuppressive therapy with mycophenolic acid analogs plus corticosteroids, at doses similar to immune complex membranoproliferative glomerulonephritis. However, the evidence for efficacy for the latter is not established. The role of complement inhibitors is being actively investigated in both immune complex membranoproliferative glomerulonephritis and C3 glomerulopathies.

PROGNOSIS

The prognosis for membranoproliferative glomerulonephritis is dependent on whether patients achieve remission of proteinuria and stabilization of kidney function.[24] Up to 50 to 60% of untreated patients will progress to end-stage kidney disease within 10 to 15 years, but 25 to 40% of untreated patients will continue to have normal renal function. Spontaneous remission or improvement occurs in less than 10% of cases. With treatment, remission rates in observational studies have varied from 30 to 50%.

GLOMERULAR DISEASES ASSOCIATED WITH GENETIC DEFECTS

Some patients with focal segmental glomerulosclerosis have abnormalities in genes encoding for podocyte proteins, ion channels, or podocyte mitochondrial constituents. Other patients, often with a history of clinical kidney disease in siblings and other relatives, have other forms of hereditary nephritis.[25]

Alport Syndrome

Alport syndrome is a hereditary form of glomerulonephritis that often manifests with asymptomatic urinary findings. In approximately 85% of cases, it is an X-linked condition with hematuria and proteinuria, often in association with high-pitched hearing loss and abnormalities of the lens of the eye (lenticonus). X-linked form of disease are due to mutation in the α_5 chain of type IV collagen *(COL4A5)*. Mutations in the α_3 and α_4 chains of type IV collagen *(COL4A3, COL4A4)* cause dominant or recessive forms of disease.[26] Recessive forms of disease have severe, early-onset presentation, whereas dominant forms of disease have a very variable clinical course, ranging from normal, stable kidney function to progressive kidney failure. Patients with heterozygous pathogenic variants in *COL4A3/COL4A4* are often underdiagnosed and are frequently labeled as kidney disease of unknown cause. Although the light microscopy findings vary from mild mesangial proliferative to advanced sclerosing lesions depending on the stage of biopsy, electron microscopy typically shows areas of glomerular basement membrane thinning and other areas of glomerular basement membrane splitting with lamellations.

Use of ACE inhibitors (Table 64-7) at the onset of proteinuria delays progression of kidney failure, but males with X-linked Alport syndrome *(COL4A5)* often have progressive glomerulosclerosis and develop end-stage kidney disease. Owing to random X-inactivation, females with *COL4A5* mutations tend to have milder disease and may only progress to kidney failure late in life.

Fabry Disease

Fabry disease (Chapter 192), which is caused by an X-linked recessive genetic defect of α-galactosidase, leads to the deposition of ceramide trihexose in the kidneys and other organs. It may cause progressive proteinuria and kidney insufficiency in males and in some female carriers. It is associated with telangiectasias of the skin, typically in the bathing suit area, acroparesthesias, cardiac abnormalities, and eye changes. Replacement with intravenous recombinant enzyme agalsidase β is associated with clinical improvement.

Nail-Patella Syndrome

Nail-patella syndrome, associated with skeletal and nail deformities, is a rare cause of the nephrotic syndrome. It is due to an autosomal dominant mutation in the LMX1B transcription factor that regulates collagen, nephrin, and podocin gene expression. Progression to end-stage kidney disease is variable and estimated to be 1 to 15%. The use of maximally tolerated doses of ACE inhibitors or angiotensin receptor blockers (Table 64-7) may reduce proteinuria.

OTHER GLOMERULAR DISEASES

SYSTEMIC LUPUS ERYTHEMATOSUS

The pattern and degree of kidney involvement greatly influences the course and therapy of systemic lupus erythematosus (Chapter 245). Although the incidence of clinical kidney disease in systemic lupus erythematosus varies from 15 to 75%, histologic evidence of kidney involvement is found in most biopsy specimens.

The classification of lupus nephritis can provide a guide to therapy and prognosis (Table 107-9).[27] In general, patients with class I and II disease have mild lesions that require no therapy directed at the kidney, whereas all patients with class IV lesions (diffuse proliferative lupus nephritis) on biopsy (Fig. 107-14) require vigorous therapy. Many patients with class III (focal proliferative lupus nephritis) disease, especially patients who have active necrotizing lesions and large amounts of subendothelial deposits, also benefit from vigorous therapy. For patients with class V (membranous lupus nephritis) disease, the optimal therapy is less clear, and recommendations vary from uniform vigorous treatment to reserving such therapy for patients with serologic activity or more severe nephrotic syndrome.

TABLE 107-9 INTERNATIONAL SOCIETY OF NEPHROLOGY/RENAL PATHOLOGY SOCIETY CLASSIFICATION OF LUPUS NEPHRITIS

CLASS	CLINICAL FEATURES
I. Minimal mesangial lupus nephritis	Normal glomeruli by light microscopy but mesangial immune deposits by immunofluorescence
II. Mesangial proliferative lupus nephritis	Purely mesangial hypercellularity by light microscopy, with mesangial immune deposits
III. Focal lupus nephritis < 50% glomeruli involved A. Active A/C. Active and chronic C. Chronic	Active or inactive focal, segmental, or global endo- or extracapillary glomerulonephritis involving <50% of all glomeruli, typically with focal subendothelial immune deposits, with or without mesangial alterations
IV. Diffuse lupus nephritis (>50% glomeruli involved); all may be with segmental or global involvement (S or G) A. Active A/C. Active and chronic C. Chronic	Active or inactive diffuse, segmental or global endo- or extracapillary glomerulonephritis involving ≥50% of all glomeruli, typically with diffuse subendothelial immune deposits, with or without mesangial alterations
V. Membranous lupus nephritis glomerulonephritis	Global or segmental subepithelial immune deposits or their morphologic sequelae by light microscopy and by immunofluorescence or electron microscopy, with or without mesangial alterations
VI. Advanced sclerotic lupus nephritis	≥90% of glomeruli globally sclerosed without residual activity

Based on Weening JJ, D'Agati VD, Schwartz MM, et al. The classification of glomerulonephritis in systemic lupus erythematosus revisited. *J Am Soc Nephrol*. 2004;15:241-250; and Bajema IM, Wilhelmus S, Alpers CE, et al. Revision of the International Society of Nephrology/Renal Pathology Society classification for lupus nephritis: clarification of definitions, and modified National Institutes of Health activity and chronicity indices. *Kidney Int*. 2018;93:789-796.

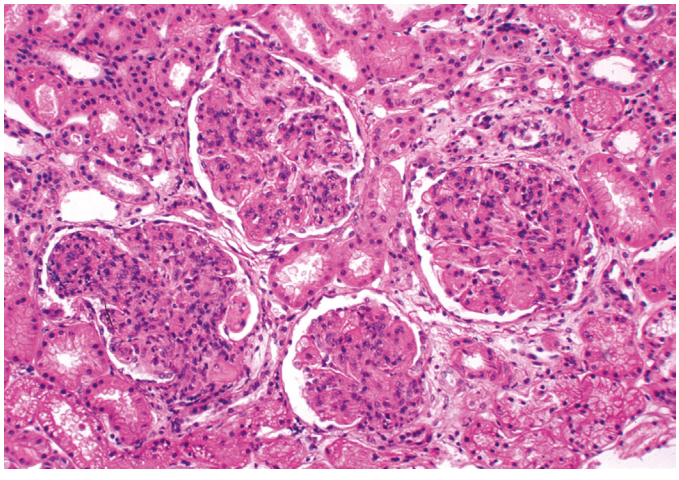

FIGURE 107-14. Diffuse proliferative lupus nephritis. Note involvement of all glomeruli.

TREATMENT

All patients with lupus nephritis should be treated with hydroxychloroquine (6.5 mg/kg ideal weight/day or 400 mg/day) or an equivalent antimalarial if there are no contraindications. For patients with class I or class II lupus nephritis with normal or low-grade proteinuria, no specific treatment is needed beyond what is given for extrarenal lupus. Patients who have class I/II lupus nephritis with nephrotic range proteinuria are considered to have lupus podocytopathy; treatment is as for minimal change disease (see earlier).

Initial therapy for patients with active class III or IV lupus nephritis, with or without a membranous component, is corticosteroids, with either low-dose intravenous cyclophosphamide or mycophenolic acid analogues (Fig. 107-15).[28]

A novel calcineurin inhibitor, voclosporin (23.7 mg twice daily), has been used with a mycophenolic acid analog and corticosteroids in patients with eGFR ≥45 mL/min/1.73 m^2 with improved response rates.[A14] Similarly, the addition of belimumab, a monoclonal antibody that inhibits B-cell activating factor (at 10 mg/kg intravenously), to standard therapy increases the response rate when added to initial therapy.[A15]

After the induction period, the prednisone dose should be tapered to below 5 to 7.5 mg/day and other medications should be discontinued. For maintenance therapy, mycophenolate mofetil (1000 mg twice daily) is preferred over azathioprine (2 mg/kg/day). If neither is tolerated, alternatives include tacrolimus (trough approximately 4 to 6 ng/mL or 5 to 7.4 nmol/L) or cyclosporine A (trough approximately 60 to 100 ng/mL or 50 to 83 nmol/L) or mizoribine (3 mg/kg/day).

Corticosteroids

Intravenous methylprednisolone
(0.25 to 0.50 g daily for 1 to 3 days)
then
oral prednisone
(0.6 to 1.0 mg/kg/day, maximum 80 mg)

plus

A. Cyclophosphamide

500 mg intravenously every 2 weeks for 6 doses,
0.5 to 1.0 g/m^2 intravenously monthly for 6 months,
or 1.0 to 1.5 mg/kg/day orally for up to 6 months

OR

B. Mycophenolic Acid Analogs

Mycophenolate mofetil (1.0 to 1.5 g orally twice daily)
or
mycophenolate acid sodium (0.72 to 1.08 g orally twice daily)

plus

A. Belimumab

(10 mg/kg intravenously every 2 weeks for 3 doses, then every 4 weeks)

OR

B. Calcineurin Inhibitors

Voclosporin (23.7 mg orally twice daily if eGFR >45 mL/min/1.73 m^2)

FIGURE 107-15. Initial therapy of active class III/IV with or without class V lupus nephritis. eGFR= estimated glomerular filtration rate. (Adapted from Kidney Disease: Improving Global Outcomes [KDIGO] Glomerular Diseases Work Group. KDIGO 2021 clinical practice guideline for the management of glomerular diseases. *Kidney Int*. 2021;100:S1-S276.)

Many patients with lupus nephritis (40 to 50%) produce autoantibodies against certain phospholipids, including anticardiolipin antibodies. Those patients who experience clotting in the glomeruli and arterioles require anticoagulation with either warfarin (Chapter 70) or antiplatelet agents (e.g., aspirin 81 to 325 mg/day) or with both, as well as immunosuppressive medications.

PROGNOSIS

Despite aggressive therapy, 10 to 30% of patients with lupus nephritis develop kidney failure. Moreover, patients with lupus nephritis have a higher risk for death compared with lupus patients without kidney involvement (Chapter 245). The risk of recurrence of lupus nephritis in kidney allografts is low.

DIABETES MELLITUS

Diabetic nephropathy, which is the most common form of glomerular disease in developed countries, is discussed in detail in Chapter 109.

MONOCLONAL GAMMOPATHY OF RENAL SIGNIFICANCE

Monoclonal gammopathy of renal significance refers to the association of B-cell or plasma-cell clonal disorders that per se do not fulfill criteria for cancer yet produce a nephrotoxic monoclonal immunoglobulin that leads to kidney disease. The toxicity of light chains results from multiple mechanisms, and kidney biopsy typically shows monotypic (single light and/or heavy chain) immunoglobulin deposition associated with a variety of morphologic patterns.[29]

AMYLOIDOSIS

Renal amyloid deposits, whether due to AL, AA, or hereditary-genetic forms of amyloid, are predominantly found within the glomeruli, where they often appear as amorphous eosinophilic extracellular nodules (Chapter 174). In all amyloidosis, proteins form β-pleated sheets, which are deposited in organs. All amyloid subtypes display apple-green birefringence under polarized light with the Congo red stain. By electron microscopy, amyloid appears as nonbranching rigid fibrils 8 to 10 nm in diameter. In AL amyloid, overproduction of an abnormal light chain (λ 80%, κ 20%) can be detected by immunofluorescence staining that shows monotypic λ or κ light chains. Most patients have a clonal proliferation of plasma cells and do not meet criteria for multiple myeloma. In AA amyloid, antisera to the AA protein stain the glomeruli. Some patients with kidney amyloidosis have genetic variants that lead to the production of amyloidogenic proteins such as transthyretin, LECT2, and apolipoproteins.

Almost 80% of patients with AL amyloid have kidney disease. Kidney manifestations include albuminuria and renal insufficiency. Extrarenal amyloid involvement may cause cardiac disease (Chapter 47) or neuropathy (Chapter 388). Diagnosis may be made from organ biopsy other than the kidney (e.g., myocardial, rectal, or fat pad biopsy). Treatment strategies for kidney AL amyloidosis are similar to those for multiple myeloma and other plasma cell dyscrasias: stem cell transplantation and the use of anti-plasma cell agents such as proteasome inhibitors (bortezomib, carfilzomib, daratumumab), dexamethasone, and lenalidomide (Chapter 173).

AA amyloid is associated with chronic inflammatory conditions such as rheumatoid arthritis (Chapter 243), familial Mediterranean fever (Chapter 240), inflammatory bowel disease (Chapter 127), osteomyelitis (Chapter 251), and other chronic infections. Treatment is directed at the underlying inflammatory process. Specific therapy against the primary inflammatory disease (e.g., anti–tumor necrosis factor therapy in rheumatoid arthritis and colchicine in familial Mediterranean fever) can reduce the production of serum AA protein in patients with AA amyloid.

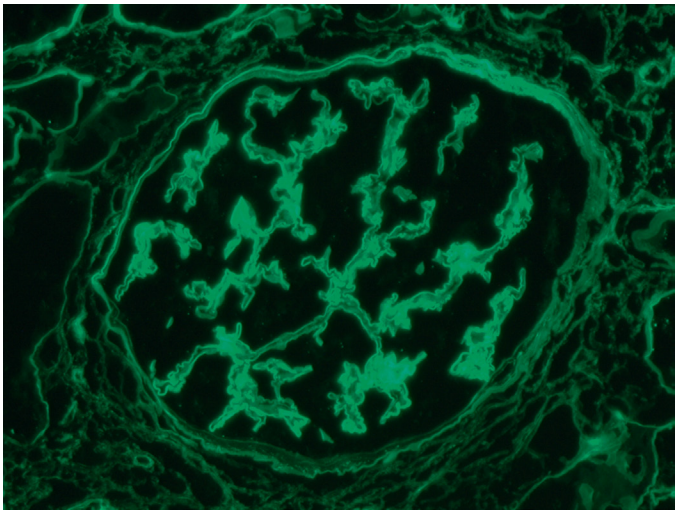

FIGURE 107-16. Light-chain deposition disease. Immunofluorescence shows linear staining of glomerular and tubular basement membranes for κ light chain.

LIGHT-CHAIN DEPOSITION DISEASE

Light-chain deposition disease, like AL amyloidosis, is a systemic disease caused by the overproduction and extracellular deposition of a monoclonal immunoglobulin light chain (Chapter 173). However, the deposits do not form β-pleated sheets, do not stain with Congo red, and are granular rather than fibrillar. Most patients with light chain deposition disease have a lymphoplasmacytic B-cell disease similar to multiple myeloma (Chapter 173).

Albuminuria is common, and the nephrotic syndrome is found in half of patients at presentation, often accompanied by hypertension and kidney insufficiency. On light microscopy, most glomeruli contain eosinophilic mesangial glomerular nodules. Some biopsy samples show associated light-chain cast nephropathy with eosinophilic laminated and fracturing casts obstructing the tubules, as seen in myeloma. By immunofluorescence, a single class of immunoglobulin light-chain (κ in 80% of cases) stains in a diffuse linear pattern along the glomerular basement membrane, in the nodules and along the tubular basement membranes (Fig. 107-16). The treatment for most patients with light-chain deposition disease is chemotherapy similar to that for myeloma (Chapter 173).

FIBRILLARY GLOMERULOPATHY–IMMUNOTACTOID GLOMERULOPATHY

Some patients with kidney disease have glomerular lesions with deposits of nonamyloid fibrillar proteins ranging in size from 12 to more than 50 nm.

Patients with these lesions have been divided into two groups. Patients with fibrillary glomerulonephritis have fibrils of 20 nm in diameter that are deposited in a random fashion in the glomerular basement membrane and are associated with deposits of the DNAJB9 protein in deposits. Immunotactoid glomerulonephritis is a much rarer disease often associated with lymphoproliferative disorders, in which the fibrils are much larger (30 to 50 nm) and have a tubular substructure. Proteinuria is found in almost all patients, and hematuria, the nephrotic syndrome, and kidney insufficiency eventually develop in most patients. No therapy is of proven benefit for the fibrillary glomerulopathy per se, and a search for a treatable underlying B cell disorder is important.[30]

HUMAN IMMUNODEFICIENCY VIRUS–ASSOCIATED NEPHROPATHY

Infection with HIV (Chapter 355) is associated with a number of patterns of kidney disease, including acute kidney injury (Chapter 106) and a unique form of glomerulopathy now called HIV-associated nephropathy. HIV-associated nephropathy is characterized by heavy proteinuria and rapid progression to kidney failure. On light microscopy, biopsies show global collapse of the glomerular tufts, severe tubulointerstitial changes with interstitial inflammation, edema, microcystic dilation of tubules, and severe tubular degenerative changes. On electron microscopy, tubuloreticular inclusions can be seen in the glomerular endothelium.[31] The use of ACE inhibitors or angiotensin receptor blockers (see Table 64-7 in Chapter 64) and antiretroviral therapy may decrease proteinuria and slow the progression to kidney failure. In addition, corticosteroids (e.g., prednisone, 1 mg/kg for 1 month followed by a taper over several months) may be beneficial in selected patients with HIV-associated nephropathy.

COVID-19–ASSOCIATED NEPHROPATHY

Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) and the coronavirus disease 2019 (COVID-19) that it causes can be associated with acute kidney injury. Postmortem examination in fatal cases shows diffuse acute tubular injury with a possible contribution of focal macrovascular and microvascular thrombi. Renal biopsies in patients with proteinuria and hematuria have demonstrated a glomerular-dominant pattern of injury, most notably a collapsing glomerulopathy similar to the findings seen in HIV-infected individuals with apolipoprotein L-1 *(APOL1)* risk allele variants. Other glomerular manifestations associated with COVID-19 include membranous nephropathy, ANCA-vasculitis, anti–glomerular basement membrane disease, and thrombotic microangiopathy.[32] Furthermore, acute flares of lupus nephritis, IgA nephropathy, and minimal change disease have been reported. SARS-CoV-2 vaccines have been rarely reported to be associated with relapsing or de novo glomerular disease, including IgA nephropathy, minimal change disease, ANCA-vasculitis, and others. The pathogenesis of glomerular disease associated with COVID-19 or vaccines is not understood, but is postulated to be related to immune activation.[33,34]

MIXED CRYOGLOBULINEMIA

Cryoglobulinemia (Chapter 173) is caused by the production of circulating immunoglobulins that precipitate on cooling and resolubilize on warming. Cryoglobulinemia may be found in association with infections, collagen vascular disease, and lymphoproliferative diseases such as multiple myeloma and Waldenström macroglobulinemia. Many patients with what was originally described as glomerulonephritis resulting from essential mixed cryoglobulinemia have been found to have hepatitis C–associated kidney disease. Some patients develop an acute nephritic picture with acute kidney insufficiency. Most patients have proteinuria, and approximately 20% present with the nephrotic syndrome. Hypocomplementemia, especially of the early components C1q to C4, is a characteristic finding in cryoglobulinemic glomerulonephritis, whether hepatitis C–related or idiopathic. Treatment of hepatitis C–associated cryoglobulinemia includes antiviral therapy (Chapter 135). When significant kidney disease is present, various combinations of corticosteroids with or without rituximab or cyclophosphamide or plasmapheresis have been used under expert guidance. Most patients with kidney disease have a slow, indolent course characterized by proteinuria, hypertension, hematuria, and renal insufficiency.

THROMBOTIC MICROANGIOPATHIES

A number of systemic diseases, including hemolytic-uremic syndrome (Chapters 110 and 158), thrombotic thrombocytopenic purpura (TTP; Chapter 158), and the antiphospholipid syndrome (Chapter 67), as well as microangiopathy associated with drugs such as mitomycin and cyclosporine, are characterized by microthromboses of the glomerular capillaries and small arterioles. The kidney findings may be dominant or only part of a more generalized picture of microangiopathy.

Kidney manifestations of the thrombotic microangiopathies may include gross or microscopic hematuria, proteinuria that is typically less than 2 g/day but may reach nephrotic levels, and renal insufficiency. Patients may have oliguric or nonoliguric acute kidney injury. In addition to glomerular chronic capillary thromboses, the histologic findings in all of the microangiopathies include a membranoproliferative glomerulonephritis pattern on light microscopy with no immune deposits or complement by immunofluorescence or electron microscopy, areas of ischemic damage, and intimal proliferation with luminal narrowing by thrombi of arterioles and small arteries.

In all thrombotic microangiopathies, treatment includes correcting hypovolemia, controlling hypertension, and the use of dialytic support for those with severe kidney failure. In TTP associated with an acquired or hereditary deficiency of the von Willebrand convertase ADAMTS-13 and in some other cases, plasmapheresis with fresh-frozen plasma is beneficial (Chapter 158).

In some patients whose hemolytic-uremic syndrome is not associated with Shiga toxin, defects in the alternate complement system are found. These patients with atypical hemolytic-uremic syndrome may benefit from eculizumab or ravulizumab, which inhibit complement C5 (Chapter 158). In the antiphospholipid syndrome, anticoagulation with heparin and then warfarin is useful (Chapter 67).

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108 INTERSTITIAL NEPHRITIS

CYBELE GHOSSEIN AND ERIC G. NEILSON

DEFINITION

Interstitial nephritis is characterized by an inflammatory infiltrate in the interstitium of the kidney. It can be primary and begin in the tubulointerstitium or appear as a secondary event and spread from blood vessels, including the glomerular capillaries. Injury to the tubulointerstitial compartment can be the result of autoimmunity, toxic insult, infection, or exposure to drugs. In all cases, however, the inflammatory process has an immunologic component that leads to the release of tissue cytokines, which attract T lymphocytes and other monocytes, which eventually convert tubular epithelia into fibroblasts to produce fibrosis.[1]

Interstitial nephritis can be arbitrarily divided into acute and chronic types. The acute form often begins abruptly. When inciting events subside, so does the nephritis. If this occurs in a matter of days/weeks, the glomerular filtration rate tends to normalize, with little residual damage except in patients with preexisting disease. Any cause of acute interstitial nephritis can transform into chronic interstitial nephritis.

Chronic interstitial nephritis is persistent and over time reduces the number of functioning nephrons by encasing and dismantling them with irreversible fibrosis. Sometimes acute and chronic injury is difficult to distinguish because global destruction of the tubulointerstitium can occur within a matter of weeks.

EPIDEMIOLOGY

Acute interstitial nephritis appears unexpectedly in otherwise healthy individuals from a variety of causes. Approximately 1% of patients with hematuria and proteinuria have acute interstitial nephritis, and it is seen in 1 to 15% of autopsy series. In recent decades its prevalence has increased in individuals over age 65 years, perhaps owing to their more frequent exposure to prescription drugs.

Although the most common cause of acute interstitial nephritis is the use of pharmaceuticals,[2,3] other important causes include infection and autoimmune diseases (Table 108-1). Almost any class of drugs can cause acute interstitial nephritis, but antibiotics, diuretics, proton pump inhibitors, immune checkpoint inhibitors, and nonsteroidal anti-inflammatory drugs (NSAIDs) top the list. NSAIDs cause both acute interstitial nephritis and chronic analgesic nephropathy. Diphtheria in children (Chapter 272), legionellosis (Chapter 290), leptospirosis (Chapter 298), histoplasmosis (Chapter 308), tuberculosis (Chapter 299), and DNA viruses, such as cytomegalovirus (Chapter 347), Epstein-Barr virus (Chapter 348), and severe acute respiratory syndrome coronavirus-2[4] (Chapter 336), are well-recognized causes of acute interstitial nephritis. Anti–tubular basement membrane disease is a rare cause of autoimmune interstitial nephritis.

Although sarcoidosis or the tubulointerstitial nephritis and uveitis syndrome can manifest as acute interstitial nephritis, they often quickly evolve into chronic disease. Initially described in the MesoAmerican region, a new entity named chronic interstitial nephritis in agricultural communities (CINAC) has become an epidemic in many parts of the world. Initially thought to be due to episodic heat-related volume depletion, evidence now suggests that pesticide exposure may be causative factor.[5]

All forms of injury to the kidney, regardless of origin, progress to end-stage renal disease through a terminal phase of chronic interstitial nephritis. A wide variety of kidney diseases, such as the glomerulonephritides (Chapter 107), cystic diseases (Chapter 112), and diabetes (Chapter 210), will start slowly in the tubulointerstitium and often go unrecognized until late in the course, when biopsy shows chronic interstitial nephritis.

Primary chronic interstitial nephritis can be caused by a variety of toxic, metabolic, hematologic, obstructive, and infectious processes (Table 108-2). Chronic ingestion of six or more tablets per day of acetaminophen, aspirin, and NSAIDs, in combination for at least 3 years, can also put patients at risk for analgesic nephropathy. Light chains can cause tubular injury in patients with multiple myeloma (Chapter 173). More recently, immune checkpoint inhibitors frequently have been associated with acute interstitial nephritis that may progress to severe acute kidney injury.[6,7]

TABLE 108-1 CAUSES OF ACUTE INTERSTITIAL NEPHRITIS

DRUGS

Antibiotics
- Penicillins
- Rifampin, ethambutol
- Sulfa
- Vancomycin
- Cephalosporins
- Erythromycin
- Fluroquinolones
- Trimethoprim-sulfamethoxazole
- Acyclovir

Nonsteroidal Anti-Inflammatory Drugs
- Selective and nonselective
- Cyclooxygenase-2 inhibitors

Diuretics
- Thiazides
- Furosemide
- Triamterene

Miscellaneous
- Captopril
- Ranitidine
- Proton pump inhibitors
- Phenobarbital
- Phenytoin
- Sodium valproate
- Carbamazepine
- Allopurinol
- Interferon
- Interleukin-2
- All-*trans*-retinoic acid
- Immune checkpoint inhibitors
- Nucleotide polymerase inhibitors
- Tyrosine kinase inhibitors

INFECTIONS

Bacteria
- *Legionella*
- *Brucella*
- *Diphtheria*
- *Streptococcus*
- *Staphylococcus*
- *Yersinia*
- *Salmonella*
- *Escherichia coli*
- *Campylobacter*

Viruses
- Epstein-Barr virus
- Cytomegalovirus
- Hantavirus
- Herpes simplex virus
- Hepatitis B virus
- Severe acute respiratory syndrome coronavirus-2

Other
- *Mycoplasma*
- *Rickettsia*
- *Leptospira*
- *Mycobacterium tuberculosis*
- *Schistosoma mekongi*
- *Toxoplasma*
- *Chlamydia*

AUTOIMMUNE DISEASES

Anti–tubular basement membrane disease
Tubulointerstitial nephritis and uveitis (TINU) syndrome
Kawasaki disease

PATHOBIOLOGY

Pathophysiology

Regardless of the origin of renal inflammation, the kidneys do not irreversibly fail until fibrosis and tubular atrophy develop. Chronic interstitial nephritis is the pathologic equivalent of clinical progression because it is the final common pathway to permanent tissue damage. The degree of reduction in the glomerular filtration rate correlates with the degree of interstitial injury. Urinary flow is impeded by

ABSTRACT

Interstitial nephritis is the final common pathway to chronic renal failure. Interstitial lesions may be a primary kidney lesion or secondary to many forms of glomerulonephritis, hypertension, or diabetes. Acute interstitial nephritis is seen following use of pharmaceutical drugs, infections, or idiopathic autoimmune diseases. Kidney biopsy may be useful in assessing cause and extent of damage. Treatment of early disease depends on removal of inciting factors, and in the absence of improvement, use of short courses of immunosuppressive drugs.

KEYWORDS

interstitial nephritis
renal tubular acidosis
kidney biopsy
pharmaceutical drugs
immunosuppression

TABLE 108-2 CAUSES OF CHRONIC INTERSTITIAL NEPHRITIS

HEREDITARY DISEASES
Mitochondrial mutations
Karyomegalic nephritis
Autosomal dominant tubular interstitial kidney disease
METABOLIC DISTURBANCES
Hypercalcemia, nephrocalcinosis
Hyperoxaluria
Hypokalemia
Hyperuricemia
Cystinosis
Methylmalonic acidemia
DRUGS AND TOXINS
Analgesics
Cadmium
Lead
Health food botanicals, herbs
Lithium
Cyclosporine, tacrolimus
Cisplatin, methotrexate
Nitrosoureas
Pesticides
AUTOIMMUNE DISEASES
Renal allograft rejection
Granulomatosis with polyangiitis
Immunoglobulin G4–related tubulointerstitial nephropathy
Sjögren syndrome
Systemic lupus erythematosus, vasculitis
Tubulointerstitial nephritis and uveitis (TINU) syndrome
Sarcoidosis
HEMATOLOGIC DISTURBANCES
Multiple myeloma, light chains
Lymphoma
Sickle cell disease
INFECTIONS
Complicated pyelonephritis
Human immunodeficiency virus (HIV)
Epstein-Barr virus
Malakoplakia
Xanthogranulomatous pyelonephritis
OBSTRUCTIVE NEPHROPATHY
Tumors
Stones
Outlet obstruction
Vesicoureteral reflux
MISCELLANEOUS
Age-related vascular disease
Hypertension
Ischemia
Balkan (endemic) nephropathy
Radiation nephritis
Oxalate nephropathy
Cholesterol emboli

tubular obstruction. Increased vascular resistance causes progressive tubular injury and fibrosis. A net reduction in the cross-sectional area of peritubular vessels increases postglomerular resistance to the extent that the compensatory increase in glomerular hydrostatic pressure cannot fully restore filtration to normal levels. Tubuloglomerular feedback assumes increasing importance in the transition from acute to chronic glomerulonephritis when autoregulation of renal blood flow is disrupted by tubulointerstitial fibrosis. Loss of autoregulation by tubuloglomerular feedback results from the absence or insensitivity of the afferent arteriole. Perhaps more significant is the effect of interstitial pressure on the sensitivity of the feedback mechanism. Tubular atrophy may disrupt the normal renal osmotic gradient by decreasing sodium chloride transport along the proximal tubule or thick ascending loop of Henle. The result is poor abstraction of water from the filtrate, with hyposthenuria and polyuria. Such an increase in solute and water within the tubular fluid results in adaptive downregulation of the glomerular filtration process.

Patients with Fanconi syndrome exhibit proximal tubular epithelium alterations that variably impair transporter function in the area of injury. These tubular defects are classically and occasionally seen in light-chain myeloma, cystinosis, Lowe syndrome, and the tubulointerstitial nephritis and uveitis syndrome, as well as after exposure to selected drugs, such as tenofovir or ifosfamide.

The antigen targets engaging the inflammasome and the immune system in interstitial nephritis are slowly unfolding. Drugs act as haptens, mimic endogenous structures in the interstitium, alter regulation of the immune system, or function in some combination of the foregoing. Bacteria, fungi, and viruses can infect the kidney and cause mononuclear cell infiltration or activate toll-like receptors on tubular epithelia, which subsequently educate the adaptive immune response to events in the interstitium. Renal-specific autoimmune diseases such as anti–tubular basement membrane disease or spontaneous interstitial nephritis remain confined to the kidney, whereas systemic diseases spread to the kidney, where they cause persistent chronic interstitial nephritis.

Although the adaptive immune response is similar to that of other tissues, T-cell activation figures prominently in interstitial nephritis. Antibodies (e.g., anti–tubular basement membrane disease) and/or immune complex deposition along the tubular basement membrane (e.g., systemic lupus erythematosus) are rarely seen. Antigens presented by class II major histocompatibility complex molecules on macrophages, dendritic cells, and adjacent tubular epithelia, in conjunction with associative recognition molecules, engage the CD4/CD8 T-cell repertoires. The resultant cytokine and protease activity injures tubular nephrons and basement membranes and causes fibroblasts to form locally by epithelial-mesenchymal transition and to proliferate. Transforming growth factor-β (TGF-β), fibroblast growth factor 2, and platelet-derived growth factor are particularly active in this transition. If the nephritis persists, fibrogenesis dismantles nephrons and causes tubular atrophy; in late stages, the inflammatory reaction outgrows its survival factors and lymphocytes, and fibroblasts disappear by apoptosis and leave an acellular fibrotic scar.

Rarely, patients may have autosomal dominant tubulointerstitial kidney disease (Chapter 112)[8,9] caused by mutations in various genes, including uromodulin (*UMOD*), hepatocyte nuclear factor-1β (*HNF1B*), renin (*REN*), and mucin-1 (*MUC1*). Viruses, including Epstein-Barr virus, have been long suspected of contributing to idiopathic chronic interstitial nephritis. Malakoplakia and xanthogranulomatous pyelonephritis are probably not defects in nephrogenesis but rather are destructive responses to bacterial inflammation in the interstitium. Focal abnormalities in kidney structure can be a nidus for infections associated with perinephric, psoas, or peritoneal abscesses. Children with vesicoureteral reflux (Chapter 113) can have chronic or repeating episodes of pyelonephritis, but whether the reflux or the infection is more important to progression to renal failure is unclear. There is also no agreement on whether recurrent pyelonephritis by itself produces chronic interstitial nephritis in adults.

Pathology

Both kidneys are typically involved, except in cases of unilateral infection, obstruction, or trauma. The inflammatory reaction in acute interstitial nephritis consists mainly of T lymphocytes and monocytes, but neutrophils, plasma cells, and eosinophils can be present. The T cells are of a mixed phenotype with a distinct preference for $CD4^+$ lymphocytes. The infiltrative process is associated with interstitial edema, which displaces tubules away from one another and causes the kidneys to swell. The tubular basement membrane may be disrupted in more severe cases, but immune deposits are rarely found by immunofluorescence. In patients on anti-programmed cell death protein-1 (PD-1) and anti-programmed death ligand-1 (PD-L1) therapy, immunohistochemistry may show positive PD-1 or PD-L1 staining in patients with acute interstitial nephritis from these therapies.[10]

On gross inspection, the kidney in chronic interstitial nephritis has an irregular contour or contracted appearance. Pathologically, the tubular epithelia sit on thickened or disrupted tubular basement membranes and are often effaced against dilated lumens; the tubules eventually dismantle and atrophy. *Chronic* is a relative term, because fibrotic changes can be seen within 7 to 10 days of continuing inflammation. In primary interstitial nephritis, the glomerular compartment eventually succumbs to the ongoing fibrotic process; normal glomeruli are surrounded by periglomerular fibrosis and subsequently undergo segmental or global sclerosis. Chronic vascular thickening and glomerular changes are present in advanced stages of disease, so pathologic determination of the primary cause may be difficult in some biopsy samples. Progressive glomerular

TABLE 108-3 TYPICAL CLINICAL MANIFESTATIONS OF ACUTE INTERSTITIAL NEPHRITIS

History of drug hypersensitivity or recent infection and taking antibiotics
Sudden onset of fever lasting several days to weeks
Variable degrees of hypertension
Rise in creatinine with FE_{Na} > 1.0; no expected acute tubular necrosis or glomerulonephritis
Kidney size normal or increased
Hematuria with mild proteinuria (<1.0 g)
Presence of WBC casts and WBCs on urinalysis; rarely eosinophils

FE_{Na} = fractional excretion of sodium; WBC = white blood cell.

sclerosis also occurs with aging and must be factored in when interpreting the biopsy findings.

A third pathologic category, granuloma formation, can be seen in either acute or chronic interstitial nephritis. In acute granulomatous interstitial nephritis, granulomas are sparse and non-necrotic and giant cells are rare. In chronic interstitial nephritis, granulomas contain an abundance of giant cells, and those caused by tuberculosis may become necrotic. Drugs are a common cause of this lesion in the acute setting, and most of the drugs associated with acute interstitial nephritis have been reported to cause granuloma formation. When numerous granulomas are present in the absence of drug exposure, sarcoidosis (Chapter 83), granulomatosis with polyangiitis (Chapter 249), histoplasmosis (Chapter 308), or tuberculosis (Chapter 299) should be considered, depending on the context. The kidney granulomas seen in granulomatosis with polyangiitis are almost always accompanied by glomerular and vascular pathology.

ACUTE INTERSTITIAL NEPHRITIS

CLINICAL MANIFESTATIONS

Most patients present with an asymptomatic rise in the serum creatinine level or an abnormal urinalysis, and it is important to consider acute interstitial nephritis in any patient with an unexplained precipitous diminution in kidney function.[11] Because kidney injury is often asymptomatic, patients already may have substantial kidney dysfunction on initial presentation. Patients also may present with nonspecific symptoms such as lethargy or weakness, and some patients may have fever. Oliguria may be present in patients who have severe acute kidney injury (Chapter 106).

Several features can distinguish acute interstitial nephritis from acute tubular necrosis (Chapter 106) or glomerulonephritis (Chapter 107; Table 108-3).[12] Fever and occasional flank pain, owing to acute distention of the kidney capsule, may occur in infection or with drug-induced acute interstitial nephritis. Allergic reactions can be associated with maculopapular rash, fever, and eosinophilia, but this triad is seen in less than 33% of all patients with acute interstitial nephritis; this triad is more common in antibiotic-related acute interstitial nephritis and is rarely seen when NSAIDs are the cause. These signs and symptoms of drug reaction have been codified and referred to as the DRESS syndrome (*d*rug *r*ash, *e*osinophilia, and *s*ystemic *s*ymptoms; Chapter 407), which is associated with interstitial nephritis in up to 40% of patients with persistent exposure to selected drugs.

The course of kidney failure in acute interstitial nephritis progresses over several days to weeks and follows the kinetics of the primary immune response. However, kidney failure can be precipitous, especially in patients re-exposed to a previous agent. Rarely, the course can be protracted, with the glomerular filtration rate declining over a period of months if the diagnosis is not recognized.

The onset of drug-induced nephritis ranges from days to weeks after the initiation of therapy, depending on previous drug exposure history. The classic setting for a drug reaction is a febrile patient with an infectious process and who defervesces while taking antibiotics but then develops recurrent fever several days later.

DIAGNOSIS

A careful history often points to the diagnosis (see Table 108-1). Urinalysis is particularly helpful. Mild-to-moderate proteinuria and hematuria are seen in most cases. The sediment typically shows red and white blood cells, as well as white blood cell casts. However, a bland urine sediment does not exclude the diagnosis of acute interstitial nephritis. A red blood cell cast (see Fig. 100-8) suggests a glomerular diagnosis. The finding of eosinophils in the urine supports the diagnosis of allergic interstitial nephritis, but the positive predictive value is low, even with more than 5% eosinophils in the urine, and the absence of eosinophiluria does not exclude the diagnosis of acute interstitial nephritis.

TABLE 108-4 WHEN TO CONSIDER A RENAL BIOPSY TO DIAGNOSE ACUTE INTERSTITIAL NEPHRITIS

The setting, history, or clinical findings do not support a diagnosis of acute tubular necrosis or volume depletion
The clinical setting warrants a tissue diagnosis to determine the type of lesion, the extent of involvement, or the degree of fibrosis
The patient is stable enough to undergo biopsy and receive immunosuppressive drugs
The physician believes that the choice of therapy or the length of treatment is partially determined by the type of tissue injury

An elevated serum creatinine level is usually the first abnormal laboratory result in interstitial nephritis. The normal serum creatinine of 0.6 to 1.3 mg/dL varies with muscle mass, age, and gender. Early recognition of acute interstitial nephritis requires a high degree of clinical suspicion because the serum creatinine level may be only mildly elevated even after the kidneys lose half their function.

Given the lack of glomerular involvement in acute interstitial nephritis, the degree of proteinuria is nearly always less than 3 g per 24 hours and is more typically less than 1 g per 24 hours. Nephrotic-range proteinuria is not seen except in the presence of a coexisting glomerular lesion, such as a concurrent minimal-change lesion, which can be seen in NSAID-induced interstitial nephritis. Many patients with acute interstitial nephritis also have a fractional excretion of sodium (FE_{Na}) greater than 1 and occasionally are oliguric.

Imaging is of little diagnostic value. The kidney in acute interstitial nephritis is usually normal or slightly increased in size on echographic or tomographic images. Increased cortical echogenicity may correlate with diffuse interstitial infiltrates on renal biopsy.

Differential Diagnosis

It is sometimes difficult to distinguish among nonoliguric acute tubular necrosis, acute interstitial nephritis, and glomerulonephritis without a biopsy.[13] Exposure to pharmaceuticals is responsible for most cases of acute interstitial nephritis, followed by infections and autoimmune disease. Selective tubular defects and tubular syndromes, such as proximal acquired Fanconi syndrome or distal renal tubular acidosis, can be seen in subacute or chronic interstitial nephritis but are unusual in acute interstitial nephritis.

Biopsy

Ultimately, the diagnosis can be established with certainty only by renal biopsy, which confirms and assesses the extent of acute interstitial inflammation. A biopsy should be performed in patients who have acute kidney failure, who have suggestive signs or symptoms of an interstitial process, and in whom prerenal azotemia and obvious acute tubular necrosis cannot be excluded on clinical grounds (Table 108-4). In primary acute interstitial nephritis, the biopsy demonstrates inflammatory cells that typically spare the glomeruli until late in the course (Fig. 108-1A). Lesions that reduce kidney function are usually diffuse, but drug-induced interstitial injury is often patchy and commonly begins deep in the cortex, closer to the corticomedullary junction, before spreading.

TREATMENT

The principal intervention for acute interstitial nephritis is to remove the inciting drug or treat the underlying cause, whether it be infectious or autoimmune.[14] In observational series, patients treated with steroids seem to do somewhat better, so a trial of prednisone (starting at 0.75 to 1.0 mg/kg/day orally) can be given daily for approximately 1 week, and the response can be assessed clinically. In patients whose autoimmune disease does not respond to steroids or who develop steroid toxicity, another immunosuppressive agent such as mycophenolate mofetil, azathioprine, or cyclophosphamide can be tried under expert guidance. These agents also can be used as steroid-sparing agents if long-term therapy is needed. High-dose immunosuppression should not be continued without some evidence of benefit because immunosuppressive drugs in patients with azotemia can lead to serious infection and even death. In such cases, these drugs can be reserved to use with kidney transplantation (Chapter 117) if the primary disease does not respond.

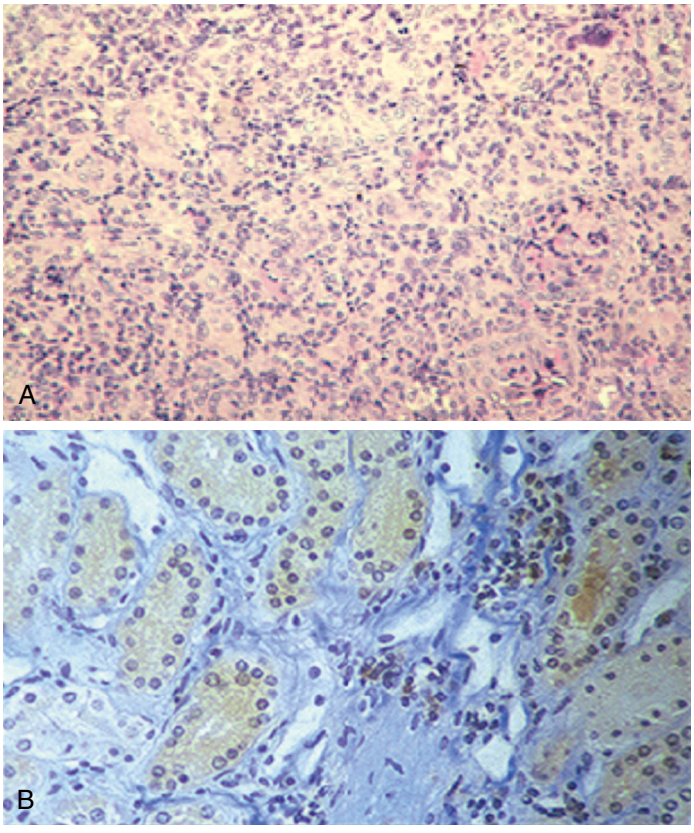

FIGURE 108-1. Interstitial nephritis on biopsy. A, Acute interstitial nephritis can be most aggressive when the interstitium is crowded with mononuclear cells and giant cells that destroy nearly all tubular nephrons (hematoxylin and eosin). **B,** Chronic interstitial nephritis is a slower process, with substantial collagen deposition (*blue color;* trichrome), tubular dropout, and fibroblasts in the interstitial spaces widened by fibrosis.

PROGNOSIS

The prognosis for acute interstitial nephritis is good if it is recognized early in the setting of minimal fibrosis.[15] Early removal of offending agents or prompt treatment of the underlying disorder when appropriate is essential. However, acute kidney tubular injury can be a catalyst for the development of chronic kidney disease.[16]

CHRONIC INTERSTITIAL NEPHRITIS

CLINICAL MANIFESTATIONS

Patients with primary chronic interstitial nephritis typically have elevated serum creatinine levels and signs and symptoms of kidney failure, including hematuria, isosthenuria or hyposthenuria, nocturia, fatigue, and nausea. Before the glomerular filtration rate falls below 25 to 30 mL/min, tubular acidosis is common. Anemia is often out of proportion to the degree of renal failure, and many patients have hypertension but only minimal edema until they develop advanced stages of kidney failure. Acquired Fanconi syndrome can be seen in patients with a serum creatinine level less than 2.5 mg/dL in the setting of drug exposure, myeloma, human immunodeficiency virus (HIV) infection, lead exposure, and herbal nephropathy.

DIAGNOSIS

A careful history including drug or toxin exposure, kidney imaging, and laboratory findings can often point to a probable diagnosis (see Table 108-2). As for any patient with evidence of kidney failure, the evaluation includes laboratory tests to determine possible causes and severity. These tests include measures of renal function (serum creatinine level and blood urea nitrogen level), as well as levels of serum electrolytes, calcium, phosphate, uric acid, and albumin. Urinalysis typically shows a fixed specific gravity of approximately 1.010, occasional glycosuria, and proteinuria (often <1 g/L); and red cells, white cells, and granular casts may be seen. Depending on the clinical situation, the search for specific causes may include serum and urine protein electrophoresis, blood and urine cultures, serologic tests for autoimmune diseases (e.g., cryoglobulin level, antinuclear antibodies, anti–neutrophil cytoplasmic antibody, and anti–glomerular basement membrane antibody levels [see Table 236-3]), or viral infection, particularly after renal transplantation (Chapter 117).

Selective tubular defects and tubular syndromes, such as proximal acquired Fanconi syndrome (bicarbonaturia with a plasma carbon dioxide [CO_2] content <20 mEq/L, aminoaciduria, phosphate wasting, uricosuria, and glycosuria) or distal renal tubular acidosis type 1 (urine pH >5.6, plasma CO_2 content <20 mEq/L, with low or high potassium) can be seen occasionally in subacute or chronic interstitial nephritis. Patients with Fanconi syndrome quickly develop an alkaline urine (pH >7.5) and increased fractional excretion of urine bicarbonate when the serum bicarbonate is elevated above 20 mEq/L by intravenous infusion.

Ultrasound images may show increased echogenicity and/or atrophic kidneys. Classic images of analgesic nephropathy on tomography are quite specific (Fig. 108-2) and show a decrease in overall kidney size, with atrophic scars and an irregular cortical contour, sometimes accompanied by papillary necrosis.

On biopsy (see Table 108-4), chronic interstitial nephritis is manifest by a cellular infiltrate that is eventually replaced by tubulointerstitial fibrosis (see Fig. 108-1B). Infiltrates of lymphocytes and rare neutrophils are scattered and less abundant than in acute interstitial nephritis. Genetic testing may detect a genetic tubulopathy (Chapters 108 and 113) in a substantial minority of patients.[17]

Specific Causes

Analgesics

Aspirin, acetaminophen, and NSAIDs in combination are a source of toxic metabolites and can induce medullary ischemia and papillary necrosis, sometimes with papillary calcification.[18] Uroepithelial malignancies also occur with increased frequency in this group of patients.

Aristolochic Acid Nephropathy

Aristolochic acid has been implicated as a cause of Balkan nephropathy and so-called Chinese herbal nephropathy. A growing number of people are taking vitamins and herbal preparations purchased from health food stores (Chapter 30), and some of these remedies contain botanicals that produce chronic interstitial nephritis. Patients who are dieting often use these remedies and are first seen when they already have late-stage disease, which increases the risk for uroepithelial malignancies (Chapter 182).

Human Immunodeficiency Virus Tubulointerstitial Nephropathy

Predominate tubulointerstitial nephropathy accounts for about 25% of the renal lesions seen on biopsy in HIV-infected patients (Chapter 359).[19] Biopsies show two general forms: a tubulopathy or an interstitial nephritis. In the tubulopathy, damage is to the proximal tubule. About 80% of cases are associated with drug exposure, particularly tenofovir (Chapter 357), but poorly controlled HIV is an even more important risk factor. Approximately 30% of patients improve with time. Patients in the tubulointerstitial nephritis group have a mononuclear infiltration and more persistent viral loads, but 50 to 60% recover.

Tubulointerstitial Nephritis with Uveitis Syndrome

Seen at any age but more commonly in young women and children, this syndrome may be idiopathic, genetic, or in response to pharmaceutical exposure.[20] Unilateral or bilateral anterior panuveitis (Chapter 391) may precede or follow evidence of interstitial nephritis that starts acutely but may persist as chronic kidney injury. If the renal function is not greatly impaired, concomitant Fanconi syndrome may suggest proximal tubular involvement.

Vascular Disease

Chronic renal ischemia from vascular injury can lead to interstitial nephritis, nephrosclerosis, and fibrosis, which are the classic renal lesions of untreated essential hypertension (Chapter 64). Similar injury is seen with aging, diabetes (Chapter 109), sickle cell disease (Chapter 149), and radiation nephritis (Chapter 18). This interstitial injury from vascular diseases is quite different from the aggressive necrosis seen with acute vasculitis. In patients who are taking calcineurin inhibitors such as cyclosporine or tacrolimus, renal ischemia from vasoconstriction can cause interstitial fibrosis that is sometimes difficult to distinguish from chronic allograft rejection (Chapter 117).

Immunoglobulin G4–Related Interstitial Nephritis

Immunoglobulin G4 (IgG4)-related interstitial nephritis is a systemic syndrome that presents in the kidney as inflammatory masses associated with

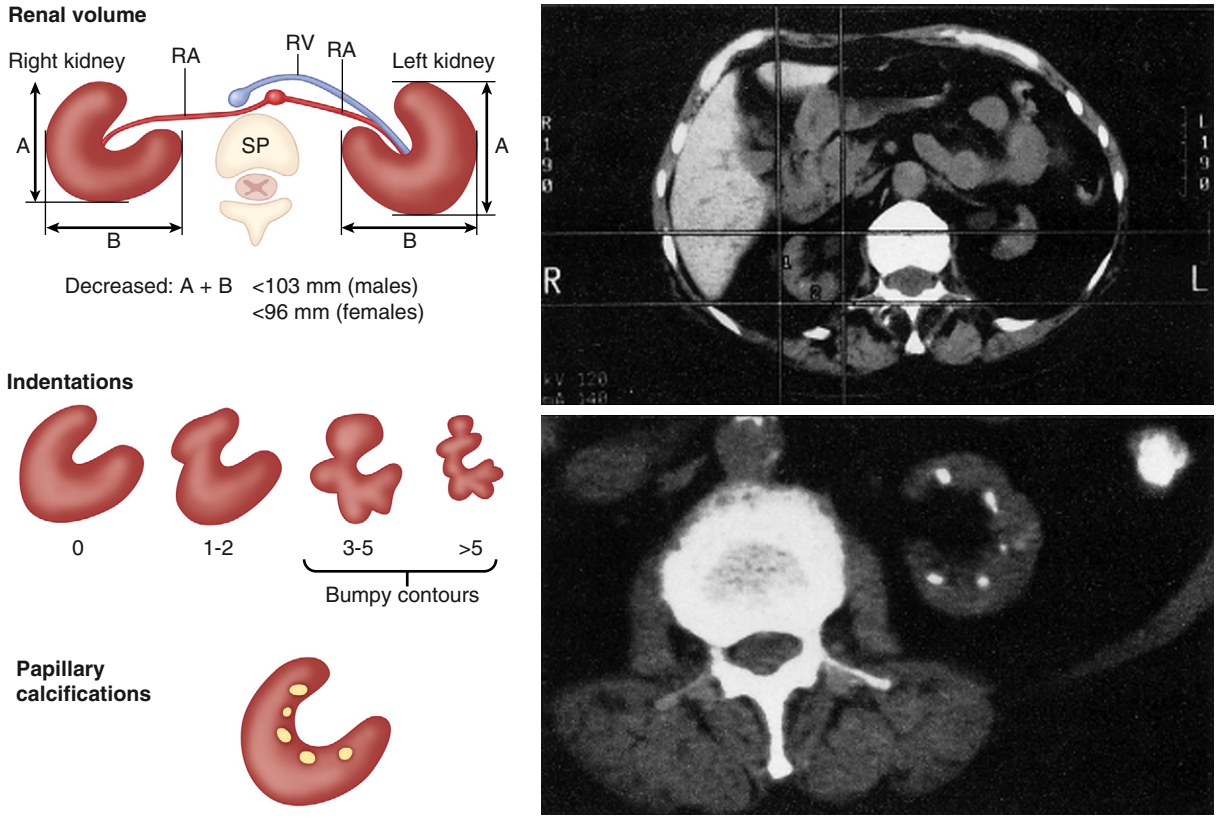

FIGURE 108-2. Renal changes in analgesic nephropathy seen by tomographic imaging. Structural changes, including reduced volume, nodularity, and calcifications, are seen on computed tomography. RA = right artery; RV = right vein; SP = spinal vertebra. (From Elseviers MM, De Schepper A, Corthouts R, et al. High diagnostic performance of CT scan for analgesic nephropathy in patients with incipient to severe renal failure. *Kidney Int*. 1995;48:1316.)

plasma cells, interstitial mononuclear cell infiltrates, and storiform fibrosis. Patients may have lesions in other organs, such as the liver, pancreas, parotids, thyroid, and myocardium.[21] Eosinophilia and low complement levels can be seen. Serum IgG4 levels and tissue plasma cells are increased, but it is not clear whether the IgG4 antibodies are a biomarker or causative. IgG4 is also separately associated with membranous nephropathy (Chapter 107) and nephrotic-range proteinuria.

Obstruction

Significant urinary obstruction, regardless of its etiology, is an important cause of chronic interstitial nephritis. Complete or partial urinary tract obstruction is accompanied by a decline in glomerular filtration and classic tubular abnormalities, including diminished reabsorption of solutes, impaired excretion of H^+ and K^+, and a vasopressin-resistant concentrating defect in the medulla. Obstruction is associated with a fall in the glomerular filtration rate because of reduced plasma flow and hydraulic pressure associated with the release of angiotensin II, leukotrienes, and nitric oxide, a process leading to mononuclear cell infiltration. Growth factors such as TGF-β, which is released by infiltrating cells, may contribute to the interstitial and glomerular fibrosis. Obstruction is more common in men than in women and is part of the routine assessment of kidney failure by kidney ultrasound (Chapters 106 and 114). Almost all obstructed kidneys eventually become infected if the obstruction is not relieved.

Hypercalcemia

Hypercalcemia can decrease glomerular filtration via renal vasoconstriction, a decrease in the glomerular ultrafiltration coefficient, and volume depletion as a result of a vasopressin-resistant concentrating defect associated with nephrocalcinosis and calcium deposition around the basement membranes of the distal tubules and collecting ducts. Such deposition secondarily leads to mononuclear cell infiltration and tubular death. Nephrocalcinosis also occurs in normocalcemic disorders of augmented calcium absorption through the gut (e.g., sarcoidosis [Chapter 83], vitamin D intoxication [Chapter 227]), skeletal breakdown (neoplasms or multiple myeloma [Chapter 173]), or classic distal renal tubular acidosis (Chapter 104).

Myeloma

The chronic kidney disease of multiple myeloma (Chapter 173) is caused by several mechanisms, including cast nephropathy ("myeloma kidney"), coexistent volume depletion, hypercalcemia (Chapter 227), nephrocalcinosis (Chapter 227), and uric acid nephropathy.[22] Proteinaceous casts form in dilated, atrophic distal nephron segments that are surrounded by multinucleated giant cells in interstitial infiltrates. The casts typically contain both Tamm-Horsfall protein and a pathologic light chain. Interstitial plasma cells and mononuclear infiltrates, calcifications in the interstitium, and amyloid deposits in the vessels and glomeruli are often present. Light chains are nephrotoxic by directly damaging tubular cells or by intrarenal obstruction because of the formation of casts. In the setting of excess production of light chains, the reabsorptive capacity of proximal tubule is overwhelmed, thereby leading to their urinary excretion as Bence Jones proteins. Proximal tubular damage may also lead to Fanconi syndrome.

Lead Toxicity

Epidemiologic analyses support the association between an excess burden of lead (Chapter 20) and chronic kidney disease. Blood lead levels reflect only recent, not chronic, exposure and can be normal in patients who have a significant burden of lead. Lead preferentially deposits in the proximal tubule, and nuclear inclusions within proximal tubular cells are characteristic of lead nephropathy. Ingestion of moonshine liquor, with its high lead content, as well as certain occupations, such as lead smeltering, can be an important historical clue to the diagnosis.

In adults, lead nephropathy produces chronic interstitial nephritis, fibrosis, and nephrosclerosis. Proximal tubular dysfunction may produce isolated tubule defects or a full Fanconi syndrome. Patients often have recurrent gout with gouty tophi, hyperuricemia, hypertension, and anemia. Some laboratories can measure δ-aminolevulinic acid dehydratase, which is inhibited by lead. Although chelation studies may document body lead burden, this test is difficult to perform in patients who have renal failure. X-ray fluorescent measurements of in vivo skeletal lead stores correlate well with ethylenediaminetetraacetic acid (EDTA) chelation tests and have the advantage of being rapid and noninvasive.

Cadmium Toxicity

Cadmium nephropathy (Chapter 20) is seen in regions where contamination from smelters results in prolonged low-level exposure. Cadmium is bound to metallothionein, and proximal tubular cells take up these complexes. The

liver and kidney are the two major organs in which cadmium accumulates. Cadmium's half-life in the body is longer than 10 years. As with blood levels of lead, blood levels of cadmium fall after acute exposure because of extensive tissue deposition. Once a threshold of kidney deposition is exceeded, excess cadmium is excreted in urine. Cadmium intoxication produces irreversible proximal tubular dysfunction, hypercalciuria, nephrolithiasis, and metabolic bone disease with pain (called "ouch-ouch" disease in Japan).

Oxalate Nephropathy

Oxalate nephropathy results from the deposition of calcium oxalate in the tubular interstitium, thereby leading to mild secondary inflammation and tubular atrophy and fibrosis. Although oxalate nephropathy can occur in patients who have primary inborn errors of glycolate metabolism that lead to overproduction of oxalate (Chapter 189), more commonly it occurs in patients who have secondary causes of increased oxalate excretion (e.g., patients with roux-en-y gastric bypass, inflammatory bowel disease, or short bowel syndrome) because of increased intestinal availability and permeability of oxalate or decreased degradation of oxalate. Diagnosis requires a high index of suspicion. A 24-hour urine collection to measure oxalate excretion can help, but ultimately a kidney biopsy is needed to make the diagnosis.[2,3]

Autosomal Dominant Tubular Interstitial Diseases

Autosomal dominant tubular interstitial diseases are a rare group of inherited syndromes that lead to progressive chronic kidney disease and eventually lead to kidney failure (Chapter 112). The several subtypes of autosomal dominant tubular interstitial disease have an autosomal dominant inheritance pattern, present in late childhood or early adulthood, and are slowly progressive. Some patients may have early-onset gout. Kidney imaging may show small medullary cysts. Kidney biopsy will usually show nonspecific findings. A provisional diagnosis can made by obtaining a thorough family history in the appropriate clinical context. Genetic testing for mutations in uromodulin (*UMOD*) will confirm the clinical diagnosis in the majority of patients, whereas other patients will have mutations in renin (*REN*), hepatocyte nuclear factor-1β (*HNF1B*), or Mucin-1 (*MUC1*).

TREATMENT

Inciting factors such as obstruction, infection, drugs, or toxins should be removed whenever possible. Chronic interstitial fibrosis rarely responds to aggressive treatment. However, in immunoglobulin G4–related interstitial nephritis, the renal lesions in many patients respond briskly to corticosteroid treatment. In addition, treatment of tubulointerstitial nephritis with uveitis syndrome is with varying doses of methylprednisolone followed by oral prednisone under expert guidance may be beneficial in some patients. Varying durations of supplemental or steroid-sparing immunosuppression with mycophenolate mofetil or cyclophosphamide also have been used. Immunosuppression may also be helpful in sarcoidosis (Chapter 83).

Otherwise, the treatment is like that of other causes of chronic kidney disease. Angiotensin-converting enzyme inhibitors or angiotensin II receptor blockers (Table 64-7) are used early to slow disease progression, with a systolic blood pressure goal of 120/80 mm Hg (Chapters 64 and 117). Sodium glucose cotransporter-2 inhibitors (see Table 210-6) may be indicated in patients who have a glomerular filtration rate <75 mL/min (but not <45 mL/min for empagliflozin or <25 mL/min for dapagliflozin except in special circumstances under expert supervision) and an albumin to creatinine ratio >200 mg/g to slow the progression of kidney disease. Early treatment of acidosis with sodium bicarbonate (starting at 650 mg twice daily) is important to reach a goal bicarbonate level of 23 mEq/L. Other treatment goals include treatment of symptomatic anemia with erythropoiesis-stimulating agents to maintain a hemoglobin concentration between 10 and 11 g/L, treatment of hyperphosphatemia with oral phosphate binders, and hyperparathyroidism with activated vitamin D analogues (Chapters 116 and 117).

For certain specific causes of chronic interstitial nephritis, specific therapeutic approaches are warranted. For analgesic nephropathy, stopping analgesic use can help reduce progression. For hypercalcemia (Chapter 227), therapy is directed toward the primary disease—reduction of the serum calcium concentration, when appropriate, and correction of acid-base disturbances.

Appropriate therapy for presumed cast nephropathy in multiple myeloma includes chemotherapy to ameliorate excess production of light chains (Chapter 173), treatment of hypercalcemia (Chapter 227), alkalinization of the urine with the addition of bicarbonate to hypotonic fluids, and avoidance of radiocontrast agents, which may enhance the nephrotoxicity of light chains. Loop diuretics should be used with caution, particularly in the setting of volume depletion.

EDTA is advocated as chelation therapy for lead toxicity (Chapter 20). The goal of chelation is to normalize the EDTA mobilization test. In occasional patients, this treatment may arrest or reverse the progression of the kidney failure.

PROGNOSIS

Chronic interstitial nephritis tends to progress slowly. However, the prognosis is highly variable and depends on the underlying condition, the degree of fibrosis, the presence of glomerulosclerosis on kidney biopsy, and the patients' comorbid conditions, including cardiovascular disease and diabetes mellitus.

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109 DIABETES AND THE KIDNEY

RAYMOND C. HARRIS

EPIDEMIOLOGY

In the industrialized world, diabetes mellitus is the single leading cause of end-stage renal disease (ESRD). Despite the improved care of patients with diabetes, both the incidence and prevalence of ESRD secondary to diabetes continue to rise. In the United States, almost 50% of patients undergoing either dialytic therapy or renal transplantation have ESRD as a result of diabetic nephropathy, and more than 40% of the new (incident) cases of ESRD are attributable to diabetes. Currently, more than 200,000 U.S. patients receive ESRD care as a result of diabetic nephropathy.

In the United States, Europe, and Japan, more than 90% of patients with diabetes have type 2 rather than insulinopenic type 1 diabetes (Chapter 210). In patients with type 1 and type 2 diabetes, the incidence rate of renal disease is equivalent when patients are monitored for an extended period of time, and more than 80% of the ESRD secondary to diabetes in the United States is seen in patients with type 2 diabetes. The demographics of ESRD secondary to type 2 diabetes mirror the prevalence of type 2 diabetes in the U.S. population, with a higher incidence in females and in Black Americans, Hispanic Americans, Native Americans, and Asian Americans, with a peak incidence in the fifth to seventh decades. Much of the increased mortality in both type 1 and type 2 diabetes is associated with the prevalence of nephropathy.

Given the global epidemic of obesity, the incidence of diabetic nephropathy is increasing worldwide.[1,2] Smoking, hypertension, and elevated blood cholesterol levels may be predisposing factors for the development of diabetic nephropathy in patients with type 2 diabetes.

PATHOBIOLOGY

Hyperglycemia

The metabolic sequelae of hyperglycemia appear to be the most important causative factor in the development of diabetic nephropathy.[3] Hyperglycemia leads to increased generation of reactive oxygen species; depletion of the reduced form of nicotinamide dinucleotide (phosphate); activation of the polyol pathway, which can lead to de novo synthesis of diacylglycerol and increased protein kinase C activity; alterations in the hexosamine pathway; and nonenzymatic protein glycation (advanced glycosylation end products). All of these pathways have been implicated in the development of diabetic nephropathy, and better glucose control generally reduces the risk of nephropathy and other microvascular diabetic complications.[4] For example, patients who have glucokinase mutations, which are associated with milder hyperglycemia (average hemoglobin A_{1c} [HbA_{1c}] levels 6.9%), have far less proteinuria, microalbuminuria, or nephropathy than patients who have long-standing type 2 diabetes with HbA_{1c} levels averaging 7.8%. Furthermore, randomized interventional studies clearly demonstrate that relatively better control of blood sugar decreases the development of nephropathy in type 1 diabetes, and observational studies with repeat renal biopsies show that the renal lesions of diabetic nephropathy may reverse after long-term functioning pancreas transplantation.

Hemodynamics

Patients with type 1 and, to a lesser extent, type 2 diabetes exhibit an increased glomerular filtration rate (GFR), so-called hyperfiltration, that is mediated by proportionately greater relaxation of the afferent arteriole than the efferent

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liver and kidney are the two major organs in which cadmium accumulates. Cadmium's half-life in the body is longer than 10 years. As with blood levels of lead, blood levels of cadmium fall after acute exposure because of extensive tissue deposition. Once a threshold of kidney deposition is exceeded, excess cadmium is excreted in urine. Cadmium intoxication produces irreversible proximal tubular dysfunction, hypercalciuria, nephrolithiasis, and metabolic bone disease with pain (called "ouch-ouch" disease in Japan).

Oxalate Nephropathy

Oxalate nephropathy results from the deposition of calcium oxalate in the tubular interstitium, thereby leading to mild secondary inflammation and tubular atrophy and fibrosis. Although oxalate nephropathy can occur in patients who have primary inborn errors of glycolate metabolism that lead to overproduction of oxalate (Chapter 189), more commonly it occurs in patients who have secondary causes of increased oxalate excretion (e.g., patients with roux-en-y gastric bypass, inflammatory bowel disease, or short bowel syndrome) because of increased intestinal availability and permeability of oxalate or decreased degradation of oxalate. Diagnosis requires a high index of suspicion. A 24-hour urine collection to measure oxalate excretion can help, but ultimately a kidney biopsy is needed to make the diagnosis.[2,3]

Autosomal Dominant Tubular Interstitial Diseases

Autosomal dominant tubular interstitial diseases are a rare group of inherited syndromes that lead to progressive chronic kidney disease and eventually lead to kidney failure (Chapter 112). The several subtypes of autosomal dominant tubular interstitial disease have an autosomal dominant inheritance pattern, present in late childhood or early adulthood, and are slowly progressive. Some patients may have early-onset gout. Kidney imaging may show small medullary cysts. Kidney biopsy will usually show nonspecific findings. A provisional diagnosis can made by obtaining a thorough family history in the appropriate clinical context. Genetic testing for mutations in uromodulin (*UMOD*) will confirm the clinical diagnosis in the majority of patients, whereas other patients will have mutations in renin (*REN*), hepatocyte nuclear factor-1β (*HNF1B*), or Mucin-1 (*MUC1*).

TREATMENT

Inciting factors such as obstruction, infection, drugs, or toxins should be removed whenever possible. Chronic interstitial fibrosis rarely responds to aggressive treatment. However, in immunoglobulin G4–related interstitial nephritis, the renal lesions in many patients respond briskly to corticosteroid treatment. In addition, treatment of tubulointerstitial nephritis with uveitis syndrome is with varying doses of methylprednisolone followed by oral prednisone under expert guidance may be beneficial in some patients. Varying durations of supplemental or steroid-sparing immunosuppression with mycophenolate mofetil or cyclophosphamide also have been used. Immunosuppression may also be helpful in sarcoidosis (Chapter 83).

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ABSTRACT

Diabetic nephropathy, which is also known as diabetic kidney disease, is one of the most prominent "microvascular" complications of diabetes and is a major source of morbidity and mortality. Both the incidence and the prevalence of diabetic nephropathy continue to rise. The vast majority of incident and prevalent cases of diabetic nephropathy are secondary to type 2, obesity-prone diabetes. With the global rise in obesity, an increasing incidence of diabetic nephropathy is being reported worldwide. Patients who develop diabetic nephropathy classically progress from initial presentation with microalbuminuria to development of nephrotic-range proteinuria and progressive decline in glomerular filtration rate until the development of end-stage kidney disease. Diabetic nephropathy is the underlying reason why almost 50% of all patients are currently receiving renal replacement therapy in the United States. Control of hyperglycemia and blood pressure can decrease the incidence of diabetic nephropathy but does not completely eliminate the risk. Therapeutic options include medications that interfere with the renin-angiotensin system (ACE inhibitors or angiotensin receptor blockers) as well as sodium-glucose cotransporter-2 (SGLT2) inhibitors, glucagon-like peptide-1 (GLP-1) analogues, and nonsteroidal mineralocorticoid receptor antagonists. Appropriate use of these agents can slow the progression of diabetic nephropathy, reduce cardiovascular complications, and increase longevity.

KEYWORDS

diabetic nephropathy
microvascular complication
hyperglycemia
nephrotic syndrome
renin-angiotensin inhibitors
dialysis
SGLT2 inhibitors
mineralocorticoid inhibitors
GLP
renal transplantation

arteriole. This hyperfiltration leads to increased glomerular blood flow and elevated glomerular capillary pressure. With poorly controlled diabetes, patients also develop glomerular hypertrophy, with an increased glomerular capillary surface area. These intraglomerular hemodynamic and structural alterations may contribute to the development or progression (or both) of diabetic renal injury. Blockade of the renin-angiotensin system with angiotensin-converting enzyme (ACE) inhibitors or angiotensin receptor blockers and the use of sodium-glucose cotransporter-2 (SGLT2) inhibitors reduce this elevated intraglomerular capillary pressure in experimental animals, so this hyperfiltration hypothesis potentially explains how these medications slow the progression of diabetic nephropathy.

Hormones and Cytokines

A number of cytokines, hormones, and intracellular signaling pathways are implicated in the development and/or progression of diabetic nephropathy, notably transforming growth factor β, connective tissue growth factor, angiotensin II, vascular endothelial growth factor, endothelin, prostaglandins, and nitric oxide.[5] Because these factors have also been implicated in a variety of nondiabetic kidney diseases, they are not specific for diabetic nephropathy. However, agents that interrupt production and signaling of angiotensin II are very effective in slowing the progression of diabetic nephropathy.

Genetics

Although poor glycemic and blood pressure control undoubtedly contribute to the development of diabetic nephropathy, nephropathy may or may not occur in an individual patient even after many years of hypertension and hyperglycemia. Type 1 diabetic patients whose siblings have diabetic nephropathy have a greater than 70% lifetime risk of developing diabetic nephropathy themselves. Patients with type 2 diabetes also appear to have a hereditary predisposition for or against the development of diabetic nephropathy.

However, diabetic nephropathy is likely to be a polygenic disease, and its development and progression are likely related to the inheritance of multiple polymorphisms with variable effect sizes. For example, Black Americans with apolipoprotein-1 genetic risk genotypes do not have an increased predisposition to develop diabetic nephropathy, but nephropathy has an accelerated progression in such patients. In addition, the lack of nephropathy in patients with glucokinase mutations may be more pronounced than can be explained just by their relatively lower HbA_{1c} levels. Studies also suggest a long-term programming or memory effect in the development of diabetic kidney disease, such that patients whose type 1 diabetes was poorly controlled in the past will develop nephropathy at an increased rate despite subsequent excellent glycemic control. These findings suggest the possible role for epigenetic programming—such as for the glomerular expression of enzymes in glycolytic, sorbitol, methylglyoxal, and mitochondrial pathways—in type 1 diabetic patients who develop diabetic nephropathy.

CLINICAL MANIFESTATIONS

Diabetic kidney disease progresses through four stages at variable rates in different patients.[6,7]

Natural History

Diabetic nephropathy progresses through four relatively distinct stages (Fig. 109-1).

Stage I

In stage I, which commences soon after the overt manifestations of diabetes, renal blood flow and GFR increase by up to 50%, and the kidney's glomeruli and tubules hypertrophy compared with age- and weight-matched normal control subjects. Although patients with type 2 diabetes also tend to have an elevated GFR during the early course of their disease, the GFR increases are not usually as pronounced as seen with insulin-dependent diabetes mellitus. At this stage, macroalbuminuria (>300 mg per 24 hours) is not detectable, but transient microalbuminuria (30 to 300 mg per 24 hours) can occasionally be measured by radioimmunoassay, enzyme-linked immunosorbent assay, or special dipsticks, especially when induced by stress, physical exertion, concurrent illness, or poor glycemic control.[8] Hypertension is usually absent in the early stages in type 1 diabetic patients but is present in 10 to 25% of type 2 diabetic patients at initial evaluation.

Stage II

Approximately 30% of type 1 diabetic patients progress to stage 2, which is characterized by fixed microalbuminuria after a median of about 10 years of diabetes. Although the GFR either remains elevated or is within the normal range at this stage, renal histology becomes abnormal and is manifested as glomerular and tubular basement membrane thickening and the inception of mesangial matrix expansion. Microalbuminuria is more likely in patients who have evidence of other microvascular insults, especially proliferative retinopathy. Microalbuminuria is a more specific sign of diabetic nephropathy in type 1 diabetes than in type 2 diabetes because of the high incidence of hypertension, which itself may lead to microalbuminuria, in the latter.

Stage III

The majority of patients who are initially seen with fixed microalbuminuria progress to overt nephropathy (stage III) within 5 to 7 years. In this stage, patients have overt proteinuria (>500 mg of total protein per 24 hours) and macroalbuminuria, which are detectable with a routine urinary protein dipstick. With the onset of stage III, estimated glomerular filtration rate (eGFR) is usually below normal levels for age and continues to decrease as the disease progresses, but the serum creatinine level may remain in the normal range. Blood pressure begins to rise in type 1 diabetic patients with stage III nephropathy. In type 2 diabetic patients, who frequently have preexistent hypertension, blood pressure commonly becomes more difficult to control.

Stage IV

Stage IV, or advanced diabetic nephropathy, is characterized by a relentless decline in renal function and progression to ESRD. Patients typically have heavy or nephrotic-range proteinuria (>3.5 g/24 hr) and systemic hypertension but have no evidence of inflammatory glomerular (red blood cell casts) or tubulointerstitial (white blood cells, white blood cell casts) lesions. The kidneys may be inappropriately large for the observed degree of renal insufficiency. However, a subset of patients with type 2 diabetes develops chronic kidney disease without nephrotic-range proteinuria. Whether this difference represents a fundamental difference in the pathophysiology of the two conditions or represents the synergistic effects of other kidney injuries, such as hypertensive renal disease, is unclear.

Other Renal Complications

Patients with diabetes also have an increased rate of other kidney and genitourinary abnormalities. Type IV (hyporeninemic, hypoaldosteronemic) metabolic acidosis (Chapter 104) with hyperkalemia is commonly encountered in diabetic patients who have mild to moderate renal insufficiency. These patients should be carefully monitored for the development of severe hyperkalemia (Chapter 103) in response to volume depletion or after the initiation of drugs that interfere with the renin-angiotensin system, such as ACE inhibitors, angiotensin II receptor blockers, β-adrenergic blockers, nonsteroidal anti-inflammatory agents, and heparin, as well as potassium-sparing diuretics.

Patients with diabetes have an increased incidence of bacterial and fungal infections of the genitourinary tract (Chapter 263). In addition to lower urinary tract infections, they have an increased risk for pyelonephritis as well as for intrarenal and perinephric abscesses (Chapter 263).

Unilateral or bilateral renal artery stenosis (Chapter 110) occurs more frequently in the type 2 diabetic population than in age-matched nondiabetic individuals and should be considered if a diabetic patient has intractable hypertension or a rapidly rising serum creatinine level immediately after initiation of therapy with an ACE inhibitor or angiotensin receptor blocker. Other causes of acute deterioration in renal function include papillary necrosis with ureteral obstruction owing to sloughing of a papilla, obstructive uropathy caused by bladder dysfunction as a result of autonomic neuropathy, and contrast media–induced acute tubular necrosis (Chapter 106). In addition, prerenal azotemia or acute tubular necrosis may develop in diabetic patients as a result of heart failure or volume depletion owing to vomiting induced by gastroparesis (Chapter 210) or diarrhea from autonomic neuropathy.

DIAGNOSIS

The diagnosis of overt diabetic nephropathy[9] is made by three main criteria: the presence of proteinuria within an appropriate time frame, the presence of retinopathy (90 to 95% in type 1 and 60 to 65% in type 2), and the absence of other causes of nephrotic syndrome or renal insufficiency. For patients who have type 1 diabetes and who develop diabetic nephropathy, significant proteinuria is seen within 11 to 23 years of the onset of diabetes. Although microalbuminuria does not always progress to overt proteinuria in these patients, it always precedes overt proteinuria in the patients who do progress. All patients with type 1 diabetes should be screened for microalbuminuria 5 years after the diagnosis and yearly thereafter. Patients who have type 2 diabetes should be screened for microalbuminuria at the time of diagnosis and yearly thereafter.

	Stage I	Stage II	Stage III	Stage IV
Median year of onset	0	10	15-17	18-20
Patients with diabetes (%)	100	30-35	30	30

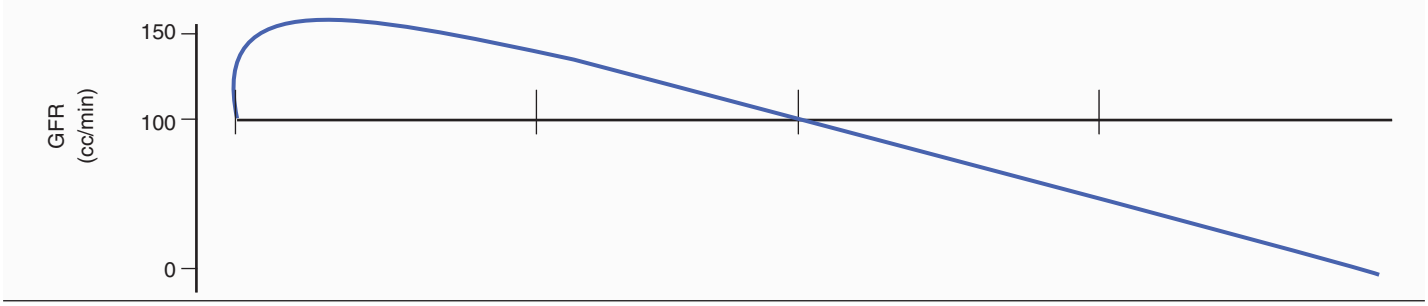

Urinary protein	Occasional and transient microalbuminuria	Fixed microalbuminuria	Proteinuria (>500 mg/24 hr) and microalbuminuria (200 mg/24 hr)	Nephrotic-range proteinuria (<3.5 g/24 hr)
Systemic manifestations	Hypertension: absent in type 1; often present in type 2	Hypertension: absent in type 1; typical in type 2	Hypertension: absent in type 1 and worsening in type 2	Manifestations of chronic renal insufficiency
Renal morphology and history	Kidney hypertrophy	Glomerular basement membrane thickening and mesangial matrix expansion	Focal glomerulosclerosis (± nodular or Kimmelstiel-Wilson lesions) Microvascular hyalinosis and tubulointerstitial fibrosis	Kidney may still be inappropriately large for level of renal insufficiency Global glomerulosclerosis and tubulointerstitial fibrosis

FIGURE 109-1. Stages of diabetic nephropathy. GFR = glomerular filtration rate.

Renal Biopsy

Renal biopsy is rarely required to make the diagnosis unless another cause of proteinuria and renal failure is suspected (Chapters 100, 107, and 108). If performed, the biopsy will reveal diffuse or nodular (Kimmelstiel-Wilson) glomerulosclerosis. Although the Kimmelstiel-Wilson lesion is considered pathognomonic of advanced diabetic nephropathy, only approximately 25% of patients manifest this lesion. A nodular pattern of glomerulopathy mimicking Kimmelstiel-Wilson lesions may also be seen in light chain nephropathy (Chapter 173). Nodular glomerular lesions can also be observed in amyloidosis (Chapter 174) and membranoproliferative glomerulonephritis type II (Chapter 107). An additional pathognomonic feature of diabetic nephropathy is the finding of both afferent and efferent arteriolar hyalinosis, which can be distinguished from the isolated afferent arteriolar lesion of essential hypertension. In overt diabetic nephropathy, tubular alterations owing to tubular hypoxia may mediate the progressive decline in renal function, and progressive tubulointerstitial fibrosis correlates most closely with the decline in renal function.

PREVENTION AND TREATMENT

Glycemic Control

Glycemic control significantly lessens the incidence of nephropathy in patients with type 1 diabetes for at least 20 or more years but does not completely eliminate the risk (Fig. 109-2).[10] In patients with type 2 diabetes, tight control reduces the progression of microvascular complications but appears to be less effective in reducing the risk of macrovascular complications. The goal of diabetic treatment is an HbA_{1c} of 7% or less unless patients have significant comorbid conditions or an increased risk for hypoglycemia.[A1,11]

In latent (stage II) and overt (stage III) diabetic nephropathy, renal function declines. With declining renal function, some oral hypoglycemic agents become contraindicated (Chapter 210). Because of the increased risk of prolonged hypoglycemia, use of sulfonylureas is contraindicated in patients with stage 3b chronic kidney disease or worse (e.g., a GFR <45). Because of the potentially increased risk of lactic acidosis with metformin therapy in patients who have renal insufficiency, treatment guidelines currently recommend not administering it to patients with serum creatinine of greater than 1.7. In addition, as GFR declines, insulin requirements may decrease owing to reduced insulin degradation and clearance by the failing kidney (Chapter 210).

The treatment of diabetic kidney disease has been revolutionized by the advent of SGLT2 inhibiting agents,[12,13] which reduce glucose levels without causing hypoglycemia.[A2] In multiple studies, treatment with canagliflozin (initial dose of 100 mg once daily, increasing to 300 mg starting from week 13),[A3] empagliflozin (10 or 25 mg once daily),[A4] or dapagliflozin (10 mg once daily)[A5] has reduced cardiovascular events, including the progression of renal disease, in patients with type 2 diabetes (Chapter 210).[A6] In addition to glycosuria, these inhibitors reduce intraglomerular pressure through tubuloglomerular feedback, promote an osmotic diuresis and natriuresis, and lower blood pressure. These agents increase the risk of urinary tract infections, and they are currently not approved for treatment of patients with type 1 diabetes because of the potential risk of developing ketoacidosis. Since the glucose-lowering effect of SGLT2

Stage I	Tight glucose control BP control—consider use of ACEI or ARB
Stage II	Tight glucose control BP control ACEI or ARB SGLT2 inhibitor* Finerenone Smoking cessation Weight reduction Exercise Annual eye examination
Stage III	BP control ACEI or ARB SGLT2 inhibitor or GLP-1 analogue* Finerenone Restriction of dietary protein (to 0.8 g/kg/day of ideal body weight) Antihyperlipidemic medications
Stage IV	BP control ACEI or ARB SGLT2 inhibitor or GLP-1 analogue† Finerenone Treat manifestations of nephrotic syndrome and chronic renal insufficiency Prepare for renal replacement therapy, including prevention of abnormalities in calcium and phosphorus metabolism and prevention of anemia by early use of erythropoietin

FIGURE 109-2. Treatment of diabetic nephropathy. ACEI = angiotensin-converting enzyme inhibitor; ARB = angiotensin-receptor blocker; BP = blood pressure; GLP-1 = glucagon-like peptide; SGLT2 = sodium glucose cotransporter 2. *SGLT2 inhibitor preferred, but GLP-1 analogue is the alternative if they cannot be used or are not tolerated †See text for adjustments/discontinuation in stage IV.

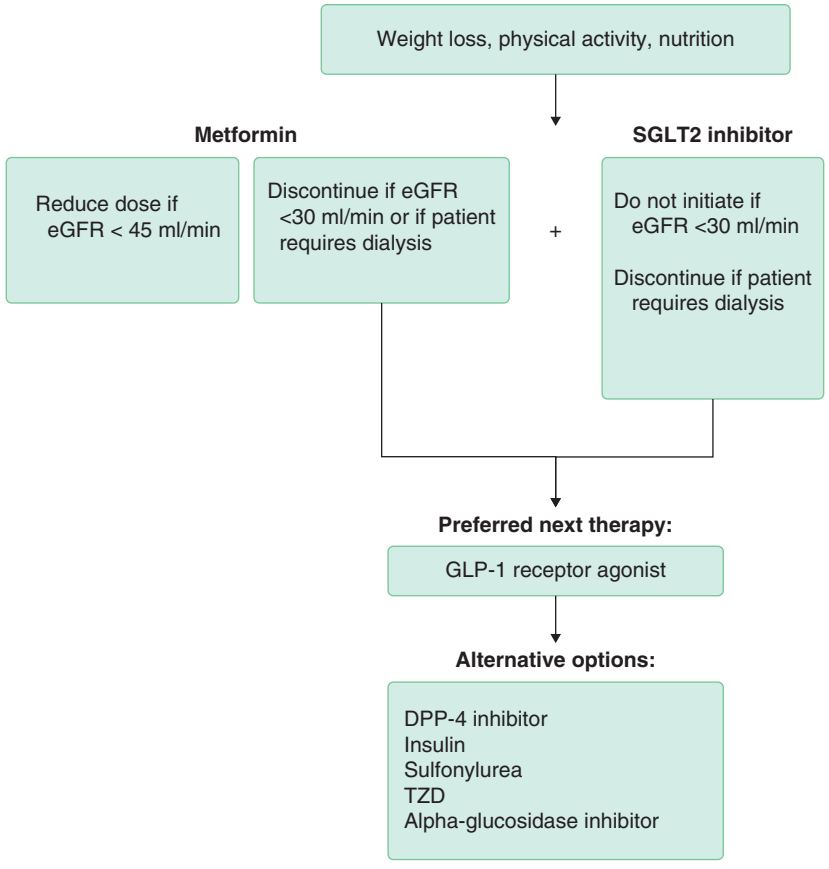

FIGURE 109-3. Approach to oral hypoglycemic agents in type 2 diabetic kidney disease. DPP-4 = dipeptidyl peptidase 4; eGFR = estimated glomerular filtration rate; GLP-1 = glucagon-like peptide 1; SGLT2 = sodium glucose cotransporter 2; TZD = thiazolidinedione.

inhibitors depends on glomerular filtration, the current recommendation is that they should be discontinued when the eGFR falls below 30 mL/min.

An alternative approach, especially when the GFR is too low to use SGLT2 inhibitors, is to use one of the subcutaneous glucagon-like receptor 1 (GLP-1) analogues (Fig. 109-3):[A7] liraglutide (1.2 or 1.8 mg once daily, added to basal insulin),[A8] semaglutide (starting dose of 0.25 mg for 4 weeks, then increasing to 0.5 mg for 4 weeks until a maintenance dose of 0.5 mg or 1.0 mg weekly is achieved),[A9] or dulaglutide (1.5 mg weekly).[A10] Efpeglenatide (4 to 6 mg subcutaneously weekly) is another experimental option.[A11] These agents also can slow the progression of diabetic nephropathy and reduce cardiovascular events in type 2 diabetes, and they can be continued until the GFR falls to 15 mL/min. These agents do not cause ketoacidosis but can induce hypoglycemia.

Blood Pressure Control

Elevated blood pressure is an important risk factor in the progression of diabetic nephropathy. To slow the progression of diabetic nephropathy, some guidelines recommend a blood pressure goal of <140/90 mm Hg whereas others recommend a target of <130/80 mm Hg.[14–16]

Medications that interfere with the renin-angiotensin system, either ACE inhibitors or angiotensin receptor blockers, are the preferred agents (see Tables 64-8 and 64-9), with calcium-channel antagonists as second-line therapy.[A12] SGLT2 inhibitors also lower blood pressure and can reduce the need for additional antihypertensive agents.[A13]

Because of the high prevalence of type IV renal tubular acidosis (Chapter 104) and renal artery stenosis (Chapter 110) associated with diabetic nephropathy, patients treated with ACE inhibitors or angiotensin receptor blockers should have their serum potassium and creatinine levels monitored closely in the first week after the initiation of therapy. If blood pressure control is not achieved with these agents, diuretics and other antihypertensive agents, including cardioselective β-blockers, α-blockers, and nondihydropyridine calcium-channel blockers, can be added (Chapter 64).[A14] Dihydropyridine calcium-channel blockers induce selective afferent arteriolar vasodilation and may increase intraglomerular capillary pressure, so they are usually reserved for patients who do not achieve blood pressure control with other agents.

Nonsteroidal Mineralocorticoid Antagonism

The addition of a nonsteroidal mineralocorticoid antagonist, finerenone (20 mg daily to standard of care with an ACE inhibitor or an angiotensin receptor blocker can significantly slow loss of kidney function[A15] and protect against cardiac complications in patients with type 2 diabetic nephropathy.[A16] Although hyperkalemia is a rare complication, careful monitoring and management of potassium levels are indicated when adding this agent.

General Measures

Because morbidity and mortality from cardiovascular disease are significantly increased in patients with diabetic nephropathy, physicians should encourage smoking cessation (Chapter 363) and should prescribe statins for patients with hyperlipidemia (Chapter 190). Judicial restriction of dietary protein to 0.8 g/kg of ideal body weight per day is also recommended. Although further dietary protein restriction may retard the progression of diabetic nephropathy, considerations of such restrictions must be balanced against the individual patient's nutritional requirements.

Renal Replacement Therapy

In general, the management of a diabetic patient nearing ESRD is similar to that of a nondiabetic patient (Chapter 116). Stage III patients should be under the care of a nephrologist, and planning should be initiated for the modality of dialysis. Although dialysis is generally initiated when the GFR declines to less than 10 mL/min, earlier initiation of dialysis is sometimes necessary in diabetic patients in whom issues such as volume-dependent hypertension or hyperkalemia may not otherwise be manageable without renal replacement therapy. Uremia and gastroparesis also can lead to malnutrition or uncontrollable recurrent emesis. More than 80% of patients with end-stage diabetic nephropathy receive dialysis as their modality of renal replacement therapy (Chapter 117), with about five times as many undergoing hemodialysis as compared with peritoneal dialysis (Chapter 117).

Approximately 25% of renal transplants performed in the United States are in diabetic patients. Pancreas and combined kidney-pancreas transplantation can significantly improve the quality of life of patients with diabetic nephropathy by improving autonomic neuropathy, by retarding or possibly correcting retinopathy, and by avoiding the potential complications of insulin administration. However, all transplantation options remain limited by organ availability.

PROGNOSIS

Diabetic nephropathy is relentlessly progressive, even though appropriate medical therapy may slow the progression. Epidemiologic data suggest that diabetic nephropathy is associated with about a 15-year reduction in life expectancy because of the microvascular and macrovascular complications of diabetes (Chapter 210) as well as the kidney disease itself.

Because of their associated cardiovascular, cerebrovascular, and peripheral vascular disease, as well as their increased risk for infection, the mortality of diabetic patients who receive dialysis (Chapter 117) is 1.5 to 2.0 times worse

than in nondiabetic patients, corresponding to a 5-year survival rate of less than 20% in diabetic patients undergoing maintenance dialysis. Outcomes are worse in patients whose HbA_{1c} levels are above 8.5%. Long-term survival and quality of life are generally superior after kidney transplantation compared with chronic dialysis. However, the other microvascular complications (retinopathy, neuropathy) are not improved by renal transplantation alone.

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110 VASCULAR DISORDERS OF THE KIDNEY

THOMAS M. COFFMAN AND STEPHEN R. SMITH

Vascular disorders of the kidney include renal artery stenosis, atheromatous embolization, renal infarction, and renal vein thrombosis. Each of these abnormalities has characteristic clinical manifestations, but treatment options are limited, except for fibromuscular dysplasia. The kidneys also can be affected by systemic vasculitis, thrombotic thrombocytopenic purpura, malignant hypertension with fibrinoid necrosis, extrinsic compression of the renal vessels, trauma, dissection, and radiation-induced injury.

RENAL ARTERY STENOSIS

DEFINITION

Renal artery stenosis is defined as narrowing of one or both renal arteries, thereby resulting in reduction in blood flow to the kidney. The leading cause is atherosclerosis (about 90% of cases), followed by fibromuscular dysplasia. Although renal artery stenosis is often clinically silent, its major clinical sequelae are hypertension and reduced kidney function. A subset of patients with renal artery stenosis has renovascular hypertension, a diagnosis that can be confirmed when an intervention to correct renal artery stenosis results in a significant decline in blood pressure or a reduction in medications needed to control blood pressure.

EPIDEMIOLOGY

Some degree of renal artery stenosis is present in 10 to 20% of patients who have severe or therapy-resistant hypertension, recent-onset hypertension, hypertension developing at an early age, or hypertension with an abdominal bruit. A similar prevalence is observed in patients whose renal arteries are imaged during coronary arteriography for known or suspected coronary artery disease.

Atherosclerosis is the most common cause of renal artery stenosis, accounting for about 90% of clinically identified cases.[1,2] For atherosclerotic renal artery stenosis, epidemiologic risk factors mirror those of atherosclerotic vascular disease (Chapter 40), including risk factors such as hyperlipidemia (Chapter 190), diabetes (Chapter 210), hypertension (Chapter 64), smoking (Chapter 363), and increasing age. Most patients have evidence of widespread atherosclerosis involving the coronary, cerebral, and/or peripheral arteries.

Fibromuscular dysplasia (Chapter 66), which is a distinctly less frequent cause of renal artery stenosis compared with atherosclerosis, typically manifests between ages 20 to 60 years and is more common in women. Although its exact prevalence in the general population is not clear, mild, non-obstructive fibromuscular lesions are seen in about 4% of individuals undergoing renal arteriograms for evaluation as renal transplant donors. Although familial clusters of patients with fibromuscular dysplasia have been reported, most cases are sporadic, and no genetic associations have yet been identified.[3] Rare causes of renal artery stenosis include renal artery dissection, emboli, and extrinsic compression.[4]

PATHOBIOLOGY

The pathobiology of atherosclerotic renal artery stenosis is no different than for atherosclerosis in other arteries (Chapter 41). Fibromuscular dysplasia is an idiopathic, segmented, noninflammatory disease principally of medial layers of the artery (Chapter 63). Any artery can be involved, and about 90% of affected individuals have multifocal disease.

The pathobiologic sequelae of apparent renal artery stenosis depend on the extent and the acuity of the reduction of renal blood flow, as well as whether one or both renal arteries are affected. When the renal artery has a 70% or greater stenosis and a 20 to 25% peak systolic gradient across that stenosis, reduced perfusion pressure to the kidney triggers the release of renin by the juxtaglomerular apparatus, thereby activating the renin–angiotensin–aldosterone system and causing vasoconstriction, the retention of fluid and sodium, and hypertension, sometimes accompanied by flash pulmonary edema.

With bilateral renal artery stenosis or unilateral stenosis in a patient with a solitary functioning kidney, sustained reductions in the glomerular filtration rate can lead to chronic kidney disease, referred to as ischemic nephropathy. Although the kidneys are high-flow organs whose relatively low oxygen consumption provides some protection against the downstream consequences of reduced renal blood flow, critical stenosis sustained for prolonged periods can cause irreversible loss of kidney function. Non-hemodynamic mechanisms, such as activation of pro-inflammatory and pro-fibrotic pathways, also likely play a role. Impaired expression of angiogenic factors, such as vascular endothelial growth factor, results in pathologic remodeling of the renal microvasculature. These non-hemodynamic factors may explain, at least in part, why kidney function may not significantly improve after procedures that successfully restore a normal patency of the renal artery.

The nature of vascular disease in renal artery stenosis differs depending on the cause. With atherosclerosis, stenosis is caused by intrusion of atherosclerotic plaques, which may originate in the aorta, into the lumen of the main renal arteries. In atherosclerotic disease, the stenosis is commonly seen at the ostial segment at the origin of the renal artery, although stenoses can also occur along the entirety of one or both renal arteries. By contrast, fibromuscular dysplasia can be focal but more commonly is multifocal and characterized by areas of post-stenotic dilatation, thereby leading to the angiographic appearance of beads on a string. In fibromuscular dysplasia, lesions are typically located away from the origin of the renal artery, often in the midportion of the vessel or at the first arterial bifurcation.

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ABSTRACT

Renal artery stenosis, atheromatous embolization to the kidneys, renal vein thrombosis, and renal infarction are the principal vascular disorders of the kidney. Renal artery stenosis is usually atherosclerotic in origin and treated with antihypertensive medications. By comparison, fibromuscular renal artery stenosis responds well to interventional therapies, which may even cure the hypertension. Atheromatous renal embolization is usually a sequela of an intra-arterial intervention and portends a poor prognosis. Renal vein thrombosis is often related to a hypercoagulable state, such as seen in the nephrotic syndrome, but can also be caused by trauma or tumor.

KEYWORDS

renal artery stenosis
fibromuscular dysplasia
atheromatous embolization
renal vein thrombosis
kidney infarction

CLINICAL MANIFESTATIONS

The clinical manifestations of renal artery stenosis may be minimal in many patients, and the diagnosis is often made incidentally during the course of unrelated vascular studies. The most common clinical manifestation of significant renal artery stenosis is arterial hypertension (Chapter 64). Flash pulmonary edema also can be observed and may be more common in patients who have had prior manifestations of heart failure.

Renovascular hypertension from fibromuscular dysplasia should be suspected in patients who have the onset of hypertension at an early age, especially in women, whereas atherosclerotic renal artery hypertension should be considered when an elderly patients or a patient with atherosclerosis in other organ systems develops new-onset hypertension or the sudden worsening of previously well-controlled existing hypertension. The presence of an abdominal bruit on physical examination should further increase the index of suspicion.

In renal artery stenosis caused by atherosclerosis, kidney damage (i.e., a reduction in the glomerular filtration rate) is generally slowly progressive without proteinuria or an active urinary sediment. By comparison, a progressive reduction in the glomerular filtration rate is uncommon with fibromuscular dysplasia. An acute precipitous decrease in the estimated glomerular filtration rate after initiating therapy with an inhibitor of the renin angiotensin system may indicate bilateral renal artery stenosis or unilateral stenosis in a patient with one functioning kidney.

TABLE 110-1 CLINICAL SITUATIONS IN WHICH STENTING OR SURGICAL REVASCULARIZATION IS LIKELY APPROPRIATE FOR ATHEROSCLEROTIC RENAL ARTERY STENOSIS

Flash pulmonary edema or recurrent acute coronary syndrome with hypertension and moderate or more renal artery stenosis with a resting translesional mean gradient ≥10 mm Hg
Stage IV chronic kidney disease with bilateral moderate renal artery stenosis and a resting translesional mean gradient ≥10 mm Hg and a kidney size >7 cm in pole-to-pole length
Stage IV chronic kidney disease and global renal ischemia with unilateral severe renal artery stenosis in a solitary kidney or bilateral severe renal artery stenosis without another explanation
Uncontrolled hypertension despite maximally tolerated doses of at least three antihypertensive agents, one of which is a diuretic agent, and bilateral or solitary severe renal artery stenosis

DIAGNOSIS

Since establishing the diagnosis of atherosclerotic renal artery principally influences the choice among medical therapies (Table 64-9) rather than guiding interventional therapies, specific diagnosis is helpful only in limited situations in which careful antihypertensive therapy is unsuccessful (Table 110-1).[5] By comparison, diagnosis and interventional treatment of fibromuscular muscle dysplasia can potentially cure hypertension and avoid its complications, so prompt diagnosis is important.

The diagnosis of renal artery stenosis requires an imaging study using Doppler ultrasound, computed tomographic angiography (CTA), magnetic resonance angiography (MRA), or conventional arteriography, with arteriography considered the gold standard for diagnosis. The choice among these options depends on the patient's characteristics, local imaging expertise, and whether the diagnosis would modify therapy. Doppler ultrasound requires a skilled operator and is typically less sensitive and specific than contrast-based approaches. CTA and MRA require exposure to iodinated or gadolinium-based contrast material, respectively, both of which can have toxicities, especially in individuals with reduced kidney function. Another option is MRA using ferumoxytol, which is an iron-containing contrast agent with no risk of nephrogenic sclerosis or nephrotoxicity but with somewhat lower resolution. However, noninvasive tests carry a significant likelihood of overestimating the degree of stenosis compared with conventional arteriography, so confirmatory catheter angiography is typically required for patients who are considered candidates for angioplasty or stenting.

Atherosclerotic stenoses are generally irregular and can be bilateral (Fig. 110-1), whereas stenoses of fibromuscular dysplasia typically show a "string of beads" appearance (Fig. 110-2). Isolated measurements of peripheral vein plasma renin activity are of limited utility in the diagnosis of renal artery stenosis, but measuring peripheral or renal vein plasma renin activity after a single dose of captopril may be of some value in determining whether an observed stenosis is hemodynamically significant.

TREATMENT

Atherosclerotic Renal Artery Stenosis

For atherosclerotic renal artery stenosis, neither percutaneous angioplasty nor stenting provide improved overall outcomes compared with best medical treatment.[A1,A2] Nevertheless, some individuals (i.e., patients whose severe hypertension requires three medications, who have had a recent acute decline in kidney function, or who have episodes of flash pulmonary edema) may have better subsequent blood pressure control or kidney function following stenting or surgical revascularization (see Table 110-1).[6–8]

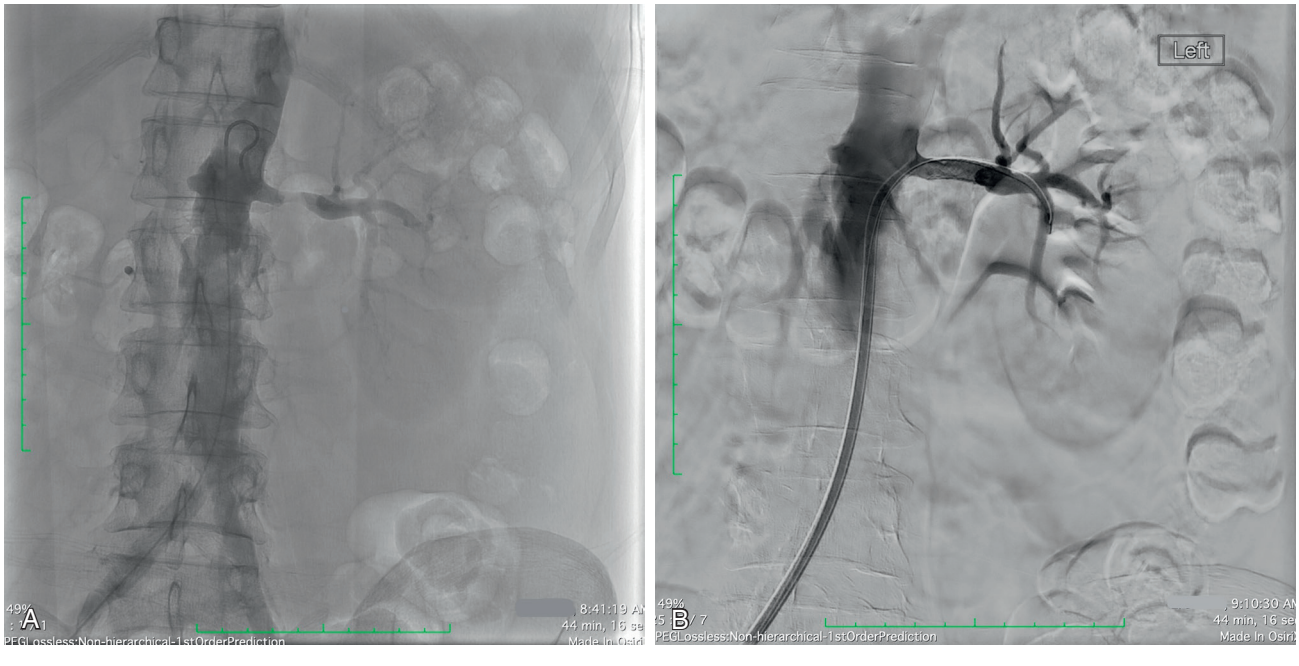

FIGURE 110-1. Renal artery atherosclerosis. A, Renal arteriogram showing moderate atherosclerotic stenosis of the left renal artery and total occlusion of the right renal artery in a patient with resistant hypertension and chronic kidney disease. **B,** Left renal artery with stent in place. The patient's blood pressure did not improve with stenting of the left renal artery but did improve dramatically with resection of the atrophic right kidney, not seen on the arteriogram.

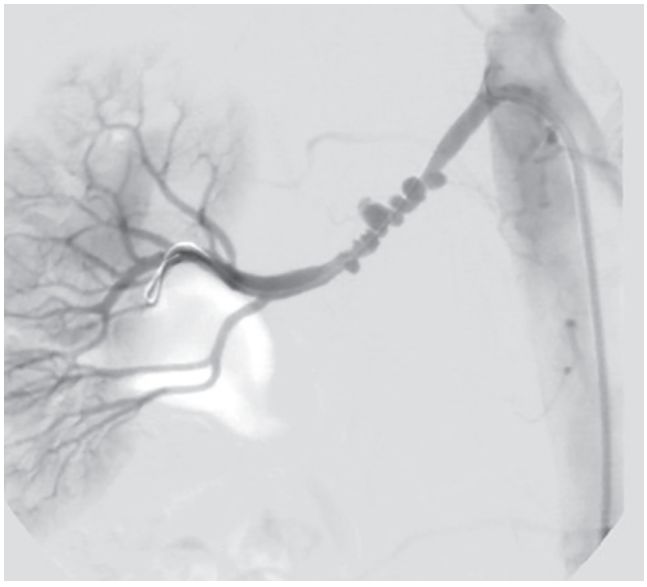

FIGURE 110-2. Right renal arteriogram showing "beads on a string" appearance of fibromuscular dysplasia.

As a result, medical management is the preferred therapeutic approach for the majority of individuals with atherosclerotic renal artery stenosis. The best medical therapy, based on expert opinion, includes smoking cessation (Chapter 363), management of hyperlipidemia (Chapter 190), aspirin (75 to 100 mg per day), and control of hypertension (Chapter 64) with inhibitors of the renin–angiotensin system (Tables 64-7 and 64-9) while carefully monitoring kidney function.

Fibromuscular Dysplasia

By comparison, nonrandomized data support a benefit from percutaneous angioplasty for patients who have fibromuscular dysplasia in terms of improved blood pressure control in 35 to 70% of patients.[9] Young women with severe hypertension may particularly benefit. Stenting is not generally required for lesions of fibromuscular dysplasia. Since fibromuscular dysplasia can be multifocal (Chapter 66), patients also may require angioplasty for lesions in other vascular beds or may need repeat renal angioplasty for recurrent disease in renal arteries years after successful angioplasty.

PROGNOSIS

Because atherosclerotic renal artery stenosis typically is a manifestation of severe systemic disease, it is a poor prognostic sign and patients are at markedly increased risk for ischemic events in other organs and the progression of renal insufficiency. For patients with fibromuscular dysplasia, prognosis depends on successful treatment of the hypertension as well as the severity and treatability of lesions in other vascular beds (Chapter 66).

ATHEROMATOUS EMBOLIZATION OF THE RENAL ARTERIAL SYSTEM

DEFINITION

Atheromatous cholesterol embolization (Chapter 66) is a multiorgan syndrome, which rarely can be caused by a spontaneous rupture of an atheromatous plaque but more commonly is a complication associated with interventional vascular procedures or the use of anticoagulants and thrombolytic agents. A shower of small particles, including cholesterol crystals from the larger central arteries to the distal circulation, can affect both native and transplanted kidneys. The clinical syndrome is distinct from arterial thromboembolism, in which larger thrombi lodge in downstream arteries and cause acute infarction.

EPIDEMIOLOGY

The precise incidence of renal atheromatous embolization is difficult to determine. Among patients known to have abdominal aortic aneurysms, the incidence is about 3% over 15 months, whereas the incidence is only 1% over 3 years in patients with thoracic aortic aneurysm.[10] Atheromatous embolization occurs in about 0.4% of patients undergoing left heart catheterization (Chapter 59),[11] and about two thirds of such cases affect the kidneys. Of patients who develop atheromatous embolization in the absence of a vascular procedure, about 7% have been taking anticoagulants or have received thrombolytic therapy. In patients over age 60 years who undergo a kidney biopsy for acute kidney injury (Chapter 106), about 5% have evidence of atheroembolic disease. Consistent with the epidemiology of atherosclerosis, atheroembolic disease is more commonly seen in older patients who have a high burden of systemic vascular disease.

PATHOBIOLOGY

Because of their small size, cholesterol emboli do not typically cause significant impairment of renal blood flow but instead tend to lodge and occlude smaller 100- to 200-μm arterioles such as arcuate and interlobular arteries and the glomerular capillaries. The presence of the crystals in vascular lumens leads to a complex inflammatory response with associated ischemia and necrosis. The glomerular lesion is presumably related to secondary effects of atheroembolization, including activation of immune and inflammatory mediators. The early phase of the inflammatory reaction includes neutrophils and eosinophils, but then a subsequent foreign body reaction is characterized by multinucleated giant cells and macrophages. The NLRP3 inflammasome has been implicated in the genesis of the inflammatory response. Complement is activated, as is the renin–angiotensin system, and some patients have reduced serum levels of complement. Emboli may be cleared over time by fibrinolysis and uptake by the endothelial cells, followed by their release into the perivascular space.

CLINICAL MANIFESTATIONS

Although a preceding invasive vascular procedure is an important precipitating event, the clinical manifestations can become apparent from days to months after the procedure. Involvement of other vascular beds is common and the presence of extrarenal atheroemboli such as livedo reticularis (Fig. 66-4), a petechial or purpuric rash (Chapter 66), ischemic toes, or amaurosis fugax with Hollenhorst plaques on fundoscopic examination strongly support the diagnosis.

The clinical presentation of atheromatous embolization to the kidneys is notoriously variable, but hypertension and slowly declining glomerular filtration rate are consistent features. Accordingly, the differential diagnosis is large and often includes acute tubular necrosis (Chapter 106), contrast nephrotoxicity (Chapter 59), allergic interstitial nephritis (Chapter 108), and vasculitis (Chapter 249).[12]

DIAGNOSIS

No pathognomonic laboratory tests are available, but peripheral blood eosinophilia may occur early in the course, and complement levels are low in a minority of cases. Inflammatory markers such as the erythrocyte sedimentation rate and the C-reactive protein level are typically elevated. Urinalysis is usually bland, but heavy proteinuria can occur. A urinary sediment with red cells is suggestive of acute glomerulonephritis and is rarely seen.

Tissue biopsy, typically of kidney, skin, or muscle, provides a definitive diagnosis but is not required in patients who have a history of a recent vascular procedure accompanied by physical findings suggestive of embolization. On kidney biopsy, the pathognomonic histologic feature on light microscopy is the presence of cholesterol crystal clefts (Fig. 110-3). The histopathologic process is patchy, and the sensitivity of kidney biopsy can be improved from about 75% with a single biopsy core to about 95% with the standard two cores. Focal segmental glomerulosclerosis is also seen in a substantial portion of biopsies.

TREATMENT

Although corticosteroids are often prescribed, no specific treatments are proven to be beneficial. Nevertheless, moderate- to high-dose statin therapy (Table 190-2) may be associated with better outcomes, whether at baseline or started after diagnosis. In the absence of effective medical therapy, prevention of further embolization emphasizes the avoidance, if possible, of anticoagulants and interventional vascular procedures. Blood pressure control, preferably with an angiotensin-converting enzyme inhibitor or angiotensin receptor blocker (Table 64-9), is recommended.

PROGNOSIS

Prognosis of patients with renal atheroembolism is poor.[13] Approximately 30% of patients progress to end-stage kidney disease that requires dialysis, although a minority of patients who initiate dialysis may eventually recover sufficient kidney function to discontinue dialysis. Median survival from the time of diagnosis is about 5.5 years, and most patients die from cardiovascular complications as a reflection of the severity of their underlying atherosclerotic vascular disease.

RENAL INFARCTION

Occlusion of a main or segmental renal artery is an uncommon occurrence, accounting for 0.004 to 0.007% of emergency department visits. The cause can usually be traced to one of three processes: thromboembolism, a renal

vascular abnormality, or thrombosis in the setting of hypercoagulability (Chapter 67). Despite a rigorous evaluation,[14] up to 20 to 30% of cases have no identifiable cause.

The most common source of thromboembolism causing renal infarction is atrial fibrillation (Chapter 52), but thromboemboli to the kidney may also arise from endocarditis (Chapter 61), paradoxical embolus through a patent foramen ovale (Chapter 55), an atrial myxoma (Chapter 47), or aortic aneurysm (Chapter 63). Although renal infarction from thromboembolism usually affects only one kidney, bilateral disease also can be observed, and multiple segmental areas of infarction are typically seen.

The most common vascular abnormalities associated with renal infarction are spontaneous dissection of a renal artery aneurysm and fibromuscular dysplasia. However, infarction also can be seen after trauma and after endovascular procedures.

Hypercoagulable disorders associated with renal infarction, often bilateral, include thrombophilia (Chapter 67), the antiphospholipid syndrome (Chapter 160), the hypercoagulable state associated with nephrotic syndrome (Chapter 107), and in the setting of coronavirus-2019 (COVID-19)-associated hypercoagulability (Chapter 336).[15] Vasculitis (Chapter 249) is a very rare cause of renal infarction.

CLINICAL MANIFESTATIONS AND DIAGNOSIS

The clinical presentation of renal infarction can be fairly nonspecific and may resemble other more common disorders such as pyelonephritis (Chapter 263) or nephrolithiasis (Chapter 111).[16] Flank pain is the most common presenting symptom, sometimes accompanied by nausea and fever and often accompanied by increased blood pressure, which may be dramatically elevated. If the cause is embolic, symptoms ascribable to emboli in other vascular beds may be present. Leukocytosis and elevations in the erythrocyte sedimentation rate, C-reactive protein level, and lactate dehydrogenase level are common.

Diagnosis is confirmed by cross-sectional imaging, usually by a CT angiogram, which is rapid and accurate, showing typical findings of a segmental lack of enhancement indicative of infarction. In individuals with a reduced glomerular filtration rate, MRA imaging using a non–gadolinium-based contrast such as ferumoxytol is a safe alternative. If a lesion in the main renal artery is suspected, catheter-based contrast arteriography may be warranted.

TREATMENT

Treatment is based on the suspected cause of the infarction. If a renal artery is totally occluded by thrombus, intra-arterial infusion of a thrombolytic agent may be of benefit. If embolism from the heart is suspected, immediate systemic anticoagulation is indicated with unfractionated or low-molecular-weight heparin (Table 70-3) followed by long-term anticoagulation therapy. Whether direct-acting anticoagulants (see Table 70-6) are superior to warfarin over the long term in this condition is unknown. The long-term benefit of systemic anticoagulation in patients with idiopathic renal infarction is uncertain. Surgical or percutaneous intervention is usually limited to patients who have bilateral occlusions, occlusions to a solitary kidney, traumatic renal artery thrombosis, or procedure-related thrombosis.

PROGNOSIS

The prognosis in renal infarction correlates with the extent of the kidney parenchyma that is affected and whether treatment can re-establish perfusion within 60 to 90 minutes. Because the lesions are typically segmental, are self-limited, and do not involve the entire kidney, prospects for maintaining adequate kidney function are better than for patients with atheroembolic disease, in which the injury tends to be diffuse. By 60 months, about 45% of patients have hypertension and two-thirds have stage 3 or higher chronic kidney disease (Chapter 116).[17] Follow-up imaging often shows that the affected kidney is smaller in size and has reduced function compared with the unaffected contralateral kidneys, but most patients do not require dialysis.

RENAL VEIN THROMBOSIS

Complete or partial thrombotic occlusion of one or both renal veins is a rare condition that occurs almost exclusively when at least two of three of the Virchow triad are present: low blood flow or stasis, trauma to the endothelium, and hypercoagulability. Males are affected more often than females, and the left renal vein is involved more often than the right, rarely because of extrinsic compression of the left renal vein by the superior mesenteric artery and aorta.[18] The most common setting for renal vein thrombosis is the nephrotic syndrome (Chapter 107), in which severe hypoalbuminemia is associated with the urinary loss of inhibitors of coagulation (e.g., protein S and antithrombin III), an increase in procoagulant factors (e.g., fibrinogen and β-thromboglobulin), and low oncotic pressure. Of the causes of nephrotic syndrome, membranous glomerulopathy is most commonly associated with renal vein thrombosis, although the incidence of 1% is not high enough to warrant routine screening. Primary causes of hyper-coagulability (Chapter 67), such as factor V Leiden and antiphospholipid antibody syndrome, are also associated with renal vein thrombosis.[19,20] Trauma can cause renal vein thrombosis, most often after kidney transplantation when mechanical stress or kinking of the renal vein in combination with low post-transplant blood flow may cause thrombosis. Renal cell carcinoma (Chapter 182) invading the renal vein and inferior vena cava can induce thrombosis. Profound volume depletion can lead to low blood flow in the renal veins and rarely cause thrombosis.

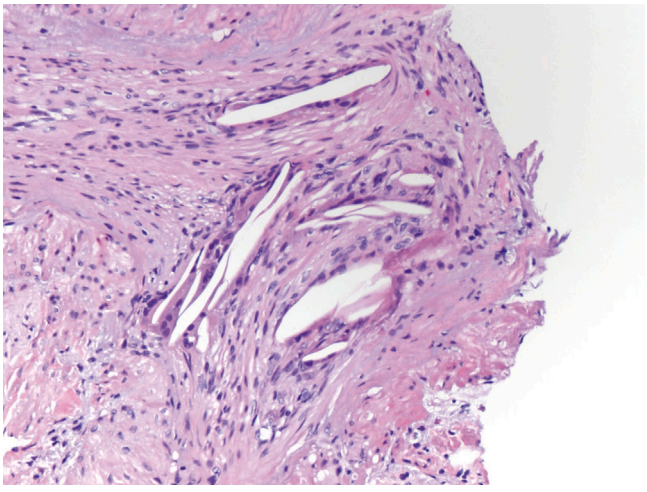

FIGURE 110-3. Hematoxylin and eosin–stained kidney biopsy showing cholesterol clefts in a renal arteriole.

CLINICAL MANIFESTATIONS AND DIAGNOSIS

Renal vein thrombosis may be asymptomatic, particularly if chronic. In the acute setting, however, flank pain, fever, nausea, and vomiting may occur along with gross hematuria. The differential diagnosis often includes pyelonephritis (Chapter 263) and nephrolithiasis (Chapter 111). If the left renal vein is involved, the gonadal vein may become distended, thereby causing the pelvic congestion syndrome in females and painful swelling of the left testicle in males.

Although Doppler ultrasound is a reasonable screening test and is often the study of choice for detecting renal vein thrombosis after kidney transplantation, the diagnosis is most readily made in native kidneys by CT angiography or MRI venography. Characteristic findings include enlargement of the kidney and renal vein, delayed excretion of contrast with a persistent nephrogram, and distortion of the renal pelvis and calyces. In more chronic cases, ureters may be notched by compressing venous varicosities.

TREATMENT

Patients who have asymptomatic unilateral renal vein thrombosis and good kidney function may not require anticoagulation. For patients with acute symptomatic renal vein thrombosis, anticoagulation with unfractionated or low-molecular-weight heparin (Table 70-3) should be followed by oral anticoagulation with warfarin to a target international normalized ratio of 2.0 to 3.0[21] to avoid further thromboembolic events and preserve kidney function, unless patients have contraindications to such treatment. Instillation of thrombolytic agents in the renal vein or, rarely, surgical thrombectomy is reserved for acute bilateral renal vein thrombosis or for unilateral renal vein thrombosis in a solitary functioning kidney. Long-term low-molecular-weight heparin may be preferred for renal vein thrombosis associated with a renal cell carcinoma. The optimal duration of systemic anticoagulation is unknown, but anticoagulation can be discontinued in patients whose membranous nephropathy goes into remission.

PROGNOSIS

Systemic anticoagulation is generally successful in preventing further thromboembolic events with an acceptable rate of bleeding complications, particularly if anti-platelet therapy is not used concurrently. Renal prognosis depends largely on the cause of the renal vein thrombosis and whether that cause resolves, persists, or recurs.[22]

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111 NEPHROLITHIASIS

DAVID A. BUSHINSKY

Kidney stones are composed of crystals in a protein matrix. Most crystals contain calcium, which is generally complexed with oxalate, phosphate, or both, whereas other stones are composed of uric acid, magnesium ammonium phosphate (struvite), or cystine, alone or in combination. Kidney stones form when the saturation of their components exceeds the solubility of the solid phase in urine.

EPIDEMIOLOGY

The annual incidence of kidney stones in industrialized nations exceeds 1 per 1000 persons, with a lifetime risk of about 10% in women and about 15% in men. The incidence of stone formation peaks in the fourth and fifth decades, and prevalence increases with age until approximately 70 years in men and 60 years in women. In the United States, the prevalence of nephrolithiasis has increased from 3% in the late 1970s to more than 5%, an increase that is likely due to changes to diet and lifestyle, as well as more accurate diagnosis.[1] The estimated yearly economic cost of kidney stones exceeds $5 billion in the United States.

In the United States, Whites are more likely to develop renal stones than are other ethnic groups. Stones are more common in hot, dry climates, perhaps because greater fluid loss through the skin and respiratory epithelium leads to more concentrated urine. Many occupations make it inconvenient to utilize a restroom, and these individuals often avoid fluids in an effort to avoid urination, thereby leading to excretion of concentrated urine. Insufficient rehydration among people who engage in physical activity and have large insensible losses also leads to concentrated urine.

Obesity is correlated with the risk for kidney stone formation. Individuals weighing more than 220 pounds or having a body mass index greater than 30 are significantly more likely to form stones than are individuals who weigh less than 150 pounds or have a body mass index between 21 and 22.9.

The types of stones vary around the world,[2] but in the United States, the majority of stones are calcium oxalate and/or calcium phosphate (>80%), and less than 10% are pure uric acid stones. By comparison, about 70% of stones in the Mediterranean and Middle East are composed of uric acid. Magnesium ammonium phosphate (struvite) stones account for 1 to 25% of stones, whereas cystine stones comprise 1 to 2% of stones.[3]

PATHOBIOLOGY

Human bone is composed of calcium and phosphate, principally in the form of apatite. Once humans reach their adult height and their skeleton is fully mineralized, the net amount of calcium that is absorbed by nonpregnant individuals must be excreted in the urine. Similarly absorbed phosphate that is not needed for bone mineralization or cell growth must be excreted. Oxalate is an end product of metabolism, and it too must be excreted in the urine. The need for water conservation by terrestrial humans often leads to excretion of these ions in relatively scant amounts of urine, thereby promoting increased saturation with respect to the solid phases of calcium oxalate and/or calcium phosphate. Increasing saturation drives the formation of the solid crystal phase and is expressed as the ratio of calcium oxalate (or phosphate) ion activity to its solubility. At ratios of greater than 1, termed supersaturation, a solid phase can form, whereas the substances remain in solution at ratios less than 1. When urine is supersaturated, ions can bond to form the more stable, solid phase, which is termed *nucleation*. Homogeneous nucleation refers to the bonding of similar ions into crystals. The more common and thermodynamically favored heterogeneous nucleation occurs when crystals grow on dissimilar crystals or substances as cellular debris in the urine. Although humans produce inhibitors of stone formation, such as osteopontin and Tamm-Horsfall protein, supersaturation can overwhelm this inhibition, and a solid phase will form.

Calcium Stones

About 70 to 80% of kidney stones contain calcium, which is often complexed with oxalate or phosphate. Calcium-containing kidney stones are most often caused by excessive excretion of calcium (hypercalciuria), oxalate (hyperoxaluria), or urate (hyperuricosuria) or insufficient excretion of citrate (hypocitraturia).[4]

Calcium-containing stone formation has a strong genetic component.[5] Idiopathic hypercalciuria is thought to be a polygenic disorder in which a generalized dysregulation of calcium transport in the kidney, intestine, and bone leads to increased urinary calcium. A number of single-nucleotide polymorphisms, in genes coding for the calcium-sensing receptor, the vitamin D receptor, and osteopontin, and others, have been associated with calcium nephrolithiasis. Overall, 14 monogenic mutations account for 15% of nephrolithiasis/nephrocalcinosis, and genetic factors appear to explain about 20 to 35% of the interindividual variation in excretion of ions critical to stone formation.

Urinary oxalate is derived from endogenous metabolism of glyoxylate and ascorbic acid or from dietary sources, such as cocoa, nuts, tea, and certain leafy green vegetables such as spinach. The three main causes of hyperoxaluria are excessive oxalate ingestion *(dietary oxaluria)*, excessive intestinal absorption of oxalate *(enteric oxaluria)* that is paradoxically observed in malabsorptive gastrointestinal disorders, and excessive endogenous oxalate production seen in certain hepatic enzyme deficiencies (*primary hyperoxaluria*; Chapter 189). Additionally, ethylene glycol, a common automobile antifreeze, is metabolized to oxalate and can cause excessive urinary oxalate excretion in conjunction with severe metabolic acidosis and renal failure (Chapter 96).

Enteric oxaluria results in elevated urinary oxalate levels (60 to 100 mg/day).[6] In gastrointestinal malabsorptive conditions such as Crohn disease (Chapter 127), celiac sprue (Chapter 126), jejunoileal bypass (Chapter 201), and chronic pancreatitis (Chapter 130), malabsorbed fatty acids bind dietary calcium, thereby leaving oxalate free to pass into the colon, where it is more likely to be absorbed owing to the presence of bile acids; this excess oxalate is then subsequently filtered by the glomerulus and excreted in the urine. Intestinal bacteria also can influence oxalate levels by degrading it, preventing its absorption, or even stimulating its secretion from the circulation into the intestine.

Primary hyperoxaluria (Chapter 189) results from defects in hepatic enzymes in the liver glyoxylate pathway; the results are substantial endogenous oxalate production and a marked elevation of urinary oxalate (80 to 300 mg/day).[7] Oxalate deposits in numerous organs, including the heart, bone marrow, muscle, and renal parenchyma, where they lead to renal failure, cardiomyopathy, and bone marrow suppression at an early age. In type 1 primary hyperoxaluria, which accounts for about 80% of cases, the hepatic enzyme alanine glyoxylate aminotransferase, which converts glyoxylate to glycine, is deficient because of one of a large number of mutations in the *AGXT* gene. With deficient alanine glyoxylate aminotransferase, the glyoxylate is converted to oxalate. In the milder type 2 primary hyperoxaluria, which represents approximately 10% of cases, patients lack D-glycerate reductase and glyoxylate reductase owing to mutations in the *GRHPR* gene. Type 3 primary hyperoxaluria, which accounts for about 5% of cases, is a result of mutations in the *HOGA1* gene that catalyzes the cleavage of 4-hydroxy-2-oxoglutarate to pyruvate and glyoxylate.

Nephrolithiasis and nephrocalcinosis can also result from a variety of monogenic disorders, such as Dent disease (X-linked recessive nephrolithiasis; Chapter 113), McCune-Albright syndrome (Chapters 212 and 229), osteogenesis imperfecta type 1 (Chapter 239), and congenital lactase deficiency (Chapter 126).

Citrate inhibits stone formation by combining with calcium to form a soluble complex that reduces the availability of calcium to bind with oxalate or phosphate. The principal risk factor for hypocitraturia is a high protein intake. Men often have lower urinary citrate concentrations than women. Distal renal tubular acidosis (Chapter 104) promotes the formation of calcium phosphate stones owing to bone demineralization and an alkaline tubular pH.

Calcium oxalate kidney stones form on calcium phosphate deposits, termed Randall plaques, which are located in the renal papillae. Randall plaque formation is positively correlated with urine calcium excretion and negatively

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Urinary oxalate is derived from endogenous metabolism of glyoxylate and ascorbic acid or from dietary sources, such as cocoa, nuts, tea, and certain leafy green vegetables such as spinach. The three main causes of hyperoxaluria are excessive oxalate ingestion *(dietary oxaluria)*, excessive intestinal absorption of oxalate *(enteric oxaluria)* that is paradoxically observed in malabsorptive gastrointestinal disorders, and excessive endogenous oxalate production seen in certain hepatic enzyme deficiencies (*primary hyperoxaluria*; Chapter 189). Additionally, ethylene glycol, a common automobile antifreeze, is metabolized to oxalate and can cause excessive urinary oxalate excretion in conjunction with severe metabolic acidosis and renal failure (Chapter 96).

Enteric oxaluria results in elevated urinary oxalate levels (60 to 100 mg/day).[6] In gastrointestinal malabsorptive conditions such as Crohn disease (Chapter 127), celiac sprue (Chapter 126), jejunoileal bypass (Chapter 201), and chronic pancreatitis (Chapter 130), malabsorbed fatty acids bind dietary calcium, thereby leaving oxalate free to pass into the colon, where it is more likely to be absorbed owing to the presence of bile acids; this excess oxalate is then subsequently filtered by the glomerulus and excreted in the urine. Intestinal bacteria also can influence oxalate levels by degrading it, preventing its absorption, or even stimulating its secretion from the circulation into the intestine.

Primary hyperoxaluria (Chapter 189) results from defects in hepatic enzymes in the liver glyoxylate pathway; the results are substantial endogenous oxalate production and a marked elevation of urinary oxalate (80 to 300 mg/day).[7] Oxalate deposits in numerous organs, including the heart, bone marrow, muscle, and renal parenchyma, where they lead to renal failure, cardiomyopathy, and bone marrow suppression at an early age. In type 1 primary hyperoxaluria, which accounts for about 80% of cases, the hepatic enzyme alanine glyoxylate aminotransferase, which converts glyoxylate to glycine, is deficient because of one of a large number of mutations in the *AGXT* gene. With deficient alanine glyoxylate aminotransferase, the glyoxylate is converted to oxalate. In the milder type 2 primary hyperoxaluria, which represents approximately 10% of cases, patients lack D-glycerate reductase and glyoxylate reductase owing to mutations in the *GRHPR* gene. Type 3 primary hyperoxaluria, which accounts for about 5% of cases, is a result of mutations in the *HOGA1* gene that catalyzes the cleavage of 4-hydroxy-2-oxoglutarate to pyruvate and glyoxylate.

Nephrolithiasis and nephrocalcinosis can also result from a variety of monogenic disorders, such as Dent disease (X-linked recessive nephrolithiasis; Chapter 113), McCune-Albright syndrome (Chapters 212 and 229), osteogenesis imperfecta type 1 (Chapter 239), and congenital lactase deficiency (Chapter 126).

Citrate inhibits stone formation by combining with calcium to form a soluble complex that reduces the availability of calcium to bind with oxalate or phosphate. The principal risk factor for hypocitraturia is a high protein intake. Men often have lower urinary citrate concentrations than women. Distal renal tubular acidosis (Chapter 104) promotes the formation of calcium phosphate stones owing to bone demineralization and an alkaline tubular pH.

Calcium oxalate kidney stones form on calcium phosphate deposits, termed Randall plaques, which are located in the renal papillae. Randall plaque formation is positively correlated with urine calcium excretion and negatively

ABSTRACT

The prevalence of kidney stones has increased over the last several decades, almost certainly due to changes in diet and the increased prevalence of obesity. Most kidney stones consist of calcium complexed with oxalate and/or phosphate. The most common metabolic abnormality found in kidney stone formers is idiopathic hypercalciuria, which is due to a systemic dysregulation of calcium transport at all major calcium transporting sites and has a strong genetic component. Stones form when the saturation of the major components of the stone exceeds the solubility of the associated solid phase. Stones often present as acute colic, and their spontaneous passage is directly correlated with their size. Alpha blockers such as tamsulosin can promote passage of smaller stones. Every patient who forms a kidney stone should undergo a metabolic evaluation to prevent recurrent stones. The depth of the evaluation is dependent on a number of factors, including the age when the first stone is diagnosed and the frequency of recurrent stones. Treatment for recurrent calcium stones rests on the 4 pillars of increased hydration (goal urine volume >2 liters per day), moderation of sodium intake (goal <2000 mg/day), moderation of protein intake (~1 g/kg/day), and an age- and gender-appropriate calcium intake derived mainly from dairy products and not from supplements. If these measures do not lower urinary supersaturation adequately, then thiazide diuretics and/or potassium citrate may be required. The recurrence rate of calcium oxalate nephrolithiasis is about 25% at 3 to 5 years.

KEYWORDS

nephrolithiasis
kidney stone
hypercalciuria
hyperoxaluria
calcium stones

correlated with urine volume and pH. These calcium phosphate crystals, in the form of apatite, originate around the thin loop of Henle and then extend into the interstitium without eroding into the tubular lumen or damaging the tubular cells. The crystals move toward the urinary space, where they form Randall plaques, which are visible on cystoscopy and also may be seen as medullary calcifications on computed tomography (CT). In the presence of urine that is supersaturated with respect to calcium oxalate, these ions may form a crystal that increases in size to several millimeters or even a centimeter. The stone can break off from the Randall plaque and then migrate to, irritate, and possibly obstruct the ureter.

Uric Acid Stones

The incidence of uric acid stones appears to be rising in the United States in parallel with the increase in obesity, which leads to renal insulin resistance and a very low urine pH.[8] Over 5 times as much uric acid is soluble in a urine with a pH of 6.5 compared with a pH of 5.3. Diarrhea and diets high in animal protein can contribute to an acidic urinary pH. Most patients with uric acid stones have a reduced urine pH, and some have low urine volumes or elevated urinary uric acid levels. Uric acid stone formers have greater body weight and a higher incidence of insulin resistance and type 2 diabetes mellitus. Insulin resistance also leads to impaired urinary ammonium excretion, thereby resulting in the excretion of more hydrogen ions as titratable acids and lower urine pH, which reduces the solubility of ammonium.

Hyperuricosuria may be seen in patients who ingest large quantities of dietary purine, such as organ meats, shellfish, certain fish (e.g., anchovies, sardines, herring, and mackerel), meat extracts (e.g., bouillon and consommé), and protein. Hyperuricemic disorders, including gout (Chapter 252), myeloproliferative disorders, tumor lysis syndrome, and certain inborn errors of metabolism, can also contribute to an increased urinary uric acid. Medications such as salicylates and probenecid can be hyperuricosuric.

Struvite Stones

Struvite stones, sometimes called *triple phosphate stones, magnesium ammonium phosphate stones*, and *infection stones*, comprise only about 10 to 25% of all stones but constitute the majority of staghorn calculi, which are large stones that extend beyond a single renal calyx.[9] Struvite stones are far more common in women than in men, in large part owing to women's increased susceptibility to upper urinary tract infections (Chapter 263). Similarly, any patient with urinary stasis, such as patients with neurogenic bladders, indwelling urinary catheters, or spinal cord lesions, is susceptible to struvite stones.

Struvite stones form only in the presence of both increased production of ammonium and an alkaline urine (pH ≥ 7), which occur only with urease-producing bacteria. *Proteus mirabilis* (Chapter 281) is a common urease-producing bacterium, but other gram-negative and gram-positive bacteria, such as *Klebsiella* spp. and *Staphylococcus epidermidis*, as well as *Mycoplasma* spp. (Chapter 293) and yeast species, have been implicated in urease production. By comparison, *Escherichia coli* does not produce urease.

Cystine Stones

Cystinuria (Chapter 113), which is an autosomal dominant disorder with incomplete penetrance or an autosomal recessive disorder caused by mutations of the *SLC3A1* gene or the *SLC7A9* gene, results in decreased renal tubular reabsorption and excessive urinary excretion of the dibasic amino acids cystine, ornithine, lysine, and arginine.[10] The resulting urinary excretion of cystine

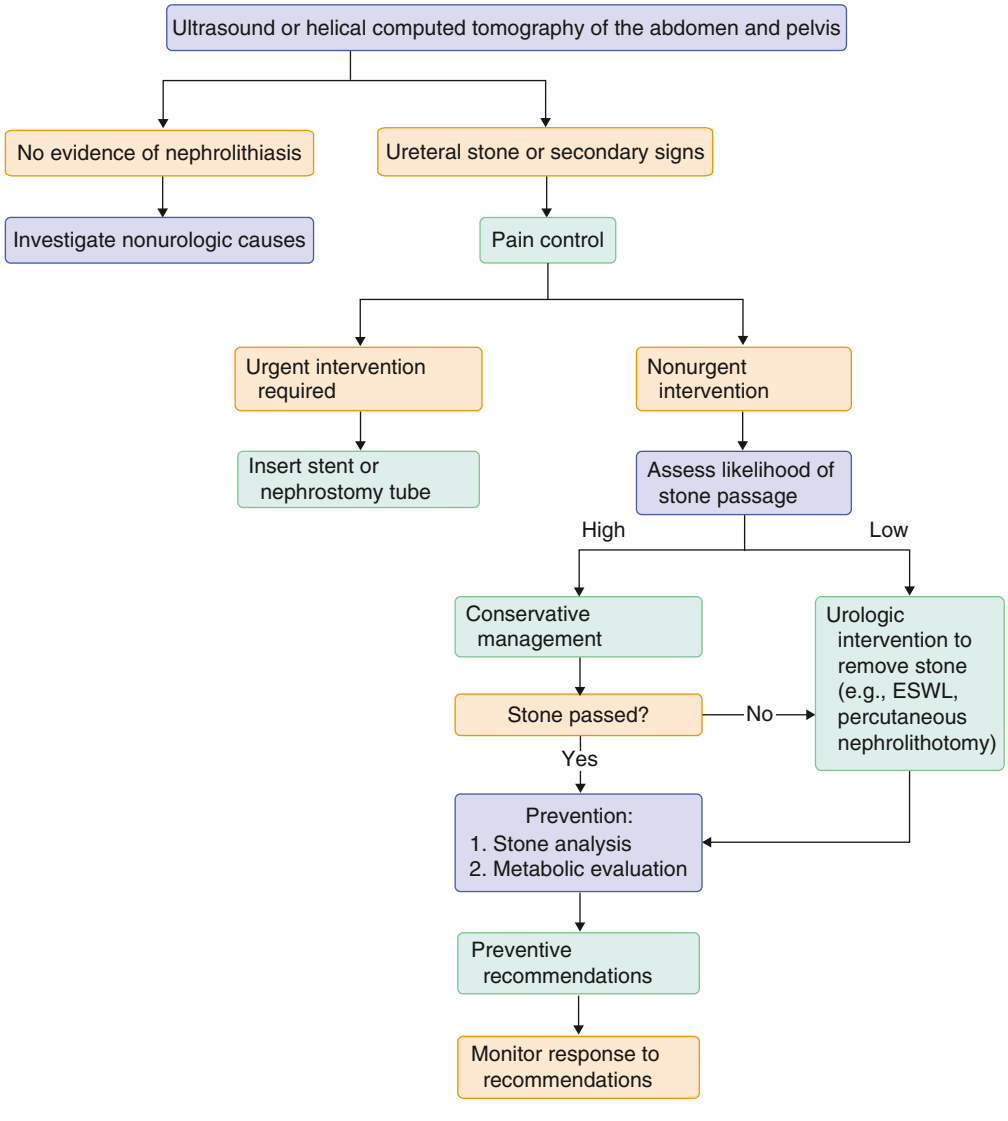

FIGURE 111-1. Algorithm for evaluation of suspected renal colic. ESWL = extracorporeal shock wave lithotripsy. (From Curhan GC. Nephrolithiasis. In: Goldman L, Schafer AI, eds. *Goldman's Cecil Textbook of Medicine*. 24th ed. Philadelphia: Elsevier Saunders; 2012.)

in the typical volume of urine exceeds its solubility of about 250 mg/L and enables stone formation. Although normal people excrete about 30 to 50 mg of cystine per day, heterozygotes for cystinuria excrete about 400 mg/day, and homozygotes often excrete about 600 mg/day. Thus, homozygotes must continually excrete more than 2 L of urine each day to avoid stone formation. Cystinuria is unrelated to the much more severe disorder *cystinosis* (Chapter 113), which results in extensive intracellular cystine accumulation.

CLINICAL MANIFESTATIONS

Patients with kidney stones often present with pain and/or hematuria, and less often present with urinary tract infections (Chapter 263) or acute kidney injury (Chapter 106), either owing to bilateral obstruction or unilateral obstruction in a single functioning kidney (Fig. 111-1). Patients often complain of severe ureteral colic. The pain is of abrupt onset and can intensify into severe, excruciating flank pain. The pain may migrate anteriorly along the abdomen and inferiorly to the groin, testicles, or labia majora as the stone moves down the ureter toward the ureterovesical junction. The pain resolves only after the stone passes or is removed. Microscopic or gross hematuria is common, and patients occasionally present with painless hematuria (see Fig. 100-3). The finding of a stone on radiographic examination does not preclude another cause. Conversely, even large calculi may be asymptomatic and be discovered during the investigation of unrelated symptoms. Obstruction caused by calculi may also be painless, and nephrolithiasis should always be considered in the differential diagnosis of unexplained acute or chronic kidney disease (Chapters 106 and 116).

DIAGNOSIS

The physical examination can provide clues to the diagnosis of kidney stones but is not diagnostic. Some patients have demonstrable flank tenderness, and a rare patient with hyperuricemia will have tophi (Chapter 252). However, the physical examination is most helpful for not showing other potential causes of pain. The suspicion of a kidney stone generally obligates radiographic evaluation. Radiographic studies can be deferred, however, in patients in whom the clinical diagnosis is clear, who have no evidence of infection, who are able to eat and drink, and who can be managed on oral analgesics.

Ultrasonography is an easy and rapid way to detect possible urinary obstruction without exposing the patient to ionizing radiation. Ultrasound can detect clinically significant renal calculi, with about an 85% sensitivity for detecting the ureteral stones that cause acute symptoms. Among emergency department patients with suspected nephrolithiasis, those who undergo ultrasonography have a lower cumulative radiation exposure than those randomized to CT without any significant differences in high-risk diagnoses, serious adverse events, pain scores, or subsequent rehospitalizations or emergency department visits.[A1] A helical CT scan or a low radiation CT scan without radiographic contrast can detect kidney stones with both a sensitivity and a specificity exceeding 95% (Fig. 111-2).[11] Based on the density of the stone, it also can often differentiate a calcium-containing stone from a cystine or uric acid stone. An added benefit is that helical CT is often helpful in determining the cause of nonstone abdominal pain (Chapter 119). In certain situations, such as in human immunodeficiency virus (HIV)–infected patients thought to have stones induced by a protease inhibitor, a helical CT scan with contrast is often required because the stones are not radiopaque and do not obstruct the ureter.

Approximately 90% of kidney stones are radiopaque and may be detected on a simple abdominal radiograph. Unfortunately, however, the stone is often obscured by stool, vertebrae, or abdominal gas, so the sensitivity of a plain abdominal radiograph is about 55%, and its specificity is only about 75%. Uric acid stones are radiolucent and cannot be detected radiographically without contrast.

Intravenous pyelography has a sensitivity of about 75% and a specificity of more than 90% for detecting renal calculi. Intravenous pyelography is also useful for identifying structural abnormalities of the urinary tract, such as a medullary sponge kidney (Chapter 112), that predisposes to stone formation. However, an intravenous pyelogram often does not detect nonobstructing radiolucent stones because they do not create a filling defect. An intravenous pyelogram exposes the patient to more radiation than a plain radiograph but less than a CT scan. It also carries the risk of radiographic contrast material, which is greater in individuals with underlying renal compromise. With the widespread availability of ultrasonography and helical CT scans, an intravenous pyelogram is rarely indicated.

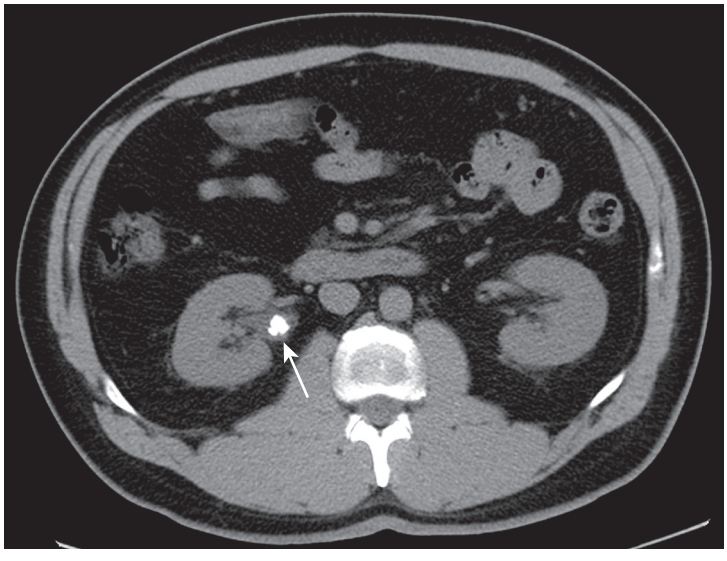

FIGURE 111-2. **High-resolution helical computed tomographic (CT) scan of the upper part of the abdomen demonstrating a stone in the right renal pelvis (*arrow*). There is no hydronephrosis. (From Curhan GC. Clinical crossroads: a 44-year-old woman with kidney stones. *JAMA*. 2005;293:1107-1114.)**

TREATMENT

Medical Therapy

Because the pain of renal colic can be excruciating, pain control is critical after the definitive diagnosis has been made. If nausea and vomiting prevent the use of oral medication, parenteral medication is typically required. Nonsteroidal anti-inflammatory drugs (NSAIDs; Table 26-4) are as or more effective compared with opiates for renal colic and are preferred because they have fewer side effects.[A2,A3] An intravenous or intramuscular option is ketorolac (15 to 30 mg), and an oral option is ibuprofen (200 to 400 mg/dose every 4 to 6 hours with a maximum daily dose of 1.2 g) in patients who can tolerate oral medication. Because NSAIDs can cause acute kidney injury, especially in patients who are dehydrated or have pre-existing kidney injury, adequate hydration (e.g., normal saline at 75 to 150 mL/hour) is essential, but neither high-volume fluid therapy nor diuretics promote the passage of the stone. If necessary, oral oxycodone (5 to 15 mg every 4 to 6 hours as needed) may be added to ibuprofen for outpatient pain control. The dose and frequency of administration of oxycodone should be reduced in patients who have renal impairment.

Medical Expulsive Therapy

Kidney stones 5 mm or smaller have about a 70% probability of passing spontaneously, whereas stones between 5 and 7 mm have a 60% chance, stones 7 to 9 mm have a 48% chance, and stones 9 mm or larger have a 25% chance of passing spontaneously. Stones located more distally in the ureter are more likely to pass spontaneously. Medical expulsive therapy may be cautiously attempted with ureteral stones smaller than 10 mm diameter for 4 to 6 weeks if pain is controlled, kidney function is normal, and there is no evidence of urinary tract infection or significant obstruction.[12] The patient must be followed closely, generally with repeat ultrasound examinations every week or 2 weeks.

Expulsive therapy can reduce ureteral spasm and increase spontaneous passage rates by about 50%. Meta-analyses demonstrate an overall benefit for the α-blocker tamsulosin (0.4 mg orally daily),[A4,A5] which appears to promote the passage of the stone more quickly and effectively than the calcium-channel blocker nifedipine (nifedipine XL 30 mg daily or twice daily). Other options include a phosphodiesterase type 5 inhibitor (e.g., tadalafil 10 mg/day for 10 days) or a selective α_{1a}-receptor blocker (e.g., silodosin 4 mg/day). Silodosin appears more effective than tamsulosin for promoting the passage of large, distal ureteral stones.[A6]

Initial Surgical Treatment

Stones that cause obstruction, infection, acute kidney injury, or intractable pain must be removed expeditiously. In general, larger and more proximal stones are less likely to pass spontaneously, even with medical expulsive therapy, and are often an indicator for earlier intervention. Approximately 15% of all kidney stones require an intervention to remove them. For example, removal of small, asymptomatic kidney stones at the time of surgery to remove a ureteral or contralateral stone reduces the rate of relapse.[A7]

The approach to stone removal depends on its size, location, and composition, as well as on urinary tract anatomy. The major options for ureteral stone removal include percutaneous nephrolithotomy, extracorporeal shock wave lithotripsy, and ureteroscopy; open surgical extraction is rarely required. Percutaneous nephrolithotomy involves the passage of a flexible scope through the kidney and into the urinary space. Extracorporeal shock wave lithotripsy focuses external sound waves onto the kidney stone, thereby causing it to

fragment into smaller stones that can more easily be passed spontaneously. Ureteroscopy involves the passage of a ureteroscope into the ureter with removal or laser fragmentation of the stone. Meta-analyses suggest that ureteral stones should be treated with ureteroscopy or shock wave lithotripsy rather than percutaneous nephrolithotomy and that percutaneous nephrolithotomy is the treatment of choice for lower pole renal stones and the majority of large kidney stones (≥15 mm),[A8] because it results in longer stone-free rates and a lower need for retreatment, even though it is associated with more complications, usually minor, and a longer hospitalization compared with shock wave lithotripsy.

Medical Evaluation

After an initial stone episode, the recurrence rate in nontreated patients is estimated to be about 25% at 3 to 5 years and about 50% at 5 to 10 years. As a result, every patient who forms an initial stone should undergo evaluation with the goal of preventing recurrent stones. The history should focus on uncovering factors that predispose to stone formation. All stones should be analyzed to assist in defining the underlying metabolic abnormality and to guide therapy.[13]

A careful dietary history, including an estimate of fluid intake, is essential. Many stone formers are erroneously instructed to eliminate all calcium from their diet, a practice that not only increases stone formation but also may induce bone demineralization. Sodium intake should be estimated because sodium excretion obligates calcium excretion, thereby potentially leading to urinary supersaturation. Excessive animal protein intake increases metabolic acid production, which increases bone demineralization and calciuria.

Hypercalcemic disorders—including malignancy (Chapter 227), hyperparathyroidism (Chapter 227), and sarcoidosis (Chapter 83)—often result in hypercalciuria, increased urinary supersaturation, and calcium stone formation. Malabsorptive gastrointestinal disorders, such as Crohn disease (Chapter 127) and celiac disease (Chapter 126), or weight reduction surgery (Chapter 201), such as ileal resection or jejunoileal bypass, will often result in calcium oxalate stone formation from increased oxalate absorption and excretion as well as volume depletion.

Medications that can cause calcium stone formation include loop diuretics, which increase urinary calcium excretion, as well as salicylates and probenecid, which increase urinary uric acid excretion. Various medications that can themselves precipitate into stones include intravenous acyclovir, high-dose sulfadiazine, triamterene, and the antiretroviral agents indinavir and nelfinavir. Other medications that inhibit renal tubular carbonic anhydrase activity, such as acetazolamide and topiramate, can lead to metabolic acidosis, bone resorption, hypercalciuria, lower urinary citrate excretion, and higher urinary pH, all of which promote the formation of calcium phosphate stones.

The number and frequency of stones formed, the patient's age at the time of the first stone, the size of the stone, and an analysis of the composition of the stone are also important clues. Stones that develop at a young age suggest a genetic disorder, such as primary hyperoxaluria or cystinuria. Large staghorn calculi in elderly patients are consistent with struvite stones. A stone's response to intervention is also helpful: cystine stones do not fragment well with lithotripsy, and stones that recur frequently in a single kidney suggest a unilateral anatomic abnormality.

Basic laboratory testing should include levels of serum electrolytes (sodium, potassium, chloride, and bicarbonate), creatinine, calcium, phosphorus, uric acid, 25-hydroxyvitamin D, and thyroid-stimulating hormone. If the serum calcium is above and the serum phosphorus is below the midrange of normal, a serum parathyroid hormone level should be obtained.

An elevated urine specific gravity suggests inadequate fluid intake. Hematuria may indicate irritation to the urothelial lining by a stone. Characteristic crystals (see Fig. 100-10) are more common than in nonstone formers. The presence of hexagonal crystals (see Fig. 100-9) mandates that cystinuria be excluded. Patients with struvite stones generally have an elevated urine pH (>7.4) owing to the splitting of urea into ammonia and bicarbonate, whereas a low urinary pH (<5.5) raises the suspicion of uric acid stones. An elevated urine pH combined with bacteriuria (Chapter 263) suggests struvite stones. Because urease production may stimulate struvite stone formation despite low bacterial colony counts, the laboratory must identify all bacteria and determine antibiotic sensitivities even with low colony counts. If no bacteria are isolated, cultures for *Ureaplasma urealyticum* should be requested. The combination of an elevated urinary pH (6.5 to 7.2) with a low serum potassium and serum bicarbonate level strongly suggests distal renal tubular acidosis (Chapter 104).

In patients with recurrent stones and/or high-risk characteristics for recurrence, a 24-hour urine collection can determine the levels of calcium, oxalate, citrate, sodium, urate, phosphorus, and creatinine, as well as the calculation of supersaturation with respect to calcium oxalate, calcium phosphate, and uric acid (Table 111-1). Increased ion excretion of the components of a stone leads to increased rates of forming recurrent stones. An elevated supersaturation should lead the clinician to determine the individual components of the urine that are causing the increased supersaturation, and efforts can then be made to rectify these abnormalities. Cystine should also be measured at least once in every stone former to exclude cystinuria and regularly in patients who form cystine stones. Multivitamins should be discontinued about 5 days before the collection to prevent any antioxidant effect on the urine sample.

TABLE 111-1 OPTIMAL 24-HOUR URINE VALUES IN PATIENTS WITH NEPHROLITHIASIS

PARAMETER	VALUE
Volume	>2-2.5 L
pH	>5.5 and <7.0 (24-hr specimen not required)
Calcium	<250 mg
Oxalate	<40 mg
Sodium	<2000 mg
Uric acid	<750 mg
Phosphorus	<1100 mg
Citrate	>320 mg
Supersaturation with respect to calcium oxalate	<5
Supersaturation with respect to calcium phosphate	0.5-2
Supersaturation with respect to uric acid	0-1

Urine creatinine should be measured to ensure the adequacy of collection and should be >15 mg/kg in men and >10 mg/kg in women. Supersaturation is the ratio of the ion activity product and its solubility product.

PREVENTING RECURRENT STONES

Preventive treatment (Fig. 111-3) emphasizes advising the patient to increase oral fluid intake to produce a urine volume greater than 2 L per day, an oral intake that will reduce recurrent stone formation by about 50%.[A9,A10]

Calcium Stones

Because urine calcium excretion is directly correlated with urine sodium excretion, decreasing sodium intake will decrease urine calcium excretion and reduce supersaturation.[14] Patients with calcium stones should limit daily sodium intake to no more than 2 g per day and reduce animal protein intake to 0.8 to 1.0 g/kg per day.

The recommended calcium intake for a 19- to 50-year-old man or woman is 1000 mg of elemental calcium per day, and a number of studies demonstrate decreased formation of calcium stones when people consume diets adequate in calcium, presumably because appropriate calcium intake is needed for intestinal binding of dietary oxalate to prevent its absorption. Dairy products are preferred over calcium supplements because clinical studies indicate that women taking supplemental vitamin D and calcium have a significant increase in stone formation.

Patients with persistent hypercalciuria often benefit from longer-acting thiazide diuretics (e.g., chlorthalidone 12.5 to 25 mg/day), which directly lower urinary calcium and reduce recurrent stone formation by about 50%.[A11] However, a short-acting thiazide diuretic given once daily does not reduce symptomatic recurrences.[A12] Thiazides are effective only if patients restrict dietary sodium. In patients with hypercholesterolemia or hyperglycemia, indapamide (1.25 to 5 mg/day) can be used because it has less effect on these parameters. If patients develop hypokalemia, dietary potassium intake should be increased, or a potassium supplement can be administered. Allopurinol should be prescribed as for gout (300 mg daily; see Chapter 252). Potassium citrate (10 to 40 mEq/day) will increase urinary citrate excretion, bind urinary calcium, and further decrease recurrent stone formation.[A13] Potassium citrate is available as a wax-matrix tablet. A 24-hour urine collection can be repeated in a month or two to assess the response to therapy. Sodium-glucose cotransporter-2 (SGLT2) inhibitors appear to reduce the risk of nephrolithiasis by 50%[A14] but are not currently recommended for routine prophylactic use.

Patients with diet-related hyperoxaluria should be instructed to limit or avoid foods with high oxalate content such as cocoa, nuts, tea, and green leafy vegetables such as spinach. Because dietary calcium and oxalate bind in the gut, patients should consume these foods with calcium-containing foods. For enteric hyperoxaluria, treatment is first directed at the underlying disorder and then at instituting therapy for the cause of the steatorrhea (Chapter 126). Dietary oxalate should be restricted, and dietary calcium and oxalate should be ingested at the same meal. A diet that is low in fat; that is high in fruits, vegetables, and low-fat dairy products; that is rich in grains, fish, poultry, beans, seeds, and nuts; and that contains fewer sweets and less added sugar and red meat appears to be a reasonable alternative to a low-oxalate diet. Additional fluid intake and potassium citrate are often beneficial. Reloxaliase, which is an oral nonabsorbable oxalate-degrading enzyme,[15] is currently in clinical trials.

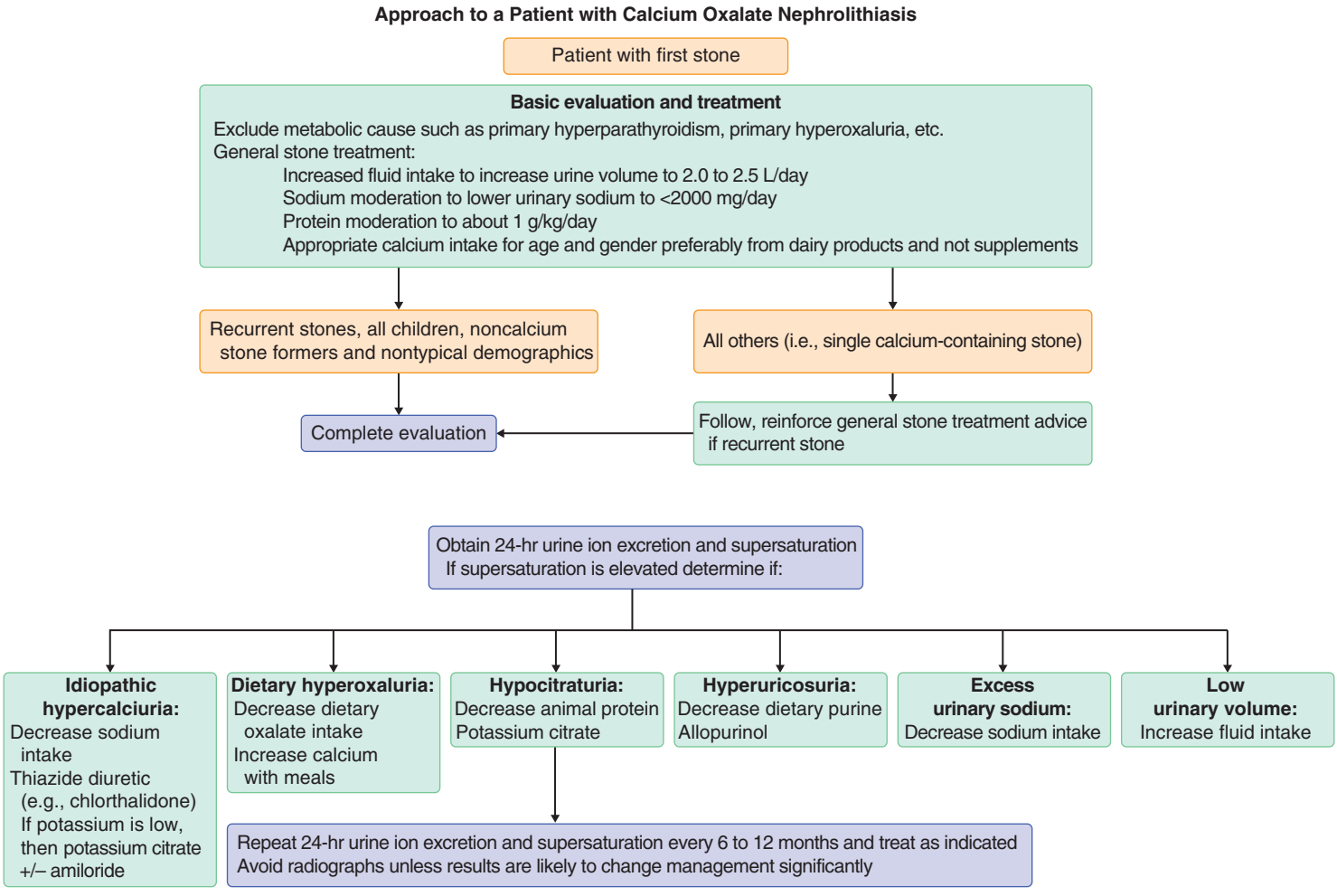

FIGURE 111-3. **Approach to a patient with calcium oxalate nephrolithiasis.**

In some patients with type 1 primary hyperoxaluria, pyridoxine (vitamin B_6) can increase enzyme activity and reduce oxalate production. These patients should also be treated with measures that reduce the precipitation of calcium oxalate, such as ample fluid intake and potassium citrate (10 to 40 mEq/day). Lumasiran, which is a small interfering RNA that decreases the levels of glycolate oxidase thereby resulting in less production of oxalate, reduces urinary oxalate levels by approximately 50% and reduces plasma oxalate levels into the normal range in patients who have type 1 primary hyperoxaluria.[A15] Lumasiran has the potential to eliminate the clinical manifestations, such as renal failure, of type 1 primary hyperoxaluria and to prevent the need for curative liver transplantation. All patients with type 1 primary hyperoxaluria should be seen by specialists and be considered for treatment with this therapy.

Calcium stones may be found in patients with hyperuricosuria. These patients often excrete excess amounts of urinary uric acid but normal amounts of urinary calcium and oxalate. Compared with patients with pure uric acid stones, they generally have a higher urinary pH (about 5.5). The mechanism by which uric acid promotes calcium stone formation is unclear. Therapy generally consists of dietary purine restriction, increased fluid intake, and the addition of allopurinol (300 mg daily) if necessary.

If moderation of dietary protein is not successful in patients with hypocitraturia, oral potassium citrate is given (10 to 40 mEq/day). Serum levels of potassium and bicarbonate must be closely monitored, especially in patients with chronic kidney disease.

Uric Acid Stones

Uric acid stones are radiolucent and are thus most often visualized with CT. Therapy for patients with uric acid stones begins with nonspecific measures such as increasing fluid intake, a low purine diet, and lowering animal protein intake to increase urinary pH. Ideally, the urinary pH should be elevated to approximately 6.5 to 7.0, a level that not only prevents new stone formation but also can dissolve existing uric acid stones without promoting calcium phosphate deposition. Potassium citrate (10 to 40 mEq/day) may be required to raise the urinary pH sufficiently. If all else fails, the carbonic anhydrase inhibitor acetazolamide (250 to 500 mg/day) may be initiated to raise urine pH. Because concomitant hyperuricemia may be present, allopurinol (100 to 300 mg daily) may be indicated to lower the serum uric acid level.

Struvite Stones

Struvite stones rapidly grow to a large size and may promptly recur if not completely removed. Therapy requires complete surgical stone removal coupled with appropriate long-term antibiotics (Chapter 263), selected on the basis of cultures of stone fragments retrieved from surgery. Antibiotics should be continued at full doses until the urine is sterile and then continued at a lower dose. Monthly surveillance cultures should be performed until the urine remains sterile for 3 consecutive months. Antibiotics can then be discontinued with monthly surveillance urine cultures for another year.

Cystine Stones

Cystine kidney stones, which usually develop by the second or third decade of life, are radiopaque and may appear as staghorn calculi or multiple stones. The disease should be suspected in any patient with an early onset of stones, frequently recurrent nephrolithiasis, and a family history of the disease. Although the presence of the classic hexagonal cystine crystals in the urine (see Fig. 100-9 in Chapter 100) may suggest the diagnosis, anyone suspected of the disorder should have a quantitative cystine measurement on a 24-hour urine sample.[16]

The goal of treatment is to lower the urinary cystine concentration below the limits of solubility.[17] Patients are advised to drink sufficient quantities of water to maintain excreted cystine in solution. Patients should moderate intake of sodium and animal protein foods, which contain large amounts of methionine, which is a precursor of cystine. Because cystine is more soluble at a higher pH, urinary alkalinization with potassium citrate (10 to 40 mEq/day) can be used to maintain a urinary pH ≥ 7.0. Chelating agents reduce the free cystine concentration by forming more soluble compounds and should be prescribed by a specialist owing to their high incidence of side effects.

PROGNOSIS

The recurrence rate of calcium oxalate nephrolithiasis is about 25% at 3 to 5 years and about 50% at 5 to 10 years, and the rate is higher for cystine, uric acid, and struvite stones.[18] For stones that have not yet caused symptoms, the risk of developing symptoms varies widely among studies, but the size of the stone is not predictive of future symptomatic nephrolithiasis.[19] Patients with kidney stones often have an increase in aortic calcification and a decrease in bone mineral density, thereby supporting the concept that there is dysregulation in calcium homeostasis in patients who form calcium-containing stones. Patients with nephrolithiasis have a higher risk of losing kidney function[20] and also have an increased risk for coronary heart disease and stroke.

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112 CYSTIC KIDNEY DISEASES

M. AMIN ARNAOUT

DEFINITION AND EPIDEMIOLOGY

The term *cystic kidney diseases* refers to a heterogeneous group of hereditary and acquired disorders characterized by the presence of unilateral or bilateral renal cysts.[1] When acquired singly or in small numbers and in the absence of any other pathology, renal cysts are termed *simple cysts*, which are present in approximately 50% of individuals older than 40 years, are usually not loculated, and tend to bulge out from the renal surface (Fig. 112-1). The polycystic kidney diseases (PKDs), by comparison, constitute a clinically important group of genetically mediated disorders characterized by prominent, expanding, typically bilateral renal cysts. PKDs are classified as dominant, recessive, or X-linked, based on their pattern of inheritance. Autosomal dominant PKD,

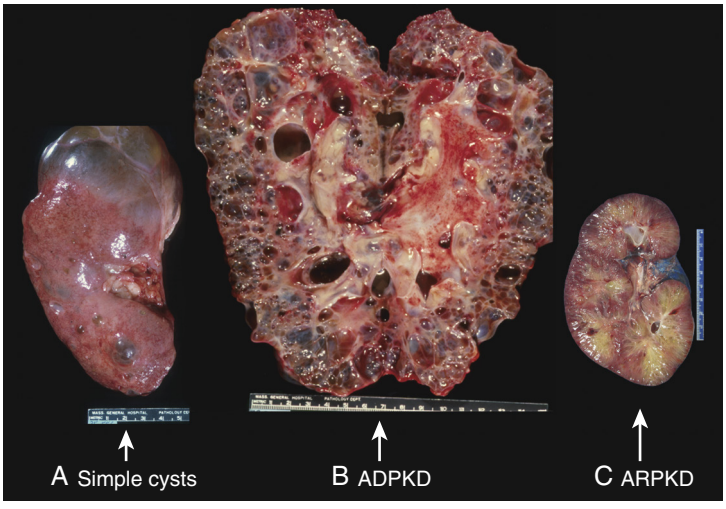

FIGURE 112-1. Gross pathology of selected cystic kidney diseases. A, Photograph of a kidney with multiple simple cysts. The cysts bulge out from the surface of a normal-sized kidney. **B**, Sagittal cross section of a kidney from an adult with autosomal dominant polycystic kidney disease (ADPKD). Multiple macroscopic cysts have resulted in an enlarged but still reniform kidney (note the evidence of prior hemorrhage within some of the cysts). (Courtesy Dr. Robert Colvin, Massachusetts General Hospital.) **C**, Sagittal cross section of a kidney segment from a patient with autosomal recessive polycystic kidney disease (ARPKD). It shows multiple, small, slit-like radially oriented cysts (ranging from 0.2 cm up to 1.8 cm in greatest dimension) that replace the entire cortex and medulla and are arranged perpendicular to the external surface. Patchy foci of hemorrhage are also present. (Courtesy Dr. Alyaa Al-Ibraheemi, Boston Children's Hospital.)

with a prevalence rate between 1 in 400 and 1 in 2000,[2] is among the most common monogenic diseases in humans and accounts for about 8 to 10% of all end-stage renal disease in the United States. Autosomal dominant PKD develops in an age-dependent manner and affects mainly adults. Autosomal recessive PKD, by contrast, is a relatively rare childhood disorder that appears in 1 in every 6000 to 50,000 live births. Renal cysts are also seen in several other rare hereditary kidney diseases and in several syndromic PKDs (Table 112-1). Collectively, the hereditary PKDs generally affect both sexes and all races equally and cost more than $1 billion annually to manage in the United States alone. *Acquired cystic kidney disease* refers to the multiple bilateral renal cysts that occur in 90% of patients who have received renal replacement therapy for 8 years or longer. Acquired cystic kidney disease is associated with increased rates of renal cell carcinoma.

AUTOSOMAL DOMINANT POLYCYSTIC KIDNEY DISEASE

PATHOBIOLOGY

Autosomal dominant PKD is a systemic disorder characterized by cyst formation in multiple organs, including the kidneys, other ductal organs, and the cardiovascular system. Renal cysts originate as outpouchings of tubules and may arise from any portion of the nephron, with up to 1% of nephrons involved. The outpouchings expand and eventually separate from the parent tubules, yielding cysts (Fig. 112-2). Cyst growth is caused by proliferation of the cyst lining cells and by abnormal fluid accumulation that results when chloride-driven fluid secretion outpaces absorption. Cyst expansion and fibrosis (induced by cystic epithelium-derived chemokines, cytokines, and growth factors that attract macrophages and fibroblasts) cause compression and obstruction of noncystic normal tubules, thereby resulting in upstream tubular dilation. The kidneys become massively enlarged, and kidney function progressively declines.

Genetics

Heterogeneous mutations in *PKD1* and *PKD2* cause ADPKD and account for approximately 80% and 15% of the cases, respectively. Mutations in *GANAB*, *DNAJB11*,[3] and *ALG9*, which code for endoplasmic reticulum enzymes involved in the protein biosynthetic pathway, account for fewer than 1% of cases. Carriers of loss-of-function mutations in *GANAB*, which encodes GIIα, have mild autosomal dominant PKD and variable degrees of polycystic liver disease. Carriers of inactivating mutations in *DNAJB11*, which encodes the chaperon protein ERdj3, have a phenotypic hybrid of autosomal dominant PKD and autosomal dominant tubulointerstitial kidney disease (TKD), characterized

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PROGNOSIS

The recurrence rate of calcium oxalate nephrolithiasis is about 25% at 3 to 5 years and about 50% at 5 to 10 years, and the rate is higher for cystine, uric acid, and struvite stones.[18] For stones that have not yet caused symptoms, the risk of developing symptoms varies widely among studies, but the size of the stone is not predictive of future symptomatic nephrolithiasis.[19] Patients with kidney stones often have an increase in aortic calcification and a decrease in bone mineral density, thereby supporting the concept that there is dysregulation in calcium homeostasis in patients who form calcium-containing stones. Patients with nephrolithiasis have a higher risk of losing kidney function[20] and also have an increased risk for coronary heart disease and stroke.

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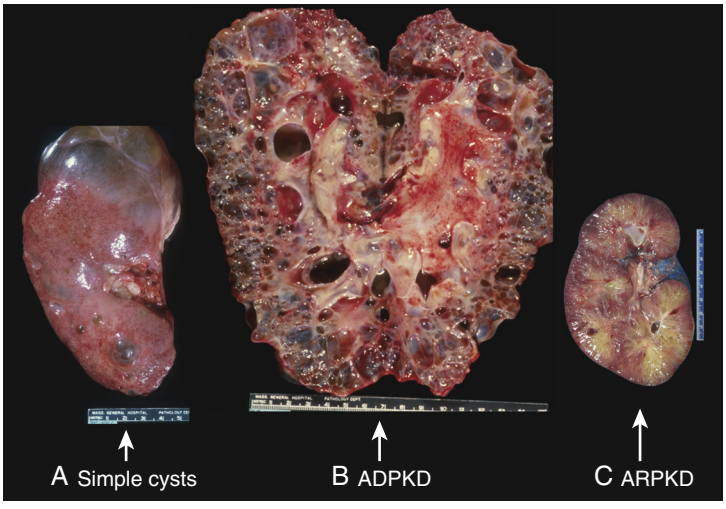

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ABSTRACT

Kidney cysts affect nearly 50% of individuals older than age 40 years. Although most are simple cysts with no associated pathology, polycystic kidney disease (PKD) has multiple etiologies, with a variable onset, presentation, and rate of progression to end-stage renal disease. In PKD, cysts arise as tubule dilations involving any or specific renal tubular segments, are fueled by tubular cell proliferation, and expand by fluid secretion. Compression and obstruction of adjacent noncystic tubules and disruption of normal kidney architecture lead to fibrosis and progressive loss of kidney function. Large cysts are a prominent feature of autosomal dominant PKD, the most common form of PKD, whereas most other forms are characterized by small cysts. Both genetic and nongenetic factors are involved in controlling the rate of progression of kidney disease. PKD is most often inherited and is commonly associated with systemic manifestations that reflect the extrarenal loss of function of the defective gene. Many of the PKD genes are involved in the formation, maintenance, and/or regulating function of primary cilia, thus linking ciliary defects to PKD genesis. Diagnosis of PKD is aided by a positive family history, various imaging modalities, and genotyping, the latter being increasingly utilized especially in pre-implantation and prenatal diagnosis. Treatment varies with the underlying disease. Recent data show that inhibition of the vasopressin receptor 2 slows the decline in kidney function in autosomal dominant polycystic kidney disease. Other therapies are aimed at control of hypertension, infection, pain, nephrolithiasis, renal salt wasting, and metabolic complications.

KEYWORDS

kidney cysts
aneurysms
hypertension
primary cilia
cell proliferation
fibrosis
kidney failure
genetics

TABLE 112-1 COMPARISON OF CLINICAL FEATURES OF CYSTIC KIDNEY DISEASES

DISEASE	INHERITANCE	FREQUENCY	GENE PRODUCT	AGE OF ONSET	CYST ORIGIN	RENOMEGALY	CAUSE OF ESRD	OTHER MANIFESTATIONS
Simple cysts	No	50% in persons age 40 yr and older	None*	Adulthood	Anywhere (usually cortical)	No	No	None
ACKD	No	90% of ESRD patients at 8 yr	None*	Years after onset of ESRD	Proximal and distal tubules	Rarely	No	None
ADPKD	AD	1 : 400-1000	Polycystin-1(PC1); Polycystin-2 (PC2); GIIα; ERdj3; ALG9	20s and 30s	Anywhere (including Bowman capsule)	Yes No (for ERdi3, ALG9)	Yes (for PC1, PC2, or ERdj3) No (for GIIα or ALG9)	Primarily in PKD1/PKD2-disease: liver cysts, cerebral aneurysms, hypertension, mitral valve prolapse, kidney stones, urinary tract infections
ARPKD	AR	1 : 10,000-40,000	Fibrocystin/polyductin; DZIP1L	First year of life	Distal nephron, collecting duct	Yes	Yes	Hepatic fibrosis Hypertension Pulmonary hypoplasia
NPH	AR	1 : 80,000	Nephrocystins (NPH1–20) MAPKBP1	Childhood or adolescence	Loop of Henle, distal convoluted tubule	No	Yes	Retinal degeneration Neurologic, skeletal, hepatic, and cardiac malformations
ADTKD-UMOD	AD	Rare	Uromodulin	Adolescence	Cortico-medullary	No	Yes	Gout
ADTKD-MUC1	AD	Rare	Mucin-1	Adolescence	Cortico-medullary	No	Yes	Gout (less prevalent and later onset)
ADTKD-REN	AD	Rare	Renin	Childhood	Cortico-medullary	No	Yes	Anemia Early-onset gout Hyperkalemia Mild hypotension
ADTKD-SEC61A1	AD	Rare	α1 subunit of Sec61 translocon	Childhood	Glomerular	No	Yes	Anemia Recurrent infections Early-onset gout Developmental defects Cognitive impairment
ADTKD-HNF1B	AD; spontaneous	Rare	HNF1β	Childhood or adulthood	Cortico-medullary	Rarely	Variable	Early-onset diabetes and pancreatic hypoplasia Hypomagnesemia Hyperthyroidism Liver function abnormalities Gout Renal and urogenital anomalies Intellectual disability Risk of renal cell carcinoma
MSK	No; AD	1 : 5000-20,000	None*	Adulthood	Medullary collecting duct	No	No	Kidney stones
Bardet-Biedl syndrome	AR	1 : 65,000-160,000	BBS 1-21	Childhood	Renal calyces	Rarely	Yes	Syndactyly and polydactyly Obesity Retinal dystrophy Male hypogenitalism Hypertension Intellectual disability
Oral-facial-digital syndrome-1	XD	1 : 250,000	OFD1 protein	Childhood or adulthood	Renal glomeruli	Rarely	Yes	Malformation of the face, oral cavity, and digits Liver cysts Intellectual disability
HIPKD	AR	Rare	Phospho-mannomutase 2	Childhood	Renal glomeruli	Yes	Yes	Hypoglycemic seizures Occasional liver cysts ARPKD-like phenotype
Tuberous sclerosis	AD	1 : 10,000	Hamartin (TSC1), tuberin (TSC2)	Childhood	Loop of Henle, distal convoluted tubule	Rarely	Rarely	Renal cell carcinoma Tubers Seizures Angiomyolipomas Hypertension
VHL syndrome	AD	1 : 40,000	VHL protein	20s	Cortical nephrons	Rarely	Rarely	Retinal angioma CNS hemangioblastoma Renal cell carcinoma Pheochromocytoma

*No known genetic susceptibility.

ACKD = acquired cystic kidney disease; AD = autosomal dominant; ADPKD = autosomal dominant polycystic kidney disease; ADTKD = autosomal dominant tubulointerstitial kidney disease; ALG9 = α-1,2-mannosyltransferase; AR = autosomal recessive; ARPKD = autosomal recessive polycystic kidney disease; CNS = central nervous system; DZIP1L = DAZ interacting protein 1-like; ERdj3 = ER DnaJ homologue glycoprotein encoded by DnaJ homolog subfamily B member 11; ESRD = end-stage renal disease; GIIα = glucosidase II alpha subunit; HIPKD = PKD with hyperinsulinemic hypoglycemia; HNF1β = hepatocyte nuclear factor 1 β; MSK = medullary sponge kidney; MUC1 = mucin-1; NPH = nephronophthisis; REN = renin; UMOD = uromodulin; VHL = von Hippel-Lindau; XD = X-linked dominant.

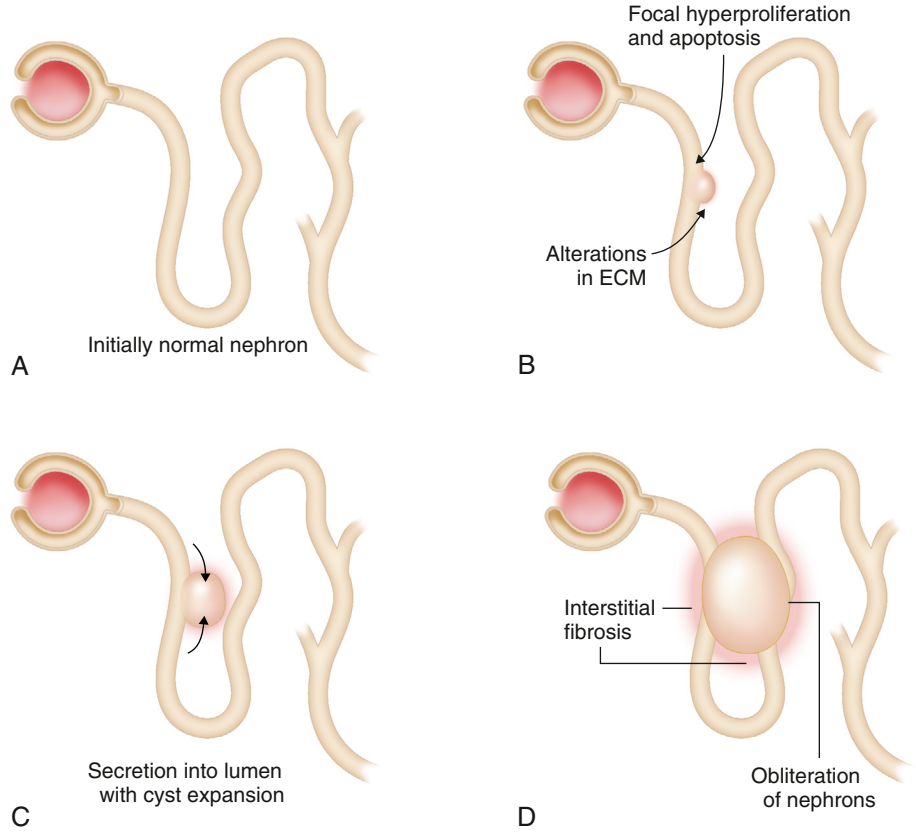

FIGURE 112-2. A to D, Steps involved in cyst formation in autosomal dominant polycystic kidney disease. Note that this process occurs hundreds or thousands of times during the natural history of the disease. ECM = extracellular matrix.

by normal-sized cystic kidneys, liver cysts, and progressive interstitial fibrosi that lead to late-onset end-stage renal disease and is reminiscent of autosomal dominant TKD-UMOD (defective proteostasis caused by *DNAJB11* variants might affect uromodulin trafficking as well). Carriers of inactivating mutations in *ALG9*, which encodes alpha-1,2-mannosyltransferase, develop both kidney and liver cysts, but they have milder disease than typical autosomal dominant PKD. In *GANAB*-, *DNAJB11*- and *ALG9*-associated ADPKD, cystogenesis appears to be driven by variable defects in the folding and maturation of PC1. In a minority of autosomal dominant PKD cases, no demonstrable mutations are found in these genes, thereby suggesting that additional genes may be involved.[4]

PKD1 is 54 kb long and is located on chromosome 16p13.3, adjacent to the tuberous sclerosis 2 (*TSC2*) gene. *PKD1* has 46 exons, generates a 14-kb transcript, and encodes a 4302-residue protein called polycystin-1 (PC1), the first described member of an expanding polycystin protein family. The 5′ region of human *PKD1* (to exon 33) is replicated on the same chromosome, resulting in approximately six copies of *PKD1*-like pseudogenes, which must be distinguished from the *PKD1* gene in direct mutational analysis. Most mutations in *PKD1* are inactivating truncation mutations or affect protein biogenesis, trafficking, or stability. To date, over 2300 mutations have been identified throughout the gene (http://pkdb.mayo.edu/) but especially in the 3′ half. Loss of function mutations and mutations in the 5′ half of the gene are associated with more severe disease, with only about 20% of patients retaining adequate renal function at 60 years of age (compared with about 40% of those with 3′ mutations).

The 68-kb *PKD2* gene is located on chromosome 4q13-23, transcribes 15 exons, and generates a 5-kb transcript, which encodes a protein of 968 residues called polycystin-2 (PC2). To date, 278 heterogeneous mutations in *PKD2* have been identified. The greater number of cysts that occur at an early age in *PKD1* compared with *PKD2* disease is likely a result of a higher frequency of mutations in the longer *PKD1* coding region and the presence of six *PKD1*-like pseudogenes that may be involved in recombination-based gene conversion and rearrangements.

Because renal cysts develop from approximately 1% of nephrons, somatic inactivation of the normal *PKD1* or *PKD2* allele (somatic second hit model) has been proposed as the main mechanism of cyst initiation. Alternatively, the *PKD1* or *PKD2* haploinsufficiency state may produce wide stochastic fluctuations in levels of the normal gene product and may reduce it to below a critical disease-causing threshold in the absence of a somatic second hit (haploinsufficiency model). The genomic instability associated with the *PKD1* or *PKD2* haploid state may increase the likelihood of somatic second hits, which contribute to disease progression by providing cysts with a growth or survival advantage.

There are wide variations in the onset and severity of autosomal dominant PKD even among affected members of the same family. This variability could arise from variable frequency and timing of the somatic inactivation of the respective normal allele. Variability in disease onset and severity can also result from bilineal inheritance of *PKD1* and *PKD2* mutant alleles or by inheritance of hypomorphic or incompletely penetrant variants of either gene. Mosaicism in a parent in whom a mutation has arisen de novo could result in one sibling having the disease while another is disease free despite sharing the identical inherited haplotype at the *PKD* locus. Digenic inheritance of mutant *PKD1, PKHD1, TSC2*, or *HNF1B* alleles can result in ADPKD in infancy. Other modifier loci beyond the known disease genes as well as nongenetic risk factors (e.g., smoking, caffeine, acute kidney injury, and male sex hormones) may also modulate the formation of renal cysts.

Gene Products

PKD1 encodes PC1, which consists of a large 11-pass receptor-like glycoprotein with a relatively short cytoplasmic carboxyl terminus (E-Fig. 112-1). The PC1 ectodomain contains multiple functional motifs, which are also present in cell adhesion receptors, thereby suggesting a role in cell-cell or cell-matrix interactions or both. PC2, which is encoded by *PKD2*, is a 6-pass atypical transient receptor potential-type channel with cytoplasmic amino- and carboxy-termini. Its six-transmembrane segment exhibits homology to the carboxyl terminal six-transmembrane segment of PC1. PC1 binding to PC2 and the cleavage of PC1 at the G protein–coupled receptor proteolytic site (resulting in N-terminal and C-terminal fragments that remain tethered) are necessary for their normal folding and export from the endoplasmic reticulum to the Golgi apparatus and subsequently to the surface of the cell. Emerging evidence suggests that the primary function of the PC1/PC2 complex is in primary cilia that are ubiquitously expressed on cell surfaces. The PC1/PC2 complex

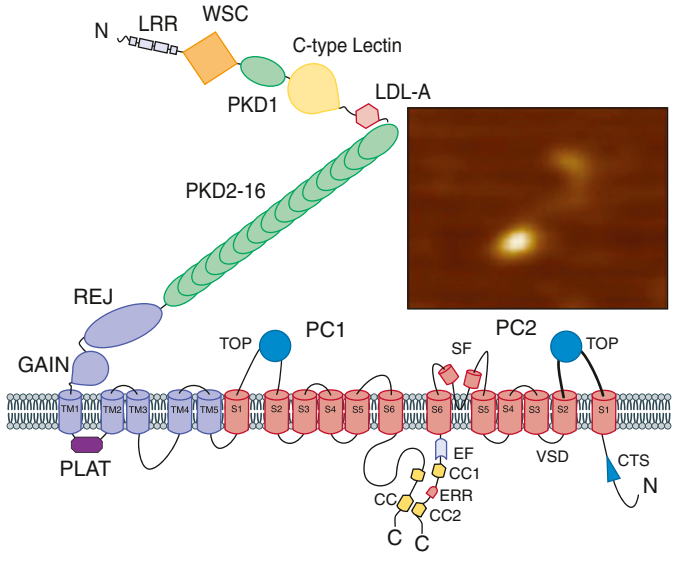

E-FIGURE 112-1. Schematic of polycystin-1 (PC1) and polycystin-2 (PC2). PC1 is a multidomain glycoprotein with 11 putative transmembrane (TM) segments, the C-terminal six of which (S1-S6, colored in rose) bear homology to the six transmembrane segments of PC2. PC1 contains a leucine-rich region (LRR); cell wall and stress component (WSC); C-type lectin; low-density lipoprotein receptor A-like domain (LDL-A); immunoglobulin-like domains (PKD1-16); receptor for egg jelly domain (REJ); G protein–couple receptor autoproteolysis-inducing domain (GAIN), which contains the G protein–coupled receptor proteolytic site (GPS) needed for PC1 activation; a PC1–lipoxygenase–α-toxin domain (PLAT); and a tetragonal opening for polycystins (TOP) domain. The PC1 schematic is drawn after atomic force microscopy imaging of PC1 (*inset*), where full-length PC1 appeared as two unequally sized blobs. The smaller one represents the N-terminal LRR, LDL-A, PKD1, and C-type lectin, whereas the larger one includes the REJ and GAIN domains. The 35-nm string connecting the two blobs likely consists of the tandem PKD2-16 domains. The PC2 monomer includes a TOP domain; a voltage sensor domain (VSD) comprising S1-S4; a pore domain between S5 and S6, which includes two pore helices that surround the selectivity filter (SF); an EF-hand calcium-binding motif; an endoplasmic reticulum retention signal (ERR); a coiled–coiled (CC) domain that interacts with a CC domain in PC1; and a ciliary targeting sequence (CTS).

transitions from the Golgi apparatus via polycystin-bearing vesicles to the transition fibers and then undergoes facilitated trafficking to enter the cilium.[5]

PC1 and PC2 are widely expressed with overlapping non-identical distributions in tissues. PC1 expression is highest during kidney development and progressively declines thereafter, becoming mainly limited to the collecting duct in the normal adult kidney, although it can be upregulated in response to renal injury. By comparison, renal expression of PC2 is maintained throughout development and predominates in the medullary thick ascending limb and distal cortical tubules in the normal adult kidney. Disruption of the PC1/PC2 complex in primary cilia appears to be critical to the genesis of the PKD phenotype, but the precise function the PC1/PC2 complex plays in primary cilia remains obscure.

Experimental studies have suggested that developing renal tubules with high proliferative indices are more sensitive to the reduction in PC1 or PC2 levels, with disease severity radically altered depending on the time of gene inactivation. Maintenance of higher proliferative indices in the distal nephron epithelium relative to that in the proximal nephron may explain the predominance of cysts in the distal nephron in adult human autosomal dominant PKD.

CLINICAL MANIFESTATIONS

Autosomal dominant PKD has a highly variable presentation, even within families. The clinical features of *PKD2*-associated autosomal dominant PKD are indistinguishable from those of *PKD1*-associated disease. However, *PKD2* disease is milder, with an older average age of onset—about 75 years versus 55 years for *PKD1*-associated disease—owing to the development of fewer cysts at an early age rather than to a slower cyst growth rate.

Despite an estimated 100% penetrance by age 90 years, only half the individuals with heterozygous mutations in *PKD1* or *PKD2* are ever diagnosed clinically with autosomal dominant PKD. Of these, the majority present in the third or fourth decade of life with symptoms referable to renal cystic disease. However, autosomal dominant PKD can develop at any age, including infancy, and it can have a nonrenal presentation. Renomegaly may predominate the clinical picture, with abdominal distention, discomfort, or pain; however, renomegaly also can be discovered incidentally on physical examination or after radiographic studies of the abdomen.

Nocturia, one of the earliest signs of abnormal renal function in autosomal dominant PKD, reflects the early impairment in the ability to concentrate urine owing to disruption of renal architecture by the cysts. Hematuria is typical, but proteinuria is less prominent than in many other renal diseases. Cyst hemorrhage and sometimes rupture, which can occur spontaneously or after trauma, present as sharp pain and hematuria. Recurrent cyst infection (Chapter 263), usually by common urinary tract-infecting organisms, is characterized by flank or abdominal pain, fever, rigors, leukocytosis, and occasionally sepsis. Kidney stones (Chapter 111) occur in 20 to 36% of patients, with uric acid stones slightly more common than calcium oxalate stones; predisposing factors include urinary stasis, defective trapping of urea in the medulla, low urine pH, hypocitraturia, hyperoxaluria, hypercalciuria, and hypomagnesuria. Anemia features less prominently than in other renal diseases, probably because of the relatively well-preserved secretion of erythropoietin.

Cardiovascular disease, which is common in autosomal dominant PKD, manifests as biventricular diastolic dysfunction even in young patients with normal blood pressure and renal function, thoracic and abdominal aortic aneurysms, and cervicocephalic and coronary aneurysms. Arterial hypertension is present in approximately 70% of cases before renal dysfunction is detected. Development of hypertension at a young age is associated with a four-fold increased risk of end-stage renal disease and increased cardiovascular morbidity. The risk for preeclampsia is also higher than in the general population.

Intracranial aneurysm occurs in 4 to 8% of asymptomatic autosomal dominant PKD patients, but the incidence is higher in patients with a family history of nonruptured (10% risk) or ruptured intracranial aneurysm (20% risk; Chapter 377). Autosomal dominant PKD-associated aneurysms tend to rupture at a smaller size and in younger individuals—on average, 10 years younger than among the general population. Although usually clinically silent, intact cerebral aneurysms can present with focal neurologic symptoms and headaches. By contrast, aneurysms that rupture lead to subarachnoid hemorrhage (Chapter 377) and have dramatic presentations that include severe headaches, seizures, altered sensorium, and death. Aortic and coronary artery aneurysms are also more prevalent in patients with autosomal dominant PKD, and the frequency of aortic insufficiency is increased.

Although almost never severe enough to cause end-stage liver disease, age-dependent hepatic cysts occur in 30 to 80% of patients with autosomal dominant PKD and can lead to signs and symptoms of mass effect, infection, hemorrhage, and rupture.[6] Estrogen intake and multiparity in women are risk factors for developing larger and more symptomatic liver cysts. The cysts that occasionally form in other organs, such as the pancreas, spleen, brain, ovaries, epididymis, and prostate, are usually asymptomatic. Sperm abnormalities and defective motility may occur but rarely cause male infertility. Bronchiectasis (Chapter 78) is three-fold more common, inguinal hernias may be more prevalent, and colonic diverticulosis and diverticulitis are more common in end-stage renal disease patients with autosomal dominant PKD.

DIAGNOSIS

Renomegaly, typically presenting in the third or fourth decade of life with a positive family history and common extrarenal manifestations, such as hypertension, are useful findings in making a presumptive diagnosis of autosomal dominant PKD. In these cases, renal ultrasonography is frequently diagnostic. Because only about 75% of individuals give a family history of autosomal dominant PKD, ultrasound screening of asymptomatic parents or grandparents may be required to uncover diagnostically relevant silent autosomal dominant PKD.[7]

A diagnosis of autosomal dominant PKD can be made in an asymptomatic individual by ultrasonography (Fig. 112-3A). To account for the common age-dependent appearance of simple cysts, autosomal dominant PKD is diagnosed if at least three renal cysts (distributed in one or both kidneys) are present in individuals 15 to 29 years old (sensitivity, 0.82; specificity, 1.0) or 30 to 39 years old (sensitivity, 0.96; specificity, 1.0), if at least two renal cysts are present in each kidney in individuals 40 to 59 years old (sensitivity, 1.0; specificity, 0.99), or if at least four renal cysts are detected in each kidney in individuals 60 years of age or older (sensitivity, 1.0; specificity, 1.0). Fewer than two renal cysts in an individual from an autosomal dominant PKD family with an unknown genotype age 40 years or older or the absence of renal cysts in such an individual age 30 to 39 years is sufficient to exclude the disease, with negative predictive values of 100% and 99.3%, respectively. A negative ultrasound result is less accurate in excluding disease in individuals younger than 30

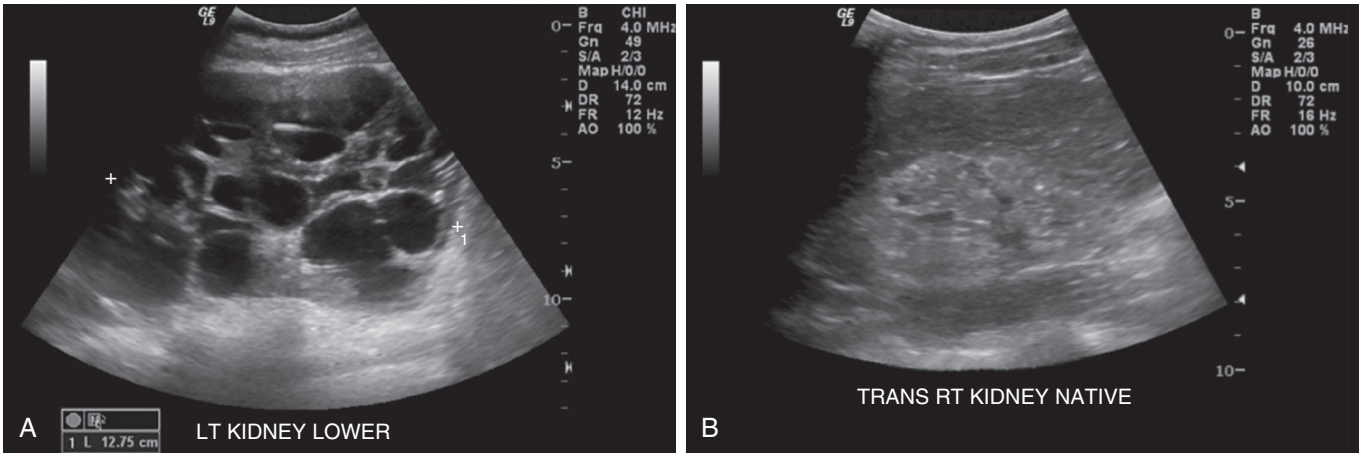

FIGURE 112-3. A, Ultrasound image of a kidney from a patient with autosomal dominant polycystic kidney disease. B, Ultrasound image of a kidney from a patient with autosomal recessive polycystic kidney disease. (Courtesy Dr. Javier M. Romero and Jennifer A. McDowell, Massachusetts General Hospital.)

years, so computed tomography (CT) or magnetic resonance imaging (MRI) is recommended. When a young relative is being considered as a potential kidney donor to a family member with end-stage autosomal dominant PKD, contrast-enhanced, three-dimensional CT or magnetic resonance angiography is required because these tests can detect 3-mm cysts compared with ultrasonography's ability to detect 10-mm cysts.

Cerebral aneurysms are increasingly being detected with MRI in autosomal dominant PKD patients. Four-vessel cerebral angiography remains the gold standard and is often used for surgical planning.

DNA-based diagnosis of autosomal dominant PKD by means of direct sequencing is commercially available and detects mutations in more than 90% of affected individuals. Whole-genome sequencing may have a much higher sensitivity and specificity for the diagnosis because it is better at distinguishing the *PKD1* gene from six similar pseudogenes.[8] It also can detect mosaicism, which accounts for about 10% of cases otherwise missed by genetic testing.[9] Testing is recommended when imaging study results are equivocal, in a young transplant donor from an autosomal dominant PKD family when imaging study results are negative, or to facilitate preimplantation genetic diagnosis.[10]

Monitoring Progressive Renal Disease

Despite ongoing renal cyst expansion, the glomerular filtration rate (GFR) and the serum creatinine level are generally maintained within the normal range in autosomal dominant PKD patients until the fourth to sixth decade of life. These markers are therefore insensitive for monitoring disease progression, especially in young patients. Reduced renal blood flow is the most sensitive prognostic indicator of renal progression. Estimating height-adjusted total kidney volume from measurements of kidney length, width, and thickness using MRI, CT, or ultrasonography can reliably monitor disease progression in the early stages of autosomal dominant PKD when the GFR is still in the normal range, and each 100-mL increment of height-adjusted total kidney volume increases the odds of reaching stage 3 chronic kidney disease by about 1.5-fold. Although gadolinium-enhanced MRI provides excellent detail of kidney structures, MRI without gadolinium is recommended to monitor kidney volume, especially in autosomal dominant PKD patients with a reduced GFR, because of concern about nephrogenic systemic fibrosis (Chapter 246) and further impairment of renal function associated with its use. Height-adjusted total kidney volume progressively increases in most patients who have autosomal dominant PKD but at widely differing rates, ranging from less than 1% to more than 10% annually. Renal function declines as the kidneys enlarge,[11] and patients who have rapidly progressive autosomal dominant PKD are most likely to benefit from treatment.[12]

PREVENTION AND TREATMENT

Management strategies are aimed at monitoring for complications of autosomal dominant PKD and treating them, as well as providing genetic counseling.[13] Frequent monitoring and effective treatment of hypertension (Chapter 64; see Tables 64-7 and 64-9) are essential because hypertensive patients have a greater annual increase in kidney volume, as well as a higher prevalence of left ventricular hypertrophy, ischemic heart disease, and stroke, compared with normotensive patients. The goals of blood pressure control are the same as for other patients with renal disease, including the attainment of a symptom-free blood pressure of 120/80 mm Hg or less. Angiotensin-converting enzyme inhibitors or angiotensin receptor blockers are the first-line antihypertensive drugs in autosomal dominant PKD. Hypertensive autosomal dominant PKD patients who are young (15 to 49 years), have stage 1 or 2 cystic kidney disease, and do not have diabetes mellitus or significant cardiovascular comorbidities may benefit from blood pressures of 95/60 to 110/75 mm Hg, a level associated with a slower increase in total kidney volume, a greater decline in left-ventricular-mass index, and a greater reduction in urinary albumin excretion, but not a delay in the reduction in the glomerular filtration rate. Dietary salt restriction also may be beneficial in the management of autosomal dominant PKD.

Oral tolvaptan (45 to 90 mg in the morning and 15 to 30 mg in the afternoon as tolerated) slows the increase in total kidney volume and the decline in kidney function in patients with normal creatinine clearance and in patients with moderate-to-advanced kidney disease.[A1,14,15] It can also reduce kidney pain.[A2] The small but significant clinical effect may be the result of reduced cell proliferation, direct intrarenal hemodynamic effects, or both. Tolvaptan induces a four-fold increased risk of hepatocellular injury, so liver function testing before initiation and at specific intervals (at 2 and 4 weeks, then monthly for 18 months, then every 3 months thereafter) is required in all patients with autosomal dominant PKD.[16] Overall, nearly 25% of patients do not tolerate tolvaptan, and it is not routinely used in children.

Treatment of urinary tract infection (Chapter 263) and prevention of nephrolithiasis (Chapter 111) are the same as in the general population and include standard antimicrobial therapy and increased fluid intake, respectively. Renal and hepatic cyst infections are optimally treated with lipophilic antibiotics that possess cyst-penetrating capabilities, including ciprofloxacin, trimethoprim, clindamycin, and vancomycin. Blood or urine cultures and sensitivities are used to guide the choice of antibiotic therapy.

Cyst hemorrhage and rupture, with resultant pain and hematuria, are usually managed conservatively with rest and analgesics; nonsteroidal anti-inflammatory drugs (NSAIDs) are avoided owing to their antiplatelet action and potential renal toxicity. Alternatives include acetaminophen 500 mg up to every 4 hours for mild to moderate pain, nonopiates such as tramadol 50 mg up to every 4 hours for moderate to severe pain, and the addition of an oral or transdermal opioid (see Table 26-6 in Chapter 26) as needed. Patients with enlarged kidneys should be advised to avoid playing contact sports, and those with massively enlarged kidneys should refrain from wearing belts and seatbelts. Some patients with unusually painful cysts respond to cyst fluid aspiration, cyst deroofing, or ethanol-induced sclerosis.

Nephrectomy is rarely indicated before the onset of end-stage renal disease. Renal replacement therapies, including renal transplantation (Chapter 117), are at least as effective as in other causes of end-stage renal disease.[17]

The massive cystic enlargement of the liver commonly seen by midlife in women with autosomal dominant PKD makes it prudent to avoid estrogen intake and repeated pregnancies. Partial hepatectomy has been successful in improving the quality of life in patients with massive liver enlargement, but liver transplantation is the only curative therapy.[18]

Magnetic resonance angiography screening is not routinely recommended for asymptomatic patients without a family history of cerebral aneurysm or subarachnoid hemorrhage, but it is recommended for patients with a positive personal or family history and for patients who experience a new onset of severe headache or central nervous system symptoms or signs. It also may be considered in those with high-risk occupations, such as airline pilots, and for patients with incapacitating anxiety. The risk of a patient with a positive family history developing a new aneurysm after an initially negative magnetic resonance angiography result is 2.6% at a mean follow-up period of 9.8 years, so rescreening every 5 to 10 years in such cases may be appropriate, especially in patients with early-onset hypertension or a history of heavy smoking. Asymptomatic patients with positive family history of cerebral aneurysms and positive magnetic resonance angiography results should be followed closely with a neurosurgeon and monitored by annual magnetic resonance angiography screening. The decision to perform surgical clipping or endovascular embolization should take into consideration the age of the patient, the size of the aneurysm and its location, and a previous history of cerebral bleeding (Chapter 377).

Patients should be advised that their children have a 50% probability of inheriting a disease-causing germline mutation. DNA-based diagnostics are most useful in identifying the germline mutation prenatally or preimplantation. As DNA-based diagnostics become more widely available and less expensive and as promising new treatment options are developed, genetic counseling will become an increasingly important component of prevention.

Experimental Therapies

Current therapeutic efforts are targeting increased cell proliferation of cystic epithelium and abnormal fluid secretion into cysts (E-Fig. 112-2).[19] The metabolically stable somatostatin analogue octreotide (long-acting release at a dose of 40 mg every 28 days)[20] can slow the expansion of renal cysts but does not slow the decline in renal function and also is associated with substantial side effects.[A3] Indirect inhibition of mTOR via activation of AMPK with metformin (E-Fig. 112-2) has shown promise in a phase II trial.[A4] Bosutinib, an oral dual Src/Bcr-Abl tyrosine kinase inhibitor, can reduce the rate of kidney enlargement but has not been shown to slow the decline in glomerular filtration.[A5] A trial evaluating the value of tesevatinib, which is a multi-kinase inhibitor, on the progression of height-adjusted total kidney volume in autosomal dominant PKD is ongoing.

PROGNOSIS

The rate of progression of renal disease is highest in men with poorly controlled hypertension, an early age at diagnosis, mutations (particularly truncations) in *PKD1*, and higher initial height-adjusted total kidney volume.[21] Higher salt intake but not higher protein intake is associated with more rapidly progressive disease.[22] Kidney cysts develop earlier in *PKD1* than in *PKD2* disease, but the rate of expansion is similar, indicating that the basic difference in phenotype is in cyst initiation, not expansion. Whereas the presence of one affected family member who developed end-stage renal disease by age 60 years is highly predictive of PKD1 disease (positive predictive value, 100%; sensitivity, 75%), the development of end-stage renal disease after age 70 years in a family member is highly predictive of PKD2 disease (positive predictive value, 95%; sensitivity, 75%). Approximately 5% of all autosomal dominant PKD patients with cerebral aneurysms die from aneurysmal rupture.

AUTOSOMAL RECESSIVE POLYCYSTIC KIDNEY DISEASE

DEFINITION AND EPIDEMIOLOGY

Autosomal recessive PKD is a multisystem childhood disorder characterized by severe and early PKD dominated by dilation of the kidney collecting ducts,

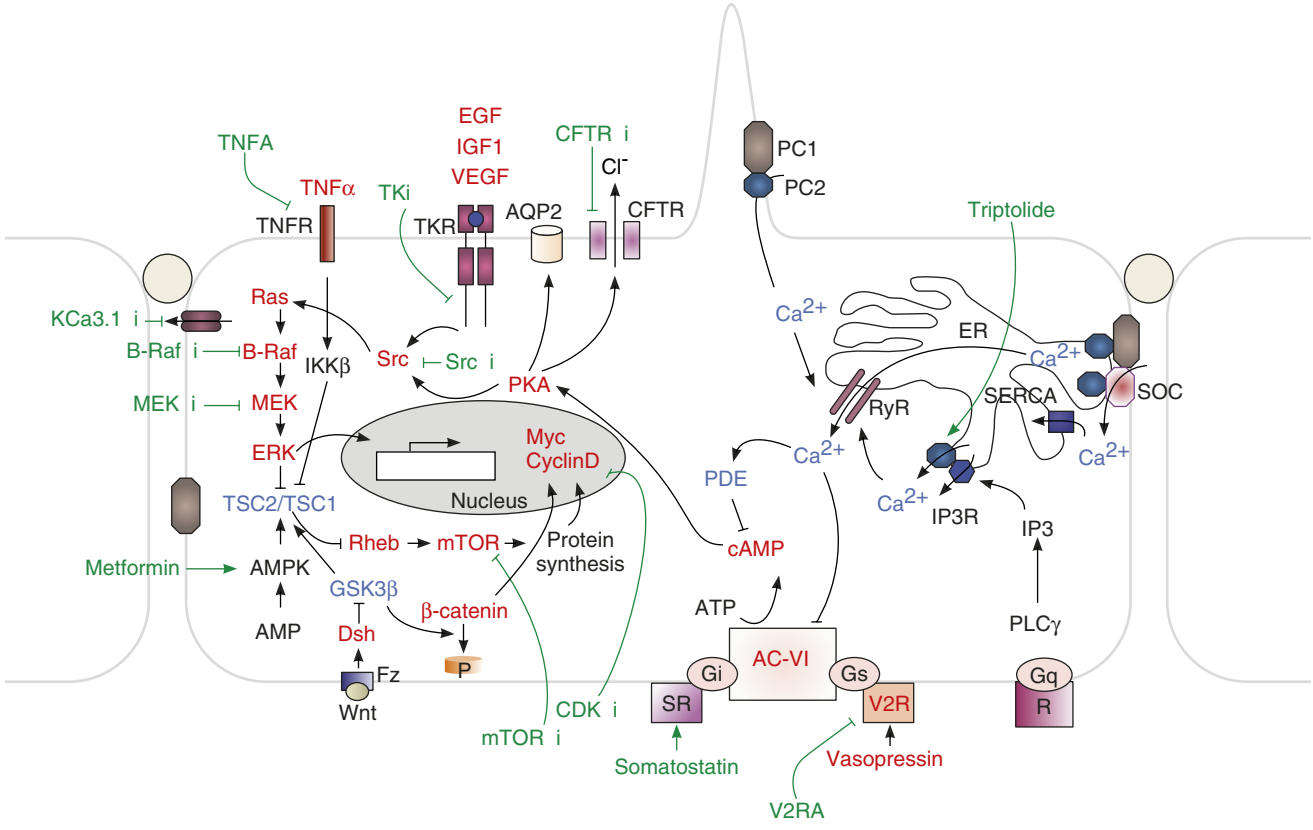

E-FIGURE 112-2. Signaling pathways that are upregulated or downregulated in polycystic kidney disease and sites of current therapeutic interventions. Upregulated pathways are in *red,* downregulated pathways are in *blue,* and potential drugs are in *green.* Ciliary PC1/PC2 complex appears to mediate calcium (Ca^{2+}) entry into the cell, where it triggers Ca^{2+} release from the endoplasmic reticulum (ER) via the ryanodine receptor (RyR). PC1/PC2 complex regulates Ca^{2+} channel (SOC) activity, and it interacts with inositol 1,4,5-triphosphate (IP3) receptor (IP3R) to regulate calcium release from the ER. Reduced PC1/PC2–mediated calcium influx increases intracellular cyclic adenosine monophosphate (cAMP, which stimulates, via protein kinase A (PKA), chloride and water secretion across the luminal membrane through cystic fibrosis transmembrane conductance regulator (CFTR) and the vasopressin-sensitive aquaporin-2 (AQP2) channels, respectively, and activates mitogen-activated protein kinase (MAPK) signaling. The ATP-activated chloride channel TMEM16A (not shown) may also contribute to chloride secretion. Phosphorylation of tuberin by MAPK, its inadequate targeting to the plasma membrane owing to defective interaction with PC1, upregulation of tumor necrosis factor-α (TNFα), or downregulation of 5′ AMP = activated protein kinase (AMPK) signaling may dissociate the tuberin-hamartin complex, leading to activation of *R*as *h*omolog *e*nriched in *b*rain (Rheb) guanosine triphosphate binding protein and mammalian target of rapamycin (mTOR). MAPK and mTOR activation promote G1/S transition and cell proliferation through upregulation of cyclin D and protein translation, respectively. Upregulation of Wnt signaling, via PI3K/NF-kB pathway (not shown), also activates mTOR and the β-catenin mitogenic pathway. Downregulation of the AMPK/TSC pathway and of GSK3β as well as upregulation of MYC and HIF1α (not shown) promote aerobic glycolysis that fuels cell proliferation. AC-VI = adenylate cyclase 6, the predominant AC in collecting duct principal cells; CDK = cyclin-dependent protein kinase; Dsh = dishevelled; Fz = frizzled receptor; Gq R = G-protein q–coupled receptors; GSK3β = glycogen synthase kinase 3 beta; HIF1α = hypoxia-inducible factor 1-alpha; i = inhibitor; KCa3.1 = Ca^{2+}-dependent K^+ channel 3.1; MYC = c-myc protooncogene; P = proteosome; PDE = phosphodiesterase (PDE1 in collecting duct principal cells); PKA = protein kinase A; PLCγ = phospholipase Cγ; SERCA = sarcoplasmic reticulum Ca^{2+} pump; SR = somatostatin sst2 receptor; TNFA = tumor necrosis factor antagonist; TSC = tuberous sclerosis proteins hamartin (TSC1) and tuberin (TSC2); V2R = vasopressin V2 receptor; V2RA = vasopressin V2 receptor antagonists. (Originally modified from Torres VE, Harris PC. Autosomal dominant polycystic kidney disease. *Kidney Int.* 2009;76:149-168.)

systemic hypertension, biliary ductal plate dysgenesis in neonates, and portal tract fibrosis in older children.[23]

PATHOBIOLOGY

Autosomal recessive PKD is mainly caused by heterogeneous mutations in *PKHD1* (polycystic kidney and hepatic disease 1) and rarely by mutations in *DZIP1L*. Located on chromosome 6q21, *PKHD1* has 67 exons and spans a genomic region of approximately 470 kb, the longest open reading frame of which is 12,222 base pairs long. *PKHD1* encodes a unique type I membrane protein, fibrocystin/polyductin, comprising 4074 amino acids, with a large extracellular segment that contains multiple IPT/TIG (*I*g-like, *P*lexins, *T*ranscription factors) domains, a PA14 domain, a PbH1 (*P*arallel β-helix repeat) domain, 2 G8 domains, a cleavage site, and a short cytoplasmic carboxyl terminus that includes a cilia targeting signal. The precise physiologic function of fibrocystin/polyductin in collecting duct and biliary duct epithelium is not clear, but its domains are known to mediate cell motility and invasion (IPT domains), extracellular protein and carbohydrate binding, and catalytic processing (PA14, PbH1, and G8 domains). Alternatively spliced transcripts of *PKHD1* encode a membrane protein with variable extracellular domains, as well as forms lacking the transmembrane segment. Biallellic truncating mutations in *PKHD1* are associated with perinatal renal disease, whereas patients with biallelic missense mutations may present later because some functional protein is produced.

Fibrocystin is predominantly expressed in the cortical and medullary collecting ducts, the thick ascending limbs of Henle and bile ducts. It is also found to a lesser degree in the pancreas, liver, and lungs, which are also affected in autosomal recessive PKD. Fibrocystin interacts with PC2 within the PC1/PC2 complex, where loss of fibrocystin downregulates PC2. Fibrocystin–PC2 interactions may regulate function of the ciliary PC1/PC2 complex.

Located on chromosome 3q22, 1-q23 *DZIP1L* encodes DZIP1L, which is widely expressed and is localized primarily to the centrioles and distal end of basal bodies. The localization of PC1 and PC2 to the ciliary membrane is compromised in DZIP1L-mutant cells, thereby suggesting that DZIP1L is required for regulating the integrity of the transition zone.

CLINICAL MANIFESTATIONS

Although autosomal recessive PKD can present as renal cysts discovered radiographically either antenatally or during adulthood, it usually manifests as bilateral abdominal masses and renal insufficiency in infancy. It carries a 30% mortality rate owing to severe pulmonary hypoplasia; oligohydramnios, presumably linked to in utero renal disease, likely accounts for the pulmonary hypoplasia. Hypertension is almost universal, typically develops before renal impairment is apparent, and probably accelerates the decline in renal function. Findings related to renal tubular dysfunction may be present and include polyuria, enuresis, hyponatremia, and hyperchloremic metabolic acidosis. Cystic complications related to infection and rupture also occur, although hematuria is an infrequent finding.

Hepatic fibrosis, secondary to dilation of the intrahepatic and extrahepatic bile ducts, manifests as recurrent ascending cholangitis (Chapter 141) and portal hypertension with splenomegaly and esophageal varices. Pancreatic fibrosis is rarely a clinical concern.

DIAGNOSIS

The demonstration by abdominal ultrasonography (see Fig. 112-3B) or CT of symmetrically enlarged polycystic kidneys that retain their reniform shape (owing to uniform microcystic dilation of the distal tubules and collecting ducts) and hepatic fibrosis is sufficient to diagnose autosomal recessive PKD. In contrast to autosomal dominant PKD cysts, autosomal recessive PKD cysts tend to retain their connections with the originating nephron.

Aside from an occasional affected sibling, a family history is often not elicited. Distinguishing autosomal recessive PKD from autosomal dominant PKD, especially in patients presenting in childhood or adulthood, may require a liver biopsy to document otherwise undetectable hepatic fibrosis. Gene-based diagnostics in autosomal recessive PKD are helpful in making a firm diagnosis,[24] especially in patients with late-onset disease, and they are useful in preimplantation and prenatal diagnosis. Mutations in *DZIP1L* is considerably rarer than mutations in *PKHD1,* perhaps in part owing to the larger size of *PKHD1*.

TREATMENT AND PREVENTION

In the absence of specific therapy for autosomal recessive PKD, management goals focus on early detection and on treatment of the complications of hypertension, urinary tract or cyst infection, end-stage renal disease, and portal hypertension. Kidney transplantation may be necessary in late childhood in patients with autosomal recessive PKD who present with renal disease perinatally. Treatment of portal hypertension may require liver transplantation or portosystemic shunting (Chapter 140). Treatment of hypertension begins with ACE inhibitors and angiotensin receptor blockers (see Tables 64-7 and 64-9 in Chapter 64), which are generally effective. As in all children with end-stage renal disease, attention to nutrition and renal osteodystrophy is paramount (Chapter 116). With improving sensitivity of gene-based diagnostics, prenatal counseling will play a more active role in prevention.

PROGNOSIS

For patients with autosomal recessive PKD, the highest mortality rates occur during the first year of life. Males and females are equally affected. Approximately 50 to 80% of patients who survive this period live past 15 years of age. End-stage renal disease with macroscopic cysts, interstitial fibrosis, and shrunken kidneys can take up to 20 years to develop; but in rare instances, it never occurs.

NEPHRONOPHTHISIS

DEFINITION AND EPIDEMIOLOGY

Nephronophthisis is the most common genetic cause of end-stage renal disease in childhood and adolescence, during which it accounts for 5 to 15% of cases of end-stage renal disease. It is an autosomal recessive kidney disorder caused by mutations in a number of genes that encode nephronophthisis proteins (nephrocystins), which are expressed in the centrosome and basal body of primary cilia, with some also localizing to adherens junctions or focal adhesions in epithelia.[25] Homozygotic and compound heterozygotic mutations in at least 20 known genes (*NPH1* through *NPH20* and *MAPKBP1*) account for about 30% of cases. Infantile, juvenile, and adolescent variants have been described based on the median age of onset of ESRD. Infantile nephronophthisis is characterized by mutations in the *NPH2* gene. The juvenile form is the most common and is caused by mutations in *NPH1*. The adolescent form is caused by mutations in *NPH3*. Mutations in *MAPKBP1*, which encodes MAPKABP1, a microtubule-binding protein, are a rare cause of late-onset cilia-independent nephronophthisis.

Nephronophthisis is characterized pathologically by renal interstitial fibrosis, tubular atrophy with basement membrane thickening and disruption, and renal cysts and diverticula that are largely restricted to the loops of Henle and distal tubules at the corticomedullary junctions. Kidney size is generally normal or reduced, except in the rare infantile variant that leads to end-stage renal disease by 3 years of age. Expression of *NPH* genes at extrarenal sites accounts for the associated retinal, neural, liver, and skeletal abnormalities. Each of the *NPH* genes is associated with a somewhat different phenotype, although some share common phenotypes, explained by protein-protein interactions between two or more nephrocystins. Cerebello-ocular-renal syndromes associated with nephronophthisis can sometimes include early-onset retinitis pigmentosa when the syndrome is caused by mutations in *NPH5* and *NPH6*.

CLINICAL MANIFESTATIONS

Presenting symptoms include polyuria, growth failure, and anemia. Polyuria occurs early, owing to reduced urinary concentrating ability and to salt wasting. A decreased growth rate is related to chronic dehydration, and growth failure and anemia occur with the onset of end-stage renal disease. Blood pressure is normal, and edema is absent before the onset of renal failure. Hematuria and proteinuria are absent or minimal. Patients with mutations in specific *NPH* genes may also present with eye defects, oculomotor apraxia, congenital amaurosis, retinitis pigmentosa, neural anomalies, cerebellar ataxia, seizures, liver fibrosis, skeletal defects, scoliosis, cleft palate, and situs inversus.

DIAGNOSIS

The diagnosis relies on clinical suspicion of the disorder in a pediatric or adolescent patient who presents with end-stage renal disease and extrarenal manifestations such as abnormal eye movements, intellectual disability, and polydactyly. Differential diagnosis includes renal dysplasia, early-onset autosomal dominant PKD, urinary tract obstruction, autosomal dominant TKD, and autosomal recessive PKD. Abdominal ultrasonography, MRI (without gadolinium), electroretinography, and full neurologic and ophthalmologic

evaluations should assess the patient's renal, liver, retinal, and neurologic status. Renal ultrasonography showing loss of corticomedullary differentiation, increased parenchymal echogenicity, and occasionally small medullary or corticomedullary cysts in normal-sized or moderately small kidneys is highly suggestive of juvenile nephronophthisis in a child with severe uremia. Genetic testing may be required for a conclusive diagnosis. A renal biopsy showing evidence of chronic tubulointerstitial nephritis may be necessary to confirm the diagnosis if genetic testing is not available.

TREATMENT AND PREVENTION

Treatment is largely supportive, focusing on the progressive renal failure and the need for dialysis and transplantation. Prenatal genetic testing in families with a genetic diagnosis of nephronophthisis is feasible. DNA-based diagnostics are most useful in identifying the germline mutation prenatally or preimplantation.

AUTOSOMAL DOMINANT TUBULOINTERSTITIAL KIDNEY DISEASE (MEDULLARY CYSTIC KIDNEY DISEASE)

Autosomal dominant tubulointerstitial kidney disease is a group of genetic disorders characterized by an autosomal dominant inheritance, medullary cysts, and slowly progressive loss of kidney function beginning in the teenage years.[26] It shares a number of histologic features with nephronophthisis, including tubular basement membrane disintegration, tubular cyst formation, and tubulointerstitial inflammation and fibrosis.

Mutations in one of five genes—*UMOD/MCKD2*, *MUC1/MCKD1*, *REN*, *SEC61A1* and *HNF1B*—cause autosomal dominant tubulointerstitial kidney disease. *UMOD* on chromosome 16p12 encodes an 85-kD nonciliary protein, uromodulin, which is expressed on the luminal side of renal epithelium in the thick ascending limb of Henle loop and early distal convoluted tubules. Uromodulin kidney disease (also known as familial juvenile hyperuricemic nephropathy type 1, uromodulin storage disease, and glomerulocystic kidney disease) is the most common subtype, accounting for the majority of cases. Recent data indicate that *UMOD* mutations in uromodulin are encountered in 2 to 3% adults with chronic kidney disease. The mutations impair trafficking of furosemide-sensitive Na-K-2Cl transporter to the apical membrane of the thick ascending limb, thereby causing mild sodium wasting and volume contraction, with a secondary increase in proximal tubule urate reabsorption and hyperuricemia. Intracellular accumulation of the mutant protein causes tubular cell death. Affected patients do not have an increased incidence of urinary tract infections or renal calculi.

MUC1 on chromosome 1q21 encodes mucin-1, a transmembrane protein expressed in the distal nephron, the gastrointestinal and respiratory tracts, and skin, with no known function. The autosomal dominant TKP-MUC1 phenotype, which is limited to the kidneys, accounts for approximately 30% of autosomal dominant tubulointerstitial kidney disease. Gout and hyperuricemia occur late, secondary to loss of kidney function.

Mutations in *REN*, which encodes renin on chromosome 1q32.1, are rarer causes of autosomal dominant tubulointerstitial kidney disease. The clinical and laboratory manifestations resemble other low renin states. Anemia, caused by decreased levels of angiotensin II (a positive regulator of erythropoiesis), precedes the development of chronic kidney disease. Hyperuricemia develops early, likely owing to relative hypotension and increased proximal absorption of uric acid. Accumulation of the abnormal renin leads to tubular cell death and chronic kidney disease.

HNF1B nephropathy results from mutations in the gene encoding the widely expressed transcription factor hepatocyte nuclear factor-1-beta. *HNF1B* is located on chromosome 17q12 and mediates the development of a variety of tissues, including the kidney, liver, pancreas, and genital tract. This cystic renal disease may be accompanied by variable renal and extra renal manifestations (see Table 112-1). Renal function may be normal or may decline to end-stage renal disease. Neither mutation type nor position correlates with severity of disease.

DIAGNOSIS

Corticomedullary cysts, which are present in most adult patients with autosomal dominant tubulointerstitial kidney disease, cannot always be recognized on ultrasonography or computed tomography because they tend to be very small. A presumptive diagnosis is based on a strong family history and a bland urinary sediment with minimal proteinuria. Mutational analysis is necessary to make a definitive diagnosis.

TREATMENT

Except for the treatment of hyperuricemia and gout, when present (Chapter 252), the management of pancreatic insufficiency (in autosomal dominant tubulointerstitial kidney disease—HNF1B) and of low blood pressure and hyperkalemia (in autosomal dominant tubulointerstitial kidney disease—REN) is similar to that of patients with nephronophthisis.

MEDULLARY SPONGE KIDNEY

Medullary sponge kidney, a rare disorder of unknown pathogenesis, is characterized by congenitally acquired inner medullary and papillary collecting duct dilations, hypercalciuria, and a mild defect in urinary concentration and acidification secondary to tubular dysfunction.[27] Medullary sponge kidney is usually nonhereditary, but autosomal dominant inheritance has been described in several families.

Patients present with microscopic or gross hematuria and recurrent kidney stones, usually by the second or third decade of life. Medullary sponge kidney also may be an incidental finding on an intravenous pyelogram that shows the characteristic pooling of contrast material within the cystic collecting ducts. Differential diagnosis includes other causes of medullary nephrocalcinosis such as hyperparathyroidism, renal tubular acidosis type I, hypervitaminosis D, milk-alkali syndrome, and sarcoidosis.

TREATMENT AND PROGNOSIS

Basic treatment is aimed at controlling stone formation by stabilizing urinary pH. End-stage renal disease is uncommon, and long-term prognosis is excellent.

OTHER INHERITED CYSTIC SYNDROMES

TUBEROUS SCLEROSIS AND VON HIPPEL-LINDAU SYNDROME

Autosomal dominant renal cyst formation is seen in tuberous sclerosis and von Hippel-Lindau syndrome (Chapter 385). In tuberous sclerosis, cyst formation is commonly associated with hypertension; this disorder can resemble autosomal dominant PKD and is associated with about a 5% incidence of renal cell carcinoma. In von Hippel-Lindau syndrome, cyst formation can also lead to features of autosomal dominant PKD; more importantly, the syndrome is associated with a 25% incidence of renal cell carcinoma.

TREATMENT

Treatment is discussed in Chapter 385.

RARE CHILDHOOD SYNDROMES

Bardet-Biedl syndrome is an autosomal recessive disorder characterized by vision loss, obesity, hypertension, delayed development of motor skills, behavioral problems, and dystrophy of the hands, kidneys, and male genitals. Mutations in at least 21 genes involved in maintenance and function of cilia have been identified. About 45% of cases result from mutations in *BBS1* or *BBS10*, but in about 25% of cases, the defective gene remains to be identified. Calyceal cysts and calyceal clubbing predominate the renal lesion and are best diagnosed by intravenous urography rather than ultrasonography. Renal impairment is frequent and is an important cause of death.

Oral-facial-digital syndrome is a rare neurodevelopmental ciliopathy characterized by malformations of the brain, face, oral cavity, and digits. It is inherited in an X-linked dominant pattern and is caused by defects in the *OFD1* gene, which encodes OFD1 protein expressed in the centrosome and basal body of primary cilia but has an undetermined function. Renal (primarily glomerular) cysts are found in as many as 50% of patients, all females; males carrying the mutation die in utero. End-stage renal disease has been reported in affected girls and women ranging in age from 11 to 72 years.

Polycystic kidney disease with hyperinsulinemic hypoglycemia, is caused by biallelic mutations in *PMM2*, which encodes phosphomannomutase 2, an isomerase involved in synthesis of dolichol-P-oligosaccharides. Hyperinsulinemic hypoglycemic polycystic kidney disease presents in early childhood with hypoglycemic seizures owing to altered insulin secretion, enlarged glomerulocystic kidneys and occasional liver cysts. The severity of cystic kidney disease is variable, with few patients progressing to end-stage renal disease.[28]

TREATMENT

Control of blood pressure (Chapter 64) is important. For hyperinsulinemic hypoglycemic polycystic kidney disease, chronic diazoxide therapy can treat the hypoglycemia. No specific treatments are currently available for these conditions, and the affected children should be managed at specialized centers.

ACQUIRED CYSTIC KIDNEY DISEASE

Acquired cystic kidney disease is largely confined to the end-stage renal disease population on dialysis (Chapter 117). Cysts arise from proximal and distal tubule dilations in small end-stage kidneys regardless of cause, mode of dialysis, or presence of a functioning kidney transplant. Identifiable risk factors include duration of end-stage renal disease, older age, male sex, Black race, and chronic hypokalemia.

CLINICAL MANIFESTATIONS AND DIAGNOSIS

Acquired cystic kidney disease is usually asymptomatic, but it occasionally leads to enlarged kidneys with associated abdominal discomfort and pain. Cyst hemorrhage, which is more common than cyst infection, presents with flank pain, anemia, or hematuria. The most significant complication of acquired cystic kidney disease is malignant conversion of cysts into renal cell carcinoma (Chapter 182). Carcinomas commonly present as hematuria and are 2 to 200 times more common in patients with acquired cystic kidney disease than in the general dialysis population.

Acquired cystic kidney disease is diagnosed by ultrasonography or computed tomography (CT), demonstrating multiple and bilateral renal cysts in a patient with preexisting chronic renal failure or end-stage renal disease. In contrast to autosomal dominant or recessive PKD, the kidneys are usually not enlarged, and there is no family history of PKD. Renal CT or MRI is preferable to detect cysts in small kidneys and to assess for malignant conversion.

TREATMENT AND PREVENTION

No strategies are available to prevent the appearance or delay the expansion of renal cysts in patients on hemodialysis, but cysts may stabilize or regress after successful renal transplantation. New or frank hematuria raises the concern of renal cell carcinoma (Chapter 182), which should be assessed using ultrasonography and contrast-enhanced CT. Any evidence of septa formation, solid material, or contrast enhancement within a cyst is suspicious for carcinoma and warrants consideration of nephrectomy.

PROGNOSIS

Asymptomatic acquired cystic kidney disease does not affect survival. The incidence of renal cell carcinoma in patients with acquired cystic kidney disease is approximately 0.18% per year. Although metastasis is less common at the time of diagnosis in patients with acquired cystic kidney disease than in other patients with renal cell carcinoma, the 5-year mortality rates are higher, likely related to the almost invariable coexistence of end-stage renal disease.

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113

HEREDITARY NEPHROPATHIES AND DEVELOPMENTAL RENAL/URINARY ABNORMALITIES

LISA M. GUAY-WOODFORD

HEREDITARY NEPHROPATHIES

The proximal tubule is responsible for reclaiming most of the filtered glucose, amino acids, uric acid, phosphate, bicarbonate, and low-molecular-weight proteins. The loop of Henle and the distal nephron reabsorb approximately 30% of the filtered sodium chloride and 50% of the filtered divalent cations. The collecting duct, under the regulatory control of aldosterone, fine-tunes sodium reabsorption and secretes hydrogen and potassium ions. In the terminal collecting duct, antidiuretic hormone regulates water reabsorption and urinary concentration.

Inherited renal tubular disorders are a group of conditions in which the normal renal tubular reabsorption of ions, organic solutes, and water (Chapter 102) is disrupted because of defects in single genes.[1] These defects can be categorized by the nephron segment affected (Table 113-1).

DISORDERS OF PROXIMAL TUBULE FUNCTION

CYSTINURIA

Cystinuria is characterized by defective proximal tubular reabsorption of cystine and dibasic amino acids, thereby resulting in increased excretion of cystine and the risk of forming cystine-containing urinary stones (Chapter 111).[2] This autosomal recessive trait has an estimated prevalence of 1 in 7000 individuals. Two cystinuria genes have been identified: *SLC3A1,* which encodes the heavy subunit, rBAT; and *SLC7A9,* which encodes the light subunit, $b^{O,+AT}$. Several large studies indicate that mutations in *SLC3A1* are more common than mutations in *SLC7A9*. Mutations in *SLC3A1* cause cystinuria type A, mutations in *SLC7A9* cause cystinuria type B, and mutations in both genes cause mixed genotype cystinuria.

CLINICAL MANIFESTATIONS AND DIAGNOSIS

Although the severity of the disease is similar in all types of cystinurias, the clinical presentation can be quite variable, and the onset of disease may occur from infancy to the seventh decade of life. Cystine stones are radiopaque and often form the nidus for secondary calcium oxalate stones. Symptoms include renal colic, which may be associated with urinary tract obstruction and/or infection. Affected children can be identified by elevated urinary cystine levels, but testing must be performed after tubular transport has fully matured (at age 2 years). Genetic testing is available, but not mandatory for diagnosis, which can be established by stone analysis and/or quantitative 24-hour urine analysis.

TREATMENT

Conservative therapy with hydration (target specific gravity <1.005), reduced intake of sodium (children 1 to 1.5 mEq/day; adults 100 mEq/day), reduced intake of dietary methionine, and urinary alkalinization is sufficient for many patients with cystinuria. However, recurrent stones may cause renal damage, so such patients should be treated with thiol-containing agents such as D-penicillamine (pediatric dose, 20 to 30 mg/kg/day in four divided doses; adult dose, 0.5 to 1.2 g/day in four divided doses) or tiopronin (pediatric dose, 15 to 40 mg/kg/day in three divided doses; adult dose 800 to 1500 mg/day divided in three doses). Therapy should maintain the unbound urinary cystine concentration below 250 mg/L.

CYSTINOSIS

Cystinosis is the most common inherited cause of renal Fanconi syndrome. It also affects the eyes, muscles, central nervous system, lungs, and various endocrine organs. This autosomal recessive disorder is caused by mutations in the gene *CTNS,* which encodes cystinosin, a lysosomal cystine transporter. Defects in this transporter lead to the accumulation of intralysosomal cystine crystals and widespread cellular destruction.

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Control of blood pressure (Chapter 64) is important. For hyperinsulinemic hypoglycemic polycystic kidney disease, chronic diazoxide therapy can treat the hypoglycemia. No specific treatments are currently available for these conditions, and the affected children should be managed at specialized centers.

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113 HEREDITARY NEPHROPATHIES AND DEVELOPMENTAL RENAL/URINARY ABNORMALITIES

LISA M. GUAY-WOODFORD

HEREDITARY NEPHROPATHIES

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CLINICAL MANIFESTATIONS AND DIAGNOSIS

Although the severity of the disease is similar in all types of cystinurias, the clinical presentation can be quite variable, and the onset of disease may occur from infancy to the seventh decade of life. Cystine stones are radiopaque and often form the nidus for secondary calcium oxalate stones. Symptoms include renal colic, which may be associated with urinary tract obstruction and/or infection. Affected children can be identified by elevated urinary cystine levels, but testing must be performed after tubular transport has fully matured (at age 2 years). Genetic testing is available, but not mandatory for diagnosis, which can be established by stone analysis and/or quantitative 24-hour urine analysis.

TREATMENT

Conservative therapy with hydration (target specific gravity <1.005), reduced intake of sodium (children 1 to 1.5 mEq/day; adults 100 mEq/day), reduced intake of dietary methionine, and urinary alkalinization is sufficient for many patients with cystinuria. However, recurrent stones may cause renal damage, so such patients should be treated with thiol-containing agents such as D-penicillamine (pediatric dose, 20 to 30 mg/kg/day in four divided doses; adult dose, 0.5 to 1.2 g/day in four divided doses) or tiopronin (pediatric dose, 15 to 40 mg/kg/day in three divided doses; adult dose 800 to 1500 mg/day divided in three doses). Therapy should maintain the unbound urinary cystine concentration below 250 mg/L.

CYSTINOSIS

Cystinosis is the most common inherited cause of renal Fanconi syndrome. It also affects the eyes, muscles, central nervous system, lungs, and various endocrine organs. This autosomal recessive disorder is caused by mutations in the gene *CTNS,* which encodes cystinosin, a lysosomal cystine transporter. Defects in this transporter lead to the accumulation of intralysosomal cystine crystals and widespread cellular destruction.

ABSTRACT

Renal tubular disorders are a heterogeneous group of hereditary and acquired conditions that disrupt the normal, regulated reabsorption of ions, organic solutes, and water in various nephron segments. The clinical consequences involve fluid losses, as well as abnormalities in electrolyte and acid-base homeostasis. This chapter focuses on the inherited renal tubular disorders, highlights the genes involved, describes the resulting nephron segment dysfunction, and provides guidelines for clinical management. Congenital abnormalities of the kidney and urinary tract (CAKUT) occur in 1 : 500 newborns and comprise approximately 20 to 30% of all anomalies identified in the prenatal period. CAKUT disorders result from disruption of normal nephrogenesis, due to single gene defects and/or environmental factors. Some urinary tract anomalies are asymptomatic and inconsequential, but many renal tract malformations are important causes of infant mortality, as well as morbidity in older children and adults, including the progression to renal failure. This chapter presents an overview of the CAKUT disorders and the associated structural defects that involve the kidneys and urinary tract.

KEYWORDS

renal tubular disorders
genetics
kidney
congenital abnormalities
urinary tract

TABLE 113-1 HEREDITARY NEPHROPATHIES BY NEPHRON SEGMENT

NEPHRON SEGMENT	DISORDER	INHERITANCE	MAJOR RENAL FEATURES
PROXIMAL TUBULE			
	Renal glycosuria	AR	Isolated glycosuria
	Proximal renal tubular acidosis	AR	Hyperchloremic, hypokalemic, metabolic acidosis
	Carbonic anhydrase II deficiency	AR	Mixed proximal and distal renal tubular acidosis
	Hartnup disease	AR	Neutral aminoaciduria
	Lysinuric protein intolerance	AR	Protein intolerance, basic aminoaciduria
	Cystinuria	AR	Type A: Urinary calculi Type B: Urinary calculi
	Cystinosis	AR	Infantile: Renal Fanconi syndrome Late-onset: Renal Fanconi syndrome Non-nephropathic: Renal Fanconi syndrome
	Hypophosphatemic rickets	X-linked AD AR	Renal phosphate wasting, hypophosphatemia Renal phosphate wasting, hypophosphatemia Renal phosphate wasting, hypophosphatemia
	Dent disease	X-linked	Dent disease 1: Nephrocalcinosis, urinary calculi; low-molecular-weight proteinuria Dent disease 2: Nephrocalcinosis, urinary calculi; low-molecular-weight proteinuria
	Lowe syndrome	X-linked	Renal Fanconi syndrome
	Hereditary fructose intolerance	AR	Renal Fanconi syndrome
	Tyrosinemia, type I	AR	Renal Fanconi syndrome
	Wilson disease	AR	Renal Fanconi syndrome
	Fanconi-Bickel syndrome	AR	Renal Fanconi syndrome with hepatorenal glycogenosis
	Renal hypouricemia	AR	Hypouricemia, nephrolithiasis, and exercise-induced acute renal failure
LOOP OF HENLE			
	Bartter syndrome	AR AD	Type 1: Hypokalemic, hypochloremic metabolic alkalosis Type 2: Hypokalemic, hypochloremic metabolic alkalosis Type 3: Hypokalemic, hypochloremic metabolic alkalosis Type 4: Hypokalemic, hypochloremic metabolic alkalosis Type 5: Hypokalemic, hypochloremic metabolic alkalosis
DISTAL TUBULE			
	Gitelman syndrome	AR	Hypokalemic, hypochloremic, metabolic alkalosis
	Familial hypomagnesemia with hypercalciuria	AR	Severe renal magnesium and calcium wasting
	Isolated hypomagnesemia	AD	Renal magnesium wasting
	SeSAME syndrome (EAST syndrome)	AR	Hypokalemia, metabolic alkalosis, and hypomagnesemia
COLLECTING DUCT			
	Liddle syndrome	AD	Low renin hypertension
	Glucocorticoid-remediable hyperaldosteronism	AD	Low renin hypertension
	Apparent mineralocorticoid excess	AR	Low renin hypertension
	Pseudohypoaldosteronism, type 1	AR AD	AR: Hyponatremic, hypokalemic, metabolic acidosis AD: Hyponatremic, hypokalemic, metabolic acidosis
	Pseudohypoaldosteronism, type 2 (Gordon syndrome)	AD	Low renin hypertension with hyperkalemia
	Distal renal tubular acidosis	AR AD	AR: Hyperchloremic, hypokalemic, metabolic acidosis AD: Hyperchloremic, hypokalemic, metabolic acidosis
	Carbonic anhydrase II deficiency	AR	Mixed proximal and distal renal tubular acidosis
	Nephrogenic diabetes insipidus	X-linked AR and AD	X-linked: Urinary concentrating defect AR and AD: Urinary concentrating defect

AD = autosomal dominant; AR = autosomal recessive; SeSAME = seizures, sensorineural deafness, ataxia, intellectual disability (mental retardation), and electrolyte imbalances.

CLINICAL MANIFESTATIONS AND DIAGNOSIS

Three clinical presentations have been described. The most severe is infantile (classic) cystinosis, which manifests in the first year of life with renal tubular acidosis, impaired growth, and evidence of renal Fanconi syndrome, including aminoaciduria, glucosuria, phosphaturia, and low-molecular-weight proteinuria.

In untreated patients, progressive renal damage results in end-stage kidney disease by 10 years of age. A less severe, late-onset (juvenile or intermediate) form causes renal dysfunction in adolescence and involves cystine deposits in the cornea. The mildest form, an ocular, non-nephropathic form, features photophobia but no renal issues.

TREATMENT AND PROGNOSIS

The mainstay of therapy is oral cysteamine (dose: 60 to 90 mg/kg/day or 1.35 to 1.90 g/m^2/day, divided every 6 hours), which is an aminothiol that can lower intracellular cystine content by 90%.[3] In well-treated patients, cysteamine delays renal functional decline, enhances growth, prevents hypothyroidism, and lowers muscle cystine content. Therefore, early diagnosis and prompt, proper treatment are critical for preventing or significantly delaying the complications of cystinosis. Twice-daily dosing with delayed-release cysteamine bitartrate (at approximately 70% of the patient's usual dose) is as efficacious as cysteamine for reducing white blood cell cystine levels in patients with nephropathic cystinosis.

DENT DISEASE

Dent disease is an X-linked recessive renal tubular disorder characterized by low-molecular-weight proteinuria, hypercalciuria with nephrocalcinosis, and progressive renal failure. Low-molecular-weight proteinuria is the most consistent clinical feature, but there is wide variability in other manifestations of proximal tubular dysfunction. Atypical presentations have been reported, including amino aciduria, glycosuria, uricosuria/hypouricemia, kaliuresis/hypokalemia, and phosphaturia/hypophosphatemia. In two thirds of patients, the disease is caused by mutations in the *CLCN5* gene (Dent-1). A smaller proportion of patients (15 to 20%) have mutations in *OCRL* (Dent-2), the gene associated with Lowe oculocerebrorenal syndrome.

TREATMENT AND PROGNOSIS

No specific treatment is available, so treatment is designed to reduce nephrolithiasis and nephrocalcinosis with thiazide diuretics and often potassium citrate (see Chapter 111). End-stage kidney disease occurs at a median age of 40 years.[4]

DISORDERS OF LOOP OF HENLE AND DISTAL TUBULE FUNCTION

THE BARTTER-GITELMAN DISORDERS

The Bartter-Gitelman syndromes are a group of disorders that are characterized by markedly reduced salt transport in the thick ascending limb of Henle (Bartter syndrome) or in the distal convoluted tubule (Gitelman syndrome).[5]

Bartter syndrome is an autosomal recessive disorder that is caused by mutations in one of five genes—*SLC12A2,* encoding the sodium-potassium-chloride cotransporter NKCC2; *KCNJ1,* encoding the ROMK1 potassium ion channel; *CLCNKB,* encoding the ClC-Kb basolateral chloride ion channel; *BSND,* encoding barttin, a regulatory subunit required for basolateral chloride channel targeting to the membrane; and *MAGED,* encoding the melanoma antigen D2 (MAGE-D2). Defects in these genes cause Bartter syndrome types I, II, III, IV, and V, respectively. All five syndromes are characterized by disrupted salt transport in the thick ascending limb. In addition, severe gain-in-function mutations in *CASR,* the gene encoding the extracellular calcium ion–sensing receptor CaSR, can cause a Bartter-like phenotype (referred to as the Bartter-like subform of familial hypocalcemia) that is distinguished from the others by autosomal dominant transmission and associated hypocalcemic hypercalciuria. Most patients with Gitelman syndrome have defects in *SLC12A3,* the gene that encodes the sodium-chloride cotransporter NCCT. However, a minority of patients with the Gitelman phenotype have mutations in *CLCNKB.*

CLINICAL MANIFESTATIONS AND DIAGNOSIS

Individuals with Bartter syndrome exhibit renal salt wasting, lowered blood pressure, polyuria, hypokalemic metabolic alkalosis,[6] and hypercalciuria with a variable risk of nephrocalcinosis. Bartter syndrome mimics the effects of long-term furosemide treatment (E-Fig. 113-1). In comparison, individuals with Gitelman syndrome have a disorder resembling the effects of long-term thiazide administration: milder renal salt wasting, normal blood pressure, hypokalemic metabolic alkalosis, hypomagnesemia, and hypocalciuria. Clinical differences between Bartter and Gitelman syndromes relate to the severity of salt wasting, whereas phenotypic differences among Bartter types I through V correlate with the specific physiologic roles played by the individual transporters or channels in the kidney and other organs.

Genetic testing can confirm these diagnoses by detecting the specific mutation. However, it is not usually required in clinical practice.

TREATMENT

The mainstay of treatment includes replacing salt and water losses and providing potassium supplementation to maintain serum levels greater than 3 mEq/dL.[7] For patients with perinatal (types I, II, IV, V) Bartter syndrome, nonsteroidal anti-inflammatory drugs (e.g., indomethacin 2 to 4 mg/kg/day in two to four divided doses) may be beneficial. In patients with Gitelman syndrome and some patients with Bartter syndrome type III, oral magnesium supplementation may be required to maintain serum levels above 1.2 mg/dL. In patients who have Gitelman syndrome with persistent symptomatic hypokalemia despite therapeutic adherence or who have unacceptable side effects, treatment with potassium-sparing diuretics (e.g., amiloride 10-20 mg/day), a selective aldosterone antagonist (eplerenone 150 mg/day), or a combination of these agents may be effective.

DISORDERS OF COLLECTING DUCT FUNCTION

LIDDLE SYNDROME (PSEUDOALDOSTERONISM)

Liddle syndrome is an autosomal dominant form of salt-sensitive hypertension (Chapter 64) caused by mutations in the β or γ subunit of the epithelial sodium channel, which is expressed at the apical surface of collecting duct cells and plays a critical role in maintaining salt balance and blood pressure.[6] Both the β and γ subunits regulate the channel activity of the α subunit. Mutations in either of these regulatory subunits result in increased epithelial sodium channel activity and Liddle syndrome. Severe hypertension typically manifests in childhood, with features of hypokalemic metabolic alkalosis that resemble primary aldosteronism. However, the secretion of renin and aldosterone is suppressed in this disorder.

TREATMENT

The clinical abnormalities can be ameliorated by a low-salt diet plus a potassium-sparing diuretic (e.g., amiloride 5 to 20 mg/day or triamterene 100 to 200 mg twice daily), which acts as an antagonist of the epithelial sodium channel. Spironolactone is not useful because genetic alterations in the regulatory subunits disrupt mineralocorticoid regulation of the channel.

DISTAL RENAL TUBULAR ACIDOSIS

Distal renal tubular acidosis results from failure of the collecting duct α-intercalated cells to excrete fixed acids (see Fig. 104-1 in Chapter 104). Both autosomal dominant and autosomal recessive forms of distal renal tubular acidosis have been described. Mutations in the *CA2* gene encoding carbonic anhydrase II or the *SLC4A1* gene encoding the chloride-bicarbonate exchanger AE1 cause autosomal dominant distal renal tubular acidosis and are rarely associated with recessive forms of the disease. Mutations in genes encoding subunits of the vacuolar hydrogen–adenosine triphosphatase (V-type H^+-ATPase) proton pump are the primary causes of autosomal recessive distal renal tubular acidosis. V-type ATPases are ubiquitous, multisubunit protein complexes that mediate the ATP-dependent transport of protons. In the kidney, V-type ATPases are the major proton-secreting pumps in the distal nephron and are involved in net proton secretion (bicarbonate generation) or proton reabsorption (net bicarbonate secretion). Defects in two genes, *ATP6V1B1* and *ATP6V0A4,* which encode subunits of the H^+-ATPase, cause distal renal tubular acidosis with or without associated sensorineural deafness.

CLINICAL MANIFESTATIONS AND DIAGNOSIS

Clinical consequences include hypokalemic, hyperchloremic metabolic acidosis; impaired growth; hypercalciuria; hypocitraturia; nephrocalcinosis; nephrolithiasis; rickets in children; and osteomalacia in adults. Classic distal renal tubular acidosis can be distinguished from other metabolic acidoses by an inappropriately high urine pH (>5.5), diminished net acid excretion,

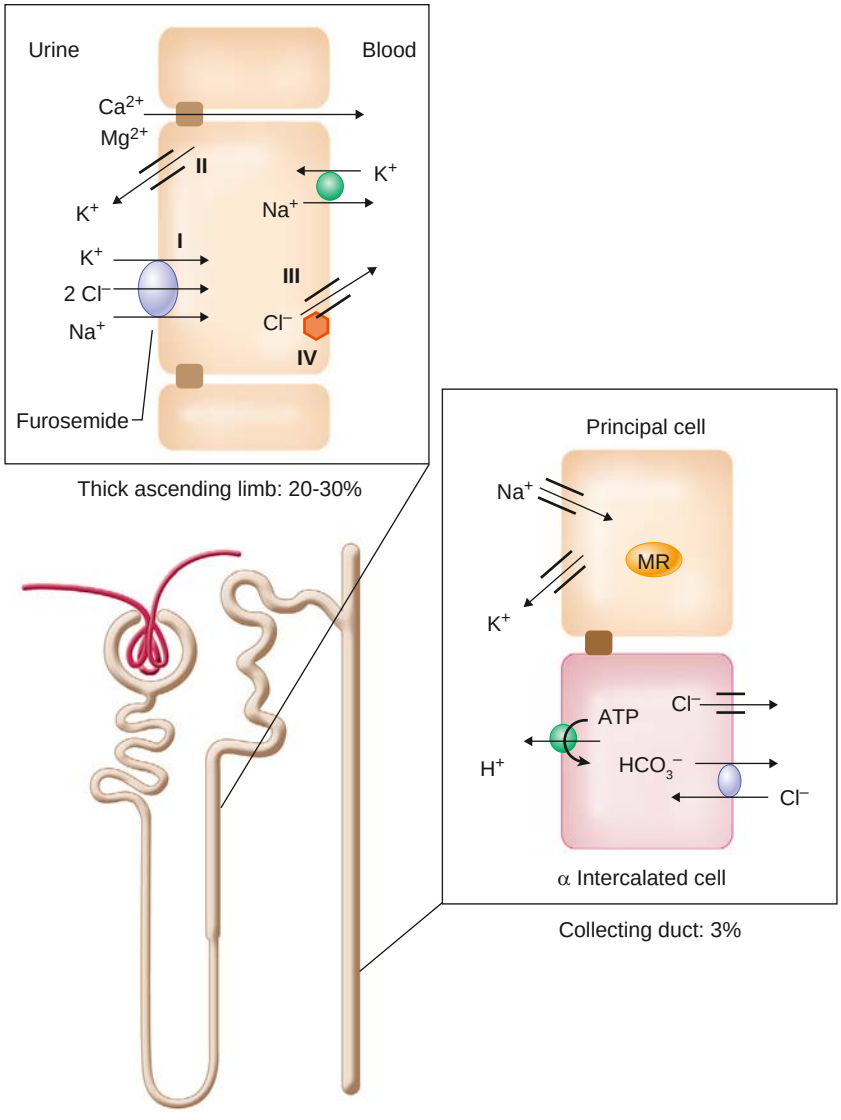

E-FIGURE 113-1. Transport in the thick ascending limb (TAL) and the pathophysiology of Bartter syndrome. Sodium (Na^+), potassium (K^+), and chloride (Cl^-) are reabsorbed across the apical membrane via the sodium-potassium-chloride cotransporter NKCC2 (defective in Bartter syndrome type I). NKCC2 can be inhibited by furosemide. Mutations in the gene encoding MAGE-D2 cause a transient decrease in NKCC2 expression, resulting in Bartter syndrome type V. The optimal function of NKCC2 requires the binding of all three ions. Potassium is recycled through the ROMK1 channel (defective in Bartter syndrome type II). These apical transport processes result in a relative excess of positive charges in the tubular lumen, providing the driving force for paracellular absorption of calcium (Ca^{2+}) and magnesium (Mg^{2+}). Na^+ exits across the basolateral membrane via the sodium-potassium adenosine triphosphatase (Na^+, K^+-ATPase) pump, whereas Cl^- exits through the chloride channels ClC-Kb (defective in Bartter syndrome type III) and ClC-Ka. Both channels require barttin (defective in Bartter syndrome type IV) for proper membrane localization. The TAL reabsorbs approximately 25% of the filtered sodium load, whereas the collecting duct (CD) is responsible for reabsorbing about 3% of the sodium load. The profound defect in TAL sodium reabsorption leads to salt wasting, stimulation of the renin-aldosterone system, and an aldosterone-induced increase in potassium and hydrogen ion secretion in the CD, with resultant hypokalemic metabolic alkalosis. HCO_3^- = bicarbonate; MR = mineralocorticoid receptor.

positive urinary anion gap, and low urinary ammonium concentration (Table 113-2).[8]

TREATMENT

Treatment with alkali supplementation as citrate salts (1 to 2 mEq/kg/day in adults and 3 to 6 mEq/kg/day in children) corrects the metabolic acidosis as well as the hypocitraturia, thereby preventing nephrolithiasis.[9] In contrast to proximal renal tubular acidosis, urinary potassium wasting can be ameliorated with alkali therapy alone.

DEVELOPMENT OF THE KIDNEY AND URINARY TRACT

The human kidney and urogenital tract develop from three principal embryonic structures: the metanephric mesenchyme, the mesonephric (wolffian) duct, and the cloaca (Fig. 113-1). At 4 to 5 weeks of gestation, the ureteric bud originates as a diverticulum of the mesonephric duct. Reciprocal interactions between the branching ureteric bud and the metanephric mesenchyme induce kidney development, with the metanephros undergoing an epithelial transformation to form the glomeruli and the proximal and distal tubules. The ureteric bud branches give rise to the collecting ducts, the renal pelvis, the ureter, and the bladder trigone. Approximately 60% of the nephron mass is formed in the second half of gestation, and the number of nephrons in the normal human kidney varies widely from about 250,000 to over 2 million.

Concurrent with the initial nephrogenic events, the urorectal fold divides the cloaca into the urogenital sinus and the future rectum. The mesonephric duct develops into the trigone of the urinary bladder, which is the posterior part of the bladder wall. Between 5 and 6 weeks of gestation, the second genital duct (müllerian duct) appears and runs in parallel with the wolffian duct. In males, the müllerian duct subsequently regresses, and the wolffian duct proceeds to form the epididymis, the vas deferens, the seminal vesicle, and the ejaculatory duct. In females, the wolffian duct regresses, and the müllerian ducts fuse to form the ureterovaginal primordium, which merges with the urogenital sinus and eventually gives rise to the uterus, the oviducts, and the proximal vagina. The remnants of the allantois form the urachus, a fibrous cord that connects the bladder to the umbilicus.

ABNORMALITIES OF THE URINARY TRACT

Congenital abnormalities of the kidney and urinary tract encompass a diverse set of structural malformations that result from defects in the developing urinary system.[10] These abnormalities occur in 3 to 11% of the population and account for approximately 50% of all congenital abnormalities.[11] Although 10 to 20% of cases are attributable to single gene mutations or genomic disorders, the majority of sporadic cases appear to involve complex interactions of multiple genetic variants and environmental factors.[12,13]

The most common malformation (~20%) is ureteropelvic junction obstruction. Renal parenchymal anomalies include agenesis, hypoplasia, dysplasia, malrotation, and ectopia. Pelviureteral abnormalities include megaureter, ectopic ureter, horseshoe kidney, duplex collecting system, and vesicoureteral reflux. Abnormalities of posterior urethral valves can occur concurrently. Prenatal ultrasonographic surveillance has substantially improved detection and prompt initiation of treatment, but these disorders remain important causes of infant mortality, as well as morbidity in older children and adults, including progression to renal failure.

RENAL AGENESIS

Renal agenesis reflects a complete failure of nephrogenesis. Unilateral agenesis can occur as an isolated abnormality or as a component of syndromic disorders, such as Turner syndrome (Chapter 214). As an isolated entity, the complete absence of one kidney occurs in 1 in 1000 to 1500 individuals. The incidence is higher in males and occurs somewhat more frequently on the left side; in about half the patients, the ipsilateral ureter and hemitrigone are also absent. The remaining kidney is usually enlarged owing to compensatory hypertrophy, but it may be ectopic or malrotated. Vesicoureteral reflux is observed on the contralateral side in about 30% of patients.

Renal agenesis is commonly associated with genital anomalies, thereby suggesting that it represents a developmental field defect. In females, absence of the ipsilateral oviduct and malformation of the uterus and vagina result from maldevelopment of the müllerian duct, whereas in males, wolffian duct–derived structures, such as the vas deferens and the seminal vesicles, are often absent. Other associated anomalies can involve the cardiovascular system (30%), musculoskeletal system (14%), and adrenal gland (10%). Unilateral renal agenesis is found in 30% of patients with the VACTERL syndrome, an association of vertebral, anal, cardiac, trachea-esophageal, renal, and limb defects.

Bilateral renal agenesis has an estimated incidence of 1 in 4000 births and is associated with the Potter sequence, which includes pulmonary hypoplasia, a characteristic facies, and deformities of the spine and limbs. At birth, these neonates have a critical degree of pulmonary hypoplasia that is incompatible with survival. The familial association of unilateral and bilateral renal agenesis, renal dysplasia, and congenital hydronephrosis occurs in hereditary renal adysplasia syndrome (Online Mendelian Inheritance in Man entry 191830), a rare autosomal dominant disorder with variable penetrance.

RENAL HYPOPLASIA

The term *renal hypoplasia* describes small kidneys with normally differentiated nephrons that are reduced in number. *Oligomeganephronia* describes a form of bilateral renal hypoplasia with a marked reduction in nephron number and associated hypertrophy of individual glomeruli and tubules. This abnormality occurs sporadically as an isolated developmental defect that must be differentiated from acquired renal atrophy and the genetic disorders nephronophthisis and autosomal dominant tubulointerstitial kidney disease (formerly known as medullary cystic kidney disease). Renal function declines slowly, with progression to end-stage kidney failure in the second to third decade of life.

RENAL DYSPLASIA

Renal dysplasia, which can be associated with various abnormalities of kidney size, results from abnormal metanephric differentiation that causes anomalous and/or incompletely differentiated renal elements. Small dysplastic kidneys are commonly referred to as *aplastic*. Large dysplastic kidneys are often cystic; the most extreme type is referred to as *multicystic dysplastic kidney*.

Unilateral dysplasia may be asymptomatic well into adult life. Small aplastic and large multicystic dysplastic kidneys are nonfunctioning and can be distinguished from renal agenesis by imaging studies. The ipsilateral ureter is typically atretic. Contralateral malformations, including obstruction and vesicoureteral reflux, are common. Unilateral multicystic kidneys involute over time and often disappear. Unilateral aplasia and multicystic dysplasia may be manifestations of the hereditary renal adysplasia syndrome. Bilateral multicystic dysplastic kidneys are incompatible with neonatal survival.

TABLE 113-2 FEATURES OF THE INHERITED RENAL TUBULAR ACIDOSES

DISORDER	RENAL TRANSPORT DEFECT	MINIMAL URINE pH DURING ACIDOSIS	ALKALI SUPPLEMENTATION	UAG DURING ACIDOSIS
Proximal renal tubular acidosis	↓ Proximal bicarbonate reabsorption	<5.5	Children: 10-15 mEq HCO_3^-/kg/day	0 or +
Carbonic anhydrase II deficiency	↓ Proximal bicarbonate reabsorption and ↓ distal acidification	Variable	Variable	0 or +
Distal renal tubular acidosis	↓ Distal acidification	>5.5	Adults: 1-2 mEq HCO_3^-/kg/day Children: 3-6 mEq HCO_3^-/kg/day	+ +

HCO_3^- = bicarbonate; UAG = urinary anion gap = $[Na^+] + [K^+] - [Cl^-]$. In renal tubular acidosis, the UAG is usually 0 or positive. By comparison, the UAG is negative in metabolic acidosis associated with diarrheal illness.

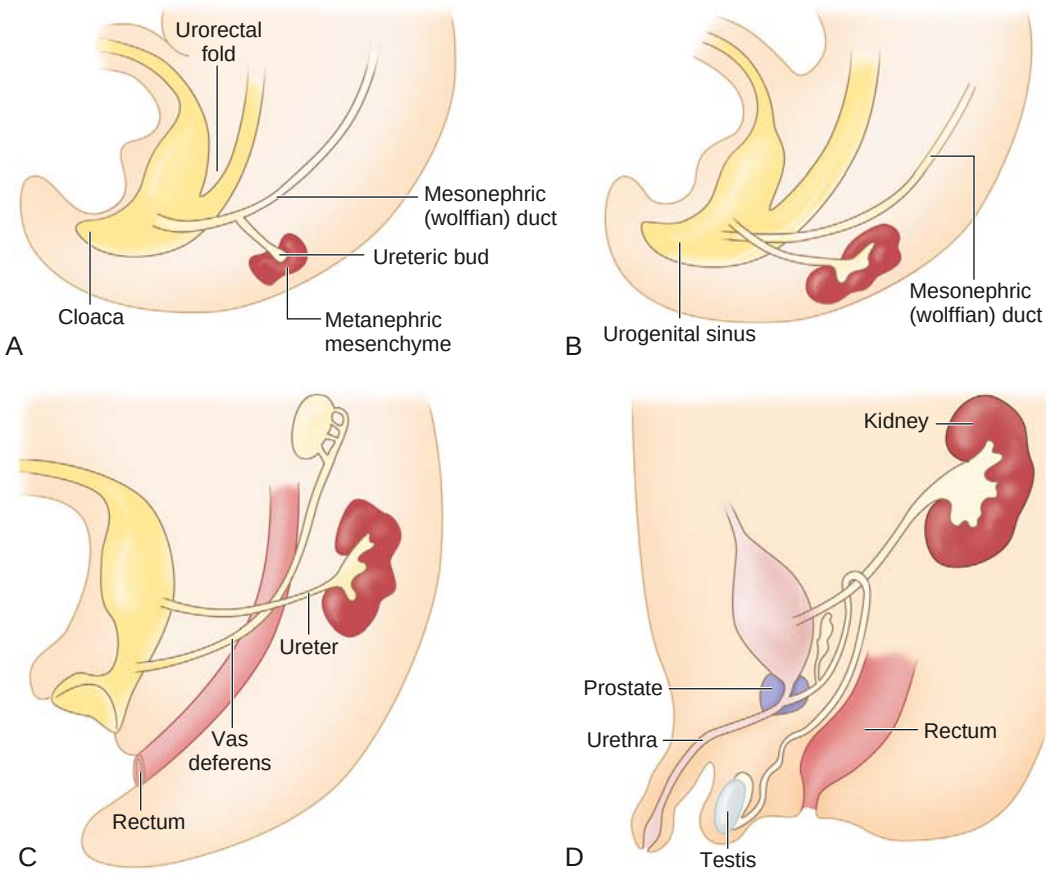

FIGURE 113-1. Key events in the development of the male urinary tract. In the 4-week embryo, the ureteric bud emerges from the wolffian duct (**A**). Reciprocal interactions between the branching ureteric bud and the metanephric mesenchyme induce kidney development. Concurrently, the cloaca is divided by the urorectal fold into the urogenital sinus and the future rectum (**B**). In the 8-week male embryo, the wolffian duct begins to give rise to the epididymis, the seminal vesicles, and the caudal part of the vas deferens (**C**). By 9 weeks, axial growth of the fetal spine prompts the developing kidney to ascend from the pelvis to its final lumbar position. The external genitalia develop between 8 and 16 weeks, and testicular descent begins in month 7 of gestation (**D**).

RENAL AND URETERAL STRUCTURAL ABNORMALITIES

RENAL MALROTATION AND ECTOPIA

Metanephric kidney development begins caudally. By 9 weeks of gestation, the kidney has ascended to its normal level (L1-L3), and the renal pelvis has rotated 90 degrees toward the midline. Anomalies of ascent and/or failure of rotation are common. Bilateral renal ectopia is often associated with kidney fusion. The most common fusion anomaly is the horseshoe kidney, which occurs in 1 in 500 newborns with a 2 : 1 male predominance. Renal ascent is prevented by the root of the inferior mesenteric artery (Fig. 113-2A). Crossed renal ectopia can occur with or without fusion. Supernumerary (extra) kidneys are typically ectopic and vary in location. Although almost one third of patients with renal ectopia remain asymptomatic, the associated malrotation of the renal pelvis increases the risk of hydronephrosis, infection, and stone formation.

PELVIURETERAL ABNORMALITIES

Obstruction of the ureteropelvic junction impedes the flow of urine from the renal pelvis into the ureter. It is one of the most frequently occurring urinary tract anomalies in infants, occurring in 1 in 1000 live births with male predominance. In congenital obstruction of the ureteropelvic junction, urologic anomalies in the contralateral system are common, including renal agenesis, renal dysplasia, multicystic dysplasia, and vesicoureteral reflux. Ureteropelvic junction obstruction may occur in adults secondary to external compression, kinking, or stenosis of the proximal ureter. Surgical intervention is indicated if there is associated renal function impairment, pyelonephritis, stones, or pain.

Hydrocalyx or *hydrocalycosis* refers to dilation of a major calyx that can result from intrinsic obstruction, such as in infundibular stenosis, or in the context of extrinsic compression of the pelvis, caused by a vessel or a parapelvic cyst. In comparison, *megacalycosis* represents a nonobstructive, dysplastic lesion found primarily in males, in which the calyces are dilated and usually increased in number. Associated renal medullary hypoplasia causes malformation of the renal papillae.

Calyceal diverticula are cystic structures connected by a narrow channel to an adjacent minor calyx. In imaging studies, these diverticula typically fill with contrast material, which distinguishes them from renal parenchymal cysts.

Partial duplication of the renal pelvis and ureter is a common anomaly that occurs more frequently in females, is typically unilateral, and is clinically insignificant.

URETERIC ANOMALIES

Ectopic ureters usually reflect complete ureteric and renal duplication. Approximately 10% are bilateral. The ectopic ureter typically drains the dysplastic upper pole of a duplex kidney and inserts below the normal vesicoureteral junction into the lower trigone of the bladder or the proximal urethra. Ectopic ureters occur more frequently in females, and the insertion sites can include the vagina and the vulva, with resulting incontinence. An ectopic ureter is often associated with a ureterocele, which is a cystic dilation of the terminal ureter (see Fig. 113-2B). In children, ureteroceles can be associated with urinary tract infection and obstruction of the bladder neck or even of the contralateral ureter. In adults, the clinical presentation usually involves associated infection, ureteric stones, or both.

A *megaureter,* or grossly dilated ureter, has multiple potential causes, including intrinsic ureteric obstruction by a stone, bladder outflow obstruction, vesicoureteral reflux, and external compression of the distal ureter. In contrast, primary megaureter results from a functional obstruction of the distal ureter caused by an aperistaltic segment (see Fig. 113-2C).

VESICOURETERAL REFLUX

In the normal urinary tract, urinary reflux from the bladder into the ureters is prevented by a functional valve-like mechanism at the vesicoureteral junction. The competence of this valve is dependent on several critical factors, such as the intramural length of the ureter, the position of the ureteric orifice in the bladder, and the integrity of the bladder wall musculature.

Primary vesicoureteral reflux results from incompetence of the vesicoureteral junction owing to the shortened length of the ureter's submucosal segment

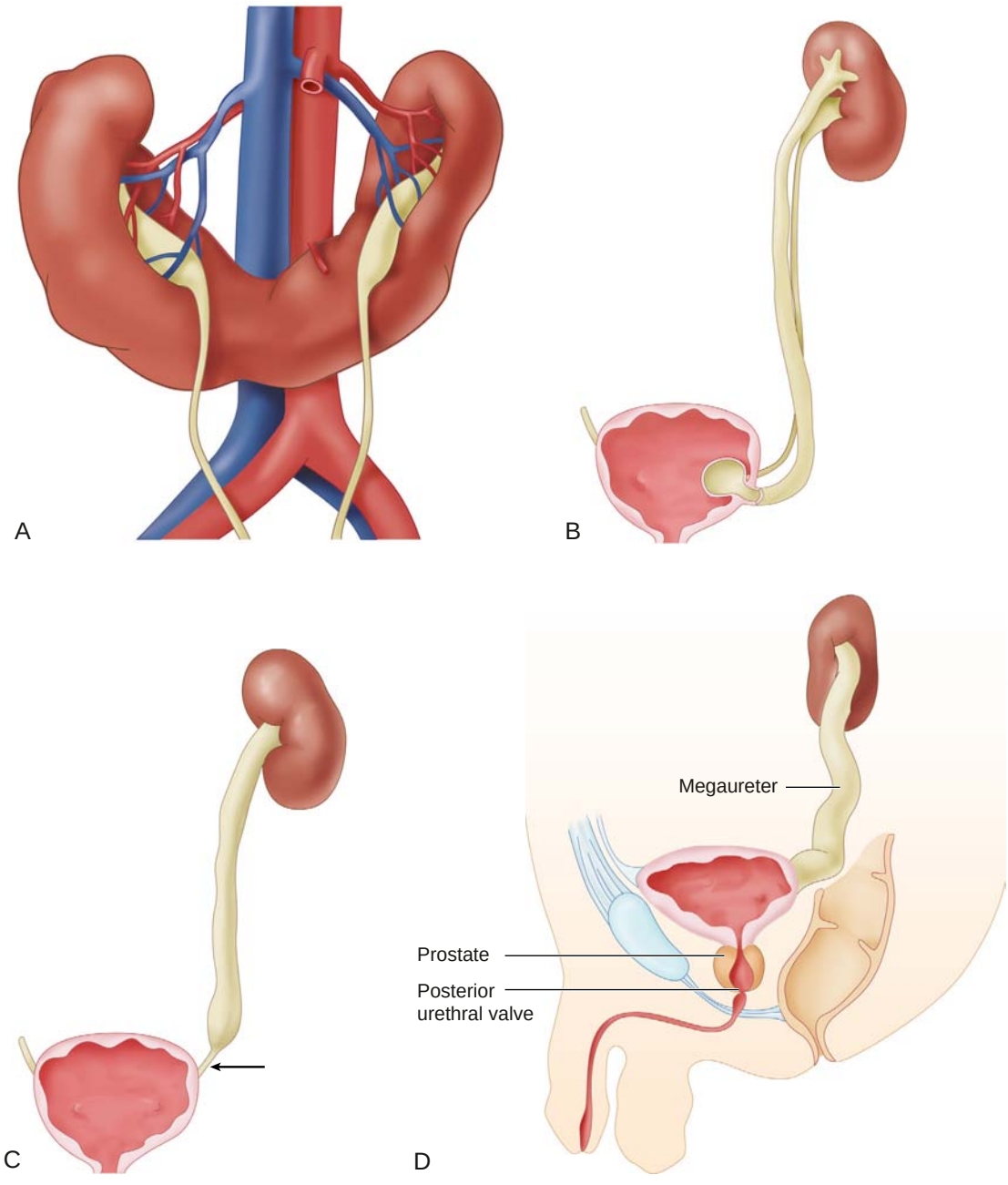

FIGURE 113-2. Developmental abnormalities of the urinary tract. A, Horseshoe kidney. B, Ectopic ureter associated with a ureterocele. C, Megaureter with the aperistaltic segment *(arrow)*. D, Bladder outlet obstruction caused by posterior urethral valves.

and the lateral, ectopic position of its orifice. It is estimated to occur in 1 to 2% in children. Familial clustering of vesicoureteral reflux suggests that genetic factors contribute to the pathogenesis, but each implicated gene accounts for only a small number of affected patients.[14]

As the intramural ureter lengthens with age, primary vesicoureteral reflux tends to remit or disappear. Vesicoureteral reflux can also occur secondary to obstructive maldevelopment of the lower urinary tract in children, such as in triad syndrome and posterior urethral valves, or secondary to masses that obstruct the bladder or urethra (in adults). In both primary and secondary vesicoureteral reflux, intrarenal reflux can lead to the development of reflux nephropathy, a tubulointerstitial lesion (Chapter 108) associated with gross scarring at the renal poles. In addition, the development of a glomerular lesion consistent with focal and segmental glomerulosclerosis (Chapter 107) can cause proteinuria, hypertension, and progressive loss of renal function.

Primary vesicoureteral reflux is diagnosed in about 30 to 40% of children who have imaging studies after urinary tract infections (Chapter 263). Frequent urinary tract infection, higher grades of vesicoureteral reflux, and the presence of bladder and bowel dysfunction are risk factors for renal cortical scarring, and the rates of spontaneous resolution of reflux and of endoscopic surgical success depend upon bladder and bowel dysfunction.

TREATMENT

For children with grade I through IV vesicoureteral reflux, antimicrobial prophylaxis does not decrease the risk of renal scarring,[A1] which occurs significantly more frequently in kidneys with grade IV reflux than in kidneys with low-grade or no reflux. For most patients, conservative management is preferred, using an individualized, risk-based approach under expert supervision. One endoscopic injection of a dextranomer/hyaluronic acid copolymer provides an efficient and safe long-term treatment in about 80% of treated patients with advanced vesicoureteral reflux,[15,16] but surgery has a higher cure rate.[A2] Further studies are needed to determine whether this minimally invasive approach should replace traditional surgical correction as the first-line therapy in many patients.

LOWER URINARY TRACT ABNORMALITIES

TRIAD SYNDROME (PRUNE-BELLY SYNDROME, EAGLE-BARRETT SYNDROME)

Triad syndrome, also referred to as prune-belly syndrome or Eagle-Barrett syndrome, involves a constellation of anomalies including congenital absence or deficiency of the abdominal wall musculature, gross ureteral dilation, bladder wall thickening, prostatic hypoplasia, and bilateral undescended testes (cryptorchidism). The full syndrome is expressed only in males, and surviving individuals are typically infertile. Patients with an incomplete syndrome can have anomalies of the abdominal wall musculature, bladder, and upper urinary tract; 3 to 5% of these patients are females. Although the specific molecular causes have yet to be defined, defects in mesenchymal development appear to cause poor prostate and bladder differentiation, ureteral smooth muscle aplasia with consequent ureteral aperistalsis, and varying degrees of renal dysplasia. Patients with triad syndrome have associated anorectal malformations, musculoskeletal anomalies, and, rarely, cardiac anomalies. In the immediate postnatal period, prognosis depends on the severity of extra-genitourinary defects. Long-term outcome correlates with the degree of renal dysplasia and the success of urodynamic management.

BLADDER ABNORMALITIES

Bladder exstrophy results from a midline closure defect involving the lower anterior abdominal wall, the bladder, and the external genitalia. These abnormalities have been attributed to a primary defect in the differentiation of the cloacal membrane, but the precise molecular events remain unclear. Variants in genes involved the morphogenesis of the urinary tract are linked to the pathogenesis of bladder exstrophy.[17] In severe cases, bladder exstrophy may be associated with imperforate anus and rectal atresia. Clinical studies suggest a correlation between the success of bladder reconstruction and long-term preservation of renal function.

In adults, neuropathic or neurogenic bladder (Chapter 115) has numerous etiologic contributors, including central nervous system trauma, stroke, disorders such as Parkinson disease, spinal trauma, multiple sclerosis, and peripheral nerve damage caused by trauma or surgery. In children, myelomeningocele (spina bifida) is the most common cause of neurogenic bladder dysfunction. Other forms of myelodysplasia, such as spinal dysraphism (spina bifida occulta) and sacral agenesis, are less common causes.

TREATMENT

Treatment focuses on the management of incontinence (Chapter 115) and the prevention and treatment of urinary tract infections (Chapter 263).

POSTERIOR URETHRAL VALVES

In male infants, posterior urethral valves are the most common cause of bladder outflow obstruction, with resulting bilateral hydronephrosis and megaureters. However, among all infants with hydronephrosis, only 10% have posterior urethral valves. The urethral obstruction results from defective reabsorption of mucosal folds in the posterior urethra, just distal to the verumontanum of the prostatic urethra. As a result, dilation of the proximal urethra, bladder wall hypertrophy and trabeculation, associated vesicoureteral reflux, and varying degrees of renal dysplasia are present (see Fig. 113-2D). Surgical management strategies are dictated by the age of the child and the degree of associated renal insufficiency. Survival and long-term renal outcome depend on the severity of the associated renal dysplasia.

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For the General References and other additional features, please visit Elsevier eBooks+ at https://ebooks.health.elsevier.com.

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114

BENIGN PROSTATIC HYPERPLASIA AND PROSTATITIS

STEVEN A. KAPLAN

BENIGN PROSTATIC HYPERPLASIA

DEFINITION

The prostate gland is composed of four zones: peripheral, central, transitional, and stroma. It can also be divided by lobes: anterior, posterior, lateral, and median (Fig. 114-1).

A normal prostate volume in young men is about 20 mL (where 1 mL is equivalent to 1 gram), but it increases from an average of about 24 mL to 38 mL between ages 50 to 80 years. In benign prostatic hyperplasia (BPH), the calculated volume exceeds 30 mL, but the degree of prostatic enlargement that causes symptoms is highly variable.

EPIDEMIOLOGY

Age is the major risk factor for BPH. A histologic diagnosis of BPH will develop in approximately 50% of men older than 50 years of age and 90% of men in their 80s. Of these men, approximately 50% will develop notable lower urinary tract symptoms, which increase in prevalence in a linear fashion between the ages of 40 and 80 years. With increasing worldwide longevity, BPH has become a major global challenge.[1]

PATHOBIOLOGY

As the bladder fills with urine, it normally is able to maintain a low intravesical pressure via sympathetic nerve stimulation despite the increasing volume. However, an enlarged prostate may cause lower urinary tract symptoms by directly obstructing the flow of urine or by increasing the muscle tone of the prostate. Men with bladder outlet obstruction due to BPH often have overactive bladder detrusor function, thereby resulting in urinary retention. In addition, changes in the vascularity of the prostate or the urinary bladder can contribute to the development of symptoms. The growth of the prostate gland is dependent on androgens and androgen receptors, and it is reduced by 5α-reductase inhibitors that block the conversion of testosterone to dihydrotestosterone.[2]

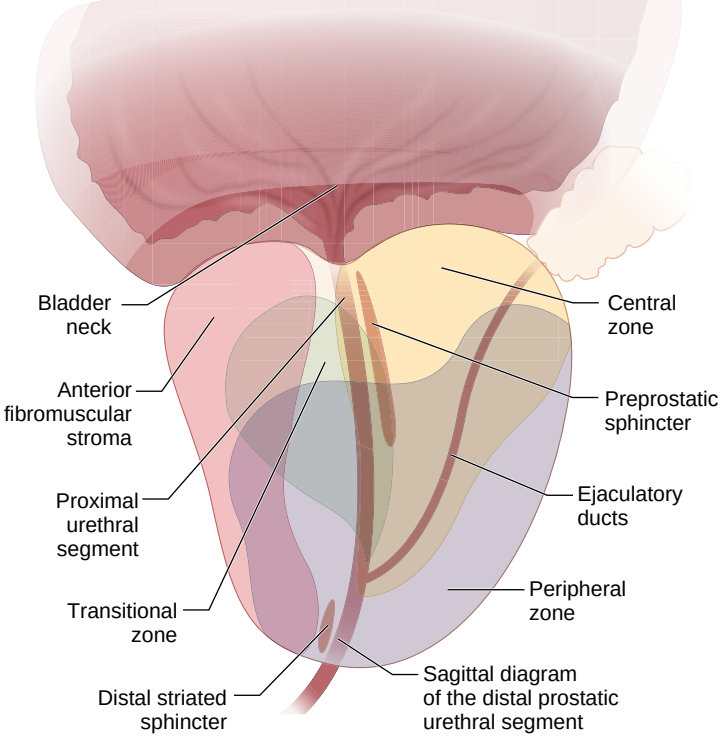

FIGURE 114-1. Anatomy of the prostate.

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LOWER URINARY TRACT ABNORMALITIES

TRIAD SYNDROME (PRUNE-BELLY SYNDROME, EAGLE-BARRETT SYNDROME)

Triad syndrome, also referred to as prune-belly syndrome or Eagle-Barrett syndrome, involves a constellation of anomalies including congenital absence or deficiency of the abdominal wall musculature, gross ureteral dilation, bladder wall thickening, prostatic hypoplasia, and bilateral undescended testes (cryptorchidism). The full syndrome is expressed only in males, and surviving individuals are typically infertile. Patients with an incomplete syndrome can have anomalies of the abdominal wall musculature, bladder, and upper urinary tract; 3 to 5% of these patients are females. Although the specific molecular causes have yet to be defined, defects in mesenchymal development appear to cause poor prostate and bladder differentiation, ureteral smooth muscle aplasia with consequent ureteral aperistalsis, and varying degrees of renal dysplasia. Patients with triad syndrome have associated anorectal malformations, musculoskeletal anomalies, and, rarely, cardiac anomalies. In the immediate postnatal period, prognosis depends on the severity of extra-genitourinary defects. Long-term outcome correlates with the degree of renal dysplasia and the success of urodynamic management.

BLADDER ABNORMALITIES

Bladder exstrophy results from a midline closure defect involving the lower anterior abdominal wall, the bladder, and the external genitalia. These abnormalities have been attributed to a primary defect in the differentiation of the cloacal membrane, but the precise molecular events remain unclear. Variants in genes involved the morphogenesis of the urinary tract are linked to the pathogenesis of bladder exstrophy.[17] In severe cases, bladder exstrophy may be associated with imperforate anus and rectal atresia. Clinical studies suggest a correlation between the success of bladder reconstruction and long-term preservation of renal function.

In adults, neuropathic or neurogenic bladder (Chapter 115) has numerous etiologic contributors, including central nervous system trauma, stroke, disorders such as Parkinson disease, spinal trauma, multiple sclerosis, and peripheral nerve damage caused by trauma or surgery. In children, myelomeningocele (spina bifida) is the most common cause of neurogenic bladder dysfunction. Other forms of myelodysplasia, such as spinal dysraphism (spina bifida occulta) and sacral agenesis, are less common causes.

TREATMENT

Treatment focuses on the management of incontinence (Chapter 115) and the prevention and treatment of urinary tract infections (Chapter 263).

POSTERIOR URETHRAL VALVES

In male infants, posterior urethral valves are the most common cause of bladder outflow obstruction, with resulting bilateral hydronephrosis and megaureters. However, among all infants with hydronephrosis, only 10% have posterior urethral valves. The urethral obstruction results from defective reabsorption of mucosal folds in the posterior urethra, just distal to the verumontanum of the prostatic urethra. As a result, dilation of the proximal urethra, bladder wall hypertrophy and trabeculation, associated vesicoureteral reflux, and varying degrees of renal dysplasia are present (see Fig. 113-2D). Surgical management strategies are dictated by the age of the child and the degree of associated renal insufficiency. Survival and long-term renal outcome depend on the severity of the associated renal dysplasia.

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For the General References and other additional features, please visit Elsevier eBooks+ at https://ebooks.health.elsevier.com.

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114

BENIGN PROSTATIC HYPERPLASIA AND PROSTATITIS

STEVEN A. KAPLAN

BENIGN PROSTATIC HYPERPLASIA

DEFINITION

The prostate gland is composed of four zones: peripheral, central, transitional, and stroma. It can also be divided by lobes: anterior, posterior, lateral, and median (Fig. 114-1).

A normal prostate volume in young men is about 20 mL (where 1 mL is equivalent to 1 gram), but it increases from an average of about 24 mL to 38 mL between ages 50 to 80 years. In benign prostatic hyperplasia (BPH), the calculated volume exceeds 30 mL, but the degree of prostatic enlargement that causes symptoms is highly variable.

EPIDEMIOLOGY

Age is the major risk factor for BPH. A histologic diagnosis of BPH will develop in approximately 50% of men older than 50 years of age and 90% of men in their 80s. Of these men, approximately 50% will develop notable lower urinary tract symptoms, which increase in prevalence in a linear fashion between the ages of 40 and 80 years. With increasing worldwide longevity, BPH has become a major global challenge.[1]

PATHOBIOLOGY

As the bladder fills with urine, it normally is able to maintain a low intravesical pressure via sympathetic nerve stimulation despite the increasing volume. However, an enlarged prostate may cause lower urinary tract symptoms by directly obstructing the flow of urine or by increasing the muscle tone of the prostate. Men with bladder outlet obstruction due to BPH often have overactive bladder detrusor function, thereby resulting in urinary retention. In addition, changes in the vascularity of the prostate or the urinary bladder can contribute to the development of symptoms. The growth of the prostate gland is dependent on androgens and androgen receptors, and it is reduced by 5α-reductase inhibitors that block the conversion of testosterone to dihydrotestosterone.[2]

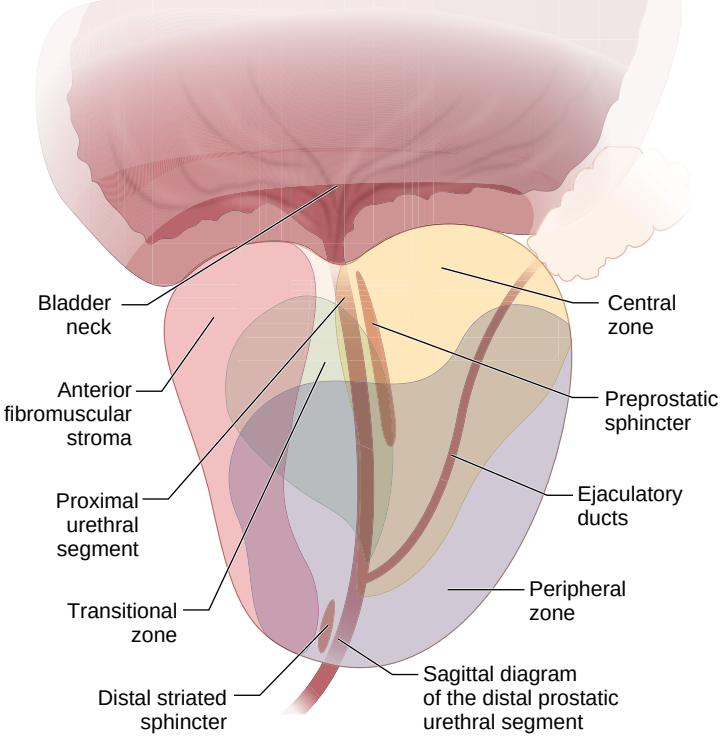

FIGURE 114-1. Anatomy of the prostate.

ABSTRACT

Benign prostatic hyperplasia develops in about 50% of men over age 50 years and 90% of men in their 80s. About half of these men will develop clinically important lower urinary tract symptoms, including urgency, hesitancy, frequency, nocturia, and incomplete emptying. Treatment emphasizes alpha adrenergic antagonists, 5-alpha-reductase inhibitors, and phosphodiesterase type 5 inhibitors; many men require combination therapy. When medications are inadequate, a variety of minimally invasive surgical options can remove sufficient prostate tissue to reduce symptoms substantially. Prostatitis, which is inflammation of the prostate gland, is typically chronic and often associated with local discomfort as well as symptoms similar to benign prostatic hypertrophy. Chronic bacterial prostatitis may respond, at least transiently, to empiric antibiotic therapy. Acute bacterial prostatitis requires urgent antibiotics, with the intravenous route sometimes required.

KEYWORDS

benign prostatic hypertrophy
prostatic hypertrophy
prostatitis
bacterial prostatitis
chronic pelvic pain syndrome

Enlargement typically is a combination of stromal hypertrophy and glandular hyperplasia, mostly in the central zone. BPH is a histologic diagnosis defined by the proliferation of smooth muscle and epithelial cells within the prostatic transition zone.

CLINICAL MANIFESTATIONS

Benign prostatic hyperplasia can lead to lower urinary tract symptoms, which can have a significant negative impact on quality of life. The presence of lower urinary tract symptoms is often indicative of bladder outlet obstruction secondary to BPH. Symptoms may significantly impair health-related quality of life and are classified as voiding (i.e., hesitancy, weak stream, straining, and prolonged voiding), storage (i.e., frequency, urgency, nocturia, urge incontinence, and voiding of small volumes), or postmicturition (i.e., postvoid dribble, incomplete emptying).[3] Most patients who have lower urinary tract symptoms present with a combination of these symptoms. The symptoms of overactive bladder (Chapter 115) and lower urinary tract symptoms secondary to BPH often overlap.

DIAGNOSIS

Assessment should begin with a medical history and review of the patient's medications. The medical history should include any causes that may lead to bladder dysfunction, such as cerebrovascular disease, previous surgical procedures, and a history of prostatic disease. Diuretics and over-the-counter preparations, such as nasal decongestants and antihistamines, may exacerbate the patient's urinary symptoms. Furthermore, dietary factors such as water, caffeine, alcohol, and artificial sweeteners can be important contributors to the overall clinical manifestations of symptoms because they serve as direct bladder irritants and diuretics. Urinary symptoms should be assessed in a standardized fashion with validated instruments such as the International Prostate Symptom Score (IPSS) (Fig. 114-2) and observed over time.

Abdominal examination should be performed to identify the presence of a palpable bladder, which could be a sign of urinary retention. The physical examination should include a prostate examination to evaluate its size and the possible presence of nodules. The digital rectal examination gives only an approximate estimate of size because only the posterior half is palpated. A focused neurologic examination is also important to assess a patient's mental status, ambulatory status, lower extremity neuromuscular function, and anal sphincter tone.

Laboratory Findings

Urinalysis should be performed to screen for hematuria and urinary tract infection (Chapter 263). A serum prostate-specific antigen (PSA) level should be measured because it can detect asymptomatic prostate cancer (Chapter 186) that may require treatment even in men who would not be candidates for treatment if they were asymptomatic. However, the results must be interpreted with caution because the serum PSA level correlates with prostatic volume even in the absence of cancer. Objective parameters such as maximum urinary flow by uroflowmetry and bladder postvoid residual by ultrasound should also be measured if the diagnosis is in question.[4] Although there is not a direct correlation between lower urinary tract symptoms and objective parameters such as prostate size or flow rate, prostate volume and serum PSA levels generally predict worsening of symptoms. Long-standing bladder outlet obstruction can progress to incomplete bladder emptying, bilateral hydroureteronephrosis, and ultimately acute and/or chronic renal insufficiency. Given the myriad of new minimally invasive and surgical therapeutic options, measurement of prostate volume by either the abdominal or transrectal route should be considered.

Other causes of bladder dysfunction that should be considered during the assessment of men presenting with lower urinary tract symptoms include bladder cancer (Chapter 182), diabetes (Chapter 210), urethral strictures, and bladder stones. The absence of hematuria makes bladder cancer very unlikely, but patients with BPH symptoms require cystoscopy if they also have hematuria. Neurologic disorders including Parkinson disease (Chapter 378) and multiple sclerosis (Chapter 380) may also cause lower urinary tract symptoms in men.

TREATMENT

The treatment of BPH aims to improve subjective symptoms and quality of life as well as to prevent progression of the disease.[5] Over time, treatment has evolved away from surgical therapy and largely to medical therapy.[6,7]

Men who are mildly symptomatic, defined as a score of 7 or less on the IPSS questionnaire, can be observed (Fig. 114-3). Lifestyle changes that may improve symptoms include fluid restriction, timed voiding, and double voiding. Patients who have moderate symptoms, defined as 8 to 19 points on the IPSS, and who are not seriously bothered by their symptoms may also be observed with periodic reassessment to monitor whether urinary retention, refractory hematuria, infections, or other complications develop. Men with more substantial symptoms should be treated medically.[8]

Medications

α-Adrenergic antagonists, which decrease bladder outlet resistance by relaxing urethral smooth muscle and possibly striated sphincter tone, are considered the first-line treatment of male lower urinary tract symptoms[A1] (Table 114-1). Their side effects include orthostatic hypotension, sexual dysfunction, and dizziness. All medications in this class should be discontinued before cataract surgery for fear of floppy-iris syndrome.

The 5α-reductase inhibitors dutasteride and finasteride are also effective for the treatment of BPH, with evidence suggesting that dutasteride is preferred.[A2] These agents reduce prostate size by suppressing testosterone and dihydrotestosterone production. As a result, these agents reduce the number of episodes of acute urinary retention and decrease the need for surgical treatment of BPH, and they are particularly helpful for the treatment of patients with higher prostate volumes. Side effects of these medications include erectile dysfunction, reduced libido, and decreased ejaculate volume.

The phosphodiesterase type 5 inhibitor tadalafil also improves lower urinary tract symptoms and IPSS scores secondary to BPH.[A3] However, tadalafil is not as efficacious as α-adrenergic antagonists or 5α-reductase inhibitors for improving maximal urinary flow.

Antimuscarinic agents, which target the muscarinic cholinergic receptors in the bladder to reduce overactivity that occurs as a result of changes in detrusor function, are safe and efficacious for the treatment of BPH. Options include tolterodine, solifenacin, and fesoterodine.

Another class of agents used to treat overactive bladder symptoms are β_3-agonists such as mirabegron and vibegron. Mirabegron and vibegron stimulate β_3-receptors, thereby causing smooth muscle relaxation in the bladder.[A4]

Combination drug therapy is an option when single-drug therapy is insufficient. Data suggest that the best combination is adding a 5α-reductase inhibitor to an α-adrenergic blocker,[A5] although the combination of an α-adrenergic blocker and a phosphodiesterase 5 inhibitor is also efficacious.[A6,A7] Similarly, the combination of tamsulosin, dutasteride, and an antimuscarinic agent or A β_3-agonists (see Table 114-1) can improve overactive bladder symptoms that have responded inadequately to tamsulosin alone.[A8] Saw palmetto, the most commonly used phytotherapeutic agent, does not improve urinary parameters during a treatment period of 12 months in randomized trials and is not recommended even as add-on therapy.

Surgical Treatments

Many minimally invasive treatment options are available for BPH.[9,10] Prostatic urethral lift delivers permanent transprostatic implants through a cystoscope to open the prostatic parenchyma mechanically. This treatment is limited to patients with a prostate smaller than 80 g and without significant middle lobe hypertrophy, in whom it is as good as or better than surgical prostatectomy.[A9] Transurethral radiofrequency-induced water therapy induces a delayed coagulation necrosis of prostatic tissue, thereby resulting in a decrease in prostate volume.[A10] The advantages of these procedures (i.e., lower risks for retrograde ejaculation, strictures, hematuria, and blood transfusions) must be balanced against increased risks for dysuria, urinary retention, recurrent symptoms, and the need for retreatment compared with transurethral resection of the prostate.[A11]

Electrosurgically based transurethral resection of the prostate, either via a monopolar or bipolar approach, is the "gold standard" in endoscopic treatment of symptomatic BPH. Because of improvements in medical therapy and minimally invasive options, the number of transurethral resection of the prostate procedures performed in the United States has declined, although it still remains the most commonly performed urologic procedure.

Bipolar transurethral resection of the prostate uses bipolar instead of monopolar electrocautery and saline as an irrigant. This procedure resects large amounts of prostatic tissue from the transitional zone and central zone but decreases complications, such as hyponatremia and perioperative bleeding requiring transfusion. For patients with very large prostate glands (i.e., 80 g and larger), transurethral resection of the prostate procedures may require prolonged operative times, and an open surgical approach may be necessary for adequate debulking of the obstructing prostatic tissue.

Other surgical technologies include various laser vaporization techniques[A12] or microwave therapy.[A13] Laser technologies can be effective alternatives to electrosurgical approaches, although their long-term durability remains to be defined. Prostatic artery embolization is another possible treatment, though data on its efficacy and safety are limited.[A14]

	Not at all	Less than 1 time in 5	Less than half the time	About half the time	More than half the time	Almost always
1. Over the past month or so, how often have you had a sensation of not emptying your bladder completely after you finished urinating?	0 ☐	1 ☐	2 ☐	3 ☐	4 ☐	5 ☐
2. Over the past month or so, how often have you had to urinate again less than two hours after you finished urinating?	0 ☐	1 ☐	2 ☐	3 ☐	4 ☐	5 ☐
3. Over the past month or so, how often have you found you stopped and started again several times when you urinated?	0 ☐	1 ☐	2 ☐	3 ☐	4 ☐	5 ☐
4. Over the past month or so, how often have you found it difficult to postpone urination?	0 ☐	1 ☐	2 ☐	3 ☐	4 ☐	5 ☐
5. Over the past month or so, how often have you had a weak urinary stream?	0 ☐	1 ☐	2 ☐	3 ☐	4 ☐	5 ☐
6. Over the past month or so, how often have you had to push or strain to begin urination?	0 ☐	1 ☐	2 ☐	3 ☐	4 ☐	5 ☐

7. Over the past month, how many times did you most typically get up to urinate from the time you went to bed at night until the time you got up in the morning?

0 ☐ none	1 ☐ 1 time	2 ☐ 2 times	3 ☐ 3 times	4 ☐ 4 times	5 ☐ 5 or more times

Total IPSS Score = sum of questions 1–7 = _____

Quality of life due to urinary symptoms

If you were to spend the rest of your life with your urinary condition just the way it is now, how would you feel about that?

Delighted	Pleased	Mostly satisfied	Mixed—about equally satisfied and dissatisfied	Mostly dissatisfied	Unhappy	Terrible
0 ☐	1 ☐	2 ☐	3 ☐	4 ☐	5 ☐	6 ☐

FIGURE 114-2. International Prostate Symptom Score (IPSS). The seven symptom questions constitute a scale initially developed by the American Urological Association. The eighth question about quality of life is scored separately. (From Barry MJ, Fowler FJ Jr, O'Leary MP, et al. The American Urological Association symptom index for benign prostatic hyperplasia: the Measurement Committee of the American Urological Association. *J Urol*. 1992;148:1549.)

PROGNOSIS

Over time, the symptoms of BPH often increase and require medications or a procedure. Recurrent episodes of prostatitis can exacerbate symptoms. Patients should be counseled about the likelihood of progression, the natural history of lower urinary tract symptoms (including the risk for urinary tract infections [Chapter 263]) related to BPH, and the treatment options that can be offered.

PROSTATITIS

EPIDEMIOLOGY AND PATHOBIOLOGY

Prostatitis is usually a clinical diagnosis based on signs and symptoms that occur as a result of inflammation of the prostate gland. The overall prevalence of prostatitis is approximately 8%, and it affects men of a wide age range. Swelling or inflammation of the prostate gland, which may be due to various causes, can have a significant impact on quality of life. The current classification system defines the various types of prostatitis on the basis of whether it is acute or chronic, associated with infection, or associated with pelvic pain (Table 114-2).

The causative organisms of acute bacterial prostatitis are usually similar to those that cause other common genitourinary infections (Chapter 263) and include *Escherichia coli* and *Enterococcus* spp. About 60% of patients with chronic bacterial prostatitis have evidence of ongoing infection based on polymerase chain reaction (PCR) testing of their expressed prostatic secretions, with *Chlamydia trachomatis, Ureaplasma urealyticum, Mycoplasma genitalium,* and *Mycoplasma hominis* the most common organisms detected. The pathogenesis of chronic prostatitis/chronic pelvic pain syndrome, however, remains unclear.

CLINICAL MANIFESTATIONS

Acute bacterial prostatitis (type I) is characterized by acute infection of the prostate gland. Presenting symptoms include pelvic, perineal, penile, or ejaculatory pain as well as irritative or obstructive voiding symptoms and sexual dysfunction. Patients with severe infections can present with fever and chills and can become septic (Chapter 94). Type II prostatitis is characterized by recurrent or relapsing infection caused by the same organism. These patients tend to be less sick during each episode and usually present with voiding symptoms and pain.

Type III prostatitis is characterized by pelvic discomfort or pain for more than 3 of the 6 months before evaluation. Type III patients have repeatedly negative urine cultures. Classification into type IIIa or IIIb is contingent on the presence of leukocytes in semen, post–prostate massage urine, or prostatic secretions. Patients with type IV prostatitis do not experience any symptoms of prostatitis. Leukocytes or inflammatory cells are found in prostate tissue, semen, or expressed prostatic secretions.

DIAGNOSIS

The diagnosis of prostatitis requires a careful history, physical examination, and examination of the urine. The physician must ask pertinent questions about voiding history, sexual history, symptoms, pain, neurologic disorders, and prior pelvic surgery. The National Institutes of Health Chronic Prostatitis Symptom Index (NIH-CPSI), which is a standardized tool for the evaluation and assessment of prostatitis, consists of nine parts that outline three major areas of prostatitis: pain, urinary symptoms, and quality of life (Fig. 114-4). The NIH-CPSI is not specifically for making the diagnosis of prostatitis, but it is very useful for longitudinally monitoring changes in symptoms over time after a diagnosis of prostatitis has been established. The physical examination should include an abdominal, external genital, perineal, and digital rectal examination. Attention should be placed on identifying pelvic wall discomfort, structural abnormalities, or prostatic pain on digital rectal examination.

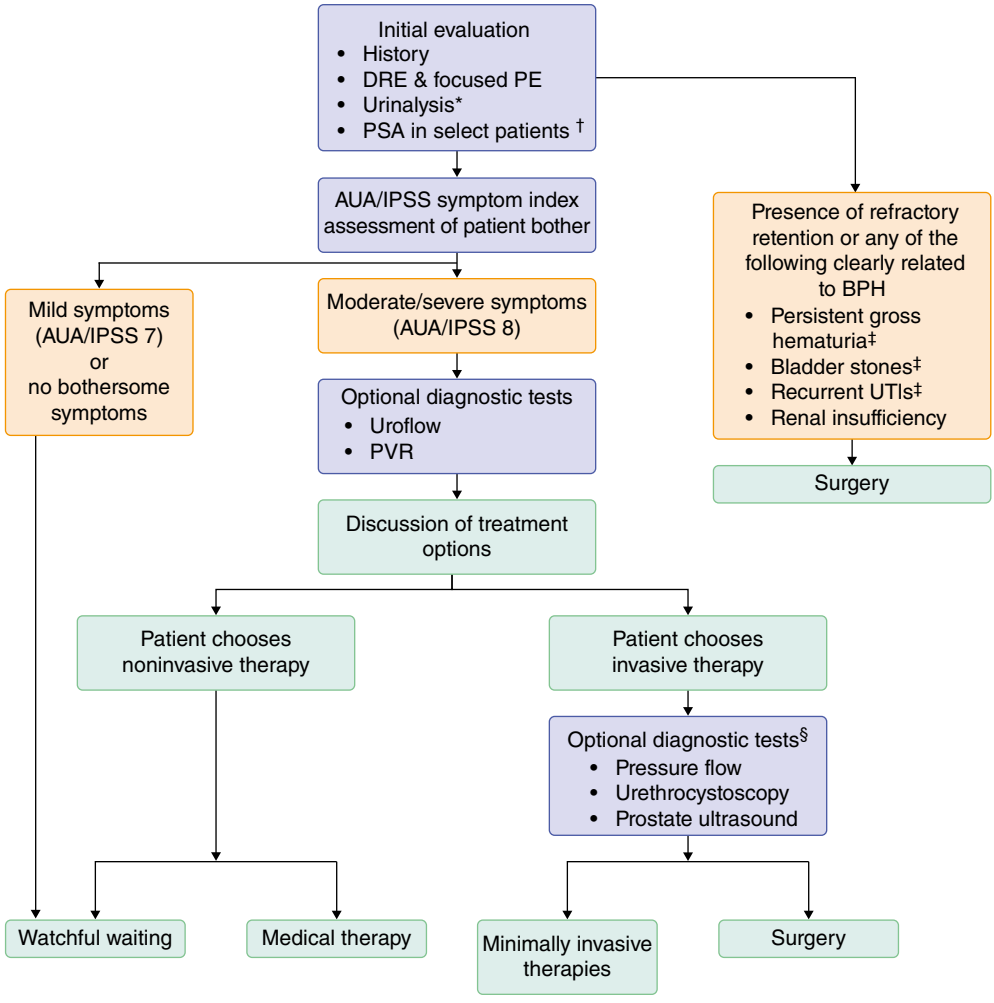

FIGURE 114-3. **Algorithm of management of benign prostatic hyperplasia (BPH).** *In patients with clinically significant prostatic bleeding, a course of a 5 alpha-reductase inhibitor may be used. If bleeding persists, tissue ablative surgery is indicated. †Patients with at least a 10-year life expectancy for whom knowledge of the presence of prostate cancer would change management or patients for whom the PSA measurement may change the management of voiding symptoms. ‡After exhausting other therapeutic options. §Some diagnostic tests are used in predicting response to therapy. Pressure-flow studies are most useful in men prior to surgery. AUA = American Urological Association; DRE = digital rectal exam; IPSS = International Prostate Symptom Score; PE = physical exam; PSA = prostate-specific antigen; PVR = postvoid residual urine; UTI = urinary tract infection. (©2003 American Urological Association Educations and Research, Inc.)

TABLE 114-1 ORAL MEDICATIONS AND RECOMMENDED DAILY DOSES FOR MALE LOWER URINARY TRACT SYMPTOMS

α-BLOCKERS	5α-REDUCTASE INHIBITORS	α-BLOCKER AND 5α-REDUCTASE INHIBITOR	ANTIMUSCARINICS	PHOSPHODIESTERASE TYPE 5 INHIBITORS	β_3-ADRENERGIC RECEPTOR ACTIVATOR
Alfuzosin 10 mg	Dutasteride 0.5 mg	Dutasteride and tamsulosin 0.5/0.4 mg	Darifenacin 7.5, 15 mg	Tadalafil 5 mg	Mirabegron 25, 50 mg
Doxazosin 1-8 mg	Finasteride 5 mg		Fesoterodine 4, 8 mg	Sildenafil and vardenafil not FDA approved for BPH	Vibegron 75 mg
Tamsulosin 0.4 mg			Oxybutynin 5, 10, 15 mg		
Terazosin 1-10 mg			Oxybutynin XL 5, 10, 15 ER mg		
Silodosin 4, 8 mg			Tolterodine 1, 2 mg Tolterodine LA 2, 4 ER mg Trospium 20, 60 mg Solifenacin 5, 10 mg		

BPH = benign prostatic hypertrophy; ER = extended-release; FDA = U.S. Food and Drug Administration; LA = long acting; XL = extended release.

TABLE 114-2 CLASSIFICATION OF PROSTATITIS

	CATEGORIES			
	I	II	III	IV
Term	Acute bacterial prostatitis	Chronic bacterial prostatitis	Chronic prostatitis/chronic pelvic pain syndrome (CP/CPPS) IIIa. Inflammatory CPPS IIIb. Noninflammatory CPPS	Asymptomatic inflammatory prostatitis
Characteristics	Acute infection of prostate gland	Recurrent or relapsing infection caused by the same organism; not acute	90% of cases of chronic prostatitis are presumed to be nonbacterial; diagnosis of exclusion Characteristic symptoms Discomfort or pain in pelvic region for more than 3 months within the past 6 months Pelvic, perineal, penile, or ejaculatory pain; irritative or obstructive voiding symptoms, sexual dysfunction No documented recurrent urinary tract infections; repeated negative cultures Classification into IIIa or IIIb determined by presence of leukocytes in semen, post–prostate massage urine, or prostatic secretion	No symptoms of prostatitis Leukocytes or inflammatory cells present in prostate tissue, semen, or expressed prostatic secretions

Laboratory Evaluation

Urinalysis and urine culture should be performed for every patient. Historically, the four-specimen test was recommended, with specimens obtained from the initial voided bladder urine, midstream voided bladder urine, expressed prostatic secretions obtained during prostate massage, and voided bladder urine collected after prostate massage. Leukocytes in the third specimen suggest the diagnosis of prostatitis. Leukocytes without bacteria suggest inflammation consistent with nonbacterial prostatitis. However, this four-step approach is rarely used today because it has not proved to be useful as a diagnostic tool or for directing treatment. It has been replaced by either a semen culture or a midstream urine culture and by examination of a voided urine specimen after prostate massage.

Urodynamic methods offer valuable insight for patients experiencing predominantly voiding symptoms. Other conditions, such as prostatic obstruction, primary bladder neck obstruction, dysfunctional voiding, urethral obstruction, and detrusor-sphincter dyssynergia, may be defined with the help of postvoid residual, pressure-flow urodynamics, or videourodynamics. These conditions, in comparison to prostatitis, have many effective treatment options.

Measurement of a postvoid residual urine volume by ultrasound can be used to assess incomplete emptying because urinary retention can be a risk factor for recurrent infections.[11] Low maximum urine flow rates suggest bladder outlet obstruction, decreased detrusor contractility, or both as an alternative explanation for lower urinary tract symptoms and poor flow. However, for those who fail to respond to treatment, PCR analysis of semen to evaluate for possible fastidious organisms (e.g., *C. trachomatis, U. urealyticum, Mycoplasma* species, and *Neisseria gonorrhoeae*) may be useful for the evaluation of chronic prostatitis. Cultures of urethral swabs may be used to evaluate patients with potentially undiagnosed sexually transmitted diseases (Chapter 264). Other diagnostic tests include semen analysis and culture, which are useful for patients with complaints of abnormal-smelling semen or infertility.

Cystoscopy is an adjunct to urodynamics in the evaluation of chronic prostatitis/chronic pelvic pain syndrome, especially before any surgical intervention. Cystoscopy is also performed for evaluation of hematuria or abnormal cytology findings because prostate cancer (Chapter 186) or bladder cancer (Chapter 182) can cause symptoms similar to chronic pelvic pain syndrome.

PSA testing should be ordered on the basis of prostate cancer screening (Chapter 186) but has no specific role in evaluation of prostatitis symptoms. Acute prostatitis can increase the serum level of PSA, but it usually returns to normal levels with appropriate antibiotics within 1 to 3 months. PSA can be elevated and even can wax and wane in patients with chronic prostatitis/chronic pelvic pain syndrome. Patients with chronic prostatitis have a less well-defined decrease in PSA after a course of antibiotics. Anywhere from one third to two thirds of men undergoing prostate biopsy have chronic inflammation, but the correlation with symptoms of prostatitis is unclear.

Transrectal ultrasound can identify a prostatic abscess and is generally recommended for patients who have recurrent prostatitis or who do not respond to treatment. The potential utility of pelvic computed xerographic scanning and transrectal magnetic resonance imaging is unclear.

TREATMENT

Acute Bacterial Prostatitis

Oral or intravenous antibiotics are usually effective for curing acute prostatitis, and progression to chronic bacterial prostatitis is uncommon.[12] Typical first-course antibiotics include oral fluoroquinolones (e.g., levofloxacin 500 mg once daily or ofloxacin 300 mg twice daily) and sulfonamides (e.g., trimethoprim/sulfamethoxazole 160 mg/800 mg twice daily) for 6 weeks. Patients who are unable to tolerate oral medications and patients with signs of sepsis may require broad-spectrum intravenous antibiotics (e.g., ampicillin 2 g every 6 hours plus gentamicin 1.5 mg/kg every 8 hours until afebrile) followed by 6 weeks of oral therapy as before. A prostatic abscess may require interventional therapy.[13]

Chronic Bacterial Prostatitis

Antibiotic therapy is the mainstay of treatment for chronic bacterial prostatitis.[14] Antibiotics with good lipid solubility, good enteric bacterial coverage, and a high pK_a have the best prostatic penetration. These antibiotics include quinolones, sulfa-based preparations, macrolides, tetracyclines, and aminoglycosides. The fluoroquinolones (e.g., ciprofloxacin 500 mg twice daily, levofloxacin 500 mg once daily, or ofloxacin 300 mg twice daily) have equivalent success rates in patients with chronic bacterial prostatitis and are generally the first-line treatment. In cases in which atypical bacteria, such as chlamydia, are suspected to be the cause of chronic bacterial prostatitis, better results may be achieved by macrolide antibiotics, such as azithromycin (500 mg twice daily). Most studies demonstrate effective treatment with 30 days of therapy, but some clinicians prescribe 6 weeks of therapy as for acute prostatitis because the recurrence rate is as high as 40% within a year. Delivery of antibiotics by intraprostatic injection or anal submucosal injection is rarely used.

Treatments for Chronic Prostatitis/Chronic Pelvic Pain Syndrome

The optimal regimen for the treatment of chronic prostatitis/chronic pelvic pain syndrome is not known, and the response to treatment is often disappointing.[15] Prolonged courses of antibiotics generally are not effective. One option is to perform PCR testing of expressed prostatic secretions and to use antibiotics only if the test result is positive. Current empirical therapy uses a combination of α-blockers, adrenergic antagonists, phosphodiesterase 5 inhibitors,[A15,A16] and anti-inflammatory agents (e.g., ibuprofen 400 mg three times daily or naproxen 200 mg twice daily). Neuroleptics, such as gabapentin, have been tried but appear to be no better than placebo and have side effects. The potential value of allopurinol is unclear. Many phytotherapies have been tried, but improvements have not been dramatic or consistent in various trials.

Conservative supportive therapies include warm sitz baths and special diets that avoid spicy foods, caffeine, alcohol, and other urinary irritants. Behavioral therapies and stress reduction can augment the efficacy of medications,[A17] and therapies that aim to improve relaxation and to re-educate pelvic floor muscle function can improve symptoms in highly stressed individuals with dysfunctional voiding. Options include biofeedback and bladder retraining. Unproven treatments include trigger point massage combined with relaxation and electromagnetic pelvic floor therapy, acupuncture, and percutaneous tibial nerve stimulation.[A18] Prostate massage can be combined with other therapies, but its efficacy has been variable.

PROGNOSIS

Most patients with type I prostatitis are effectively treated with oral or intravenous antibiotics, although some cases do not respond to treatment and

NIH-Chronic Prostatitis Symptom Index (NIH-CPSI)

Pain or Discomfort

1. In the last week, have you experienced any pain or discomfort in the following areas?

	Yes	No
a. Area between rectum and testicles (perineum)	❑1	❑0
b. Testicles	❑1	❑0
c. Tip of the penis (not related to urination)	❑1	❑0
d. Below your waist, in your pubic or bladder area	❑1	❑0

2. In the last week, have you experienced:

	Yes	No
a. Pain or burning during urination?	❑1	❑0
b. Pain or discomfort during or after sexual climax (ejaculation)?	❑1	❑0

3. How often have you had pain or discomfort in any of these areas over the last week?

❑ 0 Never
❑ 1 Rarely
❑ 2 Sometimes
❑ 3 Often
❑ 4 Usually
❑ 5 Always

4. Which number best describes your AVERAGE pain or discomfort on the days that you had it, over the last week?

❑ ❑ ❑ ❑ ❑ ❑ ❑ ❑ ❑ ❑ ❑
0 1 2 3 4 5 6 7 8 9 10

NO PAIN — PAIN AS BAD AS YOU CAN IMAGINE

Urination

5. How often have you had a sensation of not emptying your bladder completely after you finished urinating, over the last week?

❑ 0 Not at all
❑ 1 Less than 1 time in 5
❑ 2 Less than half the time
❑ 3 About half the time
❑ 4 More than half the time
❑ 5 Almost always

6. How often have you had to urinate again less than two hours after you finished urinating, over the last week?

❑ 0 Not at all
❑ 1 Less than 1 time in 5
❑ 2 Less than half the time
❑ 3 About half the time
❑ 4 More than half the time
❑ 5 Almost always

Impact of Symptoms

7. How much have your symptoms kept you from doing the kinds of things you would usually do, over the last week?

❑ 0 None
❑ 1 Only a little
❑ 2 Some
❑ 3 A lot

8. How much did you think about your symptoms, over the last week?

❑ 0 None
❑ 1 Only a little
❑ 2 Some
❑ 3 A lot

Quality of Life

9. If you were to spend the rest of your life with your symptoms just the way they have been during the last week, how would you feel about that?

❑ 0 Delighted
❑ 1 Pleased
❑ 2 Mostly satisfied
❑ 3 Mixed (about equally satisfied and dissatisfied)
❑ 4 Mostly dissatisfied
❑ 5 Unhappy
❑ 6 Terrible

Scoring the NIH-Chronic Prostatitis Symptom Index Domains

Pain: Total of items 1a, 1b, 1c,1d, 2a, 2b, 3, and 4 = _____

Urinary Symptoms: Total of items 5 and 6 = _____

Quality of Life Impact: Total of items 7, 8, and 9 = _____

FIGURE 114-4. National Institutes of Health (NIH) Chronic Prostatitis Symptom Index. (Modified from Litwin MS, McNaughton-Collins M, Fowler FJ Jr, et al. The National Institutes of Health chronic prostatitis symptom index: development and validation of a new outcome measure. Chronic Prostatitis Collaborative Research Network. *J Urol*. 1999;162:369-375.)

progress to type II prostatitis. The natural history of type II, type III, and type IV prostatitis remains undefined.

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115 URINARY INCONTINENCE

NEIL M. RESNICK AND CATHERINE E. DUBEAU

DEFINITION

Urinary incontinence is the involuntary leakage of urine sufficient to be a health or social problem.

EPIDEMIOLOGY

More than twice as common in women than in men, the prevalence of incontinence increases with age, although at least some degree of urinary incontinence is reported by 11% of women aged 22 to 27 years.[1] Incontinence afflicts 15 to 30% of older adults living at home, one third of those in acute care settings, and more than half of those in nursing homes. Its estimated cost in the United States exceeded $83 billion in 2020, with out-of-pocket costs for patients of more than $500.

Urinary incontinence predisposes to perineal rashes, pressure ulcers, urinary tract infections, falls, and fractures, and it is associated with embarrassment, stigmatization, isolation, depression, anxiety, sexual dysfunction, and risk for institutionalization. Many seriously ill elderly consider it an outcome worse than death.

Despite its prevalence and adverse consequences, geriatric incontinence remains largely neglected, by patients and physicians alike. This neglect is unfortunate because its increased prevalence with age relates more to age-associated diseases and functional impairments than to age itself. Most important, incontinence is usually treatable and often curable at all ages, even in the frail, although the approach in older patients must be broader than that employed in younger patients.[2]

PATHOBIOLOGY

At any age, continence depends not only on the integrity of lower urinary tract function but also on the presence of adequate mentation, mobility, motivation, and manual dexterity. Although incontinence in younger patients is rarely associated with deficits in these domains, such deficits occur commonly in older patients and can cause or exacerbate incontinence or influence therapeutic approaches. Some data suggest that genomics[3] and the microbiome[4] may play a role in increasing susceptibility, particularly for urge incontinence.

With age, bladder capacity does not change, but bladder sensation and contractility decrease.[5] At the cellular level, detrusor smooth muscle develops a "dense band pattern" characterized by dense sarcolemmal bands with depleted caveolae. This depletion may mediate the age-related decline in bladder contractility. In addition, an incomplete disjunction pattern characterized by scattered protrusion junctions develops and may underlie the high prevalence of involuntary bladder contractions (detrusor overactivity) in older adults of both sexes. Bladder ischemia and/or inflammation likely also contribute.[6] Urethral length and sphincter strength decrease in women, whereas the prostate enlarges in most men and causes obstruction in about 50% of them. The postvoid residual volume in the bladder also increases in both sexes but normally to less than 100 mL. In addition, older persons often excrete most of their fluid intake at night, even in the absence of venous insufficiency, renal disease, heart failure, or prostatic obstruction. Because this shift in nocturnal fluid excretion is coupled with an age-associated increase in sleep disorders, most older adults have at least one episode of nocturia per night.

None of these age-related changes causes incontinence, but all predispose to it. This predisposition, combined with the increased likelihood that an older person will encounter an additional pathologic, physiologic, or pharmacologic insult, explains the increased prevalence of incontinence with age. Thus, the onset or exacerbation of incontinence in an older person is often due to precipitants that are outside the lower urinary tract and that are amenable to medical intervention.

Causes of Transient Incontinence

Incontinence is transient in up to one third of community-dwelling elderly individuals and in up to half of acutely hospitalized patients. Although most transient causes are outside the lower urinary tract (Table 115-1), three points warrant emphasis. First, the risk for transient incontinence is increased if, in addition to physiologic changes of the lower urinary tract, there also are pathologic changes. Anticholinergic agents are more likely to cause retention and overflow incontinence in individuals with a weak or obstructed bladder, whereas excess urine output is more likely to cause urge incontinence in individuals with detrusor overactivity or impaired mobility. Second, these transient causes may persist if left untreated and should not be dismissed merely because incontinence is long-standing. Third, identification of the most common cause is of little value because causes vary among individuals, and geriatric incontinence is rarely due to just one cause.

Causes of Established Incontinence Related to the Lower Urinary Tract

Detrusor Overactivity

Detrusor overactivity, also called involuntary bladder contraction or *overactive bladder*, generally causes *urge incontinence* and is the most common type of lower urinary tract dysfunction in incontinent elderly people, in whom it accounts for about two thirds of cases. Histologically, detrusor overactivity is associated with the complete disjunction pattern, with widening of the intercellular space, reduction of normal (intermediate) muscle cell junctions, and emergence of novel protrusion junctions and ultraclose abutments that connect cells together in chains. These connections may mediate a change in cell coupling from a mechanical to an electrical mechanism that results in involuntary bladder contraction. Other potential causes include ischemia, abnormalities in suburothelial myofibroblasts, and changes in central nervous system structural and functional control mechanisms.

At any age, detrusor overactivity is usually idiopathic, but it can be associated with a variety of other causes that may affect prognosis and management. Such conditions include cerebral disease, upper motor neuron lesions (Chapters 369 and 387), urethral obstruction, stress incontinence, bladder calculus, and bladder carcinoma (Chapter 182).

Stress Incontinence

Stress incontinence, which is the second most common cause of incontinence in older women and the dominant cause in middle-aged women, usually reflects

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ABSTRACT

Urinary incontinence is prevalent, morbid, and costly, especially in women and older individuals. Although urinary incontinence is never normal at any age, can be effectively treated, and often can be cured, the majority of patients with incontinence remain unknown to their physician and untreated. Among younger patients, incontinence is usually caused by abnormalities of the lower urinary tract: stress incontinence associated with pelvic floor laxity in women and urge incontinence associated with detrusor overactivity ("overactive bladder") in men. Although an overactive bladder may occur in men with or without concurrent prostatic obstruction, women are rarely obstructed. Men rarely have stress incontinence unless they have had a prior *radical* prostatectomy. Middle-aged women often have a combination of urge and stress ("mixed") incontinence. Among older adults, detrusor overactivity is the most frequent cause in both sexes. At all ages, comorbidity, functional impairment, fluid intake, frequency of voiding, medications, urinary tract infection, and constipation can contribute to incontinence, but these factors are especially important among the elderly; addressing them can often improve or cure incontinence, even in the presence of urinary tract dysfunction. For patients with persistent urgency incontinence or prostatic obstruction, pharmacotherapy can complement lifestyle and behavioral approaches. Anticholinergic and β-3 adrenergic agents are equally effective, although the former can have adverse cognitive effects. An α-adrenergic antagonist can be used for men in whom prostate obstruction is suspected; a 5-α reductase inhibitor may be added, although its clinical benefit is delayed for months. Surgical correction of obstruction is also effective. For women with stress incontinence, pelvic muscle exercises, weight loss, and physical maneuvers can reduce or eliminate leakage; if these approaches fail, surgical correction is effective.

KEYWORDS

incontinence
aging
geriatrics
syndromes
voiding

TABLE 115-1 CAUSES OF TRANSIENT INCONTINENCE: DIAPERS MNEMONIC

Delirium	Result of underlying illness or medication; incontinence is secondary and abates once the cause of delirium is corrected	
Infection—*symptomatic* UTI	Acute, symptomatic UTI may cause or worsen incontinence, but the far more common *asymptomatic* bacteriuria does not	
Atrophic urethritis/vaginitis	Characterized by vaginal erosions, telangiectasia, petechiae, and friability; may cause or contribute to incontinence	
Pharmaceuticals	*Drug type:*	*Potential effects on continence:*
	Sedative-hypnotics (e.g., long-acting benzodiazepines; alcohol)	Sedation, delirium, decreased mobility
	Anticholinergics (dicyclomine, disopyramide, sedating antihistamines, antipsychotics, tricyclic antidepressants, cyclobenzaprine, anti-Parkinson, antidepressants [not SSRIs])	Urinary retention, overflow incontinence, delirium, impaction; the antipsychotics also decrease mobility
	Opiates	Urinary retention, stool impaction, sedation, delirium
	α-Adrenergic antagonists	Relax sphincter; may induce stress incontinence in women
	α-Adrenergic agonists	Urinary retention in men (tighten sphincter, prostate)
	Calcium-channel blockers, especially the dihydropyridines	Nocturnal diuresis due to fluid retention
	"Loop" diuretics (thiazide-like agents only rarely cause it)	Polyuria, frequency, urgency
	NSAIDs	Nocturnal diuresis due to fluid retention
	Thiazolidinediones	Nocturnal diuresis due to fluid retention
	Some nociceptives (gabapentin, pregabalin)	Nocturnal diuresis due to fluid retention; sedation; delirium
	Dopamine receptor agonists (e.g., ropinirole, pramipexole)	Nocturnal diuresis due to fluid retention
	Angiotensin-converting enzyme inhibitors	Drug-induced cough leads to stress incontinence in women
	Vincristine	Urinary retention due to neuropathy
	Cholinesterase inhibitors	Urinary incontinence
Excess urine output	From large intake, diuretic agents (caffeinated beverages, alcohol), and metabolic disorders (hyperglycemia, hypercalcemia); nocturnal incontinence may result from obstructive sleep apnea or mobilization of peripheral edema (heart failure, venous insufficiency, side effects of medications)	
Restricted mobility	Often results from overlooked, correctable conditions such as arthritis, pain, foot problems, postprandial hypotension, or fear of falling	
Stool impaction	May cause both fecal and urinary incontinence that remit with disimpaction	

NSAIDs = nonsteroidal anti-inflammatory drugs; SSRI = selective serotonin reuptake inhibitor; UTI = urinary tract infection.
Adapted from Resnick NM, Tadic SD, Yalla SV. Geriatric incontinence and voiding dysfunction. In: Wein AJ, Novick AC, Partin AW, et al, eds. *Campbell-Walsh Urology*, 10th ed. St. Louis: Elsevier; 2012.

insufficient urethral support plus some degree of sphincter weakness. Obese women are more likely to progress to mixed incontinence over time.[7] Stress incontinence is rare in men but can result from sphincter damage following radical, but not transurethral, prostatectomy.

Urethral Obstruction

Urethral obstruction is the second most common cause of established incontinence in older men, although most obstructed men are not incontinent. When obstruction is associated with incontinence, it usually presents as urge incontinence owing to the associated detrusor overactivity; overflow incontinence is uncommon. Outlet obstruction is rare in women but may result from a bladder neck suspension or from urethral kinking associated with a large cystocele.

Detrusor Underactivity

Detrusor underactivity is usually idiopathic. When it causes incontinence, it is associated with overflow incontinence (<10% of incontinence).

Damaged Innervation

Damage to lower urinary tract innervation can cause several types of dysfunction. A brain lesion may cause detrusor overactivity. A spinal cord lesion (Chapters 175 and 369) above the sacral level can cause both detrusor overactivity and detrusor-sphincter dyssynergia, a condition in which the sphincter contracts rather than relaxes during detrusor contraction; the result can be severe outlet obstruction and hydronephrosis. A spinal cord lesion below the sacral level can cause detrusor underactivity, sphincter weakness, or both. Peripheral and autonomic nerve damage can cause still additional problems, such as decreased bladder emptying and sensation in postural tachycardia syndrome.[8] Thus, because *neurogenic bladder* is such a nonspecific term, it is preferable to refer to the specific dysfunction causing incontinence.

Causes of Incontinence Unrelated to the Lower Urinary Tract (Functional Incontinence)

"Functional" incontinence, which is often cited as a distinct type of geriatric incontinence and attributed to deficits of cognition and mobility, implies that urinary tract function is normal. However, normal urinary tract function is the exception, even in continent elderly people, and is rarely observed in incontinent elderly people. Moreover, incontinence is not inevitable, even with dementia or immobility. Among the most severely demented institutionalized residents, nearly 20% are continent; among those who can transfer from a bed to a chair, nearly half are continent. Functionally impaired individuals also are the most likely to suffer from factors that cause transient incontinence, and a diagnosis of functional incontinence may result in failure to detect these reversible causes. Finally, if functionally impaired individuals also have urethral obstruction or stress incontinence, they may benefit from targeted therapy. Nonetheless, functional impairment often contributes to incontinence, and addressing its causes and those of transient incontinence may ameliorate incontinence sufficiently to obviate the need for further investigation.

CLINICAL MANIFESTATIONS

The manifestations of transient incontinence depend on the underlying condition. Occasionally, patients present with incontinence that is more difficult to characterize clinically without further testing.

Detrusor Overactivity

Detrusor overactivity usually manifests as *urge incontinence*, characterized by leakage that follows the *abrupt* onset or intensification of a desire to void and the leakage of a moderate to large amount of urine. Urinary frequency (>8 voids/day) and nocturia are also frequently present. Some patients with detrusor overactivity may present with precipitant leakage without urgency symptoms.

Detrusor overactivity exists as two subsets in elderly people: one in which contractile function is preserved and one in which it is impaired. The latter condition, termed *detrusor hyperactivity with impaired contractility*, has several implications. First, because the bladder is weak, these patients may develop urinary retention, which can mimic that seen in patients with outlet obstruction and detrusor underactivity. Second, even in the absence of retention, detrusor hyperactivity with impaired contractility mimics other lower urinary tract causes of incontinence. For instance, if the involuntary detrusor contraction occurs coincident with a stress maneuver and if the weak contraction is not detected, detrusor hyperactivity with impaired contractility will be misdiagnosed as stress incontinence. Alternatively, because detrusor hyperactivity with impaired contractility may be associated with urinary urgency, frequency, weak flow rate, elevated residual urine (e.g., >150 mL), and bladder trabeculation, in men, it may mimic prostatic obstruction. Third, use of a bladder relaxant for detrusor hyperactivity with impaired contractility may result in urinary retention owing to bladder weakness, thereby requiring a lower dose or an alternative therapeutic approach.

Stress Incontinence and Mixed Incontinence

Stress incontinence is leakage that coincides *instantaneously* with both the onset and cessation of a cough or other cause of increased abdominal pressure; nocturnal leakage is rare. Some women report both urge and stress incontinence, termed *mixed incontinence*. To plan treatment, it is useful to determine which component is the most bothersome. In men with sphincter damage following radical prostatectomy, leakage resembles the intermittent drip of a leaky faucet.

DIAGNOSIS

Older persons in particular should be screened for incontinence. In addition to a targeted clinical evaluation (Table 115-2),[9,10] a bladder diary can provide diagnostic clues and guide therapy (E-Fig. 115-1). For example, incontinence occurring only between 8 AM and noon may be caused by a morning loop diuretic. Incontinence that occurs at night in a demented man with heart failure, but not during a 4-hour nap in his wheelchair, is likely due to nocturnal diuresis associated with his heart failure and not to dementia, impaired mobility, or prostatic obstruction. A woman with volume-dependent stress incontinence may leak only on the way to void after a full night's sleep, when her bladder contains more than 400 mL—more than it ever does during her continent waking hours.

Because urinary retention is difficult to detect by examination and can affect diagnosis and therapy, the postvoid residual volume usually should be determined, except in a middle-aged woman who desires only behavioral therapy for a classic presentation of stress incontinence.[11,12] Urodynamic testing is generally recommended only when diagnostic certainty is required or before nonroutine surgery (not required prior to most surgery for uncomplicated stress incontinence) or if there is evidence of a serious underlying cause of the incontinence, such as a brain or spinal cord lesion, or hydronephrosis. Urodynamic evaluation comprises a battery of tests designed to assess the lower urinary tract during the filling and voiding phases of micturition. The selection among tests depends on the clinical setting and question to be answered; for instance, measuring detrusor pressure and urine flow during voiding can determine whether urethral obstruction is present, whereas monitoring bladder and urethral pressures during the filling phase and with coughing may be helpful for patients with an atypical presentation of mixed incontinence.

TABLE 115-2 CLINICAL EVALUATION OF URINARY INCONTINENCE

HISTORY
Symptom type (urge, stress, overflow, or mixed)
Incontinence frequency, severity, and duration
Pattern (diurnal, nocturnal or both; also, e.g., after taking medications)
Precipitants
Associated symptoms (straining to void, incomplete emptying, dysuria, hematuria, suprapubic/perineal discomfort or numbness)
Alteration in bowel habit/sexual function (because of proximity to the bladder and shared innervation)
Other relevant factors (cancer, acute illness, neurologic disease, pelvic or lower urinary tract surgery/radiation therapy
Medications, including nonprescription agents (see Table 115-1)
PHYSICAL EXAMINATION
General examination to identify and/or assess relevant medical conditions (e.g., heart failure, peripheral edema)
Brief assessment of cognitive and physical function (e.g., MiniCog, Get Up and Go [see Chapters 361 and 371])
If stress incontinence is suspected, determine whether leakage *coincides* with the onset *and* cessation of a single, forceful cough
Palpate for bladder distention after voiding
Pelvic examination to detect atrophic vaginitis, lichen sclerosis, mass, prolapse (if beyond the vagina, there is increased risk for urinary retention)
Rectal examination for skin irritation, resting tone and voluntary control of anal sphincter, prostate nodule; fecal impaction (*note:* prostate size correlates poorly with presence of urethral obstruction)
Neurologic examination, especially mental status and elemental examination, including sacral reflexes and perineal sensation
INITIAL INVESTIGATION
Bladder diary (see E-Fig. 115-1)
Metabolic survey (electrolytes, calcium, glucose, and urea nitrogen as appropriate)
Measure postvoid residual volume, by portable ultrasound if available
Urinalysis to detect sterile hematuria or infection; culture if new-onset or worsening incontinence
Renal ultrasound to detect hydronephrosis in men whose postvoid residual volume urine exceeds about 200 mL
Urine cytology for patients with hematuria, pain, or unexplained new-onset or worsening incontinence
Uroflowmetry for men in whom urethral obstruction is suspected
Cystoscopy for patients with hematuria, suspicion of lower urinary tract pathology (e.g., bladder fistula, stone, or tumor; urethral diverticulum), or need for lower urinary tract surgery

Adapted from Resnick NM, Yalla SV. Management of urinary incontinence in the elderly. *N Engl J Med.* 1985;313:800-805.

TREATMENT

Optimal therapy requires a multifactorial approach (Table 115-3), including treatment of any associated causes, underlying medical conditions, functional impairments, fluid intake, and the urinary tract abnormality itself.[13] Treatment of the precipitants alone may be sufficient to restore continence, even if there is coexisting urinary tract dysfunction. For example, a flare of hip arthritis in a woman with age-related detrusor overactivity may decrease mobility sufficiently to convert her urinary urgency into incontinence. Treatment of the arthritis, rather than the involuntary detrusor contractions, will not only restore continence but also lessen pain and improve mobility. Because of their frequency, reversibility, and association with morbidity beyond incontinence, any transient causes (see Table 115-1) should be addressed first.

Although pads and diapers have a role, they remain an adjunct to more specific therapy. Urinary catheters should rarely be used for chronic incontinence because of the high risk of urinary tract infection (Chapter 263).

Lifestyle Interventions

Lifestyle interventions include education, self-monitoring with a bladder diary, adjustment of fluid and caffeine intake, weight loss for overweight women with stress incontinence, smoking cessation, and use of aids (e.g., a bedside urinal).[A1] Phone-based apps also show promise for the self-management of urge and mixed incontinence.[A2] Helpful online resources are available for patients.[14–16]

Behavioral Therapy

Behavioral therapy[17] includes pelvic muscle exercises and bladder retraining (progressively increasing voiding intervals, strategies to cope with urgency).[A3] For each option, group education is an effective alternative to individual instruction.[A4]

For stress incontinence, pelvic muscle exercises are effective but less so than surgery,[A5] and combining the two does not enhance efficacy.[A6] Acupuncture[A7] and pessaries[18] can also be effective.

For urge incontinence, behavioral therapy is as effective as pharmacotherapy. However, combining the two is more effective than either alone[A8] because neither therapy generally abolishes involuntary bladder contractions.

For institutionalized patients who are cognitively impaired but can state their name and are partly mobile, regular daytime reminders to void ("prompted voiding") have proved effective for daytime incontinence. Wet checks and protective garments are appropriate for the others.[A9]

Pharmacotherapy

Currently approved drugs have not proved effective for stress incontinence or overflow incontinence. For urge incontinence, several bladder relaxants are modestly and equally effective (Table 115-4), including in vulnerable older patients.[A10] All anticholinergic agents can cause dry mouth, constipation, and visual blurring, with some variation among agents. Their use can also be associated with short- and long-term cognitive impairment, although this complication appears to be very uncommon.[19] Nevertheless, each may be well tolerated, even in cognitively impaired elderly patients, when they are prescribed properly and cognitive status is monitored. Patients who are taking a cholinesterase inhibitor, which can cause incontinence, have three options: delay intervention because the incontinence will often subside, reconsider the benefits of continued cholinesterase treatment, or consider adding a non-anticholinergic agent.

The choice among these drugs may also depend on other considerations. For instance, immediate-release oxybutynin has the quickest onset of action, thereby making it an inexpensive and effective choice for patients who need control at predictable times. Other drugs, although more expensive, can be used less often and can be better tolerated for daily use.

The β_3-adrenergic agonists mirabegron[A11] and vibegron have efficacy similar to the anticholinergic agents and may be preferable when there is concern for anticholinergic or cognitive adverse effects. If needed, mirabegron also may be combined with an anticholinergic for improved efficacy. Desmopressin should be avoided in older persons due to the risk of severe hyponatremia.

Ultimately, the choice of medication should depend on ease of use, cost, and avoidance of adverse effects in an individual patient. Regardless of the drug

Date	Time	Volume Voided (mL)	Are You Wet or Dry?	Approximate Volume of Incontinence	Comments
4/5	3:40 pm	240	Wet	Slight	
	6:05 pm	210	Dry		
	8:15 pm	150	Dry		Running water
	10:20 pm	150	Wet	15 mL	Bowel movement
	10:30 pm	30	Dry		
4/6	3:15 am	270	Wet	Slight	
	6:05 am	300	Wet	Slight	
	7:40 am	200	Dry		
	9:50 am	?	Dry		
	11:20 am	200	Dry		
	12:50 pm	180	Dry		
	1:40 pm	240	Dry		
	3:35 pm	160	Dry		
	6:00 pm	170	Dry		
	8:20 pm	215	Wet	Slight	Running water
	10:25 pm	130	Dry		

E-FIGURE 115-1. Sample bladder diary. Bladder diary of an incontinent 75-year-old man. Urodynamic evaluation excluded urethral obstruction and confirmed a diagnosis of detrusor hyperactivity with impaired contractility. Note the 24-hour urine output of nearly 3 liters due to the belief that drinking 10 glasses of fluid per day was "good for my health." (He did not mention this until queried about the voiding record.) Given the typical voided volume of 150 to 250 mL and a measured postvoid residual of 150 mL, excess fluid intake was overwhelming his usual bladder capacity of 400 mL (150 + 250 mL). Although involuntary bladder contractions were present, the easily reversible volume component of the problem, combined with the risk for precipitating urinary retention with an anticholinergic agent, prompted treatment with volume restriction alone. After daily urinary output dropped to 1500 mL, frequency abated, and incontinence resolved. (Adapted from DuBeau CE, Resnick NM. Evaluation of the causes and severity of geriatric incontinence: a critical appraisal. *Urol Clin North Am*. 1991;18:243-256.)

selected, the key is to begin with a low dose and increase it slowly, realizing that full benefit may not apparent be for 2 to 3 months and that adverse effects may offset the benefit. With such titration, urge incontinence can be controlled in about one third of patients and substantially improved in another one third. Success rates are lower in patients with moderate-severe dementia.

For urinary incontinence in the setting of atrophic vaginitis, a 3- to 12-month course of topical estrogen can be useful, although oral estrogen can worsen incontinence.[A12]

Surgical Procedures

Stress Incontinence

For women with stress incontinence or stress-predominant mixed incontinence, surgery has proved effective and relatively durable at all ages. Periurethral bulking injection can help frail women or those with mild stress incontinence, but it does not generally restore continence.[20] However, urethral sling and mid-urethral tape suspension procedures can cure most women for at least 5 years. For women with more complex stress incontinence and women who have adequate cognitive and functional capacity, an artificial sphincter can be moderately effective, although experience is still limited.

Urge Incontinence

For urge incontinence, surgical intervention, including neuromodulation,[21] tibial nerve stimulation,[22] and injections of onabotulinum toxin,[A13] are third-line agents. Limited available data suggest that their efficacy may be only modestly better than the efficacy of pharmacotherapy and that older patients may not fare as well as younger ones. Older patients treated with onabotulinum toxin also are more likely to develop urinary retention and urinary tract infections.

Issues Specific to Men

Apart from atrophic vaginitis, the transient causes of incontinence in men are the same as in women. However, owing to the frequency of prostate enlargement, urinary retention occurs more often in the setting of conditions that suppress detrusor contractility (e.g., fecal impaction) or use of drugs such as anticholinergics, α-adrenergic agonists, and opiates. Urge incontinence is equally common in men as in women, but it may be associated with an obstructive prostate. Therapeutic considerations for incontinence related to prostatic hypertrophy include α-adrenergic agonists and 5-α reductase inhibitors, as well as prostate surgery (see Table 115-3, Fig. 114-3, and Table 114-1). Antimuscarinics and mirabegron (both used in combination with an α-blocker) are also helpful. Botulinum toxin may be useful as well, but it appears to be less effective than in women.[A14] Stress incontinence is rare in men unless they have undergone radical (not transurethral) prostatectomy for carcinoma.[23] In such cases, anti-incontinence surgery, such as a male sling operation or creation of an artificial urinary sphincter, is moderately successful[A15] but is usually reserved for incontinence that is moderate to severe and persists for more than a year in men who otherwise have a good prognosis. As in women, overflow incontinence is uncommon but, when present, in men it is more likely due to obstruction.

PREVENTION

Data suggest that group- or community-based education and behavioral modification programs may be helpful in older women. Weight loss can reduce the risk for stress incontinence.[24]

TABLE 115-3 STEPWISE APPROACH TO TREATMENT OF URINARY INCONTINENCE*

CONDITION	CLINICAL TYPE OF INCONTINENCE†	TREATMENT
Detrusor overactivity with normal contractility	Urge	1. Bladder retraining or prompted voiding regimens. 2. ± Bladder relaxant medication if needed and not contraindicated (see Table 115-4). If treatment fails, consider posterior tibial neurostimulation, sacral neuromodulation, or intradetrusor injection of onabotulinumtoxinA. 3. Indwelling catheterization alone is often unhelpful because detrusor spasms often increase, leading to leakage around the catheter. 4. In selected cases, induce urinary retention pharmacologically and add intermittent or indwelling catheterization.‡
Detrusor hyperactivity with impaired contractility	Urge§	1. If bladder empties adequately, behavioral methods (as above) ± bladder relaxant medication (low doses; especially feasible if sphincter incompetence coexists). 2. If residual urine >150 mL, augmented voiding techniques¶ or intermittent catheterization (± bladder relaxant medication). If neither is feasible, undergarment or indwelling catheter.‡ 3. In selected cases, induce urinary retention pharmacologically and add intermittent or indwelling catheterization.‡
Stress incontinence	Stress	1. Conservative methods (weight loss if obese; treatment of cough or atrophic vaginitis; physical maneuvers to prevent leakage [e.g., tighten pelvic muscles before cough, cross legs]; occasionally, use of tampon or pessary is helpful). 2. If leakage threshold ≥150 mL identified, adjust fluid excretion and voiding intervals appropriately. 3. Pelvic muscle exercises ± biofeedback/weighted intravaginal cones; must continue indefinitely. 4. Surgery (sling, artificial sphincter, periurethral bulking injections).
Urethral obstruction (see Chapter 114)	Urge/overflow‖	1. Conservative methods (including adjustment of fluid excretion, bladder retraining/prompted voiding) if hydronephrosis, recurrent symptomatic UTI, and hematuria have been excluded. 2. α-Adrenergic antagonist (α_{1a} specific may be better tolerated in patients with orthostatic hypotension). 3. Also consider adding a bladder relaxant if detrusor overactivity coexists, postvoid residual volume is small, and surgery is not desired/feasible; *monitor postvoid residual volume!* 4. 5-α Reductase inhibitor, if not contraindicated and the patient either prefers it or is not a surgical candidate; clinical benefit takes months. 5. Surgery (incision, prostatectomy) is an effective alternative before or after these steps.
Underactive detrusor	Overflow	1. Decompress for at least several days (the larger the postvoid residual volume, the longer should be the decompression [up to a month]) and then perform a voiding trial. 2. Exclude urethral obstruction if this has not already been done. 3. If cannot void or if postvoid residual volume remains large, try augmented voiding techniques¶ ± α-adrenergic antagonist but only if some voiding possible; bethanechol *rarely* useful. 4. If fails or voiding is not possible, intermittent or indwelling catheterization.‡

*These treatments should be initiated only after adequate toilet access has been ensured, contributing conditions have been treated (e.g., atrophic vaginitis, UTI, fecal impaction, heart failure), fluid management has been optimized, and unnecessary or exacerbating medications have been addressed. For additional details, see text.

†*Urge:* leakage in the absence of stress maneuvers and urinary retention, usually preceded by *abrupt* onset or intensification of the need to void; stress: leakage that coincides instantaneously with stress maneuvers, in the absence of urinary retention or detrusor contraction; overflow: frequent leakage of small amounts associated with urinary retention.

‡UTI prophylaxis can be used for recurrent symptomatic UTIs but only if catheter is not indwelling.

§May also mimic stress or overflow incontinence.

‖Also can cause postvoid "dribbling" alone, which is treated conservatively (e.g., by sitting to void and allowing more time, "double voiding," and in men by gently "milking" the urethra after voiding).

¶Augmented voiding techniques include Credé (application of suprapubic pressure) and Valsalva (straining) maneuvers and double voiding. They should be performed only after voiding has begun.

UTI = urinary tract infection.

Adapted and updated from Resnick NM. Voiding dysfunction and urinary incontinence. In: Beck JC, ed. *Geriatric Review Syllabus.* New York: American Geriatrics Society; 2011:141-154.

TABLE 115-4 BLADDER RELAXANT AGENTS FOR URGE INCONTINENCE

- Anticholinergic
  - Oxybutynin IR, 7.5-20 mg daily (2.5-5 mg three or four times daily; doses >2.5 mg four times daily can be problematic and rarely helpful); oxybutynin XL, 5-30 mg once daily; oxybutynin patch (3.9 mg/day) twice weekly; oxybutynin 10% gel (1 g topically once per day)
  - Tolterodine, 1-2 mg twice daily; tolterodine LA, 4 mg once daily
  - Darifenacin, 7.5-15 mg once daily
  - Solifenacin, 5-10 mg once daily
  - Trospium, 20 mg daily to twice daily; 60 mg (extended release) once daily
  - Fesoterodine, 4-8 mg once daily
- β_3-Adrenergic agonist
  - Mirabegron, 25-50 mg once daily
  - Vibegron 75 mg daily

PROGNOSIS

Incontinence is associated with sexual dysfunction and other adverse effects on quality of life.[25] Limited data suggest that incontinence progresses in about one third of patients and remits in about 10 to 15%, although it is unclear how much of the remission reflects intervention or improvement in functional or medical status.

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116 CHRONIC KIDNEY DISEASE

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Chronic kidney disease represents a heterogeneous group of disorders that become increasingly common as the population ages. Diabetes (Chapter 210), hypertension (Chapter 64), and autoimmune glomerular diseases (Chapter 107) are the most common causes of chronic kidney disease worldwide, but systemic infections, drug toxicity, and environmental exposures are important causes in selected populations. Irrespective of the cause, many kidney diseases follow a progressive course and cause complications in virtually every organ system. In patients in whom the rate of disease progression is fast or life expectancy is long, the disease may culminate in kidney failure that leads to uremia and death.

DEFINITION

Chronic kidney disease is defined as the presence of either a marker of kidney damage, such as more than 30 mg/day of albuminuria, or a glomerular filtration rate less than 60 mL/min/1.73 m^2 for 3 or more months.[1] The threshold value for albuminuria reflects a more than three-fold elevation above the normal value of 5 to 10 mg/day, whereas the threshold glomerular filtration rate reflects a more than 50% reduction below the normal value of approximately 125 mL/min/1.73 m^2. Irrespective of age, both of these abnormalities are associated with an increased risk of progressive kidney disease, altered metabolism and excretion of many drugs by the kidney, complications, and death (E-Fig. 116-1).[2]

EPIDEMIOLOGY

The prevalence of chronic kidney disease in U.S. adults is approximately 11.5% (Fig. 116-1), including approximately 4.7% of the population that has increased albuminuria with a glomerular filtration rate greater than 60 mL/min/1.73 m^2 (stages G1 and G2) and 6.8% of the population that has a glomerular filtration rate less than 60 mL/min/1.73 m^2 (stages G3 to G5). The glomerular filtration rate declines by an average rate of approximately 1 mL/min/1.73 m^2 per year after about age 40 years, but with a wide range among individuals. The cause of the decline with age is not well understood, but the decline may be due to senescence, kidney disease, or both. Irrespective of cause, 25% of individuals in the United States have a glomerular filtration rate less than 60 mL/min/1.73 m^2 by age 70 years and older.

In the United States, an estimated 800,000 or so individuals, equivalent to about 0.25% of the population, have kidney failure (stage G5) and require kidney replacement therapy with dialysis or transplantation (Chapter 117), and this prevalence has been rising by approximately 20,000 per year due to the growth and aging of the population.[3] The age-adjusted incidence of the initiation of kidney replacement therapy has been declining, however, perhaps related to better and earlier management. Unfortunately, the rising prevalence of obesity may increase incidence of kidney failure in future years because of the earlier onset of diabetes and hypertension.

The worldwide prevalence of kidney disease in adults and children is estimated to be about 9%, or about 700 million people.[4] About 30% of chronic kidney disease is attributed to diabetes. The annual mortality from chronic kidney disease is about 1.2 million owing to kidney failure itself and 1.4 million owing to an increased incidence of cardiovascular disease, thereby representing about 4.6% of total mortality and making it the twelfth leading worldwide cause of death. The disability-adjusted life years lost vary widely among regions of the world (E-Fig. 116-2). The risk for chronic kidney disease is associated with increased susceptibility (e.g., old age, family history, history of acute kidney disease, member of ethnic or racial minority in the United States, reduced nephron mass because of low birthweight or a prior partial or complete nephrectomy), or with exposure to conditions that cause chronic kidney disease, such as diabetes and hypertension [Table 116-1]). Chronic kidney disease is more common in older, male, Black, and Hispanic individuals in the United States.[5]

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TABLE 115-4 BLADDER RELAXANT AGENTS FOR URGE INCONTINENCE

- Anticholinergic
  - Oxybutynin IR, 7.5-20 mg daily (2.5-5 mg three or four times daily; doses >2.5 mg four times daily can be problematic and rarely helpful); oxybutynin XL, 5-30 mg once daily; oxybutynin patch (3.9 mg/day) twice weekly; oxybutynin 10% gel (1 g topically once per day)
  - Tolterodine, 1-2 mg twice daily; tolterodine LA, 4 mg once daily
  - Darifenacin, 7.5-15 mg once daily
  - Solifenacin, 5-10 mg once daily
  - Trospium, 20 mg daily to twice daily; 60 mg (extended release) once daily
  - Fesoterodine, 4-8 mg once daily
- β_3-Adrenergic agonist
  - Mirabegron, 25-50 mg once daily
  - Vibegron 75 mg daily

PROGNOSIS

Incontinence is associated with sexual dysfunction and other adverse effects on quality of life.[25] Limited data suggest that incontinence progresses in about one third of patients and remits in about 10 to 15%, although it is unclear how much of the remission reflects intervention or improvement in functional or medical status.

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For the General References and other additional features, please visit Elsevier eBooks+ at https://ebooks.health.elsevier.com.

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116 CHRONIC KIDNEY DISEASE

ANDREW S. LEVEY AND MARK J. SARNAK

Chronic kidney disease represents a heterogeneous group of disorders that become increasingly common as the population ages. Diabetes (Chapter 210), hypertension (Chapter 64), and autoimmune glomerular diseases (Chapter 107) are the most common causes of chronic kidney disease worldwide, but systemic infections, drug toxicity, and environmental exposures are important causes in selected populations. Irrespective of the cause, many kidney diseases follow a progressive course and cause complications in virtually every organ system. In patients in whom the rate of disease progression is fast or life expectancy is long, the disease may culminate in kidney failure that leads to uremia and death.

DEFINITION

Chronic kidney disease is defined as the presence of either a marker of kidney damage, such as more than 30 mg/day of albuminuria, or a glomerular filtration rate less than 60 mL/min/1.73 m^2 for 3 or more months.[1] The threshold value for albuminuria reflects a more than three-fold elevation above the normal value of 5 to 10 mg/day, whereas the threshold glomerular filtration rate reflects a more than 50% reduction below the normal value of approximately 125 mL/min/1.73 m^2. Irrespective of age, both of these abnormalities are associated with an increased risk of progressive kidney disease, altered metabolism and excretion of many drugs by the kidney, complications, and death (E-Fig. 116-1).[2]

EPIDEMIOLOGY

The prevalence of chronic kidney disease in U.S. adults is approximately 11.5% (Fig. 116-1), including approximately 4.7% of the population that has increased albuminuria with a glomerular filtration rate greater than 60 mL/min/1.73 m^2 (stages G1 and G2) and 6.8% of the population that has a glomerular filtration rate less than 60 mL/min/1.73 m^2 (stages G3 to G5). The glomerular filtration rate declines by an average rate of approximately 1 mL/min/1.73 m^2 per year after about age 40 years, but with a wide range among individuals. The cause of the decline with age is not well understood, but the decline may be due to senescence, kidney disease, or both. Irrespective of cause, 25% of individuals in the United States have a glomerular filtration rate less than 60 mL/min/1.73 m^2 by age 70 years and older.

In the United States, an estimated 800,000 or so individuals, equivalent to about 0.25% of the population, have kidney failure (stage G5) and require kidney replacement therapy with dialysis or transplantation (Chapter 117), and this prevalence has been rising by approximately 20,000 per year due to the growth and aging of the population.[3] The age-adjusted incidence of the initiation of kidney replacement therapy has been declining, however, perhaps related to better and earlier management. Unfortunately, the rising prevalence of obesity may increase incidence of kidney failure in future years because of the earlier onset of diabetes and hypertension.

The worldwide prevalence of kidney disease in adults and children is estimated to be about 9%, or about 700 million people.[4] About 30% of chronic kidney disease is attributed to diabetes. The annual mortality from chronic kidney disease is about 1.2 million owing to kidney failure itself and 1.4 million owing to an increased incidence of cardiovascular disease, thereby representing about 4.6% of total mortality and making it the twelfth leading worldwide cause of death. The disability-adjusted life years lost vary widely among regions of the world (E-Fig. 116-2). The risk for chronic kidney disease is associated with increased susceptibility (e.g., old age, family history, history of acute kidney disease, member of ethnic or racial minority in the United States, reduced nephron mass because of low birthweight or a prior partial or complete nephrectomy), or with exposure to conditions that cause chronic kidney disease, such as diabetes and hypertension [Table 116-1]). Chronic kidney disease is more common in older, male, Black, and Hispanic individuals in the United States.[5]

ABSTRACT

Chronic kidney disease can be caused by a wide spectrum of kidney diseases, including diabetes, hypertension, autoimmune conditions, systemic infections, drug toxicity, and environmental exposure as well as by inherited diseases or obstructive uropathy. The signs (e.g., hypertension, fluid overload), symptoms (e.g., fatigue, loss of appetite), and laboratory findings (e.g., acidosis, hyperkalemia) of chronic kidney disease are principally related to the level of the glomerular filtration rate and the degree of albuminuria rather than to the underlying cause. Cause-specific treatments are often helpful, and treatments related to the level of glomerular filtration rate and the degree of albuminuria can slow the progression of disease, independent of its cause. In patients who have hypertension, whether it is the cause or a complication of chronic kidney disease, systolic blood pressure should be lowered to <130 mm Hg, and patients who have albuminuria should initially receive an angiotensin receptor blocker or angiotensin-converting enzyme inhibitor, with careful monitoring of their serum potassium level. Sodium glucose cotransporter-2 inhibitors can slow the rate of progression of chronic kidney disease and have become a cornerstone of therapy except in patients who have type 1 diabetes. In patients who have type 2 diabetes and albuminuria, glucagon-like peptide 1 agonists and mineralocorticoid receptor antagonists are additional options to slow the progression of chronic kidney disease. Dialysis and kidney transplantation are effective treatments for kidney failure when the complications cannot be controlled and begin to compromise quality of life or survival.

KEYWORDS

CKD
progressive loss of kidney function
nutritional therapy for CKD
hypertension in CKD
metabolic acidosis

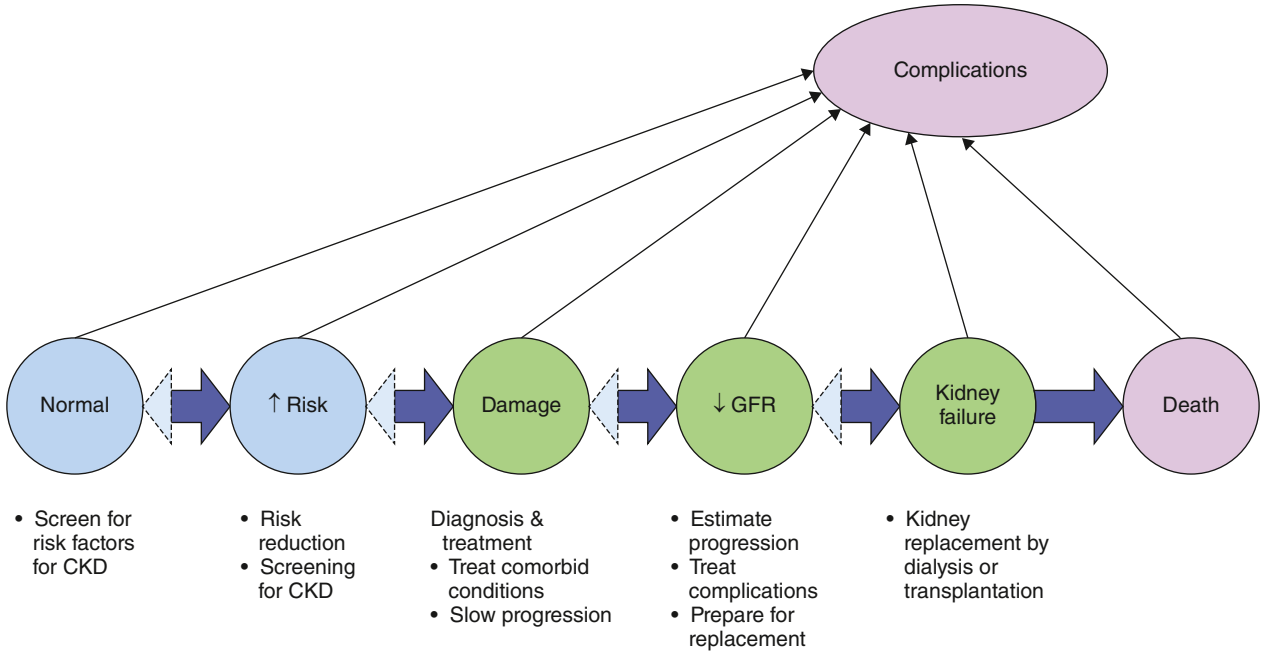

E-FIGURE 116-1. Conceptual model for chronic kidney disease. The diagram presents the continuum of development, progression, and complications of chronic kidney disease (CKD) and strategies to improve outcomes. Green represents stages of CKD; blue represents potential antecedents of CKD; purple represents consequences of CKD. *Horizontal arrows* represent the development, progression, and remission of CKD. *Arrows* pointing from left to right emphasize the progressive nature of CKD. *Dashed arrowheads* pointing from right to left signify that remission is less frequent than progression. *Diagonal arrows* represent complications, referring to conditions that occur more commonly in patients with vs. without CKD. Complications may also arise from adverse effects of interventions to prevent or treat the disease. CKD = chronic kidney disease; GFR = glomerular filtration rate. (From Levey AS. A decade after the KDOQI CKD guidelines. *Am J Kidney Dis*. 2012;60:683-685.)

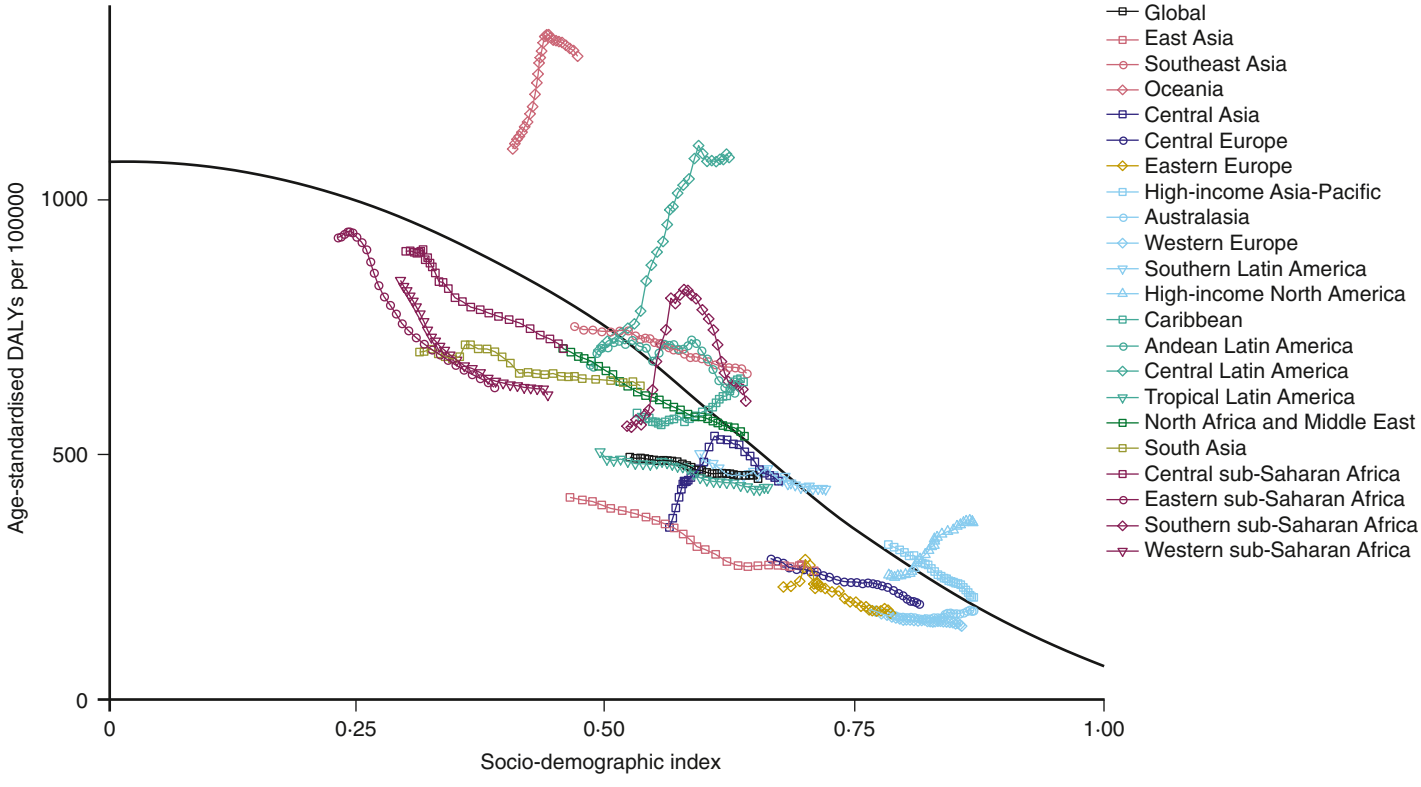

E-FIGURE 116-2. Age-standardized rate of disability-adjusted life years for chronic kidney disease for 21 world regions according to the sociodemographic index, 1990–2017. *Solid black line* shows expected values for disability-adjusted life years across the spectrum of the sociodemographic index. DALY = disability-adjusted life-year (the sum of years of life lost to death and disability). (From Bikbov B, Purcell CA, Levey AS, et al. Global, regional, and national burden of chronic kidney disease, 1990-2017: a systematic analysis for the Global Burden of Disease Study 2017. *Lancet*. 2020;395:709-733.)

Stages of the Glomerular Filtration Rate (mL/min/1.73m^2)		Stages of Albuminuria (description and range)		
		A1	A2	A3
		normal to mildly increased	moderately increased	severely increased
		<30 mg/g <3 mg/mmol	30-299 mg/g 3-29 mg/mmol	≥300 mg/g ≥30 mg/mmol
	G1, normal or high, >90	56%	2%	0.4%
	G2, mildly decreased, 60-89	33%	2%	0.3%
	G3, mildly to moderately decreased, 45-59	4%	0.8%	0.2%
	G3b, moderately to severely decreased, 30-44	1.0%	0.4%	0.2%
	G4, severely decreased, 15-29	0.2%	0.1%	0.1%
	G5, kidney failure, <15	0%	0%	0.1%

FIGURE 116-1. Approximate percentage of the U.S. population by glomerular filtration rate and albuminuria. For population studies, chronic kidney disease is generally defined as albuminuria greater than 30 mg/day or a decreased glomerular filtration rate (<60 mL/min/1.73 m^2). The prevalence of chronic kidney disease in U.S. adults is 11.5%, which is the rounded sum of all shaded cells. Albuminuria stages A_2 and A_3 correspond to microalbuminuria and macroalbuminuria, respectively. Albuminuria stage A3 includes nephrotic-range albuminuria (greater than about 2000 mg/day). Albuminuria (in mg/day) equals albuminuria (in mg/g) if the urinary creatinine excretion equals 1.0 g/day. For albuminuria: 1.0 mg/g = 0.113 mg/mmol. GFR = glomerular filtration rate. Prognosis is color coded: white = low risk; yellow = moderately increased risk; orange = high risk; red = very high risk. (Modified from Kidney Disease: Improving Global Outcomes [KDIGO]. KDIGO 2012 clinical practice guideline for the evaluation and management of chronic kidney disease. *Kidney Int Suppl*. 2013;3:1-150 and based on data from the National Health and Nutrition Examination Survey [NHANES] 1999-2006.)

Causes of kidney disease are classified according to the site of pathologic findings (e.g., glomerular, tubulointerstitial, vascular, and cystic and congenital diseases that affect multiple sites), as well as the presence or absence of systemic disease affecting the kidney. Among older adults, diabetes and hypertension are the most common causes in Europe and North America, whereas congenital anomalies of the kidney and urinary tract (Chapter 113) and glomerular diseases (Chapter 107) are more common in children and young adults. Autoimmune glomerular diseases are also common in East Asia (Chapter 107). Chronic infections causing glomerular and interstitial diseases are more common in low- and middle-income nations. Tubulointerstitial diseases are known to be endemic in certain areas due to exposure to aristolochic acid, heavy metals, fine particulate matter, or extremes of heat and agricultural work (Chapter 108). An important risk factor in people of West African ancestry is inheritance of two of the G1 or G2 variants of *APOL1*, likely reflective of a selective advantage from resistance to *Trypanosoma brucei*,[6] which confers an approximately four-fold greater risk of kidney failure.

PATHOBIOLOGY

Irrespective of the initial mechanism, most kidney diseases progress through a final common pathway that culminates in pathologic features of glomerular, interstitial, and vascular sclerosis in which tubular atrophy coexists with glomerular and tubular hypertrophy and the formation of cysts. These pathologic changes result in a progressive increase in albuminuria and a decline in the glomerular filtration rate.

In health, proteinuria is minimal because of low permeability of the glomerular capillary wall to high-molecular-weight plasma proteins and the efficient receptor-mediated tubular reabsorption of filtered low-molecular-weight plasma proteins (Fig. 116-2).[7] The normal urine protein excretion rate and albumin excretion rate are generally less than 50 and 10 mg/day, respectively. Proteinuria can be classified by increased glomerular permeability to macromolecules (glomerular; Chapter 107), decreased tubular reabsorption of filtered proteins (tubular; Chapter 108) due to disorders of tubular epithelium; or increased filtered load of low-molecular-weight proteins, such as immunoglobulin light chains. Regardless of the cause, the presence of albumin and other macromolecules in glomerular filtrate may be associated with progressive tubular and interstitial damage, thereby contributing to the subsequent decline in glomerular filtration rate.

Large increases in albuminuria (greater than approximately 2.0 g/day, corresponding to proteinuria above approximately 3.5 g/day) can give rise to nephrotic syndrome (Chapter 107), with a decreased serum albumin level, edema, hypercholesterolemia, and hypercoagulability (Table 116-2). Loss of albumin in the urine lowers plasma oncotic pressure, thereby resulting in redistribution of plasma to the interstitial space, increased renal tubular reabsorption of sodium chloride and water, and retention of extracellular fluid (Chapter 107). Decreased oncotic pressure stimulates increased production of plasma proteins by the liver, including apolipoproteins, thereby leading to hyperlipidemia. The urinary loss of anticoagulant proteins (e.g., antithrombin,

TABLE 116-1 CAUSES OF CHRONIC KIDNEY DISEASE

	EXAMPLES OF SYSTEMIC DISEASES AFFECTING THE KIDNEY	EXAMPLES OF PRIMARY KIDNEY DISEASE (ABSENCE OF SYSTEMIC DISEASES AFFECTING THE KIDNEY)
Glomerular diseases (Chapter 107)	Diabetes (Chapter 210), obesity (Chapter 201), systemic autoimmune diseases (systemic lupus erythematosus [Chapter 245], antineutrophil cytoplasmic antibody–associated vasculitis, cryoglobulinemia, Henoch-Schonlein purpura [Chapter 249], Goodpasture syndrome), systemic infections (bacterial endocarditis or endovascular infection [Chapter 47], human immunodeficiency virus [Chapter 359], hepatitis B virus, hepatitis C virus [Chapter 135], schistosomiasis [Chapter 326]), drugs (vascular endothelial growth factor inhibitors, gold, penicillamine, pamidronate), neoplasia (light chain deposition disease, amyloidosis [Chapter 174])	Diffuse, focal, or crescentic proliferative glomerulonephritis (postinfectious, immunoglobulin A nephropathy, complement factor 3 glomerular nephritis, anti–glomerular basement membrane nephritis); focal and segmental glomerulosclerosis, membranous nephropathy, minimal change disease, inherited podocytopathies
Tubulointerstitial diseases (Chapter 108)	Systemic infections (*Legionella* [Chapter 290], leptospirosis, streptococci [Chapter 268]), autoimmune (acute interstitial nephritis, tubulointerstitial nephritis, and uveitis [Chapter 108], systemic lupus erythematosus [Chapter 245], Sjogren syndrome [Chapter 247], immunoglobulin G4 interstitial nephritis), sarcoidosis (Chapter 83), drugs (nonsteroidal anti-inflammatory drugs, iodinated contrast, calcineurin inhibitors, aminoglycoside antibiotics, β-lactam antibiotics, vancomycin, tenofovir, amphotericin, cis-platinum, ifosfamide), metabolic disorders (hyperuricemia due to tumor lysis, hypokalemia [Chapter 103], hypercalcemia [Chapter 227]), environmental toxins (heavy metals, aristolochic acid; Chapter 20), neoplasia (e.g., multiple myeloma; Chapter 173)	Urinary tract infections (bacteria, *Mycobacteria*, schistosomiasis), stones, obstruction, inherited tubulointerstitial diseases (autosomal dominant [medullary cystic disease], autosomal recessive [nephronophthisis])
Vascular diseases	Atherosclerosis (Chapter 65), hypertension (Chapter 64), ischemia (Chapter 110), cholesterol emboli (Chapter 66), thrombotic microangiopathy (hemolytic uremic syndrome [Chapter 158], thrombotic thrombocytopenic purpura [Chapter 158]), systemic sclerosis (Chapter 246)	Fibromuscular dysplasia, radiation
Cystic and congenital diseases	Polycystic kidney disease (Chapter 112), Alport syndrome, Fabry disease (Chapter 192)	Congenital anomalies of the kidney and urinary tract (CAKUT)

Genetic diseases are not considered separately because some diseases in each category are now recognized as having genetic determinants.
Adapted from Kidney Disease: Improving Global Outcomes (KDIGO). KDIGO 2012 clinical practice guideline for the evaluation and management of chronic kidney disease. *Kidney Int Suppl*. 2013;3:1-150.

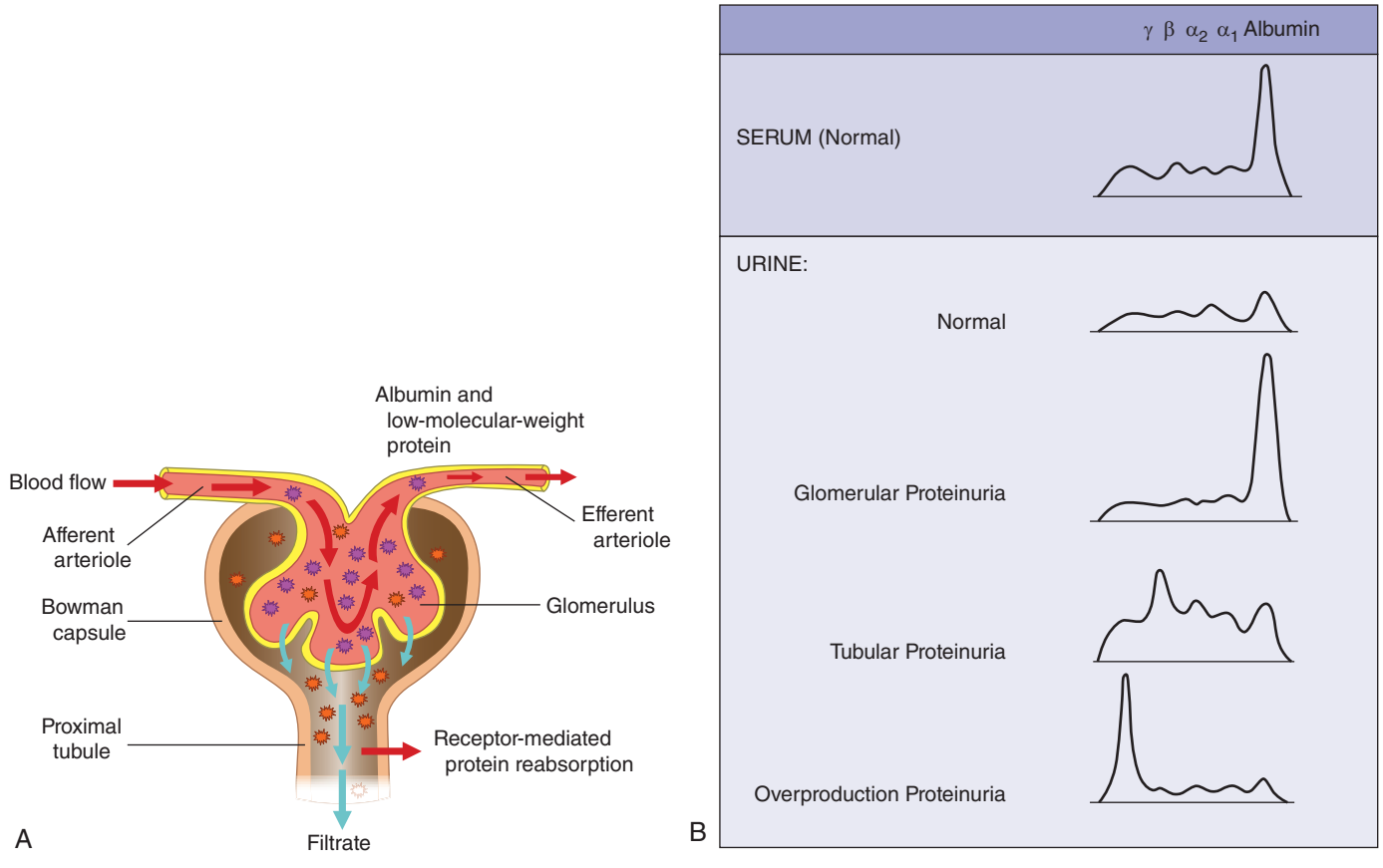

FIGURE 116-2. Pathophysiology of proteinuria. A, Glomerular filtration barrier to macromolecules (albumin) and tubular reabsorption of low-molecular-weight proteins. **B**, Normal serum protein electrophoresis and patterns of proteinuria. **A**, In health, proteinuria is minimal because of the low permeability of glomerular capillary wall to high-molecular-weight serum proteins, such as albumin (*purple symbols*, approximately 65,000 daltons) and gamma globulins (approximately 150,000 daltons), as well as the efficient receptor-mediated tubular reabsorption of filtered low-molecular-weight serum proteins, such as α-1, α-2, and β-globulins (e.g., β-2 microglobulin, cystatin C, β-trace protein, and immunoglobulin light chains; *orange symbols*, approximately 10,000 to 20,000 daltons). Other proteins in normal urine include proteins secreted by the tubule, such as uromodulin (the most abundant protein in normal urine and present in aggregates of up to several million daltons), and from the lower urinary and genital tracts. **B**, Normal serum protein electrophoresis showing separate peaks for albumin and globulins (α-1, α-2, β, and γ), according to molecular weight and charge (albumin is most anionic). Normal urine protein electrophoresis shows minimal amounts of all serum proteins. Glomerular proteinuria shows predominantly albumin; tubular proteinuria shows predominantly α-1, α-2, and β-globulins; and overproduction proteinuria shows light-chain immunoglobulins. These patterns can also be detected by measurement of urinary albumin and total protein, specific low-molecular-weight serum protein or light chains, and immunofixation. (From Stevens LA, Lafayette LA, Perrone RD, et al. Laboratory evaluation of kidney disease. In: RW Schrier, ed. *Diseases of the Kidney and Urinary Tract*. Philadelphia: Lippincott Williams & Wilkins; 2007:299-336.)

TABLE 116-2 CHRONIC KIDNEY DISEASE CLINICAL DISORDERS, MECHANISM, MANIFESTATIONS, AND MANAGEMENT (CLINICAL ACTION PLAN) BY GLOMERULAR FILTRATION RATE AND ALBUMINURIA STAGES

ALBUMINURIA STAGE	ALBUMIN EXCRETION RATE (mg/24 h) AND APPROXIMATELY EQUIVALENT ALBUMIN TO CREATININE RATIO (mg/g)*	DISORDER	MECHANISM	MANIFESTATIONS	MANAGEMENT (CLINICAL ACTION PLAN)*
A1	<30				Diagnose and treat the cause Treat comorbid conditions Evaluate for reversible CKD risk factors Start measures to slow CKD progression and reduce CVD risk (lifestyle and diet, blood pressure control, glycemic control in diabetes, lipid-lowering and antithrombotic therapy if indicated)
A2	30-299	Increased risk for GFR decline	Tubulointerstitial damage from uptake of filtered macromolecules	CKD progression	ACE inhibitors or angiotensin receptor blockers; SGLT2 inhibitors; mineralocorticoid-receptor antagonists and GLP1 agonists in diabetes
		Increased risk for CVD	Pro-inflammatory and prothrombotic state	Clinical CVD	
A3	≥300	Nephrotic syndrome if albumin to creatinine ratio above about 2000 or protein to creatinine ratio above about 3500	Low serum oncotic pressure; increased hepatic synthesis of lipoproteins; loss of serum anticoagulant proteins; kidney edema	Low serum albumin (<3.5 g/dL), edema, hyperlipidemia, DVT, acute GFR decline	Diuretics, statins, anticoagulants, albumin infusions as necessary for refractory edema or acute GFR decline

GFR STAGE	GFR (mL/min/1.73 m²)	DISORDER	MECHANISM	MANIFESTATIONS	MANAGEMENT (CLINICAL ACTION PLAN)*
G1	>90				Diagnose and treat the cause Treat comorbid conditions Evaluate for reversible CKD risk factors Start measures to slow CKD progression and reduce CVD risk (lifestyle and diet, blood pressure control, glycemic control in diabetes, lipid-lowering and antithrombotic therapy if indicated)
G2	60-89				Estimate progression
G3a†	45-59	Increased risk for GFR decline			Consider alkali therapy, dietary protein restriction
G3b†	30-44	Increased risk for CVD	CKD-related nontraditional CVD risk factors	Hypertension, heart failure, myocardial ischemia, stroke	Consider intensifying CVD risk factor management
		Drug toxicity	Decreased drug excretion	Increased serum drug concentrations, side effects, drug-drug interactions	Adjust medication dosages as indicated
		Metabolic bone disease, vascular and soft tissue calcification	Decreased active vitamin D_3, increased PTH and fibroblast growth factor 23	High serum phosphorus, normal or low serum calcium, increased bone reabsorption (osteitis fibrosa cystica), decreased bone formation (osteomalacia)	Dietary phosphate restriction, phosphate-binding agents, calcitriol, calcimimetics
		Anemia	Decreased erythropoietin, increased hepcidin, relative iron deficiency, shortened red blood cell survival	Low hemoglobin, normal MCV, low reticulocyte count	Iron, erythropoietin-stimulating agents, hypoxia inducible factor stabilizers, red blood cell transfusions
		Malnutrition	Decreased protein and energy intake	Weight loss, low serum albumin	Referral to registered dietitian nutritionist, appropriate protein intake
		Metabolic acidosis, hyperkalemia	Decreased renin and aldosterone (in some patients), decreased acid secretion, decreased potassium secretion	Low serum bicarbonate, high or normal serum anion gap, high serum potassium	Alkali therapy, dietary potassium restriction, potassium-binding agents
		Sexual and reproductive disorders	Increased prolactin	Amenorrhea, menorrhagia, impotence, oligospermia, galactorrhea	
G4	15-29			Many of the disorders noted earlier (for example, hypertension, 75%; anemia, 30%; hyperphosphatemia, 20%)	Prepare for kidney replacement therapy (transplantation and/or dialysis) or comprehensive conservative treatment

TABLE 116-2 CHRONIC KIDNEY DISEASE CLINICAL DISORDERS, MECHANISM, MANIFESTATIONS, AND MANAGEMENT (CLINICAL ACTION PLAN) BY GLOMERULAR FILTRATION RATE AND ALBUMINURIA STAGES—cont'd

GFR STAGE	GFR (mL/min/1.73 m²)	DISORDER	MECHANISM	MANIFESTATIONS	MANAGEMENT (CLINICAL ACTION PLAN)*
G5	<15	Symptoms of uremia	Retention of toxic solutes	Fatigue, anorexia, nausea, vomiting, peripheral neuropathy, pruritus, serositis (pericardial and pleural effusions), encephalopathy, increased risk for infections, coagulopathy with gastrointestinal bleeding More of the disorders noted earlier (for example, hypertension, 75%; anemia, 50%; hyperphosphatemia, 30%)	If symptoms of uremia are present, start kidney replacement therapy or comprehensive conservative treatment Treat symptoms

*Clinical action plan is cumulative, meaning that the plan for later stages (lower GFR and higher albuminuria) includes the plan from earlier stages (higher GFR and lower albuminuria).
†There is wide variability in the level of GFR at which clinical manifestations occur. Manifestations can be detected by laboratory testing at stages G3a to G3b. Treatment is often deferred until stages G3b to G4.
ACEI = angiotensin-converting enzyme inhibitor; ARB = angiotensin II receptor blocker; CKD = chronic kidney disease; CVD = cardiovascular disease; DVT = deep vein thrombosis; GFR = glomerular filtration rate; GLP1 = glucagon-like peptide 1; MCV = mean corpuscular volume; MRA = mineralocorticoid receptor antagonist; PTH = parathyroid hormone; SGLT2 = sodium-glucose transport protein 2.

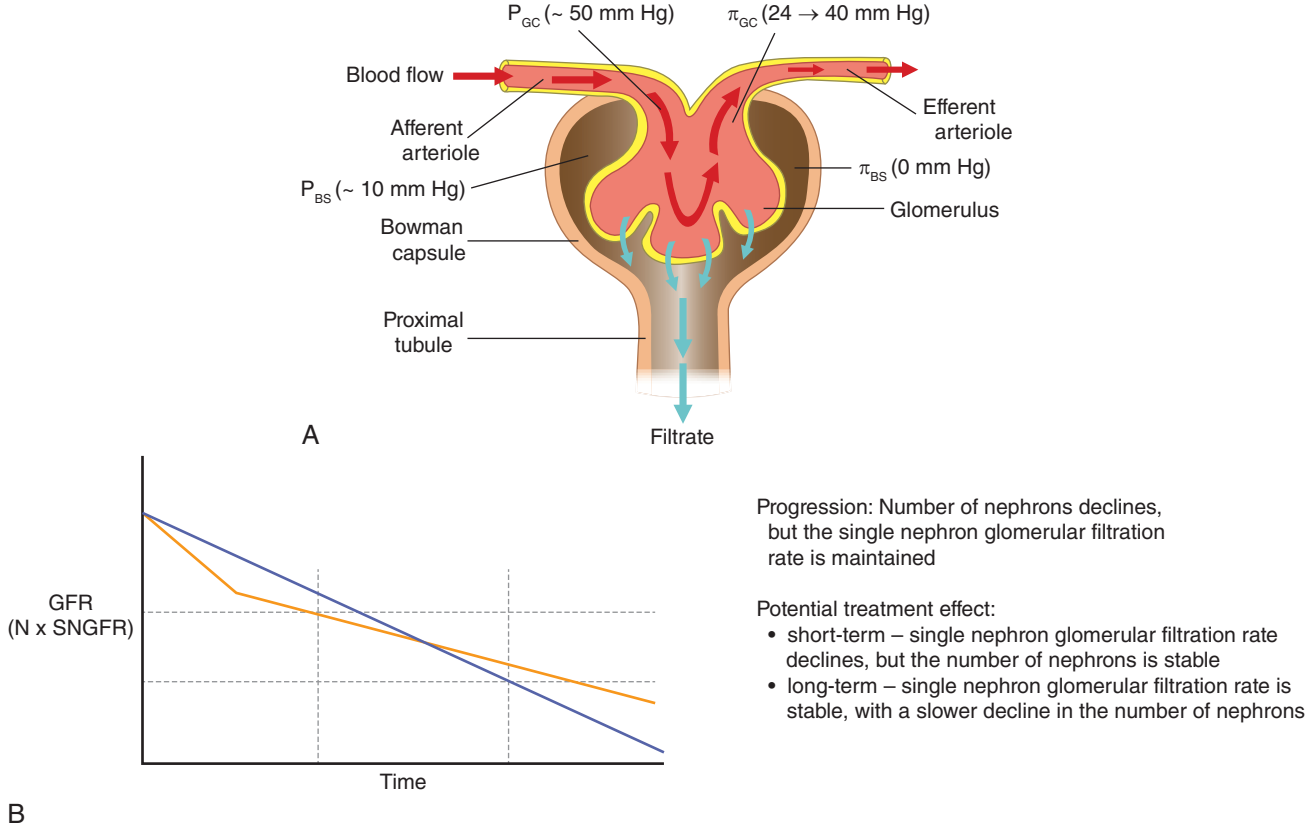

FIGURE 116-3. Pathophysiology of decreased glomerular filtration rate. A, Hemodynamic determinants of the single-nephron glomerular filtration rate. **B,** Mechanism of interventions to slow glomerular filtration rate decline. **A,** In health, a high glomerular filtration rate reflects a high filtration pressure gradient across the glomerular capillary wall (the difference between the hydrostatic pressure gradient [the hydrostatic pressure in the glomerular capsule (P_{GC}) compared with the pressure in Bowman space (P_{BS})] and oncotic pressure gradients [the oncotic pressure in the glomerular capillary (π_{GC}) compared with the oncotic pressure in Bowman space (π_{BS})]) and the high ultrafiltration coefficient of the glomerular capillary wall (K_f, the product of surface area times hydraulic permeability). **B,** Glomerular filtration rate is the product of the number of nephrons times the average single nephron glomerular filtration rate. A decline in glomerular filtration reflects a loss of nephrons. Some therapies for chronic kidney disease reduce the single-nephron glomerular filtration rate but slow the loss of nephrons, thereby initially lowering the glomerular filtration rate (short-term effect) but subsequently slowing the rate of decline of glomerular filtration (long-term effect). GFR = glomerular filtration rate; SNGFR = single nephron GFR.

proteins S and C) and increased liver production of clotting factors and other procoagulant proteins results in hypercoagulability that can manifest as renal vein or deep vein thrombosis.[8] Decreased plasma volume and interstitial edema in the kidney may cause acute kidney injury. Smaller increases in albuminuria (30 to 2000 mg/day, A2 to A3, subnephrotic range) may parallel endothelial damage in other organs and be associated with pro-inflammatory or prothrombotic signals that increase the risk of cardiovascular disease and other complications of chronic kidney disease.

In health, the normal glomerular filtration rate is approximately 125 mL/min/1.73 m² in young adults owing to a high filtration pressure gradient (the difference between hydrostatic and oncotic pressure gradients) across the glomerular capillary wall and its high ultrafiltration coefficient (the product of surface area times hydraulic permeability) (Fig. 116-3). In principle, the glomerular filtration rate is the product of the nephron number (approximately 1 million per kidney) times the mean single-nephron glomerular filtration rate. A decreased glomerular filtration rate is often caused by a decreased number of nephrons and increased nephron glomerular filtration rate per remnant

nephron (single nephron hyperfiltration). This hyperfiltration is caused by the combined effect of glomerular hypertrophy and increased filtration pressure from decreased glomerular capillary resistance, with greater reduction in afferent than efferent resistance. These changes may be considered adaptive because the increase in the single nephron glomerular filtration rate enables continued excretion of solutes despite a decreased number of nephrons, but it is also maladaptive because the increased pressure may damage remnant nephrons, thereby leading to progressive loss of nephrons and a further decline in the glomerular filtration rate. The number of nephrons may also be reduced in premature and low-birthweight infants, thereby leading to subsequent higher risk for the development of chronic kidney disease.[9] Numerous other mechanisms, with or without hyperfiltration and proteinuria, may contribute to the progression of kidney disease.

Therapies targeted to the glomerular adaptations can lower filtration pressure either by increasing afferent resistance or by decreasing efferent resistance and inducing an initially faster glomerular filtration rate decline (short-term or acute effect) followed by a subsequent slowing in the rate of decline in glomerular filtration (long-term or chronic effect), presumably by slowing of the loss of nephrons (Fig. 116-3B). Albuminuria is also generally reduced by such therapies.

The uremic syndrome, which occurs at a glomerular filtration rate below 15 mL/min/1.73m^2 (stage G5, kidney failure), is characterized by retention of solutes that are normally excreted by the kidney (e.g., urea, creatinine, phosphorus, hydrogen ion, potassium, sodium, chloride, unmeasured anions, low-molecular-weight proteins, lipids, and carbohydrates; see Table 116-2). The increased concentration of retained solutes can be directly toxic to cells, such as cells of the neuromuscular and immune systems. In addition, the retention of solutes may also stimulate regulatory systems to try to maintain their net excretion by decreasing their reabsorption or increasing their secretion. However, these tubular adaptations may be maladaptive because they have adverse consequences in other organ systems. For example, parathyroid hormone (PTH) is increased in response to the retention of phosphate; the result is reabsorption of bone and the potential for tertiary hyperparathyroidism if the hyperparathyroidism becomes autonomous (Chapter 227). The kidney's endocrine and metabolic functions also tend to decline in parallel with decreased excretory function; examples include decreased production of erythropoietin and 1,25-dihydroxycholecalciferol (activated vitamin D_3), as well as decreased urinary production of ammonia.

With smaller decreases in glomerular filtration rate, the retention of solutes is less marked but still may cause complications (see Table 116-2). For example, most patients with chronic kidney disease have hypertension, often with onset at stages G1 to G2, due to a combination of increased extracellular fluid volume from the retention of sodium chloride and increased systemic vascular resistance from a deficiency in nitric oxide and a failure to suppress the sympathetic nervous system and the renin-angiotensin system.

Increased PTH and deficiency of active vitamin D_3 are among the earliest complications of decreased glomerular filtration rate, generally occurring at stage G3a. The metabolic bone disease of chronic kidney disease includes renal osteodystrophy as well as vascular and soft tissue calcification. Renal osteodystrophy is characterized by a combination of bone lesions from increased secretion of PTH (osteitis fibrosa cystica) and a deficiency of active vitamin D_3 (osteomalacia).

The anemia of chronic kidney disease (Chapter 144) is hypoproliferative and normochromic, largely due to a deficiency in erythropoietin, the accumulation of hepcidin, and relative iron deficiency. However, the survival of red cells is also diminished. Anemia generally first appears at stage G3a to G3b but is usually mild (hemoglobin >10 g/dL) until stage G4.

Muscle and fat wasting is primarily due to decreased intake of protein and energy owing to anorexia, although gastrointestinal symptoms (nausea, vomiting, and diarrhea) may contribute at stage G5. Micronutrient deficiencies may also occur. Other causes of muscle and fat wasting may include the accumulation of leptin, ghrelin deficiency, inflammation, and metabolic acidosis. Malnutrition may also be a side effect of dietary restrictions.

Metabolic acidosis (Chapter 104) in chronic kidney disease is caused by retention of hydrogen ion owing to decreased tubular secretion. The most common cause (uremic acidosis) is the decreased production of ammonia owing to decreased nephron mass at stages G3b to G5. A concomitant elevation in the anion gap occurs at stage G4 to G5 owing to the reduced filtration of unmeasured anions. Nevertheless, an acid urine pH is preserved, and the serum bicarbonate level usually stabilizes between 12 and 18 mEq/L because of buffering of retained hydrogen ions in bone. Causes of metabolic acidosis in chronic kidney disease at stage G1 to G2 include impaired acidification (e.g., distal renal tubular acidosis, nonacid urinary pH , usually with hypokalemia), impaired bicarbonate reabsorption (proximal renal tubular acidosis, alkaline urine pH during the generation phase but acid urine pH in the steady-state phase, usually with hypokalemia), and hyporeninemic hypoaldosteronism (type 4 renal tubular acidosis, acid urine pH, usually with hyperkalemia).

Hyperkalemia (Chapter 103), which generally begins at stages G3b to G4, is usually caused by the retention of potassium owing to a combination of excessive dietary intake, decreased filtered load, and decreased tubular secretion. Potassium retention directly stimulates the secretion of aldosterone by the adrenal zona glomerulosa, thereby leading to increased tubular secretion of potassium. The inhibition of the renin-angiotensin system leads to impaired secretion of aldosterone and to type 4 renal tubular acidosis with resulting hyperkalemia. Causes of hyperkalemia without potassium retention include a transcellular shift of potassium from intracellular to extracellular fluid (for example, due to metabolic acidosis, hyperglycemia, or β-adrenergic blockade) or cell lysis.

As the glomerular filtration rate falls, prolactin is retained. Elevated prolactin levels contribute to disturbances in the hypothalamic-pituitary axis and can cause sexual and reproductive disorders at stage G3b to G4. The toxicity of numerous retained solutes leads to peripheral neuropathy, uremic encephalopathy, and an increased risk of infections at stage G5.

Chronic kidney disease is a risk factor for cardiovascular disease, including atherosclerosis (e.g., coronary ischemia and myocardial infarction, cerebral ischemia and stroke, and aortic and peripheral vascular disease), left ventricular hypertrophy, and heart failure. In addition to the increased prevalence of traditional risk factors (e.g., older age, male sex, diabetes, hypertension, hyperlipidemia, obesity, smoking, and physical inactivity) in patients with chronic kidney disease, chronic kidney disease itself also appears to be a risk factor for left ventricular hypertrophy and cardiovascular disease, due in part to increased levels of fibroblast growth factor 23 as well as to pro-inflammatory and prothrombotic states.

CLINICAL MANIFESTATIONS

Clinical manifestations depend on the degree of albuminuria and the severity of the reduction in the glomerular filtration rate (see Table 116-2).[10] Chronic kidney disease is usually silent in its early stages. The earliest manifestation may be the new onset or worsening of hypertension, abnormalities on a urinalysis, electrolyte or acid-base abnormalities, or the development of edema. Often symptoms are nonspecific, such as fatigue or lassitude.

Albuminuria generally indicates glomerular damage and is the earliest marker of kidney damage in conditions such as diabetes, hypertension, and obesity. Subnephrotic-range albuminuria (30 to 2000 mg/day, stages A2 to A3) has few clinical manifestations but is associated with increased risk of cardiovascular disease, anemia, infections, and cognitive impairment. Nephrotic syndrome can cause severe edema, deep vein thrombosis or pulmonary embolism, or acute kidney injury.

A decreased glomerular filtration rate may lead to the accumulation of drugs that are excreted by the kidney, with an increased risk for side effects owing to toxicity and drug-drug interactions. Side effects can also occur due to increased renal toxicity of radiographic contrast agents that contain iodine and the systemic toxicity of gadolinium (Chapter 246). Superimposed acute kidney injury (Chapter 106) is common due to side effects of drugs used to treat chronic kidney disease, cardiovascular disease, and other frequently occurring comorbid conditions.

Many clinical manifestations of decreased glomerular filtration rate may occur at stages G3b to G4. Renal osteodystrophy may cause pathologic fractures and soft tissue masses. Hyperphosphatemia may elevate the calcium-phosphate concentration product in excess of its solubility in extracellular fluid, causing soft tissue and vascular calcification, leading to noncompliant large arteries, left ventricular hypertrophy, heart failure, and, rarely, necrosis of skin and underlying soft tissue owing to ischemia (calciphylaxis). Anemia may cause weakness and contribute to heart failure. Muscle and fat wasting may cause weight loss, often superimposed on preexisting obesity. At stage G3b, the serum anion gap may be in the normal range (normal anion gap metabolic acidosis). At stage G4 to G5, the serum anion gap is usually increased due to retention of inorganic anions (phosphates and sulfates), and high anion gap metabolic acidosis appears. Consequences of chronic metabolic acidosis in chronic kidney disease include osteopenia due to dissolution of calcium salts, as well as muscle wasting and faster progression of kidney disease. Mild hyperkalemia (serum potassium 5.0 to 5.5 mEq/L; Chapter 103) is common, especially in patients treated with drugs that inhibit the renin-angiotensin-aldosterone system. Moderate hyperkalemia (serum potassium 5.5 to 6.5 mEq/L) is more common at stage G3b, and severe hyperkalemia (serum

potassium >6.5 mEq/L) is seen with more advanced chronic kidney disease. Sexual and reproductive disorders may include amenorrhea, menorrhagia, impotence, oligospermia, or galactorrhea.

Kidney failure (glomerular filtration rate <15 mL/min 1.73 m^2, stage G5) can give rise to signs of uremia. The uremic syndrome includes hypertension, extracellular fluid overload, metabolic bone disease, anemia, malnutrition, peripheral neuropathy, pruritus, gastrointestinal symptoms, pericarditis (Chapter 62), encephalopathy, and an increased risk for infections.

DIAGNOSIS

Patients with possible chronic kidney disease should be evaluated systematically (Table 116-3) to define whether they meet the diagnostic criteria (Table 116-4), based on the degree of their albuminuria (>30 mg/day), the decline in their glomerular filtration rate (<60 mL/min 1.73 m^2), and the chronicity of these changes (3 or more months) (Table 116-5). In patients who are determined to have chronic kidney disease, the disease should be classified according to its severity, based on the degree of albuminuria and the glomerular filtration rate (see Fig. 116-1 and see Table 116-2), as well as on its cause (see Table 116-1).

TABLE 116-3 GUIDE FOR THE DETECTION, EVALUATION, AND MANAGEMENT OF CHRONIC KIDNEY DISEASE

1. **Recognition of increased risk of chronic kidney disease**	• Increased susceptibility to chronic kidney disease • Exposure to conditions that cause chronic kidney disease
2. **Testing for chronic kidney disease**	• Measure serum creatinine to estimate glomerular filtration rate • Measure urinary albumin • Assess other markers of kidney damage that are specific to the risk (urine sediment, imaging abnormalities, renal tubular syndromes, kidney biopsy) • Perform confirmatory tests (if indicated)
3. **Detection of chronic kidney disease**	• Duration >3 months (documented or inferred) • Markers of kidney damage • Glomerular filtration rate <60 mL/min per 1.73 m^2 (estimated or measured)
4. **Evaluation of clinical diagnosis for implementation of cause-specific therapy**	• Diabetic kidney disease (type 1 or 2) • Nondiabetic kidney disease (glomerular disease other than diabetic glomerulosclerosis, vascular diseases, tubulointerstitial diseases, cystic or congenital diseases) • Kidney disease in kidney transplant recipients
5. **Assessment of stage for implementation of stage-based cause-independent therapy**	• Albuminuria stages • Glomerular filtration rate stages
6. **Prognosis (risk assessment with detection, evaluation, and management tailored to patient's risk)**	• Predictive instruments using level of albuminuria and glomerular filtration rate plus other factors specific for the outcome (kidney failure, kidney disease progression, acute kidney injury, chronic kidney disease, cardiovascular disease and other complications, mortality)

Modified from Levey AS, Coresh J. Chronic kidney disease. *Lancet*. 2012;379:165-180.

TABLE 116-4 CRITERIA FOR CHRONIC KIDNEY DISEASE (ANY OF THE FOLLOWING PRESENT FOR >3 MONTHS)

Markers of kidney damage (one or more)	Albuminuria (albumin excretion rate ≥30 mg/24 hr; albumin to creatinine ratio ≥30 mg/g; albumin to creatinine ratio stages A2-A3) Urine sediment abnormalities Imaging abnormalities Electrolyte and other abnormalities due to tubular disorders Pathologic abnormalities History of kidney transplantation
Decreased GFR	Glomerular filtration rate <60 mL/min/1.73 m^2 (glomerular filtration rate stages G3a-G5)

From Kidney Disease: Improving Global Outcomes (KDIGO). KDIGO 2012 clinical practice guideline for the evaluation and management of chronic kidney disease. *Kidney Int Suppl*. 2013;3:1-150.

Evaluation of Duration

Evaluation of duration of the kidney disease distinguishes chronic kidney disease (>3 months) from acute kidney injury (Chapter 106).[11] The duration can be documented either by review of past medical records or inferred from specific findings. For example, oliguria or a decreased glomerular filtration rate in the setting of acute illness suggests acute kidney injury. Small kidneys on imaging studies or chronic illness signifies chronic kidney disease. Many kidney diseases can cause either acute or chronic disease, but acute tubular necrosis, the most common cause of acute kidney injury, does not have a chronic phase, and diabetic kidney disease, the most common cause of chronic kidney disease, does not have an acute phase.

Evaluation of Markers of Kidney Damage

Albuminuria signifies increased glomerular permeability, and a large quantity of albuminuria generally signifies a glomerular disease. The albumin excretion rate in a timed urine sample is the gold standard for assessing albuminuria, but an albumin to creatinine ratio in an untimed "spot" urine sample is recommended as the initial test because of its specificity and convenience.[12] As a rough guide, an albumin excretion rate of less than 30 mg/day corresponds approximately to a protein excretion rate of less than 150 mg/day and a dipstick protein reading of negative to trace positive. An albumin excretion rate of greater than 300 mg/day corresponds approximately to a protein excretion rate greater than 500 mg/day and a dipstick that is 1+ positive or greater. Renal tubular disorders may cause abnormalities of serum and urine electrolytes as well as urine pH, glucose, amino acids, and low-molecular-weight proteins in the absence of other markers of kidney damage or a decreased glomerular filtration rate. The evaluation of these disorders usually requires referral to specialists.

Evaluation of the urine sediment can be helpful to determine whether hematuria or pyuria reflect kidney damage (Chapter 101). Dysmorphic red blood cells (RBCs) indicate a glomerular disease (Chapter 107), RBC casts suggest a proliferative glomerulonephritis (Chapter 107), and white blood cell casts suggest pyelonephritis (Chapter 263) or tubulointerstitial nephritis (Chapter 108). Oval fat bodies and fatty casts are found in diseases with proteinuria. Renal tubular epithelial cells and casts may be seen in any parenchymal kidney disease; in the absence of hematuria and proteinuria, such cells may indicate acute tubular necrosis.

Ultrasound is generally the first imaging modality because it is noninvasive, does not require contrast, and has high sensitivity for detecting hydronephrosis, cortical scarring, masses (Chapters 182 and 186), stones (Chapter 111), polycystic kidney disease (Chapter 112), and large or small kidneys. CT and MRI with contrast or diagnostic angiography may be necessary for further delineation of the kidney structures, and percutaneous antegrade or cystoscopic retrograde procedures may be necessary to evaluate the renal collecting system.

Pathologic abnormalities are the gold standard for kidney damage, but biopsy of the kidney is an invasive procedure that is generally reserved for evaluation of markers of kidney damage or decreased glomerular filtration rate when knowledge of the pathologic findings will affect treatment. The main complication of percutaneous biopsy is bleeding, which occurs more frequently in patients who have hypertension, a lower glomerular filtration rate, and biopsy of native as compared with transplanted kidneys.

Evaluation of the Glomerular Filtration Rate

Approximately 90% of clinical laboratories in the United States report an estimated glomerular filtration rate (eGFR) whenever a serum creatinine is measured. Equations to estimate the eGFR use serum concentrations of creatinine and cystatin (Table 116-6), which are endogenous filtration markers that vary inversely with the glomerular filtration rate, plus demographic variables (e.g., with age, with or without sex, and without race), which serve as surrogates for factors other than the glomerular filtration rate that influence their serum concentrations.[13,14] Factors other than glomerular filtration rate that influence the serum creatinine concentration include its generation by muscle and diet, tubular secretion, and extrarenal elimination by intestinal bacteria. Unfortunately, the eGFR lacks precision; in populations with no systematic bias, only 80 to 90% of eGFR calculations are within 30% of the measured glomerular filtration rate. Systematic underestimation of the measured glomerular filtration rate can be observed in individuals who have a large muscle mass, who eat large amounts of meat, who take creatine supplements, or who are treated with medications that inhibit the tubular secretion of creatinine (e.g., trimethoprim, fenofibrate,

TABLE 116-5 EVALUATION OF CHRONIC KIDNEY DISEASE

Duration >3 mo on the basis of documentation or inference. Duration is necessary to distinguish chronic kidney disease from acute kidney injury

- Clinical assessment can indicate duration
  - Review of previous laboratory data
  - Acute illness or oliguria suggests acute kidney injury
  - Chronic illness or small kidneys indicate chronic kidney disease
- Documentation of duration is not usually available in epidemiologic studies

Kidney damage as defined by structural abnormalities or functional abnormalities other than decreased glomerular filtration rate. Markers of kidney damage may suggest cause of disease

Albuminuria as a marker of kidney damage. Increased glomerular permeability, urine albumin to creatinine ratio >30 mg/g

- The normal urinary albumin to creatinine ratio in young adults is ≤10 mg/g. Urine albumin to creatinine ratio stages 10-29, 30-300, and >300 mg are high-normal, high, and very high, respectively
- Threshold value of 30 mg/g roughly corresponds to urine dipstick values of trace or 1+, dependent on urine concentration
- High urinary albumin to creatinine ratio can be confirmed by urine albumin excretion in a timed urine collection

Abnormalities in urinary sediment as markers of kidney damage

- Dysmorphic red blood cells in glomerular disease
- Red blood cell casts in proliferative glomerulonephritis
- White blood cell casts in pyelonephritis or interstitial nephritis
- Oval fat bodies or fatty casts in diseases with proteinuria
- Granular casts and renal tubular epithelial cells in many parenchymal diseases (nonspecific)

Imaging abnormalities as markers of kidney damage (ultrasound, computed tomography, and magnetic resonance imaging with or without contrast, isotope scans, angiography)

- Hydronephrosis due to obstruction
- Cortical scarring due to infarcts, pyelonephritis, or vesicoureteral reflux
- Polycystic kidney disease
- Kidney stones
- Renal artery stenosis
- Renal masses or enlarged kidneys due to infiltrative diseases
- Small and echogenic kidneys (common in late stages of chronic kidney disease because of many parenchymal diseases)

Renal tubular syndromes as markers of kidney damage

- Renal tubular acidosis
- Nephrogenic diabetes insipidus
- Bartter and Gittelman syndromes
- Fanconi syndrome
- Cystinuria
- Familial hypomagnesemia with hypercalciuria and nephrocalcinosis

Pathologic abnormalities as markers of kidney damage

- Glomerular diseases
- Vascular diseases
- Tubulointerstitial diseases
- Cystic diseases
- Congenital diseases

Glomerular filtration rate (GFR) <60 mL/min per 1.73 m^2

- Glomerular filtration rate is the best overall index of kidney function in health and disease
- Normal glomerular filtration rate in young adults is about 125 mL/min per 1.73 m^2; glomerular filtration rate <15 mL/min per 1.73 m^2 is defined as kidney failure
- Glomerular filtration rate may be assessed by measurement of clearances of exogenous filtration markers (measured glomerular filtration rate) or estimated from serum concentrations of endogenous filtration markers (estimated glomerular filtration rate)
- Estimated glomerular filtration rate using serum creatinine is the first step in glomerular filtration rate evaluation
  - Non–glomerular filtration rate determinants of serum creatinine include generation by muscle or diet, tubular secretion, and extrarenal elimination by gastrointestinal tract bacterial creatininase
  - In populations with acute illness or chronic comorbid illness, estimated glomerular filtration rate from creatinine may have systematic error (bias) compared to measured glomerular filtration rate
  - In populations in which estimated glomerular filtration rate from creatinine does not have bias, estimated glomerular filtration rate from creatinine lacks precision: only 80-90% of estimated glomerular filtration rates are within 30% of measured glomerular filtration rate
- Confirmatory tests for decreased estimated glomerular filtration rate from creatinine include estimated glomerular filtration rate using serum cystatin C or the combination of serum creatinine and cystatin C; measured creatinine clearance; or measured glomerular filtration rate using inulin, iothalamate, iohexol, ethylene-diamine tetracetic acid, or diethylene triamine pentaacetic acid

Cause of chronic kidney disease. Classification of cause is based on

- Site of documented or presumed pathologic abnormalities
- Presence or absence of systemic disease affecting the kidneys

Modified from Levey AS, Coresh J. Chronic kidney disease. *Lancet*. 2012;379:165-180.

ritonavir, cobicistat, dolutegravir, and other antiviral agents) or inhibit bacterial creatininase (broad-spectrum antibiotics). In contrast, systematic overestimation of the measured glomerular filtration rate can be observed in individuals who have muscle wasting, eat a vegetarian or low-protein diet, or have large losses of creatinine-containing extravascular fluid, such as when pleural or peritoneal effusions are continuously drained and replaced with intravenous fluids. Cystatin C is an alternative filtration marker that is recommended as a confirmatory test to estimate the glomerular filtration rate. Serum cystatin C is not affected by muscle mass, diet, or tubular secretion, but it is affected by smoking, obesity, inflammation, thyroid hormones, and glucorticosteroids, independent of glomerular filtration rate. The estimation of glomerular filtration rate by cystatin C is not more accurate than a

TABLE 116-6 EQUATIONS FOR ESTIMATING THE GLOMERULAR FILTRATION RATE

Using the serum creatinine level only $142 \times \min(Scr/k,1)^{\alpha} \times \max(Scr/k,1)^{-1.200} \times 0.9938^{age} \times 1.012$ [if female] where Scr is serum creatinine, k is 0.7 for females and 0.9 males, α is −0.241 for females and −0.302 for males, min indicates the minimum of Scr/k or 1, max indicates the maximum of Scr/k or 1
Using the serum cystatin level only $133 \times \min(Scys/0.8,1)^{-0.499} \times \max(Scys/0.8,1)^{-1.328} \times 9962^{age} \times 0.932$ [if female] where Scys is serum cystatin C
Using both the serum creatinine and serum cystatin level $135 \times \min(Scr/k,1)^{\alpha} \times \max(Scr/k,1)^{-0.544} \times \min(Scys/0.8,1)^{-0.323} \times \max(Scys/0.8,1)^{-0.778} \times 0.9961^{age} \times 0.963$ [if female] where Scr is serum creatinine, Scys is serum cystatin C, k is 0.7 for females and 0.9 males, α is −0.219 for females and −0.144 for males, min indicates the minimum of Scr/k or 1, max indicates the maximum of Scr/k or 1

From National Kidney Foundation calculator: https://kidney.org/professionals/kdoqi/gfr_calculator.

glomerular filtration rate estimated by creatinine, but together they are more accurate than either alone.

Evaluation of Cause

For evaluation of cause, the classification can be simplified into diabetic (Chapter 109) versus nondiabetic diseases of native kidneys and diseases in kidney transplant recipients (Chapter 117). In general, further diagnostic testing should be guided by the likelihood of detecting a treatable disease (Chapter 100).

Diabetic kidney disease is the most common cause of kidney disease in adults in high-income nations, and the clinical features of diabetic glomerulosclerosis can be easily recognized without specialized diagnostic tests (Chapter 109). Slowly worsening albuminuria, hypertension, and a progressive decline in glomerular filtration rate are typical, whereas hematuria, pyuria, and imaging abnormalities are usually absent.

Among the nondiabetic kidney diseases, hypertensive nephrosclerosis (Chapter 64) is the most common. It has no distinct markers, but increased albuminuria can occur before or after the onset of a decreased glomerular filtration rate. Hypertensive retinopathy (Fig. 391-24) and left ventricular hypertrophy are common, whereas hematuria, pyuria, and imaging abnormalities are typically absent. However, hypertension is a common complication of other kidney diseases, and an abnormal urine sediment or a family history of early onset of kidney disease suggests another primary cause of the kidney disease. Many cases of presumed hypertensive nephrosclerosis in individuals of West African descent may be associated with *APOL1* pathogenic variants (Chapter 107).

TREATMENT

General Principles

Management, which is based on the cause of chronic kidney disease and its stage, should begin as soon as the disease is detected. Cause-specific therapy that is directed at factors that cause chronic kidney disease may induce remission and slow progression. Stage-based therapies, which are directed by the level of albuminuria and the glomerular filtration rate, aim to slow the progression and prevent complications of chronic kidney disease, irrespective of the cause (see Table 116-2). Stage-based recommendations are cumulative, so recommendations for late stages include recommendations for early stages. Although many common problems can be managed with existing guidelines by non-nephrologists, specialty nephrology referral is recommended for patients with an uncertain diagnosis, an albumin to creatinine ratio greater than 300 mg/g (stage A3), a glomerular filtration rate less than 30 mL/min/1.73 m^2 (stage G4 to G5), or complications that are difficult to manage.

Cause-Specific Treatment for Chronic Kidney Disease

Glycemic control (Chapter 210) can retard the development of diabetic glomerulosclerosis, and blood pressure control (Chapter 64) can retard the development of hypertensive nephrosclerosis. However, no specific treatment can reverse either disease. For patients who have diabetic kidney disease, the recommended HbA_{1c} target is similar as for patients who have diabetes without kidney disease, although less strict targets may be appropriate for patients with comorbid conditions. Specific treatments (see Table 116-1) are available for many other causes of nondiabetic kidney disease, including glomerular diseases (Chapter 107) and the withdrawal of exposure to toxic drugs (Chapter 106).

Stage-Based Treatment Independent of Cause

Therapies to slow the progression of chronic kidney disease and reduce cardiovascular risk in patients with chronic kidney disease are the mainstays of treatment for most patients. Patients must avoid drugs that are toxic to the kidneys and reduce the dosage of drugs that are excreted by the kidney

Lifestyle and Diet Recommendations

As in the general population, a healthy eating pattern, physical activity, and tobacco cessation are recommended to reduce the risk of cardiovascular disease. A healthy eating pattern accounts for all foods and beverages within an appropriate calorie level and limits saturated fats and trans fats, added sugars, and sodium. A Mediterranean-type diet (Fig. 13-1) may improve lipid profiles, and a DASH-sodium diet (Table 13-4) may lower blood pressure and reduce the production of acid.[15] Dietary sodium restriction (<2.0 g/day) is recommended for patients who have hypertension. The recommended dietary allowance for protein for the general population is approximately 0.8 g/kg/day, which is far below the average protein intake in high-income nations. Some guidelines recommend a dietary protein intake of 0.6 to 0.8 g/kg/day at stage G3 to G5 because of its favorable effect on ameliorating solute retention and the potential to slow the progression of chronic kidney disease. Maintenance of a total energy intake of 25 to 35 kcal/kg/day while consuming a low-protein diet is recommended to avoid protein-calorie malnutrition. Involvement of a registered dietitian nutritionist is essential.

Blood Pressure Control

A systolic blood pressure less than 130 mm Hg is key, and a systolic blood pressure less than 120 mm Hg (using standardized office-based measurements) is recommended by some guidelines.[16] Caution is advised because a lower blood pressure goal may initially be associated with an increased risk of reducing the glomerular filtration rate, especially in older patients with comorbid conditions. Renin-angiotensin-aldosterone system inhibition with an ACE inhibitor or an angiotensin receptor blocker (Tables 64-7 and 64-9) is recommended for patients with albuminuria with or without diabetes to reduce albuminuria and slow the decline in the glomerular filtration rate,[A1] with diuretics[A2] and calcium channel antagonists as additional agents and calcium channel antagonists as the third agent (Chapter 64). Nonsteroidal mineralocorticoid receptor antagonists (e.g., finerenone 20 mg once daily if the glomerular filtration rate is greater than 60 mL/min/1.73m^2 and 10 mg once daily if it is 25 to 59 mL/mm/1.73m^2) are also effective in patients with diabetes and albuminuria.[A3,A4]

Sodium Glucose Transport Protein 2 (SGLT2) Inhibition and Glucagon-like Peptide 1 Agonists

SGLT2 inhibitors reduce sodium glucose cotransport in the proximal tubule, thereby resulting in natriuresis, weight loss, and lower blood pressure. Treatment with these medications[17] reduces albuminuria, slows the decline of the glomerular filtration rate, and reduces the risk for kidney failure and cardiovascular disease in patients who have albuminuria with diabetic (Chapter 109) or nondiabetic kidney disease.[A5–A7] These agents (e.g., canagliflozin 100 mg daily, dapagliflozin 5 mg daily, and empagliflozin 10 mg daily) recommended for patients with albuminuria who have type 2 diabetes (Chapter 109) or who do not have diabetes, but they are not approved for use in patients who have type 1 diabetes. Glucagon-like peptide-1 agonists also reduce albuminuria and slow the decline in glomerular filtration rate in patients with type 2 diabetes and albuminuria.[18]

Lipid-Lowering Therapy and Antithrombotic Agents

Patients with chronic kidney disease are at increased risk of cardiovascular disease (Chapter 40). A healthy diet (Chapters 13 and 201), statins (Chapter 190), and other therapies are recommended to reduce low-density lipoprotein (LDL) cholesterol levels and thereby reduce this risk.[19] When clinically indicated, antithrombotic agents appear to have similar efficacy as in patients who do not have chronic kidney disease; however, the risk of hemorrhagic side effects is higher in patients with chronic kidney disease, and the dose of antithrombotic agents often must be adjusted (Chapter 70). In contrast to their cardiovascular benefit, neither lipid-lowering therapy nor antithrombotic agents appear to have a beneficial effect on the progression of the kidney disease itself.

Treatment of Complications of Albuminuria

Diuretics are generally needed to control edema due to nephrotic syndrome (Chapter 107). In refractory cases, albumin infusion can be administered at the same time.[20] ACE inhibitors and angiotensin receptor blockers (Table 64-7) are useful to reduce albuminuria, but they may cause hypotension and hyperkalemia. Anticoagulants can be used to prevent or treat deep vein thrombosis (Chapter 68) and renal vein thrombosis (Chapter 110).

Treatment of Complications of a Decreased Glomerular Filtration Rate

Exogenous alkali can prevent and treat metabolic acidosis due to chronic kidney disease. It also can slow the decline in the glomerular filtration rate in patients with or without metabolic acidosis and in diabetic and nondiabetic kidney disease.[A8] A reasonable starting dose is sodium bicarbonate at 650 mg twice daily, titrated to a target serum bicarbonate of approximately 22 to 24 mEq/L.

Extracellular fluid volume retention may be a potential risk of therapy with sodium bicarbonate.

Mild hyperkalemia (potassium level 5 to 5.5 mEq/L) generally requires no treatment other than education to avoid foods with large concentrations of potassium. Levels higher than 5.5 mEq/L generally require treatment[21] (Chapter 103). Urgent therapy for higher levels may include calcium gluconate to prevent cardiac arrhythmias; insulin, glucose, and bicarbonate to shift potassium from extracellular to intracellular fluid; loop diuretics, potassium-binding agents, and dialysis to remove potassium from the body; and treatment of reversible causes of hyperkalemia. If there are no reversible disorders, prevention includes dietary potassium restriction (<2 g/day) and potassium-binding agents (Chapter 103).

Metabolic bone disease is treated with phosphate-binding agents to maintain a normal serum phosphorus level (Chapter 105) and with activated vitamin D_3 (e.g., calcitriol starting at 0.25 μg to 0.5 μg orally every day or every other day depending on the glomerular filtration rate and the PTH level) or its analogues. In dialysis patients, calcimimetics (e.g., cinacalcet starting at 30 mg orally daily) should be used to suppress PTH. Subtotal parathyroidectomy is required in refractory cases of tertiary hyperparathyroidism (Chapter 207).

Treatment of symptomatic anemia includes iron repletion if indicated, erythropoiesis-stimulating agents, and red cell transfusions. To stimulate erythropoiesis, erythropoiesis-stimulating agents (e.g., darbepoetin alpha starting at 0.45 μg/kg every 4 weeks) are generally begun when the hemoglobin level is less than 9 g/dL in patients who have symptoms of anemia, who are likely to need red cell transfusions, and in whom the goal is to reduce the risk of alloimmunization or other transfusion-related risks (Chapter 162). Erythropoiesis-stimulating agents are associated with an increased risk of deep vein thrombosis and cardiovascular disease, so they are generally reserved for patients with stages G4 to G5 chronic kidney disease and are used to raise the hemoglobin level only to 10 to 11 g/dL because higher levels are associated with more cardiovascular complications. Hypoxia-inducible factor-stabilizing agents also are effective for raising the hemoglobin level[A9,A10] but are not currently approved in the United States for patients who are not being treated by dialysis because of safety concerns.

Kidney Replacement Therapy and End-of-Life Care

Kidney failure (glomerular filtration rate <15 mL/min/1.73 m^2), which is the end stage of chronic kidney disease, is treated for as long as possible with comprehensive conservative care, which is management of clinical disorders and symptoms of uremia to maintain quality of life without dialysis. When such care is no longer adequate for controlling symptoms and signs, kidney replacement therapy (Chapter 117) is required. Dialysis is effective in resolving the most severe symptoms and signs, but it is associated with many complications and often does not result in full resolution of symptoms and signs. Since both quality of life and survival are limited with dialysis, especially for older patients, kidney transplantation is preferred, whenever possible, to resolve symptoms and extend life. Unfortunately, it is not available to all patients.

End-of-life care (Chapter 3) refers to maintaining comfort at the end of life in patients treated by transplantation, dialysis, or comprehensive conservative care. A shared decision model is recommended for implementation of these modalities of therapy, and planning should begin well in advance of the onset of uremic symptoms.

PREVENTION

Primary prevention of chronic kidney disease refers to the prevention and treatment of risk factors for chronic kidney disease, including diabetes, hypertension, cardiovascular disease, and other associated systemic disorders, as well as reducing exposure to drugs and environmental toxins that cause kidney disease. Adoption of public health guidelines for a healthy lifestyle and diet can lower the prevalence of hypertension, diabetes, obesity, and cardiovascular disease. Secondary prevention to slow the progression of kidney disease relies upon early detection, such as evaluating albuminuria to assess kidney damage and the serum creatinine level to estimate the glomerular filtration rate, in patients who have hypertension, diabetes, cardiovascular disease, and other systemic diseases associated with an increased risk for chronic kidney disease.[22] Failure to assess markers of kidney damage delays the detection of chronic kidney disease and the ability to implement measures to slow its progression. Detection of albuminuria or other markers of kidney damage enables implementation of measures to slow progression before glomerular filtration rate declines, thereby potentially increasing the interval until the onset of kidney failure (E-Fig. 116-3). Tertiary prevention in chronic kidney disease refers to kidney replacement therapy for kidney failure to prevent complications and death.

PROGNOSIS

The prognosis in chronic kidney disease depends primarily on the cause of disease, the level of albuminuria and glomerular filtration rate, and the availability of treatment. Kidney disease often progresses even after the diseases that initially caused it are no longer active. Explanations include systemic hypertension, proteinuria, increased glomerular capillary pressure with increased glomerular filtration, and accumulation of nephrotoxins.

Risk stratification is an important consideration for the detection, evaluation, and management of chronic kidney disease. The Kidney Failure Risk Equation (https://ckdpcrisk.org/kidneyfailurerisk/) predicts the 2-year and 5-year risk of kidney failure with replacement therapy in people with glomerular filtration rate less than 60 mL/min/1.73 m^2 using four variables (age, sex, glomerular filtration rate, and albumin to creatinine ratio) or eight variables (the same four variables plus serum albumin, bicarbonate, calcium, and phosphorus). The Timing of Clinical Outcomes in CKD with Severely Decreased GFR instrument (https://ckdpcrisk.org/lowgfrevents/) predicts the 2-year and 4-year risk of kidney failure with replacement therapy, cardiovascular disease, and death in people with glomerular filtration rate less than 30 mL/min/1.73 m^2 from 10 variables (age, sex, race, glomerular filtration rate, albumin to creatinine ratio, systolic blood pressure, body mass index, presence or absence of diabetes, history of smoking, and history of cardiovascular disease).[23]

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117 TREATMENT OF IRREVERSIBLE RENAL FAILURE

DAVID COHEN AND ANTHONY MICHAEL VALERI

Chronic kidney disease (Chapter 116) tends to progress over time as glomerular capillary hypertension leads to glomerular hyperfiltration, which in turn precipitates progressive injury, glomerulosclerosis, tubulointerstitial fibrosis, and progressive loss of nephrons, regardless of the original insult. Irreversible and advanced end-stage renal disease requires renal replacement therapy, which can be broadly categorized as hemodialysis, peritoneal dialysis, and renal transplantation. In the United States, about 800,000 people receive some form of renal replacement therapy; approximately 480,000 people receive in-center hemodialysis, 16,000 people receive home hemodialysis, 65,000 people are on peritoneal dialysis, and 245,000 have a functioning kidney transplant. Approximately 180,000 people develop end-stage renal disease every year.[1]

Renal replacement therapy must be initiated when fluid and electrolyte derangements, particularly hyperkalemia, acidosis, or volume overload, can

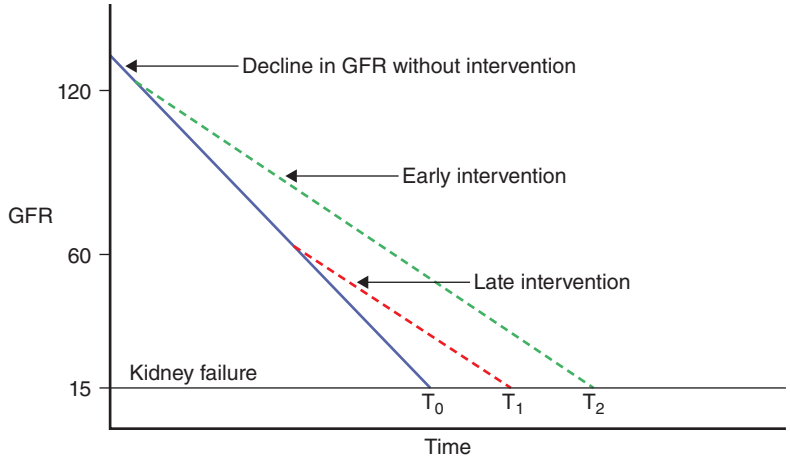

E-FIGURE 116-3. Beneficial effect of early vs. late intervention for CKD. Plot shows GFR decline vs. time since onset of CKD in the absence of intervention (blue line), after late intervention (red line), and after early intervention (green line). T_0 represents the interval from onset of CKD until onset of kidney failure (stage G5, 15 mL/min/1.73 m^2) in the absence of treatment. T_1 represents the interval until onset of kidney failure if treatment is initiated when decreased GFR is detected (G3a, <60 mL/min/1.73 m^2). T_2 represents the interval until onset of kidney failure if treatment is initiated before GFR declines when markers of kidney damage are detected (G1, >90 mL/m/min/1.73 m^2). The intervals from T_0 to T_2 and T_1 represent the benefit of early vs. late intervention, respectively. CKD = chronic kidney disease; GFR = glomerular filtration rate.

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Extracellular fluid volume retention may be a potential risk of therapy with sodium bicarbonate.

Mild hyperkalemia (potassium level 5 to 5.5 mEq/L) generally requires no treatment other than education to avoid foods with large concentrations of potassium. Levels higher than 5.5 mEq/L generally require treatment[21] (Chapter 103). Urgent therapy for higher levels may include calcium gluconate to prevent cardiac arrhythmias; insulin, glucose, and bicarbonate to shift potassium from extracellular to intracellular fluid; loop diuretics, potassium-binding agents, and dialysis to remove potassium from the body; and treatment of reversible causes of hyperkalemia. If there are no reversible disorders, prevention includes dietary potassium restriction (<2 g/day) and potassium-binding agents (Chapter 103).

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End-of-life care (Chapter 3) refers to maintaining comfort at the end of life in patients treated by transplantation, dialysis, or comprehensive conservative care. A shared decision model is recommended for implementation of these modalities of therapy, and planning should begin well in advance of the onset of uremic symptoms.

PREVENTION

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Renal replacement therapy must be initiated when fluid and electrolyte derangements, particularly hyperkalemia, acidosis, or volume overload, can

ABSTRACT

When conservative medical management is no longer adequate to manage patients with advanced kidney disease, renal replacement therapy becomes the only option. Treatments include dialysis and renal transplantation. In the United States, approximately 800,000 patients are currently receiving renal replacement therapy. Hemodialysis involves the flow of blood from the patient to the dialyzer, where diffusion of solutes along their concentration gradient and bulk convection of plasma water across a semipermeable membrane correct many of the acid-base and electrolyte abnormalities in the blood. The cleaned blood is then returned to the patient. Peritoneal dialysis involves the instillation of dialysis fluid into the patients' peritoneal cavity via an indwelling catheter. This technique relies upon diffusion and convection of solutes across the peritoneal membrane from the patient's blood into the peritoneal dialysis fluid, which is then drained via the peritoneal dialysis catheter. Renal transplantation, which involves surgically implanting a single kidney from a living or deceased donor, allows more complete correction of these problems and results in improved long-term survival compared with either form of dialysis. However, renal transplantation requires long-term immunosuppressive therapy to prevent rejection, with its attendant increased risk of infection and malignancy. Not all patients are medically suitable for renal transplant, and there remains a substantial shortage of available kidneys (approximately 90,000 patients on the waiting list and only about 25,000 transplants performed annually from about 19,000 deceased donors and about 6000 live donors). Although short-term success rates of kidney transplant are excellent, long-term results remain disappointing.

KEYWORDS

renal replacement therapy
hemodialysis
hemodiafiltration
frequent hemodialysis
peritoneal dialysis

no longer be adequately controlled with dietary modifications and medications (Chapter 116) or if uremic symptoms, such as anorexia, nausea, vomiting, gastritis pericarditis, or encephalopathy, develop (Table 117-1). Renal replacement therapy typically is required when the estimated glomerular filtration rate (eGFR) is below 10 mL/minute, although it may be needed at an eGFR of 10 to 15 mL/minute when comorbid conditions, particularly heart failure, make medical management even more challenging and difficult. In one small randomized trial of critically ill patients with stage 2 acute kidney injury (defined as a serum creatinine level ≥2 times baseline or urinary output <0.5 mL/kg/hour for ≥12 hours and a plasma neutrophil gelatinase-associated lipocalin level >150 ng/mL), early initiation of renal replacement therapy reduced 90-day mortality compared with delayed initiation.[A1] However, larger randomized trials of intensive care unit patients with stage 3 acute kidney injury showed no reduction in mortality, and patients whose dialysis was delayed tended to have earlier diuresis, fewer adverse events, and a shorter duration of renal replacement therapy.[A2,A3] The routine initiation of dialysis (creatinine level 7.5 mg/dL) is no better than standard dialysis beginning at a creatinine level of approximately 10 mg/dL.[A4] Furthermore, intensive dialytic renal support therapy is no better than standard dialytic therapy, and intermittent hemodialysis and continuous renal replacement therapy lead to similar clinical outcomes in acute renal failure. It also is important to verify that the prescribed dialysis is received and that standardized measures are achieved. Some patients—especially patients in an increased catabolic state, trauma patients, and patients receiving glucocorticoids—may require dialysis more than three times per week to achieve adequate therapy. Neither furosemide nor low-dose dopamine improves outcome, even though low-dose dopamine may temporarily improve metrics of renal physiology.

Hemodialysis relies on diffusion across a semipermeable artificial membrane, whereas peritoneal dialysis brings the blood and the dialysate solution in contact across a natural biologic membrane. The diffusion of solutes along their respective concentration gradients across a semipermeable membrane removes nitrogenous waste products and corrects imbalances of potassium, calcium, magnesium, phosphorus, and acid. In addition, plasma water filters across the membrane and, by convection, drags solutes across the membrane in approximately the same concentration as in the plasma water. The electrolyte concentrations in the dialysate solution are not necessarily physiologic but are intentionally varied with respect to their potassium, calcium, magnesium, and bicarbonate concentrations to favor correction of the plasma toward a more normal physiologic state. For example, a typical dialysate solution might use a potassium concentration of 2 mEq/L and a bicarbonate concentration of 35 mEq/L to enable correction of hyperkalemia and uremic metabolic acidosis. Convection across the dialysis membrane is driven by either a hydrostatic pressure gradient applied across the membrane (hemodialysis) or an oncotic pressure gradient using high-dextrose concentrations or a large, poorly absorbed carbohydrate polymer in the dialysate solution (peritoneal dialysis) for the removal and filtration of excess salt and water from the body.

DIALYSIS

HEMODIALYSIS

Conventional hemodialysis is typically provided at an outpatient dialysis unit where patients are treated three times per week for 3 or 4 hours per session. The measures used for determining the adequacy of treatment are based on urea clearance (as a surrogate marker molecule for the generation and clearance of small-molecular-weight nitrogenous waste products, <500 daltons). The simplest measure is the urea reduction ratio, which is the percentage fall in the blood urea nitrogen level with each dialysis session, with a goal of 65% or greater, or a single pool normalized urea clearance based on the single pool variable volume urea kinetic model *(spKt/V)* of 1.2 or greater on a thrice-weekly dialysis schedule. More precise measurements can fine-tune the dialysis in an individual patient. A more intensive protocol for increased urea clearance with a 40% increase in the *spKt/V* from 1.32 to 1.53 on a thrice-weekly schedule does not improve survival, perhaps because it increases the likelihood of hypotension during dialysis. More frequent hemodialysis, whether as in-center hemodialysis or nocturnal home hemodialysis six times per week, improves outcomes such as kidney-specific measures of quality of life, blood pressure, regression of left ventricular hypertrophy, and serum phosphorus levels, but it did not reduce mortality at 12 months, although longer follow-up (median of 3.6 years) showed a 46% reduction in mortality.[A5]

Patients on hemodialysis are exposed to a large volume of dialysate solution (typically 36 to 48 L/hour during dialysis) and must be protected against even small quantities of impurities, such as trace minerals, bacteria, and bacterial endotoxins, in the dialysis solution. To this end, dialysate solutions are prepared from concentrates diluted with water prepared by reverse osmosis systems or deionizer tanks to remove undesired trace cations and anions and then filtered through small micron-sized pore filters to remove bacteria and their byproducts. Exposure to low levels of bacteria and bacterial byproducts may contribute to the chronic inflammation seen in some patients on hemodialysis.

In critically ill patients who are hemodynamically unstable, one alternative is continuous venovenous hemofiltration, which requires central venous access (double-lumen catheter) and blood flows between 150 and 300 mL/minute. Plasma water under pressure passes across one side of a highly permeable membrane, thereby allowing both water and solutes up to about 60 kD to be removed. In contrast to hemodialysis, urea, creatinine, and phosphate are cleared at similar rates (convective clearance) during hemofiltration, but with improved clearance of larger molecular weight solute ("middle molecules"). The filtrate is discarded, and the fluid lost is partially replaced with a solution containing the major crystalloid components of the plasma at physiologic levels. However, there is no evidence from randomized trials that continuous venovenous hemofiltration offers a survival advantage compared with intermittent hemodialysis in patients with acute renal failure.

New modes of hemodialysis, used predominantly outside the United States, have sought to take advantage of convection to increase the clearance of middle molecules by using high-flux dialysis membranes and ultrafiltration rates of more than 20 L of fluid per dialysis session. In a large randomized trial, this approach, termed high-efficiency postdilution online hemofiltration, reduced all-cause mortality by 30%.

Uremic toxins are classified as low molecular weight (<500 daltons), middle molecular weight (500-60,000) protein-derived metabolites/solutes, and protein-bound solutes. Conventional hemodialysis is most efficient at the removal of low-molecular-weight uremic solutes (<500 daltons). One method to increase the removal of larger-molecular-weight uremic solutes ("middle molecules" in the 500 to 5000 dalton range) is by extending the time on dialysis to permit greater diffusion of these molecules across the dialysis membrane. However, the benefits of this approach remain unclear. Another method of increasing the clearance of middle-molecular-weight uremic solutes is by the use of membranes with larger pore sizes (referred to as medium cutoff dialyzers), which are able to achieve clearances comparable to or, for molecules at the higher end of this range, superior to hemodiafiltration with standard dialyzers. The concern, however, is the filtration and loss of albumin and the long-term implications in terms of overall nutritional status.[A6–A8]

The most common complications during hemodialysis are vascular access problems, hypotension, muscle cramps, nausea, vomiting, headache, and chest pain. Excessive fluid removal is the most frequent cause of hypotension, but persistent hypotension may be caused by sepsis (Chapter 94), myocardial ischemia (Chapter 57), pericardial tamponade (Chapter 62), arrhythmias (Chapters 49 to 53), and active bleeding. A rare complication is an air embolus (Chapter 68), which is manifested with agitation, cough, dyspnea, and chest pain. The patient should be given 100% oxygen and positioned with the left side down (Duran position) in Trendelenburg, or flat and supine, in an attempt to trap air in the right ventricle.

TABLE 117-1 INDICATIONS FOR DIALYSIS IN CHRONIC KIDNEY DISEASE

Uremic encephalopathy or neuropathy
Pericarditis or pleuritis
Bleeding attributable to uremia
Fluid overload refractory to diuretics
Hypertension poorly responsive to medication
Persistent hyperkalemia, metabolic acidosis, hypercalcemia, hypocalcemia, or hyperphosphatemia refractory to medical therapy
Malnutrition or weight loss
Persistent nausea and vomiting

From Tolkoff-Rubin N. Treatment of irreversible renal failure. In: Goldman L, Schafer AI, eds. *Goldman's Cecil Medicine*. 24th ed. Philadelphia: Elsevier Saunders; 2012.

PERITONEAL DIALYSIS

Peritoneal dialysis,[2] which is an alternative mode of renal replacement therapy, is usually performed at home by the patient or the patient's family. A peritoneal dialysis catheter is implanted through a surgically created tunnel in the abdominal wall and inserted into the peritoneal cavity. The catheter's tip in the pelvis is used to instill a dialysis solution into the peritoneal cavity and then to drain the solution from it. Peritoneal dialysis uses the peritoneal

membrane, which consists of the visceral peritoneum, the interstitial tissues, and the mesenteric capillaries, as the filter across which the diffusion of solutes and convection of plasma water occur. Different forms include continuous ambulatory peritoneal dialysis, which is typically performed with 1.5- to 3-L exchanges of peritoneal dialysis solution instilled in the abdomen through a Tenckhoff catheter four times per day; automated peritoneal dialysis, which is performed with a cycler machine at night cycling 1.5 to 3 L of peritoneal dialysis fluid into and out of the abdomen four or five times overnight; and continuous cyclic peritoneal dialysis, a hybrid of continuous ambulatory peritoneal dialysis and automated peritoneal dialysis that uses cycler therapy at night combined with one or two manual exchanges during the day. *Kt/V* urea is the total volume clearance of urea (*Kt*) normalized to the urea space, *V*, which is approximately equal to total body water. For patients who are treated with peritoneal dialysis, residual renal function is often important for ensuring adequate clearance of uremic toxins. For such patients, residual renal function is measured periodically by a 24-hour urine collection. Then the amount of clearance of urea is also measured from the fluid drained from the patient's abdominal cavity after a dialysate exchange to be sure that total urea clearance, from the dialysate plus residual renal function, meets the minimal clearance that is recommended for the patient.

Clearance of small solutes is a key predictor of survival in patients undergoing peritoneal dialysis, and residual renal function also plays a critical role. Current guidelines advocate a minimal target *Kt/V* urea of at least 1.7 per week. Every effort should be made to maintain residual renal function as long as possible by avoiding nephrotoxins such as nonsteroidal anti-inflammatory drugs, iodinated contrast agents, and aminoglycosides. As residual renal function diminishes over time, the peritoneal dialysis prescription needs to be adjusted accordingly.

MEDICAL ISSUES

Renal replacement therapy is concerned not only with adequate dialytic clearance of nitrogenous waste products, the restoration of acid-base and electrolyte balance, and the control of salt and water balance but also with preserving adequate access sites for dialysis, nutrition, and the management of anemia, bone diseases, and cardiovascular risk.

Access Issues

The optimal dialysis access for hemodialysis is a native vein arteriovenous fistula, which can be created by the surgical anastomosis of the radial artery to the cephalic vein or of the brachial artery to either the brachiocephalic or the basilic vein. If a patient's veins are inadequate, a synthetic graft can be placed between the radial, brachial, or axillary artery and the brachiocephalic, basilic, or axillary vein as an alternative. Most commonly, these grafts are made from a synthetic polymer, expanded polytetrafluoroethylene. Less frequently, urgent temporary access can be obtained with a dual-lumen central venous dialysis catheter that is inserted into the internal jugular (preferable) or subclavian vein (right preferred to left). Dialysis access requires periodic Doppler monitoring to detect stenoses that can lead to reduced or even inadequate blood flow, thereby resulting in inadequate urea clearance and, if untreated, thrombosis. These stenoses can be treated by percutaneous transluminal angioplasty, with drug-coated balloons preferable to standard angioplasty,[A9] although stenting is sometimes required to maintain adequate luminal patency.

Nutrition

Adequate nutrition is important for optimizing outcome with renal replacement therapy, and rates of hospitalization are reduced when patients ingest at least 1 g/kg/day of protein. Another marker of nutritional status is the serum albumin level, which generally serves as a reasonable predictor of outcomes with renal replacement therapy.

Anemia

Anemia in end-stage renal disease is due to the reduced production of erythropoietin by the diseased kidneys, a shortened half-life of red blood cells, and the potential loss of red blood cells in the extracorporeal dialysis circuit and the gastrointestinal tract (related to intermittent anticoagulation for the hemodialysis procedure). Erythropoietic stimulating agents should aim to avoid transfusion by maintaining the hemoglobin level generally above 9 g/dL but not higher than 11 g/dL because higher levels are associated with more cardiovascular complications. Patients who have relative or absolute iron deficiency, as evidenced by a transferrin saturation below 20 to 25% or a serum ferritin level below 200, are often relatively resistant to erythropoietic stimulating agents and can benefit from the concurrent administration of a 1-g course (during 8 to 10 dialysis sessions) of intravenous iron (iron sucrose, ferric gluconate, ferumoxytol, or ferric carboxymaltose).[A10]

Unlike the original class of erythropoietic stimulating agents, which were erythropoietin or modified forms of it, a new class of agents (e.g., roxadustat, vadadustat, and daprodustat) inhibits the metabolism and degradation of the α subunit of hypoxia-inducible factor.[A11–A13] This factor stimulates the production of erythropoietin from the kidney and liver and also enhances the mobilization and utilization of iron from stores in the reticuloendothelial system by suppressing the production of hepcidin in the liver. Daprodustat is the first of these drugs to be approved by the U.S. Food and Drug Administration for the treatment of anemia in end-stage renal disease patients on dialysis.

Metabolic Bone Disease

Metabolic bone disease and phosphorus imbalance are common in end-stage renal disease. Clinical manifestations of renal osteodystrophy (Chapter 116) can range from adynamic bone disease to osteomalacia (Chapter 226) to secondary hyperparathyroidism (Chapter 227) and osteitis fibrosa cystica. The goals of therapy are to achieve a serum phosphorus level within or close to the normal physiologic range, typically about 2.5 to 5.5 g/dL; a corrected calcium (0.8 × [4 − Serum albumin level] + Serum calcium level])–phosphorus product less than 55; and an intact parathyroid hormone level within two to nine times the upper limit of normal.[3] Management includes the restriction of dietary phosphate to 750 to 1000 mg/day of elemental phosphorus; the use of phosphate binders (calcium carbonate or acetate, sevelamer carbonate, lanthanum carbonate, or potentially other cationic agents, magnesium or ferric ion) with meals to bind phosphate in the intestines and to reduce its absorption; the use of activated forms of vitamin D (e.g., calcitriol [0.5 to 4 μg IV or 0.5 to 1 μg PO], paricalcitol [1 to 15 μg IV or PO], or doxercalciferol [1 to 6 μg IV or 5 to 20 μg PO] at each hemodialysis session) to stimulate the parathyroid cells to suppress parathyroid hormone secretion; and cinacalcet (30 to 180 mg daily) to reduce secondary hyperparathyroidism significantly by nearly 70%, even though it does not provide a survival benefit over activated vitamin D therapy alone. Etelcalcetide, which is an intravenous calcimimetic, that is, administered during dialysis sessions, appears to be an equally effective alternative to daily oral cinacalcet.[A14]

Hyperphosphatemia can also lead to pruritus, which occurs in about 50% of patients. If moderate-to-severe pruritus persists, however, intravenous difelikefalin (0.5 μg/kg three times per week) can significantly reduce itching and improve itch-related quality of life.[A15] Reducing the serum phosphorus level is the key treatment.

Cardiovascular Disease

Cardiovascular disease is the leading cause of morbidity and mortality in patients on dialysis. The mainstay of blood pressure control in renal replacement therapy is to achieve the lowest tolerated postdialysis weight to facilitate blood pressure control and enhance the body's sensitivity to antihypertensive agents. The general approach to antihypertensive medication therapy is similar to the approach for other patients, with the exception that diuretics are not helpful (see Tables 64-7 and 64-9). The ideal or goal interdialytic blood pressure for the patient with end-stage renal disease is probably 125 to 145 mm Hg systolic.

Dialysis-dependent chronic kidney disease is an indicator for the same type of aspirin therapy and β-adrenergic blockade used in survivors of a myocardial infarction (Chapters 57 and 58). Statin therapy (Chapter 190) is often recommended, but statins are not of proven benefit for reducing major cardiovascular events or overall mortality in dialysis patients despite clinically relevant reductions in low-density lipoprotein cholesterol levels. The addition of spironolactone (25 mg daily) can reduce the risk of a cardiovascular or cerebrovascular event by about 50%. Control of diabetes (Chapter 210) is important, but mortality in hemodialysis patients is not increased until the hemoglobin A_{1c} level is 8.5% or higher. In patients with chronic kidney disease and stable moderate or severe coronary disease, an initial invasive coronary strategy is no better than a conservative guideline-based strategy.[A16,A17]

Amyloidosis

Dialysis-associated amyloidosis (Chapter 174), typically seen in patients who have been on dialysis for more than 10 to 12 years, is caused by the deposition of end-products of β_2-microglobulin catabolism as amyloid fibrils. The clinical syndrome includes carpal tunnel syndrome (Chapter 388), arthropathy, and autonomic neuropathy (Chapter 386).

Infection

Infection is the second leading cause of morbidity and mortality in dialysis patients. For example, patients on hemodialysis account for about 8% of all patients who develop bacterial endocarditis (Chapter 61), with *S. aureus* and enterococcal endocarditis being equally common.[4]

In hemodialysis, vascular access sites are the primary sources of bacteria and account for about 75% of all cases of bacteremia. In a patient with possible catheter-related bacteremia, blood culture specimens should be obtained both from the catheter and from a peripheral vein. Most vascular access infections are caused by staphylococcal organisms (Chapter 267) and should be treated empirically with vancomycin (15 to 20 mg/kg or approximately 1 g) at the end of each dialysis session, adjusted to blood levels, unless another organism is cultured. In patients with systemic sepsis (Chapter 94) with hemodynamic instability, the line should be pulled promptly and reinserted only after blood cultures are negative for at least 48 hours and the patient has defervesced. Interim dialysis can use an alternative access site, such as a temporary nontunneled catheter. A prolonged course of antibiotic therapy (4 to 8 weeks) is recommended for bacteremia or fungemia that persists after the catheter is removed or in patients with evidence of endocarditis (Chapter 61), septic arthritis (Chapter 251), osteomyelitis (Chapter 251), epidural abscess (Chapter 381), or other metastatic infection.

With peritoneal dialysis, infection is the most frequent reason that the catheter must be removed and therapy discontinued. Infection is suspected by erythema, tenderness, induration, or purulent or bloody drainage. Peritonitis must be suspected in patients with abdominal pain and cloudy dialysate; the physical examination usually shows abdominal tenderness, often with rebound. The peritoneal fluid white blood cell count is typically above 100/μL with a predominance of neutrophils, although lymphocytes may predominate with fungal or mycobacterial infections. Polymicrobial infections should raise the possibility of a perforated diverticulum (Chapter 128), ruptured appendix (Chapter 128), ischemic bowel (Chapter 129), incarcerated hernia (Chapter 128), pancreatitis (Chapter 130), or gynecologic conditions (Chapters 184, and 219) and should prompt an emergent abdominal computed tomography scan. *Staphylococcus epidermidis* (Chapter 267) is the most common cause of peritonitis, but *Pseudomonas* species (Chapter 282) account for 5 to 8% of cases. Recommended initial empirical treatment is intraperitoneal, unless there is evidence of bacteremia or hematogenous spread of the infection. Options include vancomycin (15 to 30 mg/kg in one exchange every 5 to 7 days as guided by serum levels) or a cephalosporin (e.g., cefazolin, 15 to 20 mg/kg in one exchange daily) together with intravenous or intraperitoneal administration of a third-generation cephalosporin with antipseudomonal activity (e.g., ceftazidime, 1 to 1.5 g in one exchange daily) or gentamicin (0.6 mg/kg in one exchange daily) for at least 2 weeks.

Staphylococcus aureus (Chapter 267) is the most common organism for exit site and tunnel infections. Treatment options include empirical oral penicillinase-resistant penicillins (e.g., dicloxacillin, 250 to 500 mg twice daily), fluoroquinolones (e.g., ciprofloxacin, 250 mg twice daily or 500 mg daily), trimethoprim-sulfamethoxazole (e.g., 80 mg/400 mg twice daily or 160 mg/800 mg daily), and cephalosporins (e.g., cephalexin, 500 mg two to three times per day). Vancomycin should be avoided as first-line therapy except for methicillin-resistant *S. aureus*. Mupirocin nasal ointment applied to the exit site twice daily for 5 days every 4 weeks significantly reduces the incidence of *S. aureus* exit site infections.

PROGNOSIS

The prognosis of patients with end-stage renal disease on chronic dialysis depends on their age and other comorbid conditions, especially diabetes. On average, the 5-year survival rate is about 40 to 50% and is similar for hemodialysis and peritoneal dialysis. Survival rates are markedly lower than for the age-matched U.S. population (Table 117-2). The leading cause of death is arrhythmic cardiac arrest, but about 15% of deaths are related to withdrawal of dialysis.

RENAL TRANSPLANTATION

For appropriate patients, renal transplantation continues to be the best treatment for advanced chronic kidney disease. The success of renal transplantation has increased dramatically during the past several decades owing to improved surgical technique, improved medical care, and safer and more effective immunosuppressive medications. Although transplant recipients do not have a normal life expectancy, current 5-year survival rates are nearly twice as high as for similar patients who remain on dialysis or on the transplant waiting list. Several long-held axioms have been proved false, most notably the need for long-term steroid therapy, the impossibility of transplantation in the face of antidonor human leukocyte antigen (HLA) antibodies (positive crossmatch), the inability to transplant ABO-incompatible donor-recipient pairs, and the inability to create long-term tolerance. Despite this remarkable progress, the number of patients on the waiting list far exceeds the number of available kidneys, and the long-term survival rates for kidneys and patients remain disappointing.

EPIDEMIOLOGY

Over 26,000 total renal transplants, including combined kidney-pancreas, kidney-liver, and kidney-heart, are performed annually in the United States. The most common disease leading to renal transplantation is diabetic nephrosclerosis (Chapter 109), followed by hypertensive nephrosclerosis (Chapter 110) and other forms of glomerulonephritis (Chapter 107). Kidney transplant recipients vary in age from infants to older than 80 years, with the majority being between 35 and 64 years of age. About 65% of the kidneys transplanted

TABLE 117-2 EXPECTED REMAINING YEARS OF LIFE IN PREVALENT PATIENTS WITH END-STAGE RENAL DISEASE AND IN THE GENERAL POPULATION, BY AGE, SEX, AND END-STAGE RENAL DISEASE TREATMENT MODALITY

	END-STAGE RENAL DISEASE PATIENTS, 2020					
	DIALYSIS		*TRANSPLANT*		*GENERAL U.S. POPULATION*	
AGE	**FEMALE**	**MALE**	**FEMALE**	**MALE**	**FEMALE**	**MALE**
40-44	8.9	9.4	26.7	24.4	39.6	35.3
45-49	7.7	8.2	23.0	20.8	35.0	30.9
50-54	6.8	7.0	19.6	17.4	30.6	26.8
55-59	5.9	6.0	16.5	14.5	26.3	22.8
60-64	5.1	5.0	13.6	11.9	22.2	19.1
65-69	4.4	4.2	10.9	9.7	18.2	15.7
70-74	3.7	3.6	8.7	7.7	14.5	12.4
75-79	3.3	3.0	6.9*	6.0*	11.1	9.4
80-84	2.8	2.6			8.1	6.9
85+	2.4	2.1			3.8	3.3

*For patients age 75+ years.

Table shows the expected remaining lifetime, in years, for the 2020 prevalent end-stage renal population and the general U.S. population. The table illustrates the markedly foreshortened projected lifespan for patients with end-stage renal disease relative to those without. In individuals aged 40-44 years, for example, there is a >25-year projected lifespan difference between men receiving dialysis (expectancy 9.4 years) and men in the general population (expectancy 35.3 years); the difference was >30 years for women receiving dialysis.

Data Source: USRDS ESRD database. 2022 Annual Data Report, End Stage Renal Disease Chapter 6, Table 6-1, https://usrds-adr.niddk.nih.gov/2022, and National Vital Statistics Report Volume 71, 2022. United States Life Tables 2020, Tables 2,3.

in the United States are from deceased donors, with the other 35% from living donors, who include both living genetically related family members and genetically unrelated donors, most often spouses or friends. The number of deceased kidney donors has increased in recent years, in part due to the opioid epidemic, whereas the number of living donors has remained relatively constant, as has the number of patients on the active transplant waitlist. Currently, the number of patients on the active waitlist is three times larger than the supply of kidneys; and, as a result, the median waiting time for a patient listed for kidney transplantation exceeds 4 years. Fewer than 50% of candidates on the waitlist are transplanted within 5 years of listing, and approximately one third either die or are removed from the waitlist without having received a transplant. Due to improved survival and reduced costs of kidney transplantation compared with dialysis, the U.S, government has recently taken initiatives to encourage increased rates of transplantation for patients with end-stage renal disease.[5]

Renal Transplant Success Rates

For deceased donor kidney transplants, the overall 1-year success rate is approximately 93%, and the 10-year success rate is approximately 50%. For recipients of live donor kidney transplants, the overall 1-year success rate is more than 97%, and the 10-year success rate is 65%.

KIDNEY DONATION

Potential *living kidney donors* undergo a thorough evaluation to ensure that age-adjusted renal function is normal, that the surgical risk of donor nephrectomy is acceptably low, and that there are no medical conditions that would increase the risk of future renal disease in the donor. In addition, all donors are screened for transmissible infections or malignant neoplasms.

Potential donors must be capable of understanding the risks and benefits of live kidney donation, cannot be coerced into donating, and cannot condition the donation on the receipt of money or other valuable goods. Federal law prohibits the buying and selling of organs. Although recent data suggest that live kidney donors have a 3.5- to 5.3-fold higher risk for developing end-stage renal disease compared with healthy non-donors during the 10 years after donation, the absolute risk remains less than 1%.[6] Gestational hypertension or preeclampsia also is more likely in kidney donors than in matched nondonors.

Potential recipients who have a willing and medically and psychosocially suitable live donor, but who either have preformed antidonor HLA antibodies or are blood group incompatible with their potential donor, can receive successful transplants by desensitization protocols that involve intravenous immune globulin and plasmapheresis to reduce the level of antidonor HLA antibodies or isoagglutinins. Despite remarkable short-term success, the high incidence of antibody-mediated rejection has made long-term success rates somewhat disappointing, at about 60 to 70% at 5 years. However, data indicate that patients who receive kidney transplants from HLA-incompatible live donors still realize a substantial survival benefit compared with similar patients who wait for compatible transplants from deceased donors or who remain on the waitlist. An increasingly popular alternative to desensitization is kidney-paired donation. In this scenario, two recipients, each with an incompatible live donor who is compatible with the other recipient, exchange donors, thereby creating two immunologically compatible donor-recipient pairs. Over 1000 annual paired donation transplants in the United States now account for approximately 15% of all living-donor transplants. In some situations, more complicated exchanges may involve multiple donor-recipient pairs.

The majority of deceased donors are brain dead, as a result of head trauma (Chapter 368), cerebrovascular catastrophe (Chapter 377), or anoxia (Chapter 50), but continue to maintain a normal circulation. The Uniform Anatomical Gift Act of 1968 and subsequent revisions equate brain death with death (Chapter 2) and permit organ donation after a declaration of brain death, provided there is consent from the family of the deceased. Events surrounding brain death and organ procurement may result in acute kidney injury, and renal biopsies are frequently performed before implantation to assess kidney quality and potential longevity.

The shortage of available donor organs continues to plague the field of clinical transplantation. Attempts to increase the number of donor organs have included the use of lower quality kidneys, such as kidneys from older donors or donors with a history of diabetes mellitus or hypertension. Deceased donor kidneys are now rated on a continuous grading system—the Kidney Donor Profile Index (KDPI). Characteristics used to calculate the KDPI include the donor's age, height and weight, serum creatinine, history of hypertension, history of diabetes, hepatitis C status, whether the donation was after a cardiac death, and the cause of death. Lower KDPI values—higher quality kidneys—are associated with a lower inherent estimated risk of kidney failure (longer anticipated function after transplantation), whereas transplantation of kidneys with higher KDPI values will result in shorter estimated allograft survival times. This prognosis allows for better informed decision making on the part of both patients and physicians. Developing algorithms to facilitate the optimal use of suboptimal kidneys will continue to be a challenge. Protocols have also been developed to allow organ recovery from deceased donors after cessation of cardiac function (donation after cardiac death [DCD] donors). These kidneys function as well as those recovered by traditional donation after brain death.

Initiatives to increase the deceased donor pool include kidney transplantation from a human immunodeficiency virus (HIV)-positive donor to an HIV-infected recipient. With the availability of curative treatment for hepatitis C (Chapter 135), infected donor kidneys can now be used for hepatitis C-negative recipients, who then receive antiviral therapy immediately after transplantation.[7,8]

WHO IS A CANDIDATE FOR RENAL TRANSPLANTATION?

All patients with advanced chronic kidney disease must be informed about the option of transplantation. Candidates must undergo an age and gender appropriate comprehensive medical and psychosocial evaluation to determine their suitability. The major elements of the evaluation include an assessment of cardiovascular risk,[9,10] urologic suitability, cancer screening, risk of infection, and overall frailty. Because cardiovascular disease is common in end-stage renal disease patients, cardiovascular testing is often undertaken in patients older than 50 years and in patients with a history of diabetes (Chapter 401). In general, contraindications to transplant include active uncontrolled infection, cancer not amenable to treatment, advanced untreatable cardiac disease, cirrhosis, advanced chronic lung disease, inability to follow the post-transplant medical regimen owing to psychosocial reasons, and poor perioperative risk. For otherwise suitable patients with advanced liver, lung, cardiac disease, combined liver-kidney, lung-kidney, or heart-kidney transplantation may be an appropriate option. Despite consensus guidelines, the criteria for listing a candidate for transplant vary among transplant centers.[11]

ALLOCATION

The national systems in the U.S. (the United Network for Organ Sharing) and in virtually every country oversee the distribution of deceased donor kidneys. Given the imbalance between demand and supply, this allocation system attempts to balance equity and utility. Some prioritization is given to patients who are likely to have the best allograft survival, but all suitable candidates have a chance to receive a kidney.

The national system for the allocation of deceased donor organs in the United States is divided into 58 donor service areas, each with an organ procurement organization responsible for procuring and allocating deceased donor organs. The distribution of these organs is first local, then regional, and finally national if no local compatible recipient exists. Waiting time for active listing can begin from the date a patient first starts dialysis, or when their eGFR is <20 mL/minute. The current allocation system largely prioritizes waitlisted candidates with longest waiting time as first in line for the next available compatible kidney within their blood group. Each waitlisted patient receives an Estimated Post-Transplant Survival (EPTS) score based on four factors: time on dialysis, current diagnosis of diabetes, prior solid organ transplants, and age. Patients with low EPTS scores (longer predicted post-transplant survival) are prioritized to receive donor organs with longer anticipated function, beginning the practice of longevity matching in kidney allocation. Special consideration is given to children who are waitlisted prior to age 18 years, patients with high levels of anti-HLA antibodies (for whom compatible donors are difficult to find), patients receiving combined (heart-kidney, liver-kidney, or lung-kidney) transplants, and patients for whom a potential donor has a high degree of HLA matching.[12]

IMMUNOSUPPRESSION

Notwithstanding several reports of successful medication-free long-term renal allograft survival in small numbers of carefully selected patients undergoing complicated conditioning regimens, long-term immunosuppression remains obligatory in virtually all patients to achieve long-term renal allograft survival. The principal drivers of the immune response to an organ allograft and the principal obstacle to organ acceptance are the HLA antigens (Chapter 38). HLA-identical siblings enjoy the best long-term survival rates, and increasing degrees of HLA antigen *mis*match continue to be associated with inferior long-term outcomes (Chapter 38).

Immunosuppressive treatment can be divided into three phases: induction, maintenance, and antirejection (Table 117-3). Induction immunosuppression consists of antilymphocyte antibodies given within the first week immediately after transplantation. Maintenance immunosuppression refers to those medications given daily as long as the allograft is functioning. Antirejection therapy is given to treat episodes of acute or chronic rejection.

For about two thirds of patients, the standard maintenance therapy for the long-term prevention of renal allograft rejection is a three-drug regimen: a calcineurin inhibitor, a purine synthesis inhibitor, and a corticosteroid—tacrolimus, mycophenolate, and prednisone. In the approximately one third of patients with a low-to-moderate risk of rejection, corticosteroids can be safely withdrawn within the first week after transplantation,[A18] and a dual-therapy regimen of mycophenolate and tacrolimus is continued. Outcomes appear to be similar with either regimen. In a randomized trial, however, substituting belatacept (a costimulation blocker) for cyclosporine reduced the 7-year risk of death from graft failure more than 40% and resulted in significantly improved allograft function without an increase in any adverse events, despite a higher number of early acute rejection episodes.[A19]

Induction therapy consists of polyclonal or monoclonal antilymphocyte antibodies administered in the first week after transplantation. Approximately 80% of kidney transplant recipients are in centers that administer induction therapy, the majority with rabbit-derived polyclonal antilymphocyte serum (usually 6 mg/kg total dose) and the others with either basiliximab (20 mg, day 0 and day 4) or alemtuzumab (30-mg single dose). The goals of induction therapy include a reduction in the number of acute rejection episodes in the first several weeks or months after transplantation, a long-term reduction in the overall number of acute rejection episodes, and a resulting improvement in long-term success rates. The addition of cell-based biologic products (regulatory T cells, dendritic cells, or macrophages) is an experimental approach under investigation, with the goal of permitting a reduction in long-term immunosuppression, without any compromise in results (Chapter 38).[13]

REJECTION AND ITS TREATMENT

Despite the availability of more effective and safer immunosuppressive medications, rejection remains an ever-present threat, and a significant proportion of allograft failures are ultimately caused by immune-mediated injury. Classically, there are three types of rejection: hyperacute, acute, and chronic. Histological definitions of acute and chronic rejection are based on criteria (Banff Classification) established and periodically updated by a working group of pathologists and clinicians. Most recently, the category of chronic T-cell mediated rejection has been recognized, and criteria for its diagnosis have been outlined.[14]

Hyperacute rejection occurs when a kidney is transplanted into a recipient who is presensitized to the donor. The recipient's circulating preformed antidonor antibodies may target HLA antigens, blood group (ABO) antigens, or endothelial cell antigens expressed on the donor kidney. The result is immediate endothelial injury and irreversible thrombosis of the transplant. Because of the prescreening of all donor-recipient pairs for the presence of such antidonor antibodies, hyperacute rejection occurs in less than 1% of all renal transplants.

Acute rejection is characterized clinically by an increase in the serum creatinine level over days to weeks, often in the absence of symptoms. On pathologic examination, acute rejection is most frequently "cellular" and characterized by T-lymphocyte infiltration of the tubules, interstitium, and of the vascular structures in more severe rejection. Acute rejection now occurs in only 10 to 15% of transplant patients during the first post-transplantation year and about another 10% in the second year. The majority of acute rejections occur in the first 3 to 6 months after transplantation and are clinically mild, treatable, and reversible. Other causes of allograft dysfunction (e.g., hemodynamic factors such as hypotension and volume depletion, urinary tract obstruction, drug-induced nephrotoxicity, and BK polyomavirus nephropathy) must be excluded. Percutaneous biopsy of the allograft is required to establish the diagnosis with certainty, to determine the type and severity of the rejection, and to guide therapeutic decisions. Acute cellular rejection should be treated immediately, either with high-dose intravenous corticosteroid therapy for milder forms or with polyclonal antilymphocyte sera for steroid-resistant or more severe acute rejection episodes. Such treatment is usually effective at resolving the episode.

Between 10 and 20% of patients have acute antibody-mediated rejection injury, due either to preformed antidonor antibodies or to the development of de novo donor specific antibodies. A hallmark of acute antibody-mediated rejection is the deposition of C4d, a metabolite of a complement component C4, in the peritubular capillaries, accompanied by inflammatory cells in the peritubular capillaries. This antibody-mediated rejection may occur alone or in combination with cellular rejection. Early antibody-mediated rejection is much more common in patients with a prior history of exposure to alloantigen through transfusion, pregnancy, or prior transplantation. The development of sensitive reagents for detection of circulating antidonor antibodies has greatly facilitated the diagnosis of antibody-mediated rejection. Treatment is more problematic, and patients frequently receive plasmapheresis to remove antidonor antibodies, high dose corticosteroids, and/or polyclonal antilymphocyte globulin, as well as various regimens of intravenous immune globulin. Although

TABLE 117-3 IMMUNOSUPPRESSIVE MEDICATIONS USED IN RENAL TRANSPLANTATION

CLASS	DRUGS	HOW USED	MECHANISM OF ACTION	MAJOR ADVERSE EFFECTS
Steroids	Prednisone, methylprednisolone	Induction, maintenance, antirejection	Multiple sites, anti-inflammatory; inhibit production of multiple cytokines	Poor wound healing, weight gain, diabetes, acne, hypertension, cushingoid appearance
Calcineurin inhibitors	Tacrolimus and cyclosporine	Maintenance	Inhibit calcineurin, prevent interleukin-2 production	Nephrotoxicity, hypertension, diabetes mellitus
Purine synthesis inhibitors	Azathioprine	Maintenance	Metabolized to 6-mercaptopurine	Anemia, leukopenia, thrombocytopenia
	Mycophenolic acid	Maintenance	Inhibits purine synthesis by the inhibition of inosine monophosphate dehydrogenase, specific for the purine de novo pathway on which lymphocytes depend	Anemia, leukopenia, thrombocytopenia; teratogenic
mTOR inhibitors	Sirolimus, everolimus	Maintenance	Inhibit mTOR (mammalian target of rapamycin), block lymphocyte response to growth factors	Poor wound healing, proteinuria, hyperlipidemia
Costimulation blockade	Belatacept	Maintenance	Human recombinant fusion protein combining the extracellular portion of cytotoxic T lymphocyte–associated antigen-4 (CTLA-4) with the Fc fragment of human IgG; this binds to the CTLA-4 receptor, preventing engagement of CTLA-4 on the T cell, preventing costimulation	Central nervous system post-transplantation lymphoproliferative disease
T cell–depleting antibodies	Thymoglobulin	Induction, antirejection	Rabbit-derived polyclonal antilymphocyte serum (multiple targets)	Infusion reaction, leukopenia, thrombocytopenia
	Alemtuzumab	Induction	Anti-CDS2	
Anti-IL2R monoclonal antibodies	Basiliximab	Induction	Block interleukin-2 receptor (IL2R)	Rare infusion reaction

Ig = immunoglobulin.

this treatment is often effective in reversing acute antibody-mediated rejection, successful elimination of antidonor antibody and prevention of alloantibody resynthesis are much more difficult. Chronic antibody-mediated rejection frequently follows an episode of acute antibody-mediated rejection.

Chronic rejection is characterized by a slow decline in allograft function, generally during a period of months to years, and frequently accompanied by proteinuria. Although it can occur in the absence of documented episodes of acute rejection and after many years of stable allograft function, early acute rejection is a major risk factor for later chronic rejection and allograft failure. The development of donor-specific anti-HLA antibodies appears to be a strong risk factor for subsequent allograft failure. Antibodies targeting non-HLA loci are also likely to play an important role.[15,16] Anti-HLA antibodies are detectable in a high percentage of cases of chronic allograft dysfunction.[17] Biopsy may show evidence of T cell–induced injury, antibody-induced injury with deposits of C4d, transplant glomerulopathy, or a combination of these findings. In many patients with long-term deterioration of allograft function, however, the only findings are interstitial fibrosis and tubular atrophy, often accompanied by arteriolar hyalinosis, without clear-cut evidence as to the cause. Unfortunately, no treatment has been proved to be effective for chronic T cell or chronic antibody-mediated rejection, which are common causes of long-term allograft failure.

OTHER COMPLICATIONS OF RENAL TRANSPLANTATION

Immunosuppression in renal transplant recipients is associated with a number of adverse effects, the most important of which are infection, malignant neoplasia, and nephrotoxicity.

Infection

Infections occurring in the first few weeks after transplantation are generally nosocomial (Chapter 260), donor derived, present in the recipient at the time of transplantation, or a result of complications of the surgical procedure, such as wound, catheter-associated, or urinary tract infections (Chapter 263) (Fig. 117-1). Next is a period of 5 to 6 months during which opportunistic infection or reactivation of latent infection, such as cytomegalovirus (CMV) infection (Chapter 347) or Epstein-Barr virus (EBV) infection (Chapter 348), is most likely to occur. Later in the course, when the doses of immunosuppressive medication are decreased, community-acquired infections are most common. This timeline is partly a function of infection prophylaxis, given to all renal transplant recipients to minimize infectious complications during periods of highest risk, including perioperative antibiotics to prevent wound and urinary tract infection (Chapter 263), trimethoprim-sulfamethoxazole to prevent *Pneumocystis jiroveci* pneumonia (Chapter 313), oral nystatin or clotrimazole to prevent oral candidiasis (Chapter 310), and oral valganciclovir (see Table 328-4) to prevent CMV disease (Chapter 347). Urinary tract infections (Chapter 263) are the most frequent bacterial infections that lead to hospitalizations in kidney transplant recipients, and the most common organism is *Escherichia coli*.

Up to 30% of patients develop active infection with the BK polyomavirus (Chapter 341), which is trophic for the urinary epithelia. In 5 to 10% of patients, this infection leads to tubulitis and interstitial nephritis, which may result in significant allograft injury. Histologically, BK polyomavirus nephritis is often difficult to distinguish from acute rejection without the use of a special SV40 stain that identifies the large T antigen of BK virus. Approximately 80 to 90% of the general population has serologic evidence of exposure to BK polyomavirus, so infection in the renal transplant recipient may be due to reactivation, superinfection, or primary infection. Interestingly, BK nephropathy is very rare in equally immunosuppressed recipients of other organ transplants. The most important noninvasive indicator of possible BK viral nephropathy is BK viremia, which can be documented in about 10 to 20% of renal transplant recipients. It is presently estimated that 5 to 10% of all renal transplant recipients develop BK virus–induced nephritis and allograft dysfunction, which leads to allograft failure in about half of these patients. Monitoring for BK viremia or virurla is strongly recommended, especially in the first year post-transplant. BK viremia and BK viral nephropathy should be treated initially with a reduction in immunosuppression. No effective antiviral therapy exists for patients who do not respond to lowered immunosuppression.

CMV infection (Chapter 347) continues to be a major cause of morbidity in renal transplant recipients. CMV is widely distributed in the general population, with seroprevalence rates from 40 to 90%, so infections may be due to reactivation, superinfection, or primary infection. CMV disease may be limited to fever and malaise, but frequently causes significant morbidity and even mortality after infecting the gastrointestinal tract, lungs, or liver. Most transplant centers use oral valganciclovir (see Table 328-4) for CMV prophylaxis for 7 months or more after transplantation for all patients at risk, especially seronegative

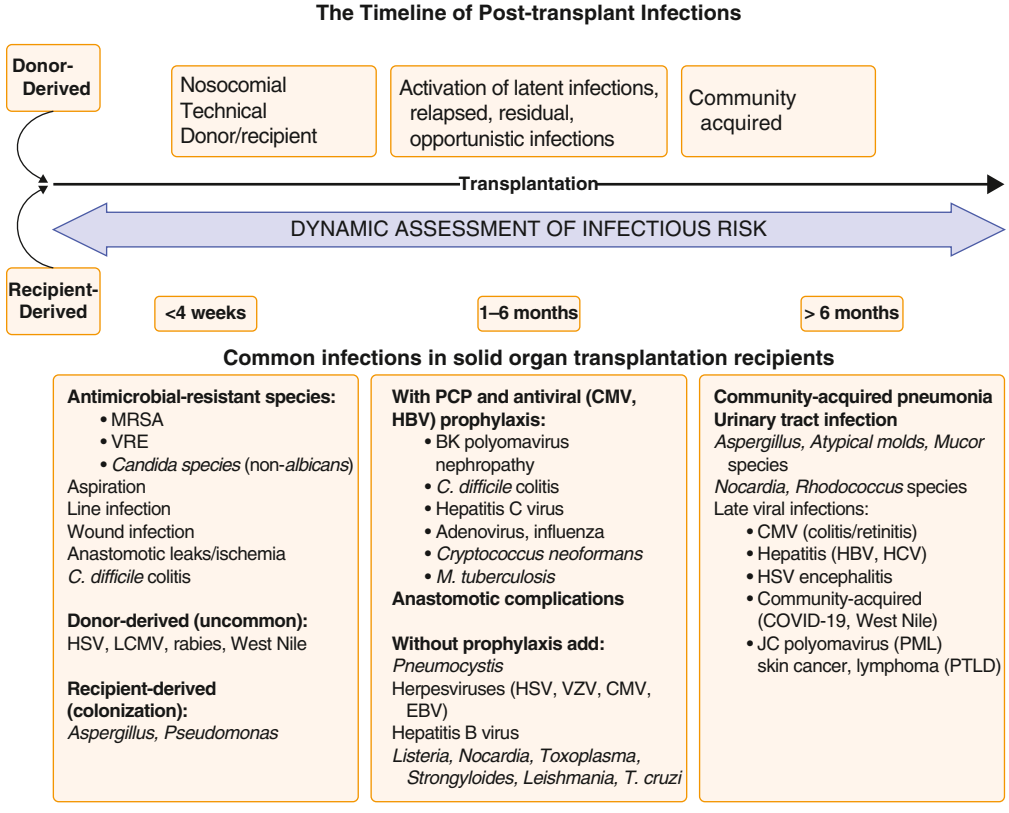

FIGURE 117-1. Timeline of post-transplantation infections. CMV = cytomegalovirus; COVID-19 = coronavirus disease 2019; EBV = Epstein-Barr virus; HBV = hepatitis B virus; HCV = hepatitis C virus; HSV = herpes simplex virus; LCMV = lymphocytic choriomeningitis virus; MRSA = methicillin-resistant *Staphylococcus aureus;* PCP = *Pneumocystis* pneumonia; PML = progressive multifocal leukoencephalopathy; PTLD = post-transplantation lymphoproliferative disease; VRE = vancomycin-resistant enterococci; VZV = varicella-zoster virus. (From Fishman JA. Introduction: infection in solid organ transplant recipients. *Am J Transplant*. 2009;9[Suppl 4]:S3-S6.)

recipients who receive transplants from seropositive donors. Another alternative is frequent post-transplantation monitoring, with treatment reserved for patients who develop viremia. Regardless of the initial strategy, approximately 10% of patients have later viral activation and require additional treatment. Antiviral therapy (Chapters 328) is usually highly effective.

EBV infection (Chapter 348) also may represent a primary infection, reactivation, or superinfection. EBV may cause a mononucleosis-like syndrome, but the more serious concern in renal transplant patients is a form of lymphoma termed post-transplantation lymphoproliferative disease (Chapters 171 and 348).

Renal transplant patients who are infected with severe acute respiratory syndrome coronavirus-2 have a higher mortality (15 to 30%) than the general population.[18] There is no agreed-upon protocol for the safe reduction of immunosuppression that will protect the allograft while mitigating the course of the infection. Vaccination against coronavirus disease 2019 (COVID-19) appears effective and protective against severe disease, albeit less so than in the non-immunosuppressed population.[19]

Malignant Neoplasia

Renal transplant patients develop some malignant neoplasms at higher rates than in the general population.[20] These malignancies include post-transplantation lymphoproliferative disorder related to EBV, Kaposi sarcoma (Chapter 359) caused by human herpesvirus 8 (Chapter 345), and cervical (Chapter 184) and anal (Chapter 131) carcinomas caused by human papillomavirus (Chapter 344). Post-transplantation lymphoproliferative disease most commonly involves the renal allograft, but it may involve any organ, including the gastrointestinal tract, lung, and central nervous system. Treatment usually involves a reduction in immunosuppression and chemotherapy (Chapter 171). Long-term patient survival rates approach 75%.

The relative risks of many common solid carcinomas are also elevated about two-fold, but with the exception of nonmelanoma skin cancers, the absolute risks remain low. Lifetime risk of nonmelanoma skin cancers (Chapter 188) may be as high as 70%. Annual skin screening and the attentive use of ultraviolet-blocking skin creams are strongly recommended. Otherwise, transplant recipients should follow the same standard screening guidelines as the general population for breast (Chapter 183), colon (Chapter 179), prostate (Chapter 186), and lung (Chapter 177) cancer. Whether immunosuppression should be reduced in patients who develop malignant neoplasms other than post-transplantation lymphoproliferative disease is unknown.

Calcineurin Inhibitor–Induced Nephrotoxicity

Calcineurin inhibitors (cyclosporine and tacrolimus; Chapter 28), which are arguably the most effective antirejection medications used in kidney transplantation, ironically cause a chronic, usually mild and stable, impairment of GFR in virtually all patients who receive them. Superimposed, acute reversible cyclosporine or tacrolimus nephrotoxicity may occur in patients who experience sudden elevations in drug blood levels. These acute episodes usually resolve when the dose of cyclosporine or tacrolimus is reduced. Of greater concern is long-term, irreversible calcineurin inhibitor–induced nephrotoxicity, which can cause allograft failure. This diagnosis is often difficult to make because there are few if any absolutely specific histologic biopsy findings. As a result, careful monitoring of blood calcineurin inhibitor levels is essential to avoid supratherapeutic levels (risking nephrotoxicity and infection) or subtherapeutic levels (risking rejection).

New-Onset Diabetes

By 36 months after transplantation, 30 to 40% of patients develop glucose intolerance or frank diabetes, which may be caused by corticosteroids, tacrolimus, and, to a lesser extent, cyclosporine. Treatment is as for diabetes in the general population (Chapter 210), with appropriate adjustment in the dose of insulin and oral agents for renal function. Patients who develop diabetes have poorer outcomes, including higher rates of cardiovascular events, graft failure, and death. Sodium glucose cotransporter 2 (SGLT2) inhibitors may be safe and appropriate treatment options for transplant patients, perhaps even for patients without diabetes mellitus.[A20]

MANAGEMENT OF THE PATIENT AFTER RENAL TRANSPLANTATION

In the initial few months after transplantation, patients are generally seen weekly. The interval then typically expands to once monthly for the remainder of the first year and every 2 to 6 months thereafter. Routine testing includes measurement of blood pressure, renal function, calcineurin inhibitor blood levels, lipid levels, glucose levels, BK polyomavirus assays, and proteinuria. Polymerase chain reaction analysis for CMV or EBV is indicated in selected patients. Monitoring for metabolic bone disease is also recommended, by parathyroid hormone and vitamin D levels as well as by bone densitometry. Influenza and pneumococcal vaccinations are strongly recommended for renal transplant recipients, but live vaccines are contraindicated (Chapter 15).

PROGNOSIS

Five-year kidney allograft survival is approximately 90% for recipients of living donor kidneys and 75% for recipients of deceased donor kidneys. Ten-year survival rates are approximately 70% and 45 to 50%, respectively.[21] Allograft failure with return to dialysis or retransplantation accounts for about 50% of long-term allograft failures.[22] Progressive loss of function in the long-term renal allograft is most commonly the result of chronic rejection but also may be due to nonimmunologic causes, such as calcineurin inhibitor nephrotoxicity, hypertension, diabetes, or recurrent glomerular disease (Table 117-4). A standardized evaluation (Table 117-5) can help establish the cause.

The importance of immunologic (or alloantigen-dependent) factors is illustrated by the fact that death-censored living donor transplants between HLA-identical siblings have a 94% 10-year graft survival, compared with 81% for parental or other less well-matched living donor kidneys and 40 to 50% overall for cadaveric kidney recipients.[23] Deceased donor kidneys with zero or one HLA-A, B, or DR mismatches have a higher success rate (close to 65% at 10 years) than do deceased donor kidneys with two or more antigen mismatches, which have 15 to 30% lower absolute survival rates.

Factors unrelated to anti-allograft immunity are also associated with reduced long-term success rates. These include hypertension, a kidney from an older (>50 years) donor, hyperlipidemia, diabetes mellitus, calcineurin inhibitor nephrotoxicity, recurrent glomerular disease, and a maladaptive response to hemodynamic injury, which is caused by elevated glomerular flow and pressure. Chronic calcineurin inhibitor toxicity leads to end-stage renal disease in at least 5 to 10% of recipients of nonrenal transplants and is likely to have at least a comparable long-term impact in renal transplant patients. Virtually all primary glomerular diseases (Chapter 107), including focal segmental glomerulosclerosis, membranous nephropathy, membranoproliferative glomerulonephritis, and immunoglobulin A (IgA) nephropathy, can recur after transplantation. Recurrent glomerulonephritis is a common cause of proteinuria and nephrotic syndrome after transplantation and may be responsible for up to 10% of all graft failures. For example, graft failure is significantly higher in patients with membranoproliferative glomerulonephritis, focal segmental glomerulosclerosis, membranous nephropathy, and IgA nephropathy compared with adult polycystic kidney disease. Renal biopsy is required to establish the diagnosis in a long-term renal allograft with deteriorating function or proteinuria and to distinguish immune-related from non–immune-related causes. Whether noninvasive biomarkers of actual or impending allograft injury (e.g., circulating donor-derived cell-free DNA or gene expression panels in peripheral blood or urine) will substitute for renal biopsy, in at least some

TABLE 117-4 COMMON CAUSES OF RENAL ALLOGRAFT DYSFUNCTION

Volume depletion: Nausea, vomiting, diarrhea, poor fluid intake, hemorrhage
Medication induced: Diuretics, antihypertensive medications, nonsteroidal anti-inflammatory drugs, calcineurin inhibitors, angiotensin-converting enzyme inhibitors
Urinary tract obstruction: Bladder outlet obstruction, ureteral obstruction
Transplant renal artery stenosis
Infection: Bacteremia, urinary tract infection
Rejection: Cell mediated, antibody mediated

TABLE 117-5 EVALUATION OF RENAL ALLOGRAFT DYSFUNCTION

History: Fluid intake and loss, medication changes, fever
Physical examination: Blood pressure, pulse rate, temperature, weight, edema, allograft tenderness or swelling
Laboratory tests: Serum creatinine level, BK virus detection by polymerase chain reaction analysis of urine or blood, calcineurin inhibitor levels, antidonor antibody testing, urine protein analysis, urine and blood cultures
Doppler ultrasound to assess for possible urinary tract obstruction or transplant renal artery stenosis
Renal biopsy

situations, is an area of active investigation. In the other 50% of failures, a patient dies with a functioning allograft. The most common cause of death in these patients is cardiovascular, due to the high prevalence of diabetes, hypertension, and hyperlipidemia, as well as the high burden of preexisting cardiovascular disease in transplant candidates. Although there are no specific guidelines for the prevention, monitoring, or management of cardiovascular disease after renal transplantation, standard risk factor reduction guidelines are generally considered applicable, including the use of statins (Chapter 190), and antihypertensive medications, to meet blood pressure targets (Chapter 64). The other leading causes of long-term death in renal transplant recipients are infection, sepsis, and malignant disease, all of which are complications of long-term immunosuppression.

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118 APPROACH TO THE PATIENT WITH GASTROINTESTINAL DISEASE

KENNETH R. MCQUAID

The luminal gastrointestinal (GI) tract (esophagus, stomach, duodenum, small and large intestine, and anus) and pancreas are responsible for digestion, for the absorption of nutrients and fluids, and for the temporary storage and excretion of undigested waste. The GI tract has an epithelial lining with an enormous surface area that provides nutrient absorption and serves as a barrier to microorganisms. In addition, the GI tract has a large innate and adaptive immune system that interfaces with luminal food antigens, host proteins, commensal and pathogenic bacteria, and parasites and must decide which antigens to tolerate and which require immune activation.[1] The GI tract also contains an extensive enteric endocrine system that regulates food intake, weight control, and glucose homeostasis as well as secretions from the stomach, intestine, and pancreas. Finally, it has an enteric nervous system that is integrated with the autonomic and central nervous systems to control gastric emptying, intestinal motility, and defecation.[2]

Numerous diseases within and outside the GI tract may alter normal function by causing structural damage (erosion, ulceration, perforation, stenosis, or obstruction), bleeding, inflammation, abnormal absorption or secretion of nutrients and electrolytes, or abnormal motility. Despite its anatomic and physiologic complexity, the GI system has only a limited repertoire of symptoms and signs to express conditions that may be either serious or clinically insignificant: abdominal pain, heartburn, regurgitation, dysphagia, odynophagia, dyspepsia, nausea and vomiting, gas and bloating, weight loss, diarrhea, constipation, overt or occult GI tract bleeding, and incontinence.

GENERAL APPROACH TO PATIENTS WITH GASTROINTESTINAL SIGNS AND SYMPTOMS

An appropriate history and physical evaluation usually can narrow the differential diagnosis of GI complaints. A specific diagnosis can almost always be established thereafter by the judicious use of laboratory, endoscopic, or imaging studies (Table 118-1). Not surprisingly, the site of the abdominal pain has a significant correlation with the organ involved.[3]

CLINICAL HISTORY

The clinician should elicit the nature of the complaint, including its acuity, severity, location, radiation, duration, pattern (steady vs. colicky; abrupt vs. gradual onset), and relationship to food, meals, and bowel movements. Symptoms that arise from the GI tract are almost always improved or worsened by eating or by bowel movements. For symptoms of recent onset, it is important to elicit recent dietary intake, a medication history, potential exposure to enteric infections, coronavirus disease 2019 (COVID-19), or sexually transmitted infections (Chapter 264), and recent travel. It is also useful to establish whether there are signs or symptoms that suggest a systemic illness, including fever, weight loss, arthralgias, fatigue, weakness, and rash.

Most nonsurgical GI diseases are manifested with mild to moderate symptoms that develop gradually and do not require immediate attention. Acute symptoms that require urgent assessment are severe abdominal pain and overt GI bleeding (Chapter 121) that is manifested by hematemesis, melena, or large-volume hematochezia. Severe or dramatic abdominal pain that develops acutely during minutes to hours requires urgent evaluation to determine whether surgical intervention is required. Severe vomiting or diarrhea with signs of dehydration also warrants urgent attention.

Mild to moderate chronic or intermittent symptoms that have been present for a long period can be evaluated in a deliberate fashion. A substantial proportion of chronic GI complaints has no obvious organic or biochemical basis and ultimately is classified as *functional* GI disorders (Chapter 123). Complaints that have been ongoing for years rarely are attributable to readily remedied structural disorders. In patients with chronic GI symptoms, it is important to elicit and to address the current reason for seeking evaluation, which may include concern for underlying serious illness (especially cancer), a change in the character or severity of symptoms, life stressors, and depression. Asking the patient what he or she thinks or fears may provide insights into the proportion of the complaint attributable to these amplifying issues, regardless of whether the problem is functional or structural in origin.

A dietary history (Chapter 198) should be obtained. For acute symptoms of nausea, vomiting, diarrhea, or abdominal pain, intake during the previous 24 to 48 hours should be reviewed for clues to a food-borne illness, including possible exposure to a contaminated food or water source and similar symptoms in other people (Chapter 262). Possible exposure to COVID-19 during the previous 10 days should be assessed.[4] For chronic or intermittent complaints, a recall of meals and types of foods eaten during the previous 1 to 2 days provides insight into eating habits and the amounts and types of fruits and vegetables, whole grains, fiber, protein, fat, and dairy products ingested. A relationship between specific foods and symptoms may be found. For example, dairy products (lactose intolerance), whole grains, legumes or cruciferous vegetables, or fatty meals (malabsorption) may cause pain, flatulence, or diarrhea, and a low-fiber diet may cause chronic constipation. Recent and long-term changes in body weight should be elicited. Involuntary loss of more than 5% of body weight during the prior 12 months is worrisome for serious disease and significant malnutrition (Chapter 197).

The number and consistency of bowel movements should be elicited, and any change in bowel habits must be explored. Signs of acute GI bleeding (melena or hematochezia) or inflammatory colitis (blood, mucus, or pus) should be elicited. Improvement in symptoms after passage of flatus or a bowel movement suggests a disorder of the colon or anorectum.

PAST MEDICAL HISTORY

The past medical history should be reviewed for conditions that may cause acute or chronic GI symptoms, including endocrine disorders such as diabetes (Chapter 210) and thyroid dysfunction (Chapter 207), cardiovascular diseases such as heart failure (Chapter 45) and peripheral vascular disease (Chapter 65), chronic liver disease and portal hypertension (Chapter 139), neurologic conditions such as Parkinson disease (Chapter 378) and neuromuscular disorders (Chapter 366), and rheumatologic and collagen vascular disorders (Chapter 236). In addition to their impact on GI tract function, the severity of these conditions must be considered in weighing the risks of diagnostic studies, especially endoscopy. Patients with symptomatic or advanced respiratory insufficiency (Chapter 90), sleep apnea (Chapter 374), valvular heart disease (Chapter 60), coronary artery disease (Chapter 39), heart failure (Chapter 45), cirrhosis (Chapter 139), cerebrovascular disease (Chapter 375), neuromuscular disease (Chapter 390), or dementia (Chapter 371) have an increased risk of sedation-related complications during endoscopy.

A list of prescription and nonprescription medications, vitamins, minerals, and other nutritional supplements should be obtained, paying particular attention to any that were recently initiated or changed. Herbal supplements (Chapter 30) are commonly used but are seldom reported without direct questioning. Medications are potential causes of odynophagia, dyspepsia, nausea or vomiting, abdominal pain, diarrhea, and constipation. The use of antiplatelet agents and anticoagulants should be determined. The risks of stopping versus continuing these medications must be weighed in patients who have acute or chronic GI bleeding or in whom a therapeutic procedure is to be performed.

SOCIAL HISTORY

The patient's personal relationships, employment history, quality of life, alcohol intake (Chapter 364), and smoking (Chapter 363) history should be determined. It can be very informative to observe both verbal and nonverbal interactions between the patient and a partner or caregiver during an interview. Alcohol may cause heartburn, dyspepsia, nausea, diarrhea, or chronic liver disease. Many patients are reluctant to disclose the full extent of their alcohol intake on direct questioning; therefore, in addition to asking how often they imbibe (days/week and drinks/day), it may be revealing to inquire about their preferred beverage and how it is purchased (location, volume, and frequency). Cigarette smoking is associated with an increased risk of heartburn, peptic ulcer disease, Crohn disease, and GI malignant neoplasms.

Clinicians should inquire about the degree to which GI symptoms are disrupting a patient's life. GI illness may affect dietary and bowel habits, sleep, and sense of vitality. Concerns about dietary intolerances, inability to eat, inability to have comfortable bowel movements, uncontrolled diarrhea or gas, fecal urgency, or fecal incontinence may affect a patient's social life, personal and sexual relationships, employment, and sense of optimism.

The social history should also be reviewed for recent stressors that may precipitate or exacerbate GI symptoms, including marital or interpersonal

ABSTRACT

Diseases within and outside the gastrointestinal (GI) tract alter physiologic function by causing structural damage, bleeding, inflammation, nutrient malabsorption, or dysmotility. GI conditions manifest with a limited number of symptoms and signs, including abdominal pain, heartburn, dysphagia, dyspepsia, nausea, vomiting, gas and bloating, weight loss, diarrhea, constipation, incontinence, and acute or chronic bleeding. A specific diagnosis can be established in most patients after a targeted history, physical examination, and laboratory testing, as well as appropriate radiographic and endoscopic imaging. The clinical history should focus on the acuity, severity, location, duration, and pattern of symptoms, as well as their relationship with meals and bowel movements. The past medical history should elicit endocrine, cardiovascular, and neuromuscular disorders, including medications that may cause symptoms or increase the risk of diagnostic studies (including endoscopy). The social history should explore factors that may contribute to symptoms and determine the impact of GI symptoms on the patient's quality of life. The physical examination should assess for signs of weight loss, malnutrition, and pulmonary, cardiovascular, or neuropsychiatric conditions that may cause GI disease or increase the risk of endoscopic evaluation. The abdominal examination includes inspection, percussion, and light and deep palpation to detect hernias, distention, abdominal tenderness, peritoneal irritation, an enlarged liver or spleen, abdominal masses, and ascites. Routine blood tests include a complete blood count, liver tests, and serum chemistries. Stool examination sometimes is obtained for occult blood and infectious agents. Further evaluation with radiologic imaging (commonly abdominal ultrasound, computed tomography, or magnetic resonance imaging) and endoscopy (commonly upper endoscopy or colonoscopy) is guided by the suspected underlying disorder.

KEYWORDS

abdominal pain
dyspepsia
gas and bloating
nausea
vomiting
diarrhea
constipation
gastrointestinal bleeding

discord, personal or family illness, bereavement, financial pressures, job loss, and change in employment. To elicit such information, it may be helpful to tell patients that stress worsens many conditions and to inquire whether they believe stress may be contributing to their problem.

For elderly, disabled, or marginally housed patients, it is important to elicit how they obtain and prepare their meals and how they access toilet facilities. For patients undergoing GI procedures, it is important to determine whether they have mental, physical, or social barriers that would make it difficult to comply with preprocedural instructions (including bowel preparation) and whether they have an able-bodied adult who can accompany them to the procedure and observe them at home, if necessary, afterward.

FAMILY HISTORY

The family history should be reviewed for GI disorders with a heritable component, especially celiac disease (Chapter 126), inflammatory bowel diseases (Chapter 127), and neoplasms of the GI, gynecologic, and genitourinary tracts.

PHYSICAL EXAMINATION

Nonabdominal Examination

The nonabdominal examination should assess nutritional status (Chapter 198) and any signs of systemic conditions that may cause GI symptoms or that must be considered in weighing the risks and benefits of further testing, especially endoscopy. Vital signs should be obtained in all patients. Low-grade fever (<100.5° F) is common in inflammatory conditions, including gastroenteritis, inflammatory bowel disease, appendicitis, cholecystitis, and diverticulitis. High fever (>102° F) suggests sepsis, pelvic or intra-abdominal infections (e.g., cholangitis, pelvic inflammatory disease, pyelonephritis), or peritonitis. Hemodynamic instability (hypotension or tachycardia) suggests intravascular depletion due to poor oral intake, acute GI or intra-abdominal bleeding, severe diarrhea, or peritonitis. A body mass index of less than 18 suggests malnourishment.

A general survey should be performed to assess for signs of weight loss (fat and muscle wasting), malnutrition (dry or thin skin, hair loss, edema, anasarca), and vitamin deficiencies (pellagra, scurvy). Skin lesions may provide clues to systemic conditions such as liver disease (jaundice, spider telangiectasias, palmar erythema), inflammatory bowel disease (erythema nodosum, pyoderma gangrenosum), celiac disease (dermatitis herpetiformis), vasculitis, and rare GI malignant neoplasms, polyposis syndromes, and pancreatic endocrine tumors (Chapters 178, 179, and 213). An oral examination looks for mucocutaneous candidiasis (which may reflect immunosuppression), ulcerations (which may reflect inflammatory bowel disease, vasculitis, viral infection, or vitamin deficiencies), and glossitis or angular cheilitis (which may reflect vitamin deficiencies). With the exception of supraclavicular lymph nodes, peripheral lymph nodes are uninvolved with GI diseases but should be examined when systemic infection or advanced malignant disease is suspected (Chapter 154). Examination of the lungs and cardiovascular system should focus on evidence of conditions that might increase the risk of moderate sedation in the event that endoscopy is required (respiratory insufficiency, heart failure) and of conditions that increase the risk of intestinal ischemia (atrial fibrillation, valvular heart disease, peripheral vascular disease) (Chapter 129). The extremities should be evaluated for edema and peripheral pulses. Finally, a brief neurologic assessment should be performed to screen for intracranial mass lesions or other neurologic disorders that may be manifested with GI symptoms.

Abdominal Examination

The abdominal examination begins with a visual inspection of the abdomen and inguinal region for scars (due to prior surgeries or trauma), asymmetry (suggesting a mass or organomegaly), distention (due to obesity, ascites, or intestinal ileus or obstruction), prominent periumbilical veins (suggesting portal hypertension), or hernias (umbilical, ventral, inguinal). The examination proceeds with auscultation followed by percussion, and it ends with light and deep palpation.

In patients *without* abdominal pain, auscultation of bowel sounds to assess intestinal motility has limited usefulness and may be omitted. Percussion may be performed before or in conjunction with light and deep palpation. Initial cursory light percussion across the upper, mid, and lower abdomen is useful to denote areas of dullness and tympany as well as to elicit unanticipated areas of pain or tenderness before palpation. More extensive percussion provides limited but useful information about the size of the liver and spleen, gastric or intestinal distention, bladder distention, and ascites (Chapters 132 and 139). Gentle, light palpation promotes abdominal relaxation and allows the detection of muscle resistance (guarding), abdominal tenderness, and superficial masses of the abdominal wall or abdomen. Deeper palpation of the abdominal organs (liver, spleen, kidneys, aorta) and abdominal cavity may detect enlargement or abnormal masses. Superficial or deep masses should be assessed for size, location, mobility, content (solid, liquid, or air), and the presence or absence of tenderness. The consistency of a patient's response to palpation with and without distraction is particularly useful in those with suspected chronic functional abdominal discomfort. Superficial masses include hernias, lymph nodes, subcutaneous abscesses, lipomas, and hematomas. Neoplasms (liver, gallbladder, pancreas, stomach, intestine, kidney), abscesses (appendicitis, diverticulitis, Crohn disease), or aortic aneurysms may represent deep abdominal masses.

Examination of the right upper quadrant should assess the liver size, contour, texture, and tenderness. Liver size is crudely estimated by percussion of the upper and lower borders of liver dullness in the midclavicular line. Liver contour and tenderness are best assessed during held inspiration by deep palpation along the costal margin. Examination of the left upper quadrant is useful to detect splenomegaly (Chapter 154), although a normal-sized or even an enlarged spleen often cannot be detected. Percussion in the left upper quadrant near the tenth rib (posterior to the midaxillary line) may detect splenic dullness that is distinct from gastric or colonic tympany. The tip of an enlarged spleen may be palpated during inspiration if the examiner supports the left costal margin with the left hand while palpating below the costal margin with the right hand. Ascites should be suspected in a patient with a protuberant abdomen and bulging flanks. To screen for ascites, percussion of the flanks should be performed to assess the level of dullness. If the level of flank dullness appears to be increased, the most sensitive test for ascites is to check for "shifting" dullness when the patient rolls from the supine to the lateral position.

Digital Rectal and Pelvic Examinations

The digital rectal examination is intrusive and uncomfortable and should be performed only when necessary, such as in patients with perianal or rectal symptoms, incontinence, difficult defecation, suspected inflammatory bowel disease, and acute abdominal pain. The digital examination, with or without fecal occult blood testing, is not a useful screening test for colorectal cancer (Chapter 179). However, in patients with acute or chronic GI bleeding (Chapter 121), it is a rapid means of assessing the stool for color and occult blood. The perianal area should be visually inspected for rashes, soilage (suggesting incontinence or fistula), fistulas, fissures, skin tags, external hemorrhoids, and prolapsed internal hemorrhoids (Chapter 131). After gentle digital insertion, the anal canal should be assessed for resting tone and voluntary squeeze. The distal rectal vault should be swept circumferentially to palpate for mass lesions, tenderness, or fluctuance.

LABORATORY STUDIES

Blood Tests

Blood tests routinely obtained in the evaluation of patients with GI symptoms include a complete blood count, liver tests (Chapter 133), serum chemistries, and, in selected cases, pancreatic enzymes and markers of inflammation. GI causes of anemia include acute or chronic GI blood loss, inflammatory bowel disease, nutrient malabsorption (folate, iron, or vitamin B_{12}), and chronic liver disease. Microcytosis suggests iron deficiency due to chronic GI blood loss or malabsorption. Macrocytosis may be attributable to folate or B_{12} malabsorption, medications (e.g., immunomodulators used for inflammatory bowel disease), or chronic liver disease. An elevated platelet count suggests chronic inflammation (e.g., inflammatory bowel disease) or GI blood loss with compensatory marrow production. A low platelet count may be attributable to portal hypertension with splenic sequestration. Low serum albumin may be caused by chronic GI disorders that result in weight loss, nutrient malabsorption, chronic inflammation, loss of protein across abnormal GI mucosa (i.e., protein-losing enteropathy), or decreased hepatic synthesis (e.g., chronic liver disease). Abnormal liver test results may be due to acute or chronic liver diseases, disorders of the pancreas or biliary tract, and medications (Chapter 133). Serum amylase and lipase are obtained to screen for pancreatitis (Chapter 130) in patients with acute abdominal pain. Increased levels of inflammatory markers, such as an elevated erythrocyte sedimentation rate and C-reactive protein, are nonspecific but useful in the management of patients with inflammatory bowel disease (Chapter 127).

Serum ferritin reflects total body iron and may be decreased in patients with chronic GI blood loss or intestinal malabsorption (e.g., celiac disease). Deficiencies in the fat-soluble vitamins (A, D, E, K) (Chapter 126) may reflect disorders of malabsorption that result in steatorrhea. The serum international

TABLE 118-1 APPROACH TO COMMON GASTROINTESTINAL SYMPTOMS AND SIGNS

	ABDOMINAL PAIN	GI BLEEDING	DIARRHEA	STEATORRHEA	CONSTIPATION
History (ascertain the following)	Duration: acute vs. chronic Onset: sudden vs. 1-2 hr vs. gradual Character: visceral (vague or dull, steady or cramping, diffuse) or parietal (severe, well localized, worse with movement) Location: upper, middle, or lower; radiation Associated symptoms: vomiting, hematemesis, diarrhea, hematochezia, melena, constipation, obstipation, jaundice Previous episodes Other diseases	Acute vs. chronic (duration); intermittent vs. continuous; quantity; hematemesis, melena, or hematochezia; associated pain and location; symptoms of anemia (e.g., dyspnea, chest pain, lightheadedness); medication use (especially aspirin, NSAIDs, anticoagulants); previous episodes; risk factors for chronic liver disease (alcohol, hepatitis)	Acute (<2 wk) vs. chronic (duration); fever, weight loss, or abdominal pain; stool character: number per 24 hr, watery or bloody, large vs. small volume, change in volume with eating, greasy; dietary history (especially lactose); history of IBD, pancreatic disease, intestinal surgery, DM; recent change in medications or antibiotic use; community outbreak or similar symptoms in family members; potential exposure to contaminated food; elderly immunosuppressed host; risk of HIV or sexually transmitted disease; COVID-19 exposure	Duration; weight loss; stool number, consistency (greasy), presence of blood; abdominal pain; flatulence; history of excessive alcohol, chronic liver disease, pancreatitis, intestinal dysmotility, surgery, DM; history of easy bruising, night blindness, bone pain, osteoporosis, dermatitis herpetiformis	Acute vs. chronic (duration); age; number of stools per week; difficulty with defecation (straining, incomplete evacuation, digital manipulation); bloating or discomfort; blood on stools, weight loss; dietary fiber and fluid intake; chronic illness (DM, neuromuscular, endocrine); abdominal surgeries; medications, impaired mobility
Physical findings (evaluate for the following)	Fever, HR, BP Appearance: calm, restless, motionless Inspect: skin, distention, hernias Bowel sounds: present, absent, roaring Percussion and palpation: organomegaly, mass (abscess), focal tenderness, guarding Peritoneal signs: sharp pain with cough, shaking, percussion, light palpation	HR, BP, orthostatic findings; abdominal pain present or absent; signs of chronic liver disease and portal hypertension (which may indicate varices); jaundice, spider angiomas, hepatosplenomegaly; ascites; examine nasogastric aspirate for blood ("coffee grounds" vs. bright red); examine stool for blood (Hemoccult) and color (melena, maroon, or bright red)	HR, BP, orthostatic findings; fever; wasting; presence of abdominal tenderness or mass; perianal disease; extraintestinal symptoms of IBD (e.g., oral ulcers, arthritis, erythema nodosum)	Wasting, presence or absence of abdominal mass or tenderness; rash (vitamin deficiencies) or excessive bruising (vitamin K deficiency); jaundice or signs of chronic liver disease	Assess mobility and chronic medical conditions; abdominal distention; palpable stool within bowel in left lower quadrant; rectal examination—impacted stool, anal fissure, rectal prolapse, pelvic floor descent with straining, rectocele
Laboratory tests	CBC, BUN, Cr, glucose, amylase, lipase, liver tests (ALT, AST, bilirubin, alkaline phosphatase), albumin, INR, U/A, urine β-HCG; nasal swab for COVID-19	CBC, BUN, Cr, liver tests, INR, type and cross	CBC, BUN, Cr, glucose, electrolytes, liver tests, albumin, C-reactive protein Selected cases: consider serum chromogranin A, VIP, calcitonin, gastrin, glucagon, urinary 5-HIAA; stool for culture, ova, parasites or multiplex PCR tests; nasal swab for COVID-19; consider fecal weight, fat, elastase, calprotectin, electrolytes, laxative screen	CBC, glucose, liver tests, albumin, electrolytes, celiac disease antibody (IgA anti-tTG or EMA or IgG DGP, if IgA deficiency); assessment of vitamin and mineral absorption (A, D) and INR (K is fat soluble), folate, iron, calcium, phosphate, B_{12}; stool for fecal elastase and qualitative fat; stool for quantitative fecal fat; breath test for bacterial overgrowth	CBC, Chem-7, calcium, magnesium, phosphate, TFTs; selected patients with severe constipation may undergo anal manometry with balloon expulsion,
Endoscopy	EGD, colonoscopy	EGD, colonoscopy, enteroscopy, wireless capsule study	Colonoscopy (including ileal inspection) with biopsies; EGD with duodenal biopsies; wireless capsule study	EGD with duodenal biopsies	Colonoscopy if recent change in bowel habits
Imaging	CT scan or ultrasound; MR or CT enterography; angiography	CT angiography, angiography	Small bowel enterography: CT, MRI, (Crohn disease); somatostatin receptor scintigraphy	CT of the abdomen (pancreatic calcifications; biliary dilation)	Usually not necessary; colonic transit studies; MRI or barium defecography

5-HIAA = 5-hydroxyindoleacetic acid; ALT = alanine transaminase; AST = aspartate transaminase; BP = blood pressure; BUN = blood urea nitrogen; CBC = complete blood count; CNS = central nervous system; COPD = chronic obstructive pulmonary disease; COVID-19 = coronavirus disease 2019; Cr = creatinine; CT = computed tomography; DGP=deamidated gliadin peptide; DM = diabetes mellitus; EGD = esophagogastroduodenoscopy; EMA=endomysial antibody; ESR = erythrocyte sedimentation rate; GERD = gastroesophageal reflux disease; GI = gastrointestinal; HbA_{1C} = hemoglobin A_{1C}; HCG = human chorionic gonadotropin; HIV = human immunodeficiency virus; HR = heart rate; IBD = inflammatory bowel disease; INR = international normalized ratio; KCl = potassium chloride; MRI = magnetic resonance imaging; NSAIDs = nonsteroidal anti-inflammatory drugs; RBC = red blood cell; TFTs = thyroid function tests; tTG = tissue transglutaminase; U/A = urinalysis; VIP = vasoactive intestinal polypeptide.

Modified from Proctor DD. Approach to the patient with gastrointestinal disease. In: Goldman L, Ausiello D, eds. *Cecil Textbook of Medicine,* 23rd ed. Philadelphia: Saunders-Elsevier; 2008.

normalized ratio may be elevated in patients with cholestasis because of malabsorption of vitamin K or in patients with chronic liver disease because of decreased hepatic synthetic function. Serum B_{12} may be decreased in patients with autoimmune gastritis (pernicious anemia), gastric bypass surgery, or malabsorption because of small bowel bacterial overgrowth or disease of the terminal ileum (e.g., Crohn disease).

Specialized laboratory tests that may be useful for the diagnosis of specific diseases include stool *Helicobacter pylori* antigen in patients with duodenal ulcer disease or dyspepsia, antibodies to tissue transglutaminase immunoglobulin A (IgA) or deamidated gluten peptide (IgG) in celiac disease, and CA19-9 in pancreaticobiliary malignant disease.

Stool Examination

Fecal occult blood testing is useful to evaluate iron deficiency anemia and acute or chronic GI blood loss. In patients with acute diarrhea, assessment for infectious agents is indicated if diarrhea is bloody, severe, associated with severe abdominal pain or fever, or if the patient is immunocompromised. In most clinical settings, molecular testing of stool specimens is now preferred for initial screening of a panel of bacteria (including *Clostridioides difficile*), viruses, and parasites, with results available within 1 to 5 hours.[5,6] Stool specimens also may be submitted for leukocyte or lactoferrin testing, culture for routine bacterial pathogens (e.g., *Salmonella, Campylobacter, Shigella*), and, in selected patients, testing for *C. difficile, Escherichia. coli 0157:H7*, Shiga toxin, and parasites (*Giardia, Entamoeba histolytica*). To distinguish among the causes of chronic diarrhea (Chapter 126), stool samples may be sent for assessment of electrolytes, leukocytes (microscopy, calprotectin, or lactoferrin), elastase, and fecal fat.

ENDOSCOPY AND RADIOLOGY

Endoscopy (Chapter 120) and radiographic studies (Chapter 119) play a major role in the evaluation and management of many GI disorders. Esophageal manometry and esophageal pH and impedance monitoring can be useful for the evaluation of heartburn, reflux, and other esophageal symptoms (Chapter 124). Anorectal manometry may be useful in some patients with fecal incontinence and defecatory dysfunction (Chapter 131). Breath tests are commonly used to diagnose *H. pylori* infection (a urease breath test; Chapter 125), lactose intolerance, and small bowel bacterial overgrowth (a hydrogen and methane breath test with lactulose or glucose; Chapter 126).

The diagnosis of a functional GI disorder is made after organic disorders have been excluded by clinical evaluation and limited, directed diagnostic testing. "Overtesting" should be avoided. Thereafter, the emphasis should switch from finding a "cause" of the symptoms to implementing successful coping and adaptive behaviours.

ABDOMINAL PAIN

Abdominal pain, which is a frequent complaint among outpatients in the office setting and emergency department, may be benign and self-limited or the presenting symptom of severe, life-threatening disease. Chronic abdominal pain that has been present for months or years in the absence of other organic illness is almost always functional in origin and does not require urgent evaluation. By contrast, most patients with severe acute abdominal pain require a thorough but emergent evaluation, which may quickly reveal an acute surgical illness (Chapter 128).

PATHOBIOLOGY

Stimulation of hollow abdominal viscera is mediated by splanchnic afferent fibers within the muscle wall, visceral peritoneum, and mesentery that are sensitive to distention and contraction. Visceral afferent nerves are loosely organized, innervate several organs, and enter the spinal cord at several levels. Thus, visceral pain is vague or dull in character and diffuse; patients attempting to localize the pain often move their entire hand over the upper, middle, or lower abdomen. Most visceral pain is steady, but cramping, intermittent pain or "colic" results from peristaltic contractions caused by partial or complete obstruction of the small intestine, ureter, or uterine tubes. In contrast to visceral innervation, a dense network of nerve fibers that follow a spinal T6 to L1 somatic distribution innervates the parietal peritoneum. Pain fibers of the parietal peritoneum are stimulated by stretch or distention of the abdominal cavity or retroperitoneum; direct irritation from infection, pus, or secretions (e.g., caused by a ruptured viscus); or inflammation caused by contact between the parietal peritoneum and an adjacent inflamed organ (e.g., appendicitis). Parietal pain is sharp, well characterized, and localized by the patient to a precise location on the abdomen, often by pointing with one finger.

The GI viscera (liver, biliary system, pancreas, and GI tract) arise during embryologic development from midline structures that have bilateral innervation. Thus, GI visceral pain is typically localized to the abdominal midline.

ACUTE ABDOMINAL PAIN

CLINICAL MANIFESTATIONS

History

The history should determine the time course, character, and location and radiation pattern of the pain (Table 118-2). Severe abdominal pain that begins

TABLE 118-2 TYPICAL MANIFESTATIONS OF KEY CAUSES OF ACUTE AND CHRONIC ABDOMINAL PAIN

CONDITION	LOCATION	QUALITY	ONSET	AGGRAVATING OR RELIEVING FACTORS	ASSOCIATED SYMPTOMS OR SIGNS	DIAGNOSTIC STUDIES
Peptic ulcer disease (Chapter 125)	Epigastric, occasionally RUQ, rarely LUQ	Dyspepsia: mild to moderate aching discomfort, pain, burning, gnawing, postprandial fullness	Days	Variable relief with antacids; may be relieved by, worsened by, or unrelated to meals	Recurrent; associated factors (e.g., *Helicobacter pylori*, aspirin, NSAIDs)	Anemia, upper endoscopy, *H. pylori* testing
Acute pancreatitis (Chapter 130)	Epigastric, radiates to midback (occasionally RUQ or LUQ)	Diffuse, steady, stabbing, penetrating	1-2 hr	Aggravated by food; better when lying still and with narcotics	Severe nausea and vomiting; reduced or absent bowel sounds; associated factors (e.g., alcohol, gallstones)	Elevated amylase and lipase, CT
Acute cholecystitis (Chapter 141)	Epigastric, then moves to RUQ; may radiate to right scapula	Gradual, steady increase, moderate to severe	Hours	May follow a fatty meal; better with narcotics and surgery	Nausea, some vomiting, fever	Elevated WBC count, US or CT
Acute appendicitis (Chapter 128)	Periumbilical, then moves to RLQ	Vague initially; gradual, steady increase to intense, localized, pain	Hours	Unprovoked; better with narcotics and surgery	Anorexia, nausea, obstipation; occasional vomiting, fever late	Elevated WBC count, US or CT
Diverticulitis (Chapter 128)	LLQ or suprapubic	Moderate to severe, steady or cramping, sharp or aching, localized	Hours to days	Unprovoked; better with narcotics and antibiotics or surgery	Anorexia, nausea, distention, constipation or loose stools; partial relief with passage of flatus or BM; fever late	Elevated WBC count, CT
Ruptured viscus and peritonitis (Chapter 128)	Diffuse	Intense	Minutes to hours	Worse with cough or movement; better when lying still or with narcotics or surgery	Fever, anorexia, nausea, vomiting; lack of bowel sounds; tenderness with percussion, light touch, rebound; guarding and rigidity (late); loath to move	Elevated WBC count, CT

TABLE 118-2 TYPICAL MANIFESTATIONS OF KEY CAUSES OF ACUTE AND CHRONIC ABDOMINAL PAIN—cont'd

CONDITION	LOCATION	QUALITY	ONSET	AGGRAVATING OR RELIEVING FACTORS	ASSOCIATED SYMPTOMS OR SIGNS	DIAGNOSTIC STUDIES
Intestinal ischemia (Chapter 129)	Small intestine—periumbilical; proximal (right) colon—periumbilical or RLQ; distal colon—LLQ	Severe, stabbing pain out of proportion to physical findings	Minutes	Chronic ischemia—occurs after eating; acute ischemia—usually unprovoked; better with narcotics, thrombus dissolution, stenting, surgical resection	Nausea, bloody diarrhea; associated factors (e.g., hypotension, cardiac arrhythmias)	Elevated WBC count, CT or MR with angiography, or colonoscopy (colonic ischemia)
Strangulated hernia (Chapter 128)	Localized	Sharp, localized, intense; crampy or steady	Minutes to hours	Previous hernia history; unprovoked; better with narcotics and decompression, including surgery	Anorexia, nausea, vomiting, no stool or flatus passage if obstruction; bowel sounds variable—hyperactive early if obstruction present, but absent bowel sounds late, especially with peritonitis	Elevated WBC count, CT, US
Small or large bowel obstruction (Chapter 128)	Small intestine—periumbilical; proximal (right) colon—periumbilical or right abdomen; distal (left) colon—LLQ	Early—diffuse, colicky, crampy; late—steady and better localized	Hours to days	Aggravated by food; better with narcotics, NGT decompression, or surgery	Distention, anorexia, nausea, vomiting; no stool or flatus passage; small intestine—increased hyperperistaltic (rushes) bowel sounds (early) or quiet abdomen (late); large intestine—bowel sounds variable; associated factors (e.g., hernia, previous surgery)	CT
Abdominal abscess (Chapter 128)	Located over the abscess, usually LLQ or RLQ	Insidious, intense, constant	Days	May be aggravated by movement; better with abscess drainage	Fever, anorexia, nausea, abdominal mass	Elevated WBC count, CT
Acute hepatitis (Chapter 134)	RUQ	Dull or intense; localized	Days	Worse with deep inspiration	Jaundice, anorexia, nausea; liver enlarged and tender to palpation; associated factors (e.g., alcohol, infection)	Abnormal liver test results
GERD (Chapter 124)	Substernal or epigastric	Burning, gnawing	Days to years	Provoked by large or fatty meals or recumbency; relief with antacids	Recurrent; may have regurgitation, dysphagia, or extraesophageal manifestations (e.g., asthma, chronic cough, laryngitis)	Upper endoscopy (usually normal), ambulatory pH/impedance probe
Nonulcer (functional) dyspepsia (Chapter 123)	Epigastric	Mild to moderate discomfort, pain, burning, gnawing, postprandial fullness	Years	May be worsened by meals; cannot be reliably distinguished from ulcer disease by history alone	Other symptoms of functional disorders (IBS, fibromyalgia, pelvic pain)	Normal EGD
IBS (Chapter 123)	Variable; usually lower abdomen	Vague, crampy, sense of urgency	Years	Pain may be precipitated by dietary factors or stress; associated with change in bowel characteristics (e.g., frequency, form, difficulty with passage); relieved with stool passage	Bloating and abdominal distention	Normal sigmoidoscopy, colonoscopy, and CT, but these are usually not necessary for diagnosis
Chronic pancreatitis (Chapter 130)	Epigastric or periumbilical, radiates to midback	Intense, localized	Days to years	Aggravated by food; better with narcotics	Anorexia, nausea, vomiting; associated factors (e.g., alcohol); DM (with advanced disease)	Amylase and lipase may be normal; CT may show calcifications, dilated pancreatic duct, pseudocyst; increased fecal fat and decreased fecal elastase if pancreatic insufficiency
Inflammatory or infectious enterocolitis (Chapters 128 and 262)	Small intestine—periumbilical; large intestine—right or left side of the abdomen over the colon; rectum—tenesmus	Crampy	Hours to days	Better with stool passage and treatment of underlying cause	Nausea, vomiting, bloody diarrhea; associated factors (e.g., infectious—food transmission; IBD—prolonged duration, family history)	Stool studies for culture, colonoscopy with biopsies

CT = computed tomography; DM = diabetes mellitus; EGD = esophagogastroduodenoscopy; GERD = gastroesophageal reflux disease; IBS = irritable bowel syndrome; LLQ = left lower quadrant; LUQ = left upper quadrant; MR = magnetic resonance; NGT = nasogastric tube; NSAIDs = nonsteroidal anti-inflammatory drugs; RLQ = right lower quadrant; RUQ = right upper quadrant; US = ultrasound; WBC = white blood cell count.

suddenly during seconds to minutes indicates a catastrophic event, such as esophageal rupture, perforated peptic ulcer or viscus, ruptured ectopic pregnancy, ruptured aortic aneurysm, acute mesenteric ischemia, or myocardial infarction. Pain that progresses within 1 to 2 hours is consistent with a rapidly progressive inflammatory disorder (e.g., cholecystitis, appendicitis, pancreatitis), acute obstruction of a viscus (small intestinal obstruction, which is often related to adhesions from prior intraperitoneal surgery[7]; ureteral colic), or organ ischemia caused by a strangulated blood supply (volvulus, strangulated hernia, ovarian torsion). Pain that is less severe and develops during several hours is more commonly caused by a medical rather than a surgical condition, including upper GI disorders (dyspepsia), intestinal disorders (gastroenteritis, inflammatory bowel disease), liver disorders (hepatitis, abscess), urinary disorders (cystitis, pyelonephritis), and gynecologic infections; however, the slow evolution of surgical disorders such as cholecystitis (Chapter 141), appendicitis or diverticulitis (Chapter 128), and intra-abdominal abscesses must not be overlooked.

The character of the pain provides important information about whether the symptoms are due to visceral stimulation or parietal stimulation (peritonitis). Patients with peritonitis may report severe localized pain or irritation with activities or maneuvers that stretch or move the parietal peritoneum, such as walking, moving in bed, and coughing; as a result, they tend to lie quietly to avoid painful stimulation. By contrast, patients with visceral pain may move or walk restlessly or attempt a bowel movement in an effort to relieve their symptoms.

The location of pain in the upper, middle, or lower abdomen is a crude but important indicator of the diagnosis (Fig. 118-1). Visceral pain arising from the foregut (esophagus, stomach, proximal duodenum, bile duct, gallbladder, pancreas) most often is manifested in the epigastrium. Pain derived from the midgut (small intestine, appendix, ascending colon, proximal transverse colon) occurs in a periumbilical location. Pain derived from the hindgut (distal transverse colon, left colon, rectum) localizes to the lower midline between the umbilicus and symphysis pubis. Paired intra-abdominal organs such as the kidneys, ureters, ovaries, and fallopian tubes have unilateral innervation that localizes pain to the side of the involved organ. As some surgical conditions progress, the character and location of the pain shift from a visceral to a parietal pain pattern. Thus, early cholecystitis (Chapter 141) may be manifested with vague midline epigastric pain that progresses to sharp right upper quadrant pain as localized peritoneal irritation develops. Likewise, appendicitis (Chapter 128) commonly begins with vague, diffuse periumbilical pain that evolves to sharp, well-localized right lower quadrant pain as peritonitis ensues.

Anorexia, vomiting, diarrhea, distention, and constipation are commonly seen with abdominal pain caused by both medical and surgical disorders. Although nonspecific, the *absence* of any of these symptoms is evidence against an emergent surgical or medical disorder because severe illness usually leads to reflex stimulation or inhibition of gastric and intestinal peristalsis. Vomiting is common in medical and surgical disorders involving the upper GI tract, including acute gastroenteritis, pancreatitis, gastric and small intestinal obstruction, and biliary tract disease. Pain that precedes the onset of vomiting is typical of surgical conditions, whereas the reverse is true of medical conditions (e.g., food poisoning, gastroenteritis). Abdominal pain with prominent diarrhea is most commonly caused by a medical condition (e.g., gastroenteritis, inflammatory bowel disease). Although constipation alone is a nonspecific complaint, the absence of stool passage and flatus is consistent with complete bowel obstruction or paralytic ileus.

Jaundice accompanying acute abdominal pain virtually always indicates a hepatobiliary disorder (Chapter 133), including obstruction of the biliary duct (choledocholithiasis, pancreatic carcinoma, cholangiocarcinoma), complications of acute cholecystitis, acute hepatitis (viral, ischemic), and hepatic malignant neoplasms. The possibility of cholangitis should be considered and excluded in all patients with acute abdominal pain and jaundice, especially if the patient has fever, chills, hypotension, altered mental status, or leukocytosis. Hematemesis with upper abdominal pain suggests a Mallory-Weiss tear, alcoholic gastritis, or peptic ulcer disease. Hematochezia with abdominal pain is most commonly caused by medical conditions such as infectious gastroenteritis or inflammatory bowel disease, but it also may be caused by ischemic colitis or mesenteric ischemia. Gross hematuria may be due to cystitis (Chapter 263) or a ureteral stone (Chapter 111). Abdominal pain with weight loss may be due to inflammatory bowel disease, chronic mesenteric ischemia, or advanced GI malignant neoplasms. In women, a missed menstrual period, adnexal pain, spotting, or cramping may suggest pregnancy, ectopic pregnancy, or spontaneous abortion. Acute pain between cycles may be caused by ovarian follicles or ruptured corpus luteum cysts. Pelvic pain with fever, chills, or cervical discharge suggests pelvic inflammatory disease.

The past medical history and review of systems can provide clues about systemic and extra-abdominal conditions that may be manifested with abdominal pain. Acute coronary syndromes (Chapter 57), heart failure (Chapter 45),

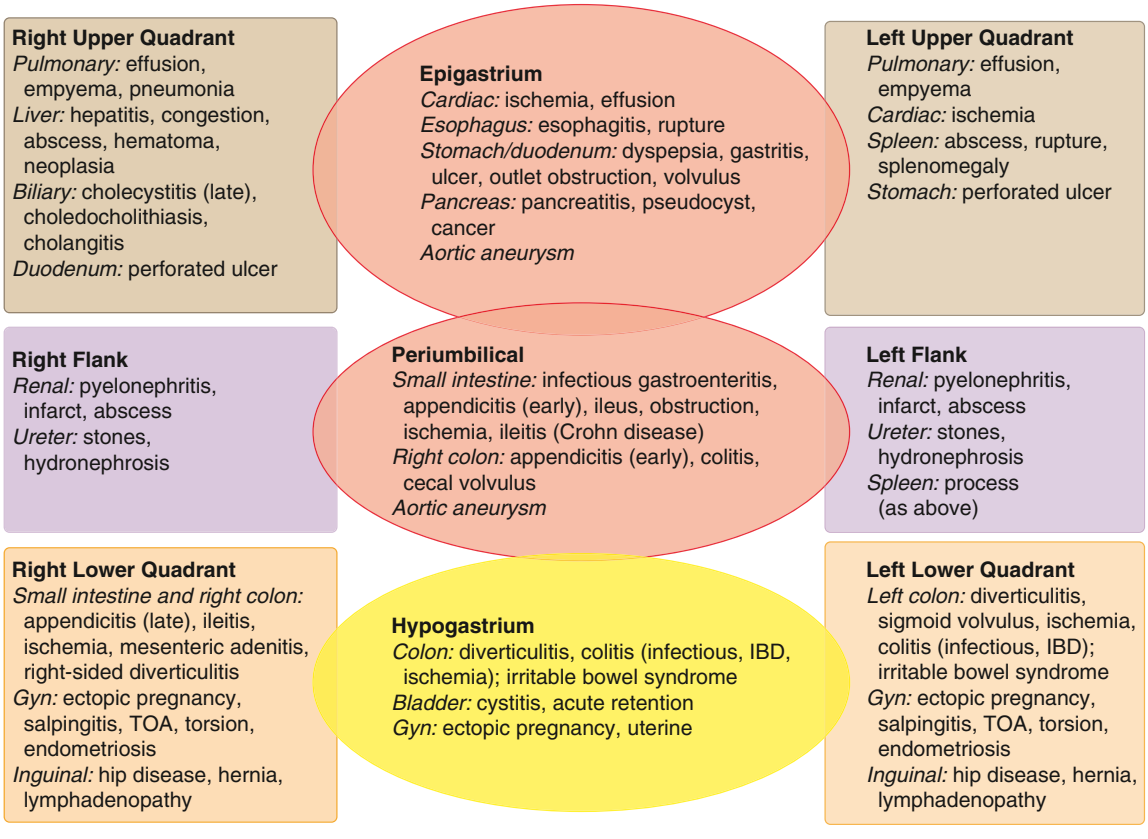

FIGURE 118-1. Differential diagnosis of abdominal pain by its initial location. Gyn = gynecologic; IBD = inflammatory bowel disease; TOA = tubo-ovarian abscess.

pneumonia (Chapter 85), or empyema may cause dyspepsia, epigastric or right or left upper quadrant pain, nausea, and vomiting. Metabolic conditions such as uremia (Chapter 116), diabetes with hyperglycemia or ketoacidosis (Chapter 210), hypercalcemia (Chapter 227), or acute adrenocortical insufficiency (Chapter 208) may cause pain, nausea, vomiting, and diarrhea. Acute intermittent porphyria (Chapter 194) and familial Mediterranean fever (Chapter 254) may cause recurrent episodes of severe pain and peritonitis that may be misdiagnosed, leading to unnecessary surgeries. Other causes of acute abdominal pain include narcotic withdrawal (Chapter 365), insect or reptile bites (Chapter 98), and lead or arsenic poisoning (Chapter 20).

Physical Examination

The physical examination must identify life-threatening illnesses that require urgent surgical evaluation. Nevertheless, the examination must be orderly, careful, and complete. If the examiner immediately palpates the site of maximal pain, the patient is unlikely to relax and to cooperate for the remainder of the examination.

First, the patient should be observed and the abdomen inspected. Most patients remain calm, cooperative, and freely capable of moving during the examination. Patients who are writhing or restless may have pain due to visceral distention (e.g., renal colic, intestinal obstruction), whereas patients who lie motionless may have peritonitis. Gentle shaking of the bed or having the patient cough may elicit sharp, well-localized pain in patients with parietal but not with visceral pain. Auscultation should be performed before percussion or palpation so that intestinal activity is undisturbed. An abdomen that is quiet except for infrequent squeaks or tinkles suggests peritonitis or ileus. Loud peristaltic rushes that occur in synchrony with abdominal pain suggest small bowel obstruction. Light percussion across the upper, middle, and lower abdomen can determine any site of focal tenderness suggestive of peritonitis. Light palpation should be performed with one or two fingers (not the whole hand), beginning away from where the patient localizes the pain and gradually moving to the site of pain. Thereafter, gentle, deeper palpation of the entire abdomen is performed gradually, including the region of tenderness. An attempt should be made to palpate for an abdominal aortic aneurysm (Chapter 63). Examination also should include the inguinal and femoral canals, umbilicus, and surgical scars for evidence of incarcerating hernias. The presence of focal tenderness indicates parietal peritoneal irritation. Voluntary or involuntary tightening of the muscle wall ("guarding") may occur during palpation. With gentle, steady compression of the abdomen with one hand, voluntary guarding usually subsides, allowing the examination to proceed. Persistent involuntary guarding indicates peritonitis with reflex muscle wall contraction. Testing for "rebound tenderness" in patients with suspected peritonitis is not recommended because it causes significant pain and is usually not necessary to establish the diagnosis. When the presentation strongly suggests a nonserious GI disorder but the patient has significant tenderness with palpation, it is useful to use the stethoscope ostensibly to listen for bowel sounds but actually to reproduce the pressure of palpation. A significant discrepancy in the tenderness elicited by the stethoscope and by digital palpation may be seen in patients who are anxious, have functional complaints, or are seeking secondary gain. A digital rectal examination should be performed in most patients with acute abdominal pain to evaluate for tenderness or fluctuance that suggests a perirectal abscess and to assess the stool for signs of overt or occult blood. Women with lower abdominal pain should have a pelvic examination by a skilled examiner to evaluate for gynecologic disease. Some specific and dramatic findings point to particular diagnoses (Table 118-3).

TABLE 118-3 PHYSICAL SIGNS IN PATIENTS WITH ACUTE ABDOMINAL PAIN

SIGN	DESCRIPTION	DIAGNOSIS
Murphy sign	Cessation of inspiration during right upper quadrant examination	Acute cholecystitis
McBurney sign	Tenderness located midway between anterior superior iliac spine and umbilicus	Acute appendicitis
Cullen sign	Periumbilical bluish discoloration	Retroperitoneal hemorrhage Pancreatic hemorrhage Ruptured abdominal aortic aneurysm
Grey Turner sign	Bluish discoloration of flanks	Retroperitoneal hemorrhage Pancreatic hemorrhage Ruptured abdominal aortic aneurysm
Kehr sign	Severe left shoulder pain	Splenic rupture Ectopic pregnancy rupture
Obturator sign	Pain with flexed right hip rotation	Appendicitis
Psoas sign	Pain with straight leg raising against resistance (right side)	Appendicitis

Special Populations

Increased diligence is required in the evaluation of patients in whom abdominal signs and symptoms may be minimal until the disease process is far advanced. Such patients include the elderly (Chapter 24) and patients who have dementia (Chapter 371), psychiatric disturbances (Chapter 362), or spinal cord injuries. An admitting diagnosis of "altered mental status," "failure to thrive," "obstipation," or "fever of unknown origin" may stem from serious intra-abdominal conditions. Disorders that may be overlooked in the elderly include bowel perforation, bowel obstruction, cholecystitis, diverticulitis, volvulus, mesenteric ischemia, and abdominal aortic aneurysm. In patients with chronic liver disease, the presence of ascites may mask the signs and symptoms of serious surgical conditions such as cholecystitis, appendicitis, and diverticulitis. Even in the presence of perforation, signs of peritonitis may be lacking because the ascites fluid separates the visceral peritoneum and parietal peritoneum. Likewise, immunocompromised populations, who are at risk for infectious, drug-related, and iatrogenic complications, may manifest few physical findings or laboratory abnormalities. Owing to the limitations of the clinical evaluation in these vulnerable populations, there should be a low threshold for the use of abdominal imaging.

Abdominal Pain Developing in the Hospital

When pain develops as a new problem in a hospitalized patient, it is usually caused by a limited number of conditions. Postprocedural complications may cause perforation, infection, or bleeding (intraperitoneal, retroperitoneal, or within solid organs). Shunting of splanchnic blood flow in severely ill medical or surgical patients may cause stress gastritis, nonocclusive mesenteric ischemia, or acalculous cholecystitis. Adynamic ileus or acute colonic pseudo-obstruction is common in critically ill or postoperative patients and is manifested as diffuse abdominal pain and distention. *C. difficile* (Chapter 271) colitis is a common cause of pain, diarrhea, and distention, especially in patients receiving antibiotics. Constipation (Chapter 122), which is a common problem in hospitalized patients, may go unnoticed until pain and distention develop. Finally, many medications can cause dyspepsia and abdominal pain.

DIAGNOSIS

Patients with acute abdominal pain should have a complete blood count with differential; leukocytosis is present in most acute surgical conditions (Fig. 118-2). A pregnancy test is required in women of childbearing age. Serum levels of electrolytes, glucose, blood urea nitrogen, and creatinine assess hydration, acid-base status, and renal function. Liver chemistries and pancreatic enzymes should be obtained in most patients, but especially in those with upper abdominal pain, jaundice, or vomiting. An elevation in aspartate or alanine aminotransferase levels may reflect choledocholithiasis with acute biliary obstruction (Chapter 141), acute gallstone pancreatitis (Chapter 130), or a hepatocellular process (Chapter 134). Painful jaundice with a significant rise in the alkaline phosphatase level usually reflects cholestasis caused by extrahepatic biliary obstruction (Chapter 141). Amylase and lipase levels are elevated in most patients with acute pancreatitis, but minor amylase elevations also occur with a perforated viscus or mesenteric ischemia (Chapter 129). Urinalysis may demonstrate pyuria, hematuria, or bacteriuria due to ureteral calculi (Chapter 111) or urinary tract infection (Chapter 263).

Imaging

Ultrasound is preferred in suspected pregnancy and to evaluate for other acute gynecologic disorders, such as tubo-ovarian abscess, ruptured corpus luteum cyst, or ovarian torsion; it is also preferred for the initial evaluation of suspected acute cholecystitis (Chapter 141) and ureteral stones with hydronephrosis and for the bedside evaluation of unstable patients. In most other settings, abdominal computed tomography (CT) with oral and intravenous administration of contrast material (when possible) is preferred and can provide

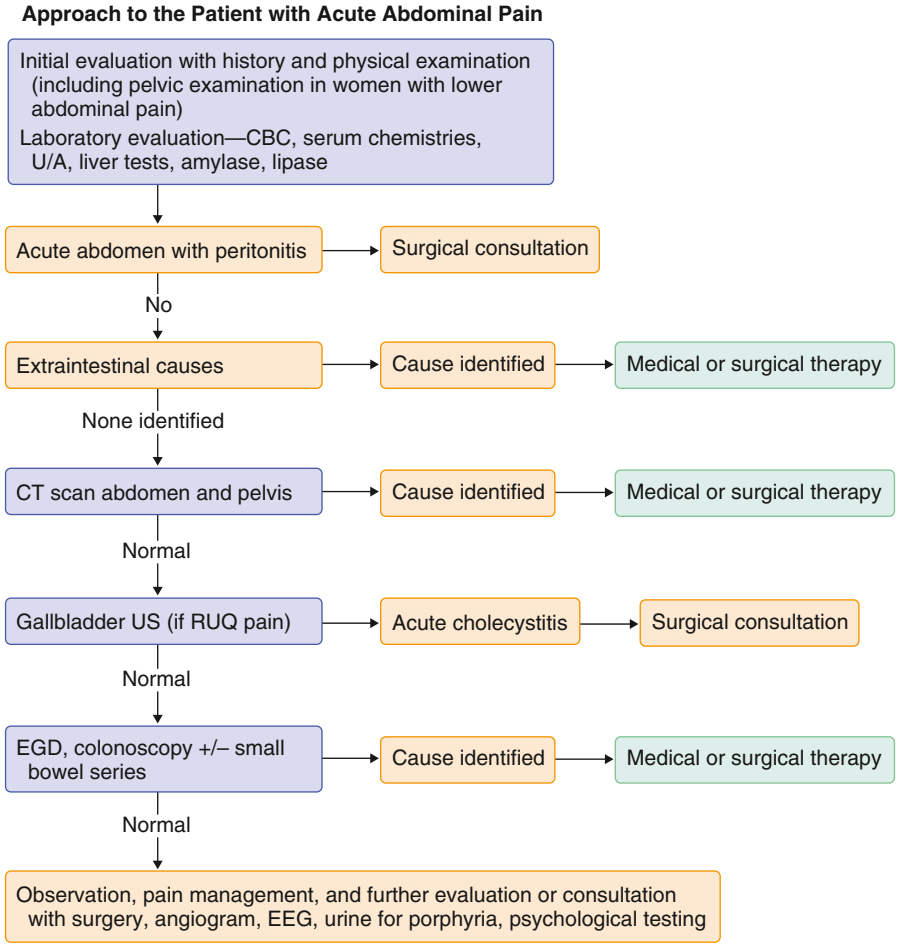

FIGURE 118-2. Approach to the patient with acute abdominal pain. CBC = complete blood count; CT = computed tomography; EEG = electroencephalography; EGD = esophagogastroduodenoscopy; RUQ = right upper quadrant; U/A = urinalysis; US = ultrasonography.

a definitive diagnosis in up to 90% of patients with acute severe abdominal pain[A1] (Chapter 119). Abdominal CT may be falsely negative early in the course of acute pancreatitis, mesenteric ischemia, cholecystitis, appendicitis,[8] and diverticulitis, especially if it is performed without contrast enhancement.

TREATMENT

Once the diagnosis is clear, treatment of the underlying condition is initiated. For uncomplicated acute appendicitis diagnosed by CT scan, antibiotics are an alternative to urgent surgery,[A2] but they are associated with a 25 to 30% rate of readmission or surgery in the next year. As a result, the international consensus is generally for urgent surgery.[9] In patients with diverticulitis, antibiotics are the usual first-line therapy (Chapter 128).[10] In patients with nonspecific acute abdominal pain and no clear diagnosis, early laparoscopy is useful for diagnosis, but outcomes such as complication rates, readmission rates, and length of hospitalization are no better than with a strategy of active observation.

CHRONIC ABDOMINAL PAIN

Chronic or recurrent abdominal pain that has been present for months to years may be caused by structural (organic) disease, but the majority of patients have a functional disorder such as irritable bowel syndrome (Chapter 123). Common organic causes of chronic abdominal pain include medications with GI side effects, peptic ulcer disease (Chapter 125), inflammatory bowel disease (Chapter 127), chronic pancreatitis (Chapter 130), biliary tract disease (Chapter 141), GI cancers (Chapters 178 and 179), and endometriosis (Chapter 218). The clinician should attempt to distinguish patients with symptoms or signs of organic disease, in whom further diagnostic investigation is warranted, from those with probable functional disease (Fig. 118-3). Although functional disorders occur in all age groups, the symptoms usually begin before the age of 40 years. "Alarm" features that suggest a structural disorder and are inconsistent with a functional disorder are fever, severe pain, significant weight loss, jaundice, progressive dysphagia, recurrent vomiting, nocturnal pain or diarrhea, and stools that are bloody or positive for fecal occult blood. Laboratory study findings should be normal with functional disorders; therefore, an unrevealing evaluation for anemia; leukocytosis; and levels of iron, albumin, C-reactive protein, and vitamins A, D, or B_{12} argues against structural or organic disease.

In patients younger than 50 years with a suspected functional disorder and no alarm features (e.g., family history of colon cancer or inflammatory bowel disease or abnormalities on screening blood tests), further testing should be minimized, and the emphasis should be shifted to managing symptoms, coping, and making lifestyle changes (Chapter 123). In patients who may have organic disease, testing often includes a combination of upper GI endoscopy, colonoscopy, and ultrasound or CT imaging.

GAS AND BLOATING

BELCHING

Belching (eructation), which is the involuntary or voluntary release of gas from the esophagus or stomach, commonly occurs during or after a meal. Virtually all belching is caused by swallowed air, which may be increased by eating quickly, drinking carbonated beverages, chewing gum, and smoking. Gas also may be produced within the stomach by antacids, especially sodium bicarbonate, which rapidly neutralize gastric acid and release carbon dioxide. Belching seldom reflects serious GI dysfunction but may be increased in patients with gastroesophageal reflux (Chapter 124), functional dyspepsia (Chapter 123), or gastroparesis (Chapter 122). Chronic, excessive, repetitive supragastric belching is a functional disorder caused by transient ingestion of air into the esophagus (caused by subconscious diaphragmatic contraction and upper esophageal sphincter relaxation) and its subsequent expulsion; it is treated with behavioral modification.

FLATUS

Flatus, or "gas," is a normal byproduct of digestion. Otherwise healthy adults pass flatus 10 to 20 times daily and excrete up to 1500 mL. Thus, it is difficult to distinguish patients with abnormal or excessive gas production from those with only a heightened awareness of or sensitivity to normal production. Increased flatulence with diarrhea may be symptomatic of disorders of malabsorption,

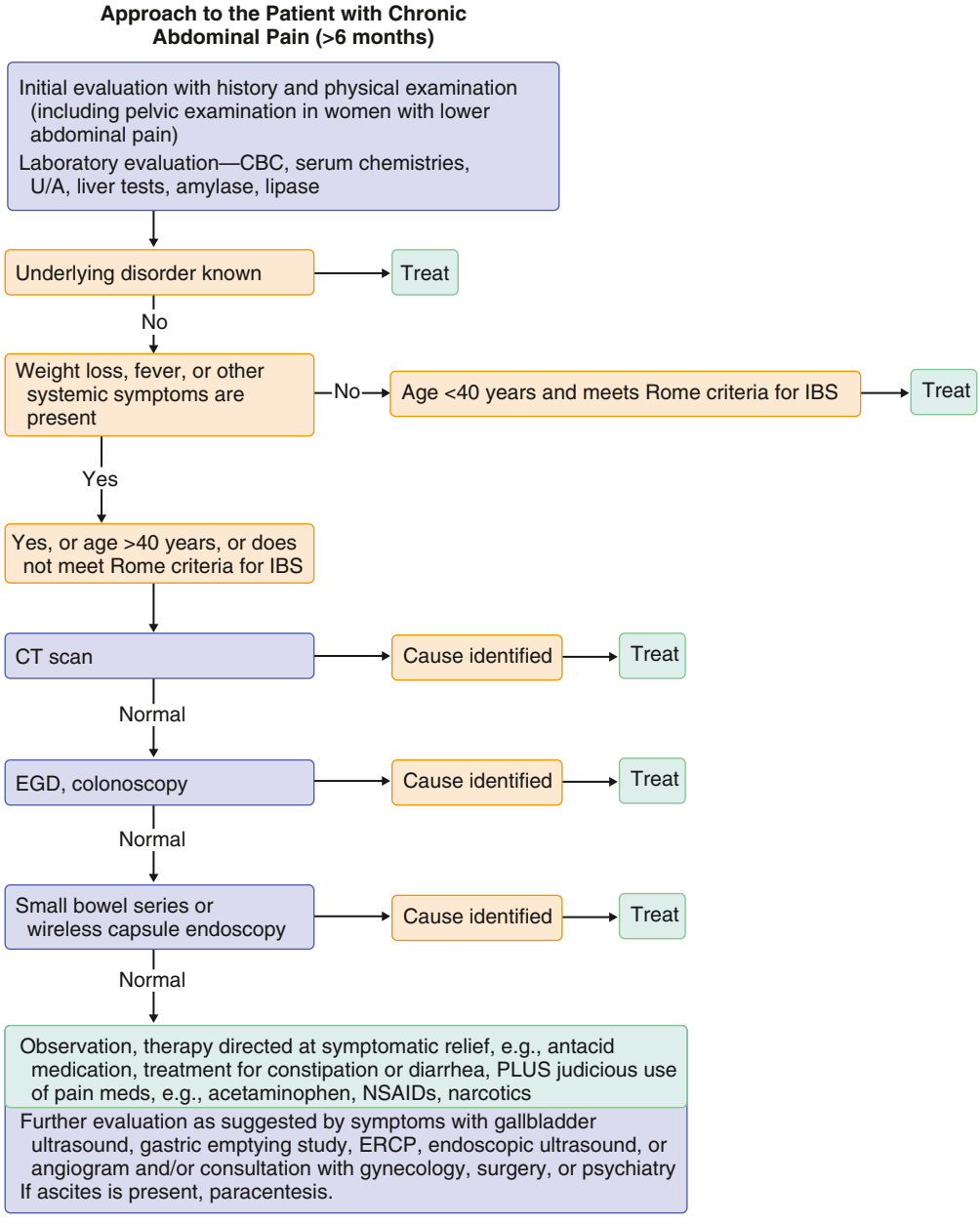

FIGURE 118-3. Approach to the patient with chronic abdominal pain. CBC = complete blood count; CT = computed tomography; EGD = esophagogastroduodenoscopy; ERCP = endoscopic retrograde cholangiopancreatography; IBS = irritable bowel syndrome; NSAIDs = nonsteroidal anti-inflammatory drugs; U/A = urinalysis.

including celiac disease (Chapter 126), pancreatic insufficiency (Chapter 130), and small intestinal bacterial overgrowth (Chapter 126).

In normal adults, flatus is derived from two sources: swallowed air and colonic bacterial fermentation of FODMAPs (fermentable oligosaccharides, disaccharides, and monosaccharides and polyols), which are short-chain carbohydrates that may be incompletely absorbed in the small intestine and result in the colonic production of carbon dioxide or methane. FODMAPs include lactose (dairy products), fructose, fructans, polyols, and galacto-oligosaccharides. Fructose is present in fruit, especially apples and pears, and is a major component of corn syrups that are widely used as sweeteners. Polyols include sorbitol, which is a natural sugar in stone fruit (peaches, apricots, plums, prunes) and a common added sweetener in sugar-free candies, as well as trehalose, which is present in mushrooms. Fructans and oligosaccharides are plentiful in cruciferous vegetables (cabbage, broccoli, cauliflower, Brussels sprouts, turnips, rutabagas), garlic, onions, legumes (beans, soy, lentils, peas), pasta, and whole grains.[11]

BLOATING AND DISTENTION

Bloating and distention are common complaints among patients with functional GI disorders (Chapter 123).[12] As chronic, isolated symptoms, they are almost never caused by serious structural disease. Functional bloating may be caused by heightened sensitivity to minor increases in intestinal gas or impaired transit of gas, even though the total volume of intestinal gas is within normal limits.

The acute onset of distention in conjunction with alarm symptoms such as cramping pain, weight loss, nausea, vomiting, obstipation, or diarrhea warrants further evaluation for disorders that cause intestinal obstruction (Chapter 128) or malabsorption (Chapter 126).

TREATMENT

Patients with long-standing flatulence in the absence of other symptoms or signs of GI disease can be treated conservatively. Avoidance of carbonated beverages, chewing gum, sorbitol- and fructose-containing sweeteners, and gas-producing vegetables improves symptoms in most patients.[A3] Lactase deficiency may be confirmed by a lactose breath test. Underlying GI illness is suggested by the recent onset of flatulence with other symptoms of organic disease, including weight loss, abdominal pain, diarrhea, distention, and abnormal laboratory studies (Chapter 126). A positive fecal fat analysis confirms malabsorption and merits further investigation (see Table 126-6). Suspected small bowel bacterial overgrowth may be confirmed by carbohydrate breath tests[A4] or treated empirically with antibiotics.

Rifaximin (550 mg three times daily for 2 weeks) is effective for functional bloating, pain and loose or watery stool, but dietary and behavioral changes and reassurance may also be useful.[A5] Although some clinical studies suggest benefit with probiotics, the overall data are inconclusive.[13] In one randomized trial of patients with irritable bowel syndrome with predominant bloating, fecal transplantation improved bloating, pain, and flatulence.[A6]

INVOLUNTARY WEIGHT LOSS

The unintentional loss of more than 5% of baseline weight within a 12-month period is frequently due to a serious underlying medical or psychiatric illness.[14] Weight loss is seldom the sole presenting sign of medical disorders, but it is often revealed during the clinical evaluation of other complaints. Chronic weight loss in the elderly is commonly caused by depression; dementia; difficulty with chewing or swallowing; malignant disease; medications; alcoholism; or physical and social limitations to procuring, preparing, and eating meals (Table 118-4) (Chapter 23). Gradual, mild weight loss occurs in some elderly patients because of the loss of lean body mass. In young patients, weight loss is more commonly caused by eating disorders (Chapter 200), endocrine disorders (Chapters 207 and 208), or chronic GI conditions such

TABLE 118-4 CAUSES OF INVOLUNTARY WEIGHT LOSS

CONDITION	QUALITY	DURATION	AGGRAVATING OR RELIEVING FACTORS	ASSOCIATED SYMPTOMS OR SIGNS	DIAGNOSTIC STUDIES
WEIGHT LOSS SECONDARY TO GASTROINTESTINAL CAUSES					
GI, pancreatic, or hepatobiliary malignant disease (Chapters 178-181)	Progressive, fast	Months	Better with cancer therapy (e.g., surgery, XRT, chemotherapy)	Dysphagia (esophageal); anorexia, nausea, vomiting (gastric, small or large bowel obstruction); visible or occult blood in stool; altered bowel habits; jaundice or hepatomegaly (biliary obstruction, hepatic tumor, metastatic disease); iron deficiency anemia	CBC, FOBT, ferritin, CEA, CA19-9, AFP, EGD, colonoscopy, abdominal CT, PET
Malabsorption (Chapter 126) (poor absorption of nutrients due to pancreatic insufficiency, small intestinal mucosal disorders, or bacterial overgrowth)	Progressive, slow	Months to years	Diarrhea or steatorrhea, excessive flatulence; worse with eating and resolves with NPO status	Usually associated with increased appetite; may have anemia (iron, B_{12}, folate), osteoporosis, or osteomalacia (vitamin D, calcium, phosphorus); easy bruising (vitamin K), night blindness (vitamin A)	Stool for fecal fat (qualitative or quantitative); fecal elastase; vitamins A and D and INR; calcium, ferritin, B_{12}, albumin; celiac disease antibodies (e.g., IgA anti-tTG, or antiendomysial antibodies, IgG deamidated gliadin peptide); EGD with small bowel biopsy; breath test for bacterial overgrowth
Inflammatory bowel disease (especially Crohn disease) (Chapter 127)	Progressive, slow	Months	Eating causes pain, cramps, increased diarrhea and urgency; improved by low-residue diet or NPO status	Bloody stools, abdominal cramps and pain, perianal disease, extraintestinal manifestations (e.g., oral ulcers, uveitis, erythema nodosum, arthralgias)	CBC, albumin, ESR, CRP, fecal calprotectin, colonoscopy with biopsies, CT or MR enterography, wireless capsule study
GI motility disorders (Chapter 122)	Intermittent, slow	Years	Worse with eating	Nausea, vomiting, distention, diarrhea, or constipation may be present	EGD and colonoscopy, gastric emptying study, CT or MR enterography, surgical full-thickness intestinal biopsies
Cirrhosis (Chapter 139)	Muscle wasting with edema, so weight may increase	Months to years	Worse with salt or fluid intake	Ascites, peripheral edema	Liver biopsy
Chronic intestinal ischemia (Chapter 129)	Progressive	Months to years	Worse with eating	Afraid to eat; postprandial abdominal pain, nausea; associated atherosclerotic disease	CT or MR angiography
WEIGHT LOSS SECONDARY TO NONGASTROINTESTINAL CAUSES					
Poor or inadequate calorie intake due to social factors (Chapter 197)	Intermittent or progressive, acute (hospitalized) or chronic	Days to months to years	Common in elderly, teenagers; exacerbated by poor dentition or poorly fitting dentures	Will eat if food is made available	Review dietary log and how food is obtained and prepared
Medications	Intermittent or progressive	Months	Worse with medication; resolves with discontinuation of offending drug	Anorexia, nausea, vomiting	Review alcohol, recreational drugs, and prescription medications (stimulants, antidepressants, metformin, glucagon-like peptide-1 analogs, dopamine, anticholinergics, cardiovascular agents)
Non-GI malignant disease	Progressive	Months	Better with cancer therapy (e.g., surgery, XRT, chemotherapy)	Anorexia, nausea, vomiting; pain; metastatic disease	Calcium, cortisol; CT for underlying disease, PET
Endocrine disorders: DM, hyperthyroidism, adrenal insufficiency (Chapters 207, 208,and 210)	DM—appetite increased or decreased, early satiety; hyperthyroidism—increased appetite	Months to years	Worse with disease chronicity	DM: gastroparesis, neuropathy, retinopathy, nephropathy Adrenal insufficiency: nausea, vomiting, diarrhea, abdominal pain	Serum glucose, Hgb A_{1c}, TFT, cortisol

TABLE 118-4 CAUSES OF INVOLUNTARY WEIGHT LOSS—cont'd

CONDITION	QUALITY	DURATION	AGGRAVATING OR RELIEVING FACTORS	ASSOCIATED SYMPTOMS OR SIGNS	DIAGNOSTIC STUDIES
Chronic infections, including HIV and TB (Chapters 299 and 359)	Progressive, fast	Months	Better with directed therapy, megestrol acetate (Megace)	Nausea, anorexia, other infections	HIV test, PPD, cultures, biopsies if necessary
Systemic inflammatory disorders	Progressive, moderate	Months to years	Better with directed therapy, megestrol acetate (Megace)	Arthritis, rash, vasculitis	ANA, RF, ESR, CRP
Chronic renal failure (Chapter 116)	Progressive, slow; edema may increase weight	Months to years	Better with dialysis, megestrol acetate (Megace)	Nausea, anorexia, weight gain	BUN, Cr, 24-hr creatinine clearance
Advanced COPD or heart failure (Chapters 45 and 76)	Progressive, slow	Months to years	Better with oxygen and specific treatment	Fatigue, dyspnea, edema, wasting	Pulmonary function testing or two-dimensional echocardiography
Psychiatric illness: depression, manic-depressive illness (Chapter 362)	Progressive, slow	Months to years	Depression common in elderly; flat affect; manic phase associated with hyperactivity and decreased intake	Psychological testing	
Psychogenic eating disorders—anorexia nervosa, bulimia (Chapter 200)	Intermittent or progressive	Months to years	Worse with stressors	Refusal to eat, loss of tooth enamel, calluses and healing ulcerations of hand	Psychiatric testing
Substance abuse (alcohol, opiates, CNS stimulants)	Intermittent or progressive	Months	Resolves with discontinuation	Anorexia, nausea, vomiting	Careful interview; patients may deny or minimize

AFP = α-fetoprotein; ANA = antinuclear antibody; BUN = blood urea nitrogen; CBC = complete blood count; CEA = carcinoembryonic antigen; CNS = central nervous system; COPD = chronic obstructive pulmonary disease; Cr = creatinine; CRP = C-reactive protein; CT = computed tomography; DM = diabetes mellitus; EGD = esophagogastroduodenoscopy; ESR = erythrocyte sedimentation rate; FOBT = fecal occult blood test; GI = gastrointestinal; Hgb = hemoglobin; HIV = human immunodeficiency virus; INR = international normalized ratio; MR = magnetic resonance; NPO = nothing orally; PET = positron emission tomography; PPD = purified protein derivative; RF = rheumatoid factor; TB = tuberculosis; TFT = thyroid function test; tTG = tissue transglutaminase; XRT = x-ray therapy.
Modified from Proctor DD. Approach to the patient with gastrointestinal disease. In: Goldman L, Ausiello D, eds. *Cecil Textbook of Medicine,* 23rd ed. Philadelphia: Saunders-Elsevier; 2008.

as inflammatory bowel disease (Chapter 127) or celiac disease (Chapter 126). In chronic medical conditions, involuntary weight loss is usually caused by a combination of decreased appetite (anorexia) and varying degrees of cachexia; examples include advanced malignant disease, chronic infections (human immunodeficiency virus [HIV], tuberculosis), heart failure, chronic kidney or liver disease, end-stage lung disease, and adrenal insufficiency. Weight loss that occurs in the presence of normal or increased appetite suggests increased metabolism and energy expenditure caused by endocrine disorders, such as poorly controlled diabetes (Chapter 210) or hyperthyroidism (Chapter 207), or GI disorders that result in food malabsorption (Chapter 126). Chronic GI disorders that cause progressive narrowing or obstruction of the esophagus (cancer, achalasia), stomach (cancer, peptic ulcer disease with gastric outlet obstruction), small intestine (Crohn disease), or arterial circulation (chronic mesenteric ischemia) may cause weight loss as a result of dysphagia, vomiting, or postprandial pain that limits the ability to ingest sufficient calories.

DIAGNOSIS

The cause of weight loss (see Table 118-4) is usually evident from the history, physical examination, and routine laboratory studies, including complete blood count, electrolytes, liver chemistries, thyroid-stimulating hormone, urinalysis, and, when appropriate, HIV serology (Fig. 118-4). A chest radiograph should be obtained in patients who smoke, have any respiratory symptoms, or are older than 40 years. In one large study, patients with involuntary weight loss had a two- to three-fold increased risk of a new cancer diagnosis within the next 2 years, but the absolute rate of such a diagnosis was only 2.2%.[15]

Signs of dehydration or severe malnutrition may require an assessment for nutritional deficiencies (Chapter 197) and nutritional support (Chapter 198). Other symptoms and signs necessitate consideration of additional diagnostic testing. Weight loss with increased appetite merits an assessment of thyroid function (Chapter 207), glucose intolerance (Chapter 210), and malabsorption (Chapter 126). Suspected malabsorption may be confirmed by a positive fecal fat analysis. GI symptoms suggesting obstruction or occult GI malignant disease can be evaluated with upper GI endoscopy, upper GI radiographic series, colonoscopy, or abdominal CT. Psychiatric evaluation may be warranted in patients with signs of depression, early dementia, or eating disorders. In up to 25% of patients, no cause of weight loss is found.[16]

NAUSEA AND VOMITING

Nausea is an unpleasant feeling of the impending need to vomit. *Vomiting* is the forceful oral expulsion of gastric contents as a result of retrograde contraction of the duodenum and antrum with compression of the thoracoabdominal musculature. Nausea and vomiting may be caused by a number of GI and non-GI disorders, but they are best categorized according to chronicity and the presence of abdominal pain. The acute onset of vomiting *with* severe abdominal pain suggests a serious illness potentially requiring surgical intervention, including GI obstruction (Chapter 128), mesenteric ischemia (Chapter 129), pancreatitis (Chapter 130), biliary colic (Chapter 141), and conditions causing peritonitis (Chapter 128), such as appendicitis or a perforated viscus. Acute vomiting *without* abdominal pain is most commonly caused by pregnancy (Chapter 221), myocardial infarction (Chapter 58), medications (including chemotherapy), migraine headache (Chapter 367), food poisoning (Chapter 262), infectious gastroenteritis (Chapter 262), hepatitis (Chapters 134 and 135), upper GI bleeding, postoperative ileus, motion sickness (Chapter 396), vestibular neuritis (Chapter 396), or acute central nervous system disease. Gastrointestinal symptoms (nausea, vomiting, or watery diarrhea) are present in up to 10% of patients who are infected with severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2; Chapter 336) and may precede respiratory symptoms. Chronic or recurrent nausea and vomiting *with* abdominal pain are commonly caused by GI disorders that result in the partial or intermittent obstruction of the stomach or small intestine and conditions that result in chronic intestinal pseudo-obstruction (Chapter 122). Chronic nausea and vomiting *without* abdominal pain may be due to disorders that impair gastric emptying or small intestine motility and non-GI causes, including medications, cannabinoids,[17] pregnancy, intracerebral disorders, cardiac disease, endocrine disease, labyrinth disorders, psychiatric disease (including bulimia), gastroparesis, cyclical vomiting syndrome, and functional disorders. Vomiting of undigested food eaten hours earlier suggests gastric obstruction or gastroparesis. Abdominal distention or feculent emesis suggests obstruction of the small intestine.

DIAGNOSIS

Most cases of acute vomiting without abdominal pain are self-limited and require no evaluation (Fig. 118-5). Medication-related symptoms and pregnancy should be excluded. With severe vomiting, serum electrolyte values

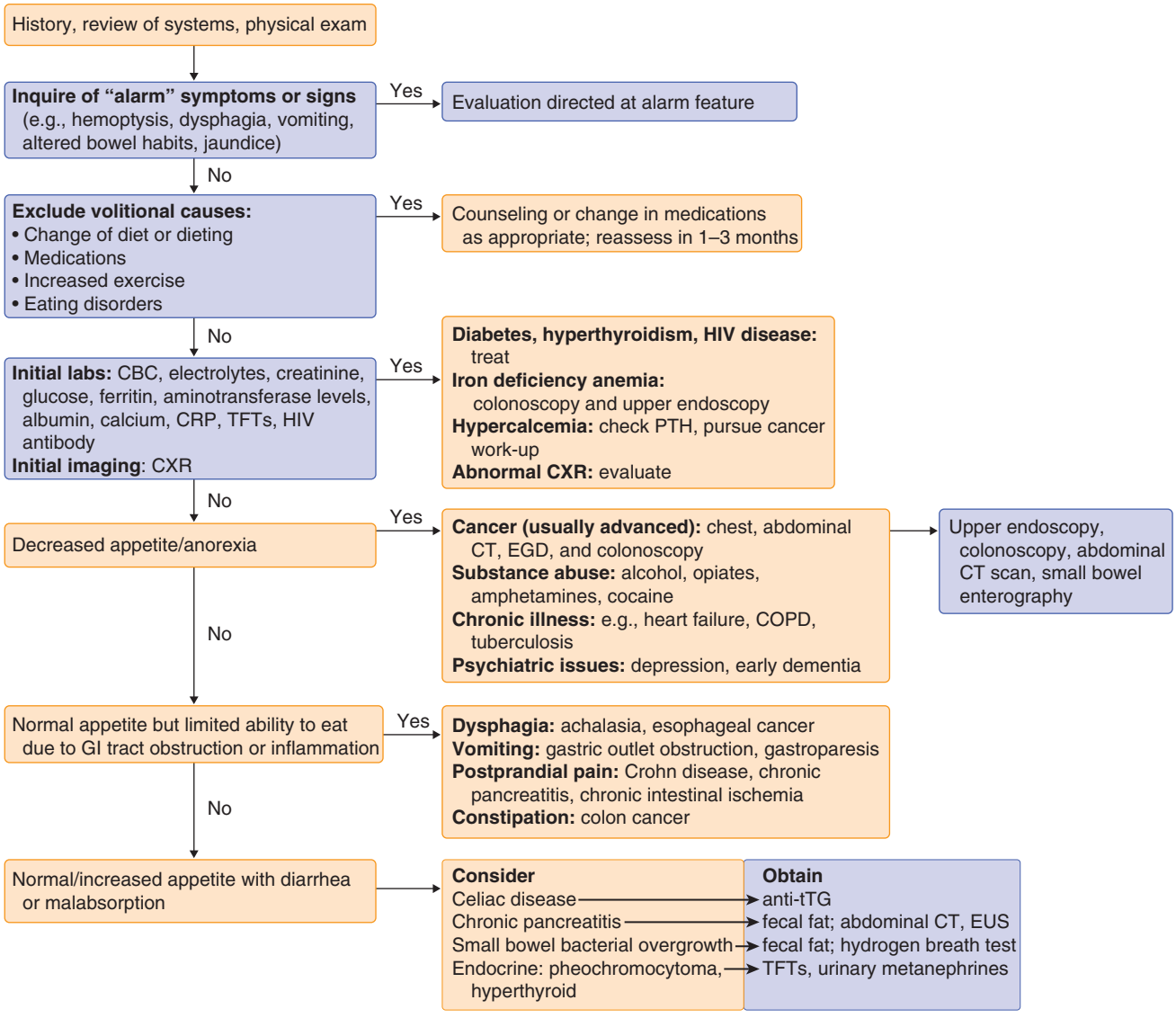

FIGURE 118-4. **Approach to the patient with unintentional weight loss of more than 5%.** CBC = complete blood count; COPD = chronic obstructive pulmonary disease; CRP = C-reactive protein; CT = computed tomography; CXR = chest radiograph; EGD = esophagogastroduodenoscopy; EUS = endoscopic ultrasound; GI = gastrointestinal; HIV = human immunodeficiency virus; PTH = parathyroid hormone; TFTs = thyroid function tests; tTG = tissue transglutaminase.

should be obtained. Hyperglycemia may cause acute gastroparesis. Increased liver chemistries or pancreatic enzymes suggest hepatobiliary or pancreatic disease. In patients with acute abdominal pain and vomiting, abdominal plain radiography or CT is performed to look for evidence of GI obstruction, a perforated viscus, or pancreaticobiliary disease. In patients with chronic vomiting of uncertain cause, the goal is to distinguish structural GI disorders, GI motility disorders, and non-GI disorders. Esophagogastroduodenoscopy, enterography, abdominal cross-sectional imaging, GI motility studies, and head CT or magnetic resonance imaging may be indicated.

TREATMENT

The approach to the medical treatment of nausea and vomiting depends on the cause (Table 118-5). Patients who are receiving moderately emetogenic chemotherapy are frequently managed with a 5-HT_3 receptor antagonist[18] and dexamethasone; a neurokinin-1 receptor antagonist[19] or olanzapine[A7] can be added for highly emetogenic regimens.[20] For patients with mildly emetogenic regimens or vomiting from other causes, treatment with single or combinations of anticholinergic agents, dopamine receptor antagonists, 5-HT_3 receptor antagonists,[A8] or cannabinoids[A9] usually provide symptomatic relief.[21] For refractory vomiting due to gastroparesis, gastric electrical stimulation[A10] or peroral endoscopic pyloromyotomy[22] may be considered.

CONSTIPTION

Constipation (Chapter 122), which is the most common digestive symptom, occurs in 15% of the population. Constipation may refer to fewer than three bowel movements per week; hard or lumpy stools; or difficulty during defecation, characterized by straining, a sensation of obstruction or incomplete evacuation, or the need to engage in manual manipulations to promote evacuation. Constipation may be caused by systemic conditions that slow colonic transit, including neuromuscular disease, endocrine disorders, and electrolyte abnormalities, or by lesions that obstruct the passage of stool through the distal colon or anorectum, such as neoplasms, strictures, prolapse, and aganglionosis (Hirschsprung disease).[23] Opioid-induced constipation is increasingly common owing to the opioid epidemic.

TREATMENT

Most patients do not have an apparent cause and are deemed to have chronic idiopathic constipation owing to colonic inertia, dyssynergic defecation, or functional disorders (e.g., irritable bowel syndrome). Most patients can be successfully treated with adequate fluids, fiber supplements, osmotic agents (polyethylene glycol), and/or nonprescription stimulant laxatives (e.g., once-daily bisacodyl, 5 to 10 mg, or senna, 17.6 to 34.4 mg).[A11] Management of chronic refractory constipation may require linaclotide (72 to 290 μg daily), plecanatide (3 mg daily), lubiprostone (24 μg twice daily), or prucalopride (1 to 2 mg daily; see Table 122-3), whereas patients with dyssynergia may respond to biofeedback.[24] For opioid-induced constipation, a combination of an osmotic and stimulant laxative is recommended as initial treatment. Patients who have an inadequate response may benefit from the addition of a peripherally acting μ-opioid receptor antagonist (e.g., naloxone, naloxegol, or naldemedine) or the serotonin-4 receptor agonist prucalopride (1 to 2 mg daily; Table 122-3).[A12]

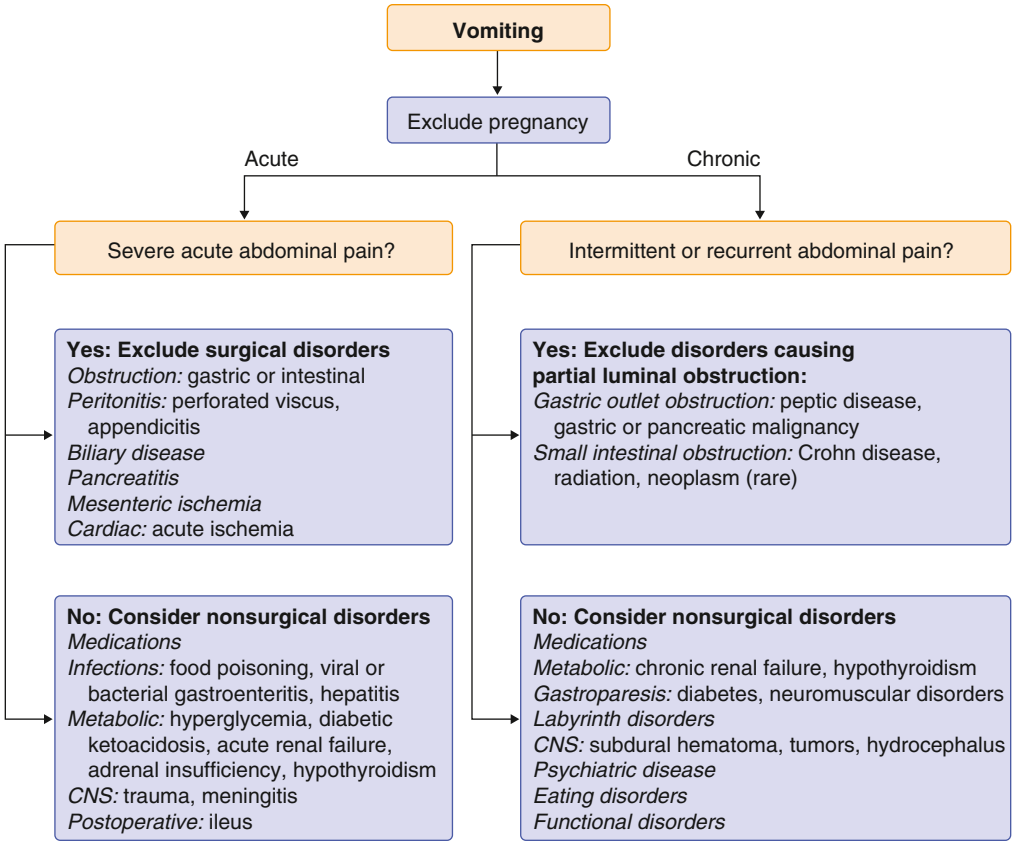

FIGURE 118-5. Approach to the patient with vomiting. CNS = central nervous system.

TABLE 118-5 MEDICAL TREATMENT OF NAUSEA AND VOMITING

DRUG	USUAL INDICATIONS	USUAL DOSE (RANGE)	ROUTE	COMMENTS
ANTICHOLINERGIC-ANTIHISTAMINE AGENTS	Most commonly: GIDz, motion sickness, vertigo			Side effects: sedation, dizziness, delirium, blurred vision, glaucoma, bronchospasm, tachycardia, urinary retention Avoid concomitant alcohol or CNS depressants; use with caution in elderly patients
Scopolamine patch	MS	1.5 mg/72 hr	Patch	
Dimenhydrinate	MS	50 mg (50-100 mg) q4-6h	PO, IM, IV	Maximum 400 mg/24 hr
Cyclizine	MS, GIDz	50 mg q8h	PO, IM	Maximum 200 mg/24 hr
Meclizine	MS, V	25-50 mg q24h	PO	
Diphenhydramine	GIDz	25-50 mg q6h 50-100 mg q6h	PO, IV IM	
Promethazine	GIDz, PONV, MS	25 mg (12.5-25 mg) q6-12h 25 mg (12.5-50 mg) q4-6h	PO, PR IV, IM	Phenothiazine derivative, but lacks significant antidopaminergic effects Avoid perivascular extravasation or subcutaneous injection(severe tissue necrosis)
Trimethobenzamide	GIDz, PONV	200 mg q6-8h	IM	
DOPAMINE RECEPTOR ANTAGONISTS	Most commonly: acute, nonsurgical gastrointestinal disorders (viral gastroenteritis), PONV, CTX			Side effects: neuromuscular (extrapyramidal) symptoms—agitation, restlessness, involuntary movements, dystonia, torticollis, laryngospasm, Parkinson-like features
Prochlorperazine	GIDz, PONV, CTX with low-emetic risk	5-10 mg q6-8h 25 mg q12h	PO, IV, IM PR	Maximum dose 20-40 mg/24 hr; avoid subcutaneous injection (irritation)
Metoclopramide	GIDz Mildly emetogenic CTX	10 mg (10-20 mg) q6-8h 1-2 mg/kg before and 2 hr after CTX	PO, IV, IM IV	Modest efficacy at these doses High doses infrequently used owing to availability of safer, more effective CTX regimens; use with diphenhydramine to reduce adverse side effects
Droperidol	PONV	2.5 mg (1.25-5 mg) preinduction and q4-6h as needed	IV, IM	May cause QTc prolongation and torsades de pointes; use is restricted to patients who fail to respond to other agents

TABLE 118-5 MEDICAL TREATMENT OF NAUSEA AND VOMITING—cont'd

DRUG	USUAL INDICATIONS	USUAL DOSE (RANGE)	ROUTE	COMMENTS
Olanzapine	Highly emetogenic CTX: used in combination with 2-3 other antiemetic agents	10 mg q24h on days 1-4	PO	Antipsychotic that blocks dopamine D2 and serotonin 5HT-2 receptors; side effects include sedation and hyperglycemia
CORTICOSTEROIDS				
Dexamethasone	PONV CTX	4-8 mg once preinduction 8-20 mg on day 1; 8 mg on days 2-4	PO, IV PO, IV	Most beneficial when used with other agents (e.g., 5-HT_3 RA, neurokinin-1 RA)
BENZODIAZEPINES				Used to reduce anxiety and anticipatory vomiting
Lorazepam	CTX	1-2 mg q4-6h	PO, IV	
CANNABINOIDS				May stimulate appetite; adverse side effects (sedation, dizziness, dysphoria, dry mouth) limit use
Dronabinol	GIDz, CTX	5-10 mg q6-8h	PO	
Nabilone	GIDz, CTX	1-2 mg q12h	PO	
5-HT_3 RECEPTOR ANTAGONISTS	PONV, CTX			All except palonosetron may cause QTc prolongation (dose-dependent) with risk of cardiac arrhythmias PONV prevention: give IV immediately before anesthesia induction Prevention of CTX-induced vomiting: give single dose 30 min (IV) to 1 hr (PO) before CTX
Ondansetron	PONV CTX, RadTx	4 mg once 4-8 mg 8 mg once	IV PO IV	
Granisetron	CTX, RadTx	1 mg twice daily 1 mg once	PO IV	
Dolasetron	CTX, PONV	100 mg once daily	PO only	
Palonosetron	CTX PONV	0.25 mg once 0.5 mg 0.075 mg	IV PO, 1-3 days IV	Second generation antagonist with higher affinity for 5-HT3 receptors and longer half-life; does not cause QTc prolongation
NEUROKININ-1 RECEPTOR ANTAGONISTS	Highly emetogenic CTX			Used exclusively in combination with a 5-HT_3 RA or dexamethasone
Aprepitant		125 mg on day 1; 80 mg on days 2-3	PO	
Rolapitant		180 mg 1-2 hr before CTX	PO	
Fosaprepitant		150 mg on day 1	IV	Aprepitant 80 mg PO on days 2-3
Netupitant 300 mg/palonosetron 0.5 mg combination		1 capsule 1 hr before CTX	PO	
ANTIEMETIC REGIMENS FOR CHEMOTHERAPY				
Mildly emetogenic CTX	Option 1 Option 2 Option 3	Dexamethasone 8 mg Dopamine receptor antagonist 5-HT_3 RA	IV or PO	One dose only One dose only One dose only
Moderately emetogenic CTX		Day 1: 5-HT_3 RA plus dexamethasone 8 mg with or without neurokinin-1 RA	IV or PO	Days 2-3: continue oral 5-HT_3 RA and/or dexamethasone 8 mg to reduce delayed emesis
Highly emetogenic CTX		Day 1: 5-HT_3 RA plus dexamethasone 12 mg plus neurokinin-1 RA plus olanzapine	IV or PO	Days 2-4: olanzapine and dexamethasone 8 mg PO daily; if aprepitant given on day 1, continue 80 mg PO days 2-4. Regimens may vary.

5-HT_3 = serotonin or 5-hydroxytryptamine$_3$; CNS = central nervous system; CTX = chemotherapy; GIDz = acute, nonsurgical gastrointestinal disorders associated with nausea and vomiting (e.g., viral gastroenteritis); IM = intramuscularly; IV = intravenously; MS = motion sickness; PO = orally; PONV = postoperative nausea and vomiting; PR = per rectum; RA = receptor antagonist; RadTx = radiation therapy–induced nausea and vomiting; V = vertigo.

Modified from Proctor DD. Approach to the patient with gastrointestinal disease. In: Goldman L, Ausiello D, eds. *Cecil Textbook of Medicine*, 23rd ed. Philadelphia: Saunders-Elsevier; 2008.

GASTROINTESTINAL BLEEDING

GI bleeding (Chapter 121) may be acute and clinically apparent (overt) or chronic, slow, and clinically inapparent (occult). The location of acute GI bleeding is described as either upper or lower, according to whether the source is proximal or distal to the ligament of Treitz (distal duodenum). Upper GI bleeding, which is three times more common than lower GI bleeding, is manifested by bloody emesis (hematemesis), coffee ground emesis, and, in most cases, black stools (melena). Common causes of significant bleeding are peptic ulcer disease, esophageal varices, Mallory-Weiss tears, erosive gastritis or esophagitis, and vascular ectasias.[25] Major lower GI bleeding is manifested by large-volume maroon or bright red bloody stools (hematochezia). Although 80 to 90% of patients with hematochezia have a lower source of bleeding, massive upper GI bleeding also may cause hematochezia. Approximately 95% of major lower GI bleeding arises from the colon and 5% from the small intestine. Lower GI bleeding is increased in patients older than

50 years, in whom diverticulosis accounts for 60% of cases; the remainder are due to ischemia, neoplasms, ulcers, vascular ectasias, or hemorrhoids. In patients younger than 50 years, bleeding is more commonly attributable to inflammatory bowel disease, hemorrhoids, or infectious colitis, but the incidence of colonic neoplasia is increasing in patients ages 40 to 50 years.[26]

Occult GI bleeding refers to GI blood loss that is small in volume and not apparent to the patient but is detectable by tests for fecal occult blood. Chronic occult bleeding may result in iron deficiency anemia.[27] Both upper endoscopy and colonoscopy should be performed to look for a source of occult bleeding, most commonly gastroesophageal or colonic neoplasia, erosive esophagitis or gastritis, ulcer disease, or vascular ectasia. In patients with recurrent iron deficiency and occult blood loss in whom no source is found on upper and lower endoscopy, video capsule endoscopy, CT enterography, or enteroscopy is performed to look for a small bowel source (vascular ectasia, ulcer, or neoplasm)

FECAL INCONTINENCE

Fecal incontinence (Chapter 131) is dependent on a number of factors, including a solid or semisolid stool, a compliant and distensible rectal reservoir, the ability to sense rectal fullness, an intact internal anal sphincter (an involuntary muscle innervated by the enteric nervous system), an intact external anal sphincter and puborectalis (voluntary muscles innervated by the pudendal nerve), and the mental and physical ability to reach a toilet facility when needed.[28] Minor incontinence, which occurs in 10% of people older than 70 years, is characterized by the inability to control flatus or by the seepage of fecal matter that results in soiling of the perianal area and undergarments. It tends to be intermittent, occurring after bowel movements; when coughing, lifting, or passing flatus; or when stools are loose. Major incontinence is characterized by the partial or complete inability to control bowel movements reliably, resulting in gross, involuntary loss of feces and the need to wear a diaper. It occurs in less than 1% of the population and is virtually always caused by a central nervous system disorder that results in diminished awareness of bowel needs, neuropathy, or damage to the anal sphincters.

OTHER GASTROINTESTINAL COMPLAINTS

Heartburn, esophageal regurgitation, dysphagia,[29] odynophagia, and noncardiac chest pain suggest esophageal disease (Chapter 124). *Dyspepsia*, which refers to bothersome, intermittent, mild to moderate upper abdominal or epigastric symptoms (burning, pain, early satiation, postprandial fullness) can be caused by peptic ulcer disease (Chapter 125) or esophageal disease (Chapter 124), or it can be functional in origin (Chapter 123).[30] An orderly diagnostic approach (Fig. 118-6) can help distinguish among the various causes, avoid unnecessary testing, and minimize symptoms.

Diarrhea, which is defined pathophysiologically as an increase in stool weight to more than 200 g/day, can be caused by malabsorption of osmotically active substances or by increased intestinal secretion of electrolytes and water. In clinical practice, however, stool weight is seldom quantified, and the term *diarrhea* refers to an increase in stool liquidity or frequency (more than three bowel movements per day). Acute and chronic diarrhea (Chapter 126) should be distinguished because the evaluation and treatment are different. In young adults with chronic diarrhea, the leading causes are irritable bowel syndrome (Chapter 123), inflammatory bowel disease (Chapter 127), microscopic colitis (Chapter 126), bile acid diarrhea,[31] malabsorption, drugs, food additives, and diabetes (Chapter 210).

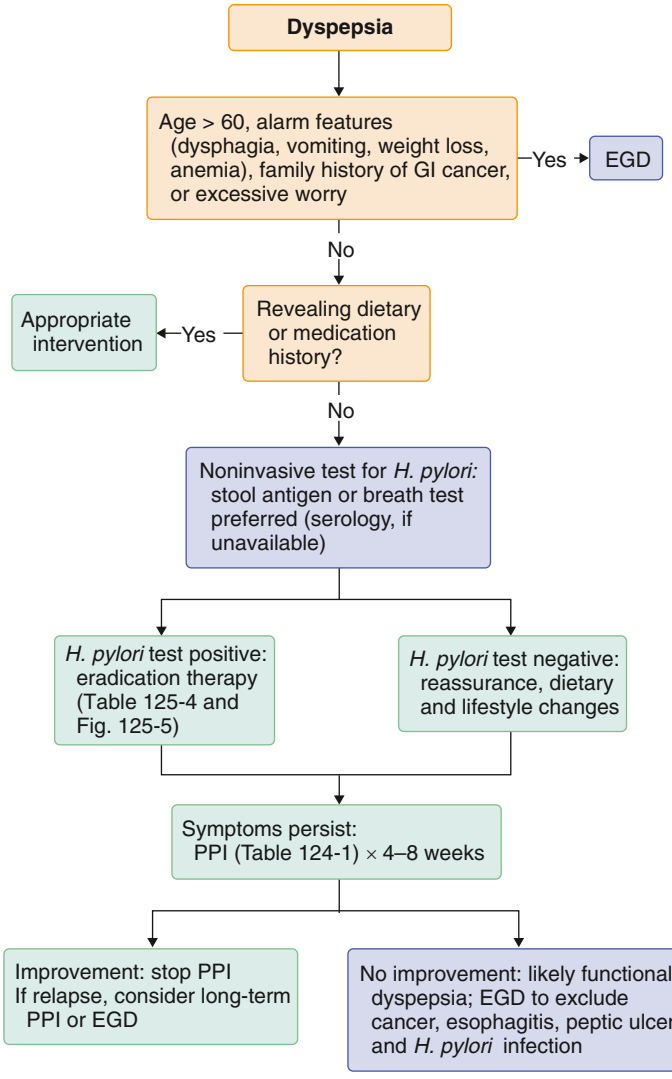

FIGURE 118-6. Approach to the patient with dyspepsia. EGD = esophagogastroduodenoscopy; GI = gastrointestinal; PPI = proton pump inhibitor.

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119 DIAGNOSTIC IMAGING PROCEDURES IN GASTROENTEROLOGY

LAURA R. CARUCCI

A variety of imaging procedures may be performed to evaluate the gastrointestinal (GI) tract and hepatobiliary system for a spectrum of symptoms, including abdominal pain (Chapter 118), nausea (Chapter 118), vomiting, heartburn (Chapter 123), diarrhea (Chapter 126), constipation (Chapter 122), bloating, GI bleeding (Chapter 121), weight loss (Chapter 118), or abnormal laboratory test results. Imaging modalities utilized for these procedures include radiography, fluoroscopy, ultrasound, computed tomography (CT), magnetic resonance imaging (MRI), and nuclear medicine. Each modality provides varying utility with advantages and disadvantages.[1,2] In addition, these modalities offer advanced techniques for GI and hepatobiliary imaging, including CT and MR enterography, CT colonography (virtual colonoscopy), MR cholangiopancreatography (MRCP), MR elastography, CT and MR angiography, and positron emission tomography (PET)/CT.

RADIOGRAPHIC PLAIN FILMS

Radiography provides quick, low-cost, readily available, and portable evaluation of the abdomen and pelvis. Abdominal radiographs may be ordered to evaluate acute abdominal pain and to assess for obstruction, ileus, perforation, post-surgical changes, tubes, and catheters. Different tissue types absorb a varying amount of the radiation beam. Bone absorbs more of the beam and will appear white, whereas gas will transmit more of the beam to the detector and appear black. Radiographs therefore can be utilized to evaluate the bowel gas pattern, calcifications, radiopaque foreign bodies, and the osseous structures, and they may also provide some information about the soft tissues. Although radiography is a readily available first-line modality, abdominal radiographs are less sensitive and specific than CT for many processes involving the abdomen and pelvis, and CT can provide much more detailed information on the overall extent and severity of disease processes.

Abdominal radiographs show the distribution of bowel gas and caliber of bowel. A combination of supine and upright or decubitus radiographs is preferred over supine imaging alone and can provide more detail about potential bowel obstruction or extraluminal air. The pattern of bowel gas and air-fluid levels can help distinguish between entities such as small bowel obstruction (Fig. 119-1), colonic obstruction, volvulus, or ileus. In addition to bowel gas, radiographs may reveal gas in atypical or unexpected locations, including pneumoperitoneum (Fig. 119-2), pneumatosis (Fig. 119-3), pneumobilia, portal venous gas, retroperitoneal gas, subcutaneous emphysema, gas in an abscess, or gas in the gallbladder.

Pneumoperitoneum may be recognized on supine radiographs by the appearance of gas on both sides of the bowel wall (Rigler sign); linear, angulated, or triangular areas of lucency; gas in the most non-dependent portion of the abdomen in the midline, under the central tendon of the diaphragm; or outlining spaces and structures such as the falciform ligament (see Fig. 119-2). An upright or decubitus radiograph increases the sensitivity for detecting free air. With optimal patient positioning and technique, as little as 1 to 2 mL of free air can been seen on abdominal radiography. However, pneumoperitoneum may be identified in only 50% of patients with documented visceral perforation because of technical limitations, including poor image quality, suboptimal field of view, and exclusion of the uppermost peritoneal cavity on the image. CT is the most accurate and sensitive diagnostic modality for detecting pneumoperitoneum.

Abdominal radiographs are also useful to evaluate radiopaque foci such as calcifications (gallstones, renal stones, fecoliths), foreign bodies (ingested or inserted foreign bodies, ballistic fragments), surgical devices (bariatric lap band) (Fig. 119-4), drains, tubes, and retained surgical material (sponge, lap pads, needles). Radiography can localize radiopaque intra-abdominal foreign bodies with a sensitivity of 90% and specificity of 100%.

FLUOROSCOPY

Fluoroscopy studies use contrast agents that may be swallowed, injected, or instilled into the GI tract in conjunction with radiographic images. Fluoroscopy studies are relatively quick, inexpensive, minimally or noninvasive, and widely available. Typical GI fluoroscopy procedures that may be performed include modified barium swallow, esophagram, upper GI series, upper GI series with small bowel follow-through, contrast enema, colostomy enema, and defecography.

Contrast agents utilized include water-soluble iodinated contrast material, barium, and air. Water-soluble contrast is preferred for possible leaks,

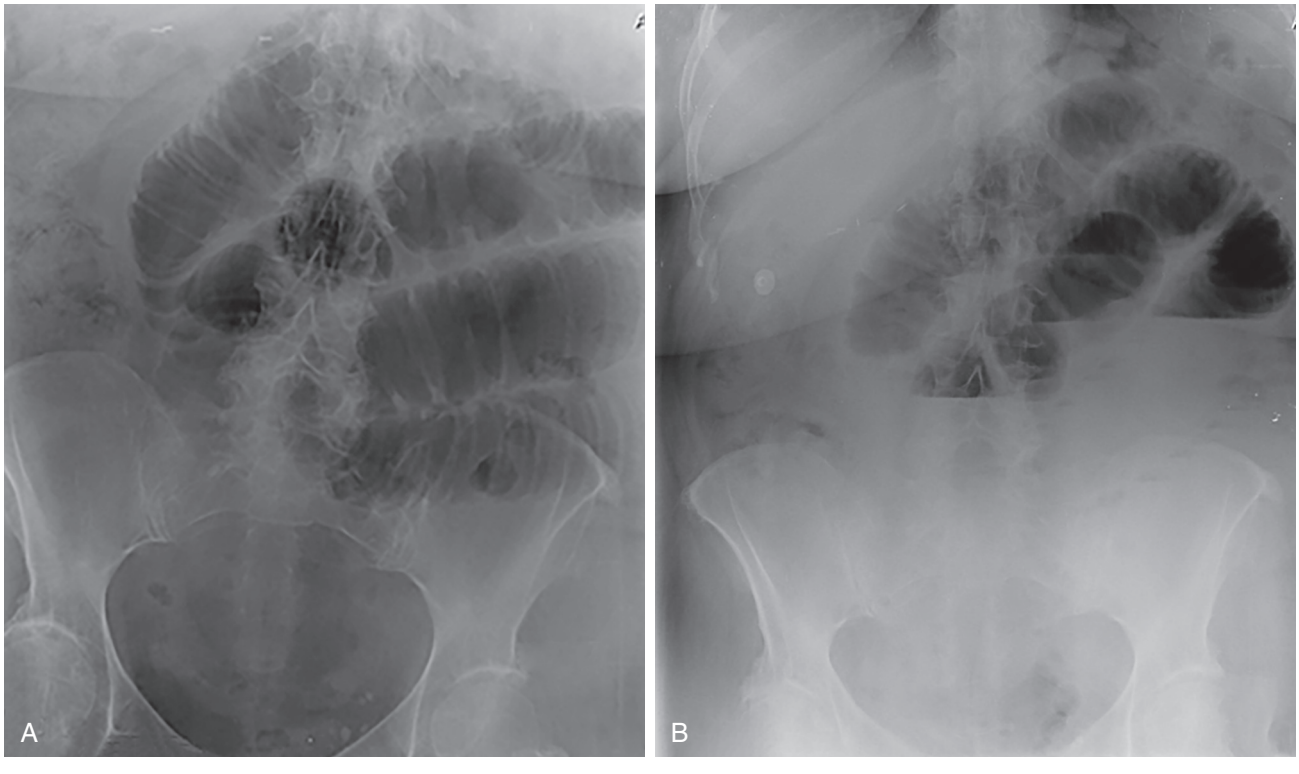

FIGURE 119-1. Small bowel obstruction. Supine (A) and upright (B) radiographs of the abdomen show dilated gas-filled loops of small bowel with a small amount of gas in the colon. The colon is not dilated. Small bowel air-fluid levels are noted on the upright radiograph. The findings are consistent with small bowel obstruction.

ABSTRACT

A variety of imaging procedures may be performed to evaluate the gastrointestinal (GI) tract and hepatobiliary system for a spectrum of symptoms, including abdominal pain, nausea, vomiting, heartburn, diarrhea, constipation, bloating, GI bleeding, weight loss, or abnormal laboratory test results. Imaging modalities utilized for these procedures include radiography, fluoroscopy, ultrasound (US), computed tomography (CT), magnetic resonance imaging (MRI), and nuclear medicine. Each modality provides varying utility with advantages and disadvantages. In addition, the modalities offer advanced imaging techniques for GI and hepatobiliary imaging, including CT and MR enterography, CT colonography (virtual colonoscopy), MR cholangiopancreatography (MRCP), MR elastography, CT and MR angiography, and PET/CT. Many of these modalities may also be utilized for interventional procedures.

KEYWORDS

radiography
ultrasound
computed tomography
magnetic resonance imaging
nuclear medicine

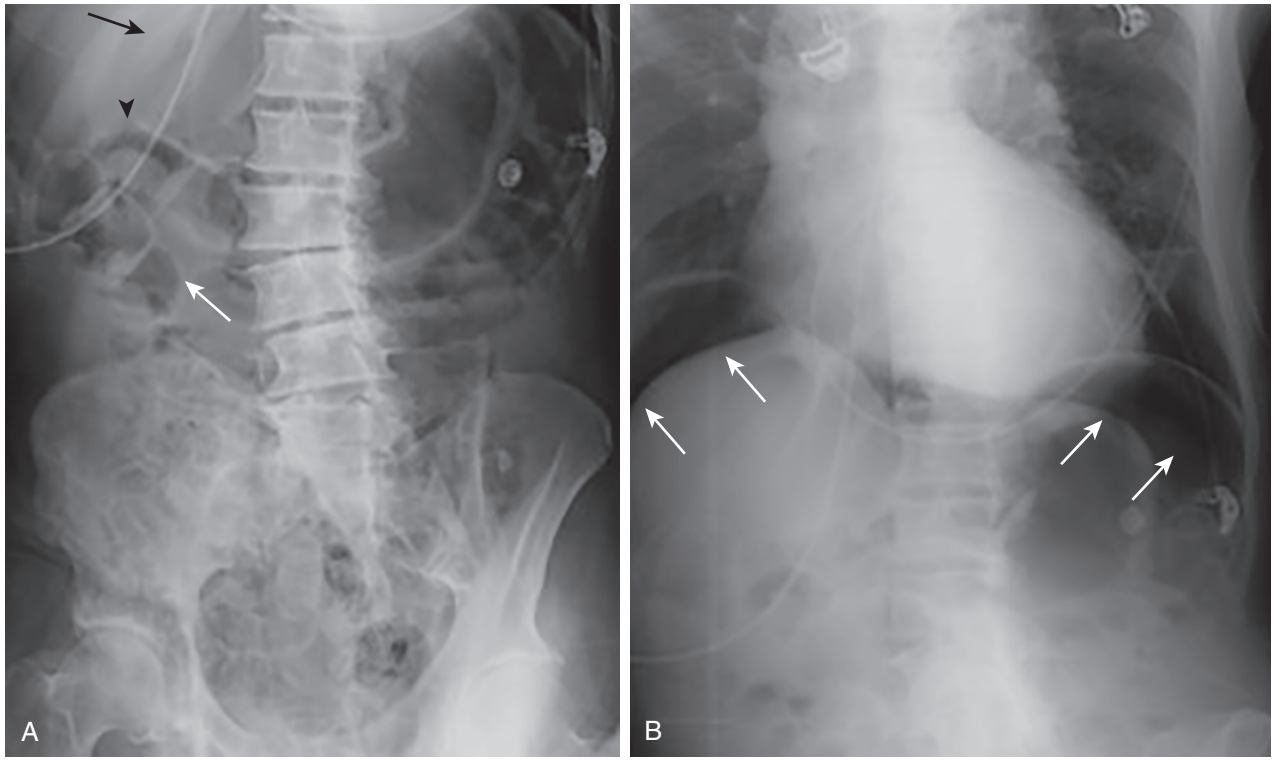

FIGURE 119-2. Pneumoperitoneum. A, A supine radiograph of the abdomen shows pneumoperitoneum. There is increased lucency throughout the upper abdomen (*black arrow*) with angulated gas in the right upper quadrant (*arrowhead*), and both sides of the bowel wall are visible (Rigler sign) (*white arrow*). **B,** An upright radiograph confirms a large amount of free air layering under the diaphragm (*arrows*).

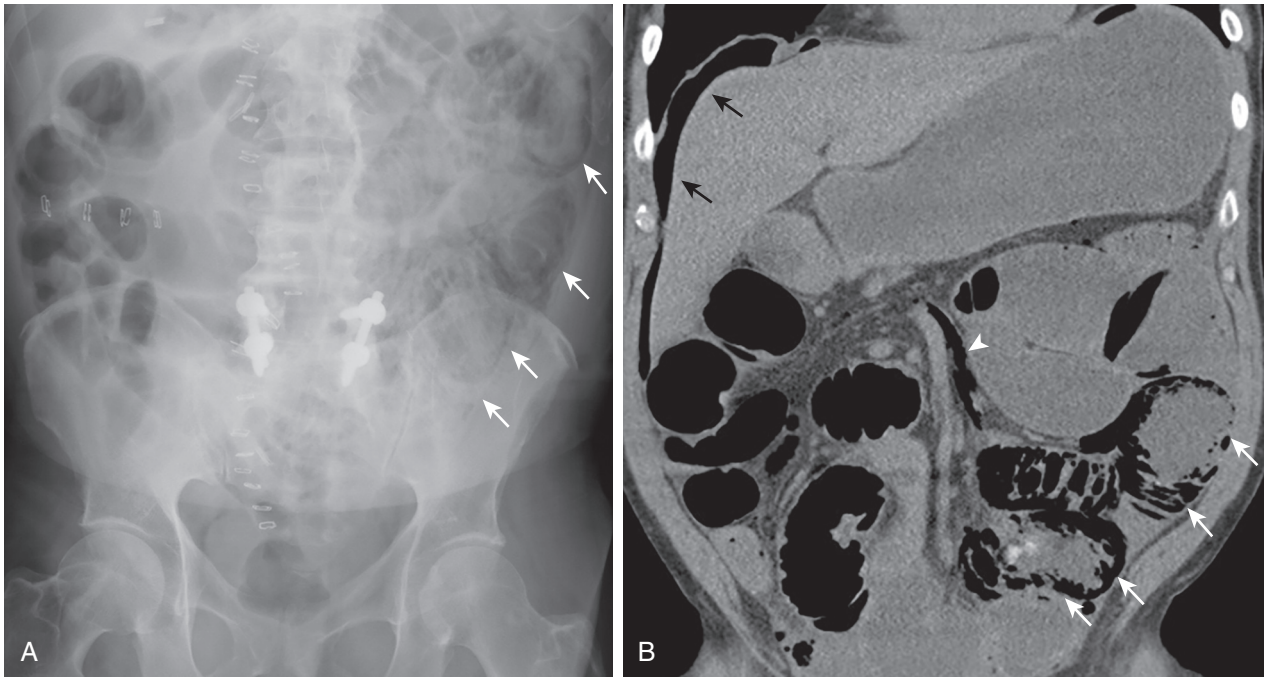

FIGURE 119-3. Pneumatosis. A, A supine radiograph of the abdomen shows dilated small bowel loops with lucency in the bowel wall due to pneumatosis (*arrows*). Also note skin staples and hardware in the lumbar spine. Pneumatosis is much more readily visible on the coronal computed tomographic (CT) image without intravenous contrast (*white arrows*). **B,** Also seen on the CT is associated mesenteric venous gas (*arrowhead*) and free air (*black arrows*).

perforations, suspected impacted foreign bodies, and following trauma, surgery, or instrumentation. Barium is preferred otherwise.

Double contrast techniques, which utilize barium in conjunction with air to distend the lumen, are best for mucosal detail (Fig. 119-5). Single contrast techniques are used for debilitated or postoperative patients and to evaluate for leaks (Fig. 119-6).

GI fluoroscopy studies evaluate the bowel lumen but provide limited information about surrounding structures other than secondary findings, such as mass effect and displacement. Fluoroscopy studies provide anatomic, structural, mucosal, and functional information about the bowel. In particular, fluoroscopy studies may detect congenital anomalies, infectious or inflammatory conditions (including inflammatory bowel disease; Chapter 127), filling defects (polyps, masses) (see Fig. 119-5), outpouchings (e.g., ulcers [Chapter 125], diverticula [Chapter 128]), extravasation (leak) (see Fig. 119-6), fistulae, and obstruction (e.g., mass, stricture, adhesive disease, intussusception). Also, fluoroscopic studies are ideally suited to evaluate post-surgical anatomy and complications

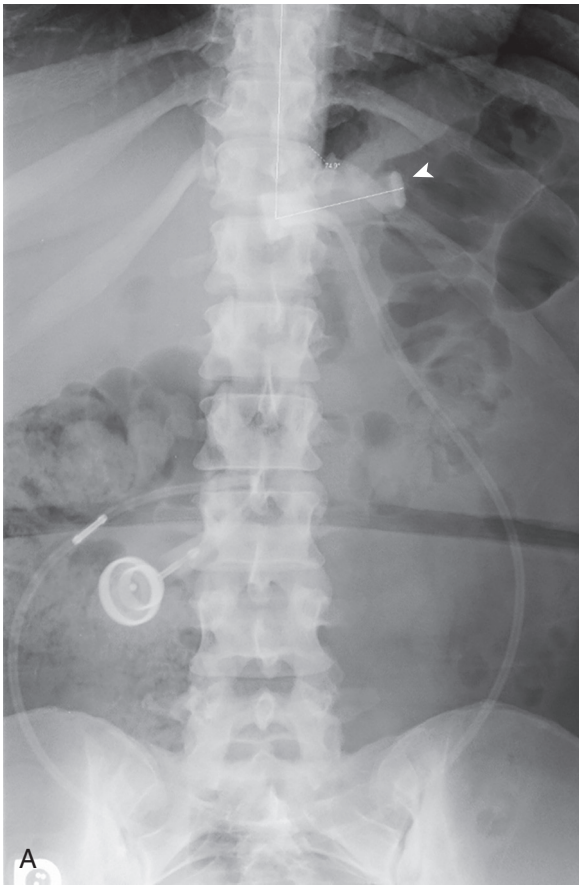

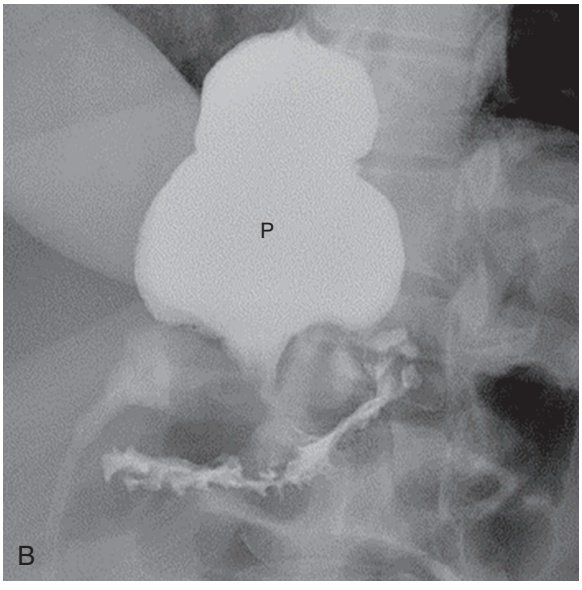

FIGURE 119-4. Gastric band bariatric surgery: band slippage with fundic herniation. **A,** A supine radiograph of the abdomen shows a gastric band device. The radiograph allows for evaluation of the surgical components, including the band itself (*arrowhead*), the connecting tubing, and the injectable reservoir. The inflatable band around the proximal stomach is too inferiorly located and horizontal in position (*arrowhead*). **B,** An upper gastrointestinal fluoroscopic spot image shows a dilated gastric pouch (*P*) above the band, with partial obstruction owing to band slippage with fundic herniation.

(see Fig. 119-4). Although CT is a high-yield study for diagnosis of small bowel obstruction and its cause, upper GI series with small bowel follow-through can further evaluate the cause and degree of obstruction and provide useful information about bowel transit time. Fluoroscopy can also be used for interventions, including feeding tube and drainage catheter placement and repositioning. For patients with inflammatory bowel disease, however, CT and MR enterography are now much more commonly performed than is a fluoroscopic small bowel follow-through. Similarly, CT colonography is more often performed than a double contrast barium enema to screen for colorectal cancer.

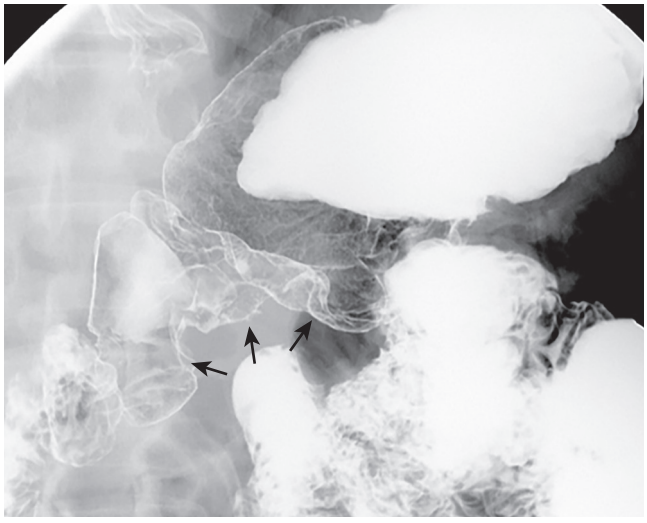

FIGURE 119-5. Gastric cancer. A double contrast upper gastrointestinal fluoroscopic spot image shows a lobulated mass along the greater curvature of the gastric body (*arrows*), consistent with a primary gastric neoplasm.

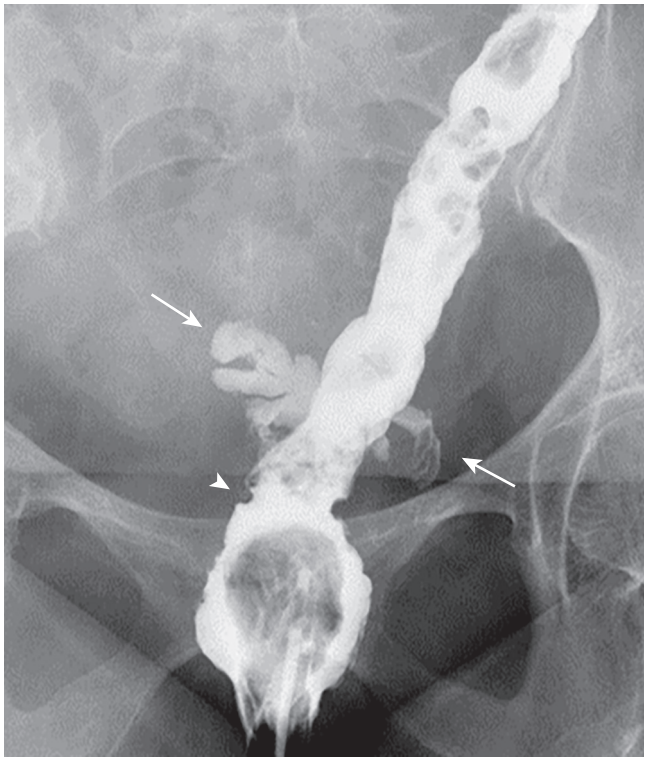

FIGURE 119-6. Colorectal anastomotic leak. A single contrast enema utilizing water-soluble contrast shows a colorectal anastomosis (*arrowhead*) as well as a large collection of amorphous extraluminal contrast (*arrows*) owing to anastomotic leak.

Fluoroscopy, which allows for real-time imaging and observing changes over time, can be used to evaluate the swallowing mechanism, esophageal motility and reflux, and bowel transit time. For example, an esophagram can assess for a spectrum of structural and mucosal abnormalities (including ulcer, stricture, mass, and hiatal hernia), evaluate esophageal motility, and detect gastroesophageal reflux and its complications (Fig. 119-7).[3] Modified barium swallow studies and esophagrams constitute a larger percentage of fluoroscopy studies now performed,[4] because the pharynx and esophagus are not as readily evaluated with cross sectional techniques.[5] Modified barium swallow can evaluate the swallowing mechanism, assess for aspiration using various consistencies and compensatory maneuvers, and determine potential strategies to improve swallowing function[6]; it is particularly useful in patients who have neurologic and musculoskeletal conditions, trauma, recurrent upper respiratory infections, and aspiration pneumonia.

FIGURE 119-7. Barrett esophagus. A fluoroscopic spot image from an esophagram shows a patulous gastroesophageal junction; marked spontaneous gastroesophageal reflux was also seen at fluoroscopy. A focal stricture with mild associated irregularity in the mid to upper thoracic esophagus (*arrow*) is due to Barrett esophagus.

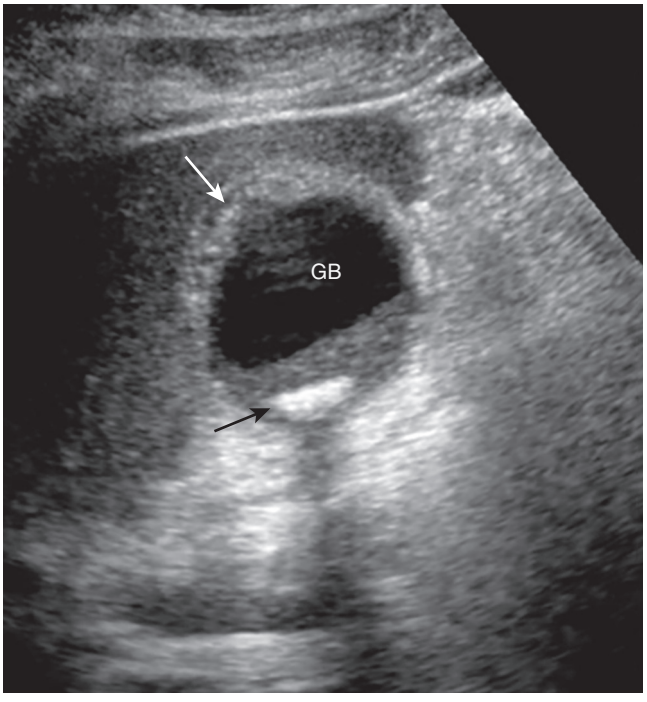

FIGURE 119-8. Cholelithiasis and acute cholecystitis. Ultrasound of the gallbladder (*GB*) shows echogenic, shadowing stones (*black arrow*) surrounded by layering sludge. Also noted is gallbladder wall thickening (*white arrow*) with trace adjacent fluid. A sonographic Murphy sign was also noted upon scanning.

ULTRASOUND

Abdominal ultrasound provides real-time imaging that utilizes high-frequency sound waves emitted by a transducer or probe, most often placed on the skin surface. Sound waves bounce back to the transducer to varying degrees based on the type of tissue, thereby creating images of the solid organs and vasculature of the abdomen. Ultrasound is noninvasive, portable, and does not utilize ionizing radiation or iodinated contrast material. These characteristics make ultrasound an excellent first test to evaluate patients who have suspected disease or abnormalities of the liver, gallbladder, biliary tree, spleen, pancreas, kidneys, and the abdominal cavity, as well as the inferior vena cava, aorta, and portal vein. Ultrasound may also be performed utilizing transvaginal, transrectal, or endoscopic probes, and it may be utilized for image-guided biopsy and intervention.

However, images are acquired only where the probe is placed, and ultrasound is therefore operator dependent. Also, it may be difficult to evaluate the entire contents of the abdomen owing to a large body habitus, the patient's positioning, artifact from skin dressings, and artifact from bowel gas. Ultrasound waves are blocked by bowel gas, thereby often limiting evaluation of the common bile duct and pancreas. As a result, more detailed evaluation often requires CT or other modalities.

A liver Doppler examination provides more detailed information about the hepatic vasculature and can evaluate vascular patency, direction of flow, and vascular waveforms. Doppler ultrasound techniques can also be used to diagnose vascular thrombosis (Chapter 129), varices (Chapter 139), cavernous transformation of the portal vein, aneurysms, and vascular anomalies (Chapter 129).

Ultrasound is well suited to evaluate the gallbladder (Chapter 141) and right upper quadrant pain.[7] Sound waves travel through fluid, thereby making ultrasound an ideal modality to evaluate the gallbladder. The normal gallbladder is fluid-filled, transmits sound, and appears hypoechoic (dark) on ultrasound. Gallstones appear echogenic (bright) and result in "acoustic shadowing" as the sound waves fail to propagate through stones (Fig. 119-8). Ultrasound is the method of choice for the diagnosis of gallstones with high sensitivity and accuracy (>95%), and ultrasound can differentiate cholelithiasis from sludge, polyps, or masses. In the setting of acute cholecystitis, ultrasound may reveal gallstones, gallbladder wall thickening, adjacent fluid, gallbladder distension (see Fig. 119-8), and a sonographic Murphy sign (focal tenderness corresponding to a sonographically localized gallbladder). Biliary ductal dilation may be recognized, but the cause may not be revealed if the common duct and pancreas are obscured by bowel gas. MR or CT may be performed to evaluate for the etiology of biliary obstruction (i.e., pancreatic mass, choledocholithiasis).

Ultrasound is useful to assess for diffuse hepatic processes, and it can evaluate the liver's size, morphology, and echotexture. In cirrhosis (Chapter 139), the liver appears echogenic, heterogeneous, and nodular in contour (Fig. 119-9).[8] Ultrasound can also identify findings of portal hypertension, including splenomegaly, ascites, and collateral vessels. Ultrasound can detect focal solid organ lesions and can readily determine a cystic or solid nature of a lesion. Doppler techniques can be utilized to determine the lesion's vascularity (see Fig. 119-9). CT and MR are superior to ultrasound overall to characterize liver lesions (i.e., benign lesions, primary tumor, metastasis), but contrast-enhanced ultrasound can assist in characterizing a liver lesion sonographically. Ultrasound following intravenous (IV) injection of a contrast agent, consisting of gas within microbubbles, can show enhancement of the lesions.

COMPUTED TOMOGRAPHY

CT, which uses x-ray technology, can image the entire contents of the abdomen and pelvis within only a few minutes, while providing excellent anatomic detail. Images can be reconstructed in multiple planes, and 3D images can also be generated. Abdominopelvic CT, which allows for evaluation of the bowel as well as solid organs, mesentery, peritoneum, and vasculature, is often performed with iodinated intravenous contrast to provide more detailed evaluation of abdominal contents. Oral contrast may be administered as well to help evaluate the bowel. Contrast may also be administered rectally or injected into the bladder, a fistula, or a drainage catheter prior to imaging.

CT of the abdomen and pelvis is ideally suited to evaluate patients who present with an acute abdomen (Chapters 118 and 128), because CT can detect even minimal pneumoperitoneum and can evaluate the entirety of the bowel and abdominal vasculature. Free air, pneumatosis, abscesses, and signs of infection, including peritonitis, are more readily visualized on CT than with radiography (see Fig. 119-3). CT also can evaluate for bowel processes, including appendicitis (Chapter 128 and Figs 128-3 and 128-4),[9] diverticulitis (Chapter 128 and Fig 128-6; Fig. 119-10),[10] volvulus, intussusception (Fig. 119-11), infectious and inflammatory conditions (including inflammatory bowel disease; Chapter 127), ischemia (Chapter 129),[11] trauma, perforation,

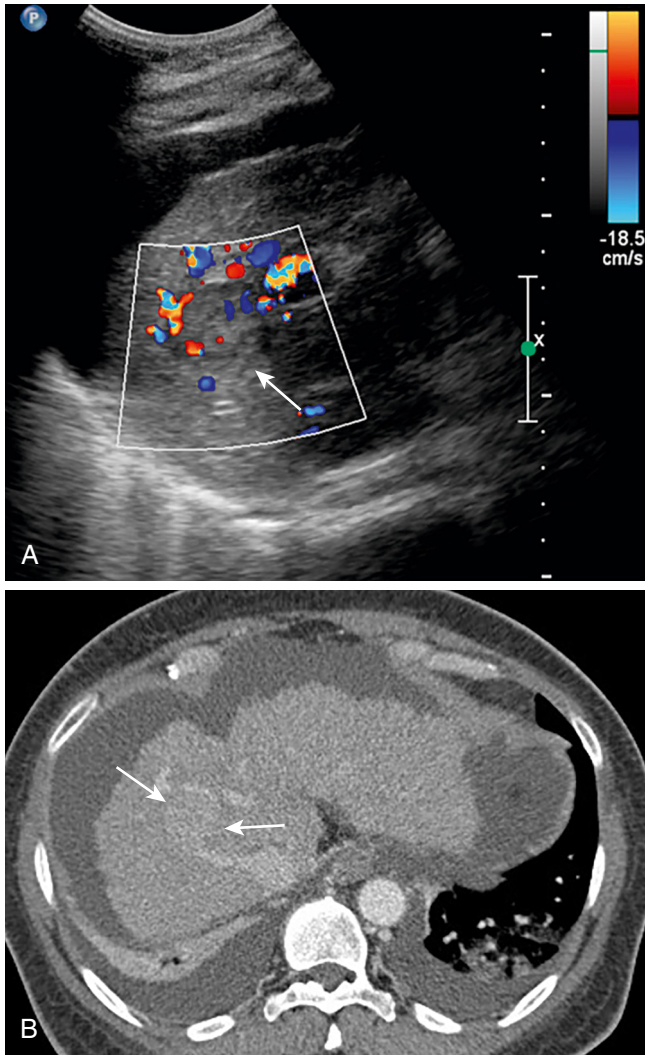

FIGURE 119-9. Cirrhosis with hepatocellular carcinoma. A, Abdominal ultrasound using color Doppler technique shows a small, nodular, echogenic, and heterogeneous liver due to cirrhosis. A focal mass is noted with internal vascularity seen with color Doppler (*arrow*). There is perihepatic fluid. **B,** Contrast-enhanced axial computed tomographic image in the same patient shows a nodular, cirrhotic liver; ascites; and a corresponding enhancing liver lesion (*arrows*) consistent with hepatocellular carcinoma.

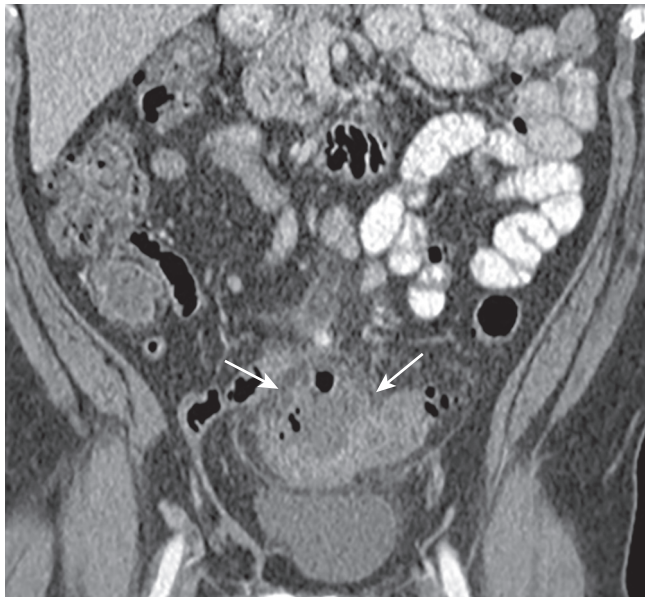

FIGURE 119-10. Acute sigmoid diverticulitis with abscess. A coronal contrast-enhanced computed tomographic image reveals diverticulosis in the sigmoid colon. There is focal sigmoid colon wall thickening with adjacent inflammatory change and an abscess (*arrows*) along the sigmoid colon due to diverticulitis.

FIGURE 119-11. Small bowel obstruction due to intussusception following Roux-en-Y gastric bypass. A coronal contrast-enhanced CT image shows markedly dilated small bowel consistent with obstruction and due to intussusception (*arrows*) at the jejunojejunal anastomosis in a patient status post Roux-en-Y gastric bypass. Note clips near the gastrojejunal anastomosis (*arrowhead*).

fistulas, bowel obstruction, and intrinsic or extrinsic masses. CT also allows for diagnosis of relatively benign entities that may mimic more severe pathology by presenting with an acute abdomen, such as epiploic appendagitis and omental infarction.

CT can detect diffuse processes involving the liver, including cirrhosis, along with its possible associated findings and complications, such as splenomegaly, ascites, collateral vessels, or hepatocellular neoplasm (see Fig. 119-9). Diffuse pancreatic processes, such as pancreatitis (Chapter 130) and its associated complications (such as ascites, fluid collections, vascular thromboses, and pseudoaneurysms), also are well characterized with CT. CT is better than ultrasound for detailing whether a lesion is likely benign or malignant (i.e., hepatic hemangioma, cyst, primary tumor, or metastasis).

Ultrasound, which is more sensitive than CT for the detection of cholelithiasis, should be the first-line procedure for the evaluation of the gallbladder itself. However, CT allows for visualization of the entire biliary tree and the underlying cause of biliary obstruction (i.e., pancreatic mass), but MR is more sensitive for the detection of choledocholithiasis.

In addition to bowel and solid organs, the mesentery and peritoneum are also included in their entirety on CT, thereby allowing for diagnosis of mesenteric masses, tumor implants, adenopathy, hematoma, abscesses, ascites, peritonitis, and carcinomatosis. CT can assess for disease spread throughout the abdomen and pelvis. CT with IV contrast also allows for evaluation of the mesenteric and hepatic vasculature (Fig. 119-12), aorta, inferior vena cava, and any potential collateral vessels. CT is often utilized to diagnose and stage primary tumors in the abdomen and pelvis and to assess for metastases to lymph nodes, solid organs, the peritoneum, and bone (Fig. 119-13). CT is also utilized to evaluate the therapeutic response of tumors.

CT angiography is useful to diagnose atherosclerotic disease, arterial thrombosis, embolic disease, vasculitis, aneurysms, dissections, vascular encasement by tumor, mesenteric ischemia, or GI bleeding. Slight protocol and image timing modifications allow for more optimal evaluation of these processes, and noninvasive CT angiography has largely replaced conventional angiography for many indications.

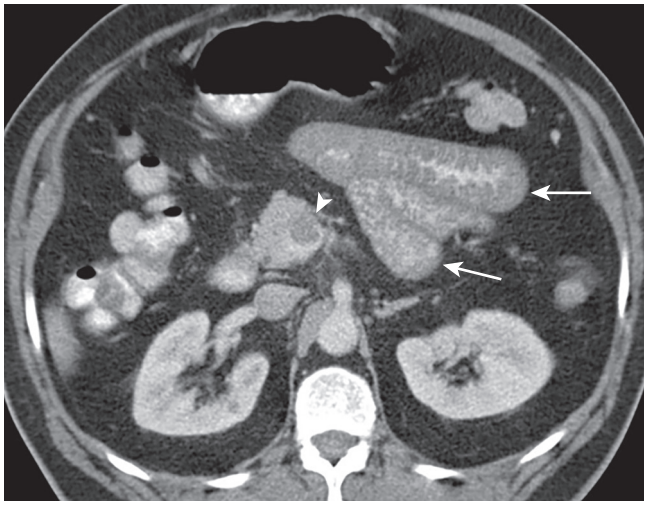

FIGURE 119-12. Superior mesenteric vein (SMV) thrombosis. An axial computed tomographic image with intravenous contrast shows a filling defect in the SMV consistent with thrombus (*arrowhead*). Associated jejunal wall thickening (*arrows*) is due to ischemic changes.

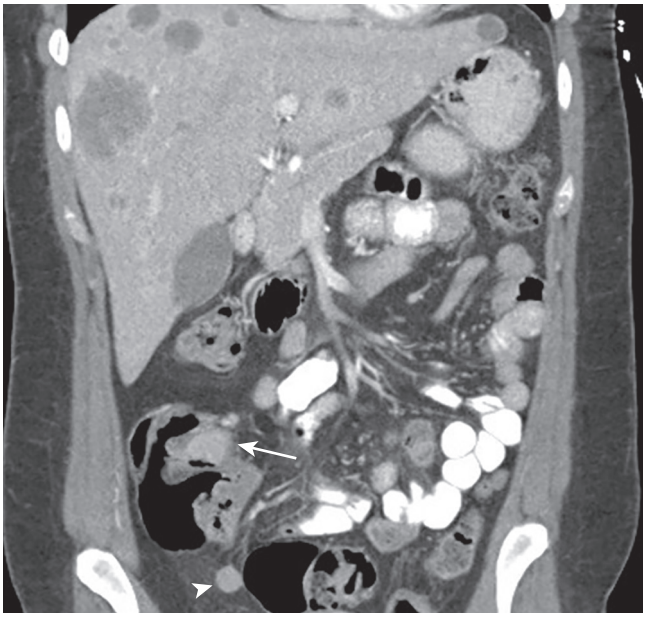

FIGURE 119-13. Metastatic neuroendocrine tumor. A coronal contrast-enhanced computed tomographic image shows an enhancing mass along the ileocecal valve (*arrow*) consistent with a primary neuroendocrine tumor. Multiple hepatic metastases are noted as well as a peritoneal tumor implant in the right lower quadrant (*arrowhead*).

CT enterography is a CT study optimized to evaluate the small bowel. Neutral oral contrast is administered to distend the bowel, and IV contrast is given to evaluate the bowel wall and its enhancement pattern. CT enterography can identify areas of bowel involvement and active inflammation in inflammatory bowel disease, as well as assess for complications such as strictures, fistulas, abscess, and obstruction. CT enterography can also evaluate for possible small bowel masses and determine a cause for low-grade, intermittent, or chronic small bowel obstruction.

CT colonography, or virtual colonoscopy, is a low-radiation-dose, noninvasive, safe, and effective screening examination for colorectal cancer. CT colonography can detect pre-cancerous polyps before cancer develops.[12] The entire colon is evaluated without the need for the patient to be sedated. 2D and 3D display techniques are utilized to "fly-through" the inside of the colon (Fig. 119-14). CT colonography is now widely accepted as an alternative to conventional colonoscopy for screening for colorectal cancer.[13]

MAGNETIC RESONANCE IMAGING

MRI, which utilizes a strong magnetic field to generate high-resolution images that can be acquired in any plane, provides excellent soft tissue detail, thereby allowing for better characterization of focal lesions as compared with CT. As with CT, MRI can image the entire abdominal contents. MRI allows for many imaging options, and studies are typically tailored for a specific provided indication. However, MRI requires much longer time for image acquisition and therefore may lead to problems with claustrophobia as well as respiratory or motion artifact. The strong magnetic field necessary for MRI also leads to artifacts, safety issues, and certain contraindications, largely related to implanted devices (infusion pumps, vascular clips, implants, certain pacemakers).

MRI can evaluate diffuse processes involving a solid organ, such as the liver, and associated findings. MRI allows for detection and characterization of focal lesions even better than CT. For example, MRI can differentiate focal liver lesions based on their tissue properties, including cysts, biliary hamartomas, hemangiomas, focal nodular hyperplasia, hepatocellular carcinomas (Chapter 181), and metastases (Fig. 119-15). Intravenous gadolinium-based contrast media aid in the characterization of lesions and vascular involvement (Fig. 119-16). The characterization of liver lesions in particular may be further improved with hepatocyte-specific gadolinium contrast agents that are taken up by the liver and excreted in bile, thereby allowing for the differentiation of lesions such as focal nodular hyperplasia versus metastasis. MRI may also be used to diagnose and stage tumors, such as rectal cancer; MRI can localize the

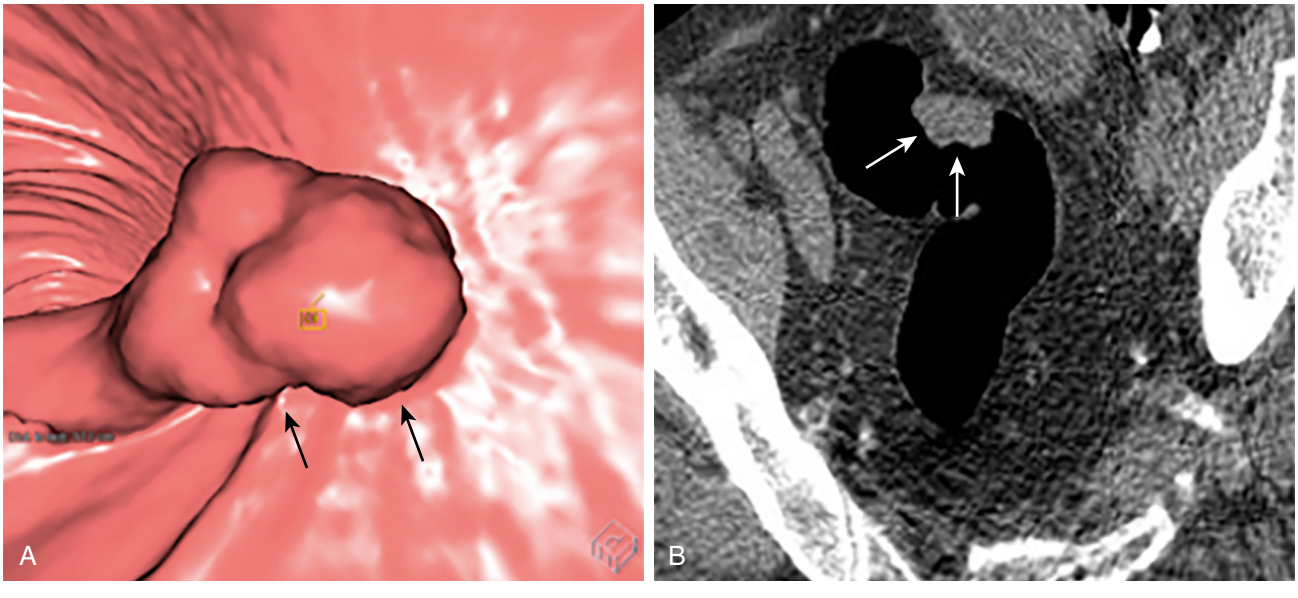

FIGURE 119-14. Polypoid lesion in the sigmoid colon on screening computed tomographic colonography. A, 3D intraluminal fly-though and (B) 2D axial computed tomographic image show a 2.5-cm lobulated polypoid lesion in the sigmoid colon (*arrows*).

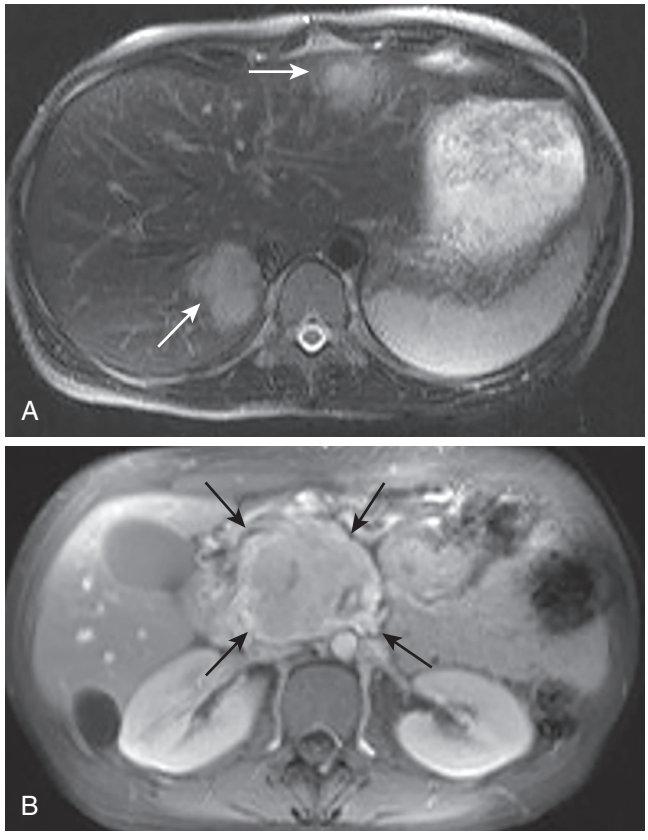

FIGURE 119-15. Pancreatic neuroendocrine tumor with liver metastases. A, Axial T2-weighted magnetic resonance (MR) image shows two moderately bright lesions in the liver (*arrows*). Heterogenous enhancement was seen following contrast (not shown). Imaging features are consistent with hepatic metastatic disease. **B,** Axial post contrast T1 fat-suppressed MR image in the abdomen more inferiorly shows a large heterogenous mass in the proximal pancreas (*arrows*) consistent with pancreatic neuroendocrine tumor.

tumor, evaluate the extent of tumor in the rectal wall, and assess for involvement of surrounding lymph nodes and other structures.

MRI allows for quantitative evaluation in the liver. MRI can be used to detect and quantify hepatic fat (hepatic steatosis) (Fig. 119-17) and hepatic iron deposition (hemosiderosis, hemochromatosis; Chapter 196).[14] In addition, MR elastography is a noninvasive technique to evaluate for liver stiffness and therefore estimate and stage fibrosis in patients with liver disease.[15]

MRI can identify biliary obstruction and determine its cause, including choledocholithiasis and pancreatic masses (Fig. 119-18). MR cholangiopancreatography (MRCP), which is a noninvasive method to evaluate the biliary

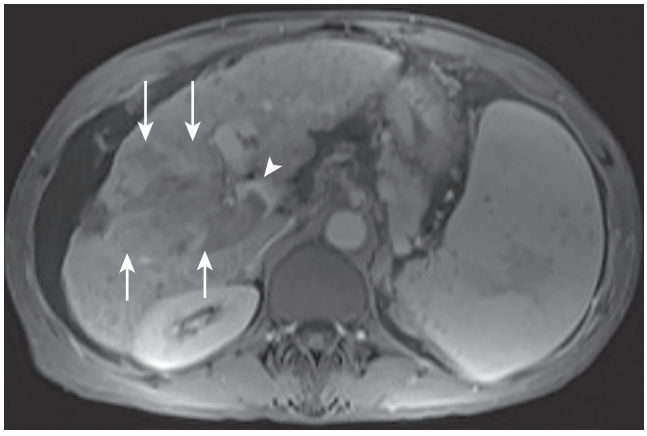

FIGURE 119-16. Hepatocellular carcinoma with tumor thrombus in the main portal vein. Axial post contrast T1 fat-suppressed MR image of the abdomen shows cirrhosis with ascites and splenomegaly. There is a large ill-defined mass in the right lobe (*arrows*) consistent with hepatocellular carcinoma. There is extent into the main portal vein with tumor thrombus (*arrowhead*).

and pancreatic ducts, has replaced endoscopic retrograde cholangiopancreatography for many diagnostic indications. MRCP sequences are optimized to show fluid, such as in the biliary tree and pancreatic duct. This technique is useful to diagnose biliary stones (Fig. 119-19), strictures, cholangitis, masses, variant anatomy, and the relationship of masses to the ducts.

MR angiography may be especially useful in patients who cannot undergo CT angiography because of renal insufficiency or allergy to iodinated contrast agents. MR enterography can evaluate disease activity and response to therapy in patients with inflammatory bowel disease, as well as associated complications, such as stricture (Fig. 119-20), fistula, obstruction, and abscesses. As with CT enterography, neutral oral contrast and IV contrast are administered to determine the bowel wall enhancement pattern. MRI allows for a more detailed evaluation of bowel wall thickening and can determine the presence of edema or fibrosis in the bowel wall. Since it has no ionizing radiation, MR enterography is especially useful in younger patients who have inflammatory bowel disease and who will need multiple examinations over time.

NUCLEAR MEDICINE

Functional nuclear medicine studies for GI processes include gastric emptying and hepatobiliary scintigraphy. A gastric emptying study can diagnose gastroparesis and delayed gastric emptying (Chapter 122). A small meal tagged with radioactive material is ingested and images are obtained over the stomach over time to determine how the stomach empties. Hepatobiliary scintigraphy (cholescintigraphy, hepatobiliary iminodiacetic acid [HIDA] scan) can diagnose problems with hepatic function, the bile ducts, and the

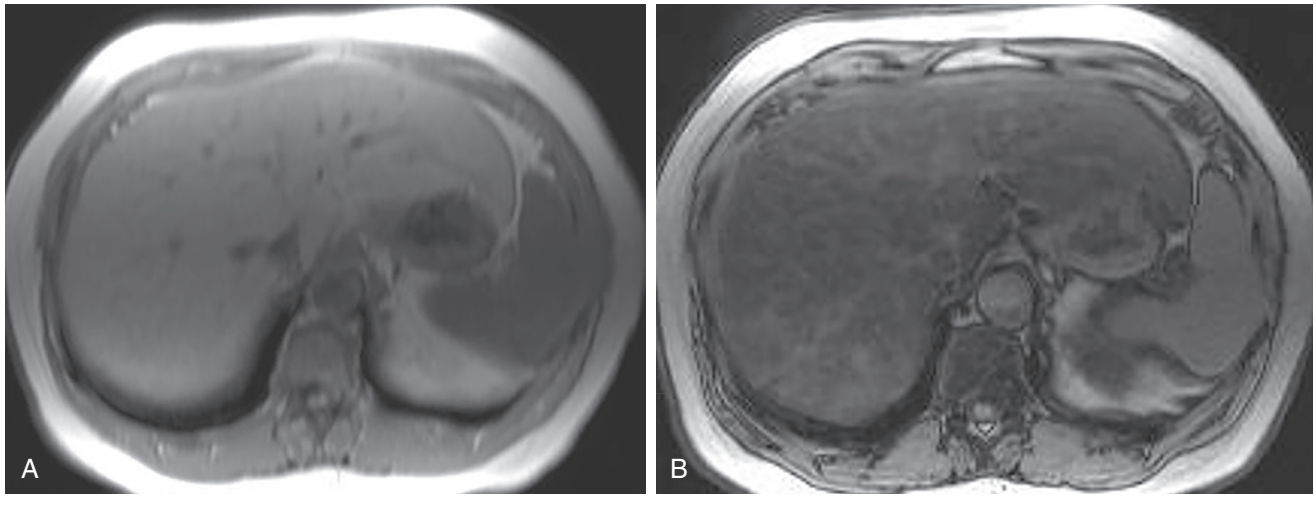

FIGURE 119-17. Hepatic steatosis with chemical shift imaging. Axial T1 in-phase **(A)** and out-of-phase **(B)** magnetic resonance images show pronounced loss of signal intensity throughout the liver on out-of-phase images as compared with in-phase images (the liver is darker) due to diffuse hepatic steatosis.

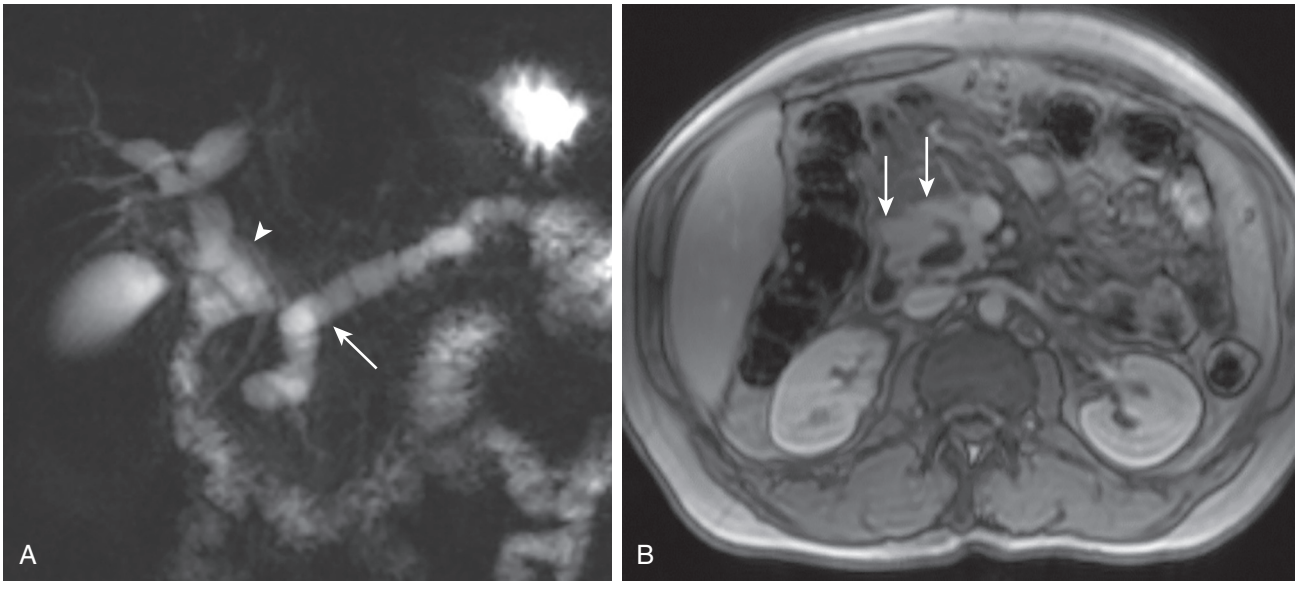

FIGURE 119-18. Biliary and pancreatic ductal dilatation due to pancreatic head cancer. A, Coronal thick slab T2-weighted magnetic resonance cholangiopancreatography image shows a double duct sign with biliary (*arrowhead*) and pancreatic (*arrow*) ductal dilatation with abrupt transition in the proximal pancreas. There is an indwelling biliary stent. **B,** Axial post contrast T1 fat-suppressed magnetic resonance image shows a mass in the pancreatic head (*arrows*) consistent with primary pancreatic cancer.

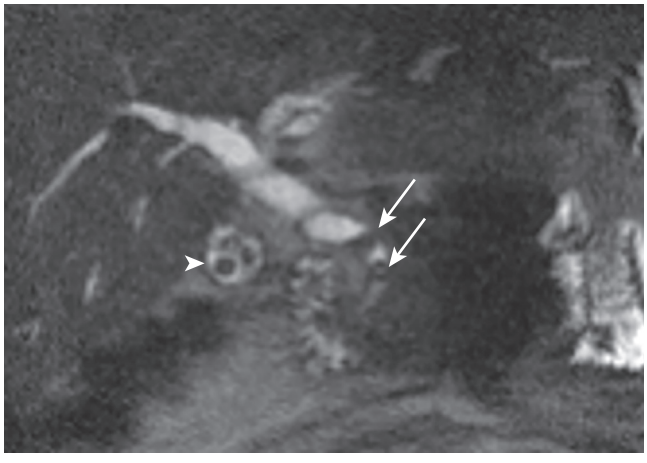

FIGURE 119-19. Choledocholithiasis. Coronal T2-weighted magnetic resonance cholangiopancreatography image shows biliary ductal dilatation with two filling defects in the common duct (*arrows*) consistent with choledocholithiasis. Also note stones in the gallbladder (*arrowhead*).

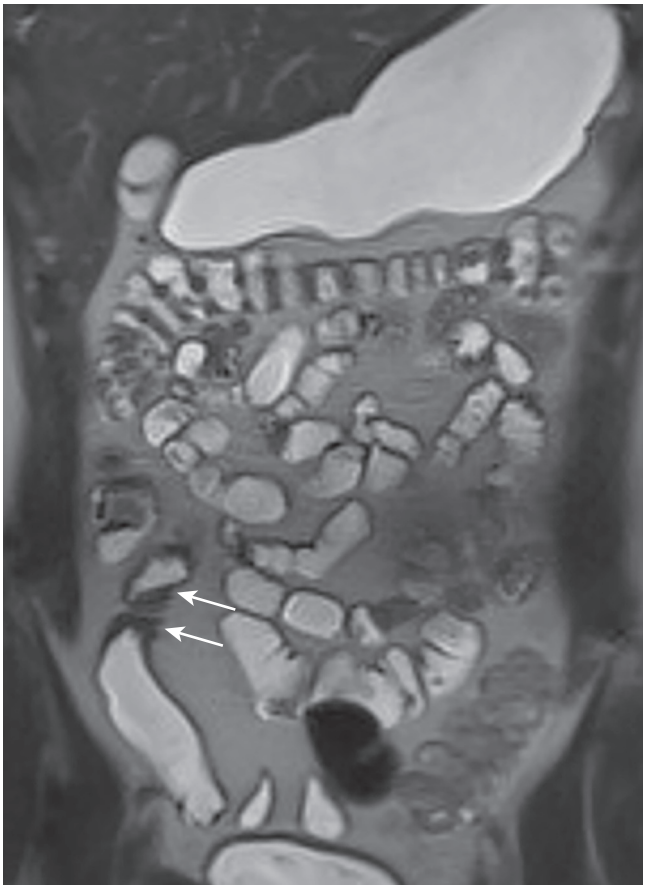

FIGURE 119-20. Crohn disease on magnetic resonance (MR) enterography. A coronal T2-weighted MR image shows Crohn involvement of the distal ileum with wall thickening and associated fibrofatty proliferation of the mesentery. There is a mild stricture (*arrows*) with mild proximal dilatation.

gallbladder (Chapter 141). A radiolabeled agent is injected intravenously, taken up by the liver, excreted in bile, and subsequently enters the small bowel. Images over time show how well the gallbladder empties and can be used to diagnose acute cholecystitis, acalculous cholecystitis, biliary obstruction, bile leaks or fistulas, and congenital biliary anomalies. This study may be especially useful following an indeterminant ultrasound for possible acute cholecystitis.

GI bleeding scintigraphy is a noninvasive means to diagnose and localize a site of active GI bleeding (Chapter 121), with a reported sensitivity of 93% and specificity of 95%. This study, which is most often performed with 99mTc-tagged red blood cells, can detect active bleeding into the bowel lumen at a rate as low as 0.1 mL/min. This study also allows for imaging over several hours, so it may be especially beneficial in the setting of intermittent bleeding.

Nuclear medicine studies are also useful to diagnose and stage tumors. A ^{111}In-labeled octreotide study (Octreoscan) can be used to visualize tumors bearing somatostatin receptors, because octreotide is a somatostatin analog. This approach is especially useful for diagnosis, staging, and follow-up of neuroendocrine tumors (gastrinoma, insulinoma, and glucagonoma; Chapter 213), carcinoid tumors, paragangliomas, and pancreatic islet cell tumors (Chapter 211).

Positron emission tomography with ^{18}F-labeled fluorodeoxyglucose (^{18}F-FDG PET) is a powerful imaging tool for evaluating many cancers and provides functional information about cancer cells. ^{18}F-FDG, a glucose analog, accumulates in malignant tissues because malignant cells have an elevated rate of glycolytic activity as compared with normal surrounding cells. Malignant cells therefore exhibit increased uptake of ^{18}F-FDG on imaging. ^{18}F-FDG PET used in conjunction with CT (i.e., PET/CT) can provide biologic, functional, and anatomic information, and areas of increased uptake can be correlated with accompanying CT images (Fig. 119-21). This approach can be used to diagnose and stage tumors, to search for metastatic disease, and to assess for residual or

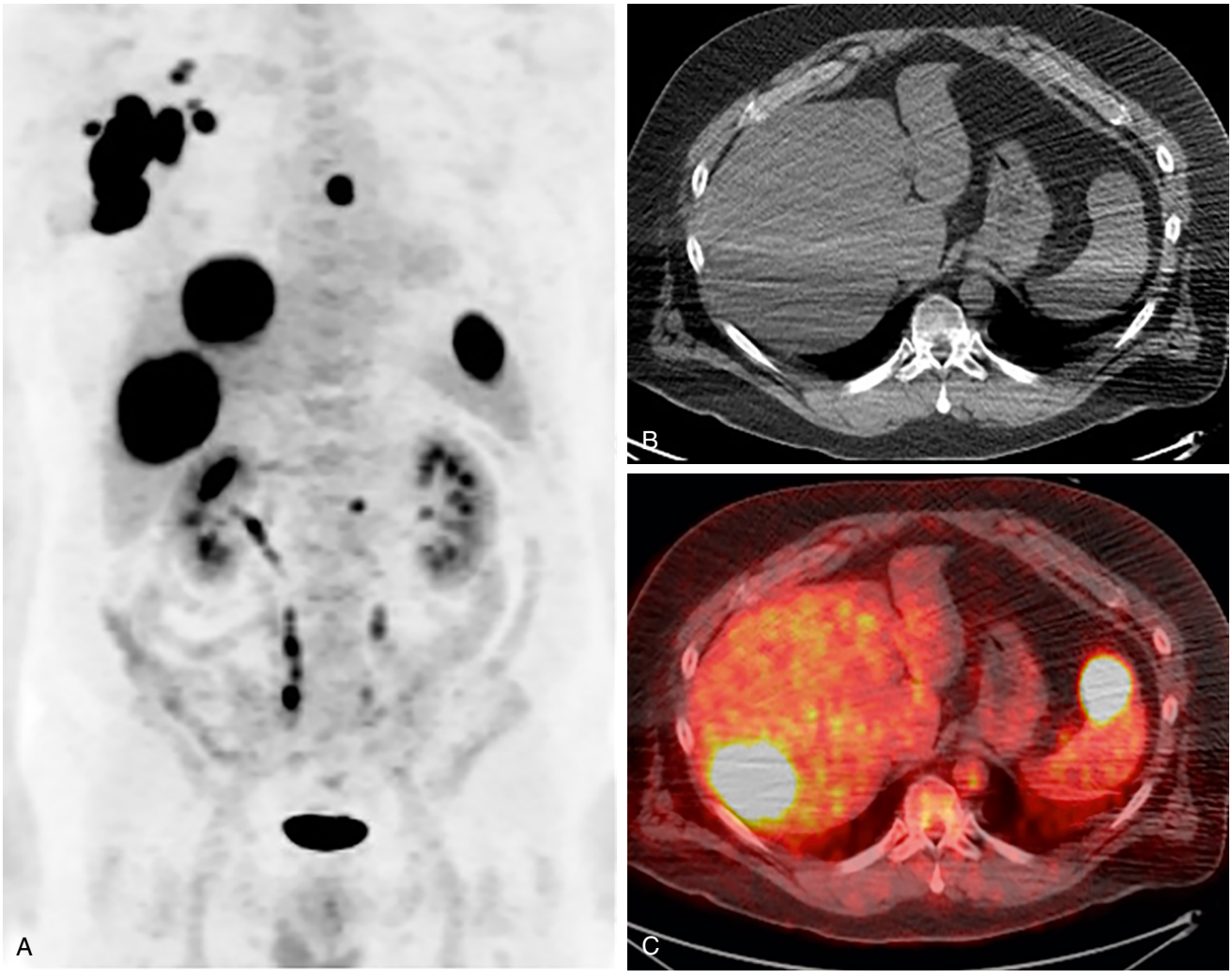

FIGURE 119-21. **Metastatic disease on positron emission tomography/computed tomography (PET/CT). A,** Coronal PET image shows increased uptake in right axillary lymphadenopathy and mediastinal lymphadenopathy as well as liver and spleen involvement. **B,** Lesions in the liver and spleen are barely perceptible on the axial noncontrast CT image. **C,** These lesions are much more conspicuous on the fused axial PET/CT image.

recurrent tumor after treatment. Because PET provides metabolic information, it is superior to CT alone to distinguish active tumor from treated scar. PET/MR, which utilizes high-resolution MR images in conjunction with PET, is a promising new technology with similar attributes but is currently much less readily available than PET/CT.

INTERVENTIONAL PROCEDURES

A variety of interventional procedures (Chapter 120) may be performed in the GI tract and hepatobiliary system using fluoroscopy, ultrasound, or CT guidance. In some cases, a combination of modalities may allow for the safest procedure. MR guidance is much less common because of the longer time needed to acquire images and special considerations owing to the magnetic field.

Interventional image-guided procedures include fine needle aspiration or core biopsy of a mass, drainage of an abscess, placement of a percutaneous cholecystostomy tube, biliary drainage and intervention, paracentesis, and placement of a feeding tube. CT- or ultrasound-guided tumor ablation (including cryoablation, thermal ablation, and alcohol ablation) may be performed for liver tumors (Chapter 181), and is especially useful for unresectable tumors and in patients who are poor surgical candidates.

Vascular interventional procedures include treatment of aneurysms or pseudoaneurysms (such as from pancreatitis), diagnosis and treatment of GI bleeding, placement of a transjugular intrahepatic portosystemic shunt (Chapter 139), and chemoembolization. Chemoembolization may be used to treat primary or metastatic liver lesions (Chapter 181). Chemotherapeutic agents are injected directly into the artery that supplies a tumor, and the artery is then embolized, thereby trapping the medications in the area of the tumor and allowing for treatment with higher chemotherapeutic doses but less systemic toxicity.

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120 GASTROINTESTINAL ENDOSCOPY

KENNETH K. WANG

The three major applications of gastrointestinal (GI) endoscopy in medicine include: diagnostic applications to define the source of gastrointestinal bleeding, to stage gastrointestinal cancers, and to obtain samples for histology or culture; therapeutic applications, such as providing hemostasis, resecting lesions, remodeling of the GI tract to manage obesity and to create passages, either between lumens or to fluid collections; and combined modality procedures with interventional radiology or surgery. In current practice, GI endoscopy has evolved from being primarily a straightforward diagnostic endoscopic technique for the colon and upper GI lumen to being a more versatile diagnostic and now therapeutic technique.

In the United States, endoscopy in healthy individuals is typically performed under deep sedation with propofol, but conscious sedation with midazolam and fentanyl is an alternative in straight-forward procedures (Chapter 400). In appropriate patients who desire to drive soon after the procedure or who cannot be accompanied by a family member or friend, the procedure can be performed without sedation.

Ideally, patients should discontinue anticoagulants and antiplatelet agents long enough before the procedure to reverse their effects (Chapter 70) and restart them in consultation with the specialists who recommended them (Table 120-1).[1] Bridging anticoagulation (Fig. 399-3) generally increases the risk of periprocedural bleeding without reducing the risk of thromboembolism[A1] and should be considered only in patients who are at very high risk of thromboembolism.[2]

Each procedure has specific indications but also carries risks (Table 120-2).

DIAGNOSTIC ENDOSCOPY

UPPER GI ENDOSCOPY

Upper endoscopy consists of examination of a portion of the posterior pharynx including the epiglottis, upper esophageal sphincter area, larynx, and vallecula.

TABLE 120-1 ANTITHROMBOTIC THERAPY FOR ELECTIVE ENDOSCOPY

Thrombotic Risk Low to High	*ENDOSCOPIC RISK OF BLEEDING*	
	LOW*	**HIGH†**
	Continue anticoagulant	Discontinue warfarin, then restart warfarin on same day of procedure Delay reinitiating DOAC until adequate hemostasis is achieved
	Continue antiplatelet agent	Continue aspirin and discontinue $P2Y_{12}$ inhibitors for at least 5 days and switch to aspirin (or continue aspirin if on dual therapy)
		If high risk for thrombosis,‡ strongly consider bridge therapy with LMWH (e.g., enoxaparin, 1.5 mg/kg q24h or 1.0 mg/kg q12h) until oral anticoagulant is again effective Delay reinitiating DOACs until adequate hemostasis is achieved

*Diagnostic upper gastrointestinal endoscopy, colonoscopy, or flexible sigmoidoscopy, including mucosal biopsy; endoscopic retrograde cholangiopancreatography; capsule endoscopy; enteral stent deployment (controversial); endoscopic ultrasound without fine-needle aspiration; argon plasma coagulation; Barrett ablation.

†Polypectomy, biliary or pancreatic sphincterotomy, treatment of varices, percutaneous endoscopic gastrostomy or jejunostomy, therapeutic balloon-assisted enteroscopy, endoscopic ultrasound with fine-needle aspiration, endoscopic hemostasis, tumor ablation, cystogastrostomy, ampullary resection, endoscopic mucosal resection, endoscopic submucosal dissection, pneumatic or bougie dilation.

‡Any mitral valve prosthesis, any caged-ball or tilting disc aortic valve prosthesis, recent (within 6 months) cerebrovascular accident or transient ischemic attack, recent (within 3 months) venous thromboembolism, severe thrombophilia (deficiency of protein C, protein S, or antithrombin; antiphospholipid antibodies).

DOAC = direct-acting oral anticoagulant; LMWH = low-molecular-weight heparin.

Adapted from ASGE Standards of Practice Committee, Acosta RD, Abraham, NS, et al. The management of antithrombotic agents for patients undergoing GI endoscopy. *Gastrointest Endosc.* 2016;83:3-16.

The entire esophagus and stomach are visualized. The duodenal bulb as well as the first and second portions of the duodenum are part of the standard examination.

INSTRUMENT

Flexible endoscopes are equipped with a high-resolution video chip at the end of a flexible tube and two fiberoptic light bundles. The endoscope has a water channel for irrigation of the camera lenses and a suction channel that can remove liquids and doubles as an instrument channel through which a variety of accessories (e.g., biopsy forceps to obtain tissue, brushes to obtain cytologic specimens, snares to remove polyps, or bipolar probes to cauterize bleeding vessels) can be passed.

PREPARATION

All upper endoscopic procedures require fasting for at least 6 hours prior to the procedure to permit adequate visualization. Patients who are receiving a per oral endoscopic myotomy for achalasia should be on clear liquids for 2 days prior to the procedure. Broad spectrum antibiotics (e.g., cefazolin 2 g intravenously preprocedure) are routinely given due to the stasis and bacterial overgrowth in the esophagus. Chronic medications can be taken orally the morning of the procedure, with minimum oral fluids to help pass the pills.

In patients who have a history of aspiration or cognitive impairment, preprocedural tracheal intubation may be advisable to protect the airway. Preprocedural intubation also is often required to prevent aspiration of blood in patients who have an active upper GI bleed, especially patients who are known to have cirrhosis and portal hypertension, because they will not be fully alert after the procedure. Patients with gastroparesis or with gastric or esophageal obstruction should also be considered for airway protection because of the likelihood of retained food.

INDICATIONS

A common indication for upper GI endoscopy is to determine the presence of a GI disease such as ulcers or esophagitis and/or and to explain a symptom (Table 120-3).

THE PROCEDURE

Unless the patient is intubated, the procedure is performed with the patient in the left lateral position to decrease the chance of aspiration. The esophagus is inspected, especially for esophagitis and varices, and then the stomach is inspected for gastric varices, ulcers, evidence of intestinal metaplasia or gastritis, and neoplasms (Fig. 120-1). Retroflexion is necessary in the fundus of the stomach to visualize the gastric cardia as well as the incisura, which is one of the most likely sites for intestinal metaplasia. The endoscope then is passed down to the second portion of the duodenum. The standard endoscope visualizes the papilla of Vater in only about 50% of cases because it is on the side wall of the duodenum and not within the field of view.

Adjuncts to Standard Endoscopy

Contrast agents that can increase the visibility of flat neoplasms include Lugol solution, which is diluted and sprayed on the surface of the squamous esophagus to help diagnose squamous neoplasia. The normal squamous mucosa takes up the iodine and appears brown, whereas neoplastic areas with either cancer or dysplasia will not take up the iodine and appear as unstained tissue that should be biopsied or resected depending on the degree of suspicion. A widely used alternative is narrow-band imaging, which uses blue light to illuminate the mucosa and highlight its features, particularly the small mucosal capillary patterns that become distorted in dysplastic tissue. In the stomach, a mixture of acetic acid and indigo carmine can detect gastric carcinoma and also enhance its borders to guide en bloc removal. Despite their utility, however, dyes are not popular in Western countries because of the difficulties in application and the contamination they create in the endoscope. Nonetheless, in high-risk patients, such as those with Lynch syndrome (Chapter 179), contrast agents can enhance detection of small early gastric cancers. Other tools to aid in the diagnosis of premalignant disease include devices such as confocal laser endomicroscopy that can magnify the views of the mucosa and assess the leakiness of the microvascular system, but this approach is infrequently used clinically in part because it requires administration of intravenous fluorescein. Volume laser endomicroscopy, which is a version of optical coherence tomography, has the potential to scan large areas of tissue at high resolution without contrast agents and is commercially available for scanning the esophagus.

ABSTRACT

Gastrointestinal endoscopy, which is an important tool for the diagnosis and treatment of gastrointestinal diseases, can also be the easiest way to diagnose systemic disorders, such as amyloidosis or graft versus host reactions. In addition to standard procedures, such as endoscopy, colonoscopy, and instrumentation of the biliary and pancreatic ducts, endoscopic procedures can be used to resect neoplasms, create a myotomy, reshape the stomach, and repair postsurgical leaks or complications. These minimally invasive techniques often can replace traditional surgical or radiological procedures or be used synergistically with them.

KEYWORDS

gastrointestinal endoscopy
esophagogastroduodenoscopy
colonoscopy
endoscopic ultrasound
endoscopic retrograde cholangiopancreatography
endoscopic suturing
endoscopic plication
endoscopic antireflux procedures

TABLE 120-2 COMPLICATIONS OF ENDOSCOPY

ENDOSCOPIC COMPLICATION	INCIDENCE (%)	SPECIFIC PROPHYLAXIS
GENERAL COMPLICATIONS		
Complications related primarily to sedation (cardiovascular and postprocedure respiratory depression, aspiration)	0.6-0.7	Airway protection with massive upper gastrointestinal bleeding Preprocedure medical evaluation, intraprocedure and postprocedure monitoring Anesthesiology consultation for high-risk patients
Perforation	0.1-0.3 (upper endoscopy) 0.14-0.25 (colonoscopy)	None (except careful technique, possible benefit to "underwater" technique)
Bleeding	0.3 (upper endoscopy) 0.7-2.5 (polypectomy)	Carefully balance risk and benefits Discontinue or reduce anticoagulant use before high-risk procedures
Bacteremia and infection complications (endocarditis, bacterial ascites)	<0.1	Antibiotics for patients at risk for endocarditis (patients with artificial valves, pulmonary-systemic shunts, previous history of endocarditis), with synthetic vascular grafts, and with bacterial ascites (cirrhotics)
Death	0.6 (upper endoscopy) 0.2 (colonoscopy)	
COMPLICATIONS ASSOCIATED WITH SPECIALIZED PROCEDURES		
Pancreatitis (ERCP)	3-20	Rectal indomethacin
Cholangitis (ERCP)	0.1-2	Preprocedure antibiotics
Wound infections (PEG)	3-4	Preprocedure antibiotics

ERCP = endoscopic retrograde cholangiopancreatography; PEG = percutaneous endoscopic gastrostomy.
From Pasricha PJ. Gastrointestinal endoscopy. In: Goldman L, Schafer AI, eds. *Goldman-Cecil Medicine*, 26th ed. Philadelphia: Elsevier; 2020:834-840.

TABLE 120-3 INDICATIONS FOR UPPER GI ENDOSCOPY

- Dyspepsia unresponsive to medical therapy
- Development of alarm symptoms including dysphagia, odynophagia, weight loss
- Persistent symptoms of reflux despite medical therapy
- Surveillance for upper GI malignancy
- Bleeding thought to be due to upper GI source or occult GI bleeding

GI = gastrointestinal.

ENDOSCOPIC ULTRASONOGRAPHY

Endoscopic ultrasonography combines an endoscope with an ultrasound array at its tip to visualize anatomy in three dimensions. Pulse doppler signals can assess blood flow, and elastography can assess tissue characteristics.

INSTRUMENT

A circular array instrument is best for mapping out the visceral surface of the esophagus and duodenum, whereas a linear array ultrasound endoscope is used for needle aspiration and biopsy because it can use Doppler ultrasound to ensure that the needle bypasses vascular structures and can observe the needle throughout its entire passage into a lymph node or organ.

PREPARATION

The preparation for an upper GI endoscopic ultrasound is similar to endoscopy. Coagulation parameters should be normalized before endoscopic ultrasonography, fine-needle aspiration, or biopsy may be performed. Deep sedation is generally used because of the length of the procedure.

INDICATIONS

The most common indications for endoscopic ultrasound are to stage esophageal, gastric, pancreatic, and biliary cancers by determining their depth, degree of circumferential involvement, and overall size.[3,4] Fine-needle biopsy is indicated for lesions that require more knowledge of tissue architecture (e.g., lymphoma) or type of infiltration (e.g., autoimmune pancreatitis). Ultrasound can guide fine-needle aspiration of lymph nodes or metastases to solid organs, especially in the liver. It can also be an adjunctive test to stage pulmonary cancer when lymph nodes are not accessible from the bronchi. Other indications include defining a lesion's vascularity, measuring portal pressure, or assessing and treating arterial vessels that feed bleeding lesions such as ulcers.

PROCEDURE

The echoendoscope is passed into the esophagus like a routine endoscope. However, the transducer portion of the endoscope is rigid and is of greater diameter than an endoscope, so passage can be more difficult in the presence of mechanical obstructions, such as an esophageal diverticulum or bone spurs in the cervical spine. Scanning begins in the posterior pharynx, where structures such as the thyroid gland and carotid arteries are very apparent. The aortic arch, aortic-pulmonic window, descending aorta, left atrium, and pulmonary vessels can be examined. Generally, examinations follow the aorta into the abdomen, where visualization of the gastro-hepatic ligament, superior mesenteric artery, and celiac axis provides landmarks in the abdomen. The celiac axis gives rise to the splenic artery and allows visualization of the body and tail of the pancreas. The left lobe of the liver is easily scanned, as is the gallbladder. From the duodenum, the portal vessel, biliary tree, and pancreatic head can be visualized, and ultrasound can be used to guide biopsy of a pancreatic mass (Fig. 120-2). Any lesions such as lymph nodes can be sampled with the linear echoendoscope. Some lesions that appear obvious on computed tomographic (CT) scanning may be invisible to ultrasound, but small lesions around the pancreas are generally better visualized on endoscopic ultrasound. Biopsies and aspirates can be routinely performed.

Under ultrasound guidance, therapeutic stents can be placed across the gastric wall into the gallbladder to decompress an inflamed gallbladder[5] or into the jejunum to bypass an obstruction caused by pancreatic cancer. Vascular access with endoscopic ultrasound can measure portal pressures, embolize arterial bleeding sites that cannot be approached by interventional radiology, and define feeder vessels for bleeding ulcers.

ENDOSCOPIC RETROGRADE CHOLANGIOPANCREATOGRAPHY (ERCP)

Endoscopic retrograde cholangiopancreatography (ERCP) can examine the biliary tree and pancreatic ducts. ERCP commonly includes fluoroscopy to visualize the dye infused within the pancreatic or biliary system, so all patients should be appropriate candidates for exposure to contrast agents and radiation.

INSTRUMENT

The typical side viewing endoscope has a rigid tip very similar in length to the echoendoscope, with the same issues regarding passage into the esophagus. The therapeutic duodenoscope is about 125 cm long with a 4.2-mm working channel that allows for passage of accessories such as the cholangioscope. The channel also has a lever that permits the user to angle a catheter into the ampulla of Vater.

PREPARATION

Patients should be fasting as for routine upper GI endoscopy. The instrument visualizes at 90 degrees to the axis of the endoscope and has no forward viewing capacity, so the esophagus must be known to be free of diverticula, strictures, or tumors. In preparation for the injection of dye and for the interventional procedure, coagulation status must be determined and normalized if possible. If the risk of precipitating pancreatitis is high (i.e., younger patient age, female

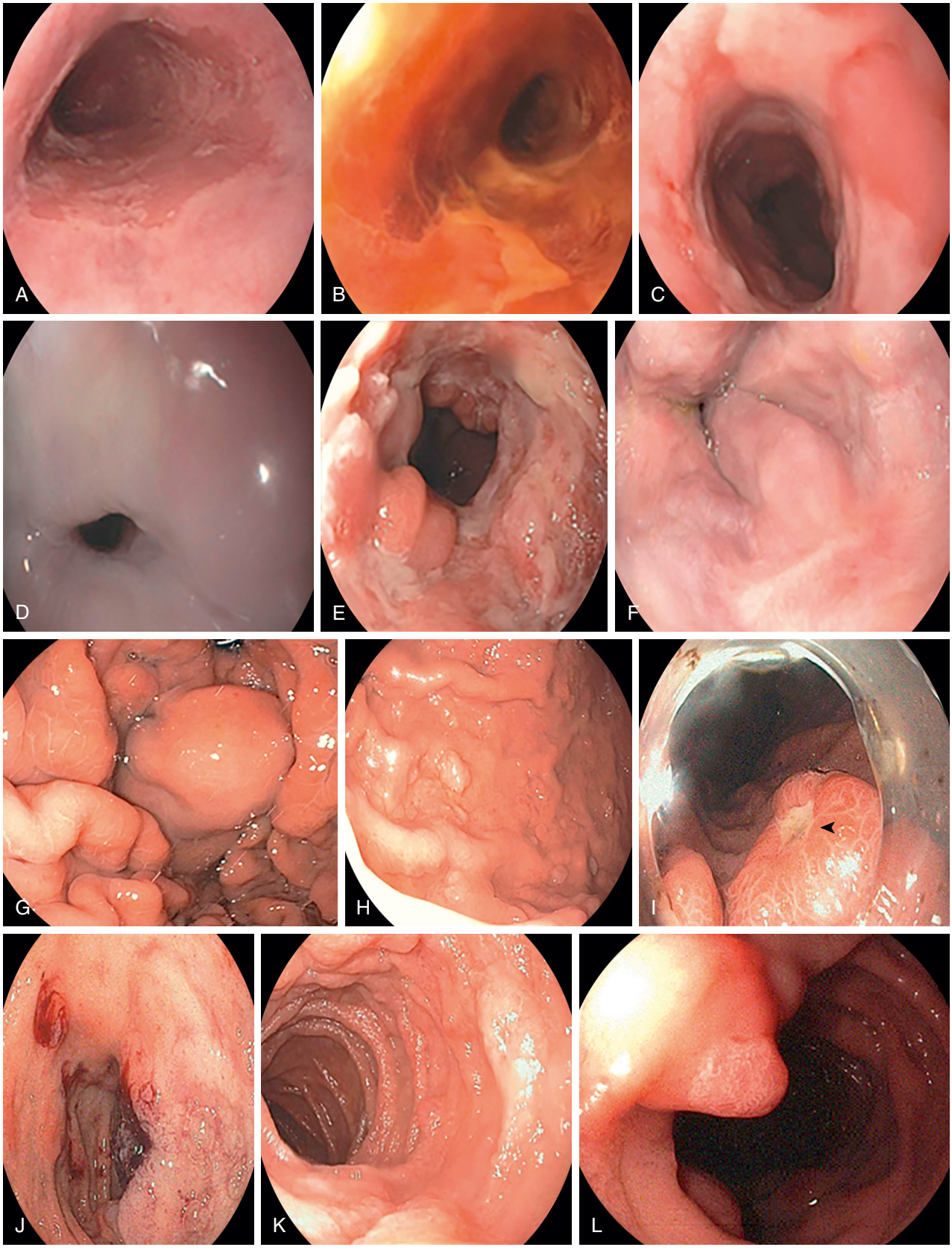

FIGURE 120-1. **Endoscopic images of abnormalities that can be observed in the upper gastrointestinal tract. A,** Barrett esophagus with areas of salmon colored mucosa indicative of esophageal intestinal metaplasia. **B,** After Lugol solution has been applied to the esophageal mucosa, areas of whitish appearing mucosa that do not take up iodine suggest dysplasia. **C,** Streaks of inflammation consistent with relatively severe erosive esophagitis. **D,** Esophageal stricture with narrowing of the esophageal lumen but no evidence of inflammation. **E,** Excavating distal esophageal cancer. **F,** Submucosal esophageal varices near the gastroesophageal junction without evidence of recent bleeding. **G,** Rugal folds in the stomach, with the expanded fold in the center of the figure representing a gastric varix. **H,** Hyperplastic polyp, which is common in patients who are taking proton pump inhibitors and generally are benign, in the center of the field. **I,** Ulcer (*black arrow*) elevated in the body of the stomach. **J,** Duodenal ulcer in the bulb of the duodenum. **K,** Adenoma (the center of the image) in the duodenum, where adenomatous polyps can be found, although benign Brunner glands are often found in the duodenal bulb. **L,** Normal ampulla of Vater.

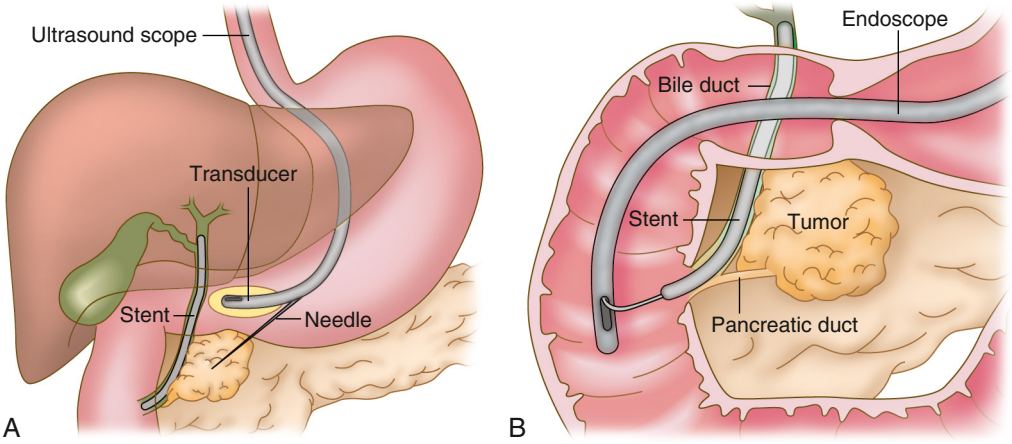

FIGURE 120-2. **Biopsy of a pancreatic mass guided by endoscopic ultrasonography (A) and the placement of a stent into a malignant bile duct stricture with endoscopic retrograde cholangiopancreatography (B).** (From Brugge WR, Van Dam J: Pancreatic and biliary endoscopy. *N Engl J Med*. 1999;341:1808-1816. Copyright ©1999 Massachusetts Medical Society. All rights reserved.)

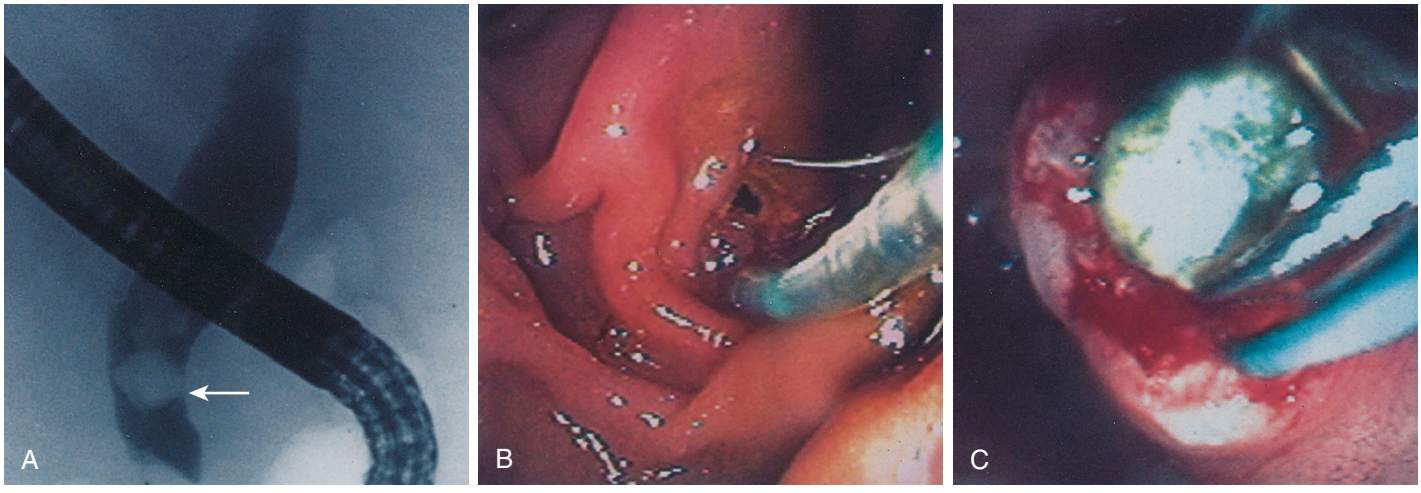

FIGURE 120-3. **Biliary sphincterotomy and stone removal from the bile duct. A,** Endoscopic retrograde cholangiographic image showing stones (*arrow*) in the distal common bile duct. **B,** Endoscopic image of a sphincterotome in the bile duct with the wire cutting the roof of the ampulla (sphincter). **C,** A stone is being removed from the bile duct by an endoscopically passed basket. (Courtesy of Pankaj Jay Pasricha, MD.)

gender, sphincter of Oddi dysfunction, previous pancreatitis, abnormal serum bilirubin), pre-procedural prophylaxis with a sulindac (100 mg) enema can decrease the risk of ERCP-induced pancreatitis.[A2]

INDICATIONS

ERCP is usually performed to evaluate obstructive jaundice, pancreatitis, or a pancreatic mass when other imaging tests are equivocal or demonstrate lesions that require therapy, such as a common bile duct stone. For example, suspected choledocholithiasis warrants ERCP for diagnosis and potential treatment (Fig. 120-3). ERCP also is often performed for chronic pancreatitis and ampullary polyps. In acute pancreatitis (Chapter 130), ERCP is often delayed until inflammation has subsided unless suspected pancreatic ductal disruption necessitates stenting. Indeterminate biliary or pancreatic ductal strictures found on magnetic resonance cholangiopancreatography (Chapter 119) may require brushings and biopsies on ERCP to define their histology.

PROCEDURE

The endoscope is typically introduced in a blind fashion using manual guidance. When the instrument passes into the second portion of the duodenum, the ampulla of Vader can be identified. The pancreatic duct is usually found directly perpendicular to the mucosa, whereas the common bile duct is much more angulated. In patients who have a pancreas divisum, the minor papilla, which is usually found at the first portion of duodenum, may need to be cannulated to access the main pancreatic duct. Once the appropriate duct is identified on fluoroscopy with contrast or with the use of a guidewire through the endoscope, accessories can be introduced for therapeutic (e.g., to extract a stone or to place a stent to bypass a stenosis or tumor) or diagnostic (e.g., to obtain tissue from an indeterminate stricture or mass) purposes. Small caliber endoscopes can be passed through a therapeutic duodenoscope (larger operating channel required) to visualize the pancreatic or biliary ducts and take small biopsies or cytologic specimens from any suspicious lesions.[6]

ENTEROSCOPY

In standard upper GI endoscopy, visualization usually extends only to the second portion of the duodenum. The easiest way to visualize the entire duodenum and a significant distance (about a half meter) into the jejunum is to use push enteroscopy, which is generally performed with a pediatric colonoscope. Most occult bleeding GI lesions (Chapter 121) are visible using this technique. Other accessories permit the endoscopist to extract foreign bodies, take specimens for diagnosis, perform a polypectomy, place a stent, dilate strictures, and even treat bleeding lesions such as telangiectasias. If the lesion is beyond the reach of these instruments, more technically difficult procedures can be employed.

PREPARATION

Preparation is as for upper GI endoscopy.

INSTRUMENT

The standard push enteroscope is usually a dedicated pediatric colonoscope that is passed orally through the stomach and into the small bowel. Single balloon enteroscopy with an overtube allows the enteroscope to be guided into the small bowel. Single balloon procedures can examine altered anatomy, such as in patients who have had bariatric surgery with a Roux-Y anastomosis.

To traverse the full jejunum, a double balloon system, with balloons on both an overtube and on the distal end of the endoscope, can be inflated and deflated to plicate the small bowel onto the shaft of the endoscope. By collapsing the small bowel onto its sheath, the endoscope can be slowly manipulated through the entire small bowel. A motorized spiral enteroscopy[7] device with an overtube that corkscrews the intestine over the tube is an emerging alternative to using a balloon to pull the intestine over the overtube. An endoscopic tattoo can be placed at the furthest distal extent of the antegrade enteroscopy, so that a colonoscopic examination from below can advance through the ileocecal valve and then to the tattoo, thereby confirming that the entire small bowel has been investigated.

INDICATIONS

The indications for enteroscopy are usually related to occult gastrointestinal bleeding (Chapter 121) or further definition of a lesion visualized on small bowel imaging. It can be used to define extent of disease, such as in celiac sprue (Chapter 126) or inflammatory bowel disease (Chapter 127), if needed. Therapeutic uses include aid in placing jejunal feeding tubes, dilating strictures, aid in performing ERCP in cases of altered anatomy such as after bowel bypass, and removal of small intestinal polyps.

PROCEDURE

Patients are positioned in the left lateral position to reduce the risk of aspiration. The advancement of this device requires fluoroscopy to confirm the location of the enteroscope when lesions are found. In addition, treatment options are limited given the long length (200 cm) of the instrument. The instrument is valuable in the diagnosis of conditions that have eluded other techniques, such blood loss in the small intestine (Chapter 121), small intestinal masses (Chapter 179), and inflammatory and malabsorptive conditions of the intestines (Chapter 126).

COLONOSCOPY

Colonoscopy is used for diagnostic and therapeutic purposes from the rectum to the ileocecal valve. Use of a colonoscope requires familiarity with the anatomy of the colon and the tendency of the colon to twist and form loops in the sigmoid and transverse colon, thereby causing difficulty in advancing the instrument unless these loops can be reduced. The colon's haustral folds also can make visualization more difficult.

INSTRUMENT

A standard adult colonoscope is about 168 cm in length and has a larger channel for suction and passage of accessories compared with an upper GI endoscope. However, the diameter of the colonoscope is also larger and the insertion tube is more flexible to allow retroflexion at various critical points in the colon, such as in the cecum or in the rectum. The diameter of the colonoscope can identify significant colonic strictures because it will be unable to pass through them.

PREPARATION

A good colonic preparation, which is essential for a complete examination,[8] often is the most unpleasant part of the procedure, and patients will be more adherent if they are strongly encouraged to take the preparations as directed.[A3] Common high-volume preparations use a nonabsorbable osmotic agent (polyethylene glycol) mixed with water and drunk by the patient in a split-dose fashion (half the evening prior to the procedure and the other half the morning of the procedure). This split-dose method is better tolerated and more effective in clearing stool than are single-dose regimens.[A4] Refrigerating the solution is often beneficial in decreasing its taste, and sucking on lemon wedges or ice cubes also can blunt its flavor. Some patients find that drinking the solution through a straw also can decrease its unpleasant taste. Finally, chewing gum before drinking a glass of the solution also makes the preparation more palatable. Although patients often rely on the color of the effluent and the absence of solid stool as indicators of adequate preparation, patients should continue to take the complete bowel preparation until the entire preparation is consumed to ensure an adequate colonic preparation. In patients who are at risk of a poor preparation (e.g., patients who have had poor preparations in the past, nonambulatory or hospitalized patients, and patients who are unable to consume the full preparation, such as patients with diabetic gastroparesis), it also may be necessary to begin a liquid diet 24 to 36 hours before the scheduled colonoscopy and increase the amount of solution to avoid solid foods in the GI tract and to ensure adequate colonic cleansing. The consequences of inadequate preparation include the need to repeat the preparation for another procedure, the inability to detect significant lesions in the colon, and an increased risk of adverse events such as perforation or bleeding.

INDICATIONS

Colonoscopy is most commonly performed to screen for colon cancer (Chapter 179). It is also indicated to evaluate possible lower GI bleeding (Chapter 121) from conditions such as a tumor or polyp (Chapter 179), inflammatory bowel diseases (Chapter 127), diverticular disease (Chapter 128), or a mucosal telangiectasia (Figs. 120-4 and 120-5).

PROCEDURE

The procedure typically begins with the patient on the left lateral position, which generally allows easier passage into the sigmoid colon. The patient may be switched to the supine position once the splenic flexure is reached, particularly when using water immersion, which is better tolerated and very useful when removing polyps, rather than carbon dioxide insufflation, which is often uncomfortable and can produce nausea and bloating postprocedure. The water immersion technique instills warm water into the colon to distend it.

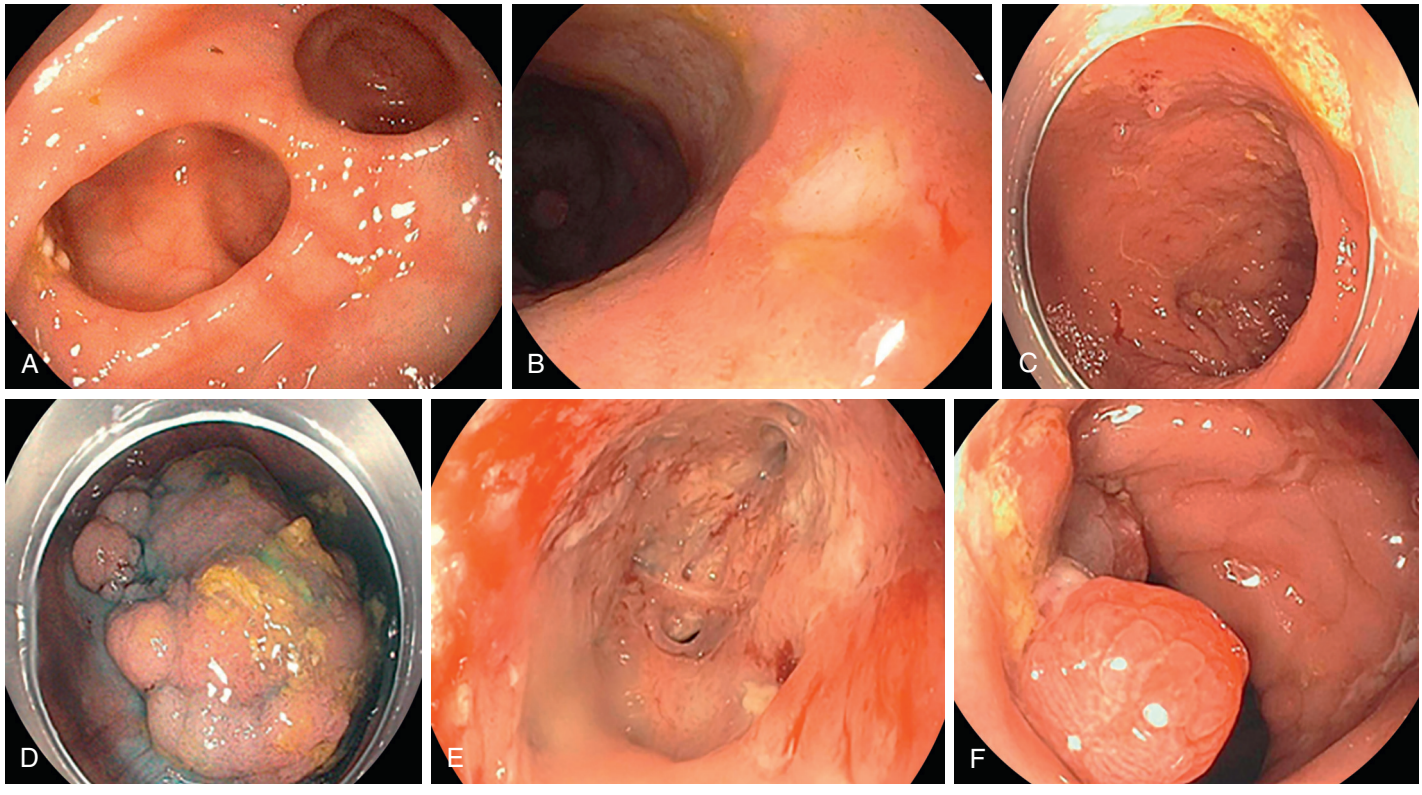

FIGURE 120-4. Images of colonic pathology. A, Large mouthed colonic diverticula, which are normal findings particularly in older patients. **B**, Colonic ulcer often found in the context of inflammatory bowel disease, most commonly Crohn disease. **C**, Chronic ulcerative colitis, with small pseudopolyps indicative of chronic disease. **D**, Large colonic polyp, likely an adenoma; despite its size this polyp can usually be removed endoscopically. **E**, Ulcerated colon with a fistula at the base. Colonic ulcers can fistulize to bladder, vagina, small bowel, and stomach depending on location of the fistula. **F**, Ulcerated polyp with polypoid edges, suspicious for malignant transformation.

FIGURE 120-5. Mucosal telangiectasia (arteriovenous malformation) in the colon. The patient presented with hematochezia. The lesion was subsequently cauterized endoscopically. (Courtesy of Pankaj Jay Pasricha, MD.)

FIGURE 120-6. Typical normal-appearing small bowel on capsule endoscopy. Although resolution is far less than standard endoscopy, villi can easily be appreciated on the capsule images.

The hypotonic nature of the fluid allows water to infiltrate the mucosa, thereby making removal of colon polyps easier. Examination of the cecum and right side of the colon is generally better on withdrawal with the patient supine.

Since polyps are often found and removed, patients must have their anticoagulants and antiplatelet medications stopped in sufficient time to ensure adequate hemostasis.[9] Removal techniques using small wire snares are routine, but specialized snares can grasp even flat polyps, and combination devices can inject fluid underneath the polyps to aid in safe removal by providing a cushion underneath the lesion. Water immersion polypectomy likewise can facilitate mucosa swelling with hypotonic fluid without the need for an injection. If a colonoscopy is being performed to evaluate gastrointestinal bleeding, however, polypectomy will often be deferred because postprocedural bleeding could easily be confused with bleeding from the original hemorrhagic site.[10]

CAPSULE ENDOSCOPY

Capsule endoscopy was initially developed to detect lesions in the small bowel. Steerable capsules can also visualize the stomach and the colon. With current high-resolution imaging, the capsule can detect bleeding sites and flag sites of mucosal abnormalities for further endoscopic review.

INSTRUMENT

The device is literally a swallowed capsule, which is about 11 mm in diameter and 26 mm in length, with a camera that is mounted on one or both ends and can take 2 to 18 images per second depending on the type of device. The cameras are battery powered and can image for a total of about 8 to 12 hours. The patient is connected to an antenna that is strapped to the skin over the abdomen and can receive and store the images for download to a workstation.

PREPARATION

Prior to imaging the small bowel for bleeding, patients are usually requested to avoid eating foods that might leave debris in the small bowel, such as fruit or vegetable seeds. Patients also should avoid iron supplements temporarily. Beginning the day before the procedure, a bowel preparation solution is usually given in the evening to help remove any food debris that may obscure important lesions. After ingesting the capsule, the patient may start ingesting clear liquids about 2 hours later and light food about 4 hours later. Patients cannot be near strong electromagnetic fields (e.g., magnetic resonance scan) until the capsule is excreted. The patient also should be sure the recorder is operational by inspecting its blinking light.

INDICATIONS

The three most common indications for capsule endoscopy are to find the site of obscure bleeding, to define the extent of inflammatory bowel disease, and to investigate a finding on other imaging, such as a suspicious lesion that is lymphoma.[11] A more controversial indication is to investigate the cause of chronic abdominal pain.

PROCEDURE

The patient returns the recorder, which can be downloaded and reviewed by an appropriately trained physician. The artificial intelligence in the software will identify areas of suspicious lesions, which are tagged for review. Areas of potential bleeding are also indicated. The physician can then review all images for potential sources of bleeding or areas of abnormality that may indicate bleeding such as ulceration (Fig. 120-6). Since images are not reviewed until after the capsule has passed, current devices cannot be used therapeutically; however, new generations of steerable capsules under magnetic control may be equipped with potential therapies, such as hemostatic sprays that could be released when a suspicious area is identified.

ADVANCED ENDOSCOPY

ADVANCED IMAGING

With the use of in vivo dyes such as fluorescein, even capillary blood flow can be visualized. The glandular structure and the microenvironment of early neoplastic lesions can be visualized using confocal laser endomicroscopy via a standard endoscope, via endoscopic ultrasound-guided fine-needle aspiration into cystic structures, or a duodenoscope to view the wall of the bile duct. Optical coherence tomography can visualize 7 linear cm of esophagus with one scan, thereby allowing reconstruction of the mucosa into two- and three-dimensional images that assess the extent of dysplasia. Electronic enhancement methods are replacing chromoendoscopy with dyes for detecting gastric neoplasia. The visualization of blood vessels in luminal tumors can predict the depth of tumor invasion with excellent accuracy.

TISSUE RESECTION

Most large polyps and early cancers can be removed with advanced endoscopic techniques. One example is endoscopic mucosal resection, by which a small cap is applied to the tip of the endoscope to allow suction to draw tissue into the cap, and then a wire snare with cautery is used to resect the tissue. The tissue is withdrawn into the cap and removed via the endoscope. Variations of this technique include the application of bands that pinch the tissue after it is drawn into the cap to allow the easier application of the snare. Endoscopic submucosal dissection can resect large lesions en bloc, thereby completely removing all neoplastic tissue by cutting around the area of neoplasia and then carefully dissecting the mucosa from the underlying muscle layer. For Barrett esophagus (Chapter 124), en bloc mucosal resection followed by ablation therapy can reduce the risk of progression from low-grade dysplasia to higher grade dysplasia.[A5,A6]

Per-oral myotomy[12] is useful for treating achalasia, with outcomes at least equivalent to open surgery in appropriate patients.[A7] It is also useful for some cases of pyloric gastric outlet obstruction and gastroparesis.[13] This technique is performed by making a mucosal incision to permit the endoscope to be passed into the submucosa to tunnel along the muscularis propria. The muscle layer can then be incised similar to a Heller myotomy, except usually only the inner circular muscle layer is cut. The tunnel can be sealed with hemostatic clips afterwards, thereby permitting easier closure.

In the colon, routine cautery of tissue surrounding a resected polyp can be performed using the avulsion technique, which entails grasping tissue with a small forceps that can apply electrocautery to the edges of the resection. This technique decreases the risk of recurrent polyps.

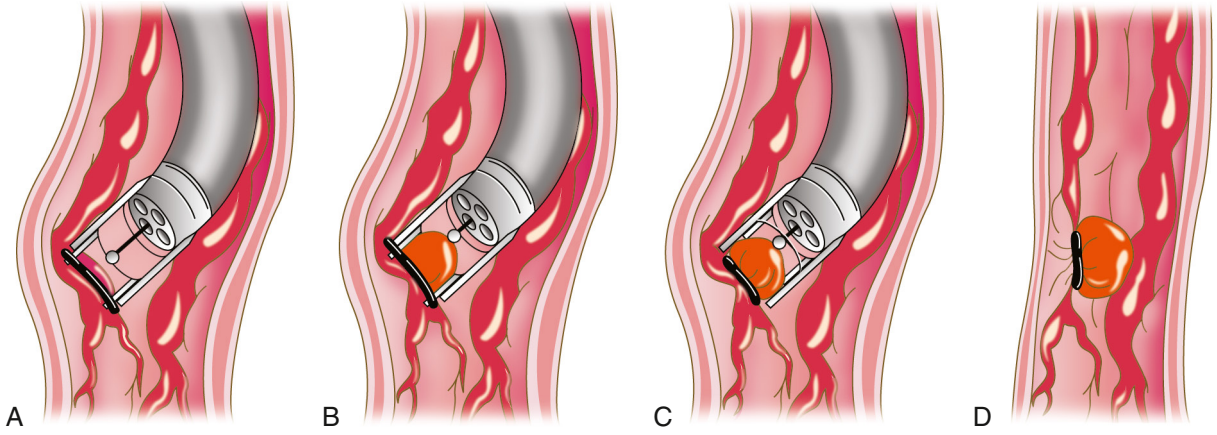

FIGURE 120-7. Endoscopic variceal ligation technique. A, The endoscope, with attached ligating device, is brought into contact with a varix just above the gastroesophageal junction. **B,** Suction is applied, drawing the varix-containing mucosa into the dead space created at the end of the endoscope by the ligating device. **C,** The tripwire is pulled, releasing the band around the aspirated tissue. **D,** Completed ligation. (From Pasricha PJ. Gastrointestinal endoscopy. In: Goldman L, Schafer AI, eds. *Goldman-Cecil Medicine,* 26th ed. Philadelphia: Elsevier; 2020:834-840.)

ESOPHAGEAL VARICES

Patients with portal hypertension commonly undergo an endoscopy to exclude possible esophageal or gastric varices (Chapter 139). Prophylactic treatment is recommended in patients who have bled previously, when large esophageal varices are present, and when the endoscopy shows variceal stigmata such as pseudoaneurysms or fibrin clots that are consistent with prior bleeding. Active variceal bleeding can be difficult to treat endoscopically because the bleeding areas may not be visible. Temporizing measures to include using a tube that can tamponade the bleeding by occluding the vessels at the gastroesophageal junction with a balloon. If this approach is unsuccessful, the esophageal balloon can then be inflated to tamponade the esophageal varices. Once bleeding is controlled, variceal banding (Fig. 120-7) can be performed to occlude the varices. Bleeding gastric varices are usually best managed by carefully injecting cyanoacrylate glue, which produces clotting within the vessel.

REMODELING ORGANS

Endoscopic devices to create a fundoplication for controlling gastroesophageal reflux disease (Chapter 124)[14] are useful only in selected cases because repair of the diaphragmatic hernia also is required in patients who have hernias that are large enough to require a procedure to control reflux.[A8] In bariatric procedures, the stomach can be plicated endoscopically, similar to a surgical gastric sleeve procedure but without removal of gastric tissue.[15] Other endoscopic procedures for weight loss include the short-term (less than 6 months) placement of gastric balloons that cause early satiety and moderate weight loss.[A9] Malabsorption can be produced either by bypassing the duodenum with a stent or by ablating the duodenal mucosa.[16]

CREATING ANASTOMOSES

The endoscopic creation of a percutaneous opening into the lumen of the GI tract can provide access for feeding into the stomach (percutaneous endoscopic gastrostomy) or jejunum (in patients at high risk for aspiration) in patients who require long-term nutrition (Chapter 198). The creation of an anastomosis between the bile duct and the stomach, using endoscopic ultrasound-guided placement of a stent under fluoroscopy, can decompress biliary obstruction in patients who have pancreatic or distal biliary cancers (Chapters 180 and 181). Placing a stent to bypass a duodenal obstruction caused by a pancreatic tumor is another palliative option.[17] However, these internal anastomoses usually provide only short-term palliation because of evolving anatomy as the tumor progresses.

REPAIR OF SURGICAL COMPLICATIONS

Endoscopic techniques can repair anastomotic leaks, drain abscesses around luminal surfaces, complete surgical resection of tumors that have positive neoplastic margins, and restore luminal integrity in areas of postoperative stenosis. For stenosis caused by surgical ischemia, temporary stenting with fully covered metal can provide short-term relief, but restenosis often occurs when the stent is removed because long-term stent deployment leads to erosion of the stent and the potential for perforation and bleeding. Drainage of abscesses can be achieved by endoscopic ultrasound-guided placement of lumen-apposing metal stents into the abscess and then cleaning out the abscess with the endoscope;[18] as the abscess drains away, the stents can eventually be removed. Sponges with low vacuum can be placed in the lumen of abscesses around the esophagus to help clear them.

COMBINED PROCEDURES

In rendezvous procedures, an interventional radiologist advances wires into the biliary system to help the endoscopist identify the location of a hidden papilla or pass a stricture that cannot be passed using wires inserted proximally via the papilla. In severe esophageal strictures, a gastrostomy can be performed, and then an endoscope can be placed into the stomach, where it is then advanced proximally toward the mouth to rendezvous with an endoscope passed by a gastroenterologist from the throat.[19] Using cutting tools, a lumen can be constructed between the two endoscopes. Full thickness resections of the gastrointestinal tract are often both more efficient and safer for the patient when performed as combined procedures by an endoscopist and surgeon, with the closure of the defect performed laparoscopically.

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121 GASTROINTESTINAL HEMORRHAGE

THOMAS O. KOVACS AND DENNIS M. JENSEN

Gastrointestinal (GI) hemorrhage can be manifested clinically as overt bleeding from the upper GI tract (esophagus, stomach, and duodenum), lower GI tract (colon), or obscure locations (usually in the small intestine).[1] Alternatively, it can occur as occult bleeding detected by iron deficiency anemia (Chapter 145) or by a positive result of fecal occult blood testing (Chapter 179).

GI hemorrhage is a common worldwide clinical problem and continues to be associated with significant morbidity and mortality. The annual hospitalization rate for upper GI bleeding is now estimated to be about 300,000 hospitalizations per year in the United States. Lower GI bleeding occurs less frequently, at about 20% of the rate of upper GI bleeding, but increases substantially with age and may occur more frequently than upper GI bleeding in the elderly. Overall, for patients hospitalized for GI bleeding, 40% occurs in the upper GI tract, 25% in the lower GI tract, and 35% in an undefined location. Mortality rates from upper GI hemorrhage are high, varying from 3.5 to 7% in the United States.

UPPER GASTROINTESTINAL BLEEDING

CLINICAL MANIFESTATIONS

Upper GI bleeding occurs proximal to the ligament of Treitz. Patients with upper GI bleeding usually present with hematemesis (vomiting blood or coffee-ground material) or melena (black, tarry stool). In large series, about 50% of patients have hematemesis and melena, about 30% have hematemesis alone, and about 20% have only melena. On occasion, however, hematochezia (passage per rectum of red blood or clots) may be the only manifestation of a bleeding ulcer, and about 15% of all patients who present with hematochezia have an upper GI source. Peptic ulcer disease (Fig. 121-1) is the most common cause of acute upper GI hemorrhage, accounting for about 40% of cases. Other common causes are esophageal and gastric varices and erosive esophagitis. Variceal bleeding, which occurs in the setting of portal hypertension, is discussed in Chapter 139. Other conditions, such as Mallory-Weiss tears (Fig. 121-2; Chapter 124), angiodysplasia, watermelon stomach, tumors, and Dieulafoy lesion, occur less frequently than peptic ulcer (Table 121-1). The mortality from nonulcer bleeding is comparable to that from ulcer hemorrhage in high-risk patients, so all causes of upper GI hemorrhage contribute to the morbidity and cost of care associated with it.

DIAGNOSIS

Initial assessment includes a medical history, vital signs, physical examination (including digital rectal examination), and laboratory evaluation. Patients should be asked questions that can help determine the diagnostic possibilities for the bleeding source. For example, peptic ulcer bleeding (Chapter 125) should be suspected in patients taking daily aspirin or nonsteroidal anti-inflammatory drugs (NSAIDs). For patients with known or suspected liver disease, bleeding related to portal hypertension (such as varices or portal hypertensive gastropathy; Chapter 139) should be strongly considered. Heavy alcohol intake or vomiting should suggest a Mallory-Weiss tear (Chapter 124). A feeding tube or a chronic nasogastric tube and a history of gastroesophageal reflux disease raise the suspicion for severe erosive esophagitis (Chapter 124).

The physician should check the vital signs with attention to signs of hypovolemia, such as hypotension, tachycardia, and orthostasis. The patient's skin should be examined for petechiae (see Fig. 158-2), purpura (see Fig. 406-10), spider angiomas, and palmar erythema (see Fig. 132-2), and the abdomen should be assessed for ascites (see Fig. 132-4), hepatomegaly, or splenomegaly, which may indicate portal hypertension. Tenderness or a mass may indicate an intra-abdominal tumor.

Routine placement of a nasogastric or orogastric tube is not recommended for patients with upper GI hemorrhage. Such a tube may, however, potentially be useful in selected patients to localize bleeding to the upper GI tract in patients with hematochezia, hemodynamic instability, and absence of overt

FIGURE 121-1. Large duodenal ulcer with a bleeding visible vessel.

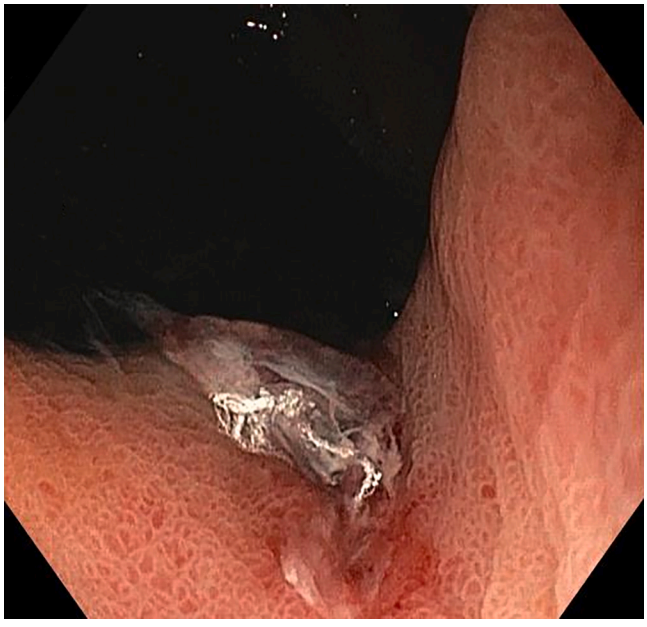

FIGURE 121-2. Mallory-Weiss tear with an overlying clot at the gastroesophageal junction.

TABLE 121-1 CAUSES OF SEVERE UPPER GASTROINTESTINAL (GI) BLEEDING IN ONE LARGE CENTER

DIAGNOSIS	%
Peptic ulcer (gastric or duodenal)	38
Gastric or esophageal varices	16
Erosive esophagitis	13
Upper GI tumors	7
Upper GI angiomas*	6
Mallory-Weiss tear	4
Gastric or duodenal erosions	4
Dieulafoy lesion	2
Other†	2
No upper GI cause found‡	8

*Upper GI angiomas include single or multiple angiectasia, watermelon stomach, and Osler-Weber-Rendu telangiectasia.
†Other lesions were surgical anastomoses, Cameron ulcers, aortoenteric fistulas, and hemobilia.
‡No cause found in esophagus, stomach, or duodenum, but 2% had mouth, nose, or pharyngeal bleeding sites.

ABSTRACT

Acute gastrointestinal bleeding is a common clinical problem associated with significant morbidity and mortality. This chapter reviews the important etiologies for upper, lower, and obscure gastrointestinal hemorrhage. The optimal diagnostic and management modalities are highlighted. Specific endoscopic therapeutic techniques to improve evaluation, prognosis, and treatment of gastrointestinal hemorrhage are detailed.

KEYWORDS

upper gastrointestinal bleeding
lower gastrointestinal bleeding
peptic ulcer bleeding
diverticular bleeding
stigmata of hemorrhage
endoscopic hemostasis
risk factors for upper GI bleeding

signs of upper GI bleeding; help clear gastric blood for better endoscopic visualization; and minimize the risk of aspiration.

Peripheral blood should be sent for standard hematology, chemistry, liver, and coagulation studies as well as for typing and crossmatching for packed red blood cells (Chapter 162). Hemoglobin concentration and hematocrit may not accurately reflect blood loss because equilibration with extravascular fluid requires 24 to 72 hours. A low platelet count suggests chronic liver disease, dilution, drug reaction, or a hematologic disorder. In upper GI bleeding, the blood urea nitrogen level typically increases to a greater extent than the creatinine level owing to increased intestinal absorption of urea after the breakdown of blood proteins. However, this phenomenon can be misleading in the setting of renal insufficiency or rapid transit of blood. An elevated international normalized ratio can be observed in chronic liver disease and in patients who are taking warfarin.

TREATMENT

Acute Management

Resuscitation efforts should be initiated simultaneously with assessment in the emergency department and continue during the hospitalization.[2] Large-bore (14- or 16-gauge) intravenous catheters are recommended, with normal saline infused as fast as necessary to maintain hemodynamic stability. A restrictive transfusion strategy (red blood cell transfusions given only at hemoglobin level <7 g/dL, with a post-transfusion target of 7 to 9 g/dL) is better than a liberal strategy for reducing 45-day mortality and further bleeding in patients with acute upper GI hemorrhage.[3] These results can be generalized to patients with nonexsanguinating upper GI bleeding[A1] but not to patients who are hypotensive due to severe hemorrhage or have associated cardiovascular disease, in whom a hemoglobin target of 9 to 10 g/dL is recommended.[4] Guidelines also advocate platelet transfusion for patients with active bleeding and a low platelet count (<50,000/μL), but there is no benefit from platelet transfusions in patients who are on antiplatelet agents but have normal platelet levels. For patients who develop upper GI hemorrhage while taking anticoagulants, such as a vitamin K antagonist or a direct-acting oral anticoagulant, it is reasonable to proceed to upper endoscopy before correcting the medication effects. To prevent aspiration, which can cause considerable morbidity and mortality, endotracheal intubation should be considered in patients with active hematemesis or altered mental status.

Nonvariceal Hemorrhage

Endoscopic Therapy

Endoscopy can identify the site of bleeding and provide therapeutic hemostasis in most patients.[5] Patients with evidence of active bleeding (hematemesis, red blood by nasogastric lavage, or hemodynamic instability) should undergo emergency endoscopy as soon as possible (within 12 hours) after medical resuscitation. An intravenous prokinetic agent (either erythromycin 250 mg or metoclopramide 10 mg) 30 to 60 minutes before endoscopy may help move blood out of the stomach and into the small intestine, thereby improving endoscopic visualization. In other patients, endoscopy between 6 and 24 hours after presentation appears to be as safe and effective as emergent endoscopy.[A2,A3]

In addition to localization of the bleeding source, endoscopic evaluation can provide prognostic information and stratify the risk of rebleeding on the basis of the presence or absence of stigmata of recent hemorrhage (Table 121-2).[6] In addition to endoscopic stigmata, other clinical and laboratory factors that predict a poor prognosis include older age, bleeding onset in the hospital, medical comorbidities (especially hepatic, renal, and malignant disease), shock, coagulopathy, fresh blood in the nasogastric lavage, and the need for multiple blood transfusions. Risk stratification using clinical scoring systems, such as the Glasgow-Blatchford score (Table 121-3), may also identify patients at very low risk (score = 0 to 1) of rebleeding or mortality and thereby allow safe, early discharge from the emergency department with outpatient follow-up.

The goal of endoscopic therapy is to stop acute bleeding and to reduce the risk of recurrent bleeding. Most endoscopic therapies were designed for peptic ulcer hemorrhage, but they can be used for other causes of nonvariceal upper GI bleeding, in which underlying arteries are the source of bleeding. Available treatments include injection (epinephrine or sclerosants such as absolute ethanol), thermal coagulation (with multipolar/bipolar or heater probe), and mechanical compression (hemostatic clips). Injection therapy is effective, safe, and inexpensive, but it is sometimes inadequate for definitive hemostasis when it is used alone. When epinephrine injection is combined with either thermal coagulation or hemoclips, hemostasis is achieved in more than 95% of patients with active bleeding, and rebleeding rates are decreased by more than 50%. A device with a larger, over-the-scope clip may be useful for re-treating patients who rebleed after initial hemostasis.[A4,A5]

Endoscopic therapy is reserved for lesions that have high-risk stigmata for rebleeding (e.g., active arterial bleeding, nonbleeding visible vessel, or adherent clot) or moderate-risk stigmata, such as oozing, bleeding without associated clot, or nonbleeding visible vessel.[7] It is not warranted for low-risk stigmata (clean-based ulcer or flat pigmented spot, unless arterial blood flow is underneath the flat spot), which have the lowest risk of rebleeding (Fig. 121-3). Some causes of upper GI bleeding, such as gastric or duodenal erosions and neoplasms, generally are not amenable to endoscopic treatment and require appropriate medical or surgical therapy.

Recurrent bleeding after endoscopic treatment directly increases mortality, raises transfusion requirements, and prolongs hospitalization. Independent

TABLE 121-2 ENDOSCOPIC STIGMATA OF RECENT HEMORRHAGE FOR PEPTIC ULCER BLEEDS

STIGMATA	PREVALENCE (%)	RISK OF REBLEEDING ON MEDICAL TREATMENT (%)	REBLEED RISK AFTER ENDOSCOPIC HEMOSTASIS (%)*
Active spurting bleeding	12	80-90	15-30
Non-bleeding visible vessel	22	40-50	15-30
Adherent clot	10	30-35	15-20
Oozing bleeding without other stigmata	14	10-20	0-5
Flat spot with underlying arterial blood flow	5	10-20	0-5
Flat spot without underlying blood flow	5	<5	—†
Clean ulcer base	32	3	—†

*Reduction in bleeding risk is with the administration of a proton pump inhibitor after successful endoscopic hemostasis.

†Endoscopic hemostasis is not recommended for clean-based ulcers or flat spots without underlying blood flow.

From Kovacs TOG, Jensen DM. Endoscopic therapy for severe ulcer bleeding gastrointestinal. *Endosc Clin N Am.* 2011;21:681-696 and Jensen DM, Kovacs TOG, Ohning GV, et al. Doppler endoscopic probe monitoring of blood flow improves risk stratification and outcomes of patients with severe non-variceal upper gastrointestinal hemorrhage. *Gastroenterology*. 2017;152:1310-1318.

TABLE 121-3 GLASGOW-BLATCHFORD SCORE

ADMISSION RISK MARKER	SCORE
Blood urea (mg/dL)	
18.2-22.3	2
22.4-27.9	3
28.0-69.9	4
≥70	6
Hemoglobin (g/dL)	
Men	
12-13	1
10-11.9	3
<10	6
Women	
10-12	1
<10	6
Systolic blood pressure (mm Hg)	
100-109	1
90-99	2
<90	3
Pulse ≥100/min	1
History and comorbidities	
Melena	1
Syncope	2
Hepatic disease*	2
Cardiac failure†	2

*Known history or clinical and laboratory findings of chronic or acute hepatic disease.

†Known history or clinical and echocardiographic findings of cardiac failure.

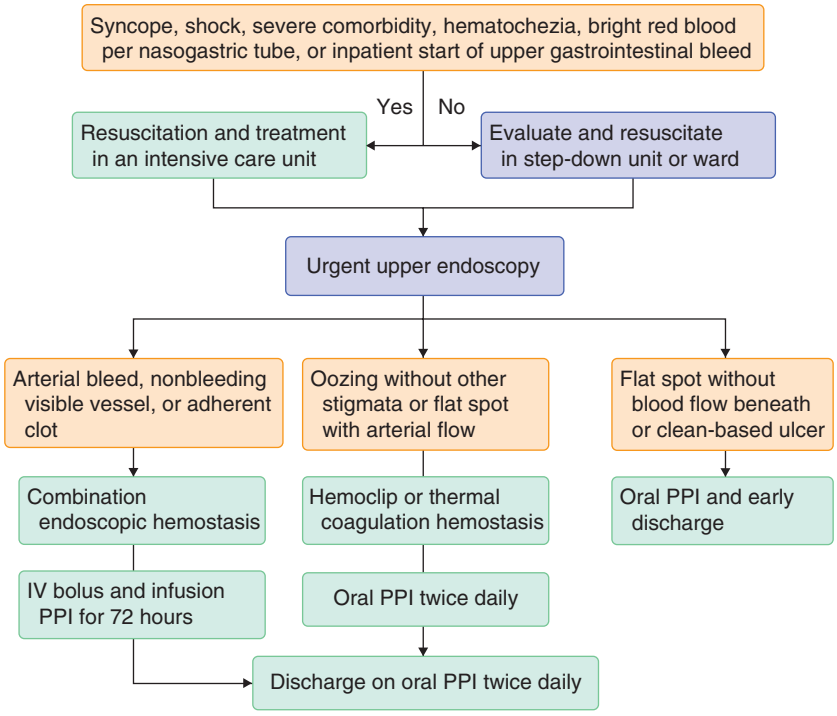

FIGURE 121-3. Management algorithm for nonvariceal upper gastrointestinal hemorrhage. IV = intravenous; PPI = proton pump inhibitor.

predictors of recurrent hemorrhage after successful endoscopic therapy include hemodynamic instability, comorbid illness, posterior duodenal location, and large ulcer size. Patients with these high-risk ulcer features may benefit from more aggressive posthemostasis triage and management.

Use of a Doppler endoscopic probe to detect blood flow underneath stigmata of a recent nonvariceal upper GI hemorrhage provides a more objective way to stratify the risk of patients with ulcer hemorrhage as well as a safe and effective method to improve outcomes. Persistence of a positive Doppler signal after endoscopic treatment correlates with rebleeding, and Doppler probe–guided endoscopic hemostasis significantly reduces 30-day rebleeding rates compared with standard, visually guided hemostasis.[A6] Patients who have residual arterial blood flow after endoscopic hemostasis have significantly higher rebleeding rates than do patients in whom arterial blood flow is successfully obliterated.

Medical Therapy

The most common cause of upper GI bleeding is peptic ulcer disease, and the most common cause of peptic ulcer disease in developed countries is NSAID use. Aspirin and other NSAIDs should be discontinued in patients with bleeding peptic ulcers, unless there is a contraindication to do so (e.g., secondary prophylaxis for stroke). Patients with documented *Helicobacter pylori* infection should be treated with combination antibiotics and a proton pump inhibitor (Chapter 125). After documentation of *H. pylori* eradication, maintenance antisecretory treatment is not needed unless the patient also requires NSAIDs or anticoagulation therapy.

Proton pump inhibitors (see Table 124-1) are the mainstay of medical therapy for hemostasis and healing of peptic lesions. Acid suppression can promote platelet aggregation and clot formation as well as reduce the risk of rebleeding. High-dose intravenous proton pump inhibitors (bolus followed by continuous infusion [e.g., pantoprazole 80 mg followed by 8 mg/hour for 72 hours]) after successful endoscopic hemostasis reduce rebleeding rates and mortality in patients with high-risk stigmata of recent hemorrhage. For patients with high-risk stigmata, either this same regimen or intermittent high-dose proton pump inhibitor therapy may be equally effective.[8] Patients with low-risk or no stigmata can be treated with an oral proton pump inhibitor (e.g., esomeprazole or pantoprazole 40 mg twice daily) and considered for early discharge. Pre-endoscopic proton pump inhibitor treatment is controversial since it does not alter clinical outcomes, but it may downstage the severity of the stigmata of recent hemorrhage and decrease the need for endoscopic intervention. Therefore, in patients with suspected ulcer bleeding, proton pump inhibitors given as an intravenous bolus may be used while waiting for the endoscopy, but this therapy cannot substitute for endoscopy and should not delay it.

The optimal management approach for patients who develop peptic ulcer–related GI bleeding while receiving antiplatelet or anticoagulant therapy is controversial, but rapid reversal of antithrombotic treatments is generally important (Chapter 70).[9] In patients who have a bleeding peptic ulcer while receiving low-dose aspirin therapy followed by successful endoscopic hemostasis and high-dose intravenous proton pump inhibitor therapy, the incidence of recurrent ulcer bleeding at 30 days is twice as high (10% vs. 5%) in patients who continue low-dose aspirin compared with those who did not. However, patients who continue low-dose aspirin have a significantly lower mortality rate compared with the placebo group because of lower rates of cardiovascular and cerebrovascular complications. Current recommendations[10] suggest that patients with upper GI hemorrhage who need secondary cardiovascular prophylaxis should resume low-dose aspirin treatment as soon as the cardiovascular risks outweigh the gastrointestinal risks, usually within 7 days, while continuing proton pump inhibitors (e.g., esomeprazole or pantoprazole 40 mg daily). Such a policy increases the risk of recurrent bleeding by about 65% but also decreases the risk of thromboembolism by about 65% and all-cause mortality by about 50%.[11] Among the direct-acting oral anticoagulants, apixaban (Chapter 70) may be associated with the lowest risk of major GI bleeding.[12]

Patients with idiopathic (non–*H. pylori*, non-NSAID) peptic ulcers should receive long-term acid suppression therapy. For this purpose, limited data suggest that proton pump inhibitors and histamine 2 receptor antagonists are about equally effective, although the former may be slightly better.[A7]

Variceal Bleeding

The treatment of variceal bleeding is discussed in Chapter 139.

LOWER GASTROINTESTINAL BLEEDING

DEFINITION AND EPIDEMIOLOGY

Lower GI hemorrhage generally refers to bleeding from the colon and anorectum. Severe lower GI bleeding occurs with an annual incidence of 20 per 100,000 population, much less frequently than upper GI bleeding. Patients are usually older and present with painless hematochezia, typically without orthostasis. If orthostasis is present, a brisk upper GI bleed, which occurs in 15 to 20% of cases of severe hematochezia, should be considered. The most common cause of severe colorectal hemorrhage is from diverticulosis (Chapter 128). Other frequent causes include internal hemorrhoids (Chapter 131), ischemic colitis (Chapter 129), rectal ulcer (Chapter 131), and delayed bleeding from postpolypectomy ulcers at a median of 8 days (range, 5 hours to 17 days) after the procedure (Table 121-4). In most patients, the bleeding stops and does not recur. The overall mortality rate from lower GI bleeding is 2 to 4%.

DIAGNOSIS

Patients with hematochezia should have a careful history, physical examination, and laboratory evaluation, analogous to the evaluation for upper GI bleeding.[13] The history may help in the differential diagnosis. A history of diverticulosis (see Figs. 128-5 and 128-6) may raise the suspicion for a diverticular bleed (Chapter 128). Abdominal cramping followed by bloody diarrhea suggests ischemic colitis (see Fig. 129-2). A recent polypectomy makes a postpolypectomy bleed more likely.

After medical resuscitation, most patients will need to undergo colonoscopy, although a flexible sigmoidoscopy or anoscopy may be an alternative in cases in which it is highly likely that the bleeding source is from the anorectum or distal colon (Fig. 121-4). Colonoscopy is critical for identifying a luminal source of bleeding as well as for potential hemostasis of amenable lesions.[14] Urgent colonoscopy within 12 hours of admission improves diagnostic yield but has not been shown to reduce either the rate of rebleeding or transfusion requirements.[A8] To cleanse the colon adequately and to visualize the colonic mucosa, a bowel purge with 6 L or more of a polyethylene glycol solution should be administered before the procedure. Colonoscopic treatment (Fig. 121-4) of focal bleeding sources with stigmata of hemorrhage (Fig. 121-5) uses the same methods (epinephrine and either thermocoagulation or hemoclips) as for upper GI bleeding. In addition, coagulation of angiectasias and bleeding biopsy sites is feasible during colonoscopy.[15]

If colonoscopy does not reveal the source of bleeding, an upper endoscopic evaluation should be performed. If both are negative, capsule endoscopy (Chapter 120), if it is locally available, may be the preferred way to look for a small intestinal source of bleeding. Alternatively, if bleeding persists or is too rapid for a colonoscopy to be performed, a tagged red blood cell nuclear scan or angiography may be performed to localize the bleeding. The red blood cell scan can help localize bleeding if it occurs at a rate of at least 0.1 mL/minute. However, a positive scan localizes bleeding to a general region of the abdomen but not to a specific anatomic site. CT angiography, which can detect bleeding rates of 0.3 to 0.5 mL/minute, is a more useful imaging test to identify the anatomic source of hemorrhage. Angiography has the advantage that it can treat the bleeding source with embolization of the bleeding vessel. However, it requires a faster bleeding rate (at least 0.5 mL/minute). These imaging studies cannot identify nonbleeding stigmata and usually do not yield an etiologic diagnosis.

TABLE 121-4 MOST COMMON COLONIC SOURCES OF SEVERE HEMATOCHEZIA IN A SERIES OF 486 CASES (EXPRESSED AS PERCENTAGE OF COLONIC SOURCES)*

Diverticulosis	32%
Internal hemorrhoids	13%
Ischemic colitis	12%
Rectal ulcers	8%
Colonic angiodysplasia, angiectasia, angiomas, or radiation proctopathy	7%
Ulcerative colitis, Crohn disease, other colitis	6%
Postpolypectomy ulcer	5%
Other lower gastrointestinal tract sources	6%

*Less common causes include surgical anastomotic ulcers or sutures, nonsteroidal anti-inflammatory agent colopathy, metastases, portal hypertensive colopathy, lymphoma, and endometriosis.

TREATMENT

Surgical management rarely is needed for hemostasis of lower GI bleeding because most bleeding is either self-limited or easily managed with medical or endoscopic therapy.[16] The main indications for surgery are malignant lesions (Chapters 131 and 179), diffusely bleeding lesions that fail to respond to medical therapy (such as ischemia; Chapter 129), and recurrent diverticular hemorrhage (Chapter 128). If the bleeding source can be localized preoperatively to a particular area of the colon, a segmental resection can be performed rather than a subtotal colectomy. In patients who have lower GI bleeding while on aspirin, the continuation of aspirin is associated with higher risk of recurrent lower GI bleeding but a lower risk of serious cardiovascular events and death.[17] Patients who develop GI bleeding while on antithrombotic medications for atherosclerotic conditions (e.g., coronary, peripheral vascular, or cerebrovascular artery disease) have a 20-fold increase in the likelihood of a new gastrointestinal cancer[18] and require the same aggressive evaluation as patients who bleed without using such medication.

OBSCURE AND OCCULT GASTROINTESTINAL BLEEDING

DEFINITION AND EPIDEMIOLOGY

Obscure GI bleeding is persistent or recurrent bleeding, despite negative initial GI evaluation—including upper endoscopy, push enteroscopy (which reaches farther into the small intestine), and colonoscopy, as well as radiologic evaluation of the small intestine, such as small bowel follow-through or CT or MR

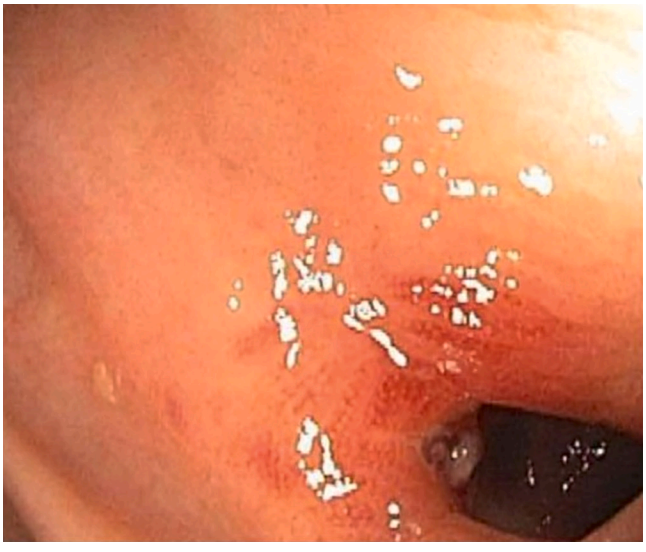

FIGURE 121-5. Colon diverticulum with a visible vessel.

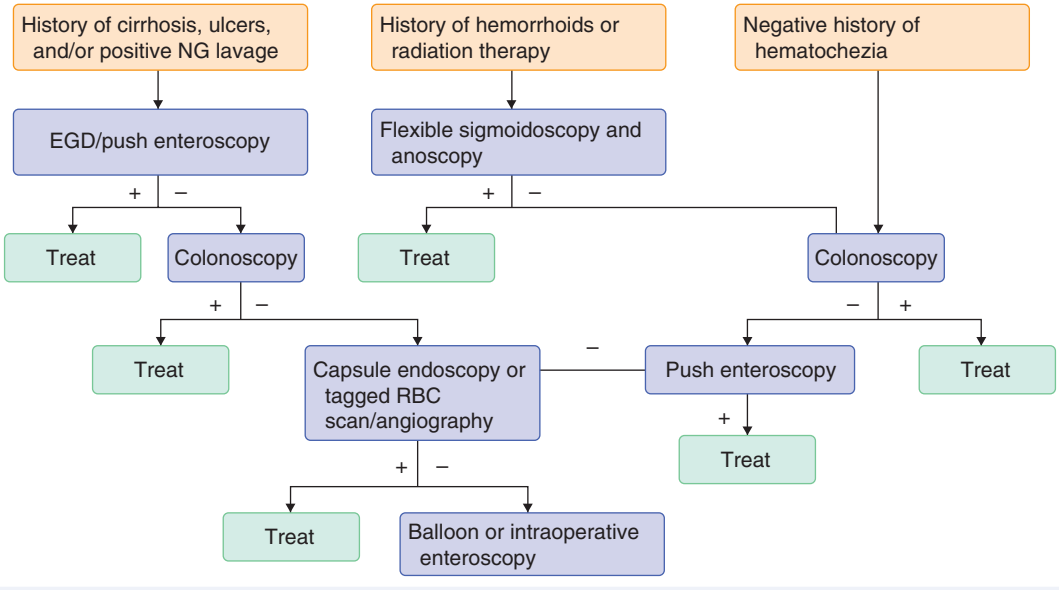

FIGURE 121-4. Management algorithm for severe hematochezia. EGD = esophagogastroduodenoscopy; NG = nasogastric; RBC = red blood cell; + = diagnostic findings; – = no diagnostic findings.

TABLE 121-5 SMALL INTESTINAL LESIONS FOUND IN 488 PATIENTS DURING DOUBLE-BALLOON ENTEROSCOPY FOR OBSCURE GASTROINTESTINAL BLEEDING

LESION	FREQUENCY (RANGE)
None	40% (0-57)
Angiectasias	31% (6-55)
Ulcerations	13% (2-35)
Malignancy	8% (3-26)
Other	6% (2-22)

enterography.[19] Obscure GI bleeding can be classified as either overt (melena, maroon stool, or hematochezia) or occult bleeding (positive result of fecal occult blood testing, usually in the setting of iron deficiency anemia).

In most large series of hospitalized patients, 5% of overt GI bleeding cases are considered to be obscure, and 75% of these patients have bleeding from the small intestine that is beyond the reach of an upper endoscope or colonoscope. Angiectasias (see Fig. 120-5) are the most common source of small intestinal bleeding, followed by ulcers and tumors (Table 121-5). Other causes for obscure GI bleeding include lesions that are within reach of standard endoscopes but that were not recognized as the bleeding site (e.g., a large hiatal hernia with lesions known as Cameron ulcers on endoscopy or internal hemorrhoids on colonoscopy) and intermittently bleeding lesions such as a Dieulafoy lesion (Fig. 121-5),[20] which is an aberrant submucosal vessel without an ulcer.

Iron deficiency (Chapter 145) has a prevalence of 2 to 5% among adult men and postmenopausal women. It can occur from overt or occult blood loss (e.g., GI tract lesions, menorrhagia), iron malabsorption (celiac disease, atrophic gastritis), and red blood cell destruction (hemolysis). It should be suspected in patients with low mean corpuscular volume, low ferritin level, or low transferrin saturation.

DIAGNOSIS

The approaches to overt and occult obscure GI bleeding are similar (Fig. 121-6). In the case of recurrent overt bleeding, upper endoscopy, push enteroscopy, and colonoscopy should be repeated, with the type of bleeding dictating which endoscopic procedure to do first. Colonoscopy with anoscopy should be done first if there is hematochezia. If there is melena, a push small bowel enteroscopy should be performed. If the first procedure is unremarkable, evaluation should be undertaken from the opposite end. If the second test result is negative, capsule endoscopy should be performed (Chapter 120).[21] If bleeding from the small intestine is seen on capsule endoscopy, further attempts to diagnose and to treat the bleeding should be performed with either deep enteroscopy (using a balloon overtube to slide much farther along into the small intestine) or intraoperative enteroscopy. All of these long enteroscopes facilitate diagnosis and hemostasis. If the capsule endoscopy is negative and rapid rebleeding recurs, a tagged red blood cell scan or angiography may be used to localize the bleeding site and assist with subsequent intraoperative enteroscopy.

For occult GI bleeding, colonoscopy should be performed first because fecal occult blood testing was designed to screen for colorectal cancer (Chapter 179). Upper endoscopy and push enteroscopy should follow if the colonoscopy is unremarkable. Afterward, the algorithm is the same as for overt bleeding; however, if the capsule endoscopy is negative, efforts should be focused toward providing supportive care rather than further evaluation.

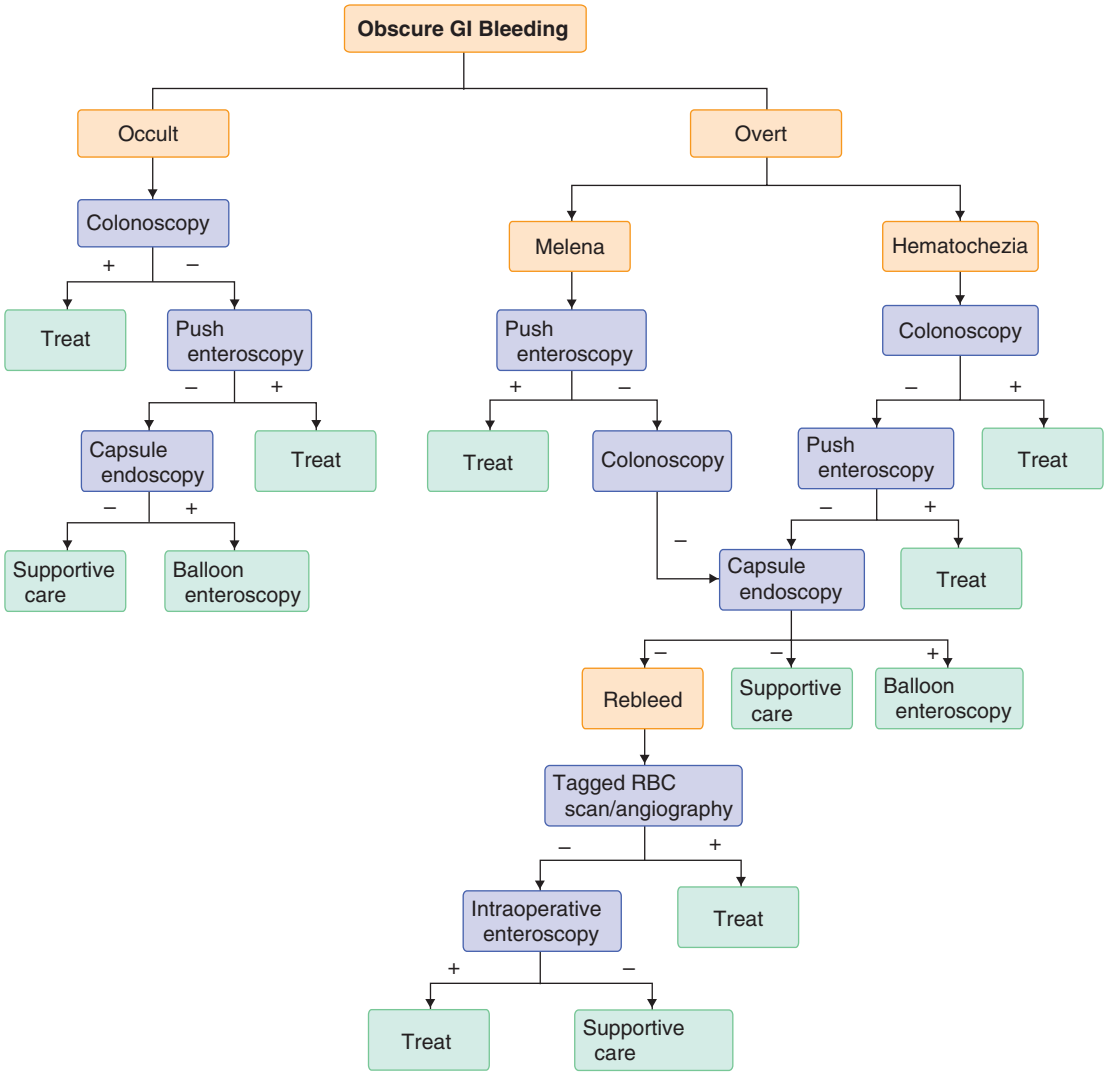

FIGURE 121-6. **Management algorithm for obscure gastrointestinal bleeding.** GI = gastrointestinal; RBC = red blood cell; + = diagnostic findings; – = no diagnostic findings.

Iron Deficiency Anemia

GI evaluation of iron deficiency anemia (Chapter 145) is indicated in adult men, regardless of age, and postmenopausal women. Women who have not reached menopause may warrant a GI evaluation after obvious or potential causes of iron deficiency and blood loss, such as chronic menorrhagia, have been excluded. Colonoscopy should be performed first, followed by upper endoscopy and push enteroscopy if the colonoscopy is negative.[22] Duodenal biopsy specimens should be taken to look for evidence of celiac disease (Chapter 126). In the absence of other potential sources of iron deficiency anemia, *H. pylori* should be treated, if present, because *H. pylori* infection decreases iron absorption and may produce microerosions that bleed. If all three of these endoscopic procedures are unrevealing, capsule endoscopy should be performed. If the capsule study is negative, investigation into non-GI causes of iron deficiency (Chapter 145) may be pursued.

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122 DISORDERS OF GASTROINTESTINAL MOTILITY

MICHAEL CAMILLERI

DEFINITION

Motility disorders result from impaired control of the neuromuscular apparatus of the gastrointestinal tract. Associated symptoms include recurrent or chronic nausea, vomiting, bloating, abdominal discomfort, and constipation or diarrhea in the absence of intestinal obstruction.

PATHOBIOLOGY

Normal Physiology

Neuroenteric Control

Motor function of the gastrointestinal tract depends on the contraction of smooth muscle cells and their integration and modulation by enteric and extrinsic nerves as well as pacemaker cells, such as the interstitial cells of Cajal. Extrinsic neural control consists of cranial and sacral parasympathetic nerves (excitatory to nonsphincteric muscle) and the thoracolumbar sympathetic supply (excitatory to sphincters, inhibitory to nonsphincteric muscle). The vagus nerve innervates from the stomach to the right colon. Parasympathetic innervation of the distal colon arises from sacral segments S2 to S4. Sympathetic fibers to proximal and mid-gut and to the colon arise from the intermediolateral column of the spinal cord (T5 to T10 and T11 to L3, respectively). The prevertebral ganglia integrate afferent impulses from the gut and mediate reflex control of abdominal viscera.

The enteric nervous system, which is capable of autonomous control of the gut, comprises about 100 million neurons organized in ganglionated plexuses. The larger myenteric or Auerbach plexus, between the longitudinal and circular muscle layers, is responsible for motility, and the submucosal or Meissner plexus controls absorption, secretion, and mucosal blood flow. The enteric nervous system also plays an important role in visceral afferent function.

Pacemaker cells, which coordinate muscle contraction and sense distortion, serve as intermediaries between the enteric nerves and the smooth muscle cells. Electrical control activity spreads through interneurons in the contiguous segments of the gut via neurochemical activation by transmitters that may be excitatory (e.g., acetylcholine, substance P) or inhibitory (e.g., nitric oxide, somatostatin).

Gastric and Small Bowel Motility

The motor functions of the stomach and small intestine are characterized by distinct patterns of motor activity in the fasting and postprandial periods (E-Fig. 122-1). The fasting period is characterized by a cyclic motor phenomenon, the interdigestive migrating motor complex. In healthy individuals, one cycle of this complex is completed every 60 to 90 minutes. The complex has three phases: quiescence (phase I), intermittent pressure activity (phase II), and an activity front (phase III) during which the stomach and small intestine contract at their highest frequencies (3 per minute in the stomach, 12 per minute in the duodenum, 8 per minute in the ileum). Another characteristic motor pattern in the distal small intestine is prolonged propagated contraction, which empties residue from the ileum into the colon in bolus transfers.

In response to the ingestion of food, the proximal stomach accommodates the food by a vagally mediated reduction in tone, thereby facilitating the ingestion of food without an increase in pressure. Liquids empty from the stomach in an exponential manner, and the rate of emptying varies with calorie content and viscosity. The half-emptying time for non-nutrient liquids in healthy individuals is usually less than 20 minutes. Solids are retained selectively in the stomach, where they undergo acid and peptic digestion as well as "churning" or trituration by high liquid shearing forces in the antrum. Digestible food particles are emptied after their size is reduced by trituration to less than 2 mm. Gastric emptying of solids is characterized by an initial lag period followed by a linear post-lag emptying phase. Secretion of hormones that mediate the motor and digestive process (e.g., gastrin for acid secretion; cholecystokinin for gallbladder contraction and bile and pancreatic secretion; and insulin, glucagon, and incretins such as glucagon-like peptide 1 for glucose regulation) is integrated with the arrival of food or chyme at different levels of the gut to ensure optimal digestion and signal satiation.

The small intestine transports solids and liquids at approximately the same rate. As a result of the lag phase for the transport of solids from the stomach, liquids typically arrive in the colon before solids. Chyme moves from ileum to colon intermittently in boluses propelled by contractions. In the postprandial period, the interdigestive migrating motor complex is replaced by an irregular pattern of contractile activity that persists for about 1 hour for each 200 kcal ingested.

Vomiting is characterized by a stereotypic sequence of motor events, including contractions of the stomach, abdominal muscles, and diaphragm. This sequence is followed immediately in the proximal small bowel by a propagated, rhythmic contractile response similar to the migrating motor complex.

Colonic Motility

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Colonic transit is slow most of the time but rapid at other times. Residue may be retained for prolonged periods in the ascending and transverse colon; alternatively, a mass movement may deliver the contents to the sigmoid colon in seconds. Feeding stimulates movement of colonic content (a gastrocolonic response). In health, the average mouth-to-cecum transit time is about 6 hours, and transit times through the right colon, left colon, and sigmoid colon are about 12 hours each. Decreased calorie intake slows colonic transit, whereas

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Colonic Motility

The normal colon displays short-duration (phasic) contractions and a background contractility or tone. Nonpropagated phasic contractions segment the colon and facilitate mixing, retention of residue, and formation of solid stool. High-amplitude propagated contractions, which exceed 75 mm Hg, propagate over a distance of at least 15 cm at a propagation velocity of 0.15 to 2.2 cm/second and contribute to the movement of feces in the colon. In health, these contractions occur on average five or six times per day, most often postprandially and between 6 am and 2 pm.

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ABSTRACT

Disorders of gastrointestinal motility comprise at least 25% of all gastroenterology practice. The manifestations of disordered neuromuscular function include gastroparesis, chronic intestinal pseudo-obstruction, chronic constipation, dumping syndrome, and diarrhea. Rectal evacuation disorders may present with constipation, abdominal discomfort, bloating, or nausea. Motility disorders result from abnormal neuroenteric, muscle, transmitter, or hormonal functions. Algorithms are provided for evaluation of patients with retardation of gastric or small bowel transit and for the very common clinical presentation of chronic constipation. The principles of treatment are based on accurate diagnosis, correction of dehydration and malnutrition, use of prokinetic or anti-motility agents, and symptomatic remedies such as antiemetics for nausea or vomiting and laxatives for constipation.

KEYWORDS

gastroparesis
dumping
constipation
neuropathy
myopathy
prokinetic
pseudo-obstruction

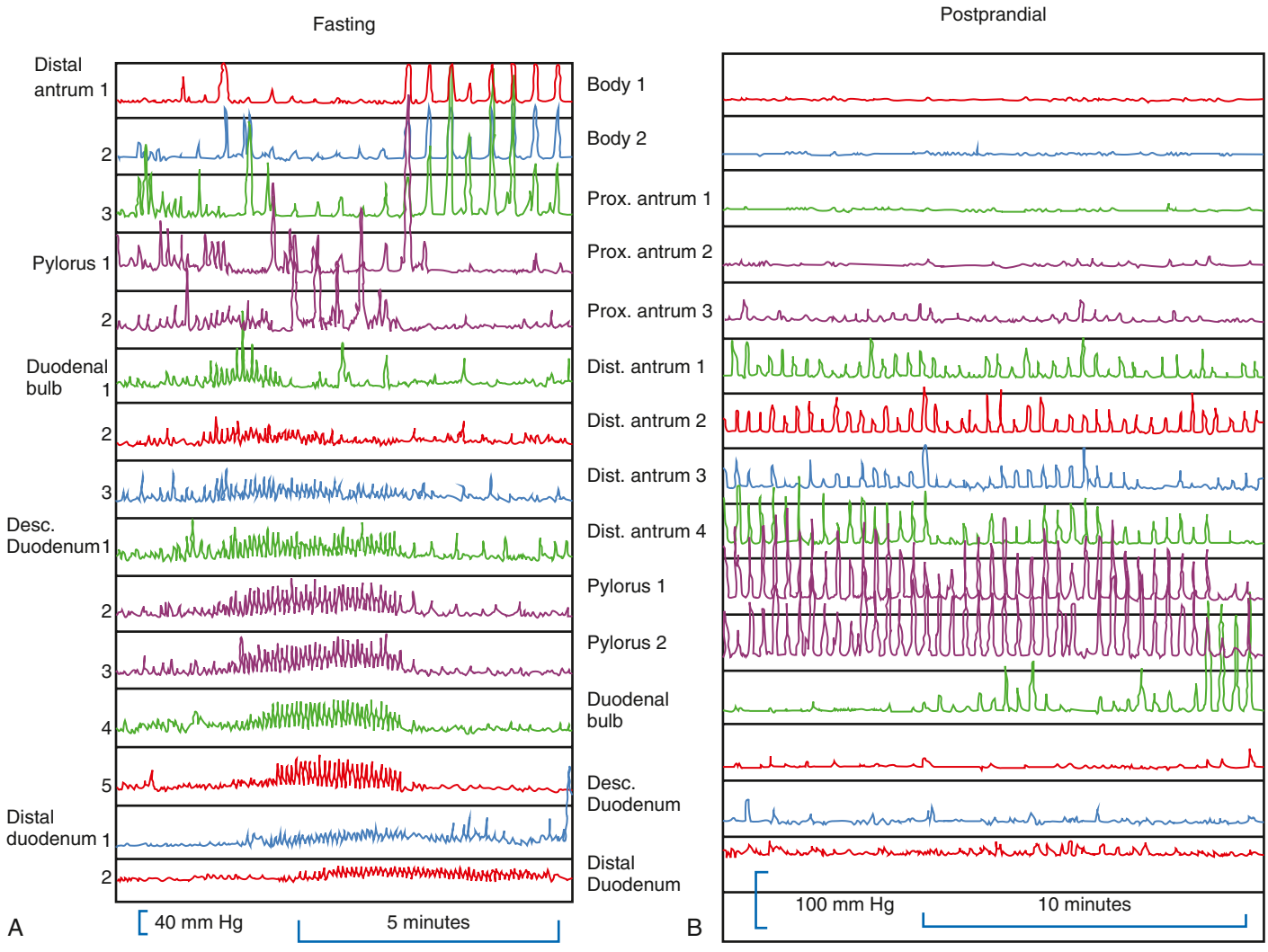

E-FIGURE 122-1. **A,** The migrating motor complex (MMC) in the gastric and small intestinal motor pattern of the interdigestive state. The interdigestive motility begins after digestion and absorption of nutrients are complete, 2 to 3 hours after a meal. Sensors in the stomach show that the MMC starts as large amplitude contractions at 3 per minute in the distal stomach. Activity in the stomach migrates into the small intestine to the ileum. (From Camilleri M. Physiological fundamentals of neurogastroenterology: motility, absorption, sensation. In: *Neurogastroenterology and Gastrointestinal Motility in Clinical Practice*. Valdovinos Diaz MA, Remes-Troche JM, Coss-Adame E, eds. Mexico City, Mexico: Permanyer Publishers, 2017.) **B,** Gastroduodenal manometry in healthy subject showing contractions in the postprandial period from the gastric body to the duodenum. Desc. = descending; Dist. = distal; Prox. = proximal. (From Nelson AD, Camilleri M, Acosta A, et al. Effects of ghrelin receptor agonist, relamorelin, on gastric motor functions and satiation in healthy volunteers. *Neurogastroenterol Motil*. 2016;28:1705-1713.)

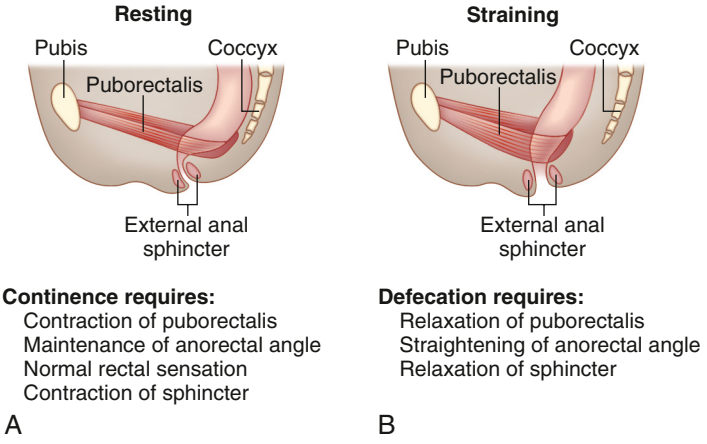

FIGURE 122-1. **Pelvic floor and anorectal functions during continence and defecation.** Sagittal view through the pelvis in the resting (A) and straining (B) postures. Coordinated functions of pelvic floor (puborectalis) and anal sphincter are essential for continence and defecation.

meals greater than 500 kcal, especially if fat-rich, stimulate colonic motility and propulsion. Outlet obstruction in patients with pelvic floor dysfunction or voluntary suppression of defecation often slow colonic transit and decrease the motor response to feeding.

Fluid reabsorption influences gastrointestinal transit. Approximately 9 L of fluid enters the gut from oral intake and endogenous secretions. The small intestine delivers about 1.5 L of fluid to the colon, where most is reabsorbed, leaving a maximum of 200 mL of water excreted in normal stool. Up to 3 L of fluid can be reabsorbed by the colon over 24 hours, unless the ileocolonic flow rate or colonic motility overwhelm the colon's capacity or reabsorption.

Defecation and Continence

Normal defecation requires a series of coordinated actions of the colon, rectum, pelvic floor, and anal sphincter muscles (Fig. 122-1). Distention of the rectum results in the relaxation of the internal anal sphincter (rectoanal inhibitory reflex) and simultaneous contraction of the external anal sphincter to maintain continence. The anal transition zone can sense the difference between solid or liquid stool and gas.

DISEASES OF SLOW TRANSIT THROUGH THE STOMACH AND SMALL BOWEL

PATHOBIOLOGY

Gastrointestinal motility disturbances (Table 122-1) result from disorders of the extrinsic nervous system, enteric nervous system, intestinal pacemakers or smooth muscle. Neuropathic patterns are characterized by normal amplitude but incoordinated contractions, whereas myopathies are characterized by low-amplitude contractions (average <40 mm Hg in the antrum and <10 mm Hg in the small bowel).

Genetic defects that result in congenital dysmotility include abnormalities of *RET*, the gene that encodes the tyrosine kinase receptor, and abnormalities in the endothelin B system. Neural crest cells migrate from the vagal and sacral crest to the developing gut and, over time, colonize the entire developing alimentary canal and its appendages. Endothelin B serves to retard maturation of migrating neural crest cells, thus facilitating colonization of the entire gut with nerve cells.

EXTRINSIC NEUROPATHIC DISORDERS

Extrinsic neuropathic processes include vagotomy, trauma, Parkinson disease (Chapter 378), diabetes (Chapter 210), amyloidosis (Chapter 174), a paraneoplastic syndrome usually associated with small cell carcinoma of the lung (Chapter 177), and effect of medications, such as α_2-adrenergic agonists, glucagon-like peptide 1 analogues, opiates, and anticholinergics, on neural control.

Damage to the autonomic nerves may lead to motor, secretory, and sensory disturbances, most frequently resulting in constipation. Fasting colonic motility and tone remain normal, but a reduced left colon response to feeding as well as decreased rectal tone and sensitivity may lead to colorectal dilation and fecal impaction.

ENTERIC AND INTRINSIC NEUROPATHIC DISORDERS

Disorders of the enteric nervous system or interstitial cells of Cajal are usually the result of an infectious (e.g., viral), degenerative, immune, or inflammatory process associated with infiltration of the myenteric plexus with inflammatory cells.

TABLE 122-1 CLASSIFICATION OF GASTROPARESIS AND PSEUDO-OBSTRUCTION

TYPE	NEUROPATHIC	MYOPATHIC
Infiltrative	Progressive systemic sclerosis Amyloidosis	Progressive systemic sclerosis Amyloidosis Systemic lupus erythematosus Ehlers-Danlos syndrome Dermatomyositis
Familial	Familial visceral neuropathies	Familial visceral myopathies Metabolic myopathies
Idiopathic	Idiopathic intestinal pseudo-obstruction	Sporadic hollow visceral myopathy
Neurologic	Porphyria Heavy metal poisoning Brain stem tumor Parkinson disease Multiple sclerosis Spinal cord transection	Myotonia Other dystrophies
Infectious	Chagas disease Cytomegalovirus Norwalk virus Epstein-Barr virus	
Drug induced	Tricyclic antidepressants Narcotic agents Anticholinergic agents Antihypertensives Dopaminergic agents Vincristine Laxatives	
Paraneoplastic	Small cell lung cancer Carcinoid syndrome	
Postsurgical/ Injury	Postvagotomy with or without pyloroplasty or gastric resection Spinal cord injury	
Endocrine	Diabetes mellitus Hypothyroidism or hyperthyroidism Hypoparathyroidism	

SMOOTH MUSCLE DISORDERS

Disturbances of smooth muscle may result in significant disorders of gastric emptying and of transit through the small bowel and colon. Motility disturbances may be the result of metabolic disorders, such as hypothyroidism (Chapter 207) and hyperparathyroidism (Chapter 227), but these patients more commonly present with constipation. Scleroderma may result in focal or general dilation, wide-mouthed diverticula, and delayed transit in the stomach, small bowel, and colon. The amplitude of contractions is reduced, and bacterial overgrowth may result in steatorrhea or pneumatosis intestinalis. Mitochondrial neurogastrointestinal encephalomyopathy is an autosomal recessive condition that may be manifested with hepatic failure in neonates, seizures or diarrhea in infants, and hepatic failure or chronic intestinal pseudo-obstruction in adults.

CLINICAL MANIFESTATIONS

The clinical features of gastroparesis[1,2] and chronic intestinal pseudo-obstruction[3] are similar and include nausea, vomiting, early satiety, abdominal discomfort, distention, bloating, and anorexia. Severe cases, which occur mostly in patients with disorders of smooth muscle, may be accompanied by dilation, weight loss, depletion of mineral and vitamin stores. Diarrhea and constipation indicate that the motility disorder extends beyond the stomach. Vomiting may result in aspiration pneumonia (Chapter 82) or Mallory-Weiss esophageal tears (Chapters 121 and 124), and patients with a generalized motility disorder may have abnormal swallowing or delayed colonic transit.

A careful family and medication history is essential. Review of systems may reveal an underlying collagen vascular disease (e.g., scleroderma) or disturbances of extrinsic autonomic neural control, including orthostatic dizziness, difficulties with erection or ejaculation, recurrent urinary tract infections, dry mouth, dry eyes, dry vagina, difficulties with visual accommodation in bright lights, and absence of sweating.

On physical examination, a succussion splash indicates stasis, typically in the stomach. The hands and mouth may reveal signs of Raynaud phenomenon or

scleroderma (Chapter 246). Testing of pupillary responses (to light and accommodation), external ocular movements, blood pressure in the lying and standing positions, and general features of a peripheral neuropathy can identify patients with an associated neurologic disturbance (e.g., diabetic neuropathy) or mitochondrial cytopathies (see under the Smooth Muscle Disorders section in this chapter).

The differential diagnosis includes mechanical obstruction, functional gastrointestinal disorders, anorexia nervosa, and the rumination syndrome. The rumination syndrome is a relatively common, underdiagnosed condition that is manifested with early (0 to 30 minutes) postprandial, effortless regurgitation of undigested food after virtually every meal.

DIAGNOSIS

Diagnosis requires documentation of delayed gastric emptying of a digestible solid meal. The clinician should assess the acuity of symptoms and the patient's state of hydration and nutrition. The goals of the evaluation are to determine what regions of the digestive tract are malfunctioning and whether the symptoms are due to a neuropathy or a myopathy (Fig. 122-2). Key steps include the following:

1. *Suspect and exclude mechanical obstruction* by upper gastrointestinal endoscopy and small bowel imaging studies, including a small bowel follow-through, computed tomographic enterography, and magnetic resonance enteroclysis. Capsule endoscopy should be avoided because of the potential risk of retention of the capsule. These studies rarely identify the cause, however, except for systemic sclerosis and mitochondrial cytopathy, which are characterized by megaduodenum, multiple small bowel diverticula, and pneumatosis intestinalis.
2. *Assess gastric and small bowel motility*. After mechanical obstruction and alternative diagnoses such as Crohn disease (Chapter 127) have been excluded, a transit profile of the stomach should be performed using a radiolabeled solid meal followed by scintigraphy at 0, 1, 2, 3, 4, and 6 hours, or a stable isotope breath test. Delayed gastric emptying is associated with symptoms of gastroparesis.[4] If the underlying cause of the motility disturbance is known, it is usually unnecessary to pursue further diagnostic testing. If the cause is unclear, gastroduodenal manometry by use of a multilumen tube with sensors in the distal stomach and proximal small intestine can differentiate a neuropathic process (normal-amplitude contractions but abnormal patterns of contractility) from a myopathic process (low-amplitude contractions in the affected segments, typically <10 mm Hg in the small intestine). A wireless motility capsule also can assess contraction amplitude if the intestine is not dilated to more than 5 cm. Manometry may also identify pylorospasm, which may respond to per-oral endoscopic myotomy.
3. *Identify the pathogenesis* (see Table 122-1). Other tests for neuropathic causes assess autonomic dysfunction (Chapter 389), autoantibodies associated with paraneoplastic syndromes, and brain stem function. In patients with a myopathic disorder of unclear cause, the evaluation should consider amyloidosis (immunoglobulin electrophoresis, fat aspirate, or rectal biopsy; Chapter 174), systemic sclerosis (topoisomerase I; Chapter 246), and thyroid disease (Chapter 207). In appropriate settings, porphyria (Chapter 194) and Chagas disease (Chapter 318) may need to be excluded. Diabetes mellitus (Chapter 210) is associated with gastroparesis, pylorospasm, intestinal pseudo-obstruction, diarrhea, constipation, and fecal incontinence.[5] In refractory cases, genetic testing or full-thickness biopsy of the small intestine (E-Fig. 122-2) may be required to identify metabolic muscle disorders and mitochondrial cytopathies (Chapter 389).
4. *Identify complications of the motility disorder, including bacterial overgrowth, dehydration, and malnutrition*. In patients presenting with diarrhea, it is important to assess nutritional status and to exclude bacterial overgrowth by culture of small bowel aspirates or glucose-hydrogen breath test (Chapter 126). Bacterial overgrowth is relatively uncommon in neuropathic disorders but is found more often in myopathic conditions, such as scleroderma, that are associated more often with dilation or low-amplitude contractions. An empirical trial of antibiotics (see later) often is used instead of formal testing.

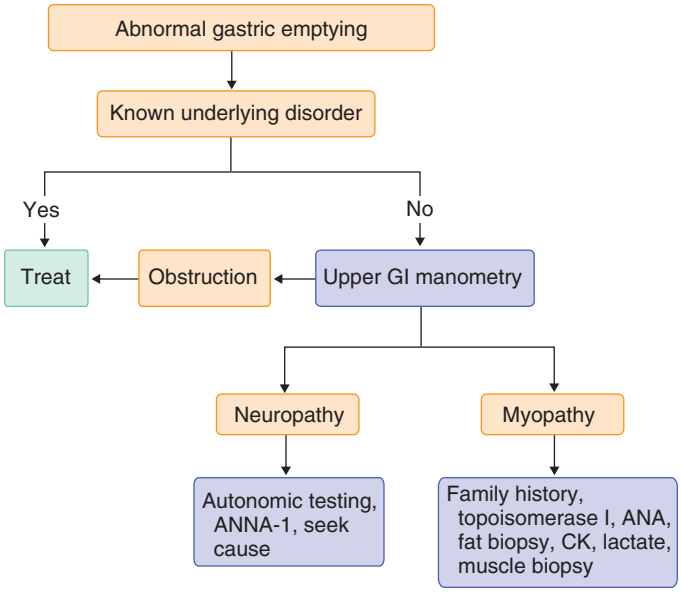

FIGURE 122-2. Flow diagram outlines steps in diagnosis of idiopathic gastroparesis and intestinal pseudo-obstruction. ANA = antinuclear antibody; ANNA-1 = type 1 antineuronal nuclear antibody; CK = creatine kinase; GI = gastrointestinal.

TREATMENT

Rehydration, electrolyte repletion, and nutritional supplementation are particularly important during acute exacerbations of gastroparesis and chronic intestinal pseudo-obstruction. Initial nutritional measures include small solid particle meals (blenderized solids) or low-fiber liquid food supplements with the addition of iron, folate, calcium, and vitamins D, K, and B_{12} at the usually recommended daily levels. In patients with more severe symptoms, enteral or parenteral supplementation may be required.[6] If it is anticipated that enteral supplementation may be needed for more than 3 months, a jejunostomy feeding tube is recommended. These tubes may be placed with the aid of endoscopy. Gastrostomy tubes should be avoided in patients with gastroparesis except for venting purposes.

Medical Therapy

Prokinetic Agents

Medications often can enhance gastric emptying and improve symptoms in patients with neuromuscular motility disorders.[A1] Tradipitant (an experimental antagonist of tachykinin receptor 1 given orally at 85 mg twice daily) can significantly reduce nausea and vomiting in patients with diabetic or idiopathic gastroparesis.[A2] Aprepitant (125 mg/day for 4 weeks) also appears to be efficacious for gastroparesis and related disorders.[A3]

Erythromycin, a macrolide antibiotic that stimulates motilin receptors at higher doses (250 to 500 mg) and cholinergic mechanisms at lower doses (40 to 80 mg) accelerates gastric emptying in gastroparesis. Erythromycin is most effective when it is used intravenously (3 mg/kg every 8 hours by slow infusion) during acute exacerbations of gastroparesis. Efficacy wanes over 14 days because of tachyphylaxis. Pyridostigmine (30 to 60 mg every 6 hours tablet or liquid formulation) is also sometimes used. In patients who do not respond to other treatments, metoclopramide (a dopamine antagonist with mild prokinetic and antiemetic properties) can be useful for up to 3 months as a rapid oral disintegrating tablet, intranasal spray, elixir, or parenteral preparation. It should be taken orally (15 to 30 minutes before meals and at bedtime). Usual doses are 5 to 10 mg four times daily, but patients may experience side effects (changes in affect, anxiety) at relatively low doses (even 30 to 40 mg/day).

Domperidone (10 to 20 mg, three times per day before meals) is another dopamine antagonist available through an investigational drug application to the U.S. Food and Drug Administration and local Institutional Review Board. Its efficacy appears similar to metoclopramide, with lower risk of involuntary movements. Domperidone-induced cardiac arrhythmias may occur in patients with specific polymorphisms in the cytochrome P-450 3A4 gene, which encodes the enzyme that metabolizes domperidone (Chapter 25). Genetic screening is not recommended in any guidelines.

Experimental medications for gastroparesis include relamorelin, an agonist of ghrelin receptor (given subcutaneously once or twice daily), which can speed gastric emptying and improve the symptoms of gastroparesis in diabetic patients,[A4] and felcisetrag, an intravenous 5-HT4 receptor agonist, which accelerates gastric emptying in idiopathic and diabetic gastroparesis.[A5]

Antiemetic Agents

Antiemetics (Table 118-5), including diphenhydramine (25 mg orally up to two times per day for up to 3 months) and promethazine (orally or by suppository, 25 mg up to two times per day) can treat nausea and vomiting in patients with gastroparesis and intestinal pseudo-obstruction. The serotonin 5-HT_3 antagonists (e.g., ondansetron, 4 or 8 mg tablet or oral dissolution tablet; or granisetron which is available as a transdermal patch) also may be used.

Other Approaches

Octreotide (50 μg subcutaneously at bedtime), a cyclized analogue of somatostatin, induces small intestinal activity that mimics phase III of the interdigestive migrating motor complex. It actually retards gastric emptying and small

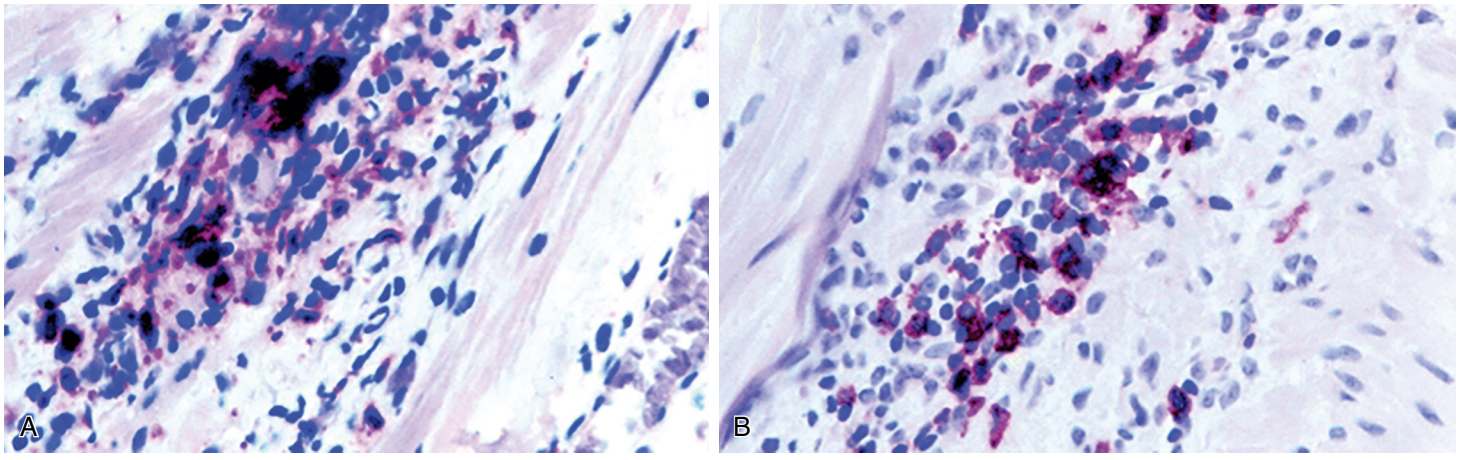

E-FIGURE 122-2. Micrographs showing both types of T lymphocytes, CD4 (A) and CD8 (B), detectable within the myenteric plexus of the small intestine (proximal ileum) of a 20-year-old man with chronic intestinal pseudo-obstruction. Note the intense CD4 and CD8 immunoreactivities that represent the predominant component of the immune infiltrate observed in cases of lymphocytic ganglionitis. Alkaline phosphatase anti–alkaline phosphatase immunohistochemical technique (×120) in A and B. (From De Giorgio R, Camilleri M. Human enteric neuropathies: morphology and molecular pathology. *Neurogastroenterol Motil*. 2004;16:515-531.)

bowel transit. Octreotide may be used before sleep to sweep residue toward the colon and to avoid bacterial overgrowth.

Antibiotic therapy, typically using different antibiotics for 7 to 10 days each month in an attempt to avoid bacterial resistance, is indicated in patients with documented, symptomatic bacterial overgrowth. Common antibiotics include doxycycline (50 to 100 mg twice daily), metronidazole (250 mg three times daily), and double-strength trimethoprim-sulfamethoxazole (two tablets twice daily). Use of antibiotics in patients with diarrhea and fat malabsorption secondary to bacterial overgrowth results in significant symptomatic relief.

Surgical and Endoscopic Therapy

Surgical decompression is rarely necessary in patients with chronic pseudo-obstruction. Venting enterostomy (jejunostomy) is effective, however, in relieving abdominal distention and bloating and in reducing the frequency with which nasogastric intubations and hospitalizations are required for acute exacerbations compared with the period before vent placement. Access to the small intestine by enterostomy also provides a means to deliver nutrients and should be considered in patients with intermittent symptoms. Surgical treatment should be considered whenever the motility disorder is localized to a resectable portion of the gut: completion gastrectomy for patients with post–gastric surgical stasis syndrome, and colectomy with ileorectostomy for intractable constipation associated with chronic colonic pseudo-obstruction.

Gastric electrical stimulation may improve symptoms in some patients with severe gastroparesis.[A6] Botulinum injection of the pylorus, followed if successful by gastric per-oral endoscopic myotomy or pyloric surgery, is a promising therapy for troublesome cases.[7]

Small bowel transplantation currently is limited to patients who have intestinal failure and reversible liver disease induced by total parenteral nutrition or who have life-threatening or recurrent catheter-related sepsis. Isolated transplantation of the small intestine is associated with higher graft and patient survival and fewer complications related to rejection and infection.

DISEASES OF RAPID TRANSIT THROUGH STOMACH AND SMALL BOWEL

DUMPING SYNDROME AND ACCELERATED GASTRIC EMPTYING

Dumping syndrome and accelerated gastric emptying typically follow truncal vagotomy and gastric drainage procedures (Chapter 125), fundoplication for gastric esophageal reflux disease (Chapter 124), or bariatric procedures such as sleeve gastrectomy or Roux-en-Y gastric bypass. A high calorie (usually carbohydrate) content of the liquid phase of the meal evokes a rapid insulin response with secondary hypoglycemia.

The management of dumping syndrome and accelerated gastric emptying emphasizes dietary maneuvers, such as avoidance of high-nutrient liquid drinks and possibly addition of guar gum or pectin to retard gastric emptying of liquids. Pharmacologic treatment with octreotide, 25 to 100 µg subcutaneously before meals, retards intestinal transit and inhibits the hormonal responses that lead to hypoglycemia.

RAPID TRANSIT DYSMOTILITY OF THE SMALL BOWEL

Rapid transit of material through the small bowel may occur in postvagotomy diarrhea (Chapter 126), short bowel syndrome (Chapter 126), diabetic diarrhea (Chapter 126), and carcinoid diarrhea (Chapter 213) and result in significant losses of fluid and electrolytes. Ileal resection or disease and idiopathic bile acid malabsorption may induce colonic secretion and secondary diarrhea. Accelerated transit may be confirmed by scintigraphic studies.

Treatment goals are to restore hydration and nutrition and to slow small bowel transit by avoiding hyperosmolar drinks and replacing with iso-osmolar or hypo-osmolar oral rehydration solutions. The fat content in the diet should be reduced to approximately 50 g/day to avoid delivery of unabsorbed fat to the colon. All electrolyte and nutritional deficiencies of calcium, magnesium, potassium, and water-soluble and fat-soluble vitamins should be corrected. In patients with less than 1 m of residual small bowel, it may be impossible to maintain fluid and electrolyte homeostasis without parenteral support. In patients with a longer residual intestinal segment, oral nutrition, pharmacotherapy, and supplements are almost always effective.

The opioid agent loperamide (2 to 4 mg 30 minutes before meals and at bedtime for a total dose of 16 mg/day) suppresses the motor response to feeding and improves symptoms. Bile acid binding, such as with cholestyramine (4 g three times daily) or colesevelam (1.875 g twice daily), is indicated for patients with suspected or proven bile acid malabsorption.[8] Clonidine (0.1 mg daily as oral tablet or dermal patch) or a 5-HT_3 antagonist (e.g., ondansetron, 4 to 8 mg three times daily) is used rarely in addition to loperamide. Octreotide (50 µg subcutaneously three times daily, 5 minutes before meals) may be used in patients for whom the oral agents are ineffective or poorly tolerated.

COLONIC MOTILITY DISORDERS

Constipation

EPIDEMIOLOGY

Constipation is a common clinical problem, reported by about 20% of the population, and 40% of Americans report needing to strain excessively to pass their bowel movements.[9]

PATHOBIOLOGY

In functional constipation, transit is normal, and there is no evacuation disorder. These patients may have pain in association with constipation, and there is overlap with constipation-predominant irritable bowel syndrome (Chapter 123). In patients with acquired slow-transit constipation, unassociated with colonic dilation, the number of interstitial cells of Cajal in the different layers of the colon is reduced compared with controls.

Idiopathic megarectum and megacolon can be either congenital or acquired; an enteric nervous system defect is suspected. In megacolon, the dilated segment shows normal phasic contractility but decreased colonic tone, with smooth muscle hypertrophy and fibrosis of the muscularis mucosa, circular muscle, and longitudinal muscle layers.

Acquired defects in the enteric nervous system may result in constipation in Chagas disease (Chapter 318), which is caused by infection with *Trypanosoma cruzi* and results in the destruction of myenteric neurons.

DIAGNOSIS

It is essential to distinguish an evacuation disorder, also called functional outlet obstruction (Table 122-2), from constipation resulting from slow transit or other causes.[10] In a tertiary center, about 25% of patients presenting with constipation have impaired evacuation, and the remainder have constipation associated with either normal transit (also called functional constipation) or delayed colonic transit (also called slow-transit constipation). Characterization of constipated patients without rectal evacuation disorders (Fig. 122-3) relies on the measurement of transit with radiopaque markers or scintigraphy.

TABLE 122-2 CLINICAL CLUES SUGGESTIVE OF AN EVACUATION DISORDER

HISTORY
Prolonged straining to expel stool
Taking up unusual postures on the toilet to facilitate stool expulsion
Support of perineum or digitation of rectum or vagina to facilitate rectal emptying
Inability to expel enema fluid
Constipation after subtotal colectomy for constipation
RECTAL EXAMINATION (WITH PATIENT IN LEFT LATERAL POSITION)
Inspection
Anus "pulled" forward during attempts to simulate strain during defecation
Anal verge descends <1 cm or >4 cm during attempts to simulate strain during defecation
Perineum balloons down during straining, and rectal mucosa prolapses through anus
Palpation
High anal sphincter tone at rest precludes easy entry of examining finger (in absence of painful perianal condition, e.g., anal fissure)
Anal sphincter pressure during voluntary squeeze is minimally higher than tone at rest
Perineum descends <1 cm or >4 cm during attempts to simulate strain during defecation
Puborectalis muscle palpable through posterior rectal wall is tender
Palpable mucosal prolapse during straining
"Defect" in anterior wall of the rectum, suggestive of rectocele
ANORECTAL MANOMETRY AND BALLOON EXPULSION (WITH PATIENT IN LEFT LATERAL POSITION)
Average anal sphincter resting tone >80 cm H_2O or squeeze pressure >240 cm H_2O
Failure of balloon expulsion despite addition of 200 g weight
ABDOMINO-PELVIC RADIOGRAPH
Rectal gas area >9 cm^2

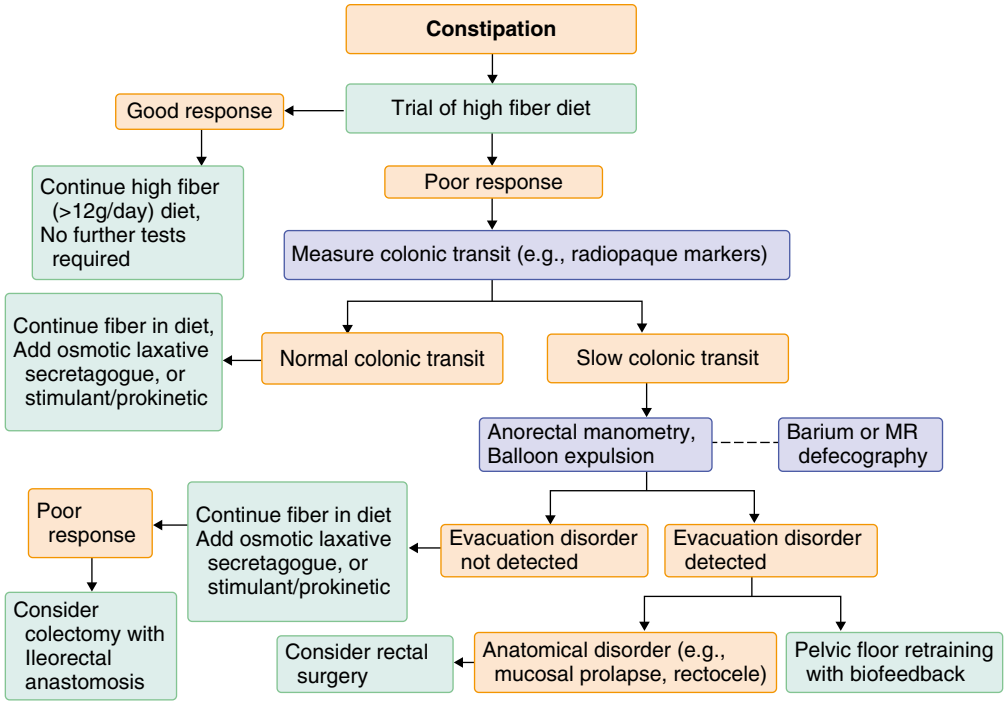

FIGURE 122-3. Algorithm in the management of constipation.

TREATMENT

The average daily fiber intake is around 12 g/day. In patients with normal-transit constipation, 20 to 30 g/day is effective to relieve constipation. In patients with slow-transit constipation, drug-induced constipation, or evacuation disorders, however, supplementation of 30 g of fiber per day does not result in any improvement in constipation. A second step is to add an osmotic laxative, such as a magnesium salt[A7] or polyethylene glycol solution, to enhance the retention of fluid within the lumen by osmotic forces, to increase fluidity, and to facilitate aboral transport of colonic contents. If these measures do not suffice, a prokinetic or stimulant agent,[11] such as bisacodyl (5 to 10 mg every 1 to 2 days) may be added (Table 122-3).[A8]

In more difficult-to-treat cases, prucalopride (1 to 2 mg daily) accelerates colonic transit and is beneficial in chronic constipation.[A9] Other pharmacologic approaches include lubiprostone (24 μg twice daily); linaclotide (72 μg, 145 μg, or 290 μg daily), or plecanatide (3 mg). These drugs as well as naloxegol (a peripheral μ-opioid antagonist at 12.5 or 25 mg daily), methylnaltrexone (0.15 mg/kg subcutaneously every other day for 2 weeks or 450 mg/day orally), naldemedine (0.2 mg daily), and the combination of oxycodone with naloxone (the latter displaces oxycodone from μ-opioid receptors in the gut) are effective in patients with opiate-induced constipation as a complication of advanced illness or noncancer pain.[A10]

When these approaches do not work, the patient should be reassessed to exclude an evacuation disorder (Chapter 131). For evacuation disorders, a biofeedback treatment program with muscle relaxation of the anal sphincters and pelvic floor results in a 70% or greater cure rate for the constipation.

Surgical Therapy

In patients whose constipation is not associated with an evacuation disorder and does not respond to aggressive medical therapies (including combinations described earlier), laparoscopic colectomy with ileorectostomy is effective in relieving constipation.

TABLE 122-3 TREATMENTS FOR CHRONIC CONSTIPATION

IDIOPATHIC CONSTIPATION
Bulk Agents
Psyllium (10 g daily), methylcellulose, calcium polycarbophil, wheat dextrin
Nonabsorbed Substances
PEG 3350 (17 g daily) Lactulose (20 g daily) Magnesium hydroxide (1 g daily)
Stimulants
Bisacodyl (5-10 mg daily) Senna (8.6 mg, 2 to 4 tabs daily) Prucalopride (1-2 mg daily)
Secretory Drugs
Lubiprostone (24 μg twice daily)* Linaclotide (72 μg, 145 μg, or 290 μg daily) Plecanatide (3 mg daily)
OPIOID-INDUCED CONSTIPATION
Opioid Receptor Antagonists
Naloxegol (12.5-25 mg daily) Naloxone/oxycodone (20 mg/40 mg) Methylnaltrexone (0.15 mg/kg subcutaneously every other day for 2 weeks or 450 mg orally per day) Naldemedine (0.2 mg daily)

*Also indicated for opioid-induced constipation.
PEG 3350 = polyethylene glycol-electrolyte.
Adapted from Wald A. Constipation: advances in diagnosis and treatment. *JAMA*. 2016;315:185-191.

HIRSCHSPRUNG DISEASE

DEFINITION

Hirschsprung disease occurs in 1 in 5000 live births. It is characterized by a localized segment of narrowing of the distal colon as a result of failure of local development of intrinsic nerves in the myenteric plexus.[12]

PATHOBIOLOGY

A relative deficiency of *KIT*-positive interstitial cells of Cajal has been reported in Hirschsprung disease and chronic intestinal pseudo-obstruction. The majority of familial and sporadic Hirschsprung disease is associated with *RET* oncogene mutations, but mutations in *EDNRB, GDNF*, and *EDN3* have been reported as well. Hirschsprung disease is well characterized histologically by the absence of ganglion cells in the myenteric and submucosal plexus and the presence of hypertrophied nerve trunks in the space normally occupied by the ganglion cells. In the muscle layers of the colon involved with Hirschsprung disease, deficiency of nerve growth factor receptors also contributes to the dysfunction. The narrowing and failure of relaxation in the aganglionic segment are thought to be due to the lack of neurons containing nitric oxide synthase.

CLINICAL MANIFESTATIONS

Hirschsprung disease is usually diagnosed at birth because of failure to pass meconium or the presence of megacolon, although it may be identified in

childhood as a result of fecal retention, constipation, or abdominal distention. Onset of symptoms or diagnosis after the age of 10 years is rare.

DIAGNOSIS

Diagnosis is based on the typical focal narrowing of the colon, the absence of the rectoanal inhibitory reflex (relaxation of anal sphincter pressure at rest during distention of a balloon in the rectum depends on natural preservation and maturation of intrinsic nerves in the distal bowel), and a deep rectal biopsy specimen showing absence of submucosal neurons with hypertrophied nerve trunks.

TREATMENT

Treatment involves excision of the affected bowel segment or a pull-through procedure by which normal bowel is anastomosed to the cuff of the lower rectum, just above the anal sphincters.

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For the General References and other additional features, please visit Elsevier eBooks+ at https://ebooks.health.elsevier.com.

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123 IRRITABLE BOWEL AND FUNCTIONAL UPPER GASTROINTESTINAL SYNDROMES

LIN CHANG

Functional gastrointestinal disorders are a spectrum of chronic gastrointestinal disorders that are characterized by specific symptoms depending on the region that is involved.[1] Functional gastrointestinal disorders have been traditionally known to be syndromes without a structural or biochemical basis to explain their clinical features. However, alterations in the bidirectional communication between the brain and the gut are increasingly being implicated in their motility disturbances, visceral hypersensitivity, altered mucosal and immune function, altered gut microbiota, and altered central nervous system (CNS) processing, all of which may vary among individuals or even in the same individual over time. As a result, these conditions are now referred to as disorders of gut-brain interaction.

The most current and widely used classification system is the Rome IV diagnostic criteria, which has defined a number of functional gastrointestinal disorders, by far the most common of which are irritable bowel syndrome, functional dyspepsia, and functional heartburn. Based on these criteria, the worldwide prevalence of functional gastrointestinal disorders is estimated to be as high as 40%.[2]

IRRITABLE BOWEL SYNDROME

DEFINITION

Irritable bowel syndrome is characterized by chronic or recurrent abdominal pain associated with alterations in stool form and/or frequency (i.e., diarrhea and/or constipation). Irritable bowel syndrome, which is frequently diagnosed in primary care and referral practices, is a functional bowel disorder attributable to the middle or lower gastrointestinal tract. It also includes functional constipation (also known as chronic idiopathic constipation), functional diarrhea, and functional abdominal bloating/distention. Functional bowel disorders are a spectrum of syndromes that can transition to another over time because of their natural history, response to therapy, or both. For example, a patient may initially present with symptoms of functional constipation, such as hard and infrequent stools and straining without abdominal pain, but later develop abdominal pain associated with constipation and meet criteria for irritable bowel syndrome with predominant constipation.

EPIDEMIOLOGY

Irritable bowel syndrome is seen worldwide, but its prevalence varies based on geographic region, diagnostic criteria, and population studied. In the United States, Canada, and the United Kingdom, the estimated prevalence of irritable bowel syndrome based on the current Rome IV diagnostic criteria is 4.6%,[3] but the prevalence was higher using older, less restrictive criteria. In a global epidemiology study in 33 countries on six continents, the worldwide prevalence of irritable bowel syndrome was 4.1% based upon Rome IV criteria, but it was more common in women (5.2%) than in men (2.9%).[4] Using predominantly a physician's diagnosis of irritable bowel syndrome, the estimated incidence is about 38 per 10,000 person-years.

The three main subtypes of irritable bowel syndrome are based upon the usual stool form (i.e., irritable bowel syndrome with predominant constipation, irritable bowel syndrome with predominant diarrhea, and irritable bowel syndrome with mixed bowel habits). Patients who have irritable bowel syndrome but whose stool form pattern does not meet criteria for one of these three bowel habit subtypes is defined as having irritable bowel syndrome unclassified. Using Rome IV criteria, irritable bowel syndrome with predominant diarrhea and irritable bowel syndrome with mixed bowel habits each accounted for 35 to 40% of irritable bowel patients, irritable bowel syndrome with predominant constipation accounted for about 25%, and less than 5% were irritable bowel syndrome unclassified. However, the subtypes of irritable syndrome can transition over time in the same patient.

Up to 50% of individuals with symptoms of irritable bowel syndrome do not seek health care, but functional bowel disorders are nevertheless estimated to generate about 4.4 million annual physician visits.[5] When they do seek health care, patients with irritable bowel syndrome are more likely to have diagnostic tests and abdominal or pelvic surgeries compared with other patients, although many of these interventions are neither necessary nor recommended by professional society guidelines. Health care–seeking about irritable bowel syndrome symptoms is associated with older age, a higher level of concern about bowel function, bloating, and a greater impact on social activities. Patients with irritable bowel syndrome also have increased health care visits and costs associated with nongastrointestinal symptoms as well as a significant comorbidity from other somatic and psychological disorders. In addition to increased direct medical expenses, irritable bowel syndrome is associated with absenteeism from work and impaired work productivity.

PATHOBIOLOGY

Irritable bowel syndrome is a multifactorial disorder that results from a dysregulation of gut-brain interactions, thereby resulting in alterations of intestinal motility, visceral perception, autonomic nervous system function, stress responsiveness, mucosal and immune function, gut microbiota, and CNS modulation of viscerosensory input. Risk factors that increase the risk of developing irritable bowel syndrome and of triggering symptomatic flares include genetic predisposition, environmental factors (e.g., adverse childhood experiences and infectious gastroenteritis), food, and stress.

Familial and Genetic Factors

Irritable bowel syndrome clusters in families, and the odds of having affected relatives are 1.75-fold to 2.75-fold higher than among relatives of unaffected persons. However, compelling evidence shows that environmental factors also

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childhood as a result of fecal retention, constipation, or abdominal distention. Onset of symptoms or diagnosis after the age of 10 years is rare.

DIAGNOSIS

Diagnosis is based on the typical focal narrowing of the colon, the absence of the rectoanal inhibitory reflex (relaxation of anal sphincter pressure at rest during distention of a balloon in the rectum depends on natural preservation and maturation of intrinsic nerves in the distal bowel), and a deep rectal biopsy specimen showing absence of submucosal neurons with hypertrophied nerve trunks.

TREATMENT

Treatment involves excision of the affected bowel segment or a pull-through procedure by which normal bowel is anastomosed to the cuff of the lower rectum, just above the anal sphincters.

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For the General References and other additional features, please visit Elsevier eBooks+ at https://ebooks.health.elsevier.com.

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123 IRRITABLE BOWEL AND FUNCTIONAL UPPER GASTROINTESTINAL SYNDROMES

LIN CHANG

Functional gastrointestinal disorders are a spectrum of chronic gastrointestinal disorders that are characterized by specific symptoms depending on the region that is involved.[1] Functional gastrointestinal disorders have been traditionally known to be syndromes without a structural or biochemical basis to explain their clinical features. However, alterations in the bidirectional communication between the brain and the gut are increasingly being implicated in their motility disturbances, visceral hypersensitivity, altered mucosal and immune function, altered gut microbiota, and altered central nervous system (CNS) processing, all of which may vary among individuals or even in the same individual over time. As a result, these conditions are now referred to as disorders of gut-brain interaction.

The most current and widely used classification system is the Rome IV diagnostic criteria, which has defined a number of functional gastrointestinal disorders, by far the most common of which are irritable bowel syndrome, functional dyspepsia, and functional heartburn. Based on these criteria, the worldwide prevalence of functional gastrointestinal disorders is estimated to be as high as 40%.[2]

IRRITABLE BOWEL SYNDROME

DEFINITION

Irritable bowel syndrome is characterized by chronic or recurrent abdominal pain associated with alterations in stool form and/or frequency (i.e., diarrhea and/or constipation). Irritable bowel syndrome, which is frequently diagnosed in primary care and referral practices, is a functional bowel disorder attributable to the middle or lower gastrointestinal tract. It also includes functional constipation (also known as chronic idiopathic constipation), functional diarrhea, and functional abdominal bloating/distention. Functional bowel disorders are a spectrum of syndromes that can transition to another over time because of their natural history, response to therapy, or both. For example, a patient may initially present with symptoms of functional constipation, such as hard and infrequent stools and straining without abdominal pain, but later develop abdominal pain associated with constipation and meet criteria for irritable bowel syndrome with predominant constipation.

EPIDEMIOLOGY

Irritable bowel syndrome is seen worldwide, but its prevalence varies based on geographic region, diagnostic criteria, and population studied. In the United States, Canada, and the United Kingdom, the estimated prevalence of irritable bowel syndrome based on the current Rome IV diagnostic criteria is 4.6%,[3] but the prevalence was higher using older, less restrictive criteria. In a global epidemiology study in 33 countries on six continents, the worldwide prevalence of irritable bowel syndrome was 4.1% based upon Rome IV criteria, but it was more common in women (5.2%) than in men (2.9%).[4] Using predominantly a physician's diagnosis of irritable bowel syndrome, the estimated incidence is about 38 per 10,000 person-years.

The three main subtypes of irritable bowel syndrome are based upon the usual stool form (i.e., irritable bowel syndrome with predominant constipation, irritable bowel syndrome with predominant diarrhea, and irritable bowel syndrome with mixed bowel habits). Patients who have irritable bowel syndrome but whose stool form pattern does not meet criteria for one of these three bowel habit subtypes is defined as having irritable bowel syndrome unclassified. Using Rome IV criteria, irritable bowel syndrome with predominant diarrhea and irritable bowel syndrome with mixed bowel habits each accounted for 35 to 40% of irritable bowel patients, irritable bowel syndrome with predominant constipation accounted for about 25%, and less than 5% were irritable bowel syndrome unclassified. However, the subtypes of irritable syndrome can transition over time in the same patient.

Up to 50% of individuals with symptoms of irritable bowel syndrome do not seek health care, but functional bowel disorders are nevertheless estimated to generate about 4.4 million annual physician visits.[5] When they do seek health care, patients with irritable bowel syndrome are more likely to have diagnostic tests and abdominal or pelvic surgeries compared with other patients, although many of these interventions are neither necessary nor recommended by professional society guidelines. Health care–seeking about irritable bowel syndrome symptoms is associated with older age, a higher level of concern about bowel function, bloating, and a greater impact on social activities. Patients with irritable bowel syndrome also have increased health care visits and costs associated with nongastrointestinal symptoms as well as a significant comorbidity from other somatic and psychological disorders. In addition to increased direct medical expenses, irritable bowel syndrome is associated with absenteeism from work and impaired work productivity.

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Irritable bowel syndrome is a multifactorial disorder that results from a dysregulation of gut-brain interactions, thereby resulting in alterations of intestinal motility, visceral perception, autonomic nervous system function, stress responsiveness, mucosal and immune function, gut microbiota, and CNS modulation of viscerosensory input. Risk factors that increase the risk of developing irritable bowel syndrome and of triggering symptomatic flares include genetic predisposition, environmental factors (e.g., adverse childhood experiences and infectious gastroenteritis), food, and stress.

Familial and Genetic Factors

Irritable bowel syndrome clusters in families, and the odds of having affected relatives are 1.75-fold to 2.75-fold higher than among relatives of unaffected persons. However, compelling evidence shows that environmental factors also

ABSTRACT

Functional gastrointestinal disorders comprise a spectrum of chronic gastrointestinal disorders that are prevalent worldwide. These disorders, which are related to bidirectional communication between the brain and the gut, can cause a wide range of symptoms: motility disturbances, visceral hypersensitivity, altered mucosal and immune function, altered gut microbiota, and altered central nervous system processing. From a clinician's perspective, the conditions include irritable bowel syndrome, functional dyspepsia, and functional heartburn, each of which has its own epidemiology, pathobiology, clinical manifestations, and treatments.

KEYWORDS

irritable bowel syndrome
functional dyspepsia
functional heartburn

influence the presence of irritable bowel syndrome, potentially to a greater degree than genetic heritability.

Large genome-wide association studies have found that polymorphisms on chromosome 9q31.2 are significantly more common in women but not men with irritable bowel syndrome compared with controls. Another large study found six independent susceptibility loci. Four of these six loci also have been associated with mood and anxiety disorders and/or genes expressed in the nervous system, thereby suggesting a key role for neuronal pathways within the brain-gut axis.

About 2 to 3% of patients with irritable bowel syndrome have rare genetic variants that may result in a functional abnormality at the level of the gastrointestinal tract.[6] These variants include functional polymorphisms of the voltage-gated channel $Na_v1.5$ (*SCN5A*) causing a channelopathy and potentially a loss of function in voltage dependence or mechanosensitivity and sucrase-isomaltase gene variants indicative of reduced levels of a disaccharide enzyme that may protect against chronic diarrhea. Other associations include a homozygous short allele of the serotonin transporter gene (*5-HTTLPR*) and polymorphisms in the genes that encode for serotonin type 3 receptors. However, all these findings must be interpreted cautiously until treatment studies validate their causality.

Postinfection Irritable Bowel Syndrome

The strongest risk factor for irritable bowel syndrome, especially irritable bowel syndrome with predominant diarrhea, is an acute gastrointestinal infection, which increases the risk of irritable bowel syndrome at 12 months by about four-fold regardless of whether the infection was bacterial, protozoal/parasitic, or viral in nature.[7] The risk is especially increased in individuals who are younger, female, or have a history of gastroesophageal reflux disease, dyspepsia, more severe diarrheal illness, anxiety, or depression.

Stressful Life Events

An important risk factor for the development and exacerbations of irritable bowel syndrome is stressful life events.[8] Implicated stressful life events include physical, sexual, or emotional/verbal abuse; history of severe illness; death or mental illness of a parent; incarceration of an individual in the household; and exposure to wartime conditions.

Increased Visceral Perception

The perception of gut stimuli is influenced by the integrated activity and communication among the gut lumen, mucosa, submucosa, enteric nervous system, and CNS.[9,10] Stimuli within the gut (e.g., contractile activity, distension) are detected and transmitted via primary afferent nerves that project to the dorsal horn of the spinal cord, with neurons located in the dorsal root ganglia. This sensory input ascends along the dorsal column and then to the contralateral ventroposterolateral nucleus of the thalamus, brainstem nuclei, and cortical regions. Visceral stimuli are assessed by the salience network and insula, which assess the importance of these signals and whether they are perceived as normal gut sensations, abdominal discomfort, or pain. The two main brain output systems to the gut are the autonomic nervous system and descending pain modulatory pathways. The autonomic nervous system regulates and modulates gut motility, immune responses, and sensation, whereas the pain facilitatory and inhibitory pathways regulate pain sensitivity at the level of the spinal cord's dorsal neurons, which receive afferent visceral input.

Increased perception of visceral stimuli and symptoms of irritable bowel syndrome develop from either greater sensitivity of visceral afferent pathways (peripheral sensitization) or central amplification of visceral afferent input at the level of the brain and spinal cord (central sensitization). Peripheral sensitization of sensory nerves occurs when nerves are activated by mediators released from immune and/or epithelial cells, such as occurs in inflammation or infection.

Patients with irritable bowel syndrome have overall lowered thresholds for pain or discomfort when exposed to rectal or colonic balloon distension (i.e., visceral hypersensitivity) compared with healthy individuals. However, this hypersensitivity typically is seen only in a subset of patients with irritable bowel syndrome and only modestly correlates with the severity of their symptoms.

Altered CNS Processing and Modulation

Multimodal brain imaging studies have demonstrated both structural and functional alterations in task-related brain networks in patients with irritable bowel syndrome. Neuroimaging findings associated with irritable bowel syndrome include greater volume and cortical thickness of the sensorimotor cortex that correlates with the severity of symptoms; alterations in resting state functional connectivity of the anterior insula and amygdala; greater engagement of the salience detection and emotional arousal networks in response to rectal balloon distension; decreased corticolimbic inhibitory feedback; and increased activation of the central autonomic network that regulates autonomic nervous system response. These findings support the role of the CNS and brain-gut interactions in irritable bowel syndrome pathophysiology.

Gut Transit and Motility

Alterations in small intestinal and colonic motility in irritable bowel syndrome include increased colonic motility during fasting, in the postprandial state, and with psychological or physical stressors. A subset of patients with irritable bowel syndrome with predominant diarrhea have a more rapid intestinal transit time that can be induced by psychological and physical stress. About 50% of patients with irritable bowel syndrome with predominant diarrhea have accelerated colon transit times.

Peripheral Gastrointestinal Factors

The gut is composed of a network of cells and mediators that affect gastrointestinal function and contribute to the symptoms of irritable bowel syndrome. This peripheral gut network can communicate with the brain via multiple routes, including neural, endocrine, and inflammatory pathways. The brain-to-gut communication is mainly mediated via the autonomic nervous system pathways to the gut.

Patients with irritable bowel syndrome have an increase in colonic mucosal nerves that express substance P, transient receptor potential vanilloid type 1 cannabinoid, and protease-activated receptors. Some patients with irritable bowel syndrome have altered mucosal barrier function and decreased expression of tight junction proteins in the jejunum and colon. Increased permeability has been associated with greater severity of abdominal pain, visceral hyperalgesia, and altered bowel habits. Immune activation involving mast cells and T lymphocytes may mediate dysfunction of the intestinal barrier, abnormalities in motility, and visceral pain in irritable bowel syndromes.

Increased immune activation has been demonstrated in the colonic mucosa of patients with irritable bowel syndromes, including increased numbers of mast cells adjacent to sensory neurons in the colonic mucosa. Mast cells release mediators such as histamine that may activate afferent nerves and result in peripheral sensitization and increased abdominal pain. Disruption of the mucosal barrier associated with changes in expression of tight junction proteins in response to food allergens suggests that patients with irritable bowel syndrome have nonclassical food allergies that may contribute to postprandial symptoms.

The fecal microbiota of patients with irritable bowel syndrome often shows an abundance of Enterobacteriaceae, family Lactobacillaceae, and genus *Bacteroides*, as well as decreased amount of Clostridiales I, genus *Faecalibacterium*, and genus *Bifidobacterium*.[11] These findings have biologic plausibility because the microbes that are increased in irritable bowel syndrome produce organic acids (e.g., lactic acid), reduce mucosal glycoproteins, or contain pathogenic bacteria. The microbes that are decreased in irritable bowel syndrome produce butyrate, which is an energy source for epithelial cells, have anti-inflammatory effects, and are thought to maintain gut health. About 25% patients with irritable bowel syndrome have bile acid diarrhea.

Dysregulated Stress Responsiveness

Growing evidence supports that irritable bowel syndrome is a stress-sensitive disorder. The stress of the hypothalamic-pituitary-adrenal axis is dysregulated in response to experimental stress or hormone challenge in patients with irritable bowel syndrome compared with healthy controls. This stress can increase visceral sensitivity, gut motility and permeability, and immune responses.

CLINICAL MANIFESTATIONS

The hallmark feature of irritable bowel syndrome is chronic or recurrent pain that is associated with diarrhea, constipation, or both.[12] Postprandial symptoms, which are reported by about two thirds of patients, include abdominal pain, bloating, and flatulence. Meal-related symptoms are often triggered by larger meals, foods rich in carbohydrates or fats, coffee, alcohol, and spicy foods.

Women with irritable bowel syndrome are more likely to have constipation and less likely to have diarrhea compared with men. Symptoms can worsen just prior to menses, when estrogen and progesterone levels decline. Irritable bowel syndrome is also more commonly diagnosed in patients under age 50 years.

Extraintestinal symptoms and conditions that may coexist with irritable bowel syndrome include temporomandibular joint disorder, interstitial cystitis/painful bladder syndrome, dysmenorrhea (Chapter 218), migraine headaches (Chapter 367), fibromyalgia (Chapter 253), chronic fatigue syndrome (Chapter 253), anxiety (Chapter 362), depression (Chapter 362), and somatization. Patients with irritable bowel syndrome also are more likely to report subjective sleep disturbances (Chapter 374), especially when they have more severe gastrointestinal symptoms.

In about one third of patients, irritable bowel syndrome can coexist with other functional gastrointestinal disorders, such as functional dyspepsia and functional heartburn.[13] Most patients note a decreased quality of life because of gastrointestinal symptoms, abdominal pain, and psychological stress. For example, patients often report difficulty concentrating; feeling self-conscious; and having a fear of leaving the house, traveling, or being in places without bathrooms.

TABLE 123-1 DIAGNOSTIC CRITERIA FOR IRRITABLE BOWEL SYNDROME

1. Symptoms:
   - A. Recurrent abdominal pain (at least 1 day per week, on average, in the last 3 months) with symptoms for at least 6 months and associated with two or more of the following:
     - Related to defecation
     - Associated with a change in frequency of stool
     - Associated with a change in form (appearance) of stool
   - B. Symptoms that cumulatively support the diagnosis of irritable bowel syndrome:
     - Abnormal stool frequency: ≤3 bowel movements per week or >3 bowel movements per day
     - Abnormal stool form: lumpy/hard stool or loose/watery stool
     - Defecation straining
     - Urgency
     - Feeling of incomplete bowel movement
     - Passing mucus
     - Bloating or feeling of abdominal distention
2. Absence of alarm symptoms, such as:
   - New-onset symptoms at age ≥50 years
   - Unintentional weight loss
   - Hematochezia or melena not related to hemorrhoids
   - Nocturnal diarrhea
   - Anemia
   - Palpable abdominal mass or lymphadenopathy
   - Family history of colorectal cancer, inflammatory bowel disease, or celiac disease

Adapted from Mearin F, Lacy BE, Chang L, et al. Bowel disorders. *Gastroenterology*. 2016;150:1393-1407 and Mayer EA. Functional gastrointestinal disorders: irritable bowel syndrome, dyspepsia, esophageal chest pain, and heartburn. In: Goldman L, Schafer A, eds. *Goldman-Cecil Medicine*, 26th ed. Philadelphia: Elsevier; 2020:852-859.

DIAGNOSIS

Symptom-Based Criteria

A systematic approach with limited diagnostic testing typically is sufficient to make the diagnosis of irritable bowel syndrome (Fig. 123-1), using the symptom-based Rome IV criteria (Table 123-1).[14] The Rome criteria also can classify irritable bowel syndrome into subtypes based on the most frequent

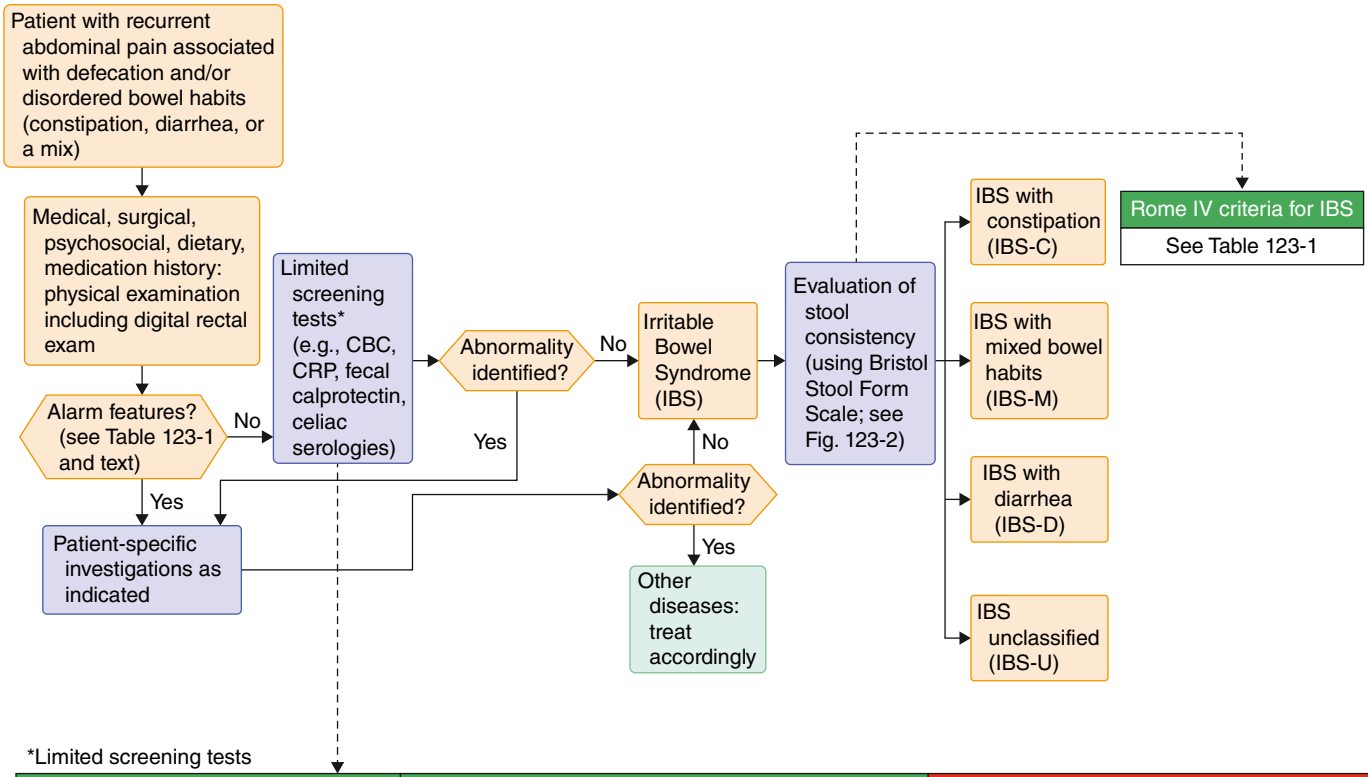

*Limited screening tests

Recommended	IBS population	Not recommended
Positive diagnostic strategy vs. diagnosis of exclusion	All IBS	Routine stool testing
Celiac serologies	IBS-D	Routine colonoscopy <45 yrs
Fecal calprotectin/lactoferrin	IBS-D	Food allergy or insensitivities testing
C-reactive protein	IBS-D	Lactulose or glucose hydrogen breath testing
Bile acid diarrhea testing	IBS-D where bile acid diarrhea is suspected	
Giardia stool antigen	IBS-D if giardia is endemic	
Anorectal physiology testing	IBS with suspected pelvic floor dysfunction and/or refractory constipation	

FIGURE 123-1. Diagnostic algorithm for irritable bowel syndrome. The recommendations for limited diagnostic testing are summarized from society guidelines. Rome IV diagnostic criteria for irritable bowel syndrome shown. CBC = complete blood count; CRP = C-reactive protein; IBS = irritable bowel syndrome. (From Chang L. How to Approach a Patient with Difficult to Treat IBS. Invited review, Gastroenterology, Mentoring, Education and Training section. *Gastroenterology* 2021;161[4]:1092-1098.)

stool form (Fig. 123-2) at a time when the patient is not taking medications to treat diarrhea or constipation.

The differential diagnosis for symptoms consistent with irritable bowel syndrome includes celiac disease (Chapter 126), inflammatory bowel disease (i.e., ulcerative colitis and Crohn disease; Chapter 127), microscopic or collagenous colitis (Chapter 126), colon cancer (Chapter 127), bile acid diarrhea (Chapter 126), and food intolerances. Alarm features or "red flags" that suggest these alternative diagnoses include the new onset of symptoms after age 50 years; rectal bleeding; weight loss; iron deficiency anemia; nocturnal diarrhea; and a family history of colon cancer, inflammatory bowel disease, or celiac disease. The presence of an alarm feature should prompt a targeted diagnostic evaluation of the clinical symptoms. However, testing often does not reveal another cause of the patient's symptoms, and many patients with red flag symptoms are ultimately diagnosed with irritable bowel syndrome.

Diagnostic Testing

Since irritable bowel syndrome is a diagnosis of exclusion, diagnostic testing (Fig. 123-1; Table 123-2) is targeted to exclude other potential causes of the patient's symptoms.[15] Guidelines recommend a serum IgA anti-tissue transglutaminase to assess for celiac disease, with a duodenal biopsy if the serologic test is positive. Since IgA deficiency is not uncommon in the general population, however, this test can be falsely negative and should be combined with a total IgA level. In IgA-deficient patients, a serum IgG anti-tissue transglutaminase level and/or an IgG deaminated gliadin peptide level should be used to screen for celiac disease.

Most guidelines do not recommend a routine colonoscopy in patients who are under the age of 45 to 50 years without alarm features.[16] If a colonoscopy is performed, random colon biopsies should be taken in patients with diarrheal symptoms to examine for microscopic or collagenous colitis.

Bristol Stool Form Scale (English for United States)

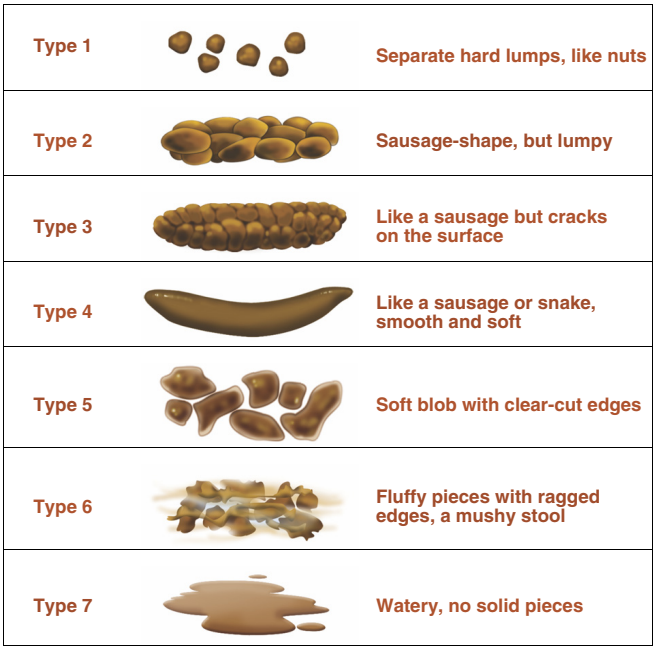

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FIGURE 123-2. The Bristol Stool Form Scale. (Distributed with the kind permission of The Rome Foundation.)

TABLE 123-2 DIAGNOSTIC TESTING IN THE EVALUATION OF SUSPECTED IRRITABLE BOWEL SYNDROME

1.	Generally recommended tests
	Complete blood count
	C-reactive protein
	Fecal calprotectin/lactoferrin
	Celiac serologies (IgA anti-tissue transglutaminase level and IgA level)
	Colonoscopy in new-onset irritable bowel syndrome symptoms at age ≥50 years
	Stool *Giardia* test (antigen or PCR) in endemic areas
	Stool testing for bacteria and parasites if a relevant travel history
2.	Tests generally NOT recommended
	Colonoscopy if age <50 years without alarm features
	Stool studies for infection without a history of travel to high-risk regions
	Food allergy or intolerance testing
	Lactose or glucose hydrogen breath tests

Ig = immunoglobulin; PCR = polymerase chain reaction.

TREATMENT

Overall Approach

A prompt and clear diagnosis can facilitate appropriate treatment in a timely manner. The patient's acceptance of the diagnosis, ability to recognize fluctuating symptom patterns, and knowledge regarding how to prevent flares and treat symptoms when they arise aids in an increased perceived sense of control over them. Providing educational resources validates irritable bowel syndrome as a real condition and empowers patients to learn how to manage their symptoms.

Treatment should consider the most bothersome symptoms, the severity of symptoms, the impact of symptoms on quality of life, the presence of comorbid conditions, psychological impact, prior treatment history, and the patient's preferences.[17–19] A clinician-patient relationship founded on effective communication is of utmost importance in providing effective care and improving patient outcomes.[20]

Mild symptoms of irritable bowel syndrome have little or no impact on the patient's quality of life and may require nothing more than a positive diagnosis of irritable bowel syndrome, education, reassurance, dietary advice, and over-the-counter medications. Moderate symptoms that affect daily activities commonly also require pharmacotherapy. Severe symptoms, which have a significant impact on quality of life, coexist with psychological distress or extraintestinal symptoms, or have failed to respond to prior treatments, require an integrated approach, usually with both pharmacologic and behavioral treatment.[21] Strategies to prevent flares include avoidance of dietary triggers and stressors that can exacerbate symptoms. For irritable bowel syndrome with predominant diarrhea (Fig. 123-2) and irritable bowel syndrome with predominant constipation (Fig. 123-3), treatments typically focus on interventions to normalize bowel habits and reduce abdominal pain.

Therapies for Multiple Types of Irritable Bowel Syndrome

Diet

Dietary treatment is a first-line treatment for irritable bowel syndrome. A 1- to 2-week food and symptom diary can help determine if symptoms are triggered by specific foods that should be avoided.[22] A diet that is low in fermentable oligosaccharides, disaccharides, monosaccharides, and polyols (FODMAPs) can improve global irritable bowel symptoms, especially in patients with predominant diarrhea, and also can reduce abdominal pain, abdominal bloating, and abnormal bowel habits.[A1,A2] This diet is best explained and supervised by a trained dietitian, who can also guide the gradual reintroduction of foods if the strict elimination diet is succesful. By comparison, a gluten-free diet is of less clear benefit, though it may be tried in patients in whom gluten products consistently exacerbate symptoms.

Soluble Fiber

Fiber supplementation (up to 25 to 35 g of psyllium fiber daily) can be beneficial, especially in patients who have predominant constipation, and can be tried in other patients as well. However, fiber may cause abdominal discomfort and gas, so lower doses should be used initially, followed by a gradual increase.[A3] Guidelines specifically recommend soluble (e.g., psyllium) but not insoluble fiber (e.g., wheat bran). Although psyllium is less likely to improve overall symptoms compared with medications, it is also less likely to cause adverse events.

Medications

Medications can help relieve the spasms, constipation, diarrhea, and pain of irritable bowel syndrome (Table 123-3).[23]

Antispasmodics and Peppermint Oil

Antispasmodic agents, which exert their potential benefits via a direct effect on intestinal smooth muscle or via anticholinergic or antimuscarinic properties, are generally efficacious for improving symptoms of irritable bowel syndrome.[24] The most common adverse events are dry mouth, dizziness, and blurred vision. Peppermint oil also is useful to relieve abdominal pain and global symptoms of irritable bowel syndrome.

Probiotics

Combination probiotic products can reduce global symptoms of irritable bowel syndrome by about 20%,[25] but data from randomized trials are mixed and so are the recommendations of various professional societies. Probiotics may be most useful in patients who have persistent bloating.

Central Brain-Gut Neuromodulators

Centrally acting brain-gut neuromodulators can be used to treat irritable bowel symptoms and not necessarily anxiety or depression. These agents, which

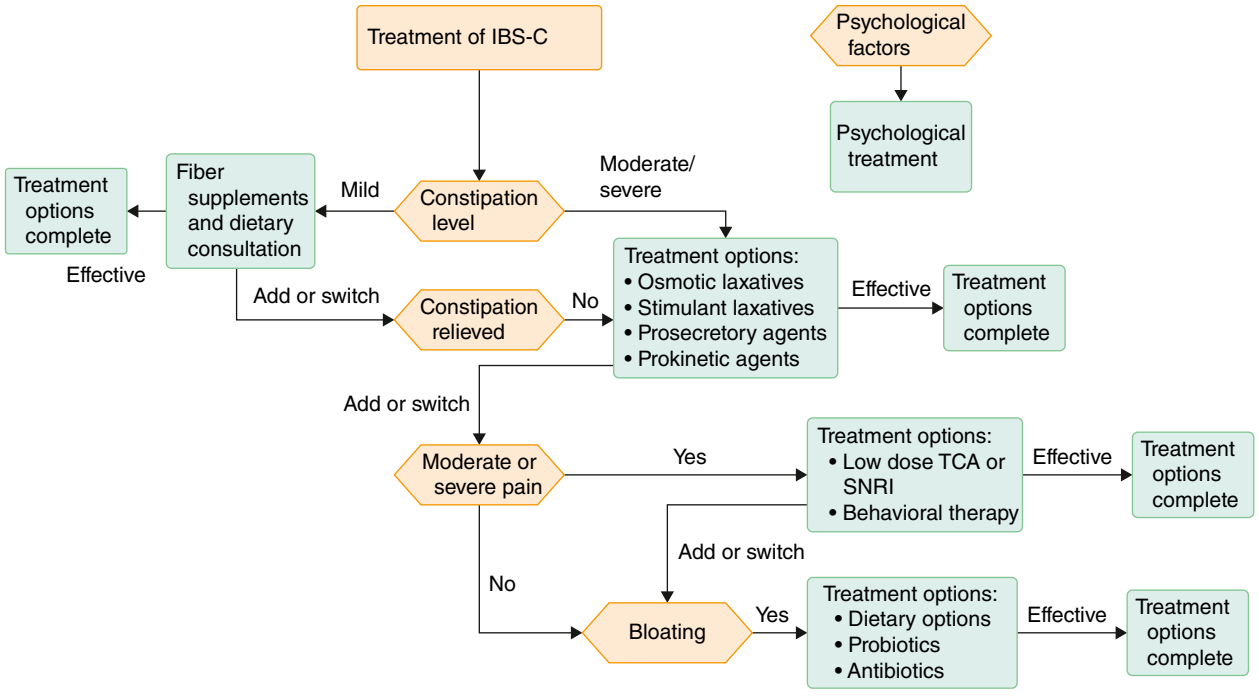

FIGURE 123-3. **Treatment algorithm for irritable bowel syndrome with constipation predominance (IBS-C).** SNRI = serotonin-norepinephrine reuptake inhibitor; TCA = tricyclic antidepressants. (Adapted with permission obtained from the Rome Foundation.)

TABLE 123-3 EVIDENCE-BASED ORAL TREATMENTS FOR IRRITABLE BOWEL SYNDROME

SYMPTOMS AND MEDICATION	DOSE	COMMON OR SERIOUS SIDE EFFECTS
PAIN AND SPASM		
Antispasmodics		
Peppermint oil	1 to 2 capsules three times daily or as needed	Heartburn, nausea, vomiting
Hyoscyamine	0.125 mg three to four times daily or as needed	Dry mouth, blurred vision, dizziness, constipation
Dicyclomine	10 mg three to four times daily or as needed	Dry mouth, blurred vision, dizziness
Central Neuromodulators		
Amitriptyline (TCA)	10 to 25 mg at bedtime, can increase gradually up to 100 mg at bedtime	Sedation, dry mouth, constipation
Desipramine (TCA)	10 to 25 mg at bedtime, can increase gradually up to 100 mg at bedtime	Dry mouth, dizziness
Nortriptyline (TCA)	10 to 25 mg at bedtime, can increase gradually up to 100 mg at bedtime	
Citalopram (SSRI)	5 to 20 mg daily	Sexual dysfunction, headache, nausea, sedation, insomnia, dizziness, sweating, withdrawal symptoms
Fluoxetine (SSRI)	20 to 40 mg daily	
Paroxetine (SSRI)	10 to 50 mg daily	
Sertraline (SSRI)	25 to 150 mg daily	
CONSTIPATION		
Laxatives and Secretory Modulators		
Polyethylene glycol 3350	17 g in 125 mL water daily	Nausea, bloating
Lactulose	10 g daily, can increase to 20 to 40 g daily	Diarrhea, bloating, cramping
Lubiprostone	8 µg twice daily	Nausea, diarrhea, headache, abdominal pain and discomfort
Linaclotide	290 µg daily	Diarrhea, abdominal pain, flatulence
Plecanatide	3 mg daily	Diarrhea, flatulence
Tenapanor	50 mg twice daily	Diarrhea, abdominal distension, flatulence
Prokinetic		
Tegaserod (5-HT4 agonist)	6 mg twice daily in women under age 65 years without a history of cardiovascular ischemic events	Diarrhea, headache, nausea, flatulence
DIARRHEA		
Opioid Receptor Agents		
Loperamide	2 mg, can increase up to 4 mg four times daily	Constipation
Eluxadoline	75 to 100 mg twice daily	Constipation, nausea, sphincter of Oddi dysfunction, pancreatitis
5HT3 Antagonists		
Alosetron	0.5 to 1.0 mg twice daily	Constipation, ischemic colitis (rare)

TABLE 123-3 EVIDENCE-BASED TREATMENTS FOR IRRITABLE BOWEL SYNDROME—cont'd

SYMPTOMS AND MEDICATION	DOSE	COMMON OR SERIOUS SIDE EFFECTS
Bile Acid Sequestrants		
Bile acid sequestrants (cholestyramine, colesevelam)	Cholestyramine: start at 2 to 4 g/day and titrate up to 24 g/day to response Colesevelam: two 625-mg tablets twice daily Colestipol: 1 g twice daily, can increase by 1 g/day every other day up to 16 g daily depending on response	Abdominal cramps, constipation
BLOATING		
Antibiotics		
Rifaximin	550 mg three times daily for 14 days	Abdominal pain, nausea
Probiotics		
Bifidobacterium infantis 35624	1 capsule per day	None
Activia	1 container twice daily	None

SSRI = selective serotonin reuptake inhibitor; TCA = tricyclic antidepressant.

Adapted from Mayer EA. Functional gastrointestinal disorders: irritable bowel syndrome, dyspepsia, esophageal chest pain, and heartburn. In: Goldman L, Schafer A, eds. *Goldman-Cecil Medicine*, 26th ed. Philadelphia: Elsevier; 2020:852-859.

include tricyclic antidepressants, selective serotonin reuptake inhibitors, and serotonin-norepinephrine reuptake inhibitors (see Table 362-5), may decrease pain perception by modulating the CNS processing of visceral stimuli, enhancing descending pain inhibitory pathways, decreasing the firing of primary sensory afferent nerves, altering gastrointestinal transit, and treating comorbid psychological symptoms.

Pooled data suggest that tricyclic antidepressants (Table 362-5) can improve global symptoms of irritable bowel syndrome in about 35% of patients[A4] and may be especially useful for abdominal pain. Preferred formulations are desipramine or nortriptyline (10 to 25 mg at bedtime), which are less likely to cause sedation, constipation, and dry mouth.

Selective serotonin reuptake inhibitors appear to have a similar efficacy for improving global symptoms, with fewer side effects than tricyclic antidepressants, but they do not seem to be as efficacious for reducing abdominal pain. Serotonin-norepinephrine reuptake inhibitors also can reduce chronic pain, particularly in patients who cannot tolerate or take tricyclic antidepressants.

Pharmacotherapy for Irritable Bowel Syndrome with Predominant Constipation (See Fig.123-2)

Medications should be used in patients who have at least moderately severe symptoms despite dietary interventions and over-the-counter remedies.[26] Medications generally should be tried sequentially for 8 to 12 weeks since their maximal effects for reducing abdominal pain, discomfort, and bloating can require at least 6 to 8 weeks of therapy. Combination therapy has not been evaluated in randomized clinical trials but can be used in clinical practice if patients have a partial response to a single treatment.

Over-the-Counter Laxatives

Osmotic laxatives, such as polyethylene glycol, are commonly used, over-the-counter, relatively inexpensive agents that are safe and well tolerated in patients with irritable bowel syndrome with predominant constipation. Polyethylene glycol is efficacious for improving the frequency and form of stools but not for reducing abdominal pain or global symptoms. Side effects include abdominal pain, diarrhea, nausea, and flatulence, all of which occur in a dose-dependent manner.

Lubiprostone

Lubiprostone (8 μg twice daily), which is a peripherally acting chloride channel activator that increases intestinal chloride secretion, can improve symptoms of constipation, stool consistency, straining, abdominal pain, bloating, and discomfort in patients with irritable bowel syndrome with predominant constipation.[A5,A6] The most common side effects of lubiprostone are nausea, which may be reduced by taking the drug with meals, and diarrhea.

Linaclotide and Plecanatide

Linaclotide and plecanatide are minimally absorbed peptides that activate guanylate cyclase C receptors on the luminal side of the intestinal epithelium, increase levels of cyclic guanosine monophosphate, and result in enhanced luminal secretion of chloride and bicarbonate. Linaclotide also may decrease firing of visceral sensory nerves, thereby reducing abdominal pain. Linaclotide (290 μg daily) can reduce abdominal pain and increase spontaneous bowel movements.[A7] Plecanatide (3 mg daily) has similar benefits.[A8] The most common side effect of both of these agents is diarrhea, which may remit if lower doses are used.

Tenapanor

Tenapanor is a minimally absorbed, small molecule inhibitor of the gastrointestinal sodium/hydrogen exchanger isoform 3, which is a transporter that is involved in the reabsorption of sodium and water. Tenapanor (50 mg twice daily) is effective for treating constipation and abdominal pain,[A9] with diarrhea as its most common adverse event.

Pharmacologic Therapies for Irritable Bowel Syndrome with Predominant Diarrhea (See Fig. 123-4)

μ-Opioid Receptor Agonists

Loperamide, which is a peripheral opioid agonist, is efficacious in reducing the frequency of stools in patients who have irritable bowel syndrome with predominant diarrhea, but it does not improve global irritable bowel syndrome symptoms or abdominal pain.[27] Because of the lack of effect on global symptoms, loperamide is a first-line treatment predominately for patients with mild abdominal pain.

Eluxadoline (starting at 100 mg twice daily but reducing the dose to 75 mg twice daily if the higher dose is not tolerated) is a μ- and a κ-opioid receptor agonist and a δ-opioid receptor antagonist that is efficacious for reducing diarrhea and abdominal pain in patients with irritable bowel syndrome with predominant diarrhea.[A10] Contraindications include mild or moderate hepatic impairment, the lack of a gallbladder, known or suspected biliary duct obstruction, pancreatic disease, sphincter of Oddi dysfunction, and alcohol use disorder. The most common side effects are nausea and constipation.

Rifaximin

Rifaximin is a broad-spectrum, minimally absorbed antibiotic that is approved for the treatment of irritable bowel syndrome with diarrhea at a dose of 550 mg three times daily for 14 days.[A11] Subsequent retreatment with up to three courses of rifaximin can also be effective. Rifaximin is generally well tolerated, but the most common side effects are nausea and abdominal pain.

Alosetron

Alosteron is a 5-HT_3 receptor antagonist that influences the brain-gut axis to slow gastrointestinal transit and reduce visceral hypersensitivity. Because alosetron can cause ischemic colitis (rate of 1.1 per 1000 patient years) and serious complications of constipation (0.66 per 1000 patient years), it is available in the United States only under a risk evaluation and mitigation strategy under expert oversight for women with severe irritable bowel syndrome with predominant diarrhea who have failed traditional treatment.

Bile Acid Sequestrants

Some patients with irritable bowel syndrome with predominant diarrhea are thought to have bile acid diarrhea (Chapter 141), which can be confirmed by fecal bile acid levels. If confirmed, bile acid diarrhea can be treated with a bile acid sequestrant (see Table 123-3), but an empiric trial of a bile acid sequestrant also may be considered.

Psychological Interventions

Psychological therapies that reduce stress-sensitive symptoms of irritable bowel syndrome include standard and minimal contact cognitive-behavioral therapy, gut-directed hypnotherapy, relaxation training/therapy, psychotherapy, mindfulness meditation, stress management, and training in emotional awareness and expression.[A12] Cognitive-behavioral therapy aims to reduce maladaptive

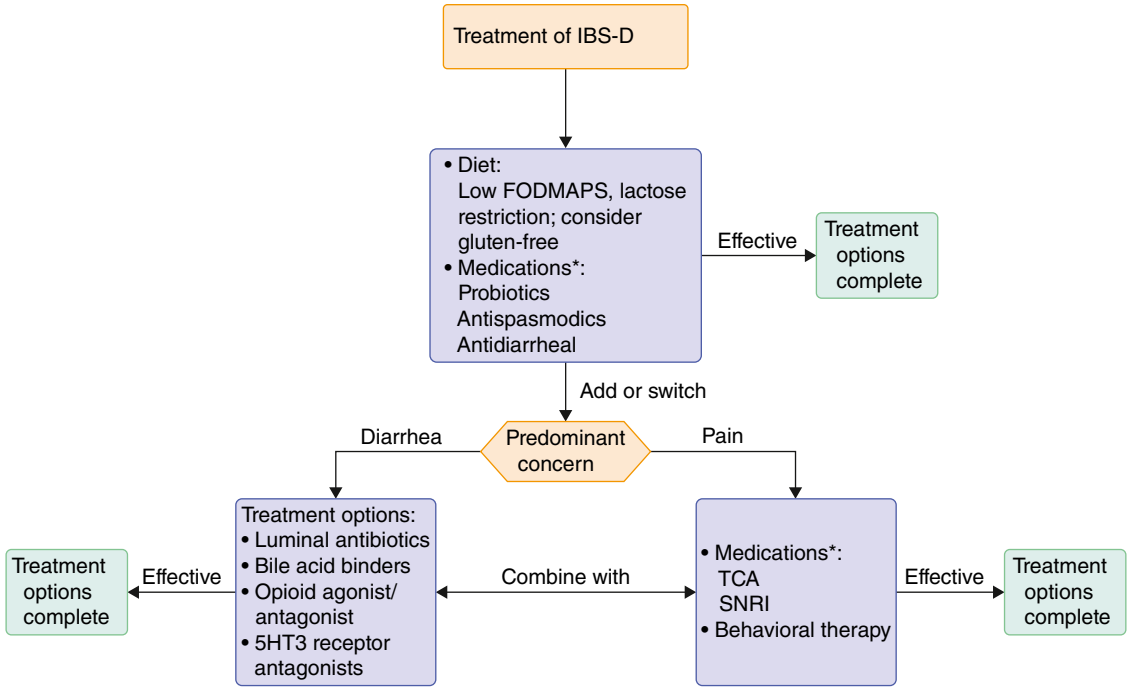

FIGURE 123-4. **Treatment algorithm for irritable bowel syndrome with diarrhea predominance (IBS-D).** *See Table 123-3. FODMAPS = fermentable oligosaccharides, disaccharides, monosaccharides, and polyols; SNRI = serotonin-norepinephrine reuptake inhibitor; TCA = tricyclic antidepressants. (Adapted with permission from the Rome Foundation.)

thoughts that can influence behaviors and emotional responses, thereby exacerbating physical symptoms. Gut-directed hypnotherapy focuses on relaxation and repeated suggestions focused on improving gut-brain communication and on reinterpretating visceral signals arising from the gut during routine activities such as digestion as being natural, comfortable, and unimportant. For patients with persistent bothersome symptoms despite standard care, an integrated care model of physicians working synergistically with dietitians, health psychologists, and even pelvic floor therapists, in person or using Internet-based programs, can improve quality of life.[28] Compared with usual care and education, psychological therapies are associated with about a 30% reduction of the symptoms of irritable bowel syndrome and are recommended for selected patients who understand the role of brain-gut behavioral therapy for irritable bowel syndrome, have the time and motivation to make behavioral changes, and experience avoidance and significant distress regarding symptoms and/or respond poorly to other therapies (see Figs. 123-2 and 123-3).

TABLE 123-4 ROME IV DIAGNOSTIC CRITERIA FOR FUNCTIONAL DYSPEPSIA*

1. One or more of the following bothersome symptoms:
   - Postprandial fullness
   - Early satiation
   - Epigastric pain
   - Epigastric burning

and

2. No evidence of structural disease (including at upper endoscopy) that is likely to explain the symptoms

*The criteria must be fulfilled for the last 3 months with onset of symptoms at least 6 months before diagnosis.

Adapted from Stanghellini V, Chan FK, Hasler WL, et al. Gastroduodenal disorders. *Gastroenterology*. 2016;150:1380-1392.

PROGNOSIS

About 30 to 45% of patients with irritable bowel syndrome have persistent symptoms for up to 12 years. Psychological symptoms, particularly anxiety and a negative perception of stressful life events, are associated with persistent symptoms. Other risk factors for persistent symptoms include female gender, younger age, and prior anxiety or depression.

FUNCTIONAL DYSPEPSIA

DEFINITION AND EPIDEMIOLOGY

Functional dyspepsia is the most common functional gastrointestinal disorder, with a prevalence of about 7%. The Rome IV diagnostic criteria for functional dyspepsia comprises bothersome (i.e., impacts usual activities) postprandial fullness, early satiety, epigastric pain, and/or epigastric burning in the absence of structural disease to explain these symptoms (Table 123-4). Heartburn, which is excluded from the definition of functional dyspepsia, may nevertheless coexist with it. Epigastric pain syndrome and postprandial distress syndrome are the two subtypes of functional dyspepsia (Table 123-5). Epigastric pain syndrome is characterized as bothersome epigastric pain or burning on one or more days per week in the past 3 months. Postprandial distress syndrome is defined as bothersome early satiety or postprandial fullness on 3 or more days per week in the previous 3 months. Almost two thirds of patients with functional dyspepsia have postprandial distress syndrome, over 15% have epigastric pain syndrome, and the remainder have symptoms that overlap both postprandial distress syndrome and epigastric pain syndrome.

Risk factors for functional dyspepsia include female sex, smoking, use of nonsteroidal anti-inflammatory drugs, acute gastroenteritis, psychological disorders (particularly anxiety), and *Helicobacter pylori* infection (Chapter 125).[29] Eradication of *H. pylori* has a statistically significant but unfortunately small likelihood of relieving symptoms of functional dyspepsia. If a patient who has symptoms of functional dyspepsia also has *H. pylori* infection and if eradication of *H. pylori* resolves these symptoms, the patient is classified as having *H. pylori* gastritis and not functional dyspepsia.

PATHOBIOLOGY

The pathobiology of functional dyspepsia includes delayed or rapid gastric emptying, visceral hypersensitivity, and impaired gastric accommodation, as well as gastric and duodenal hypersensitivity to distention, acid, low-grade inflammation (e.g., eosinophilia), mucosal permeability, and food antigens. About 30% of patients with functional dyspepsia have delayed gastric emptying time, which prompts the ongoing debate as to whether these patients should be diagnosed as having functional dyspepsia with delayed gastric emptying or as having gastroparesis (Chapter 122). However, symptoms other than severe nausea do not correlate well with gastric emptying time.[30]

CLINICAL MANIFESTATIONS AND DIAGNOSIS

The initial diagnostic evaluation of functional dyspepsia is based on the assessment of symptoms and alarm features (Fig. 123-5).[31] The presence of alarm features (Table 123-6) warrants an upper endoscopy to exclude conditions such as gastric cancer (Chapter 178) or serious esophageal disease (Chapter 124) as well as to perform a biopsy to detect *H. pylori*. If alarm features are absent and the patient is younger than age 60 years (or under age 55 years in regions with a high prevalence of gastric cancer), endoscopy is not required, but noninvasive testing for *H. pylori* (e.g., a stool antigen test [Table 125-3; Fig. 125-5]) is indicated.

TABLE 123-5 ROME IV DIAGNOSTIC CRITERIA FOR SUBGROUPS OF PATIENTS WITH FUNCTIONAL DYSPEPSIA*

POSTPRANDIAL DISTRESS SYNDROME

One or both of the following bothersome symptoms at least 3 days per week:
1. Postprandial fullness (severe enough to impact usual activities)
2. Early satiation

Supportive Criteria

1. Postprandial epigastric pain or burning, epigastric bloating, excessive belching, and nausea can also be present.
2. Vomiting warrants consideration for another diagnosis.
3. Heartburn is not a dyspeptic symptom but may often coexist.
4. Symptoms that are relieved by evacuation of feces or gas should generally not be considered as part of dyspepsia.

EPIGASTRIC PAIN SYNDROME

Must include at least one of the following bothersome symptoms at least 1 day a week:
1. Epigastric pain (i.e., severe enough to impact on usual activities)
2. Epigastric burning (i.e., severe enough to impact on usual activities)

Supportive Criteria

1. Pain may be induced by ingestion of a meal, relieved by ingestion of a meal, or may occur while fasting.
2. Postprandial epigastric bloating, belching, and nausea can also be present.
3. Persistent vomiting likely suggests another disorder.
4. Heartburn is not a dyspeptic symptom but may often coexist.
5. The pain does not fulfill biliary pain criteria.
6. Symptoms that are relieved by evacuation of feces or gas generally should not be considered as part of dyspepsia.

*The criteria must be fulfilled for the last 3 months with symptom onset at least 6 months before diagnosis.

Adapted from Stanghellini V, Chan FK, Hasler WL, et al. Gastroduodenal disorders. *Gastroenterology*. 2016;150:1380-1392.

TABLE 123-6 ALARM SYMPTOMS ASSOCIATED WITH AN UNDERLYING UPPER GASTROINTESTINAL MALIGNANCY

Unintentional weight loss
New-onset dyspepsia after age 55 years
Dysphagia
Persistent vomiting
Any overt gastrointestinal bleeding, hematemesis, or melena
Family history of esophageal or gastric cancer
Iron deficiency anemia
Palpable abdominal mass or lymph node

From Mayer EA. Functional gastrointestinal disorders: irritable bowel syndrome, dyspepsia, esophageal chest pain, and heartburn. In: Goldman L, Schafer A, eds. *Goldman-Cecil Medicine*, 26th ed. Philadelphia: Elsevier; 2020:852-859.

TREATMENT

If *H. pylori* is not detected, empiric therapy with a proton pump inhibitor (see Table 124-1) is typically recommended.[A13] If symptoms persist, additional treatment is based on the subtype of functional dyspepsia. In patients with postprandial distress syndrome, buspirone (10 mg three times daily) and mirtazapine (15 mg at bedtime) have demonstrated efficacy. Tricyclic antidepressants (see Table 362-5) can relieve symptoms compared with placebo, particularly in patients who have abdominal pain and a normal gastric emptying time.

PROGNOSIS

The long-term prognosis for functional dyspepsia is favorable in the majority of patients, and life expectancy is similar to that of the general population.

FUNCTIONAL HEARTBURN

Functional heartburn is retrosternal burning discomfort or pain that radiates retrosternally, is unresponsive to optimal antisecretory therapy, and is not

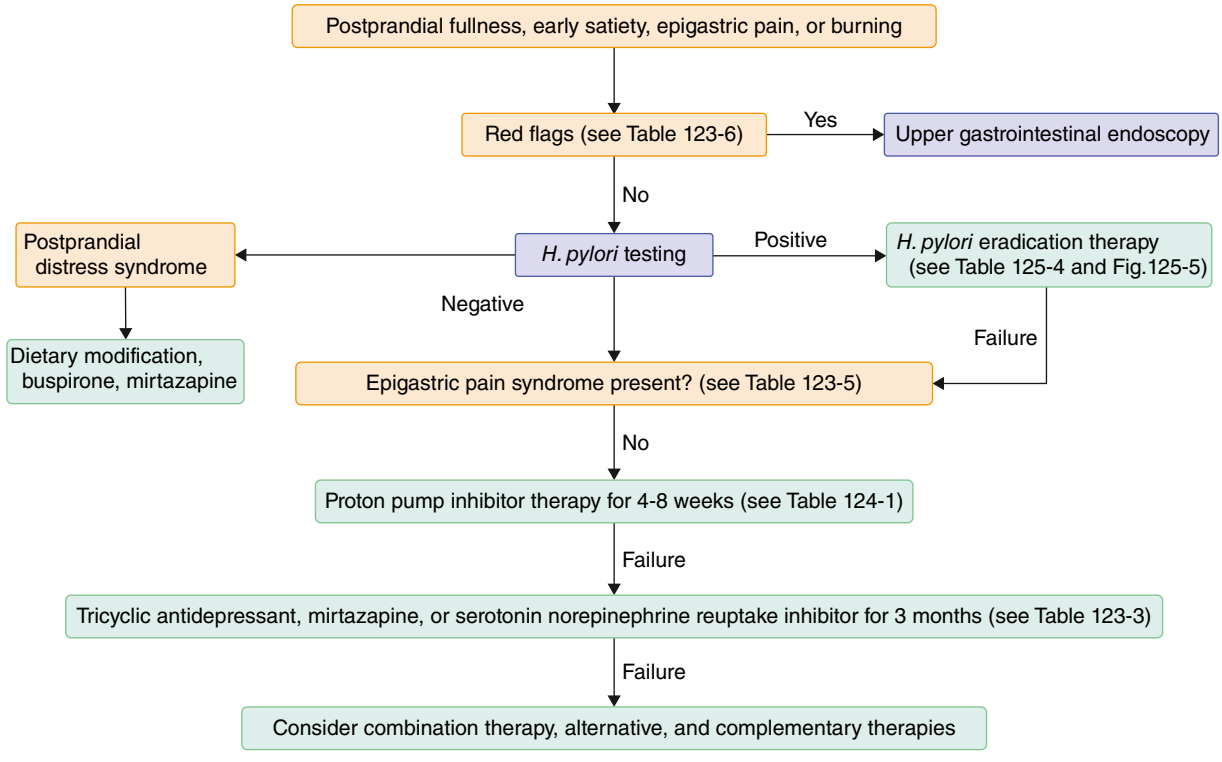

FIGURE 123-5. Algorithm for functional dyspepsia. A recommended approach to patients who present with epigastric pain, postprandial fullness, and early satiety, who meet the Rome IV diagnostic criteria for functional dyspepsia (see Table 123-4), and who lack any alarm features (see Table 123-6). In the setting of treatment failure, the physician should re-evaluate all clinical and laboratory findings to determine whether further diagnostic testing might be beneficial to assess the patients for alternative causes of the symptoms. (From Mayer EA. Functional gastrointestinal disorders: irritable bowel syndrome, dyspepsia, esophageal chest pain, and heartburn. In: Goldman L, Schafer AI, eds. *Goldman-Cecil Medicine*, 26th ed. Philadelphia: Elsevier; 2020:852-859.)

accompanied by gastroesophageal reflux disease or esophageal mucosal, motility, or structural abnormalities to explain the symptoms. Even if some gastroesophageal reflux is detected, symptoms are not correlated with it. Although patients may have some degree of epigastric discomfort, the chest symptoms predominate.

EPIDEMIOLOGY

Functional heartburn is very common. The global prevalence of functional heartburn is about 1%, but it is approximately 25% in patients whose heartburn responds to a proton pump inhibitor and 50% in patients whose heartburn does not respond to a proton pump inhibitor. The presence of coexistent irritable bowel syndrome is a strong predictor of functional heartburn.

PATHOBIOLOGY

The pathobiology of functional heartburn is likely related to visceral hypersensitivity to antral and esophageal distention, altered esophageal motility in the absence of a clinically detectable motility disorder, and psychological factors.

CLINICAL MANIFESTATIONS

Patients with functional heartburn, which unlike dyspepsia is felt in the chest rather than the abdomen, complain of typical heartburn symptoms that usually are triggered by food intake and psychosocial stress but are refractory to acid-suppressive therapy with proton pump inhibitors. By definition, they also have negative endoscopic and acid monitoring evaluations of the esophagus.

DIAGNOSIS

An endoscopy with biopsies is performed in patients whose heartburn symptoms do not respond to an adequate trial of empirical proton pump inhibitor therapy in order to exclude other esophageal or gastric diseases, such as eosinophilic esophagitis, pill-induced esophagitis, stricture, Barrett esophagus, and malignancy (Chapter 124). If endoscopy is normal, ambulatory pH monitoring alone or with impedence should be conducted without acid suppression in patients who do not have proven gastroesophageal reflux and with acid suppression in patients who have proven gastroesophageal reflux. If esophageal acid (pH <4) exposure time is less than 4% of the time of a complete study, high-resolution esophageal manometry should be performed to exclude a major esophageal motility disorder such as achalasia (Chapter 124).

Based on the Rome IV criteria (Table 123-7), functional heartburn is diagnosed if heartburn is present at least twice per week with all of the following criteria: no relief of symptoms with optimal antisecretory therapy; absence of gastroesophageal reflux, eosinophilic esophagitis, or major esophageal motor disorders (e.g., achalasia, diffuse esophageal spasm); and symptoms that are present for the past 3 months with an onset of symptoms at least 6 months prior to the diagnosis.

TREATMENT

Treatment of functional heartburn consists of lifestyle modifications, pharmacotherapy with neuromodulators, and behavioral therapy.[32] Lifestyle modifications include identifying and managing triggers such as foods, stress, or physical activities that precipitate symptoms. Antisecretory medications such as standard- or double-dose proton pump inhibitors (e.g., omeprazole 20 mg once to twice daily; see Table 124-1) can be helpful, especially if gastroesophageal reflux coexists.[33] Low doses of tricyclic antidepressants (e.g., imipramine; starting at 10 to 20 mg at bedtime) or selective serotonin reuptake inhibitors (e.g., fluoxetine 10 to 20 mg daily) are considered the mainstay of treatment for functional heartburn. For truly refractory heartburn caused by reflux, laparoscopic Nissen fundoplication is better than continued medical treatment (see Chapter 124). Cognitive-behavioral therapy may be helpful. Acupuncture and esophageal-directed hypnotherapy (Chapter 30) are reserved for refractory cases.

PROGNOSIS

The prognosis and long-term natural history of functional heartburn are not completely known. Up to two thirds of patients continue to have heartburn over 2 years of follow-up, whereas about 20% experience a reduction in symptoms.

FUNCTIONAL CHEST PAIN OF LIKELY ESOPHAGEAL ORIGIN

DEFINITION

Functional chest pain of presumed esophageal origin (Table 123-8) is a chronic midline chest pain that is not explained by cardiac causes, gastroesophageal reflux, or esophageal motility disorders (Chapters 39 and 124).

TABLE 123-7 ROME IV DIAGNOSTIC CRITERIA FOR FUNCTIONAL HEARTBURN

Must include all of the following:

- Burning retrosternal discomfort or pain
- No relief of symptoms despite optimal antisecretory therapy
- Absence of evidence that gastroesophageal reflux (abnormal acid exposure and symptoms) or eosinophilic esophagitis is the cause of symptoms
- Absence of major esophageal motor disorders (e.g., achalasia/esophagogastric junction outflow obstruction, diffuse esophageal spasm, jackhammer esophagus, absent peristalsis)

*The criteria must be fulfilled for the last 3 months with the onset of symptoms at least 6 months before diagnosis, with a frequency of at least twice per week.

Aziz Q, Fass R, Gyawali CP, et al. Functional esophageal disorders. *Gastroenterology*. 2016;150:1368-1379.

TABLE 123-8 ROME IV DIAGNOSTIC CRITERIA FOR FUNCTIONAL CHEST PAIN OF PRESUMED ESOPHAGEAL ORIGIN*

Must include all of the following:

- Retrosternal chest pain or discomfort; cardiac causes should be excluded
- Absence of associated esophageal symptoms, such as heartburn and dysphagia
- Absence of evidence that gastroesophageal reflux or eosinophilic esophagitis are the cause of the symptoms
- Absence of major esophageal motor disorders (e.g., achalasia/esophageal-gastric outflow obstruction, diffuse esophageal spasm, jackhammer esophagus, absent peristalsis)

*The criteria must be fulfilled for the last 3 months with the onset of symptoms at least 6 months before diagnosis, with a frequency of at least once a week.

From Mayer EA. Functional gastrointestinal disorders: irritable bowel syndrome, dyspepsia, esophageal chest pain, and heartburn. In: Goldman L, Schafer A, eds. *Goldman-Cecil Medicine*, 26th ed. Philadelphia: Elsevier; 2020:852-859.

EPIDEMIOLOGY AND PATHOBIOLOGY

Functional chest pain has a prevalence rate as high as 25% and is a leading cause of acute chest pain (see Table 39-2), especially in younger patients. Men and women are equally affected, and it is more commonly reported in younger individuals, perhaps because repeated reassurance decreases the complaint in other individuals. Nevertheless, many patients undergo repeated and unnecessary diagnostic cardiac evaluations. Patients with functional chest pain often have anxiety or panic attacks (Chapter 362), thereby suggesting a link between functional chest pain and psychological issues.

The pathobiology of esophageal chest pain is thought to be similar to that of functional heartburn. In addition, however, increased esophageal muscle contraction has been implicated.

CLINICAL MANIFESTATIONS

Functional chest pain is often indistinguishable from the pain of acute myocardial ischemia or myocardial infarction (Chapters 57 and 58). Although the pain is typically substernal, it can radiate to the arm and neck. The pain is unrelated to exercise and can persist for hours.

DIAGNOSIS

Patients who present with chest pain (see Table 39-2) suspicious for angina or acute myocardial infarction (Chapters 56 to 58) should undergo prompt cardiac evaluation. A trial of nitroglycerin is not helpful diagnostically because it can relieve esophageal spasm as well as myocardial ischemia. If the cardiac evaluation is negative, other causes of functional chest pain should be evaluated (Table 123-9), but repeated cardiac evaluations for recurrent symptoms usually are not helpful (Chapter 39). Chest wall pain, tenderness on palpation, or changes in pain with movement usually are musculoskeletal in origin (Chapter 39).

An association with certain foods or concurrent heartburn or dyspepsia can sometimes differentiate between acid-induced versus non–acid-related causes. In patients with alarm symptoms (see Table 123-6), such as weight loss, progressive dysphagia, or anemia, upper endoscopy is required. Testing for esophageal motility disorders (Chapter 124) is useful for severe or recurrent symptoms.

TABLE 123-9 DIFFERENTIAL DIAGNOSIS OF FUNCTIONAL CHEST PAIN

ORGANIC ESOPHAGEAL CAUSES
Gastroesophageal reflux disease
Achalasia
Virus- or pill-induced esophagitis
Eosinophilic esophagitis
NONGASTROINTESTINAL CAUSES
Cardiac chest pain
Chest wall pain
Pulmonary disease
Panic attack

From Mayer EA. Functional gastrointestinal disorders: irritable bowel syndrome, dyspepsia, esophageal chest pain, and heartburn. In: Goldman L, Schafer A, eds. *Goldman-Cecil Medicine*, 26th ed. Philadelphia: Elsevier; 2020:852-859.

TREATMENT

Many patients with functional chest pain have atypical gastroesophageal reflux disorder (Chapter 124) and benefit from a therapeutic trial with a proton pump inhibitor (e.g., omeprazole 20 mg daily). The optimal duration of treatment is unclear, but an attempt should be made to discontinue proton pump inhibitors after several months of successful therapy. If the patient's response is equivocal, 24-hour pH testing can be considered (Chapter 124). In patients who do not respond to a proton pump inhibitor, testing for esophageal motility disorders (Chapter 124) should be performed to look for conditions such as high-amplitude contractions, diffuse esophageal spasm, or achalasia. Fears regarding possible cardiac disease must be addresseed explicitly, and patients must be reassured by the negative results of the cardiac evaluation.

Low-dose tricyclic antidepressants (e.g., amitriptyline, imipramine, or desipramine 10 to 50 mg at bedtime) may be useful. For persistent symptoms, cognitive-behavioral therapy or mindfulness-based stress reduction may be beneficial.

PROGNOSIS

Functional chest pain has a benign prognosis, although many patients may request repeated cardiac evaluations if symptoms persist and diminish quality of life.

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For the General References and other additional features, please visit Elsevier eBooks+ at https://ebooks.health.elsevier.com.

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124

DISEASES OF THE ESOPHAGUS

GARY W. FALK AND DAVID A. KATZKA

NORMAL ANATOMY AND PHYSIOLOGY

The esophagus, which averages about 27 cm in length, is a hollow muscular tube consisting of the mucosa, submucosa, and muscularis layers, with the notable absence of a serosal layer. The mucosa is a stratified squamous nonkeratinized epithelium that transitions to a columnar epithelium at the gastroesophageal junction. The muscular layer of the esophagus is composed of striated muscle in the upper one third and smooth muscle in the lower two thirds. These muscular components are arranged as an inner circular and an outer longitudinal layer. Located between the circular and longitudinal muscle layers is Auerbach (myenteric) plexus, whereas Meissner plexus is located within the submucosa and innervates the muscularis mucosae. The esophagus is bound by an upper esophageal sphincter proximally and the lower esophageal sphincter distally. The upper esophageal sphincter contains functional contributions from the inferior pharyngeal constrictor proximally and the cricopharyngeus distally. By contrast, the lower esophageal sphincter is anatomically and histologically indistinguishable from the lower esophagus. Blood supply for the cervical portion is derived from branches of the inferior thyroid artery. The intrathoracic segment of the esophagus receives its blood supply from bronchial arteries and direct branches from the aorta, and the left gastric and the inferior phrenic arteries supply the abdominal portion of the esophagus. Venous drainage follows the arterial supply in the cervical and abdominal portions, whereas the thoracic esophagus drains into the azygous and hemiazygos system. Likewise, the lymphatic drainage of the esophagus is segmental, with the cervical portion draining into deep cervical lymph nodes, the thoracic portion into the superior and posterior mediastinal lymph nodes, and the abdominal portion into the gastric and celiac lymph nodes.

The motor functions of the esophagus are to transport a food bolus from the oropharynx into the stomach and then to keep food from returning to the esophagus after it has entered the stomach. The upper esophageal sphincter and the proximal third of the esophagus compose the first portion of the esophagus. The upper esophageal sphincter is approximately 2 to 4 cm in length. The recurrent laryngeal nerve inferiorly and a pharyngeal plexus superiorly supply the upper esophageal sphincter. The muscle layers close the esophageal lumen and shorten the esophagus to facilitate forward transport through the proximal esophagus. After food traverses the proximal esophagus, it moves into the distal two thirds of the esophagus, where peristalsis is achieved by sequential muscular contraction mediated through an interplay of inhibitory and excitatory neurotransmitters. Peristalsis may be primary, that is, initiated by a swallow, or secondary, that is, stimulated by refluxed gastric contents. Although local mechanisms control most esophageal motor function, vagal input is important in the distal esophagus, where smooth muscle myopathies and autonomic neuropathies can cause dysfunction. The distal esophagus is separated from the stomach by the lower esophageal sphincter, which is 4 to 5 cm in length and is functionally distinct because it maintains a tonic high-pressure zone. This sphincter relaxes nearly completely upon swallowing to allow the passage of food and then regains its tone to provide a barrier against reflux. It also relaxes transiently during normal functions, such as belching and vomiting. The vagus nerve, acetylcholine, and nitric oxide influence tone, but the lower esophageal sphincter tone is influenced by the crural diaphragm as the esophagus traverses the diaphragmatic hiatus.

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Options for esophageal functional testing include barium esophagography, high-resolution esophageal manometry, and esophageal impedance testing. Barium esophagography (Chapter 119) reveals both anatomic and physiologic information about luminal lesions, such as malignancies, ulceration, diverticula, hiatal hernia, and strictures; intramural lesions, such as leiomyomas; and extrinsic lesions, such as occur from vascular (aorta, right atrium, subclavian artery) impingement or solid lesions (pulmonary malignancy, adenopathy) that compress the esophagus. Radiography is also an excellent tool for studying motility patterns, such as peristalsis with either liquid or solid contrast material, while precisely visualizing how the esophagus handles a bolus rather than by implying function from pressure or impedance changes.

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TABLE 123-9 DIFFERENTIAL DIAGNOSIS OF FUNCTIONAL CHEST PAIN

ORGANIC ESOPHAGEAL CAUSES
Gastroesophageal reflux disease
Achalasia
Virus- or pill-induced esophagitis
Eosinophilic esophagitis
NONGASTROINTESTINAL CAUSES
Cardiac chest pain
Chest wall pain
Pulmonary disease
Panic attack

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TREATMENT

Many patients with functional chest pain have atypical gastroesophageal reflux disorder (Chapter 124) and benefit from a therapeutic trial with a proton pump inhibitor (e.g., omeprazole 20 mg daily). The optimal duration of treatment is unclear, but an attempt should be made to discontinue proton pump inhibitors after several months of successful therapy. If the patient's response is equivocal, 24-hour pH testing can be considered (Chapter 124). In patients who do not respond to a proton pump inhibitor, testing for esophageal motility disorders (Chapter 124) should be performed to look for conditions such as high-amplitude contractions, diffuse esophageal spasm, or achalasia. Fears regarding possible cardiac disease must be addresseed explicitly, and patients must be reassured by the negative results of the cardiac evaluation.

Low-dose tricyclic antidepressants (e.g., amitriptyline, imipramine, or desipramine 10 to 50 mg at bedtime) may be useful. For persistent symptoms, cognitive-behavioral therapy or mindfulness-based stress reduction may be beneficial.

PROGNOSIS

Functional chest pain has a benign prognosis, although many patients may request repeated cardiac evaluations if symptoms persist and diminish quality of life.

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For the General References and other additional features, please visit Elsevier eBooks+ at https://ebooks.health.elsevier.com.

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124

DISEASES OF THE ESOPHAGUS

GARY W. FALK AND DAVID A. KATZKA

NORMAL ANATOMY AND PHYSIOLOGY

The esophagus, which averages about 27 cm in length, is a hollow muscular tube consisting of the mucosa, submucosa, and muscularis layers, with the notable absence of a serosal layer. The mucosa is a stratified squamous nonkeratinized epithelium that transitions to a columnar epithelium at the gastroesophageal junction. The muscular layer of the esophagus is composed of striated muscle in the upper one third and smooth muscle in the lower two thirds. These muscular components are arranged as an inner circular and an outer longitudinal layer. Located between the circular and longitudinal muscle layers is Auerbach (myenteric) plexus, whereas Meissner plexus is located within the submucosa and innervates the muscularis mucosae. The esophagus is bound by an upper esophageal sphincter proximally and the lower esophageal sphincter distally. The upper esophageal sphincter contains functional contributions from the inferior pharyngeal constrictor proximally and the cricopharyngeus distally. By contrast, the lower esophageal sphincter is anatomically and histologically indistinguishable from the lower esophagus. Blood supply for the cervical portion is derived from branches of the inferior thyroid artery. The intrathoracic segment of the esophagus receives its blood supply from bronchial arteries and direct branches from the aorta, and the left gastric and the inferior phrenic arteries supply the abdominal portion of the esophagus. Venous drainage follows the arterial supply in the cervical and abdominal portions, whereas the thoracic esophagus drains into the azygous and hemiazygos system. Likewise, the lymphatic drainage of the esophagus is segmental, with the cervical portion draining into deep cervical lymph nodes, the thoracic portion into the superior and posterior mediastinal lymph nodes, and the abdominal portion into the gastric and celiac lymph nodes.

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Esophageal Functional Testing

Options for esophageal functional testing include barium esophagography, high-resolution esophageal manometry, and esophageal impedance testing. Barium esophagography (Chapter 119) reveals both anatomic and physiologic information about luminal lesions, such as malignancies, ulceration, diverticula, hiatal hernia, and strictures; intramural lesions, such as leiomyomas; and extrinsic lesions, such as occur from vascular (aorta, right atrium, subclavian artery) impingement or solid lesions (pulmonary malignancy, adenopathy) that compress the esophagus. Radiography is also an excellent tool for studying motility patterns, such as peristalsis with either liquid or solid contrast material, while precisely visualizing how the esophagus handles a bolus rather than by implying function from pressure or impedance changes.

ABSTRACT

The esophagus is a muscular tube that facilitates the transport of a food bolus into the stomach. Classic symptoms of esophageal disease include dysphagia, heartburn, regurgitation, chest pain, and food impaction. Gastroesophageal reflux disease is perhaps the most common esophageal disease and is characterized by heartburn and acid regurgitation. Treatment focuses on simple lifestyle modifications, acid suppression therapy, and antireflux surgery in selected patients. Complications of reflux disease include peptic strictures, Barrett esophagus, and esophageal adenocarcinoma. Eosinophilic esophagitis is a relatively newly recognized disease caused when an aberrant immune response to food and aeroallergens leads to chronic inflammation and fibrosis of the esophagus. Treatments include elimination of common food allergens, topical steroids, proton pump inhibitors, and endoscopic dilation. Achalasia, which is the prototypic esophageal motility abnormality, is characterized by dysphagia to solids and liquids. Treatment focuses on disruption of the lower esophageal sphincter by pneumatic dilation or by surgical or endoscopic myotomy. A variety of structural and inflammatory abnormalities that may cause esophageal symptoms are also described in this chapter.

KEYWORDS

esophagus
esophagitis
Barrett esophagus
eosinophilic esophagitis
gastroesophageal reflux
achalasia
esophageal spasm
esophageal testing

High-resolution esophageal manometry measures pressure changes generated by esophageal wall contraction and changes in tone using multiple sensors that simultaneously measure pressure from the pharynx to the lower esophageal sphincter.[1] Esophageal impedance testing detects the movement of an intraluminal bolus by measuring conductance between catheter-based electrodes based on the substance that is in contact with each electrode. Air, which is a poor conductor of electric current, will yield high impedance, whereas swallowed or refluxed liquids, which are excellent conductors of electricity, will generate a low impedance signal. From these measurements, the direction and velocity of the transport of air and bolus can help assess peristaltic function and the reflux of acid and nonacid gastric contents. Impedance can also reflect site-specific esophageal mucosal permeability, thereby providing further insight into mucosal integrity and disease in inflammatory or metaplastic conditions.

A functional luminal imaging probe is a balloon-based device that measures pressures in response to controlled volumetric distentions. When used in the esophagus, it can measure the compliance of the esophageal wall and lower esophageal sphincter, as well as esophageal body motility. This procedure is increasingly being used to evaluate disorders such as eosinophilic esophagitis, achalasia, obstruction of the esophagogastric junction outlet, and unexplained dysphagia.

Symptoms of Esophageal Disease

The most common symptom of esophageal disease is heartburn, which is defined as a sensation of substernal burning. Chest pain without typical heartburn may occur in a variety of esophageal disorders, including gastroesophageal reflux and motor disorders such as in achalasia. However, esophageal pain and even heartburn can be indistinguishable from cardiac angina (Chapter 39), so care must be taken when a patient at risk for coronary artery disease complains of heartburn for the first time.

Dysphagia, or difficulty swallowing, is another cardinal symptom of esophageal disease. Dysphagia with only solid food tends to occur with structural lesions, which cause esophageal constriction, whereas dysphagia with both liquids and solids occurs more often with motility disorders. Patients with oropharyngeal dysphagia will commonly complain of a feeling of food "sticking" in the throat or the inability to propel the bolus from the mouth to the pharynx; they may also complain of the need for multiple swallowing motions to clear the bolus. Since the cranial nerves that generally control the initial phases of swallowing are responsible for other functions as well, symptoms that may be associated with oropharyngeal dysphagia include drooling, dysarthria (due to tongue dysfunction), nasal regurgitation (due to failure to seal off the nasal passage), or coughing and aspiration (due to failure to elevate and cover the laryngeal vestibule). Dysphagia that results from abnormalities in the body of the esophagus may be referred to the chest or the neck, so the location of dysphagia does not predict the location of the disease. Dysphagia may also lead to a variety of behavioral accommodations, including maneuvers such as slow eating, food aversion, avoidance of hard solid food, and drinking of large amounts of liquids with solid meals.

Regurgitation, which is another typical esophageal symptom, may be described as the feeling of food coming up into the chest or, more dramatically, into the mouth. When regurgitation occurs early in the meal, it suggests a proximal lesion. Regurgitation later in the meal suggests a motility abnormality such as achalasia.

Food impaction is an extreme esophageal symptom. When impaction occurs in the oropharynx, it may lead to tracheal impaction or compression. With more distal esophageal lesions, impaction may occur any time during the meal, almost always from a mechanical cause. Patients experience the sudden onset of chest pain and the sensation of food sticking, typically after solids such as meats, raw vegetables, and sticky rice. With complete impaction, patients who cannot handle secretions because of the obstructing bolus are at risk for aspiration, esophageal rupture, and perforation.

GASTROESOPHAGEAL REFLUX DISEASE

DEFINITION

Gastroesophageal reflux disease (GERD) develops when the reflux of stomach contents into the esophagus causes troublesome symptoms or complications.

EPIDEMIOLOGY

It is estimated that GERD, defined as at least weekly heartburn or acid regurgitation, has a prevalence ranging from 10 to 20% in the Western world and less than 5% in Asia. In the United States, estimates are that as many as 44% of people may have had GERD symptoms and 30% have had such symptoms in the prior week. The prevalence also tends to be higher in North America than Europe and higher in northern Europe than in southern Europe. Risk factors for developing GERD include obesity, particularly central obesity, and possibly increasing age. A genetic component may also play a role because GERD is more common in patients with a positive family history and in monozygotic twins than in dizygotic twins.

PATHOBIOLOGY

The esophagus is protected from the harmful effects of refluxed gastric contents by the antireflux barrier at the gastroesophageal junction, by esophageal clearance mechanisms, and by epithelial defensive factors. The antireflux barrier consists of the lower esophageal sphincter, crural diaphragm, phrenoesophageal ligament, and angle of His, which causes an oblique entrance of the esophagus into the stomach. The attachment of the lower esophageal sphincter to the crural diaphragm results in increased pressure during inspiration and when intra-abdominal pressure increases. Disruption of normal defense mechanisms leads to pathologic amounts of reflux.

Reflux of gastric contents from the stomach into the esophagus occurs in healthy individuals, but refluxed gastric contents are normally cleared in a two-step process: volume clearance by peristaltic function and neutralization of small amounts of residual acid by weakly alkaline swallowed saliva. In normal healthy individuals, physiologic reflux occurs primarily when the lower esophageal sphincter transiently relaxes in the absence of a swallow because of a vagally mediated reflex that is stimulated by gastric distention. In GERD patients, transient relaxation of the lower esophageal sphincter or a low resting lower esophageal sphincter pressure can result in regurgitation, especially when intra-abdominal pressure is increased. In some patients, a primary increase in intra-abdominal pressure overcomes normal lower esophageal sphincter pressure. These patients may have a rumination and/or supragastric belching variant of gastroesophageal reflux.[2]

A hiatal hernia, which results in axial and vertical spatial separation between the augmenting effects of the crural diaphragm and the lower esophageal sphincter, predisposes to reflux events by widening the opening of the gastroesophageal junction and decreasing the pressure of the lower esophageal sphincter. The result is an increased exposure of the esophagus to acid and gastric contents, with increased reflux events during transient physiologic relaxation of the lower esophageal sphincter and/or increased gastric pressure. Hernias also act as a reservoir for gastric contents when normal esophageal clearance mechanisms result in trapping of fluids in the hernia sac. These contents can reflux into the esophagus when the lower esophageal sphincter relaxes during subsequent swallowing.

Normal individuals also have an unbuffered acid pocket in the gastric cardia, which escapes the buffering effects of a meal in the postprandial period. This region is a source of postprandial reflux and may explain the chronic inflammation often seen in the cardia and distal esophagus. In reflux patients, the acid pocket is more common and longer in length than in normal individuals. Displacement of the acid pocket into a hiatal hernia also appears to increase acidic reflux in patients with GERD.

Increased intra-abdominal fat associated with obesity increases intragastric pressure, which increases the gastroesophageal pressure gradient and the frequency of transient lower esophageal sphincter relaxation, thereby predisposing gastric contents to migrate into the esophagus. In addition, obesity enhances the spatial separation of the crural diaphragm and the lower esophageal sphincter, thereby predisposing obese individuals to a hiatal hernia. The metabolic syndrome (Chapter 210) that is associated with obesity also may have an independent effect in promoting esophageal injury in GERD.

The normal defense mechanisms based on peristalsis and saliva also can be impaired. Peristaltic dysfunction is associated with an increasing severity of esophagitis, and ineffective peristaltic clearance may occur when the amplitude of esophageal contractions is less than 20 mm Hg. Saliva production may be impaired by a variety of mechanisms, such as smoking and Sjögren syndrome (Chapter 247).

The esophageal mucosa contains several lines of defense. A pre-epithelial barrier constitutes a small unstirred water layer combined with bicarbonate from swallowed saliva and from the secretions of submucosal glands. A second epithelial defense is composed of cell membranes and tight intercellular junctions, cellular and intercellular buffers, and cell membrane ion transporters. The postepithelial line of defense is composed of the blood supply to the esophagus. Acid and acidified pepsin in the refluxate are the key factors that damage the intercellular junctions, increase intracellular permeability, and dilate intercellular spaces. If sufficient quantities of refluxate diffuse into the intercellular spaces, cellular damage may occur. Signs and symptoms of GERD occur when defective epithelium comes into contact with refluxed acid, pepsin, or other noxious gastric contents. In addition to the direct noxious effects of refluxed acid, pepsin, and bile, refluxed gastric juice stimulates esophageal epithelial cells to secrete chemokines that attract inflammatory cells into the esophagus, thereby damaging the esophageal mucosa.

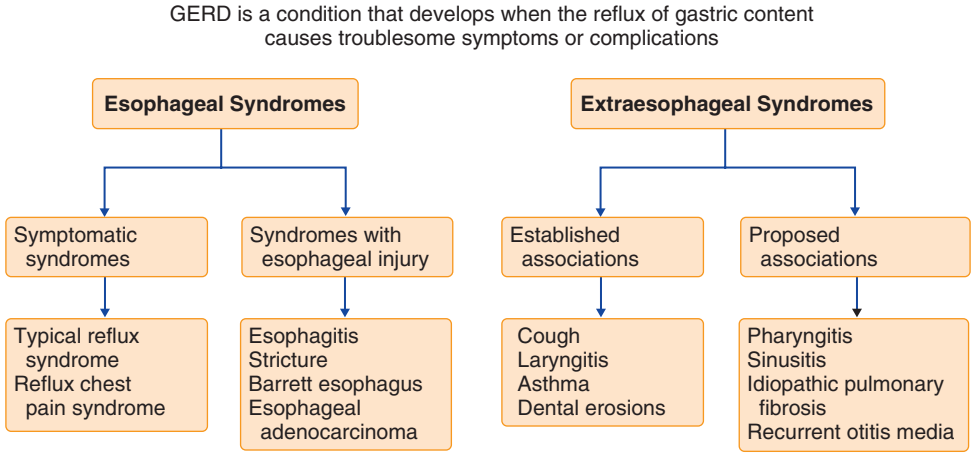

FIGURE 124-1. **Montreal classification of gastroesophageal reflux disease (GERD).** (From Vakil N, van Zanten S, Kahrilas P, et al. The Montreal definition and classification of gastroesophageal reflux disease: a global evidence-based consensus. *Am J Gastroenterol*. 2006;101:1900-1920.)

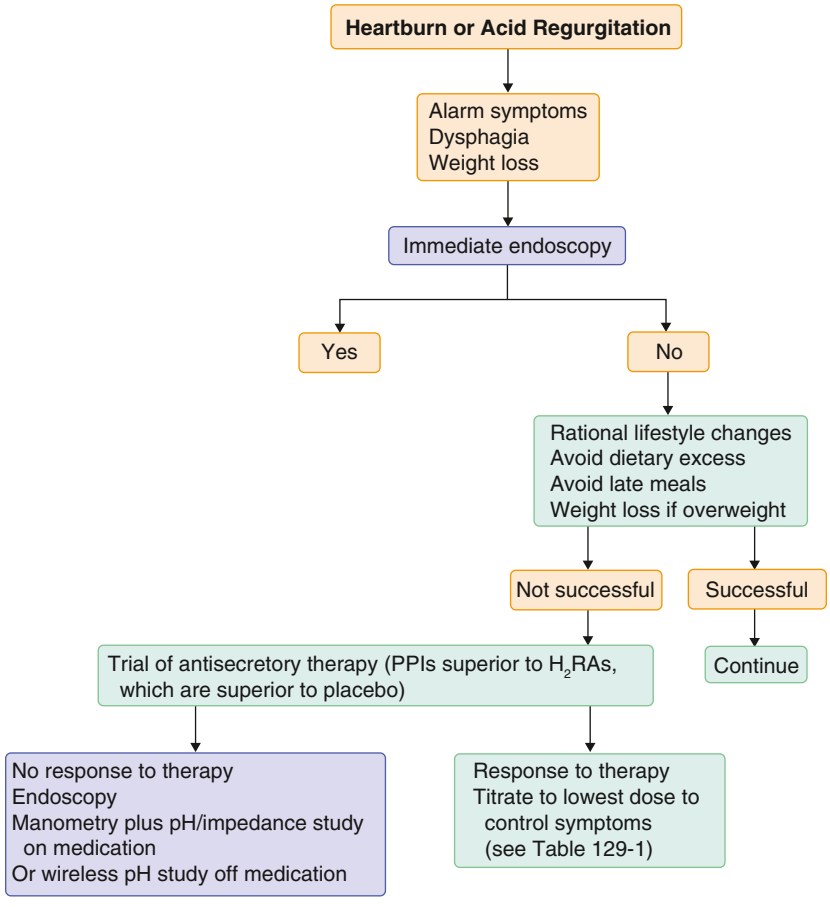

FIGURE 124-2. **Algorithm for the management of heartburn or regurgitation symptoms.** Surgery is indicated only for patients who are intolerant of antisecretory therapy or who have ongoing symptoms, especially regurgitation if reflux is well documented. H_2RA = histamine-2 receptor antagonist; PPI = proton pump inhibitor. (Based on Kahrilas PJ, Shaheen NJ, Vaezi MF. American Gastroenterological Association Institute technical review on the management of gastroesophageal reflux disease. *Gastroenterology*. 2008;135:1392-1413.)

CLINICAL MANIFESTATIONS

The classic symptoms of GERD are heartburn and acid regurgitation; atypical symptoms include chest pain, dysphagia, and odynophagia. Extraesophageal manifestations of reflux disease can include cough (Chapter 71), laryngitis (Chapter 397), asthma (Chapter 75), and dental erosions, but these symptoms are more easily attributable to GERD if accompanied by classic signs and symptoms of reflux disease and by objective testing that demonstrates increased reflux (Fig. 124-1). Other proposed associations that do not reliably respond to acid suppression and hence are not clearly related to GERD include pharyngitis, sinusitis, otitis media, throat clearing, and idiopathic pulmonary fibrosis.

When excessive gastric contents overwhelm the mucosal protective factors in the esophagus, esophagitis may be manifest as erosions or ulceration of the esophagus and may also lead to fibrosis with stricturing, columnar metaplasia (Barrett esophagus), or esophageal adenocarcinoma (Chapter 178). However, approximately two thirds of individuals with reflux symptoms have no evidence of esophageal damage by endoscopy.

DIAGNOSIS

When GERD is associated with typical signs and symptoms, such as heartburn or acid regurgitation, that are responsive to antisecretory therapy, no diagnostic evaluation is warranted,[3] except perhaps in patients who have high-risk characteristics for Barrett esophagus, such as smoking, older age, and absence of *H. pylori* infection.[4] However, recommendations on screening vary, and the cost-effectiveness of screening is uncertain.[5]

Diagnostic endoscopy is warranted in individuals who fail to respond to 4 to 8 weeks of therapy or have alarm symptoms or signs such as dysphagia, weight loss (Fig. 118-4), anemia, gastrointestinal bleeding, or persistent heartburn (Fig. 124-2). Endoscopy permits the detection of

erosive esophagitis and complications such as a peptic stricture (Fig. 124-3) and Barrett esophagus (Fig. 124-4); mucosal biopsy, which is crucial in these settings, also excludes conditions that can mimic GERD, such as eosinophilic esophagitis. However, most patients have no mucosal damage seen on endoscopy, regardless of whether they are on or off antisecretory therapy.

Esophageal manometry is useful to exclude achalasia in patients with suggestive symptoms. Esophageal reflux testing may be performed using 48- to 96-hour devices attached to the esophageal lumen, or 24-hour combined impedance and pH monitoring.[6] Testing of a patient who is not receiving antisecretory therapy can document abnormal esophageal acid exposure and establish the relationship between symptoms and reflux events. Testing of a patient who is on acid-suppression therapy should be considered only in individuals who have established GERD and in whom impedance pH monitoring can establish the relationship, if any, between refractory symptoms and reflux events, thereby permitting exclusion of GERD as the cause of persistent symptoms. Barium radiography has no role in the diagnostic evaluation of patients with uncomplicated reflux disease.

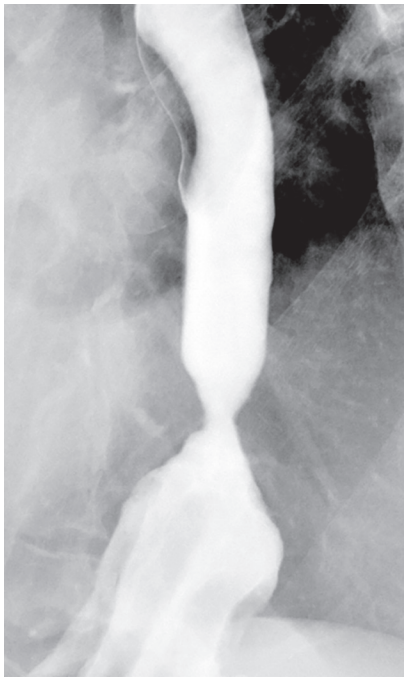

FIGURE 124-3. Barium radiograph of a peptic stricture. (Courtesy Marc Levine, MD.)

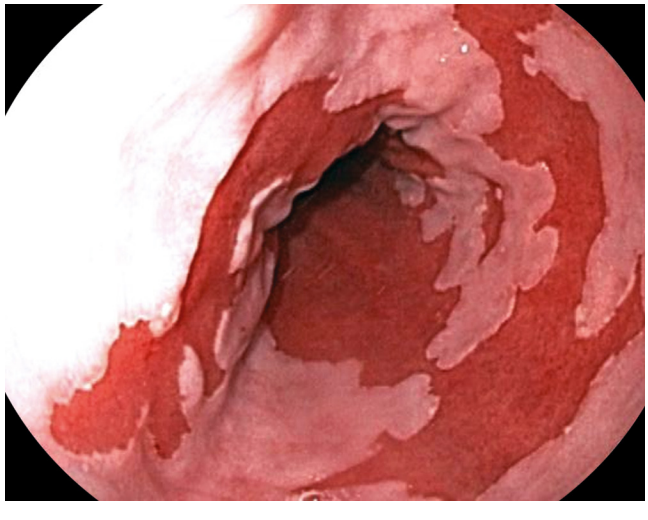

FIGURE 124-4. Endoscopic appearance of Barrett esophagus. Note the white-appearing normal squamous mucosa displaced above the true end of the esophagus. The intervening mucosa appears salmon pink.

TREATMENT

Although avoidance of foods or beverages that may provoke symptoms, such as alcohol, coffee, spicy foods, and late meals, makes physiologic sense, data from clinical trials to support these maneuvers are lacking. Elevation of the head of the bed, often with a wedge device, for patients with nocturnal regurgitation or heartburn also is logical. Given the association of obesity and GERD symptoms, weight loss should be part of any treatment program for obese patients.

Inhibition of gastric acid secretion (Table 124-1) is the cornerstone of the acute treatment of GERD,[7] and proton pump inhibitors are superior to histamine (H_2)–receptor antagonists for both the healing of esophagitis and the control of symptoms. For example, twice-daily proton pump inhibitor therapy results in more rapid endoscopic healing but not more rapid resolution of symptoms compared with once-daily treatment.[A1] However, the healing of esophagitis is more predictable than improvement in heartburn symptoms, even with proton pump inhibitors. There are no major differences in treatment efficacy among the various proton pump inhibitors.

Given the chronicity of reflux symptoms, long-term maintenance therapy with proton pump inhibitors is typically required, especially for patients with erosive esophagitis. Dosing should be titrated to the lowest dose necessary to control symptoms. Data to support the use of proton pump inhibitors in the management of extraesophageal GERD syndromes are weak, although selected patients, usually those with accompanying symptoms of classic heartburn and acid regurgitation, may benefit. The safety profile of proton pump inhibitors is excellent, but short-term adverse events such as headaches and diarrhea may occur. Long-term use of proton pump inhibitors has been associated with a variety of adverse consequences (vitamin B_{12} deficiency, *Clostridioides difficile* infection, community-acquired pneumonia, hip fracture, metabolic bone disease, diabetes mellitus, and small intestinal bacterial overgrowth), but the magnitude of any such risks is low enough that they do not offset their benefit.[8]

Although proton pump inhibitors are superior to H_2-receptor antagonists for long-term maintenance therapy as well as for short-term relief, H_2-receptor antagonists are superior to placebo and are useful in patients who cannot tolerate proton pump inhibitors. No high-quality data exist to support the common practice of using metoclopramide as either monotherapy or an adjunct to acid suppression therapy; furthermore, its potential adverse effects argue against the use of this drug in any GERD patients. In patients

TABLE 124-1 DRUG THERAPY FOR ESOPHAGEAL DISORDERS

AGENT	DOSE
ANTACIDS: LIQUID (TO BUFFER ACID AND INCREASE LESP)	
For example, Mylanta II/Maalox TC (acid-neutralizing capacity, 25 mEq/5 mL)*	15 mL qid 1 hr after meals and at bedtime or as needed
GAVISCON (TO DECREASE REFLUX VIA A VISCOUS MECHANICAL BARRIER AND BUFFER ACID)	
$Al(OH)_3$, $NaHCO_3$, Mg trisilicate, alginic acid	2-4 tablets qid and at bedtime or as needed
H_2-RECEPTOR ANTAGONISTS (TO DECREASE ACID SECRETION)	
Cimetidine	400 mg bid or 200 mg qid
Ranitidine	150 mg bid-qid or 10 mL qid; maintenance dose, 150 mg bid or 10 mL bid
Famotidine	20-40 mg bid or 2.5-5 mL bid
Nizatidine	150 mg bid
PROTON PUMP INHIBITORS (TO DECREASE ACID SECRETION AND GASTRIC VOLUME)†	
Omeprazole	20-40 mg/day; maintenance dose, 20 mg/day
Lansoprazole	15-30 mg/day; maintenance dose, 15 mg/day
Pantoprazole	40 mg/day; maintenance dose, 40 mg/day
Rabeprazole	20 mg/day; maintenance dose, 10-20 mg/day
Esomeprazole	20-40 mg/day; maintenance dose, 20 mg/day
Dexlansoprazole	30-60 mg/day; maintenance dose, 30 mg/day

*Patients with reflux are not generally hypersecretors of gastric acid, so the therapeutic doses of antacids are based on their capacity to buffer (normal) basal acid secretion rates of approximately 1 to 7 mEq/hr (mean, 2 mEq/hr) and peak meal-stimulated acid secretion rates of about 10 to 60 mEq/hr (mean, 30 mEq/hr).

†High-dose therapy is a twice-daily administration of the usually daily dose.

$Al(OH)_3$ = aluminum hydroxide; bid = twice daily; H_2 = histamine; LESP = lower esophageal sphincter pressure; Mg = magnesium; $NaHCO_3$ = sodium bicarbonate; qid = four times daily.

who have persistent symptoms despite proton pump inhibitor therapy, prolonged wireless monitoring off of proton pump therapy can identify patients whose symptoms are not acid-related and who can safely discontinue acid-suppression therapy.[A2]

If, however, patients have documented esophagitis, are intolerant of proton pump inhibitors or unresponsive to them, or regurgitate large volumes, an antireflux procedure should be considered.[9] Newer minimally invasive options in carefully selected patients (including full-thickness plication, various approaches to augment of the lower esophageal sphincter, and transoral incisionless fundoplication) can normalize esophageal acid exposure in about 50% of patients.

Antireflux surgery is an option for patients who have documented esophagitis, who are intolerant of proton pump inhibitors or unresponsive to them, or who regurgitate large volumes. Laparoscopic antireflux surgery is equivalent to continued proton pump inhibitor therapy for the healing of esophagitis and for the treatment of chronic GERD in patients who initially respond to proton pump inhibitors. In patients with persistent regurgitation despite proton pump inhibitor therapy, however, laparoscopic surgery is better than continued medical therapy for relieving symptoms,[A3,A4] even though about 15 to 20% of patients have recurrent symptoms severe enough to warrant another procedure. Surgery also has a number of serious complications that may affect quality of life, including dysphagia, vagal nerve injury, gas bloat syndrome, and diarrhea.

PROGNOSIS

Patients with GERD generally do well with conservative antireflux measures and proton pump inhibitor therapy. When surgery is required, the outcome is usually excellent.

PEPTIC STRICTURES

Esophageal strictures are a well-recognized complication of GERD, especially in older patients with long-standing reflux symptoms, but population-based studies suggest that the incidence of new and recurrent strictures is declining. Peptic strictures are thought to be a consequence of severe inflammation, which leads to fibrosis, scarring, esophageal shortening, and loss of compliance of the lumen.

CLINICAL MANIFESTATIONS AND DIAGNOSIS

Symptoms are typically dysphagia to solids with or without antecedent symptoms of heartburn or acid regurgitation. Strictures may be diagnosed by barium radiography or with upper endoscopy, but barium esophagograms (see Fig. 124-3) have a higher sensitivity for detecting subtle lesions, especially if performed with a solid challenge such as a barium-impregnated pill. However, peptic strictures must be distinguished from a wide variety of other causes of luminal narrowing, including pills, prior nasogastric tube intubation, neoplasia, infection, radiation, surgical anastomosis, some systemic diseases, caustic substances, eosinophilic esophagitis, lichen planus, and extrinsic compression. As a result, endoscopic biopsy and cytology are critical for distinguishing benign from malignant causes of strictures.

TREATMENT

Endoscopic dilation, which remains the cornerstone of therapy, should be done gradually to achieve a luminal diameter that is sufficiently large to relieve symptoms—typically a diameter of 13 mm or greater. After dilation is accomplished, patients should receive chronic proton pump inhibitor therapy (see Table 124-1). For recalcitrant peptic strictures, injection of triamcinolone into the stricture is superior to sham injection in patients who receive balloon dilation and post-procedure proton pump inhibitors.

PROGNOSIS

Endoscopic dilation will usually alleviate symptoms, but repetitive dilation is required in a significant minority of patients.

BARRETT ESOPHAGUS

Barrett esophagus, which is an acquired condition that results from severe esophageal mucosal injury, is a metaplastic change in the lining of the distal tubular esophagus, where the normal squamous epithelium is replaced by a columnar epithelium. Barrett esophagus would be of little importance if not for its well-recognized association with adenocarcinoma of the esophagus (Chapter 178). However, the risk for cancer in an individual patient with Barrett esophagus is low.

EPIDEMIOLOGY

Barrett esophagus is found in approximately 5 to 15% of patients who undergo endoscopy for symptoms of GERD.[10] Population-based studies suggest that the prevalence of Barrett esophagus is approximately 1.3 to 1.6%, but about 45% of affected patients do not have reflux symptoms. Barrett esophagus is predominantly a disease of middle-aged White men, but about 25% of patients are women or are younger than 50 years. The prevalence of Barrett esophagus increases until a plateau is reached between the seventh and ninth decades. Risk factors include frequent and long-standing reflux episodes, smoking, male sex, older age, and central male pattern obesity.

PATHOBIOLOGY

Barrett esophagus results from severe esophageal mucosal injury. Patients who develop Barrett esophagus typically have more esophageal acid and bile exposure, the former based on 24-hour pH monitoring, and almost always have a hiatal hernia, which is typically longer and associated with larger defects than in patients without Barrett esophagus. However, why some patients with GERD develop Barrett esophagus whereas others do not remains unclear, as does the cell of origin of columnar metaplasia. Candidates include dedifferentiation of squamous epithelium into columnar epithelium or stimulation of stem cells from either the basal layer of the esophageal epithelium, the esophageal submucosal glands, gastric cardia, residual embryonal stem cells at the gastroesophageal junction, or the bone marrow. The transcription factor CDX2, which can be induced by both acid and bile salts, appears to play a role in promoting the development of the columnar epithelium in the distal esophagus and gastroesophageal junction.[11] A small subset of patients may have an inherited predisposition to Barrett esophagus, although the genetics of the disease are incompletely understood.

CLINICAL MANIFESTATIONS

The development of reflux symptoms at an earlier age, an increased duration of reflux symptoms, an increased severity of nocturnal reflux symptoms, and prior complications of GERD such as esophagitis, ulceration, stricture, and bleeding may raise the likelihood of Barrett esophagus. Nevertheless, patients with Barrett esophagus are difficult to distinguish clinically from patients whose GERD is uncomplicated by a columnar-lined esophagus. Patients with Barrett esophagus may paradoxically have impaired sensitivity to esophageal acid perfusion and even lack symptoms of GERD.

DIAGNOSIS

Endoscopically, Barrett esophagus is characterized by displacement of the squamocolumnar junction so that it is now proximal to the gastroesophageal junction, which is defined by the proximal margin of gastric folds (see Fig. 124-4). The diagnosis of Barrett esophagus is established if the squamocolumnar junction is displaced 1 cm or more proximal to the gastroesophageal junction and if intestinal metaplasia, which is characterized in part by acid mucin-containing goblet cells, is detected by biopsy.[12]

The precise junction of the stomach and the esophagus may be difficult to determine endoscopically owing to the presence of a hiatal hernia, inflammation, and the dynamic nature of the gastroesophageal junction. If the squamocolumnar junction is above the level of the esophagogastric junction, as defined by the proximal margin of the gastric folds, biopsy specimens should be obtained for confirmation of columnar metaplasia.

Intestinal or columnar metaplasia may be seen in the cardia of normal individuals as well as in persons with chronic reflux disease, and the prevalence of intestinal metaplasia at a normal-appearing gastroesophageal junction varies from 5 to 36%. Dysplasia and an increased risk for carcinoma have been reported in patients who have intestinal metaplasia of the gastroesophageal junction or cardia, but the magnitude of that risk appears to be far less than that of Barrett esophagus and surveillance is not warranted.

Another potential approach to diagnosis is the cytosponge-trefoil factor 3, which is a non-endoscopic cell collection device coupled with an immunohistochemical biomarker. This small mesh sponge within a soluble gelatin capsule is attached to a string. The patient swallows the capsule, which is then retrieved about 5 minutes later. The mesh slightly abrades the esophageal mucosa, thereby collecting cells for analysis. In one randomized trial, this approach significantly increased the early diagnosis of Barrett esophagus.[A5]

TREATMENT

Patients who are diagnosed with Barrett esophagus require surveillance endoscopy at regular intervals (Fig. 124-5). They characteristically worry about cancer risk, which they may overestimate, face higher life insurance premiums, and may receive conflicting information on how best to treat their condition.

Proton pump inhibitors (see Table 124-1), which are the cornerstone of medical therapy for Barrett esophagus, consistently relieve symptoms and heal esophagitis. However, proton pump inhibitors, even at high doses, do not provide clear regression of Barrett histology, perhaps because alleviation of reflux symptoms is not necessarily equivalent to normalization of esophageal acid exposure. In fact, abnormal acid exposure persists in approximately 25% of Barrett esophagus patients despite twice-daily proton pump inhibitors. The precise importance of complete control of esophageal acid exposure in patients with Barrett esophagus remains unknown, but the combination of high-dose proton pump inhibitor therapy plus aspirin (300 to 325mg daily) can reduce the progression to high-grade dysplasia, adenocarcinoma, or death in patients with Barrett metaplasia.[A6] Antireflux surgery effectively alleviates GERD symptoms, and the indications for surgery are the same as those for patients with GERD without Barrett esophagus. Surgery should not, however, be viewed as a better cancer prevention tool.

Current practice guidelines, based on observational data, recommend endoscopic surveillance of patients with documented Barrett esophagus in an attempt to detect dysplasia and cancer at an early and potentially curable stage.[12] Before entering into a surveillance program, patients should be advised about risks and benefits, including the limitations of surveillance endoscopy as well as the importance of adhering to appropriate surveillance intervals. Other considerations include age, likelihood of survival over the next 5 years, and ability to tolerate either endoscopic or surgical interventions for early esophageal adenocarcinoma.

Systematic four-quadrant biopsies should be obtained at 2-cm intervals along the entire length of the Barrett segment after inflammation related to GERD is controlled with antisecretory therapy. Mucosal abnormalities, especially in the setting of high-grade dysplasia, should be resected endoscopically.

Surveillance intervals, determined by the presence and grade of dysplasia, are based on a limited understanding of the biology of esophageal adenocarcinoma. Surveillance for patients without dysplasia should occur every 3 to 5 years after an initial negative examination. If low-grade dysplasia is found, the diagnosis should first be confirmed by an expert gastrointestinal pathologist because of the marked interobserver variability in the interpretation of these biopsies. If confirmed, aggressive proton pump inhibitor therapy (see Table 124-1) is recommended to decrease inflammation and regeneration, which may make pathologic interpretation difficult. A repeat endoscopy should then be performed within 6 months of the initial diagnosis. If low-grade dysplasia is again confirmed, options include continued surveillance at 6- to 12-month intervals or radio frequency ablation, but ablation significantly reduces the risk for progression to high-grade dysplasia or to adenocarcinoma over the next 3 years.[A7]

If high-grade dysplasia is found, an experienced gastrointestinal pathologist should confirm the diagnosis. For patients with confirmed high-grade dysplasia, endoscopic ablation therapy with radio frequency ablation, endoscopic mucosal resection, or a combination is now recommended instead of surgery or continued surveillance.[13] For high-grade dysplasia patients with any visible abnormality, endoscopic mucosal resection is recommended for optimal diagnosis and staging. Surgery with esophagectomy is reserved only for patients who fail to respond to endoscopic ablation therapy or if the cancer is beyond stage T1a (intramucosal cancer).

PROGNOSIS

The risk that a patient with Barrett esophagus will develop esophageal adenocarcinoma is now estimated to be approximately 0.1 to 0.3% annually. With appropriate surveillance,[14] most patients with Barrett esophagus will never develop esophageal adenocarcinoma and will die of other causes.

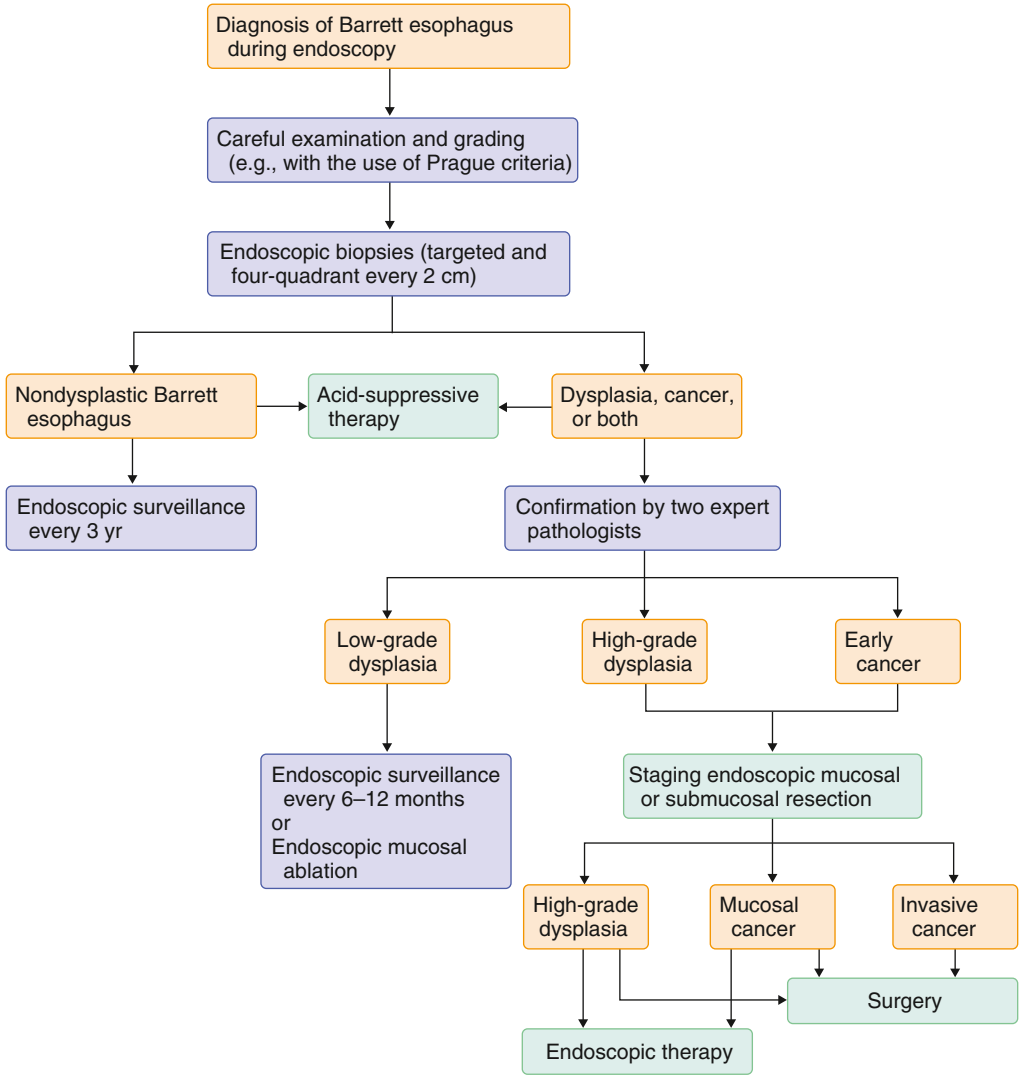

FIGURE 124-5. Proposed treatment algorithm for patients with Barrett esophagus. (From Sharma P. Barrett's esophagus. *N Engl J Med*. 2009;361:2548-2556.)

ESOPHAGITIS

EOSINOPHILIC ESOPHAGITIS

Eosinophilic esophagitis is probably caused by an aberrant immune or antigenic response to food and aeroallergens that trigger chronic inflammation with dense eosinophilia in the esophageal mucosa. The disease is most common in children, adolescents, and young adults, but middle-aged adults are often affected as well. The estimated prevalence is about 0.5 to 1 case per 1000 population. Patients often have a personal and family history of other allergic disorders. A genetic predisposition is suggested by abnormal gene profiles in almost 50% of children with this disorder.

CLINICAL MANIFESTATIONS AND DIAGNOSIS

Children present with failure to thrive, nausea, vomiting, abdominal pain, and dyspeptic symptoms, whereas adults present with solid food dysphagia, food impaction, or chest pain. Boerhaave syndrome (see later) may also occur with this disease. Diagnosis is made by classic findings on endoscopy, such as linear furrowing, white exudates, and multiple rings (Fig. 124-6), accompanied by biopsies demonstrating eosinophilic infiltration (Table 124-2) in the absence of other conditions that can cause esophageal eosinophilia, such as GERD, achalasia, vasculitis, hypereosinophilic syndrome, Crohn disease, Ehlers-Danlos syndrome, graft versus host disease, infections, and drug hypersensitivity. The severity of the condition and its response to therapy can be assessed by both endoscopic and histologic criteria.[15]

TREATMENT AND PROGNOSIS

Treatment options for eosinophilic esophagitis include food elimination diets,[A8] proton pump inhibitors (see Table 124-1), and topical steroids.[16-18] Many patients may benefit from an empiric one, two, four- (or six-) food elimination diet that eliminates cow's milk protein (casein), soy, wheat, eggs, peanut/tree nuts, and seafood. An elemental diet also may be prescribed for severe disease. A formal allergy evaluation (Chapter 230) is required only in individuals with accompanying atopic diseases. Topical steroids (e.g., swallowed fluticasone, 880 μg twice daily; budesonide orodispersible tablets, 0.5 mg twice daily; or budesonide suspension, 1 mg twice daily) can safely sustain remission in 75% of patients, whereas up to 95% of patients may relapse when treatment is stopped.[A9,A10] Dupilumab (300 mg subcutaneously weekly for 12 weeks) is a useful option.[A11,19]

Most patients do well after an initial course of treatment. However, relapse is typical once therapy is discontinued, and chronic therapy is often needed, especially for those with prior complications such as food impaction, strictures, or a narrow-caliber esophagus.

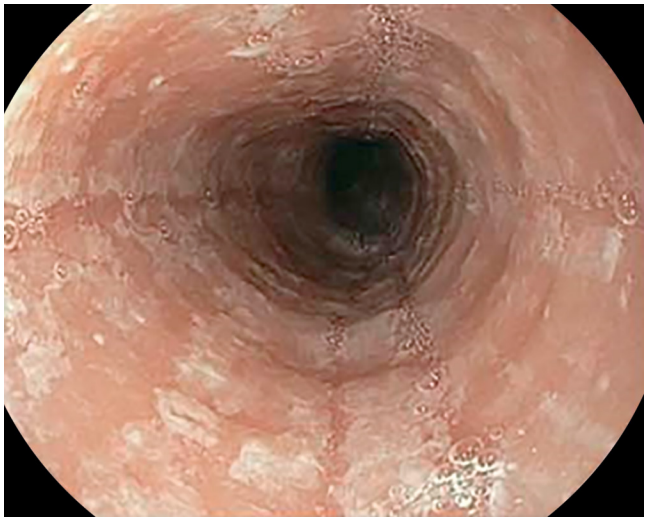

FIGURE 124-6. Endoscopic corrugated (ringed) appearance of esophagus in eosinophilic esophagitis.

TABLE 124-2 GUIDELINES FOR THE DIAGNOSIS OF EOSINOPHILIC ESOPHAGITIS

- Characteristic demographic and endoscopic findings
- Clinical symptoms of esophageal dysfunction
- *At least* 15 eosinophils in 1 high-power biopsy field
- Exclusion of other causes of esophageal eosinophilia

PILL-INDUCED ESOPHAGITIS

Pills (Table 124-3) can induce esophageal injury by producing a caustic acid solution (e.g., ascorbic acid and ferrous sulfate), producing a caustic alkaline solution (e.g., alendronate, button batteries), placing a hyperosmolar solution in contact with the esophageal mucosa (e.g., potassium chloride), or causing direct drug toxicity to the esophageal mucosa (e.g., tetracycline). Because prolonged contact is an essential part of the injury, predisposing factors for pill-induced injury include anatomic barriers, such as a stricture, a prominent aortic arch that compresses the esophagus, or improper ingestion of the pill because of inadequate fluid or improper positioning (i.e., lying down directly after taking the pill). The most common medications are tetracycline and its derivatives, but other commonly implicated medications include nonsteroidal anti-inflammatory drugs, bisphosphonates, ferrous sulfate, quinidine, and potassium chloride.

Patients usually complain of the acute onset of severe odynophagia. Radiographic or endoscopic findings may range from discrete ulceration to diffuse esophagitis. Treatment is generally supportive with discontinuation of the medication until the injury resolves. Although acid suppression is commonly recommended, there is no proof that this approach is beneficial. Patients should be given careful instructions to avoid lying down immediately after ingesting medication and to drink adequate fluids to prevent injury. Rarely, pill-induced injury may lead to strictures and even fistulas.

CAUSTIC INJURY

Potentially devastating caustic esophageal injuries may be caused by highly alkaline solutions, such as sodium hydroxide, or highly acidic solutions, such as sulfuric acid. The most common products that contain these substances are drain cleaners and industrial strength cleaners, but other corrosive substances include hair relaxers, oven and toilet bowl cleaners, and button batteries. Patients require emergent endoscopy to determine the degree of injury,

TABLE 124-3 MEDICATIONS COMMONLY ASSOCIATED WITH ESOPHAGITIS OR ESOPHAGEAL INJURY

ANTIBIOTICS
Tetracycline
Doxycycline
Clindamycin
Penicillin
Rifampin
Cloxacillin
ANTIVIRAL AGENTS
Zalcitabine
Zidovudine
Nelfinavir
BISPHOSPHONATES
Alendronate
Etidronate
Pamidronate
CHEMOTHERAPEUTIC AGENTS
Dactinomycin
Bleomycin
Cytarabine
Daunorubicin
5-Fluorouracil
Methotrexate
Vincristine
Crizotinib
NONSTEROIDAL ANTI-INFLAMMATORY DRUGS
Aspirin
Naproxen
Ibuprofen
OTHER MEDICATIONS
Quinidine
Potassium chloride
Ferrous sulfate
Ascorbic acid
Multivitamins
Theophylline

which helps predict long-term prognosis. No clear evidence supports routine steroids or antibiotics. Many patients will have lifelong disease marked by chronic strictures that require frequent dilation and even esophageal reconstruction. In patients with a severe initial injury, the risk for esophageal cancer is significantly increased.

ESOPHAGEAL MOTOR DISORDERS

OROPHARYNGEAL DYSFUNCTION

The cricopharyngeus and inferior pharyngeal constrictor are composed of striated muscle and innervated by upper motor neurons, the brain stem, and the cerebral cortex. Both primary myopathic and neuropathic disorders can result in dysfunction. The most common neurologic cause of oropharyngeal dysphagia is a cerebrovascular accident (Chapter 376). Other neuropathic disorders that may also affect function include myasthenia gravis (Chapter 390), brain stem tumors (Chapter 175), amyotrophic lateral sclerosis (Chapter 387), Parkinson disease (Chapter 378), Alzheimer disease (Chapter 371), postpolio syndrome (Chapter 349), Guillain-Barré syndrome (Chapter 388), and botulism (Chapter 271). Myogenic disorders that cause dysfunction include paraneoplastic antibody-mediated syndromes (Chapter 164), thyroid disease (Chapter 207), primary myopathies (Chapter 389) such as dermatomyositis and inclusion body myositis and drugs that cause myopathy such as statins and amiodarone.

Patients with oropharyngeal abnormalities experience dysphagia, often accompanied by postprandial coughing, hoarseness, and aspiration pneumonia. Treatment focuses on the underlying myopathic or neurologic cause and swallowing therapy, but prognosis is often poor owing to limited treatment options.

ACHALASIA

Achalasia, which is the prototypic esophageal motility disorder,[20] is characterized by insufficient relaxation of the lower esophageal sphincter accompanied by loss of esophageal peristalsis.

EPIDEMIOLOGY AND PATHOBIOLOGY

Achalasia can occur in patients of almost any age, from infants to nonagenarians, but it most commonly presents between 30 and 60 years of age. The prevalence is 10 per 100,000 in the United States, with all races affected and an equal distribution in men and women. The pathophysiology of achalasia most likely reflects an antibody-mediated autoimmune myenteric plexopathy in the lower esophageal sphincter and a generalized neuropathy in the esophageal body. The triggering event is unclear, but a viral cause is suggested. Injury to the lower esophageal sphincter neurons leads to a relative selective deficiency of nitric oxide. With this loss of the main functional inhibitory neurotransmitter, the sphincter loses its ability to relax. The neurochemical process that leads to aperistalsis is unclear.

CLINICAL MANIFESTATIONS AND DIAGNOSIS

The cardinal symptoms of achalasia are dysphagia to both liquids and solids, regurgitation, and chest pain. Some patients may have more subtle symptoms, including heartburn, presumably caused by esophageal stasis of acidic food content, weight loss, and aspiration pneumonia; in these settings, diagnosis is often delayed.

The diagnosis of achalasia relies on esophageal manometry and barium radiography. The classic radiographic appearance is esophageal dilation, stasis of contrast material, and a "bird's beak" appearance to the lower esophageal sphincter (Fig. 124-7). Manometry demonstrates high residual pressures of the lower esophageal sphincter and either simultaneous contractions or complete absence of peristaltic contractions (E-Fig. 124-1). Whether classification systems based on manometric findings can predict response is being studied. Endoscopy is recommended to exclude secondary causes of achalasia, such as gastroesophageal junctional cancer. Occasionally, patients present with a massively dilated esophagus and marked food retention. Radiographically, these patients develop a "sigmoid" esophagus with a radiographic picture similar to a sigmoid colon.

Achalasia may represent a paraneoplastic presentation of some malignancies, particularly small cell lung cancer (Chapter 177); in these patients, the tumor produces an antineuronal antibody (anti-Hu) that mediates the autoimmune lower esophageal sphincter plexopathy and produces a syndrome identical to primary achalasia. Some tumors, such as proximal gastric cancer, may also metastasize to or directly extend into the lower esophageal sphincter and produce an achalasia-like picture, possibly owing to extrinsic compression or tumor infiltration.

TREATMENT

Treatment options to decrease the functional obstruction at the level of the lower esophageal sphincter include the intrasphincteric injection of botulinum toxin, pneumatic dilation, surgical myotomy, and peroral endoscopic myotomy. Injection of botulinum toxin during endoscopy reduces symptoms and improves esophageal emptying in up to 90% of patients. Because symptoms typically recur within 6 to 24 months, this treatment is best for patients who are not candidates for more definitive therapies or to confirm the diagnosis of achalasia when clinical, radiographic, and manometric criteria are not conclusive.

In pneumatic dilation, a 30- to 40-mm pneumatic balloon is placed fluoroscopically to straddle the lower esophageal sphincter; the balloon is then inflated to tear the muscle fibers of the lower esophageal sphincter. In general, one pneumatic dilation will achieve 5 years of symptomatic remission in 70% of patients, and three dilations will succeed in 90% of patients. The downside of this procedure is the risk for perforation, which occurs in less than 1% of patients in experienced hands.

The third approach is a Heller myotomy, which is now typically performed laparoscopically. This long myotomy starts at least 2 cm below the lower esophageal sphincter and extends for about 6 cm upward past the sphincter; a loose fundoplication is performed to prevent gastroesophageal reflux. The 5-year success rate approaches 90%. Randomized controlled trials suggest that either pneumatic dilation or Heller myotomy will provide comparable clinical results over 2 years.[A12]

Peroral endoscopic myotomy is an alternative to laparoscopic myotomy. Results at 2 years are equal to or better than for pneumatic dilation[A13,A14] or laparoscopic Heller myotomy, and long-term follow-up data are encouraging; however, reflux is observed in approximately 50% of patients. As a result, patients should be aware of this issue when selecting between the endoscopic and laparoscopic approaches and should undergo endoscopy at 6 to 12 months after peroral endoscopic myotomy.[21]

In patients with massive dilation, esophageal dysfunction may warrant total esophagectomy because of life-threatening symptoms such as continued weight loss, recurrent aspiration pneumonia, or tracheal compression. In patients with underlying paraneoplastic malignancy, treatment of the tumor may be helpful, and botulinum toxin has been tried with anecdotal success.

PROGNOSIS

No treatment approach is curative, and all are palliative. Recurrent symptoms may be related to an incomplete myotomy, herniation or unwrapping of the fundoplication, esophageal strictures, Barrett esophagus, or just the natural history of the disease. Achalasia patients also may be predisposed to squamous cell carcinoma of the esophagus, although current evidence does not support cancer screening.

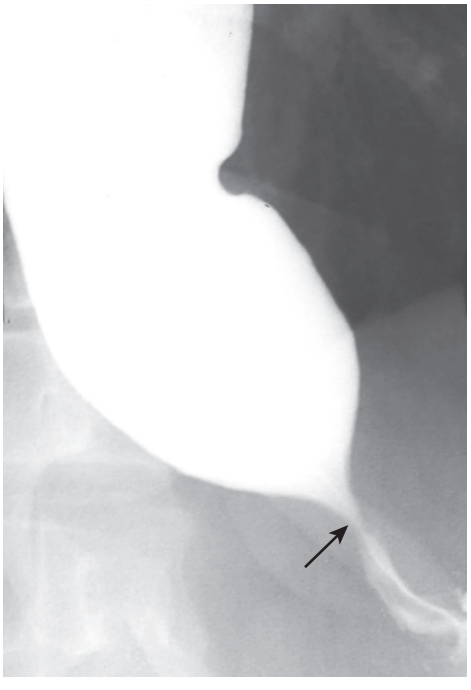

FIGURE 124-7. Esophagogram of a patient with idiopathic achalasia. Note the dilated esophagus and distal tapering result in a "bird's beak" deformity in the area of the lower esophageal sphincter *(arrow)*. (Courtesy Marc Levine, MD.)

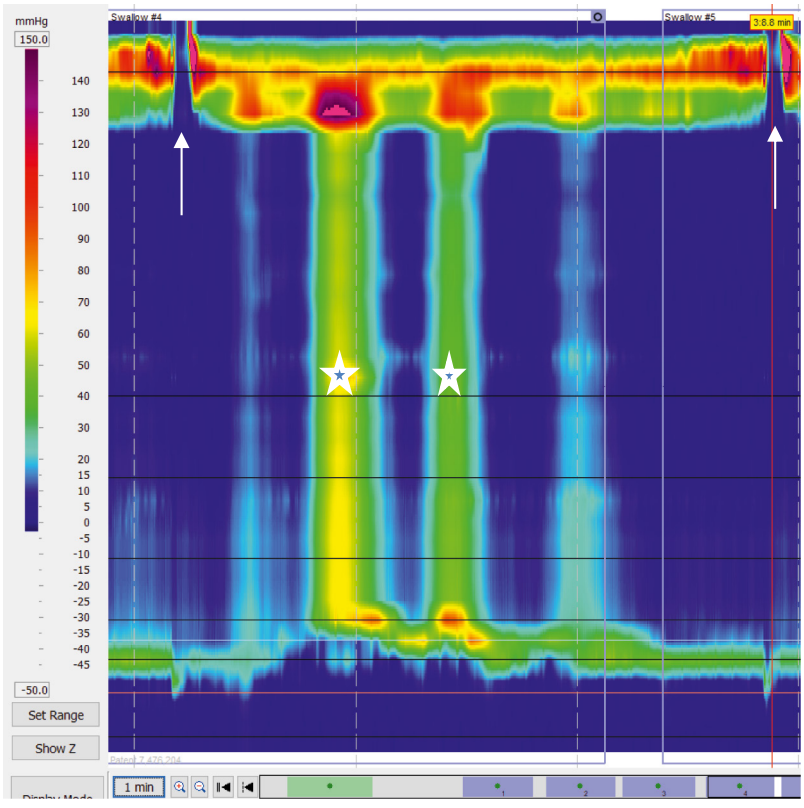

E-FIGURE 124-1. High resolution pattern of type II achalasia. Proximal high-pressure zone is upper esophageal sphincter. Lower high-pressure zone is lower esophageal sphincter. Swallows are designated by *arrows*. *Stars* represent examples of isobaric pressurizations in response to swallow. Note the lower esophageal sphincter moves proximally with swallows.

DIFFUSE ESOPHAGEAL SPASM

Diffuse esophageal spasm is found in fewer than 5% of patients who undergo manometry for symptoms of chest pain, dysphagia, or both. The pathophysiology of diffuse esophageal spasm is not well understood, but a deficiency of nitric oxide in the esophageal body may lead to a loss of control of esophageal peristalsis, high pressures, and rapid velocity contractions.

CLINICAL MANIFESTATIONS AND DIAGNOSIS

Classically, patients have symptoms of intermittent chest pain (Chapter 123), dysphagia, or both. On endoscopic ultrasound, patients may demonstrate thickening of the circular and longitudinal muscle layers. Diffuse esophageal spasm is defined manometrically by premature rapid contractions in at least 20% of all swallows, accompanied by normal peristalsis.[22] Radiographically, diffuse esophageal spasm is characterized by a "corkscrew" esophagus with multiple simultaneous contractions that obliterate the lumen (Fig. 124-8).

TREATMENT AND PROGNOSIS

Treatment of these patients is challenging, and clinical trials have not demonstrated efficacy of any therapy. Empirical therapy may be tried with agents that relax smooth muscle or augment the nitric oxide content, such as hyoscyamine (0.125 mg sublingually), calcium-channel antagonists (nifedipine, 10 mg sublingually), nitroglycerin (0.3 mg sublingually), and sildenafil (50 mg orally). Injection of botulinum toxin into the esophageal body has had equivocal results. Antidepressants, particularly low-dose tricyclics (e.g., imipramine, 10 to 50 mg before bedtime), have had some success. For patients with dysphagia, sphincter options include botulinum toxin injection and pneumatic dilation, but surgery is not indicated unless there is evidence of achalasia. Early results of peroral endoscopic myotomy are encouraging. In general, these disorders can be difficult to manage but are not life-threatening.

OTHER MOTILITY DISORDERS

Jackhammer esophagus and hypertensive peristalsis are recently described manometric diagnoses that formerly were called nutcracker esophagus. Both are characterized by high-amplitude peristaltic contractions and are of uncertain clinical significance. Antisecretory therapy with proton pump inhibitors (see Table 124-1) is often warranted.

Isolated incomplete relaxation of the lower esophageal sphincter, also known as esophagogastric junction outflow obstruction, may represent a variant of achalasia and should be treated as such in patients with dysphagia and supportive findings or functional imaging or impedance planimetry. This entity also may be seen with structural and vascular abnormalities in the vicinity of the gastroesophageal junction. Patients with manometric findings of low-amplitude contractions, failed contractions, or contractions with large breaks have weak peristalsis, which is commonly seen in patients with severe underlying GERD.

STRUCTURAL ABNORMALITIES

CRICOPHARYNGEAL BARS

A cricopharyngeal bar diagnosed by a prominent impression of the cricopharyngeus, reflects an inability to relax the upper esophageal sphincter maximally during the flow of barium, with a sustained decrease in compliance. The decrease in cross-sectional area of the upper esophageal sphincter is likely caused by fibrosis. This condition may be asymptomatic or accompanied by symptoms of oropharyngeal dysphagia to solids. Treatment of symptomatic patients is either large-caliber dilation or surgical or endoscopic myotomy; the clinical results are generally excellent.

ESOPHAGEAL DIVERTICULA

Esophageal diverticula are encountered in fewer than 1% of upper gastrointestinal radiographic studies and account for less than 5% of cases of dysphagia. Esophageal diverticula may occur in one of three locations: above the upper esophageal sphincter, in the mid-esophagus, and just above the lower esophageal sphincter.

Zenker diverticulum is a pouch that protrudes posteriorly above the upper esophageal sphincter (Fig. 124-9). This protrusion occurs through a triangular region known as Killian triangle, which is bordered above by fibers of the inferior constrictor muscle and below by the cricopharyngeal muscle. It is thought to be caused by increased hypopharyngeal pressure that results from decreased compliance and impaired opening of the upper esophageal sphincter. Small diverticula may be asymptomatic, but increasing size is associated with globus, dysphagia to solids or liquids, regurgitation of undigested food, halitosis, and aspiration. Although no treatment is needed for asymptomatic patients, open or endoscopic surgery is indicated when symptoms occur. Prognosis after surgery is excellent.

Mid-esophageal diverticula, which are focal outpouchings of the middle of the esophagus, are thought to be related to an underlying abnormality of esophageal motility. Past tuberculosis may result in such diverticula. Symptoms typically include dysphagia with or without regurgitation, and diagnosis is usually made with barium contrast radiography. Surgical diverticulectomy with myotomy or endoscopic myotomy is reserved for patients with symptoms.

Epiphrenic diverticula are herniations of mucosa and submucosa through the muscular layers of the distal 10 cm of the esophagus. They are most commonly caused by functional lower esophageal sphincter obstruction, owing to

FIGURE 124-8. Barium esophagogram showing a "corkscrew" esophagus in a patient with diffuse esophageal spasm. The patient had dysphagia, chest pain, and normal endoscopic findings. (Image courtesy of Marc Levine, MD.)

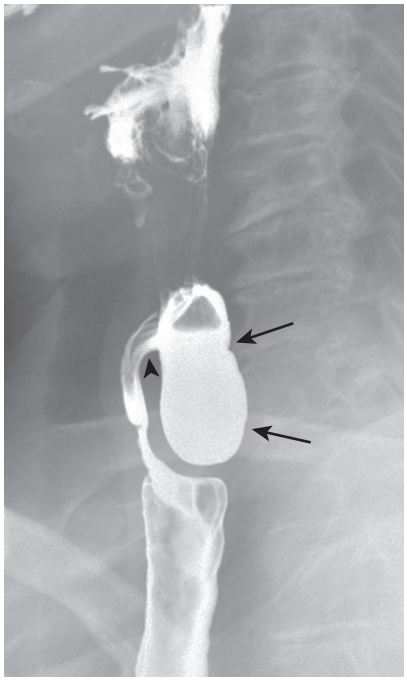

FIGURE 124-9. Barium radiograph of Zenker diverticulum *(arrows)* and cricopharyngeus *(arrowhead)*. (Courtesy Marc Levine, MD.)

underlying motility abnormalities such as achalasia or diffuse esophageal spasm, but also may be associated with mechanical obstruction, owing to a leiomyoma, prior surgery, stenosis, stricture tumor, or web. Epiphrenic diverticula may be asymptomatic or cause dysphagia, regurgitation, odynophagia, chest pain, heartburn, or aspiration. Diagnosis is typically made by barium radiography (Fig. 124-10), but endoscopy is recommended to exclude a structural cause of obstruction, and esophageal manometry is recommended to evaluate for underlying motility abnormalities. No therapy is warranted in asymptomatic patients, but symptomatic patients generally do well with surgical diverticulectomy, repair of the defect in the esophageal wall, and relief of the underlying obstruction, usually with a myotomy and partial fundoplication.

RINGS AND WEBS

Esophageal rings are concentric areas of narrowing, usually in the distal esophagus. *Schatzki ring* (Fig. 124-11) is a thin, fixed, circumferential membrane-like narrowing at the gastroesophageal junction, typically at the proximal border of a hiatal hernia. The cause may be congenital, secondary to a pleat of redundant mucosa, or related to gastroesophageal reflux. Symptoms typically occur if the ring results in a lumen that is 13 mm or less in diameter. Classic symptoms are intermittent dysphagia to solids or impaction of solid food. Diagnosis is best accomplished with barium radiography, especially for rings larger than 13 mm in diameter, which may be missed at the time of endoscopy. Treatment involves use of large-caliber dilators at least 18 mm in diameter. Long-term therapy with proton pump inhibitors (see Table 124-1) may prevent relapses. Most patients relapse after a single dilation.

Muscular rings, which are located several centimeters above the squamocolumnar junction, are composed of mucosa, submucosa, and muscle. Barium radiography and endoscopy reveal a focal constriction of variable diameter. Optimal therapy is unclear. Dilation leads to only partial or temporary relief. Other treatment modalities include injection of botulinum toxin and anticholinergic agents.

Esophageal webs are thin, eccentric, membranous areas of narrowing that may be found anywhere in the esophagus but most commonly are in the proximal region (Fig. 124-12). The pathogenesis of webs is unknown, but they are associated with a number of systemic diseases, including bullous skin disorders, chronic graft-versus-host disease, and iron deficiency anemia.

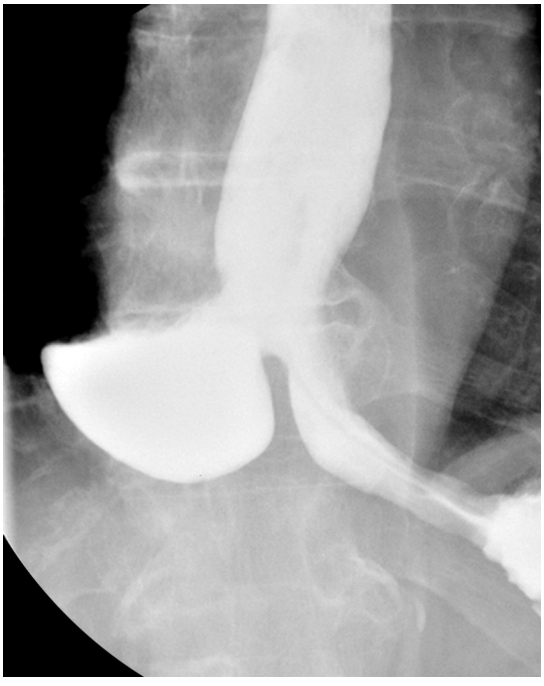

FIGURE 124-10. Barium radiograph of an esophageal epiphrenic diverticulum. (Courtesy Marc Levine, MD.)

FIGURE 124-11. Barium radiograph of Schatzki ring. (Courtesy Marc Levine, MD.)

HIATAL HERNIA

A hiatal hernia involves herniation of elements of the abdominal cavity through the diaphragmatic hiatus. A sliding, or type I, hernia, in which the gastroesophageal junction is displaced above the diaphragmatic hiatus, is the most common type. Type I hiatal hernias typically are not associated with symptoms or are associated with heartburn or acid regurgitation. Treatment is the same as for GERD.

In a type II, or true, paraesophageal hernia, which is uncommon, the gastroesophageal junction is in its normal location, but the fundus and parts of the greater curvature of the stomach herniate into the mediastinum alongside the esophagus. With type III or mixed paraesophageal hernia, the gastroesophageal junction and a large part of the stomach herniate into the mediastinum. Both types of paraesophageal hernias present with symptoms of postprandial distress, such as epigastric pain, chest pain, substernal fullness, shortness of breath, nausea, or vomiting. Iron deficiency anemia may be seen with large hiatal hernias in which at least one third of the stomach is in the chest; linear gastric erosions at the top of gastric folds at the level of the diaphragm have been implicated as a cause of chronic blood loss. Asymptomatic paraesophageal hernias do not require surgery. Symptomatic paraesophageal hernias warrant surgical therapy because of the risk for strangulation, bleeding, perforation, or obstruction.

FIGURE 124-12. Barium radiograph of an esophageal web. (Courtesy of Marc Levine, MD.)

THE ESOPHAGUS IN SYSTEMIC DISEASES

SCLERODERMA

Up to 90% of patients with scleroderma (Chapter 246) have esophageal involvement, thereby making it the most common gastrointestinal abnormality in the disease.[23] The classic manometric and radiologic findings are aperistalsis of the distal two thirds of the esophagus and hypotensive or patulous lower esophageal sphincter on manometry or radiography, respectively. Only one third of scleroderma patients have these classic findings. These findings result initially because of neuropathy and later because of the myopathy. The main clinical manifestation is severe gastroesophageal reflux. Delayed gastric emptying may also occur. Marked esophageal stasis may also lead to *Candida* esophagitis. A patulous (on radiography) or hypotensive (on manometry) lower esophageal sphincter strongly supports the diagnosis. Proton pump inhibitor therapy (see Table 124-1) is the cornerstone of treatment. Lifestyle changes, including small frequent meals and avoiding nighttime meals, may reduce the gastric symptoms. Antireflux surgery can exacerbate dysphagia by creating a functional high-pressure zone in the distal esophagus and is thus usually contraindicated. Unfortunately, many patients suffer from chronic GERD and are at risk for developing Barrett esophagus and recurrent strictures.

AMYLOIDOSIS

Amyloidosis (Chapter 174) may lead to smooth muscle and autonomic nervous system dysfunction that involves the esophagus in a pattern similar to scleroderma. Patients will have both dysphagia and severe reflux because of esophageal aperistalsis and a hypotensive lower esophageal sphincter. Dysphagia may result not only from the motility changes but also from diffuse esophageal rigidity and loss of compliance owing to amyloid infiltration of the esophageal wall. Rarely, an achalasia-like pattern may develop. No treatment improves the esophageal manifestations of amyloidosis, other than treatment for the underlying disease and high-dose proton pump inhibitors given twice daily.

OTHER SYSTEMIC DISEASES

Dermatomyositis (Chapter 248) principally involves the striated muscle of the oropharynx and proximal esophagus, but sometimes the distal esophagus may lose normal peristaltic function. Symptoms can be oropharyngeal or esophageal depending on the site of greatest muscular involvement. Dysphagia may be an early presenting symptom of dermatomyositis, and the esophagus may be involved in 10 to 50% of patients. Treatment is directed at the generalized myositis because there are no specific treatments for the esophagus. Swallowing therapy may sometimes be helpful. Return of swallowing commonly lags behind recovery of other striated muscle symptoms.

Esophageal involvement in *systemic lupus erythematosus* (Chapter 245) is not as prominent as in scleroderma, dermatomyositis, or mixed connective tissue disease. Dysphagia occurs in fewer than 15% of patients and may be caused by decreased salivation from secondary Sjögren syndrome or reduced esophageal peristalsis. Other causes of esophageal symptoms in patients with systemic lupus erythematosus include GERD, esophageal ulcers, esophageal infection, and medication-induced esophagitis. *Behçet disease* (Chapter 249) causes esophageal ulcers in less than 15% of affected patients. Ulcers are typically located in the middle third of the esophagus and are often associated with ulcers in the stomach, ileum, or colon. Rare esophageal lesions include strictures, varices, and fistulas connecting with the trachea. These complications can be severe and debilitating.

Esophageal involvement in *Crohn disease* (Chapter 127) is uncommon but has been described in up to 1 to 2% of patients. Occasionally, isolated esophageal disease may occur. Ulceration is the most common manifestation, but strictures, fissures, esophagobronchial fistulas, mediastinal abscesses, and aphthoid lesions have been described. Patients typically complain of dysphagia and odynophagia. Treatment and prognosis are as for the underlying Crohn disease.

In the *Ehlers-Danlos syndrome* (Chapter 239), hiatal hernias are common, and structural esophageal defects such as giant epiphrenic diverticula, megaesophagus, and spontaneous esophageal rupture may also be seen.

SKIN DISORDERS THAT INVOLVE THE ESOPHAGUS

Lichen planus (Chapter 405) often involves the esophagus. Patients generally present in the fourth to seventh decade of life. Histologically, the lesions in up to 25 to 50% of patients show a characteristic lymphohistiocytic inflammatory infiltrate and apoptotic basal keratinocytes known as Civatte bodies. Lesions classically occur on the buccal mucosa and the tongue, but the disease may also involve other areas of the oral cavity and the esophagus, conjunctiva, nose, larynx, stomach, bladder, and anus. Most patients are asymptomatic or have only minor symptoms, but patients with severe esophageal lichen planus often develop strictures and may present with dysphagia, odynophagia, and weight loss. Strictures are typically proximal but may be variable in length and location, sometimes involving most of the esophageal body. Patients may present with esophageal lichen planus in the absence of extraesophageal disease. Endoscopic findings, which can be subtle and nonspecific, include peeling mucosa, hyperemic focal abnormalities, and submucosal plaque or papules. High-dose systemic steroids, starting with at least 40 mg prednisone and then tapering over 1 to 2 months, are often successful, but relapse is common when steroids are tapered. Topical steroids, tacrolimus, and methotrexate also have been tried. Dilation and intralesional steroids can alleviate the symptoms associated with strictures, but symptoms frequently recur in less than a year and necessitate repeat dilations. The esophageal lesions of lichen planus may have malignancy potential.

Pemphigus vulgaris (Chapter 406) patients who experience acute flares may have upper gastrointestinal symptoms (dysphagia, odynophagia, or retrosternal burning) in 80% of cases and biopsy-proven esophageal pemphigus lesions in nearly 50% of cases. Pemphigus vulgaris may rarely be isolated to the esophagus. Paraneoplastic pemphigus (Chapter 406), most commonly reported with lymphoreticular disease, also may involve the esophagus. Like lesions on the skin, esophageal lesions may be flaccid blisters or erosions, but they may also appear as red longitudinal lines along the entire esophagus. Like cutaneous and oral pemphigus, esophageal pemphigus is generally treated with corticosteroids.

In *mucous membrane pemphigoid* (cicatricial pemphigoid; Chapter 406), the esophagus is the most common site of gastrointestinal involvement, but esophageal disease occurs in less than 15% of patients. The esophageal disease can present as long as 10 years after disease onset and may be the only presentation of the disease. Patients complain of dysphagia and odynophagia. Imaging typically shows erosions, strictures, bullae, or webs. Treatment generally is as for the skin disease.

In *dystrophic epidermolysis bullosa* (Chapter 406), approximately 70 to 95% of patients develop esophageal stenosis or strictures. Strictures are especially common in children with recessive dystrophic epidermolysis bullosa, whereas fewer than 10% of patients with dominant dystrophic epidermolysis bullosa develop strictures by age 50 years.

ESOPHAGEAL INFECTIONS

HERPES SIMPLEX VIRUS

Herpes simplex virus (HSV; Chapter 345) esophagitis, which is usually caused by HSV-1, is a well-recognized disease in immunocompromised patients but may also occur in immunocompetent hosts. HSV typically presents as severe odynophagia. Endoscopy and radiology characteristically demonstrate multiple ulcers and friable mucosa, predominantly involving the distal esophagus. Mucosal biopsies demonstrate typical intranuclear inclusion bodies. Depending on the severity of the esophageal disease and the underlying health of the patient, treatment options may include intravenous acyclovir, 5 mg/kg every 8 hours for 7 days, or oral acyclovir, 400 mg five times daily for 7 days, combined with symptomatic treatment.

CANDIDIASIS

Esophageal candidiasis is common in patients with human immunodeficiency virus (HIV) infection or with impaired cellular immunity owing to hematologic malignancies, immunosuppressive therapy, or diabetes mellitus.[24] Esophageal candidiasis is also seen in immunocompetent patients who are taking corticosteroids and in individuals with marked esophageal stasis, such as patients with advanced achalasia or scleroderma. Esophageal candidiasis characteristically presents with symptoms of odynophagia, dysphagia, and chest pain. Endoscopy demonstrates scattered or coalescent yellow-white mucosal plaques (Fig. 124-13). Given the high prevalence of esophageal candidiasis in HIV patients, some recommend treating symptomatic HIV patients empirically and reserving endoscopy for refractory symptoms. Mild oropharyngeal candidiasis may be treated with topical clotrimazole (10 mg troche five times daily for 7 to 14 days) or nystatin (600,000 units four times daily for 7 to 10 days), whereas oral fluconazole (100 mg daily for 7 to 14 days) is needed for moderate to severe oropharyngeal and esophageal candidiasis.[25] Intravenous fluconazole and amphotericin B deoxycholate (Chapter 307) are appropriate options for severe esophageal candidiasis and toxemia or for patients who cannot tolerate oral therapy.

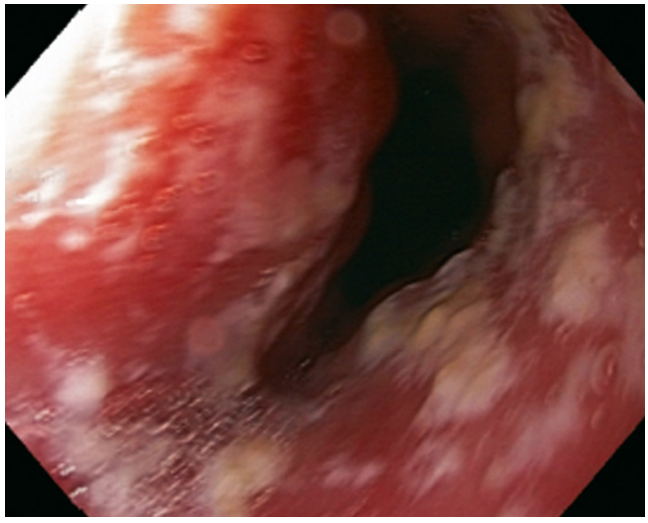

FIGURE 124-13. ***Candida*** **esophagitis.**

CYTOMEGALOVIRUS

Cytomegalovirus (CMV; Chapter 347) infection of the esophagus is almost exclusively found in immunocompromised patients. Patients infected with the HIV virus with low CD4 counts are most commonly affected, but CMV also occurs in transplant recipients on immunosuppressive therapy and in immunosuppressed patients with malignancy. Patients typically have severe odynophagia with evidence of radiographic or endoscopic esophageal ulcers. Treatment is usually with intravenous ganciclovir (5 mg/kg once or twice daily for 10 to 14 days) or foscarnet (90 mg/kg every 8 to 12 hours until healing occurs).

BACTERIAL ESOPHAGITIS

Bacterial infection of the esophagus is uncommon but can occur in immunosuppressed patients, typically those with neutropenia and malignancy. Patients present with chest pain or odynophagia, or both, and endoscopy reveals extensive erosions, usually in the distal esophagus. Biopsy and Gram stain reveal acute and chronic inflammation and bacteria, commonly gram-positive organisms, especially viridans-group streptococci, *Staphylococcus aureus, Staphylococcus epidermidis,* and *Bacillus* species. Treatment is with the appropriate antibiotics administered parenterally.

HUMAN PAPILLOMAVIRUS

Esophageal infections with human papillomavirus (HPV; Chapter 344) are typically asymptomatic. HPV lesions are most frequently found in the mid to distal esophagus as erythematous macules, white plaque, nodules, or exuberant frondlike lesions. The diagnosis is made by histologic demonstration of koilocytosis (an atypical nucleus surrounded by a ring), giant cells, or immunohistochemical stains. Treatment is usually not necessary, although large lesions may require endoscopic removal. Other treatments, such as interferon, bleomycin, and etoposide, have yielded varying results. HPV infection is a risk factor for esophageal squamous cell carcinoma (Chapter 178), but the value of endoscopic surveillance is not known.

MISCELLANEOUS ESOPHAGEAL CONDITIONS

Esophageal Emergencies

BOERHAAVE SYNDROME

Boerhaave syndrome, or spontaneous rupture of the esophagus, is a transmural full-thickness tear of the esophageal wall. A sudden rise in intraesophageal pressure during forceful vomiting is the cause in most cases. The tear is most commonly in the lower third of the esophagus, 2 to 3 cm proximal to the gastroesophageal junction.

CLINICAL MANIFESTATIONS AND DIAGNOSIS

The classic presentation is vomiting, lower thoracic pain, and subcutaneous emphysema. Other findings may include pleural effusions, especially left-sided, tachypnea, abdominal rigidity, fever, and hypotension. Because the condition is rare and classic antecedent vomiting is not always reported, rupture is often recognized only after the development of mediastinitis.

The chest radiograph may demonstrate mediastinal widening, a unilateral pleural effusion, hydropneumothorax, and pneumomediastinum. The esophagram, typically with a water-soluble agent, reveals extravasation, although false-negative results may be encountered. Computed tomography (CT) scanning with an oral contrast agent, which is perhaps the best diagnostic option, typically demonstrates air in the mediastinum.

MALLORY-WEISS TEAR

A Mallory-Weiss tear (see Fig. 124-2) is a mucosal tear, often at the gastroesophageal junction, usually caused by severe vomiting or retching. The syndrome is more common in alcoholic patients. In about 85% of patients, it is associated with acute upper gastrointestinal bleeding, which requires transfusion in about 70% of patients and urgent intervention in about 10% of cases. Mortality is about 5%, similar to the mortality in severe bleeding ulcers. Most tears heal spontaneously within about 48 hours.

IATROGENIC PERFORATION

Esophageal perforation may occur as a result of a variety of iatrogenic causes, including endoscopy, dilation, endosonography, or surgery, as well as with foreign body ingestion. Typical symptoms include chest pain with or without abdominal pain, subcutaneous emphysema, and fever. Diagnosis may be made immediately at the time of endoscopy or radiography. Chest radiographs may show pneumomediastinum, subcutaneous emphysema, hydrothorax, or hydropneumothorax. A Gastrografin swallow may show a leak, and chest CT may show mediastinal air. Acute perforations are life-threatening emergencies that warrant immediate closure before contamination of the mediastinum. For acute perforation caused by endoscopy, endoscopic clips or stents are an option. Conservative therapy also is an option for well-contained perforations with minimal mediastinal, pleural, or peritoneal contamination and no obvious signs of sepsis. Prognosis is generally good if the perforation is recognized and treated early, preferably within 12 to 24 hours.

TREATMENT AND PROGNOSIS

Successful therapy depends on early recognition and the underlying condition of the patient. The classic approach is operative repair in conjunction with broad-spectrum antibiotics and nutritional support, especially if the diagnosis is made within the first 24 hours. Aggressive conservative therapy with percutaneous drains, broad-spectrum parenteral antibiotics, and nutrition also has been successful. In selected individuals, endoscopic insertion of self-expanding covered metallic stents or over the scope clips, with or without pleural drainage as needed, is an option. The mortality rate can be as high as 100% without treatment.

FOREIGN BODIES

Impaction of food or foreign bodies is a common gastrointestinal emergency. Meat impaction is most commonly seen in adults, but other foreign objects that also may be ingested accidentally or by design include batteries, coins, and bones. Many patients have an underlying esophageal abnormality, such as Schatzki ring, stricture, eosinophilic esophagitis, tumor, or achalasia. The clinical presentation includes dysphagia, odynophagia, foreign body sensation, chest pain, excessive salivation, and difficulty handling secretions. Immediate endoscopic extraction or gentle advancing of the bolus with concomitant airway protection is recommended because prolonged impaction may result in penetration into the esophageal wall followed by perforation and mediastinitis.

ESOPHAGEAL VARICES

Esophageal varices are described in Chapter 139.

ESOPHAGEAL FISTULA

Tracheoesophageal fistulas may arise from a variety of different causes, including trauma, infectious esophagitis, necrosis after prolonged endotracheal intubation, esophageal cancer, and radiation therapy. Patients are often critically ill and may not tolerate surgery. Metallic stents are a treatment option.

Atrial-esophageal fistulas are a rare complication after radio frequency ablation (Chapter 54) for atrial fibrillation. The clinical presentation is nonspecific and includes features such as dysphagia, fever, leukocytosis, bacteremia, massive intestinal bleeding, and septic shock. Diagnosis requires a high index of suspicion and is aided by a chest CT scan. Surgery is required; the

prognosis is excellent with early recognition and treatment but can be dire if treatment is delayed.

CONGENITAL ABNORMALITIES

ESOPHAGEAL ATRESIA AND TRACHEOESOPHAGEAL FISTULA

Children with congenital esophageal anomalies commonly survive into adulthood after successful surgery. As adults, these patients typically have gastroesophageal reflux that warrants proton pump inhibitor therapy. Strictures at prior surgical anastomoses are common, and patients may require periodic endoscopic dilation. Eosinophilic esophagitis may also occur.

HETEROTOPIC GASTRIC MUCOSA (INLET PATCH)

Inlet patches, which are areas of gastric columnar epithelium, are present in up to 4.5% of adults and are usually found incidentally at the time of routine endoscopy. Typically, a red columnar patch varying in size from a few millimeters to a few centimeters is seen just below the cricopharyngeus. Inlet patches can be associated with hoarseness, sore throat, and globus sensation. Strictures, ulcers, and rare malignant transformation also have been described. Treatment options include proton pump inhibitors (see Table 124-1) and endoscopic ablation.

OTHER CONGENITAL ESOPHAGEAL DISORDERS

Duplication cysts, which may be located anywhere in the esophagus, may be in continuity with or separate from the esophageal lumen. Symptoms, which may present initially in adulthood, include dysphagia owing to luminal compression, chest pain, and regurgitation. Treatment is surgical.

Dysphagia lusoria is caused by an aberrant right subclavian artery that originates from the right aortic arch and causes partial compression of the esophagus as it crosses over to the left side. Patients may complain of dysphagia. This condition is most commonly detected incidentally during barium radiography, where it is visualized as a crossing diagonal impression at the junction of the proximal and middle thirds of the esophagus. Surgery is rarely indicated because of the complexity of the operation and the difficulty in establishing a clear relationship between the radiographic findings and symptoms.

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For the General References and other additional features, please visit Elsevier eBooks+ at https://ebooks.health.elsevier.com.

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125

ACID PEPTIC DISEASE

ERNST J. KUIPERS

Acid peptic diseases can involve the esophagus (Chapter 124), the stomach, and the duodenum. Dyspeptic symptoms also can occur in patients who have no endoscopic abnormalities, in whom it is termed *nonulcer dyspepsia* (Chapter 123).

DEFINITIONS

Gastric and duodenal ulcers usually occur in an area of inflamed mucosa. This inflammation, termed *gastritis, duodenitis*, or *bulbitis*, can be recognized by endoscopic signs of edema and erythema of the mucosa, but microscopic evaluation of endoscopic biopsy specimens is required for a definitive diagnosis of mucosal inflammation.

Gastritis is categorized by endoscopic and histologic criteria, with granulocytes predominating in active gastritis and mononuclear cells in chronic gastritis. Gastritis is classified further by the segment of the involved stomach: antral-predominant gastritis, corpus-predominant gastritis, or pangastritis. Finally, the absence or presence of premalignant stages of damage to the mucosa as a result of long-standing inflammation defines the categories of nonatrophic and atrophic gastritis, respectively. High-definition endoscopy, when combined with magnification and image enhancement, allows adequate visualization of features of gastritis, atrophy, and intestinal metaplasia. Gastritis features include antral nodularity, absence of connecting venules, and enlarged gastric folds. Sometimes, the mucosa has a typical miniature cobblestone appearance, termed *nodular gastritis* (a finding particularly in children colonized by *Helicobacter pylori*), or grossly enlarged folds without evidence of cancer, termed *hypertrophic gastritis*. Disappearance of gastric folds and enhanced mucosal vasculature are findings of *atrophic gastritis*. Atrophy may be accompanied by *intestinal metaplasia*, which appears as gray-white patches (white-light endoscopy) or light-blue lines ("light-blue crests") on the mucosal surface (narrow-band imaging).

A *peptic ulcer* is a mucosal defect at least 0.5 cm in diameter that penetrates the muscularis mucosae. Smaller mucosal defects are called *erosions* (Fig.125-1). Gastric ulcers are subdivided into proximal ulcers, located in the body of the stomach, and distal ulcers, located in the antrum and angulus of the stomach. Gastric ulcers are located mainly along the lesser curvature, in particular at the transitional zone of corpus- to antral-type mucosa. This transitional zone is often in the area of the angulus but may shift proximally. Duodenal ulcers usually are located on the anterior or posterior wall of the duodenal bulb (Fig. 125-2) or occasionally at both sites ("kissing" ulcers). Lesions distal

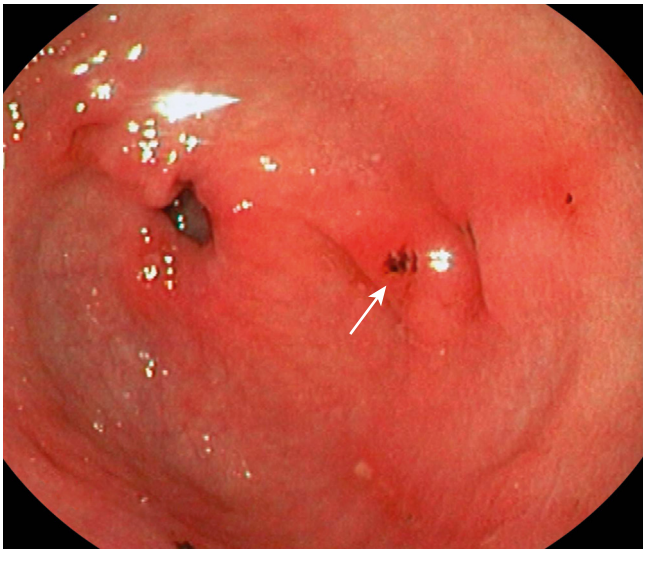

FIGURE 125-1. Endoscopic view of uncomplicated erosive gastritis. The erosion appears as a small, superficial mucosal break with a black base (*arrow*).

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prognosis is excellent with early recognition and treatment but can be dire if treatment is delayed.

CONGENITAL ABNORMALITIES

ESOPHAGEAL ATRESIA AND TRACHEOESOPHAGEAL FISTULA

Children with congenital esophageal anomalies commonly survive into adulthood after successful surgery. As adults, these patients typically have gastroesophageal reflux that warrants proton pump inhibitor therapy. Strictures at prior surgical anastomoses are common, and patients may require periodic endoscopic dilation. Eosinophilic esophagitis may also occur.

HETEROTOPIC GASTRIC MUCOSA (INLET PATCH)

Inlet patches, which are areas of gastric columnar epithelium, are present in up to 4.5% of adults and are usually found incidentally at the time of routine endoscopy. Typically, a red columnar patch varying in size from a few millimeters to a few centimeters is seen just below the cricopharyngeus. Inlet patches can be associated with hoarseness, sore throat, and globus sensation. Strictures, ulcers, and rare malignant transformation also have been described. Treatment options include proton pump inhibitors (see Table 124-1) and endoscopic ablation.

OTHER CONGENITAL ESOPHAGEAL DISORDERS

Duplication cysts, which may be located anywhere in the esophagus, may be in continuity with or separate from the esophageal lumen. Symptoms, which may present initially in adulthood, include dysphagia owing to luminal compression, chest pain, and regurgitation. Treatment is surgical.

Dysphagia lusoria is caused by an aberrant right subclavian artery that originates from the right aortic arch and causes partial compression of the esophagus as it crosses over to the left side. Patients may complain of dysphagia. This condition is most commonly detected incidentally during barium radiography, where it is visualized as a crossing diagonal impression at the junction of the proximal and middle thirds of the esophagus. Surgery is rarely indicated because of the complexity of the operation and the difficulty in establishing a clear relationship between the radiographic findings and symptoms.

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For the General References and other additional features, please visit Elsevier eBooks+ at https://ebooks.health.elsevier.com.

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125

ACID PEPTIC DISEASE

ERNST J. KUIPERS

Acid peptic diseases can involve the esophagus (Chapter 124), the stomach, and the duodenum. Dyspeptic symptoms also can occur in patients who have no endoscopic abnormalities, in whom it is termed *nonulcer dyspepsia* (Chapter 123).

DEFINITIONS

Gastric and duodenal ulcers usually occur in an area of inflamed mucosa. This inflammation, termed *gastritis, duodenitis*, or *bulbitis*, can be recognized by endoscopic signs of edema and erythema of the mucosa, but microscopic evaluation of endoscopic biopsy specimens is required for a definitive diagnosis of mucosal inflammation.

Gastritis is categorized by endoscopic and histologic criteria, with granulocytes predominating in active gastritis and mononuclear cells in chronic gastritis. Gastritis is classified further by the segment of the involved stomach: antral-predominant gastritis, corpus-predominant gastritis, or pangastritis. Finally, the absence or presence of premalignant stages of damage to the mucosa as a result of long-standing inflammation defines the categories of nonatrophic and atrophic gastritis, respectively. High-definition endoscopy, when combined with magnification and image enhancement, allows adequate visualization of features of gastritis, atrophy, and intestinal metaplasia. Gastritis features include antral nodularity, absence of connecting venules, and enlarged gastric folds. Sometimes, the mucosa has a typical miniature cobblestone appearance, termed *nodular gastritis* (a finding particularly in children colonized by *Helicobacter pylori*), or grossly enlarged folds without evidence of cancer, termed *hypertrophic gastritis*. Disappearance of gastric folds and enhanced mucosal vasculature are findings of *atrophic gastritis*. Atrophy may be accompanied by *intestinal metaplasia*, which appears as gray-white patches (white-light endoscopy) or light-blue lines ("light-blue crests") on the mucosal surface (narrow-band imaging).

A *peptic ulcer* is a mucosal defect at least 0.5 cm in diameter that penetrates the muscularis mucosae. Smaller mucosal defects are called *erosions* (Fig.125-1). Gastric ulcers are subdivided into proximal ulcers, located in the body of the stomach, and distal ulcers, located in the antrum and angulus of the stomach. Gastric ulcers are located mainly along the lesser curvature, in particular at the transitional zone of corpus- to antral-type mucosa. This transitional zone is often in the area of the angulus but may shift proximally. Duodenal ulcers usually are located on the anterior or posterior wall of the duodenal bulb (Fig. 125-2) or occasionally at both sites ("kissing" ulcers). Lesions distal

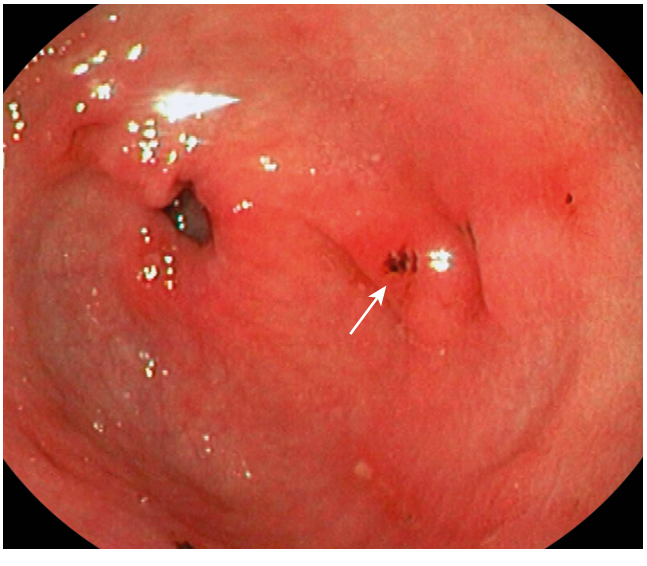

FIGURE 125-1. Endoscopic view of uncomplicated erosive gastritis. The erosion appears as a small, superficial mucosal break with a black base (*arrow*).

ABSTRACT

Gastroduodenal acid peptic diseases, in particular, gastritis and peptic ulcer, are predominantly caused by *Helicobacter pylori* infection and by use of aspirin and nonsteroidal anti-inflammatory drugs, but their pathobiology includes a wide range of other conditions. Patients with suspected acid peptic disease are often first treated empirically with acid suppression. Patients with persistent or recurrent symptoms, with new-onset symptoms at an older age, or with alarm symptoms should have *H. pylori* testing and upper gastrointestinal endoscopy to confirm the anatomic abnormality and its cause, as well as to exclude other potential causes of symptoms. Treatment should be targeted to heal mucosal breaks, address the underlying cause, and prevent recurrence. Peptic ulcer disease can be complicated by bleeding, perforation, and stenosis, each of which requires specific assessment and treatment by endoscopy, interventional radiology, or surgery.

KEYWORDS

gastritis
peptic ulcer
Helicobacter pylori
eradication treatment
NSAID
peptic ulcer bleeding

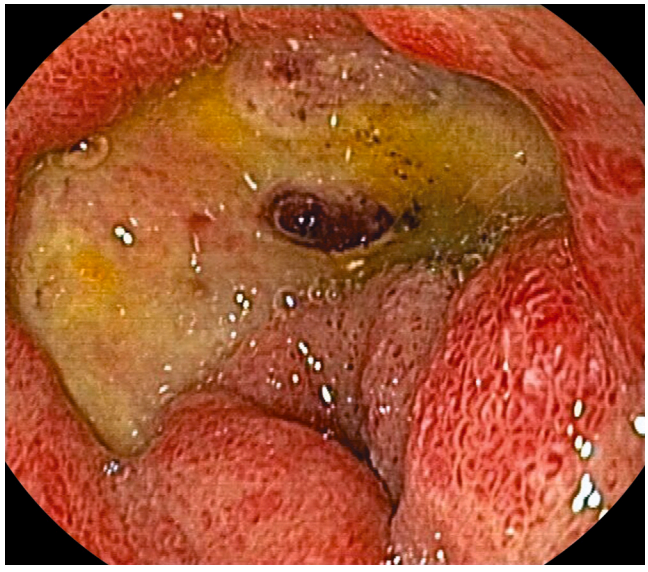

FIGURE 125-2. Endoscopic view of an ulcer at the anterior wall of the duodenal bulb. The ulcer has a clean base, with a visible vessel appearing as a dark red protruding spot close to the lower ulcer rim. The surrounding mucosa is inflamed and swollen.

to the duodenal bulb are termed *postbulbar ulcers*. Patients who previously underwent a distal gastric resection (Billroth I or II procedure) or a gastric bypass (Chapter 201) can develop ulceration at the anastomosis (*anastomotic* or *marginal ulcer*). However, ulcers occurring after Billroth II resection are located predominantly in the jejunal mucosa at the junction between the afferent and efferent loops. Other peptic ulcers can occur at sites of metaplastic or heterotopic gastric mucosa, for example, in Meckel diverticulum, the rectum, or Barrett esophagus. Patients with a large hiatal hernia can develop gastric ulceration, known as *Cameron ulcers*, at the herniation. *Dieulafoy ulcers*, which are small mucosal defects over an intramural arteriole, can lead to severe bleeding. Although these lesions can occur throughout the gastrointestinal tract, two thirds occur in the stomach.

EPIDEMIOLOGY

The worldwide prevalence of gastritis reflects the prevalence of *H. pylori*. Colonization with this bacterium is virtually always associated with chronic active gastritis, which persists as long as an individual remains colonized and only slowly disappears 6 to 24 months after bacterial eradication. An estimated 4.4 billion people worldwide are colonized with *H. pylori*.[1] Colonization usually occurs in the first decade of life and then remains lifelong. In developing countries, high colonization rates result in a high prevalence of *H. pylori* gastritis (often ≥75%) in all age groups, including children. In Western countries, the colonization pressure in children has decreased markedly in recent decades, thereby leading to a birth-cohort phenomenon for the prevalence of *H. pylori* gastritis—currently less than 20% in young adults but 40 to 60% in elderly persons. Some recent studies suggest that this decrease in *H. pylori* prevalence in children may be slowed by factors such as the increasing use of daycare facilities. Nevertheless, the decline of *H. pylori* in developed country populations has been inexorable.

Although peptic ulcer disease is strongly related to *H. pylori* gastritis and duodenitis, the epidemiology of ulcer disease has shown secular variation even when *H. pylori* was ubiquitous. The incidence of peptic ulcer disease rose steeply in Western countries in the late 19th and early 20th centuries and has decreased over the past 40 years; nevertheless, peptic ulceration remains a common disorder. The decline in incidence, associated with a decrease in hospital admissions and surgery for ulcer disease, is believed mostly to reflect the decreasing prevalence of gastric colonization with *H. pylori*. It also results from the widespread application of eradication therapy, which strongly reduced recurrent ulcers in *H. pylori*–positive patients, and the widespread use of acid-suppressive medications. Nevertheless, hospital admissions for complications of ulcers and mortality from ulcer disease have shown a far less marked decline in both the United States and other countries because the reduction in *H. pylori*–associated ulcers in younger persons has been partly counterbalanced by an increase in ulcers related to nonsteroidal anti-inflammatory drugs (NSAIDs) in older persons.

In Western countries, duodenal ulcers occur more frequently than gastric ulcers. The predominant age at which duodenal ulcers occur is between 20 and 50 years, whereas gastric ulcers most commonly occur in patients older than 40 years. The incidence of gastroduodenal ulcer disease is approximately 1 to 2 per 1000 inhabitants per year. Although the prevalence of *H. pylori* colonization is nearly identical in males and females, two thirds of patients with ulcers are male. More than 50% of patients have a recurrent ulcer within 12 months of healing in the absence of treatment. Maintenance acid-suppressive therapy reduces this recurrence rate, but only therapeutic measures that remove the underlying cause of the ulcer can prevent most ulcer recurrences.

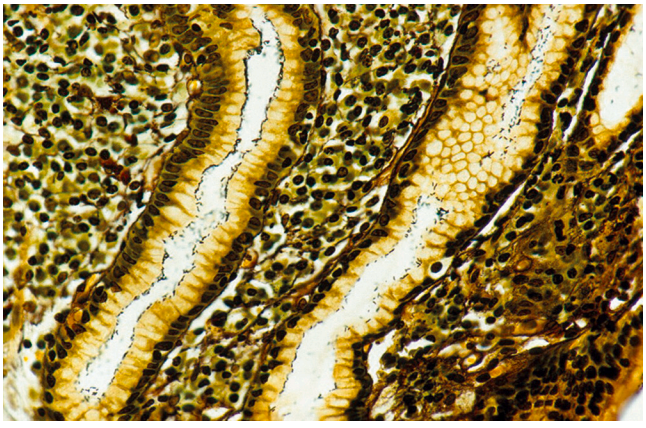

FIGURE 125-3. Gastric mucosa colonized with *Helicobacter pylori* appearing as curved bacilli on the mucosal surface.

PATHOBIOLOGY

Helicobacter pylori

Most peptic ulcers are associated with colonization with *H. pylori* (Fig. 125-3).[2] However, most persons who are *H. pylori* positive do not have any specific complaints, nor do they develop ulcer disease. The estimated risk for the development of ulcer disease during persistent *H. pylori* colonization is 5 to 15%—that is, three-fold to eight-fold higher than the risk in patients who are *H. pylori* negative. The risk for the development of an ulcer in the presence of *H. pylori* is determined by a combination of host- and bacteria-related factors. Host factors include immune response, smoking, and stress. Genome-wide association studies have identified a relationship between polymorphisms in the toll-like receptor gene and the interleukin-1β gene with the prevalence of *H. pylori*. This relationship may in part explain the variation in risk for *H. pylori* colonization and thus the risk for *H. pylori*–associated disease, including peptic ulcer. Bacterial factors that enhance mucosal inflammation and increase the risk for ulcer include a high production of the *VacA* product, which reflects the presence of the s1m1 genotype; a high level of cytokine induction, owing to the presence of genes in the *cag* pathogenicity island; and enhanced adherence to the gastric epithelium as a result of bacterial expression of *babA* and *oipA*.

Nonsteroidal Anti-inflammatory Drugs and Aspirin

The other common cause of gastroduodenal ulcer disease is the use of NSAIDs. At least 2 to 4% of the population in many countries use acetylsalicylic acid, acetic acid derivatives (diclofenac, indomethacin, sulindac), or propionic acid derivatives (ibuprofen, ketoprofen, naproxen) on a daily basis. The risk for ulcer disease is dose and duration dependent. Within 14 days after the start of such treatment, about 5% of patients develop erosions or ulcers. In patients who continue therapy for 4 weeks or longer, this proportion increases to 10%, but many are clinically silent. The concomitant presence of *H. pylori* infection increases the incidence of NSAID-related ulcers.

The risk for an ulcer during NSAID use is higher in patients who are older than 60 years; patients with a previous ulcer; patients who use corticosteroids, selective serotonin reuptake inhibitors, or aldosterone antagonists; and patients with major comorbid diseases. In patients who use anticoagulants, such as warfarin and new oral anticoagulants (thrombin and factor Xa inhibitors), or who have severe comorbid disease, an NSAID-induced ulcer is more likely to lead to life-threatening gastroduodenal hemorrhage.

On the basis of their activities, NSAIDs are divided into cyclooxygenase 1 (COX1) and COX2 inhibitors (Chapter 26). The COX1 enzyme is involved in the production of prostaglandins, which play a role in normal cell regulation. The COX2 enzyme, which is also involved in the production of prostaglandins, is induced by inflammatory responses. Most NSAIDs have a nonselective

COX inhibitory effect; selective COX2 inhibitors are associated with fewer gastroduodenal ulcers, but their use has been limited because of their adverse coronary effects (Chapter 26). The strong association between NSAIDs and ulcer disease and the risk for recurrence of ulcers with their continued use require that patients with ulcers be thoroughly assessed for any use of NSAIDs.

Helicobacter pylori–Negative, Non-NSAID Ulcer Disease

In most series, *H. pylori* and NSAID use account for 80 to 95% of cases of ulcer disease. The remaining cases are often referred to as *idiopathic* or *H. pylori–negative, non-NSAID* acid peptic disease. The proportion of ulcer disease that is idiopathic is increasing throughout the world as the prevalence of *H. pylori* decreases. Further, it is likely that some ulcers in *H. pylori*–positive patients were not caused by *H. pylori*. Consistent with this notion is the fact that some *H. pylori*–positive patients develop recurrent ulcers after successful bacterial eradication, so presumably their ulcer disease was idiopathic. It is not known whether the increase in idiopathic ulcer disease is simply proportional to the decrease in *H. pylori*–associated ulcers or whether it reflects a true increase in the incidence of idiopathic ulcers.

In patients with idiopathic ulcer disease, specific clues to the underlying cause are often provided by the medical history, including comorbidity and drug use; the endoscopic appearance of the ulcer; and the histologic features of the ulcer's margins and surroundings. In most cases, these initial data can be used to direct further diagnostic studies (Table 125-1).

Malignant Ulcer Disease

Gastroduodenal ulcers can result from underlying malignancies. In the stomach, such tumors are related to gastric adenocarcinoma and, rarely, to mucosa-associated lymphoid tissue (MALT) lymphomas (Chapter 178). Malignant ulcers in the duodenum may result from primary duodenal carcinomas or from penetrating pancreatic cancers. Duodenal cancers have an association with polyposis syndromes, especially familial adenomatous polyposis and, to a much lesser extent, *MUTYH*-associated polyposis and Peutz-Jeghers syndrome (Chapter 179). In both the stomach and the duodenum, ulcer disease also may be caused by metastatic tumors, including cancers of the breast, colon, thyroid, or kidney, or by melanoma, disseminated lymphoma, or Kaposi sarcoma. Malignant ulcers are characteristically irregular in shape with heaped borders, but they also may be flat or depressed. Current high-resolution and magnification endoscopes allow visualization of the altered mucosal structure surrounding an ulcer, including changes in the microvascular pattern. Primary gastric adenocarcinomas often occur in mucosal areas with atrophic and intestinal metaplastic changes. For a definite diagnosis of malignancy, multiple biopsy specimens are needed, usually from the ulcer margins.

Systemic Inflammatory Disorders

A few gastroduodenal ulcers are caused by systemic inflammatory diseases, in particular, Crohn disease (Chapter 127). Patients with Crohn disease affecting

TABLE 125-1 DIFFERENTIAL DIAGNOSIS OF PEPTIC ULCER DISEASE

ORIGIN	CONDITION	FREQUENCY*	DIAGNOSTIC TEST	FINDINGS
Microbes	*Helicobacter pylori*	Very common	*H. pylori* tests	Bacteria, enzymes, antigens, antibodies
			Histology	Gastritis
	Helicobacter heilmannii	Rare	Histology	Spiral bacteria, gastritis
	Treponema pallidum	Very rare	Serology	Antibodies
	Mycobacterial infection	Very rare	Histology, immune response testing, chest radiograph	Acid-fast bacteria, granuloma, immune response, pulmonary infiltrate
	Cytomegalovirus, herpes simplex virus type 1, Epstein-Barr virus	Rare	Histology, serology	Virus inclusions, antibodies
Drug use	NSAIDs, aspirin	Very common	History, urine test	NSAID use
	Bisphosphonates	Rare	History	Bisphosphonate use
	Corticosteroids	Rare	History	Corticosteroid use, comorbidity
	Amphetamines, cocaine	Rare	History, drug testing	Drug use
	Anticoagulants, coagulopathy	Rare	Endoscopy	Ulcer after intramural bleed
	Immune checkpoint inhibitors	Rare	Endoscopy	Ulceration
	Calcium polystyrene sulfonate	Rare	Endoscopy	Ulceration
Malignancy	Gastric cancer	Common	Histology	Malignancy
	Duodenal cancer	Rare	Histology, CT	Malignancy
	Pancreatic cancer	Common	Histology, CT	Malignancy
	Mucosa-associated lymphoid tissue lymphoma	Rare	Histology	Malignancy
	Metastatic cancer	Rare	Histology	Malignancy
	Gastric sarcoma	Very rare	Histology	Malignancy
Gastritis syndromes	Eosinophilic gastritis	Rare	Histology	Eosinophilic infiltration
	Lymphocytic gastritis	Rare	Histology, celiac disease screening	Lymphocytic infiltration, villous atrophy
Hyperacidity syndromes	Zollinger-Ellison syndrome	Rare	Serum gastrin, secretin test	Extreme hypergastrinemia, positive secretin test
	Antral G-cell hyperfunction	Very rare	Serum gastrin, secretin test	Moderate hypergastrinemia, negative secretin test
	Retained gastric antrum	Very rare	Medical history, gastrin	Billroth II resection, hypergastrinemia
	Systemic mastocytosis	Very rare	Histology of affected sites	Mast cell infiltration
	Chronic myelogenous leukemia	Very rare	Leukemia evaluation	Leukemia
Ischemia	Mesenteric vascular occlusion	Common	Angiography	Vascular disease
	Polycythemia vera	Rare	Blood counts	Polycythemia
Specific ulcer types	Cameron ulcer	Common	Endoscopy	Ulcer in large hiatal hernia
	Marginal ulcer	Common	Endoscopy	Ulcer at anastomosis
	Dieulafoy ulcer	Common	Endoscopy	Singular bleeding focus with minimal mucosal disruption
Systemic inflammation	Crohn disease	Common	Histology, ileocolonoscopy	Inflammation, granulomas
	Vasculitides	Rare	Histology, systemic evaluation	Vasculitis, signs of systemic disease
	Gastric amyloidosis	Very rare	Histology	Amyloid deposition
Other conditions	Stress ulcer	Fairly common in patients in intensive care units	Endoscopy	—
	Radiation therapy, chemotherapy	Rare	Endoscopy, history	—

*Frequency as a cause of gastroduodenal ulcer disease.
CT = computed tomography; NSAID = nonsteroidal anti-inflammatory drug.

the proximal gastrointestinal tract often have multiple ulcers characterized by irregular longitudinal shapes. Ulcers in the duodenum occur on top of Kerckring folds. Patients with gastroduodenal ulcers from Crohn disease do not invariably have evidence of disease elsewhere in the digestive tract, nor do blood tests always suggest an active inflammatory bowel disorder. The demonstration of ulcerative inflammation elsewhere in the digestive tract, in particular in the terminal ileum and colon, strongly supports the diagnosis of Crohn disease, as do noncaseating granulomas on biopsy specimens. However, the absence of granulomas does not exclude Crohn disease, and these lesions are not specific for Crohn disease; they also are associated with *H. pylori* gastritis and other conditions, particularly sarcoidosis (Chapter 83). Sarcoidosis can also lead to gastroduodenal ulcer disease.

Other inflammatory disorders that can cause gastritis or gastroduodenal ulcers include various forms of vasculitis affecting the mesenteric system, in particular, Behçet disease (Chapter 249), Henoch-Schönlein purpura (Chapter 249), Takayasu arteritis (Chapters 63 and 249), polyarteritis nodosa (Chapter 249), systemic lupus erythematosus (Chapter 245), Churg-Strauss syndrome (Chapter 249), and granulomatosis with polyangiitis (Chapter 249). Lymphocytic gastroduodenitis, which is strongly associated with celiac disease (Chapter 126), may lead to duodenal ulceration and subsequent stenotic web formation. Ulcer disease also may occur in patients with polycythemia vera (Chapter 152), possibly in relation to reduced mucosal blood flow. Vasculitis underlying ulcer disease should be considered in patients with chronic or recurrent ulceration in whom other causes have been excluded. Lymphocytic phlebitis, which is a rare vasculitic inflammatory disorder that affects the mesenteric veins, may cause gastric ulcers. Systemic amyloidosis (Chapter 174) affecting the stomach wall may lead to gastric ulcers. Rare cases of duodenal ulceration have been described in the presence of annular pancreas or congenital bands obstructing the descending duodenum.

Hypergastrinemic Syndromes

Peptic ulcers can result from chronic gastric hyperacidity related to hypergastrinemia. The most important hypergastrinemic disorder is Zollinger-Ellison syndrome (Chapter 213), a condition of marked hyperacidity leading to severe peptic ulcer disease caused by a gastrin-producing endocrine tumor. These patients usually have multiple bulbar and postbulbar duodenal ulcers that are resistant to conventional acid-suppressive therapy. The diagnosis can be confirmed by the presence of a high fasting serum gastrin level (often, but not always, ≥10-fold increased and >1000 pg/mL). Similar gastrin levels are sometimes seen in patients treated for chronic ulcer disease with high-dose proton pump inhibitors. For clarification, secretin testing can be performed: in patients with Zollinger-Ellison syndrome, the injection of secretin (1 U/kg) increases serum gastrin levels by more than 50%, or 120 pg/mL or greater, in persons with fasting gastrin levels less than 10-fold above normal. Imaging techniques, such as computed tomography (CT), magnetic resonance imaging, isotope scanning, endoscopic ultrasonography, videocapsule endoscopy, and balloon-assisted enteroscopy, may be used to detect the primary tumor, which is often located in either the pancreas or the proximal small bowel. In some patients, Zollinger-Ellison syndrome occurs as part of the multiple endocrine neoplasia syndrome (Chapter 212), particularly in association with hyperparathyroidism. Other hypergastrinemic hyperacidity syndromes are retained gastric antrum syndrome (see later) and antral G-cell hyperfunction. In the latter, fasting serum gastrin levels are only modestly increased and do not rise after the injection of secretin, but they respond in an exaggerated way to meals, thereby leading to hyperacidity. When the condition occurs in an *H. pylori*–positive patient, bacterial eradication therapy may be curative. However, some patients with G-cell hyperfunction are *H. pylori* negative.

Ischemia

Stenosis or occlusion of the celiac trunk or the superior mesenteric artery (Chapter 129) also can lead to ulceration in the mucosa of the proximal digestive tract (Fig. 125-4). These ulcers typically occur in elderly patients who have known severe atherosclerosis or risk factors for it, but they can also occur in younger subjects with mesenteric obstruction due to other causes, as well as in patients with marked chronic heart failure. Ischemic ulcers tend to heal slowly and to recur. Pallor of the mucosa, consistent with decreased mucosal blood flow, may be noted at endoscopy. Upper mesenteric ischemia is often associated with upper abdominal pain, which can be elicited by a meal or by physical activity. These symptoms may cause patients to decrease their food intake, leading to weight loss before their clinical presentation. The prevalence of upper mesenteric ischemia with secondary ulcer disease is unknown, in part owing to its variable presentation, often with a history of gradual symptoms; the lack of standardized and reliable diagnostic tests; and clinicians' unfamiliarity with the condition.[3] Diagnostic evaluation includes a duplex ultrasound scan for vascular flow and conventional or CT angiography of the affected arteries. Gastroduodenal mucosal perfusion can be functionally measured by means of tonometry and by directly measuring mucosal oxygen saturation during endoscopy; however, these tests are not widely available.

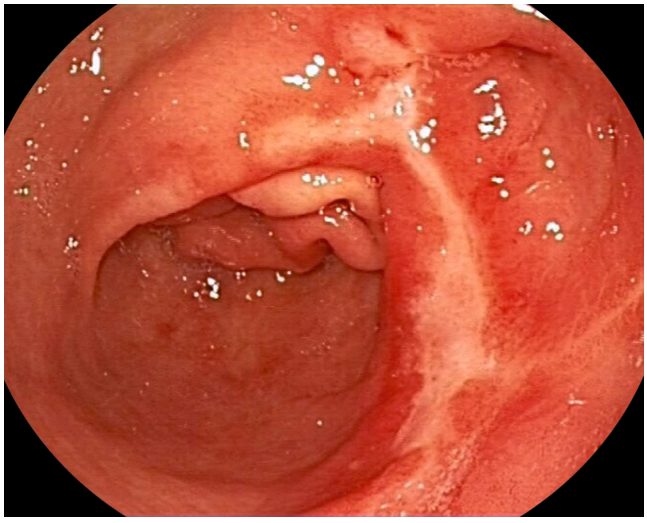

FIGURE 125-4. Endoscopic view of an irregular gastric ulcer at the posterior wall and smaller curvature in a patient with chronic mesenteric ischemia due to subtotal stenosis of the celiac trunk.

Stress Ulcers

Patients with severe medical conditions, such as major trauma, sepsis, extensive burns, head injury, or multiorgan failure, can develop stress ulcers in the stomach or duodenum. Major risk factors for stress ulceration in severely ill patients include mechanical ventilation, coagulopathy, and hypotension, but factors such as hepatic and renal failure and the use of ulcerogenic medications may contribute. Stress ulcers occur independently of *H. pylori* colonization. Ulcers associated with head injury are known as Cushing ulcers, and ulcers associated with extensive burns are known as Curling ulcers. Stress ulcers were once common in patients in intensive care units, but improvements in overall management, including respiratory and hemodynamic care, acid inhibition, and emphasis on adequate feeding, have reduced the incidence of these ulcers, which currently affect 1 to 2% of these patients. Stress ulcers may be asymptomatic, but they can also cause complications, especially bleeding.

Other Factors

Cameron Ulcer

Patients with large hiatal hernias (Chapter 124) may present with proximal gastric ulcers, termed *Cameron ulcers*, at the level of the hiatus, where the stomach is compressed. These ulcers are usually asymptomatic but may cause occult or overt bleeding. During upper gastrointestinal endoscopy, patients with large hiatal hernias and iron deficiency anemia should be carefully examined in normal and retroverted positions for the presence of Cameron ulcers.

Anastomotic or Marginal Ulceration

Patients who have undergone partial gastrectomy sometimes develop recurrent ulcers, often located at the anastomosis or within the jejunum immediately opposite the anastomosis. Ischemia and chronic inflammation, in particular resulting from biliary reflux, may cause such ulcers. If biopsies exclude cancer, treatment includes acid suppression and *H. pylori* eradication, if needed. Anastomotic ulcers after bariatric gastric surgery appear to be related to local ischemia. They have no clear correlation with *H. pylori*, and preoperative *H. pylori* eradication does not appear to reduce the incidence of such ulcers. However, proton pump inhibitor therapy may reduce their incidence. Peptic ulcer disease can also be associated with the retained gastric antrum syndrome when the antrum is not completely excised from the detached duodenum during partial gastrectomy surgery. Because it then lacks exposure to acid and therefore is not physiologically downregulated, it continues to secrete gastrin despite normal or even high acid levels. Marginal ulcers can also occur after bariatric Roux-en-Y gastric bypass surgery.

Other Microbial Organisms

Colonization with *Helicobacter heilmannii* (formerly known as *Gastrospirillum hominis*), which is probably a zoonotic organism, is associated with mild gastritis and sometimes with transient ulcer disease. Ulcer disease also may be infectious, resulting from secondary syphilis (Chapter 295), mycobacterial infection (Chapter 299), infection with herpes simplex virus type 1 (Chapter 371), varicella-zoster virus (Chapter 346), cytomegalovirus infection (Chapter 347), or Epstein-Barr virus (Chapter 348).

Alcohol

Short-term heavy alcohol use or long-term moderate to heavy alcohol use can lead to signs of acute and chronic gastritis. No evidence indicates that this type of gastritis is associated with a significant risk for peptic ulceration, although alcohol use increases the risk for bleeding in patients with peptic ulcer disease.

Hyperhistaminic Syndromes

Similar to the hypergastrinemic syndromes, persistent elevation of histamine can lead to hyperacidity as a result of the chronic stimulation of parietal cells. Elevated histamine levels are observed in two rare syndromes. *Systemic mastocytosis* (Chapter 235) is characterized by a proliferation of mast cells in the bone marrow, skin, liver, spleen, and gastrointestinal tract, often associated with both spontaneous and trigger-induced (e.g., alcohol) release of histamine and other vasoactive substances. Patients with systemic mastocytosis often have gastrointestinal symptoms, including pain, diarrhea, and blood loss. Ulceration results from chronic gastric acid hypersecretion. Clues to the diagnosis include symptoms of pruritus, urticaria, or rash. The bone marrow and affected organ mast cell infiltrates carry a specific *C-kit* mutation and express CD2 and CD25. Histamine hypersecretion leading to peptic ulcer disease also can occur in *chronic myelogenous leukemia* (Chapter 170) with basophilia.

Other Drugs

Oral bisphosphonates, used widely for osteoporosis (Chapter 225), may induce gastric erosions and ulcerations in an estimated 3 to 10% of treated patients. The risk for ulcer disease may be synergistically increased by NSAID use but is probably independent of *H. pylori* colonization. Although corticosteroid treatment can be complicated by peptic ulcer disease, the relative risk is only slightly increased, except in patients with serious comorbid diseases, patients using long-term or high-dose therapy, or patients with prior ulcers. Other patients who use corticosteroids are not at serious risk for ulcer disease and therefore do not require measures to prevent ulcers. Similarly, the use of aldosterone antagonists is also associated with an increased risk for peptic ulcer and ulcer bleeding, likely related to impaired mucosal healing.

Persons who use amphetamines and crack cocaine (Chapter 365) frequently develop ulcer disease, often with perforation, possibly as a result of vascular insufficiency. Chemotherapy, particularly when given selectively as a high-dose intra-arterial infusion in the celiac system, can be complicated by ulcer disease. Patients on anticoagulant therapy and those with other coagulopathies may rarely develop intramural hematoma of the gastrointestinal tract. Depending on the location, these hematomas may cause obstruction, but they can also leave large ulcers when they rupture into the lumen. Radiation therapy of the upper abdomen is sometimes complicated by chronic ischemic ulceration, especially as a late complication.

CLINICAL MANIFESTATIONS

The clinical manifestations of acid peptic disease (Table 125-2) do not always predict the various morphologic presentations found at endoscopy. Indeed, a silent ulcer may be recognized only when it presents abruptly with a complication, most commonly hemorrhage or perforation, or it may be discovered incidentally when a diagnostic test is performed for other reasons. Nevertheless, the typical presentation of acid peptic disease is recurrent episodes of pain. The pain is almost invariably located in the epigastrium and may radiate to the back or, less commonly, to the thorax or other regions of the abdomen (see Table 125-2). Some patients describe the pain as burning or piercing, whereas others describe it as an uncomfortable feeling of emptiness of the stomach, referred to as *painful hunger*. Indeed, the pain may improve with the ingestion of food, only to return in the postprandial period. The timing of the pain in relation to meals and to the soothing effects of food is nonspecific, however, and may also occur in patients with functional dyspepsia without ulcer. Nocturnal epigastric pain that awakens a patient several hours after a late meal is more likely to represent ulcer pain.

TABLE 125-2 KEY SYMPTOMS AND SIGNS OF PEPTIC ULCER

UNCOMPLICATED ULCER
No symptoms ("silent ulcer" in up to 40% of cases)
Epigastric pain
Pain may radiate to the back, thorax, other parts of the abdomen (cephalad most likely, caudad least likely)
Pain may be nocturnal (most specific), "painful hunger" relieved by food, or continuous (least specific)
Nausea
Vomiting
Heartburn (mimics or associated with gastroesophageal reflux)
COMPLICATED ULCER
Severe abdominal pain
Shock
Abdominal boardlike rigidity (and rebound and other signs of peritoneal irritation)
Free intraperitoneal air
Hemorrhage
Hematemesis and/or melena
Hemodynamic changes, anemia
Previous history of ulcer symptoms (80%)
Gastric outlet obstruction
Satiation, inability to ingest food, eructation
Nausea, vomiting (and related disturbances)
Weight loss

Aside from the pain during symptomatic episodes, patients may complain of retrosternal burning (heartburn) or acidic regurgitation into the throat, symptoms that reflect associated gastroesophageal reflux (Chapter 124), which is aggravated by hyperacidity or delayed gastric emptying. Nausea and vomiting may also occur but are nonspecific. The presence of significant diarrhea should raise the possibility of Zollinger-Ellison syndrome (Chapter 213), but diarrhea also may result from the intensive use of magnesium-containing antacids. In untreated patients, symptoms tend to be intermittent, with flares of daily pain lasting 2 to 8 weeks, separated by prolonged asymptomatic intervals. During periods of remission, patients may feel well and may be able to eat even heavy or spicy meals without apparent discomfort.

Physical Examination

The physical examination is usually unrevealing. If significant bleeding has occurred (Chapter 121), the patient may present with pallor and may be hypovolemic (Chapter 92). It is always useful to inquire about the characteristics of the stool because ulcer-related bleeding may manifest not only obviously in the form of hematemesis but also insidiously as melena (black feces). In the case of massive ulcer bleeding with the rapid bowel passage of blood, patients may also present with red rectal blood loss. When a patient has acute perforation, severe epigastric and abdominal pain usually develops, and the patient appears distressed. Characteristically, intense contracture of the abdominal muscles is apparent on palpation, together with rebound tenderness and other signs of peritoneal irritation. With large amounts of intra-abdominal air, percussion may reveal hypertympany over the liver.

DIAGNOSIS

In a patient who presents with symptoms consistent with ulcer disease, the diagnostic evaluation should proceed along two different but complementary paths: confirmation of the anatomic abnormality and investigation of its cause (Table 125-3). In most patients, it is advisable to follow both diagnostic paths simultaneously, but sometimes it is reasonable to skip the anatomic verification as a cost-saving strategy and proceed to management based on probable cause.

Anatomic Diagnosis

Upper gastrointestinal endoscopy (Chapter 120) is the primary investigative tool in patients suspected of having acid peptic disease. This technique can detect erosive gastritis (see Fig. 125-1) or an ulcer in the gastric wall or duodenal bulb (see Fig. 125-2). Because of the high prevalence and the spontaneous improvement of dyspeptic symptoms, endoscopy generally should not be performed immediately; rather, its use should be restricted to patients with persistent or recurrent symptoms. However, immediate endoscopy is indicated in patients with alarm symptoms such as weight loss, dysphagia, anorexia, considerable vomiting, anemia, or signs of occult or overt bleeding.

TABLE 125-3 DIAGNOSTIC PATHS AND TOOLS IN ULCER DISEASE

PATH 1: MORPHOLOGIC DIAGNOSIS
Gastroduodenoscopy Barium contrast (inferior alternative) Endoscopic ultrasound (selected cases only) Computed tomography (useful in selected cases)
PATH 2: ETIOLOGIC DIAGNOSIS
***Helicobacter pylori* Testing**
Histologic examination of gastric mucosa with appropriate stains Serum antibodies Stool antigen test Carbon-13 urea breath test
Ulcer Associated with Nonsteroidal Anti-inflammatory Drug Use
History of drug ingestion Decreased platelet aggregation Molecular identification of drugs, pro-drugs, metabolites (complex, expensive)
Acid Hypersecretory Syndromes
Serum gastrin elevation Gastrin provocative tests (intravenous secretin, meal) Gastric analysis (acid titration)

Endoscopy, which is the gold standard for diagnosis, is both highly sensitive and highly specific for the detection of ulcer disease. The most common locations for a peptic ulcer are the stomach and duodenal bulb, but peptic ulcers sometimes occur in the esophagus, the small bowel, and a Meckel diverticulum lined with heterotopic gastric mucosa. Endoscopic ultrasound may detect an unsuspected submucosal component or enlarged lymph nodes, such as may occur in gastric neoplasia, especially lymphoma and linitis plastica (Chapter 178). Ulcers in the dorsal wall of the duodenal bulb, especially at the transition from the bulb to the postbulbar descending portion of the duodenum, are most difficult to visualize. They sometimes require a side-viewing endoscope, particularly when endoscopic treatment is needed. Other regions where gastroduodenal ulcers can be easily missed are the cardia and the gastric angulus. Dieulafoy lesions may be difficult to diagnose because of their small mucosal defects and intermittent bleeding. Some patients require more than one endoscopy, preferably during acute bleeding, to localize the lesion. Endoscopy is also useful for ascertaining the presence of concomitant disorders, including esophagitis and duodenitis, or complications, such as bleeding or a visible vessel (see Fig. 125-2); obtaining biopsy specimens for histologic examination and to assess for *H. pylori* (see Fig. 125-3); and performing therapeutic interventions.

In rare cases, such as stenosis that blocks the advancing endoscope, conventional barium contrast radiographs (Chapter 119) are indicated. Additional investigations by endosonography or CT are needed when underlying malignant disease is suspected. The endoscopist should obtain biopsy samples from all gastric ulcers, especially those with a suspicious appearance, to exclude potential malignant disease. Because duodenal ulcers are less likely to be malignant, biopsies are usually not required unless malignancy is specifically suspected.

Etiologic Diagnosis

Diagnosis must focus on establishing the cause of the ulcer. The first step is to determine whether *H. pylori* or NSAID use is present because these are the major risk factors for peptic ulcers and can be contributing factors in ulcers with other precipitating causes.

Testing for *Helicobacter pylori*

In populations with high *H. pylori* prevalence, nearly all patients with peptic ulcer disease are positive for *H. pylori*, so diagnostic testing has little value except when antimicrobial susceptibility testing is needed. The prevalence of *H. pylori* remains high in immigrants from developing countries, where most people become *H. pylori* positive in youth. In Western countries, approximately 50% of individuals who are older than 65 years are colonized with *H. pylori*, but the prevalence is less than 20% in those younger than 30 years. In these younger persons, the proportion of patients with ulcers who are *H. pylori* negative is higher than in older patients, making diagnostic testing for *H. pylori*, followed by targeted therapy in those who are positive for the bacterium, more attractive than empirical therapy.

The presence of *H. pylori* can be ascertained by four possible approaches: gastric biopsies, serum, stool, or breath test.[4] The first method, *gastric mucosal biopsies*, is the standard procedure when diagnostic endoscopy is initially performed. Routine hematoxylin and eosin staining is sensitive and specific for *H. pylori*. However, the accuracy of this technique may be affected by sampling error, improper orientation of the specimen, and recent therapy with proton pump inhibitors or antibiotics. The presence of *H. pylori* in gastric mucosal biopsies also can be assessed by rapid urease testing, which has a high positive predictive value, although false-negative tests occur in patients using proton pump inhibitors or antibiotics and in patients with marked atrophic gastritis and intestinal metaplasia. Finally, biopsies can be cultured for *H. pylori* when it is important to assess antimicrobial resistance in patients with recurrent disease after previous antibiotic treatment.

A second option is *serology*, which is simple, inexpensive, and accurate, although its predictive value is lower in areas where the prevalence of *H. pylori* is low. Serology is not helpful to verify whether *H. pylori* has been eradicated with antibiotics because it may take more than 6 months or even 1 to 2 years for *H. pylori* antibodies to decrease to undetectable levels.

A third option is a *stool H. pylori antigen test*, which is similar in accuracy to standardized serologic testing. Finally, the *carbon-13* or *carbon-14 urea breath test*, which relies on the detection of *H. pylori* urease activity, is a noninvasive and relatively simple test, but it is more expensive than stool or blood testing. Although the test usually becomes negative as soon as *H. pylori* treatment is begun, a minimum interval of 6 to 8 weeks after therapy has ended is recommended to reduce false-negative results.

Nonsteroidal Anti-inflammatory Drugs

NSAIDs are usually established as the putative cause of an ulcer based on information obtained from the patient. Assessment of NSAID use in an individual patient presenting with ulcer disease can be difficult both because NSAID use is common and often intermittent and because many different NSAIDs are widely available over the counter in most countries. NSAID use is usually evaluated by detailed medical history, focusing not only on current and recent drug use, and especially over-the-counter treatments, but also on symptoms of pain, including musculoskeletal complaints. Further information from family members, family practitioners, and pharmacists is sometimes helpful. If surreptitious use of NSAIDs is suspected, direct serum and urine testing for aspirin and NSAID derivatives is feasible, or aspirin use can be assessed indirectly by a platelet adherence assay; however, these tests are not commonly used in clinical practice.

Hypersecretory Syndromes

Hypersecretory syndromes not related to *H. pylori* or NSAIDs are rare causes of ulcer disease and are diagnosed by special tests (see Table 125-3). Zollinger-Ellison syndrome should be strongly considered in patients with multiple ulcers, particularly in atypical locations such as distal to the duodenal bulb, and when diarrhea is present because these findings are uncommon in *H. pylori*–related peptic ulcer disease. Hypergastrinemic syndromes (e.g., Zollinger-Ellison syndrome, antral G-cell hyperplasia) are best diagnosed by a determination of serum gastrin levels, both basal and after stimulation with intravenous secretin (gastrinoma detection) or a test meal (antral G-cell hyperplasia detection). When detected early, gastrinomas may be resectable (Chapter 213).

Gastric analysis, by quantified aspiration of gastric juice through a nasogastric tube (both basal and after stimulation with subcutaneous pentagastrin), is indicated in only two rare circumstances: patients with elevated serum gastrin levels suggestive of Zollinger-Ellison syndrome or antral G-cell hyperplasia but with equivocal responses to standard gastric provocative tests, and patients with indirect signs of gastric hypersecretion (e.g., enlarged folds and abundant clear fluid at endoscopy), normal gastrin levels, and negative provocative gastrin tests but who may still be hypersecretors, such as patients with recurrent ulcer disease despite a prior vagotomy with or without antrectomy. A basal acid output greater than 15 mEq/hour or greater than 5 mEq/hour in a postoperative patient is considered a positive test result.

The diagnosis of Zollinger-Ellison syndrome is best confirmed by gastric analysis showing a basal acid output greater than 15 mEq/hour in conjunction with a fasting serum gastrin level exceeding 1000 pg/mL in the presence of gastric pH less than 2. To bypass the cumbersome gastric analysis, a gastric pH determination showing a fasting pH of 2 or less is adequate. For serum gastrin levels in the range of 100 to 1000 pg/mL and intragastric pH>2, an increase in the serum gastrin to more than 200 pg/mL after a secretin stimulation test is suggestive of the diagnosis. An elevated serum gastrin level alone is not sufficient to diagnose Zollinger-Ellison syndrome because serum gastrin levels

tend to increase over time with atrophic gastritis and also can be markedly increased in patients receiving proton pump inhibitor therapy.

Other Causes

In patients in whom a gastroduodenal ulcer cannot be ascribed to colonization with *H. pylori*, use of NSAIDs, or a hypersecretory syndrome, the establishment of a definite etiologic diagnosis may require a more thorough evaluation, starting with a medical history that focuses on the use of other ulcerogenic agents and the presence of symptoms that could suggest an underlying systemic disease. The next step is to evaluate biopsy samples from ulcer borders and from the antrum, corpus, and duodenum. The ulcer specimens may reveal overt or suspicious signs of malignancy, in particular adenocarcinoma (Chapter 178) or lymphoma. In these cases, further diagnostic evaluation should include staging of the malignancy. Alternatively, the biopsies may provide evidence of other infectious conditions, specific types of gastritis, celiac disease, ischemia, amyloidosis, or a systemic inflammatory condition. These data can be combined with clues provided by the endoscopic evaluation, including the character and location of the ulcer, signs of ischemia, and signs of inflammation at other locations. Further evaluation should focus on the presence of systemic disorders and may include a chest radiograph, angiography, colonoscopy, and abdominal CT.

Differential Diagnosis

The differential diagnosis of ulcer-like symptoms includes many disorders of the upper abdominal organs, including malignant diseases of the stomach (Chapter 178), duodenum (Chapter 179), pancreas (Chapter 180), or bile ducts (Chapter 181). The differential diagnosis of upper abdominal symptoms also includes liver and gallstone disease (Chapter 141), pancreatitis (Chapter 130), and motility disorders (Chapter 122). In many patients with upper abdominal dyspeptic complaints, no underlying cause can be identified. In this "nonulcer" or functional dyspepsia group, complaints characteristic of gastroesophageal reflux, ulcer symptoms, or dysmotility symptoms may be prominent. Some patients (generally 5%) benefit from eradication of *H. pylori*, with a slow decrease of dyspeptic complaints over 12 to 24 months, but functional dyspepsia is not a proven or widely accepted indication for treatment of *H. pylori*. If such treatment is considered, both the patient and the physician should be prepared for persistent symptoms despite eradication of *H. pylori* and potentially for the emergence of antimicrobial-resistant *H. pylori*, which may result in a spiral of multiple courses of therapy in an attempt to remove resistant organisms.

Diagnostic Scenarios: Acute or Initial Clinical Presentation

Younger (≤45 years old) patients without alarm symptoms or signs such as anemia, rapid weight loss, or other evidence of serious disease do not necessarily require endoscopy, and malignant gastric disease is unlikely. When a physician is treating a patient who lives in an area of the world with a relatively high prevalence of *H. pylori* infection (>10% of the population is positive), a test-and-treat approach can begin with an *H. pylori* stool antigen determination, urea breath test, or *H. pylori* serologic examination. However, although commonly practiced, the test-and-treat approach has never been documented to improve outcomes, except in the setting of endoscopically confirmed peptic ulcer disease. If the *H. pylori* test is positive, the patient can be treated with the appropriate *H. pylori* eradication drugs (see later) and observed for 4 to 6 weeks. If a patient with dyspeptic symptoms is taking an NSAID, either orally or parenterally, the first therapeutic approach is to discontinue these drugs and to prescribe a proton pump inhibitor for 4 to 6 weeks. In patients who test negative for *H. pylori* and who are not taking NSAIDs or who do not improve after these drugs are discontinued, endoscopy is indicated to determine whether an ulcer is present.

Conversely, gastroenterologists more commonly proceed directly to endoscopy. If no abnormalities are apparent or the endoscopic study shows only "gastritis" without an overt ulcer, a biopsy should be obtained to ascertain by histologic examination or urease testing whether *H. pylori* is present. If *H. pylori* is present, then eradication treatment may be pursued. However, the efficacy of *H. pylori* eradication for the relief of functional dyspeptic symptoms is only about 6 to 12% greater than with placebo,[A1] and eradication therapy increases the risk for reflux-related symptoms (Chapter 124), especially in Asian patients.

If endoscopic examination reveals an ulcer, its location determines the subsequent approach. An ulcer in the duodenal bulb has only a remote chance of representing a malignant lesion and need not routinely be examined by biopsy. By contrast, biopsy is mandatory for a gastric ulcerative lesion identified at endoscopy because malignant gastric disease may present with similar clinical manifestations and may resemble benign ulcer disease morphologically. Even if histologic assessment does not identify a malignant process, repeat endoscopy is recommended about 1 month after therapy to verify complete healing and for biopsy of the scar.

TREATMENT

Helicobacter pylori–Associated Ulcers

H. pylori–associated ulcers often heal spontaneously, but acid-suppressive therapy accelerates healing and ameliorates symptoms. Four weeks of acid-suppressive therapy heals 70 to 80% of ulcers, and this number increases to more than 90% after 8 weeks of therapy. If *H. pylori* colonization persists, however, ulcers recur in 50 to 90% of patients within 12 to 24 months; this rate can be reduced to 20 to 30% with maintenance acid suppression and to less than 5% with *H. pylori* eradication.[A2] Eradication treatment is therefore mandatory (Table 125-4).[5,6] The success of eradication treatment strongly depends on therapy adherence and antimicrobial resistance.[7,8] Resistance of *H. pylori* to metronidazole varies between 20 and 80% throughout the world. Clarithromycin resistance is increasing and ranges between 10 and 50% in many regions owing to the widespread use of macrolides to treat upper respiratory infections. Resistance to amoxicillin and tetracycline is rare and is not usually relevant in clinical practice. Levofloxacin resistance was very rare a decade ago, but it now ranges between 10 and 50% in many regions of the world. Because of this worldwide increase in prevalence of antimicrobial resistance, *H. pylori* eradication regimens continue to evolve.

The conventional regimen is empiric "triple" therapy for 14 days.[9,10] This treatment remains a standard regimen for regions and populations with a clarithromycin resistance below 15%, such as in Northern Europe and North America. Triple therapy combines a proton pump inhibitor or potassium-competitive acid blocker (vonoprazan 20 mg twice daily)[A3] with two antibiotics, usually combinations of amoxicillin, a nitroimidazole, and clarithromycin, with the latter sometimes being replaced by levofloxacin.[A4] Double-dose proton pump inhibitor therapy (dose equivalent to omeprazole 40 mg twice daily) also increases eradication rates by approximately 10% and is preferred. For patients in whom such therapy fails, a 14-day course of quadruple therapy (see later) eradicates *H. pylori* in an additional 80% of patients (Fig. 125-5). Adding probiotic capsules to standard triple therapy appears to hasten the resolution of symptoms and increase the eradication of *H. pylori*.[A5]

Because of the increased prevalence of antimicrobial resistance, initial empiric "quadruple" therapies[A6] or susceptibility-guided antibiotic treatment[A7] are increasingly being recommended over initial empiric "triple therapy" because of their better first-line efficacy. Bismuth-based quadruple therapy consists of a proton pump inhibitor, a bismuth compound, and two antibiotics, usually tetracycline and a nitroimidazole (see Table 125-4). This regimen leads to eradication in about 85 to 90% of patients. Non–bismuth-based quadruple therapies consist of a proton pump inhibitor plus three antibiotics, usually given for 14 days (see Table 125-4). The three forms of non–bismuth-based quadruple therapy (sequential, hybrid, and concomitant therapy) differ in their antibiotic dosing schedule. Sequential therapy consists of a proton pump inhibitor with amoxicillin, usually given for 5 days, followed by a proton pump inhibitor with clarithromycin and a nitroimidazole for another 5 days. Ten-day sequential therapy is equally effective as 14-day triple therapy.[A8] Hybrid therapy starts with the same 5-day combination of a proton pump inhibitor with amoxicillin and then continues the amoxicillin for the next 5 days together with clarithromycin and metronidazole. Concomitant therapy, which gives these same drugs all together for 14 days, is the most effective, in particular when given for 14 days with a proton pump inhibitor in a dose of 40 mg twice daily.

Continuation of acid-suppressive therapy after antibiotic treatment is needed only when symptoms persist or in cases of complicated ulcer disease until eradication of *H. pylori* has been confirmed. Ascertainment of therapeutic efficacy must be delayed at least 1 month after the end of treatment to prevent false-negative results related to the organism's temporary suppression but not eradication. When repeat endoscopy is needed (e.g., a gastric ulcer requires repeated histologic examination to exclude underlying malignancy), repeat screening for *H. pylori* can be performed using gastric biopsy specimens for histologic examination, culture, or urease testing. If no clinical indication exists for repeat endoscopy, *H. pylori* status can be determined by a carbon-13 urea breath test, stool *H. pylori* antigen, or repeated serology. Serologic determination is based on a more than 40 to 50% decrease in immunoglobulin G antibody levels in the first 6 months after treatment compared with pretreatment levels in that patient; ideally, the (frozen) pretreatment and post-treatment specimens should be examined simultaneously by the same laboratory using the same assay.

After successful *H. pylori* eradication, the risk for recurrent infection in most populations is less than 1% per year. In a minority of patients, ulcers recur either owing to reinfection or in the presence of another ulcerogenic factor, particularly NSAID use. Quinolone-based quadruple therapy (including bismuth) for 10 or more days is an excellent second-line therapy for patients who do not respond to initial therapy.[11]

Disease Related to Nonsteroidal Anti-inflammatory Drug Use

In patients who are diagnosed with acid peptic disease while they are taking NSAIDs or aspirin, the first step is to stop such therapy. Acid suppression with a proton pump inhibitor (in doses similar to those used for *H. pylori*) leads

TABLE 125-4 OVERVIEW OF ORAL ANTIBIOTICS USED FOR *HELICOBACTER PYLORI* ERADICATION

DRUG CLASS	DRUG	TRIPLE THERAPY* DOSE	BISMUTH-BASED QUADRUPLE THERAPY† DOSE	NON–BISMUTH-BASED QUADRUPLE THERAPY‡ DOSE
Acid suppression	Proton pump inhibitor	40 mg bid§	20-40 mg bid§	20-40 mg bid§
	Potassium competitive acid blocker	20 mg bid††	20 mg bid††	20 mg bid††
Standard antimicrobials	Bismuth compound‖		2 tablets bid	
	Amoxicillin	1 g bid	1 g bid	1 g bid
	Metronidazole¶	500 mg bid	500 mg tid	500 mg bid
	Clarithromycin	500 mg bid		500 mg bid
	Tetracycline		500 mg qid	
Salvage antimicrobials	Levofloxacin**	500 mg qd	500 mg od	500 mg qd
	Rifabutin	150 mg bid	150 mg bid	
	Furazolidone	100 mg bid	100 mg bid	
	Doxycycline		100 mg bid	100 mg bid
	Nitazoxanide		500 mg bid	500 mg bid

*Triple therapy consists of a proton pump inhibitor or bismuth compound, together with two of the listed antibiotics, usually given for 7 to 14 days.

†Bismuth-based quadruple therapy consists of a proton pump inhibitor plus the combination of a bismuth compound and two antibiotics, usually given for 7 to 14 days.

‡Non-bismuth-based quadruple therapy consists of a proton pump inhibitor, plus three antibiotics usually given for 10 days and sometimes extended to 14 days. The three forms of non–bismuth-based quadruple therapy differ in their antibiotic dosing schedules: (1) sequential therapy gives amoxicillin for the first half of the course and then metronidazole and clarithromycin for the second half; (2) hybrid therapy starts with amoxicillin for the first half and then continues the second half with amoxicillin, clarithromycin, and metronidazole; (3) concomitant therapy combines all three antibiotics throughout the usual 10- to 14-day therapy. Other combinations of antibiotics are occasionally used.

§Proton pump inhibitor dose equivalent to omeprazole 20 to 40 mg bid. (See Table 124-1 for doses of other proton pump inhibitors.)

‖Bismuth subsalicylate or subcitrate.

¶An alternative is tinidazole 500 mg bid.

**Alternatives are moxifloxacin 400 mg qid and sitafloxacin 100 mg bid.

††Equivalent to vonoprazan 20 mg bid.

bid = twice daily; qd = daily.

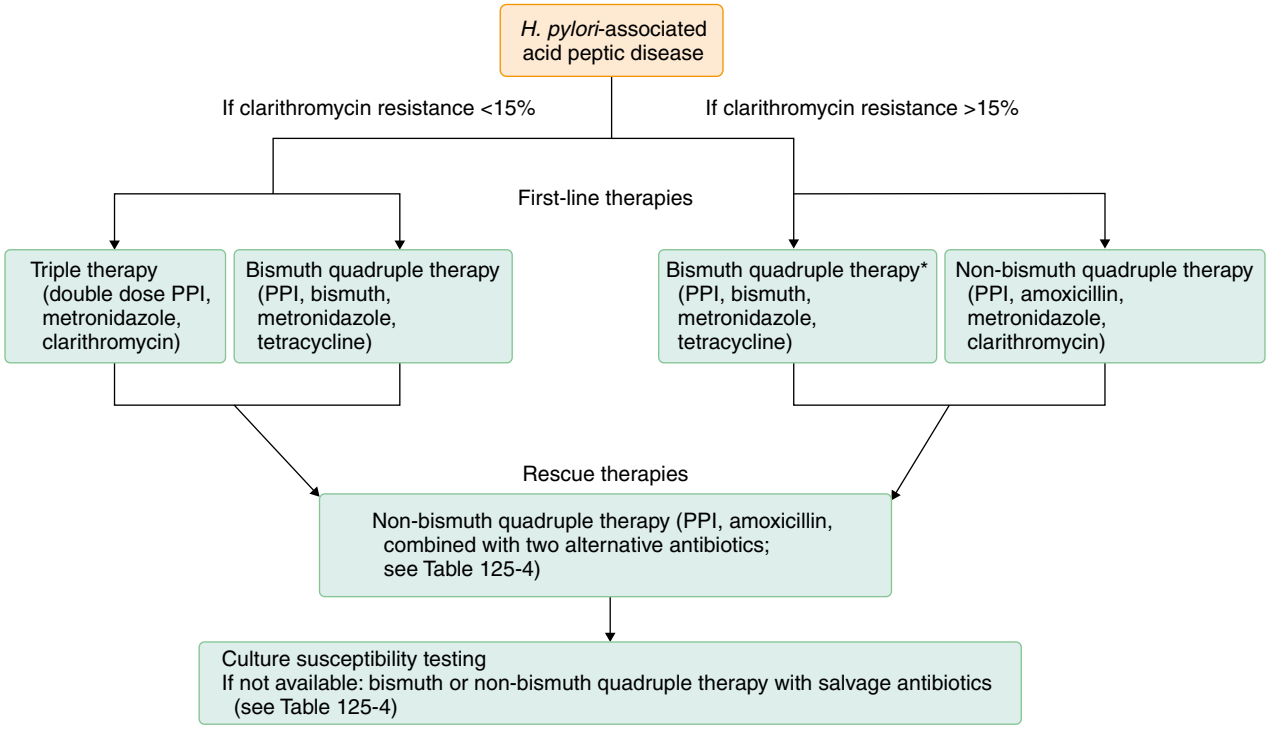

FIGURE 125-5. Management of *H. pylori*–associated acid peptic disease. See text and Table 125-4 for duration of therapy. PPI = proton pump inhibitor. *Preferred therapy if clarithromycin resistance >15%.

to healing of 85% of NSAID-induced gastric ulcers and more than 90% of duodenal ulcers within 8 weeks of therapy, whereas acid suppression with a histamine-2 (H_2)-receptor blocker, equivalent to ranitidine 300 mg twice daily (see Table 125-1), heals approximately 70% of ulcers within 8 weeks. The mucosal-protective drug misoprostol (200 mg four times daily) has a similar effect to the H_2 blockers. Treatment must be continued for at least 8 weeks, and maintenance therapy is needed in patients who continue to take NSAIDs. Gastric ulcers, larger lesions, and recurrent lesions heal more slowly.

Ulcer occurrence during NSAID therapy suggests a causal relationship, but patients should also be tested for *H. pylori*. In patients who are *H. pylori* positive, eradication therapy should be considered because there are no clear clinical parameters distinguishing between these etiologic factors.

Idiopathic Ulcer Disease

Patients with idiopathic ulcer disease despite a thorough assessment for underlying causes are treated primarily with an acid suppressant, usually a proton pump inhibitor, because they are at considerable risk for recurrent ulcer disease. After the underlying cause is identified and adequately treated, acid-suppressive therapy can be withdrawn if there are no additional risk factors for ulcer disease, such as NSAID therapy or *H. pylori* infection. If the cause of the idiopathic ulceration is not clarified and there is doubt about the adequacy of the diagnostic testing for *H. pylori*, empirical eradication therapy can be considered, especially when there is histologic evidence of chronic active gastritis without further explanation. If related to unidentified *H. pylori*, gastritis should slowly disappear after successful eradication therapy.

PREVENTION

Primary Prevention

A test-and-treat strategy for *H. pylori* colonization is sometimes considered for patients with dyspeptic symptoms, but there is no specific way to prevent *H. pylori*–associated ulcer disease. By contrast, primary prevention of NSAID-associated ulcer disease is widely advocated for patients at high risk because of a prior ulcer, severe concomitant disease, or use of warfarin or high-dose corticosteroids as well as for critically ill patients in intensive care units. H_2 blockers (at a dose equivalent to ranitidine 300 mg twice daily; Table 124-1) partially prevent duodenal ulcer disease during NSAID therapy but have no effect on preventing gastric ulcers unless a higher dose (equivalent to famotidine 40 mg twice daily) is given. Proton pump inhibitors[A9] (at a dose equivalent to omeprazole 20 mg once daily; Table 124-1) and misoprostol (in doses varying between 400 and 800 mg/day) partially protect against both gastric and duodenal ulcers during NSAID use. Misoprostol and proton pump inhibitors are equally effective, but adherence with therapy is lower with misoprostol owing to its side effects. Patients should be advised of the importance of adherence because less than 80% adherence to gastroprotection is associated with a more than two-fold increased risk for ulcer disease compared with those who are fully adherent. During low-dose aspirin therapy, primary prevention of ulcers is advocated for the same risk groups, using a proton pump inhibitor or an H_2-receptor antagonist.[A10] *H. pylori* eradication also can reduce aspirin-associated peptic ulcer bleeding.[A11] For the prevention of stress ulcers in patients in intensive care units,[12] proton pump inhibitors and histamine-2 receptor blockers are approximately equally effective, but some data suggest that proton pump inhibitors may be preferred.[A12]

Secondary Prevention

Secondary prevention of *H. pylori*–associated ulcer disease is mandatory and consists of successful bacterial eradication. Testing to ascertain *H. pylori* status after eradication therapy is indicated in patients with prior complicated ulcer disease or with persistent or recurrent symptoms after therapy, as well as in patients who fail to complete the therapeutic course.

Secondary prevention of NSAID-related ulcer disease is preferentially achieved by the withdrawal of NSAIDs. In patients who must continue taking NSAIDs, a change to a selective COX2 inhibitor[A13] in combination with a proton pump inhibitor at a dose equivalent to esomeprazole 20 mg twice daily is advocated, especially for patients with complicated ulcer disease. This combination is associated with a lower risk for secondary peptic ulcer complications than treatment with a COX2 inhibitor alone.

Secondary prevention of recurrent ulcers in patients who use aspirin may depend on *H. pylori* status. In *H. pylori*–positive patients, *H. pylori* eradication is as effective as a proton pump inhibitor for the prevention of recurrent ulcers. *H. pylori*–negative patients require additional acid-suppressive therapy at a dose equivalent to esomeprazole 20 mg twice daily.[A14] Secondary prevention of idiopathic ulcer disease consists primarily of maintenance therapy with a proton pump inhibitor and treatment of the underlying condition. When there is doubt about the accuracy of the diagnostic assessment for *H. pylori*, an empirical course of eradication treatment can be considered.

Complications

Hemorrhage

Hemorrhage (Chapter 121), which is the most common complication of peptic ulcer disease, occurs in about one in six patients with ulcers over the course of their ulcer activity. Ulcers caused by NSAIDs account for a larger proportion of these hemorrhages. Peptic ulcer is thus the most common cause of nonvariceal upper gastrointestinal bleeding, accounting for 40 to 60% of cases in most populations. Bleeding is associated with a 5 to 15% risk for rebleeding and up to a 10% risk for mortality. Hemorrhage may occur along a continuum from a serious acute event associated with hemodynamic shock and high mortality to slow or intermittent blood loss leading to chronic anemia. Approximately 80% of patients with bleeding ulcers describe a prior history of symptomatic disease, and about 20 to 30% have suffered a previous hemorrhage. Assessment of the magnitude of bleeding is of paramount importance in determining the need for transfusion and subsequent management (Table 125-5). Initial hematocrit levels may be misleading and are likely to

TABLE 125-5 PARAMETERS OF THE ROCKALL, BLATCHFORD, AND AIMS65 SCORING SYSTEMS FOR UPPER GASTROINTESTINAL BLEEDING*

SCORING CATEGORIES	SCORING PARAMETERS	ROCKALL SYSTEM† PARAMETER	ROCKALL SYSTEM† SCORE	BLATCHFORD SYSTEM‡ PARAMETER	BLATCHFORD SYSTEM‡ SCORE	AIMS65§ PARAMETER	AIMS65§ SCORE
Age	Age (yr)	60-79 ≥80	1 2	N/A	—	>65	1
Clinical status	Systolic blood pressure	<100	2	100-109 90-99 <90	1 2 3	≤90	1
	Pulse	>100	1	>100	1	N/A	—
	Melena	N/A	—	Present	1	N/A	—
	Syncope	N/A	—	Present	1	N/A	—
	Altered mental status	N/A	—	N/A	—	Present	1
	Comorbidities	Any major comorbidity Renal or liver failure, or disseminated malignancy	2 3	Hepatic disease Cardiac failure	2 2	N/A	—
Laboratory parameters	Blood urea, mmol/L	N/A	—	6.5-7.9 8.0-9.9 10-24.9 >25.0	2 3 4 6	N/A	—
	Hemoglobin, g/dL	N/A	—	Men: 12.0-13.0 Women: 10.0-12.0 Men: 10.0-12.0 Men and women: <10.0	1 1 3 6	N/A	—
	INR	N/A	—	N/A	—	>1.5	1
	Albumin	N/A	—	N/A	—	<3.0 g/dL	1
Endoscopy	Endoscopic diagnosis	No focus, or Mallory-Weiss tear Upper GI malignancy All other diagnoses	0 2 1	N/A	—	N/A	—
	Endoscopic SRH	None/dark spot only Blood/clot/vessel	0 2	N/A	—	N/A	—

*The Blatchford (Stanley AJ, Ashley D, Dalton HR, et al. Outpatient management of patients with low-risk upper-gastrointestinal haemorrhage: multicentre validation and prospective evaluation. *Lancet*. 2009;373:42-47) and AIMS65 (Saltzman JR, Tabak YP, Hyett BH, et al. A simple risk score accurately predicts in-hospital mortality, length of stay, and cost in acute upper GI bleeding. *Gastrointest Endosc*. 2011;74:1215-1224) systems are pre-endoscopy scoring systems; the Rockall system (Rockall TA, Logan RF, Devlin HB, et al. Risk assessment after acute upper gastrointestinal haemorrhage. *Gut*. 1996;38:316-321) has a pre- and post-endoscopy component. The Blatchford system is a tool to select patients for early discharge and later endoscopy during office hours. The Rockall score can help to assess the risk for rebleeding and mortality. The AIMS65 predicts mortality.

†Scores before and after endoscopy. Low risk defined as scores of ≤2, high risk defined as scores ≥6.

‡Low risk defined as score of 0.

§Low risk defined as score of ≤1, high risk as score of ≥2.

GI = gastrointestinal; INR = international normalized ratio; N/A = not applicable; SRH = stigmata of recent hemorrhage.

fall because of hemodilution. Rapid bleeding is usually apparent on the basis of clinical signs (pallor, systolic blood pressure ≤100 mm Hg, pulse ≥100 beats/minute); immediate fluid resuscitation is indicated to prevent circulatory collapse. Transfusion is needed in patients with marked anemia. Restrictive transfusion using a hemoglobin threshold of 70 to 80 g/L is associated with fewer transfusions and lower risks for rebleeding and mortality.[A15] Mortality is particularly related to complications of the bleed, such as aspiration, and exacerbation of underlying disease, such as pulmonary, cardiovascular, renal, and hepatic disease. On rare occasions, patients may actually bleed to death, especially when a larger artery is affected, such as when an ulcer in the posterior wall of the duodenal bulb perforates the gastroduodenal artery. The stopping of such bleeding is therefore a medical emergency.[13]

Initial treatment aims at hemodynamic stabilization. Endoscopy is the mainstay of therapy and should be performed emergently or within 24 hours of presentation in high-risk cases, especially patients who are hemodynamically unstable, require transfusion, or have more severe comorbidities.[14] Endoscopy can be performed to ascertain the origin of the bleeding and, if necessary, provide therapy to stop the bleed and reduce the risk for rebleeding.

The appearance of the ulcer determines the need for endoscopic treatment and the risk for rebleeding (Table 125-6) and mortality. "Clean base" ulcers and those with flat and pigmented spots carry a low risk for rebleeding and do not require endoscopic treatment. In contrast, ulcers with active bleeding or stigmata of recent bleeding, in particular a visible vessel or adherent clot, require treatment to stop the bleed and reduce the otherwise high risk for recurrence.

Endoscopic therapy may lead to a three-fold reduction in episodes of recurrent bleeding and in the need for surgical intervention, as well as a 40% reduction in mortality. Treatment modalities include injection therapy with epinephrine or a sclerosant, thermocoagulation, and mechanical pressure by means of clips. Thermocoagulation can be performed by direct contact, such as with a heater probe, or by a noncontact method, such as argon plasma coagulation. The efficacy of these methods is generally comparable, except that epinephrine injection alone is inferior to the other modalities but can be useful when combined with any of the others. If an adherent clot is found, an attempt should be made to remove it by water flushing or snaring to allow an assessment of the underlying ulcer base and the treatment of any underlying visible vessels to reduce the risk for rebleeding.

Pre-endoscopy administration of intravenous proton pump inhibitor therapy (at a dose equivalent to a bolus of 80 mg esomeprazole, followed by a continuous infusion of 8 mg/hour until endoscopy) reduces bleeding and the need for emergent endoscopic treatment, but it has no effect on the need for transfusion or the occurrence of rebleeding or death. For patients with active bleeding or stigmata of recent bleeding, endoscopic treatment should be followed by an intravenous proton pump inhibitor given as a bolus at a dose equivalent to 80 mg esomeprazole over 30 minutes, followed by a continuous infusion at a dose equivalent to esomeprazole 8 mg/hour for 72 hours to reduce rebleeding and the need for further intervention. Intermittent oral or intravenous therapy at 6- to 12-hour intervals in a cumulative daily dose equivalent to 80 to 160 mg esomeprazole may be equally effective, although more evidence is needed in patients from Western countries. Other therapies, including tranexamic acid, vasopressin, somatostatin, and octreotide, should be considered experimental (Chapter 121). Second-look endoscopy is not routinely indicated but can be considered in very high-risk cases, particularly when there is doubt about the adequacy of initial visualization or treatment.

About 70 to 80% of rebleeds occur within the first 3 days and generally should be managed by repeat endoscopy. If endoscopy fails to stop the bleed or prevent further rebleeding, surgery and interventional radiology are equivalent options. Surgery includes stitching of the ulcer and occlusion of the feeding artery, usually the gastroduodenal artery. Interventional radiology uses angiography to insert coils in the culprit vessel at the site of the bleed. Single-center observational experience suggests that each of these methods is equally effective in the hands of experienced clinicians, and the choice depends on local availability and expertise.

The risk for a fatal outcome of an upper gastrointestinal hemorrhage can be estimated based on five clinical and endoscopic parameters (see Table 125-5). In several studies, mortality in patients with a bleeding peptic ulcer was less than 2% among those with a score of 2 points or less, 10% in those with 3 to 5 points, and up to 46% in those with 6 points or more. Management of patients who recover after a peptic ulcer hemorrhage is similar to the treatment of patients with uncomplicated ulcers. Eradication of *H. pylori* provides excellent protection against both recurrence and rebleeding of *H. pylori*–related ulcers. NSAID-induced ulcers are preferentially managed by the withdrawal of NSAIDs or, if this is not feasible, by the combination of a COX2 inhibitor and a proton pump inhibitor at a dose equivalent to esomeprazole 20 mg twice daily. In patients with a history of ulcer bleeding and concomitant cardiovascular disease requiring antiplatelet therapy, the combination of low-dose aspirin and a proton pump inhibitor at a dose equivalent to esomeprazole 20 mg twice daily is associated with a lower risk for complicated ulcer than is clopidogrel monotherapy. If a patient who requires antiplatelet therapy presents with a bleeding ulcer, antiplatelet therapy should be continued or restarted as soon as possible if the risk for a cardiovascular event outweighs the risk for recurrent bleeding.

Perforation

Perforation may manifest as an acute event, whereby gastric contents spill into the peritoneal cavity, or more insidiously as the ulcer slowly penetrates into surrounding tissues. Acute free perforation typically causes abrupt and severe abdominal pain associated with abdominal muscular spasm that produces boardlike rigidity of the abdomen and other manifestations of peritoneal irritation. Secondary hemodynamic shock is common. The clinical diagnosis can be confirmed in approximately 80% of patients by a plain chest radiograph with the patient standing (Fig. 125-6); a CT scan can be obtained if doubt persists. Leukocytosis and elevated C-reactive protein levels develop rapidly, and mild hyperamylasemia may occur. Treatment begins by correcting hemodynamic, fluid, and electrolyte imbalances. Nasogastric suction is helpful, and prophylactic antibiotics (e.g., amoxicillin-clavulanic acid 1 g every 8 hours intravenously) are usually administered. Unless a specific contraindication exists, emergency surgery is usually indicated,[15] although more conservative approaches are sometimes appropriate. Given the success in achieving the long-term cure of ulcer disease through the eradication of *H. pylori* and the

TABLE 125-6 ENDOSCOPY RESULTS IN PATIENTS WITH BLEEDING ULCERS

ENDOSCOPY RESULT	ULCER CHARACTERISTICS*	RISK FOR RECURRENT BLEEDING (%)
Active bleeding	Arterial bleeding	80-90
	Oozing bleeding	10-30
Stigmata of recent bleeding	Nonbleeding visible vessel	50-60
	Adherent clot	25-35
	Flat pigmented spot	0-8
No signs of bleeding	Clean ulcer base	0-12

*The ulcer characteristics determine the risk for recurrent bleeding during follow-up.

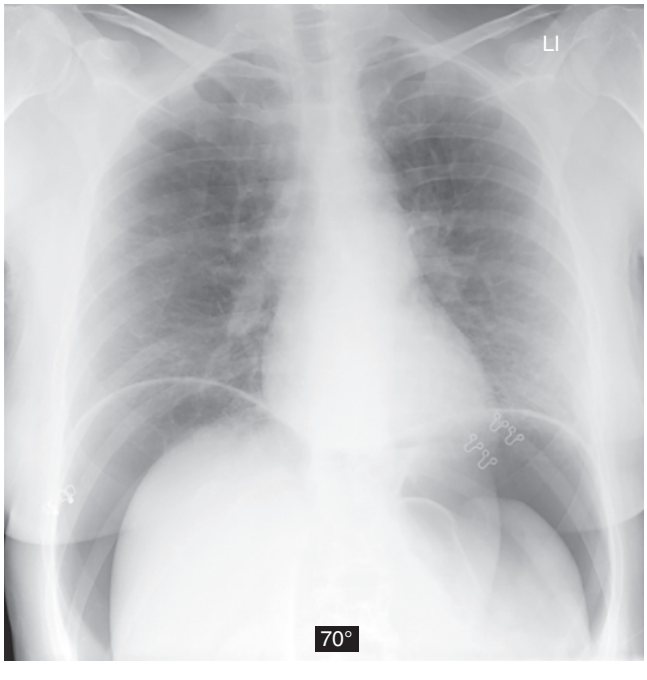

FIGURE 125-6. Plain chest radiograph in an upright patient with a perforated ulcer. The radiograph shows free air under the diaphragm.

withdrawal of NSAIDs, suturing of the perforated ulcer may be adequate, permitting the patient to avoid a more radical vagotomy with or without gastric resection.

Intractability

Intractability is a term strictly applied to an ulcer that persists even after intensive and prolonged proton pump inhibitor therapy. Symptoms may or may not be present. These rare cases may result from poor compliance with recommended treatment, surreptitious use of ulcerogenic drugs, or other diseases (e.g., Crohn disease, ischemia, infection with bacteria other than *H. pylori*, viral infection). If these issues are recognized and these diagnoses are pursued, further complications and interventions such as surgical vagotomy and pyloroplasty can almost always be avoided.

Acid peptic disease related to alcohol or bisphosphonates should be addressed by discontinuing the precipitating agent. Treatment of Zollinger-Ellison syndrome requires high-dose proton pump inhibitors and/or surgery (Chapter 213). Rare ulcers caused by Crohn disease (Chapter 127), vasculitis (Chapter 249), sarcoidosis (Chapter 83), polycythemia vera (Chapter 152), amyloidosis (Chapter 174), and other rare disorders should be addressed by treating the underlying condition. Stress ulcers and Cameron ulcers are treated by potent acid-suppressive therapy (e.g., omeprazole 20 mg twice daily).

Stenosis

Gastric outlet obstruction is now a rare complication of ulcer disease because of the early detection and treatment of most ulcers. Most patients who develop clinically relevant gastric outlet obstruction have had an ulcer in the duodenal bulb and/or pyloric channel. Edema and inflammation play an important role, and occasionally a patient with active disease presents with symptoms of outlet obstruction as manifested by nausea, vomiting, and gastric stasis without a tight, chronic stenosis. Management therefore involves three key steps. The first is nasogastric tube aspiration and gastric lavage to clear the stomach of retained debris, followed by early endoscopy. This step facilitates an accurate diagnosis. Nasogastric suction may need to be maintained for several days if vomiting resumes when the tube is clamped. The second step consists of intense antisecretory therapy using intravenous proton pump inhibitors in a dose equivalent to a bolus of 80 mg esomeprazole over 30 minutes, followed by a continuous infusion of 8 mg/hour. Finally, the cause of the ulcer needs to be addressed, usually by eradicating *H. pylori* and withdrawing NSAIDs. If the initial treatment resolves the clinical situation and the patient can resume eating, it is often not necessary to undertake further treatment of the outlet stenosis; however, tight, fibrous scarring may require endoscopic balloon dilation or surgery.

PROGNOSIS

Most peptic ulcers heal spontaneously within weeks to months. However, if the underlying condition is not adequately treated, a large proportion of ulcers recur. Both initial and recurrent ulcers can give rise to complications. The four major complications are intractability, perforation, hemorrhage, and stenosis. Each distinct situation requires specific management approaches. Patients with complicated ulcer disease are at particular risk for recurrent complications and need careful assessment for secondary prevention. In patients who take long-term acid suppressive therapy, especially with proton pump inhibitors, the risks for community-acquired pneumonia and vitamin B_{12} deficiency (Chapters 150 and 199) are increased but overall mortality is not.[16] The treatment of *H. pylori* infection appears to reduce the risk of gastric cancer.[17,A16]

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126 APPROACH TO THE PATIENT WITH DIARRHEA AND MALABSORPTION

CAROL E. SEMRAD

DEFINITIONS

Normal stool frequency ranges from three times per week to three times per day. As a symptom, diarrhea can be described as a decrease in stool consistency (increased fluidity), stools that cause urgency or abdominal discomfort, or an increase in the frequency of stool. Consistency is defined as the ratio of fecal water to the water-holding capacity of fecal insoluble solids, which are composed of bacterial mass and dietary fiber. Because it is difficult to measure stool consistency and because stool is predominantly (60 to 85%) water, stool weight becomes a reasonable surrogate of consistency.

As a sign, diarrhea is defined by the weight or volume of stool measured over a 24- to 72-hour period. Daily stool weights of children and adults are less than 200 g, and greater stool weights are an objective definition of diarrhea; however, this definition misses 20% of diarrheal symptoms in patients who have loose stools that are less than this daily weight.

Acute diarrheas persist for less than 2 to 3 weeks or, rarely, 6 to 8 weeks. The most common cause of acute diarrhea is infection. Chronic diarrheal conditions persist for at least 4 weeks and, more typically, 6 to 8 weeks or longer. The four mechanisms of diarrhea are osmotic, secretory, exudative, and altered motility. Because many diarrheal diseases are due to more than one of these mechanisms, it is clinically useful to categorize diarrhea as malabsorptive (fatty), watery, and inflammatory.

EPIDEMIOLOGY

Diarrhea is a leading cause of mortality worldwide and is particularly problematic for elderly people and for children younger than 5 years of age in developing nations. Infectious diarrheal conditions cause approximately 445,000 worldwide childhood deaths annually, despite the improved use of oral rehydration solutions, zinc, and vitamin A supplements. Rotavirus infection (Chapter 350) is the most common cause of fatal childhood diarrhea, but the introduction of the oral monovalent rotavirus vaccine has significantly decreased its mortality rate in both developing and developed nations.

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withdrawal of NSAIDs, suturing of the perforated ulcer may be adequate, permitting the patient to avoid a more radical vagotomy with or without gastric resection.

Intractability

Intractability is a term strictly applied to an ulcer that persists even after intensive and prolonged proton pump inhibitor therapy. Symptoms may or may not be present. These rare cases may result from poor compliance with recommended treatment, surreptitious use of ulcerogenic drugs, or other diseases (e.g., Crohn disease, ischemia, infection with bacteria other than *H. pylori*, viral infection). If these issues are recognized and these diagnoses are pursued, further complications and interventions such as surgical vagotomy and pyloroplasty can almost always be avoided.

Acid peptic disease related to alcohol or bisphosphonates should be addressed by discontinuing the precipitating agent. Treatment of Zollinger-Ellison syndrome requires high-dose proton pump inhibitors and/or surgery (Chapter 213). Rare ulcers caused by Crohn disease (Chapter 127), vasculitis (Chapter 249), sarcoidosis (Chapter 83), polycythemia vera (Chapter 152), amyloidosis (Chapter 174), and other rare disorders should be addressed by treating the underlying condition. Stress ulcers and Cameron ulcers are treated by potent acid-suppressive therapy (e.g., omeprazole 20 mg twice daily).

Stenosis

Gastric outlet obstruction is now a rare complication of ulcer disease because of the early detection and treatment of most ulcers. Most patients who develop clinically relevant gastric outlet obstruction have had an ulcer in the duodenal bulb and/or pyloric channel. Edema and inflammation play an important role, and occasionally a patient with active disease presents with symptoms of outlet obstruction as manifested by nausea, vomiting, and gastric stasis without a tight, chronic stenosis. Management therefore involves three key steps. The first is nasogastric tube aspiration and gastric lavage to clear the stomach of retained debris, followed by early endoscopy. This step facilitates an accurate diagnosis. Nasogastric suction may need to be maintained for several days if vomiting resumes when the tube is clamped. The second step consists of intense antisecretory therapy using intravenous proton pump inhibitors in a dose equivalent to a bolus of 80 mg esomeprazole over 30 minutes, followed by a continuous infusion of 8 mg/hour. Finally, the cause of the ulcer needs to be addressed, usually by eradicating *H. pylori* and withdrawing NSAIDs. If the initial treatment resolves the clinical situation and the patient can resume eating, it is often not necessary to undertake further treatment of the outlet stenosis; however, tight, fibrous scarring may require endoscopic balloon dilation or surgery.

PROGNOSIS

Most peptic ulcers heal spontaneously within weeks to months. However, if the underlying condition is not adequately treated, a large proportion of ulcers recur. Both initial and recurrent ulcers can give rise to complications. The four major complications are intractability, perforation, hemorrhage, and stenosis. Each distinct situation requires specific management approaches. Patients with complicated ulcer disease are at particular risk for recurrent complications and need careful assessment for secondary prevention. In patients who take long-term acid suppressive therapy, especially with proton pump inhibitors, the risks for community-acquired pneumonia and vitamin B_{12} deficiency (Chapters 150 and 199) are increased but overall mortality is not.[16] The treatment of *H. pylori* infection appears to reduce the risk of gastric cancer.[17,A16]

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126 APPROACH TO THE PATIENT WITH DIARRHEA AND MALABSORPTION

CAROL E. SEMRAD

DEFINITIONS

Normal stool frequency ranges from three times per week to three times per day. As a symptom, diarrhea can be described as a decrease in stool consistency (increased fluidity), stools that cause urgency or abdominal discomfort, or an increase in the frequency of stool. Consistency is defined as the ratio of fecal water to the water-holding capacity of fecal insoluble solids, which are composed of bacterial mass and dietary fiber. Because it is difficult to measure stool consistency and because stool is predominantly (60 to 85%) water, stool weight becomes a reasonable surrogate of consistency.

As a sign, diarrhea is defined by the weight or volume of stool measured over a 24- to 72-hour period. Daily stool weights of children and adults are less than 200 g, and greater stool weights are an objective definition of diarrhea; however, this definition misses 20% of diarrheal symptoms in patients who have loose stools that are less than this daily weight.

Acute diarrheas persist for less than 2 to 3 weeks or, rarely, 6 to 8 weeks. The most common cause of acute diarrhea is infection. Chronic diarrheal conditions persist for at least 4 weeks and, more typically, 6 to 8 weeks or longer. The four mechanisms of diarrhea are osmotic, secretory, exudative, and altered motility. Because many diarrheal diseases are due to more than one of these mechanisms, it is clinically useful to categorize diarrhea as malabsorptive (fatty), watery, and inflammatory.

EPIDEMIOLOGY

Diarrhea is a leading cause of mortality worldwide and is particularly problematic for elderly people and for children younger than 5 years of age in developing nations. Infectious diarrheal conditions cause approximately 445,000 worldwide childhood deaths annually, despite the improved use of oral rehydration solutions, zinc, and vitamin A supplements. Rotavirus infection (Chapter 350) is the most common cause of fatal childhood diarrhea, but the introduction of the oral monovalent rotavirus vaccine has significantly decreased its mortality rate in both developing and developed nations.

ABSTRACT

Diarrhea is one of the most common gastrointestinal problems encountered in the outpatient, emergency department, and hospitalized settings. There are many infectious, dietary, drug, gastrointestinal, extraintestinal, and surgical causes. An understanding of the physiology and pathophysiology of nutrient digestion and intestinal absorption can guide the diagnostic approach. This chapter provides an understanding of key concepts of intestinal physiology, pathophysiology, and clinical presentation to make a specific diagnosis in patients who present with diarrhea or suspected malabsorption.

KEYWORDS

diarrhea
malabsorption
celiac disease
pathobiology

In the United States, norovirus has surpassed rotavirus as the leading cause of gastroenteritis requiring medical care. Approximately 48 million Americans suffer from food-borne illness each year, including about 128,000 annual hospitalizations and 3000 deaths, most in elderly people. The major pathogens that cause diarrhea result in an estimated $17.6 billion in annual health care costs and days lost from work.

PATHOBIOLOGY

Fluid and Electrolyte Transport

Whether a hypotonic meal, such as a steak and water, or a hypertonic meal, such as milk and a doughnut, is consumed, the volume of the meal is augmented by gastric, pancreatic, biliary, and duodenal secretions. The permeable duodenum then renders the meal approximately isotonic with an electrolyte content similar to that of plasma by the time it reaches the proximal jejunum. As the intestinal slurry moves toward the colon, the Na^+ concentration in the luminal fluid remains constant, but Cl^- is reduced to 60 to 70 mmol/L, and bicarbonate (HCO_3^-) is increased to a similar concentration as the result of Cl^- and HCO_3^- transport mechanisms in the enterocyte and HCO_3^- secretion in the ileum (E-Fig. 126-1A and B). In the colon, K^+ is secreted, and the Na^+ transport mechanism of the colonocyte, together with the low epithelial permeability, extracts Na^+ and fluid from the stool. As a result, the Na^+ content of stool decreases to 30 to 40 mmol/L; K^+ increases from 5 to 10 mmol/L in the small bowel to 75 to 90 mmol/L; and poorly absorbed divalent cations, such as Mg^{2+} and Ca^{2+}, are concentrated in stool to values of 5 to 100 mmol/L. The anion concentrations in the colon change drastically because bacterial degradation of carbohydrate (i.e., unabsorbed starches, sugars, and fiber) creates short-chain fatty acids that attain concentrations of 80 to 180 mmol/L; at colonic pH, organic anions, such as acetate, propionate, and butyrate, are present. In the setting of carbohydrate malabsorption, the generation of high concentrations of these short-chain fatty acids may decrease stool pH to 4 or lower. The osmolality of the stool is approximately that of plasma (280 to 300 mOsm/kg H_2O) when it is passed.

At the cellular level, Na^+ transport by the epithelium from lumen to blood (by Na^+-coupled sugar and amino acid transport in the small intestine, by Na^+/H^+ exchange proteins in the small intestine and proximal colon, and by aldosterone-regulated Na^+ channels [ENaC] in the distal colon) creates a favorable osmotic gradient for absorption (see E-Fig. 126-1A and C). Chloride transport by the epithelium from blood to lumen (by cystic fibrosis transmembrane conductance regulator [CFTR] and the calcium-activated chloride channel in the small intestine and colon) creates an osmotic gradient for secretion (see E-Fig. 126-1B). Normally, the intestine is in a net absorptive state, regulated by extrinsic adrenergic nerves and proabsorptive neuropeptides and hormones (see E-Fig. 126-1D). Stimulation of secretion by neurotransmitters, hormones, and inflammatory mediators (Table 126-1) can offset this balance. A heterozygous missense mutation (c.2519 G→T) in GUCY2C on chromosome 12 causes familial diarrhea by increasing GC-C signaling.

Diarrhea is due primarily to alterations of intestinal fluid and electrolyte transport and less to smooth muscle function. Each 24 hours, 8 to 10 L of fluid enters the duodenum. The diet supplies 2 L of this fluid; the remainder comes from salivary, gastric, hepatic, pancreatic, and intestinal secretions. The small intestine normally absorbs 8 to 9 L (80%) of this fluid and presents 1.5 L to the colon for absorption. Of the remaining fluid, the colon absorbs all but approximately 100 mL. Diarrhea can result from increased secretion by the small intestine or the colon if the maximal daily absorptive capacity of the colon (4 L) is exceeded. Alternatively, if the colon is diseased so that it cannot absorb even the 1.5 L normally presented to it by the small intestine, diarrhea results.

Watery diarrheas may be due to osmotic, secretory, or inflammatory mechanisms. With ingestion of a poorly absorbed (e.g., Mg^{2+}) or unabsorbable (polyethylene glycol, lactulose, or, in lactase-deficient individuals, lactose) solute, the osmotic force of the solute pulls water and secondarily sodium and chloride ions into the intestinal lumen. A considerable proportion of the osmolality of stool results from the nonabsorbed solute. This gap between stool osmolality and the sum of the electrolytes in the stool causes osmotic diarrhea.

Active chloride secretion or inhibited sodium absorption, which also creates an osmotic gradient favorable for the movement of fluids from blood to lumen, explains the pathophysiology of the secretory diarrheas. Agents that increase enterocyte cyclic adenosine monophosphate (cAMP) (e.g., cholera toxin, prostaglandins), cyclic guanosine monophosphate (cGMP) (e.g., *Escherichia coli* stable toxin), or intracellular ionized calcium (Ca^{2+}) (e.g., acetylcholine) (see Table 126-1) inhibit non-nutrient Na^+ absorption and stimulate Cl^- secretion (see Table 126-1 and E-Fig. 126-1B and D).

TABLE 126-1 STIMULI OF INTESTINAL SECRETION

AGENT	INTRACELLULAR MEDIATOR	RELATED DIARRHEAL ILLNESS
Cholera, *Escherichia coli* heat labile toxin, *Salmonella, Yersinia*	cAMP	Travelers, endemic
E. coli heat stable toxin	cGMP	Travelers, endemic
Rotatoxin (NSP4)	?	Viral gastroenteritis
Serotonin, PAF	Ca	Inflammatory, allergic
PG, leukotrienes	cAMP, Ca	Invasive enteric bacteria,* inflammatory bowel diseases
PG	cAMP	Villous adenoma
Histamine	Ca	Intestinal allergies, mastocytosis, scombroid poisoning
VIP	cAMP	VIPoma, ganglioneuromas
5-HT, substance P, bradykinin	Ca	Malignant carcinoid
Calcitonin	?	Medullary carcinoma thyroid
Acetylcholine	Ca	Insecticides, nerve gas poisoning, cholinergic drugs
Ricinoleic acid	cAMP, Ca	Laxative abuse†
Caffeine	cAMP	Coffee, sodas, tea

5-HT = 5-hydroxytryptamine; Ca = calcium; cAMP = cyclic adenosine monophosphate; cGMP = cyclic guanosine monophosphate; PAF = platelet-activating factor; PG = prostaglandin; VIP = vasoactive intestinal peptide.

**Shigella* spp, *Clostridioides difficile,* enteroinvasive, *Escherichia coli, Vibrio parahaemolyticus, Clostridium perfringens.*

†Also phenolphthalein, anthraquinone, bisacodyl, dioctyl sodium sulfosuccinate, and senna.

Inflammatory diarrhea, which may be watery or bloody, are characterized by enterocyte damage, villus atrophy, and crypt hyperplasia. The damaged enterocyte membrane of the small intestine has decreased disaccharidase and peptide hydrolase activity, reduced or absent Na^+-coupled sugar or amino acid transport mechanisms, and reduced or absent sodium chloride absorptive transporters. Conversely, the hyperplastic crypt cells maintain their ability to secrete Cl^- (and perhaps HCO_3^-). If the inflammation is severe, immune-mediated vascular damage or ulceration allows blood, pus, and protein to leak (exudate) from capillaries and lymphatics and contribute to the diarrhea. Activation of lymphocytes, phagocytes, and fibroblasts releases various inflammatory mediators that induce intestinal chloride secretion (see E-Fig. 126-1D). Interleukin-1 (IL-1) and tumor necrosis factor (TNF), which also are released into the blood, cause fever, anorexia, and malaise.

ACUTE DIARRHEA

CLINICAL MANIFESTATIONS

Approximately 80% of acute diarrheas are due to infections with viruses, bacteria, and parasites. The remainder are due to medications that have an osmotic force, stimulate intestinal fluid secretion, damage the intestinal epithelium, or contain poorly absorbable or nonabsorbable sugars (e.g., sorbitol), or less commonly fecal impaction, pelvic inflammation (e.g., acute appendicitis [Chapter 128]), or intestinal ischemia (Chapter 129).

Food-Borne and Water-Borne Infectious Diarrhea

Most infectious diarrheas are acquired through fecal-oral transmission from water, food, or person-to-person contact (Table 126-2). Patients with infectious diarrhea often complain of nausea, vomiting, and abdominal cramps that are associated with watery, malabsorptive, or bloody diarrhea and fever (dysentery). As documented using polymerase chain reaction (PCR) methods of diagnosis, most outbreaks of nonbacterial acute gastroenteritis in the United States and other countries are caused by noroviruses (Norwalk agent; Chapter 350). Rotavirus (Chapter 350) predominantly causes diarrhea in infants, usually in the winter months, but also may cause nonseasonal acute diarrhea in adults, particularly in elderly people.[1] Mechanisms for diarrhea include decreased fluid absorption due to destruction of villus enterocytes and stimulation of fluid secretion by NSP4 rotatoxin and viral activation of the enteric nervous system. Ebola virus *(Filoviridae)* infects endothelial cells, macrophages, and dendritic cells. The mechanism for the massive watery diarrhea is not known.

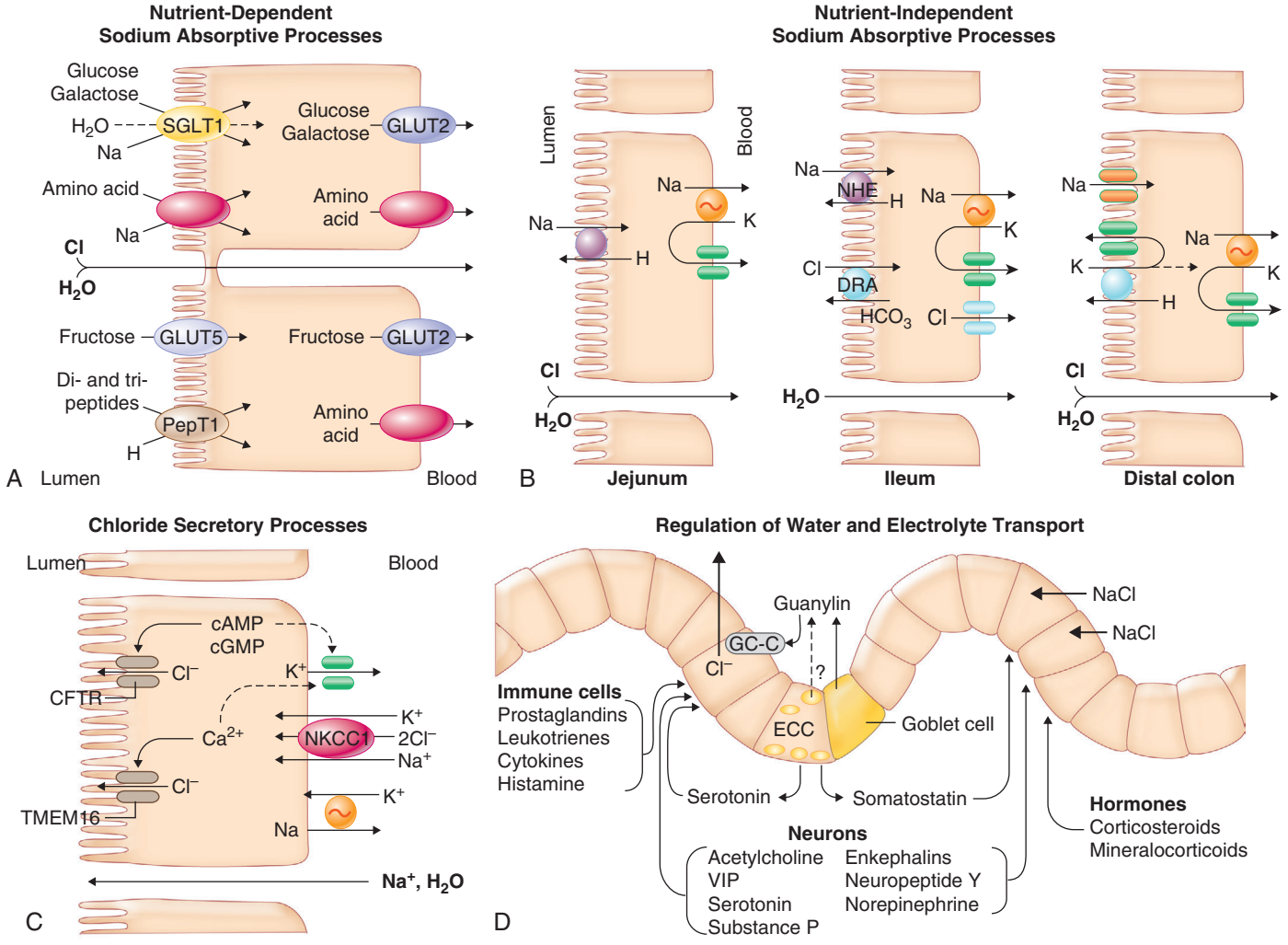

E-FIGURE 126-1. **Mechanisms of intestinal transport of water and electrolytes. A**, Sodium is absorbed by nutrient-dependent and nutrient-independent transport processes in the small intestine and by a sodium channel (ENaC) in the colon. The Na^+/H^+ (NHE) and Cl^-/HCO_3^- (DRA) exchangers are inhibited by agents that elevate intracellular cyclic adenosine monophosphate (cAMP), cyclic guanosine monophosphate (cGMP), or calcium. **B**, Chloride secretion by intestinal crypt cells. Chloride can be secreted actively throughout the small intestine and colon. Intracellular mediators of secretion (cAMP, cGMP, Ca^{2+}) open apical Cl^- channels (cystic fibrosis transmembrane conductance regulator [CFTR], calcium-activated chloride channel [TMEM16]) and basolateral K^+ channels. Chloride moves from crypt cells into the intestinal lumen, favoring movement of Cl^- from the blood into cells by the $Na^+/K^+/2Cl^-$ cotransporter (*NKCC1*). Bicarbonate (HCO_3^-) also may be secreted via the CFTR channel. **C**, Intestinal sodium absorption. Sodium is actively absorbed in villus cells of the small intestine and surface cells of the colon. The sodium-potassium adenosine triphosphatase (Na^+,K^+-ATPase) present on the cell basolateral membrane maintains a low intracellular Na^+ concentration and an electronegative cell interior favoring Na^+ movement across the apical membrane from lumen into cell. In the small intestine, glucose and galactose are taken up with sodium and water at the apical membrane by the sodium-glucose ligand transporter (SGLT1). Several different sodium-dependent amino acid carriers, some with overlapping substrate specificities, transport cationic, anionic, and neutral amino acids into villus cells. Dipeptides and tripeptides are transported by a hydrogen-coupled oligopeptide carrier, *PepT1*, that is driven by luminal hydrogen ions generated by the epithelial Na^+/H^+ exchanger. Fructose is taken up by the facilitative glucose transporter (GLUT5). **D**, Regulation of intestinal water and electrolyte transport. Normally, the intestine is in a net absorptive state under the control of extrinsic adrenergic nerves from the sympathetic nervous system. Guanylin, the natural ligand for the *Escherichia coli* stable-toxin receptor (membrane-bound guanylyl cyclase [GC-C]), may be important in regulating local chloride secretion. The normal tone of the intestine is modified by the enteric nervous system, endocrine and inflammatory cells in the intestinal mucosa, and circulating hormones. The enteric nervous system releases a variety of neurotransmitters, some that stimulate chloride secretion (e.g., vasoactive intestinal peptide [VIP], acetylcholine) and others that promote sodium absorption (e.g., enkephalins, neuropeptide Y). Hormones produced locally from enterochromaffin cells (ECC) in the intestinal epithelium and inflammatory mediators released from immune cells directly affect enterocytes and nearby nerves. Circulating hormones (e.g., aldosterone, glucocorticoids) enhance sodium absorption in the intestine. Glucocorticoids also inhibit release of arachidonic acid and production of prostaglandin by inflammatory cells. DRA (SLC26) = downregulated in adenoma gene; NHE (SLC9) = sodium-hydrogen exchanger.

TABLE 126-2 EPIDEMIOLOGY OF ACUTE INFECTIOUS DIARRHEA AND INFECTIOUS FOOD-BORNE ILLNESS

VEHICLE	CLASSIC PATHOGENS
Water (including foods washed in such water)	*Vibrio cholerae,* norovirus (Norwalk agent), *Giardia, Cryptosporidium*
Food	*Salmonella, Campylobacter, Shigella* spp
Poultry	Enterohemorrhagic *Escherichia coli*
Beef, unpasteurized fruit juice	Tapeworm
Pork	*V. cholerae, Vibrio parahaemolyticus,* and *Vibrio vulnificus; Salmonella* and *Shigella* spp; hepatitis A and B viruses; tapeworm; anisakiasis
Seafood and shellfish (including raw sushi and gefilte fish)	*Listeria* spp
Cheese, milk	*Salmonella* spp
Eggs	Staphylococcal and clostridial food poisonings
Mayonnaise-containing foods and cream pies	*Bacillus cereus*
Fried rice	*Cyclospora* spp
Fresh berries	*Clostridium* spp
Canned vegetables or fruits	Enterohemorrhagic *E. coli, Salmonella* spp
Sprouts	*Salmonella, Campylobacter, Cryptosporidium,* enterohemorrhagic *E. coli,* and *Giardia* spp
Animal-to-person (pets and livestock) contact	All enteric bacteria, viruses, and parasites
Person-to-person (including sexual) contact	*Shigella, Campylobacter, Cryptosporidium,* and *Giardia* spp; viruses; *Clostridioides difficile*
Daycare center	*C. difficile*
Hospitalization, antibiotics, or chemotherapy	*Giardia* and *Cryptosporidium* spp
Swimming pool	*E. coli* of various types; *Salmonella, Shigella, Campylobacter, Giardia,* and *Cryptosporidium* spp; *Entamoeba histolytica*
Foreign travel	

spp = species.
Modified from Powell DW. Approach to the patient with diarrhea. In : Yamada T, Alpers DH, Owyang C, et al, eds. *Textbook of Gastroenterology,* 3rd ed. Philadelphia: Lippincott-Raven; 1999.

The incidence of food-borne bacterial diseases in the United States decreased significantly during the coronavirus disease 2019 (COVID-19) pandemic, in large part because of less international travel but also likely because of increased hand-washing, closure of some child care centers, and decreased restaurant dining.[2] Incidence is highest for *Campylobacter jejuni* (Chapter 279), followed by *Salmonella* (Chapter 284) and *E. coli* O157:H7 (Chapter 280), and less commonly *Shigella* (Chapter 285), *Yersinia, Vibrio* (Chapter 278), *Cyclospora* (Chapter 324), and listeria (Chapter 272). *Vibrio* infection is predominantly due to the consumption of raw shellfish. Outbreaks of *E. coli* O157:H7 have been associated with petting zoos, uncooked ground beef, and green leafy vegetables. These bacteria most often invade the distal small bowel and colon, where they multiply intracellularly and damage the epithelium. Diarrhea is due to the stimulation of intestinal secretion by inflammatory mediators, decreased absorption across the damaged epithelium, and exudation of protein into the lumen. *Shigella* spp and enterohemorrhagic *E. coli* produce a similar toxin, the "Shiga toxin," which is cytotoxic to intestinal epithelial cells and causes inflammation, cell damage, and diarrhea with blood and pus.

Outbreaks of *Cryptosporidium* (Chapter 321) have been reported in water parks. This parasite causes diarrhea by adhering and fusing to the epithelial cell membrane in the small bowel, thereby causing cell damage. Organisms that are specific for seafood include *Vibrio parahaemolyticus* (Chapter 278), which causes either watery or bloody diarrhea, and *Vibrio vulnificus,* which causes watery diarrhea and, especially in patients with liver disease, a fatal septicemia. Ingestion of meat contaminated by anthrax (Chapter 272) causes fever, diffuse abdominal pain, and bloody stool or vomitus. Anthrax invades the intestinal mucosa; the organism, or anthrax toxin, causes inflammation, ulceration, and necrosis.

In addition to enteric infections, certain systemic infections (e.g., viral hepatitis [Chapter 134], listeriosis [Chapter 272], legionellosis [Chapter 290]), mycoplasma, and emerging infections (e.g., Hanta virus [Chapter 351], severe acute respiratory syndrome coronavirus 2 [SARS-CoV-2; Chapter 336], avian influenza [Chapter 332]) may cause or manifest with substantial diarrhea.

Environmental and Food Poisonings

Food poisoning refers to the accumulation of toxin in food owing to the growth of toxin-producing organisms, most commonly *Staphylococcus aureus* (Chapter 267), *Bacillus cereus, Clostridium perfringens* (Chapter 271), and *Clostridium botulinum* (Chapter 271). Diarrhea is usually of rapid onset, as early as 4 hours after ingestion, and is often associated with vomiting. Natural toxins also are responsible for mushroom *(Amanita)* poisoning (Chapter 96), which can also cause acute liver and kidney failure.

Environmental poisonings may be caused by heavy metals (arsenic from rat poison, gold, lead, mercury) that impair cell energy production. Arsenic (Chapter 20) also induces cardiovascular collapse at high doses. Insecticide (organophosphates and carbamates) poisoning occurs most commonly in field workers or from the ingestion of contaminated herbs or teas (Chapter 96); diarrhea, excessive saliva, and pulmonary secretions are caused by acetylcholine-stimulated chloride secretion in intestine and other epithelia. Patients often have associated vomiting and abdominal cramps.

Seafood is a common source of food poisoning, particularly fin fish and bivalve shellfish. Most of these toxins cause varying combinations of gastrointestinal (nausea, vomiting, diarrhea) and neurologic (tingling and burning around the mouth, facial flushing, sweating, headache, palpitations, and dizziness) symptoms within hours of seafood ingestion (Chapter 98). Similar symptoms are reported in patients with scombroid poisoning, which is caused by ingestion of decaying flesh of blood fish (tuna, mahi-mahi, marlin, or mackerel) that release large amounts of histamine (Chapter 98).

Marine dinoflagellates (algae) produce toxins that can cause paralytic shellfish poisoning, diarrhetic shellfish poisoning, and ciguatera (Chapter 98). Sporadic outbreaks of diarrhetic shellfish poisoning "red tides" occur when bivalve mollusks ingest dinoflagellates that produce saxitoxins (voltage-sensitive sodium-channel blocker) and okadaic acid (a lipid-soluble toxin that inhibits serine and threonine protein phosphatases 1 and 2A). Ingestion of contaminated mollusks by humans results in diarrhea and neurologic symptoms. Saxitoxins cause predominantly neurologic symptoms (paralytic, neurotoxic, or amnestic shellfish poisonings) and okadaic acid gastrointestinal symptoms (diarrhetic shellfish poisoning).

Food-chain passage of another dinoflagellate spp *(Gambierdiscus toxicus)* to fin fish (mackerel, amberjack, snapper, grouper, or barracuda) results in the accumulation of ciguatoxin (Chapter 98) that causes a seafood poisoning called ciguatera. Ciguatoxin activates voltage-sensitive sodium channels and causes neurologic and gastrointestinal symptoms. Fish from the Albemarle-Pamlico estuary (eastern United States) ingest toxic dinoflagellates that cause *Pfiesteria piscicida* poisoning. The dinoflagellate toxins cause nausea, vomiting, abdominal pain, diarrhea, and neurologic symptoms such as fatigue, myalgias, pruritus, circumoral paresthesias, reversal of hot and cold sensation, psychiatric abnormalities, and memory loss. The neurologic symptoms may persist for months to years. Puffer fish poisoning by tetrodotoxin, a voltage-sensitive sodium-channel blocker produced by the fish, causes neurologic symptoms, respiratory paralysis, and death.

Traveler's Diarrhea

North American travelers to developing countries and travelers on airplanes and cruise ships are at high risk for acute infectious diarrhea. Common causes of traveler's diarrhea (Chapter 265) include norovirus, enterotoxic or enteroaggregative *E. coli, Shigella,* and giardiasis.[3] *E. coli* heat-stable toxin binds to guanylate cyclase in the enterocyte brush-border membrane, where it results in elevation of intracellular cGMP. *E. coli* heat-labile toxin, similar to cholera toxin, binds to the monosialoganglioside GM_1 in the brush-border membrane,

thereby resulting in the activation of adenylate cyclase and the elevation of intracellular cAMP. cAMP and cGMP stimulate intestinal chloride secretion and inhibit the nutrient-independent absorption of sodium and chloride. Sodium-glucose absorption is not affected, hence the basis for oral rehydration therapy. Cholera toxin permanently binds to adenylate cyclase until the natural turnover of the intestinal epithelium in 5 to 7 days, thereby resulting in persistent secretion and severe diarrhea. DNA sequencing to detect genome sequences of *Vibrio cholerae* isolates suggests human introduction as the cause of recent outbreaks. Of the annual average of six cases of cholera reported in the United States, most are associated with travel.

Antibiotic-Associated Diarrhea

Antibiotics are a common cause of hospital-acquired diarrhea that occurs in approximately 20% of patients receiving broad-spectrum antibiotics, with approximately 30% of cases caused by *Clostridioides difficile* (Chapter 271). Strains that produce increased levels of toxins A and B and a binary toxin have emerged. These strains are associated with an increase in the incidence and severity of *C. difficile* infections, including fulminant *C. difficile* colitis that can lead to colectomy or even death. The A and B toxins produced by *C. difficile* can cause diarrhea. In animal models, IL-8, substance P, and leukotriene B_4 were found to mediate toxin A–stimulated intestinal fluid secretion. *C. difficile* can cause severe diarrhea, pseudomembranous colitis, or toxic megacolon.

Nosocomial Hospital Diarrhea

Diarrhea is the most common nosocomial illness among hospitalized patients and residents in long-term care facilities. Common causes include antibiotic-associated diarrhea, *C. difficile* infection, medications, fecal impaction, tube feeding, and underlying illness. Magnesium-containing laxatives, antacids, and lactulose cause osmotic diarrheas. Bisacodyl laxatives cause secretory diarrhea. Liquid formulations of medications cause diarrhea (elixir diarrhea) because of the high content of sorbitol or other nonabsorbable sugars (e.g., mannitol) used to sweeten the elixir; patients prescribed liquid medications through feeding tubes may receive more than 20 g of sorbitol daily. An important but poorly understood cause of diarrhea is enteral (tube) feeding (Chapter 198), particularly in critically ill patients, who often develop diarrhea. Dysmotility, increased intestinal permeability, and low sodium content in enteral formulas may be contributing factors.

Patients in mental health institutions and nursing homes have a high incidence of nosocomial infectious diarrhea (e.g., *C. difficile* and less commonly *Shigella, Salmonella,* hemorrhagic *E. coli, Giardia, Entamoeba histolytica*). Infectious diarrhea, 50% or more of which is caused by *C. difficile,* is also common in acute care hospitals. Severe *C. difficile* infection also has been reported among peripartum women. If outside foods are not brought to hospitalized patients, the likelihood of a nosocomial infection caused by *Salmonella* or *Shigella* is extremely rare. Immunosuppressed patients are also susceptible to nosocomial viral infections (rotavirus, norovirus, adenovirus, and coxsackievirus).

Cancer Treatment and Medication-Related Diarrhea

Abdominal or whole-body radiation virtually always causes an increased frequency of bowel movements that are often watery. Cancer chemotherapy with amsacrine, azacitidine, cytarabine, dactinomycin, daunorubicin, doxorubicin, floxuridine, 5-fluorouracil, 6-mercaptopurine, methotrexate, plicamycin, IL-2, and resveratrol may cause mild to moderate diarrhea. Irinotecan (CPT-11) or oxaliplatin and the combination of 5-fluorouracil plus leucovorin are frequent causes of severe watery diarrhea.

Immune checkpoint inhibitors of cytotoxic T-lymphocyte antigen (CTLA-4) and programmed death ligand PD-(L) cause diarrhea in up to 40% of patients. Colitis with or without enteritis is the cause. Evaluation of patients with significant diarrhea (>4 stools over baseline) includes exclusion of infection, measurement of fecal calprotectin or lactoferrin, and/or endoscopic biopsies.[4] If unrecognized and untreated, this form of severe colitis can be fatal.

Olmesartan, an angiotensin II receptor antagonist (ARB), causes severe diarrhea as a result of a sprue-like enteropathy. Angiotensin-converting enzyme (ACE) inhibitors may cause abdominal pain and diarrhea resulting from visceral angioedema. Colchicine, neomycin, methotrexate, and *para*-aminosalicylic acid damage the enterocyte membrane. Cholestyramine, colestipol, and colesevelam bind bile salts and can result in malabsorptive diarrhea, especially in patients who have had an ileal resection. Gold therapy causes intestinal inflammation and diarrhea.

Daycare Diarrhea

More than 7 million children in the United States attend daycare, where diarrhea is extremely common, and secondary infection of family members occurs in 10 to 20% of cases. Most outbreaks of diarrhea are due to rotavirus or norovirus; less common causes are *Shigella* (Chapter 285), *Giardia* (Chapter 322), and *Cryptosporidium* (Chapter 321).

Runner's Diarrhea

Diarrhea occurs in 10 to 25% of individuals who exercise vigorously, especially women marathon runners and triathletes. Some athletes have associated abdominal cramps, urgency, nausea, or vomiting. The pathophysiology of runner's diarrhea is unknown. Release of intestinal secretogogues, especially prostaglandins, hormones, or ischemia, may be involved.

DIAGNOSIS

Acute watery diarrhea may be due to infections, food toxins, or medications, or the acute diarrhea may signal the onset of a chronic disease (Fig. 126-1; see Tables 126-1 and 126-2). Multiplex PCR testing on stool is a rapid and sensitive method to detect bacterial, viral, and parasitic pathogens (Chapter 262), but it does not distinguish particles from live organisms or provide antibiotic sensitivity. The diagnostic approach in patients with fever and watery or bloody diarrhea should focus on multiplex PCR testing of stool for pathogens.[5] A positive result requires a culture for antimicrobial sensitivity and contact tracing. A test for *Vibrio* is needed in those who recently traveled to a cholera-endemic area.

Routine stool testing is not indicated when diarrhea occurs after 3 to 5 days of hospitalization, except in patients with neutropenia, human immunodeficiency virus (HIV) infection, or signs of enteric infection. In patients with more than three watery stools daily, particularly patients who have recently used antibiotics, been hospitalized, or are peripartum, a two-test approach is recommended for the diagnosis of *C. difficile* infection (Chapter 271). A positive stool PCR or glutamate dehydrogenase test is followed by an enzyme-based immunoassay for toxins to help distinguish true infection from a carrier state.[6]

Organisms that cause diarrhea but are not routinely cultured by clinical microbiology laboratories include *Yersinia* (Chapter 288), *Plesiomonas,* enterohemorrhagic *E. coli* serotype O157:H7 (Chapter 280), *Aeromonas, Cyclospora,* microsporidia, and noncholera *Vibrio* (Chapter 278). Parasites such as *Giardia* (Chapter 322), *Cryptosporidium* (Chapter 321), and *Strongyloides* (Chapter 327) can be difficult to detect in stool but may be diagnosed by stool antigen testing or intestinal biopsy (Chapter 262).

TREATMENT

Goals for the treatment of diarrhea include fluid replacement, antidiarrheal agents, nutritional support, and antimicrobial therapy when indicated. Because death in patients with acute diarrhea is caused by dehydration, the first task is to assess the degree of dehydration and to replace fluid and electrolyte deficits.

Fluid Replacement

Severely dehydrated patients should be treated with intravenous lactated Ringer solution or saline solution, with additional potassium and bicarbonate as needed. Oral rehydration solutions, which are used extensively to replace diarrheal fluid and electrolyte losses, are effective because they contain sodium, sugars, and, often, amino acids that use nutrient-dependent sodium uptake transporters. In alert patients with mild to moderate dehydration, oral rehydration solution is equally effective as intravenous hydration in repairing fluid and electrolyte losses. Oral rehydration solutions can be given to infants and children in volumes of 50 to 100 mL/kg over 4 to 6 hours; adults may need to drink 1000 mL/hour. Reduced-osmolarity solutions (Na^{2+} 75 mmol/L, osmolarity 245 mmol/L versus Na^{2+} 90 mmol/L, osmolarity 311 mmol/L in standard solutions) are better tolerated and effective in noncholera diarrhea but may cause hyponatremia in patients with high-volume diarrhea, particularly children. Glucose-based solutions, although effective in rehydrating the patient, may worsen the diarrhea. In contrast to glucose-based solutions, polymeric rice-based solutions decrease diarrhea in cholera victims; rice is digested to many glucose monomers that aid in the absorption of intestinal secretions. These solutions may not decrease stool output in acute diarrhea, but they will effectively rehydrate the patient despite continued diarrhea. After rehydration has been accomplished, oral rehydration solutions are given at rates equaling stool loss plus insensible losses until the diarrhea ceases.

Reducing Diarrhea

Bismuth subsalicylate (Pepto-Bismol, 525 mg orally every 30 minutes to 1 hour for five doses, may repeat on day 2) is safe and efficacious in bacterial infectious diarrhea. Opiates and anticholinergic drugs are not recommended for invasive bacterial infectious diarrhea because these drugs paralyze intestinal motility and predispose to increased colonization, invasion, and prolonged excretion of infectious organisms. The opiate loperamide is safe in acute or traveler's diarrhea, provided that it is not given to patients with dysentery (high fever, with blood or pus in the stool), and especially when administered concomitantly with effective antibiotics. A combination of loperamide (2 mg orally four times daily)

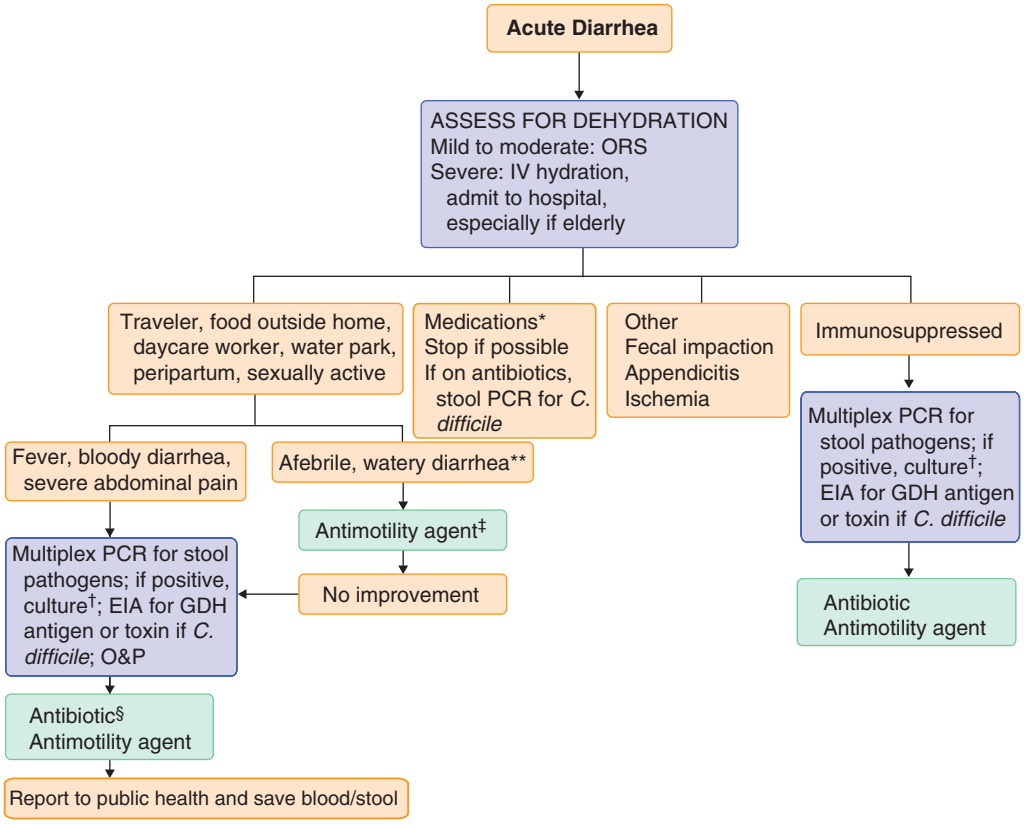

FIGURE 126-1. Approach to the diagnosis of acute diarrhea. *More than 700 medications cause diarrhea, including caffeine, protease inhibitors, immune checkpoint inhibitors, thyroid preparations, metformin, mycophenolate mofetil, sirolimus, cholinergic drugs, colchicine, selective serotonin reuptake inhibitors, proton pump inhibitors, histamine-2 blockers, 5-ASA derivatives, angiotensin-converting enzyme inhibitors and receptor blockers, bisacodyl, senna, aloe, anthraquinones, and magnesium- or phosphorus-containing medications. †Specifically request culture for *Yersinia, Plesiomonas, Vibrio,* enterohemorrhagic *Escherichia coli* serotype O157:H7, and *Aeromonas* if suspected. **_Vibrio_ testing if travel to cholera-endemic area. ‡If high suspicion for *Clostridioides difficile* or invasive bacterial infection, wait for PCR studies before starting. Racecadotril has antisecretory effects without paralyzing intestinal motility and can be used if available. §Not recommended for patients with bloody diarrhea due to *E. coli* O157:H7. EIA = enzyme-based immunoassays; GDH = glutamate dehydrogenase; IV = intravenous; O&P = ova and parasites; ORS = oral rehydration solution; PCR = polymerase chain reaction.

plus simethicone (125 mg orally four times daily) may reduce the abdominal cramps and duration of traveler's diarrhea. Racecadotril (100 mg orally three times daily in adults, 1.5 mg/kg of body weight orally three times daily in children), an intestinal enkephalinase inhibitor that is antisecretory but does not paralyze intestinal motility, is effective in the treatment of acute diarrhea in children and adults. The diarrhea associated with enteral nutrition (Chapter 198) often can be managed with pectin (4 g/kg body weight daily) or, if there are no contraindications, with loperamide (2 mg orally four times daily for 3 to 7 days, maximal dose 16 mg daily), and diarrhea is not a reason to stop tube feeding unless stool volumes exceed 1 L/day.

Anxiolytics (e.g., diazepam 2 mg orally two to four times daily) and antiemetics (e.g., promethazine 12.5 to 25 mg orally once or twice daily) that decrease sensory perception may make symptoms more tolerable and are safe. Some foods or food-derived substances (green bananas, pectins [amylase-resistant starch], zinc) lessen the amount or duration of diarrhea in children. Unabsorbed amylase-resistant starches are metabolized in the colon to short-chain fatty acids that enhance fluid absorption. Zinc supplementation (20 mg of elemental zinc orally once daily) is effective in preventing recurrences of diarrhea in malnourished children; copper deficiency is a potential complication of prolonged zinc therapy. Probiotics are not beneficial in children with acute diarrhea,[A1] but large randomized trials have not been reported in adults.

Antibiotics

While the clinician is awaiting stool culture results to guide specific therapy (Chapter 266), the fluoroquinolones (e.g., ciprofloxacin, 500 mg orally twice daily for 1 to 3 days, or levofloxacin, 500 mg orally daily for 1 to 3 days) are the treatment of choice when antibiotics are indicated (see Fig. 126-1). Trimethoprim-sulfamethoxazole (1 double-strength tablet orally twice daily for 5 days or 2 single-strength tablets orally twice a day for 5 days) is second-line therapy. If the symptom complex suggests *Campylobacter* infection, azithromycin (500 mg/day orally for 3 days) should be added. Regardless of the cause of infectious diarrhea, patients should be treated with antibiotics if they are immunosuppressed; have valvular, vascular, or orthopedic prostheses; have congenital hemolytic anemias (especially if salmonellosis is involved); or are extremely young or old.

Certain infectious diarrheas should be treated with antibiotics, including those associated with shigellosis (Chapter 285), cholera (Chapter 278), pseudomembranous enterocolitis (Chapter 271), parasitic infestations (Chapter 321 to 323), and sexually transmitted diseases (Chapter 264). Treatment of *E. coli* serotype O157:H7 infection is not recommended at present because current antibiotics do not appear to be helpful and the incidence of complications (hemolytic-uremic syndrome) may be greater after antibiotic therapy. Antibiotics are not effective for viral diarrhea or cryptosporidiosis.

For traveler's diarrhea, ciprofloxacin (500 mg orally twice daily for 3 days) is an effective treatment. The nonabsorbable antibiotic rifaximin (200 mg taken orally three times daily or 400 mg twice daily for 3 days) is safe and effective for treatment of traveler's diarrhea in Mexico, but it may not be effective against *Campylobacter* and *Shigella* infections.

Fluoroquinolone-resistant and trimethoprim-sulfamethoxazole–resistant strains of *Shigella, E. coli, Salmonella, Campylobacter*, and *C. difficile* have emerged. Azithromycin (500 mg orally on day 1 and 250 mg/day orally for 4 days) may be an effective alternative treatment for resistant strains of *Shigella* and *Campylobacter* and for traveler's diarrhea acquired in Mexico.

If *C. difficile* is suspected on an epidemiologic basis, fidaxomicin (200 mg orally twice a day for 10 days) is superior to vancomycin (125mg orally four times daily for 10 days)[A2] to prevent of recurrent infection. Other antibiotics and gastric acid suppressants, which are risk factors for recurrent infection, should be discontinued if possible.[7] In patients with recurrent *C. difficile* infection or a high risk for recurrence, immunotherapy with bezlotoxumab (a monoclonal antibody against *C. difficile* toxin B, given as a one-time dose of 10 mg/kg intravenously [IV] infused over 1 hour) decreases recurrence rates.[A3] Fecal microbiota transplantation is more effective than vancomycin for the treatment of recurrences, with resolution rates of 90% compared with 30% for vancomycin.[A4] Non–*C. difficile* antibiotic-induced diarrhea is generally mild and self-limited, and it usually clears spontaneously or in response to cholestyramine therapy (4 g orally four times daily for 2 weeks).

Treatment for chemotherapy-induced and radiation-induced mild to moderate diarrhea includes loperamide (2 mg orally four times daily) and nonsteroidal anti-inflammatory drugs (NSAIDs) (e.g., naproxen, 250 to 500 mg orally twice daily). Octreotide may be an effective treatment in those with severe diarrhea in doses up to 700 μg/day subcutaneously (SQ). Treatment of diarrhea due to checkpoint inhibitor enterocolitis includes discontinuing the offending agent and starting systemic glucocorticoids (the equivalent of 0.5 to 2 mg/kg prednisone given orally or intravenously), with a 4- to 6-week taper. If no response is seen in 72 hours or the response is incomplete after 1 week, infliximab (5 mg/kg) or vedolizumab (300 mg) should be given intravenously at weeks 0, 2, and 6.

PREVENTION

Rotavirus vaccination (Chapter 350) reduces the risk for infection and death and generally results in milder symptoms among those infected. Travelers to high-risk countries (Central America and parts of Latin America, Africa, Asia, the Middle East) should avoid ingestion of tap water and ice and of raw meat, raw seafood, and raw vegetables (Chapter 265). An oral cholera vaccine against recombinant toxin B subunit and killed whole-cell (rBS-WC) is effective in preventing infection from the O1 El Tor strain and partially effective against enterotoxigenic *E. coli* strains. Cholera vaccination is recommended for relief workers and health professionals who work in endemic countries and for individuals who are immunocompromised or have chronic illnesses or hypochlorhydria. To stop cholera outbreaks in endemic countries, vulnerable communities must be vaccinated and have access to clean drinking water.

Bismuth subsalicylate (525 mg orally four times daily for up to 3 weeks) is effective in preventing traveler's diarrhea when compared to placebo. Rifaximin (200 to 1100 mg/day orally for 2 weeks) is effective for reducing the risk for traveler's diarrhea in Mexico and is recommended for those at high risk for health complications.[A5] The combination of rifaximin plus loperamide is better than either one alone. Loperamide and NSAIDs are taken prophylactically by many runners who are susceptible to runner's diarrhea, but it is not clear whether they are effective. Oral probiotics (e.g., lactobacilli and bifidobacteria) are not effective for preventing antibiotic-associated acute diarrhea.

PERSISTENT ACUTE DIARRHEA

Persistent diarrhea for more than 2 weeks develops in about 3% of individuals who travel to developing countries. Common causes include parasitic infections (e.g., *Giardia* [Chapter 322], *Cryptosporidium* [Chapter 321]) and bacterial infections (e.g., enteroaggregative *E. coli* [Chapter 280], *Shigella* [Chapter 285], and *Salmonella* [Chapter 284]). The evaluation should include culture for bacterial pathogens and methods for detecting bacterial, viral, and protozoal infections (e.g., multiplex PCR) as well as microscopy for protozoal infections. Antimicrobial therapy can be empirically given to patients who have recently returned from the developing world but should preferably be given based on the results of laboratory testing.

CHRONIC DIARRHEA

An estimated 5% of the U.S. population suffers from chronic diarrhea, and approximately 40% of these individuals are older than 60 years of age. The causes of chronic diarrhea include persistent infectious or inflammatory diarrheas, malabsorptive syndromes, and watery diarrheas (Table 126-3).

CLINICAL MANIFESTATIONS

Patients with malabsorption (Table 126-4) can present with a variety of gastrointestinal or extraintestinal manifestations (Table 126-5). Significant malabsorption of fat and carbohydrate usually causes chronic diarrhea, abdominal cramps, gas, bloating, and weight loss. Steatorrhea (fat in the stool) manifests as oily, foul-smelling stools that are difficult to flush down the toilet. Stools may be large and bulky (e.g., pancreatic insufficiency) or watery (e.g., bacterial overgrowth, mucosal diseases). Individuals with malabsorption also can present with manifestations of vitamin and mineral deficiencies. Dyspnea can be caused by anemia from iron, copper, folate, or vitamin B_{12} deficiency. Manifestations of calcium, magnesium, or vitamin D malabsorption include paresthesias and tetany resulting from hypocalcemia or hypomagnesemia and bone pain from osteomalacia or osteoporosis-related fractures. Paresthesias and ataxia are manifestations of cobalamin and vitamin E deficiency. Alternatively, neuropathy may be due to malnutrition or copper deficiency. Dermatitis herpetiformis (Chapter 406) is a blistering, burning, itchy rash on the extensor surfaces and buttocks that is associated with celiac disease.

Inflammatory diarrheas may manifest with fever and abdominal pain or with edema to suggest chronic protein loss. Patients may have multiple, low-volume, bloody stools with tenesmus to suggest proctitis or have severe diarrhea as a result of graft-versus-host disease (GVHD) or celiac disease. Systemic manifestations of inflammatory bowel disease include polymigratory arthritis, sacroiliitis, erythema nodosum, pyoderma gangrenosum, leukocytoclastic angiitis, uveitis, and oral aphthous ulcers.

DIAGNOSIS

A detailed history and physical examination lead to a diagnosis in 25 to 50% of patients with chronic diarrheas (see Table 126-1 and Fig. 126-2). In young adults with chronic diarrhea, the leading causes are irritable bowel syndrome, inflammatory bowel disease, microscopic colitis, bile acid diarrhea, malabsorption, drugs, food additives, thyroid disease, and diabetes mellitus. The addition

TABLE 126-3 CAUSES OF CHRONIC DIARRHEA

- Persistent infectious diarrheas (see Table 126-2)
  - Brainerd diarrhea
- Malabsorptive syndromes (see Tables 126-4 and 126-6)
  - Common causes
    - Celiac disease
    - Infection (*Giardia lamblia,* HIV/AIDS-related)
    - Tropical sprue
    - Crohn disease
    - Radiation enteritis
    - Gastric bypass surgery
    - Dumping syndrome
    - Chronic pancreatitis
    - Intestinal bacterial overgrowth
- Watery diarrhea
    - Osmotic diarrhea
    - Disaccharidase deficiencies (lactase, sucrase)
    - Magnesium, sodium phosphate, sulfate
    - Sorbitol, fructose
  - Alcohol
  - Factitious
  - Functional watery diarrhea (irritable bowel syndrome)
- Pure secretory
  - Hormone-secreting tumors (VIPoma, neuroendocrine, gastrinoma, medullary thyroid cancer)
  - Systemic mastocytosis
  - Villous adenoma
- Idiopathic
- Inflammatory diarrheas
  - Inflammatory bowel disease
  - Eosinophilic gastroenteritis
  - Microscopic colitis (collagenous or lymphocytic)
  - Food allergy

AIDS = acquired immunodeficiency syndrome; HIV = human immunodeficiency virus; VIP = vasoactive intestinal peptide.

TABLE 126-4 CAUSES OF MALABSORPTION

MECHANISM OF MALABSORPTION	CONDITIONS
Impaired mixing	Partial/total gastrectomy Gastric bypass surgery
Impaired lipolysis	Chronic pancreatitis Pancreatic cancer Congenital lipase or colipase deficiency Gastrinoma
Impaired micelle formation	Severe liver disease Bacterial overgrowth Crohn disease Ileal resection Gastrinoma
Impaired mucosal absorption	Lactase deficiency Abetalipoproteinemia Giardiasis Celiac disease Tropical sprue Agammaglobulinemia Amyloidosis AIDS-related Radiation enteritis Graft-versus-host disease Whipple disease Eosinophilic gastroenteritis Drugs Lymphoma Autoimmune enteritis Short-bowel syndrome
Impaired nutrient delivery	Congenital lymphangiectasia Lymphoma Tuberculosis Constrictive pericarditis Severe congestive heart failure
Unknown	Hypoparathyroidism Adrenal insufficiency Hyperthyroidism Carcinoid syndrome

AIDS = acquired immunodeficiency syndrome.

TABLE 126-5 CLINICAL CONSEQUENCES OF MALABSORPTION OF NUTRIENTS, WATER, AND ELECTROLYTES

NUTRIENT MALABSORBED	CLINICAL MANIFESTATION
Protein	Wasting, edema
Carbohydrate and fat	Diarrhea, abdominal cramps and bloating, weight loss, growth retardation
Fluid and electrolytes	Diarrhea, dehydration
Iron	Anemia, cheilosis, angular stomatitis
Calcium and vitamin D	Bone pain, fractures, tetany
Magnesium	Paresthesias, tetany
Vitamin B_{12} and folate	Anemia, glossitis, cheilosis, paresthesias, ataxia (vitamin B_{12} only)
Vitamin E	Paresthesias, ataxia, retinopathy
Vitamin A	Night blindness, xerophthalmia, hyperkeratosis, diarrhea
Vitamin K	Ecchymoses
Riboflavin	Angular stomatitis, cheilosis
Zinc	Dermatitis, hypogeusia, diarrhea
Selenium	Cardiomyopathy
Essential fatty acids	Dermatitis
Copper	Anemia, mental deterioration, neuropathy

of stool culture and examination for ova and parasites, determination of stool fat, and flexible sigmoidoscopy or colonoscopy with biopsy raises the diagnostic rate to approximately 75%. The remaining 25% of patients with chronic diarrhea may need extensive testing and perhaps hospitalization to make a diagnosis.

A history of 10 to 20 daily bowel movements that do not respond to fasting suggests secretory diarrhea (Fig. 126-3).[8] A history of peptic ulcer should suggest gastrinoma (Chapter 213) or systemic mastocytosis (Chapter 235). Physical examination is helpful only if the thyromegaly of medullary carcinoma (Chapter 207), the cutaneous flushing of the neuroendocrine tumors and systemic mastocytosis, the dermatographism of systemic mastocytosis, or the migratory necrolytic erythema of glucagonoma (Chapter 213) is evident. Autonomic dysfunction (e.g., postural hypotension, impotence, gustatory sweating) is almost invariably present in diabetic diarrhea.

Evaluation for malabsorption begins with a careful elicitation of bowel habits and a description of the stool; weight loss; travel; food or milk tolerance; underlying gastrointestinal, pancreatic, or liver diseases; abdominal surgery; radiation or chemotherapy treatments; family history; and drug and alcohol use.

Blood Tests

Blood measurements (see Fig. 126-2) of iron, folate, vitamin B_{12}, prothrombin time (vitamin K), and other fat-soluble vitamins (A, E, and D) help evaluate malabsorption. Specific antibody tests should be sent when celiac disease is suspected (see later). Peripheral blood findings of leukocytosis, eosinophilia, elevated erythrocyte sedimentation rate or C-reactive protein, hypoalbuminemia, or low total serum protein suggest an inflammatory diarrhea, whose hallmark is the presence of blood, either overt or occult, and leukocytes or calprotectin (a nondegradable leukocyte protein) in the stool.

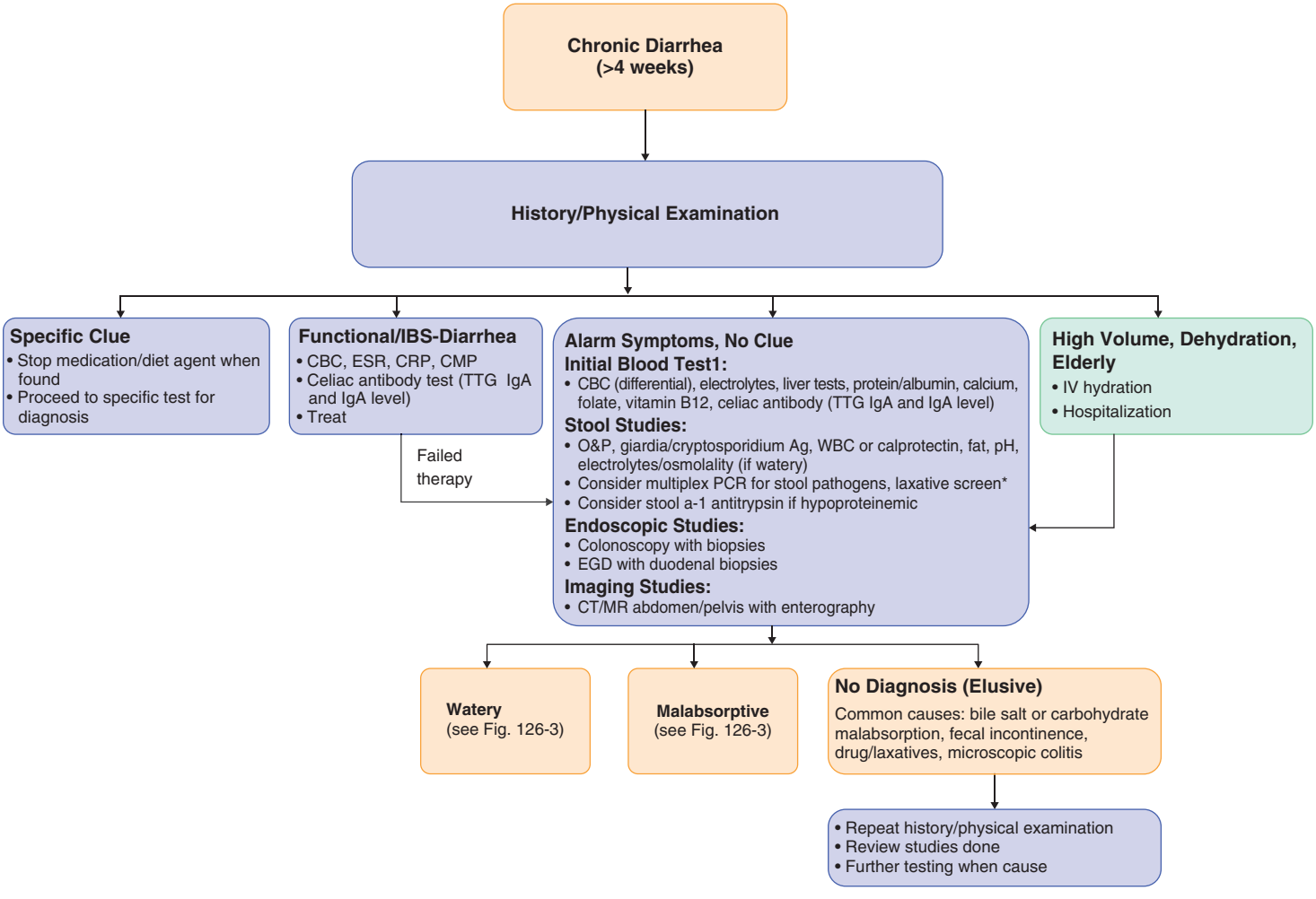

FIGURE 126-2. Initial approach to chronic diarrhea. *Perform multiplex PCR for stool pathogens in those who are immunosuppressed; perform laxative screen if laxative abuse is suspected. Ag = antigen; CBC = complete blood count; CMP = comprehensive metabolic panel; CRP = C-reactive protein; CT = computed tomography; EGD = esophagogastroduodenoscopy; EIA = enzyme-based immunoassay; ESR = erythrocyte sedimentation rate; IgA = immunoglobulin A; IV = intravenous; MR = magnetic resonance; O&P = ova and parasites; PCR = polymerase chain reaction; TTG = tissue transglutaminase; WBC = white blood cells.

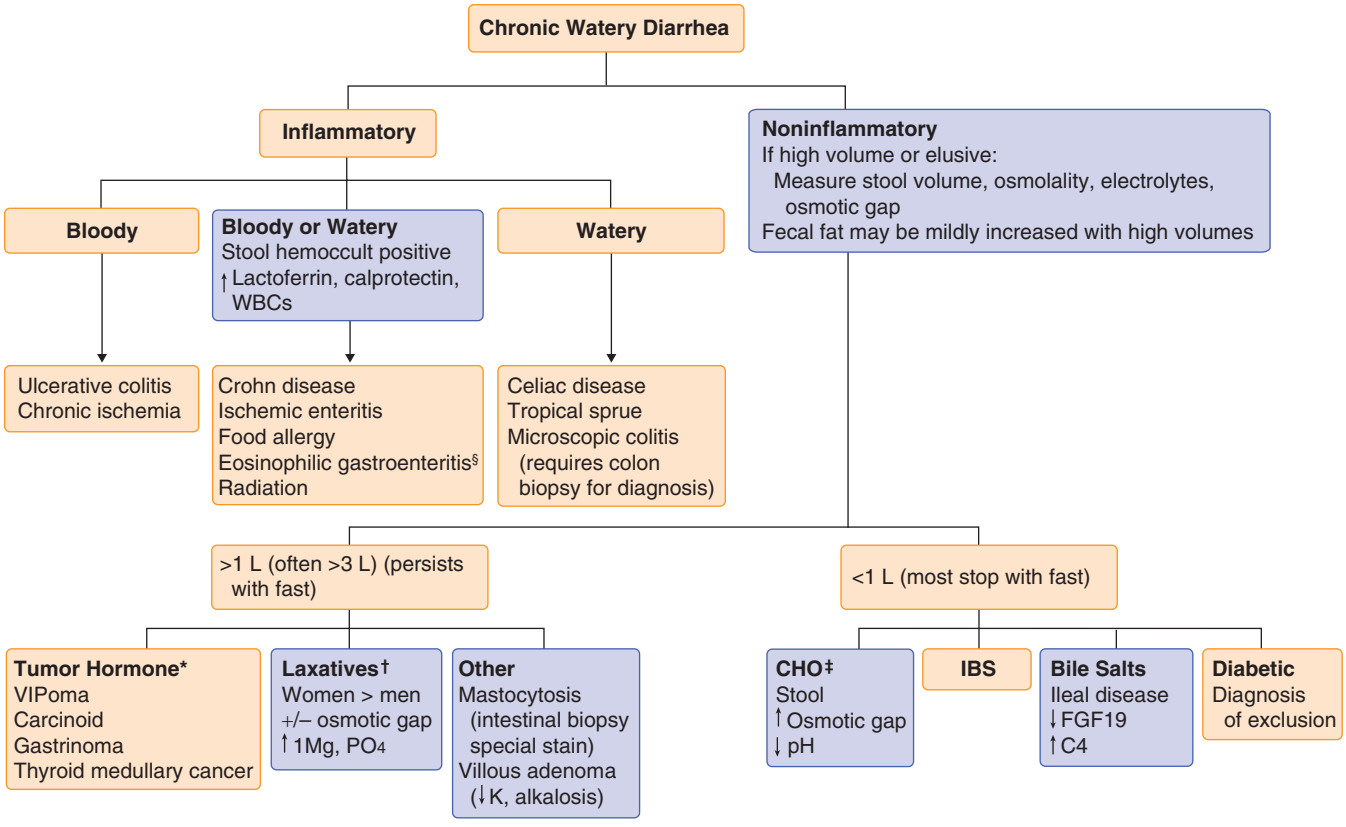

FIGURE 126-3. Approach to the evaluation of watery diarrhea. Many diarrheas have more than one mechanism (i.e., osmotic, secretory, inflammatory). Other causes include medications, postsurgical (vagotomy, Nissan wrap, cholecystectomy), hyperthyroidism, and alcohol. *VIPoma: >3 L output daily "pancreatic cholera," elevated VIP level. Carcinoid: elevated urine 5-hydroxyindole acetic acid, positive OctreoScan. Gastrinoma: elevated gastrin level, positive secretin stimulation test, diarrhea due to high volume of acid secretion. Thyroid medullary cancer: elevated calcitonin level. †Stool volume may be high or low volume depending on dose ingested, may respond to fasting. ‡Carbohydrate malabsorption (CHO) may be due to lactase deficiency, dietary fructose, sorbitol in diabetic candies or liquid medications. §Full-thickness biopsy may be needed for diagnosis. C4 = 7α-hydroxy-4-cholesten-3-one; FGF = fibroblast growth factor; IBS = irritable bowel syndrome; WBCs = white blood cells.

Imaging

Malabsorption may be suggested if a flat plate radiograph of the abdomen shows pancreatic calcification (Chapter 119). Some diseases (e.g., previous gastric surgery, gastrocolic fistulas, blind loops from previous intestinal anastomoses, small intestine strictures, multiple jejunal diverticula, abnormal intestinal motility that could lead to bacterial overgrowth) may be shown by computed tomography (CT) or magnetic resonance imaging (MRI) of the abdomen after administration of oral contrast agents or by a traditional upper gastrointestinal and small bowel barium studies. CT or magnetic resonance (MR) enterography, which uses oral neutral contrast to enhance the bowel wall, may show diagnostic evidence of advanced inflammatory bowel disease or changes suggestive of lymphoma, eosinophilic gastroenteritis, or radiation enterocolitis. Somatostatin receptor scintigraphy with gallium-68 or copper-64–labeled dotatate positron emission tomography (PET) scan is useful in localizing neuroendocrine tumors.

Endoscopy and Biopsy

Upper endoscopy with duodenal biopsies should be undertaken if serologic tests for celiac disease are positive or diagnostic clues suggest small bowel mucosal malabsorption (Chapter 120). Some patients with celiac disease may have mild inflammation or patchy mucosal disease and require duodenal bulb biopsies or enteroscopy with jejunal biopsies for diagnosis. Wireless video capsule endoscopy (Chapter 120) and balloon-assisted enteroscopy are used to diagnose refractory celiac disease and other diseases that reside deep in the small bowel. Patients with severe watery or elusive diarrhea should have a colonoscopy to the terminal ileum to assess for villous adenomas, microscopic colitis, mastocytosis, or early inflammatory bowel disease. Colonoscopy also may show brown pigmentation suggestive of melanosis coli due to chronic use of anthracene laxatives. Terminal ileal ulcers may indicate infectious or inflammatory bowel disease.

Other Laboratory Tests

Malabsorption

If chronic diarrhea is the presenting symptom, a stool examination for ova and parasites and a PCR test for *Giardia* or stool antigen-capture enzyme-linked immunosorbent assay (ELISA) should be obtained. A stool test for fat on a high-fat diet (70 to 100 g/day) is the best available screening test for malabsorption (Table 126-6). If the fecal fat test result is negative, selective carbohydrate malabsorption or other causes of watery diarrhea should be considered. If the fecal fat test result is positive, further testing should be based on clinical suspicion for particular diseases. If pancreatic insufficiency is suspected, imaging studies of the pancreas should be performed. If bacterial overgrowth is suspected, culture of an intestinal aspirate or a breath test should be obtained. Small bowel contrast imaging is useful in detecting structural abnormalities that predispose to bacterial overgrowth (Table 126-7). If proximal mucosal damage is suspected, multiple duodenal biopsies should be obtained. If there are no clues, CT or MR enterography may help to detect middle and distal small bowel mucosal diseases. Some individuals with celiac disease present with selective nutrient deficiencies without diarrhea. In these cases, a tissue transglutaminase (tTG) immunoglobulin A (IgA) antibody test and total IgA level should be performed. In patients hospitalized for severe diarrhea or malnutrition, a more streamlined evaluation usually includes a multiplex PCR stool test for pathogens; stool fat test; an abdominal imaging study; and a biopsy of the small intestine and colon.

Watery Diarrhea

Breath tests to measure the respiratory excretion of H_2 and methane after administration of carbohydrates can assess carbohydrate malabsorption or bacterial overgrowth (see Table 126-6).

The diagnosis of rare neuroendocrine tumors, such as carcinoids, gastrinoma, VIPoma, medullary carcinoma of the thyroid, glucagonoma, somatostatinoma, and systemic mastocytosis, is made by showing elevated blood levels of serotonin, chromogranin A, or urinary 5-hydroxyindoleacetic acid and serum levels for gastrin, vasoactive intestinal peptide, calcitonin, glucagon, somatostatin, histamine, or prostaglandins (Chapter 213). Somatostatin receptor scintigraphy and PET dotatate scanning are useful in the diagnosis and evaluation of neurodendocrine tumors (Chapter 213).

TABLE 126-6 TESTS FOR THE EVALUATION OF MALABSORPTION*

TEST	COMMENTS
GENERAL TESTS OF ABSORPTION	
Quantitative stool fat test	Gold standard test of fat malabsorption. Requires ingestion of a high-fat diet (70-100 g) for 2 days before and during the collection. Stool is collected for 2-3 days. Normally, <7 g/24 hr is excreted on a high-fat diet. Borderline abnormalities of 8-14 g/24 hr may be seen in secretory or osmotic diarrheas that are not caused by malabsorption. There are false-negative findings if fat intake is inadequate. False-positive results can occur if the nonabsorbable fat olestra is ingested or mineral oil laxatives or rectal suppositories (e.g., cocoa butter) are given to the patient before stool collection.
Qualitative stool fat test	The nuclear magnetic resonance method determines the percentage of fat in the stool (normal, <20%). The test depends on an adequate fat intake (100 g/day). There is high sensitivity (90%) and specificity (90%) with fat malabsorption of >10 g/24 hr. Sensitivity drops with stool fat in the range of 6-10 g/24 hr.
Hydrogen breath test	Most useful in the diagnosis of lactase deficiency. An oral dose of lactose (25 g) is administered after measurement of basal breath H_2 levels. The sole source of H_2 in the mammal is bacterial fermentation; unabsorbed lactose makes its way to colonic bacteria, resulting in excess breath H_2. A *late peak* within 3-6 hr of >20 ppm of exhaled H_2 after lactose ingestion suggests lactose malabsorption. Absorption of other carbohydrates (e.g., sucrose, glucose, fructose) also can be tested.
SPECIFIC TESTS FOR MALABSORPTION	
Tests for Pancreatic Function	
Secretin stimulation test	The gold standard test of pancreatic function. Requires duodenal intubation with a double-lumen tube and collection of pancreatic juice in response to intravenous secretin. Allows measurement of bicarbonate (HCO_3^-) and pancreatic enzymes. A sensitive test of pancreatic function, but labor intensive and invasive.
Secretin-enhanced MRCP	Noninvasive test for the detection of exocrine dysfunction in early chronic pancreatitis. The signal intensity ratio of pancreas to spleen has a significant positive correlation with the pancreatic fluid bicarbonate level as measured by the ductal secretin test. A ratio of 1 : 2 has a 77% sensitivity and 83% specificity for diagnosing pancreatic exocrine dysfunction, and it also has a strong correlation with histopathology of non-calcific chronic pancreatitis.
Fecal elastase-1 test	Stool test for pancreatic function. Equal sensitivity to the secretin stimulation test for the diagnosis of moderate to severe pancreatic insufficiency. Unreliable with mild insufficiency. False-positive results occur with increased stool volume and intestinal mucosal diseases.
Tests for Bacterial Overgrowth	
Quantitative culture of small intestinal aspirate	Gold standard test for bacterial overgrowth. Greater than 10^3 colony-forming units (CFU)/mL in the jejunum suggests bacterial overgrowth. Requires special anaerobic sample collection, rapid anaerobic and aerobic plating, and care to avoid oropharyngeal contamination. False-negative results occur with focal jejunal diverticula and when overgrowth is distal to the site aspirated.
Hydrogen breath test	The 50-g glucose breath test has a sensitivity of 90% for growth of 10^5 colonic-type bacteria in the small intestine. If bacterial overgrowth is present, increased H_2 is excreted in the breath. An early hydrogen level (<90 min) of >20 ppm suggests bacterial overgrowth. Specificity is increased when performed with simultaneous nuclear scintigraphy to define transit time to the cecum. False-positive results occur in patients with rapid transit. False-negative results occur with non–hydrogen-producing organisms. Concomitant measurement of breath methane improves test sensitivity.
Tests for Mucosal Disease	
Small bowel biopsy	Obtained for a specific diagnosis when there is a high index of suspicion for small intestinal disease. Several biopsy specimens (4-5) must be obtained to maximize the diagnostic yield. Distal duodenal biopsy specimens are usually adequate for diagnosis, but occasionally duodenal bulb biopsies or enteroscopy with jejunal biopsy specimens is necessary. Small intestinal biopsy provides a specific diagnosis in some diseases (e.g., intestinal infection, Whipple disease, abetalipoproteinemia, agammaglobulinemia, lymphangiectasia, lymphoma, amyloidosis). In other conditions, such as celiac disease and tropical sprue, the biopsy specimens show characteristic findings, but the diagnosis is made by positive celiac serology or improvement after specific treatment.
Test of Ileal Function	
^{75}SeHCAT test	This is a test of bile acid absorption. Seven days after ingestion of radiolabeled synthetic selenium–homocholic acid conjugated with taurine (^{75}SeHCAT), whole-body retention is measured by a gamma-counting device. The result is expressed as a fraction of baseline ingestion. Retention values of <10% are abnormal and indicate bile acid malabsorption with a sensitivity of 80-90% and specificity of 70-100%. The radiation dose is equivalent to that of a plain chest x-ray. Liver disease and bacterial overgrowth may give false results. Not approved for use in the United States.

*Not all these tests are readily available. A strong suspicion for any disease warrants forgoing an extensive work-up and obtaining the test with highest diagnostic yield. In some cases, empirical treatment, such as removing lactose from the diet of an otherwise healthy individual with lactose intolerance, is warranted without any testing.
MRCP = magnetic resonance cholangiopancreatography.

Inflammatory Diarrhea

Stool occult blood, white blood cells, and calprotectin are helpful tests for bowel inflammation. Video capsule endoscopy of the small bowel may detect ulcerations deep in the small bowel not reachable by standard upper or lower endoscopy and not detected with conventional radiologic imaging. However, the risk for capsule retention in the small bowel is high in patients with Crohn disease or heavy NSAID use, particularly when there is a history of obstructive symptoms. The most sensitive test for protein-losing enteropathy is measurement of intestinal protein loss by 24-hour stool excretion or clearance of α_1-antitrypsin.

Stool Examination in Elusive Diarrhea

An important adjunct to diagnosing the cause of diarrhea is to examine the stool. The greasy, bulky stool of steatorrhea and the bloody stool of gut inflammation are distinctive. Stool collections (see Table 126-6) can be analyzed for weight, volume, fat, electrolytes (Na^+, K^+, Cl^-), osmolality, pH, and a laxative screen (SO_4^{2-}, PO_4^{2-}, Mg^{2+}). Stool or urine can be analyzed for emetine (a component of ipecac), bisacodyl, castor oil, or anthraquinone.

Carbohydrate malabsorption lowers stool pH because of colonic fermentation of carbohydrate to short-chain fatty acids. Stool pH less than 5.3 usually means pure carbohydrate malabsorption, whereas in the generalized malabsorptive diseases, stool pH is greater than 5.6 and usually greater than 6.0.

The normal stool osmotic gap, which is the difference between stool osmolality (or 290 mOsm) and twice the stool Na^+ and K^+ concentrations, is 50 to 125. In secretory diarrheas, the colon's capacity for adjusting electrolyte concentrations is overwhelmed, the stool osmotic gap is less than 50, and stool electrolytes more nearly resemble plasma electrolytes (Na^+ concentrations are usually >90 mmol/L, K^+ concentrations usually <10 mmol/L), except for higher HCO_3^- concentrations (usually >50 mmol/L). In osmotic diarrhea, the

TABLE 126-7 ABNORMALITIES CONDUCIVE TO BACTERIAL OVERGROWTH

STRUCTURAL
Blind intestinal loops
End or side-to-side intestinal anastomoses
Ileocecal valve resection
Duodenal and jejunal diverticula
Strictures (Crohn disease, radiation enteritis)
Adhesions (postsurgical)
Gastrojejunocolic fistulas
MOTOR
Scleroderma
Diabetes mellitus
Idiopathic pseudo-obstruction
HYPOCHLORHYDRIA
Atrophic gastritis
Proton pump inhibitors
MISCELLANEOUS
Immunodeficiency states
Pancreatitis
Cirrhosis
Chronic renal failure

presence of uncharged solute or unmeasured cation in the colonic lumen draws in water, depresses stool Na^+ (usually <60 mmol/L) and K^+ concentrations, and results in a stool osmotic gap greater than 125. Stools with Na^+ concentrations between 60 and 90 mmol/L and calculated osmotic gaps between 50 and 100 can result from either secretory or malabsorptive abnormalities. Patients with Mg^{2+}-induced diarrhea may be diagnosed by fecal Mg^{2+} values of more than 50 mmol/L. Sodium anion–induced diarrheas (Na_2SO_4, Na_2PO_4) mimic secretory diarrhea because the stool Na^+ content is high (>90 mmol/L) and there is no osmotic gap; this diarrhea may be diagnosed by determining stool Cl^- concentration because these anions displace stool Cl^-, resulting in a depressed stool Cl^- value (usually <20 mmol/L). A low stool osmolality suggests contamination of stool with dilute urine or water in the case of factitious diarrhea.

SPECIFIC CAUSES OF CHRONIC DIARRHEA

PROLONGED, PERSISTENT INFECTIOUS DIARRHEAS

Prolonged infectious diarrheas (>2 weeks) may be due to persistent or recurrent infections. These diarrheas occur most commonly in children exposed to unsafe drinking water in developing countries, patients who have acquired immunodeficiency syndrome (AIDS) or are immunosuppressed for other reasons, and recent travelers. Recurrent or prolonged infectious diarrhea may lead to severe malnutrition and death (mortality rate, 50%). Treatment for children includes nutrition support with supplemental vitamin A (200,000 IU orally twice yearly) and zinc (20 mg elemental orally daily for 14 days). Severe disease may require total parenteral nutrition.

In patients with AIDS, protracted diarrhea may be caused by treatable agents such as *E. histolytica, Giardia*, or *Strongyloides* or by organisms such as *Cryptosporidium, Isospora belli,* and microsporidia that are difficult to treat or untreatable. The most effective treatment is retroviral therapy to improve the immune system (Chapter 357).

In travelers returning from developing countries who have infectious diarrhea that persists for longer than 3 to 4 weeks, stool should be examined for culture and for ova and parasites. In patients with a recent history of antibiotic use, stool also should be sent for *C. difficile* toxin or PCR. Any specific organisms that are identified should be treated. If treatment with trimethoprim-sulfamethoxazole or a fluoroquinolone has been unsuccessful, tetracycline (250 mg orally four times daily for 7 to 10 days), doxycycline (100 mg orally two times a day for 7 to 10 days), or metronidazole (250 mg orally three times daily for 7 to 10 days) can be tried. After documented infectious diarrhea, 25% of patients experience pain, bloating, urgency, a sense of incomplete evacuation, and loose stools for 6 months or longer; some of these patients have celiac disease, so screening (see later) is warranted in this setting. When no other cause is found, these patients are deemed to have postinfectious irritable bowel syndrome.

Sporadic outbreaks of severe, prolonged diarrhea, often greater than 1 year in duration, occasionally have been reported. This form of prolonged diarrhea is called *Brainerd diarrhea*. The organism has yet to be identified. The diarrhea is difficult to treat; cholestyramine (4 g orally three times daily) may be helpful.

MALABSORPTIVE SYNDROMES

Malabsorption is caused by many different diseases, drugs (e.g., the lipase inhibitor orlistat; Chapter 201), and nutritional products (the nonabsorbable fat olestra) that impair intraluminal digestion, mucosal absorption, or delivery of the nutrient to the systemic circulation (E-Fig. 126-2; see Table 126-4). Dietary fat is the nutrient most difficult to absorb. Fatty stools (steatorrhea) are the hallmark of malabsorption; a stool test for fat is the best screening test. Malabsorption does not always cause diarrhea. Clinical signs of vitamin or mineral deficiencies may occur in the absence of diarrhea. A careful focused history is crucial in guiding further testing to confirm the suspicion of malabsorption and to make a specific diagnosis (Fig. 126-4). The goals of treatment are to correct or treat the underlying disease and replenish losses of water, electrolytes, and nutrients.

CONDITIONS THAT IMPAIR INTRALUMINAL DIGESTION

Most digestion and absorption of nutrients occur in the small intestine (see E-Fig. 126-2). Carbohydrates and most dietary proteins are water soluble and readily digested by pancreatic enzymes. Pancreatic proteases (trypsinogen, chymotrypsinogen, procarboxypeptidases) are secreted from acinar cells in inactive forms. The cleavage of trypsinogen to trypsin by the duodenal brush-border peptidase enteropeptidase (enterokinase) allows trypsin to cleave the remaining trypsinogen and other proteases to their active form.

Most dietary lipids (long-chain triglycerides, cholesterol, and fat-soluble vitamins) are water insoluble and must undergo lipolysis and incorporation into mixed micelles before they can be absorbed across the intestinal mucosa. Pancreatic lipase, in the presence of its cofactor, colipase, cleaves long-chain triglycerides into fatty acids and monoglycerides. The products of lipolysis interact with bile salts and phospholipids to form mixed micelles, which also incorporate cholesterol and fat-soluble vitamins (D, A, K, and E) in their hydrophobic centers. Bicarbonate secreted from pancreatic duct cells is physiologically important to neutralize gastric acid because pancreatic enzyme activity and bile salt micelle formation are optimum at a luminal pH of 6 to 8.

IMPAIRED MIXING

Surgical alterations, such as partial gastrectomy with gastrojejunostomy (Billroth II anastomosis) or gastrointestinal bypass surgeries for obesity, result in the release of biliary and pancreatic secretions into the intestine at a site remote from the site of entry of gastric contents. This imbalance can result in impaired lipolysis and impaired micelle formation, with subsequent fat malabsorption. Bypass of the duodenum also impairs absorption of iron, folate, and calcium. Rapid transit through the jejunum contributes to the malabsorption of nutrients. Individuals with these conditions also have surgical anastomoses that predispose to bacterial overgrowth.

DUMPING SYNDROME

After esophageal (distal esophagectomy, myotomy for achalasia), gastric (gastrectomy, non–pylorus-sparing Whipple surgery, gastrojejunostomy, Nissan wrap, and hiatal hernia repair), and bariatric (Roux-en-Y gastric bypass) surgeries, the unregulated delivery of concentrated sugars and food into the duodenum and jejunum results in altered insulin regulation, maldigestion, osmotic movement of fluid into the intestinal lumen, and rapid transit such that intestinal contact time is insufficient for absorption of nutrients. Glucagon-like peptide-1 (GLP-1) plays a key role in the pathophysiologic response of hyperinsulinemic hypoglycemia following the ingestion of concentrated sweets.[9] Patients may present with severe diarrhea, malabsorption, abdominal cramping, gas, and weight loss. Some patients have associated sweatiness, dizziness, and altered cognition because of postprandial hypoglycemia. Diagnosis is made by characteristic symptoms and a mixed meal tolerance test or continuous glucose monitoring for hypoglycemia.

Treatment is with a diet that is low in concentrated sugars divided into six small meals. Administration of pectin (15 g with each meal) may slow gastric emptying in patients who have a stomach. In patients who are refractory to dietary measures, a short-acting somatostatin analogue (e.g., octreotide, 25

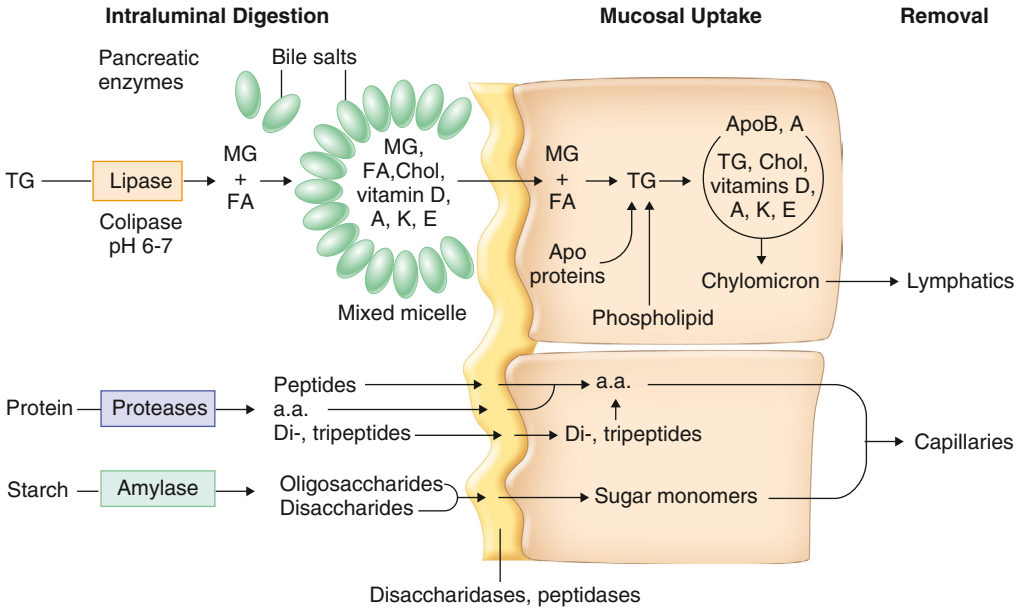

E-FIGURE 126-2. Phases of intestinal digestion and absorption of dietary fat, protein, and carbohydrate. a.a. = amino acids; ApoB, A = apolipoproteins B and A; Chol = cholesterol; FA = fatty acids; MG = monoglycerides; TG = triglycerides.

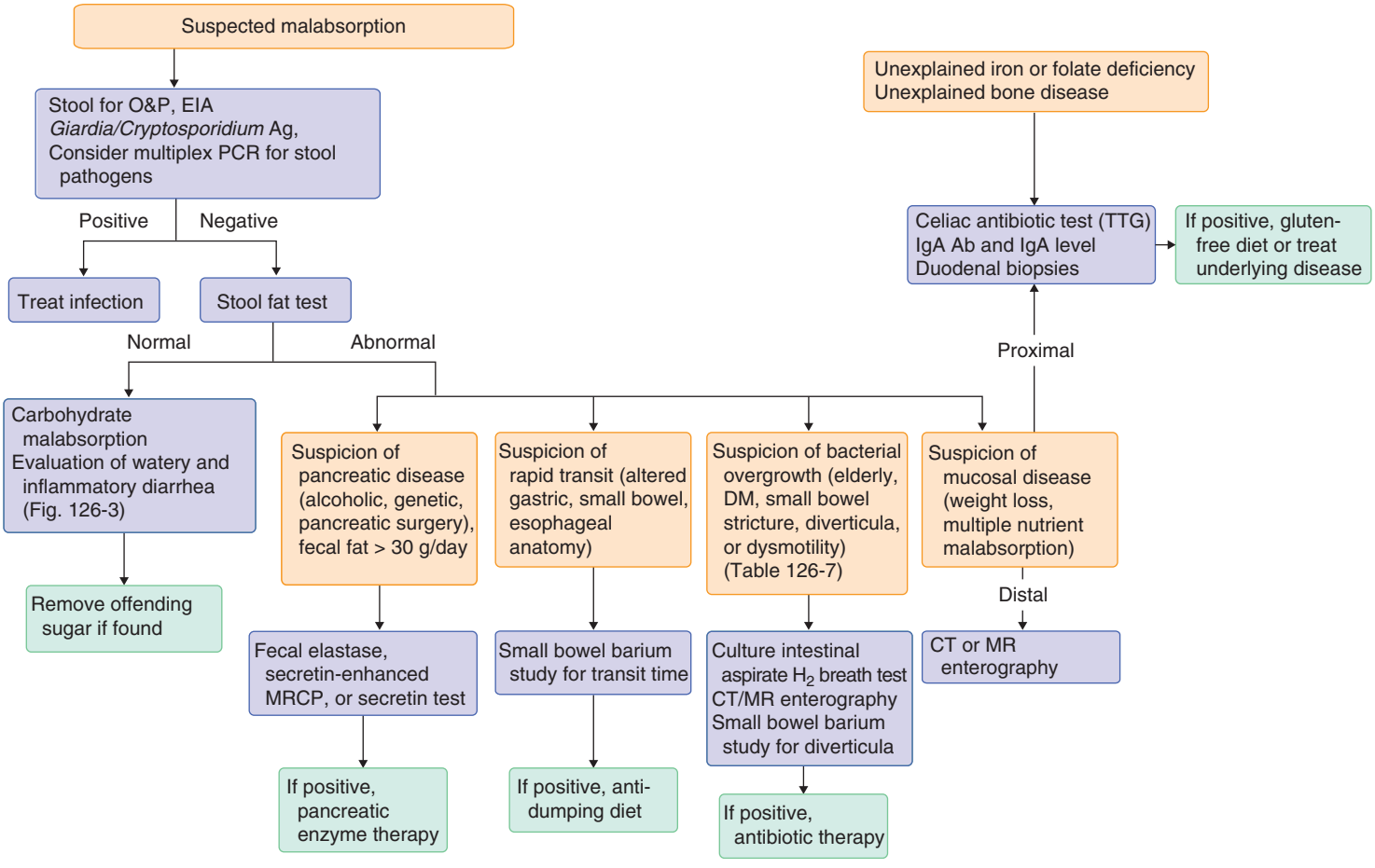

FIGURE 126-4. Approach to the diagnosis of malabsorption. Ab = antibody; Ag = antigen; CT = computed tomography; DM = diabetes mellitus; EIA = enzyme immunoassay; Ig = immunoglobulin; MR = magnetic resonance; MRCP = magnetic resonance cholangiopancreatography; O&P = ova and parasites; PCR = polymerase chain reaction; TTG = tissue transglutaminase.

to 200 μg SQ three times daily) or the better tolerated intramuscular preparation (10 to 20 mg monthly) improves dumping symptoms. In patients with predominant reactive hypoglycemia 1 to 3 hours after a meal (late dumping), an α-glycosidase hydrolase inhibitor (e.g., acarbose, 50 to 100 mg orally three times daily) that blocks carbohydrate absorption in the small bowel may be beneficial. Continuous jejunal tube feeding is also effective. GLP-1 receptor agonists also are a promising therapy for patients with symptomatic hypoglycemia.

IMPAIRED LIPOLYSIS

A deficiency in pancreatic lipase may be caused by the congenital absence of pancreatic lipase or by destruction of the pancreatic gland as a result of alcohol-related pancreatitis, cystic fibrosis, or pancreatic cancer. Pancreatic lipase also can be denatured by excess secretion of gastric acid (e.g., gastrinoma; Chapter 213). In such cases, lipase denaturation can be offset by treatment with a high-dose proton pump inhibitor (e.g., omeprazole 60 mg/day orally) to block acid secretion.

CHRONIC PANCREATITIS

Chronic pancreatitis (Chapter 130) is the most common cause of pancreatic insufficiency and impaired lipolysis. In the United States, chronic pancreatitis most commonly results from alcohol use disorder; in contrast, tropical (nutritional) pancreatitis is most common worldwide. Malabsorption of fat does not occur until more than 90% of the pancreas is destroyed.

CLINICAL MANIFESTATIONS

Individuals with pancreatic causes of malabsorption typically present with bulky, fat-laden stools (usually >30 g of fat daily), abdominal pain, and diabetes, although some present with diabetes in the absence of gastrointestinal symptoms. Stools usually are not watery because undigested triglycerides form large emulsion droplets with little osmotic force and, in contrast to fatty acids, do not stimulate water and electrolyte secretion in the colon. Deficiency of fat-soluble vitamins is seen only rarely, presumably because gastric and residual pancreatic lipase generates enough fatty acids for some micelle formation. In severe disease, subclinical protein malabsorption, manifested by the presence of undigested meat fibers in the stool, and subclinical carbohydrate malabsorption, manifested by gas-filled, floating stools, can occur. Weight loss, when it occurs, is most often caused by decreased oral intake to avoid abdominal pain or diarrhea and less commonly by malabsorption. Pancreatic enzyme replacement and analgesics are the mainstays of treatment for chronic pancreatitis (see Table 130-5 in Chapter 130).

DIAGNOSIS

Between 30 and 40% of individuals with alcohol-related chronic pancreatitis have calcifications on abdominal radiographs. A qualitative or quantitative test for fecal fat is positive in individuals whose pancreas is more than 90% destroyed. Noninvasive tests of pancreatic function are not sensitive enough to detect mild to moderate insufficiency, so secretin-enhanced magnetic resonance cholangiopancreatography (MRCP) or the endoscopic secretin stimulation test is preferred (see Table 126-6) if it can be obtained.

IMPAIRED MICELLE FORMATION

Bile salt concentrations in the intestinal lumen can fall to less than the critical concentration (2 to 3 mmol/L) needed for micelle formation because of decreased bile salt synthesis (severe liver disease), decreased bile salt delivery (cholestasis), or removal of luminal bile salts (bacterial overgrowth, terminal ileal disease or resection, cholestyramine therapy, acid hypersecretion). Fat malabsorption resulting from impaired micelle formation is generally not as severe as malabsorption resulting from pancreatic lipase deficiency, presumably because fatty acids and monoglycerides can form lamellar structures, which to a certain extent can be absorbed. Malabsorption of fat-soluble vitamins (D, A, K, and E) may be marked, however, because micelle formation is required for their absorption.

Decreased Bile Salt Synthesis and Delivery

Malabsorption can occur in individuals with cholestatic liver disease or bile duct obstruction, as well as in occasional patients who have undergone prior cholecystectomy.[10] The clinical consequences of malabsorption are seen most

often in women with primary biliary cirrhosis because of the prolonged nature of the illness. Although these individuals can present with steatorrhea, osteoporosis or, less commonly, osteomalacia is the most common presentation. The cause of bone disease in these patients is poorly understood and often is not related to vitamin D deficiency. Bone disease is treated with calcium supplements (and vitamin D if a deficiency is documented), weight-bearing exercise, and a bisphosphonate (e.g., alendronate, 10 mg/day orally or 70 mg orally once weekly).

Intestinal Bacterial Overgrowth

In health, only small numbers of lactobacilli, enterococci, gram-positive aerobes, or facultative anaerobes can be cultured from the upper small bowel lumen. Motility and acid are the most important factors in keeping the number of bacteria in the upper small bowel low. Any condition that produces local stasis or recirculation of colonic luminal contents allows development of a predominantly "colonic" flora (coliforms and anaerobes, such as *Bacteroides* and *Clostridium*) in the small intestine (see Table 126-7).[11] Anaerobic bacteria cause impaired micelle formation by releasing cholylamidases, which deconjugate bile salts. The unconjugated bile salts, with their higher pK_a, are more likely to be in the protonated form at the normal upper small intestinal pH of 6 to 7 and can be absorbed passively. As a result, the concentration of bile salts decreases in the intestinal lumen and can fall to less than the critical micellar concentration, causing malabsorption of fats and fat-soluble vitamins. Vitamin B_{12} deficiency and carbohydrate malabsorption also can occur with generalized bacterial overgrowth. Anaerobic bacteria ingest vitamin B_{12} and release proteases that degrade brush-border disaccharidases. Although anaerobic bacteria use vitamin B_{12}, they synthesize folate. Individuals with bacterial overgrowth may have low serum vitamin B_{12} levels but normal or high folate levels; this helps distinguish bacterial overgrowth from tropical sprue, in which vitamin B_{12} and folate levels are usually low because of decreased mucosal uptake.

CLINICAL MANIFESTATIONS

Individuals with bacterial overgrowth can present with diarrhea, abdominal cramps, gas and bloating, anorexia, weight loss, and signs and symptoms of vitamin B_{12} and fat-soluble vitamin deficiency. Watery diarrhea occurs because of the osmotic load of unabsorbed carbohydrates and stimulation of colonic secretion by unabsorbed fatty acids.

DIAGNOSIS

The diagnosis of bacterial overgrowth should be considered in elderly people and in individuals with predisposing underlying disorders (see Table 126-7).[12] Bacterial overgrowth may be associated with the irritable bowel syndrome. The identification of greater than 10^3 CFU/mL in a culture of small intestinal aspirate is the gold standard in diagnosis but is not readily available. Noninvasive options, which have a wide range of sensitivities and specificities compared with those of intestinal culture, are the carbohydrate substrate-based glucose hydrogen and methane breath tests (see Table 126-6). In individuals with low vitamin B_{12} levels, a Schilling test before and after antibiotic therapy can be diagnostic if available (Chapter 150).

TREATMENT

The goals of treatment are to correct the structural or motility defect, if possible; to eradicate offending bacteria; and to provide nutritional support.[13] Acid-reducing agents should be stopped, if possible. Treatment with antibiotics should be based on culture results whenever possible; otherwise, empirical treatment is given. Rifaximin (400 mg orally three times daily) is effective,[A6] but less so in individuals with an excluded (blind) intestinal loop. Tetracycline (250 to 500 mg orally four times daily), doxycycline (100 mg orally two times daily), or a broad-spectrum antibiotic against aerobes and enteric anaerobes (ciprofloxacin, 500 mg orally twice daily; amoxicillin-clavulanic acid, 250 to 500 mg orally three times daily; cephalexin, 250 mg orally four times daily with metronidazole, 250 mg orally three times daily) should be given for 14 days. In patients with small bowel dysmotility, prokinetic agents such as prucalopride (2 to 4 mg orally once daily), metoclopramide (10 mg orally four times daily) or erythromycin (250 to 500 mg orally four times daily) can be tried. Octreotide (50 μg subcutaneously every day) may improve motility and reduce bacterial overgrowth in individuals with scleroderma. If the structural abnormality or motility disturbance cannot be corrected, the patient is at risk for malnutrition and deficiencies of vitamin B_{12} and fat-soluble vitamins. Cyclic treatment (1 to 3 weeks of every 4 to 6 weeks) with rotating antibiotics may be required in these patients to prevent recurrent bouts of bacterial overgrowth. If supplemental calories are needed, medium-chain triglycerides should be given because they do not depend on micelle formation for their absorption. Monthly treatment with vitamin B_{12} should be considered, along with supplemental vitamins D, A, K, and E and calcium.

ILEAL DISEASE

Disease of the terminal ileum is most commonly due to Crohn disease, which also may lead to ileal resection, but it also can be caused by radiation enteritis, tropical sprue, tuberculosis, *Yersinia* infection, or idiopathic bile salt malabsorption. These diseases cause bile salt wasting in the colon.

The clinical consequences of bile salt malabsorption are related directly to the length of the diseased or resected terminal ileum. In an adult, if less than 100 cm of ileum is diseased or resected, watery diarrhea results because of stimulation of colonic fluid secretion by unabsorbed bile salts. Bile acid diarrhea responds to cholestyramine (2 to 4 g taken at breakfast, lunch, and dinner).[14] If more than 100 cm of ileum is diseased or resected, bile salt losses (>3 g/day) in the colon exceed the capacity for increased bile salt synthesis in the liver, the bile salt pool shrinks, and micelle formation is impaired. As a result, steatorrhea ensues, and fatty acid–induced intestinal secretion synergizes with the bile acid–induced secretion to cause diarrhea. Treatment is with a low-fat diet, vitamin B_{12} (300 to 1000 μg subcutaneously or intramuscularly once every month), dietary supplements of calcium (500 mg orally two or three times daily, monitor 24-hour urine calcium for adequacy of dose), and a multiple vitamin and mineral supplement. An antimotility agent should be given for diarrhea. Bile salt binders may worsen diarrhea. Screening for fat-soluble vitamin deficiencies (vitamins A and E, 25-OH vitamin D, and prothrombin time) and bone disease (bone densitometry, serum calcium, intact parathyroid hormone, 24-hour urine for calcium) should be done.

Three long-term complications of chronic bile salt wasting and fat malabsorption are renal stones, bone disease (osteoporosis and osteomalacia), and gallstones. Oxalate renal stones occur as a consequence of excess free oxalate absorption in the colon. Free oxalate is generated when unabsorbed fatty acids bind luminal calcium, which is then unavailable for binding oxalate. Renal oxalate stones sometimes can be avoided with a low-fat, low-oxalate diet and calcium supplements. Bone disease is caused by impaired micelle formation with a resulting decrease in absorption of vitamin D; year-round sun exposure reduces this complication. Vitamin D (50,000 U orally one to three times per week) and calcium supplements (500 mg orally two to three times daily) should be given to susceptible individuals, but vitamin D levels and serum and urinary calcium must be monitored for response to treatment because excess vitamin D can be toxic. The mechanism of gallstone formation in these individuals is unclear; pigmented gallstones are most common.

CONDITIONS THAT IMPAIR MUCOSAL ABSORPTION

PATHOBIOLOGY

Nutrients are absorbed along the entire length of the small intestine, with the exception of iron and folate, which are absorbed in the duodenum and proximal jejunum, and bile salts and cobalamin (vitamin B_{12}), which are absorbed in the distal ileum. The efficiency of nutrient uptake at the mucosa is influenced by the number of villus absorptive cells, the presence of functional hydrolases and specific nutrient transport proteins on the brush-border membrane, and transit time. Transit time determines the contact time of luminal contents with the brush-border membrane and influences the efficiency of nutrient uptake across the mucosa.

Mucosal malabsorption can be caused by specific (usually congenital) brush-border enzyme or nutrient transporter deficiencies or by generalized diseases that damage the small intestinal mucosa or result in surgical resection or bypass of the small intestine. The nutrients malabsorbed in these general malabsorptive diseases depend on the site of intestinal injury (proximal, distal, or diffuse) and the severity of damage. The main mechanism of malabsorption in these conditions is a decrease in surface area available for absorption. Some conditions (infection, celiac disease, tropical sprue, food allergies, and GVHD) are characterized by intestinal inflammation and villus flattening; others are characterized by ulceration (ulcerative jejunitis, NSAIDs, Crohn disease), infiltration (amyloidosis), or ischemia (radiation enteritis, mesenteric ischemia).

Long-chain fatty acids are transported across the microvillus membrane of villus epithelial cells by CD36 and the fatty acid transport protein FATP4. The bile salts from mixed micelles remain in the intestinal lumen and are absorbed in the distal ileum by sodium-dependent cotransport. Oligosaccharides and larger oligopeptides (products of pancreatic enzyme digestion), sucrose, and lactose are hydrolyzed further by enzymes present in the brush-border membrane of villus epithelial cells before they are absorbed. Although only

sugar monomers (glucose, galactose, fructose) can be taken up at the apical epithelial cell membrane, dipeptides and tripeptides are readily taken into the cell.

Water-soluble vitamins are readily absorbed throughout the small intestine. Fat-soluble vitamins, minerals, and cobalamin are more difficult to absorb because of the requirement for micelle formation (vitamins D, A, K, and E), a divalent charge (magnesium, calcium, iron), or selected sites of uptake in the intestine (iron, cobalamin). Calcium is absorbed best in the proximal small intestine by a vitamin D–dependent calcium channel (TRPV6). Magnesium is absorbed in the small intestine by members of the transient receptor potential family (TRPM6 and TRPM7). Mutations in TRPM6 have been identified in the rare disorder hereditary hypomagnesemia. Ferrous iron is transported into intestinal epithelial cells by a proton-coupled metal-ion transporter (DMT1 or Nramp2) that has specificity for Fe^{2+} and other divalent cations (Mn^{2+}, Co^{2+}, Cd^{2+}, Cu^{2+}, Ni^{2+}, and Pb^{2+}). The reduced form of copper (Cu^{1+}) is absorbed by the copper transporter 1 (CTR1). Zinc (Zn^{2+}) is predominantly absorbed by the Srt-, Irt-like protein ZIP4. The absorption of calcium and nonheme iron is enhanced by solubilization with hydrochloric acid. Intraluminal compounds such as oxalate, phytate, and long-chain fatty acids bind to calcium and magnesium, decreasing their absorption. Individuals with severe mucosal disease or short-bowel syndrome with high fecal fluid outputs lose magnesium and zinc from endogenous secretions.

Folates (Chapters 150 and 199) are both taken in the diet and produced by bacteria in the colon. Dietary folates are reduced to their monoglutamate form in the lumen of the proximal intestine and absorbed predominantly by a proton-coupled folate transporter. Deficiency can be caused by poor intake or malabsorption secondary to intestinal disease or drugs.

The cobalamins (Chapters 150 and 199) are abundant in foods containing animal proteins (e.g., meat, seafood, eggs, milk). Dietary cobalamin is released from food in the stomach by acid-peptic digestion and binds to haptocorrin at gastric pH. Pancreatic enzymes degrade haptocorrin, thereby freeing cobalamin to bind to gastric intrinsic factor, which that is secreted from parietal cells. The intrinsic factor–cobalamin complex then travels to the distal ileum and binds to the cubam complex (cubulin and amnionless). Once transported into ileal enterocytes, intrinsic factor is degraded; cobalamin binds to transcobalamin II and is transported in the blood stream to target tissues. Various mutations in the factors required for these processes can cause hereditary juvenile cobalamin deficiency. Cobalamin (vitamin B_{12}) deficiency in industrialized countries is rarely due to poor dietary intake but rather reflects the inability to absorb cobalamin. This inability may be caused by a lack of intrinsic factor, consumption of cobalamin by overgrowth of anaerobic bacteria in the small bowel lumen, ileal disease or resection, or defective transcobalamin II. Large amounts of cobalamin are present in the liver (2 to 5 mg), and cobalamin is reabsorbed from bile through the enterohepatic circulation, thereby limiting daily losses to less than 1 µg. It usually takes 10 to 12 years for cobalamin deficiency to develop after it is eliminated from the diet, but deficiency can occur more rapidly (2 to 5 years) with malabsorptive syndromes. If lack of gastric acid causes food-cobalamin malabsorption, treatment with oral cyanocobalamin supplementation (Chapter 150) is curative.

LACTASE DEFICIENCY

EPIDEMIOLOGY

Acquired lactase deficiency is the most common cause of selective carbohydrate malabsorption. Most individuals, except those of northern European descent, begin to lose lactase activity by the age of 2 years. The prevalence of lactase deficiency is highest (85 to 100%) in persons of Asian, African, and Native American descent.

PATHOBIOLOGY

The persistence or nonpersistence of lactase activity is associated with a single nucleotide polymorphism C/T_{-13910} that is found upstream of the lactase gene on chromosome 2q21-22. Hypolactasia is associated with the C/C_{-13910} genotype in diverse ethnic groups. The mechanism by which this variant downregulates the lactase gene is not known, but functional studies suggest genotype-dependent alterations in levels of messenger RNA.

CLINICAL MANIFESTATIONS

Adults with lactase deficiency typically complain of gas, bloating, and diarrhea after the ingestion of milk or dairy products but do not lose weight. Unabsorbed lactose is osmotically active, drawing water followed by ions into the intestinal lumen.[15] On reaching the colon, bacteria metabolize lactose to short-chain fatty acids, carbon dioxide, and hydrogen gas. Short-chain fatty acids are transported with sodium into colonic epithelial cells, facilitating the reabsorption of fluid in the colon. If the colonic capacity for the reabsorption of short-chain fatty acids is exceeded, an osmotic diarrhea results (see later discussion of carbohydrate malabsorption in watery diarrhea).

DIAGNOSIS

The diagnosis of acquired lactase deficiency can be made by empirical treatment with a lactose-free diet, which results in resolution of symptoms; by the hydrogen breath test after oral administration of lactose; or by genetic testing. Many intestinal diseases cause secondary reversible lactase deficiency, including viral gastroenteritis, celiac disease, giardiasis, and bacterial overgrowth.

CELIAC DISEASE

DEFINITION AND EPIDEMIOLOGY

Celiac disease is a chronic inflammatory condition of the small intestine precipitated by the ingestion of wheat, rye, and barley in individuals with certain genetic predispositions.[16] The prevalence in general populations worldwide is approximately 1%. High-risk groups for celiac disease include first-degree relatives and individuals with type 1 diabetes mellitus, autoimmune thyroid disease, autoimmune liver disease, and Down, Turner, or Williams syndromes. Approximately 5% of patients diagnosed with diarrhea-predominant irritable bowel syndrome or with microscopic (lymphocytic) colitis have celiac disease.

PATHOBIOLOGY

Environmental and genetic factors are important in the development of celiac disease, with data suggesting a relationship with prior reovirus infection.[17] Approximately 10% of first-degree relatives of affected individuals are found to have celiac disease. Predisposition has been mapped to the human leukocyte antigen (HLA)-D region on chromosome 6. More than 90% of northern Europeans with celiac disease have the DQ2 heterodimer encoded by alleles DQA1*0501 and DQB1*0201, compared with 20 to 30% of controls. A smaller celiac group carries HLA-DQ8. Many non-HLA alleles identified in genome-wide association studies account for a small portion of genetic risk. Most such genes are involved in adaptive and innate immune responses. Overlap variants have been identified in diabetes, rheumatoid arthritis, and Crohn disease.

The alcohol-soluble protein fraction of wheat gluten, the gliadins, and similar prolamins in rye and barley trigger intestinal inflammation in susceptible individuals. Oat grains, which have prolamins rich in glutamine but not proline, are rarely toxic. Gliadins and similar prolamins with high proline content are relatively resistant to digestion by human proteases. Many gliadin and prolamin peptides have been identified that stimulate HLA-DQ2– and HLA-DQ8–restricted intestinal T-cell clones from individuals with celiac disease. In blood lymphocyte comprehensive screen assays, three immunodominant prolamin peptides have been identified from wheat, barley, and rye in DQ2 celiac individuals; dominant peptides differ in those with DQ8. The DQ2 protein expressed on antigen-presenting cells has positively charged binding pockets; tTG (the autoantigen recognized by endomysial antibody) may enhance intestinal inflammation by deamidation of select glutamine residues in gliadin and similar prolamins to negatively charged glutamic acid. In the deamidated form, most gliadin peptides have a higher binding affinity for DQ2 and are more potent stimulants of gluten-sensitized T cells. Villous atrophy may be caused by inflammation that is triggered by γ-interferon released from DQ2- or DQ8-restricted CD4 T cells in the lamina propria. Intraepithelial lymphocytes also directly kill intestinal epithelial cells under the influence of IL-15 released from stressed enterocytes.

CLINICAL MANIFESTATIONS

Celiac disease usually manifests early in life, at approximately 2 years of age (after wheat has been introduced into the diet), or later in the second to fourth decades of life, but it can occur at any age. It may first manifest clinically after abdominal surgery or an episode of infectious diarrhea.

Adults with celiac disease in the United States often present with anemia or osteoporosis without diarrhea and no or mild other gastrointestinal symptoms. Other extraintestinal manifestations of celiac disease include rash (dermatitis herpetiformis), neurologic disorders (peripheral neuropathy, ataxia, epilepsy), psychiatric disorders (depression, paranoia), reproductive disorders (infertility, spontaneous abortion), short stature, dental enamel hypoplasia, chronic hepatitis, and pancreatitis.

A minority of patients present with severe diarrhea, weight loss or growth retardation, and the clinical manifestations of vitamin and mineral deficiencies.

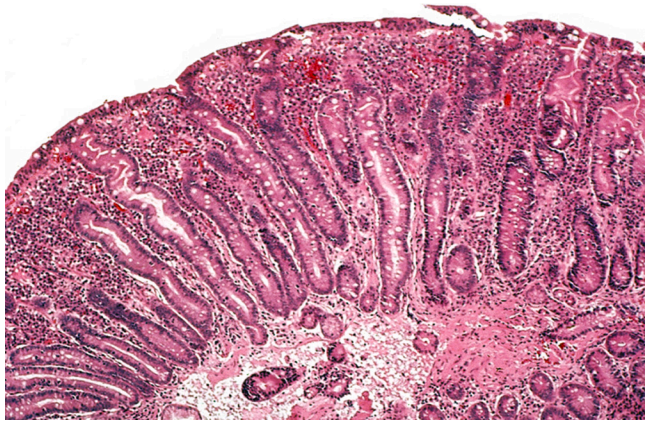

FIGURE 126-5. Intestinal biopsy appearance of flattened villi, hyperplastic crypts, and increased intraepithelial lymphocytes. (Courtesy John Hart, MD.)

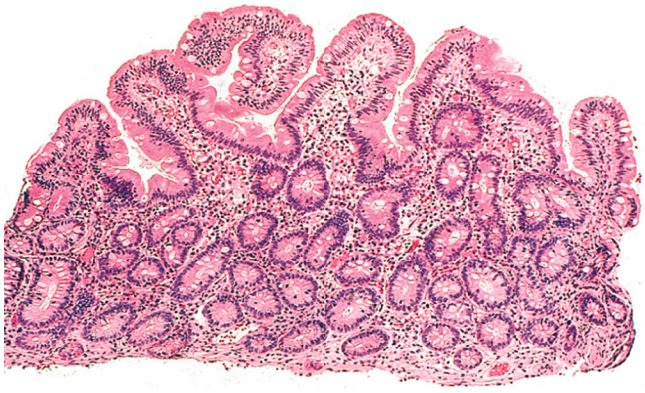

FIGURE 126-6. Regeneration of villi after initiation of a gluten-free diet. (Courtesy of John Hart, MD.)

Cobalamin deficiency is more common (10% of patients) than previously thought and usually corrects itself on a gluten-free diet. Symptomatic individuals require supplementation of vitamin B_{12}. Diarrhea is caused by many mechanisms, including a decreased surface area for water and electrolyte absorption, the osmotic effect of unabsorbed luminal nutrients, an increased surface area for chloride secretion (crypt hyperplasia), and the stimulation of intestinal fluid secretion by inflammatory mediators and unabsorbed fatty acids. Some individuals have impaired pancreatic enzyme secretion caused by decreased mucosal cholecystokinin release or bacterial overgrowth that may contribute to diarrhea. Individuals with nonceliac gluten sensitivity have wheat-related intestinal and extraintestinal symptoms similar to those of celiac disease but lack intestinal inflammation or celiac serologic markers. Fermentable oligosaccharides, disaccharides, monosaccharides, and polyols (FODMAPs) and gluten or nongluten wheat proteins (amylase trypsin inhibitors) may be the offending agents.

DIAGNOSIS

Routine screening for celiac disease is not recommended. In individuals who have subtle symptoms or in symptomatic high-risk groups, however, screening with anti-tTG IgA antibody testing is a cost-effective strategy.[18] High titer (>10-fold) of the anti-tTG IgA antibody is virtually diagnostic of celiac disease. EMA IgA antibodies, detected by indirect immunofluorescence, are highly sensitive (90%) and specific (95 to 99%) for active celiac disease in skilled laboratory testing. An ELISA test to detect antibodies against tTG has equal sensitivity to the EMA test but is less specific at lower titers. The anti-deamidated gliadin (a biotinylated synthetic γ-gliadin peptide with glutamic acid substituted for glutamine), antibody immunofluorometric assay has an inferior sensitivity and specificity compared with the anti-tTG IgA antibody.

Patients with mild disease may have negative antibody study results.[19] Anti-tTG, gliadin peptide, and EMA IgA antibodies tests are negative in individuals with selective IgA deficiency (present in up to 3% of individuals with celiac disease). In these patients, the anti-deamidated gliadin IgG antibody, which has a sensitivity and specificity close to that of the tTG IgA antibody, is helpful in diagnosis. In equivocal cases (negative serologic findings and equivocal biopsy result or positive serologic findings and normal biopsy result), HLA genotyping is useful to exclude the diagnosis of celiac disease in persons who lack the *DQ2* or *DQ8* gene.

The diagnosis of celiac disease can be confirmed by characteristic abnormalities seen on duodenal biopsies and improving when a gluten-free diet is instituted (Figs. 126-5 and 126-6). Mucosal flattening may be observed endoscopically as scalloped or reduced duodenal folds. Characteristic features found on intestinal biopsy include blunted or absent villi (villous atrophy), crypt hyperplasia, increased intraepithelial lymphocytes, and infiltration of the lamina propria with plasma cells and lymphocytes. In some individuals, the only abnormal biopsy finding is increased intraepithelial lymphocytes. However, individuals who have a TTG IgA antibody titer greater than 10-fold positive has a high enough predictive value for an abnormal duodenal biopsy characteristic of celiac disease that no biopsy is needed in this subset of individuals.[20,21] The decision to forgo biopsy for diagnosis should be under the guidance of a gastroenterologist.

TREATMENT

Treatment consists of a lifelong gluten-free diet. Wheat, rye, and barley grains should be excluded from the diet. Rice and corn grains are tolerated. Oats (if not contaminated by wheat grain) are tolerated by most. Early referral to a registered dietitian knowledgeable in the gluten-free diet and to a reputable celiac support group or website is crucial in maintaining dietary adherence. Owing to secondary lactase deficiency, a lactose-free diet should be recommended until symptoms improve.

In a preliminary trial, inhibition of transglutaminase-2 attenuated gluten-mediated mucosal damage and tended to improve symptoms[A7] Other therapies under study include exogenous oral enzymes that degrade gluten peptides, tight junction regulators, IL-15 inhibitors, and immune therapies to promote oral gluten tolerance.

Bone densitometry should be performed on individuals diagnosed with celiac disease who are older than 30 years of age because up to 70% have osteopenia or osteoporosis. Patients with diarrhea and weight loss should be screened for vitamin and mineral deficiencies. Documented deficiencies of vitamins and minerals should be replenished (Table 126-8), and women of childbearing age should take folic acid supplements. Bone mass often improves on a gluten-free diet alone. Patients with vitamin D or calcium deficiency should receive supplements (Chapter 199), with the dose monitored by 25-OH vitamin D levels and a 24-hour urine test for calcium. Celiac disease is associated with an increased risk for hospitalization with influenza and pneumococcal infection, so vaccination against both is recommended.

Most patients with seronegative villous atrophy do not have celiac disease. Most such patients have villous atrophy due to another cause or will have spontaneous improvement despite continuing to ingest gluten.

PROGNOSIS

Of patients with celiac disease treated with a gluten-free diet, 90% experience symptomatic improvement within 2 weeks. The most common cause of a poor dietary response is continued ingestion of gluten. Other possibilities include a missed intestinal infection (see later), an alternative diagnosis (e.g., ARB use particularly in elderly patients with a sprue-like enteropathy but negative celiac serologic findings, agammaglobulinemia [diagnosed by hypogammaglobulinemia and lack of plasma cells on small bowel biopsy], autoimmune enteritis [diagnosed by a positive anti-enterocyte antibody and crypt apoptosis or loss of goblet cells on small bowel biopsy]), bacterial overgrowth, pancreatic insufficiency, microscopic colitis, or other food allergies (cow's milk, soy protein). Between 4 and 40% of patients with celiac disease with symptomatic improvement have incomplete histologic recovery on a gluten-free diet; in such patients, a stricter diet may further improve symptoms and histology. A small percentage of patients with severe symptoms and enteropathy do not improve despite a strict gluten-free diet. In such patients, repeat intestinal biopsy with special lymphocyte marker studies is indicated. Some patients will have collagen deposition beneath the surface epithelium (collagenous sprue) or a polyclonal population of intraepithelial lymphocytes (refractory celiac disease type I). Others will have ulcerative jejunitis or a monoclonal population of intraepithelial T cells with an aberrant phenotype or clonal T-cell receptor-γ gene rearrangements (refractory celiac disease type II), which are predictive of enteropathy-associated T-cell lymphoma (Chapter 171) that portends a poor prognosis. Video capsule endoscopy and device-assisted enteroscopy may be helpful in establishing these diagnoses. Patients

TABLE 126-8 VITAMIN AND MINERAL DOSES USED IN THE TREATMENT OF MALABSORPTION

VITAMIN	ORAL DOSE	PARENTERAL DOSE
Vitamin A*	Water-soluble A, 25,000 U/day†	
Vitamin E	Water-soluble E, 400-800 U/day†	
Vitamin D‡	25,000-50,000 U/day	
Vitamin K	5 mg/day	
Folic acid	1 mg/day	
Calcium§	1500-2000 mg elemental calcium/day Calcium citrate, 500 mg calcium/tablet† Calcium carbonate, 500 mg calcium/tablet†	
Magnesium	Liquid magnesium gluconate† 1-3 tbsp (12-36 mEq magnesium) in 1-2 L of ORS or sports drink sipped throughout the day Magnesium chloride hexahydrate† 100-600 mg elemental magnesium/day	2 mL of a 50% solution (8 mEq), total dose, in both buttocks IM
Zinc	Zinc gluconate† 20-50 mg elemental zinc/day‖	
Iron	150-300 mg elemental iron/day Polysaccharide-iron complex† Iron sulfate or gluconate	Iron sucrose¶ Sodium ferric gluconate complex¶ Iron dextran (as calculated for anemia) (IV or IM¶; Chapter 145)
B-complex vitamins	1 megadose tablet/day	
Vitamin B_{12}	2 mg/day	1 mg IM or SQ/mo**
Copper	Copper sulfate 2-3 mg/day	1-2 mg IV/day

*Monitor serum vitamin A level to avoid toxicity, especially in patients with hypertriglyceridemia.
†Form best absorbed or with least side effects.
‡Monitor serum calcium and 25-OH vitamin D levels to avoid toxicity.
§Monitor 24-hr urine calcium to assess adequacy of dose.
‖If intestinal output is high, additional zinc should be given. Monitor for copper deficiency with high doses.
¶Parenteral therapy should be given in a supervised outpatient setting because of the risk for fatal reactions. Decreased risk for fatal reactions when compared with iron dextran.
**For vitamin B_{12} deficiency, 1 mg IM or SQ twice per week for 4 wk, then once per month.
IM = intramuscular; IV = intravenous; ORS = oral rehydration solution; SQ = subcutaneous.

with collagenous sprue, autoimmune enteritis, or refractory celiac disease type I often respond to prednisone (20 to 40 mg/day orally) or budesonide (9 mg opened capsule orally daily).

Patients with celiac disease have a higher likelihood of having other autoimmune conditions, such as type 1 diabetes, thyroiditis, rheumatoid arthritis, inflammatory bowel disease, systemic lupus erythematosus, Sjögren syndrome, primary biliary cirrhosis, autoimmune hepatitis, vitiligo, and pancreatitis. Interestingly, approximately one third of patients with idiopathic sporadic ataxia have transglutaminase-6 antibodies, consistent with gluten-induced disease.

Individuals with celiac disease have a 15 to 35% increased risk of mortality.[22] They also are at increased risk for cancer, particularly T cell lymphoma (Chapter 171) and small bowel carcinoma[23] (Chapter 171), with highest risks in the first year of after diagnosis and in patients over age 60 years. T-cell lymphoma is rare and should be suspected in individuals who have abdominal pain, recurrence of symptoms after initial response to a gluten-free diet, or refractory celiac disease.

TROPICAL SPRUE

Tropical sprue is an inflammatory disease of the small intestine associated with the overgrowth of predominantly coliform bacteria. It occurs in residents or travelers to India, Southeast Asia, Puerto Rico, and parts of the Caribbean. With the expansion of tourism and the global economy, this may be an underrecognized cause of enteropathy or mistaken for celiac disease. Individuals classically present with diarrhea and megaloblastic anemia secondary to vitamin B_{12} and folate deficiency, but some have anemia only. Intestinal biopsy characteristically shows subtotal and patchy villous atrophy in the proximal and distal small intestine, which may be caused by the effect of bacterial toxins on gut structure or by the secondary effects of vitamin B_{12} deficiency on the gut (megaloblastic gut). Diagnosis is based on history, documentation of vitamin B_{12} and/or folate deficiency, and the presence of an abnormal small intestinal biopsy report. Treatment is a prolonged course of tetracycline (250 mg orally four times daily) or doxycycline (100 mg orally two times daily), folic acid (5 mg/day orally), and, with coexistent deficiency, vitamin B_{12} injections (1000 μg weekly) until symptoms resolve. Relapse or reinfection occurs in 20%, mainly in natives of the tropics.

GIARDIA LAMBLIA

Giardia lamblia infection (Chapter 322), the most common protozoal infection in the United States, can cause malabsorption in individuals infected with many trophozoites, especially the immunocompromised or IgA-deficient hosts. Malabsorption occurs when many organisms cover the epithelium and cause mucosal inflammation, which results in villous flattening and a decrease in absorptive surface area. Stool for ova and parasites at this stage of infection is often negative because of the attachment of organisms in the proximal small intestine. Diagnosis can be made by PCR, stool antigen-capture ELISA test, or duodenal biopsy.

HUMAN IMMUNODEFICIENCY VIRUS

Diarrhea, malabsorption, and wasting are common in individuals with AIDS but are seen less frequently with improved antiretroviral therapy (Chapter 359). In patients who are receiving highly active antiretroviral therapy, diarrhea is more likely to be due to protease inhibitors than to enteric infection.

Malabsorption is usually due to infection with cryptosporidia, *Mycobacterium avium-intracellulare* complex, *I. belli,* or microsporidia. *AIDS enteropathy* (a term used if no organism is identified) also can cause malabsorption. Mechanisms of malabsorption and diarrhea include villous atrophy, increased intestinal permeability, rapid small bowel transit (in patients with protozoal infection), and ultrastructural damage of enterocytes (in AIDS enteropathy). Among individuals with AIDS and diarrhea, results of fecal fat absorption are frequently abnormal. Serum albumin, vitamin B_{12}, and zinc levels are often low. Vitamin B_{12} deficiency is caused mainly by ileal disease, but low intrinsic factor and decreased transcobalamin II may be contributing factors. Management of malabsorption should focus on restoring the immune system by treating the underlying HIV infection with antiviral therapy. If possible, the offending organism should be treated with antibiotics. If the organism cannot be eradicated, chronic diarrhea and malabsorption result; treatment in these cases consists of antimotility agents and a lactose-free, low-fat diet. Pancreatic enzyme replacement therapy can be tried in HIV-infected individuals who are taking highly active antiretroviral therapy or nucleoside analogues and who have fat malabsorption of obscure origin. If supplemental calories are needed, liquid oral supplements that are predigested and high in medium-chain triglycerides (semi-elemental) are tolerated best. Vitamin and mineral deficiencies should be screened for and treated.

WHIPPLE DISEASE

Whipple disease (Chapter 305), which is a rare cause of malabsorption, manifests with gastrointestinal complaints in association with systemic symptoms, such as fever, joint pain, or neurologic manifestations.[24] Approximately one third of patients have cardiac involvement, most commonly culture-negative endocarditis. Occasionally, individuals present with ocular or neurologic disease without gastrointestinal symptoms. The gram-positive actinomycete, *Tropheryma whippelii,* can be detected by PCR of duodenal biopsy specimens, gastric juice, saliva, urine,[25] or stool. Small intestinal biopsy shows villous blunting and infiltration of the lamina propria with large macrophages that stain positive with the periodic acid–Schiff method and are filled with the organism. It is important to distinguish these macrophages from macrophages infected with *M. avium-intracellulare* complex (Chapter 300), which stain positive on acid-fast staining and are found in individuals with AIDS. Treatment is with a prolonged course of broad-spectrum antibiotics (e.g., ceftriaxone 2 g/day IV or meropenem 1 g IV three times daily; then trimethoprim 160 mg and sulfamethoxazole 800 mg orally two times daily for 1 year or trimethoprim 160 mg and sulfamethoxazole 800 mg orally two times daily for 1 year). Relapses occur, but initial treatment with parenteral ceftriaxone or meropenem appears to be associated with a low relapse rate.

GRAFT-VERSUS-HOST DISEASE

Diarrhea occurs frequently after allogeneic hematopoietic stem cell transplantation (Chapter 163). Immediately after transplantation, diarrhea is caused by the toxic effects of cytoreductive therapy on the intestinal epithelium. From 20 to 100 days after transplantation, diarrhea is usually due to GVHD or infection. Patients with GVHD present clinically with a skin rash, hepatic cholestasis, buccal mucositis, anorexia, nausea, vomiting, abdominal cramps, and diarrhea. The diagnosis of GVHD in the gastrointestinal tract can be made on biopsy of the stomach, small intestine, or colon. In mild cases, the mucosa appears normal on inspection at endoscopy, but apoptosis of gastric gland or crypt cells can be found on biopsy. In severe cases, denudation of the intestinal epithelium results in diarrhea and malabsorption and often requires parenteral nutritional support. Octreotide (50 to 250 μg SQ three times daily) may be helpful in controlling voluminous diarrhea. Treatment of acute GVHD is with steroids (or antithymocyte globulin or ruxolitinib for steroid-refractory disease) combined with parenteral nutritional support until intestinal function returns.

SHORT-BOWEL SYNDROME

Malabsorption caused by small bowel resection or surgical bypass is called the short-bowel syndrome. The most common causes in the United States are massive resection of the jejunum, owing to strangulated bowel, volvulus, or ischemia (mesenteric or after intra-abdominal surgery), and jejunal exclusion, owing to gastric bypass surgery. Short-bowel syndrome resulting from Crohn disease and radiation enteritis now is less common because of improved medical and radiation therapies. The severity of malabsorption depends on the site and extent of resection; the capacity for adaptive hyperplasia, dilation, and elongation; and the function of the residual bowel. Mechanisms of malabsorption after small bowel resection include a decreased absorptive surface area, decreased luminal bile salt concentration, rapid transit, and bacterial overgrowth. Limited jejunal resection is tolerated best because bile salt and vitamin B_{12} absorption remain normal. Ileal resection is less well tolerated because of the consequences of bile salt wasting and the limited capacity of the jejunum to undergo adaptive hyperplasia. Adaptive hyperplasia in residual small bowel after resection depends on nutrients, endogenous secretions (pancreatic and biliary juice), local factors (trefoil peptides, prostaglandins, polyamines), growth hormone and growth factors (epidermal growth factor [EGF], insulin-like growth factor-1 [IGF1], transforming growth factor-α [TGF-α], IL-11). The glucagon-like peptide-2 (GLP2) produced in L cells in the terminal ileum and colon is a potent stimulant of adaptive hyperplasia in the jejunum in response to a meal. Using intestinal stem cell technology, epithelial organoids have been successfully grown in culture systems, but bowel regeneration has not yet been accomplished.

When less than 100 cm of jejunum remains, the colon takes on an important role in caloric salvage and fluid reabsorption. Malabsorbed carbohydrates are digested by colonic bacteria to short-chain fatty acids, which are absorbed in the colon.

TREATMENT

In patients who have a colon, parenteral nutrition may be avoided using a diet rich in complex carbohydrates, oral rehydration solution, an acid-reducing agent, and an antimotility agent (loperamide 2 to 8 mg orally up to four times a day; diphenoxylate and atropine 1 to 2 tablets orally up to four times a day; codeine 15 to 60 mg orally up to four times a day).[26] In comparison, individuals with fewer than 100 cm of jejunum and no colon have high jejunostomy outputs and often require intravenous fluids or parenteral nutrition to survive. These individuals waste sodium, chloride, bicarbonate, magnesium, zinc, and water in their ostomy effluent. Dietary modifications should include a high-salt, nutrient-rich diet given in small meals. An oral rehydration solution with a sodium concentration 75 to 90 mmol/L is absorbed best. Oral vitamin and mineral doses higher than the usual U.S. recommended daily allowances are required (see Table 126-8). Vitamin B_{12} should be given parenterally (500 to 1000 μg intramuscularly or subcutaneously every month). Magnesium deficiencies are often difficult to replenish with oral magnesium because of its osmotic effect in the intestinal lumen. A liquid magnesium preparation added to an oral rehydration solution and sipped throughout the day may minimize magnesium-induced fluid losses. Potent antimotility agents, such as tincture of opium (0.3 to 1 mL orally four times daily) or liquid morphine 20 mg/mL (1 mL orally four times daily), often are needed to slow transit and maximize contact time for nutrient absorption. High-volume jejunostomy outputs can be lessened by inhibiting endogenous secretions with a proton pump inhibitor (e.g., omeprazole, 40 mg orally one time daily, or lansoprazole, 30 mg orally one time daily) and, in severe cases (>3 L/day output), octreotide (100 to 250 μg subcutaneously three times daily; if effective, convert to an equivalent long-acting monthly dosage). The benefit of octreotide may be offset by its potential to inhibit intestinal adaptation and impair pancreatic enzyme secretion with doses greater than 300 μg/day.

In the most severe cases, supplemental calories must be provided by nocturnal tube feeding or parenteral nutrition. Treatment with growth hormone (0.1 mg/kg/day SQ) with or without glutamine (30 g/day orally) for 4 weeks may reduce parenteral nutrition requirements in patients who have had massive intestinal resections. Teduglutide (0.05 mg/kg/day SQ), a glucagon-like peptide-2 analogue that stimulates adaptive hyperplasia in remnant intestine after resection, improves absorption, and reduces parenteral nutrition requirements. Small bowel transplantation should be considered for individuals who require parenteral nutrition to survive and then develop progressive liver disease or venous access problems. Bioengineering of intestine using organoids and scaffolding systems is a promising future therapy.[27]

PROGNOSIS

Long-term complications include bone disease, renal stones (oxalate stones if the colon is present, urate stones with a jejunostomy), gallstones, bacterial overgrowth, fat-soluble vitamin deficiencies, essential fatty acid deficiency, and D-lactic acidosis.

CONDITIONS THAT IMPAIR NUTRIENT DELIVERY TO THE SYSTEMIC CIRCULATION

Insoluble lipids (present in chylomicrons) are exocytosed across the basolateral membrane of epithelial cells into the intestinal lymphatics. From there, they enter the mesenteric lymphatics and the general circulation through the thoracic duct. Sugar monomers, amino acids, and medium-chain fatty acids are transported across the basolateral membrane of intestinal epithelial cells into capillaries and into the portal circulation. Sugar monomers are transported across the basolateral membrane by the facilitative glucose transporter isoform (GLUT2) and amino acids by facilitative amino acid carriers (see E-Fig. 126-1C).

IMPAIRED LYMPHATIC DRAINAGE

Diseases that cause intestinal lymphatic obstruction, such as primary congenital lymphangiectasia (malunion of intestinal lymphatics), and diseases that result in secondary lymphangiectasia (lymphoma, tuberculosis, Kaposi sarcoma, retroperitoneal fibrosis, constrictive pericarditis, severe heart failure) result in fat malabsorption. The increased pressure in the intestinal lymphatics leads to leakage and sometimes rupture of lymph into the intestinal lumen, with the loss of lipids, γ-globulins, albumin, and lymphocytes. The diagnosis of lymphangiectasia can be made by intestinal biopsy, but the specific cause may be more difficult to identify. Individuals with lymphangiectasia malabsorb fat and fat-soluble vitamins and have protein loss into the intestinal lumen. The most common presentation is hypoproteinemic edema. Nutritional management includes a high protein and low-fat diet and supplementation with medium-chain triglycerides, which are absorbed directly into the portal circulation. Fat-soluble vitamins should be given if deficiencies develop.

CONGENITAL MALABSORPTION AND DIARRHEA

A number of congenital disorders, mostly autosomal recessive, alter nutrient digestion, epithelial cell transport, or villus epithelial architecture. These disorders usually present within the first few weeks of life and may become targets for stem cell therapy.

Mutations in sugar disaccharidases include lactase (rare), sucrose-isomaltase, maltase-glucoamylase, and trehalase (digests trehalose in mushrooms) deficiencies. These disorders are characterized by osmotic diarrhea when the offending sugar is introduced into the diet. Diagnosis is made by a low stool pH (owing to conversion of malabsorbed sugar to short-chain fatty acids by colonic bacteria), reduced enzyme activity on duodenal biopsy, and genetic testing. The treatment is to feed alternative sources of carbohydrates. Congenital enterokinase (enteropeptidase) deficiency due to missense mutations in the gene causes severe protein malabsorption owing to the inability to activate trypsinogen and other pancreatic proteases in the intestinal lumen. Treatment is with supplemental pancreatic enzymes.

Defects in epithelial transport proteins include congenital glucose-galactose malabsorption (mutation in the *SGLT1* gene) that results in severe carbohydrate malabsorption. Congenital chloride and sodium diarrheas are rare autosomal recessive disorders caused by mutations in the epithelial Cl^-/HCO_3^- (SLC26A) and the Na^+/H^+ exchanger (SCL9A3, GUCY2C), respectively. These disorders cause maternal polyhydramnios and fluid-filled bowel loops in utero as well as severe diarrhea at birth. Diagnosis in the newborn is made by high stool chloride levels and metabolic alkalosis in congenital chloride diarrhea, high

stool sodium levels and metabolic acidosis in congenital sodium diarrhea, and genetic testing.

Abetalipoproteinemia is due to defects in chylomicron formation and exocytosis at the basolateral membrane of intestinal epithelial cells that are necessary for the delivery of lipids to the systemic circulation. Mutations in the microsomal triglyceride transfer protein (MTP), apolipoprotein B gene, and SAR1B (triggers coat protein of vesicles in the endoplasmic reticulum) result in chylomicron retention in epithelial cells. Children with this disorder have fat malabsorption and the consequences of vitamin E deficiency (retinopathy and spinocerebellar degeneration). Biochemical tests show low plasma levels of apoprotein B, triglyceride, and cholesterol. Membrane lipid abnormalities result in red blood cell acanthosis (burr cells). Intestinal biopsy, which is diagnostic, is characterized by engorgement of epithelial cells with lipid droplets. Treatment is with a low-fat diet containing medium-chain triglycerides and high doses of fat-soluble vitamins, especially vitamin E.

Homozygous loss-of-function mutations in the gene encoding CD55 (decreased decay-accelerating factor with hyperactivation of complement) cause protein-losing enteropathy, often accompanied by primary intestinal lymphangiectasia, edema due to hypoproteinemia, and malabsorption. Affected individuals often may have recurrent infections and angiopathic thromboembolic disease (CHAPLE syndrome).

Defects in villus epithelial cell structure presents at birth with severe malabsorption. Microvillus inclusion disease is due to defects in intraepithelial cellular protein transport and epithelial polarization. Mutations have been identified in myosin type 5 motor protein *(MYO5B)* and syntaxin-3 *(STX3)* genes. Tufting enteropathy is characterized by disorganized enterocytes at villus tips (tufts). Mutations have been identified in EpCAM and SPINK2 to suggest disorders in tight junction formation. Most infants with these disorders require parenteral nutrition or small bowel transplantation for survival.

WATERY DIARRHEA

Watery diarrhea may be due to osmotic, secretory, inflammatory, or often combined mechanisms (see Fig. 126-3).

INGESTION OF NONABSORBABLE OR POORLY ABSORBABLE SOLUTES

MAGNESIUM AND SODIUM PHOSPHATE AND SULFATE DIARRHEAS

Magnesium, phosphate, and sulfate are poorly absorbed minerals. Individuals who ingest significant amounts of magnesium-based antacids or high-potency multimineral and multivitamin supplements or those who surreptitiously ingest magnesium-containing laxatives or nonabsorbable anion laxatives, such as Na_2PO_4 (neutral phosphate) or Na_2SO_4 (Glauber or Carlsbad salt), may develop osmotically induced, watery diarrhea that may be high volume.

SORBITOL AND FRUCTOSE DIARRHEA

Dietetic food, chewing gum, candies, and medication elixirs that are sweetened with sorbitol, which is an unabsorbable carbohydrate, can cause diarrhea. Excessive consumption of pears, prunes, peaches, and apple juice, which also contain sorbitol and fructose, a poorly absorbable sugar, can result in diarrhea. Most soft drinks are now sweetened with fructose-containing corn syrup and may be a cause of diarrhea when ingested in high concentrations.

RAPID INTESTINAL TRANSIT

A small amount of carbohydrate in the diet is unabsorbed by the normal small intestine. Diets that are high in carbohydrate and low in fat may allow rapid gastric emptying and rapid small intestinal motility, thereby leading to carbohydrate malabsorption and osmotic diarrhea. Rapid transit time also occurs in thyrotoxicosis (Chapter 207). Because of the production of H_2 and carbon dioxide gas by colonic bacteria, abdominal gas and cramping may be the predominant symptoms.

BILE ACID DIARRHEA

Ileal malabsorption of bile salts results in the stimulation of colonic fluid secretion and watery diarrhea. Three types of bile acid malabsorption induce diarrhea. Type 1 results when severe disease (e.g., Crohn disease), resection, or bypass of the distal ileum allows bile salts to escape absorption (see earlier). Type 2 may be congenital: rarely owing to a defect in the intestinal sodium bile acid transporter but more commonly owing to increased bile salt production (associated with decreased levels of fibroblast growth factor 19 [FGF19], an intestinal fibroblast growth factor that normally downregulates bile salt synthesis in the liver, and increased levels of 7-α-hydroxy-4-cholesten-3-one [7αC4], which is a marker of bile acid synthesis, in blood). The result is increased bile salt production that overwhelms reabsorption in the ileum. Type 3 is caused by various conditions, including prior cholecystectomy, celiac disease, pancreatic insufficiency, microscopic colitis, bacterial overgrowth, gastric surgery, or vagotomy. Postulated mechanisms include a bile salt storage problem, increased production, decreased recycling, or saturation of absorption.

Primary (type 2) bile acid diarrhea is now thought to account for up to 30% of cases of functional or irritable bowel syndrome with chronic diarrhea (Chapter 123).[28] The diagnosis is made by selenium homocholic acid taurine (^{75}SeHCAT) testing (see Table 126-6), a 48-hour stool collection for bile acids on a high-fat diet, or fasting blood tests that measure FGF19 and C4 levels.

TREATMENT

Diarrhea due to types 1 and 2 often responds to cholestyramine (2 to 4 g orally two to four times daily), colestipol (5 g orally two or three times daily), or the more potent and better tolerated bile salt binder colesevelam (625-mg tablet orally two to six times daily). Obeticholic acid (25 mg orally daily), a farnesoid X receptor agonist that stimulates FGF19 production, may lessen the frequency of bile acid diarrhea but may cause pruritis.[29] Fat-soluble vitamin deficiency is a potential risk with chronic use of bile salt binders. Although many patients with type 3 respond to cholestyramine or colesevelam, some do not. In these patients, motility-altering drugs such as opiates (e.g., loperamide, 2 to 4 mg orally two to four times daily) and anticholinergics (e.g., hyoscyamine sulfate, 0.125 to 0.250 mg orally two to four times daily) may be of benefit.

TRUE SECRETORY DIARRHEAS

High-volume secretory diarrheas (see Fig. 126-3) can be caused by hormones or cytokines that are secreted by rare endocrine tumors, including carcinoid tumors (Chapter 213), gastrinomas (Chapter 213), VIPomas of the pancreas (Chapter 213), and medullary carcinoma of the thyroid (Chapter 207). Diarrhea is also seen in 60 to 80% of patients with systemic mastocytosis (Chapter 235). Diarrhea resulting from gastrinoma is distinct in that it is caused by high volumes of hydrochloric acid secretion that overwhelm the reabsorptive capacity of the colon and by maldigestion of fat owing to pH inactivation of pancreatic lipase and precipitation of bile salts.

VILLOUS ADENOMAS

Large (4 to 18 cm) villous adenomas, particularly in the rectum or occasionally the sigmoid colon, may cause secretory diarrhea of 500 to 3000 mL/24 hours characterized by hypokalemia, chloride-rich stool, and metabolic alkalosis. Increased numbers of goblet cells and increased prostaglandin E_2 are responsible for the diarrhea. Chloride wasting in the stool and metabolic alkalosis are also found in congenital chloridorrhea, which is caused by a defect in the intestinal Cl^-/HCO_3^- transporter. The metabolic alkalosis distinguishes these two diarrheas from most other diarrheas that cause metabolic acidosis. A villous adenoma is usually diagnosed by colonoscopy. The prostaglandin antagonist indomethacin (25 to 100 mg/day orally) reduces the diarrhea in some patients; resection is curative.

DIABETES MELLITUS–RELATED DIARRHEA

Constipation is more common than diarrhea in patients with diabetes (Chapter 210). High-volume, watery diarrhea, often with nocturnal incontinence, occurs in 20% of patients with poorly controlled type 1 diabetes. These patients usually have concomitant neuropathy, nephropathy, and retinopathy. The diarrhea may be due to several causes, including celiac disease, anal incontinence, bacterial overgrowth related to dysmotility, medications (metformin, acarbose), and autonomic neuropathy. If no specific cause is found, clonidine (initial dose 0.1 mg orally twice daily and titrated slowly to a maximal dose of 0.5 to 0.6 mg orally twice daily) may be helpful. Patients with neuropathy frequently have impaired anal sphincter function, and high-dose loperamide (4 mg orally four times daily) may improve the incontinence.

ALCOHOL-RELATED DIARRHEA

Diarrhea related to alcohol ingestion (Chapter 364) may be due to rapid intestinal transit, decreased bile and pancreatic secretion, nutritional deficiencies such as folate or vitamin B_{12}, or alcohol-related enteric neuropathy. Diarrhea may be acute with binge drinking, or it may be chronic and watery and persist for days or weeks. The diarrhea slowly resolves with abstinence from alcohol, proper nutrition, and the repletion of vitamin deficiencies.

FACTITIOUS DIARRHEA

Approximately 30% of patients referred to tertiary centers have chronic diarrhea from laxative abuse. The diarrhea is usually severe and watery, often with nocturnal symptoms. Some patients may have abdominal pain, weight loss, nausea, vomiting, hypokalemic myopathy, and acidosis. Stool volumes range from 300 to 3000 mL/day depending on the dose of laxative ingested. In the United States, bisacodyl is the most common cause. Other culprits include anthraquinone (senna, cascara, aloe, rhubarb) or osmotic laxatives (neutral phosphate, Epsom salts, and magnesium citrate). Some patients abuse other agents that cause diarrhea, such as the diuretics furosemide and ethacrynic acid.

More than 90% of laxative abusers are women who have underlying eating disorders such as anorexia nervosa or bulimia (Chapter 200) or middle-aged women who have complicated medical histories and who often work in health care. In patients with unexplained diarrhea, laxative screening of stool and urine (see later) should be performed to exclude this syndrome before an extensive medical evaluation is performed for other causes of chronic diarrhea.

CHRONIC IDIOPATHIC SECRETORY DIARRHEA

In a small subset of patients with secretory diarrhea, no cause is found despite an extensive evaluation. These cases are labeled as chronic idiopathic secretory diarrhea. In most patients, the diarrhea resolves within 6 to 24 months, which suggests a possible postinfectious or Brainerd diarrhea. If no diagnosis is found after thorough testing and a search for surreptitious laxative abuse, a therapeutic trial with bile salt–binding drugs (e.g., cholestyramine, 4 g orally before meals three times daily, or the more potent colesevelam, 625-mg tablet two to six times daily) or opiates (e.g., loperamide, 2 mg orally four times daily, maximal dose 16 mg daily) is warranted.

INFLAMMATORY DIARRHEAS

Diarrhea resulting from inflammation is characterized by watery or bloody stools, fecal leukocytes, and loss of protein in the stool (see Fig. 126-3).

INFLAMMATORY BOWEL DISEASE

See Chapter 127.

EOSINOPHILIC GASTROENTERITIS

Eosinophilic gastroenteritis is an increasingly recognized condition of unknown etiology characterized by infiltration of eosinophils in the mucosa, muscle, or serosal layers of the gastrointestinal tract.[30] Mast cells play a role in the pathogenesis. Approximately 50% of patients have atopic histories. Infestation with nematodes (Chapter 327) must be excluded before this diagnosis is made. Diarrhea occurs in 30 to 60% of patients with mucosal disease. Patients with involvement of the muscle layer often present with abdominal pain, nausea, and vomiting indicative of gastric outlet or intestinal obstruction. Peripheral eosinophilia is present in about 70% of patients. The disease may involve the entire gastrointestinal tract from esophagus to anus, or it may be isolated to a segment. With diffuse involvement, patients may have steatorrhea, protein-losing enteropathy, and blood loss.

Management includes an elimination diet or an elemental diet. Budesonide (9 mg orally daily) or prednisone (0.5 to 1 mg/kg orally daily) is highly effective, but relapses are common when corticosteroids are tapered. Lirentelimab, a monoclonal antibody against siglec-8 (sialic acid-binding immunoglobulin-like lectin 8 expressed on eosinophils and mast cells) is a promising therapy that significantly decreases tissue eosinophil counts and improves clinical symptoms.[A8]

MICROSCOPIC (COLLAGENOUS AND LYMPHOCYTIC) COLITIS

These two conditions, collectively known as *microscopic colitis,* may or may not be the same disease or variants of the same disease.[31] Lymphocytic colitis is equally prevalent in men and women, whereas collagenous colitis occurs 10 times more often in middle-aged or elderly women. These conditions may be associated with autoimmune disease or with NSAID use. There is an increased prevalence (5%) of microscopic colitis among individuals with celiac disease. These diseases may be categorized as either inflammatory or secretory diarrheas. An epidemiologic relationship to medications such as NSAIDs, proton pump inhibitors, selective serotonin reuptake inhibitors, and smoking has been reported, and increased luminal prostaglandin levels may cause the diarrhea. Enteric infections, food hypersensitivity, and intraluminal bile have been proposed as triggers for prostaglandin release from lymphocytes.

Antidiarrheal agents such as loperamide (2 mg orally four times daily) are the mainstay of therapy for mild diarrhea, which usually has a benign and self-limited course. Budesonide (4.5 to 9 mg orally daily) is the most effective therapy.[A9] In patients who do not tolerate or respond to it, an alternative is bismuth subsalicylate therapy (8 chewable 262-mg tablets orally daily). Patients with refractory disease may require corticosteroids (e.g., prednisone, 40 mg/day orally), a trial of azathioprine, or anti–TNF-α antibodies.

FOOD ALLERGY AND HYPERSENSITIVITY

Food allergies or sensitivities, especially to cow's milk and egg protein, are a well-established cause of enterocolitis in children, with an estimated frequency of 5%. Symptoms of abdominal cramps, diarrhea, and sometimes vomiting occur shortly after ingestion of the allergen (Chapter 233). Food hypersensitivity reactions are reported in 20 to 25% of adults and can lead to anxiety and disordered eating.[32] The role of food allergy in causing diarrhea in adults is less clear owing to the lack of a reliable diagnostic test. Allergy testing correlates poorly with intestinal allergy. The most common food allergens are milk, soy, eggs, seafood, nuts, and wheat. Sequential elimination diets can be diagnostic and therapeutic.

RADIATION ENTERITIS

Patients who receive pelvic radiation for malignancies of the female urogenital tract, gastrointestinal tract, or the male prostate may develop chronic radiation enterocolitis[33] 6 to 24 months after total doses of radiation greater than 40 to 60 Gy (Chapters 18 and 128), but symptoms can develop as late as 20 years after treatment. Early abnormalities include an increase in inflammatory mediators, an increase in cholinergic stimulation of intestinal tissue, and endothelial cell apoptosis that precedes epithelial cell apoptosis. The last finding suggests that vascular injury is the primary event. Diarrhea may be caused by bile acid malabsorption if the ileum is damaged, by bacterial overgrowth if radiation causes small intestinal strictures or bypass, or by radiation-induced chronic inflammation of the small intestine and colon. Rapid transit also may contribute to malabsorption and diarrhea.

TREATMENT

Treatment is often unsatisfactory. Anti-inflammatory drugs (mesalamine, corticosteroids) and antibiotics have been tried with little success. Cholestyramine (4 g orally three times daily) and NSAIDs (e.g., naproxen, 250 to 500 mg orally twice daily) may help, as may opiates (loperamide, 2 mg orally four times daily, or loperamide-*N*-oxide, 3 mg orally two times daily). Hyperbaric oxygen therapy may be useful for refractory disease. Surgery carries a high morbidity.

PROTEIN-LOSING GASTROENTEROPATHY

Severe protein loss through the gastrointestinal tract can be caused by mucosal diseases such as lymphangiectasia, lymphatic obstruction, bacterial or parasitic infection, gastritis (Chapter 125), gastric cancer, collagenous colitis, inflammatory bowel disease (Chapter 127), celiac disease, sarcoidosis (Chapter 83), lymphoma (Chapter 171), tuberculosis (Chapter 299), Ménétrier disease (Chapter 178), eosinophilic gastroenteritis, and food allergies. A variety of extraintestinal diseases, including systemic lupus erythematosus (Chapter 245), heart failure (Chapter 45), and constrictive pericarditis (Chapter 62), also can be causative. Patients with systemic lupus erythematosus (Chapter 245) may present with protein-losing enteropathy as the only manifestation of their disease.

The typical clinical presentation is hypoproteinemia with edema. Diarrhea is a frequent symptom but not always present. Depending on the cause, patients may have lymphocytopenia (from lymphatic obstruction), steatorrhea, and fat-soluble vitamin deficiencies (especially with primary intestinal lymphangiectasia or celiac disease).

Evaluation includes exclusion of renal, liver, heart disease as a cause followed by testing for suspected gastrointestinal mucosal diseases. MRI may play a role in detecting intestinal/mesenteric edema and lymphatic dilation. The α1-antitrypsin clearance test is useful for diagnosis and to evaluate the magnitude of protein loss.[34] Treatment focuses on the underlying disease.

MISCELLANEOUS DISEASES

Although acute mesenteric arterial or venous thrombosis manifests as an acute bloody diarrhea, chronic mesenteric vascular ischemia (Chapter 129) may manifest as watery diarrhea. Gastrointestinal tuberculosis (Chapter 299) and histoplasmosis (Chapter 308) manifest as diarrhea that may be either bloody or watery, as do certain immunologic diseases, such as Behçet syndrome and Churg-Strauss syndrome. All of these diseases may be misdiagnosed as inflammatory bowel disease

(Chapter 127). Neutropenic enterocolitis, an ileocolitis that occurs in patients with neutropenia and leukemia, sometimes is caused by *C. difficile* infection.

TREATMENT

Antidiarrheal agents are of two types: those used for mild to moderate diarrheas and those used for severe secretory diarrheas. A major shortcoming of opiates, the most commonly prescribed antidiarrheal agents, is that they have no antisecretory effect. Rather, they act by decreasing intestinal motility, thereby allowing longer contact time with the mucosa for improved fluid absorption. The exception is racecadotril, an enkephalinase inhibitor, that blocks intestinal fluid secretion without affecting motility.

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127 INFLAMMATORY BOWEL DISEASE

GARY R. LICHTENSTEIN

DEFINITION

Inflammatory bowel disease refers to two chronic idiopathic inflammatory disorders: ulcerative colitis and Crohn disease. Characteristic clinical, endoscopic, and histologic features are critical for the diagnosis of these disorders, but no single individual finding is absolutely diagnostic for one disease or the other. Mucosal ulceration in Crohn disease may be transmural and may occur anywhere in the gastrointestinal tract, most commonly in the distal ileum and proximal colon. The hallmark of ulcerative colitis is continuous ulceration starting in the rectum and limited to the colon. Approximately 10% of patients with inflammatory bowel disease have what is called "inflammatory bowel disease-undetermined," a term used when Crohn colitis cannot be distinguished from ulcerative colitis.

EPIDEMIOLOGY

Inflammatory bowel disease occurs worldwide, but the highest incidence is found in North America, the United Kingdom, and northern Europe. Data suggest an increasing incidence and prevalence over time and in different regions around the world, although ulcerative colitis remains slightly more prevalent than Crohn disease. The incidence of ulcerative colitis in North America is estimated to be about 19 per 100,000 person-years and 24 per 100,000 person-years in Europe, with a prevalence of approximately 280 per 100,000 persons in North America and up to 500 per 100,000 persons in Europe. The incidence of Crohn disease in North America is estimated to be about 20 per 100,000 person-years and 13 per 100,000 person-years in Europe, with a prevalence of approximately 320 per 100,000 person-years in North America and in Europe.[1]

Crohn disease and ulcerative colitis may occur at any age, but both have their peak incidence in the second to fourth decade, with a second peak in the seventh decade. The female-to-male ratio for both ulcerative colitis and Crohn disease suggests no gender preference.

Crohn disease and ulcerative colitis are complex polygenic disorders, for which having a family history of inflammatory bowel disease is a risk factor. Crohn disease and ulcerative colitis occur in all ethnic and socioeconomic groups, but their incidence is highest in White and Jewish people of Eastern European (Ashkenazi) descent. In North America and the United Kingdom, however, the incidence of Crohn disease in African Americans and African Caribbeans appears to be approaching that of Whites. Studies of migrants from certain developing countries in South Asia to the United Kingdom suggest an increased prevalence of inflammatory bowel disease in subsequent generations, presumably because of environmental influences.

Cigarette smoking is associated with a worse prognosis in patients with Crohn disease but an improved course in ulcerative colitis. Nonsteroidal anti-inflammatory drugs (NSAIDs) appear to be associated with new onset of inflammatory bowel disease and with exacerbations of disease. Appendectomy for an inflammatory indication has been suggested as protective against the development of ulcerative colitis. Diet does not clearly affect the course of inflammatory bowel disease.

PATHOBIOLOGY

Although the trigger for inflammatory bowel disease is not known, three major pathways likely activate the disease: a genetic predisposition, immune

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127 INFLAMMATORY BOWEL DISEASE

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DEFINITION

Inflammatory bowel disease refers to two chronic idiopathic inflammatory disorders: ulcerative colitis and Crohn disease. Characteristic clinical, endoscopic, and histologic features are critical for the diagnosis of these disorders, but no single individual finding is absolutely diagnostic for one disease or the other. Mucosal ulceration in Crohn disease may be transmural and may occur anywhere in the gastrointestinal tract, most commonly in the distal ileum and proximal colon. The hallmark of ulcerative colitis is continuous ulceration starting in the rectum and limited to the colon. Approximately 10% of patients with inflammatory bowel disease have what is called "inflammatory bowel disease-undetermined," a term used when Crohn colitis cannot be distinguished from ulcerative colitis.

EPIDEMIOLOGY

Inflammatory bowel disease occurs worldwide, but the highest incidence is found in North America, the United Kingdom, and northern Europe. Data suggest an increasing incidence and prevalence over time and in different regions around the world, although ulcerative colitis remains slightly more prevalent than Crohn disease. The incidence of ulcerative colitis in North America is estimated to be about 19 per 100,000 person-years and 24 per 100,000 person-years in Europe, with a prevalence of approximately 280 per 100,000 persons in North America and up to 500 per 100,000 persons in Europe. The incidence of Crohn disease in North America is estimated to be about 20 per 100,000 person-years and 13 per 100,000 person-years in Europe, with a prevalence of approximately 320 per 100,000 person-years in North America and in Europe.[1]

Crohn disease and ulcerative colitis may occur at any age, but both have their peak incidence in the second to fourth decade, with a second peak in the seventh decade. The female-to-male ratio for both ulcerative colitis and Crohn disease suggests no gender preference.

Crohn disease and ulcerative colitis are complex polygenic disorders, for which having a family history of inflammatory bowel disease is a risk factor. Crohn disease and ulcerative colitis occur in all ethnic and socioeconomic groups, but their incidence is highest in White and Jewish people of Eastern European (Ashkenazi) descent. In North America and the United Kingdom, however, the incidence of Crohn disease in African Americans and African Caribbeans appears to be approaching that of Whites. Studies of migrants from certain developing countries in South Asia to the United Kingdom suggest an increased prevalence of inflammatory bowel disease in subsequent generations, presumably because of environmental influences.

Cigarette smoking is associated with a worse prognosis in patients with Crohn disease but an improved course in ulcerative colitis. Nonsteroidal anti-inflammatory drugs (NSAIDs) appear to be associated with new onset of inflammatory bowel disease and with exacerbations of disease. Appendectomy for an inflammatory indication has been suggested as protective against the development of ulcerative colitis. Diet does not clearly affect the course of inflammatory bowel disease.

PATHOBIOLOGY

Although the trigger for inflammatory bowel disease is not known, three major pathways likely activate the disease: a genetic predisposition, immune

ABSTRACT

Inflammatory bowel disease represents idiopathic inflammatory disorders comprised primarily of ulcerative colitis and Crohn disease, both of which are chronic disorders that are increasing in prevalence and occur worldwide. Better understanding of pathogenesis, including the roles of genetics and the intestinal microbiome, has led to transformational changes in medical treatments, fewer extraintestinal manifestations, lower rates of surgery, and improved quality of life.

KEYWORDS

Crohn disease
inflammatory bowel disease
ulcerative colitis
ileitis
colitis

dysregulation, and an environmental trigger.[2] A possible explanation is that the inability of the innate immune system to clear microbial antigens, combined with increased intestinal epithelial permeability to antigens, eventually leads to an overactive adaptive immune response.[3]

Genetics

Of patients with inflammatory bowel disease, 5 to 20% have another family member with inflammatory bowel disease. First-degree relatives have a 10- to 15-fold increased risk for developing inflammatory bowel disease. The concordance rate of developing Crohn disease in identical twins, siblings, and first-degree relatives is 50%, 0 to 3%, and 5 to 10%, respectively. Ulcerative colitis follows similar genetic patterns but with slightly lower risk rates. Twenty percent of patients with a positive family history of inflammatory bowel disease will have discordant disease type: one family member with Crohn disease and another with ulcerative colitis.

More than 200 gene susceptibility loci have been linked to inflammatory bowel disease, with at least 30 specific for Crohn disease and more than 20 specific for ulcerative colitis.[4] *NOD2/CARD15*, which is located on chromosome 16 (16q12) and expressed in intestinal epithelial Paneth cells, macrophages, and dendritic cells, is involved in the expression of an intracellular receptor that senses muramyl dipeptide, which is a peptidoglycan component of gram-positive bacteria. Activation of *NOD2* leads to activation of nuclear factor κ-B (NF-κB), which mediates transcription of numerous proinflammatory cytokines. A mutation in the leucine-rich domain of the NOD2 protein, which interacts with bacterial lipopolysaccharide, leads to failure in activation of NF-κB and is associated with the development of Crohn disease.

The *ATG16L1* gene on chromosome 2 and the *IRGM* gene on chromosome 5 also have been associated with increased susceptibility to Crohn disease. Both are members of a family of genes involved in autophagy, an autonomous process that involves the maintenance of cellular homeostasis and organelle turnover, as well as the processing of intracellular pathogens, the subsequent presentation of antigens, and the regulation of cell signaling. Toll-like receptor-4 gene polymorphisms are associated with both Crohn disease and ulcerative colitis. Polymorphisms of the interleukin-23 (IL-23) receptor gene are associated with ulcerative colitis and a varied risk for Crohn disease. The presence of an adenylate cyclase 7 (*ADCY7*) missense mutation leads to an excessive inflammatory response that predisposes to ulcerative colitis. Human leukocyte antigen (HLA) class II polymorphisms, especially in HLA-DR molecules, may confer increased risk for ulcerative colitis and possibly Crohn as well. The *OCTN1* gene (located on chromosome 5q31) and the *DLG5* gene (located on chromosome 10) are associated with Crohn disease. *DLG5* encodes a scaffolding protein that is important for maintaining epithelial integrity in various organs, whereas *OCTN1* encodes for an ion channel that regulates cell-to-cell signaling in the intestinal epithelium.

Inflammatory bowel disease also has been associated with Turner syndrome (Chapter 214), glycogen storage type Ib (Chapter 191), and the Hermansky-Pudlak syndrome (triad of albinism, platelet aggregation defect, and accumulation of ceroid-like pigment in tissue) (Chapter 159). Inflammatory bowel disease also is associated with various diseases that have known genetic predisposition, including ankylosing spondylitis (Chapter 244), psoriasis (Chapter 405), atopy (Chapter 230), eczema (Chapter 405), celiac sprue (Chapter 126), cystic fibrosis (Chapter 77), primary sclerosing cholangitis (Chapter 141), multiple sclerosis (Chapter 380), autoimmune thyroid disease (Chapter 207), autoimmune hemolytic anemia (Chapter 146), primary biliary cirrhosis (Chapter 141), myasthenia gravis (Chapter 390), and Cogan syndrome (Chapter 249).

PATHOPHYSIOLOGY

Microbes likely play a part in the development of inflammatory bowel disease. In several animal models of colitis, colitis does not develop in a sterile environment but can be induced after the introduction of commensal bacteria. For instance, helminth infection protects mice with *Nod2* mutations, which otherwise make them susceptible to Crohn disease, by inhibiting colonization by an inflammatory *Bacteroides* species. *Debaryomyces hansenii* (also known as *Candida famata*) has recently been implicated as a fungus that is found in Crohn disease tissue and can lead to dysregulated healing.[5]

Diverting the fecal stream away from active mucosal inflammation, such as in an ileostomy, also helps alleviate inflammation in Crohn disease. Crohn disease and ulcerative colitis preferentially occur in the terminal ileum and colon, which contain the highest concentration of bacteria, on the order of approximately 10^{12} organisms per gram of luminal contents. Antibiotics, particularly antibiotics with broad-spectrum anaerobic coverage, are helpful in the treatment of Crohn disease. More recently, several genetic polymorphisms associated with sensing the intestinal microbial environment and triggering an immune response have been linked to inflammatory bowel disease.

Both Crohn disease and ulcerative colitis are products of a dysregulated innate immune system that triggers T cells and a humoral response. T_H17 cells, which are activated in Crohn disease and ulcerative colitis, are stimulated by IL-23, which is produced by antigen-presenting cells.

Western-type diets (which are typically high in protein, fat, salt, sugar, other additives, and preservatives but low in fruit, vegetables, and fiber) are associated with almost a two-fold increased risk of developing inflammatory bowel disease.[6] Such foods and additives may disrupt the gut microbiota and propagate of immune activation.

Pathology

Crohn Disease

As a result of a dysregulated immune system, patients with Crohn disease develop aphthous ulcers, which are superficial mucosal ulcers. As the disease progresses, the ulceration becomes deeper, transmural, and discrete; it may form a serpiginous pattern and may occur anywhere from the mouth to the anus in a noncontinuous pattern. The most common location for ulceration is the ileocecal region. In some patients, chronic disease leads to the formation of fibrotic strictures, and approximately 30% of patients may develop fistulas in the course of their disease.

In early Crohn disease, the histopathologic findings are characterized by an acute inflammatory infiltrate in the lamina propria, with cryptitis, and crypt abscesses. Later in the disease process, the crypt architecture becomes distorted, with a lymphocytic infiltrate and a resulting branching and shortening of the crypts. Noncaseating granulomas, which may be found in up to 15% of endoscopic biopsy specimens and up to 70% of surgical specimens, are not unique to Crohn disease but help confirm the diagnosis when other classic features are present.

Surgical specimens also may show transmural intestinal wall inflammation and fat creeping on the serosal surface.

Ulcerative Colitis

In mild ulcerative colitis, the mucosa is granular, hyperemic, and edematous in appearance. As the disease becomes more severe, the mucosa ulcerates, and the ulcers may extend into the lamina propria. Ulcerative colitis starts in the rectum and may extend proximally in a continuous pattern, but it affects only the colon. Pseudopolyps may form owing to epithelial regeneration after recurrent acute attacks. With chronic disease, the colonic mucosa may lose the normal fold pattern, the colon may shorten, and the colon may appear narrowed.

In early ulcerative colitis, the histopathologic findings are characterized by epithelial necrosis, an acute inflammatory infiltrate in the lamina propria, with cryptitis and crypt abscesses. In chronic disease, a predominant lymphocytic infiltrate and distortion of crypt architecture are seen.

CLINICAL MANIFESTATIONS

Symptoms of inflammatory bowel disease are varied and may be a consequence of the location of the disease, the duration of disease, and any anatomic complications of the disease, such as strictures and fistulas in Crohn disease (Table 127-1).

TABLE 127-1 CLINICAL CHARACTERISTICS OF CROHN DISEASE AND ULCERATIVE COLITIS

CHARACTERISTICS	CROHN DISEASE	ULCERATIVE COLITIS
Peak age of onset (years of age)	15-30, 2nd peak in the 7th decade	20-40, 2nd smaller peak beyond the 7th decade
Sex distribution (F/M)	1.2/1	1/1
Potential sites of gastrointestinal involvement	Esophagus to anus	Colon
Skipped areas of involvement	+	–
Transmural inflammation	+	–
Type of ulceration	Usually discrete	Continuous
Fistula	+	–
Stricture	+	–
Perianal disease (fissure, skin tags)	+	–

Symptoms

Crohn Disease

The terminal ileum is affected in about 70% of patients with Crohn disease. Primary ileal disease occurs in 30% of patients, whereas ileocolonic disease occurs in 40%. Symptoms may include abdominal pain, typically in the right lower quadrant, diarrhea, hematochezia, and fatigue. With more severe disease, fever and weight loss may be present. Some patients may present with obstructive symptoms, such as abdominal pain, abdominal distention, and nausea.[7]

Only approximately 5% of patients develop Crohn disease in the upper gastrointestinal tract, and esophageal Crohn disease occurs in fewer than 2% of patients. Subjects with upper gastrointestinal Crohn disease may present with dysphagia, odynophagia, chest pain, or heartburn. Gastroduodenal disease occurs in 0.5 to 4% of patients and commonly occurs along with distal disease. Symptoms may include upper abdominal pain. Isolated jejunal disease is rare; if the jejunum is involved, there is also distal small bowel involvement. Up to 30% of patients have perianal disease (Chapter 131) that may include the development of fistulas, abscesses, fissures, and skin tags. Symptoms of perianal disease include pain and discharge. Fever may be present if there is an abscess.

Fistulae, which are internal tracts that connect one organ to another (e.g. rectovaginal, enterovesicular, perianal) or to the skin surface (e.g., anus to skin), can occur anywhere in the gastrointestinal tract and develop in 20 to 40% of Crohn patients. Penetrating Crohn disease also may cause intra-abdominal and perianal abscesses owing to a fistula with a blind end or intestinal perforation. External fistulas, which present with symptoms of fluid discharge from the cutaneous opening, can be enterocutaneous or perianal. Internal fistulas can be enteroenteric, rectovaginal, or enterocolonic. Patients may present with persistent abdominal pain and fever with an abscess in this location.

Ulcerative Colitis

As with Crohn disease, symptoms and signs of ulcerative colitis depend on the extent and severity of disease. At the time of diagnosis, 14 to 37% of patients have pancolitis, 36 to 41% have disease extending beyond the rectum, and 44 to 49% have proctosigmoiditis. Symptoms include hematochezia, diarrhea, tenesmus, production of excessive mucus, urgency to defecate, and abdominal pain. In the setting of proctitis or proctosigmoiditis, patients may have constipation with difficulty defecating. With more extensive and severe colonic involvement, patients also may have weight loss and fever. They also may have nausea and vomiting because of abdominal pain, fatigue because of anemia, and peripheral edema as a consequence of hypoalbuminemia.

Physical Examination

Signs on physical examination are representative of the type of disease as well as its location and severity. Oral ulcers may be present in Crohn disease. The location of abdominal tenderness usually reflects the location of intestinal involvement. In Crohn disease, abdominal tenderness is classically in the right lower quadrant and may include fullness or a mass depending on the severity of inflammation. Peritoneal signs may occur when penetrating Crohn disease causes intestinal perforation. Rectal examination may reveal skin tags, hemorrhoids, fissure, and fistulae. Additionally, the finding of a rectal stricture maybe a sign of current or past Crohn involvement.

Extraintestinal Manifestations

Arthropathy, the most common extraintestinal manifestation (Table 127-2), affects up to 10 to 20% of subjects. Peripheral arthralgias, arthritis, ankylosing spondylitis (Chapter 244), and sacroiliitis may exacerbate with gastrointestinal symptoms. Dermatologic disorders, such as erythema nodosum (in 10 to 15% of patients; see Fig. 407-24) and pyoderma gangrenosum (in 1 to 2% of patients; Chapter 240), develop in up to 15% of patients. Ocular disorders, especially uveitis and episcleritis (Chapter 391), may occur in 5 to 15% of patients with irritable bowel disease. Patients with inflammatory bowel disease also have up to a 10% risk for renal calculi, especially calcium oxalate stones (Chapter 111), in the setting of fat malabsorption with Crohn disease in the small bowel. Uric acid stones can occur in the setting of severe volume depletion. Patients with inflammatory bowel disease, especially patients with ulcerative colitis, are at increased risk for primary sclerosing cholangitis—2 to 7.5% of patients develop this disorder, and 70 to 80% of patients with this disorder have underlying inflammatory bowel disease (Chapter 141).

Extraintestinal Complications

Patients with inflammatory bowel disease are susceptible to extraintestinal complications from the disease itself or medications used to treat disease.

TABLE 127-2 EXTRAINTESTINAL COMPLICATIONS OF INFLAMMATORY BOWEL DISEASE

COMPLICATIONS	CROHN DISEASE	ULCERATIVE COLITIS
Ocular disorders (uveitis, episcleritis)	+	+
Arthropathy	+	+
Oral ulcers	+	–
Skin disorders (pyoderma gangrenosum, erythema nodosum)	+	+
Nephrolithiasis	+	+
Primary sclerosing cholangitis	+	+
Bone disorders (osteoporosis, osteomalacia)	+	–
Thromboembolic disease	+	+
B_{12} deficiency	+	–

These complications include osteoporosis, osteomalacia, arthritic complications, thromboembolic events, pulmonary disease,[7] and renal, dermatologic, and neurologic complications. Osteoporosis occurs in approximately 15% of patients, and steroid therapy (Chapter 28) is the major risk factor; avascular necrosis of the hip and septic arthritis are unusual complications of steroids or other immunosuppressive therapies. Cheilitis may be a result of iron deficiency anemia (Chapter 145). Patients with inflammatory bowel disease are at an increased risk for thromboembolic disease, especially in the setting of active intestinal disease, even when compared with other autoimmune diseases such as rheumatoid arthritis and celiac disease. Secondary amyloidosis with renal involvement can be a consequence of chronic inflammation. Asthma is the most common pulmonary disorder observed in association with Crohn disease. Patients also are at risk for optic neuritis and multiple sclerosis (Chapter 380), as well as for peripheral neuropathy (Chapter 388) from vitamin B_{12} deficiency, which may occur as a result of poor absorption owing to active small bowel disease, surgical resection, or small intestinal bacterial overgrowth.

DIAGNOSIS

When diarrhea (Chapter 126) is the predominant symptom, the initial evaluation should include a thorough medical history, testing for infectious colitis (Chapter 126), and screening for endocrine-metabolic disorders such as hyperthyroidism (Chapter 207) and hypocalcemia (Chapter 227). Infections with organisms such as *Salmonella* (Chapter 284), *Shigella* (Chapter 285), *Amoeba* (Chapter 323), *Giardia* (Chapter 322), *Escherichia coli* O157:H7 (Chapter 280), and *Campylobacter* (Chapter 279) can be accompanied by bloody diarrhea, abdominal cramps, and an endoscopic mucosal appearance identical to that of ulcerative colitis. Stool studies are needed to diagnose or exclude these infections. If hematochezia and abdominal pain are the predominant symptoms, the differential diagnosis is broad (Table 127-3).

Diagnostic Evaluation

Endoscopic Evaluation

In a patient with symptoms suggestive of inflammatory bowel disease and no evidence for an infection to explain the symptoms, endoscopic evaluation is essential. Colonoscopy is the initial endoscopic test for patients who present with lower gastrointestinal symptoms such as diarrhea and hematochezia, except in the presence of acute severe peritoneal symptoms. Colonoscopy up to and including the terminal ileum is important if there is a potential diagnosis of inflammatory bowel disease. Small bowel imaging (such as small bowel follow-through or computed tomography [CT] enterography, or magnetic resonance imaging [MRI] enterography) also may be needed to determine whether there is small bowel disease or to determine the distribution of disease. Capsule endoscopy is useful if all other endoscopic and radiologic testing is nondiagnostic, but Crohn disease of the small bowel is still suspected. Findings on capsule endoscopy should be followed by endoscopy to obtain biopsies. Capsule endoscopy should not be performed if Crohn disease is complicated by a known small bowel stricture. If it is uncertain whether a stricture is present, a patency capsule can be used initially to discern if it passes.

TABLE 127-3 DIFFERENTIAL DIAGNOSIS OF ILEITIS AND COLITIS

INFECTIONS
Bacterial
- *Aeromonas*
- *Campylobacter jejuni*
- *Chlamydia (proctitis)*
- *Clostridioides difficile*
- *Mycobacterium tuberculosis*
- *Salmonella*
- *Shigella*
- Enterohemorrhagic *Escherichia coli*
- *Yersinia*

Viral
- Cytomegalovirus
- Herpes simplex virus (proctitis)
- Human immunodeficiency virus

Fungal
- *Histoplasma capsulatum*

Parasitic
- *Entamoeba histolytica*
- *Helminths*

VASCULAR
Collagen Vascular Disease
- Behçet disease
- Churg-Strauss syndrome
- Henoch-Schönlein purpura
- Systemic lupus erythematosus
- Polyarteritis nodosa

Ischemia

MEDICATIONS/TOXINS
- Nonsteroidal anti-inflammatory drugs
- Pancreatic enzyme supplements—fibrosing colopathy
- Phosphosoda bowel preparations
- Radiation

INFLAMMATORY
- Appendicitis
- Diverticular disease
- Eosinophilic gastroenteritis
- Nongranulomatous ulcerative jejunoileitis (celiac disease)

NEOPLASIA
- Carcinoid
- Carcinoma primary or metastatic
- Lymphoma
- Mycosis fungoides
- Malignant histiocytosis

MISCELLANEOUS
- Amyloidosis
- Sarcoidosis
- Endometriosis
- Tubo-ovarian abscesses

Modified from Aberra FN, Lichtenstein GR. Crohn disease. In: Talley NJ, Kane SV, Wallace MD, eds. *Practical Gastroenterology and Hepatology: Small and Large Intestine*. Wiley-Blackwell; 2010:225-235.

FIGURE 127-1. Endoscopic appearance of Crohn disease with cobblestoning.

Crohn Disease

Early endoscopic findings in Crohn disease include superficial small mucosal ulcers, also called aphthous ulcers. As the severity of Crohn disease progresses, the ulcerations become deeper and may become round, linear, or serpiginous. Intersecting longitudinal and transverse ulcers cause a cobblestone mucosal appearance, with "stone" areas representing normal mucosa (Fig. 127-1). Areas of ulceration, which are typically interspersed with normal "skip" areas, may occur anywhere from the esophagus to anus but are most common in the ileocecal region. Isolated colonic disease occurs in 25% of patients, and 60% will have rectal involvement, thereby making it at times difficult to differentiate from ulcerative colitis.

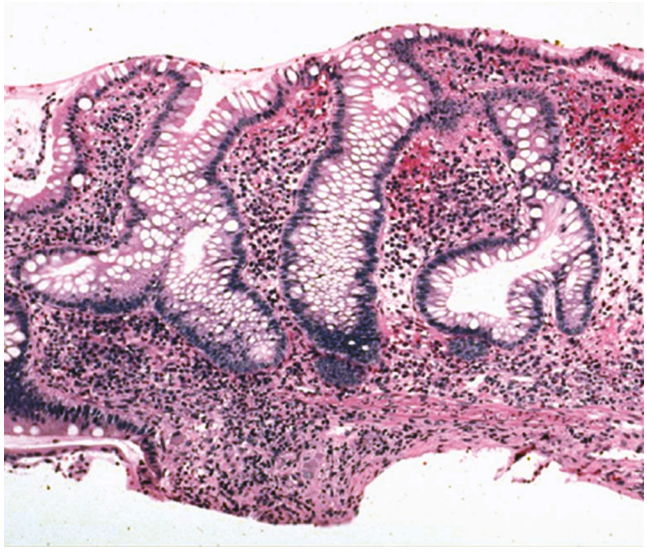

FIGURE 127-2. In ulcerative colitis, histopathology from colonic biopsies reveals features of crypt distortion and lymphocytic infiltration in the mucosa. (Modified from AGA Institute Slides 2010.)

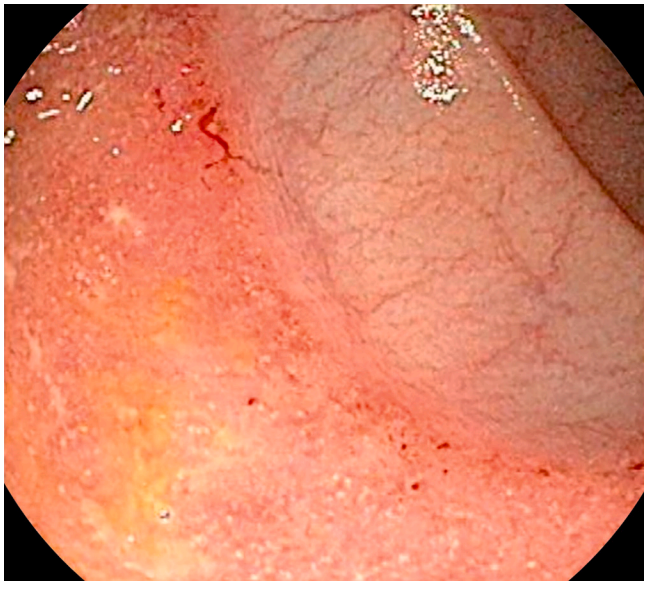

FIGURE 127-3. Endoscopic appearance of ulcerative colitis.

The diagnosis of inflammatory bowel disease is contingent upon accurate histopathologic results, so biopsy of the affected area(s) is key. Findings of an inflammatory infiltrate in the lamina propria and distortion of the crypt architecture support the diagnosis (Fig. 127-2). The diagnosis of Crohn disease may be made by histopathologic examination alone if noncaseating granulomas are seen, but granulomas are rarely found on endoscopic biopsies. The diagnosis of Crohn disease is usually based on a combination of information gleaned from histopathologic findings, colonoscopy, and small bowel imaging. A skip pattern of ulceration, ulceration in the small bowel or upper gastrointestinal tract, or the presence of fistulas support the diagnosis of Crohn disease. Colonic and small bowel ulceration occur in several other disorders, including infections that may not be detected by routine stool studies (such as enterohemorrhagic *E. coli*), vascular disorders, immune-related enterocolitis, neoplasia, diverticulitis, radiation, and medications such as NSAIDs (see Table 127-3).

Ulcerative Colitis

The diagnosis of ulcerative colitis is based on endoscopic findings (Video 127-1) and histopathology.[8] Early in the disease process, patients develop diffuse mucosal erythema with loss of the normal mucosal vascular pattern. In mild disease, the mucosa may have a granular and edematous appearance. As the disease becomes more severe, the mucosa becomes more friable, bleeds easily when the mucosa is touched, and may eventually ulcerate (Fig. 127-3). Endoscopic findings, which start in the rectum and may extend proximally

in a continuous pattern, affect only the colon. The term "backwash ileitis" describes a spillover effect from ulcerative colitis and should not be construed as actual involvement of the terminal ileum by ulcerative colitis. Pseudopolyps may form owing to epithelial regeneration after recurrent attacks in patients with long-standing disease. The presence of pseudopolyps is thought to be a marker of more severe disease. With chronic disease, the colonic mucosa may lose its normal fold pattern, and the colon may shorten and appear narrowed. Careful endoscopic observation—including the observed vascular pattern, bleeding, and ulceration—can assess the severity of ulcerative colitis and monitor its response to treatment.

Features such as crypt distortion, continuous mucosal inflammation starting from the rectum, absence of granulomas, and absence of small bowel disease are consistent with ulcerative colitis. Early in the disease process, chronic inflammatory findings, such as crypt distortion, may not be present, and the diagnosis may be more difficult to establish.

Radiology

Radiologic imaging is vital and almost always should be obtained when inflammatory bowel disease, particularly Crohn disease, is suspected. CT enterography and magnetic resonance imaging (MRI) enterography have supplanted barium studies (such as an upper gastrointestinal series, small bowel follow-through, and barium enema) to diagnose the extent, severity, and type of disease (strictures and fistulas) of Crohn disease. CT and MRI enterography are also useful for the detection of abdominal abscesses and perineal abscesses.

Laboratory Findings

Anemia may result from chronic disease, blood loss, or nutritional deficiencies of iron, folate, or vitamin B_{12}. A modestly elevated leukocyte count is indicative of active disease, but a marked elevation suggests an abscess or another suppurative complication. The erythrocyte sedimentation rate and C-reactive protein are nonspecific serum inflammatory markers that are commonly used to monitor the activity of disease. Fecal calprotectin levels tend to be elevated in active disease and lower when patients are in remission.[9] Hypoalbuminemia is an indication of malnutrition and is common with active disease. Ileal disease or resection of more than 100 cm of distal ileum results in a diminished serum vitamin B_{12} level because of malabsorption.

Serologic Markers

Serologic markers are supportive but may not be used independently to diagnose inflammatory bowel disease. Anti–*Saccharomyces cerevisiae* antibodies (ASCA), which are antibodies to yeast, are present in 40 to 70% of patients with Crohn disease and in less than 15% of patients with ulcerative colitis. The combination of elevated ASCA immunoglobulin A (IgA) and IgG titers is highly specific for Crohn disease, ranging from 89 to 100%. Perinuclear antineutrophil cytoplasmic antibodies (pANCA) are present in 20% of Crohn patients, primarily in colon-predominant disease, and in 55% of patients with ulcerative colitis. ASCA-positive and pANCA-negative disease are associated with a sensitivity of 55% and specificity of 93% for Crohn disease. The antimicrobial antibodies anti-I2 (Crohn disease–related protein from *Pseudomonas fluorescens*), anti-Cbir1 (flagellin-like antigen), and anti-OmpC (*E. coli* outer membrane porin C) are also associated with Crohn disease.

TREATMENT

The aim of medical therapy is to reduce inflammation and subsequently induce and maintain clinical remission while simultaneously healing the mucosa. Medications used to treat inflammatory bowel disease include the categories of 5-aminosalicylate (5-ASA), antibiotics, corticosteroids, immunomodulators (azathioprine, mercaptopurine, methotrexate, and ozanimod), and biologics (infliximab, adalimumab, certolizumab pegol, golimumab, vedolizumab, natalizumab, and ustekinumab; Table 127-4). The specific medical therapy selected[10] is based on the location, extent (nonpenetrating and nonstricturing, stricturing, and penetrating and fistulizing disease), severity of disease, and future prognosis. Patients with high-risk disease (high potential for future surgery or complications such as fistula and abscess) or high disease activity are considered candidates for biologic therapy.[11] Supportive medical therapy, such as antidiarrheal and antispasmodic medications, also may be used. In patients over age 60 years, who represent about 15% of newly diagnosed cases, the risk-benefit ratio of more aggressive therapies may be less favorable.[12]

Categories of Medical Therapy

5-Aminosalicylate

5-ASA, which acts as a topical anti-inflammatory within the lumen of the intestine, is used to treat mild to moderate ulcerative colitis and as maintenance therapy for patients in remission.[A1,A2] Sulfasalazine is the combination of a sulfapyridine with 5-ASA; 5-ASA is responsible for the anti-inflammatory property of this drug, whereas sulfapyridine is the carrier that allows 5-ASA to be delivered to the colon. Other oral formulations of 5-ASA allow it to be delivered to the intestine by different mechanisms. Mesalamine is released in the intestine based on a pH delivery model, whereas sulfasalazine, olsalazine, and balsalazide are released in the intestine by bacterial cleavage of a covalent bond between 5-ASA and a prodrug. For rectal and sigmoid disease, 5-ASA suppository and enema preparations are also effective for induction and maintenance of remission in patients with ulcerative colitis. Adverse events associated with 5-ASAs are uncommon but may include nausea, dyspepsia, hair loss, headache, pancreatitis, worsening diarrhea, and hypersensitivity reactions.

Corticosteroids

Corticosteroids are primarily used to treat flares of ulcerative colitis and Crohn disease. Oral formulations may be used for mild to moderate disease, whereas systemic corticosteroids are used for moderate to severe disease.

Enteric-coated budesonide, a pH-dependent ileal release formulation, is an oral corticosteroid with high topical activity and low systemic bioavailability (10%). Enteric-coated budesonide is indicated for treatment of active mild to moderate ileocecal Crohn disease. Budesonide MMX is released in the colon and is available for treatment of mild to moderately active ulcerative colitis. Budesonide foam is administered rectally with an applicator in the colon for mild to moderately active ulcerative colitis limited to the rectum and sigmoid colon. Oral corticosteroids such as prednisone and methylprednisolone are used for moderate to severe disease, starting at doses ranging from 40 to 60 mg/day for 1 to 2 weeks, then typically tapered over a period of 8 to 12 weeks. Intravenous methylprednisolone is used for severe disease, with dosing ranging from 40 to 60 mg/day. When symptoms are controlled, systemic corticosteroids are not recommended because of their substantial side effects and their lack of efficacy for maintaining remission (Chapter 28).

Immunomodulation

In patients who remain symptomatic despite 5-ASA therapy or who have moderate to severe Crohn disease[A3] or ulcerative colitis,[A4] immunomodulators can provide substantial benefit.[13]

Janus-Kinase Inhibition

Tofacitinib (an oral, nonselective inhibitor of the Janus kinase family) has a more rapid onset of activity for moderate to severe ulcerative colitis[A5] at 10 mg orally twice daily for at least 8 weeks, then 5 or 10 mg twice daily with the medication discontinued if an adequate therapeutic benefit is not achieved by 16 weeks. Side effects include activation of nonsystemic herpes zoster, an abnormal lipid profile, thrombosis, and the potential risk of lymphoma.

Upadacitinib (an oral, selective inhibitor of the Janus kinase family) has a rapid onset of activity and is approved for the treatment of moderate to severely active ulcerative colitis.[A6] The induction dose (45 mg once daily for 8 weeks) should be followed by a maintenance dose (usually 15 mg once daily, but 30 mg once daily can be considered for patients who have refractory, severe, or extensive disease), but dosing should be at the lowest effective dose in the individual patient. Upadacitinib should be discontinued if adequate therapeutic response is not achieved with the 30 mg dosage.

Anti–Tumor Necrosis Factor-α Agents

Monoclonal antibody therapy directed against tumor necrosis factor-α (anti–TNF-α) include infliximab (which is a chimeric mouse-human IgG1 monoclonal antibody that is infused intravenously), adalimumab and golimumab (which are fully human IgG1 antibodies that are self-administered subcutaneously), and certolizumab pegol (which is a chimeric pegylated Fab fragment IgG-4 to TNF-α administered subcutaneously). Infliximab is effective against moderate to severe Crohn disease, fistulizing Crohn disease, and moderate to severe ulcerative colitis that has failed to respond to conventional therapy, as well as in patients who have ulcerative colitis with high-risk prognostic indicators. Adalimumab and certolizumab pegol are effective for moderate to severe Crohn disease that has failed to respond to conventional therapy, and adalimumab and golimumab are useful for moderate to severe ulcerative colitis that has failed to respond to conventional therapy or have high active disease with high-risk prognostic indicators.

In patients with early Crohn disease, timely use and escalation of anti–TNF-α treatment based on symptoms and biomarkers (e.g., a fecal calprotectin ≥250 μg/g of stool, a C-reactive protein level ≥5 mg/L, a Crohn Disease Activity Index ≥150 [E-Table 127-1], or prednisone use in the previous week) results in better clinical and endoscopic outcomes than does symptom-driven decisions alone. Before anti-TNF therapy is considered, however, risk versus benefit needs to be assessed in each individual patient, given the potential risks, including infection and malignancy.

Other Biologics

Natalizumab (a humanized IgG4 monoclonal antibody, against the α_4 subunit of $\alpha_4\beta_1$ and $\alpha_4\beta_7$ integrins expressed on all leukocytes except neutrophils) is useful for treatment of moderate to severe Crohn disease that is refractory to other therapies, but strict guidelines must be followed because of its associated risk for progressive multifocal leukoencephalopathy (Chapter 341). Another small adhesion molecule, vedolizumab (see Table 127-4) is used in patients who have

E-TABLE 127-1 CROHN DISEASE ACTIVITY INDEX

CLINICAL OR LABORATORY VARIABLE	WEIGHTING FACTOR
Number of liquid or soft stools each day × 7 days	× 2
Abdominal pain (graded from 0-3 on severity) each day × 7 days	× 5
General well-being, subjectively assessed from 0 (well) to 4 (terrible) each day × 7 days	× 7
Presence of complications (see below)	× 20
Taking diphenoxylate-atropine or opiates for diarrhea	× 30
Presence of an abdominal mass (0 = none, 2 = questionable, 5 = definite)	× 10
Hematocrit of <0.47 in men or <0.42 in women	× 6
Percentage deviation from standard weight	× 1

TABLE 127-4 MEDICAL THERAPIES FOR INFLAMMATORY BOWEL DISEASE

DRUG	DOSE	RELEASE SITE
5-AMINOSALICYLATES		
Sulfasalazine (Azulfidine)	2-6 g PO/day	Colon
Mesalamine (Asacol, Lialda, Apriso)	2.4-4.8 g PO/day	Distal ileum, colon
Olsalazine (Dipentum)	1-3 g PO/day	Colon
Balsalazide (Colazal)	6.25 g PO/day	Colon
Mesalamine (Pentasa)	2-4 g PO/day	Duodenum, jejunum, ileum, colon
Mesalamine (Rowasa), enema, suppository	4 g/day (enema) 1 g/day (suppository)	Rectum/sigmoid Rectum
Mesalamine (Canasa), suppository	1 g/day (suppository)	Rectum
CORTICOSTEROIDS		
Budesonide (Entocort EC)	Induction: 9 mg PO daily Maintenance: 6 mg PO daily	Small intestine
Budesonide (MMX, UCERIS)	Induction 9 mg PO daily	Colon
Budesonide (UCERIS foam)	2 mg budesonide per metered dose 1 metered dose administered twice daily for 2 weeks followed by 1 metered dose administered once daily for 4 weeks	Colon
Prednisone	0.25-0.75 mg/kg PO daily	Systemic
Methylprednisolone	40-60 mg IV daily	Systemic
IMMUNOMODULATORS		
Upadacitinib	45 mg PO once daily for 8 weeks then 15 mg PO a day further for at least 8 weeks. A maintenance dose of 30 mg PO once daily can be considered for patients who have refractory, severe, or extensive disease. Upadacitinib should be discontinued if an adequate therapeutic response is not achieved with the 30 mg dose	
Tofacitinib	10 mg PO twice daily for 8 weeks then 5 to 10 mg PO twice daily for 8 weeks further then 10 mg twice daily for at least 8 weeks; followed by 5 or 10 mg twice daily, depending on therapeutic response	Systemic
6-Mercaptopurine	1.5 mg PO/kg/day	Systemic
Azathioprine	2.5 mg PO/kg/day	Systemic
Methotrexate	Induction: 25 mg SQ weekly for 4 months Maintenance: 15-25 mg SQ weekly	Systemic
Cyclosporine	2-4 mg/kg/day IV	Systemic
Ozanimod	1 mg PO daily	Systemic
BIOLOGICS		
Infliximab	Induction: 5 mg/kg IV weeks 0, 2, 6 Maintenance: 5-10 mg/kg IV every 8 weeks	Systemic
Adalimumab	Induction: 160 mg SQ week 0, 80 mg week 2 Maintenance: 40 mg SQ every other week	Systemic
Golimumab	Induction: 200 mg SQ week 0 and 100 mg week 2 Maintenance: 100 mg SQ every 4 weeks	Systemic
Certolizumab pegol	Induction: 400 mg SQ weeks 0, 2, 4 Maintenance: 400 mg SQ every 4 weeks	Systemic
Natalizumab	300 mg IV every 4 weeks	Systemic
Vedolizumab	Induction: 300 mg IV at 0, 2, and 6 weeks Maintenance: 300 mg IV every 8 weeks	Systemic
Ustekinumab	Induction: intravenous: Up to 55 kg: 260 mg; greater than 55 kg to 85 kg: 390 mg; greater than 85 kg: 520 mg Maintenance: 90 mg SQ every 8 weeks	
Risankizumab	Induction: 600 mg IV at 0, 4, and 8 weeks Maintenance: 180 mg or 360 mg SQ at week 12 and every 8 weeks thereafter	

IV = intravenously; PO = orally; SQ = subcutaneously.

moderate to severe ulcerative colitis and adult patients with moderate to severe Crohn disease when one or more standard therapies (corticosteroids, immunomodulators, or TNF blocker medications) have not provided an adequate response. Ustekinumab (a monoclonal antibody to the p40 subunit of interleukin-12 and interleukin-23), used as intravenous induction therapy followed by subcutaneous maintenance therapy, can induce and maintain clinical remission in patients with moderately to severely active ulcerative colitis.[A7] Risankizumab (a monoclonal antibody to the p19 subunit of interleukin-23) given as an intravenous induction followed by subcutaneous maintenance therapy (see Table 127-4) can induce and maintain clinical remission in patients with moderately to severely active Crohn disease.[A8,A9] Ozanimod (an oral sphingosine phosphate agonist that reduces lymphocytes at 1 mg orally daily) has rapid onset of action and can induce and maintain remission in patients with moderate to severe ulcerative colitis.[A10]

Other Immunomodulators

The use of azathioprine, 6-mercaptopurine, and methotrexate has fallen out of favor as primary therapy for patients with ulcerative colitis and Crohn disease, because of the superior efficacies and safety profiles of biologic and other agents. These immunomodulators have a slow onset of action, often requiring

several months of administration before their benefits are achieved, so they are used principally for maintenance of remission.

Azathioprine, the prodrug of 6-mercaptopurine, typically is prescribed at a dose of 2 to 3 mg/kg/day; the equivalent dose of 6-mercaptopurine is 1.5 mg/kg/day. Side effects include allergic reactions, pancreatitis, myelosuppression, nausea, infections, hepatotoxicity, and malignancy, especially lymphoma. The white blood cell count and liver chemistries must be monitored routinely. Methotrexate, which is a folic acid antagonist, is given as 25 mg intramuscularly or subcutaneously once per week for 16 weeks for active Crohn disease and 15 mg to 25 mg intramuscularly or subcutaneously once per week for maintaining remission. In addition to its use as primary therapy for Crohn disease, methotrexate has been used in conjunction with other biologic agents to reduce immunogenicity.

Antibiotics

The exact mechanism for the beneficial effect of broad-spectrum antibiotics in the treatment of inflammatory bowel disease is not known. Potential mechanisms include eliminating small intestinal bacterial overgrowth, eradicating a bacterially mediated antigenic trigger by altering the intestinal microbiome, and potential immunosuppressive properties (e.g., metronidazole). The primary role of antibiotics is in Crohn disease, where metronidazole (10 to 20 mg/kg/day for 4 to 8 weeks), ciprofloxacin (500 mg orally [PO] twice daily for 4 to 8 weeks), or both are primary inductive therapies for perianal fistulae. Antibiotics are not used as primary therapy for ulcerative colitis or luminal Crohn disease because they do not induce mucosal healing.

Crohn Disease Medical Therapy

Mild to Moderate Crohn Disease

Sulfasalazine (3 to 6 g/day) is superior to placebo for treating active symptoms of ileocolonic and colonic Crohn disease, with response rates ranging from 45 to 55% for mild to moderate disease.[14] However, sulfasalazine is not clearly effective for small bowel disease alone (Fig. 127-4) and has not been demonstrated to heal the colonic or ileal mucosa. For mild to moderate Crohn disease involving the distal small intestine or proximal colon, enteric-coated budesonide (9 mg/day) provides approximately a 70% response rate after 8 weeks and is significantly more effective than mesalamine (4 g/day) for distal ileal and right colonic disease. Early combined immunosuppression with an anti–TNF-α antagonist and an antimetabolite is more effective than conventional management and more effective than either agent as monotherapy.

Upper gastrointestinal Crohn disease (jejunal, duodenal, gastric, and esophageal) is uncommon, and few clinical trials are available to assess therapies for this location. Because local therapies such as 5-ASAs and budesonide are not released in these locations, systemic immunosuppressants (azathioprine, mercaptopurine, methotrexate, infliximab, adalimumab, and certolizumab pegol, natalizumab, vedolizumab, risankizumab, and ustekinumab; see Table 127-4 for doses) are the mainstays of therapy.[15] In the absence of comparative trials, initial therapy might include the use of anti-TNF therapy alone on in combination with an antimetabolite (6-mercaptopurine, azathioprine, or methotrexate), ustekinumab, risankizumab, or vedolizumab.

Moderate to Severe Crohn Disease

Patients with moderate to severe disease are often initially treated with systemic corticosteroids, but corticosteroids should not be used as maintenance therapy. Biologics can be used initially as therapy for patients with high-risk disease or severe disease activity.[16,17] A meta-analysis suggests that either adalimumab, infliximab plus azathioprine, or ustekinumab are the three most effective therapies for induction and maintenance of remission of Crohn disease.[A1.1] For example, infliximab (5 mg/kg at 0, 2, and 6 weeks and then every 8 weeks) alone or infliximab plus azathioprine (2.5 mg/kg/day) is more effective than azathioprine alone, and initial combined therapy (corticosteroids, daily azathioprine, and infliximab) is preferable to reserving it only for patients who do not respond to corticosteroids plus azathioprine or who have aggressive disease. However, the benefit of using these medications as combination therapy versus individual monotherapy must be assessed in the context of the potential risk of long-term use.

Of patients with Crohn disease who are treated for at least 1 year with infliximab and azathioprine, approximately 50% will experience a relapse within 1 year after discontinuation of infliximab. Given the significant escalated risk for lymphoma in patients under the age 35 years, especially in men, methotrexate is often used in place of azathioprine or 6-mercaptopurin in this patient population. Patients who do not respond to conventional therapy, including an anti-TNF agent (e.g., adalimumab or certolizumab pegol), may be considered for vedolizumab, ustekinumab, or natalizumab (see Table 127-4 for dosing).

For severe Crohn disease, patients should be hospitalized, given nothing by mouth, rehydrated with intravenous fluids, and administered parenteral corticosteroids. Patients who respond to parenteral corticosteroids should be switched to high-dose oral corticosteroids (prednisone, 40 to 60 mg/day), with the dose of prednisone gradually reduced. Patients who have severe Crohn disease and who do not respond to parenteral corticosteroids within 3 to 5 days should be considered for either infliximab or surgery. A course of total parenteral nutrition (Chapter 198) may be useful as adjunctive therapy.

Fistulizing Crohn Disease

Fistulas (Chapter 131) occur in one third of patients with Crohn disease, and perianal fistulas represent the most common location. Asymptomatic internal fistulas rarely require therapy. A concomitant abscess, which may occur in the setting of a fistula, must be excluded before initiating immunosuppressive therapy. Surgery may be required. Medical treatment depends on the location and associated complications.

High-output enterocutaneous fistulas in the setting of proximal small bowel involvement can lead to outputs of more than 500 mL/day and can cause severe volume depletion. Initial management requires volume repletion. In the postoperative setting, a fistulous opening is usually in the area of a wound, and it is imperative to protect the healing skin from infection caused by the drainage

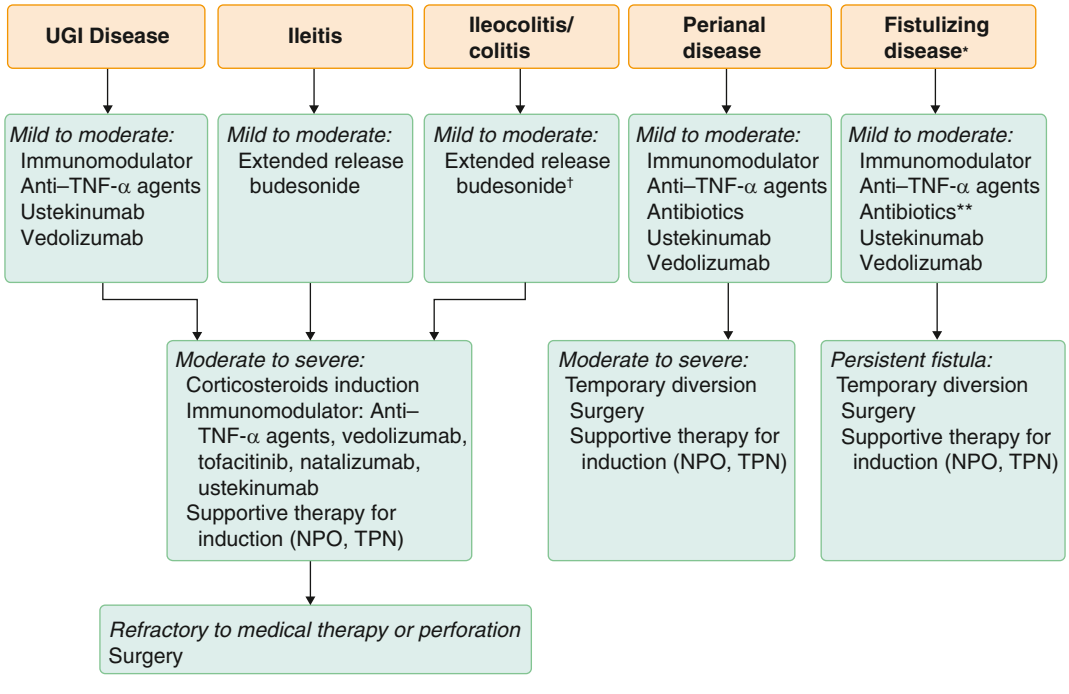

FIGURE 127-4. Crohn disease treatment algorithm. *Abscess should be excluded before initiating medical therapy. †Proximal colon disease involvement. **Perianal location. NPO = nothing by mouth; TNF-α = tumor necrosis factor-α; TPN = total parenteral nutrition; UGI = upper gastrointestinal.

from either an ostomy bag or a catheter used for a high-output fistula. High-output fistulas will rarely close spontaneously and typically will require surgical closure. Low-output fistulas are usually treated initially with anti–TNF-α therapy (e.g., infliximab, adalimumab, or certolizumab; see Table 127-4 for dosing).

Perianal fistulas are classified into simple and complex (Chapter 131). A simple fistula is located below the dentate line (i.e., most of the anal sphincter) and has one track. A complex fistula passes through the intersphincteric (high location), transsphincteric, or suprasphincteric region and may have multiple tracks. Simple fistulas respond well to medical therapy, initially with metronidazole (10 to 20 mg/kg/day PO for 4 to 8 weeks) and/or ciprofloxacin (500 mg PO twice daily for 4 to 8 weeks), but patients will also require additional treatment of the fistula and of any coexisting mucosal disease under expert supervision. Anti–TNF-α agents, ustekinumab, and vedolizumab (see Table 127-4 for dosing) are the first-line medical therapy. Patients with fistulas without rectal mucosal Crohn disease may respond well to fistulotomy, whereas patients with mucosal involvement may benefit from seton placement rather than fistulotomy. Complex fistulas usually require a combination of surgical and medical therapy. In the setting of intractable disease, colonic or ileal diversion may allow for rectal and perianal healing; in severe cases, proctocolectomy may be necessary.

For Crohn disease–related rectovaginal fistulas, medical therapy with anti–TNF-α agents (see Table 127-4 for dosing) or even azathioprine or 6-mercaptopurine is usually considered before surgery. Surgical therapy, such as fistulotomy and mucosal advancement flap surgery, may be considered.

Enterovesicular or colovesicular fistulas may be treated with antimetabolite therapy or anti–TNF-α agents, or both, but recurrent urinary tract infection is an indication for surgery. Surgery usually involves resection of involved bowel and closure of the bladder defect.

Asymptomatic internal fistulas, such as enteroenteric fistulas, do not require surgical intervention, but treatment with an anti-TNF agent (see Table 127-4 for dosing) or perhaps azathioprine or 6-mercaptopurine and/or a biologic agent may be considered. Internal fistulas, such as cologastric and coloduodenal, may cause substantial symptoms because of bypass of part of the intestine. If medical management fails or if an abscess forms, surgery is recommended.

Medical Management of Ulcerative Colitis

The decision guiding which therapy is appropriate for a specific patient with ulcerative colitis is dependent upon several factors, including anatomic distribution of disease; severity of disease activity; and risk (prognosis) of disease (Figure 127-5).[18] When focusing on anatomic distribution of ulcerative colitis as a guide to therapies, several options exist, including suppositories, retention enemas, topical foam, oral therapy, and parenteral therapy. Suppositories are effective to treat proctitis in the distal 20 cm of the colon. Topical foam and enemas are effective for distal and left-sided colitis. Oral therapy and parenteral therapy are effective for all locations of disease.[19]

Proctitis

For active ulcerative proctitis, topical 5-ASA (enema and suppository) in combination with oral treatment is superior to oral treatment alone.[20] Topical 5-ASA is superior to topical corticosteroids for treatment of active ulcerative proctitis; rectal 5-ASA therapy produces a faster response when given with oral 5-ASA. Corticosteroid enemas, suppositories, or foam[A12] also can be used if 5-ASA fails. 5-ASA or corticosteroid retention enemas can be used for active disease up to the splenic flexure (i.e., the rectum, sigmoid colon, and descending colon). Another approach to proctitis or distal colitis is an oral aminosalicylate, although a response may not be evident for 3 to 4 weeks. Additionally, once-a-day extended-release budesonide (budesonide MMX) and topical budesonide foam[A13] are effective for mild to moderately active ulcerative proctosigmoiditis, with fewer steroid-related side effects than conventional corticosteroids.

Extensive Colitis, Mild to Moderate

In patients with mild to moderate activity ulcerative colitis extending proximal to the splenic flexure, the initial drug of choice is an oral 5-ASA; efficacy increases with increasing doses. Even with more extensive disease, supplementation of oral 5-ASA with 5-ASA enemas or suppositories may help reduce the symptoms of fecal urgency that result from rectal involvement, and budesonide MMX provides incremental benefit. In patients with more than five or six bowel movements per day, in patients in whom a more rapid response is desired, or in patients who have not responded to 3 to 4 weeks of 5-ASA, the treatment of choice is oral corticosteroids. Patients with severe diarrhea, systemic symptoms, or significant amounts of blood in their stool should be started on prednisone 40 mg/day; most patients respond to oral corticosteroids within a few days. After the symptoms are controlled, prednisone can be tapered gradually by 5 mg every 1 to 2 weeks. Patients who respond to oral prednisone and can be fully withdrawn from it should be maintained on 5-ASA.

Severe Colitis

If patients with severe ulcerative colitis do not begin to respond to corticosteroids at the equivalent dose of methylprednisolone 60 mg IV within 3 to 5 days or do not completely respond within 7 to 10 days, options include colectomy, infliximab, or cyclosporine[21] (see Table 127-4 for dosing). Tofacitinib (10 mg twice daily) also can improve symptoms and maintain remission in patients with moderate to severe active ulcerative colitis.[22] Ozanimod (1 mg orally daily) also is effective in this situation for inducing and maintaining remission.

For patients whose disease flares whenever the corticosteroids are withdrawn or their corticosteroid dose is lowered, temptation to continue high-dose corticosteroid must be avoided. If the patient requires a substantial dose (>15 mg/day of prednisone) for more than 4 months, a trial of a biologic agent (infliximab, adalimumab, golimumab, vedolizumab, or ustekinumab) or an immunomodulator (azathioprine, mercaptopurine, ozanimod, tofacitinib, or upadacitinib) should be considered for maintenance of remission.[A14–A16] All those agents are efficacious, but vedolizumab may be the most efficacious and safe option.[A17] The choice among these agents requires expert guidance and consideration of the presence or absence of extraintestinal manifestations, the severity of the disease, the presence or absence of other comorbid conditions, the patient's preferences, and insurance coverage. Attempts should be made to reduce the steroid dose, and the goal of treatment is complete steroid withdrawal.

Fecal microbial transplantation is an experimental approach to the treatment of ulcerative colitis. Data so far are promising but inconclusive.[23]

Acute Flare

The most common indication for hospitalization in patients with ulcerative colitis is intractable diarrhea, although blood loss is also common. Patients with severely active ulcerative colitis should be evaluated for toxic megacolon by abdominal radiography or CT. Antidiarrheal medications and anticholinergic medications are contraindicated in patients with severe ulcerative colitis because of the risk for precipitating toxic megacolon. The mainstays of

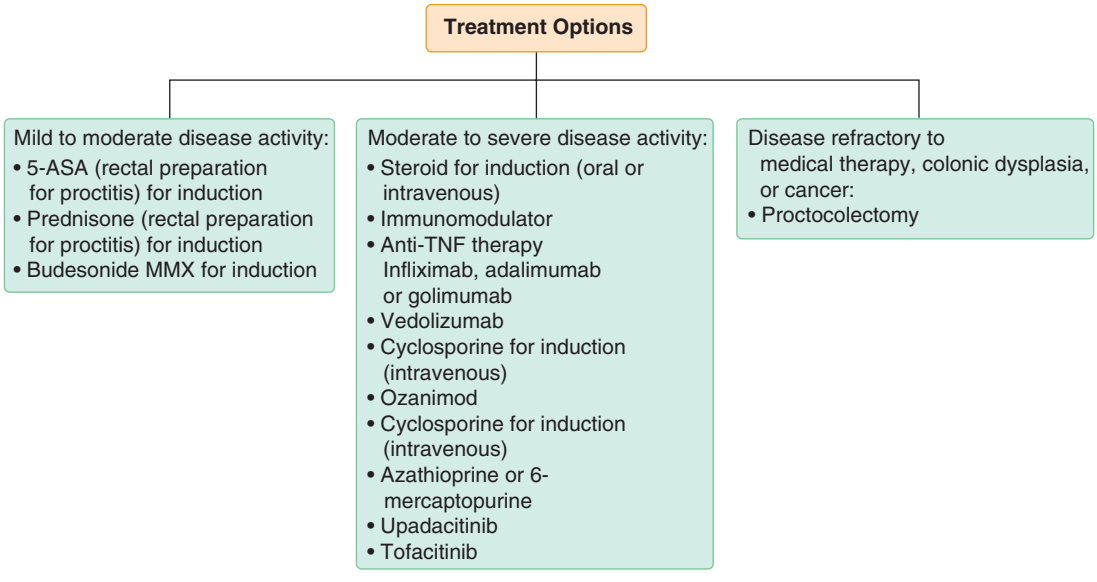

FIGURE 127-5. Ulcerative colitis treatment algorithm. 5-ASA = 5-aminosalicylic acid; MMX = multi-matrix system; TNF = tumor necrosis factor.

therapy for severe ulcerative colitis are rehydration with intravenous fluids and intravenous corticosteroids (hydrocortisone, 300 mg/day; prednisolone, 60 to 80 mg/day; or methylprednisolone, 40 to 60 mg/day). Total parenteral nutrition (Chapter 198) may be necessary in patients with malnutrition. Patients with peritoneal signs or signs of systemic infection should be treated with parenteral antibiotics (Chapter 128). Patients who do not respond in 3 to 5 days should be considered for either colectomy, a trial of intravenous cyclosporines, or a trial of infliximab (see Table 127-4 for dosing).

Maintenance Therapy

Aminosalicylates reduce recurrent disease in patients with ulcerative colitis, and essentially all patients should receive maintenance therapy with a 5-ASA preparation. However, the utility of 5-ASA preparations in patients who are using biologic agents is less well established, and data suggest that once a patient initiates a biologic, aminosalicylates do not add clinical benefit and can be discontinued. Corticosteroids are not effective as maintenance therapy and should not be used in this way. Azathioprine, 6-mercaptopurine, tofacitinib, upadacitinib, ozanimod, infliximab, adalimumab (160 mg at week 0, 80 mg at week 2, and then 40 mg every other week), ustekinumab, and golimumab (see Table 127-4 for dosing) are effective for maintenance therapy in patients whose ulcerative colitis is not controlled by 5-ASA.

Surgical Therapy

Crohn Disease

Since surgical resection does not cure Crohn disease and recurrences are likely after resection, the approach should be conservative in terms of the amount of bowel resected. Failure of medical management is a common cause for resection in patients with Crohn disease, but complications (e.g., obstruction, fistula, and abscess) are often the indications for resection. Overall, the overall 1-, 5-, and 10-year risks of surgery in patients with Crohn disease are about 12%, 18%, and 26%.

For Crohn disease of the small bowel, the most common surgical procedure is segmental resection for obstruction or fistula; the incidence of a recurrence severe enough to require repeat surgery after ileal or ileocolic resection is approximately 25% after 10 years and 35% after 15 years in the absence of biologic therapies. For patients with extensive colonic disease that includes the rectum, the procedure of choice is total proctocolectomy with a Brooke (end) ileostomy. Total colectomy with ileal pouch anal anastomosis is not appropriate in Crohn colitis because recurrent disease in the ileal segment of the new pouch would require a repeat operation and loss of a long segment of ileum. Anti-TNF monotherapy (e.g., infliximab, adalimumab, or certolizumab; see Table 127-4 for dosing) appears to be the most effective strategy for postoperative prophylaxis for Crohn disease,[A18] but ustekinumab and vedolizumab (see Table 127-4 for dosing) also may be effective.

Ulcerative Colitis

For ulcerative colitis, colectomy is a curative procedure. Emergency colectomy may be required in patients with toxic megacolon or a severe fulminant attack without toxic megacolon. Fortunately better medical therapy has substantially reduced the need for colectomy for refractory disease to about 3% at one year, 7% after 5 years, at 10% after 10 years.[24] The decision for or against colectomy and among types of surgery requires expert consultation. The standard operation for ulcerative colitis is proctocolectomy and a Brooke ileostomy, but creating a pouch from the terminal 30 cm of ileum and pulling the distal end of the pouch through the anal canal can preserve anal function and avoid an ileostomy. Ileoanal anastomosis is sometimes complicated by inflammation in the ileal pouch (termed *pouchitis*), which can be treated with antibiotics (typically, metronidazole, 500 mg three times daily or 20 mg/kg/day, or ciprofloxacin, 500 mg twice daily for 2 weeks). The risk for malignancy (see later) also can be an indication for colectomy.

Complications

Crohn Disease

Abscesses

Abscesses, which are common complications in Crohn disease, result from extension of a mucosal fissure or ulcer through the intestinal wall and into extraintestinal tissue. Leakage of intestinal contents through a fissure into the peritoneal cavity results in an abscess. Abscesses occur in 15 to 20% of patients with Crohn disease, especially in the terminal ileum. The typical clinical manifestation of an intra-abdominal abscess is fever, abdominal pain, abdominal tenderness, and leukocytosis. A CT scan is the preferred modality to diagnose intra-abdominal abscess. Broad-spectrum antibiotic therapy, including anaerobic coverage, is indicated. Percutaneous drainage of abscesses in patients with Crohn disease may improve the clinical picture but does not provide adequate therapy because of persistent communication between the abscess cavity and the intestinal lumen. Resection of the involved intestine is usually required for definitive therapy.

Obstruction

Obstruction is a common complication of Crohn disease, particularly in the small intestine, and is a leading indication for surgery. In Crohn disease, mucosal thickening from acute inflammation, muscular hyperplasia and scarring as a result of previous inflammation, or adhesions may cause small bowel obstruction. Obstruction also may occur because of impaction of a bolus of fibrous food in a stable, long-standing stricture. Cramping abdominal pain and diarrhea, which worsen after meals and resolve with fasting, suggest obstruction. Strictures may be evaluated by CT enterography, MRI enterography, oral contrast studies, barium enema, or colonoscopy, depending on the anatomic location. Corticosteroids (e.g., methylprednisolone, 40 to 60 mg/day IV, or hydrocortisone, 200 to 300 mg/day IV for 5 to 14 days) are useful if acute inflammation is an important component of the obstructive process, but not if the obstruction is caused by fibrosis. A common error in the management of Crohn disease is inappropriate treatment with long courses of corticosteroids in patients who have obstructive symptoms from fixed anatomic lesions. If the obstruction does not resolve with nasogastric suction and corticosteroids, surgery is necessary.[25]

Perianal Disease

Perianal disease is a potentially disabling complication of Crohn disease. Ulcerations in the anal canal may coalesce and result in fistula formation (Chapter 131). The fistulous openings are most commonly found in the perianal skin but can occur in the groin, vulva, or scrotum. Fistulas are accompanied by drainage of serous or purulent material. If the fistula does not drain freely, there is local accumulation of pus (perianal abscess) with redness, pain, and induration. The pain of a perianal abscess is exacerbated by local pressure that may result from defecation, sitting, or walking. The typical physical manifestation of an abscess is redness with tenderness on digital examination; fluctuance also may be present. Persistent severe perianal Crohn disease can result in destruction of the anal sphincter and subsequent fecal incontinence. Adequate evaluation of perianal disease generally requires endoscopic examination under anesthesia. Cross-sectional CT or MRI can define the presence and extent of perianal abscesses. The goals of therapy for perianal disease are relief of local symptoms and preservation of the sphincter. Limited disease can be approached with sitz baths and metronidazole, but most cases also require adequate external drainage. Infliximab, adalimumab, certolizumab pegol, ustekinumab, vedolizumab, azathioprine, or 6-mercaptopurine (see Table 127-4 for dosing) may be useful in healing perianal disease, but the disease may reactivate when the drug is stopped. Allogeneic, expanded, adipose-derived stem cells are an experimental treatment for complex perianal fistulas in patients whose Crohn disease does not respond to conventional or biologic treatments or both.

Ulcerative Colitis

One of the most significant complications of ulcerative colitis is toxic megacolon, which is dilation of the colon to a diameter greater than 6 cm associated with worsening of the patient's clinical condition and the development of fever, tachycardia, and leukocytosis. Physical examination may reveal postural hypotension, abdominal tenderness over the distribution of the colon, and absent or hypoactive bowel sounds. Agents that reduce gastrointestinal motility, such as antispasmodics and antidiarrheal agents, have the potential to initiate or exacerbate toxic megacolon. Medical therapy is designed to reduce the likelihood of perforation and return the colon to normal motor activity as rapidly as possible. The patient is given nothing by mouth, and nasogastric suction is begun. Intravenous fluids should be administered to replete water and electrolyte abnormalities, broad-spectrum antibiotics (e.g., ampicillin-sulbactam, given as 1 g ampicillin plus 0.5 g sulbactam, 1.5 to 3 g every 6 hours for 5 to 14 days; levofloxacin, 500 mg/day IV, plus metronidazole, 500 mg IV or PO twice daily; cefazolin, 500 mg IV three times daily, plus metronidazole, 500 mg IV or PO twice daily; or trimethoprim-sulfamethoxazole, 8 to 10 mg/kg/day IV or PO in two to four divided doses, plus metronidazole, 500 mg IV or PO twice daily for approximately 7 days or until symptomatic improvement) are given in anticipation of possible peritonitis as a result of perforation, and parenteral corticosteroids are administered at a dose equivalent to more than 40 to 60 mg of prednisone per day. Signs of improvement include a decrease in abdominal girth and the return of bowel sounds. Deterioration is marked by the development of rebound tenderness, increasing abdominal girth, and cardiovascular collapse. If the patient does not begin to show signs of clinical improvement during the first 24 to 48 hours of medical therapy, the risk for perforation increases markedly, and surgical colectomy is indicated.

Follow-Up

Colon Cancer, Dysplasia, and Colonoscopic Surveillance

The risk for colorectal cancer (Chapter 179) is increased beginning after 8 years of disease and continues to increase in subsequent years.[26] The incidence of colorectal adenocarcinoma is 60 to 100% higher in persons with inflammatory bowel disease than in the general population but has been decreasing over time, likely at least in part because of advances in modern therapies. Patients with extensive ulcerative colitis have a markedly increased risk for colon cancer, patients with left-sided disease have an intermediate risk, and patients with long-standing ulcerative colitis are at risk for colorectal cancer even if their symptoms have been relatively mild or even quiescent for 10 to 15 years.

Colon cancers may be submucosal and may be missed at colonoscopy. Colon cancer in patients with ulcerative colitis is most commonly associated with dysplastic changes in the mucosa, often at multiple sites in the colon. Although

recent data have demonstrated that most dysplasia is visible, not all dysplasia can be identified by visual inspection, so microscopic examination of biopsy specimens is required.

In patients with long-standing ulcerative colitis, current practice guidelines recommend colonoscopy with surveillance using chromoendoscopy or narrow band imaging, with biopsies of abnormal lesions or random colon biopsies, beginning 8 years after the onset of disease and repeated every 1 to 2 years.[27] If the specimens show dysplasia and if a discrete polypoid lesion with well-defined borders cannot be identified, colectomy is recommended.[28]

The risk for colon cancer in patients with Crohn colitis is similar to the risk in patients with a similar extent of ulcerative colitis. Surveillance colonoscopy is also recommended in patients with Crohn colitis.

Pregnancy

Fertility in women with inflammatory bowel disease usually is normal or only minimally impaired, and the incidence of prematurity, stillbirth, and developmental defects in the offspring of women with inflammatory bowel disease, except fetal complications may be somewhat more likely when the mother's disease is clinically active, regardless of drug therapy. Previous proctocolectomy or the presence of an ileostomy is not an impediment to successful completion of a pregnancy, but women who have had ileal pouch anal anastomosis surgery with a total proctocolectomy have markedly reduced fertility.

If a woman's disease is inactive at the time of conception, it is likely that it will remain inactive during the course of the pregnancy. Ulcerative colitis that is active at the time of conception tends to worsen. In patients with active Crohn disease at the time of conception, the degree of activity remains the same in two thirds of women; of the other one third, some improve clinically and others deteriorate.

Sulfasalazine does not harm the fetus, but pregnant women have an increased requirement for folic acid and sulfasalazine interferes with folate absorption by competitively inhibiting the jejunal enzyme folate conjugase. Therefore, women who are taking sulfasalazine and who are pregnant or considering pregnancy should receive folate supplementation (1 mg twice daily) to ensure that the fetus receives adequate amounts for normal development. The use of corticosteroids by pregnant women with inflammatory bowel disease is associated with an increased rate of premature rupture of the membranes and a higher rate of cleft lip. In general, it appears that the risk to the pregnancy of treatment with sulfasalazine or corticosteroids is less than the risk in allowing disease activity to go untreated.

Most of the data on the teratogenicity of azathioprine and 6-mercaptopurine in pregnancy are derived from the transplant literature and involve higher doses than are commonly used for inflammatory bowel disease. Reported fetal effects in the transplant population include congenital malformations, immunosuppression, prematurity, and growth retardation. The risks of these medications in the inflammatory bowel disease population are not completely known, given that only a small number of such patients have been formally studied.

Infliximab, adalimumab, golimumab, certolizumab pegol, vedolizumab, and ustekinumab are considered to be safe during pregnancy, but the risks of these agents are not completely known, because only a relatively small number of patients have been formally studied. To date, data are inadequate to assess fetal risk and guide therapy with ozanimod upadacitinib, and tofacitinib during pregnancy.

PROGNOSIS

Ulcerative Colitis

Recurrent flares and remissions characterize typical ulcerative colitis. A rapidly progressive initial attack results in serious complications in approximately 10% of patients. Complete recovery after a single attack may occur in another 10% of patients. Some patients may actually have had an acute undetected infection rather than true ulcerative colitis. The probability that a patient with clinically inactive disease will remain in remission the following year is 80 to 90%. By comparison, patients with clinically active disease have a 70% probability of relapse during the following year.

Patients who present with ulcerative proctitis have the best overall prognosis, and only approximately 5% of patients with proctitis will require colectomy over a lifetime. Severe complications are very uncommon, but the disease will extend more proximally in the colon in up to 50% of patients. Ulcerative colitis–related mortality has decreased substantially since the introduction of corticosteroids, and recent studies suggest that long-term survival rates for patients with ulcerative colitis are similar to those of the general population.

Crohn Disease

The manifestations of Crohn disease can wax and wane. A patient with clinically active Crohn disease has a 70 to 80% chance of having active disease in the subsequent year, whereas 80% of patients in remission will remain so over the following year. Over the course of a 4-year period, approximately 25% of patients will have persistently active disease after diagnosis, 25% will remain in remission, and 50% will have a fluctuating course with years of remission and years with clinically active disease. Approximately 75 to 80% of all patients with luminal and fistulizing Crohn disease will require surgical intervention for their disease, with approximately 50% of them requiring surgery within 6 months of diagnosis. The rate for a second surgery for luminal Crohn disease ranges from 25 to 38% within 5 years, and 40 to 70% will need reoperation by 15 years.

Patients with Crohn disease have an increased mortality rate, approximately 1.3 to 1.5 times higher than the general population, unrelated to whether they have small intestine or large intestine involvement, or both. This excess mortality, which is most notable in the first few years after diagnosis, is most commonly related to complications of Crohn disease (e.g., colorectal cancer, shock, volume depletion, protein-calorie malnutrition, and anemia). Whether aggressive use of immunomodulators and biologic therapy will alter the natural course of disease is unknown.

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128 INFLAMMATORY AND ANATOMIC DISEASES OF THE INTESTINE, PERITONEUM, MESENTERY, AND OMENTUM

JOHN F. KUEMMERLE

CONGENITAL STRUCTURAL ABNORMALITIES

MECKEL DIVERTICULUM

Meckel diverticulum, which is the most common congenital anomaly of the gastrointestinal (GI) tract, is present in 2 to 3% of the population and is more common in men. Meckel diverticulum occurs when the omphalomesenteric or vitelline duct connecting the fetal yolk sac to the primordial gut fails to close during development. Located on the antimesenteric border, the Meckel diverticulum is commonly found within about 100 cm of the ileocecal valve and typically is 1 to 10 cm in size. Heterotopic tissue is found in about 50% of Meckel diverticula, most commonly gastric or pancreatic tissue but usually not both. The presence of heterotopic tissue correlates with the development of symptomatic complications, with a lifetime risk of about 6%.

CLINICAL MANIFESTATIONS

The complications from a Meckel diverticulum include lower GI bleeding, obstruction, diverticulitis, and perforation.[1] Bleeding can occur when the production of acid from heterotopic gastric mucosa causes ileal ulcerations. Obstruction can result from volvulus around the diverticulum, intussusception of the diverticulum into the intestine, or herniation of the diverticulum and adjacent intestine. Inguinal, femoral, and umbilical hernias all can occur. Repeated and chronic inflammation at the neck of the diverticulum and nearby ileum also can lead to intestinal fibrosis and bowel obstruction. The most common complications are intestinal bleeding in children and obstruction in adults.

DIAGNOSIS

The diagnosis of a Meckel diverticulum can be challenging. Radionuclide imaging with sodium pertechnetate (^{99m}Tn) can be used in cases of bleeding because both normal and heterotopic gastric mucosa take up the tracer (Fig. 128-1). This test has high sensitivity and specificity in children but higher rates of false-positive and false-negative tests in adults. Crohn disease (Chapter 127) and other ileal inflammatory diseases can yield false-positive results. Radiographic imaging with a barium small bowel follow-through typically is not helpful because the diverticulum does not fill with barium contrast. Enteroclysis increases the yield of barium imaging by increasing the pressure and filling of the diverticulum. Angiography can visualize the vestigial vitelline artery that arises from the superior mesenteric artery or a superior mesenteric artery branch that directly feeds the diverticulum or adjacent ileum. Both small bowel capsule endoscopy (Chapter 120) and double-balloon enteroscopy can identify a Meckel diverticulum during the evaluation of obscure bleeding.

TREATMENT AND PROGNOSIS

The management of bleeding, obstruction, or perforation that occurs in association with a Meckel diverticulum is open or laparoscopic surgical resection of the diverticulum and possibly of adjacent ulcerated and bleeding ileum. The surgical resection of a Meckel diverticulum incidentally identified at the time of surgery for another condition is controversial given the low lifetime risk of complications but can be considered in young men, patients with large diverticula, or patients with suspected heterotopic tissue. After identification and treatment, the prognosis is excellent because the Meckel diverticulum is removed, and the risk of complications is eliminated.

INTESTINAL ATRESIA AND STENOSIS, MALROTATION, GASTROSCHISIS, AND OMPHALOCELE

The congenital disorders of intestinal atresia and stenosis, malrotation, gastroschisis, and omphalocele disorders usually present early in infancy and childhood, but sometimes the diagnosis of stenosis or malrotation may be made in adulthood. With the exception of pyloric stenosis, significant long-term morbidity and mortality are associated with these anomalies even after surgical correction. Patients with malrotation or gastroschisis typically present with complications of their surgery, including adhesions, bowel obstruction, or abdominal wall hernias. Patients with intestinal atresia and resulting short gut syndrome also have significant morbidity and mortality related to intestinal failure and the need for long-term total parenteral nutrition.

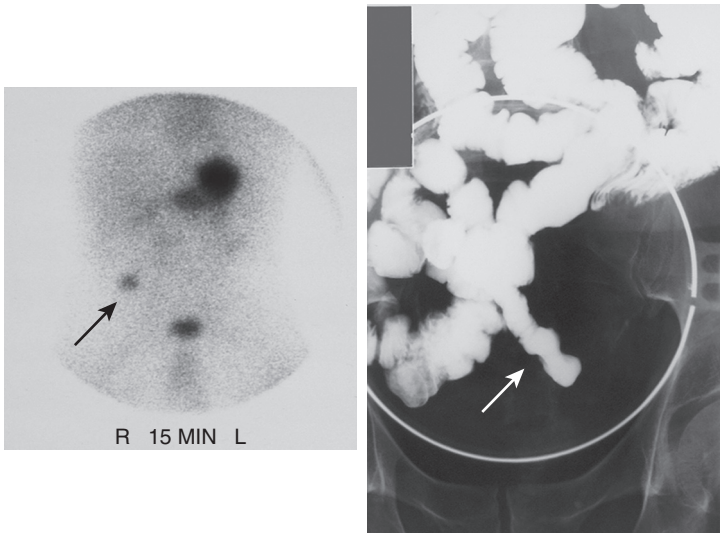

FIGURE 128-1. Meckel diverticulum. Nuclear medicine imaging with ^{99m}Tn pertechnetate scan shows tracer uptake in a Meckel diverticulum (*arrow* in left panel) and in the stomach and bladder. Barium radiography in the same patient also shows the Meckel diverticulum (*arrow* in right panel).

ACQUIRED STRUCTURAL DISORDERS

VOLVULUS

Intestinal volvulus, which is pathologic twisting of the intestine around the mesentery, can result in obstruction of the proximal bowel. Because the mesentery is involved, possible complications include vascular compromise, bowel necrosis, bowel perforation, and peritonitis. The most susceptible regions for volvulus are the sigmoid colon, cecum, and occasionally the transverse colon, with an estimated annual incidence of two to six cases per 100,000. Sigmoid volvulus is most common in men, with a peak age in the 80s, whereas cecal volvulus is more common in women, who typically present in their 60s. Elderly institutionalized individuals are at the highest risk. Small bowel volvulus is uncommonly observed in U.S. adults but can result from preexisting anomalies such as malrotation or congenital bands of Ladd.

CLINICAL MANIFESTATIONS

Volvulus can present with symptoms and signs of acute bowel obstruction, including pain that may be out of proportion to physical findings. Nausea and vomiting are usually present. The presentation also can be more insidious or intermittent with constipation, laxative use, and a previously recognized dilated colon. Physical findings include abdominal distention, tympanic percussion, rebound, guarding, and rigidity. Escalating pain and tenderness can indicate colonic ischemia and perforation.

DIAGNOSIS

The diagnosis of colonic volvulus can be made using abdominal radiographs, which demonstrate a distended colon, loss of haustrations, and a typical "bent inner tube" sign with the apex in the right upper quadrant of the abdomen (Fig. 128-2A) or the "omega" sign (Fig. 128-2B). In cases of a cecal volvulus, the dilated cecum is observed in the epigastrium or in the left upper quadrant. A water-soluble contrast-enhanced radiograph can identify the point of obstruction due to volvulus.

TREATMENT AND PROGNOSIS

Patients with colonic volvulus should have nothing per oral cavity (NPO) with nasogastric (NG) tube decompression and receive appropriate fluid volume resuscitation. In the absence of complete obstruction or signs of ischemia or perforation, patients with a sigmoid volvulus can undergo emergent colonoscopy

ABSTRACT

This chapter reviews the presentation, diagnosis, and treatment of common inflammatory and anatomic diseases of the abdominal organs. Structural disorders include volvulus, hernias, and intussusception. Diverticulitis and appendicitis are common inflammatory disorders of the colon. Rarer disorders of the mesentery and omentum are discussed also.

KEYWORDS

volvulus
diverticulitis
appendicitis
abdominal hernias
peritonitis

and attempted reduction, which is successful in up to 75% of cases.[2] Surgical intervention is indicated for volvulus involving the cecum, transverse colon, or small intestine, as well as after colonoscopic reduction of a sigmoid volvulus because of the risk of recurrence. The mortality rate is about 9% for sigmoid volvulus, 7% for cecal volvulus, and about 17% for combined sigmoid and cecal volvulus or transverse colon volvulus.

INTUSSUSCEPTION

Intestinal intussusception occurs when a segment of bowel invaginates into the adjacent distal intestine and results in bowel obstruction and ischemia. Intussusception usually involves just the small intestine, but it can also present as small intestinal intussusception into the colon. Although intussusception is a common cause of small bowel obstruction in pediatric patients, especially after rotavirus vaccination (Chapter 350), it is rare in adults and accounts for only about 5% of small bowel obstruction. The cause of intussusception is infrequently identified in children, but a cause can be identified in about 90% of adult cases. Typical precipitating causes in adults include small intestinal polyps, benign tumors (including leiomyomas and neurofibromas), malignant tumors, inflammatory bowel disease (Chapter 127), postoperative adhesions, Meckel diverticulum, and feeding tubes.[3]

CLINICAL MANIFESTATIONS

Most patients present with symptoms of partial bowel obstruction, including pain, nausea, and vomiting, and some patients have diarrhea with occult or overt bleeding. The clinical picture can be confusing when the patient has intermittent symptoms from a spontaneously resolved event. A mass may be palpable on examination. Passage of "currant jelly" stools is characteristic of intussusception, especially in children.

DIAGNOSIS

The diagnosis of intussusception is usually made using computed tomography (CT), which reveals a characteristic alternating high- and low-attenuation target-like or sausage-shaped lesion that represents the invaginated intestinal segments. However, because of the confusing presentation of intussusception in adults, a combination of plain radiographs, upper GI series, and barium enema frequently is required for an adequate evaluation.

TREATMENT AND PROGNOSIS

Colonic intussusceptions are treated surgically in adults because of the high likelihood that a colonic malignancy is the causative lesion. For small intestinal intussusception, a randomized trial showed that hydrostatic reduction is superior to pneumatic reduction in children.[A1] This approach has been tried in adults in whom no other significant causative lesion is present. However, adults with small intestinal intussusception frequently have an underlying pathologic cause, so their treatment consists primarily of surgical intervention and bowel resection, which not only resolves the obstruction but also provides a diagnosis of the causative lesion. If the predisposing cause can be diagnosed and corrected, the prognosis is good, and recurrence rates are low. If the underlying cause is not fully correctable such as with neurofibromatosis (Chapter 385) or adhesions, intussusceptions may recur.

HERNIAS

Anatomically, hernias comprise a herniated viscus, the hernial sac (internal wall of the hernia lined by peritoneum), and the hernial ring. Whereas an external hernia occurs when the viscus lies outside the abdomen, an internal hernia occurs when the viscus lies in an abnormal location within the abdominal cavity. Secondary hernias can occur at previous sites of incision or injury. Incisional, inguinal, and umbilical hernias comprise 90% of all hernias. Hernias are common and occur in about 5% of the population within their lifetimes. For inguinal hernias alone, the lifetime cumulative incidence is estimated to be 43% in men and 6% in women. By comparison, femoral, umbilical, and incisional hernias occur twice as often in women.

CLINICAL MANIFESTATIONS, DIAGNOSIS, AND TREATMENT OF SPECIFIC HERNIAS

Epigastric hernias

Epigastric hernias occur at sites of congenital weakness in the midline between the xiphoid and umbilicus along the linea alba. Small epigastric hernias may be asymptomatic or difficult to identify. Larger epigastric hernias can present as nodules, sometimes with tenderness. Multiple hernias may be present. Diagnosis is made by physical examination complemented by ultrasound or CT imaging. They can be repaired surgically if symptomatic or if complications are present.

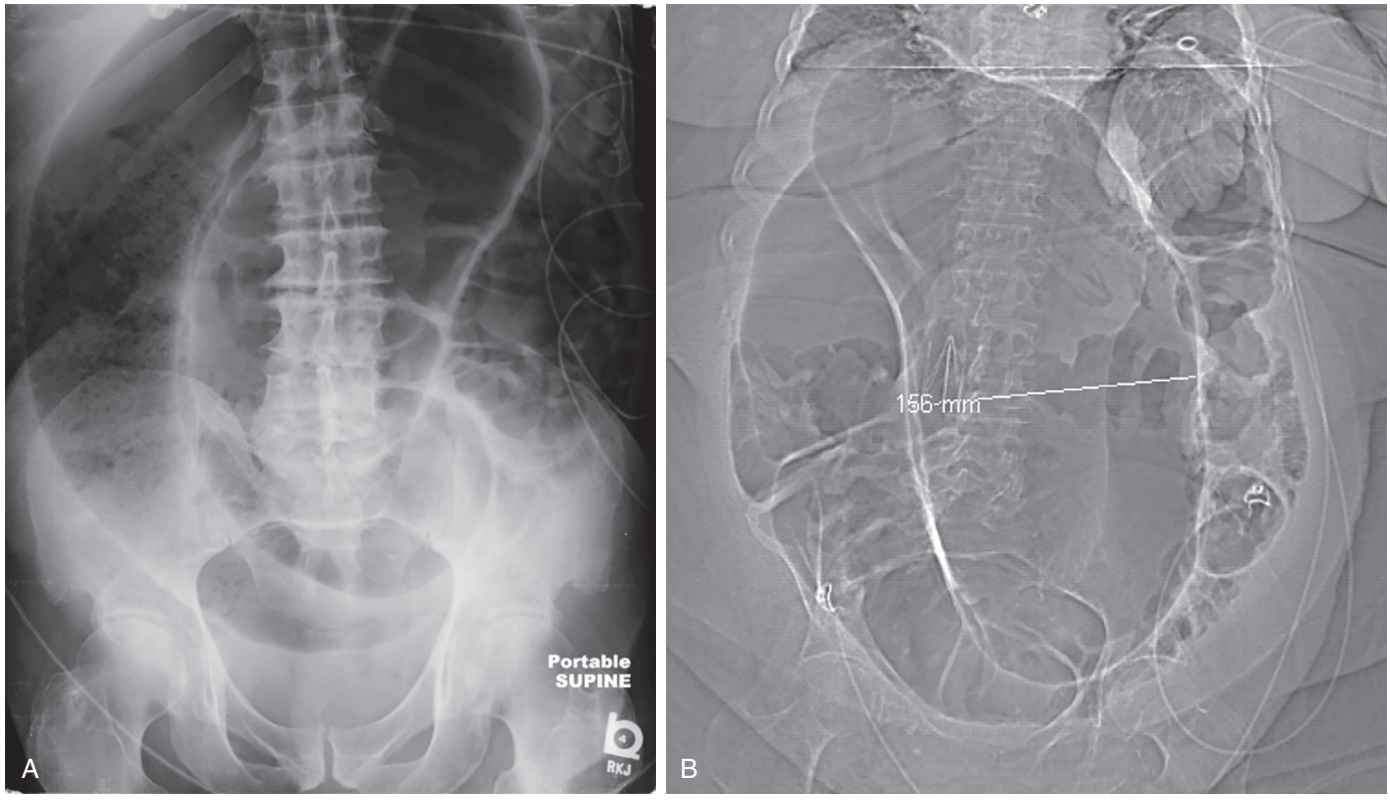

FIGURE 128-2. Sigmoid volvulus. Plain abdominal radiograph shows the presence of a sigmoid volvulus. **A,** "Bent inner tube" sign. **B,** "Omega" or "coffee bean" sign.

Umbilical hernias

Umbilical hernias occur in association with obesity, in multiparous women, and in patients with ascites. They present as a protuberant mass palpable at the umbilicus. Incarceration of small bowel or omentum is common, and strangulation occurs in about one third of umbilical hernias. Umbilical hernias can be repaired surgically, with mesh repair preferable to suture repair,[A2] if they are symptomatic or associated with complications, but ascites should be controlled for the hernia repair to succeed.

Groin hernias

Groin hernias present with bulging in this region, particularly with Valsalva maneuvers. Whereas direct inguinal hernias occur at the site of weakness at the base of the Hesselbach triangle, indirect inguinal hernias occur lateral to the Hesselbach triangle. Both direct and indirect inguinal hernias are above the inguinal ligament. Femoral hernias occur below the inguinal ligament in the femoral canal. Pain is typically mild, but more severe pain or colicky abdominal pain suggests incarceration or strangulation. Palpation can reveal the presence of a groin hernia that increases in size with standing or increased intra-abdominal pressure, such as a Valsalva maneuver, but palpation may be difficult in obese patients. In unclear cases, CT imaging can be helpful. The differential diagnosis of an inguinal bulge also includes adenopathy, lipoma or other tumors, testicular torsion of an undescended testicle, and abscess. Femoral hernias should be repaired when first diagnosed because of their risk for strangulation. Because the presence of strangulation can reliably be made only at surgery, more severe symptoms warrant early surgical intervention.

Watchful waiting is an acceptable option for men with minimally symptomatic inguinal hernias, although the majority of men will ultimately be referred for surgery, primarily because of pain, within 10 years.[4] The treatment of symptomatic groin hernias is surgical, now usually by open mesh-based techniques or laparoscopic repair, with mesh techniques probably providing slightly better long-term results.[A3] Open repair can be performed under local anesthesia, whereas laparoscopic repair, which generally results in less postoperative pain and an earlier return to normal activities, requires general anesthesia and carries a small risk of major intra-abdominal injury.[5]

Pelvic hernias

Pelvic hernias occur through a weakened pelvic floor and are six-fold more common in women, especially with advancing age. The most common form is an obturator hernia, but less common forms include a sciatic hernia through the sciatic foramen or perineal hernias through the pelvic floor musculature. Most obturator hernias present with acute bowel obstruction. A tender mass may be palpable near the obturator canal on rectal or vaginal examination. Inner thigh pain on internal rotation of the hip may be present in 50% of patients. Diagnosis can be aided using CT imaging. The treatment is surgical.

Incisional hernias

Incisional hernias can develop after 1 to 4% of laparotomy incisions. Incisional hernias may cause chronic abdominal discomfort, especially with maneuvers that increase intra-abdominal pressure. Repair is usually performed with prosthetic mesh, which appears to provide better outcomes than suture repair[6] and is also useful for prophylaxis against a future incisional hernia at the time of a midline laparotomy.[A4]

More rare hernias include lumbar hernias (which are more common in men and after surgery for trauma), Spigelian hernias occurring through the linea semilunaris in elderly patients, and internal hernias that occur when an intraperitoneal organ protrudes into a separate compartment within the abdomen. Some hernias occur in surgically created defects or because of congenital defects (e.g., paraduodenal, pericecal, or foramen of Winslow). Up to 15% of internal hernias occur through mesenteric or omental defects. Most patients present with intermittent symptoms of pain and bowel obstruction or strangulation. Radiologic studies can be of variable assistance. The differential diagnosis should include volvulus, adhesions, and tumors. The diagnosis can be made using barium studies and CT imaging. Surgery is needed to reduce the herniated viscus and close any defect.

INFLAMMATION OF THE INTESTINE AND COLON

APPENDICITIS

Appendicitis, which is the most common intra-abdominal pathology that requires emergency surgery, affects about 1 per 1000 adults annually worldwide.[7] The lifetime prevalence of appendicitis is 8.7% in men and 6.9% in woman. Lifetime rates of appendectomy are higher, 12% in men and 23% in women, because the diagnosis may be difficult to confirm noninvasively and because of the practice of operating on patients in whom the condition is highly suspected.[8] About one third of patients have luminal obstruction of the vermiform appendix, most commonly caused by an appendicolith but also occasionally by lymphoid hyperplasia or tumors, including carcinoid tumors (Chapter 213). Gangrenous appendicitis is almost always associated with luminal obstruction.

CLINICAL MANIFESTATIONS AND DIAGNOSIS

The differential diagnosis of appendicitis is extensive (Table 128-1). Current guidelines for diagnosis include characteristic history and physical findings of abdominal pain; localized tenderness; or other signs of acute appendicitis, including increased right lower quadrant pain with cough, pain with flexion and internal rotation of the hip, pain with passive extension of the right hip, and increased right lower quadrant pain during palpation of the left lower quadrant. Laboratory evidence of inflammation includes leukocytosis, greater than 10,000/μL but usually less than 18,000/μL unless perforation has occurred, with left shift, and elevated markers such as the C-reactive protein or procalcitonin level. The use of a standardized approach, the Adult Appendicitis Score (Table 128-2),[9] can reduce unnecessary imaging and hospital admissions.[A5] However, none of these tests are accurate enough to make or exclude the diagnosis of appendicitis in patients with an intermediate probability score. The preferred diagnostic test is multidetector CT, preferably using a low-dose, 2 mSv CT, which has a sensitivity and specificity of at least 94%[A6] and perhaps higher and can also detect perforation (Figs. 128-3 and 128-4). Nonenhanced CT is nearly as good as contrast-enhanced CT for diagnosing acute appendicitis,[10] while limiting exposure to iodinated contrast and its potential adverse effects in patients for whom it is a concern. A point-of-care ultrasound is helpful if positive, but a negative test does not exclude the diagnosis. Even expert ultrasonography is less sensitive and specific, 83% and 93%, respectively than CT, but it is useful when CT is contraindicated, such as in pregnant women or a suspected ectopic pregnancy. Magnetic resonance imaging is no better than CT but is an accurate option for pregnant women.[11]

TREATMENT AND PROGNOSIS

When acute appendicitis is suspected, emergent surgical consultation and appendectomy are indicated. Laparoscopic appendectomy is preferred over open appendectomy because of lower rates of postoperative complications and a more rapid return to normal eating and activity, except open appendectomy is preferred in patients with evidence of perforation.[A7] Preoperative antibiotics (e.g., cefotetan, 2 g intravenously, or cefoxitin, 2 g intravenously followed by three postoperative doses or ticarcillin–clavulanic acid) reduce infectious complications in otherwise uncomplicated appendicitis. Because perforation of the appendix increases the risk of mortality from 0.0002% to 3% and increases the morbidity rate from 3% to 47%, the traditional approach is that a negative laparotomy is an acceptable trade-off to missing true appendicitis.

A nonoperative approach using antibiotics to treat uncomplicated appendicitis[12] can reduce routine surgical morbidity but at the expense of more than

TABLE 128-1 DIFFERENTIAL DIAGNOSIS OF ACUTE APPENDICITIS

SURGICAL CAUSES
Intestinal obstruction
Intussusception
Acute cholecystitis (Chapter 141)
Mesenteric adenitis (especially from adenoviral infection; Chapter 333)
Meckel diverticulitis
Right-sided colonic diverticulitis
UROLOGIC CAUSES
Right nephrolithiasis (Chapter 111)
Right pyelonephritis (Chapter 263)
GYNECOLOGIC CAUSES
Ectopic or tubal pregnancy
Ruptured or torsed ovarian cyst
Right-sided salpingitis or tubo-ovarian abscess (Chapter 264)
MEDICAL CAUSES
Yersinia (Chapter 288) or *Campylobacter* (Chapter 279) enterocolitis
Crohn ileitis (Chapter 127)
Pneumonia (Chapter 85)
Diabetic ketoacidosis (Chapter 210)
Herpetic neuralgia (especially right 10th and 11th nerves; Chapter 346)
Porphyria (Chapter 194)
Tuberculous colitis (Chapter 299)

TABLE 128-2 ADULT APPENDICITIS SCORE

	VARIABLE	VALUE
Symptoms and findings	RLQ pain	2
	Pain relocation	2
	RLQ tenderness	
	Woman age 16-49 years	1
	All others	3
	Guarding	
	Mild	2
	Moderate or severe	3
Laboratory	Leukocytosis (WBC/μL)	
	≥7,200 and <10,900	1
	≥10,900 and <14,900	2
	≥14,000	3
	Proportion of neutrophils (%)	
	≥62 and <75	2
	≥75 and <83	3
	≥83	4
	CRP (mg/L) and symptoms <24 h	
	≥4 and <11	2
	≥11 and <25	3
	≥25 and <83	5
	≥83	1
	CRP (mg/L) and symptoms >24 h	
	≥12 and <53	2
	≥53 and <152	2
	≥152	1
Total score	≤10 low probability 11-15 intermediate probability ≥16 high probability	

CRP = C-reactive protein; RLQ = right lower quadrant; WBC = white blood cell count. Online calculator: http://www.appendicitisscore.com/.

From Sammalkorpi HE, Mentula P, Leppäniemi A. A new adult appendicitis score improves diagnostic accuracy of acute appendicitis—a prospective study. *BMC Gastroenterol.* 2014;14:114.

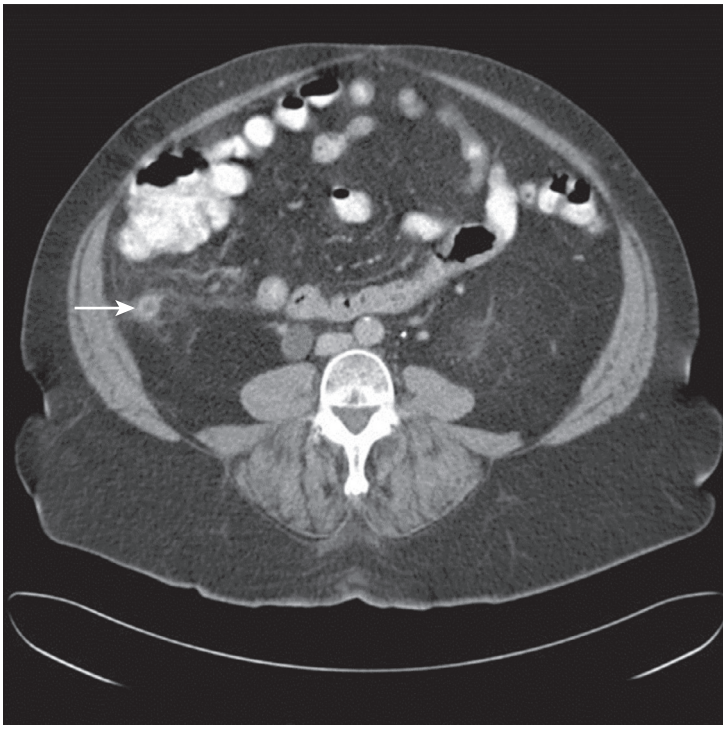

FIGURE 128-3. Appendicitis. A computed tomography scan shows an inflamed appendix with a diameter greater than 1 cm (*arrow*) consistent with acute, uncomplicated appendicitis.

a two-fold increase in complications, including about a 2% risk of rupture, a 1% risk of gangrenous appendicitis, and a 25 to 30% need for readmission or surgery within 3 to 12 months.[A8,A9] If antibiotics are chosen for uncomplicated appendicitis, 2 days of intravenous ertapenem (1 g daily) followed by 5 days of oral levofloxacin (500 mg daily) and metronidazole (500 mg three times daily) is slightly better than 7 days of oral moxifloxacin (400 mg daily).[A10]

The benefits of surgery are most notable in patients with an appendicolith. In the United States, the professional consensus tends to favor surgical appendectomy, except in patients who have had prior surgical complications, but informed decision making is recommended because many patients may prefer a nonoperative approach.[12]

For a perforated appendix with abscess formation, immediate appendectomy yields similar results to a strategy of percutaneous ultrasound- or CT-guided drainage, intravenous (IV) antibiotics, and laparoscopic appendectomy about 10 weeks later. In the setting of perforation, once-daily dosing with ceftriaxone and metronidazole for 7 to 10 days is as good as triple-dose therapy.

Complications develop in more than 15% of patients, with an overall mortality rate of about 3% in patients with perforated appendicitis. Complications are uncommon in surgically treated nonperforated appendicitis. Patients who have appendectomies for suspected but not confirmed appendicitis have a prognosis that depends on whether they had an underlying disease, such as Crohn disease (Chapter 127) or carcinoid tumor (Chapter 213). In adults over age 40 years, the risk of developing a right-sided colon cancer may be increased by as much as 10-fold,[13] so careful follow-up is warranted.

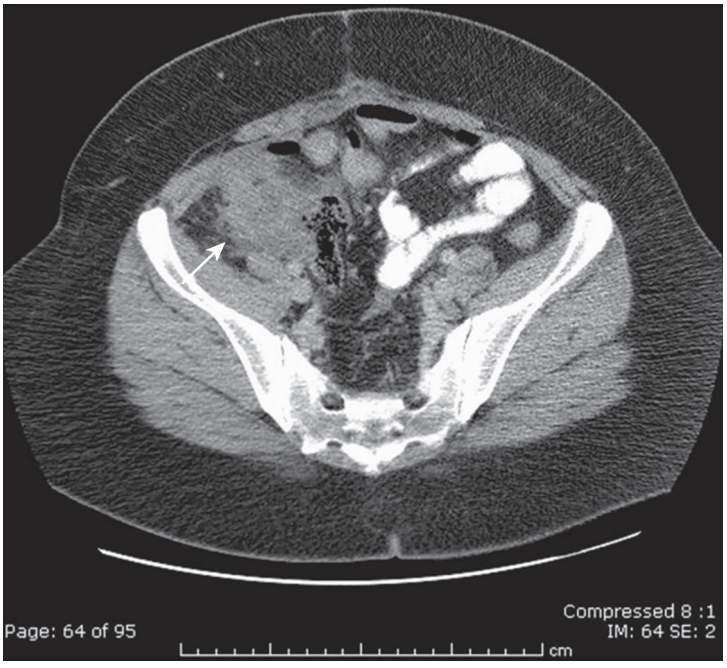

FIGURE 128-4. Appendicitis. A computed tomography scan shows appendicitis complicated by perforation with abscess formation (*arrow*). (Courtesy of Charlene Prather, MD.)

DIVERTICULITIS OF THE COLON

Colonic diverticula are technically pseudodiverticula. They form when the colonic mucosa and submucosa herniate through the muscularis propria of the colon. A spectrum of problems can result from diverticulosis, including diverticulitis, which is an infected diverticulum, or diverticular bleeding, which is manifested as acute lower GI bleeding (Chapter 121).[14] Diverticular disease (Fig. 128-5 and E-Fig. 128-1) affects about 10% of middle-aged adults and increases in prevalence up to about 80% in elderly adults. Acute diverticulitis is now more common than acute appendicitis in the emergency departments of developed countries.[14]

Colonic diverticula form at the site where the nutrient artery, the vasa recta, penetrates the muscularis propria. Diverticulosis in Western populations is most common in the left colon and has been thought to be associated with the low-fiber content of the typical Western diet, although recent epidemiologic studies cast doubt on this hypothesis. Diverticulosis can occur anywhere in the colon, however, and it is more commonly observed in the right colon in Asian populations.

The lifetime risk of diverticulitis is up to 25%. Diverticulitis is thought to occur when impacted material in the diverticulum compresses the blood supply, thereby resulting in a microperforation. Diverticulitis can be complicated further by free perforation, abscess, or fistula formation.

E-FIGURE 128-1. Colonic diverticula. An abdominal flat plate shows residual barium in diverticula scattered throughout the colon. (Courtesy of Charlene Prather, MD.)

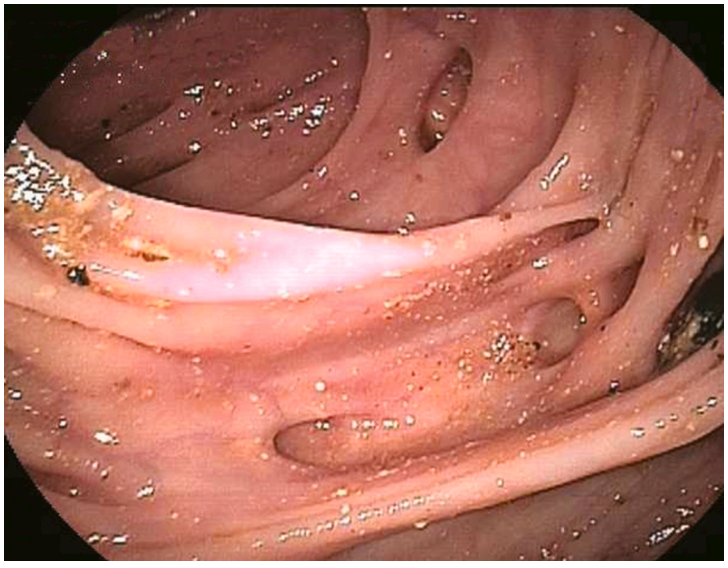

FIGURE 128-5. Sigmoid diverticulosis. The colonoscopic appearance of sigmoid diverticulosis coli.

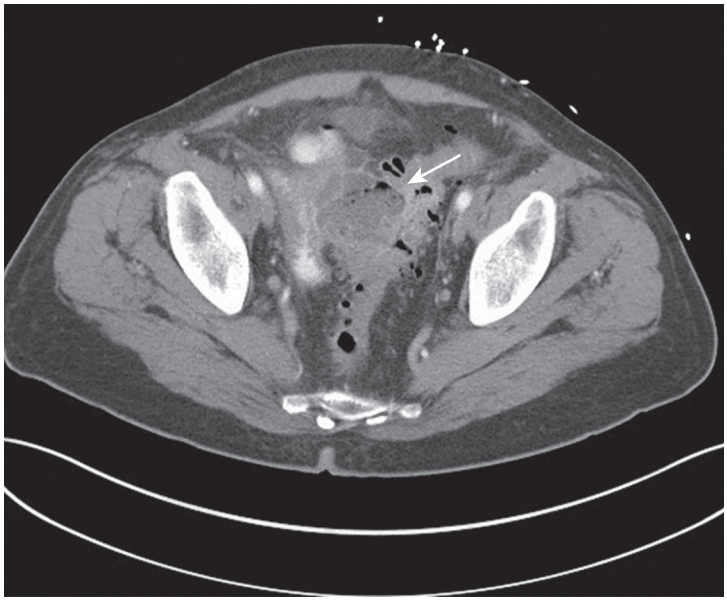

FIGURE 128-6. Diverticulitis. A computed tomography scan shows acute diverticulitis with perforation. An abscess (*arrow*) is seen presenting as a fluid and air-filled collection.

CLINICAL MANIFESTATIONS

The majority of patients with colonic diverticulosis are asymptomatic. Patients with diverticulitis commonly present with localized pain, fever, and anorexia. The pain may radiate to the back, flank, or suprapubic region. Nausea and vomiting, constipation or diarrhea, or urinary symptoms may be variably present. Physical examination typically reveals left lower quadrant tenderness, sometimes with localized guarding or a palpable mass. Rebound tenderness or peritoneal signs should suggest the presence of free perforation. Visible diverticular bleeding is rare in the setting of acute diverticulitis. Leukocytosis is present. When the acutely inflamed diverticulum is adjacent to the bladder, sterile pyuria may be found.

DIAGNOSIS

The clinical suspicion of acute diverticulitis is correct in only about 40 to 56% of cases, so the diagnosis must be confirmed in the appropriate setting by leukocytosis plus an ultrasound examination or a CT scan showing diverticulosis coli with localized inflammation of the colonic wall and pericolic fat at the site of acute diverticulitis.[15,16] A CT scan also can demonstrate free perforation, abscess, or fistula formation (Fig. 128-6). Because of the increased risk of perforation, invasive testing such as barium enema or colonoscopy is contraindicated when a diagnosis of acute diverticulitis is being entertained. The differential diagnosis of acute diverticulitis includes inflammatory bowel disease (Chapter 127), gastroenteritis, appendicitis, and colon cancer (Chapter 179) with perforation.

TREATMENT

Perforated diverticulitis with rupture of fecal material into the full peritoneum is a life-threatening surgical emergency. For diverticulitis with purulent but non-fecal peritonitis, randomized trials comparing laparoscopic peritoneal lavage with surgical resection have shown essentially no difference in outcomes.[A11] For diverticulitis with focal abscess formation, treatment is percutaneous CT-guided drainage and subsequent surgery, usually laparoscopic, typically after 6 weeks.[17]

Uncomplicated acute diverticulitis is usually treated with antibiotics, but antibiotics have limited benefit.[A12] A 7- to 10-day course of oral antibiotics (e.g., amoxicillin–clavulanate[18] [500 mg/125 mg] alone or ciprofloxacin [750 mg twice daily] plus metronidazole [500 mg four times daily]), perhaps after a single IV dose of antibiotics, is as effective and safe as hospitalization for IV antibiotics.[19] Patients who can tolerate clear liquids can be treated in the outpatient setting with gradual advancement of their diet. Patients who are unable to tolerate eating should be admitted to the hospital for IV fluids and antibiotics (e.g., levofloxacin 750 mg daily and metronidazole 500 mg every 6 hours or piperacillin–tazobactam 3.375 g every 6 hours). For diverticular and other intra-abdominal infections that have had adequate surgical treatment, fixed-duration antibiotic therapy of approximately 4 days provides similar outcomes to longer courses until after the resolution of physiologic abnormalities (about 8 days).

Although the risks associated with one episode of uncomplicated diverticulitis are low, with a mortality rate that is less than 1%, complicated diverticulitis, defined as diverticulitis with abscess, fistula formation, free perforation, or obstruction, is associated with increased inpatient morbidity in up to 25% of cases and has a mortality rate as high as 5%. Furthermore, these risks increase with a second episode of complicated diverticulitis. Elective segmental colectomy typically has been recommended to patients after two to three episodes of complicated diverticulitis and in young patients even after a first episode. However, recent evidence suggests that the risk of complicated diverticulitis after recovery from uncomplicated diverticulitis is only about 5% and is actually lower, not higher, after subsequent episodes of uncomplicated diverticulitis. However, prophylactic elective surgery is probably preferable in patients who have either three or more episodes of acute diverticulitis within 2 years or have persistent abdominal complaints for more than 3 months after a confirmed episode of left-sided diverticulitis.[A13–A15]

Acute diverticulitis can be complicated by colitis or late stricture formation. About 40% of patients with complicated diverticulitis have significant morbidity, and their mortality rate is about 6%, but it is only about 2% in patients without perforation. There is no convincing evidence that a high-fiber diet prevents recurrent diverticular disease or that nuts or any particular foods should be favored or avoided.

OTHER INTESTINAL INFLAMMATORY CONDITIONS

SMALL INTESTINAL ULCERS

Most primary idiopathic ulcers are found in the mid- to distal ileum, where they can be solitary or multiple. A careful history is necessary to exclude other precipitating causes of small intestinal ulcers, including drug exposure and other systemic diseases (Table 128-3). Pathologically, these ulcers can be differentiated from Crohn disease or chronic ulcerative jejunoileitis by the absence of granulomas. Barium contrast studies including enteroclysis can make the diagnosis, and CT or magnetic resonance enterography also can be helpful. In the absence of bowel obstruction, video capsule endoscopy is often the preferred test. Therapy with anti-inflammatory or immunosuppressive medications has not proven helpful. Therapy is typically directed to complications, including perforation and obstruction, with segmental surgical resection. However, the risk of ulcer recurrence is high.

Drug-induced ulcerations are common and can result from nonsteroidal anti-inflammatory drugs (NSAIDs), potassium chloride preparations, vasoactive medications, antimetabolites, and cocaine. Video capsule endoscopy can make the diagnosis (Fig. 128-7). NSAID-induced injury is similar to Crohn disease, with transmural injury and the risk of stricture formation. Treatment is aimed at avoiding the offending agent, if possible. A recent randomized trial demonstrated that adding a proton pump inhibitor to a non-selective NSAID actually increased the short-term risk of drug-induced small bowel injury.[A16]

A variety of systemic conditions also can manifest with small intestinal ulcerations. Patients with Crohn disease (Chapter 127) can have ulcers of

TABLE 128-3 CAUSES OF SMALL INTESTINAL ULCERS

CATEGORY	CAUSES
Acidic	Meckel diverticulum, Zollinger-Ellison syndrome
Drug-induced	Potassium chloride, NSAID, antimetabolite
Idiopathic	Primary ulcer, Behçet disease
Infectious	Tuberculosis, typhoid, *Yersinia*, *Strongyloides* superinfection
Inflammatory	Crohn disease, SLE, chronic jejunoileitis
Metabolic	Uremia
Neoplastic	Malignant histiocytosis, lymphoma, adenocarcinoma
Radiation	Radiation enteritis
Vascular	Mesenteric vascular insufficiency, vasculitis, arteritis

NSAID = nonsteroidal anti-inflammatory drug; SLE = systemic lupus erythematosus.

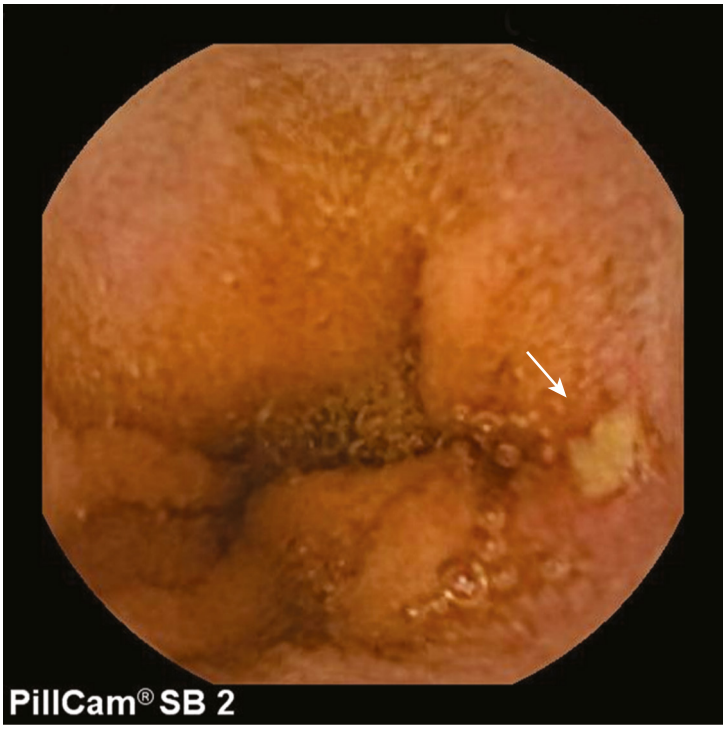

FIGURE 128-7. Nonsteroidal anti-inflammatory drug (NSAID)–induced enteropathy. The wireless capsule endoscopy appearance of a jejunal ulceration (*arrow*) caused by NSAID use.

any portion of the GI tract. Systemic lupus erythematosus (Chapter 245), rheumatoid arthritis (Chapter 243), scleroderma (Chapter 246), polyarteritis nodosa (Chapter 249), and Henoch-Schönlein purpura (Chapter 249) can present with small intestinal ulcerations that are thought to be secondary to microthrombosis and vasculitis. Mesenteric vasculitis presents as nausea, vomiting, fever, and GI bleeding.

Behçet disease (Chapter 249) is a systemic process that causes intestinal ulcers, typically in the ileocecal region, in fewer than 1% of cases. Although symptoms are similar to those of Crohn disease, pathologically Behçet disease-related ulcers are deep and do not have surrounding inflammation or granulomas. The optimal treatment of this disease has yet to be delineated. Patients frequently are treated with immunomodulators (Chapter 249), and surgery is reserved for ulcer-related complications.

Sarcoidosis (Chapter 83) uncommonly involves the intestine. Its presentation is similar to Crohn disease, with small and large intestinal ulceration and noncaseating granulomas. Patients commonly have nausea, vomiting, diarrhea, abdominal pain, and protein-losing enteropathy. Treatment is targeted to controlling the systemic disease.

Mycobacterium tuberculosis (Chapter 299) typically involves the distal ileum and cecum. A waxing and waning course can mimic the symptoms and location commonly seen in Crohn disease. The diagnosis is suspected based on a history of exposure, particularly in endemic regions, and confirmed by colonoscopy with biopsy, stains, and culture. Treatment is as for disseminated tuberculosis (Chapter 299).

Histoplasma capsulatum (Chapter 308) presents with ulcerations and polypoid masses that mimic tumors, typically in an immunocompromised patient. Patients present with diarrhea, bleeding, and obstruction. The granulomas seen on biopsy must be differentiated from Crohn disease, tuberculosis, and sarcoidosis. Treatment involves managing the systemic infection.

Neutropenic enterocolitis, or typhlitis (E-Fig. 128-2),[20] is an inflammation of the intestine or colon, usually during the neutropenic phase 10 to 14 days after high-dose induction chemotherapy. It involves right lower quadrant abdominal pain, distention, and diarrhea, sometimes with bleeding. These findings in themselves are nonspecific and are similar to *Clostridioides difficile*–associated colitis (Chapter 271) and ischemic colitis (Chapter 129). Diagnosis is based on typical CT scan findings of thickened bowel wall; bowel distention, especially of the cecum; and associated inflammatory changes. Treatment is conservative, with bowel rest and decompression when bowel dilation is present, and broad-spectrum antibiotics. Leukocyte-stimulating agents are often used to reverse the neutropenia (Chapter 153). Treatment of bleeding is supportive with transfusions and correction of any coagulopathy. Surgery is indicated in the setting of intractable bleeding or perforation. The symptoms resolve rapidly with resolution of neutropenia.

VISCERAL ANGIOEDEMA

Visceral angioedema can be idiopathic, or it can be a complication of hereditary and acquired C1 esterase inhibitor deficiency (Chapter 232), hypocomplementemia, drugs (especially angiotensin-converting enzyme inhibitors), or foods. Patients with GI angioedema commonly present with abdominal pain and distention, nausea, vomiting, and diarrhea. Some patients also have evidence of mucous membrane swelling, hives, wheezing, or dyspnea. On CT scan, thickened, fluid-filled loops of small bowel and ascites also may be seen. Symptoms commonly occur episodically, persist for 1 to 3 days and may recur periodically. The diagnosis is established by discontinuing the implicated drug or food, low serum levels of C4, low C1 esterase quantitative levels, or reduced C1 esterase functional activity. C1 esterase inhibitor deficiency can be treated successfully with C1 inhibitor therapy (Chapter 232).

RADIATION ENTERITIS

Radiation injury[21] can occur in the small or large intestine as a result of therapy for gynecologic, urologic, rectal, or retroperitoneal tumors. Acute injury, which can occur during the course of treatment, is associated with nausea, diarrhea, and abdominal or rectal discomfort. The risk is related to radiation dose. Chronic injury typically presents 6 months to 2 years after treatment and presents with progressive bowel obstruction owing to continued inflammation and fibrosis. Patients with radiation proctitis present with rectal pain, bleeding, and occasionally diarrhea.

Acute radiation injury is usually self-limited to the period of treatment, but up to 5% of patients can progress to chronic radiation injury to the small intestine, and up to 15% of patients experience chronic radiation proctitis. Radiation enteritis and stricture formation can be seen on barium radiographs or CT scans. The characteristic neovascularization pattern of telangiectasias from radiation proctitis is seen on endoscopy.

One-third to one-half of patients develop bleeding, which can be minor and intermittent or more substantial. Whereas patients who do not require transfusion have a 70% chance of remission, patients with chronic radiation enteritis who need transfusion have a low rate of remission (20%) and have subsequent high morbidity and even mortality rates. Radiation proctitis can be difficult to treat.

Two therapies, endoscopic argon plasma coagulation and rectal formalin infusion, were demonstrated to have similar efficacy in a recent RCT.[A17] Surgery for intestinal radiation enteritis, which can be required in up to one third of patients with strictures or bleeding, is associated with a high complication rate and should be avoided if possible.

PERITONEAL DISORDERS

PERITONITIS

Peritonitis, which is a local or generalized inflammation that involves the visceral and parietal peritoneum, can occur as a primary or secondary process. Primary peritonitis in adults is the spontaneous infection of ascites in a patient with cirrhosis (Chapter 139) in the absence of an overt intra-abdominal source. The use of acid-suppressive therapy appears to increase the risk of

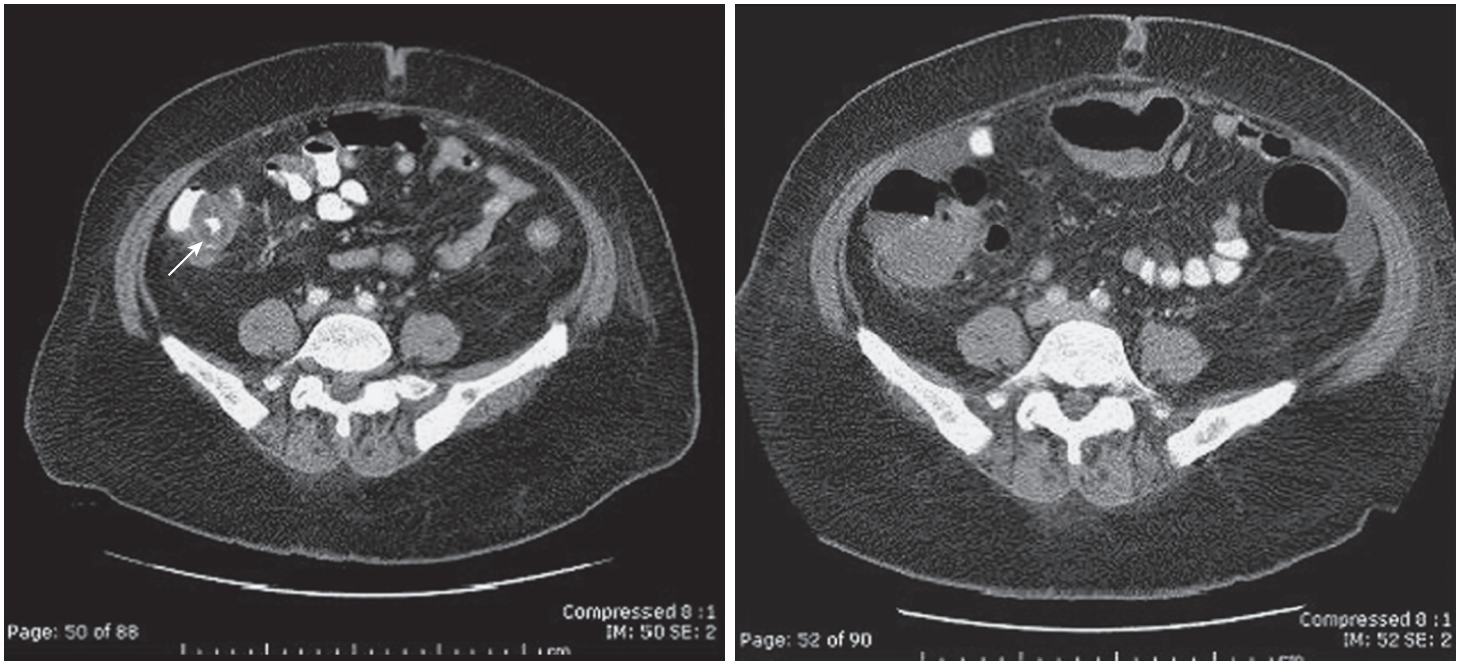

E-FIGURE 128-2. Computed tomography scans showing neutropenic colitis. The *left* scan shows a thickened cecal wall (*arrow*). Eight days later, a follow-up scan shows resolution (*right* scan). (Courtesy of Charlene Prather, MD.)

developing spontaneous bacterial peritonitis three-fold in hospitalized patients with cirrhosis.

Secondary peritonitis develops when disease or injury to the intestine results in bacterial contamination from a perforated viscus (e.g., peptic ulcer disease, appendicitis, diverticulitis, penetrating trauma, or iatrogenic), from iatrogenic causes (e.g., peritoneal dialysis or surgical contamination), from granulomatous disease (e.g., tuberculosis or fungal infections), or from chemical or aseptic exposures (e.g., bile, urine, or radiographic barium).

CLINICAL MANIFESTATIONS AND DIAGNOSIS

Abdominal pain is the hallmark of peritonitis. It can be sudden in onset in the setting of a perforated viscus or more insidious in nature in the setting of granulomatous or chemical causes. Patients with peritonitis typically lie supine with flexed knees and exhibit shallow breathing. Physical examination reveals a distended abdomen with tenderness to palpation, localized or generalized guarding, and rigidity. Associated symptoms include fever, nausea, vomiting, and leukocytosis with a left shift. Some patients with bacterial peritonitis rapidly develop septic shock (Chapter 94).

Granulomatous peritonitis has a more insidious presentation, and 70% of patients have symptoms for 4 months before diagnosis. Systemic symptoms include fever, malaise, anorexia, and weight loss. The abdomen is diffusely tender. Leukocytosis can be absent.

Patients with tuberculous peritonitis (Chapter 299) often have a positive skin test result or infiltrates on their chest radiograph. The peritoneal fluid typically has a high protein level (<3 g/dL), a low glucose (<30 mg/dL), and elevated leukocytes (<250 cells/μL); fluid stains and cultures are unhelpful, but polymerase chain reaction (PCR)–based tests can be diagnostic. The laparoscopic appearance of tuberculous peritonitis is characteristic, with fibrous masses from the parietal peritoneum and granulomas.

Plain abdominal radiographs may show evidence of paralytic ileus, and free air under the diaphragm on upright views confirms the presence of a perforated viscus. CT scan is more sensitive, 70 to 100%, than plain radiographs for detecting free air and may also demonstrate the underlying cause (Fig. 128-8). CT/positron emission tomography can be useful for distinguishing tuberculous peritonitis from peritoneal carcinomatosis.[22]

In young patients, appendicitis and a perforated duodenal ulcer (Chapter 125) are common causes. In older patients, perforated diverticula and cancer (Chapter 179) are more common. In women of child-bearing age, tubal pregnancy and a ruptured tubo-ovarian abscess must be considered (Chapters 264 and 275). Secondary peritonitis is usually caused by a mixed flora of bacteria, including *Escherichia coli, Streptococcus faecalis, Pseudomonas aeruginosa, Klebsiella mirabilis, Bacteroides fragilis, Clostridium* spp, and anaerobic streptococci.

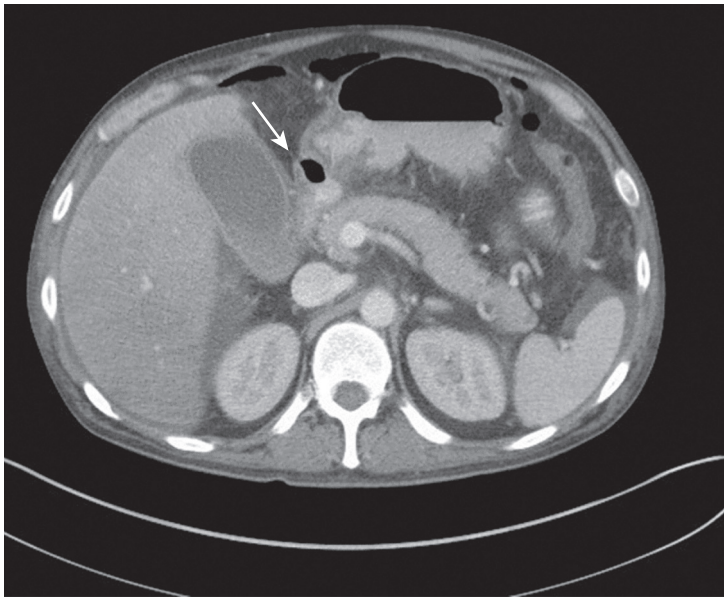

FIGURE 128-8. Peritonitis. A computed tomography scan in a patient with peritonitis showing a thickened duodenal wall from a perforated duodenal ulcer (*arrow*) found at the time of surgical exploration.

TREATMENT AND PROGNOSIS

Treatment of acute suppurative peritonitis relies on prompt adequate resuscitation with IV fluids and broad-spectrum IV antibiotics. Treatment regimens include: piperacillin–tazobactam, 3.375 g every 6 hours; ampicillin–sulbactam, 3.0 g every 6 hours; ciprofloxacin, 500 mg every 12 hours, and metronidazole, 1 g every 12 hours; levofloxacin, 750 mg every 24 hours; cefepime, 2 g every 12 hours, and metronidazole, 1 g every 12 hours; or imipenem–cilastatin sodium, 500 mg every 6 hours.[A18] Early diagnosis and surgical intervention for acute peritonitis from perforated viscus is critical. The mainstay of treatment for tuberculous peritonitis is at least 6 months of a multidrug regimen (Chapter 299).

Chemical aseptic peritonitis can be complicated by secondary bacterial infection. Treatment is similar to that of acute suppurative peritonitis, with intervention to control the source of peritoneal contamination.

The outcome of peritonitis depends on its cause as well as the rapidity of treatment. The mortality rate can be as low as 15% in patients who have correctable causes, such as a perforated appendix, and who do not develop multiorgan failure before treatment but as high as 50% for postoperative infective peritonitis.

PERITONITIS AS A COMPLICATION OF CHRONIC AMBULATORY PERITONEAL DIALYSIS

The most common complication of chronic ambulatory peritoneal dialysis is infectious peritonitis from bacterial contamination (Chapter 117), which commonly results from poor technique. In contrast to polymicrobial acute suppurative peritonitis, peritonitis complicating chronic ambulatory peritoneal dialysis is typically monomicrobial with gram-positive cocci in the majority of cases and gram-negative species in the remainder of cases. Fungal peritonitis is rare. Symptoms can be milder than in other forms of peritonitis, with patients often presenting with diffuse abdominal pain, low-grade fever, and leukocytosis. The exchange fluid is characteristically turbid and may be the only sign of infection. The diagnosis is based on these physical findings, turbid dialysate with less than 100 leukocytes/μL, and a positive dialysate culture that determines the microbe involved. Treatment is with intraperitoneal antibiotics. The dialysis catheter should be removed in the setting of an inadequate response to therapy, fungal or tuberculous peritonitis, or concomitant skin infection. The risk of peritonitis can be reduced by the judicious use of prophylactic intravenous vancomycin and oral nystatin or fluconazole.[A19]

ADHESIONS

Peritoneal adhesions, which are the most commonly observed cause of bowel obstruction,[23] can occur at any time after a laparotomy,[24] with rates about one-third lower with laparoscopic as compared with open surgery.[25] Adhesions are also the most common cause of small bowel obstruction in patients who have not had prior abdominal surgery.[26] Patients who have had intra-abdominal infection, ischemia, and peritonitis are at increased risk. Patients present with complete or incomplete bowel obstruction, which is usually manifested as colicky abdominal pain, nausea, and vomiting (including feculent vomiting), abdominal distention, and an absence of flatus or stooling. Bowel obstruction can be diagnosed on plain radiographs or CT scan from the presence of dilated bowel and air-fluid levels, with decompressed bowel distal to the site of obstruction (Fig. 128-9). Treatment of bowel obstructions is with NG tube decompression and fluid resuscitation. A nonoperative approach can be attempted in cases of partial bowel obstruction or in patients who have had numerous prior laparotomies, which make surgical exploration more complicated. However, urgent laparotomy for lysis of adhesions must be performed before bowel ischemia develops. In patients with chronic abdominal pain, surgical exploration for the intent of lysing adhesions without clear evidence of obstructing adhesions should be avoided. Patients who develop postoperative adhesions can progress to bowel obstruction and develop recurrent adhesions despite surgical lysis of the adhesions.

PERITONEAL CARCINOMATOSIS AND MALIGNANT ASCITES

Peritoneal carcinomatosis results when malignancy spreads throughout the peritoneal cavity and eventually encases the viscera. The cause can be primary tumors of the peritoneal cavity (e.g., mesothelioma and sarcoma), dissemination of an intra-abdominal malignancy (e.g., gastric, colon, pancreatic, ovarian, or neuroendocrine tumors), lymphomas, metastatic spread from extra-abdominal malignancy (e.g., breast, lung, or melanoma), and pseudomyxoma peritonei (a rare condition with gelatinous peritoneal implants from mucinous neoplasms of the appendix or ovary).

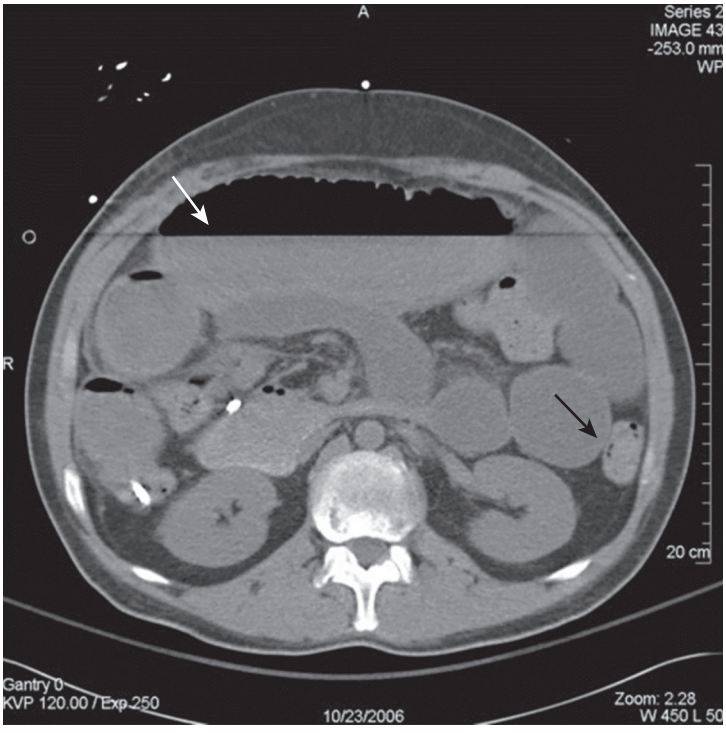

FIGURE 128-9. Small bowel obstruction. A computed tomography scan shows dilated, fluid-filled small bowel (*white arrow*) and a nondilated colon (*black arrow*) in a patient with a small bowel obstruction from adhesions found at the time of surgical exploration.

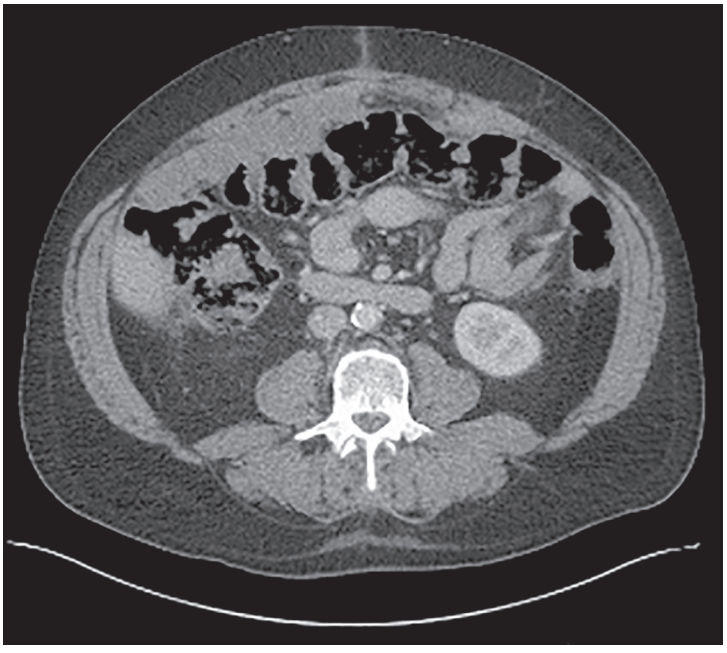

FIGURE 128-10. Carcinomatosis. A computed tomography scan shows peritoneal carcinomatosis in a patient with colon cancer.

CLINICAL MANIFESTATIONS AND DIAGNOSIS

The presentation of peritoneal carcinomatosis is nonspecific, with complaints of abdominal pain, anorexia, nausea, vomiting, malaise, and weight loss. Ascites is the most common physical finding. Malignant ascites is rare, accounting for less than 10% of cases of ascites.

Although ultrasound examination may document ascites, CT is preferred to identify carcinomatosis and the origin of the underlying cause (Fig. 128-10). Diagnostic paracentesis can be performed to obtain cell count and differential, culture, and cytologic examination. A serum to ascites albumin ratio of less than 1.1 mg/dL suggests malignant ascites, but the differential diagnosis also includes pancreatic ascites (Chapter 130), nephrotic syndrome (Chapter 107), and peritoneal tuberculosis. Laparoscopy can disclose the typical tumor implant stubbing the peritoneum. Biopsy and appropriate stains can verify the presence of mesothelioma (Chapters 86 and 177) by detecting hyaluronic acid on Alcian stain in a specimen that has a negative carcinoembryonic antigen stain and no mucin on a periodic acid–Schiff stain. By contrast, carcinomas have no hyaluronic acid but show mucin and have a positive carcinoembryonic antigen stain.

TREATMENT AND PROGNOSIS

Treatment is typically palliative owing to the late presentation of disease. Malignant ascites responds poorly to diuretic therapies, and repeated therapeutic paracentesis may be needed. Recent data suggest some benefit from cytoreductive surgery and hyperthermic intraperitoneal chemotherapy.

DISEASES OF THE MESENTERY AND OMENTUM

The differential diagnosis of mesenteric and omental disorders include a variety of rare disorders, including inflammation, cysts, and tumors that can be benign or malignant (Table 128-4).

Mesenteric panniculitis presents in middle or later age with a slight male predilection. Symptoms typically include nonspecific abdominal pain, weight loss, nausea, vomiting, and low-grade fever, but patients occasionally can present with an acute abdomen. A palpable mass is felt in the majority of patients. The diagnosis can be confirmed by CT scan. Lesions should be biopsied to exclude malignancy but generally are not amenable to complete resection. Significant improvement in the symptoms of this generally self-limited process has been reported with progesterone, corticosteroids, azathioprine, or cyclophosphamide, but evidence to recommend their general use is lacking.

TABLE 128-4 MESENTERIC DISEASES

PRIMARY INFLAMMATORY DISEASE
Panniculitis
Retractile mesenteritis
CYSTS
Developmental
Traumatic
Neoplastic
Infectious
TUMORS
Benign tumors
Lipoma
Leiomyoma
Hemangioma
Malignant tumors
Liposarcoma
Leiomyosarcoma
Rhabdomyosarcoma
Metastatic tumor
Mesenteric fibromatosis

Mesenteric and omental cysts and solid tumors are rare disorders. Patients present with a constellation of nonspecific symptoms. They can be identified with CT scan. Surgical resection will provide the definitive diagnosis and determine whether a benign or malignant condition is present.

Mesenteric fibromatosis (desmoid tumors) is a rare noninflammatory condition that may be associated with familial adenomatosis polyposis (Chapter 179). Fibromatoses are locally aggressive tumors that may present as stable or rapidly growing intra-abdominal masses. They have a high rate of recurrence after incomplete surgical resection, in patients with multicentric disease, or if precipitated by surgical trauma itself.

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129 VASCULAR DISEASES OF THE GASTROINTESTINAL TRACT

CHARLES J. KAHI

INTESTINAL ISCHEMIA

Intestinal ischemia can be caused by a variety of disorders that result in decreased blood supply to the bowel. The injury itself, as well as its presentation, management, and outcome, vary depending on acuity, the splanchnic vessel(s) affected, the presence or absence of collateral circulation, the segment and the length of bowel involved, and whether the arterial or venous circulation is compromised. Recognition and appropriate management are crucial to improve patients' outcomes.[1]

EPIDEMIOLOGY

About 1 in 1000 hospital admissions is related to intestinal ischemia. Intestinal ischemia can be occlusive or nonocclusive, and can also be classified as acute or chronic, arterial or venous, and small bowel or colonic ischemia. Risk factors for intestinal ischemia include older age and conditions that predispose to arterial disease (e.g., atherosclerosis, fibromuscular dysplasia, abdominal aortic aneurysm, trauma, vasculitis), embolism (e.g., cardiac arrhythmias, cardioversion, heart failure, cardiomegaly, dyskinesia, valvular heart disease, recent myocardial infarction, cardiac catheterization, intracardiac thrombus, atheromatous cholesterol embolism), low-flow states (e.g., sepsis, dialysis, reduced cardiac output, vasoconstrictive drugs), or pathologic thromboses (hypercoagulable and hyperviscosity states, portal hypertension, trauma, malignancy, inflammation). Intestinal arterial and venous thrombosis have also been seen as complications of severe acute respiratory syndrome coronavirus 2 (Chapter 336).[2]

PATHOBIOLOGY

Blood flow to the digestive system is largely supplied by the celiac axis, superior mesenteric artery, and inferior mesenteric artery. The celiac axis gives rise to the left gastric artery, common hepatic artery, and splenic artery. These arteries and their branches (gastroduodenal, right gastroepiploic, and anterior superior pancreaticoduodenal) supply portions of the esophagus (also supplied from the aorta, right intercostal, bronchial, inferior thyroid, short gastric, and left phrenic arteries), stomach, duodenum, pancreas, and liver. The superior mesenteric artery supplies the majority of the small intestine and right colon via the inferior (anterior and posterior) pancreaticoduodenal arteries, the middle colic, right colic, and ileocolic arteries. The inferior mesenteric artery supplies the left colon via the left colic artery and proximal rectum via the superior rectal artery. The distal rectum receives its arterial supply from the internal iliac artery. Collateral vessels connect the three major systems: the superior and inferior mesenteric arteries can communicate through the marginal artery of Drummond, which runs along the mesenteric border, the meandering mesenteric artery (arc of Riolan) at the base of the mesentery, and the central anastomotic artery. The celiac axis and superior mesenteric artery are connected via the pancreaticoduodenal arcade (formed from the superior pancreaticoduodenal branch of the celiac axis and inferior pancreaticoduodenal branch of the superior mesenteric artery), the arc of Barkow, and the arc of Buhler. Collateral vessels vary from person to person, but in general, the stomach, duodenum, and rectum have extensive collaterals and are thus more resistant to ischemic events. Conversely, the splenic flexure and descending colon have more limited collaterals, thereby creating "watershed" areas that are more vulnerable to ischemia during low blood flow states.

Blood flow to the intestine is regulated by the sympathetic nervous system, angiotensin II, vasopressin, and prostaglandins. Under normal conditions, intestinal blood flow accounts for nearly 10% of cardiac output, and it may increase to 25% in the postprandial state. The bowel can withstand a 75% reduction of blood flow for up to 12 hours, whether due to arterial, venous, occlusive, or nonocclusive causes. This adaptability is because only a fraction of mesenteric capillaries are open under normal circumstances, and the bowel responds to reduced blood flow by increasing capillary flow and the efficiency of oxygen extraction. However, prolonged and severe reduction in blood flow can result in generalized mesenteric vasoconstriction, which diminishes flow through collaterals, thereby leading to potentially irreversible ischemia even if the underlying cause is corrected. Diminished delivery of oxygen and nutrients to the bowel results in ischemic injury; reperfusion after an ischemic episode can also injure the bowel. These insults are mediated by oxygen radicals, reduced endothelial synthesis of nitric oxide, and an enhanced cellular inflammatory response. In early stages, the damage involves the bowel mucosa, but it may progress to transmural necrosis.

ACUTE MESENTERIC ISCHEMIA

Acute mesenteric ischemia of the small bowel is considered a medical emergency, and delays in identification and management can result in death within a short period of time. Acute mesenteric ischemia should be distinguished from colonic ischemia, which has a generally better prognosis. Categories of acute mesenteric ischemia include superior mesenteric artery embolus or thrombosis, nonocclusive mesenteric ischemia, focal segmental ischemia, and mesenteric venous thrombosis.

CLINICAL MANIFESTATIONS

A high index of suspicion is critical so the diagnosis can be made before the intestine suffers irreversible damage. A cardinal symptom is abdominal pain, which is typically out of proportion to the amount of abdominal tenderness elicited on physical examination.[3] The pain can be periumbilical or ill-defined. In general, acute mesenteric ischemia should be considered in older patients who develop rapid-onset abdominal pain in the context of a cardiac arrhythmia, heart failure, a recent myocardial infarction, a retrograde aortic catheterization, or hypotension. It should also be suspected in younger patients who have hypercoagulable states (Chapter 67) or who use vasoactive substances (Chapter 365) and who have persistent and unexplained abdominal pain. Other features at presentation may include fever, nausea and vomiting, diarrhea, and abdominal distention. In elderly patients, the presenting symptoms may be nonspecific, such as an altered mental state.

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CLINICAL MANIFESTATIONS

A high index of suspicion is critical so the diagnosis can be made before the intestine suffers irreversible damage. A cardinal symptom is abdominal pain, which is typically out of proportion to the amount of abdominal tenderness elicited on physical examination.[3] The pain can be periumbilical or ill-defined. In general, acute mesenteric ischemia should be considered in older patients who develop rapid-onset abdominal pain in the context of a cardiac arrhythmia, heart failure, a recent myocardial infarction, a retrograde aortic catheterization, or hypotension. It should also be suspected in younger patients who have hypercoagulable states (Chapter 67) or who use vasoactive substances (Chapter 365) and who have persistent and unexplained abdominal pain. Other features at presentation may include fever, nausea and vomiting, diarrhea, and abdominal distention. In elderly patients, the presenting symptoms may be nonspecific, such as an altered mental state.

ABSTRACT

The vascular diseases of the gastrointestinal tract encompass a wide variety of disorders. Intestinal ischemia is caused by reduced blood flow to the digestive tract, thereby resulting in injuries that depend on acuity, splanchnic vessel involvement, and other factors. Acute mesenteric ischemia involving the small bowel is considered a medical emergency, and prompt recognition and management are critical to improve patient outcomes. The most common causes are thrombotic, embolic, nonocclusive, and mesenteric venous thrombosis. Diagnosis depends on a high index of suspicion in the appropriate clinical context and imaging of the mesenteric vessels. Multidisciplinary management includes supportive measures, antibiotics, anticoagulants, vasodilators, and surgical or radiologic revascularization. Colon ischemia generally has a better prognosis than acute mesenteric ischemia, except in the case of isolated right-sided colon ischemia. The systemic vasculitides can affect the gastrointestinal tract, and the manifestations depend on the size of the vessels affected. Vascular anomalies of the digestive tract are common, especially in older age; endoscopic treatment is effective and indicated if there is evidence of blood loss.

KEYWORDS

splanchnic circulation
mesenteric ischemia
mesenteric vascular occlusion
colitis
ischemic
gastrointestinal hemorrhage
angiodysplasia
vasculitis

The pattern and rapidity of the onset of symptoms can offer clues to the etiology. Patients with an embolism can present with abrupt abdominal pain and forceful bowel movements, whereas a more indolent onset and course are generally seen in mesenteric venous thrombosis. In nonocclusive mesenteric ischemia, pain may be absent or not a dominant feature. Occult gastrointestinal bleeding is common in acute mesenteric ischemia, but overt bleeding is not (in contrast to colonic ischemia); its occurrence is usually a late and ominous development, which suggests intestinal infarction. If acute mesenteric ischemia progresses, abdominal findings may become more apparent and include tenderness, distention, and peritoneal signs.

DIAGNOSIS

Laboratory findings may initially be normal and generally lack sufficient reliability for early diagnosis.[4] D-dimer is a sensitive early marker, but it has high false-positive rates. Leukocytosis (>15,000/mL with a neutrophilic shift) and elevations in levels of serum amylase, phosphate, lactate dehydrogenase, creatine kinase, aminotransferases, and lactate may be seen, but these are usually associated with later-stage disease and lack sufficient sensitivity and specificity. Novel serologic markers are actively being studied but have not yet entered routine practice.

Plain radiographs are usually unrevealing in early acute mesenteric ischemia. With progression of the ischemic injury, abnormalities may include ileus, thumbprinting (due to submucosal hemorrhage), pneumatosis linearis, or portal venous gas. Although these findings are nonspecific, their presence correlates with a worse prognosis, and plain radiographs are useful to exclude other conditions. Doppler ultrasonography is generally not recommended because it only allows evaluation of the proximal aspects of the celiac axis and superior mesenteric artery, and it is not reliable in the assessment of nonocclusive mesenteric ischemia. Computed tomography (CT) scans of the abdomen and pelvis may be normal in early acute mesenteric ischemia or may reveal bowel wall thickening, submucosal hemorrhage, mesenteric venous thrombosis, mesenteric stranding, pneumatosis, or portal venous gas in more advanced cases (Fig. 129-1).

Standard contrasted CT is most useful for the diagnosis of mesenteric venous thrombosis, but it is generally less helpful for diagnosing acute mesenteric ischemia, especially in its early stages. CT angiography is the diagnostic imaging modality of choice,[5] with a sensitivity and specificity of about 95%, while also allowing concomitant evaluation of other abdominal structures. CT angiography should be performed without oral contrast owing to the risk of obscuring the mesenteric vessels and delaying diagnosis. Magnetic resonance (MR) angiography also has high diagnostic accuracy and may be preferred for patients who are hypersensitive to iodinated contrast dye, but it is less readily available and more time-consuming to obtain than CT angiography. Although CT angiography and MR angiography perform well for occlusive acute mesenteric ischemia, they are both less reliable for nonocclusive mesenteric ischemia. The gold standard for the diagnosis and specific classification of acute mesenteric ischemia is selective mesenteric angiography, which also has therapeutic applications for the delivery of medications or the placement of a stent. However, given its wide availability and ease of performance, CT angiography has largely replaced conventional angiography for the primary diagnosis of acute mesenteric ischemia.

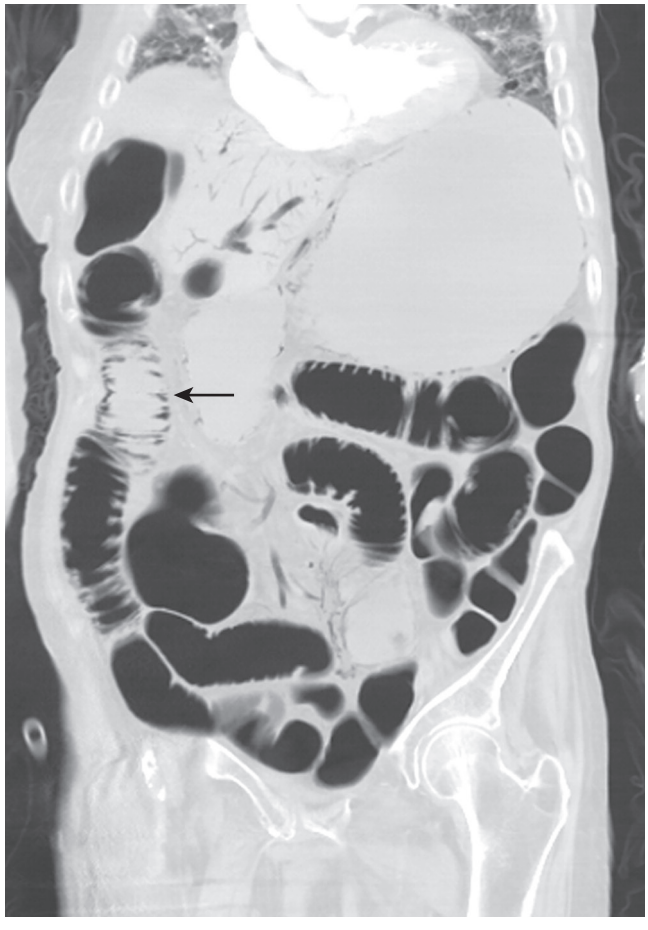

FIGURE 129-1. Pneumatosis *(arrow)* and intrahepatic portal venous gas in a patient with cardiac arrhythmias and small intestinal ischemia. (From Gore RM, Yaghmai V, Thakrar KH, et al. Imaging in intestinal ischemic disorders. *Radiol Clin North Am*. 2008;46:845-875.)

PROGNOSIS

Untreated acute mesenteric ischemia resulting in intestinal infarction is associated with a mortality rate of over 70%, but prompt diagnosis and treatment significantly improve outcomes. Two-year survival rates are nearly 90% using intensive multidisciplinary and multimodal approaches.

TREATMENT

Arterial acute mesenteric ischemia involving the small bowel is associated with high mortality (greater than 70% if there is intestinal infarction). Prompt diagnosis and management are essential,[6] and patients benefit from a multidisciplinary approach (Fig. 129-2).

Initial management for all patients should include intravascular volume resuscitation, broad-spectrum antibiotics with gram-negative and anaerobic coverage to prevent sepsis secondary to bacterial translocation from the gut (e.g., a third-generation cephalosporin or fluoroquinolone plus metronidazole and piperacillin-tazobactam; see Table 266-4), and attention to any underlying precipitating factors such as heart failure (Chapter 46) or cardiac arrhythmias (Chapters 52 and 53). The presence of peritoneal signs or of imaging findings suggestive of transmural intestinal necrosis should prompt urgent exploratory laparotomy. If feasible, preoperative angiography is useful because it can help tailor the surgical approach and is associated with significantly lower postoperative morbidity and mortality, particularly for occlusive acute mesenteric ischemia. Depending on the subtype of mesenteric ischemia and severity of the patient's condition, surgery may include embolectomy, thrombectomy, resection of necrotic bowel, and vascular bypass.[7] Papaverine (60-mg bolus followed by 30 to 60 mg/hr continuous infusion for 12 to 48 hours) is a phosphodiesterase inhibitor that is used pre- and postoperatively for occlusive acute mesenteric ischemia (superior mesenteric artery embolism and superior mesenteric artery thrombosis) and as a primary treatment modality for nonocclusive mesenteric ischemia to minimize splanchnic vasoconstriction and decrease the risk of reperfusion injury. Other vasodilators such as alprostadil (20-μg bolus followed by 60 to 80 μg/24 hr infusion until clinical improvement) can also be used.[8] Options for selected patients with occlusive acute mesenteric ischemia who do not require surgery include thrombolysis and endovascular stent placement. Long-term care involves addressing underlying predisposing factors (e.g., smoking cessation, lipid-lowering therapy), lifelong therapy with aspirin in patients who undergo surgery, and dual antiplatelet therapy (usually with aspirin plus clopidogrel) in patients who undergo endovascular intervention (Chapter 59).

SPECIFIC ACUTE MESENTERIC ISCHEMIA SYNDROMES

Superior Mesenteric Artery Thrombosis

Superior mesenteric artery thrombosis, also referred to as acute mesenteric arterial occlusive disease, is estimated to account for more than 50% of cases of acute mesenteric ischemia. It can occur in the context of preexisting symptomatic chronic mesenteric ischemia (see later) in 20 to 50% of cases. These patients typically report preexisting postprandial abdominal pain, weight loss, and sitophobia (fear of eating). Atherosclerotic disease involving other vascular beds (coronary, carotid, peripheral arterial) is common, and risk factors overlap with those of atherosclerosis in general (age, smoking, hypertension, diabetes, hyperlipidemia). The most common site of thrombosis is just distal to the origin of the superior mesenteric artery. The diagnosis can be established by CT angiography or MR angiography, although selective mesenteric catheter angiography is often used to direct and administer therapy. Papaverine (e.g., a 60-mg bolus followed by 30 to 60 mg/hr continuous infusion for 12 to 48 hours) or another vasodilator such as alprostadil (20- μg bolus followed by 60 to 80 μg/24 hr infusion until clinical improvement) is administered into the superior mesenteric artery to

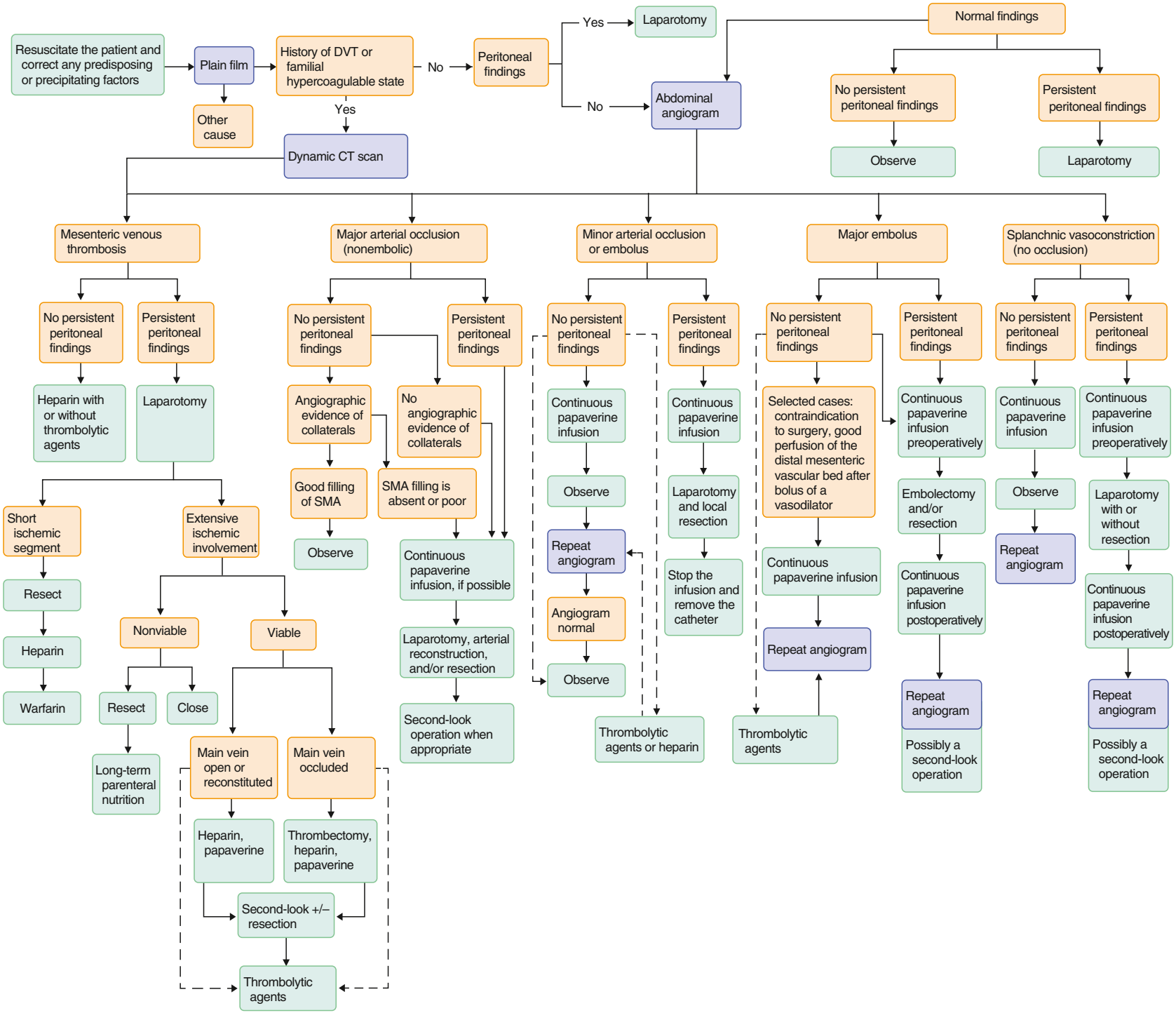

FIGURE 129-2. Algorithm for managing patients with suspected acute mesenteric ischemia: diagnosis and management. Solid lines indicate an accepted management plan; dashed lines indicate an alternative management plan. CT = computed tomography; DVT = deep vein thrombosis; SMA = superior mesenteric artery. (From American Gastroenterological Association Medical Position Statement: guidelines on intestinal ischemia. *Gastroenterology*. 2000;118:951-953 [corrected algorithm in *Gastroenterology*. 2000;119:281].)

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alleviate reflex splanchnic vasoconstriction. Thrombolytic therapy (using tissue plasminogen activator infused at a rate of 0.5 to 1 mg/hr), with or without angioplasty and endovascular stenting, is an option in selected cases; however, most patients require surgical thrombectomy and bypass grafting.

Superior Mesenteric Artery Embolism

Superior mesenteric artery embolism is responsible for about 30% of cases of acute mesenteric ischemia. It usually results from left atrial or left ventricular mural thrombi (due to atrial fibrillation, for example), which tend to lodge just distal to the origin of the superior mesenteric artery (E-Fig. 129-1). Selected patients with minor emboli (distal to the ileocolic artery take-off) or with incomplete occlusion may be candidates for thrombolytic therapy with tissue plasminogen activator, administered via a catheter inserted in the vicinity of the embolus, to lyse clot material and alleviate abdominal pain. Emboli that occur proximal to the take-off of the ileocolic artery are termed major, and such patients usually require laparotomy, as do patients with peritoneal signs. Surgical interventions, including embolectomy and bowel resection, depend on operative findings. Some patients will require a second-look surgery within 24 hours to reassess the viability of the small bowel and the adequacy of resection. Vasodilators such as papaverine or alprostadil are used similarly to the management of superior mesenteric artery thrombosis. Patients with superior mesenteric artery embolism may benefit from systemic anticoagulation with unfractionated heparin to prevent clot propagation and further distal embolization, although this benefit must be balanced against the risk of hemorrhage. If surgery is performed, anticoagulation is resumed 24 hours postoperatively. Patients with atrial fibrillation and embolic events generally require long-term anticoagulation (Chapter 52).

Nonocclusive Mesenteric Ischemia

Nonocclusive mesenteric ischemia is the cause of up to 20% of cases of acute mesenteric ischemia. The syndrome results from splanchnic vasoconstriction, which initially occurs as a protective mechanism during low arterial blood flow to the intestine, such as seen in patients with cardiac arrhythmias, heart failure, myocardial infarction, shock, sepsis, burns, pancreatitis, hemorrhage, dialysis, and vasospasm due to vasoactive substances (e.g., cocaine, digoxin, vasopressin, amphetamines). In patients with nonocclusive mesenteric ischemia, the splanchnic vasoconstriction persists despite correction of the precipitating event, thereby leading to bowel ischemia. Abdominal pain may not be a major hallmark and is sometimes overshadowed by other clinical features, such as cardiovascular instability. Given the underlying pathophysiology, the standard of care for nonocclusive mesenteric ischemia is correction of the precipitating event(s), diagnosis by selective mesenteric angiography, and treatment with a continuous infusion of a vasodilator (see earlier) into the superior mesenteric artery to reverse splanchnic vasoconstriction. The infusion is continued until angiography (generally repeated daily) demonstrates that the vasoconstriction is resolved (Figs. 129-3A and 129-3B). Surgical exploration with resection of necrotic bowel is indicated in the presence of peritoneal signs.

Focal Segmental Ischemia

Focal segmental ischemia has a better prognosis than other forms of acute mesenteric ischemia because the length of involved bowel and the extent of necrosis are usually more limited. Causes include atheromatous emboli (Chapter 66), vasculitis (see later), strangulated hernias (Chapter 128), radiation therapy (Chapter 18), and oral contraceptives (Chapter 220). Some patients may develop a chronic enteritis with strictures that can mimic Crohn disease. Treatment is surgical resection of the involved bowel.

Mesenteric Venous Thrombosis

Splanchnic[9] and mesenteric venous thromboses, which account for nearly 10% of cases of acute mesenteric ischemia, have acute and subacute forms that are distinguished based on the duration since the onset of symptoms. Patients with subacute mesenteric venous thrombosis may present with fluctuating symptoms (abdominal pain, nausea, distention, diarrhea) persisting weeks to months. Many patients have an underlying inherited or acquired hypercoagulable state (Table 129-1) or portal hypertension, but some have no identifiable cause. The superior mesenteric vein, often with involvement of the portal and splenic veins, is most frequently thrombosed, and the inferior mesenteric vein is rarely affected. Presenting symptoms in acute thrombosis are similar to those of the arterial forms of acute mesenteric ischemia, notably pain out of proportion to physical examination findings. Gastrointestinal bleeding, if present, usually indicates bowel infarction.

CT with IV contrast has greater than 90% accuracy for the diagnosis of mesenteric venous thrombosis and is the modality of choice given its availability and ease of performance. Findings may include thickening and enhancement of the bowel wall, distention, hazy mesentery, indistinct bowel wall margins, new ascites, and enlargement of the superior mesenteric vein with an intraluminal thrombus. MR venography has very high diagnostic accuracy but is less readily available, more time-consuming, and more costly. Selective mesenteric angiography can help establish the diagnosis and guide therapy (Fig. 129-4) but is generally not needed when standard CT is diagnostic.

Therapy follows similar principles as for arterial acute mesenteric ischemia: fluid resuscitation, antibiotics with gram-negative and anaerobic coverage (e.g., a third-generation cephalosporin or fluoroquinolone plus metronidazole and piperacillin-tazobactam; see Table 266-4), avoidance of vasoconstrictors,

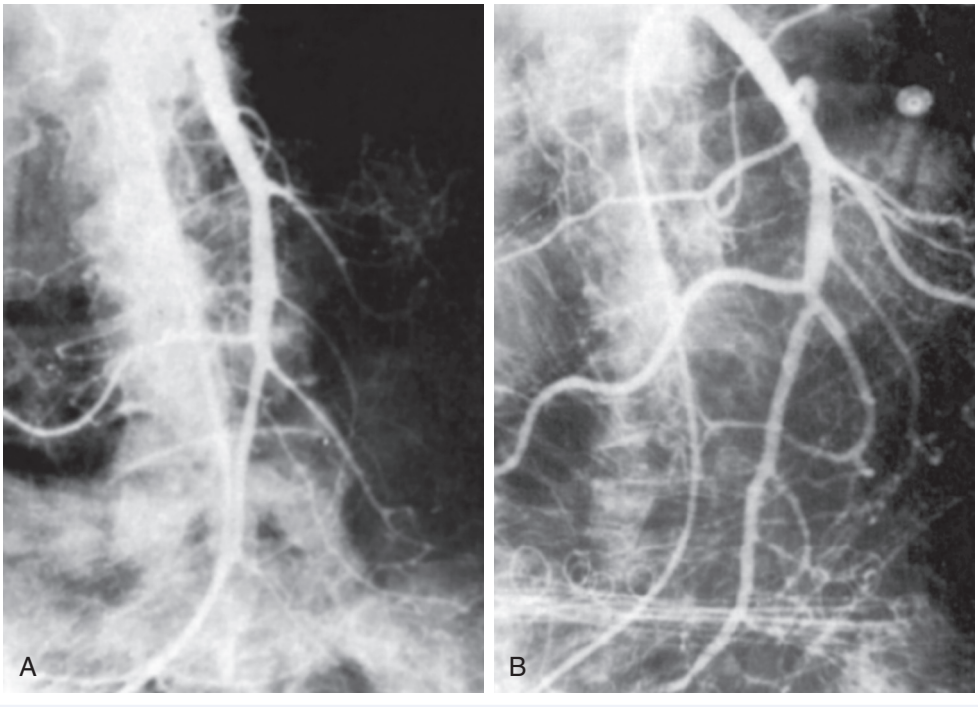

FIGURE 129-3. Selected films from superior mesenteric angiography. A, Diffuse vasoconstriction characteristic of nonocclusive mesenteric ischemia. **B,** Intra-arterial infusion of papaverine (30 to 60 mg/hr) resulted in vasodilation.

E-FIGURE 129-1. Superior mesenteric arterial ischemia. Computed tomographic angiography showing a low-density thrombus (*arrow*) within the superior mesenteric artery. (From Gore RM, Yaghmai V, Thakrar KH, et al. Imaging in intestinal ischemic disorders. *Radiol Clin North Am*. 2008;46:845-875.)

TABLE 129-1 CONDITIONS ASSOCIATED WITH MESENTERIC VENOUS THROMBOSIS

PROTHROMBOTIC STATES (See Chapter 67)
Antithrombin deficiency
Protein C deficiency
Protein S deficiency
Factor V Leiden
Prothrombin gene G20210A mutation
Antiphospholipid antibodies
Hyperhomocysteinemia
Oral contraceptives
Pregnancy
Neoplasms
INTRA-ABDOMINAL INFLAMMATION AND SEPSIS
Peritonitis
Pancreatitis
Diverticulitis
Inflammatory bowel disease
Appendicitis
Cholecystitis
HEMATOLOGIC DISORDERS
Paroxysmal nocturnal hemoglobinuria
Polycythemia vera
Essential thrombocythemia
Sickle cell disease
LIVER CIRRHOSIS
Portal hypertension
Variceal sclerotherapy
OTHERS
Abdominal surgery
Blunt abdominal trauma

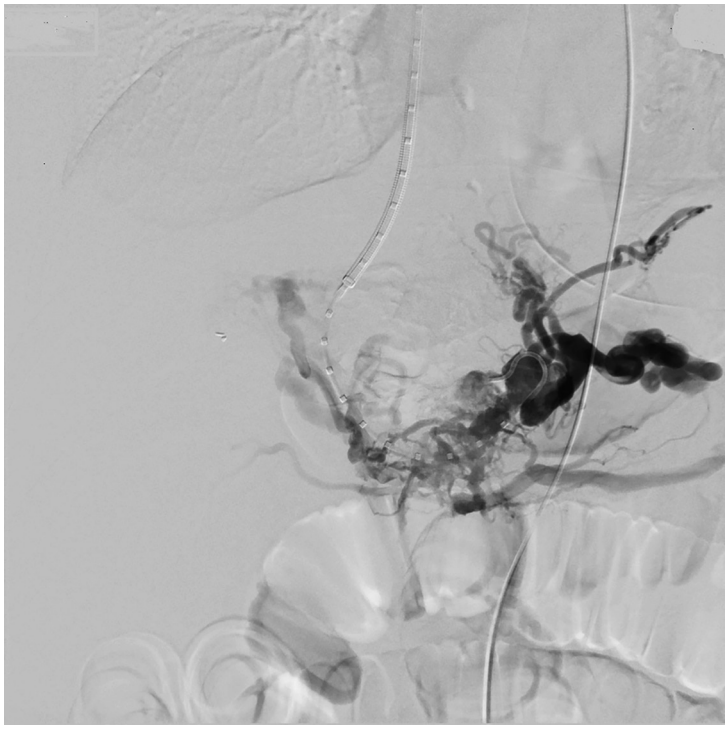

FIGURE 129-4. Selective mesenteric angiogram of a patient with superior mesenteric venous thrombosis and extrahepatic portal vein thrombosis.

and systemic anticoagulation with heparin (Table 68-6).[10] The presence of peritoneal signs or other findings suspicious for bowel infarction require laparotomy with or without bowel resection and infusion of a vasodilator. Selected patients may benefit from thrombolytic therapy. Patients with mesenteric venous thrombosis and an underlying hypercoagulable state should receive lifelong anticoagulation therapy with warfarin or a direct-acting oral

FIGURE 129-5. Computed tomographic angiography of a patient who had chronic mesenteric ischemia and who was treated with endovascular stenting of the celiac axis and superior mesenteric artery. Note the extensive atherosclerotic disease.

anticoagulant (Table 70-6);[11] otherwise, a 3- to 6-month course of anticoagulation is thought to be adequate. The prognosis of mesenteric venous thrombosis is generally better than that of the arterial variants of acute mesenteric ischemia.

Chronic mesenteric venous thrombosis is distinct from the acute and subacute forms; patients may present with gastrointestinal bleeding from esophageal or gastric varices owing to portal or splenic vein thrombosis in the absence of symptoms at the time of the initial thrombotic event. Treatment is aimed at controlling hemorrhage and underlying portal hypertension.

CHRONIC MESENTERIC ISCHEMIA

Chronic mesenteric ischemia, which is almost always caused by atherosclerotic disease of the mesenteric vessels, generally involves the origins of at least two of the three major mesenteric arteries (celiac axis, superior mesenteric artery, inferior mesenteric artery) (Fig. 129-5). The risk factors are the same as for atherosclerosis (Chapter 40), including age, smoking, hypertension, diabetes, and hyperlipidemia, and many patients have atherosclerotic disease involving other vascular beds.

CLINICAL MANIFESTATIONS

A hallmark symptom is postprandial pain in the upper or mid-abdomen, starting within 30 minutes after eating, increasing in severity, and gradually subsiding over a few hours. Weight loss may occur as a result of sitophobia; other symptoms include nausea, vomiting, bloating, diarrhea, and constipation. The syndrome may progress with time, and episodes of pain may become more prolonged and unrelated to eating, indicative of worsening vascular narrowing and increased risk of acute thrombosis. The occurrence of sudden severe pain in a patient with known or suspected chronic mesenteric ischemia implies a superimposed acute thrombotic event. Uncommon associations are unexplained gastroduodenal ulcerations that do not heal with acid suppression, small bowel biopsy findings of villous atrophy, and delayed gastric emptying. Physical findings in patients with advanced disease may include cachexia or an abdominal bruit.

DIAGNOSIS

The diagnosis of chronic mesenteric ischemia may be challenging: the prevalence of atherosclerosis is high in older patients, and abdominal pain may not

FIGURE 129-6. Magnetic resonance angiography in a patient with chronic mesenteric ischemia. This image shows severe stenosis at the origins of the celiac axis and the superior mesenteric artery. (Courtesy Thomas Casciani, MD.)

necessarily be due to mesenteric vascular occlusive disease. Available imaging modalities, such as CT angiography, can reveal stenoses in the mesenteric vessels but cannot ascertain whether ischemia is present. Doppler ultrasonography can screen for stenoses in the proximal aspects of the celiac axis and superior mesenteric artery; increased flow velocities of at least 200 cm/sec (celiac axis) and 275 cm/sec (superior mesenteric artery) are associated with a stenosis of at least 70%. Both CT angiography and MR angiography (Fig. 129-6 and Video 129-1) are useful for detecting arterial stenoses, but neither is sensitive enough to exclude chronic mesenteric ischemia when the pretest probability is high. Gastric tonometry exercise testing, which measures the gastric-arterial P_{CO_2} gradient (an increase after exercise is indicative of ischemia), has shown promise for diagnosing ischemia but is not widely available. Selective mesenteric angiography remains a cornerstone of the evaluation, because the diagnosis requires the presence of clinical symptoms, occlusion of at least two of the three major mesenteric vessels, and exclusion of other potential causes of postprandial abdominal pain (e.g., cancer, gastroparesis, volvulus, bowel obstruction, pancreatobiliary disease, paraesophageal hernias).

TREATMENT

In patients who have symptoms consistent with chronic mesenteric ischemia, have appropriate angiographic findings, and have no other potential causes, revascularization is indicated. Mesenteric angioplasty with or without stent placement is the treatment of choice, with open surgery reserved for selected younger patients and patients who are not suitable for endovascular repair,[12,13] and is associated with shorter hospital stay and lower morbidity. However, surgery is more effective long-term because it is associated with better long-term patency rates and a lower risk of recurrent symptoms.

COLON ISCHEMIA

Colon ischemia is the most common ischemic syndrome of the bowel. It is diagnosed in about 10 to 20% of patients who present to the hospital with lower gastrointestinal bleeding, and its incidence is estimated at about 16 per 100,000 person-years in the general population. Colon ischemia is also referred to as "ischemic colitis"; however, an inflammatory phase is not consistently found, so the preferred term is colon ischemia. Colon ischemia encompasses a spectrum of injury, including reversible colopathy (most common, about 50%), transient colitis, chronic colitis, stricture, gangrene, and fulminant universal colitis. Most cases occur in older patients (>60 years old), in whom the most common cause is transient nonocclusive hypoperfusion of a colonic segment, often without apparent cause. Although older patients are prone to colon ischemia in "watershed areas" of the colon (splenic flexure-descending colon), a segmental pattern of involvement is common, most often involving the left colon. In younger patients, colon ischemia is more likely to be caused by the use of vasoactive substances (e.g., cocaine, methamphetamines), vasculitis, or hypercoagulable states (Table 129-2).

TABLE 129-2 CONDITIONS AND MEDICATIONS ASSOCIATED WITH COLON ISCHEMIA

CARDIOVASCULAR
Atherosclerosis
Atrial fibrillation
Cerebrovascular disease
Congestive heart failure
Ischemic heart disease
Hypertension
Hypotension
Peripheral vascular disease
Shock
PULMONARY
Chronic obstructive pulmonary disease
GASTROINTESTINAL
Constipation
Diarrhea
Irritable bowel syndrome
OTHER MEDICAL CONDITIONS
Diabetes
Rheumatologic disorders
SURGERY
Abdominal surgery
Cardiovascular (including aortic) surgery
Ileostomy
Laparoscopy
MEDICATIONS AND DRUGS
Constipation-inducing medications
Immunomodulators (antitumor necrosis factor-α, interferon)
Illicit drugs (amphetamines, cocaine)
Antibiotics
Appetite suppressants
Chemotherapeutic agents (including taxanes)
Decongestants (including pseudoephedrine)
Diuretics
Ergot alkaloids
Hormonal therapies (including oral contraceptives)
Laxatives
Psychotropics
Serotoninergics (including alosetron)

Adapted from Brandt LJ, Feuerstadt P, Longstreth GF, et al. ACG clinical guideline: epidemiology, risk factors, patterns of presentation, diagnosis, and management of colon ischemia (CI). *Am J Gastroenterol.* 2015;110:18-44.

CLINICAL MANIFESTATIONS

Most patients with colon ischemia present acutely with abdominal pain, often in the left lower quadrant, associated with fecal urgency, diarrhea, and hematochezia. Passage of maroon stool may also occur, but bleeding is rarely severe. Patients may have fever and tachycardia. The physical examination typically reveals tenderness over the affected portion of colon, as well as abdominal distention. Patients with isolated right-sided colon ischemia tend to have more severe pain, which overshadows bleeding. As with acute mesenteric ischemia, the presence of peritoneal signs mandates prompt surgical consultation. About 25% of cases of colon ischemia are isolated right-side colon ischemia, which can complicate low-flow states such as hypotension and sepsis, chronic kidney disease, and hemodialysis, presumably secondary to intravascular fluid shifts.

DIAGNOSIS

No single test can conclusively diagnose colon ischemia, but the diagnosis can be established with judicious use of diagnostic modalities in the appropriate clinical context.[14] The differential diagnosis includes inflammatory bowel disease (ulcerative colitis and Crohn disease; Chapter 127), infectious colitis

FIGURE 129-7. Colon ischemia. There is mural thickening (*arrows*) of the proximal descending colon and submucosal edema. (From Gore RM, Yaghmai V, Thakrar KH, et al. Imaging in intestinal ischemic disorders. *Radiol Clin North Am*. 2008;46:845-875.)

(Chapter 126), and mechanical obstruction due to colorectal cancer (Chapter 179), fecal impaction, or stricture.

Laboratory findings may be normal, but the presence of leukocytosis and elevated blood levels of urea nitrogen and lactate are indicative of a more severe course. Plain radiographs may be normal or show thumbprinting. A CT scan with IV contrast, which is useful to exclude other diagnostic possibilities and to assess the severity and distribution of the ischemic process, may show segmental colonic edema and inflammation with or without pericolonic inflammatory stranding (Fig. 129-7); however, these findings are nonspecific and can also be seen in inflammatory bowel disease, infectious colitis, and diverticulitis. Colonoscopy is the best test to diagnose colon ischemia, because it allows direct visualization of the mucosal biopsy and assessment of the distribution and severity of the disease process. Most colonoscopic findings are nonspecific (erythema, edema, segmental patchy ulcerations, subepithelial hemorrhages), but the presence of a "single stripe sign" (E-Fig. 129-2) in the left colon is a reliable indicator of colon ischemia. Visceral angiography is typically not required. However, patients with isolated right-sided colon ischemia tend to have a more aggressive course. This is because the superior mesenteric artery supplies blood to the right side of the colon and most of the small intestine, so ischemia confined to the right colon may be a sentinel event for ischemia involving the small intestine (E-Fig. 129-3).

Unlike patients with left-sided colon ischemia, those with isolated right-sided colon ischemia should undergo CT angiography or traditional angiography to evaluate the mesenteric circulation for possible occlusion of the superior mesenteric artery.

TREATMENT

Colon ischemia is usually self-limited, and symptoms generally resolve within 2 to 3 days with supportive care: volume replacement, bowel rest, correction of conditions leading to hypoperfusion such as systemic hypotension, avoidance of vasoconstrictive medications, and broad-spectrum antibiotics (e.g., third-generation cephalosporin or fluoroquinolone plus metronidazole, and piperacillin-tazobactam; see Table 266-4) with gram-negative and anaerobic coverage, especially in patients with severe colon ischemia (Fig. 129-8). Surgery is reserved for patients with signs and symptoms of gangrene, perforation, or massive bleeding.[15] Patients with persistent symptoms have a higher incidence of complications, including gangrene, perforation, segmental colitis, and stricture. Strictures, which can form over weeks to months, may require surgical resection.

VASCULITIS

Vasculitis (Chapter 249) can involve the gastrointestinal tract, usually in association with systemic involvement. The gastrointestinal manifestations, which depend on the size of the vessels involved, include abdominal pain, nausea or vomiting, diarrhea, and overt bleeding. The ischemic process is typically due to immune complex deposition that leads to the activation of complement and resulting inflammation, which may then lead to focal segmental ischemia. Treatment usually requires immunosuppressive medications (Chapter 28) or surgical resection in selected situations.

LARGE VESSEL VASCULITIS

Takayasu disease and *giant cell arteritis* (Chapter 63) rarely involve the mesenteric circulation. Takayasu arteritis most often affects young women of Asian background and has been associated with ulcerative colitis and Crohn disease (Chapter 127).

MEDIUM VESSEL VASCULITIS

Polyarteritis nodosa (Chapter 249) is the most common underlying diagnosis in vasculitis involving the gastrointestinal tract. The disease is characterized by segmental microaneurysms, which occur more frequently in the small bowel than in the colon. The gallbladder, spleen, liver, and pancreas may be involved. The syndrome may be associated with chronic hepatitis B infection (Chapter 135). Abdominal pain is the most common symptom, but gastrointestinal bleeding and perforation have also been reported.

Infantile febrile mucocutaneous lymph node syndrome (Kawasaki disease; Chapter 249) is a necrotizing vasculitis that can affect young children and cause abdominal pain, ileus, obstruction, and perforation.

Malignant atrophic papulosis (Degos disease) is a rare occlusive vascular disease affecting mainly the skin and intestine. Spontaneous perforation may occur owing to ischemia, and the disease has a poor prognosis.

SMALL VESSEL VASCULITIS

Systemic lupus erythematosus (Chapter 245) is associated with a variety of gastrointestinal manifestations.[16] Lupus vasculitis involving the mesenteric vessels may present with a clinical syndrome of focal segmental ischemia or chronic mesenteric ischemia, but some patients develop significant gastrointestinal bleeding. Lupus mesenteric vasculitis requires prompt recognition and immunosuppressive management.

Antineutrophil cytoplasmic antibody (ANCA)–associated vasculitis includes granulomatosis with polyangiitis, microscopic polyangiitis, and eosinophilic granulomatosis with polyangiitis (Churg-Strauss syndrome; Chapter 249). Gastrointestinal tract involvement is variable, with abdominal pain and bleeding the most common symptoms.

Henoch-Schönlein purpura (Chapter 249) typically presents in children with palpable purpura, arthritis, and abdominal pain. The cause is deposition of immunoglobulin A immune complexes in blood vessel walls. Gastrointestinal involvement is common and usually manifested by pain and bleeding owing to mucosal and submucosal hemorrhages.

Hypersensitivity vasculitis rarely involves the splanchnic vessels and is associated with a variety of drugs, chemicals, and infections.

Behçet disease (Chapter 249) is characterized by oral and genital ulcers. Both large-vessel and small-vessel vasculitis may occur. Gastrointestinal manifestations include abdominal pain, diarrhea, overt bleeding, and perforation due to deep ulcerations. The ileocecal area is most commonly involved.[17]

For each of these conditions, treatment is aimed at the underlying vasculitis.

VASCULAR ANOMALIES AND DISORDERS

Vascular anomalies of the gastrointestinal tract are common, especially with older age. *Angioectasia* (also referred to as vascular ectasia) is a general term that refers to the process whereby a blood vessel is lengthened or dilated. *Angiodysplasia* has often been used interchangeably with angioectasia. *Telangiectasia* is similar, but the term is usually used in the context of systemic disorders, such as hereditary hemorrhagic telangiectasia and scleroderma. *Arteriovenous malformation* is a congenital lesion, whereas *angioma* is a vascular neoplasm that can be benign (hemangioma) or malignant (angiosarcoma).

ANGIOECTASIA

Angioectasia is the most common vascular abnormality of the gastrointestinal tract, and its prevalence increases with age. Angioectasias consist

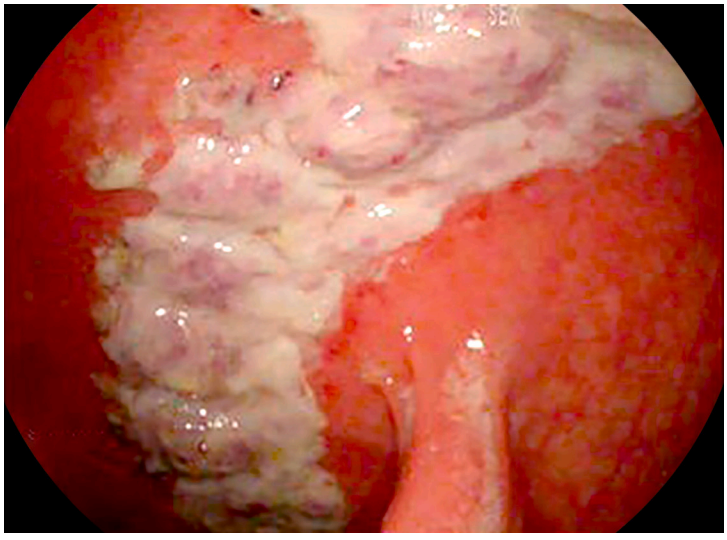

E-FIGURE 129-2. "Single stripe sign," a linear ulceration along the longitudinal axis of the colon. (From Brandt LJ, Feuerstadt P. Beyond low flow: how I manage ischemic colitis. *Am J Gastroenterol*. 2016;111:1672-1674.)

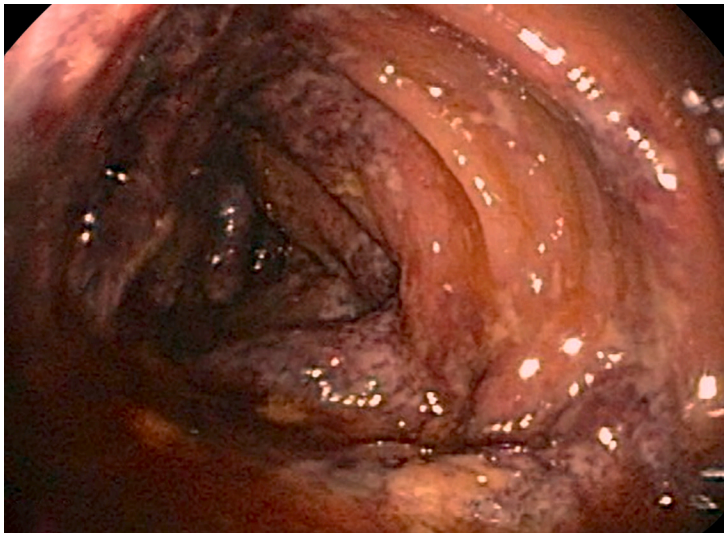

E-FIGURE 129-3. Severe inflammation and necrosis in the ascending colon of a patient with colon ischemia.

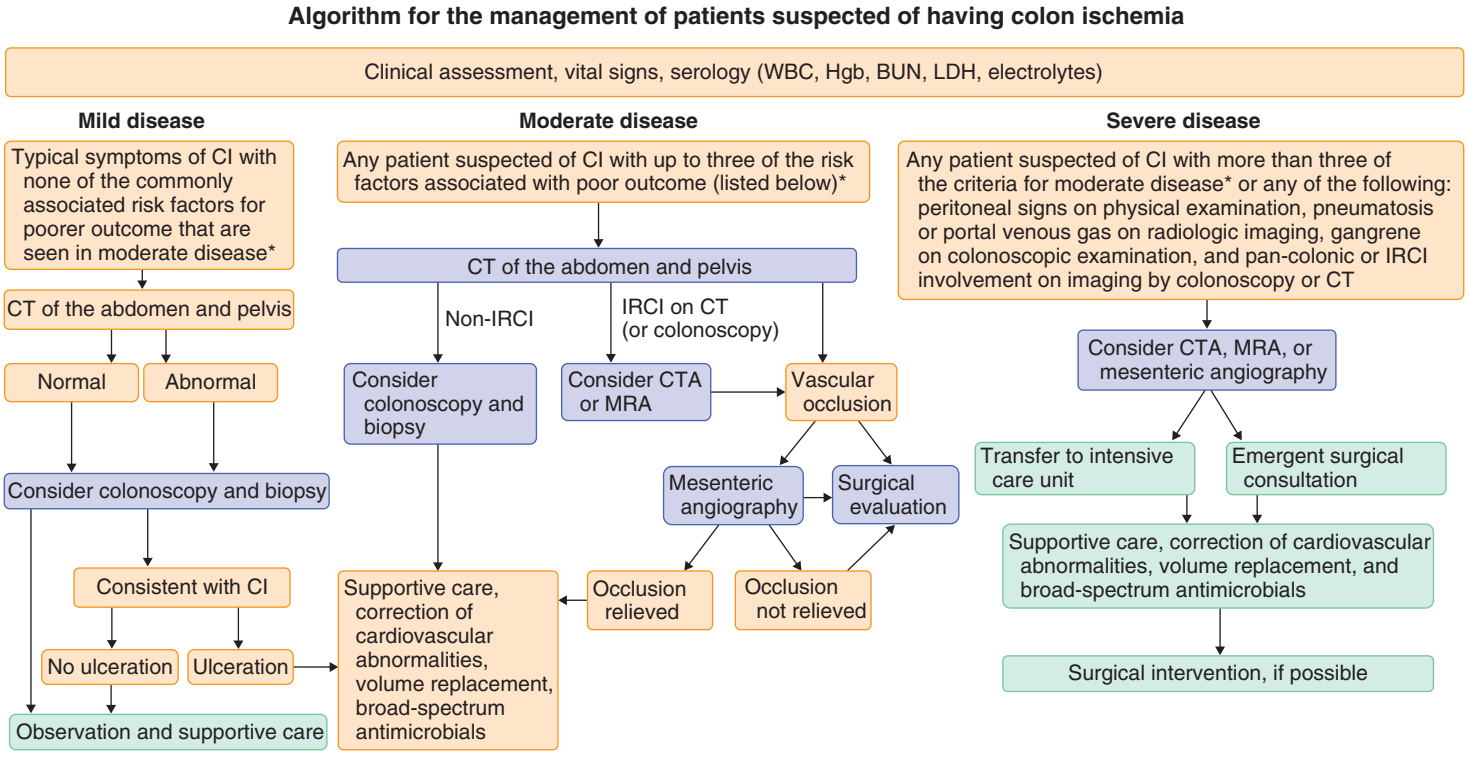

FIGURE 129-8. Colon ischemia algorithm. Diagnosis and treatment of colon ischemia (CI) based upon disease severity. *Risk factors associated with poor outcome: male gender, hypotension (systolic blood pressure <90 mm Hg), tachycardia (HR >100 beats per min), abdominal pain without rectal bleeding, BUN >20 mg/dL, Hgb <12 g/dL, LDH >350 U/l, serum sodium <136 mEq/L(mmol/L), WBC >15 × 10^9/cmm. BUN = blood urea nitrogen; CT = computed tomography; CTA = computed tomography angiography; Hgb = hemoglobin; IRCI = isolated right-colon ischemia; LDH = lactate dehydrogenase; MRA = magnetic resonance angiography; MRI = magnetic resonance imaging; WBC = white blood cell count. (From Brandt LJ, Feuerstadt P, Longstreth GF, et al. ACG clinical guideline: epidemiology, risk factors, patterns of presentation, diagnosis, and management of colon ischemia [CI]. *Am J Gastroenterol*. 2015;110:18-44.)

of thin-walled, distorted mucosal and submucosal arterioles, venules, and capillaries. Angioectasias are most frequently located in the cecum and ascending colon, can be single or multiple, and can sometimes be found concomitantly in the small intestine and stomach. Associations include systemic sclerosis (Chapter 246), chronic renal failure (Chapter 116), von Willebrand disease (Chapter 159), aortic stenosis (Chapter 60), and left ventricular assist devices (Chapter 93).

CLINICAL MANIFESTATIONS

Most angioectasias are asymptomatic and found incidentally during endoscopy. However, some may cause painless bleeding, which can be occult or overt (hematochezia, melena, hematemesis).[18] The bleeding is typically recurrent and mild, but about 15% of patients develop massive bleeding.

DIAGNOSIS

The diagnosis is most often established at endoscopy, either incidentally or during investigations for anemia or gastrointestinal bleeding (Fig. 129-9). The lesions may be difficult to discern in patients who are hypovolemic or have received meperidine for sedation; in the latter situation, naloxone can be considered to reverse the opioid effect and improve visualization. Small bowel angioectasias beyond the reach of endoscopes require videocapsule endoscopy[19] or small bowel balloon-assisted enteroscopy for diagnosis and treatment (Chapter 121).

TREATMENT

Incidental angioectasias found at endoscopy or colonoscopy in asymptomatic individuals do not require intervention. Endoscopic modalities, which can effectively control hemorrhage from angioectasias, include bipolar electrocoagulation, argon plasma coagulation (E-Figs. 129-4A and 129-4B), and application of hemoclips. Rebleeding occurs in some patients and requires repeat intervention. When endoscopic hemostasis is not feasible owing to active bleeding or inaccessible lesion location, visceral angiography can be diagnostic and therapeutic by allowing embolization of the bleeding lesion. Thalidomide (25 mg orally 4 times daily) has antiangiogenic properties and has been reported to be effective in some patients with refractory bleeding from intestinal angioectasias. Other pharmacologic options include octreotide (50 to 100 μg subcutaneously twice a day) and bevacizumab (5 mg/kg every 2 weeks for a total of six infusions).

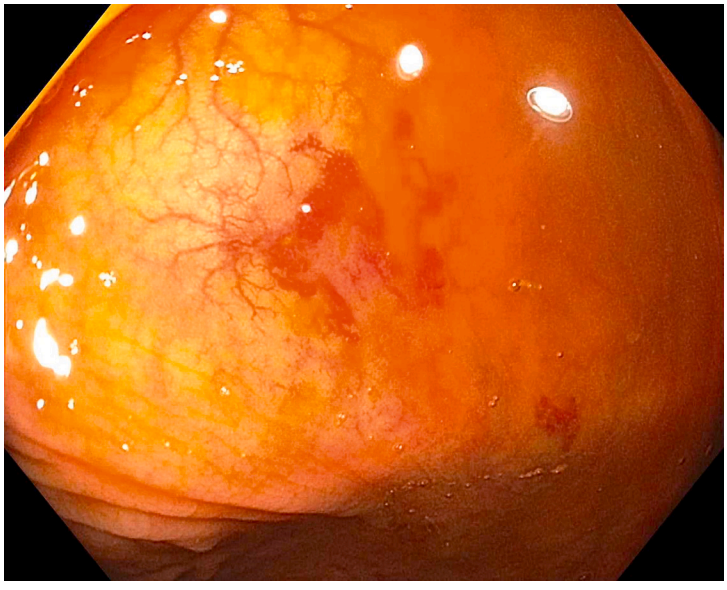

FIGURE 129-9. Colonic angioectasia.

DIEULAFOY LESION

Dieulafoy lesion is a persistently large submucosal artery with an overlying mucosal defect. This lesion is most often found in the proximal portion of the stomach within 6 cm of the gastroesophageal junction, but it has also been reported in the esophagus, small intestine, colon, and rectum. Clinical manifestations include overt bleeding (Chapter 121), which can be brisk, massive, and recurrent (Fig. 129-10). In some patients, diagnosis may be delayed because the vascular protuberance can be subtle and difficult to visualize at endoscopy.

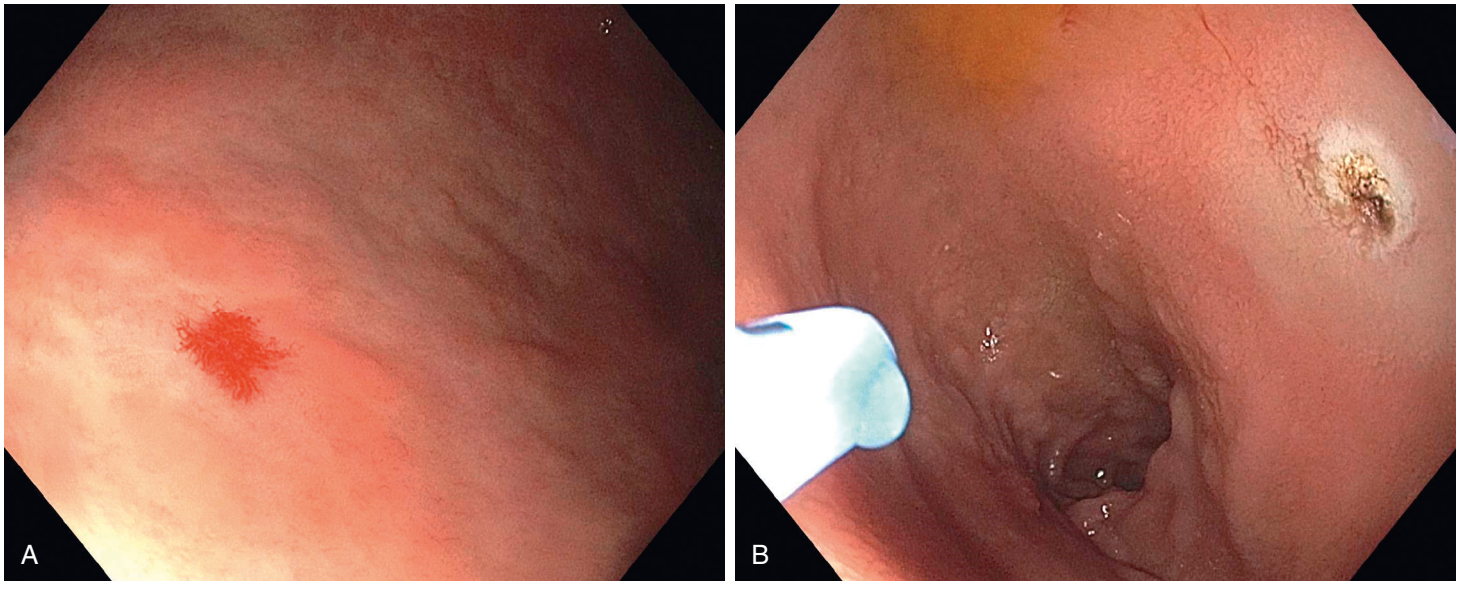

E-FIGURE 129-4. **Gastric angioectasia. A,** Gastric angioectasia in a patient with iron deficiency anemia. **B,** After ablation with argon plasma coagulation.

FIGURE 129-10. Brisk bleeding from a Dieulafoy lesion in the stomach of a patient with melena.

Endoscopic treatment is usually effective.[20] Options include injection, electrocoagulation, argon plasma coagulation, band ligation, and hemoclip application.

HEREDITARY HEMORRHAGIC TELANGIECTASIA

Hereditary hemorrhagic telangiectasia, also known as Osler-Weber-Rendu disease (Chapter 159), is an inherited autosomal dominant disorder. Patients typically have visible telangiectasias on their lips and mucous membranes, as well as telangiectasias in their gastrointestinal tract and other organs. The spectrum of symptoms varies with age: affected children tend to have frequent epistaxis, whereas overt recurrent gastrointestinal bleeding predominates in older age groups. Telangiectasias on the lips (see Fig. 159-3), buccal mucosa, and tongue are highly suggestive. Most patients have recurrent melena (sometimes compounded by swallowed blood from epistaxis), and some patients become transfusion-dependent. Diagnosis is based on clinical criteria (epistaxis, telangiectasias, visceral lesions, hereditary hemorrhagic telangiectasia in a first-degree relative) and can be confirmed by testing for mutations in the endoglin and activin receptor-like kinase-1 genes. Endoscopic therapy is the mainstay of management, particularly for actively bleeding lesions.

OTHER ECTASIAS

Patients with *Turner syndrome* (Chapter 217), *scleroderma* (Chapter 246), and *CREST syndrome* (Chapter 246) may also have gastrointestinal tract telangiectasias. In patients with portal hypertension (Chapter 139), vascular ectasias can involve venules and capillaries in the stomach (*congestive gastropathy*), in the small bowel (*congestive enteropathy*), and in the colon (*congestive colopathy*). In the stomach, ectasia and thrombosis can result in so-called watermelon stomach (gastric antral vascular ectasia), in which erythematous streaks, similar to the stripes on a watermelon, are visible by endoscopy in the antrum and radiate toward the pylorus and even the gastric cardia. Occult bleeding is common, and melena can occur. If iron replacement alone is not adequate, argon plasma coagulation is the treatment of choice.

AORTOENTERIC FISTULAS

After abdominal aortic aneurysm surgery (Chapter 63), an *aortoenteric fistula* can develop, often because of infection of the graft. Fistulas typically communicate with the third or fourth portion of the duodenum and can occur several years after surgery. Massive and even fatal gastrointestinal bleeding may result. When gastrointestinal bleeding develops in patients who have had prior abdominal aortic surgery, the evaluation must include urgent upper endoscopy to exclude another definitive source of the bleeding. CT aids the diagnosis, which should be suspected in the appropriate clinical context. If no alternative bleeding source can be definitively found, explorative surgery is indicated.

An *atrioesophageal fistula* may be caused by thermal damage to the heart or esophagus. Examples of precipitating events include radiofrequency ablation procedures for arrhythmias (Chapter 54) or for Barrett esophagus (Chapter 124).

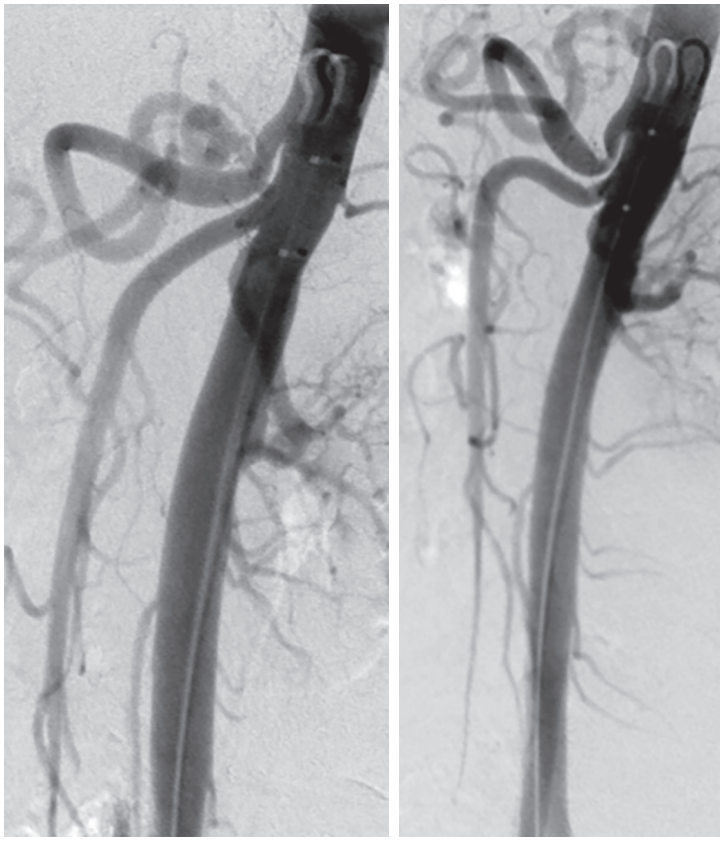

FIGURE 129-11. Celiac artery compression syndrome is caused by a low-lying median arcuate ligament, which results in compression of the celiac artery. This phenomenon is accentuated during expiration. (Courtesy Himanshu Shah, MD.)

CELIAC ARTERY COMPRESSION SYNDROME

Celiac artery compression syndrome, also known as median arcuate ligament syndrome, is a rare and poorly understood pseudo-ischemic syndrome. Most patients are young and otherwise healthy. Postprandial upper abdominal pain and diarrhea may be caused by extrinsic compression of the celiac axis by the median arcuate ligament of the diaphragm or by pressure on the celiac ganglion itself. Sitophobia can result in considerable weight loss, and some patients have an epigastric bruit that intensifies with expiration. Visceral angiography supports the diagnosis (Fig. 129-11), although asymptomatic patients also can have a localized bruit and even celiac axis compression on angiography. Surgical therapy is an option if patients have otherwise unexplained symptoms that are consistent with the syndrome.

SUPERIOR MESENTERIC ARTERY SYNDROME

Superior mesenteric artery syndrome refers to impingement of the duodenum by the superior mesenteric artery owing to narrowing of the angle between the superior mesenteric artery and aorta. The resulting mechanical obstruction can cause rapid weight loss because gastric outlet obstruction results in abdominal pain and postprandial vomiting. Imaging typically shows evidence of obstruction in the third portion of the duodenum, with a cutoff and proximal dilation. Treatment of the underlying condition (adequate nutrition and weight gain) can be curative, but surgery is sometimes needed.

HEMANGIOMAS

Hemangiomas are uncommon, usually benign vascular tumors that can be found throughout the gastrointestinal tract, often in the rectum or colon. They may be single or multiple and can be classified as cavernous, capillary, or mixed. Cavernous rectal hemangiomas tend to be large and bleed profusely, but colonic hemangiomas may cause slow, occult bleeding. Small hemangiomas can be treated endoscopically, but large or multiple lesions may require

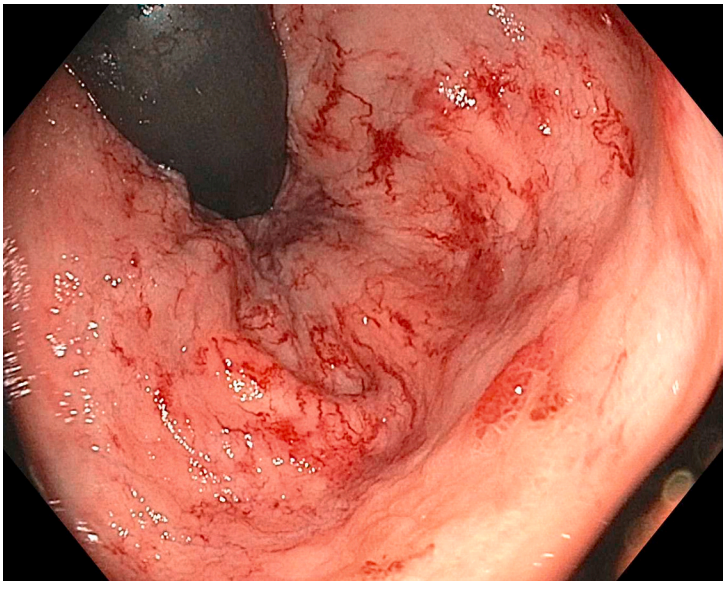

FIGURE 129-12. Radiation proctopathy. Retroflexed view of the rectum showing multiple large and serpiginous vascular ectasias in a patient with hematochezia and history of radiation for prostate cancer.

surgical resection. Rare vascular malignant neoplasms of the gastrointestinal tract include *angiosarcomas* and *hemangioendotheliomas*.

RADIATION PROCTOPATHY

A common radiation-mediated injury to the gastrointestinal tract is radiation proctopathy (Chapter 128), typically in patients treated for prostate cancer. Patients with acute radiation proctopathy (within 6 weeks of therapy) can present with tenesmus and diarrhea, whereas those with chronic radiation proctopathy (onset 6 to 24 months after therapy) can have significant hematochezia owing to radiation-associated vascular ectasias. Endoscopy reveals mucosal fibrosis and a proliferation of vascular ectasias, which are the source of bleeding (Fig. 129-12). Argon plasma coagulation is usually an effective treatment for bleeding.

HEPATIC AND SPLENIC VASCULAR DISEASE

Abnormalities of the hepatic and splenic arteries and veins affect fewer than 1 person per 2000.

BUDD-CHIARI SYNDROME

Budd-Chiari syndrome can be the result of any process that interferes with the normal outflow of blood through the hepatic vein, such as constrictive pericarditis (Chapter 62) and veno-occlusive disease (Chapter 136). The most common cause is thrombosis of one, two, or all three of the major hepatic veins, with or without extension of thrombus and even occlusion into the inferior vena cava.[21] More than 50% of cases of Budd-Chiari syndrome are related to a hypercoagulable state (Chapter 67), such as a factor V (Leiden) gene mutation, antiphospholipid antibody syndrome, protein C deficiency, protein S deficiency, antithrombin III deficiency, a chronic myeloproliferative disorder (e.g., polycythemia vera [Chapter 152], essential thrombocythemia [Chapter 152], myeloid metaplasia [Chapter 152]), paroxysmal nocturnal hemoglobinuria, or other hypercoagulable state conditions (Chapter 67). Other causes include malignancies (direct compression or invasion of hepatic veins), infections (liver abscess), pregnancy, inflammatory disorders (e.g., sarcoidosis, inflammatory bowel disease, connective tissue disease), membranous obstruction (webs) of the inferior vena cava, or spontaneous thrombosis, owing to a hypercoagulable state (Chapter 67).

CLINICAL MANIFESTATIONS

Budd-Chiari syndrome usually progresses insidiously over weeks to months as patients develop hepatomegaly, upper abdominal pain, and ascites. Rare patients may present acutely with encephalopathy, jaundice, ascites, and liver failure.

DIAGNOSIS

Most patients have only mild to moderate nonspecific elevations in serum aspartate and alanine aminotransferase levels. *JAK2* mutation analysis may detect a chronic myeloproliferative disorder. Screening for factor V (Leiden); antiphospholipid antibodies; and deficiencies in protein C, protein S, and antithrombin III is appropriate if the cause is not clear. Doppler ultrasound of the liver is the initial diagnostic test of choice[22]; contrast CT scanning or MR angiography can detect the absence of hepatic venous flow or venous thrombosis (or both). The diagnosis can be confirmed by hepatic venography (see Fig. 129-7), which also can guide therapy.

TREATMENT

Therapy includes diagnosis and treatment of underlying conditions, anticoagulation (intravenous heparin; see Table 68-6 in Chapter 68) to prevent the propagation of thrombi, and treatment of the ascites (e.g., diuretics; Chapter 139). Most patients require interventional radiologic procedures, such as angioplasty, stenting, or transjugular intrahepatic portosystemic shunts, to restore hepatic venous flow.[23] If endovascular procedures are not successful, a surgical shunt can drain the portal and/or mesenteric veins into the inferior vena cava. Liver transplantation (Chapter 140) should be considered for fulminant liver failure or cirrhosis, or both. Most patients require lifelong anticoagulation with warfarin or a newer oral anticoagulant (Chapter 70), even after liver transplantation.

PROGNOSIS

The 5-year survival rate is more than 80%, but about 50% of patients will have a major bleed, often related to invasive therapy.

PORTAL VEIN THROMBOSIS

The most common causes of acute portal vein thrombosis are cirrhosis, hypercoagulable states, intra-abdominal malignancy, inflammatory disorders (e.g., pancreatitis, Crohn disease), and medical procedures (e.g., splenectomy, cholecystectomy, gastrectomy, liver transplantation, transjugular intrahepatic portosystemic shunt). As with Budd-Chiari syndrome, many patients have a *JAK2* mutation.

CLINICAL MANIFESTATIONS AND DIAGNOSIS

Clinical manifestations include portal hypertension with variceal bleeding and ascites (Chapter 139).[24] Abdominal pain may indicate intestinal ischemia as the thrombus extends into the superior mesenteric vein. Fever, chills, and liver tenderness suggest pylephlebitis, which can result in systemic sepsis. The diagnosis is usually established by Doppler ultrasound or by CT or MR angiography.

TREATMENT

Anticoagulation with warfarin (Tables 70-2 and 70-4) to an international normalized ratio (INR) of 2 to 3 or enoxaparin (1 mg/kg subcutaneously twice a day) is recommended for at least 3 months and should be continued chronically in patients who have persistent risk factors for thrombosis or whose thrombus extends into the mesenteric veins.[25] Pylephlebitis usually requires intravenous parenteral antibiotics (e.g., piperacillin/tazobactam, ticarcillin/clavulanate, carbapenem, or a third-generation cephalosporin plus metronidazole; see Chapter 266). Parenteral antibiotics are typically given for about 2 weeks, and total treatment duration is at least 6 weeks, with the choice of antibiotics guided by blood culture results.

In patients who have cirrhosis complicated by acute or chronic portal vein thrombosis, endoscopy is recommended to diagnose and treat esophageal varices (Chapter 120).

Patients with *chronic* portal vein thrombosis can be asymptomatic but often have portal hypertension and hypersplenism. A biliary cholangiopathy may cause jaundice that requires biliary stenting. After varices are treated, noncirrhotic patients benefit from rivaroxaban (15 mg daily) if they do not have major risk factors for thrombosis[A1] and may benefit from chronic warfarin anticoagulation (Chapter 68) if they have ongoing risk factors for thrombosis. Transjugular intrahepatic portosystemic shunting is more effective than endoscopic band ligation plus propranolol to prevent future variceal bleeding in such patients (Chapter 139).[A2]

PROGNOSIS

Mortality rates in treated patients are less than 10%.

SPLENIC VEIN THROMBOSIS

Splenic vein thrombosis is usually caused by a tumor (e.g., pancreatic cancer), pancreatitis, or trauma. Isolated gastric varices and splenomegaly often develop. Liver function and portal pressure are normal. Doppler ultrasound, MR, and

CT can help make the diagnosis. In symptomatic patients, splenectomy is the treatment of choice.

HEPATIC AND SPLENIC ARTERIAL DISEASE

Nonocclusive hepatic arterial disease (*ischemic hepatitis*) develops if the arterial blood supply to the liver is inadequate, usually as a result of severe or sustained shock (Chapter 92), hypotension, volume depletion, or sepsis. Aminotransferase levels typically rise acutely to greater than 1000 U/L and return to their baseline by about 40 to 60% per day after restoration of adequate hepatic arterial blood.

Hepatic artery thrombosis is extremely rare except after liver transplantation (Chapter 140), where it can present with abnormal liver function tests, bile duct injury (e.g., biliary stricture, cholangitis, liver abscess), or liver failure. Doppler ultrasound and angiography will confirm the diagnosis. Patients often require biliary stenting with drainage of any abscesses, followed by surgical reconstruction of the hepatic artery or repeat liver transplantation.

Splenic or hepatic artery aneurysms are usually caused by atherosclerosis, vasculitis, trauma, portal hypertension, pancreatitis, infection, or pregnancy. Clinical manifestations can include abdominal pain and intra-abdominal hemorrhage. Hepatic artery aneurysms can cause hemobilia. The diagnosis is established by angiography. Symptomatic aneurysms (generally 1 cm or larger in the hepatic artery and 2 cm or larger in the splenic artery) require surgery. When a splenic artery aneurysm is discovered during pregnancy, the high likelihood of bleeding is an indication for treatment, usually by interventional radiology.

Fistulas from the hepatic artery to the portal vein are rarely seen in hereditary hemorrhagic telangiectasia or as a result of trauma or malignancy. The resultant portal hypertension may cause abdominal pain, ascites, and gastrointestinal bleeding. Involvement of the hepatic artery may lead to biliary strictures and hepatobiliary infection. Radiographic embolization, surgery, or liver transplantation may be required.

MISCELLANEOUS VASCULAR DISORDERS

Blue rubber bleb nevus syndrome is characterized by purple-blue cutaneous venous malformations, which can affect the gastrointestinal tract, most commonly the small intestine. Gastrointestinal bleeding may occur, but endoscopic therapy is usually contraindicated because the lesions can involve the full thickness of the bowel. Surgical resection is usually needed.

In *Klippel-Trenaunay* syndrome, port-wine-colored cutaneous hemangiomas, hemihypertrophy, and varicose veins are seen. The *Parkes Weber* form includes arteriovenous fistulas; gastrointestinal involvement is uncommon.

In *Ehlers-Danlos syndrome type IV* (Chapter 239), small bowel ischemia and perforation as well as arterial rupture may develop. Patients with *pseudoxanthoma elasticum type I* (Chapter 239) are at risk for gastrointestinal or intraperitoneal hemorrhage, as are patients with *visceral arterial aneurysms* that result from atherosclerosis, fibrodysplasia, vasculitis, trauma, portal hypertension, pancreatitis, or pregnancy.

Thromboangiitis obliterans (Berger disease; Chapter 66) typically affects young men who smoke cigarettes. Mesenteric involvement is uncommon and usually manifested by distal occlusions of the mesenteric circulation.

Malignant atrophic papulosis (Degos disease) is a rare occlusive vascular disease affecting mainly the skin and intestine. Spontaneous perforation may occur owing to ischemia, and the disease has a poor prognosis.

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130

PANCREATITIS

CHRIS E. FORSMARK

ACUTE PANCREATITIS

DEFINITION

Acute pancreatitis is a discrete episode of cellular injury and inflammation in the pancreas, usually with symptoms of abdominal pain, nausea, and vomiting. It is accompanied by elevations in serum levels of amylase or lipase and/or radiographic evidence of pancreatic inflammation, edema, or necrosis. Although the pancreas can recover normal function and appearance after an episode, recovery may not be complete, especially if the necrosis is substantial. In patients with recurrent episodes, there can be a shift from acute inflammation, necrosis, and apoptosis to chronic inflammation and fibrosis that are characteristic of chronic pancreatitis. Acute and chronic pancreatitis are on a continuum, and it may be difficult to differentiate acute relapsing pancreatitis from evolving chronic pancreatitis.

EPIDEMIOLOGY

The incidence of acute pancreatitis in the United States is around 40 cases per 100,000 population, with about 300,000 hospital admissions annually, thereby making acute pancreatitis one of the most common gastrointestinal discharge diagnoses in U.S. hospitals. The cost of caring for these patients is about $4 to $6 billion annually. The incidence of acute pancreatitis is increasing in the United States and many other countries,[1] owing to more frequent use of diagnostic tests and to an increasing prevalence of gallstones and other risk factors in the setting of the obesity epidemic.

PATHOBIOLOGY

Acute pancreatitis is caused by premature activation of digestive enzymes within pancreatic acinar cells. Increased intracellular calcium and the activation of trypsinogen to trypsin appear to be the critical initial steps, with trypsin then activating other proteases within the gland.[2] These activated enzymes produce cell injury and necrosis. Necrosis can involve the pancreas as well as surrounding fat and structures, thereby leading to fluid extravasation into the surrounding retroperitoneal spaces ("third space" losses). Necrosis sufficient to be visible on a contrast-enhanced computed tomographic (CT) scan is termed acute necrotizing pancreatitis and distinguished from the milder interstitial pancreatitis, in which necrosis is not visible on a CT scan. In addition to the pancreatic damage, the release of pro-inflammatory cytokines and activated digestive enzymes into the systemic circulation can produce a systemic inflammatory response syndrome and organ system failure, including hypotension, renal failure, and acute respiratory distress syndrome (Chapter 90). Gallstones (Chapter 141) and alcohol (Chapter 364) together account for around two thirds of all cases of acute pancreatitis, but causes vary by age and sex, and the cause is unknown in a significant proportion of cases (Table 130-1).

Gallstones (Chapter 141)

Passage of a gallstone through the ampulla of Vater with transient obstruction of the pancreatic duct is the initiating event for gallstone pancreatitis. Only about 5% of all patients with gallstones develop pancreatitis, and patients with smaller gallstones (≤5 mm), which can pass the cystic duct and reach the ampulla, are at highest risk. Microlithiasis, defined as tiny gallstones and/or biliary sludge that are not easily visible on routine imaging, is often the cause in patients initially labeled as having acute idiopathic pancreatitis.

Alcohol (Chapter 364)

More than 5 years of alcohol intake averaging more than 5 to 8 drinks daily is usually required before pancreatitis develops, but most people with this level of intake do not develop pancreatitis.[3] A variety of cofactors have been proposed, including a high-fat diet, genetic variability in detoxifying enzymes, coexistent genetic mutations, and cigarette smoking. The evidence is strongest for smoking. By the time patients have a first clinical episode of acute alcoholic pancreatitis, most already have evidence of underlying chronic pancreatitis.

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Alcohol (Chapter 364)

More than 5 years of alcohol intake averaging more than 5 to 8 drinks daily is usually required before pancreatitis develops, but most people with this level of intake do not develop pancreatitis.[3] A variety of cofactors have been proposed, including a high-fat diet, genetic variability in detoxifying enzymes, coexistent genetic mutations, and cigarette smoking. The evidence is strongest for smoking. By the time patients have a first clinical episode of acute alcoholic pancreatitis, most already have evidence of underlying chronic pancreatitis.

ABSTRACT

Acute pancreatitis, which is most often caused by gallstones and alcohol, can cause systemic organ failure, pancreatic necrosis, and death. However, complications can be reduced and recurrence can be prevented by urgent diagnosis, an accurate identification of the cause, and effective management. Chronic pancreatitis, which has numerous genetic and environmental risk factors, can be difficult to diagnose early in its clinical course. Management includes identification of complications, assessment of residual pancreatic function, and treatment of pain, exocrine insufficiency, and endocrine insufficiency.

KEYWORDS

acute pancreatitis
chronic pancreatitis
pancreatic pseudocyst
exocrine insufficiency
endocrine insufficiency

TABLE 130-1 CAUSES OF ACUTE PANCREATITIS

ETIOLOGY	EXAMPLES
Gallstones	Gallstones (Chapter 141) Microlithiasis
Drugs and toxins	Ethyl and methyl alcohol (Chapters 364 and 96) Tobacco (Chapter 363) Azathioprine, 6-mercaptopurine, pentamidine, didanosine, sulfonamides, thiazides, aminosalicylates, valproic acid, and others Scorpion venom (Chapter 98) Organophosphate insecticides (Chapter 96)
Metabolic	Hypertriglyeridemia (Chapter 190) Hypercalcemia (Chapter 227)
Trauma	Post-ERCP (Chapter 120) Blunt or penetrating trauma Postoperative
Obstruction of the pancreatic duct	Benign pancreatic duct stricture Benign ampullary stricture (e.g., celiac disease, Crohn disease, diverticulum) Ampullary adenoma or adenocarcinoma (Chapter 181) Pancreatic ductal adenocarcinoma (Chapter 180) Intraductal papillary mucinous neoplasm (Chapter 180)
Infections	Cytomegalovirus (Chapter 347), mumps (Chapter 340), rubella (Chapter 339), Coxsackie B (Chapter 349), *Candida* (Chapter 310), histoplasmosis (Chapter 308), *Ascaris* (Chapter 327)
Genetics	*PRSS1* mutations *CFTR* mutation *SPINK1* mutation Other mutations
Autoimmune pancreatitis	Type 1 Type 2
Idiopathic pancreatitis	

ERCP = endoscopic retrograde cholangiopancreatography.

The peak of alcoholic pancreatitis is in ages of 20 to 50, and it is more common in men. The mechanism of alcoholic pancreatic injury involves a mixture of direct toxicity, oxidative stress, and alterations in pancreatic enzyme secretion.

Drugs, Toxins, and Metabolic Factors

Drug-induced pancreatitis is a rare and generally idiosyncratic event. Although many drugs have been implicated, the evidence is most compelling for 6-mercaptopurine and azathioprine (up to a 4% attack rate), as well as for valproic acid (the leading cause in an analysis of over 1000 cases of drug-induced acute pancreatitis).[4] Other agents include L-asparaginase, didanosine, pentamidine, valproic acid, furosemide, mesalamine, ciprofloxacin, prednisone, olanzapine, sulfonamides, and aminosalicylates. Toxins that may cause acute pancreatitis include methyl alcohol, organophosphate insecticides, and venom from certain scorpions.

Levels of serum triglycerides above 500 mg/dL, and usually greater than 1000 mg/dL, can cause acute pancreatitis, but the mechanism is not known.[5] The risk appears to be higher in overweight persons.[6] Hypercalcemia is an exceedingly rare cause of acute pancreatitis.

Trauma

Iatrogenic trauma to the pancreas and pancreatic duct during performance of an endoscopic retrograde cholangiopancreatography (ERCP; Chapter 120) can cause pancreatitis, with the risk averaging less than 5% for patients with simple common bile duct stones or malignancy but up to 20% in some high-risk subgroups.

Penetrating and blunt trauma, ranging from a contusion to severe crush injury and even transection of the gland, can cause pancreatitis. Acute presentation is the rule, but some patients with milder injury may present in a subacute or chronic fashion. Ischemic injury to the gland can occur after surgical procedures, especially cardiopulmonary bypass, and cause severe pancreatitis.

Obstruction of the Pancreatic Duct

Obstruction of the pancreatic duct by a pancreatic ductal adenocarcinoma (Chapter 180), an ampullary adenoma or carcinoma, or an intraductal papillary mucinous neoplasm can cause acute pancreatitis. The diagnosis of pancreatic duct obstruction is usually established with magnetic resonance imaging (MRI) with magnetic resonance cholangiopancreatography (MRCP) or with endoscopic ultrasound. Benign strictures of the pancreatic duct at the ampulla of Vater may be caused by celiac disease (Chapter 126), duodenal Crohn disease (Chapter 127), and periampullary diverticulum. Current evidence does not support the role of sphincter of Oddi dysfunction as a cause of acute pancreatitis. Studies of pancreas divisum as a potential cause of acute pancreatitis are ongoing.

Infections

Ascaris lumbricoides (Chapter 327) may cause pancreatitis by obstructing the pancreatic duct as the worms migrate through the ampulla of Vater. Viruses that may infect the pancreatic acinar cells directly and may cause pancreatitis include cytomegalovirus (Chapter 347), Coxsackie B virus (Chapter 349), adenovirus (Chapter 349), and mumps virus (Chapter 340).

Autoimmune Pancreatitis

Two forms of autoimmune pancreatitis have been identified.[7] The most common presentation is obstructive jaundice that mimics pancreatic adenocarcinoma or chronic pancreatitis. These are discussed under "Chronic Pancreatitis."

Genetics

Mutations in the cationic trypsinogen gene *(PRSS1)*, which have been identified in families with hereditary pancreatitis, are more commonly seen in association with chronic pancreatitis but can present early in the course as acute pancreatitis. Many additional mutations and polymorphisms are associated with both acute and chronic pancreatitis. These affected genes include the cystic fibrosis conductance regulator *(CFTR)*, serine protease inhibitor kazal type 1 *(SPINK1)*, chymotrypsin C, calcium-sensing receptor, carboxy ethyl lipase, claudins, and others.

CLINICAL MANIFESTATIONS

Abdominal pain, nausea, and vomiting are the hallmark symptoms of acute pancreatitis. The abdominal pain is usually in the epigastric region and often radiates to the back. The pain is steady, reaches its maximum intensity over 30 to 60 minutes, and persists for days. These characteristic symptoms may be masked in patients who present with delirium, multiple organ system failure, or coma.

The physical examination usually reveals tachycardia. Hypotension, tachypnea, dyspnea, and low-grade fever are observed in more severe cases. Confusion, delirium, and, rarely, even coma may be present. The abdomen is often distended with diminished bowel sounds. Tenderness to palpation of the abdomen, which may be epigastric or more diffuse, is typical, whereas rebound and guarding are unusual. Dullness to percussion in the lower lung fields may be noted owing to pleural effusion. Rare physical findings include ecchymoses of the flank (Grey-Turner sign) or umbilicus (Cullen sign), which occur when fluid and blood track into these spaces from the retroperitoneum. Jaundice may be present if there is biliary obstruction by a stone. The presence of systemic inflammatory response syndrome (Chapter 94) is predictive of more severe pancreatitis. Tachycardia, dyspnea, tachypnea, orthostatic hypotension, pleural effusion, oxygen desaturation, or shock signals more substantial third-space losses, a higher likelihood of a variety of complications, and a worse prognosis. More severe pancreatitis is characterized by more substantial pancreatic and peripancreatic necrosis, more peripancreatic fluid collections, and more dysfunction of extrapancreatic organs.

DIAGNOSIS

The diagnosis of acute pancreatitis is suggested by clinical features and confirmed by laboratory and imaging studies that exclude other serious intra-abdominal conditions and help define the severity and most likely cause of the pancreatitis.[8]

The diagnosis of acute pancreatitis requires at least two of the following three criteria: abdominal pain consistent with pancreatitis, serum amylase or lipase of at least three times the upper limit of normal, or imaging findings consistent with acute pancreatitis on imaging (contrast CT, MRI, or ultrasound). Patients with mild pancreatitis have no local (pancreatic fluid collection or necrosis) or systemic complications (organ failure complications), patients with moderate pancreatitis have local complications and/or transient organ system failure that persists for less than 48 hours, and patients with severe pancreatitis have organ failure that persists for more than 48 hours.

Laboratory Tests

Amylase and Lipase

Most patients with acute pancreatitis have elevations in serum levels of amylase or lipase within a few hours of the onset of symptoms. Lipase is generally preferred over amylase as a diagnostic test because of its superior specificity. Although elevation to more than three times the upper limit of normal is the recommended cutoff for diagnosing acute pancreatitis, up to 25% of cases may not reach this threshold. Lipase levels tend to remain elevated longer than amylase levels, but both decline gradually over several days. Elevations more than three times the upper limit of normal are most specific for acute pancreatitis. Amylase and lipase levels may be normal in patients with acute pancreatitis, particularly if the measurement is delayed for several days after the onset of symptoms, and marked hypertriglyceridemia can interfere with their accurate measurement. Both enzymes are cleared by the kidney, and renal failure can falsely raise the level of these enzymes up to five times the upper limit of normal in the absence of pancreatitis.

Amylase and lipase levels also can be elevated in a variety of other conditions that may mimic acute pancreatitis, including intestinal ischemia and infarction (Chapter 129), bowel obstruction (Chapter 128), cholecystitis (Chapter 141), and choledocholithiasis (Chapter 141). In addition, amylase levels may be elevated from ectopic pregnancy, acute salpingitis, and a variety of extra-abdominal conditions such as parotitis (Chapter 340), lung cancer (Chapter 177), and head trauma (Chapter 368).

In some patients, only the amylase level or the lipase level may be elevated. Serial measurements of amylase or lipase in patients with established acute pancreatitis are not useful in clinical decision making. In patients with recurrent attacks of pancreatitis, the peak level of amylase or lipase tends to diminish progressively.

Other Laboratory Tests

In severe pancreatitis, leukocytosis, azotemia, and hemoconcentration may be seen. Failure of the blood urea nitrogen (BUN) level or hematocrit to normalize with fluid resuscitation is associated with more substantial third-space losses and a worse prognosis. Hyperglycemia, hypocalcemia, and mild hypertriglyceridemia also can develop. Elevations in alanine aminotransferase levels more than three times the upper limit of normal are most suggestive of gallstones, although any significant elevation in liver chemistries should raise the possibility of gallstone pancreatitis (Chapter 141).

Determining Etiology

To identify the cause of acute pancreatitis, the history should focus on alcohol and tobacco use, previous biliary colic, drug history, family history, and recent trauma. Because gallstones are the leading cause of acute pancreatitis, accounting for about 40% of cases, all patients should have an abdominal ultrasound examination to look for gallstones. Gallstone pancreatitis should be suspected if stones or a dilated bile duct is seen on imaging studies or if abnormal liver chemistries are present.

A careful history, often with corroboration from family members, will help diagnose alcoholic pancreatitis, which accounts for about 20% of cases, as well as medication- or toxin-induced pancreatitis and traumatic pancreatitis. Serum chemistries will help identify unusual cases caused by severe (>1000 mg/dL) hypertriglyceridemia.

If these initial approaches are unrevealing, MRI with MRCP or endoscopic ultrasound (EUS) can detect small gallstones, microlithiasis, or underlying premalignant or malignant causes (particularly in patients over age 40 years).[9] More specialized investigations, such as genetic testing, are usually reserved for patients who have had multiple attacks of unexplained pancreatitis.

Of the 25% of patients who do not have an identified cause after a basic initial evaluation, microlithiasis is the most common underlying explanation. With additional evaluation and testing, only about 10% of patients are ultimately labeled as having truly idiopathic pancreatitis. Idiopathic pancreatitis is more common in women, and especially elderly women, than in men.

Imaging Studies

Imaging studies are used not only in establishing the diagnosis but also in determining the cause and prognosis. In most patients, both ultrasound and CT are used in a complementary fashion.

Abdominal ultrasonography can confirm the presence of acute pancreatitis by documenting pancreatic enlargement, edema, or associated peripancreatic fluid collections. Visualization of the pancreas may be limited owing to body habitus or overlying intestinal gas. In patients with gallstone pancreatitis, ultrasonography is more accurate than CT in identifying gallstones in the gallbladder or a dilated common bile duct.

CT is more accurate than ultrasonography in confirming the diagnosis of acute pancreatitis and in documenting the presence of pancreatic necrosis and peripancreatic fluid collections. CT is also particularly helpful in excluding intra-abdominal conditions that can mimic acute pancreatitis. Pancreatic parenchyma that opacifies on CT with intravenous contrast is still viable, whereas parenchyma that does not enhance is necrotic (Fig. 130-1). The extent of pancreatic necrosis has prognostic importance but is generally not clearly visible on CT until at least 3 days after presentation. CT scans are not routinely required in all patients with acute pancreatitis but should be performed when the diagnosis is not clear and in patients who have a first attack, severe disease, systemic complications, or disease that is slow to improve.

MRI is equivalent to CT in its ability to document acute pancreatitis, identify necrosis, and diagnose or exclude other diseases that could mimic acute pancreatitis. In addition, MRCP is much better than CT for identifying gallstones. In critically ill patients, MRI is more difficult than CT to perform.

ERCP and endoscopic ultrasonography are important in both diagnosis and therapy of acute pancreatitis. Endoscopic ultrasonography, which is primarily used to establish the cause when the initial evaluation is unrevealing, is particularly accurate in identifying underlying malignancy, premalignant lesions such as ampullary adenoma, and small gallstones or microlithiasis. ERCP is not used for diagnosis, but it can be very useful for therapeutic purposes.

Determining Severity

Severe pancreatitis is characterized by organ system failure and by local pancreatic complications such as necrosis, fluid collections, or pseudocysts.[10] Organ failure can be single or multiple, early- or late-onset, and progressive, persistent, or transient. In severe acute pancreatitis, renal failure, pulmonary failure, and circulatory failure most commonly occur as part of the systemic inflammatory response.

During the acute attack, poorly demarcated fluid collections around the pancreas track into various retroperitoneal and peritoneal spaces. Much of this inflammatory fluid will resolve, but some will form into a more rounded and circumscribed fluid collection, called a pseudocyst (Fig. 130-2). Similarly, areas of pancreatic and peripancreatic necrosis will eventually develop a surrounding wall and begin to soften and liquefy, thereby becoming "walled-off pancreatic necrosis." For both fluid and necrosis, this process usually takes several weeks. It is important to distinguish pseudocysts from walled-off pancreatic necrosis; they appear similar on a CT scan but are easily distinguishable on MRI or endoscopic ultrasonography, because necrotic collections contain both solid and liquid material. Greater degrees or amounts of necrosis generally correlate with a higher risk of an adverse outcome, particularly if infection develops in the devitalized necrotic tissue. Although many patients with pancreatic

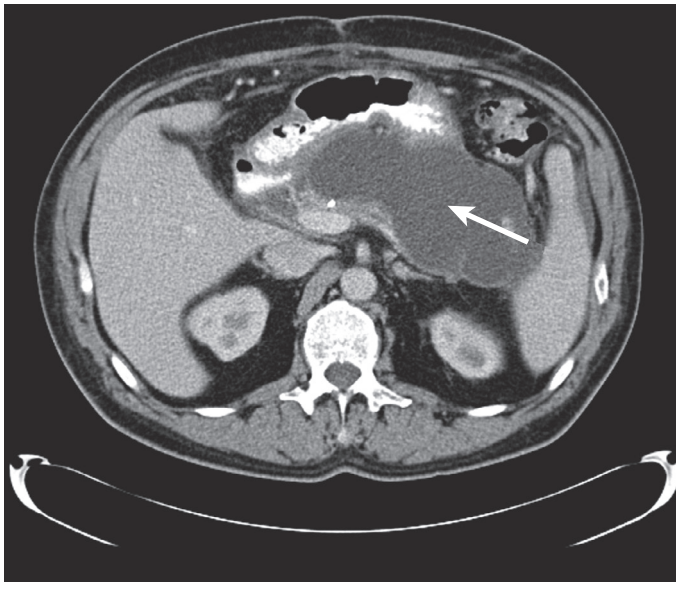

FIGURE 130-1 A computed tomographic scan demonstrating a large area of pancreas that does not enhance with intravenous contrast (*arrow*), consistent with pancreatic necrosis.

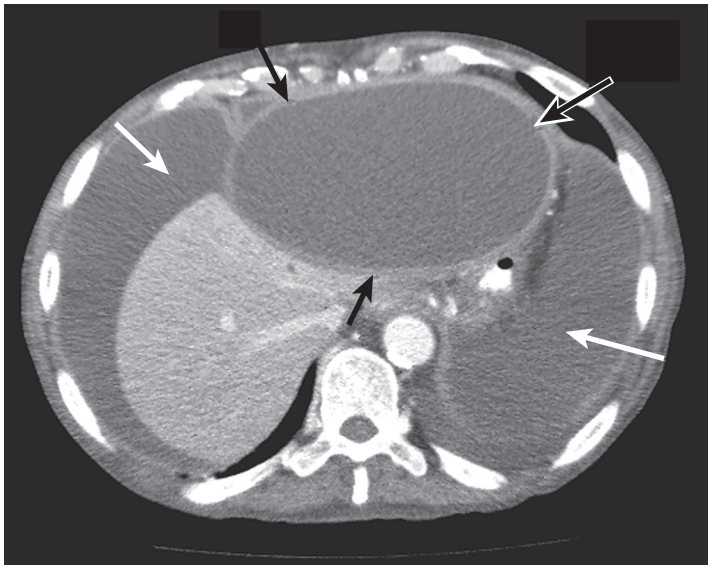

FIGURE 130-2. **A large pseudocyst is seen (*black arrows*). In addition, ascites surrounding the liver (*white arrows*) is noted due to a leak from the pseudocyst (pancreatic ascites).**

necrosis may not develop organ system failure, organ system failure is quite rare in the absence of pancreatic necrosis.

Risk Stratification

A number of clinical features identify patients at higher risk, including patients who are older, obese, or have more serious or more numerous comorbid conditions. Obesity in particular dramatically increases the risk of more severe pancreatitis. Additional clinical features that can be predictive include the presence of the systemic inflammatory response syndrome, particularly if it persists for more than 48 hours, and laboratory features consistent with intravascular volume depletion (elevated hematocrit or BUN). In addition to this qualitative estimate of prognosis, a number of multiple-factor scoring systems have been developed in an attempt to help guide clinicians in gauging prognosis, but there is no evidence that these complex multiple-factor scoring systems are superior to experienced clinical judgment.

TREATMENT

General Supportive Care

The majority of patients will recover within several days, but it is usually not possible to identify these patients at the time of admission.

All patients should initially be given nothing by mouth (NPO). Pain control often requires parenteral narcotics, and hydromorphone (in divided doses of 1 to 2 mg IV every 4 to 6 hours initially, with titration as needed) is generally preferred.

However, nonsteroidal anti-inflammatory agents (NSAIDs) may be as successful as narcotics by 24 hours.[A1] Patients with significant third-space loss, often augmented by prior poor oral intake or fluid losses through vomiting, will have evidence of intravascular fluid depletion. Even in mild pancreatitis, fluid losses may be substantial. Appropriate fluid resuscitation (Chapter 92) is recommended in all practice guidelines.[11] Moderate fluid resuscitation (1.5 mL/kg/hour of lactated Ringer solution in all patients, preceded by a 10 mL/kg bolus only if the patient is hypovolemic), with reassessments and adjustments at 12, 24, 48, and 72 hours[A2] to correct blood pressure and pulse, to reduce the hematocrit and BUN to normal, and to ensure a urine output of at least 0.5 mL/kg/hour, is preferred. More aggressive infusion of fluid worsens outcomes, primarily by increasing the risk of respiratory failure owing to fluid overload but also by increasing the risk of organ system failure, heart failure, and an abdominal compartment syndrome. To avoid these potential adverse effects, fluid therapy must be guided by whether the patient has the physiologic reserve to handle it.

Treatment of nausea and vomiting may be needed, and 5-HT3 antagonists (Table 118-5) are generally preferred. Nasogastric suction is rarely needed.

Patients with mild or moderate pancreatitis can be fed when they feel able to tolerate it, even before enzyme levels are completely normalized or pain is entirely absent. Beginning oral feeding within 48 hours after hospitalization is as safe as starting later and also reduces hospital length of stay. There is no need to begin with a clear liquid diet: feeding can be initiated with a low-fat solid diet as the first meal.

TABLE 130-2 COMPLICATIONS OF ACUTE PANCREATITIS

COMPLICATION	EXAMPLES
Systemic complications	Hypotension and shock Adult respiratory distress syndrome Acute renal failure Disseminated intravascular coagulation Hypocalcemia Hypertriglyceridemia Hyperglycemia Encephalopathy and coma
Gastrointestinal bleeding	Stress ulceration Pseudoaneurysm
Local (pancreatic) complications	Acute peripancreatic fluid collection Pseudocyst (infected and sterile) Acute necrotic collection Walled-off pancreatic necrosis (infected and sterile) Duodenal and biliary obstruction

In patients with more severe pancreatitis (based upon early organ system failure, substantial third-space fluid losses, or comorbid conditions), admission to an intermediate care unit or intensive care unit (ICU) is appropriate. Careful monitoring for progressive organ system failure, metabolic complications, and fluid status is critical in these patients. In patients with severe pancreatitis, enteral nutrition (oral or tube feeding) is safer and less expensive than total parenteral nutrition, which should be utilized exceedingly rarely. Patients who appear to have sufficiently severe disease that they might not be able to eat for 5 to 7 days can be considered for tube feeding. Alternatively, waiting for up to 5 days to see if patients with severe acute pancreatitis can eat is reasonable, with tube feeding reserved for those who are unable to eat after 5 days.[12] In patients given tube feeding, there is no difference if the tube is nasogastric, nasoduodenal, or nasojejunal. In addition, there is no evidence that elemental or semi-elemental formulas are better than standard polymeric formulas.

Treatment of Complications

Most patients who develop acute gallstone pancreatitis have already passed the offending stone into the duodenum, but patients with a persistent or multiple stones are at higher risk of developing cholangitis and (possibly) more severe pancreatitis. Current practice guidelines recommend urgent ERCP in patients whose gallstone pancreatitis is complicated by evidence of cholangitis (e.g., fever, jaundice, right upper quadrant pain) and early ERCP for patients with evidence of a persistent bile duct stone (e.g., visible persistent stone on imaging study, jaundice, persistently dilated bile duct, or worsening liver chemistries at 48 hours after admission). In patients who have severe pancreatitis, as evidenced by early and progressive organ system failure but who do not have cholangitis, early ERCP is not better than conservative care.[A3]

The systemic complications (Table 130-2) that develop in patients with severe acute pancreatitis include some that are similar to those commonly encountered in other ICU patients (e.g., ventilator-associated pneumonia, line sepsis) as well as the specific metabolic complications of severe pancreatitis[13] Hyperglycemia is common and may contribute to higher rates of infections. In severe acute pancreatitis, ionized calcium levels are usually normal, but hypocalcemia is common owing to a diminished serum albumin level; treatment is not needed in the absence of signs of hypocalcemia, such as tetany or a Chvostek sign (Chapter 227). Mild hypertriglyceridemia is common, but underlying hypertriglyceridemia does not cause acute pancreatitis unless triglyceride levels surpass 1000 mg/dL. Triglyceride levels drop promptly when the patient is made NPO.

Infections in patients with acute pancreatitis include urinary tract infections, pneumonia, line infections, and *Clostridioides difficile*. High-quality nursing care, antibiotic stewardship, and careful attention to catheters and lines can minimize these infections. In addition, patients with necrotizing pancreatitis may develop infected pancreatic necrosis. Although infected necrosis has a substantial impact on prognosis, prophylactic antibiotics are not beneficial for patients with sterile necrosis. Infected necrosis typically occurs 2 to 3 weeks into the illness and is heralded by fever, leukocytosis, and worsening abdominal pain. The responsible organisms are usually gram-negative rods and other gut flora, but *Staphylococcus aureus* is an important agent as well. If infected necrosis is suspected, a contrast CT scan should be obtained. The finding of gas in the necrotic collection is a specific but not sensitive sign of infected necrosis. A CT-directed fine-needle aspiration of the necrotic area can be obtained for culture and Gram stain but is not required in patients in whom clinical features, such as fever, leukocytosis, and worsening abdominal pain, are strongly suggestive of infected pancreatic necrosis. Antibiotics with deferred surgery if needed is as good as immediate surgical drainage for infected necrotizing pancreatitis.[A4] Antibiotics with appropriate penetration into necrosis (e.g., imepenem/cilastatin 500 mg IV/q 8 hours, meropenem 500 mg IV/q 8 hours, metronidazole 500 mg

IV/q 8 hours plus ciprofloxacin 400 mg IV/q 8 hours, or ceftazidime 500 mg IV/q 8 hours; see Table 266-4 in Chapter 266) should be initiated if infection is suspected or documented, and the specific regimen can be tailored to the organism if known. Intravenous antibiotics should be continued for several weeks to allow the necrotic material to demarcate fully, begin to liquefy, and become encapsulated. If patients become septic, it is reasonable to place a percutaneous drain into the collection to stabilize the patient. When this walled-off necrosis is sufficiently liquefied to allow less invasive approaches, therapy can include percutaneous, endoscopic, or minimally invasive surgical therapy.[14] Endoscopic transgastric necrosectomy is generally preferred, although minimally invasive surgical approaches are also effective.[A5-A7] Open surgical drainage should be avoided.

Fluid collections around the pancreas (acute peripancreatic fluid collections) are common in acute pancreatitis and do not require any specific therapy. Most will resolve spontaneously, but some will mature into an encapsulated pseudocyst. It is important to distinguish a pseudocyst (usually outside the confines of the pancreas and filled with fluid) from an area of necrosis (usually inside the confines of the pancreas and a mixture of solid and liquid material). Therapy also is not needed for asymptomatic pseudocysts, even if they are large, but therapy is indicated for pseudocysts that cause abdominal pain, obstruct a surrounding hollow viscus, or are associated with infection or bleeding. A pseudocyst can be treated successfully using endoscopic, percutaneous, or minimally invasive surgical techniques, and the choice among these approaches can be determined by local expertise and anatomic location.

Bleeding may complicate a pseudocyst, and bleeding into the cyst may reach the intestine through the pancreatic duct. In some patients, bleeding into the pseudocyst may be caused by a pseudoaneurysm of a nearby visceral artery; this type of bleeding may be massive. Unexplained gastrointestinal bleeding or a sudden, unexplained drop in the hematocrit in a patient with pancreatitis or a pseudocyst should prompt an emergent contrast CT scan, followed by embolization if a pseudoaneurysm is identified.

Treatment to Prevent Relapsing Pancreatitis

Preventing relapse requires a clear knowledge of the precipitating cause. Abstinence from alcohol and tobacco should be strongly encouraged, including referral to appropriate resources. Cholecystectomy prevents subsequent attacks of gallstone pancreatitis and should be accomplished within the index hospitalization.[A8] In patients with presumed "idiopathic" acute pancreatitis, an empiric cholecystectomy can be considered, provided that alternative causes have been excluded,[15] because many of these patients have gallstones as the etiology.[A9] In patients who have gallstone pancreatitis but who are not surgical candidates, endoscopic biliary sphincterotomy provides reasonable protection from subsequent attacks. Control of serum lipids prevents subsequent attacks of hypertriglceridemic pancreatitis. Therapy of lesions that obstruct the pancreatic duct, such as strictures and ampullary adenomas, may also prevent relapse.

The risk of post-ERCP pancreatitis is reduced with careful patient selection, the use of peri-procedural NSAID suppositories, by aggressive intravenous hydration, or by the placement of small-caliber temporary pancreatic duct stents.[A10]

PROGNOSIS

More than 80% of all patients with acute pancreatitis recover promptly without developing severe pancreatitis, but up to 30% may ultimately develop diabetes or exocrine pancreatic insufficiency. Mortality is usually from progressive multiple organ system failure, either from the acute pancreatitis itself or from hospital-acquired infections, including infection of pancreatic fluid collections or necrotic pancreatic tissue. Early organ failure (within 24 hours of admission), multiple organ system failure, and persistent or progressive (present beyond 48 hours after admission) organ failure are associated with prolonged hospitalization, ICU admission, need for surgery, and death. Overall mortality is about 2%, but it can approach 30% in patients with more severe comorbid conditions (and particularly obesity) and in patients who develop pancreatic necrosis, infection, or organ system failure. Although high-quality ICU care reduces mortality, no specific therapy is currently proven to reduce these risks.

For patients with acute alcoholic pancreatitis, long-term mortality is about four-fold higher than in the general population, mostly owing to alcohol-related conditions. Acute pancreatitis due to hypertriglyceridemia also has an adverse prognosis. For other causes, long-term mortality is minimally elevated compared with the general population.

CHRONIC PANCREATITIS

DEFINITION

Chronic pancreatitis is a syndrome associated with a wide spectrum of predisposing risk factors and environmental triggers. Chronic pancreatitis usually evolves after episodes of recurrent acute pancreatitis, and the transition between acute and chronic pancreatitis may be difficult to identify. Common features include abdominal pain, exocrine and/or endocrine insufficiency, and imaging evidence of pancreatic atrophy, calcification, or dilated pancreatic duct.[16] The progression of chronic pancreatitis is variable, but it often culminates in irreversible and widespread pancreatic fibrosis with chronic inflammation and damage to nerves, ducts, acini, and islets.

EPIDEMIOLOGY

The prevalence of symptomatic chronic pancreatitis in Western countries is about 40 to 70 per 100,000 persons, with an estimated incidence of 5 to 8 cases/100,000. In the United States, chronic pancreatitis accounts for about 125,000 outpatient visits and 25,000 hospitalizations annually. Interestingly, the prevalence of histologic evidence of chronic pancreatitis in autopsy studies approaches 5%, indicating that many people develop some pancreatic damage as a consequence of normal aging, other diseases (e.g., diabetes), or exposure to toxins (such as smoking or consumption of alcohol) but do not develop any symptoms or signs of chronic pancreatitis during life.

PATHOBIOLOGY

Multiple genetic polymorphisms and mutations can predispose to chronic pancreatitis, and various environmental and immunologic triggers can initiate the disease.[17] Episodes of acute inflammation, whether clinical or subclinical, eventually change the inflammatory milieu of the pancreas, with a shift to chronic inflammation, cell injury, cell death, the activation of pancreatic stellate cells, and the progression to fibrosis. This process becomes self-sustaining and produces the characteristic histologic damage.

The mechanisms of pain of chronic pancreatitis are complex. Damage to pancreatic nociceptive nerves and neuroimmune interaction driven by the chronic inflammatory state is the primary cause of pain, but the chronic pain can eventually produce visceral, spinal cord, and central hyperalgesia.

Alcohol and Tobacco

Alcohol causes about 50% of all cases of chronic pancreatitis in the United States. The risk is dose dependent, but it usually requires sustained ingestion of alcohol of 4 to 5 drinks daily over more than 5 years. The majority of people (95%) who consume this much alcohol do not develop chronic pancreatitis, pointing to important cofactors such as genetic risk factors and cigarette smoking. Smoking increases the risk of chronic pancreatitis by two- to three-fold, with a dose-dependent effect. Smoking is estimated to account for 25% of the attributable risk of chronic pancreatitis, and continued smoking after diagnosis accelerates the course of the disease. These risks also appear to be synergistic, such that the combination of alcohol and tobacco is more than an additive effect.

Genetic

Hereditary pancreatitis is an autosomal dominant disease characterized by early onset of acute and chronic pancreatitis, the development of exocrine and endocrine pancreatic insufficiency, and a high risk of pancreatic adenocarcinoma (Chapter 180). Mutations in the *PRSS1* gene in these families appear to cause a gain in function in which the mutant trypsinogen, once activated to trypsin, is difficult to inactivate. This trypsin, if present in an amount that overwhelms normal protective mechanisms, can activate other pancreatic enzymes and lead to pancreatic damage and eventually to chronic pancreatitis. One of the protective mechanisms is a trypsin inhibitor called the *SPINK1* protein. Loss-of-function mutations in *SPINK1* predispose to chronic pancreatitis. Major mutations in the *CFTR* lead to cystic fibrosis (Chapter 77), which may be associated with chronic pancreatitis and pancreatic atrophy, depending upon the location of the mutation. Certain mutations in *CFTR* predispose to chronic pancreatitis, without causing the sinopulmonary features of classic cystic fibrosis. A number of additional genetic polymorphisms in the calcium-sensing receptor, chymotrypsin C, carboxyethyl lipase, claudins, and others are also associated with chronic pancreatitis. With the exception of *PRSS1*, these polymorphisms predispose to chronic pancreatitis and may function as modifying genes but are not sufficient to cause chronic pancreatitis.

Pancreatic Duct Obstruction

Chronic obstruction of the pancreatic duct by benign, premalignant, and malignant conditions can cause chronic pancreatitis to develop in the gland upstream from the obstruction. Examples include duodenal diseases causing obstruction at the ampulla (celiac disease, Crohn disease, ampullary adenoma or carcinoma) and benign (after severe pancreatitis, pancreatic surgery, or

abdominal trauma) and malignant pancreatic duct strictures (pancreatic ductal adenocarcinoma, intraductal papillary mucinous neoplasms).

Other Causes

Autoimmune pancreatitis is a disease that most often presents as a masslike lesion in the pancreas with obstructive jaundice, mimicking cancer, but it also may present as chronic pancreatitis and rarely as acute pancreatitis.[18] Because cancer is more common than autoimmune pancreatitis, it must be excluded (usually with endoscopic ultrasonography). Type 1 autoimmune pancreatitis is characterized by diffuse swelling of the pancreas, elevation of the serum IgG4 level, and involvement of other organs, especially with biliary strictures, salivary gland inflammation, retroperitoneal fibrosis, and renal lesions. Histologically, these organs are infiltrated by chronic inflammatory cells, especially plasma cells bearing IgG4 on their surface, as is part of the spectrum of IgG4-related disease.[19] Type 2 autoimmune pancreatitis, which affects only the pancreas and is not associated with elevations in IgG4, may have potential overlap with autoimmune cholangitis.

Although most chronic pancreatitis follows multiple episodes of acute pancreatitis, a single severe acute attack that causes substantial pancreatic necrosis can cause a ductal stricture or destroy enough gland to produce exocrine and endocrine insufficiency. Other diseases that cause repeated attacks of pancreatitis can lead to chronic pancreatitis. For example, hypertriglyceridemia causes recurrent acute pancreatitis that leads to chronic pancreatitis.

CLINICAL MANIFESTATIONS

Abdominal pain is the most common symptom and is responsible for the greatest negative impact on quality of life. The pain may be episodic or constant, and it is generally present in the epigastrium with radiation to the back.[20] Some patients will present initially with an episode of acute pancreatitis and thereafter develop evidence of chronic pancreatitis, but others will have obvious chronic pancreatitis at their first presentation. If pain is episodic, the patient may be labeled as having acute pancreatitis or an acute flare of chronic pancreatitis. When pain is severe, nausea and vomiting may occur. Pain may worsen, improve, or remain stable over time. Up to 5% of patients do not have pain and instead present with exocrine (steatorrhea, weight loss) or endocrine (diabetes mellitus) pancreatic insufficiency. The disease tends to be progressive over time, even if the original cause (e.g., alcohol) is removed. The pain also may become self-perpetuating even if therapy is successful.

DIAGNOSIS

The diagnosis may be suspected based on the clinical features but should be confirmed by tests that identify structural damage to the pancreas or derangements in pancreatic function (Table 130-3).[21] Serum levels of amylase or lipase are not useful for diagnosing chronic pancreatitis. Serum trypsinogen (also called trypsin) is abnormally low in patients with chronic pancreatitis that is advanced enough to cause steatorrhea but is often normal in patients with less advanced disease. Serum glucose levels will be elevated in patients with endocrine insufficiency.

Chronic pancreatitis is a slowly progressive disease in which visible damage to the gland (e.g., on a CT scan) and functional failure (e.g., steatorrhea or diabetes mellitus) may not be apparent for years. All diagnostic tests are most accurate when the disease is far advanced, and all are far less accurate in the early stages of disease.

TABLE 130-3 DIAGNOSTIC TESTS FOR CHRONIC PANCREATITIS*

STRUCTURAL	FUNCTIONAL
Biopsy	Hormonal (secretin) test
Endoscopic ultrasonography	Fecal elastase
Magnetic resonance imaging with magnetic resonance cholangiopancreatography, with or without secretin infusion	Serum trypsin level
	Fecal fat
	Blood glucose level
Computed tomography	
Endoscopic retrograde cholangiopancreatography	
Ultrasonography	
Plain abdominal radiography	

*Listed in approximate order of decreasing sensitivity.

From a practical perspective, the diagnosis is established in most patients by CT or MRI.[22] The diagnostic challenge lies with patients who present with a severe pain syndrome suggestive of chronic pancreatitis but who have a normal or minimally abnormal CT or MRI. In these patients, MRI with secretin-MRCP or endoscopic ultrasonography is the best choice, unless a secretin-based pancreatic function test is available. ERCP should not be used for diagnostic purposes alone.

In about 20% of patients, no clear cause of chronic pancreatitis is identified, and this may be more common in women. Some patients may have underlying genetic mutations, and others may be surreptitiously using alcohol and/or tobacco. Two general forms of idiopathic chronic pancreatitis are observed. In the first, pain is the predominant feature, and the onset of disease is in young adulthood. In the second, the onset is in middle age, and exocrine and endocrine insufficiency, rather than abdominal pain, are the major clinical manifestations. As more genetic polymorphisms are identified, the relative prevalence of idiopathic pancreatitis is shrinking.

Tests of Pancreatic Structure

Plain abdominal radiographs may demonstrate diffuse or focal pancreatic calcification in patients with advanced chronic pancreatitis). Although specific for chronic pancreatitis, these findings are detected only after years of disease.

Abdominal ultrasound is of limited utility because overlying gas often limits the ability to visualize the pancreas. An abnormal pancreatic duct, pancreatic calcifications, gland atrophy, or changes in echotexture are seen in about 60% of patients.

CT is the most widely used diagnostic test for chronic pancreatitis, and high-quality images can be obtained of the pancreas and pancreatic duct. Characteristic findings include a dilated pancreatic duct, ductal or parenchymal calcifications, and atrophy (Fig. 130-3). These structural changes take years to develop, so CT is not as accurate in early or less advanced disease. Like CT, MRI allows detailed images of the pancreas, and the addition of MRCP allows even better assessment of pancreatic duct morphology. Secretin can be administered at the time of MRCP to allow better visualization of the pancreatic duct. MRI with secretin-MRCP is more sensitive for detecting the early changes of chronic pancreatitis than is CT.

Endoscopic ultrasonography allows very detailed images of the pancreatic parenchyma and duct (Fig. 130-4). Normal endoscopic ultrasonography essentially excludes chronic pancreatitis, whereas very abnormal endoscopic ultrasonography is highly consistent with chronic pancreatitis. ERCP provides the most detailed images of the pancreatic duct, as well as the opportunity to provide therapy (see later). Changes in the duct include dilation, irregularity, ductal stones, and strictures (Fig. 130-5). However,

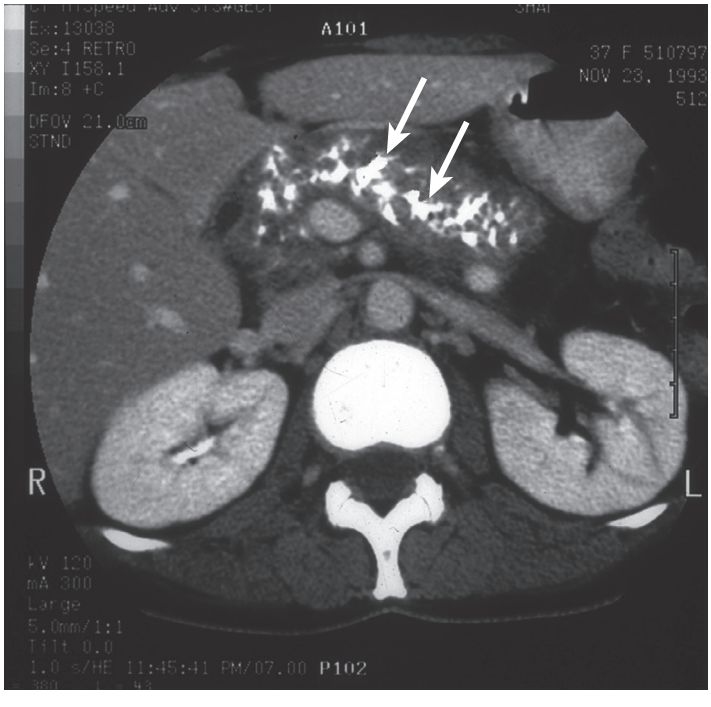

FIGURE 130-3. A computed tomographic scan demonstrating diffuse pancreatic calcification in a patient with long-standing chronic pancreatitis (*arrows*).

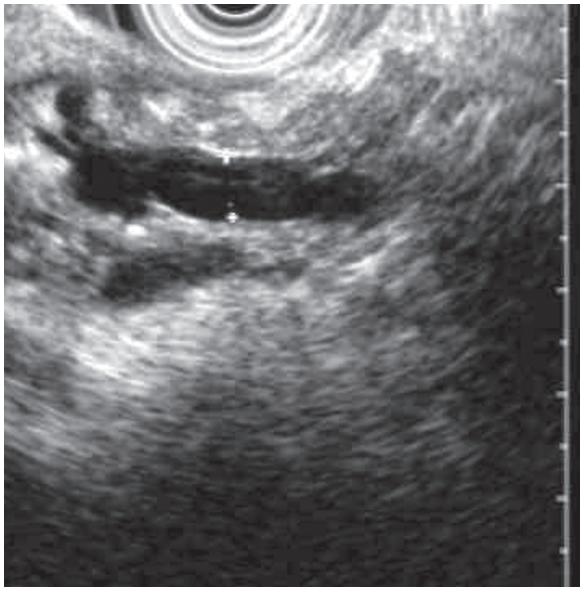

FIGURE 130-4. An endoscopic ultrasound in a patient with chronic pancreatitis, demonstrating a dilated pancreatic duct (*marks on margin of main duct*).

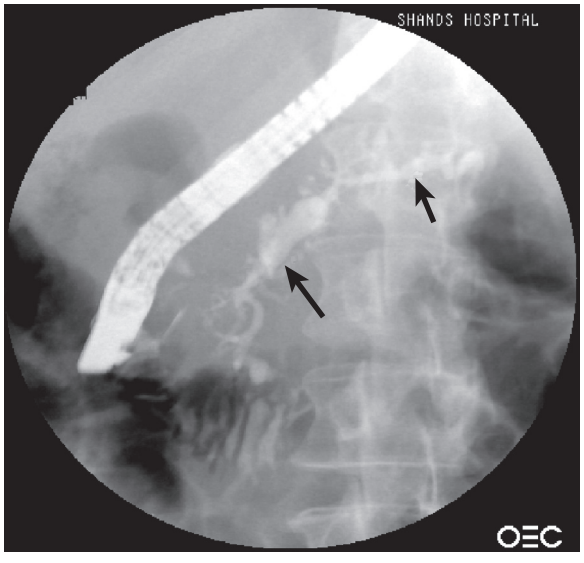

FIGURE 130-5. An endoscopic retrograde cholangiopancreatography demonstrating a very irregular pancreatic duct with areas of dilation and stricturing in a patient with chronic pancreatitis (*arrows*).

ERCP carries a risk of causing pancreatitis, so it should be utilized only when therapy is planned.

Tests of Pancreatic Function

Quantification of fat in stool during a 72-hour collection while on a high-fat diet can be used to document steatorrhea but is rarely performed. Qualitative analysis of fat with Sudan staining of a stool specimen has poor sensitivity and specificity. Fecal levels of pancreatic elastase are diminished to less than 200 µg/g in patients with exocrine pancreatic insufficiency. The test can be performed while patients are taking pancreatic enzyme therapy.

For a direct pancreatic function test, a tube or endoscope is passed into the duodenum, where pancreatic secretions are collected and analyzed for bicarbonate concentration, after a supraphysiologic dose of secretin is administered. A normal study is defined by at least one of the samples having a bicarbonate concentration of 80 mEq/L or more. The test becomes abnormal earlier in the disease process than any other test, so it is best suited to diagnose chronic pancreatitis earlier in its clinical course. However, the test is not widely available or used.

TREATMENT

Medical therapy starts with vigorous attempts to assist patients in stopping alcohol and tobacco, if applicable.

Treatment of Pain

Many patients will require analgesics. It is appropriate to start with the less potent agents first (such as NSAIDs or tramadol 50 to 100 mg every 6 hours). In most patients, it is helpful to add an adjunctive agent such as a gabapentoid (e.g., pregabalin starting at 75 mg two times daily), a tricyclic antidepressant (e.g., amitriptyline starting at 50 mg at night or nortriptyline starting at 10 mg at night), a selective serotonin reuptake inhibitor, or a combined serotonin and norepinephrine uptake inhibitor at the usual starting dose (Table 362-5).[23] Combinations of these adjunctive agents are also utilized. Antioxidants (mixtures of selenium, vitamins E and C, β-carotene, and methionine) may also have some beneficial effect on pain in selected patients with preexisting deficiencies.

Sudden worsening of pain should lead to a search for specifically treatable complications, including pseudocyst, obstruction of a surrounding hollow organ (e.g., duodenum or bile duct), or superimposed carcinoma. A good-quality CT or MRI is usually sufficient to exclude these possibilities. These imaging tests may also help in choosing appropriate therapy. Patients with a dilated duct (generally >5 mm) are the best candidates for endoscopic and surgical therapy for pain. Patients without ductal dilation are not suitable for most endoscopic and surgical therapy and must rely instead on medical therapy (Table 130-4). Unfortunately, pain often persists despite therapy. A celiac plexus block using bupivacaine can be performed relatively easily and safely, but substantial relief of pain is unpredictable and at best is achieved for only weeks.

Other Medical Therapy

Pancreatic enzyme therapy is commonly used to treat exocrine insufficiency and occasionally to treat pain, although evidence is lacking on its effectiveness for

TABLE 130-4 TREATMENT FOR PAIN

Medical therapy	Analgesics and adjunctive agents • Tramadol 50 mg, 1-2 three times daily • Pregabalin, starting at 75 mg two times daily • Gabapentin, starting at 100 mg at night • Amitryptiline, starting at 50 mg at night • Nortriptyline, starting at 10 mg at night • SSRIs (e.g., citalopram, fluoxetine, sertraline, paroxetine) at recommended starting dose (see Table 362-5) Antioxidants • Typical mixture containing vitamin C (1000 mg), vitamin E (300 IU), selenium (500 µg), methionine (2 g), and β-carotene (10,000 IU) total daily dose
Nerve block	Endoscopic ultrasonography–guided nerve block
Endoscopic therapy	Stent Stone removal, lithotripsy
Surgical therapy	Pancreaticojejunostomy (modified Puestow operation) Partial pancreatic resection (Whipple operation, duodenum preserving pancreatic head resection, others) Total pancreatectomy with islet-cell auto-transplantation

CT = computed tomography; SSRI = selective serotonin reuptake inhibitor.

TABLE 130-5 ENZYME THERAPY FOR EXOCRINE PANCREATIC INSUFFICIENCY

PRODUCT	FORMULATION	LIPASE CONTENT/CAPSULE OR PILL*
Zenpep	Enteric-coated porcine	3000; 5000; 10,000; 15,000; 20,000; 25,000; 40,000
Creon	Enteric-coated porcine	3000; 6000; 12,000; 24,000; 36,000
Pancreaze	Enteric-coated porcine	4200; 10,500; 16,800; 21,000; 37,000
Pertzye	Enteric-coated porcine with bicarbonate	4000; 8000; 16,000; 24,000
Viokace	Non–enteric-coated porcine tablet†	10,440; 20,880

*In USP units.
†Must be co-administered with an H_2 blocker (e.g., famotidine 20 mg twice daily) or a proton pump inhibitor (e.g., omeprazole 20 mg/day).

pain. Autoimmune pancreatitis responds promptly to steroid therapy (usually 40 mg of prednisone daily for 4 weeks, with a taper of 5 mg/week over the next 7 weeks), but relapse commonly occurs, particularly in patients with biliary obstruction. Continuing prednisone at a low daily dose (e.g., 5 to 7.5 mg for 3 years),[A11] or the use of alternative agents (e.g., azathioprine or rituximab, under the direction of a specialist), may be required to maintain remission.

Endoscopic Therapy and Lithotripsy

ERCP can be used to dilate strictures and place stents across the stricture. Ductal stones, if they are not too large and are not impacted, may also be removed. Larger stones usually require lithotripsy to reduce the stone to fragments that are manageable. ERCP is most useful in patients who have a dominant obstruction in the pancreatic head with upstream ductal dilation. Such ERCP therapy is technically successful in more than 80% of carefully selected patients, and pain relief may be seen in 70 to 80% of patients, although treatment usually requires several endoscopic procedures.[24]

Surgical Therapy

Surgery also generally requires a dilated pancreatic duct and is somewhat more effective and more durable than is endoscopic therapy.[A12] Surgery can involve decompression of the pancreatic duct, resection of the pancreas, or a combination of the two. The most commonly performed procedure, the modified Puestow procedure, involves a longitudinal incision of the pancreatic duct from the body of the pancreas to as close to the duodenum as possible, and this duct is overlaid with a defunctionalized small intestinal limb to drain it. At the time of surgery, ductal strictures can be incised and ductal stones can be removed. The procedure is relatively simple in patients with a dilated pancreatic duct (>5 mm). Pain relief in the short term is good (>80%), with about 50% obtaining long-term relief of pain. Alternative surgical procedures for pain include partial resection of the pancreas, typically the head of the gland. These operations, which include the classic pancreatico-duodenectomy (Whipple operation), as well as several variations of a duodenum-preserving pancreatic head resection, provide equal short-term pain relief[A13] and better long-term pain relief than a modified Puestow but perhaps with higher morbidity. Some evidence suggests surgery earlier in the clinical course is more effective.[A14] Total pancreatectomy, usually coupled with auto-transplantation of harvested islet cells, is currently considered a therapy of last resort in adults.

Exocrine Insufficiency

Steatorrhea and maldigestion do not occur until approximately 90% of pancreatic enzyme secretion is lost, usually after at least 5 to 10 years of disease. Patients may note weight loss and oily stools but often do not complain of diarrhea.[25] Patients with chronic pancreatitis and exocrine insufficiency maldigest fat, protein, and carbohydrates, but fat maldigestion is usually most severe (including fat-soluble vitamins, particularly vitamin D). The diagnosis of exocrine insufficiency is usually suggested by symptoms of oily or floating stools and weight loss. A formal 72-hour stool fat analysis is the most accurate method to document steatorrhea and to gauge effectiveness of therapy but is rarely done. Instead, the clinical features and a fecal elastase lower than 200 µg/g stool, coupled with an appropriate response to enzyme replacement therapy, is the best substitute for 72-hour fecal fat testing.

Pancreatic enzyme replacement therapy (Table 130-5) can normalize fat and fat-soluble vitamin absorption, maintain normal nutrition and weight, and prevent complications such as osteoporosis.[A15] Both enteric-coated capsules and non–enteric-coated tablets are available. Enzymes are identified by the lipase content of the pill or capsule, although they all contain proteases and amylase as well. The goal of enzyme therapy is to provide at least 10% of normal pancreatic output with each meal (90,000 USP units of lipase/meal). Since most patients are still producing some enzymes (including gastric lipase), it may not be necessary to prescribe the full dosage of 90,000 USP units with each meal; 40,000 to 50,000 is a reasonable starting point.

If non–enteric-coated preparations are selected, cotreatment with an H_2-blocker (e.g., famotidine 20 mg twice daily or equivalent) or proton pump inhibitor (e.g., omeprazole 20 mg daily or equivalent) is required to prevent acid denaturation of lipase; such cotreatment is not needed with enteric-coated preparations. Enzymes should be taken during the meal. Supplementation with vitamin D (400 to 1000 IU daily) and calcium (1.0 to 1.5 g daily) is appropriate because of the risks of osteoporosis (Chapter 225) and osteopenia. Measurement of fat-soluble vitamin levels and periodic bone mineral density testing are recommended. The success of enzyme therapy is generally defined as weight gain, reduction or absence of visible oil in the stool, and correction of fat-soluble vitamin levels. Failure of enzyme therapy is most often due to an inadequate dose. Increasing the dose up to the full 90,000 USP units during meals and encouraging compliance is appropriate as a first step. No generic products are available in the United States, so cost may be a major cause of noncompliance. Some patients may not respond owing to the presence of a second disease that also causes malabsorption, such as small intestinal bacterial overgrowth.

Endocrine Insufficiency

Similar to exocrine insufficiency, diabetes mellitus (Chapter 210) is a very late complication of chronic pancreatitis, occurring years or decades after the onset of disease. In contrast to type 1 diabetes mellitus, destruction of the entire islet, which has been termed type 3C diabetes mellitus, reduces secretion of both insulin and glucagon.[26] The absence of glucagon increases the risk that overly aggressive insulin therapy may lead to hypoglycemia. In most patients, therefore, insulin treatment is not aimed at exceedingly tight glucose control. Unfortunately, these patients are at similar risk for microvascular complications as are all other patients with diabetes.

Pancreatic Pseudocyst

Pancreatic pseudocysts, when they are discovered in patients with chronic pancreatitis, are generally mature and have a visible capsule surrounding them. As in acute pancreatitis, benign pseudocysts in chronic pancreatitis do not require therapy if they are not producing symptoms and are not infected. However, some cystic structures in and around the pancreas are cystic neoplasms (Chapter 180), not pseudocysts. Symptomatic pseudocysts require drainage, whereas neoplasms require resection. Features that suggest a cystic neoplasm include a cyst with a thick or nodular wall, a cyst with multiple internal septations, or a cyst occurring in a patient who does not have a history of pancreatitis. Any combination of these features should lead to further investigation, generally with endoscopic ultrasonography and aspiration.

Symptomatic pseudocysts can be treated with endoscopic, percutaneous, or surgical therapy with equal efficacy. In most centers, endoscopic ultrasonography-guided drainage is becoming first-line therapy with excellent short- and long-term results. Complications of pseudocysts include infection, bleeding (discussed earlier), and rupture. Pseudocysts may leak into the peritoneal compartment (pancreatic ascites) or track into the chest (pancreatic pleural effusion). Patients usually present with abdominal distension or dyspnea, rather than abdominal pain. Amylase level in the fluid is usually greater than 4000 U/L. Endoscopic therapy with stent placement across the connection between pseudocyst and pancreatic duct is highly effective in this situation.

Malignancy

Chronic pancreatitis is a strong risk factor for pancreatic ductal adenocarcinoma (Chapter 180), with a lifetime risk of about 4%, which is 8- to 16-fold above the general population.[27] *KRAS* mutations may be found in chronic pancreatitis. The risk of cancer is higher in patients who have hereditary pancreatitis and who also smoke, in whom the risk may be as high as 40%. Other genetic causes and smoking also increase the risk of secondary pancreatic malignancy, as may type 3C diabetes mellitus. It may be difficult to visualize cancer in an already diseased pancreas.

PREVENTION

Currently, there are no reliable methods to prevent chronic pancreatitis. Patients at risk for chronic pancreatitis, such as members of families with hereditary pancreatitis or patients with strong genetic predispositions, should avoid alcohol and tobacco. Similarly, patients with established chronic pancreatitis should avoid these agents, which hasten the progression of the disease.

PROGNOSIS

With prolonged follow-up of 10 to 20 years, the majority of patients will develop exocrine or endocrine insufficiency. Overall mortality is increased three- to six-fold compared with age-matched controls. Patients who are older, smoke, or have alcohol as the cause are at highest risk of mortality. Overall, 10-year survival approximates 70%, and 20-year survival is about 45%. Death is usually not due to pancreatitis itself but rather to malignancy, postoperative complications, and complications of alcohol (Chapter 364) or tobacco (Chapter 363).

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131 DISEASES OF THE RECTUM AND ANUS

ROBERT D. MADOFF AND GENEVIEVE B. MELTON

ANATOMY

The Rectum

The rectum and anal canal make up the final portion of the hindgut. In general, the colon transitions distally to the rectum at the level of the sacral promontory, where the taeniae coli splay to form a continuous longitudinal muscle layer and then extends approximately 12 to 18 cm distally. The peritoneum covers the upper two thirds of the rectum anteriorly and is usually more limited laterally. The rectum and its mesentery are surrounded posteriorly by endopelvic fascia, and this anatomic package contains the relevant lymphovascular structures that should be removed intact during rectal cancer surgery. The rectum also has two or three curves within its lumen created by submucosal folds called the valves of Houston. The second valve is often used as a rough guideline for the intraperitoneal cavity anteriorly.

Blood supply to the rectum originates from the inferior mesenteric artery proximally and internal iliac arteries distally. The inferior mesenteric artery terminates as the superior rectal artery, which supplies the rectum and the upper one third of the anal canal. Additionally, internal iliac arteries give off the middle rectal arteries and the inferior rectal arteries (inferior via the internal pudendal artery) to supply the distal rectum and anal canal. The proximal rectum drains predominantly into the superior rectal venous plexus and then to the inferior mesenteric vein and portal venous system. By contrast, the caudal rectum and anal canal drain mainly into the systemic venous circulation through the inferior and middle rectal veins into the internal iliac veins and inferior vena cava. Generally, the lymphatic drainage of the rectum follows the arterial supply, so the lymphatic spread of rectal tumors is to the inferior mesenteric and internal iliac lymph nodes. As a result of the rectum's dual blood supply and drainage, pulmonary metastatic spread occurs earlier and more often with rectal cancers than with colon cancers. Innervation to the rectum involves both the sympathetic and parasympathetic plexus. The sympathetic nerves arise from the first three lumbar segments of the spinal cord, whereas the parasympathetic nerve supply originates from the caudal three sacral nerve roots.

The Anal Canal

The anal canal, which begins at the level of the *levator ani* muscle and extends to the anal verge opening, is about 2.5 to 5 cm in length and is surrounded by the internal and external anal sphincter muscles. The anorectal junction, which can be easily appreciated on digital rectal examination, is the point where the rectum angulates posteriorly from the axis of the anal canal. The internal anal sphincter, which is responsible for about 70% of the resting anal tone, is an extension of the inner circular smooth muscle layer of the rectum. The external sphincter muscle comprises skeletal muscle and is under voluntary control. The dentate line is located about 2 cm proximal to the anal verge (anal opening). Hemorrhoids are classified as internal versus external according to their relative location proximal or distal to the dentate line.

The mucosal lining changes histologically along the course of the anal canal. Superiorly, the anal canal consists of columnar epithelium that mirrors the rectum. Approximately 1 to 2 cm above the level of the dentate line is a transitional zone, where columnar, cuboidal, transitional, and squamous epithelia cells are found. This admixture of cells constitutes the derivation of the term "basaloid" as it relates to anal canal cancers and marks the proximal boundary for anal cancer surveillance. Distal to this line, the squamous epithelium extends to the anal verge and perianal skin, eventually adding glandular and hair follicles that resemble skin elsewhere on the body. Infected anal glands are a frequent cause of perianal abscess and fistula. Below the dentate line, lymphatic drainage generally goes to the inguinal nodes. The external anal sphincter is innervated by fibers from S4 and the internal pudendal nerve. Somatic sensation of the anal canal comes from the inferior rectal nerve via the pudendal nerve. This somatic sensation ceases 1 to 2 cm above the dentate line, which explains why some procedures such as hemorrhoid ligation can be performed in the office without anesthesia.

SPECIFIC ANORECTAL CONDITIONS

Hemorrhoids

EPIDEMIOLOGY AND PATHOBIOLOGY

An estimated 15 million or more individuals, about 5 to 12% of adults, in the United States experience symptoms related to hemorrhoids each year, and these individuals generate over 4 million annual office visits. However, the true incidence and prevalence of hemorrhoids are unknown because several anorectal conditions that are commonly attributed to "hemorrhoids" are actually caused by other conditions.

Despite a commonly held notion that hemorrhoids are always abnormal, they actually are normal structures that are identifiable even in the fetus. Hemorrhoids are vascular cushions that consist of connective tissue, smooth muscle, and both arterioles and veins. Functionally, they likely aid with overall fecal continence by serving as a malleable gasket that improves the seal of the anal canal.

Hemorrhoids are *not* rectal varices, which are distinct vascular entities that can develop in the setting of portal hypertension. *Hemorrhoidal disease* is a more appropriate term to describe the pathologic state with hemorrhoids that generates symptoms. The hemorrhoidal arteriolar component explains why hemorrhoidal bleeding is typically bright red in color and can be copious in quantity. Causative factors that can provoke hemorrhoidal symptoms include constipation, diarrhea, older age, pregnancy, and prolonged straining with defecation. Over time, repeated stretching of the anal canal damages the supporting tissue and results in downward displacement of the vascular cushions. Although none of these precipitating factors has been established rigorously, each can cause either increased abdominal pressure or obstruction of venous return, thereby leading to engorgement and enlargement of the vascular cushions.

CLINICAL MANIFESTATIONS AND DIAGNOSIS

The most common symptom of internal hemorrhoids is bright red bleeding. This bleeding is typically painless and is most often seen on the toilet tissue or in the toilet bowl. The quantity of blood is variable, but patients may occasionally describe blood dripping or squirting into the toilet bowl. Passage of dark blood or blood mixed in the stool suggests a more proximal source. Internal hemorrhoids are classified based on the symptoms they cause. As internal hemorrhoids enlarge, they are also associated with redundant rectal mucosa that protrudes from the anus with defecation. Early hemorrhoids bleed but do not prolapse (grade 1). Initial protrusion reduces spontaneously (grade 2); more advanced protrusion requires digital reduction (grade 3) and, at its most advanced form, becomes irreducible (grade 4) (Fig. 131-1). Internal hemorrhoids are insensate and do not themselves result in pruritus, but they can cause itching owing to associated perianal soiling or mucus deposition caused by mucosal prolapse. Additionally, patients may complain of anal discomfort or pressure, mucus discharge, extra tissue at the verge (i.e., mucosal prolapse), or a sensation of incomplete evacuation.

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131 DISEASES OF THE RECTUM AND ANUS

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ANATOMY

The Rectum

The rectum and anal canal make up the final portion of the hindgut. In general, the colon transitions distally to the rectum at the level of the sacral promontory, where the taeniae coli splay to form a continuous longitudinal muscle layer and then extends approximately 12 to 18 cm distally. The peritoneum covers the upper two thirds of the rectum anteriorly and is usually more limited laterally. The rectum and its mesentery are surrounded posteriorly by endopelvic fascia, and this anatomic package contains the relevant lymphovascular structures that should be removed intact during rectal cancer surgery. The rectum also has two or three curves within its lumen created by submucosal folds called the valves of Houston. The second valve is often used as a rough guideline for the intraperitoneal cavity anteriorly.

Blood supply to the rectum originates from the inferior mesenteric artery proximally and internal iliac arteries distally. The inferior mesenteric artery terminates as the superior rectal artery, which supplies the rectum and the upper one third of the anal canal. Additionally, internal iliac arteries give off the middle rectal arteries and the inferior rectal arteries (inferior via the internal pudendal artery) to supply the distal rectum and anal canal. The proximal rectum drains predominantly into the superior rectal venous plexus and then to the inferior mesenteric vein and portal venous system. By contrast, the caudal rectum and anal canal drain mainly into the systemic venous circulation through the inferior and middle rectal veins into the internal iliac veins and inferior vena cava. Generally, the lymphatic drainage of the rectum follows the arterial supply, so the lymphatic spread of rectal tumors is to the inferior mesenteric and internal iliac lymph nodes. As a result of the rectum's dual blood supply and drainage, pulmonary metastatic spread occurs earlier and more often with rectal cancers than with colon cancers. Innervation to the rectum involves both the sympathetic and parasympathetic plexus. The sympathetic nerves arise from the first three lumbar segments of the spinal cord, whereas the parasympathetic nerve supply originates from the caudal three sacral nerve roots.

The Anal Canal

The anal canal, which begins at the level of the *levator ani* muscle and extends to the anal verge opening, is about 2.5 to 5 cm in length and is surrounded by the internal and external anal sphincter muscles. The anorectal junction, which can be easily appreciated on digital rectal examination, is the point where the rectum angulates posteriorly from the axis of the anal canal. The internal anal sphincter, which is responsible for about 70% of the resting anal tone, is an extension of the inner circular smooth muscle layer of the rectum. The external sphincter muscle comprises skeletal muscle and is under voluntary control. The dentate line is located about 2 cm proximal to the anal verge (anal opening). Hemorrhoids are classified as internal versus external according to their relative location proximal or distal to the dentate line.

The mucosal lining changes histologically along the course of the anal canal. Superiorly, the anal canal consists of columnar epithelium that mirrors the rectum. Approximately 1 to 2 cm above the level of the dentate line is a transitional zone, where columnar, cuboidal, transitional, and squamous epithelia cells are found. This admixture of cells constitutes the derivation of the term "basaloid" as it relates to anal canal cancers and marks the proximal boundary for anal cancer surveillance. Distal to this line, the squamous epithelium extends to the anal verge and perianal skin, eventually adding glandular and hair follicles that resemble skin elsewhere on the body. Infected anal glands are a frequent cause of perianal abscess and fistula. Below the dentate line, lymphatic drainage generally goes to the inguinal nodes. The external anal sphincter is innervated by fibers from S4 and the internal pudendal nerve. Somatic sensation of the anal canal comes from the inferior rectal nerve via the pudendal nerve. This somatic sensation ceases 1 to 2 cm above the dentate line, which explains why some procedures such as hemorrhoid ligation can be performed in the office without anesthesia.

SPECIFIC ANORECTAL CONDITIONS

Hemorrhoids

EPIDEMIOLOGY AND PATHOBIOLOGY

An estimated 15 million or more individuals, about 5 to 12% of adults, in the United States experience symptoms related to hemorrhoids each year, and these individuals generate over 4 million annual office visits. However, the true incidence and prevalence of hemorrhoids are unknown because several anorectal conditions that are commonly attributed to "hemorrhoids" are actually caused by other conditions.

Despite a commonly held notion that hemorrhoids are always abnormal, they actually are normal structures that are identifiable even in the fetus. Hemorrhoids are vascular cushions that consist of connective tissue, smooth muscle, and both arterioles and veins. Functionally, they likely aid with overall fecal continence by serving as a malleable gasket that improves the seal of the anal canal.

Hemorrhoids are *not* rectal varices, which are distinct vascular entities that can develop in the setting of portal hypertension. *Hemorrhoidal disease* is a more appropriate term to describe the pathologic state with hemorrhoids that generates symptoms. The hemorrhoidal arteriolar component explains why hemorrhoidal bleeding is typically bright red in color and can be copious in quantity. Causative factors that can provoke hemorrhoidal symptoms include constipation, diarrhea, older age, pregnancy, and prolonged straining with defecation. Over time, repeated stretching of the anal canal damages the supporting tissue and results in downward displacement of the vascular cushions. Although none of these precipitating factors has been established rigorously, each can cause either increased abdominal pressure or obstruction of venous return, thereby leading to engorgement and enlargement of the vascular cushions.

CLINICAL MANIFESTATIONS AND DIAGNOSIS

The most common symptom of internal hemorrhoids is bright red bleeding. This bleeding is typically painless and is most often seen on the toilet tissue or in the toilet bowl. The quantity of blood is variable, but patients may occasionally describe blood dripping or squirting into the toilet bowl. Passage of dark blood or blood mixed in the stool suggests a more proximal source. Internal hemorrhoids are classified based on the symptoms they cause. As internal hemorrhoids enlarge, they are also associated with redundant rectal mucosa that protrudes from the anus with defecation. Early hemorrhoids bleed but do not prolapse (grade 1). Initial protrusion reduces spontaneously (grade 2); more advanced protrusion requires digital reduction (grade 3) and, at its most advanced form, becomes irreducible (grade 4) (Fig. 131-1). Internal hemorrhoids are insensate and do not themselves result in pruritus, but they can cause itching owing to associated perianal soiling or mucus deposition caused by mucosal prolapse. Additionally, patients may complain of anal discomfort or pressure, mucus discharge, extra tissue at the verge (i.e., mucosal prolapse), or a sensation of incomplete evacuation.

ABSTRACT

Diseases of the anus and rectum can range from benign to serious conditions. A good understanding of anorectal anatomy, a thorough history, and a careful examination of the anorectum are highly valuable in assessing most anorectal complaints and differentiating among the various entities that patients will often call "hemorrhoids." Recent advances have substantially improved the treatment of several more serious anorectal issues, including rectal prolapse and fecal incontinence. Human papillomavirus vaccine plays a pivotal role in prevention of sexually transmitted anal dysplasia and cancer.

KEYWORDS

hemorrhoids
anal fistula
anal fissure
anal dysplasia
fecal incontinence
rectal prolapse

FIGURE 131-1. Grade 4 nonreducible internal and external hemorrhoids.

FIGURE 131-2. Thrombosed external hemorrhoid.

Individuals with anorectal symptoms frequently present complaining of "hemorrhoids" or are even referred from other physicians with a diagnosis of hemorrhoids. Although hemorrhoids may be present, they are often not the source of the underlying complaint. Therefore, it is always incorrect—and sometimes dangerous—for the physician to apply this diagnosis without completing an adequate evaluation. Fortunately, the initial evaluation is simple, and the correct diagnosis is often suspected based on history alone and confirmed by a limited visual and endoscopic examination. Internal hemorrhoids are best visualized with a slotted anoscope.

Rectal bleeding should never be attributed to hemorrhoids alone, even if hemorrhoids are visible; at a minimum, flexible sigmoidoscopy is required to exclude more proximal pathology. For more concerning symptoms or high-risk patients (e.g., personal or family history of colorectal cancer, persistent bleeding despite adequate treatment, unscreened individuals over age 45 years), a full evaluation of the large intestine should be performed by colonoscopy. The rising incidence of colon and rectal cancers (Chapter 179) in individuals under age 45 years serves to emphasize the point that unexplained rectal symptoms require thorough evaluation at all ages and should not simply be attributed to "hemorrhoids."

External hemorrhoids are usually asymptomatic and should be differentiated from perianal skin tags, which may cause difficulties with perianal hygiene, particularly when they are large or elongated. External hemorrhoids become symptomatic when they thrombose, thereby causing acute-onset pain and swelling (Fig. 131-2). Thrombosed external hemorrhoids, which are usually diagnosed by simple inspection of the anus, appear as an external lump, covered by anoderm and skin, with the underlying thrombosis giving it a purple appearance. Occasional patients who present with extensive, circumferential thrombosis require urgent surgical consultation.

TABLE 131-1 INTERNAL HEMORRHOIDS: GRADING AND MANAGEMENT

GRADE	SYMPTOMS AND SIGNS	MANAGEMENT
1	Bleeding No prolapse	Dietary modifications* Rubber band ligation Infrared coagulation Injection sclerotherapy
2	Prolapse with spontaneous reduction Bleeding, seepage	Rubber band ligation Infrared coagulation Dietary modifications* Injection sclerotherapy Doppler hemorrhoidal artery ligation
3	Prolapse requiring digital reduction Bleeding, seepage	Surgical hemorrhoidectomy Rubber band ligation Dietary modifications* Doppler hemorrhoidal artery ligation
4	Prolapsed, cannot be reduced Strangulated	Surgical hemorrhoidectomy Urgent hemorrhoidectomy

*Dietary modifications include increasing the consumption of fiber, bran, or psyllium and water. Dietary modifications are always appropriate for the management of hemorrhoids and to prevent recurrence after banding or surgery (or both).

TREATMENT

Grade 1 hemorrhoids often respond to dietary manipulation alone: increased dietary fiber, addition of a fiber supplement, and increased water intake (Table 131-1).[1,2] The goal, which may not be readily achievable, is approximately 25 to 30 g of fiber and 8 glasses of water daily. Patients often require a dietary fiber supplement to reach the recommended fiber intake. Patient education should also include maintaining proper bowel habits, including limiting time on the commode and avoiding straining with defecation.

More advanced hemorrhoids require specific therapy, which is almost always office-based. The most popular and simplest technique is rubber band ligation, whereby a tiny rubber band (internal diameter approximately 1 mm) is placed around some of the redundant rectal mucosa and prolapsing hemorrhoid well above the dentate line. The banded tissue sloughs in 7 to 14 days, an event occasionally heralded by rectal bleeding, which can be significant in rare cases. The result of surgery is a pexy effect for the prolapsing hemorrhoid and ligation of part of the blood flow to the hemorrhoid pile. Recovery is relatively straightforward for most patients. Banding can be repeated at 3- to 4-week intervals until bleeding and protrusion are controlled. Bands placed too close to the dentate line cause immediate severe pain and must be removed promptly. Patients who are at high risk of bleeding because of intrinsic coagulopathies or treatment with anticoagulant agents should not undergo rubber band ligation, unless these agents can be discontinued prior to the procedure, owing to the increased risk of postprocedure bleeding. Alternative office therapies for moderate internal hemorrhoids include injection sclerotherapy and infrared coagulation. Thrombosed external hemorrhoids that are early in their course (up to 72 hours since onset), have not responded to conservative therapy, or have thrombosed repeatedly also can be treated by excision in the office under local anesthesia or, if required because of size and location, may require excision in the operating room.

Operative hemorrhoidectomy is needed in only a minority of patients with advanced disease. Indications for hemorrhoidectomy include irreducible prolapse, a substantial external component, and failure of more conservative therapies. The most common approach is an excisional hemorrhoidectomy, which is generally performed on an outpatient basis. Excisional hemorrhoidectomy can also be performed using a coagulation device that seals the tissue, with comparable results and potentially less recurrence (weak evidence).[A1] An alternative approach is Doppler-guided hemorrhoidal artery ligation, after which recurrence rates of 3 to 60% have been reported. Recurrent hemorrhoids are less frequent after hemorrhoidal artery ligation than after a single rubber band ligation,[A2] but hemorrhoidal artery ligation typically must be performed in the operating room and is associated with more pain. Stapled hemorrhoidopexy, which entails resecting a ring of rectal mucosa proximal to the internal hemorrhoids using a circular stapling device, has mostly fallen out of favor because of its higher recurrence rate and a small but worrisome risk of significant complications, such as chronic pain, rectovaginal fistula, and staple line bleeding.

PERIANAL ABSCESS

EPIDEMIOLOGY AND PATHOBIOLOGY

Several superficial and deep spaces around the rectum and anal canal normally contain loose areolar tissue that can serve as potential spaces for perianal infections. Perianal abscess is a common condition, but its incidence is not

well documented. Approximately 80% of perianal abscesses are caused by infection of the anal glands that track toward the skin, whereas other causes include simple skin infections, trauma, inflammatory bowel disease, anorectal surgery, malignancy, and immunosuppression.

CLINICAL MANIFESTATIONS AND DIAGNOSIS

Patients most commonly present with complaints of perianal pain and swelling with or without antecedent events such as trauma. In most cases, a local area of erythema, tenderness, and fluctuance can be appreciated on physical examination. However, these findings are often absent in abscesses in certain locations, including intersphincteric abscesses in the plane between the internal and external sphincter muscles, as well as in supralevator and deep ischiorectal locations. These abscesses should still be suspected based on a history of increasing pain and fever, as well as focal perianal tenderness on the physical examination.

As with all acutely painful anal conditions, digital examination should generally be avoided. Likewise, office instrumentation with an anoscope or proctoscope is contraindicated because these examinations cause substantial pain and typically yield little, if any, diagnostic information. When the cause of the acute pain cannot be determined in the office, prompt examination under anesthesia should be performed. Adjunctive computed tomographic (CT) scanning, magnetic resonance imaging (MRI), or endorectal ultrasound can provide valuable information, particularly in settings of occult, recurrent, or complex disease.

TREATMENT

Treatment for perianal abscess is prompt incision and drainage, which usually can be performed in the office.[3] Large or deep (e.g., postanal or horseshoe) abscesses are best evaluated in the operating room with proper sedation. Antibiotics do not adequately penetrate abscess cavities, and extension of a local infection can lead to sepsis and complex long-term problems. Therefore, antibiotic therapy is inadequate and should never be given in an attempt to avoid or delay incision and drainage. After incision and drainage, antibiotics (e.g., 7 days of oral metronidazole 500 mg every 8 hours and ciprofloxacin 500 mg every 12 hours in addition to standard care) may reduce the rate of subsequent fistula formation.[A3] Antibiotics are especially recommended in immunocompromised patients (e.g., patients with poorly controlled HIV or diabetes mellitus, transplant recipients, and patients undergoing chemotherapy), patients with extensive cellulitis or severe systemic symptoms, and patients at high risk for endovascular infection (e.g., patients with cardiac shunts or prosthetic valves). In patients who fail to improve following incision and drainage, prompt surgical reevaluation is warranted because the problem is likely to be a residual abscess that requires further drainage.

ANAL FISTULA

EPIDEMIOLOGY

An anal fistula, which represents the chronic form of a perianal abscess in which the tract from the infected anal gland to the abscess cavity does not adequately heal, can occur in 30 to 50% of patients following a perianal abscess.[4] This usually manifests as one or more chronic tracts from the anal canal to the perianal skin. The incidence of anal fistula is about 8.6 per 100,000. Fistulae are two to three times more common in men than in women.

PATHOBIOLOGY

After a perianal abscess is drained, the internal opening—the site at the dentate line where the infected gland originated—can remain patent, thereby leaving a source for recurrent infection as well as a tract from the internal anal gland to the abscess cavity and its drainage site. Multiple or atypical anal fistulae should always raise the diagnostic suspicion of Crohn disease, which can occasionally be isolated to the perianal area.

Anal fistulae are characterized by their relationship to the sphincter complex. The simplest and most common (approximately 70%) fistula is intersphincteric—located in the plane between the internal and external sphincter muscles. Transsphincteric fistulas (about 20 to 25%), which traverse both the internal and external sphincter muscles, are classified either as low fistulae, which traverse only the distal external sphincter, or high fistulae, which traverse the more proximal portions of the external sphincter. Suprasphincteric fistulae originate at the dentate line and loop over the entire sphincter complex. Extrasphincteric fistulae have internal openings remote from the dentate line; most originate from a pelvic abscess caused by a ruptured appendix (Chapter 128), diverticulitis (Chapter 128), or Crohn disease (Chapter 127).[5] A horseshoe fistula, which has external openings with associated tracts on both sides of the midsagittal plane, most commonly has a single internal opening in the posterior midline.

CLINICAL MANIFESTATIONS AND DIAGNOSIS

Anal fistulae sometimes present as recurrent abscesses in the same location as the original one or as persistent and sometimes intermittent purulent drainage from an abscess site that has failed to heal completely. Patients may often think the area has healed for several weeks or longer prior to experiencing the same feeling of a "boil" forming in the identical area, spontaneously rupturing, and relieving their symptoms.

The diagnosis of an anal fistula is established by history and by visualization of an external opening in the perianal skin. A fibrous fistula tract can sometimes be palpated along the course of the fistula from the skin toward the anal canal. An internal opening is occasionally visible on anoscopy, but a visible internal opening is not necessary to identify a fistula and to make a presumptive diagnosis.

TREATMENT

Treatment of anal fistulae is surgical. Most fistulae are cured by being laid open via a fistulotomy to eliminate the original source of infection at the internal opening. The fistula tract can then heal by secondary intention. However, this approach divides sphincter muscle and puts the patient at risk for impaired fecal continence in proportion to the quantity of muscle involved. In general, intersphincteric and low transsphincteric fistulae can be safely laid open if the patient has normal baseline continence and no underlying predisposing factors for diarrhea (e.g., colitis) or recurrent fistulae (e.g., Crohn disease). Because the anterior sphincter mechanism is relatively short and subject to injury following vaginal delivery, fistulotomy for anterior fistulae in women must be undertaken only after careful consideration.

When a high or complex fistula is identified, the first step is often placement of a seton, a suture, or other material (now commonly a Silastic vessel loop) that is passed though the fistula tract, out the anus, and secured to itself. The seton guarantees that the external fistula opening will not heal over, so a recurrent abscess is much less likely to supervene. After being left in for several weeks, the tract often scars around the seton and becomes fibrotic. Treatment options to eliminate the internal opening include endorectal advancement flap repair and ligation of the intersphincteric fistula tract. Because Crohn disease–associated fistulae tend to be multiple and recurrent, fistulotomy is avoided, except for the most superficial fistulae. In general, patients with Crohn disease are best served by placement of long-term draining setons and medical therapy for their underlying disease (Fig. 131-3).

PROGNOSIS

After appropriate surgery, about 85% of anal fistules are healed at 6 years.

ANAL FISSURE

EPIDEMIOLOGY

Anal fissures can occur at any age but most frequently affect young adults. Men and women are equally affected.

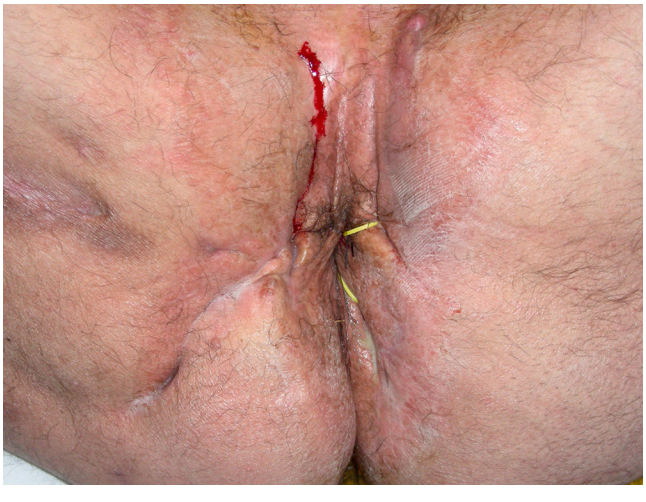

FIGURE 131-3. Crohn disease fistulae. Silastic setons in place with several additional draining tracts and evidence of prior surgery.

FIGURE 131-4. Anal fissure. This longitudinal tear occurs just inside the anal margin.

PATHOBIOLOGY

An anal fissure, which is a longitudinal tear typically with ulceration in the anoderm, occurs just inside the anal margin (Fig. 131-4). The underlying pathophysiology of anal fissures is hypertonia of the internal anal sphincter. Typical anal fissures occur at the midline; most commonly they occur posteriorly, but about 15% are found anteriorly or both anteriorly and posteriorly. "Off-the-midline" fissures may represent a routine fissure, but they generally require examination under anesthesia with culture, biopsy, and pathologic evaluation to exclude other causes such as anal cancer, Crohn disease, syphilis, HIV, leukemia, or tuberculosis.

CLINICAL MANIFESTATIONS AND DIAGNOSIS

Patients with anal fissures generally present with pain during and after bowel movements. Fissures are sometimes precipitated by a bout of constipation or a period of excessive diarrhea, but no specific precipitating event is usually noted. Patients typically describe severe anal pain that may persist for hours or even continue until exacerbation by the next bowel movement. There is sometimes an association with minor bright red bleeding, most commonly seen in small quantities that streak the stool or the toilet tissue. Whereas an acute anal fissure appears as a superficial split in the perianal skin and anoderm, chronic anal fissures, defined by their presence for at least 6 to 8 weeks, are often associated with a "sentinel" skin tag (so-called because its presence should suggest the presence of an underlying fissure) or a hypertrophied anal papilla located just proximal to the fissure at the dentate line, as well as more extensive tearing and ulceration. Well-established fissures may have fibrotic margins with "rolled edges" of the anoderm and visible internal anal sphincter fibers at their base.

Most fissures can be readily observed on physical examination by applying opposing traction to the buttocks. In general, no further examination is performed at that time when a classic anal fissure is identified. Digital and endoscopic examination typically should be delayed until the patient has healed to avoid causing pain. However, patients should be advised that they will require subsequent examination, which may include anoscopy or colonoscopy to exclude other anorectal or more proximal pathology.

TREATMENT

In addition to treating any instigating bowel abnormalities (e.g., constipation or diarrhea), most therapies for anal fissures are directed at the underlying hypertonia of the internal anal sphincter.[6] Approximately 40% of fissures heal with fiber supplementation and increased fluid intake alone, including the great majority of acute fissures. Patients are also advised to take warm sitz baths for symptomatic relief, especially following bowel movements.

Two pharmacologic approaches can augment diet and sitz baths: topical sphincter relaxants and botulinum toxin injection. Topical nitroglycerine (0.2 to 0.8%) or a topical calcium-channel blocker such as diltiazem gel (2%) applied externally around the anal orifice two to four times daily reduces sphincter tone and often leads to healing. Both drugs have similar efficacy, but nitroglycerine has the disadvantage of causing headaches, lightheadedness, or syncope owing to systemic vasodilation in approximately 25% of patients. Botulinum toxin injection into the internal anal sphincter appears to promote healing with recurrence rates similar to topical treatments. Overall, these more conservative approaches unfortunately are only marginally better than placebo for healing chronic fissures, and recurrent fissures occur in approximately 50% of patients.

For patients who fail medical therapy or who are simply too subjectively miserable to pursue pharmacologic treatment, lateral internal sphincterotomy is an appropriate and generally safe approach that is easily performed under monitored local anesthesia in an outpatient setting.[A4] Recovery after lateral internal sphincterotomy is rapid, and fissure healing is expected in more than 90% of cases. Sphincterotomy as first-line therapy provides higher healing rates, fewer relapses, and fewer side effects than topical nitroglycerine, with fewer symptoms, greater satisfaction, and no difference in continence at long-term follow-up. However, a small percentage of patients who undergo sphincterotomy develop minor seepage or even actual incontinence. Therefore, the sphincterotomy should be "tailored" to adjust the amount of internal anal sphincter according to the size of the fissure and the patient's overall amount of internal anal sphincter to maintain sufficient sphincter muscle. When such patients have refractory fissures, a trial of botulinum toxin injection, potentially in conjunction with a topical sphincter relaxant, is often a good alternative. A new experimental treatment is the injection of recently collected autologous adipose tissue, which has been reported to heal up to 55% of perianal fistulas in patients with Crohn disease.[7]

PRURITUS ANI

EPIDEMIOLOGY

The reported incidence of pruritus ani ranges from 1 to 5% in the general population, though it is likely much higher. Men are more commonly affected than women (4 : 1), and this condition is most common in the fourth through the sixth decades of life. Primary or idiopathic pruritus is responsible for 50 to 90% of all cases of pruritus ani.

CLINICAL MANIFESTATIONS AND DIAGNOSIS

Pruritus ani, or perianal itching, is a very common symptom but is not a disease in and of itself. The most common cause is likely inadequate perianal hygiene, often exacerbated by scratching, which leads to excoriation of the skin, further inflammation, and worsening pruritus.[8] Secondary causes include dermatologic, infectious, systemic, and lower gastrointestinal disease, as well as local irritants. Some of these sources include prolapsing hemorrhoids, anal fistulas, and anal incontinence, as well as specific dermatologic conditions such as contact dermatitis, psoriasis, lichen sclerosis, squamous intraepithelial neoplasia (formerly called Bowen disease), and perianal Paget disease (intraepidermal adenocarcinoma).

Diagnosis is typically based on a history of intractable itching despite trials of several over-the-counter medications and physical examination to exclude an obvious inciting source. The severity of the condition can be classified as stage 0—normal skin; stage 1—red and inflamed skin; stage 2—lichenified skin; and stage 3—lichenified skin as well as coarse ridges and often ulcerations.

TREATMENT

A therapeutic trial of symptomatic empiric management is effective in more than 90% of patients. Options include improved hygiene, avoidance of potential contact allergens (e.g., soaps and over-the-counter topical treatments), and use of either talc to absorb excess moisture or a barrier cream such as zinc oxide.[9] Mechanical scratching will perpetuate the cycle of inflammation and must be strictly avoided. Some patients benefit from the avoidance of certain foods, including caffeinated beverages, alcohol, milk, chocolate, and tomatoes. Mild topical steroids such as 1% hydrocortisone are sometimes helpful, but stronger steroid preparations are frequently counterproductive and should be avoided when they are not indicated for a specific dermatologic diagnosis. The placement of a small fluff of absorbent cotton at the anal verge can help to wick away moisture and collect any drainage before it can be in prolonged contact with the skin. Other adjuncts include drying the perianal skin with a hairdryer after bathing and replacing toilet paper with nondetergent, nondeodorant, nonalcoholic hypoallergenic wipes. Skin biopsies and dermatologic consultation should be obtained when a primary dermatologic condition is suspected or when the perianal irritation fails to heal with conservative therapy.

FECAL INCONTINENCE

EPIDEMIOLOGY AND PATHOBIOLOGY

Involuntary loss of stool or flatus is a relatively common problem that, when severe, can be socially isolating and debilitating. About 2% of individuals in the United States report incontinence symptoms, but the prevalence is more common in women and the elderly, and it also is substantially higher in patients who visit primary care providers and gastroenterologists. Almost half of U.S. nursing home patients suffer from fecal incontinence. Factors such as embarrassment, denial, and the degree of symptoms hinder a determination of true prevalence. Patients presenting with fecal incontinence often have concomitant urinary incontinence (Chapter 115), and up to 25% of women with fecal incontinence have at least one associated pelvic floor disorder.

Normal continence involves the coordinated interaction between multiple different neuronal pathways and the pelvic and perineal structures. In addition, several factors including bowel motility, stool consistency, evacuation efficiency, mental status, and sphincter integrity all play a role in normal regulation.[10] Sphincter disruption related to vaginal delivery is a common cause that often affects young women; many incontinent women who present later in life have an underlying sphincter injury for which they can no longer compensate. Other causes of incontinence include fecal impaction, surgical or traumatic sphincter injury, rectal prolapse, neurologic disorders (e.g., diabetic neuropathy, stroke, multiple sclerosis, brain or spinal cord injury), chronic diarrheal states, dementia, impaired mobility, and poor access to toilet facilities.

CLINICAL MANIFESTATIONS AND DIAGNOSIS

Because fecal incontinence is a symptom and not a disease, the diagnosis is based on history alone. Specific evaluation of the incontinent patient can include anal manometry, anal ultrasound, pudendal nerve testing, and defecography. Anal endoscopic ultrasonography, which is generally a helpful test, accurately depicts sphincter anatomy and reliably identifies sphincter defects. Some patients with fecal incontinence may have concomitant disorders such as impaired evacuation, pelvic prolapse, or urinary incontinence; urogynecologic evaluation should be performed when appropriate.

TREATMENT

Mild incontinence is often treated successfully by the addition of a fiber supplement to make stools less liquid and the use of an antimotility agent, such as loperamide 2 to 4 mg up to four times daily, to treat diarrhea. Biofeedback also is sometimes successful.

For individuals with significant sphincter disruptions, surgical repair (sphincteroplasty) usually leads to substantial improvement (Fig. 131-5). Unfortunately, this improvement tends to wane over time, so sacral nerve modulation, which requires placement of an electrical lead into the S3 sacral foramen and implantation of an electrical stimulator, is usually a better option. Sacral nerve modulation is highly effective for fecal incontinence,[11] with about 40% of patients regaining continence and another 45% noting improvement at 36 months.

For patients without a sphincter defect, sacral nerve modulation is one option, but another option is transanal submucosal injection of dextranomer in stabilized hyaluronic acid. These injections add bulk to the perianal tissues, thereby allowing the perianal tissues to coapt together. As a result, injection therapy is most effective in patients who have a small amount of leakage and not loss of full bowel movements. After two treatments of four injections each, reported fecal incontinence decreases by about 50%, but many patients require repeat injections. This treatment should not be used in patients who are immunosuppressed or who have had prior radiation therapy, rectal prolapse, or inflammatory bowel disease.

For patients with severe refractory incontinence, creation of a colostomy should be strongly considered. Initial reluctance notwithstanding, most patients regain control of their bowel function and report a substantially improved quality of life.

RECTAL PROLAPSE

EPIDEMIOLOGY AND PATHOBIOLOGY

Rectal prolapse is a full-thickness protrusion of the rectum beyond the anal sphincter. It occurs in about 1% of adults over age 65 years, and about 90% of cases are in women. Prolapse is caused by an internal rectal intussusception that eventually becomes more severe and then progresses so that the full thickness of the rectal wall protrudes externally. Risk factors include multiparity, a history of pelvic surgery, higher body mass index, chronic diarrhea or constipation with significant straining, connective tissue disorders, and neurologic diseases. Uncorrected prolapse also frequently leads to fecal incontinence by mechanically stretching the sphincter complex and causing a stretch injury to the pudendal nerves, with frank loss of fecal material when the rectal mucosa prolapses externally.

CLINICAL MANIFESTATIONS AND DIAGNOSIS

The main clinical manifestation of rectal prolapse is the protruding rectal mass (Fig. 131-6). The protrusion most commonly occurs with bowel movements, but with time it may occur with coughing or sneezing, and eventually it can occur spontaneously. Approximately 75% of patients have at least minor complaints of fecal incontinence, whereas complaints of "constipation,"

FIGURE 131-6. Rectal mucosal prolapse. The main clinical manifestation of rectal prolapse is the protruding rectal mass.

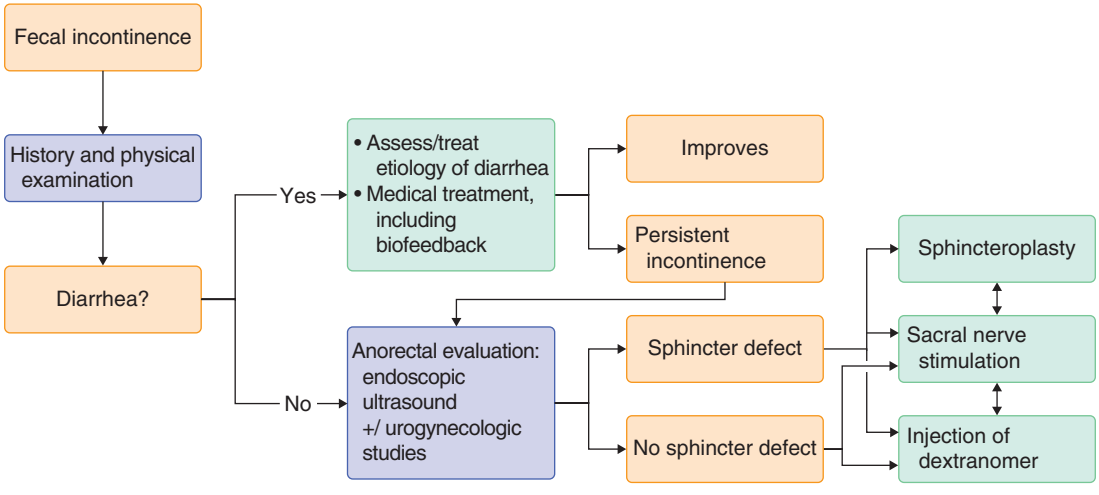

FIGURE 131-5. Algorithm for fecal incontinence. (Adapted from Madoff RD, Parker SC, Varma MG, et al. Fecal incontinence in adults. *Lancet*. 2004;364:621-632.)

which are often caused by unsuccessful attempts to evacuate the intussusceptingrectum, occur in 15 to 65%. Other associated symptoms include chronic mucus discharge, pelvic discomfort, and minor bleeding. Patients can also rarely present with an incarcerated or strangulated prolapse that mandates urgent intervention.

The diagnosis of rectal prolapse is confirmed on physical examination. Full-thickness prolapse, which is characterized by concentric mucosal folds of the rectum, must be differentiated from circumferential mucosal prolapse, which is characterized by radial folds alone. The prolapse is often best demonstrated by having the patient strain on a commode. Ancillary studies do not routinely alter management, but colonoscopy should be performed to help exclude other pathology. Defecography is also helpful to diagnose internal rectal intussusception and associated pelvic floor abnormalities, such as rectocele and enterocele.

TREATMENT

Nonoperative measures will not correct rectal prolapse, so conservative measures should be considered only in patients who have very minor and minimally symptomatic prolapse or who are poor surgical candidates. A ventral rectopexy with mesh (either biologic or nonabsorbable), which involves mobilizing the rectum anteriorly, suturing the mesh to the anterior rectal wall, and then fixing the mesh to the sacrum, is the procedure of choice. This operation, which can be performed laparoscopically or robotically, can help to correct rectoceles and is associated with less postoperative constipation and recurrence than prior surgical alternatives.[A5]

HUMAN PAPILLOMAVIRUS

EPIDEMIOLOGY AND PATHOBIOLOGY

Human papillomavirus (HPV), which is the most common sexually transmitted infection, is a cause of anal dysplasia and cancer. The approximately 40 HPV subtypes that can cause anogenital infections are divided into low-risk types (e.g., types 6 and 11) that cause anal warts (condyloma acuminata) and high-risk types (e.g., types 16, 18, and 33) that can cause anal dysplasia and cancer. HPV infection is associated with cervical, vulvar, vaginal, and penile cancers, and some patients have HPV-related dysplasia or cancer in multiple sites. Over 90% of anal cancers are attributable to HPV infection.

The incidence of anal cancer has been steadily increasing, from 0.6 per 100,000 in 1973 to 1.0 per 100,000 in 2001 and 2.0 per 100,000 in 2018. In the United States alone, an estimated 9090 individuals develop anal cancer annually, and approximately 1400 will die from it.[12] These epidemiologic trends have been attributed to a particularly rapid increase in anal cancers among men who have sex with men, especially men infected with HIV. Anal HPV, including the high-risk serotypes, is highly prevalent in at-risk populations (sex workers, intravenous drug users, transplant recipients, men who have sex with men, and HIV-positive men and women). Furthermore, anal dysplasia is common in at-risk populations, as evidenced by the 30 to 50% prevalence of high-grade anal dysplasia among HIV-positive men who have sex with men seen in specialty clinics in New York and San Francisco. Other associated risk factors for both dysplasia and anal cancer include a history of other HPV-related genital dysplasia or malignancy (cervical, vaginal, or vulvar), prior sexually acquired diseases, anoreceptive intercourse, multiple sexual partners, and cigarette smoking.

ANAL WARTS

CLINICAL MANIFESTATION AND DIAGNOSIS

Anal warts can occur in the perianal skin and within the anal canal. The lesions are raised, epithelialized (when external), and narrow based. Their spectrum of appearances can range from scattered individual warts to a confluent mass of warts (Fig. 131-7).

TREATMENT

External warts can be treated with topical podophyllin or imiquimod, but extensive warts usually require surgical excision or fulguration. Untreated warts can rarely progress to form Bushke-Löwenstein tumors—giant, locally invasive condyloma acuminata that frequently contain in situ or invasive cancer. Anal warts, especially in high-risk patients, have a high risk of recurrence, can progress to dysplasia and anal cancer,[13] and often require multiple local treatments and ongoing surveillance to prevent cancer.

FIGURE 131-7. Anal condyloma. These can occur as individual warts or as a confluent mass.

ANAL CANCER

Anal cancer is almost always a manifestation of HPV infection (Chapter 344), especially HPV 16 and 18.[14] Other significant but less common anal cancers include adenocarcinoma, melanoma, and Paget disease.

Anal cancer is a common problem in the HIV-positive population, especially in men who have sex with men. In the United States, anal cancer is nearly 20 times more common in HIV-positive individuals than in the uninfected population. However, the incidence has been declining by 7% per year since 2008, presumably because of more effective antiretroviral therapy. Other independent risk factors include low nadir CD4 counts, alcohol use, and smoking.

CLINICAL MANIFESTATIONS AND DIAGNOSIS

The most common symptoms of anal cancer are bleeding, pain, and a palpable mass. The cancer may be seen externally as an ulcerated mass or may be palpated within the anal canal. Anal dysplastic lesions may appear as anal warts or as flat, pigmented lesions, or they may be invisible to the naked eye. They are best visualized using anal microscopy after topical application of 3 to 5% acetic acid (see later). Biopsy is necessary to make the diagnosis.[15]

Thorough palpation of the inguinal lymph nodes is important to detect the presence of any clinically relevant adenopathy, but proper staging for anal canal malignancies requires a chest, abdominal, and pelvic CT scan. Pelvic MRI is useful to assess the size and depth of the lesion as well as the presence and location of any involved regional lymph nodes.

The great majority of anal cancers are variants of squamous cell carcinoma. The terms *anal dysplasia, anal intraepithelial neoplasia*, and *squamous intraepithelial lesion* differ slightly but have often been used interchangeably. Squamous intraepithelial lesions are divided into low-grade (LSIL) and high-grade (HSIL) groups; the former may be transient, but the latter are generally considered to be premalignant even though they may clear spontaneously in about 20% of patients, especially patients below age 45 years without persistent HPV16.[16] Anal intraepithelial neoplasia (AIN), an older term that is being supplanted by the squamous intraepithelial terminology, is divided into grades 1, 2, and 3, with grades 2 and 3 being classified as high-grade lesions. Squamous cell carcinoma in situ corresponds to high-grade squamous intraepithelial lesion and grade 3 anal intraepithelial neoplasia.

Squamous cell carcinoma of the anus is divided into two groups based on tumor location: cancers of the anal margin (extending from the anal orifice for a distance up to 5 cm) and cancers of the anal canal. Tumors visible externally but extending into the anal canal are considered anal canal lesions.

TREATMENT

Management of the patient with anal dysplasia is controversial. Many authorities advocate a screening and treatment approach based on that used for cervical cancer (Chapter 184), which is another HPV-associated disease. High-risk individuals are screened with anal Papanicolaou smears, and high-definition anal microscopy (analogous to colposcopy of the cervix) is performed when abnormal cytology is detected. Using this technique, dysplastic lesions can be identified and focally ablated[A6] or treated with topical imiquimod or 5-fluorouracil. Reported complete response rates vary significantly (≈30 to 80%), and side effects (pain, irritation, and ulceration) may require withdrawal of therapy. More extensive dysplasia requires microscopy-directed targeted ablation in the operating room.

Chemoradiotherapy is standard first-line treatment for squamous cell cancer of the anal canal. Current radiation protocols most frequently use 45-Gy external beam radiation therapy in 25 fractions, with a boost to the primary tumor and involved inguinal nodes to a total dose of 54 to 59 Gy. Standard chemotherapy utilizes 5-fluorouracil (1000 mg/m^2 per 24 hours, continuous infusion for 96 hours, starting on days 1 and 29) in combination with mitomycin C (most commonly 10 mg/m^2 intravenous bolus on days 1 and 29). Abdominoperineal resection with permanent colostomy is reserved for tumors that fail to respond to chemoradiation and those that recur. Similarly, groin dissection is performed only when involved inguinal nodes fail chemoradiation.

Early squamous cell cancers of the anal margin can be locally excised if a satisfactory margin can be obtained without injuring the anal sphincter and if there is no evidence of nodal spread. More advanced anal margin tumors are treated with chemoradiotherapy as described for anal canal tumors. Combined chemoradiation therapy is the primary treatment for most squamous cell carcinomas of the anal canal.

PREVENTION

In addition to its proven efficacy in the prevention of cervical neoplasia in women, HPV vaccination appears to be effective in preventing external genital lesions and intraepithelial neoplasm in HIV-uninfected men. The use of an HPV vaccine may reduce anal intraepithelial neoplasm in men who have sex with men, but it does not appear to benefit HIV-infected men.[A7]

Routine HPV vaccination is recommended at age 11 to 12 years, but it can be administered starting at age 9 years in both males and females (Chapter 15).[17] A catch-up vaccination is recommended in previously unvaccinated females between ages 13 and 26 years and in males between ages 13 and 21 years and in individuals who did not complete the vaccine series. For males 22 to 26 years, catch-up HPV vaccination is recommended in men who have sex with men and in immunocompromised men (including HIV-infected males).

OTHER SEXUALLY TRANSMITTED ANORECTAL DISEASES

A number of sexually transmitted diseases (Chapter 264) of the anorectum occur most frequently in individuals who practice anoreceptive intercourse. Common causative agents include *Treponema pallidum* (Chapter 295), *Neisseria gonorrhoeae* (Chapter 275), *Chlamydia trachomatis* (Chapter 294), herpes simplex (Chapter 345), and HIV (Chapter 353). Other sexually transmitted pathogens are *Shigella* (Chapter 285), *Campylobacter jejuni* (Chapter 279), *Haemophilus ducreyi* (Chapter 276), *Calymmatobacterium granulomatis* (Chapter 292), *Entamoeba histolytica* (Chapter 323), *Giardia lamblia* (Chapter 322), and *Isospora belli* (Chapter 324).

The widely variable presentations range from asymptomatic to anal pain, pruritus, discharge, fever, cramps, and bloody diarrhea. Clinical suspicion followed by appropriate and specific testing is necessary to make the correct diagnosis, and clinicians should consider the possibility of simultaneous infections. Treatment addresses the specific infection.

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132 APPROACH TO THE PATIENT WITH LIVER DISEASE

PAUL MARTIN

The liver serves multiple key functions, including metabolism of the products of ingested food, production of amino acids to form proteins, detoxification of ingested drugs, conversion of nitrogenous substances from the gut into urea, formation of clotting factors, metabolism of bilirubin, processing of lipids absorbed from the intestine, and excretion of its products as bile. The liver also stores glycogen, which is a source of glucose, and helps contain infections by removing bacteria from the blood stream. These diverse functions reflect the activities of hepatocytes, bile duct cells called cholangiocytes, Kupffer cells, endothelial cells, and portal fibroblasts.

The liver has a dual blood supply: 70% is delivered by the portal vein, which drains the intestine, and the remainder is delivered by the hepatic artery. After arrival in the liver, nutrient-rich portal blood passes along the hepatic sinusoids in close contact with lining hepatocytes before draining into the hepatic vein. The hepatocytes detoxify, metabolize, and synthesize the products of digestion. Bilirubin, which is produced by breakdown of red cells and other hemoproteins by reticuloendothelial cells predominantly in the liver and spleen, is transported to the hepatocytes, bound to albumin, and solubilized by them for biliary excretion.

Liver disease causes loss of hepatocellular capacity, with diminished detoxification, excretory, and synthetic functions. Hepatocyte dysfunction results in impaired production of clotting factors, albumin, and other proteins, as well as reduced endogenous formation of lipids. Hepatocyte injury from a variety of causes, including viruses, alcohol, autoimmune disorders, and drug hepatotoxicity, is accompanied by leakage of cellular enzymes into the systemic circulation (Chapter 133). Coagulopathy, decreased serum albumin, and hyperbilirubinemia are observed with more profound hepatocellular injury. Portal hypertension occurs because of disruption of the low-pressure intrahepatic blood flow from the portal to the systemic venous circulation owing to hepatic fibrosis. Consequences of portal hypertension include accumulation of abdominal ascites and the development of portal-systemic venous collaterals with portal-systemic shunting, with formation of varices and development of hepatic encephalopathy. Vascular disorders, including portal vein thrombosis, can result in portal hypertension in the absence of parenchymal liver disease.

The diversity of the liver's functions, its complicated blood supply, and its intimate relationship with the biliary tree contribute to the divergent manifestations of liver disease. The initial complaint often reflects whether the cause is diffuse, such as acute viral hepatitis with widespread hepatocyte injury that manifests as malaise or fatigue, or whether the cause is discrete, such as when biliary obstruction from a gallstone in the common bile duct manifests as severe abdominal pain. Patients may present with multiple complaints, such as nausea and anorexia owing to hepatocellular disease accompanied by right upper quadrant discomfort due to stretching of the hepatic capsule by parenchymal cell edema and inflammation. Patients with more advanced liver disease, such as decompensated cirrhosis (Chapter 139), may have substantial hepatocellular dysfunction with jaundice and coagulopathy in addition to portal hypertension with ascites and bleeding esophageal varices. Many patients who present with hepatic symptoms or signs may have extrahepatic disease; for example, a tender, enlarged liver may be caused by a systemic disorder, such as heart failure with hepatic congestion, rather than a primary hepatic disorder. In patients with cirrhosis, the initial presentation of previously unrecognized liver disease may be a major complication such as variceal hemorrhage, which in turn can precipitate hepatic encephalopathy and other features of frank hepatic decompensation.

HISTORY

Patients with liver disorders come to medical attention for a variety of reasons,[1] ranging from the incidental discovery of abnormal liver chemistries[2] to decompensated cirrhosis. Many complaints related to liver disease, such as fatigue, are nonspecific; unless liver disease is considered in the differential diagnosis, recognition of the hepatic origin of these complaints may be delayed.

In clinical practice, a frequent manifestation of asymptomatic liver disease is discovery of abnormal liver biochemistries during a life insurance application, annual physical examination, or attempt to donate blood. It is important to inquire about occasions when liver biochemistries may have been obtained to determine whether hepatic dysfunction is long-standing or more recent. In a patient with hepatic dysfunction, inquiry should be made about the presence of malaise, anorexia, fatigue, and weight change. Jaundice (Chapter 133) is a dramatic manifestation of possible liver disease. A patient may first notice lighter-colored stools or dark urine rather than scleral icterus. The absence of these latter changes suggests that unconjugated hyperbilirubinemia is due to hemolysis rather than intrinsic liver disease. Not infrequently, a patient may be unaware of jaundice until it is noted by others.

Abdominal pain (Chapter 118) related to liver disease can have a variety of explanations. Symptomatic gallstones (Chapter 141) can present with the abrupt onset of severe epigastric or right upper quadrant discomfort, often after a large meal and frequently associated with nausea and vomiting. The pain is often steady rather than colicky and can radiate widely, including to the chest and back. A patient may not be able to achieve a position that lessens the pain, which may last several hours. More persistent pain, particularly if associated with weight loss and jaundice, raises concern about malignant bile duct obstruction. Pain is also common in parenchymal liver disease in the absence of biliary tract disease. Many patients with chronic hepatocellular disorders, such as chronic hepatitis C (Chapter 135) or nonalcoholic fatty liver disease (NAFLD) (Chapter 138), complain of vague right upper quadrant discomfort that has no particular relieving or aggravating factors. Abdominal pain, which can be severe, is also frequent in acute viral hepatitis (Chapter 134), as well as with the hepatic congestion that results from back pressure in heart failure or hepatic vein occlusion, as in Budd-Chiari syndrome (Chapter 129).

Fatigue, anorexia, and malaise can be present in both acute and chronic liver disease. In acute liver disorders such as acute viral hepatitis (Chapter 134), drug-induced liver disease (Chapter 136), or an acute manifestation of autoimmune hepatitis (Chapter 135), patients may report profound fatigue, nausea, and malaise with decreased appetite and substantial associated weight loss. Distaste for cigarettes is said to be characteristic of acute viral hepatitis. Fatigue is also prominent in chronic liver disease such as chronic hepatitis C (Chapter 135). Pruritus is a prominent feature of cholestatic disorders, such as primary biliary cirrhosis, sclerosing cholangitis, or cholestatic drug reactions, particularly when patients are frankly icteric; however, pruritus also occurs in chronic parenchymal liver disease, most notably chronic hepatitis C, and in acute viral hepatitis. Easy bruising in patients with liver disease reflects coagulopathy and/or thrombocytopenia.

Fever in a patient with hepatic dysfunction is experienced in the prodrome of acute hepatitis A, as well as in alcoholic hepatitis and drug-induced liver disease. In a patient with suspected biliary obstruction, fever suggests complicating bacterial cholangitis or acute cholecystitis. Ascites is most frequently a manifestation of cirrhosis and portal hypertension in a patient with liver disease. Patients note increasing abdominal girth, which may be preceded by ankle edema. Weight gain owing to fluid retention may be masked by concomitant loss of muscle mass. The onset of ascites in the absence of a history of liver disease suggests a vascular event, such as hepatic vein occlusion (Chapter 129), or a nonhepatic cause of ascites, such as nephrotic syndrome or heart failure. Accumulation of ascites in a patient with liver disease may be subtle, with a slowly increasing waist circumference, or it may be more rapid, such as in a cirrhotic patient who receives fluid resuscitation after gastrointestinal bleeding. Although ascites in a patient with liver disease implies the presence of cirrhosis, ascites also can complicate severe acute liver disease, including alcoholic hepatitis and viral hepatitis, in which it suggests a poor prognosis.

Hepatic encephalopathy (Chapter 139), which is a neuropsychiatric disorder in patients with liver disease, can range from subtle cognitive impairment to deep coma.[3] Early symptoms include a disturbed sleep pattern with nocturnal insomnia and daytime somnolence. More advanced encephalopathy can result in impairment of memory, confusion, and difficulty completing routine tasks. However, new-onset confusion or coma in a patient with liver disease should not be presumed to reflect hepatic encephalopathy unless other explanations, such as sedative overdose or subdural hematoma, have been excluded. Important precipitants of hepatic encephalopathy in a cirrhotic patient include gastrointestinal bleeding, bacterial infection (e.g., spontaneous bacterial peritonitis), electrolyte imbalance, and renal insufficiency, all of which need to be excluded during the initial clinical evaluation. In a patient with acute liver failure, coma as a consequence of cerebral edema may be impossible to distinguish from advanced hepatic encephalopathy unless the increased intracranial pressure results in papilledema.

Gastrointestinal hemorrhage resulting from bleeding varices is usually profuse and often abrupt in onset. It typically presents with hematemesis or

ABSTRACT

The liver has a variety of important roles, including metabolism of food products from the gut, synthesis of proteins and clotting factors, detoxification of drugs, processing of lipids and bilirubin, and formation of bile. It also stores glycogen for conversion into glucose and helps contain infection by removing bacteria from the blood stream. Liver disease can result from a diffuse insult such as acute viral hepatitis or a more discrete process such as obstruction of the common bile duct by a gallstone. The pattern of the biochemical abnormality can provide important clues to the possible cause. Physical examination can elicit signs of chronic liver disease and portal hypertension, as well as more acute presentations such as a tender gallbladder in acute cholecystitis. An asymptomatic liver mass is a common clinical scenario, and its nature can often be determined by imaging. A number of hereditary disorders have prominent hepatic features, including Wilson disease, hemochromatosis, and alpha-1-antitrypsin deficiency.

KEYWORDS

liver function
hepatocellular
jaundice
ascites
liver mass

melena (Chapter 121), and frequently coexisting postural hypotension or presyncope indicates major blood loss. The increased protein load in the gut can precipitate hepatic encephalopathy. Nonvariceal causes of gastrointestinal bleeding in a patient with liver disease include portal gastropathy (Chapter 121).

RISK FACTORS FOR LIVER DISEASE

An important aspect of the history is identification of possible risk factors for liver disease. The history should include directed questioning about alcohol consumption, including frequency and pattern (Chapter 364). The age of initial alcohol use and whether consumption has increased with age should be ascertained. Family members also should be asked about their perception of the patient's alcohol use and whether it has resulted in difficulties in personal relationships or work performance. Other clues to alcohol abuse are a history of convictions for driving under the influence of alcohol, motor vehicle accidents, and physical symptoms of alcohol dependence (Chapter 364). More circumspect questioning may be required to elicit a history of recreational drug use. Not infrequently, a patient with suspected viral hepatitis admits to smoking marijuana or snorting cocaine but does not acknowledge intravenous drug use. With the increasing frequency of nonalcoholic fatty liver disease as a cause of hepatic dysfunction (Chapter 138), comorbid conditions such as diabetes mellitus, hyperlipidemia, sleep apnea, and weight gain should be noted.

Medication use, whether prescription or over-the-counter, must be assessed because drug-induced liver disease is an important cause of apparently cryptogenic hepatic dysfunction and is not limited to therapeutic drugs (Chapter 136).[1] Increasingly, herbal and "natural" products (Chapter 30) are ingested for a variety of maladies, and patients may fail to disclose their use because they do not perceive these agents to have side effects or may sense that the physician does not endorse their use. As with alcohol, it is important to quantify the amount of medication ingested and over what period. The social history should include details about recent travel and contact with individuals with viral hepatitis through intimate, household, or occupational contact. It is also important to ask about vigorous physical activity that can result in elevated aminotransferase levels of nonhepatic origin.

ASSESSING DURATION OF LIVER DISEASE

The differential diagnosis in a patient with liver disease is determined to a large extent by the presentation, such as jaundice or ascites. In many patients, however, the timing of more subtle findings such as elevated aminotransferases is difficult to determine. Prior blood test results should be retrieved to determine whether hepatic dysfunction is long-standing or more recent. Hepatic dysfunction of less than 6 months' duration is regarded as acute and is frequently self-limited, whereas abnormalities that persist for more than 6 months are unlikely to resolve spontaneously. If the patient has had a cholecystectomy, it is important to determine the indication. Incidental gallstones are sometimes assumed to be the cause of abnormal liver chemistries in a patient with parenchymal liver disease and can lead to an unnecessary cholecystectomy. Thrombocytopenia owing to portal hypertension in a patient with unrecognized cirrhosis may have been investigated in the past without a firm conclusion being reached.

REVIEW OF OTHER ORGAN SYSTEMS

While focusing on liver-related symptoms, it is important not to overlook other diagnostic clues, associated disorders, and complications. Sicca symptoms, including dry eyes and mouth, are common in primary biliary cholangitis (Chapter 141); florid features of scleroderma and CREST syndrome (Chapter 246) are other associations. Dyspnea in a patient with hepatic dysfunction may reflect cardiac failure with hepatic congestion (Chapter 45). Other explanations include hepatopulmonary syndrome (Chapter 139), with the characteristic complaint of platypnea-dyspnea (often with chest tightness) that is worse in the upright position owing to aggravation of the ventilation-perfusion mismatch because of intrapulmonary shunting. A hydrothorax in decompensated cirrhosis can cause dyspnea, as can emphysema in patients with liver disease caused by α_1-antitrypsin deficiency. A history of premature menopause is common in middle-aged women with cirrhosis, as is decreased libido and sexual potency in cirrhotic men. Arthralgias are often reported in viral hepatitis, and hemochromatosis (Chapter 196) may manifest with involvement of the proximal interphalangeal joints or chondrocalcinosis of the knees; increased skin pigmentation and diabetes mellitus are other features of this disorder. Accelerated osteopenia occurs in many liver diseases, including primary cirrhosis, primary sclerosing cholangitis, and alcoholic cirrhosis; osteopenia may be aggravated by corticosteroid use in autoimmune hepatitis. Alcoholic peripheral neuropathy (Chapter 384) can manifest with pain and paresthesias. Tremor and inattentiveness in a younger patient with hepatic dysfunction suggest Wilson disease (Chapter 195). Diarrhea and rectal bleeding in a patient with cholestatic liver disease suggest associated inflammatory bowel disease (Chapter 127).

FAMILY HISTORY

The family history should include an inquiry not only about relatives with liver disease but also associated extrahepatic conditions. Hereditary hepatic conditions (see later), such as Wilson disease and hemochromatosis, may occur in several members of a sibship. In α_1-antitrypsin deficiency, some family members may experience predominantly emphysema rather than cirrhosis. Similarly, renal failure in a family member of a patient with hepatic cysts suggests adult polycystic disease (Chapter 112). A family history of inflammatory bowel disease may be a clue to primary sclerosing cholangitis in a patient with cholestatic liver chemistries. The history in patients with suspected alcoholic liver disease may reveal other family members with alcoholism.

PHYSICAL EXAMINATION

GENERAL CONDITION

In a patient with suspected liver disease, it is crucial to resist the temptation to palpate the abdomen immediately, thus potentially ignoring other important diagnostic clues. Apart from seeking icterus, the initial observation should note whether muscle wasting, cutaneous stigmata of liver disease, abdominal distention, and peripheral edema are present. The vital signs may reflect the hyperdynamic circulation characteristic of cirrhosis, with a resting tachycardia, wide pulse pressure, and low blood pressure resulting from peripheral vasodilation. Fetor hepaticus, which is described as a musty smell, may be detected when a cirrhotic patient exhales and must be distinguished from more frequent halitosis caused by poor dental hygiene.

MUCOCUTANEOUS FINDINGS

Icterus (Fig. 132-1) is best confirmed by examination of the sclera or, if necessary, under the tongue, where elastin tissue retains bilirubin. Grayish skin discoloration in hemochromatosis may be most evident in the skin folds in the groin or axilla. Acanthosis nigricans can be observed in nonalcoholic fatty liver disease (Chapter 138). A Kayser-Fleischer ring (see Fig. 195-2), caused by the deposition of copper in the Descemet membrane, is a brownish circle around the periphery of the iris and may require slit lamp examination to detect; it always should be sought in a patient with suspected Wilson disease (Chapter 195). Poor dentition is characteristic in alcoholic or drug-abusing individuals, and excessive dental caries may result from decreased saliva production in sicca syndrome. Parotid gland swelling is occasionally observed in alcoholic patients. Central cyanosis and clubbing are found in the hepatopulmonary syndrome. Temporal muscle wasting and "paper money" facial skin, owing to atrophy with telangiectasia, are signs of advanced liver disease. Xanthelasma from lipid deposits may be observed on the eyelids and skin around the orbits in patients with cholestatic liver disease. Spider nevi on the face and thorax are not pathognomonic of liver disease, especially in women, but they are suggestive if more than a few are present. Palmar erythema (Fig. 132-2) may be normal in women but suggests liver disease in men. Dupuytren contracture (see Fig. 138-1), the retraction of the palmar fascia with subsequent contracture of the palms and fingers, can be a sign of alcoholic liver disease, although it

FIGURE 132-1. Scleral icterus.

FIGURE 132-2. Palmar erythema.

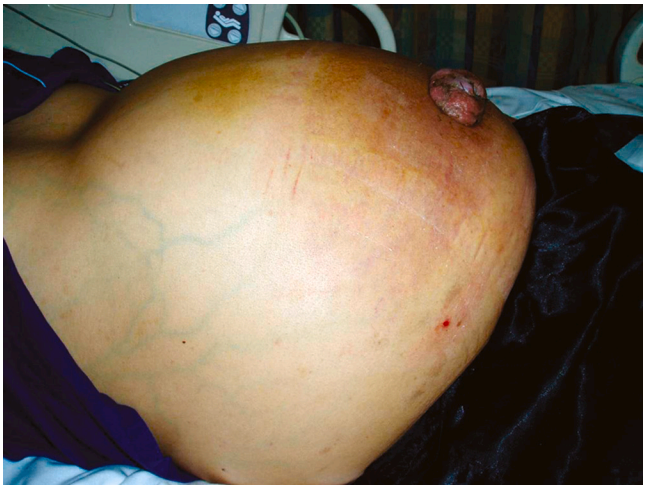

FIGURE 132-4. Ascites.

FIGURE 132-3. Caput medusae. Photograph shows caput medusae accentuated by a large amount of ascites in a patient being prepared for liver transplantation. An extensive plexus of veins is seen emanating from the umbilical region and radiating across the anterior abdominal wall. Note the large vein coursing inferiorly along the right flank (*arrows*). This is the superficial epigastric vein, which drains into the external iliac vein. (From Henseler KP, Pozniak MA, Le FT, et al. Three-dimensional CT angiography of spontaneous portosystemic shunts. *Radiographics*. 2001;21:691-704.)

is also described in patients with epilepsy or diabetes mellitus, as well as in individuals who have work-related contractures. Petechiae and ecchymoses reflect impaired production of clotting factors and hypersplenism in advanced liver disease. Patches of white discoloration on the nails may be present in advanced liver disease. Scratch marks from pruritus may be observed on the trunk and extremities of patients with cholestatic liver disease. Sparing of the center of the back can lead to a less pigmented butterfly-shaped area because patients cannot reach that area with their fingernails.

EXAMINATION OF THE ABDOMEN

Abdominal distention with ascites and dilation of collateral veins owing to portal hypertension represent florid signs of advanced liver disease. Caput medusae (Fig. 132-3) in the periumbilical area implies recanalization of the umbilical vein with portal hypertension.

Abdominal percussion may confirm the presence of ascites (Fig. 132-4). Shifting dullness results from movement of ascites to the most dependent portion of the abdomen. The subject should be examined in the supine position, with percussion of the abdomen from the midline toward the right or left flank. A change from a tympanic sound to a dull sound signifies a change from air to fluid, and the location of that change identifies the surface of the fluid pool. Next, the examiner should percuss below the point at which dullness is elicited and ask the subject to turn toward the examiner. With the subject on his or her side, the examiner percusses again at the same point where tympany converted to dullness. If that spot is now tympanic, shifting dullness has been detected as a result of movement of the air-fluid boundary; this finding supports the presence of ascites. This maneuver should be performed sequentially on each side for confirmation. A fluid wave can be felt by placing the medial border of one hand on the abdomen and tapping the right or left lateral abdominal walls; the resulting wave is felt by the first hand. Scrotal edema and abdominal wall hernias are often present in patients with long-standing ascites. Abdominal tenderness in a patient with ascites suggests peritonitis (e.g., spontaneous bacterial peritonitis or the result of a perforated viscus). However, it is important to note that abdominal tenderness is frequently absent in spontaneous bacterial peritonitis.

The liver is dull to percussion. Percussion of the right upper quadrant can determine the liver span, normally 6 to 12 cm in the midclavicular line. The liver span may be diminished in a patient with cirrhosis, whereas hepatomegaly (Fig. 132-5) is detected in hepatic congestion resulting from heart failure, nonalcoholic fatty liver disease, and cholestatic forms of cirrhosis. The liver is best examined with the patient in the supine position, arms parallel to the side of the body and knees bent to relax the abdominal muscles. Palpation should begin in the right lower quadrant of the abdomen and move upward toward the rib cage so that the liver edge is felt on the way up. A normal liver edge is smooth and sometimes slightly tender when palpated. In general, a liver edge that is felt up to 2 cm below the right costal margin is considered normal, but a normal-sized liver can be displaced downward by other abnormalities, such as emphysema. In thin subjects, the liver edge may be felt on deep inspiration, even if it is normal in size.

The liver can feel hard and irregular, as in cirrhosis, or slightly tender, enlarged, and smooth, as in acute viral hepatitis, alcoholic hepatitis, or hepatic congestion, as occurs with right heart failure. The liver can extend across the midline, and the left lobe can be felt in the epigastrium. When the location of the edge of the liver is unclear, the scratch test may be more accurate than palpation.[A1] The bell of the stethoscope is placed on the right upper quadrant over the rib cage while scratching the surface of the abdominal wall from the mid-abdomen toward the liver; the sound of the scratch is amplified in an area under which the liver lies. In the presence of ascites, the liver edge may be detected by exerting quick pressure with the fingertips below the rib cage.

A palpable gallbladder suggests obstruction of the biliary system, whereas tenderness elicited by palpation during inspiration (the Murphy sign) suggests acute cholecystitis. Marked hepatic tenderness with hepatomegaly is observed in patients with a hepatic abscess (Chapter 137).

Splenomegaly (Chapter 154) is suggested by dullness to percussion between the 9th and 11th ribs in the left midaxillary line. A palpable spleen tip implies portal hypertension in a patient with chronic liver disease, although an enlarged spleen also can be detected in acute viral hepatitis and infiltrative disorders that involve both the liver and the spleen (see Table 154-5). Rectal examination is obligatory if gastrointestinal bleeding is suspected because of melena, anemia, or unexplained hepatic encephalopathy.

COMPLETE PHYSICAL EXAMINATION

The presence of rales and elevation of the jugular venous pressure suggest heart failure or pericardial disease as a cause of hepatic congestion.[5] Loss of secondary sexual characteristics in liver disease is reflected by a loss of axillary and

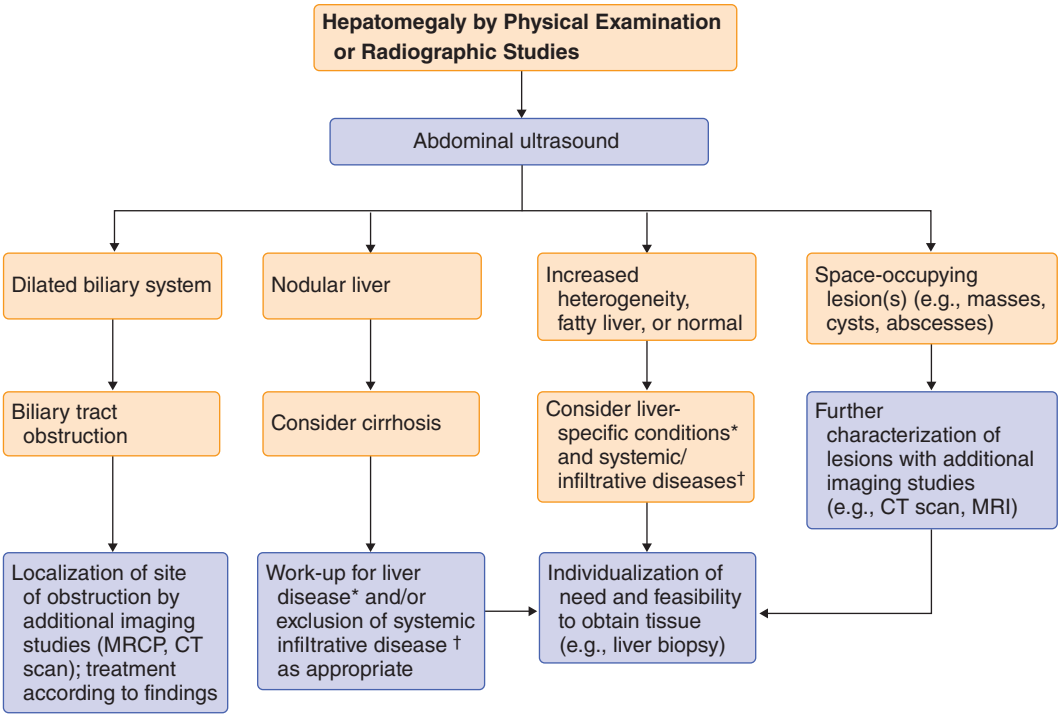

FIGURE 132-5. Diagnostic approach to hepatomegaly. *Conditions to be excluded include viral hepatitis, alcohol- and drug-induced liver disease, steatohepatitis, autoimmune liver diseases, and metabolic disorders, including hemochromatosis, Wilson disease, and α_1-antitrypsin deficiency. †Systemic and infiltrative diseases include amyloidosis, lymphoma, sarcoidosis, and infectious processes such as disseminated tuberculosis and fungemia. CT = computed tomography; MRCP = magnetic resonance cholangiopancreatography; MRI = magnetic resonance imaging.

TABLE 132-1 APPROACH TO COMMON HEPATIC COMPLAINTS

PRESENTATION	COMMON SYMPTOMS	COMMON PHYSICAL SIGNS	DIAGNOSTIC STUDIES	COMMON DIAGNOSES
Ascites	Abdominal distention and pain, ankle edema	Flank dullness Shifting dullness Fluid wave	Ultrasound with Doppler Diagnostic paracentesis Urinalysis	Cirrhosis Budd-Chiari syndrome Heart failure Nephrotic syndrome
Hepatic encephalopathy	Sleep disorientation, confusion, coma	Asterixis Altered mentation Fetor hepaticus	Serum ammonia Blood cultures Stool Hemoccult Serum creatinine and electrolytes	Decompensated cirrhosis Acute liver failure Other metabolic encephalopathies (renal, respiratory)
Hepatic mass	None or abdominal pain	Hepatic bruit or rub	α-Fetoprotein Ultrasound CT scan MRI Biopsy	Benign lesions: Hemangioma, adenoma, focal nodular hyperplasia Malignant lesions: Hepatocellular carcinoma, cholangiocarcinoma, metastases
Abdominal pain	Nausea, vomiting, fever	Right upper quadrant tenderness Palpable gallbladder Murphy sign	Ultrasound HIDA scan Paracentesis for ascites if present	Biliary colic Acute cholecystitis Hepatic congestion Hepatic metastases

CT = computed tomography; HIDA = hepatobiliary iminodiacetic acid; MRI = magnetic resonance imaging.

pubic hair, as well as feminization of body habitus in a male patient. Testicular atrophy also may be present. Peripheral edema is common in decompensated cirrhosis and may occur before ascites is obvious.

Neuropsychiatric alterations can include subtle changes in personality or more overt hepatic encephalopathy. Constructional apraxia (e.g., inability to draw a five-pointed star or to write legibly) in a fully conscious patient is a typical finding in hepatic encephalopathy. Asterixis, which is characterized by a series of extensor and flexor wrist movements, can be elicited by having the patient extend the arms, with dorsiflexion of the wrists, while separating the fingers for at least 15 seconds. Tremors (Chapter 379) are nonspecific but are also common in advanced cirrhosis.

DIAGNOSTIC STUDIES (TABLE 132-1)

LABORATORY STUDIES

The initial evaluation of liver disease involves a battery of blood tests, which can assess hepatic necroinflammation (serum aminotransferases), cholestatic biliary tract dysfunction (alkaline phosphatase, γ-glutamyl transpeptidase), excretory function (bilirubin), and synthetic function (coagulation factors, albumin) (Chapter 133). In hepatocellular dysfunction caused by viral hepatitis (Chapter 134), aminotransferase levels are elevated, with the serum alanine aminotransferase (ALT) level higher than the aspartate aminotransferase (AST) level. In alcoholic hepatitis (Chapter 138), AST elevation exceeds that of ALT. In patients with biliary obstruction or cholestatic liver diseases (Chapter 141), such as primary biliary cirrhosis or a cholestatic drug reaction, bilirubin and generally alkaline phosphatase levels are elevated. Impairment of synthetic function leads to a decreased serum albumin level over days to weeks. The prothrombin time, expressed as the international normalized ratio (INR), is a more sensitive test of hepatic synthetic function and becomes prolonged within several hours after a major hepatic insult. Portal hypertension owing to advanced hepatic fibrosis or cirrhosis results in a decreased platelet count resulting from hypersplenism. Although these general patterns of liver dysfunction are helpful in the initial evaluation of liver disease, they are nonspecific. For

example, a patient with a predominantly hepatocellular process and elevated aminotransferase levels may also have elevated bilirubin and alkaline phosphatase levels as well as a low serum albumin level if liver injury is severe. Nevertheless, initial blood tests should identify the predominant pattern of abnormality and direct further diagnostic evaluation with serologic studies and abdominal imaging, which should be carefully selected and focused based upon the initial clinical evaluation.

ABDOMINAL IMAGING

Plain abdominal radiographs generally do not have a major role in the evaluation of suspected liver disease. An exception is a patient with severe abdominal pain, in whom it is important to exclude a perforated viscus suggested by free air under the diaphragm.

Ultrasonography should be the initial investigation in patients with obstructive jaundice. It can confirm dilated bile ducts in patients with biliary obstruction and often can identify the cause, such as a pancreatic mass or a gallstone lodged in the common bile duct. Ultrasonography also can determine whether the hepatic parenchyma is diffusely abnormal, such as in acute viral hepatitis; it can identify bright hepatic echo texture in nonalcoholic fatty liver disease or a coarsened echo texture in cirrhosis. In addition to confirming the presence of ascites, ultrasonography can identify other signs of portal hypertension, such as splenomegaly or intra-abdominal varices. A Doppler flow study can evaluate blood flow through the portal and hepatic vessels. An ultrasound study can identify hepatic masses and distinguish a cystic mass from a solid lesion (see later). Computed tomography (CT) and magnetic resonance imaging (MRI) add greater detail to the assessment of the hepatic vasculature, hepatic masses, and hepatic vascular structures. For the evaluation of focal liver lesions, the sensitivities of ultrasonography, contrast, CT, and MRI are similar. MRI can obtain a detailed cholangiogram, thereby avoiding a more invasive endoscopic retrograde cholangiopancreatography in many patients with suspected bile duct obstruction or disease (Chapters 119 and 120).

Transient elastography assesses hepatic fibrosis by measuring liver stiffness based on the propagation of shear waves in liver tissue, and it has largely replaced liver biopsy for this purpose.[6] In addition to measuring liver stiffness, transient elastography, often combined with standard ultrasonography, can assess the degree of attenuation by fat and thereby can also estimate hepatic steatosis. Magnetic resonance–based elastography may be preferred in the presence of ascites or obesity.[7] A low stiffness score and a normal platelet count can identify patients who are at low risk for variceal bleeding.[8]

MEASUREMENT OF TRANSJUGULAR PRESSURE

Transjugular pressure measurements are indicated in patients who have atypical presentations of portal hypertension (e.g., when it is unclear whether liver disease is the cause) or occasionally to assess whether portal hypertension is severe enough to warrant prophylaxis against variceal hemorrhage (Chapter 139). A catheter is advanced under fluoroscopy into the hepatic vein, and the free hepatic venous pressure is measured. The catheter is then advanced further until it becomes "wedged" in a small hepatic vein venule. A small balloon occludes the venule, and the wedged hepatic vein pressure, which reflects hepatic sinusoidal pressure, is obtained. The portal pressure gradient, which is derived by subtracting the free pressure measurement from the wedged pressure measurement, is normally less than 5 mm Hg. Varices form at a gradient greater than 10 mm Hg, whereas ascites and variceal hemorrhage occur only when the gradient is greater than 12 mm Hg. A transjugular approach also increases the safety of liver biopsy in the presence of ascites, coagulopathy, or thrombocytopenia when standard percutaneous liver biopsy is hazardous.

LIVER BIOPSY

Although liver biopsy had been the definitive test to assess the severity of hepatic inflammation and fibrosis in diffuse hepatocellular disease, its use has diminished in large part due to the availability of transient elastography. Nevertheless, it retains an important role in the diagnosis of autoimmune hepatitis (Chapter 135), drug hepatotoxicity (Chapter 136), and small duct primary sclerosing cholangitis (Chapter 141).[9] However, because of its potential complications, such as intra-abdominal bleeding, biopsy is recommended only when less invasive testing does not yield a definitive diagnosis or prognosis or when additional information,[10] such as quantitative determination of hepatic copper in Wilson disease or hepatic iron in hemochromatosis, is necessary for definitive diagnosis (see later). Liver biopsy under radiographic guidance is also indicated if a hepatic mass cannot be characterized as benign or malignant by noninvasive means.[11]

APPROACH TO NEW-ONSET ASCITES

The three leading causes of ascites in the United States are cirrhosis (85%; Chapter 139), peritoneal malignancy (7%), and heart failure (3%; Chapter 46), with nephrotic syndrome (Chapter 107) and tuberculosis (Chapter 299) accounting for the remainder. Diagnostic paracentesis, which is the appropriate initial test, has a low complication rate, including ascitic fluid leak (in about 5% of patients with cirrhosis) and bleeding or infection (less than 2% of patients). A serum-ascites albumin gradient (defined as serum albumin concentration minus ascitic albumin concentration) level of 1.1 g/dL or greater indicates portal hypertension, with a sensitivity of 97% and specificity of 90%. If the ascitic fluid protein level is less than 2.5 g/dL, cirrhosis is the most likely cause of the portal hypertension. If the ascitic fluid protein level is more than 2.5 g/dL, heart failure is the likely cause of the portal hypertension (see Table 139-3), and the diagnosis can be confirmed by an elevated brain natriuretic protein level (Chapter 45). If the gradient is less than 1.1 g/dL and the ascitic fluid protein is low, malignancy is most likely. Malignant ascites also is usually associated with an ascitic white blood cell count greater than 500/μL. Spontaneous bacterial peritonitis (Chapter 128) is diagnosed based on an ascitic neutrophil count above 250 cells/μL or more if secondary causes of peritonitis can be excluded.

APPROACH TO A HEPATIC MASS

A hepatic mass may be discovered under a number of different circumstances and is often an incidental finding on abdominal imaging performed for another indication. The initial evaluation depends upon whether the mass is cystic or solid (Fig. 132-6).[12]

HEPATIC CYSTS

Most hepatic cysts are benign and incidental. Simple hepatic cysts are typically solitary and asymptomatic, although larger cysts may cause abdominal discomfort. Ultrasonography, which is usually diagnostic, shows an anechoic fluid-filled space, an imperceptible wall, and posterior acoustic enhancement (Fig. 132-7A and B). Worrisome features, including the presence of symptoms or increasing size, require exclusion of a cystadenoma. On ultrasound a cystadenoma is hypoechoic with irregular walls and septations. Hepatic resection is indicated because malignant transformation can occur.

Multiple hepatic cysts may suggest the presence of autosomal dominant adult polycystic disease.[13] Polycystic liver disease can occur in conjunction with polycystic kidney disease (Chapter 112) or without it. Isolated polycystic liver disease is associated with mutations in the *PRCKSCH* gene, which encodes the glucosidase 2 subunit β enzyme, and in Sec63, which is part of a large protein complex involved in protein translocation in the endoplasmic reticulum, but many other genetic mutations have also been described.[14] Adult polycystic liver disease typically is asymptomatic, although some patients note dull right upper quadrant pain, fullness, sense of a mass, and increasing abdominal girth. Rupture of a cyst, hemorrhage into a cyst, infection of a cyst, or torsion of a cyst may cause severe pain. Physical examination may include hepatomegaly, cachexia due to weight loss, and ascites. As cysts increase in number and size with age, they may become palpable. On ultrasound, multiple fluid-filled cysts are present without internal echoes unless bleeding or infection has occurred. Treatment with long-acting somatostatin analogues (e.g., lanreotide 120 mg subcutaneously every 4 weeks) can modestly reduce the volumes of liver cysts.[A2] Interventions indicated for symptoms include aspiration or resection. Polycystic liver disease usually does not result in clinical hepatic impairment, and prognosis depends on the severity of any concurrent polycystic renal disease. In some cases, however, large, symptomatic, or bleeding cysts may raise the consideration of liver transplantation,[15] often with combined kidney transplantation (Chapter 117) for associated renal cysts and kidney failure.

Caroli disease, which is a rare congenital abnormality with cystic dilation of the intrahepatic biliary tree, can be associated with cholangitis and biliary stones.[16] Many patients ultimately develop cholangiocarcinoma (Chapter 141). Magnetic resonance cholangiopancreatography demonstrates intrahepatic dilations with normal ducts in between and a normal common bile duct. Endoscopic treatment is indicated for cholangitis, although resection or liver transplantation may ultimately be required.

SOLID HEPATIC MASS

Most solid hepatic masses are asymptomatic, but some patients may have vague right upper quadrant discomfort. The abrupt onset of more severe pain suggests a complication, such as hemorrhage or rupture. The approach to a solid hepatic mass (Fig. 132-8) is influenced by the presence or absence of underlying chronic liver disease, such as chronic viral hepatitis, as well as

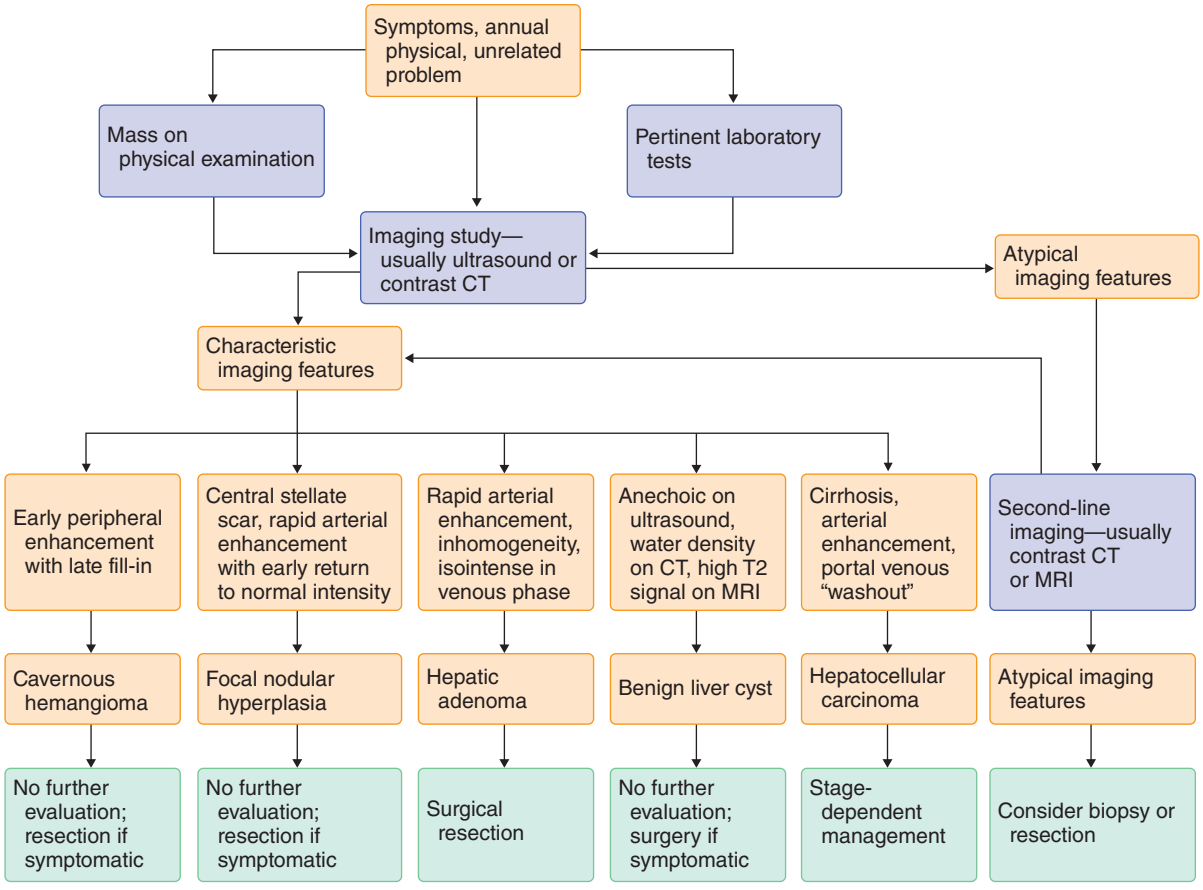

FIGURE 132-6. Approach to evaluating the patient with a mass lesion in the liver. This flowchart shows an algorithm for evaluating and managing common liver mass lesions. CT = computed tomography; MRI = magnetic resonance imaging. (From Roberts LR. Liver and biliary tract tumors. In: Goldman L, Schafer AI, eds. *Goldman's Cecil Medicine*, 24th ed. Philadelphia: Saunders; 2012.)

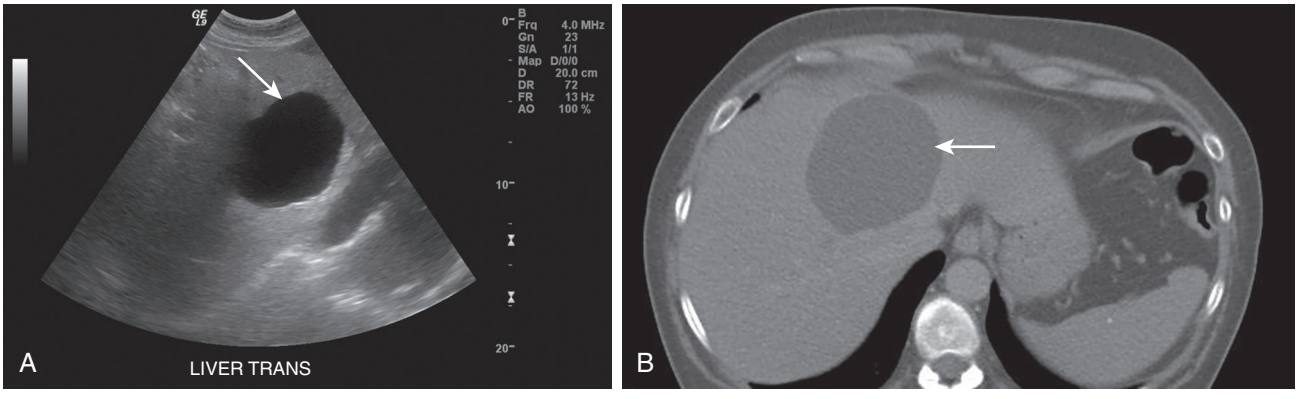

FIGURE 132-7. Simple hepatic cyst. A, Ultrasound demonstrates clear contents and an imperceptible wall (*arrow*). **B,** On a computed tomographic scan, a simple hepatic cyst is characterized by the lack of septation and an imperceptible wall (*arrow*). (Courtesy of Dr. B. Madrazo.)

whether an extrahepatic malignancy with hepatic metastases is a consideration. If chronic liver disease is present, a solid mass must be assumed to represent primary hepatocellular carcinoma (Chapter 181) until proven otherwise. By comparison, a solid lesion in the absence of underlying liver disease is more likely to be benign and incidental. Benign hepatic adenomas are commonly discovered in young to middle-aged women and are not associated with hepatic dysfunction. With modern contrast studies, it is usually possible to make a confident radiologic diagnosis about the nature of a solid hepatic mass. Important examples include the initial peripheral filling and retention of contrast dye by a hemangioma (see Fig. 132-8A, B, and C), the rapid arterial filling of a hepatocellular carcinoma with subsequent "washout" of contrast during the portal venous phase (see Fig. 181-4), or the central scar typical of focal nodular hyperplasia (see Fig. 132-8D). If a benign etiology cannot be adequately determined noninvasively, then biopsy may be necessary.

Hepatic hemangiomas are the most common benign solid hepatic mass. On ultrasound, the lesion is hyperechoic, with a typical hypervascular appearance on contrast-enhanced abdominal CT or MRI. Generally, no intervention is required unless there is a clear association with abdominal symptoms, increasing size, or a complication such as rupture.

Hepatic adenomas (Chapter 181) are benign epithelial hepatic tumors associated with the use of oral contraceptives with a higher estrogen content. On ultrasound, adenomas are hyperechoic, reflective of their fat content, but become anechoic if hemorrhage has occurred. Contrast CT and MRI show arterial enhancement and varying signal intensity reflecting steatosis and hemorrhage, if present. Biopsy may be needed for diagnosis. Potential complications of adenomas, especially if greater than 5 cm, include spontaneous hemorrhage and rupture. Malignant transformation is more common in men and in adenomas with a β-catenin exon 3 mutation. Such patients and patients

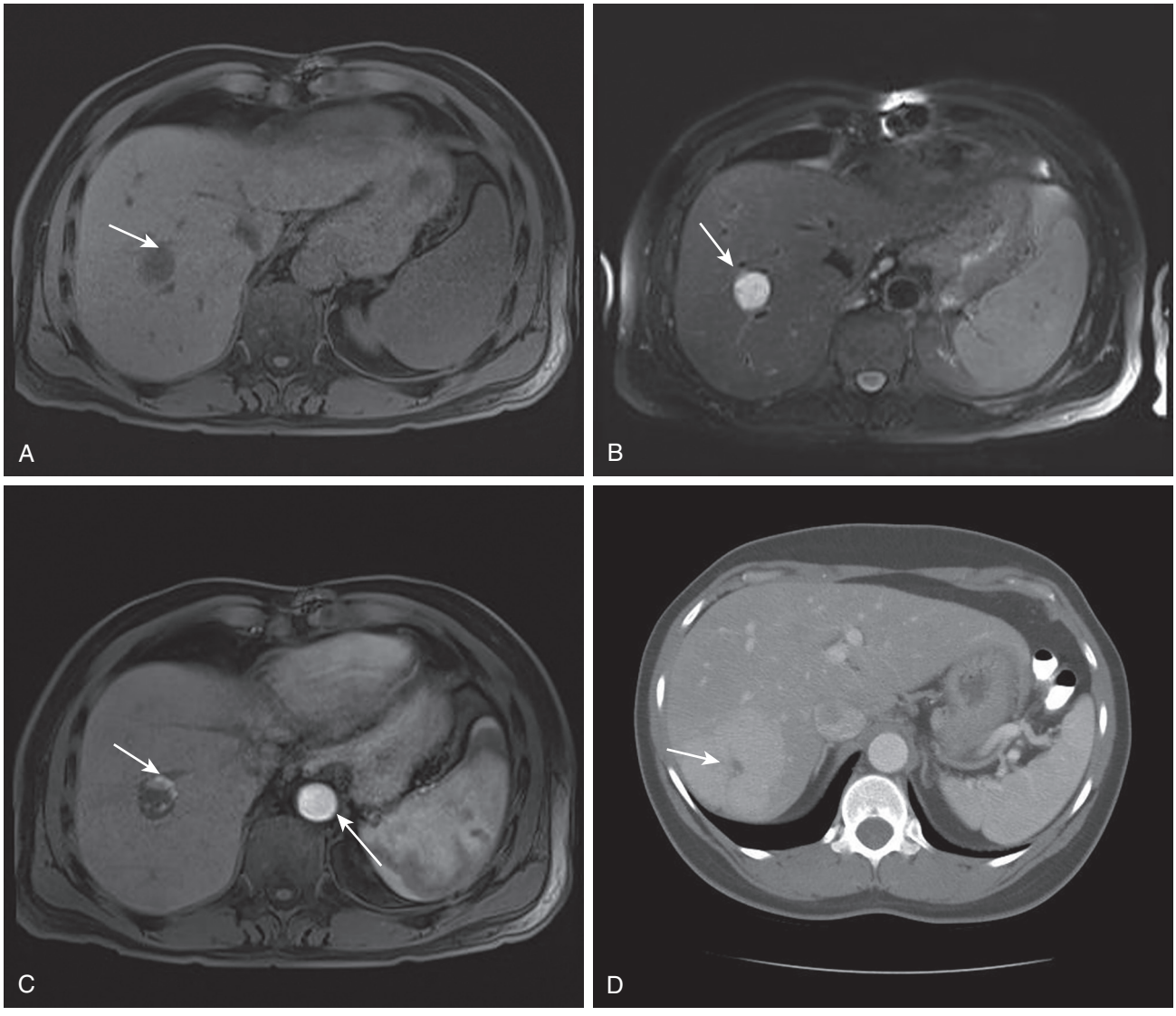

FIGURE 132-8. **Solid hepatic mass. A**, Hemangioma seen as a solid mass (*arrow*) on the T1 phase of a magnetic resonance (MR) imaging scan. **B**, Hemangioma on MR T2 image is characterized by a high signal density (*arrow*). **C**, A hemangioma fills slowly (*shorter arrow*) from the periphery after intravenous contrast is administered (*longer arrow*). **D**, Focal nodular hyperplasia is characterized by a central scar (*arrow*) in the late venous phase of a contrast computed tomographic scan. (Courtesy of Dr. B. Madrazo.)

with adenomas greater than 5 cm should undergo prophylactic hepatic resection.[17] Discontinuation of oral contraceptives may lead to a decrease in size.

Focal nodular hyperplasia, which is a benign lesion characterized by a central scar, is thought to represent a hyperplastic response due to a vascular malformation. Identification of the scar by ultrasound, CT, or MRI is diagnostic (see Fig. 132-8D). Observation in the absence of symptoms is advised.

Multiple regenerative 1- to 3-mm nodules clustered around the portal triads characterize nodular regenerative hyperplasia. It is associated with a variety of systemic disorders, predominantly autoimmune, including rheumatoid arthritis, systemic lupus erythematosus, and polymyalgia rheumatica; neoplastic such as myeloproliferative syndromes; and medications, including thiopurines. Symptoms, if present, reflect associated portal hypertension. Diagnosis is by biopsy, which shows hypertrophied hepatocytes clustered around the center of the nodules with peripheral atrophy. Management is directed to the associated portal hypertension (Chapter 139).

Hepatocellular carcinoma (Chapter 181) is a frequent complication of cirrhosis of any cause as well as chronic hepatitis B infection even in the absence of cirrhosis. Patients usually will have evidence of cirrhosis with hepatic dysfunction. Because surveillance for hepatocellular carcinoma is now recommended in individuals at risk, this tumor is increasingly identified when asymptomatic and potentially curable. On ultrasound, hepatocellular carcinoma appears solid. Owing to its predominantly arterial blood supply compared with that of normal hepatic parenchyma, intravenous contrast is rapidly taken up by a hepatic cellular carcinoma and then "washes out" on CT scan or MR imaging (see Fig. 181-4). Serum α-fetoprotein is elevated in approximately 60% of cases. Therapeutic options depend on the tumor's size and severity of associated liver disease.

APPROACH TO THE PATIENT WITH INHERITED LIVER DISEASE

The major inherited liver diseases in adults are hemochromatosis, Wilson disease, cystic fibrosis, and α_1-antitrypsin deficiency. These disorders may be suspected by their extrahepatic manifestations or may be detected during evaluation of unexplained hepatic dysfunction.

Hereditary hemochromatosis (Chapter 196), which is the most common inherited liver disorder, is most frequently due to mutations in the *HFE* gene (located on chromosome 6p22.2), typically at C282Y and H63D. Approximately 1 in 250 individuals of Northern European descent are homozygous for C282Y, the major *HFE* mutation, although only a minority develop phenotypic manifestations.[18] Liver blood test abnormalities, if present, are nonspecific. Definitive diagnosis is confirmed by detection of C282Y homozygote or compound heterozygote (C282Y/H63D). MRI or CT scan can confirm excessive hepatic iron. Liver biopsy is unnecessary for diagnosis but is advised for a serum ferritin greater than 1000 μg/L because the patient is likely to be cirrhotic. Iron accumulates in hepatocytes, but not in Kupffer cells, in a periportal to pericentral gradient (Fig. 132-9). By comparison, secondary iron overload accumulates in Kupffer cells in conditions such as ineffective erythropoiesis. Quantitative iron measurement in liver tissue, calculated as the μmol of iron/g dry weight liver/age, can confirm the diagnosis. Treatment of hemochromatosis is by phlebotomy (Chapter 196).

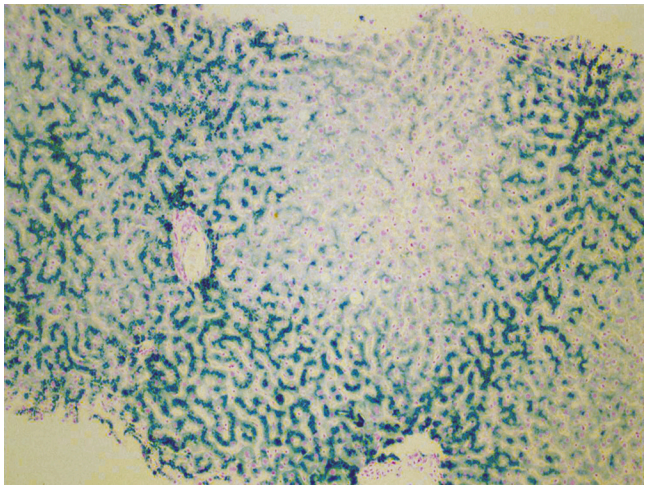

FIGURE 132-9. Liver biopsy in hemochromatosis (Prussian blue stain for iron). Iron deposition is found in a periportal distribution, predominantly in parenchymal cells (hepatocytes). (From Bacon BR. Inherited and metabolic disorders of the liver. In: Goldman L, Schafer AI, eds. *Goldman's Cecil Medicine*, 24th ed. Philadelphia: Saunders; 2012.)

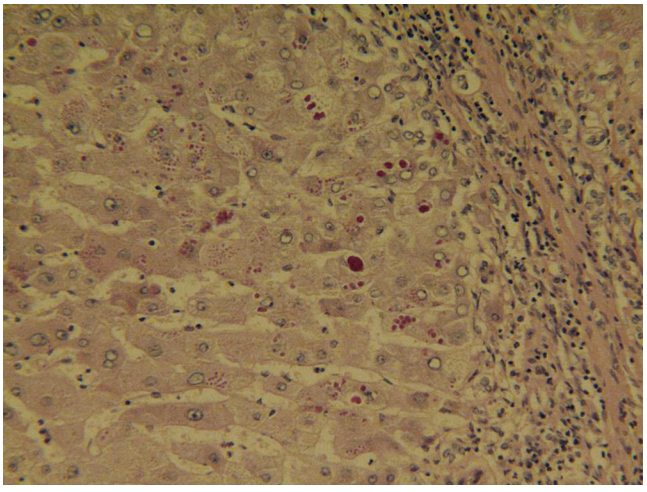

FIGURE 132-10. Liver biopsy in α_1-antitrypsin deficiency. On a periodic acid–Schiff, diastase-resistant stain, α_1-antitrypsin globules, with a characteristic magenta color, are found at the periphery of the lobule. (From Bacon BR. Inherited and metabolic disorders of the liver. In: Goldman L, Schafer AI, eds. *Goldman's Cecil Medicine*, 24th ed. Philadelphia: Saunders; 2012.)

α_1-Antitrypsin deficiency, which results from inherited mutations in this serine protease inhibitor, prevents its export from hepatocytes, where its accumulation causes liver inflammation, fibrosis, and cirrhosis.[19] Deficiency of circulating α_1-antitrypsin results in panlobular emphysema (Chapter 76) even in nonsmokers. The disease is most frequent in persons of European ancestry. Inheritance is autosomal recessive with codominant inheritance because each allele provides 50% of circulating α_1-antitrypsin. A large number of alleles have been identified in the proteinase inhibitor (Pi) gene, with MM associated with normal circulating α_1-antitrypsin levels and the most common abnormal alleles, S and Z, associated with reduced levels. PiZZ homozygotes, who have the most severe α_1-antitrypsin deficiency, have only 15% of normal circulating levels and are prone to liver and lung disease. Liver disease has a bimodal distribution, with neonatal hepatitis and cholestatic jaundice manifesting in early life and cirrhosis in adulthood. Only approximately one third of adults with the PiZZ phenotype develop cirrhosis, thereby implying that other cofactors are involved in disease progression. For example, Pi*Z heterozygosity, found in 2.4% of Whites, increases the risk of cirrhosis secondary to either alcoholic or nonalcoholic fatty liver disease (Chapter 139) by about six-fold.[20] Other phenotypes with α_1-antitrypsin deficiency (e.g., PiMZ or PiSZ) increase the risk for liver disease, whereas null variants have lung but not liver disease. The condition may be suspected as the result of a low α_1-1 globulin level on protein electrophoresis, and the diagnosis can be confirmed by demonstration of a low serum α_1-antitrypsin level followed by Pi testing to determine the phenotype. Liver function test abnormalities are generally nonspecific, although the albumin level can be low and the INR prolonged if cirrhosis is present. Liver biopsy, which shows the extent of fibrosis, is characterized by periodic acid–Schiff (PAS)-positive, diastase-resistant globules in the periphery of the lobule (Fig. 132-10). Weekly intravenous α_1-antitrypsin protein concentrate infusions, which are approved by the U.S. Food and Drug Administration, might prevent progression of lung disease by restoring serum and alveolar α_1-antitrypsin levels. Fazirsiran, which is an RNA interference therapeutic, is an experimental approach to improving liver enzyme abnormalities.[21]

Wilson disease (Chapter 195) is excessive copper accumulation in liver and extrahepatic tissues owing to an inherited disorder in copper transport from hepatocytes to bile. Hepatic manifestations include chronic hepatitis and cirrhosis, most typically appearing by the fourth decade of life, although they can manifest later. A characteristic finding in a fulminant manifestation of Wilson disease is hemolysis with an abnormally low alkaline phosphatase level, jaundice, and coagulopathy. More typically, patients have elevated aminotransferase levels without hemolysis at presentation. Diagnosis usually is based on an elevated 24-hour urinary copper level and low serum ceruloplasmin levels, but in unclear cases the quantification of increased hepatic copper content by biopsy is definitive.[22] Copper chelation prevents disease progression.

Cystic fibrosis (Chapter 77) is usually dominated by pulmonary complications, but liver disease is an important cause of morbidity and mortality in adults.[23] In patients with elevated alkaline phosphatase and bilirubin levels, biliary cirrhosis (Chapter 141) can develop owing to abnormal bile viscosity. Whether new therapies for cystic fibrosis lung disease will improve liver disease is unknown. Ursodeoxycholic acid may improve biochemical test results but has no clear benefit on outcome. Liver transplantation (Chapter 140) may be necessary for decompensated cirrhosis.

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133 APPROACH TO THE PATIENT WITH JAUNDICE OR ABNORMAL LIVER TESTS

KEVIN M. KORENBLAT

JAUNDICE AND HYPERBILIRUBINEMIA

DEFINITION

Jaundice, from the French *jaune* ("yellow"), is the yellow-orange discoloration of the skin, conjunctivae, and mucous membranes that results from an elevated plasma bilirubin level. Mild hyperbilirubinemia may be clinically undetectable, but jaundice becomes evident at plasma bilirubin greater than 3 to 4 mg/dL, depending on the patient's skin pigmentation, the conditions of observation, and the bilirubin fraction that is elevated. Hyperbilirubinemia may result from increased bilirubin production or inherited or acquired defects in the metabolism of hepatic bilirubin.

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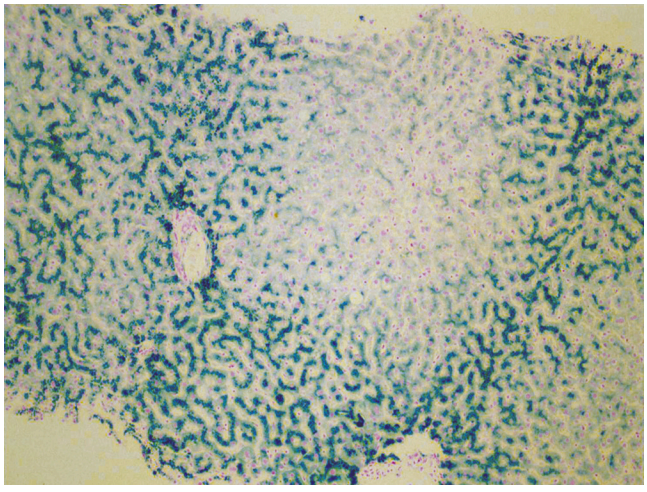

FIGURE 132-9. Liver biopsy in hemochromatosis (Prussian blue stain for iron). Iron deposition is found in a periportal distribution, predominantly in parenchymal cells (hepatocytes). (From Bacon BR. Inherited and metabolic disorders of the liver. In: Goldman L, Schafer AI, eds. *Goldman's Cecil Medicine*, 24th ed. Philadelphia: Saunders; 2012.)

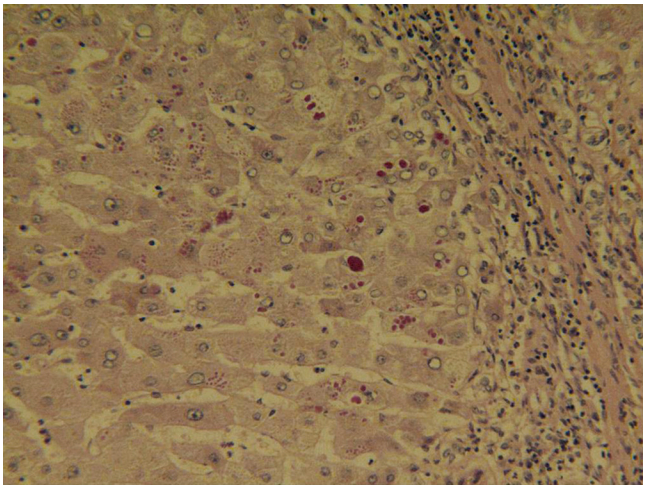

FIGURE 132-10. Liver biopsy in α_1-antitrypsin deficiency. On a periodic acid–Schiff, diastase-resistant stain, α_1-antitrypsin globules, with a characteristic magenta color, are found at the periphery of the lobule. (From Bacon BR. Inherited and metabolic disorders of the liver. In: Goldman L, Schafer AI, eds. *Goldman's Cecil Medicine*, 24th ed. Philadelphia: Saunders; 2012.)

α_1-Antitrypsin deficiency, which results from inherited mutations in this serine protease inhibitor, prevents its export from hepatocytes, where its accumulation causes liver inflammation, fibrosis, and cirrhosis.[19] Deficiency of circulating α_1-antitrypsin results in panlobular emphysema (Chapter 76) even in nonsmokers. The disease is most frequent in persons of European ancestry. Inheritance is autosomal recessive with codominant inheritance because each allele provides 50% of circulating α_1-antitrypsin. A large number of alleles have been identified in the proteinase inhibitor (Pi) gene, with MM associated with normal circulating α_1-antitrypsin levels and the most common abnormal alleles, S and Z, associated with reduced levels. PiZZ homozygotes, who have the most severe α_1-antitrypsin deficiency, have only 15% of normal circulating levels and are prone to liver and lung disease. Liver disease has a bimodal distribution, with neonatal hepatitis and cholestatic jaundice manifesting in early life and cirrhosis in adulthood. Only approximately one third of adults with the PiZZ phenotype develop cirrhosis, thereby implying that other cofactors are involved in disease progression. For example, Pi*Z heterozygosity, found in 2.4% of Whites, increases the risk of cirrhosis secondary to either alcoholic or nonalcoholic fatty liver disease (Chapter 139) by about six-fold.[20] Other phenotypes with α_1-antitrypsin deficiency (e.g., PiMZ or PiSZ) increase the risk for liver disease, whereas null variants have lung but not liver disease. The condition may be suspected as the result of a low α_1-1 globulin level on protein electrophoresis, and the diagnosis can be confirmed by demonstration of a low serum α_1-antitrypsin level followed by Pi testing to determine the phenotype. Liver function test abnormalities are generally nonspecific, although the albumin level can be low and the INR prolonged if cirrhosis is present. Liver biopsy, which shows the extent of fibrosis, is characterized by periodic acid–Schiff (PAS)-positive, diastase-resistant globules in the periphery of the lobule (Fig. 132-10). Weekly intravenous α_1-antitrypsin protein concentrate infusions, which are approved by the U.S. Food and Drug Administration, might prevent progression of lung disease by restoring serum and alveolar α_1-antitrypsin levels. Fazirsiran, which is an RNA interference therapeutic, is an experimental approach to improving liver enzyme abnormalities.[21]

Wilson disease (Chapter 195) is excessive copper accumulation in liver and extrahepatic tissues owing to an inherited disorder in copper transport from hepatocytes to bile. Hepatic manifestations include chronic hepatitis and cirrhosis, most typically appearing by the fourth decade of life, although they can manifest later. A characteristic finding in a fulminant manifestation of Wilson disease is hemolysis with an abnormally low alkaline phosphatase level, jaundice, and coagulopathy. More typically, patients have elevated aminotransferase levels without hemolysis at presentation. Diagnosis usually is based on an elevated 24-hour urinary copper level and low serum ceruloplasmin levels, but in unclear cases the quantification of increased hepatic copper content by biopsy is definitive.[22] Copper chelation prevents disease progression.

Cystic fibrosis (Chapter 77) is usually dominated by pulmonary complications, but liver disease is an important cause of morbidity and mortality in adults.[23] In patients with elevated alkaline phosphatase and bilirubin levels, biliary cirrhosis (Chapter 141) can develop owing to abnormal bile viscosity. Whether new therapies for cystic fibrosis lung disease will improve liver disease is unknown. Ursodeoxycholic acid may improve biochemical test results but has no clear benefit on outcome. Liver transplantation (Chapter 140) may be necessary for decompensated cirrhosis.

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133 APPROACH TO THE PATIENT WITH JAUNDICE OR ABNORMAL LIVER TESTS

KEVIN M. KORENBLAT

JAUNDICE AND HYPERBILIRUBINEMIA

DEFINITION

Jaundice, from the French *jaune* ("yellow"), is the yellow-orange discoloration of the skin, conjunctivae, and mucous membranes that results from an elevated plasma bilirubin level. Mild hyperbilirubinemia may be clinically undetectable, but jaundice becomes evident at plasma bilirubin greater than 3 to 4 mg/dL, depending on the patient's skin pigmentation, the conditions of observation, and the bilirubin fraction that is elevated. Hyperbilirubinemia may result from increased bilirubin production or inherited or acquired defects in the metabolism of hepatic bilirubin.

ABSTRACT

Bilirubin metabolism reflects the balance between bilirubin production and clearance. Jaundice is the clinical manifestation of hyperbilirubinemia and the result of bilirubin overproduction, decreased bilirubin clearance, or a combination of both processes. Bilirubin is commonly categorized as either indirect or direct. Indirect hyperbilirubinemia arises from increased bilirubin production from the increased turnover of heme-containing protein or decreased bilirubin conjugation with compounds that aid its clearance. Gilbert syndrome, which is the most frequent disorder of indirect hyperbilirubinemia, is associated with a UDG-glucuronosyltransferases 1A1 gene polymorphism that results in its decreased transcription. Direct or mixed hyperbilirubinemia often reflects disorders of bilirubin clearance at all stages of bilirubin removal, including inherited and acquired disruption of canalicular bile transport, liver diseases that impair organ function, mechanical obstruction of bile flow, or disruption of enterohepatic circulation. The cause of the bilirubin elevation can be deduced by the bilirubin fraction that is elevated, the presence of forms of bilirubin in urine, the clinical history, and other laboratory findings, particularly hepatic enzymes and protein products. Similar to the approach to bilirubin, the evaluation of abnormal liver biochemistries relies on an appreciation of the origin and pattern of the biochemical abnormalities, as well as the clinical context in which they occur. Biochemical abnormalities can be described as hepatocellular, cholestatic (affecting bile flow), or mixed. The diagnosis of the cause of biochemical abnormalities often requires serologic studies, liver imaging, and liver biopsy.

KEYWORDS

bilirubin metabolism
jaundice
cholestasis
liver

PATHOBIOLOGY

Bilirubin Metabolism

Bilirubin Production

Bilirubin is the degradation product of the heme moiety of hemoproteins, a class of proteins involved in the transport or metabolism of oxygen (E-Fig. 133-1). Normal adults produce approximately 4 mg of bilirubin per kilogram of body weight per day. Between 70 and 90% of bilirubin is derived from the hemoglobin in erythrocytes, which are sequestered and destroyed by the mononuclear phagocytic cells of the reticuloendothelial system, principally in the spleen, liver, and bone marrow. The remainder is from the turnover of nonhemoglobin hemoproteins, such as myoglobin, the P-450 cytochromes, catalase, and peroxidase, principally in the liver. Ineffective erythropoiesis, which is the premature destruction of newly formed erythrocytes in the bone marrow, contributes a minor fraction. Bilirubin is more than just a byproduct of a degradatory pathway; it has antioxidant and immune modulating properties, and it is a ligand for cellular receptors.[1]

The two-step conversion of heme to bilirubin begins with the opening of the heme molecule at its α bridge carbon by the microsomal enzyme *heme oxygenase*, a process that results in the formation of equimolar quantities of carbon monoxide and the green tetrapyrrole biliverdin. This nontoxic, water-soluble pigment is the main excretory product of heme in birds, reptiles, and amphibians. However, biliverdin cannot cross the placenta. Accordingly, its reduction to bilirubin in mammals by a second enzyme, *biliverdin reductase*, allows its transplacental removal from the fetus into the maternal circulation, from which it can be excreted by the maternal liver. The unconjugated bilirubin produced in the periphery is transported in plasma to the liver. Because of its insolubility in aqueous media, it is kept in solution by tight but reversible binding to albumin. A number of compounds, including salicylates, sulfonamides, furosemide, and radiographic contrast agents, can competitively displace bilirubin from its binding sites on albumin, a phenomenon that is of little clinical significance except in neonates, in whom the resulting increased concentration of unbound bilirubin raises the risk for kernicterus.

Disposition of Bilirubin by the Liver

Excretion of bilirubin from the body is a major function of the liver (see E-Fig. 133-1), where the specialized microanatomy enhances the extraction of protein-bound compounds from the circulation. Hepatic translocation of bilirubin from blood to bile involves four distinct steps: (1) uptake of unconjugated bilirubin, principally by facilitated transport and, to a lesser extent, diffusion; (2) intracellular binding, mainly to various cytosolic proteins of the glutathione-*S*-transferase family; (3) conversion in the endoplasmic reticulum of unconjugated bilirubin to bilirubin monoglucuronides and diglucuronides by a specific uridine 5′-diphospho-glucuronosyltransferase (UDP-glucuronosyltransferase) isoform designated UGT1A1, encoded by the *UGT1* gene complex; and (4) transfer of bilirubin monoglucuronides and diglucuronides into bile by a canalicular membrane adenosine triphosphate (ATP)–dependent transporter designated multidrug resistance–associated protein 2 (MRP2) and also known as canalicular multispecific organic anion transporter (cMOAT) or ATP-binding cassette sub-family C member 2 (ABCC2). MRP2 is encoded by the gene *ABCC2*, a member of the ATP-binding cassette (ABC) transporter superfamily of genes. Conjugated bilirubin is secreted also across the hepatocyte sinusoidal membrane by multidrug resistance–associated protein 3 (MRP3), particularly when the transport capacity of MRP2 is exceeded. MRP2 and MRP3 share a 48% amino acid identity.

Conjugation of unconjugated bilirubin to bilirubin monoglucuronides and diglucuronides is a critical process that greatly increases the aqueous solubility of bilirubin, thereby enhancing its elimination from the body while simultaneously reducing its ability to diffuse across biologic membranes, including the blood-brain barrier. In newborn infants, a decreased capacity to conjugate bilirubin leads to unconjugated hyperbilirubinemia (physiologic jaundice of the newborn). If severe, this hyperbilirubinemia may then lead to kernicterus. Phototherapy by exposure to light in the blue spectrum (390 to 470 nm) converts bilirubin to water-soluble photoisomers that are readily excreted in bile, thereby protecting the central nervous system from bilirubin toxicity. Gilbert syndrome and Crigler-Najjar syndrome types 1 and 2, which result from genetic defects in bilirubin conjugation, are characterized by unconjugated hyperbilirubinemia; by contrast, Dubin-Johnson syndrome, which results from inheritable defects in MRP2, is characterized by conjugated or mixed hyperbilirubinemia. Loss of function of the membrane organic ion transport proteins OATP1B1 and OATP1B3 causes Rotor syndrome, also a conjugated or mixed hyperbilirubinemia.

Enterohepatic Circulation and Excretion of Bilirubin

Normal human bile contains an average of less than 5% unconjugated bilirubin, 7% bilirubin monoconjugates, and 90% bilirubin diconjugates. Following canalicular secretion, conjugated bilirubin passes down the gastrointestinal tract without reabsorption by either the gallbladder or intestinal mucosa. Although some bilirubin reaches the feces, most is converted to urobilinogen and to related compounds by bacteria within the ileum and colon. Urobilinogen is reabsorbed and returns to the liver through the portal circulation, where it is re-excreted into bile. This process of enterohepatic recirculation occurs with urobilinogen, bile salts, and some medications. Any urobilinogen not taken up by the liver reaches the systemic circulation, from which it is cleared by the kidneys. Normal urine urobilinogen excretion is 4 mg/day or less. Hemolysis increases the load of bilirubin entering the gut and therefore the amount of urobilinogen formed and reabsorbed. Liver disease decreases hepatic extraction of bilirubin; as a result, plasma urobilinogen levels rise and more urobilinogen is excreted in the urine. Cholestasis, bile duct obstruction, or antibiotics that reduce or eliminate the bacterial conversion of bilirubin to urobilinogen decrease the formation and urinary excretion of urobilinogen.

Unconjugated bilirubin ordinarily does not reach the gut except in neonates or, by ill-defined alternative pathways, in the presence of severe unconjugated hyperbilirubinemia (e.g., Crigler-Najjar type 1). In these circumstances, unconjugated bilirubin is reabsorbed from the gut, thereby amplifying the hyperbilirubinemia.

Measurement of Bilirubin in Plasma

The total plasma bilirubin concentration in normal adults is less than 1 to 1.5 mg/dL. Modern analytic techniques show that normal plasma contains principally unconjugated bilirubin, with only a trace of conjugated bilirubin. Clinical laboratories quantify plasma bilirubin by a reaction in which bilirubin is cleaved by a diazo reagent under acidic conditions to form azobilirubin that is quantitated spectrophotometrically. Bilirubin conjugates react rapidly ("prompt" or "direct"-reacting bilirubin). Unconjugated bilirubin reacts slowly because the site of attack by the diazo reagent is protected by internal hydrogen bonding. Measurement of the total plasma bilirubin concentration requires addition of an agent, such as a detergent, to solubilize the unconjugated bilirubin.

The "indirect"-reacting bilirubin is calculated by subtracting the direct-reacting bilirubin from the total. Although physicians traditionally equate the direct-reacting fraction of bilirubin in plasma with conjugated bilirubin and the indirect fraction with unconjugated bilirubin, this approach is, at best, an approximation. The unqualified interpretation of direct and indirect fractions as reflecting conjugated and unconjugated bilirubin, respectively, may lead to diagnostic errors, particularly in the diagnosis of hereditary hyperbilirubinemias. In common practice, 10 to 20% of the bilirubin in normal plasma gives a prompt (direct) diazo reaction even though more than 95% of total bilirubin in normal plasma is unconjugated. Thus, at virtually any total bilirubin concentration, a direct-reacting fraction of less than 15% of the total bilirubin can be considered as essentially all unconjugated.

When the direct-reacting fraction is greater than 15%, a simple dipstick test for bilirubinuria may clarify the situation. Unconjugated bilirubin is not excreted in urine regardless of the height of its plasma concentration because its binding to albumin is too tight for effective glomerular filtration and it is not secreted by the tubules. In comparison, conjugated bilirubin in the blood under conditions of parenchymal liver disease or bile duct obstruction is loosely bound to albumin and readily filtered at the level of the glomerulus. Even modest degrees of conjugated hyperbilirubinemia result in bilirubinuria, which is *always* a pathologic finding. With prolonged conjugated hyperbilirubinemia, some of the conjugated bilirubin binds *covalently* to albumin and produces what is designated the delta (δ)-bilirubin fraction. Although δ-bilirubin gives a direct diazo reaction, it is not filterable by the glomerulus and does not appear in the urine; it disappears slowly from the plasma, with the 14- to 21-day half-life of the albumin to which it is bound. δ-Bilirubin can account for the slow rate at which a mixed or predominantly conjugated (direct) hyperbilirubinemia resolves as hepatitis improves or biliary obstruction is relieved. Although δ-bilirubin is not easily measured, its presence can be inferred when an elevated direct-reacting bilirubin persists after bilirubinuria resolves.

Transcutaneous bilirubinometry is an alternative method for measuring bilirubin in infants with neonatal jaundice. The method is based on the measurement of the light reflected from the percutaneous transmission of visible light and can be used to screen newborns.

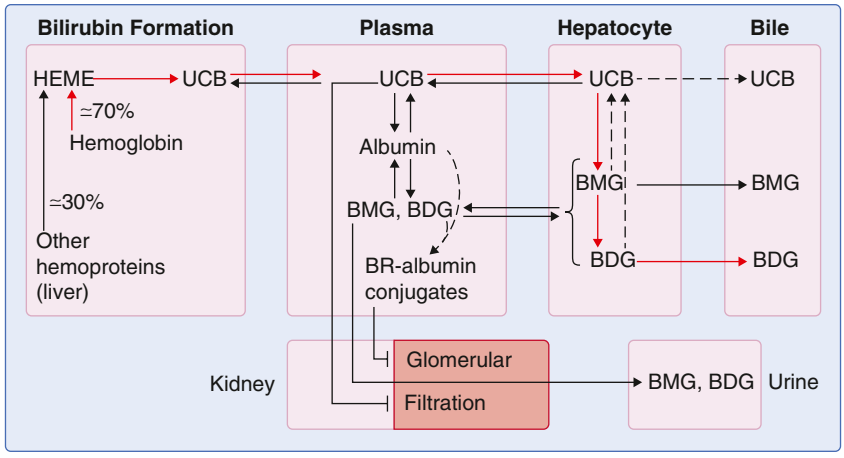

E-FIGURE 133-1. Overview of bilirubin metabolism. Unconjugated bilirubin (UCB) formed from the breakdown of heme from hemoglobin and other hemoproteins is transported in plasma reversibly bound to albumin and is converted in the liver to bilirubin monoglucuronide (BMG) and diglucuronide (BDG), the latter being the predominant form secreted in bile. BMG and BDG together normally account for less than 5% of normal serum bilirubin. In patients with hepatobiliary disease, BMG and BDG accumulate in plasma and appear in urine. Bilirubin glucuronides in plasma also react nonenzymatically with albumin and possibly other serum proteins to form protein conjugates, which do not appear in urine and have a plasma half-life similar to that of albumin. BR = bilirubin.

Bilirubin Kinetics

The plasma unconjugated bilirubin concentration ([UCB]) is determined by a balance between the bilirubin production rate (BRP) and hepatic bilirubin clearance (C_{BR}) according to the relationship:

$$[UCB] \approx BRP/C_{BR}$$

C_{BR} is analogous to the creatinine clearance test of kidney function; it is a measure of the rate at which bilirubin is extracted from plasma, and it is a true quantitative test of liver function. This equation indicates that [UCB] is directly proportional with increases in BRP and inversely proportional with C_{BR}, thereby providing a basis for classifying unconjugated hyperbilirubinemias according to their pathogenesis.

Increased Bilirubin Production

An increased production of bilirubin can be caused by hemolysis, an accelerated destruction of transfused erythrocytes, resorption of hematomas, or ineffective erythropoiesis owing to lead poisoning, megaloblastic anemia related to deficiency of either folic acid or vitamin B_{12}, sideroblastic anemia, congenital erythropoietic porphyria, or myeloproliferative or myelodysplastic diseases. In these settings, other liver tests are typically normal and the hyperbilirubinemia is modest, rarely exceeding 4 mg/dL; higher values imply concomitant hepatic dysfunction. However, after brisk blood transfusion or resorption of massive hematomas caused by trauma, the increased bilirubin load may be transiently sufficient to lead to observable jaundice. The causes of hemolysis are numerous (Chapters 146 and 147). Besides specific blood disorders, mild hemolysis accompanies many acquired diseases. In the setting of systemic disease, which may include a degree of hepatic dysfunction, hemolysis may produce a component of conjugated hyperbilirubinemia in addition to an elevated unconjugated bilirubin concentration. Prolonged hemolysis may lead to the formation of pigmented gallstones that contain calcium salts of bilirubin.

Decreased Hepatic Bilirubin Clearance

Decreased Bilirubin Uptake

Bilirubin uptake by hepatocytes involves both facilitated transport and passive diffusion. Decreased bilirubin uptake is believed to explain the initial increase in unconjugated bilirubin associated with rifampin use.

Impaired Bilirubin Conjugation

The most frequent cause of decreased bilirubin clearance is a decrease in bilirubin conjugating activity. Bilirubin conjugation with glucuronic acid is catalyzed principally by a UDP-glucuronosyltransferase, which is designated UGT1A1 and encoded by the *UGT1* gene complex. The *UGT1A1* gene is assembled by alternative splicing of a bilirubin-specific variant of exon 1, designated exon A_1, with four common exons (exons 2 to 5) that encode the shared carboxyl terminal end of all *UGT1*-encoded proteins. Its promoter region normally contains an $A(TA)_6TAA$ TATA box–like construct.

APPROACH TO THE PATIENT WITH HYPERBILIRUBINEMIA

Hyperbilirubinemia and jaundice may result from isolated disorders of bilirubin metabolism, liver disease, or obstruction of the biliary tract. Jaundice represents the most visible sign of hepatobiliary disease of many causes (Table 133-1).

GENETIC DISORDERS OF BILIRUBIN CONJUGATION

The hereditary hyperbilirubinemias (Table 133-2) are a group of five syndromes in which hyperbilirubinemia occurs as an isolated biochemical abnormality, without evidence of liver disease.

CRIGLER-NAJJAR AND GILBERT SYNDROMES

Crigler-Najjar syndrome types 1 and 2 and Gilbert syndrome are hereditary forms of unconjugated hyperbilirubinemia that have been known for more than two decades to result principally from mutations in *UGT1A1*. In Crigler-Najjar type 1, essentially no functional enzyme activity is present; in Crigler-Najjar type 2, enzymatic activity can be as much as 10% of normal; and in Gilbert syndrome, the enzymatic activity is 10 to 33% of normal levels. The resulting bilirubin concentrations are 18 to 45, 6 to 25, and 1.5 to 4 mg/dL, respectively (Table 133-2). Because total UGT1A1 enzymatic activity must be less than 50% of normal to produce unconjugated hyperbilirubinemia, phenotypic expression of mutations in this enzyme requires either homozygosity or double heterozygosity, and each of these disorders is inherited in an autosomal recessive pattern. Individuals of Black or White ancestry with Gilbert syndrome are typically homozygous for an $A(TA)_7TAA$ promoter mutation; this polymorphism is designated *UGT1A1*28*. Structural mutations in exon 1 of *UGT1A1* causing modest reductions in enzymatic activity have been reported in some Japanese patients with Gilbert syndrome. To date, at least 130 different mutations in *UGT1A1* associated with hereditary hyperbilirubinemia have been identified, including ones linked to Crigler-Najjar type 1 and type 2. Other studies in patients with unconjugated hyperbilirubinemia have also identified mutations and polymorphism in multiple additional regions of *UGT1A*, including its promoter region, in the solute carrier protein SCLO1B1, and in the enzymes heme oxygenase and biliverdin reductase A that influence serum bilirubin concentrations.

Crigler-Najjar Syndrome Type 1

Crigler-Najjar type 1 is characterized by a striking unconjugated hyperbilirubinemia that appears in the neonatal period, persists for life, and is unresponsive to phenobarbital.[2] Most patients (type 1A) exhibit defects in the glucuronide conjugation of a spectrum of substrates in addition to bilirubin as the result of homozygous or compound heterozygous mutations in one of the common exons (2 to 5) of the *UGT1* complex. In a smaller subset (type 1B), a mutation in the bilirubin-specific exon A1 limits the defect to bilirubin conjugation. Fifty-nine structurally diverse *UGT1A1* mutations can cause Crigler-Najjar type 1; their common feature is that they all encode proteins with absent or, at most, traces of enzymatic activity.

Before the availability of phototherapy, most patients with Crigler-Najjar type 1 died of bilirubin encephalopathy (kernicterus) in infancy or early childhood. Optimal treatment for a neurologically intact patient includes approximately 12 hours/day of phototherapy from birth throughout childhood, perhaps supplemented by exchange transfusion in the neonatal period; use of oral calcium phosphates to bind bilirubin isomers generated by phototherapy and, thereby, disrupt enterohepatic circulation; and early liver transplantation, before the onset of brain damage. Plasmapheresis can temporarily control abrupt increases in bilirubin.

Crigler-Najjar Syndrome Type 2

Bilirubin concentrations are typically lower in Crigler-Najjar type 2, and plasma bilirubin levels can be reduced to 3 to 5 mg/dL by phenobarbital. At least 48 different mutations of *UGT1A1* have been associated with Crigler-Najjar type 2; all encode a bilirubin-UDP-glucuronosyltransferase with markedly reduced but detectable enzymatic activity. Although much less common in Crigler-Najjar type 2, kernicterus has occurred at all ages, typically associated with factors that temporarily raise the plasma bilirubin concentration above baseline (e.g., fasting, intercurrent illness). For this reason, phenobarbital therapy is often recommended; a single bedtime dose usually maintains clinically safe plasma bilirubin concentrations.

Gilbert Syndrome

Gilbert syndrome is the most common form of the hereditary hyperbilirubinemias.[3] The most common polymorphism is the homozygous $A(TA)_7TAA$ promoter polymorphism designated as the UGT1A1*28 allele. Approximate allelic frequencies are 42%, 30%, and 10% in Black, White, and Asian populations, respectively. In Asian populations, polymorphisms in coding regions are more common than the *28 allele. The high prevalence of Gilbert syndrome often explains the frequency of mild unconjugated hyperbilirubinemia in liver transplant recipients and why population-level studies of bilirubin levels tend to skew toward higher levels. Plasma bilirubin concentrations are most often less than 3 mg/dL, although both higher and lower values are frequent, with increases of two-fold to three-fold commonly occurring with fasting and intercurrent illness. The phenotypic distinction between mild Gilbert syndrome and a normal state is often blurred. Phenobarbital's ability to induce hepatic enzyme activity normalizes both the bilirubin concentration and C_{BR}. Oxidative drug metabolism and the disposition of many, but not all, xenobiotics that are metabolized by glucuronidation appear to be normal in Gilbert syndrome. A critical exception is the antitumor agent irinotecan (CPT-11), whose active metabolite (SN-38) is glucuronidated specifically by UGT1A1. In patients with Gilbert syndrome, irinotecan can cause intractable diarrhea, myelosuppression, and other serious toxicities. The estrogen modulator raloxifene is also a substrate for UGT1A1, and the presence of the homozygous *28 allele results in a two-fold higher exposure to the medication and a greater increase

TABLE 133-1 DIFFERENTIAL DIAGNOSIS OF HYPERBILIRUBINEMIA AND JAUNDICE

DISORDERS OF BILIRUBIN METABOLISM WITHOUT LIVER DISEASE
Unconjugated Hyperbilirubinemia
Increased bilirubin production
Examples: Hemolysis, ineffective erythropoiesis, blood transfusion, resorption of hematomas
Decreased hepatocellular uptake
Examples: Drugs (e.g., rifampin)
Decreased conjugation
Examples: Gilbert and Crigler-Najjar syndromes, physiologic jaundice of the newborn, breast milk jaundice, HIV protease inhibitors
Conjugated or Mixed Hyperbilirubinemia
Decreased canalicular transport: Dubin-Johnson syndrome
Decreased reuptake of bilirubin conjugates: Rotor syndrome
LIVER DISEASE
Acute or Chronic Hepatocellular Dysfunction
Acute or subacute hepatocellular injury
Examples: Viral hepatitis A, B, C, E; hepatotoxins (e.g., ethanol, acetaminophen, mushroom *[Amanita phalloides]* poisoning); drugs (e.g., isoniazid, diclofenac); metabolic diseases (e.g., Wilson disease, Reye syndrome); pregnancy-related (e.g., acute fatty liver of pregnancy, HELLP); hepatic ischemia (e.g., shock)
Chronic hepatocellular disease
Examples: Hepatitis B, B and D, C, and E; hepatotoxins (e.g., organic solvents, vitamin A); nonalcoholic and alcoholic fatty liver disease; autoimmune hepatitis; metabolic disease (Wilson disease, hemochromatosis, α_1-antitrypsin deficiency)
Hepatic Disorders with Cholestasis
Familial cholestatic disorders
Single gene disorders
Examples: Benign recurrent intrahepatic cholestasis; progressive familial intrahepatic cholestasis; Navajo neurohepatopathy syndrome; North American Indian cholestasis
Diffuse infiltrative disorders
Familial cholestatic disorders of unknown pathogenesis
Examples: Aagenaes syndrome
Examples: Granulomatous diseases (e.g., bacterial, mycobacterial, fungal, rickettsial, and trepenomal infections, sarcoidosis, lymphoma), medications (e.g., phenytoin, carbamazepine), amyloidosis, infiltrative malignancies, extramedullary hematopoiesis
Inflammation of intrahepatic bile ductules and/or portal tracts
Examples: Primary biliary cholangitis, liver allograft rejection, graft-versus-host disease
Miscellaneous conditions
Examples: Uncommon presentations of viral or alcoholic hepatitis, intrahepatic cholestasis of pregnancy, contraceptive jaundice, estrogens, anabolic steroids, postoperative cholestasis, cholestasis of sepsis, total parenteral nutrition, drug-induced liver injury (amoxicillin-clavulanate)
BILE DUCT OBSTRUCTION
Choledocholithiasis
Diseases of the Bile Ducts
Inflammation, infection
Examples: Primary sclerosing cholangitis, AIDS cholangiopathy, hepatic artery thrombosis, hepatic arterial infusion pump chemotherapy, postsurgical biliary strictures
Neoplasms (e.g., cholangiocarcinoma)
Extrinsic Compression of the Biliary Tree
Neoplasms
Examples: Pancreatic carcinoma, metastatic lymphadenopathy, hepatoma
Pancreatitis with or without pseudocyst formation
Vascular enlargement (e.g., aneurysm, cavernous transformation of portal vein)

AIDS = acquired immunodeficiency syndrome; HELLP = hemolysis, elevated liver enzymes, and low platelets; HIV = human immunodeficiency syndrome.

in bone density. Although Gilbert syndrome has no association with disease, occasional reports have suggested an association of the UGT1A1*28 allele with a decreased risk for cardiovascular and inflammatory diseases, an association that has been attributed to the vasodilatory and antioxidant effects of bilirubin and heme oxygenase.[4]

UNCONJUGATED HYPERBILIRUBIN IN THE NEWBORN PERIOD

Most neonates develop mild, physiologic jaundice from unconjugated hyperbilirubinemia between days 2 and 5 after birth because of hepatic immaturity and low UGT1A1 levels. Neonates can also experience early and late-onset jaundice from breast milk from two processes. Early onset jaundice occurs within 1 to 3 days of life and is attributed to the reduced calorie intake associated with breastfeeding. Late-onset jaundice occurs within 4 to 5 days of birth and can arise from the inhibition of bilirubin conjugation by the progestational steroid 3α,20β-pregnanediol and certain fatty acids present in breast milk. Peak bilirubin levels are typically less than 5 to 10 mg/dL, and levels return to normal within 2 weeks as mechanisms fostering bilirubin disposition mature. Prematurity, with or without hemolysis, is associated with higher bilirubin levels that may require phototherapy.

CONJUGATED OR MIXED HYPERBILIRUBINEMIA

Two phenotypically similar but mechanistically distinct inherited disorders, Dubin-Johnson syndrome and Rotor syndrome, are characterized by conjugated or mixed hyperbilirubinemia with normal values for other standard liver tests (see Table 133-2). Dubin-Johnson syndrome results from any of several mutations in the *ABCC2* gene that encodes MRP2, and Rotor syndrome is associated with mutations in *SLCO1B1* and *SLCO1B3*. Serum bilirubin levels tend to be modestly elevated (2 to 5 mg/dL), and aminotransferase levels tend to be normal.

In both Dubin-Johnson and Rotor syndromes, liver function is normal. The syndromes can be distinguished from other conditions and from one another by analysis of urine porphyrin excretion. In Dubin-Johnson syndrome, total urine coproporphyrin levels are normal, but coproporphyrin I constitutes 80% of the total; typically coproporphyrin III is 75% of the total.[5] In Rotor syndrome, total coproporphyrin levels are elevated two- to five-fold.

LIVER AND BILIARY TRACT DISEASE

Jaundice is a common sign of generalized hepatobiliary dysfunction, both acute and chronic. Icteric hepatobiliary disease is readily distinguished from the isolated disorders of bilirubin metabolism because the increase in plasma bilirubin concentration occurs in association with other markers of hepatobiliary disease (Fig. 133-1).

Liver diseases can be categorized as those in which the primary injury results from inflammation and hepatocellular necrosis, inhibition of bile flow (cholestasis), or a combination of the two. The cholestatic disorders can be further subdivided into those resulting from mechanical obstruction of the bile duct flow and those from intrahepatic cholestasis, from a multitude of conditions that include several familial cholestatic syndromes; infiltrative disorders, inflammatory or neoplastic conditions; and drug-induced liver injury (see Table 133-1).

TABLE 133-2 PRINCIPAL FEATURES OF THE HEREDITARY DISORDERS OF BILIRUBIN METABOLISM

FEATURE	CRIGLER-NAJJAR SYNDROME TYPE 1	CRIGLER-NAJJAR SYNDROME TYPE 2	GILBERT SYNDROME	DUBIN-JOHNSON SYNDROME	ROTOR SYNDROME
Incidence	Very rare	Rare	Up to 12% of population	Rare	Rare
Total serum bilirubin (mg/dL)	18-45 (usually >20), unconjugated	6-25 (usually ≤20), unconjugated	Typically ≤4 in absence of fasting or overt hemolysis; mostly unconjugated	Typically 2-5, less often ≤25; approximately 60% direct reacting	Usually 3-7, occasionally ≤20; approximately 60% direct reacting
Defect(s) in bilirubin metabolism*	Bilirubin UGT1A1 conjugating activity markedly reduced: trace to absent	Bilirubin UGT1A1 conjugating activity reduced: ≤10% of normal	Complex haplotype Bilirubin UGT1A1 conjugating activity typically reduced to 10-33% of normal; reduced bilirubin uptake in some cases; mild hemolysis in up to 50% of patients	Impaired canalicular secretion of conjugated bilirubin owing to MRP2 mutation	Impaired hepatic secretion or storage of conjugated bilirubin owing to impaired reuptake of bilirubin conjugates resulting from simultaneous OATP1B1 and OATP1B3 mutations
Routine liver tests	Normal	Normal	Normal	Normal	Normal
Serum bile acids	Normal	Normal	Normal	Usually normal	Normal
Pharmacologic responses/ special features	No response to phenobarbital	Phenobarbital reduces bilirubin by ≤75%	Phenobarbital reduces bilirubin, often to normal	Increased bilirubin concentration with estrogens; diagnostic urine coproporphyrin isomer pattern (total is normal, with isomer I increased to ≥80% of total)	Characteristic urine coproporphyrin excretion pattern (total is increased ≤2.5-fold in ≈65% of cases but isomer I always <80% of total)
Major clinical features	Kernicterus in infancy if untreated; may occur later despite therapy	Rare late-onset kernicterus with fasting	None	Occasional hepatosplenomegaly	None
Hepatic morphology/ histology	Normal	Normal	Normal; occasionally increased lipofuscin pigment	Liver grossly black; coarse, dark centrilobular pigment	Normal
Bile bilirubin fractions†	>90% unconjugated	Largest fraction (mean 57%) monoconjugates	Mainly diconjugates but monoconjugates are increased (mean 23%)	Mixed conjugates, reported increase in diconjugates	Increased conjugates
Inheritance (all autosomal)	Recessive	Recessive	Promoter mutation is recessive; missense mutation often dominant	Recessive; rare kindred appears dominant	Recessive
Diagnosis	Clinical and laboratory findings, lack of response to phenobarbital	Clinical and laboratory findings, response to phenobarbital	Clinical and laboratory findings; promoter genotyping; liver biopsy rarely necessary	Clinical and laboratory findings; liver biopsy unnecessary if coproporphyrin studies available	Clinical and laboratory findings; urine coproporphyrin analysis
Treatment	Phototherapy or tin protoporphyrin as short-term therapy; liver transplantation definitive	Consider phenobarbital if baseline bilirubin ≥8 mg/dL	None necessary	Avoid estrogens; no other therapy necessary	No treatment necessary

*UGT1A1 = bilirubin specific isoform of the UGT1 family of uridine diphosphate glucuronosyltransferases.
†Bilirubin in normal bile: <5% unconjugated bilirubin, with an average of 7% bilirubin monoconjugates and 90% bilirubin diconjugates.

FAMILIAL CHOLESTASIS SYNDROMES

Bile secretion, which is essential both for the elimination of metabolic wastes and for the solubilization and subsequent absorption of specific nutrients, is a complex, energy-dependent process in which three genes encoding ABC (ATP binding cassette) transporters (*ATP8B1*, *ABCB11*, and *ABCB4*) play critical roles. Cholestatic disorders of childhood (E-Table 133-1) can be caused by a wide range of developmental, heritable, and acquired conditions. Congenital disorders of bile duct development include extrahepatic biliary atresia, progressive familial intrahepatic cholestasis,[6] and Alagille syndrome.[7]

Signs and symptoms associated with progressive familial intrahepatic cholestasis 1 include stunted growth, diarrhea, jaundice, and pruritus.[8] The pruritus from cholestatic disorders can be treated by interruption of the enterohepatic circulation by blockade of the apical bile salt transporter in the ileum.[9] Odevixibat (40 mcg/kg orally once daily) is indicated for the treatment of pruritus in patients 3 months of age and older with progressive familial intrahepatic cholestasis, and maralixibat (190 mcg/kg orally daily for 7 days, then 380 mcg/kg daily, as tolerated) is indicated for treatment of cholestatic pruritus in patients 1 year of age or older with Alagille syndrome.[A1] Treatment can also include reduction of bile acids by partial biliary external diversion, in which bile from the gallbladder is drained by a jejunal conduit externally.

Benign recurrent intrahepatic cholestasis is a rare, autosomal recessive disorder characterized by recurrent attacks of sometimes disabling malaise, pruritus, and jaundice, beginning in childhood or adulthood and varying in duration from weeks to months. Intervals between attacks may vary from months to years, and care is directed at managing the symptoms of fatigue and pruritus. Some cases are associated with progressive hepatic fibrosis.

ACQUIRED CONJUGATION DEFECTS

A modest reduction in bilirubin conjugating capacity occurs in advanced hepatitis or cirrhosis (Chapter 139). In these settings, however, conjugation is better preserved than canalicular excretion. Pharmacologic and

E-TABLE 133-1 CHOLESTATIC DISORDERS ASSOCIATED WITH SINGLE GENE DISORDERS

DISORDER	GENE	CHROMOSOME	PROTEIN	CLINICAL PHENOTYPE
Progressive familial intrahepatic cholestasis type 1	*ATP8B1*	18q21-22	Phosphatidylserine flippase	Cholestasis, mild; lobular fibrosis
Progressive familial intrahepatic cholestasis type 2	*ABCB11*	2q24	Canalicular bile salt translocase	Canalicular cholestasis
Progressive familial intrahepatic cholestasis type 3	*ABCB4*	7q21	Phosphatidylcholine (lecithin) floppase	Cholestasis
Progressive familial intrahepatic cholestasis type 4	*TJP2*	9q21.11	Tight proteins; organization of intercellular junctions	Cholestasis; progressive liver disease in early childhood
Progressive familial intrahepatic cholestasis type 5	*NR1H4*	12q23.1	Nuclear bile acid receptor FXR	Neonatal-onset cholestasis; severe vitamin K–independent coagulopathy
Progressive familial intrahepatic cholestasis type 6	*MYO5B*	18q21.1	Maintenance hepatocyte polarity	Cholestasis
Benign recurrent intrahepatic cholestasis	*ATP8B1; ABCB11*	18q21-22; 2q24	Phosphatidylserine flippase; canalicular bile salt translocase	Cholestasis
Alagille syndrome	*JAG1*	20p12.2	Ligand for NOTCH	Bile duct paucity; congenital heart disease; ophthalmologic and vertebral abnormalities
Navajo neurohepatopathy	*MPV17*	2p23.3	Inner mitochondrial membrane protein	Cirrhosis; sensorimotor neuropathy; metabolic acidosis; failure to thrive
North American Indian cholestasis	*CIRH1A*	16q22	Nucleolar protein	Neonatal jaundice; progressive hepatic fibrosis; also reports of individuals with homozygous mutations without disease phenotype

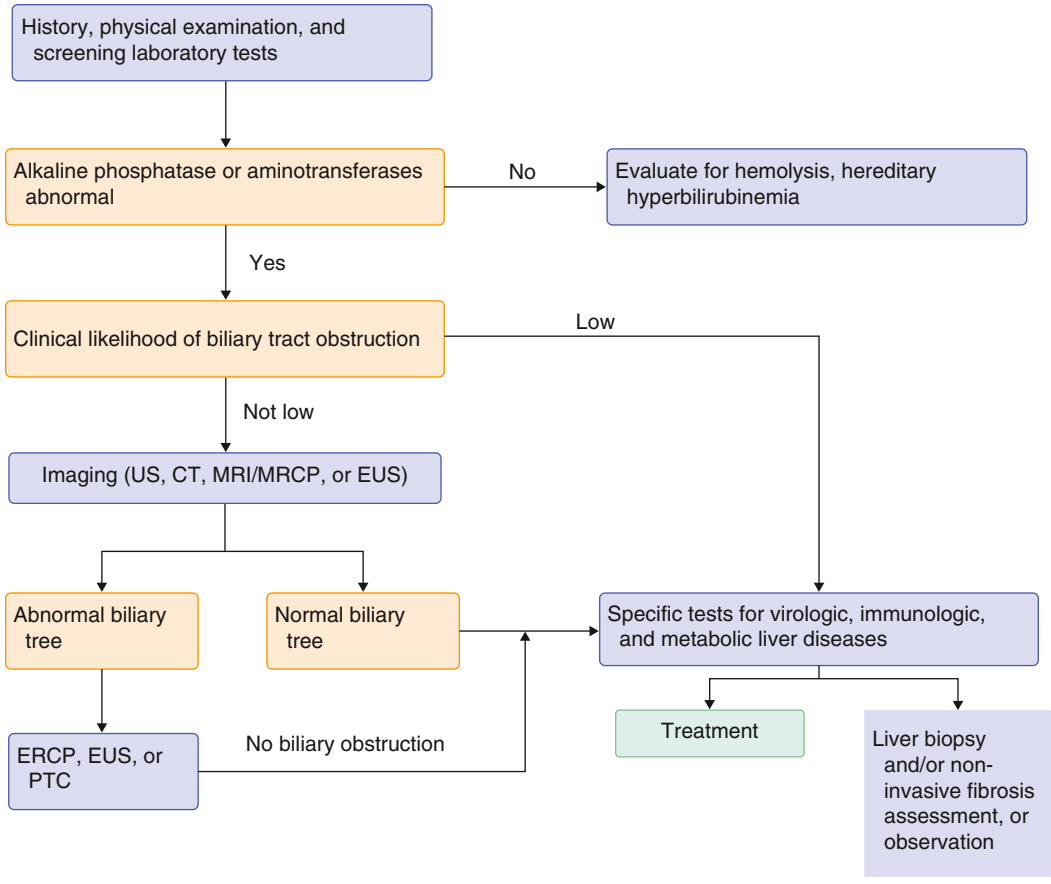

FIGURE 133-1. Diagnostic algorithm for the evaluation of hyperbilirubinemia and other liver test abnormalities and signs and symptoms suggestive of liver disease. CT = computed tomography; ERCP = endoscopic retrograde cholangiopancreatography; EUS = endoscopic ultrasound; MRCP = magnetic resonance cholangiopancreatography; MRI = magnetic resonance imaging; PTC = percutaneous transhepatic cholangiogram; US = ultrasound. (Modified from Lidofsky SD, Scharschmidt BF. Jaundice. In: Feldman M, Scharschmidt BF, Sleisenger MH, eds. *Gastrointestinal and Liver Disease*. 6th ed. Philadelphia: WB Saunders; 1998:227.)

metabolic perturbations may lead to acquired reductions in bilirubin conjugation. Medications known to inhibit UGT1A1 function include the human immunodeficiency virus (HIV) protease inhibitors (indinavir and atazanavir) and sorafenib, which is a multikinase inhibitor. Various other drugs (e.g., pregnanediol and the antibiotics chloramphenicol and gentamicin) also may cause unconjugated hyperbilirubinemia by inhibiting UGT1A1. In all settings in which UGT1A1 inhibitors cause unconjugated hyperbilirubinemia, the presence of Gilbert syndrome amplifies the hyperbilirubinemia.

JAUNDICE IN PREGNANCY

Jaundice in pregnancy (Chapter 221) includes any liver disease that occurs during pregnancy.[10] Conditions unique to pregnancy include elevation of aminotransferase and bilirubin levels during the first trimester with hyperemesis gravidarum. Intrahepatic cholestasis of pregnancy, which occurs during the second and third trimesters, is associated with intrauterine demise and resolves spontaneously after delivery. Mutations and sequence variations in genes encoding biliary transporters, especially *ABCB4* and *ABCB11*, have been reported in some but not all cases. Acute fatty liver or HELLP (*h*emolysis, *e*levated *l*iver enzymes, and *l*ow *p*latelets) syndrome occurs in association with preeclampsia in the third trimester. Acute fatty liver may resemble fulminant hepatic failure, with early delivery a prerequisite to maternal recovery.

POSTOPERATIVE JAUNDICE

This multifactorial syndrome can be caused by increased bilirubin production (e.g., breakdown of transfused erythrocytes, resorption of hematomas), decreased hepatic bilirubin clearance (e.g., bacteremia, endotoxemia, parenteral nutrition, perioperative hypoxia), or both. Postoperative hyperbilirubinemia (Chapter 401) is often accompanied by a several-fold increase in levels of alkaline phosphatase, GGT, or both. Aminotransferase levels are, at most, minimally elevated, and synthetic function is typically normal. The differential diagnosis includes biliary obstruction (Chapter 141) or hepatocellular injury related to shock, medication-induced liver injury (Chapter 136), or viral hepatitis (Chapters 134 and 135). The resolution of postoperative jaundice tends to parallel the overall postoperative course.

DIAGNOSIS

Accurate diagnosis and the distinction between acute and chronic disease often depend on appropriate selection and interpretation of laboratory and imaging studies. Tests used in initial evaluation of liver disease fall into two categories: tests that indicate injury, most commonly the aminotransferase levels, and tests that measure, or at least reflect, actual function. The results of laboratory testing can be informative for the magnitude of their deviation from the reference range, or as binary data to distinguish normal from abnormal. Serial determinations often can be helpful to assess the course of disease or the outcome of an intervention.

Serum Enzyme Tests

The levels of hepatic enzymes found in plasma are a measure of hepatocyte turnover or injury. Enzymes released during normal hepatocyte turnover are believed to be the basis for normal circulating levels. Cell injury and cell death activate phospholipases that create holes in the plasma membrane, thereby increasing the release of intracellular contents.

Aminotransferases

The aminotransferases catalyze transfer of the α-amino group of aspartate (aspartate aminotransferase [AST]) or alanine (alanine aminotransferase [ALT]) to the α-keto group of α-ketoglutarate, with pyridoxal phosphate (vitamin B_6) as a cofactor. Laboratory methods that assay aminotransferase activity require supplementation with vitamin B_6 to avoid falsely decreased activity in subjects who are vitamin B_6 deficient.

Normal serum levels, which are established locally from samples obtained from normal populations, may vary appreciably in different populations but are typically 40 IU/L or less (see Appendix). Deviations from the reference ranges should be expressed as multiples of the upper limits of the reference range.

Values >20 times the upper limit of normal can occur with acute hepatocyte injury from shock, viral infection, or immune- or medication-induced injury. ALT is a purely cytosolic enzyme. Distinct isoforms of AST are present in cytosol and mitochondria, and AST is also found on the plasma membrane. Expression of the mitochondrial isoform and its physiologic export from the hepatocyte are upregulated by ethanol.

Circulating levels of AST and ALT are elevated in most hepatic diseases,[11] and the degree of aminotransferase activity found in plasma roughly reflects the current activity of the disease process. There are, however, exceptions, and aminotransferases can both underestimate and overestimate the degree of hepatic injury. In alcohol-related hepatitis (Chapter 138), aminotransferase levels greater than 10 times the upper limit of normal are uncommon, and levels exceeding this threshold may suggest an additional cause of organ injury. In nonalcoholic fatty liver disease (Chapter 138), normal values for ALT may be found in an appreciable fraction of patients with steatohepatitis, fibrosis, or even cirrhosis. By contrast, conditions as diverse as papillary stenosis, transient choledocholithiasis (Chapter 141), and some forms of acute viral hepatitis (Chapter 134) manifest minimal histologic changes despite aminotransferase levels in excess of 10 times the upper limit of normal. Conversely, aminotransferase levels may decline during the course of massive hepatic necrosis because liver injury is so extensive that little enzyme activity remains. In rare circumstances, antibodies to AST result in an antibody-enzyme complex called a macroenzyme that has a delayed clearance from the circulation.

Aminotransferase levels are useful in several distinct ways. First, they provide a relatively specific screening test for hepatobiliary disease, including the diagnosis of previously unsuspected chronic hepatitis B or C. Although AST levels may be increased with diseases of other organs (notably myocardial and skeletal muscle), the source of increased aminotransferase activity can often be elucidated by consideration of the clinical context in which it arises. Aminotransferase levels are also used to monitor the activity of an acute or chronic parenchymal liver disease and its response to therapy.

Aminotransferase levels also can be elevated in patients with severe systemic disease. For example, aminotransferase levels may be elevated in over 90% of patients hospitalized with coronavirus 2019 (COVID-2019; Chapter 336) infection,[12] in whom they appear to indicate hepatic injury.

Aminotransferase levels may provide diagnostic clues. In most liver diseases, the ratio of AST to ALT is usually 1 or less; however, ratios are typically 2 or higher in alcoholic fatty liver and alcoholic hepatitis (Chapter 138) as a reflection of increased synthesis and secretion of mitochondrial AST into plasma and selective loss of ALT activity because of the pyridoxine deficiency commonly seen in alcoholism. An elevated AST/ALT ratio also occurs in acute liver failure from Wilson disease (Chapter 195).

Alkaline Phosphatases

Alkaline phosphatases are widely distributed enzymes (e.g., liver, bile ducts, intestine, bone, kidney, placenta, and leukocytes) that catalyze the release of orthophosphate from ester substrates at an alkaline pH. The normal activity level in adult serum is dependent on the patient's age and sex, as well as the method of measurement.[13] Two widely used current methods have upper limits of normal in adults of 85 and 110 IU/L (see Appendix). Serum levels higher than the reference range are normal in children and in pregnancy. Bone alkaline phosphatase participates in the deposition of hydroxyapatite in osteoid. In other sites, including the liver, its phosphatase activity may facilitate movement of molecules across cell membranes. Serum alkaline phosphatase activity principally reflects the contribution of hepatic and bone isoforms; the intestinal form may account for 20 to 60% of the total after a fatty meal, and blood groups B and O are associated with sustained increases. There is a substantial placental contribution to the alkaline phosphatase level late in pregnancy; the Regan isozyme, a variant that appears identical to the placental form, is associated with hepatocellular cancer (Chapter 181), lung cancer (Chapter 177), and other neoplasms.

Elevations in the serum alkaline phosphatase in cholestatic hepatobiliary disease result from two distinct mechanisms: increased synthesis and secretion of the enzyme and solubilization from the apical (canalicular) surface of hepatocytes and the luminal surface of biliary epithelial cells by the increased local concentrations of bile acids that occur with cholestasis. The first step in the evaluation of alkaline phosphatase is to elucidate the source of the elevation. The placenta, bone, and intestine are non-hepatobiliary sources, and increases in activity can be seen in pregnancy and disorders of increased bone turnover, including Paget disease (Chapter 228), osteomalacia (Chapter 226), and osseous metastatic disease. When the source of the alkaline phosphatase is inapparent from the clinical history, elevation of the gamma-glutamyl transferase (GGT) or 5'-nucleotidase (5'-NT) make a hepatobiliary source likely. The interpretation of a normal GGT is more complicated; although the GGT can be normal in non-hepatobiliary disorders, it is also typically normal in intrahepatic cholestasis of pregnancy, and in some familial cholestatic disorders. With a serum half-life of approximately 1 week, serum alkaline phosphatase levels may remain elevated for days to weeks after resolution of biliary obstruction. This delay may be especially misleading when accompanied by prolonged direct-reacting hyperbilirubinemia owing to delayed clearance of delta bilirubin.

Modest increases in serum alkaline phosphatase (<3 times the upper limit of normal) occur in many hepatic parenchymal disorders, including hepatitis and cirrhosis. Greater increases (3 to 10 times the upper limit of normal) usually indicate obstruction of bile flow. Although the highest levels usually reflect obstruction of the common bile duct, elevations also can occur with obstruction of intrahepatic bile ducts from infiltrative conditions that arise from granulomatous processes (sarcoidosis [Chapter 83], mycobacterial infection [Chapters 299 and 300]), malignancy (lymphoma, cholangiocarcinoma, or metastatic cancer), or amyloidosis (Chapter 174).

Other Hepatic Enzymes

5′-nucleotidase (5′-NT) is a plasma membrane enzyme that cleaves orthophosphate from the 5′ position on the pentose sugar of adenosine or inosine phosphate. Leucine aminopeptidase (LAP) is a ubiquitous cellular peptidase. The serum levels of both usually increase in cholestasis. Accordingly, their major use is to confirm whether an elevated alkaline phosphatase is of hepatobiliary origin. Both enzymes may be increased in the later stages of a healthy pregnancy.

Gamma-glutamyl transpeptidase (GGT) is present in many tissues. Its serum activity increases in hepatobiliary disease but also in neuromuscular diseases, pancreatic disease (even in the absence of biliary obstruction), pulmonary disease, and during the ingestion of ethanol and other inducers of microsomal enzymes. Nevertheless, because serum GGT levels are usually normal in bone disease, the enzyme may be helpful in confirming the hepatic origin of alkaline phosphatase. Lactate dehydrogenase levels are often elevated in hepatic ischemia and other conditions that result in hepatic necrosis.

Tests Based on Clearance of Metabolites and Drugs

A major function of the liver is to remove various metabolites and toxins from the blood. In liver disease, clearance of such molecules may be impaired because of loss of parenchymal cells, diminished bile secretion, biliary obstruction, decreased cellular uptake or metabolism, or reduced or heterogeneous hepatic blood flow. Serum levels of metabolites produced at a relatively constant rate (e.g., bilirubin) can be particularly useful indicators of liver function.

Bilirubin

The differential diagnosis of hyperbilirubinemia (see earlier) includes generalized liver disease, inherited disorders of bilirubin metabolism (e.g., Gilbert, Crigler-Najjar, Dubin-Johnson, and Rotor syndromes), and nonhepatic conditions (e.g., hemolysis). Higher bilirubin levels correlate with a poorer prognosis in most forms of chronic liver disease.

Ammonia

Ammonia, a byproduct of amino acid metabolism, is removed from blood by the liver, converted to urea in the Krebs-Henseleit cycle, and excreted by the kidneys. In the setting of portosystemic shunting or severe hepatic dysfunction, ammonia levels rise. Measurements of blood ammonia are typically used to confirm a diagnosis of hepatic encephalopathy (Chapter 139); however, they do not strongly correlate with the severity of the encephalopathy (Chapter 139). The correlations may be improved if the measurement is made rapidly on an iced arterial blood sample. Elevated ammonia levels also occur when ammonia production is increased by intestinal flora, by the kidney (in response to metabolic alkalosis or hypokalemia), or in rare genetic diseases that affect the pathway of urea synthesis.[14]

Tests Reflecting Hepatic Synthetic Function

Coagulation Tests

Prothrombin Time

The prothrombin time (PT) reflects the plasma concentrations of both extrinsic and common pathway factors, that is, factors VII, X, and V; prothrombin; and fibrinogen. A prolonged PT most often results from vitamin

K deficiency, liver disease, or the therapeutic use of warfarin-like anticoagulants. Vitamin K, a fat-soluble vitamin, is found in many foods and is also synthesized by gut bacteria (Chapter 161). Vitamin K deficiency can be caused by poor dietary intake and malabsorptive states, including the fat malabsorption that results from cholestasis, and with antibiotic suppression of gut flora, particularly in patients who receive inadequate vitamin K replacement.

The half-lives of clotting factors are typically less than 1 day. Factor VII, which has the shortest half-life, is usually the earliest and most severely depressed during periods of defective hepatic synthesis. Because the PT is dependent on factor VII, it responds rapidly with changes in hepatic synthetic function; it is useful for following the course of acute liver diseases, in which a significant or growing prolongation of the PT may indicate a poor prognosis (Chapters 139 and 140). An abnormal PT that is due solely to vitamin K deficiency usually becomes normal within 24 to 48 hours after parenteral repletion; however, if decreased synthesis of clotting factors reflects hepatocyte dysfunction, there may be little or no response to vitamin K.

Although the prolongation of PT with liver disease is generally accepted as indicative of defective clotting factor synthesis, the synthesis of both procoagulant and anticoagulant proteins is disturbed in liver disease. The physiologic consequences of this rebalancing of coagulation may preserve the coagulation response. Prolongation of the PT may also reflect an acquired dysfibrinogenemia or spur cell hemolytic anemia, both of which can occur in decompensated cirrhosis (Chapter 139).

Albumin

Albumin is produced solely by the liver. Its plasma concentration reflects a balance between its synthetic rate of approximately 100 to 200 mg/kg/day and plasma half-life of approximately 21 days. The synthetic rate is affected by the patient's nutritional state, thyroid and glucocorticoid hormone levels, plasma colloid osmotic pressure, exposure to hepatotoxins (e.g., alcohol), and presence of systemic disorders, liver disease, or both. Many conditions increase albumin losses and shorten its plasma half-life, including nephrotic syndrome (Chapter 107), protein-losing enteropathy (Chapter 126), severe burns (Chapter 97), exfoliative dermatitis, and major gastrointestinal bleeding (Chapter 121). Hypoalbuminemia in cirrhosis indicates diminished hepatic synthetic function.

Hematologic Tests in Liver Disease

In moderate to severe acute liver diseases, varying degrees of cytopenias can be seen with all three cell lineages. The most common finding is thrombocytopenia from hypersplenism, which can be a surrogate marker of portal hypertension. Anemia may reflect low-grade hemolysis or marrow depression. Bone marrow suppression may be caused by ethanol or drugs, and aplastic anemia has an uncommon but recognized association with acute viral hepatitis. Zieve syndrome (spur cell hemolytic anemia and hypertriglyceridemia) is a rare but well-characterized complication of severe alcoholic liver disease (Chapter 138). Modest leukopenia, often with atypical lymphocytes, also may be present. Chronic liver disease, especially if cholestatic, may be accompanied by target cells, erythrocytes with an expanded cell membrane that reflects abnormalities in serum lipids.

APPROACH TO THE PATIENT WITH JAUNDICE OR ABNORMAL LIVER TESTS

History, Physical Examination, and Initial Laboratory Studies

Patients with liver disease may present with jaundice or other signs or symptoms, or the disease may be detected in the asymptomatic patient by the finding of abnormal liver tests during a routine evaluation. Regardless of how the patient comes to medical attention, the diagnostic approach (see Fig. 133-1) begins with a careful history, physical examination, and screening laboratory studies (measurement of total and direct bilirubin, ALT, AST, alkaline phosphatase levels, and PT) to formulate an initial differential diagnosis.[15,16] The ability to distinguish between liver disease and biliary tract obstruction is the major goal of the initial evaluation (Table 133-3).

Historic details relevant to the assessment of liver disease include quantification of alcohol consumption, use of medications including complementary and alternative supplements, injection drug use, prior hepatobiliary surgery, and a family history of liver disease. Physical evidence of cirrhosis (e.g., spider angiomas, gynecomastia, ascites, splenomegaly) supports the diagnosis of chronic parenchymal disease. Laboratory testing should help to distinguish primary hepatocellular injury from a cholestatic or mixed pattern. Hepatic synthetic function and signs of portal hypertension (thrombocytopenia) should be assessed. Serologic testing can further elucidate the causes of liver disease. It is also important to recognize that laboratory patterns alone commonly are not sufficient to make or exclude a diagnosis.

TABLE 133-3 OBSTRUCTIVE JAUNDICE VERSUS CHOLESTATIC LIVER DISEASE

FEATURE	SUGGESTS OBSTRUCTIVE JAUNDICE	SUGGESTS PARENCHYMAL LIVER DISEASE
History	Abdominal pain Fever, rigors Prior biliary surgery Acholic stools	Anorexia, malaise, myalgias, suggestive of viral prodrome Known infectious exposure Use of injection drugs or intranasal cocaine Exposure to known hepatotoxin Family history of jaundice
Physical examination	High fever Abdominal tenderness Palpable abdominal mass	Ascites Other stigmata of liver disease (e.g., prominent abdominal veins, gynecomastia, spider angiomata, asterixis, encephalopathy, Kayser-Fleischer rings)
Laboratory studies	Elevated alkaline phosphatase level with varying degrees of hyperbilirubinemia Prothrombin time that is normal or normalizes with vitamin K administration	Elevated aminotransferase levels Prolonged prothrombin time that does not correct with vitamin K administration Blood tests indicative of specific liver disease

Imaging Studies

If extrahepatic obstruction is suspected, its site and nature can be determined in virtually all patients. A reasonable initial step is the use of a noninvasive imaging study such as ultrasonography or magnetic resonance cholangiopancreatography (MRCP) to determine whether the intrahepatic or extrahepatic biliary system, or both, are dilated, thereby implying mechanical obstruction. Because of its lesser expense, portability, and convenience, ultrasound is often the procedure of choice for the diagnosis of cholelithiasis (Chapters 132 and 141). Biliary obstruction may be less apparent in cirrhosis, and mild biliary dilation without obstruction is common after cholecystectomy.

The biliary tree can be examined by endoscopic retrograde cholangiopancreatography (ERCP; Chapter 120) or percutaneous transhepatic cholangiography. Endoscopic ultrasound (EUS) (Chapter 120) is a complementary approach that permits internal ultrasonographic analysis of the pancreas, extrahepatic bile ducts, and regional lymph nodes and blood vessels. EUS combined with fine needle aspiration permits tissue sampling of abnormalities in areas such as the bile ducts and pancreas that typically have been difficult to sample percutaneously.

Selection of Imaging Tests

Liver ultrasound is an ideal screening test to evaluate the liver architecture, assess for surface nodularity and parenchymal mass lesions, and exclude biliary obstruction. Ultrasound is relatively inexpensive in comparison to other imaging modalities, is widely available, and avoids ionizing radiation. The identification of mass lesions on ultrasound will commonly prompt further cross-sectional imaging with either computed tomography or magnetic resonance imaging. If imaging reveals evidence of biliary obstruction or if obstruction is still considered likely despite imaging findings, cholangiography by ERCP or PTC, both of which offer therapeutic and diagnostic capabilities, may be an appropriate choice. In patients with an intermediate probability of obstruction, MRCP is a reasonable study. Individual radiology units have different levels of expertise for these procedures, and the local radiology staff may be quite helpful in recommending the best procedure for a given patient.

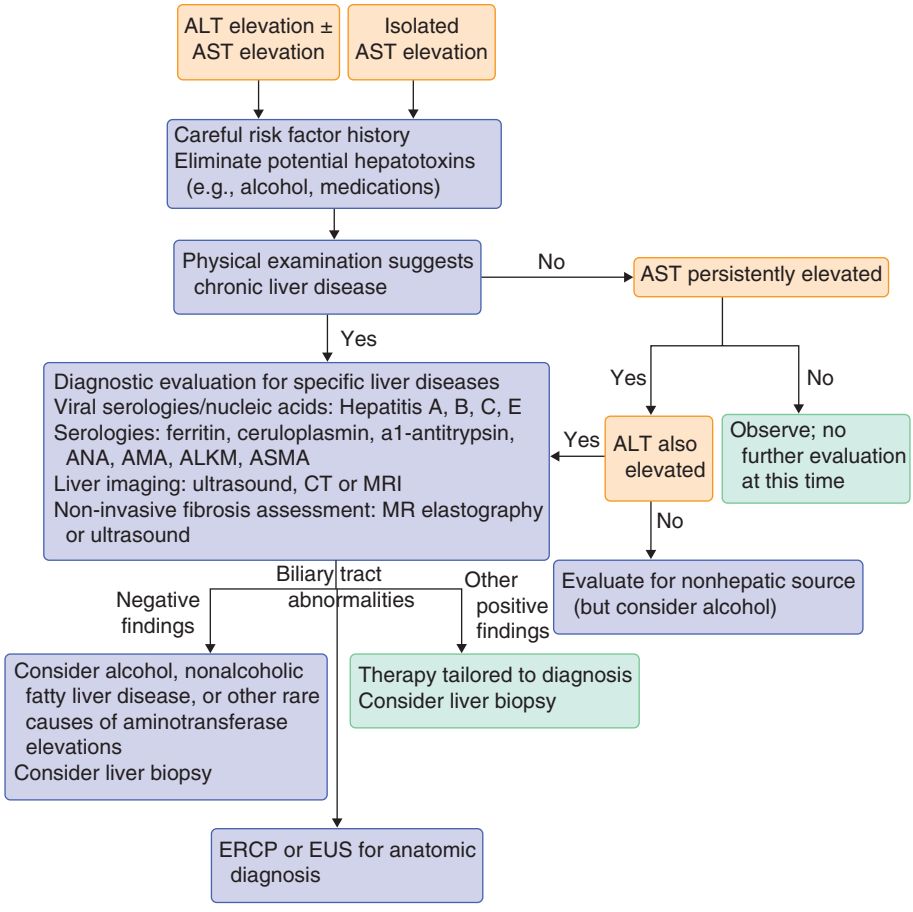

FIGURE 133-2. Approach to the evaluation of isolated elevated levels of serum alanine aminotransferase (*ALT*), aspartate aminotransferase (*AST*), or both in the asymptomatic patient. ALKM = anti–liver/kidney microsomal antibody; ANA = antinuclear antibody; AMA = antimitochondrial antibody; ASMA = anti–smooth muscle antibody; CT = computed tomography; ERCP = endoscopic retrograde cholangiopancreatography; EUS = endoscopic ultrasound; MR = magnetic resonance; MRI = magnetic resonance imaging. WWW.BOOKBAZ.IR

Asymptomatic Aminotransferase Abnormalities

Epidemiologic data suggest that up to 25% of asymptomatic adult Americans have a mild to moderate elevation of aminotransferase levels. The incidental discovery of such abnormalities is currently the most frequent means by which liver disease is first recognized. Whereas up to one third of such patients have no elevation on subsequent testing, others may prove to have any of the common forms of liver disease including chronic viral hepatitis (Chapter 135) and nonalcoholic fatty liver disease (Chapter 138). Persistent elevations of liver test levels should prompt careful clinical evaluation (Fig. 133-2), including laboratory testing of aminotransferase levels and hepatic synthetic function. Serologic studies for viral, autoimmune, and metabolic conditions can provide further insights into diagnosis. When appropriate, changes in aminotransferase levels observed in response to weight loss, the withdrawal of medications, or alcohol sobriety can be very helpful. The evaluation can be further aided by elastography to assess for hepatic fibrosis or liver biopsy when tissue characterization is necessary for a diagnosis (Chapter 132).

Alkaline Phosphatase Elevation

A careful history identifies patients at risk for intrahepatic cholestasis related to drugs or toxins (Chapter 136). The presence of hilar adenopathy or arthritis may implicate sarcoidosis (Chapter 83), although hepatic sarcoidosis can be present without extrahepatic disease. Many patients with isolated elevation of the alkaline phosphatase level have nonhepatic causes, such as pregnancy or bone disease. The origin of an elevated alkaline phosphatase can be determined by fractionation into its constituent fractions (Fig. 133-3). A hepatic source is highly likely if the serum GGT is also abnormal.

Imaging of the liver and biliary tree is necessary when the alkaline phosphatase is of hepatobiliary origin. The diagnostic approach typically begins with liver ultrasound, but MRCP may be an appropriate first choice in, for example, individuals who have inflammatory bowel disease (Chapter 127), in which the probability of primary sclerosing cholangitis (Chapter 141) is increased. Serologic studies should include an antimitochondrial antibody; a positive result suggests primary biliary cholangitis. Other less common (and nonexhaustive) causes of cholestatic liver test include amyloidosis (Chapter 174), tuberculosis (Chapter 299), fungal infections, extramedullary hematopoiesis, Langerhans cell histiocytosis (Chapter 155), infiltrative neoplasms, and sepsis.

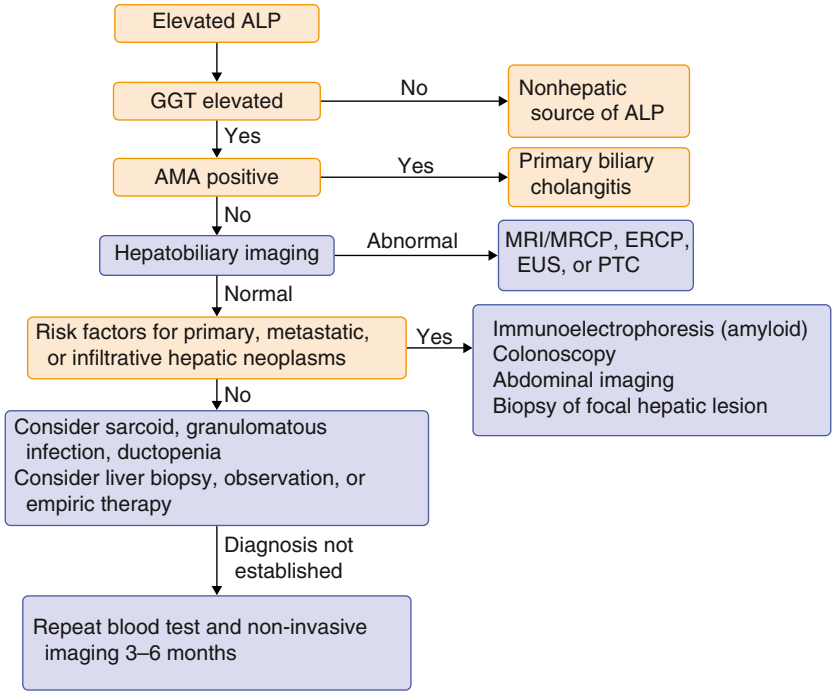

FIGURE 133-3. Approach to the asymptomatic patient with isolated elevated levels of serum alkaline phosphatase (*ALP*). In cases with a high index of suspicion of biliary tract disease (e.g., sclerosing cholangitis), cholangiography may be warranted even in the face of normal ultrasound imaging. AMA = antimitochondrial antibody; ERCP = endoscopic retrograde cholangiopancreatography; EUS = endoscopic ultrasound; GGT = γ-glutamyl transpeptidase; MRCP = magnetic resonance cholangiopancreatography; MRI = magnetic resonance imaging; PTC = percutaneous transhepatic cholangiogram; US = ultrasonography.

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134 ACUTE VIRAL HEPATITIS

JEAN-MICHEL PAWLOTSKY

Infection with a hepatotropic virus causes an acute episode of liver inflammation, referred to as *acute hepatitis*, which can lead to either spontaneous clearance of the infectious agent or its persistence, which in turn leads to chronic infection for a subset of these viruses. Five hepatitis viruses are responsible for the vast majority of acute hepatitis cases (Table 134-1):[1] hepatitis A virus (HAV); hepatitis B virus (HBV); hepatitis C virus (HCV); hepatitis D, or delta, virus (HDV), which is a defective viroid using the hepatitis B surface antigen (HBsAg) as its envelope; and hepatitis E virus (HEV).[2] Other viruses may cause acute inflammatory liver disease, including members of the Herpesviridae family such as human cytomegalovirus, Epstein-Barr virus, and herpes simplex virus. In one study from Spain, the most common causes of acute viral hepatitis cases were: 28% hepatitis B, 18% hepatitis C, 14% hepatitis A, and 14% Epstein-Barr virus (Chapter 348),[3] but severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection also is often accompanied by acute hepatitis. Adenovirus infection has led to outbreaks of hepatitis in children. It is unclear to what extent other viruses, such as parvovirus B19 or human herpesvirus 6, can also cause acute hepatitis. Patients who present with an acute viral hepatitis syndrome but negative virologic tests are referred to as having non–A-to-E hepatitis, perhaps attributable to hepatotropic viruses that have yet to be identified. The worldwide incidence of acute viral hepatitis is decreasing because of global improvements in hygiene and the development and use of efficient vaccines against HBV, to a lesser extent against HAV, and perhaps in the future, HEV.

TABLE 134-1 VIRUSES RESPONSIBLE FOR ACUTE VIRAL HEPATITIS AND LIKELIHOOD OF CHRONIC EVOLUTION

VIRUS	EVOLUTION TO CHRONIC VIRAL HEPATITIS
Hepatitis A virus	Never
Hepatitis B virus	>90% (perinatal acquisition) to <1% (adult infection)
Hepatitis C virus	50-80%
Hepatitis D or delta virus	2% (coinfection) to 90% (superinfection)
Hepatitis E virus	Occasionally in immunosuppressed patients
Other viruses Human cytomegalovirus Epstein-Barr virus Herpes simplex virus Human herpesvirus 6 Parvovirus B19 SARS-CoV-2	May establish chronic infection (except SARS-CoV-2), not associated with chronic hepatitis

GENERAL FEATURES OF ACUTE VIRAL HEPATITIS

PATHOBIOLOGY

Acute viral hepatitis is characterized by acute necroinflammation of the liver. Because none of the hepatotropic viruses is cytopathic, liver injury is mediated by a strong cytotoxic T cell–mediated reaction against infected hepatocytes that express viral antigens at their surface. Pro-inflammatory cytokines, natural killer cells, and antibody-dependent cellular cytotoxicity also appear to play a role in liver necroinflammation. Successful immune elimination may lead to viral clearance, which may or may not be associated with lifelong immunity, depending on the infecting agent. The immune reaction is sometimes so potent that the patient develops subfulminant or even fulminant hepatitis that requires liver transplantation (Chapter 140). In some patients—the proportion varies, according to the virus responsible for acute hepatitis—the immune response fails and chronic infection is established (Chapter 135).

CLINICAL MANIFESTATIONS

After infection, there is an incubation period from a few days to a few weeks, depending upon the causative agent (Fig. 134-1). This incubation period is generally characterized by nonspecific symptoms, including fatigue, nausea, loss of appetite, flulike symptoms, and/or right upper quadrant pain (Table 134-2). The incubation period is often characterized by leukopenia and relative

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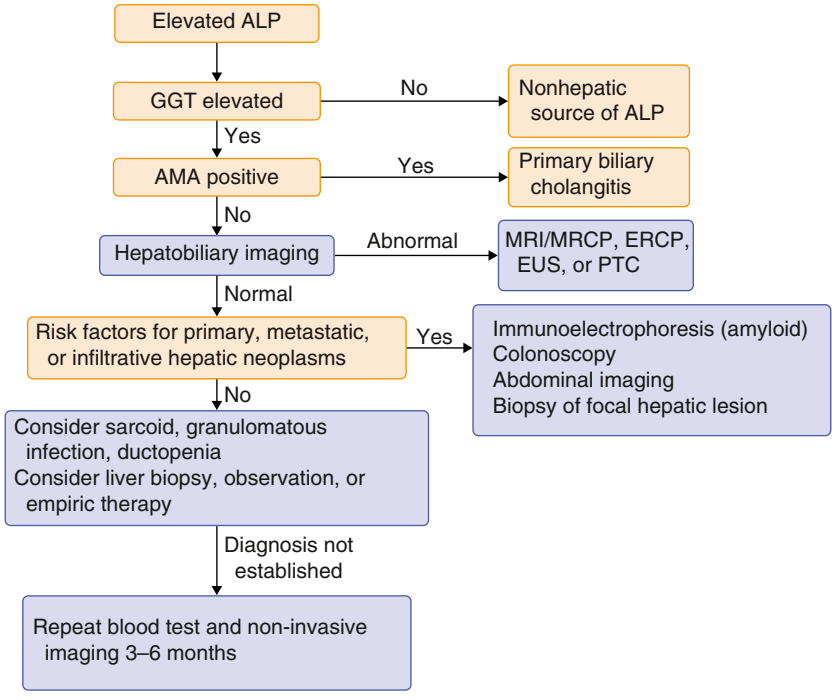

FIGURE 133-3. Approach to the asymptomatic patient with isolated elevated levels of serum alkaline phosphatase (*ALP*). In cases with a high index of suspicion of biliary tract disease (e.g., sclerosing cholangitis), cholangiography may be warranted even in the face of normal ultrasound imaging. AMA = antimitochondrial antibody; ERCP = endoscopic retrograde cholangiopancreatography; EUS = endoscopic ultrasound; GGT = γ-glutamyl transpeptidase; MRCP = magnetic resonance cholangiopancreatography; MRI = magnetic resonance imaging; PTC = percutaneous transhepatic cholangiogram; US = ultrasonography.

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134 ACUTE VIRAL HEPATITIS

JEAN-MICHEL PAWLOTSKY

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GENERAL FEATURES OF ACUTE VIRAL HEPATITIS

PATHOBIOLOGY

Acute viral hepatitis is characterized by acute necroinflammation of the liver. Because none of the hepatotropic viruses is cytopathic, liver injury is mediated by a strong cytotoxic T cell–mediated reaction against infected hepatocytes that express viral antigens at their surface. Pro-inflammatory cytokines, natural killer cells, and antibody-dependent cellular cytotoxicity also appear to play a role in liver necroinflammation. Successful immune elimination may lead to viral clearance, which may or may not be associated with lifelong immunity, depending on the infecting agent. The immune reaction is sometimes so potent that the patient develops subfulminant or even fulminant hepatitis that requires liver transplantation (Chapter 140). In some patients—the proportion varies, according to the virus responsible for acute hepatitis—the immune response fails and chronic infection is established (Chapter 135).

CLINICAL MANIFESTATIONS

After infection, there is an incubation period from a few days to a few weeks, depending upon the causative agent (Fig. 134-1). This incubation period is generally characterized by nonspecific symptoms, including fatigue, nausea, loss of appetite, flulike symptoms, and/or right upper quadrant pain (Table 134-2). The incubation period is often characterized by leukopenia and relative

ABSTRACT

Infection with a hepatotropic virus causes an acute episode of liver inflammation, referred to as acute hepatitis, which can lead to either spontaneous clearance of the infectious agent or its persistence, which in turn leads to chronic infection for a subset of these viruses. Five hepatitis viruses are responsible for the vast majority of acute hepatitis cases: hepatitis A virus (HAV), hepatitis B virus (HBV), hepatitis C virus (HCV), hepatitis D or delta virus (HDV), and hepatitis E virus (HEV). Hepatitis B and C viruses can cause chronic infections. HDV infection can become chronic in chronic HBV carriers. Finally, HEV may become chronic in profoundly immunosuppressed patients. Antiviral treatment is indicated only for the treatment of acute hepatitis C because of the high risk (50 to 80%) of chronicity. The other causes of acute viral hepatitis are self-resolving in the vast majority of cases. Prevention is based on: the improvement of hygiene (HAV and HEV); safe medical and surgical procedures, as well as safe injection drug practices (HBV, HCV, and HDV); treatment of mother-to-infant transmission (HBV); and HBV vaccination (HBV and HDV).

KEYWORDS

acute hepatitis
hepatitis A virus
hepatitis B virus
hepatitis C virus
hepatitis D virus
hepatitis E virus
vaccination

lymphocytosis. Immune-mediated symptoms, including rash, hives, arthralgias, angioneurotic edema, and fever, are observed in 10 to 20% of patients during the preicteric phase.

During the acute stage of the disease, symptoms may vary widely, from asymptomatic to subicteric, icteric or severe, and fulminant. The icteric form, which is not frequent, is characterized by fatigue, anorexia, nausea, dysgeusia, jaundice, dark urine, light-colored stool, and weight loss. Physical examination reveals jaundice and hepatic tenderness. Hepatomegaly and splenomegaly may be present. On laboratory testing, acute viral hepatitis is characterized by elevated total and direct serum bilirubin levels and aminotransferase levels that are often greater than 10 times the upper limit of normal. Cholestatic acute hepatitis is associated frequently with prolonged and fluctuating jaundice and pruritus. After 1 to 3 weeks, on average, both clinical and laboratory signs progressively improve and return to normal. Some patients, however, may experience a relapse before definitive resolution.

Signs of hepatic failure (Chapter 140), including changes in personality, aggressive behavior, sleeping disorders, and hepatic encephalopathy, characterize fulminant forms of acute viral hepatitis. Coma can supervene rapidly, and widespread hemorrhage may develop.

DIAGNOSIS

The diagnosis of acute hepatitis is suspected based on elevated serum aminotransferase levels, which are generally more than 10 times the upper limit

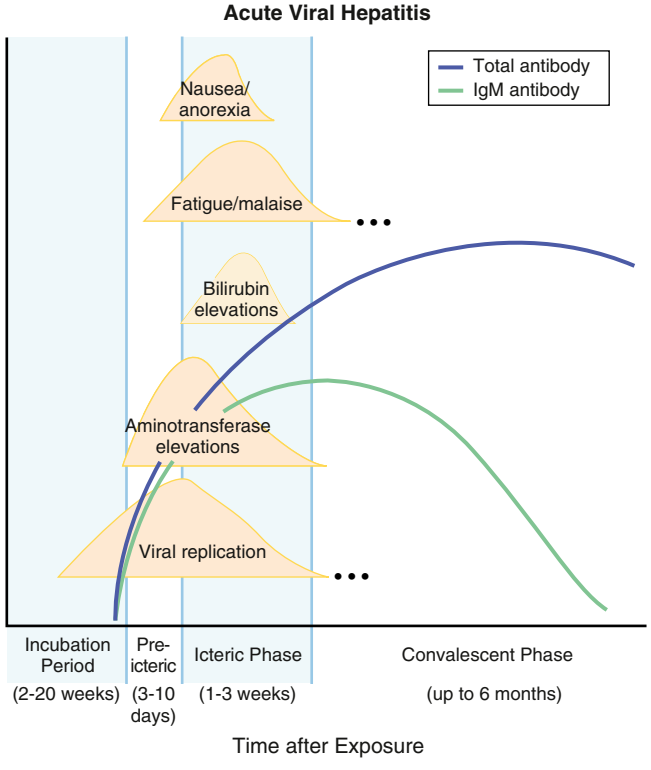

FIGURE 134-1. Typical course of acute viral hepatitis. IgM = immunoglobulin M.

of normal (Table 134-3). Total and direct bilirubin levels are elevated if the acute hepatitis is subicteric or icteric. Alkaline phosphatase levels may be elevated in cases of cholestatic hepatitis.

Serologic and eventually molecular testing identifies the causal agent. Liver biopsy or a non-invasive assessment of liver inflammation and fibrosis are generally not required. All cases of acute hepatitis should be reported to the local, state, or national health department as soon as possible after diagnosis.

TREATMENT

In addition to virus-specific therapy for HBV and HCV,[4] patients with acute viral hepatitis should avoid alcohol consumption and acetaminophen. Sexual contact should be avoided if the partner is not protected (i.e., not HBV vaccinated). Patients with subfulminant or fulminant hepatitis should be supported in an intensive care unit setting and evaluated for possible liver transplantation (Chapter 140).

TABLE 134-2 COMMON CLINICAL MANIFESTATIONS OF ACUTE VIRAL HEPATITIS

PHASES OF INFECTION	DURATION*	MANIFESTATIONS*
Incubation	2-20 weeks	Virus detectable in blood Aminotransferase and bilirubin levels normal No antibody detectable
Preicteric	3-10 days	Nonspecific symptoms: fatigue, anorexia, nausea, vague right upper quadrant pain Viral titers peak Aminotransferase levels begin to rise Immune complex-mediated hypersensitivity reaction (≈10-20% of cases) with rash, hives, arthralgias, fever
Icteric	1-3 weeks	Jaundice appears; dark urine and light stools seen Nonspecific symptoms worsen Weight loss, dysgeusia, pruritus may occur Hepatosplenomegaly may develop Aminotransferase levels typically >10 times normal Antibodies appear Viral titers decline Rare extrahepatic manifestations (aseptic meningitis, encephalitis, seizures, ascending flaccid paralysis, nephrotic syndrome, seronegative arthritis)
Recovery	Up to 6 months	Symptoms resolve gradually Antibody levels rise Aminotransferase and bilirubin levels normalize
Chronic	After 6 months	See Chapter 135

*Varies by virus.

TABLE 134-3 LABORATORY TESTING FOR SUSPECTED ACUTE VIRAL HEPATITIS

GENERAL EVALUATION
Alanine aminotransferase Aspartate aminotransferase Alkaline phosphatase International normalized ratio (INR)
FIRST-LINE DIAGNOSTIC TESTS
Anti-HAV IgM HBsAg, anti-HBc IgM Anti-HCV antibodies HCV RNA Anti-HEV IgM
SECOND-LINE DIAGNOSTIC TESTS
Anti-HAV IgM present: none advised HBsAg and anti-HBc IgM present: HDV antigen, anti-HDV antibodies HCV RNA present with or without anti-HCV antibodies: none advised Anti-HEV IgM present: none advised No virologic marker: See Fig. 134-3

HAV = hepatitis A virus; HBc = hepatitis B core; HBsAg = hepatitis B surface antigen; HBV = hepatitis B virus; HCV = hepatitis C virus; HDV = hepatitis D virus; HEV = hepatitis E virus; IgM = immunoglobulin M.

PROGNOSIS

Prognosis depends on the degree of prolongation of the prothrombin time, as well as the degree of elevation of the bilirubin and lactate levels. A factor V level less than 40% or any signs of encephalopathy are indications for hospitalization. Death is extremely rare and occurs only in fulminant cases. Other signs of poor prognosis are persistently worsening jaundice, ascites, and an acute decrease in the size of the liver. Serum aminotransferase levels and viral genome levels have no prognostic value.

HEPATITIS A

DEFINITION

The Pathogen

HAV is a member of the Picornaviridae family, genus *Hepatovirus*. The hepatitis A viral particle is a 27-nm nonenveloped icosahedral nucleocapsid that expresses the hepatitis A antigen and contains a positive-stranded RNA genome approximately 7.5 kb long. Three different HAV genotypes have been described in humans (genotypes I, II, and III, further divided into subtypes A and B), with genotype I predominating worldwide. Other genotypes have been isolated in nonhuman primates. It is currently unclear to what extent different genotypes are associated with distinct clinical courses of infection.

EPIDEMIOLOGY

HAV infection has a worldwide distribution, and infections can be sporadic or occur in epidemic outbreak. The incidence of acute cases and the seroprevalence vary according to the hygiene, sanitation, housing, and socioeconomic standards of a given region, with a seroprevalence as low as approximately 13% in Sweden but up to 100% in many countries with poor sanitary conditions and hygienic practices. In developing countries, infection generally occurs at a young age and most of the population has been exposed and is protected after age 10 years. In countries with good sanitary and hygienic conditions, however, infection can occur at any age, and the prevalence of exposed, immune subjects slowly increases with age. In the United States, according to the Centers for Disease Control and Prevention, the incidence of acute hepatitis A declined from 12.0 cases per 100,000 individuals in 1995 to 0.5 cases per 100,000 individuals by 2012, but has subsequently increased to 3.8 cases per 100,000 individuals in 2018 owing to widespread outbreaks among persons reporting drug use and homelessness.

HAV is generally transmitted via the fecal-oral route, most often directly from person to person or through the ingestion of fecally contaminated food[5] or water. Transmission by blood transfusion has been reported, and isolated cases of apparent perinatal transmission have been described. High-risk groups for acute hepatitis A include travelers to developing countries, children in day care centers and their parents, men who have sex with men, injection drug users, homeless persons, patients who receive plasma products for hemophilia, and persons in institutions.[6]

PATHOBIOLOGY

The genome serves as a messenger RNA and contains a single open reading frame that encodes both structural and non-structural viral proteins. After attachment to a specific receptor at the surface of hepatocytes, the virus penetrates into cells and is uncoated. Subsequent events occurring exclusively in the cytoplasm include translation of the single open reading frame into a polyprotein that is later processed to generate the mature viral proteins; replication in a membrane-bound replication complex that generates new viral genomes, which are subsequently used for viral protein production and viral particle assembly; and packaging of newly formed genomes into new particles that are exported out of the cells. The virus is secreted into bile and, to a lesser extent, serum.

CLINICAL MANIFESTATIONS

Typically, the incubation period is 15 to 45 days (see Table 134-2). In most cases, acute infection takes a mild and unrecognized course. The incidence of symptomatic, icteric cases increases with the age at infection.[7] Acute hepatitis A in adults may require hospitalization in up to 13% of cases; prolonged courses of 6 to 9 months have been reported in 10% of adult patients with a diagnosis of acute hepatitis A. Hepatitis A is the most common cause of relapsing cholestatic hepatitis.

DIAGNOSIS

The diagnosis of acute hepatitis A is based on the detection of anti-HAV immunoglobulin M (IgM) in serum by enzyme immunoassay. IgM serum levels peak during the second month of infection (Fig. 134-2). HAV RNA can be transiently detected in stool and other body fluids by polymerase chain reaction (PCR) 3 to 10 days before the onset of illness and for 1 to 2 weeks thereafter; however, HAV RNA testing is not necessary. When the infection resolves, anti-HAV IgM disappears after 4 to 12 months, but anti-HAV IgG persists for life and confers definitive and durable protection against infection.

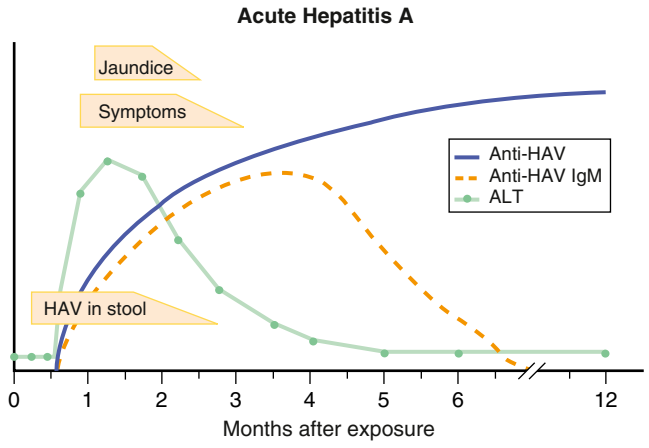

FIGURE 134-2. Serologic course of acute hepatitis A. ALT = alanine aminotransferase; HAV = hepatitis A virus; IgM = immunoglobulin M.

TREATMENT

Because HAV infection is self-limited, no specific antiviral treatment is required. In severe cases, patients may need to be hospitalized. If liver function is deteriorating, patients may need to be assessed for liver transplantation, which is the only therapeutic option for acute liver failure (Chapter 140).

PREVENTION

HAV vaccines (Chapter 15) consist of inactivated hepatitis A antigen purified from cell culture. Two doses of the vaccine are recommended at a 6- to 18-month interval. All vaccines are highly immunogenic, and virtually all healthy persons who are vaccinated develop protective anti-HAV antibodies. Patients with chronic liver disease also respond to vaccination but may display lower anti-HAV titers. An accelerated vaccine schedule, with vaccination on days 0, 7, and 21, is also effective and may be recommended for those planning to travel to endemic areas. HAV vaccines are well tolerated, and no serious adverse events have been linked with their administration; they can be safely administered with other vaccines or immunoglobulins without compromising the development of protective antibodies. A combination HAV and HBV vaccine is also available. Seroconversion rates are lower in immunocompromised individuals.

HAV vaccination is recommended for nonimmune individuals who plan to travel to endemic countries, medical health professionals, men who have sex with men, persons who are in contact with hepatitis A patients, and individuals with chronic liver diseases. A childhood vaccination program leads to a significant decline in HAV infection, justifying its use as part of control efforts in endemic countries. Serologic testing for anti-HAV IgG can be performed before vaccination in adults born in endemic countries and in individuals older than 50 years born in industrialized areas; persons with detectable IgG are protected and should not be vaccinated. For postexposure prophylaxis, both HAV vaccination and immunoglobulin are about 98% effective, with vaccination having the advantage of preventing secondary cases. HAV vaccine and immunoglobulin commonly are used together in this setting.

Long-term follow-up studies after complete HAV vaccination show that anti-HAV IgG titers sharply decline during the first year after vaccination but remain detectable in almost all individuals for at least 10 years. Protective anti-HAV antibody titers persist for at least 27 years after the successful vaccination of children and young adults.

PROGNOSIS

Acute hepatitis A infection generally resolves without complications in 3 to 4 weeks and never evolves to chronic infection. Prolonged elevation of serum aminotransferase levels has been reported. Relapses a few weeks after the acute case also have been observed. Prolonged courses may occur in children and immunosuppressed individuals.

Cholestatic hepatitis A is unusual and has a good prognosis, with full recovery within a few weeks. Fulminant hepatitis A is rare, occurring in less than 0.1% of cases, but its incidence and mortality increase with the patient's age at acquisition. In the United States, 4% of all cases of fulminant hepatitis are caused by HAV infection. Overall, mortality of acute hepatitis A is 1.8% in

patients older than 50 years. In patients with chronic hepatitis B, superinfection with HAV is associated with a 6- to 23-fold higher morbidity and mortality.

ACUTE HEPATITIS B

DEFINITION

The Pathogen

HBV is a member of the Hepadnaviridae family, genus *Hepadnavirus*. The infectious virion, the Dane particle, is 42 to 47 nm in diameter. It possesses an envelope and a capsid or core that contains the partially double-stranded, circular DNA genome and the HBV polymerase. The HBV genome is the smallest known human virus genome, with approximately 3000 nucleotides.

EPIDEMIOLOGY

Two billion individuals worldwide have been in contact with HBV, and approximately 300 million individuals have chronic infection. In the United States, approximately 0.3% of the population is chronically infected. Although the worldwide incidence of chronic HBV infection is decreasing as a result of prevention and vaccination, the absolute prevalence of chronically infected individuals has increased as a result of the increase in the world population. HBV virions are produced and circulate in very high amounts in HBV-infected individuals, who are highly contagious. Four principal routes of transmission are responsible for acute HBV infections: (1) sexual transmission, which is the principal route in industrialized areas; (2) perinatal mother-to-infant transmission, which is associated with a very high (>90%) rate of chronic infection and is the principal cause of HBV transmission in Asia; (3) horizontal transmission through nonsexual interindividual contact, which is frequent at a young age in Africa and is associated with evolution to chronicity in approximately 15% of cases; and (4) percutaneous transmission by blood and blood products, unsafe medical or surgical materials, or injection drug use.

In industrialized countries, groups at high risk for HBV infection include individuals born in areas where HBV is endemic, including immigrants and adopted children; individuals who were not vaccinated as infants and whose parents were born in regions where HBV is endemic; household and sexual contacts of HBsAg-positive individuals; persons who have ever injected drugs; persons with multiple sexual partners or a history of sexually transmitted disease; men who have sex with men; inmates of correctional facilities; patients infected with HCV or HIV; patients undergoing renal dialysis; recipients of blood or blood products before 1987; and health care workers.[8]

PATHOBIOLOGY

The HBV genome contains four overlapping open reading frames that encode a number of structural and non-structural viral proteins. The pre-S/S gene encodes the three surface proteins—small (S), middle (M), and large (L)—that express HBsAg. The pre-C/C gene encodes the core protein, that expresses the hepatitis B core (HBc) antigen, and the hepatitis B e (HBe) protein, a secreted non-structural protein that plays a role in immune tolerance to HBV replication. The P gene encodes the HBV polymerase, whose two motifs—a reverse transcriptase motif and an RNAse H motif—code for two enzymes involved in HBV replication. Finally, the X gene encodes the X protein, which is a transactivator involved in HBV replication that bears oncogenic properties. The blood of infected patients contains not only infectious viruses but also a large excess of empty, non-infectious HBV envelopes.

The complex HBV life cycle involves multiple steps: fixation to the sodium taurocholate cotransporting polypeptide, which is the main HBV receptor molecule at the surface of hepatocytes; internalization; fusion and release of the nucleocapsid containing the HBV DNA genome and the associated HBV polymerase molecule in the cell cytoplasm; transport into the nucleus, where decapsidation occurs and the DNA genome molecule is released; transformation of the viral genome by the viral polymerase into a covalently closed circular DNA, which is the episomal form responsible for persistence of the HBV genome in the nucleus of infected hepatocytes; generation of messenger RNAs and viral protein synthesis; generation of a pregenomic RNA, which serves as a template for reverse transcription that generates the long DNA strand; degradation of the pregenomic RNA by the RNAse H activity of the viral polymerase; DNA-dependent DNA polymerase activity of the reverse transcriptase motif, which synthesizes the short complementary DNA strand in newly formed nucleocapsids; and, finally, budding into the endoplasmic reticulum, maturation, and export of newly formed virions.

Ten HBV genotypes (A through J), which differ by approximately 8% of their genomic nucleotide sequence, have different geographic distributions and may be associated with different clinical outcomes. Genotype A predominates in Northern and Western Europe, whereas genotype D is the most frequent genotype in the Mediterranean area and in Eastern Europe. In non-Asian populations in the United States, genotype A predominates in men who have sex with men, whereas genotype D is the most frequent in intravenous drug users. In Asia and in Asian immigrants living in industrialized countries, genotypes B and C predominate. Genotype C has been associated with a higher incidence of severe liver disease and hepatocellular carcinoma compared with genotype B in Asia, perhaps because this genotype spread earlier than the others.

CLINICAL MANIFESTATIONS

Typically, the incubation period is 30-150 days. Jaundice has been reported in up to one third of adult patients with acute hepatitis B, but most cases are unrecognized. Among symptomatic patients (see Table 134-2), the manifestations are similar to those of other causes of acute viral hepatitis.

DIAGNOSIS

Four markers should be sought for the diagnosis of acute hepatitis B: HBsAg, total anti-HBc antibodies, anti-HBc IgM, and anti-HBs antibodies (Table 134-4). Acute hepatitis B is characterized by the simultaneous presence of both HBsAg and anti-HBc IgM (Fig. 134-3). Total anti-HBc antibodies are also present, whereas anti-HBs antibodies are not. During the convalescence phase, patients lose HBsAg before the appearance of anti-HBs antibodies; they have isolated anti-HBc antibodies, and the diagnosis is based on the presence of anti-HBc IgM. Recovery is characterized by the appearance of anti-HBs antibodies. The presence of both total anti-HBc and anti-HBs antibodies characterizes recovery from acute hepatitis B. Anti-HBc IgG remains at high levels for the patient's lifetime, whereas anti-HBs antibody titers may fluctuate and sometimes become undetectable after several years. Quantitative HBsAg assessment may be useful during the course of acute hepatitis B because if the HBsAg level does not rapidly decrease, the patient is at risk for chronic evolution. Patients who remain positive for HBV DNA or HBeAg 6 weeks after the onset of symptoms are likely to develop chronic infection.

TREATMENT

Acute HBV infection usually does not require antiviral therapy, and most patients spontaneously clear the infection. Overall, antiviral therapy does not reduce 1-year mortality.[A1] However, antiviral therapy with a nucleoside or a nucleotide analogue (currently entecavir [0.5mg daily] or tenofovir [tenofovir disoproxil fumarate, 245 mg daily, or tenofovir alafenamide, 25 mg daily] until the signs of severity regress) is recommended in patients with severe acute hepatitis B, characterized by a coagulopathy or persistent symptoms or marked jaundice for more than 4 weeks, to prevent progression to acute liver failure and avoid subsequent liver transplantation or death.[9] Treatment should be initiated before signs of acute liver failure are present. Antiviral therapy does not cause hepatitis B to become a chronic infection.

PREVENTION

Because not everyone has been vaccinated, individuals who are aware that they are infected with HBV should take steps to avoid transmitting the infection to others. This is accomplished by ensuring that their sexual contacts and household members are vaccinated; using barrier protection during sexual intercourse; not sharing instruments such as toothbrushes, razors, and combs; cleaning blood spills with detergent or bleach; and not donating blood, organs, or sperm.

TABLE 134-4 SEROLOGIC PROFILES OBSERVED IN DIFFERENT PHASES OF ACUTE, SELF-RESOLVING HEPATITIS B

PHASE OF INFECTION	HBsAg	ANTI-HBc IgM	TOTAL ANTI-HBc ANTIBODIES	ANTI-HBs ANTIBODIES
Incubation	+	+/−	+/−	−
Acute hepatitis	+	+	+	−
Convalescence	−	+	+	−
Recovery	−	−	+	+

HBc = hepatitis B core; HBs = hepatitis B surface; HBsAg = hepatitis B surface antigen; IgM = immunoglobulin M.

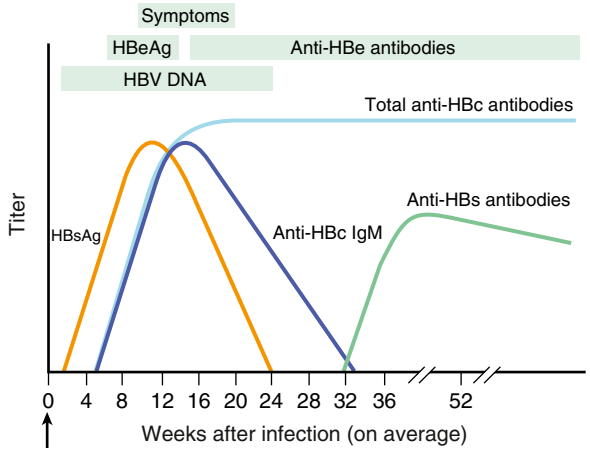

FIGURE 134-3. Kinetics of hepatitis B virus (HBV) markers during acute self-resolving hepatitis B. The *arrow* indicates infection. HBc = hepatitis B core; HBeAg = hepatitis B e antigen; HBs = hepatitis B surface; HBsAg = hepatitis B surface antigen; IgM = immunoglobulin M.

Prevention of HBV infection is based on vaccination. Universal infant vaccination programs have been initiated in many countries. High-risk individuals (e.g., health care workers, dialysis patients, family members and sexual partners of HBV carriers, pregnant women, and men who have sex with men) should be screened for HBV infection by HBsAg and anti-HBs antibody testing, and seronegative persons should be vaccinated.[10]

Vaccination consists of the administration of recombinant HBsAg in three injections at 0, 1, and 6 months in adults. A lower dose is given at the same time points in newborns, children, and adolescents. Adults on dialysis require four injections at months 0, 1, 2, and 6. HBV vaccination elicits a potent neutralizing response, characterized by the presence of isolated anti-HBs antibodies at high titers. A titer greater than 10 IU/L is considered protective. The seroconversion rate is higher than 90% in healthy individuals. HBV vaccines are well tolerated. Injection site reactions within 1 to 3 days, as well as mild general reactions, are common and transient. Post-vaccination testing for anti-HBs antibodies to document seroconversion is not routinely recommended. However, persons who remain at risk for HBV infection, such as infants of HBsAg-positive mothers, health care workers, dialysis patients, and sexual partners of HBV carriers, should be tested to determine their response to vaccination.

Of vaccinated persons, 3 to 10% respond poorly or do not respond, especially smokers, obese patients, and elderly individuals. Non-responders should receive another full course of vaccination, often with an increased dose. Other options include intradermal application and the co-administration of adjuvants and cytokines. One third to two thirds of vaccinated individuals lose their anti-HBs antibodies after 10 to 15 years. It is unclear whether these persons are still protected. Thus, persons at risk should receive booster immunization if anti-HBs antibodies have been lost.

When nonimmune persons or vaccinated individuals with an anti-HBs titer below 10 IU/L have contact with HBV-contaminated materials (e.g., needles) or have sexual intercourse with an HBV-infected person, active-passive immunization (i.e., infusion of hepatitis B immunoglobulin) plus active immunization (vaccination) is recommended within 48 hours after exposure. Vaccination alone is sufficient in persons with anti-HBs antibody titers between 10 to 100 IU/L, and no action is required if the anti-HBs titer is above 100 IU/L.

Tenofovir disoproxil fumarate (245 mg orally per day from 24 to 28 weeks of gestation until up to 12 weeks after delivery) can substantially reduce mother-to-child transmission of HBV in mothers with high viral loads (>200,000 IU/mL) or high HBsAg levels (>10,000 IU/mL).[A2] However, this long-standing practice may not be required in settings in which the baby is ensured to be given HBV immune globulin at birth as well as HBV vaccine at birth and at months 1, 2, 4, and 6.[A3]

Infants born to HBsAg-positive mothers must receive hepatitis B immunoglobulin and be vaccinated within 12 hours of birth; this regimen reduces the rate of vertical HBV transmission from 95% to less than 5%. Cesarean section is not needed if active-passive immunization is to be performed. Mothers of vaccinated infants can breast-feed, and breast-feeding is not contraindicated on tenofovir treatment.

PROGNOSIS

Fulminant hepatitis is more frequent in acute HBV infection than in other types of acute viral hepatitis, with an incidence of approximately 0.1%. Factors associated with adverse outcomes of acute hepatitis B include advanced age, female sex, and perhaps some strains of virus. Whether infection with a precore mutant strain is associated with more severe or fulminant disease is still debated.

Among patients infected at birth, the rate of spontaneous recovery after an acute HBV infection is less than 5%, whereas adult infections spontaneously resolve in 95 to 99% of cases. Spontaneous resolution confers lifelong immunity, which is usually characterized by the presence of both anti-HBs antibodies and anti-HBc antibodies. Anti-HBs antibodies may become undetectable several years after resolution, but patients rapidly produce protective antibodies if they are re-exposed to HBV.

ACUTE HEPATITIS C

DEFINITION

The Pathogen

HCV is a member of the Flaviviridae family, genus *Hepacivirus*. The genome is a single-stranded, positive, linear RNA molecule whose 5′ end contains an internal ribosome entry site involved in polyprotein translation; the genome also includes one single open reading frame and a short 3′ noncoding region involved in replication. The genome is contained in a protein capsid or core, which itself is surrounded by a lipid bilayer envelope into which two inserted viral glycoproteins mediate viral entry into target cells.

EPIDEMIOLOGY

HCV is present in all continents, and an estimated 58 million individuals are chronically infected, with about 1.5 million new infections occurring each year. In industrialized countries, the incidence of HCV infection has declined considerably owing to blood screening and measures to prevent viral infections in people who inject drugs. However, approximately 50,000 new cases of acute hepatitis C have been estimated to occur annually in the United States according to the Centers for Disease Control and Prevention, mostly in intravenous drug users. HCV incidence and prevalence are higher in developing areas of the world, where the main route of HCV infection is unsafe medical or surgical procedures; only approximately 50% of blood products are screened for anti-HCV antibodies in these countries, and approximately 40% of all injections are given with reused equipment. Egypt's estimated 7% prevalence in people 19 to 65 years is the highest worldwide, owing to unsafe injection campaigns for the treatment of schistosomiasis in the 1950s to 1960s and subsequent person-to-person transmission. Although the incidence of acute hepatitis C has declined in Egypt during the past 15 years, a substantial number of cases of acute hepatitis are still caused by HCV.

HCV is transmitted almost exclusively by infected blood. Preventive screening with highly sensitive enzyme immunoassays and, in many settings, nucleic acid testing has virtually eliminated the risk for post-transfusion HCV infection (theoretical risk: <1 in 2 million donations in the United States, 1 in 34 million donations in France). As a result, the principal route for HCV transmission in industrialized countries is now drug injection, which is responsible for 60 to 80% of new cases. The incidence of HCV infection in people who inject drugs is as high as 39 per 100 person years. In this context, imprisonment is an important risk factor for acquiring HCV infection in industrialized countries.

Nosocomial transmission through the use of improperly decontaminated materials or the contaminated hands or gloves of health care workers is responsible for a substantial number of new infections worldwide. HCV also can be transmitted by tattooing, piercing, or acupuncture if standard precautions are not implemented. Although HCV can be acquired after accidental needlestick exposure, the risk for infection is low (<1%), and health care workers have only a slightly higher prevalence of HCV than the general population. HCV can be transmitted to household members who share instruments such as scissors, razors, and combs. Sexual transmission is unusual, but outbreaks of acute hepatitis have been reported in communities of men who have high-risk sex with men. The risk for mother-to-infant transmission of HCV is less than 5% and is generally related to exposure to the mother's blood in the perinatal period. Cesarean sections are not recommended, and breast-feeding is not contraindicated (except in the presence of cutaneous nipple lesions). Factors possibly associated with high transmission rates include the level of HCV viremia and maternal intravenous drug use. In 10 to 30% of cases, no apparent risk factor for HCV infection is identifiable, suggesting other potential sources of community-acquired hepatitis C.

PATHOBIOLOGY

Entry of HCV into cells is mediated by several receptor molecules, including glycosaminoglycans, CD81, scavenger receptor B1, claudin-1, and occludin. Entry is followed by fusion. Decapsidation of viral nucleocapsids liberates free genomic RNAs into the cell cytoplasm, where they serve, together with newly synthesized RNAs, as messenger RNAs for synthesis of the HCV polyprotein. The post-translational processing of the HCV polyprotein results in the generation of 10 proteins, including 3 structural proteins (the core protein and the two envelope glycoproteins) and 7 non-structural proteins. HCV replication takes place in the replication complex (or "membranous web") that associates viral proteins, cellular components, and nascent RNA strands. It is catalyzed by the RNA-dependent RNA polymerase. Viral particle formation is initiated by the interaction of the core protein with genomic RNA. Newly produced virus particles leave the host cell via constitutive secretory pathways.

Phylogenetic analyses of HCV strains isolated in various regions of the world have identified eight main HCV genotypes, designated 1 through 8 (with genotypes 1 to 6 being the most prevalent worldwide). These HCV types comprise a large number of subtypes, identified by lowercase letters (1a, 1b, etc.). The genotypes' nucleotide sequences differ by 31 to 34%, and their amino acid sequences differ by approximately 30%; in contrast, the subtypes' nucleotide sequences differ by between 20 and 23%, with marked differences in particular genomic regions. The high prevalence and diversity of HCV genotype 3 and 6 strains in Asia and of genotype 1, 2, 4, and 5 strains in Africa suggest that these types and subtypes emerged and diversified in these regions. In industrialized countries, a small number of HCV genotypes, including 1a, 1b, 2a, 2b, 2c, 3a, and 4a, have been introduced and spread rapidly among exposed populations. Subtypes 1a and 1b predominate all over the world. The most common genotypes in the United States are 1a and 1b (≈75%), 2a, 2b and 3a (15% to 20%), and 4, 5, and 6 (below 5%). Genotype 3a is more prevalent in Western Europe, where it accounts for up to 35% of cases, especially among people who inject drugs. Genotype 4 is highly prevalent in the Middle East and Africa. Its incidence and prevalence are increasing in people who inject drugs in industrialized countries. Genotype 5 is rare outside South Africa, and genotype 6 is rare outside Southeast Asia. Genotype 7 was identified in Central Africa and genotype 8 in Punjab, India. Infections with different genotypes do not differ in terms of the clinical manifestations, progression, or disease severity.

CLINICAL MANIFESTATIONS

HCV RNA becomes detectable in the serum 3 to 7 days after exposure. HCV core antigen becomes detectable 1 to 3 days later. HCV RNA and HCV core antigen levels rise rapidly during the first weeks, followed by serum aminotransferase levels 2 to 8 weeks after exposure. Anti-HCV antibodies arise late in the course of acute hepatitis C and may not be present at the onset of symptoms and serum aminotransferase elevation.

After an incubation period that ranges from 15 to 120 days, acute hepatitis C usually remains asymptomatic and is undiagnosed. Nonspecific symptoms such as fatigue, low-grade fever, myalgias, nausea, vomiting, or itching may be present. Jaundice occurs in only 20 to 30% of patients, usually 2 to 12 weeks after infection. Serum aminotransferase levels commonly exceed 10 times the upper limit of normal in the acute stage, even in the absence of symptoms. Patients who are coinfected with human immunodeficiency virus have more severe acute symptoms.[11] Fulminant hepatitis C has been reported but appears to be exceptional in the absence of another chronic underlying liver disease.

DIAGNOSIS

When acute hepatitis C is suspected, patients should be tested for both anti-HCV antibodies by enzyme immunoassay and HCV RNA with a sensitive molecular biology technique. HCV core antigen detection by means of rapid enzyme immunoassay can be used as an alternative to HCV RNA detection.[12] Four marker profiles can be observed, based on the presence or absence of either marker (Table 134-5). The presence of HCV RNA in the absence of anti-HCV antibodies is strongly indicative of acute HCV infection, which will be confirmed by seroconversion (i.e., the appearance of anti-HCV antibodies) a few days to weeks later. Acutely infected patients can have both HCV RNA and anti-HCV antibodies at the time of diagnosis; in this case, it is difficult to distinguish acute hepatitis C from an acute exacerbation of chronic hepatitis C or acute hepatitis of another cause in a patient with chronic hepatitis C.

Acute hepatitis C is very unlikely if both anti-HCV antibodies and HCV RNA are absent or if anti-HCV antibodies are present without HCV RNA (Fig. 134-4). Patients in the latter group should be retested in a few weeks, however, because HCV RNA may be temporarily undetectable owing to transient, partial control of viral replication before the infection becomes chronic (Fig. 134-5). Apart from such cases, the presence of anti-HCV antibodies in the absence of HCV RNA is generally seen in patients who have recovered from a past HCV infection. Nevertheless, this pattern cannot be differentiated from a false-positive enzyme immunoassay result, the exact prevalence of which is unknown.

TABLE 134-5 PATTERNS OF HEPATITIS C VIRUS (HCV) MARKERS AND THEIR SIGNIFICANCE DURING ACUTE HEPATITIS C

ANTI-HCV ANTIBODIES	HCV RNA	DIAGNOSIS
–	–	Not acute hepatitis C
–	+	Acute hepatitis C
+	–	Probably not acute hepatitis C (retest in a few weeks)
+	+	Difficult to differentiate acute from chronic hepatitis C

HCV = hepatitis C virus.

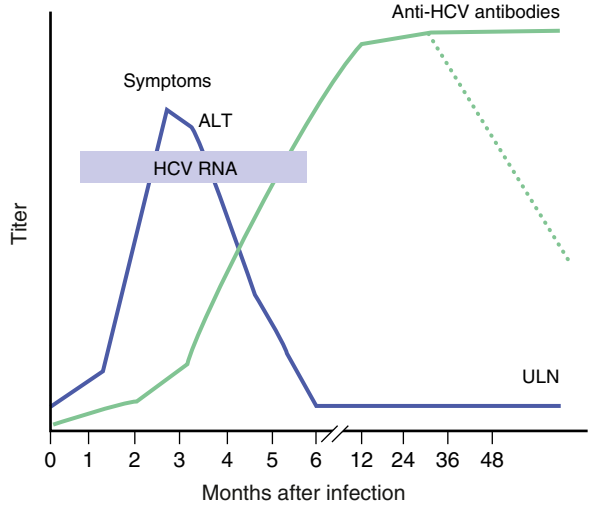

FIGURE 134-4. Kinetics of hepatitis C virus (HCV) markers during acute self-resolving hepatitis C. ALT = alanine aminotransferase; ULN = upper limit of normal.

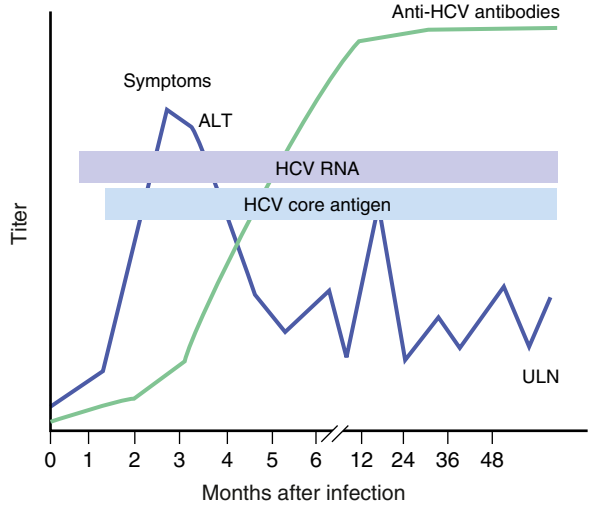

FIGURE 134-5. Kinetics of hepatitis C virus (HCV) markers during acute hepatitis C that evolves toward chronic infection. ALT = alanine aminotransferase; ULN = upper limit of normal.

TREATMENT

Treatment of acute hepatitis C should be considered not only because it prevents chronic HCV infection, which can lead to serious clinical sequelae, but also because HCV viremia is associated with a risk for transmitting HCV to other persons, especially in high-risk groups. Although 20 to 50% of patients will spontaneously clear the virus without treatment, immediate treatment is cost-effective and recommended[13] because it provides higher rates of viral clearance, mostly because asymptomatic patients tend to be less adherent with the close follow-up needed to monitor them for the institution of appropriately timed delayed therapy.[14]

Patients with acute hepatitis C should be treated with an all-oral combination of pan-genotypic, direct-acting antiviral drugs for 8 weeks. Options include the fixed-dose, once daily combination of sofosbuvir (400 mg) and velpatasvir (100 mg) or the fixed-dose combination (3 pills in the morning) of glecaprevir (100 mg) and pibrentasvir (40 mg) (see Table 134-5).[15,16] The cure of HCV infection should be assessed by HCV RNA disappearance from serum or plasma at 12 and 24 weeks post-treatment, because late relapses have been reported.

After accidental needlestick exposure, neither immunoglobulin nor post-exposure prophylaxis is recommended. Patients should be monitored with HCV RNA and aminotransferase level testing at baseline, week 2, and 4 and 6 months after exposure. Patients who have documented infection should be treated as described earlier.

PREVENTION

Prevention of HCV transmission is based on standard precautions such as screening of blood and blood products by an enzyme immunoassay for anti-HCV antibodies and/or nucleic acid testing for HCV RNA, application of standard medical and surgical hygiene procedures, and safe use of syringes and materials for drug preparation in people who inject drugs. One-time screening is also recommended for all individuals over age 18 years.[17] Needle exchange programs and education regarding the risks of drug use (including intranasal cocaine) and the risk for transmission from shared injection equipment are important. These interventions combined with effective treatment of chronic hepatitis (Chapter 135) will substantially reduce the risk of acute hepatitis C in the future.[18]

No prophylactic vaccine is or will soon be available against HCV.

PROGNOSIS

Approximately 50 to 80% of patients are unable to clear HCV spontaneously and develop chronic infection. Spontaneous recovery is more frequent if infection is acquired at birth (≈50%) and if acute hepatitis is symptomatic. It is unclear whether the genotype influences recovery rates. Other factors associated with better rates of spontaneous recovery include female sex, early decline of HCV RNA levels, and high aminotransferase or bilirubin levels. Patients who spontaneously recover may retain detectable anti-HCV antibodies for years to decades, but they are not protected against HCV reinfection.

ACUTE HEPATITIS D (DELTA)

DEFINITION

The Pathogen

HDV, which is a satellite of HBV, can be transmitted only to patients who are acutely or chronically infected with HBV. Its single, negative-strand, circular RNA genome of approximately 1700 nucleotides folds in native conditions into a nearly complementary rodlike structure that contains a ribozyme. The HDV genome encodes one single structural protein, the hepatitis D (HD) protein, which expresses HDAg. The 36-nm infectious HDV virion comprises the HD protein and the genome, both enclosed within an HBsAg-expressing coat derived from empty HBV envelopes.

EPIDEMIOLOGY

Pooled data suggest that about 5% of chronic HBV carriers, or approximately 15 million individuals worldwide, are also infected with HDV.[19] The prevalence of HDV infection in HBV-infected patients varies according to the geographic area because it is transmitted primarily through parenteral exposure. As a result, its prevalence in Western countries is 20-fold higher on average in HBsAg-positive individuals who inject drugs than in non–drug users. By comparison, the prevalence of HDV has decreased substantially in southern Europe, probably owing to universal HBV vaccination programs, improvement in hygiene and living conditions, and implementation of standard precautions to prevent HIV infection. The incidence of HDV is increasing in Russia, Eastern Europe, Japan, and India.

PATHOBIOLOGY

HDV uses host RNA polymerase II for its replication, following the rolling circle model. Within cells, HDV RNA is associated with multiple copies of the HD protein to form a ribonucleoprotein complex. This complex is exported by the HBV envelope, which contains the three HBV envelope proteins, into the Golgi apparatus before being secreted.[20]

HDV has eight genotypes (HDV-1 to HDV-8), which differ from one another by at least 20% of their nucleotide sequences. HDV genotypes can be segregated into 2 to 4 sub-genotypes, which differ from one another by at least 10% of their nucleotide sequences. HDV-1 is the most prevalent HDV genotype worldwide, whereas other genotypes have regional geographic distributions.

CLINICAL MANIFESTATIONS

HDV can be acquired at the same time as HBV (coinfection) or by a chronic HBsAg carrier (superinfection). Coinfection is characterized by one or two episodes of acute hepatitis, depending on the respective amounts of HBV and HDV present in the inoculum; acute hepatitis can range from mild to fulminant. In contrast, when chronic HBV carriers are superinfected by HDV, acute hepatitis D is generally severe, often fulminant, and generally becomes chronic.

DIAGNOSIS

Three markers of HDV infection are total anti-HD antibodies, anti-HD IgM, and HDV RNA; the latter can be detected and quantified by real-time PCR. All HBsAg-positive patients should be tested, and the diagnosis of HDV infection is based on the presence of anti-HD antibodies. Chronic HBV carriers with risk factors for HDV superinfection should be tested regularly.

In patients with a self-resolving HBV-HDV coinfection, HDV RNA and anti-HD IgM are only transiently present and are often missed. Anti-HBc IgM indicates concomitant acute HBV infection.

In HDV superinfection of a chronic HBsAg carrier, no anti-HBc IgM is present. HDV RNA is found in serum or plasma before and during the acute episode, whereas both total anti-HD antibodies and anti-HD IgM are present during the acute phase. Anti-HD antibodies and sometimes anti-HD IgM remain at high levels if the disease becomes chronic.

TREATMENT

No treatments are of proven benefit for acute hepatitis D, although several are being actively investigated.[21]

If, however, patients are coinfected with hepatitis B, then treatment of the hepatitis B should be pursued.

PREVENTION

The most effective means of preventing HDV infection is HBV vaccination, because individuals who are protected against HBV cannot be infected with HDV. In chronic HBsAg carriers, standard hygiene and behavioral precautions should be practiced to avoid superinfection with HDV.

PROGNOSIS

In patients who are acutely coinfected with HBV and HDV, only approximately 2% become chronic HDV carriers. In contrast, when HDV infection is acquired by chronic HBV carriers, approximately 90% also become chronic carriers of HDV, and the risk of developing cirrhosis is increased four-fold.[22]

ACUTE HEPATITIS E

DEFINITION

The Pathogen

HEV is a member of the genus *Orthohepevirus* in the Hepeviridae family. HEV is a small, nonenveloped virus. Its genome is a positive sense, single-stranded RNA molecule. Eight HEV genotypes (1 to 8) have been described: genotypes 1 and 2 appear to be strictly human, whereas genotypes 3 to 8 appear to be of animal origin but can also infect humans.

PATHOBIOLOGY AND EPIDEMIOLOGY

HEV transmission is principally fecal-oral. HEV is endemic in most developing areas of the world, where acute infections are sporadic or occur during large epidemics related to the contamination of drinking water. Seroprevalence data suggest that one third of the world's population has been infected with HEV.[23] Every year, an estimated 20 million HEV infections worldwide lead to an estimated 3.3 million symptomatic cases of hepatitis E.

Genotype 1 has been found principally in Asia and North Africa, whereas genotype 2 has been isolated in cases from Central America and Western Africa. No animal reservoir is known for these genotypes, and transmission appears to be linked to the contamination of food or drinking water. In industrialized countries, HEV genotypes 1 and 2 are not present. HEV genotypes 3 and 4 are endemic in various wild and domestic animal species, and zoonotic transmission appears to be the main route of transmission in Europe, the United States, and Asia. Diagnosed cases of acute hepatitis E have increased constantly in Western Europe and North America in recent years, and high HEV seroprevalence has been described in special at-risk populations, such as butchers or farmers. Transmission may be favored by the consumption of uncooked meat and direct contact with infected animals. It is now thought to be the most common cause of acute viral hepatitis worldwide. Additionally, acute HEV may be observed in immunocompromised patients.

CLINICAL MANIFESTATIONS

The incubation period is 3 to 8 weeks. HEV infection causes only mild, nonspecific symptoms in the majority of cases, especially if the infection is acquired early in life. Immunocompetent individuals clear the virus spontaneously. The peak of viremia occurs early during infection, whereas the peak of aminotransferase activity is reached approximately 6 weeks after infection. Severe disease is more frequent in pregnant women and in patients with underlying chronic liver disease, who may rarely progress to fulminant hepatic failure. Some patients with Guillain-Barré syndrome (Chapter 388) have had a preceding acute hepatitis E infection. Chronic infections have been reported in immunosuppressed patients, especially recipients of organ transplants.

DIAGNOSIS

Patients with acute hepatitis should be tested for hepatitis E. Diagnosis of acute hepatitis E is based on the detection of anti-HEV IgM antibodies, which appear within 6 weeks and persist for 3 to 12 months. No assays are yet approved by the U.S. Food and Drug Administration. HEV RNA also can be detected in feces, serum, or plasma, where its presence is transient. Anti-HEV IgG generally persists for life after acute infection.

TREATMENT

Treatment of acute hepatitis E is not recommended because the vast majority of patients recover spontaneously.[24] Severe and fulminant cases should be referred to specialized units, where ribavirin monotherapy can be successful.

PREVENTION

Improving public hygiene and eating well-cooked meat are the best defenses against hepatitis E. Travelers to areas of the world where hygiene standards are low, particularly pregnant women, should be cautioned about drinking the water and eating uncooked food. A prophylactic vaccine based on recombinant HEV proteins has been approved in China, but is not yet available elsewhere. Its efficacy remains 87% at 4.5 years.[A4] Other HEV vaccines are in the developmental phase.

PROGNOSIS

Acute cases can be severe in elderly patients, and fulminant cases are frequent among pregnant women who are infected during large-scale waterborne epidemics. Overall case fatality rates range from zero to 10%, and less than 1% of fatal cases of acute hepatitis in the United States are attributed to hepatitis E. HEV genotypes 3 and 4 are less virulent than genotypes 1 and 2. Sporadic cases in industrialized areas are generally benign. HEV does not commonly evolve into chronic infection, but immunosuppressed patients can become chronic carriers.

OTHER TYPES OF ACUTE VIRAL HEPATITIS

Infection by members of the Herpesviridae family, such as cytomegalovirus (Chapter 347), Epstein-Barr virus (Chapter 348),[25] and herpes simplex virus (Chapter 345), should be considered in the differential diagnosis of unclear episodes of elevated liver enzymes in the absence of markers of acute hepatitis virus infection, especially in immunocompromised individuals. For instance, cytomegalovirus infection can be associated with graft loss after liver transplantation (Chapter 140). Parvovirus B19 (Chapter 342) may persist in the liver and worsen liver disease in patients with chronic hepatitis B and perhaps in patients with chronic HCV infection. Human herpesvirus 6 variant A has been linked with syncytial giant-cell hepatitis. Transient anicteric elevations of aminotransferase levels are often observed in patients with SARS-CoV-2 infection. Human adenovirus infection (Chapter 333) has caused outbreaks of acute hepatitis in children.[26]

NON–A-TO-E HEPATITIS

Rare patients develop acute hepatitis of presumed viral cause but have no markers of known hepatitis viruses. Some of these cases may be due to variants of known hepatitis viruses, in particular HBV, that are not detected by the usual serologic and molecular methods. However, the existence of other, unknown hepatotropic viruses cannot be excluded.

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For the General References and other additional features, please visit Elsevier eBooks+ at https://ebooks.health.elsevier.com.

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135 CHRONIC VIRAL AND AUTOIMMUNE HEPATITIS

JEAN-MICHEL PAWLOTSKY

DEFINITION

Chronic hepatitis is defined by chronic necroinflammation of the liver and may be due to various causes, including hepatotropic viruses (Chapter 134), autoimmunity, alcohol (Chapter 138), metabolic disorders (Chapter 132), and other less common factors. Chronic infection by hepatitis viruses is by far the main cause of chronic hepatitis worldwide, with nearly 300 million individuals chronically infected with hepatitis B virus (HBV) and nearly 60 million individuals infected with hepatitis C virus (HCV). Chronic viral hepatitis B and C are the leading causes of cirrhosis (Chapter 139) and hepatocellular carcinoma (Chapter 181) worldwide and account for more than 1 million deaths per year.[1] Chronic HBV infection can be associated with infection by hepatitis D virus (HDV). Hepatitis A virus does not cause chronic hepatitis. Hepatitis E virus (HEV) generally does not cause chronic hepatitis, except in immunosuppressed patients.

CLINICAL MANIFESTATIONS

The clinical symptoms of chronic viral and autoimmune hepatitis are typically nonspecific, and many patients have no symptoms. Fatigue, sleep disorders, and right upper quadrant pain may be present. Often the diagnosis is made when liver test abnormalities are identified by blood testing during a routine health evaluation or assessment for an unrelated problem or at the time of voluntary blood donation. More advanced symptoms include poor appetite, nausea, weight loss, muscle weakness, itching, dark urine, and jaundice. Patients can progress to full-blown cirrhosis (Chapter 139), with its typical clinical manifestations. If cirrhosis is present, weakness, weight loss, abdominal swelling, edema, bruisability, gastrointestinal bleeding, and hepatic encephalopathy with mental confusion may arise. Other findings may include spider angiomas, palmar erythema (see Fig. 132-2), ascites (see Fig. 132-4), edema, and skin excoriations.

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Genotype 1 has been found principally in Asia and North Africa, whereas genotype 2 has been isolated in cases from Central America and Western Africa. No animal reservoir is known for these genotypes, and transmission appears to be linked to the contamination of food or drinking water. In industrialized countries, HEV genotypes 1 and 2 are not present. HEV genotypes 3 and 4 are endemic in various wild and domestic animal species, and zoonotic transmission appears to be the main route of transmission in Europe, the United States, and Asia. Diagnosed cases of acute hepatitis E have increased constantly in Western Europe and North America in recent years, and high HEV seroprevalence has been described in special at-risk populations, such as butchers or farmers. Transmission may be favored by the consumption of uncooked meat and direct contact with infected animals. It is now thought to be the most common cause of acute viral hepatitis worldwide. Additionally, acute HEV may be observed in immunocompromised patients.

CLINICAL MANIFESTATIONS

The incubation period is 3 to 8 weeks. HEV infection causes only mild, nonspecific symptoms in the majority of cases, especially if the infection is acquired early in life. Immunocompetent individuals clear the virus spontaneously. The peak of viremia occurs early during infection, whereas the peak of aminotransferase activity is reached approximately 6 weeks after infection. Severe disease is more frequent in pregnant women and in patients with underlying chronic liver disease, who may rarely progress to fulminant hepatic failure. Some patients with Guillain-Barré syndrome (Chapter 388) have had a preceding acute hepatitis E infection. Chronic infections have been reported in immunosuppressed patients, especially recipients of organ transplants.

DIAGNOSIS

Patients with acute hepatitis should be tested for hepatitis E. Diagnosis of acute hepatitis E is based on the detection of anti-HEV IgM antibodies, which appear within 6 weeks and persist for 3 to 12 months. No assays are yet approved by the U.S. Food and Drug Administration. HEV RNA also can be detected in feces, serum, or plasma, where its presence is transient. Anti-HEV IgG generally persists for life after acute infection.

TREATMENT

Treatment of acute hepatitis E is not recommended because the vast majority of patients recover spontaneously.[24] Severe and fulminant cases should be referred to specialized units, where ribavirin monotherapy can be successful.

PREVENTION

Improving public hygiene and eating well-cooked meat are the best defenses against hepatitis E. Travelers to areas of the world where hygiene standards are low, particularly pregnant women, should be cautioned about drinking the water and eating uncooked food. A prophylactic vaccine based on recombinant HEV proteins has been approved in China, but is not yet available elsewhere. Its efficacy remains 87% at 4.5 years.[A4] Other HEV vaccines are in the developmental phase.

PROGNOSIS

Acute cases can be severe in elderly patients, and fulminant cases are frequent among pregnant women who are infected during large-scale waterborne epidemics. Overall case fatality rates range from zero to 10%, and less than 1% of fatal cases of acute hepatitis in the United States are attributed to hepatitis E. HEV genotypes 3 and 4 are less virulent than genotypes 1 and 2. Sporadic cases in industrialized areas are generally benign. HEV does not commonly evolve into chronic infection, but immunosuppressed patients can become chronic carriers.

OTHER TYPES OF ACUTE VIRAL HEPATITIS

Infection by members of the Herpesviridae family, such as cytomegalovirus (Chapter 347), Epstein-Barr virus (Chapter 348),[25] and herpes simplex virus (Chapter 345), should be considered in the differential diagnosis of unclear episodes of elevated liver enzymes in the absence of markers of acute hepatitis virus infection, especially in immunocompromised individuals. For instance, cytomegalovirus infection can be associated with graft loss after liver transplantation (Chapter 140). Parvovirus B19 (Chapter 342) may persist in the liver and worsen liver disease in patients with chronic hepatitis B and perhaps in patients with chronic HCV infection. Human herpesvirus 6 variant A has been linked with syncytial giant-cell hepatitis. Transient anicteric elevations of aminotransferase levels are often observed in patients with SARS-CoV-2 infection. Human adenovirus infection (Chapter 333) has caused outbreaks of acute hepatitis in children.[26]

NON–A-TO-E HEPATITIS

Rare patients develop acute hepatitis of presumed viral cause but have no markers of known hepatitis viruses. Some of these cases may be due to variants of known hepatitis viruses, in particular HBV, that are not detected by the usual serologic and molecular methods. However, the existence of other, unknown hepatotropic viruses cannot be excluded.

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For the General References and other additional features, please visit Elsevier eBooks+ at https://ebooks.health.elsevier.com.

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135 CHRONIC VIRAL AND AUTOIMMUNE HEPATITIS

JEAN-MICHEL PAWLOTSKY

DEFINITION

Chronic hepatitis is defined by chronic necroinflammation of the liver and may be due to various causes, including hepatotropic viruses (Chapter 134), autoimmunity, alcohol (Chapter 138), metabolic disorders (Chapter 132), and other less common factors. Chronic infection by hepatitis viruses is by far the main cause of chronic hepatitis worldwide, with nearly 300 million individuals chronically infected with hepatitis B virus (HBV) and nearly 60 million individuals infected with hepatitis C virus (HCV). Chronic viral hepatitis B and C are the leading causes of cirrhosis (Chapter 139) and hepatocellular carcinoma (Chapter 181) worldwide and account for more than 1 million deaths per year.[1] Chronic HBV infection can be associated with infection by hepatitis D virus (HDV). Hepatitis A virus does not cause chronic hepatitis. Hepatitis E virus (HEV) generally does not cause chronic hepatitis, except in immunosuppressed patients.

CLINICAL MANIFESTATIONS

The clinical symptoms of chronic viral and autoimmune hepatitis are typically nonspecific, and many patients have no symptoms. Fatigue, sleep disorders, and right upper quadrant pain may be present. Often the diagnosis is made when liver test abnormalities are identified by blood testing during a routine health evaluation or assessment for an unrelated problem or at the time of voluntary blood donation. More advanced symptoms include poor appetite, nausea, weight loss, muscle weakness, itching, dark urine, and jaundice. Patients can progress to full-blown cirrhosis (Chapter 139), with its typical clinical manifestations. If cirrhosis is present, weakness, weight loss, abdominal swelling, edema, bruisability, gastrointestinal bleeding, and hepatic encephalopathy with mental confusion may arise. Other findings may include spider angiomas, palmar erythema (see Fig. 132-2), ascites (see Fig. 132-4), edema, and skin excoriations.

ABSTRACT

Chronic hepatitis, which is defined by chronic necroinflammation of the liver, may be due to various causes, most frequently viral hepatitis, but also autoimmunity, alcohol, or metabolic disorders. Chronic hepatitis B virus (HBV) and hepatitis C virus (HCV) infections affect more than 350 million individuals worldwide and are the leading global causes of cirrhosis and hepatocellular carcinoma, accounting for more than 1 million deaths per year. Chronic HBV infection, which can be associated with hepatitis D virus (HDV) infection, can be treated with pegylated interferon alpha for 48 weeks, but most patients receive lifelong oral therapy with entecavir, tenofovir disoproxil fumarate, or tenofovir alafenamide. Such antiviral treatment efficiently prevents the complications of chronic hepatitis B, including fibrosis, cirrhosis, decompensation of cirrhosis, and hepatocellular carcinoma. Treatment of chronic hepatitis C with pan-genotypic oral combinations of direct-acting antiviral drugs can cure more than 95% of patients and prevent the liver and extrahepatic complications of HCV infection.

KEYWORDS

chronic hepatitis
hepatitis C virus
hepatitis B virus
hepatitis D virus
hepatitis E virus
antiviral drugs

DIAGNOSIS

Levels of alanine aminotransferase (ALT) and aspartate aminotransferase (AST) are usually elevated (generally two to five times the upper limit of normal), but they can remain within the normal range for long periods of time in patients with chronic viral hepatitis B or C. The ALT level is generally higher than the AST level. Both can reach 10 to 25 times the upper limit of normal during acute exacerbations. Biologic tests can establish the etiologic diagnosis (Table 135-1).

Alkaline phosphatase and γ-glutamyl transpeptidase levels are usually minimally elevated unless cirrhosis is present. Serum bilirubin and albumin levels and the prothrombin time are normal unless the patient has advanced cirrhosis. Serum immunoglobulin levels are mildly elevated or normal in chronic viral hepatitis but may be very elevated in autoimmune hepatitis. Results that suggest the presence of advanced fibrosis are a platelet count below 160,000, AST levels higher than ALT levels, elevation in serum bilirubin, decrease in serum albumin, prolongation of the prothrombin time, elevation in α-fetoprotein levels, and presence of high globulin levels.

Liver ultrasound can determine the texture and size of the liver and spleen, exclude hepatic masses, and assess the gallbladder, intrahepatic bile ducts, and portal venous flow. Computed tomography and magnetic resonance imaging of the liver are helpful if a mass or other abnormality is found by ultrasound.

Liver biopsy has been critical for diagnosis and to determine the severity of disease. Hepatocellular necrosis is typically eosinophilic degeneration or ballooning degeneration throughout the parenchyma, greater in the periportal area, spotty, or piecemeal. Fibrosis also typically begins in the periportal regions and can link adjacent portal areas or portal and central areas (bridging fibrosis), distort the hepatic architecture, and lead to cirrhosis and portal hypertension. The histologic grade of chronic hepatitis can be determined by combining scores for periportal necrosis and inflammation, lobular necrosis and inflammation, and portal inflammation.

Recently, noninvasive physical methods (such as hepatic transient elastography or acoustic radiation force impulse imaging) and serologic markers have proved accurate for the assessment of mild fibrosis and cirrhosis, without requiring liver biopsy, in patients with chronic hepatitis B and C. However, these tests are less accurate for distinguishing moderate or advanced fibrosis, and their results may be influenced by ongoing liver inflammation, so liver biopsy remains the reference method in chronic hepatitis of nonviral causes. For example, liver biopsy can help exclude other causes of chronic hepatitis, including alcoholic liver disease, fatty liver and steatohepatitis (Chapter 138), drug-induced liver disease (Chapter 136), sclerosing cholangitis (Chapter 141), iron overload (Chapter 196), and veno-occlusive disease (Chapter 129), each of which can coexist with viral or autoimmune hepatitis.

TREATMENT AND PROGNOSIS

Chronic HBV infection is not curable, but it usually can be controlled by appropriate antiviral drugs. HCV infection is curable, and more than 95% of treated patients are cured. Autoimmune hepatitis responds to immunosuppression with corticosteroids and azathioprine.

TABLE 135-1 ETIOLOGIC DIAGNOSIS OF CHRONIC HEPATITIS

DIAGNOSIS	SCREENING TESTS	CONFIRMATORY TESTS
Chronic hepatitis B	HBsAg	HBV DNA
Chronic hepatitis C	Anti-HCV antibodies	HCV RNA
Chronic hepatitis D	Anti-HDV antibodies	HDV RNA
Autoimmune hepatitis	Auto-antibodies (ANA; anti-SMA; anti-LKM1; anti-LC1; anti-SLA/LP)	Exclusion of other causes and patterns of clinical disease
Drug-induced liver disease	History	Rechallenge, if necessary, if considered safe
Wilson disease	Ceruloplasmin	Urine copper concentration
Cryptogenic hepatitis	Exclusion of other causes	

ANA = antinuclear antibody; anti-LC1 = anti–liver cytosol type 1; anti-LKM1 = anti–liver-kidney microsomal 1 antibody; anti-SLA/LP = anti–soluble liver antigen/liver pancreas antibodies; anti-SMA = anti–smooth muscle actin; HBsAg = hepatitis B surface antigen; HBV = hepatitis B virus; HCV = hepatitis C virus; HDV = hepatitis D virus.

CHRONIC HEPATITIS B

EPIDEMIOLOGY

Approximately 300 million individuals, or 4% of the world's population, are carriers of chronic HBV.[2] Two billion individuals, or one human being in three, have been in contact with the virus. In North America, Western and Northern Europe, and Australia, less than 2% of the population are chronic hepatitis B surface antigen (HBsAg) carriers. In the United States, the prevalence is approximately 0.3%, so approximately 860,000 Americans are infected. In Eastern Europe, South America, the Mediterranean basin, and the Indian subcontinent, the prevalence of chronic HBsAg carriage is between 2 and 8%. Highly endemic areas, with a rate of chronic HBsAg carriage exceeding 8%, include China, Southeast Asia, sub-Saharan Africa, and the native populations of the Far North of America.

HBV is the main cause of primary liver cancer (hepatocellular carcinoma; Chapter 181) worldwide, with approximately 350,000 new cases attributable to HBV every year. Hepatocellular carcinoma is more likely in the presence of underlying cirrhosis, but HBV has oncogenic properties of its own, and hepatocellular carcinoma can occur in noncirrhotic HBV patients.

PATHOBIOLOGY

HBV is not a cytopathic virus. Rather, liver injury in chronic hepatitis B is a consequence of the local immune response at the immune elimination phase. In particular, liver injury is related to cytotoxic T cells that recognize and kill infected hepatocytes that express HBV antigens at their surface and to the local production of cytokines. Chronic inflammation triggers fibrogenesis through the activation of hepatic stellate cells. The hepatitis B X protein may also directly activate fibrogenesis. As a result, many patients with chronic hepatitis B have progressive fibrosis, which may evolve into cirrhosis.

The rate of chronicity after an acute HBV infection is more than 95% among infants infected at birth. This risk diminishes as the age at acquisition increases, and it is less than 5% in individuals infected as adults. Chronic HBV infection is defined by HBsAg carriage that persists for more than 6 months after the acute episode. Chronic HBsAg carriage typically evolves through three phases: immune tolerant, immune elimination, and inactive.

The immune tolerant phase is generally short if the infection occurred during adulthood, but it persists for years to decades in patients infected at birth or during early childhood. At the immune tolerant stage, the immune response of the host "tolerates" HBV infection and does not cause liver inflammation or hepatocyte destruction. The immune tolerant phase is characterized by the presence of hepatitis B e antigen (HBeAg), very high levels of HBV DNA in blood, normal serum or plasma aminotransferase levels, and no or minimal inflammatory activity on liver biopsy. However, these patients have detectable immune responses against HBV antigens, their liver histology is not strictly normal, and they display a high level of HBV DNA integration and clonal hepatocyte expansion, indicating that hepatocarcinogenesis is already underway.

The immune elimination phase is characterized by an active immune response that causes necroinflammatory lesions and triggers hepatic fibrogenesis and progressive fibrosis. ALT and AST levels are increased, but HBV DNA levels are lower than during the immune tolerant phase and frequently fluctuate. The immune elimination phase has a variable duration, ranging from a few weeks to several decades. HBeAg, when present, defines HBeAg-positive chronic hepatitis B. HBeAg can be cleared and replaced by anti-HBe antibodies, defined as HBe seroconversion. HBe seroconversion may lead to the persistence of HBV replication and chronic inflammation, defined as HBeAg-negative chronic hepatitis B, or to the inactive HBsAg carrier state. Patients with HBeAg-positive chronic hepatitis B are infected with a wild-type virus and are able to secrete the HBe protein. Patients with HBeAg-negative chronic hepatitis B are infected with so-called precore mutant viruses, which cannot produce the HBe protein because they have a stop codon in the pre-C gene, or with core promoter mutant viruses, which produce considerably lower amounts of HBe protein. Because of the prevalence of the HBV genotype D in Euro-Mediterranean and African countries, HBeAg-negative/anti–HBe-positive chronic hepatitis B is seven to nine times more frequent than HBeAg-positive disease in those locations.

The inactive HBsAg carriage phase is the result of successful immune elimination leading to HBe seroconversion. ALT and AST levels are normal, HBV DNA is undetectable or at very low levels, and patients without preexisting cirrhosis have normal liver histology.

CLINICAL MANIFESTATIONS

Patients with chronic hepatitis B are generally asymptomatic. The most common symptom is fatigue, but sleep disorders, difficulty concentrating, and upper

TABLE 135-2 VIROLOGIC MARKER PROFILES IN PATIENTS WITH CHRONIC HEPATITIS B VIRUS INFECTION

					ANTI-HBc Ab		
	HBsAg	ANTI-HBs Ab	HBeAg	ANTI-HBe Ab	IgM	TOTAL	HBV DNA
Chronic hepatitis							
HBeAg-positive	+	–	+	–	–*	+	$\geq 2 \times 10^4$ IU/mL
HBeAg-negative	+	–	–	+	–*	+	$\geq 2 \times 10^3$ IU/mL
Inactive carrier	+	–	–	+	–	+	$< 2 \times 10^3$ IU/mL
Reactivation	+	–	+/–	+/–	+/–	+	$\geq 2 \times 10^3$ IU/mL

*Anti-HBc IgM can be detected at low titers.
Ab = antibodies; Ag = antigen; HBc = hepatitis B core; HBe = hepatitis B e; HBs = hepatitis B surface; HBV = hepatitis B virus; IgM = immunoglobulin M.

right quadrant pain are often observed. Chronic hepatitis B is characterized biologically by elevated aminotransferase levels, and ALT levels can fluctuate substantially during the immune elimination phase. Moderate cholestasis, with mildly elevated alkaline phosphatase and γ-glutamyl transpeptidase levels, also can be present, especially in patients with cirrhosis.

HBeAg-negative chronic hepatitis B is generally more severe than the HBeAg-positive variety. The incidence of spontaneous HBe seroconversion among HBeAg-positive patients is 8 to 12% per year when they are in the immune elimination phase; HBe seroconversion often follows a transient ALT flare. Some of these patients evolve toward inactive HBsAg carriage, whereas others switch into an HBeAg-negative form of chronic hepatitis B, with elevated ALT levels and an HBV DNA level greater than 2000 IU/mL.

The annual incidence of cirrhosis varies from 2 to 10% in patients with chronic HBV infection, with a cumulative incidence of approximately 20% at 5 years. The risk for cirrhosis is two- to four-fold higher in HBeAg-negative patients compared with HBeAg-positive ones. The annual incidence of hepatocellular carcinoma in patients with chronic hepatitis B varies from 1% in patients without cirrhosis to 2 to 8% in cirrhotic patients, with the higher rates occurring in older patients. Patients with cirrhosis (Chapter 139), hepatocellular carcinoma (Chapter 181), or both have the typical signs associated with these conditions. Rarely, chronic HBV infection is associated with extrahepatic manifestations, including glomerulonephritis (Chapter 107), most often in children, and polyarteritis nodosa (Chapter 249), mostly in adults.

DIAGNOSIS

Serologic markers used to diagnose chronic hepatitis B (Table 135-2) include HBsAg, anti-HBs antibodies, total anti–hepatitis B core (HBc) antibodies and anti-HBc immunoglobulin M (IgM), HBeAg, and anti-HBe antibodies. Molecular markers include HBV DNA; real-time polymerase chain reaction (PCR)–based or transcription-mediated amplification (TMA)–based assays are the best way to detect and quantify HBV DNA.[3]

Chronic HBV infection is defined by the persistence of HBsAg in the serum for more than 6 months after the acute episode. The majority of subjects with isolated anti-HBc antibodies are not viremic. However, some individuals who test positive for anti-HBc antibodies, but not for HBsAg or anti-HBs antibodies, may be viremic; in these cases, some viruses' amino acid substitutions in the HBsAg sequence make HBsAg undetectable with current enzyme immunoassays. Other individuals may have such low-level HBV replication in their livers that HBV DNA is not detectable in blood ("occult" hepatitis B). Screening is recommended periodically in high-risk individuals and once (together with HCV and HIV testing) in all adults.[A1]

Serum or plasma ALT and HBV DNA levels are important markers of severity and prognosis. The assessment of severity, including the grade of necroinflammation and the stage of fibrosis, has traditionally been based on the liver biopsy (Fig. 135-1), but serologic markers, transient elastography, or acoustic radiation force impulse imaging have replaced liver biopsy in the pretreatment assessment of the severity of chronic hepatitis B in most patients.

PREVENTION AND TREATMENT

Patients with chronic hepatitis B should be vaccinated against hepatitis A virus, abstain from alcohol, and avoid immunosuppressive therapies unless absolutely necessary. HBV-infected patients who require corticosteroids, rituximab, or other chemotherapy for other conditions should receive entecavir 0.5 mg/day, tenofovir disoproxil fumarate 245 mg/day, or tenofovir alafenamide 25 mg/day during therapy and for 12 months after its cessation as prophylaxis against reactivation of hepatitis B.

The goals of chronic hepatitis B therapy are to suppress HBV replication, reduce the histologic activity of chronic hepatitis, and lessen the risk for cirrhosis and hepatocellular carcinoma.[4,5] HBV infection cannot be completely eradicated because of the persistence of covalently closed circular DNA (cccDNA) in the nucleus of infected hepatocytes. As a result, therapy attempts to reduce HBV DNA levels as much as possible—ideally, below the limit of detection of real-time PCR or TMA assays (10 to 15 IU/mL)—to ensure a degree of viral suppression that will lead to biochemical remission, histologic improvement, and prevention of complications.

Two different types of drugs for the treatment of chronic hepatitis B are pegylated interferon-α (IFN-α) and nucleoside/nucleotide analogues. Pegylated IFN-α2a, administered subcutaneously at a dose of 180 μg/week for 48 weeks, improves various markers of HBV infection in both HBeAg-positive (Table 135-3) and HBeAg-negative (Table 135-4) patients. The most frequent side effects of IFN-α are flulike symptoms after the injections, fatigue, anorexia, weight loss, and alopecia. The most concerning side effects are neutropenia, thrombocytopenia, anxiety, irritability, depression, and suicidal ideation.

Nucleoside analogues (e.g., entecavir) require triple phosphorylation to be active, whereas nucleotide analogues (e.g., tenofovir) need only two phosphorylations to be active. These drugs are given orally (PO) once daily at the following dosages: 0.5 mg for entecavir, 245 mg for tenofovir administered as the pro-drug tenofovir disoproxil fumarate, or 25 mg for tenofovir administered as the pro-drug tenofovir alafenamide. All have short-term benefits on various markers of HBV infection in HBeAg-positive (see Table 135-3) and HBeAg-negative (see Table 135-4) patients. Entecavir and tenofovir are used because they are the most potent inhibitors of HBV replication,[A2,A3] and they are the least likely to select for resistant HBV variants. These drugs are generally well tolerated. Renal impairment and decreases in mineral bone density are rarely seen with tenofovir disoproxil fumarate; these side effects are not observed with tenofovir alafenamide because the active compound is concentrated in the liver.

Patients should be considered for treatment when their HBV DNA levels are greater than 2000 IU/mL and/or their serum ALT levels are abnormal if noninvasive assessment or liver biopsy shows moderate to severe active necroinflammation, fibrosis, or both. Patients with an HBV DNA level above 20,000 IU/mL and ALT above 2 times the upper limit of normal should be treated regardless of the degree of fibrosis. Indications for treatment must also consider the patient's age and health status, as well as the availability of antiviral agents in individual countries. Patients in the immune tolerant phase and those with mild hepatitis on liver biopsy or noninvasive markers should not be treated, but follow-up ALT levels and HBV DNA assays are mandatory. Patients with compensated cirrhosis and detectable HBV DNA should be treated even if their ALT levels are normal, their HBV DNA levels are below 2000 IU/mL, or both. Patients with decompensated cirrhosis require urgent antiviral treatment.

Two treatment strategies can be considered: a 48-week course of pegylated IFN-α or long-term oral treatment with nucleoside/nucleotide analogues. Their combined use does not seem to improve the rate of sustained virologic response after treatment.

Pegylated IFN-α can provide a sustained virologic response, defined as a sustained HBe seroconversion (clearance of HBeAg, which is replaced by anti-HBe antibodies) and an HBV DNA level that remains below 2000 IU/mL after a 48-week course of treatment; an ALT flare can be observed at the time of HBeAg loss in patients in whom treatment is successful. Pegylated IFN-α treatment can be considered as an initial treatment option in patients with mild to moderate HBeAg-positive or -negative chronic hepatitis B. Practically, it should be reserved for patients with the best chance of a sustained virologic response off treatment—HBeAg-positive patients with high baseline ALT levels (more than three times the upper limit of normal) and HBV DNA levels below 2×10^6 IU/mL. Pegylated IFN-α therapy is contraindicated in patients with advanced cirrhosis and in immunosuppressed patients. Patients infected with HBV genotypes A and B generally respond better to IFN-α therapy than do patients infected with genotypes C and D, but the predictive value of the HBV genotype for an individual patient is weak. Patients who fail to achieve a sustained virologic response after a single course of pegylated IFN-α are candidates for nucleoside/nucleotide analogue therapy.

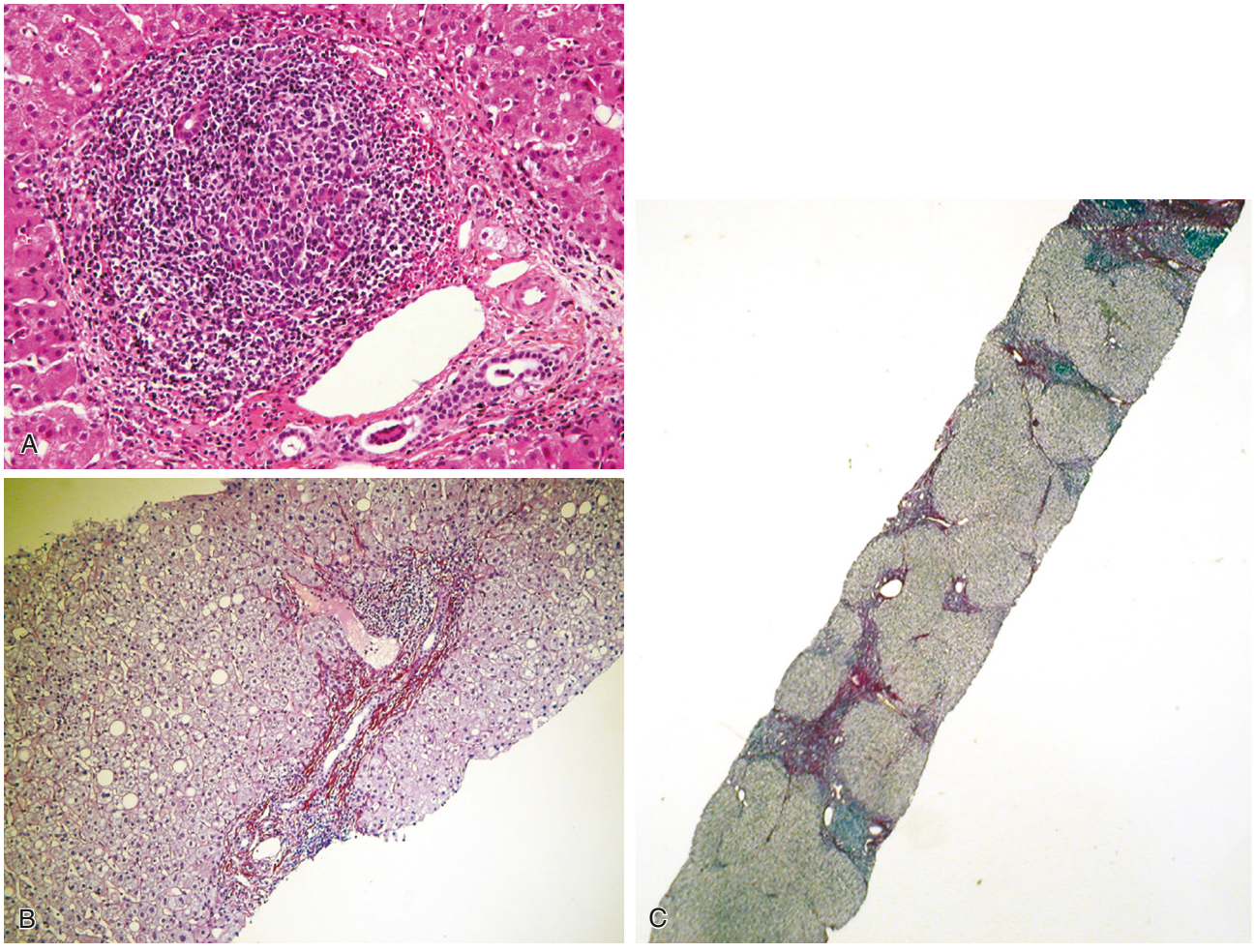

FIGURE 135-1. Liver biopsies in patients with chronic hepatitis C. A, Lymphoid nodule with germinal center; minimal interface hepatitis (hematein-eosin, magnification 200×). **B**, Mild fibrosis, Metavir score F1 (picrosirius-hemalun, magnification 100×). **C**, Extensive fibrosis, Metavir score F3 (picrosirius-hemalun, magnification 20×). (Courtesy Prof. Elie-Serge Zafrani, Department of Pathology, Henri Mondor Hospital, Créteil, France.)

Long-term treatment with nucleoside/nucleotide analogues is indicated in the majority of patients with chronic hepatitis B. Tenofovir (available as tenofovir disoproxil fumarate or liver-targeted tenofovir alafenamide) or entecavir, which are the most potent drugs with an optimal resistance profile, are recommended as first-line monotherapies. Entecavir or tenofovir alafenamide should be selected over tenofovir disoproxil fumarate in patients >60 years old, patients with bone disease (chronic steroid use or use of other medications that worsen bone density, history of fragility fracture, osteoporosis) and patients with renal alteration (eGFR <60 mL/min/1.73 m^2, albuminuria >30 mg/24 hour or moderate dipstick proteinuria, low phosphate <2.5 mg/dL, dialysis). HBV DNA should be suppressed to undetectable levels (<10 to 15 IU/mL) with a sensitive real-time PCR-based or TMA-based assay. If the HBV DNA level is reduced but still detectable in a compliant patient, the other agent may be added; however, the long-term safety of combined tenofovir and entecavir is unknown. When HBeAg-positive patients seroconvert to anti-HBe antibody-positive or HBeAg-negative patients lose their HBsAg (with or without anti-HBs seroconversion), treatment should be continued for at least an additional 12 months. In all other cases, treatment should be continued for life and adherence is particularly important.

Virologic breakthroughs—defined by a subsequent increase of the HBV DNA level of 1 log or more above the nadir level—in patients receiving entecavir or tenofovir are exclusively a result of nonadherence. Virologic breakthrough is generally followed a few weeks later by a biochemical breakthrough in which a previously normal ALT level rises above normal. In a patient who develops resistance to any nucleoside/nucleotide analogue other than entecavir or tenofovir, switching to tenofovir (either tenofovir disoproxil fumarate or tenofovir alafenamide) and possibly adding entecavir are the only efficient strategies, although the long-term safety of the combination of tenofovir and entecavir is not known. In patients with lamivudine, telbivudine, or entecavir resistance, treatment should be switched to tenofovir. Patients who have resistance to adefovir should be switched to tenofovir, and entecavir should be added if HBV DNA plateaus. Patients with multidrug resistance should receive the combination of tenofovir and entecavir. The combination of tenofovir and emtricitabine, a nucleoside analogue similar to lamivudine, in a single tablet (approved for HIV but not for HBV therapy) is also a valid option in cases of resistance to any of these drugs.

In patients with cirrhosis, nucleoside/nucleotide analogue therapy is the only option. In patients with decompensated disease, efficient antiviral treatment with entecavir or tenofovir most often stabilizes the patient's condition and can also delay or obviate the need for liver transplantation. If transplantation is needed, post-transplant administration of anti-HBV immunoglobulins in combination with entecavir or tenofovir prevents recurrent HBV in the vast majority of cases. Patients with a low risk of recurrence can discontinue anti-HBV immunoglobulins but should continue monoprophylaxis with entecavir or tenofovir.

PROGNOSIS

Every year, approximately 0.5% of inactive HBsAg carriers spontaneously lose HBsAg, and most of them acquire anti-HBs antibodies. Reactivations are possible in inactive HBV carriers, especially if they become immunosuppressed, such as when they are treated for other conditions with corticosteroids, rituximab, or other chemotherapeutic agents. HBV reactivations often evolve into a subfulminant or fulminant form.

The risk of cirrhosis (Chapter 139) in chronic hepatitis B is 2 to 10% per year, and it is significantly associated with a higher HBV DNA level, older age, alcohol consumption, coinfection with other hepatotropic viruses, and coinfection with human immunodeficiency virus (HIV). The cumulative incidence of liver decompensation is about 15 to 20% at 5 years in patients with compensated cirrhosis. The complications of cirrhosis, including hepatocellular carcinoma, are among the main causes of mortality in HBV-infected patients, and the annual incidence of death is about 3 to 4%. In patients who are treated with long-term entecavir/tenofovir, however, 8-year survival is now similar to the general population.[6] The likelihood of developing hepatocellular carcinoma (Chapter 181) is approximately 1% per year in patients without cirrhosis and

TABLE 135-3 RESULTS OF MAJOR STUDIES FOR THE TREATMENT OF HBeAg-POSITIVE CHRONIC HEPATITIS B AT 6 MONTHS FOLLOWING 48 OR 52 WEEKS OF PEGYLATED IFN-α (PEGIFN-α) AND AT 48 OR 52 WEEKS OF NUCLEOSIDE/NUCLEOTIDE ANALOGUE THERAPY

		PegIFN-α	*NUCLEOSIDE/NUCLEOTIDE ANALOGUE*		
	PLACEBO/CONTROL GROUPS	***PegIFN-α2a* 180 µg ONCE WEEKLY**	**ENTECAVIR 0.5 mg DAILY**	**TENOFOVIR DISOPROXIL FUMARATE 245 mg DAILY**	**TENOFOVIR ALAFENAMIDE 25 mg DAILY**
HBe seroconversion	4-6%	32%	21%	21%	10%
HBV DNA <60-80 IU/mL	0-17%*	14%	67%	76%	64%‡
ALT normalization†	7-24%	41%	68%	68%	72%
HBsAg loss	0-1%	3%	2%	3%	1%

*HBV DNA levels were assessed with various molecular assays, with different lower limits of detection.
†The definition of ALT normalization varied among different trials.
‡The lower limit of HBV DNA detection/quantification was different across studies (<29 IU/mL for tenofovir alafenamide studies).
Ag = antigen; ALT = alanine aminotransferase; HBe = hepatitis B e; HBs = hepatitis B surface; HBV = hepatitis B virus; IFN = interferon.
Modified from: EASL 2017 clinical practice guidelines on the management of hepatitis B virus infection. *J Hepatol*. 2017;67:370-398.

TABLE 135-4 RESULTS OF MAJOR STUDIES FOR THE TREATMENT OF HBeAg-NEGATIVE CHRONIC HEPATITIS B AT 6 MONTHS FOLLOWING 48 WEEKS OF PEGYLATED IFN-α (PEGIFN-α) AND AT 48 OR 52 WEEKS OF NUCLEOSIDE/NUCLEOTIDE ANALOGUE THERAPY

		PegIFN-α	*NUCLEOSIDE/NUCLEOTIDE ANALOGUE*		
	PLACEBO/CONTROL GROUPS	**PegIFN-α2a 180 µg ONCE WEEKLY**	**ENTECAVIR 0.5 mg DAILY**	**TENOFOVIR DISOPROXIL FUMARATE 245 mg DAILY**	**TENOFOVIR ALAFENAMIDE 25 mg DAILY**
HBV DNA <60-80 IU/mL	0-20%*	19%	90%	93%	94%‡
ALT normalization†	10-29%	59%	78%	76%	83%
HBsAg loss	0%	4%	0%	0%	0%

*HBV DNA levels were assessed with various molecular assays, with different lower limits of detection.
†The definition of ALT normalization varied among different trials.
‡The lower limit of HBV DNA detection/quantification was different across studies (<29 IU/mL for tenofovir alafenamide studies).
Ag = antigen; ALT = alanine aminotransferase; HBe = hepatitis B e; HBs = hepatitis B surface; HBV = hepatitis B virus; IFN = interferon.
Modified from: EASL 2017 clinical practice guidelines on the management of hepatitis B virus infection. *J Hepatol*. 2017;67:370-398.

2 to 8% per year in patients with cirrhosis, and it is significantly associated with a higher HBV DNA level, male sex, old age, a family history of hepatocellular carcinoma, reversion from anti-HBe–positive to HBeAg-positive, and coinfection with other hepatotropic viruses. HBV carriers who have cirrhosis or who are at risk for hepatocellular carcinoma should be screened every 6 to 12 months with an ultrasound examination and an α-fetoprotein level.

Liver histology, including necroinflammation and fibrosis, improves in patients who have chronic hepatitis B, who are on long-term nucleoside/nucleotide analogue therapy, and who maintain low/undetectable HBV DNA levels. In addition, the risks of developing cirrhosis, of decompensation of cirrhosis, and of hepatocellular carcinoma are significantly reduced but not eliminated as compared with untreated patients, especially patients who already have cirrhosis or have a family history of hepatocellular carcinoma.

CHRONIC HEPATITIS C

EPIDEMIOLOGY

HCV, which is present on all continents, is estimated to cause chronic infection in approximately 58 million individuals. The prevalence of chronic HCV infection, which varies geographically, is estimated to be about 0.7% in the United States (affecting 2.4 million individuals), 0.5% in the Americas overall, 1.3% in Europe, 0.5% in Southeast Asia, 0.9% in Africa, and 0.5% in the Western Pacific region. The highest prevalence is in Egypt (9% overall, but up to 40% in certain rural areas), where infection was initially spread by intramuscular injections for schistosomiasis during treatment campaigns several decades ago. Hepatitis C virus still causes more deaths in the United States than does HIV, largely because most cases remain undiagnosed, and it causes approximately 290,000 deaths per year worldwide.

PATHOBIOLOGY

Acute HCV infection evolves into chronic infection in 50 to 80% of cases depending on the age at acquisition (children versus adults, respectively). Even patients who spontaneously recover and maintain detectable anti-HCV antibodies are not protected against reinfection. Persistence of infection is related to a qualitatively and quantitatively altered CD4+ T-helper cell and cytotoxic T lymphocyte response that fails to eradicate infection. The plasticity of the viral genomes is responsible for the coexistence of closely related but genetically different viral populations in equilibrium in the patient's replicative environment. This genetic diversity allows continuously generated variant viral populations to be selected by timely changes in the replicative environment.

Chronic HCV infection is responsible for necroinflammatory lesions of varying severity, sometimes associated with steatosis, which is the accumulation of triglycerides in hepatocytes. HCV is not a cytopathic virus. Liver injury in chronic hepatitis C is related to the action of immune effectors that recognize and kill infected hepatocytes that express HCV antigens at their surface and the local production of various cytokines and chemokines. Chronic inflammation triggers fibrogenesis through the activation of hepatic stellate cells. Fibrosis progresses at nonlinear rates that are generally faster in older patients, in males, and in the presence of chronic alcohol intake, viral coinfections, or immunosuppression. The severity of chronic hepatitis is independent of the HCV RNA level and of the HCV genotype. This chronic inflammation and progression of fibrosis predispose patients to cirrhosis (Chapter 139), which is present in approximately 20% of HCV-infected patients, and hepatocellular carcinoma (Chapter 181), which occurs at an incidence rate of 1 to 5% per year in patients with cirrhosis.

CLINICAL MANIFESTATIONS

Acute hepatitis C (Chapter 134) is most often asymptomatic and therefore undiagnosed. The most common symptom associated with chronic HCV infection is fatigue, but it may remain inapparent for years. ALT levels are usually moderately elevated and fluctuate, but they can remain normal for weeks to months despite active hepatitis on liver biopsy. Moderate cholestasis can be present in patients with cirrhosis. Patients with cirrhosis (Chapter 139),

hepatocellular carcinoma (Chapter 181), or both have the typical signs associated with these conditions.

HCV is the main cause of type II and type III mixed cryoglobulinemia (Chapter 173). Low levels of circulating cryoglobulins, which contain HCV RNA, anti-HCV antibodies, rheumatoid factor, and low levels of complement, can be found in 50 to 70% of cases, whereas elevated rheumatoid factor (Chapter 243) is found in 70% of cases. Fewer than 1% of HCV-infected patients develop symptoms of cryoglobulinemic vasculitis (Chapter 249), including fatigue, myalgias, arthralgias, rash (purpura, hives, leukocytoclastic vasculitis), neuropathy, and membranoproliferative glomerulonephritis.[7] Cryoglobulinemia can be severe and lead to end-stage renal disease or severe neuropathies, and long-term cryoglobulinemia has been linked to non–Hodgkin B-cell lymphomas (Chapter 171).

Low titers of antinuclear and anti–smooth muscle antibodies can be found in HCV-infected patients, but they do not have any clinical significance. HCV has been reported to trigger the symptoms of porphyria cutanea tarda (Chapter 194), and an association with lichen planus (Chapter 405) has been suggested.

DIAGNOSIS

Chronic HCV infection is defined by the persistence of HCV RNA for more than 6 months. Chronic hepatitis C is diagnosed by the simultaneous presence of anti-HCV antibodies and HCV RNA (or HCV core antigen where available). Detectable HCV replication in the absence of anti-HCV antibodies is observed almost exclusively in patients who are profoundly immunosuppressed, on hemodialysis, or agammaglobulinemic.

The strategy for HCV screening varies in different areas according to the local prevalence. In the United States, screening for HCV is recommended once between the ages of 18 and 79 years for everyone. HCV screening is based upon detecting anti-HCV antibodies in a centralized laboratory. However, tests performed at the patient's care site, such as rapid diagnostic tests using fingerstick whole blood or saliva (or fingerstick whole blood sampled on dried blood spots), can improve access to screening and linkage to care. Confirmation of infection is based upon the detection of HCV RNA by a molecular method, or alternatively, HCV core antigen by enzyme immunoassay. Reflex testing (HCV RNA confirmation on the same sample as was used to detect anti-HCV antibody) is recommended to improve linkage-to-care. The level of HCV replication does not correlate with the severity of liver disease or with the risk for progression to cirrhosis or hepatocellular carcinoma.

Determination of the HCV genotype is no longer recommended. Laboratory testing often reveals high levels of monoclonal rheumatoid factor and cryoglobulins.

TREATMENT

Chronic HCV infection is curable by antiviral therapy. The goal of therapy is to achieve a sustained virologic response, defined by undetectable HCV RNA at 12 weeks (possibly 24 weeks) after the end of therapy using a sensitive HCV RNA assay with a lower limit of detection of 10 to 20 IU/mL. Sustained virologic response corresponds to a definitive cure of infection.

All treatment-naïve and previously treated patients with chronic HCV infection should be treated without delay, regardless of the severity of liver disease or extra-hepatic manifestations, except in highly unusual situations in which they have contraindications to available oral anti-HCV drugs. Noninvasive assessment of liver fibrosis prior to therapy is required to identify patients who have advanced fibrosis and cirrhosis and who therefore will need post-treatment follow-up for the possible development of hepatocellular carcinoma. Careful assessment of drug-drug interactions is also required prior to initiating therapy (www.hep-druginteractions.org).

Treatment regimens are based on combinations of orally administered antiviral drugs (Chapter 328) that have pan-genotypic antiviral properties (i.e., are active against all known HCV genotypes and subtypes). These combinations provide a sustained virologic response and cure infection in more than 95% of patients. Current anti-HCV drugs belong to three classes, including nucleotide analogues (sofosbuvir), protease inhibitors (glecaprevir, voxilaprevir), and NS5A inhibitors (daclatasvir, velpatasvir, pibrentasvir). These medications, which are available as standalone drugs (sofosbuvir, daclatasvir) or as one-pill fixed-dose combinations of two or three drugs (sofosbuvir/velpatasvir, glecaprevir/pibrentasvir, sofosbuvir/velpatasvir/voxilaprevir), are safe and well-tolerated, with headache and fatigue as the most frequently reported side effects. Generic formulations of HCV drugs are available in low- and middle-income countries and can be used, provided that quality controls are met and guaranteed by the provider.

Due to their virologic efficacy, ease of use, safety, and tolerability, pan-genotypic combination regimens must be used to treat chronic hepatitis C. Treatment is guided by the presence of compensated or decompensated cirrhosis, and prior exposure to oral anti-HCV drugs. Patients infected with HCV can be treated with one of four regimens[8-10] (Table 135-5): the fixed-dose combination of sofosbuvir and velpatasvir[A4-A6]; the fixed-dose combination of glecaprevir and pibrentasvir[A7-A12]; the fixed-dose triple combination of sofosbuvir, velpatasvir, and voxilaprevir[A13]; and the combination of sofosbuvir with the fixed-dose combination of glecaprevir and pibrentasvir. In settings where these combinations are not available or not affordable, the pan-genotypic combination of sofosbuvir and daclatasvir, often available as generic drugs, can also be used with a high probability of sustained virologic response.

Sofosbuvir/velpatasvir should be administered for 12 weeks in patients with chronic hepatitis C without cirrhosis or with compensated cirrhosis. Glecaprevir/pibrentasvir should be administered for 8 weeks in patients without cirrhosis and in patients with compensated cirrhosis who are treatment-naïve, and for 12 weeks in patients with compensated cirrhosis who failed a previous treatment with pegylated interferon α and/or sofosbuvir plus ribavirin.

For patients who do not have a sustained virologic response after treatment with oral anti-HCV drug regimens, retreatment with the triple combination of sofosbuvir, velpatasvir, and voxilaprevir for 12 weeks provides a high rate of sustained virologic response.[A14] In very difficult-to-cure patients (patients who failed twice or more to achieve a sustained virologic response after a combination regimen including a protease and/or an NS5A inhibitor), the triple combination of sofosbuvir, velpatasvir, and voxilaprevir, or the triple combination of sofosbuvir and glecaprevir/pibrentasvir for 12 weeks with weight-based ribavirin (1000 or 1200mg in patients <75 kg or ≥75 kg, respectively) should be administered, and/or treatment duration can be prolonged to 16 to 24 weeks.

Because the risk of advanced liver disease is significantly increased in patients with other coexisting causes of liver disease, patients with chronic hepatitis C should abstain from alcohol and, unless there are other contraindications, should be vaccinated for hepatitis A and B (Chapter 15).

Patients Coinfected with HIV

Patients with coexisting HIV infection should be considered like non-HIV coinfected patients in terms of treatment indications and virologic response to therapy. The only difference to take into account is potential drug-drug interactions with antiretroviral drugs.[A15,A16]

Patients with Decompensated Cirrhosis or Recurrent HCV after Liver Transplantation

In patients who have decompensated cirrhosis or a history of decompensation, protease inhibitors are contraindicated, so these patients should be treated with the combination of sofosbuvir and velpatasvir plus weight-based ribavirin (1000 mg for patients <75 kg, 1200 mg for patients ≥75 kg). When ribavirin cannot be used because of contraindications (anemia, significant coronary or cerebrovascular disease, or renal insufficiency) or poor tolerance, 24 weeks of treatment without ribavirin is recommended. Because ribavirin is teratogenic, it is essential that adequate contraception be practiced during therapy and for at least 6 months thereafter in both men and women.

For patients who have decompensated cirrhosis with an indication for liver transplantation (Chapter 140), those with a Model for End-Stage Liver Disease (MELD; Table 139-2) score below approximately 20 are likely to benefit from curing HCV prior to transplantation. In patients with more severe liver disease (MELD score >20), transplant followed by treatment of graft reinfection with sofosbuvir and velpatasvir or with glecaprevir and pibrentasvir is recommended.

PROGNOSIS

Spontaneous HCV clearance in patients with chronic hepatitis C is exceptional. The HCV RNA level has no prognostic value in chronic hepatitis C. An estimated 20% of patients with chronic hepatitis C develop cirrhosis (Chapter 139) after an average of 20 years of progression in the absence of therapy. Cirrhosis remains compensated for many years in the vast majority of patients, but decompensation occurs at an annual rate of 2 to 5% in cirrhotic patients. After a first decompensation, the mortality rate related to portal hypertension, hepatocellular insufficiency, and hepatocellular carcinoma is 10% per year, with a 50% survival rate at 5 years. The risk for death increases with advancing age, male gender, and the severity of cirrhosis.

Hepatocellular carcinoma (Chapter 181) is rare in patients with chronic hepatitis C without cirrhosis. In patients with cirrhosis, the incidence of hepatocellular carcinoma is 2 to 4% per year, most often in patients with compensated cirrhosis. HCV has become the most common cause of hepatocellular carcinoma in most industrialized countries.

After successful anti-HCV therapy, the risk of hepatocellular carcinoma is eliminated for patients who do not have cirrhosis or other causes of liver disease. The risk is considerably reduced but not eliminated in patients with cirrhosis, especially in the presence of other causes of liver disease. Late relapses in patients who have achieved a sustained virologic response are most often reinfections in individuals with high-risk practices.

CHRONIC HEPATITIS D

EPIDEMIOLOGY

HDV infection occurs only in HBsAg carriers. Only approximately 2% of patients acutely coinfected with HDV and HBV develop chronic hepatitis D. In chronic HBV carriers superinfected by HDV, however, 90% of patients become chronic HDV carriers. Overall, 4.5% of chronic HBsAg carriers, or about 12 million individuals, are chronically infected with HDV.

CLINICAL MANIFESTATIONS

Chronic hepatitis D is generally severe, with more than 80% of patients developing cirrhosis. Compared with patients who have chronic hepatitis B alone, patients with chronic infection with both HBV and HDV are three times as likely to develop hepatocellular carcinoma and twice as likely to die.

DIAGNOSIS

Markers of HDV infection should be sought at least once in every chronic HBsAg carrier. Total anti-HD antibodies remain at high levels in chronic HDV infection, and HDV RNA is present. Although all chronic HDV carriers also are chronic HBsAg carriers, chronic HDV carriers generally have low or undetectable HBV DNA levels because HDV inhibits HBV replication.

PREVENTION

Chronic HDV infection is best prevented by HBV vaccination, because individuals who are protected against HBV cannot be infected with HDV. In chronic HBsAg carriers, standard hygiene and behavioral precautions should be practiced to avoid superinfection with HDV. Once acute HDV infection occurs, no secondary prevention strategy is successful.

TREATMENT

Pegylated IFN-α2a (180 μg once weekly) for 48 weeks can provide a virologic response rate that is approximately 50% on treatment,[11] but only about 25% of patients have undetectable HDV RNA 24 weeks after the end of treatment. Longer treatment duration may increase the virologic response rates.

Bulevirtide, an HDV entry inhibitor (2 mg once daily by subcutaneous injection as monotherapy or coadministered with a nucleoside or a nucleotide analogue for treatment of underlying HBV infection),[A17] also suppresses HDV. The optimal treatment duration is unknown, and treatment should be continued as long as associated with clinical benefit. Whether HDV-infected patients might benefit from the combination of bulevirtide and pegylated IFN-α2a remains to be determined.

TABLE 135-5 ANTIVIRAL REGIMENS FOR CHRONIC HEPATITIS C INFECTION

TREATED POPULATION	CIRRHOSIS STATUS	PRIOR TREATMENT EXPERIENCE	*SOFOSBUVIR/ VELPATASVIR* — *ONE TABLET CONTAINING 400 mg OF SOFOSBUVIR AND 100 mg OF VELPATASVIR ONCE DAILY*	*GLECAPREVIR/ PIBRENTASVIR* — *THREE TABLETS CONTAINING 100 mg OF GLECAPREVIR AND 40 mg OF PIBRENTASVIR ONCE DAILY WITH FOOD*	*SOFOSBUVIR/ VELPATASVIR/ VOXILAPREVIR* — *ONE TABLET CONTAINING 400 mg OF SOFOSBUVIR, 100 mg OF VELPATASVIR AND 100 mg OF VOXILAPREVIR ONCE DAILY*	*SOFOSBUVIR +GLECAPREVIR/ PIBRENTASVIR* — *ONE TABLET CONTAINING 400 mg OF SOFOSBUVIR PLUS THREE TABLETS CONTAINING 100 mg OF GLECAPREVIR AND 40 mg OF PIBRENTASVIR ONCE DAILY WITH FOOD*	*SOFOSBUVIR + DACLATASVIR** — *ONE TABLET CONTAINING 400 mg OF SOFOSBUVIR PLUS ONE TABLET CONTAINING 60 mg OF DACLATASVIR ONCE DAILY*
Treatment-naïve or treatment-experienced (pegylated interferon-alpha and/ or sofosbuvir plus ribavirin)	No cirrhosis	Treatment-naïve	12 weeks	8 weeks	No	No	12 weeks
		Treatment-experienced	12 weeks	8 weeks	No	No	12 weeks
	Compensated cirrhosis	Treatment-naïve	12 weeks	8 weeks	No	No	12 weeks
		Treatment-experienced	12 weeks	12 weeks	No	No	12 weeks
Failure to achieve a sustained virologic response after oral direct-acting antiviral drug treatment	No cirrhosis	First failure of oral direct-acting antiviral drugs	No	No	12 weeks	No	24 weeks with ribavirin†
		Very difficult-to-cure patients (patients who failed twice or more to achieve a sustained virologic response after a combination regimen including a protease and/ or an NS5A inhibitor)	No	No	12, 16, or 24 weeks ± ribavirin†	12, 16, or 24 weeks ± ribavirin†	24 weeks with ribavirin†
	Compensated cirrhosis	First failure of oral direct acting antiviral drugs	No	No	12 weeks	No	24 weeks with ribavirin†
		Very difficult-to-cure patients (patients who failed twice or more to achieve a sustained virologic response after a combination regimen including a protease and/ or an NS5A inhibitor)	No	No	12, 16, or 24 weeks ± ribavirin†	12, 16, or 24 weeks ± ribavirin†	24 weeks with ribavirin†

TABLE 135-5 ANTIVIRAL REGIMENS FOR CHRONIC HEPATITIS C INFECTION—cont'd

TREATED POPULATION	CIRRHOSIS STATUS	PRIOR TREATMENT EXPERIENCE	*SOFOSBUVIR/ VELPATASVIR* — *ONE TABLET CONTAINING 400 mg OF SOFOSBUVIR AND 100 mg OF VELPATASVIR ONCE DAILY*	*GLECAPREVIR/ PIBRENTASVIR* — *THREE TABLETS CONTAINING 100 mg OF GLECAPREVIR AND 40 mg OF PIBRENTASVIR ONCE DAILY WITH FOOD*	*SOFOSBUVIR/ VELPATASVIR/ VOXILAPREVIR* — *ONE TABLET CONTAINING 400 mg OF SOFOSBUVIR, 100 mg OF VELPATASVIR AND 100 mg OF VOXILAPREVIR ONCE DAILY*	*SOFOSBUVIR +GLECAPREVIR/ PIBRENTASVIR* — *ONE TABLET CONTAINING 400 mg OF SOFOSBUVIR PLUS THREE TABLETS CONTAINING 100 mg OF GLECAPREVIR AND 40 mg OF PIBRENTASVIR ONCE DAILY WITH FOOD*	*SOFOSBUVIR + DACLATASVIR** — *ONE TABLET CONTAINING 400 mg OF SOFOSBUVIR PLUS ONE TABLET CONTAINING 60 mg OF DACLATASVIR ONCE DAILY*
Decompensated cirrhosis	Decompensated cirrhosis	Treatment-naïve	12 weeks with ribavirin† or 24 weeks if ribavirin contraindications	No	No	No	12 weeks with ribavirin† or 24 weeks if ribavirin contraindications
		Treatment-experienced (any treatment received)	12 weeks with ribavirin† or 24 weeks if ribavirin contraindications	No	No	No	12 weeks with ribavirin† or 24 weeks if ribavirin contraindications
Recurrent hepatitis C after liver transplant	No cirrhosis	Treatment-naïve	12 weeks	12 weeks	No	No	12 weeks
		Pretransplant treatment-experienced	12 weeks	12 weeks	No	No	12 weeks
	Compensated cirrhosis	Treatment-naïve	12 weeks	12 weeks	No	No	12 weeks
		Pretransplant treatment-experienced (any treatment received	12 weeks	12 weeks	No	No	12 weeks
	Decompensated cirrhosis	Treatment-naïve	12 weeks with ribavirin† or 24 weeks if ribavirin contraindications	No	No	No	12 weeks with ribavirin† or 24 weeks if ribavirin contraindications
		Pretransplant treatment-experienced (any treatment received)	12 weeks with ribavirin† or 24 weeks if ribavirin contraindications	No	No	No	12 weeks with ribavirin† or 24 weeks if ribavirin contraindications

*In settings where the other combinations are not available or not affordable, where they are often available as generic drugs.
†Ribavirin should be administered at the dose of 1000 or 1200 mg in patients <75 kg or ≥75 kg, respectively.

CHRONIC HEPATITIS E

HEV infection is usually an acute self-limiting disease, but in developed countries it causes chronic infection with rapidly progressive cirrhosis in organ transplant recipients, patients with hematologic malignancies that require chemotherapy, and immunosuppressed HIV-infected individuals, either from a latent virus reactivated by immunosuppression or from a virus transmitted at the time of transplantation. Almost all cases of chronic infection have been in immunosuppressed patients. About one in 3000 blood donors in England are HEV-RNA–positive, even though they are usually seronegative despite their viremia, and can transmit the infection to more than 40% of the recipients of their blood products.

CLINICAL MANIFESTATIONS AND DIAGNOSIS

Diagnosis of acute hepatitis E is based on the detection of anti-HEV IgM antibodies. HEV RNA also can be detected in blood or feces, where its presence is transient. Immunosuppressed patients, such as solid organ transplant recipients, with chronic hepatitis E harbor repeatedly positive anti-HEV antibodies and HEV RNA in blood.

TREATMENT AND PREVENTION

There is no validated treatment of chronic HEV infection.[12] In the transplant setting, reduction in the levels of immunosuppression lead to viral clearance in 30% of cases. Ribavirin (600 mg/day) is associated with about an 80% sustained virologic response rate and is considered first-line treatment.[13] Pegylated interferon-α also can be effective. Reducing the level of immunosuppression can result in viral clearance in approximately one third of patients. A vaccine to prevent HEV infection has been developed and is licensed in China but is not yet available elsewhere.

AUTOIMMUNE HEPATITIS

Autoimmune hepatitis is a chronic inflammatory liver disorder characterized by the presence of autoantibodies in serum, high levels of serum immunoglobulins, and a frequent association with other autoimmune diseases.

EPIDEMIOLOGY AND PATHOBIOLOGY

Autoimmune hepatitis typically manifests between the ages of 15 and 25 years or between the ages of 45 and 60 years, and it is more common in women. The incidence rate is approximately 1.7 per 100,000 population per year. Along with primary biliary cirrhosis (Chapter 141) and primary sclerosing cholangitis (Chapter 141), autoimmune hepatitis is one of the three major autoimmune liver diseases.

Autoimmune hepatitis is believed to be caused by autoimmune reactions against normal hepatocytes in genetically predisposed persons or persons exposed to unidentified triggers of an autoimmune process against liver antigens. Associations are seen with the human leukocyte antigen (HLA) class I B8 and class II DR3 and DRS2a loci. In Asians, autoimmune hepatitis is associated with HLA DR4.

CLINICAL MANIFESTATIONS AND DIAGNOSIS

Autoimmune hepatitis tends to be more severe at its onset than chronic hepatitis B or C, and it progresses to end-stage liver disease if not treated with immunosuppression.[14] Although it is occasionally detected by elevated serum aminotransferase levels on a routine health evaluation, most patients present with fatigue and jaundice.[15] Elevations of bilirubin or alkaline phosphatase indicate more severe or advanced disease. Patients typically have marked elevations in serum γ-globulin, specifically immunoglobulin G, as well as autoantibodies directed at non–organ-specific cellular constituents.

Type 1 autoimmune hepatitis (approximately 90% of cases) is characterized by titers of 1:80 or higher (>1:20 in children) of antinuclear, anti–smooth muscle, anti-actin, and/or anti–soluble liver antigen/liver pancreas antibodies. Type 2 autoimmune hepatitis is characterized by similar elevations of anti–liver-kidney microsomal 1 antibodies and/or anti–liver cytosol 1 antibodies, without antinuclear or anti–smooth muscle antibodies. However, auto-antibodies are not detected in 20 to 35% of cases.

Liver biopsy shows features that are typical of all chronic types of hepatitis, except plasma cell infiltrates. Noninvasive physical markers, such as transient elastography, magnetic resonance elastography, or acoustic radiation force impulse imaging, correlate strongly with the histologic stage of fibrosis, but their accuracy may be impaired by inflammation at the time of diagnosis and during the first months of treatment.

The differential diagnosis of autoimmune hepatitis includes drug-induced liver injury (Chapter 136). Sustained biochemical resolution after glucocorticoid withdrawal reinforces the diagnosis of a self-limited drug-induced liver injury, whereas recrudescence of laboratory abnormalities is consistent with autoimmune hepatitis.

TREATMENT

The clinical symptoms and liver test abnormalities of autoimmune hepatitis generally respond promptly to prednisone.[16,17] Induction therapy should be based on 0.5 to 1.0 mg/kg/day prednisone or prednisolone. If the initial response is good, azathioprine should be added gradually, up to 1.0 to 2.0 mg/kg/day, starting 2 weeks after steroid initiation, while the steroid dose is gradually tapered.[18] In patients without cirrhosis and or acute severe autoimmune hepatitis, budesonide (3 mg three times daily, reduced to twice daily following remission), can be used instead of prednisone/prednisolone in combination with azathioprine. The dose of immunosuppression should be individualized to achieve and maintain normal ALT and immunoglobulin G levels.

In cases of treatment failure, incomplete response, or intolerance to first-line agents, either mycofenolate mofetil (20 mg/kg/day initially, increased to a maximum of 3 g/day) or tacrolimus (1 to 8 mg/day) chronically can achieve and maintain biochemical remission.[19] Infliximab or rituximab are possible alternative therapies after first-line and second-line regimens have failed. After 3 years or more of remission, therapy can be carefully withdrawn, but severe and even fatal flares can occur weeks to months later.

PROGNOSIS

The prognosis is generally related to the histologic stage of the disease. Patients who initially respond to therapy may do well for many years. Patients who progress to end-stage liver disease require liver transplantation (Chapter 140).[20]

CRYPTOGENIC CHRONIC LIVER DISEASE

Cryptogenic chronic liver disease refers to chronic hepatitis or cirrhosis of unknown cause after excluding hepatitis B, C, D, and E; autoimmune hepatitis; steatohepatitis (Chapter 138); alcoholic liver disease (Chapter 138); drug-induced hepatitis (Chapter 136); and inherited and metabolic liver diseases (Chapter 132). Tests to exclude these conditions include serum levels of α_1-antitrypsin, iron, and ceruloplasmin and, if necessary, urine and liver copper concentrations. In its later stages, nonalcoholic steatohepatitis may be associated with little or no fat.

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For the General References and other additional features, please visit Elsevier eBooks+ at https://ebooks.health.elsevier.com.

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136 DRUG-INDUCED LIVER INJURY

PAUL B. WATKINS

DEFINITION

Drug-induced liver injury can be caused by drugs or by druglike substances, including herbal products. Because some drugs can cause minor abnormalities of liver chemistries that are of no health concern, drug-induced liver injury is defined in terms of threshold values for liver chemistries (Table 136-1).[1] The clinical presentation of drug-induced liver injury can be predominantly hepatocellular, cholestatic, or a mixture of each, as defined by the ratio of the serum alanine aminotransferase (ALT) level to the alkaline phosphatase level. A hepatocellular presentation primarily reflects death of hepatocytes with release of their contents, including ALT and aspartate aminotransferase (AST), into circulation, whereas a cholestatic presentation reflects injury to the bile ductular epithelium (cholangiocytes) or to processes that selectively affect the liver's ability to make and secrete bile. A mixed injury reflects a combination of these processes. Since no tests can definitively confirm most cases, the diagnosis is often one of exclusion.[2]

EPIDEMIOLOGY

Drug-induced liver injury is a rare event considering the very large number of different drugs used by patients. Estimated rates are fewer than 20 drug-induced liver injuries per 100,000 person-years in Western countries[3] but higher in mainland China. However, due to challenges in diagnosing drug-induced liver injury and incomplete reporting, the true incidence may be 10 times higher. Antimicrobial agents are the major class of implicated drugs in Western countries, whereas herbal medications are the most frequently reported cause in Asian countries.

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CLINICAL MANIFESTATIONS AND DIAGNOSIS

Autoimmune hepatitis tends to be more severe at its onset than chronic hepatitis B or C, and it progresses to end-stage liver disease if not treated with immunosuppression.[14] Although it is occasionally detected by elevated serum aminotransferase levels on a routine health evaluation, most patients present with fatigue and jaundice.[15] Elevations of bilirubin or alkaline phosphatase indicate more severe or advanced disease. Patients typically have marked elevations in serum γ-globulin, specifically immunoglobulin G, as well as autoantibodies directed at non–organ-specific cellular constituents.

Type 1 autoimmune hepatitis (approximately 90% of cases) is characterized by titers of 1:80 or higher (>1:20 in children) of antinuclear, anti–smooth muscle, anti-actin, and/or anti–soluble liver antigen/liver pancreas antibodies. Type 2 autoimmune hepatitis is characterized by similar elevations of anti–liver-kidney microsomal 1 antibodies and/or anti–liver cytosol 1 antibodies, without antinuclear or anti–smooth muscle antibodies. However, auto-antibodies are not detected in 20 to 35% of cases.

Liver biopsy shows features that are typical of all chronic types of hepatitis, except plasma cell infiltrates. Noninvasive physical markers, such as transient elastography, magnetic resonance elastography, or acoustic radiation force impulse imaging, correlate strongly with the histologic stage of fibrosis, but their accuracy may be impaired by inflammation at the time of diagnosis and during the first months of treatment.

The differential diagnosis of autoimmune hepatitis includes drug-induced liver injury (Chapter 136). Sustained biochemical resolution after glucocorticoid withdrawal reinforces the diagnosis of a self-limited drug-induced liver injury, whereas recrudescence of laboratory abnormalities is consistent with autoimmune hepatitis.

TREATMENT

The clinical symptoms and liver test abnormalities of autoimmune hepatitis generally respond promptly to prednisone.[16,17] Induction therapy should be based on 0.5 to 1.0 mg/kg/day prednisone or prednisolone. If the initial response is good, azathioprine should be added gradually, up to 1.0 to 2.0 mg/kg/day, starting 2 weeks after steroid initiation, while the steroid dose is gradually tapered.[18] In patients without cirrhosis and or acute severe autoimmune hepatitis, budesonide (3 mg three times daily, reduced to twice daily following remission), can be used instead of prednisone/prednisolone in combination with azathioprine. The dose of immunosuppression should be individualized to achieve and maintain normal ALT and immunoglobulin G levels.

In cases of treatment failure, incomplete response, or intolerance to first-line agents, either mycofenolate mofetil (20 mg/kg/day initially, increased to a maximum of 3 g/day) or tacrolimus (1 to 8 mg/day) chronically can achieve and maintain biochemical remission.[19] Infliximab or rituximab are possible alternative therapies after first-line and second-line regimens have failed. After 3 years or more of remission, therapy can be carefully withdrawn, but severe and even fatal flares can occur weeks to months later.

PROGNOSIS

The prognosis is generally related to the histologic stage of the disease. Patients who initially respond to therapy may do well for many years. Patients who progress to end-stage liver disease require liver transplantation (Chapter 140).[20]

CRYPTOGENIC CHRONIC LIVER DISEASE

Cryptogenic chronic liver disease refers to chronic hepatitis or cirrhosis of unknown cause after excluding hepatitis B, C, D, and E; autoimmune hepatitis; steatohepatitis (Chapter 138); alcoholic liver disease (Chapter 138); drug-induced hepatitis (Chapter 136); and inherited and metabolic liver diseases (Chapter 132). Tests to exclude these conditions include serum levels of α_1-antitrypsin, iron, and ceruloplasmin and, if necessary, urine and liver copper concentrations. In its later stages, nonalcoholic steatohepatitis may be associated with little or no fat.

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136 DRUG-INDUCED LIVER INJURY

PAUL B. WATKINS

DEFINITION

Drug-induced liver injury can be caused by drugs or by druglike substances, including herbal products. Because some drugs can cause minor abnormalities of liver chemistries that are of no health concern, drug-induced liver injury is defined in terms of threshold values for liver chemistries (Table 136-1).[1] The clinical presentation of drug-induced liver injury can be predominantly hepatocellular, cholestatic, or a mixture of each, as defined by the ratio of the serum alanine aminotransferase (ALT) level to the alkaline phosphatase level. A hepatocellular presentation primarily reflects death of hepatocytes with release of their contents, including ALT and aspartate aminotransferase (AST), into circulation, whereas a cholestatic presentation reflects injury to the bile ductular epithelium (cholangiocytes) or to processes that selectively affect the liver's ability to make and secrete bile. A mixed injury reflects a combination of these processes. Since no tests can definitively confirm most cases, the diagnosis is often one of exclusion.[2]

EPIDEMIOLOGY

Drug-induced liver injury is a rare event considering the very large number of different drugs used by patients. Estimated rates are fewer than 20 drug-induced liver injuries per 100,000 person-years in Western countries[3] but higher in mainland China. However, due to challenges in diagnosing drug-induced liver injury and incomplete reporting, the true incidence may be 10 times higher. Antimicrobial agents are the major class of implicated drugs in Western countries, whereas herbal medications are the most frequently reported cause in Asian countries.

ABSTRACT

Drug-induced liver injury can be caused by most medications in current clinical use. Drugs that cause liver injury can be divided into three categories: direct/intrinsic toxins, which cause liver injury that is clearly dose-related and generally occurs within days of dosing; idiosyncratic toxins, for which the relationship between the dose and liver injury is not evident and injury typically occurs suddenly after weeks to months of chronic treatment; and indirect toxicity, in which liver injury occurs as a side effect of the drug's desired therapeutic actions (typically immune suppressants that activate viral hepatitis or immune checkpoint inhibitors that result in a liver-directed T-cell response). Acetaminophen (paracetamol) is the most important cause of direct/intrinsic liver injury, not only because it is a frequent cause of liver failure but also because an antidote (N-acetyl cysteine) is effective if given soon after ingestion of an overdose. Idiosyncratic drug-induced liver injury generally reflects an adaptive immune attack on the liver. Oftentimes it is challenging to establish the diagnosis of idiosyncratic drug-induced liver injury and to identify the culprit drug in patients who are receiving multiple medications, but many drugs have characteristic clinical presentations that can be helpful for assessing causality. Aside from stopping treatment with the offending drug, treatment of idiosyncratic drug-induced liver injury is generally supportive, with liver transplantation considered in cases of liver failure. Indirect drug-induced liver injury is treated by reducing or discontinuing treatment with the culprit drug, plus antiviral treatment if indicated.

KEYWORDS

drug-induced
liver
injury
DILI
idiosyncrasy
HLA
genetics

In U.S. tertiary medical centers, about 10% of cases of severe acute hepatitis may be caused by drug-induced liver injury. Acetaminophen is the dominant cause of acute and fatal drug-induced liver injury. About 10 to 15% of cases are related to dietary and herbal supplements.

PATHOBIOLOGY

The liver is particularly susceptible to drug-induced injury because it sees the highest concentration of drugs after oral administration and because it is the major site for the metabolism of drugs, thereby resulting in a high concentration of potentially toxic drug metabolites. Drugs that cause liver injury can be divided into three categories: direct/intrinsic toxins, which cause liver injury that is clearly dose-related and generally occurs within days of dosing; idiosyncratic toxins, for which the relationship between the dose and liver injury is complex, and liver injury typically occurs suddenly after weeks to months of chronic treatment; and indirect toxicity, in which liver injury occurs as a side effect of the drug's desired therapeutic actions (typically immune suppressants that activate viral hepatitis or immune checkpoint inhibitors that result in a liver-directed T-cell response) (Table 136-2).[4] Acetaminophen (paracetamol) is the most important direct/intrinsic drug that causes liver injury, not only because it is a frequent cause of liver failure but also because an antidote (N-acetyl cysteine) is effective if given soon after ingestion of an overdose. Idiosyncratic drug-induced liver injury generally reflects an adaptive immune attack on the liver.

If drugs are not directly excreted as unchanged in the urine, the liver is the major site where they are metabolized. Most drugs are lipophilic and are transformed in the liver from nonpolar compounds into more hydrophilic metabolites via oxidative pathways mediated by the cytochromes P-450 (CYPs), often followed by conjugation to polar ligands so they can be excreted in the urine or bile. Other important metabolic pathways for some drugs may include acetylating enzymes, glutathione-*S*-transferase, and alcohol dehydrogenase.

TABLE 136-1 INTERNATIONAL CONSENSUS CRITERIA FOR DRUG-INDUCED LIVERY INJURY

A. Drug-induced liver injury is defined by any of the following peak serum values (assuming a healthy liver prior to the event):
- Serum alanine aminotransferase level 5 or more times the upper limit of normal
- Serum alkaline phosphatase level 2 or more times the upper limit of normal in the absence of bone pathology
- Serum alanine aminotransferase level 3 or more times the upper limit of normal and total serum bilirubin level 2 or more times the upper limit of normal in the absence of hemolysis or Gilbert syndrome

B. The clinical pattern of drug-induced liver injury is defined by the R-value, which is calculated as the alanine aminotransferase : alkaline phosphatase ratio, where each is expressed in terms of the upper limit of normal when the patient first meets the criteria for drug-induced liver injury:
- Hepatocellular drug injury if R ≥ 5.0
- Mixed drug injury if R > 2.0 to < 5.0
- Cholestatic drug injury if R ≤ 2.0

Drug-Induced liver Injury (DILI): Current status and future directions for drug development and post-market settings. A consensus by a CIOMS Working Group 2020. Council for International Organizations of Medical Sciences; 2020. Available at https://cioms.ch/publications/product/drug-induced-liver-injury/.

DIRECT/INTRINSIC HEPATOTOXICITY

PATHOBIOLOGY

In cases of direct/intrinsic hepatotoxicity, the parent drug or, more usually, a toxic (or "reactive") metabolite formed by the metabolism of the parent drug, directly causes injury and death to liver cells. Virtually every user will develop this liver toxicity if they receive a high enough dose, but the threshold dose that causes toxicity can vary substantially among individuals.

Acetaminophen

The most important drug that causes direct hepatotoxicity is acetaminophen (also called paracetamol), which accounts for over 50% of cases of acute liver failure in the United States, Europe, and Australia. After a person consumes a therapeutic dose of acetaminophen, the majority of the drug undergoes glucuronidation or sulfation, thereby resulting in harmless metabolites that are rapidly excreted in urine (E-Fig. 136-1). Less than 10% of acetaminophen is normally converted to the potentially toxic metabolite, N-acetyl-p-benzoquinone imine (NAPQI). Therapeutic doses of acetaminophen are generally safe because NAPQI is rapidly detoxified through conjugation to glutathione. However, when a healthy person consumes a very large dose of acetaminophen (typically more than 12 grams as a single dose), the sulfation pathway can become saturated, thereby resulting in a greater fraction of this larger dose being converted to NAPQI. The excess NAPQI results in an increase in covalent binding to cellular proteins, particularly in mitochondria. This protein binding activates a subsequent series of signaling pathways that involve c-Jun N terminal kinase and can lead to the death of hepatocytes. The time taken to activate these pathways presumably accounts for the typical 24-hour latency between consumption of a toxic dose of acetaminophen and onset of elevated liver chemistries. Patient-specific factors that can significantly reduce the dose threshold for acetaminophen toxicity include poor nutrition and fasting (which can deplete the substrate for glucuronidation), as well as excessive ethanol intake (which can induce CYP2E1; see E-Fig. 136-1). Patients with cirrhosis (Chapter 139) may also be more susceptible, thereby leading to the current recommendation not to exceed 2 g in 24 hours in this population.

Other Direct Liver Toxins

Other drugs that cause liver toxicity by direct mechanisms include cocaine, aspirin, nicotinic acid, many anticancer drugs, and pyrrolizidine alkaloids that are contained in some plant products (Table 136-3). For *Amanita* poisoning (Chapter 96) after ingestion of the mushrooms *Amanita phalloides* (death cap) or *Amanita virosa* (deadly agaric), the dose-dependent toxic effect on the liver is attributed to amatoxin, an ingredient of the mushrooms that enhances the toxic effect by its enterohepatic recirculation characteristics; the toxic effect is exerted on each cycle of the recirculation through the liver.[5]

Statin drugs (Chapter 190) can cause dose-dependent, asymptomatic elevations in serum ALT in 1 to 4% of treated individuals, but clinically significant liver injury is quite rare, and progression to liver failure is almost unheard of. Hence, no patient should be denied statin treatment over liver safety concerns.

CLINICAL MANIFESTATIONS

Acetaminophen

After a single and usually intentional overdose of acetaminophen, the clinical presentation has four potential stages (E-Fig. 136-2).[6] The first stage includes up to 24 hours after the ingestion, during which symptoms may include nausea, vomiting, and abdominal discomfort. The second stage, which marks the

TABLE 136-2 TYPICAL FEATURES OF DRUG-INDUCED LIVER INJURY

	DIRECT/INTRINSIC	IDIOSYNCRATIC	INDIRECT
Implicated drugs	Acetaminophen is major cause (see Table 136-3)	Many drugs, especially antibiotics and herbal products (see Table 136-4)	Immune modulators, including checkpoint inhibitors
Dose-related	Yes	Less likely at doses <50 mg/day	No
Latency	1 to several days	1-3 months	1-6 months
Genetic predisposition	Variants in phase 1 or phase 2 metabolism	HLA risk alleles	Unknown
Pathogenesis	Reactive metabolites	Adaptive immune attack on the liver	Viral cytolysis or an adaptive immune attack on the liver
Pathophysiology	Reactive metabolites damage organelles and initiate death-signaling pathways	Cytotoxic T cells kill liver cells	Activation of viral infection or reduced immune tolerance
Pathology	Pericentral necrosis with little inflammation	Panacinar inflammation and cell death	Variable

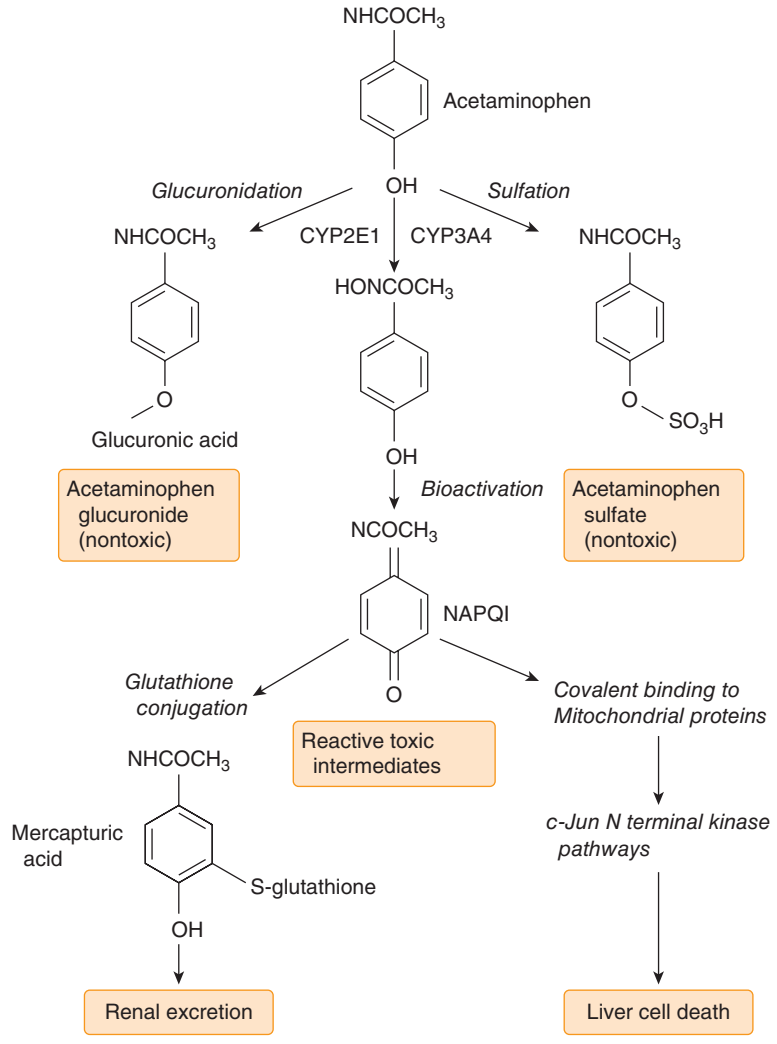

E-FIGURE 136-1. Liver metabolism of acetaminophen. After a therapeutic dose in a healthy adult, liver injury does not occur because there is sufficient glutathione present to inactivate N-acetyl-p-benzoquinone imine (NAPQI). However, after an overdose of acetaminophen, the production of NAPQI may exhaust glutathione supplies, thereby resulting in a cascade of events that lead to liver injury. N-acetyl cysteine restores glutathione and prevents injury if administered early in the course of events (see text).

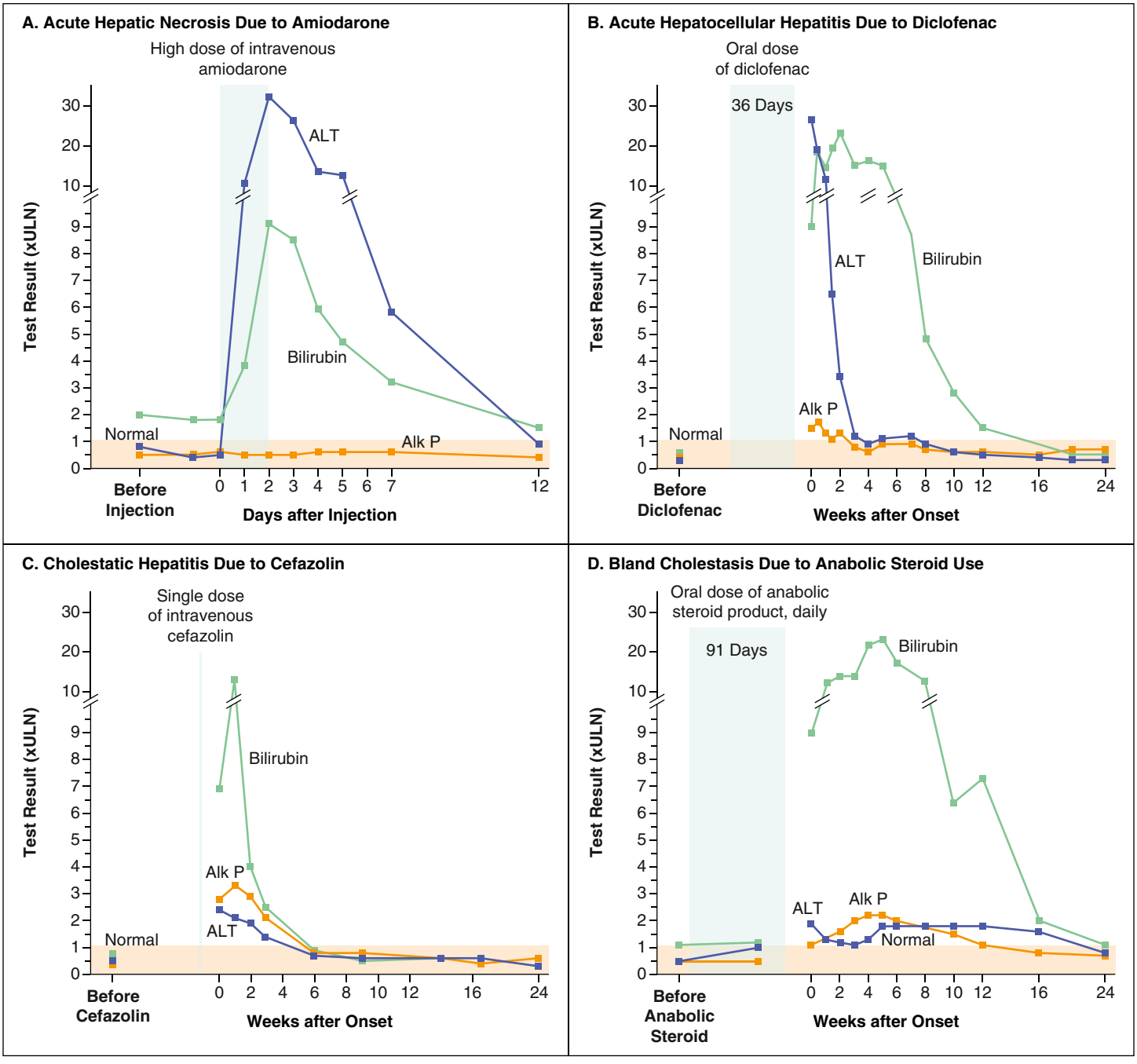

E-FIGURE 136-2. **Common clinical presentations of drug-induced liver injury A,** Direct/intrinsic hepatotoxins. Liver injury occurs soon after exposure, with rapid resolution. **B,** Idiosyncratic hepatocellular drug-induced liver injury. Latency is typically between 1 and 3 months, and resolution of jaundice can be prolonged; some patients progress to global liver dysfunction. **C,** Idiosyncratic cholestatic drug-induced liver injury. The short latency in this case supports prior sensitization to the drug-induced neoantigen or to a structurally similar peptide. **D,** Prolonged bland cholestasis, in this case in a young male bodybuilder who was consuming an androgen-containing product. ALT = alanine aminotransferase; Alk P = alkaline phosphatase; ULN = upper limit of normal. (Reproduced with permission from Hoofnagle JH, Björnsson ES. Drug-induced liver injury-types and phenotypes. *N Engl J Med*. 2019;381:264-273.)

TABLE 136-3 DRUGS AND TOXINS THAT CAUSE DOSE-RELATED INJURY

DRUG OR TOXIN
Acetaminophen
Alcohol
Amiodarone
Cocaine
Cyclophosphamide
Cyclosporine
Methotrexate
Niacin
Nonsteroidal anti-inflammatory drugs (principally bromfenac, phenylbutazone)
Oral estrogens or androgens
Tetracyclines
Toxins (yellow phosphorus, carbon tetrachloride, *Amanita* toxin, bacterial toxins)
Zidovudine

initial elevation of liver chemistries, typically starts about 24 hours after the ingestion when the patient may feel entirely well. Serum AST and ALT levels rise rapidly to very high levels, initially with AST levels typically higher than ALT levels. Elevations in the serum bilirubin level and international normalized ratio (INR) reflect significant loss of liver function. The third stage, which is marked by the peaking of serum ALT and AST, typically occurs 3 to 4 days after the ingestion. If the injury is severe, the serum bilirubin level and INR will continue to increase, and the patient may develop fulminant hepatic failure, often accompanied by kidney failure. The fourth stage is recovery with return of all liver chemistries and the INR to normal over 2 weeks. Because death of liver cells ceases after the first several days after ingestion, the serum enzymes fall at the rate of their half-lives (ALT about 2 days, AST about 1 day).

Other Direct Liver Toxins

Other direct liver toxins cause hepatic steatosis and lactic acidosis, which typically present with fatigue, nausea, and weight loss within the first month of starting treatment with the culprit drug. Drugs implicated in causing this type of liver injury include intravenous tetracycline and d-nucleosidase drugs, including zidovudine (AZT). Liver chemistries may be only minimally elevated, and liver histology reveals microvesicular steatosis similar to that observed when aspirin causes Reye syndrome. Chronic treatment with several drugs (e.g., tamoxifen or methotrexate) can cause fatty liver without lactic acidosis, often in the setting of obesity or type 2 diabetes. Acute alcoholic injury also results in fatty liver (Chapter 138).

Bland cholestasis occurs in healthy young men who consume androgen-containing supplements to build muscle bulk (see E-Fig. 136-2D).[7] Long-term use of estrogens, especially in high doses, is associated with benign liver adenomas, and long-term use of androgen-containing supplements can cause liver cancer.

Sinusoidal obstruction syndrome (previously termed veno-occlusive disease), which can be acute or subacute forms of this phenotype, presents with abdominal pain and weight gain owing to the rapid accumulation of ascites. Offending drugs are generally chemotherapeutic agents, typically alkylating agents such as cyclophosphamide.

DIAGNOSIS

In an otherwise healthy person, sudden development of extremely high (more than 50 times the upper limit of normal) ALT and AST values, followed by resolution at the half-lives of these enzymes, is almost pathognomonic for acetaminophen overdose.[8] Nevertheless, the diagnosis of acetaminophen drug-induced liver injury can be challenging during the first stage, when it is based on the history of the amount ingested and the timing of the ingestion. Since some patients may not admit to having taken an overdose and liver chemistries will generally not be abnormal during the first stage, measurement of an acetaminophen blood level is key to diagnosis. For other causes of direct liver injury, the diagnosis is based on exposure to a known toxin.

Rare exposures to other liver toxins (Table 136-3), such as poisonous mushrooms or industrial solvents, also can present with a clinical picture similar to acetaminophen poisoning. The diagnosis is based on evidence of exposure since there is no definitive diagnostic test.

TREATMENT

N-acetyl cysteine, which repletes liver stores of glutathione, is a very effective treatment for acetaminophen overdose,[A1] especially if administered during stage 1. Intravenous dosing can begin with 140 mg/kg in 300 mL of 5% dextrose given over 1 hour, followed by a dose of 70 mg/kg in 5% dextrose given over a 1-hour period every 4 hours for 48 hours. Alternatively, a loading dose of 140 mg/kg can be given orally, followed by 70 mg/kg every 4 hours for 17 doses (72 hours), with subsequent dosing dependent on the predicted and measured toxic levels of acetaminophen as a function of time since a single overdose (https://www.mdcalc.com/acetaminophen-overdose-nac-dosing#next-steps). Critically ill patients require intensive care. Liver transplantation (Chapter 140) is often required for fulminant hepatic failure.

For other direct liver injuries, no specific treatments are available. Care is supportive, with liver transplantation often required for liver failure.

PREVENTION

Patients who have accidentally overdosed should be advised to read the labels on all analgesics, cold, and sleep remedies to keep total acetaminophen dosing within the recommended range. Patients who have intentionally overdosed require psychiatric consultation (Chapter 362).

PROGNOSIS

The prognosis is excellent if NAC is administered within stage 1. If serial assessments of acetaminophen levels indicate that the half-life is longer than 5.5 hours, progressive liver injury is likely.

IDIOSYNCRATIC HEPATOTOXICITY

EPIDEMIOLOGY

Idiosyncratic drug-induced liver injury is a rare but potentially serious event that occurs during recommended dosing of the implicated drug at a frequency less than 1 : 1000 treated patients. Although idiosyncratic hepatotoxicity is not generally dose-related, it is less likely to occur when the daily dose of drug is less than 50 mg per day and can occasionally occur when the daily dose is increased after prolonged treatment (>1 year) at a lower dose. The most common drugs that cause idiosyncratic drug-induced liver injury are antimicrobial agents (e.g., fluoroquinolones) and herbal and dietary supplements (Table 136-4). Herbal supplements dominate in China[9] and other parts of Asia, and the incidence of drug-induced liver injury related to dietary and herbal supplements is increasing in the United States as well.[10] The risk appears to increase with factors such as older age and alcohol use (Table 136-5).

PATHOBIOLOGY

Idiosyncratic drug-induced liver injury often results from a cytotoxic T-cell response to drug-induced neoantigen(s) presented on the surface of liver cells. This response typically occurs because of covalent binding of a drug metabolite to an endogenous liver protein, thereby resulting in altered peptide fragments presented by class 1 HLA molecules.[11] However, creation of a novel antigen alone is not thought to be sufficient to initiate an immune attack on the liver (E-Fig. 136-3).[12] A number of genetic variants, particularly HLA alleles (Table 136-6), increase the susceptibility to idiosyncratic hepatotoxicity[13]. Due to the rarity of idiosyncratic drug-induced liver injury, however, the vast majority of patients treated with these drugs do not get drug-induced liver injury even if they carry the corresponding risk allele. Genetic variants in CYP isoenzymes likely also partially explain a predisposition to drug-induced liver injury. In addition, a polymorphism in the *PTPN22* gene, which is believed to influence T-cell activation, also is associated with about a 50% increased risk for drug-induced liver injury.

The usual response to an initial adaptive immune attack on the liver due to a drug is spontaneous resolution, even with continued exposure to the offending drug, because of immune tolerance mechanisms. The typical latency reflects, at least in part, the time needed to complete the multiple sequential steps involved (E-Fig. 136-3). Once the injury is initiated, it may progress for days or rarely weeks after discontinuing the offending drug. In some cases (see E-Fig. 136-2, panel B), the adaptive immune attack can occur within days after starting treatment, presumably as a reflection of a sufficient pre-existing

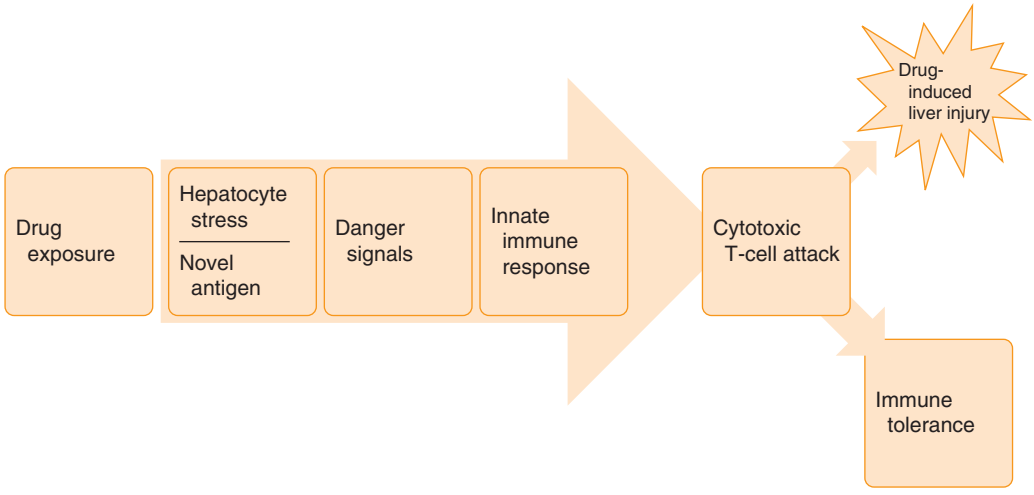

E-FIGURE 136-3. The pathogenesis of idiosyncratic drug-induced liver injury. Most idiosyncratic drug-induced liver injury is because the drug produces neoantigen(s) in the liver and hepatocytic stress (but not necessarily cell death) due to intrinsic toxicity. In susceptible individuals, these events lead to the release of signals that result in activation of innate immune cells, which in turn activate antigen-presenting cells that program cytotoxic T cells to kill liver cells. The resulting adaptive immune attack generally results in asymptomatic elevations in serum liver chemistries, but these elevations typically resolve, despite continued drug treatment, due to immune tolerance mechanisms. If immune tolerance does not promptly occur, progressive and symptomatic liver injury may result.

TABLE 136-4 MOST COMMON CAUSES OF IDIOSYNCRATIC DRUG-INDUCED LIVER INJURY

TYPE OF MEDICATION	%	SPECIFIC DRUGS*	%
Antimicrobials	32	Amoxicillin-clavulanate	8
Herbal and dietary supplements	12	Isoniazid	4
Cardiovascular agents	7	Nitrofurantoin	4
Central nervous system agents	7	Sulfamethoxazole/trimethoprim	3
Antineoplastic agents	4	Minocycline	2
Analgesics	3	Cefazolin	2
Immunomodulatory drugs	2	Azithromycin	2
Endocrine drugs	2	Ciprofloxacin	1
Rheumatologic treatments	1	Levofloxacin	1
Gastrointestinal agents	1	Diclofenac	1

*Excludes herbal and dietary supplements.
Adapted from Chalasani N, Bonkovsky HL, Fontana R, et al. Features and outcomes of 899 patients with drug-induced liver injury: the DILIN Prospective Study. *Gastroenterology*. 2015;148:1340-1352.

TABLE 136-5 FACTORS THAT MAY PREDISPOSE TO IDIOSYNCRATIC DRUG-INDUCED LIVER INJURY

Elderly age
Alcohol use
Female gender
Renal disease
Foods such as grapefruit that interfere with the metabolism of some drugs
Concomitant drugs
Genetic factors

TABLE 136-6 HLA ALLELES ASSOCIATED WITH RISK FOR IDIOSYNCRATIC DRUG-INDUCED LIVER INJURY DUE TO CERTAIN DRUGS

DRUG	HLA ALLELE	ODDS RATIO OF INCREASED RISK
Amoxicillin/clavulanic acid	A*02:01	2.3
	DRB1*15:01	2.8
Fenofibrate	A*33:01	59
Flucloxacillin	B*57:01	81
Flupirtine	DRB1*16:01-DQB1*05:02	19
Green tea extract	B*35:01	12
Lumiracoxib	DRB1*15:01-DQB1*06:02	5.0
Minocycline	B*35:02	30
Sulfamethoxazole/trimethoprim	B*14:01	9.2
Terbinafine	A*33:01	41
Ticlopidine	A*33:01	163
Ximelagatran	DRB1*07:01-DQA1*02:01	4.4

population of appropriately primed T cells prior to starting treatment with the implicated drug, perhaps due to prior treatment with the same drug, or prior exposure to a structurally similar viral antigen.

CLINICAL MANIFESTATIONS

About 50% of cases present within 30 days of starting the drug, and about 80% of cases present within 90 days (see E-Fig. 136-2, panel B).[14] Occurrences beyond 1 year of treatment are very rare and usually occur with drugs that are not taken continuously, such as minocycline for acne or nitrofurantoin for urinary tract infections.

TABLE 136-7 IDIOSYNCRATIC TOXIN AND DRUG REACTIONS

REACTION TYPE	SOME IMPLICATED DRUGS OR TOXINS
Hepatocellular	Carbamazepine, fluoroquinolones, cyclosporine, herbs, methimazole, isoniazid, lovastatin, nefazodone, trazodone, venlafaxine
Cholestatic or mixed	Anabolic steroids, captopril, carbamazepine, chlorpromazine, estrogen, erythromycin, amoxicillin/clavulanate
Fibrosis	Methotrexate, excess vitamin A
Granulomatous	Allopurinol, diltiazem, nitrofurantoin, sulfa drugs, quinidine
Autoimmune	Nitrofurantoin, minocycline
Immunoallergic	Halothane, phenytoin, sulfamethoxazole
Steatohepatitis	Amiodarone, perhexiline maleate, tamoxifen

Different drugs can cause different types of liver reactions (Table 136-7), but clinically the damage presents as a hepatocellular, cholestatic, or mixed injury. Most cases of drug-induced liver injury are hepatocellular reactions, which account for 60% of cases and are characterized by elevated levels of AST and ALT. Cholestatic reactions[15] can be caused by trimethoprim-sulfamethoxazole, captopril, and body-building dietary supplements that contain androgenic compounds. Nodular regenerative hyperplasia manifests with fatigue, weight loss, ascites, and other complications of portal hypertension, usually after at least 6 months of continuous treatment with the offending drug. Drugs implicated as causing this phenotype include azathioprine, mercaptopurine, and thioguanine.

DIAGNOSIS

The most commonly used tool to aid in the diagnosis of drug-induced liver injury is the Roussel Uclaf Causality Assessment Method (RUCAM; Table 136-8; https://www.ncbi.nlm.nih.gov/books/NBK548272/), which considers answers to a series of questions such as time to detection of drug-induced liver injury from start of treatment, rate of resolution after stopping treatment, and whether the drug is known to cause hepatotoxicity. The sum of the points (>8 = highly probable, 6 to 8 = probable, 3 to 5 = possible, 1 to 2 = unlikely, 0 = excluded) after completing the exercise corresponds to scales of confidence on a causal link.

The RUCAM instrument does not consider the characteristic clinical presentations (or signatures) of the drugs that cause idiosyncratic reactions (see Table 136-4 and https://www.ncbi.nlm.nih.gov/books/NBK548473/). However, one drug can have more than one "signature," and many drugs have similar signatures.

A liver biopsy is generally not necessary to make the diagnosis of idiosyncratic drug-induced liver injury but is generally recommended when other potentially treatable diseases that have characteristic histology are being considered, such as autoimmune hepatitis (Chapter 135). For drugs for which specific genetic polymorphisms (see Table 136-6) increase risk, genetic testing may occasionally be helpful, particularly if the patient is being treated with multiple potential culprit drugs.

TREATMENT

Other than stopping treatment with the offending drug, no specific treatments are usually recommended for idiosyncratic drug-induced liver injury.[16,17] Drug-induced liver injury due to valproate, which presents with elevated blood levels of ammonia and altered mental status, may respond to treatment with carnitine (loading dose of 100 mg/kg intravenously [6 g maximum] over 30 minutes followed by maintenance doses of 15 mg/kg every 4 hours over 10 to 30 minutes). Oral administration of cholestyramine (8 g orally 3 times daily for 11 days) can hasten removal of some lipophilic drugs with long half-lives (e.g., leflunomide). Nevertheless, corticosteroids (typically starting with the equivalent of 40 mg prednisone daily with subsequent titration and tapering according to the patient's response) are often administered if the drug-induced liver injury mimics autoimmune hepatitis (Chapter 135) or if the liver injury is progressing towards liver failure, especially if clinical signs of hypersensitivity (fever, rash, and peripheral eosinophilia) are present.[18]

TABLE 136-8 SCORING SYSTEM TO ASSESS CAUSALITY OF HEPATOCELLULAR REACTIONS

FACTOR	SCORE*
TEMPORAL RELATIONSHIP OF START OF DRUG TO START OF ILLNESS	
Initial treatment: 5-90 days; subsequent treatment course: 1-15 days	+2
Initial treatment: <5 or >90 days; subsequent treatment course: >15 days	+1
From cessation of drug: ≤15 days†	+1
COURSE	
ALT decreases ≥50% from peak within 8 days	+3
ALT decreases ≥50% from peak within 30 days	+2
If the drug is continued, inconclusive	0
RISK FACTORS	
Alcohol‡	+1
No alcohol‡	0
Age ≥ 55 yr	+1
Age < 55 yr	0
CONCOMITANT DRUG	
Concomitant drug with suggestive time of onset	−1
Concomitant drug known to be a hepatotoxin with suggestive time of onset	−2
Concomitant drug with further evidence of involvement (rechallenge)	−3
NUMBER OF NONDRUG CAUSES	
Hepatitis A, B, or C; biliary obstruction; alcoholism (AST ≥ 2 × ALT); recent hypotension; and CMV, EBV, and HSV infections all excluded	+2
4-5 causes excluded	+1
<4 causes excluded	−2
Nondrug cause highly probable	−3
PREVIOUS INFORMATION ON HEPATOTOXICITY OF DRUG IN QUESTION	
Package insert mentions	+2
Published case reports but not on package label	+1
Reaction unknown	0
RECHALLENGE	
Positive (ALT doubles with drug alone)§	+2
Compatible (ALT doubles, compounding features)§	+1
Negative (increase in ALT but ≤2 × ULN)§	−2
Not done	0

*Causality is highly probable (score >8), probable (score 6-8), possible (score 3-5), unlikely (score 1-2), or excluded (score ≤0).
†For cholestatic reactions, ≤30 days.
‡For cholestatic reactions, alcohol, or pregnancy.
§For cholestatic reactions, substitute alkaline phosphatase (or total bilirubin) for ALT.
ALT = alanine aminotransferase; AST = aspartate aminotransferase; CMV = cytomegalovirus; EBV = Epstein-Barr virus; HSV = herpes simplex virus; ULN = upper limit of normal.
Modified from Danan G, Benichou C. Causality assessment of adverse reactions to drugs. I. A novel method based on the conclusions of international consensus meetings: application to drug-induced liver injuries. *J Clin Epidemiol.* 1993;46:1323-1330; and Benichou C, Danan G, Flahault A. Causality assessment of adverse reactions to drugs. II. An original model for validation of drug causality assessment methods: case reports with positive rechallenge. *J Clin Epidemiol.* 1993;46:1331-1336.

PREVENTION

Patients who have a suspected drug-induced liver injury should have this fact prominently noted in the medical record and should not receive that drug again. To capture an idiosyncratic drug-induced liver injury early in its course and prior to the onset of jaundice, patients taking some drugs (e.g., antibiotic treatment for more than 2 weeks and many anticancer drugs, including kinase inhibitors, azathioprine, and most antiseizure drugs) should be routinely monitored with liver chemistries during the first 3 to 6 months of treatment, although the value of routine liver test monitoring has not been conclusively established by randomized trials.

PROGNOSIS

The vast majority of patients with drug-induced liver injury will recover after discontinuing treatment with the offending drug, but up to 20% will still have biochemical evidence of drug-induced liver injury at 6 months. Patients who develop hepatocellular jaundice have a greater than 10% chance of developing liver failure, regardless of the causative drug. The number of liver transplantations (Chapter 140) for liver failure caused by herbal products continues to rise.[19]

INDIRECT HEPATOTOXICITY

Indirect drug-induced liver injury refers to liver injuries that result as a consequence of the desired therapeutic actions of the drug. This phenomenon is a quite common form of drug-induced liver injury that is increasing as more immune modulatory medications enter the marketplace.

Examples of indirect drug-induced liver injury include flaring of preexisting viral hepatitis due to immune suppression that may result from treatment with corticosteroids and some monoclonal antibodies (e.g., daclizumab and anti–tumor necrosis factor alpha agents).[20] The other major type of indirect hepatotoxicity results from drugs that increase immune responses to cancer, such as checkpoint inhibitors[21] (which remove immune tolerance and spark an adaptive immune attack on the liver and other organs). Liver cell stress and neoantigen presentation must also be present for the reduction in immune tolerance to cause liver injury (E-Fig. 136-3), and concomitant treatment with a drug that can cause liver injury increases the risk.

CLINICAL MANIFESTATIONS AND DIAGNOSIS

Indirect hepatotoxicity is usually hepatocellular or mixed. It typically arises within 3 months after the start of therapy but can appear later. Many cases are anicteric and asymptomatic; sometimes, however, the hepatitis can worsen and rarely become life-threatening if untreated.

Indirect hepatotoxicity is typically detected by routine monitoring of liver chemistries during therapy with the offending agent. Reactivation of viral hepatitis is detected by serum viral counts.

TREATMENT AND PROGNOSIS

Reactivation viral hepatitis may require antiviral treatment (Chapter 134). Liver injury due to checkpoint inhibitors appears to respond to corticosteroids (e.g., 40 mg of prednisone daily, with subsequent titration and tapering according to the patient's response).

Concomitant treatment with drugs well-recognized to be hepatotoxic should be avoided. Full recovery is expected with timely recognition and appropriate treatment.

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137 BACTERIAL, PARASITIC, FUNGAL, AND GRANULOMATOUS LIVER DISEASES

K. RAJENDER REDDY

INFECTIONS OF THE LIVER

Infections of the liver can be due to a variety of pathogens, including bacteria, fungi, amebae, protozoa, helminths, spirochetes, and rickettsiae.[1] The manifestations of these infections are protean; some are generic to all infections, whereas others are specific to particular infections. The epidemiology can vary and depend upon the geographic region of the world. In endemic areas, *Entamoeba histolytica* (Chapter 323) is a key consideration in the differential diagnosis of a liver abscess (Table 137-1).

BACTERIAL INFECTIONS

PYOGENIC LIVER ABSCESS

DEFINITION

Pyogenic liver abscess is a focal collection of purulent bacterial material and necroinflammatory debris. It can be solitary or multiple and can be caused by one or more aerobic and/or anaerobic bacteria.

EPIDEMIOLOGY

Pyogenic liver abscess has an estimated global incidence of approximately 1.1 to 2.3 per 100,000 person-years, whereas in the United States the incidence is reported to be approximately 3.6 per 100,000 and has been rising. The risk is about three-fold higher in patients with diabetes.[2] Biliary obstruction, caused by a malignancy or benign disease, accounts for 50 to 60% of pyogenic liver abscesses, whereas portal pyemia, due to appendicitis or other intra-abdominal infections (e.g., diverticulitis), accounts for about 20% of cases.[3] Studies from Asia, where *Klebsiella pneumoniae* is the primary etiologic source of pyogenic liver abscess,[4] have proposed a correlation with underlying colorectal neoplasms, some of which are evident at the time of diagnosis but also with a five- to eight-fold higher risk of newly diagnosed colorectal cancers in the 3 years after diagnosis. However, it is yet to be determined whether these findings can be extrapolated to other regions of the world.

PATHOBIOLOGY

Bacteria can enter the liver via the portal system from infections in areas drained by the mesenteric system into the portal system, such as appendicitis. Other mechanisms for pyogenic liver abscess include bacterial cholangitis owing to benign or malignant obstruction and infection of the liver from a systemic bacteremia, such as an infection of the oral cavity. Pyogenic liver abscess can also be caused by blunt or penetrating trauma, including such unusual causes as the ingestion of a toothpick or fish bone that can cause an intestinal perforation, fistula to the liver, and subsequent abscess formation. Liver abscesses can occur in a transplanted graft owing to vascular compromise caused by hepatic artery thrombosis and ischemic bile duct strictures.

Multiple organisms can cause pyogenic liver abscess. The most common organism, *Klebsiella pneumoniae* (Chapter 281) often is associated with biliary tract disease. Other aerobes include *Escherichia coli*, group D streptococci, β-hemolytic streptococci, and *Staphylococcus aureus*. Anaerobic infection is often seen with colonic disease. Less common causes of liver abscesses include *Actinomyces, Nocardia asteroides, Yersinia pseudotuberculosis* and *Yersinia enterocolitica, Listeria monocytogenes, Campylobacter jejuni, Legionella pneumophila, Mycobacterium tuberculosis, Salmonella typhi* or *Salmonella paratyphi, Candida albicans*, and *Bartonella henselae*. Most often, the organism recovered from an abscess cavity is single, but multiple organisms can be isolated in as many as a third of patients. Bacteria may not be isolated from the abscess because of prior antibiotic therapy or the failure to perform proper anaerobic cultures.

CLINICAL MANIFESTATIONS

The signs and symptoms associated with a liver abscess typically include fever, right upper quadrant abdominal pain, chills, nausea, vomiting, weight loss, and jaundice. The presentation can be acute or indolent. An associated bacteremia is seen in approximately 50% of the patients, and about 15% of patients may develop septic shock. About 10% of patients develop metastatic infections in other sites.

DIAGNOSIS

Appropriate diagnosis requires a high degree of clinical suspicion, and diagnosis is sometimes delayed. Usually, however, the diagnosis is made promptly with the wide availability of the various radiologic modalities. The two common causes of liver abscesses are pyogenic and amebic abscesses, and it is important to make a distinction because the prognosis and management differ.[5] Amebic abscesses can infrequently become secondarily infected with other bacteria.

The diagnosis of an abscess is based on a constellation of clinical, bacteriologic, and radiologic features.[6] Ultrasonography and computed tomography (CT) scanning are the most common radiologic modalities to diagnose an abscess cavity reliably,[7] either as single or multiple lesions (Fig. 137-1A and B). CT is the preferred diagnostic modality to detect an abscess, with sensitivity of more than 90%. Any concurrent biliary obstruction also can be diagnosed by these imaging modalities. Approximately 50% of patients have multiple abscesses. On CT the lesion is seen as a fluid collection with irregular borders and cavity wall edema. One drawback to this imaging modality is that no specific features differentiate a pyogenic abscess from other infectious causes (i.e., amebic or fungal). Another drawback is that a very early stage abscess may not be well formed and may have characteristics more suggestive of a solid mass. On noninvasive imaging studies, it is critical to distinguish an abscess from a tumor or a simple cyst. Various events, such as bleeding into a cyst, calcification, necrosis, and bleeding into a tumor, may confuse the distinction. A finding of smaller (<2 cm) peripheral lesions that surround a central abscess (the cluster sign) can help exclude a hepatic neoplasm. Calcification suggests

TABLE 137-1 FEATURES OF BACTERIAL AND AMEBIC ABSCESSES

	DEMOGRAPHICS	RISK FACTORS	SYMPTOMS	LABORATORY FINDINGS	RADIOGRAPHIC FEATURES	DIAGNOSIS	TREATMENT
Bacterial liver abscess	50-70 years old Male = female	Recent bacterial infection, biliary obstruction, diabetes mellitus	Fevers, chills, malaise, anorexia, diarrhea, cough, pleuritic chest pain, RUQ pain	Leukocytosis, anemia, elevated alkaline phosphatase and bilirubin, low albumin, positive blood cultures (50%)	Multifocal (50%), usually right lobe, irregular margins	Aspirate (70-80% positive)	Percutaneous drainage and antibiotics
Amebic liver abscess	18-50 years old Male > female	Alcohol intake, HLA-DR3, oral and anal sex, contaminated enema apparatus, travel to or living in an endemic area	Fever, RUQ pain, hepatic tenderness, anorexia, weight loss, uncommon to have colitis	Leukocytosis, no eosinophilia, mild anemia, elevated alkaline phosphatase, elevated ESR, positive serology	Single abscess (80%), usually right lobe, wall enhancement seen on CT scan with IV contrast	Aspirate (trophozoites rarely seen) can rule out superimposed bacterial infection, positive serology and risk factors	Metronidazole and iodoquinol

CT = computed tomography; ESR = erythrocyte sedimentation rate; HLA = human leukocyte antigen; IV = intravenous; RUQ = right upper quadrant.

ABSTRACT

Infections of the liver can be due to a variety of pathogens, including bacteria, fungi, amebae, protozoa, helminths, spirochetes, and rickettsiae. The manifestations of these infections are protean; some are generic to all infections, whereas others are specific to particular infections. The epidemiology can vary depending on the geographic region of the world. In endemic areas, *Entamoeba histolytica* is a key consideration in the differential diagnosis of a liver abscess.

KEYWORDS

pyogenic liver abscess
hepatosplenic candidiasis
echinococcosis
hydatid cyst disease
schistosomiasis
granulomas
sarcoidosis

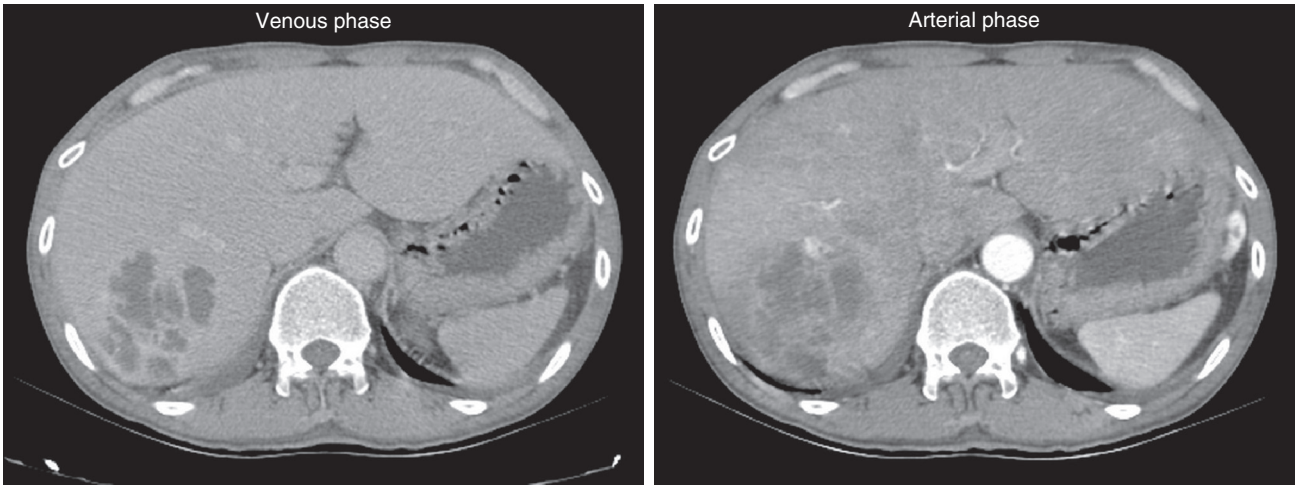

FIGURE 137-1. A and B, Computed tomographic scans of pyogenic liver abscess. (Courtesy Dr. Chalermrat Bunchorntavakul, Bangkok, Thailand.)

bleeding into a tumor, but it also can be seen in the wall of an echinococcal cyst. Nonspecific radiologic features, including elevation of the right hemidiaphragm, right lower lung lobe atelectasis, and right pleural effusion, are seen in up to 30% of patients with pyogenic liver abscesses. Magnetic resonance imaging and tagged white blood scans add little to the diagnosis of a liver abscess.

Microbial cultures are essential. In addition to blood cultures, the abscess cavity should be aspirated percutaneously, with either ultrasound or CT guidance, and the aspirate should be cultured for aerobic and anaerobic organisms as well as examined for amebae if there is any suspicion of an amebic abscess. Blood cultures are positive in only approximately 50% of cases. In approximately 15 to 20% of cases, multiple organisms are identified in the abscess cavity, but 20 to 50% of cases may have negative cultures despite appropriate culture techniques.

TREATMENT

Immediate broad-spectrum antibiotic coverage and the prompt identification and treatment of the source of the infection are essential for successful outcomes.[8] As soon as the causative bacterium is identified, the antibiotic regimen can be tailored appropriately. Recommendations should be guided by the culture and by prevailing bacterial resistance patterns. Monotherapy with a β-lactam or β-lactamase inhibitor such as ampicillin-sulbactam (3 g intravenously [IV] every 6 hours) or piperacillin-tazobactam (3.375 or 4.5 g IV every 6 hours) or ticarcillin-clavulanate (3.1 g IV every 6 hours) can be used, or a third-generation cephalosporin such as ceftriaxone (1 g IV daily or 2 g IV every 12 hours for central nervous system infections) *plus* metronidazole (500 mg IV every 8 hours) can be considered. Alternate regimens for consideration include a fluoroquinolone (such as ciprofloxacin 400 mg IV every 12 hours or levofloxacin 500 or 750 mg IV daily) *plus* metronidazole (500 mg IV every 8 hours) and monotherapy with a carbapenem such as imipenem-cilastatin (500 mg IV every 6 hours), meropenem (1 g IV every 8 hours), doripenem (500 mg IV every 8 hours), or ertapenem (1 g IV daily). The duration of therapy is partly based on the response to therapy. An average of 4 to 6 weeks of antibiotic therapy is reasonable, and the last 2 to 4 weeks of the antibiotic regimen can be administered orally. For documented *Klebsiella pneumoniae* liver abscess treated with 5 to 7 days of intravenous antibiotics, an additional 28 days of oral ciprofloxacin is as good as an additional 28 days of intravenous ceftriaxone.[A1] Abscesses that are difficult to drain or are slow to demonstrate radiographic resolution require longer courses of therapy. Importantly, radiologic abnormalities resolve more slowly than clinical and biochemical features, so the latter should be used as a guide for tailoring the therapeutic regimen.

Antibiotics alone can sometimes successfully resolve small, multiple pyogenic abscesses, but most patients (≥70%) will require drainage of the abscesses. Percutaneous drainage is recommended, with subsequent management dictated by the size and number of abscesses. Abscesses of up to 5cm in diameter can be managed with a single aspiration. Larger abscesses are probably better managed with catheter drainage[A2,A3] until the output is less than approximately 20 to 25mL per day, at which time the catheter can be removed. Endoscopic ultrasound-guided drainage is an option if the abscess cannot be accessed percutaneously.[9] Surgical drainage is seldom required because of the advancements in percutaneous drainage and is reserved for loculated abscesses and abscesses that do not respond to percutaneous drainage and antibiotics. Biliary obstruction is treated with endoscopic retrograde cholangiopancreatography or transhepatic cholangiography (Chapter 141) with accompanying biliary drainage. For pyogenic abscesses in transplanted livers, management and proper biliary drainage may be difficult to achieve because of the diffuse nature of the biliary strictures.

PROGNOSIS

Abscesses smaller than 10 cm can take up to 16 weeks to resolve, whereas abscesses larger than 10 cm may take an average of an additional 6 weeks to resolve. Mortality from pyogenic liver abscess is associated with older age and with comorbidities such as cirrhosis, diabetes, chronic renal failure, and malignancy. Jaundice is an ominous sign. In developed countries the mortality rate ranges from 2 to 12%.

NON-ABSCESS HEPATIC BACTERIAL INFECTIONS

Bacterial infections of the liver can also cause more diffuse infections without frank abscess formation. Implicated organisms include *Listeria monocytogenes* (Chapter 272), *Yersinia enterocolitica* (Chapter 288), *Salmonella typhi* and *Salmonella paratyphi* (Chapter 284), *Legionella* (Chapter 290), *Ehrlichia* (Chapter 302), and gonococci (Chapter 275). There are no specific features associated with these infections, and these organisms do not necessarily cause abscesses. Patients with chronic liver disease are especially at risk for *Listeria* infection. Patients with active enteric *Yersinia* infection can have secondary liver involvement with or without liver abscesses. Disseminated gonococcal infections (Chapter 275) can cause a perihepatitis (Fitz-Hugh-Curtis syndrome), which can be manifested with right upper quadrant pain and tenderness.

Systemic bacteremia can cause a variety of hepatobiliary abnormalities, which may range from elevated aminotransferase and alkaline phosphatase levels (Chapter 133) to the cholestasis of sepsis with the development of jaundice. Several organisms can disrupt normal liver function after entering the blood stream, the most common of which are *E. coli*, *Klebsiella* spp, *Streptococcus pneumoniae*, and *S. aureus*. Typically, in patients suffering from jaundice, sources of bacteremia include pneumonia, urinary tract infection, and soft tissue infection, although organisms may originate from a range of other sites. The hepatic biochemical abnormalities associated with bacteremia may be related to factors such as hemodynamic instability and liver hypoperfusion, as well as to the infection. Associated renal failure, a blood transfusion–derived bilirubin load, and drugs may complicate the picture. The course of cholestasis may be prolonged for several days to a few weeks, but it typically resolves with resolution of the systemic infection. There is no specific treatment for the cholestasis related to a systemic infection, but it is important to rule out drug-induced cholestasis that may evolve as a consequence of one or more of the antibiotics.

FUNGAL DISEASES OF THE LIVER

Except for hepatosplenic candidiasis, clinically significant fungal diseases of the liver are unusual. Typically, other fungal infections will also be manifested as liver granulomas but will not show the high, swinging pyrexia that is characteristic of hepatosplenic candidiasis. Tissue cultures are required to confirm a diagnosis.

HEPATOSPLENIC CANDIDIASIS

EPIDEMIOLOGY AND PATHOBIOLOGY

Hepatosplenic candidiasis typically is caused by *Candida albicans*, but other species, including *C. tropicalis*, *C. parapsilosis*, *C. glabrata*, and *C. krusei*, have occasionally been reported. It occurs as part of disseminated candidiasis (Chapter 310), most commonly in patients with solid organ or hematopoietic stem cell transplants or acute leukemia, but rarely in patients with lymphoma,

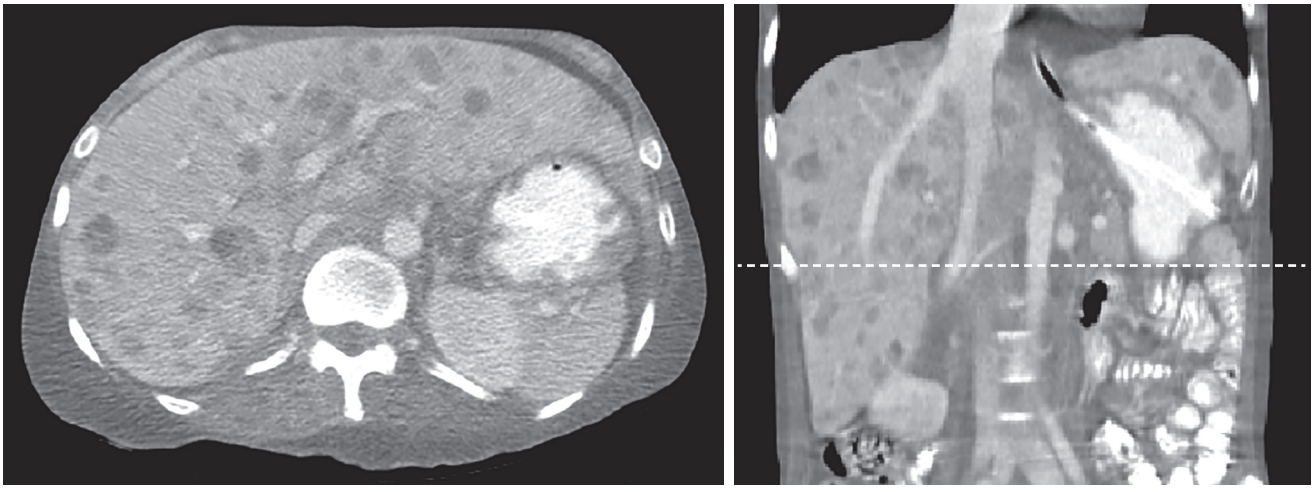

FIGURE 137-2. Multiple filling defects in the liver and spleen in a patient with hepatic and splenic candidiasis. (Courtesy of Dr. Sirina Ekpanyapong, Bangkok, Thailand.)

aplastic anemia, and sarcoma. With the current widespread use of prophylactic antifungal agents early in the course of the disease in patients with acute leukemia, hepatosplenic candidiasis develops in only 1 to 2% of patients, more commonly with acute lymphoblastic leukemia than with acute myeloid leukemia. Hepatosplenic candidiasis presumably results from translocation of *Candida* species from the gastrointestinal tract into the blood stream as a result of prolonged neutropenia and a breach in mucosal integrity.

CLINICAL MANIFESTATIONS AND DIAGNOSIS

Hepatosplenic candidiasis (Fig. 137-2) is manifested by persistent and high spiking fevers in a patient who was previously neutropenic and has now returned to a normal neutrophil count.[10] Right upper quadrant pain, nausea, vomiting, and anorexia may accompany fever.

Patients typically have elevated levels of alkaline phosphatase and less commonly of aminotransferases, bilirubin, and leukocytes. CT, which is the imaging modality of choice, classically shows multiple lucencies representing microabscesses in the liver, spleen, and kidneys. If the CT scan is nondiagnostic but clinical suspicion remains high, magnetic resonance imaging should be performed. A definitive diagnosis is usually made on a liver biopsy specimen that shows multiple granulomas and may show yeast and hyphal forms with special stains. However, biopsy often will not show evidence of infection, especially in cases in which antifungal therapy has been used. Although biopsy is the only means to establish a definitive diagnosis, it often is not required because the clinical, laboratory, and radiographic manifestations of the disease are almost always sufficient to establish a specific diagnosis.

TREATMENT AND PROGNOSIS

The mainstay of therapy is antifungal therapy. In clinically stable patients, oral fluconazole (400 mg orally, daily) can be used. In acutely ill patients a lipid formulation of amphotericin B (3 to 5 mg/kg IV daily) or an echinocandin for several weeks is recommended. The echinocandin options include caspofungin (70 mg loading dose then 50 mg IV daily), anidulafungin (200 mg loading dose then 100 mg IV daily), or micafungin (100 mg IV daily). After several weeks of such therapy, patients can be transitioned to oral fluconazole at 400 mg daily or to voriconazole (6 mg/kg IV q12 hours for first 24 hours, then 3 to 4 mg/kg IV q12 hours or 200 mg orally q12 hours) or posaconazole (IV: 300 mg IV 9 to 12 hours on day 1, then 300 mg IV daily or 300 mg orally 9 to 12 hours on day 1, then 300 mg orally daily) in fluconazole-resistant isolates. Treatment should continue until the lesions resolve on follow-up CT scans, typically within 6 months of treatment. Patients receiving chemotherapy or stem cell transplants are at a higher risk for developing hepatosplenic candidiasis; for this reason, patients who have a history of hepatosplenic candidiasis should be treated prophylactically with fluconazole (400 mg orally, daily) to prevent relapse.

PROGNOSIS

With prolonged treatment with antifungal agents, there has been good success at treating hepatosplenic candidiasis.

OTHER FUNGAL DISEASES

Several additional fungal infections affect the liver, although rarely. *Coccidioides immitis* is often asymptomatic but may lead to fungal hepatitis characterized by increased alkaline phosphatase and the development of hepatic granulomas. Hepatic *Cryptococcus neoformans* infection is rare but has a higher prevalence in patients with acquired immunodeficiency syndrome (AIDS), in whom it typically causes hepatomegaly. In the non–human immunodeficiency virus (HIV)–infected patient, disseminated cryptococcosis less frequently can result in focal granulomatous hepatitis, which may clinically mimic viral hepatitis, or can be manifested as obstructive jaundice secondary to sclerosing cholangitis. *Histoplasma capsulatum* infects individuals who inhale the fungus, but most cases are subclinical. In symptomatic hepatic histoplasmosis, two thirds of patients will present with hepatomegaly, with some showing splenic enlargement as well. On histologic examination, histoplasmosis can cause multiple granulomas diffusely distributed throughout the liver, although a more common finding is portal lymphohistiocytic infiltrate. *Paracoccidioides brasiliensis* most commonly infects adult men, and autopsy series have shown hepatic involvement in up to 50% of patients who die of this infection. Some individuals may present with hepatomegaly or jaundice, although the latter is found in less than 6% of patients. Aminotransferase levels are often elevated in the early stages of the disease; changes in alkaline phosphatase or bilirubin levels tend to occur in the later stages. Biopsy may reveal lesions ranging from small granulomas to diffuse infiltration of yeast forms and fibrosis, often with bile duct involvement. In all of these examples, fungal cultures are necessary to establish a definitive diagnosis.

PARASITIC, PROTOZOAL, AND HELMINTHIC INFECTIONS OF THE LIVER

AMEBIC LIVER ABSCESS

EPIDEMIOLOGY

Entamoeba histolytica is found throughout the world where the barriers between human feces and food and water are inadequate. After malaria, it is the second leading cause of death from parasitic diseases worldwide, accounting for an estimated 40,000 to 100,000 deaths annually. In the United States, most cases of amebiasis arise in immigrants from endemic areas and people living in states that border Mexico.[11] Travelers to endemic areas are also at risk; ingestion of amebic cysts and colonization of the gastrointestinal tract can occur years before the development of a liver abscess. Amebic liver abscesses mainly affect men between the ages of 18 and 50 years but are also more common in postmenopausal women, thereby suggesting a hormonal protective effect. Other risk factors include alcohol intake, human leukocyte antigen (HLA)-DR3, oral and anal sex, and contaminated enema apparatuses.

PATHOBIOLOGY

Entamoeba histolytica has a simple life cycle consisting of the cyst (infectious form) and trophozoite (the motile stage associated with disease); it infects only humans and some nonhuman primates. Cysts are ingested and mature into trophozoites in the intestinal lumen. The development of amebic colitis is not essential for liver abscess formation. *E. histolytica* trophozoites penetrate through the mucosa and submucosal tissues and enter the portal circulation. *E. histolytica* blocks intrahepatic portal venules. When the trophozoites reach the liver, they create their unique abscesses, which are well-circumscribed regions of dead hepatocytes, liquefied cells, and cellular debris that are surrounded by a rim of connective tissue, a few inflammatory cells, and amebic

trophozoites. The adjacent liver parenchyma is unaffected. Given the small numbers of amebae relative to the size of the abscess, it is suggested that *E. histolytica* can cause hepatocyte death without direct contact.

CLINICAL MANIFESTATIONS

Patients can present with amebic liver abscesses months to years after traveling to an endemic area, so a detailed travel history is essential for the diagnosis. The disease should be suspected in patients with an appropriate travel history, fever, right upper quadrant pain, and substantial hepatic tenderness. Jaundice is extremely uncommon. Symptoms are usually acute (<10 days in duration) but can be chronic, with anorexia and weight loss. Patients with acute disease tend to have multifocal disease, whereas patients with a more indolent course tend to have a solitary lesion. Laboratory data tend to demonstrate a leukocytosis without eosinophilia, mild anemia, an elevated alkaline phosphatase level, and a high erythrocyte sedimentation rate.

DIAGNOSIS

Although some individuals with amebic liver abscesses have concurrent amebic colitis, the majority of patients have no bowel symptoms; hence, the results of stool microscopy for *E. histolytica* trophozoites and cysts are usually negative. The diagnosis relies on identification of space-occupying lesions in the liver and a positive amebic serology.[12] Both ultrasound and CT scan are very sensitive (Fig. 137-3), but neither provides absolute specificity for amebic liver abscesses. Serologic testing is highly sensitive (>94%) and specific (>95%). False-negative test results can be obtained within the first 7 to 10 days of infection, but repeat testing will usually be positive. Polymerase chain reaction testing of the abscess aspirate has proved valuable for making the diagnosis in returning travelers. Aspiration of the lesion may be necessary to exclude a primary or secondary bacterial infection.

TREATMENT AND PROGNOSIS

Metronidazole (500 to 750 mg orally three times daily) is usually the first-line treatment. Clinical improvement is often seen within 72 to 96 hours, but treatment should be continued for 7 to 10 days. Tinidazole at 2g daily for 5 days is especially effective and may be better tolerated, in part because of its shorter treatment regimen.[A4] Alternatives include ornidazole (0.5g twice daily for 5 to 10 days) and nitazoxanide (500mg twice daily for 10 days).[A5] Drainage is not necessary, even for large abscesses of 5 to 10cm,[13] except in patients who do not respond within 5 days. The abscess usually will shrink by about 50% within a week, but the mean time to complete radiologic resolution is 3 to 9 months. Repeated imaging in a clinically improving patient may lead to unwarranted concern and unnecessary treatment.

Treatment must also address the removal of all of the cysts from the intestinal lumen in patients with evidence of intraluminal infection. A recommended treatment is iodoquinol (650 mg orally three times a day for 20 days) to prevent continued colonization and possible recurrence of the liver abscess. Alternative regimens for treating intraluminal infection include paromomycin (25 to 30 mg/kg per day orally in three divided doses for 7 days) or diloxanide furoate (500 mg orally three times day for 10 days). The overall mortality rate from amebic abscess is 1 to 3%, whereas it is less than 1% if diagnosed and treated early.

OTHER PROTOZOAL LIVER DISEASES

In addition to *E. histolytica*, other protozoal diseases that affect the liver include *Cryptosporidium* (Chapter 321), *Toxoplasma gondii* (Chapter 320), *Leishmania* (Chapter 319), *Plasmodium* (Chapter 316), and *Babesia microti* (Chapter 324) (Table 137-2).

HELMINTH INFECTIONS

Echinococcosis and Hydatid Cyst Disease

EPIDEMIOLOGY AND PATHOBIOLOGY

Human cystic echinococcosis (Chapter 325) is a zoonosis caused by the larval cestode *Echinococcus granulosus*. It is often referred to as hydatid cyst disease because of the watery cysts that characterize the infection.

The disease remains endemic in sheep-raising areas of the world, including Africa, the Mediterranean region of Europe, the Middle East, Asia, South America, Australia, and New Zealand. Dogs are the definitive hosts for *E. granulosus*, and sheep are the major intermediate hosts, although yaks, goats, and camels are other relevant intermediate hosts. Humans are only accidental hosts when they ingest food or water that is fecally contaminated with eggs. Human contact with sheepdogs, which are in frequent contact with livestock, is a major risk for infection.

The disease cycle begins when an adult tapeworm infects the intestinal tract of the definitive host (dogs usually). The adult tapeworm then produces eggs, which are expelled in the host's feces. Intermediate hosts become infected by ingesting the eggs of the parasite in fecally contaminated food. Inside the intermediate host, the eggs hatch and release tiny hooked embryos (called oncospheres), which travel in the blood stream and eventually lodge in the liver, lungs, or kidneys, where they develop into hydatid cysts. Inside these cysts grow thousands of tapeworm larvae, the next stage in the life cycle of the parasite.

CLINICAL MANIFESTATIONS

The initial infection is asymptomatic, but an enlarging hydatid liver cyst can cause abdominal pain, nausea, hepatomegaly, or a palpable mass. Patients may describe symptoms of mild upper right quadrant pain, urticarial rash, and episodes of pruritus. If the cyst ruptures, serious complications can develop. Cysts that perforate into the peritoneum can lead to the development of extrahepatic cysts and may induce an allergic reaction leading to an increase of eosinophils in the blood, pruritic urticaria, and systemic anaphylaxis. In most cases, however, cysts rupture into bile ducts, which can result in cholestatic jaundice, cholangitis, or biliary pain.

DIAGNOSIS

On ultrasound or CT scans (Fig. 137-4), the hydatid cysts are often large with a flaky appearance that is referred to as hydatid sand.[14] CT imaging also may show multiple daughter cysts or a fluid density cyst with peripheral focal areas of calcification.[15] Fluid is of variable density depending on the amount of proteinaceous debris.

Hydatid cysts of liver can be diagnosed by a serologic assay, the Weinberg reaction, but it can be falsely negative in up to 38% of cases. An enzyme-linked immunosorbent assay may be more sensitive. Eosinophilia is not a feature unless the cyst ruptures; in fact, there usually are no changes in blood chemistries.

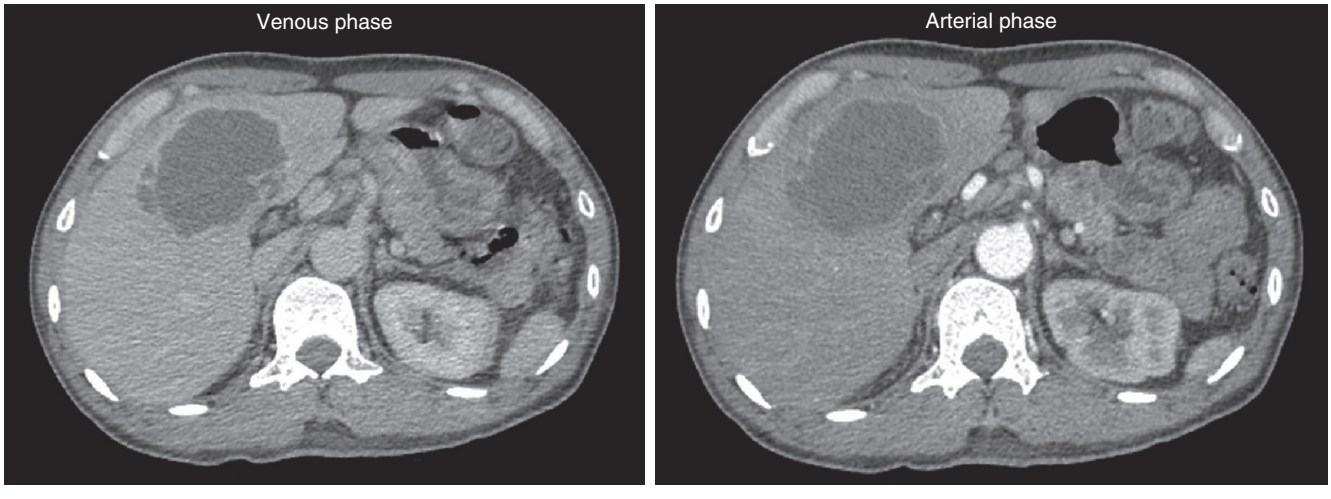

FIGURE 137-3. Computed tomographic scan of an amebic liver abscess. (Courtesy Dr. Chalermrat Bunchorntavakul, Bangkok, Thailand.)

TABLE 137-2 PARASITIC INFECTIONS INVOLVING THE LIVER

	CHARACTERISTICS	ENDEMIC AREAS	RISK FACTORS AND ENDEMIC AREAS	MAJOR HEPATIC MANIFESTATIONS	SYMPTOMS AND SIGNS	LABORATORY FINDINGS	RADIOGRAPHIC FEATURES	DIAGNOSIS	TREATMENT
MAJOR PROTOZOA									
Entamoeba histolytica	Ingested cysts develop into invasive trophozoites that colonize the colon and occasionally spread to the liver by the portal blood	Mexico, regions of Central and South America, India, and regions of Africa	Male gender, alcohol intake, HLA-DR3, oral and anal sex, and contaminated enema apparatuses	Amebic liver abscesses develop as a tissue response to trophozoite invasion with acute and chronic manifestations (see text)	Fever, RUQ pain, and substantial hepatic tenderness	Leukocytosis without eosinophilia, mild anemia, elevated serum AP, and high ESR	US, CT, and MRI can detect abscess but cannot always differentiate amebic from pyogenic. On CT or MRI, amebic abscess sometimes appears "cold" with bright rim	Imaging, serology, stool antigen test (microscopic evaluation of stool has a poor yield)	Metronidazole (500-750 mg PO tid × 7-10 days) *or* tinidazole (2 g daily × 5 days); Iodoquinol (650 mg PO tid × 20 days) *or* paromomycin (25-30 mg/kg PO daily in three divided doses × 7 days) *or* diloxanide furoate (500 mg PO tid × 10 days), also needed to eradicate intestinal colonization
OTHER PROTOZOA									
Cryptosporidium spp and microsporidia	Ingested cysts develop into trophozoites in intestinal mucosa	Worldwide distribution	AIDS	Biliary tract infection with obstruction and cholangitis	See Chapter 321	See Chapter 321	See Chapter 321	See Chapter 321	See Chapter 321
Toxoplasma gondii	Ingestion of oocysts in contaminated soil or water or in infected meat; systemic spread of tachyzoites in the circulation	Worldwide distribution	Consumption of undercooked meat, contact with soil, and travel outside the United States, Europe, or Canada	Immunocompetent: asymptomatic or hepatomegaly and mild LFT elevations Immunocompromised: occasional overt hepatitis	See Chapter 320	See Chapter 320	See Chapter 320	See Chapter 320	See Chapter 320
Leishmania spp	Sand fly bite transmits promastigotes; proliferation in the reticuloendothelial system	Worldwide distribution	Children age 10 and younger and immunocompromised adults Contact with sand flies	Hepatosplenomegaly months to years after infection	See Chapter 319	See Chapter 319	See Chapter 319	See Chapter 319	See Chapter 319
Plasmodium spp	Mosquito (*Anopheles*) bite transmits sporozoites	Multiple regions throughout the world	Exposure to anopheline mosquito bites	Proliferation in hepatocytes causes hepatomegaly, enzyme elevations, and jaundice	See Chapter 316	See Chapter 316	See Chapter 316	See Chapter 316	See Chapter 316
Babesia microti	Tick bite transmits the agent, which parasitizes erythrocytes	Europe	Asplenia is a risk for fatal hepatic failure, especially bovine babesiosis	Mild liver enzyme elevations	See Chapter 324	See Chapter 324	See Chapter 324	See Chapter 324	See Chapter 324
MAJOR HELMINTHS									
Schistosoma spp	Cercaria in fresh water penetrate the skin, travel by the circulation to portal vein radicals	*S. mansoni* found in South America, Africa, and Middle East *S. japonicum* found in Far East (mostly China and Philippines)	Contact with fresh water containing cercaria of schistosomes	Progressive presinusoidal blood flow obstruction, periportal fibrosis, portal hypertension, varices, ascites, splenomegaly	Initial infection presents as itching; later presentations include fever, diarrhea, chills, headaches, or hives Hematemesis from ruptured gastroesophageal varices	Eosinophilia and splenomegaly Seroconversion occurs within 4-6 weeks	Extensive calcification with typical "turtle-back" appearance along portal tracts	Rectal biopsy, liver biopsy, microscopic examination of stool	Praziquantel (single dose of 40 mg/kg for *S. haematobium*, *S. mansoni*, or *S. intercalatum* infections; two divided doses of 60 mg/kg for *S. japonicum* or *S. mekongi* infections) with a second dose 6-12 weeks later if necessary

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Echinococcus granulosus	Eggs of small (3-7 mm) tapeworms in stool of canid hosts; ingested eggs produce larval oncospheres that migrate to the liver and form cysts in sheep, humans, and other intermediate hosts	Worldwide distribution, found especially in sheep-raising areas (Africa, the Mediterranean region of Europe, the Middle East, Asia, South America, Australia, and New Zealand)	Ingestion of food or water fecally contaminated with eggs and human contact with sheepdogs	Initial infection asymptomatic Liver cysts increase in diameter by 1-5 cm yearly and cause variable abdominal pain, hepatomegaly, and variable eosinophilia Occasional cyst rupture, secondary bacterial infection	Enlarged hydatid cyst can cause abdominal pain, nausea, hepatomegaly, or a palpable mass Mild RUQ pain, urticaria, and episodes of pruritus	Positive Weinberg reaction (false-negative reaction in 38% of cases) or ELISA analysis Eosinophilia seen in ruptured cysts	On US or CT, cysts appear flaky, sometimes showing daughter cysts or peripheral focal calcification; fluid is of variable density	Imaging, Weinberg reaction, or ELISA	Albendazole (15 mg/kg/day, divided into two doses, up to maximum 400 mg, PO bid × 1-3 months; up to 6 months if necessary); cysts without daughter cysts can be drained percutaneously; complicated cysts, including those communicating with the biliary tree, often require surgical treatment
Echinococcus multilocularis	Eggs of small tapeworms in stool of foxes; ingested eggs produce oncospheres in the liver of rodents, humans, and other intermediate hosts	Endemic in Northern hemisphere	Human exposure increasing with growing fox populations	Metacestodes colonize the liver as a tumor-like mass of small vesicles	See Chapter 325	See Chapter 325	See Chapter 325	See Chapter 325	See Chapter 325
Fasciola spp	Leaf-shaped flukes up to 13 × 30 mm derived from ingested cysts; the fluke excysts in the duodenum, migrates directly across the bowel wall into the peritoneal cavity, and burrows directly into the liver (or occasionally out to the skin)	Worldwide distribution	Consumption of freshwater or aquatic plants contaminated by colonized livestock	Adult flukes live in the common and hepatic bile ducts, causing obstruction that leads to thickening of the ducts, dilation, and fibrosis of the proximal biliary tree	Acute: fever, abdominal pain, eosinophilia Chronic: symptomatic biliary obstruction, variable eosinophilia	Serologic tests include hemagglutination, complement fixation, ELISA, and counterimmunoelectrophoresis. Anemia, leukocytosis, eosinophilia, elevated AP, and hypergammaglobulinemia are often seen	CT is most useful: liver shows hypodense nodules or tortuous tracks; thickening of the liver capsule, subcapsular hematoma, and parenchymal calcification may also be seen	Serology, stool examination	Triclabendazole, 10 mg/kg PO once or twice
Opisthorchis spp and *Clonorchis sinensis*	Flukes of 8-25 mm derived from ingested cysts; the fluke excysts in the duodenum and migrates into the bile ducts	*Opisthorchis* spp: Southeast Asia, central and eastern Europe (particularly Siberia) *C. sinensis:* China, Japan, Vietnam, and Korea	Consumption of raw, pickled, dried, smoked, or salted freshwater fish or crayfish originating from East Asia or, in the case of *Opisthorchis felineus*, Russia and Eastern Europe	Acute: typically asymptomatic Chronic: abdominal pain, fever, anorexia, tender hepatomegaly, sometimes eosinophilia Late sequelae: intermittent biliary obstruction, cholelithiasis, cholecystitis, cholangitis, secondary bacterial abscesses, cholangiocarcinoma	Chronic infection presents as dyspepsia, abdominal pain, diarrhea, nausea, vomiting, anorexia, weight loss, fevers, hepatomegaly, and urticaria Acute presentation includes serum sickness, intrahepatic pigment stones, and facial edema Other rare complications are cholangitis, pancreatitis, and obstructive jaundice	Anemia, leukocytosis, eosinophilia, elevated AP, and hypergammaglobulinemia	US may detect flukes in biliary tree CT shows small hypodense nodules	Serology and stool examination	Praziquantel, 25 mg/kg/day PO tid × 2 days

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TABLE 137-2 PARASITIC INFECTIONS INVOLVING THE LIVER—cont'd

	CHARACTERISTICS	ENDEMIC AREAS	RISK FACTORS AND ENDEMIC AREAS	MAJOR HEPATIC MANIFESTATIONS	SYMPTOMS AND SIGNS	LABORATORY FINDINGS	RADIOGRAPHIC FEATURES	DIAGNOSIS	TREATMENT
Toxocara spp	Nematode infection disseminates to cause visceral larva migrans after ingestion of soil contaminated with dog or cat feces	Highest prevalence in southeastern United States	Consumption of food contaminated with soil containing eggs; distributed throughout the United States	Often an asymptomatic cause of eosinophilia (exclude *Trichinella, Strongyloides*, filaria, hookworm, schistosomiasis) Hepatomegaly is common, but nonhepatic manifestations dominate the clinical picture	See Chapter 327	See Chapter 327	See Chapter 327	See Chapter 327	See Chapter 327
OTHER HELMINTHS									
Ascaris lumbricoides	Ingested eggs develop into larvae that migrate to the lungs and are coughed and swallowed; develop into roundworms 15-30 mm long in the small intestine	Global distribution with higher prevalence in Africa, South America, India, and the Far East; 20% of the world's population is colonized	Consumption of fecally contaminated food or water, particularly in young children	Colonization is typically asymptomatic with eosinophilia Biliary migration of worms can cause symptomatic biliary obstruction, cholangitis, cholecystitis, and secondary bacterial liver abscess	Sensitized patients during pulmonary phase present with asthma-like symptoms, hemoptysis, chest pain, and cyanosis Urticaria and other allergic reactions sometimes seen Patients in intestinal phase show cognitive and nutritional impairment with abdominal pain, hepatomegaly, cholangitis, and obstructive jaundice	Leukocytosis with eosinophilia Hyperbilirubinemia occasionally seen	Movement of the worms within the biliary tree can sometimes be observed A "bull's-eye" appearance can be seen on cross-sectional imaging	Stool examination, imaging, and ERCP (Video 137-1)	Albendazole, 400 mg PO once
Capillaria hepatica	Ingested eggs develop into larvae in the intestinal mucosa; larvae migrate to the liver by portal blood flow and develop into short-lived roundworms	Human infection is rare	Consumption of food contaminated with rodent feces	Fever, eosinophilia, and hepatomegaly; subsequent foci of liver fibrosis, granulomas, and calcification in involved areas	Persistent fever, eosinophilia, and hepatomegaly most common Splenomegaly, anorexia, nausea, vomiting, night sweats, and altered bowel habits also seen	Anemia, eosinophilia, moderately elevated liver enzymes, increased ESR, and hypergammaglobulinemia	US shows nonspecific hyperechoic areas in the portal spaces	Stool and liver biopsy	Mebendazole, 200 mg PO bid × 20 days
Strongyloides stercoralis	Ingested eggs develop into 1.5- to 2.5-mm nematodes that invade the hepatic vasculature, lymphatics, and biliary tract	Tropical and subtropical areas including southeast United States and southern and eastern Europe	Consumption of food contaminated with soil containing eggs, infection with HTLV-1, and immunocompromised individuals	Hepatic disease in the setting of immunosuppression: jaundice, abdominal pain; eosinophilia is uncommon	Recurrent urticaria, abdominal pain, diarrhea, and cough; mild jaundice and hepatomegaly in the absence of splenomegaly	Eosinophilia and hypoalbuminemia Patients may have elevated liver enzymes	Imaging studies not used in diagnosis	Serology and stool examination	Ivermectin (single dose, 200 µg/kg orally × 1-2 days) or Albendazole (400 mg PO bid × 7 days)

AIDS = acquired immunodeficiency syndrome; AP = alkaline phosphatase; bid = twice daily; CT = computed tomography; ELISA = enzyme-linked immunosorbent assay; ERCP = endoscopic retrograde cholangiopancreatography; ESR = erythrocyte sedimentation rate; HLA = human leukocyte antigen; HTLV = human T-cell lymphotropic virus; LFT = liver function test; MRI = magnetic resonance imaging; PO = orally; RUQ = right upper quadrant; spp = species; tid = three times daily; US = ultrasonography.

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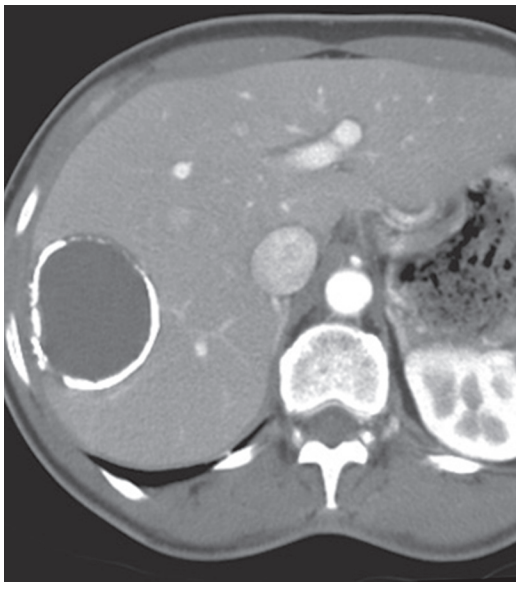

FIGURE 137-4. Computed tomographic scan of a hepatic echinococcal cyst. (Courtesy Dr. Chalermrat Bunchorntavakul, Bangkok, Thailand.)

TREATMENT AND PROGNOSIS

Uncomplicated, asymptomatic, inactive cysts can be observed without treatment.[16] Otherwise, however, drug therapy includes the antiparasitic agent albendazole (15 mg/kg/day, divided into two doses, to a maximum 400 mg orally twice daily) for 1 to 3 months, although a 6-month duration has also been used.[17] However, treatment with albendazole alone is not effective, so drainage is essential to the effective treatment of hydatid cysts. Cysts without daughter cysts can be drained percutaneously. Percutaneous drainage consisting of puncture and aspiration, followed by injection and reaspiration of a scolicidal solution is better than needle aspiration[A6] and has fewer side effects than open drainage, provided that patients receive concomitant antihelminthic therapy, such as albendazole starting 1 week before surgery and continuing 4 weeks postoperatively to minimize risk of secondary echinococcosis in the event of spillage. Chlorhexidine, hydrogen peroxide, 80% alcohol, or 0.5% cetrimide are preferred scolicidal agents rather than hypertonic saline or formalin.

Complicated cysts, however, typically require surgery. For example, if the cyst communicates with the biliary tree, injection of scolicidal agents carries an almost universal risk of secondary sclerosing cholangitis and is contraindicated. In such cases, the cyst must be treated surgically, either by cystectomy or hepatic resection.

The prognosis is generally good, with complete cure expected after successful percutaneous or surgical treatment. However, spillage occurs in 2 to 25% of cases, depending on the location of the cyst and the surgeon's experience. The operative mortality rate varies from 0.5 to 4% for the same reasons.

Schistosomiasis

EPIDEMIOLOGY AND PATHOBIOLOGY

Schistosomiasis is an infection of trematodes. *Schistosoma* (Chapter 326) cause periportal fibrosis and liver cirrhosis owing to deposition of eggs in the small portal venules.[18] *S. mansoni* and *S. japonicum* lead to liver disease. Infection with *S. mansoni* is found in parts of South America, Africa, and the Middle East. Infection with *S. japonicum* is found in the Far East, mostly China and the Philippines. Although primary infection does not occur in the United States, 5% of the world's population (200 million people) may be infected, thereby making it a major international health concern and highly prevalent in immigrants.

Humans become infected after contact with water that contains the infective stage (cercaria) of *schistosomes*. After penetration of the skin, the larvae migrate to the lungs and then to the venules of the mesentery, urinary bladder, or ureters. They release eggs in the venules of the mesentery, and the eggs enter the liver through the portal vein, where they become lodged in the terminal branches of the portal venules. The lodged eggs cause a granulomatous inflammation, and the lesions heal by periportal fibrosis. *S. japonicum* is more virulent than *S. mansoni* because its infections produce 10 times more eggs. Hepatic fibrosis may be independent of parasite burden related primarily to the host's inflammatory response.[19]

CLINICAL MANIFESTATIONS

Initial infection is manifested as itching that is caused by skin penetration by larvae. Several weeks later, patients may complain of fever, diarrhea, chills, headaches, or hives. At this time, patients will have eosinophilia. During the next 5 to 15 years, periportal liver fibrosis develops and leads to presinusoidal portal hypertension, splenomegaly (Chapter 154), and gastroesophageal varices (Chapter 124). With *S. japonicum*, however, the progression can be much more rapid, with little interval between the acute and chronic disease. Hepatic function is generally well preserved, and patients generally present with hematemesis from ruptured gastroesophageal varices.

DIAGNOSIS

Schistosomal eggs typically have lateral or terminal spines and are easy to detect on microscopic examination of feces or on a rectal biopsy specimen. Seroconversion occurs within 4 to 8 weeks of infection but cannot distinguish active infection from a history of exposure. Newer, more sensitive and specific molecular and immunodiagnostic techniques (including polymerase chain reaction–enzyme-linked immunosorbent assay systems) for detection of schistosome DNA in feces or serum and plasma have the potential to diagnose schistosomiasis in all stages of clinical disease, not only when the adult worms are producing eggs. Imaging may show extensive calcification with the typical "turtle-back" appearance along the portal tracts reflecting the clustered, calcified eggs along the portal triads. Ultrasound can assess the degree of periportal fibrosis.[20,21] Liver biopsy may demonstrate an egg of *S. mansoni* along with intense granulomatous change in the portal tract (E-Fig. 137-1).

TREATMENT AND PROGNOSIS

Praziquantel (a single dose of 40 mg/kg for *S. haematobium, S. mansoni*, or *S. intercalatum* infections; two divided doses of 60 mg/kg for *S. japonicum* or *S. mekongi* infections), which is the preferred treatment, is effective in 70 to 100% of cases. However, a second dose can be given 6 to 12 weeks later, particularly in patients with eosinophilia, high antibody titers, or persistent symptoms. Despite treatment, 5 to 20% of patients develop significant hepatic fibrosis. Treatment of portal hypertension may be necessary. The mortality is 0.05% with heavy *S. mansoni* infection and 1.8% for severe *S. japonicum* infection. Bleeding from esophageal varices is the most serious complication. Chronic infection can lead to hepatocellular carcinoma.

GRANULOMATOUS DISEASES OF THE LIVER

Granulomas, which are found in up to 15% of liver biopsies, can be an incidental finding or may represent a wide array of liver diseases (Table 137-3). A granuloma is an accumulation of epithelioid cells, including transformed macrophages, mononuclear cells, and other inflammatory cells. Granulomas may have associated necrosis (caseating), as in tuberculosis (Chapter 299), or may be non-necrotizing (noncaseating), as in sarcoidosis (Chapter 83). In addition, fibrin-ring granulomas are characterized by a vacuole encircled by a ring of fibrinoid necrosis and surrounded by lymphocytes and histiocytes, as seen in Q fever.

An incidental granuloma requires minimal further evaluation. Tuberculosis should be excluded. Sarcoidosis also should be considered because it is the most common cause of granulomas in the United States. An antimitochondrial antibody should be obtained to exclude primary biliary cirrhosis (Chapter 139). The use of potentially causative drugs should be stopped (see Table 137-3).

SARCOIDOSIS

Sarcoidosis (Chapter 83), which is the most frequently identified cause of hepatic granuloma in the United States, affects all racial and ethnic groups and occurs at all ages. In patients with sarcoidosis, the liver is the third most commonly involved organ, after the lymph nodes and lung; approximately 20 to 30% of patients with sarcoidosis have noncaseating granulomas on liver biopsy.[22] The classic granuloma is found mainly in the portal triads, with a cluster of large epithelioid cells and often with multinucleated giant cells.

CLINICAL MANIFESTATIONS AND DIAGNOSIS

Hepatic involvement of sarcoidosis is often subclinical, and only a minority of patients will present with pruritus, fever, abdominal pain, hepatomegaly,

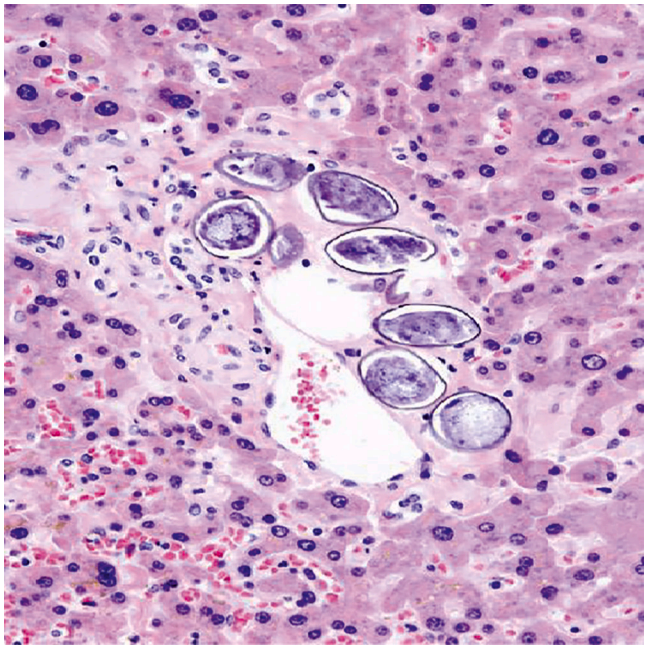

FIGURE E-137-1. Liver biopsy specimen demonstrating multiple eggs of *Schistosoma mansoni* in the portal tract. (Courtesy Raymundo Paraná Ferreira, Salvador, Brazil.)

TABLE 137-3 CAUSES OF GRANULOMATOUS LIVER DISEASE

DIAGNOSIS	SPECIAL AND UNIQUE FEATURES
Sarcoidosis	Evidence of pulmonary sarcoidosis, granulomas found on biopsy of other organs, elevated ACE level
Bacterial infections	
Mycobacterium tuberculosis	Caseating granulomas on biopsy, positive PPD response or interferon-gamma release assay, active pulmonary tuberculosis
Other mycobacteria *(M. avium-intracellulare, M. leprae, M. mucogenicum, M. bovis)*	HIV, exposure history
Other bacteria (brucellosis, listeriosis, melioidosis, tularemia, yersiniosis, Bartonellosis, Q fever, syphilis, psittacosis)	Fever, exposure history
Viral infections (cytomegalovirus, Epstein-Barr virus, hepatitis C, hepatitis B, hepatitis A)	Serology for acute or recent exposure
Fungal infections (histoplasmosis, coccidioidomycosis, blastomycosis, nocardiosis, candidiasis)	Fever, immunocompromised
Parasitic infections (schistosomiasis, *Ascaris lumbricoides*, toxoplasmosis, visceral leishmaniasis)	Travel to endemic regions, positive serologic testing
Primary biliary cirrhosis	Female sex, positive AMA, elevated IgM
Malignant diseases (Hodgkin disease, non-Hodgkin lymphoma, renal cell carcinoma)	Evidence of malignant disease in kidney or bone marrow
Drug reactions (allopurinol, chlorpropamide, phenylbutazone, sulfonamides, carbamazepine, glyburide, quinidine, quinine, diltiazem, hydralazine, rosiglitazone, phenytoin, methyldopa, procainamide, amoxicillin-clavulanic acid, mebendazole, mesalamine, acetaminophen, pyrazinamide, halothane, isoniazid, norfloxacin)	Exposure history
Toxins (beryllium, copper sulfate, Thorotrast)	Previous exposure history
Miscellaneous (talc, Crohn disease, granulomatosis with polyangiitis [formerly Wegener granulomatosis], post-jejunoileal bypass, mineral oil lipogranulomas, hepatic allograft rejection, chronic granulomatous disease)	History of IV drug use, history of liver transplantation, diarrhea

ACE = angiotensin-converting enzyme; AMA = antimitochondrial antibody; HIV = human immunodeficiency virus; IgM = immunoglobulin M; IV = intravenous; PPD = purified protein derivative.

cholestatic jaundice, or portal hypertension.[23] In some patients, the granulomatous injury and destruction of the interlobular bile ducts eventually cause ductopenia and a histologic picture similar to primary biliary cirrhosis (Chapter 141). In other patients, damage to the large bile ducts may lead to a syndrome that mimics primary sclerosing cholangitis (Chapter 141). Other patients may present with focal liver lesions suggestive of malignant neoplasm.

Patients typically have a marked elevation of the serum alkaline phosphatase level. Angiotensin-converting enzyme (ACE) levels also are characteristically elevated but may not be helpful in differentiating sarcoidosis from other chronic liver diseases, such as primary biliary cirrhosis, in which it also may be elevated. The presence of noncaseating granulomas in a patient with clinically suspected sarcoidosis generally establishes the diagnosis. However, granulomas do not correlate with liver function test results or duration of disease.

TREATMENT AND PROGNOSIS

In general, hepatic sarcoidosis does not need to be treated except in patients with other indications for treatment (Chapter 83). Corticosteroids improve liver function test results but do not alleviate portal hypertension, and serial biopsies often show little improvement. Other therapies used in uncontrolled studies include ursodeoxycholic acid, methotrexate, and azathioprine.[24] Sarcoidosis that leads to portal hypertension and fibrosis may ultimately require liver transplantation (Chapter 140), although sarcoidosis may recur in the new organ.

OTHER GRANULOMATOUS LIVER DISEASES

In addition to sarcoidosis, another major cause of granulomatous liver disease is tuberculosis (Chapter 299). Miliary tuberculosis, caused by *Mycobacterium tuberculosis*, commonly results in hepatic granulomas, and patients present with hepatomegaly, abnormal liver function test results, or both. A biopsy revealing caseating granulomas along with a positive PPD (purified protein derivative) response and active pulmonary tuberculosis can help in establishing a diagnosis. Other mycobacteria are also known to cause granulomatous liver disease including *M. avium intracellulare*, *M. genavense*, and *M. scrofulaceum* (Chapter 300).

Other causes of granulomatous liver disease include zoonotic infections such as cat-scratch disease (Chapter 291), Q fever (Chapter 302), and brucellosis (Chapter 286). Cat-scratch disease, which primarily affects children, is caused by *Bartonella henselae*, with cats serving as the main reservoir for the organism. Patients typically present with lymphadenopathy associated with persistent pyrexia of unknown origin, abdominal pain, and weight loss. *B. henselae* can be identified by a Warthin-Starry stain or an imaging study may demonstrate scattered defects in the liver. Q fever is caused by the intracellular gram-negative rickettsial organism *Coxiella burnetii*. Most infections are asymptomatic, but may have self-limited influenza-like symptoms, pneumonia, and hepatitis. A liver biopsy may demonstrate fibrin-ring granulomas (doughnut shaped) in the background of nonspecific reactive hepatitis and steatosis. Brucellosis, which is not common in the United States, is caused by at least four species of *Brucella: B. abortus*, *B. suis*, *B. melitensis*, and *B. canis*. The disease is manifested as recurrent high fevers, drenching sweats, malaise, arthralgia, fatigue, abdominal pain, anorexia, and headaches. Patients often have hepatomegaly. Hepatic biochemical abnormalities are nonspecific and show elevated serum levels of aminotransferases and alkaline phosphatase. The granulomas formed by this infection are typically smaller than those caused by sarcoidosis or tuberculosis, and a definitive diagnosis can be established by serologic testing.

It is important to keep in mind that hepatic granulomas are formed naturally as a consequence of the immune response, so they may be seen in infections with hepatic involvement. Many of the diseases noted above can manifest as granulomatous liver disease (see Table 137-3): listeriosis (Chapter 272), yersiniosis (Chapter 288), candidiasis (Chapter 310), histoplasmosis (Chapter 308), coccidioidomycosis (Chapter 308), and schistosomiasis (Chapter 326). Viral infections (e.g., cytomegalovirus, hepatitis A, hepatitis B, and hepatitis C), primary biliary cirrhosis (Chapter 139), malignancies, and certain drug reactions (Chapter 136) have all been etiologically linked to granulomatous liver disease.

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For the General References and other additional features, please visit Elsevier eBooks+ at https://ebooks.health.elsevier.com.

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138 ALCOHOLIC AND NONALCOHOLIC STEATOHEPATITIS

NAGA P. CHALASANI AND JACQUELYN MAHER

Alcohol-associated liver disease and nonalcoholic fatty liver disease (NAFLD), which represent two of the most common forms of liver disease, can lead to cirrhosis, liver cancer, liver failure, and death. Although these two conditions have different risk factors and natural histories, in both conditions (Table 138-1) the hepatocytes are characterized by macrovesicular steatosis, which is the accumulation of triglycerides as one large cytoplasmic globule that displaces the nucleus. In microvesicular steatosis, cytoplasmic accumulation of fat occurs as multiple small globules with a central (intact) nucleus.

ALCOHOL-ASSOCIATED LIVER DISEASE

DEFINITION

Excessive alcohol consumption (Chapter 364) causes alcohol-associated liver disease and can significantly worsen other liver disorders, such as viral hepatitis (Chapter 135) and hemochromatosis (Chapter 196). Although most individuals who consume alcohol do not consume it excessively and do not develop any physical or social consequences, some alcoholics consume sufficient alcohol and, presumably because of other predisposing factors, develop alcohol-associated liver disease. Alcohol-associated liver disease is a spectrum of chronic liver diseases ranging from alcoholic fatty liver to acute alcoholic hepatitis and cirrhosis.

Alcohol-associated fatty liver disease will develop in nearly 90% of individuals who consume alcohol heavily (on average, >6 drinks per day), but only a subset of individuals develop the severe conditions of alcoholic hepatitis and alcohol-associated cirrhosis. Genetic predisposition and environmental factors are likely to play a role in the pathogenesis of acute alcoholic hepatitis and alcohol-associated cirrhosis, but such factors have not been well defined. Nearly 50% of the patients with alcoholic hepatitis have preexisting cirrhosis (Chapter 139), and individuals who do not yet have cirrhosis are at high risk for its development, especially if they continue to consume alcohol.

EPIDEMIOLOGY

The true prevalence of alcoholic liver disease is not known, but nearly 1% of North American adults are thought to have alcohol-associated liver disease. Among individuals with alcohol use disorder, the prevalence of alcohol-associated liver disease is about 12%.[1] Even these figures are considered underestimates, however, because milder forms of alcohol-associated liver disease are not associated with symptoms and often are unrecognized. Alcohol-associated liver disease accounts for about 50% of deaths from cirrhosis and 40 to 45% of all deaths from liver disease. Over the last decade, alcohol-associated liver disease was the primary cause of almost one third of liver transplants (Chapter 140) in the United States, thereby replacing hepatitis C virus infection as the leading cause of liver transplantation in the United States. Based on an increase in the frequency of alcohol consumption, especially high-risk drinking, the incidence of alcoholic liver disease in the U.S. population is likely to increase significantly in the future.

PATHOBIOLOGY

The mechanisms underlying alcoholic liver injury can be broadly categorized into those caused by the effects of alcohol directly on hepatocytes and those caused by the effects mediated by Kupffer cells. The hepatocyte-specific mechanisms include the altered redox state induced by alcohol and aldehyde dehydrogenase reactions; the oxidative stress and lipid peroxidation caused by the induction of CYP2E1 enzymes and the mitochondrial electron transfer system; the effects of alcohol upon the nuclear transcription factors AMP kinase and SREBP-1c; protein adduct formation; and altered methionine and folate metabolism with resulting stress on the endoplasmic reticulum. Chronic alcohol consumption increases gut permeability, and the resulting portal endotoxemia activates Kupffer cells. Activated Kupffer cells release a number of proinflammatory mediators. These include tumor necrosis factor-α (TNF-α); transforming growth factor-β1; interleukins 1, 6, 8, and 10; and platelet-derived growth factor. TNF-α has a plethora of biologic effects and causes hepatocyte apoptosis, whereas transforming growth factor-β1 and platelet-derived growth factor play important roles in stellate cell activation, collagen production, and hepatic fibrosis.

Of the known risk factors for the development of alcohol-associated liver disease (Table 138-2), the amount of alcohol consumed is the single most important. For unclear reasons, only 30 to 35% of individuals with heavy and long-term drinking develop alcoholic hepatitis, and fewer than 20% develop cirrhosis. Women are at higher risk; for example, the risk of alcoholic cirrhosis increases after 10 years of alcohol consumption at quantities of more than 60 to 80 g/day in men, whereas in women, it can develop at quantities of only more than 20 g/day. Moreover, the peak incidence of alcohol-associated liver disease in women is approximately a decade earlier than in men. The type of alcoholic beverage consumed may not be as critical, but "spirits" and beer may be more hepatotoxic than wine. Hispanics and American Indians may be predisposed to more significant alcoholic liver injury. Both obesity and protein-calorie malnutrition, in which micronutrients and antioxidant capacity are diminished, also are important predispositions.

Polymorphisms in genes associated with lipid metabolism (*PNPLA3* and *HSD17B13*), alcohol metabolism (alcohol and aldehyde dehydrogenases and cytochrome P-450 enzymes), and dysregulated cytokine production (e.g., *TNF*) may influence susceptibility to alcohol-related liver injury. Candidate genes impacting alcohol-related cirrhosis include *PNPLA3, HSD17B13 TM6SF2* , and *MBOAT7, MARC1* , and *HNRNPUL1*.[2] In patients with other forms of chronic liver disease (e.g., viral hepatitis B or C), concomitant alcohol consumption significantly aggravates liver injury.

CLINICAL MANIFESTATIONS

Patients with alcohol-associated liver disease may have signs and symptoms from underlying alcoholism as well as those caused by liver disease. Stigmata of chronic alcoholism include palmar erythema (see Fig. 132-2), spider nevi, bilateral gynecomastia, testicular atrophy, bilateral parotid enlargement, and Dupuytren contractures (Fig. 138-1). The clinical features of liver disease will depend on the stage of alcohol-associated liver disease, that is, whether a patient has fatty liver or more advanced liver disease, such as alcoholic hepatitis and cirrhosis.

Patients with alcohol-associated fatty liver disease are generally asymptomatic, but some patients may have anorexia, fatigue, right upper quadrant discomfort, and tender hepatomegaly. These patients also may have biochemical

TABLE 138-1 COMMON CAUSES OF MACROVESICULAR AND MICROVESICULAR STEATOSIS

MACROVESICULAR STEATOSIS	MICROVESICULAR STEATOSIS
Obesity, type 2 diabetes, metabolic syndrome, and dyslipidemia (nonalcoholic fatty liver disease)	Reye syndrome
Excessive alcohol consumption	Medications (valproate, antiretroviral medicines, intravenous tetracycline)
Hepatitis C (genotype 3)	Heat stroke
Wilson disease	Acute fatty liver of pregnancy
Lipodystrophy starvation	HELLP syndrome
Jejunoileal bypass	Inborn errors of metabolism (lecithin–cholesterol acyltransferase deficiency, cholesterol ester storage disease, Wolman disease)
Parenteral nutrition	
Medications (amiodarone, methotrexate, tamoxifen, corticosteroids, antipsychotics)	

HELLP = *h*emolysis, *e*levated *l*iver enzymes, and *l*ow *p*latelets.

TABLE 138-2 RISK FACTORS FOR ALCOHOL-ASSOCIATED LIVER DISEASE AND NONALCOHOLIC FATTY LIVER DISEASE (NAFLD)

ALCOHOL-ASSOCIATED LIVER DISEASE	NAFLD
MAJOR	**MAJOR**
Amount and duration of alcohol consumption	Obesity
Female gender	Type 2 diabetes
Genetic factors	Dyslipidemia
Protein-calorie malnutrition	Metabolic syndrome
MINOR	**MINOR**
Type of beverage	Polycystic ovary syndrome
Binge drinking	Hypothyroidism
Obesity	Obstructive sleep apnea
Hispanic ethnicity	Hypopituitarism
	Hypogonadism

ABSTRACT

Nonalcoholic and alcoholic fatty liver diseases are common chronic liver diseases that can lead to cirrhosis, liver failure, and liver cancer. Alcohol-associated liver disease comprises a spectrum ranging from alcoholic fatty liver to alcoholic hepatitis, alcohol-associated cirrhosis, and related liver failure and cancer. Heavy drinking is obviously the most important risk factor, although malnutrition and genetic factors may play a role in the disease progression and decompensation. Abstinence from drinking is the most important therapeutic option. For nonalcoholic fatty liver disease, the spectrum ranges from fatty liver to steatohepatitis and related cirrhosis, to liver failure, and to cancer. Obesity, type 2 diabetes, and dyslipidemia are the most important risk factors. Weight loss, vitamin E (800 IU/day), and pioglitazone (30 mg/day) are useful treatments.

KEYWORDS

alcoholic hepatitis
alcoholic fatty liver
alcohol-associated cirrhosis
nonalcoholic fatty liver disease
nonalcoholic steatohepatitis
hepatocellular carcinoma

FIGURE 138-1. Dupuytren contracture. (From Gudmundsson KG, Jonsson T, Arngrimsson R. Guillaume Dupuytren and finger contractures. *Lancet*. 2003;362:165-168.)

evidence of alcoholism and alcohol-associated liver disease with macrocytosis as well as elevated levels of aspartate aminotransferase (AST) and γ-glutamyl transpeptidase. Patients with alcohol-associated fatty liver typically do not have jaundice, ascites, or splenomegaly.

Patients with alcoholic hepatitis may have a more dramatic presentation with severe malaise, fatigue, anorexia, fever, evidence of protein-calorie malnutrition, and features of decompensated liver disease, including jaundice, coagulopathy, ascites, and encephalopathy. However, these classic features are not universally present. Physical examination invariably shows at least some features of chronic alcoholism, and jaundice (see Fig. 132-1), ascites (see Fig. 132-4), and splenomegaly are common. The laboratory examination findings are typically abnormal. Common hematologic abnormalities include leukocytosis with neutrophil predominance, macrocytic anemia (Chapter 150), thrombocytopenia (Chapter 158), and prolonged prothrombin time. Liver biochemistries (Chapter 133) are abnormal with an elevated AST and ratio of AST to alanine aminotransferase (ALT), alkaline phosphatase, γ-glutamyl transpeptidase, and total bilirubin but decreased levels of serum albumin. The AST rarely exceeds 300 IU/L. Serum electrolyte abnormalities, including hypokalemia (Chapter 103), hypomagnesemia (Chapter 105), hypocalcemia (Chapter 227), and hypophosphatemia (Chapter 105), are frequent. Patients with alcoholic cirrhosis have the same clinical features that are common to other types of cirrhosis (Chapter 139) but also with striking features of underlying chronic alcoholism, including gynecomastia in males and significant muscle wasting.

DIAGNOSIS

The diagnosis of alcohol-associated liver disease strongly depends on the history of excessive alcohol consumption and the presence of liver disease.[3,4] Although laboratory abnormalities are not specific for alcohol-associated liver disease, they can be suggestive in the context of excessive alcohol consumption. An AST/ALT ratio of greater than 2 is typical in alcohol-associated liver disease, and ALT values greater than 150 to 200 IU/L are very rare in alcohol-associated liver disease. Serology testing for coexisting chronic viral hepatitis (Chapter 135) is critical. Diagnostic dilemmas arise when a patient denies excessive alcohol consumption in the face of clinical features that are suggestive of alcohol-associated liver disease. Interviewing family members about specific alcohol consumption may be helpful in the accurate ascertainment of alcohol consumption. Serum and urinary levels of ethyl glucuronide and ethyl sulfate are sensitive and specific markers of recent alcohol consumption, but they are not commonly measured in clinical practice. Hepatic imaging by ultrasound, computed tomography, or magnetic resonance imaging will show changes consistent with hepatic steatosis or more advanced forms of liver disease, such as cirrhosis and portal hypertension. Imaging is also important to exclude other forms of liver disease, including malignant disease and biliary obstruction. Imaging findings suggestive of alcohol-associated liver disease include an enlarged caudate lobe, greater visualization of the right posterior hepatic notch, and focal fat sparing or geographic fat distribution.

Because specific treatments for heavy alcohol drinking and alcohol-associated hepatitis may be harmful in patients with other liver diseases, it is important to exclude other predominant or coexisting liver diseases, including chronic viral hepatitis (Chapter 135) and drug-induced liver injury, especially from acetaminophen (Chapter 136), by history, blood tests, and biopsy if needed. Hyperferritinemia generally reflects an acute phase reactant, rather than an iron overload disorder, so it usually will return to normal when the acute liver injury resolves.

Liver biopsy is the key to distinguishing alcohol-associated liver disease from other entities, characterizing the nature of the liver disease, and determining whether a patient has fatty liver or more advanced alcoholic hepatitis. Histologic features of alcohol-associated fatty liver include macrovesicular steatosis that is predominantly centrilobular (zone 3) in nature. In alcoholic hepatitis, the biopsy is more striking and reveals macrovesicular steatosis, lobular neutrophilic infiltration, Mallory hyaline, ballooning degeneration of the hepatocytes, and perivenular fibrosis. In general, patients with alcoholic hepatitis also have histologic evidence of chronic liver injury in the form of more advanced fibrosis (periportal or bridging fibrosis or cirrhosis).

TREATMENT

Total abstinence, which is the most important treatment measure, is mandatory for the improvement of the clinical and histologic features of alcohol-associated liver disease. Its benefits are unequivocal, even in patients with severe decompensation. However, long-term abstinence is difficult to achieve, so a multidisciplinary approach with counseling and medications that promote abstinence should be considered. Disulfiram is not commonly used because of its poor tolerability and hepatotoxicity. Opioid antagonists, such as naltrexone (50 mg/day for up to 6 months or even longer), nalmefene (20 mg/day as maintenance), and acamprosate (333-mg tablets, two tablets three times each day for 1 year), can help promote abstinence when they are used as part of a multidisciplinary approach.

Alcohol-associated fatty liver disease requires no specific treatment other than abstinence. Patients with alcoholic hepatitis, however, have increased short- and long-term mortality and should be considered for therapeutic interventions in addition to mandatory abstinence.[5,6] If a patient's clinical manifestations and/or liver biopsy findings are consistent with alcoholic hepatitis and there is no evidence of other inflammatory liver diseases, such as hepatitis C (Chapter 135), prednisolone (40 mg/day for 4 weeks) should be given to carefully selected patients[7] with severe alcoholic hepatitis who have a score higher than 32 on the Maddrey discriminant function (4.6 × [patient's prothrombin time − control prothrombin time] + total bilirubin level) and encephalopathy but do not have gastrointestinal bleeding or systemic infection. Studies have suggested that a Model for End-Stage Liver Disease (MELD) score (see Table 139-2) higher than 21 can substitute for the Maddrey score to guide the use of prednisolone. Such therapy appears to reduce mortality at 1 month,[A1] but probably not thereafter.[A2] Adding intravenous *N*-acetylcysteine (on day 1 at a dose of 150, 50, and 100 mg/kg of body weight in 250, 500, and 1000 mL of 5% glucose solution during a period of 30 minutes, 4 hours, and 16 hours, respectively; and on days 2 through 5, 100 mg/kg/day in 1000 mL of 5% glucose solution) to prednisolone appears to be superior to prednisolone alone in terms of a significantly lower mortality at 1 month and a somewhat but not significantly lower mortality at 6 months.[A3] Pentoxifylline is not of incremental value when added to corticosteroids.[A4] A variety of newer agents are currently in clinical trials.[8]

All patients with alcoholic hepatitis and alcoholic cirrhosis should be assessed and treated for protein-calorie malnutrition and micronutrient deficiency. Hospitalized patients with severe decompensation should be considered for enteral nutrition (Chapter 198).

Complications such as ascites, spontaneous bacterial peritonitis, encephalopathy, variceal bleeding, hepatorenal syndrome, osteoporosis, and hepatopulmonary syndrome may occur in patients with decompensated alcoholic cirrhosis and must be managed carefully (Chapter 139). Liver transplantation is a reasonable option in patients with decompensated alcoholic cirrhosis, and observational data suggest that early liver transplantation can improve survival in patients with severe, medically refractory alcoholic hepatitis. Although 6 months of abstinence and strong social support are generally required for eligibility (Chapter 140),[9] liver transplantation can be performed with good outcomes in severely ill but highly selected patients with acute alcoholic hepatitis before completing 6 months of abstinence. Patients with alcoholic cirrhosis, especially males, are at risk for hepatocellular carcinoma (Chapter 181) and should be screened with semiannual liver imaging and serum α-fetoprotein levels. They also may be at risk for extrahepatic malignant disease, notably head and neck, lung, and esophageal cancer. For Dupuytren contracture, injection of collagenase *Clostridium histolyticum* can reduce the severity and improve the range of motion significantly.

PROGNOSIS

Alcoholic fatty liver is generally reversible with total abstinence for a few months. The survival of patients with alcoholic hepatitis has improved over the last decade, but about 20% of patients die within 6 months after presentation, and patients with biopsy-documented alcohol-associated liver disease have a five-fold increased risk of death compared with that of the general population.[10]

Predictors of poor outcome include the severity of disease as quantified by approaches such as the MELD score (Chapters 139 and 140), the severity of fibrosis and the neutrophilic infiltration on liver biopsy, and continued alcohol use. Some data also suggest a poorer prognosis in patients who are homozygous for the rs738409:G variant in the *PNPLA3* gene.

NONALCOHOLIC FATTY LIVER DISEASE

DEFINITIONS

On histologic examination, NAFLD resembles alcohol-associated liver disease, but it occurs in individuals without significant alcohol consumption. Average alcohol consumption of more than two drinks per day in men and more than one drink per day in women generally is not consistent with a diagnosis of NAFLD. In addition, the definition of NAFLD excludes patients with a history of exposure to steatogenic medications, such as amiodarone, methotrexate, or tamoxifen.

NAFLD encompasses a spectrum of abnormal liver histologic features, ranging from simple steatosis to nonalcoholic steatohepatitis (NASH) and cirrhosis. In simple steatosis, liver histology reveals macrovesicular steatosis without ballooning degeneration of hepatocytes or liver fibrosis. NASH, which is a more advanced form of NAFLD, is histologically characterized by macrovesicular steatosis, ballooning degeneration of the hepatocytes, and sinusoidal fibrosis.

EPIDEMIOLOGY

NAFLD is one of the most common causes of elevated liver enzymes and chronic liver disease in the Western world. Its incidence in adults and children is rising rapidly because of the ongoing epidemics of obesity (Chapter 201), type 2 diabetes mellitus (Chapter 210), and metabolic syndrome. Its prevalence is high in certain populations of patients; for example, nearly 80% of patients with type 2 diabetes and 90% of morbidly obese individuals have imaging evidence of NAFLD, but it also can occur in about 7% of non-obese individuals in the United States and over 15% of non-obese Asians. Nearly one third of adults in westernized countries are estimated to have NAFLD,[11] and about 5% of adults may have NASH.[12] These percentages compare reasonably well with other data suggesting that the prevalence of cirrhosis from NAFLD is about 2%. Hispanics and Whites are at higher risk for NAFLD, whereas its prevalence is intriguingly low in African Americans.

PATHOBIOLOGY

The major risk factors for NAFLD include obesity, type 2 diabetes mellitus (Chapter 210), metabolic syndrome, and dyslipidemia. Other comorbidities associated with NAFLD include polycystic ovary syndrome (Chapter 217), hypothyroidism (Chapter 207), hypopituitarism (Chapter 205), hypogonadism (Chapter 216), and sleep apnea (Chapter 374).

Two fundamental but related defects in NAFLD are insulin resistance/hyperinsulinemia and excessive levels of circulating nonesterified fatty acids, which are released from adipose tissue and taken up by hepatocytes.[13] An excessive influx of nonesterified fatty acids into hepatocytes results in macrovesicular steatosis, which is predominantly centrilobular in location.

In addition, patients with NAFLD have increased de novo lipogenesis in the liver. Although patients with NAFLD robustly esterify free fatty acids into neutral triglycerides, free fatty acids that remain unesterified within hepatocytes are considered the primary mediators of cell injury (lipotoxicity). In the background of hepatic steatosis, factors that promote cell injury, inflammation, and fibrosis include oxidative stress, endoplasmic reticulum stress, apoptosis, adipocytokines, and stellate cell activation. The sources of oxidative stress include mitochondria and microsomes. Adipocytokines that play an important role in the pathogenesis of NAFLD include adiponectin and TNF-α. It is unclear why some patients with NAFLD exhibit NASH, whereas other patients with a comparable risk factor profile have only simple steatosis. There is a consistent and significant relationship between *PNPLA3* genetic polymorphisms and the severity of steatosis and other histologic features of NAFLD. Other polymorphisms that correlate positively with NAFLD are formed in *GCKR, TM6SF2* , and *MBOAT7*. Conversely, a polymorphism in *HSD17B13* offers protection against NAFLD and its severity.

CLINICAL MANIFESTATIONS

NAFLD is often asymptomatic but may rarely cause fatigue and right upper quadrant pain. Physical examination may reveal hepatomegaly, palmar erythema (see Fig. 132-2), and spider nevi. If liver disease is advanced, the features of liver failure, such as ascites, encephalopathy, and abdominal collateral vessels, are present. Simple steatosis is benign with a minimal risk of cirrhosis, whereas NASH is progressive and can lead to cirrhosis (Chapter 139) and liver failure (Chapter 140). In up to 20% of patients with NASH, liver histologic features will worsen and cirrhosis will develop during a 10- to 15-year period. Severe obesity, advancing age, and diabetes are thought to be risk factors for disease progression. Progressive disease during the early phase can be identified by a repeat liver biopsy or by noninvasive imaging tests, such as vibration-controlled transient elastography or magnetic resonance elastography. In later stages, however, the signs and symptoms of portal hypertension (e.g., abdominal collateral vessels and low platelet count) indicate the development of cirrhosis. Patients with NASH-induced cirrhosis are at risk for development of hepatocellular carcinoma (Chapter 181). Patients with NAFLD have several metabolic risks that predispose them to atherosclerosis, and coronary artery disease is the most common cause of death in patients with NAFLD.

DIAGNOSIS

NAFLD is generally suspected when aminotransferase levels are asymptomatically elevated in an individual with metabolic risk factors (obesity, diabetes, or the metabolic syndrome) or when liver imaging (ultrasound, computed tomography, or magnetic resonance imaging) obtained for another reason shows fatty infiltration (Fig. 138-2).[14] The diagnosis of NAFLD requires that there is no history of previous or ongoing significant alcohol consumption, no exposure to steatogenic medications, and no evidence of other causes of liver disease, such as viral hepatitis B or C. Elevated levels of aminotransferases, although common, are not required for the diagnosis of NAFLD. In contrast to alcohol-associated liver disease, ALT levels are higher than AST levels, but they rarely exceed 250 IU/L. In general, AST and ALT levels do not have diagnostic or prognostic significance. Mild hyperferritinemia is common and should not be confused with hereditary hemochromatosis (Chapter 196). Similarly, low-grade autoantibody (antinuclear antibody, anti–smooth muscle antibody) positivity is not uncommon and should not be confused with autoimmune liver disease (Chapter 135). Because steatosis is common in patients with Wilson disease (Chapter 195), serum ceruloplasmin levels should be obtained as part of the diagnostic evaluation in individuals who are younger than age 45 years.

Fatty liver on ultrasonography has a positive predictive value of only 77% and a negative predictive value of only 67% compared with liver biopsy. Abdominal magnetic resonance imaging is more accurate, but its high cost limits its usefulness in routine practice. Because neither of these imaging tests can differentiate simple steatosis from NASH or identify cirrhosis until hepatic fibrosis has caused nodular liver or overt portal hypertension, liver biopsy is required to establish the presence of NASH or cirrhosis. Common indications for a percutaneous liver biopsy in patients with NAFLD include persistently high aminotransferase levels, inability to exclude a competing or a coexisting cause (e.g., iron overload or autoimmune liver disease), and clinical suspicion of NASH and advanced fibrosis. In patients with NASH, liver histology shows steatosis, inflammation, ballooning, and fibrosis (Fig. 138-3).[15] However, liver histology alone cannot reliably distinguish NASH

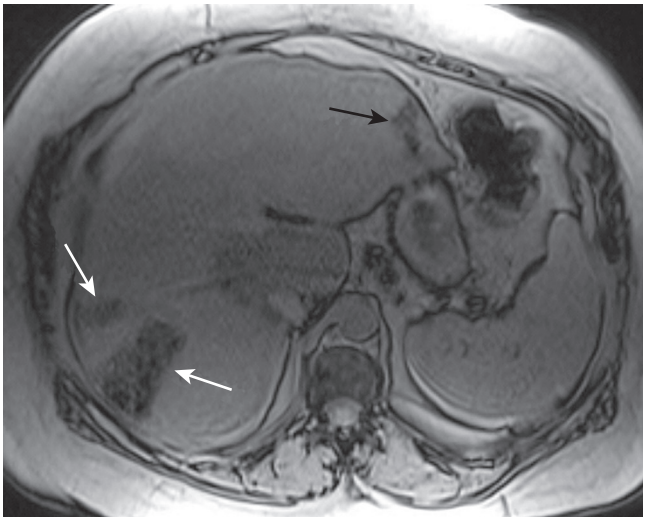

FIGURE 138-2. Magnetic resonance image of chronic liver disease due to nonalcoholic fatty liver disease. Out-of-phase T1-weighted images show focal fat infiltration of varying shapes in right lobe *(white arrows)* and left lobe *(black arrow)*. (Courtesy Professor Kumar Sandrasegaran, Indiana University School of Medicine, Indianapolis, Ind.)

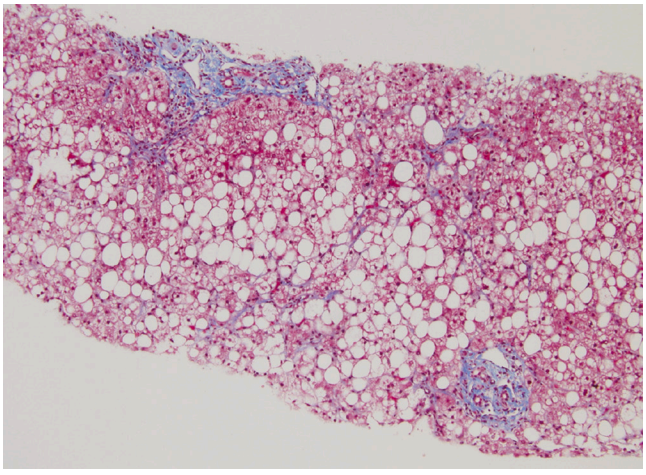

FIGURE 138-3. Liver biopsy specimen showing nonalcoholic steatohepatitis with increased fat and with early cirrhosis. (Courtesy of the NASH Clinical Research network.)

from alcoholic hepatitis because these two entities have remarkably similar microscopic features. Vibration controlled transient elastography, which now can be performed as a point-of-care test, can provide an estimate of liver fibrosis in NAFLD in clinical practice.

TREATMENT

Lifestyle modification with dietary restriction and regular exercise is the first choice of treatment for NAFLD.[16,17] Weight reduction, a low refined-sugar diet, and increased physical activity reduce liver fat, improve glucose control and insulin sensitivity, and improve histopathologic features.[A5,A6] It is generally recommended that patients with NAFLD lose 10% of their body weight in a gradual fashion, but this goal is difficult to achieve. If resources are available, a multidisciplinary approach with behavioral therapy, dietary advice, and monitoring by a professional nutritionist and an exercise expert is more successful than a prescriptive approach (Chapter 201). Weight loss via bariatric surgery in obese patients (Chapter 201) has been reported to resolve liver biopsy finding in about 80% of patients, with a progressive reduction in fibrosis.[18]

Pharmacotherapy options[19–21] include vitamin E (800 IU of α-tocopherol administered daily for 2 years), which can significantly improve liver enzymes and histologic findings in NASH and NAFLD.[A7] Statins (e.g., atorvastatin 20 mg daily) with or without vitamins C and E can improve liver test results and reduce subsequent NAFLD.[A8] Liraglutide (a glucagon-like peptide-1 agonist at 1.8 mg daily subcutaneously) can safely lead to a histologic resolution of NASH.[A9,A10] Semaglutide (subcutaneously daily at 0.4 mg for 72 weeks) also has been highly effective in resolving steatohepatitis but does not significantly improve fibrosis in individuals with NASH and clinically significant fibrosis.[A11] Lanifibranor (a peroxisome proliferator-activated receptor agonist at 1200 mg daily) can improve the inflammatory components of NASH and may reduce fibrosis.[A12]

Thiazolidinedione insulin sensitizers (pioglitazone and rosiglitazone) improve steatosis, inflammation, ballooning, and perhaps fibrosis, but with the side effect of an average gain of nearly 10 pounds.[A13] Unfortunately, the weight gain that is common with thiazolidinediones may offset the histologic benefits that they offer.

Supplemental omega-3 polyunsaturated fatty acids have shown promise in small controlled trials.[A14] Treatment with pentoxifylline (400 mg three times daily) may improve liver enzymes and liver histologic findings in individuals with NASH.

Obeticholic acid (an FXR agonist) has shown some histologic efficiency,[A15] but longer-term studies are awaited. An engineered fibroblast growth factor 19 (FGF19) administered over 12 weeks has shown dramatic improvement in hepatic fat in a proof-of-concept study in adults with NASH.[A16,A17] Inhibition of dihydroceramide desaturase 1 is a potential target for treating hepatic steatosis.[22] Another potential agent is resmetirom, a selective thyroid hormone receptor-β agonist (80 mg orally twice daily).[A18]

Patients with NAFLD often have dyslipidemia that puts them at excessive risk for coronary artery disease; their dyslipidemia (Chapter 190) should be treated aggressively with statins and other lipid-lowering agents, which can be safely administered to patients with NAFLD and NASH. In morbidly obese individuals with NASH and other significant metabolic comorbidities, foregut bariatric surgery can lead to significant improvement in hepatic histologic features,[A19] but the physician must exclude the presence of portal hypertension before offering this type of surgery. Carefully selected patients with decompensated cirrhosis due to NASH can be treated with liver transplantation (Chapter 140), but recurrence during the post-transplantation period is common.[23]

PREVENTION

The measures to prevent NAFLD include maintaining optimal body weight, exercising regularly, and treating any associated metabolic comorbidities such as diabetes and dyslipidemia. Avoidance of saturated fat, high fructose intake, and alcohol consumption may reduce the development of NAFLD.

PROGNOSIS

Steatosis alone is generally benign, whereas steatohepatitis is often progressive. Liver fibrosis on biopsy is also independently associated with long-term liver failure and mortality.[24,25] One third of NAFLD patients may have remission within 7 years, mostly depending on modest weight reduction. Otherwise, however, data are sparse regarding the risk and risk factors for the progression of NAFLD and NASH to cirrhosis and liver failure.

Because NAFLD often coexists with one or more components of the metabolic syndrome, its presence reflects guarded long-term overall prognosis. The long-term complications in patients with simple steatosis generally result from cardiovascular disease and atherosclerosis, not from liver failure (Chapter 140).[26]

Patients with NASH also are at risk for liver failure and liver cancer (Chapter 181),[27] in addition to their significantly increased risk of cardiovascular disease. For example, among patients with NASH on their initial biopsy, one third or more develop progressive fibrosis during a mean follow-up interval of about 5 years. Older age, diabetes, and ballooning and fibrosis on liver biopsy are important predictors of progression. In the United States, NAFLD is now second only to alcohol-associated liver disease as a cause of being listed for liver transplantation.

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139 CIRRHOSIS AND ITS SEQUELAE

GUADALUPE GARCIA-TSAO

DEFINITION

Cirrhosis, which can be the final stage of any chronic liver disease, is a diffuse process characterized by fibrosis and conversion of normal architecture to structurally abnormal nodules (Fig. 139-1). These "regenerative" nodules lack normal lobular organization and are surrounded by fibrous tissue. The process involves the whole liver and generally is considered irreversible. Although cirrhosis is histologically an "all-or-nothing" diagnosis, it can be classified clinically by its status as compensated or decompensated. Decompensated cirrhosis is defined by the presence of ascites, variceal bleeding, encephalopathy, or jaundice, which are complications that result from the main consequences of cirrhosis: portal hypertension and liver insufficiency.

EPIDEMIOLOGY

Because many patients with cirrhosis are asymptomatic until decompensation occurs, it is difficult to assess the real prevalence and incidence of cirrhosis in the general population. The prevalence of chronic liver disease or cirrhosis worldwide is estimated to be 100 (range, 25 to 400) per 100,000 subjects, but it varies widely by country and by geographic region.

Cirrhosis is an important cause of morbidity and mortality worldwide and in the United States. According to the latest Global Burden of Diseases study, cirrhosis annually causes more than 1.32 million deaths worldwide and about 45,000 deaths in the United States, making it the 11th leading cause of death overall.[1] Importantly, chronic liver disease and cirrhosis mainly affect individuals between 25 and 64 years of age. As chronic liver disease affects people in their most productive years of life, it has a significant impact on the economy as a result of premature death, illness, and disability.

Any chronic liver disease can lead to cirrhosis (Table 139-1). The main causes of cirrhosis in Western and industrialized countries are alcohol-related (Chapter 138) and nonalcoholic steatohepatitis (Chapter 138),[2,3] whereas viral hepatitis B (Chapter 135) is the primary cause in China and other Asian countries. Hepatitis C (Chapter 135) was the most common cause of cirrhosis in the United States until effective antiviral therapy became available. Other causes of cirrhosis include autoimmune liver diseases, such as primary biliary cholangitis (Chapter 135), primary sclerosing cholangitis (Chapter 135), autoimmune hepatitis (Chapter 135), and metabolic diseases such as hemochromatosis (Chapter 196) and Wilson disease (Chapter 195). Heterozygous carriage of the alpha1-antitrypsin Pi*Z variant, which is present in up to 10% of persons of European descent, increases the risk of liver cirrhosis in patients with liver disease or alcohol abuse (Chapter 138). When all potential causes have been investigated and excluded, cirrhosis is considered "cryptogenic." Many cases of cryptogenic cirrhosis are now thought to be due to nonalcoholic steatohepatitis (Chapter 138).

PATHOBIOLOGY

Liver Fibrosis and Cirrhosis

The key pathogenic feature underlying liver fibrosis and cirrhosis is activation of hepatic stellate cells. Hepatic stellate cells, which are known as *Ito cells* or *perisinusoidal cells*, are located in the space of Disse between hepatocytes and sinusoidal endothelial cells. Normally, hepatic stellate cells are quiescent and serve as the main storage site for retinoids (vitamin A). In response to injury, hepatic stellate cells become activated, as a result of which they lose their vitamin A, proliferate, develop a prominent rough endoplasmic reticulum, and secrete extracellular matrix (collagen types I and III, sulfated proteoglycans, and glycoproteins). In addition, they become contractile myofibroblasts.

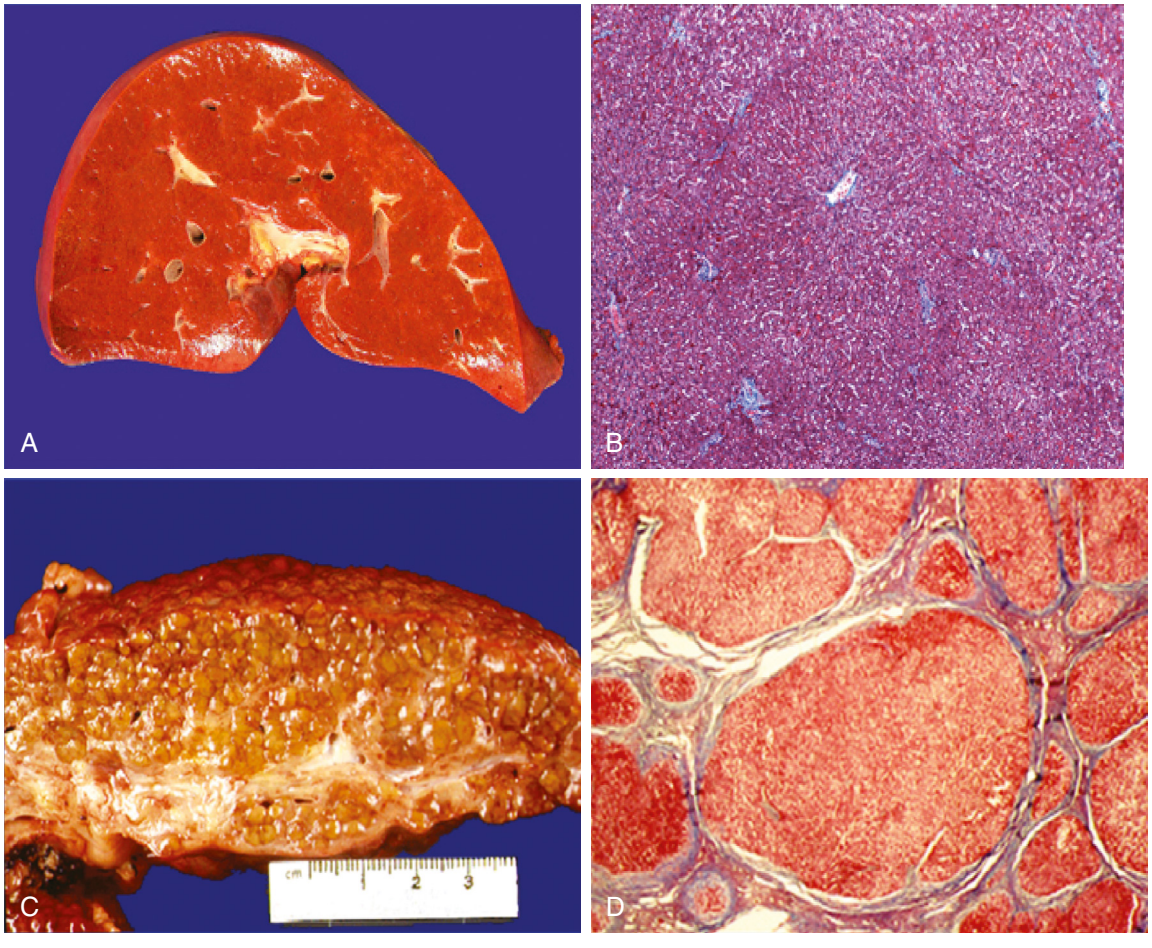

FIGURE 139-1. Gross and microscopic images of a normal and cirrhotic liver. A, Gross image of a normal liver with a smooth surface and homogeneous texture. **B,** On microscopic examination, liver sinusoids are organized, and vascular structures are normally distributed. **C,** Gross image of a cirrhotic liver. The liver has an orange-tawny color with an irregular surface and a nodular texture. **D,** On microscopic examination, the architecture is disorganized, and there are regenerative nodules surrounded by fibrous tissue.

ABSTRACT

Cirrhosis is the end stage of any chronic liver disease. It is classified in two main prognostic stages—compensated and decompensated. Decompensated cirrhosis is defined by the development of ascites, variceal hemorrhage, encephalopathy, or jaundice, all of which are consequences of portal hypertension (and the hyperdynamic circulatory state) and/or liver insufficiency. Stages and substages of cirrhosis are not only prognostically significant but have different predominant pathophysiologic mechanisms and therefore are managed differently.

KEYWORDS

cirrhosis
portal hypertension
ascites
encephalopathy
variceal hemorrhage

TABLE 139-1 CAUSES OF CIRRHOSIS

MAIN FACTORS CAUSING CIRRHOSIS
Alcoholic liver disease
Nonalcoholic fatty liver disease
Chronic hepatitis B
OTHER CAUSES OF CIRRHOSIS (<2% OF ALL CASES)
Chronic hepatitis C
Cholestatic and autoimmune liver diseases
Primary biliary cirrhosis
Primary sclerosing cholangitis
Autoimmune hepatitis
Intrahepatic or extrahepatic biliary obstruction
Mechanical obstruction
Biliary atresia
Cystic fibrosis
Metabolic disorders
Hemochromatosis
Wilson disease
α_1-Antitrypsin deficiency
Glycogen storage diseases
Abetalipoproteinemia
Porphyria
Hepatic venous outflow obstruction
Budd-Chiari syndrome
Veno-occlusive disease
Right-sided heart failure
Drugs and toxins
Intestinal bypass
Indian childhood cirrhosis

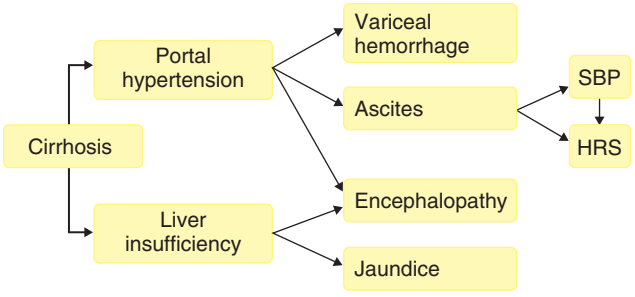

FIGURE 139-2. Complications of cirrhosis result from portal hypertension or liver insufficiency. Varices and variceal hemorrhage are a direct consequence of portal hypertension. Ascites results from sinusoidal portal hypertension and can be complicated by infection (spontaneous bacterial peritonitis [SBP]) or renal dysfunction (hepatorenal syndrome [HRS]). Hepatic encephalopathy results from portosystemic shunting (i.e., portal hypertension) and liver insufficiency. Jaundice results solely from liver insufficiency.

A number of genetic polymorphisms have been associated with a higher risk of cirrhosis related to alcohol or obesity,[4] but their clinical utility remains unclear.

Unlike other capillaries, normal hepatic sinusoids lack a basement membrane. The sinusoidal endothelial cells themselves contain large fenestrae (100 to 200 nm in diameter) that permit the passage of large molecules with molecular masses up to 250,000 daltons. Collagen deposition in the space of Disse, as occurs in cirrhosis, leads to defenestration of the sinusoidal endothelial cells ("capillarization" of the sinusoids), thereby altering exchange between plasma and hepatocytes and resulting in a decreased sinusoidal diameter that is further exacerbated by the contraction of stellate cells.

Complications of Cirrhosis

The two main consequences of cirrhosis are portal hypertension, with the accompanying hyperdynamic circulatory state, and liver insufficiency (Fig. 139-2). The development of varices and ascites is a direct consequence of portal hypertension and the hyperdynamic circulatory state, whereas jaundice occurs as a result of an inability of the liver to excrete bilirubin (i.e., liver insufficiency). Encephalopathy is the result of both portal hypertension and liver insufficiency. Ascites, in turn, can become complicated by infection, which is called *spontaneous bacterial peritonitis*, and by functional renal failure, which is called *hepatorenal syndrome*.

Portal Hypertension and the Hyperdynamic Circulatory State

In cirrhosis, portal hypertension results from both an increase in resistance to portal flow and an increase in portal venous inflow.[5] The initial mechanism is increased sinusoidal vascular resistance (Fig. 139-3) secondary to (1) deposition of fibrous tissue and subsequent compression by regenerative nodules (fixed component), which could theoretically be amenable to antifibrotic agents and could be ameliorated by resolving the underlying etiologic process, and (2) active vasoconstriction (functional component), which is amenable to the action of vasodilators such as nitroprusside and is caused by a deficiency in intrahepatic nitric oxide (NO), as well as enhanced activity of vasoconstrictors.

Early in the portal hypertensive process, the spleen grows and sequesters platelets and other formed blood cells, thereby leading to hypersplenism. In addition, vessels that normally drain into the portal system, such as the coronary vein, reverse their flow and shunt blood away from the portal system to the systemic circulation. These portosystemic collaterals are insufficient to decompress the portal venous system and offer additional resistance to portal flow. As collaterals develop, an increase in portal blood inflow, which results from splanchnic vasodilation, maintains the portal hypertensive state. Splanchnic arteriolar vasodilation is, in turn, secondary to increased production of NO. Thus, the paradox in portal hypertension is that a deficiency of NO in the intrahepatic vasculature leads to vasoconstriction and increased resistance, whereas overproduction of NO in the extrahepatic circulation leads to vasodilation and increased portal flow.

In addition to splanchnic vasodilation, there is systemic vasodilation, which by causing a decreased *effective* arterial blood volume leads to activation of neurohumoral systems (renin-angiotensin-aldosterone system), retention of sodium, expansion of plasma volume, and development of a hyperdynamic circulatory state. This hyperdynamic circulatory state maintains portal hypertension, thereby leading to the formation and growth of varices, and plays an important role in the development of all other complications of cirrhosis.

Varices and Variceal Hemorrhage

The complication of cirrhosis that results most directly from portal hypertension is the development of portal-systemic collaterals, the most relevant of which are those that form through dilation of the coronary and gastric veins and constitute gastroesophageal varices. The initial formation of esophageal collaterals depends on a threshold portal pressure, clinically established by a hepatic venous pressure gradient of 10 to 12 mm Hg, below which varices do not develop.

Development of a hyperdynamic circulatory state leads to further dilation and growth of varices and eventually to their rupture and variceal hemorrhage, one of the most dreaded complications of portal hypertension. Tension in a varix determines variceal rupture and is directly proportional to variceal diameter and intravariceal pressure and inversely proportional to variceal wall thickness.

Ascites and Hepatorenal Syndrome

Ascites, which is the accumulation of intraperitoneal fluid, in cirrhosis is secondary to sinusoidal hypertension and retention of sodium. Cirrhosis leads to sinusoidal hypertension by blocking hepatic venous outflow both anatomically by fibrosis and regenerative nodules and functionally by increased postsinusoidal vascular tone. Similar to the formation of esophageal varices, a threshold hepatic venous pressure gradient of 12 mm Hg is needed for the formation of ascites. In addition, retention of sodium replenishes the intravascular volume and allows the continuous formation of ascites. Retention of sodium results from vasodilation that is mostly due to an increase in the production of NO. With progression of cirrhosis and portal hypertension, vasodilation is more pronounced, thereby leading to further activation of the renin-angiotensin-aldosterone and sympathetic nervous systems and resulting in further sodium retention (refractory ascites), water retention (hyponatremia), and renal vasoconstriction (hepatorenal syndrome).[6]

Spontaneous Bacterial Peritonitis

Spontaneous bacterial peritonitis, an infection of ascitic fluid, occurs in the absence of perforation of a hollow viscus or an intra-abdominal inflammatory focus, such as an abscess, acute pancreatitis, or cholecystitis. Bacterial translocation, or the migration of bacteria from the intestinal lumen to mesenteric lymph nodes and other extraintestinal sites, is the main mechanism implicated in spontaneous bacterial peritonitis. Impaired local and systemic immune defenses are a major element in promoting bacterial translocation and, together with shunting of blood away from the hepatic Kupffer cells through portosystemic collaterals, allow a transient bacteremia to become more prolonged, thereby colonizing ascitic fluid. Spontaneous bacterial peritonitis occurs in patients with reduced ascites defense mechanisms, such as a low

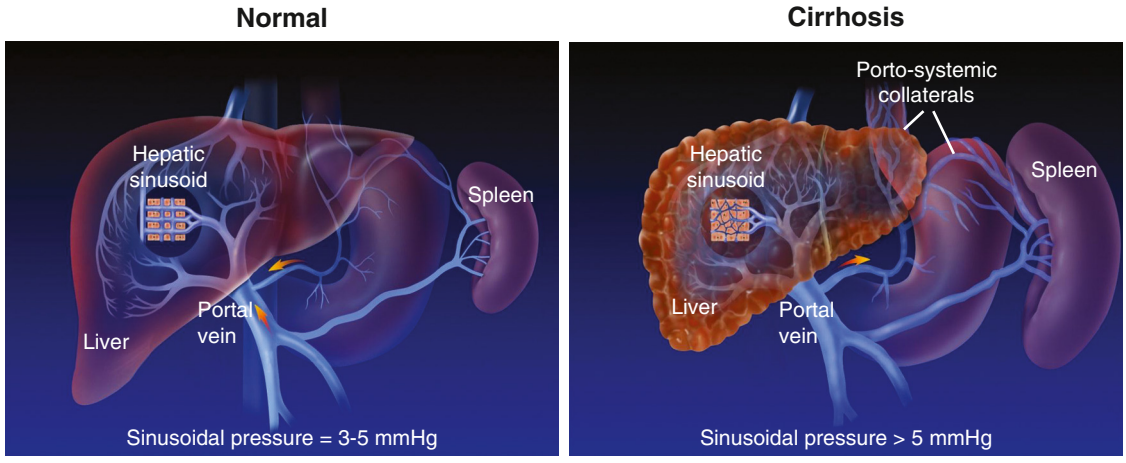

FIGURE 139-3. Hepatic sinusoidal pressure is increased in cirrhosis. In the normal liver (*left*), the intrahepatic vasculature is compliant, and the hepatic venous pressure gradient, which is a measure of sinusoidal pressure, is 5 mm Hg or lower. In the cirrhotic liver (*right*), the sinusoidal architecture is distorted by regenerative nodules and fibrosis that lead to increased intrahepatic resistance, portal hypertension, splenomegaly, and portosystemic collaterals; the hepatic venous pressure gradient is above 5 mm Hg. Complications of cirrhosis develop after the gradient increases above 10 to 12 mm Hg.

complement level in ascitic fluid. Another factor that promotes bacterial translocation in cirrhosis is intestinal bacterial overgrowth attributed to a decrease in small bowel motility and intestinal transit time. Infections, particularly from gram-negative bacteria, can precipitate renal dysfunction through worsening of the hyperdynamic circulatory state.

Encephalopathy

Hepatic encephalopathy is brain dysfunction caused by liver insufficiency, portosystemic shunting, or both.[7] Ammonia, a toxin normally removed by the liver, plays a key role in its pathogenesis. In cirrhosis, ammonia accumulates in the systemic circulation because of shunting of blood through portosystemic collaterals and decreased liver metabolism (i.e., liver insufficiency). The presence of large amounts of ammonia in the brain damages supporting brain cells or astrocytes and leads to structural changes characteristic of hepatic encephalopathy (Alzheimer type II astrocytosis). Ammonia results in upregulation of astrocytic peripheral-type benzodiazepine receptors, the most potent stimulants of neurosteroid production. Neurosteroids are the major modulators of γ-aminobutyric acid, which results in cortical depression and hepatic encephalopathy. Other toxins, such as manganese, also accumulate in the brain, particularly the globus pallidus, where they lead to impaired motor function. Other yet-to-be-elucidated toxins may also be involved in the pathogenesis of encephalopathy.

Jaundice

Jaundice (Chapter 133) in cirrhosis results from the inability of the liver to excrete bilirubin and is therefore the result of liver insufficiency. However, in cholestatic diseases leading to cirrhosis (e.g., primary biliary cirrhosis, primary sclerosing cholangitis, vanishing bile duct syndrome), jaundice is more likely due to biliary damage than to liver insufficiency. Other indicators of liver insufficiency, such as the presence of encephalopathy or prolongation of the international normalized ratio, help determine the most likely contributor to hyperbilirubinemia (Chapter 133).

Cardiopulmonary Complications

The hyperdynamic circulatory state eventually results in high-output heart failure with decreased peripheral utilization of oxygen, a complication that has been referred to as *cirrhotic cardiomyopathy*. Vasodilation at the level of the pulmonary circulation leads to arterial hypoxemia, the hallmark of hepatopulmonary syndrome. Normal pulmonary capillaries are 8 μm in diameter, and red blood cells (slightly less than 8 μm) pass through them one cell at a time, thereby facilitating oxygenation. In *hepatopulmonary syndrome*, the pulmonary capillaries are dilated up to 500 μm, so passage of red cells through the pulmonary capillaries may be many cells thick. As a result, a large number of red cells are not oxygenated, which causes the equivalent of a right-to-left shunt.

Conversely, *portopulmonary hypertension*[8] occurs when the pulmonary bed is exposed to vasoconstrictive substances that may be produced in the splanchnic circulation and bypass metabolism by the liver; the initial result is reversible pulmonary hypertension. However, because these factors result in endothelial proliferation, vasoconstriction, in situ thrombosis, and obliteration of vessels, irreversible pulmonary hypertension ensues.

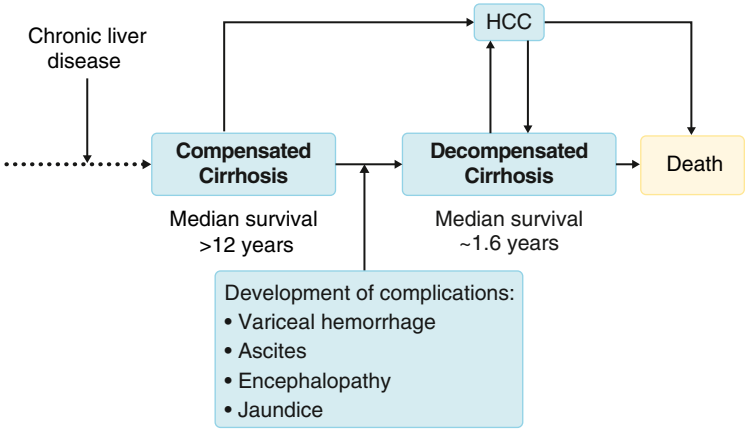

FIGURE 139-4. Natural history of cirrhosis. Any chronic liver disease will lead to cirrhosis. Initially, cirrhosis will be compensated (median survival, >12 years), but once complications (ascites, variceal hemorrhage, encephalopathy, jaundice) develop, it becomes decompensated (median survival, 1.6 years). Hepatocellular carcinoma (HCC) can develop at any stage and precipitate decompensation and death.

CLINICAL MANIFESTATIONS

The clinical manifestations of cirrhosis range widely, depending on the stage of cirrhosis, from an asymptomatic patient with no signs of chronic liver disease to a patient who is confused and jaundiced with severe muscle wasting and ascites. The natural history of cirrhosis is characterized by an initial phase, termed *compensated* cirrhosis, followed by a rapidly progressive phase marked by the development of complications of portal hypertension or liver dysfunction (or both), termed *decompensated* cirrhosis (Fig. 139-4).[9] In the compensated phase, liver synthetic function is mostly normal, and portal pressure, although increased, is below the threshold level required for the development of varices or ascites. As the disease progresses, portal pressure increases and liver function worsens, thereby resulting in the development of ascites, portal hypertensive gastrointestinal bleeding, encephalopathy, and jaundice.[10] The development of any of these clinically detectable complications marks the transition from a compensated to a decompensated phase. Progression to death may be accelerated by the development of other complications, such as recurrent gastrointestinal bleeding, renal impairment (refractory ascites, hepatorenal syndrome), hepatopulmonary syndrome, and sepsis (spontaneous bacterial peritonitis). The development of hepatocellular carcinoma (Chapter 181) may accelerate the course of the disease at any stage (see Fig. 139-4). Transition from a compensated to a decompensated stage occurs at a rate of approximately 5 to 7% per year. The median time to decompensation, or the time at which half the patients with compensated cirrhosis will become decompensated, is about 6 years.

Compensated Cirrhosis

In this stage, cirrhosis is mostly asymptomatic and is diagnosed either during the evaluation of chronic liver disease or fortuitously during routine physical examination, biochemical testing, imaging for other reasons, endoscopy showing gastroesophageal varices, or abdominal surgery in which a nodular liver is detected. Nonspecific fatigue, weight loss, decreased muscle mass, decreased libido, or sleep disturbances may be the only complaints. About 40% of patients with compensated cirrhosis have esophageal varices. Nonbleeding gastroesophageal varices are asymptomatic, and their presence (without bleeding) does not denote decompensation.

Decompensated Cirrhosis

At this stage, there are signs of decompensation: ascites, variceal hemorrhage, jaundice, hepatic encephalopathy, or any combination of these findings. Ascites, which is the most frequent sign of decompensation, is present in 80% of patients with decompensated cirrhosis.

Variceal Hemorrhage

Gastroesophageal varices are present in approximately 50% of patients with newly diagnosed cirrhosis. The prevalence of varices correlates with the severity of liver disease and ranges from 40% in Child A cirrhotic patients (Table 139-2) to 85% in Child C cirrhotic patients.

Both the development of varices and the growth of small varices occur at a rate of 7 to 8% per year. The incidence of a first variceal hemorrhage in patients with small varices is about 5% per year, whereas medium and large varices bleed at a rate of approximately 15% per year. Large varices, severe liver disease, and red wale markings on varices are independent predictors of variceal hemorrhage. Bleeding from gastroesophageal varices can be manifested as overt hematemesis, melena, or both (Chapter 121).

Ascites and Hyponatremia

Ascites is the most common cause of decompensation in cirrhosis and occurs at a rate of 7 to 10% per year. The most frequent symptoms associated with ascites are increased abdominal girth, which is often described by the patient as tightness of the belt or garments around the waist, and recent weight gain. When it is present in small to moderate amounts, ascites can be identified on examination by bulging flanks, flank dullness, and shifting dullness (Chapter 132).

Hyponatremia, which is defined as a serum sodium concentration <130 mEq/L (Chapter 102), is present in about 25% of patients with cirrhosis and ascites. However, patients with cirrhosis do not usually have the neurologic manifestations of hyponatremia, presumably because it typically develops gradually. Nevertheless, hyponatremia is a marker of the severity of cirrhosis and is associated with poorer quality of life and the development of hepatic encephalopathy.

Hepatorenal syndrome is a type of prerenal kidney injury that occurs in patients with cirrhosis and ascites.[11] It represents the extreme of the spectrum of abnormalities that lead to cirrhotic ascites and is the result of maximal peripheral vasodilation, as well as maximal activation of hormones that cause the retention of sodium and water and intense vasoconstriction of the renal arteries. Hepatorenal syndrome is divided into two types based on clinical characteristics and prognosis. Type 1 hepatorenal syndrome (now called hepatorenal syndrome–acute kidney injury) is rapidly progressive *acute* kidney injury in which the rise in serum creatinine concentration occurs within a 2-week period. Type 2 hepatorenal syndrome (now called hepatorenal syndrome–non-acute kidney injury) is more slowly progressive and associated with ascites that is refractory to diuretics. Patients with hepatorenal syndrome usually have tense ascites that responds poorly to diuretics, but no specific symptoms or signs typify this entity.

Spontaneous Bacterial Peritonitis

About one third of patients with cirrhosis are admitted for bacterial infection or acquire a bacterial infection during hospitalization, the most common being spontaneous bacterial peritonitis. The two most important predictors of the development of bacterial infection are the severity of liver disease and admission for gastrointestinal hemorrhage. The most frequent clinical manifestations of spontaneous bacterial peritonitis are fever, jaundice, and abdominal pain. On physical examination, there is typically abdominal tenderness, with or without rebound tenderness, or ileus (or both). However, up to one third of patients with spontaneous bacterial peritonitis initially may have no abdominal symptoms or symptoms of infection[12] and may present instead with encephalopathy, acute kidney injury, or evidence of shock.

Hepatic Encephalopathy

Hepatic encephalopathy, which is the neuropsychiatric manifestation of cirrhosis, occurs at a rate of approximately 2 to 3% per year. Hepatic encephalopathy associated with cirrhosis is of gradual onset and rarely fatal. It is manifested as a wide spectrum of neurologic and psychiatric abnormalities ranging from subclinical alterations to coma. Clinically, it is characterized by alterations in consciousness and behavior ranging from inversion of the sleep-wake pattern and forgetfulness (grade 1); to confusion, bizarre behavior, and disorientation (grade 2); to lethargy and profound disorientation (grade 3); to coma (grade 4). On physical examination, early stages may demonstrate only a distal tremor, but the hallmark of overt hepatic encephalopathy is the presence of asterixis. In addition, patients with hepatic encephalopathy may have sweet-smelling breath, a characteristic termed *fetor hepaticus*.

Pulmonary Complications

Hepatopulmonary syndrome is associated with exertional dyspnea, which can lead to extreme debilitation. Clubbing of the fingers, cyanosis, and vascular spiders may be seen on physical examination. Hepatopulmonary syndrome is present in approximately 5 to 10% of patients awaiting liver transplantation.

Portopulmonary hypertension is manifested as exertional dyspnea, syncope, and chest pain.[13] On examination, an accentuated second sound and right ventricular heave are prominent (Chapter 69).

TABLE 139-2 THE TWO MOST COMMONLY USED SCORING SYSTEMS IN CIRRHOSIS

1. CHILD-TURCOTTE-PUGH (CTP) SCORE (RANGE, 5-15)

	POINTS ASCRIBED		
Parameters	**1**	**2**	**3**
Ascites	None	Grade 1-2 (or easy to treat)	Grade 3-4 (or refractory)
Hepatic encephalopathy	None	Grade 1-2 (or induced by a precipitant)	Grade 3-4 (or spontaneous)
Bilirubin (mg/dL)	<2	2-3	>3
Albumin (g/dL)	>3.5	2.8-3.5	<2.8
Prothrombin time (seconds > control) or INR	<4 <1.7	4-6 1.7-2.3	>6 >2.3

CTP classification: Child A: score of 5-6; Child B: score of 7-9; Child C: score of 10-15

2. MODEL OF END-STAGE LIVER DISEASE (MELD) SCORE (RANGE, 6-40)

$[0.957 \times \text{LN (creatinine in mg/dL)} + 0.378 \times \text{LN (bilirubin in mg/dL)} + 1.12 \times \text{LN (INR)} + 0.643] \times 10$

MELD-Na is calculated first by determining the traditional MELD ($\text{MELD}_{(0)}$); if the initial $\text{MELD}_{(i)}$ score is 12 or greater, the score is adjusted by incorporating the serum sodium value

$$[\text{MELD}_{(0)} + 1.32 \times (137\text{-Na}) - [0.033 \times \text{MELD(i)} \times (137\text{-Na})]$$

INR = international normalized ratio; LN = natural logarithm.

DIAGNOSIS

The diagnosis of cirrhosis should be considered in any patient with chronic liver disease. In asymptomatic patients with *compensated cirrhosis*, typical signs of cirrhosis may not be present, and the physical examination and laboratory test findings may be entirely normal. The diagnosis may often require histologic confirmation by liver biopsy, which is the "gold standard" for the diagnosis of cirrhosis. However, liver biopsy is an invasive procedure subject to sampling error, and the presence of cirrhosis can often be confirmed noninvasively by a combination of serum biomarkers, imaging techniques, and measurements of liver stiffness.

Physical Examination

On physical examination, stigmata of cirrhosis consist of muscle atrophy, mainly involving the bitemporal muscle regions and the thenar and hypothenar eminences; spider angiomas, mostly on the trunk, face, and upper limbs; and palmar erythema involving the thenar and the hypothenar eminences and the tips of the fingers. Although muscle atrophy is a marker of liver insufficiency, spider angiomas and palmar erythema are markers of vasodilation and a hyperdynamic circulation. Men may have hair loss on the chest and

abdomen, gynecomastia, and testicular atrophy. Petechiae and ecchymoses may be present as a result of thrombocytopenia or a prolonged prothrombin time. Dupuytren contracture, which is a thickening of the palmar fascia, occurs mostly in alcoholic cirrhosis. A pathognomonic feature of cirrhosis is the finding on abdominal examination of a small right liver lobe, with a span of less than 7 cm on percussion, and a palpable left lobe that is nodular with increased consistency. Splenomegaly may also be present and is indicative of portal hypertension. Collateral circulation on the abdominal wall (caput medusae) may also develop as a consequence of portal hypertension. Absence of any of these physical findings does not exclude cirrhosis.

Laboratory Tests

Laboratory test results suggestive of cirrhosis include even subtle abnormalities in serum levels of albumin or bilirubin or elevation of the international normalized ratio. The most sensitive and specific laboratory finding suggestive of cirrhosis in the setting of chronic liver disease is a low platelet count (<150,000/μL), which occurs as a result of portal hypertension and hypersplenism. Other serum markers that are often abnormal include levels of aspartate aminotransferase, γ-glutamyl transpeptidase, hyaluronic acid, α_2-macroglobulin, haptoglobin, tissue metalloproteinase inhibitor 1, and apolipoprotein A. Combinations of these tests have been used to predict the presence of cirrhosis, but they are not as accurate as imaging studies.

Imaging Studies

Confirmatory imaging tests include computed tomography, ultrasound, and magnetic resonance imaging. Findings consistent with cirrhosis include a nodular contour of the liver, a small liver with or without hypertrophy of the left or caudate lobe, splenomegaly, and, in particular, identification of intra-abdominal collateral vessels indicative of portal hypertension (Fig. 139-5). With increasing fibrosis, the liver becomes stiff, and this stiffness can be measured by ultrasound (transient elastography, acoustic radiation force impulse imaging), or magnetic resonance imaging. Measurement of liver stiffness, a new noninvasive technique, appears to be useful in the diagnosis of cirrhosis and in excluding its presence. These tests are becoming more widely available, and typical findings on any of these imaging studies, together with a compatible clinical picture, are indicative of the presence of cirrhosis. A liver biopsy then would not be required unless the degree of inflammation or other features require investigation.

In *decompensated cirrhosis*, detection of ascites, variceal bleeding, or encephalopathy in the setting of chronic liver disease essentially establishes the diagnosis of cirrhosis, so a liver biopsy is not necessary to establish the diagnosis. Patients with decompensated cirrhosis often exhibit malnutrition, more severe muscle wasting, more numerous vascular spiders, and hypotension and tachycardia as a result of the hyperdynamic circulatory state.

Portal Pressure Measurements

Direct measurements of portal pressure involve catheterization of the portal vein, are cumbersome, and may be associated with complications. Hepatic vein catheterization with measurement of wedged and free pressure is the simplest, safest, most reproducible, and most widely used method to indirectly measure portal pressure. Portal pressure measurements are expressed as the hepatic venous pressure gradient: the gradient between wedged hepatic venous pressure, which is a measure of sinusoidal pressure, and free hepatic or inferior vena cava pressure, which is used as an internal zero reference point. In a patient with clinical evidence of portal hypertension (e.g., varices), the hepatic venous pressure gradient is useful in the differential diagnosis of the cause of portal hypertension: it will be normal (3 to 5 mm Hg) in prehepatic causes of portal hypertension, such as portal vein thrombosis, and in intrahepatic but presinusoidal causes, such as schistosomiasis (Chapter 326); but it will be abnormal (≥6 mm Hg) in sinusoidal causes of portal hypertension, such as cirrhosis, and in postsinusoidal causes, such as veno-occlusive disease. In patients with compensated viral or alcoholic cirrhosis, a hepatic venous pressure gradient of 10 mm Hg or greater ("clinically significant" portal hypertension) predicts the development of decompensation, and its reduction with pharmacologic therapy predicts a favorable outcome in patients with cirrhosis. In patients with variceal hemorrhage, a hepatic venous pressure gradient of more than 20 mm Hg predicts recurrent variceal hemorrhage and may portend death. Measurements of liver stiffness correlate with hepatic venous pressure measurements and can help stratify patients with compensated cirrhosis, regardless of etiology, into those with and without clinically significant portal hypertension.

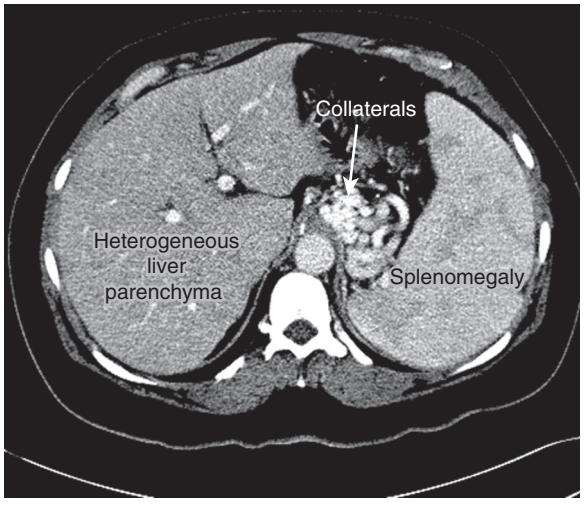

FIGURE 139-5. Computed tomography in a patient with compensated cirrhosis. The liver parenchyma is heterogeneous, there is splenomegaly, and, importantly, there are portosystemic collaterals.

Complications of Cirrhosis

Varices and Variceal Hemorrhage

Upper gastrointestinal endoscopy (Chapter 120) remains the main method for diagnosis of varices and variceal hemorrhage. Varices are classified as small (straight, minimally elevated veins above the esophageal mucosal surface), medium (tortuous veins occupying less than one third of the esophageal lumen), or large (occupying more than one third of the esophageal lumen). The diagnosis of variceal hemorrhage is made when diagnostic esophagogastroduodenoscopy shows one of the following: active bleeding from a varix, a "white nipple" overlying a varix, clots overlying a varix, or varices with no other potential source of bleeding.

Ascites

The most common cause of ascites is cirrhosis, which accounts for 80% of cases. Peritoneal malignant disease (e.g., peritoneal metastases from gastrointestinal tumors or ovarian cancer), heart failure (Chapter 45), and peritoneal tuberculosis (Chapter 299) together account for another 15% of cases. The initial, most cost-effective, and least invasive method to confirm the presence of ascites is abdominal ultrasonography.

Diagnostic paracentesis is a safe procedure that should be performed in every patient with new-onset ascites, even in those with coagulopathy. Ultrasound guidance should be used in patients in whom percussion cannot locate the ascites or in whom a first paracentesis attempt does not yield fluid. The fluid in a patient with new-onset ascites should always be evaluated for albumin (with simultaneous estimation of serum albumin), total protein, and polymorphonuclear (PMN) blood cell count, and bacteriologic cultures and cytology should be performed. The PMN cell count and bacteriologic culture are useful to exclude infection (either spontaneous or secondary bacterial peritonitis), and cytologic evaluation is needed if peritoneal carcinomatosis is suspected. Depending on the clinical setting, additional tests can be performed on the fluid: glucose and lactate dehydrogenase levels (if secondary bacterial peritonitis is suspected), smear and culture for acid-fast bacilli (if peritoneal tuberculosis is suspected), and amylase level (if pancreatic ascites is suspected).

The serum-ascites albumin gradient and ascites protein levels are useful in the differential diagnosis of ascites (Table 139-3). The serum-ascites albumin gradient correlates with sinusoidal pressure and will therefore be elevated (>1.1 g/dL) in patients in whom the source of ascites is the hepatic sinusoid (e.g., cirrhosis or cardiac ascites). Protein levels in ascitic fluid are an indirect marker of the integrity of the hepatic sinusoids: normal sinusoids are permeable structures that "leak" protein, whereas sinusoids in cirrhosis are "capillarized" and do not leak as much protein. The three main causes of ascites—cirrhosis, peritoneal malignant disease or tuberculosis, and heart failure—can easily be distinguished by combining the results of both the serum-ascites albumin gradient and ascites total protein content. Cirrhotic ascites typically has a high serum-ascites albumin gradient and low protein, cardiac ascites has a high serum-ascites albumin gradient and high protein, and ascites secondary to peritoneal malignant disease typically has a low serum-ascites albumin gradient and high protein. A high serum B-type natriuretic peptide has a high diagnostic accuracy in the diagnosis of ascites due to heart failure.

TABLE 139-3 USING THE SERUM-ASCITES ALBUMIN GRADIENT AND THE ASCITES TOTAL PROTEIN LEVEL TO DIAGNOSE THE CAUSE OF ASCITES

CONDITION	SERUM-ASCITES ALBUMIN GRADIENT*	ASCITES TOTAL PROTEIN LEVEL†
Cirrhosis	High	Low
Malignant ascites	Low	High
Cardiac ascites	High	High

*High is more than 1.1 g/dL; low is less than 1.1 g/dL.
†High is more than 2.5 g/dL; low is less than 2.5 g/dL.

Hepatorenal Syndrome

Hepatorenal syndrome is a diagnosis of exclusion, but patients typically have ascites that is unresponsive to diuretics, and most have hyponatremia. The differential diagnosis of acute kidney injury in cirrhosis includes conditions that worsen vasodilation, such as sepsis, the use of vasodilators, and large-volume paracentesis not accompanied by albumin infusion; conditions that decrease effective arterial blood volume, such as gastrointestinal hemorrhage, overdiuresis, or diarrhea (often induced by overdoses of lactulose); conditions that induce renal vasoconstriction, such as nonsteroidal anti-inflammatory drugs; and nephrotoxic insults, such as from aminoglycosides. As a result, the diagnosis of hepatorenal syndrome can only be made after diuretics have been discontinued, any condition that leads to worsening of the hemodynamic status of the cirrhotic patient has been excluded or treated, and intravascular volume has been expanded with albumin.

Spontaneous Bacterial Peritonitis

A high index of suspicion and early diagnosis are key in the management of spontaneous bacterial peritonitis. Diagnostic paracentesis should be performed in any patient with symptoms or signs of spontaneous bacterial peritonitis, including unexplained encephalopathy and renal dysfunction. Because spontaneous bacterial peritonitis is often asymptomatic and frequently community acquired, diagnostic paracentesis should be performed when any patient with cirrhosis is admitted to the hospital, regardless of the cause for admission.

The diagnosis of spontaneous bacterial peritonitis is established by an ascitic fluid PMN count >250/μL. Bacteria can be isolated from ascitic fluid in only 40 to 50% of cases, even with sensitive methods such as inoculation directly into a blood culture bottle. Spontaneous bacterial peritonitis is mostly a non-bacterial infection, usually with a gram-negative enteric organism. However, the widespread use of antibiotic prophylaxis in cirrhosis has led to an increased prevalence of infections with multidrug-resistant organisms. Anaerobes and fungi very rarely cause spontaneous bacterial peritonitis; their presence, as well as a polymicrobial infection, should raise suspicion of secondary bacterial peritonitis.

Hepatic Encephalopathy

The diagnosis of overt hepatic encephalopathy is mainly clinical and based on a history and physical examination that shows alterations in consciousness and behavior as well as the presence of asterixis. Ammonia levels are unreliable, and there is poor correlation between the grade of hepatic encephalopathy and ammonia blood levels. High levels (>150 μmol/L) are, however, indicative of hepatic encephalopathy and can be useful in the evaluation of a patient with neurocognitive disturbances of unknown origin. Psychometric tests and an electroencephalogram, which typically shows generalized slow waves and the presence of triphasic waves, are commonly used in research but are not generally used for clinical diagnosis. Minimal or subclinical hepatic encephalopathy, which is present in up to 80% of patients with cirrhosis, is diagnosed solely on the basis of abnormal results of psychometric and neuropsychological tests of attention (e.g., number connection test, digit symbol test) and psychomotor function (e.g., grooved pegboard). Screening of patients with cirrhosis for minimal hepatic encephalopathy is not widely recommended because diagnostic tests are not standardized and the benefits of treatment are uncertain.

Hepatopulmonary Syndrome and Portopulmonary Hypertension

The diagnostic criteria for hepatopulmonary syndrome are arterial hypoxemia with a PaO_2 of less than 80 mm Hg or an alveolar arterial oxygen gradient of greater than 15 mm Hg, along with evidence of pulmonary vascular shunting on contrast echocardiography (Chapter 43) or a ^{99m}Tc-labeled macroaggregated albumin scan demonstrating abnormal shunting of radioactivity to the brain. Portopulmonary hypertension is diagnosed by the presence of mean pulmonary arterial pressure higher than 25 mm Hg on right-sided heart catheterization, provided pulmonary capillary wedge pressure is less than 15 mm Hg.

TREATMENT

Treatment of cirrhosis should ideally be aimed at interruption or reversal of fibrosis. Although antifibrotic drugs have not been shown to reverse fibrosis consistently or to improve outcomes in patients with cirrhosis, eradication of the hepatitis C or the hepatitis B virus has been associated with regression of fibrosis. Treatment of compensated cirrhosis is currently directed at preventing the development of decompensation by (1) treating the underlying liver disease (e.g., antiviral therapy for hepatitis C or B) to reduce fibrosis and to prevent decompensation; (2) avoiding factors that could worsen liver disease, such as alcohol, hepatotoxic drugs, and superimposed viral infections; (3) lowering portal pressure by the use of nonselective β-adrenergic blockers (e.g., carvedilol, propranolol) that have been shown to prevent variceal hemorrhage and decompensation in patients with compensated cirrhosis; and (4) screening for hepatocellular carcinoma (so it can be treated at an earlier stage) (Fig. 139-6).[14] Treatment of decompensated cirrhosis focuses on specific decompensating events and the option of liver transplantation. Increasingly, data reveal that different therapies for the same complication may be applicable to patients with different risk profiles, mainly based on severity of the disease (see Table 139-2).

Varices and Variceal Bleeding

Reducing portal pressure decreases the risk for the development of varices and variceal hemorrhage, as well as the risk for ascites and death. Nonselective β-adrenergic blockers (propranolol, nadolol) reduce portal pressure by producing splanchnic vasoconstriction and decreasing portal venous inflow. In patients with cirrhosis and medium or large varices that have never bled, nonselective β-blockers significantly reduce the risk for first variceal hemorrhage.[A1] In patients who have compensated cirrhosis with no or small varices, nonselective β-blockers significantly reduce the risk of decompensation.[A2] Carvedilol (a nonselective β-blocker with vasodilating properties) is more effective than other β-blockers for lowering portal pressure[A3] and also reduces decompensation and death in patients who have compensated cirrhosis with significant portal hypertension.[A4] Therefore, carvedilol at a dose of 3.125 to 12.5 mg/day is now recommended to prevent decompensation.[15] In patients who cannot tolerate or have contraindications to nonselective β-blockers, endoscopic variceal ligation (see Fig. 125-3), a therapy that aims to obliterate varices by placing rubber rings on variceal columns, is at least as useful as traditional nonselective β-blockers to prevent a first variceal hemorrhage but will not prevent ascites. Ligation has no effect on portal pressure and can lead to hemorrhage from ligation-induced ulcers. Among patients who have cirrhosis, screening endoscopy should be repeated every 2 to 3 years in patients with no varices, every 1 to 2 years in patients with small varices, and sooner in patients with decompensated disease so that ligation can be instituted before the varices grow in size and bleed.

Patients with cirrhosis and variceal hemorrhage require resuscitation in an intensive care unit. However, over-transfusion should be avoided because it can precipitate rebleeding. Hemoglobin values should be maintained at about 8 g/dL. Prophylactic antibiotics should be used in this setting not only to prevent bacterial infections but also to decrease rebleeding and death. The recommended antibiotic is ceftriaxone at a dose of 1 g/day for 5 to 7 days.

The most effective specific therapy for the control of active variceal hemorrhage is the combination of a vasoconstrictor with endoscopic therapy. Safe vasoconstrictors include terlipressin, somatostatin, and the somatostatin analogues octreotide and vapreotide; they can be initiated at admission to the hospital and continued for 2 to 5 days. The vasoconstrictor currently available in the United States is octreotide, which is used as a 50-μg intravenous bolus followed by an infusion at 50 μg/hour. The preferred endoscopic therapy to control variceal hemorrhage is esophageal variceal ligation.[A5] In cases in which bleeding continues despite vasoconstrictors and ligation, an esophageal stent appears to be more effective as a bridge to a more definitive therapy and is safer than balloon tamponade, although it may not reduce mortality.[A6]

The transjugular intrahepatic portosystemic shunt (TIPS) is generally recommended for patients who fail to respond to standard therapy (Fig. 139-7). In patients at high risk of failure, Child C (score 10 to 13) patients and Child B patients who have actively bleeding varices at endoscopy, preemptive TIPS placement (24 to 48 hours after admission) is associated with a reduced failure rate and a significant improvement in survival. Therefore, preemptive "early" TIPS should be considered in high-risk subpopulations of patients with variceal hemorrhage.[A7–A9] Even though patients with cirrhosis and coagulopathy (prolonged international normalized ratio or decreased platelet count) have a higher risk of not responding to hemostasis for variceal hemorrhage or bleeding from procedures (ligation, paracentesis, TIPS, surgery), neither recombinant factor VII nor eltrombopag has proved beneficial in randomized trials, and neither is recommended.

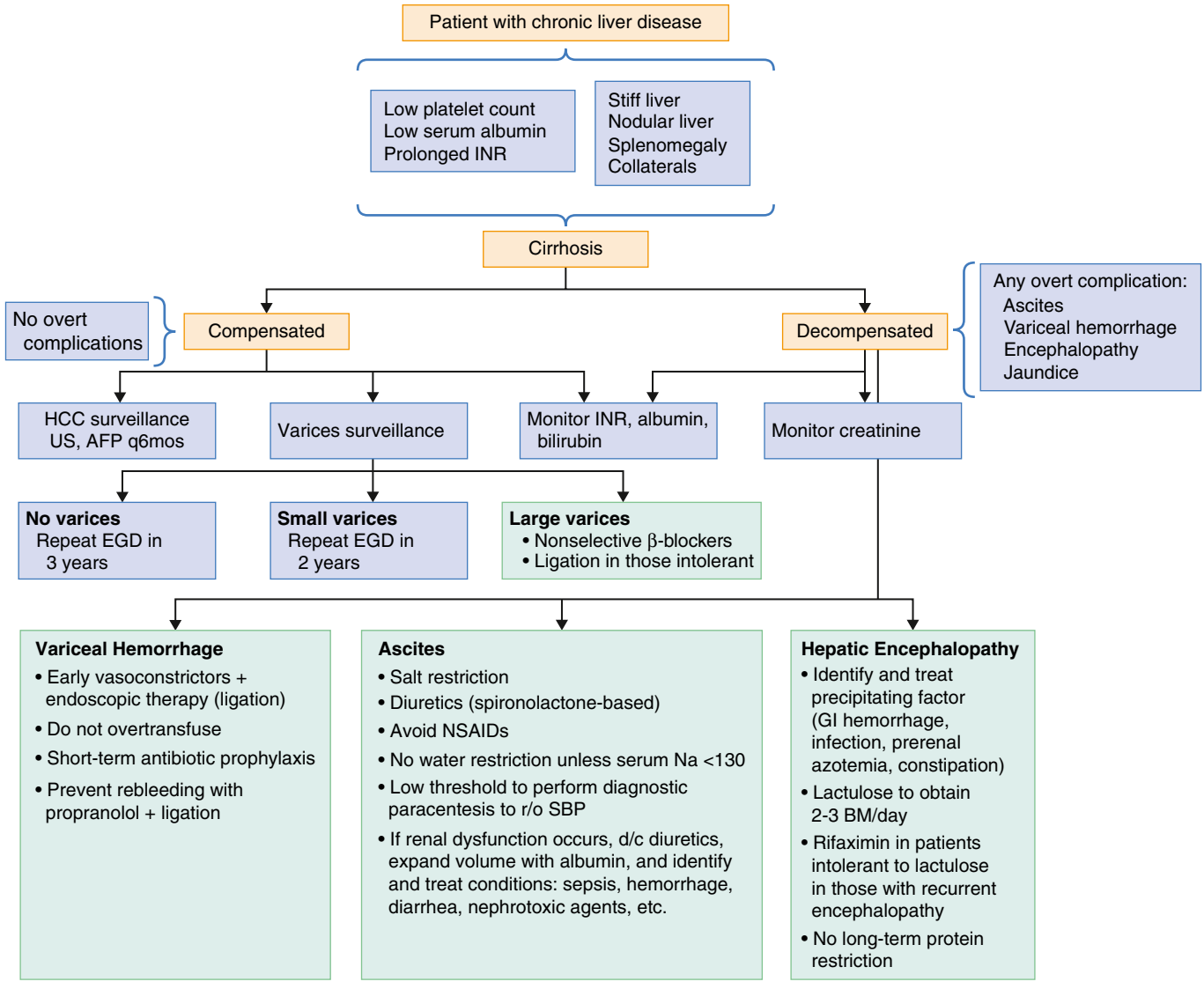

FIGURE 139-6. **Summary of the management of compensated and decompensated cirrhosis.** AFP = α-fetoprotein; BM = bowel movement; d/c = discontinue; EGD = esophagogastroduodenoscopy; GI = gastrointestinal; HCC = hepatocellular carcinoma; INR = international normalized ratio; Na = sodium; NSAIDs = nonsteroidal anti-inflammatory drugs; r/o = rule out; SBP = spontaneous bacterial peritonitis; US = ultrasound.

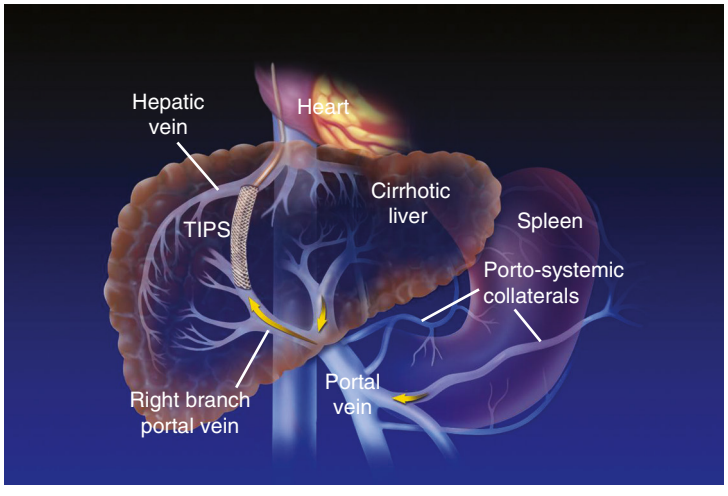

FIGURE 139-7. **Transjugular intrahepatic portosystemic shunt (TIPS).** This shunt is performed by interventional radiologists and consists of an expandable metal stent (most often coated with polytetrafluoroethylene) that connects a branch of the portal vein (high-pressure vein) to a branch of the hepatic vein (low-pressure vein). The shunt decompresses the portal system and portosystemic collaterals, and therefore it is used in the treatment of selected patients with cirrhosis and variceal hemorrhage. The shunt also decompresses the hepatic sinusoids and therefore is also used in the treatment of refractory ascites.

After control of hemorrhage, the 1-year recurrence of hemorrhage without treatment is high, at about 60%. Therefore, therapy to prevent rebleeding should be instituted before the patient is discharged. The recommended therapy is a combination of nonselective β-blockers (propranolol or nadolol) and endoscopic variceal ligation.[A10] The dose of β-blockers should be the maximum dose that is tolerated, and endoscopic variceal ligation should be repeated every 2 to 4 weeks until the varices are obliterated. Patients who had TIPS placed during the episode of acute variceal hemorrhage do not require β-blockers or ligation but do require periodic Doppler examination of the shunt to assess its patency.

Shunt therapy, either surgical or through radiologic placement of a TIPS, should be used in patients whose variceal bleeding has persisted or recurred despite combined pharmacologic and endoscopic therapy. Both types of shunts are equally effective, and the choice will depend on local expertise. Although the uncovered TIPS frequently occludes, polytetrafluoroethylene-covered stents are associated with lower occlusion rates and lower rates of hepatic encephalopathy. In a randomized trial, covered stents were more effective than β-blockers in preventing variceal rebleeding in patients with cirrhosis, but they produced slightly more adverse events without increasing survival time or quality of life.[A11]

Ascites

Salt restriction and diuretics constitute the mainstay of management of ascites.[16] Dietary sodium intake should be restricted to 2 g/day. A more restrictive diet is not recommended and may compromise nutritional status.

Spironolactone, which is more effective than loop diuretics, should be started at a dose of 100 mg/day (once a day in the morning). The dose should be adjusted every 3 to 4 days to a maximal effective dose of 400 mg/day. Furosemide, at an escalated dose from 40 to 160 mg/day, can be started concurrently with

spironolactone if ascites is tense or added subsequently if weight loss is inadequate or if hyperkalemia develops with spironolactone alone. The goal is weight loss of 1 kg in the first week and 2 kg/week subsequently. However, diuretics should be reduced if the rate of weight loss is more than 0.5 kg/day in patients without peripheral edema or more than 1 kg/day in patients with peripheral edema. Side effects of diuretic therapy include hypovolemic hyponatremia, hyperkalemia, renal dysfunction, encephalopathy, and, with spironolactone, painful gynecomastia.

In the acute setting, albumin infusion alone appears to be of no benefit and can increase the risk of pulmonary edema.[A12] However, the addition of long-term human albumin (40 g twice weekly for 2 weeks, then 40 g weekly) to spironolactone and furosemide can significantly reduce recurrent ascites[A13] and improve 18-month survival.[A14]

In the 10 to 20% of patients with ascites who are refractory to diuretics, large-volume paracentesis, aimed at removal of all or most of the fluid, plus albumin at a dose of 6 to 8 g intravenously per liter of ascites removed, particularly when more than 5L is removed at once, is a reasonable approach. The frequency of large-volume paracentesis is dictated by the rapidity at which the ascites reaccumulates. TIPS with uncovered stents is more effective than large-volume paracentesis plus albumin in preventing recurrent ascites but is associated with a higher rate of encephalopathy. In patients requiring frequent large-volume paracentesis (more than twice per month), a polytetrafluoroethylene-covered TIPS can improve survival.[A15] A peritoneovenous shunt, with use of a subcutaneously placed silicone tube that transfers ascites from the peritoneal cavity to the systemic circulation, can be used in patients who are not candidates for TIPS or liver transplantation. Automated flow pumps to move ascitic fluid to the bladder can reduce the need for large-volume paracentesis and improve quality of life in patients with medically untreatable ascites, but they require surgical placement and are at risk for infection.[A16]

Hyponatremia

Fluid restriction to 1.5 liters daily is recommended for severe hyponatremia (serum sodium concentration <130 mEq/L), but adherence with this recommendation is poor. Although V2-receptor antagonists such as tolvaptan are sometimes effective at increasing free water excretion and raising the serum sodium level in hyponatremic cirrhotic patients, they have no overall effect on survival and are not approved for this use because of potential hepatotoxicity. Because hyponatremia is a marker of neurologic dysfunction and increased mortality, short-term use of tolvaptan (15 mg/day, increased to 30 to 60 mg/day if needed) may be indicated only as a bridge to liver transplantation in patients in whom transplantation is imminent (Chapter 140).

Hepatorenal Syndrome

Hepatorenal syndrome is a functional kidney injury that results from hemodynamic abnormalities owing to end-stage liver disease and severe portal hypertension, and it is associated with a high mortality despite specific therapy. As a result, documented hepatorenal syndrome in the absence of prerenal azotemia or acute tubular necrosis represents a priority for transplantation (Chapter 140). Specific therapies for hepatorenal syndrome that have been used to "bridge" a patient to transplantation include vasoconstrictors (terlipressin, norepinephrine, octreotide plus midodrine) plus albumin, TIPS, and extracorporeal albumin dialysis, which is an experimental hemofiltration dialysis method that uses an albumin dialysate. The largest experience is with the use of terlipressin, which at a dose of 0.5 to 2.0 mg intravenously every 4 to 6 hours leads to a higher reversal rate of hepatorenal syndrome compared with placebo.[A17] However, terlipressin can also cause adverse effects, such as respiratory failure, and must be used with caution.

Spontaneous Bacterial Peritonitis

Empirical antibiotic therapy with an intravenous third-generation cephalosporin (e.g., cefotaxime 2 g intravenously every 12 hours or ceftriaxone 2 g intravenously every 24 hours) should be initiated as soon as the diagnosis is established and before culture results are available; the minimal duration of therapy should be 5 days. Response to recommended empirical antibiotics is significantly lower in patients with health care–associated infections (i.e., infections that occur in patients who have been in a health care facility within the prior 3 months) and particularly low in nosocomial infections (i.e., infections that occur >48 hours after hospitalization) because more infections are caused by multidrug-resistant organisms. In these settings, broader-spectrum antibiotics (e.g., vancomycin-tazobactam, imipenem, ertapenem [Chapter 94]) should be given initially and then modified after culture results and antibiotic sensitivities are obtained. Aminoglycosides should be avoided because of the high incidence of renal toxicity in cirrhotic patients.

Repeated diagnostic paracentesis should be performed 2 days after antibiotics are started, by which time the number of PMN neutrophils in ascitic fluid should have decreased by more than 25% from baseline. Lack of response should prompt further investigations to exclude secondary peritonitis. The renal dysfunction associated with spontaneous bacterial peritonitis can be prevented by the intravenous administration of albumin, particularly in patients who have any evidence of renal dysfunction (blood urea nitrogen >30 mg/dL or creatinine >1 mg/dL, or both) or serum bilirubin concentration higher than 4 mg/dL at the time of diagnosis. Albumin at a dose of 1.5 g per kilogram of body weight at diagnosis, repeated on the third day at an intravenous dose of 1 g per kilogram of body weight, can reduce the risk of renal failure and acute mortality. However, this dosing is empirical, should not exceed 100 g per dose, and does not reduce 3-month mortality in cirrhotic patients with infections other than spontaneous bacterial peritonitis.[A18]

The administration of nonabsorbable (or poorly absorbable) antibiotics can prevent the development of spontaneous bacterial peritonitis and other infections in cirrhosis by selectively eliminating gram-negative organisms in the gut.[17] However, norfloxacin, which was used for this purpose, was withdrawn from the U.S. market in 2014. Reasonable alternatives include oral ciprofloxacin 500 mg every day or rifaximin 600 mg twice daily.[18] Long-term antibiotic prophylaxis may be justified only in two groups: patients who have recovered from a previous episode of spontaneous bacterial peritonitis and patients who have an ascites protein level of less than 1 g/L with advanced liver and circulatory dysfunction as evidenced by the presence of jaundice, hyponatremia, or renal dysfunction.

Hepatic Encephalopathy

Treatment of overt hepatic encephalopathy starts by exclusion of alternative causes of altered mental status. Once the diagnosis of hepatic encephalopathy has been made, treatment involves identifying and treating the precipitating factor and reducing the ammonia level. Precipitating factors include infections, overdiuresis, gastrointestinal bleeding, high oral protein load, and constipation. Narcotics and sedatives contribute to hepatic encephalopathy by directly depressing brain function. TIPS is a common precipitant of hepatic encephalopathy, and shunt reduction or occlusion may be required. Among agents aimed at decreasing ammonia production in the gut, lactulose (15 to 30 mL orally twice daily adjusted to obtain two or three soft bowel movements per day) is the first choice for the treatment of episodic overt encephalopathy.[19] Polyethylene glycol 3350-electrolyte solution (4 L orally or by nasogastric tube over 4 hours), however, may lead to a more rapid clinical response. Other agents include orally administered nonabsorbable antibiotics, such as rifaximin (550 mg two times per day),[A19] neomycin (500 mg to 1 g three times per day), and metronidazole (250 mg two to four times per day). Drugs that may increase ammonia fixation in the liver, such as L-ornithine-L-aspartate, benzoate, and glycerol phenylbutyrate, are being studied.

Once an episode of overt encephalopathy has resolved, secondary prophylaxis with lactulose is recommended. If a precipitating factor has been identified and is well controlled or when liver function or nutritional status has improved, prophylactic therapy may be discontinued. In patients with recurrent encephalopathy, rifaximin together with lactulose is useful in preventing further recurrence. Switching dietary protein from an animal source to a vegetable source may be beneficial in recurrent or persistent encephalopathy, but protein restriction is not necessary and should not be used chronically. Experimental approaches can engineer gut microbiota to reduce urease activity in mice, but whether this approach can be extended to humans is unknown.

Pulmonary Complications

Hepatopulmonary syndrome rarely resolves spontaneously, and medical therapy is disappointing.[20] TIPS is not generally recommended. The only viable treatment is liver transplantation (Chapter 140).

By comparison, liver transplantation is indicated only in a subset of patients with portopulmonary hypertension. In fact, a mean pulmonary arterial pressure higher than 45 mm Hg is an absolute contraindication to liver transplantation. The use of vasodilators should be considered in these patients (Chapter 69).

Surgical Therapy

Liver Transplantation

Orthotopic liver transplantation (Chapter 140), which is the definitive therapy for cirrhosis, is indicated when the risk for dying of liver disease is greater than the risk for dying of transplantation, as determined by a Child-Pugh score of 7 or higher (see Table 139-2) or a Model for End-Stage Liver Disease (MELD) score of 15 or higher. MELD and MELD-Na (see Table 139-2), which estimate the risk for 3-month mortality, are used to determine the priority for liver transplantation. The number of available deceased donor organs is lower than the number of patients awaiting liver transplantation; as a result, 15 to 20% of patients awaiting liver transplantation in the United States die before an organ becomes available.

PREVENTION

Treatment of the underlying liver disease, before the development of cirrhosis, is a primary prevention strategy. Because the major causes of cirrhosis are related to lifestyle choices such as injection drug use (Chapter 365), alcohol consumption (Chapter 364), obesity, and unprotected sex, primary prevention programs that focus on encouraging alcohol abstinence, reducing high-risk behavior for hepatitis virus infection, weight reduction, and vaccination for hepatitis B are even better prevention strategies.

PROGNOSIS

The outcome of cirrhosis depends on the patient's stage. Patients with compensated cirrhosis die of liver disease only after transition to a decompensated stage. The 10-year survival rate of patients who remain in a compensated stage is approximately 90%, whereas their likelihood of decompensation is 50% at 10 years. Inception cohort studies of patients with compensated cirrhosis show a median survival of all patients, including those in whom decompensation develops over time, of about 10 years. Overall, the median survival after decompensation is about 2 years.[21] Survival is even lower in patients with refractory ascites, hyponatremia, or recurrent variceal hemorrhage and is lowest in patients who are hospitalized with an acute decompensating event, in whom 28-day mortality is about 30% and correlates with the number of organ failures present. Hepatocellular carcinoma develops at a fairly constant rate of 3% per year and is associated with a worse outcome at whatever stage it develops.

Predictors of survival are somewhat different in compensated and decompensated patients. Parameters of portal hypertension (varices, splenomegaly, platelet count, γ-globulin) assume greater importance in compensated patients, whereas renal dysfunction, hemorrhage, and hepatocellular carcinoma are important predictive factors in patients with decompensated cirrhosis. In clinical practice, the Child-Pugh score is applicable to all cirrhotic patients, and the MELD score is used in decompensated patients to determine priority for liver transplantation (see Table 139-2).

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140 LIVER FAILURE AND TRANSPLANTATION

ROBERT J. FONTANA

LIVER FAILURE

EPIDEMIOLOGY AND PATHOBIOLOGY

Acute liver failure, which is a rare disorder seen in 2000 to 3000 U.S. patients each year, is defined as a severe acute liver injury that precipitates the sudden onset of encephalopathy and coagulopathy (international normalized ratio [INR] > 1.5).[1] By definition, acute liver failure results from an insult within the prior 6 months. Acute-on-chronic liver failure is defined when liver injury of longer duration worsens and causes liver failure or other complications of portal hypertension.[2]

Nearly 50% of all cases of acute liver failure are caused by acetaminophen hepatotoxicity (Chapters 96 and 136), whereas idiosyncratic drug-induced liver injury (Chapter 136), autoimmune hepatitis (Chapter 135), acute hepatitis B (Chapter 134), and shock liver (Chapter 92) account for more than a quarter of cases.[3]

Acute-on-chronic liver failure can sometimes be precipitated by the same acute insults that cause acute liver failure. More commonly, however, acute-on-chronic liver failure occurs when cirrhosis (Chapter 139) decompensates because of a comparatively minor insult superimposed on serious but compensated underlying liver disease, or when ongoing alcoholic liver disease (Chapter 138), fatty liver disease (Chapter 138), or a metabolic liver disease (e.g., hemochromatosis [Chapter 196] or Wilson disease [Chapter 195]) causes severe progressive injury.

Liver failure results in loss of the liver's ability to synthesize coagulation factors and metabolize ammonia. The rapid loss of hepatocytes results in a massive release of cytokines, thereby leading to tissue hypoxia and lactic acidosis. The encephalopathy of acute liver failure is mediated by cerebral edema, not by the portosystemic shunting and portal hypertension of cirrhosis (Chapter 139).

CLINICAL MANIFESTATIONS AND DIAGNOSIS

The clinical manifestations of liver failure are the same as the manifestations of severe cirrhosis (Chapter 139). Hepatic encephalopathy and coagulopathy are the dominant features, but ascites, hepatorenal syndrome, hepatopulmonary syndrome, and portopulmonary hypertension typically occur. Variceal bleeding is more common in acute-on-chronic liver failure.

Patients with acute liver failure typically have the rapid onset of the encephalopathy and coagulopathy (INR > 1.5), but the onset can be slower in patients who have acute-on-chronic liver failure.[4] The severity of acute liver failure and the adequacy of tissue perfusion (e.g., serum pH and lactate level) can be assessed by measuring blood levels of markers that are synthesized by the liver (e.g., the INR, factor V level, and serum albumen level) or processed by the liver (e.g., serum arterial ammonia level and bilirubin level) and then monitoring them serially. Because factor V is the coagulation factor with the shortest half-life, it is the most sensitive biomarker to detect trends over time. The patient's grade of encephalopathy should be assessed on a scale of 1 (subtle, minimal change in consciousness), 2 (disoriented, inappropriate), 3 (somnolent but arousable), or 4 (comatose).

TREATMENT

Patients who have acute liver failure should be stabilized in an intensive care unit, where any neurologic, respiratory, hemodynamic, infectious, and renal complications should be addressed.[5] *N*-acetylcysteine (a 140 mg/kg loading dose followed by 70 mg/kg every 4 hours) should be administered immediately to all patients with suspected acetaminophen hepatotoxicity (Chapter 136). Based on limited data that raise the possibility of its potential benefit, N-acetylcysteine is also commonly recommended in acute liver failure caused by idiosyncratic drug-induced liver injury, hepatitis B, and autoimmune hepatitis, as well as acute liver failure of indeterminate cause, especially in patients who have grade 1 or 2 encephalopathy.[6]

Removal of the offending agent for idiosyncratic drug-induced liver injury (Chapter 136), nucleos(t)ide analogues for acute hepatitis B (Chapter 134), acyclovir for herpes simplex virus (Chapter 345), copper chelation and

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PROGNOSIS

The outcome of cirrhosis depends on the patient's stage. Patients with compensated cirrhosis die of liver disease only after transition to a decompensated stage. The 10-year survival rate of patients who remain in a compensated stage is approximately 90%, whereas their likelihood of decompensation is 50% at 10 years. Inception cohort studies of patients with compensated cirrhosis show a median survival of all patients, including those in whom decompensation develops over time, of about 10 years. Overall, the median survival after decompensation is about 2 years.[21] Survival is even lower in patients with refractory ascites, hyponatremia, or recurrent variceal hemorrhage and is lowest in patients who are hospitalized with an acute decompensating event, in whom 28-day mortality is about 30% and correlates with the number of organ failures present. Hepatocellular carcinoma develops at a fairly constant rate of 3% per year and is associated with a worse outcome at whatever stage it develops.

Predictors of survival are somewhat different in compensated and decompensated patients. Parameters of portal hypertension (varices, splenomegaly, platelet count, γ-globulin) assume greater importance in compensated patients, whereas renal dysfunction, hemorrhage, and hepatocellular carcinoma are important predictive factors in patients with decompensated cirrhosis. In clinical practice, the Child-Pugh score is applicable to all cirrhotic patients, and the MELD score is used in decompensated patients to determine priority for liver transplantation (see Table 139-2).

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140 LIVER FAILURE AND TRANSPLANTATION

ROBERT J. FONTANA

LIVER FAILURE

EPIDEMIOLOGY AND PATHOBIOLOGY

Acute liver failure, which is a rare disorder seen in 2000 to 3000 U.S. patients each year, is defined as a severe acute liver injury that precipitates the sudden onset of encephalopathy and coagulopathy (international normalized ratio [INR] > 1.5).[1] By definition, acute liver failure results from an insult within the prior 6 months. Acute-on-chronic liver failure is defined when liver injury of longer duration worsens and causes liver failure or other complications of portal hypertension.[2]

Nearly 50% of all cases of acute liver failure are caused by acetaminophen hepatotoxicity (Chapters 96 and 136), whereas idiosyncratic drug-induced liver injury (Chapter 136), autoimmune hepatitis (Chapter 135), acute hepatitis B (Chapter 134), and shock liver (Chapter 92) account for more than a quarter of cases.[3]

Acute-on-chronic liver failure can sometimes be precipitated by the same acute insults that cause acute liver failure. More commonly, however, acute-on-chronic liver failure occurs when cirrhosis (Chapter 139) decompensates because of a comparatively minor insult superimposed on serious but compensated underlying liver disease, or when ongoing alcoholic liver disease (Chapter 138), fatty liver disease (Chapter 138), or a metabolic liver disease (e.g., hemochromatosis [Chapter 196] or Wilson disease [Chapter 195]) causes severe progressive injury.

Liver failure results in loss of the liver's ability to synthesize coagulation factors and metabolize ammonia. The rapid loss of hepatocytes results in a massive release of cytokines, thereby leading to tissue hypoxia and lactic acidosis. The encephalopathy of acute liver failure is mediated by cerebral edema, not by the portosystemic shunting and portal hypertension of cirrhosis (Chapter 139).

CLINICAL MANIFESTATIONS AND DIAGNOSIS

The clinical manifestations of liver failure are the same as the manifestations of severe cirrhosis (Chapter 139). Hepatic encephalopathy and coagulopathy are the dominant features, but ascites, hepatorenal syndrome, hepatopulmonary syndrome, and portopulmonary hypertension typically occur. Variceal bleeding is more common in acute-on-chronic liver failure.

Patients with acute liver failure typically have the rapid onset of the encephalopathy and coagulopathy (INR > 1.5), but the onset can be slower in patients who have acute-on-chronic liver failure.[4] The severity of acute liver failure and the adequacy of tissue perfusion (e.g., serum pH and lactate level) can be assessed by measuring blood levels of markers that are synthesized by the liver (e.g., the INR, factor V level, and serum albumen level) or processed by the liver (e.g., serum arterial ammonia level and bilirubin level) and then monitoring them serially. Because factor V is the coagulation factor with the shortest half-life, it is the most sensitive biomarker to detect trends over time. The patient's grade of encephalopathy should be assessed on a scale of 1 (subtle, minimal change in consciousness), 2 (disoriented, inappropriate), 3 (somnolent but arousable), or 4 (comatose).

TREATMENT

Patients who have acute liver failure should be stabilized in an intensive care unit, where any neurologic, respiratory, hemodynamic, infectious, and renal complications should be addressed.[5] *N*-acetylcysteine (a 140 mg/kg loading dose followed by 70 mg/kg every 4 hours) should be administered immediately to all patients with suspected acetaminophen hepatotoxicity (Chapter 136). Based on limited data that raise the possibility of its potential benefit, N-acetylcysteine is also commonly recommended in acute liver failure caused by idiosyncratic drug-induced liver injury, hepatitis B, and autoimmune hepatitis, as well as acute liver failure of indeterminate cause, especially in patients who have grade 1 or 2 encephalopathy.[6]

Removal of the offending agent for idiosyncratic drug-induced liver injury (Chapter 136), nucleos(t)ide analogues for acute hepatitis B (Chapter 134), acyclovir for herpes simplex virus (Chapter 345), copper chelation and

ABSTRACT

Liver transplantation is a life-saving treatment for acute and acute-on-chronic liver failure caused by alcoholic liver disease, nonalcoholic steatohepatitis, viral hepatitis, autoimmune disorders, certain hepatic malignancies, and some genetic conditions. Pre-transplantation management of the acute liver failure is key. Most transplants are from deceased donors, with priority assigned based on the severity of illness and ABO compatibility. However, living donor transplants are increasingly performed. Postoperative issues include surgical complications, management of immunosuppressive agents, and prophylaxis and treatment of infections.

KEYWORDS

deceased donor
living donor
MELD
MELD-NA
OPTN/SRTR
allocation of donor livers
selection criteria
contraindications to transplantation
allograft rejection
immunosuppressive medications

plasmapheresis for Wilson disease (Chapter 195), corticosteroids for autoimmune hepatitis (Chapter 135), delivery of the infant for pregnancy-related liver disease (Chapter 221), and a continuous heparin infusion for Budd-Chiari syndrome (Chapter 129) should be implemented.

The management of varices and variceal bleeding, ascites, hyponatremia, hepatorenal syndrome, and the hepatopulmonary syndrome is as recommended for cirrhosis. Although coagulopathy is inherent to acute liver failure, routine transfusions of plasma and platelets are not recommended because the excess volume can exacerbate cerebral and pulmonary edema without significant benefit.

To prevent intracranial hypertension, the head of the bed should be elevated above 30 degrees from horizontal, and efforts should be taken to minimize movement and Valsalva maneuvers. All sedative and psychotropic drugs should be avoided because of their delayed clearance. For acute kidney injury, continuous renal replacement therapy is preferred over hemodialysis and may help improve outcomes by reducing systemic ammonia levels.[7] When patients develop grade 3 encephalopathy, their respiratory status should be carefully monitored so that they can be electively intubated with a target P_{CO_2} of 28 to 30 mm Hg to facilitate intracerebral vasoconstriction.[8]

Invasive intracranial pressure (ICP) monitoring using intraparenchymal devices should be considered to guide medical therapy in nonresponsive patients with grade 3 or 4 encephalopathy because other signs of worsening neurologic function (e.g., posturing, dilated pupils, abnormalities on a brain computed tomographic scan) are frequently not present. Placement of an ICP monitor carries a 10 to 20% risk of intracranial bleeding, so all patients should receive desmopressin (20 μg) plus individualized doses of recombinant factor VIIa, fresh frozen plasma, or plasma factor concentrate under expert supervision to lower the risk of hemorrhage to less than 5%.[9] Surges in ICP that reduce cerebral perfusion pressure may be treated with an intravenous bolus of hypertonic saline (1 to 4 mL/kg of 3 to 10% saline over 30 minutes) or mannitol (0.5 to 1 mg/kg IV), with concomitant monitoring of serum sodium and osmolarity levels. Pentobarbital (100 to 150 mg bolus followed by 1 to 3 mg/kg/hour) can be used in patients who have refractory cerebral edema. Moderate hypothermia to 32° to 33° C via external cooling blankets may be helpful, but data are currently insufficient to recommend its routine use.

Serious bacterial infections are documented in about 80% of patients with acute liver failure, including fungal infections in about 20%. Any fever requires comprehensive evaluation (Chapters 259 and 260), with a low threshold for starting empirical broad-spectrum antibiotics while awaiting culture results if patients suffer from clinical deterioration.

PROGNOSIS

The likelihood of spontaneous recovery from acute liver failure without liver transplant can be estimated by knowing its cause, the initial severity of hepatic encephalopathy, the need for vasopressor or ventilatory support, and the laboratory parameters (e.g., the INR and bilirubin level) and vital organ function over time. Acute liver failure that is pregnancy-related or caused by acetaminophen, ischemia, or hepatitis A has a higher rate of spontaneous liver recovery (50 to 70%) compared with other causes of acute liver failure (20 to 50%). Hypophosphatemia is suggestive of liver regeneration and is a positive prognostic sign.

Patients who have a predicted transplant-free survival of less than 80% (see https://appadvice.com/app/acute-liver-failure-prognostic) should be considered for early transfer to a liver transplant center for further evaluation. Even if patients initially are at lower risk, however, they may require emergency liver transplantation if they exhibit no signs of liver recovery and regeneration, despite disease-specific interventions and general supportive care. Qualifying patients should be placed on the liver transplant waiting list with the highest priority, known as status 1A. With emergency surgery, patients in acute liver failure can achieve a 2-year survival as high as 92% with excellent neurologic and clinical outcomes. However, only 30% of listed patients who have acute liver failure undergo transplantation because of either spontaneous improvement or the development of a contraindication to liver transplantation. As a result, acute liver failure accounts only for 3 to 5% of annual liver transplants in the United States.

When patients with decompensated cirrhosis (Chapter 139) develop acute-on-chronic liver failure with variceal hemorrhage, ascites, and/or hepatic encephalopathy, they should be referred for evaluation for a liver transplant because of their increased risk of short-term mortality.[10,11,12] Adult patients with compensated cirrhosis have a median survival of 12 years and typically do not require referral for a possible liver transplant unless they have a Sodium-Model for End-Stage Liver Disease (Na-MELD) score above 15 (see Table 139-2), progressive protein calorie malnutrition, or severe clinical symptoms (e.g., muscle wasting, severe pruritus, recurrent encephalopathy, ascites, or gastrointestinal bleeding) that will improve with liver transplant. Patients who have the hepatopulmonary syndrome or portopulmonary hypertension (Chapter 139) may qualify for a higher priority on the waiting list via Na-MELD exception scores.

LIVER TRANSPLANTATION

Liver transplantation is a life-saving therapy for selected patients who have severe acute or chronic liver failure, as well as patients who have certain genetic, metabolic, and intrahepatic neoplastic disorders. In the United States, over 150 liver transplant centers perform nearly 9000 liver transplants annually. Deceased donors account for about 95% of transplanted livers, whereas about 5% are from living donors (Fig. 140-1).[13] At any given time, approximately 13,000 patients are on the liver transplant waiting list. The size of the deceased organ donor pool has gradually increased owing to the use of livers from deceased donors who are elderly or have hepatic steatosis, chronic hepatitis C, or prior hepatitis B infection. Nevertheless, the pre-transplant mortality rate for patients on the waiting list remains 7 to 12 deaths per 100 waiting list-years. By comparison, the 1- and 5-year recipient survival rates are now about 93 and 82%, respectively (Fig. 140-2).

INDICATIONS FOR LIVER TRANSPLANTATION

Chronic alcohol-related liver disease (Chapter 138), is now the most common underlying indication for liver transplant (Fig. 140-3) because of the success of antiviral therapies for treating chronic hepatitis C (Chapter 135). Nonalcoholic fatty liver disease (Chapter 138) is another increasing indication for liver transplant because of the obesity epidemic in the United States and other developed and even developing countries (Chapter 201).

Acute or Acute-on-Chronic Liver Failure

Liver transplantation is reserved for patients who have acute or acute-on-chronic liver failure with a high 90-day risk of death, as well as patients who

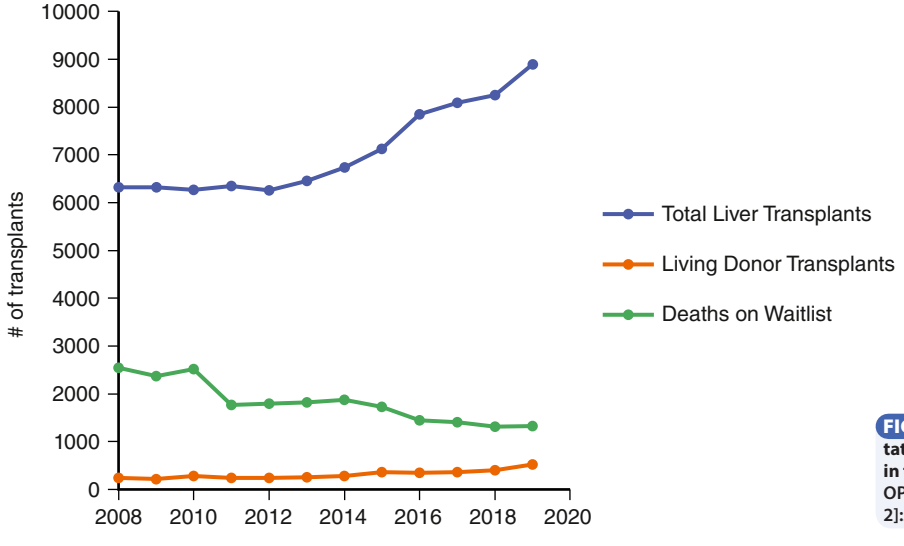

FIGURE 140-1. Annual number of patients undergoing liver transplantation, living donor liver transplantation, and dying on the waiting list in the United States. (Based on data from Kwon AJ, Kim WR, Lake JR, et al. OPTN/SRTR 2019 annual data report: river. *Am J Transplant*. 2021;21[Suppl 2]:208-315. Courtesy of Jason Pan, MD.)

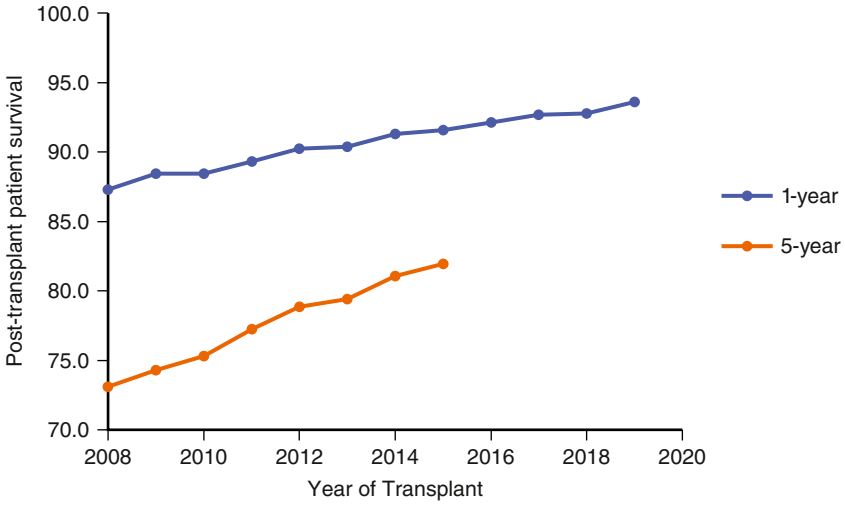

FIGURE 140-2. The 1- and 5-year adult liver transplant patient survival rates in the United States. (Based on data from Kwon AJ, Kim WR, Lake JR, et al. OPTN/SRTR 2019 annual data report: river. *Am J Transplant*. 2021;21[Suppl 2]:208-315. Courtesy of Jason Pan, MD.)

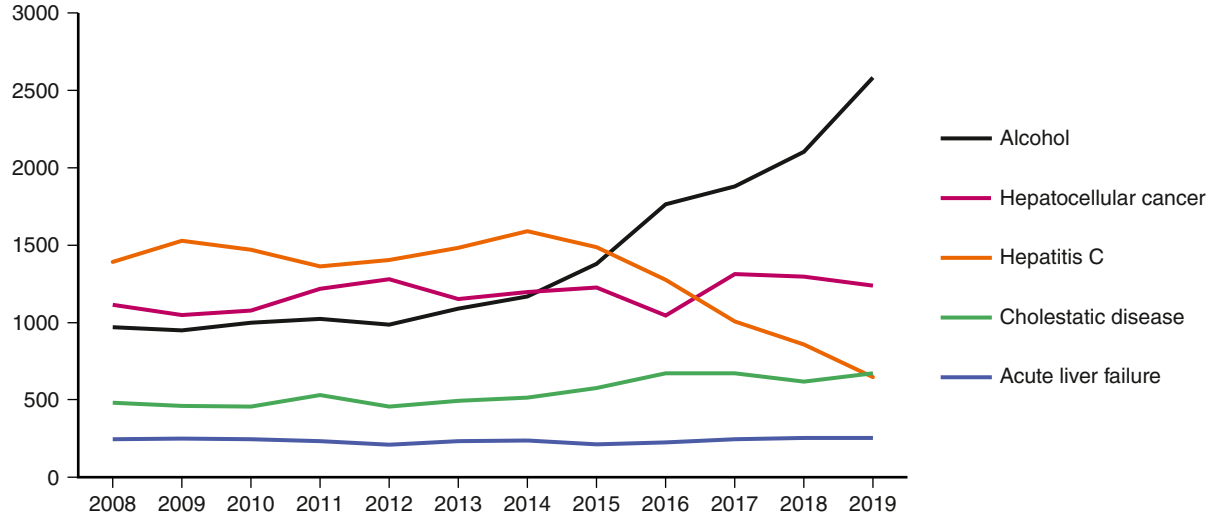

FIGURE 140-3. Leading indications for adult liver transplantation in the United States (Based on data from Kwong AJ, Kim WR, Lake JR, et al. OPTN/SRTR 2019 annual data report: liver. *Am J Transplant*. 2021;21[Suppl 2]:208-315. Courtesy of Jason Pan, MD.)

have metabolic, genetic, and neoplastic diseases that may be cured with liver transplantation.[14] When a patient with progressive cirrhosis experiences hepatic decompensation (e.g., ascites, variceal hemorrhage, portal vein thromboses, hepatic encephalopathy), progressive protein calorie malnutrition, or deteriorating laboratory indices, the patient should be referred for liver transplant evaluation. Most patients who have cirrhosis and a Na-MELD score of 15 or higher (Table 139-2) are likely to have a survival benefit with transplantation. Patients who have unique qualifying complications of portal hypertension (e.g., hepatopulmonary syndrome or refractory hepatic hydrothorax) may also receive high priority.[15]

Hepatobiliary Cancer

Hepatocellular carcinoma is the primary indication for 10 to 20% of adult liver transplants in the United States. To qualify for transplant independently of their Na-MELD score, patients must have: no evidence of extrahepatic disease or vascular invasion; one lesion that is less than 5 cm in size, or two or three lesions, each less than 3 cm in size; and a serum α-fetoprotein level less than 1000 ng/mL. Hepatocellular carcinoma patients who meet these criteria have a 5-year post-transplant survival approaching 80%.[16] If locoregional therapy, radiation, or chemoembolization (Chapter 181) reduces the size of the tumor(s), patients who do not meet these criteria may be downstaged, become eligible for transplantation, and do as well as patients who met transplantation criteria without downstaging.

Selected patients with locally advanced perihilar cholangiocarcinoma may also qualify for transplantation, regardless of their Na-MELD score if they have unresectable disease or have underlying liver disease that would make them poor candidates for resection surgery. Before transplantation, such patients should receive neoadjuvant chemotherapy and radiation (Chapter 181) and then undergo operative staging to ensure that they have no lymphatic, intrahepatic, or extrahepatic metastases. In eligible patients, the 5-year recurrence-free survival with neoadjuvant therapy and liver transplant is about 65%. Other uncommon indications for liver transplantation include hemangioendotheliomas and metastatic neuroendocrine and carcinoid tumors to the liver (Chapter 213).

Metabolic Disorders

Inborn errors of metabolism, such as primary hyperoxaluria, urea cycle disorders, and organic acidemias (Chapter 189) do not cause parenchymal liver disease or fibrosis.[17] However, liver transplantation can correct the enzymatic defects by lowering ammonia levels in urea cycle disorders and organic acidemia, lowering oxalate levels in primary hyperoxaluria, and providing normal protein in patients with familial amyloid polyneuropathy (Chapter 174). Liver transplantation also can prevent progression of systemic manifestations of these diseases but does not typically reverse preexisting systemic clinical manifestations, such as the intellectual deficits in the urea cycle disorders and organic acidemias or advanced neurologic symptoms and cardiac disease in familial amyloidosis or in patients with Wilson disease.

SELECTION FOR TRANSPLANTATION

Liver transplant candidates should be carefully evaluated by a multidisciplinary team to ensure that they have severe enough disease to warrant transplantation but also will be able to tolerate the surgery and associated immunosuppression with a favorable 5-year outcome. The presence of severe cardiopulmonary disease, active use of illicit substances or alcohol, frailty, and nonadherence with medical care are contraindications to transplantation (Table 140-1). A patient's eligibility for transplantation may vary over time and should be reassessed

TABLE 140-1 CONTRAINDICATIONS TO LIVER TRANSPLANTATION

Relapsing illicit substance or alcohol use
Inadequate social support
Severe or untreated psychiatric disease or behavioral concerns
Severe cardiopulmonary disease
Active extrahepatic malignancy
Uncontrolled sepsis or other severe infections
Active HIV infection with AIDS-defining illness
Irreversible neurologic disease
Anatomic anomalies or extensive vascular thromboses that are prohibitive to transplant
Severe malnutrition and frailty

AIDS = acquired immunodeficiency syndrome; HIV = human immunodeficiency virus.

whenever they undergo a clinical change, hospitalization, or a decompensating liver-related event.

Preoperative Medical Assessment

The pre-transplant evaluation process initially involves confirming the cause of the liver disease and determining whether any treatment other than transplantation may be effective. Then an assessment of the patient's severity of disease, operative risk, and nutritional and functional status is undertaken. Patients should complete age- and gender-appropriate cancer screenings (e.g., head and neck examination, skin examination, colonoscopy, mammography, pelvic examination, prostate-specific antigen determination). Blood typing is needed to ensure proper matching with potential donors, but matching by human leukocyte antigen (HLA) type is not required.

Liver transplantation surgery places significant stress on the heart and lungs, so patients with heart failure, inadequately treated coronary artery disease, severe valvular disease, or moderate to severe pulmonary hypertension are frequently excluded from consideration. All transplant candidates should have an electrocardiogram, a transthoracic echocardiogram with Doppler and bubble study to exclude intrapulmonary shunting, and a chest radiograph to screen for cardiopulmonary disease. Patients at risk for coronary artery disease should undergo formal cardiac stress testing with follow-up coronary angiography as indicated (Chapters 44 and 56).[18] Patients who have smoked or have underlying lung disease should undergo pulmonary function tests (Chapter 73) and pulse oximetry. Patients who have stage IV or V chronic kidney disease (Chapter 116) or who have been on hemodialysis for more than 90 days may be considered for combined liver and kidney transplantation.

Because of the need for lifelong immunosuppression, recipients of liver transplants are at risk for both bacterial and opportunistic infections. A careful dental examination is important to exclude an oral source of chronic infection. Latent pathogens such as tuberculosis (Chapter 299), Epstein-Barr virus (Chapter 348), cytomegalovirus (Chapter 347), toxoplasma (Chapter 320), and hepatitis B (Chapter 135) may reactivate in the setting of immunosuppression, so patient's prior exposure must be assessed before transplantation to plan for proper prophylaxis. Vaccinations against hepatitis A, hepatitis B, influenza, pneumococcus, herpes zoster, and COVID-19 infection (Chapter 15) are recommended before transplantation whenever possible. Patients with well-controlled human immunodeficiency virus (HIV) on stable antiretroviral therapy (Chapter 357) may undergo liver transplantation at specialized centers with good outcomes. However, patients with uncontrolled HIV infection or acquired immunodeficiency syndrome are excluded from liver transplantation because their outcomes are poor.

Patients who have severe malnutrition (Chapter 198), frailty (Chapter 24), morbid obesity (Chapter 201), or are older than age 70 years must be carefully assessed on an individual basis because they are at higher risk for postoperative complications and poor allograft function. Preoperative contrast-enhanced computed tomographic (CT) or magnetic resonance (MR) imaging of the liver is recommended in most centers for surgical planning and to evaluate for portal vein thromboses and atherosclerosis of the major vessels.

Preoperative Psychosocial Assessment

Successful liver transplantation requires long-term adherence to medication regimens, laboratory monitoring, and outpatient follow-up, as well as continued lifelong abstinence from alcohol, tobacco, and other illicit substances. Poor adherence may arise from a lack of motivation, poor social support, inability to maintain insurance coverage, and severe or untreated psychiatric conditions or substance use disorders. Long-term (≥6 months) preoperative abstinence from alcohol is desirable, in part to determine whether liver function may improve, but is not as predictive of the likelihood of recidivism as are factors such as social isolation, underlying psychiatric conditions, and family support. For example, selected patients with severe alcoholic hepatitis and a first episode of hepatic decompensation that is refractory to corticosteroids may do well after emergent liver transplantation combined with intensive post-transplantation treatment of the alcohol use disorder.[19]

A multidisciplinary team that involves hepatologists, social workers, psychiatrists, and psychologists may best identify and address any potential barriers to transplantation. In addition, liver transplantation candidates are typically screened with periodic toxicology testing, such as a serum phosphatidylethanol level, urine toxicology, urine ethyl glucuronide, and urine cotinine levels. Formal pre-transplantation education instructs patients, their families, and caregivers about the process of transplantation and the need for lifelong abstinence from illicit substances and compliance with medical treatments.

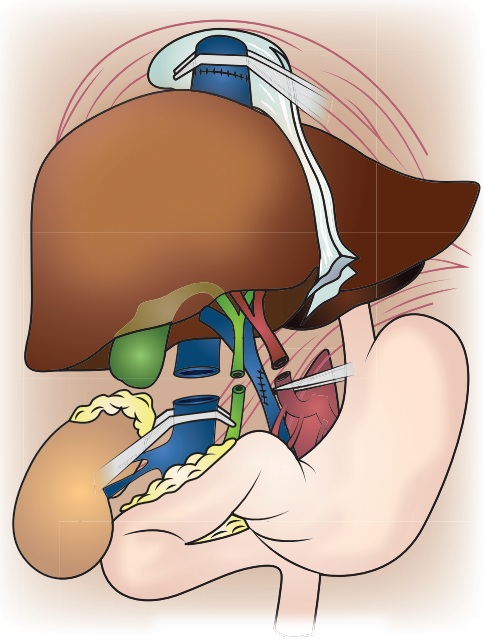

FIGURE 140-4. The four major anastomoses created during a standard liver transplant operation. The recipient's main portal vein is typically sewn to the donor's portal vein in an end-to-end manner. The venous outflow can be created via direct insertion of the individual hepatic veins onto the recipient vena cava or via a side-to-side cavocavostomy. Hepatic artery blood flow is established via an end-to-end arterial anastomosis. (From Karp SJ, Alexopoulous S. Liver transplantation. In: Townsend CM Jr, Beauchamp RD, Evers BM, et al, eds. *Sabiston Textbook of Surgery,* 21st ed. St. Louis, MO: Elsevier; 2022: 614-626.)

Listing for Liver Transplantation

Once an adult patient is medically, psychosocially, and financially approved to be added to the liver transplant waiting list, their priority is determined by their calculated Na-MELD score (Table 139-2), which is correlated with the likelihood of dying in the next 3 months without liver transplantation. The minimal Na-MELD score required to be listed for liver transplantation varies by center, but the usual requirement is a score of at least 15 points or evidence of complications of portal hypertension or progressive protein calorie malnutrition. Once on the list, organs are generally offered to ABO-identical or compatible patients who have the highest laboratory Na-MELD score, but critically ill adults may be upgraded to a higher priority if they are in an intensive care unit with fulminant liver failure, have acutely decompensated Wilson disease, or have acute failure of a previously transplanted liver.[20]

THE TRANSPLANTATION PROCEDURE

Liver transplant surgery entails three phases that requires 3 vascular and 1 biliary anastomoses: removal of the native liver, the anhepatic state, and engraftment (Fig. 140-4). Significant intra-operative bleeding typically requires large volumes of blood products and procoagulants.

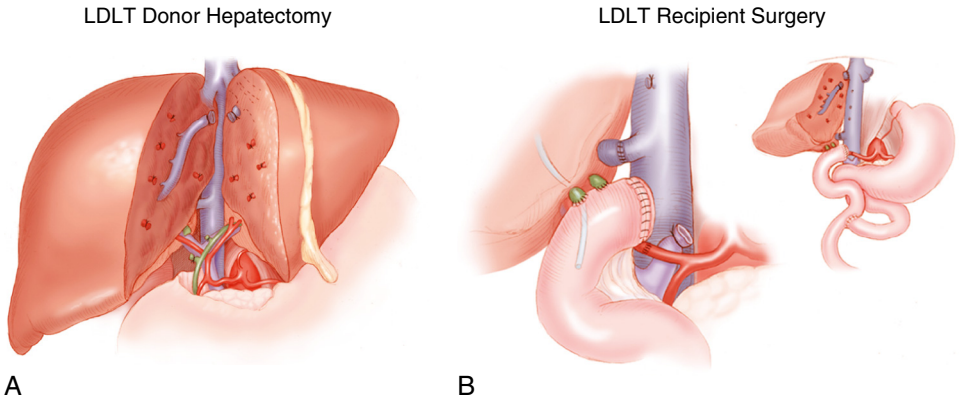

FIGURE 140-5. Living related donor hepatectomy (A) and orthotopic implantation of the right lobe graft (B). LDLT = living donor liver transplantation. (From Everson GT. Hepatic failure and liver transplantation. In: Goldman L, Schafer AI, eds. *Goldman-Cecil Medicine,* 26th ed. Philadelphia: Elsevier; 2020:998-1004.)

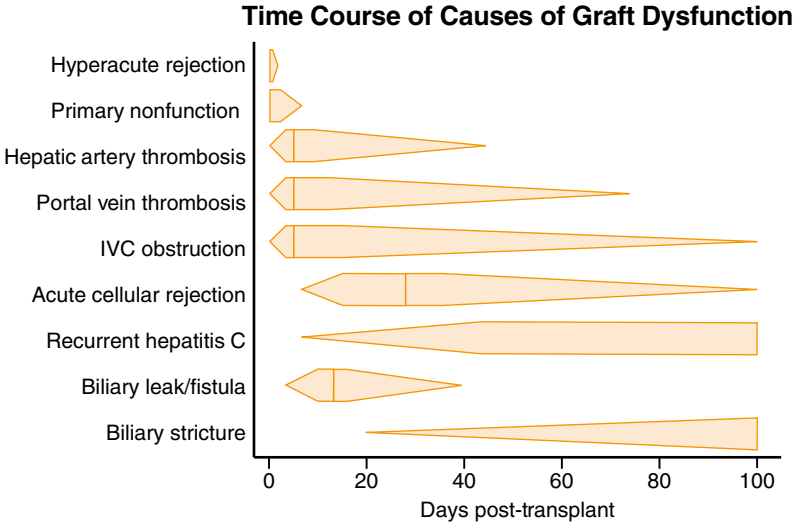

FIGURE 140-6. Time course of causes of graft dysfunction. Hyperacute rejection is rare (ABO incompatibility) but occurs in the first few hours to days. Primary nonfunction, vascular thrombosis, and biliary leaks are early events, and acute rejection episodes occur after the first 7 days. Recurrent hepatitis C may begin early but typically is manifested after the first 2 or 3 weeks after transplantation. Biliary strictures evolve more slowly and tend to be later events. IVC = inferior vena cava. (From Everson GT. Hepatic failure and liver transplantation. In: Goldman L, Schafer AI, eds. *Goldman-Cecil Medicine,* 26th ed. Philadelphia: Elsevier; 2020:998-1004.)

In the United States, approximately 95% of adult liver transplants use organs from deceased donors. Most deceased donor livers are procured from individuals who have experienced brain death due to head trauma, intracranial bleeding, or prolonged anoxia. However, about 8% are from critically ill patients who do not meet criteria for brain death (Chapter 373) but who may still qualify to be a liver donor after controlled withdrawal of life support. Livers from these latter donors have a higher risk of complications, such as ischemic cholangiopathy and primary non-function, because of prolonged warm ischemia following withdrawal of life-support. Cold ischemia time, which is the time between removal of the organ from the donor and implantation into the recipient, typically ranges from 4 to 8 hours. Advanced techniques for hypothermic[A1] and for normothermic[A2,21] perfusion can maintain the integrity of the graft during cold ischemia and may help expand the donor pool. Due to concerns of excessive travel time, livers from deceased donors over age 70 years or whose livers were harvested after cardiac death are offered to local liver transplantation programs.

Living donor liver transplantation can expedite liver transplantation and improve survival. Living donor liver transplantation is generally reserved for outpatients who have cirrhosis, liver tumors, or metabolic defects and who are not of high enough priority to qualify for a cadaveric liver (Fig. 140-5).[22] A portion of the larger right liver lobe (segments 5 to 8, which weigh 600 to 1000 grams) is typically used in an adult-to-adult transplantation (see Fig. 140-5).

POST-TRANSPLANTATION COMPLICATIONS AND CARE

Early post-transplantation complications (Fig. 140-6) related to the surgery include intra-abdominal bleeding, primary nonfunction of the graft, small-for-size syndrome, hepatic artery thrombosis, and bile leaks.[23,24] Subacute complications, which occur 1 to 3 months after surgery, include strictures of the biliary anastomosis, acute cellular rejection, and opportunistic infections. Late complications beyond 1 year include post-transplant lymphoproliferative disorder (Chapter 348), de novo malignancy, and recurrence of the original liver disease. Cardiovascular disease and malignancy are the leading causes of death after 1 year.

Surgical Complications

Primary nonfunction of the graft is the most serious perioperative complications but fortunately occurs in only 2 to 4% of recipients. Primary nonfunction is characterized by high aminotransferase levels, an elevated INR, lactic acidosis, and renal failure. Patients with primary nonfunction within 7 days of transplantation are highest priority for another transplant.

Hepatic artery thrombosis, which develops in less than 5% of patients and typically manifests with high levels of aminotransferases, coagulopathy, acidosis, or bile leaks early on and cholangiopathy later, can be diagnosed by liver ultrasound with Doppler. If surgical or radiologic interventions are not possible or successful, patients with hepatic artery thrombosis within 7 days after transplantation are highest priority for re-transplantation.

Biliary complications, such as bile leaks, biliary anastomotic strictures, and ischemic cholangiopathy, occur in 20 to 30% of recipients. Bile leaks tend to occur within days of the transplant. Ischemic cholangiopathy typically results in multiple, diffuse intrahepatic strictures that present clinically at 1 to 6 months after transplantation and may require percutaneous transhepatic cholangiography or re-transplantation for definitive management.

Infectious Complications

In the days after surgery, patients are prone to wound and surgical site infections, ventilator-associated pneumonia, catheter-associated bloodstream infections, and infections of non-anatomic fluid collections that arose during surgery (e.g., biloma, hematoma). In the first month after transplantation, high levels of immunosuppression raise the risk of infection with opportunistic pathogens (Fig. 140-7). Patients are typically prescribed trimethoprim-sulfamethoxazole[25] (usually one double strength tablet three times a week) to prevent *Pneumocystis* infections (see Table 313-2) and oral antifungal agents (e.g., fluconazole 100 mg per day) for 3 to 6 months after transplantation. The risk for cytomegalovirus is highest when the donor is anti-cytomegalovirus

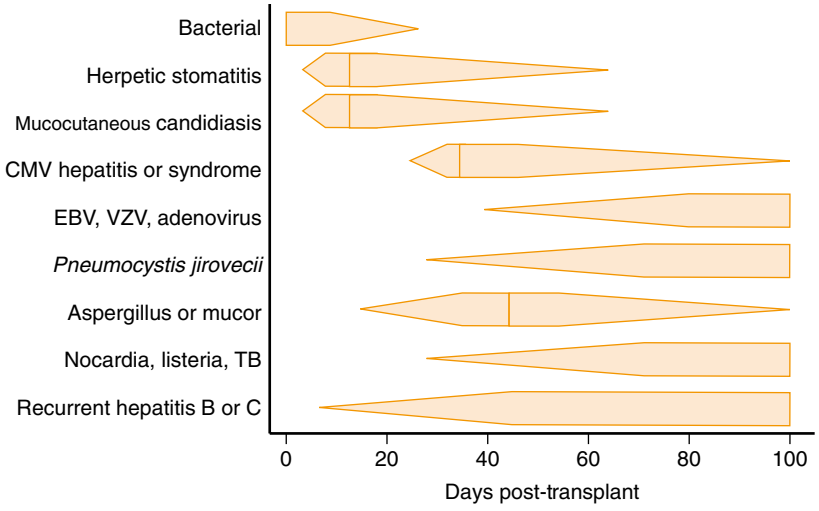

FIGURE 140-7. Time course for infectious complications. Bacterial and mucocutaneous viral or candidal infections occur early, and most of the others occur after the first 2 or 3 weeks after transplantation. CMV = cytomegalovirus (Chapter 347); EBV = Epstein-Barr virus (Chapter 348); TB = tuberculosis (Chapter 299); VZV = varicella-zoster virus (Chapter 346). (From Everson GT. Hepatic failure and liver transplantation. In: Goldman L, Schafer AI, eds. *Goldman-Cecil Medicine*, 26th ed. Philadelphia: Elsevier; 2020:998-1004.)

TABLE 140-2 ORAL IMMUNOSUPPRESSION MEDICATIONS

DRUG	DOSE	MONITORING	ADVERSE EFFECTS
CALCINEURIN INHIBITORS			
Cyclosporine	100-200 mg bid	Trough blood level 50 to 200 ng/mL	Nephrotoxicity Neurotoxicity
Tacrolimus	1-2 mg bid	Trough blood level 4 to 10 ng/mL	Hypertension Diabetes mellitus
mTOR INHIBITORS			
Sirolimus	1-3 mg daily	Trough blood level 4 to 12 ng/mL	Leukopenia, neutropenia Thrombocytopenia Hyperlipidemia Vascular thrombosis Poor wound healing Mouth ulcers Pneumonitis
Everolimus	1-2 mg bid	Trough blood level 3 to 10 ng/mL	
ANTIMETABOLITES			
Azathioprine	50-200 mg daily	CBC with platelets Chemistry panel including liver enzymes	Neutropenia Thrombocytopenia Anemia Hepatotoxicity, pancreatitis
Mycophenolate mofetil	500-1000 mg bid	CBC with platelets	Neutropenia GI disturbance Teratogen
CORTICOSTEROIDS			
Prednisone	5-20 mg daily	Clinical	Hypertension Diabetes/metabolic syndrome Osteoporosis Impaired healing

bid = twice daily; CBC = complete blood count; GI = gastrointestinal; mTOR = mammalian target of rapamycin.

IgG positive and the recipient is anti-cytomegalovirus IgG negative; in this situation, antiviral prophylaxis with valganciclovir (900 mg per day) is recommended. Beyond 6 months, patients remain at-risk for community-acquired bacterial and viral infections. When patients with hepatitis B infection undergo liver transplantation, post-transplantation oral nucleoside analogues (such as entecavir or tenofovir, see Chapter 135) are required to suppress viral replication along with hepatitis B immunoglobulins in selected individuals based on their virological profile at the time of transplantation. Recipients with detectable hepatitis C RNA can usually be cleared of infection with a 12-week course of pangenotypic, combination oral direct-acting antiviral agents (see Table 135-5).

Immunosuppression and Rejection

Immunosuppressive medications and associated prophylactic agents are generally managed by the patient's liver transplant team, but all clinicians should be familiar with the general approach and common toxicities (Table 140-2).[26] The initial immunosuppression for adult liver transplant recipients typically consists of high-dose intraoperative corticosteroids followed by tacrolimus, mycophenolate mofetil, and a steroid taper over 3 to 6 months. As early as 6 to 12 months after liver transplantation, healthy and uncomplicated liver transplant recipients may be tapered to a single calcineurin inhibitor (e.g., cyclosporine or tacrolimus).[A3] Some patients are also treated with mammalian target of rapamycin (mTOR) inhibitors (sirolimus or everolimus) combined with a low-dose calcineurin inhibitor in an effort to minimize nephrotoxicity. The target trough level of the calcineurin inhibitors and mTORs can generally be reduced over time if the patient has stable allograft function and evidence of immunologic tolerance.

Because calcineurin inhibitors and mTOR inhibitors are metabolized by cytochrome P-450 3A4/5, commonly used antifungal agents (e.g., azoles, caspofungin), some antibiotics (e.g., macrolides), non-dihydropyridine

calcium-channel blockers, amiodarone, and other agents that are also metabolized by CYP3A4 must be carefully dosed and monitored to be sure that their blood levels do not increase or result in dangerous levels of immunosuppressants. Conversely, St. John's wort, rifampin, and some anticonvulsants (e.g., carbamazepine, phenytoin) can induce P-450 levels and reduce blood levels of immunosuppressive agents.

Acute T-cell–mediated rejection of the liver is most common during the first 10 days, and over 50% of cases of acute rejection occur in the first 90 days. Acute rejection should be suspected whenever the patient has unexplained allograft dysfunction or elevations in liver biochemistries.[27,28] The gold standard for the diagnosis is liver biopsy, which demonstrates variable degrees of portal inflammation, bile duct injury, and vascular endothelial inflammation (E-Fig. 140-1). The majority of patients with acute rejection will respond to a short course of intravenous corticosteroids and an increased dose of their maintenance immunosuppression under expert care. Repeated episodes of acute rejection can also lead to chronic ductopenic rejection, which is associated with obliteration of the bile ducts. Affected patients are slower to improve and may merit consideration for re-transplantation.

Antibody-mediated rejection may arise in a small proportion of recipients due to the development of donor-specific antibodies. In such cases, an increase in immunosuppression and/or plasmapheresis or IV immunoglobulin may be required under expert care.

Post-transplant lymphoproliferative disorders typically present in the first 12 to 18 months, but they can develop in up to 5% of recipients over their lifetimes. Post-transplant lymphoproliferative disorders usually occur when a patient has uncontrolled replication of Epstein-Barr virus (Chapter 348) because they are overly immunosuppressed. The diagnosis is confirmed by biopsy of a suspicious lymph node, solid organ, or bone marrow. About 50% of patients respond to a 25 to 50% reduction in immunosuppression within 1 month. Second- and third-line treatments include antiviral agents, rituximab, and chemoradiation therapy (see Chapter 348).

Long-Term Management

Beyond the first year, recipients of liver transplants are at increased risk for accelerated atherosclerosis, obesity, chronic kidney disease, and malignancy compared with age and gender-matched controls. Cardiovascular disease risk factors (e.g., hypertension [Chapter 64], hyperlipidemia [Chapter 190], diabetes [Chapter 210], obesity [Chapter 201]) should be aggressively managed with medications and diet. Patients who are on long-term immunosuppression should undergo screening and surveillance for cancer, including annual skin examinations by a dermatologist due to the high incidence of squamous cell and basal cell carcinomas (Chapter 188). Metabolic bone disease and vitamin D deficiency are frequent, so patients should receive oral calcium, vitamin D, and bisphosphonates (Chapter 225) to reduce the risk of bone fractures. Recurrent liver disease includes primary sclerosing cholangitis (Chapter 141), primary biliary cholangitis (Chapter 141), fatty liver disease (Chapter 138), and autoimmune hepatitis (Chapter 135).

Vaccination against herpes zoster reactivation, influenzae, pneumococcus, and COVID-19 are recommended in all recipients of liver transplants (Chapter 15). However, live virus vaccines should be avoided.

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141 DISEASES OF THE GALLBLADDER AND BILE DUCTS

EVAN L. FOGEL AND STUART SHERMAN

GALLBLADDER

Gallstones

EPIDEMIOLOGY

Gallstone disease is one of the most common and costly digestive diseases, with an estimated annual direct cost of $15 billion in the United States. Newly diagnosed gallstone disease occurs in more than 1 million people annually in the United States, and more than 750,000 cholecystectomies are now performed annually. The prevalence of gallstones is about 10 to 15% in American and European adults, with women affected about twice as often as men. Cholesterol gallstones are uncommon in individuals younger than 20 years, but a sharp increase is noted with each decade up to approximately the age of 70 years, particularly in women. About 20% of women and 10% of men have gallstones by 60 years of age. Together, approximately 12% of Americans, or 36 million men and women, harbor gallstones.

In the United States, the prevalence of stones is highest in Mexican American women (26%), followed by White women (17%) and African American women (14%). The prevalence of gallstones is extremely high in Native Americans, especially in women. In Chileans and Bolivians of Indian ancestry, gallstones are also common, and gallstone-associated cancer is the most common gastrointestinal cancer in these countries.

Environmental factors and genetic predisposition are likely to play an interactive role in gallstone formation. Pregnancy may contribute to the predominance of cholesterol stones in younger women because it is associated with progesterone-induced impaired gallbladder emptying and estrogen-mediated increased cholesterol saturation of bile. The prevalence of gallbladder stones in nulliparous women is approximately one tenth of that noted in multiparous women (1.3 vs. 13%). Exogenous estrogen administration in the form of hormone replacement therapy and oral contraceptives is also associated with stone formation. Other medications, including somatostatin analogues, ceftriaxone, and clofibrate, have been associated also with an increased incidence of gallbladder stones.

Obesity is a major risk factor for the development of cholesterol stones. Obese individuals have an increase in biliary cholesterol secretion relative to bile acid and lecithin secretion, thereby resulting in bile supersaturation. However, rapid weight loss is also associated with an increased risk for gallstones. Diminished ileal absorption of bile acids, due to surgical resection or bypass or to active inflammation (e.g., Crohn disease), may also lead to an increased likelihood of gallstones. Adherence to a modified Mediterranean diet (Fig. 13-1) or Dietary Approaches to Stop Hypertension (DASH) diet (Table 13-4) is associated with lower risk of symptomatic gallstone disease.[1]

PATHOBIOLOGY

Gallstone Formation

Gallstones represent a failure to maintain certain biliary solutes, primarily cholesterol and calcium salts, in a solubilized state. Gallstones are classified by their cholesterol content as either cholesterol or pigment stones. Pigment stones are further classified as either black or brown. Most cholesterol stones contain calcium salts in their core, and pure cholesterol gallstones are uncommon (10%). In most American populations, 70 to 80% of gallstones are cholesterol,[2] and black pigment stones account for most of the remaining 20 to 30%. Potential genetic susceptibility loci for gallstone disease include a common variant (p.D19H) of the hepatic and intestinal cholesterol transporter ABCG5/G8 and loss-of-function mutations in the ABCB4 transporter.[3]

In normal bile, cholesterol is soluble in the form of mixed micelles with optimal concentration of bile salts and phospholipids. With disproportionate

Acute Allograft Rejection

Bile Duct Injury

Endothelialitis

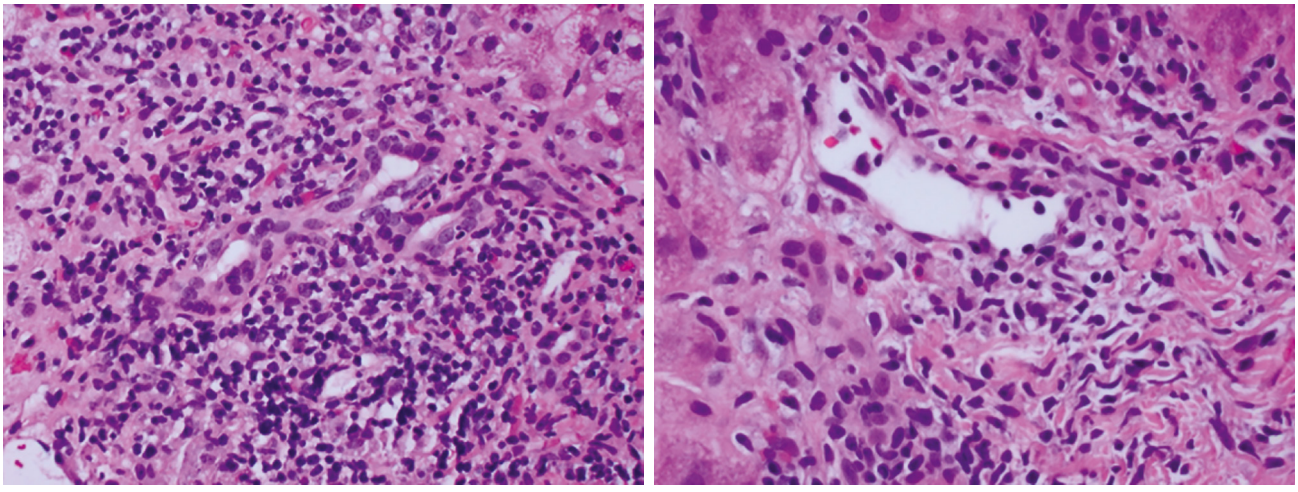

E-FIGURE 140-1. Acute allograft rejection. The immune inflammatory response is centered around the portal triad, and the typical features include a mixed cellular infiltrate (eosinophils, neutrophils, plasma cells, lymphocytes), lymphocytic cholangitis, and endothelialitis. (From Everson GT. Hepatic failure and liver transplantation. In: Goldman L, Schafer AI, eds. *Goldman-Cecil Medicine,* 26th ed. Philadelphia: Elsevier; 2020:998-1004.)

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141 DISEASES OF THE GALLBLADDER AND BILE DUCTS

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GALLBLADDER

Gallstones

EPIDEMIOLOGY

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In the United States, the prevalence of stones is highest in Mexican American women (26%), followed by White women (17%) and African American women (14%). The prevalence of gallstones is extremely high in Native Americans, especially in women. In Chileans and Bolivians of Indian ancestry, gallstones are also common, and gallstone-associated cancer is the most common gastrointestinal cancer in these countries.

Environmental factors and genetic predisposition are likely to play an interactive role in gallstone formation. Pregnancy may contribute to the predominance of cholesterol stones in younger women because it is associated with progesterone-induced impaired gallbladder emptying and estrogen-mediated increased cholesterol saturation of bile. The prevalence of gallbladder stones in nulliparous women is approximately one tenth of that noted in multiparous women (1.3 vs. 13%). Exogenous estrogen administration in the form of hormone replacement therapy and oral contraceptives is also associated with stone formation. Other medications, including somatostatin analogues, ceftriaxone, and clofibrate, have been associated also with an increased incidence of gallbladder stones.

Obesity is a major risk factor for the development of cholesterol stones. Obese individuals have an increase in biliary cholesterol secretion relative to bile acid and lecithin secretion, thereby resulting in bile supersaturation. However, rapid weight loss is also associated with an increased risk for gallstones. Diminished ileal absorption of bile acids, due to surgical resection or bypass or to active inflammation (e.g., Crohn disease), may also lead to an increased likelihood of gallstones. Adherence to a modified Mediterranean diet (Fig. 13-1) or Dietary Approaches to Stop Hypertension (DASH) diet (Table 13-4) is associated with lower risk of symptomatic gallstone disease.[1]

PATHOBIOLOGY

Gallstone Formation

Gallstones represent a failure to maintain certain biliary solutes, primarily cholesterol and calcium salts, in a solubilized state. Gallstones are classified by their cholesterol content as either cholesterol or pigment stones. Pigment stones are further classified as either black or brown. Most cholesterol stones contain calcium salts in their core, and pure cholesterol gallstones are uncommon (10%). In most American populations, 70 to 80% of gallstones are cholesterol,[2] and black pigment stones account for most of the remaining 20 to 30%. Potential genetic susceptibility loci for gallstone disease include a common variant (p.D19H) of the hepatic and intestinal cholesterol transporter ABCG5/G8 and loss-of-function mutations in the ABCB4 transporter.[3]

In normal bile, cholesterol is soluble in the form of mixed micelles with optimal concentration of bile salts and phospholipids. With disproportionate

concentrations, bile becomes supersaturated, and the excess cholesterol precipitates as monohydrate crystals. These crystals become embedded in gallbladder mucin gel with bilirubinate to form biliary sludge, which may eventually aggregate into a gallbladder stone.

Black pigment stones make up a small proportion of gallstones. These stones consist of polymerized calcium bilirubinate, precipitated as a result of exceeding the solubility of calcium and unconjugated bilirubin. In addition to increasing age, the formation of black pigment stones is more common in individuals who have conditions that create an excessive amount of unconjugated bilirubin (e.g., chronic hemolysis in hemoglobinopathies, cirrhosis, ineffective erythropoiesis), who are being fed by total parenteral nutrition (Chapter 198), or who have ileal diseases. Black pigment stones are typically tarry, are usually not associated with infected bile, and are located almost exclusively in the gallbladder.

By contrast, brown pigment stones are coarse in texture and are primarily formed in the bile duct as a result of bacterial infection that releases β-glucuronidase to hydrolyze glucuronic acid from bilirubin. Phospholipid hydrolysis also increases, thereby leading to precipitation of calcium, bilirubin, and free fatty acids and also resulting in the formation of brown pigment stones. Brown pigment stones account for 30 to 90% of gallstones in Asian populations, may also occur throughout the entire biliary tree, and are frequently associated with pyogenic cholangiohepatitis.

Gallbladder contractility is impaired in some patients with gallstones. Although gallbladder dysfunction can be the consequence of gallstone disease or of excessive cholesterol infiltration into the gallbladder's smooth muscle, evidence suggests that gallbladder stasis itself can lead to gallbladder stone formation. A normal gallbladder ejects 10 to 20% of its contents into the duodenum in response to enteric nervous stimulation. The presence of postprandial intestinal fat further increases gallbladder contractility, which is mediated by the enteric nervous system and cholecystokinin. Gallbladder stasis is frequently evident in patients with risk factors for forming gallstones, including obesity, pregnancy, rapid weight loss, and prolonged fasting (Table 141-1). Somatostatin analogues may predispose to gallstone formation by decreasing gallbladder emptying. Furthermore, gallbladder dysmotility is an independent risk factor for recurrent gallstones in patients who have been treated with extracorporeal shock wave lithotripsy.

Acute Calculous Cholecystitis

The most common complication of gallstone disease is acute cholecystitis, which occurs in 15 to 20% of symptomatic patients. Acute cholecystitis results when a stone becomes lodged at the gallbladder–cystic duct junction, where it impairs gallbladder outflow and drainage. The extent of inflammation and the progression of acute cholecystitis are related to the duration and degree of obstruction. In the most severe cases, this process can lead to ischemia and necrosis of the gallbladder wall. More often, the stone spontaneously dislodges, and the inflammation gradually resolves. Acute cholecystitis is primarily an inflammatory rather than an infectious process, but about 50% of patients with acute cholecystitis have secondary bacteriobilia, most commonly with *Escherichia coli*.

CLINICAL MANIFESTATIONS

The clinical spectrum of cholelithiasis ranges from the asymptomatic state to fatal complications. Among patients with asymptomatic gallstones, approximate annual risks are 1% for biliary pain, 0.3% for acute cholecystitis, 0.2% for symptomatic choledocholithiasis, and 0.04 to 1.5% for gallstone pancreatitis. However, these low individual percentages represent a huge population-wide number of symptomatic patients, given the frequency of gallstones. Overall, about 1 to 2% of asymptomatic individuals with gallstones develop serious symptoms or complications each year related to their gallstones.

The majority of gallstones are asymptomatic and are discovered on imaging studies performed for other indications. In such individuals, the gallbladder fills and empties normally, and the gallstones remain in the gallbladder and do not obstruct the cystic duct. Over time, however, asymptomatic gallstones can become symptomatic and be manifested as biliary colic due to impaction of a gallstone at the neck of the gallbladder or cystic duct. Although the pain is commonly termed biliary colic, the majority of patients actually note constant pain due to obstruction of the cystic duct and a progressive increase in gallbladder wall tension, rather than the paroxysmal pain of typical colic. The pain usually is located in the right upper quadrant or epigastrium and frequently radiates to the back and right scapula. Although biliary colic classically occurs after fatty meals, an association with meals is present in only 50% of patients, and the pain often develops more than 1 hour after eating. The duration of pain is typically 1 to 5 hours, but it may persist up to 24 hours. Pain persisting beyond 24 hours suggests that acute inflammation or cholecystitis is present. Episodes of biliary colic are usually less frequent than one episode per week. Other symptoms, such as nausea and vomiting, accompany each episode in 60 to 70% of cases. Bloating and belching are also present in 50% of patients. Fever and jaundice occur much less frequently with simple biliary colic. Although some patients with gallstones have continuous pain, predominantly in the back or the left upper quadrant, rather than episodic pain, alternative causes should be considered in such patients.

Acute Calculous Cholecystitis

Patients with acute cholecystitis typically present with right upper quadrant pain similar to biliary colic.[3] In acute cholecystitis, however, the pain is usually unremitting, may last several days, and is often associated with nausea, emesis, anorexia, and fever. On physical examination, patients usually have a low-grade fever, with localized right upper quadrant tenderness and guarding. The presence of a Murphy sign, an inspiratory arrest during deep palpation of the right upper quadrant, is the classic physical finding of acute cholecystitis. A palpable right upper quadrant mass is appreciated in one third of patients and usually represents omentum that has migrated to the area around the gallbladder in response to the inflammation. Mild jaundice (bilirubin level <6 mg/dL) may be present. Significant jaundice is rare with acute cholecystitis but when present suggests the presence of common bile duct stones, cholangitis, or obstruction of the common hepatic duct by severe pericholecystic inflammation because of the impaction of a large stone in the Hartmann pouch, which mechanically obstructs the bile duct (i.e., Mirizzi syndrome; Fig. 141-1). Mirizzi syndrome, which occurs in about 0.1% of patients with gallstones and 0.7 to 4% of patients after cholecystectomy, may lead to chronic inflammation, compression of the bile duct associated with clinical jaundice (Mirizzi type A), necrosis, and fibrosis. Ultimately, a cholecystocholedochal fistula may occur (Mirizzi type B). High fever suggests ascending cholangitis, often with bacterial infection (Fig. 141-2). Acute cholecystitis may coexist with choledocholithiasis or its complications of acute cholangitis and gallstone pancreatitis.

TABLE 141-1 RISK FACTORS ASSOCIATED WITH GALLSTONE FORMATION

NONMODIFIABLE FACTORS	MODIFIABLE FACTORS
Increasing age	Pregnancy and parity
Female gender	Obesity
Ethnicity	Low-fiber, high-calorie diet
Genetics, family history	Prolonged fasting
	Medications: clofibrate, estrogens, octreotide
	Low-level physical activity
	Rapid weight loss
	Hypertriglyceridemia, low high-density lipoprotein
	Metabolic syndrome
	Gallbladder stasis
	Terminal ileal disease or resection
	Total parenteral nutrition, fasting state

DIAGNOSIS

Transabdominal ultrasound is the radiologic procedure of choice to identify gallstones (Fig. 141-3). Because the ultrasound waves cannot penetrate the stones, acoustic shadowing is seen posterior to the stones, thereby facilitating diagnosis. Free-floating gallbladder stones will also move to a dependent position when the patient is repositioned during scanning. If both of these features are present, the positive predictive value of ultrasound approaches 100%. Nonshadowing echoes alone, however, may be caused by gallbladder polyps. Gallstones may be missed because of a lack of contrasting bile around the stones, as may occur with an impacted cystic duct stone or when the gallbladder is filled with stones. Small gallstones may not cast an acoustic shadow. An ileus with increased abdominal gas, as can occur with acute cholecystitis or pancreatitis (Chapter 130), may limit visualization of the gallbladder. Overall, the false-negative rate of ultrasound for detection of gallstones is less than 5% but may increase to 15% with acute cholecystitis. Ultrasound may also demonstrate dilation of the intrahepatic and extrahepatic bile ducts. Dilated ducts may signify obstruction due to stones in the common bile duct, distal strictures, or malignant obstruction (Chapters 180 and 181).

ABSTRACT

Gallstone disease is one of the most common and costly digestive diseases, with an estimated annual direct cost of $15 billion in the United States. The prevalence is about 10 to 15% of American and European adults, but age, gender, nationality, environmental, genetic, and other demographic features alter this prevalence. Gallstones can be diagnosed by a variety of abdominal imaging tests, but transabdominal ultrasound remains a highly sensitive, specific, simple, low-cost technology for the diagnosis. Cholecystectomy is the most frequently performed operation in the United States. Although gallstones may remain silent for years and often are found incidentally, nearly 750,000 people in the United States undergo gallbladder surgery on an annual basis for symptomatic gallstone disease, complications thereof, acute acalculous cholecystitis, or a functional gallbladder disorder. Patients whose gallstones do not cause symptoms rarely require cholecystectomy. However, patients with or without symptomatic gallstones should undergo cholecystectomy if they are found to have a porcelain gallbladder or anomalous pancreaticobiliary union. Cholecystectomy should be considered for patients who are undergoing liver transplantation or bariatric surgery, have sickle cell disease, or have gallstones larger than 3 cm in diameter. Disorders of the bile ducts may lead to chronic cholestasis, liver damage, or acute and potentially life-threatening consequences. In this chapter, we discuss benign and malignant diseases of the gallbladder and bile ducts, with an emphasis on epidemiology, pathobiology, clinical manifestations, diagnosis, and treatment of these disorders.

KEYWORDS

gallstones
cholecystitis
gallbladder cancer
choledocholithiasis
cholangitis
biliary strictures
ampullary tumors

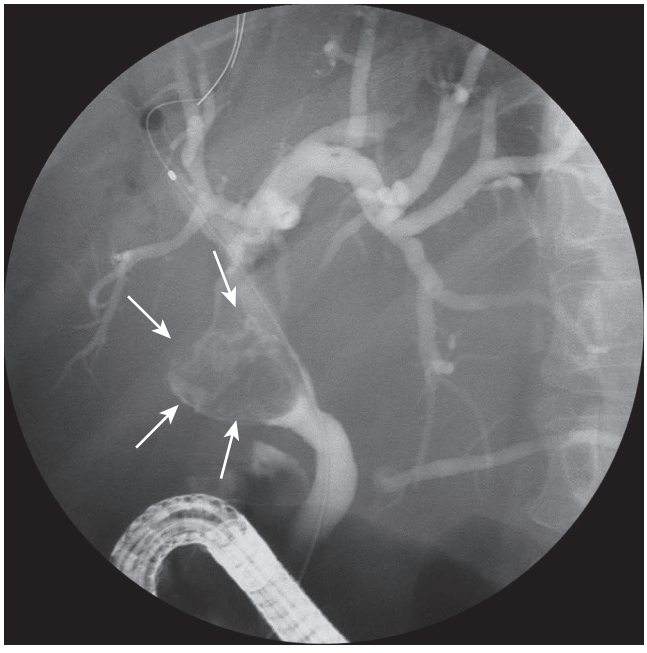

FIGURE 141-1. **A bile duct stricture is seen at endoscopic retrograde cholangiopancreatography, representing Mirizzi syndrome (type A), with a large stone (*arrows*) in the proximal cystic duct, causing extrinsic compression of the bile duct.**

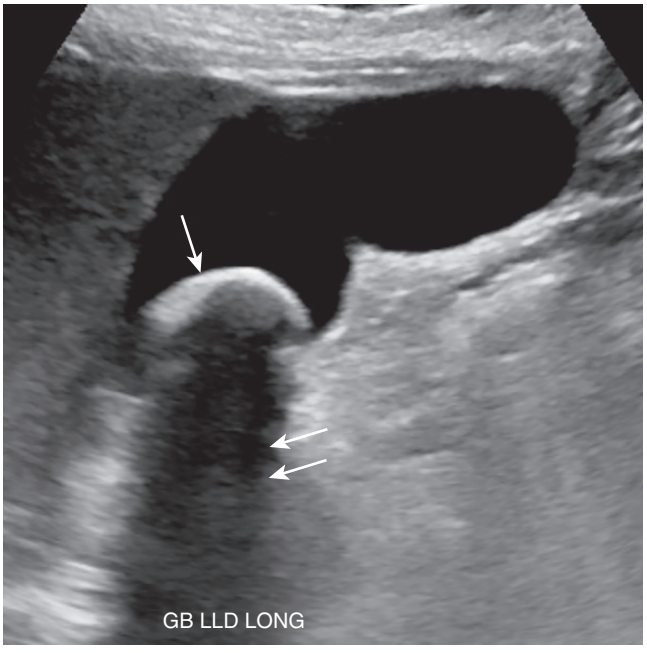

FIGURE 141-3. **Ultrasound image of the long axis of the gallbladder.** The image shows a dependent gallstone *(single arrow)* and acoustic shadow *(double arrows).*

FIGURE 141-2. **Endoscopic image of pus exiting the biliary orifice in this patient who presented with ascending cholangitis secondary to choledocholithiasis (note several small stones in duodenum).**

Ultrasound has a sensitivity and specificity of 85% and 95%, respectively, for the diagnosis of acute cholecystitis. In addition to the presence of gallstones, findings suggestive of acute cholecystitis include thickening of the gallbladder wall (>4 mm) and the presence of pericholecystic fluid. Focal tenderness directly over the gallbladder (sonographic Murphy sign) also is suggestive of acute cholecystitis.

Cholescintigraphy provides a noninvasive, anatomic, and functional evaluation of the liver, gallbladder, bile duct, and duodenum, although it has generally been superseded by ultrasound for this purpose, except in certain situations, such as identification of a suspected occult bile leak after cholecystectomy or a functional gallbladder disorder (see later). In this procedure, technetium 99 m (^{99m}Tc)–labelled iminodiacetic acid derivatives are injected intravenously, taken up by the liver, and excreted into the bile. These hepatobiliary iminodiacetic acid (HIDA) scans provide functional information about the liver's ability to excrete radiolabelled substances into a nonobstructed biliary tree. The tracer should be taken up by the liver, gallbladder, common bile duct, and duodenum within 1 hour. Nonvisualization of the gallbladder 1 hour after the injection of the radioisotope with filling of the bile duct and duodenum indicates an obstructed cystic duct and in the acute clinical setting is highly sensitive (95%) and specific (95%) for acute cholecystitis, although false-positive results are often seen in the setting of gallbladder stasis (e.g., critically ill patients, total parenteral nutrition). Slow uptake of the tracer by the liver suggests hepatic parenchymal disease. Filling of the gallbladder and bile duct with delayed or absent filling of the intestine may suggest an obstruction at the level of the major papilla.

Abdominal computed tomography (CT) is less sensitive than ultrasound for the diagnosis of gallstones and is primarily indicated for the diagnosis of complications of gallstone disease, such as acute cholecystitis, choledocholithiasis, pancreatitis, and gallbladder cancer. By comparison, *plain abdominal radiographs* are of little value in the evaluation of gallbladder disease because only 15% of gallstones contain sufficient calcium to appear radiopaque. Plain films can be useful, however, for the diagnosis of other causes of acute abdominal pain (e.g., perforated viscus, bowel obstruction). Rarely, abdominal films may show a calcified gallbladder wall (Fig. 141-4) in chronic cholecystitis or findings such as pneumobilia or gallstone-associated ileus in acute cholecystitis.

A CT scan also is frequently performed to evaluate an acutely ill patient with abdominal pain. The CT scan can detect gallstones, gallbladder wall thickening, pericholecystic fluid and edema, and air in the gallbladder or gallbladder wall (emphysematous cholecystitis), but it is generally much less sensitive than ultrasonography for finding these conditions.

Magnetic resonance imaging is highly sensitive for the diagnosis of both gallstones and common duct stones, but stones smaller than 3 mm may be missed. Endoscopic ultrasound provides excellent imaging of the gallbladder and biliary tree but is rarely the primary imaging modality for detection of a gallbladder stone. Endoscopic collection of bile for crystal analysis may serve as a surrogate for microlithiasis not seen on transabdominal ultrasound.

With cholecystitis, laboratory evaluation can show a mild leukocytosis, with a white blood cell count of 12,000 to 15,000 cells/μL. However, many patients have a normal white blood cell count. Leukocytosis greater than 20,000 cells/μL should suggest further complications of cholecystitis, such as gangrene, perforation, or cholangitis. Mild elevations in serum bilirubin, alkaline phosphatase, aminotransferase, and amylase levels may also be seen with acute cholecystitis.

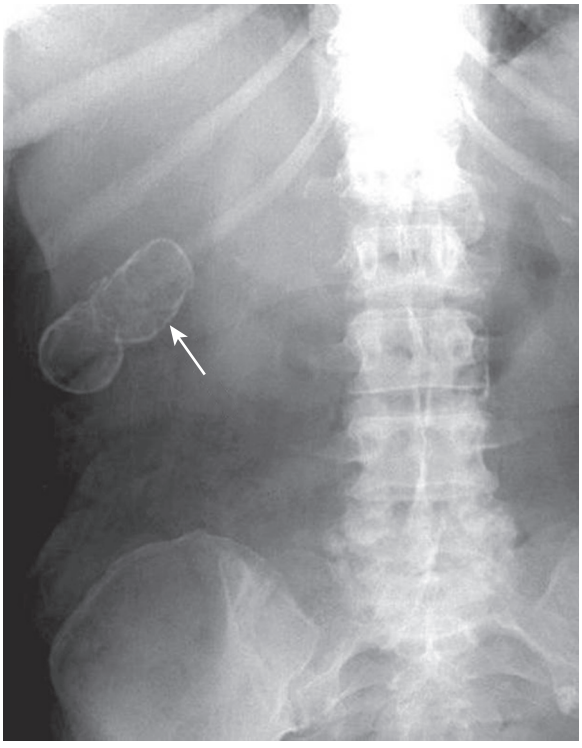

FIGURE 141-4. Plain abdominal radiograph illustrating a porcelain gallbladder. Note the calcified gallbladder wall.

TREATMENT

The treatment approach to gallstones depends on symptoms, complications, and whether there are stones in the common bile duct (Fig. 141-5).

Silent Gallstones

The longer that stones remain silent, the less likely they are to cause symptoms. In one large series, 20% of patients with initially silent gallstones developed events (8% uncomplicated, 12% complicated) at a median of 17 years. Risks were higher in women and in patients with multiple stones or a stone larger than 10 mm. Almost all patients will develop symptomatic disease before developing one of the serious complications of gallstones. Therefore, prophylactic cholecystectomy is not generally indicated in patients with asymptomatic gallstones.

In select groups of patients, however, prophylactic cholecystectomy should be considered, even when gallbladder stones are absent. A porcelain gallbladder with a calcified gallbladder wall is associated with a 5% or higher risk for malignant transformation, high enough to justify cholecystectomy. Patients with a long common channel between the bile and pancreatic ducts (i.e., anomalous pancreaticobiliary duct junction; see later) also are at significant risk for gallbladder cancer and should undergo prophylactic cholecystectomy. Acute cholecystitis is a potentially life-threatening condition in immunosuppressed patients, so prophylactic cholecystectomy is generally recommended before or at the time of major organ transplantation. Data also support cholecystectomy in patients undergoing bariatric weight loss surgery even in the absence of gallstones because of their nearly 30% risk for developing gallstones and requiring cholecystectomy during rapid weight loss in the first year after surgery. Prophylactic cholecystectomy adds minimal morbidity and mortality risks to most bariatric operations[4] and is clearly indicated in patients with gallstones. Some patients with silent gallbladder stones may also benefit from prophylactic cholecystectomy. In patients with sickle cell disease (Chapter 149), for example, cholecystitis can precipitate a crisis with substantial operative risks. Large gallstones (>3 cm) are more frequently associated with acute cholecystitis and gallbladder carcinoma. Because gallbladders containing stones that are larger than 3 cm in diameter have a 10-fold greater risk for developing malignancy than do those containing stones that are smaller than 1 cm, prophylactic cholecystectomy may also be indicated in these patients.

Symptomatic Gallstones in Outpatients

Although initial conservative management followed by elective surgery is reasonable in patients with mild symptoms,[A1] early surgery within 24 hours is generally preferred for patients with uncomplicated biliary colic. If patients do not have severe pain that lasts for >15 minutes, is located in the epigastrium or right upper quadrant, radiates to the back, and responds to simple analgesics, a conservative strategy of delaying surgery may be a reasonable alternative.[A2]

Day surgery is as safe and effective as an overnight stay.[A3] More than 95% of cholecystectomies are performed laparoscopically, with about 3% of elective procedures converted to an open procedure in the operating room. Contraindications to laparoscopic surgery include significant bleeding and Child class C cirrhosis (Chapter 139). Some patients with severe chronic obstructive pulmonary disease or heart failure may not tolerate the pneumoperitoneum required for laparoscopic surgery, and the prior upper abdominal surgery may increase the difficulty of or preclude laparoscopic cholecystectomy. Serious complications of laparoscopic cholecystectomy are rare, with a reported incidence of 0.6 to 1.5% for any bile duct leaks and 0.3 to 0.6% for a major bile duct injury. Although these risks are higher than for open surgery, the overall mortality rate (<0.3%) is lower for laparoscopic surgery, and the postoperative recovery is much easier. Outcomes for laparoscopic cholecystectomy are comparable among low- and high-volume centers. Robotic-assisted cholecystectomy appears to be as effective as laparoscopic cholecystectomy but is associated with a significant increase in complications and costs.[5]

Inpatient Acute Calculous Cholecystitis

In patients with an acute attack of cholecystitis warranting hospital admission, medical stabilization with intravenous fluids as needed, broad-spectrum antibiotics (e.g., piperacillin-tazobactam 3.375 g every 6 hours; or ceftriaxone 1 to 2 g once daily, plus metronidazole 500 mg every 6 hours; or levofloxacin, 500 mg once daily, plus metronidazole) and parenteral analgesics are indicated (see Table 26-4 in Chapter 26). The duration of antibiotic therapy is tailored to clinical improvement.

Early laparoscopic cholecystectomy within 2 days of the onset of symptoms is the treatment of choice for acute cholecystitis unless there are contraindications.[A4] Such surgery significantly reduces morbidity,[6] length of hospital stay,[A5] and time to return to work compared with open surgery. However, the conversion rate to an open procedure is about 25% compared with a rate of about 3% for elective laparoscopic surgery. If the bilirubin level is less than 4 mg/dL with no signs of cholangitis (i.e., intermediate risk for the presence of a bile duct stone), initial cholecystectomy with intraoperative cholangiography results in a shorter length of stay and fewer bile duct investigations compared with sequential common duct endoscopic assessment followed by subsequent surgery, without increasing morbidity. Laparoscopic fenestrating or reconstituting subtotal cholecystectomy is a safe "bailout" procedure in difficult operative situations.[7] Reconstituting subtotal cholecystectomy, which retains a small remnant gallbladder, may have better outcomes, but these techniques depend on intraoperative findings and surgical expertise.[A6]

In high-risk patients whose medical conditions preclude cholecystectomy, endoscopic gallbladder drainage is preferred over percutaneous cholecystostomy so as to allow prompt gallbladder drainage.[A7,A8] In expert hands, endoscopic retrograde cholangiopancreatography (ERCP)–guided stent drainage may be possible if contrast and a subsequent guidewire can be passed through the cystic duct, thereby allowing access to the gallbladder via the major papilla. Placement of a metal stent between the gallbladder and alimentary tract using endoscopic ultrasound is an alternative that does not depend on a patent cystic duct. Both techniques have success rates higher than 90%, with improved pain scores and lower reintervention rates than percutaneous drainage.[8]

If such drainage and appropriate antibiotics do not lead to clear improvement within 24 hours, however, laparotomy is indicated because failure to improve after percutaneous drainage is usually caused by gangrene of the gallbladder or perforation. If cholecystostomy is successful and the acute episode resolves, the patient can electively undergo either cholecystectomy or percutaneous stone extraction and removal of the cholecystostomy tube. Ideal timing of cholecystectomy after cholecystostomy is uncertain,[9,10] and nearly two thirds of patients may not proceed to cholecystectomy within the same calendar year.

Nonsurgical options for the treatment of gallstone disease are rarely used today because of their limited efficacy and the widespread application of laparoscopic cholecystectomy. Oral dissolution therapy (e.g., ursodeoxycholic acid, 15 mg/kg/day) may be considered in patients who have cholesterol gallstones, but it completely dissolves stones in only 40% of patients, and stones recur in up to 50% of patients within 5 years after therapy is stopped. Lifelong therapy, therefore, may be necessary. The direct infusion of organic solvents (methyl *tert*-butyl ether) into the gallbladder also is efficacious only for cholesterol gallstones, and the recurrence rate is similar to that of oral dissolution therapy. Extracorporeal shock wave lithotripsy can be considered for a single radiopaque stone that is 0.5 to 2 cm in diameter, regardless of its type, but only a small percentage of symptomatic patients fit these criteria. As a result, this therapy is limited to an extremely select group of patients.

PREVENTION

Moderate physical activity and dietary management (high fiber intake, avoidance of saturated fatty acids) may lower the risk for gallstone disease. Daily administration of cholecystokinin (3.5 μg) in patients receiving prolonged total parenteral nutrition may prevent formation of gallbladder sludge. Oral ursodeoxycholic acid (15 mg/kg/day) is beneficial to prevent gallstone disease during rapid weight loss and in patients who need long-term somatostatin

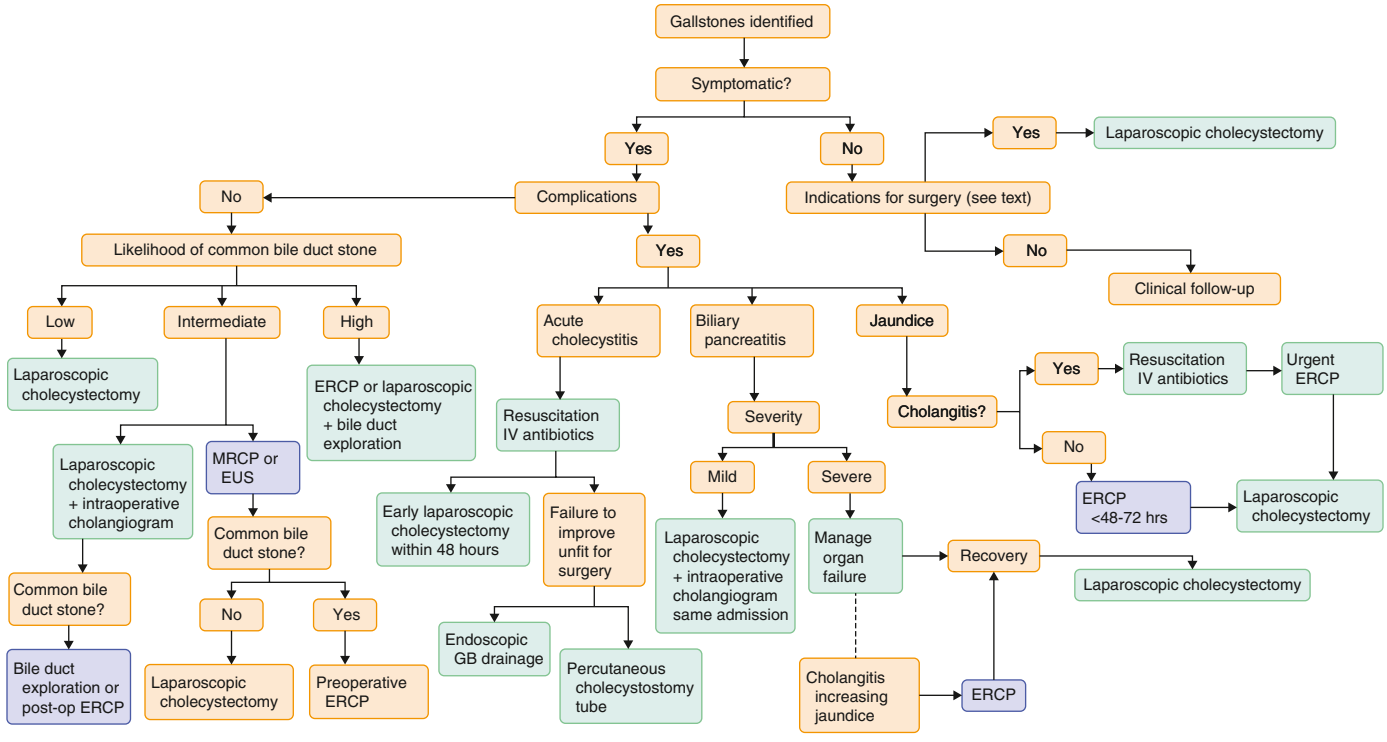

FIGURE 141-5. Algorithm for the treatment of gallstones. ERCP = endoscopic retrograde cholangiopancreatography; EUS = endoscopic ultrasound; GB = gallbladder; IV = intravenous; MRCP = magnetic resonance cholangiopancreatography.

therapy. For secondary prevention (i.e., in patients with gallstones already present), there are insufficient data to support the use of any medical therapy.

Complications of Acute Calculous Cholecystitis

Several complications of acute cholecystitis include empyema of the gallbladder, emphysematous cholecystitis, and gangrene leading to gallbladder perforation. Each of these complications can be associated with significant morbidity and mortality and therefore requires prompt surgical intervention. In 1 to 2% of patients with acute cholecystitis, the gallbladder will perforate into an adjacent hollow viscus, thereby creating a cholecystenteric fistula; the duodenum (79%) and the hepatic flexure of the colon (17%) are the most common sites. The episode of acute cholecystitis generally resolves as the gallbladder spontaneously decompresses after the fistula forms. If a large gallstone passes from the gallbladder into the small intestine, a mechanical bowel obstruction, termed gallstone ileus, may result. Gallstone ileus occurs in 10 to 15% of patients with a cholecystenteric fistula. Patients with gallstone ileus present with signs and symptoms of intestinal obstruction—nausea, vomiting, and abdominal pain. Abdominal films will demonstrate small bowel distention and air-fluid levels and may give additional clues to the source of the obstruction (pneumobilia or a calcified gallstone distant from the gallbladder). The initial management of gallstone ileus includes relieving the obstruction. Most frequently, this goal can be achieved by removing the gallstone through an enterotomy, although endoscopic retrieval of the offending stone can be done, depending on where the stone is located.

Acute Acalculous Cholecystitis

Acute acalculous cholecystitis, which accounts for 5 to 10% of all cases of acute cholecystitis, usually occurs in critically ill patients after trauma, burns, long-term parenteral nutrition, and major nonbiliary operations (e.g., abdominal aneurysm repair, cardiopulmonary bypass). The cause of acute acalculous cholecystitis remains unclear, although gallbladder stasis with increased bacterial colonization and ischemia have been implicated.

The symptoms and signs of acute acalculous cholecystitis are similar to those of acute calculous cholecystitis, with right upper quadrant pain and tenderness, fever, and leukocytosis. The disease often has a more fulminant course than acute calculous cholecystitis and more frequently progresses to gangrene, empyema, or perforation. Except for the absence of gallstones, ultrasound and CT findings are similar to those of calculous cholecystitis, including gallbladder wall thickening and pericholecystic fluid. On cholescintigraphy, the gallbladder does not fill; however, the false-positive rate (absent gallbladder filling without acute acalculous cholecystitis) may be as high as 40%.

Emergency cholecystectomy is recommended if the diagnosis is established or even if clinical suspicion is high because the risk for gangrene, perforation, or empyema exceeds 50%. Cholecystectomy rather than cholecystostomy is usually required, but percutaneous cholecystostomy or endoscopic gallbladder stenting is recommended in patients unable to undergo surgery. The mortality rate for acute acalculous cholecystitis can be as high as 40%, mostly because of the concomitant illnesses in patients who develop this disease.

FUNCTIONAL GALLBLADDER DISORDER

Some patients present with typical symptoms of biliary colic but do not have any evidence of gallstones on ultrasound examination. If further investigations such as liver chemistries, amylase and lipase levels, CT scan, and even upper gastrointestinal endoscopy are unremarkable, the diagnosis of a functional gallbladder disorder should be considered. The pathobiology is poorly understood, but one possibility is that the obesity epidemic has increased the population-wide accumulation of fat in the gallbladder wall—cholecystosteatosis—thereby decreasing the gallbladder's ability to empty. Some patients may have intermittent gallbladder outlet obstruction due to cystic duct spasm, poor coordination between the contraction of the gallbladder and the sphincter of Oddi, or dysmotility of the gallbladder. In a cholecystokinin-stimulated ^{99m}Tc-HIDA scan, cholecystokinin is infused intravenously after the gallbladder has filled with the ^{99m}Tc-labeled radionuclide, and a gallbladder ejection fraction is calculated 20 minutes later. An ejection fraction of less than 35% at 20 minutes is considered abnormal, and most of these patients have histopathologic evidence of chronic cholecystitis, although a low gallbladder ejection fraction is not specific for a functional gallbladder disorder (Table 141-2). The efficacy of laparoscopic cholecystectomy is controversial in this setting, but the Society of American Gastrointestinal and Endoscopic Surgeons recommends it. The percentage of patients undergoing cholecystectomy for functional gallbladder disorder in the United States during the past 15 years has increased from less than 5% to more than 20% of patients having the gallbladder removed. Additionally, patients who have symptoms of typical biliary colic and a markedly high gallbladder ejection fraction (i.e., gallbladder hyperkinesia) may also benefit from cholecystectomy, even though they do not have gallstones.[A9]

TUMORS OF THE GALLBLADDER

Benign

Cholesterol polyps are not true neoplasms but rather are cholesterol-filled projections of gallbladder mucosa that protrude into the lumen. These polyps account for approximately 50% of all polypoid gallbladder lesions, are usually

TABLE 141-2 SETTINGS IN WHICH A LOW GALLBLADDER EJECTION FRACTION MAY BE IDENTIFIED

Functional gallbladder disorder (chronic acalculous cholecystitis)
Cystic duct obstruction
Sphincter of Oddi dysfunction
Asymptomatic, healthy individuals
Diabetes
Pregnancy
Cirrhosis
Obesity
Celiac disease
Medications (narcotic analgesics, calcium-channel antagonists, oral contraceptive agents, benzodiazepines, histamine-2 receptor antagonists)

smaller than 1 cm, are typically found incidentally on imaging studies as nonmobile filling defects, are usually asymptomatic unless associated with gallstones, and do not have malignant potential.

Adenomyosis consists of a hypertrophic gallbladder muscle layer with mucosal diverticula called Rokitansky-Aschoff sinuses. This condition may affect the gallbladder locally, particularly in the fundus, where it appears as a hemispheric lesion with a central dimple; segmentally, as an annular stricture; or diffusely, when it involves the entire gallbladder wall. The cause is not entirely clear but may be secondary to a gallbladder motility disorder. Isolated adenomyosis can cause biliary-type symptoms and can progress to gallbladder cancer, so prophylactic cholecystectomy is recommended.

Gallbladder adenomas are benign epithelial tumors with malignant potential. Adenomas usually are manifested as solitary, nonmobile filling defects on ultrasound. Polyps smaller than 0.5 cm, regardless of total polyp number, can be observed with serial imaging studies, namely ultrasound, every 12 months. Larger polyps, however, may harbor a carcinoma in situ, and cholecystectomy is recommended for polyps larger than 1 cm and for any patients older than 50 years with biliary symptoms.

Malignancy

Gallbladder cancer is the most common biliary tract malignant neoplasm and fifth most common gastrointestinal cancer overall, with approximately 7000 new cases diagnosed annually in the United States (2.5 cases/100,000 population). The usual age at onset is the sixth or seventh decade, with a female-to-male ratio of 3 : 1. Gallbladder cancer is more common in Native Americans, Mexicans, Alaskans, and American Hispanics, as well as in residents of Israel, Chile, and northern Japan.

Perhaps because of chronic inflammation, gallbladder cancer is strongly associated with gallstones, which are identified in more than 90% of patients with gallbladder carcinoma. Conversely, only 1% of patients with gallstones develop gallbladder carcinoma. Choledochal cysts are associated with an increased risk for malignant neoplasms throughout the biliary tree, including the gallbladder, perhaps because of increased stasis, chronic inflammation, and infection. In patients with choledochal cysts, excision of extrahepatic cysts is recommended to avoid biliary tract cancer. By comparison, biliary sphincterotomy alone may be adequate for a type III extrahepatic cyst.

About 90% of gallbladder cancers are adenocarcinomas (90% scirrhous, 5% papillary, 5% colloid). The remaining tumors are anaplastic or squamous cell cancers. Gallbladder cancers spread by local extension and direct invasion of adjacent structures, including the common hepatic duct, liver, duodenum, and colon. Lymphatic drainage is to adjacent lymph nodes, and disseminated disease is to the liver and the peritoneal surface.

Most patients (80%) present with abdominal pain of less than 1 month in duration, which may be difficult to distinguish from symptoms of biliary colic or acute cholecystitis. Nausea and vomiting (50%) and weight loss (40%) are often present, and jaundice (30%) is a poor prognostic sign that typically signifies porta hepatis involvement with tumor. Up to 20% of gallbladder cancers are found at cholecystectomy performed for gallstones, whereas incidental cancers are found at 1% of cholecystectomies.

Diagnosis may be difficult preoperatively because laboratory test results may be normal or nonspecific even when advanced disease is manifested by hypoalbuminemia and anemia. There is no reliable tumor marker. Liver test results are abnormal when the tumor or periportal lymphadenopathy is associated with biliary obstruction. Ultrasonography has a sensitivity of 75 to 80% for detection of gallbladder cancer, with findings ranging from a complex luminal mass to gallbladder wall thickening, polypoid mass, or gallstones. Doppler ultrasound has a sensitivity and specificity of about 80% for the diagnosis of gallbladder cancer. Detection of color flow within a lesion supports the diagnosis, but its absence does not exclude malignancy.[11] CT or magnetic resonance cross-sectional imaging can assess the extent of disease, including regional and distant metastases. Endoscopic ultrasound may aid in determining the extent of local invasion and nodal involvement, but it rarely is necessary in the preoperative evaluation. ERCP is indicated only in patients who have clinical evidence of biliary obstruction and are being considered for stent placement to palliate their jaundice.

PREVENTION AND TREATMENT

Patients with gallstones larger than 3 cm have a 10-fold increased risk for development of gallbladder cancer, so prophylactic cholecystectomy should be considered even in an asymptomatic patient. A porcelain gallbladder, with diffuse calcification of the gallbladder wall, is an indication for cholecystectomy in the asymptomatic patient because of the increased risk for cancer. Cholecystectomy also is indicated for any gallbladder polyp larger than 1 cm, in patients with choledochal cysts other than type III, in anomalous pancreaticobiliary union, and in adenomyosis of the gallbladder.

The resectability rates for gallbladder cancer range from 15 to 30%. When the tumor does not extend beyond the lamina propria layer of the gallbladder wall (T1a), simple cholecystectomy alone may be curative, with a 5-year survival rate approaching 100%.[12] Tumors that involve the muscularis propria (T1b) may gain access to the lymphatic system and be associated with occult metastases. Current recommendations for pT1b cancers involve complete operative staging with laparoscopy, portal lymphadenectomy, cystic duct margin assessment, and partial central liver excision. Tumors that extend through the gallbladder wall (stage II/III) require a more extensive resection (cholecystectomy, partial central hepatectomy, lymph node dissection). Stage II tumors (no invasion beyond the gallbladder serosa) may have up to a 60 to 80% 5-year survival rate, whereas stage III tumors have a 25% 5-year survival rate. Median survival with unresectable (stage IV) disease is typically less than 6 months. Radiation therapy has not been shown to be effective, whereas chemotherapy regimens in unresectable disease (typically similar to regimens for pancreatic cancer [Chapter 180]) are associated with response rates of approximately 20%. Capecitabine (1250 mg/m^2 twice daily on days 1 to 14 of a 21-day cycle, for eight cycles) appears to improve overall survival in patients with resected cancer when used as adjuvant therapy,[A10] while second-line FOLFOX (folinic acid, fluorouracil, and oxaliplatin) chemotherapy leads to a clinically meaningful increase in 6- and 12-month overall survival rates after progression on cisplatin and gemcitabine.[A11] Molecular-targeted therapies may be helpful in a subset of patients.[13] Because of the late presentation of this disease and spread of tumor at diagnosis, the overall 5-year survival is less than 10%.

BILE DUCTS

Bile Duct Stones

PATHOBIOLOGY

Bile duct stones, or choledocholithiasis, can be classified as either primary or secondary. Primary duct stones develop de novo within the bile ducts, whereas secondary stones develop in the gallbladder and subsequently pass into the bile duct. In the Western world, more than 85% of all bile duct stones are secondary. Primary duct stones typically occur in conditions associated with bile stasis (e.g., benign biliary strictures, sclerosing cholangitis, choledochal cysts, periampullary diverticula), which promotes bacterial overgrowth with subsequent bilirubin deconjugation and the breakdown of biliary lipids, thereby resulting in the formation of brown pigment stones.

CLINICAL MANIFESTATIONS

Bile duct stones are discovered incidentally in 5 to 12% of patients during the evaluation of gallbladder stones and suspected cholecystitis. It is difficult to determine whether the existing bile duct stones are asymptomatic in patients who present with biliary pain alone because pain can originate from either the gallbladder stones or bile duct stones. More than 50% of patients with retained bile duct stones experience recurrent symptoms during a follow-up period of 6 months to 13 years, and 25% of cases develop serious complications.

Common clinical symptoms and signs of bile duct stones include epigastric or right upper quadrant pain, fever, and jaundice (referred to as the Charcot triad). Pain can be mild or severe, and severe episodes must be differentiated from other potentially life-threatening events. Occasional patients may present with painless jaundice and weight loss mimicking pancreaticobiliary malignant disease (Chapter 180).

DIAGNOSIS

Patients with cholangitis, with or without associated pancreatitis (Chapter 130), typically have elevated serum aminotransferase levels. The serum bilirubin level usually is less than 15 mg/dL with choledocholithiasis because most bile duct stones cause intermittent, incomplete biliary obstruction. In unusual cases, the serum aminotransferase levels can be profoundly elevated (up to 2000 IU/L), mimicking acute viral hepatitis.

Although ultrasound is the most common initial test for patients with suspected gallbladder stones, it has a low sensitivity rate (25 to 60%) for detection of bile duct stones, in part because the bile duct may not be dilated in acute obstruction. CT scan may demonstrate calcified bile duct stones (Fig. 141-6), but its sensitivity for this purpose is generally little better. CT is useful, however, for identifying other potential causes of biliary obstruction (e.g., mass lesion) and local complications, such as a liver abscess (Chapter 137). Magnetic resonance cholangiopancreatography (MRCP) and endoscopic ultrasound can detect bile duct stones with an accuracy comparable to that of ERCP (Fig. 141-7). Because of potential procedure-related risks, ERCP is now reserved for patients with confirmed or a high suspicion of biliary disease who are likely to require therapeutic intervention.

TREATMENT

Given the potential serious complications of bile duct stones (i.e., cholangitis, pancreatitis),[14] specific therapy is generally required regardless of symptoms. About 85 to 90% of bile duct stones can be removed at ERCP by standard balloon dilation and basket extraction after biliary endoscopic sphincterotomy, with a complication rate, including pancreatitis, bleeding, cholangitis, cholecystitis, and perforation, of less than 10%. Data are conflicting on whether asymptomatic patients are at increased risk for post-ERCP pancreatitis compared with patients who have symptomatic bile duct stones.[15–17] Endoscopic biliary orifice dilation without sphincterotomy may reduce some acute complications but increases the risk for pancreatitis and may lead to more subsequent procedures.[18]

The 10 to 15% of bile duct stones that cannot be removed by standard ERCP are generally larger than 1.5 cm, impacted, or located above a stricture.[19] Alternative therapies include the use of large-diameter dilation balloons (12 to 18 mm)[A12] and fragmentation by mechanical or electrohydraulic lithotripsy. Whenever stones cannot be completely removed endoscopically, biliary stents should be placed to ensure adequate biliary drainage and to prevent recurrent symptoms while awaiting further therapy. Long-term biliary stenting can also be used in patients with severe comorbid medical conditions that preclude surgery or repeated endoscopic interventions.

Ideally, patients with concomitant gallbladder and bile duct stones would be best treated with a single laparoscopic cholecystectomy and bile duct exploration, which is preferable to ERCP followed by cholecystectomy.[A13] However, only a minority of surgeons can successfully perform laparoscopic bile duct exploration, so open common bile duct exploration is generally performed if endoscopic and laparoscopic approaches are unsuccessful. A novel combined laparoendoscopic rendezvous procedure, where ERCP is facilitated by transcystic wire passage into the bile duct and duodenum at the time of cholecystectomy, is equivalent to the two-stage procedures in terms of ductal stone clearance, with less pancreatitis, lower morbidity, and shorter hospital stay despite a longer procedural time.[A14]

Complications of Bile Duct Stones

Cholangitis is a potentially life-threatening disease that results from bacterial infection of obstructed bile. Systemic toxicity occurs when intraductal pressure is sufficiently elevated to cause reflux of bacteria or endotoxin into the blood. About 80 to 90% of cases of acute cholangitis is caused by choledocholithiasis, with the remaining cases caused by a benign biliary stricture (e.g., primary sclerosing cholangitis, chronic pancreatitis, postoperative bile duct injury, or narrowing at an anastomosis) or by malignant biliary obstruction, typically after previous endoscopic instrumentation and stent placement. In certain parts of the world, parasitic biliary obstruction (e.g., *Ascaris*; Chapter 327) may be manifested with cholangitis. The most common bacteria are gram-negative bacilli and *Streptococcus* spp, but *Enterococcus* species are frequently seen in patients with occluded biliary stents. Prompt antibiotic therapy (e.g., intravenous ceftriaxone 1 to 2 g once daily; ampicillin-sulbactam 1.5 to 3 g every 6 hours; piperacillin-tazobactam 3.375 g every 6 hours; ciprofloxacin 400 mg twice daily; or levofloxacin 500 mg orally once daily) is critical and usually can permit conservative management with endoscopic biliary decompression within 24 to 48 hours.[A15] However, urgent decompression is indicated if improvement is not seen within a few hours. The advantages of ERCP are that it can delineate the cause of obstruction, obtain bile for culture, and rapidly decompress the biliary tree definitively by removing the stone or temporarily by placing a stent without removing the stone. Routine stenting is not indicated after successful stone removal unless the adequacy of biliary drainage is uncertain.

Acute gallstone pancreatitis accounts for up to 50% of cases of acute pancreatitis in Western countries (Chapter 130). Most patients quickly respond to conservative therapy, but some develop severe pancreatitis. Although early ERCP with biliary sphincterotomy and stone removal (Fig. 141-8) would appear to be an attractive therapeutic option, early ERCP does not reduce mortality or complications except in patients with biliary obstruction or clear evidence of cholangitis.[A16] After recovery from an episode of biliary pancreatitis, laparoscopic cholecystectomy with intraoperative cholangiography is recommended to prevent further episodes, preferably during the same hospital admission.[A17] If a common bile duct stone is found at intraoperative cholangiography, laparoscopic or open common bile duct exploration and stone removal can be accomplished with high success rates in experienced hands, or postoperative ERCP can remove any retained stones.[A18]

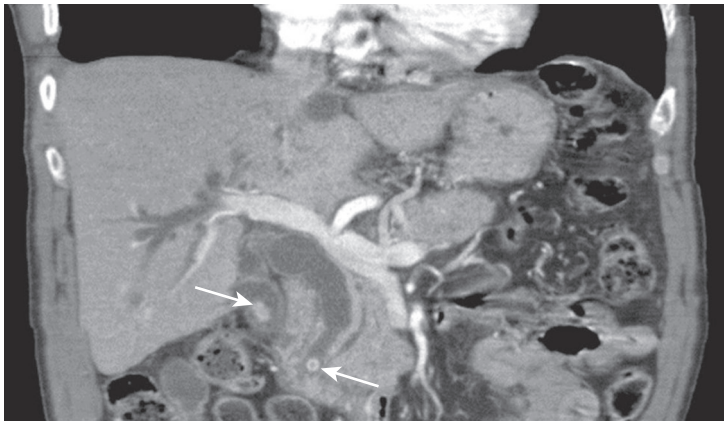

FIGURE 141-6. Computed tomography scan demonstrating calcified gallstones and a distal bile duct stone.

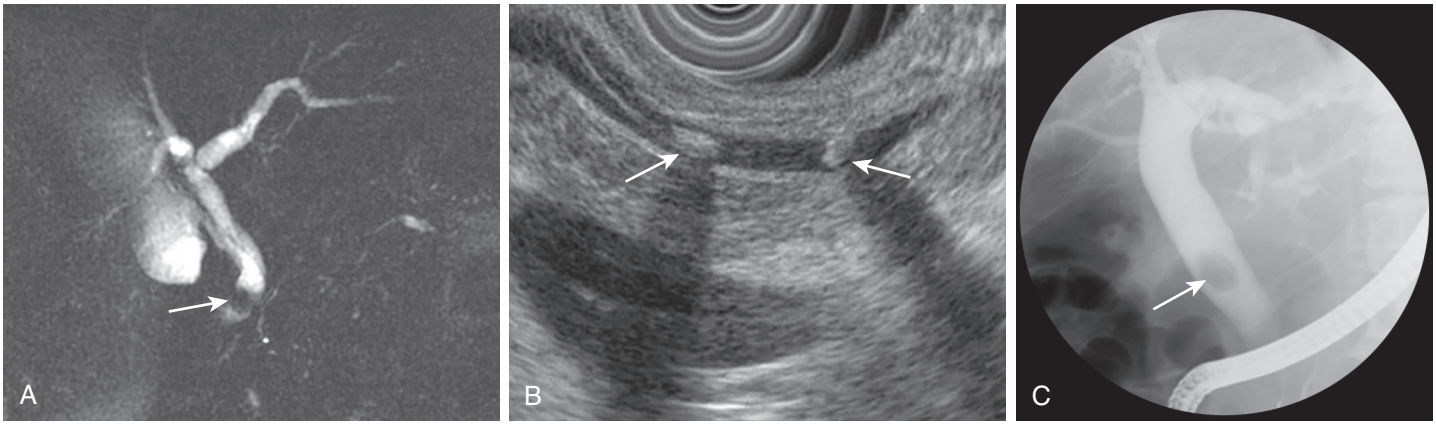

FIGURE 141-7. Common bile duct stones seen at magnetic resonance cholangiopancreatography (A), endoscopic ultrasound (B), and endoscopic retrograde cholangiopancreatography (C).

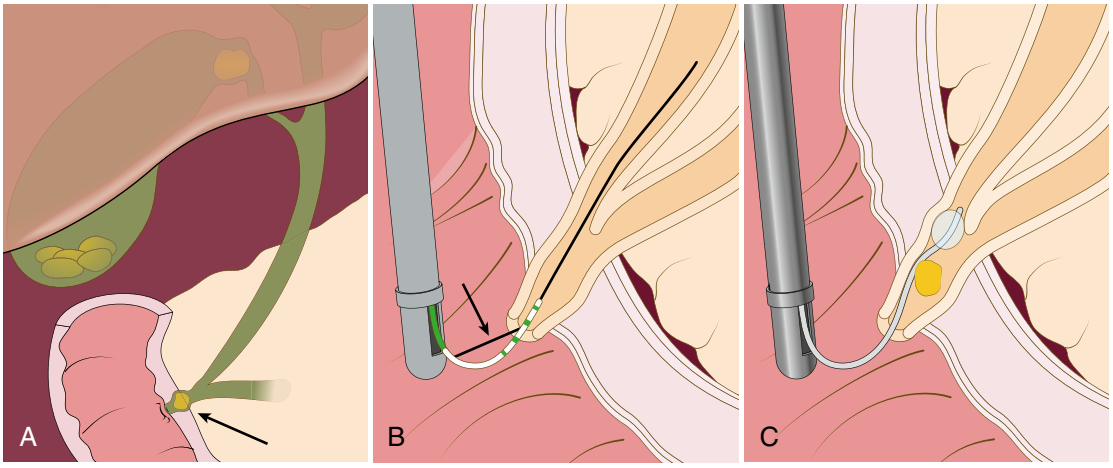

FIGURE 141-8. A, A stone that is impacted in the distal bile duct is causing biliary pancreatitis, with gallbladder stones also seen. B, Performance of biliary sphincterotomy. C, Subsequent stone removal by balloon sweep.

PREVENTION

Up to 25% of patients may have recurrent bile duct stones, with or without a gallbladder, but it remains uncertain what proportion of these recurrent stones are in fact overlooked residual stones from a prior event. A dilated extrahepatic bile duct (≥13 mm) and periampullary diverticula are risk factors for recurrent stones, perhaps by increasing biliary stasis. Identification and treatment of biliary strictures, papillary stenosis, and gallstones in patients with gallbladder in situ are essential for preventing recurrent stones. Unfortunately, no preventive therapy has been proved effective, although ursodeoxycholic acid (15 mg/kg/day) appears to reduce the risk for gallstones during weight loss.

BENIGN BILIARY STRICTURES

Postoperative extrahepatic bile duct strictures occur after 0.25 to 1% of cholecystectomies. Most of these lesions are manifested as abnormal liver test results, obstructive jaundice, and cholangitis within 2 to 3 months postoperatively, although the presentation can be delayed. The cholangiogram commonly shows a short, smooth narrowing near the cystic duct stump with proximal duct dilation (Fig. 141-9). Strictures typically must be redilated, and stents are exchanged at 3- to 4-month intervals for 8 to 12 months until the stricture is nearly as open as the downstream bile duct. About 80% of patients will have a good result. Covered self-expandable metal stents are as good as multiple plastic stents for resolving strictures, with fewer ERCP procedures needed to achieve resolution.[A19] However, some patients will ultimately require a bilioenteric bypass. Strictures more than 2 cm in length, strictures with clips placed securely across the duct, or strictures associated with resected segments of duct require surgical intervention.

Intrapancreatic common bile duct strictures, which may occur in 3 to 46% of patients with chronic pancreatitis, can lead to secondary biliary cirrhosis or recurrent cholangitis. With the complication of cholangitis or jaundice, intervention is clearly indicated, typically with ERCP and stent placement. In the absence of cholangitis or jaundice, either surgical repair or endoscopic biliary decompression with multiple plastic stents (Fig. 141-10) has traditionally been recommended when the alkaline phosphatase level is consistently more than twice the upper limit of normal during a 6-month period of observation. Biliary strictures that complicate liver transplantation (Chapter 140) are usually treated similarly with good results.

Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) frequently targets the liver, but a rapidly progressive cholangiopathy has also been reported.[20] The pathogenesis of this disorder remains poorly understood, and no specific treatment options are currently available.

ORIENTAL CHOLANGIOHEPATITIS

Recurrent cholangitis with hepatolithiasis has a prevalence of more than 10% in parts of East Asia, especially in Taiwan, owing to infection with *Ascaris lumbricoides* (Chapter 327) and *Clonorchis sinensis* (Chapter 326). This condition results in local strictures and dilation of the intrahepatic biliary tree. Biliary stasis and subsequent bacterial infection cause brown stones to form. Most patients have recurrent cholangitis, but cholangiocarcinoma can also ensue. Ultrasound or CT can establish the diagnosis. Treatment includes intravenous fluids and antibiotics. Endoscopic stone removal is usually the preferred treatment, but localized surgical resection targeted to the cultured organisms may be necessary.

PRIMARY SCLEROSING CHOLANGITIS

DEFINITION

Primary sclerosing cholangitis is a chronic cholestatic disease characterized by fibrosing inflammation of segments of the intrahepatic and extrahepatic bile ducts.[21] It results in progressive narrowing of the duct lumen and ultimately may be manifested with recurrent episodes of ascending cholangitis or, alternatively, may progress to secondary biliary cirrhosis and its associated complications. Cholangiocarcinoma (Chapter 181) is a dreaded complication with a reported incidence of 25 to 40% at autopsy or liver transplantation.

EPIDEMIOLOGY

The true prevalence of primary sclerosing cholangitis is unknown, but current estimates are 0.2 to 8.5 per 100,000 in the U.S. population. Its prevalence is much higher in populations in which inflammatory bowel disease (Chapter 127) is more common. Affected men outnumber women in a 2 : 1 ratio, with the mean age at diagnosis of 32 to 40 years. However, primary sclerosing cholangitis has been reported in infants, children, and the elderly.

PATHOBIOLOGY

The cause of primary sclerosing cholangitis and the mechanisms responsible for its progression are unknown. However, autoimmune and genetic causes are supported by its frequent association with inflammatory bowel disease and the increased prevalence of the HLA B8, DR3 haplotype. Evidence from both fecal- and mucosa-associated microbial studies suggests that patients with primary sclerosing cholangitis harbour an abnormal enteric microbiome. About two thirds of patients with primary sclerosing cholangitis have ulcerative colitis or Crohn colitis, and it is rarely associated with Crohn disease that is limited to the small bowel. However, only 1 to 13% of patients with colitis are diagnosed with primary sclerosing cholangitis during their lifetime. First-degree relatives of patients with primary sclerosing cholangitis have a 9- to 39-fold increased risk for development of the disease.

On pathologic examination, involved segments of bile ducts in strictured areas show diffuse thickening with a mononuclear inflammatory cell infiltrate. The most characteristic biopsy features are bile duct proliferation, periductal fibrosis, periductal inflammation, and loss of bile ducts. Obliterative cholangitis with a chronic inflammatory cell infiltrate and periductular "onion ring" fibrosis is strongly associated with primary sclerosing cholangitis but is infrequently observed in biopsy specimens. Given the patchy nature of the disease and possible lack of significant intrahepatic involvement, however, the histologic appearance of primary sclerosing cholangitis is variable and may resemble extrahepatic biliary obstruction, chronic active hepatitis, or, rarely, primary biliary cirrhosis.

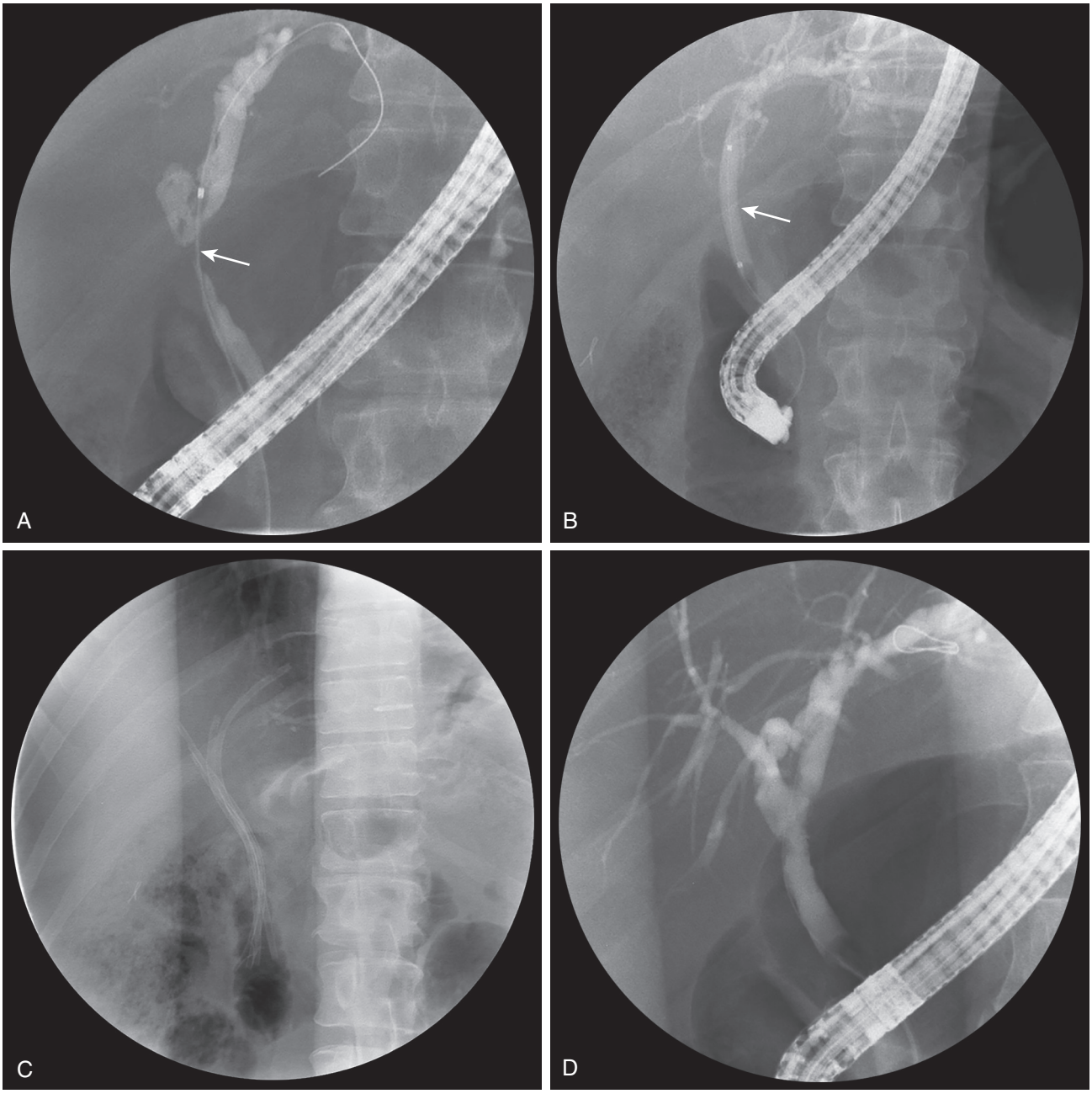

FIGURE 141-9. **Endoscopic retrograde cholangiopancreatography images obtained from a patient who presented with painless jaundice 8 months after cholecystectomy. A, Benign common hepatic duct stricture. B, Balloon dilation of the stricture. C, Multiple stents placed. D, Resolution of stricture after a 1-year stenting interval.**

CLINICAL MANIFESTATIONS

Most patients with primary sclerosing cholangitis are asymptomatic at presentation and are identified after investigation of an elevated alkaline phosphatase level (Chapter 133).[22] Overall, about 90% of patients have an elevated alkaline phosphatase level, with or without mildly elevated serum aminotransferase levels. Fatigue, anorexia, malaise, and weight loss are common but may erroneously be attributed to a patient's inflammatory bowel disease. Patients may exhibit signs or symptoms of cholestatic liver disease, including pruritus, upper abdominal pain, and fever. The serum bilirubin concentration is elevated in only about 40% of patients at presentation. Some patients have anemia, hypoalbuminemia, or hypergammaglobulinemia, and a prolonged international normalized ratio suggests biliary obstruction or synthetic dysfunction. Nearly 90% of patients will have a positive perinuclear antineutrophilic cytoplasmic antibody, but this antibody is also nonspecific and may be found in both ulcerative colitis (Chapter 127) and autoimmune hepatitis (Chapter 135). Antinuclear or anti–smooth muscle antibodies are found in 25% of patients but are not specific, and a positive antimitochondrial antibody suggests primary biliary cholangitis as the diagnosis.

DIAGNOSIS

Cholangiography is necessary to establish the diagnosis of primary sclerosing cholangitis (Fig. 141-11).[23] MRCP generally is the test of choice, but ERCP may be indicated if MRCP is inconclusive, particularly when the disease is confined to small intrahepatic ducts. The role of biopsy remains uncertain owing to the segmental nature of the disease and the overlap of the histologic features with other disease states. Diffuse multifocal strictures are usually short, with intervening normal or dilated segments that give a beaded appearance. Other frequent findings on cholangiography include pseudodiverticula, mural irregularities, and biliary stones and sludge. Secondary causes of sclerosing cholangitis include obstruction (postoperative, autoimmune cholangiopathy, choledocholithiasis, and recurrent pyogenic cholangitis), ischemic (hepatic artery instillation of the chemotherapeutic agent 5-fluorouracil, radiation, and paroxysmal nocturnal hemoglobinuria), and neoplastic (cholangiocarcinoma, hepatocellular carcinoma, lymphoma, and metastasis).

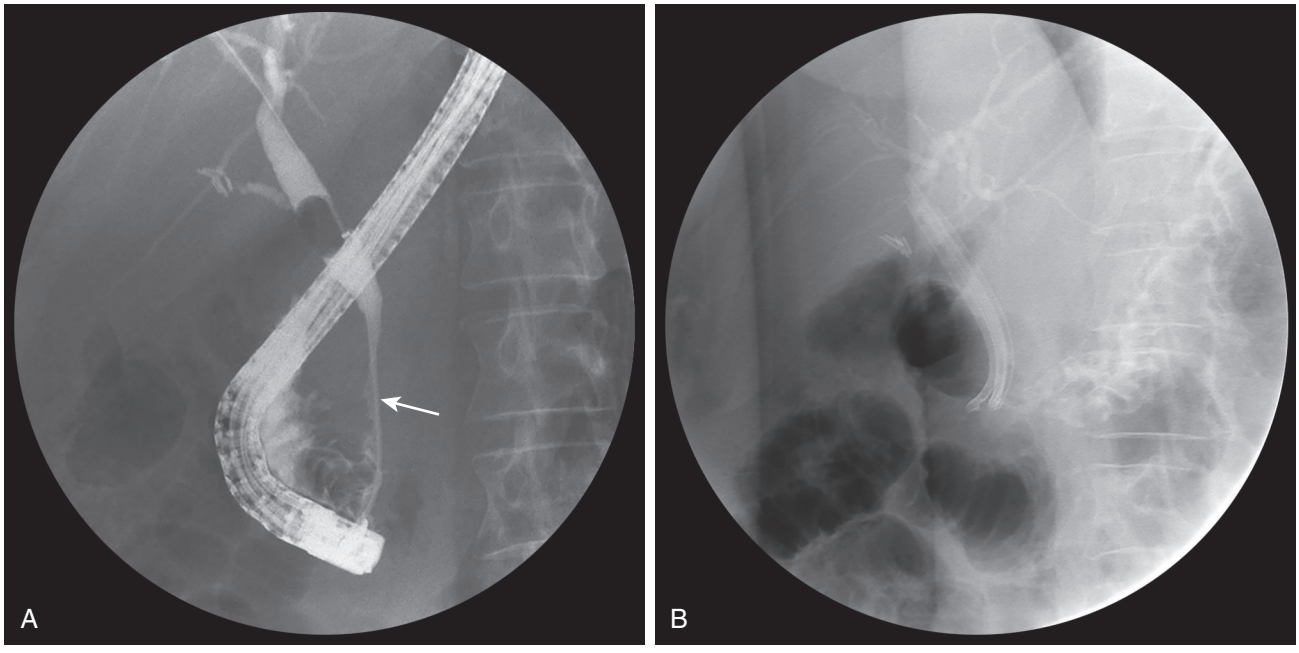

FIGURE 141-10. Endoscopic retrograde cholangiopancreatography images obtained from a patient with a history of alcohol abuse who presented with pruritus and was found to have a markedly elevated alkaline phosphatase level. A, A smooth distal bile duct stricture is seen (*arrow*). **B**, Four stents have been placed through the stricture.

TREATMENT

The chronic cholestasis of primary sclerosing cholangitis can be treated with cholestyramine (4 to 8 g/day), ursodeoxycholic acid (15 mg/kg/day), rifampicin (300 to 600 mg/day), or phenobarbital (30 to 120 mg/day) with modest success. Obeticholic acid, which is a potent farnesoid X receptor agonist approved for the treatment of primary biliary cholangitis (at 5 to 10 mg once daily), reduces the serum alkaline phosphatase level in patients with primary sclerosing cholangitis, although its effects on disease progression are not known.[A20] Another experimental farnesoid X receptor agonist, cilofexor, has shown promise in patients who have large-duct primary sclerosing cholangitis.[A21] Fat-soluble vitamin deficiencies (Chapter 199) must be corrected. The prevalence of osteoporosis (Chapter 225) in primary sclerosing cholangitis is between 4 and 10%, so bone densitometry should be performed at diagnosis and every 2 to 3 years thereafter. Supplementation with oral vitamin D and calcium seems prudent, even in the absence of symptomatic deficiency. Treatment with bisphosphonates (Chapter 225) is reserved for patients with confirmed osteoporosis. Unfortunately, no medical treatment slows the progression of disease; ursodeoxycholic acid, D-penicillamine, corticosteroids, cyclosporine, methotrexate, and colchicine have all been shown to be ineffective for improving survival or delaying the time to liver transplantation. Whether repeated endoscopic treatment to maintain bile duct patency can improve outcomes is unknown, although patients with a dominant stricture may benefit.[24] Furthermore, short-term stents are not superior to balloon dilatation and are associated with a significantly higher occurrence of treatment-related adverse events (e.g., cholangitis, pancreatitis).[25]

Liver transplantation (Chapter 140) is the only potentially curative therapy. The 1-year and 5-year survival rates typically are in the 90% and 80% range, respectively. Primary sclerosing cholangitis may recur in the transplanted organ in 15 to 20% of patients.

PROGNOSIS

The natural history of primary sclerosing cholangitis is variable and incompletely understood. Asymptomatic patients have a much better prognosis than symptomatic patients, with 10-year actuarial survival rates of 80% and 50%, respectively. In symptomatic patients, the median time of survival until death or liver transplantation is 9 years, compared with 12 to 18 years for all patients with primary sclerosing cholangitis, regardless of symptoms. An elevated serum bilirubin level and hepatomegaly appear to correlate with a poor prognosis, whereas cholangiographic appearance, the presence or absence of inflammatory bowel disease, and the patient's age do not. Cholangiocarcinoma (Chapter 181) is a dreaded complication of primary sclerosing cholangitis, and the risk appears to be greatest in patients with long-standing ulcerative colitis and cirrhosis.

FIGURE 141-11. Magnetic resonance cholangiopancreatography demonstrating the typical cholangiographic features of primary sclerosing cholangitis. Note the narrowed segment of the common bile duct (*arrow*) as well as the diffuse strictures and dilated segments of several intrahepatic bile ducts, giving the classic "beaded" appearance.

CHOLEDOCHAL CYSTS AND ANOMALOUS PANCREATICOBILIARY DUCT JUNCTION

Choledochal cysts are uncommon anomalies of the biliary tree that are manifested as cystic dilation of the intrahepatic or extrahepatic ducts (or both). The incidence is 1 in 100,000 to 150,000 births in Western populations and 1 in 1000 in Asian populations. There is a 3 : 1 to 4 : 1 female-to-male preponderance.

TABLE 141-3 CLASSIFICATION OF CHOLEDOCHAL CYSTS

TYPES	DESCRIPTION	PROPORTION OF CHOLEDOCHAL CYSTS
I	Segmental or diffuse fusiform dilation of the bile duct	50-80%
II	Choledochal diverticulum	2%
III	Dilation of the intraduodenal portion of the bile duct	1.4-5%
IVa	Multiple intrahepatic and extrahepatic cysts	15-35%
IVb	Multiple extrahepatic cysts	
V (Caroli disease)	Single or multiple dilations of the intrahepatic ducts	20%
VI	Dilatation of the cystic duct between the neck of the gallbladder and the common hepatic duct	Rare

These cysts (E-Fig. 141-1) usually involve only the extrahepatic biliary tree, but they can present as extrapancreatic bile duct diverticula, involve only the intraduodenal part of the common bile duct, or present as multiple intrahepatic and extrahepatic cysts (Table 141-3). An anomalous pancreaticobiliary duct junction (E-Fig. 141-2) is frequently associated with choledochal cysts but may be found in isolation, especially in Asian populations.

Patients with choledochoceles commonly have biliary colic, cholangitis, jaundice, or unexplained pancreatitis. Bile reflux may also result in acute pancreatitis or predispose to biliary cancers.

Cholangiography, preferably by ERCP, is the diagnostic "gold standard," although MRCP can also delineate the anatomy noninvasively. Because of the increased risk for development of biliary tract cancers, cyst resection (including cholecystectomy) is the generally recommended treatment, although it does not eliminate the risk entirely.[26]

BILIARY FISTULA

A biliary fistula represents an injury to the bile duct, most commonly seen as a complication of cholecystectomy, common bile duct exploration, or inadvertent operative injury of the bile duct or as a consequence of a local infection. Rarely, biliary fistulas result from long-standing untreated biliary tract disease. With more widespread use of laparoscopic cholecystectomy, the incidence of bile duct injury, including biliary fistula, has increased, but it remains less than 0.5% in most published series.

Postoperative bile duct leaks are usually manifested within a week after surgery, with patients presenting with abdominal pain (90%), tenderness (80%), fever (75%), nausea and vomiting (50%), and jaundice (40%). Clinically detectable ascites is rare. Biochemical testing is usually nonspecific, with variable elevations in serum liver test values and the white blood cell count.

Patients with suspected biliary fistulas often undergo abdominal ultrasonography or CT to look for evidence of a biloma as well as a hepatobiliary scan to diagnose the leak. However, ERCP is the most sensitive test to detect a biliary fistula. Treatment options for biliary leaks include percutaneously or endoscopically placed biliary drains or stents and surgical drainage and repair of the leak.

VANISHING BILE DUCT SYNDROMES

The vanishing bile duct syndrome is characterized by a paucity of intrahepatic bile ducts, an elevated alkaline phosphatase level, and cholestasis. Causes include primary biliary cholangitis, primary sclerosing cholangitis, autoimmune hepatitis (Chapter 135), graft-versus-host disease, chronic liver transplant rejection (Chapter 140), ischemia, intrahepatic chemotherapy, drug toxicity (e.g., ampicillin, amoxicillin, flucloxacillin, erythromycin, tetracycline, doxycycline, cotrimoxazole), human immunodeficiency virus (HIV) infection (Chapter 359), sarcoidosis (Chapter 83), and histiocytosis. Ursodeoxycholic acid (15 mg/kg/day) can increase bile flow, but the condition inexorably progresses to biliary cirrhosis, which ultimately requires liver transplantation.

PRIMARY BILIARY CHOLANGITIS

Primary biliary cholangitis, previously known as primary biliary cirrhosis, is an obliterative autoimmune cholangiopathy that involves the small and medium-sized bile ducts and that slowly progresses during a decade or so. As the ducts are obliterated, patients develop cholestasis, fibrosis, and, ultimately, liver failure.[27]

EPIDEMIOLOGY

About 95% of patients with primary biliary cholangitis are women, and the peak age at onset is between 20 and 60 years. The incidence of the disease may be increasing. In the United States, the estimated annual incidence is about 4.5 per 100,000 per year for women and 0.7 for men. Because of the limited life expectancy of affected patients, the age- and gender-adjusted prevalence of primary biliary cholangitis is about 65 per 100,000 in women and about 12 per 100,000 in men.

PATHOBIOLOGY

Although the mechanism of progressive destruction of the small interlobular ducts is unknown, primary biliary cholangitis is considered to be an autoimmune disorder. Genome-wide studies show an association with HLA, interleukin-12A, and interleukin-12RB2 variants, suggesting that interleukin-12 signaling might be important. The disease progresses slowly and can eventually lead to biliary cirrhosis, portal hypertension, and liver failure. The classic histologic finding is noncaseating granulomas and paucity of bile ducts in the portal tracts.

CLINICAL MANIFESTATIONS

The most common symptoms are fatigue (50%), which can be debilitating and is unrelated to the degree of underlying liver disease, and pruritus (30%), but about 50% of patients are asymptomatic at the time of diagnosis. Many patients are initially seen by dermatologists for pruritus, which may be first noticed in pregnancy but persists after delivery.

Autoimmune syndromes associated with primary biliary cholangitis include autoimmune thyroid dysfunction (Chapter 207), Sjögren syndrome (Chapter 247), Raynaud phenomenon (Chapter 246), and celiac disease (Chapter 126). Vitamin D malabsorption can also lead to metabolic bone disease (Chapters 225 and 226).[28]

DIAGNOSIS

The first clue to primary biliary cholangitis is an elevated serum alkaline phosphatase level, which should be confirmed by an elevated γ-glutamyl transpeptidase level (Chapter 133). The antimitochondrial antibody level has a sensitivity and specificity of more than 95% when the titer is higher than 1 : 40, and it may be positive even before there is any clinical or biochemical evidence of the disease. By comparison, the bilirubin level often is not elevated until later in the course of the disease, with most of the elevation typically due to an elevation in conjugated bilirubin. Total immunoglobulins are generally normal, but immunoglobulin M levels can be elevated.

An ultrasound examination of the biliary tree is critical to confirm the absence of extrahepatic disease. A liver biopsy is occasionally needed to confirm the diagnosis, particularly in antimitochondrial antibody–negative patients, and to stage the disease.

TREATMENT

Ursodeoxycholic acid therapy (12 to 15 mg/kg/day) improves serum bilirubin, alkaline phosphatase, and cholesterol levels and has a variable effect on pruritus.[29] Unfortunately, it does not relieve fatigue, reduce mortality, or delay the need for liver transplantation. In patients who do not respond to ursodeoxycholic acid, obeticholic acid in a daily dose of 10 mg can significantly reduce alanine aminotransferase, alkaline phosphatase, and γ-glutamyl transpeptidase levels, but its effect on clinical outcomes such as liver failure and the need for liver transplantation is unknown.[A22] Bezafibrate therapy also improves liver chemistry test results and pruritus[A23] but has not been shown to reduce liver-related mortality or overall mortality. Saroglitazar, a peroxisome proliferator–activated receptor agonist, may also lead to improved alkaline phosphatase levels in patients who are resistant to or intolerant of ursodeoxycholic acid.[30]

There is no definite benefit from steroids, colchicine, azathioprine, or methotrexate. Bisphosphonates (Chapter 225) are commonly prescribed for the accompanying metabolic bone disease, but their benefit is uncertain. Liver transplantation (Chapter 140) is indicated for refractory disease. The posttransplantation prognosis is excellent, with 2-year and 5-year survival rates of 80% and 70%, respectively. However, studies suggest an 8 to 40% recurrence in the transplanted liver.

PROGNOSIS

Up to two thirds of asymptomatic patients become symptomatic within 2 to 4 years. Significant bridging fibrosis or cirrhosis on biopsy carries a worse prognosis. Prognosis is also influenced by the serum bilirubin and albumin levels,

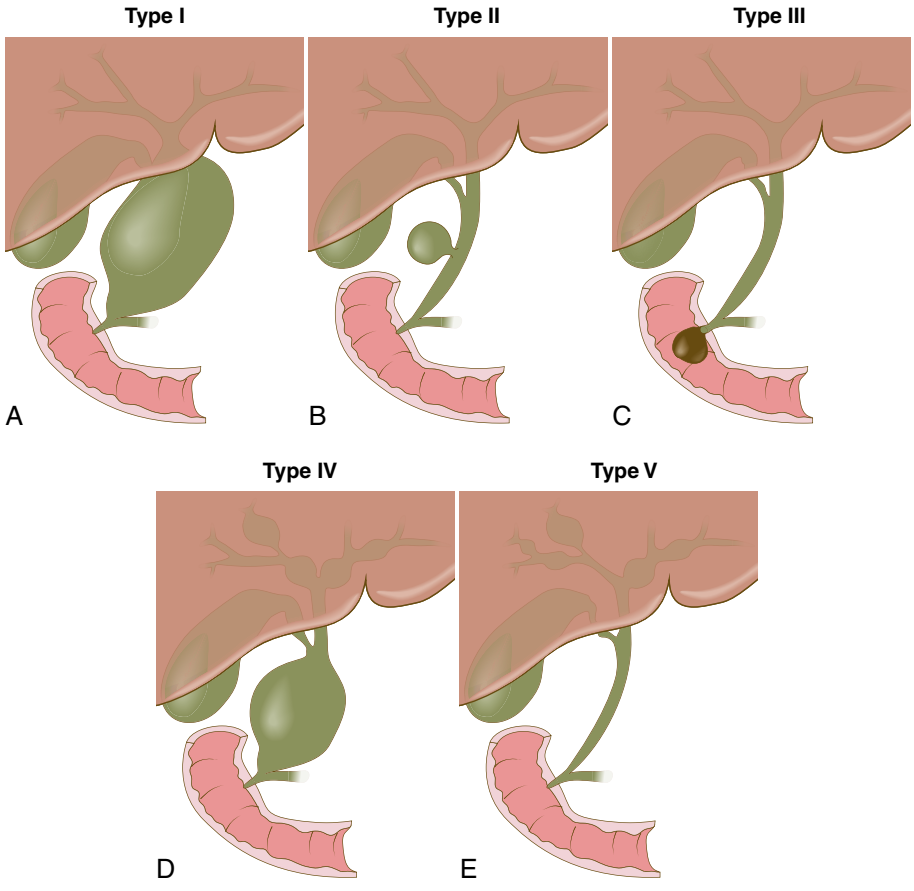

E-FIGURE 141-1. Schematic diagram of choledochal cysts.

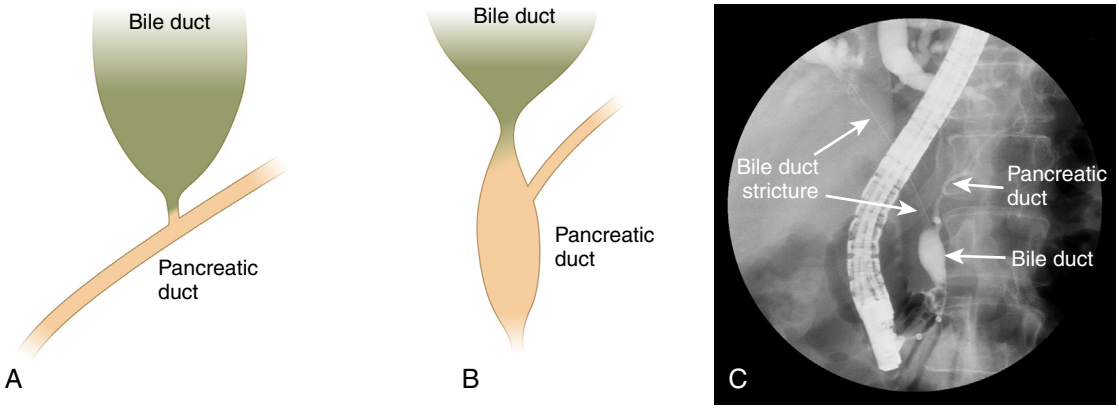

E-FIGURE 141-2. **A**, Schematic diagram of anomalous pancreaticobiliary duct junction, with the terminal bile duct draining directly into the pancreatic duct (B-P type). **B**, Schematic diagram of P-B type of anomalous pancreaticobiliary duct junction. **C**, Endoscopic retrograde cholangiopancreatography image illustrating the P-B type of anomalous pancreaticobiliary duct junction, with a bile duct stricture due to gallbladder cancer.

the international normalized ratio, older age, and the presence of peripheral edema. Liver failure develops in about 25% of patients within 10 years after diagnosis, and median survival after diagnosis is 12 to 15 years.

BILE DUCT TUMORS

BENIGN

Benign bile duct tumors are exceedingly rare compared with malignant tumors and are much less common than benign gallbladder tumors. They can be divided into three histologic types (papillomas, adenomas, cystadenomas), may be solitary or multiple, and often are found incidentally during the evaluation of bile duct dilation or intraductal filling defects. Patients may be asymptomatic or have symptoms of biliary obstruction. Treatment typically consists of surgical bile duct resection with hepaticojejunostomy reconstruction. Even benign tumors tend to recur after excision, and some undergo malignant change.

CHOLANGIOCARCINOMA

Cholangiocarcinoma is discussed in Chapter 181.

AMPULLARY TUMORS

Benign ampullary lesions seen on endoscopic or radiologic studies include heterotopic gastric mucosa, a lipoma, or an impacted common bile duct stone. Primary tumors of the ampulla of Vater can be premalignant or malignant, but the overwhelming majority (>95%) are either adenomas or adenocarcinomas. The prevalence of ampullary adenomas has been estimated to be 0.04 to 0.12% in autopsy series, but the prevalence is higher in patients with hereditary polyposis syndromes (Chapter 179), in which ampullary adenomas occur in up to 80% of individuals and progress to malignancy in 4%.

Malignant ampullary lesions are most commonly adenocarcinomas, although metastatic breast cancer, renal cell cancers, and melanomas also have been identified. Carcinoid tumors (Chapter 213) and other neuroendocrine tumors are rare. Ampullary adenomas probably follow an adenoma-to-carcinoma sequence similar to colorectal adenocarcinoma (Chapter 179), with a 25 to 85% risk for transformation to carcinoma.

Patients with ampullary lesions may present with biliary colic, obstructive jaundice, pancreatitis, or nonspecific upper abdominal pain, with or without fluctuating serum liver test results, malaise, and anorexia. However, ampullary lesions are often found incidentally on cross-sectional imaging or during upper endoscopy performed for a different indication.

For ampullary adenomas, options include observation with surveillance biopsies and attempts to resect the lesion completely through endoscopy or surgery. Surveillance of an ampullary adenoma in the setting of familial adenomatous polyposis is reasonable if the lesion is small (<1 cm) and asymptomatic, but resection is preferred if advanced histology (e.g., villous features, dysplasia) is identified. Surgical resection has been the standard for ampullary tumors. Treatment modalities include pancreatoduodenectomy, which has a high rate of morbid and even fatal complications, and transduodenal excision, which is associated with high recurrence rates. The 5-year survival rates after pancreaticoduodenectomy range from 64 to 80% for patients with node-negative disease and from 17 to 50% for node-positive disease. Limited data exist regarding adjuvant therapy, the benefits of which are uncertain. A common practice is to treat these patients in a manner similar to patients with resected pancreatic adenocarcinomas (Chapter 180). Patients who present with unresectable disease tend to receive combination gemcitabine (1000 mg/m^2) plus cisplatin (25 mg/m^2) chemotherapy, each administered on days 1 and 8, every 3 weeks for eight cycles. Palliative biliary stenting can be performed in individuals who have a short life expectancy.

In patients with small, localized, and clearly benign ampullary adenomas, endoscopic resection represents an alternative to surgical therapy in appropriately selected patients (E-Fig. 141-3). Whether endoscopic resection is effective for larger or higher-risk adenomas is uncertain. Furthermore, recurrence rates after endoscopic papillectomy approach 20%, thereby emphasizing the need for careful follow-up endoscopic surveillance.

SPHINCTER OF ODDI DYSFUNCTION

Sphincter of Oddi dysfunction is a benign, noncalculous obstruction to the flow of bile or pancreatic juice through the pancreaticobiliary junction. It may be manifested clinically by pain, pancreatitis (Chapter 130), abnormal liver test results, or abnormal pancreatic enzymes. Post-cholecystectomy pain resembling the patient's preoperative biliary colic occurs in at least 10 to 20% of patients.

Evaluation of patients with suspected sphincter of Oddi dysfunction includes standard serum liver chemistries, serum amylase and lipase levels, and an abdominal ultrasound examination or CT scan. The specimens for serum enzyme studies should be drawn during bouts of pain, if possible. Mild elevations (less than two times the upper limits of normal) are frequent in sphincter of Oddi dysfunction, whereas greater abnormalities are more suggestive of stones, tumors, and parenchymal liver disease. The findings on CT and abdominal ultrasound studies are usually normal, but abnormal liver or pancreatic enzymes or a dilated bile duct or pancreatic duct may occasionally be found. ERCP and sphincter of Oddi manometry may be considered in patients who have objective evidence of pancreatic or biliary disease (abnormal liver or pancreatic enzymes or a dilated bile or pancreatic duct) or clinically significant or disabling symptoms and in whom definitive sphincter ablation is planned if abnormal sphincter function is found. In patients without objective evidence of pancreatic or biliary disease, ERCP and manometry are no longer recommended.[A24]

Medical therapy with nonspecific antispasmodics (e.g., dicyclomine 10 to 20 mg every 6 hours; hyoscyamine 0.375 mg every 12 hours) or smooth muscle relaxants (e.g., nifedipine 60 mg daily) for a 1-month trial should be considered in patients with pancreaticobiliary-type pain (with or without abnormal liver enzyme, amylase, or lipase levels) or a dilated bile or pancreatic duct. If patients do not respond satisfactorily, ERCP and endoscopic sphincterotomy can improve pain in 55 to 95% of patients with abnormal findings on laboratory testing or abdominal imaging. Alternatively, only about 25% of patients without objective evidence of pancreatic or biliary disease improve after sphincterotomy.

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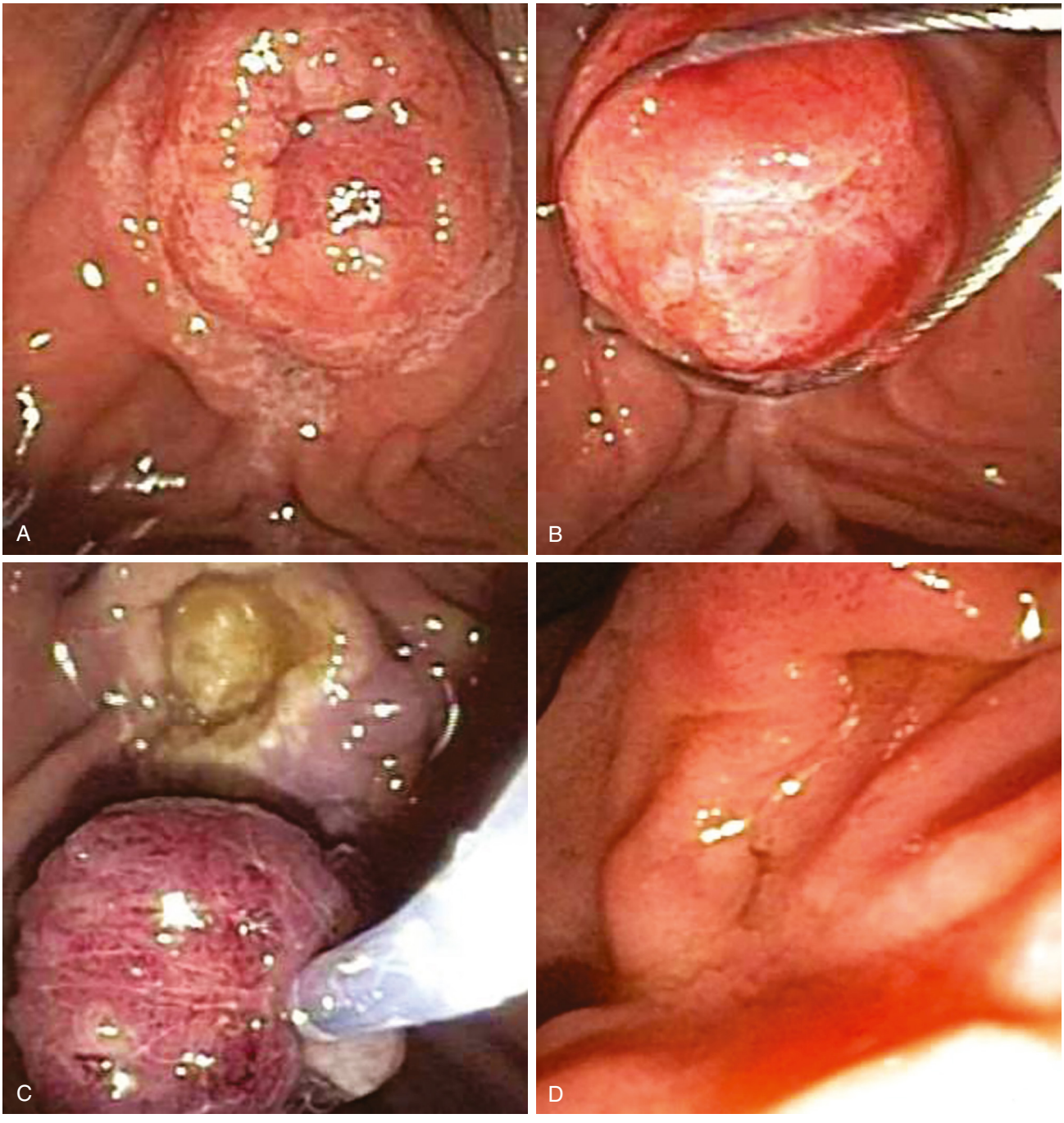

E-FIGURE 141-3. A 58-year-old man was found to have a prominent major papilla during upper endoscopy performed for evaluation of dysphagia. A duodenoscopy confirmed these findings (**A**), and biopsies revealed this to be a tubulovillous adenoma. This was grasped with a polypectomy snare (**B**), removed in one piece by electrocautery, and retrieved for pathologic analysis (**C**). A temporary pancreatic duct stent was placed (not shown), and rectal indomethacin was given to minimize the risk for postprocedure pancreatitis. No residual adenoma was seen on surveillance endoscopy 1 year later (**D**).

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142 HEMATOPOIESIS AND HEMATOPOIETIC GROWTH FACTORS

KENNETH KAUSHANSKY

Hematopoiesis is the process by which bone marrow stem cells develop into all of the cell types present in the blood (erythrocytes, neutrophils, eosinophils, basophils, monocytes, platelets, T lymphocytes, B lymphocytes, and natural killer cells) (Fig. 142-1). The regulation of the numbers of each cell type is carefully controlled by paracrine and endocrine hematopoietic growth factors, which exert antiapoptotic, proliferative, and differentiative effects on hematopoietic stem, progenitor, and maturing blood cells. Many of these glycoproteins are now produced by recombinant DNA technology and have been among the most successful therapeutics in modern medicine.

HEMATOPOIETIC STEM AND PROGENITOR CELLS

Hematopoietic stem cells comprise 1 in 10^5 to 10^6 marrow cells and are not morphologically distinguishable from other progenitors or small lymphocytes but can be purified to homogeneity using physical characteristics and combinations of monoclonal antibodies (including $CD34^+$) to cell surface proteins. The two critical characteristics of a hematopoietic stem cell are its ability to differentiate into all blood cell types and to self-renew. The decision to self-renew or differentiate is a stochastic process, at the stem cell stage and at the subsequent multipotent or unipotent stages of differentiation, that can be influenced by a number of cell extrinsic (growth factors and stromal proteins) and cell intrinsic (transcription factors) molecules. Hematopoietic stem cells reside in specialized microenvironments (niches) within the bone marrow. The complex and diverse stromal cell populations that comprise the critical perivascular stem cell niche include endothelial cells, CXCL12 abundant reticular [CAR] cells, nestin+ mesenchymal stem cells, and megakaryocytes and provide signals that support stem cell maintenance, self-renewal, and long-term multilineage repopulation ability.[1]

Clonal hematopoiesis with somatic mutations, which can be detected by DNA sequencing, is more common with advancing age (currently referred to as clonal hematopoiesis of undetermined potential [CHIP]),[2] and is associated with higher risks of hematologic cancer and all-cause mortality.[3] Some genes that are mutated in patients with myeloid cancers are frequently mutated in apparently healthy persons; these mutations may represent characteristic early events in the development of hematologic cancers[4] and are associated with increased risk of atherosclerotic cardiovascular disease.[5] Interestingly, the concordance of clonal hematopoiesis among twins is limited, thereby suggesting in utero or subsequent environmental influences.[6] Evidence based on recapitulating the genetic changes in patients with CHIP in engineered mice strongly suggests that dysregulated inflammation in the affected monocytes/macrophages is responsible for the excess cardiovascular and cerebrovascular disease seen in such patients.[7,8]

HEMATOPOIETIC CELL EXPANSION: HEMATOPOIETIC GROWTH FACTORS

A large number of transcription factors regulate stem cell number and differentiation state. Several molecular switches have been identified that determine hematopoietic cell fate.

Equally important to hematopoiesis is a group of hematopoietic growth factors that share structural homology and bind to nonredundant type I transmembrane proteins belonging to the cytokine receptor family. Many of these proteins are the physiologic regulators of a specific lineage of blood cells (e.g., erythropoietin, granulocyte colony-stimulating factor, thrombopoietin); others appear to represent redundant hematopoietic growth-promoting activities of molecules essential for other biologic functions (e.g., interleukin-3 [IL-3], interleukin-11 [IL-11], granulocyte-macrophage colony-stimulating factor).

Erythropoietin is produced predominantly by the kidneys and to a lesser extent in the liver and acts on marrow erythroid progenitors to enhance their survival, proliferation, and differentiation. Levels of erythropoietin are inversely related to hemoglobin concentrations in the blood, sensed as renal oxygen tension. In the presence of tissue (renal) hypoxia, the transcription factor hypoxia-induced factor (HIF) 1α is stabilized against proteasome-mediated

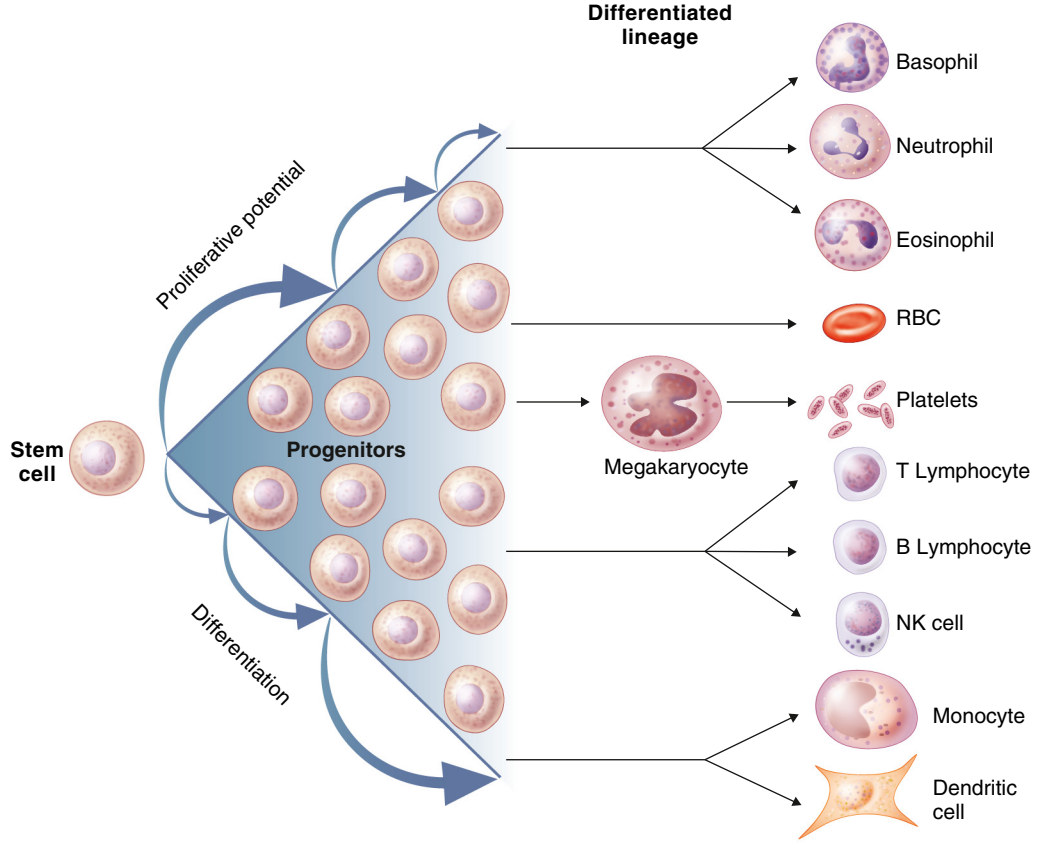

FIGURE 142-1. Hierarchical model of lymphohematopoiesis. NK = natural killer; RBC = red blood cell.

ABSTRACT

Hematopoiesis is the process by which marrow hematopoietic stem cells expand and differentiate into all the formed elements of the blood. The process is under strict control to assure adequate cell numbers to carry oxygen and carbon dioxide to and from the tissues, to fight infection, and to carry out hemostasis. A wide variety of glycoprotein hormones have now been identified that regulate hematopoiesis, many of which have been developed as therapeutics for patients with inadequate numbers of erythrocytes, neutrophils, lymphocytes, and/or platelets.

KEYWORDS

hematopoiesis
erythropoietin
granulocyte colony-stimulating factor
thrombopoietin
marrow niche
cytokine signaling

destruction and drives erythropoietin transcription by binding to a critical hypoxia responsive element located in the 3′ untranslated region of the gene. Genetic elimination of erythropoietin or its receptor results in embryonic lethality, establishing that although other cytokines can influence erythropoiesis, red blood cell production is absolutely dependent on the hormone.

Granulocyte colony-stimulating factor stimulates the production of neutrophils from their marrow progenitors (Fig. 142-2). Levels of the hormone are also inversely related to neutrophil numbers but are regulated primarily by inflammatory stimuli, including tumor necrosis factor-α (TNF-α) and IL-1α acting on endothelial cells, fibroblasts, and macrophages. Similar to the action of erythropoietin on erythroid progenitors, granulocyte colony-stimulating factor acts to enhance the survival, proliferation, and differentiation of neutrophil progenitors.[9] In addition, the cytokine acts to functionally activate the mature cells it helps to produce. Genetic elimination of granulocyte colony-stimulating factor or its receptor in mice reduces neutrophil levels to 25% of normal, the only hormone known to exert this great an impact on granulopoiesis.

Thrombopoietin, the primary regulator of platelet production, is produced in the liver and by marrow stromal cells. Plasma levels of the hormone are normally inversely related to platelet mass and are regulated by the level of senescent platelet uptake, mediated by the hepatocyte Ashwell-Morrell receptor; inflammation, mediated by IL-6; removal of thrombopoietin by circulating platelets; and by transcriptional feedback inhibition of the thrombopoietin gene in marrow stromal cells by platelet granule proteins. Similar to erythropoietin and granulocyte colony-stimulating factor, thrombopoietin stimulates the survival, proliferation, and differentiation of its corresponding lineage, megakaryocytes and their precursors, and primes mature platelets to respond to platelet activation agonists.[10] But unlike the other two cytokines, thrombopoietin also has important, nonredundant effects on the hematopoietic stem cell, which has important implications for leukemogenesis. Genetic elimination of thrombopoietin or its receptor in mice or congenital nonsense or missense mutations in the gene for the thrombopoietin receptor in humans results in platelet levels approximately 10% of normal and a reduction in stem cells, eventuating in aplastic anemia in children by 1 to 2 years of age.

Chemokines and other cytokines also regulate hematopoiesis. The chemokine ligands CXCR2 and CXCL4 affect the survival and self-renewal of hematopoietic stem cells,[11] as does interferon signaling, the effects of which vary with the type of interferon but can play an important role during inflammation.[12] Additional cytokine-receptor systems are essential for one or more aspects of hematopoiesis and mature blood cell function and include IL-7, critical for all types of lymphocyte production; IL-5, the primary regulator of eosinophil production; IL-4, responsible for immunoglobulin class switching in B lymphocytes; IL-15, essential for normal natural killer cell differentiation; and IL-2, a lymphocyte activation cytokine.

Although the effects of these hematopoietic cytokines are clear, a number of lines of evidence suggest that they may exert additional effects outside of blood cell production. For example, both erythropoietin and the leukocyte colony-stimulating factors (GM-CSF and G-CSF) have been found to protect neurons against damage in experimental models of traumatic and ischemic brain injury.[13,14] Although holding much promise, initial clinical trials of erythropoietic stimulating agents in such settings have not yet proven clear efficacy.[15]

The molecular mechanisms by which the hematopoietic growth factors affect blood cell survival, proliferation, and differentiation are becoming increasingly well understood. Binding of cognate ligand to each of the hematopoietic cytokine receptors results in activation of one or more tyrosine kinases, either tethered cytoplasmic kinases of the Janus (JAK) family for the hematopoietic cytokine receptor family or the intrinsic kinase of the cytokines that use the receptor tyrosine kinase class of receptors (stem cell factor, Flt3 ligand, and macrophage colony-stimulating factor). After activation, these kinases phosphorylate tyrosine residues within the cytoplasmic domains of each receptor, providing docking sites for cytoplasmic signaling intermediates possessing Src homology (SH)2 domains. Among the best characterized SH2 domain-containing proteins that bind to hematopoietic receptors are nascent transcription factors, such as the signal transducers and activators of transcription (STAT) proteins; adapter proteins, including Grb2, Gab1, tensin2, and SHC; phosphatases, for example, SHP1 and SHP2; and the regulatory subunit (p85) of phosphoinositol-3-kinase (PI3K). When bound to one or more of the newly induced phosphotyrosine residues of the cytokine receptor or receptor tyrosine kinase, these secondary molecules are phosphorylated, either by JAK or other kinases, making them competent to bind additional molecules (e.g., the adapters that ultimately activate Ras, and p85 PI3K that binds its kinase [p110] subunit) or are activated as transcription factors (e.g., STATs). The downstream effector molecules then activated include a number of kinases, transporter molecules, and transcription factors, ultimately leading to hematopoietic cell survival, proliferation, and differentiation.

CLINICAL USES OF HEMATOPOIETIC CELLS AND GROWTH FACTORS

The clinical development of erythropoietin and related compounds (erythropoietic stimulating agents), granulocyte colony-stimulating factor, and thrombopoietin receptor agonists represent some of the very best examples of harnessing recombinant DNA technology for therapeutic benefit. Patients with renal failure, widespread inflammation, or bone marrow replacement and those undergoing chemotherapy for cancer all experience variable degrees of anemia that is often very debilitating. Administration of erythropoietic stimulating agents (ESAs) almost invariably results in a rapid reticulocyte response and correction of the anemia. Most patients undergo an enhanced sense of well-being as the blood hemoglobin concentration rises to 10 g/dL. Clinical trials have demonstrated the efficacy of these agents in patients with renal failure and with cancer, although recent analyses call into question the safety of these agents in some settings.[A1] For example, patients receiving higher levels of the drug for anemia secondary to kidney failure progressed to requiring dialysis more frequently and experienced increased cardiovascular events, such as myocardial infarction and stroke, than patients on low levels of the hormone sufficient to maintain their blood Hgb at 10 g/dL or lower. The only patients who regularly demonstrate a poor response are individuals with severe inflammation. Overall, erythropoietic stimulating agents are safe and effective drugs for patients with anemia caused by a wide range of conditions, but their use and dose must be carefully considered.

Many patients undergoing cytotoxic therapy for cancer experience severe neutropenia and are thus at substantial risk for life-threatening infection. Clinical trials of recombinant granulocyte colony-stimulating factor in patients undergoing aggressive chemotherapy for leukemia and solid tumors resulted in the Food and Drug Administration (FDA) approval of the drug for use in patients undergoing chemotherapy of intensity sufficient to produce severe neutropenia (Chapter 153). The use of the drug and its numerous biosimilars

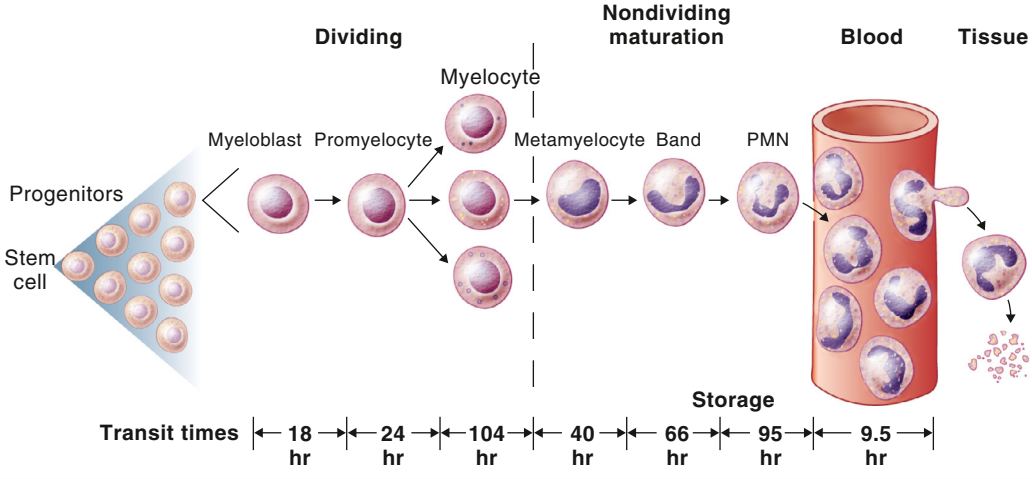

FIGURE 142-2. Neutrophil production system. PMN = polymorphonuclear leukocyte.

is associated with the more rapid return of neutrophils to safe levels if administered soon after the inciting chemotherapy is completed, but not at the nadir of neutrophil production, and results in lower risk of severe infections. However, the use of granulocyte colony-stimulating factor has not enhanced survival in patients with any tumor type. And similar to the use of erythropoietin in patients with cancer, the administration of granulocyte colony-stimulating factor to some patients receiving cytotoxic chemotherapy for cancer (e.g., breast cancer) has been associated with a statistically significant increase in cancer recurrence, although this finding is controversial.

Thrombopoietin was cloned and characterized in 1994 and was quickly advanced to clinical trials following the model of granulocyte colony-stimulating factor use in patients undergoing cancer chemotherapy. Initial results with the intact hormone and a truncated version that included only the receptor-binding domain were mixed, and use of the truncated form of the drug, administration to healthy volunteer donors to improve platelet apheresis yields, resulted in a significant number of subjects developing antidrug antibodies that cross-reacted with their native thrombopoietin, resulting in severe thrombocytopenia. This experience caused manufacturers of thrombopoietin to cease clinical trials. Instead, several small molecules that bind to and stimulate the thrombopoietin receptor and stimulate thrombopoiesis have been developed for clinical use.[A2,A3] Two such drugs approved by the FDA for use in patients with severe immune thrombocytopenia include a peptibody that contains four copies of a thrombopoietin receptor–binding peptide grafted onto an immunoglobulin scaffold and a small organic molecule that is orally bioavailable and binds to a spatially distinct site on the thrombopoietin receptor. The use of each drug results in a high rate of platelet responses into the normal range in patients with severe immune thrombocytopenia (Chapter 158) who were refractory to conventional therapies. It was initially thought that although thrombopoietin receptor agonists would stimulate platelet production in excess of immune destruction, they would not alter the pathophysiology of immune thrombocytopenia purpura (ITP), and hence be required for very long periods of time. However, a growing number of patients who have extremely refractory ITP have been reported no longer to require a thrombopoietin receptor agonist after a variable number of months of therapy, thereby suggesting that these drugs might be able to alter the immune response in such patients. In addition to the treatment of patients with ITP, thrombopoietin receptor agonists have been approved for use in patients with thrombocytopenia secondary to interferon treatment of hepatitis C viral infection and for patients with aplastic anemia. Additional clinical indications are being tested.

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143 THE PERIPHERAL BLOOD SMEAR

BARBARA J. BAIN

With the development of sophisticated automated instruments to count and characterize blood cells, Romanowsky (Wright-Giemsa or May-Grünwald-Giemsa)–stained peripheral blood smears are now performed on only a minority of blood specimens received in a hematology laboratory. Nevertheless, the blood smear remains important for a number of reasons: it can (1) verify the result of an automated instrument, (2) provide an immediate specific diagnosis, or (3) indicate a narrow range of diagnostic possibilities, permitting focused rather than indiscriminate investigation.[1-3] A blood film can provide a rapid diagnosis in cases in which speed is crucial, such as in acute promyelocytic leukemia, thrombotic thrombocytopenic purpura, Burkitt lymphoma, and certain infections.[4] It also can aid in the rapid diagnosis of malaria (Chapter 316)[5] and babesiosis (Chapter 324).[6] Sometimes a smear reveals an error in an automated blood count[7] or provides unexpected information that is of value in patient management.[8]

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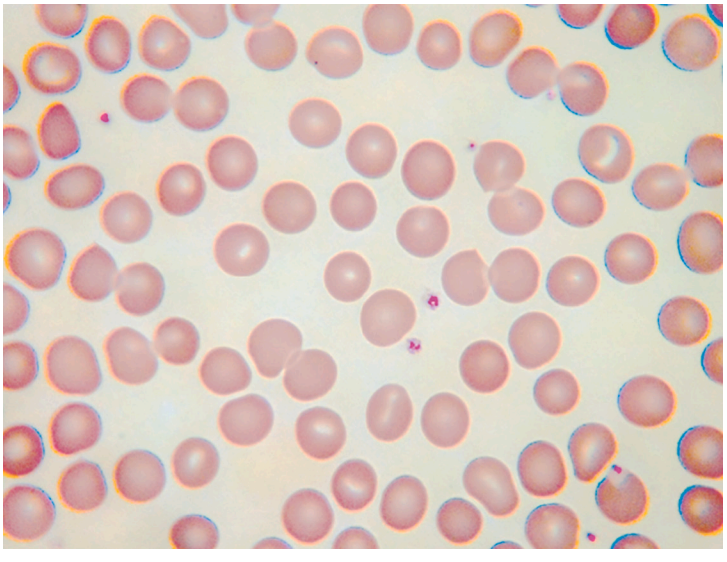

FIGURE 143-1. Normal peripheral blood smear. These normal red cells are described as *normocytic* (i.e., of normal size) and *normochromic* (i.e., their staining characteristics are normal). Normal erythrocytes are biconcave discs, causing them to have an area of central pallor that does not exceed one third the diameter of the cell. There are also scattered normal platelets (×1000).

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is associated with the more rapid return of neutrophils to safe levels if administered soon after the inciting chemotherapy is completed, but not at the nadir of neutrophil production, and results in lower risk of severe infections. However, the use of granulocyte colony-stimulating factor has not enhanced survival in patients with any tumor type. And similar to the use of erythropoietin in patients with cancer, the administration of granulocyte colony-stimulating factor to some patients receiving cytotoxic chemotherapy for cancer (e.g., breast cancer) has been associated with a statistically significant increase in cancer recurrence, although this finding is controversial.

Thrombopoietin was cloned and characterized in 1994 and was quickly advanced to clinical trials following the model of granulocyte colony-stimulating factor use in patients undergoing cancer chemotherapy. Initial results with the intact hormone and a truncated version that included only the receptor-binding domain were mixed, and use of the truncated form of the drug, administration to healthy volunteer donors to improve platelet apheresis yields, resulted in a significant number of subjects developing antidrug antibodies that cross-reacted with their native thrombopoietin, resulting in severe thrombocytopenia. This experience caused manufacturers of thrombopoietin to cease clinical trials. Instead, several small molecules that bind to and stimulate the thrombopoietin receptor and stimulate thrombopoiesis have been developed for clinical use.[A2,A3] Two such drugs approved by the FDA for use in patients with severe immune thrombocytopenia include a peptibody that contains four copies of a thrombopoietin receptor–binding peptide grafted onto an immunoglobulin scaffold and a small organic molecule that is orally bioavailable and binds to a spatially distinct site on the thrombopoietin receptor. The use of each drug results in a high rate of platelet responses into the normal range in patients with severe immune thrombocytopenia (Chapter 158) who were refractory to conventional therapies. It was initially thought that although thrombopoietin receptor agonists would stimulate platelet production in excess of immune destruction, they would not alter the pathophysiology of immune thrombocytopenia purpura (ITP), and hence be required for very long periods of time. However, a growing number of patients who have extremely refractory ITP have been reported no longer to require a thrombopoietin receptor agonist after a variable number of months of therapy, thereby suggesting that these drugs might be able to alter the immune response in such patients. In addition to the treatment of patients with ITP, thrombopoietin receptor agonists have been approved for use in patients with thrombocytopenia secondary to interferon treatment of hepatitis C viral infection and for patients with aplastic anemia. Additional clinical indications are being tested.

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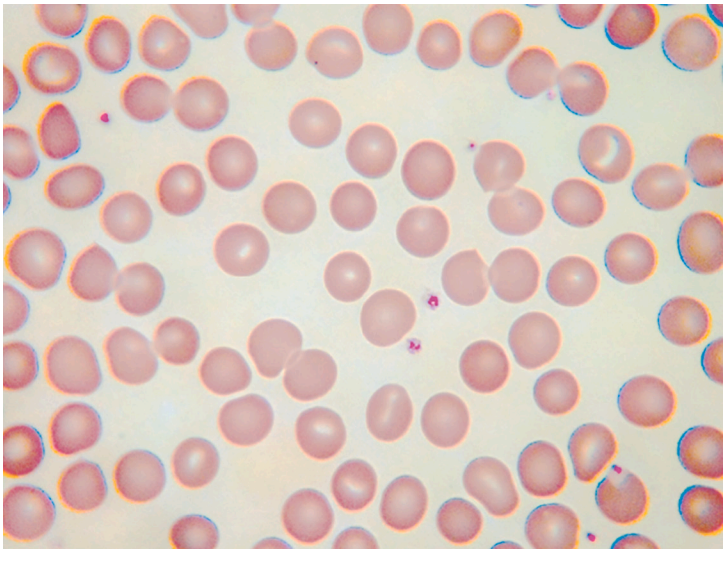

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ABSTRACT

Despite major advances in other diagnostic methods, the blood smear remains very useful in hematologic diagnosis. Sometimes it is critical, either because it yields a diagnosis very quickly or because it provides information that is not available in any other way. Blood smear examination permits other tests to be targeted to confirming a diagnosis or exploring a differential diagnosis.

KEYWORDS

blood smear
diagnosis
anemia
hemolysis
thrombocytopenia
thrombocytosis
leukocytosis
leukopenia
leukemia
lymphoma

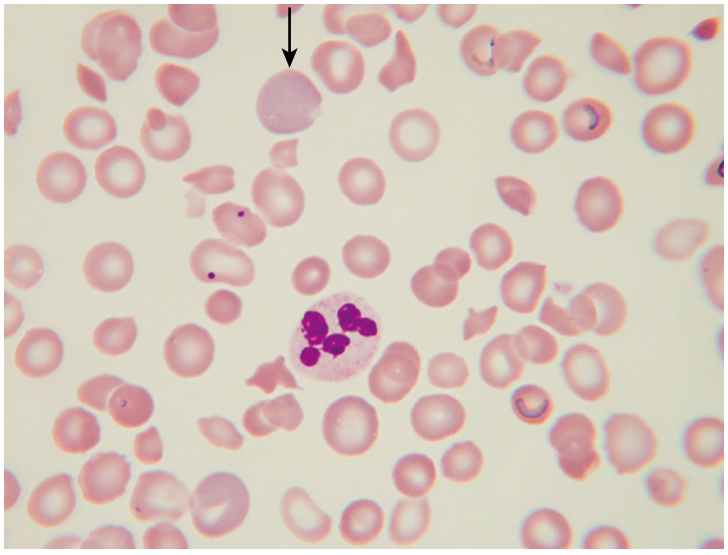

FIGURE 143-2. Smear showing multiple abnormalities. There is *anisocytosis*, defined as an increased variation in cell size; *poikilocytosis*, defined as an increased variation in cell shape; and *polychromasia*, defined as the presence of erythrocytes with a blue tinge to their cytoplasm—indicating a young cell recently released from the bone marrow in which the polychromasia is due to the presence of RNA. *Polychromatic cells* are erythrocytes with a blue tinge; because polychromatic cells are larger than normal mature erythrocytes, they are known as *polychromatic macrocytes* (*arrow*). The film also shows two cells containing bluish purple *Howell-Jolly bodies;* these inclusions are nuclear remnants (×1000).

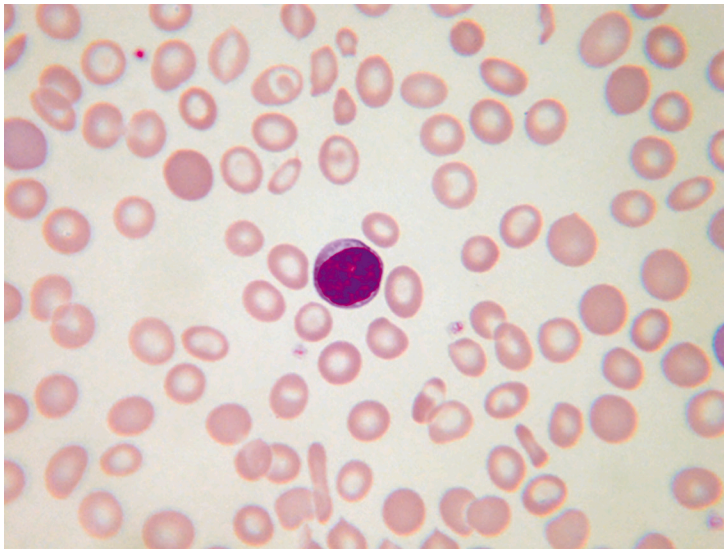

FIGURE 143-3. Microcytic red cells from a case of thalassemia minor (β-thalassemia heterozygosity). In a blood smear, a *microcyte* can be defined as a cell with a diameter less than that of the nucleus of a normal small lymphocyte (generally 7 to 8 μm). There are also some cells showing *hypochromia*, an area of central pallor that is larger than one third of the diameter of the red cell. In addition, there are two *target cells*, with a hemoglobinized area in the center of the area of pallor (×1000).

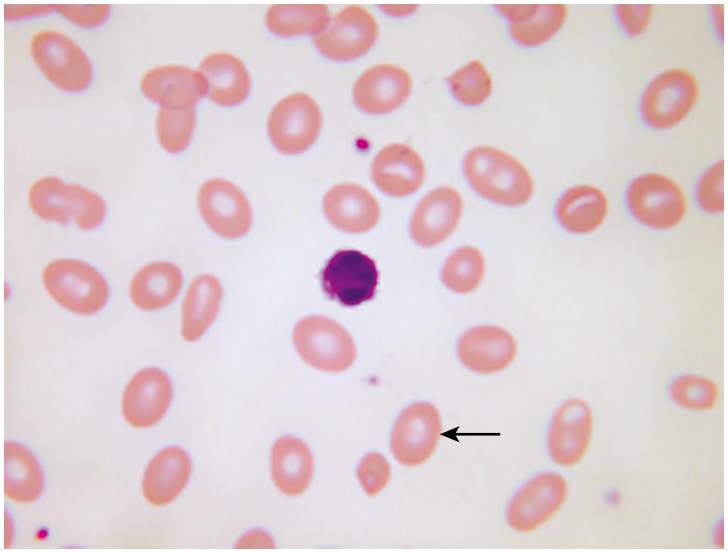

FIGURE 143-4. Macrocytic anemia. A *macrocyte* is recognized on a blood film as a cell with a diameter that is considerably greater than that of the nucleus of a small lymphocyte. In addition, this smear shows *oval macrocytes* (also known as *macro-ovalocytes*), defined as cells that are larger than normal and oval in shape (*arrow*). They are of considerable diagnostic importance, being characteristic of megaloblastic anemia and Southeast Asian ovalocytosis; they can also be seen in dyserythropoiesis (×1000).

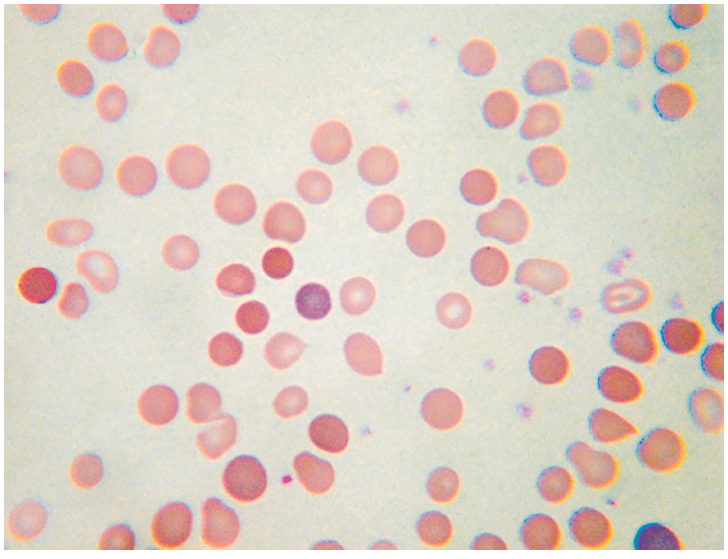

FIGURE 143-5. Hereditary spherocytosis. A *spherocyte* is a red cell that lacks central pallor because of its spherical shape. In hereditary spherocytosis, there are usually cells in which the central pallor is reduced rather than absent, and they are intermediate in shape between a spherocyte and a *discocyte*, which is an erythrocyte with the normal shape of a biconcave disc (×1000).

possibility of the presence of blast cells, reactive or other atypical lymphocytes, granulocyte precursors, or nucleated red blood cells. Some instruments can enumerate nucleated red blood cells. Instruments using a cytochemical reaction for peroxidase to help identify neutrophils, eosinophils, and monocytes may flag the appearance of large, unstained (i.e., peroxidase-negative) cells; such cells may indicate a harmless inherited peroxidase deficiency, but sometimes such cells are lymphoma cells, reactive lymphocytes, or leukemic blast cells. Instruments often flag the possibility of an erroneous platelet count, such as when there is an overlap in size between platelets and red cells or when light-scattering characteristics suggest the presence of platelet aggregates (a potential cause of pseudothrombocytopenia). A reported increase in basophil count should generally also be regarded as a flag because it often represents a pseudobasophilia, resulting from the presence of leukemia or lymphoma cells. Some instruments alert the instrument operator to the possible presence of malaria parasites.

International consensus guidelines indicate which automated instrument results require blood smear review. Whether a review is needed is determined in part by whether that specimen is the first one obtained from that patient and whether there has been a significant change from a previously validated result (referred to as a *delta check*). Laboratory computers can be programmed to indicate when a result meets the criteria for smear review.

Automated red cell measurements can, to some extent, replace examination of the blood film.[11] An increased red cell distribution width indicates the presence of anisocytosis. A decreased mean cell volume is usually a reliable indicator of microcytosis. A reduction in the mean cell hemoglobin concentration indicates hypochromia (for most instruments, however, this measurement is less sensitive than the human eye in the detection of hypochromia). An increased mean cell volume usually indicates macrocytosis, but examination of a smear is necessary both to confirm that the result is not an artifact and to elucidate the cause. Some instruments can measure the hemoglobin concentration in individual cells and thus flag the presence of hyperdense cells; however, a blood film is still necessary to distinguish spherocytes from irregularly contracted

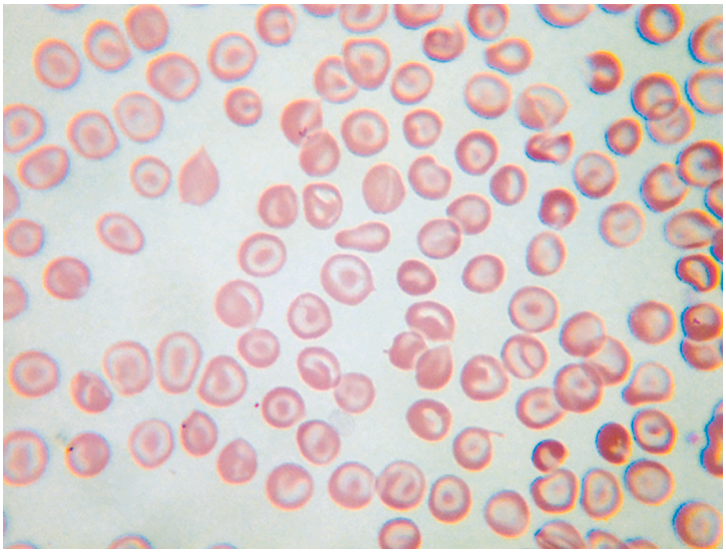

FIGURE 143-6. Target cells. A *target cell* is an erythrocyte with a hemoglobinized area in the middle of the normal area of central pallor (×1000).

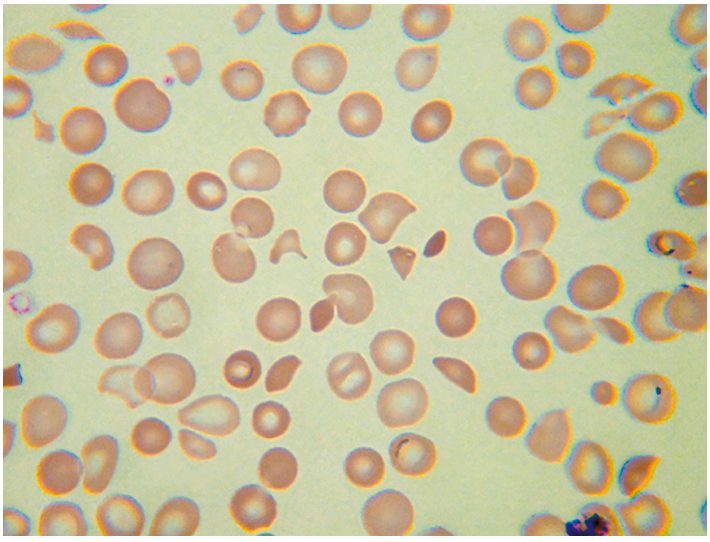

FIGURE 143-8. Red cell fragmentation. *Red cell fragments* or *schistocytes* are defined as fragments of erythrocytes. In addition to small angular fragments, there may be *microspherocytes*, cells of reduced size and spherical in form (also known as *spheroschistocytes*), and *keratocytes*, cells with two or four hornlike projections. Keratocytes can result from removal of a Heinz body, as well as from red cell fragmentation. Some schistocytes are referred to as *helmet cells* because of their typical shape. Schistocytes are seen in microangiopathic hemolytic anemias and in mechanical hemolysis (×1000).

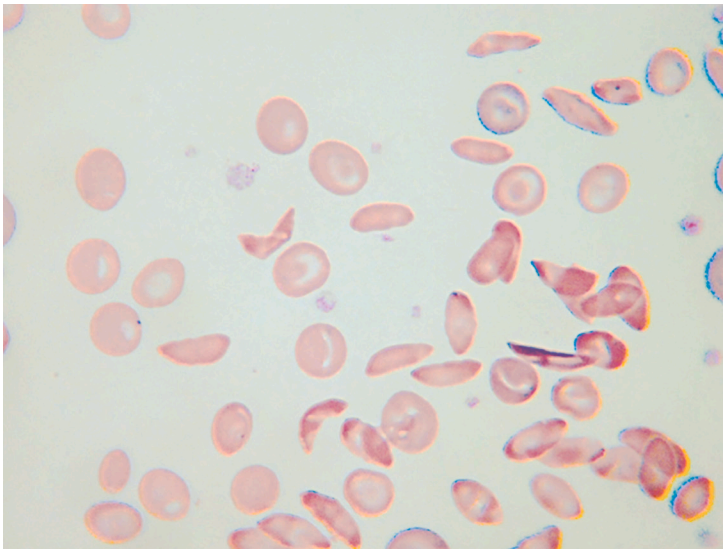

FIGURE 143-7. Sickle cells. A *sickle cell* is a cell with a sickle or crescent shape resulting from the polymerization of hemoglobin S. These cells are seen in sickle cell anemia (homozygosity for hemoglobin S) as well as in compound heterozygous states such as sickle cell/hemoglobin C disease and sickle cell/β-thalassemia, which also lead to sickle cell disease. This smear also shows target cells and boat-shaped cells with a lesser degree of polymerization of hemoglobin S than in a classic sickle cell (×1000).

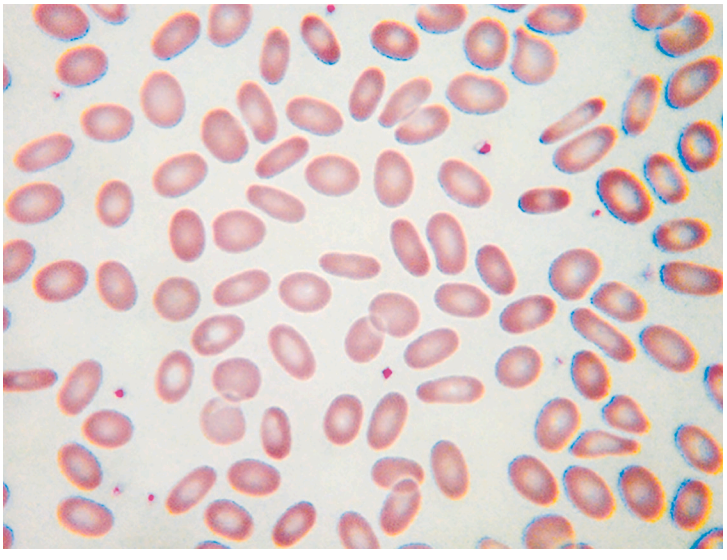

FIGURE 143-9. Hereditary elliptocytosis. An *elliptocyte* is an elliptical red cell. When seen in the numbers present in this smear, they are indicative of hereditary elliptocytosis; smaller numbers are seen in other conditions such as iron deficiency anemia, in which they are sometimes referred to as *pencil cells* (×1000).

cells, sickle cells, and other cells that have an increased hemoglobin concentration. Most instruments produce a histogram of the size distribution of red cells, and some do the same for the distribution of hemoglobin concentration; either of these graphic representations may show dimorphic red cells (i.e., two populations of cells).

THE BLOOD SMEAR IN THE DIFFERENTIAL DIAGNOSIS OF ANEMIA

MICROCYTIC ANEMIAS

In microcytic anemias (Chapter 145), the automated count is of considerable importance and may permit a distinction between iron deficiency and thalassemia heterozygosity. In iron deficiency, there is initially a normocytic normochromic anemia; only when the deficiency becomes more severe is there microcytosis. Conversely, in β-thalassemia heterozygosity, there is usually a normal or near-normal hemoglobin concentration, but the red blood cell count is increased, and there is marked microcytosis (low mean cell volume) together with a parallel reduction in mean cell hemoglobin. The blood film provides supplementary information that can favor one diagnosis or the other. Iron deficiency is more likely to be associated with hypochromia and elliptocytes ("pencil cells"), whereas in β-thalassemia heterozygosity, there is microcytosis, hypochromia is less marked, and there are more likely to be target cells and basophilic stippling. Individuals with α-thalassemia involving the deletion of two α genes (−α/−α) or (− −/α α) have red cell indices similar to those of β-thalassemia heterozygosity; in this case, the blood film usually does not provide any additional diagnostically useful information, although individuals with nondeletional α-thalassemia due to hemoglobin Constant Spring have prominent basophilic stippling. When there is deletion of a single α gene, the blood count is either less abnormal or normal, and the blood smear does not provide any extra diagnostically useful information. The blood smear is, however, a useful supplement to the blood count in suggesting a diagnosis of hemoglobin H disease (Chapter 148). The blood count shows anemia, marked microcytosis (low mean cell

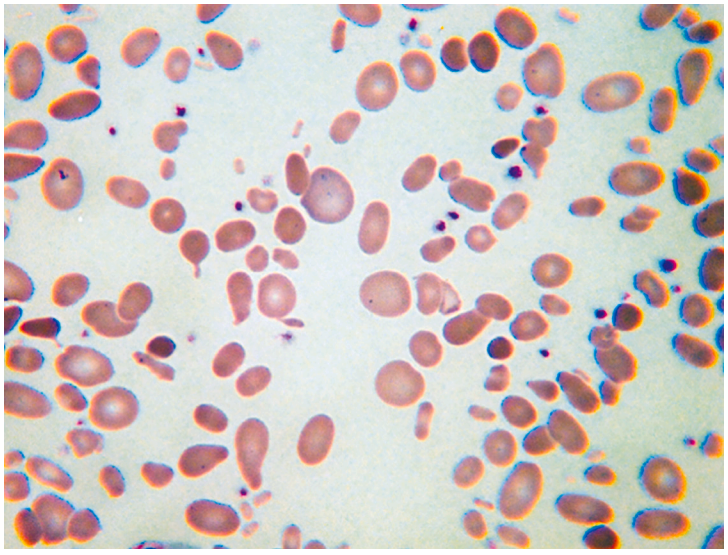

FIGURE 143-10. Hereditary pyropoikilocytosis. This smear shows striking poikilocytosis, including elliptocytes, microspherocytes and other fragments, as well as teardrop cells. Hereditary pyropoikilocytosis is a congenital condition, similar to hereditary elliptocytosis, which usually results from the inheritance of two different mutated genes, one from each parent, and is characterized by a severe hemolytic anemia (×1000).

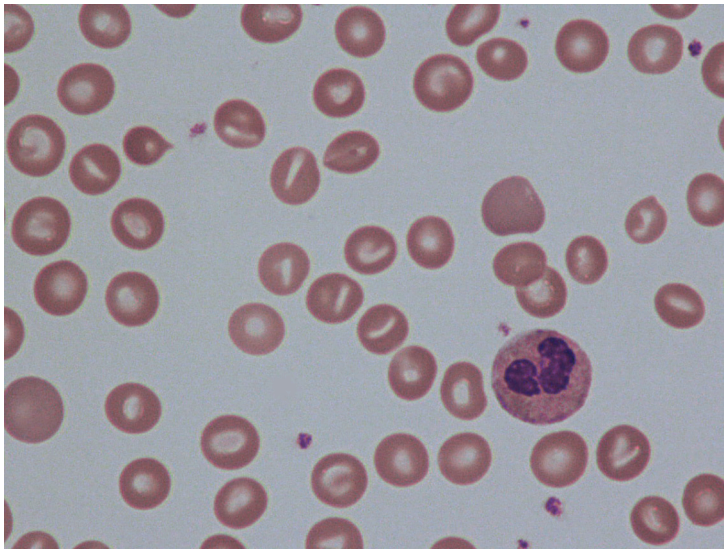

FIGURE 143-12. Stomatocytosis. A *stomatocyte* is a cell that appears to have a central mouth-shaped or slitlike stoma. Among the less common causes are hereditary stomatocytosis and phytosterolemia (also known as sitosterolemia). Alcohol and hydroxycarbamide (hydroxyurea) therapy are more common causes (×1000).

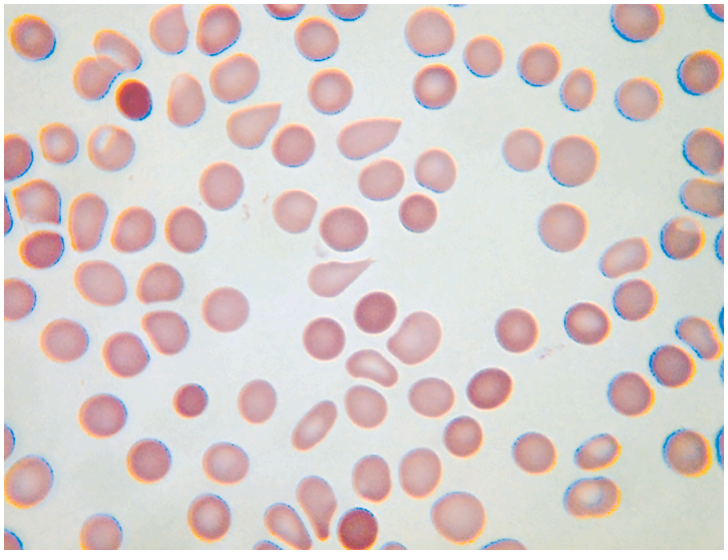

FIGURE 143-11. Teardrop poikilocytes. *Teardrop poikilocytes*, or *dacrocytes*, are teardrop-shaped red cells; they are characteristic of primary myelofibrosis but are also seen in myelofibrosis following other myeloproliferative neoplasms or secondary to bone marrow infiltration and in megaloblastic anemia (×1000).

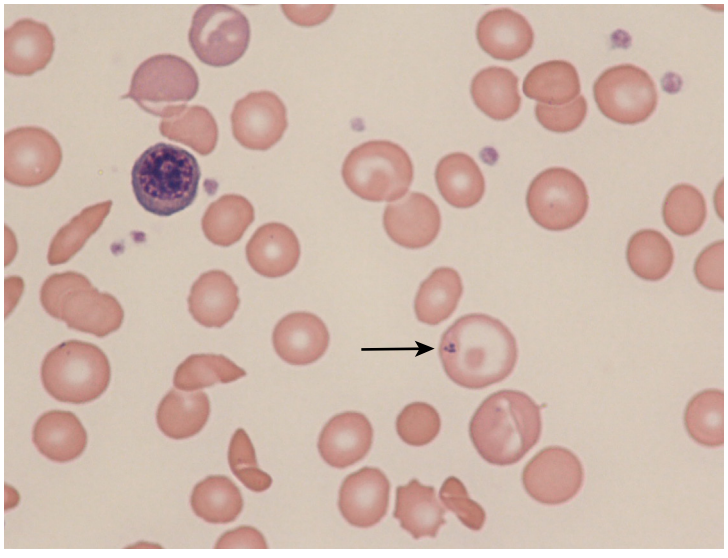

FIGURE 143-13. A cluster of Pappenheimer bodies within a target cell in sickle cell anemia. A *Pappenheimer body* is an iron-containing red cell inclusion. It is smaller and more angular than a Howell-Jolly body and stains navy blue rather than purple. Pappenheimer bodies are seen following splenectomy, in other hyposplenic states, and in sideroblastic anemias. The smear also shows boat-shaped cells, a nucleated red blood cell, polychromatic macrocytes, and a polychromatic stomatocyte (×1000). A Perls stain confirms the iron content in a Pappenheimer body.

volume and mean cell hemoglobin), and usually a reduction in the mean cell hemoglobin concentration. The smear usually shows marked poikilocytosis in addition to microcytosis, and there may be polychromasia, correlating with an elevated reticulocyte count. Iron deficiency anemia should also be distinguished from anemia of chronic disease. The blood counts may be quite similar in the two conditions, but microcytosis is less common in anemia of chronic disease, and the smear often shows features of inflammation, such as increased rouleaux formation, background staining (as a result of increased plasma proteins), and sometimes neutrophilia. Other rare microcytic anemias that must be distinguished from iron deficiency include congenital sideroblastic anemia (Chapter 145) and lead poisoning. In congenital sideroblastic anemia, the film is dimorphic, with one population of hypochromic microcytes and another of normochromic normocytic cells. In lead poisoning, the presence of basophilic stippling and polychromasia in a patient with microcytosis can suggest the diagnosis. Sometimes a blood film provides the first clue that apparent microcytosis is actually the result of red cell fragmentation.

MACROCYTIC ANEMIAS

A blood film can be important in distinguishing true macrocytosis from factitious macrocytosis as a result of the presence of red cell agglutinates (see Fig. 143-16). Diagnostic features that can suggest the cause of macrocytosis are shown in Table 143-2.

A smear is particularly important in evaluating the possibility of a megaloblastic anemia (Chapter 150) (Figs. 143-4 and 143-21). Sometimes assays of vitamin B_{12} and folate are normal despite a deficiency, and only the blood film features suggest the true diagnosis and indicate the need for further investigation.

NORMOCYTIC NORMOCHROMIC ANEMIA

A blood smear is only occasionally useful in determining the cause of a normocytic normochromic anemia. Signs of inflammation may be present in

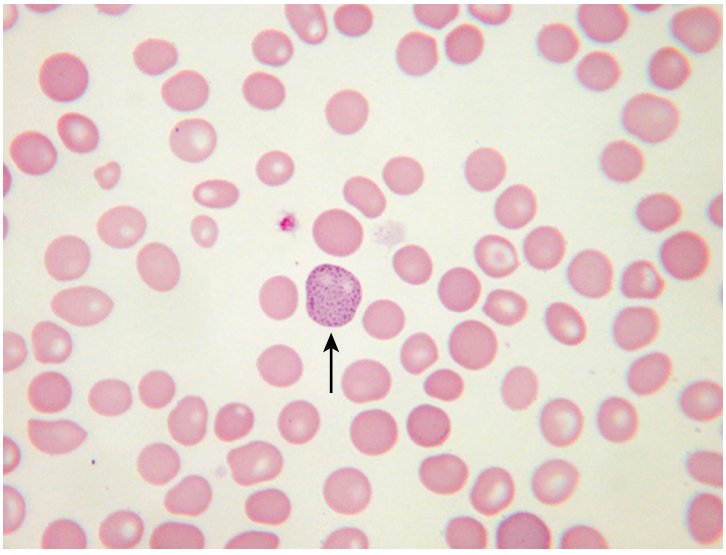

FIGURE 143-14. Basophilic stippling. *Basophilic stippling*, also known as punctate basophilia, means that there are fine (as in this case) or coarse purplish blue dots dispersed through the red cell (*arrow*). They are a very nonspecific feature occurring in thalassemia trait, lead poisoning, pyrimidine 5′-nucleotidase deficiency, and dyserythropoiesis in general (×1000).

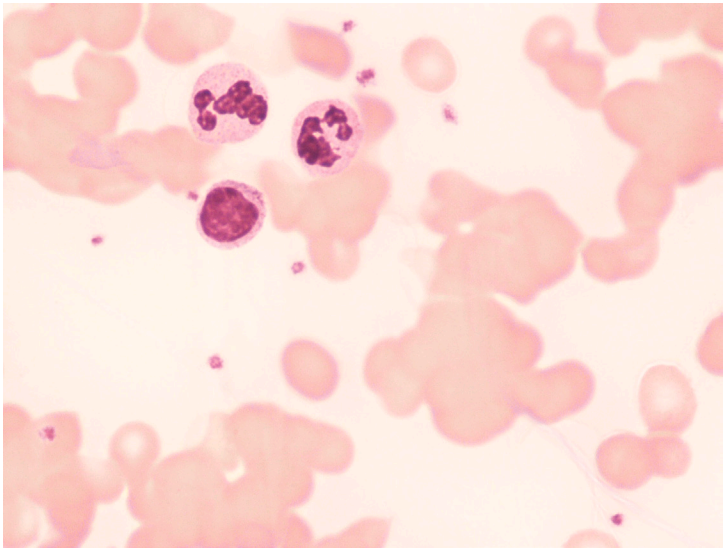

FIGURE 143-16. Red cell agglutination. *Red cell agglutinates* are irregular aggregates of red cells, often seen in *Mycoplasma pneumoniae* infection; other infections, such as infectious mononucleosis; and in chronic cold hemagglutinin disease (×1000).

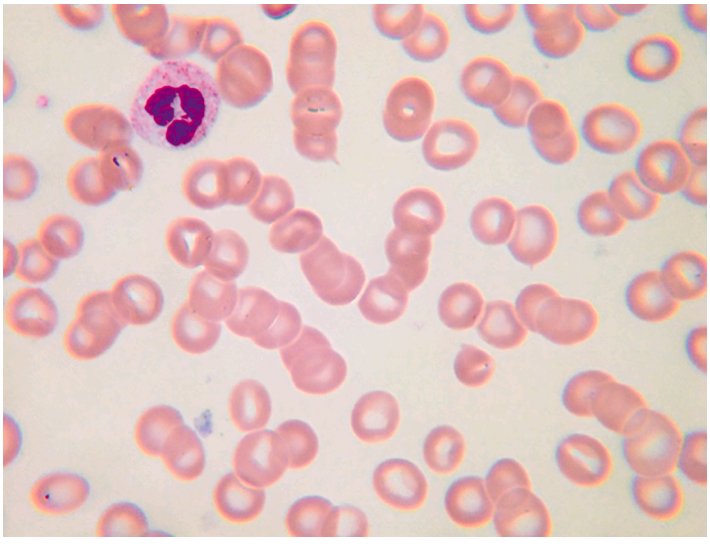

FIGURE 143-15. Rouleaux formation. *Rouleaux* are stacks of red cells, often compared to stacks of coins. Rouleaux formation results from an increase of high-molecular-weight globulins in the plasma, either as a reactive change or as a result of secretion of a paraprotein in a plasma cell neoplasm (×1000).

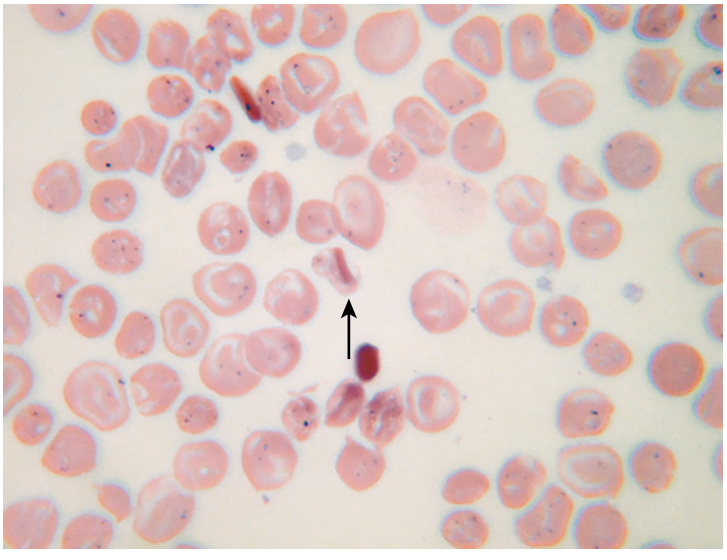

FIGURE 143-17. Homozygous hemoglobin C or hemoglobin C disease. Three *hemoglobin C crystals* are present, one indicated by an *arrow*. Hemoglobin C crystals are usually six-sided, with a long axis having parallel edges. In addition to hemoglobin C disease, these crystals can also be seen in sickle cell/hemoglobin C compound heterozygosity and in hemoglobin C/β^0 thalassemia (×1000).

anemia of chronic disease. Rouleaux formation and increased background staining can also indicate multiple myeloma. Polychromasia suggests the possibility of young red cells as a result of recent blood loss or hemolysis. Small numbers of acanthocytes may indicate hypothyroidism or anorexia nervosa. Dysplastic features, such as hypogranular or pseudo-Pelger neutrophils, suggest a myelodysplastic syndrome.

HEMOLYTIC ANEMIAS

The possibility of hemolysis is suggested by the presence of polychromasia and macrocytosis. Specific causes of hemolysis are suggested by the presence of various poikilocytes, as shown in Table 143-3.

The distinction between spherocytes and irregularly contracted cells is important; both are dense cells with absent central pallor, but the differential diagnosis is quite different. Recognition of the features of oxidant damage is important in diagnosing glucose-6-phosphate dehydrogenase (G6PD) deficiency because sometimes an assay for G6PD performed during an acute hemolytic episode is normal (Chapter 147). In addition to irregularly contracted cells, there may be ghost cells, hemi-ghost cells ("blister cells"), and even Heinz bodies protruding from the red cells and confirmed on a Heinz body preparation. The observation of these features is an indication to repeat the assay when the acute hemolytic episode is over.

ASSESSMENT OF THROMBOCYTOPENIA, THROMBOCYTOSIS, AND PLATELET MORPHOLOGY

A blood smear is essential to validate the count whenever an automated count shows thrombocytopenia (e.g., a count $<60 \times 10^9$/L) (Chapter 158). This should be done quickly before patient management is altered, such as by postponing surgery or initiating further diagnostic workup. A platelet transfusion should never be given for an unexpected thrombocytopenia without microscopic confirmation of the count. A factitiously low platelet count is often the result of in vitro platelet aggregation (Chapter 157) and is occasionally the result of platelet satellitism (platelets surrounding neutrophils, generally seen in samples anticoagulated with EDTA), and possibly also with platelet phagocytosis. To detect aggregates reliably, the edges and the tail of the smear

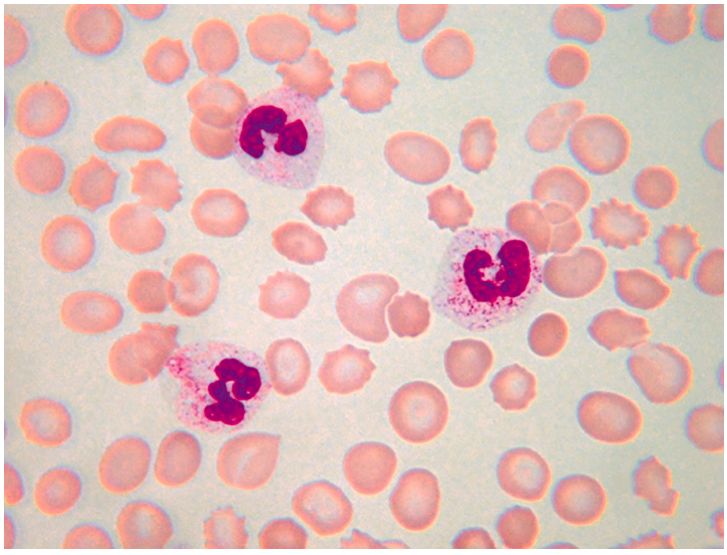

FIGURE 143-18. Toxic granulation. *Toxic granulation* refers to heavy staining of azurophilic granules of neutrophils. When accompanied by neutrophil vacuolation, it is often indicative of infection, but toxic granulation can also result from inflammation, tissue damage, administration of granulocyte colony-stimulating factor, and normal pregnancy. Rarely it results from chronic neutrophilic leukemia or a leukemoid reaction to multiple myeloma (×1000).

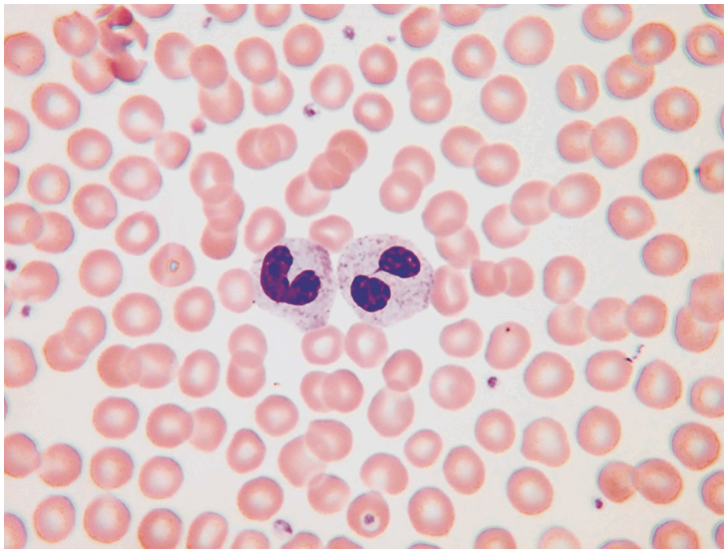

FIGURE 143-20. Pelger-Huët anomaly. A *Pelger-Huët anomaly* is a cytologic abnormality of neutrophils in which there is hypolobulation of nuclei and increased chromatin clumping. Nuclei may have a shape resembling a peanut or a pince-nez, as in the example shown. The Pelger-Huët anomaly is inherited, but similar pseudo-Pelger neutrophils are seen in myelodysplastic syndromes, in which the neutrophils may also be hypogranular (×1000). They can also be seen as an acquired reversible phenomenon in response to specific drugs, including tacrolimus and mycophenolate mofetil.

FIGURE 143-19. Döhle body. A *Döhle body* (*arrow*) is a pale blue-gray amorphous inclusion near the cell membrane of a neutrophil. Döhle bodies can result from infection and inflammation. Similar but different inclusions (larger and more angular) are seen in the May-Hegglin anomaly (MYH9-related disorder) (×1000).

TABLE 143-1 CLINICAL FEATURES SUGGESTING THE NEED FOR A BLOOD SMEAR

CLINICAL FEATURE	REASON TO PERFORM A BLOOD SMEAR
Lymphadenopathy or splenomegaly	May be indicative of infectious mononucleosis or another reactive condition or of leukemia or lymphoma
Clinically evident anemia	Helps in the differential diagnosis
Bruising or bleeding tendency, including unexplained retinal hemorrhages	May confirm thrombocytopenia or show morphologically abnormal platelets (which may have defective function); sometimes shows acute leukemia or other condition causing bone marrow failure
Acute kidney injury	Hemolytic-uremic syndrome and thrombotic thrombocytopenic purpura should be confirmed or excluded
Jaundice and hypertension in a pregnant woman	May show schistocytes, supporting a diagnosis of HELLP syndrome
Bone pain	May indicate multiple myeloma, bone marrow infiltration, or sickle cell disease
Unexplained chest or abdominal pain or acute splenic enlargement in a child	Possible sickle cell disease
Unexplained hyperbilirubinemia	Assessment of possible hemolysis

HELLP = hemolysis, elevated liver enzymes, low platelets.

should be examined. The presence of fibrin strands also suggests the activation of coagulation and an erroneous platelet count.

If a low platelet count is confirmed, the film may give clues to the cause (Chapter 158).[12] Giant platelets (Figs. 143-22 and 143-23) occur in a number of inherited thrombocytopenias, including Bernard-Soulier syndrome and MYH9-related disorders (the May-Hegglin anomaly and related conditions).[13] Small platelets are less common but are a feature of Wiskott-Aldrich syndrome. Agranular platelets occur in gray platelet syndrome, and platelets with a reduced number of larger-than-normal granules are seen in Jacobsen/Paris-Trousseau syndrome. The presence of May-Hegglin inclusions (Döhle-like bodies; see Fig. 143-19) in neutrophils indicates that the cause of the thrombocytopenia is a mutation in *MYH9*. In acquired thrombocytopenias, increased platelet turnover is often accompanied by the presence of large platelets, whereas bone marrow failure is associated with platelets of normal size. It is important to look for red cell fragments to confirm or exclude a diagnosis of thrombotic thrombocytopenic purpura and atypical hemolytic-uremic syndrome in any patient with the apparent recent onset of thrombocytopenia; because platelet transfusions are usually contraindicated in these conditions, the smear should be examined before platelet transfusion is contemplated. Occasionally the smear reveals clinically unsuspected malaria. The smear of any patient with the apparent recent onset of severe thrombocytopenia should be examined carefully for evidence of acute promyelocytic leukemia; the leukemic cells may be infrequent in the circulating blood. Hemorrhagic manifestations and a low platelet count can also be indicative of meningococcal septicemia; in some patients, organisms are seen in the blood smear and the diagnosis is confirmed; in other patients, only marked toxic changes in neutrophils are detected.

Thrombocytosis should also be confirmed on a smear. Factitiously elevated counts may be the result of the presence of red cell fragments (in

TABLE 143-2 USEFUL FEATURES FOR DETERMINING THE CAUSE OF MACROCYTIC ANEMIA

CAUSE	SMEAR FEATURES
Megaloblastic anemia (vitamin B_{12} or folic acid deficiency)	Oval macrocytes, teardrop poikilocytes, hypersegmented neutrophils; when severe, marked anisocytosis and poikilocytosis, which may include red cell fragments
Ethanol excess	Target cells and stomatocytes; anisocytosis and poikilocytosis less than in megaloblastic anemia
Liver disease	Target cells, stomatocytes
Myelodysplastic syndromes, including sideroblastic anemias	Other dysplastic features such as hypogranular and hypolobulated neutrophils; if erythropoiesis is sideroblastic, a population of hypochromic microcytic cells and Pappenheimer bodies
Chronic hemolytic anemia	Polychromasia; characteristic poikilocytes sometimes present (e.g., irregularly contracted cells if there is an unstable hemoglobin)

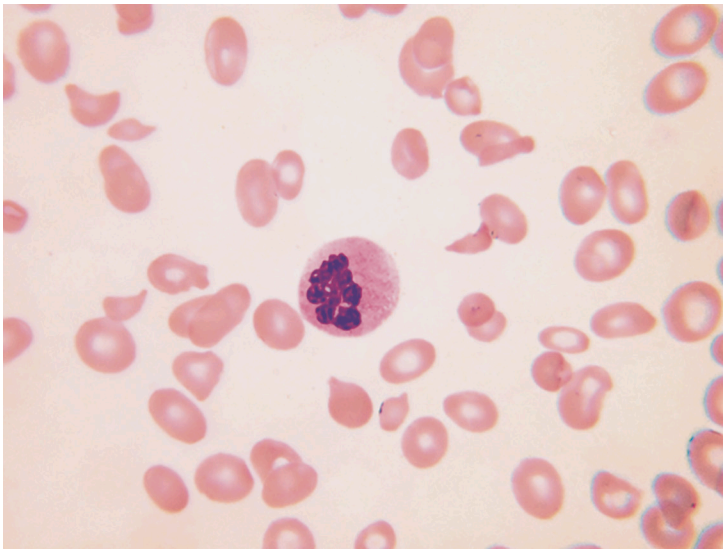

FIGURE 143-21. Hypersegmented neutrophils. A *hypersegmented neutrophil* is one in which the nucleus has more than five lobes, as in this example from an individual with megaloblastic anemia. Neutrophil hypersegmentation is also said to be present if there are increased numbers of neutrophils with five lobes or if the median lobe count is increased. Hypersegmented neutrophils should be distinguished from macropolycytes, in which an increased lobe count results from a doubled content of DNA (×1000).

microangiopathic or mechanical hemolytic anemia, burns, or accidental in vitro heating of the blood sample), white cell fragments (in acute leukemia and, less often, in lymphoma), cryoglobulin precipitates, or microorganisms (particularly *Candida* species). If the count is confirmed, the blood smear may be useful to indicate a likely cause (e.g., features of hyposplenism or the presence of basophilia in a myeloproliferative disorder).

It is sometimes necessary to examine a smear to confirm that an apparently normal platelet count is valid. This should always be done in patients with acute leukemia and an elevated white cell count; the presence of white cell fragments of a similar size to platelets can suggest that the platelet count is at a safe level when it is in fact dangerously low. Counting the ratio of platelets to other particles of similar size permits the count to be corrected. Any unexpectedly normal count should be confirmed; for example, the sudden rise of the automated platelet count in a patient being treated for a hematologic neoplasm may be the result of fungi that have colonized an indwelling intravenous line and are being shed into the blood stream.

LEUKOCYTOSIS AND LEUKOPENIA

The finding of leukocytosis is not necessarily an indication for a blood smear (Chapter 153). For example, this finding would be expected in a patient with infection or following surgery or trauma, in which case smear confirmation is not required. However, unexpected leukocytosis requires examination of a smear.

TABLE 143-3 BLOOD SMEAR FEATURES SUGGESTING A SPECIFIC CAUSE OF INHERITED OR ACQUIRED HEMOLYTIC ANEMIA

BLOOD SMEAR FEATURES	CONDITIONS SUGGESTED
Spherocytes	Hereditary spherocytosis, autoimmune hemolytic anemia, alloimmune hemolytic anemia (e.g., hemolytic disease of the newborn, delayed hemolytic transfusion reaction), drug-induced immune hemolytic anemia, *Clostridium perfringens* sepsis
Elliptocytes	Hereditary elliptocytosis
Oval macrocytes plus stomatocytes	Southeast Asian ovalocytosis
Irregularly contracted cells	Glucose-6-phosphate dehydrogenase deficiency, oxidant damage from chemicals or drugs in individuals with normal red cell enzymes (e.g., dapsone administration), liver failure due to Wilson disease (release of copper from liver), unstable hemoglobin, hemoglobin C homozygosity
Sickle cells and boat-shaped cells	Sickle cell disease (e.g., sickle cell anemia or compound heterozygous states such as S/C, S/D-Punjab, S/O-Arab, S/β-thalassemia)
Target cells	Hemoglobin C homozygosity, other hemoglobinopathies, hereditary xerocytosis
Stomatocytes	Hereditary stomatocytosis, phytosterolemia
Acanthocytes	Liver failure (spur cell hemolytic anemia)
Basophilic stippling	Lead poisoning, pyrimidine 5'-nucleotidase deficiency
Red cell fragments (schistocytes)	Microangiopathic hemolytic anemia (including hemolytic-uremic syndrome, thrombotic thrombocytopenic purpura, HELLP syndrome, and sometimes hemolysis associated with disseminated intravascular coagulation), mechanical hemolytic anemia (e.g., defective cardiac prosthetic valve, march hemoglobinuria)
Erythrophagocytosis	Paroxysmal cold hemoglobinuria
Red cell agglutinates	Acute or chronic cold antibody-induced hemolysis

HELLP = hemolysis, elevated liver enzymes, low platelets.

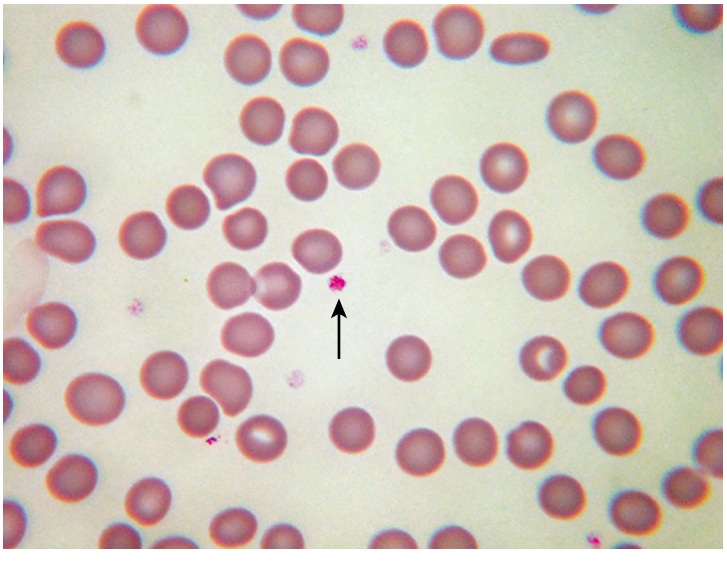

FIGURE 143-22. Normal-sized platelet *(arrow)*. Platelets have central granules, although this is not apparent in this photomicrograph (×1000).

Artifactual white count elevation is unusual but can occur as a result of cryoglobulinemia, hyperlipidemia, or the presence of *Candida* species. Distinguishing reactive changes from leukemia on the basis of morphology is usually straightforward for neutrophil leukocytosis but more difficult for lymphocytosis. In

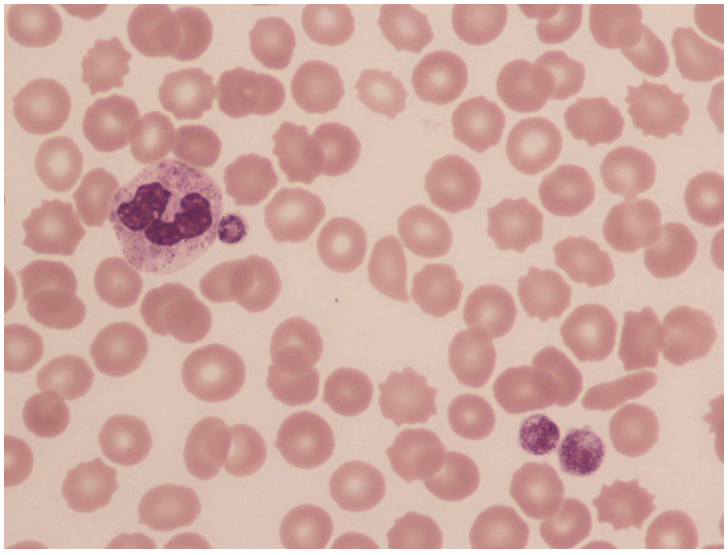

FIGURE 143-23. Giant platelets. Giant platelets are as large as or larger than normal red cells. Giant platelets can indicate increased platelet turnover or an inherited or acquired defect in thrombopoiesis (×1000).

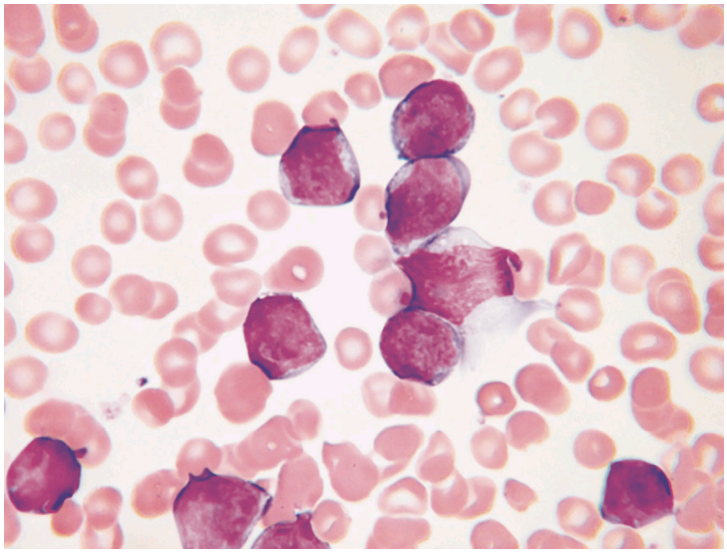

FIGURE 143-24. Acute lymphoblastic leukemia. Numerous agranular blast cells with a high nuclear-to-cytoplasmic ratio are present. Platelets are decreased in number (×1000).

reactive leukocytosis, there is usually toxic granulation, and Döhle bodies may be present (see Figs. 143-18 and 143-19). Vacuolation is particularly characteristic of bacterial infection, and there may be some degranulation of neutrophils. The hematologist should be aware of the changes induced by granulocyte colony-stimulating factor so that they are not confused with a response to infection. Granulocyte colony-stimulating factor can cause toxic granulation, Döhle bodies, vacuolation, and the presence of macropolycytes (giant neutrophils) and circulating neutrophil precursors. The changes typical of leukemia are discussed later.

Leukopenia (Chapter 153) usually requires a film for confirmation and elucidation. The exception is when it is expected in a given clinical context, such as when a patient has had recent chemotherapy. Rarely, an apparent leukopenia is artifactual, owing to the aggregation of neutrophils mediated by an autoantibody or resulting from infection-induced changes in adhesion molecules of the leukocyte surface membrane.

With some automated instruments, it is necessary to confirm that reported neutropenia is real. If the automated count is based on peroxidase cytochemistry, the presence of an inherited deficiency will lead to an apparent neutropenia associated with an increase of large, unstained (i.e., peroxidase-negative) cells. The scatter plot is characteristic, but because the same features could be due to acute leukemia with neutropenia and circulating blast cells, a smear is needed for confirmation.

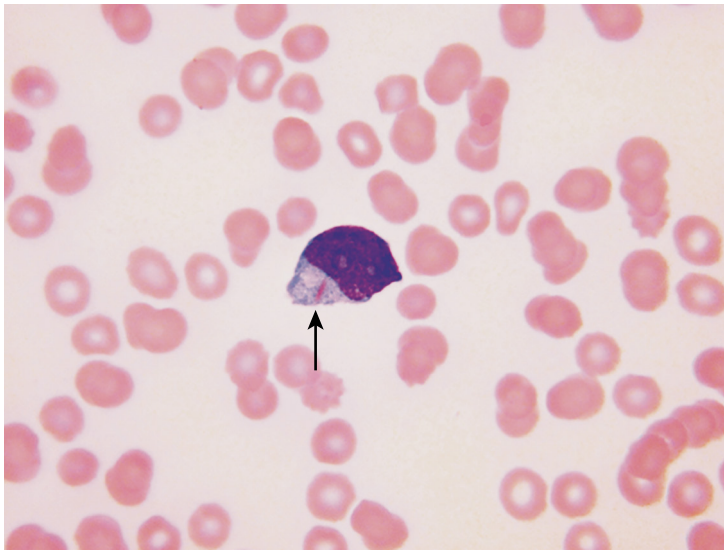

FIGURE 143-25. Auer rod. An Auer rod (*arrow*) is a rod-shaped inclusion in the cytoplasm of cells of myeloid lineage formed by the crystallization of azurophilic granule constituents. Auer rods are seen only in acute myeloid leukemia and high-grade myelodysplastic syndromes. They are usually seen in blast cells but are occasionally found in maturing cells (×1000).

LEUKEMIAS AND LYMPHOMAS

The blood smear is critical in the diagnosis of leukemias and lymphomas. The lymphoblasts of acute lymphoblastic leukemia are usually medium-sized agranular cells with relatively scanty cytoplasm (Fig. 143-24), whereas in acute myeloid leukemia, blast cells are generally larger, with more plentiful cytoplasm that may contain granules or Auer rods (Fig. 143-25). Myeloid blast cells vary in appearance according to whether they are myeloblasts or monoblasts. Myeloblasts are usually medium sized and may have plentiful granules, scanty granules, or no visible granules; they may contain Auer rods or, rarely, giant granules. Monoblasts are much larger cells with plentiful cytoplasm containing few granules and, very rarely, Auer rods. Megakaryoblasts are present in some patients and are sometimes cytologically distinctive because of their tendency to form cytoplasmic blebs or develop platelet-type granules.

Chronic myeloid leukemia has a very characteristic blood smear (Fig. 143-26) in which the most numerous cells are myelocytes and mature neutrophils. Eosinophils and basophils are also present. Dysplastic features are generally absent. In atypical Philadelphia chromosome–negative chronic myeloid leukemia, monocytosis is more frequent and dysplastic features are present. Chronic myelomonocytic leukemia is characterized by increased monocytes, some of them immature, with inconspicuous dysplastic features and infrequent granulocyte precursors. Chronic neutrophilic leukemia and a neutrophilic leukemoid reaction to a plasma cell neoplasm have similar hematologic features and need to be distinguished by supplementary tests, including analysis for a *CSF3R* mutation.[14]

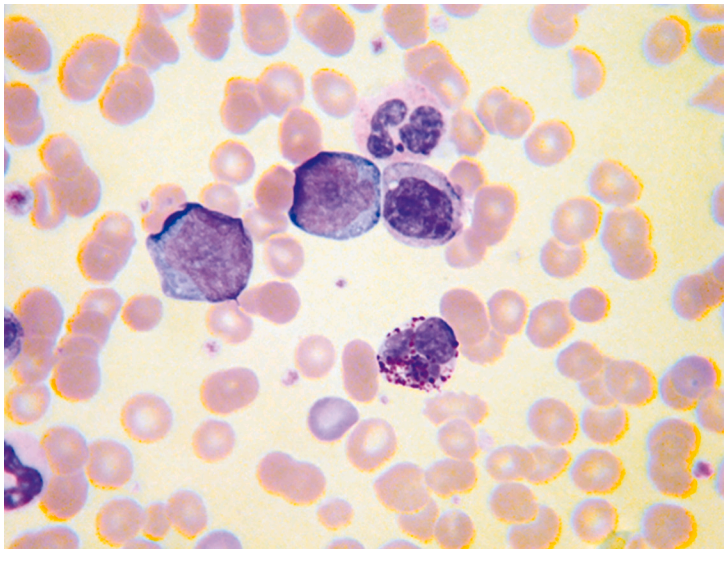

FIGURE 143-26. Chronic myeloid leukemia. In this view there are myeloblasts, a myelocyte, a basophil, and a segmented neutrophil (×1000).

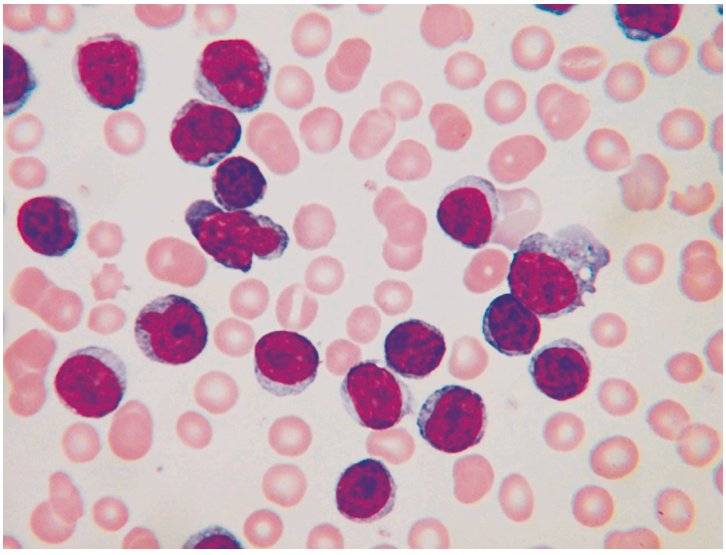

FIGURE 143-27. Chronic lymphocytic leukemia. There are large numbers of rather monotonous, mature small lymphocytes with chromatin clumping. Smear cells (or smudge cells), reflecting the mechanical fragility of the cells, are characteristic but are not seen in this photomicrograph (×1000).

TABLE 143-4 INCIDENTAL BUT CLINICALLY RELEVANT BLOOD SMEAR OBSERVATIONS

OBSERVATION	POSSIBLE SIGNIFICANCE
Acanthocytes	Abetalipoproteinemia, neuroacanthocytosis (includes choreoacanthocytosis, McLeod phenotype, Huntington-like disease 2, and pantothenate-kinase–associated neurodegeneration)
Howell-Jolly bodies, target cells, and acanthocytes	Hyposplenism (congenital, previous splenectomy, celiac disease, amyloidosis)
Cryoglobulin precipitates	Hepatitis C, multiple myeloma, Waldenström macroglobulinemia
Vacuolated lymphocytes	Inherited metabolic disorders
Parasites (e.g., malaria parasites, *Babesia*, microfilaria, trypanosomes, *Leishmania*)	Parasitic infection
Fungi (*Candida* spp, *Histoplasma capsulatum, Talaromyces marneffei, Cryptococcus neoformans, Malassezia furfur*)	Disseminated fungal infection or, in the case of *Candida*, colonization of an indwelling intravenous line
Bacteria (e.g., pneumococcus, meningococcus, *Capnocytophaga canimorsus, Borrelia, Ehrlichia, Anaplasma, Yersinia pestis*)	Bacterial infection
Leukoerythroblastic blood film	Bone marrow infiltration (e.g., metastatic malignancy)

Chronic lymphocytic leukemia also has a very characteristic blood film, with an increase of small, mature lymphocytes of rather uniform appearance. The chromatin is often irregularly clumped, creating a mosaic effect (Fig. 143-27). Smear cells (or smudge cells) are almost always increased in number but are not pathognomonic.

Lymphoma in the leukemic phase often has cytologic features that aid in the diagnosis. Follicular lymphoma (cleft nuclei), Burkitt lymphoma (hyperbasophilic vacuolated cytoplasm), and splenic marginal zone lymphoma (villous lymphocytes) can all be distinctive.

THE INCIDENTAL DETECTION OF CLINICALLY SIGNIFICANT ABNORMALITIES

Sometimes the examination of a blood film reveals unexpected but clinically significant information. Examples are given in Table 143-4. Detection of microorganisms is particularly likely in patients with acquired immunodeficiency syndrome (AIDS), hyposplenic patients, and patients with overwhelming sepsis, but sometimes they are detected in immunologically normal patients with only trivial symptoms. It should be noted that microorganisms in blood smears sometimes represent contaminants, particularly if specimens have been obtained by skin prick or from the umbilical cord and if there has been a delay in making the film.

CONCLUSION

Despite major advances in other diagnostic methods, the blood smear remains very useful in hematologic diagnosis. Sometimes it is critical either because it yields a diagnosis very quickly or because it provides information that is not available in any other way.

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144 APPROACH TO THE ANEMIAS

ROBERT T. MEANS, JR.

Anemia is defined as a significant reduction in the volume of erythrocytes, or red blood cells, in the body. The red blood cell is an anucleate biconcave disc, approximately 8 μm in diameter, composed of various enzymes and chemicals surrounded by a lipid bilayer. The major component of the red blood cell is hemoglobin. A normal red blood cell contains 30 to 40 pg of hemoglobin. Hemoglobin is a highly specialized molecule, optimally enabled to deliver oxygen from the lungs through the circulation to the peripheral tissues and to remove carbon dioxide from the peripheral tissues and return it to the lungs for expiration. The red blood cell is generated in the bone marrow from erythroid precursors (Chapter 142) and survives approximately 120 days in the circulation before its clearance by the reticuloendothelial system.

The direct measurement of the red cell mass is a complex process; therefore, surrogate measures are used to define anemia in the clinical setting. The most common measures are the blood hemoglobin concentration and the hematocrit. The red blood cell count per microliter is also reported in routine hematologic analysis but is rarely used to define anemia. The hematocrit derives its name from the graduated tube in which blood was centrifuged for analysis. The percentage of the blood column represented by red cells compressed by centrifugation (also called packed cell volume) is the quantity physically represented by the hematocrit. Hematocrit values determined by centrifugation-based techniques are used mainly in limited-resource environments where electronic cell counting is not available. In laboratories where complete blood counts are performed using electronic cell counting methods, the hematocrit is a calculated value reflecting the product of the red blood cell count and the mean corpuscular volume of the red cells, both of which are measured directly. Because the hemoglobin concentration is directly measured rather than calculated, many physicians prefer to use the measurement of hemoglobin in the definition of anemia.

PATHOBIOLOGY

Anemia and Oxygen Delivery

The function of hemoglobin is to deliver oxygen to tissues. Oxygen delivery is a function of blood flow, blood hemoglobin content as reflected by hemoglobin concentration, and the gradient between arterial and venous oxygen content (Fick equation). The effect of anemia on blood hemoglobin content is readily apparent, and it also has a role in the other elements of the Fick equation.

In severe anemia associated with blood volume loss or in severe anemia with preserved blood volume, heart rate typically increases, and blood flow is

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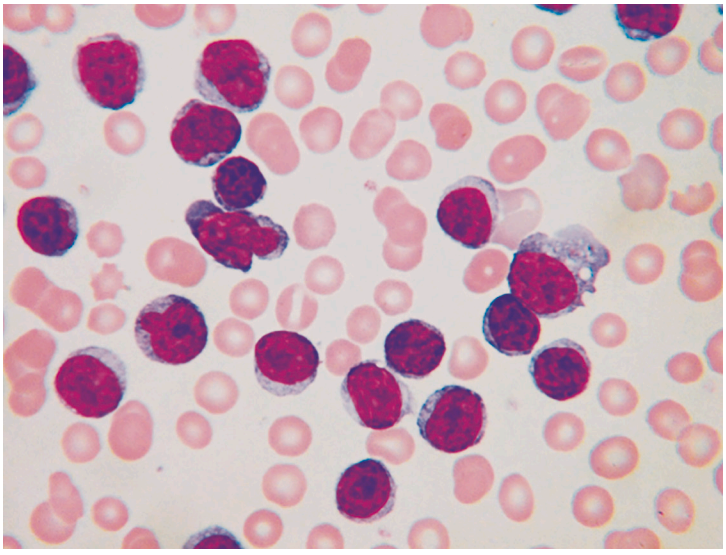

FIGURE 143-27. Chronic lymphocytic leukemia. There are large numbers of rather monotonous, mature small lymphocytes with chromatin clumping. Smear cells (or smudge cells), reflecting the mechanical fragility of the cells, are characteristic but are not seen in this photomicrograph (×1000).

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Cryoglobulin precipitates	Hepatitis C, multiple myeloma, Waldenström macroglobulinemia
Vacuolated lymphocytes	Inherited metabolic disorders
Parasites (e.g., malaria parasites, *Babesia*, microfilaria, trypanosomes, *Leishmania*)	Parasitic infection
Fungi (*Candida* spp, *Histoplasma capsulatum, Talaromyces marneffei, Cryptococcus neoformans, Malassezia furfur*)	Disseminated fungal infection or, in the case of *Candida*, colonization of an indwelling intravenous line
Bacteria (e.g., pneumococcus, meningococcus, *Capnocytophaga canimorsus, Borrelia, Ehrlichia, Anaplasma, Yersinia pestis*)	Bacterial infection
Leukoerythroblastic blood film	Bone marrow infiltration (e.g., metastatic malignancy)

Chronic lymphocytic leukemia also has a very characteristic blood film, with an increase of small, mature lymphocytes of rather uniform appearance. The chromatin is often irregularly clumped, creating a mosaic effect (Fig. 143-27). Smear cells (or smudge cells) are almost always increased in number but are not pathognomonic.

Lymphoma in the leukemic phase often has cytologic features that aid in the diagnosis. Follicular lymphoma (cleft nuclei), Burkitt lymphoma (hyperbasophilic vacuolated cytoplasm), and splenic marginal zone lymphoma (villous lymphocytes) can all be distinctive.

THE INCIDENTAL DETECTION OF CLINICALLY SIGNIFICANT ABNORMALITIES

Sometimes the examination of a blood film reveals unexpected but clinically significant information. Examples are given in Table 143-4. Detection of microorganisms is particularly likely in patients with acquired immunodeficiency syndrome (AIDS), hyposplenic patients, and patients with overwhelming sepsis, but sometimes they are detected in immunologically normal patients with only trivial symptoms. It should be noted that microorganisms in blood smears sometimes represent contaminants, particularly if specimens have been obtained by skin prick or from the umbilical cord and if there has been a delay in making the film.

CONCLUSION

Despite major advances in other diagnostic methods, the blood smear remains very useful in hematologic diagnosis. Sometimes it is critical either because it yields a diagnosis very quickly or because it provides information that is not available in any other way.

GENERAL REFERENCES

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144 APPROACH TO THE ANEMIAS

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Anemia is defined as a significant reduction in the volume of erythrocytes, or red blood cells, in the body. The red blood cell is an anucleate biconcave disc, approximately 8 μm in diameter, composed of various enzymes and chemicals surrounded by a lipid bilayer. The major component of the red blood cell is hemoglobin. A normal red blood cell contains 30 to 40 pg of hemoglobin. Hemoglobin is a highly specialized molecule, optimally enabled to deliver oxygen from the lungs through the circulation to the peripheral tissues and to remove carbon dioxide from the peripheral tissues and return it to the lungs for expiration. The red blood cell is generated in the bone marrow from erythroid precursors (Chapter 142) and survives approximately 120 days in the circulation before its clearance by the reticuloendothelial system.

The direct measurement of the red cell mass is a complex process; therefore, surrogate measures are used to define anemia in the clinical setting. The most common measures are the blood hemoglobin concentration and the hematocrit. The red blood cell count per microliter is also reported in routine hematologic analysis but is rarely used to define anemia. The hematocrit derives its name from the graduated tube in which blood was centrifuged for analysis. The percentage of the blood column represented by red cells compressed by centrifugation (also called packed cell volume) is the quantity physically represented by the hematocrit. Hematocrit values determined by centrifugation-based techniques are used mainly in limited-resource environments where electronic cell counting is not available. In laboratories where complete blood counts are performed using electronic cell counting methods, the hematocrit is a calculated value reflecting the product of the red blood cell count and the mean corpuscular volume of the red cells, both of which are measured directly. Because the hemoglobin concentration is directly measured rather than calculated, many physicians prefer to use the measurement of hemoglobin in the definition of anemia.

PATHOBIOLOGY

Anemia and Oxygen Delivery

The function of hemoglobin is to deliver oxygen to tissues. Oxygen delivery is a function of blood flow, blood hemoglobin content as reflected by hemoglobin concentration, and the gradient between arterial and venous oxygen content (Fick equation). The effect of anemia on blood hemoglobin content is readily apparent, and it also has a role in the other elements of the Fick equation.

In severe anemia associated with blood volume loss or in severe anemia with preserved blood volume, heart rate typically increases, and blood flow is

ABSTRACT

Anemia is a significant issue in clinical medicine, whether as a disease in itself or as a sign of disease. For anemia more than for many syndromes in medicine, appropriate treatment is based on diagnosis. Diagnosis in turn requires appropriate use of laboratory testing informed by the history, physical examination, and prevalence of diseases in the population relevant to the patient. After an outline of the basic physiology regulating red cell production, an approach to anemia is outlined, based on classification by the reticulocyte response to anemia and further refined by division into normocytic, microcytic, and macrocytic anemia syndromes. In addition, specific anemia syndromes are discussed including methemoglobinemia, anemia of chronic kidney disease, anemia of liver disease, anemia of endocrine deficiencies, physiologic anemia of pregnancy, and unexplained anemia of aging.

KEYWORDS

anemia
hemolytic anemia
normocytic anemia
microcytic anemia
macrocytic anemia
differential diagnosis of anemia
classification of anemia

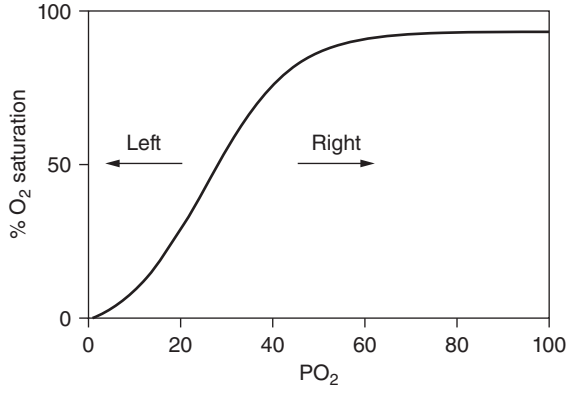

FIGURE 144-1. Oxyhemoglobin dissociation curve. Directions of right and left shift indicated. The curve plots the percentages of hemoglobin in its saturated (oxygen-laden) form on the vertical axis as a function of ambient oxygen tension on the horizontal axis. A rightward shift of the curve indicates a decreased affinity of hemoglobin for oxygen, making it easier for hemoglobin to release its oxygen to supply hypoxic tissue through which the blood passes.

shunted from the periphery to critical organs such as the brain, liver, kidneys, and coronary circulation to preserve oxygen delivery.

The arterial/venous oxygen gradient is also affected by anemia. When the oxyhemoglobin dissociation curve is shifted to the right, the oxygen affinity of hemoglobin is decreased—it requires a higher partial pressure of oxygen to attain a given level of hemoglobin saturation, and oxygen is more readily released to the tissues (Fig. 144-1). In anemia, the principal cause of a right shift is increased intracellular 2,3 diphosphoglycerate (DPG, also called 2,3 bisphosphoglycerate), a product of red cell metabolism. A right shift can also be induced by hyperthermia, hypercapnia, or acidosis. The opposite conditions can produce a left shift, resulting in oxygen being held more tightly by hemoglobin (high affinity).

Methemoglobin

Hemoglobin is composed of two α-globin chains and two β-globin chains, each of which has a covalently bound iron-containing porphyrin ring. Movement of the iron atom in relation to the plane of the porphyrin ring results in changes in the oxygen affinity of hemoglobin. Iron in normal hemoglobin is in the reduced ferrous state (Fe^{2+}). When hemoglobin iron becomes oxidized to the ferric state (Fe^{3+}), it is no longer able to bind oxygen and is called methemoglobin. Under normal circumstances, red cells contain a cytochrome b_5-based enzymatic system that rapidly reduces methemoglobin iron back to the ferrous state.

Methemoglobinemia occurs when this system fails. It may be a congenital condition, or it may be the result of exposure to toxic agents, perhaps in association with a subclinical cytochrome b_5 deficiency (Table 144-1). There are also mutations in globin genes that result in variant hemoglobins (M-hemoglobin) in which iron stabilizes in the ferric state.

Patients with methemoglobin concentrations greater than 10% show cyanosis (bluish discoloration of the skin) with normal oxygen saturation on arterial blood gas. Pulse oximetry may be inaccurate in methemoglobinemia. Arterial blood in methemoglobinemia is a chocolate brown color that does not become red with oxygen exposure. However, addition of potassium cyanate (KCN) to the blood sample will cause the blood to become red with methemoglobinemia but not with M-hemoglobins. Most blood gas machines, particularly in hospitals, can quantify methemoglobin.

Congenital methemoglobinemia patients typically do well even with methemoglobin concentrations of 30 to 40% because of adaptation and primarily have the cosmetic or social problem of cyanosis. Ascorbic acid (vitamin C) may be helpful, or methylene blue can be used. In contrast, acute methemoglobinemia from toxic exposure can be life threatening. Lethargy or headache can occur at methemoglobin levels around 20%. Above 40%, confusion, altered consciousness, and dyspnea can be noted. At concentrations above 50 to 60%, coma and death may occur. The treatment for acute methemoglobinemia is methylene blue 1 to 2 mg/kg, although higher doses up to 6 to 7 mg/kg can be required. M-hemoglobins do not require treatment.

Regulation of Red Cell Production

The primary regulator of red cell production is the effectiveness of oxygen delivery. This critical need may explain why hemoglobin concentration or hematocrit are controlled in a relatively narrow normal range as compared to the white blood count or platelet count, where the upper limit of normal may be two or three times the lower limit of normal. The mediator that translates peripheral oxygen need to red cell production is the hormone erythropoietin. After birth, the predominant physiologic site of erythropoietin production is the kidney, although the liver retains some limited capacity for erythropoietin production. Neoplasms arising from liver, kidney, or other tissues may secrete erythropoietin in an unregulated manner. Anemia results in decreased oxygen tension in the renal cortex, thereby inducing the transcription factor HIF (hypoxia-inducible factor), which in turn upregulates erythropoietin production. Erythropoietin binds to specific receptors on erythroid progenitors in the marrow leading to increased red cell production. When correction of anemia normalizes the oxygen tension in the renal cortex, erythropoietin production falls back to basal levels. Ambient hypoxia, or underoxygenation of the blood by a right-to-left cardiopulmonary shunt, also leads to the production of erythropoietin. This hypoxia causes the erythrocytosis seen in dwellers at high altitudes and in individuals with uncorrected cyanotic heart disease.

Although an adequate supply of other factors such as iron, vitamin B_{12}, or folate is required for red cell production, polycythemia does not occur in the absence of an increased erythropoietin stimulus. Red cell production has feedback regulation of iron availability through the erythroferrone/hepcidin/ferroportin axis (Chapter 145).

TABLE 144-1 CAUSES OF METHEMOGLOBINEMIA

CONGENITAL*
Cytochrome b_5 reductase deficiency
Type I: erythrocyte enzyme deficiency only
Type II: generalized enzyme deficiency (persistent neurologic features)
ACQUIRED
Local Anesthetics
Benzocaine
Lidocaine
Procaine
Phenazopyridine (Pyridium)
Anti-infectives
Dapsone
Nitrofurantoin
Primaquine
Sulfonamides
Nitrates/Nitrites
Amyl nitrate
Isobutyl nitrite
Nitroglycerin
Other Medications
Acetaminophen
Rasburicase
Zopiclone
Other Compounds
Aniline dyes
Henna (2-hydroxy-1,4-napthoquninone)
Phenylhydroxylamine

*Congenital M-hemoglobins clinically and functionally resemble methemoglobins but are biochemically and genetically distinct.

CLINICAL MANIFESTATIONS

Symptoms

In general, the symptoms of anemia are nonspecific and highly dependent on the patient's general physical condition or other comorbid illnesses. Anemia of rapid onset, as may be seen with massive acute hemolysis or with acute blood loss, is more likely to be symptomatic than anemia from red cell underproduction or from slow gastrointestinal blood loss. In both of these cases, the total blood volume is preserved, and there is time for the cardiovascular system to accommodate to the changes in hematocrit. Preservation of blood volume and cardiovascular accommodation are likely the reasons that patients with slow-onset anemias such as B_{12} deficiency are traditionally reported to become symptomatic at much lower hemoglobin concentrations or hematocrits than patients with iron deficiency anemia from blood loss. A person with coronary artery disease or chronic obstructive lung disease is more likely to become symptomatic than an anemic individual without those disorders who has the same hemoglobin concentration.

Common symptoms in anemia include fatigue but typically not dyspnea. Palpitations or a sense of the heart racing or pounding may occur, representing a more rapid heart rate and increased ejection fraction in order to maintain oxygen delivery. Symptomatology in anemia syndromes that develop as a

consequence of some other disease (such as the anemia of inflammation in association with rheumatoid arthritis) will most likely be dominated by the symptoms of the associated disease. Pica, the desire to eat nonnutritive substances such as ice, is very specific to iron deficiency. Restless leg syndrome may also be a manifestation of iron deficiency.

Physical Findings

Pallor may occur in patients with anemia but may be difficult to appreciate in patients seen for the first time due to the widespread differences in skin pigmentation among healthy individuals, but its presence in mucous membranes obviates that variable. Pallor can also occur in other conditions associated with shunting of blood away from the periphery to the critical organs. In the assessment of anemia, pallor of the conjunctival mucosa or of the creases in the palm are more specific than pallor in other sites. Pallor of the conjunctival mucosa generally indicates a hemoglobin concentration less than 9 g/dL, and failure of the palmar creases to become more prominent when the extended fingers are pushed down, thereby extending the palm, generally indicates a hemoglobin no higher than 7 to 8 g/dL. Tachycardia and a systolic ejection murmur may develop as a result of anemia and cardiovascular accommodation to it. Peripheral edema, which may be occasionally seen with moderately severe anemia, may reflect a combination of high-output heart failure and loss of oncotic pressure associated with fewer blood cells. On rare occasions, retinal hemorrhages may be seen on fundoscopic examination in severe anemia. All of these vascular and cardiac manifestations of anemia will resolve with correction of anemia.

DIAGNOSIS

Medical History

The initiating step of any evaluation for anemia is demonstration by hemoglobin concentration or hematocrit that the patient is anemic (see Tables 144-2 and 144-3). A number of elements in the history and physical examination can guide the subsequent laboratory evaluation (Tables 144-4 and 144-5). Duration of anemia assists in distinguishing congenital from chronic or acute causes. Because iron deficiency is the most common etiology of anemia in clinical medicine, dietary history (vegetarian or vegan) and a history of blood loss should always be pursued. In women, this questioning should also include asking about the number of previous pregnancies and whether iron supplementation was used during pregnancy. Every child delivered at term represents an investment of 800 mg of maternal iron (Chapter 145). Persistent jaundice suggests active hemolysis, and episodic jaundice is frequently observed in individuals with congenital hemolytic anemias, whether they result from metabolic defects such as glucose-6-phosphate dehydrogenase (G6PD) deficiency or from red cell membrane defects such as hereditary spherocytosis. A history of cholelithiasis in early adulthood is suggestive of congenital hemolytic disorders. A history of chronic inflammatory disorders raises the possibility of the anemia of inflammation (Chapter 145). A history of petechiae or easy bruising or a history of recurrent infection raises the possibility of a hematopoietic disorder not limited to the erythroid lineage. A family history of a specific diagnosis, such as sickle cell anemia or thalassemia, is obviously helpful. Similarly, a history of family members with episodes of jaundice following minor illnesses suggests a congenital hemolytic anemia. In contrast, a history of a similar disorder in the mother, aunts, and sisters of a female patient with suspected iron deficiency is not particularly helpful in the diagnosis of anemia.

Physical Examination

Certain physical findings may help guide the evaluation of anemia by providing clues to specific syndromes, underlying disorders, or bleeding (Table 144-5). Evidence of bleeding mandates evaluation for iron deficiency. Petechiae, purpura, or thrush suggests abnormalities of the platelets or white cells and raises the possibility of a generalized marrow disorder not limited to the erythroid lineage. Frontal bossing (prominence of the forehead due to expansion of red marrow in the skull) is seen in congenital hemolytic anemias but can be a normal variant; in general, adults with hemolytic anemia and this physical finding have had their diagnosis defined earlier in life. The neurologic findings of B_{12} deficiency generally require a more thorough examination than is part of the routine physical examination (Chapter 150).

Complete Blood Counts

The usual complete blood count provided by automated cell counters includes a variety of directly measured and calculated parameters, which at a minimum include the white blood cell count, the red blood cell count, the hemoglobin concentration and hematocrit, the platelet count, and the red cell indices described later. Many automated counters also provide a differential white blood count and a semiquantitative description of red cell abnormalities. Decreased counts of white blood cells and platelets are discussed in Chapters 153 and 158, respectively. Typical values are shown in Table 144-2. Clinicians should become familiar with the normal values specific to the laboratories they use.

The hemoglobin, hematocrit, and red cell counts are all concentrations, which means that a change in the plasma volume can elevate them or decrease them relative to the actual total body red cell mass. An example of an anemia associated with a normal or slightly increased red cell mass occurs in the second trimester of normal pregnancy. In contrast, an elevated hemoglobin concentration or hematocrit with a normal or decreased total body red cell mass can be seen in dehydration or the capillary leak syndrome

Red cells can also be described by parameters called red cell indices, which are routinely calculated by most electronic cell counters. These include the mean corpuscular volume (MCV), the mean corpuscular hemoglobin (MCH),

TABLE 144-2 NORMAL RED BLOOD CELL MEASUREMENTS

MEASUREMENT	NORMAL RANGE
Hemoglobin concentration	12-16 g/dL Female 13.5-17.5 g/dL Male
Hematocrit	36-48% Female 40-52% Male
Red blood cell (RBC) count	$4.0\text{-}5.4 \times 10^6$/μL Female $4.5\text{-}6.0 \times 10^6$/μL Male
Mean corpuscular volume (MCV)	81-99 fL
Mean corpuscular hemoglobin (MCH)	30-34 pg
Mean corpuscular hemoglobin concentration (MCHC)	30-36 g/dL
RBC size distribution width (RDW) RDW-CV RDW-SD	 12-15% 37-47 fL
Reticulocyte percentage*	0.5-1.5%
Absolute reticulocyte count	20,000-100,000/μL
Reticulocyte production index	0.5-2.5%

*The same normal range applies to corrected reticulocyte counts.
RDW-CV = RDW-coefficient of variation; RDW-SD = RDW-standard deviation.

TABLE 144-3 DEFINITION OF RED CELL INDICES AND RETICULOCYTE PARAMETERS

$$\text{Mean corpuscular volume (MCV)} = \frac{\text{Hematocrit}}{\text{Red blood cell count}}$$

$$\text{Mean corpuscular hemoglobin (MCH)} = \frac{\text{Hemoglobin concentration}}{\text{Red blood cell count}}$$

$$\text{Mean corpuscular hemoglobin concentration (MCHC)} = \frac{\text{MCH}}{\text{MCV}} \text{ or } \frac{\text{Hemoglobin concentration}}{\text{Hematocrit}}$$

$$\text{Absolute reticulocyte count} = \text{Reticulocyte percentage} \times \text{Red blood cell count}$$

$$\text{Corrected reticulocyte count (hematocrit)} = \text{Reticulocyte percentage} \times \frac{\text{Hematocrit}}{42}$$

$$\text{Corrected reticulocyte count (hemoglobin)} = \text{Reticulocyte percentage} \times \frac{\text{Hemoglobin concentration}}{15}$$

$$\text{Reticulocyte production index (RPI)} = \frac{\text{Corrected reticulocyte count (hematocrit)}}{\text{Maturation factor}}$$

HEMATOCRIT RANGE	MATURATION FACTOR
36-45%	1.0
26-35%	1.5
16-25%	2.0
Less than 16%	2.5

TABLE 144-4 MEDICAL HISTORY IN THE APPROACH TO ANEMIA

GENERAL
Duration (lifelong; chronic; intermittent; acute)
Previous blood transfusion
Family history of anemia
CLUES TO IRON DEFICIENCY/BLOOD LOSS
Change in bowel habits (melena, hematochezia, diarrhea)
Other bleeding
Surgical procedures
Pica (ice)
Restless leg symptoms
CLUES TO HEMOLYSIS
Jaundice (episodic, sustained, family history)
Hemoglobinuria
Cholelithiasis/cholecystectomy in early adulthood
CLUES TO SYSTEMIC HEMATOLOGIC DISEASE
Purpura/petechiae
Recurrent infections, including oral candidiasis
CLUES TO SYSTEMIC DISORDERS ASSOCIATED WITH ANEMIA
Rheumatologic/collagen vascular disease (anemia of inflammation)
Renal disease (anemia of chronic kidney disease)
Infections (recent or chronic, anemia of inflammation)
Endocrinopathy (anemia associated with endocrine deficiency)
Malignancy (anemia of inflammation)
Weight loss (anemia of inflammation; also nonspecific)

TABLE 144-5 PHYSICAL EXAMINATION FINDINGS IN THE APPROACH TO ANEMIA

FACTORS THAT MAY CAUSE OVER- OR UNDERESTIMATION OF THE DEGREE OF ANEMIA
Edema/anasarca
Other signs of congestive heart failure
Orthostatic hypotension/poor skin turgor
CLUES TO IRON DEFICIENCY/BLOOD LOSS
Heme-positive stool
Telangiectasias
CLUES TO HEMOLYSIS
Jaundice
Splenomegaly
Right upper quadrant abdominal tenderness
Frontal bossing (hemoglobinopathy/thalassemia)
CLUES TO B_{12}/FOLATE DEFICIENCY
Glossitis
Decreased vibratory sensation/proprioception
CLUES TO SYSTEMIC HEMATOLOGIC DISEASE
Purpura/petechiae
Oral thrush
Splenomegaly
Lymphadenopathy

and the mean corpuscular hemoglobin concentration (MCHC) (Table 144-3). Another parameter automatically calculated by most electronic cell counters is the red cell distribution width (RDW), which represents either the coefficient of variation of the distribution curve of red cell sizes (RDW-CV) or the standard deviation of the red cell distribution width curve (RDW-SD) and is a marker of red cell anisocytosis (variation in size).

Red blood cell parameter determinations (Table 144-2) will vary between laboratories depending upon the equipment used and on the population serving as the basis for the normal range. For example, the normal red cell values among patients living at high altitude are higher than those in normal subjects at sea level due to lower ambient oxygen tension driving higher erythropoietin production. Normal values are different between newborns, children, and adults and between men and women after puberty. The difference in normal hemoglobin concentration, hematocrit, and red cell count between adult men and women is attributed to the action of testosterone in sensitizing erythroid progenitors to erythropoietin.

Reticulocyte Count

Red cells newly released from the bone marrow that have shed their nuclei but still contain some nuclear material in the cytoplasm are called reticulocytes. Reticulocytes were traditionally measured through supravital staining on fresh smears, but now are most frequently measured by flow cytometry technology incorporated into electronic blood counters. On the routine Wright-Giemsa–stained peripheral blood smear, reticulocytes are slightly larger than red cells, have little or no central pallor, and have a more grayish (polychromatic) tinge to the cytoplasm. The reticulocyte activity in a particular specimen can be expressed in a variety of ways (Table 144-3). All are based on the principle that the reticulocyte response of the marrow to anemia varies with the degree of anemia. The uncorrected reticulocyte count, sometimes called the reticulocyte percentage, represents the percentage of red blood cells that are reticulocytes. However, an uncorrected reticulocyte count of 2% would be entirely normal in a person with a hematocrit of 42% or hemoglobin concentration of 14 g/dL but would be grossly inadequate in a person with a hematocrit of 20% or hemoglobin concentration of 7 g/dL. The other reticulocyte parameters represent an effort to adjust this uncorrected value for the degree of anemia. The simplest and most common adjustment is to express the reticulocyte count as the absolute reticulocyte count, which is the reticulocyte percentage multiplied by the red blood cell count. The most complex is the reticulocyte production index (RPI), which corrects the reticulocyte count for the degree of anemia and then adjusts by a factor that compensates for the release of less mature reticulocytes into the circulation under circumstances of more severe anemia.

Reticulocyte counts are helpful in the initial approach to anemia in distinguishing anemias due to underproduction of red cells from those associated with adequate or increased production but shortened survival in the circulation. During treatment of anemia, increases in the reticulocyte count can predict response to therapy prior to increments in the hemoglobin concentration or hematocrit. Alternately, failure of the reticulocyte count to increase at the expected time can predict failure of current therapy and dictate a change of approach.

Blood Smear Examination

Even in the era of more sophisticated electronic hematologic analysis, including ability of device software to provide descriptions of red cells, value remains in the examination of peripheral blood smear (Chapter 143) by a physician familiar with the clinical situation of the patient. In congenital hemolytic anemias, the morphologic changes characteristic of red cell membrane abnormalities may be seen (spherocytes, elliptocytes, etc.). The "bite" and "blister" red cells found in hereditary defects of red cell oxidative metabolism are unlikely to be appreciated except by direct examination by a clinician. Sideroblastic anemia is characterized as a microcytic anemia (see later) but is frequently associated with a normal MCV because the sideroblastic clone is not large enough to alter the average red cell size. The finding of a dimorphic red cell population is a significant clue to this disorder but may also be seen in partially treated iron deficiency. Macroovalocytes and hypersegmented neutrophils are highly suggestive of B_{12} deficiency.

Bone Marrow Examination

Bone marrow aspiration and biopsy are required for the diagnosis of many primary marrow disorders giving rise to anemia. In general, it is most likely to be indicated in underproduction anemias rather than in those associated with an appropriate or increased reticulocyte response. However, paroxysmal nocturnal hemoglobinuria (PNH), which can include elements of both hemolysis and marrow failure, is an exception. Disorders that require bone marrow examination for diagnosis at the present time are aplastic anemia and pure red cell aplasia, myelodysplastic syndromes, and anemias associated with marrow replacement (lymphoma, leukemia, myelofibrosis, myeloma, or metastatic cancer). Marrow examination is rarely required for assessment of iron status, given the availability of other diagnostic tools (Chapter 145). Bone marrow examination for the diagnosis of anemia should include both aspiration and biopsy and routinely include Prussian blue staining for evaluation of iron stores and possible detection of ringed sideroblasts. Flow cytometry to phenotype myeloid or lymphoid/plasma cell populations should also be performed, as should standard cytogenetics, when suspecting a clonal disorder. If there is suspicion on clinical grounds of a specific disease associated with a molecular abnormality, polymerase chain reaction (PCR) or fluorescence in situ hybridization (FISH) testing for that abnormality should be performed. Molecular studies for parvovirus in cases of possible pure red cell aplasia can be performed on peripheral blood. A more recent discovery is that clonal abnormalities of hematopoiesis can be identified on peripheral blood molecular testing, particularly in the elderly (Chapter 142).[1] It is possible that such testing may obviate the need for bone marrow examination in certain selected populations.[2]

TABLE 144-6 INITIAL ASSESSMENT OF ANEMIA

INPATIENT/HOSPITAL-BASED CLINIC SETTING*
History and physical examination
Complete blood counts with indices
Reticulocyte count
Peripheral blood smear review
AMBULATORY CLINIC SETTING
History and physical examination
Complete blood counts with indices
Reticulocyte count
Peripheral blood smear review (if/when possible)
Iron assessment for iron deficiency anemia/anemia of inflammation
Serum iron concentration
Serum total iron binding capacity and serum percent transferrin saturation
Serum ferritin concentration

*This approach would also apply in an ambulatory setting with in-office laboratory capacity.

Initial Laboratory Approach to Anemia

The traditional approach to the evaluation of anemia has been to obtain a complete blood count with indices and reticulocyte count, categorize the anemia on that basis, and then proceed with specific testing indicated by reticulocyte count and MCV, informed by the findings on history and physical examination and review of the blood smear. This is an appropriate and intellectually valid approach at any time, but particularly in the inpatient or hospital-based clinic settings. In the ambulatory practice environment for many internists, third-party payers may mandate that laboratory studies be sent to outside reference laboratories. The consequence of such policies is that blood count and reticulocyte count results may not be available on the day of the visit, and personal review of the blood smear may be challenging. In such a practice environment, it is reasonable to include an assessment of iron status in the initial laboratory evaluation of anemia. Iron deficiency anemia and the anemia of inflammation (also called anemia of chronic disease)[3] can both be diagnosed by these tests and are the two most common etiologies of anemia (Chapter 145). Although iron deficiency anemia is more likely to be microcytic and anemia of inflammation is more likely to be normocytic, both of these syndromes can be either microcytic or normocytic; therefore, it is likely that iron testing will be needed in nearly all circumstances not associated with an elevated reticulocyte response. This approach is outlined in Table 144-6.

ANEMIAS ASSOCIATED WITH INCREASED RETICULOCYTE PRODUCTION

Anemia associated with increased reticulocyte production after adjustment for anemia suggests the presence of either blood loss or hemolysis (Fig. 144-2). In certain situations, bleeding or hemolysis may not be associated with an appropriate reticulocyte response; these situations typically indicate some concurrent restriction on red cell production such as iron or folate deficiency.

ANEMIA DUE TO BLOOD LOSS

The symptoms of acute blood loss are dependent on the rapidity and volume of blood loss and secondarily on the site of blood loss. They are heavily influenced by effects of hypovolemia. Hypovolemia and loss of the oxygen-carrying capacity of red cells may impair oxygen delivery to tissues.

In the initial setting of acute blood loss, plasma and red cells are depleted in their same relative ratio. The result of this is that the hemoglobin concentration and hematocrit do not change acutely. As the intravascular volume is expanded, either rapidly with exogenous intravenous colloid or crystalloid in the setting of trauma, or more slowly by endogenous redistribution of plasma from the extravascular space, the hematocrit and hemoglobin concentration will begin to move downward over hours to days to reveal the true extent of loss of circulating red cell mass. In this setting, therefore, the degree of blood loss is initially underestimated by the blood counts. Further complicating the situation in the case of acute trauma is cytokine activation and the "coagulopathy of trauma." For this reason, trauma transfusion protocols have been developed in which packed red blood cells, fresh frozen plasma, and platelet concentrate are administered in specific ratios in order to return as quickly as possible to the physiologic state.[4]

Clinical findings vary with the volume and site of blood loss. Bleeding into the gastrointestinal tract can lead to hematemesis, melena, and/or hematochezia, depending on the location and rate of bleeding. The serum blood urea nitrogen (BUN) concentration will rise out of proportion to the creatinine level even with relatively modest gastrointestinal bleeding due to the breakdown and absorption of hemoglobin protein. When a patient has a large hematoma, whether intracavitary or between tissue planes, hyperbilirubinemia and occasionally clinically apparent jaundice, as well as some rise in BUN, may occur as the extravascular hemoglobin breaks down. Bleeding may be associated with reactive thrombocytosis and occasionally leukocytosis.

The management of massive blood loss is by transfusion (Chapter 162) and correction of the cause of bleeding. In smaller-volume acute blood loss, where the hemoglobin concentration comes to equilibrium at a point that does not impair oxygen delivery in that specific patient, patients may be allowed to recover on their own, mobilizing their own iron stores. When there is concern about adequate iron stores, iron replacement can be given.

Chronic blood loss is rarely at a level that produces acute volume shifts and the dramatic symptomatology of acute blood loss. The reticulocyte count remains appropriately elevated until iron becomes depleted by its utilization for increased erythropoiesis, at which time the reticulocyte response decreases and the hemoglobin concentration and hematocrit begin to drift downward. The decline in MCV begins shortly after the hemoglobin concentration and hematocrit fall below the normal range.

ANEMIA DUE TO HEMOLYSIS

Hemolysis (Chapters 146 to 149) indicates a reduction in the survival of red cells in the circulation from increased red cell destruction. Some reduction in red cell survival is an element in many hematologic syndromes, including the anemia observed with chronic kidney disease, the anemia seen with inflammation, and the anemia seen with liver disease (distinct from spur cell anemia). Microangiopathic hemolytic morphology is occasionally seen in disseminated intravascular coagulation.

Certain laboratory studies raise suspicion of a hemolytic anemia and some confirm it (Table 144-7). These are not specific to any etiology of hemolytic anemia. The distinction between extravascular hemolysis (which includes hemolysis in the spleen) and intravascular hemolysis is helpful in understanding these disorders at the pathophysiologic level. However, it is not absolute in terms of diagnostic testing. While the haptoglobin tends to become lower in intravascular hemolysis, it is generally decreased in extravascular hemolysis also. Hemoglobinemia and hemoglobinuria are specific for intravascular hemolysis.

The causes of hemolysis (Table 144-8) can be grouped using a classification that separates etiologies that are (1) entirely external to the red cell (e.g., immunologic, mechanical, or toxic processes); (2) defects that are intrinsic to the red cell membrane (e.g., hereditary spherocytosis or spur cell anemia), and (3) processes primarily related to red cell metabolism or to abnormalities of hemoglobin. The enzymatic defects producing hemolysis are typically related to oxidative metabolism and particularly to oxidative stress, such as that induced by medications.

The approach to the diagnosis of the various classes of hemolytic anemia syndromes (Fig. 144-2) begins with the examination of the peripheral smear. Identification of the characteristic microangiopathic changes of thrombotic thrombocytopenic purpura immediately provides direction to life-saving therapy. Similarly, congenital defects in the intrinsic proteins of the red cell membrane produce specific morphologic features, which can lead rapidly to a confirmable diagnosis. If the morphology on the peripheral blood smear is normal or shows only a small number of spherocytes, then evaluation for an immunologic etiology of hemolysis should be pursued. In general, autoimmune hemolytic anemia is associated with an abnormal direct antiglobulin (Coombs) test. In individuals with a previous transfusion history or a history of pregnancy in which fetal-maternal transfusion may have occurred, the possibility of other immune hemolytic mechanisms arises, and an antibody screen (also called the indirect antiglobulin test) should be ordered. If negative, metabolic or toxic causes of hemolysis should be considered.

Sustained hemolysis of any etiology creates an increased demand for folic acid, and it is reasonable to supplement individuals with chronic hemolysis with folate (1 mg/day). In countries that do not routinely fortify food with folic acid, a higher level of supplementation may be needed. During pregnancy, when folate demands are increased, a higher level of supplementation than the recommended 0.8 mg/day is reasonable for individuals with chronic hemolysis. Hemolysis that is primarily extravascular is generally not associated with increased iron demands, because the hemoglobin iron from the hemolyzed red cells is recycled in the reticuloendothelial system. In intravascular hemolysis, the haptoglobin/hemopexin system for recycling heme iron is readily overwhelmed and iron supplementation may be necessary.

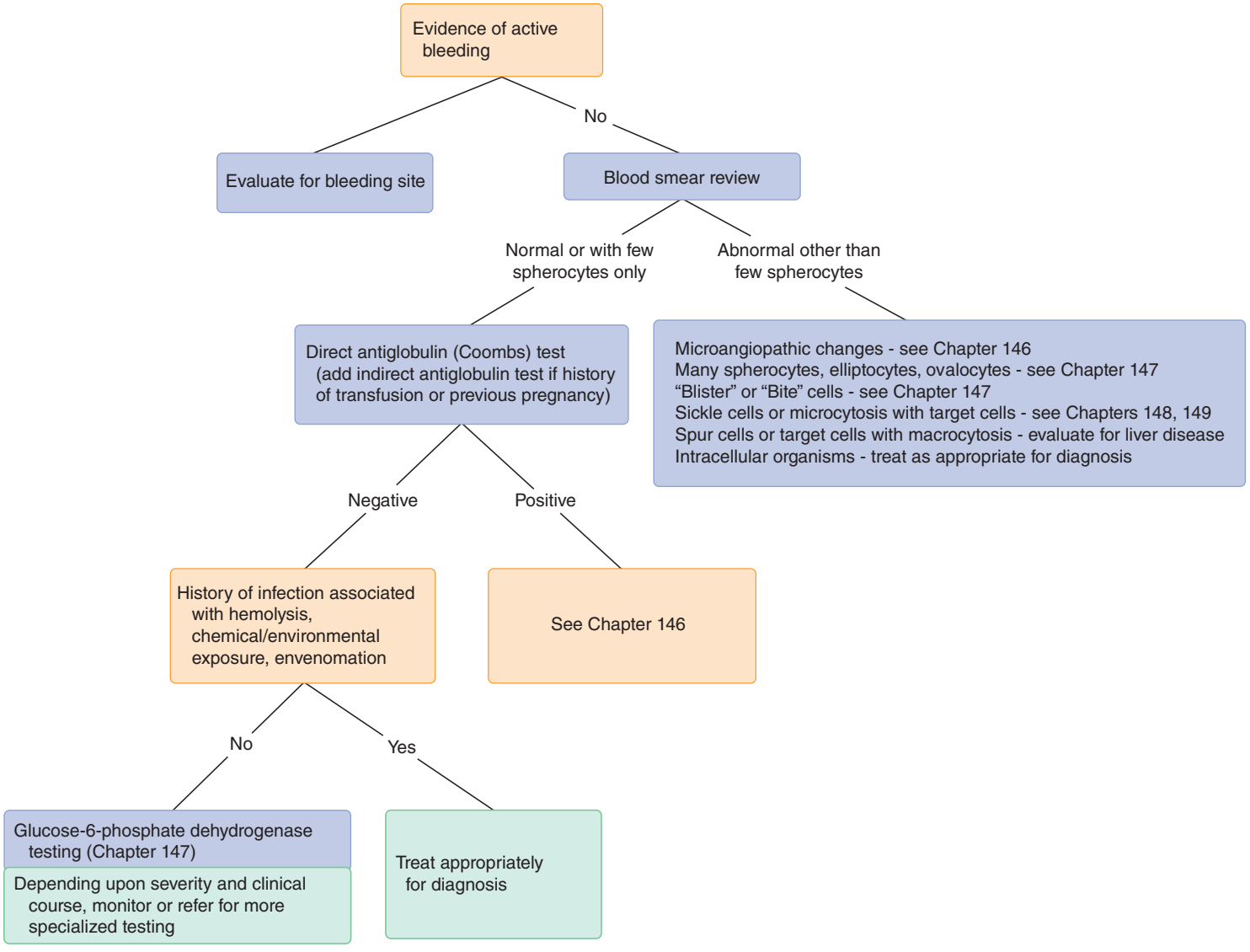

FIGURE 144-2. **Approach to the workup of hemolysis, beginning with examination of the peripheral blood smear.** (See Chapter 143.)

TABLE 144-7 GENERAL LABORATORY FINDINGS IN HEMOLYTIC ANEMIA

FINDINGS SUGGESTIVE OF HEMOLYSIS
Peripheral blood smear
Polychromasia
Abnormal red cell morphology
Elevated reticulocyte count (adjusted for anemia)
Elevated serum bilirubin (indirect/unconjugated)
Elevated serum lactate dehydrogenase
Slightly elevated serum aspartate aminotransferase
FINDINGS CONFIRMATORY OF HEMOLYSIS
Decreased serum haptoglobin (lower in intravascular hemolysis)
Increased plasma hemoglobin
Increased urobilinogen
Hemoglobinuria (intravascular hemolysis)
Hemosiderinuria (intravascular hemolysis; chronic or recurrent)

ANEMIAS ASSOCIATED WITH INADEQUATE RETICULOCYTE RESPONSE (UNDERPRODUCTION ANEMIAS)

The vast majority of anemias seen in adults are associated with decreased red cell production. A useful approach to the evaluation of these anemias is to classify them by MCV as microcytic, normocytic, or macrocytic (Table 144-9 and Fig. 144-3). A limitation to this approach is that the MCV used in defining this model was based on examination of the blood smear and not necessarily on the measured MCV value provided by the electronic cell counter. The dimorphic population of microcytic and normocytic red cells seen in sideroblastic anemia has already been mentioned. In the presence of concurrent inflammation or of elevated serum immunoglobulin (whether polyclonal or monoclonal), stacking of red cells ("rouleaux formation") as they pass through the aperture of the counter may artifactually elevate the measured MCV.

MICROCYTIC ANEMIAS

Microcytic anemias (Chapter 145) share the common pathogenesis of defective cellular hemoglobin synthesis. These defects may be at the globin level, as in the hemoglobinopathies and thalassemia, or may affect synthesis of the heme moiety. Lead poisoning suppresses ferrochelatase, interfering with synthesis of the heme porphyrin ring. Anemia of inflammation (anemia of chronic disease) is typically normocytic but may be associated with a slight reduction in MCV. In general, an MCV less than 75 fL would not be seen in the anemia of inflammation. The lowest MCVs will be seen in the hemoglobinopathies and thalassemias. A normal RDW in microcytic anemia is more likely to represent a hemoglobinopathy or thalassemia rather than iron deficiency.

MACROCYTIC ANEMIAS

Macrocytic anemias (Chapters 150, 151, and 167) represent a variety of diagnoses and pathophysiologic mechanisms. Inflammation or hypergammaglobulinemia can produce a laboratory artifact resulting in an elevated reported MCV. The elevated MCV in reticulocytosis is not an artifact because reticulocytes are larger than mature red cells. Liver disease or alcohol use are frequently associated with a mildly macrocytic anemia due to changes in red cell membrane lipids. Although the anemia of hypothyroidism is most commonly associated with a normal MCV, macrocytosis is

TABLE 144-8 ETIOLOGIES OF HEMOLYTIC ANEMIA

EXTERNAL TO RED BLOOD CELL
Hypersplenism
Immunologic
Autoimmune
Alloimmune
Microangiopathic
Thrombotic microangiopathy
Thrombotic thrombocytopenic purpura
Hemolytic uremic syndrome (typical/atypical)
Mechanical fragmentation
Valvular heart disease (native and prosthetic)
Foot-strike hemolysis (march hemoglobinuria)
Malignant hypertension
Giant hemangioma/Kasabach-Merritt
Thermal injury
Infections
Malaria (blackwater fever)
Clostridial sepsis
Babesiosis
Toxic/Metabolic
Chemical
Arsine
Copper
Lead
Venoms
Snake bite
Spider bite (brown recluse)
MEMBRANE DEFECT
Acquired
Paroxysmal nocturnal hemoglobinuria
Spur cell anemia
Congenital
Red cell membrane protein defect
Hereditary spherocytosis, similar disorders
INTERNAL DEFECT
Hemoglobinopathy
Sickle hemoglobin syndromes
Other hemoglobinopathy syndromes
Thalassemia syndromes
Red cell metabolic abnormalities
Glucose-6-phosphate dehydrogenase deficiency, similar disorders
Hypophosphatemia (acquired)

TABLE 144-9 CLASSIFICATION OF ANEMIA BY MEAN CORPUSCULAR VOLUME (MCV)

MICROCYTIC: DEFECTS IN CELLULAR HEMOGLOBIN SYNTHESIS
Iron deficiency anemia
Hemoglobinopathy*
Thalassemia
Sideroblastic anemia (congenital)
Anemia of inflammation (some cases)
Lead poisoning
NORMOCYTIC
Iron deficiency anemia (early)
Sickle cell anemia—homozygous or sickle cell trait
Anemia of inflammation (most cases)
Unexplained anemia of the elderly
Anemia of chronic kidney disease
Physiologic anemia of pregnancy
Anemia of endocrine deficiency
Hypothyroidism—most cases
Adrenal insufficiency
Androgen deficiency
Myelodysplastic syndrome
Marrow replacement
Pure red cell aplasia
Aplastic anemia (many cases)
MACROCYTIC
Laboratory artifacts
Inflammation
Hypergammaglobulinemia
Reticulocytosis
Anemia of liver disease
Alcohol
Anemia of hypothyroidism (some cases)
Copper deficiency
Primary marrow failure
Diamond Blackfan anemia
Myelodysplastic syndrome (including acquired sideroblastic anemia)
Aplastic anemia (some cases)
Megaloblastic anemia
Cobalamin (B_{12}) deficiency
Folate deficiency
Hydroxyurea therapy

*Homozygous sickle cell anemia (SS), sickle cell trait (AS), and hemoglobin C trait are normocytic. Compound heterozygote sickle cell syndromes like sickle-thalassemia are microcytic.

sometimes reported, and it is frequently classified as a macrocytic anemia. The syndromes outlined earlier are usually associated with an MCV less than 105 to 115 fL.

Other macrocytic anemias result from impaired DNA synthesis. These disorders include the classic megaloblastic anemias from cobalamin (B_{12}) and folate deficiency as well as primary marrow failure disorders such as the myelodysplastic syndromes and Diamond Blackfan anemia. These causes of anemia are frequently associated with abnormalities of other cell lineages. The myelosuppressive agent hydroxyurea also produces striking macrocytosis as part of its expected effect. In primary marrow failure disorders, the MCV is typically less than 110 fL. Megaloblastic anemia may be associated with extremely elevated MCV: as the MCV rises above 115 fL, the likelihood of cobalamin or folate deficiency increases. Hydroxyurea can produce elevated MCV in a similar range. Copper deficiency may be confused with cobalamin deficiency because it also is associated with neurologic findings, but the MCV is typically less than 110 fL.

NORMOCYTIC ANEMIAS

Normocytic anemias also represent a mixed group of disorders. In some cases, they are caused by a primary marrow failure state, as in pure red cell aplasia or aplastic anemia. In most other circumstances, they represent anemia associated with another systemic disorder.[5]

Iron deficiency anemia in its early stages, like the anemia of acute blood loss, is associated with a normal MCV. After iron stores are depleted, a process of iron-depleted erythropoiesis begins. As the red cells produced under these conditions become a larger proportion of the total red cell population, the MCV begins to decline. The anemia of inflammation[6] (Chapter 145) is likely the most common normocytic anemia syndrome after acute blood loss or early iron deficiency.

Myelodysplastic syndromes and other primary bone marrow failure disorders can be normocytic in many cases. Pure red cell aplasia presents as an isolated normochromic normocytic anemia with striking reticulocytopenia. In patients with isolated anemia and a reticulocyte count of 0.1% or less or an absolute reticulocyte count less than 10,000/μL, a bone marrow examination should be performed to evaluate for this diagnosis.

SPECIFIC ANEMIA SYNDROMES

ANEMIA OF CHRONIC KIDNEY DISEASE

Anemia is almost invariable in significant renal insufficiency, beginning when the estimated glomerular filtration rate (eGFR) falls below 45 mL/min/1.73 m^2 body surface area. Anemia is a less frequent complication of polycystic kidney disease because of secretion of erythropoietin by the cysts.

The major pathogenetic factor in the anemia of chronic kidney disease is erythropoietin deficiency. The use of recombinant erythropoietin (erythropoiesis-stimulating agents) has substantially mitigated this problem, although even in the erythropoietin era 48% of predialysis patients and 28% of hemodialysis patients have hematocrit values <30%. Other mechanisms contributing to the anemia of kidney disease are suppression of the erythroid progenitor response to anemia and shortened red cell survival. Shortened red cell survival has a number of proposed mechanisms, including decreased ability to regulate cellular oxidative stress, effects of toxic metabolites accumulated in uremia, and membrane lipid peroxidation.

Red cells are normocytic and normochromic. Echinocytes ("burr cells") are sometimes present. The reticulocyte count is decreased for the degree of anemia. Erythropoietin concentrations are generally not helpful in making a diagnosis because the usual feedback relationship between hemoglobin concentration/hematocrit and erythropoietin secretion is lost. eGFR <45 mL/min/

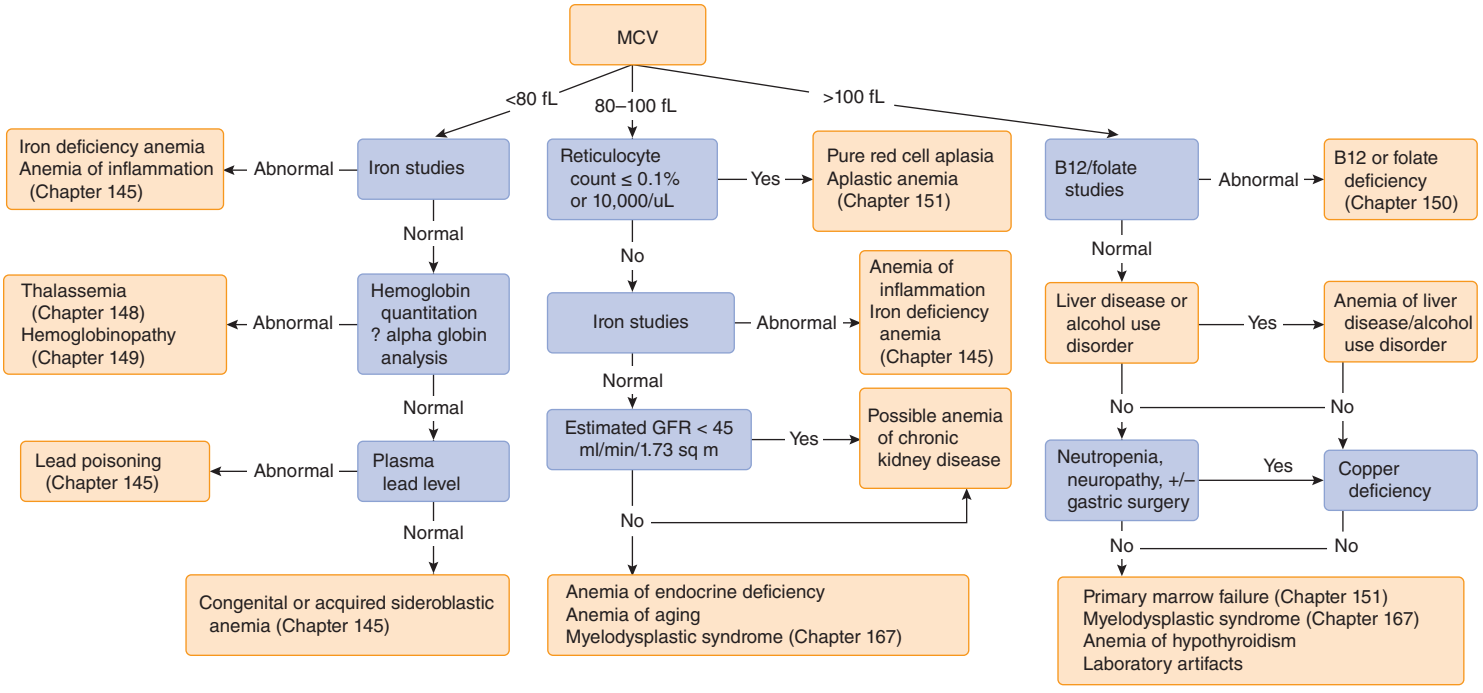

FIGURE 144-3. **Approach to anemia based on the mean corpuscular volume (MCV).** GFR = glomerular filtration rate.

1.73 m^2 surface area is the principal "permissive" condition for anemia of chronic kidney disease.

TREATMENT

The anemia of chronic kidney disease (Chapter 116 and 117) is treated with recombinant erythropoietin or an erythropoietin analog aiming for a hemoglobin level of 9 to 11 g/dL.[A1,A2] Daprodustat, which is an oral inhibitor of hypoxia-inducible factor prolyl hydroxylase and which stimulates erythropoiesis and regulates iron metabolism, is approved by the U.S. Food and Drug Administration (FDA) for patients who are on dialysis.[A3] To avoid the adverse complications of overcorrection or even just correction to normal with erythropoiesis-stimulating agents (such as seizures, accelerated hypertension, or thrombosis), treatment is not started until the hemoglobin concentration is less than 9 g/dL, and is suspended when the hemoglobin target of 9 to 11 g/dL is reached.[7] Iron supplementation should be considered when the transferrin saturation is less than 30% or serum ferritin concentration is less than 500 ng/mL. Hepcidin effects impair iron absorption in renal failure,[8] and intravenous iron is more effective for supplementation than is oral iron.[9] Resistance to erythropoietin therapy most commonly reflects iron deficiency or concurrent inflammation; folate deficiency may also contribute to erythropoietin resistance.

ANEMIA OF LIVER DISEASE

The majority of patients with chronic liver disease are mildly anemic.[10] Total blood volume in cirrhosis and other chronic liver diseases is typically increased 10 to 15%, but may be expanded as much as 30%. Dilution of the red cell mass by expanded plasma volume is a major element in the anemia of liver disease.

The hemoglobin concentration is typically 10 to 12 g/dL in cirrhosis. Red cells are generally macrocytic with an average MCV of 107 fL. Chronic alcohol abuse or even binges of alcohol consumption without established liver disease also cause mild macrocytosis, although the MCV remains generally less than 105 fL. Although alcohol abusers are at increased risk for dietary folate deficiency, folate deficiency typically is not the cause of these changes. Target cells may be present. Target cells in liver disease have an increased diameter that distinguishes them from the microcytic target cells of hemoglobinopathies or thalassemia. The reticulocyte count is generally near the appropriate level for the degree of anemia. Marked reticulocytosis may be seen with spur cell anemia or when recovering from heavy acute alcohol ingestion.

The major pathogenetic factor in the anemia of liver disease is shortened red cell survival. Many mechanisms contribute, with abnormalities in the lipid composition of the red cell membrane likely the most important. Splenic sequestration or abnormalities of oxidative metabolism may also contribute. Other factors that may contribute include suppression of erythroid progenitors by alcohol, dietary folate deficiency, or gastrointestinal blood loss and possible iron deficiency. Spur cell anemia, a morphologically distinctive consequence of abnormal red cell lipid composition in liver disease, may be associated with striking reticulocytosis. Greater than 5% spur cells in the red cell population is associated with decreased survival in liver disease.

Specific treatment of uncomplicated anemia of liver disease is not required, beyond encouraging good nutrition and alcohol abstinence. Patients should be evaluated for concurrent blood loss and iron or folate deficiency.

ANEMIA OF ENDOCRINE DEFICIENCY

Anemia in endocrine deficiencies such as hypothyroidism and adrenal or androgen insufficiency is "adaptive" in a sense, since it reflects an adjustment to downregulated basal metabolism. The degree of anemia is typically mild to moderate and of itself rarely causes symptomatology. These diagnoses should be considered after more significant etiologies of anemia such as iron deficiency or renal insufficiency have been ruled out. Less than one-third of cases of anemia in hypothyroidism are macrocytic; otherwise, anemia in endocrine deficiency is normocytic. Anemia in adrenal insufficiency may be masked by volume contraction. Anemia may be the only finding in androgen deficiency. Treatment of the underlying deficiency corrects the anemia of endocrine deficiency.

PHYSIOLOGIC ANEMIA OF PREGNANCY

A decrease in the hemoglobin concentration is a normal feature of pregnancy. Beginning around the seventh week of pregnancy, the red cell mass begins to expand up to 15 to 25% above prepregnancy baseline. At roughly the same time, the plasma volume begins to expand disproportionately, ultimately reaching 40 to 50% above baseline during weeks 16 to 24.[11] This dilutional anemia with increased red cell mass is referred to as "physiologic anemia of pregnancy." Normocytic anemia with a hemoglobin concentration greater than 11 g/dL in the late first trimester or 10 g/dL in the second and third trimesters of an uncomplicated pregnancy can be attributed to the physiologic anemia of pregnancy without further testing. Lower hemoglobin concentrations or microcytic or macrocytic anemia require evaluation. The mostly likely contributors to anemia in pregnancy are iron deficiency or folate deficiency, demand for both of which is increased during pregnancy. In the absence of a preexisting deficiency or an increased demand induced by hemolysis, the 0.8-mg daily folate dose recommended for neural tube defect prophylaxis is sufficient to avoid folate deficiency during pregnancy in countries where food fortification with folate is standard. Higher doses may be required in other circumstances.[A4] Although routine iron supplementation during pregnancy is generally not recommended in guidelines, it is quite common in the United States; such patients have a lower likelihood of developing iron deficiency in pregnancy or postpartum.

ANEMIA OF AGING

The frequency of anemia in both men and women increases after the age of 50. By age 65, roughly 10% of men and women are anemic. The prevalence of anemia is three- to four-fold increased in African Americans over 65 compared to persons of White European ancestry but only slightly elevated in Latino populations. However, gender-specific mean hemoglobin/hematocrit values for older patients are nearly identical to the overall population mean values.[12] Anemia contributes to frailty and morbidity in aging.

The increased frequency of anemia with aging in part reflects age-related declines in renal function, gastric acidity (required for iron or B_{12} absorption), and testosterone in men, as well as an increased frequency of other pathology.[13] When large populations of anemic elderly patients are evaluated, approximately one third have iron, B_{12}, and/or folate deficiency (with iron deficiency predominant); one third have anemia of inflammation and/or anemia of chronic kidney disease (with anemia of inflammation three times more frequent); and one third have other etiologies, with the largest component being normocytic anemia described as "unexplained anemia of aging." Studies of this entity suggest that it is a cytokine/hepcidin-driven analog of the anemia of inflammation/anemia of chronic disease. Specific treatment is not required. In elderly individuals with persistent unexplained anemia and abnormalities in other lineages or mild macrocytosis, bone marrow examination or molecular analysis to detect clonal disorders such as the myelodysplastic syndromes should be considered.

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145 MICROCYTIC AND HYPOCHROMIC ANEMIAS

THOMAS G. DELOUGHERY

IRON DEFICIENCY

DEFINITION

Iron deficiency occurs when the body iron stores are insufficient to support iron metabolism. Iron deficiency can occur without anemia; in this setting, the lack of iron in tissues leads to fatigue, alopecia, and other symptoms. Further depletion of iron stores, however, will lead to a progressive microcytic anemia. In functional iron deficiency, iron stores are adequate, but the affected individual is unable to mobilize them to support erythropoiesis.

EPIDEMIOLOGY

In the United States, the prevalence of iron deficiency is about 1 to 2% in men but is much higher in women. Women are at greater risk for developing iron deficiency due to obligate iron losses through menstruation, with an average loss of 35 mL of blood and 16 mg of iron per menstrual period. Iron requirements in women average 1 to 3 mg per day, with higher needs for women with heavier menses. Dietary iron intake is often inadequate to maintain iron balance.[1] For example, bone marrow stores may be absent in 25% of healthy college-age women and reduced in another 33%. The average pregnancy requires 900 mg of iron stores, with requirements rising to 6 mg/day at the end of the third trimester. Furthermore, approximately 15% of women lose over 500 mL of blood at delivery, thereby adding further stress on iron stores.[2]

After menstrual blood loss, gastrointestinal bleeding is the second leading cause of iron deficiency. Some bleeding is acute, but gastrointestinal lesions also can cause gradual blood loss over long periods of time (Chapter 121). Gastrointestinal cancer, especially colon cancer but also gastric cancer, is found in up to 10% of older patients with iron deficiency anemia. Ulcers and gastritis are common nonmalignant causes of blood loss.

Iron deficiency is also seen more commonly in the elderly likely due to dietary factors in combination with chronic health conditions. The incidence of iron deficiency also is much higher in developing countries due to the lack of bioavailable dietary sources of iron.

PATHOBIOLOGY

Iron is found in a variety of foods. Meat is the richest source of heme iron, in which iron is in the ferrous form (Fe^{2+}). Iron from nonheme sources is largely in the ferric form (Fe^{3+}), which is reduced by stomach acid to the ferrous form (Fig. 145-1). In the jejunum, two receptors on the mucosal cells absorb iron. One receptor, which is specific for heme-bound iron, absorbs 30 to 40% of ingested heme iron. The other receptor, divalent metal transporter (DMT1), takes up inorganic (nonheme) iron but is much less efficient, thereby explaining the superior absorption of heme iron compared with inorganic iron. Iron is exported from the enterocyte via the transmembrane protein ferroportin (SCL40A1). Iron is subsequently delivered to plasma transferrin, which can carry up to two iron molecules and is the main transport molecule for iron. Transferrin delivers iron to the marrow, where it binds to the transferrin receptor on the red cell membrane.[3] This complex of transferrin-receptor is internalized into the cell by endocytosis. The lower pH of the endosome results in release of iron from the complex. The iron-less complex recycles to the cell surface, transferrin is released, and the cycle restarts. In a growing red cell, about 80,000 transferrin molecules bind on and off every second. Excess iron is taken to the liver, where it is stored. Ferritin, which is the storage protein for iron, consists of 24 ferritin subunits that create a shell that can store up to 4500 iron molecules. In dying red cells, iron contained in hemoglobin is reprocessed by binding to ferritin in macrophages, and it is then transferred to transferrin for recycling, either into newly developing red cells or to storage in the liver. This iron cycle is extremely efficient and loses less than 5% of iron contained in the total red cell mass.

The key protein of iron metabolism, hepcidin, controls iron absorption and the release of iron from its stores.[4] Hepcidin binds to ferroprotein, thereby leading to its degradation. When hepcidin degrades ferroprotein, iron cannot be released from the enterocyte or hepatocytes, thereby leading to both a lack of iron absorption and a halt in iron release to developing red cells. Hepcidin synthesis is upregulated not only by iron but also by inflammation. Hypoxia reduces levels of hepcidin, whereas erythropoiesis and iron deficiency increase levels of hepcidin. Rare mutations in proteins of iron absorption can lead to severe iron deficiency, but these conditions most commonly present in childhood.

The two major causes of iron deficiency are blood loss and reduced absorption of iron. Blood loss, most commonly from gynecologic or gastrointestinal sources, is the predominant cause for iron deficiency. The other mechanisms for iron deficiency are issues with the absorption of iron and the influence of iron-poor diets (Table 145-2). For example, the increasing avoidance of dietary meat is leading to an increase in iron deficiency because nonheme iron can be inadequate to maintain iron stores, especially in women. Lactovegetarians are at even higher risk.[5]

Gastrointestinal Causes

Any source of gastrointestinal bleeding (Chapter 121) can cause iron deficiency, but some gastrointestinal diseases have additional adverse effects on iron balance. For example, *Helicobacter pylori* infections can result in iron deficiency because of bleeding from ulcers (Chapter 125), but infection also results in achlorhydria, which impairs the ability to convert iron from its ferric to its ferrous form and thereby decreases the absorption of iron. *Heliobacter pylori* infections may also lead to autoimmune gastritis, which leads to iron deficiency in its early stages and to B_{12} deficiency in its later stages.

Obese patients are often iron deficient, with about 8% of obese patients having elevated hepcidin levels as a marker of reduced iron absorption. After bariatric surgery, the prevalence of iron deficiency can be as high as 50%,

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Iron deficiency is also seen more commonly in the elderly likely due to dietary factors in combination with chronic health conditions. The incidence of iron deficiency also is much higher in developing countries due to the lack of bioavailable dietary sources of iron.

PATHOBIOLOGY

Iron is found in a variety of foods. Meat is the richest source of heme iron, in which iron is in the ferrous form (Fe^{2+}). Iron from nonheme sources is largely in the ferric form (Fe^{3+}), which is reduced by stomach acid to the ferrous form (Fig. 145-1). In the jejunum, two receptors on the mucosal cells absorb iron. One receptor, which is specific for heme-bound iron, absorbs 30 to 40% of ingested heme iron. The other receptor, divalent metal transporter (DMT1), takes up inorganic (nonheme) iron but is much less efficient, thereby explaining the superior absorption of heme iron compared with inorganic iron. Iron is exported from the enterocyte via the transmembrane protein ferroportin (SCL40A1). Iron is subsequently delivered to plasma transferrin, which can carry up to two iron molecules and is the main transport molecule for iron. Transferrin delivers iron to the marrow, where it binds to the transferrin receptor on the red cell membrane.[3] This complex of transferrin-receptor is internalized into the cell by endocytosis. The lower pH of the endosome results in release of iron from the complex. The iron-less complex recycles to the cell surface, transferrin is released, and the cycle restarts. In a growing red cell, about 80,000 transferrin molecules bind on and off every second. Excess iron is taken to the liver, where it is stored. Ferritin, which is the storage protein for iron, consists of 24 ferritin subunits that create a shell that can store up to 4500 iron molecules. In dying red cells, iron contained in hemoglobin is reprocessed by binding to ferritin in macrophages, and it is then transferred to transferrin for recycling, either into newly developing red cells or to storage in the liver. This iron cycle is extremely efficient and loses less than 5% of iron contained in the total red cell mass.

The key protein of iron metabolism, hepcidin, controls iron absorption and the release of iron from its stores.[4] Hepcidin binds to ferroprotein, thereby leading to its degradation. When hepcidin degrades ferroprotein, iron cannot be released from the enterocyte or hepatocytes, thereby leading to both a lack of iron absorption and a halt in iron release to developing red cells. Hepcidin synthesis is upregulated not only by iron but also by inflammation. Hypoxia reduces levels of hepcidin, whereas erythropoiesis and iron deficiency increase levels of hepcidin. Rare mutations in proteins of iron absorption can lead to severe iron deficiency, but these conditions most commonly present in childhood.

The two major causes of iron deficiency are blood loss and reduced absorption of iron. Blood loss, most commonly from gynecologic or gastrointestinal sources, is the predominant cause for iron deficiency. The other mechanisms for iron deficiency are issues with the absorption of iron and the influence of iron-poor diets (Table 145-2). For example, the increasing avoidance of dietary meat is leading to an increase in iron deficiency because nonheme iron can be inadequate to maintain iron stores, especially in women. Lactovegetarians are at even higher risk.[5]

Gastrointestinal Causes

Any source of gastrointestinal bleeding (Chapter 121) can cause iron deficiency, but some gastrointestinal diseases have additional adverse effects on iron balance. For example, *Helicobacter pylori* infections can result in iron deficiency because of bleeding from ulcers (Chapter 125), but infection also results in achlorhydria, which impairs the ability to convert iron from its ferric to its ferrous form and thereby decreases the absorption of iron. *Heliobacter pylori* infections may also lead to autoimmune gastritis, which leads to iron deficiency in its early stages and to B_{12} deficiency in its later stages.

Obese patients are often iron deficient, with about 8% of obese patients having elevated hepcidin levels as a marker of reduced iron absorption. After bariatric surgery, the prevalence of iron deficiency can be as high as 50%,

ABSTRACT

Microcytic and hypochromic anemias are anemias in which the size of the red blood cell (mean corpuscular volume or MCV) is reduced due to impaired production of hemoglobin, thereby resulting in a reduced hemoglobin content (mean corpuscular hemoglobin or MCH) and mean corpuscular hemoglobin concentration (MCHC). Iron deficiency anemia is caused by inadequate iron stores, anemia of chronic disease is a consequence of iron sequestration, and inherited microcytic anemias are caused by a variety of mutations in the iron absorption pathway. Thalassemia is caused by reduced synthesis of the normal hemoglobin protein. Finally, the rare sideroblastic anemias are microcytic because of defects in the synthesis of heme. Treatment requires identification of its cause. Iron can be replaced orally or intravenously.

KEYWORDS

iron deficiency
anemia of chronic inflammation
sideroblastic anemia
iron metabolism
iron-refractory iron deficiency anemia

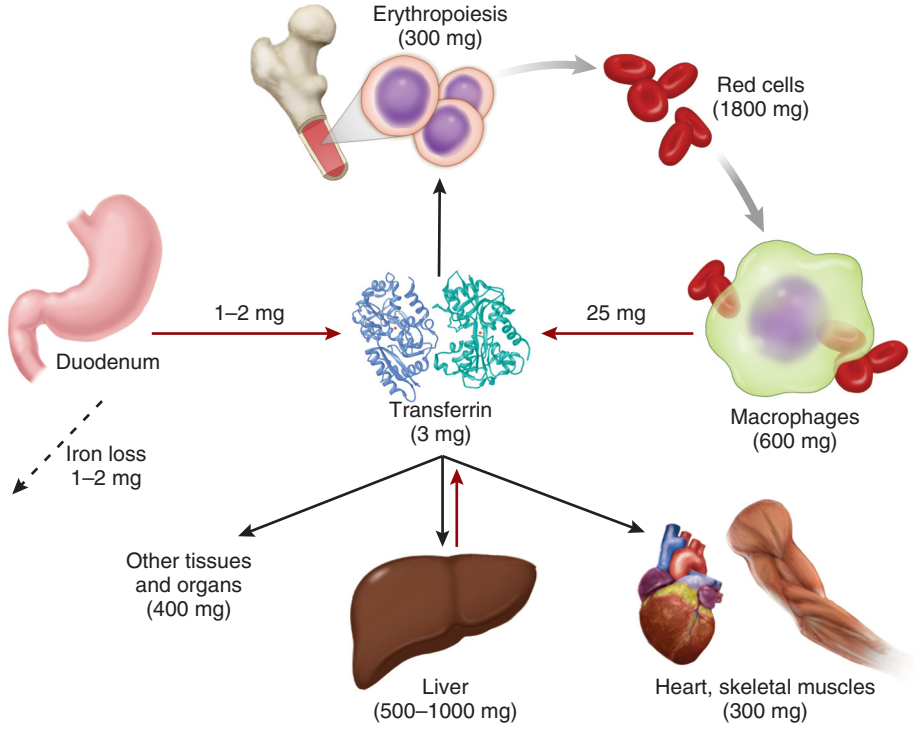

FIGURE 145-1. Iron distribution in the body. Schematic representation of iron distribution in the body. The iron carrier transferrin transports iron to all organs. The average content of iron in different tissues/organs for an adult male is shown in parentheses. Most iron is consumed for hemoglobin synthesis in red blood cells. Iron recycling from macrophages, which clear senescent red cells by phagocytosis, provides most usable iron. Duodenal iron absorption is limited to 1 to 2 mg daily and corresponds to the daily physiologic loss. (From Camaschella C. Microcytic and hypochromic anemias. In: Goldman L, Schafer AI, eds. *Goldman-Cecil Medicine*. 26th ed. Philadelphia: Elsevier; 2020:1035-1040.)

TABLE 145-1 MICROCYTIC HYPOCHROMIC ANEMIA

- Iron deficiency
  - See Table 145-2
- Anemia of inflammation – blocked delivery of iron to the developing red cell
- Thalassemia – disruption of hemoglobin protein synthesis
- Sideroblastic anemia – disruption of heme synthesis
  - Congenital
    - *ALAS2* mutations
    - *SLC25A38* mutations
    - *GLRX5* mutations
  - Acquired
    - Myelodysplastic syndromes
    - Drugs/toxins
      - Ethanol
      - Isoniazid
      - Linezolid
      - Pyrazinamide
    - Copper deficiency

TABLE 145-2 CAUSES OF IRON DEFICIENCY

- Menstrual losses
- Pregnancy and delivery
- Gastrointestinal causes
  - Cancer
  - Gastritis
  - *Helicobacter pylori*
    - Atrophic gastritis
    - Ulcers
  - Bariatric surgery
  - Celiac disease (even with gluten-free diet)
  - Hookworm and other parasites
  - Inflammatory bowel disease
  - Meckel diverticulum
  - Vascular malformations
- Diet
- Drugs
  - Aspirin
  - Nonsteroidal anti-inflammatory agents
  - Proton pump inhibitors
- Hematuria
- Athletes undergoing intense training
- Obesity
- Inherited defects in iron metabolism

with the prevalence increasing every subsequent year after surgery. Since the main site of gastrointestinal iron absorption is the duodenum, surgeries that bypass this part of the bowel are associated with a higher incidence of iron deficiency. For example, the risk is higher for more complex surgeries, such as the Roux-en-Y, than sleeve gastrectomy.[6]

Athletes are at risk for iron deficiency, with gastrointestinal blood loss as the major cause. Furthermore, exercise-induced hemolysis, caused by foot striking and perhaps also by intense muscle contractions, can lead to urinary losses of iron. Decreased iron absorption may also contribute because levels of hepcidin are often elevated in athletes due to training-induced inflammation.

Patients who have inflammatory bowel disease (Chapter 127) have a high prevalence of iron deficiency because bowel inflammation results in reduced absorption of iron as well as gastrointestinal blood loss. In addition, the marked inflammatory state leads to a rise in hepcidin levels, thereby blocking iron absorption. Celiac disease (Chapter 126) can also be accompanied by severe iron deficiency, owing to reduced absorption of iron, gastrointestinal blood loss, and increased hepcidin levels. Even when on a gluten-free diet, patients may not be able to absorb enough iron to avoid long-term iron deficiency.[7]

Both aspirin and nonsteroidal anti-inflammatory agents can lead to iron deficiency through overt bleeding from ulcers and/or increased subtle gastrointestinal blood loss. For example, a daily aspirin increases blood loss from 0.8 mL/day to 5.0 mL/day. Protein pump inhibitors reduce stomach acid, hinder the conversion of ferric to ferrous iron, and can lead to iron deficiency. This risk of iron deficiency is less with H_2-blockers.

Parasitic infections are a common cause of gastrointestinal blood loss in developing countries. Hookworm infections (Chapter 327) are classically associated with iron deficiency, with each worm capable of ingesting 0.5 mL of blood a day. Other parasites associated with iron deficiency are whipworm (Chapter 327) and schistosomiasis (Chapter 326).

Other Causes

Another source of blood loss is the genitourinary system. Bladder or renal lesions that result in chronic hematuria can lead to iron deficiency over time. In women, a frequent source of excess menstruation is dysfunctional uterine bleeding and fibroids (Chapter 184). In chronic hemolytic disorders (Chapters 146 and 147), ongoing hemoglobinuria can rarely result in iron deficiency.

Patients who have heart failure (Chapter 45) have an increased prevalence of both overt and functional iron deficiency, with rates of true iron deficiency as high as 13 to 42% and an even higher percentage having functional iron deficiency. In patients who are on renal dialysis (Chapter 117), blood loss with dialysis and the use of erythropoiesis-stimulating agents lead to depletion of iron stores. The effective use of erythropoiesis-stimulating agents requires efficient mobilization of stored iron, but this process can be blunted by the inflammation of renal disease.

CLINICAL MANIFESTATIONS

Because iron deficiency anemia often slowly worsens, otherwise healthy patients may tolerate marked anemia. As a result, iron deficiency anemia is often first suggested based on a complete blood count ordered for routing screening. Iron deficiency anemia is usually suspected or diagnosed from results of blood tests pointing to microcytic anemia, low serum iron, and low ferritin.[8]

Iron deficiency can lead to symptoms due to both the lack of iron itself and the resultant anemia. The most common and disabling symptom of iron deficiency anemia is fatigue, which can occur with even modest reductions in iron stores. Older patients with underlying comorbid conditions typically develop dyspnea and may even develop new onset or worsening angina.

A common complaint in iron-deficient women is hair loss, with increased loss reported in women with ferritins under 100 ng/dL. The pattern most associated with iron deficiency is diffuse nonscarring scalp alopecia (Chapter 409). Another common symptom of iron deficiency is cold intolerance, perhaps because iron is important for the effectiveness of thyroid hormone. Restless leg syndrome (Chapter 374), in which patients have leg cramps, unpleasant leg sensations, and the need to move the legs at night, is also a symptom of low iron stores.[9] Some patients report increased bruising and/or generalized pruritus. In advanced iron deficiency, patients may develop glossitis, angular stomatitis, brittle or spoon nails (koilonychia), or dysphagia due to esophageal webs (Plummer-Vinson syndrome).

Pica, which is an unusual craving for eating ice or clay, is a common symptom in patients with iron deficiency. While this overall condition is not specific for iron deficiency, the preference for eating ice may be both sensitive and specific for the condition.

DIAGNOSIS

The serum ferritin level correlates with body iron stores in healthy patients and is the most reliable and cost-effective test to diagnose iron deficiency. Since ferritin is an acute phase reactant, an iron-replete patient may have a very high ferritin level, but it is rare for an iron-deficient patient to have a ferritin level over 100 ng/mL. A ferritin level of less than 15 ng/mL is very specific for iron deficiency, but iron deficiency cannot be excluded in older patients or in patients who have inflammatory conditions unless the ferritin level is greater than 100 ng/mL. Ferritin values under 50 ng/mL should be considered abnormal in a symptomatic patient.

The anemia of iron deficiency is classically a microcytic anemia (Table 145-1) without reticulocytosis (Fig. 145-2), but these findings are neither sensitive nor specific (Table 145-3) since thalassemia and the anemia of inflammation (Chapter 144) can also lead to microcytosis. A low red cell mean corpuscular volume is generally a late finding seen with severe iron deficiency, but concurrent medical issues such as liver disease, folate deficiency, or B_{12} deficiency (Chapter 144) may blunt or obscure the decrease in red cell size.

A serum iron level is not effective as a diagnostic test since it is low in the anemia of inflammation, can be falsely elevated with oral iron intake in iron-deficient patients, and varies markedly from day to day. An elevated total iron binding capacity (TIBC) is specific for iron deficiency, but its sensitivity is low because it is reduced by inflammation, aging, and poor nutrition. Iron saturation percentages are also unreliable because they depend on both the TIBC and serum iron level, so saturation is also low in the anemia of chronic disease. Serum levels of soluble transferrin receptor are increased in iron deficiency, and levels also can be increased in any condition associated with increased red cell mass, such as in hemolytic anemias. The gold standard for iron deficiency is the bone marrow iron stain, but this invasive and expensive procedure is rarely, if ever, indicated.

Determining the Underlying Cause

A priority in care of the patient with iron deficiency is determining the cause. Given that the body has no natural mechanisms for eliminating iron, blood loss must always be assumed.[10] Testing of the stool for blood can identify patients with blood loss; however, most stool tests require 10 mL or more of daily blood loss to be positive, and losses less than 10 mL/day can still lead to iron deficiency. Because of this limitation, any man with unexplained iron deficiency or any iron-deficient woman over age 40 years should undergo both upper and lower gastrointestinal endoscopy to evaluate for occult blood loss (see Fig. 121-6). In problematic cases, capsule endoscopy may be required (Chapter 121).[11] Premenopausal women over age 40 years should also undergo testing, as should any person with gastrointestinal symptoms, family history of colon cancer, weight loss, or blood in the stool. A thorough menstrual history should be also obtained. A urinalysis is important, although occult hematuria is rarely persistent enough to lead to iron deficiency.

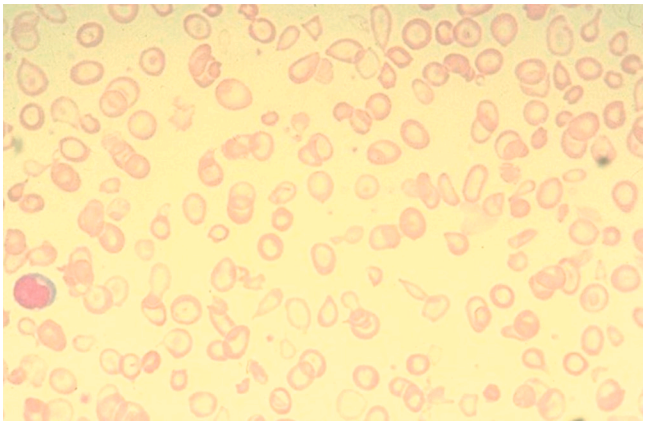

FIGURE 145-2. Microcytic hypochromic blood smear.

Differential Diagnosis

Iron deficiency anemia must be distinguished from α- or ß-thalassemia, in which serum iron and serum ferritin levels are normal or high. A low serum iron level with a high ferritin level is typical of the anemia of chronic inflammation, in which serum hepcidin levels are normal or high, and inflammatory markers such as the erythrocyte sedimentation rate and the C-reactive protein level are usually elevated. Sideroblastic anemia is associated with iron overload and an increased ferritin level; it can be confirmed by finding ringed sideroblasts on bone marrow smears.

TREATMENT

Repletion of iron can ameliorate symptoms of iron deficiency and restore a normal red blood cell mass. Eating a diet higher in bioavailable iron can help treat iron deficiency[A1] and can maintain iron stores, but even the best diet alone is usually inadequate to replete iron stores. Meat is the food that is richest in iron due to its heme iron. Cooking with iron skillets can also increase dietary iron, but the amount of iron enrichment is variable.

Oral Iron Supplementation

Ferrous sulfate (325 mg once daily) is effective for patients without conditions that preclude oral therapy. However, lower doses (15 to 20 mg of elemental iron daily) can be as effective and are better tolerated with fewer gastrointestinal side effects.[12]

Multiple oral iron preparations exist (Table 145-4), and no one compound appears to be superior to another.[A2] If ferrous sulfate is not tolerated, then ferrous gluconate, which has less elemental iron per tablet, can be tried.

The iron supplement is best taken on an empty stomach or with meat protein (cow, pork, and fish) to increase its absorption. Vitamin C may also increase the absorption of iron, whereas concomitant calcium and fiber can decrease its absorption. Tea, which is a potent inhibitor of iron absorption, can reduce absorption by 90%. Coffee also decreases iron absorption by about 60%.

With oral supplementation, the reticulocyte count should rise within 1 week, and hemoglobin concentration should start rising by the second week of therapy. Iron should be continued until iron stores are replete, with a goal ferritin level of 50 to 100 ng/dL.

Gastrointestinal side effects of oral iron are common, with 30 to 50% of patients reporting symptoms that may be related to esophageal erosions and gastritis. The side effects of stomach pain and constipation can hinder compliance. Taking a smaller dose of elemental iron and even decreasing to every other day can maintain effectiveness[A3] while reducing these symptoms. In patients whose iron deficiency does not respond to oral iron, adherence to and tolerability of oral iron should be assessed. Conditions to consider include celiac disease (Chapter 126), autoimmune gastritis (Chapter 125), *Helicobacter pylori* infections, persistent menorrhagia, and ongoing gastrointestinal losses.

TABLE 145-3 DIAGNOSIS OF IRON DEFICIENCY

TEST	IRON DEFICIENCY	ANEMIA OF CHRONIC INFLAMMATION	IRON DEFICIENCY AND INFLAMMATION	SIDEROBLASTIC ANEMIA
Serum iron	Decreased	Decreased	Decreased	Often increased
Mean corpuscular volume	Decreased/Normal	Decreased/Normal	Decreased/Normal	Normal
Total iron-binding capacity	Increased	Decreased	Decreased/Normal	Normal
Saturation (%)	Decreased (usually <16%)	Decreased (usually <30%)	Decreased (usually <20%)	Increased (usually >45%)
Ferritin (μg/L)	Decreased (usually <15 ng/mL)	Increased (usually >200 ng/mL)	Decreased (usually <100 ng/mL)	Increased (usually >200 ng/mL)

TABLE 145-4 COMMONLY PREPARED IRON PREPARATIONS

AGENT	TYPICAL SINGLE DOSE
ORAL	
Ferrous sulfate	325 mg (65 mg elemental iron)
Ferrous gluconate	325 mg (35 mg elemental iron)
Iron bisglycinate	25 mg elemental iron
INTRAVENOUS	
Ferric carboxymaltose	750-1000 mg
Ferric derisomaltose	1000 mg
Ferumoxytol	510-1020 mg
Low molecular weight iron dextran	1000 mg

Intravenous Iron Therapy

Parenteral iron should be used in any iron-deficient patient who is not responding to or cannot tolerate oral iron. If the hemoglobin concentration has not responded within 2 weeks, it is unlikely the patient will respond to oral iron. In patients who have ongoing bleeding, the iron loss may be too great for oral iron to overcome. Bowel issues, such as surgical resection or inflammatory bowel disease, can also lead to resistance to oral iron. *H. pylori* infection and celiac disease lead to impaired absorption of iron. Patients with known absorption problems, such as history of bowel surgery or bariatric procedures, should preferentially receive intravenous iron. In pregnancy, intravenous iron has been shown to be superior to oral iron.[A4]

Replacement iron formulations include low molecular weight iron dextran (given as a 1000 mg single replacement dose over one hour), ferumoxytol (given as 510 mg over 15 minutes, repeated once in 3 to 8 days), ferric carboxymaltose (given as two 750 mg doses a week apart), and ferric derisomaltose (up to 1000 mg over 20 minutes). Patients who need a magnetic resonance imaging scan must inform their doctors if they received ferumoxytol because it can function as a contrast agent. With iron carboxymaltose, about 75% of recipients experience a fall in the serum phosphorus level to less than 2.0 mg/dL,[A5] and symptomatic hypophosphatemia can occur.

All intravenous iron preparations contain carbohydrates that bind the elemental iron to prevent reactions. Nevertheless, a disadvantage of intravenous iron is an infusion reaction, which is not a true allergic reaction but rather is related to the activation of complement by the labile free iron (complement activation-related pseudoallergy). Since these reactions are not allergic in nature, administering a test dose is not helpful. Rates of mild reactions are about 1 in 200, and rates of major reactions are about 1 in 200,000. Reactions that require hospitalization are very rare but can be seen with any iron product.[13] Iron infusion should be administered under the supervision of experienced clinicians who are skilled and equipped to deal with infusion reactions. All patients should be observed for 30 minutes after the infusion. Diphenhydramine premedication should be avoided because it can worsen symptoms.

In general, the infusion is stopped for mild reactions and then resumed at a slower rate once symptoms resolve. For more severe reactions, fluids (e.g., 500 mL of normal saline) and corticosteroids (e.g., 150 to 500 mg of hydrocortisone) are helpful. If patients do not respond or develop anaphylaxis (Chapter 233), they should also be treated with epinephrine intravenously (1 mL or a 1/10,000 solution) or intramuscularly (0.3 to 0.5 mL of a 1/1000 solution), oxygen, and more fluids; such patients should be transferred to an acute care setting.

Formulas that calculate the total iron deficit tend to be unreliable, so the most pragmatic approach is to use a 1000-mg replacement dose. Patients with severe iron deficiency anemia may have deficits that exceed 1 g, so a ferritin level should be checked 2 to 4 weeks after an infusion. If the ferritin is not higher than 50 ng/dL at that time, another iron dose should be given. After a patient receives intravenous iron, the ferritin should be checked every 3 to 4 months; if it falls below 50 ng/dL, the iron infusion should be repeated. Patients with ongoing gastrointestinal bleeding should have the ferritin level checked more often and may require frequent infusions.

Oral iron supplementation in iron-deficient but not anemic women (serum ferritin measurements under 50 ng/mL) improves fatigue. In patients who have heart failure, repletion of deficient iron stores can improve cardiac function and quality of life, and also to reduce hospitalization.[A6–A8] In such patients, intravenous iron replacement appears to be superior to oral replacement.[A9] In patients who have restless leg syndrome (Chapter 374) with abnormal ferritin levels, iron replacement can markedly reduce symptoms.[A10] In patients who are on hemodialysis, proactive iron treatment is preferred over reactive treatment.[A11]

PREVENTION

The recommended dietary iron intake is 8 mg/day for adults and postmenopausal women, 18 mg for premenopausal women, and 27 mg/day during pregnancy. Meats are rich in heme iron, and iron in meat is much more effectively absorbed. Nonmeat sources of iron contain less bioavailable iron, and it is difficult to ingest large enough amounts to meet iron requirements.

PROGNOSIS

The prognosis of iron deficiency is excellent once stores are replete. Some patients, especially those who have had bariatric surgery or inflammatory bowel disease, may require chronic iron infusions.

ANEMIA OF CHRONIC DISEASE (ANEMIA OF INFLAMMATION)

Any type of illness can be accompanied by an anemia that is due to direct results of the inflammatory state. Although this type of anemia especially accompanies cancer and severe infections, it is increasingly recognized as a complication of conditions such as heart failure[14] and chronic pulmonary disease.[15]

PATHOBIOLOGY

Inflammation leads to anemia by several different mechanisms.[16] Inflammatory cytokines such as interleukin (IL)-6 increase the levels of serum hepcidin, which blocks the absorption of iron. The impaired release of iron from its stores results in iron-restricted erythropoiesis. Normally, ferroportin allows export of iron from enterocytes, macrophages, and hepatocytes. However, hepcidin binds to and leads to the degradation of ferroportin, which blocks the export of iron to the blood and to developing red cells. These cytokines also suppress the production of erythropoietin, so serum erythropoietin levels will be lower than predicted for a given degree of anemia. In addition, the half-life of the red cell is shorter.

CLINICAL MANIFESTATIONS AND DIAGNOSIS

The degree of anemia varies with the degree of inflammation. Most patients will have hemoglobin concentrations in the 8 to 10 g/dL range, but concentrations can be as low as 7 g/dL. The anemia of inflammation can be microcytic, owing to the impaired delivery of iron to the developing erythrocyte, but it is rare to be less than 70 fL. The anemia can further add to the symptomatic burden of the underlying disorder.

The diagnosis is typically made by excluding other causes for the anemia (e.g., nutritional deficiencies of iron, folate, or vitamin B_{12}, multiple myeloma in older patients, bone marrow disorders) and documenting the presence of adequate iron stores (serum ferritin > 100 ng/dL). Serum levels of erythropoietin are lower than would be expected for the degree of anemia. Due to iron sequestration, the iron saturation percentage is decreased.

TREATMENT

The most effective therapy of anemia of chronic disease is treatment of the underlying disorder. Unless the patient is frankly iron deficient, patients do not benefit from either oral or intravenous iron unless they are also receiving an indicated erythropoiesis-stimulating agent. Such agents are commonly prescribed in chronic kidney disease (Chapters 116 and 117) and sometimes prescribed in cancer patients who are undergoing chemotherapy, but they are not generally used for other causes. In the future, the use of hepcidin antagonists may be of benefit.

SIDEROBLASTIC ANEMIA

The rarest cause of microcytic anemia are the sideroblastic anemias. By definition, ringed sideroblasts must be seen on bone marrow examination. Ringed sideroblasts are abnormal red cell precursors in which aggregates of iron surround the nucleus due to disruption of the synthesis of heme.[17]

Sideroblastic anemia can be acquired or inherited.[18] The most common inherited form is X-linked sideroblastic anemia due to mutations in the *ALAS2* gene. The enzyme product of this gene controls the first step in the synthesis of heme, so mutations lead to disruption of its synthesis. Rarer autosomal recessive forms include mutations in *SLC25A38*, which is needed to import the amino acid glycine that is required for the synthesis of heme, and glutaredoxin 5, which impairs *ALAS2* gene translation.

Acquired forms of sideroblastic anemia can be due to myelodysplastic syndromes (Chapter 167) or to drugs or toxins that interfere with the synthesis of heme. Implicated drugs include ethanol, isoniazid, pyrazinamide, and linezolid. Copper deficiency, either because of inadequate dietary intake or overabundant ingestion of zinc, can lead to ringed sideroblasts.[19]

CLINICAL MANIFESTATIONS AND DIAGNOSIS

Given the number of entities that can lead to sideroblastic anemia, presentations can vary. Younger patients presenting with inherited sideroblastic anemia will present with microcytic anemia. In acquired forms, red cells can range from microcytic to macrocytic, but the blood smear will show a population of microcytic red cells. In copper deficiency, patients often have neurologic manifestations such as myelopathy.

Diagnosis is made by a bone marrow examination that shows ringed sideroblasts (Fig. 145-3). Precise diagnosis can be made by use of molecular diagnostic techniques once drugs and toxins have been excluded.

TREATMENT AND PROGNOSIS

Treatment of inherited sideroblastic anemia is supportive with transfusion and management of the subsequent iron overload, although some patients will respond to high-dose vitamin B6 (pyridoxine) or to a stem cell transplant.[20] For acquired forms, discontinuation of the toxic agent is crucial and, as in the case of alcohol-induced sideroblastosis (Chapter 364), may lead to rapid resolution with adequate nutrition. For myelodysplastic syndrome (Chapter 167), treatment of the underlying marrow disease is indicated.

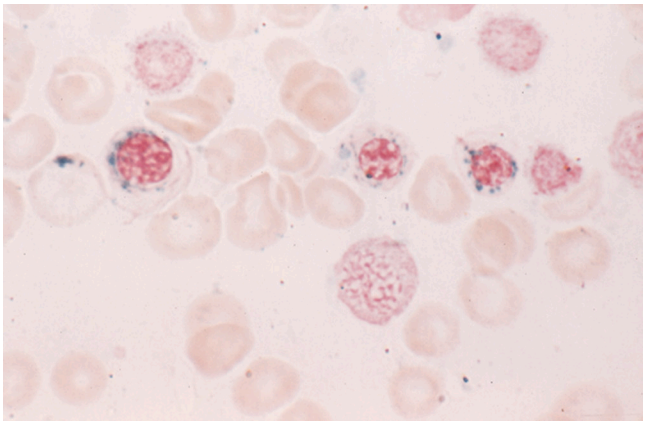

FIGURE 145-3. Ringed sideroblasts. Prussian blue iron stain of the bone marrow shows ringed sideroblasts, which are erythroblasts with perinuclear rings of iron-laden mitochondria. (From Camaschella C. Microcytic and hypochromic anemias. In: Goldman L, Schafer AI, eds. *Goldman-Cecil Medicine*. 26th ed. Philadelphia: Elsevier; 2020:1035-1040.)

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146 AUTOIMMUNE AND INTRAVASCULAR HEMOLYTIC ANEMIAS

MARC MICHEL

DEFINITION

Hemolytic anemia is defined as an anemia due to a shortened lifespan of mature red blood cells (RBCs) in the peripheral blood. According to the cause, hemolysis and accelerated destruction of RBCs can take place within the vasculature (intravascular hemolysis) and/or in the liver or spleen (extravascular hemolysis). Hemolytic anemia can be the consequence of an intrinsic (intracorpuscular) and often genetically determined defect of the red cell membrane or a red cell constituent (hemoglobin structure or enzyme machinery). Alternatively, hemolytic anemia can result from an extrinsic (extracorpuscular) and typically acquired abnormality that attacks the RBC's membrane (immune, infectious, toxic) (Table 146-1).

Autoimmune hemolytic anemia is a rare acquired autoimmune disease in which autoantibodies directed toward autologous red cell membrane antigens lead to their accelerated destruction.[1] The diagnosis of autoimmune hemolytic anemia is thus based on the presence of a positive direct antiglobulin (Coombs) test and on the absence of any other hereditary or acquired cause of hemolysis.[2] In autoimmune hemolytic anemia, hemolysis is mainly extravascular, but some features of concomitant intravascular hemolysis may be present at onset. In addition to autoimmune hemolytic anemia, other causes of immune-mediated hemolytic anemias that are not mediated by autoantibodies may occur, including some drug-induced hemolytic anemias or post-transfusional hemolytic reactions due to the presence of alloantibodies or to other more complex mechanisms. Paroxysmal nocturnal hemoglobinuria (PNH) is a rare and potentially life-threatening acquired clonal blood disorder with protean manifestations in which RBCs are abnormally vulnerable to activation of complement. The resulting chronic intravascular hemolysis is the hallmark of the classic hemolytic form of the disease, with the release of free hemoglobin contributing to many of its clinical manifestations.

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TREATMENT

The most effective therapy of anemia of chronic disease is treatment of the underlying disorder. Unless the patient is frankly iron deficient, patients do not benefit from either oral or intravenous iron unless they are also receiving an indicated erythropoiesis-stimulating agent. Such agents are commonly prescribed in chronic kidney disease (Chapters 116 and 117) and sometimes prescribed in cancer patients who are undergoing chemotherapy, but they are not generally used for other causes. In the future, the use of hepcidin antagonists may be of benefit.

SIDEROBLASTIC ANEMIA

The rarest cause of microcytic anemia are the sideroblastic anemias. By definition, ringed sideroblasts must be seen on bone marrow examination. Ringed sideroblasts are abnormal red cell precursors in which aggregates of iron surround the nucleus due to disruption of the synthesis of heme.[17]

Sideroblastic anemia can be acquired or inherited.[18] The most common inherited form is X-linked sideroblastic anemia due to mutations in the *ALAS2* gene. The enzyme product of this gene controls the first step in the synthesis of heme, so mutations lead to disruption of its synthesis. Rarer autosomal recessive forms include mutations in *SLC25A38*, which is needed to import the amino acid glycine that is required for the synthesis of heme, and glutaredoxin 5, which impairs *ALAS2* gene translation.

Acquired forms of sideroblastic anemia can be due to myelodysplastic syndromes (Chapter 167) or to drugs or toxins that interfere with the synthesis of heme. Implicated drugs include ethanol, isoniazid, pyrazinamide, and linezolid. Copper deficiency, either because of inadequate dietary intake or overabundant ingestion of zinc, can lead to ringed sideroblasts.[19]

CLINICAL MANIFESTATIONS AND DIAGNOSIS

Given the number of entities that can lead to sideroblastic anemia, presentations can vary. Younger patients presenting with inherited sideroblastic anemia will present with microcytic anemia. In acquired forms, red cells can range from microcytic to macrocytic, but the blood smear will show a population of microcytic red cells. In copper deficiency, patients often have neurologic manifestations such as myelopathy.

Diagnosis is made by a bone marrow examination that shows ringed sideroblasts (Fig. 145-3). Precise diagnosis can be made by use of molecular diagnostic techniques once drugs and toxins have been excluded.

TREATMENT AND PROGNOSIS

Treatment of inherited sideroblastic anemia is supportive with transfusion and management of the subsequent iron overload, although some patients will respond to high-dose vitamin B6 (pyridoxine) or to a stem cell transplant.[20] For acquired forms, discontinuation of the toxic agent is crucial and, as in the case of alcohol-induced sideroblastosis (Chapter 364), may lead to rapid resolution with adequate nutrition. For myelodysplastic syndrome (Chapter 167), treatment of the underlying marrow disease is indicated.

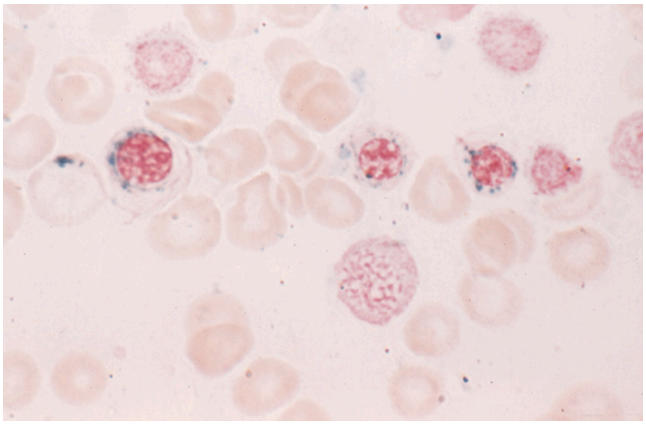

FIGURE 145-3. Ringed sideroblasts. Prussian blue iron stain of the bone marrow shows ringed sideroblasts, which are erythroblasts with perinuclear rings of iron-laden mitochondria. (From Camaschella C. Microcytic and hypochromic anemias. In: Goldman L, Schafer AI, eds. *Goldman-Cecil Medicine*. 26th ed. Philadelphia: Elsevier; 2020:1035-1040.)

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146 AUTOIMMUNE AND INTRAVASCULAR HEMOLYTIC ANEMIAS

MARC MICHEL

DEFINITION

Hemolytic anemia is defined as an anemia due to a shortened lifespan of mature red blood cells (RBCs) in the peripheral blood. According to the cause, hemolysis and accelerated destruction of RBCs can take place within the vasculature (intravascular hemolysis) and/or in the liver or spleen (extravascular hemolysis). Hemolytic anemia can be the consequence of an intrinsic (intracorpuscular) and often genetically determined defect of the red cell membrane or a red cell constituent (hemoglobin structure or enzyme machinery). Alternatively, hemolytic anemia can result from an extrinsic (extracorpuscular) and typically acquired abnormality that attacks the RBC's membrane (immune, infectious, toxic) (Table 146-1).

Autoimmune hemolytic anemia is a rare acquired autoimmune disease in which autoantibodies directed toward autologous red cell membrane antigens lead to their accelerated destruction.[1] The diagnosis of autoimmune hemolytic anemia is thus based on the presence of a positive direct antiglobulin (Coombs) test and on the absence of any other hereditary or acquired cause of hemolysis.[2] In autoimmune hemolytic anemia, hemolysis is mainly extravascular, but some features of concomitant intravascular hemolysis may be present at onset. In addition to autoimmune hemolytic anemia, other causes of immune-mediated hemolytic anemias that are not mediated by autoantibodies may occur, including some drug-induced hemolytic anemias or post-transfusional hemolytic reactions due to the presence of alloantibodies or to other more complex mechanisms. Paroxysmal nocturnal hemoglobinuria (PNH) is a rare and potentially life-threatening acquired clonal blood disorder with protean manifestations in which RBCs are abnormally vulnerable to activation of complement. The resulting chronic intravascular hemolysis is the hallmark of the classic hemolytic form of the disease, with the release of free hemoglobin contributing to many of its clinical manifestations.

ABSTRACT

Autoimmune hemolytic anemia is a rare acquired autoimmune disease in which autoantibodies directed toward autologous membrane antigens on red blood cells (RBCs) lead to their accelerated destruction. The presence of RBC-bound autoantibodies is demonstrated by a positive direct antiglobulin test, and autoimmune hemolytic anemia is classified into warm or cold autoimmune hemolytic anemia according to the temperature at which autoantibodies bind optimally to RBCs. Autoimmune hemolytic anemia may lead to various degrees of both extravascular and intravascular hemolysis and can sometimes be life-threatening. Paroxysmal nocturnal hemoglobinuria (PNH) is a very rare cause of hemolytic anemia and should be suspected in an adult with an acquired direct antiglobulin test–negative intravascular hemolytic anemia.

KEYWORDS

hemolysis
autoimmune hemolytic anemia
intravascular hemolytic anemia
direct antiglobulin test
cold agglutinin disease
warm antibodies
paroxysmal nocturnal hemoglobinuria

TABLE 146-1 MAIN CAUSES OF HEMOLYTIC ANEMIAS

INTRACORPUSCULAR	EXTRACORPUSCULAR
DISORDERS OF THE RBC MEMBRANE	**IMMUNOLOGIC**
Inherited	• Autoimmune HA
• Hereditary spherocytosis	• Alloimmunization
• Hereditary elliptocytosis	• Delayed hemolytic transfusion reaction
• Hereditary stomatocytosis	• Drug-induced HA
Acquired	**MECHANICAL**
• Paroxysmal nocturnal hemoglobinuria	• Thrombotic thrombocytopenic purpura
HEMOGLOBINOPATHY	• Atypical or typical hemolytic-uremic syndrome
Qualitative defect in hemoglobin	• Other microangiopathies
• Sickle cell disease	• HELLP syndrome
• Unstable hemoglobins	• Prosthetic heart valve dysfunction (valve hemolysis)
Quantitative defect in hemoglobin	• Acanthocytosis
• β-Thalassemia	**INFECTIOUS**
• α-Thalassemia	• Malaria
RBC ENZYME ABNORMALITY	• Babesiosis, *Clostridium perfringens*, gram-positive bacteria
• G6PD deficiency	**TOXIC**
• Pyruvate kinase deficiency	• Exogenous: thermal burns; industrial copper, lead poisoning, spider bite, snake bite, mushrooms ingestion.
• Others: pyrimidine 5′ nucleotidase deficiency	• Endogenous: Wilson disease (copper overload)
	• Drug related

G6PD = glucose-6-phosphate dehydrogenase; HA = hemolytic anemia; HELLP = hemolysis, elevated liver, low platelets; RBC = red blood cell.

IMMUNE HEMOLYTIC ANEMIAS

Autoimmune Hemolytic Anemia

EPIDEMIOLOGY

Autoimmune hemolytic anemia can affect both children (mainly before the age of 5 years) and adults, and its estimated overall (not age-adjusted) annual incidence is 2.4 per 100,000 individuals.[3] In children, males tend to be more frequently affected; the female : male sex ratio is 1.5:2 in adults. Median age at onset is 58 years in adults, with more than two thirds of the patients age 40 years and above. This age distribution may be related to the increased frequency of lymphoproliferative malignancies in the elderly, with an age-related increase in secondary autoimmune hemolytic anemia due to lymphoma.

The estimated annual incidence of cold-agglutinin disease, which is a rare form of autoimmune hemolytic anemia, is 0.18/100,000. The median age at diagnosis is 67 years,[4,5] with a female prevalence.

Most cases of autoimmune hemolytic anemias occur sporadically but may be sometimes associated, mostly in children, with an underlying hereditary primary immunodeficiency. Autoimmune hemolytic anemia usually occurs as an isolated immune cytopenia but can sometimes be associated, either concomitantly or sequentially, with immune thrombocytopenia (ITP; Chapter 158) and/or autoimmune neutropenia in the setting of Evans syndrome. Among autoimmune hemolytic anemias, the so-called warm autoimmune hemolytic anemia (see Diagnosis and Classification) accounts for 70 to 80% of all cases and almost 90% of the cases in children. Paroxysmal cold hemoglobinuria is a very uncommon subtype of autoimmune hemolytic anemia seen almost exclusively in children. Autoimmune hemolytic anemia can be primary (or idiopathic) or associated with an underlying disease or condition (secondary autoimmune hemolytic anemia).

PATHOBIOLOGY

The pathogenesis of autoimmune hemolytic anemia is a complex multistep process involving not only the autoantibodies but also various effectors of the immune system, including the complement system and macrophages, as well as B and T lymphocytes.[6] Whereas the mechanisms leading to hemolysis are partially elucidated (antibody-dependent cell-mediated cytotoxicity and complement dependent cytotoxicity being primarily involved), the mechanisms leading to the breakdown of self-tolerance are far from fully understood and are mainly extrapolated from mouse models.

Immunoglobulin G (IgG) anti–red cell autoantibodies mediate the destruction of RBCs outside the circulating blood (extravascular hemolysis). In contrast, when lytic components of the complement system participate in the process, the destruction of red cells usually occurs directly within the circulation (intravascular hemolysis) and/or in the liver.[7]

In warm autoimmune hemolytic anemia, the autoantibody targeting RBCs is mainly of the IgG_1 isotype. It is able to bind to macrophage Fc gamma receptor; therefore, extravascular hemolysis takes place mainly in the reticuloendothelial system of the spleen. Autoantigens on RBC membranes targeted by autoantibody are, by decreasing frequency, (1) peptides from the Rhesus system (in approximately one third of cases); (2) band 3 protein; and (3) glycophorin A, an RBC membrane glycoprotein. In other cases, the antibodies have specificity for antigens in the Kell or Duffy blood group system and very rarely for ABO antigens. In less than 10% of the cases of warm autoimmune hemolytic anemia, no specificity can be found. In contrast to warm autoimmune hemolytic anemia, cold agglutinins are IgM autoantibodies that react at cold temperatures with polysaccharides on the red cell surface and mainly with i and I antigens and less commonly with the Pr glycoprotein and sialylated polysaccharides. Cold agglutinins associated with *Mycoplasma pneumoniae* infection have an anti-I specificity, whereas those related to infectious mononucleosis have anti-i specificity. More recently, infection with the severe acute respiratory syndrome virus coronavirus-2 (SARS-CoV2), whose protein spike shares some homology with ankyrin 3, has also been recognized as a viral trigger of autoimmune hemolytic anemia. In cold agglutinin disease, the cold agglutinins are almost always anti-I monoclonal IgM antibodies with a VH4-34 heavy chain, a heavy chain shape of the antigen-binding surface that favors attachment to polysaccharides.

DIAGNOSIS

Clinical Symptoms

The clinical symptoms of autoimmune hemolytic anemia are those of anemia (e.g., unusual fatigue, exertional dyspnea, tachycardia) and/or those due to active hemolysis (jaundice with or without dark urine, especially when there is intravascular hemolysis). In patients with high-affinity cold agglutinins, exposure to cold can also precipitate episodes of acrocyanosis by inducing massive agglutination of RBCs in the capillary circulation of the hands, feet, or even nose tip and ears. Mild splenomegaly may be present especially in warm autoimmune hemolytic anemia, whereas splenomegaly is uncommon in cold agglutinin disease unless there is an underlying B-cell lymphoma.

General Laboratory Tests

Elevated serum levels of indirect bilirubin and lactate dehydrogenase (LDH) and decreased serum haptoglobin are the usual, albeit nonspecific, features of hemolytic anemia. Laboratory signs of intravascular destruction of RBCs (hemoglobinemia, hemoglobinuria, and hemosiderinuria) are unusual in the setting of autoimmune hemolytic anemia. Once hemolytic anemia has been recognized, the diagnosis of autoimmune hemolytic anemia is usually relatively easy and based first on the identification of anti-RBC autoantibody by means of the direct antiglobulin (Coombs) test, and then on the exclusion of other causes of hemolytic anemia. A careful examination of the peripheral blood smear is essential, keeping in mind that an increase in the number of spherocytes (particularly microspherocytes) can be observed in approximately 30 to 40% of cases of autoimmune hemolytic anemias (Chapter 147).[8]

The Direct Antiglobulin (Coombs) Test

The direct antiglobulin (Coombs) test reveals antibody-coated RBCs central to the diagnosis of autoimmune hemolytic anemia. The indirect antiglobulin (Coombs) test evaluates the presence of incomplete antibodies in the patient's serum. As presently used, the standard antiglobulin reagent contains antibodies to test for the presence of all four classes of IgG and components of complement (usually C3 and C4) on standard gel tubes.

A positive direct antiglobulin test requires cautious interpretation when there are no other features of autoimmune hemolytic anemia. False-positive test results are not unusual. The reported incidence of positive antiglobulin (Coombs) tests in normal blood donors and the general populations of hospitalized patients varies widely—from 1 in 100 to 1 in 15,000. Differences in the technique used to perform the test account for this variation. The usual reason for a false-positive direct antiglobulin test is nonspecific, low-avidity adherence of serum IgG to red cells whereas some patients with systemic lupus erythematosus or B-cell lymphoid malignancies may produce true anti-RBC auto-antibodies without active hemolysis. False-negative direct antiglobulin tests in true autoimmune hemolytic anemia are rare (~5% of all autoimmune hemolytic anemias) and are usually due to low-affinity autoantibodies that spontaneously elute from the red cell surfaces in vitro, or to IgA antibodies, or to amounts of erythrocyte-coating antibodies that are below

the limit of detection by the antiglobulin test. The diagnosis of direct antiglobulin test–negative autoimmune hemolytic anemia can be considered only after the exclusion of other potential causes of hereditary and acquired hemolytic anemia.

Classification of Autoimmune Hemolytic Anemia: Warm versus Cold Autoimmune Hemolytic Anemia

Once the diagnosis of autoimmune hemolytic anemia is established, classification of the type of autoimmune hemolytic anemia involved is essential.[9] According to the direct antiglobulin test pattern and the optimal temperature at which the autoantibody reacts with human RBCs, autoimmune hemolytic anemias (warm and cold) are typically subdivided into four major subtypes: warm autoimmune hemolytic anemia; cold autoimmune hemolytic anemia (including chronic cold agglutinin disease); mixed-type autoimmune hemolytic anemia; and the exceptional paroxysmal cold hemoglobinuria.[10] The great majority of cold-reactive autoantibodies are called "cold agglutinins;" cold hemolysins are much less common. A small proportion (~5%) of patients may exhibit both cold-reactive and warm-reactive autoantibodies, indicating a mixed autoimmune hemolytic anemia type. The distinction between cold autoimmune hemolytic anemia and warm autoimmune hemolytic anemia is very important because the mechanisms of RBC injury, the primary site of hemolysis, and the therapeutic approaches are different. Table 146-2 summarizes the main features of the different types of autoimmune hemolytic anemia.

In warm autoimmune hemolytic anemias, which represent 70 to 80% of all autoimmune hemolytic anemias in adults, the direct antiglobulin test pattern is either solely IgG-positive or IgG plus C_3–positive. Autoantibodies are mainly of the IgG_1 isotype, and they bind and react optimally with RBCs at a temperature of 37° C (range, 35 to 40° C). In warm autoimmune hemolytic anemia, the hemolysis is mainly extravascular and occurs predominantly in the spleen. On the other hand, in autoimmune hemolytic anemia, due to cold autoantibodies, which account for 15 to 20% of AIHAs, the usual direct antiglobulin test pattern is IgG-negative and C3-positive, and circulating cold agglutinins are detectable in the serum at a significant titer (i.e., >1/64). Cold antibodies are almost exclusively of IgM isotype, which are able to activate the classical complement pathway but are seldom found fixed on the RBC membrane in vitro as they are rapidly eluted ex vivo before the test can be performed. Cold antibodies typically react with RBCs at temperatures below 30° C (optimum, 4° C) and lead to various degrees of extravascular hemolysis, predominantly in the liver rather than the spleen. In rare cases of AIHAs (~5 to 10%) known as mixed-type AIHAs, autoantibodies (mostly of IgM isotype) can react with RBCs within a wide range of temperature (thermal amplitude from 4 to 37° C). Last, paroxysmal cold hemoglobinuria is a very uncommon AIHA subtype seen almost exclusively in children; it is due to an IgG hemolysin reacting with autologous RBCs at low temperatures (2 to 10° C) that can be detected only by means of the Donath Landsteiner test, a test available only in few referral laboratories. In addition to these four distinct subtypes of AIHAs, drug-induced hemolytic anemias must be regarded as a distinct entity (see Drug-Induced Hemolytic Anemia). Besides the distinction between warm autoimmune hemolytic anemia and cold autoimmune hemolytic anemia; autoimmune hemolytic anemias are also classified as primary (or idiopathic) or secondary, depending on the presence or absence of an underlying disease or condition promoting immune dysregulation. On average, 50 to 60% of warm autoimmune hemolytic anemias are secondary (see Table 146-3 for associated conditions) and, therefore, a minimal workup must be performed at the time of diagnosis in every patient to search for an underlying disease or condition (Table 146-4). It is important to emphasize that a presumably primary form of warm autoimmune hemolytic anemia can precede by many years the finding of a non-Hodgkin lymphoma; therefore, patients with warm autoimmune hemolytic anemia must be followed beyond remission.

Regarding autoimmune hemolytic anemias due to cold autoantibodies, in children and young adults, these are mainly secondary to either bacterial (*M. pneumoniae* infection) or viral (Ebstein-Barr virus or cytomegalovirus) infection, whereas in adults aged over 50, although rare, chronic cold agglutinin disease is by far the main cause of cold autoimmune hemolytic anemia. Although cold agglutinin disease has long been considered as a primary (i.e., idiopathic) form of autoimmune hemolytic anemia, it is now recognized that about 90% of cases of cold agglutinin disease are associated with a monoclonal

TABLE 146-2 MAIN CHARACTERISTICS OF VARIOUS TYPES OF AUTOIMMUNE HEMOLYTIC ANEMIA

AUTOIMMUNE HEMOLYTIC ANEMIA TYPE	EPIDEMIOLOGY/ TYPE OF HEMOLYSIS	RATE OF SECONDARY AUTOIMMUNE HEMOLYTIC ANEMIA	AUTOANTIBODY ISOTYPE	OPTIMAL TEMPERATURE	DIRECT ANTIGLOBULIN TEST PATTERN	ELUATE	AUTOANTIBODY SPECIFICITY (TARGETED ANTIGENS)
Warm autoimmune hemolytic anemia	~70-80% of all autoimmune hemolytic anemia Adult > children (mean age 3 years), mostly EV hemolysis, subacute onset (rarely abrupt with associated IV hemolysis)	~50% of the cases (see Table 146-3)	IgG >> IgA, IgM	37° C	IgG ± C_3	IgG	Antigens of the Rh system, band 3, glycophorin, A
Cold agglutinin syndrome	~20-30% of all autoimmune hemolytic anemia cases in adults Age >50 years EV ± IV hemolysis	Mainly secondary monoclonal IgM kappa gammopathy in 90% of the cases ± features of definite clonal B-cell lymphoproliferative disorder	IgM >>> IgA or IgG Cold agglutinins titer >1/500	4° C	C_3	negative	I antigen> i >> Pr
Cold transient autoimmune hemolytic anemia	Children, young adults IV hemolysis	Infections (*Mycoplasma pneumoniae*, Ebstein-Barr virus, etc.)	Polyclonal IgM Cold agglutinins titer ≥1/64	4° C	C_3	negative	I > i antigens
Paroxysmal cold hemoglobinuria	Children (rare), exceptional in adults Acute IV hemolysis	Infections (*Mycoplasma pneumoniae* virus)	IgG (Donath-Landsteiner hemolysin)	>30° C	C_3	negative	P + c antigens (biphasic hemolysins)
Mixed-type autoimmune hemolytic anemia	Adult Mainly EV hemolysis	Mainly B-cell lymphoma	IgG, IgM ± AF ~ 1/500	Wide range (4°-37° C)	IgG ± C_3	IgG	Polyreactivity

EV = extravascular; Ig = immunoglobulin G; IV = intravascular.

TABLE 146-3 MAIN DISORDERS OR CONDITIONS ASSOCIATED WITH WARM AUTOIMMUNE HEMOLYTIC ANEMIA

Hematologic disorders and lymphoproliferative diseases:
- Chronic lymphoid leukemia,* acute lymphoblastic leukemia,† LGL leukemia
- B-cell lymphoma,* Hodgkin lymphoma
- Angioimmunoblastic T-cell lymphoma
- Castleman disease
- Myelodysplasias, myelofibrosis

Solid tumors: thymoma/ovarian dermoid cyst/carcinoma

Autoimmune and inflammatory diseases
- Systemic lupus erythematosus, antiphospholipid syndrome
- Rheumatoid arthritis
- Ulcerative colitis, pernicious anemia/thyroiditis
- Myasthenia gravis
- Autoimmune hepatitis, giant cell hepatitis*
- Sarcoidosis
- Eosinophilic fasciitis

Infections:
- Virus: Epstein-Barr virus,* hepatitis C, cytomegalovirus, SARS-CoV-2
- Bacteria: tuberculosis/brucellosis/syphilis/babesiosis

Drugs

Primary immunodeficiencies
- Common variable immunodeficiency
- Hyper-IgM syndrome,† ALPS†
- CTLA4† or LRBA deficiency†
- IPEX syndrome,† APECED syndrome†

Others
- Pregnancy
- Postallogenic bone marrow transplantation or liver or small bowel transplant*
- Rosai-Dorfman disease

*Diseases that can also be associated with cold autoimmune hemolytic anemia.
†Seen almost exclusively in childhood.
ALPS = autoimmune lymphoproliferative syndrome; APECED = autoimmune polyendocrinopathy-candidiasis-ectodermal dystrophy; CTLA4 = cytotoxic T lymphocyte–associated protein 4; IgM = immunoglobulin M; IPEX = immune dysregulation, polyendocrinopathy, enteropathy X-linked syndrome; LGL = large granular lymphocytes; LRBA = lipopolysaccharide-responsive and beige-like anchor protein; SARS-CoV-2 = severe acute respiratory syndrome coronavirus 2.

TABLE 146-4 RECOMMENDED WORKUP IN WARM AUTOIMMUNE HEMOLYTIC ANEMIA

1. Antinuclear antibodies (± anti-DNA antibodies if ANA-positive)
2. Anticardiolipin antibodies and lupus anticoagulant*
3. Serum protein electrophoresis and immunoelectrophoresis
4. Immunophenotyping of peripheral lymphocytes (flow cytometry)
5. CT scan of the chest, abdomen, and pelvis (in the absence of obvious SLE of APS)
6. Bone marrow biopsy: recommended in the presence of hypogammaglobulinemia and/or monoclonal gammopathy and/or abnormal lymphadenopathy on the CT imaging

*Especially in case of a previous episode of venous and/or arterial thrombosis or in case of recurrent miscarriage in women and systematically before splenectomy.
ANA = antinuclear antibodies; APS = antiphospholipid syndrome; CT = computed tomography; SLE = systemic lupus erythematosus.

IgM kappa and with other features of indolent clonal B cell lymphoproliferative disorder. As a result, it must be distinguished from Waldenström macroglobulinemia (Chapter 173) or lymphoplasmacytic lymphoma in the bone marrow (Chapter 171). Hemolytic anemia is seldom very severe in the setting of cold agglutinin disease, and it is classically exacerbated by exposure to cold or infections.

DRUG-INDUCED IMMUNE HEMOLYTIC ANEMIA

There are several mechanisms by which a drug can induce hemolytic anemia, and true drug-induced autoimmune hemolytic anemias are rare. Many drugs or drug metabolites have the potential to elicit antidrug antibodies. Drugs that form covalent bonds with proteins in the red cell membrane can bind antidrug antibodies to the red cell surface, thereby causing a positive direct antiglobulin test and, in some cases, initiating antibody-mediated destruction of red cells. Other drugs, such as the cephalosporins, can bind to red cell membranes and take up IgG nonspecifically from plasma. In these cases, there is no antidrug antibody. The diagnosis of drug-induced immune-mediated hemolytic anemia should be considered if the patient has a history of taking a suspected medication, there is acute complement-mediated hemolysis, only complement components are detectable on the red cell surface, or the patient's serum reacts with red cells in the presence of the suspected drug. Some drugs can induce true autoantibodies against red cells. Fludarabine, a purine nucleoside analogue used in the treatment of chronic lymphocytic leukemia, and monoclonal antibodies against tumor necrosis factor-α (infliximab and adalimumab), T cells (alemtuzumab), α4 integrin (natalizumab), and interleukin-2 receptor (daclizumab) also have this property, the cause of which is unknown. Notably, there is no definitive way of distinguishing drug-induced autoimmune hemolytic anemia from primary autoimmune hemolytic anemia. Immune checkpoint inhibitors, mostly anti-PD1 agents but also to a lesser extent anti-PDL1 and anti-CTLA4 monoclonal antibodies, which are currently used worldwide to treat various cancers, have become an important and increasing cause of drug-induced autoimmune hemolytic anemias.

TREATMENT

Supportive Care and Transfusion

Regardless the type of autoimmune hemolytic anemia, folic acid supplementation (5 to 10 mg/day) is warranted in patients with active autoimmune hemolytic anemia and increased erythropoiesis to prevent its depletion, which may be misinterpreted as a treatment failure. RBC transfusions are also indicated in patients with disabling symptoms of anemia and/or a significant underlying cardiovascular disorder (e.g., coronary artery disease or heart failure). Although younger patients may tolerate a stable hemoglobin level as low as 6 g/dL, maintaining a hemoglobin level of at least 8 g/dL is usually recommended in patients with major comorbidities. It is important for the managing physician to understand that no patient with symptomatic autoimmune hemolytic anemia should be denied blood transfusions because of an "incompatible crossmatch." The blood bank should be informed of the patient's status. Indeed, the patient's positive direct antiglobulin test almost always interferes with compatibility testing, so the role of the blood bank is to provide packed red cells that are the least incompatible ones in regard to the specificity of the patient's autoantibody. Close communication and cooperation between the clinician and the specialist in transfusion medicine are therefore essential for reducing the risks associated with transfusion in patients with autoimmune hemolytic anemia. Because transfused RBCs can be destroyed by the patient's autoantibodies, rapid transfusion of large volumes of RBCs must be avoided because they can have serious consequences. This risk is increased if the patient also has alloantibodies induced by previous transfusions or pregnancy. Units of packed RBCs should therefore not be administered at a rate that exceeds 1 mL/kg/hour. In cold autoimmune hemolytic anemia and cold agglutinin disease, prewarmed (at a temperature close to 37° C) packed RBCs are recommended. Plasma exchange is sometimes used for patients with life-threatening autoimmune hemolytic anemia, but there is no robust evidence supporting its efficacy and safety in the literature.

In transfusion-dependent patients with inadequate reticulocytosis, the transient off-label use of an erythropoiesis-stimulating agent by specialists may provide a 70% response rate for increasing the hemoglobin level and avoiding a transfusion.[11] Plasma exchanges can be temporarily helpful in cases of severe hemolysis and/or in preparation for surgery (e.g., cardiac surgery) that requires cold exposure.[12]

Treatment of Transient (Acute) Cold Autoimmune Hemolytic Anemias

In cases of transient cold autoimmune hemolytic anemias induced by an infection, the onset is usually abrupt, and the degree of anemia may be profound and sometimes life-threatening, requiring transfusion of prewarmed packed RBCs, which must not be postponed (Fig. 146-1). In addition to supportive care, the use of antibiotics is justified in case of pneumonia due to *M. pneumoniae*. A short course of corticosteroids can sometimes be considered in case of severe cold autoimmune hemolytic anemia secondary to a viral infection (Epstein-Barr virus) in order to reduce the duration of anemia, but this practice is neither consensual nor evidence-based.

Management of Chronic Cold Agglutinin Disease

The management of cold agglutinin disease has long been only supportive and symptomatic (see Fig. 146-1). Avoidance of exposure to cold is still the mainstay in management of cold agglutinin disease, especially to avoid cold-induced circulatory symptoms, but this measure is often not sufficient to avoid episodes of hemolysis. In cases of infections and other acute phase reactions, the levels of both C3 and C4 increase due to their enhanced production, resulting in exacerbation of complement-dependent cytotoxicity directed toward autologous RBCs and increased hemolysis. Consequently, prompt treatment of febrile infections or other illnesses as well as the prevention of infection by influenza and/or pneumococcal vaccines are strongly recommended in patients

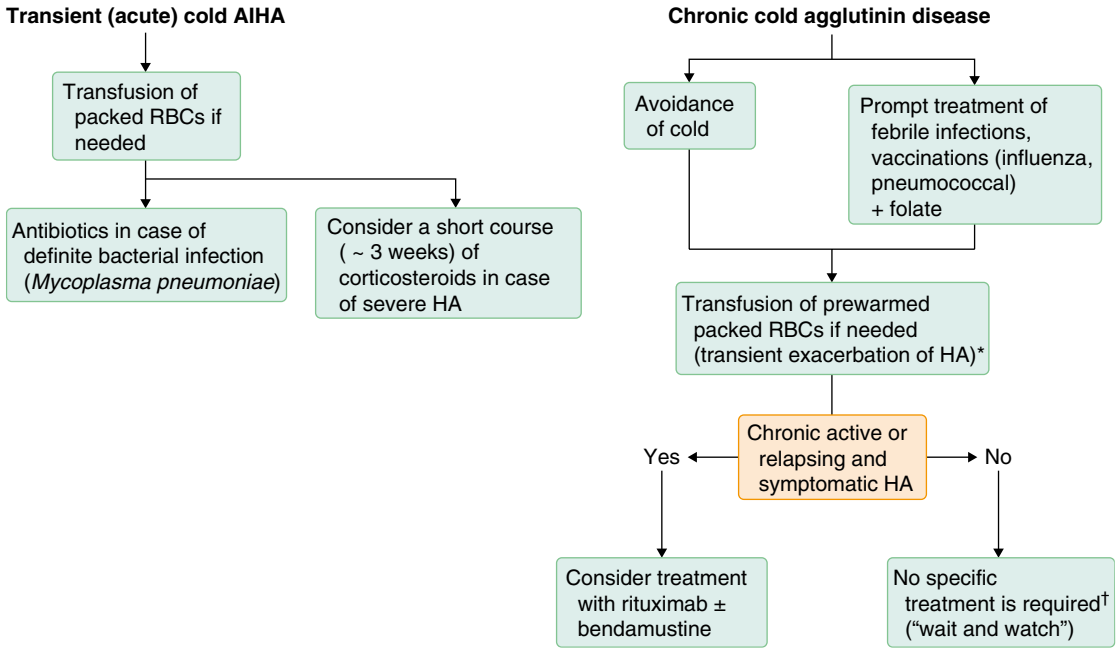

FIGURE 146-1. **Proposed algorithm for the management of cold autoimmune hemolytic anemias (AIHAs). *The transient use of erythropoiesis-stimulating agents can be considered off-label, †unless the underlying B cell–clonal lymphoproliferative disorder requires specific management. HA = hemolytic anemia; RBCs = red blood cells.**

with cold agglutinin disease. In case of exacerbation of hemolysis and severe anemia, transfusion of prewarmed packed RBCs must be considered because patients with cold agglutinin disease are often elderly with significant comorbid conditions. Whereas cold agglutinin disease is usually considered a relatively indolent and slowly progressive lymphoproliferative disorder with a relatively good prognosis, transfusion dependency may be observed in some patients with recurrent episodes of active hemolysis.

For patients with active or relapsing symptomatic episodes of cold hemolytic anemia that warrants treatment, rituximab either alone or in combination with bendamustine[A1] offers the best response rate (up to 75% response), but the toxicity of bendamustine and the increased risk of severe infection is a limitation for frail elderly patients. Another potential option for patients who require transfusions is sutimlimab,[13] which is a selective upstream inhibitor of the classical complement pathway (given at 45 to 60 mg/kg intravenously weekly for 4 weeks, then every 2 weeks).[A2] Some responses also have been reported in smaller studies with bortezomib plus dexamethasone or with ibrutinib.

In transfusion-dependent patients with normal or only slightly elevated reticulocyte counts, the transient use of an erythropoiesis-stimulating agent off-label may be useful as a transfusion-sparing strategy. Plasma exchange can be temporarily helpful in cases of severe hemolysis and/or in preparation for surgery requiring cold exposure such as lung-heart surgery.

Management of Primary Warm Autoimmune Hemolytic Anemias

First-Line Treatment: Corticosteroids

Primary warm autoimmune hemolytic anemias usually have a chronic course, and except for the few patients with mild compensated hemolysis with a normal or almost normal hemoglobin level, treatment is usually needed (Fig. 146-2). In contrast to cold agglutinin disease, corticosteroids are the cornerstone of therapy in warm autoimmune hemolytic anemias and should be given as first-line treatment. Intravenous immunoglobulin (IVIG) has only little efficacy in warm autoimmune hemolytic anemias and should be considered (at 2 g/kg over 2 days) only as potential rescue therapy for severe, transfusion-dependent autoimmune hemolytic anemia in the absence of response to corticosteroids. The corticosteroid regimen is usually based on oral prednisone or prednisolone at an initial daily dose of 1 to 2 mg/kg daily. By analogy with other autoimmune diseases, the use of intravenous methylprednisolone at a dose of 250 to 1000 mg/day for 1 to 3 days may be considered in patients with profound anemia, although no clinical trials supporting its superior efficacy are available. The starting dose of oral prednisone is usually maintained for 3 to 4 weeks and then tapered progressively if at least a partial response is achieved. There is no consensus concerning the total duration of treatment, but because the likelihood of early relapse is high when the treatment is prematurely stopped, corticosteroids should be maintained for at least 3 months after a complete response is achieved (defined by normalization of hemoglobin with no evidence of active hemolysis). Except for children, the use of alternate-day prednisone before stopping the treatment is not recommended. The efficacy of corticosteroids can take a few days to 2 weeks, so blood transfusions may be necessary at autoimmune hemolytic anemia onset, especially in case of severe anemia in young children or elderly adults for maintaining a "safe" hemoglobin level. After 2 to 3 weeks of treatment with corticosteroids, a clinically significant response is observed in 80 to 85% of the cases. Except for the few patients who are truly refractory to corticosteroids, the major issue that clinicians have to deal with when treating patients with warm autoimmune hemolytic anemia is that approximately 50 to 60% of them are found to be dependent on corticosteroids to suppress hemolysis. Thus, flares of relapses of warm autoimmune hemolytic anemia may occur either within weeks after withdrawal of corticosteroids or even on treatment when the dose of daily prednisone is decreased below a threshold, which is usually between 10 to 15 mg daily, a dose that is associated with several long-term adverse effects. Overall, only one third of patients can be considered to be in complete remission off-treatment 1 year after the onset of disease.

Second-Line Treatment

Rituximab

The efficacy of rituximab, the chimeric monoclonal antibody that targets the CD20 antigen on B lymphocytes, was first shown in refractory warm autoimmune hemolytic anemia in children with a response rate reaching up to 100% in some studies. In adults, rituximab was also shown to have significant efficacy in primary warm autoimmune hemolytic anemias in randomized trials, with a 75% overall response rate at 1 year.[A3,A4] The usual dose is 375 mg/m^2 by intravenous infusion once a week for 4 weeks, but other regimens such as fixed doses of 1000 mg 2 weeks apart as in rheumatoid arthritis can be used. Safety is usually good, although late-onset neutropenia and opportunistic infections such as *Pneumocystis jiroveci* pneumonia may rarely occur, so primary prophylaxis (Table 146-4) with trimethoprim-sulfamethoxazole (160 mg/800 mg) three times per week (Chapter 313) is wise when patients with autoimmune hemolytic anemia treated are with rituximab. Taken together, the data from the literature clearly support, whenever possible, the use of rituximab (off-label) as an early second-line treatment and before splenectomy for patients with warm autoimmune hemolytic anemia who have had no or little response to corticosteroids and for elderly patients with comorbidities such as diabetes who are at high risk for developing corticosteroid-induced side effects. When rituximab is administered before splenectomy, vaccination against *Streptococcus pneumoniae, Haemophilus influenzae* type B, and/or *Neisseria meningitidis* should be administered whenever possible 2 weeks before rituximab because splenectomy may be required thereafter (see Chapter 154 for specific recommendations).

Splenectomy

Splenectomy has long been the preferred second-line option for primary warm autoimmune hemolytic anemias. The rate of sustained response after splenectomy is approximately 60 to 70%, but clear predicting factors for response are still lacking. The perioperative risk of laparoscopic splenectomy is low and acceptable, with a mortality rate of less than 1%. The most feared complications, even after the laparoscopic procedure, remain the rare but unpredictable risk of overwhelming sepsis and the risk of postoperative thromboembolic complications, especially in the splanchnic veins. Perioperative low-molecular-weight heparin is therefore recommended in patients who have warm autoimmune hemolytic anemia and who undergo splenectomy and especially in those who also have positive antiphospholipid antibodies. The best time for splenectomy

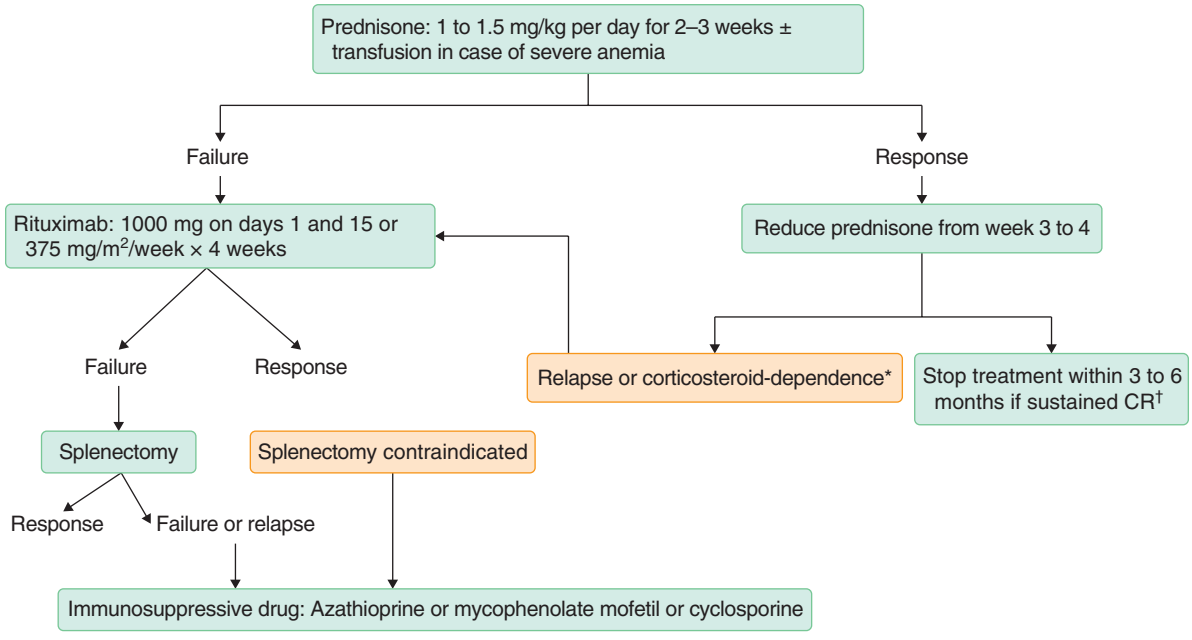

FIGURE 146-2. Proposed algorithm for the treatment of primary warm-reactive autoimmune hemolytic anemia in adults. *Need to maintain daily prednisone at more than 10 mg to maintain at least a partial remission (i.e., hemoglobin level ≥10 g/dL with at least a 2-g increase from baseline). †Complete remission (CR) = hemoglobin level >12 g/dL without hemolysis.

is controversial now that alternatives such as rituximab are available at least in some countries. In children aged less than 5 to 7 years, this procedure should be avoided or delayed as long as possible. In adults, it must be considered early in the course of the disease in patients who have failed to respond to both corticosteroids (or need high and unacceptable doses to maintain at least a partial remission) and rituximab.

Danazol

In patients dependent on corticosteroids, the use of danazol, an attenuated androgen analogue, at 400 to 800 mg/day can be helpful as a corticosteroid-sparing strategy in adults requiring a dose of daily prednisone greater than 15 mg to maintain a remission. However, because of its common androgenic side effects, its use is usually limited in female patients, and its potential liver toxicity makes long-term use difficult also in men.

Other Treatment Lines

Immunosuppressive and Cytotoxic Agents

In patients with refractory warm autoimmune hemolytic anemia in whom splenectomy and rituximab have failed or in patients those who are reluctant to undergo splenectomy or are not suitable candidates for splenectomy, the management is mainly based on experience and mostly retrospective data in the literature, as opposed to controlled, prospective, comparison trials. The efficacy of azathioprine, cyclophosphamide, and to a lesser extent cyclosporine and mycophenolate mofetil has been reported in small case series. The choice depends on the efficacy/safety ratio individualized for each patient. These drugs should be reserved for patients who have failed to respond to rituximab and to splenectomy or are not suitable candidates for splenectomy. For multirefractory patients, promising results have been reported with the combination of bortezomib and dexamethasone under expert supervision.

PAROXYSMAL NOCTURNAL HEMOGLOBINURIA

DEFINITION

Paroxysmal nocturnal hemoglobinuria (PNH) is a rare and potentially life-threatening clonal blood disorder with protean manifestations caused by an acquired somatic mutation in the phosphatidylinositol glycan (*PIG-A*) gene. In pluripotent hematopoietic stem cells, the mutation in *PIG-A* leads to a deficiency of glycosylphosphatidylinositol (GPI) anchors and GPI-anchored proteins, including the complement regulatory proteins CD55 and CD59 normally expressed on the surface of RBCs. PNH RBCs are therefore highly vulnerable to activation of complement on their surfaces (especially in case of fever, acidosis, or hypoxia) and the formation of the membrane attack complex (Chapter 37). The resulting chronic intravascular hemolysis is the hallmark of the classic hemolytic form of the disease, and the release of free hemoglobin contributes to most of its clinical manifestations (dysphagia, recurrent abdominal pain, erectile dysfunction).

EPIDEMIOLOGY

PNH can occur at any age but is most common between 10 and 50 years. The mean age at diagnosis is about 34 years (median age is about 40), and the female : male ratio is close to 1. Median survival after diagnosis is approximately 20 years. It is a rare disorder with an estimated prevalence in the population of about one per million in the population. There is no sex preference, and a family history of PNH is highly unusual.

PATHOBIOLOGY

PNH is due to a somatic mutation that causes a defect in the red cell membrane. The disease begins in a single hematopoietic stem cell when the *PIG-A* gene on the short arm of the active X chromosome acquires a mutation. The *PIG-A* gene encodes PIG-A, an enzyme that is essential for the synthesis of GPI. The location of *PIG-A* on the X chromosome allows a single mutation in the gene to affect GPI synthesis. This lipid normally forms a peptide link with the C-terminal amino acid of numerous proteins, anchoring them to the red cell membrane. Molecular genetic studies indicate that the PNH clone upregulates genes that make the PNH clone resistant to apoptosis and immune attack. The mutation in a hematopoietic stem cell affects *PIG-A* in blood cells of all lineages. Almost 150 different mutations of *PIG-A* have been identified. Most of them inactivate *PIG-A* and cause total loss of GPI in the descendants of the carrier stem cell. Red cells with complete deficiency of GPI are termed *PNH III erythrocytes*, and those with partial deficiency are called *PNH II erythrocytes*. The coexistence of PNH III and PNH II red cells in the same patient indicates the presence of two mutant clones. A small number of hematopoietic stem cells in normal people bear the *PIG-A* mutation; they have no proliferative advantage and persist in small numbers. In normal blood, the frequency of *PIG-A*–deficient cells is about 1 in 50,000 red cells. In contrast to those with PNH, however, the deficient cells in normal subjects arise from committed hematopoietic cells. The presence of *PIG-A*–deficient cells in normal subjects suggests that PNH involves not only the *PIG-A* mutation but also a second step, perhaps a mutation, that allows expansion of the mutated clone.

Functional Consequences of Deficiency of GPI

The membrane inhibitor of reactive hemolysis (CD59, or protectin) and CD55, an inhibitor of C3 convertase, are two of the many proteins that GPI normally anchors to the red cell. They prevent polymerization of C9, the final step in assembly of the membrane attack complex that begins with cleavage of C5 to C5b. Deficiencies of CD59 and CD55 allow unimpeded assembly of the membrane attack complex on the erythrocyte surface, thereby initiating intravascular hemolysis. A variety of nonspecific factors, such as a reduction in the pH of blood, can activate complement. The morning hemoglobinuria

that occurs in some cases of PNH is probably the result of subtle acidification of blood during sleep.

CLINICAL MANIFESTATIONS

Classically, some patients with PNH arise in the morning and pass dark urine. The typical paroxysms of hemoglobinuria occur on a background of chronic, low-grade intravascular hemolysis that causes constant hemosiderinuria in PNH. About one third of cases evolve into aplastic anemia (Chapter 151). Transformation to acute myelogenous leukemia is a rare event. Abdominal pain, dysphagia, and erectile dysfunction are additional clinical features. The basis of these symptoms is probably scavenging by free plasma hemoglobin of endogenous nitric oxide, a regulator of vasomotor and smooth muscle tone. In about one third of cases, venous thrombosis occurs in unusual sites and can cause intra-abdominal splanchnic vein thrombosis involving the hepatic veins (Budd-Chiari syndrome), the portal veins, or less frequently cerebral vein thrombosis (Chapter 140). Splenomegaly is uncommon; hepatomegaly and ascites point to the complication of intra-abdominal venous thrombosis. Hemosiderinuria is the result of chronic intravascular hemolysis. Subtle or overt signs of bone marrow damage (leukopenia and thrombocytopenia) are frequent. The extent of red cell destruction in PNH depends on the number of PNH red cells in blood, the level of GPI on the red cell membrane (PNH III cells are devoid of GPI), and the surface activation of complement. The anemia is often aggravated by iron deficiency caused by chronic urinary iron loss in the form of hemosiderinuria. A direct antiglobulin test–negative hemolytic anemia associated with iron deficiency should raise the suspicion of PNH. The basis of the tendency to develop venous thrombosis is unclear. Hypercoagulability caused by the release of prothrombotic materials in red cell and platelet membranes (which are also abnormal in PNH) and impaired fibrinolysis have been implicated. Nitric oxide scavenging by free plasma hemoglobin may also damage endothelial cells and cause aggregation of platelets.

DIAGNOSIS

The diagnosis of PNH is suspected in case of an acquired and Coombs-negative intravascular hemolytic anemia and can be established by flow cytometry demonstrating a deficiency of GpI-linked proteins (CD24/CD57 and CD14) on both neutrophils and monocytes, as well as CD59 on RBCs. Another reagent with utility in flow cytometry is aerolysin, a bacterial protein that binds to the GPI anchor. Data strongly suggest that the fluorescent aerolysin variant (FLAER) is the best and most reliable reagent to study GPI-linked antigens on leukocytes, helpful for diagnosing PNH.

The clone size in PNH is usually correlated with the degree of intravascular hemolysis.

TREATMENT

Eculizumab, a humanized monoclonal antibody against C5, reduces the signs of intravascular hemolysis, the requirement for transfusions, and the incidence of thrombosis in PNH.[A5] In PNH, it is usually given at a dose of 600 mg every week for 4 weeks, followed 1 week later by a 900-mg dose, and then at 900 mg every other week.[14,15] Complement blockade is not always complete. Before being treated with eculizumab, every patient should be vaccinated against *Meningococcus A, B,* and *C* and, in many countries, a long-term prophylaxis with oral penicillin is also strongly recommended. Beyond transfusion-dependent hemolytic anemia, the occurrence of disease-related venous thrombosis is also a strong indication for eculizumab in the setting of PNH in combination with anticoagulation. Ravulizumab (given as a single weight-based loading dose of 2400 to 3000 mg followed by 3000 to 3600 mg every 8 weeks starting 2 weeks later) is another complement inhibitor that also binds to C5, has a much longer terminal half-life compared with eculizumab, and can provide equivalent results.[A6,A7] Crovalimab is a subcutaneous C5 inhibitor that may prove useful, especially in patients who are resistant to eculizumab and ravulizumab.[16] Subcutaneous pegcetacoplan (1080 mg subcutaneously twice weekly), which targets complement protein C3 rather than C5, can inhibit extravascular as well as intravascular hemolysis and may provide even better disease control than the C5 inhibitors.[A8] Combined inhibition of both C3 and C5 under expert supervision may become an option in persistent cases.[17] Hematopoietic stem cell transplantation is curative but is reserved for patients who have some pancytopenia that does not respond to complement therapy.

PROGNOSIS

With current therapy, long-term survival is expected. However, progression to bone marrow failure (Chapter 151) is associated with a poorer prognosis.

HEMOLYTIC TRANSFUSION REACTIONS

The cause of hemolytic transfusion reactions (Chapter 162) is intravascular lysis of the donor's red cells by antibodies (alloantibodies or isoantibodies) in the recipient that bind to one or more blood group antigens on the transfused cells. The recipient's isoantibodies can be natural anti-A or anti-B antibodies, or they can be induced by previous transfusions or pregnancy. Whether IgM or IgG, the isoantibodies trigger the assembly of lytic complement components on the surface of the donor's red cells. The rapid formation of large amounts of C3a and C5a fragments causes hypotension and bronchospasm. Renal failure is a consequence of severe, prolonged hypotension; the main renal lesion is renal cortical ischemia secondary to shunting of blood away from the kidneys. Hemoglobin itself is not nephrotoxic. The signs and symptoms of a hemolytic transfusion reaction are nonspecific and include fever, back pain, urticaria, dyspnea, hypotension, and evidence of disseminated intravascular coagulation. These nonspecific signs appear and worsen during administration of the transfusion. Immediate steps must be taken to stop the transfusion, submit the transfused blood and a sample of the patient's blood to the blood bank, and order tests of plasma and urine for free hemoglobin. Hydration is key to prevent renal failure. Intravenous fluid, usually normal saline, should be started at once and be combined with a diuretic (usually furosemide) in amounts needed to sustain a urine flow rate of at least 100 mL/hour. Patients with sickle cell disease (Chapter 149) are at high risk of delayed hemolytic transfusion reaction, a complication that can be life-threatening and require prompt management (Chapter 162).[18]

OTHER CAUSES OF INTRAVASCULAR HEMOLYSIS

Conditions in which vascular abnormalities (e.g., valve hemolysis), toxins (e.g., venomous snake bites), infections (e.g., malaria, babesiosis, clostridial sepsis), or drugs damage RBCs, cause them to lose pieces of membrane, and ultimately fragment into free hemoglobin-releasing particles should be considered in the differential diagnosis of intravascular hemolysis (Tables 146-2 and 146-3). Most of these conditions are readily apparent from the history and physical examination. Treatment focuses on the underlying cause of the hemolysis.

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For the General References and other additional features, please visit Elsevier eBooks+ at https://ebooks.health.elsevier.com.

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147 HEMOLYTIC ANEMIAS: RED BLOOD CELL MEMBRANE AND METABOLIC DEFECTS

PATRICK G. GALLAGHER

The mature erythrocyte differs from all other cells in the body. Lacking a nucleus, DNA, RNA, and ribosomes, it cannot synthesize RNA, DNA, or protein. It does not divide, it has no mitochondria, it cannot perform the Krebs cycle, and it lacks an electron transport system for oxidative phosphorylation. After enucleation, the reticulocyte, the precursor of the mature erythrocyte, leaves the marrow and enters the circulation equipped with a full complement of enzymes, transporters, signaling molecules, and all other proteins necessary to perform the essential functions of the red blood cell (RBC) during its lifespan.

The erythrocyte membrane accounts for only about 1% of the total weight of an RBC, yet it plays a critical role in the maintenance of normal RBC homeostasis through a number of mechanisms. These include retention of vital compounds and removal of metabolic waste, regulation of erythrocyte metabolism and pH, and import of iron required for hemoglobin (Hb) synthesis during erythropoiesis. The membrane maintains a slippery exterior so that erythrocytes do not aggregate or adhere to endothelial cells. The membrane skeleton, a network of proteins on the inner surface of the RBC, provides the strength and flexibility needed to maintain the normal shape and deformability of the erythrocyte.

The principal functions of erythrocyte metabolism in the mature erythrocyte include maintenance of adequate supplies of adenosine triphosphate (ATP), production of reducing substances to act as antioxidants, and control of oxygen affinity of Hb by production of adequate amounts of 2,3-diphosphoglycerate (2,3-DPG). Because the mature erythrocyte has lost its ability to perform oxidative phosphorylation, its energy is supplied by anaerobic glycolysis though the Embden-Meyerhof pathway, by oxidative glycolysis through the hexose monophosphate shunt, and through nucleotide salvage pathways.

THE ERYTHROCYTE MEMBRANE

NORMAL FUNCTION

Composed of a lipid bilayer and an underlying cortical membrane skeleton (Fig. 147-1), the membrane provides the erythrocyte the deformability and stability required to withstand its travels through the circulation. In one circulatory cycle throughout the body, an erythrocyte is subjected to high shear stress in the arterial system, dramatic size and shape changes in the microcirculation with capillary diameters as small as 7.5 μm, and marked fluctuations in tonicity, pH, and Po_2.[1]

Membrane Lipids

Red blood cell membrane lipids are asymmetrically distributed across the bilayer membrane, reflecting a steady state involving a constant exchange of phospholipids between the two bilayer hemileaflets. Glycolipids and cholesterol are intercalated between the phospholipids in the bilayer with their long axes perpendicular to the bilayer plane. Glycolipids, located in the external half of the bilayer with their carbohydrate moieties extending into the aqueous phase, carry several important RBC antigens and serve other significant functions. Phospholipids are asymmetrically organized; choline phospholipids, phosphatidylcholine, and sphingomyelin are primarily in the outer half of the bilayer, whereas amino phospholipids, phosphatidylethanolamine, and phosphatidylserine (PS) are in the inner half of the bilayer. In pathologic states such as thalassemia, sickle cell disease, and diabetes, loss of phospholipid asymmetry with externalization of PS leads to activation of blood clotting through conversion of prothrombin to thrombin and facilitates macrophage attachment to erythrocytes, marking them for destruction. Mature erythrocytes are unable to synthesize fatty acids, phospholipids, or cholesterol de novo and depend on lipid exchange and fatty acid acylation as mechanisms for phospholipid repair and renewal.

Membrane Proteins

Membrane proteins are classified as either *integral*, penetrating or crossing the lipid bilayer and interacting with the hydrophobic lipid core, or *peripheral*, interacting with integral proteins or lipids at the membrane surface but not penetrating into the bilayer core. Integral membrane proteins include the glycophorins, Rh proteins, Kell and Duffy antigens, and transport proteins such as band 3 (AE1, anion exchanger 1, SLC4A1), Na^+,K^+-ATPase, Ca^{2+}-ATPase, and Mg^{2+}-ATPase. Numerous membrane receptors and antigens are present on integral membrane proteins. Peripheral membrane proteins are on the cytoplasmic membrane face and include enzymes such as glyceraldehyde-3-phosphate dehydrogenase and the structural proteins of the spectrin-actin–based membrane skeleton.

Integral Membrane Proteins

Band 3, the major integral protein of the RBC, has two primary functions: ion transport and maintenance of protein–protein interactions. Band 3 mediates chloride–bicarbonate exchange and provides a binding site for glycolytic enzymes, Hb, and the skeletal proteins ankyrin, protein 4.1, and protein 4.2.

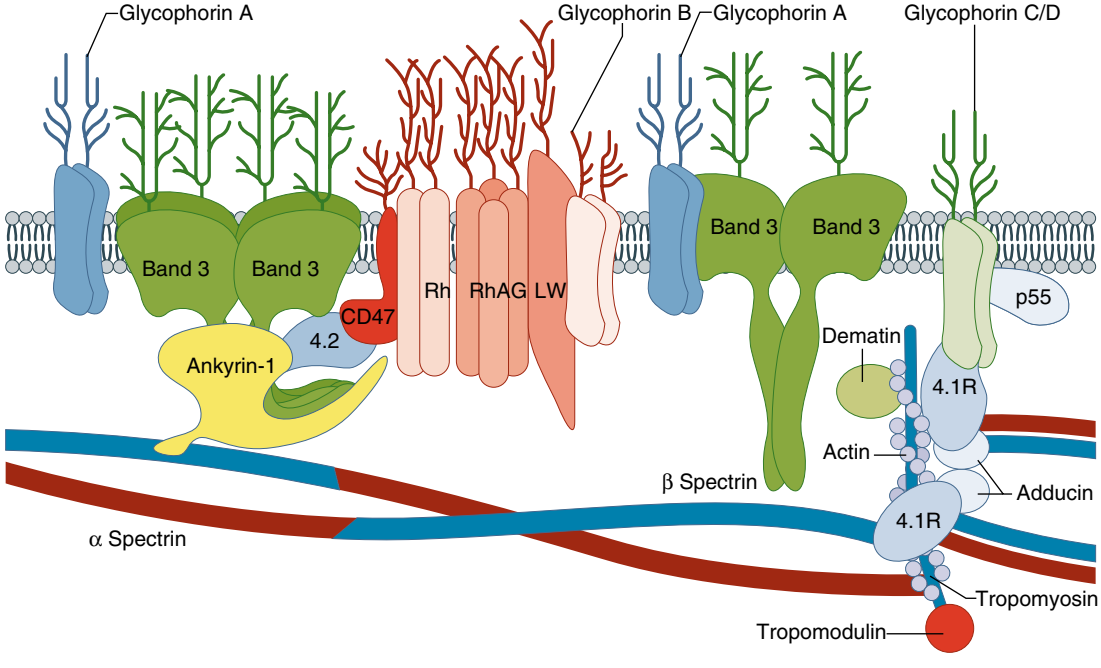

FIGURE 147-1. The erythrocyte membrane. A model of the major proteins of the erythrocyte membrane is shown: α and β spectrin, ankyrin, band 3 (the anion exchanger), 4.1 (protein 4.1) and 4.2 (protein 4.2), actin, and glycophorin. LW = Landsteiner Wiener glycoprotein; Rh = Rhesus polypeptide; RhAG = Rh-associated glycoprotein. (From Perrotta S, Gallagher PG, Mohandas N. Hereditary spherocytosis. *Lancet*. 2008;372:1411-1426.)

ABSTRACT

Disorders of the erythrocyte membrane and erythrocyte metabolism comprise an important group of inherited hemolytic anemias. Abnormalities of proteins of the membrane and its underlying cytoskeleton compromise the strength and flexibility of the erythrocyte needed to maintain the normal shape and deformability needed to survive its travels through the circulation. Qualitative and quantitative membrane protein defects lead to various abnormalities of erythrocyte shape associated with varying degrees of hemolysis. In many cases, red blood cell shape abnormalities provide a clue to the pathobiology and diagnosis of the underlying disorder. Disorders of erythrocyte volume homeostasis associated with abnormalities in membrane proteins are now beginning to be understood. Abnormalities of metabolism are particularly crippling to the erythrocyte, because without a nucleus or mitochondria, the cell is left to depend on the array of proteins available after enucleation to maintain its metabolic functions. These include maintaining adequate supplies of energy via production of ATP, producing reducing substances to allow antioxidant production and activity, and controlling oxygen affinity of hemoglobin. Clinical, laboratory, and genetic manifestations of metabolic disorders of the erythrocyte are heterogeneous.

KEYWORDS

membrane
metabolism
spherocytosis
elliptocytosis
pyropoikilocytosis
stomatocytosis

A single *N*-glycan chain attached to an asparagine in the membrane spanning domain of band 3 is composed of *N*-acetyl-d-lactosamine units arranged in an unbranched, linear fashion in fetal erythrocytes (i antigen) and in a branched fashion in adult cells (I antigen).

The glycophorins are the next most abundant family of integral membrane proteins. They provide most of the negative surface charge required by RBCs to avoid sticking to each other and to the vascular wall. They are involved in transmembrane signaling and carry receptors for *Plasmodium falciparum*, a number of viruses and bacteria, and several blood group antigens.

Peripheral Membrane Proteins

Spectrin is the major component of the membrane skeleton. It is composed of two subunits, α and β spectrin, that are structurally related but functionally distinct. Spectrin is highly flexible and assumes a variety of conformations, an unusual property that may be critical for normal membrane pliancy. The spectrin-based membrane skeleton is linked to the plasma membrane through the actin–protein 4.1 junctional complex; through spectrin–ankyrin interactions; and through binding of a multiprotein complex containing Rh proteins, Rh-associated glycoproteins, CD47, LW, glycophorin B, and protein 4.2 to ankyrin. Protein 4.1, a protein necessary for normal membrane stability, interacts with spectrin, actin, and other proteins of the RBC membrane. Ankyrin serves as the primary linkage protein for the high-affinity binding of spectrin to the inner membrane through interactions with the cytoplasmic domain of band 3. Protein 4.2 is a peripheral membrane protein that helps link the skeleton to the lipid bilayer through interactions with ankyrin and band 3.

Erythrocyte membrane disorders result from alterations in the quantity or quality (or both) of individual proteins and their dynamic interactions with each other. Disruption of the vertical protein–protein interactions of the membrane, that is, the spectrin-ankyrin–band 3 linkage or the band 3–protein 4.2 interaction, leads to uncoupling of the membrane skeleton from the lipid bilayer. This leads to membrane instability with loss of lipids and some integral membrane proteins, resulting in loss of membrane surface area and the phenotype of spherocytosis. Disruption of the horizontal interactions of membrane skeleton proteins, including perturbation of spectrin self-association or junctional complex protein–protein interactions, leads to membrane instability, altered membrane deformability and mechanical properties, and the phenotype of elliptocytosis.

Erythrocyte membrane disorders also result from abnormal cation permeability or disturbed erythrocyte hydration (see later section on "Hereditary Stomatocytosis Syndromes.")

DISORDERS OF THE ERYTHROCYTE MEMBRANE

Hemolytic anemias caused by defects in the erythrocyte membrane comprise an important group of hereditary anemias. Hereditary spherocytosis, hereditary elliptocytosis, and hereditary pyropoikilocytosis are the most common disorders among this group.[2] Detailed clinical studies carried out years ago have now been complemented by biochemical and genetic studies, providing a better understanding of the pathogenesis of these disorders as well as the normal biology of the erythrocyte membrane.

HEREDITARY SPHEROCYTOSIS

DEFINITION

Hereditary spherocytosis is a group of disorders characterized by spherical erythrocytes on the peripheral blood smear (Fig. 147-2A). Clinical, laboratory, and genetic heterogeneity characterize this group of disorders.

EPIDEMIOLOGY

Hereditary spherocytosis affects approximately one in 2000 to 4000 individuals of northern European ancestry.[3] Found worldwide, it is much more common in Whites than individuals of African ancestry.

PATHOBIOLOGY

The primary defect in hereditary spherocytosis is the loss of erythrocyte membrane surface area caused by defects in erythrocyte membrane proteins,

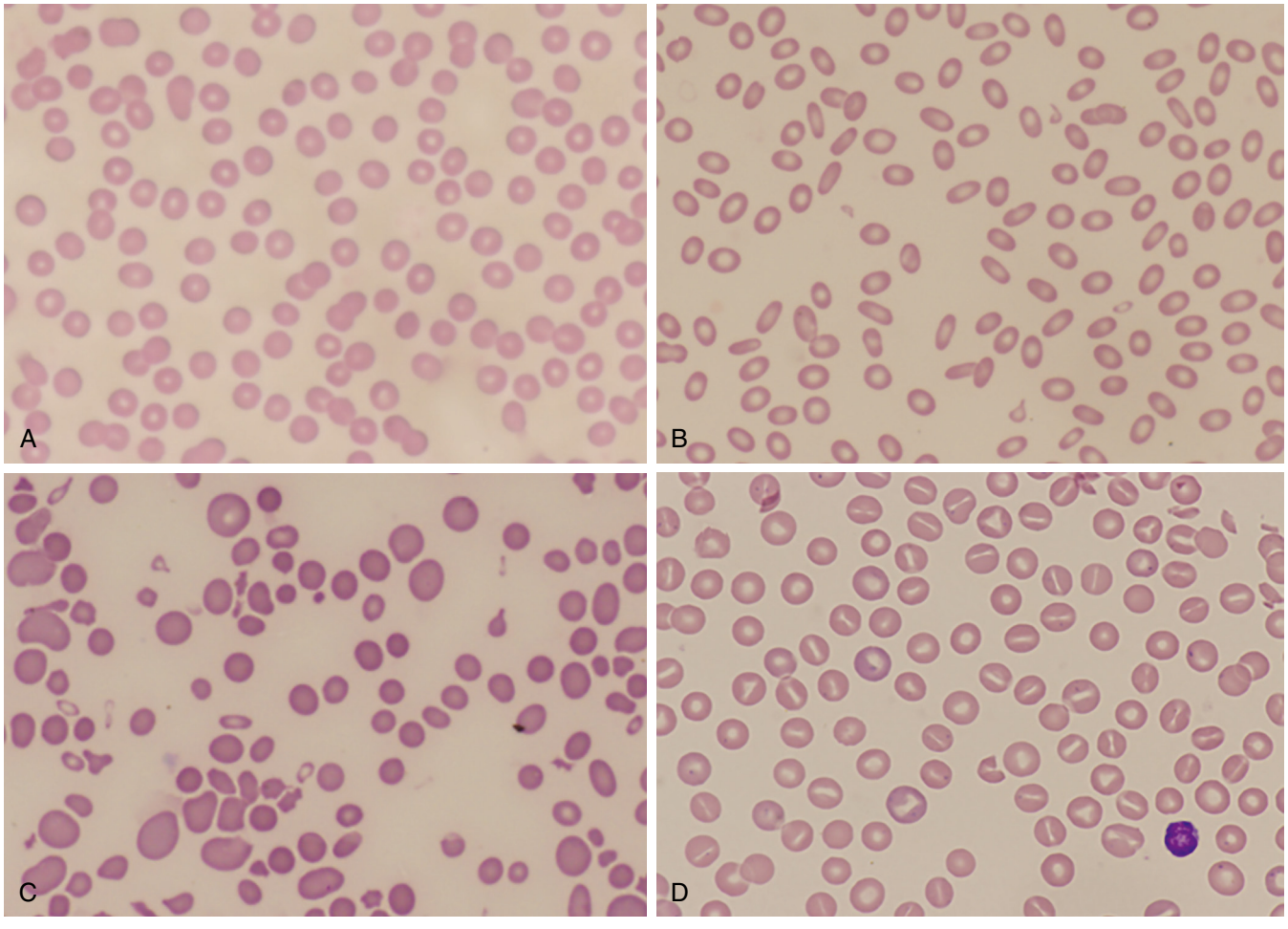

FIGURE 147-2. Peripheral blood smears in disorders of erythrocyte shape. A, Hereditary spherocytosis. Characteristic small spherocytes lacking central pallor are seen. **B,** Hereditary elliptocytosis. Smooth, cigar-shaped elliptocytes are seen. **C,** Hereditary pyropoikilocytosis. Pronounced microcytosis, poikilocytosis, fragmentation of erythrocytes, and elliptocytes are seen. **D,** Hereditary stomatocytosis.

including α spectrin, β spectrin, ankyrin, band 3, and protein 4.2. Qualitative or quantitative defects of one or more of these membrane proteins lead to membrane instability, which, in turn, leads to membrane loss. In approximately two thirds of hereditary spherocytosis patients, inheritance is autosomal dominant. In the remaining patients, inheritance is nondominant owing to either a de novo mutation or autosomal recessive inheritance. Cases with autosomal recessive inheritance are caused by defects in either α spectrin or protein 4.2. Rare cases of homozygous hereditary spherocytosis have been reported, resulting in fetal death or severe hemolytic anemia. In most cases, hereditary spherocytosis mutations are "private," that is, each individual has a unique mutation, implying that there is no selective evolutionary advantage to hereditary spherocytosis.

The spleen plays a critical, albeit secondary, role in the pathophysiology of hereditary spherocytosis. Splenic destruction of poorly deformable spherocytes is the primary cause of hemolysis experienced by hereditary spherocytosis patients. Abnormal erythrocytes are trapped in the splenic microcirculation and ingested by phagocytes. Moreover, the splenic environment is hostile to erythrocytes, with low pH, low glucose, and low ATP concentrations and high local concentrations of toxic free radicals produced by adjacent phagocytes, all contributing to membrane damage.

CLINICAL MANIFESTATIONS

The clinical manifestations of the spherocytosis syndromes vary widely[4] and are determined by the density and deformability of the abnormal red cells.[5] The classic triad of hereditary spherocytosis is anemia, jaundice, and splenomegaly. Rarely, patients may have severe hemolytic anemia presenting in utero or shortly after birth and continuing through the first year of life. These patients may require multiple blood transfusions, and in some cases, splenectomy in infancy. Many patients with hereditary spherocytosis escape detection throughout childhood. In these patients, the diagnosis of hereditary spherocytosis is not made until they are being evaluated for unrelated disorders later in life or when complications related to anemia or chronic hemolysis occur. Although the lifespan of an erythrocyte in these patients may be shortened to only 20 to 30 days, they adequately compensate for their hemolysis with increased bone marrow erythropoiesis.

Chronic hemolysis leads to the formation of bilirubinate gallstones (Chapter 141), the most frequently reported complication in patients with hereditary spherocytosis. Although gallstones have been observed in early childhood, most appear in adolescents and young adults.

Other complications of hereditary spherocytosis include aplastic, hemolytic, and megaloblastic crises. Aplastic crises occur after virally-induced bone marrow suppression and present with anemia, jaundice, fever, and vomiting. The most common etiologic agent in these cases is parvovirus B19 (Chapter 342). Hemolytic crises, usually associated with viral illnesses and occurring before 6 years of age, are generally mild and present with jaundice, increased spleen size, and a decrease in hematocrit. Megaloblastic crises occur in hereditary spherocytosis patients with increased folate demands, such as the pregnant patient, growing children, or patients recovering from an aplastic crisis.

Uncommon manifestations of hereditary spherocytosis include skin ulceration, gout, chronic leg dermatitis, cardiomyopathy, spinal cord dysfunction, movement disorders, and extramedullary erythropoiesis. In patients with untreated severe hereditary spherocytosis, poor growth and findings attributable to extramedullary hematopoiesis, such as hand and skull deformities, may be observed.

DIAGNOSIS

Patients with hereditary spherocytosis may present at any age, usually with anemia, hyperbilirubinemia, or an abnormal blood smear. In evaluating a patient with suspected hereditary spherocytosis, particular attention should be paid to the family history, including questions about anemia, jaundice, gallstones, and splenectomy. The initial laboratory investigation should include a complete blood count with a peripheral smear, reticulocyte count, direct antiglobulin test (Coombs test), and serum bilirubin. When the peripheral smear or family history is suggestive of hereditary spherocytosis, flow cytometric analysis of eosin-5-maleimide–labelled erythrocytes (EMA binding) or an incubated osmotic fragility test (discussed later) should be obtained. Rarely, additional, specialized testing is required to confirm the diagnosis.

Overall, laboratory findings in hereditary spherocytosis are heterogeneous. Erythrocyte morphology (Chapter 143) is distinctive but not diagnostic (Fig. 147-2A). Typical hereditary spherocytosis patients have blood smears with easily identifiable spherocytes lacking central pallor. Some patients present with only a few spherocytes on peripheral smear, but others present with numerous small, dense spherocytes and bizarre erythrocyte morphology. Specific morphologic findings have been identified in patients with certain membrane protein defects such as pincered erythrocytes (band 3) or spherocytic acanthocytes (β spectrin). When examining a peripheral blood smear in a case of suspected spherocytosis, it is important to have a high-quality smear with the erythrocytes well separated and some cells with central pallor in the field of examination because spherocytes are a common artifact on peripheral blood smears. Other disorders with spherocytes on peripheral blood smear are listed in Table 147-1.

TABLE 147-1 DISORDERS WITH SPHEROCYTES ON PERIPHERAL BLOOD FILM

Hereditary spherocytosis
Autoimmune hemolytic anemia
Thermal injuries
Microangiopathic and macroangiopathic hemolytic anemias
Hepatic disease
Clostridial septicemia
Transfusion reactions with hemolysis
Poisoning with certain snake, spider, and *Hymenoptera* venoms
Severe hypophosphatemia
Heinz body anemias
ABO incompatibility (neonates)

The mean corpuscular hemoglobin concentration (MCHC) is increased (between 34.5 and 38) in patients with hereditary spherocytosis owing to relative cellular dehydration. The mean corpuscular volume (MCV) is usually normal or slightly decreased. Many cell counters provide a histogram of MCHCs claimed to be accurate enough to identify nearly all patients with hereditary spherocytosis.

In a normal erythrocyte, a redundancy of cell membrane gives the cell its characteristic discoid shape and provides it abundant surface area. In spherocytes, there is a decrease in surface area relative to cell volume, resulting in their abnormal shape. This change is reflected in the increased osmotic fragility found in these cells. Osmotic fragility is tested by adding increasingly hypotonic concentrations of saline to RBCs. Normal erythrocytes are able to increase their volume by swelling, but spherocytes, which are already at maximal volume for surface area, burst at higher saline concentrations than normal. Approximately one fourth of hereditary spherocytosis individuals will have a normal osmotic fragility on freshly drawn RBCs, with the osmotic fragility curve approximating the number of spherocytes seen on peripheral smear. However, after incubation at 37° C for 24 hours, hereditary spherocytosis RBCs lose membrane surface area more readily than normal because their membranes have become leaky and unstable. Thus, incubation accentuates the defect in hereditary spherocytosis erythrocytes and brings out the defect on osmotic fragility, making incubated osmotic fragility the standard test in diagnosing hereditary spherocytosis (Fig. 147-3, *bottom panel*). When the spleen is present, a subpopulation of very fragile erythrocytes that have been conditioned by the spleen form the tail of the osmotic fragility curve. This tail disappears after splenectomy. The osmotic fragility test suffers from poor sensitivity, with as many as 20% of mild cases of hereditary spherocytosis missed after incubation. It is unreliable in patients who have small numbers of spherocytes and in patients who have been recently transfused. It is abnormal in other conditions in which spherocytes are present.

Eosin-5-maleimide (EMA) binding is a flow cytometry–based test used in the diagnosis of hereditary spherocytosis.[6] EMA is a fluorescent dye that binds to band 3 and Rh-related proteins in the erythrocyte membrane. In hereditary spherocytosis, the mean fluorescence of EMA-stained erythrocytes is lower compared with control because of the reduction of band 3 and related proteins, typically decreased to approximately 65% of normal (Fig. 147-3, *top panel*). Although primary defects of band 3 protein are seen in only about 25% of hereditary spherocytosis patients, decreased fluorescence intensity is also observed in the erythrocyte membranes of hereditary spherocytosis patients with defects in other membrane proteins such as ankyrin and spectrin. This is thought to be attributable to transmission of long-range effects of mutant protein defects across the membrane lattice, ultimately influencing the amount of EMA binding to band 3. EMA binding has good sensitivity and specificity and is simple and rapidly performed.[7]

Specialized testing is available for studying difficult cases or cases in which additional information is desired. Useful tests for these purposes include structural and functional studies of erythrocyte membrane proteins, such as protein

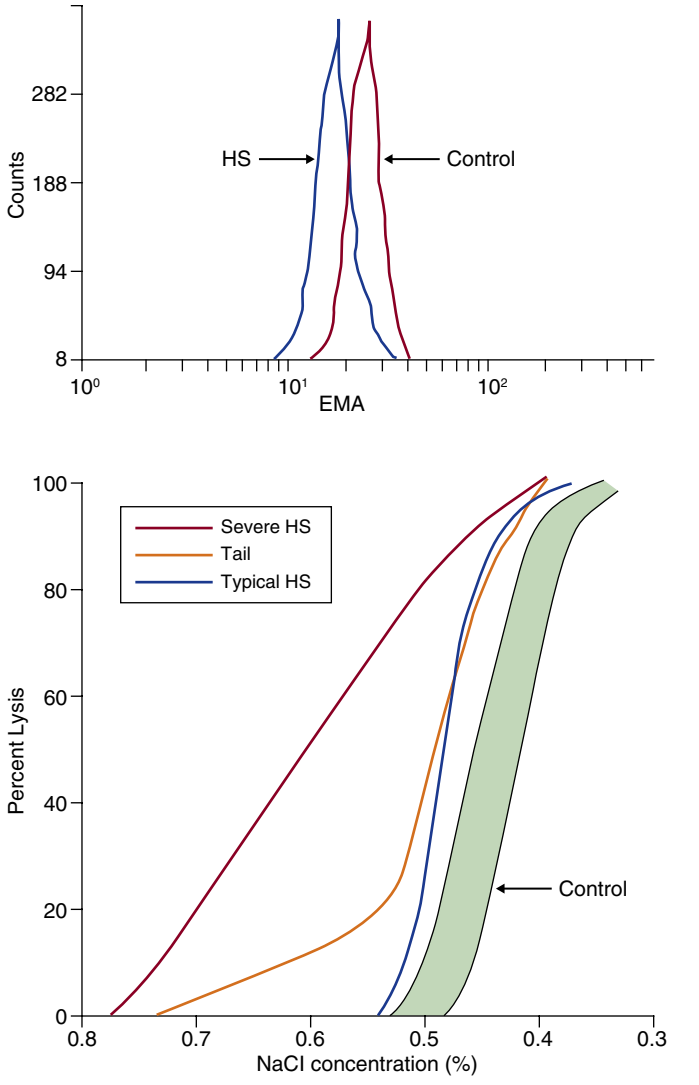

FIGURE 147-3. Testing in hereditary spherocytosis. *Top panel*, Eosin-5-maleimide (EMA) binding. Histogram of fluorescence of EMA-labeled erythrocytes from a normal control and a patient with typical hereditary spherocytosis. Decreased fluorescence is observed from hereditary spherocytosis (HS) erythrocytes. *Bottom panel*, Osmotic fragility curves in hereditary spherocytosis. The *shaded region* is the normal range. Results representative of both typical and severe spherocytosis are shown. A tail, representing fragile erythrocytes conditioned by the spleen, is common in spherocytosis patients prior to splenectomy. (From Gallagher PG. Abnormalities of the erythrocyte membrane. *Pediatr Clin North Am* 2013;60:1349-1352.)

quantitation, limited tryptic digestion of spectrin, spectrin, and ion transport. Membrane deformability may be examined using an ektacytometer.

Genetic diagnosis of hereditary spherocytosis has become widely available and the associated costs continue to decrease. The precise role of molecular diagnosis is evolving. Next-generation sequencing panels could become a cost-effective approach to molecular diagnosis of hereditary hemolytic anemia, especially when the family history is uninformative or when routine laboratory testing fails to identify the causative hemolytic process.[8] In difficult cases, such as when there is transfusion dependence, genetic testing may be diagnostic. Some experts recommend genetic testing to verify the diagnosis prior to splenectomy.

Other laboratory manifestations in hereditary spherocytosis are manifestations of ongoing hemolysis. Increased serum bilirubin, increased lactate dehydrogenase, increased urinary and fecal urobilinogen, and decreased serum haptoglobin reflect increased erythrocyte destruction. Because of the high risk for gallstones, routine interval ultrasonography to detect gallstones is recommended even if patients are asymptomatic.

After diagnosing a patient with hereditary spherocytosis, family members should be examined for presence of the disease. This can be of great epidemiologic importance, particularly for very old and very young patients. Prenatal diagnosis of hereditary spherocytosis has been made in a few cases, but this is rarely necessary.

TREATMENT AND PROGNOSIS

Splenic sequestration and destruction is the primary determinant of erythrocyte survival in hereditary spherocytosis patients. Splenectomy cures or alleviates anemia in most patients, reducing or eliminating the need for transfusions. The risk for cholelithiasis is also decreased to nearly background levels. After splenectomy, spherocytes remain in the peripheral blood, but their lifespan becomes near normal.

In the past, splenectomy was routinely performed in all patients with hereditary spherocytosis.[9] However, the risk of overwhelming post-splenectomy infection; the emergence of penicillin-resistant pneumococci; and the growing recognition of the increased risk of post-splenectomy cardiovascular disease (particularly thrombosis, pulmonary hypertension, and increased risk of atherosclerosis) have led to reevaluation of the role of splenectomy in the treatment of hereditary spherocytosis (Chapter 154).[10,11] In addition, with growing globalization, the important role of the spleen in protection of individuals living in or traveling to geographic regions where parasitic diseases such as malaria or babesiosis occur have reemerged. When splenectomy is considered, health care providers, the patient, and family members must review and weigh the benefits of splenectomy against the immediate and long-term risks of the procedure. Considering the risks and benefits, a reasonable approach is to splenectomize all patients with severe spherocytosis and all patients who have significant signs or symptoms of anemia, including growth failure, skeletal changes, leg ulcers, and extramedullary hematopoietic tumors. Other candidates for splenectomy are older patients who have hereditary spherocytosis and also have vascular compromise of vital organs. Whether patients with moderate hereditary spherocytosis and compensated, asymptomatic anemia should undergo splenectomy is controversial.

When splenectomy is indicated, laparoscopic splenectomy has become the method of choice. This technique results in less postoperative discomfort, a quicker return to preoperative diet and activities, shorter hospitalization, decreased costs, and smaller scars. Even massive spleens can be removed laparoscopically because the spleen is placed in a large bag, diced intraoperatively, and eliminated through suction catheters. Partial splenectomy was initially advocated for infants and young children with significant anemia associated with erythrocyte membrane disorders to allow for palliation of hemolysis and anemia while maintaining some residual splenic immune function. This procedure is now being suggested by some for most hereditary spherocytosis patients.[12] Guidelines, which reflect changes in current opinion about surgical management, include (1) preference for a laparoscopic approach, (2) performance of splenectomy ideally after the age of 6 years, (3) no indication for extended thrombosis prophylaxis after splenectomy for hereditary spherocytosis, and (4) avoidance of splenectomy in patients with some forms of hereditary stomatocytosis because of an increased risk of venous thromboembolism.

Before splenectomy (Chapter 154), patients should be immunized with vaccines against pneumococcus, *Haemophilus influenzae* type B, and meningococcus. Post-splenectomy care includes counseling of patients (or parents) to seek prompt medical care in case of febrile illness, to seek medical care after dog or cat bites, and to receive prophylaxis if traveling to malaria-endemic areas. Use of routine antibiotics after splenectomy for prevention of pneumococcal sepsis is controversial and data are lacking to indicate or refute their prescription. Many providers prescribe daily oral penicillin prophylaxis, 250 to 500 mg twice a day, for 2 or more years post-splenectomy. Before splenectomy and post-splenectomy if hemolysis does not abate, hereditary spherocytosis patients should take folic acid (1 mg/day orally) to prevent folate deficiency.

HEREDITARY ELLIPTOCYTOSIS AND RELATED DISORDERS

DEFINITION

Hereditary elliptocytosis is characterized by the presence of elliptical or oval cigar-shaped erythrocytes on peripheral blood smears of affected individuals (see Fig. 147-2B).

EPIDEMIOLOGY

Hereditary elliptocytosis has been estimated to occur in approximately one in 2000 to 4000 individuals. The true incidence of hereditary elliptocytosis is unknown because its clinical severity is heterogeneous, and many patients are asymptomatic. It is common in African Americans and people of Mediterranean ancestry, presumably because elliptocytes confer some resistance to malaria. In parts of Africa, the incidence of hereditary elliptocytosis approaches one in 100.

PATHOBIOLOGY

The principal defect in hereditary elliptocytosis is mechanical weakness or fragility of the erythrocyte membrane skeleton. Qualitative and quantitative defects in a number of RBC membrane proteins have been described in hereditary elliptocytosis, including α spectrin, β spectrin, protein 4.1, and glycophorin C. Most defects occur in spectrin, the principal structural protein of the erythrocyte membrane skeleton. αβ Spectrin heterodimers self-associate

into tetramers and higher order oligomers that are critical for erythrocyte membrane stability as well as erythrocyte shape and function. Most spectrin defects in hereditary elliptocytosis impair the ability of spectrin dimers to self-associate into tetramers and oligomers, thereby disrupting the membrane skeleton. Structural and functional defects of protein 4.1 appear to disrupt the spectrin–actin contact in the membrane skeleton. Glycophorin C variants are also deficient in protein 4.1. The precise pathobiology of how elliptocytes are formed in these syndromes is unclear.

Genetically, hereditary elliptocytosis is heterogeneous with multiple genetic loci. A wide variety of mutations have been described in the α spectrin, β spectrin, protein 4.1, and glycophorin C genes, including point mutations, gene deletions and insertions, and messenger RNA processing defects. Several mutations have been identified in a number of individuals of the same genetic background, suggesting a "founder effect" for these mutants, which supports the hypothesis that there has been genetic selection for elliptocytosis because these RBCs confer some resistance to malaria. Most cases of hereditary elliptocytosis are inherited in an autosomal dominant pattern, with rare cases of de novo mutations.

CLINICAL MANIFESTATIONS

The clinical presentation of hereditary elliptocytosis is heterogeneous, ranging from asymptomatic carriers to patients with severe, life-threatening anemia. Most patients with hereditary elliptocytosis are asymptomatic and are diagnosed incidentally during testing for unrelated conditions. Asymptomatic carriers have been identified who possess the same molecular defect as an affected hereditary elliptocytosis relative but who have normal peripheral blood smears. The erythrocyte lifespan is decreased in only about 10% of patients. This subset of patients with hereditary elliptocytosis and decreased erythrocyte lifespan experience hemolysis, anemia, splenomegaly, and intermittent jaundice. Many of these patients have parents with typical hereditary elliptocytosis and thus are homozygotes or compound heterozygotes for defects inherited from each of the parents. Symptoms may vary among members of the same family; indeed, they may vary in the same individual at different times.

HEREDITARY PYROPOIKILOCYTOSIS

Hereditary pyropoikilocytosis is a rare cause of anemia with distinctive erythrocyte morphology on peripheral blood smear (see Fig. 147-2C) and has a picture similar to that seen in patients with severe burns. Patients typically present in infancy with severe anemia and peripheral blood smear findings of elliptocytosis, poikilocytosis, pyknocytosis, and fragmentation. Microspherocytosis is common, and the MCV is usually very low (50 to 70 fL). Most patients are of African ancestry. At least one third of hereditary pyropoikilocytosis patients have a parent or sibling with typical hereditary elliptocytosis, as they share common mutations in the self-association site of spectrin. Patients with hereditary pyropoikilocytosis tend to experience severe hemolysis and anemia in infancy that gradually improves, evolving toward typical hereditary elliptocytosis later in life.

DIAGNOSIS

Cigar-shaped elliptocytes on peripheral blood smear are the hallmark of hereditary elliptocytosis (see Fig. 147-2B). These normochromic, normocytic elliptocytes vary in number from a few to 100%. The likelihood of hemolysis does not correlate with the number of elliptocytes present. Ovalocytes, spherocytes, stomatocytes, and fragmented cells may also be seen. In some cases, pyknocytes may be prominent. Elliptocytes may be seen in association with other disorders, including megaloblastic anemias, hypochromic microcytic anemias (iron deficiency anemia and thalassemia), myelodysplastic syndromes, and myelofibrosis; however, elliptocytes generally make up fewer than one third of RBCs in these conditions. History and additional laboratory testing usually clarify the diagnosis of these disorders. In typical cases, the incubated osmotic fragility is normal, but in severe hereditary elliptocytosis and hereditary pyropoikilocytosis, incubated osmotic fragility is increased, and EMA binding is decreased.

Other laboratory findings in hereditary elliptocytosis are similar to those found in other hemolytic anemias and are nonspecific markers of increased erythrocyte production and destruction. The reticulocyte count generally is less than 5% but may be higher when hemolysis is severe.

Similar to hereditary spherocytosis, specialized laboratory procedures are available to study the erythrocyte membranes of hereditary elliptocytosis and hereditary pyropoikilocytosis patients. These studies are not routinely required to make the diagnosis of hereditary elliptocytosis or hereditary pyropoikilocytosis, but they may be helpful in studying problematic cases and in elucidating the underlying molecular defects.

TREATMENT

Therapy is rarely needed in patients with hereditary elliptocytosis. In rare cases, occasional RBC transfusions may be required. In cases of severe hereditary elliptocytosis and hereditary pyropoikilocytosis, splenectomy has been palliative because the spleen is the site of erythrocyte sequestration and destruction. Many practitioners think that the same indications for splenectomy in hereditary spherocytosis should be applied to patients with symptomatic hereditary elliptocytosis or hereditary pyropoikilocytosis. Post-splenectomy patients with hereditary elliptocytosis or hereditary pyropoikilocytosis experience increased hematocrits, decreased reticulocyte counts, and improvement in clinical symptoms. Similar post-splenectomy guidelines as outlined for hereditary spherocytosis should be followed.

Patients should be followed for signs of decompensation during acute illnesses. Interval ultrasonography to detect gallstones should be performed. In patients with significant hemolysis, folate (1 mg/day orally) should be administered daily.

HEREDITARY STOMATOCYTOSIS SYNDROMES

Red blood cell hydration is primarily determined by the intracellular concentration of monovalent cations. A net increase in sodium and potassium ions causes water to enter, forming *stomatocytes* (see Fig. 147-2D) or *hydrocytes*, but a net loss of sodium and potassium produces dehydrated RBCs, or *xerocytes*. Numerous descriptions of congenital or familial hemolytic anemias associated with abnormal cation permeability and, in some cases, disturbed RBC hydration have been reported.[13] These span the range from severe hydrocytosis to severe xerocytosis. In many cases, the molecular bases of this group of disorders are unknown. An unusual characteristic of the stomatocytosis syndromes is a predisposition to thrombosis after splenectomy. Acquired stomatocytosis has been associated with acute alcoholism and hepatobiliary disease, vinca alkaloid administration, neoplasms, and cardiovascular disease. Stomatocytosis is also sometimes observed as a processing artifact.

Overhydrated Hereditary Stomatocytosis (Hydrocytosis)

This group of disorders is characterized by stomatocytes, erythrocytes with a mouth-shaped (stoma) area of central pallor on peripheral blood smear (see Fig. 147-2D), severe hemolysis, macrocytosis (110-150 fL), elevated erythrocyte sodium concentration, reduced potassium concentration, and increased total Na^+ and K^+ content. The excess cations expand cell water, producing large, osmotically fragile cells with low MCHCs (24 to 30%). The clinical severity of overhydrated hereditary stomatocytosis is variable; some patients experience hemolysis and anemia, but others are asymptomatic. Missense mutations in the Rh-associated glycoprotein (*RHAG*) and in band 3 (*SLC4A1*) have been identified in discrete subsets of hydrocytosis patients.

Dehydrated Hereditary Stomatocytosis (Xerocytosis)

Blood smears from patients with dehydrated hereditary stomatocytosis exhibit contracted and spiculated RBCs, dessicytes, a variable number of stomatocytes, and target cells. Most patients have nearly normal erythrocyte morphology, with only a few target cells and an occasional echinocyte or stomatocyte. The MCV (95-115 fL) and MCHC are increased, and the osmotic fragility is reduced (i.e., resistance to osmotic lysis). The characteristic biochemical abnormality is a decreased potassium concentration and total monovalent cation content. Dominantly inherited mutations in PIEZO1 are found in most xerocytosis patients. PIEZO proteins are the recently identified pore-forming subunits of channels that mediate mechanotransduction in mammalian cells. In erythrocytes, PIEZO1 carries the Er blood group antigens.[14] Association of PIEZO variants with changes in erythrocyte hydration suggest that these proteins play an important role in erythrocyte volume homeostasis. A few hereditary xerocytosis patients have been found to have mutations in the Gardos channel, encoded by *KCNN4*, important in the pathogenesis of erythrocyte dehydration in sickle cell disease.

Intermediate Syndromes and Hereditary Stomatocytosis Variants

Hydrocytosis and xerocytosis represent the extremes of a broad spectrum of RBC permeability defects. In fact, families with features of both conditions have been reported. Some patients with severe permeability defects have little or no hemolysis. The proportion of stomatocytes and the degree of sodium influx do not correlate with each other, and neither correlates with the amount of hemolysis or anemia.

ERYTHROCYTE METABOLISM

NORMAL METABOLISM

The primary functions of the erythrocyte, gas transport and exchange, are maintained without a net change in energy state. However, several critical functions of the erythrocyte depend on the production and expenditure of energy. As erythrocytes age, glucose utilization and ATP levels fall, leading to decreased membrane deformability and, ultimately, a shortened lifespan. Lower potassium levels, higher sodium levels, and decreased membrane lipids are also seen in ATP-deficient, aging erythrocytes.

Erythrocytes do not undergo oxidative phosphorylation and do not store glycogen; thus, they must constantly catabolize glucose from the blood stream through the Embden-Meyerhof pathway and the hexose monophosphate shunt as a source of energy (Fig. 147-4). Erythrocytes incorporate glucose from the plasma through facilitated transfer, with erythrocyte glucose levels rapidly equilibrating with changes in blood glucose levels. Glucose is the preferred carbohydrate of the RBC, but fructose and mannose are metabolized almost as readily. Inside the erythrocyte, glucose is converted to glucose-6-phosphate or to fructose by sorbitol. Glucose-6-phosphate follows one of three pathways: (1) most (≈90%) enters the Embden-Meyerhof pathway, where it is converted into lactate, pyruvate, and ATP; (2) some (≈5 to 10%) enters the hexose monophosphate shunt to produce reduced intermediates and ribulose 5-phosphate, the latter of which eventually enters the Embden-Meyerhof pathway; and (3) a tiny fraction (<1%) is converted to glucose-1-phosphate and then to glycogen.

Embden-Meyerhof Pathway

The Embden-Meyerhof pathway of glycolysis is the primary source of ATP, 2,3-DPG and nicotinamide adenine dinucleotide, reduced form (NADH) in erythrocytes (see Fig. 147-4). Most of the energy generated by erythrocytes is through the Embden-Meyerhof pathway followed by storage as high-energy phosphates such as ATP or as reducing energy in the form of glutathione or pyridine nucleotides (NADH and nicotinamide adenine dinucleotide phosphate, reduced form [NADPH]). This pathway metabolizes about 90% of erythrocyte glucose with the catabolism of 1 mole of glucose yielding 2 moles of ATP and 2 moles of lactate. Two moles of ATP per mole of metabolized glucose seems insignificant compared with the Krebs cycle of intermediary metabolism, in which 1 mole of glucose metabolized produces 38 moles of ATP. However, this ATP production is adequate to renew 150 to 200% of the total RBC ATP every hour.

The Embden-Meyerhof pathway is also the primary source of NADH, a necessary cofactor for NADH methemoglobin reductase, which maintains heme iron in the reduced state. Without this reaction, heme iron would be oxidized to methemoglobin, which is not a functional oxygen transporter.

Finally, the Rapoport-Luebering shunt of the Embden-Meyerhof pathway (see Fig. 147-4) produces 2,3-DPG, a compound found in high concentrations in erythrocytes but in low concentrations in other cells. After it is formed, under physiologic conditions of pH and solute concentrations, 2,3-DPG binds reversibly to tetramers of deoxyhemoglobin with greater affinity than it does to oxyhemoglobin. By binding to deoxyhemoglobin, it allosterically upregulates the release of the remaining oxygen bound to the Hb, enhancing the ability of erythrocytes to release oxygen near tissues that need it most.

Hexose Monophosphate Shunt (Pentose Phosphate Pathway)

In the hexose monophosphate shunt (see Fig. 147-4), glucose-6-phosphate undergoes oxidation followed by a series of reactions to yield

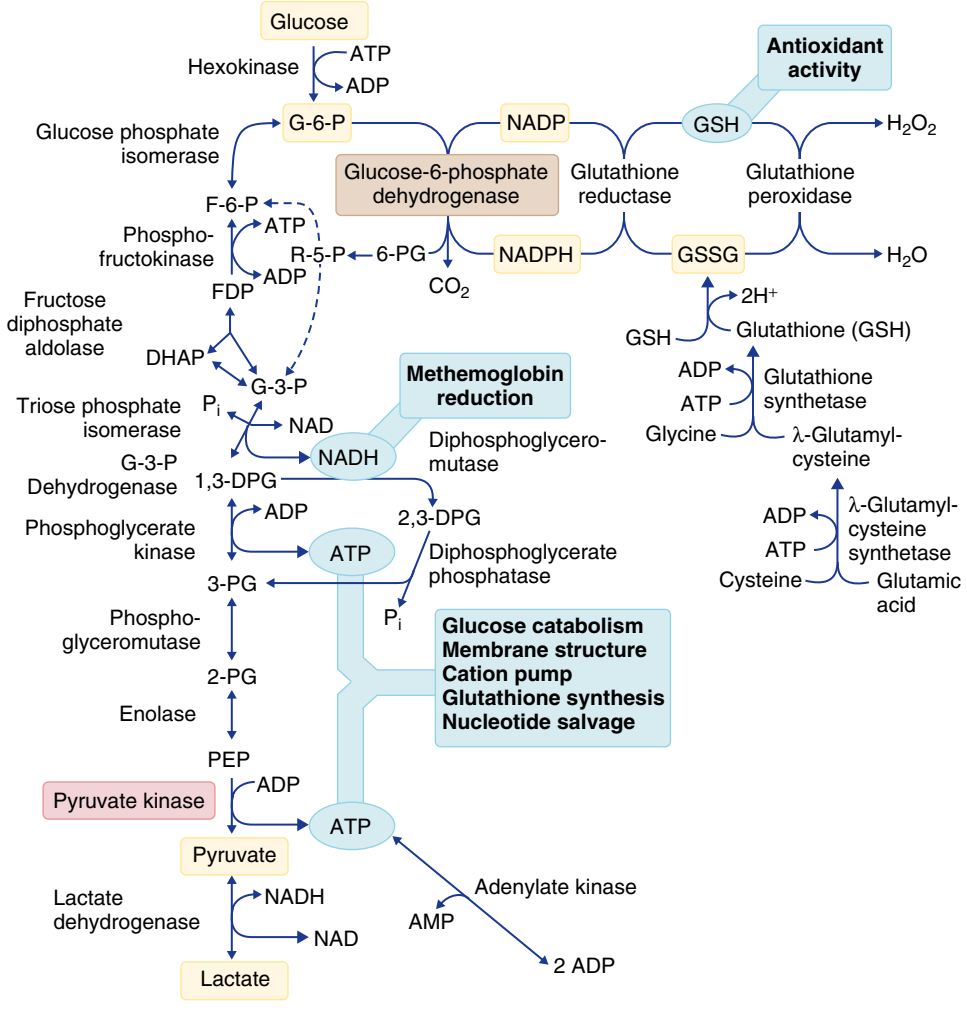

FIGURE 147-4. Pathways of energy metabolism in the erythrocyte. Glucose-6-phosphate may be degraded anaerobically to lactate through the Embden-Meyerhof pathway or oxidatively through the hexose monophosphate shunt. Pentose phosphates (R-5-P) can reenter anaerobic glycolysis as fructose-6-phosphate (F-6-P) and glyceraldehyde-3-phosphate (G-3-P) after conversion by enzymes of the terminal pentose phosphate pathway or as a product of adenosine or inosine degradation. 2,3-Diphosphoglycerate (2,3-DPG) may be generated instead of adenosine triphosphate (ATP) through diversion of triose through the Rapoport-Luebering shunt. Glutathione may be synthesized directly from constituent amino acids; its cycling from oxidized (GSSG) to reduced forms (GSH) depends on reduced pyridine cofactor (NADPH) generation. ADP = adenosine diphosphate; DHAP = dihydroxyacetone phosphate; FDP = fructose-1,6-diphosphate; NAD = nicotinamide adenine dinucleotide; NADP = nicotinamide adenine dinucleotide phosphate; NADPH = nicotinamide adenine dinucleotide phosphate, reduced form; PEP = polyestradiol phosphate.

fructose-6-phosphate and glyceraldehyde-3-phosphate, intermediates in the glycolytic pathway. The hexose monophosphate shunt is the primary source of erythrocyte NADPH, with 2 moles of NADPH produced for each mole of glucose metabolized. NADPH is required for the reduction of oxidized glutathione and some protein sulfhydryl groups.

Mature erythrocytes synthesize large amounts of reduced glutathione. Glutathione protects erythrocytes from oxidants, including hydrogen peroxide (H_2O_2), superoxide anions (O_2^-), and hydroxyl radicals (OH), which are produced as byproducts of the oxidation of heme by oxygen. Oxidants are also produced by activated phagocytes (e.g., during infection) and by erythrocytes after exposure to certain agents. When oxidants accumulate, they damage cellular proteins and lipids. Detoxification of H_2O_2 is significantly enhanced by glutathione peroxidase. Glutathione is converted to oxidized glutathione and to mixed disulfides with protein thiols. Glutathione levels are restored by glutathione reductase. In this process, NADPH is oxidized to nicotinamide adenine dinucleotide phosphate (NADP), which stimulates the hexose monophosphate shunt to regenerate NADPH. After oxidant stress, hypoxia, or acidosis, erythrocytes can increase the amount of glucose metabolized through the hexose monophosphate shunt up to 10- to 20-fold to generate increased amounts of reduced glutathione. The tight coupling of glutathione metabolism with the hexose monophosphate shunt protects the mature erythrocyte from oxidative stress.

DISORDERS OF ERYTHROCYTE METABOLISM

Congenital nonspherocytic hemolytic anemia traditionally includes erythrocyte disorders not due to defects of the RBC membrane or hemoglobin, immune-mediated disease, or other diseases such as paroxysmal nocturnal hemoglobinuria. Congenital nonspherocytic hemolytic anemia is a heterogeneous group of disorders associated with various metabolic abnormalities of the erythrocytes, including enzymopathies of glucose, glutathione, and nucleotide metabolism. Similar to the membrane disorders, clinical, biochemical, and genetic heterogeneity are typical within the enzymopathies. Hemolysis may develop as a result of either enzyme or antioxidant deficiency or dysfunction (e.g., abnormal substrate or cofactor binding), altered activation or inhibition characteristics, or decreased stability or specific activity.

Peripheral blood smears in congenital nonspherocytic hemolytic anemia, with the exception of pyrimidine 5′-nucleotidase deficiency, are unremarkable. Osmotic fragility of fresh erythrocytes is normal. Response to splenectomy is variable. Inheritance is heterogeneous. A thorough family history is important and may be of assistance in determining the diagnosis. Manifestations of the metabolic defect are usually confined to the erythrocyte but may occasionally involve nonerythroid cells.

Definitive diagnosis of metabolic abnormalities of the erythrocyte depends on qualitative or quantitative assays of specific enzyme activity or identification of the specific genetic mutation by DNA analysis. Results of enzyme assays should be interpreted with caution because they only sample surviving RBCs in the peripheral blood and the metabolic milieu of these cells is not necessarily comparable to cells already hemolyzed; in vitro enzyme assay conditions may not accurately reflect the in vivo environment; transfusions before the assay may obscure the underlying metabolic defect; and leukocyte contamination may lead to spurious results. Finally, average enzyme activity may not accurately reflect activity in subpopulations of erythrocytes. This is particularly true when there is reticulocytosis, which may yield artificially elevated mean enzyme activity owing to higher enzyme levels found in reticulocytes.

DISORDERS OF THE EMBDEN-MEYERHOF PATHWAY

Defects of the Embden-Meyerhof pathway are inherited in an autosomal recessive fashion, and usually hemolysis is seen only in homozygotes or compound heterozygotes. Heterozygotes, whose erythrocytes contain less than normal amounts of mutant enzyme, are clinically normal. An exception is phosphoglycerate kinase deficiency, an X-linked disorder with hemolysis found only in males. In this group of disorders, hemolysis is chronic, is not typically influenced by drugs or other inciting agents, and is attributed to insufficient levels of erythrocyte ATP. Splenomegaly from trapping of mutant erythrocytes is common. The hostile splenic environment contributes to the shortened erythrocyte lifespan. When performing specific diagnostic enzyme assays, measurement of glycolytic intermediates may assist in diagnosis because concentrations of intermediates are increased upstream of a defect and decreased downstream of a defect.

Pyruvate Kinase Deficiency

Pyruvate kinase deficiency accounts for approximately 90% of inherited defects of the Embden-Meyerhof pathway and is the second most common inherited erythrocyte enzymopathy associated with anemia after glucose-6-phosphate dehydrogenase (G6PD) deficiency (see later). Pyruvate kinase deficiency is found worldwide, but it is most common in individuals of northern European descent.

PATHOBIOLOGY

Pyruvate kinase catalyzes the conversion of phosphoenolpyruvate (PEP) to pyruvate, generating ATP. Deficient or defective pyruvate kinase leads to decreased levels of erythrocyte ATP, disturbing many cellular processes such as signaling and maintenance of water and ion content, leading to energy failure and dehydration. Upstream catabolites accumulate in the erythrocyte, including 2,3-DPG, which shifts the oxygen dissociation curve to the right, enhancing tissue oxygenation and ameliorating some of the physiologic effects of anemia. Early pyruvate kinase-deficient reticulocytes retain the ability to use oxidative phosphorylation to produce ATP, bypassing their defect. This ability is lost as reticulocytes mature and is markedly dampened in the hypoxic environment of the spleen.

Pyruvate kinase deficiency is inherited in an autosomal recessive manner. Affected individuals are homozygous or compound heterozygotes for pyruvate kinase defects. Heterozygotes are clinically normal or exhibit very minimal hemolysis. Mutation studies reveal a wide range of variants, with a few mutations enriched in certain populations.[15]

CLINICAL MANIFESTATIONS

Clinical manifestations in pyruvate kinase deficiency are heterogeneous, ranging from asymptomatic to transfusion-dependent hemolytic anemia.[16] More severely affected patients present in infancy or early childhood with anemia, jaundice, and splenomegaly. Occasionally, patients may escape detection until later in life when complications related to anemia and chronic hemolysis occur such as cholelithiasis or aplastic crisis or when the diagnosis is made during evaluation of the patient for another condition.

DIAGNOSIS

The peripheral blood smear demonstrates normocytic, normochromic erythrocytes, sometimes with spiculations (Fig. 147-5A). Poikilocytes and acanthocytes may also be seen. Reticulocytosis is common. Osmotic fragility of fresh erythrocytes is usually normal. Occasional patients exhibit a population of osmotically fragile cells after incubation.

NADH fluorescence is a commonly used screening test for pyruvate kinase deficiency. PEP and NADH are mixed with the patient's blood, incubated, and spotted on filter paper, and fluorescence is measured. Direct enzyme assay, which uses PEP as substrate for pyruvate kinase, performed on leukocyte-free hemolysate, is the gold standard for the diagnosis of pyruvate kinase deficiency. This detects all but the few rare patients with dysfunctional, thermolabile enzyme variants without enzyme deficiency. Leukocytes must be carefully depleted from the samples because they contain more than 300 times the pyruvate kinase activity of erythrocytes. Genetic diagnosis for pyruvate kinase deficiency is now widely available. Molecular diagnosis is particularly helpful in patients after transfusion, when prenatal diagnosis is desired, and when sample shipping and preparation precludes direct enzyme assay. To ascertain the diagnosis most accurately using molecular techniques, study of parental DNA is required, unless the patient is homozygous for a deleterious mutation, to determine if the variants detected are in *cis* or *trans* for precise diagnosis.

TREATMENT

Most patients require expectant management, with only rare transfusions, such as during an aplastic episode.[17] Mitapivat, an oral, small-molecule allosteric activator of pyruvate kinase in red cells,[18] can increase the hemoglobin level in adults with pyruvate kinase deficiency and a missense *PKLR* mutation.[A1] In severe cases, patients may be transfusion dependent. In these cases, splenectomy typically lessens hemolysis and ameliorates the anemia. After splenectomy, some patients develop marked reticulocytosis, up to 50 to 70%. This paradoxical reticulocytosis is attributed to increased reticulocyte survival after removal of the hostile splenic environment.

Other Disorders of the Embden-Meyerhof Pathway

Other abnormalities of the Embden-Meyerhof pathway have been described. Hexokinase deficiency is quite uncommon, with great phenotypic variability in reported cases. Severely affected patients have had anemia beginning in infancy and may require blood transfusions. Glucose phosphate isomerase (GPI) deficiency is the third most common hemolytic enzymopathy. GPI deficiency

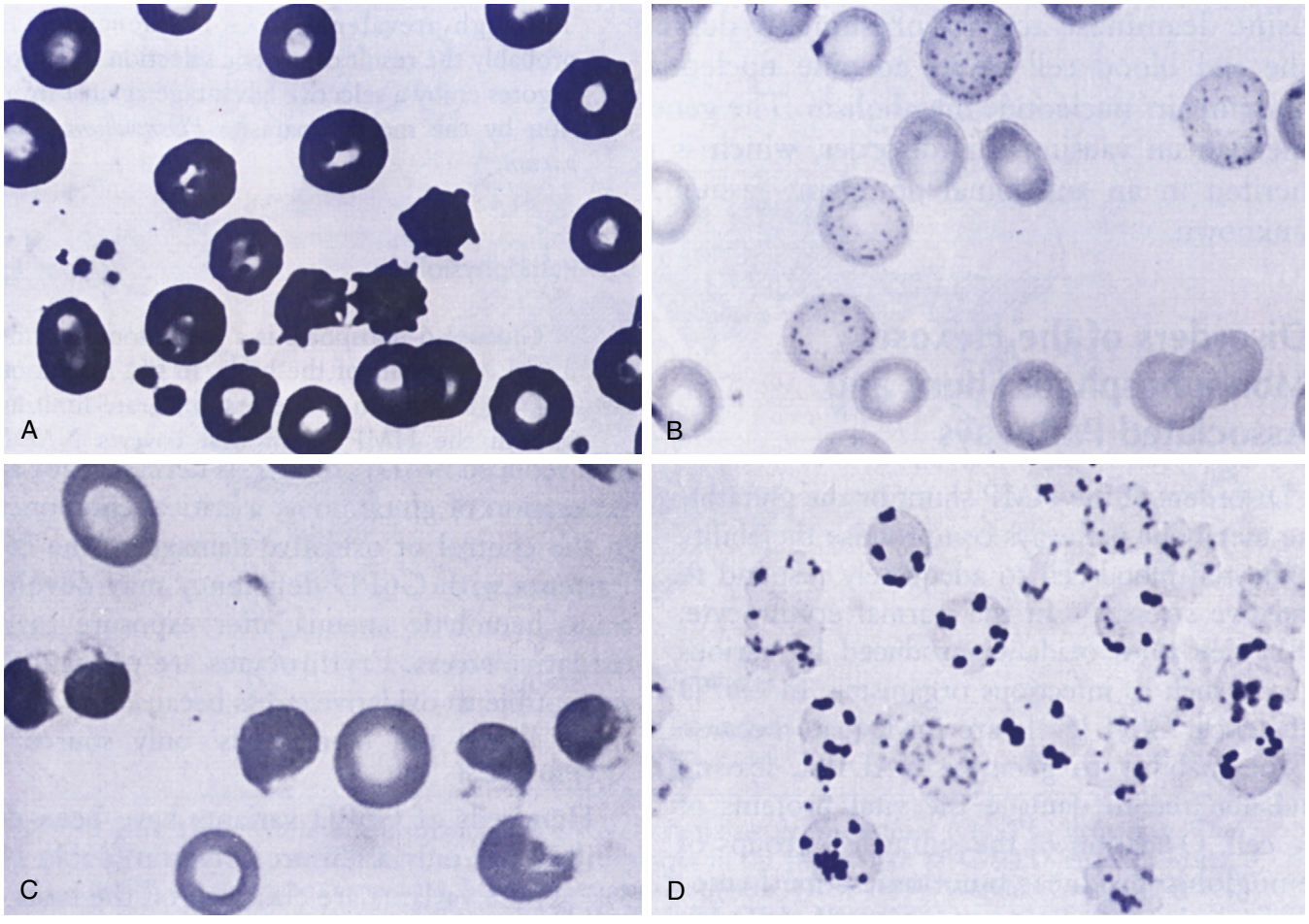

FIGURE 147-5. **Peripheral blood smears in erythrocyte enzymopathies. A**, Pyruvate kinase deficiency. **B**, Pyrimidine 5′-nucleotidase deficiency. **C**, Glucose-6-phosphate dehydrogenase (G6PD) deficiency. **D**, Heinz bodies in G6PD deficiency. (**B** from Paglia DE. Disorders of erythrocyte glycolysis and nucleotide metabolism. In: Handin RI, Lux SE, Stossel TP, eds. *Blood: Principles and Practice of Hematology*. Philadelphia: JB Lippincott; 1995:1877-1896.)

usually presents in infancy or early childhood with moderate to severe hemolytic anemia. Rare cases of GPI deficiency may also be complicated by neurologic symptomatology. Phosphofructokinase deficiency may involve erythrocytes, muscle, or both. The presentation is usually in adolescence with exertional myopathy. Hemolytic anemia has been described in isolated cases of 2,3-bisphosphoglycerate mutase deficiency and phosphoglycerate kinase deficiency.

DISORDERS OF NUCLEOTIDE METABOLISM

Mature erythrocytes lack the ability to synthesize purine and pyrimidine nucleotides de novo. However, they are able to form some nucleotides through salvage pathways.

Pyrimidine 5′-Nucleotidase Deficiency

Pyrimidine 5′-nucleotidase degrades the pyrimidine nucleotides of RNA to cytidine and uridine, which can diffuse out of the cell. When pyrimidine 5′-nucleotidase is deficient, nondiffusible, partially degraded RNAs accumulate, leading to the marked basophilic stippling characteristic of pyrimidine 5′-nucleotidase-deficient erythrocytes (see Fig. 147-5B). These accumulated pyrimidine nucleotides inhibit the transport of oxidized glutathione out of RBCs, leading to high levels of erythrocyte glutathione. Clinically, the patient has mild to moderate hemolytic anemia and splenomegaly. The cause of the hemolysis remains cryptic. Typically, splenectomy does not ameliorate the hemolysis and anemia.

DISORDERS OF THE HEXOSE MONOPHOSPHATE SHUNT (PENTOSE PHOSPHATE PATHWAY) AND ASSOCIATED PATHWAYS

Disorders of the hexose monophosphate shunt or of the glutathione metabolic pathways (see Fig. 147-4) compromise the ability of the RBC to respond adequately to oxidative stress. In normal erythrocytes, glutathione detoxifies oxidants produced by various agents and infection. In G6PD-deficient erythrocytes, because of the inability to generate NADPH, glutathione levels are inadequate, leaving the cell susceptible to oxidant stress. Oxidation of Hb sulfhydryl groups leads to the production of methemoglobin and intracellular Hb precipitates called *Heinz bodies*. Heinz bodies (see Fig. 147-5D), usually visualized on peripheral blood smears with supravital stains such as methyl violet, attach to and damage the erythrocyte membrane. They induce clustering of immunoglobulins and band 3 protein, marking the erythrocyte for opsonization by phagocytes and eventual removal from the circulation. Heinz bodies are "pitted" from circulating cells by the spleen and are commonly seen on smears of patients after splenectomy. "Bite cells," erythrocytes with localized invaginations, possibly at the site of Heinz body injury or removal, are seen during acute hemolytic episodes (Chapter 143). In addition to damage from Heinz body formation, glutathione-deficient erythrocytes undergo peroxidation of membrane phospholipids and oxidative cross-linking of spectrin, decreasing membrane deformability and further promoting splenic trapping.

Glucose-6-Phosphate Dehydrogenase Deficiency

G6PD deficiency is the most common inherited disorder of erythrocyte metabolism, affecting more than 400 million people worldwide.[19,20] The high prevalence of G6PD deficiency is thought to be attributable to genetic selection because G6PD-deficient erythrocytes have a selective advantage against invasion by the malaria parasite *Plasmodium falciparum*.

EPIDEMIOLOGY AND PATHOBIOLOGY

G6PD is the initial and rate-limiting step in the hexose monophosphate shunt (see Fig. 147-4), which converts NADP into NADPH. NADPH is required for the generation of glutathione, a critical constituent in the prevention of oxidative damage to the cell. G6PD-deficient patients may develop acute hemolytic anemia after exposure to oxidative stress. Although G6PD is a ubiquitous enzyme, erythroid cells are particularly susceptible to oxidative stress because the hexose monophosphate shunt is their only source of NADPH.

Hundreds of G6PD variants have been described, but only a few are common. Variants are classified on the basis of biochemical characteristics, electrophoretic mobility, ability to use substrate analogue, Km for NADP and G6PD, pH

TABLE 147-2 FEATURES OF G6PD VARIANTS

VARIANT	GENOTYPE	ENZYME ACTIVITY (% OF NORMAL)	ENZYME THERMAL STABILITY	ENZYME THERMAL ACTIVITY (K_{CAT} S^{-1})	ENZYME CATALYTIC CLASSIFICATION	WHO CLINICAL DISTRIBUTION
G6PD B	None	100	Normal	275	IV	Worldwide
G6PD A+	Val68Met	85	Normal	247	IV	Africa
G6PD A-	Val68Met, Asn126AsP	10-23	Low	137	III	Africa
G6PD Mahidol	Gly163Ser	0.6	Normal	207	II	Southeast Asia
G6PD Mediterranean	Ser188Phe	<5	Low	98	II	Middle East, Southcentral Asia
G6PD Canton	Arg463Leu	4	Slight decrease	123	II	North Vietnam and South China

From Luzzatto L, Ally M, Notaro R. Glucose-6-phosphate dehydrogenase deficiency. *Blood*. 2020;136:1225-1240.

activity profile, and thermal stability. The normal enzyme, Gd^B, is present in 99% of White Americans and 70% of African Americans. A normal variant, Gd^{A+}, found in 20% of African Americans, has a faster electrophoretic mobility than Gd^B. Gd^{A-}, the most common variant associated with hemolysis, is found in about 10% of African Americans and in many Africans. Gd^{A-} has decreased catalytic ability compared with Gd^{A+}. Gd^{Med}, the second most common variant associated with hemolysis, is common in the Mediterranean area, in India, and in Southeast Asia, with a prevalence of up to 5 to 50%. Gd^{Med} exhibits markedly decreased catalytic activity. Gd^{Canton}, a variant common in Asian populations, produces a clinical syndrome similar to Gd^{A-}. Features of several G6PD variants are shown in Table 147-2.

Gd^B activity decreases as normal cells age, with a half-life of approximately 60 days. Despite very low levels of or no active G6PD, older erythrocytes maintain the ability to produce NADPH and maintain a glutathione response to oxidative stress. The Gd^{A-} variant has a half-life of only 13 days, so young cells have a normal amount of enzyme activity, but older RBCs are grossly deficient. Because of this heterogeneity in G6PD levels, individuals with the Gd^{A-} variant experience only limited hemolysis after oxidant exposure.

More than 100 mutations in the *G6PD* gene, localized to Xq28, have been described. Most mutations are amino acid substitutions that influence enzyme kinetics, stability, or both, with a few rare deletions and splicing mutations described. Because it is X-linked, G6PD deficiency primarily affects males. Males have only one G6PD allele and express only one G6PD type. Females can express one or two G6PD types. The Lyon hypothesis specifies that only one X chromosome is active in any given cell; thus, any given cell in a heterozygous female is either normal or deficient. In females who are heterozygous for G6PD deficiency, average G6PD activity may be normal or mildly, moderately, or severely reduced, depending on the degree of lyonization. G6PD-deficient erythrocytes in heterozygous females are susceptible to the same oxidant stress as G6PD-deficient cells in males, but, typically, the overall degree of hemolysis is less because there is a smaller population of vulnerable cells.

CLINICAL MANIFESTATIONS

G6PD deficiency is divided into five classes based on clinical severity and degree of enzyme deficiency. Class I is characterized by congenital nonspherocytic hemolytic anemia without precipitating cause and severe G6PD deficiency. Class II is characterized by intermittent hemolysis and severe G6PD deficiency. Class III is characterized by hemolysis after oxidant stress and mild G6PD deficiency. Class II and III together represent more than 90% of G6PD variants. Classes IV and V are clinically asymptomatic. The most clinically significant syndromes of G6PD deficiency are acute hemolytic anemia; neonatal jaundice; and rarely, congenital nonspherocytic hemolytic anemia.

Acute hemolytic anemia is the most dramatic clinical presentation of G6PD deficiency with acute intravascular hemolysis after exposure to an oxidative stress. Oxidative stresses include ingestion of certain drugs such as primaquine or sulfa-containing compounds, exposure to naphthalene (mothballs), ingestion of fava beans, or infection, the latter being the most common cause of hemolysis. Table 147-3 lists drugs that should be avoided in G6PD-deficient patients. Presenting symptoms include irritability, fever, nausea, abdominal pain, and diarrhea within 48 hours of oxidant exposure. Hemoglobinuria, jaundice, and anemia ensue. The spleen and liver may be enlarged and tender. Cases with severe anemia may precipitate congestive heart failure. Laboratory findings include a normochromic, normocytic anemia with anisocytosis and reticulocytosis. Poikilocytes and bite cells may be seen. Heinz bodies, a classic finding in G6PD deficiency, may be seen but are an inconsistent finding because these damaged cells are rapidly cleared from the circulation in the spleen. Additional laboratory findings may include hemoglobinuria and the presence of free Hb in the blood.

TABLE 147-3 AGENTS TO BE AVOIDED BY GLUCOSE-6-PHOSPHATE DEHYDROGENASE–DEFICIENT PATIENTS*

ANTIMALARIALS

Primaquine (people with the African A^- variant may take it at reduced dosage, under surveillance)
Pamaquine
Chloroquine (may be used under surveillance when required for prophylaxis or treatment of malaria)

SULFONAMIDES AND SULFONES

Sulfanilamide
Sulfapyridine
Sulfadimidine
Sulfacetamide (Albucid)
Acetyl sulfisoxazole (Gantrisin)
Salicylazosulfapyridine (Salazopyrin)
Dapsone
Sulfoxone
Glucosulfone sodium (Promin)
Sulfamethoxazole-trimethoprim (Bactrim, Septra)

OTHER ANTIBACTERIAL COMPOUNDS

Nitrofurans—nitrofurantoin, furazolidone, nitrofurazone
[Nalidixic acid]
Chloramphenicol
p-Aminosalicylic acid

ANALGESICS

Acetylsalicylic acid (aspirin): moderate doses can be used
Acetophenetidin (Phenacetin)
Safe alternative: Paracetamol

ANTHELMINTICS

β-Naphthol
Stibophen
Niridazole

MISCELLANEOUS

Vitamin K analogues (1 mg of menaphthone can be given to babies)
Naphthalene (moth balls)
Probenecid
Dimercaprol (BAL)
Methylene blue
Arsine†
Phenylhydrazine†
Acetylphenylhydrazine†
Toluidine blue
Mepacrine

*Drugs in bold print should be avoided by people with all forms of glucose-6-phosphate dehydrogenase (G6PD) deficiency. Drugs in normal print should be avoided, in addition, by G6PD-deficient people of Mediterranean, Middle Eastern, and Asian origin. Items in normal print and within square brackets apply only to people with the African A^- variant.
†These drugs or chemicals may cause hemolysis in normal people if given in large doses. Many other drugs may produce hemolysis in certain individuals.

Another clinically significant syndrome of G6PD deficiency is neonatal jaundice. Jaundice is seldom present at birth, with the peak incidence of onset between days 2 and 3 of life. The severity of hyperbilirubinemia is variable. It may be severe, resulting in kernicterus or even death. In most cases, however, hyperbilirubinemia is adequately treated with phototherapy. In neonatal jaundice, it is important to note that the anemia is very rarely severe. The etiology of neonatal jaundice remains controversial. Neonatal jaundice is increased in G6PD-deficient infants who also carry a polymorphism of the uridine diphosphoglucuronyl transferase (*UDPGT1*) gene associated with Gilbert syndrome.

Chronic nonspherocytic hemolytic anemia is associated with uncommon variants of G6PD deficiency, usually mutant enzymes unable to maintain basal NADPH production. Presentation may be in the neonatal period when neonatal jaundice is accompanied by anemia in a male. The degree of chronic anemia in congenital nonspherocytic hemolytic anemia caused by G6PD deficiency has been variable. Some patients have compensated hemolysis, but others require intermittent transfusions. Transfusion dependence occurs in the most severe cases.

G6PD deficiency, which suppresses the antioxidant system, has been suggested to worsen severity of COVID-19 infection which activates pro-oxidant responses. This association was not identified in a genome-wide association study of patients with severe COVID-19.[21] This possible association needs to be further explored in clinical trials.

DIAGNOSIS

The G6PD reaction (glucose-6-phosphate + $NADP^+ \rightarrow$ 6-phosphogluconolactone + NADPH + H^+) reduces $NADP^+$ to NADPH. Formation of NADPH and NADH can be observed directly because they fluoresce in the visible spectrum when illuminated with long-wave ultraviolet light. Based on this observation, several simple screening tests performed using inexpensive long-wave ultraviolet light have been devised, and rapid testing has a very high sensitivity. However, these tests are semiquantitative, categorizing a sample as normal or deficient. They are unreliable after an acute hemolytic episode and do not typically detect female heterozygotes. Positive screening test results should be confirmed by spectrophotometric assay or DNA studies because of the risk of false-positive results.

Definitive assay of the enzyme depends on direct spectrophotometric measurement of NADPH production. Although more sensitive than screening tests, this still requires 20 to 30% G6PD-deficient cells to obtain an abnormal result. Sensitivity can be increased by comparing the level of G6PD deficiency with levels of other age-dependent erythrocyte enzymes, especially when testing is temporally in close proximity to an acute hemolytic episode. The cyanide-ascorbate test measures the ability of erythrocytes to prevent the oxidation of Hb by ascorbate. Using intact erythrocytes, as few as 10 to 15% deficient cells can be detected, making this test useful for detecting female heterozygotes and males after a hemolytic episode. This test also detects other perturbations of the hexose monophosphate shunt or glutathione metabolism. Genetic testing can be performed in difficult cases or when a molecular diagnosis is desired.[22]

TREATMENT

The best treatment for an individual with acute hemolytic anemia is careful prescription of medications and avoidance of inciting agents (see Table 147-3).[23,24] Outside of acute hemolytic episodes, these patients do not require any special therapy. Acute hemolytic anemia episodes are managed with particular attention to hematologic, cardiopulmonary, and renal complications of hemolysis. Management of neonatal jaundice does not differ from that recommended for other causes of neonatal hyperbilirubinemia. In congenital nonspherocytic hemolytic anemia, management is expectant. Exposure to oxidant stresses should be avoided. Blood transfusions may be necessary during acute hemolytic episodes. In severe cases of congenital nonspherocytic hemolytic anemia, splenectomy may ameliorate the anemia.

DISORDERS OF GLUTATHIONE METABOLISM

Defects of glutathione metabolism may be associated with hemolysis. Erythrocytes from patients lacking glutathione synthetase or γ-glutamylcysteine synthetase, enzymes involved in glutathione synthesis, have very low levels of glutathione. Clinically, these disorders resemble G6PD deficiency. There is mild to moderate chronic hemolytic anemia with increased susceptibility to oxidant stress.

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For the General References and other additional features, please visit Elsevier eBooks+ at https://ebooks.health.elsevier.com.

Grade A **Grade A Reference**

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148 THE THALASSEMIAS

MARIA DOMENICA CAPPELLINI

DEFINITION

The thalassemias, or more comprehensively the thalassemia syndromes, are a heterogeneous group of inherited hemolytic anemias characterized by deficient or absent production of one of the globin chains of hemoglobin. This deficiency leads to an imbalance in the synthesis of globin chains, an imbalance that is the hallmark of all the thalassemia syndromes.

EPIDEMIOLOGY

Taken together, the thalassemias are the most common recessive single-gene disorders in the world, with approximately 270 million or more people carrying one recessive gene. Each year, more than 40,000 children are born with one of the thalassemia syndromes, and about half of these individuals will become transfusion dependent. The extremely high frequency of the hemoglobin disorders compared with other monogenic diseases reflects natural selection mediated by the relative resistance of carriers against *Plasmodium falciparum* malaria (Chapter 316). Other factors that may be involved include the widespread practice of consanguineous marriage, increased maternal age in poorer countries, gene drift, and founder effects. For these reasons, the thalassemias are most frequent in southeastern and southern Asia,[1] in the Middle East, in the Mediterranean countries, and in northern and central Africa. However, as the result of recent mass migrations from the Middle East, Africa, and South East Asia, thalassemias are now encountered worldwide.

PATHOBIOLOGY

Normal adult red cells contain 97% adult hemoglobin (HbA: $\alpha_2\beta_2$), with approximately 2.5% of the minor component HbA_2 ($\alpha_2\delta_2$) and a small amount of fetal hemoglobin (HbF: $\alpha_2\gamma_2$). Because the stable tetramer $\alpha_2\beta_2$ is the major component of hemoglobin after birth, the two main forms of thalassemia are α-thalassemias and β-thalassemias. Because β-chain synthesis is fully activated only after birth, it follows that β-thalassemias are not expressed as a disease in intrauterine life; rather, they are manifested as γ-chain synthesis declines during the first year of life. In contrast, because α chains are shared by both fetal and adult hemoglobin, α-thalassemias are manifested in both fetal and adult life.

The thalassemia syndromes can be classified based on their genetics, clinical phenotypes, and transfusion requirements (Table 148-1).[2] Patients with transfusion-dependent β-thalassemia (β-thalassemia major or severe HbE–β-thalassemia) require lifelong, regular transfusions for survival, whereas patients with non–transfusion-dependent β-thalassemia (β-thalassemia intermedia or mild to moderate HbE–β-thalassemia) require no transfusions, occasional transfusions because of specific circumstances (e.g., pregnancy, surgery, or acute infection), or frequent transfusions but for a limited period (e.g., to support a growth spurt during childhood or manage a clinical complication).[3]

Genetics

Six different types of globin chains (α, β, γ, δ, ε, ζ) are found in normal human hemoglobin at different stages of development. In the very early embryo, hemoglobin synthesis is restricted to the yolk sac and the production of hemoglobins Gower 1 ($\zeta_2\varepsilon_2$), Gower 2 ($\alpha_2\varepsilon_2$), and Portland ($\zeta_2\gamma_2$). Subsequently, at about

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Another clinically significant syndrome of G6PD deficiency is neonatal jaundice. Jaundice is seldom present at birth, with the peak incidence of onset between days 2 and 3 of life. The severity of hyperbilirubinemia is variable. It may be severe, resulting in kernicterus or even death. In most cases, however, hyperbilirubinemia is adequately treated with phototherapy. In neonatal jaundice, it is important to note that the anemia is very rarely severe. The etiology of neonatal jaundice remains controversial. Neonatal jaundice is increased in G6PD-deficient infants who also carry a polymorphism of the uridine diphosphoglucuronyl transferase (*UDPGT1*) gene associated with Gilbert syndrome.

Chronic nonspherocytic hemolytic anemia is associated with uncommon variants of G6PD deficiency, usually mutant enzymes unable to maintain basal NADPH production. Presentation may be in the neonatal period when neonatal jaundice is accompanied by anemia in a male. The degree of chronic anemia in congenital nonspherocytic hemolytic anemia caused by G6PD deficiency has been variable. Some patients have compensated hemolysis, but others require intermittent transfusions. Transfusion dependence occurs in the most severe cases.

G6PD deficiency, which suppresses the antioxidant system, has been suggested to worsen severity of COVID-19 infection which activates pro-oxidant responses. This association was not identified in a genome-wide association study of patients with severe COVID-19.[21] This possible association needs to be further explored in clinical trials.

DIAGNOSIS

The G6PD reaction (glucose-6-phosphate + $NADP^+ \rightarrow$ 6-phosphogluconolactone + NADPH + H^+) reduces $NADP^+$ to NADPH. Formation of NADPH and NADH can be observed directly because they fluoresce in the visible spectrum when illuminated with long-wave ultraviolet light. Based on this observation, several simple screening tests performed using inexpensive long-wave ultraviolet light have been devised, and rapid testing has a very high sensitivity. However, these tests are semiquantitative, categorizing a sample as normal or deficient. They are unreliable after an acute hemolytic episode and do not typically detect female heterozygotes. Positive screening test results should be confirmed by spectrophotometric assay or DNA studies because of the risk of false-positive results.

Definitive assay of the enzyme depends on direct spectrophotometric measurement of NADPH production. Although more sensitive than screening tests, this still requires 20 to 30% G6PD-deficient cells to obtain an abnormal result. Sensitivity can be increased by comparing the level of G6PD deficiency with levels of other age-dependent erythrocyte enzymes, especially when testing is temporally in close proximity to an acute hemolytic episode. The cyanide-ascorbate test measures the ability of erythrocytes to prevent the oxidation of Hb by ascorbate. Using intact erythrocytes, as few as 10 to 15% deficient cells can be detected, making this test useful for detecting female heterozygotes and males after a hemolytic episode. This test also detects other perturbations of the hexose monophosphate shunt or glutathione metabolism. Genetic testing can be performed in difficult cases or when a molecular diagnosis is desired.[22]

TREATMENT

The best treatment for an individual with acute hemolytic anemia is careful prescription of medications and avoidance of inciting agents (see Table 147-3).[23,24] Outside of acute hemolytic episodes, these patients do not require any special therapy. Acute hemolytic anemia episodes are managed with particular attention to hematologic, cardiopulmonary, and renal complications of hemolysis. Management of neonatal jaundice does not differ from that recommended for other causes of neonatal hyperbilirubinemia. In congenital nonspherocytic hemolytic anemia, management is expectant. Exposure to oxidant stresses should be avoided. Blood transfusions may be necessary during acute hemolytic episodes. In severe cases of congenital nonspherocytic hemolytic anemia, splenectomy may ameliorate the anemia.

DISORDERS OF GLUTATHIONE METABOLISM

Defects of glutathione metabolism may be associated with hemolysis. Erythrocytes from patients lacking glutathione synthetase or γ-glutamylcysteine synthetase, enzymes involved in glutathione synthesis, have very low levels of glutathione. Clinically, these disorders resemble G6PD deficiency. There is mild to moderate chronic hemolytic anemia with increased susceptibility to oxidant stress.

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148 THE THALASSEMIAS

MARIA DOMENICA CAPPELLINI

DEFINITION

The thalassemias, or more comprehensively the thalassemia syndromes, are a heterogeneous group of inherited hemolytic anemias characterized by deficient or absent production of one of the globin chains of hemoglobin. This deficiency leads to an imbalance in the synthesis of globin chains, an imbalance that is the hallmark of all the thalassemia syndromes.

EPIDEMIOLOGY

Taken together, the thalassemias are the most common recessive single-gene disorders in the world, with approximately 270 million or more people carrying one recessive gene. Each year, more than 40,000 children are born with one of the thalassemia syndromes, and about half of these individuals will become transfusion dependent. The extremely high frequency of the hemoglobin disorders compared with other monogenic diseases reflects natural selection mediated by the relative resistance of carriers against *Plasmodium falciparum* malaria (Chapter 316). Other factors that may be involved include the widespread practice of consanguineous marriage, increased maternal age in poorer countries, gene drift, and founder effects. For these reasons, the thalassemias are most frequent in southeastern and southern Asia,[1] in the Middle East, in the Mediterranean countries, and in northern and central Africa. However, as the result of recent mass migrations from the Middle East, Africa, and South East Asia, thalassemias are now encountered worldwide.

PATHOBIOLOGY

Normal adult red cells contain 97% adult hemoglobin (HbA: $\alpha_2\beta_2$), with approximately 2.5% of the minor component HbA_2 ($\alpha_2\delta_2$) and a small amount of fetal hemoglobin (HbF: $\alpha_2\gamma_2$). Because the stable tetramer $\alpha_2\beta_2$ is the major component of hemoglobin after birth, the two main forms of thalassemia are α-thalassemias and β-thalassemias. Because β-chain synthesis is fully activated only after birth, it follows that β-thalassemias are not expressed as a disease in intrauterine life; rather, they are manifested as γ-chain synthesis declines during the first year of life. In contrast, because α chains are shared by both fetal and adult hemoglobin, α-thalassemias are manifested in both fetal and adult life.

The thalassemia syndromes can be classified based on their genetics, clinical phenotypes, and transfusion requirements (Table 148-1).[2] Patients with transfusion-dependent β-thalassemia (β-thalassemia major or severe HbE–β-thalassemia) require lifelong, regular transfusions for survival, whereas patients with non–transfusion-dependent β-thalassemia (β-thalassemia intermedia or mild to moderate HbE–β-thalassemia) require no transfusions, occasional transfusions because of specific circumstances (e.g., pregnancy, surgery, or acute infection), or frequent transfusions but for a limited period (e.g., to support a growth spurt during childhood or manage a clinical complication).[3]

Genetics

Six different types of globin chains (α, β, γ, δ, ε, ζ) are found in normal human hemoglobin at different stages of development. In the very early embryo, hemoglobin synthesis is restricted to the yolk sac and the production of hemoglobins Gower 1 ($\zeta_2\varepsilon_2$), Gower 2 ($\alpha_2\varepsilon_2$), and Portland ($\zeta_2\gamma_2$). Subsequently, at about

ABSTRACT

The thalassemia syndromes are a heterogeneous group of inherited hemolytic anemias characterized by deficient or absent production of one of the globin chains of hemoglobin. This deficiency leads to an imbalance in globin chain synthesis, an imbalance that is the hallmark of all the thalassemias. Underlying molecular defects in the α- or β-globin gene clusters form the basis of the various inherited forms of α- or β-thalassemias. The clinical manifestations of thalassemia syndromes are extremely variable and depend on the degree of imbalance in the production of globin chains. The clinical spectrum of α-thalassemias correlates well with the number of the affected α genes, that is, from normal to the loss of all four genes. The β-thalassemias are quite heterogeneous and are characterized by a reduced output of the β chains of adult hemoglobin. The clinical classification includes thalassemia major (transfusion dependent), thalassemia intermedia (of intermediate severity, non–transfusion dependent), and thalassemia minor (asymptomatic). The severity of the clinical manifestations correlates well with the degree of imbalance of globin chains; depending on the β-globin gene defects and their interaction, the production of β-globin chains is quantitatively reduced to different degrees, thereby resulting in accumulation of excess unmatched α-globin chains in the erythroid precursors.

KEYWORDS

hemoglobin production
thalassemias
thalassemia intermedia
ineffective erythropoiesis
iron overload
α-thalassemia
β-thalassemia

TABLE 148-1 GENETIC AND CLINICAL CLASSIFICATIONS OF THE THALASSEMIAS

	GENETIC	CLINICAL	TRANSFUSION REQUIREMENT
α-Thalassemias	α^0 α^+ Deletion (−α) Nondeletion (α^T)	α-Minor HbH disease Hydrops fetalis	No transfusion Occasional transfusions NA
β-Thalassemias	β^0 β^+ Variant with high HbA_2 Normal HbA_2 Silent Dominant Unlinked to β-gene cluster	β-Minor Thalassemia intermedia Thalassemia major	No transfusions Occasional transfusions Regular transfusions
δβ-Thalassemias	$(\delta\beta)^0$ $(\delta\beta)^+$ $(^A\gamma\delta\beta)^0$	δβ-Minor Thalassemia intermedia	Occasional transfusions
HPFH	Deletion Nondeletion Unlinked to β-gene cluster	Silent increase in HbF	No transfusions

HbA = adult hemoglobin; HbF = fetal hemoglobin; HbH = hemoglobin H; HPFH = hereditary persistence of fetal hemoglobin.

8 weeks of gestation, the fetal liver takes over, synthesizing predominantly HbF ($\alpha_2\gamma_2$) and a small amount (<10%) of HbA. Between about 18 weeks and birth, the bone marrow progressively replaces the liver as the major site of red cell production; this shift is accompanied in the later stages of gestation by a reciprocal switch in production of HbA rather than HbF, so that HbF production drops to less than 2% by the end of the first year of life.

The globin genes are encoded in separate gene clusters. The α cluster (ζ,α_2,α_1) lies at the telomere of chromosome 16, whereas the β cluster ($\varepsilon,^G\gamma$ and $^A\gamma,\delta,\beta$) lies at chromosome 11p15.5. In both clusters, the genes are aligned 5′ to 3′ in the order in which they are expressed during development. Both sets of genes are under the regulation of enhancer-like elements (hypersensitive site [HS]–40 for α cluster and locus control region for β cluster) that lie some distance away at the 5′ end of the cluster. Deletion of these enhancer elements results in inactivation of any related globin gene. There are two α genes/alleles (α_2 and α_1) that differ by a few nucleotides in intron 2 and the 3′ untranslated region but nevertheless produce identical protein products. The output of the α_2 gene exceeds that of the α_1 gene by two- to three-fold.

The region around a DNase1 hypersensitive site at 40 kilobases (kb) upstream of the ζ-globin gene (HS-40) is the major regulator of α-globin gene expression. The β cluster contains a single pseudo-β gene, whereas the β cluster enhancer consists of five elements marked by erythroid-specific DNase1 hypersensitive sites lying 6 to 20 kb upstream of the ε-globin gene, with each element containing several binding sites for erythroid-specific and other transcription factors. All together, these elements are known as the locus control region, and each element contributes to the overall locus control region activity. In addition, there is an erythroid-specific hypersensitive site approximately 20 kb downstream of the β-globin gene; when the cluster is activated, the upstream and downstream hypersensitive sites are brought into proximity with the gene promoters to activate their transcription.

The individual globin genes share many general features; for example, each consists of three coding sequence exons separated by two introns in identical position but of variable length for a total length of approximately 1500 nucleotides. This structure has been highly conserved throughout evolution. The upstream regions flanking the first exon contain a number of sequence motifs that are necessary for specifying correct transcriptional initiation. A TATA box is found at 30 base pairs upstream of the initiation site together with one or more CCAAT sites at 70 base pairs upstream. The gene promoters also contain a CACCC or CCGCCC box that binds erythroid Krüppel-like factor (EKLF) 1, and some have binding sites for erythroid transcription factor GATA-1. In model systems, mutations introduced into such sequences lead to reduction in the level of transcription.

All the thalassemias have a similar pattern of inheritance; in most cases, the gene defects are transmitted in a mendelian autosomal recessive fashion. Thus, the severe, symptomatic varieties usually result from the interaction of more than one genetic determinant, for example, compound heterozygosity or homozygosity. The inheritance of α-thalassemia is more complicated because it involves the products of the linked pairs of α genes (αα) (see Clinical Manifestations).

Molecular Basis of Thalassemias

The α- and β-thalassemias are divided into disorders in which no chains are produced from the affected chromosomes (α^0 and β^0) and disorders in which the output of the chains is reduced (α^+ and β^+). For the α-thalassemias, the most common molecular defects are deletions of one or both α genes, which are designated −α and − −, respectively. The single α gene is thought to have arisen by crossover between two misaligned α genes on the homologous chromosome that can give rise to chromosomes with either single (−α) or triplicated (ααα) α-globin genes. To date, more than 40 different deletions that involve both α genes, resulting from illegitimate or nonhomologous recombination, have been reported. The lengths of deletion vary from 5.2 to more than 40 kb; the most common are those from Southeast Asia, the Mediterranean, and the Philippines, designated $--^{SEA}$, $--^{MED}$, and $--^{FIL}$, respectively. Nondeletion types of α-thalassemia (α^α) are much less common than the deletion forms; in most cases, they result from single oligonucleotide mutations in regions where the α gene sequence is critical for normal expression. Because expression of the α_2 gene is two to three times greater than that of the α_1 gene, it is not surprising that most of the nondeletion mutants predominantly affect expression of the α_2 gene. The mutations may affect the initiation codon or splicing signals, cause frame shifts, or introduce premature stop codons. At least five single-nucleotide variants affect the natural termination codon (TAA) of the α_2-globin gene. Among these, hemoglobin Constant Spring ($\alpha^{cs}\alpha$) is the most common and extensively studied. Finally, there are several α-globin variants that are so unstable that they undergo rapid, post-synthetic degradation. In such situations, β chains remain in excess within the red cell, and the patient carriers of these α-chain variants, by definition, have α-thalassemia. To date, 17 unstable α variants have been shown to produce the phenotype of α-thalassemia to a greater or lesser extent.

Like the α-thalassemias, the β-thalassemias are classified as β^0 (in which no β-globin is produced) and β^+ (in which some but less than normal β-globin is produced). In some cases, the defects in β-chain production are so mild that they are designated β^{++}. So far, more than 400 different thalassemic mutations of the β-globin gene have been reported; most are point mutations within the gene or its immediate flanking sequence. A few β-thalassemia mutations that segregate independently of the β-globin gene cluster have been described, presumably involving *trans*-acting regulatory factors. The distribution of alleles is highly variable from one population to another; but within each population, only a few alleles are common. The nondeletion forms of β-thalassemia account for most β-thalassemia alleles. An updated list of mutations (including transcriptional mutations, RNA processing mutations, and mutations affecting translation) is accessible at the Globin Gene Server website (http://globin.cse.psu.edu).

Simple deletions of the β-globin gene are rare, ranging in size from 290 base pairs to more than 60 kb. The 619–base pair deletion at the 3′ end of the β gene is relatively common among Sind and Punjabi populations in India and Pakistan. The remaining deletions are restricted to single families, are necessarily β^0-thalassemias, and interestingly are associated with unusually high levels of HbA_2 in heterozygotes. Large deletions that affect the entire β-globin gene cluster $(\varepsilon\gamma\gamma\delta\beta)^0$ are rare and restricted to single families. Finally, some highly unstable β-chain variants may be manifested as a dominant form of β-thalassemia.

The δβ-thalassemias and hereditary persistence of fetal hemoglobin are the result of deletions affecting various parts of the β-globin locus. These deletions are partially compensated by an increased expression of the γ genes that raises the level of HbF. The length of deletion accounts for different forms of δβ-thalassemia, including both $^G\gamma$ and $^A\gamma$ genes or only $^A\gamma$, and varies from 9 to 100 kb. Hemoglobin Lepore is a hybrid of δ and β chains resulting from a crossover between the two misaligned genes; this hemoglobin is synthesized inefficiently and gives rise to a form of δβ-thalassemia. Deletions of δ and β genes are also the molecular basis for many forms of hereditary persistence of fetal hemoglobin that, usually have higher levels of compensatory HbF production than the δβ-thalassemias. Hereditary persistence of fetal hemoglobin also can be caused by point mutations in the promoter region upstream from the transcription start site in either the $^G\gamma$ or $^A\gamma$ genes that alter the binding of one or more transcription factors. Genetic studies have identified three major quantitative trait loci that account for 20 to 50% of the common variation in

HbF levels in patients with β-thalassemia and sickle cell disease as well as in healthy adults.

CLINICAL MANIFESTATIONS

The clinical manifestations (phenotype expression) of thalassemia syndromes are extremely variable and depend on the degree of globin chain imbalance.[5]

α-Thalassemias

There are two major classes of α-thalassemias: α^0, in which both α genes are inactivated (− −/); and α^+, in which only one of the pair is defective because of α gene deletion or mutation (−α or $\alpha\alpha^T$). The clinical spectrum of α-thalassemias correlates well with the number of the affected α genes, that is, from normal to the loss of all four genes.

The α-thalassemias are common in areas where β-thalassemias are also found at a high frequency. Thus, the coinheritance of α- and β-thalassemia trait may occur and even ameliorate the hematologic parameters. In families in which α- and β-thalassemias are present, genotyping is essential. The unstable mutant Hb^{CT} causes a severe reduction in α_2-globin expression from the affected chromosome; therefore, the carriers and particularly the homozygotes have a more severe phenotype than α-thalassemia minor but not as severe as most cases of HbH disease.

α-Thalassemia Minor

The inheritance of a normal allele (αα) with one of the α^+ or α^0 alleles most frequently results in α-thalassemia minor (− −/αα; −α/αα; $-\alpha^T/\alpha\alpha$; $\alpha^T\alpha/-\alpha;-\alpha/-\alpha$). In general, carriers of such genotypes have lower levels of total hemoglobin, mean corpuscular volume, and mean cell hemoglobin but higher red blood cell counts than normal. The greatest differences are seen in mean cell hemoglobin, which is usually less than 26 pg. The peripheral blood smear shows various degrees of hypochromia with some target cells and occasional poikilocytes (Chapter 143). In carriers of α^0-thalassemia (− −/αα), it is possible to generate a few red cell HbH inclusions (β_4). The carriers of nondeletional forms ($\alpha\alpha^T/\alpha\alpha$) show slightly more marked hematologic changes than those for deletional forms. The hemoglobin constitution of adult carriers of α^+- or α^0-thalassemia is indistinguishable from normal but has slightly lower levels of HbA_2. Traces of hemoglobin Bart (γ_4) in the neonatal period are detectable in a large proportion of neonates with α-thalassemia, and they decline during the first 6 months after birth.

Hemoglobin H Disease

HbH disease most frequently results from the co-presence of α^+- and α^0-thalassemia, and not surprisingly most patients originate from the populations of southeastern Asia, the Mediterranean, and the Middle East. HbH disease is a diagnosis attributed to subjects older than 6 months having a sufficient globin imbalance to produce detectable levels of HbH (>1 to 2%) in their peripheral blood together with inclusion bodies (β_4 tetramers) in their red cells on peripheral smear. The clinical phenotypes encompass a wide spectrum from mild clinical manifestations to thalassemia intermedia and are included in the so-called non–transfusion-dependent thalassemias. The predominant features of HbH disease are a hypochromic, microcytic anemia with jaundice, and hepatosplenomegaly. Because the main mechanism of the anemia is hemolysis rather than dyserythropoiesis, only a few patients have clinical evidence of an expanded erythron. The most common complication of HbH disease is the development of hypersplenism due to severe splenomegaly (Chapter 154). Other complications include gallstones, leg ulcers, increased risk for infection, folic acid deficiency, and increased risk for venous thrombosis mainly after splenectomy. Hemoglobin levels range in different series from 3 to 12 g/dL, with fluctuations that may occur after exposure to an oxidant drug, infection, or transient aplasia possibly due to intercurrent viral infection. Rarely, patients with HbH disease require regular blood transfusions. The anemia is associated with reticulocytosis and typical thalassemic changes of the red cell indices. The relative amount of HbH varies from 1 to 40%. The values of HbA_2 are always reduced. The peripheral blood film shows hypochromia with variable anisopoikilocytosis, target cells, and basophilic stippling. The characteristic feature of HbH disease is that it is always possible to generate multiple inclusions in the red cells after incubation with brilliant cresyl blue. The bone marrow shows marked erythroid hyperplasia.

Hydrops Fetalis

The most severe form of α-thalassemia is hydrops fetalis, in which all four α-globin genes are deleted (genotype − −/− −). Because α-globin chains are absent during gestation, hemoglobin Bart (γ_4) becomes the dominant hemoglobin. Because of its high oxygen affinity, hemoglobin Bart is unable to deliver oxygen to tissues, and the intrauterine consequences are progressive severe anemia, severe ineffective erythropoiesis with marked extramedullary erythropoiesis, massive organomegaly, heart failure, severe hypoalbuminemia, and edema. The hemoglobin levels range from 3 to 20 g/dL; the peripheral blood film is characterized by marked anisopoikilocytosis, large hypochromic macrocytes, and many nucleated red cells. The hemoglobin consists almost entirely of hemoglobin Bart (80 to 90%), with some remaining HbH and Portland. Mothers of these infants often have a history of previous neonatal deaths. Without medical care, women carrying these fetuses may have delivery and postpartum complications (e.g., retained placenta, eclampsia, sepsis) (Chapter 221).

Several reports describe α-thalassemia in association with intellectual disability (so-called ATR-16 syndrome). These conditions are mainly due to large deletions (one or two megabases) of the tip of chromosome 16, including the α-globin gene cluster. However, several cases have no deletions or other apparent abnormalities of the α-globin gene cluster. It has been shown that these patients with a peculiar phenotype characterized by severe mental retardation, dysmorphic facies, genital abnormalities, and α-thalassemia have a disorder that maps to the X chromosome (ATR-X syndrome).

β-Thalassemias

The β-thalassemias, which include a considerably heterogeneous group of disorders of hemoglobin synthesis, are characterized by a reduced output of the β chains of adult hemoglobin.[6] The clinical classification includes thalassemia major (transfusion dependent), thalassemia intermedia (of intermediate severity, non–transfusion dependent), and thalassemia minor (asymptomatic) (Fig. 148-1 and see Table 148-1). The severity of the clinical manifestations correlates well with the degree of imbalance of globin chains. Depending on the β-globin gene defects and their interaction, the production of β-globin chains is quantitatively reduced to different degrees, whereas the synthesis of α-globin continues as normal. The result is an accumulation of excess unmatched α-globin chains in the erythroid precursors. The free α-globin chains, which are not able to form stable tetramers, precipitate in the erythroid precursors where they form inclusion bodies that damage the red cell membrane, thereby causing premature destruction of erythroid precursors in the bone marrow (ineffective erythropoiesis). Ineffective erythropoiesis leads to a sequence of events responsible for bone marrow expansion, anemia, hemolysis, splenomegaly, and increased iron absorption. Any factor that reduces the degree of chain imbalance and the magnitude of α-chain excess, such as coinheritance of α-thalassemia or an innate ability to increase fetal hemoglobin, will ameliorate the clinical expression of the disease (Fig. 148-2).[7]

β-Thalassemia Minor

Thalassemia minor is the heterozygous state of β-thalassemia. Subjects with thalassemia minor are "carriers" of a single β-globin gene defect, and they are usually asymptomatic except for a mild microcytic anemia. The carriers are usually identified incidentally[8] during an intercurrent illness, in the course of a family study, or as part of a population survey. Carriers of β-thalassemia may have a triplicated α-gene allele: its coinheritance may cause a mild thalassemia intermedia phenotype due to the excess of α chains production.

The anemia is mild, microcytic, and hypochromic, and it is usually associated with a diagnostic elevation (>3.5%) in the level of HbA_2. However, coincidental iron deficiency can lower elevated HbA_2 levels to the normal range. Carriers of β-thalassemia with normal HbA_2 also have been observed in settings in which an individual with mild thalassemia intermedia was found to have one parent with typical β-thalassemia minor with elevated HbA_2, whereas the other showed either minimal or no hematologic abnormalities and normal HbA_2. Subjects with normal HbA_2 are usually carriers of silent β^{++} mutations (β^{++}). The blood smear shows characteristic microcytosis and hypochromia, with some variation in size and shape of the red cells. The presence of target cells is variable. The hematologic features are remarkably similar among different ethnic groups.

β-Thalassemia Intermedia

Thalassemia intermedia, which is a non–transfusion-dependent thalassemia disorder, describes patients with anemia, splenomegaly, and a wide spectrum of clinical severity without the full manifestations found in thalassemia major.[9] Mildly affected patients, who are almost completely asymptomatic until adult life, experience only mild anemia and spontaneously maintain hemoglobin levels between 7 and 10 g/dL. Patients with more severe thalassemia intermedia

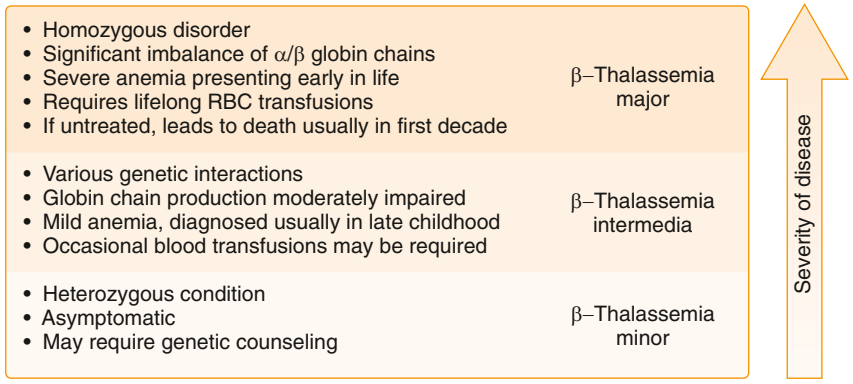

A

	Thalassemia major more likely	Thalassemia intermedia more likely
Clinical		
Presentation (years)	< 2	> 2
Hb levels (g/dL)	< 7	7–10
Liver/spleen enlargement	Severe	Moderate to severe
Hematologic		
HbF (%)	> 50	10–50 (may be up to 100%)
HbA2 (%)	> 3.5	< 4
Genetic		
Parents	Both carriers of high HbA2 β-thalassemia	One or both atypical carriers: high HbF β-thalassemia, borderline HbA2
Molecular		
Type of β-chain mutation	Severe	Mild/silent
Coinheritance of α-thalassemia	No/rare	Yes
Hereditary persistence of fetal hemoglobin	No	Yes
δβ-thalassemia	No	Yes
Gy XmnI polymorphism	No	Yes

B

FIGURE 148-1. **A, Clinical classification of β-thalassemias, from β-thalassemia minor to β-thalassemia major, according to the disease severity. β-Thalassemia minor subjects are asymptomatic, whereas at the severe extreme, β-thalassemia major patients are transfusion dependent. In between is a wide spectrum of clinical phenotypes labeled thalassemia intermedia because of different genetic interactions characterized by moderate to severe transfusion-independent anemia. B, Tentative criteria to differentiate thalassemia major from thalassemia intermedia at presentation. HbA = adult hemoglobin; HbF = fetal hemoglobin; RBC = red blood cell.**

generally present between the ages of 2 and 6 years; although they are able to survive without regular transfusion therapy, growth and development can be retarded. Most thalassemia intermedia patients are homozygotes or compound heterozygotes for mild to moderate β-gene mutations (β^+/β^+;β^0/β^+); less commonly, only a single β-globin gene is affected. Because the clinical severity of the disease is dictated by the different extent of globin chain imbalance, at least three different mechanisms may promote the mild clinical characteristics of thalassemia intermedia compared with thalassemia major: inheritance of mild or silent β-gene mutations; coinheritance of determinants associated with increased γ-chain production, which contributes to neutralizing the large proportion of unbound α chains; and coinheritance of α-thalassemia, which reduces the synthesis of α chains, thereby reducing the α/non-α chain imbalance.

Three main factors are responsible for the clinical sequelae in patients with thalassemia intermedia: degree of ineffective erythropoiesis, chronic anemia, and iron overload.[10] The ineffective erythropoiesis primarily depends on the underlying molecular defects and is due to precipitation of free α chains in erythroid precursors in the bone marrow, where they cause membrane damage and premature cell death. The degree of ineffective erythropoiesis is the primary determinant of the anemia of thalassemia intermedia; peripheral hemolysis of mature, circulating red cells, and an overall reduction in hemoglobin synthesis are secondary. Hemolysis and damaged red cells that expose negatively charged membrane phosphatidyl-serine residues have been linked to the development of a hypercoagulable state and increased risk for pulmonary hypertension (Chapter 69) in patients with thalassemia intermedia.

Chronic anemia and chronic ineffective erythropoiesis lead to an inappropriate increase in gastrointestinal iron absorption, thereby resulting in iron overload even in the absence of blood transfusion. The mechanism is a reduced expression of hepcidin, a hepatic peptide that plays a central role in iron homeostasis (Chapter 196). Moreover, the growth and differentiation factor 15 (GDF15), which is secreted by erythroid precursors and overexpressed in the presence of ineffective erythropoiesis, may suppress the synthesis of hepcidin. Erythroferrone, secreted by erythroblasts, may also play a role in hepcidin regulation. Taken together, ineffective erythropoiesis (leading to increased GDF15) and chronic anemia/hypoxia result in hepcidin suppression, increased dietary iron absorption from the gut, and increased release of recycled iron from the reticuloendothelial system, thereby leading to an iron overload situation similar to that observed in patients with hereditary hemochromatosis syndromes (which also are characterized by impaired hepcidin production; Chapter 196).

As a consequence of these pathophysiologic processes, several complications are seen in patients with thalassemia intermedia but not with thalassemia major, especially in non-splenectomized patients. Cholelithiasis is much more common in thalassemia intermedia than in thalassemia major because of ineffective erythropoiesis and peripheral hemolysis. Extramedullary hematopoiesis, as a compensatory mechanism, leads to the formation of erythropoietic tissue masses that primarily involve the spleen, liver, lymph nodes, and vertebrae. These masses may cause neurologic problems, such as spinal cord compression (sometimes causing paraplegia) and intrathoracic masses. Leg ulcers that are rare in well-transfused patients with thalassemia major are common in adult patients with thalassemia intermedia. Thrombotic risk is definitely increased in patients with thalassemia intermedia, especially after splenectomy. Although stroke is rare in thalassemia intermedia, asymptomatic brain damage, including ischemia,

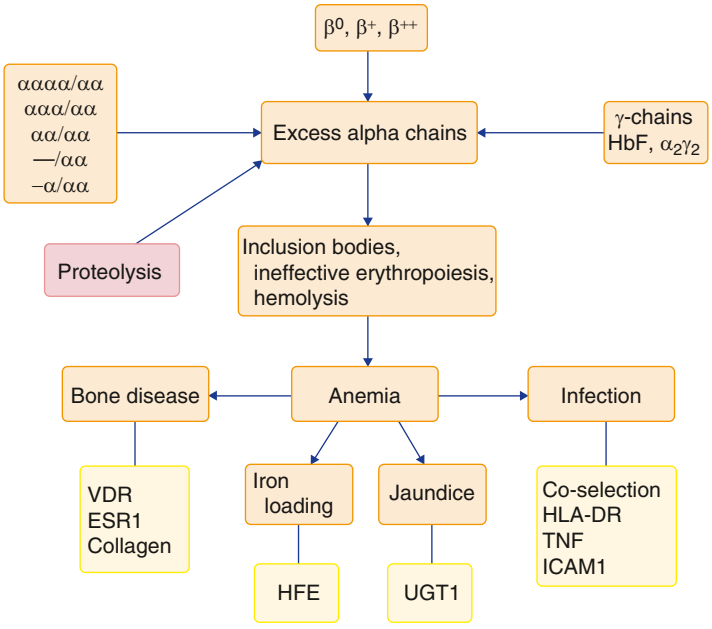

FIGURE 148-2. Pathophysiology of β-thalassemias and modifiers of globin chain imbalance. The severity of ineffective erythropoiesis is dependent on the degree of excess free α chains that result primarily from three different mechanisms: (1) inheritance of severe, mild, or silent β-chain mutations; (2) coinheritance of determinants associated with increased γ-chain production; and (3) coinheritance of α-thalassemia. A phenotype of thalassemia intermedia may result from the increased production of α-globin chains by a triplicated (αααα) or quadruplicated (ααααα) α genotype associated with β heterozygosity. Inheritance of polymorphisms or mutations of genes involved in bone, iron, and bilirubin metabolism as well as in infection may contribute to modify the clinical course of the disease. ESR1 = estrogen receptor 1; HbF = fetal hemoglobin; HFE = hereditary hemochromatosis gene; HLA = human leukocyte antigen; ICAM1 = intercellular adhesion molecule 1; TNF = tumor necrosis factor; UGT1 = UDP-glucose : glycoprotein glucosyltransferase 1; VDR = vitamin D receptor.

has been documented by magnetic resonance imaging (MRI) and computed tomography. Pulmonary hypertension (Chapter 69) is prevalent in thalassemia intermedia patients (approximately 60%) and is thought to be the primary cause of heart failure in this patient population. Liver disease due to viral infection is less frequent than in thalassemia major; however, abnormal liver enzymes are frequently observed in patients with thalassemia intermedia, primarily because of hepatocyte damage resulting from iron overload. In some of the oldest patients with thalassemia intermedia, long-term overload has resulted in cirrhosis (Chapter 139) and hepatocellular carcinoma (Chapter 181), similar to what may be found in hereditary hemochromatosis (Chapter 196).

β-Thalassemia Major

The major forms of β-thalassemia (still sometimes called Cooley anemia) are disorders in which life can be sustained only by regular blood transfusions. This condition usually results from the homozygous state or from the compound heterozygous state for severe β-gene mutations (β^0). The typical forms of thalassemia major become manifested during the first year of life, during which γ chains are switched off but not replaced by β-chain synthesis. Left untreated, these infants are incapable of maintaining a hemoglobin level above 5 g/dL, show marked bone deformities and growth retardation, and are considered as "transfusion-dependent thalassemia patients." They develop the "thalassemic" facies due to frontal bossing of the skull and protrusion of the jaws and cheekbones. The magnitude of the increase in erythropoiesis may result in extramedullary masses arising usually from the sternum and ribs. Progressive hepatosplenomegaly, which is a constant finding, leads to pancytopenia. The early childhood of the untreated or inadequately treated thalassemia major patients is interspersed with various complications, including recurrent infections, spontaneous fractures, gallstones, and leg ulcers.[11]

Heart failure in thalassemia major is multifactorial but is thought to be principally related to chronic anemia and the toxic effects of iron overload in the myocardium (Chapters 47 and 196). Liver disease is due to iron overload (Chapter 196), but other genetic modifiers may affect the outcome of complications in different ways. For example, the presence of a polymorphic variant in the UGT1A1 promoter responsible for Gilbert syndrome (Chapter 133) may increase the predisposition to cholelithiasis, which is already a common complication in thalassemia. Likewise, polymorphisms in genes involved in iron homeostasis or bone metabolism may affect negatively or positively the degree of iron overload or the osteopenia and osteoporosis (Chapter 225), respectively (see Fig. 148-2).[12] Environmental factors, including social conditions, nutrition, and the availability of medical care, have also been implicated in the variable severity of clinical manifestations of thalassemia major.

δβ-Thalassemia and Hereditary Persistence of Fetal Hemoglobin

The clinical manifestations of $(\delta\beta)^0$-thalassemias are similar to those of non–transfusion-dependent thalassemia intermedia, whereas the heterozygotes are distinguished from β-thalassemia heterozygotes by normal levels of HbA_2 together with an increased HbF level of 5 to 20%. Homozygotes for Hb_{Lepore} may have phenotypes similar to either thalassemia major or thalassemia intermedia. Subjects affected by deletion or nondeletion forms of hereditary persistence of fetal hemoglobin are usually asymptomatic.

Any of the β-thalassemia defects may be coinherited with β-chain variants (HbS, HbC, HbE) and cause a clinically relevant β-thalassemia phenotype of different severity. These variants further illustrate that β-thalassemia syndromes have a wide clinical spectrum and that specific therapeutic approaches may completely change the clinical course and the natural history of these disorders (Fig. 148-3).

Hemoglobin E and Hemoglobin E Thalassemias

Hemoglobin E (HbE) is caused by a substitution of glutamic acid by lysine at codon 26 of the β-globin gene. It is a common mutation, especially in the Indian subcontinent and Southeast Asia and among people who have emigrated from those regions. The frequency of HbE approaches 60% in many regions of Thailand, Laos, and Cambodia. HbE results in reduced synthesis of the β-E chain and therefore has the phenotype of a mild form of β-thalassemia. HbE trait has little clinical significance; it may be associated with slight microcytosis without anemia, but it could be mistaken for iron deficiency without appropriate laboratory testing. Homozygous HbEE individuals have mild anemia and microcytosis, occasional splenomegaly, and peripheral blood smears showing red cell changes similar to those seen in thalassemia trait, including target cells. In this condition, hepcidin is suppressed, thereby leading to iron accumulation—even in the absence of blood transfusions and certainly worsened by them.

HbE interacts with different forms of α-thalassemia to produce a wide variety of clinical disorders.[13] Its coinheritance with β-thalassemia, a condition called HbE/β-thalassemia, is the most common severe form of β-thalassemia in Asia and globally represents about 50% of the clinically severe β-thalassemias.

DIAGNOSIS

The diagnosis of thalassemia may be required in a patient with an appropriate, suggestive clinical picture or for the identification of a heterozygote subject as part of a family study or population screening program. The general approach is common to any form of thalassemia, regardless of presentation (Fig. 148-4). The primary evaluation is based on the red cell indices by electronic cell counter and the red cell morphology on a well-stained blood film. Individuals with mean corpuscular volume below 80 fL and mean corpuscular hemoglobin below 27 pg with normal iron parameters require further investigation. The red blood cell number is usually higher than normal. In the presence of anemia with thalassemic red cell changes, the next step is the evaluation of hemoglobin fractions (HbA, HbA_2, HbF, or hemoglobin variants) by electrophoresis on cellulose acetate at alkaline pH or, even better, by high-performance liquid chromatography that enables the precise measurement of HbA_2, HbF, and HbA and the provisional identification of a large number of hemoglobin variants, including HbE. An HbA_2 level above 3.5% associated with hypochromic microcytic red cells is diagnostic of β-thalassemia minor. HbA_2 values between 3.2 and 3.5% (borderline) should be interpreted with care because they could be due to interaction of more than one thalassemic defect (α and β), a silent β mutation, or concomitant iron deficiency. If iron deficiency is present, it should be corrected and the HbA_2 estimation repeated. The majority of individuals with thalassemic red cell indices with normal or low HbA_2 and normal HbF will be α^0-thalassemia carriers or α^+-thalassemia homozygotes. Carriers of α^0-thalassemia may have a few red cells with HbH inclusions. Microcytosis with low or normal HbA_2 levels with elevated HbF (2 to 20%) indicates heterozygosity for δβ-thalassemia. Patients with hereditary persistence of fetal hemoglobin usually have normal red blood cell indices but increased levels of HbF with different intercellular distribution (homogeneous or

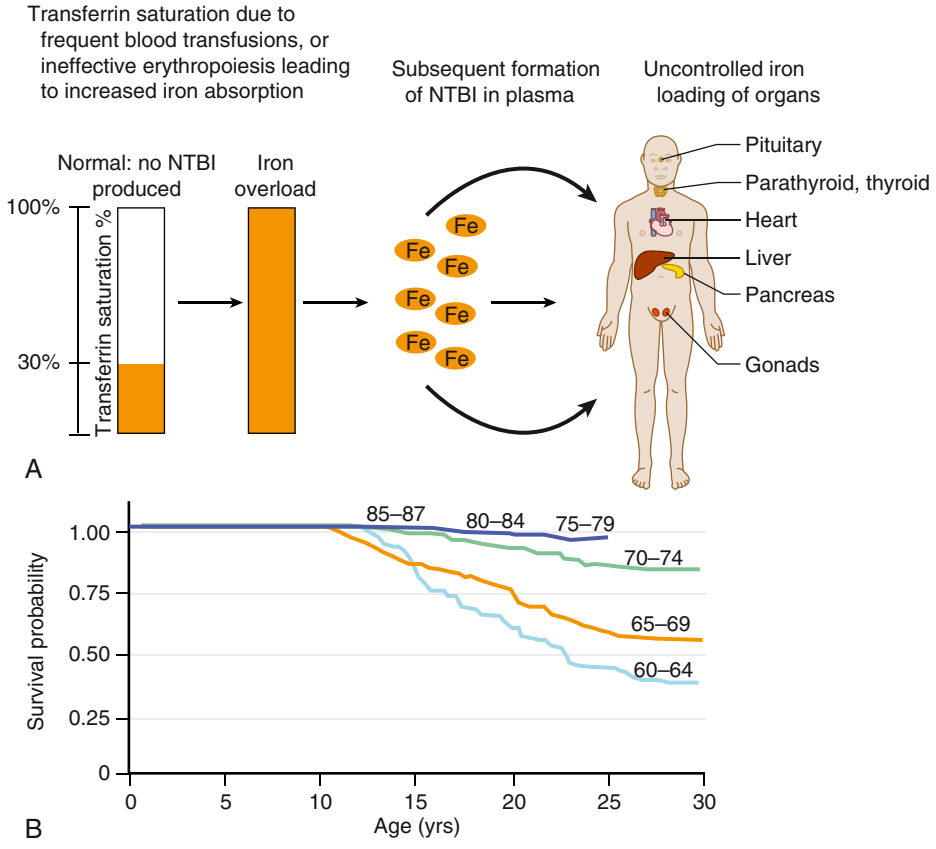

FIGURE 148-3. A, Transfusion iron overload and specific organ loading. B, Survival of Italian thalassemia major patients by cohort of birth. NTBI = non–transferrin-bound iron.

pancellular with the exception of heterocellular hereditary persistence of fetal hemoglobin) compared with δβ-thalassemia (uneven or heterocellular).

The definitive diagnosis of the thalassemia syndromes involves the identification of the underlying mutations by polymerase chain reaction (PCR) restriction enzyme analysis, PCR allele-specific oligonucleotides, gap PCR, and direct sequencing that at present is probably the easiest and most reliable method. For deletion forms of α-thalassemia, the multiplex ligation-dependent probe amplification is a recently introduced, useful method.

TREATMENT AND PROGNOSIS

Life expectancy is normal in patients with β-thalassemia minor. Other patients affected by different forms of thalassemia develop a variety of complications mainly due to iron overload, which requires monitoring to direct iron chelation therapy. The most notable are heart failure and iron overload in the liver.

Medical Treatment

Thalassemia Minor

No specific treatment is required for α- or β-thalassemia heterozygotes (carriers, thalassemia minor), but they should receive appropriate genetic counseling. During pregnancy, thalassemia-carrying women may become more anemic, so they should be observed carefully, mainly during the second and third trimesters, and supported with folic acid. When true iron deficiency is associated with thalassemia traits, iron supplementation should be provided, and levels of transferrin saturation and ferritin should be monitored.

Hemoglobin H Disease

HbH patients in general have higher hemoglobin levels (8 to 9 g/dL) and do not need regular blood transfusion. Supplementation with folic acid (2 to 5 mg/day) is generally recommended, especially in pediatric patients. The major complications in HbH disease are hemolytic crises that may occur during or after acute infections; in such cases, immediate intervention, including blood transfusions and treatment for infections, should be promptly administered. Prognosis generally depends on the degree of transfusion-dependency and iron overload.

Thalassemia Intermedia and Major

The clinical management of thalassemia intermedia and thalassemia major remains challenging. Prolongation of life, now well into the third or fourth decade, is accompanied by several complications, partly due to the underlying disorder and partly as a consequence of the treatment with blood transfusions and iron overload.

Patients with thalassemia intermedia generally experience puberty late, but they have normal sexual development and are usually fertile. Women with thalassemia intermedia may have successful pregnancies, although complications may occur during pregnancy. Overall prognosis generally depends on the degree of transfusion-dependency and iron overload.

In untreated β-thalassemia major, the mortality rate is high around puberty. However, children who are well transfused to maintain a hemoglobin level above 9 g/dL have relatively normal growth and development, and if they are adequately transfused and are fully adherent with iron chelation therapy (see Iron Overload) can enter puberty and become sexually mature. Unfortunately the current adult population of thalassemia major patients often suffers from now-avoidable side effects of long-term treatment, including transfusion-associated infections (particularly hepatitis B and hepatitis C infection [Chapters 134 and 135] and, in some populations, HIV infection [Chapter 355]), as well as end-organ damage (liver, heart, endocrine glands) due to unsatisfactory long-term iron chelation. The main causes of death in adult thalassemia major patients still remain cardiac complications, mainly in poorly chelated patients, although liver cirrhosis is also increasing because of the prolongation of life.

The supportive treatment of thalassemia major patients, best provided by a team of experts, includes regular transfusion therapy and iron chelation. The optimal transfusion regimen involves regular blood transfusions, usually administered every 2 to 5 weeks, to maintain the pretransfusion hemoglobin levels above 9 to 10.5 g/dL. The decision to initiate lifelong transfusion therapy should be based on a definitive diagnosis of severe thalassemia, taking into account the molecular defects, the severity of anemia on repeated measurement, the level of ineffective erythropoiesis, and the clinical criteria (such as failure to thrive or bone changes). It is advisable that thalassemia major patients receive leukoreduced packed red cells to minimize transfusion reactions and the transmission of pathogens. Adverse reactions to red blood cell transfusions may occur during or after transfusion and can be hemolytic and nonhemolytic. Transfusion-related acute lung injury is rare but severe and must be immediately managed (Chapter 162).

Many patients with thalassemia major commonly require splenectomy because of hypersplenism, but optimal management may delay or even obviate the need for splenectomy. Splenectomy should be considered only for patients whose annual blood consumption increases progressively and is responsible for significant increases in iron stores despite good chelation therapy or in the presence of symptoms due to splenic enlargement or hypersplenism. The major complication of splenectomy is severe and sometimes overwhelming infection (Chapter 154). Because removal of the spleen may reduce the primary immune response to encapsulated organisms, it is advisable to delay splenectomy until patients are at

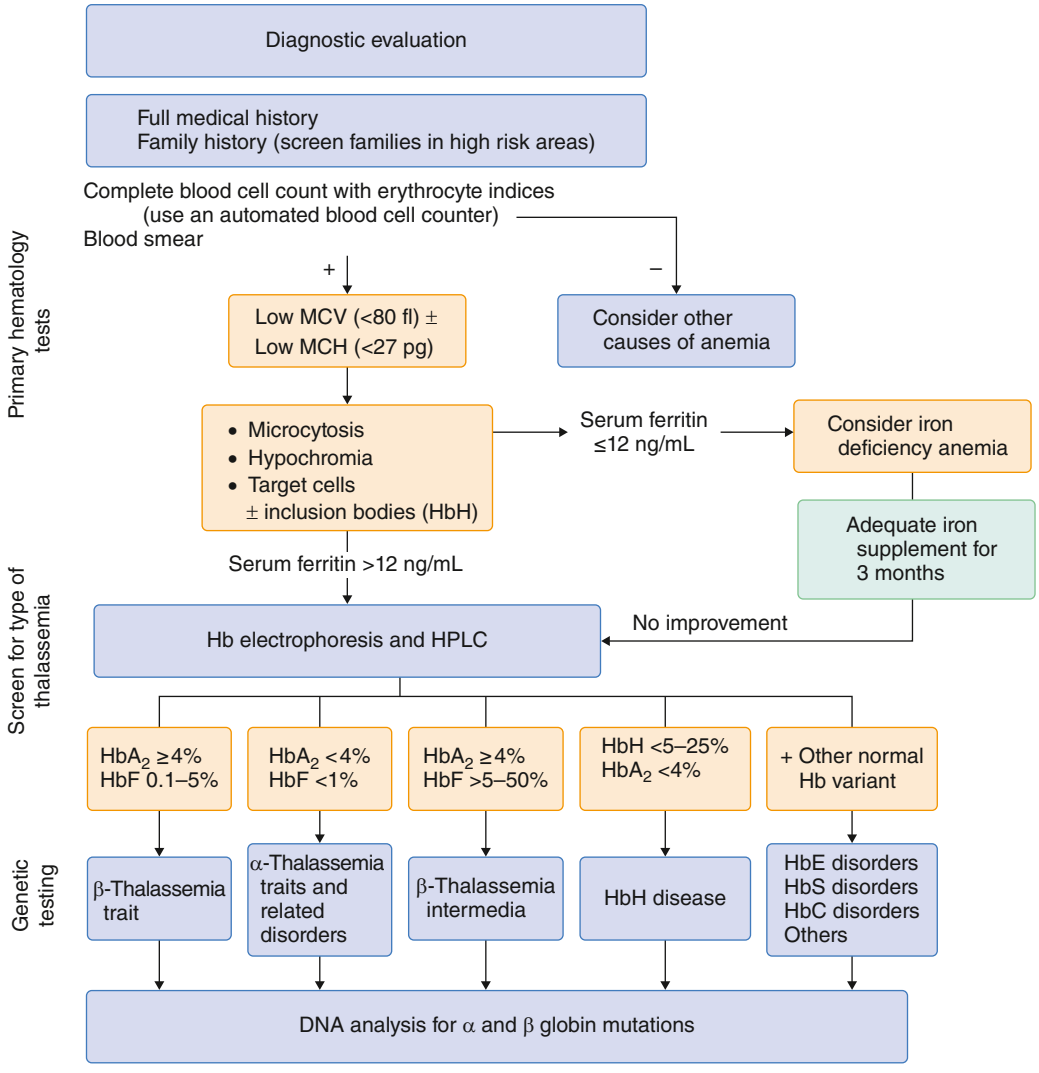

FIGURE 148-4. Diagnostic approach to suspected thalassemia. Hb = hemoglobin; HPLC = high-performance liquid chromatography; MCH = mean corpuscular hemoglobin; MCV = mean corpuscular volume.

least 5 years old. The mortality rate for overwhelming infection after splenectomy in patients with thalassemia is approximately 50% despite intensive supportive care. Therefore, it is mandatory to adopt preventive measures including immunoprophylaxis (vaccination against *Streptococcus pneumoniae*, pneumococcus, and meningococcus) (Chapter 154), chemoprophylaxis, and education of the parent and patient to recognize and to report febrile illnesses. After splenectomy, patients with thalassemia also have an increased risk of thrombosis.

The management of non–transfusion-dependent thalassemia intermedia is more complicated because of the wide heterogeneity of phenotypes. However, increasing evidence supports the benefit of preventive transfusion therapy to decrease the incidence of complications rather than reserving transfusion for when complications develop. The initiation of iron chelation therapy in patients with thalassemia intermedia depends not only on the amount of excess iron but also on the rate of iron accumulation, the duration of exposure to excess iron, and various other factors in individual patients.

Increasing Red Cell Release

Two new molecules, sotatercept[14] and luspatercept,[15] which are activin-type IIA and IIB receptor fusion proteins, can increase the release of mature erythrocytes into the circulation by acting mainly on late-stage erythropoiesis. Luspatercept (a recombinant fusion protein that binds to select transforming growth factor β superfamily ligands, given subcutaneously at a dose of 1.00 to 1.25 mg/kg every 3 weeks) is approved for adults with transfusion-dependent β-thalassemia, in whom it can reduce the transfusion burden by at least 33%, with analogous reductions in serum ferritin levels and no clinically meaningful changes in liver or myocardial iron concentrations.[A1]

Stimulation of Hemoglobin F Synthesis

An alternative treatment of β-thalassemia consists of the pharmacologic stimulation of HbF synthesis. In humans, hemoglobin switch from HbF to HbA occurs in the period around birth as a result of γ- to β-globin gene switching. A number of pharmacologic agents able to reactivate HbF synthesis have been identified, including hypomethylating agents, histone deacetylase inhibitors, and hydroxyurea. Whereas the effect of these pharmacologic treatments (particularly hydroxyurea) in sickle cell disease is clear (Chapter 149), their benefit on the clinical course of β-thalassemia is presently limited, perhaps because of the higher level of HbF required in β-thalassemia to achieve clinical results compared with those observed in sickle cell disease.

The reduction of α-globin expression may provide an equally plausible approach to ameliorating clinically severe forms of β-thalassemia, especially in patients with hemoglobin E β-thalassemia, who comprise about 50% of all patients born each year with severe β-thalassemia.

Experimental Therapies

Gene therapy (Chapter 34) using a lentivirus vector[16] or genome editing through CRISPR/Cas9 technology[17] is a potentially useful approach for increasing fetal hemoglobin production in patients who have thalassemia syndromes. Ongoing clinical trials are assessing efficacy in patients with transfusion-dependent β-thalassemia. New molecules with the potential ability to correct ineffective erythropoiesis or to generate iron-restricted erythropoiesis are in phase 2 clinical trials.

Iron Overload

Iron overload, which is an inevitable and serious complication of long-term blood transfusion therapy and hyperabsorption of dietary iron, requires adequate treatment to prevent early death, mainly from iron-induced cardiac disease.[18] The principal methods of determining body iron levels (Chapter 196) are measurements of the serum ferritin level and assessment of liver iron concentration from biopsy tissue or, as an alternative noninvasive method, by R2 MRI. High serum ferritin levels (>2500 μg/L) and high liver iron concentration (>15 g/dry weight) indicate high risk for significant morbidity and mortality. A cut-off of 800 μg/L ferritin and more than 7 g/dry weight liver iron concentration have been associated with high risk for morbidity in thalassemia intermedia and other forms of non–transfusion-dependent thalassemias.

Cardiac iron can be measured by a T2* MRI procedure that allows estimation of the cardiac iron load. MRI T2* values below 10 milliseconds are always associated with severe iron load and high risk for heart failure within 1 year. MRI T2* values above 20 milliseconds are considered normal, meaning no iron in the heart. Echocardiography also may be useful to evaluate functional changes.

For other organs, including liver disease, endocrinopathies, lung disease, thrombophilia, and bone disease, the diagnostic approaches are similar to those used in hemochromatosis (Chapter 196).

The oral iron chelator deferasirox is effective and safe in removing excess iron from different organs, including the heart[A2,A3] and is the first-line treatment in most countries.[19] The dose should be individualized according to age, history of adherence with previous chelation, and other factors. Monitoring and adjustment of iron chelation by repeated measurements of ferritin, calculation of iron intake by transfusions, and, whenever possible, measurement of cardiac and liver iron at least once by MRI are mandatory.

Prior to the availability of oral agents, the standard chelation therapy was deferoxamine, given for 10 to 24 hours daily as a slow, continuous, subcutaneous infusion 5 to 7 days per week. Unfortunately, adherence with the rigorous regimen of daily subcutaneous infusions is a serious limiting factor, and life expectancy in nonadherent patients is not different from that of untreated patients. The combination of deferasirox plus deferoxamine can further reduce iron overload compared with deferasirox alone.[A4]

Another oral iron chelator, deferiprone (75 to 100 mg/kg/day), may be more effective than deferoxamine in protecting the heart from the accumulation of iron.[A5] However, its use is restricted to U.S. patients who are unable to use deferoxamine or patients with an unsatisfactory response to deferoxamine, as judged by serum ferritin levels and by liver iron concentrations. A potential benefit of combined deferoxamine and deferiprone therapy has been observed, and this combination should be considered for patients with high levels of heart iron or cardiac dysfunction.

In patients with thalassemia major and cardiac siderosis, amlodipine added to chelation therapy reduces cardiac iron more effectively than chelation therapy alone,[A6,A7] but larger studies will be required to inform the evaluations. The use of proton pump inhibitors may further reduce serum ferritin levels.[A8]

Hydrops Fetalis

Infants with hydrops fetalis syndrome almost always die either in utero (30 to 40 weeks' gestation) or soon after birth, but some infants with hemoglobin Bart hydrops fetalis can survive with in utero blood transfusions and premature delivery by caesarean section. However, subsequent development is abnormal, and survivors require regular blood transfusions after birth.

Bone Marrow Transplantation

Allogeneic hematopoietic cell transplantation (Chapter 163) in thalassemia syndromes has been increasingly successful during the past two decades, mainly in β-thalassemia major.[20] Predictors of poor transplant outcome are hepatomegaly, history of irregular chelation, and hepatic fibrosis. Patients are categorized into three risk classes. Class 1 patients have none of these adverse risk factors, class 2 patients have one or two adverse risk factors, and class 3 patients have all three. The probabilities of thalassemia-free survival for patients younger than age 17 years at the time of hematopoietic cell transplantation from a human leukocyte antigen (HLA)-identical relative were 87% and 85%, respectively, in patients belonging to class 1 and class 2 and much lower in young patients in class 3. The progressive adjustment of conditioning regimens in class 3 patients and in adults (>17 years old) has significantly reduced the incidence of transplant-related mortality in patients in class 3. Only 25 to 30% of patients with diseases potentially curable by hematopoietic cell transplantation have a suitable HLA-compatible sibling. Bone marrow transplantation from unrelated donors increases significantly the incidence of acute and chronic graft-versus-host disease, particularly in thalassemia. A study from the Eurocord cooperative group reported the outcome of 33 patients with class 1 and class 2 thalassemia who received cord blood hematopoietic stem cells from an HLA-identical sibling; no patient died of transplant-related complications, suggesting that related cord blood hematopoietic cell transplantation is a safe procedure for thalassemia patients.

UNSTABLE HEMOGLOBINOPATHIES

More than 80 rare mutant hemoglobins have been reported to cause hemolytic anemia by either amino acid replacements or deletions that significantly lower the solubility of hemoglobin. These mutant hemoglobins thereby form intracellular precipitates that can be detected as so-called Heinz bodies when the blood smear is exposed to a supravital stain. Structural abnormalities include mutations that weaken the linkage between heme and globin, disrupt secondary (α-helical) structure, or introduce a charged or polar side group into the hydrophobic interior of the globin subunit.

This disorder, sometimes called congenital Heinz body hemolytic anemia, is inherited in an autosomal dominant manner. Severely affected individuals have jaundice, splenomegaly, and, on occasion, dark brown urine due to the release of heme and aberrant conversion to dipyroles. The instability of a few of these globin mutants is so extreme that they cannot be detected by routine laboratory methods. The result is a thalassemia phenotype with microcytosis and ineffective erythropoiesis. Like individuals with glucose-6-phosphate dehydrogenase deficiency (Chapter 147), patients with unstable hemoglobin mutants often lack clinical symptoms and signs of hemolysis until they develop an infection or are exposed to an oxidant drug.

The diagnosis can be established by a combination of a positive Heinz body preparation and either abnormal hemoglobin electrophoresis or demonstration of a precipitate after exposure of a hemolysate to heat or isopropanol. Some clinics have access to a reference laboratory that can identify the specific mutation by α- and β-globin DNA sequencing.

Most individuals with this disorder do not require treatment, but some are symptomatic from severe anemia. Splenectomy generally results in a significant increase in red cell mass. However, the fraction of Heinz body–positive red cells increases markedly after splenectomy, and these patients are at significant risk for development of pulmonary hypertension and cor pulmonale.

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149 SICKLE CELL DISEASE AND OTHER HEMOGLOBINOPATHIES

JO HOWARD

SICKLE CELL DISEASE

DEFINITION

Sickle cell disease is caused by a mutation in the β-globin gene. The resulting clinical syndromes are characterized by chronic hemolytic anemias and can be complicated by vaso-occlusion and vasculopathy that can cause widespread acute and chronic organ damage as well as premature mortality.

EPIDEMIOLOGY

The sickle mutation became prominent several thousands of years ago in Sub-Saharan African and Arab-Indian populations. Its persistence was due to a selective advantage in areas where falciparum malaria was endemic, with sickle trait carriers estimated to have approximately 90% protection against severe malaria infection. The carrier frequency is now highest in West and Central Africa (up to 50%), in Arab populations in the Middle East, and in

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Cardiac iron can be measured by a T2* MRI procedure that allows estimation of the cardiac iron load. MRI T2* values below 10 milliseconds are always associated with severe iron load and high risk for heart failure within 1 year. MRI T2* values above 20 milliseconds are considered normal, meaning no iron in the heart. Echocardiography also may be useful to evaluate functional changes.

For other organs, including liver disease, endocrinopathies, lung disease, thrombophilia, and bone disease, the diagnostic approaches are similar to those used in hemochromatosis (Chapter 196).

The oral iron chelator deferasirox is effective and safe in removing excess iron from different organs, including the heart[A2,A3] and is the first-line treatment in most countries.[19] The dose should be individualized according to age, history of adherence with previous chelation, and other factors. Monitoring and adjustment of iron chelation by repeated measurements of ferritin, calculation of iron intake by transfusions, and, whenever possible, measurement of cardiac and liver iron at least once by MRI are mandatory.

Prior to the availability of oral agents, the standard chelation therapy was deferoxamine, given for 10 to 24 hours daily as a slow, continuous, subcutaneous infusion 5 to 7 days per week. Unfortunately, adherence with the rigorous regimen of daily subcutaneous infusions is a serious limiting factor, and life expectancy in nonadherent patients is not different from that of untreated patients. The combination of deferasirox plus deferoxamine can further reduce iron overload compared with deferasirox alone.[A4]

Another oral iron chelator, deferiprone (75 to 100 mg/kg/day), may be more effective than deferoxamine in protecting the heart from the accumulation of iron.[A5] However, its use is restricted to U.S. patients who are unable to use deferoxamine or patients with an unsatisfactory response to deferoxamine, as judged by serum ferritin levels and by liver iron concentrations. A potential benefit of combined deferoxamine and deferiprone therapy has been observed, and this combination should be considered for patients with high levels of heart iron or cardiac dysfunction.

In patients with thalassemia major and cardiac siderosis, amlodipine added to chelation therapy reduces cardiac iron more effectively than chelation therapy alone,[A6,A7] but larger studies will be required to inform the evaluations. The use of proton pump inhibitors may further reduce serum ferritin levels.[A8]

Hydrops Fetalis

Infants with hydrops fetalis syndrome almost always die either in utero (30 to 40 weeks' gestation) or soon after birth, but some infants with hemoglobin Bart hydrops fetalis can survive with in utero blood transfusions and premature delivery by caesarean section. However, subsequent development is abnormal, and survivors require regular blood transfusions after birth.

Bone Marrow Transplantation

Allogeneic hematopoietic cell transplantation (Chapter 163) in thalassemia syndromes has been increasingly successful during the past two decades, mainly in β-thalassemia major.[20] Predictors of poor transplant outcome are hepatomegaly, history of irregular chelation, and hepatic fibrosis. Patients are categorized into three risk classes. Class 1 patients have none of these adverse risk factors, class 2 patients have one or two adverse risk factors, and class 3 patients have all three. The probabilities of thalassemia-free survival for patients younger than age 17 years at the time of hematopoietic cell transplantation from a human leukocyte antigen (HLA)-identical relative were 87% and 85%, respectively, in patients belonging to class 1 and class 2 and much lower in young patients in class 3. The progressive adjustment of conditioning regimens in class 3 patients and in adults (>17 years old) has significantly reduced the incidence of transplant-related mortality in patients in class 3. Only 25 to 30% of patients with diseases potentially curable by hematopoietic cell transplantation have a suitable HLA-compatible sibling. Bone marrow transplantation from unrelated donors increases significantly the incidence of acute and chronic graft-versus-host disease, particularly in thalassemia. A study from the Eurocord cooperative group reported the outcome of 33 patients with class 1 and class 2 thalassemia who received cord blood hematopoietic stem cells from an HLA-identical sibling; no patient died of transplant-related complications, suggesting that related cord blood hematopoietic cell transplantation is a safe procedure for thalassemia patients.

UNSTABLE HEMOGLOBINOPATHIES

More than 80 rare mutant hemoglobins have been reported to cause hemolytic anemia by either amino acid replacements or deletions that significantly lower the solubility of hemoglobin. These mutant hemoglobins thereby form intracellular precipitates that can be detected as so-called Heinz bodies when the blood smear is exposed to a supravital stain. Structural abnormalities include mutations that weaken the linkage between heme and globin, disrupt secondary (α-helical) structure, or introduce a charged or polar side group into the hydrophobic interior of the globin subunit.

This disorder, sometimes called congenital Heinz body hemolytic anemia, is inherited in an autosomal dominant manner. Severely affected individuals have jaundice, splenomegaly, and, on occasion, dark brown urine due to the release of heme and aberrant conversion to dipyroles. The instability of a few of these globin mutants is so extreme that they cannot be detected by routine laboratory methods. The result is a thalassemia phenotype with microcytosis and ineffective erythropoiesis. Like individuals with glucose-6-phosphate dehydrogenase deficiency (Chapter 147), patients with unstable hemoglobin mutants often lack clinical symptoms and signs of hemolysis until they develop an infection or are exposed to an oxidant drug.

The diagnosis can be established by a combination of a positive Heinz body preparation and either abnormal hemoglobin electrophoresis or demonstration of a precipitate after exposure of a hemolysate to heat or isopropanol. Some clinics have access to a reference laboratory that can identify the specific mutation by α- and β-globin DNA sequencing.

Most individuals with this disorder do not require treatment, but some are symptomatic from severe anemia. Splenectomy generally results in a significant increase in red cell mass. However, the fraction of Heinz body–positive red cells increases markedly after splenectomy, and these patients are at significant risk for development of pulmonary hypertension and cor pulmonale.

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For the General References and other additional features, please visit Elsevier eBooks+ at https://ebooks.health.elsevier.com.

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149 SICKLE CELL DISEASE AND OTHER HEMOGLOBINOPATHIES

JO HOWARD

SICKLE CELL DISEASE

DEFINITION

Sickle cell disease is caused by a mutation in the β-globin gene. The resulting clinical syndromes are characterized by chronic hemolytic anemias and can be complicated by vaso-occlusion and vasculopathy that can cause widespread acute and chronic organ damage as well as premature mortality.

EPIDEMIOLOGY

The sickle mutation became prominent several thousands of years ago in Sub-Saharan African and Arab-Indian populations. Its persistence was due to a selective advantage in areas where falciparum malaria was endemic, with sickle trait carriers estimated to have approximately 90% protection against severe malaria infection. The carrier frequency is now highest in West and Central Africa (up to 50%), in Arab populations in the Middle East, and in

ABSTRACT

Sickle cell disease is caused when a homozygous GAG-to-GTG mutation in codon 6 of the β-globin chain of human hemoglobin results in a single amino acid substitution, Glu6Val. This point mutation is sufficient to cause increased polymerization of hemoglobin in red blood cells that are deoxygenated during transit through the microcirculation of tissues and organs, thereby leading to distortion of red cell shape from round, pliable biconcave discs to rigid sickle cells that occlude the microvasculature. The clinical sequelae of this pathophysiology include episodic vaso-occlusive events that are associated with pain crises, hemolytic anemia, stroke, acute chest syndrome, pulmonary hypertension, urologic and renal complications that can lead to chronic kidney disease, and other ischemic organ involvement. Individuals who are heterozygous for the mutation have sickle trait that does not cause disease but can be infrequently associated with specific complications. Curative options include hematopoietic stem cell transplantation and gene therapy, but at present both are associated with significant morbidity and mortality. In addition to well-coordinated palliative care, the use of hydroxyurea and transfusion therapy, including exchange transfusions, can favorably affect the natural history of the disease in certain situations. Newer treatment options that can reduce symptoms and complications include crizanlizumab, voxelotor, and L-glutamine.

KEYWORDS

sickle cell
vaso-occlusive pain crisis
stroke
acute chest syndrome
priapism
hydroxyurea
exchange transfusion
hematopoietic stem cell transplantation

some populations in India (Fig. 149-1). Forced movement of African populations during the slave trade and, more recently, migration because of war and economic pressures have led to increasing numbers of carriers and affected individuals in the Americas, the Caribbean, Europe, and worldwide.

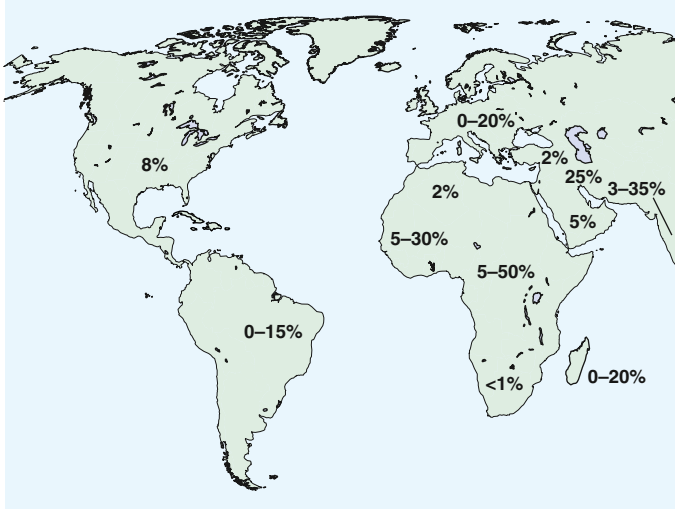

FIGURE 149-1. Worldwide prevalence of the sickle cell trait. Shown are the percentages of individuals with sickle cell trait in regions of the world where the hemoglobin S (HbS) gene is often present. In each geographic area, the prevalence of sickle cell trait can vary markedly according to racial or ethnic group, by historical migration patterns, and even from village to village. Not shown is the high concentration of the HbS gene in areas of Europe, such as London, Manchester, and Paris, where migrants from Africa or Afro-Caribbean populations have settled.

The prevalence of sickle cell disease and sickle trait varies across the world, but more than 75% of the estimated 300,000 to 400,000 births affected annually with sickle cell anemia (HbSS) occur in Sub-Saharan Africa, with these numbers predicted to increase.[1]

PATHOBIOLOGY

Globin, which is the protein portion of hemoglobin, has an iron-containing porphyrin heme ring that allows the molecule to transport oxygen efficiently. Mutations that cause changes in the amino acid sequence of the globin polypeptide can cause clinically significant diseases, including sickle cell disease, that collectively are termed hemoglobinopathies. Sickle hemoglobin (HbS:$\alpha_2\beta_2^s$), which is caused by an adenine (A) to thymidine (T) substitution (GAG to GTG) in codon 6 of the β-globin gene (HBB), results in a valine residue (Glu6Val) instead of the normal glutamic acid residue (Fig. 149-2). Homozygous sickle cell disease (HbSS) is an autosomal recessive condition, so each offspring of two sickle cell carrier parents has a 25% chance of being affected (Fig. 149-3AI).

HbS polymerizes when it becomes deoxygenated, and this polymerization distorts the shape of red cells into the characteristic sickle shape (Fig. 149-3Aii) and leads to red cell damage, hemolysis, and vaso-occlusion. The deoxygenation of red cells occurs in the circulation as they cross the capillary bed; but as they return to the lungs, oxygen uptake occurs, and the polymers deaggregate. This sickling–desickling cycle is repeated as the red cell recirculates, but if the passage of red cells is delayed, cell sickling, membrane damage, and vaso-occlusion occur before transit through the microvasculature is complete. The formation of polymers (and the severity of sickling) may be increased by a higher intracellular hemoglobin concentration, low pH, and raised temperature and can be decreased by the presence of other intracellular hemoglobins, such as fetal hemoglobin (HbF).

The polymerization of sickle hemoglobin leads to red cell damage by several mechanisms that result in red cell destruction (hemolysis) and vaso-occlusion.[2] Most hemolysis is extravascular because it occurs when macrophages

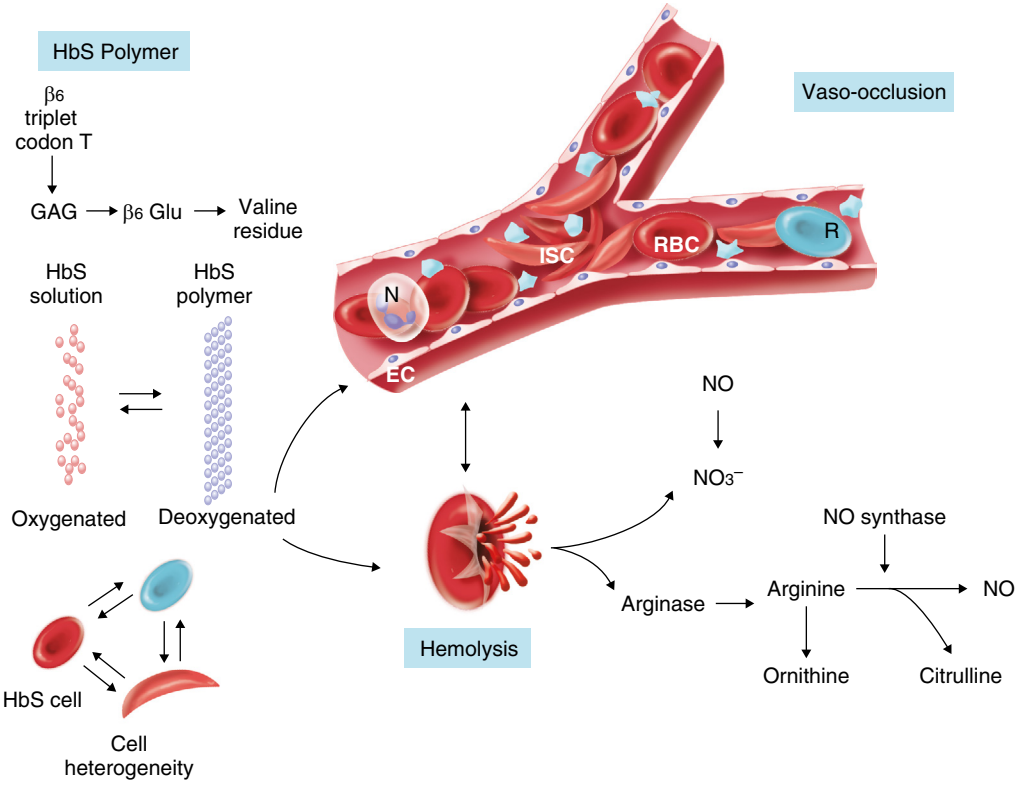

FIGURE 149-2. Pathophysiology of sickle cell disease. An adenine (A) to thymidine (T) transversion (A6T) at codon 6 in the β-hemoglobin gene on chromosome 11 (*HBB*) leads to the substitution of a glutamic acid codon by a valine codon. β6 valine allows the hemoglobin S (HbS) molecule ($\alpha_2\beta_2^5$) to polymerize when it is deoxygenated. DeoxyHbS polymer injures the erythrocyte and leads to a heterogeneous population of sickle cells with damaged membrane cytoskeleton, reduced cation and water content, and altered distribution of membrane lipids. In the vasculature, sickle cells interact with endothelium and other blood cells to cause vaso-occlusion. Some damaged erythrocytes hemolyze intravascularly, thereby releasing heme into the plasma to scavenge nitric oxide (NO) and to reduce hemoglobin to methemoglobin and nitrate. NO, by binding soluble guanylate cyclase, converts cyclic guanosine triphosphate to guanosine monophosphate, thereby relaxing vascular smooth muscle and causing vasodilation. A state of reduced endothelial NO bioavailability in sickle cell disease impairs the homeostatic vascular functions of NO, such as inhibition of platelet activation and aggregation and transcriptional repression of genes transcribing cell adhesion molecules. Hemoglobin, heme, and heme iron catalyze the production of oxygen radicals and protein nitration, potentially further limiting NO bioavailability and activating endothelium. Lysed erythrocytes also liberate arginase, which destroys L-arginine, the substrate for NO production, providing another mechanism for endothelial NO deficiency. The normal balance of vasoconstriction versus vasodilation is therefore skewed toward vasoconstriction as well as endothelial activation and proliferation. EC = epithelial cell; ISC = irreversibly sickled cell; N = neutrophil; R = reticulocyte; RBC = red blood cell.

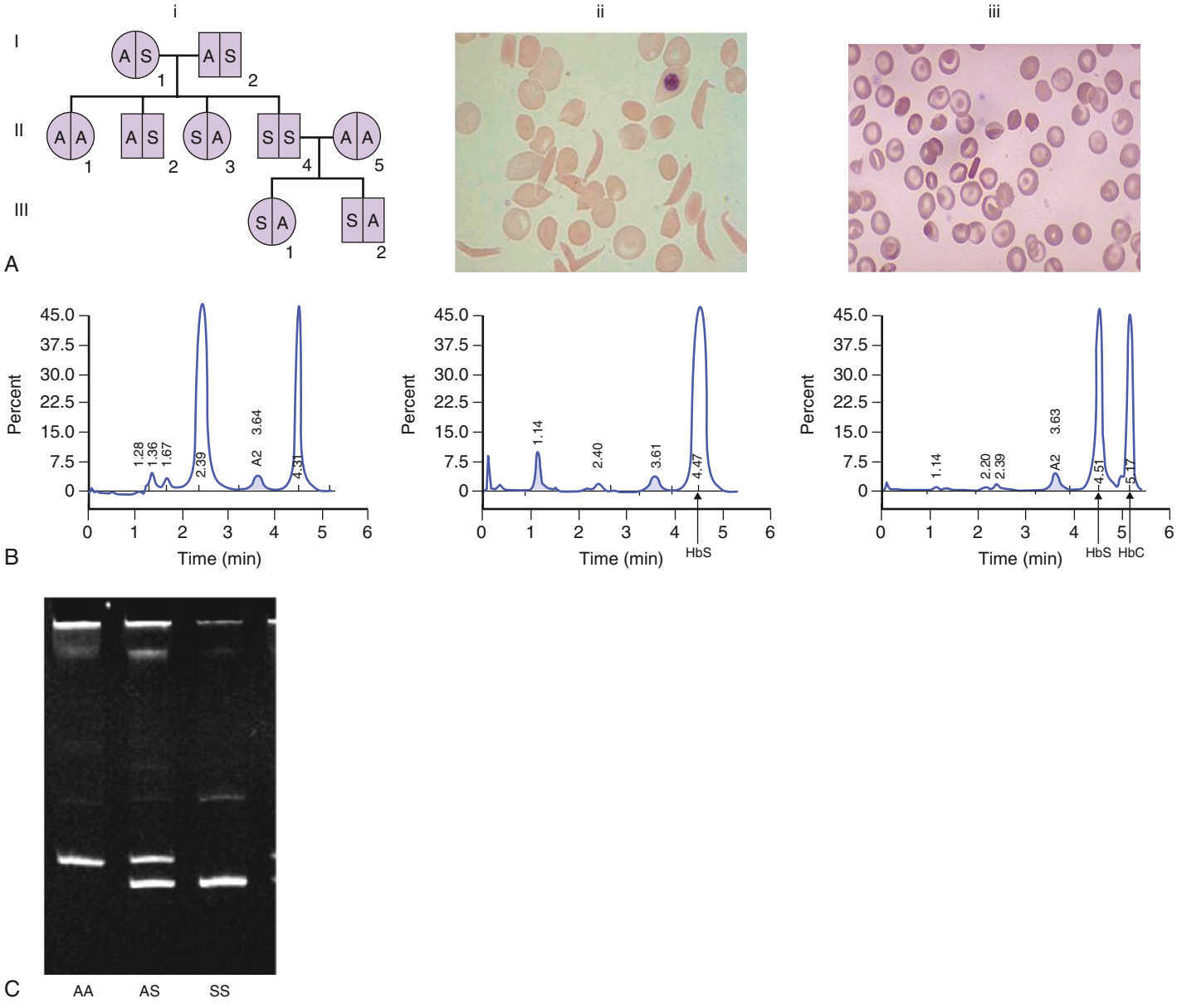

FIGURE 149-3. Diagnosis of sickle cell disease. A, A prototypical family structure in which both parents (I) have sickle cell trait and each offspring (II) has a 25% chance of having sickle cell anemia (SS). Each child of an affected parent (III) will have sickle cell trait (SA) if the other parent has a normal hemoglobin (AA) genotype. The blood films (*center* and *right*) are from patients with sickle cell anemia and hemoglobin SC (HbSC) disease, respectively. Note the irreversibly sickled cells in the former and the hemoglobin C (HbC) crystal and target cells in the latter. **B**, High-performance liquid chromatography profiles from patients with sickle cell trait *(left)*, sickle cell anemia *(center)*, and HbSC disease *(right)*. **C**, Amplification-refractory mutation system–based separation of the β-globin genes from a normal subject (AA), a carrier of sickle cell trait (AS), and a patient with sickle cell anemia (SS).

recognize damaged sickle erythrocytes, thereby resulting in erythrophagocytosis. Intravascular hemolysis liberates hemoglobin into the circulation, where it binds to, and thereby depletes, free plasma haptoglobin and scavenges nitric oxide (NO). In addition, these sickled red cells adhere to activated vascular endothelial cells, thereby promoting inflammation as well as leukocyte and platelet adherence to endothelium. These interactions with endothelium lead to vascular obstruction, tissue ischemia, and then vaso-occlusion. Endothelial cells respond to biologic modifiers that are generated during these vaso-occlusive episodes and the resulting inflammation. The initiation of vaso-occlusion is complex, and mechanisms include the following:

- Cellular damage from adhesive interactions among sickle cells, leucocytes, endothelial cells, and platelets and involving cell adherence molecules such as P selectin, which is expressed on endothelial cells and platelets when they are activated. Leukocytes are then captured on the endothelium.
- Adherent sickle cells and shear stresses that release reactive oxidant species express endothelin and disturb NO balance.
- Reperfusion injury, which can activate endothelial cells and stimulate inflammation.
- Reticulocytes, which are prematurely released from the bone marrow and have adhesive ligands that augment interactions between erythrocytes and endothelial cells.

Hemoglobin variants that have the β-globin gene Glu6Val substitution (HbS) are prone to polymerization. Accumulation of these HbS polymers within sickled erythrocytes causes cellular injury, thereby leading to the clinical syndrome of sickle cell disease. In homozygous sickle cell disease (HbSS) or coinheritance of HbS and β^0-thalassemia (HbSβ^0-thalassemia), the cells contain HbS and no HbA and have the greatest clinical severity (sickle cell anemia). The coinheritance of HbS with other hemoglobin variants (e.g., HbC, HbE, HbSβ^+-thalassemia, HbSD^{Punjab}, HbSO^{Arab}) are also associated with sickling disorders of varying severity (Table 149-1). Although most of the more than 1000 hemoglobin mutations are clinically insignificant, others can occasionally affect the stability and function of hemoglobin and cause hemolytic anemia, disordered oxygen transport, or methemoglobinemia (Chapter 144).

CLINICAL MANIFESTATIONS

Sickle Cell Trait (Sickle Cell Carrier; HbAS)

Approximately 18 to 25% of the population of Sub-Saharan Africa are sickle cell carriers and have what is termed sickle cell trait. Carriers are protected against intracellular sickling because the red cells contain a predominance of HbA compared with HbS (usually 35 to 40% HbS) and because the HbA inhibits hemoglobin polymerization, except under extreme conditions (prolonged

TABLE 149-1 GENETIC AND LABORATORY FEATURES OF COMMON SICKLE HEMOGLOBINOPATHIES*

GENOTYPE	GENETICS	PREVALENCE AMONG AFRICAN AMERICANS†	HEMATOCRIT (%)	MCV (fL)	HbS (%)	HbA_2 (%)	HbF (%)	SEVERITY‡
Sickle cell anemia (HbSS)	Homozygous HbS	1 : 600	18-28	85-95	>85	2-3	2-15	4
HbSS-α-thalassemia	Homozygous HbS α^+-thalassemia	30% of HbSS patients	25-33	70-85	>85	4-6	2-15	4
HbSC disease (HbSC)	Compound heterozygous HbS, HbC	1 : 800	28-40	70-85	50	2-3	1-8	2
HbS-β^0-thalassemia (HbS-β^0-Thal)	Compound heterozygous HbS, β^0-thalassemia	1 : 1600	20-30	65-75	>85	4-6	5-15	4
HbS-β^+-thalassemia (HbS-β^+-Thal)	Compound heterozygous HbS, β^+-thalassemia	1 : 1600	30-40	60-70	70-95	4-6	2-10	1-3
HbSE disease (HbSE)	Compound heterozygous HbS, HbE	Rare§	30-45	70-80	60	2-3	1	1-2
HbS-HPFH	Compound heterozygous HbS and gene deletion HPFH	Rare	38-45	70-80	70	2	20-30	0
Sickle cell trait (HbAS)¶	Heterozygous HbS	1 : 12	38-50	80-90	35-40	2-3	<1	0
Normal (HbAA)	Homozygous HbA	—	38-50	80-90	0	2-3	<1	—

*Many other abnormal globin genes can be found as compound heterozygotes with the HbS gene. The most common of these are α-thalassemia, HbD, HbO (Arabia), HbG (Philadelphia), HPFH, Hb Hope, and Hb Lepore. Average ranges of laboratory values are shown, but these can vary according to the patient's age.

†These figures differ by the prevalence of the involved genes in the population studied. In West and Central Africa, where the disease is most common, approximately 2% of all newborns have sickle cell disease. The prevalence of the HbC trait in African Americans is 3%, and that of the β-thalassemia trait is 1%. About 30% of African Americans carry an α-thalassemia gene, which can alter the phenotype of sickle cell disease by causing microcytosis, reduced cell density, and less hemolysis.

‡Severity of disease compared with sickle cell anemia, clinically the most severe genotype. This is a qualitative ranking of the clinical severity of each genotype; within each genotype, there is great clinical heterogeneity.

§Although this combination is still a rare genotype, the rising Asian population in the United States (HbE is a Southeastern Asian gene) will make it more frequent with time. With few cases reported compared with the other genotypes, the phenotype of HbSE disease is not totally defined. It may resemble HbS-β^+-thalassemia, with symptoms appearing mainly in adults.

¶Sickle cell trait should not be classified as a form of sickle cell disease. About 8% of African Americans are carriers of HbS. Carriers are hematologically normal with a normal life expectancy. The few abnormalities traceable to the presence of HbS, besides the renal lesions, include a four-fold increased risk for pulmonary embolism, an increased risk for splenic infarction at high altitude, and a higher risk for dying during the course of exertional heat illness.

Hb = hemoglobin; HbF = fetal hemoglobin; HPFH = hereditary persistence of HbF; MCV = mean corpuscular volume.

hypoxia, acidosis, or dehydration). The carrier state is not generally regarded as harmful; carriers have a normal life expectancy but may experience clinical complications.[3]

Limited epidemiologic studies of individuals with sickle cell trait suggest an increased risk for extreme exercise- and physical exertion–related injury, broadly including exertional rhabdomyolysis, heat-associated collapse, and unexplained sudden death.[4,5] Sickle cell trait can likewise be a cause of death during training and competition in athletes.

Renal abnormalities are among the most common manifestations of sickle cell trait, including hematuria and impaired urinary concentrating ability, and can lead to albuminuria and chronic kidney disease. Individuals with sickle cell trait are at increased risk for venous thromboembolism, specifically pulmonary embolism.[6]

Sickle Cell Disease

Sickle cell disease has remarkably variable clinical manifestations. An individual patient can have almost all known complications, whereas others may have virtually no complications but nevertheless die suddenly. Some individuals have severe complications but do not demonstrate other manifestations. Thus, the phenotypic variability of sickle cell disease is striking despite being a prototypical "single-gene" mendelian disorder. Specific sickle cell genotypes have differing severity, with HbSS and HbSβ^0-thalassemia following a similarly severe disease course, whereas HbSC, HBSβ^+-thalassemia (and the other genotypes) tend to have a milder disease phenotype. However, some patients with HbSS may have infrequent pain episodes and few complications, whereas some patients with HbSC may experience frequent severe pain crises. Factors causing this phenotypic variability include coinheritance of disease-modifying genes, including HbF and α-thalassemia, as well as variations in genes that affect inflammation, nitric oxide biology, oxidant injury, cell-cell interactions, vasoregulation, coagulation, and hemostasis.

Multiorgan Disease and Variation with Age

Although sickle cell disease is most commonly associated with anemia and repeated pain episodes, the pathophysiologic process can affect all organs in the body (Table 149-2). Acute complications include an increased risk for infection, stroke, and chest complications. Chronic complications include chronic lung disease, chronic renal failure, pulmonary hypertension, and ophthalmologic complications.

TABLE 149-2 ACUTE AND CHRONIC COMPLICATIONS OF SICKLE CELL DISEASE

SYSTEM	ACUTE COMPLICATIONS	CHRONIC COMPLICATIONS
Neurologic	Acute ischemic stroke Acute hemorrhagic stroke Venous sinus thrombosis	Silent cerebral ischemia Vasculopathy (moyamoya disease) Headache Cognitive dysfunction
Cardiorespiratory	Acute chest syndrome	Pulmonary hypertension Asthma Chronic sickle lung disease Sleep-disordered breathing Myocardial impairment
Renal	Acute renal failure Hematuria Urinary tract infection	Enuresis Proteinuria Chronic renal failure
Urologic	Priapism	Erectile dysfunction
Orthopedic	Osteomyelitis	Avascular necrosis
Ophthalmologic	Vitreous hemorrhage Retinal detachment Retinal artery occlusion	Retinopathy
Others	Acute splenic sequestration Acute hepatic sequestration Gallstone disease (biliary colic, cholecystitis)	Chronic splenomegaly Splenic dysfunction Sickle hepatopathy Leg ulceration

Complications typically vary with age. Dactylitis (pain crisis affecting hands and feet) is often the first symptom seen in young children when the levels of

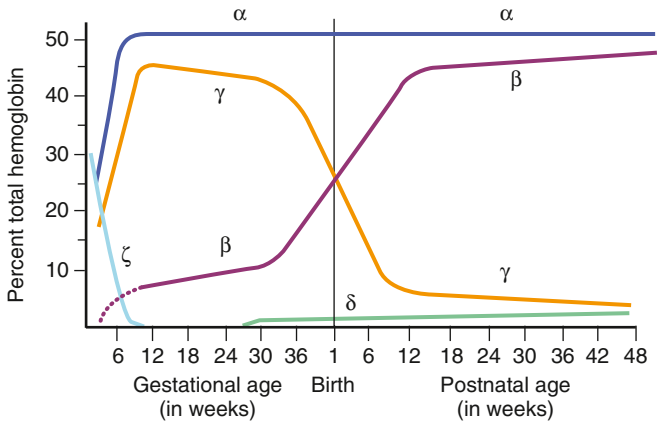

FIGURE 149-4. Human globin genes. Expression of globin genes during development. The α chains are expressed throughout gestation and adult life, the fetal γ-globin chains are expressed predominantly in utero, and the β-globin and δ-globin genes are expressed mainly postnatally. This switching of gene expression patterns accounts for the different hemoglobins present in the embryo, fetus, and adult. This phenomenon also accounts for the observation that disorders of α-globin can affect both fetus and adult, whereas β-globin chain diseases usually are not clinically apparent in the first months of life, when fetal hemoglobin levels are still high.

HbS increase between 6 and 12 months of age as hemoglobin switches from HbF to HbS (Fig. 149-4). Splenic dysfunction, which occurs early in life, increases susceptibility to infection and results in high rates of infective deaths in the absence of antibiotic prophylaxis and vaccination. Splenic sequestration is most common in affected individuals who are younger than age 5 years before the development of splenic infarction, although it may occur later in persons with milder disease phenotypes. Before the introduction of transcranial Doppler screening and primary stroke prevention (see later), stroke was most common in young children and in older adults; the risk is now markedly less in children but not in adults.

Most chronic organ damage does not become clinically significant until adulthood, but invariably organ damage will begin in early childhood. For example, although evidence of renal dysfunction (e.g., hyposthenuria and microalbuminuria) occurs in early childhood, end-stage renal failure is uncommon before late adulthood. Similarly, acute chest syndrome, asthma, and sleep-disordered breathing are all common in children, but severe chronic lung disease becomes apparent in adulthood. Pulmonary hypertension, retinopathy, leg ulcers, and avascular necrosis are all uncommon in childhood but much more common in adults. With an increasing life expectancy, sickle cell disease has now evolved into a debilitating disorder with substantial morbidity resulting from ongoing sickle cell vasculopathy and multiorgan damage.[7] Patients should be offered the option of curative therapies as their best option for improved long-term survival and quality of life.

Pain

Acute Pain

Acute pain episodes (vaso-occlusive crises) are the hallmark of sickle cell disease, occur with unpredictable frequency, may be triggered by infection, dehydration, or stress, or may occur with no precipitant. Pain crises are the most common reason for hospital admission in patients with sickle cell disease, but pain is also experienced frequently in the community and can have a significant impact on quality of life. Almost 30% of adults with sickle cell disease have pain on more than 95% of days, and only about 15% have pain on fewer than 5% of days. Overall, patients experience pain on about 50% of days but use health care on fewer than 5% of days.

Young children typically experience pain in the fingers and toes (dactylitis), but older children and adults tend to experience pain in the arms, legs, and trunk. Examination of the affected area is usually normal, but swelling and acute tenderness may be evident. No diagnostic tests exist for sickle crisis, so diagnosis is usually based on the patient's history. An individual patient will usually describe the pain as typical for sickle cell disease, and atypical pain requires further investigation to look for alternative causes.

Chronic Pain

Chronic pain refers to pain that persists for more than 3 months. In patients with sickle cell disease, chronic pain may be due to an identifiable underlying cause, most commonly avascular necrosis. However, some patients experience severe daily pain with no clear stimulus, perhaps because of central sensitivity syndromes that are associated with an increased sensitivity to painful and nonpainful stimuli and are precipitated and reinforced by repeated painful and stressful stimuli.

Anemia

Patients with HbSS/HbSβ^0-thalassemia usually have a baseline hemoglobin of 6 to 9 g/dL, whereas patients with HbSC and HbSβ$^+$-thalassemia will have a higher baseline hemoglobin of 8 to 12 g/dL. Patients usually tolerate this degree of anemia, although some patients experience significant fatigue. Anemia, sometimes associated with renal dysfunction, often worsens in older adulthood.

Acute anemia (a decrease in hemoglobin of >2 g/dL) may be associated with worsening symptoms of fatigue and breathlessness, and intervention with transfusion may be required. Causes of acute anemia include worsening hemolysis, parvovirus (erythrovirus) B19 infection (potentially causing pure red cell aplasia or hypoplasia), splenic sequestration, folate deficiency, and any cause of anemia seen in non–sickle cell disease patients. Parvovirus B19 (Chapter 342), which causes slapped-cheek syndrome in children, usually manifests as an acute viral illness with profound anemia and reticulocytopenia. Splenic sequestration is most common in young children before splenic infarction and is characterized by anemia and splenic enlargement.

Neurologic Complications

Acute Ischemic Stroke

In untreated children and adults with sickle cell disease, strokes occur in approximately 10% of patients by age 20 years and 25% by age 40 years. Cerebral vasculopathy is the most common cause in children, but adults also have comorbid conditions such as diabetes, hypertension, and atrial fibrillation. Acute ischemic stroke can also occur in the context of acute pain crisis or acute anemia. The typical features of acute ischemic stroke (Chapter 376) include hemiparesis, facial droop, or dysphasia, but patients may present with loss of consciousness or behavioral change.

Acute Hemorrhagic Stroke

Patients with sickle cell disease also are at increased risk for intracerebral, intraventricular, subdural, and subarachnoid hemorrhage (Chapter 377), often related to the underlying cerebral vasculopathy. The prevalence of both moyamoya (a rare, chronic occlusive cerebrovascular disease characterized by progressive stenosis of the intracranial terminal carotid arteries with an abnormal vascular network at the base of the brain) and cerebral aneurysms are increased in this group of patients. Presentation with headache and decreased consciousness is more common than with focal neurologic signs.

Silent Cerebral Infarction and Other Neurologic Complications

MRI of patients with sickle cell disease frequently shows small ischemic lesions that are not associated with neurologic deficits. These silent cerebral infarcts increase with increasing age and are associated with cognitive impairment, including a reduction in IQ. MRI screening of children may identify affected individuals at an early age. Venous sinus thrombosis, posterior reversible encephalopathy syndrome, and headaches are also more common in patients with sickle cell disease.

Cardiorespiratory Complications

Acute Chest Syndrome

Acute chest syndrome is an acute illness characterized by fever and/or respiratory symptoms accompanied by a new pulmonary infiltrate on chest radiograph. Patients may present to the hospital with acute chest syndrome, or it may develop 1 to 3 days after admission for an acute pain crisis. Etiologies include infection (bacterial or viral), fat embolism, and pulmonary infarction (Chapter 68). Severity is variable, but it may result in severe hypoxia, respiratory failure, and death.

Pulmonary Hypertension

Pulmonary hypertension, with a mean pulmonary artery pressure of 25 mm Hg or greater, is reported in 6 to 11% of adults with sickle cell disease and is associated with increased mortality. Pathogenesis is multifactorial and includes left-sided heart disease, chronic lung disease, chronic thromboembolic disease, and intravascular hemolysis. *N*-terminal pro–brain natriuretic peptide (BNP) levels are typically elevated, and echocardiography is the best noninvasive test.

Chronic Lung Disease and Sleep-Disordered Breathing

About 20% of children with sickle cell disease have asthma, which may be caused by increased pulmonary capillary blood flow or by the chronic inflammation

of the lungs. The prevalence of asthma is not increased in adults with sickle cell disease, but about 70% of adults with sickle cell disease develop restrictive lung defects, which can be associated with daytime hypoxia, chest pain, and progressive restrictive lung defects and fibrosis on high-resolution CT scanning. Sleep-disordered breathing (Chapter 374), with nocturnal hypoxia and obstructive sleep apnea, is seen in up to 40% of children and 60% of adults with sickle cell disease.

Renal and Urologic Complications

Renal complications are seen in up to 60% of patients with sickle cell disease, commencing in early childhood and progressing with increasing age. A distal renal tubule–concentrating defect, which is an early manifestation of renal damage, results in hyposthenuria (an inability to concentrate urine), nocturnal enuresis, and a predisposition to dehydration. An increased glomerular filtration rate (GFR), owing to anemia and high cardiac output, leads to glomerular hypertrophy and damage and then to microalbuminuria, which is seen in 20% of children and 60% of adults with sickle cell disease and can progress to unselective proteinuria and even nephrotic syndrome (Chapter 107).

Hematuria, which is also common in sickle cell disease as well as in sickle cell trait (see earlier), can be due to renal papillary necrosis. This syndrome can be painful and profuse. Renal medullary carcinoma is a highly aggressive malignancy that predominantly afflicts young adults and adolescents with sickle cell hemoglobinopathies.

Acute kidney injury (Chapter 106) occurs in 2 to 10% of patients who are admitted with acute painful crisis and can be precipitated by dehydration, sepsis, and drugs. Cortical ischemia, perhaps due to sickling in the low-flow low-oxygen cortical areas of the kidney, also can contribute to tubular interstitial disease (Chapter 108). Progressive renal dysfunction can result in end-stage kidney disease, with a requirement for dialysis or renal transplantation.

Priapism

Priapism is a persistent, prolonged, and painful penile erection unrelated to sexual stimulation. Priapism is common in men and boys with sickle cell disease and may occur as short, intermittent, self-limited episodes (stuttering priapism) or as severe acute episodes lasting for more than an hour (fulminant priapism). Acute priapism may be preceded by stuttering priapism and can result in long-term erectile dysfunction.

Infection

Sickle cell patients experience increased morbidity and mortality from infection, in part due to functional asplenia or hyposplenia (Chapter 154), and also due to increased rates of gram-negative sepsis. Hyposplenia develops from infancy and leads to a deficiency in response to encapsulated bacteria and hence increased risk for invasive infection with organisms such as *Streptococcus pneumoniae* (Chapter 268), *Neisseria meningitides* (Chapter 274), and *Haemophilus influenzae* type b (Chapter 277). Patients with sickle cell disease are more likely to have adverse outcomes from coronavirus disease 2019 (COVID-19) infection (Chapter 336).[8]

DIAGNOSIS

Routine Blood Tests

The usual steady-state hemoglobin level is 5 to 10 g/dL in HbSS and is higher in the milder phenotypes. The anemia in HbSS is typically normochromic and normocytic, but microcytosis is often seen in HbSC disease, and marked microcytosis and hypochromia are seen in HbSβ-thalassemia. Most affected individuals have reticulocytosis and evidence of hemolysis with a raised bilirubin and lactate dehydrogenase (LDH). The blood film in HbSS will show numerous sickle cells, polychromasia, and features of hyposplenism (in adults). In addition, hypochromia is also prominent in HbSβ-thalassemia. In HbSC disease, target cells, densely staining contracted boat-shaped red cells, and HbC crystals may be seen with less sickled cells and polychromasia than in HbSS (see Figs. 149-3Aii and 149-3Aiii).

Analysis of Hemoglobin Type

High-pressure liquid chromatography (HPLC) is now the most common method of hemoglobin analysis. Variant hemoglobins are identified by their elution time from an ion exchange column and can be quantified. HPLC is quick, is reliable, and allows high throughput of samples (see Fig. 149-3B). Confirmatory testing should be performed with alternative techniques. These include the following:

- The sickle solubility test will detect sickling of hemoglobin in solution by treatment with a reducing agent. It is specific for sickle hemoglobin but does not differentiate among HbAS, HbSS, and other compound heterozygotes of sickle cell hemoglobin.
- Hemoglobin electrophoresis was the first method used to demonstrate hemoglobin variants but is time-consuming and labor-intensive.
- DNA sequence analysis identifies the specific globin gene mutation (see Fig. 149-3C).
- Tandem mass spectrometry identifies the specific amino acid change in the globin chain.

Screening

Screening for sickle cell trait is currently required in some branches of the U.S. Armed Forces because of an increased risk from complications of extreme exercise. Antenatal screening aims to identify couples at high risk for an affected pregnancy to enable counseling and prenatal diagnosis (via chorionic villus sampling or amniocentesis) early enough to allow reproductive choice. Preconceptual screening provides couples with information about the risks of an affected birth before conception and allows them to consider the option of preimplantation diagnosis.

TREATMENT AND PREVENTION

General Measures

Sickle cell disease is a chronic disease for which good nutrition and a high fluid intake should be encouraged. Patients and their families should be educated about acute complications and should be taught how to palpate the spleen, how to manage simple pain crises, and when to go to the emergency department. Regular outpatient clinic visits will ensure appropriate screening for chronic disease complications (including screening for stroke risk) and early intervention.[9] The increased production of red blood cells, combined with inadequate nutrition, leads to accelerated consumption of folic acid; supplementary folic acid is typically recommended, although patients with a good dietary intake may not require it. There are significant psychosocial implications of chronic illness, and patients and their families should be offered psychological and social support if needed. The transition from pediatric to adult care is a time of heightened vulnerability and should be managed in a structured way.

Management of Complications

Pain

Mild acute pain episodes can be managed at home with simple analgesia (acetaminophen, nonsteroidal anti-inflammatory drugs; Table 26-4), fluids, and rest, but more severe pain crises may need hospital admission for strong opiate analgesia (Table 26-6). Patients and their families should be made aware of situations when they should be seen in the hospital (Table 149-3).

Inpatients typically require parenteral analgesic. Patients often find patient-controlled analgesic devices beneficial, and the use of patient-controlled analgesic may reduce total opiate intake. Patients being treated with opiates should be monitored for respiratory depression and excessive sedation and should be offered adjuvant therapy to manage opiate side effects (emesis [Table 118-5], constipation [Table 122-3], and pruritus [Table 403-10]). Doses of opiate pain relief should be titrated down as soon as pain settles.

Patients with acute pain episodes should be monitored for the development of other complications, particularly acute chest syndrome, which typically begins 24 to 72 hours after the onset of an acute pain crisis and is more common in patients who have chest and back pain. Early incentive spirometry may reduce the subsequent incidence of acute chest syndrome, and regular monitoring of oxygen saturations will allow early identification of those with worsening hypoxia, which can be a precursor to acute chest syndrome. Patients with recurrent acute pain crisis should be offered hydroxyurea therapy.

TABLE 149-3 SYMPTOMS THAT SHOULD PROMPT HOSPITAL ADMISSION: "RED FLAG" EVENTS

- Severe pain not settling with usual analgesia
- Atypical pain
- Temperature >38° C
- Chest pain
- Shortness of breath
- Neurologic symptoms (e.g., weakness of a limb or facial droop, diminished level of consciousness)
- Pain associated with unusually severe headaches
- Severe lethargy
- Priapism
- Severe jaundice

Chronic pain can be difficult to treat and worsened by opiate therapy. Referral to chronic pain services is often helpful (Chapter 26).

Infection and Infection Prophylaxis

Vaccination for pneumococcus, meningococcus, and *Haemophilus* (Chapter 15) decreases the risk for early mortality and morbidity from invasive bacterial disease, but vaccine-resistant serotypes can still cause serious infections. Infections, especially with encapsulated organisms, require prompt antibiotic treatment.

Stroke

For patients with suspected strokes, urgent magnetic resonance imaging (MRI) or MR angiography can confirm and localize the stroke, although computed tomography (CT) may be used in emergency situations to exclude acute hemorrhagic stroke. Xanthochromia in cerebrospinal fluid can confirm a subarachnoid hemorrhage.

After initial management with hydration and oxygenation, urgent exchange transfusion should be performed to minimize ischemic damage and improve perfusion of the brain. If there is marked anemia (hemoglobin <6 g/dL), simple transfusions may be given to achieve a post-transfusion hemoglobin concentration of about 10 g/dL and HbS percentage of less than 30%, but initial exchange transfusion may prevent recurrent stroke more effectively than initial simple transfusion.[10] In adults with sickle cell disease, thrombolysis appears to be safe in the absence of hemorrhagic transformation.[11]

For an acute hemorrhagic stroke, treatment should be on a specialized neurosurgery unit and should generally be similar to treatment of patients without sickle cell disease. However, exchange transfusion therapy should be considered before neurosurgical intervention.

The risk for recurrent stroke is high, and transfusion therapy seems to be more effective than hydroxyurea in preventing recurrent stroke. Patients should be offered long-term blood transfusion to maintain HbS percentage of less than 30%, most effectively by repeated automated or manual exchange transfusions, although the optimal duration of such therapy is uncertain.[A1] Surgical revascularization may be indicated for patients with recurrent acute ischemic stroke or progressive vasculopathy.

Children who have silent cerebral infarction may benefit from educational or medical intervention. Chronic transfusion therapy may be of benefit, particularly in patients who have abnormal transcranial Doppler studies.

On transcranial Doppler screening in children, a raised time-averaged mean of maximal velocity is associated with an increased risk of stroke. In such children, a blood transfusion strategy to maintain HbS% at less than 30% can reduce the risk of stroke by 90%. As a result, transcranial Doppler scanning is now routine in children ages 2 to 16 years. Stopping transfusions after 3 years leads to an increased risk of recurrent stroke, whereas changing to hydroxyurea therapy after 1 year of transfusions is as effective as continuing with transfusion.[A2]

Cardiorespiratory

Initial treatment of the acute chest syndrome is supportive with pain relief, antibiotics, and oxygen therapy, but more severe presentations may require treatment with simple or exchange transfusion and/or noninvasive or invasive respiratory support.[12] Patients with severe or recurrent acute chest syndrome should be offered treatment with hydroxyurea.

Patients with catheterization-proved pulmonary hypertension should be offered sickle cell disease–modifying therapy or specific therapy for pulmonary hypertension (see Fig. 69-6) under the guidance of an expert. For sleep-disordered breathing (Chapter 374), treatment with nocturnal oxygen or noninvasive respiratory support may be required.

Renal and Urologic Disease

Hematuria may require blood transfusion and occasionally interventional radiology or surgery. Hematuria in patients older than age 40 years, particularly if painless, always should be evaluated by a urologist.

Proteinuria is associated with progression of chronic kidney disease, so patients should be offered screening for proteinuria (with albumin-creatinine or protein-creatinine ratio). Early intervention with angiotensin-converting enzyme inhibitors or angiotensin receptor blockers is indicated in patients who have significant proteinuria (protein-creatinine ratio >50 mg/mmol). Renal function should be monitored regularly to allow optimization of the treatment of hypertension and proteinuria and thereby slow progression.

Priapism

Young men with sickle cell disease should be educated about priapism and encouraged to come to the emergency department for episodes that persist for more than 1 hour. Initial conservative management includes pain relief, fluids, gentle exercise and urination, and oral α-adrenergic agents (etilefrine). If the priapism fails to resolve, a urologist should be contacted to perform penile aspiration, which can be combined with the injection of α-adrenergic agents into the corpus cavernosa. The procedure will often cause detumescence; if not, further surgical intervention will be needed. Transfusion therapy may be helpful to support surgery and possibly to relieve persistent priapism. Treatment of stuttering priapism should be considered for symptomatic relief and with the aim of preventing future episodes of fulminant priapism. Oral α-adrenergic agents and antiandrogens should be considered under guidance of an expert urologist, and phosphodiesterase type 5 (PDE5) inhibitors also may be considered.

Management of Pregnancy

Although most women with sickle cell disease should expect to have successful pregnancies and healthy babies, these pregnancies are associated with an increased rate of maternal and fetal morbidity and mortality. Complications include increased sickle complications (pain, chest complications), pregnancy complications (infection, raised blood pressure), and high rates of premature birth and fetal growth restriction. Women should be counseled about the risks of pregnancy during their routine outpatient appointments, and preconceptual care should include partner screening, review of medications, and evaluation of chronic complications that may affect the pregnancy. When pregnant, women should be enrolled into multidisciplinary antenatal care with an obstetrician who has experience in sickle cell disease and a hematologist. Caregivers should consider prescribing daily low-dose aspirin (e.g., 81 mg daily) for prevention of preeclampsia (Chapter 221). Patients should be followed regularly throughout pregnancy with blood pressure, urinalysis, and ultrasound monitoring. Prophylactic transfusion is not recommended for all pregnancies but may reduce the risk for pain crisis, chest complications, and fetal complications. If there are no obstetric complications, the pregnancy should be allowed to continue to term, anticipating spontaneous labor and normal delivery. Women with sickle cell disease are at increased risk for venous thrombosis (Chapter 68), and their risk should be assessed using appropriate tools and the need for thromboprophylaxis considered (Chapter 221).[13]

Management of Surgery

General anesthesia is associated with increased risk for complications, in particular, increased pain crises and acute chest crises. These complications can be reduced with careful preoperative care (hydration, oxygenation) and consideration of preoperative blood transfusion. In low- to moderate-risk surgery in patients with non-HbSS genotypes, transfusion may not be needed. Simple transfusion aiming for a hemoglobin concentration of more than 9 g/dL is as effective as exchange transfusion for low- and moderate-risk surgery, but high-risk surgery (cardiac or neurosurgery) requires preoperative exchange transfusion.[14]

Disease-Modifying Therapies

Hydroxyurea

Hydroxyurea increases HbF levels and reduces cellular adhesion and hemolysis. Randomized controlled trials in various settings have shown that hydroxyurea reduces acute pain episodes, chest crises, and rates of hospitalization in adults and children with sickle cell anemia with few side effects regardless of the severity of symptoms.[A3] Dose-escalation protocols (up to 30 mg/kg/day) are superior to fixed-dose protocols (at 20 mg/kg/day).[A4] In addition, hydroxyurea reduces the risk of stroke in patients who have elevated transcranial Doppler studies. Adherence to hydroxyurea clearly reduces emergency visits and hospitalizations.[15] Hydroxyurea should be offered to all infants, children, and adolescents with sickle cell anemia, irrespective of severity, and to adults with recurrent pain episodes, severe or recurrent acute chest syndrome, and symptomatic anemia.

Hydroxyurea is well tolerated. Its main side effect is myelosuppression, and regular blood monitoring is required while on the drug. Because of suggestive evidence regarding teratogenicity and effects on spermatogenesis, hydroxyurea should be avoided in patients who are trying to conceive.

Anemia and Blood Transfusion

Red cell transfusion is used both to treat the acute complications of sickle cell disease and as long-term disease-modifying therapy. Patients who have chronic anemia may need intervention with hydroxyurea, transfusions, or erythropoiesis-stimulating agents. Acute anemia typically requires blood transfusion, aiming for a return to the patients' baseline hemoglobin concentration.

Acute indications for transfusion include acute anemia, acute chest syndrome, stroke, and multiorgan failure. Transfusion is not indicated for the treatment of simple acute pain crises. Long-term transfusion is indicated for primary and secondary stroke prevention and for the prevention of recurrent pain episodes or recurrent acute chest syndrome if there has not been a response to hydroxyurea therapy.

Blood can be administered as a simple or "top-up" transfusion to increase hemoglobin levels and improve oxygen-carrying capacity or as an exchange transfusion (manual or automated). Exchange transfusion allows a more marked reduction of HbS compared with HbA and is more likely to reduce vaso-occlusion.[16] In view of the increased risk for alloimmunization and delayed hemolytic transfusion reactions in patients with sickle cell disease, blood should be ABO Rh (CcDEe) and Kell compatible, and blood should be antigen-negative for clinically significant antibodies that are currently or have previously been detected (Chapter 162).

Long-term or frequent intermittent transfusion can result in iron overload and iron deposition in the liver and other organs. The patient should be monitored with ferritin and liver iron quantification by MRI, and iron chelation therapy should be instigated if the patient is iron-loaded (see Chapter 196). Both deferasirox and desferrioxamine are effective and licensed for use in sickle cell disease. Deferiprone is not currently licensed for use in sickle cell disease but is also effective.

TABLE 149-4 NEW MEDICATIONS FOR TREATMENT OF SICKLE CELL DISEASE

DRUG NAME	MODE OF ACTION	DOSE	LICENSED INDICATIONS (UNITED STATES)
L-Glutamine	Antioxidant	5 g-15 g orally, twice daily based on body weight	Reduction of acute complications in sickle cell disease in adults and pediatric patients 5 years and older
Crizanlizumab	Anti-P selectin	5 mg/kg IV infusion over 30 min on Week 0, 2, and every 4 weeks thereafter	Reduction in the frequency of vaso-occlusive crises in adults and pediatric patients 16 years and older with sickle cell disease
Voxelotor	HbS polymerization inhibitor	1500 mg orally, daily	The treatment of sickle cell disease in adults and pediatric patients 12 years and older

HbS = hemoglobin S; IV = intravenous.

Other Disease Modifying Therapies (Table 149-4)

L-Glutamine, an antioxidant, can reduce the rate of vaso-occlusive pain crises and hospital admissions.[A5] Crizanlizumab, an anti-P selectin agent, reduces the frequency of vaso-occlusive cries and increases the median time to first and second crisis.[A6] Both drugs are useful to reduce the frequency of vaso-occlusive pain events in patients who have frequent pain crises. Voxelotor, which is a hemoglobin modifier that inhibits the polymerization of hemoglobin and reduces hemolysis, raises hemoglobin by 1.0 g/dL in over 50% of recipients without adverse events.[A7]

Other promising agents currently in development for the acute or long-term treatment of sickle cell disease act through different mechanisms. Examples include drugs targeting HbS polymerization (e.g., pyruvate kinase activators),[17] histone deacetylase inhibitors, and drugs targeting inflammation (e.g., interleukin 1-beta [IL-1b] blockade). A randomized trial of canakinumab, which is an IL-1b blocker, did not show a pre-specified reduction in pain but did show reduction in markers of inflammation, sickle cell disease–related adverse events, and hospitalization rates.[A8]

Curative Therapies

Stem Cell Therapy

Successful hematopoietic stem cell transplantation (Chapter 163) is a potentially curative option for sickle cell disease. When performed in young patients, hematopoietic stem cell transplantation from human leukocyte antigen (HLA)–matched siblings results in excellent overall survival and event-free survival.[18] The utility of this approach is limited because only about 10 to 20% of sickle cell disease patients will have HLA-identical siblings available as donors. Hematopoietic stem cell transplantation from alternative donors (particularly haplo-identical transplants) have shown good outcomes in small studies but are associated with increased morbidity and mortality. There is increasing evidence of the efficacy of reduced-intensity conditioning approaches in adults, associated with reduced adverse effects.[19]

Gene Therapy

Gene therapy (Chapter 34), which is another potentially curative option for sickle cell disease, involves manipulation of hematopoietic stem cells to correct or circumvent the sickle mutation followed by autologous transplantation of the manipulated cells. Clinical trials using lentiviral vectors to add modified antisickling β-globin variants have showed sustained production of the modified β-globin with reduced hemolysis and resolution of severe vaso-occlusive events.[20] Gene-editing techniques using CRISPR/Cas9 technology to encourage production of fetal hemoglobin (HbF) also can be effective, with persistence of high levels of HbF and elimination of vaso-occlusive pain crises for at least 1 year.[21]

PROGNOSIS

In resource-rich countries with universal neonatal screening, antibiotic prophylaxis, improved supportive care, and successful research trials, most children with sickle cell disease reach adulthood. In the United States, nearly 95% of persons with sickle cell disease reach age 18 years. Nevertheless, adults with sickle cell disease still have a high burden of pain and comorbidity, and the median age of death is 43 years.[22] The extent to which newer drugs will impact chronic organ damage, quality of life, and longevity is unclear. In Sub-Saharan Africa, by contrast, where almost 80% of the projected 306,000 newborns worldwide with sickle cell disease are born, mortality remains 50 to 90% before age 5 years.

OTHER HEMOGLOBINOPATHIES

Hemoglobin C trait is a benign condition in which lysine replaces glutamic acid at the same sixth position on the hemoglobin beta chain where valine causes the sickle cell mutation. Homozygous HbC disease is associated with a mild hemolytic anemia and splenomegaly. HbC disease is characterized by a peripheral smear with a large population of target cells (see Fig. 149-3Aiii), with some red cells containing crystals. Individuals with HbC disease generally do not have clinical sickle crises or other complications. HbS/HbC disease occurs in about 1 per 1100 Black Americans. Patients who have HbS/HbC disease tend to have a clinical syndrome intermediate in severity between homozygous hemoglobin C disease and homozygous sickle cell anemia. Treatments, when needed, are similar to those for sickle cell anemia.

Hemoglobin E and the HbE thalassemias are discussed in Chapter 143.

Other than HbS, HbC, and HbE, most hemoglobinopathies do not cause clinical abnormalities. Among those that may have some clinical complications are some of the unstable hemoglobin variants, in which the mutant hemoglobin tends to precipitate intracellularly and causes a so-called Heinz body hemolytic anemia. These conditions are covered in the section on "Unstable Hemoglobinopathies" in Chapter 143. Another group of hemoglobinopathies are globin chain mutations that cause increased binding of oxygen by the abnormal hemoglobin, that is, the high-oxygen-affinity hemoglobin variants. These individuals generally have a secondary erythrocytosis as a compensatory response to their relative ineffectiveness in releasing O_2 to tissues. High-oxygen-affinity hemoglobinopathies are best diagnosed by formal study of the patient's oxyhemoglobin dissociation curve and P-50 values, which can be obtained with a commercially available instrument such as the Hemox-Analyzer, which measures in vitro deoxygenation of the sample using nitrogen gas and simultaneously determines oxygen tension with a Clarke electrode. Estimations of the P-50 by blood gas analyzers on venous blood are more convenient but have not been well validated in the screening of hemoglobin variants with high oxygen affinity. Despite their polycythemia, these patients do not have the other diagnostic characteristics of polycythemia vera (Chapter 152).

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150 MEGALOBLASTIC ANEMIAS

SALLY P. STABLER

DEFINITION

Megaloblastic anemia is defined as an anemia or pancytopenia resulting from failure of DNA synthesis and imbalance of maturation between the nucleus and the cellular cytoplasm resulting in large cells subject to maturation arrest and early destruction. Large, macrocytic, red blood cells are also seen in conditions other than megaloblastic anemia (Table 150-1). In practical terms, however, many of the causes of macrocytic red blood cells overlap with those of full-blown megaloblastic anemias. The most frequent causes of severe megaloblastic anemia are deficiencies of cobalamin (vitamin B_{12}) and folate, two vitamins with interrelated roles in the synthesis of thymidine and purines for DNA synthesis[1,2] (Table 150-2).

EPIDEMIOLOGY

Cobalamin Deficiency

Cobalamin is synthesized only by microorganisms, and humans obtain the vitamin through ingestion of animal-source foods because plants do not utilize cobalamin.[3] There are many populations in the world that do not consume adequate cobalamin-containing food due to scarcity and expense of animal-source food or belief systems against the use of such foods. Recommended daily allowances in the United States have been set at 2.4 μg/day, which is readily achieved with an omnivorous diet containing meat, dairy, eggs, fish, or shellfish. Lactovegetarians are at high risk for dietary deficiency,[4] and foods targeted to vegetarian populations in high-resource countries can be supplemented with cobalamin.[5] The fetus and breast-feeding infant obtain cobalamin from the mother, and thus requirements are increased to 2.6 μg for pregnancy and 2.8 μg for lactating women. The breast milk of cobalamin-deficient women has low concentrations of the vitamin and their infants can have severe developmental and growth impairment. An efficient enterohepatic circulation of cobalamin prevents loss of the vitamin so that individuals on deficient or marginal diets will take years to become deficient if the gastrointestinal tract is functioning.[6]

Cobalamin is a trace component of food-bound proteins in the diet, and most causes of severe deficiency relate to the inability to absorb the vitamin. The failure of secretion of gastric intrinsic factor due to an autoimmune disease of the gastric mucosa is known as pernicious anemia and results in life-threatening anemia, pancytopenia, or myeloneuropathy unless treated.[7] Surgery or disease of the stomach, pancreas, or ileum also will cause deficiency.[8] The normal processes of cobalamin absorption are shown in Fig. 150-1.

The incidence of pernicious anemia is reported to range from 1 to 50 per 100,000 persons per year, depending on the criteria used for diagnosis. The prevalence has been described as 50 to 4000 cases per 100,000 persons, again depending on diagnostic criteria. Pernicious anemia becomes more common with age, and the highest prevalence occurs in persons of African or European ancestry with lower incidence and prevalence in East Asians.[9] Mild atrophic gastritis with protein-bound cobalamin malabsorption occurs in up to 20% of older adults, particularly Whites. Dietary cobalamin deficiency is population dependent, but can range from 30 to 50% in areas of South America, Africa, and India.

Folate Deficiency

In contrast to cobalamin, folates are abundant in foods of plant origin and are also found in dairy and organ meats. Folates are susceptible to loss in cooking, particularly if the cooking water is discarded and not incorporated into the dish. Populations with limited access to or distaste for vegetables, legumes, or fruits may have folate deficiency. Alcohol and some other drugs interfere with folate absorption or promote excretion and are major causes of folate deficiency seen clinically. Folates are absorbed mainly in the upper small

TABLE 150-1 CAUSES OF MACROCYTOSIS

NONMEGALOBLASTIC DISORDERS
Reticulocytosis
Alcohol abuse/heavy use
Chronic liver disease
Thyroid disorders (hypothyroidism)
Chronic lung disease with hypoxemia
Cold agglutinins and paraproteinemias
Hyperglycemia
Primary bone marrow disorders (e.g., myelodysplasia)
MEGALOBLASTIC ANEMIAS (SEE TABLE 150-2)
Cobalamin (vitamin B_{12}) deficiency
Folate deficiency
Other megaloblastic anemias

TABLE 150-2 CAUSES OF MEGALOBLASTIC ANEMIA

COBALAMIN (VITAMIN B_{12}) DEFICIENCY
Lack of intrinsic factor
Pernicious anemia (type A gastritis)
Gastrectomy, gastric bypass
Congenital defect in gastric intrinsic factor
Food cobalamin malabsorption
Atrophic gastritis (type B gastritis)
Gastric or achlorhydria
Exocrine pancreatic dysfunction
Disorders of the distal ileum
Surgical resection of distal 1-2 ft.
Inflammatory bowel disease
Surgical reconstruction—ileal conduit or cystoplasty
Congenital defects of cubam receptor (Imerslund-Gräsbeck syndrome)
Usurpation of intestinal cobalamin
Tropical sprue, bacterial overgrowth, blind loops
Parasitic infection—*Diphyllobothrium latum* and *Giardia lamblia*
Nutritional cobalamin deficiency
Breast-fed infant of a deficient mother
Diet lacking animal source food, such as vegan, lacto-ovo vegetarian, or impoverished low-meat diet
Drug-induced cobalamin deficiency
Nitrous oxide abuse or anesthesia in a cobalamin-deficient patient
Metformin, histamine blocking or proton pump inhibitor drugs
Inborn errors of cobalamin metabolism
Transport—transcobalamin deficiency
Cellular metabolism—mutations that cause combined methylmalonic acidemia and homocystinuria (CblC-J)
FOLATE DEFICIENCY
Nutritional folate deficiency
Lack of fresh fruit, green leafy vegetables, legumes, organ meats
Anorexia nervosa and other eating disorders
Alcohol abuse combined with poor nutrition
Folate malabsorption
Celiac or tropical sprue
Crohn disease and other small intestinal diseases
Increased demand or loss
Pregnancy
Hemolytic anemias
Proliferative skin diseases
Leukemias
Hemodialysis
Drug-caused folate deficiency
Antifolates—methotrexate, pemetrexed, pralatrexate, pyrimethamine, sulfasalazine, trimethoprim
Anticonvulsants—phenytoin, carbamazepine, valproic acid
Methylation-requiring drugs—L-Dopa, high-dose niacin, α-lipoic acid
Inborn errors of folate metabolism
MTHFD1 deficiency
PCFT (*SLC46A1*) mutation
MEGALOBLASTIC ANEMIA NOT DUE TO COBALAMIN OR FOLATE DEFICIENCY
Inborn errors
Thiamine responsive megaloblastic anemia (*SLC19A2* mutation)
Hereditary orotic aciduria
Lesch-Nyhan syndrome
Drugs affecting DNA synthesis
Cancer chemotherapy—hydroxyurea, azathioprine, others
Antiretrovirals—zidovudine, stavudine
Tyrosine kinase inhibitors—imatinib, sunitinib, others

CblC-J = cobalamin C, D, E, F, G, and J (defects); MTHFD1 = methylenetetrahydrofolate dehydrogenase 1; PCFT = proton-coupled folate transporter.

ABSTRACT

The most common causes of megaloblastic anemia are cobalamin (B_{12}) or folate deficiencies. Methylmalonic acid is the most sensitive and specific marker of cobalamin deficiency. Folate deficiency is rare in countries with folate-fortified food sources and is usually associated with alcohol abuse. Cobalamin deficiency can be treated with injections or high-dose oral preparations. The severity of myeloneuropathy due to cobalamin deficiency is inversely related to the severity of megaloblastic anemia, but the myelopathy is reversible if treated early.

KEYWORDS

vitamin B_{12}
cobalamin
folate
methylmalonic acid
homocysteine

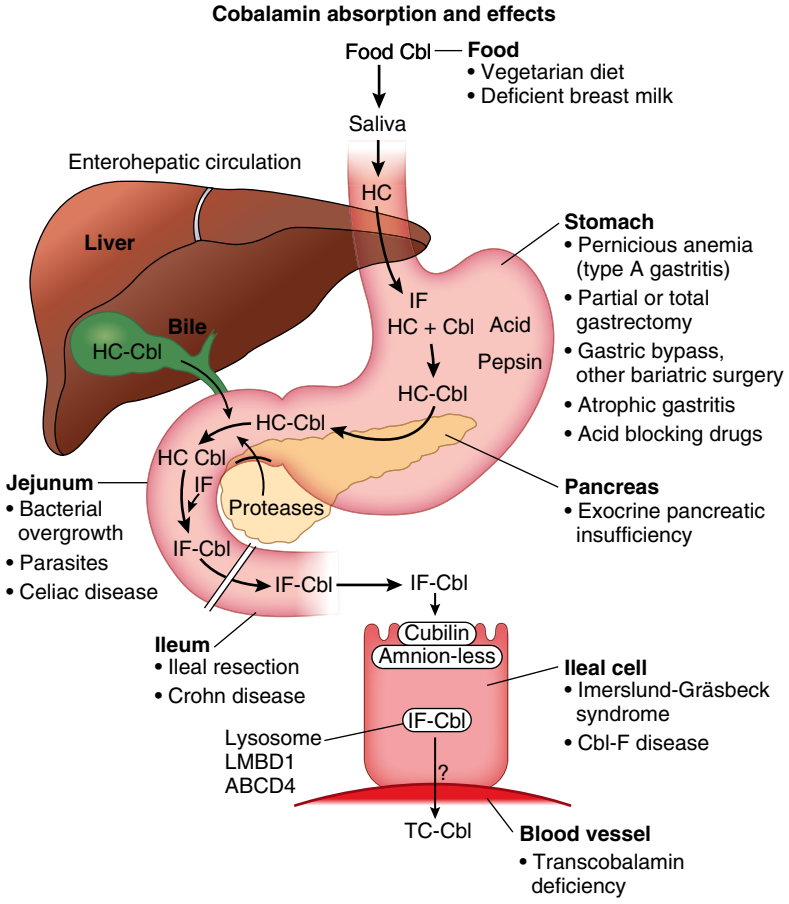

FIGURE 150-1. The normal processes of cobalamin (Cbl) absorption and associated defects are shown. ABCD4 = ATP binding cassette subfamily D member 4 (defect); Cbl = cobalamin; Cbl-F = cobalamin F (defect); HC = haptocorrin (also called R-protein or R-factor); IF = intrinsic factor; LMBD1 = probable lysosomal cobalamin transporter (defect); TC = transcobalamin. (Adapted from Stabler SP. Megaloblastic anemias: pernicious anemia and folate deficiency. In: Young NS, Green SL, High KA, eds. *Clinical Hematology*, Philadelphia: Mosby Elsevier; 2006:242-251.)

intestine; thus, diseases such as celiac or tropical sprue, bacterial overgrowth, or inflammatory bowel diseases are complicated by clinical folate deficiency. Many countries including the United States, Canada, Chile, Costa Rica, and South Africa have fortified grain products with folic acid. This has virtually eliminated folate deficiency except in those persons with impaired absorption or high alcohol intake. Countries without fortification may have a significant folate-deficient population depending on customary dietary food patterns which in resource-poor countries provide less than 50% of recommended folate intake.[10,11]

A recommended daily allowance for folate in the United States is 400 µg for adult men and nonpregnant women. The requirement has been increased to 600 µg for pregnant women and 500 µg for lactating women. Food folates are polyglutamated and are less bioavailable than the synthetic folic acid used to fortify food and supplements, which has made estimation of total folate intake more difficult in fortified populations.

PATHOBIOLOGY

Cobalamin

Cobalamin is necessary for only two enzymatic reactions in higher animals. In one reaction methyl-cobalamin is a cofactor for the enzyme methionine synthase, which uses methyl-tetrahydrofolate (methyl-THF) to methylate homocysteine to form methionine. Methionine can be activated to S-adenosylmethionine, which is the methyl donor for many reactions including the important synthesis of creatine, lipids, neurotransmitters, DNA methylation, and many other compounds. The demethylated folate product, THF, is the precursor for the other folate coenzymes. One coenzyme, 5, 10-methyleneTHF, participates in the formation of thymidine from dUMP by thymidylate synthase. Thymidine is critical for DNA synthesis and the accumulation of uracil is harmful; if incorporated into DNA it can cause prolongation of the cell cycle, chromosomal damage, and maturation arrest. Apoptosis may occur due to the impaired DNA repair with cell fragmentation and resulting cell death.

The buildup of methyl-THF, which cannot be converted to THF due to the decrease in methionine synthase activity, is referred to as the "methylfolate trap." This build-up causes a secondary state of folate deficiency in the cobalamin-deficient patient. Methyl-THF is not a good substrate for polyglutamation and therefore it diffuses out of cells and will be lost in the urine. The impairment in methionine synthase activity is the primary cause for the indistinguishable megaloblastic anemia seen with either cobalamin or folate deficiency. When methionine synthase activity is impaired, serum homocysteine levels increase (Chapter 193).

The second cobalamin-dependent reaction uses adenosyl-cobalamin to convert a product of propionic acid metabolism, L-methylmalonyl-CoA, to succinyl-CoA by the enzyme L-methylmalonyl-CoA mutase. When the mutase is blocked by deficiency of adenosyl-cobalamin, the methylmalonyl-CoA is hydrolyzed to methylmalonic acid, a compound with unknown metabolic fate. Elevated methylmalonic acid has been shown to be a sensitive indicator of impaired mutase activity and thus of cobalamin deficiency in many experimental cellular or animal models as well as in human patients.[12] There are no roles for folate metabolism in this pathway.

Cobalamin Absorption

The cobalamin in unfortified food consists of the coenzyme forms bound to the two enzymes. Because there are only trace amounts of cobalamin (average 4 to 6 µg in omnivorous diets) there is a multistep process involving binding proteins and receptors to provide for absorption of the vitamin. The normal processes of absorption are shown in Fig. 150-1 and reviewed elsewhere in detail. Food is mixed with saliva and digested in the stomach where pepsin and gastric acid release cobalamin from the food protein allowing it to bind to haptocorrin (HC), also called R-protein or R-factor, a glycoprotein present in saliva. The HC-cobalamin complex moves to the duodenum where it is joined by HC-cobalamin recycled from bile. Pancreatic proteases with bicarbonate digest the HC releasing cobalamin to be bound by intrinsic factor (IF), which had been secreted by the gastric parietal cells. IF binding is specific for true cobalamin and does not bind the cobalamin analogues found widely in the

environment. The IF-cobalamin complex travels to the distal ileum where it is bound by the cubam receptor, a complex of cubilin and amnionless. The IF-cobalamin complex is internalized in lysosomes and two specific exporters (products of the LMBD1 and ABCD4 genes) are required to export it into the cytoplasm. Eventually cobalamin is bound to transcobalamin (TC), which is the physiologic delivery protein. A specific transcobalamin receptor (CD 320) facilitates cellular uptake wherein the TC is degraded by lysosomes and the cobalamin becomes available for intracellular processes. There are many intracellular transporters and enzymes responsible for the eventual appearance of the coenzyme forms of methyl-cobalamin on methionine synthase and adenosyl-cobalamin on L-methylmalonyl-Co-A mutase. The study of congenital defects in these enzymes, which are designated Cbl A-Cbl J, has elucidated much of this complicated metabolism. Some of these disorders are included in Table 150-2.

Cobalamin Transport

About 80% of total cobalamin in blood is bound to HC and only 10 to 20% to the delivery protein, TC. TC is known to be the most important carrier because inborn errors in TC lead to infantile megaloblastic anemia and severe disability. In contrast, deficiencies of HC are moderately common and do not appear to result in disease. HC binds analogues of cobalamin that are abundant in the human colon, foods, and the environment and may have a role in sequestering the analogues to facilitate their excretion. HC is present in white blood cells such as granulocytes. HC-cobalamin is taken up by the asialoglycoprotein receptors in the liver, which may facilitate the removal of analogues by secretion into the bile. There are problems in interpreting total cobalamin values because the cobalamin bound to TC is a small part of the circulating total, as discussed in the section on Diagnosis.

Malabsorption of Cobalamin as a Cause of Deficiency

Pernicious Anemia

Pernicious anemia was recognized many decades before cobalamin was identified because of the histamine-fast achlorhydria found in some patients with fatal progressive macrocytic pancytopenia. It is misnamed because it is a gastric disease, and many patients may not even have anemia. Pernicious anemia is due to a chronic inflammatory attack on the mucosa of the fundus and body of the stomach in which there are inflammatory infiltrates and an immune response to gastric H/K ATPase in the parietal cells. With atrophy of the gastric mucosa there is loss of the gastric parietal cells which produce IF in addition to stomach acid. This type A gastritis takes many years to develop and initially may cause iron deficiency anemia before the lesion is severe enough to result in the loss of IF.

Patients may produce anti-intrinsic factor antibodies, which can also block absorption of cobalamin. The cobalamin secreted into bile is lost in pernicious anemia because there is no IF in the duodenum to bind the cobalamin. Thus, instead of the usual normal loss of about 1 μg of cobalamin per day there may be 5 to 9 μg lost, greatly shortening the time to develop deficiency.

Helicobacter pylori is another cause of chronic gastritis, although it mostly affects the antrum of the stomach (Type B gastritis). Whether *H. pylori* plays a role in the progression of pernicious anemia and cobalamin deficiency is still undefined.

Pernicious anemia is found in association with other autoimmune disorders such as endocrinopathies like autoimmune thyroid disease, type I diabetes mellitus, and vitiligo. Relatives of patients with pernicious anemia may have the full spectrum of autoimmune diseases. The relationship between Graves disease and pernicious anemia is especially strong with about a quarter of the patients having both illnesses. It is important that women with autoimmune thyroid disease have adequate cobalamin status prior to pregnancy and throughout lactation.

Protein-Bound Cobalamin Malabsorption

Less severe forms of gastric atrophy appear in older adults, most frequently in those of European ancestry, wherein a loss of pepsin and gastric acid prevents the total release of cobalamin[13] from protein binding in food. Stomach acid–blocking medications may also impair the absorption of protein-bound cobalamin. The actual risk is uncertain because these medications are used frequently in an aging population that also has age-related gastric atrophy. Patients with gastric atrophy may be identified by serum markers as discussed in the Diagnosis section.

Cobalamin Malabsorption Due to Surgery

Total gastrectomy invariably results in severe cobalamin deficiency due to the loss of IF after 1 to 5 years depending on the underlying status of cobalamin stores. Bariatric surgery such as the Roux-en-Y gastric bypass and sleeve gastrectomy cause the food-cobalamin stream to be separated from the cells secreting IF because the stomach is bypassed. The cubam receptor is present in the distal 1 to 2 feet of ileum, so its loss due to inflammatory bowel disease or the surgical use of distal ileum to create an ileal conduit diversion or ileal cystoplasty causes cobalamin deficiency.

Other Causes of Malabsorption

Exocrine pancreatic dysfunction may cause failure of digestion of HC and release of cobalamin for binding by IF. Bacterial overgrowth as seen in tropical sprue has been shown to cause both cobalamin and folate deficiency. Infestation with a freshwater fish tapeworm, *Diphyllobothrium latum*, is an uncommon cause of usurpation of cobalamin in the duodenum. *Giardia lamblia* is a more common protozoal intestinal infection that may cause decreased cobalamin absorption.

Congenital Malabsorption of Cobalamin

Abnormal gastric IF (GIF) manifests as megaloblastic anemia in infancy or childhood, depending on the underlying cobalamin status at birth. Much more common disorders include mutations in the cubam receptor which have been found in either the cubilin or amnionless protein. This was initially described in Scandinavia and was given the name Imerslund-Gräsbeck disease, but it is particularly common in the Middle East. It is not known whether heterozygotes for these mutations might be more predisposed to nutritionally or atrophic gastritis-induced cobalamin deficiency.

Cobalamin Deficiency Due to Drugs

Many studies have reported on the effects of metformin on cobalamin status. Although it does appear to decrease serum cobalamin levels and may cause malabsorption in the ileum, it is not known whether it can induce full-blown megaloblastic anemia. The anesthetic agent nitrous oxide is a definite cause of cobalamin deficiency, usually manifesting as myeloneuropathy. The gas inactivates methionine-synthase and increases excretion of cobalamin, therefore repeated use induces a severe deficiency. Prolonged continuous use will cause bone marrow aplasia in about 10 days. Persons at risk are often employed in dental or medical offices where nitrous oxide is available or abuse nitrous oxide–containing whipping cream dispensers. There are also reports of a subacute neurologic progression of cobalamin deficiency occurring in patients with unrecognized pernicious anemia after only one episode of nitrous oxide anesthesia, symptoms occurring over days to weeks.[14] Often neurologic damage is permanent despite adequate replacement with cobalamin.

Folate

Folate Metabolism

The role of methyl-THF as a cofactor for methionine synthase was described above. However, there are other folate coenzymes that function as cofactors for many enzymes involved in amino acid metabolism, purine synthesis, methylation reactions, one carbon metabolism, and regulatory functions. Inhibition of these reactions due to folate deficiency can cause decreased cellular growth and proliferation, which is exploited in the use of antifolates for cancer chemotherapy. One cellular form, 5,10-methyleneTHF, is at a branch point to be used by thymidylate synthase to produce the thymidine necessary for DNA synthesis, or is reduced irreversibly by 5,10-methylenetetrahydrofolate reductase (MTHFR) to methyl-THF. As discussed above, methyl-THF must be converted by cobalamin-dependent methionine synthase before the folate can be used in other reactions. A common polymorphism in MTHFR (C677T), known as the thermolabile mutation, renders the enzyme somewhat less efficient and results in higher homocysteine and lower folate levels when folate intake is low. The prevalence of the polymorphism is quite variable, ranging from less than 1% in Africans to 30% in Mediterranean, Mexican, and northern Chinese populations. Its association with risk for various human disorders has been extensively studied but not clearly defined. The polymorphism changes the proportions of folate coenzyme forms, decreasing methyl-THF, and thus circulating folate levels. The increase in homocysteine levels and decrease in folate levels is most apparent in populations on low or marginal folate intakes.

Folate Absorption and Transport

Natural food folates are polyglutamated and must be hydrolyzed by an upper small intestinal brush border enzyme, folylpolyglutamate hydrolase. Folate monoglutamate is transported into the cells by a surface protein–coupled folate transporter (PCFT). Folic acid (nonreduced folate), a stable form, is used in supplements and fortified grains and has a bioavailability of about 90%. Folic

acid is reduced to THF and then methylated and released into the plasma. The reduced folate carrier (RFC, solute carrier family, SLC19A1) transports folates into and out of the cell. Absorbed folates in the portal circulation are taken up in the liver, polyglutamated, and retained or released into the circulation or bile. Circulating folates are bound to proteins, particularly albumin. Red blood cells accumulate folates during erythropoiesis, and thus the red cell folate level may more constantly reflect long-term folate status than serum folate. Concentrations of folates in CSF are three-fold higher than in blood, and the choroid plexus has abundant receptors for uptake and transport.

Causes of Nutritional Folate Deficiency

Nutritional folate deficiency occurs in the areas of the world that do not currently have folate food fortification. The foods containing the highest amount of naturally occurring folate are dark green leafy vegetables, beans and other legumes, nuts, orange juice, and liver or other organ meats. Potatoes, many fruits, and eggs have moderate amounts of folate but dairy items and muscle meat are much lower in folate. In high-resource countries, cereals, snack bars, sport drinks, and other foods promoted for health and exercise are often fortified with folic acid. Natural food folate intake has been estimated to be roughly 200 μg/day with an extra 200 μg in nonsupplement users from the added folic acid in fortified grains in persons in the United States. Total folate in supplement users was much higher, between 700 to 1000 μg per day. Low serum folate was found in approximately 15% in surveys of the U.S. population prior to the food folate fortification program. Nutritional folate deficiency is common in areas of the world with limited opportunity for consumption of fresh vegetable foods and is particularly a problem for women of childbearing age who require increased quantities to prevent folate deficiency–associated pregnancy complications. Folate-deficient diets are often deficient in other nutrients such as vitamin C, iron, and other vitamins and minerals.

Malabsorption of Folate

The serum folate level decreases within 3 weeks of severe folate malnutrition or malabsorption and megaloblastic bone marrow changes occur after 15 to 20 weeks. Folate malabsorption occurs in diseases of the upper small intestine and is rarely seen after gastrectomy or with Roux-en-Y gastric bypass. Celiac disease, which causes villous atrophy of the small intestine, causes folate deficiency in up to half of the patients. Tropical sprue, a cause of chronic diarrhea and progressive small intestinal villous atrophy, also causes folate deficiency with or without cobalamin deficiency. Inflammatory bowel disease, particularly Crohn disease, causes folate deficiency in addition to iron and vitamin B_{12} deficiency.

Conditions with Increased Folate Requirements

Diseases in which there is increased cellular proliferation may result in folate depletion. This includes skin diseases such as psoriasis and chronic hemolytic anemias, particularly sickle cell disease. Folates and other water-soluble vitamins are lost during renal hemodialysis.

Alcohol and Folate Deficiency

Alcohol abuse is the most common cause of folate deficiency manifesting megaloblastic anemia. Even well-nourished alcoholics may have macrocytosis and elevated homocysteine values, often when serum folate and hemoglobin are still normal. Alcohol-induced impairment of folate metabolism is exacerbated by poor nutrition. Megaloblastic anemia due to alcohol-associated folate deficiency still occurs despite the food folate fortification program in the United States. Folate-deficient alcoholics have been shown to have impaired intestinal absorption of folate, oxidative destruction of folates, impaired hepatic uptake, reduced storage, and enhanced renal excretion. Effects on the enzymes of methionine metabolism, particularly methionine synthase, are likely due to the toxic metabolites of ethanol. It may be difficult to recognize megaloblastic anemia in alcoholics because their frequently coexisting iron deficiency due to gastrointestinal bleeding may mask macrocytosis. In addition, alcohol induces sideroblastic anemia, an iron utilization defect, which can also mask macrocytosis. Nonalcohol related causes of cirrhosis can cause macrocytosis due to membrane abnormalities in the red cells, even with adequate folates.

Drugs That Cause Folate Deficiency

There are many drugs that interfere with folate metabolism (Table 150-2). The anticonvulsants, particularly carbamazepine, phenytoin, valproate, and phenobarbital have all been shown to cause macrocytosis, folate depletion, and hyperhomocysteinemia. Folic acid supplements improve folate status without preventing the antiseizure efficacy. There are many antifolates in common use, being exploited for their inhibitory effect on cellular proliferation such as methotrexate, pemetrexed, and pralatrexate used in cancer chemotherapy and in rheumatic diseases. It is interesting that the beneficial effect of methotrexate in rheumatoid arthritis is not counteracted by providing supplemental folic acid. Some antibiotics such as trimethoprim, pyrimethamine, and some sulfa derivatives are antifolates. Sulfasalazine used for inflammatory bowel disease will also cause folate depletion. Functional folate deficiency can be induced by drugs that require methylation for metabolism by depleting the normal stores of methyl groups. Drugs such as L-dopa, high-dose niacin, and an over-the-counter agent, α-lipoic acid, all raise homocysteine.

Inborn Errors of Folate Metabolism

There are two inborn errors of folate that present as megaloblastic anemia: methylenetetrahydrofolate dehydrogenase deficiency (MTHFD1) and hereditary folate malabsorption due to mutations in the protein-coupled folate transporter (PCFT). MTHFD1 deficiency has been found in six infants and children with megaloblastic anemia, immunodeficiency, or inflammatory conditions and hyperhomocysteinemia. Treatment with high doses of folic acid or folinic acid were beneficial in several of the patients. It is not yet known whether this disorder will be found in adult medicine.

Severe deficiencies of MTHFR (not the common thermolabile polymorphism) cause hyperhomocysteinemia with low methionine, but **not** megaloblastic anemia. These patients may present with thrombotic complications of hyperhomocysteinemia (Chapter 67) and neurologic deficits (Chapter 384). Treatment with betaine and folic acid greatly improves the prognosis.

CLINICAL MANIFESTATIONS

Definition of Macrocytosis

The best definition of macrocytosis is red blood cell mean cell volume (MCV) that is higher than the expected value for any individual patient. Clinicians who rely on laboratory reported ranges such as 80 to 100 fL will make errors in diagnosis because the MCV is affected by ethnicity and age. For instance, 30% of persons with African ancestry in the United States have one deleted α hemoglobin subunit and their median MCV is about 84 fL. It would take much longer for these individuals to increase the MCV to greater than 100 fL than someone whose normal MCV was 92 fL. Persons with β-thalassemia trait, hemoglobin E, and iron deficiency will also not usually have an increase in MCV to more than 100 fL despite the coexistence of severe megaloblastic anemia. Individuals with a combination of microcytic red cell indices and megaloblastosis may have oval macrocytes visible on the peripheral blood smear and a high red cell distribution width (RDW).

The causes of macrocytosis are shown in Table 150-1. As indicated, macrocytosis is not equivalent to megaloblastosis: there are many causes of macrocytic peripheral red blood cell indices that are not associated with a megaloblastic state. Reticulocytes, newly released red cells that are less than 24 hours old, are at their largest size and decrease as they age over 120 days in the circulation. Thus, reticulocytosis will increase the MCV, in many cases to over 100 fL. A rise in MCV may be the first sign of autoimmune hemolytic anemia and is also commonly found in patients with fragmentation anemia, sickle cell anemia, or with hemolysis due to infectious agents. Macrocytosis can be seen in patients who are post-splenectomy or have liver disease of any type, especially with associated alcoholism. Severe portal hypertension causes macrocytosis with thrombocytopenia and leukopenia mimicking a true megaloblastic anemia when examining only the peripheral blood smear. Chronic lung disease, particularly with associated hypoxia-induced polycythemia, is frequently macrocytic. Hypothyroidism and severe hyperglycemia also cause macrocytosis. The primary bone marrow disorders such as aplastic anemia, pure red cell aplasia, myelodysplastic syndrome, idiopathic myelofibrosis, and multiple myeloma may cause striking macrocytosis, with or without associated cytopenias. Cold agglutinins and paraproteinemias cause red cell clumping, which may lead to rouleau formation that can cause an erroneously high MCV. Drugs with effects on DNA synthesis, such as antiretrovirals, chemotherapy agents, and antifolates, cause macrocytosis.

Complications of Megaloblastic Anemias

Examples of peripheral blood smears and bone marrow aspirate and biopsy in megaloblastic anemia are shown in Fig. 150-2A-D (also see Chapter 143). The hallmark of megaloblastic pathology in the marrow is that cells are large ("megalo") and their nuclei have not matured ("blastic"); thus there are oval macrocytes and occasionally even a megaloblastic nucleated red blood cell detected on the peripheral blood smear. Other red blood cells are misshapen and fragmented and can be mistaken for schistocytes as seen in fragmentation anemias. There may be thrombocytopenia and leukopenia when

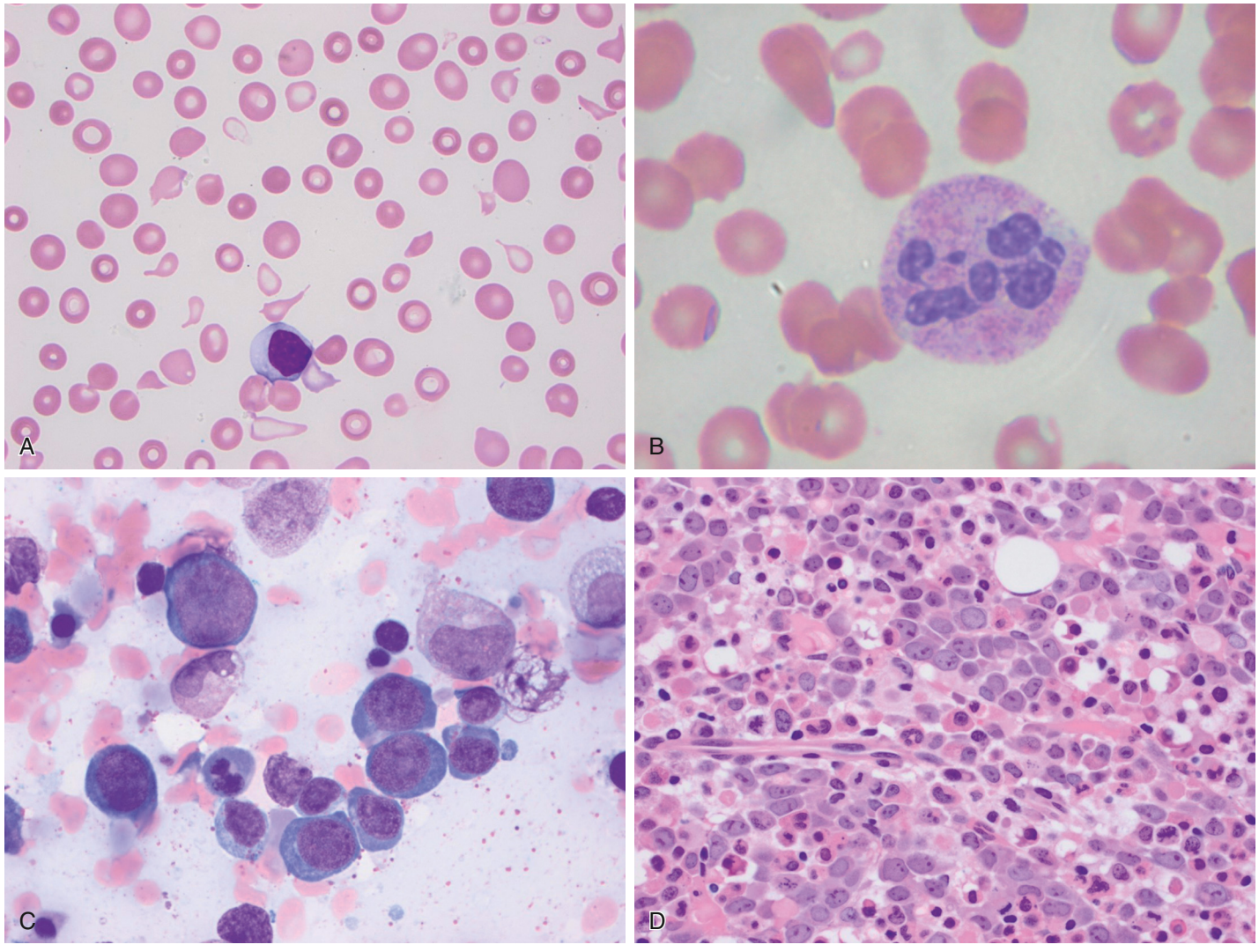

FIGURE 150-2. **Photomicrographs of peripheral smear, bone marrow aspirate, and biopsy are shown. A**, Oval macrocytes and fragmented red blood cells are present in a smear from a patient with severe cobalamin deficiency and thalassemia trait, demonstrating an extreme range in size and shape of the red blood cells. **B**, Hypersegmented neutrophil. **C**, A group of megaloblastic red cell precursors all with an open lacy chromatin pattern is shown from a bone marrow aspirate. Red cell dysplasia and giant metamyelocytes are also present. **D**, The bone marrow biopsy shows hypercellularity with a predominance of large erythroblasts and many mitotic figures, all potentially confused with acute leukemia. The erythroid hyperplasia in the bone marrow of a patient with megaloblastic anemia is due to "ineffective erythropoiesis." (Photomicrographs: 2B courtesy of John W. Ryder, MD, Department of Pathology, University of Colorado School of Medicine; 2 A, C, and D courtesy of Zenggang Pan, MD, PhD, Department of Pathology, University of Colorado School of Medicine.)

anemia becomes severe. Hypersegmented granulocytes are present. The presence of one 6-lobed or five 5-lobed granulocytes per 100 cells is considered abnormal. Some red blood cells may show basophilic stippling. A megaloblastic blood smear with oval macrocytes and fragmented red blood cells with thrombocytopenia has frequently been mistaken for microangiopathic hemolytic anemia such as thrombotic thrombocytopenia, as documented by case reports. Reticulocytopenia in megaloblastic anemias differentiates these microangiopathic-appearing red cells in the peripheral smear from hemolytic anemias. The bone marrow biopsy and aspirate smear is hypercellular with a decreased myeloid : erythroid ratio. There is delayed maturation of erythroblasts, which to the inexperienced observer may even suggest a diagnosis of acute leukemia because they are large cells with open chromatin and blue cytoplasm. The normal process of shrinking and condensing of the nucleus during erythropoiesis is impaired so that the chromatin pattern remains open and lacy (i.e., "megaloblastic"). Although nuclear maturation is delayed, cytoplasmic maturation (e.g., hemoglobinization of the cytoplasm) proceeds unimpaired, leading to the morphologic phenomenon of "nuclear cytoplasmic dissociation." These red cell precursors have poor survival within the bone marrow and pathologic abnormalities suggestive of cellular dysplasia with nuclear fragments in the red cells are present. The cellular apoptosis causes intramedullary hemolysis or "ineffective erythropoiesis." Maturation of white cell precursors is delayed, producing giant metamyelocytes and bands. Flow cytometry of the bone marrow demonstrates left shifts in erythroblasts and white cell precursors which again could lead the unwary to diagnose acute leukemia. Cytogenetic studies may show chromosomal fragmentation and in some cases even clonal abnormalities which correct with vitamin replacement and resolution of megaloblastic anemia.

Intramedullary hemolysis causes indirect hyperbilirubinemia, low serum haptoglobin, and sometimes extreme values for lactate dehydrogenase. The presence of markers of hemolysis and fragmented cells on a peripheral blood smear accompanied by a normal instead of low reticulocyte count can mimic hemolytic anemia. Furthermore, defects of cobalamin metabolism, such as a cobalamin-C mutation, can present with the hemolytic-uremic syndrome.

Other tissues that have rapid cellular turnover may become likewise megaloblastic. This abnormality is particularly common in the gastrointestinal tract, where it sometimes causes malabsorption. Cells of the uterine cervix can become megaloblastic and appear dysplastic. Impairment of spermatogenesis can cause infertility. Atrophy and glossitis of the tongue mucosa may occur. Some individuals may have areas of skin hyperpigmentation.

Neurologic Abnormalities Due to Cobalamin Deficiency

Cobalamin is necessary for the development and initial myelination and maintenance of the spinal cord and brain. Demyelination can be demonstrated on imaging in both brain and spinal cord as depicted schematically in Fig. 150-3. Cobalamin-deficient infants may have delay or failure in normal myelination which occurs during the first year of life. The demyelinating lesion, often termed "subacute combined degeneration," begins with symptoms of symmetric paresthesia, usually in the lower extremities but sometimes involving

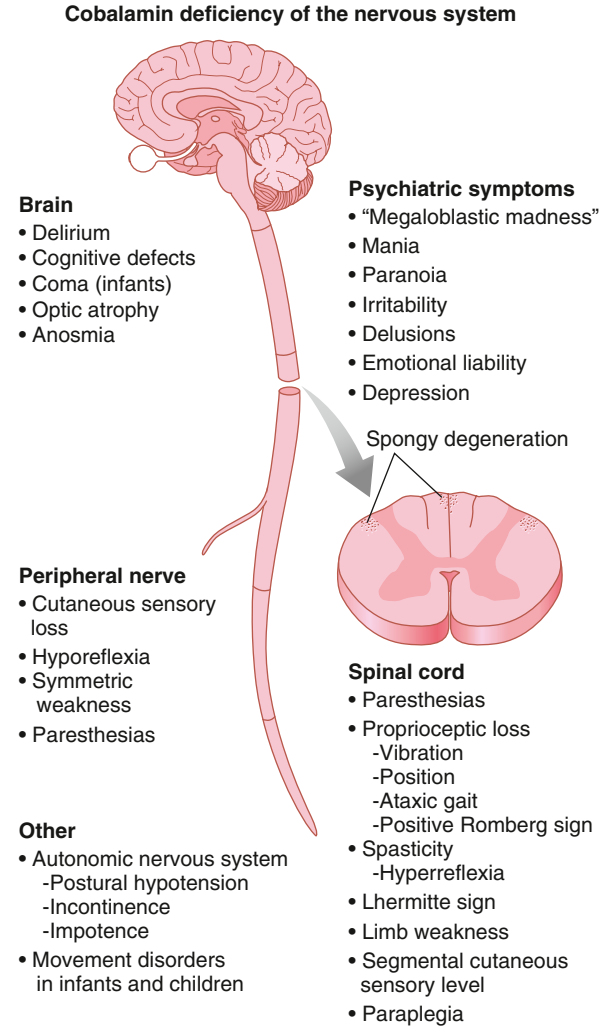

FIGURE 150-3. The myriad symptoms and signs of cobalamin deficiency of the nervous system are shown. These range from paresthesias without objective signs to severe motor loss, even quadriplegia. The spongy degeneration shown in the cross-section depiction of the spinal cord may be seen on magnetic resonance imaging as increased signal intensity on T2 weighted images often described as an inverted "V" sign. Also see Chapter 388. (Adapted from Stabler SP. Megaloblastic anemias: pernicious anemia and folate deficiency. In: Young NS, Green SL, High KA, eds. *Clinical Hematology*, Philadelphia: Mosby Elsevier; 2006:242-251.)

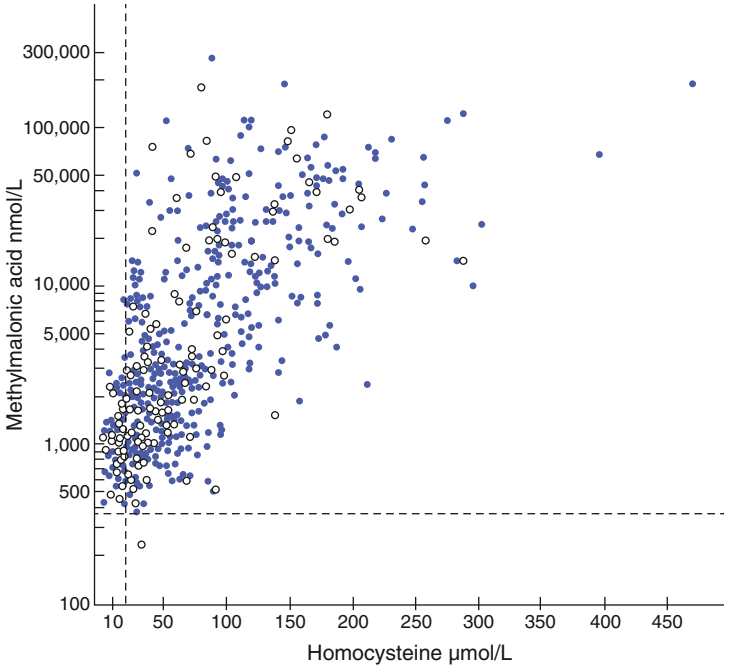

FIGURE 150-4. Serum methylmalonic acid plotted against serum homocysteine in patients with clinically ascertained and documented cobalamin deficiency. The serum methylmalonic acid plotted against homocysteine in about 500 patients with clinically ascertained cobalamin deficiency. Patients had either megaloblastic anemia (closed circles), which in most cases was proven to respond to cobalamin treatment, or a neurologic syndrome compatible with that found in cobalamin deficiency. Those shown as open circles had hematocrit values over 38%. Values were equal for methylmalonic acid and homocysteine whether the patients had anemia or mainly neurologic abnormalities. Methylmalonic acid was greater than 1000 nmol/L in 90% of these clinically proven patients. Hatched lines represent methylmalonic acid 376 nmol/L and homocysteine 21.3 μmol/L. (Previously published in Stabler S. Vitamin B12. In: Erdman, Jr. JW, McDonald IA, Zeisel SH, eds. *Present Knowledge in Nutrition*. 10th ed. Ames, IA: Wiley-Blackwell; 2012.)

the hands first. There is early impairment of proprioception ending with loss of vibration and position sense manifesting as ataxic gait. Other common signs and symptoms are shown in Fig. 150-3. As the severity of the spinal lesions increases weakness develops, with spasticity and hyperreflexia, and eventually patients may develop a segmental cutaneous sensory level and even paraplegia. Altered mental status occasionally occurs particularly with irritability, delusions, paranoia, lability, even mania called "megaloblastic madness" in the past.

The underlying biochemical lesions causing the neurologic disease are still unknown, although changes in lipids, growth factors, cytokines, or methylation status of proteins have all been studied. There is a strong inverse relationship between the severity of the neurologic abnormalities and the hematologic abnormalities. Therefore, the coexistence of anemia is helpful in a patient with a compatible neurologic disorder in suggesting cobalamin deficiency but is not required. Patients with a normal hemoglobin level and a neurologic presentation have similar metabolic abnormalities as do patients with anemia (Fig. 150-4). There is also an inverse relationship between the duration of neurologic abnormalities prior to diagnosis and the completeness of correction after adequate cobalamin replacement, so early diagnosis is imperative (see Chapter 384).

DIAGNOSIS

Cobalamin and Folate Biochemical Assays

Measurement of the serum cobalamin or folate level has been a time-honored method of screening. Original tests have been replaced today with automated assays of cobalamin levels performed on instruments with platforms for multiple analytes. These methods rely on purified intrinsic factor (IF) as the cobalamin binder, often using chemiluminescent microparticle immunoassays for detection. It has been reported that denaturation of anti-IF antibodies present in samples from patients with pernicious anemia can be incomplete, and thus normal to even high values of cobalamin are reported falsely. In general, the values reported from these automated methods are higher than with the historical assays, which complicates comparison of reference ranges. Extremely low values of serum cobalamin (<70 pg/mL) usually reflect deficiency associated with clinical abnormalities that will improve with treatment, but such patients are rare. There is a large equivocal range (100 to 300 pg/mL) in which further testing with metabolites is needed to distinguish between false-positive low and true-positive low or low normal values.

A low serum folate (<3 ng/mL) is clinically significant when found in food folate fortified countries such as the United States. Most authorities have, however, raised the lower limit of the reference range to 5 to 6 ng/mL, values that overlap with the median in populations without fortification. Red blood cell folate should be a good marker of longer-term folate status but the methodology of measuring folate in the presence of the red cell protein matrix has led to poor reproducibility, and the assay cannot be recommended for routine clinical use outside of research investigations.

An assay of the amount of cobalamin bound to transcobalamin, holo-transcobalamin (Holo-TC or "active B_{12}"), is available in Europe and Canada but not yet FDA-approved in the United States. Anti-intrinsic factor antibodies, which are present in pernicious anemia, do not affect this assay, but a polymorphism in the TC gene prevents measurement using this method. Holo-TC increases after oral intake of a large amount of cobalamin and thus is being developed as a test for absorption.

Methylmalonic Acid and Homocysteine Markers of Deficiency

Excess methylmalonic acid is produced when L-methylmalonyl-Co-A mutase is blocked by cobalamin deficiency. Therefore, elevated serum or urine methylmalonic acid has been proven to be a very sensitive indicator of cobalamin status. Patients who have low cobalamin values but normal serum methylmalonic

acid do not respond to treatment and have false-positive low cobalamin levels. The methylmalonic acid value is the first test to become abnormal in infrequently treated patients with proven pernicious anemia. The methylmalonic value decreases immediately after treatment, normalizing within days to weeks. Thus, methylmalonic acid must be assayed prior to treatment. A common clinical error is to treat a patient who likely has a false-positive low cobalamin level and when anemia or the clinical symptoms do not respond, to proceed with assaying methylmalonic acid. After treatment, serum methylmalonic acid normalizes or decreases into the high normal range in seniors (<400 nmol/L) and others with mild renal insufficiency.

Methylmalonic acid values increase above the reference range in renal insufficiency but are usually less than 1000 nmol/L even in patients on renal dialysis. A related metabolite, 2-methylcitric acid, is measured with methylmalonic acid by some commercial testing laboratories and, if higher than the simultaneous methylmalonic acid value, will diagnose renal insufficiency rather than vitamin deficiency. Methylmalonic acid is a product of propionic acid metabolism; thus gut bacterial overgrowth can cause higher values sometimes responsive to antibiotics. A polymorphism in HIBCH, an enzyme in valine catabolism, may cause a mild increase in methylmalonic acid.

Patients with severe inborn errors of cobalamin metabolism rarely normalize methylmalonic acid, even with very intensive parenteral treatment. Such individuals are occasionally detected in adult medicine practices and should be referred to a metabolic center.

Homocysteine

Homocysteine levels increase when either cobalamin or folate deficiency impairs the activity of methionine synthase and cannot be used to distinguish between cobalamin or folate deficiency, because serum homocysteine levels are elevated in 95% of clinically proven folate-deficient individuals. When patients with elevated serum homocysteine levels are treated with the wrong vitamin, the homocysteine level does not decrease. Elevated homocysteine responds to treatment with the correct vitamin very rapidly, often within hours; thus, as in the case of methylmalonic acid, it must be measured prior to any treatment. Even nutritious hospital food may correct elevated homocysteine. Adding vitamins to intravenous fluids for suspected alcoholic patients in the emergency department will correct serum folate levels, and if homocysteine is not assayed rapidly it too will have fallen, yet the patient will still have unexplained megaloblastic anemia. There is a strong relationship between folate intake and homocysteine values in populations that are cobalamin replete. U.S. population serum homocysteine values fell by several μmol/L after folate food fortification. Renal failure increases homocysteine by unclear mechanisms because homocysteine is not dependent on urinary clearance, although the kidney is rich in homocysteine-metabolizing enzymes. Homocysteine can be elevated in hypothyroidism, severe pyridoxine deficiency, and in the presence of antifolate drugs.

If cobalamin is measured because of vague complaints of fatigue and nonspecific neurologic or psychiatric symptoms, most values lower than 200 pg/mL will be false-positive low. The sensitivity of a low cobalamin value (<200 pg/mL) is about 60%.

The sensitivity of a serum methylmalonic acid value higher than 400 nmol/L is about 98% for clinical deficiency, but its specificity for clinical abnormalities is much less because serum methylmalonic acid rises quickly in response to cobalamin depletion. It may be mildly abnormal in patients with other causes of anemia or neurologic syndromes, as seen frequently in seniors or vegetarians. Patients with modest elevations of methylmalonic acid (<700 nmol/L) may not have any clinical syndrome attributable to cobalamin deficiency.

Diagnosis of Pernicious Anemia

Blocking anti-intrinsic factor antibodies are found in 50 to 70% of patients. Anti–parietal cell antibodies are found in a higher percentage (90%) but are less specific because they are found in other autoimmune diseases and forms of gastritis. Demonstration of histamine-fast achlorhydria is rarely performed but is very specific for pernicious anemia. The gastric antrum is spared in pernicious anemia, and the gastrin-producing cells may become hyperplastic. Elevated fasting serum gastrin is suggestive of pernicious anemia. Another marker of the gastric mucosa is pepsinogen-1, which is low in pernicious anemia. These markers, however, are affected by the widespread use of proton pump inhibitor medications. At least a week after a cobalamin injection should elapse before testing for anti-intrinsic factor antibodies.

Endoscopy with gastric biopsy is the best method of diagnosing atrophic gastritis, and some experts recommend that patients with pernicious anemia have at least one screening endoscopy because they are at greater risk for carcinoid tumors and adenocarcinoma of the stomach. This approach would be mandatory for patients who have symptoms consistent with gastric neoplasm or coexisting iron deficiency.

A radio-labeled cobalamin absorption test known as the Schilling test is no longer available. A test using the increase in holo-TC values after three doses of unlabeled oral cobalamin is being investigated and may prove to be a good substitute.

Folate Malabsorption

There are no specific tests for folate malabsorption. The presence of a disease of the upper small intestine such as celiac disease, tropical sprue, or Crohn disease will point to folate malabsorption. Folate deficiency is often associated with iron and multiple other nutrient deficiencies in contrast to cobalamin deficiency due to pernicious anemia.

TREATMENT

Cobalamin Deficiency

The primary goals of treatment of cobalamin deficiency are to restore the normal tissue content of cobalamin (between 2 to 5 mg in an adult human) and prevent relapse. Parenteral administration of either cyano- or hydroxy-cobalamin is rapidly effective. Common treatment regimens in severely symptomatic patients would be daily intramuscular or subcutaneous injection of 1 mg (1000 μg) for 7 days or every other day for 2 weeks, followed by weekly injections for 8 weeks, then monthly. Less symptomatic patients could be loaded with biweekly or weekly doses for 8 weeks followed by monthly administration. Hydroxycobalamin is retained better than cyano-cobalamin and after loading can be given at 2- to 4-month intervals instead of monthly. About 150 μg is retained after an injection of 1 mg, which is why it is necessary to provide multiple injections during the loading treatment phase to achieve the replacement of 2 to 5 mg. However, a single 10,000 μg dose can correct pernicious anemia for at least 3 months.[15] Methylmalonic acid remains elevated in about 20% of pernicious anemia patients injected monthly with cyano-cobalamin, which will normalize with a shorter time interval between injections. There is no toxicity upper limit for cobalamin, and patients may claim that their well-being is enhanced by injections as frequent as every 2 to 3 weeks.

A small percentage (0.5 to 2%) of a high dose of oral cobalamin is absorbed by mass action in the upper intestinal tract without IF or an intact ileum. Randomized trials comparing parenteral and high oral doses (1000 to 2000 μg/day) have shown equivalent clinical correction, rise in serum cobalamin, and normalization of elevated methylmalonic[A1,A2] acid and homocysteine levels.[16] Patients with severe abnormalities should receive at least 2000 μg/day initially, so they absorb 20 to 40 μg/day. High-dose cobalamin tablets containing 500 μg to 2.5 mg dosages are available without prescription in the United States. Physician error is one of the leading causes of discontinuation of treatment in pernicious anemia. Patients should be taught to start self-directed treatment with high-dose oral tablets if denied medical follow-up for cobalamin deficiency. High-dose preparations may be less available in other parts of the world. There are also preparations designed for intranasal or sublingual use, which have been less studied in patients with true pernicious anemia. Patients and providers may have preferences as to cost, convenience, compliance, and comfort relating to injected versus oral treatment.[17]

The alternative cobalamin forms methyl- and adenosyl-cobalamin are also available for replacement but are unstable, converting to the aquo(hydroxy) form on exposure to light. There is no advantage in using these expensive alternatives because they will undergo the same metabolic conversions as does cyano- or hydroxyl-cobalamin. Treatment of neuropathic pain with methylcobalamin may be an exception.[18]

Treatment of Dietary Deficiency

Patients with dietary deficiency should be loaded with high-dose oral or parenteral cobalamin to replete tissue stores (2 to 5 mg). This is crucial for vegetarian women contemplating pregnancy, especially from countries with high prevalence of cobalamin deficiency. The amount of cobalamin in maternal vitamins is too low to replete stores quickly; IF-mediated absorption is limited to 2 to 5 μg per day, so it would take an entire pregnancy to replace 1 to 2 mg, and the infant could be born deficient. The breast-feeding mother should also be loaded to normal stores because her breast milk will be deficient if only small supplements are used. The cobalamin-replete vegetarian can supplement smaller quantities such as in multivitamin tablets (i.e., 3 to 9 μg/day). Persons who avoid animal-source foods are often also deficient in iron and many other vitamins. There is a large literature on methods to improve growth and development of children in resource-poor countries with combinations of protein, iron, folic acid, cobalamin, and other nutrients.

Recommendations for Treatment of Seniors

The incidence of both true pernicious anemia and atrophic gastritis increase with age. The high usage of metformin and stomach acid–blocking drugs is also more prevalent with age, which compounds the potential malabsorption of

cobalamin. Elevated methylmalonic acid, which corrects with cobalamin treatment, is very prevalent (up to 40%) in studies of the oldest old. Theoretically, smaller doses of cobalamin should be effective in patients who still have some residual IF, but studies in seniors have shown that at least 500 μg/day is necessary to correct most individuals with elevated methylmalonic acid. The Food and Nutrition Board recommended that seniors take an unspecified dose of cobalamin daily. It seems prudent to recommend a supplement of at least 1000 μg/day for individuals at risk for malabsorption. Many clinical trials of cobalamin and folate replacement in correcting diseases of aging such as cognitive impairment[A3,19,20] or osteoporosis have been disappointing. A possible exception is a trial of cobalamin in improving nerve conduction in seniors.

Treatment of Folate Deficiency

Because either cobalamin or folate deficiency causes megaloblastic anemia and elevated homocysteine levels, it is important to distinguish which vitamin is deficient or to treat potential deficiency of both. If serum methylmalonic acid is elevated then there is at least cobalamin deficiency (Table 150-3). This consideration is particularly important in countries with food folate fortification where almost all elevated homocysteine is due to cobalamin deficiency and not folate deficiency. Pharmacologic doses of folic acid (i.e., 1 mg daily) can partially correct megaloblastic anemia in cobalamin-deficient anemia, which has been termed "masking of pernicious anemia." Unfortunately, if neurologic lesions are present they will continue to progress and may become irreversible if a cobalamin-deficient patient is treated with only folate. Over-the-counter folic acid supplements are topped at 800 μg in the United States to prevent inadvertent use by patients with pernicious anemia. Prescription doses of 1 to 5 mg daily of oral folic acid are acceptable treatments for replacement. Patients who have ongoing alcoholism, gut malabsorption, hemolytic anemia, or other unknown pathology should remain on replacement indefinitely. Folic acid 1 mg daily can also be given to patients taking methotrexate for rheumatologic disease, or to patients taking niacin or L-dopa to prevent hyperhomocysteinemia. Pretreatment with folic acid and cobalamin is used with the multitargeted antifolate chemotherapy agents. There is no advantage to treating with methyl-THF over folic acid.

Treatment of Hyperhomocysteinemia

Severe hyperhomocysteinemia (homocysteine >50 μmol/L) is a prothrombotic condition whether due to classical homocystinuria, other inborn errors of metabolism, or vitamin deficiency (Chapter 193). There are many case reports of thrombosis as the presenting complaint in pernicious anemia. The association of hyperhomocysteinemia with vascular disease and thrombosis prompted many large trials of folic acid or combination B vitamin (high-dose cobalamin, vitamin B_6, plus folate) therapy in vascular disease, but the trials have not been successful or have been even harmful,[A4] except for a decrease the incidence of stroke in folate-deficient populations.[21] For example, a randomized trial of antihypertensive medication with or without folic acid, 800 μg daily, in China demonstrated a hazard ratio of 0.79 for decreased risk of stroke,[A5] and a trial of high-dose combination cobalamin, folic acid, and vitamin B_6 in high-altitude soldiers in India decreased thrombotic events by 54%.[A6] Beneficial effects of folic acid or combination B vitamin treatment are easier to prove in populations that are not already eating folate fortified food. Trials in patients with renal failure, especially on dialysis, have not shown benefit in homocysteine lowering and perhaps harm in diabetic kidney disease.

Any patient with extreme hyperhomocysteinemia (>100 μmol/L) should be investigated thoroughly with assay of methylmalonic acid and methionine and a documented response to treatment after replacement. Patients with milder types of pyridoxine-responsive classic homocystinuria may present in adulthood with thrombotic disease, although not with megaloblastic anemia. All patients with nonresponsive hyperhomocysteinemia should be referred to a metabolic center.

TABLE 150-3 USING METABOLITES TO DIAGNOSE COBALAMIN AND FOLATE DEFICIENCY

If methylmalonic acid is elevated >400 nmol/L, consider cobalamin deficiency
If homocysteine is elevated >14 μmol/L, then consider either cobalamin or folate or both deficiencies
Pretreatment metabolite testing will distinguish between true-positive and false-positive low cobalamin values
Metabolite testing is prudent in severe anemia/pancytopenia or demyelinating central nervous system disease regardless of vitamin levels

PREVENTION

Severe consequences of cobalamin deficiency can be prevented by investigating those patients at highest risk, which includes patients with autoimmune thyroid disease, vitiligo, history of gastrointestinal surgery, and family histories of pernicious anemia and autoimmunity. The tragedy of the cobalamin-deficient breast-fed infant should be completely avoidable if attention is paid to the prepregnancy cobalamin status of women who are at risk for deficiency especially with Graves or other autoimmune thyroid disease, vitiligo, status post bariatric or other gastrointestinal surgery, inflammatory bowel disease, and those who avoid animal-source foods. Women who limit animal-source food and immigrants from countries with known cobalamin deficiency should be proven to be cobalamin replete prior to pregnancy. Newborn screening programs using tandem mass spectrometry have revealed that there are as many infants with nutritional cobalamin deficiency as with the inborn errors of cobalamin metabolism. It is possible that prompt treatment of these infants will prevent the worst of the growth failure and neurodevelopmental abnormalities seen when they are discovered later.[22]

The widespread cobalamin and other micronutrient deficiencies in resource-poor areas of the world and in populations who shun animal-source foods is a difficult problem. Increasing meat, dairy, and other animal foods is an expensive approach for populations eating mostly plant-based proteins. Some fermented plant foods such as enset, tempeh, and algae derivatives do contain cobalamin although the concentrations are likely variable. Innovative approaches such as supplementing toothpaste have been tested and could potentially be useful.[A7] Another approach such as fortifying tea bags in India with both cobalamin and folic acid might be useful.

Prevention of Folate Deficiency

Folate food fortification, which has been adopted by many countries, can effectively raise folate levels.[A8] The programs were designed to increase folate status in women to prevent neural tube defects. Neural tube defects have decreased by 25 to 50% depending on the preexisting folate status of the population. Despite food fortification, women of childbearing age in the United States are recommended to take supplements of 400 μg of folic acid daily. Prenatal vitamins are fortified with folic acid at 1 mg/day and are recommended prior to conception and throughout gestation and breastfeeding. Folic acid supplements of 1 mg daily should be given to patients with inflammatory bowel disease, celiac disease, on methotrexate or older anticonvulsants, and to those with chronic hemolytic anemias. Dietary folate deficiency can be corrected by adding green leafy vegetables, legumes, fruits, and organ meats to the diet.

PROGNOSIS

Megaloblastic Anemia

Megaloblastic anemia due to cobalamin or folate deficiency should correct completely with the appropriate vitamin so long as there are no comorbidities. There is an increase in reticulocyte count within 5 days, and the hemoglobin normalizes by 1 to 2 months. Some patients can produce a unit of blood per week with replacement. Thrombocytopenia and leukopenia also correct within the first 2 weeks. Iron deficiency will manifest as a blunting of the hemoglobin response, a fall in MCV into the microcytic range, and a decrease in serum ferritin and iron saturation. The anemia of chronic renal failure may coexist in seniors with cobalamin deficiency and could be treated if appropriate with erythropoiesis-stimulating agents (Chapter 116). Patients with intestinal diseases may need combination cobalamin and folic acid treatment.

The most likely diagnosis in a failure of vitamin treatment is that of an incorrect diagnosis due to a false-positive low vitamin level. There may be cobalamin deficiency with coexisting myelodysplastic syndrome or other bone marrow disease. Folate-deficient alcoholics often have multifactorial anemia and a prolonged period of abstinence with folic acid treatment may be required, especially if the bone marrow is sideroblastic.

Correction of glossitis and other megaloblastic abnormalities in the intestinal tract may manifest as positive weight gain in malnourished patients.

Recurrent macrocytosis or anemia during adequate cobalamin replacement may suggest associated autoimmune disease, particularly thyroid disorders or autoimmune hemolytic anemia. Recurrent iron deficiency due to malabsorption from achlorhydria could be a continuing problem, especially pertinent in patients who have undergone bariatric surgery.

Cobalamin Deficiency of the Central Nervous System

The demyelinating nervous system pathology is not always reversible with cobalamin treatment (Chapter 384). The duration of and severity of symptoms before treatment is inversely correlated with the extent of correction of the abnormalities. Paresthesias and behavioral changes are the quickest and most likely to correct. Spinal cord lesions that have progressed to

severe sensory loss and motor weakness usually do not correct fully. The cobalamin-deficient infant often has residual impairments and permanent disability. There is an occasional patient who develops paresthesias in the first few days after cobalamin replacement, which will resolve with further treatment.

It is important to document elevated methylmalonic acid or homocysteine in a patient who presents without megaloblastic anemia because there is a significant probability of a false-positive low cobalamin level in such patients. Lack of improvement or progression of neurologic symptoms and signs when cobalamin has been adequately replaced is proof that there is another cause for the symptoms. Diseases such as spinal stenosis or multiple sclerosis will not respond to cobalamin replacement, and delay in diagnosis during futile cobalamin therapy may harm the patient.

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For the General References and other additional features, please visit Elsevier eBooks+ at https://ebooks.health.elsevier.com.

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151 APLASTIC ANEMIA AND RELATED BONE MARROW FAILURE STATES

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IDIOPATHIC APLASTIC ANEMIA

DEFINITION

Idiopathic aplastic anemia is a hematopoietic stem cell disorder associated with markedly reduced marrow cellularity and markedly decreased hematopoiesis. The decreased hematopoiesis may disproportionately affect fewer lineages in early stages, but aplastic anemia is ultimately associated with trilineage hypoplasia.

EPIDEMIOLOGY

Aplastic anemia can be inherited or acquired. The majority of cases of acquired aplastic anemia are idiopathic, but causative conditions include viral infections and medications (Table 151-1).

Aplastic anemia is chiefly a disease of children and younger adults, with a second peak in incidence observed in patients age 60 years and older. Aplastic anemia is rare in Western Europe and the United States (fewer than two cases per million population per year). The incidence of aplastic anemia is higher in Asia at five to six cases per million population per year. The higher incidence in Asian countries has been linked to environmental factors such as chemicals or infections more than genetic factors. Both males and females are equally affected.

TABLE 151-1 PRIMARY AND SECONDARY CAUSES OF ACQUIRED APLASTIC ANEMIA

PRIMARY
Idiopathic aplastic anemia
Pregnancy-associated aplastic anemia
Classical paroxysmal nocturnal hemoglobinuria syndrome (Chapter 146)
SECONDARY
Drug associated (see E-Table 151-1)
Iatrogenic/cytotoxic
Radiation-associated
Viruses (Epstein-Barr virus, cytomegalovirus, hepatitis A, B, or C))
Autoimmune (autoimmune hepatitis and pancytopenia of autoimmune disease)

PATHOBIOLOGY

Acquired aplastic anemia is believed to be the result of an autoimmune attack directed at hematopoietic progenitor cells (Chapter 142). The immune attack is primarily directed by cytotoxic T cells that target hematopoietic stem cells and cause apoptosis, thereby leading to hematopoietic failure.[1,2]

Aplastic anemia is most often associated with normal cytogenetics. An abnormal karyotype in a patient with a hypocellular marrow is more consistent with a diagnosis of myelodysplastic syndrome (Chapter 167), although chromosomal abnormalities such as trisomy 8 or deletion 13q may still be consistent with an aplastic anemia diagnosis.

Acquired aplastic anemia generally lacks germline mutations, whereas inherited forms are driven by a germline mutation.[3] About 60 to 70% of idiopathic aplastic anemia patients demonstrate acquired clonality at the time of diagnosis on sensitive next-generation sequencing and array-based karyotyping using comparative genomic hybridization. The clones often remain despite therapies other than hematopoietic stem cell transplant and are frequently the source of relapse and/or progression.

CLINICAL MANIFESTATIONS

At initial presentation, many patients with aplastic anemia manifest symptoms of anemia, including fatigue, weakness, pallor, and headaches. Severe thrombocytopenia (Chapter 158) causes petechiae of the skin and mucous membranes, epistaxis, and/or gum bleeding. Fever and infections can also be seen in the presence of neutropenia (Chapter 153). However, some patients are identified earlier in the course of disease because of cytopenias found on routine laboratory testing before they have any symptoms or signs of the disease.

DIAGNOSIS

The diagnosis of aplastic anemia requires either a bone marrow with <25% of the normal cellularity or bone marrow with <50% normal cellularity in which less than 30% of the cells are hematopoietic. Cellularity is often profoundly decreased (<10%; Fig. 151-1), but small islands of hematopoiesis can be seen. The marrow aspirates in aplastic anemia do not show overt dysplastic changes, and blastic forms are not increased. The peripheral blood in aplastic anemia shows pancytopenia with a relative lymphocytosis, but is otherwise unremarkable.

Idiopathic aplastic anemia is a diagnosis of exclusion, and no single test can consistently distinguish aplastic anemia from other causes of bone marrow failure. However, extensive historical questions, findings on the physical examination, and laboratory diagnostics can help determine the cause of bone marrow failure (Table 151-2). Congenital forms must be excluded, especially in younger patients, prior to making a diagnosis of acquired aplastic anemia.[4] Aplastic anemia must be differentiated from hypoplastic myelodysplastic syndrome (Chapter 167), in which the mutational spectrum overlaps with aplastic anemia, as well as from inherited bone marrow failure disorders for which the phenotypic presentations might be indiscernible.

Aplastic anemia is further classified by the severity of the depression of peripheral blood counts. *Severe aplastic anemia* is defined by depression of blood counts involving at least two hematopoietic lineages (i.e., absolute reticulocyte count <60,000/μL, absolute neutrophil count <500/μL, or a platelet count <2000/μL) and bone marrow hypocellularity (<30%, excluding lymphocytes). *Very severe aplastic anemia* has an absolute neutrophil count of <200/μL, whereas *moderate aplastic anemia* is characterized by depression of blood counts not fulfilling the definition of severe disease (Table 151-3).

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severe sensory loss and motor weakness usually do not correct fully. The cobalamin-deficient infant often has residual impairments and permanent disability. There is an occasional patient who develops paresthesias in the first few days after cobalamin replacement, which will resolve with further treatment.

It is important to document elevated methylmalonic acid or homocysteine in a patient who presents without megaloblastic anemia because there is a significant probability of a false-positive low cobalamin level in such patients. Lack of improvement or progression of neurologic symptoms and signs when cobalamin has been adequately replaced is proof that there is another cause for the symptoms. Diseases such as spinal stenosis or multiple sclerosis will not respond to cobalamin replacement, and delay in diagnosis during futile cobalamin therapy may harm the patient.

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151 APLASTIC ANEMIA AND RELATED BONE MARROW FAILURE STATES

AMY E. DEZERN AND ROBERT A. BRODSKY

IDIOPATHIC APLASTIC ANEMIA

DEFINITION

Idiopathic aplastic anemia is a hematopoietic stem cell disorder associated with markedly reduced marrow cellularity and markedly decreased hematopoiesis. The decreased hematopoiesis may disproportionately affect fewer lineages in early stages, but aplastic anemia is ultimately associated with trilineage hypoplasia.

EPIDEMIOLOGY

Aplastic anemia can be inherited or acquired. The majority of cases of acquired aplastic anemia are idiopathic, but causative conditions include viral infections and medications (Table 151-1).

Aplastic anemia is chiefly a disease of children and younger adults, with a second peak in incidence observed in patients age 60 years and older. Aplastic anemia is rare in Western Europe and the United States (fewer than two cases per million population per year). The incidence of aplastic anemia is higher in Asia at five to six cases per million population per year. The higher incidence in Asian countries has been linked to environmental factors such as chemicals or infections more than genetic factors. Both males and females are equally affected.

TABLE 151-1 PRIMARY AND SECONDARY CAUSES OF ACQUIRED APLASTIC ANEMIA

PRIMARY
Idiopathic aplastic anemia
Pregnancy-associated aplastic anemia
Classical paroxysmal nocturnal hemoglobinuria syndrome (Chapter 146)
SECONDARY
Drug associated (see E-Table 151-1)
Iatrogenic/cytotoxic
Radiation-associated
Viruses (Epstein-Barr virus, cytomegalovirus, hepatitis A, B, or C))
Autoimmune (autoimmune hepatitis and pancytopenia of autoimmune disease)

PATHOBIOLOGY

Acquired aplastic anemia is believed to be the result of an autoimmune attack directed at hematopoietic progenitor cells (Chapter 142). The immune attack is primarily directed by cytotoxic T cells that target hematopoietic stem cells and cause apoptosis, thereby leading to hematopoietic failure.[1,2]

Aplastic anemia is most often associated with normal cytogenetics. An abnormal karyotype in a patient with a hypocellular marrow is more consistent with a diagnosis of myelodysplastic syndrome (Chapter 167), although chromosomal abnormalities such as trisomy 8 or deletion 13q may still be consistent with an aplastic anemia diagnosis.

Acquired aplastic anemia generally lacks germline mutations, whereas inherited forms are driven by a germline mutation.[3] About 60 to 70% of idiopathic aplastic anemia patients demonstrate acquired clonality at the time of diagnosis on sensitive next-generation sequencing and array-based karyotyping using comparative genomic hybridization. The clones often remain despite therapies other than hematopoietic stem cell transplant and are frequently the source of relapse and/or progression.

CLINICAL MANIFESTATIONS

At initial presentation, many patients with aplastic anemia manifest symptoms of anemia, including fatigue, weakness, pallor, and headaches. Severe thrombocytopenia (Chapter 158) causes petechiae of the skin and mucous membranes, epistaxis, and/or gum bleeding. Fever and infections can also be seen in the presence of neutropenia (Chapter 153). However, some patients are identified earlier in the course of disease because of cytopenias found on routine laboratory testing before they have any symptoms or signs of the disease.

DIAGNOSIS

The diagnosis of aplastic anemia requires either a bone marrow with <25% of the normal cellularity or bone marrow with <50% normal cellularity in which less than 30% of the cells are hematopoietic. Cellularity is often profoundly decreased (<10%; Fig. 151-1), but small islands of hematopoiesis can be seen. The marrow aspirates in aplastic anemia do not show overt dysplastic changes, and blastic forms are not increased. The peripheral blood in aplastic anemia shows pancytopenia with a relative lymphocytosis, but is otherwise unremarkable.

Idiopathic aplastic anemia is a diagnosis of exclusion, and no single test can consistently distinguish aplastic anemia from other causes of bone marrow failure. However, extensive historical questions, findings on the physical examination, and laboratory diagnostics can help determine the cause of bone marrow failure (Table 151-2). Congenital forms must be excluded, especially in younger patients, prior to making a diagnosis of acquired aplastic anemia.[4] Aplastic anemia must be differentiated from hypoplastic myelodysplastic syndrome (Chapter 167), in which the mutational spectrum overlaps with aplastic anemia, as well as from inherited bone marrow failure disorders for which the phenotypic presentations might be indiscernible.

Aplastic anemia is further classified by the severity of the depression of peripheral blood counts. *Severe aplastic anemia* is defined by depression of blood counts involving at least two hematopoietic lineages (i.e., absolute reticulocyte count <60,000/μL, absolute neutrophil count <500/μL, or a platelet count <2000/μL) and bone marrow hypocellularity (<30%, excluding lymphocytes). *Very severe aplastic anemia* has an absolute neutrophil count of <200/μL, whereas *moderate aplastic anemia* is characterized by depression of blood counts not fulfilling the definition of severe disease (Table 151-3).

ABSTRACT

Bone marrow failure syndromes are a heterogeneous group of clinically and pathologically distinct disorders associated with cytopenias and a lack of normal hematopoiesis. The clinical and biologic complexity, as well as their overlapping features, can pose a diagnostic and therapeutic challenge. Aplastic anemia is the prototypical disorder of bone marrow failure. Symptoms related to anemia, thrombocytopenia, and neutropenia can result in considerable clinical consequences to patients. Though aplastic and other bone marrow failure conditions are not considered overtly malignant, they confer a significant risk of morbidity and even mortality. Improvement in diagnostic tests, molecular screening, and novel treatments are advancing the care for patients with bone marrow failure syndromes.

KEYWORDS

bone marrow failure
aplastic anemia
paroxysmal nocturnal hemoglobinuria
large granular lymphocytosis
anemia
pure red cell aplasia
Fanconi anemia

E-TABLE 151-1 DRUGS AND TOXINS ASSOCIATED WITH APLASTIC ANEMIA

DOSE DEPENDENT

Antineoplastic Agents
Antimetabolites
Alkylating and cross-linking agents
Cytotoxic antibiotics
Plant alkaloids
Topoisomerase inhibitors

Antimicrobial Agents
Chloramphenicol, dapsone, fluorocytosine

Anti-Inflammatory and Antirheumatic Agents
Colchicine, allopurinol

Insecticides
Chlordane, chlorophenothane (DDT), lindane, parathion

Other Chemicals
Benzene
Benzene-containing chemicals: kerosene, chlorophenols, carbon tetrachloride

DOSE INDEPENDENT
Idiosyncratic, likely immune mediated

Antimicrobial Agents
Chloramphenicol, dapsone, sulfonamides, tetracycline, methicillin, amphotericin, quinacrine, chloroquine, pyrimethamine

Anticonvulsants
Hydantoins, carbamazepine, phenacemide, primidone, ethosuximide

Anti-Inflammatory Agents
Phenylbutazone, indomethacin, ibuprofen, oxyphenbutazone, sulindac, naproxen, dipyrone, piroxicam

Antiarrhythmic Drugs
Quinidine, tocainide, procainamide

Metals
Gold, arsenic, mercury, bismuth

Antihistamines
Cimetidine, ranitidine, chlorpheniramine, pyrilamine, tripelennamine

Diuretics
Acetazolamide, furosemide, chlorothiazide, methazolamide

Hypoglycemic Agents
Chlorpropamide, tolbutamide

Antithyroid Drugs
Propylthiouracil, potassium perchlorate, methylthiouracil, methimazole, carbimazole

Antihypertensive Agents
Methyldopa, enalapril, captopril

Sedatives
Chlordiazepoxide, chlorpromazine, meprobamate, prochlorperazine

From: Bagby GC. Aplastic anemia and related bone marrow failure states. In: Goldman L, Schafer AI. *Goldman-Cecil Medicine*, 26th ed. Philadelphia: Elsevier; 2020.

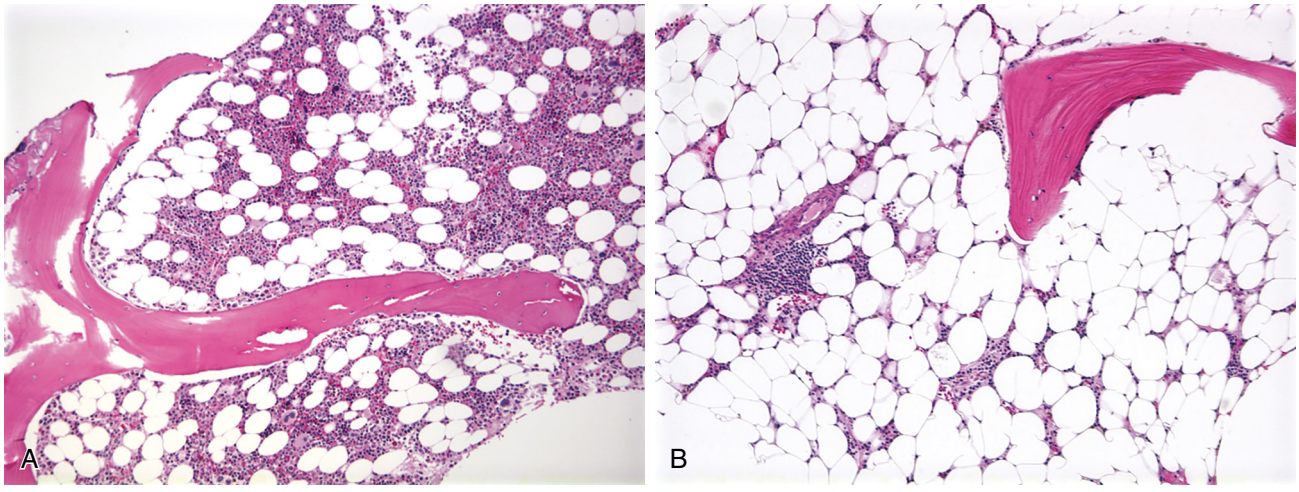

FIGURE 151-1. Two bone marrow biopsy samples from different patients. A, This specimen, from a normal individual, shows an abundance of hematopoietic cells, including myeloid and erythroid precursors and normal-appearing megakaryocytes. **B,** A specimen from a patient with severe aplastic anemia shows few detectable hematopoietic cells, and those that can be seen (one small nest) are lymphocytes. Some lymphoid cells are usually detectable and probably play an important pathophysiologic role in many cases of acquired idiopathic aplastic anemia, a disorder that is most often immunologically mediated. (Courtesy Dr. Ken Gatter, Oregon Health and Science University.)

TREATMENT

Definitive treatment with either immunosuppressive therapy or allogeneic hematopoietic stem cell transplantation (Chapter 163) is necessary for patients with severe or very severe aplastic anemia, but no standard of care exists for moderate aplastic anemia. Younger age (typically age <40 years) and the presence of a matched sibling donor favor the use of allogeneic hematopoietic stem cell transplantation, whereas older age (age >40 years) and absence of a matched sibling donor typically favor the use of immunosuppressive therapy. However, hematopoietic stem cell transplantation from haploidentical or unrelated donors is increasingly being used as front-line therapy for children and younger adults.

Hematopoietic Stem Cell Transplantation (HSCT)

Adolescents and young adults who meet criteria for severe disease and who have an HLA-matched sibling donor should proceed directly to hematopoietic stem cell transplantation (Chapter 163).[5] Predictors of survival following hematopoietic stem cell transplantation include matched sibling donor, recipient age <16 years, early transplant within 12 weeks of diagnosis, and a non-radiation conditioning regimen. Compared with standard immunosuppressive therapy, hematopoietic stem cell transplantation markedly reduces the risk of relapse and mitigates the risk for the later development of sequelae such as myelodysplasia, acute myeloid leukemia, or classical paroxysmal nocturnal hemoglobinuria. With increasingly good results with haploidentical[6] as well as unrelated donor hematopoietic stem cell transplantation, more patients are receiving hematopoietic stem cell transplantation for aplastic anemia (Fig. 151-2).

Immunosuppressive Therapy

Immunosuppressive therapy is often first-line therapy for adolescents and young adults who have severe aplastic anemia and who lack matched sibling donors as well as for medically fit adults (over age 40 years). Immunosuppressive therapy typically uses a combination of anti-thymocyte globulin (ATG), cyclosporine (12 to 15 mg/kg in divided doses twice daily), and eltrombopag[7] (a thrombopoetin-receptor agonist at 150 mg daily) in adults. Of the two ATG preparations commonly used in clinical practice, horse ATG (40 mg/kg/day for 4 days) appears to be superior in the front-line treatment of severe aplastic anemia.[A1] Eltrombopag increases response rates by about 20% compared with ATG and cyclosporine alone.[A2] Corticosteroids are also administered during the first 2 weeks under expert oversight to prevent serum sickness.

General Care

Supportive long-term care is imperative for patients who have aplastic anemia. Placement of a central venous catheter should be strongly considered for all patients given the frequency of phlebotomy, transfusions, and administration of therapeutic medications. Patients who have severe cytopenias require frequent and sometimes urgent blood product support. Blood products should be irradiated (to prevent transfusion-associated graft-versus-host disease) and leukocyte-reduced (to prevent alloimmunization and reduce the incidence of cytomegalovirus infections; see Chapter 162).

Fungal and bacterial infections are a major cause of death in patients with severe aplastic anemia, but an active fungal infection should not delay more definitive therapy such as immunosuppressive therapy or hematopoietic stem cell transplantation. Approaches to prophylactic antibiotic therapy vary among institutions, but adding prophylactic granulocyte colony stimulating factor to immunosuppressive therapy is not of incremental value.[A3]

Aplastic Anemia During Pregnancy

Aplastic anemia can rarely present during pregnancy. Spontaneous remission can occur in 25 to 30% of patients, often upon birth or termination of the pregnancy. Pregnant patients can be followed with stringent supportive care, or cyclosporine may be considered. Complications appear to be more likely in pregnant patients who have low platelet counts and associated paroxysmal nocturnal hemoglobinuria (Chapter 146).

PROGNOSIS

The hematopoietic response rate after immunosuppressive therapy is about 70 to 80%, and the probability of survival at 5 years ranges from 60 to 85%. Patients who are treated with horse ATG plus cyclosporine can have about a 60% overall survival at 15 years, but failure-free survival (survival without relapse or secondary clonal disease beyond 10 years) after immunosuppressive therapy is less than 50%. Survival outcomes continue to improve for alternative donor hematopoietic stem cell transplantation, and haploidentical transplantation with post-transplant cyclophosphamide represents a potential cure in patients who have severe aplastic anemia.

PAROXYSMAL NOCTURNAL HEMOGLOBINURIA

Paroxysmal nocturnal hemoglobinuria is a rare clonal disorder in which the activation of complement causes hemolytic anemia and sometimes bone marrow failure. A clone of paroxysmal nocturnal hemoglobinuria cells is seen in at least 50% of patients who have true aplastic anemia. Classical paroxysmal nocturnal hemoglobinuria is discussed in Chapter 146.

LARGE GRANULAR LYMPHOCYTE LEUKEMIA

DEFINITION AND EPIDEMIOLOGY

Large granular lymphocyte leukemia is a clonal lymphoid disorder characterized by a peripheral lymphocytosis of cytotoxic T-lymphocytes with concomitant cytopenias. Although an increase in the number of large granular lymphocytes can be associated with other entities, such as aplastic anemia or myelodysplastic syndrome, large granular lymphocyte leukemia is a distinct clinical entity.

Males and females are equally affected. The median age at diagnosis is 60 years, with very rare occurrence in younger children. The estimated incidence of large granular lymphocyte leukemia in the United States is 1 in 10,000,000 individuals. Large granular lymphocyte leukemia is associated with myelodysplastic syndrome (Chapter 167) in about 10% of cases.

PATHOBIOLOGY

The exact mechanism underlying the development of large granular lymphocyte leukemia is not fully understood. The leading hypothesis is the acquisition

TABLE 151-2 STANDARD EVALUATION OF A PATIENT WITH SUSPECTED APLASTIC ANEMIA TO ENCOMPASS RISK OF INHERITED DISORDERS

EVALUATION	PURPOSE
HISTORY AND PHYSICAL EXAMINATION	
Hematologic: Long-standing cytopenia(s) or macrocytosis Unexplained cytopenia(s) or macrocytosis, aplastic anemia, myelodysplastic syndrome, acute myeloid leukemia in one or more close relative(s)	Could suggest inherited bone marrow failure disorder due to identification of cytopenias at early age
Developmental: Short stature, physical anomalies (especially thumb or radial ray, cardiac, or renal)	Fanconi anemia or dyskeratosis congenita or thrombocytopenia-absent radius syndrome
Immunologic/Infectious Disease: Severe, recurrent, or atypical infections (e.g., mycobacterial, viral, fungal)	Could suggest GATA2 deficiency
Dermatologic: Gray hair prior to 25 Leukoplakia or nail dysplasia Reticulated skin pigmentation, café au lait macules	Could suggest dyskeratosis congenita or another short telomere syndrome
Pulmonary: Pulmonary fibrosis and/or early onset emphysema, pulmonary alveolar proteinosis, fungal or mycobacterial infection	Could suggest dyskeratosis congenita, another short telomere syndrome, or GATA2 deficiency
Abdominal: Pancreatic insufficiency, liver fibrosis, renal anomaly or malplacement	Could suggest dyskeratosis congenita, another short telomere syndrome, or Diamond Blackfan anemia
Oncologic: Head, neck, or anogenital squamous cell carcinoma, or early onset gastrointestinal cancer or multiple cancers in patient or close relatives	Could suggest short telomere syndrome
LABORATORY TESTING	
Complete blood count with differential and blood smear review	Assess severity of cytopenias and consider alternative etiologies
Reticulocyte count	Assess marrow response to anemia and use to assess the severity of aplastic anemia
Hemoglobin F%	Elevated levels may indicate an inherited bone marrow failure disorder
Levels of vitamin B_{12}, folate, copper, zinc, ferritin	Exclude vitamin or mineral deficiencies as cause or contributor to cytopenias
Serologies for hepatitis A/B/C, Epstein-Barr virus, parvovirus, and cytomegalovirus	Rule out infectious disease contributors to cytopenias and identify co-management needs during treatment and transplant
LDH, haptoglobin	Exclude a hemolytic component to anemia
Paroxysmal nocturnal hemoglobin clone	Assess presence or absence of GPI-anchored protein expression; presence suggests acquired rather than inherited disease
Antinuclear antibodies (plus anti-double-stranded DNA if positive)	Assess for systemic lupus erythematosus
Quantification of immunoglobulins A, G, M	Assess for additional immune deficits
Flow cytometry to assess numbers of B lymphocytes, T lymphocytes, and natural killer cells	Assess for additional immune deficits
Telomere length measurement of peripheral blood lymphocytes by fluorescence in situ hybridization	If telomere length <1st percentile, patient may have a short telomere syndrome and be at risk of increased transplant-related toxicity with standard preparative regimens
Chromosome breakage analysis on peripheral blood	If test is positive and consistent with a diagnosis of Fanconi anemia, Fanconi anemia–specific regimen should be utilized and patient is at increased risk of transplant-related toxicity.
Bone marrow aspirate and biopsy	Assess cellularity, iron stores, and reticulin fibrosis; exclude other marrow pathologies
Conventional karyotyping	Examine chromosomes in a sample of cells to identify genetic (acquired or inherited) problems as the cause of cytopenias
HLA typing	Determine HLA profile for stem cell donor search
Myeloid malignancy gene sequencing from peripheral blood or bone marrow	Evaluate for mutations in genes recurrently mutated in aplastic anemia (e.g., *PIGA*, *BCOR*, *BCORL1*) and/or myelodysplastic syndrome (e.g., epigenetic mutations, *TP53*).
Inherited bone marrow failure gene panel sequencing	Evaluate for multiple inherited bone marrow failure disorders (see E-Table 151-2) at once. Universal testing of young patients is also warranted.
Erythrocyte adenosine deaminase	Screen for Diamond Blackfan anemia

GPI = glycosylphosphatidylinositol; HIV = human immunodeficiency virus; HLA = human leukocyte antigen; LDH = lactase dehydrogenase.
Modified from DeZern AE, Churpek JE. Approach to the diagnosis of aplastic anemia. *Blood Adv*. 2021;5:2660-2671.

abnormalities in pathways that enhance survival, since normal large granulocytic lymphocytes undergo faster apoptosis whereas neoplastic lymphocytes appear to undergo reduced apoptosis. Mutations in *STAT3* are increased in patients with large granular lymphocyte leukemia, but these mutations are also detected when aplastic anemia, myelodysplastic syndrome, or pure red cell aplasia is associated with large granular lymphocytes.

CLINICAL MANIFESTATIONS

Patients most commonly present with asymptomatic neutropenia (Chapter 153) with or without concomitant anemia on routine laboratory evaluation, but some patients present with symptoms related to cytopenias. Large granular lymphocyte leukemia is also the most common cause of pure red cell aplasia in adults. Splenomegaly (Chapter 154), which is a common finding on physical

E-TABLE 151-2 DISTINGUISHING CLINICAL FEATURES OF THE INHERITED BONE MARROW FAILURE SYNDROMES THAT MAY BE INITIALLY DIAGNOSED IN ADULTHOOD

DISTINGUISHING FEATURES	FANCONI ANEMIA	SHORT TELOMERE SYNDROMES (DYSKERATOSIS CONGENITA)	DIAMOND-BLACKFAN ANEMIA
History	Skeletal and renal malformations, low birthweight, pancytopenia, family member with bone marrow failure, myelodysplasia, acute myelogenous leukemia, or squamous cell carcinoma at an early age Family member with Fanconi anemia	Intrauterine growth retardation, developmental delay, and short stature Family history of myelodysplasia, acute myelogenous leukemia, marrow failure, abnormal fingernails or toenails, leukoplakia, head and neck cancer, or pulmonary fibrosis	Low birthweight, arm and thumb deformities at birth
Physical findings	Thumb and radial malformations, hyperpigmented skin lesions (café au lait spots), short stature, myelodysplasia, acute myelogenous leukemia, squamous cell carcinoma at young age, renal and cardiac malformations, microcephaly, hypogonadism If physical manifestations are mild, this syndrome may not be recognized until adulthood	Lacy reticular pigmentation of skin, dystrophic fingernails and toenails, premature graying of hair, hair loss, short stature, oral leukoplakia, squamous cell cancer of head and neck, pulmonary fibrosis, osteopenia, hypogonadism	Triphalangeal thumbs, short stature, arm anomalies
Genes inactivated and (synonyms)	*FANCA,* FANCC,* FANCG,* FANCB, FANCD1 (BRCA2), FANCD2, FANCE, FANCF, FANCI, FANCJ (BRIP1), FANCL, FANCM, FANCN (PALB2), FANCO (RAD51C), FANCP (SLX4), FANCQ (ERCC4), FANCR (RAD51), FANCS (BRCA1), FANCT (UBE2T), FANCU (XRCC2), FANCV (REV7)* These genes encode proteins known to protect the genome from excessive damage induced by chemical cross-linking agents	*DKC1,† TERC,† TERT,† TINF2,† NOLA2 (NHP2), NOLA3 (NOP10) WRAPS3, STN1, NAF1, PARN, CTC1, ACD, RTEL1, POT1* These genes encode proteins known to participate in maintenance of telomeres	Ribosomal Genes *RPS19,‡ RPL11,‡ RPS26,† RPS10,‡ RPS35a,‡ RPS24,‡ RPS7, RPS17, RPL5, RPS20, RPS27, RPS28, RPS29, RPL15, RPL17, RPL26, RPL27, RPL31* Non-Ribosomal Gene Mutations *GATA1, TSR2*
Screening and diagnostic tests	1. Mitomycin C or diepoxybutane induced chromosomal breakage test using skin fibroblasts or peripheral blood lymphocytes 2. Gene sequencing	1. Quantitative analysis of telomere length (flow-FISH) in lymphocytes 2. Gene sequencing	*Note:* Isolated erythroid failure is more common than pancytopenic aplastic anemia. 1. No screening tests, although serum ADA is often elevated 2. Gene sequencing

*Mutations of these account for 85% of cases.
†Mutations of these genes account for 40-45% of cases. The 14 genes identified to date account for 70% of patients with clinically diagnosed dyskeratosis congenita.
‡Mutations of these genes account for 40-45% of cases.
ADA = adenosine deaminase; FISH = fluorescence in situ hybridization.

TABLE 151-3 CAMITTA CRITERIA FOR CLASSIFICATION OF APLASTIC ANEMIA

PERIPHERAL BLOOD CYTOPENIAS	NON-SEVERE (MODERATE) APLASTIC ANEMIA*	SEVERE APLASTIC ANEMIA†	VERY SEVERE APLASTIC ANEMIA‡
Bone marrow cellularity	<25%	<25%	<25%
Absolute neutrophil count		<500/μL	<200/μL
Platelet count		<20,000/μL	
Reticulocyte count		<1.0% corrected or <60,000/μL	

*Not meeting criteria for severe disease.
†Any 2 of 3.
‡Meets criteria for severe disease plus a lower absolute neutrophil count (<200/μL).

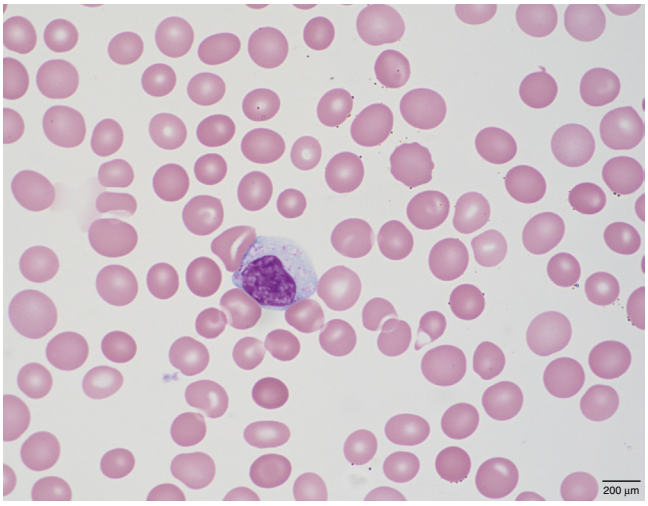

FIGURE 151-3. Large granular lymphocyte. (Courtesy of Rena Xian, MD, PhD.)

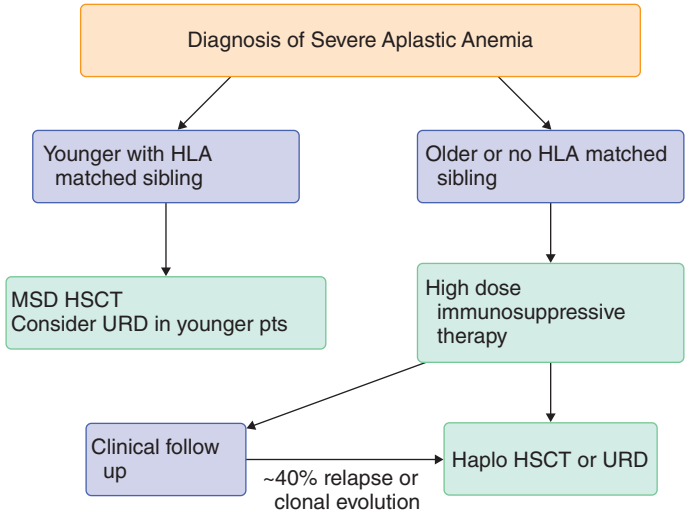

FIGURE 151-2. Therapeutic considerations for severe aplastic anemia. Haplo = haploidentical; HLA = human leukocyte antigen; HSCT = hematopoietic stem cell transplantation; MSD = matched sibling donor; URD = unrelated living donor.

examination, is seen in 25 to 50% of cases and is classically associated with rheumatoid arthritis (Chapter 243) in males.

DIAGNOSIS

No single laboratory test is diagnostic of large granular lymphocyte leukemia. In the appropriate clinical context, however, a combination of histomorphology and flow cytometry with molecular diagnostic studies are sufficient for diagnosis.[8]

The peripheral blood often shows neutropenia with a relative lymphocytosis. Large granulocytic lymphocytes with relatively abundant pale cytoplasm, scattered eosinophilic granules, mature chromatin, and smooth nuclear borders (Fig. 151-3) are best seen in the peripheral blood rather than in a bone marrow sample.

However, large granulocytic lymphocytes can be increased not only in true large granular lymphocyte leukemia but also in reactive conditions, other non-neoplastic bone marrow failure conditions, and neoplastic hematologic malignancies. Distinguishing true large granular lymphocyte leukemia from these conditions can be challenging. Large granulocytic lymphocytes also are often transiently increased in patients with viral infections and can even be increased in individuals with normal white blood cell counts. By comparison, cytotoxic T-lymphocytes are elevated for more than 6 months in the peripheral blood, and the increase is not attributable to any other cause. As a result, flow cytometry is critical for diagnosis and will reveal an immunophenotypic profile that is indicative of an activated cytotoxic T cell (e.g., $CD3^+$, T cell receptor [TCR]-$\alpha\beta^+$, $CD57^+$, $CD4^-$, $CD5^{dim}$, $CD8^+$, $CD16^+$, $CD27^-$, $CD28^-$). Demonstration of clonal T-cell gene rearrangements is also an important part of the diagnostic evaluation.

TREATMENT

Asymptomatic patients are best observed with routine blood counts and clinical follow-up, but treatment is indicated if patients are symptomatic because of severe cytopenias, recurrent infections, constitutional symptoms, or problematic splenomegaly (Chapter 154). Therapies commonly used under expert supervision include methotrexate, cyclophosphamide, cyclosporine, and alemtuzumab.[9] Patients often receive multiple sequential therapies because the disease often relapses.

When large granular lymphocyte leukemia is associated with the myelodysplastic syndrome (Chapter 167), it should be considered a paraneoplastic phenomenon; treatment should focus on the underlying myelodysplastic syndrome. The opposite is true with large granular lymphocyte leukemia–associated pure red cell aplasia, which often is more immune-responsive than pure red cell aplasia from other causes.

PROGNOSIS

Most cases of large granular lymphocyte leukemia follow a chronic course. Prognosis varies depending on the response to immunosuppressive therapy, as well as any underlying conditions, such as the myelodysplastic syndrome.

PURE RED CELL APLASIA

Pure red cell aplasia is a syndrome characterized by a severe normochromic, normocytic anemia (Chapter 144); reticulocytopenia; and the absence of erythroblasts from an otherwise normal bone marrow. Pure red cell aplasia is classified by the clinical course (acute or chronic) and underlying etiology (idiopathic or secondary).

PATHOBIOLOGY

Although pure red cell aplasia has numerous causes, the underlying etiology is thought to be immune-mediated.[10] Pure red cell aplasia may represent a primary hematologic disorder in the absence of any other disease or may develop secondary to parvovirus infection (Chapter 342), human immunodeficiency virus infection, a collagen vascular disease, leukemia, lymphoma, thymoma, solid tumors, treatment with recombinant human erythropoietin or other drugs, ABO-incompatible hematopoietic stem cell transplantation, and pregnancy.

CLINICAL MANIFESTATIONS

The acquired form of pure red cell aplasia presents either as an acute self-limited disease, predominantly seen in children, or as a chronic illness that is more frequently seen in adults. In adults, pure red cell aplasia presents as isolated anemia with normal (or slightly low) white blood cell and platelet counts. Large granular lymphocytes may be increased.

DIAGNOSIS

Evaluation for the possible causes of pure red cell aplasia includes assessing for a history of drug use, toxin exposure, or infections; abnormalities in liver and kidney function; immunologic examination for auto-antibodies; virologic studies to detect parvovirus B19 DNA, especially in patients with immunodeficiency and/or hemolytic anemia; and computed tomographic scanning

to assess for a thymoma. Peripheral-blood flow cytometry should also be performed to quantify the concentration of large granulocytic lymphocytes.

However, the diagnosis of pure red cell aplasia requires a bone marrow biopsy and is often a diagnosis of exclusion. Bone marrow biopsies show normal to hypocellular marrow with absent or nearly absent erythroid precursors. Colony formation assays specifically for burst forming unit-erythroid may be informative. Increased colony formation assay growth is often seen in pure red cell aplasia, in keeping with the immune-mediated nature of this disorder, and higher growth correlates with a positive response to immunosuppressive therapy.

TREATMENT

During the initial evaluation, red cell transfusions can be given as necessary. Since about 10% of patients who have primary idiopathic pure red cell aplasia will have self-limited disease, other treatments can be delayed for about 1 month while watching for signs of recovery of erythropoiesis.

Immunosuppression is the mainstay of therapy for persistent pure red cell aplasia.[11] Corticosteroids (e.g., prednisone 20 to 60 mg) produce about a 75% response rate, but relapse occurs in up to 80% of patients when the dosage is tapered during the 24 months after remission. Cyclosporine under expert oversight yields an overall response rate of about 65%, but many patients do not remain in remission when cyclosporine is discontinued. Cyclophosphamide can provide an overall response rate of 40 to 60% after approximately 11 to 12 weeks of treatment.

For secondary pure red cell aplasias, removal of the inciting factor is critical. Pure red cell aplasia that is secondary to parvovirus B19 can be treated with intravenous immunoglobulin under expert oversight. About 25 to 30% of causes of thymoma-associated pure red cell aplasia show a hematologic response after surgical resection.

PROGNOSIS

Depending on the cause, the course can be acute and self-limiting or chronic with rare spontaneous remissions. In patients who have spontaneous remissions, no specific therapy is required other than transfusion for symptomatic anemia and cessation of possible offending drugs. For acquired chronic pure red cell aplasia, remissions can be attained with treatment, but the aplasia commonly recurs when therapy is discontinued.

INHERITED BONE MARROW FAILURE SYNDROMES

The inherited bone marrow failure syndromes are heterogeneous disorders in which at least one clinically significant cytopenia is present.[12] Many of the inherited bone marrow failure syndromes are associated with characteristic physical findings as well as notably increased risks of both solid and hematologic neoplasms.

FANCONI ANEMIA

Fanconi anemia is a genetic disorder that manifests as developmental abnormalities, progressive bone marrow failure, and an increased risk of developing both hematologic malignancies and carcinomas of the head, neck, and anogenital region at a relatively young age. The vast majority of families with Fanconi anemia exhibit autosomal recessive inheritance, but about 2% of cases are X-linked recessive. Fanconi anemia has an incidence of about 1/200,000 to 400,000 in most populations, but the incidence is higher in Ashkenazi Jews (about 1/30,000) and Afrikaners from South Africa (about 1/22,000). Most patients are diagnosed in the first decade of life, though some cases with milder phenotypes present later in life. Abnormalities in at least 23 genes that participate in a common DNA repair pathway called the Fanconi anemia pathway can result in defective DNA repair, which, in turn, leads to an increased mutation rate and oncogenesis.

CLINICAL MANIFESTATIONS AND DIAGNOSIS

Fanconi anemia is a very heterogeneous disease, with different mutations associated with different patterns of disease and severity. On physical examination, patients with Fanconi anemia show heterogeneous but characteristic physical findings, including café au lait spots, abnormalities of the thumbs, malformation of the ears and eyes, small stature, hypogonadism, and abnormalities of the gastrointestinal, genitourinary, cardiopulmonary, and central nervous systems. Patients typically present with an unusual macrocytosis and then later develop pancytopenia, thrombocytopenia, and ultimately bone marrow failure. Diagnosis is based on chromosomal fragility in blood lymphocytes, especially after exposure to alkylating agents, diepoxybutane, or mitomycin C.[13] Skin fibroblasts are often required for conclusive diagnosis.

TREATMENT

Approximately 50% of patients with Fanconi anemia initially respond to androgens under expert supervision, but androgen therapy has significant side effects such as liver toxicity, acne, and behavioral anomalies. Allogeneic hematopoietic stem cell transplantation provides a potential cure.

PROGNOSIS

Patients with low blood counts or cytogenetic abnormalities in the marrow have a relatively poor prognosis. By age 25 years, approximately 10% of patients develop acute leukemia (Chapter 168) and approximately 5% develop myelodysplastic syndrome. Even after a successful hematopoietic stem cell transplantation, patients remain at an increased risk of developing solid tumors[14] and should be regularly monitored.

DYSKERATOSIS CONGENITA AND SHORT TELOMERE SYNDROMES

Telomeres, which are tandem TTAGGG repeats at the ends of eukaryotic chromosomes, protect the integrity of the genetic material. Telomeres decrease in length with cell division. When the telomeres become too short, the resulting genomic instability allows for an increased rate of mutations and predisposes to oncogenesis. Nine proteins are currently known to participate in the maintenance of telomeres, and approximately 60% of patients with dyskeratosis congenita have a mutation in one of these genes.

The inheritance of dyskeratosis congenita may be autosomal dominant, autosomal recessive, or X-linked, and some patients also have de novo germline mutations. The median age at diagnosis is at about 15 years (range 0 to 75), and males are disproportionately affected, with a male:female ratio of approximately 3:1.

CLINICAL MANIFESTATIONS AND DIAGNOSIS

Dyskeratosis congenita is most often associated with a triad of characteristic skin and nail changes, bone marrow failure, and a predisposition for the development of cancers, particularly squamous cell carcinomas of the head and neck and anogenital region. Additional clinical findings may include premature graying, pulmonary fibrosis, short stature, immune deficiencies, avascular necrosis of the femur or humerus, and liver cirrhosis. Short telomere syndromes encompass a broader spectrum of disorders with both marrow failure and other systemic manifestations.[15]

The bone marrow is initially cellular, but all three lineages demonstrate gradual aplasia. Patients may progress to develop myelodysplastic syndrome or acute myeloid leukemia. Verification of shortened telomeres in white blood cells evaluated by flow cytometry with fluorescent in situ hybridization can confirm the diagnosis.

TREATMENT AND PROGNOSIS

Allogeneic hematopoietic stem cell transplantation, which is the only curative option, should be offered if the platelet count is 3000/μL, the absolute neutrophil count is <1000/μL, and the hemoglobin concentration is <8 g/dL. Without successful transplant, mean survival is 30 years, with most deaths related to infections, bleeding, and malignancy.[16]

DIAMOND–BLACKFAN ANEMIA

Diamond-Blackfan anemia is a rare congenital hypoplastic anemia that usually presents early in infancy. In familial cases, the pattern of inheritance is generally autosomal dominant, but a significant number of cases represent new mutations.

Diamond-Blackfan anemia is a ribosomopathy, and approximately 50% of patients carry known mutations that result in defective ribosomal function, especially mutations in the large or small subunit gene *RPS19*. The clinical disease is caused by insufficient production of a particular ribosomal protein (haploinsufficiency).

CLINICAL MANIFESTATIONS AND DIAGNOSIS

Very young patients present with anemia and reticulocytopenia, with an increase in mean corpuscular volume, hemoglobin F, and red cell adenosine deaminase. The hematologic findings are often accompanied by facial

deformities (characterized by a short nose with a broad nasal bridge, widely spaced eyes, and thick upper lip), triphalangeal thumbs, microcephaly, congenital cataracts, and genitourinary and cardiac defects.

The bone marrow shows a selective loss of erythroid precursors. The myeloid lineage shows a full range of maturation, and megakaryocytes are normal in number and morphology. The finding of an elevated adenosine deaminase level in the serum is strongly suggestive of this disease, and the genetic diagnosis usually can be made with a Diamond-Blackfan anemia panel.

TREATMENT AND PROGNOSIS

Up to 80% of patients respond to corticosteroids (e.g., prednisone starting at 2 mg/kg/day, followed by a 0.5 mg/kg/day maximum maintenance dose).[17] Patients who do not respond within a month are considered steroid-refractory and require RBC transfusion support. Hematopoietic stem cell transplantation improves red cell production but does not protect against the development of the myelodysplastic syndrome or acute myeloid leukemia; as a result, matched unrelated hematopoietic stem cell transplantation is best reserved for steroid-refractory patients who require regular transfusions.

The outcomes of Diamond-Blackfan anemia are usually excellent, in particular for patients younger than age 10 years. However, Diamond-Blackfan patients have a marked increased risk for colon cancer, and all patients should be referred to a gastroenterologist for appropriate screening at around age 20 years.

OTHER MARROW FAILURE DISORDERS

Other extremely rare marrow failure disorders that can be seen, especially in children, typically require specific genetic panels or whole exome sequencing by an expert hematologist. Examples include mutations in *SAMD9* (sterile alpha motif domain protein 9) and *SAMD9L* (its paralogue SAMD9-like), sideroblastic anemia (Chapter 145), monosomy 7 predisposition syndromes, thrombocytopenia-absent radii syndrome, Pearson syndrome, and MonoMac (*GATA2*) syndrome.[18]

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152 POLYCYTHEMIA VERA, ESSENTIAL THROMBOCYTHEMIA, AND PRIMARY MYELOFIBROSIS

JASON GOTLIB

DEFINITION

In the 2022 International Consensus Classification, the major category of myeloproliferative neoplasms comprises seven diseases (Table 152-1), including polycythemia vera, essential thrombocythemia, and primary myelofibrosis.[1]

TABLE 152-1 2022 INTERNATIONAL CONSENSUS CLASSIFICATION OF MYELOPROLIFERATIVE NEOPLASMS

DISEASE
Chronic myeloid leukemia
Chronic neutrophilic leukemia
Polycythemia vera
Primary myelofibrosis Prefibrotic/early primary myelofibrosis Overt primary myelofibrosis
Essential thrombocythemia
Chronic eosinophilic leukemia, not otherwise specified
Myeloproliferative neoplasm, unclassifiable

The umbrella term "*BCR::ABL1*-negative myeloproliferative neoplasms" is used to distinguish these disorders from chronic myeloid leukemia (CML), which is also included in the myeloproliferative neoplasm category and molecularly defined by the *BCR::ABL1* fusion oncogene. (CML is discussed in Chapter 170.) Polycythemia vera, essential thrombocythemia, and myelofibrosis are chronic myeloid stem cell disorders characterized by excessive production of terminally differentiated cells and variable potential to evolve into acute myeloid leukemia (AML), also referred to as blast-phase myeloproliferative neoplasm. Although these neoplasms exist along a continuous disease spectrum, they each exhibit heterogeneous molecular, biologic, and clinical features that translate into unique natural histories.

EPIDEMIOLOGY

According to a meta-analysis of 34 studies, the combined annual incidence rates (IRs) for polycythemia vera, essential thrombocythemia, and primary myelofibrosis were 0.84, 1.03, and 0.47 per 100,000, respectively. Data from 2001 to 2012 found that the age-adjusted IRs were highest for polycythemia vera (10.9 per 1 million person-years) and essential thrombocythemia (IR = 9.6), and relatively lower for primary myelofibrosis (IR = 3.1). The median ages at diagnosis ranged from 65 to 70 years for the three myeloproliferative neoplasms. Excluding essential thrombocythemia, which predominates among females especially younger than 60 years of age, polycythemia vera and primary myelofibrosis are more commonly diagnosed in males. For all three myeloproliferative neoplasms, IRs are significantly lower among Hispanic Whites, Asian-Pacific Islanders, and Blacks compared to non-Hispanic Whites. Based on data from two large U.S. health plans spanning 2008 to 2010, prevalence rates ranged from 44 to 57 per 100,000 individuals for polycythemia vera, 38 to 57 per 100,000 for essential thrombocythemia, and 0.3 to 5.7 per 100,000 for myelofibrosis.

Risk factors associated with the development of myeloproliferative neoplasms require further study but have included Jewish descent, autoimmune conditions (e.g., Crohn disease), and male-predominant occupations including agricultural or other rural-sector workers with potential exposure to benzene or petroleum. The individual genetic background can influence the propensity for developing a myeloproliferative neoplasm. A five- to seven-fold increased risk of myeloproliferative neoplasm development was identified in first-degree relatives of patients with a myeloproliferative neoplasm.

PATHOBIOLOGY

A point mutation at base pair 1849 (G→T) in the *JAK2* gene results in substitution of the normal valine to phenylalanine in codon 617 (V617F) of exon 14. The somatic V617F mutation has been identified as a highly recurrent mutation in polycythemia vera, essential thrombocythemia, and primary myelofibrosis.[2,3] The mutation affects the autoinhibitory pseudokinase domain of *JAK2*, relieving inhibition of JAK2 kinase activity, and resulting in constitutive JAK-STAT signaling (Fig. 152-1). *JAK2* V617F is found in ≈95 to 98% of polycythemia vera patients and 50 to 60% of essential thrombocythemia and primary myelofibrosis patients; other myeloid neoplasms rarely exhibit *JAK2* mutations. Small in-frame insertions and deletions in exon 12 of the *JAK2* gene (e.g., codons 530 to 540 s) are restricted to ≈2% of polycythemia vera patients who are negative for the V617F mutation (Fig. 152-2).

The *JAK2* V617F mutation arises in a multipotent hematopoietic progenitor or hematopoietic stem cell. It is identified in all cells derived from the myeloid lineage but can also be found in B and NK cells and, more rarely, in

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ABSTRACT

The major clinical disorders that are grouped under the heading of "*BCR::ABL1*-negative myeloproliferative neoplasms" are polycythemia vera, essential thrombocythemia, and primary myelofibrosis. (*BCR::ABL1*-positive chronic myeloid leukemia [CML]) is covered in Chapter 170). These are all neoplasms arising in a pluripotent hematopoietic stem cell with differences in phenotypic expression being driven, at least in part, by now well-established somatic mutations. These genomic alterations include the *JAK2* V617F mutation (which is the driver mutation in 95 to 98% of patients with polycythemia vera but also occurs in 50 to 60% of patients with essential thrombocythemia and myelofibrosis), *JAK2* exon 12/13 mutations, and mutations in *MPL* and *CALR*. Polycythemia vera must be differentiated from many other (secondary) causes of erythrocytosis; essential thrombocythemia must be differentiated from other, secondary (reactive) causes of thrombocytosis, and marrow fibrosis can be found in conditions other than myelofibrosis. The characteristic genomic alterations that occur primarily in the myeloproliferative neoplasms have made the differential diagnosis easier. The only curative treatment for myeloproliferative neoplasms is allogeneic hematopoietic stem cell transplantation which, because of its high risk of morbidity and mortality, is reserved for only a select group of patients, particularly those with myelofibrosis. In other cases, treatment is directed at palliation of symptoms and/or control of the high blood counts to prevent thrombotic, vascular, and bleeding complications.

KEYWORDS

polycythemia vera
essential thrombocythemia
myeloid metaplasia
primary myelofibrosis
somatic mutation
secondary erythrocytosis
secondary thrombocytosis
secondary myelofibrosis
JAK2 V617F

T cells. It has been identified in endothelial cells of the spleen and of splanchnic veins in patients with myelofibrosis or patients with a myeloproliferative neoplasm and the Budd-Chiari syndrome. *JAK2* V617F can evolve from a heterozygous to homozygous state due to uniparental disomy (copy-neutral loss of heterozygosity) involving the short arm of chromosome 9 (9p loss of heterozygosity) where the *JAK2* gene is located. The *JAK2* V617F variant allele frequency in granulocytes from myeloproliferative neoplasm patients can vary widely. The variant allele frequency is usually low (e.g., below 50%) in essential thrombocythemia and higher in polycythemia vera and primary myelofibrosis (frequently over 50%, attributable to loss of heterozygosity). Similarly, very high variant allele frequencies are commonly observed in myelofibrosis that evolves from polycythemia vera (post-polycythemia vera myelofibrosis) or myelofibrosis that evolves from essential thrombocythemia (post-essential thrombocythemia myelofibrosis).

Activating mutations in the gene encoding the thrombopoietin receptor *MPL* (most commonly *MPL* W515 L/K) are found in less than 5% of patients with essential thrombocythemia and up to 10% of individuals with myelofibrosis (see Fig. 152-2). These mutations in exon 10 (including the rare S505N variant) occur in the juxtamembrane, intracytosolic portion and stabilize the receptor in an active dimeric configuration. Mutations in exon 9 of the calreticulin (*CALR*) gene have been found in the overwhelming majority of nonmutated *JAK2*/*MPL* patients and account for 20 to 35% of all patients with essential thrombocythemia and myelofibrosis (see Fig. 152-2). Although more than 50 types of mutations have been described, *CALR* variants fall into two predominant subtypes: type 1 (52 base-pair deletion), which is more common in patients with myelofibrosis, and type 2 (5 base-pair insertion) mutations, which is more prevalent in essential thrombocythemia. All exon 9 mutations result in a +1 frameshift in the coding sequence, resulting in a modified carboxy terminus which lacks a KDEL motif responsible for preventing secretion of the protein from the endoplasmic reticulum (ER). The mutant CALR C-terminus also acquires a greater positive charge that leads to loss of multiple calcium-binding sites. Recent investigations have uncovered that mutant CALR binds to the extracellular domain of the thrombopoietin receptor, MPL (Chapter 142), resulting in activation of the JAK-STAT axis. The positive charge of the mutant CALR C-terminus and the protein's lectin activity are required to mediate this neomorphic oncogenic activity.[4] These findings highlight a new paradigm of a mutated ER chaperone protein activating a cytokine receptor, leading to cellular transformation.

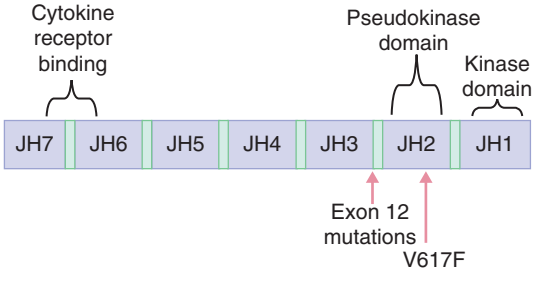

FIGURE 152-1. Exon 12 and *JAK2* V617F gene mutations. Scheme of the *JAK2* gene showing the positions of the V617F (exon 14) and exon 12 mutations. (From Levine RL, Gilliland DG. Myeloproliferative disorders. *Blood.* 2008;112:2190-2198. Fig. 2.)

LNK (SH2B3) is a negative regulator of JAK2 and normally functions to inhibit downstream STAT activation. Mutations in *LNK* have been found in 1 to 2% of patients with essential thrombocythemia or myelofibrosis, and rarely in patients with idiopathic erythrocytosis or polycythemia vera. Secondary *LNK* mutations may also occur during disease progression in *JAK2*- or *CALR*-mutant patients.

Approximately 10% of patients with essential thrombocythemia or primary myelofibrosis do not exhibit the canonical *JAK2*, *MPL*, or *CALR* driver mutations (so-called "triple-negative" myeloproliferative neoplasm patients) (see Fig. 152-2). Some of these patients exhibit cytogenetic abnormalities without evidence for a driver mutation, but no evidence of clonal hematopoiesis can be found in other patients. Rare patients exhibit alternative *JAK2* or *MPL* mutations that are present in the germline, consistent with a hereditary thrombocytosis.

Additional Molecular Abnormalities

Exome sequencing of a large cohort of patients with myeloproliferative neoplasm revealed that the median number of mutations in both polycythemia vera and essential thrombocythemia was 6.5, compared with 13 in myelofibrosis, consistent with it being a more advanced, genetically heterogeneous disease (Table 152-2). Besides *JAK2*, *CALR*, and *MPL*, mutations are found in genes encoding epigenetic regulators (*TET2*, *DNMT3A*, *ASXL1*, *EZH2*, *IDH1*, and *IDH2*), components of the splicing machinery (*SF3B1*, *SRSF2*, *U2AF1*), signal transduction (*CBL*, *SH2B3 [LNK]*), and tumor suppressor function (*TP53*).[5] Although identified in chronic-phase myeloproliferative neoplasms, acquisition of *TP53* mutations is commonly associated with disease acceleration, including transformation of myelofibrosis to blast-phase disease.

Genotype-Phenotype Correlations

The high prevalence of the *JAK2* V617F mutation in three clinically distinct myeloproliferative neoplasms raises the question of which factors contribute to the phenotypic diversity among polycythemia vera, essential thrombocythemia, and primary myelofibrosis. Differences in mutant allele burden of *JAK2* V617F likely modulate phenotype. Murine retroviral transplant models resulting in high levels of *JAK2* V617F expression produced a polycythemia vera–like phenotype with marked erythrocytosis. In contrast, transgenic models with more physiologic levels of *JAK2* V617F expression resulted in phenotypes resembling essential thrombocythemia and primary myelofibrosis. These animal models corroborate findings in patients, in whom the frequency of the *JAK2* V617F variant allele tends to be the highest in polycythemia vera and primary myelofibrosis, with lower levels in essential thrombocythemia. For patients with essential thrombocythemia, positivity for *JAK2* V617F tends to confer a polycythemia vera–like phenotype, with higher hemoglobin and lower platelet counts than in *JAK2* V617F–negative essential thrombocythemia patients.

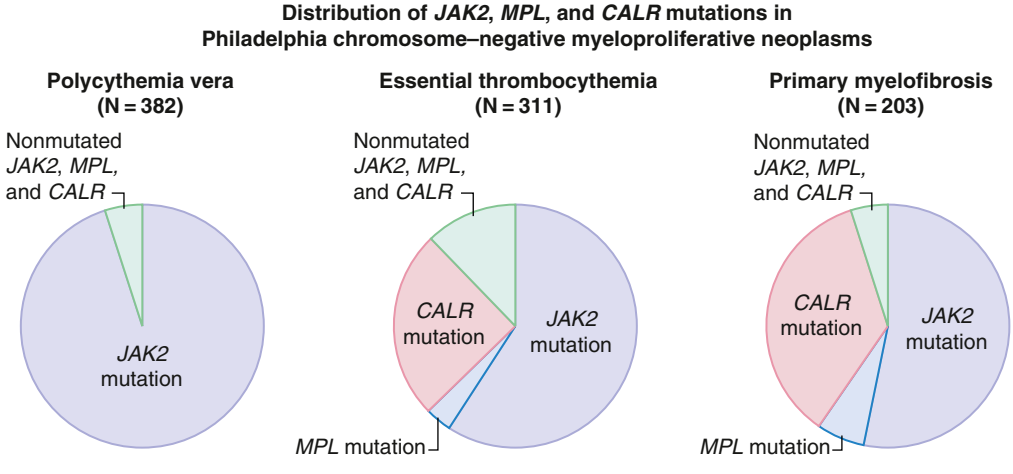

FIGURE 152-2. Distribution of canonical *JAK2*, *MPL*, and *CALR* mutations in polycythemia vera, essential thrombocythemia, and primary myelofibrosis. Relative distribution of *JAK2*, *CALR*, and *MPL* mutations in polycythemia vera, essential thrombocythemia, and primary myelofibrosis. All three mutations lead to constitutive activation of the Janus kinase/signal transducer and activator of transcription (JAK-SKAT) signaling axis. (From Klampfl T, Gisslinger H, Harutyunyan AS, et al. Somatic mutations of calreticulin in myeloproliferative neoplasms. *N Engl J Med*. 2013;369:2379-2390, Fig. 1a.)

TABLE 152-2 MUTATIONAL LANDSCAPE OF CHRONIC- AND BLAST-PHASE MYELOPROLIFERATIVE NEOPLASMS AND PROGNOSTIC RELEVANCE OF MOLECULAR ABNORMALITIES

MUTATION	CHROMOSOME LOCATION	FREQUENCY	PATHOGENETIC RELEVANCE	PROGNOSTIC ASSOCIATIONS
JAK2 (Janus kinase 2): *V617F*	9p24	PV: ≈96% ET: ≈55% PMF: ≈65%	Contributes to abnormal myeloproliferation and progenitor cell growth factor hypersensitivity	Intermediate prognosis and higher risk of thrombosis compared to patients with *CALR* mutation (PMF)
JAK2 exon 12 mutation	9p24	PV: ≈3%	Contributes to primarily erythroid myeloproliferation	Younger age, increased mean hemoglobin/hematocrit, and lower mean white blood cell and platelet counts at diagnosis compared to those with *JAK2* V617F-mutated PV. Both *JAK2* mutations are associated with similar rates of thrombosis, evolution to myelofibrosis or leukemia, and death in PV
CALR (Calreticulin): exon 9 deletions and insertions	19p13.2	PMF: ≈25% ET: ≈20% PV: 0%	Wild-type *CALR* is a multifunctional Ca^{2+} binding protein chaperone mostly localized in the endoplasmic reticulum	Improved survival compared to *JAK2* mutation and "triple-negative" PMF. Lower risk of thrombosis compared to *JAK2* mutation (ET, PMF) No difference in overall survival or myelofibrotic or leukemic transformation compared to *JAK2*-mutated ET *CALR* type 1/type 1-like with improved overall survival compared to *CALR* type 2/type 2-like and *JAK2* V617F mutation (PMF)
MPL (myeloproliferative leukemia virus oncogene): MPN-associated *MPL* mutations involve exon 10	1p34	ET: ~3% PMF: ~10%	Contributes to primarily megakaryocytic myeloproliferation	Intermediate prognosis and higher risk of thrombosis compared to patients with *CALR* mutation (PMF)
LNK, or *SH2B3* (a membrane-bound adaptor protein): MPN-associated mutations are monoallelic and involve exon 2	12q24.12	PV: rare ET: rare PMF: rare BP-MPN: ≈10%	Wild-type *LNK* is a negative regulator of JAK2 signaling	Inferior overall survival in ET
TET2 (TET oncogene family member 2): mutations involve several exons	4q24	PV: ≈16% ET: ≈5% PMF: ≈17% BP-MPN: ≈17%	TET proteins catalyze conversion of 5mC to 5hmC, which favors demethylated DNA. Both TET1 and TET2 display this catalytic activity. *IDH* and *TET2* mutations might share a common pathogenetic effect.	
ASXL1 (additional sex combs-like 1): exon 12 mutations	20q11.1	ET: ≈3% PMF: ≈13% BP-MPN: ≈18%	Wild-type *ASXL1* is needed for normal hematopoiesis and might be involved in coactivation of transcription factors and transcriptional repression	Independently associated with inferior overall survival and leukemia-free survival (PMF) Survival longest for *CALR* (+)/*ASXL1*(−) patients (median 10.4 years) and shortest in *CALR*(−)/*ASXL1*(+) patients (median 2.3 years). Intermediate survival (median 5.8 years) for *CALR*(+)/*ASXL1*(+) or *CALR*(−)/*ASXL1*(−) patients (PMF); worse overall and MF-free survival in PV
IDH1/IDH2 (isocitrate dehydrogenase): exon 4 mutations	2q33.3/15q26.1	PV: ≈2% ET: ≈1% PMF: ≈4% BP-MPN: ≈20%	*IDH* mutations induce loss of activity for the conversion of isocitrate to 2-KG and gain in function in the conversion of 2-KG to 2-HG. 2-HG might be the mediator of impaired TET2 function in cells with mutant *IDH* expression	Independently associated with inferior leukemia-free survival (PMF); worse overall (*IDH1*) and leukemia-free survival (*IDH2*) in PV; inferior overall survival in ET (*IDH2*)
EZH2 (enhancer of zeste homolog 2): mutations involve several exons	7q36.1	PV: ≈3% PMF: ≈7% MDS: ≈6%	Wild-type *EZH2* is part of a histone methyltransferase (polycomb repressive complex 2 associated with H3 Lys-27 trimethylation). MPN-associated *EZH2* mutations might have a tumor suppressor activity, which contrasts with the gain-in-function activity for lymphoma-associated *EZH2* mutations	Independently associated with inferior overall survival (PMF); inferior overall and leukemia-free survival in ET
DNMT3A (DNA cytosine methyltransferase 3a): most frequent mutations affect amino acid R882	2p23	PV: ≈7% PMF: ≈7% BP-MPN: ≈14%	DNA methyl transferases are essential in establishing and maintaining DNA methylation patterns in mammals	
CBL (Casitas B-lineage lymphoma proto-oncogene): exon 8/9 mutations	11q23.3	PV: rare ET: rare MF: ≈6%	CBL is an E3 ubiquitin ligase that marks mutant kinases for degradation. Transforming activity requires loss of this function.	
IKZF1 (IKAROS family zinc finger 1): mostly deletions including intragenic	7p12	CP-MPN: rare BP-MPN: ≈19%	IKZF1 is a transcription regulator and putative tumor suppressor	
TP53 (tumor protein p53): exons 4 through 9	17p13.1	PMF: ≈4% BP-MPN ≈27%	A tumor suppressor protein that targets genes that regulate cell cycle arrest, apoptosis, and DNA repair	Associated with leukemic transformation (PMF and ET)

TABLE 152-2 MUTATIONAL LANDSCAPE OF CHRONIC- AND BLAST-PHASE MYELOPROLIFERATIVE NEOPLASMS AND PROGNOSTIC RELEVANCE OF MOLECULAR ABNORMALITIES—cont'd

MUTATION	CHROMOSOME LOCATION	FREQUENCY	PATHOGENETIC RELEVANCE	PROGNOSTIC ASSOCIATIONS
SF3B1 (splicing factor 3B subunit 1): mostly exons 14 and 15	2q33.1	PMF: ≈7%	SF3B1 is a component of the RNA spliceosome. *SF3B1* mutations are closely associated with ring sideroblasts.	Inferior overall and MF-free survival in ET
SRSF2 (serine/arginine-rich splicing factor 2): exon 2	17q25.1	PMF: ≈17%	SRSF2 is a component of the RNA spliceosome, whose dysfunction promotes defects in alternative splicing	Independently associated with inferior overall survival and leukemia-free survival (PMF); worse overall survival in PV, ET
U2AF1 (U2 small nuclear RNA auxiliary factor 1)	21q22.3	PMF: ≈16%	U2AF1 is a subunit of the U2 small nuclear ribonucleoprotein auxiliary factor involved in pre-mRNA processing	Independently associated with anemia (PMF); inferior overall survival with *U2AF1* Q157 compared to *U2AF1*-unmutated PMF; worse overall and MF-free survival in ET
Triple-negative (negative for *JAK2*, *MPL*, or *CALR* mutations)				Inferior leukemia-free survival compared to patients with *JAK2*- and/or *CALR*-mutated PMF. Inferior overall survival compared to patients with *CALR*-mutated PMF.

2-HG = 2-hydroxyglutarate; 2-KG = 2-ketoglutarate; 5hmC = 5-hydroxymethylcytosine; 5mC = 5-methylcytosine; BP-MPN = blast-phase MPN; CP-MPN= chronic-phase MPN; ET = essential thrombocythemia; MDS = myelodysplastic syndrome; MF includes both PMF and post-ET/PV myelofibrosis; MPN = myeloproliferative neoplasms; PMF = primary myelofibrosis; PV = polycythemia vera.

CLINICAL MANIFESTATIONS

Essential Thrombocythemia

Up to one half of patients may present with incidental thrombocytosis (defined as platelet count >450,000/μL) without symptoms. The frequency of vasomotor symptoms differs widely between series; such microvascular disturbances can manifest as headaches, lightheadedness, syncope, chest pain, visual disturbances (amaurosis fugax, scintillating scotomata, ophthalmic migraine), and erythromelalgia (Fig. 152-3) which manifests as burning pain of the hands or feet associated with erythema and warmth.[6] Incidence rates of arterial (e.g., cerebrovascular event, myocardial infarction, peripheral arterial disease) and venous (deep vein thrombosis, pulmonary embolism, superficial thrombophlebitis) thrombosis as well as hemorrhage also vary; however, rates of major thrombosis or bleeding are less than 10% at diagnosis and follow-up. Thrombosis of unusual sites such as the abdomen (e.g., mesenteric, portal, hepatic vein thrombosis [Budd-Chiari syndrome]) and central nervous system (e.g., cerebral venous sinus thrombosis; retinal vein or artery thrombosis) may also be observed. Differences in diagnostic criteria used for essential thrombocythemia as well as the potential for inclusion of patients with prefibrotic myelofibrosis may account for the variability in reported rates of splenomegaly (typically mild), which range from <10% to approximately 50% of patients.

In one study of 150 patients with essential thrombocythemia, the median platelet count ranged from 454,000 to 3,460,000/μL. There is no correlation between the degree of thrombocytosis and risk of thrombosis; however, patients with a platelet count higher than about 1.5 million/μL are at an increased risk for bleeding, attributable, in part, to acquired von Willebrand disease. Acquired von Willebrand disease is due to increased binding of large von Willebrand factor multimers, which are the most hemostatically effective components of the von Willebrand factor protein, to platelets and their removal from the plasma; the finding of decreased ristocetin cofactor activity (e.g., <30%) and loss of high-molecular-weight von Willebrand multimeric proteins on multimer analysis can help establish the diagnosis (Chapter 159).

Polycythemia Vera

Most patients with polycythemia vera are incidentally discovered to have an elevated hemoglobin (defined as hemoglobin >16.5 g/dL in men or >16.0 g/dL in women) and elevated hematocrit (defined as >49% in men or >48% in women). Increased blood hyperviscosity can lead to a constellation of physical examination findings, including hypertension, facial plethora, injection of the conjunctival small vessels and engorgement of the retinal veins on funduscopic examination, erythromelalgia (similar to essential thrombocythemia), splenomegaly (more frequent than hepatomegaly), and tophaceous gout.[7] Relatively common complaints include fatigue, aquagenic pruritus (itching following a warm bath or shower), headache, difficulty concentrating, lightheadedness/dizziness, and nondescript gastrointestinal symptoms such as epigastric discomfort and abdominal fullness/early satiety (E-Table 152-1). Neurologic symptoms, including tinnitus, paresthesias, and the aforementioned visual disturbances, are also encountered in polycythemia vera. In a large international study of patients with polycythemia vera, arterial thrombotic complication, venous thrombosis, or major hemorrhage were noted prior to or at the time of diagnosis in 16, 7, and 4% of patients, respectively.

FIGURE 152-3. Erythromelalgia of the hands in a patient with polycythemia vera characterized by an exon 12 *JAK2* mutation.

Primary Myelofibrosis

The major clinical issues related to primary myelofibrosis include debilitating constitutional symptoms, splenomegaly, progressive cytopenias, potential for evolution to AML (15 to 20% of patients), and reduced survival. With advancing disease, the spleen can become massive in size (filling the left side of the abdomen and to the pelvic brim), resulting in abdominal pain (sometimes with referred left shoulder pain), early satiety, weight loss, and complications including splenic infarction.[8] Extramedullary hematopoiesis resulting in hepatomegaly is also common; complications of extramedullary hematopoiesis include portal hypertension, esophageal or gastric varices, and ascites. Myelofibrosis-associated anemia may be due to several causes, including ineffective hematopoiesis, splenic sequestration, gastrointestinal bleeding, autoimmune hemolytic anemia, or nutritional deficiencies (e.g., vitamin B_{12}). Extramedullary hematopoiesis may involve other sites besides the liver and spleen, such as the paravertebral space, lymph nodes, retroperitoneum, lungs or pleura, genitourinary organs, skin, and bowel. Pulmonary hypertension may be underdiagnosed in myelofibrosis and other myeloproliferative neoplasms and has been associated with increased symptoms (e.g., fatigue and dyspnea) and decreased survival. The incidence of arterial and venous thrombosis is similar to that of essential thrombocythemia.

E-TABLE 152-1 ALL-INCLUSIVE AND GENDER-STRATIFIED PRESENTING FEATURES IN 1545 PATIENTS WITH POLYCYTHEMIA VERA

	N EVALUABLE	ALL PATIENTS (N = 1545)	FEMALES, N = 785 (51%)	MALES, N = 760 (49%)	P-VALUES
Median age, years (range)	1545	61 (18-95)	62 (18-92)	59 (19-95)	**<0.01**
Ages below 40/50 years	1545	10/24%	10/23%	10/26%	0.58
Hemoglobin, median in g/dL (range)	1545	18.4 (15.1-26.5)	17.7 (15.1-24.5)	18.9 (17.1-26.5)	**<0.01**
Hematocrit (median and range)	1545	55 (36-78)	54 (36-76)	57 (42-78)	**<0.01**
Leukocyte count, median × 10^3/μL (range)	1545	10.4 (3-171.6)	10.3 (3-125.5)	10.5 (4.2-171.6)	0.85
Leukocytosis (>10.5 × 10^3/μL), *n* (%)	1545	751 (49%)	375 (48%)	376 (49.5%)	0.5
Platelet count, median × 10^3/μL (range)	1545	466 (7-2370)	509 (7-2370)	419 (37-1410)	**<0.01**
Thrombocytosis (≥450 × 10^3/μL), *n* (%)	1545	817 (53%)	472 (60%)	345 (45.4%)	**<0.01**
Extreme thrombocytosis (≥1000 × 10^3/μL), *n* (%)	1545	58 (4%)	46 (6%)	12 (1.6%)	**<0.01**
Palpable spleen, *n* (%)	1477	534 (36%)	241 (32%)	293 (40.3%)	**<0.01**
Pruritus, *n* (%)	1349	485 (36%)	240 (35.4%)	245 (36.6%)	0.64
Vasomotor symptoms, *n* (%)	1412	403 (28.5%)	213 (30%)	190 (27%)	0.26
Arterial thrombosis before/at diagnosis, *n* (%)	1545	246 (16%)	108 (14%)	138 (18%)	**0.02**
Venous thrombosis before/at diagnosis, *n* (%)	1545	114 (7.4%)	73 (9.3%)	41 (5.4%)	**<0.01**
Major hemorrhage before/at diagnosis, *n* (%)	572	24 (4.2%)	16 (5.5%)	8 (2.8%)	0.11
↑ Lactate dehydrogenase, *n* (%)	732	368 (50%)	203 (54%)	165 (47%)	0.07
Leukoerythroblastic smear, *n* (%)	1056	63 (6%)	28 (5%)	35 (7%)	0.26
Abnormal karyotype, *n* (%)	631	77 (12%)	29 (9%)	48 (15%)	**0.02**
JAK2 mutation, *n* (%)	1268	1239 (98%)	626 (98%)	613 (97.3%)	0.68
V617F/other *JAK2* mutation (%)	1268	95%/3%	95.6%/2.5%	95%/3%	0.68
Serum Epo ↓/normal/↑ (%)	1058	81%/17%/2%	83%/15%/2%	79%/19%/1%	0.17
EEC, *n* (%)	454	331 (73%)	182 (76%)	149 (69.3%)	0.10
Increased red cell mass, *n* (%)	306	277 (91%)	149 (87.7%)	128 (94%)	0.06
Hemoglobin >18.5 g/dL (>16.5 ♀) *n* (%)	1545	1122 (73%)	652 (83%)	470 (62%)	**<0.01**
History of tobacco use, *n* (%)	1301	206 (16%)	74 (11.3%)	132 (20.4%)	**<0.01**
History of diabetes, *n* (%)	1149	97 (8.4%)	41 (7%)	56 (11%)	0.11
History of hyperlipidemia, *n* (%)	1073	196 (18.3%)	98 (18%)	98 (18.5%)	0.85
History of hypertension, *n* (%)	1388	638 (46%)	339 (48%)	299 (43.7%)	0.09

Bold numerals indicate differences that were statistically relevant.
EEC = endogenous erythroid colony; Epo = erythropoietin.
From Tefferi A, Rumi E, Finazzi G, et al. Survival and prognosis among 1545 patients with contemporary polycythemia vera: an international study. *Leukemia*. 2013;27:1874-1881, Table 1.

TABLE 152-3 2022 INTERNATIONAL CONSENSUS CLASSIFICATION DIAGNOSTIC CRITERIA FOR POLYCYTHEMIA VERA, ESSENTIAL THROMBOCYTHEMIA, AND PRIMARY MYELOFIBROSIS

CRITERIA	POLYCYTHEMIA VERA*	ESSENTIAL THROMBOCYTHEMIA†	PRIMARY MYELOFIBROSIS‡
Major criteria	1. Elevated hemoglobin concentration (>16.5 g/dL in men; >16.0 g/dL in women) or elevated hematocrit (>49% in men; >48% in women) or increased red blood cell mass (>25% above mean normal predicted value) 2. Bone marrow biopsy showing age-adjusted hypercellularity with trilineage growth (panmyelosis), including prominent erythroid, granulocytic, and megakaryocytic proliferation with pleomorphic, mature megakaryocytes 3. Presence of *JAK2* V617F or *JAK2* exon 12 mutation	1. Platelet count ≥450,000/μL 2. Bone marrow biopsy showing proliferation mainly of the megakaryocytic lineage, with increased numbers of enlarged, mature megakaryocytes with hyperlobulated nuclei, no significant increase or left shift in neutrophil granulopoiesis or erythropoiesis; very rarely or minor (grade 1) increase in reticulin fibers 3. ICC criteria for *BCR::ABL1*-positive chronic myeloid leukemia, polycythemia vera, primary myelofibrosis, or other myeloid neoplasms are not met 4. *JAK2*, *CALR*, or *MPL* mutation	1. Megakaryocytic proliferation and atypia, without reticulin fibrosis grade >1, accompanied by increased age-adjusted bone marrow cellularity, granulocytic proliferation, and (often) decreased erythropoiesis (**PREFIBROTIC**)§ 2. Megakaryocytic proliferation and atypia, accompanied by reticulin and/or collagen fibrosis grades 2 or 3 (**OVERT**)‖ 3. ICC criteria for *BCR::ABL1*-positive chronic myeloid leukemia, polycythemia vera, essential thrombocythemia, myelodysplastic syndromes, or other myeloid neoplasms are not met 4. *JAK2* or *CALR* or *MPL* mutation, or presence of another clonal marker,¶ or absence of reactive myelofibrosis**
Minor criteria	Subnormal erythropoietin level	Presence of a clonal marker¶ or absence of reactive thrombocytosis	Presence of at least one of the following, confirmed on two separate determinations: • Anemia not attributed to a comorbid condition • Leukocytosis ≥11,000/μL • Palpable splenomegaly • LDH above the upper limit of normal • Leukoerythroblastosis (only in overt primary myelofibrosis)

*The diagnosis of polycythemia vera requires either all three major criteria or the first two major criteria plus the minor criteria. Major criterion 2 (bone marrow biopsy) may not be required in patients with sustained absolute erythrocytosis (hemoglobin concentration in men >18.5 g/dL or >16.5 g/dL in women and hematocrit values >55.5% in men and >49.5% in women) if the major criterion 3 and the minor criteria are present. However, initial myelofibrosis (present in as many as 20% of patients) can only be detected by bone marrow biopsy, and this finding may predict a more rapid progression to overt myelofibrosis (post–polycythemia vera myelofibrosis).

†The diagnosis of essential thrombocythemia requires that all major criteria or the first three major criteria plus the minor criteria are met.

‡The diagnosis of primary myelofibrosis requires that all three major criteria and at least one minor criterion are met.

§First major criterion definition for prefibrotic/early myelofibrosis only (not applicable to overt myelofibrosis).

‖First major criterion definition for overt myelofibrosis only (not applicable to prefibrotic/early myelofibrosis).

¶In the absence of any of the three major clonal mutations, a search for other mutations associated with myeloid neoplasms (e.g., *ASXL1*, *EZH2*, *TET2*, *IDH1*, *IDH2*, *SRSF2*, and *SF3B1* mutations) may be of help in determining the clonal nature of disease.

**Minor (grade 1) reticulin fibrosis secondary to infection, autoimmune disorder, or other chronic inflammatory conditions, hairy cell leukemia, or another lymphoid neoplasm, metastatic malignancy, or toxic (chronic) myelopathies.

ICC = International Consensus Classification; LDH = lactate dehydrogenase.

Patients with myelofibrosis exhibit the greatest symptom burden among the Philadelphia chromosome–negative myeloproliferative neoplasms. In addition to mechanical symptoms referable to splenomegaly, hypercatabolic signs and symptoms such as fatigue, night sweats, low-grade fevers, weight loss, pruritus, gout, and joint or bone pain (most commonly involving the lower extremities) tend to become more omnipresent and severe with disease evolution.

DIAGNOSIS

Diagnostic Criteria for Polycythemia Vera, Essential Thrombocythemia, and Primary Myelofibrosis

The International Consensus Classification uses a combination of histopathologic, laboratory, and molecular data to establish major and minor criteria for the diagnosis of polycythemia vera, essential thrombocythemia, and primary myelofibrosis (Table 152-3). To mitigate the risk of periprocedural bleeding, testing for acquired von Willebrand disease (Chapter 159) should be considered in patients who have elevated platelet counts (e.g., 1 to 1.5 million/μL) associated with major bruising or bleeding or in patients undergoing surgery or delivery of a pregnancy.

Other Causes of Erythrocytosis and Thrombocytosis

For patients presenting with an elevated hemoglobin, history taking should first try to determine whether a spurious erythrocytosis may be present due to hemoconcentration (seen in patients with volume depletion related to conditions such as burns, diarrhea, and diuretics). Family history is important for evaluating congenital forms of erythrocytosis, including causes associated with a decreased p50 (the oxygen tension at which hemoglobin is 50% saturated) such as a high-oxygen-affinity hemoglobin, 2,3-bisphosphoglycerate (2,3-BPG) deficiency, or methemoglobinemia (Chapter 144). Congenital forms of erythrocytosis associated with a normal p50 include mutations in the genes encoding *EPO*[9] or the *EPO* receptor and mutations of genes involved in the oxygen-sensing pathway (e.g., *VHL*, *HIF2A*, and *PHD2*) (Table 152-4). Erythrocytosis mutation panels are now commercially available to test for such variants.

In secondary types of acquired erythrocytosis (see Table 152-4), only red blood cells are increased, whereas in polycythemia vera, red blood cells, as well as the white blood count and platelet count, may be increased because only the latter is a pluripotent hematopoietic stem cell disorder. Molecular testing has greatly facilitated the evaluation of acquired forms of erythrocytosis; in this clinical context, identification of *JAK2* V617F (in 95 to 98% of patients with polycythemia vera) or an exon 12 *JAK2* mutation establishes the diagnosis of polycythemia vera. Iron deficiency and a subnormal EPO level (the latter is a minor diagnostic criterion) are common laboratory findings in polycythemia vera.

Similar to erythrocytosis, the evaluation of thrombocytosis is first directed to ruling out reactive causes, which are much more common than essential thrombocythemia (see Table 152-5). Hereditary forms of thrombocytosis are rare and may be related to germline mutations in the genes encoding thrombopoietin (*THPO*), gelsolin, or *MPL* and *JAK2*, which are distinct from the somatic *MPL* W515 L/K and *JAK2* V617F variants.

If essential thrombocythemia or primary myelofibrosis is suspected and molecular testing is negative for *JAK2* V617F, screening for *CALR* and/or *MPL* mutations is undertaken. Bone marrow examination with expert pathology interpretation is critical to distinguish between essential thrombocythemia (Fig. 152-4), prefibrotic myelofibrosis, and overt primary myelofibrosis (Fig. 152-5) and between clonal and reactive forms of myeloproliferation, particularly in cases where a clonal marker cannot be found (e.g., triple-negative patients). The peripheral blood smear may demonstrate large or giant platelets in all three myeloproliferative neoplasms. In primary myelofibrosis, variable degrees of leukoerythroblastosis may be observed, consisting of circulating immature granulocytes and nucleated and teardrop red blood cells (dacrocytes) (Chapter 143). Increased numbers of circulating $CD34^+$ cells can be detected in the blood, and their numbers increase with disease severity. The bone marrow reveals myeloid hyperplasia, clustered atypical megakaryocytes, and variable degrees of reticulin (or collagen) fibrosis (as well as osteosclerosis) depending on disease stage (see Fig. 152-5). Specific clinical and laboratory criteria have been codified for a diagnosis of post–polycythemia vera myelofibrosis

TABLE 152-4 DIFFERENTIAL DIAGNOSIS OF ERYTHROCYTOSIS

SPURIOUS ERYTHROCYTOSIS (also referred to as relative polycythemia, stress erythrocytosis, stress polycythemia, benign polycythemia, Gaisböck syndrome, and pseudopolycythemia)

A. Cases are characterized by an increased hematocrit and normal or decreased red blood cell (RBC) total mass resulting from a decreased plasma volume. Hemoconcentration can result from vomiting or diarrhea, burns, aggressive diuretic therapy, decreased fluid intake, diabetic ketoacidosis, and renal disease. Stress and hypertension can also be associated with a decreased plasma volume.

CONGENITAL ERYTHROCYTOSIS

A. Associated with reduced p50 (partial pressure of oxygen at which 50% of hemoglobin is saturated with oxygen)
  i. Mutant high-oxygen-affinity hemoglobinopathy
  ii. 2,3-Bisphosphoglycerate deficiency
  iii. Methemoglobinemia
B. Associated with normal p50
  i. *VHL* mutations (Chuvash polycythemia)
  ii. *PHD2* mutations
  iii. *HIF2A* mutations
  iv. *EPO* receptor mutations
  v. *EPO* gain-of-function mutation

ACQUIRED ERYTHROCYTOSIS

A. Primary (clonal): Polycythemia vera (associated with low EPO level)
B. Secondary (associated with normal to high EPO levels)
  i. Chronic hypoxia states
    (1) Chronic lung disease
    (2) Right-to-left cardiopulmonary shunts
    (3) High-altitude habitat
    (4) Tobacco use or carbon monoxide poisoning
    (5) Sleep apnea or hypoventilation syndrome
    (6) Renal artery stenosis
  ii. Hypoxia-independent
    (1) Use of androgens (e.g., testosterone; danazol)
    (2) Use of erythropoietin
    (3) Post–renal transplant
    (4) Anti-VEGF therapy
    (5) Erythropoietin-secreting tumors: hepatocellular carcinoma, renal cell carcinoma, (cerebellar) hemangioblastoma, uterine leiomyoma, meningioma, carcinoid tumor, metanephric adenoma, pheochromocytoma, parathyroid adenoma
    (6) POEMS

EPO = erythropoietin; POEMS = polyneuropathy, organomegaly, endocrinopathy, M protein, and skin (changes) syndrome; VEGF = vascular endothelial growth factor.

TABLE 152-5 DIFFERENTIAL DIAGNOSIS OF THROMBOCYTOSIS

PRIMARY (CLONAL)	SECONDARY (REACTIVE)
ESSENTIAL THROMBOCYTHEMIA	**INFECTION**
OTHER MYELOID NEOPLASMS	Acute bacterial/viral infections
Primary myelofibrosis	Chronic infections (e.g., tuberculosis)
Chronic myeloid leukemia	**NONMALIGNANT BLOOD CONDITIONS**
Del(5q) myelodysplastic syndrome	Iron deficiency anemia
Myelodysplastic/myeloproliferative neoplasms with ring sideroblasts and thrombocytosis (MDS)/MPN-RS-T	Acute blood loss
	Acute hemolytic anemia
	Rebound following use of chemotherapy
	Rebound following treatment of ITP
	Rebound from ETOH-related thrombocytopenia
	AUTOIMMUNE/INFLAMMATORY CONDITIONS
	Inflammatory bowel disease
	Vasculitides
	Rheumatoid arthritis
	Celiac disease
	MALIGNANCIES
	Lymphoma
	Metastatic cancer
	POEMS
	MEDICATIONS
	Thrombopoietin receptor agonists
	All-trans retinoic acid (ATRA)
	Interleukin-1β
	Vincristine
	Epinephrine
	Glucocorticoids
	TISSUE DAMAGE
	Severe trauma, burns
	Acute pancreatitis
	Myocardial infarction
	Postsurgical period (e.g., CABG)
	ALLERGIC REACTION
	EXERCISE

CABG = coronary artery bypass graft; ETOH = alcohol; ITP = immune (or idiopathic) thrombocytopenic purpura; MDS = myelodysplastic syndrome; POEMS = polyneuropathy, organomegaly, endocrinopathy, M protein, and skin (changes) syndrome.

and post–essential thrombocythemia myelofibrosis, including confirmation of a prior diagnosis of polycythemia vera or essential thrombocythemia and minimal thresholds of bone marrow fibrosis. Table 152-6 lists other causes of fibrosis involving the bone marrow.

TREATMENT

Essential Thrombocythemia and Polycythemia Vera

For patients with essential thrombocythemia and polycythemia vera, no therapy has been shown to alter the natural history of disease (e.g., transformation to post–polycythemia vera or post–essential thrombocythemia myelofibrosis, acute myeloid leukemia, or overall survival), and therapies are aimed at mitigating the risk of future vascular events and disease-related constitutional symptoms.[10] The therapeutic approaches to the two conditions have many similarities (Table 152-7).

Aspirin

Low-dose aspirin (100 mg daily), which is foundational to the treatment of polycythemia vera regardless of risk group, results in an approximately 60% reduction in the relative risk of the composite end point of nonfatal myocardial infarction, nonfatal stroke, or death from cardiovascular causes, without significantly increasing the risk of major bleeding.

In essential thrombocythemia, treatment decisions are based on the classification of patients into very low-, low-, intermediate-, and high-risk groups according to the revised International Prognostic Score for Essential Thrombocythemia (IPSET)–thrombosis risk stratification. For patients with very low-risk essential thrombocythemia (age ≤60 years, no *JAK2* mutation, no prior history of thrombosis), aspirin or observation alone may be considered. Pharmacologic data suggest an optimal aspirin regimen of 100 mg twice daily to maximize platelet inhibition without adverse effects.[A1] For a patient with low-risk essential thrombocythemia (age ≤60 years, with *JAK2* mutation, no prior history of thrombosis) or intermediate-risk essential thrombocythemia (age >60 years, no *JAK2* mutation, no prior history of thrombosis), only aspirin (81 mg daily) is recommended.

Cytoreductive Therapy

Cytoreductive therapy should be administered to patients who have high-risk essential thrombocythemia (history of thrombosis at any age or age >60 years with *JAK2* mutation), patients who have high-risk polycythemia vera, and patients who have lower-risk forms of essential thrombocythemia or polycythemia vera but who develop any signs or symptoms of new thrombosis, acquired von Willebrand disease, disease-related major bleeding, symptomatic progressive splenomegaly, progressive leukocytosis or thrombocytosis, worsening disease-related symptoms (pruritus, night sweats, fatigue), or vasomotor/microvascular disturbances (headaches, chest pain, erythromelalgia) refractory to aspirin.[11]

For polycythemia vera, intensive treatment to maintain a hematocrit target of less than 45% results in an almost four-fold reduction in the risk of cardiovascular death and major thrombosis compared with a hematocrit target of 45 to 50%. A lower hematocrit cutoff (42%) may be appropriate for females (attributed to their lower red blood cell mass compared with males) or for patients with progressive symptoms, but no randomized data are available to support this recommendation.

Hydroxyurea or pegylated interferons are generally considered front-line therapy, but interferons have become increasingly preferred in younger patients due to their ability to elicit high rates of hematologic remissions and molecular responses, without evidence of leukemogenicity.

Hydroxyurea

In high-risk essential thrombocythemia, hydroxyurea can reduce the risk of thrombosis from about 25% to about 5%. Hydroxyurea plus low-dose aspirin is at least as good as anagrelide plus low-dose aspirin and is recommended as first-line therapy for essential thrombocytopenia.[12] Initial and subsequent dosing of hydroxyurea is tailored to individual blood counts and tolerance. A typical starting dose is 500 to 1000 mg daily.

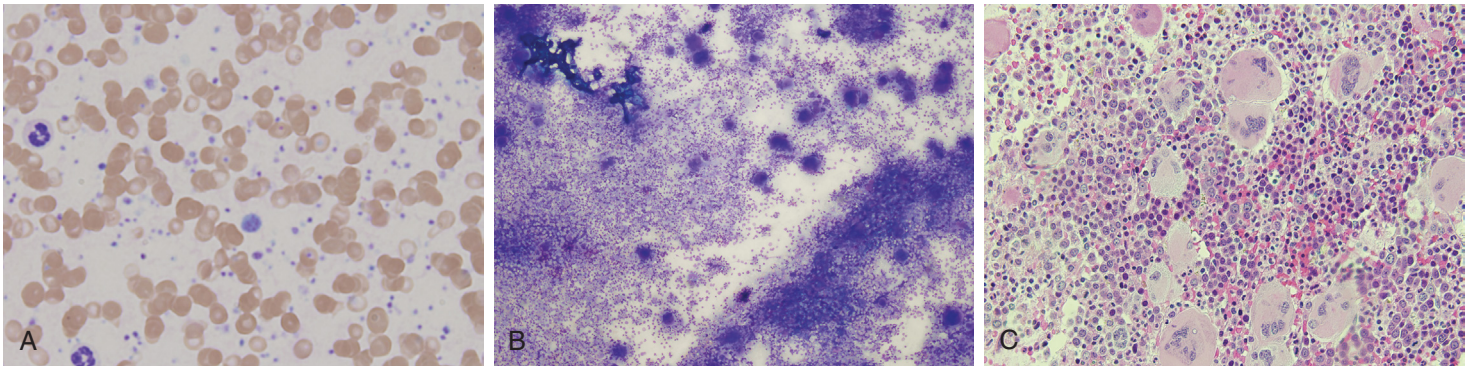

FIGURE 152-4. Histopathology of essential thrombocythemia. A, Peripheral blood demonstrating increased numbers of platelets, including large forms. Bone marrow aspirate (**B**) and core biopsy (**C**) revealing a marked increase in numbers of megakaryocytes.

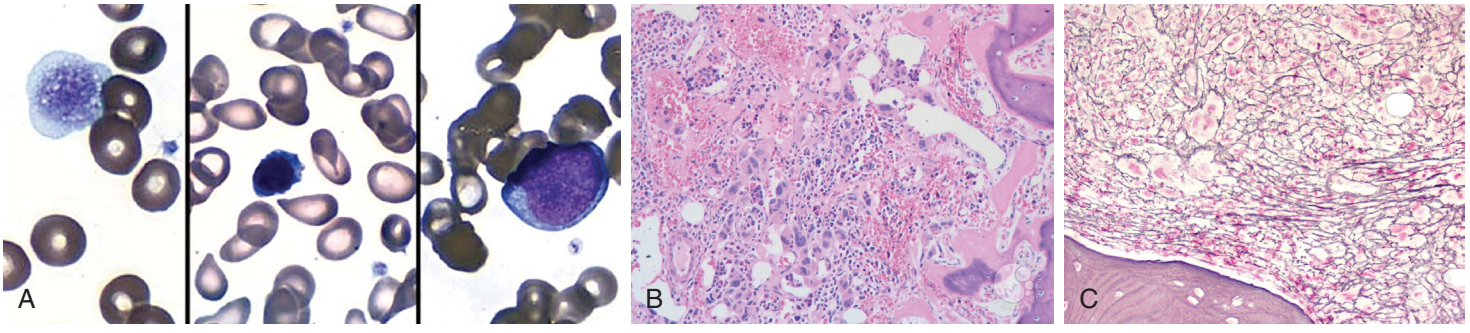

FIGURE 152-5. Histopathology of primary myelofibrosis. A, Leukoerythroblastic blood findings in primary myelofibrosis including a large platelet, teardrop red blood cells (dacrocytes), and a myeloblast. **B,** Core bone marrow biopsy showing megakaryocyte clustering with thick irregular bone trabeculae with osteomyelosclerosis (H&E stain × 100). **C,** Reticulin stain of bone marrow biopsy confirms extensive (grade MF-3) fibrosis. (*B and C,* Courtesy American Society of Hematology image bank, https://imagebank.hematology.org/.)

TABLE 152-6 CAUSES OF BONE MARROW FIBROSIS

MYELOID NEOPLASMS/DISORDERS
Primary myelofibrosis
Chronic myeloid leukemia
Myelodysplastic syndromes
Myelodysplastic/myeloproliferative neoplasms
Systemic mastocytosis
Chronic eosinophilic leukemias
Acute myeloid leukemias (including acute myelofibrosis/acute megakaryocytic leukemia)
Gray platelet syndrome
LYMPHOID NEOPLASMS
Hairy cell leukemia
Multiple myeloma
Lymphomas
HISTIOCYTIC AND DENDRITIC CELL NEOPLASMS
Langerhans cell histiocytosis
NONHEMATOLOGIC CONDITIONS
Autoimmune myelofibrosis
Connective tissue disorders
Chronic infections (e.g., tuberculosis)
Vitamin D deficiency (rickets)
Renal osteodystrophy
Pulmonary hypertension
Metastatic cancers (e.g., prostate, breast, gastric)

TABLE 152-7 RISK-BASED STRATIFICATION OF TREATMENT OPTIONS IN ESSENTIAL THROMBOCYTHEMIA AND POLYCYTHEMIA VERA

RISK GROUP*	ESSENTIAL THROMBOCYTHEMIA	POLYCYTHEMIA VERA
Very-low	Observation	N/A
Low	Low-dose aspirin	Low-dose aspirin + phlebotomy
Intermediate	Low-dose aspirin	N/A
High	Low-dose aspirin + cytoreduction Cytoreduction options: Hydroxyurea† or Interferons (based on patient-specific variables)‡ or Anagrelide	Low-dose aspirin + phlebotomy + cytoreduction Cytoreduction options: Hydroxyurea or Interferons (based on patient-specific variables)‡ Ruxolitinib for hydroxyurea-resistant or intolerant patients
	Manage cardiovascular risk factors; monitor for new thrombosis or bleeding; progressive disease-related signs and symptoms (e.g., splenomegaly, leukocytosis, thrombocytosis, pruritus, night sweats, fatigue)	

*Risk groups are defined in the text.
†For older patients, busulfan may be considered in patients not responding to or tolerating hydroxyurea.
‡Interferon alfa-2b, peginterferon alfa-2a, or ropeginterferon alfa-2b (approved in the European Union and United States).
N/A = not applicable.

In polycythemia vera, the use of hydroxyurea plus phlebotomy as needed significantly reduces the risk of thrombosis compared with phlebotomy alone, probably without increasing the risk for leukemic transformation. As a result, hydroxyurea is a first-line cytoreductive therapy for polycythemia vera.[13]

Interferons

For patients with essential thrombocythemia or polycythemia vera, interferons (interferon alfa-2b, PEG-interferon alfa-2a, or PEG-interferon alfa-2b) are an alternative first-line treatment to hydroxyurea, particularly for younger patients or for pregnant women who need cytoreductive therapy (see Table 152-7). The addition of a polyethylene glycol (PEG) moiety to IFN-α results in a longer half-life, which translates into less frequent administration, more drug stability, less immunogenicity, and less toxicity and is favored by most practitioners. Nevertheless, depending on the study, PEG-interferons have resulted

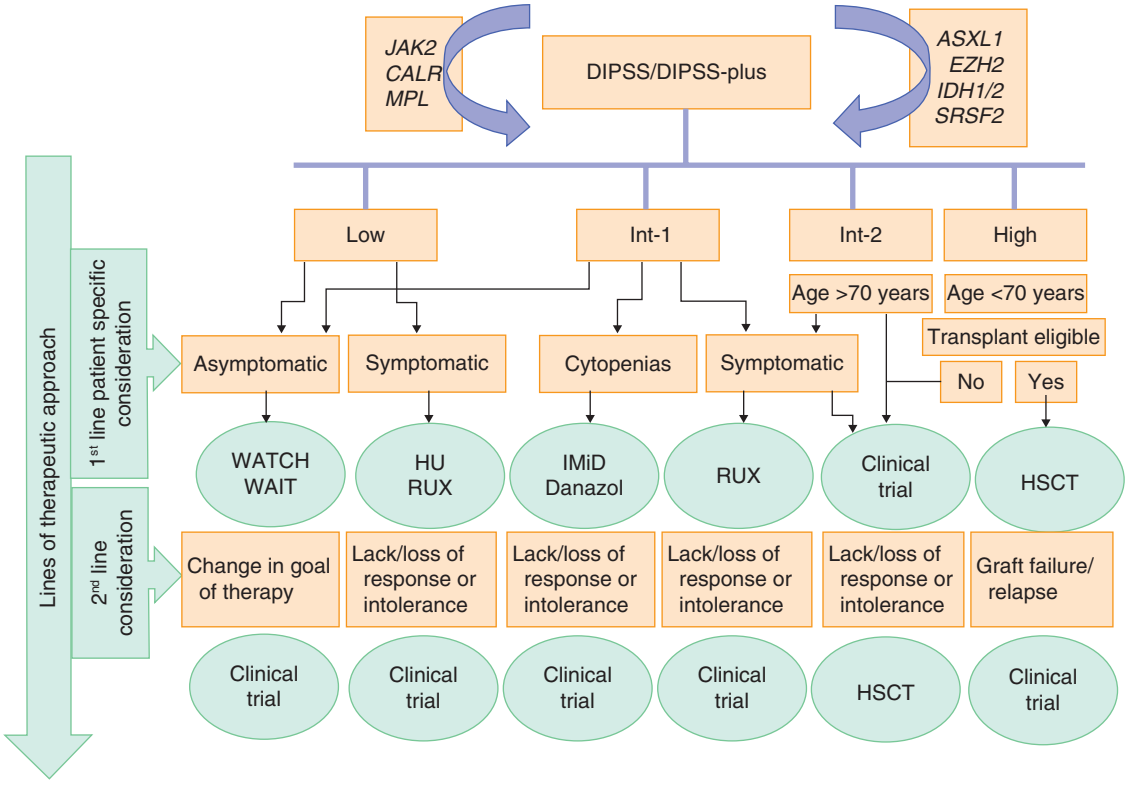

FIGURE 152-6. Risk-based stratification for treatment decision making in myelofibrosis. DIPSS = Dynamic International Prognostic Scoring System (see text under "Prognosis" for "Primary Myelofibrosis"); HSCT = hematopoietic stem cell transplant; HU = hydroxyurea; IMiD = immunomodulatory agents; Int = intermediate; RUX = ruxolitinib. (From Mascarenhas J. Looking forward: novel therapeutic approaches in chronic and advanced phases of myelofibrosis. *Hematology Am Soc Hematol Educ Program*. 2015;2015:329-339, Fig 3.)

in treatment discontinuation rates of 15 to 40%. Toxicities include myelosuppression, flulike symptoms (e.g., fatigue, myalgias/arthralgias), transaminitis, autoimmune phenomena, hypothyroidism, and depression.

Studies of PEG-interferon-alfa-2a in patients with polycythemia vera and essential thrombocythemia reveal complete hematologic remission rates of 75 to 95% and complete molecular remission of the *JAK2* V617F mutation in 17 to 24% of patients. The presence of *TET2, ASXL1, EZH2, DNMT3A*, and *IDH1/2* mutations is associated with failure to achieve a complete molecular remission.

In a randomized trial of pegylated IFN-alfa-2a compared with hydroxyurea in high-risk polycythemia vera and essential thrombocythemia, no significant differences were noted in response rates after 24 months.[A2] However, ropeginterferon-alfa-2b provides superior and durable hematologic and molecular response rates compared with hydroxyurea at 5 years.[A3] In low-risk polycythemia vera patients, ropeginterferon-alfa-2b can also increase the ability to maintain the hematocrit <45% in about 85% of patients compared with 60% of patients with phlebotomy alone (p = .0075).[A4]

Anagrelide

Anagrelide (starting at 1 mg twice daily and not to exceed 10 mg/day), which inhibits the maturation of megakaryocytes, can reduce the platelet count in essential thrombocythemia.[A5] However, it may be associated with more thrombotic and bleeding events than hydroxyurea.[A6] As a result, it is a second-line agent.

Ruxolitinib

Ruxolitinib, a *JAK1/JAK2* inhibitor (starting dose 10 mg twice daily), is useful in patients who have phlebotomy-dependent polycythemia vera with or without splenomegaly and an inadequate response to or intolerance of hydroxyurea. It can provide durable responses and improvement of disease-related symptoms, with generally good tolerability.[A7]

Other Agents

Busulfan is an alkylating agent that can be used as an alternative cytoreductive agent in older patients with polycythemia vera or essential thrombocythemia. Special care has to be given to adjusting the dose based on blood counts because prolonged severe myelosuppression/aplasia has been reported.

In polycythemia vera, iron deficiency and increased red blood cell production result in suppression of the master iron homeostasis hormone hepcidin, which in turn leads to increased iron availability for erythropoiesis. Clinical trials are now in progress evaluating whether hepcidin mimetics can reduce phlebotomy requirements in patients with polycythemia.[14]

Primary Myelofibrosis

The Dynamic International Prognostic Scoring System (DIPSS)-(Plus) risk stratification scheme is used to guide decision making regarding treatment options (Fig. 152-6), with clinical trials encouraged in all risk groups. Allogeneic hematopoietic stem cell transplantation is the only curative modality, and all other therapies are used with palliative intent. Transplant generally should be recommended for patients with intermediate-2 or high-risk disease, nontransplant therapy should be recommended for low-risk disease, and more individualized risk counseling is required for patients with intermediate-1 risk disease for which the risk-benefit ratio is less clear. In such individuals, low platelet counts and identification of potentially high molecular–risk mutations (e.g., *ASXL1*) may assist with decision making.

Individuals with asymptomatic low-risk primary myelofibrosis do not require treatment and are monitored regularly for symptoms and signs of disease progression.[15,16] Symptomatic patients with low- or intermediate-risk disease have demonstrated responses in splenomegaly and constitutional symptoms with ruxolitinib in nonrandomized studies. Although interferons can elicit hematologic responses, reduction of splenomegaly, and improvement of bone marrow histopathology in earlier stages of myelofibrosis, responses in more advanced forms of disease are modest.

Medical Therapy

Ruxolitinib, with dosing based on platelet count under expert supervision, is recommended to treat patients with intermediate- to high-risk primary, post–polycythemia vera myelofibrosis and post–essential thrombocytopenia myelofibrosis to mitigate symptomatic splenomegaly (Fig. 152-7) and disease-related symptoms. Ruxolitinib also is associated with about a 30% reduction in the risk of death. Therapy is generally continued until loss of response (e.g., worsening splenomegaly and/or symptoms or unacceptable toxicity).

The majority of patients treated with ruxolitinib do not experience significant reductions in *JAK2* V617F allele burden or bone marrow fibrosis. High-grade anemia and thrombocytopenia are common with ruxolitinib, usually improve after the first 8 to 12 weeks of therapy, and require careful dose adjustment to maximize efficacy while minimizing myelosuppression. Ruxolitinib is also associated with an increased risk of opportunistic infections, including herpes zoster, reactivation of hepatitis B virus, tuberculosis, and rare cases of progressive multifocal leukoencephalopathy.

JAK inhibitors are useful and reasonably well-tolerated.[17] The JAK2 inhibitor fedratinib (400 mg daily) is first- or second-line therapy for adult patients with intermediate-2 or high-risk primary or secondary (post–polycythemia vera or post–essential thrombocythemia) myelofibrosis and a baseline platelet count of ≥50,000 μL based on its ability to reduce splenic volume.[A8] However, it has a black box warning because of a potential increased risk of serious and fatal Wernicke encephalopathy. Thiamine levels must be checked in all patients prior to starting fedratinib and periodically during treatment.

Another *JAK1/JAK2* inhibitor, momelotinib (200 mg daily), is noninferior to ruxolitinib in reducing splenic volume,[A9] but is not as good for reducing the

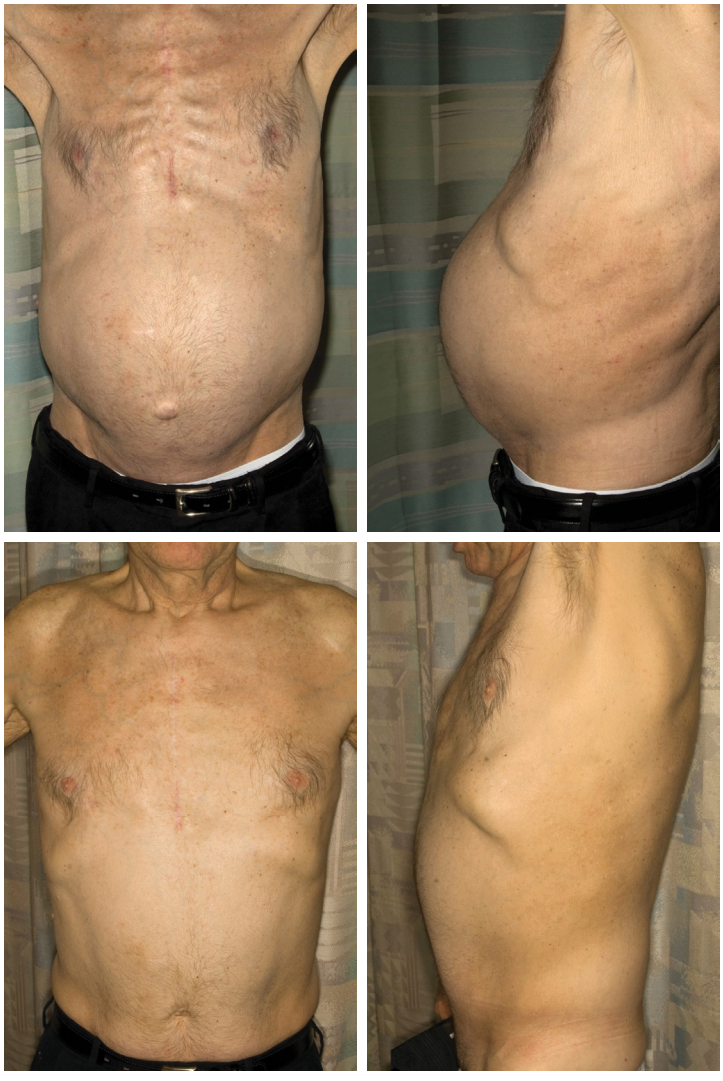

FIGURE 152-7. JAK inhibition in myelofibrosis. Marked reduction in massive splenomegaly after 2 months of JAK inhibitor therapy. (Photos courtesy Dr. Srdan Verstovsek, MD Anderson Cancer Center.)

symptomatic burden. In patients previously treated with ruxolitinib, momelotinib is not superior to best available therapy in reducing spleen volume.[A10] However, momelotinib may be useful to mitigate myelofibrosis-associated anemia by reducing hepcidin levels.

Pacritinib (200 mg twice daily)[A11,A12] is an oral multikinase inhibitor that targets JAK2 (as well as FLT3, CSF1R, and IRAK1) that can reduce splenic volume and improve symptoms, even in patients with severe baseline cytopenias. It is FDA-approved for myelofibrosis patients with a platelet count <50,000/μL.

Other drugs being evaluated as monotherapy or in combination with JAK inhibitors in the front- or second-line therapy include telomerase inhibitors (imetelstat), BET inhibitors (e.g., CPI-06010), BCL-2 inhibitors (e.g., navitoclax), lysine-specific demethylase 1 (LSD1) inhibitors (e.g., bomedemstat), MDM2 blockade (e.g., KRT-232), and various antifibrotic agents that target the bone marrow microenvironment.

Anemia is an unmet need not served (and often worsened) with ruxolitinib treatment. In addition to support with red blood cell transfusions, erythropoiesis-stimulating agents under expert supervision have exhibited responses in about one-third of patients with myelofibrosis. Androgens such as danazol (200 to 300 mg twice daily) can improve anemia in 20 to 30% of individuals, more commonly in non–transfusion-dependent patients. Prostate cancer screening and monitoring of liver function tests are recommended for patients receiving danazol. Luspatercept, which is an erythroid maturation agent that acts as an activin receptor type IIB fusion protein ligand trap that targets the transforming growth factor beta pathway, is currently under evaluation in myelofibrosis patients with anemia.

Splenectomy

The need for splenectomy has probably decreased since the availability of ruxolitinib. Nevertheless, patients who have symptomatic splenomegaly refractory to JAK inhibitors and hydroxyurea may respond to splenectomy, with about a 67% response rate for splenomegaly-related discomfort, a 50% response rate for portal hypertension, and a 23% response rate for transfusion-dependent anemia. However, surgical-related mortality is about 9%, and surgical-related morbidity is about 30%. Postsplenectomy complications (Chapter 154) include infection, bleeding, thrombosis, hepatomegaly, and extreme thrombocytosis or leukocytosis.

Radiation Therapy

Radiation therapy is an option for both hepatosplenic and nonhepatosplenic extramedullary hematopoiesis, which can be associated with complications such as spinal cord compression, pleural effusion or ascites, pulmonary hypertension, cardiac tamponade, and hydronephrosis. Splenic irradiation (100 to 500 cGy in 5 to 10 fractions) induces transient reduction in splenomegaly but can be associated with persistent, life-threatening pancytopenia. Lower doses of radiation (100 cGy total dose in four daily fractions of 25 cGy) have been shown to be safe and effective.

Allogeneic Hematopoietic Stem Cell Transplantation

Allogeneic hematopoietic stem cell transplantation (Chapter 163) is the only potentially curative therapy for myelofibrosis. Candidacy for transplantation is based on age, performance status, major comorbid conditions, psychosocial status, patient preference, and availability of caregiver(s). Myeloablative conditioning is associated with higher rates of treatment-related nonrelapse mortality compared with reduced-intensity conditioning, whereas the latter is associated with a higher risk of disease relapse. Long-term survival is observed in approximately 30 to 60% of patients and depends on the conditioning regimen and the source of stem cells (e.g., matched-sibling compared with unrelated donor). In prospective trials and retrospective analyses of reduced-intensity allogeneic transplantation, the respective 5-year overall survival and nonrelapse mortality rates have ranged from 47 to 67% and 16 to 24%.

For patients with accelerated-phase myelofibrosis (10 to 19% circulating blasts), reduced-intensity allogeneic hematopoietic stem cell transplantation can provide an estimated 5-year overall survival of 65% and a 5-year incidence of relapse of 30%.[18]

Special Situations

Pregnancy in the setting of polycythemia vera and essential thrombocythemia is a higher-risk clinical situation that warrants consultation with a high-risk obstetrician. Patients with essential thrombocythemia have an increased risk of first trimester pregnancy loss. The *JAK2* V617F mutation is an adverse prognostic factor for pregnancy outcome, and retrospective analyses have shown that low-dose aspirin is associated with a reduction in pregnancy complications, especially in patients with *JAK2*-mutated essential thrombocythemia. In low-risk pregnancy, low-dose aspirin is recommended throughout pregnancy, and low-molecular-weight heparin for 6 weeks postpartum; for high-risk pregnancy (previous microcirculatory disturbances, presence of two or more hereditary thrombophilic factors, severe complications in a previous pregnancy, age >35 years, and platelet count >1,000,000/μL), prophylactic low-molecular-weight heparin with low-dose aspirin is recommended throughout pregnancy and the postpartum period. Interferon is generally considered safe during pregnancy and is the preferred agent when cytoreduction is required and its benefits to the mother outweigh potential risks to the fetus. Hydroxyurea should be avoided, including during the breast-feeding period.

Given the thrombohemorrhagic diatheses observed in myeloproliferative neoplasms, optimization of blood counts (e.g., with phlebotomy or cytoreduction) is a high priority before elective surgery. Multidisciplinary collaboration with the surgical team is recommended to evaluate the type and duration of prophylactic antiplatelet or anticoagulation therapy needed in the perioperative setting, in conjunction with close surveillance of thromboembolism.

PROGNOSIS

Polycythemia Vera and Essential Thrombocythemia

Survival

In polycythemia vera, older age, leukocytosis, venous thrombosis, and abnormal karyotype adversely affect survival, with median survivals ranging from about 11 years to about 28 years. The cumulative incidence of transformation to leukemia is 2.3% at 10 years, 5.5% at 15 years, and 7.9% at 20 years. Resistance to hydroxyurea is associated with a 5.6-fold increase in the risk of death and a 6.8-fold increase in the risk of transformation to post–polycythemia vera myelofibrosis and AML.

In patients with essential thrombocythemia, age 60 years or older, leukocyte count of ≥11,000/μL, and prior thrombosis are associated with poorer survival. Based on weighted points assigned to these variables, patients were allocated to three risk categories: low (0 points; median survival not reached); intermediate (1 to 2 points; median survival 24.5 years); and high (3 to 4 points; median survival 13.8 years) (E-Table 152-2). The incidence of leukemic transformation is less than 5% in patients with essential thrombocythemia.

E-TABLE 152-2 PROGNOSTIC MODELS OF SURVIVAL AND THROMBOSIS IN ESSENTIAL THROMBOCYTHEMIA

PROGNOSTIC MODEL	RISK GROUPS AND CLINICAL RELEVANCE
Conventional score for prediction of vascular complications (European LeukemiaNet recommendations)	
At least one of the following risk factors: • Age ≥60 yr • Previous thrombosis or major bleeding • PLT count ≥1,500,000/μL	Low risk: age <60 yr AND no history of thrombosis or major bleeding AND PLT count <1,500,000/μL, that is, none of the three major risk factors High risk: age ≥60 yr AND/OR history of thrombosis or major bleeding AND/OR PLT count ≥1,500,000/μL, that is, at least one of the three major risk factors While low-risk patients are just followed (observation alone) or given low-dose aspirin, high-risk patients are given a cytoreductive treatment plus low-dose aspirin
IPSET-thrombosis (International Prognostic Score for Essential Thrombocythemia: estimates the risk of thrombosis)	
Risk factors (weight): • Age ≥60 yr (1 point) • Previous thrombosis (2 points) • Cardiovascular risk factors* (1 point) • *JAK2*(V617F) mutation (2 points)	Low risk: 0-1 point (probability of thrombotic events: 1.03% of patients/year) Intermediate risk: 2 points (2.35% of patients/year) High risk: ≥3 points (3.56% of patients/year) Potential therapeutic implications: (1) observation alone may be adequate in patients with no risk factors; (2) low-dose aspirin should be used in all patients with *JAK2* (V617F) and/or cardiovascular risk factors; (3) older patients (≥60 yr) without additional risk factors may not need a cytoreductive treatment; (4) conversely, a cytoreductive treatment may be considered in younger patients (<60 yr) with *JAK2*-mutant essential thrombocythemia and concomitant cardiovascular risk factors, even in the absence of previous thrombosis
IPSET (International Prognostic Score for Essential Thrombocythemia: predicts survival)	
Risk factors (weight): • Age ≥60 yr (2 points) • Previous thrombosis (1 point) • Leukocyte count >11 × 10^9/L (1 point)	Low risk: 0 (median survival not reached) Intermediate risk: 1-2 points (median survival, 24.5 yr) High risk: 3-4 points (median survival, 13.8 yr)

*Cardiovascular risk factors include hypertension, diabetes, and tobacco use.

PLT = platelets.

From Rumi E, Cazzola M. Diagnosis, risk stratification, and response evaluation in classical myeloproliferative neoplasms. *Blood*. 2017;129:680-692, Table 4.

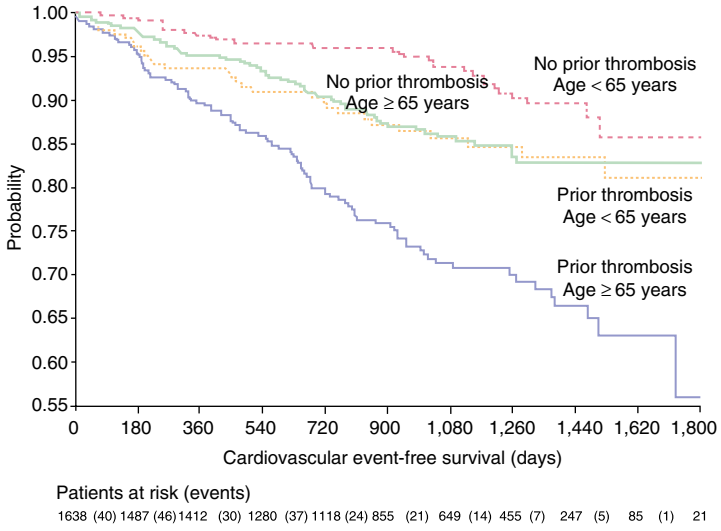

Risk group	# events/ 100 persons/year
Age <65 without prior thrombosis	2.5
Age ≥65 without prior thrombosis	4.9
Age <65 with prior thrombosis	5.0
Age ≥65 with prior thrombosis	10.9

FIGURE 152-8. Cardiovascular event–free survival of 1638 patients with polycythemia vera according to age and history of thrombosis.

Thrombosis

Conventional assessment of thrombosis risk in essential thrombocythemia (and polycythemia vera) separates patients into low- and high-risk categories based on the absence or presence of either age older than 60 years or history of thrombosis (Fig. 152-8). Marked thrombocytosis (e.g., platelet count >1.5 million/μL) is associated with a higher risk of bleeding than thrombosis.

An international study of patients with essential thrombocythemia identified cardiovascular risk factors and *JAK2* V617F mutation status as additional independent risk factors that were used to validate a three-tiered prognostic model (IPSET-thrombosis) consisting of low-, intermediate-, and high-risk patients with respective thrombosis risks of 1.03%, 2.35%, and 3.56% of patients/year (see E-Table 152-2). IPSET-thrombosis outperformed the two-tiered (low-risk 0.95% of patients/year vs. high-risk 2.86% of patients/year) risk stratification in predicting future vascular events.

Subsequent analysis of IPSET-thrombosis revealed that among low-risk patients, thrombosis risk was significantly lower in patients with nonmutated *JAK2* in the absence of cardiovascular risk factors (0.44%) compared with when they are present (1.05%). In addition, the risk of thrombosis in the presence of the *JAK2* mutation without cardiovascular risk factors and in the presence of both *JAK2* mutation and cardiovascular risk factors were 1.59% and 2.57%, respectively. These observations led to the development of the revised IPSET-thrombosis scoring system, which has been independently validated and stratifies patients into four risk groups: very low risk (age ≤60 years, no prior history of thrombosis, and no *JAK2* mutation); low risk (age ≤60 years, no prior history of thrombosis, and having a *JAK2* mutation); intermediate risk (age >60 years, no prior history of thrombosis, and no *JAK2* mutation), and high risk (prior history of thrombosis and/or age >60 years with a *JAK2* mutation).

Primary Myelofibrosis

The Dynamic International Prognostic Scoring System (DIPSS)-Plus utilizes eight clinical and laboratory parameters to refine risk prognostication in patients with primary myelofibrosis: age >65 years, hemoglobin <10 g/dL, leukocyte count >25,000/μL, circulating blasts ≥1%, constitutional symptoms, unfavorable karyotype, red cell transfusion need, and platelet count <100,000/μL. Four risk categories were generated based on the number of adverse points: low

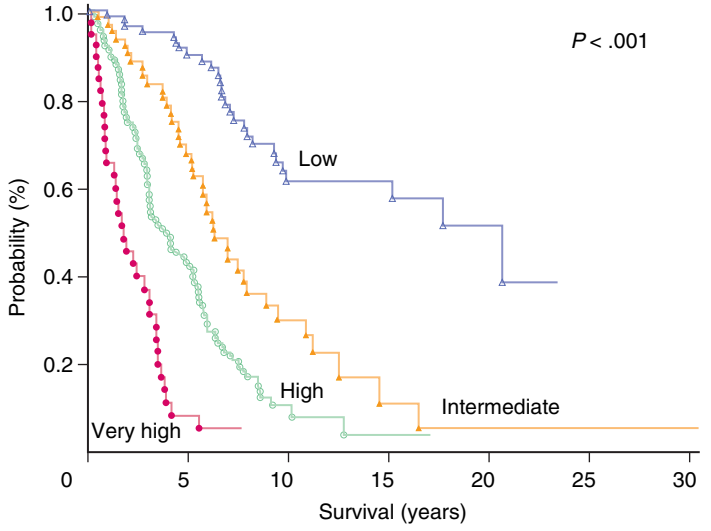

FIGURE 152-9. Mutation-enhanced International Prognostic Score System 70-Plus: mutation-enhanced international prognostic score system for patients with primary myelofibrosis. Mayo training cohort. (Adapted from Guglielmelli P, Lasho TL, Rotunno G, et al. MIPSS70: mutation-enhanced international prognostic score system for transplantation-age patients with primary myelofibrosis. *J Clin Oncol*. 2018;36:310-318, Fig 1 and Table 3.)

risk (zero adverse points); intermediate-1 risk (1 adverse point); intermediate-2 risk (2 to 3 adverse points); and high risk (4 to 6 adverse points), with respective median survivals of 180, 80, 35, and 16 months. In a multivariate analysis, platelet count <100,000/μL and unfavorable cytogenetics were independent predictors of leukemia-free survival. The Mutation-enhanced International Prognostic Scoring System (MIPSS)-Plus prognostic scoring system integrates mutational data (absence of *CALR* type-1 mutation, presence of a high–molecular risk mutation [i.e., *ASXL1*, *EZH2*, *SRSF2*, *IDH1/2*], and presence of two or more high–molecular risk mutations) in addition to clinical and cytogenetic information to improve risk stratification in transplantation-eligible patients (Fig. 152-9).[19] The MIPSS70+ version 2.0 prognostic scoring system provides additional information about risk with the addition of a very high-risk cytogenetic category and the high-risk *U2AF1* Q157 mutation.

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For the General References and other additional features, please visit Elsevier eBooks+ at https://ebooks.health.elsevier.com.

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153 LEUKOCYTOSIS AND LEUKOPENIA

NANCY BERLINER

The normal peripheral white blood cell count (WBC) ranges between 4500/μL and 10,000/μL, with a mean of 7500/μL, and is composed of neutrophils, lymphocytes, monocytes, basophils, and eosinophils. Because neutrophils usually represent about 60% of the peripheral WBC, derangement in the WBC usually reflects elevation or reduction in the absolute neutrophil count. Leukocytosis (an elevated WBC) and leukopenia (a depressed WBC) may be secondary to an underlying disease or exposure, or they may be manifestations of a primary hematologic disorder.

NORMAL NEUTROPHIL DYNAMICS

Neutrophils arise in the bone marrow from multipotent progenitor cells that also give rise to erythrocytes, megakaryocytes, eosinophils, basophils, and monocytes. Neutrophil precursors in the marrow mature over 6 to 10 days to form a storage pool of mature neutrophils (Fig. 153-1). Acetylation of C/EBPε, a member of the CCAAT/enhancer binding protein family of transcription factors, is required for secondary and tertiary granule formation and for terminal neutrophil differentiation. Together, the marrow populations make up about 95% of the body's total granulocyte mass (20% neutrophil precursors, 75% mature bands and neutrophils). The circulating neutrophil pool thus represents only the remaining approximately 5% of the body's total neutrophils, just over half of which at any given time are adherent to the vascular endothelium and pooled in the spleen, a phenomenon termed *margination*. Marginated neutrophils are poised for immediate release into the circulation during stress. The lifespan of neutrophils in the peripheral blood is up to 3 to 4 days. Once in the circulation, neutrophils subsequently migrate into tissues, where they can survive for 1 to 4 days. Changes in neutrophil number reflect these dynamics.

Neutrophilia can occur as the result of increased marrow production, increased release of neutrophils from the storage pool, or mobilization of neutrophils from the marginated pool. Neutropenia may be due to decreased marrow production, increased margination with or without sequestration by the spleen, or increased destruction of peripheral cells.

NEUTROPHILIA

Neutrophilia is usually reactive or secondary to an underlying inflammatory process such as infection, chronic inflammation, stress, drugs, nonhematologic malignancy, marrow stimulation (as in hemolysis or idiopathic thrombocytopenic purpura), or splenectomy. Primary causes of neutrophilia may be congenital, including hereditary neutrophilia, Down syndrome, and leukocyte adhesion deficiency, or they can be acquired, as in chronic myelogenous leukemia (CML) (Chapter 170) and other myeloproliferative neoplasms (Chapter 152) (Table 153-1).

EPIDEMIOLOGY AND PATHOBIOLOGY

Secondary Causes of Neutrophilia

Infection

Many acute bacterial infections can present with leukocytosis with a "left shift," referring to the circulation of more immature myeloid cells. This left shift most commonly is restricted to release of an increased number of band forms; however, in severe stress, one may also see circulating metamyelocytes and even earlier cells ("leukemoid reaction") (see Fig. 153-1) in the peripheral blood. Leukocytosis occurs within minutes to hours of infection owing to release of neutrophils from both the marrow and marginated pools. Examination of these neutrophils on peripheral smear may reveal evidence

TABLE 153-1 DIFFERENTIAL DIAGNOSIS OF NEUTROPHILIA

- Primary hematologic etiologies
  - Congenital neutrophilia
    - Hereditary neutrophilia
    - Chronic idiopathic neutrophilia
    - Down syndrome
    - Leukocyte adhesion deficiency (LAD)
      - LAD-1
      - LAD-2
  - Acquired hematologic neoplasms
    - Myeloproliferative neoplasm
      - Chronic myelogenous leukemia
      - Polycythemia vera
- Secondary to other disease entities
  - Infection
    - Acute via release from marginated and storage pools
    - Chronic via increased myelopoiesis (e.g., tuberculosis, fungal infection, chronic abscess, other chronic infections)
  - Chronic inflammation
    - Rheumatic disease: juvenile rheumatoid arthritis, rheumatoid arthritis, Still disease, and others
    - Inflammatory bowel disease
    - Granulomatous disease
    - Chronic hepatitis
  - Cigarette smoking
  - Stress
  - Myocardial infarction
  - Drug induced
    - Corticosteroids
    - β-Agonists
    - Lithium
    - Recombinant cytokine administration
  - Nonhematologic malignancy
    - Cytokine-secreting tumors (lung, tongue, kidney, urothelial tumors)
    - Marrow metastasis (myelophthisis)
  - Marrow stimulation
    - Hemolytic anemia, immune thrombocytopenia
    - Recovery from marrow suppression
    - Recombinant cytokine administration
  - Post-splenectomy

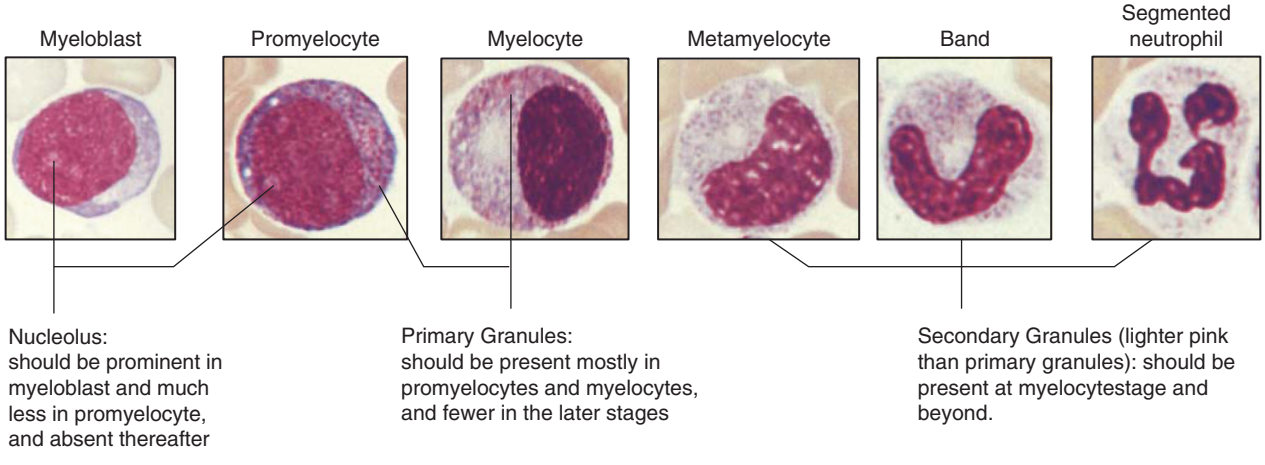

FIGURE 153-1. Myeloid maturation in the bone marrow. Nucleoli are prominent in myeloblasts, much less frequent in promyelocytes, and absent in more mature forms. Primary granules are present in the cytoplasm of promyelocytes and myelocytes, and secondary granules predominate beyond the myelocyte stage.

ABSTRACT

Disruption of the normal peripheral white blood cell count may reflect primary hematologic disease or may be secondary to a host of other diseases. Leukocytosis and leukopenia usually reflect disorders of neutrophils since neutrophils are the primary component of the white blood cell compartment. Leukocytosis is most commonly reactive and secondary to nonhematologic disorders, thereby reflecting the normal response of a healthy bone marrow to infectious or inflammatory stress. Evaluation should focus on identifying the underlying disorder, and bone marrow examination is rarely necessary. Primary myeloproliferative neoplasms leading to leukocytosis are much less common but can largely be identified by molecular testing for pathognomonic mutations on peripheral blood. By contrast, neutropenia is often a primary disorder, either congenital or acquired, and requires more intensive hematologic evaluation. Outside of chronic neutropenic disorders, leukopenia may also occur because of immune-mediated destruction of neutrophils, either as a reaction to a drug or toxin, or in the setting of autoimmune disease. Age of onset and chronicity can help guide the evaluation of patients with leukopenia. Most patients with unexplained neutropenia require bone marrow examination, although repeated examination is not indicated in patients with chronic idiopathic neutropenia.

KEYWORDS

leukocytosis
leukopenia
neutrophilia
neutropenia
immune neutropenia
congenital neutropenia

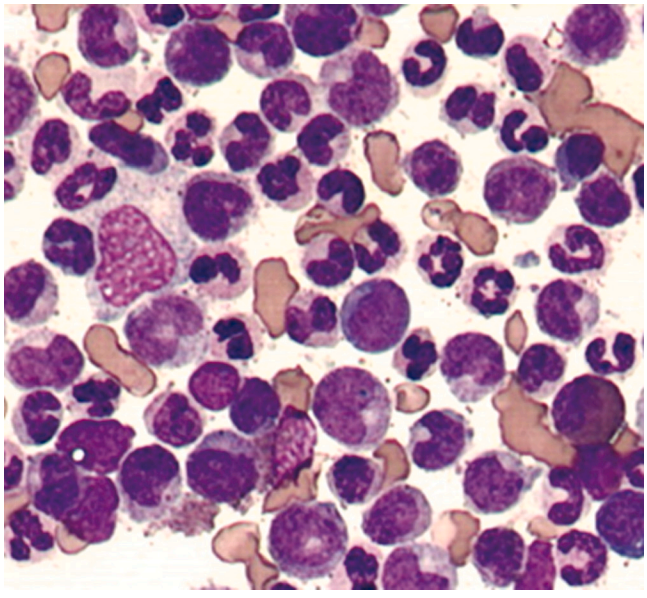

FIGURE 153-2. Peripheral blood from a patient with leukemoid reaction. From this smear, it would be impossible to distinguish a leukemoid reaction from chronic phase chronic myelogenous leukemia (Chapter 170). Distinction would depend on determination of the presence or absence of *BCR-ABL* fusion.

of toxic granulation (see Fig. 143-18), Döhle bodies (see Fig. 143-19), and cytoplasmic vacuoles. Certain infections (e.g., *Clostridioides difficile* or tuberculosis in particular) are known to cause elevations in the WBC to greater than 30,000/μL in about one fourth of infected patients and may result in a *leukemoid reaction*,[1] defined as a WBC greater than 50,000/μL with a pronounced left shift (Fig. 153-2).

Chronic Inflammation

Leukocytosis due to chronic inflammation results from increased leukocyte (specifically neutrophil and monocyte) production as opposed to altered neutrophil distribution. Mature neutrophil pools become depleted with ongoing inflammation, and the marrow myeloid compartment expands to increase neutrophil production. Myriad cytokines, including tumor necrosis factor-α (TNF-α), granulocyte colony-stimulating factor (G-CSF), granulocyte-macrophage colony-stimulating factor (GM-CSF), macrophage inflammatory protein-1 (MIP-1), interleukin-1 (IL-1), IL-6, and IL-8, have been implicated in this marrow stimulation. Chronic inflammatory conditions that are commonly associated with leukocytosis and neutrophilia include juvenile rheumatoid arthritis, rheumatoid arthritis, Still disease, Crohn disease, ulcerative colitis, granulomatous infection, and chronic hepatitis. The WBC and neutrophil elevation in these cases is typically more modest than that seen in acute infection or inflammation.

Cigarette Smoking

Cigarette smoking can cause a neutrophilia in about 25 to 50% of chronic smokers and can persist for up to 5 years after smoking cessation. The mechanism of neutrophilia is unknown, although evidence suggests that cigarette smoke slows neutrophil apoptosis.

Stress

Within minutes of exercise, surgery, or stress, the number of circulating neutrophils increases, presumably because catecholamines stimulate the demargination of neutrophils. Some cases of stress-induced neutrophilia can be prevented by pretreatment with β-adrenergic antagonists (e.g., propranolol), thereby supporting the role of catecholamines in the demargination process. Exercise-induced neutrophilia, however, is not blocked by propranolol, thereby suggesting that it may instead be due to flow and mechanical perturbation of neutrophils in the lungs.

Myocardial Infarction

An elevated WBC has been described in the setting of acute myocardial infarction. The etiology of this leukocytosis is likely multifactorial and related, in part, to inflammation. Data suggest that individuals with higher white blood cell counts have poorer short- and long-term prognoses.

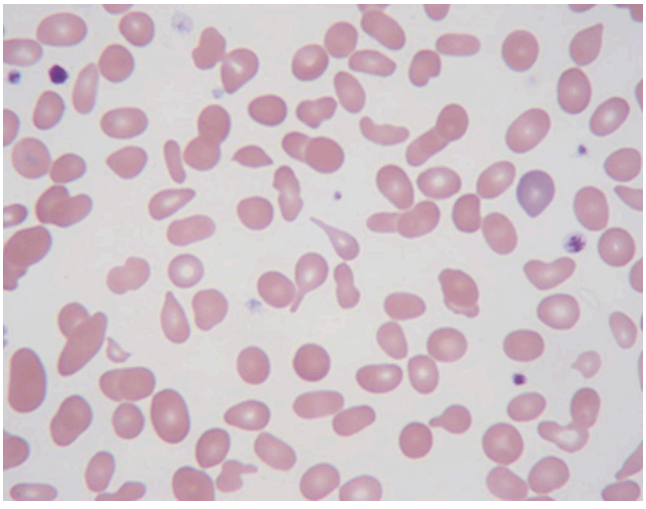

FIGURE 153-3. Myelophthisic changes in erythrocyte morphology. Note prominent teardrop forms. (From Rose M, Berliner N. Disorders of red blood cells. In: Andreoli TE, Benjamin IJ, Griggs RC, et al, eds. *Andreoli and Carpenter's Cecil Essentials of Medicine*, 8th ed. Philadelphia: Saunders; 2010:522, Fig. 49-2.)

Drug Induced

The most well-known and widely used drugs associated with leukocytosis are corticosteroids. Other drugs that elevate the neutrophil count include β-agonists and lithium. Lithium causes neutrophilia by increasing the production of endogenous colony-stimulating factors (CSFs). G-CSF or GM-CSF treatment (Chapter 142) likewise causes neutrophilia, and although this is the desired effect, the neutrophilia can be quite pronounced.

Nonhematologic Malignancy

Leukocytosis can be seen in a number of nonhematologic malignancies. Some tumors (lung, head and neck, kidney, bladder) may secrete G-CSF as an ectopic hematopoietic growth factor. In cancer patients with hyperleukocytosis, genomic testing can discriminate myeloproliferative neoplasms from a paraneoplastic leukemoid reaction. Other tumors (lung, stomach, breast), when metastatic to the bone marrow, can cause a *leukoerythroblastic reaction*, characterized by left-shifted leukocytosis, thrombocytosis, and red cell abnormalities including nucleated and teardrop-shaped red blood cells (Fig. 153-3). The presence of nonhematopoietic entities invading the bone marrow (metastatic cancer, fibrosis, granulomatous disease) is termed *myelophthisis*.

Marrow Stimulation

Peripheral destruction of red cells and platelets, as seen with hemolytic anemia and idiopathic thrombocytopenic purpura, can result in stimulation of the bone marrow and a "spillover" leukocytosis. Recovery of cell counts following marrow suppression, as in the case of chemotherapy, can result in a rebound leukocytosis that may last several weeks.

Primary Causes of Neutrophilia

Hereditary Neutrophilia

Hereditary neutrophilia is an autosomal dominant genetic disease that is characterized by an elevated WBC in the 20,000 to 100,000/μL range with splenomegaly and widened diploe of the skull. The neutrophils function normally, and patients have no increased risk for bacterial infection or other sequelae. Hereditary neutrophilia can be caused by an autosomal dominant *GCSF3* gene mutation, which leads to constitutive activation of the G-CSF receptor.

Chronic Idiopathic Neutrophilia

Chronic idiopathic neutrophilia is a condition marked by leukocytosis in the 11,000 to 40,000/μL range with a normal bone marrow biopsy. In one series with a 20-year follow-up, patients with this condition had no medical sequelae from the elevated WBC.

Pelger-Huët Anomaly

Patients with the Pelger-Huët anomaly are often misdiagnosed as having a left-shifted WBC because many of their mature neutrophils are misinterpreted as band forms. Although these patients do not have leukocytosis, the Pelger-Huët anomaly often raises suspicion for an acute infection because of this apparent left shift. Pelger-Huët anomaly is due to a mutation in the lamin B

receptor gene and manifests with mature neutrophils and condensed, clumped chromatin within a bilobed nucleus (see Fig. 143-20). A number of drugs can reversibly induce pseudo–Pelger-Huët anomaly, including colchicine, sulfonamides, ibuprofen, taxoids, and valproate. Pseudo–Pelger-Huët anomaly is also seen in some patients with myelodysplasia (Chapter 167). Vitamin B_{12} or folate deficiency can cause increased nuclear lobation of neutrophils in patients with Pelger-Huët anomaly, perhaps leading to a missed diagnosis. With correction of the vitamin deficiency, however, the aberrant neutrophil nuclear morphology returns.

Down Syndrome

Up to 10% of patients with Down syndrome develop a transient myeloproliferative disorder manifesting as peripheral blood leukocytosis with blasts in association with an accumulation of megakaryoblasts in the blood, liver, and marrow. Similar reactions have also been reported in phenotypically normal individuals with trisomy 21 mosaicism. Transient myeloproliferative disorder usually resolves spontaneously but can progress to acute megakaryoblastic leukemia in 23 to 30% of affected patients. This disorder is attributable to acquisition of mutations in the *GATA1* gene, which encodes a key transcription factor for hematopoietic regulation, leading to loss of normal GATA-1 expression and expression of a truncated GATA-1 protein. Evidence supports that these mutations are acquired during fetal life, and patients present in early infancy with transient myeloproliferative disorder. The pathogenesis of progression to acute megakaryoblastic leukemia presumably involves additional genetic and epigenetic events and is the focus of intense study.

Leukocyte Adhesion Deficiency

Patients with leukocyte adhesion deficiency also have persistent leukocytosis, defects in stimulus-dependent activation of neutrophils, recurrent infections, and delayed separation of the umbilical cord. Leukocyte adhesion deficiency is an abnormality of leukocyte adhesion reflecting the loss of surface adhesion molecules. Leukocyte adhesion deficiency-1 is due to absence or marked reduction in the common β chain of β2 integrins, resulting in loss of expression of leukocyte function–associated antigen 1 (LFA-1), the C3bi receptor, and GP150;95. This results in a failure to ingest and kill microbes opsonized by C3bi. In leukocyte adhesion deficiency-2, neutrophils lack sialyl Lewis X, the ligand for L-selectin expressed on endothelial cells. Neutrophils appear morphologically normal but are defective in chemotaxis, adherence, and phagocytosis.

Familial Cold Urticaria

Familial cold urticaria is marked by episodic fevers, leukocytosis, urticaria, rash, conjunctivitis, and muscle and skin tenderness with cold exposure. The rash is composed of infiltrating neutrophils. The syndrome appears to be related to decreased levels of C1-esterase inhibitor and is associated with mutations in the *CIAS1* gene on chromosome 1q.

Chronic Myelogenous Leukemia and Other Myeloproliferative Neoplasms

Chronic myelogenous leukemia (CML; Chapter 170), chronic neutrophilic leukemia, and the other myeloproliferative neoplasms (namely polycythemia vera and essential thrombocythemia; Chapter 152) are the principal acquired primary hematologic disorders associated with neutrophilia. CML on presentation should be distinguished from a leukemoid reaction. In contrast to a leukemoid reaction, CML is characterized by the presence of abnormalities of other blood cell lines ("panmyelosis") and by the presence of specific abnormalities. Therefore, the peripheral blood smear in CML (but not leukemoid reaction) demonstrates increased numbers in all cells of the neutrophilic series, classically with a greater proportion of myelocytes to metamyelocytes, and may display concomitant basophilia, eosinophilia, anemia, and thrombocytosis. Chronic neutrophilic leukemia, a rare myeloproliferative neoplasm, is characterized by hepatosplenomegaly and leukocytosis of at least 25,000/μL, with more than 80% of leukocytes being segmented neutrophil/band forms and less than 10% being immature granulocytes.[3] At least 50% of patients with chronic neutrophilic leukemia harbor mutations in the receptor for CSF-3 (*CSF3R; GCSFR*). Polycythemia vera and essential thrombocythemia, on the other hand, are notable for also having a marked increase in red cell mass and a marked thrombocytosis, respectively, which is often accompanied by leukocytosis.

Post-splenectomy

Patients develop leukocytosis following splenectomy, often long-standing, reflecting the loss of a major site of neutrophil margination. This is of no clinical importance, except insofar as it leads to unnecessary evaluation for other pathology.

CLINICAL MANIFESTATIONS AND DIAGNOSIS

As outlined previously, acquired leukocytosis is most commonly the result of acute or chronic infection or inflammation. When leukocytosis occurs in the absence of fever, aberrations in acute phase reactants, effusions, edema, or other signs and symptoms of inflammation, it may be secondary to drugs or an underlying nonhematologic malignancy. As such, leukocytosis should be seen as the sign of a healthy hematopoietic system responding to an outside stress. Bone marrow evaluation is therefore rarely indicated. However, persistence of leukocytosis in the absence of signs and symptoms of inflammation or infection, nonhematologic malignancy, and offending drugs should prompt an evaluation for a primary myeloproliferative disease or clonal hematologic neoplasm, particularly when there is evidence of a leukoerythroblastic reaction. CML and other myeloproliferative neoplasms can be ruled out by molecular diagnosis on the peripheral blood, as described in Chapter 170. In this setting of unexplained leukocytosis, bone marrow examination is indicated to evaluate for marrow infiltration by infection, tumor, or fibrosis and should include cultures for tuberculosis and fungal infection as well as cytogenetics and flow cytometry (Fig. 153-4).

LEUKOCYTOSIS DUE TO EXPANSION OF OTHER CELL LINES

Monocytosis and lymphocytosis can also elevate the WBC. Monocytosis, defined by an absolute monocyte count of greater than 500/μL, usually occurs in chronic inflammation resulting from infections (e.g., tuberculosis, syphilis, some viruses, and subacute bacterial endocarditis), autoimmune or granulomatous disease, and sarcoidosis.[3] Monocytosis can also be seen in malignancies, (e.g. preleukemic states, nonlymphocytic leukemia including acute myelomonocytic and monocytic leukemia, histiocytosis, Hodgkin disease, non-Hodgkin lymphoma, and various carcinomas).[4] Finally, monocytosis can be seen in the setting of chronic neutropenia, after splenectomy, and in the setting of recovery from marrow suppression (Table 153-2).

Lymphocytosis is defined by an absolute lymphocyte count of more than 5000/μL. The most common causes of lymphocytosis are viral infections such as Epstein-Barr virus (Chapter 348) and the hepatitis viruses (Chapter 134 and 135). Although most bacterial infections cause neutrophilia, pertussis and cat-scratch disease due to *Bartonella henselae* can cause lymphocytosis. Other infections that may cause a secondary lymphocytosis include toxoplasmosis and babesiosis. Hypersensitivity reactions due to drugs or serum sickness may also be associated with lymphocytosis.

Primary disorders causing lymphocytosis include chronic lymphocytic leukemia and monoclonal B-cell lymphocytosis (Table 153-3; see also Chapter 169). Low-count monoclonal B lymphocytosis can be detected in about 5% of adults over age 40 years and rarely progresses to chronic lymphocytic leukemia. By comparison, high-count monoclonal B lymphocytosis progresses to chronic lymphocytic leukemia at a rate of 1 to 2% per year.[5]

Eosinophilia (Chapter 156) is defined by an absolute eosinophil count of more than 400/μL.[6] Eosinophils proliferate under the influence of IL-5 and play a role in phagocytosis and modulating toxicity due to mast cell degranulation in hypersensitivity reactions. Eosinophilia is therefore most often seen in the setting of drug reactions, allergy, atopy, and asthma. A variety of infections, particularly parasitic infections and, to a lesser degree, fungal infections, can cause eosinophilia. Eosinophilia can also be the result of autoimmune and inflammatory conditions, as in eosinophilic granulomatosis with polyangiitis (formerly Churg-Strauss vasculitis). Atheroembolic disease and adrenal insufficiency may also cause eosinophilia. A number of cancers have been associated with polytypical expansion of eosinophils, including lymphomas and solid tumors. Clonal disorders of eosinophils have been observed in the setting of some leukemias. Finally, there is a heterogeneous group of disorders termed *hypereosinophilic syndromes* (Chapter 156). A *FIP1L1-PDGFRA* fusion gene has confirmed that some of these are primary clonal disorders of eosinophils; the clonality of other hypereosinophilic syndromes can be difficult to establish (see Table 156-1).

NEUTROPENIA

The risk for infection with neutropenia is highly dependent on the size of the neutrophil storage pool. Although neutropenia is defined by an absolute neutrophil count of less than 1500/μL, patients with neutrophil counts below this number have different risks and rates of infection depending on

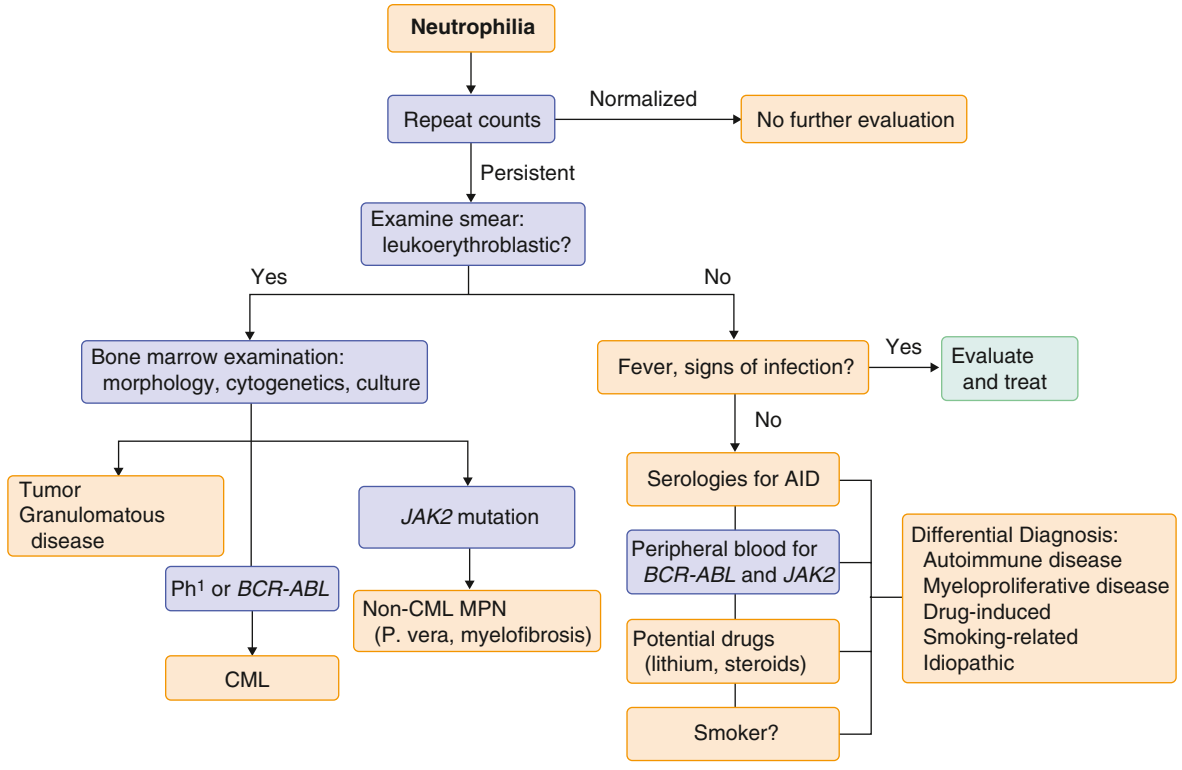

FIGURE 153-4. Diagnostic approach to neutrophilia. AID = autoimmune disease; CML = chronic myelogenous leukemia; ET = essential thrombocytopenia; MPN = myeloproliferative neoplasm; Ph¹ = Philadelphia chromosome; PV = P. vera.

TABLE 153-2 DIFFERENTIAL DIAGNOSIS OF MONOCYTOSIS

- Infection
  - Granulomatous disease (tuberculosis, fungal disease)
  - Endocarditis
  - Syphilis
- Autoimmune diseases
  - Lupus, rheumatoid arthritis
  - Giant cell arteritis
  - Vasculitis
- Inflammatory bowel disease
- Sarcoid
- Malignancy
  - Primary hematologic malignancy
    - Chronic myelomonocytic leukemia
    - Acute myelomonocytic leukemia
    - Lymphoma
  - Solid tumors
- Neutropenia
  - Associated with chronic neutropenia
  - Recovery form marrow suppression
- Post-splenectomy

TABLE 153-3 DIFFERENTIAL DIAGNOSIS OF LYMPHOCYTOSIS

- Infection
  - Viral infection
    - Epstein-Barr virus
    - Cytomegalovirus
    - Hepatitis
  - Bacterial infection
    - Pertussis
    - Bartonella
    - Tuberculosis
    - Syphilis
    - Rickettsia
    - Babesia
- Hypersensitivity reactions
  - Serum sickness
  - Drug hypersensitivity
- Primary hematologic disease
  - Chronic lymphocytic leukemia
  - Monoclonal B-cell lymphocytosis
  - Non-Hodgkin lymphoma

the cause of neutropenia. Patients who are neutropenic from chemotherapy, marrow failure, or marrow exhaustion experience infection at much higher rates than those with chronic neutropenic syndromes and immune-mediated neutropenia. Neutropenia may be congenital or acquired. The following sections first discuss congenital neutropenic disorders, the study of which has provided critical insights into normal myelopoiesis, and then the secondary causes of neutropenia (Table 153-4).

EPIDEMIOLOGY AND PATHOBIOLOGY

Primary Causes of Neutropenia

Normal Neutrophil Count for Duffy A-B- Individuals

The normal range of the neutrophil count is genetically determined and is variable. Several racial and ethnic groups have a relatively large proportion of individuals who are neutropenic by comparison to the published normal range, usually based on young, largely White individuals.[7] Single-nucleotide polymorphisms in the gene for the Duffy antigen receptor for chemokine are postulated to explain racial and ethnic differences in neutrophil counts. This polymorphism is seen among a variety of ethnic groups, including Blacks, Yemenite Jews, Falasha Jews, and African Bedouins.[8] Blood bank testing for Duffy A and B will demonstrate negativity for both antigens, thereby confirming this normal variant. An autosomal dominantly inherited condition called *benign familial neutropenia* is characterized by neutrophil counts in the 800 to 1400/μL range. Neither of these two forms of neutropenia is associated with *any* increased risk for infection.

Severe Congenital Neutropenia

Severe congenital neutropenia presents in the neonatal period with recurrent bacterial infections and neutrophil counts of less than 500/μL. Infections usually occur in the first months of life and often include omphalitis and perirectal abscesses. There is often an increase in monocytes and eosinophils. Bone marrow biopsy reveals a "maturation arrest" with an absence of mature neutrophil elements. Severe congenital neutropenia can follow autosomal

TABLE 153-4 DIFFERENTIAL DIAGNOSIS OF NEUTROPENIA

- Congenital neutropenia
  - Benign familial (constitutional) neutropenia
  - Duffy-null associated neutrophil count (DANC)
  - Severe congenital neutropenia
    - Autosomal dominant (*ELANE* mutation)
    - Autosomal recessive (Kostmann syndrome; *HAX2* mutation)
    - X-linked (*WASP* mutation)
    - Other rare defects (*G-CSFR* mutation, unknown)
  - Cyclic neutropenia
  - Shwachman-Diamond syndrome
  - Fanconi anemia
  - Dyskeratosis congenita
  - Glycogen storage disease type Ib
  - Myelokathexis
  - Chédiak-Higashi syndrome
  - Griscelli syndrome type II
  - Hermansky-Pudlak syndrome II
  - Barth syndrome
- Acquired neutropenia
  - Infection
  - Postinfection
  - Drug induced
  - Immune neutropenia
    - Primary immune neutropenia
    - Secondary to autoimmune disease
      - Rheumatoid arthritis
        - Felty syndrome
        - Large granular lymphocyte disease
      - Systemic lupus erythematosus
      - Granulomatosis with polyangiitis (formerly Wegener granulomatosis)
      - Hyperthyroidism
    - Pure white cell aplasia associated with thymoma
    - Large granular lymphocyte disease (independent of rheumatoid arthritis)
  - Primary bone marrow failure
    - Aplastic anemia
    - Myelodysplastic syndrome
    - Acute leukemia
  - Margination and hypersplenism
  - Vitamin and mineral deficiencies (including B_{12}, folate, copper)
  - Chronic idiopathic neutropenia in adults (CINA)

ELANE = neutrophil elastase gene; G-CSFR = granulocyte colony-stimulating factor receptor; WASP = Wiskott-Aldrich syndrome protein.

TABLE 153-5 CONGENITAL NEUTROPENIA SYNDROMES

SYNDROME	INHERITANCE PATTERN	GENE
SEVERE CONGENITAL NEUTROPENIA	Autosomal dominant	*ELANE* (~60%)
	Autosomal recessive	*HAX1* (~5%)
	X-linked	*WASP* (~5%)
	X-linked	*TAZ* (rare)
	Autosomal recessive	*G6PC3* (~2%)
	Autosomal dominant	*Gfi1* (rare)
	Autosomal dominant	*G-CSFR* (rare)
CYCLIC NEUTROPENIA	Autosomal dominant	*ELANE*
OTHER CONGENITAL SYNDROMES		
Shwachman-Diamond syndrome	X-Linked	*SBDS*
Fanconi anemia	Autosomal recessive	*FANCA-FANCO*
Dyskeratosis congenita	Variable	Telomerase and related genes
Glycogen storage disease type 1b	Autosomal recessive	*G-6-PT*
Myelokathexis	Autosomal dominant	*CXCR4*
Chédiak-Higashi syndrome	Autosomal recessive	*LYST*
Griscelli syndrome type 2	Autosomal recessive	*RAB27A*
Hermansky-Pudlak syndrome type 2	Autosomal recessive	*AP3B1*

ELANE = neutrophil elastase gene; *G6PC3* = glucose-6-phosphatase catalytic subunit 3 gene; G-6-PT = glucose-6-phosphatase translocase; *G-CSFR* = granulocyte colony-stimulating factor receptor gene; *LYST* = lysosomal trafficking regulatory gene; SBDS = Shwachman-Bodian-Diamond syndrome; *WASP* = Wiskott-Aldrich syndrome protein gene.

dominant and recessive and X-linked patterns of inheritance and is associated with mutations in a variety of genes (Table 153-5).[9]

Neutrophil elastase (ELANE) is a serine protease that is synthesized at high levels in the promyelocyte stage of neutrophil maturation and is packaged in primary granules. Though originally hypothesized to cause defective cellular trafficking and cytoplasmic accumulation leading to neutrophil apoptosis, newer evidence supports that ELANE mutations lead to accumulation of mutant elastase in the endoplasmic reticulum, with apoptosis resulting from activation of the unfolded protein response. Severe congenital neutropenia due to ELANE mutations is inherited in an autosomal dominant fashion.

Hax-1 is a mitochondrial protein with weak homology to bcl-2, and its absence results in mitochondrial-dependent apoptosis. Although all severe congenital neutropenia cases were originally referred to as Kostmann syndrome, that term is now reserved for this subgroup of autosomal recessive cases.

Wiskott-Aldrich syndrome protein regulates actin polymerization in hematopoietic cells, and deficiency of this protein results in the Wiskott-Aldrich syndrome, characterized by small platelets in low number, sinopulmonary infections, and eczema. Another phenotype of mutated Wiskott-Aldrich syndrome protein, however, is X-linked thrombocytopenia and neutropenia. Mutations in the glucose-6-phosphatase catalytic subunit 3 (*G6PC3*) are a more recently discovered cause of severe congenital neutropenia; homozygous loss of this metabolic enzyme also appears to lead to activation of the unfolded protein response and increased apoptosis of neutrophil precursors.

Severe congenital neutropenia was formerly a disease of infancy and early childhood because few, if any, patients survived to adulthood. However, G-CSF can raise neutrophil counts and prevent infection in most patients, thereby allowing most patients with severe congenital neutropenia to survive. Some patients require very high doses of G-CSF, but responses are seen in 80 to 90% of individuals. Increased survival led to the realization that severe congenital neutropenia predisposes to the development of myelodysplasia and acute myeloid leukemia (myelodysplasia/AML), with the development of myelodysplasia/AML at a rate of approximately 2% per year and a cumulative risk of about 20 to 30% over 10 years. Patients refractory to, or requiring very high doses of, G-CSF have a higher risk for leukemic transformation. The development of myelodysplasia/AML is often associated with the acquisition of a G-CSF receptor gene mutation. Considerable controversy exists concerning the role of lifelong G-CSF administration in the acquisition of other mutations and their contribution to malignant transformation in patients with severe congenital neutropenia (see Treatment later).

Two classes of G-CSF receptor mutations have been associated with severe congenital neutropenia and either hyper-responsiveness or hyporesponsiveness of the receptor. Initial studies aimed at demonstrating that severe congenital neutropenia was caused by mutation of the G-CSF or G-CSF receptor gene did not implicate such mutations in its pathogenesis. However, a small number of patients have been shown to have mutations in the G-CSF receptor gene that block ligand binding and produce a G-CSF–resistant form of severe congenital neutropenia. More important, however, the studies identified an acquired missense mutation that introduces a stop codon that leads to the deletion of the distal intracellular domain of the receptor known to be responsible for differentiation signaling. This mutation has been shown to cause hypersensitivity to G-CSF, suggesting that the mutation may play a role in the development of myelodysplasia/AML. However, whether this mutation in fact influences the development of myelodysplasia/AML and whether G-CSF increases the risk for developing the mutation remain subjects of significant controversy. Even in the presence of the G-CSF mutation, development of AML is associated with the acquisition of other myeloid leukemia–associated gene mutations.[10]

Cyclic Neutropenia

Cyclic neutropenia is defined by periods of neutropenia (≤200/μL) lasting 3 to 5 days and occurring at approximately 21-day intervals. Neutropenic periods may be marked by recurrent fevers, mouth sores, and infections of the skin, upper respiratory tract, and ears. Cyclic neutropenia can be dominantly inherited or sporadic, and it is associated with ELANE mutations in virtually all cases. Acquired cyclic neutropenia has been rarely associated with systemic diseases such as large granular lymphocytosis or T-cell lymphoma.

Other Congenital Syndromes with Associated Neutropenia

Several congenital disorders are associated with neutropenia.[11] These include Shwachman-Diamond syndrome, Fanconi anemia, dyskeratosis congenita, glycogen storage disease Ib, myelokathexis, Chédiak-Higashi syndrome, Griscelli syndrome II, and Hermansky-Pudlak syndrome II.

Shwachman-Diamond syndrome usually begins as an isolated neutropenia but progresses to marrow failure and is also associated with pancreatic dysfunction and skeletal abnormalities. The responsible gene, the Shwachman-Bodian-Diamond syndrome gene (*SBDS*), is involved in the regulation of ribosomal RNA. These patients carry an increased risk for leukemic transformation.

Fanconi anemia (Chapter 151) is due to mutations in genes involved in DNA repair, and as such, marrow failure develops later in these patients (median age, 7 years). Patients with Fanconi anemia often have concomitant short stature with upper limb anomalies and hyperpigmented café-au-lait spots, although about one third have no physical abnormalities. Screening is done by chromosomal fragility testing following exposure to diepoxybutane or mitomycin C and by direct assessment for known Fanconi gene mutations.

Dyskeratosis congenita (Chapter 151) is a syndrome of nail dystrophy, leukoplakia, and skin pigmentation abnormalities with associated neutropenia or aplastic anemia that typically does not present until the second decade of life. It is inherited in an autosomal dominant or recessive or X-linked fashion and is associated with mutations in genes involved in telomere maintenance. Dyskeratosis congenita is one of several diseases associated with telomere abnormalities, with wide-ranging manifestations including pulmonary fibrosis and hepatic cirrhosis as well as bone marrow failure.

Glycogen storage disease Ib (Chapter 191) is inherited as an autosomal recessive disorder characterized by intermittent neutropenia due to defects in the neutrophil respiratory burst with subsequent apoptosis of circulating neutrophils. Hepatomegaly and metabolic crises are also the hallmarks of this disease and are due to mutations in the gene for the glucose-6-phosphatase translocase enzyme.

The neutropenia of *myelokathexis* is due to retention of mature neutrophils in the bone marrow. During infection, however, patients with myelokathexis typically have a sudden rise in their neutrophils, making their clinical course relatively more benign. There is an association between this condition and hypogammaglobulinemia and warts: WHIM syndrome (*w*arts, *h*ypogammaglobulinemia, *i*mmunodeficiency, and *m*yelokathexis). Myelokathexis is caused by heterozygous mutations in the gene encoding chemokine receptor CXCR4.

Chédiak-Higashi syndrome, Griscelli syndrome II, and *Hermansky-Pudlak syndrome II* are all syndromes of albinism and neutropenia due to defects in vesicular trafficking. Chédiak-Higashi syndrome is due to mutations in a lysosomal trafficking regulatory gene (*LYST*) and is characterized by oculocutaneous albinism, bleeding, progressive neurologic disease, and increased susceptibility to hemophagocytic syndrome. Griscelli syndrome II, with nearly identical clinical manifestations as Chédiak-Higashi syndrome, is caused by mutations in the gene encoding the small guanosine triphosphatase RAB27A, which is involved in the release of myeloperoxidase from the primary granules of neutrophils. Hermansky-Pudlak syndrome II is due to mutations in the *AP3B1* gene, which encodes a part of a protein transport complex involved in vesicular trafficking and appears to be involved in the trafficking of neutrophil elastase. It is also marked by albinism, platelet abnormalities, and pulmonary fibrosis.

Barth syndrome is an X-linked autosomal recessive disorder characterized by neutropenia, cardiomyopathy, and growth retardation, with a high early childhood mortality from the associated heart disease. The causative mutation is in the *TAZ* gene, which encodes the tafazzin protein that is critical to remodeling cardiolipin in the mitochondrial membrane.

Secondary Causes of Neutropenia

Infection-Related Neutropenia

Several viral infections cause a transient neutropenia that typically resolves as the viremia abates. These include varicella, measles, rubella, hepatitis A and B, Epstein-Barr virus, influenza, parvovirus, and cytomegalovirus. The mechanisms are diverse and involve redistribution, decreased production, and immune destruction of neutrophils. Human immunodeficiency virus and acquired immunodeficiency syndrome also cause multifactorial leukopenia and neutropenia (Chapter 355). Patients often have splenomegaly and sequestration, but more commonly, the neutropenia reflects immune-mediated destruction. A myriad of atypical infections like *Mycobacterium tuberculosis*, ehrlichiosis, rickettsia, tularemia, brucellosis, and some staphylococcal infections can cause moderate neutropenia. Any infection leading to overwhelming sepsis can cause neutropenia, but this usually reflects consumption of marrow neutrophil reserves and is typically seen in newborns and elderly patients with limited marrow reserves. There is also increased margination of neutrophils during sepsis due to systemic activation of complement, exacerbating the neutropenia.

Drug-Induced Neutropenia and Neutropenia Due to Marrow Injury

Drug-induced neutropenia is the most common cause of neutropenia. Multiple drugs have been implicated in neutropenia and agranulocytosis, in both predictable and idiosyncratic patterns. Drug-induced neutropenias may reflect either suppression of marrow granulopoiesis or increased destruction of peripheral neutrophils. Many drugs cause direct dose-dependent marrow suppression, which is predictable and often mild. Others incite an idiosyncratic immune-mediated destruction that can present with profound agranulocytosis. Drug-induced neutropenia typically presents with a marked decline in neutrophils occurring after 1 to 2 weeks of exposure to the drug with recovery within 3 to 10 days of stopping the drug. However, atypical cases can present long after drug initiation, and others may be associated with a markedly delayed recovery (Fig. 153-5). Patients with drug-induced agranulocytosis may present with acute sepsis, leading to significant acute mortality. Recovery is often preceded by the appearance of monocytes and immature neutrophil forms. The more hypercellular the marrow is at diagnosis, the earlier marrow recovery may occur. Some common drugs known to cause neutropenia, in addition to antineoplastic, antiviral, and immunosuppressive agents, include clozapine;

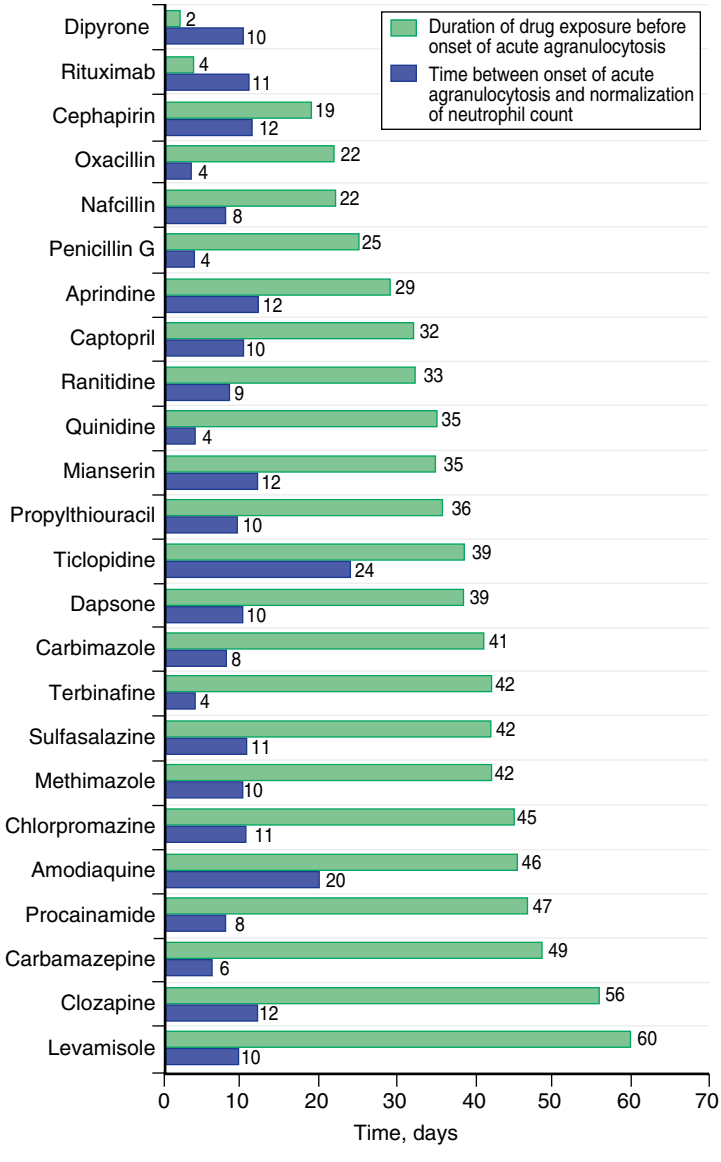

FIGURE 153-5. Median duration of treatment and neutropenia. Only drugs with more than three definite or probable reports of the time between onset of acute agranulocytosis and normalization of neutrophil count and the duration of treatment before onset of acute agranulocytosis were considered. (From Andersohn F, Konzen C, Garbe E. Systematic review: agranulocytosis induced by nonchemotherapy drugs. *Ann Intern Med*. 2007;146: 657-665.)

the antithyroidal thioamides including carbimazole, methimazole, and propylthiouracil; quinidine; procainamide; sulfasalazine; and levamisole, which is widely used as a cocaine adulterant and causes cocaine-associated neutropenia. Neutrophil recovery is speeded by G-CSF.

Radiation can induce marrow injury leading to acute or chronic marrow failure; in high doses, it is also a risk factor for the development of myelodysplasia and leukemia. These malignant hematopoietic diseases can themselves cause marrow failure because the malignant cells proliferate within the marrow and can also cause marrow fibrosis, both of which lead to cytopenias. These diseases are discussed in greater detail in Chapters 151 and 167, respectively. Likewise, metastatic carcinoma to the marrow can also cause marrow failure as the marrow becomes replaced by the metastatic cells.

Immune Neutropenia

Immune neutropenia can occur as an isolated phenomenon (primary immune neutropenia) or as a manifestation of an underlying systemic autoimmune disease (secondary immune neutropenia).[12] Primary autoimmune neutropenia is generally a disease of children, with a median age of onset of 6 to 12 months. Although infectious risk is increased, treatment is restricted to prophylactic antibiotics, with G-CSF reserved for acute infectious episodes. Ninety-five percent of patients undergo spontaneous remission within 2 years. Nearly all of these patients have antineutrophil antibodies directed against antigens derived from the FcγIIIb receptor; these antibodies mediate neutrophil destruction by either sequestration in the spleen or complement-mediated neutrophil lysis.

Secondary autoimmune neutropenia is a disease of adults and can be seen in association with hyperthyroidism, Wegener granulomatosis, rheumatoid arthritis, and systemic lupus erythematosus (SLE).[13] The role of antineutrophil antibodies in these patients is less clear. More than 50% of patients with SLE, for example, have antineutrophil antibodies, but many have normal neutrophil counts, and there is a poor correlation between the presence of the antibodies and neutrophil number.

Felty syndrome and *large granular lymphocyte syndrome* deserve separate mention. Felty syndrome occurs in association with long-standing rheumatoid arthritis (Chapter 243) and is characterized by splenomegaly and profound neutropenia. Large granular lymphocyte syndrome (Chapter 151) can occur either in the setting of rheumatoid arthritis or as an isolated phenomenon. Both Felty syndrome and large granular lymphocyte syndrome are associated with a proliferation of large granular lymphocytes, with a characteristic surface phenotype ($CD3^+$, $CD8^+$, $CD16^+$, and $CD57^+$). In rheumatoid arthritis, these two syndromes were originally thought to be separate diseases, with Felty syndrome being polyclonal and large granular lymphocyte syndrome representing a monoclonal proliferation. However, with increasing sensitivity of detection of monoclonal populations of lymphocytes, this distinction has become blurred. More than 90% of rheumatoid arthritis patients with either syndrome are human leukocyte antigen (HLA)-DR4-positive, leading to the postulate that the two entities represent the extremes of a single disease spectrum. This HLA restriction is not found among non–rheumatoid arthritis patients with large granular lymphocyte syndrome. Both syndromes cause immune-mediated neutrophil destruction by multiple mechanisms, including antineutrophil antibodies and cell-mediated destruction. Some patients may also have G-CSF resistance mediated by inhibitory G-CSF antibodies. The pathophysiology of large granular lymphocyte syndrome is incompletely understood. However, up to 50% of patients have activating mutations in Stat3, and all patients show constitutive activation of the Stat3 signaling pathway.

There are other rare forms of immune neutropenia. Isoimmune neonatal neutropenia is a moderate to severe neutropenia of the newborn due to transplacental passage of maternal antibodies against alleles inherited from the father, resulting in neutropenia in a manner similar to the development of anemia in Rh hemolytic disease. Pure white cell aplasia is a rare disease highlighted by a complete absence of myeloid precursors on bone marrow examination. The condition is associated with severe pyogenic infections and with thymoma in more than two thirds of cases. Pure white cell aplasia has also occurred following ibuprofen therapy.

Neutropenia Due to Increased Margination and Hypersplenism

Complement activation can result in both acute and chronic neutropenia as a result of increased margination of the circulating neutrophil pool. The increased neutrophil margination has been attributed to the fact that C5a renders neutrophils more adherent and prone to aggregation within the pulmonary vasculature and has been seen in patients suffering from burns and transfusion reactions. Complement activation may also lead to neutrophil destruction, as in paroxysmal nocturnal hemoglobinuria. Neutropenia can also reflect hypersplenism, although this is typically less common and less pronounced than the anemia and thrombocytopenia seen in patients with splenomegaly.

Neutropenia Due to Nutritional Deficiency

B_{12}, folate (Chapter 150), and copper deficiency are each associated with neutropenia. Copper deficiency is an underrecognized cause of neutropenia (usually seen with anemia), found especially in situations like total parenteral nutrition without copper supplementation, protein-losing enteropathies, celiac disease, gastric bypass surgery and postgastrectomy, malabsorption syndromes, and zinc toxicity. In addition to low serum copper and ceruloplasmin levels, distinct morphologic findings include hypogranularity and hypolobated nuclei (Pelger-Huet anomaly) on peripheral smear and cytoplasmic vacuolization of myeloid, as well as erythroid precursors and ringed sideroblasts.

Deficiencies in these vitamins and minerals result in ineffective myelopoiesis, maturation arrest, and megaloblastic changes with nuclear-cytoplasmic dyssynchrony. The characteristic finding in the setting of megaloblastic anemia is hypersegmentation of the neutrophil (Fig. 153-6).

Chronic Idiopathic Neutropenia

Chronic idiopathic neutropenia in adults is an acquired disorder characterized by prolonged neutropenia in the absence of any apparent underlying etiology. Chronic neutropenia is often an incidental finding on routine blood tests, making it impossible to know the duration of the neutropenia. Patients have no evidence of autoimmune disease, nutritional deficiency, or myelodysplasia. The syndrome is heterogeneous, with a wide range of neutrophil counts. A group of adults from Greece with chronic idiopathic neutropenia were found to have increased production of transforming growth factor-β (TGF-β), linked to a genetic polymorphism in the TGF-β locus, and consequent suppression of granulopoiesis by the bone marrow. These patients tend to have very mild neutropenia, with an absolute neutrophil count that is rarely less than 800. However, these patients should be distinguished from other adults with chronic idiopathic neutropenia, many of whom have an absolute neutrophil count below 200. The etiology of neutropenia in these patients is completely unknown, but the natural history of chronic idiopathic neutropenia in adults, even in the face of very low neutrophil counts, is generally benign. Most patients require no therapy, although those with very low counts may require G-CSF if they manifest severe infections. Some patients with recurrent infections or troublesome aphthous ulcers require chronic G-CSF treatment. These patients typically respond to low doses of G-CSF, and there is no increase in the development of myelodysplasia/AML.

CLINICAL MANIFESTATIONS AND DIAGNOSIS

Neutropenia is not usually associated with clinical signs and symptoms other than those of the underlying condition causing the low WBC. It becomes

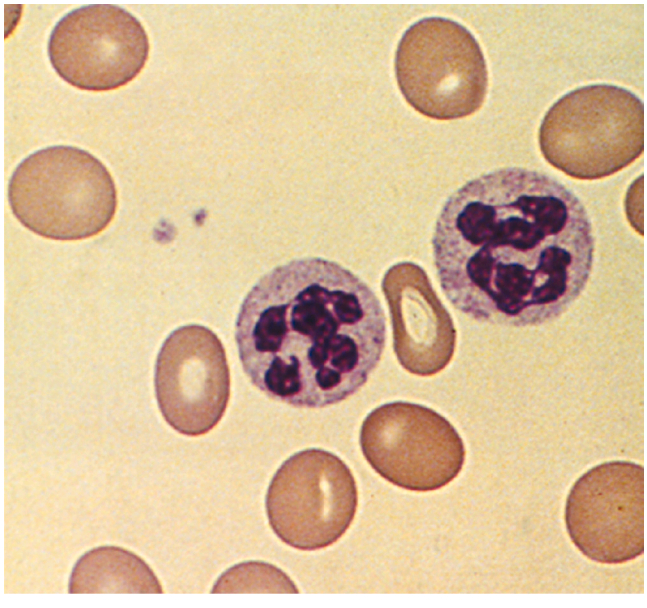

FIGURE 153-6. Peripheral blood with macrocytosis and hypersegmented neutrophils in megaloblastic anemia.

clinically evident, however, when it results in infection. Although patients with an absolute neutrophil count below 1000/μL have a slightly increased risk for infection, the risk increases substantially when the neutrophil count falls below 500/μL. With few neutrophils, the signs and symptoms of infection may be attenuated; pneumonia may be present with minimal infiltrate on chest radiograph, or a urinary tract infection may yield only a very mild pyuria. Therefore, fever in any neutropenic patient must be considered an emergency with prompt acquisition of cultures and rapid administration of empirical antibiotic therapy.

Because drug-induced neutropenia is the most common cause of acquired neutropenia, a careful inventory for drugs and toxins is warranted. Likewise, patients should be evaluated for potential precipitating malignant and inflammatory conditions. The time course of the neutropenia and infections can provide insight into the etiology (acute versus chronic, persistent versus cyclic, neonatal versus childhood versus adult onset). Attention should be paid to the skin, bones, appendages, and nails because abnormalities in these may point toward one of the congenital neutropenia syndromes. Evaluation of the complete blood count, peripheral blood smear, and vitamin B_{12} and folate levels should also be performed.

When the neutropenia is mild and associated with anemia and thrombocytopenia, the possibility of hypersplenism should be considered. Diagnosis can often be made by the finding of palpable splenomegaly. However, especially in obese patients, abdominal imaging may be used to evaluate spleen size. Abdominal ultrasound also allows the assessment of portal venous flow with Doppler studies. If splenic enlargement is confirmed, the etiology of the splenomegaly (Chapter 154) should be determined. The diagnosis of cyclic neutropenia formerly required demonstration of transient neutropenia through frequent blood counts over a course of 6 weeks but now can be established by sequencing of the elastase gene.

In other patients with chronic neutropenia without a history of infection, drug or toxin exposure, or B_{12} or folate deficiency, bone marrow examination should be performed to exclude myelodysplasia, with assessment of morphology, flow cytometry for the large granular lymphocyte syndrome, and cytogenetics. Once a normal marrow has been obtained, further bone marrow examination is not indicated in adults with chronic idiopathic neutropenia (Fig. 153-7).

TREATMENT

Management of the neutropenia patient is nuanced and depends on the etiology of the depressed count, its severity, and the presence or absence of fever.

Neutropenia After Chemotherapy

In *afebrile* adults with acquired neutropenia following chemotherapy, antibiotic prophylaxis with a quinolone (ciprofloxacin 500 mg orally twice a day, switched to 200 mg intravenously twice a day if the patient develops severe mucositis or intolerance to the oral formulation) or oral sulfamethoxazole/trimethoprim (1 double-strength tablet daily) can reduce all-cause mortality and is recommended along with antifungal prophylaxis (e.g., oral voriconazole 200 mg twice daily) in patients who are expected to have profound, protracted neutropenia (<100 neutrophils/μL for >7 days).[14] Trimethoprim-sulfamethoxazole is specifically recommended in patients at risk for *Pneumocystis jirovecii* pneumonia (Chapter 313), based on neutropenia in the setting of the equivalent of 20 mg or more of prednisone/day for 1 month or longer.

In afebrile neutropenia, the routine prophylactic administration of colony-stimulating factors does not appear to be beneficial,[A1] but many oncologic professional society guidelines recommend the use of prophylactic G-CSF in patients who are receiving chemotherapy and who have a 20% or greater risk for developing febrile neutropenia based on their age, comorbid illnesses, disease characteristics, and the myelotoxicity of the chemotherapy regimen. G-CSF is also recommended during hematopoietic stem cell transplantation (Chapter 163), for patients receiving chemotherapy for non-Hodgkin lymphoma (Chapter 171) or dose-dense chemotherapy, and for patients with a history of febrile neutropenia receiving further chemotherapy. In afebrile neutropenia, granulocyte transfusions may reduce the risk of infection but do not reduce mortality.[A2]

The approach to the patient with fever and neutropenia is discussed in detail in Chapter 260. Neutropenia with fever is a clinical emergency because patients are at risk for hemodynamic collapse and septic shock. Therefore, such patients should be evaluated thoroughly and cultured promptly, and empiric antibiotics should be administered within 30 to 60 minutes of presentation while awaiting culture results. The timely administration of antibiotics in neutropenic patients

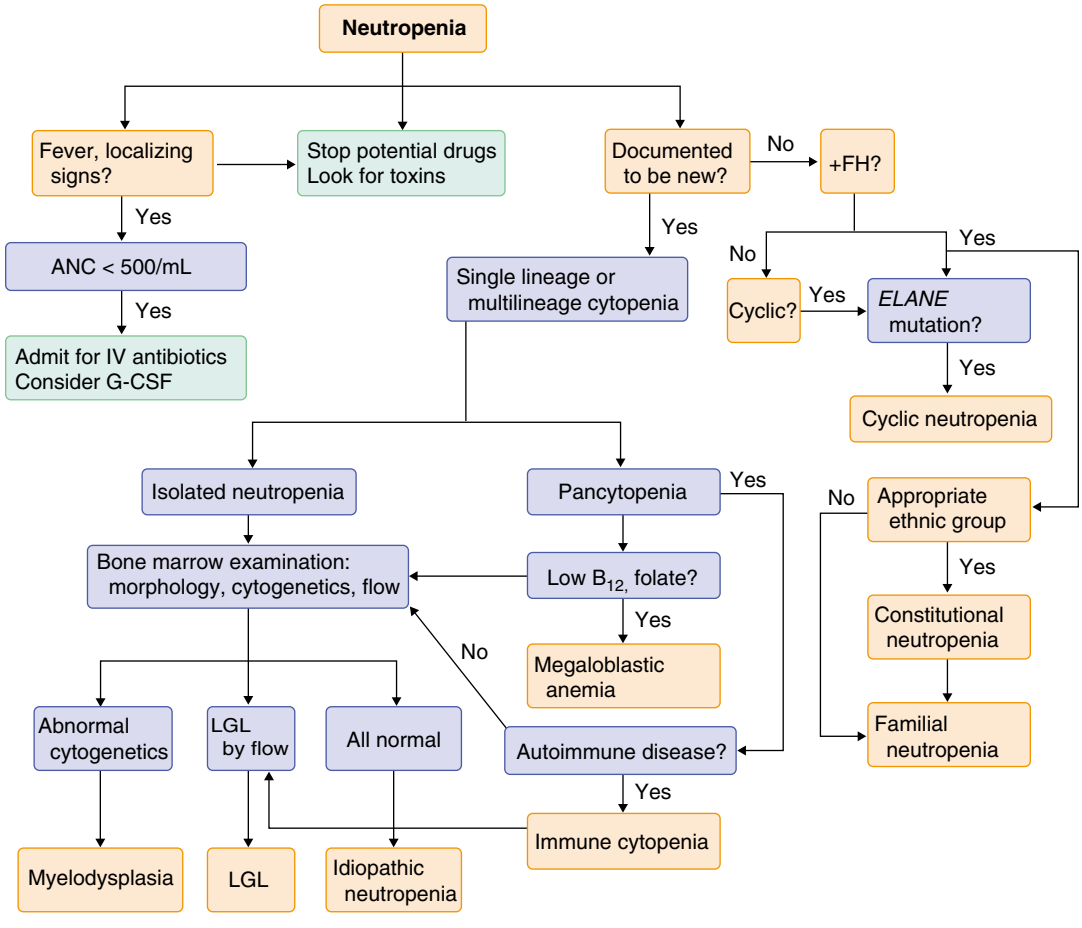

FIGURE 153-7. Diagnostic approach to neutropenia. ANC = absolute neutrophil count; *ELANE* = neutrophil elastase gene; FH = family history; G-CSF = granulocyte colony-stimulating factor; IV = intravenous; LGL = large granular lymphocyte syndrome.

at the onset of fever confers significant clinical benefit, with more rapid response and improved survival. The choice of treatment of patients with fever and neutropenia in the setting of cancer chemotherapy is based on the initial history and physical examination as well as a structured assessment of risk (Chapter 260).[15]

Other Neutropenias

Patients with immune neutropenia are typically treated with immunosuppressive therapy, including steroids, antithymocyte globulin, or cyclosporine, aimed primarily at treatment of the underlying autoimmune disease. Patients usually respond to G-CSF, although this treatment may induce a flare of joint symptoms in the setting of rheumatoid arthritis. Patients with the large granular lymphocyte syndrome often respond to low-dose methotrexate (10 mg/m^2 orally once a week), cyclosporine (100 to 600 mg or 2 to 10 mg/kg orally daily), or low-dose cyclophosphamide (50 to 100 mg orally daily).

Patients with *congenital neutropenia*, including idiopathic, severe congenital, or cyclic neutropenia, are usually successfully managed with G-CSF for years. With G-CSF, however, life expectancy has been extended into adulthood. Therapy is daily and chronic, given by subcutaneous injection, with doses varying by the type of neutropenia and the individual responsiveness to therapy. It is usually well tolerated, although accelerated bone loss has been observed. Growth and development appear unaffected. Patients with severe congenital neutropenia typically require the highest doses, whereas those with idiopathic neutropenia require the lowest.

In adults with *chronic idiopathic neutropenia*, G-CSF should be reserved for acute febrile episodes unless the patient has recurrent infections. Adults with chronic idiopathic neutropenia treated with G-CSF may experience significant side effects, including fever, gastrointestinal symptoms, and splenomegaly. Consequently, when adults with chronic idiopathic neutropenia require chronic G-CSF, it should be administered at the lowest dose necessary to prevent infections; it is usually sufficient to treat to maintain the absolute neutrophil count in the range of 300 to 500. Cyclic neutropenia is successfully treated with G-CSF and is not associated with an increased risk for leukemic transformation.

Pure white cell aplasia is immune mediated, and removal of the thymoma in thymoma-associated cases may not be sufficient for remission. Adjuvant therapy with cyclophosphamide, corticosteroids, cyclosporine, and intravenous immunoglobulin may be needed.

For patients with an inflammatory, infectious, or drug-induced neutropenia, the recommendation is to treat the underlying condition or stop the offending agent.

The use of antibiotics to prevent infection in other patients with chronic neutropenias has not been extensively studied but is typically not recommended and should be based on clinical context. There is no evidence that a low bacterial diet can prevent infection or mortality in neutropenic cancer patients.[A3]

Stem cell transplantation (Chapter 163) can be curative for a number of the congenital neutropenia and bone marrow failure syndromes, including Fanconi anemia. It is, however, not without risk and should therefore be reserved for patients with severe neutropenia complicated by recurrent infection definitively shown to be due to marrow failure.

LEUKOPENIA DUE TO DEFICIENCY OF OTHER CELL LINES

Lymphocyte production takes place in a variety of anatomic sites, and lymphocyte trafficking from those sites is bidirectional, making it difficult to understand lymphocyte dynamics in the same way that we do for neutrophils. Despite this, the peripheral lymphocyte count seems to be maintained in a narrow range at 2000 to 4000/μL, 20% of which are B cells and 70% of which are T cells. Lymphocytopenia is a total lymphocyte count of less than 1500/μL. It can reflect decreased production, defective trafficking, or increased loss or destruction. Decreased production can result from protein and calorie malnutrition; lymphocyte progenitor pool injury secondary to radiation, chemotherapy, or immunosuppressive agents; and congenital immunodeficiency states. Endogenous or exogenous glucocorticoid excess can cause lymphocytopenia by altering lymphocyte trafficking. This can also occur as the result of acute bacterial or fungal infections, certain viral infections, and granulomatous disease. Finally, many viruses cause direct destruction of lymphocytes, as do antilymphocyte antibodies seen in patients with underlying autoimmune diseases. Lymphocytes can also be lost from intestinal lymphatics in cases of protein-losing enteropathy, primary disease of the gut or intestinal lymphatics, or gut edema secondary to severe heart failure. Lymphocytopenia should prompt comprehensive assessment of the immune system, including lymphocyte subtyping, quantitative immunoglobulins, and skin testing to detect deficiencies of cell-mediated immunity. Treatment is aimed at the underlying disease, but intravenous immunoglobulin can be administered to patients with hypogammaglobulinemia, and transplantation can be performed in patients with severe deficiencies of cell-mediated immunity due to impaired lymphocyte production and function.

Monocytopenia, eosinopenia, and basophilopenia can accompany bone marrow failure syndromes or acute infection, malignancy, or severe injury and is thought to reflect elevations in glucocorticoids, prostaglandins, and epinephrine. These humoral factors have the greatest impact on eosinophils, and absence of eosinopenia in these settings should prompt suspicion for adrenal insufficiency, a primary myeloproliferative syndrome, parasitic infection, or primary hypereosinophilic syndrome. Monocytopenia is less frequent, probably owing to the diverse roles monocytes play in normal human physiology; prolonged and extreme monocytopenia may not be compatible with life.

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154 APPROACH TO THE PATIENT WITH LYMPHADENOPATHY OR SPLENOMEGALY

JANE N. WINTER

LYMPHADENOPATHY

Lymphadenopathy is very common in children and adolescents but is less common in adults. Lymph nodes are secondary lymphoid tissues located along the course of the lymphatic vessels. These round or bean-shaped structures typically measure less than 1 cm in diameter and are strategically situated to filter lymphatic fluid and to intercept microorganisms and other antigens. The hilus is the point of indentation in these otherwise round tissues where blood vessels enter and leave the lymph node. Lymphatic fluid enters the lymph node in afferent lymphatic vessels that empty into the subcapsular sinus, traverses the lymph node, and then leaves through a single efferent lymphatic at the hilus. Lymph nodes consist of B and T lymphocytes, macrophages, and dendritic cells that interact to generate an immune response to the antigens transported in the lymphatic fluid. These cells function together to generate the normal immune response by means of antigen processing, presentation, and recognition and the resulting proliferation of effector B and T lymphocytes.[1]

Lymph node enlargement generally results from cellular proliferation and expansion of lymph node components associated with the normal immune response to foreign antigens. Alternatively, it can be caused by infiltration of the lymph node by a neoplastic process or deposition of a foreign substance (e.g., in storage disease).

CLINICAL MANIFESTATIONS

Lymphadenopathy is usually noted incidentally by the patient on self-examination or is noted by a family member. Sometimes it is first detected by a physician on a physical examination. However, an increasing number of patients with lymphadenopathy are identified incidentally when they undergo imaging for unrelated issues (e.g., chest radiography for infectious symptoms; magnetic resonance imaging [MRI] of the spine for back pain related to a disc herniation). Occasionally an enlarged lymph node can become tender or become large enough to cause direct symptoms.

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at the onset of fever confers significant clinical benefit, with more rapid response and improved survival. The choice of treatment of patients with fever and neutropenia in the setting of cancer chemotherapy is based on the initial history and physical examination as well as a structured assessment of risk (Chapter 260).[15]

Other Neutropenias

Patients with immune neutropenia are typically treated with immunosuppressive therapy, including steroids, antithymocyte globulin, or cyclosporine, aimed primarily at treatment of the underlying autoimmune disease. Patients usually respond to G-CSF, although this treatment may induce a flare of joint symptoms in the setting of rheumatoid arthritis. Patients with the large granular lymphocyte syndrome often respond to low-dose methotrexate (10 mg/m^2 orally once a week), cyclosporine (100 to 600 mg or 2 to 10 mg/kg orally daily), or low-dose cyclophosphamide (50 to 100 mg orally daily).

Patients with *congenital neutropenia*, including idiopathic, severe congenital, or cyclic neutropenia, are usually successfully managed with G-CSF for years. With G-CSF, however, life expectancy has been extended into adulthood. Therapy is daily and chronic, given by subcutaneous injection, with doses varying by the type of neutropenia and the individual responsiveness to therapy. It is usually well tolerated, although accelerated bone loss has been observed. Growth and development appear unaffected. Patients with severe congenital neutropenia typically require the highest doses, whereas those with idiopathic neutropenia require the lowest.

In adults with *chronic idiopathic neutropenia*, G-CSF should be reserved for acute febrile episodes unless the patient has recurrent infections. Adults with chronic idiopathic neutropenia treated with G-CSF may experience significant side effects, including fever, gastrointestinal symptoms, and splenomegaly. Consequently, when adults with chronic idiopathic neutropenia require chronic G-CSF, it should be administered at the lowest dose necessary to prevent infections; it is usually sufficient to treat to maintain the absolute neutrophil count in the range of 300 to 500. Cyclic neutropenia is successfully treated with G-CSF and is not associated with an increased risk for leukemic transformation.

Pure white cell aplasia is immune mediated, and removal of the thymoma in thymoma-associated cases may not be sufficient for remission. Adjuvant therapy with cyclophosphamide, corticosteroids, cyclosporine, and intravenous immunoglobulin may be needed.

For patients with an inflammatory, infectious, or drug-induced neutropenia, the recommendation is to treat the underlying condition or stop the offending agent.

The use of antibiotics to prevent infection in other patients with chronic neutropenias has not been extensively studied but is typically not recommended and should be based on clinical context. There is no evidence that a low bacterial diet can prevent infection or mortality in neutropenic cancer patients.[A3]

Stem cell transplantation (Chapter 163) can be curative for a number of the congenital neutropenia and bone marrow failure syndromes, including Fanconi anemia. It is, however, not without risk and should therefore be reserved for patients with severe neutropenia complicated by recurrent infection definitively shown to be due to marrow failure.

LEUKOPENIA DUE TO DEFICIENCY OF OTHER CELL LINES

Lymphocyte production takes place in a variety of anatomic sites, and lymphocyte trafficking from those sites is bidirectional, making it difficult to understand lymphocyte dynamics in the same way that we do for neutrophils. Despite this, the peripheral lymphocyte count seems to be maintained in a narrow range at 2000 to 4000/μL, 20% of which are B cells and 70% of which are T cells. Lymphocytopenia is a total lymphocyte count of less than 1500/μL. It can reflect decreased production, defective trafficking, or increased loss or destruction. Decreased production can result from protein and calorie malnutrition; lymphocyte progenitor pool injury secondary to radiation, chemotherapy, or immunosuppressive agents; and congenital immunodeficiency states. Endogenous or exogenous glucocorticoid excess can cause lymphocytopenia by altering lymphocyte trafficking. This can also occur as the result of acute bacterial or fungal infections, certain viral infections, and granulomatous disease. Finally, many viruses cause direct destruction of lymphocytes, as do antilymphocyte antibodies seen in patients with underlying autoimmune diseases. Lymphocytes can also be lost from intestinal lymphatics in cases of protein-losing enteropathy, primary disease of the gut or intestinal lymphatics, or gut edema secondary to severe heart failure. Lymphocytopenia should prompt comprehensive assessment of the immune system, including lymphocyte subtyping, quantitative immunoglobulins, and skin testing to detect deficiencies of cell-mediated immunity. Treatment is aimed at the underlying disease, but intravenous immunoglobulin can be administered to patients with hypogammaglobulinemia, and transplantation can be performed in patients with severe deficiencies of cell-mediated immunity due to impaired lymphocyte production and function.

Monocytopenia, eosinopenia, and basophilopenia can accompany bone marrow failure syndromes or acute infection, malignancy, or severe injury and is thought to reflect elevations in glucocorticoids, prostaglandins, and epinephrine. These humoral factors have the greatest impact on eosinophils, and absence of eosinopenia in these settings should prompt suspicion for adrenal insufficiency, a primary myeloproliferative syndrome, parasitic infection, or primary hypereosinophilic syndrome. Monocytopenia is less frequent, probably owing to the diverse roles monocytes play in normal human physiology; prolonged and extreme monocytopenia may not be compatible with life.

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154 APPROACH TO THE PATIENT WITH LYMPHADENOPATHY OR SPLENOMEGALY

JANE N. WINTER

LYMPHADENOPATHY

Lymphadenopathy is very common in children and adolescents but is less common in adults. Lymph nodes are secondary lymphoid tissues located along the course of the lymphatic vessels. These round or bean-shaped structures typically measure less than 1 cm in diameter and are strategically situated to filter lymphatic fluid and to intercept microorganisms and other antigens. The hilus is the point of indentation in these otherwise round tissues where blood vessels enter and leave the lymph node. Lymphatic fluid enters the lymph node in afferent lymphatic vessels that empty into the subcapsular sinus, traverses the lymph node, and then leaves through a single efferent lymphatic at the hilus. Lymph nodes consist of B and T lymphocytes, macrophages, and dendritic cells that interact to generate an immune response to the antigens transported in the lymphatic fluid. These cells function together to generate the normal immune response by means of antigen processing, presentation, and recognition and the resulting proliferation of effector B and T lymphocytes.[1]

Lymph node enlargement generally results from cellular proliferation and expansion of lymph node components associated with the normal immune response to foreign antigens. Alternatively, it can be caused by infiltration of the lymph node by a neoplastic process or deposition of a foreign substance (e.g., in storage disease).

CLINICAL MANIFESTATIONS

Lymphadenopathy is usually noted incidentally by the patient on self-examination or is noted by a family member. Sometimes it is first detected by a physician on a physical examination. However, an increasing number of patients with lymphadenopathy are identified incidentally when they undergo imaging for unrelated issues (e.g., chest radiography for infectious symptoms; magnetic resonance imaging [MRI] of the spine for back pain related to a disc herniation). Occasionally an enlarged lymph node can become tender or become large enough to cause direct symptoms.

ABSTRACT

Lymphadenopathy is usually first noted by the patient on self-examination, but both lymphadenopathy and especially splenomegaly are often first detected incidentally when imaging is performed for an unrelated issue. The differential diagnosis of lymphadenopathy and splenomegaly is broad, with infections, autoimmune disorders, and malignancies representing the vast majority of cases. A careful and complete history is the first and most important step in the assessment of the patient with lymphadenopathy and/or splenomegaly, including travel history and possible exposures to infectious agents as well as sexual and family history. Similarly, the physical examination must be complete, with attention to the distribution of the adenopathy, as well as to the size and associated erythema or tenderness of the enlarged nodes. In the patient with splenomegaly, its overall size, the presence of associated lymphadenopathy, tonsillar enlargement, and hepatomegaly are of particular importance. A complete blood count with review of the peripheral smear may be especially helpful in identifying the underlying cause. Biopsy is indicated when malignant lymphadenopathy is suspected. For splenomegaly, however, close observation rather than biopsy or splenectomy is often the best course of action in the asymptomatic patient.

KEYWORDS

lymphadenopathy
lymphoproliferative disorder
splenomegaly
hypersplenism
splenectomy

TABLE 154-1 TAKING A COMPLETE HISTORY IN THE ADULT PATIENT WITH LYMPHADENOPATHY

History of present illness
Duration, recent changes
Associated symptoms: fevers, drenching night sweats, shaking chills, weight loss, sore throat, arthritis or arthralgias, rash or skin lesions, pruritus, shortness of breath, chest pain
Ill contacts, recent and remote travel, tick or insect bites
Past medical history
Autoimmune disease, history of immunosuppressive therapy, history of infectious disease, history of recent vaccination
Family history
Malignancy, especially hematologic malignancy, or infection
Autoimmune disease
Social history
Sexual activity—risk for HIV infection, other sexually transmitted diseases
Occupation—exposure to toxins, livestock, pets
Smoking or drinking
Medications: immunosuppressive agents, phenytoin, allopurinol, antibiotics

HIV = human immunodeficiency virus.

TABLE 154-2 CLUES TO THE CAUSE OF LYMPHADENOPATHY

Age
Symptoms
Localized versus generalized lymphadenopathy
Specific location/distribution
Tenderness, warmth, overlying erythema, mobility, pulsatile
Size

DIAGNOSIS

Lymph nodes that are larger than 1 cm are generally considered to be abnormal, although adenopathy in some locations is considered abnormal and worthy of investigation even when subcentimeter in size (supraclavicular, epitrochlear, or popliteal lymph nodes).

History and Physical Examination

A careful and complete history is the first and most important step in the evaluation of the patient with lymphadenopathy (Table 154-1). The age of the patient, recent travel history, possible infectious or toxic exposures through employment or hobbies, recent immunizations (e.g., COVID-19 vaccination is a frequent cause of unilateral axillary adenopathy),[2] current medications, and social, sexual, and family history may provide important clues to the cause (Table 154-2). A complete review of systems is required. Not only can the presence of symptoms be informative, but also their pattern, character, and duration (e.g., the high spiking fevers characteristic of Hodgkin lymphoma, known as Pel-Ebstein fevers) may suggest a cause. Similarly, particular symptoms such as pruritus suggest specific diagnoses (e.g., also Hodgkin lymphoma).

The physical examination must also be meticulous with attention not only to the distribution of the adenopathy but also to the presence of other physical findings (e.g., tonsillar enlargement in the patient with cervical adenopathy and Burkitt lymphoma [Chapter 171], parotid enlargement in Sjögren syndrome [Chapter 247], rash in T-cell lymphomas [Chapter 171], joint findings in autoimmune disorders, or a breast mass in the patient with axillary lymphadenopathy) (Table 154-3). Malignant lymph nodes are generally painless, whereas nodes that represent infection may be tender. Although exceptions occur, lymphadenopathy resulting from metastatic solid tumor is characteristically hard and may be fixed or matted, whereas lymphadenopathy representing hematologic malignancies is typically soft and may be mobile. Although borderline and slightly enlarged lymph nodes are commonly related to infectious causes, sizeable nodes are worrisome for malignancy and warrant prompt investigation. Often, no cause is identified, and careful follow-up is required.

Differential Diagnosis

The differential diagnosis of lymphadenopathy is vast. Whether lymphadenopathy is localized or generalized, its location, and the age of the patient all help to focus the investigation into its cause. Diffuse lymphadenopathy may occur in the setting of generalized infections, systemic disorders of the immune system, or widespread neoplasia (Table 154-4).

TABLE 154-3 EVALUATING THE PATIENT WITH LYMPHADENOPATHY

Complete physical examination with particular attention to:
Tonsillar enlargement, evidence of superior vena cava syndrome
Attention to all lymph node groups including epitrochlear, femoral
Hepatosplenomegaly
Rash
Joints, deformities
Preliminary laboratory examination
Complete blood count with differential, platelet count
Sedimentation rate, testing for mononucleosis in the right setting
Imaging
Chest radiograph (assess for mediastinal mass, hilar enlargement, infiltrate)
Ultrasound for children up to age 14 years
CT with intravenous contrast or contrast-enhanced MRI
PET/CT not recommended unless diagnosis of lymphoma or other malignancy
Pathologic diagnosis
Needle aspiration for investigation of infectious causes
Core biopsy if excisional biopsy unsafe
Excisional biopsy preferred especially if malignancy suspected

CT = computed tomography; MRI = magnetic resonance imaging; PET = positron emission tomography.

TABLE 154-4 DIFFERENTIAL DIAGNOSIS OF LYMPHADENOPATHY

CAUSES	EXAMPLES
Infectious	
Bacteria	Group A streptococcus, staphylococcal skin infections, syphilis, cat-scratch disease, *Chlamydia trachomatis*, typhoid fever, tuberculosis
Fungi	Histoplasmosis, blastomycosis, coccidioidomycosis
Parasites	Malaria, toxoplasmosis
Viruses	Infectious mononucleosis (Epstein-Barr virus), cytomegalovirus, HIV
Immune mediated	
Autoimmune disorders	Rheumatoid arthritis, systemic lupus erythematosus
Drug reactions	
Malignant	
Hematologic	Lymphoma, leukemia, myeloproliferative neoplasms
Solid tumors	Metastatic to lymph nodes
Unusual	
Storage disease	Gaucher disease, Niemann-Pick disease
Sarcoidosis	
Castleman disease	
Kawasaki vasculitis	
Kikuchi lymphadenitis	
Kimura disease	
Endocrinopathies	Addison disease
Sinus histiocytosis with massive lymphadenopathy (Rosai-Dorfman disease)	

HIV = human immunodeficiency virus.

Localized lymphadenopathy usually but not always results from a regional problem, such as infection or malignancy. The particular site may be informative. For example, recurrent sore throats and upper respiratory infections are regularly associated with tender submandibular and/or cervical adenopathy.[3] However, although cervical adenopathy in adults can be reactive hyperplasia from systemic infection, it is commonly caused by malignancies such as head and neck carcinomas, adenocarcinomas, small cell lung cancer, and lymphoma.[4] Epitrochlear or supraclavicular adenopathy is problematic in any adult or child, and it signifies likely disease. Inguinal adenopathy is common, often related to infection or trauma to the lower extremities, and often of little concern in the absence of other findings. Thoracic and mediastinal adenopathy may be caused by lung cancer (Chapter 177) but also by a variety of nonmalignant

conditions including sarcoidosis (Chapter 83) and Castleman disease (Chapter 359) in addition to infection.[5]

Worldwide, infection by bacteria, mycobacteria, fungi, chlamydia, parasites, and viruses are the major causes of lymph node enlargement. Lymph node enlargement in the drainage region of any pyogenic infection is expected. Dramatic regional lymph node enlargement with fluctuant lymph nodes (i.e., buboes) is a hallmark of infection with the coccobacillus *Yersinia pestis* (Chapter 288), which causes bubonic plague. In cat-scratch fever, enlarged nodes close to the site of the flea bite carrying *Bartonella henselae* are common presenting signs (Chapter 291). Mediastinal lymphadenopathy may occur in inhalational anthrax (Chapter 272). Cervical adenopathy is commonly a manifestation of tuberculosis (Chapter 299). In contrast, diffuse adenopathy may represent a systemic infection with Epstein-Barr virus (i.e., infectious mononucleosis; Chapter 348), cytomegalovirus (Chapter 347), or human immunodeficiency virus (HIV; Chapter 359), or with the parasite *Toxoplasma gondii* (Chapter 320).

Autoimmune disorders may be associated with either localized or generalized lymphadenopathy. Lymph node enlargement in this setting is especially challenging given the increased frequency of malignant lymphoproliferative disorders in these patients. Biopsy (excisional when possible) and expert hematopathology consultation are required to exclude the possibility of lymphoma. Lymphadenopathy occurring as a result of a drug reaction is uncommon,[6] but it may be exceptionally difficult to distinguish histopathologically from malignant lymphoma. A wide range of drugs, including antiepileptics and antibiotics, have been reported to cause lymphadenopathy, but associated rash, eosinophilia, and liver function abnormalities are helpful in distinguishing a drug reaction (Chapter 234) from other causes.

Malignancy commonly manifests as lymphadenopathy. Enlarged lymph nodes (Fig. 154-1) may be involved or replaced by a hematologic malignancy such as Hodgkin (Chapter 172) or non-Hodgkin lymphoma (Chapter 171), or they may represent a site of metastasis from a solid tumor, most often occurring in the drainage area of the primary tumor.[7] For example, breast cancer (Chapter 183) is often accompanied by ipsilateral axillary nodal involvement and prostate cancer by iliac node involvement. Distant spread to the lymph nodes may also occur.

In addition to infectious, autoimmune, and malignant causes of lymphadenopathy, less common causes include storage diseases (as in Gaucher or Niemann-Pick disease; Chapter 192) or amyloidosis (Chapter 174; associated with a hematologic malignancy such as multiple myeloma or non-Hodgkin lymphoma, an inherited form of the disease, or with chronic inflammation). Sarcoidosis (Chapter 83) may manifest as enlarged lymph nodes, as can endocrinopathies such as thyroid disease (Chapter 207) or adrenal insufficiency (Chapter 208). Benign entities such as congenital lymphovascular malformations and branchial cleft cysts may present as a neck mass in a child.

Blood Testing

A routine complete blood count should be obtained. When signs and symptoms are consistent with an infectious cause, atypical lymphocytosis suggests Epstein-Barr virus infection, which can be confirmed by serology (Chapter 348).

Imaging

Imaging with computed tomography (CT) or MRI, with the latter preferred when radiation exposure is to be avoided such as during pregnancy, is the first step in the evaluation of worrisome palpable adenopathy in adults.[8] Ultrasonography is recommended as the preferred approach for children with cervical adenopathy and is also useful in adults for determining the size of the node and the possible presence of multiple nodes.[9,10] Clearly, borderline adenopathy or lymphadenopathy associated with symptoms or history suggestive of a benign origin (e.g., mononucleosis in a college student) does not merit immediate imaging and may be watched. Combined positron emission tomography (PET) and CT (PET/CT) should not be an initial test[11] but is very useful for staging and evaluation during and after treatment of patients who are diagnosed with a malignant lymphoma or a variety of solid tumors (Fig. 154-2).

Studies for infectious agents including cultures and special stains for infectious agents, immunophenotypic analysis by flow cytometry, and molecular studies complement morphology in making a diagnosis. In contrast, if head and neck cancer is in the differential diagnosis, the patient should have a complete ear, nose, and throat examination at the outset to avoid complicating subsequent surgery.

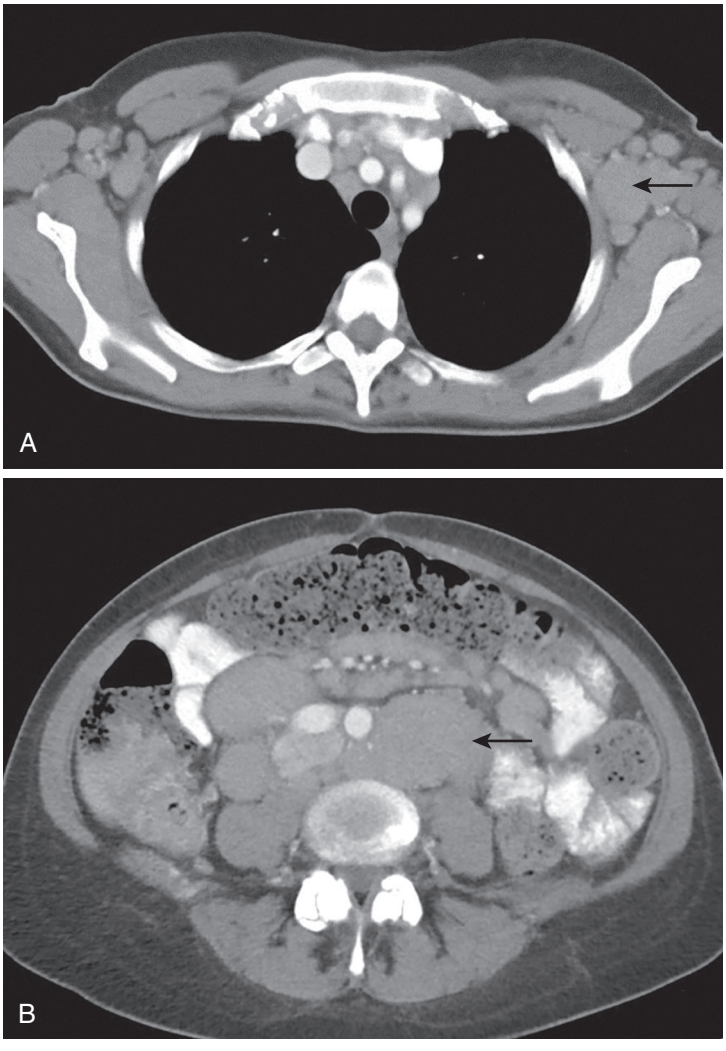

FIGURE 154-1. Axillary (A) and retroperitoneal lymph nodes (B) in a patient with follicular lymphoma. *Arrows* indicate examples of enlarged lymph nodes.

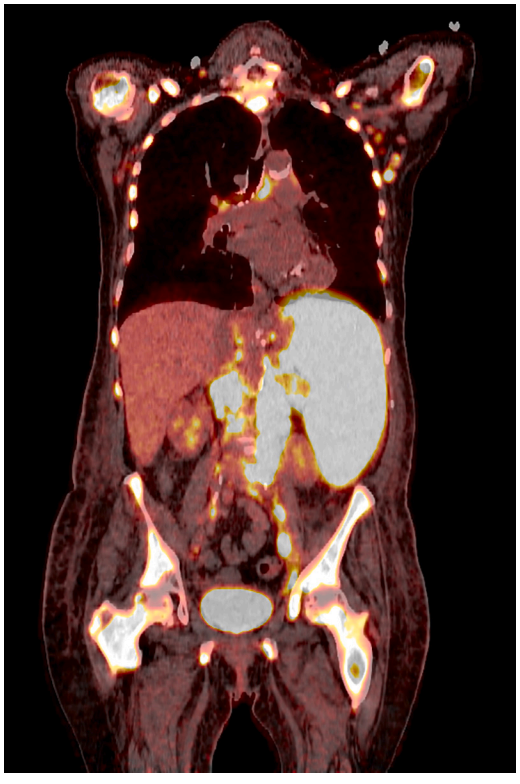

FIGURE 154-2. Fluorodeoxyglucose (FDG)-positron emission tomography (PET)/computed tomographic (CT) scan. The FDG-PET/CT scan demonstrates involvement of the spleen, lymph nodes, and bone in a patient with lymphoma.

Evaluation of a patient with incidentally noted lymphadenopathy on an imaging study poses a special challenge. For example, evaluation of the patient with incidentally noted intra-abdominal or pelvic adenopathy, like that of the patient with a new palpable mass, requires that the clinician integrate the clinical history and radiographic findings. A comparison of the radiologic findings to prior imaging studies can often eliminate concern if the findings are discovered to be long standing. Imaging findings considered worrisome by the American College of Radiology include (1) short axis diameter 1 cm or larger in the retroperitoneum; (2) abnormal architecture (round, indistinct hilum); (3) presence of enhancement (necrosis; hypervascularity); and (4) increased number of nodes defined as a cluster of three or more in a single nodal station or two or more in at least two regions. Biopsy should be considered if the nodes fall into any of these categories and there is clinical or laboratory evidence supporting the presence of a lymphoproliferative disorder. In many cases, the patient may be followed with repeat imaging in 3 to 6 months. If stable for 1 year, an abnormal lymph node or group of lymph nodes is most likely benign.

The location of the enlarged node(s), size, consistency, presence of generalized lymphadenopathy or hepatosplenomegaly, or associated symptoms are all helpful in developing an individualized approach. If nodes are large, 2 to 3 cm in size, and firm with associated symptoms, the risk for malignancy is high, and a diagnostic procedure should be performed expeditiously. A complete blood count with differential and examination of the peripheral smear along with a plain chest radiography may be helpful in sorting out which patient is best served by observation for what may be infectious mononucleosis or another infectious and uncomplicated process and who should proceed quickly to biopsy. A short course of antibiotics with close observation is often the preferred strategy with little risk if the patient is reliable and will return if the lump grows rather than regresses. Steroids should be avoided because they may mask the symptoms and cause shrinkage of the nodes in hematologic malignancies.

Biopsy

The decision to perform a biopsy of a lymph node depends on the clinical history and presentation as well as the ease with which a biopsy can be performed. For patients with symptoms, an early biopsy of a palpable lymph node may provide an answer to a puzzling case[12] but may add to the confusion if the biopsy result is not definitive. An excisional rather than a core biopsy is most likely to provide a definitive diagnosis,[13] but it is not practical in all cases. When no easily accessible peripheral nodes are available for biopsy, a core biopsy may be obtained by the interventional radiologists with the assistance of ultrasound or CT guidance. Fine-needle aspiration may be adequate to diagnose a solid tumor or infection but is insufficient for distinguishing malignant lymphoma from a reactive lymph node, and it is discouraged if lymphoma is in the differential diagnosis. An excisional biopsy remains the gold standard. Face-to-face discussion between the clinician and the pathologist is the most effective approach to determining a diagnosis, especially for the most challenging cases.

TREATMENT AND PROGNOSIS

The treatment of lymphadenopathy focuses on treatment of the underlying disease, which also determines prognosis. In some tumors, such as breast cancer (Chapter 183) and ovarian cancer (Chapter 184), removal of local lymph nodes is an important part of therapy.

SPLENOMEGALY

Splenomegaly is present in about 2% of adults in the United States, with no predilection by gender, age, or ethnicity. Causes include a wide variety of infections, primary liver disease, benign hematologic diseases, and malignancies.

The spleen is the largest lymphatic organ in the body, and some liken it to a very large lymph node. Similar to lymph nodes, the spleen has multiple and diverse functions, including its role as a filter removing defective red blood cells and infectious agents, its important role in immune response to blood-borne antigens, and a role in regulating blood volume.

Consistent with its multiple functions and its role as a massive filter, the spleen has an open circulation with three compartments: the white pulp, marginal zone, and red pulp. Blood enters the spleen through the splenic artery and its branches, filters through the splenic cords and periarterial lymphatic sheath, and is exposed in the white pulp to immunologically active cells including macrophages, B lymphocytes, and T lymphocytes. In the white pulp, microorganisms and foreign proteins are recognized, and an immune response to blood-borne antigens is initiated. In splenectomized individuals, the absence of this splenic function predisposes to certain infections, especially infections with encapsulated organisms such as *Streptococcus pneumoniae*.

Separating white pulp from red, the marginal zone acts as a transition zone. More than half the volume of the spleen is composed of splenic red pulp and consists primarily of erythrocytes along with macrophages, dendritic cells, and other white blood cells. Senescent or defective red blood cells are identified and destroyed in the red pulp. The process of hemolysis may be mechanical and/or immunologic as in autoimmune hemolytic anemia, in which the antibody-coated red blood cells are phagocytosed by macrophages. Perhaps less well appreciated, the spleen plays a role in regulating blood volume by means of a variety of mechanisms, including release of blood through splenic contraction and the splenorenal reflex that promotes retention of fluid and sodium by the kidneys during septic shock.

CLINICAL MANIFESTATIONS

Splenomegaly is commonly detected as an incidental finding on imaging performed for what appears to be an unrelated issue such as diverticulitis or nephrolithiasis. Given the obesity epidemic and the increasing reliance on testing rather than careful physical examination, it is uncommon for splenomegaly to be detected first on physical examination except as part of a careful evaluation of a patient who has a known predisposing condition.

Except with massive splenomegaly or acute obliteration of the splenic artery or vein, the patient is unlikely to have specific complaints related to splenomegaly itself. Pain in the left upper quadrant sometimes radiating to the left shoulder may be the first indication of a splenic infarct or an enlarged spleen. Rarely, the catastrophic signs and symptoms of splenic rupture are the first indications of splenomegaly. Unexplained weight loss related to early satiety caused by compression of the stomach by the enlarged spleen or unexplained cytopenias caused by hypersplenism may be the first indication of splenomegaly.

DIAGNOSIS

In contrast to lymphadenopathy, an enlarged spleen discovered on physical examination is nearly always abnormal and requires explanation. As with lymphadenopathy, the differential diagnosis of splenomegaly is wide ranging (Table 154-5), and the same principles hold. First, a careful history and physical examination, with attention to the age of the patient, the size of the spleen, and associated symptoms, will often but not always guide the investigation to the underlying cause. The majority of cases are due to infection, autoimmune disorders, or malignancies, but oftentimes no cause is identified, so careful follow-up is required.

TABLE 154-5 DIFFERENTIAL DIAGNOSIS OF SPLENOMEGALY

CAUSES	EXAMPLES
Infectious	
Bacteria	Endocarditis, brucellosis, syphilis, tuberculosis, Rocky Mountain spotted fever
Fungi	Histoplasmosis, toxoplasmosis
Parasites	Malaria, leishmaniasis
Viruses	Infectious mononucleosis (Epstein-Barr virus), HIV, cytomegalovirus
Immune mediated	
Autoimmune disorders	Rheumatoid arthritis, systemic lupus erythematosus, autoimmune hemolytic anemia
Drug reaction	Phenytoin
Malignant	
Hematologic	Lymphoma, leukemia, myeloproliferative neoplasm
Solid tumor	Metastatic to spleen
Congestive	Liver disease, portal vein thrombosis, congestive heart failure
Nonmalignant hematologic disorders	Hereditary spherocytosis, congenital or acquired hemolytic anemias, hemoglobinopathies, extramedullary hematopoiesis
Unusual	
Storage disease	Gaucher disease, Niemann-Pick disease
Sarcoidosis	
Cysts, pseudocysts	
Amyloidosis	

HIV = human immunodeficiency virus.

History

Similar to the approach to lymphadenopathy, a careful and complete history is the first and most important step in the evaluation of the patient with splenomegaly. The age of the patient, travel history, possible infectious or toxic exposures through employment or hobbies, recent immunizations, current medications, and social, sexual, and family history all may contribute important clues to the cause. A complete review of systems is required. A review of old records including imaging may provide evidence that splenomegaly is long-standing.

Physical Examination

Despite many approaches to palpating the spleen, a borderline or slightly enlarged spleen may be difficult to appreciate on examination. Positioning the patient in the right lateral decubitus position with knees slight flexed is a useful approach, especially for right-handed examiners. The examination should begin very low in the pelvis and work upwards to the left upper quadrant so as not to miss the edge of a massively enlarged spleen. Inspection and percussion combined with palpation provide the best chance of identifying the enlarged spleen. The patient should take deep breaths while checking for the tip of the spleen as it descends with deep inspiration. Splenomegaly is typically recorded as the number of centimeters the spleen descends below the left costal margin in the midclavicular line on deep inspiration. The physical examination in the patient with splenomegaly should be meticulous, including attention to the presence of lymphadenopathy, jaundice, tonsillar enlargement, joint effusions or swelling, and hepatomegaly.

Differential Diagnosis

The infectious causes of splenomegaly are myriad.[14,15] Geography and travel history are often important clues to an underlying infection. The most likely causes of splenomegaly in equatorial Africa or in a recent African immigrant are different from the causes in a North American urbanite. Bacterial infections commonly associated with splenomegaly include endocarditis (Chapter 61), brucellosis (Chapter 286), typhoid fever (Chapter 284), and rickettsial disorders such as Rocky Mountain spotted fever (Chapter 302). Mycobacterial infections including typical (Chapter 299) and atypical (Chapter 300) mycobacteria may manifest with splenomegaly, as can fungal infections such as histoplasmosis (Chapter 308). Among the parasitic disorders, malaria (Chapter 316) is nearly always accompanied by an enlarged spleen and should be high on the differential diagnosis list in the proper setting. Epstein-Barr virus (Chapter 348), which is the cause of infectious mononucleosis, is a common cause of splenomegaly that is usually self-limited. HIV (Chapter 359) may also be associated with splenomegaly, although often the causative agent is a coexisting infection with hepatitis C virus.

Autoimmune disorders such as rheumatoid arthritis (Chapter 243) and systemic lupus erythematosus (Chapter 245) are commonly associated with mild to moderate splenomegaly. Felty syndrome is characterized by splenomegaly, usually in the setting of long-standing rheumatoid arthritis, with associated neutropenia. Autoimmune hemolytic anemia (Chapter 146) is characterized by splenomegaly. Reactions to a variety of commonly prescribed drugs such as antibiotics may result in splenomegaly because of direct effects on the spleen, serum sickness (Chapter 36), or indirectly through effects on the liver.

Hematologic malignancies including myeloproliferative neoplasms frequently manifest with splenomegaly. Patients with lymphoproliferative disorders such as chronic lymphocytic leukemia (Chapter 169) or mantle cell lymphoma (Chapter 171) will in many cases have easily appreciated lymphadenopathy in addition to a palpable spleen. Isolated splenomegaly without associated lymphadenopathy is characteristic of hairy cell leukemia and myeloproliferative neoplasms such as primary myelofibrosis (Chapter 152).[16] Splenomegaly with weight loss related to compression of the stomach and early satiety may be the presenting complaint. Solid tumors may sometimes metastasize to the spleen and result in its enlargement, but this occurrence is unusual. Among solid tumors, malignant melanoma (Chapter 188) is the one most likely to be associated with splenic involvement, but even so, palpable splenomegaly is rare.

Congestive splenomegaly may occur as the result of chronic liver disease with portal hypertension (Chapter 139) or in the setting of splenic or portal vein thrombosis (Chapter 129). Disorders that result in excessive destruction of abnormal red blood cells such as hereditary spherocytosis (Chapter 147) or hemoglobinopathies are also associated with splenomegaly. Storage diseases such as Gaucher disease (Chapter 192), sarcoidosis (Chapter 83), amyloidosis (Chapter 174), thyrotoxicosis (Chapter 207), and hemophagocytic lymphohistiocytosis (Chapter 155) are among the other less common causes of splenomegaly.

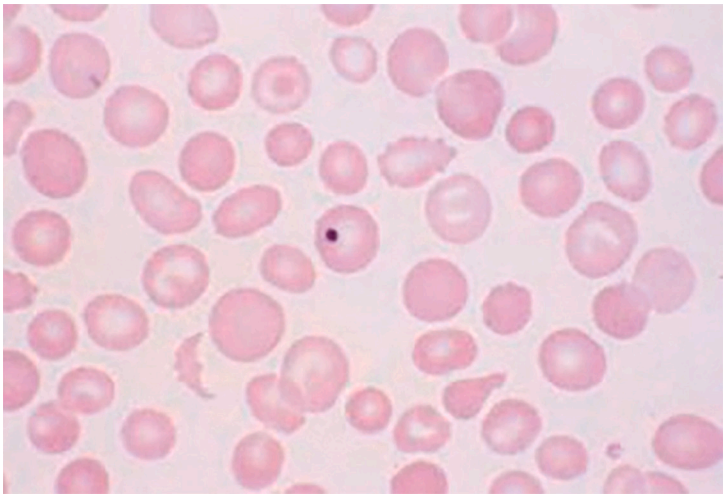

FIGURE 154-3. Howell-Jolly body in an erythrocyte. This finding is evidence of prior splenectomy or a nonfunctional spleen.

Laboratory Evaluation

Although the otherwise asymptomatic patient may be monitored, the symptomatic patient requires a diagnosis so that appropriate treatment may be initiated. Laboratory studies, especially the complete blood count and peripheral blood smear, are important tools in the investigation of the patient with splenomegaly. An enlarged spleen is frequently hyperfunctional ("hypersplenism") and sequesters red cells and platelets, thereby leading to anemia and thrombocytopenia. Leukopenia may also occur. In the presence of hypersplenism, examination of the peripheral smear (Chapter 143) in the patient with splenomegaly may show nucleated red blood cells and red cell abnormalities characteristic of chronic liver disease. The presence of abnormal lymphocytes (e.g., cells with projections as in hairy cell leukemia or with villous projections in splenic marginal zone lymphoma with villous lymphocytes) suggests the presence of a malignant leukemia or lymphoma. The presence of lymphoblasts points to acute lymphoblastic leukemia. In the absence of a functioning spleen, basophilic inclusions representing nuclear remnants, known as *Howell-Jolly bodies*, are seen in circulating red blood cells. The presence of Howell-Jolly bodies (Fig. 154-3) in peripheral blood indicates that the patient has either undergone splenectomy or has a nonfunctioning spleen, as in patients with sickle cell disease who have experienced repeated splenic infarcts.

Flow cytometric analysis can identify the abnormal cell population in many cases. A bone marrow aspirate and biopsy with immunohistochemistry, special stains, flow cytometric analysis, fluorescent in situ hybridization, cytogenetics, and additional molecular testing for particular mutations may be required for the complete evaluation of the patient with splenomegaly and a hematologic malignancy.

Elevated lactate dehydrogenase and uric acid levels are seen in lymphoid malignancies such as Burkitt lymphoma or other aggressive non-Hodgkin lymphomas, but also in myeloid malignancies. Examination of thick smears in patients suspected of malaria may show the offending parasite. Genetic testing may confirm a suspected diagnosis (e.g., in hemophagocytic lymphohistiocytosis).

Imaging

Not all palpable spleens are abnormal, especially in very thin individuals. The least invasive and most inexpensive approach to imaging the spleen is ultrasound, an approach that allows for sequential and accurate measurements. By ultrasound criteria, a spleen that is 13 cm or greater in length and more than 5 cm in thickness qualifies as enlarged.

In comparison with ultrasound, CT scans generally focus on the entire abdomen, not just the spleen, and provide important information that often provides an explanation for the splenomegaly. CT scans also will show

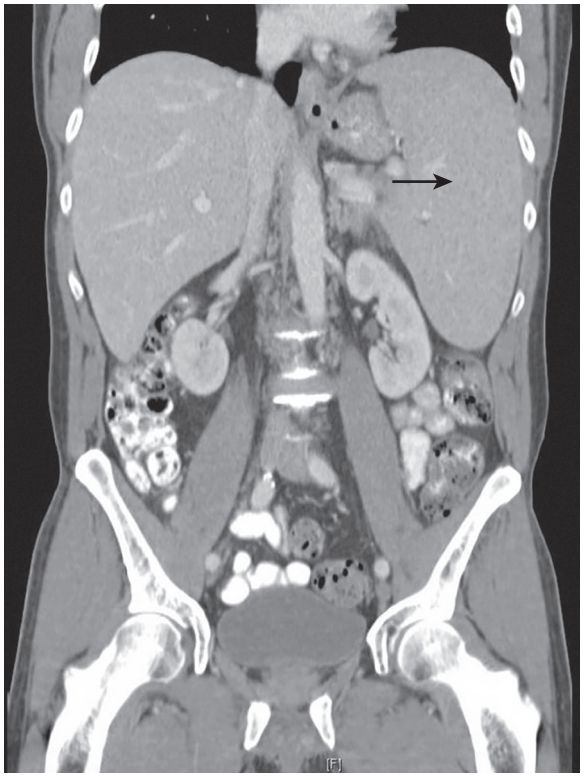

FIGURE 154-4. Splenomegaly (indicated by *arrow*) in a patient with hemophagocytic lymphohistiocytosis.

whether the spleen is diffusely enlarged or enlarged because of multiple nodules (Fig. 154-4). Fluorodeoxyglucose-PET does not distinguish among a variety of malignancies, infections, and other causes of splenomegaly, and it generally is not useful in the diagnostic evaluation of the patient with splenomegaly.

Biopsy

Because of the spleen's location and propensity to bleed, needle aspiration or core biopsy of the spleen is performed only at centers skilled and experienced in the procedure. If an extensive evaluation has not provided a likely explanation for splenomegaly and observation is judged to be imprudent, splenectomy may be performed laparoscopically or by laparotomy.[17,18] Because of the risk of surgical complications and long-term susceptibility to infection in splenectomized individuals, the relative risks and benefits of the procedure must be given serious consideration.[19] Once splenectomy is a possibility, immunization should proceed promptly in an attempt to reduce long-term risks. Appropriate vaccination before splenectomy and in asplenic individuals is of utmost importance (Table 154-6). Partial splenectomy is performed in some children with hereditary spherocytosis, splenic tumors, or splenic trauma in an attempt to reduce the long-term risk of sepsis.[20]

TABLE 154-6 RECOMMENDATIONS FOR PNEUMOCOCCAL, MENINGOCOCCAL, AND *HAEMOPHILUS INFLUENZAE* VACCINATION FOR ASPLENIC INDIVIDUALS

The following vaccines are used:	
Meningococcus	Quadrivalent meningococcal conjugate vaccine (Menveo) Meningococcal serogroup B vaccine (Trumenba or Bexsero)
Pneumococcus	23-valent pneumococcal vaccine (PPSV23, Pneumovax) 15-valent conjugate vaccine (PCV 15; Vaxneuvance); 20-valent conjugate vaccine (PCV 20; Prevnar 20)
Haemophilus influenzae	*H. influenza* type b (Hib) conjugate vaccine
GENERAL GUIDELINES	
• Adults with functional asplenia (e.g., those with sickle cell disease) or those who require surgical splenectomy should be immunized with pneumococcal, meningococcal, and *H. influenza* vaccines • If undergoing elective splenectomy, meningococcal, pneumococcal, and *H. influenzae* vaccines should be given at least 14 days before surgery. If not possible, they should be given after no less than 14 days after splenectomy • Some recommend that the same vaccine combination be given again 8 weeks after the initial doses • Multiple vaccines can be given at the same visit but injected at separate sites • There is some variation in the specific recommendations listed below between guidelines from the U.S. Centers for Disease Control (CDC), the U.S. Advisory Committee on Immunization Practices, various institutions, and some European agencies	
MENINGOCOCCAL VACCINES	
• Quadrivalent meningococcal conjugate vaccines: two doses of Menveo or MenQuadfi, given 2 months apart *plus* • Serogroup B meningococcal vaccines: either Trumenba (three doses at 0, 1-2, and 6 months apart) *or* Bexsero (two doses at least 1 month apart) • Boost every 5 years with Menveo, Menactra, or MenQuadfi • The two serogroup B vaccines are not interchangeable; the same vaccine product must be used for all doses in a series	
PNEUMOCOCCAL VACCINES	
• For before splenectomy: Prevnar 20 alone or Vaxneuvance followed by Pneumovax at least 8 weeks apart • For functional asplenia: Prevnar 20 alone or Vaxneuvance followed by Pneumovax at least 8 weeks apart	
***HAEMOPHILUS INFLUENZAE* VACCINE**	
• Most adults are not at risk because they have already acquired specific antibodies against it through routine childhood vaccination or previous infection. However • One dose of Hib vaccine can be given before splenectomy • One dose of Hib vaccine can be given to functionally asplenic individuals	

TREATMENT

If a likely cause, such as infectious mononucleosis or another infectious process, is identified and confirmed by testing, appropriate management should follow. The associated splenomegaly should resolve over time. Splenectomy may be indicated as part of the treatment of refractory immune thrombocytopenic purpura (Chapter 158) or inherited anemias such as hereditary spherocytosis (Chapter 147) or in cases of splenic abscess. Splenectomy also occasionally may be required for severe hypersplenism with cytopenias.

PROGNOSIS

Most incidentally identified splenic masses in asymptomatic patients will prove to be benign. When borderline in size, the significance of the incidentally noted spleen, like marginally enlarged lymph nodes, is unclear and requires follow-up. Follow-up imaging in short intervals (3 to 6 months) may establish a lesion to be unchanged and provide reassurance of its benign nature. Additional imaging modalities (e.g., MRI, PET/CT, and ultrasound) may be helpful in selecting appropriate patients for further investigation, including biopsy.

The patient without an obvious explanation for splenomegaly presents a difficult diagnostic challenge. Occult liver disease or an undiagnosed autoimmune process may emerge over time as an explanation for persistent splenomegaly in some of these patients.

Splenectomy or biopsy of focal splenic lesions may be the only diagnostic option in patients with persistent symptoms or progressive cytopenias. Splenectomy may have unintended consequences in patients with occult liver disease and portal hypertension and should be avoided in that setting. In the asymptomatic patient, close observation is often preferable to splenectomy.

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155 HISTIOCYTOSES

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The histiocytoses comprise a family of diseases characterized by an accumulation of abnormal cells with features reminiscent of macrophages or dendritic cells. The term *histiocyte* refers to tissue macrophages that are the cell of origin for some histiocytoses. However, many of the other histiocytoses derive from nonmacrophage lineages or from hematopoietic stem cells.

The diagnostic category of histiocytosis embraces a number of heterogeneous but distinct clinical entities, some of which may co-occur in a single patient. Recent advances in molecular genetics provide the basis for a revised nosology that places histiocytic diseases into five groups (Table 155-1)[1,2]:

- L group. These include Langerhans cell histiocytoses and Erdheim-Chester disease because the occasional appearance of both diseases in the same patient suggests a common origin and because both diseases are characterized by somatic mutations in genes of the mitogen-activated protein kinase (MAPK) pathway. Indeterminate cell histiocytosis is also placed in the L group because it shares some characteristics with Langerhans cell histiocytosis.
- C group. These are non-Langerhans cell histiocytoses that involve the skin and/or mucosal surfaces. As in the L group, patients may present with mixtures of C group histiocytoses. They are subdivided into the xanthogranuloma and nonxanthogranuloma diseases. Some C group diseases also have a major systemic component, and mutations in MAPK pathway genes may be seen.
- M group. These are the malignant histiocytoses, which include primary malignancies such as malignant histiocytosis and secondary malignant histiocytoses that occur in the setting of leukemias, lymphomas, or other hematologic neoplasms. Mutations in MAPK pathway genes may occur in these diseases.
- R group. The paradigmatic member of this group is Rosai-Dorfman-Destombes disease, also known as sinus histiocytosis with massive lymphadenopathy. However, the R group also includes all of the other miscellaneous noncutaneous, non-Langerhans cell histiocytoses. Mutations in MAPK pathway genes may occur in these diseases.
- H group. This group contains the varieties of hemophagocytic lymphohistiocytosis and macrophage activation syndromes.

TABLE 155-1 CLASSIFICATION OF HISTIOCYTOSES AND MACROPHAGE/DENDRITIC CELL NEOPLASMS

L group	Langerhans cell histiocytosis (LCH) Indeterminate cell histiocytosis (ICH) Erdheim-Chester disease (ECD)
C group	Cutaneous non-Langerhans cell histiocytoses Xanthogranuloma (XG) family Juvenile xanthogranuloma (JXG) Adult xanthogranuloma (AXG) Solitary reticulohistiocytoma (SRH) Benign cephalic histiocytosis (BCH) Generalized disruptive histiocytosis (GEH) Progressive nodular histiocytosis (PNH) Xanthoma disseminatum (XD) Nonxanthogranuloma (non-XG) family Cutaneous Rosai-Dorfman-Destombes disease (RDD) Necrobiotic xanthogranuloma (NXG) Multicentric reticulohistiocytosis (MRH) Cutaneous non-Langerhans cell histiocytoses with major systemic involvement
R group	Familial Rosai-Dorfman-Destombes disease (RDD), also known as sinus histiocytosis with massive lymphadenopathy (SHML) Sporadic RDD Classical RDD Extranodal RDD RDD with neoplasia or immune disease Not otherwise classified
M group	Primary malignant histiocytoses Secondary malignant histiocytoses (associated with hematologic neoplasia) Subtypes: histiocytic, interdigitating, Langerhans, indeterminate
H group	Primary hemophagocytic lymphohistiocytosis (HLH) Secondary HLH HLH of unknown or uncertain origin

L GROUP LANGERHANS CELL HISTIOCYTOSIS

EPIDEMIOLOGY

Langerhans cell histiocytosis occurs predominantly in children (median age, 3.8 years) but is also seen in adults.[3] Its overall incidence is 2.6 cases per million child years for all children younger than 14 years of age but with a strong trend toward a higher incidence in younger children. There is a slight excess of cases in male patients (1.2 : 1). The incidence of high-risk Langerhans cell histiocytosis is lower in Blacks than in Whites and higher in Hispanics than in non-Hispanics. The incidence in adults has been estimated at 1 to 2 cases per million. Pulmonary Langerhans cell histiocytosis, which occurs primarily in adults, is strongly associated with a smoking history.

PATHOBIOLOGY

The cardinal feature of Langerhans cell histiocytoses is an accumulation of abnormal histiocytes having abundant pale cytoplasm and a single kidney- or coffee bean–shaped nucleus (Fig. 155-1A). All pathologic Langerhans cells express the surface marker CD1a (Fig. 155-1B), and most express CD207, a mannose-binding lectin also known as Langerin. A majority of cells contain intracellular organelles called Birbeck granules, which can be detected by electron microscopy and are composed of CD207 molecules. The lesions are commonly accompanied by a robust inflammatory infiltrate the quality of which may vary depending on the clinical subtype (e.g., abundant eosinophils in eosinophilic granuloma of bone) (see Clinical Manifestations).

Langerhans cell histiocytosis is a neoplastic disease with clonal cells, most of which carry somatic activating mutations in genes that encode members of the MAPK pathway. Specifically, 50 to 60% have mutated *BRAF* (predominantly, but not exclusively, the mutation that encodes the oncogenic variant BRAF V600E), and 25 to 30% have activating mutations of *MAP2K1*. All cases show evidence for activation of extracellular signal-regulated kinase (ERK), the target of this kinase pathway, and the remaining 10 to 25% of cases without *BRAF* or *MAP2K1* mutations have mutations in other genes that activate the pathway, including *ARAF* and *RAS* family members, or translocations resulting in fusion proteins that activate *BRAF*.[4]

Historically, Langerhans cell histiocytosis was acknowledged to be a disease of histiocytes, but because the origin of Langerhans cell histiocytes was unknown, the disease was called histiocytosis X. Langerhans histiocytosis cells express CD1a and CD207 and have Birbeck granules, all of which are characteristic of normal Langerhans cells. However, the profile of genes expressed by Langerhans histiocytosis cells is closer to that of myeloid precursor cells than mature Langerhans cells. In addition, *BRAF* mutations can be detected in hematopoietic stem cells of patients whose Langerhans histiocytosis cells have *BRAF* mutations, a finding suggesting that Langerhans cell histiocytosis is more properly viewed as a myeloid neoplasm in which myeloid precursors may partially differentiate in a direction that allows them to acquire attributes that are also characteristic of Langerhans cells.

CLINICAL MANIFESTATIONS

Langerhans cell histiocytoses may occur at any age and involve any organ. However, the disease is more common in children, and the organs most frequently affected include the following:

- Bone (80% of cases). Skeletal lesions may be asymptomatic or may be associated with tenderness and swelling. The most common locations (in descending order of frequency) are skull, pelvis, femur, ribs, humerus, mandible, and spine, where they appear as punched-out lytic lesions without sclerosis on radiographs (Fig. 155-1C). Resorption of alveolar bone can lead to the appearance of so-called "floating teeth."
- Skin (33% of cases). The rash may be intensely petechial and include scaly and encrusted papules (Fig. 155-1D and E). When skin involvement is the presenting manifestation, the rash may be confused with seborrheic dermatitis and "cradle cap" in infants.
- Hypothalamus and pituitary stalk (25% of cases). Pituitary involvement can lead to diabetes insipidus, which was historically observed to occur in

ABSTRACT

The histiocytoses are characterized by the accumulation in various organs of abnormal cells having features reminiscent of macrophages or dendritic cells. These diseases are heterogeneous in their clinical behaviors and outcomes, but recent advances in molecular genetics have led to a new nosology that divides histiocytic diseases into five categories: L Group: Langerhans cell histiocytosis (LCH), Erdheim-Chester disease, and indeterminate cell histiocytosis; C Group: non-Langerhans cell histiocytoses involving skin or mucosa and comprising both xanthogranuloma and nonxanthogranuloma subtypes; M Group: primary and secondary malignant histiocytoses; R Group: Rosai-Dorfman-Destombes disease and other noncutaneous, non-Langerhans cell histiocytoses; H Group: hemophagocytic lymphohistiocytosis and macrophage activation syndrome. The discovery of constitutive activation of the mitogen-activated protein kinase pathway, due largely to mutations in *BRAF* and *MAP2K1*, in Langerhans cell histiocytoses and Erdheim-Chester disease has led to clinical trials and observational studies describing major clinical responses to BRAF and MEK1 inhibitors. Targeted therapies based on gene mutations in other histiocytoses have also been effective. However, the role of these interventions in the standard treatment of these diseases awaits the results of ongoing clinical trials. In its familial form, hemophagocytic lymphohistiocytosis is associated with null germline mutations in genes encoding immune proteins such as perforin. Acquired hemophagocytic lymphohistiocytosis, triggered by malignancy, infection, or autoimmune disease, may be associated with hypomorphic alleles of these genes. Both forms are treated by immune suppression; hematopoietic stem cell transplantation may also be considered.

KEYWORDS

histiocytosis
dendritic cell
mitogen-activated protein kinase
BRAF
perforin

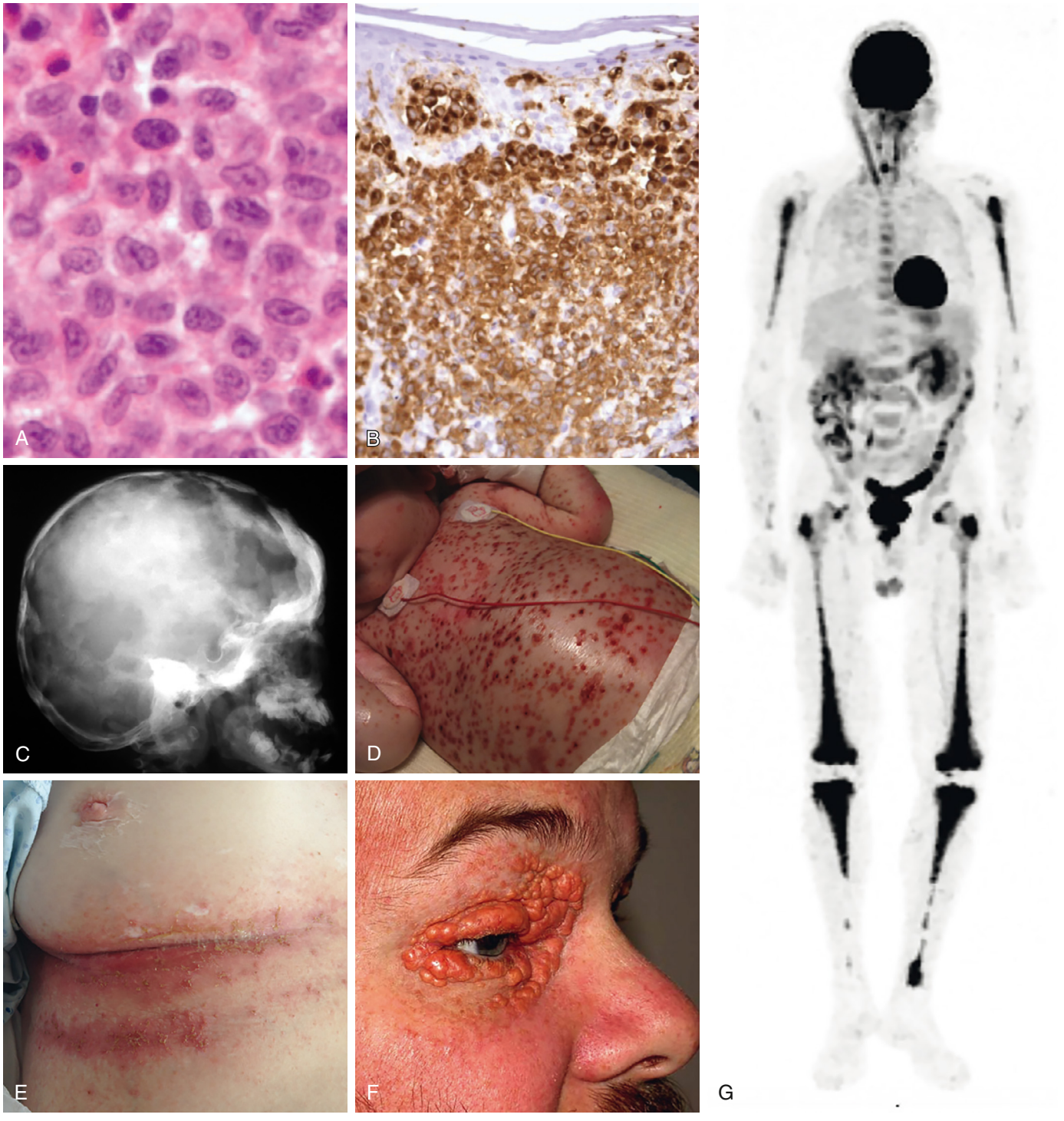

FIGURE 155-1. **Histologic, radiographic, and cutaneous features of Langerhans cell histiocytosis (LCH) and Erdheim-Chester disease (ECD). A,** Hematoxylin and eosin stain of a Langerhans cell histiocytosis bone lesion demonstrating the characteristic kidney- or coffee bean–shaped nuclei and abundant pink cytoplasm of Langerhans cell histiocytes (1000× magnification). **B,** CD1a immunostain of a Langerhans cell histiocytosis skin lesion showing uniformly stained Langerhans cell histiocytes infiltrating the upper dermis and focally involving the epidermis (200× magnification). **C,** Radiographic image showing lytic skull bone lesions in Langerhans cell histiocytosis. **D,** Cutaneous lesions in a child with multisystem Langerhans cell histiocytosis. **E,** Intertriginous lesion in an adult with cutaneous Langerhans cell histiocytosis. **F,** Periorbital xanthelasma in a patient with ECD. **G,** Fluorine-18–radiolabeled fluorodeoxyglucose positron emission tomographic (PET) scan of a patient with ECD showing bilateral and symmetrical abnormal signals in femora, tibiae, and humeri. (**A and B,** From Degar, BA, Fleming, MD, Rollins, BJ, Rodriguez-Galindo C. Histiocytoses. In: Orkin SH, Fisher DE, Ginsburg D, et al, eds. *Nathan and Oski's Hematology and Oncology of Infancy and Childhood*. 8th ed. Philadelphia: Elsevier Saunders; 2015:2104; **C to G,** From Emile J-F, Abla O, Fraitag S, et al. Revised classification of histiocytoses and neoplasms of the macrophage-dendritic cell lineages. *Blood*. 2016;127:2672-2781.)

25 to 50% of patients with Langerhans cell histiocytosis. With earlier diagnosis and effective chemotherapy, the contemporary incidence of diabetes insipidus has been reduced to 7 to 20%.

Involvement of the liver, spleen, bone marrow, or lungs occurs in 15% of cases; involvement of lymph nodes in 5 to 10%, and central nervous system (CNS; excluding pituitary) in 2 to 4%. Lung involvement is more frequent in adults than in children.

The clinical manifestations of Langerhans cell histiocytoses are extraordinarily diverse. However, some presentations were sufficiently stereotypic that they had been recognized as separate entities before the understanding that they are manifestations of the same disease. Importantly, the eponyms for these entities are no longer in use but are listed here to aid in understanding older literature:

- Hand-Schüller-Christian disease: triad of exophthalmos, diabetes insipidus, and bone lesions (especially cranial) in children; 15 to 40% of cases
- Letterer-Siwe disease (or Abt-Letterer-Siwe disease): multisystem disease involving skin, bone, lymph nodes, liver, and spleen in infants; poor prognosis
- Eosinophilic granuloma: bone only, often solitary; 60 to 80% of cases

TABLE 155-2 CLINICAL CLASSIFICATION OF LANGERHANS CELL HISTIOCYTOSIS*

CLINICAL GROUP	INVOLVED SYSTEM	INVOLVED ORGANS
1	Multisystem	Any risk organ†
2	Multisystem	≥2 organs *not including risk organs*
3	Single system • Multifocal‡ or special site§	≥2 lesions in one organ or in a special site§
—	Single system • Unifocal or localized	1 lesion in 1 organ

*Developed for the Langerhans Cell Histiocytosis-III (LCH-III) trial.
†Risk organs: bone marrow, liver, or spleen. (Lung is no longer classified as a risk organ.)
‡Multiple sites of involvement in a single organ system.
§Special sites confer increased risk of specific complications and include intracranial soft tissue extension or vertebral lesions with intraspinal soft tissue extension.

- Hashimoto-Pritzker disease (or congenital self-healing reticulohistiocytosis): self-limited skin involvement in newborns

The contemporary classification of Langerhans cell histiocytoses is based on clinical attributes that correlate with risk and therefore guide therapy. The two dimensions of risk are the number of organs involved (single system vs. multisystem disease) and the presence of disease in "risk organs" (defined as bone marrow, liver, or spleen; Table 155-2).

A late manifestation of Langerhans cell histiocytoses is neurodegeneration, which occurs in about 10% of surviving patients. Manifestations include ataxia, dysarthria, and dysmetria, along with neurocognitive decline and psychological difficulties. Magnetic resonance imaging (MRI) shows signal intensity changes in the cerebellar peduncles, basal ganglia, and pons. The clinical manifestations may wax and wane, but the disease is relentlessly progressive.

DIAGNOSIS

Because the clinical manifestations of Langerhans cell histiocytoses are nonspecific, clinicians must have a high index of suspicion in adult patients who present with a nonhealing seborrheic rash or solitary osteolytic lesion. In patients with diabetes insipidus, characteristic infiltration of the pituitary stalk may be seen on MRI. Pulmonary Langerhans cell histiocytoses should be considered in young smokers with dyspnea or a nonproductive cough whose plain chest radiographs show diffuse bilateral reticulonodular disease in the middle and upper lung zones. Computed tomography (CT) may show nodules or cysts.

Tissue analysis is mandatory. Histopathologic examination shows an infiltrate of histiocytic cells with pale cytoplasm and a single kidney- or coffee bean–shaped nucleus accompanied by varying numbers and types of inflammatory cells (see Fig. 155-1A). Eosinophils may be abundant. Definitive diagnosis requires a demonstration that the histiocytes stain for CD1a (see Fig. 155-1B). Positive staining for CD207 may further support the diagnosis of Langerhans cell histiocytosis. Electron microscopic examination for Birbeck granules has been supplanted by CD207 staining.

TREATMENT

Treatment strategies are evolving rapidly based on molecular testing, but decisions about specific therapies and their intensity have historically been driven by risk stratification. For example, patients with single system disease without organ dysfunction have an excellent prognosis and can be treated with local therapy (e.g., surgical curettage or radiation) or simply monitored and treated when symptomatic. More extensive disease requires systemic therapy, which typically begins with vinblastine and prednisone under expert supervision. Prolonging treatment in patients with multisystem disease decreases the risk of relapse from 54 to 37%. Thus, current standard of care for multisystem disease is vinblastine and prednisone induction followed by 12 months of continued therapy. Adding etoposide to the induction therapy may benefit patients with risk organ involvement.

Various approaches are available for relapsed or recurrent Langerhans cell histiocytosis, referred to historically as "reactivation," which occurs in 20 to 50% of patients. These patients can be placed into low-risk and high-risk categories. Low-risk patients are those who initially had low-risk multisystem Langerhans cell histiocytosis (i.e., no risk organ involvement or multifocal bone disease). Responses to a variety of second-line therapies have been documented, including 6-mercaptopurine and methotrexate, indomethacin, bisphosphonates, and nucleoside analogues such as cladribine, cytarabine, and clofarabine. High-risk patients are those who had risk organ involvement at presentation or showed a poor response to first-line treatment. Cladribine[5] and high-dose cytarabine may be effective in this setting, as is hematopoietic stem cell transplantation, but mortality is still significant.

The discovery of activating mutations in genes encoding MAPK pathway components has led to the use of rapidly advancing fibrosarcoma (RAF) and MAP kinase/ERK kinase 1 (MEK1) inhibitors, primarily in the relapsed setting.[6] In general, patients carrying sensitive mutations in *BRAF* or *MAP2K1*, including heavily pretreated patients, show remarkable responses to inhibitors of RAF (e.g., vemurafenib and dabrafenib), or MEK1 (e.g., cobimetinib, which has been approved by the FDA for use in patients with histiocytic neoplasms that do not carry the mutation encoding BRAF V600E). Optimal dosing has not yet been explored in a clinical trial, and treatment has generally been devised based on efficacy in other diseases. Most reports indicate that patients continue to respond to these inhibitors for as long as they are treated and have relapses when treatment is discontinued. Therefore, despite the remarkable efficacy of these agents, the roles that these inhibitors may play in curative or first-line treatment of Langerhans cell histiocytoses are currently unclear.

For adults with pulmonary Langerhans cell histiocytosis, smoking cessation is usually sufficient treatment. If not, these patients may be treated with corticosteroids. Patients with refractory cases may require lung transplantation.

PROGNOSIS

Outcomes in single system and low-risk disease are quite good. Overall survival for single system disease is more than 99%, with a relapse rate of 18%. In low-risk multisystem disease 5-year overall survival is 99% despite a 40 to 50% cumulative rate of relapse. Nonetheless, morbidities associated with the initial site of disease, especially orthopedic problems, may be long standing and significant. Patients with multisystem high-risk disease have an 84% 5-year overall survival with a 27% relapse rate in Langerhans cell histiocytosis-III. Failure to respond to initial therapy carries a dismal prognosis. Neurodegeneration may appear in up to 10% of patients several years after otherwise successful treatment and in the absence of active histiocytic disease. Sclerosing cholangitis (Chapter 141) may lead to long-term morbidity. The risk of developing leukemia or lymphoma is also higher than in the general population.[7]

ERDHEIM-CHESTER DISEASE

EPIDEMIOLOGY

Erdheim-Chester disease is extremely rare. Fewer than 1000 cases have been reported, and its precise incidence and prevalence are unknown. In contrast to Langerhans cell histiocytosis, Erdheim-Chester disease occurs primarily in adults between 40 and 70 years of age (mean age at diagnosis of 53 years),[8] although it may occur in children and infants. Male patients outnumber female patients by a ratio of nearly 3:1.

PATHOBIOLOGY

Histopathologic examination of lesions shows infiltration by foamy mononuclear histiocytes often accompanied by fibrosis and inflammation involving lymphocytes, neutrophils, or plasma cells. Occasional multinucleated giant cells may be observed. Because the histiocytes stain for CD68 and CD163, and not for CD1a, Erdheim-Chester disease histiocytes are thought to derive from the monocyte-macrophage lineage. Although these characteristics distinguish Erdheim-Chester disease from Langerhans cell histiocytosis, 20% of patients with Erdheim-Chester disease have concurrent Langerhans cell histiocytosis.

As in Langerhans cell histiocytosis, about 50% of patients with Erdheim-Chester disease have somatic mutations encoding BRAF V600E. Essentially all remaining patients have other genetic variants that activate the MAPK pathway, including mutations in *MAP2K1*, *ARAF*, *KRAS*, and *NRAS*, as well as gene fusions that activate *BRAF*, *ALK*, and *NTRK*. Mutations in *PIK3CA* have been observed and may co-occur with *BRAF* mutations.

CLINICAL MANIFESTATIONS

Histiocytic infiltration of bone occurs in nearly all patients, manifesting as symmetrical cortical sclerosis of diaphyseal and metaphyseal areas of long bones, often in the lower extremities (Fig. 155-1G). Patients may complain of mild juxta-articular pain but may also be asymptomatic in the presence of radiographic disease. Osteosclerosis of facial bones or other bones of the skull may also occur. CT or MRI may be necessary to detect lesions not seen on plain radiographs.

Cardiovascular involvement by fibrosis occurs in the majority of patients, may manifest as valvular abnormalities, conduction defects, or periaortic coating, and is one of the main causes of morbidity and mortality in Erdheim-Chester

disease. Similar fibrosis may occur in the retroperitoneum, encircling the kidneys and leading to a progressive obstructive nephropathy. About 50% of patients with Erdheim-Chester disease have pulmonary disease involving the pleura, parenchyma, or both. About 40% of patients have CNS disease, including pituitary involvement leading to diabetes insipidus and mass lesions in various parts of the brain. CNS involvement portends a worse outcome. Cognitive impairment and behavioral changes may also occur in the absence of MRI-documented infiltration or masses, although they may be associated with gray matter volume loss. Cutaneous disease occurs in about 25% of patients and usually manifests as xanthelasma, most frequently involving the eyelids (Fig. 155-1F).

DIAGNOSIS

Diagnosis must be made by histologic examination of involved sites, preferably osteosclerotic bone. Because genetic analysis for mutations in MAPK pathway genes informs clinical care and because decalcification for histologic examination may preclude such analysis, sufficient material must be collected and processed separately for both histologic and genetic testing. Absence of CD1a or CD207 staining will distinguish Erdheim-Chester disease from Langerhans cell histiocytosis. However, 20% of patients with Erdheim-Chester disease have concurrent Langerhans cell histiocytosis. Clinical manifestations of Erdheim-Chester disease may be confused with those of Paget disease or POEMS (polyneuropathy, organomegaly, endocrinopathy, myeloma protein, and skin changes) syndrome (Chapter 173), but the histopathologic picture of these disorders is distinct. Juvenile xanthogranuloma is a histiocytic disease of the C group (see later), and its histopathologic features are very similar to those of Erdheim-Chester disease. However, juvenile xanthogranuloma typically occurs in young children and only rarely involves extracutaneous sites. When juvenile xanthogranuloma is disseminated, lesional cells may harbor activating mutations in genes of the MAPK pathway, which is reminiscent of Erdheim-Chester disease and places this form of juvenile xanthogranuloma in the L group.

When the tissue diagnosis of Erdheim-Chester disease is confirmed, the extent of disease should be determined. A full endocrine evaluation should be performed to assess pituitary involvement, and imaging studies should include long bones, skull, and pelvis, as well as CT or MRI evaluation of the brain, the full length of the aorta, and the retroperitoneum. These studies may reveal characteristic periaortic thickening ("coated" aorta) and retroperitoneal fibrosis ("hairy kidneys"). Fluorine-18–radiolabeled fluorodeoxyglucose uptake demonstrated by positron emission tomography has been reported to provide high specificity in the setting of osteosclerosis (Fig. 155-1G). The presence of cardiac conduction abnormalities should be evaluated by electrocardiography. Macrophage-like cells that stain for S100 and show emperipolesis may be seen histologically and could suggest a diagnosis of Rosai-Dorfman-Destombes disease, but the clinical presentation of Erdheim-Chester disease is distinct from that of Rosai-Dorfman-Destombes disease (see later).

TREATMENT

Because most cases of Erdheim-Chester disease are indolent, asymptomatic patients who have no CNS disease may be followed without treatment.[9] If patients have CNS disease or develop troublesome symptoms, systemic treatment is warranted. The nearly universal presence of mutations in genes encoding components of the MAPK pathway in this disorder has moved targeted therapies to the forefront. A basket trial of the RAF inhibitor vemurafenib, given to patients with a variety of diseases carrying a somatic mutation encoding BRAF V600E and including several cases of Erdheim-Chester disease, resulted in prolonged responses in 6 of 18 patients. Thus RAF inhibitors may be administered under expert supervision to patients whose disease carries activating mutations in *BRAF* or *ARAF*. Patients without these mutations may be treated with the MEK inhibitor cobimetinib which the FDA has approved for treating BRAF V600E-negative Erdheim-Chester disease.

If targeted therapies cannot be used, treatment with interferon (IFN) alfa (conventional or pegylated) is recommended because of a suggestion of survival benefit in a retrospective analysis. For patients in whom IFN treatment fails, cladribine or cyclophosphamide may produce responses. Glucocorticoids, interleukin-1 receptor (IL-1R) antagonists, and anti-TNF agents may also have activity. Radiotherapy may provide relief of local symptoms.

PROGNOSIS

Although therapies targeted against BRAF V600E or MEK1 produce impressive symptomatic and radiographic responses in most patients with Erdheim-Chester disease, the impact of these drugs on survival is currently unknown. In one small study of patients treated with IFN-alfa, 1- and 5-year overall survival rates were 93 and 41%, respectively, versus 86 and 28% in patients who did not receive interferon.

INDETERMINATE CELL HISTIOCYTOSIS

Indeterminate cell histiocytosis is an exceedingly rare disease that may manifest as a cutaneous eruption mimicking Langerhans cell histiocytosis, although some cases may involve lymph nodes only. It occurs in adults and may predominantly affect women, although no rigorous epidemiologic analyses have been performed. Histologic analysis of lesions shows a nonepidermotropic infiltration of histiocytes that may stain for CD1a, similar to Langerhans cell histiocytosis, but do not express CD207. One report describes a case with a somatic mutation encoding BRAF V600E and may support the notion that indeterminate cell histiocytosis is related to Langerhans cell histiocytosis. However, another report collected four cases, three of which showed the same *ETV3-NCOA2* gene fusion. Although the pathogenic relevance of this translocation is unknown, its recurrent appearance in indeterminate cell histiocytosis and its absence from Langerhans cell histiocytoses indicate that these are distinct entities.

C GROUP

These non-Langerhans cell histiocytoses are divided into those that are predominantly cutaneous versus those that have a significant systemic component. Each group is further divided into the xanthogranuloma and nonxanthogranuloma categories.

XANTHOGRANULOMA FAMILY

EPIDEMIOLOGY

This group comprises several diseases that are distinguished primarily on the basis of clinical presentation: patient age, anatomic site of involvement, and whether lesions are solitary, multiple, or disseminated. Juvenile xanthogranuloma is the most commonly occurring non-Langerhans cell histiocytosis. Although its published prevalence is 0.5% of pediatric tumors, the benign nature of juvenile xanthogranuloma likely leads to underreporting. A slight excess of cases in female patients has been observed (1.4:1).

PATHOBIOLOGY

Lesions contain a dermal infiltrate that includes histiocytes, occasional multinucleated giant cells that may have the features of Touton cells, and nonspecific inflammatory cells. Regressing lesions show replacement by fibrous tissue. Histiocytes stain for CD68, CD14, CD163, factor XIIIa, and fascin; S100 staining may be absent or variable, and the cells do not stain for CD1a or CD207.

Juvenile xanthogranuloma may occur in association with neurofibromatosis type 1, although the relationship between genetic abnormalities in NF1 and JXG is unknown. Mutations involving *NRAS*, *KRAS*, *BRAF*, *ARAF*, *MAP2K1*, and *MAPK1* have been reported, as well as activating RNF11/BRAF and MRC1/PDGFRB fusions. Mutations in *PIK3CD* have also been reported. To date, MAPK pathway mutations have been described only in disseminated and not cutaneous cases. Because of the phenotypic similarities between disseminated JXG and Erdheim-Chester disease, and because of the presence of mutations in MAPK genes in both, disseminated juvenile xanthogranuloma has been classified in the L group. Cutaneous juvenile xanthogranuloma remains in the C group.

CLINICAL MANIFESTATIONS

Juvenile xanthogranuloma is a benign disease in which a variable number of small (<2.0-cm) yellow-red skin nodules appear most commonly on the head, neck, or upper trunk, although they may occur anywhere. About 70% of lesions are solitary. Systemic disease occurs rarely and may involve liver, lung, spleen, lymph nodes, bone, and gastrointestinal tract. Both cutaneous and systemic lesions generally resolve spontaneously within a few months or years, with no clinically significant sequelae. Some cases of disseminated juvenile xanthogranuloma in newborns or juvenile xanthogranuloma producing symptoms may require treatment.

Xanthoma disseminatum is also in the xanthogranuloma family and manifests as a cutaneous eruption of brown papules or nodules on flexor and periorbital areas. It involves mucosal surfaces and has a significant visceral component. Xanthoma disseminatum primarily affects young adult men and has a chronic clinical course that may include diabetes insipidus.

DIAGNOSIS

The clinical appearance of cutaneous xanthogranuloma may be sufficiently characteristic that a diagnosis can be made by observation alone. Biopsy and

immune staining may be required for ambiguous cases. Xanthogranuloma histiocytes stain for CD68, CD163, factor XIIIa, and fascin and do not stain for CD1a, CD207, and, generally, S100. Differential diagnosis includes the following: Langerhans cell histiocytosis, which can be distinguished by immune staining; papular xanthoma, the lesions of which contain more foam cells and fewer giant cells than xanthogranuloma; eruptive xanthoma, generally in hypertriglyceridemic adults; Spitz nevi; mastocytoma; and dermatofibroma.

TREATMENT

Patients with cutaneous juvenile xanthogranuloma may be observed without treatment. Patients with ocular involvement by juvenile xanthogranuloma or xanthoma disseminatum should be referred to an ophthalmologist for evaluation. Symptomatic visceral involvement may be treated, if necessary, with surgical excision, radiation therapy, or chemotherapy under expert supervision. Chemotherapeutic regimens used for Langerhans cell histiocytes may be effective in this setting.

PROGNOSIS

Cutaneous and visceral xanthogranuloma lesions spontaneously resolve, and the overall prognosis is excellent. Treatment outcomes for symptomatic visceral lesions are also good. Fatalities may occur rarely in infants with extensive hepatic involvement or CNS disease.

NONXANTHOGRANULOMA FAMILY

EPIDEMIOLOGY

Necrobiotic xanthogranuloma occurs in adults (average age of onset is in the sixth decade) and is accompanied by monoclonal gammopathy in 80% of patients.[10] There is no sex predilection. Multicentric reticulohistiocytosis is a disease of women in their 50s and 60s.[11] Rosai-Dorfman-Destombes disease may rarely be confined to the skin and in this manifestation should be considered a nonxanthogranuloma group C disease.

PATHOBIOLOGY

The pathobiology of necrobiotic xanthogranuloma is not understood, but its association with paraproteinemias has suggested that it may be a histiocytic reaction to the deposition of immunoglobulins. Histopathologic examination shows histiocytic xanthogranulomas with bands of necrosis in the dermis, accompanied by giant cells that may have a characteristic morphology for this disease. Lymphoid nodules and plasma cells may be seen.

One fourth of patients with multicentric reticulohistiocytosis have an underlying malignancy, thus raising the possibility that this is a paraneoplastic syndrome. However, no pathogenetic mechanism has been identified. Associated malignancies include breast and gastric cancers, as well as hematologic neoplasms.

CLINICAL MANIFESTATIONS

The cutaneous lesions of necrobiotic xanthogranuloma are discolored and indurated papules and nodules that may coalesce to form plaques, the centers of which may be atrophic. Periorbital areas are the most common site of involvement, but lesions may occur elsewhere on the face, trunk, arms, legs, and genitalia. The most common site of extracutaneous involvement is the eye and can manifest as uveitis or scleritis. Visceral involvement may also occur in a variety of sites but most commonly in the respiratory tract or cardiac structures.

The cutaneous lesions of multicentric reticulohistiocytosis are discolored papules that appear predominantly on the face, hands, forearms, and ears. The oral or nasal mucosa may also be involved. Periungual lesions may have a characteristic "coral bead" appearance. Patients with multicentric reticulohistiocytosis have a rapidly progressive destructive polyarthritis with systemic symptoms such as fever and weight loss.

DIAGNOSIS

Periorbital yellowish plaques with associated erythema and central atrophy or telangiectasias are highly suggestive of necrobiotic xanthogranuloma. Skin biopsy should be performed to confirm the diagnosis. Serum and urine electrophoresis should be performed to test for the presence of monoclonal gammopathy, and further hematologic work-up should be dictated by the results. Imaging of the chest, abdomen, and pelvis should be performed to assess visceral disease. The periorbital lesions of necrobiotic xanthogranuloma are distinguished from xanthelasmas or plane xanthomas by the former's larger size, induration, and erythema. Ocular involvement may be documented by conjunctival biopsy. Necrobiotic xanthogranuloma should also be distinguished from necrobiosis lipoidica, which occurs in patients with diabetes mellitus and has a histopathologic picture distinct from that of necrobiotic xanthogranuloma.

Histopathologic examination of multicentric reticulohistiocytosis shows frequent multinucleated giant cells and macrophages with eosinophilic cytoplasm. Multicentric reticulohistiocytosis may be reminiscent of fibroblastic rheumatism, although skin lesions in the latter are characterized histologically by fibrosis.

TREATMENT

Unlike xanthogranuloma, necrobiotic xanthogranuloma requires treatment because it does not spontaneously resolve and can produce disfiguring sequelae. No rigorous studies have identified an ideal treatment. Case reports suggest that alkylators such as chlorambucil or melphalan, with or without steroids, may be effective first-line therapy under expert supervision. Intravenous immunoglobulin has been used as second-line therapy, and lenalidomide has been used in patients with monoclonal gammopathy even in the absence of clinically documented multiple myeloma. Treatment of multicentric reticulohistiocytosis should be directed toward the underlying neoplasm if present.

PROGNOSIS

Scarring and ulceration may be common sequelae of cutaneous necrobiotic xanthogranuloma lesions. Patients with necrobiotic xanthogranuloma have an increased risk of developing hematologic malignancies and should be monitored. Treatment of the underlying neoplasm may not lead to resolution of multicentric reticulohistiocytosis.

R GROUP

The R group is composed primarily of the various manifestations of Rosai-Dorfman-Destombes disease, also known as sinus histiocytosis with massive lymphadenopathy.

EPIDEMIOLOGY

Sporadic Rosai-Dorfman-Destombes is a rare disease that occurs more commonly in children and young adults, with a peak incidence in the second and third decades. Overall prevalence is 5 per 100,000. The disease occurs more frequently in males and in individuals of African ancestry. Rosai-Dorfman-Destombes occurs in the lymph nodes of 20% of patients with H syndrome, which is associated with mutation in the *SLC29A3* gene. Nodal involvement also occurs in 41% of patients with autoimmune lymphoproliferative syndrome (ALPS) type Ia in which germline mutations affect *TNFRSF6*, which encodes Fas.

PATHOBIOLOGY

Nodal Rosai-Dorfman-Destombes is characterized by an accumulation in lymph node sinuses of large, polyclonal histiocytes with hypochromatic nuclei and pale cytoplasm, often showing emperipolesis (the presence of an intact cell within the cytoplasm of another cell). The histiocytes express macrophage markers, including S100, CD68, CD14, HLA-DR, and CD163, and do not express CD1a or CD207. Cortical regions of involved lymph nodes often have abundant plasma cells and activated B lymphocytes. Histiocytes may also accumulate in extranodal sites accompanied by plasma cells. The plasma cells are often immunoglobulin 4 (IgG4) positive. In some cases, histiocytes may harbor somatic mutations in MAPK pathway genes, *NRAS*, *KRAS*, *BRAF*, *ARAF*, and *MAP2K1*, suggesting that a subset of Rosai-Dorfman-Destombes disease may be associated with oncogenic driver mutations.

CLINICAL MANIFESTATIONS

Patients with nodal Rosai-Dorfman-Destombes present with nontender, massively enlarged cervical lymphadenopathy along with systemic inflammatory signs such as fever, leukocytosis, elevated erythrocyte sedimentation rate, and a polyclonal hypergammaglobulinemia. Nasal or tracheal obstruction may occur. Other involved nodal sites may include axilla, mediastinum, retroperitoneum, and inguinal regions. Extranodal involvement occurs in 43% of sporadic Rosai-Dorfman-Destombes cases, most commonly skin, nasal cavity, retro-orbital tissue, dura, bone, and soft tissue.

DIAGNOSIS

Diagnosis of Rosai-Dorfman-Destombes requires histopathologic examination of involved lymph nodes or extranodal tissues. The immunohistochemical staining pattern of the characteristic histiocytes is described earlier.

Rosai-Dorfman-Destombes disease can be distinguished from Langerhans cell histiocytosis by the absence of CD1a or CD207 staining. In cases of cutaneous involvement, differentiation from juvenile xanthogranuloma may be difficult. Intracranial Rosai-Dorfman-Destombes may have the radiographic appearance of meningioma, but characteristic cells may be seen in cerebrospinal fluid. Frequent IgG4-positive plasma cells in this disease may also raise a suspicion of IgG4-related disease (also known as hyper-IgG4 syndrome), although the clinical manifestations are distinct.

TREATMENT

Sporadic Rosai-Dorfman-Destombes disease generally has a favorable outcome and may resolve spontaneously over months to years. Symptomatic disease may be treated with corticosteroids, clofarabine, or radiation therapy under expert supervision. KRAS- or MEK-variant disease may respond to cobimetinib under expert oversight.[12]

PROGNOSIS

The prognosis of sporadic Rosai-Dorfman-Destombes is generally favorable.

M GROUP

The M group consists of malignant histiocytoses, which can be primary or can occur in association with other neoplasms.

EPIDEMIOLOGY

Malignant histiocytosis is rare, and its true incidence is unknown. It is a disease of adults, with a median age of diagnosis for the histiocytic sarcoma subtype in the mid-40s to mid-50s, and no sex imbalance. Secondary malignant histiocytosis may occur in the context of hematologic diseases such as acute lymphoblastic leukemia (but not acute myeloid leukemia), chronic lymphocytic leukemia, hairy cell leukemia, myelodysplastic syndrome, chronic myelomonocytic leukemia, follicular lymphoma, mediastinal germ cell tumors, and Langerhans cell histiocytosis.

PATHOBIOLOGY

Malignant histiocytosis cells are anaplastic and have frequent mitotic figures and atypical mitoses. Cells do not stain for epithelial markers such as keratins and epithelial membrane antigen (EMA), melanoma antigens such as melan-A and HMB45, B- and T-lymphocyte markers, and follicular dendritic cell markers. Malignant histiocytosis cells must express at least two of the histiocytic or dendritic cell markers CD68, CD163, CD4, or lysozyme and not express other histiocytosis markers such as S100, CD1a, or CD207. Malignant histiocytosis may manifest with various cellular phenotypes that are reminiscent of specific histiocytic cell types, and some pathologists have classified these as histiocytic, interdigitating dendritic cell, Langerhans cell, or indeterminate cell sarcomas. Recent recommendations suggest that the term *malignant histiocytosis* should be applied to the entire family of diseases and that the cellular phenotypes should be considered subtypes. In secondary malignant histiocytosis, clonal immunoglobulin rearrangements, translocations, or somatic mutations may appear both in the malignant histiocytosis cells and the cells of the underlying malignancy, a finding suggesting an evolutionary relationship between the two diseases.

CLINICAL MANIFESTATIONS

Patients may present with symptomatic mass lesions that can be accompanied by fever and weight loss. However, some lesions may be discovered incidentally through imaging studies. Disease may be unifocal or multifocal and can involve any organ, but malignant histiocytosis most commonly manifests in the intestinal tract, skin, or soft tissue. Malignant histiocytosis tumors generally progress rapidly.

DIAGNOSIS

Diagnosis depends on the presence of the histopathologic features described earlier. Other histiocytic or dendritic cell disorders such as Langerhans cell histiocytosis or hemophagocytic lymphohistiocytosis must be excluded. Malignant histiocytosis must also be distinguished from myeloid sarcomas, which are soft tissue collections of myeloid leukemia cells that are identical to leukemia cells in the circulation or bone marrow. Most challenging may be distinguishing the anaplastic cells of malignant histiocytosis from other aggressive malignancies such as diffuse large cell lymphoma, metastatic melanoma, and some metastatic carcinomas. Immunohistochemical staining patterns are useful to rule out these disorders.

TREATMENT

There is no standard of care for malignant histiocytosis. Depending on the sites of disease, effective approaches could include surgery, radiation therapy, or systemic chemotherapy, particularly regimens developed for aggressive lymphomas under expert supervision. A response to an RAF inhibitor in a histiocytic sarcoma carrying a BRAF V600E mutation has been reported, but this cannot be considered a standard therapeutic approach.

PROGNOSIS

A spectrum of outcomes can be seen in these patients, from spontaneous remission to recurrent and refractory disease. No markers have been described that reliably predict response to therapy.

H GROUP, INCLUDING HEMOPHAGOCYTIC LYMPHOHISTIOCYTOSIS

The H group comprises hemophagocytic lymphohistiocytosis, a disorder of immune hyperactivity that was originally described and characterized in infants and young children but is increasingly recognized as a disorder also seen in adults. In children, hemophagocytic lymphohistiocytosis is predominantly a congenital syndrome associated with homozygous genetic abnormalities that abolish the expression of key immune response genes necessary for normal T-cell and NK-cell responses (Chapter 231), although it may also be seen in association with certain infections and as a complication of systemic autoimmune disease. In adults, hemophagocytic lymphohistiocytosis is most commonly associated with lymphoid malignancy, but it also may be a complication of infection or autoimmune disease; in a subset of cases, no inciting abnormality can be found.[13]

EPIDEMIOLOGY

The estimated incidence of familial hemophagocytic lymphohistiocytosis is widely variable, reflecting both geographic variation and rate of successful detection. Estimates range from 1 to more than 200 in 300,000 births. Although it is a rare syndrome outside the pediatric population, the incidence of hemophagocytic lymphohistiocytosis in adults is impossible to estimate because it has been recognized as a syndrome occurring in adults only for the last 15 to 20 years. With increased recognition of the syndrome, it has become apparent that it is less rare than was previously appreciated. Hemophagocytic lymphohistiocytosis appears to be more common in China and Japan than it is in the West.

PATHOBIOLOGY

Hemophagocytic lymphohistiocytosis reflects an uncontrolled immune activation resulting from a failure of cytotoxic T-cell and NK-cell cytotoxicity. On recognition of antigen, these effector cells release perforin-containing cytolytic granules that contribute to lysis of the antigen-expressing target cell. Under normal conditions, target cell elimination limits antigen exposure, leading to downregulation of the immune response, termed *activation-induced cell death.* In familial hemophagocytic lymphohistiocytosis, however, homozygous null mutations in one of a series of genes involved in the synthesis, trafficking, and function of cytotoxic granules from cytotoxic immune cells, including *PRF1, UNC13D, STX11, STXBP2, RAB27A, LYST*, and *AP3B*, leads to inability to clear antigenic stimuli, thus causing a persistent and amplified immune response. The persistently activated cytotoxic T cells and NK cells release high levels of inflammatory cytokines, leading to macrophage activation, hemophagocytosis, and other manifestations of "cytokine storm." The inciting stimulus to the presentation of familial hemophagocytic lymphohistiocytosis is usually an infection, most frequently with Epstein-Barr virus (EBV). In children, secondary hemophagocytic lymphohistiocytosis may occur as a result of infection or autoimmune disease. In the setting of autoimmune disease, it is termed *macrophage activation syndrome.*

Hemophagocytic lymphohistiocytosis was nearly unrecognized as a disease that occurred in adults until the last 15 to 20 years. Since then it has become clear that, although rare, it is being increasingly diagnosed worldwide. It is not clear whether the increasing recognition of adult hemophagocytic lymphohistiocytosis reflects a higher incidence or greater ascertainment.

Most, if not all, adults with hemophagocytic lymphohistiocytosis are thought to have "secondary" or "acquired" hemophagocytic lymphohistiocytosis. The triggers of adult hemophagocytic lymphohistiocytosis include malignancy,

infection, and systemic autoimmune disease. Malignancy (especially lymphoma) is the trigger for hemophagocytic lymphohistiocytosis in more than one half of adult patients. The mechanism of acquired hemophagocytic lymphohistiocytosis is much less well understood, although the pattern of immune hyperactivity and cytokine excess is similar.

With the increasing recognition of hemophagocytic lymphohistiocytosis in adults, significant attention has focused on polymorphisms and potential heterozygous mutations in the familial hemophagocytic lymphohistiocytosis genes that may predispose patients to acquire hemophagocytic lymphohistiocytosis in the presence of other triggers. In the original study examining the presence of genetic mutations in familial hemophagocytic lymphohistiocytosis genes in samples from adults suspected of having hemophagocytic lymphohistiocytosis, about 15% were found to have presumed hypomorphic alleles in the familial hemophagocytic lymphohistiocytosis genes. The most common mutation is in the perforin gene (*A92V*), and it is a polymorphism present in 5 to 8% of the general population. The effect of these mutations is unclear, although modeling suggests they may reduce the function of their cognate proteins, and some individuals have had detectable subtle abnormalities in NK-cell function. These mutations likely represent predisposing factors that are part of the pathogenesis of the disease in the setting of other triggers; however, the frequency of some of the mutations and their presence in asymptomatic family members suggest that they are not a driver of the disease.

CLINICAL MANIFESTATIONS

Familial hemophagocytic lymphohistiocytosis typically manifests in the first year of life, nearly always in the setting of infection, most commonly with Epstein-Barr virus. Children usually have prominent CNS symptoms, whereas this is much less frequent in adults. Adults may present with secondary hemophagocytic lymphohistiocytosis at any age. Patients frequently present with a fulminant picture of fever, cytopenias, and multiorgan failure, and they are often suspected of having septic shock. Because the inciting event in hemophagocytic lymphohistiocytosis is most commonly an infection, treatment of the infection may improve the patient's clinical status. However, recrudescence of symptoms is common because once hemophagocytic lymphohistiocytosis is triggered it is usually not self-limited without directed intervention. As delineated later in the diagnostic criteria for hemophagocytic lymphohistiocytosis, fever and cytopenias are often accompanied by splenomegaly, coagulopathy, dyslipidemia, liver function abnormalities, and elevated serum ferritin. Bone marrow aspiration frequently, although not always, demonstrates hemophagocytosis. Many of the clinical features of hemophagocytic lymphohistiocytosis are nonspecific, and diagnosis may be delayed. As discussed in the next section, the diagnosis, especially in adults, may be challenging.

DIAGNOSIS

The diagnostic criteria for hemophagocytic lymphohistiocytosis (Table 155-3) are based on pediatric hemophagocytic lymphohistiocytosis, but they generally perform well in diagnosing the disease in adults.[14] Other diagnostic algorithms have been designed with the intent of improving diagnostic accuracy, especially in adults, but they probably add little to the ability to diagnose hemophagocytic lymphohistiocytosis in adult patients, except perhaps at initial presentation or when some specialized tests such as the soluble IL-2 receptor (sIL2r or sCD25) are unavailable.

TABLE 155-3 DIAGNOSTIC CRITERIA FOR HEMOPHAGOCYTIC LYMPHOHISTIOCYTOSIS

Molecular diagnosis of familial disease
OR
At least 5 of the following 8 criteria:
Fever
Cytopenia of ≥2 lineages
Splenomegaly
Hypertriglyceridemia and/or hypofibrinogenemia
Ferritin >500 ng/mL
Soluble CD25/sIL2r >2400 U/mL
Hemophagocytosis in bone marrow, spleen, or lymph nodes
Low or absent NK-cell activity

NK = natural killer; sIL2r = soluble interleukin-2 receptor.

The first critical step in the diagnosis of hemophagocytic lymphohistiocytosis is to consider the diagnosis because until recently it was rarely entertained in adult patients. In considering the diagnosis, a thorough history should include details regarding recent infections, history of autoimmune disease, underlying malignancy, and underlying immune disorders. Testing should include complete blood count, full metabolic panel, triglycerides, fibrinogen, ferritin, and sIL2r where available. Thorough evaluation for bacterial, parasitic, mycobacterial, and fungal infection should be performed, as well as evaluation for viral infection to include both serology and viral titers for Epstein-Barr virus, cytomegalovirus, human immunodeficiency virus, influenza, hepatitis B and C, herpes simplex virus, varicella-zoster virus, parvovirus, adenovirus, and human herpesvirus-8. Patients should be evaluated for evidence of systemic autoimmune disease. Importantly, because lymphoma is a trigger of hemophagocytic lymphohistiocytosis in about half of adult patients, every effort should be made to find evidence for lymphoma. Patients should undergo marrow examination, and marrow samples should be sent for flow cytometry and T-cell gene rearrangement studies in addition to routine studies. When possible, full evaluation for lymphoma, including a positron emission tomographic (PET) scan, should be performed before initiation of therapy because therapy for hemophagocytic lymphohistiocytosis is likely to mask accompanying lymphoma and thereby impede its timely diagnosis.

Diagnosis of hemophagocytic lymphohistiocytosis requires demonstration of homozygous or compound heterozygous null mutations in familial hemophagocytic lymphohistiocytosis genes (seen in children) or fulfillment of five of eight criteria (see Table 155-3): fever, cytopenias, hypofibrinogenemia or hypertriglyceridemia, elevated ferritin, elevated soluble IL-2 receptor (sIL2r or sCD25), splenomegaly, hemophagocytosis in the bone marrow, and impaired NK-cell function. Because NK-cell function is highly variable outside of familial hemophagocytic lymphohistiocytosis and rarely tested, diagnosis in adults is usually made by satisfying five of the other seven criteria in Table 155-3.

Fever and cytopenias are universal findings in patients presenting with hemophagocytic lymphohistiocytosis. These signs are reflective of the exuberant secretion of inflammatory cytokines released by activated T and NK cells and macrophages, including IFN-γ, tumor necrosis factor-α, IL-2, IL-4, IL-6, and IL-10. Splenomegaly has been reported to occur in about half of adults with hemophagocytic lymphohistiocytosis, and its presence may reflect the duration of the illness before diagnosis. Hypertriglyceridemia and/or hypofibrinogenemia occur in at least 50% of adults with hemophagocytic lymphohistiocytosis. Elevated liver function test results, although not a criterion for the diagnosis, are seen in almost all patients.

Hyperferritinemia has often been considered the hallmark of hemophagocytic lymphohistiocytosis and macrophage activation syndrome. In children, a serum ferritin level higher than 10,000 mg/dL has been demonstrated to be more than 90% sensitive and specific for hemophagocytic lymphohistiocytosis. However, in adults, ferritin is less powerful for establishing the diagnosis. Survey of a database of patients for elevated ferritin revealed that even with ferritin levels higher than 50,000 mg/dL, fewer than 20% of patients will have hemophagocytic lymphohistiocytosis; conversely, among adults diagnosed with hemophagocytic lymphohistiocytosis, the ferritin level ranges from 600 mg/dL to more than 50,000 mg/dL. Therefore, the negative predictive value of a normal ferritin result is high, but it is not a discerning marker for hemophagocytic lymphohistiocytosis in adults. Because hyperferritinemia is a nonspecific consequence of macrophage activation, it is also elevated in other chronic inflammatory conditions, hemolytic anemia, and renal failure, all of which are more common in adults than in children.

The soluble form of the IL-2 receptor (sIL2r, sCD25) is also elevated in hemophagocytic lymphohistiocytosis. The IL-2 receptor is widely expressed by lymphocytes, monocytes, eosinophils, and NK cells; is cleaved by macrophage gelatinase (MMP9) to release the soluble form of the receptor; and is a marker of immune activation in many inflammatory disorders. Although it is elevated in nearly all, if not all, patients with hemophagocytic lymphohistiocytosis, it is not a readily available test. However, it can be an extremely valuable diagnostic marker. In particular, in adults, it is usually extremely elevated in lymphoma-associated hemophagocytic lymphohistiocytosis because the malignant lymphoma cells themselves express high levels of IL2r. The ratio of sIL2r to ferritin can help distinguish lymphoma-associated hemophagocytic lymphohistiocytosis from other forms of hemophagocytic lymphohistiocytosis in adults: the ratio is usually less than 1 in the absence of malignancy and greater than 2 in the setting of lymphoma-associated hemophagocytic lymphohistiocytosis.

Hemophagocytosis is often a prominent feature of hemophagocytic lymphohistiocytosis, but it is neither sensitive nor specific for the diagnosis. In adults, hemophagocytosis is often prominent, but many other diagnoses are associated with hemophagocytosis (e.g., acute viral infections and hemolytic anemias).

Evaluation for genetic mutations in familial hemophagocytic lymphohistiocytosis genes may be helpful in later management, but it is not urgent for the initial evaluation.

TREATMENT

Therapy of hemophagocytic lymphohistiocytosis is aimed at suppressing the abnormal immune response, usually through a combination of immunosuppressive and targeted anti–T-cell therapy (Fig. 155-2).[15] Because there have been no large trials of therapy for adult hemophagocytic lymphohistiocytosis, most adults are treated with the HLH-94 protocol, which was studied in a large prospective trial for pediatric hemophagocytic lymphohistiocytosis (Table 155-4). This therapy entails dexamethasone and etoposide with an 8-week induction course under expert supervision. Children with neurologic symptoms receive intrathecal methotrexate, but it is rarely necessary in adults. Following completion of the 8-week course, patients can be put on maintenance therapy with the addition of calcineurin inhibitors to intermittent dexamethasone and etoposide, usually as a bridge to stem cell transplantation. An alternative is the modified HLH-2004 protocol (Table 155-4). Patients with significant liver dysfunction can have initial dose reduction of etoposide with dose increases as function improves. Renal failure may also require dose reduction. Treatment should not usually be withheld for cytopenias, which often reflect disease activity rather than drug toxicity. However, adults often do not tolerate the initial bi-weekly dosing of etoposide, and it is usual to hold at least one of the initial four doses, or start immediately with weekly dosing.

TABLE 155-4 HLH-94 AND HLH-2004 PROTOCOLS FOR TREATMENT OF HEMOPHAGOCYTIC LYMPHOHISTIOCYTOSIS (HLH)

HLH-94 PROTOCOL

Initial Therapy for the First 8 Weeks:

- **Dexamethasone** at 10 mg/m^2 orally per day weeks 1-2; 5 mg/m^2 per day weeks 3-4; 2.5 mg/m^2 per day weeks 5-6; 1.25 mg/m^2 per day week 7; taper during week 8
- **Etoposide** at 150 mg/m^2 orally twice weekly for weeks 1-2; then once weekly
- **Intrathecal MTX (for children with neurologic symptoms only)** at 12 mg per dose, given at weeks 3 and 4, with two additional doses at weeks 5 and 6 if progressive neurologic symptoms and/or abnormal CSF not improved after 2 weeks

Continuation Therapy/HSCT:

- **Dexamethasone** at 10 mg/m^2 per day for 3 days, given every 2nd week
- **Etoposide** 150 mg/m^2 × 1 in alternate weeks
- **Cyclosporine A** beginning at week 9, dosing aimed at trough level of 200 µg/L

HLH-2004 PROTOCOL

Initial Therapy for the First 8 Weeks:

Same as HLH-94 Protocol, except (1) cyclosporine A beginning at day 1 and continuing into the Continuation phase. Recommend starting cyclosporine A at a daily dose of 6 mg/kg, with dosing aimed at trough level of 200 µg/L; and (2) adding prednisone to MTX for intrathecal injections (for children with neurologic symptoms only)

Continuation Therapy/HSCT as Soon as an Accepted Donor Is Identified

CSF = cerebrospinal fluid; MTX = methotrexate.

Modified from Bergsten E, Horne A, Aricó M, et al. Confirmed efficacy of etoposide and dexamethasone in HLH treatment: long-term results of the cooperative HLH-2004 study. *Blood*. 2017;130:2728-2738.

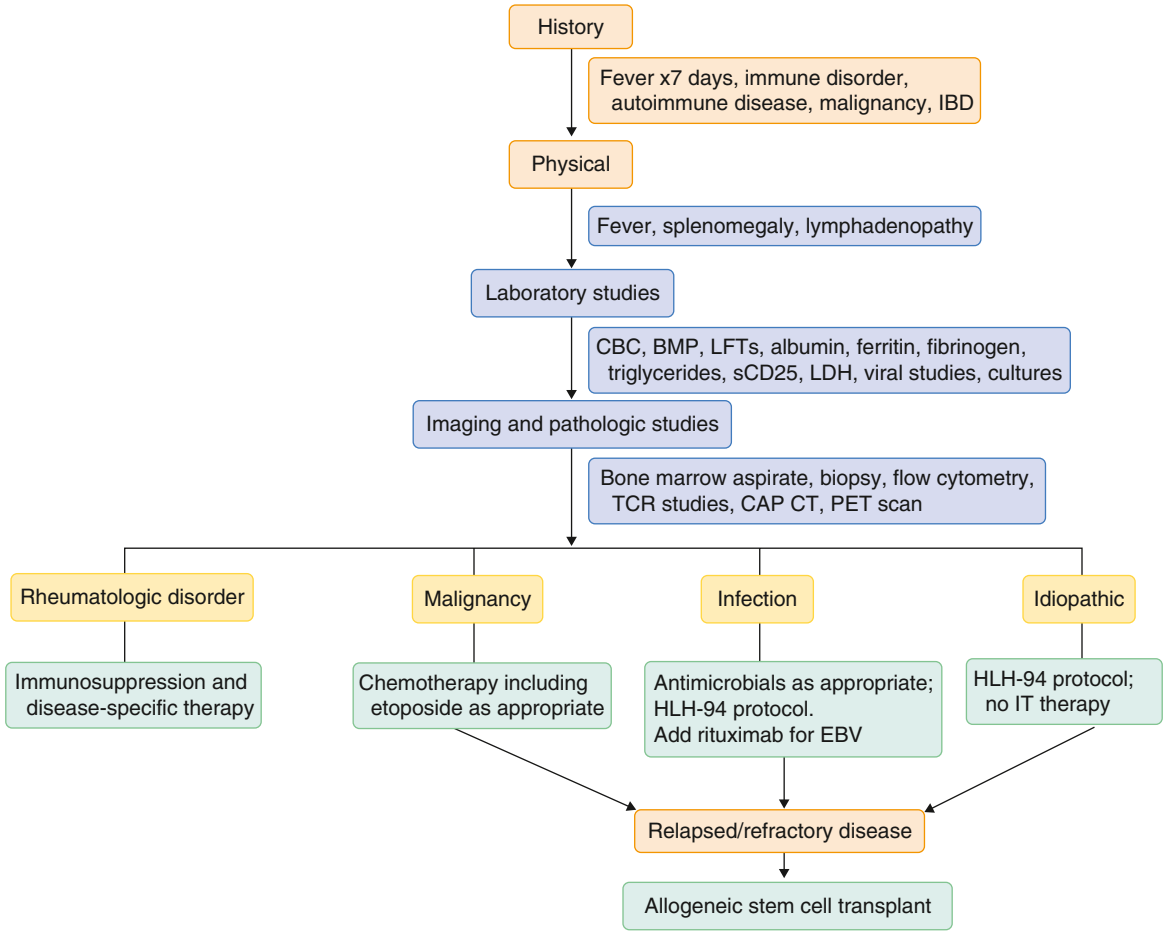

FIGURE 155-2. Approach to diagnosis and treatment of adult hemophagocytic lymphohistiocytosis (HLH). BMP = basic metabolic panel; CAP CT = chest, abdomen, pelvis computed tomography; CBC = complete blood count; EBV = Epstein-Barr virus; HLH-94 protocol (see text and grade A reference A2); IBD = inflammatory bowel disease; IT = immunotherapy; LDH = lactate dehydrogenase; LFTs = liver function tests; PET = positron emission tomography; sCD25 = soluble CD25; TCR = T-cell receptor.

Therapy is tailored to the underlying trigger for the syndrome. In patients with malignancy-associated hemophagocytic lymphohistiocytosis, treatment for the malignancy should be initiated immediately. Because most malignancy-associated hemophagocytic lymphohistiocytosis accompanies a lymphoma, therapy with an etoposide-containing regimen is recommended, and steroid therapy should be continued until the hemophagocytic lymphohistiocytosis has resolved. Epstein-Barr virus-related hemophagocytic lymphohistiocytosis is driven by viral infection of T lymphocytes, so treatment with the HLH-94 protocol should be administered without delay. In addition, rituximab is recommended to clear the B-cell reservoir of virus. Patients with no clear precipitating trigger ("idiopathic hemophagocytic lymphohistiocytosis") should receive the HLH-94 protocol with continued evaluation for underlying undiagnosed lymphoma or infection.

The one exception to the recommendation for cytotoxic therapy for adult hemophagocytic lymphohistiocytosis is for patients with macrophage activation syndrome. This subtype of hemophagocytic lymphohistiocytosis is often difficult to distinguish from an acute flare of the patient's underlying systemic autoimmune disease. Macrophage activation syndrome usually responds to intensification of immunosuppressive therapy for the primary disease and does not usually require cytotoxic therapy.

Patients who fail to respond to the HLH-94 protocol may receive salvage therapy with alemtuzumab, a monoclonal anti-CD52 antibody that destroys mature T cells, under expert supervision. This agent should be viewed as a bridge to stem cell transplant in eligible patients. In this setting, alemtuzumab has also been demonstrated to reduce the incidence of graft versus host disease (GVHD) after stem cell transplantation and is now incorporated into the conditioning regimen before stem cell transplantation for hemophagocytic lymphohistiocytosis.

The role of hematopoietic stem cell transplantation (HSCT) (Chapter 163) in hemophagocytic lymphohistiocytosis is evolving. Familial hemophagocytic lymphohistiocytosis is uniformly fatal without HSCT, but the necessity for other patients with HLH to undergo HSCT is less clear. In many children with infection-associated hemophagocytic lymphohistiocytosis, hemophagocytic lymphohistiocytosis resolves completely with HLH-94 therapy. The outcomes in adults are less clear, but adult patients who have refractory or relapsed disease or who have had life-threatening disease at presentation should be evaluated for transplantation. Patients must be in remission at the time of HSCT because patients with active hemophagocytic lymphohistiocytosis at the time of transplantation fare poorly and usually die of overwhelming GVHD. Outcomes are superior with reduced intensity conditioning. Successful HSCT is curative.

Novel therapies that may have an increasing role in the treatment of hemophagocytic lymphohistiocytosis include emapalumab and ruxolitinib. Emapalumab (1 mg/kg by intravenous infusion every 3-4 days, with dose increases up to 10 mg/kg based on clinical response and toxicity) is an FDA-approved antibody that targets IFN-γ and has been moderately effective for the treatment of refractory hemophagocytic lymphohistiocytosis in children.[16] It also may be useful for adults with hemophagocytic lymphohistiocytosis when combined with dexamethasone (5 to 10 mg/m^2) for the duration of treatment, although clinical studies in the adult population have not yet been performed. The Janus kinase 1/2 inhibitor ruxolitinib has been studied in early clinical trials and is not FDA approved for use in hemophagocytic lymphohistiocytosis, but it is a possible adjunct to therapy under expert supervision, especially in patients with intractable symptoms.

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156 EOSINOPHILIC SYNDROMES

AMY D. KLION

DEFINITIONS

Eosinophils are terminally differentiated cells of the myeloid lineage that circulate in low numbers in the peripheral blood. Although normal ranges vary depending on the laboratory, blood eosinophilia is typically defined as an absolute eosinophil count of greater than 450/μL and hypereosinophilia as an absolute eosinophil count of 1500/μL or greater. Percentages of eosinophils in the total white blood count (WBC) can be misleading because they are affected by the relative numbers of neutrophils, which can be impacted by a number of factors (e.g., low neutrophil counts seen in certain racial/ethnic groups presumably due to polymorphisms in the Duffy antigen receptor [see Chapter 153] or the selective increase in neutrophils seen in response to glucocorticoids or bacterial infection). Tissue hypereosinophilia is loosely defined as extensive eosinophil infiltration in the opinion of the pathologist and may or may not be accompanied by blood eosinophilia. Consensus thresholds for tissue hypereosinophilia have not been defined, except for bone marrow eosinophilia (20% of nucleated cells) and eosinophilic esophagitis (≥15 eosinophils/high-power field).[1]

The hypereosinophilic syndrome can be defined by blood or tissue hypereosinophilia on at least two occasions with evidence of clinical manifestations attributable to the eosinophilia, regardless of the underlying etiology. This definition encompasses a number of clinical subtypes that differ in etiology and/or clinical manifestations and have prognostic and therapeutic implications (Table 156-1).[2] Hypereosinophilia or hypereosinophilic syndrome can be due to neoplastic or clonal proliferation of eosinophils (myeloid hypereosinophilia or hypereosinophilic syndrome), aberrant lymphocyte production of cytokines that promote eosinophilia (lymphoid hypereosinophilia or hypereosinophilic syndrome), inherited genetic abnormalities (familial hypereosinophilia or hypereosinophilic syndrome), or unknown causes (idiopathic hypereosinophilia or hypereosinophilic syndrome).[3,4] Overlap hypereosinophilic syndrome refers to eosinophilic disorders involving a single organ system, such as eosinophilic gastrointestinal disorders and eosinophilic fasciitis, or defined clinical entities, such as eosinophilic granulomatosis with polyangiitis (Chapter 249) or episodic angioedema and eosinophilia (Gleich syndrome), that overlap in clinical presentation with other subtypes of hypereosinophilic syndrome. Finally, secondary or associated hypereosinophilia or hypereosinophilic syndrome can complicate a wide variety of diseases and conditions, including helminth infection (Chapters 325 to 327), neoplasia, and drug hypersensitivity.

EPIDEMIOLOGY

Eosinophilia (absolute eosinophil count >450 eosinophils/μL) is common, occurring in 5 to 15% of the general population depending on the setting. The most frequent cause of mild to moderate eosinophilia worldwide is helminth infection, although atopic disease is the most likely culprit in industrialized settings. In contrast, hypereosinophilic syndrome (with the exception of some of the single-organ variants) is extremely rare, with an overall estimated prevalence of 0.3 to 6.3 per 100,000 in North America. The prevalence of eosinophilic esophagitis (Chapter 124) appears to be increasing, in keeping with an overall increase in the incidence of atopic disease, and has been estimated at 2.5 to 5 per 10,000 in the United States and Europe. Racial and ethnic differences have also been described.

PATHOBIOLOGY

Eosinophil Biology and Mediators of Tissue Damage

Eosinophils develop from pluripotent hematopoietic stem cells in the bone marrow (Chapter 142) under the influence of a complex array of transcription factors and cytokines, the most important of which is interleukin-5 (IL-5). Mature eosinophils are characterized by the presence of cytoplasmic granules that stain red with the acidic dye eosin. These granules contain four cationic proteins (major basic protein [MBP1], eosinophilic cationic protein [ECP], eosinophil-derived neurotoxin [EDN], and eosinophil peroxidase [EPO]) and a panoply of preformed cytokines and chemokines within a complex membranovesicular network. Release of granule proteins and mediators can occur in an indiscriminate way (through cytolysis or classic exocytosis) or selectively through a process called piecemeal degranulation.

Under homeostatic conditions, mature eosinophils are released into the blood, where they remain in the circulation for up to 36 hours before trafficking to the tissues. Data suggest that these "resident" eosinophils may play important regulatory roles in the maintenance of tissue integrity and cell-cell interactions. When eosinophils become activated, irrespective of the cause, they can cause tissue damage and other clinical manifestations through direct and indirect mechanisms. The latter include tissue deposition of cytotoxic eosinophil granule proteins and reactive oxygen intermediates, recruitment of inflammatory cells through the selective secretion of cytokines and chemokines, formation of lipid bodies with production of leukotrienes and other inflammatory mediators, and activation of mast cells, fibroblasts, and endothelial cells to promote fibrogenesis and thrombosis. Modulation of surface receptor expression and increased

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ABSTRACT

Eosinophils are terminally differentiated cells of the myeloid lineage that are primarily tissue based and circulate in low numbers in the blood of healthy individuals. Increased levels of blood eosinophils are associated with a wide variety of conditions, ranging from atopic disorders and helminth infections to rare hypereosinophilic syndromes. Since the clinical manifestations of eosinophilia are protean and can be very similar regardless of the underlying etiology, a careful history is essential to narrow the differential diagnosis. Treatment is guided by the acuity and severity of clinical manifestations and the most likely cause of the eosinophilia. Whereas glucocorticoids have been the mainstay of treatment for many eosinophilic disorders, the availability of therapies that directly target the eosinophils is rapidly changing the therapeutic paradigm.

KEYWORDS

eosinophil
hypereosinophilic syndrome
myeloid neoplasm
drug hypersensitivity
helminth infection

TABLE 156-1 CLINICAL SUBTYPES OF HYPEREOSINOPHILIA/HYPEREOSINOPHILIC SYNDROMES

CLINICAL SUBTYPE	DEFINITION	EXAMPLES
Myeloid (clonal, neoplastic)	Presumed or proven primary neoplastic or clonal eosinophilia	*PDGFR*-associated myeloid neoplasms Chronic eosinophilic leukemia–not otherwise specified
Lymphocytic	Eosinophilia secondary to production of interleukin-5 or other eosinophil-promoting cytokines by aberrant and/or clonal lymphocytes	—
Familial	Hypereosinophilia in multiple generations	Autosomal dominant familial eosinophilia
Idiopathic	Unknown cause and exclusion of other clinical subtypes	—
Overlap	Clinically defined eosinophilic disorders, including those with single organ involvement, that overlap in clinical presentation with idiopathic or lymphocytic variant hypereosinophilic syndrome	Eosinophilic gastrointestinal disease Eosinophilic fasciitis Eosinophilic granulomatosis with polyangiitis Wells syndrome Episodic angioedema and eosinophilia
Secondary (associated)	Eosinophilia in the setting of a distinct diagnosis in which eosinophilia has been described in a subset of patients	See Table 156-2
Hypereosinophilia of unknown significance	Asymptomatic hypereosinophilia without evidence of end-organ manifestations or a primary myeloid etiology	—

PDGFR = platelet-derived growth factor receptor.

responsiveness to chemokines following activation also play important roles in eosinophil recruitment to the tissues and, ultimately, in disease pathogenesis.

Mutations

A number of recurrent genetic mutations have been described in clonal (neoplastic) eosinophilia.[5] The most common of these, an interstitial deletion in chromosome 4 leading to formation of the fusion gene *FIP1L1::PDGFRA*, likely causes eosinophil activation through a network of molecules including the IL-5 receptor, *JAK2*, and Lyn. The mechanisms of eosinophil activation in the setting of other mutations associated with clonal eosinophilia remain largely unexplored. Disease risk loci have been identified in a number of allergic disorders characterized by eosinophil accumulation and activation in tissues, including eosinophilic esophagitis.[6] Some of these, such as 5q22, encode genes known to be involved in eosinophil activation.

CLINICAL MANIFESTATIONS

The clinical manifestations of eosinophilia are very varied and include asymptomatic eosinophilia detected on a routine blood count, nonspecific symptoms such as fatigue and myalgia, and signs and symptoms related to eosinophilic tissue infiltration and/or complications of eosinophil-associated hypercoagulability. Although skin, pulmonary, and gastrointestinal manifestations are most frequent, any organ can be affected.[7] Moreover, there is considerable heterogeneity in the clinical manifestations within any given organ system. For instance, common presentations of eosinophilic skin involvement include intractable pruritus without rash, eczematous rash, urticaria, bullous lesions, and mucosal ulcerations. Although some clinical manifestations are more common in specific subtypes of hypereosinophilic syndrome (e.g., skin manifestations in lymphoid hypereosinophilic syndrome), there is considerable overlap in presentation among clinical subtypes. Moreover, the most serious clinical manifestations, such as endomyocardial fibrosis (Chapter 47)[8] and thromboembolism, can occur in any of the varied hypereosinophilic syndrome subtypes, including secondary or associated hypereosinophilic syndrome caused by untreated helminth infection or drug hypersensitivity.

DIAGNOSIS

Initial Diagnostic Evaluation

The first step in the diagnostic evaluation of the patient with eosinophilia is confirmation of the eosinophil count, while keeping in mind that fever, bacterial infection, and therapies, including glucocorticoids, that may be prescribed for other reasons can all suppress eosinophilia.[9] Once eosinophilia is confirmed, the next step is a search for secondary causes that require specific therapy directed at the underlying disorder (associated hypereosinophilic syndrome). If such a cause is identified, the patient should be treated and reassessed for resolution of the eosinophilia.

Differential Diagnosis

Patients with persistent eosinophilia and those without evidence of a clear secondary cause should undergo an initial evaluation aimed at the identification of end-organ involvement and classification by clinical subtype (Fig. 156-1). The

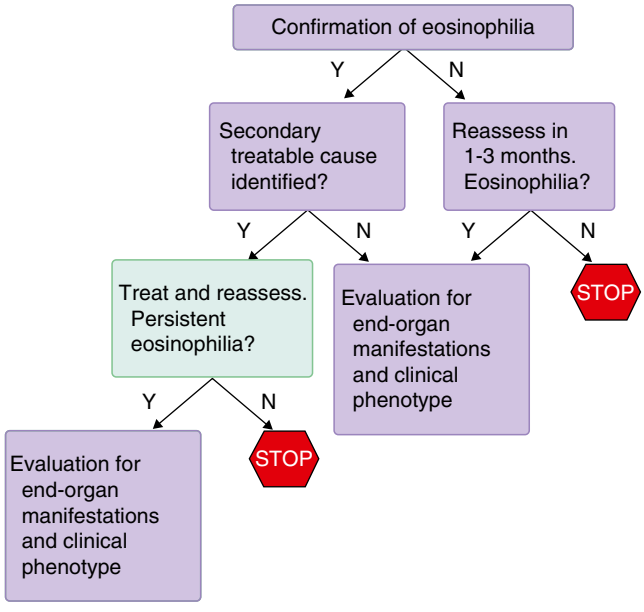

FIGURE 156-1. Initial approach to the clinically stable patient with unexplained eosinophilia. *Patients with idiopathic hypereosinophilia who are asymptomatic without end-organ manifestations are considered to have hypereosinophilia of undetermined significance (HEus).

diagnostic evaluation should be performed in a step-wise manner beginning with a careful history and physical examination, complete blood count with differential, and routine chemistries (including liver function tests and serum immunoglobulins). When possible, this evaluation should occur before institution of therapy because many diagnostic tests are affected by glucocorticoids and other therapies. However, treatment should not be delayed if life-threatening or disabling complications are present or imminent.

Although the differential diagnosis of eosinophilia is very broad, ranging from common allergic disorders to rare idiopathic hypereosinophilic syndromes, a careful history can substantially narrow the possibilities. Particular attention should be paid to medications and supplements, travel and exposures, risk factors for neoplasia, and prior medical history (especially asthma, atopic disease, and/or recurrent infections) because these may provide clues to secondary causes of eosinophilia, such as helminth infection, neoplasia, and immunodeficiency syndromes, that require therapy directed at the underlying cause rather than the eosinophilia itself (Table 156-2).[10] Whereas common allergic disorders, including asthma (Chapter 75) and atopic dermatitis (Chapter 405), can be associated with hypereosinophilia, especially in children, extremely high absolute eosinophil counts (≥5000/μL) should prompt evaluation for another cause. A detailed review of systems should

TABLE 156-2 SELECTED SECONDARY CAUSES OF EOSINOPHILIA REQUIRING TREATMENT DIRECTED AT THE UNDERLYING CAUSE

CATEGORY	ETIOLOGIES	COMMENTS
Infection		
Helminthic	Varied	Most pronounced early in infection and with tissue invasive species
Protozoan	*Isospora belli* infection *Sarcocystis* infection	Other protozoan infections are not associated with eosinophilia
Ectoparasitic	Scabies Myiasis	Hypersensitivity reactions
Viral	HIV infection	Advanced disease
Bacterial	Chronic tuberculosis	Rare
Fungal	Coccidioidomycosis Cryptococcosis	Eosinophilia can complicate a wide variety of fungal infections
Neoplasia	Lymphoma	Hodgkin, non-Hodgkin
	Leukemia	Especially T-cell leukemias and pre-B cell ALL
	Carcinoma	Most commonly adenocarcinoma
Drug hypersensitivity	Varied	Prescription and nonprescription drugs, dietary supplements
Immunodeficiency	Varied	Hyper-IgE syndromes Omenn syndrome
Autoimmune and other immunologic disorders	Varied	Sarcoidosis Inflammatory bowel disease IgG4 disease Others
Other	Cholesterol embolism Hypoadrenalism Radiation Post-transplant status Cytokine therapy: IL-2, GM-CSF	—

ALL = acute lymphoblastic leukemia; GM-CSF = granulocyte-macrophage colony-stimulating factor; HIV = human immunodeficiency virus; IgE = immunoglobulin E; IgG4 = immunoglobulin G4; IL-2 = interleukin-2.

be obtained in all patients because the pattern of clinical manifestations can be suggestive of a particular diagnosis. For example, a history of aspirin sensitivity in an eosinophilic patient with worsening asthma and sinusitis is highly suggestive of aspirin-exacerbated respiratory disease (Chapters 75 and 394),[11] whereas symptoms of peripheral neuropathy in a similar patient should point to a diagnosis of eosinophilic granulomatosis with polyangiitis (Chapter 249).

It is extremely important to identify patients with primary myeloid disorders presenting as hypereosinophilic syndrome because these patients often have aggressive disease, and the approach to therapy is quite different from that of other eosinophilic disorders (see the Treatment section). Clinical and laboratory features suggestive of a primary myeloid disorder include dysplastic eosinophils and eosinophil precursors in the blood, anemia or erythrocytosis, thrombocytopenia, splenomegaly, and elevated serum levels of vitamin B_{12} and/or tryptase. Male gender should raise suspicion for *PDGFR*-associated myeloid neoplasms in this setting.

An initial screen for evidence of myeloid or lymphocytic variant hypereosinophilic syndrome should include serum vitamin B_{12} and tryptase levels, as well as immunophenotyping for T- and B-cell clonality by flow cytometry. Abnormal results, a peripheral eosinophil count of 5000/μL or greater, or other evidence suggestive of a hematologic malignancy (including lymphadenopathy, splenomegaly, or dysplastic or precursor cells on peripheral blood smear) should prompt a bone marrow aspirate and biopsy with standard cytogenetic analysis. Specific testing for recurrent molecular abnormalities associated with hypereosinophilic syndrome should be guided by the clinical features and, if suspected, should be included with the bone marrow examination, where their yield may be higher than in peripheral blood.[12] Although the recommended testing for end-organ damage depends on the clinical signs and symptoms, serum troponin levels, echocardiography, and pulmonary function tests should be performed in all patients to assess clinically evident or occult cardiopulmonary involvement such as endomyocardial fibrosis that can be suggested by echocardiographic abnormalities. Radiologic imaging of the chest, abdomen, and pelvis should also be considered in all patients to identify splenomegaly, lymphadenopathy, and clinically silent neoplastic or inflammatory disease.

TREATMENT

Initial Therapy

The most appropriate initial treatment for a patient with eosinophilia depends on its most likely cause, acuity, and accompanying severity of the clinical signs and symptoms. Glucocorticoids remain the first-line agent for most hypereosinophilic disorders, with four important exceptions: hypereosinophilic syndrome secondary to a treatable cause (associated hypereosinophilic syndrome), primary clonal or neoplastic hypereosinophilic syndrome with an identified mutation for which targeted therapy is available (i.e., imatinib-sensitive, *PDGFR* mutation–positive hypereosinophilic syndrome), eosinophilic gastrointestinal disease (which can sometimes be treated with dietary intervention alone), and patients with hypereosinophilia of unknown significance (who may not require therapy at all). The most appropriate dose of glucocorticoids for an individual patient has not been adequately studied, but the clinical subtype appears to be a useful predictor of systemic glucocorticoid response in hypereosinophilic syndrome.[13] Some eosinophilic disorders, including eosinophilic esophagitis (Chapter 124) and eosinophilic dermatitis, can be successfully managed with topical steroid therapy alone. If life-threatening or disabling complications, such as endomyocardial fibrosis, respiratory failure, or neurologic impairment, are present or imminent, high-dose glucocorticoid therapy (40 mg of prednisone or more daily under expert oversight) should be initiated without delay, even in the setting of associated hypereosinophilic syndrome, unless a treatable secondary cause is identified and is likely to respond rapidly to specific therapy. Ivermectin (200 μg/kg/day for 1 to 2 days) should be administered prior to glucocorticoid therapy in patients with potential exposure to *Strongyloides stercoralis* at any time during their life to prevent hyperinfection syndrome. The most appropriate second agent for treatment of glucocorticoid-refractory patients depends on the clinical subtype and most likely etiology of the eosinophilia, as discussed later.

Initial treatment of myeloid neoplasms that present as a hypereosinophilic syndrome should be guided by the molecular findings. Imatinib (100 mg orally daily; Chapter 170) is clearly the therapy of choice in *PDGFR* mutation–associated disease, with near 100% response rates reported in most series and the possibility of cure in some patients with long-term therapy.[14] Results with other targeted therapies, including *JAK* inhibitors, have been variable in patients with myeloid forms of hypereosinophilic syndrome to date, even in the presence of mutations in the corresponding gene. Consequently, glucocorticoids are often used initially with rapid addition of hydroxyurea or other second-line agents as needed under expert oversight. This approach is likely to change, however, as more experience is gained with targeted therapies.

Second-Line Agents

The selection of a second-line agent depends on a variety of factors, including the clinical subtype, physician's and patient's preference, and cost. Conventional agents used to treat glucocorticoid-resistant, *PDGFR* mutation–negative patients include hydroxyurea, interferon-α, methotrexate, and imatinib. Patients who are *PDGFR* mutation positive and who are intolerant of or resistant to imatinib should be treated with a second- or third-generation tyrosine kinase inhibitor with activity against *PDGFR*, with early consideration of hematopoietic stem cell transplant in nonresponders.

Targeted Therapies

The availability of therapeutic agents that specifically target eosinophils is rapidly changing the approach to the treatment of eosinophilic disorders. Three biologics that target eosinophils through the IL-5 axis, mepolizumab, reslizumab, and benralizumab, have been approved for the treatment of eosinophilic asthma based on randomized trials documenting reduction in asthma exacerbations with little or no toxicity (Chapter 75).[A1,A2] Mepolizumab (300 mg subcutaneously every 4 weeks) improves remission rates and length of remission in patients with treatment-refractory or relapsing eosinophilic granulomatosis with polyangiitis[A3,A4] and reduces disease flares in patients with steroid-responsive *PDGFRA*-negative hypereosinophilic syndrome.[A5] In phase II trials, benralizumab (30 mg subcutaneously every 4 weeks) reduced eosinophilia and improved clinical manifestations in patients with treatment-refractory hypereosinophilic syndrome,[A6] and a phase III study is ongoing. Although dupilumab (a monoclonal antibody to the IL-4 receptor) is approved by the U.S. Food and Drug Administration for the treatment of a number of eosinophilic disorders, including atopic dermatitis, asthma, and eosinophilic esophagitis,[A7] it has been associated with transient hypereosinophilia and, rarely, eosinophilic complications, so it should be used with caution in patients with elevated eosinophil counts.[15] Other novel agents currently in development for eosinophilic disorders, including biologics targeting eotaxin, lirentelimab (a monoclonal antibody to Siglec 8) and dexpramipexole, are likely to provide additional therapeutic options for the heterogeneous group of eosinophilic disorders.

PROGNOSIS

Although the prognosis of an individual patient with hypereosinophilic syndrome depends substantially on the clinical subtype, the severity of clinical manifestations at presentation, and treatment responsiveness, the overall prognosis has improved dramatically (>90% 5-year survival in most series) with advances in diagnostic tools and therapeutic approaches. The most clear-cut example has been the dramatic decrease in mortality in patients with clinical features consistent with an eosinophilic myeloid neoplasm (the majority of whom have *FIP1L1::PDGFRA*–associated disease) with imatinib therapy. In fact, mortality and morbidity in this group of patients (which were 30 to 50% at 5 years before the introduction of imatinib) are now almost entirely restricted to patients who present with irreversible cardiac or other life-threatening manifestations. Progression to lymphoma remains a concern in patients with the lymphocytic variant, particularly in patients with CD3-CD4$^+$ T-cell clones.

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157 APPROACH TO THE PATIENT WITH BLEEDING OR THROMBOSIS

ANDREW I. SCHAFER

MECHANISMS OF HEMOSTASIS AND THROMBOSIS

NORMAL HEMOSTASIS

The coagulation system is normally quiescent, and blood fluidity within blood vessels is maintained by the actions of a continuous monolayer of endothelial cells that line the intimal surface of the vasculature throughout the circulatory tree. At a site of vascular damage, the antithrombotic properties of endothelium are lost, and thrombogenic constituents of the subendothelial vessel wall become exposed to circulating blood. The result is rapid formation of a hemostatic clot that consists of platelets and fibrin and is localized to the area of vascular injury. Activation of platelets and formation of fibrin occur essentially simultaneously and interdependently to effect hemostasis. Subsequently, vascular repair is accomplished by thrombolysis and recanalization of the occluded site.[1]

Platelet activation at a site of vascular injury begins with the adhesion of platelets to the locally de-endothelialized intimal surface (i.e., platelet–vessel wall interaction). Platelet adhesion is mediated by von Willebrand factor, which sticks circulating platelets to the area of the damaged vessel wall by binding to its receptors located in platelet membrane glycoprotein Ib. The adherent platelets then undergo a "release reaction," during which they discharge constituents of their storage granules, including adenosine diphosphate (ADP), and simultaneously elaborate thromboxane A_2 from arachidonic acid through the aspirin-inhibitable cyclooxygenase reaction. ADP, thromboxane A_2, and other components of the release reaction act in concert to recruit and activate additional platelets from the circulation to the site of vascular injury. These activated platelets expose binding sites for fibrinogen by forming the surface membrane glycoprotein IIb/IIIa complex. In the process of platelet aggregation (platelet-platelet interactions), fibrinogen (or von Willebrand factor under conditions of high shear stress) mediates the final formation of an occlusive platelet plug.

Fibrin, which anchors the hemostatic platelet plug, is formed from soluble plasma fibrinogen by the action of the potent protease enzyme thrombin (Fig. 157-1). The fibrin mesh is stabilized by covalent cross-linking mediated by factor XIII. Thrombin is formed from its inactive (zymogen) plasma precursor, prothrombin, by the action of activated factor X (Xa) and its cofactor, factor Va. This sequence of reactions has classically been referred to as the *common pathway* of coagulation. Factor X can be activated by either the *tissue factor (extrinsic) pathway* or the *contact activation (intrinsic) pathway* of coagulation. The tissue factor pathway is now considered to be the major physiologic initiator of coagulation activation. It is triggered by the formation of the complex of tissue factor, which is exposed on the surfaces of activated vascular and blood cells, with activated factor VII (VIIa). The contact activation pathway involves a series (or cascade) of zymogen-protease reactions that are initiated by factor XII, high-molecular-weight kininogen, and prekallikrein. Activated factor XII (XIIa) converts factor XI to XIa, which in turn activates factor IX to IXa. Factor IXa is an enzyme that converts factor X to Xa, a reaction that requires factor VIIIa as a cofactor.

PHYSIOLOGIC ANTITHROMBOTIC MECHANISMS

Intact, normal endothelium promotes blood fluidity by inhibiting platelet activation. It likewise plays a crucial role in preventing fibrin accumulation.

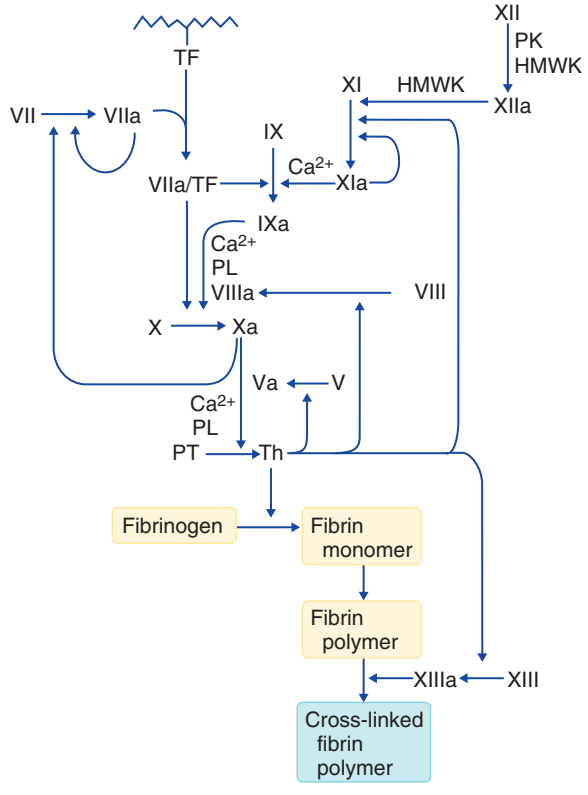

FIGURE 157-1. Coagulation cascade. This scheme emphasizes an understanding of (1) the importance of the tissue factor pathway in initiating clotting in vivo, (2) the interactions among pathways, and (3) the pivotal role of thrombin in sustaining the cascade by feedback activation of coagulation factors. HMWK = high-molecular-weight kininogen; PK = prekallikrein; PL = phospholipid; PT = prothrombin; TF = tissue factor; Th = thrombin. Roman numerals are coagulation factors (e.g., VII); when followed by a lowercase "a," they are the activated forms of those factors (e.g., VIIa). (From Schafer AI. Coagulation cascade: an overview. In: Loscalzo J, Schafer AI, eds. *Thrombosis and Hemorrhage*. Cambridge, MA: Blackwell Scientific Publications; 1994:3-12.)

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ANDREW I. SCHAFER

MECHANISMS OF HEMOSTASIS AND THROMBOSIS

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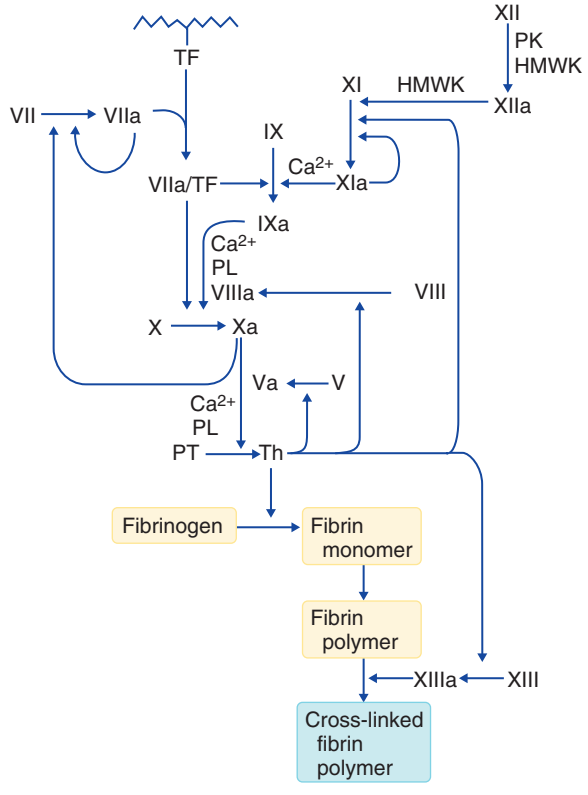

FIGURE 157-1. Coagulation cascade. This scheme emphasizes an understanding of (1) the importance of the tissue factor pathway in initiating clotting in vivo, (2) the interactions among pathways, and (3) the pivotal role of thrombin in sustaining the cascade by feedback activation of coagulation factors. HMWK = high-molecular-weight kininogen; PK = prekallikrein; PL = phospholipid; PT = prothrombin; TF = tissue factor; Th = thrombin. Roman numerals are coagulation factors (e.g., VII); when followed by a lowercase "a," they are the activated forms of those factors (e.g., VIIa). (From Schafer AI. Coagulation cascade: an overview. In: Loscalzo J, Schafer AI, eds. *Thrombosis and Hemorrhage*. Cambridge, MA: Blackwell Scientific Publications; 1994:3-12.)

ABSTRACT

Physiological coagulation in response to injury is referred to as *hemostasis*. Blood platelets and coagulation factors participate together in forming a hemostatic plug. Pathological coagulation, however, is referred to as *thrombosis*, which occurs when coagulation is abnormally hyperactive and is unneeded. Systemic bleeding disorders are caused by quantitative deficiencies or functional abnormalities in the coagulation cascade and in platelets. Thrombosis, particularly venous thrombosis, can be the result of deficiencies or functional abnormalities in physiological antithrombotic proteins (like antithrombin III, protein C, and protein S). Screening tests for systemic bleeding disorders (platelet count, prothrombin time [PT], and activated partial thromboplastin time [aPTT]) can rule out most, but not all, clinically significant coagulation abnormalities. For example, factor XIII deficiency or only mildly low coagulation factor levels will not be picked up by a prolonged PT or aPTT. Algorithms for more specialized tests are provided, and newer global coagulation and point-of-care tests are discussed. Evaluation of hypercoagulable states requires a panel of blood tests, since no well-validated screening tests are available.

KEYWORDS

hemostasis
thrombosis
bleeding disorders
coagulation factors
platelets
inhibitors

Among the physiologic antithrombotic systems that produce this latter effect are (1) antithrombin III, (2) protein C and protein S, (3) tissue factor pathway inhibitor (TFPI), and (4) the fibrinolytic system. Antithrombin is the major protease inhibitor of the coagulation system: it inactivates thrombin and other activated coagulation factors. Heparin functions as an anticoagulant by binding to antithrombin and greatly accelerating these reactions. Heparin and heparin sulfate proteoglycans are naturally present on endothelial cells, so antithrombin inactivation of thrombin and other coagulation proteases most likely occurs physiologically on vascular surfaces rather than in fluid plasma. Activated protein C, with its cofactor protein S, functions as a natural anticoagulant by destroying factors Va and VIIIa, two essential cofactors of the coagulation cascade. Thrombin itself is the activator of protein C, and this reaction occurs rapidly only on the surfaces of intact vascular endothelial cells, where thrombin binds to the glycosaminoglycan thrombomodulin. TFPI is a plasma protease inhibitor that specifically quenches tissue factor–induced coagulation. Finally, what little fibrin can be produced, despite these potent physiologic antithrombotic mechanisms, is digested rapidly by the endogenous fibrinolytic system. Fibrinolysis is mediated by the protease plasmin, which is generated from plasminogen in plasma by the action of endothelium-derived plasminogen activators.

EVALUATION OF THE PATIENT WITH A POSSIBLE BLEEDING DISORDER

HISTORY AND PHYSICAL EXAMINATION

A thorough history is paramount in evaluating a patient for a possible systemic bleeding disorder. In addition to asking the patient about spontaneous bleeding episodes in the past, the responses to specific hemostatic challenges should be recorded. A bleeding tendency may be suspected if a patient previously experienced excessive hemorrhage after surgery or trauma, including common events such as circumcision, tonsillectomy, labor and delivery, menses, dental procedures, vaccinations, and injections. Conversely, a history of normal blood clotting after such specific challenges in the recent past is just as important to note. It may be a better test of the integrity of systemic hemostasis than any laboratory measurement can provide.

In a patient with a history of excessive or unexplained bleeding, the initial goal is to determine whether the cause is a systemic coagulopathy or localized anatomic or mechanical problem with a blood vessel. This situation is encountered most frequently in patients with excessive postoperative bleeding, which could be due to either local surgical trauma or a coagulation abnormality, or both. A history of prior bleeding suggests a coagulopathy, as does the finding of bleeding from multiple sites. However, this is not always the case. Even diffuse bleeding may arise from anatomic rather than hemostatic abnormalities, due to inherited or acquired primary vascular disorders rather than fluid-phase clotting abnormalities. Examples (Table 157-1) include Ehlers-Danlos syndrome; angiodysplasia; spontaneous, non-traumatic intracerebral hemorrhage caused by deep perforator arteriopathy or cerebral amyloid angiopathy; and recurrent mucosal hemorrhage in patients with hereditary hemorrhagic telangiectasia (Chapter 159). Conversely, a single episode of bleeding from an isolated site may be the initial manifestation of a systemic coagulopathy.

The history must include a survey of coexisting systemic diseases and drug ingestions that could affect hemostasis. Renal failure and the myeloproliferative neoplasms are associated with impaired platelet–vessel wall interactions and qualitative platelet abnormalities, connective tissue diseases and lymphomas are associated with thrombocytopenia, and liver disease causes a complex coagulopathy (Chapter 161). Ingestion of aspirin and other nonsteroidal anti-inflammatory drugs (NSAIDs) that cause nonselective inhibition of cyclooxygenase leads to platelet dysfunction; these drugs are often contained in over-the-counter preparations that patients may neglect to report without specific questioning. Other drugs, such as antibiotics, also may be associated with a bleeding tendency by causing abnormal platelet function or thrombocytopenia.[2] Finally, it is important to elicit a family history of bleeding problems. Although a positive history provides an important clue to a possible inherited coagulopathy, a negative history does not exclude a familial cause; for example, 20% of patients with classic hemophilia have a completely negative family history of bleeding.

Mild bleeding events are commonly reported by patients with and without subsequently laboratory-documented bleeding disorders, sometimes making it difficult for hematologists to define a "significant bleeding history." Using a web-based questionnaire, 25% of subjects in a healthy population reported epistaxis, 18% easy bruising (more commonly in women), 18% prolonged bleeding after dental extraction, and 47% of women heavy menstrual bleeding. Regarding the latter, in a study of 200 consecutive adolescents referred for heavy menstrual bleeding, a systemic bleeding disorder was diagnosed in 33%: low von Willebrand factor levels in 16%, von Willebrand disease in 11%, and qualitative platelet dysfunction in 4.5%.[3] More precise quantification of bleeding symptoms is being attempted by using "bleeding score" instruments such as the Vicenza bleeding score to help discriminate, in conjunction with laboratory testing, between healthy subjects and those with mild bleeding disorders.

Patterns of clinical bleeding, as revealed by the history and physical examination, may be characteristic of certain types of coagulopathy (Table 157-2). In general, patients with thrombocytopenia or qualitative platelet or vascular disorders present with bleeding from superficial sites in the skin and mucous membranes. These may involve petechiae, which are pinpoint cutaneous hemorrhages that appear particularly over dependent extremities (characteristic of severe thrombocytopenia), ecchymoses (common bruises), purpura, gastrointestinal and genitourinary tract bleeding, epistaxis, and hemoptysis. In these types of disorders, bleeding tends to occur spontaneously or immediately after trauma. In contrast, patients with inherited or acquired coagulation factor deficiencies, such as hemophilia, or those on anticoagulant therapy tend to bleed from deeper tissue sites (e.g., hemarthroses, deep hematomas, or retroperitoneal hemorrhage) and in a delayed manner after trauma.

LABORATORY TESTING

Screening Tests of Hemostasis

A few simple screening tests have traditionally been used in the initial evaluation of patients with a suspected coagulopathy: platelet count, bleeding time, prothrombin time (PT) (also reported as the INR), activated partial thromboplastin time (aPTT), and thrombin time (TT).[4] The North American Specialized Coagulation Laboratory Association (NASCOLA) has reported that most coagulation laboratories currently perform these tests as their "bleeding disorder panels."

Thrombocytopenia, reported by electronic particle counting, should be verified by examination of the peripheral smear. Pseudothrombocytopenia, a laboratory artifact of ex vivo platelet clumping, may be caused by the ethylenediaminetetraacetic acid (EDTA) anticoagulant used in tubes for blood cell counts, by other anticoagulants, or by nonphysiologic cold agglutinins acting at room temperature. It should be suspected whenever a very low platelet count is unexpectedly reported in a patient who does not exhibit any clinical

TABLE 157-1 CHARACTERISTIC PATTERNS OF BLEEDING IN SYSTEMIC DISORDERS OF HEMOSTASIS

TYPE OF DISORDER	*SITES OF BLEEDING*				ONSET OF BLEEDING	CLINICAL EXAMPLES
	GENERAL	SKIN	MUCOUS MEMBRANES	OTHER		
Platelet-vascular disorders	Superficial surfaces	Petechiae, ecchymoses	Common: oral, nasal, gastrointestinal, genitourinary	Rare	Spontaneous or immediately after trauma	Thrombocytopenia, functional platelet disorder, vascular fragility, disseminated intravascular coagulation, liver disease
Coagulation factor deficiency	Deep tissues	Hematomas	Rare	Common: joint, muscle, retroperitoneal	Delayed after trauma	Inherited coagulation factor deficiency, acquired inhibitor, anticoagulation, disseminated intravascular coagulation, liver disease

TABLE 157-2 FEATURES OF COAGULATION FACTOR DEFICIENCIES

DEFICIENCY	TYPICAL LABORATORY FINDINGS	APPROXIMATE PREVALENCE
Fibrinogen	Afibrinogenemia: TT ↑↑, aPTT ↑↑, PT ↑↑ Dysfibrinogenemia and hypofibrinogenemia: TT ↑, aPTT ↑, PT ↑↑	1 in 1 million
Prothrombin	TT normal, aPTT ↑, PT ↑	1 in 2 million
Factor V	TT normal, aPTT ↑, PT ↑	1 in 1 million
Combined factor V and VIII	TT normal, aPTT ↑, PT ↑	1 in 1 million
Factor VII	TT normal, aPTT normal, PT ↑	1 in 500,000
Factor X	TT normal, aPTT ↑, PT ↑	1 in 1 million
Factor XI	TT normal, aPTT ↑, PT normal	1 in 1 million
Factor XIII	TT, aPTT, and PT normal; specific assays required	1 in 2 million
Vitamin K–dependent coagulation factors	TT normal, aPTT ↑, PT ↑↑	<50 families reported

aPTT = activated partial thromboplastin time; PT = prothrombin time; TT = thrombin time.
Adapted from Palla R, Peyvandi F, Shapiro AD. Rare bleeding disorders: diagnosis and treatment. *Blood*. 2015;125:2052-2061.

bleeding. Pseudothrombocytopenia is indicated by the finding of platelet clumps on the peripheral smear, and the diagnosis is supported by the finding of simultaneously normal platelet counts in blood samples obtained by finger stick, in tubes containing other anticoagulants, or in a tube maintained at 37° C before platelet counting. Examination of the blood smear can also reveal clues to the cause of real thrombocytopenia, such as fragmented red blood cells in thrombotic thrombocytopenic purpura.

The bleeding time was a widely used clinical screening test for disorders of platelet–vessel wall interactions. It measures the time to cessation of bleeding after a standardized incision over the volar aspect of the forearm. However, the test is prone to problems related to quality control, reproducibility, sensitivity, and specificity. Therefore, because von Willebrand disease is the most common genetic cause of abnormal platelet–vessel wall interactions, most experts now recommend replacing the bleeding time with specific tests for von Willebrand disease (vWd screen) in the initial evaluation of patients with a suspected coagulopathy (Chapter 159). The entity of "low von Willebrand factor" activity (≥30 and ≤50 IU/dL), not meeting the diagnostic criteria of von Willebrand disease, has been associated with a bleeding tendency.[5] As an additional replacement for the bleeding time, especially when a functional (qualitative) abnormality of platelets is suspected by characteristic mucocutaneous bleeding or bruising, a global assay of platelet function can be appended to the panel of screening tests. This is most commonly a platelet function analyzer (PFA) closure time. The PFA and other platelet function studies (see later) must be performed after discontinuation of drugs that interfere with platelet function (e.g., aspirin and other NSAIDs).

The PT measures the integrity of the extrinsic and common pathways of coagulation (factors VII, X, and V; prothrombin; and fibrinogen) (Fig. 157-2). The aPTT measures the integrity of the intrinsic and common pathways of coagulation (high-molecular-weight kininogen; prekallikrein; factors XII, XI, IX, VIII, X, and V; prothrombin; and fibrinogen). The sensitivity of the PT and aPTT in detecting coagulation factor deficiencies may vary with the reagents used to perform these tests, and each laboratory must determine its own reference standards. It is important to note that the PT and aPTT are generally not sensitive enough to detect mild coagulation factor deficiencies, where the deficient factor level is >25%. For example, an individual with mild hemophilia (with factor VIII level of 35%) is likely to have a normal aPTT.[6] The TT is a screen for quantitative deficiencies and qualitative defects of plasma fibrinogen.

Follow-Up of Abnormal Screening Tests

Abnormalities in these screening tests of hemostasis may be pursued by more specialized tests to establish a specific diagnosis (Fig. 157-3).

An abnormal von Willebrand disease screen should be followed up with more specialized tests, including von Willebrand factor multimer analysis, to identify the type of von Willebrand disease involved. Abnormalities in the PFA closure time should be followed by more specialized light transmission aggregometry (LTA) of platelets using a panel of agonists (ADP, epinephrine, collagen, arachidonic acid, ristocetin) that induce characteristic changes in light transmission (or optical density) in stirred suspensions of freshly isolated platelets in plasma (PRP). LTA is still considered the "gold standard" for platelet function testing[7] (Chapter 159). In patients who have clinical bleeding problems, inherited disorders of platelet function are increasingly diagnosed by genomic testing.[8]

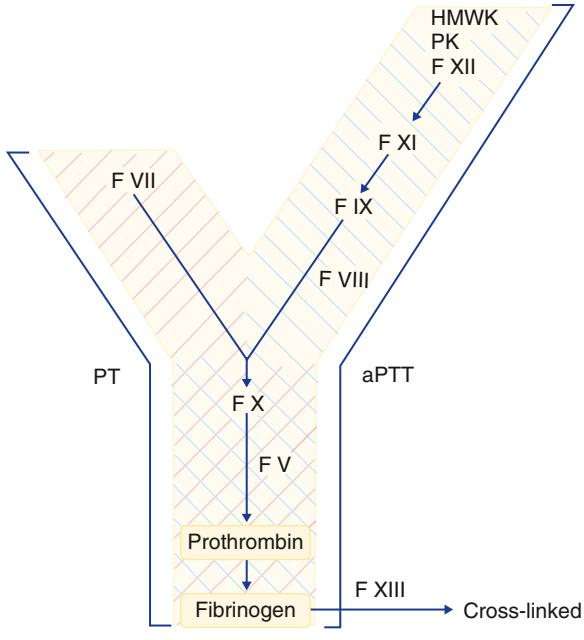

FIGURE 157-2. Classic coagulation cascade. The prothrombin time (PT) measures the integrity of the extrinsic and common pathways, whereas the activated partial thromboplastin time (aPTT) measures the integrity of the intrinsic and common pathways. Factor (F) XIII deficiency is not detected by PT or aPTT. HMWK = high-molecular-weight kininogen; PK = prekallikrein.

The finding of a prolonged PT and/or aPTT indicates either a deficiency of one or more coagulation factors or the presence of an inhibitor (Fig. 157-4), usually an antibody, directed at one or more components of the coagulation system. These two possibilities can be distinguished by performing a simple inhibitor screen, which involves a 1:1 mix of the patient's plasma and normal plasma. The premise of the test is that even if the patient's plasma is completely deficient (0% level) in a certain factor, mixing it 1:1 with normal plasma (100% level) should bring the concentration of that factor to 50% in the mixture; this is sufficient to correct the prolonged PT or aPTT. If correction occurs with the inhibitor screen, individual coagulation factor levels should be assayed for a specific deficiency state. If the 1:1 mix fails to correct the prolonged PT and/or aPTT, an inhibitor is likely to be present, and it is interfering with coagulation in vitro in both the patient's plasma and the normal plasma. Specific assays should then be performed to determine whether there is a true inhibitor against a coagulation factor (e.g., factor VIII antibody) or whether the inhibitor is a lupus anticoagulant. A prolonged TT, with or without prolongation of the PT and/or aPTT, suggests the presence of a quantitative deficiency or a qualitative defect of fibrinogen. These can then be distinguished by following up with simultaneously performed clottable (functional) and antigenic assays of fibrinogen: a disproportionately low clottable fibrinogen points to a functional fibrinogen abnormality (dysfibrinogenemia), whereas

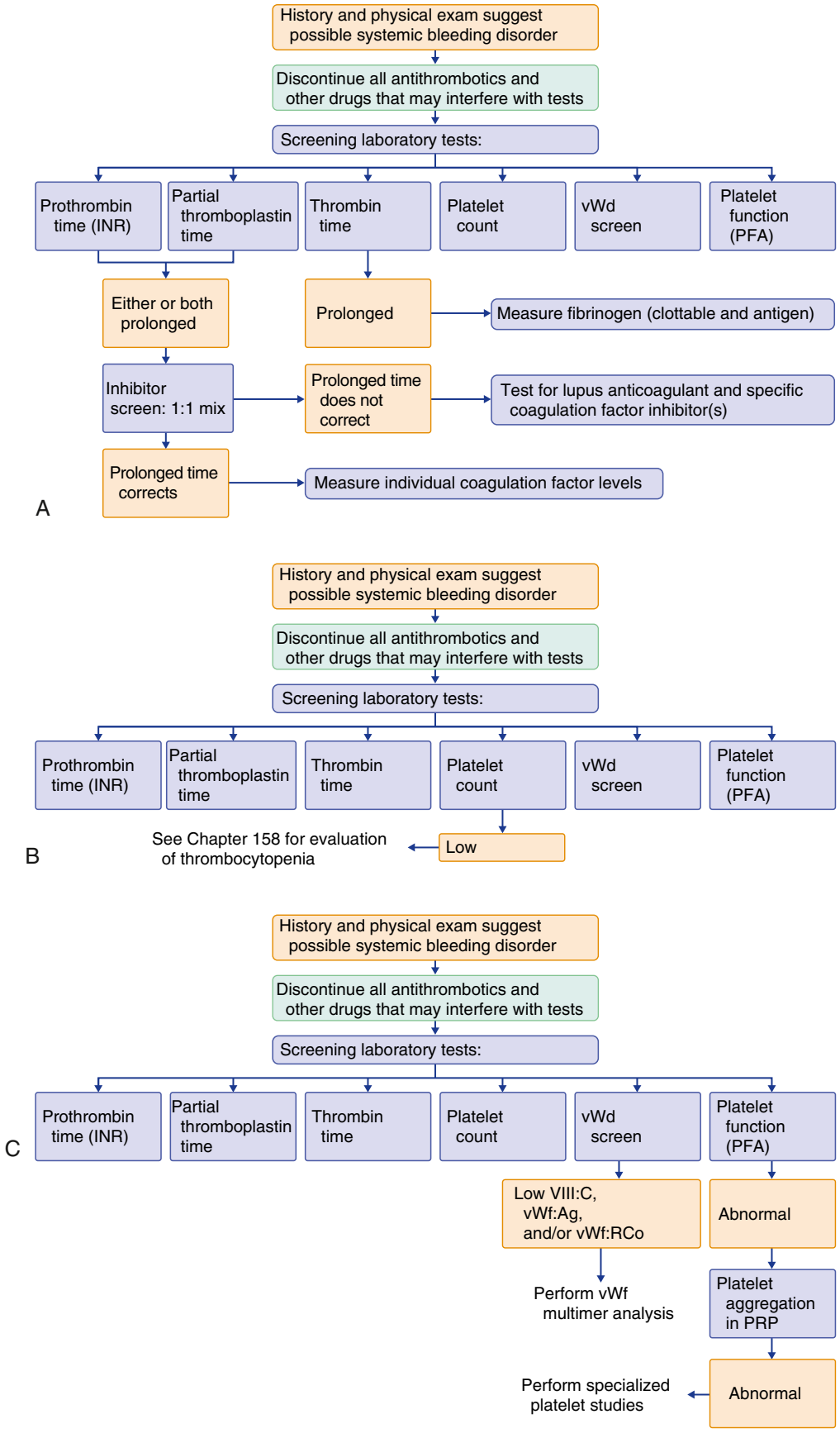

FIGURE 157-3. **Algorithms for clinical and laboratory approach to the diagnosis of a patient with a suspected systemic bleeding disorder (coagulopathy). A to C,** The critical importance of a thorough personal and family history and physical examination is emphasized before initiating a laboratory work-up. INR = international normalized ratio; PFA = platelet function analyzer; PRP = platelet-rich plasma; VIII:C = factor VIII coagulant activity; vWD = von Willebrand disease; vWf = von Willebrand factor; vWf:Ag = von Willebrand factor antigen; vWf:RCo = von Willebrand factor: ristocetin cofactor activity.

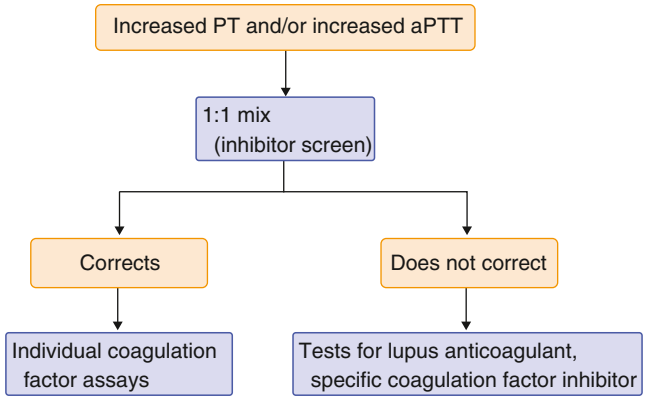

FIGURE 157-4. Approach to evaluating patients with prolonged prothrombin time (PT) or activated partial thromboplastin time (aPTT).

proportionately reduced levels of clottable and antigenic fibrinogen suggest a quantitative deficiency (hypofibrinogenemia or afibrinogenemia) (see Fig. 157-3A and Chapter 160).

Suspected Coagulopathy Despite Negative Screening Tests

Normal results for all these screening tests of hemostasis essentially usually exclude any clinically significant systemic coagulopathy. When all screening tests of coagulation are normal in a patient who is strongly suspected of having a systemic bleeding disorder, further testing might be necessary. Individual coagulation factor assays can reveal a mild factor deficiency even when the PT and aPTT are normal. Activated factor XIII catalyzes the covalent cross-linking of polymerized fibrin to solidify clot formation in vivo. However, the PT, aPTT, and thrombin time tests in vitro detect the formation of only fibrin that is not yet cross-linked (see Fig. 157-2). Therefore, since factor XIII deficiency (Chapter 160) is not detected by the PT and aPTT, specific testing for factor XIII activity is required.

Rare disorders of fibrinolysis also may be associated with normal screening tests, thereby necessitating more specialized tests when indicated (Chapter 161). Bleeding due to hyperfibrinolysis can be caused by increased levels of the fibrinolytic enzyme, plasmin. In turn, increased plasmin generation can be due to increased activators (tissue-plasminogen activator [tPA]), decreased plasmin substrate (hypoplasminogenemia), or decreased fibrinolytic inhibitors (α2-antiplasmin, plasminogen activator inhibitor-1 [PAI-1], or thrombin activatable fibrinolysis inhibitor [TAFI]). All of these proteins, as well as quantitative D-dimer levels, can be measured in clinical laboratories.[9]

Newer coagulation tests, known as global assays, have the potential to offer a more complete evaluation of a patient's overall clot-forming capability. These global assays, including thrombin generation tests and viscoelastic assays, have not yet advanced from experimental research to routine clinical practice.

Global Coagulation Laboratory and Point-of-Care Tests

Thrombin Generation Tests

Thrombin generation tests require separation of platelet-poor plasma (PPP) or platelet-rich plasma (PRP) from centrifuged whole blood. Thrombin generation in the patient's plasma can be then measured by comparing it to a calibrator of known thrombin activity, using automated fluorescence or chromogenic readouts. These tests measure primarily the coagulation arm of hemostasis and have been shown to be promising in evaluating thrombophilias in guiding antithrombotic therapy. The tests are limited at this time by their lack of validation as a clinical tool.

Clot Waveform Analysis

This test is based on the activated partial thromboplastin time (aPTT) assay, but with a prolonged light transmission readout that can monitor both the acceleration and deceleration of clotting, thereby reflecting the whole process of clot formation and clot lysis. It shows promise as a global test of disseminated intravascular coagulation (DIC) and for sensitive detection of mild coagulation factor deficiencies, but the method needs further validation and standardization.

Thromboelastography

Two types of semiautomated commercial devices available provide global assays of coagulation and fibrinolysis using point-of-care technology: the ROTEM (rotational thromboelastometry) analyzer and the thromboelastography analyzers. These tests are whole blood clotting tests in which a small aliquot of blood is rotated in a cuvette, and the strength, elasticity, and dissolution of the forming clot are measured with a torsion wire or by optical detection. The markedly increasing use of this technology is understandable; it is inherently attractive to have a bedside test that provides immediate, real-time, visualized monitoring and analysis of clot formation and lysis in whole blood incorporating the totality of the hemostatic system, including coagulation, fibrinolysis, and platelets.[10] A randomized trial of thromboelastography-guided blood component use in patients with cirrhosis and nonvariceal bleeding found that it leads to a significantly lower use of blood components than transfusions guided by INR and platelet count.[A1] However, systematic reviews have concluded at this time that most meaningful data on thromboelastography have come from their use in cardiac surgery involving cardiopulmonary bypass, where it has indeed reduced the need for transfusion of blood products.[A2] Randomized clinical trials have found that the use of thromboelastography-guided algorithms in place of traditional transfusion parameters in cirrhotic patients with severe coagulopathy (i.e., platelets <50,000 and/or INR >1.8) who are having active bleeding reduces the number of platelet, plasma, and cryoprecipitate transfusions.[A3] Its impact on producing other favorable clinical end points remains open to study.[11] For example, in two randomized trials, adding viscoelastography to routine coagulation studies did not improve overall outcomes after major trauma,[A4] and adding thromboelastography to such studies led to only a small reduction in blood loss from postpartum hemorrhage.[A5]

Other Point-of-Care Tests of Hemostasis

Other, more specialized but established point-of-care tests of hemostasis include the activated clotting time (ACT), which is used to monitor heparinization during extracorporeal circuits in cardiac bypass surgery and extracorporeal membrane oxygenation; handheld devices to measure the international normalized ratio (INR) for self-management at-home monitoring in patients taking vitamin K antagonists; and platelet function analyzers (i.e., the VerifyNow system), which measure platelet aggregation across fibrinogen-coated polystyrene beads in separate cartridges for assessment of resistance to antiplatelet drugs including aspirin, thienopyridines, and glycoprotein IIb-IIIa antagonists.

High-Throughput Sequencing

High-throughput sequencing can detect a molecular diagnosis in about 50% of all patients with a thrombotic, coagulation, platelet count, or platelet function disorder. In patients with otherwise unexplained bleeding disorders and normal hemostatic test results, it can find a molecular diagnosis in about 3% of patients.[12]

EVALUATION OF THE ASYMPTOMATIC PATIENT WITH ABNORMAL COAGULATION TESTS

In asymptomatic individuals who are discovered incidentally to have abnormalities in screening laboratory tests of hemostasis, the first critical question to ask is whether the findings are clinically relevant. Patients with inherited deficiencies of one of the contact activation coagulation factors (factor XII, high-molecular-weight kininogen, prekallikrein) characteristically have a markedly prolonged aPTT, yet they do not have a clinical bleeding tendency. Likewise, patients with lupus anticoagulants typically have prolongation of the aPTT and sometimes also the PT; they much more often have thrombotic rather than bleeding complications. In patients with heparin-induced thrombocytopenia, a marked decrease in the platelet count is sometimes associated with arterial and venous thrombosis rather than bleeding. It is crucial to view the clinical setting, history, physical examination, and screening laboratory tests as complementary facets of the approach to patients with suspected coagulopathies.

EVALUATION OF THE PREOPERATIVE PATIENT

Routine screening of all preoperative patients with a platelet count, bleeding time, PT, and aPTT is not only uninformative but also may be counterproductive if follow-up testing causes unnecessary expense and delays in surgery (Chapter 399). Preoperative bleeding time, PT, and aPTT do not predict surgical bleeding risk in patients who are not found to be at increased risk on clinical grounds, so a thorough clinical assessment should guide the need for these preoperative screening tests. Laboratory testing and possibly further specialized tests of coagulation are indicated for patients whose bleeding histories

are suspicious for a hemostatic abnormality. Preoperative screening tests of coagulation are probably warranted for patients who cannot cooperate with an adequate clinical assessment and for those who will be undergoing procedures in which even minimal postoperative hemorrhage could be hazardous. Recent guidelines for preinterventional and preoperative hemostatic evaluation have likewise concluded that bleeding risk requires a detailed personal and family history of hemorrhagic events and physical examination; but individuals with a negative history and without conditions that may interfere with systemic hemostasis should not undergo coagulation testing.[13]

EVALUATION OF THE PATIENT WITH A POSSIBLE HYPERCOAGULABLE STATE

Most patients with venous thromboembolism (VTE) have an inherited basis for hypercoagulability (Chapter 67). Patients with inherited hypercoagulable states (or thrombophilia) typically present with an initial episode of VTE in early adulthood, but thrombotic manifestations may begin at any time from early childhood to old age. Patients usually have deep vein thrombosis of the lower extremities or pulmonary embolism, but other uncommon sites of venous thrombosis may be involved. Arterial thrombosis is not characteristically associated with inherited hypercoagulable states. Arterial thrombosis that occurs prematurely or in the absence of apparent risk factors should trigger a different line of investigation, possibly including evaluation for vasculitis, myeloproliferative neoplasms, hyperhomocysteinemia, antiphospholipid syndrome, and potential sources of systemic embolization.

The primary or hereditary hypercoagulable states (see Table 67-1) result from specific mutations or polymorphisms that lead to decreased levels of physiologic antithrombotic proteins or increased levels of procoagulant proteins. In contrast, the secondary or acquired hypercoagulable states are a heterogeneous group of disorders that predispose to thrombosis by complex mechanisms. VTE is often provoked by the combination of an underlying hypercoagulable genotype and an acquired prothrombotic, hypercoagulable state such as pregnancy, immobilization, or the postoperative state. Certain clinical characteristics suggest the presence of an inherited hypercoagulable state (Table 157-3). Patients with recurrent thrombosis should be tested for these disorders and, in most cases, committed to lifelong prophylactic anticoagulation. It is not clear whether it is essential to order these tests after a single episode of VTE. Counterintuitively, it has been found that most of the common inherited hypercoagulable states—which, to varying extents, clearly increase the risk for a *first* episode of VTE—are at best only weak predictors of *recurrent* VTE. It has been argued, therefore, that making a specific thrombophilia diagnosis after an initial episode of VTE will not influence the decision about the duration of prophylactic anticoagulation.[14] However, the increased risk for recurrent VTE with the more strongly prothrombotic mutations (e.g., antithrombin III, protein C or S deficiency), combined inherited thrombophilias, or antiphospholipid syndrome may necessitate long-term anticoagulation, and therefore their diagnosis after a first episode of VTE would in fact alter decisions about the duration of anticoagulation (see Fig. 67-1). Even if they are not maintained on long-term anticoagulation, patients with diagnosed primary hypercoagulable states should receive prophylactic anticoagulation during situations that pose a high risk for thrombosis, such as the peripartum period. There is no simple screening test for primary hypercoagulable states, and the timing of obtaining these tests is crucial to avoid erroneous diagnoses.[15] Acute thrombosis itself can cause transient decreases in the levels of antithrombin, protein C, and protein S. Heparin therapy can cause a decrease in plasma antithrombin activity. Warfarin therapy lowers the functional levels of protein C and protein S. Inherited deficiency states can be diagnosed spuriously under these conditions. Use of one of the newer anticoagulants can also interfere with laboratory tests, especially for lupus anticoagulant.

Patients who present with VTE have an increased risk for harboring an occult malignancy. This association is increased further in patients with recurrent and unprovoked thrombosis. There are conflicting opinions on whether an evaluation for occult malignancy in these patients must be exhaustive. Most recommend that evaluation can be limited to a thorough history, physical examination, routine complete blood cell count and chemistries, test of fecal occult blood, urinalysis, mammogram (in women), and chest radiograph, with further testing guided by any abnormalities found in this initial evaluation. Routine computed tomography scanning of the chest, abdomen, and pelvis is not indicated[A6] unless other testing suggests an abnormality[16] (see algorithm in Fig. 67-3).

In addition to classic deep vein thrombosis and pulmonary embolism, certain characteristic types of thrombosis may provide important clues to the cause and trigger a more directed evaluation. Migratory, superficial thrombophlebitis (Trousseau syndrome) or nonbacterial thrombotic endocarditis strongly suggests the presence of an occult malignancy (Chapter 67). Hepatic vein thrombosis (Budd-Chiari syndrome; Chapter 129) or portal vein thrombosis may indicate a myeloproliferative neoplasm (Chapter 152) or paroxysmal nocturnal hemoglobinuria (Chapter 146). Extensive inferior vena cava thrombosis may occur with renal cell carcinoma (Chapter 182). Warfarin-induced skin necrosis strongly suggests underlying protein C or protein S deficiency. Recurrent, spontaneous miscarriages are characteristic of the antiphospholipid syndrome (Chapter 160), although they are also associated with other thrombophilias.

TABLE 157-3 CLINICAL CHARACTERISTICS OF PATIENTS WITH INHERITED HYPERCOAGULABLE STATES (THROMBOPHILIA)

Venous thromboembolism (>90% of cases)
Deep vein thrombosis or pulmonary embolism most common
Splanchnic or cerebral vein thrombosis rare but characteristic
Frequent family history of thrombosis
Typically autosomal dominant
First episode of thrombosis typically in young adulthood (<40 years)
Often apparently unprovoked (but an acquired thrombosis trigger is frequently identified with a careful history)
More common thrombophilias (factor V Leiden, prothrombin 20210 G→A) are associated with a lower thrombosis risk; rarer thrombophilias (antithrombin III, protein C, protein S deficiency) are associated with a higher thrombosis risk
Warfarin-induced skin necrosis or neonatal purpura fulminans with protein C or protein S deficiency (very rare)

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158 THROMBOCYTOPENIA

CHARLES S. ABRAMS

DEFINITION

Thrombocytopenia is defined as a platelet count lower than the normal range, typically below 140,000/μL.

EPIDEMIOLOGY

With the widespread use of the routine complete blood count (CBC), asymptomatic individuals with incidentally discovered mild thrombocytopenia are being increasingly recognized. The clinical significance of mild thrombocytopenia (platelet counts between 100,000/μL and 150,000/μL) in the absence of

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158 THROMBOCYTOPENIA

CHARLES S. ABRAMS

DEFINITION

Thrombocytopenia is defined as a platelet count lower than the normal range, typically below 140,000/μL.

EPIDEMIOLOGY

With the widespread use of the routine complete blood count (CBC), asymptomatic individuals with incidentally discovered mild thrombocytopenia are being increasingly recognized. The clinical significance of mild thrombocytopenia (platelet counts between 100,000/μL and 150,000/μL) in the absence of

ABSTRACT

Thrombocytopenia can be caused by three general mechanisms: increased destruction of circulating platelets; impaired production of platelets by the bone marrow; or increased splenic sequestration of circulating platelets. Splenic sequestration is a passive rather than actively destructive process caused by expansion of the splenic platelet pool and splenic enlargement of congestive (e.g., portal hypertension) or infiltrative (e.g., lymphoma or storage disease) etiologies. Destructive thrombocytopenias can be immune- or nonimmune-mediated. The former includes immune thrombocytopenia purpura (ITP) and drug-induced thrombocytopenia; the latter can be caused by TTP, HUS, DIC, and intravascular devices. Before initiating an extensive workup for the cause of the thrombocytopenia, the peripheral blood smear should be examined for artifactual platelet clumping ("pseudothrombocytopenia"), an idiosyncratic in vitro phenomenon that should be especially suspected in a patient reported to have an unexpectedly low platelet count in the absence of any clinical bleeding. Mild thrombocytopenia can be congenital or occur physiologically with the progression of a normal pregnancy (gestational thrombocytopenia).

KEYWORDS

immune (idiopathic) thrombocytopenic purpura (ITP)
thrombotic thrombocytopenic purpura (TTP)
hemolytic-uremic syndrome (HUS)
disseminated intravascular coagulation (DIC)
pseudothrombocytopenia

other CBC abnormalities can be difficult to ascertain. Many, and perhaps most, of these individuals with mild chronic thrombocytopenia represent outliers of the normal distribution of platelet counts. However, others have thrombocytopenia that represents the early manifestation of an unrecognized disease.

After a decade, approximately 10% of patients with mild immune thrombocytopenia will develop ITP or another autoimmune disorder. However, approximately 90% of the subjects will continue to manifest borderline thrombocytopenia without developing another disorder during this period of time. It can be concluded that most individuals with isolated and asymptomatic chronic mild thrombocytopenia simply represent the lower end of the normal platelet count distribution. Consequently, international consensus groups have set the threshold for the diagnosis of ITP at a platelet count of less than 100,000/μL.

PATHOBIOLOGY

The causes of thrombocytopenia can be divided into three major categories: increased destruction of platelets, such as seen in immune-mediated causes; decreased production of platelets, usually due to an underlying bone marrow disorder; or sequestration of platelets within the spleen, as occurs in conditions that cause splenomegaly (hypersplenism).

Increased Platelet Destruction

In the absence of splenomegaly, the presence of increased megakaryocytes in an otherwise normal bone marrow implies that thrombocytopenia is due to increased platelet destruction. An acute drop in a patient's platelet count also implies that a peripheral destructive process is the likely cause. For example, a patient who develops abrupt thrombocytopenia during hospitalization most likely has a low platelet count caused by an infection or by the introduction of a new medication. Both nonimmune and immune processes can lead to a shortened platelet lifespan. Nonimmune reasons for the accelerated destruction of platelets include sepsis, disseminated intravascular coagulation (DIC), thrombotic thrombocytopenic purpura (TTP), hemolytic-uremic syndrome (HUS), preeclampsia or eclampsia, cardiopulmonary bypass, and giant cavernous hemangioma. Thrombocytopenia that occurs in these circumstances usually resolves with treatment of the underlying disorder, and platelet transfusions are rarely necessary. Thrombocytopenia due to TTP, HUS, or heparin-induced thrombocytopenia (HIT) is more characteristically associated with microvascular occlusion or thrombosis than with bleeding (Table 158-1).

Immune-mediated platelet destruction can result from drugs, alloimmune sensitization, or autoimmunity. Medications should always be considered as a possible cause of acute thrombocytopenia. The list of potential offending agents is long, but drugs with strong evidence of antibody-mediated platelet destruction include quinine, quinidine, sulfonamides (such as trimethoprim-sulfamethoxazole), β-lactam antibiotics (both penicillins and cephalosporins), vancomycin, procainamide, and gold salts. In addition to stopping the offending medication, platelet transfusions might be required for severe thrombocytopenia.

Decreased Platelet Production

Decreased platelet production occurs in primary diseases of the bone marrow, such as acute leukemia and aplastic anemia; myelophthisic processes in which bone marrow is affected by metastatic carcinoma, fibrosis, or other clonal hematopoietic disorders; following toxin-induced (such as chemotherapy or ethanol exposure) or radiation therapy–induced myelosuppression; and during infections with viruses such as HIV, cytomegalovirus (CMV), Epstein-Barr virus (EBV), and varicella. Thrombocytopenia also occurs when normal megakaryocyte proliferation is impaired by myelodysplasia.

Thrombocytopenia due to decreased platelet production is often accompanied by abnormalities of the white blood cells or red blood cells. This should be readily apparent by inspection of the CBC and review of the peripheral blood smear. When thrombocytopenia in this setting is accompanied by bleeding, the bleeding usually requires treatment by platelet transfusion. Additionally, when decreased platelet production is profound (less than 10,000/μL) and cannot be readily reversed, prophylactic platelet transfusion to prevent bleeding should be considered. However, as will be discussed in the following section, prophylactic platelet transfusion is problematic because of the short lifespan of platelets and the potential to develop alloantibodies that will limit the effectiveness of future platelet transfusions.

TABLE 158-1 DISORDERS THAT CAUSE BOTH THROMBOCYTOPENIA AND THROMBOSIS

Thrombotic thrombocytopenic purpura (TTP)
Hemolytic-uremic syndrome (HUS)
Heparin-induced thrombocytopenia (HIT)
Disseminated intravascular coagulation (DIC)
Paroxysmal nocturnal hemoglobinuria (PNH)
Vasculitis (such as systemic lupus erythematosus)
Antiphospholipid antibody syndrome

Platelet Sequestration

Approximately 30 to 40% of the circulating platelet mass is normally sequestered within the spleen. Enlargement of the spleen due to portal hypertension or infiltration is accompanied by expansion of the splenic platelet pool. Because hypersplenism by itself rarely causes a platelet count of less than 40,000/μL to 50,000/μL, bleeding due to thrombocytopenia from hypersplenism alone is unusual. In addition, if a patient with a large spleen has a platelet count of less than 40,000/μL, an additional etiology for the thrombocytopenia should be considered.

CLINICAL MANIFESTATIONS

In the absence of qualitative platelet defects (Chapter 159), excessive bleeding does not occur in thrombocytopenic patients following trauma or surgery unless the platelet count is lower than 75,000/μL. In otherwise hemostatically normal patients, spontaneous hemorrhage typically does not occur unless platelet counts are below 30,000/μL. Patients with platelet counts of less than 5000/μL to 10,000/μL are at a high risk for spontaneous, life-threatening hemorrhage. However, there is no absolute threshold for spontaneous bleeding due to thrombocytopenia. Bleeding may occur at higher counts when fever, sepsis, severe anemia, and other hemostatic defects are present, or when platelet function is impaired by medication. It is sometimes said that patients with wet purpura (mucocutaneous bleeding with blood blisters) are at particularly high risk for sudden catastrophic bleeding events. Therefore, it is critical that the physician consider the gamut of possibilities when diagnosing and managing a patient with a low platelet count.

DIAGNOSIS

Typically, the first step in diagnosing a patient with a low platelet count is to determine whether the thrombocytopenia is attributable to increased platelet destruction, decreased platelet production, or hypersplenism (Fig. 158-1). Since no single test can differentiate among the three possibilities, clinical evaluation is critical. A thorough history and physical examination, with attention to possible alternative explanations for thrombocytopenia, are mandatory. Particular attention should be paid to the duration of symptoms, which helps to determine whether the patient has acute or chronic thrombocytopenia. The clinician should also focus on the patient's recent exposure to new medications that might induce thrombocytopenia as a side effect.

Preliminary laboratory tests include a CBC with a differential, along with an examination of the peripheral blood smear (Chapter 143). Abnormalities in the number or morphology of the leukocytes or erythrocytes may indicate a systemic inflammatory disorder or a pathology within the bone marrow; fragmentation of red cells may suggest a microangiopathy such as thrombotic thrombocytopenic purpura (TTP), hemolytic-uremic syndrome (HUS), or disseminated intravascular coagulation (DIC). Clumping of the platelets on the peripheral blood smear may indicate that the patient has pseudothrombocytopenia (Chapter 157). This anomaly is usually due to an antibody that binds to and thereby agglutinates platelets only in the presence of hypocalcemia induced by ethylenediaminetetraacetic acid (EDTA) in the blood collection tube or when the blood sample is allowed to cool to room temperature. Repeating the platelet count in a blood sample that has been anticoagulated with heparin and kept warm until it is analyzed can help exclude this spurious diagnosis. Any additional testing to determine the cause of thrombocytopenia is based solely on the available clinical information derived from the history and examination of the patient. For example, testing for human immunodeficiency virus (HIV) would be prudent in a patient with risk factors. A bone marrow aspirate and biopsy are typically not required for a patient with thrombocytopenia who has an otherwise normal CBC and peripheral blood smear. However, a bone marrow aspirate and biopsy should be considered in older patients and in patients whose thrombocytopenia is progressive or in whom standard therapy has not been effective.

TREATMENT

For patients with decreased platelet production, the cornerstone of treatment is platelet transfusion (Chapter 162). For patients with other specific causes, however, platelet transfusions may or may not be a beneficial therapeutic option.

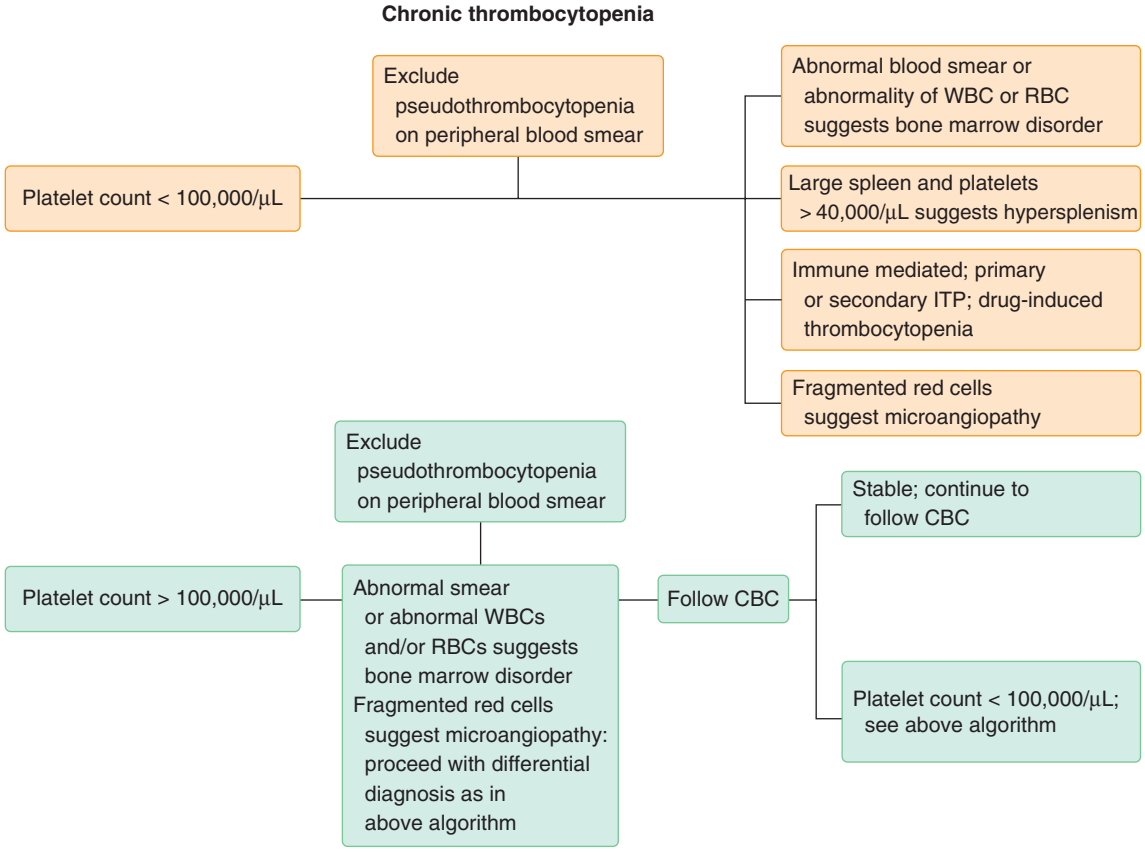

FIGURE 158-1. Systematic approach to the evaluation of chronic thrombocytopenia. CBC = complete blood count; ITP = immune (idiopathic) thrombocytopenic purpura; RBC = red blood cells; WBC = white blood cells.

FIGURE 158-2. Petechiae. Multiple pinpoint, nonblanching, erythematous macules found predominantly on skin of dependent extremities in patients with severe thrombocytopenia.

Platelet Transfusions

Clinicians usually consider "wet" bleeding to be much more ominous than "dry" bleeding. Signs of wet bleeding include epistaxis, gingival bleeding, gastrointestinal bleeding, genitourinary bleeding, and bleeding around intravenous sites. Dry bleeding is defined as ecchymosis or petechiae (Fig. 158-2). Overt wet bleeding that is clearly due to thrombocytopenia is usually treated with platelet transfusion (Chapter 162). Prophylactic platelet transfusion for patients who are not bleeding is controversial. When making the decision whether to treat a nonbleeding patient with thrombocytopenia, the practitioner must consider the short lifespan of platelets (10 days), the 5- to 7-day shelf life of stored platelets, and the potential for the patient to develop transfusion-induced platelet alloantibodies. In patients undergoing treatment for acute leukemia, clinical trials have supported the practice of prophylactic platelet transfusions when the platelet count is below 5000/μL or 10,000/μL, rather than waiting until bleeding occurs in the severely thrombocytopenic patient.[1]

The indications for prophylactic platelet transfusions before interventional procedures are predominantly based on clinical experience and expert opinions, rather than on clinical trials. Current guidelines recommend platelet transfusion in patients with therapy-induced hypoproliferative thrombocytopenia and a platelet count of less than 10,000/μL. Prophylactic platelet transfusion is also indicated for patients having elective central venous catheter placement with a platelet count less than 20,000/μL and for patients having elective diagnostic lumbar puncture or major elective nonneuraxial surgery with a platelet count less than 50,000/μL (Table 158-2).[2] Platelet transfusions should continue for several days following procedures where the risk for bleeding or the complications resulting from bleeding are high. For extremely high-risk procedures that involve the nervous and ocular systems, the prophylactic platelet transfusions should be continued for at least 7 to 10 days.

A donated unit of blood contains approximately 50 billion platelets. Infusing this number of platelets into a patient should increase his or her platelet count by 20,000/μL divided by the patient's body surface area in square meters. Therefore, transfusion of one unit into an average-sized adult patient should increase the individual's platelet count by approximately 10,000/μL to 12,000/μL. Bags of platelets used for transfusions are typically obtained by pooling platelets derived from four to six blood donors. Therefore, a "unit" at one hospital may be derived from more donors than a "unit" obtained at another hospital.

Large quantities of platelets can be derived from a single donor by using apheresis technology (plateletpheresis) (Chapter 162). Because there is minimal loss of red blood cells with this technique, plateletpheresis allows one individual to donate very large numbers of platelets (equivalent to the number of platelets obtained from 6 units of donated blood). The risk for platelet alloimmunization is partially dependent on the number of individuals donating platelets to a patient. Therefore, single-donor plateletpheresis can minimize the risk of alloimmunization. To minimize exposure to blood products (Chapter 162), a strategy of low-dose (110 billion/m^2) transfusions requires more frequent platelet transfusions but ultimately results in fewer transfused platelets without the risk of bleeding complications compared with higher-dose transfusions in patients who require prophylactic platelet transfusion therapy for hypoproliferative thrombocytopenia.[3]

Several complications of platelet transfusion therapy must be kept in mind (also see Chapter 162). First, some patients can become alloimmunized against platelet antigens and can become refractory to future platelet transfusion therapy (discussed in detail later). Second, bacterial contamination of stored

TABLE 158-2 SUGGESTED MINIMUM PLATELET COUNTS BEFORE INVASIVE PROCEDURES

VERY HIGH-RISK PROCEDURES—75,000/μL TO 100,000/μL
Neurosurgery
Ocular surgery (except cataract extraction)
Thyroid surgery
Prostatectomy
MODERATE-RISK PROCEDURES—50,000/μL
Liver biopsy
Dental extraction
Most surgical procedures
LOW-RISK PROCEDURES—30,000/μL
Endoscopy without biopsy
Bronchoscopy without biopsy
VERY LOW-RISK PROCEDURES—NO PLATELET TRANSFUSIONS NECESSARY
Bone marrow biopsy
Cataract extraction

platelets is a much more common complication than the infectious risk associated with red blood cell transfusions. Unlike red blood cells, which are stored frozen after being harvested from donated blood, platelets are sensitive to cool temperatures and therefore need to be stored at room temperature. This method of storage results in more bacterial overgrowth in the transfusion bags. Transfusion-associated bacterial sepsis is one of the most frequently reported causes of transfusion-induced mortality in the United States, and platelet transfusions are the most common blood products associated with sepsis. In contrast to the risk for bacterial infection, the risk for viral infection from platelet transfusions is no higher than it is for red blood cell transfusions. From a single unit of platelets, the risk for being exposed to HIV is less than 1 in 1.5 to 2 million, the risk for exposure to hepatitis B virus is less than 1 in 200,000, and the risk for exposure to hepatitis C virus is less than 1 in 1 to 2 million.

For thrombocytopenia caused by TTP or HIT, there is usually no indication for platelet transfusions because thrombosis occurs much more frequently than hemorrhage in these disorders. However, platelet transfusions may be considered under expert oversight for patients who have profound thrombocytopenia with life-threatening hemorrhage.

The Transfusion-Refractory Patient

Many patients do not have an optimal increase in their platelet count following transfusion. Although there are various definitions of platelet refractoriness, it is simplest to base this definition on the timing of platelet loss following transfusion. Patients who do not have the predicted rise in their platelet count (between 10,000/μL and 12,000/μL for every unit of donated platelets) should have their platelet count analyzed before their next platelet transfusion, 1 hour after that transfusion, and again 24 hours later. If their platelet count rises appropriately 1 hour after the transfusion but falls substantially 24 hours later, the patient has ongoing platelet consumption. This is often seen in patients with sepsis, DIC, severe active hemorrhage, or sometimes drug-mediated immune destruction of platelets. In these situations, the best therapy is to treat the underlying cause and to continue to support the patient with platelet transfusions as clinically indicated. Alternatively, some patients fail to have a significant increase in platelets even 1 hour after a transfusion. These patients may have hypersplenism, an autoantibody that eliminates not only endogenous platelets but also allogeneic donor platelets (as seen in patients with ITP or some patients with drug-mediated immune destruction of platelets), or alloantibodies that react with antigens on the transfused platelets.

Alloantibodies develop in approximately 20% of patients who are repeatedly exposed to platelet transfusions, and these patients present some of the most challenging management issues in transfusion medicine (Chapter 162). The alloantibodies may be directed against human leukocyte antigen (HLA) class I antigens (HLA-A and HLA-B) or against platelet-specific antigens present on the surface of the platelets. Because it appears that HLA class II antigens present on the surface of leukocytes are essential for the development of antibodies directed against HLA class I antigens, efforts to remove the contamination of leukocytes in platelet transfusion preparations can minimize alloantibody formation. Therefore, filters that trap leukocytes during transfusions are useful to prevent patients from becoming refractory to future platelet transfusions. After a patient develops alloantibodies against transfused platelets, the clinician and the blood bank should attempt to identify whether the alloantibody is directed against an HLA class I antigen or against a platelet-specific antigen. If the alloantibody can be identified, platelets derived from donors matched for an HLA class I antigen or the platelet-specific antigen can be used. Corticosteroids, intravenous immunoglobulin, splenectomy, and recombinant factor VIIa are probably of no value in maintaining hemostasis in platelet-refractory thrombocytopenic patients. Antifibrinolytic agents (e.g., ε-aminocaproic acid) under expert oversight might be helpful for patients with bleeding that is predominantly in the oral cavity or in the genitourinary tract. However, antifibrinolytic agents are contraindicated in patients with DIC (Chapter 161) because these agents can precipitate thrombotic events.

SPECIFIC CAUSES OF THROMBOCYTOPENIA

Drug-Induced Thrombocytopenia

PATHOBIOLOGY

Drug-induced thrombocytopenia is one of the most frequent causes of cytopenias evaluated by physicians.[4] Typically, drug-induced thrombocytopenia is the result of an immune reaction elicited by either the drug or by one of its metabolites. Sometimes the drug is simply deposited on the platelet surface, and antidrug antibodies lead to accelerated platelet clearance, primarily in the spleen. More frequently, the drug binds to a protein on the platelet surface and alters the conformation of the platelet protein in a way that is ultimately targeted by the immune system. In the absence of the drug or drug metabolites, this platelet neoantigen disappears, and the thrombocytopenia slowly resolves as new platelets are released from the bone marrow. Immune-mediated platelet destruction explains most drug-induced thrombocytopenias, but there are some exceptions. For example, chemotherapy and other bone marrow toxins can decrease platelet production and thereby induce thrombocytopenia by a mechanism independent of the immune system.

CLINICAL MANIFESTATIONS

The thrombocytopenia induced by medications can have a mild, moderate, or even severe course. Almost all types of drug-induced thrombocytopenia predispose the patient to the risk of hemorrhagic but not thrombotic complications. The notable exception to this rule is heparin-induced thrombocytopenia (discussed separately in the next section). A common difficult clinical situation occurs when an infected or otherwise critically ill patient develops abrupt thrombocytopenia. In this situation, it can be difficult to discern whether the thrombocytopenia is the result of the recent illness (such as a bacterial or viral infection) or its treatment (such as an antibiotic or another unrelated medication). It is also frequently challenging to discern drug-induced thrombocytopenia from ITP. For this distinction, the patient's medical history may be helpful. A gradually progressive thrombocytopenia over months to years is more consistent with ITP than with thrombocytopenia that is induced by a medication. Conversely, the rapid onset of thrombocytopenia following the initiation of a new medication indicates that the drug is the most likely culprit. The time between the initiation of the offending drug and the development of thrombocytopenia has not been well documented for most medications. However, thrombocytopenia typically begins days to a few weeks after the administration of most medications with this type of toxicity. Presumably, this lag time represents the period required for the patient to develop an immune response against the drug-platelet complex. Medications that have been taken safely for years before the onset of thrombocytopenia are unlikely to be the offending agents. In addition to an assessment of the patient's prescribed medications, a careful and comprehensive evaluation of the patient's over-the-counter medications is also necessary. Agents that contain quinine lead the list of often nonprescribed drugs that can induce life-threatening thrombocytopenia. Quinine is frequently contained in over-the-counter pills for leg cramps. Even the quinine in tonic water can induce severe thrombocytopenia ("gin and tonic purpura") when ingested by certain patients, since a drug-induced, immune-mediated thrombocytopenia usually is not related to the dose of the offending drug.

DIAGNOSIS

Some medications are much more likely to induce thrombocytopenia than others. Table 158-3 contains a partial list of drugs that frequently induce this type of toxicity. One particularly useful online database (www.ouhsc.edu/platelets/ditp.html) lists and periodically updates the level of evidence for specific drugs that may induce thrombocytopenia. With the exception of tests for HIT, laboratory tests for drug-induced thrombocytopenia do not have widespread applicability. Usually, drug-induced thrombocytopenia is proved

TABLE 158-3 DRUGS THAT ARE STRONGLY ASSOCIATED WITH THROMBOCYTOPENIA

ANTIBIOTICS AND ANTIVIRALS
Quinine, quinidine
Penicillin
Cephalosporin
Vancomycin
Trimethoprim-sulfamethoxazole
Sulfonamides, sulfonylureas
Linezolid
Valacyclovir
Ganciclovir
Indinavir
CARDIOVASCULAR MEDICATIONS
Abciximab
Tirofiban
Eptifibatide
Salicylates
Digoxin
Furosemide
MISCELLANEOUS
Cimetidine
Ranitidine
Famotidine
Valproate
Interferon
Oxaliplatin

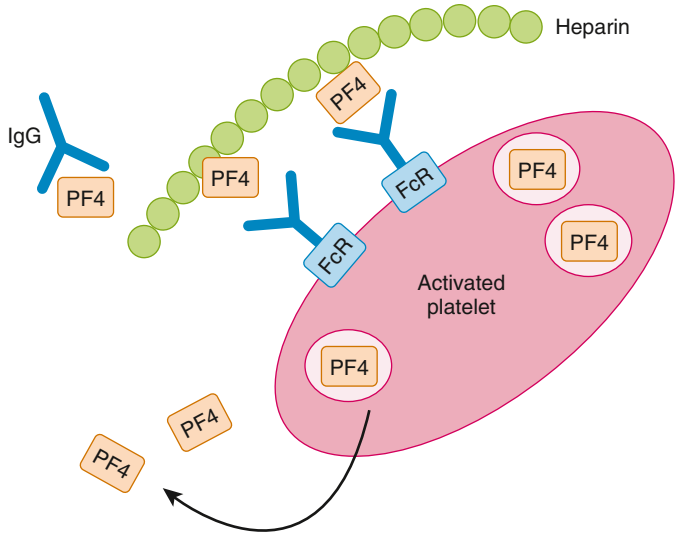

FIGURE 158-3. Pathophysiology of heparin-induced thrombocytopenia. Platelet factor 4 (PF4) is a protein that is stored in platelet granules and that is secreted from platelets upon their activation. Heparin can bind to PF4 and induce a conformational change within PF4 that in some patients produces an antibody-mediated immune response. Large complexes of immunoglobulin (Ig), heparin, and PF4 can accumulate on the platelet surface and stimulate the platelet when the Fc portion of the antibody interacts with the platelet's FcγRII receptor (FcR). Once activated, the platelets contribute to thrombosis. Additionally, the activated platelets secrete more PF4, which perpetuates the process.

only in retrospect, when the platelet count rises after the discontinuation of the suspected medication. Even then, the diagnosis is not conclusive unless thrombocytopenia recurs after rechallenging the patient with the offending drug (a practice that is almost never recommended).

TREATMENT

The best method for treating drug-induced thrombocytopenia is to stop all suspected offending medications.[5] Usually, no additional therapy is indicated. The thrombocytopenia typically begins to resolve without further intervention within days to a week of stopping the drug. The notable exceptions involve drugs with particularly long half-lives. Sulfonamides, quinine, and quinidine are notorious for inducing severe or even life-threatening thrombocytopenia. In patients with profound thrombocytopenia (<10,000/μL to 15,000/μL) or at a high risk for bleeding, platelet transfusions are indicated. When ITP cannot be confidently excluded and the thrombocytopenia is life-threatening, specific treatment for ITP can also be initiated (see later in this chapter).

HEPARIN-INDUCED THROMBOCYTOPENIA

EPIDEMIOLOGY

A special case of drug-induced immune-mediated thrombocytopenia associated with arterial and venous thrombosis, rather than bleeding, is heparin-induced thrombocytopenia (HIT).[6,7] It is seen in 2 to 5% of patients exposed to unfractionated heparin and in 0.7% of patients given low-molecular-weight heparin. HIT almost never occurs in patients who are exposed only to fondaparinux.

PATHOBIOLOGY

Platelets can secrete a protein called platelet factor 4 (PF4) that can bind to heparin. HIT is caused by an antibody that binds to this PF4-heparin complex (Fig. 158-3). Large complexes of antibodies directed against heparin-bound PF4 accumulate on the surface of platelets. At times, these anti-PF4 immunoglobulins bind to Fc receptors that are also present on the platelet surface, leading to activation of the platelet, release of more PF4, and a cycle of events that causes the stimulation of even more platelets. Ultimately, this also leads to the activation of the coagulation cascade, likely through exposure of tissue factor on the surface of activated macrophages. The activation of platelets and the clotting cascade results in the formation of both thrombi and thrombocytopenia.

CLINICAL MANIFESTATIONS AND DIAGNOSIS

Given the extensive use of heparin in hospitalized patients, HIT must always be considered when thrombocytopenia develops in this setting. However, patients with this syndrome often have multiple potential causes of thrombocytopenia, such as infections or other medications, so it is important to consider these other causes. Large retrospective studies of HIT have suggested that the onset of thrombocytopenia relative to the initiation of heparin therapy is useful in establishing or excluding this diagnosis. Immune-mediated HIT typically occurs 5 to 14 days after patients are given heparin by any route. HIT can even occur after subcutaneous injections of "minidose" heparin or following extremely low doses by heparin flush of intravenous lines. The 5- to 14-day lag between heparin exposure and the appearance of HIT is due to the time it takes for the immune response to generate the requisite antibodies against the heparin-PF4 complex. Some patients who have been exposed to heparin within the past several months may already have preexisting antibodies against the heparin-PF4 complex in their circulation. Therefore, when these patients are re-exposed to heparin, they may develop an acute onset of HIT even within the first day of the reinitiation of heparin. Whether or not pre-exposed to heparin, however, platelet-activating HIT antibodies are detectable at the onset of the HIT-related platelet count fall.

The unique timing of acute-onset HIT within hours of heparin re-exposure and the more typical development of HIT within 4 to 14 days of initial heparin exposure emphasize the importance of conducting a careful and critical history in establishing the diagnosis. HIT should be suspected in any patient who develops thrombocytopenia while on heparin therapy. Since the normal platelet count varies widely (140,000/μL to 450,000/μL), some patients may have a substantial decrease in their platelet count but still remain within the normal range. Therefore, a greater than 50% decrease in the platelet count of a patient on heparin should raise the suspicion of this syndrome. HIT should also be suspected in any patient who develops a thrombotic event while on heparin therapy. Some have used the 4 T scoring system to clinically assess the likelihood of HIT, as opposed to a different cause of thrombocytopenia. The 4 T score uses a combination of platelet count fall, timing of platelet count fall, coexisting occurrence of thrombosis, and other potential causes of thrombocytopenia to arrive at a clinical likelihood of HIT that is low probability, intermediate probability, or high probability.

Although antibodies against the heparin-PF4 complex are almost always present in patients with HIT, these antibodies are also frequently present in heparin-treated patients who do not have this disorder (i.e., those patients with neither thrombocytopenia nor thrombosis). There are two general categories of laboratory assays for the diagnosis of HIT: functional assays and immunologic assays (Table 158-4). Functional assays analyze whether the combination of heparin and the patient's plasma can induce normal platelets to aggregate or to secrete serotonin; these assays have very high specificity but relatively low sensitivity.[8] Immunologic assays test the patient's plasma for antibodies that bind to the heparin-PF4 complex; these assays have very high

TABLE 158-4 LABORATORY ASSAYS FOR HEPARIN-INDUCED THROMBOCYTOPENIA

ASSAY	SENSITIVITY (%)	SPECIFICITY (%)
Functional assay (e.g., serotonin release assay)	56-100%	>95%
PF4/heparin enzyme immunoassay (ELISA)	99%	30-70%

ELISA = enzyme-linked immunosorbent assay; PF4 = platelet factor 4.

sensitivity but lack specificity. Some studies show a good correlation between the amount of anti-PF4 antibodies present (such as determined by the optical density of an ELISA-based immunoassay) and the chance that the patient has clinically meaningful HIT. A *negative immunologic assay* is extremely useful in excluding this diagnosis, and a *positive functional assay* is useful in confirming the diagnosis of HIT. Several days may elapse before the test results are available. Therefore, in practice, these laboratory assays provide only confirmatory information. Urgent clinical decisions should *not* be deferred until such test results are available. The timing of the thrombocytopenia with respect to the heparin exposure and the degree of the platelet drop are the most important pieces of information needed by the physician when evaluating a patient suspected of having HIT.

Because platelets are consumed as they become activated, the clinical presentation of HIT is thrombocytopenia. However, it is unusual for the thrombocytopenia to actually cause bleeding in patients with HIT. Instead, HIT is a highly prothrombotic disorder. Both venous and arterial thromboses are common in HIT. Patients with HIT who do not have thrombosis on initial presentation still have a 20 to 30% chance of developing a thrombus within the next month. Nevertheless, the incidence of HIT-related clinical events is greatest immediately after diagnosis. More importantly, clinical studies report that the cessation of heparin alone frequently fails to prevent the development of new thrombotic events.

TREATMENT AND PREVENTION

If a patient is suspected of having HIT, all heparin should be stopped immediately. This includes subcutaneous injections of "minidose" heparin, heparin flushes of intravenous lines, and low-molecular-weight heparin; even heparin-coated intravenous catheters should be withdrawn. Alternative anticoagulation, such as the direct thrombin inhibitor argatroban, should be used (Chapter 70). Although not as well studied (nor FDA approved), both bivalirudin and fondaparinux appear to be viable alternatives. Accumulating evidence also suggests that the direct-acting oral anticoagulants (Table 70-6) can be used in patients with HIT,[9] using doses similar to what are used for the treatment of an acute venous thromboembolism but with a higher dose administered at the beginning of therapy (e.g., rivaroxaban 15 mg twice daily with food for 21 days then 20 mg with food once per day). Warfarin should not be used initially in cases of acute HIT because of its delayed therapeutic effect and its association with venous limb gangrene. However, when the platelet count has returned to a normal level as the acute episode of HIT starts to resolve, warfarin can be slowly introduced at a dose of 5 mg or less daily while an alternative anticoagulant such as argatroban is still being used. The warfarin dose can be gradually increased to achieve an international normalized ratio (INR) of 2 to 3. If the patient has had an acute thrombosis attributable to their HIT, they should be treated for a minimum of 3 months of anticoagulation. If the patient has thrombocytopenia but no thrombosis, anticoagulation is usually given for 4 to 6 weeks. Because patients rarely become profoundly thrombocytopenic as a result of HIT alone, platelet transfusions are typically not required and may actually precipitate thrombotic complications.

If low-molecular-weight heparin is used for prophylaxis instead of unfractionated heparin, the risk of HIT is much lower. However, low-molecular-weight heparins should never be used in the treatment of HIT because this drug can cross-react with the pathologic HIT antibodies.

CORONAVIRUS-2019

Coronavirus-2019 (COVID-19) infection (Chapters 335, 336, and 337) or vaccination against it can rarely result in immune thrombotic thrombocytopenia caused by platelet-activating antibodies against platelet factor 4.[10,11] The clinical manifestations are similar to autoimmune heparin-induced thrombocytopenia, with a predilection for venous thrombosis, pulmonary embolism, and cerebral venous sinus thrombosis.[12] The treatment is anticoagulation, but the precise best regimen is not currently known.

SEPSIS

Along with the exposure to certain drugs, bacterial and viral infections are among the most common causes of acute thrombocytopenia in hospitalized patients. Acute thrombocytopenia can be caused by the deposition of antibody-antigen complexes on the platelet surface through an "innocent bystander" phenomenon. These antibody-coated platelets are then cleared from the circulatory system by Fc receptor–expressing macrophages in the spleen. Thrombocytopenia associated with infections can also be due to DIC (as discussed in Chapter 161). It is notable that patients who are infected with severe acute respiratory syndrome coronavirus 2 (Chapter 334) usually have normal or elevated platelet counts despite having high D-dimer levels like patients with DIC. The treatment of sepsis-induced thrombocytopenia is directed at treating the underlying cause, along with the administration of platelet transfusions as clinically indicated.

IMMUNE THROMBOCYTOPENIC PURPURA

DEFINITION

ITP is an autoimmune disorder caused by circulating antiplatelet autoantibodies. An ITP-like picture can also be found in patients with autoimmune diseases, such as in systemic lupus erythematosus (Chapter 245); in low-grade lymphoproliferative disorders, such as chronic lymphocytic leukemia (Chapter 169); and in HIV infection (Chapter 359).

CLINICAL MANIFESTATIONS

ITP was classically thought to be a disease of young women. Although this description is appropriate for many individuals with this disorder, it is now appreciated that ITP can occur in patients of either sex and at any age. ITP is a chronic, recurring disorder in most adults, in stark contrast to pediatric patients, who usually suffer from acute ITP and much less frequently have chronic thrombocytopenia.

In contrast to patients with coagulation factor deficiencies who present with bleeding deep within their tissues, individuals with ITP (or other platelet disorders) typically have excessive mucocutaneous bleeding. Consequently, the clinician should inquire whether the patient has noticed epistaxis, gingival bleeding, easy bruising, hematuria, melena, or hematochezia. Female patients should also be asked about irregular or excessive vaginal bleeding. The physical examination should pay particular attention to signs of mucocutaneous bleeding. The patient should be thoroughly examined for petechiae (see Fig. 158-2) and ecchymosis as well as for evidence of hemorrhage within the conjunctiva, retina, and central nervous system.

DIAGNOSIS

In patients with ITP, the CBC is usually normal except for the thrombocytopenia, and their peripheral blood smear is remarkable only for a decreased number of platelets, some of which may be larger than normal. Splenomegaly is absent unless the ITP is due to an underlying disorder, such as lymphoma that is associated with splenomegaly. A bone marrow examination is usually not necessary in the absence of abnormalities other than thrombocytopenia on the CBC and peripheral blood smear. If performed, the bone marrow aspirate and biopsy of ITP patients typically show normal or increased numbers of megakaryocytes. However, the rest of their bone marrow is otherwise normal. These bone marrow findings are similar to what is observed in the bone marrows of patients who have other forms of destructive thrombocytopenia such as drug-induced thrombocytopenia. Antiplatelet antibody assays are neither sensitive nor specific and therefore should not be done. ITP must be distinguished from the rare syndrome of cyclic thrombocytopenia in which platelet counts spontaneously rebound, and bleeding, even at the nadir of the platelet count, tends to be mild.[13]

TREATMENT

First-Line Treatment

Initial management of ITP is guided by both symptoms and platelet count (Table 158-5).[14] Asymptomatic patients with platelet counts >30,000/μL can be followed without treatment.[15] If the patient is bleeding or has a platelet count <30,000/μL, either prednisone (1 mg/kg orally daily) or high-dose dexamethasone (4-day pulses of 40 mg intravenously per day every 28 days for several cycles) are both effective (Table 158-6), with a few trials showing better results with dexamethasone, and others (including the largest trial) showing no difference in long-term response rates.[A1] Oral prednisone has the advantage of allowing the dose to be titrated according to the platelet count. Although corticosteroids remain the first-line therapeutic modalities, mycophenolate mofetil under expert supervision is emerging as another first-line option.[A2]

TABLE 158-5 WHO SHOULD BE TREATED FOR IMMUNE THROMBOCYTOPENIC PURPURA (ITP)?

Guidelines for treatment of adult patients with ITP include the following recommendations:

1. Treatment should be administered to newly diagnosed patients if platelets are <30,000/μL.
2. First-line treatment should be a longer course of corticosteroids. IVIG should be used with corticosteroids when a more rapid increase in platelet count is required. Either IVIG or anti-D (where appropriate) should be used as first-line treatment if corticosteroids are contraindicated. If IVIG is used, the dose should be 1 g/kg once a day for 2 consecutive days.
3. Recommended second-line treatment in patients who are unresponsive to or relapse after the initial course of corticosteroids should be rituximab or a thrombopoietin receptor agonist. Splenectomy can be considered if treatment has been required for more than a year since it can produce lifelong responses in some patients.

IVIG = intravenous immunoglobulin.

TABLE 158-6 THERAPY FOR THE INITIAL MANAGEMENT OF IMMUNE THROMBOCYTOPENIC PURPURA

ORAL CORTICOSTEROIDS	
The effect is dose dependent—approximately 80% of patients respond to 1 mg/kg/day. Toxicity also increases with the dose and duration of treatment, and side effects include glucose intolerance, immunosuppression, osteoporosis, and cataracts. Relapse is typical once therapy is tapered and discontinued. High-dose dexamethasone (40 mg/day for 4 days) has been reported to have a higher initial response rate and may be generally better tolerated than prednisone 1 mg/kg/day for 4 weeks followed by taper as initial first-line therapy.	
INTRAVENOUS IMMUNOGLOBULIN	
The effect is more rapid than daily prednisone. Administered at a dose of 1 g/kg/day for 2 consecutive days or 0.4 g/kg/day for 5 consecutive days. The response rates are approximately 80%, and the effects typically last 2 to 4 weeks. Toxicity includes headache, allergic reactions, and rarely, thrombosis.	
ANTI-D IMMUNOGLOBULIN	
It is administered at a dose of 50 to 75 μg/kg intravenously and should only be given to patients who have an Rh+ blood group. The response rates are dose dependent but can approach 75 to 80%. Hemolysis is a common toxicity but is usually mild. Rarely, hemolysis can be life threatening and can be associated with disseminated intravascular coagulation, renal failure, and end-organ infarction. It is generally ineffective in patients who have failed splenectomy.	

TABLE 158-7 THERAPY FOR THE MANAGEMENT OF REFRACTORY IMMUNE THROMBOCYTOPENIC PURPURA

ORAL PREDNISONE	
The effect is dose dependent and rapidly dissipates after discontinuation of the medication. Some patients can be maintained on a very low and tolerable daily dose (e.g., 5 mg). Long-term use is associated with infections, diabetes, osteoporosis, avascular necrosis, weight gain, and cataracts.	
ORAL DEXAMETHASONE	
This is administered at a dose of 40 mg/day for 4 consecutive days, repeated every 2 to 4 weeks for several months. Sustained response rates of 29 to 42% have been reported, although response rates are widely believed to be lower. Toxicity is similar to that of oral prednisone.	
SPLENECTOMY	
Durable (often lifelong) significant responses are seen in 65 to 70% of patients who undergo this procedure. More modest benefits are seen in another 10 to 15% of patients. There is no useful way to predict who will respond. Splenectomy is associated with surgical morbidity and some mortality (≈1-2%). Splenectomy produces lifelong immunosuppression to encapsulated and gram-positive organisms. Splenectomy is also associated with a small long-term risk of thrombosis.	
RITUXIMAB	
This is given at a dose of 375 mg/m^2/wk intravenously for a total of 4 weeks. Significant responses are seen in up to 60% of patients, and these responses typically last for months. Toxicity includes reactivation of hepatitis B, immunosuppression, and rarely, progressive multifocal leukoencephalopathy.	
THROMBOPOIETIN RECEPTOR AGONISTS	
These are administered daily (eltrombopag and avatrombopag) or weekly (romiplostim). An effect typically starts to be seen in 2 to 3 weeks and disappears shortly after the discontinuation of the medication. However, sustained, long-term effectiveness has been demonstrated while on the drug. Toxicity from long-term use is not well known but may include excessive thrombosis and bone marrow fibrosis.	

Second-Line Treatment

Rituximab, a "humanized" murine monoclonal antibody against CD20 (a B-cell antigen), is widely used in patients who are unresponsive to first-line therapy. Complete response rates are seen in approximately 40% of patients, and meaningful response rate with platelet counts above 50,000/μL are seen in approximately 60% of patients. The combination of rituximab (375 mg/m^2 intravenously weekly for 4 weeks) plus dexamethasone (40 mg per day orally for 4 days) can induce higher response rates and longer time to relapse than dexamethasone alone.[16] However, the risk of grade 3 to 4 adverse events is increased when rituximab is combined with dexamethasone. Since the effect of rituximab usually requires 3 or more weeks, another therapy (such as corticosteroids) should be used initially if the patient is profoundly thrombocytopenic.

Peptides have been developed that bind to and activate the thrombopoietin (TPO) receptor; these agents are called TPO receptor agonists or thrombopoiesis stimulating agents. Because these recombinant drugs bear little structural similarity to native TPO, they do not trigger autoimmune anti-TPO antibodies. The FDA has approved two of these drugs, and several more are being used in other countries.

Romiplostim is a TPO receptor agonist composed of several copies of a receptor–binding peptide spliced into a recombinant antibody; it competes with endogenous TPO for binding to the TPO receptor and activates the receptor as would endogenous TPO.[A3] It is usually initiated at 2 to 3 μg/kg subcutaneously weekly, then slowly escalated to 10 μg/kg per week if needed. Eltrombopag[A4] and avatrombopag also activate the TPO receptor and improve thrombocytopenia and have the advantage of being administered orally. Eltrombopag is initiated at 50 mg orally daily (25 mg once daily in individuals with liver insufficiency or of East Asian ancestry), whereas avatrombopag is initiated at 20 mg orally per day. Subcutaneously administered romiplostim, orally administered eltrombopag, and orally administered avatrombopag are all capable of increasing platelet counts in approximately 70 to 90% of patients with ITP.[A5]

Remarkably, these drugs can also increase the platelet counts of patients whose ITP is refractory to other treatment modalities, including splenectomy. However, adverse events, including bone marrow fibrosis and thromboembolism, have been reported. Unfortunately, these drugs' effects disappear soon after their discontinuation.

Fostamatinib, which is an oral inhibitor of Syk kinase (dosed at 100 mg twice daily, increasing to 150 mg twice daily if the platelet count remains below 50,000/mL after 4 weeks of therapy), can be useful in patients who have not responded to multiple other therapies.[A6] It results in a 40 to 45% initial response rate and 18% stable response rate with continuous therapy in previously treated patients with chronic immune thrombocytopenia. Side effects include diarrhea, nausea, hypertension, and neutropenia.[17]

Refractory ITP

Refractory patients may require immunosuppressive medications or splenectomy (Table 158-7). Immunosuppressive options include immunomodulating agents, such as intravenous immunoglobulin (IVIG), anti-Rh immunoglobulin (anti-D), cyclophosphamide, azathioprine, cyclosporine, mycophenolate mofetil, dapsone, interferon, and etanercept.[18]

Splenectomy can provide a durable complete response in approximately 66 to 70% of patients.[19,20] Approximately half of the remaining patients who do not have normal platelet counts following splenectomy achieve a partial response that is clinically meaningful. Unfortunately, 10 to 15% of patients derive no benefit from splenectomy. There is no test to predict whether a particular patient will respond to this treatment, although initial steroid responders and younger patients tend to have a better outcome. It should be noted that splenectomy is associated with small long-term risks of both infections and thrombosis (Chapter 154).

Patients who have ITP with severe thrombocytopenia (<5000/μL) or internal bleeding should be promptly treated with both high doses of pulse corticosteroids and IVIG. Platelet transfusions may be given concurrently with IVIG for critical bleeding.

THROMBOTIC THROMBOCYTOPENIC PURPURA

DEFINITION

Thrombotic thrombocytopenic purpura (TTP) is a consumptive thrombocytopenia associated with a mechanical hemolytic anemia.[21] The classic pentad

of symptoms, which are thrombocytopenia, anemia, fever, neurologic problems, and renal abnormalities, are fully present in less than 10% of patients. Many patients today have only hemolytic anemia and thrombocytopenia. A good working definition for this diagnosis is thrombocytopenia along with a microangiopathic hemolytic anemia that is not associated with acute renal failure at presentation, disseminated intravascular coagulation, or another apparent cause. The poor specificity of the clinical features of this disease and the nonspecific laboratory abnormalities historically made TTP difficult to diagnose, but this has improved with the availability of ADAMTS13 testing. In the past, patients with untreated TTP had a mortality rate of 90% within 3 months. With modern therapy, patients with TTP have a mortality rate of approximately 10 to 20%.

PATHOBIOLOGY

Vascular endothelial cells normally secrete von Willebrand factor (vWF) (Chapter 159) that is composed of a large range of multimer sizes, including the so-called "ultralarge multimers." These latter forms bind to platelets very tightly even at low shear forces and therefore have the potential to create platelet aggregates in the circulation that might form microvascular occlusive thrombi, an undesirable result of vWF circulating with ultralarge multimers. However, a metalloproteinase identified as ADAMTS13 (*a d*isintegrin-like *a*nd *m*etalloprotease with *t*hrombospondin type 1 motif, member 13) is also normally present in blood and acts to cleave the ultralarge multimers of vWF, thereby preventing the formation of microvascular occlusions by platelet aggregates.[22] Most patients with adult-onset TTP have autoantibodies against ADAMTS13, thus causing an acquired deficiency of the enzyme and thereby permitting the circulation of thrombogenic ultralarge vWF multimers. Rare patients with inherited and recurrent TTP (Upshaw-Schulman syndrome) have a congenital deficiency of ADAMTS13.[23] Inherited or acquired ADAMTS13 deficiency causes the accumulation of ultralarge multimers of von Willebrand factor in plasma, which leads to platelet activation and the microvascular thrombosis that is characteristic of TTP (Fig. 158-4).

Characteristically, the thrombotic occlusions are in small terminal arterioles and capillaries and are composed mainly of platelets and von Willebrand factor within the damaged vascular lumen. In contrast to the pathology usually found in typical blood clots, the occlusions found in TTP patients contain very little fibrin and are referred to as hyaline thrombi.

Clinical assays of ADAMTS13 enzymatic activity are useful in diagnosing TTP. However, many patients can have a partial deficiency of ADAMTS13 without having TTP, so the absolute amount of deficiency is important. Levels of ADAMTS13 below 10% of normal are highly suggestive of TTP, while levels greater than 30% strongly argue against this diagnosis. Levels between 10 and 30% of normal are not very helpful.

Some patients reportedly developed TTP soon after taking an antiplatelet drug of the thienopyridine class. For example, clopidogrel can induce TTP, but the incidence is rare, about 1 in 250,000. Because the incidence of TTP in the general population is approximately 1 in 100,000, it is difficult to determine whether there is a significant risk for TTP in patients who are prescribed clopidogrel. The thienopyridine-derivative prasugrel has also been implicated in rarely causing TTP. Some patients have been diagnosed with TTP that was attributed to medications that directly injure the vascular endothelium (such as cyclosporine or tacrolimus). Most of these patients do not have TTP but have the related disorder HUS, discussed later in this chapter.

CLINICAL MANIFESTATIONS AND DIAGNOSIS

In TTP, patients can occasionally present with symptoms of excessive mucocutaneous bleeding, but they might also present with signs of a thrombotic event (including phlebitis, myocardial infarction, or stroke).[24] Abdominal pain is present in some patients, which is presumably due to intestinal ischemia. Signs of central nervous system disease, somnolence, and even coma can also be seen on presentation.

The two major hallmarks of TTP are microangiopathic hemolytic anemia and thrombocytopenia.[25] Microangiopathic hemolytic anemia is a non-immune-mediated hemolytic anemia caused by red cell fragmentation (Chapter 146). Patients with this disorder have typical laboratory findings of hemolytic anemia, including a high lactate dehydrogenase (LDH) level, elevated indirect bilirubin, low haptoglobin, and an increased reticulocyte count. Examination of the peripheral blood smear (Chapter 143) shows torn or fragmented red blood cells (schistocytes), and frequently also shows early red blood cell precursor cells (nucleated red blood cells). The thrombocytopenia may be mild if the disease is diagnosed at an early stage, but advanced cases of TTP can have platelet counts of less than 10,000/μL. Unlike most patients with typical thrombocytopenia, who tend to bleed excessively, patients with TTP have few hemorrhagic complications. Instead, they are markedly predisposed to thrombosis. In fact, a thrombotic complication in a thrombocytopenic patient is an important clue that TTP might be the cause of the thrombocytopenia (see Table 158-1). In the absence of plasmapheresis, TTP typically progresses and causes renal disease, neurologic symptoms, and fever. Since TTP now is often diagnosed in its early stages, patients usually only have microangiopathic hemolysis and thrombocytopenia.

TREATMENT

The prompt initiation of plasma exchange (plasmapheresis with plasma replacement) reduces the mortality rate associated with TTP from 90% to approximately 15%.[26] The mechanism of this benefit is partially due to the replacement of ADAMTS13. A randomized trial demonstrated that plasma exchange is more beneficial than plasma infusion for the treatment of TTP. This implies that some of the benefit of plasmapheresis is attributable to the removal of a pathologic substance from the patient's plasma. Assuming that the pathogenesis of most acquired forms of TTP is the antibody-mediated inhibition of ADAMTS13, plasma exchange has two benefits. First, it helps to remove the pathogenic antibody from the plasma. Second, the normal plasma infused into the patient during plasmapheresis repletes the deficiency of ADAMTS13.

Because patients with TTP can develop sudden thrombotic events (including stroke and myocardial infarction), and because patients can deteriorate quickly, it is prudent to initiate plasma exchange as rapidly as possible. Given the morbidity and mortality of untreated TTP, and given the relatively low risk of administering plasmapheresis, this therapy should be initiated even when

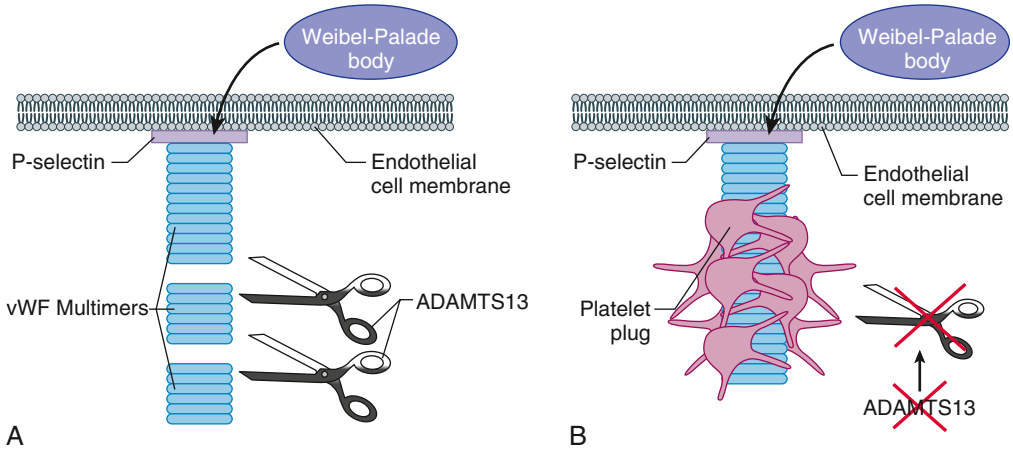

FIGURE 158-4. Pathophysiology of thrombotic thrombocytopenia purpura (TTP). A, Von Willebrand factor (vWF) is synthesized in endothelial cells and stored in Weibel-Palade bodies. The vWF is assembled into ultralarge multimers that are cleaved after they are released into the blood stream by the protease ADAMTS13. The resultant smaller multimers of vWF only bind to platelets to participate in normal hemostasis. **B,** Most patients with TTP have severe deficiency of ADAMTS13 (less than 10% of normal). This results in the accumulation of ultralarge multimers of vWF within the circulation, which promote the excessive adhesion of platelets. The consequence is the formation of large plugs composed of vWF and platelets that can cause vascular occlusions.

the diagnosis is not certain and without waiting for the results of ADAMTS13 testing. Plasmapheresis is not beneficial in children with Shiga toxin–induced HUS or in patients who develop HUS following their exposure to endothelium-toxic drugs, such as chemotherapy or calcineurin inhibitors (e.g., cyclosporine or tacrolimus).

Plasma exchange is administered to replace one entire plasma volume. An average-sized individual requires 20 to 30 units of fresh-frozen plasma for each plasmapheresis session. Therapy is usually administered daily, and patients are monitored for signs of improvement in their thrombocytopenia, hemolysis, neurologic symptoms, fever, and renal disease. Appropriate daily laboratory tests to monitor the patient are CBC, LDH, reticulocyte count, and creatinine. After the thrombocytopenia and hemolysis have been corrected for a few days, the daily plasmapheresis can either be discontinued or continued every other day for several more days. Most patients with TTP will start to respond within 3 to 5 days. A typical duration of therapy is 1 to 2 weeks, although some patients require treatment far beyond this usual time course.

A glucocorticoid is usually initiated at the start of treatment to decrease the production of anti-ADAMTS13 antibodies. Typically prednisone 1 mg/kg is administered daily, although some clinicians prefer to start with methylprednisolone 1000 mg daily for 3 days prior to starting prednisone.

Caplacizumab is an anti–von Willebrand factor, single-variable-domain immunoglobulin that inhibits the interaction between ultralarge von Willebrand factor multimers and platelets. Two randomized trials of patients with TTP showed that caplacizumab (10 mg subcutaneously daily) during plasma exchange and for 30 days afterward hastened resolution of the acute TTP episode and reduced the composite endpoint of TTP-related death, recurrent TTP, or a thromboembolic event.[A7,A8] Although caplacizumab can mildly shorten the number of days of plasma exchanges,[27] the very high cost of the drug has raised questions about its cost-effectiveness,[28] and suggests that it is best considered in patients who have neurologic or cardiac symptoms and in whom a very rapid response is needed to prevent impending catastrophic damage to these vital organs.

Additional immunosuppression with rituximab may be beneficial, but this drug does not decrease antibody production for weeks to months after its administration. If rituximab has any benefit in the treatment of TTP, it is probably only to minimize the incidence of late relapses.

Approximately one third to as many as one half of patients relapse after plasmapheresis is discontinued. These patients require a reinitiation of plasma exchange as well as administration of rituximab if this has not already been given.

Major complications of plasmapheresis do occur and are often attributable to the use of a central venous catheter. Hypotension, bacteremia, hemorrhage, and thrombosis are among the most common life-threatening complications of plasmapheresis therapy. Two specific complications deserve emphasis. First, patients taking an angiotensin-converting enzyme (ACE) inhibitor are susceptible to plasmapheresis-induced hypotension. This is due to these drugs' interference with bradykinin catabolism. Second, a patient who develops recurrent thrombocytopenia and a fever several days to a week into treatment may not be having an exacerbation of TTP, but rather may be developing central line–induced sepsis. Therefore, a vigorous investigation for infection should be initiated in patients who appear to be relapsing early.

HEMOLYTIC-UREMIC SYNDROME

DEFINITION

HUS is another cause of microangiopathic hemolytic anemia, and it may be difficult to distinguish from TTP.[29] When acute renal failure is predominant and there are no neurologic symptoms, many clinicians consider the syndrome to be HUS, not TTP. In contrast to TTP, HUS is not caused by a deficiency of ADAMTS13. Instead, HUS is probably caused by damage to endothelial cells leading to thrombosis in small blood vessels and fragmentation of red blood cells as they squeeze past the clots.

PATHOBIOLOGY AND CLINICAL MANIFESTATIONS

There are three major causes for HUS. The first, and most common, cause of HUS is a Shiga toxin–producing *E. coli* infection. This "typical" form of HUS occurs a few days after a bloody diarrhea syndrome induced by toxigenic *E. coli* (typically serotypes 157:H7 or O104:H4). The Shiga toxin binds to and damages glomerular endothelium, leading to localized thrombus formation, shearing of red cells, and kidney failure.

The next most common type of HUS is in patients who have inherited dysregulation of the alternative complement cascade (Chapter 37), now called complement-mediated (but formerly called atypical) HUS. The best-described genetic mutations cause a deficiency of factor H, which is a complement regulatory protease. HUS-inducing mutations in other components of complement regulation include those found in C3, factor B, CD46, and factor I. In complement-mediated HUS, complement is activated on endothelial cells. Frequently, an upper respiratory tract infection will precede the episode of microangiopathic hemolytic anemia. However, in contrast to typical HUS that is induced by an infection, the infection is only a trigger for complement-mediated HUS in a genetically susceptible host.

The least common variety of HUS is secondary HUS. This is usually caused by drugs or other medical conditions that directly or indirectly promote endothelial cell damage. Several drugs can also induce HUS by directly damaging the endothelial cells. These include calcineurin inhibitors, such as tacrolimus and cyclosporine; sometimes, lowering the dose of these drugs can reverse the microangiopathic hemolytic anemia. Cytotoxic drugs such as mitomycin C, cisplatin, and bleomycin can also induce HUS by directly damaging the endothelial cells. Secondary HUS can also be induced by a variety of autoimmune diseases, cancer, and pregnancy.

TREATMENT AND PREVENTION

Reducing the spread of Shiga toxin–producing *E. coli* is vital because antibiotics and antimotility drugs do not lower the risk for developing HUS symptoms. In contrast to TTP, there is little evidence that plasma exchange is beneficial in these cases. The clinical course and outcome of *E. coli* O104:H4–induced HUS are similar to infections with the more common O157:H7–induced HUS. Aggressive antibiotic therapy appears to be beneficial for reducing seizures and death. However, neither plasmapheresis nor glucocorticoids seem to be helpful for typical or secondary HUS. The infusion of plasma or plasmapheresis is uncertain in the treatment of the forms of HUS that are caused by the dysregulation of complement. Patients with complement-mediated HUS respond better to eculizumab or ravulizumab, which work by inhibiting the terminal complement cascade.

DISSEMINATED INTRAVASCULAR COAGULATION

Disseminated intravascular coagulation, which is a pathologic condition that depletes components of the coagulation system, including platelets, is discussed in detail in Chapter 161.

THROMBOCYTOPENIA DURING PREGNANCY

Thrombocytopenia occurs in approximately 10% of pregnant women.[30] It may be due to a normal variant of pregnancy (gestational thrombocytopenia), a pregnancy-specific condition (preeclampsia and HELLP [*h*emolysis, *e*levated *l*iver enzymes, and *l*ow *p*latelets]) syndrome, or a condition exacerbated by pregnancy (ITP, vasculitis, TTP). Thrombocytopenia occurs in approximately 7 to 10% of pregnancies, and about 75% of these cases are due to gestational thrombocytopenia, 15 to 20% are secondary to hypertensive disorders, 3 to 4% are due to an immune process, and the remaining 1 to 2% are rare constitutional thrombocytopenias, infections, and malignancies. The prognosis and treatment vary tremendously based on the underlying cause.

Gestational Thrombocytopenia

Gestational thrombocytopenia (incidental thrombocytopenia of pregnancy) is a mild, asymptomatic thrombocytopenia that typically occurs late in pregnancy. It occurs predominantly because of hemodilution from expanded plasma volume, although it is possible that there is also a component of increased platelet clearance. Gestational thrombocytopenia is not associated with fetal thrombocytopenia, and this form of maternal thrombocytopenia resolves spontaneously after delivery. Other than thrombocytopenia during previous pregnancies, women with gestational thrombocytopenia have no prior history of a low platelet count. This lack of previous thrombocytopenia helps to distinguish gestational thrombocytopenia from ITP. Additionally, in contrast to other causes of maternal thrombocytopenia, gestational thrombocytopenia does not occur before mid-second trimester, usually does not cause the platelet count to drop below 100,000/μL, and almost never causes a platelet count lower than 75,000/μL. Consequently, deviation from standard obstetric care is not required for a patient with gestational thrombocytopenia.

Preeclampsia

Preeclampsia causes proteinuria and hypertension during the later stages of pregnancy (Chapter 221). A minority of women with preeclampsia progress to have seizures; when this occurs, the syndrome is called *eclampsia*. Approximately 50% of women with preeclampsia have thrombocytopenia. Platelet counts are usually above 100,000/μL, and typically not less than 50,000/μL unless there is another coexisting reason. Some patients have an

unusually severe form of preeclampsia called HELLP syndrome that is associated with a more significant thrombocytopenia, a microangiopathic hemolytic anemia, and markedly elevated liver function tests. Preeclampsia and HELLP syndrome are thought to result from a factor produced within the placenta because these syndromes usually resolve rapidly and spontaneously after delivery. However, the syndrome can also present postpartum. If these syndromes do not resolve spontaneously within 3 days, alternative diagnoses, such as ITP, TTP, or DIC should be considered. Consequently, immediate delivery of the child is recommended, if possible, because the microangiopathic process stops soon thereafter. If no improvement is seen by the third postpartum day and other causes, such as DIC, have been excluded, standard management for TTP, including plasma exchange, is recommended.

Immune Thrombocytopenia

ITP

Although a far less common cause of thrombocytopenia in a pregnant woman than gestational thrombocytopenia or preeclampsia, immune-mediated thrombocytopenia, particularly ITP, is the most common reason for a maternal platelet count less than 50,000/μL. Other than the magnitude of the thrombocytopenia, there is no laboratory test to differentiate ITP from gestational thrombocytopenia. Most patients with ITP or vasculitis during pregnancy have a history of thrombocytopenia before pregnancy. However, pregnancy can exacerbate or even unmask previously unrecognized autoimmune disorders like ITP. The antiplatelet IgG antibodies that cause ITP in the mother can cross the placenta and lead to thrombocytopenia in the fetus. Importantly, the platelet count in the unborn child does not correlate well with the platelet count of the mother, and attempts to sample fetal blood to monitor platelet counts are associated with significant risk.

Because most children born to women with ITP have a platelet count high enough for a successful delivery, the management of ITP focuses on keeping the maternal platelet count acceptable for the mother's safety. A platelet count above 30,000/μL is considered safe in the early stages of pregnancy and for vaginal delivery (although a platelet count above 80,000/μL is recommended for neuraxial anesthesia). A platelet count above 50,000/μL is acceptable for cesarean section. This can be managed by the use of oral glucocorticoids, and if necessary, by the administration of IVIG. Rituximab is not teratogenic but can cause prolonged lymphopenia in both the mother and the neonate. Although there are case reports of using romiplostim during pregnancy, the safety of thrombopoiesis-stimulating agents during pregnancy is not known. Splenectomy is rarely required and has a risk for inducing miscarriage when performed during the first trimester. This operation is also technically difficult during the later stages of pregnancy because of uterine enlargement.

TTP

The diagnosis of TTP during pregnancy can be difficult to make because many of the symptoms are identical to those of preeclampsia. If the symptoms develop during the early stages of pregnancy, when preeclampsia is unlikely, the diagnosis of TTP is more certain. The presence of hyperuricemia, hypoproteinemia, elevated liver transaminases, and direct bilirubin is more consistent with preeclampsia. The absence of elevated liver function abnormalities and the presence of a platelet count less than 20,000/μL or neurologic symptoms support the diagnosis of TTP. A very low (<10%) ADAMTS13 level also supports the diagnosis of TTP, but the results of this test might take some time.

POST-TRANSFUSION PURPURA AND NEONATAL ALLOIMMUNE THROMBOCYTOPENIA

Post-transfusion thrombocytopenia is due to the sensitization to platelet alloantigens, such as PlA1 (HPA-1a).[31] These alloimmune antibodies can cause profound thrombocytopenia approximately a week after a blood transfusion (post-transfusion purpura, or PTP). PTP is often induced by exposure to the small number of platelets that contaminate most red blood cell transfusions. It can be treated with IVIG or by plasma exchange. A similar alloimmune antibody produced by a pregnant woman can cause thrombocytopenia in her fetus (neonatal alloimmune thrombocytopenia, or NAIT). In this condition, the mother herself is not affected, but the neonate might have severe thrombocytopenia and bleeding. Neonatal alloimmune thrombocytopenia is treated with the transfusion of platelets derived from a PlA1-negative donor (most conveniently, the newborn's mother). Corticosteroids and IVIG have also been used.

VASCULITIS

Autoimmune diseases such as systemic lupus erythematosus (Chapter 245), rheumatoid arthritis (Chapter 243), and other forms of vasculitis can also cause thrombocytopenia. This cause is typically an ITP-like process that occurs in patients with a propensity for the development of autoantibodies. The treatment for these patients is immunosuppression, similar to the treatment for other patients with ITP. Some patients with active vasculitis and endothelial inflammation consume circulating platelets by promoting their adhesion to the damaged vessel wall. This creates a clinical picture that is difficult to distinguish from that of TTP without a tissue diagnosis that documents vasculitis or a very low (<10%) ADAMTS13 level. Because of the difficulty of discerning TTP from a flare-up of vasculitis, these patients are often treated with both plasma exchange and immunosuppression.

DILUTIONAL THROMBOCYTOPENIA

Thrombocytopenia does not typically occur after blood loss, possibly in part owing to the release of platelets from the splenic pool. Thrombocytopenia occasionally occurs after a massive hemorrhage. However, this is only when the hemorrhage is severe enough to necessitate the replacement of 1.5 to 2 times the total blood volume, which usually requires the transfusion of at least 15 to 20 units of packed red blood cells over a short period of time. Even in this circumstance, the thrombocytopenia is usually only mild to moderate. Therefore, the clinician should remain vigilant for another cause of the thrombocytopenia (such as DIC resulting from hemorrhage-induced hypotension and shock). When indicated, dilutional thrombocytopenia can be readily corrected with platelet transfusions.

CONGENITAL THROMBOCYTOPENIAS

Lifelong thrombocytopenia can be due to an inherited defect that affects platelet production or survival. Improved access to genetic testing has demonstrated that inherited thrombocytopenia is much more common than previously realized. Mutations in at least 32 genes can cause inherited thrombocytopenia. These disorders can be autosomal dominant (May-Hegglin anomaly and Sebastian syndrome), autosomal recessive (Bernard-Soulier disease, Fanconi anemia, gray platelet syndrome, thrombocytopenia with absent radius syndrome, and Paris Trousseau), or X-linked (Wiskott-Aldrich syndrome, GATA1-related, and FLNA-related). Many of these disorders are associated with other abnormalities in addition to thrombocytopenia such as kidney failure, cataracts, deafness, and predisposition to bone marrow failure or hematologic malignancies. A congenital cause of thrombocytopenia should be suspected in a patient who has long-standing moderate thrombocytopenia that was presumed to be treatment-refractory ITP. However, the majority of patients with chronic borderline thrombocytopenia and platelet counts greater than 100,000/μL continue to have stable platelet counts a decade later,[32] and many are likely to be outliers at the lower range of physiologic platelet counts.

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159 VON WILLEBRAND DISEASE AND HEMORRHAGIC ABNORMALITIES OF PLATELET AND VASCULAR FUNCTION

JORGE DI PAOLA AND JAMES S. O'DONNELL

VON WILLEBRAND DISEASE

DEFINITION AND EPIDEMIOLOGY

Von Willebrand disease, which is the most common inherited bleeding disorder, is caused by quantitative or qualitative reductions in plasma von Willebrand factor (VWF). Significant bleeding symptoms due to reduced levels of von Willebrand factor are present in approximately 1 in 1000 individuals, with a prevalence that appears to be relatively consistent across different races and ethnicities. Importantly, however, population studies have demonstrated that not all people with reduced plasma levels of von Willebrand factor have clinically relevant bleeding, and the true prevalence of asymptomatic von Willebrand disease is less certain.

PATHOBIOLOGY

The human *VWF* gene consists of 52 exons and spans 178 kb on chromosome 12. Von Willebrand factor is a large multimeric plasma glycoprotein that plays two essential roles in normal hemostasis. First, it mediates platelet adhesion to exposed subendothelial tissues at sites of vascular injury. Second, von Willebrand factor acts as a carrier molecule for procoagulant factor VIII, thereby protecting it from premature proteolytic degradation and clearance. Von Willebrand factor and factor VIII circulate together in a noncovalent complex in normal plasma. In vivo, expression of von Willebrand factor is limited to endothelial cells and megakaryocytes. Von Willebrand factor that is synthesized within megakaryocytes is subsequently stored within the α-granules of their platelet progeny. This platelet von Willebrand factor accounts for 10 to 20% of the total amount that is present in normal platelet-rich plasma. In contrast, von Willebrand factor that is synthesized within endothelial cells is either released directly into the plasma through a constitutive secretory pathway or stored in dedicated organelles known as Weibel-Palade bodies. Consequently, under normal steady-state conditions, plasma von Willebrand factor is derived chiefly from endothelial cells. Regulated secretion of von Willebrand factor from its stores within Weibel-Palade bodies can be triggered by a variety of different secretagogues including histamine, thrombin, and desmopressin (DDAVP [1-desamino-8-D-arginine vasopressin]). Similarly, von Willebrand factor is secreted from α-granules following platelet activation.

Within endothelial cells, von Willebrand factor undergoes complex post-translational modification prior to its secretion into the plasma. In the endoplasmic reticulum, individual monomers of von Willebrand factor are assembled into dimers through the formation of C-terminal disulphide bonds. Subsequently, von Willebrand factor dimers form high-molecular-weight multimers in the Golgi after another round of N-terminal disulphide bond formation. As a result, von Willebrand factor circulates in the form of heterogeneous multimers that contain a variable number of subunits, ranging from a minimum of 2 to a maximum of 100. The largest multimers have molecular weights in excess of 20,000 Kd. Multimeric composition is a critical determinant of von Willebrand factor's functional activity. High-molecular-weight multimers bind both collagen and platelets with higher affinities, and they are more efficient in inducing platelet aggregation under high-shear conditions. In normal plasma, the multimeric composition of circulating von Willebrand factor is tightly regulated by a specific cleaving metalloprotease termed ADAMTS13 (a disintegrin and metalloproteinase with a thrombospondin type 1 motif, member 13).[1]

To facilitate platelet-plug formation at sites of vascular injury, von Willebrand factor also must be able to bind to exposed subendothelial collagen. Specific domains of von Willebrand factor interact with different types of collagen. For example, the A3 domain binds to collagen types I and III, whereas the principal binding site for types IV and VI collagen is located within the A1 domain.

In the normal population, plasma levels of von Willebrand factor typically vary between 50 to 150 IU/dL, and von Willebrand disease is classified into three distinct subtypes (Table 159-1). Type 1 von Willebrand disease is characterized by a partial quantitative deficiency in plasma levels of von Willebrand factor (<50 IU/dL) and accounts for the majority (about 75%) of cases. Type 2 von Willebrand disease includes patients who have qualitative disorders that impair one or more aspects of von Willebrand factor's normal functional activity. In these patients, the total amount of von Willebrand factor antigen (VWF:Ag) in the plasma may be normal or slightly reduced. In contrast, however, functional assays of von Willebrand factor are significantly reduced. Type 2 von Willebrand disease accounts for about 25% of cases and is further subdivided (type 2A, 2B, 2M, and 2N respectively) based upon the nature of the underlying qualitative defect of von Willebrand factor (Table 159-1). Type 3 von Willebrand disease is a rare (1 per million; about 1% of cases) and severe bleeding disorder characterized by near-complete deficiency in plasma von Willebrand factor.[2]

CLINICAL MANIFESTATIONS

Bleeding symptoms in patients with von Willebrand disease vary depending upon the residual levels of plasma VWF activity levels and the disease subtype. Patients typically present with mucocutaneous bleeding including epistaxis, gum bleeding, easy bruising, and bleeding from minor wounds. Recurrent gastrointestinal bleeding is a common presentation, particularly in patients with types 2 or 3 von Willebrand disease.[3]

Although von Willebrand disease is inherited in an autosomal manner, clinical disease is more prevalent in females because they face greater hemostatic challenges. For example, heavy menstrual bleeding occurs in up to 80% of women with von Willebrand disease and is often associated with iron deficiency (Chapter 145). Furthermore, undiagnosed von Willebrand disease is common (about 15% of cases) in women who present for investigation of

TABLE 159-1 CLASSIFICATION AND DIAGNOSIS OF VON WILLEBRAND DISEASE

TYPE VWD	DESCRIPTION	FVIII	RCo	VWF	RCo:VWF RATIO	MULTIMERS	SPECIAL TESTING
Normal range		50-150%	50-200%	50-200%	>0.7	Normal	
Type 1	Quantitative deficiency	↓ or N	<30%	<30%	>0.7	Normal distribution; decreased quantity	VWF propeptide:VWF ratio >0.6 in type 1 C; exon 28 DNA testing
Type 2A	Qualitative VWF defect	↓ or N	↓	N to ↓	<0.7	Loss of HMW forms	Exon 28 DNA testing
Type 2B	Qualitative gain of function; depletes HMW multimers	↓ or N	↓	N to ↓	<0.7	Loss of HMW forms	↑ RIPA low doses; exon 28 DNA testing
Type 2M	Qualitative defect	↓ or N	↓	N to ↓	<0.7	Normal	↓ CB
Type 2N	Qualitative defect only in FVIII binding	↓↓	N	N	>0.7	Normal	↓ VWF:FVIII binding study
Type 3	Near absence of VWF	↓↓	<3%	<3%	NA	None	
"Low VWF"	Borderline values	N	30-50%	30-50%	>0.7	Normal	

Typical or classical laboratory findings are described for each diagnosis. Expert interpretation is often required for patients without classical findings.
CB = collagen binding activity for VWF function; FVIII = factor VIII activity; HMW = high-molecular-weight; N = normal; Plt-VWD = platelet-type von Willebrand disease; RCo = ristocetin cofactor activity for VWF function; RIPA = ristocetin-induced platelet aggregation; VWF = von Willebrand factor antigen; ↑ = increased; ↓ = decreased value, with more arrows reflecting greater extent of decrease.
Data from Leebeek FWG, Eikenboom JCJ. Von Willebrand's disease. *N Engl J Med.* 2016;375:2067-80.

ABSTRACT

Von Willebrand disease, which is the most common inherited bleeding disorder, affects about 0.1% the population. A careful bleeding history can guide specialized testing to determine the specific type of von Willebrand disease. Treatments include desmopressin, which stimulates release of the patient's own von Willebrand factor, and infusion of von Willebrand factor concentrates. Tranexamic acid is useful for acute bleeding episodes. Acquired von Willebrand disease syndrome is often associated with paraproteinemias and hematologic malignancies, and its treatment focuses on ameliorating the precipitating condition. Functional platelet defects can be congenital or acquired, usually related to drugs that are used therapeutically as antiplatelet agents. Uncommon primary vascular disorders that lead to bleeding, including hereditary hemorrhagic telangiectasia and Ehlers-Danlos syndrome, currently have no specific effective treatment.

KEYWORDS

von Willebrand disease
Bernard-Soulier syndrome
Glanzmann thrombasthenia
platelet function disorders
delta storage pool disease

unexplained heavy menstrual bleeding. Significant bleeding can also occur in von Willebrand disease patients after hemostatic challenges, including dental extractions or surgical procedures.[4] Although plasma levels of von Willebrand factor progressively increase during pregnancy, women with von Willebrand disease have increased rates of both primary and secondary postpartum hemorrhage. Patients with type 3 von Willebrand disease have markedly reduced plasma factor VIII levels and present with recurrent spontaneous bleeding into joints. As in patients with severe hemophilia (Chapter 160), they can ultimately develop progressive arthropathy.

DIAGNOSIS

Clinical Assessment

A complete medical history and clinical examination are important in patients who undergo investigation for a possible bleeding tendency (Fig. 159-1). This history should include any family bleeding tendency or consanguinity, as well as a comprehensive list of current medications and health supplements. Clinical examination may demonstrate evidence of bleeding such as petechiae, ecchymosis, or hematomas. Signs of collagen vascular disorders (including skin laxity, joint hypermobility, joint dislocations, delayed wound healing) should be investigated. Any signs suggesting other inherited or acquired causes of bleeding disorders (e.g., senile purpura hereditary hemorrhagic telangiectasia, Cushing syndrome [Chapter 208], scurvy [Chapter 199], liver disease [Chapter 161], amyloidosis [Chapter 174], hypothyroidism [Chapter 207], paraproteinemia [Chapter 173], and myeloproliferative disorders) should be noted.

In clinical practice, the diagnosis of von Willebrand disease is based upon a bleeding phenotype combined with abnormal laboratory testing, sometimes aided by a family history. Investigation begins with an objective assessment of bleeding history (Fig. 159-1), which is best achieved using a standardized bleeding assessment tool (Table 159-2) to evaluate bleeding symptoms across different domains. Normal bleeding scores are less than 4 in males and less than 6 in females, so laboratory testing for von Willebrand disease and other bleeding disorders is indicated in males who score 4 or more or females who score 6 or more.[5]

Laboratory Evaluation

The prothrombin time (PT) and activated partial thromboplastin time (APTT) may be normal in patients with von Willebrand disease. Initial laboratory testing should also include measurement of plasma levels of von Willebrand factor antigen.[6] In view of the variability in plasma levels of von Willebrand factor, assays should be repeated on two separate occasions several weeks apart. Undetectable plasma levels of von Willebrand factor antigen (typically <3 IU/dL) are consistent with a diagnosis of type 3 von Willebrand disease, whereas partial quantitative deficiency (levels of 3 to 50 IU/dL) are diagnostic of type 1 von Willebrand disease (Fig. 159-1).[7] Since von Willebrand disease can be quantitative or qualitative in nature, laboratory testing must also include assessment of the various functional activities of von Willebrand factor (interactions with platelet GpIbα, collagen, and factor VIII). The von Willebrand factor ristocetin cofactor activity assay traditionally has been the gold standard test of von Willebrand factor function, but platelet-dependent von Willebrand factor activity is better measured by assays of von Willebrand factor glycoprotein 1b recombinant and von Willebrand factor glycoprotein 1b mutant. Commercial assays (typically containing types I and/or III collagen) can measure the binding of von Willebrand factor to collagen. Testing for the binding of von Willebrand factor to collagen types IV and VI has mainly been limited to research laboratories.

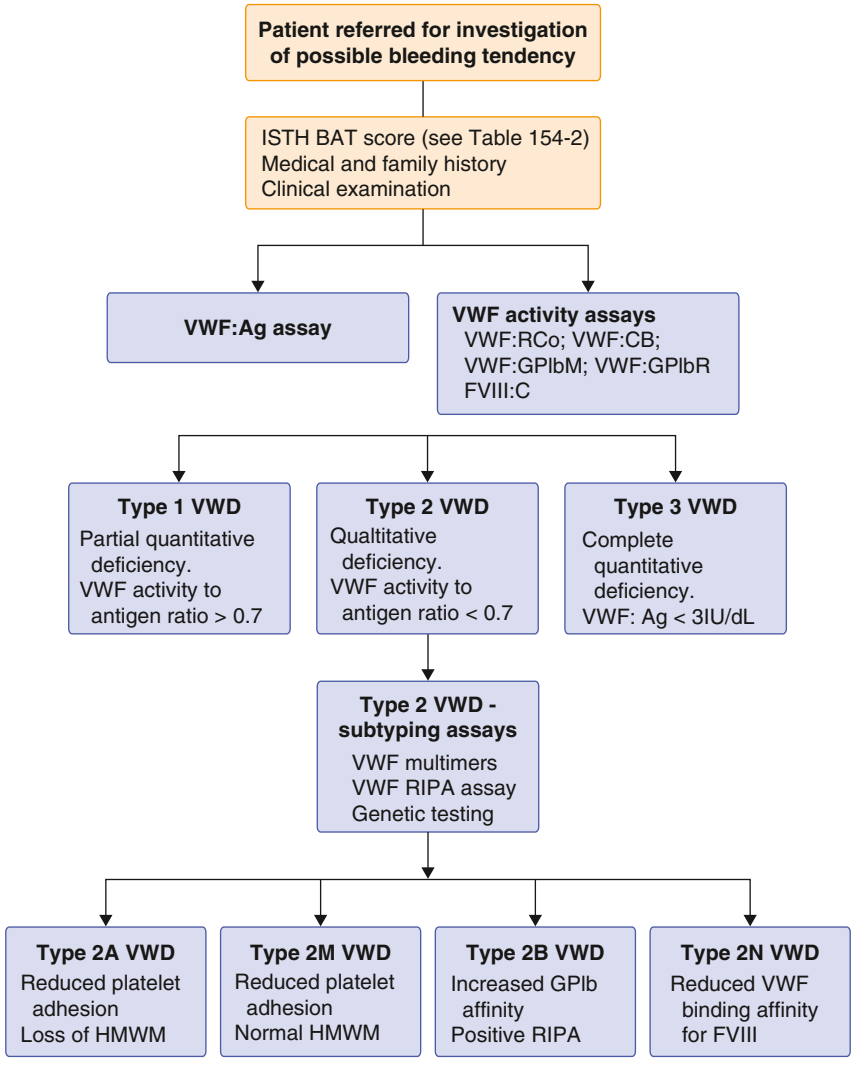

FIGURE 159-1. Diagnostic algorithm for von Willebrand disease. FVIII = factor VIII; FVIII:C = factor VIII procoagulant activity; HMWM = high-molecular-weight multimers; ISTH BAT = International Society on Thrombosis and Haemostasis Bleeding Assessment Tool; RIPA = ristocetin-induced platelet aggregation; VWD = von Willebrand disease; VWF = von Willebrand factor; VWF:Ag = von Willebrand factor antigen; VWF:CB = von Willebrand factor collagen binding; VWF:GPIbM = von Willebrand factor glycoprotein 1b mutant; VWF:GPIbR = von Willebrand factor glycoprotein 1b recombinant; VWF:RCo = von Willebrand factor ristocetin cofactor.

TABLE 159-2 INTERNATIONAL SOCIETY ON THROMBOSIS AND HAEMOSTASIS—SCIENTIFIC AND STANDARDIZATION COMMITTEE BLEEDING ASSESSMENT TOOL

	SCORE				
SYMPTOMS (UP TO THE TIME OF DIAGNOSIS)	**0***	**1***	**2**	**3**	**4**
Epistaxis	No/trivial	≥5/year or >10 minutes	Consultation only†	Packing or cauterization or antifibrinolytic	Blood transfusion or replacement therapy (use of hemostatic blood components and recombinant factor VIIa) or desmopressin
Cutaneous	No/trivial	For bruises 5 or more (>1 cm) in exposed areas	Consultation only†	Extensive	Spontaneous hematoma requiring blood transfusion
Bleeding from minor wounds	No/trivial	≥5/year or >10 minutes	Consultation only†	Surgical hemostasis	Blood transfusion, replacement therapy, or desmopressin
Oral cavity	No/trivial	Present	Consultation only†	Surgical hemostasis or antifibrinolytic	Blood transfusion, replacement therapy, or desmopressin
Gastrointestinal bleeding	No/trivial	Present and not associated with ulcer, portal hypertension, hemorrhoids, or angiodysplasia	Consultation only†	Surgical hemostasis or antifibrinolytic	Blood transfusion, replacement therapy, or desmopressin
Hematuria	No/trivial	Macroscopic	Consultation only†	Surgical hemostasis or iron therapy	Blood transfusion, replacement therapy, or desmopressin
Tooth extraction	No/trivial or never performed	Reported in ≤25% of all procedures, no intervention‡	Reported in ≥25% of all procedures, no intervention‡	Resuturing or packing	Blood transfusion, replacement therapy, or desmopressin
Surgery	No/trivial or never performed	Reported in ≤25% of all procedures, no intervention‡	Reported in ≥25% of all procedures, no intervention‡	Resuturing or packing	Blood transfusion, replacement therapy, or desmopressin
Menorrhagia	No/trivial	Consultation only† or Changing pads more frequently than every 2 hours or Clot and flooding	Time off work/school >2/year or Requiring antifibrinolytics or hormonal or iron therapy	Requiring combined treatment with antifibronlytics and hormonal therapy or present since menarche and >12 months	Acute menorrhagia requiring hospital admission and emergency treatment, requiring blood transfusion, replacement therapy, or desmopressin; or requiring dilatation and curettage or endometrial ablation or hysterectomy
Postpartum hemorrhage	No/trivial or no deliveries	Consultation only† or use of syntocin or lochia >6 weeks	Iron therapy or antifibrinolytics	Requiring blood transfusion, replacement therapy, or desmopressin; or requiring examination under anesthesia and/or the use of uterine balloon/package to tamponade the uterus	Any procedure requiring critical care or surgical intervention (e.g., hysterectomy, internal iliac artery legation, uterine artery embolization, uterine brace sutures)
Muscle hematomas	Never	Post-trauma, no therapy	Spontaneous, no therapy	Spontaneous or traumatic, requiring desmopressin or replacement therapy	Spontaneous or traumatic, requiring surgical intervention or blood transfusion
Hemarthrosis	Never	Post-trauma, no therapy	Spontaneous, no therapy	Spontaneous or traumatic, requiring desmopressin or replacement therapy	Spontaneous or traumatic, requiring surgical intervention or blood transfusion
Central nervous system bleeding	Never			Subdural, any intervention	Intracerebral, any intervention
Other bleeding§	No/trivial	Present	Consultation only†	Surgical hemostasis or antifibrinolytics	Blood transfusion, replacement therapy, or desmopressin

SCORE

*Distinction between 0 and 1 is of critical importance. Score 1 means that the symptom is judged as present in the patient's history by the interviewer but does not qualify for a score 2 or more.

†Consultation only: the patient sought medical evaluation and was either referred to a specialist or offered detailed laboratory investigation.

‡Example: one extraction/surgery resulting in bleeding (100%): the score to be assigned is 2; two extractions/surgeries, one resulting in bleeding (50%): the score to be assigned is 2; three extractions/surgeries, one resulting in bleeding (33%): the score to be assigned is 2; four extractions/surgeries, one resulting in bleeding (25%): the score to be assigned is 1.

§Includes umbilical stump bleeding, cephalohematoma, cheek hematoma caused by sucking during breast/bottle feeding, conjunctival hemorrhage or excessive bleeding following circumcision or venipuncture. Their presence in infancy requires detailed investigation independently from the overall score.

From Rodeghiero F, Tosetto A, Abshire T, et al. ISTH/SSC bleeding assessment tool: a standardized questionnaire and a proposal for a new bleeding score for inherited bleeding disorders. *J Thromb Haemost.* 2010;8:2063-2065; Elbatarny M, Mollah S, Grabell J, et al. Normal range of bleeding scores for the ISTH-BAT adult aoject. *Haemophilia.* 2014;20:831-835; and isth-ssc_bleeding_assessment.pdf

By definition, patients with type 2 von Willebrand disease have a qualitative defect in von Willebrand factor. Consequently, their plasma antigen levels of von Willebrand factor are typically normal or only mildly reduced. However, a marked reduction in one or more aspects of the functional activity of von Willebrand factor results in an activity to antigen ratio below 0.7. In patients confirmed to have type 2 von Willebrand disease, the next step is to subclassify the abnormality based upon the specific nature of their qualitative defect using additional laboratory assays, including von Willebrand factor multimer analysis and the ristocetin-induced platelet aggregation assays (Fig. 159-1). Type 2A von Willebrand disease includes qualitative variants with reduced platelet

adhesion and loss of high-molecular-weight multimers. In contrast, type 2M von Willebrand disease incorporates variants that have reduced platelet adhesion not caused by loss of high molecular multimers. Type 2B von Willebrand disease involves variants in which gain-of-function mutations lead to increased affinity for platelet GpIbα. Consequently, patients with type 2B von Willebrand disease can have fluctuating thrombocytopenia. Finally, type 2N von Willebrand disease is characterized by qualitative variants with decreased affinity for factor VIII.

Guidelines also recommend genetic testing for the diagnosis and subclassification of patients with type 2 von Willebrand disease, especially to distinguish type 2N from mild hemophilia A. Molecular analysis may also be useful for counseling and prenatal diagnosis in families with type 3 von Willebrand disease. In contrast, the utility of genetic testing in patients with type 1 von Willebrand disease remains unclear, because a variety of different sequence variants have been described spanning the *VWF* gene (https://databases.lovd.nl/shared/genes/VWF).

TREATMENT

Where possible, patients with von Willebrand disease should be managed in comprehensive referral centers with a multidisciplinary team that is experienced in treating patients who have bleeding disorders.[8] For elective procedures or bleeding complications, individualized treatment plans should be developed under expert oversight based on both patient- and procedure-related factors (Table 159-3). Patient-related factors to consider include the type of von Willebrand disease and the nadir levels of plasma von Willebrand factor antigen, von Willebrand factor activity, and factor VIII. Plasma levels of von Willebrand factor and factor VIII increase with aging in many patients with type 1 von Willebrand disease and may sometimes correct into the normal range, but even such levels may not result in a complete correction of the bleeding phenotype. Although the Bleeding Assessment Tool score can provide objective data on previous bleeding, it is less useful in patients who have had limited prior exposure to hemostatic challenges.

Tranexamic Acid

Tranexamic acid, which is a fibrinolytic inhibitor that is widely used in the treatment of von Willebrand disease, can be administered orally (typical dose 15 to 25 mg/kg three times daily) or intravenously (typical dose 15 mg/kg three times daily).[9] Even in high-risk populations (e.g., trauma, postpartum hemorrhage, major orthopedic surgery), tranexamic acid is associated with minimal thrombotic risk. However, tranexamic acid is usually avoided in patients with significant hematuria because it has been associated with clot retention and urinary obstruction.

TABLE 159-3 VON WILLEBRAND FACTOR REPLACEMENT GUIDELINES FOR BLEEDING/PROCEDURES

PROCEDURES/BLEEDING EVENTS DURATION	DOSING RECOMMENDATIONS
Major surgery: 7-14 days Cardiothoracic Cesarean section Craniotomy/Spinal cord Abdominal Prostatectomy	Initial dose: 40-60 RCo units/kg Maintenance doses: 20-40 RCo units/kg every 8-24 hr Monitor: FVIII and RCo trough and peak daily Targets: troughs >50%; peaks <200% RCo, <250% FVIII In responsive patients; may use desmopressin later in treatment
Minor surgery: 1-5 days Biopsies Complex dental extractions Gingival surgery Indwelling catheter placement Laparoscopies	Initial dose: 30-60 RCo units/kg Maintenance doses: 20-40 RCo units/kg every 12-48 hr Monitor: RCo and FVIII Targets: troughs >50%; peaks <200% RCo, <250% FVIII In responsive patients; may use desmopressin later in treatment Antifibrinolytic agent for 7-10 days is useful adjunct for dental procedures
Other procedures: one dose Cardiac catheterization Endoscopy with or without biopsies Liver biopsy Lacerations Simple dental extractions	Dose: 20-40 RCo units/kg Rare need for subsequent doses with multiple endoscopic biopsies Monitor: typically not done/required Desmopressin may suffice in very responsive patients Antifibrinolytic agent for 7-10 days useful adjunct for dental procedures

FVIII = factor VIII; RCo = ristocetin cofactor activity for von Willebrand factor function.

Adapted from Neff AT, Sidonio RF Jr. Management of VWD *Hematology Am Soc Educ Program*. 2014;1:536-541. From: Neff AT. Von Willebrand disease and hemorrhagic abnormalities of platelet and vascular function. In: Goldman L, Schafer AI. *Goldman-Cecil Medicine*. 26th ed. Elsevier; Philadelphia: 2020.

DDAVP

DDAVP, which is a synthetic analog of L-arginine vasopressin, induces secretion of von Willebrand factor from Weibel-Palade body stores within endothelial cells and thereby can be used to elevate plasma levels of von Willebrand factor transiently. It can be administered intravenously (typical dose 0.3 μg/kg in 100 mL of normal saline infused over 20 minutes, maximum dose 25 to 30 μg) or can be given intranasally (300 μg total dose or 150 μg per nostril for persons >50 kg body weight). DDAVP is widely used in the treatment of type 1 von Willebrand disease and may also be useful in some patients with types 2A and 2M von Willebrand disease. However, it is generally avoided in type 2B von Willebrand disease, in which it can trigger significant thrombocytopenia, and it is not useful in patients with type 3 von Willebrand disease. Importantly, the increases in plasma levels of von Willebrand factor following DDAVP treatment vary significantly among individual patients with von Willebrand disease, so a DDAVP trial should be performed in each patient to define their individual response. Plasma levels of von Willebrand factor and factor VIII should be measured at 30 minutes and 4 hours post-DDAVP to assess both peak levels and the duration of the response. For acute bleeding or surgical procedures, DDAVP can be repeated every 12 to 24 hours, but tachyphylaxis can diminish the rise in the von Willebrand factor level following repeated treatments. DDAVP can cause fluid retention with secondary hyponatremia and seizures, so fluid restriction (1500 mL over 24 hours) is commonly instituted following DDAVP therapy. Plasma sodium levels should also be measured prior to any repeat dosing. DDAVP is generally avoided in elderly patients who have cardiovascular risk factors.

Plasma-Derived Concentrates of von Willebrand Factor

A number of different plasma-derived concentrates containing von Willebrand factor are licensed for use in patients whose von Willebrand disease fails to respond to DDAVP or who have contraindications to it.[10] In normal individuals, von Willebrand factor has a plasma half-life of approximately 12 to 16 hours, so treatment with DDAVP or plasma-derived von Willebrand factor concentrates can generally be administered once daily to prevent perioperative bleeding or to treat patients who present with acute bleeding. Current guidelines recommend that plasma activity levels of von Willebrand factor and factor VIII should be maintained at ≥50 IU/dL for at least 3 days after surgical procedures. Repeated infusions of factor VIII–containing von Willebrand factor concentrates have been associated with elevated levels of plasma factor VIII procoagulant activity and rare cases of thrombosis.

Recombinant von Willebrand Factor

Recombinant human von Willebrand factor (rVWF) concentrate, which differs from plasma-derived von Willebrand factor concentrates in that it is enriched in high-molecular-weight multimers and does not contain significant amounts of factor VIII, is highly effective.[A1] However, co-infusion of recombinant factor VIII may be necessary with the first dose of recombinant von Willebrand factor to ensure immediate hemostatic factor VIII levels are achieved. In the absence of concurrent recombinant factor VIII infusion, 6 hours may be required following the infusion of recombinant von Willebrand factor before plasma factor VIII procoagulant activity levels rise to above 40 IU/dL in patients with type 3 von Willebrand disease.

Platelet Transfusion

About 10 to 20% of von Willebrand factor is stored within platelet α-granules. Anecdotal reports suggest that platelet transfusion may be a useful adjunctive therapy in managing resistant bleeding in patients who have von Willebrand disease.

Von Willebrand Disease Management Strategies

Routine prophylaxis with von Willebrand factor usually is not required, except in patients who have severe disease or recurrent gastrointestinal bleeding.[11] Episodic treatment is key at the time of bleeding and prior to procedures that typically precipitate bleeding (Fig. 159-2). Prior to surgery, DDAVP or a von Willebrand factor concentrate should be infused.[12] Plasma von Willebrand factor activity and factor VIII procoagulant activity levels should then be assessed to ensure hemostatic levels have been achieved (≥ 50 IU/dL for minor procedures and ≈100 IU/dL for major surgery; Table 159-2). In addition, tranexamic acid should be commenced preoperatively and continued during the postoperative period. Following major surgery, trough levels of von Willebrand factor activity and factor VIII procoagulant activity levels should be repeated on a daily basis, with additional DDAVP or von Willebrand factor concentrate administered daily to maintain trough levels ≥50 IU/dL for at least 5 to 10 days (Table 159-2).[13,14]

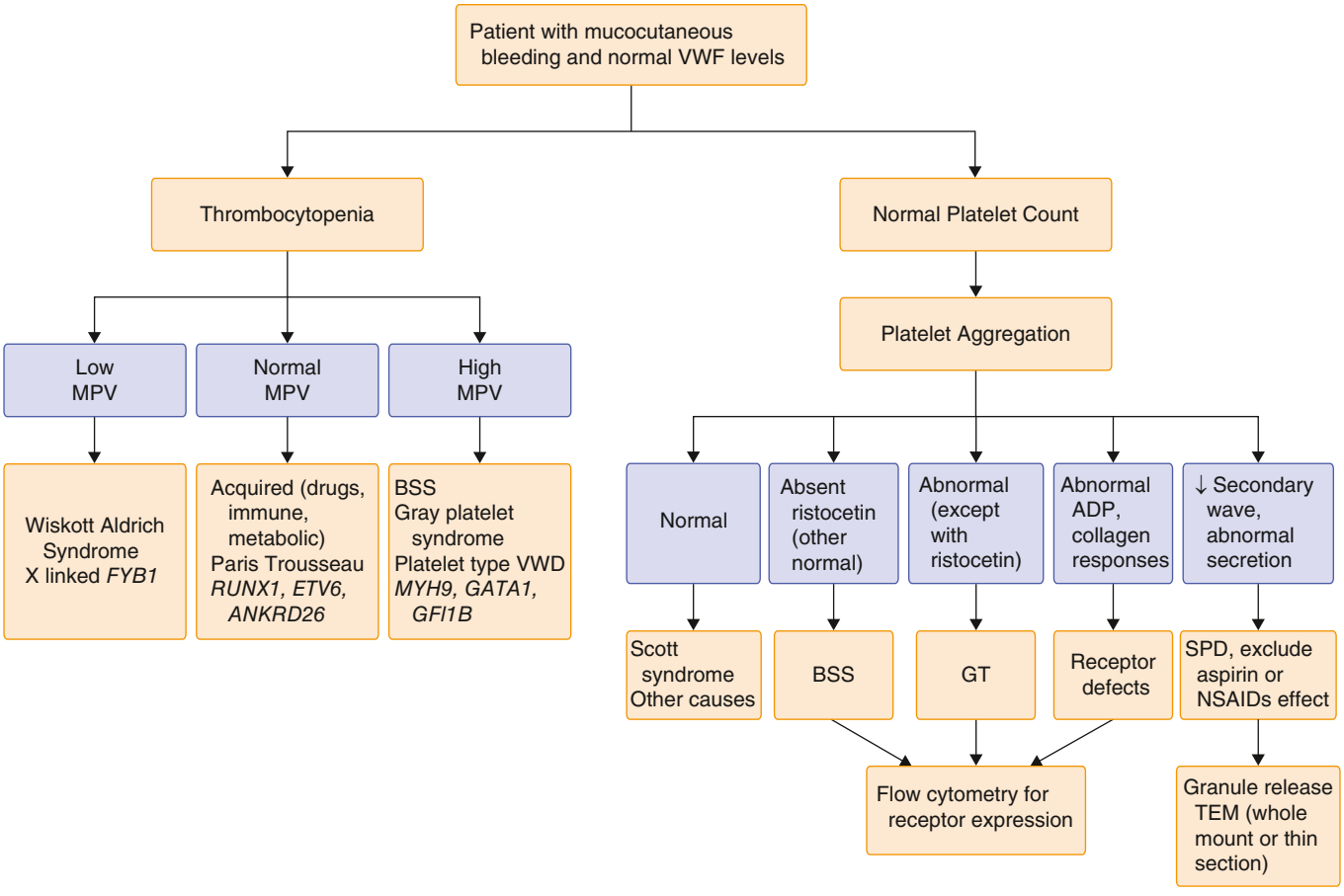

FIGURE 159-2. Platelet disorder diagnostic algorithm. ADP = adenosine diphosphate; BSS = Bernard-Soulier syndrome; GT = Glanzmann thrombasthenia; MPV = mean platelet volume; NSAIDs = nonsteroidal anti-inflammatory drugs; SPD = storage pool defect; TEM = transmission electron microscopy; VWD = von Willebrand disease.

PROGNOSIS

Some patients with type 1 and type 2 von Willebrand disease require specific treatment only around times of surgery, injury, or childbirth. However, other patients with severe type 1 and type 2 von Willebrand disease have recurrent lifelong bleeding issues that significantly impair their quality of life. Recurrent gastrointestinal bleeding often worsens with age, particularly in patients with type 2 VWD. Spontaneous joint bleeds can lead to progressive arthropathy in patients with type 3 VWD.

ACQUIRED VON WILLEBRAND SYNDROME

Acquired von Willebrand syndrome is an uncommon bleeding disorder that results from reduced plasma activity of von Willebrand factor in individuals who have no prior personal or family history of von Willebrand disease.[15] Acquired von Willebrand syndrome often occurs in association with underlying conditions, with 30 to 50% being associated with underlying lymphoproliferative disorders such as monoclonal gammopathy of undetermined significance (Chapter 173), multiple myeloma (Chapter 173), Waldenström macroglobulinemia (Chapter 173), non-Hodgkin lymphoma (Chapter 171), chronic lymphocytic leukemia (Chapter 168), and hairy cell leukemia (Chapter 168). Acquired von Willebrand syndrome has also been associated with a variety of other myeloproliferative disorders, autoimmune disorders, and malignancies. Mechanisms implicated in the pathogenesis of acquired von Willebrand syndrome include anti–von Willebrand factor antibodies that are associated with markedly enhanced clearance of von Willebrand factor. Cardiovascular disorders associated with pathological shear stress (e.g., aortic stenosis, extracorporeal membrane oxygenation, and left ventricular assist devices) can lead to loss of high-molecular-weight multimers due to enhanced proteolysis of von Willebrand factor by ADAMTS13.

TREATMENT

Management should focus primarily on treating any underlying conditions. Acute bleeding episodes can be difficult to manage and may be refractory to standard treatment options for von Willebrand disease. For example, although DDAVP and infusions of von Willebrand factor concentrate may cause an initial increase in levels of von Willebrand factor and factor VIII, these levels typically decline rapidly, so frequent monitoring is essential. Some patients with paraproteins may respond to intravenous immunoglobulin (IVIg), although responses in levels of von Willebrand factor and factor VIII may be delayed for several days. A combination of intravenous immunoglobulin and von Willebrand factor concentrate under expert supervision may be useful in managing elective procedures in some patients. Other treatment options include tranexamic acid, plasmapheresis, and recombinant factor VIIa.[16] Prognosis is generally determined by the prognosis of the underlying cause.

QUALITATIVE PLATELET DISORDERS

Inherited Platelet Bleeding Disorders

EPIDEMIOLOGY AND PATHOLOGY

Inherited disorders of platelet function are rare. These disorders include platelet receptor defects, platelet storage pool disorders, and a variety of other defects.

Each day, bone marrow megakaryocytes generate about 10^{11} anucleate platelets to maintain a platelet count of 150,000 to 450,000/μL. Platelets circulate in plasma and activate at sites of vascular injury to form a platelet clot. When the subendothelium is exposed due to injury, platelets bind to collagen, von Willebrand factor, and other extracellular matrix proteins via the von Willebrand factor receptor glycoprotein 1b/IX/V complex and collagen receptors such as $\alpha_2\beta_1$ and glycoprotein VI. This adhesion process triggers intracellular signaling events that lead to the activation of the fibrinogen receptor GPIIbIIIa, which is also known as integrin $\alpha_{2b}\beta_3$. The binding of fibrinogen leads to further signaling that causes platelets to change shape, granules to be released, and eventually the flipping of the membrane phospholipid layer to expose phosphatidyl serine, which provides docking sites for coagulation factors and ultimately supports the formation of a fibrin clot. In every step in the process, inherited platelet defects can compromise the performance and efficiency of these functions, thereby potentially leading to clinical bleeding.

CLINICAL MANIFESTATIONS

As with von Willebrand disease, bleeding associated with platelet disorders is often mucocutaneous (petechiae, purpura, ecchymoses, and hematomas), whereas joint or deep muscle bleeds are relatively uncommon. Affected women can have excessive menstrual bleeding (menorrhagia) and postpartum hemorrhage. Platelet dysfunction should also be suspected in the presence of increased bleeding following dental extraction, tonsillectomy, or other surgical procedures.

DIAGNOSIS

The bleeding assessment tool score used for von Willebrand disease is also useful in identifying patients with platelet function disorders, with a 99% probability if von Willebrand disease is excluded. A careful history may provide clues about whether the bleeding disorder is acquired or congenital, because platelet dysfunction may be related to other systemic disorders.

If studies for a plasma coagulation factor deficiency and von Willebrand disease are negative, functional platelet studies that should be performed at specialized centers include light transmission aggregometry, flow cytometry, and assays of platelet granule content and release (Fig. 159-2). Gene panels can test for inherited thrombocytopenias and disorders of platelet function in patients who have normal platelet counts, although the interpretation of such panels[17] can be challenging and they can miss large structural variants and deep intronic regions.[18]

SPECIFIC QUALITATIVE PLATELET DISORDERS

Platelet Receptor Defects

The most commonly diagnosed receptor defects are Bernard-Soulier syndrome and Glanzmann thrombasthenia. Other platelet receptor defects associated with clinical bleeding include defects in the thromboxane, adenosine diphosphate, and collagen receptors, but these deficiencies are extremely rare and described in only a few families or cases.[19]

Bernard-Soulier Syndrome

Bernard-Soulier syndrome is an autosomal recessive disorder characterized by macrothrombocytopenia and caused by deficiency or dysfunction of GP1b/IX/V complex due to mutations in *GP1BA*, *GP1BB*, and *GP9*. In this disorder, platelets respond poorly to ristocetin in platelet aggregation studies but respond normally to other commonly used agonists, such as adenosine diphosphate (ADP), arachidonic acid, collagen, and epinephrine. The clinical presentation can be variable, but mucocutaneous bleeding is typically present. Flow cytometry usually confirms the absence of the receptor on the platelet surface, although some forms can present with a hypofunctional receptor expressed at lower levels than normal. The monoallelic form is much less severe and is associated with large platelets and somewhat low platelet counts; it can be diagnosed only by flow cytometry or genetic studies.

Glanzmann Thrombasthenia

Glanzmann thrombasthenia, which is also an autosomal recessive disorder of platelet aggregation, is caused by mutations in the genes *ITGA2B* and *ITGB3* that encode for the fibrinogen receptor GPIIbIIIa. Although the clinical presentation is also variable, bleeding tends to be severe since childhood. Patients exhibit normal platelet counts and normal platelet structure. Platelet light transmission aggregometry shows a normal response to ristocetin because the GPIb/IX/V complex is preserved, but responses to ADP, collagen, epinephrine, and arachidonic acid are very depressed or absent. The diagnosis of Glanzmann thrombasthenia can be confirmed by flow cytometry for the GPIIbIIIa receptor density and genetic testing. The complete absence of the receptor is defined as type 1, whereas moderate decreases to 10 to 20% of normal are defined as type 2.

Platelet Granule Defects

Disorders of platelet granules are rare. The most commonly diagnosed platelet function disorder is the platelet dense granule storage pool deficiency, which is usually diagnosed by a combination of mild bleeding, abnormal platelet aggregation (lack of secondary wave), and a decrease in the number of dense granules assessed by wet mount or thin section transmission electron microscopy. Bleeding is usually mild but can be more severe. In the autosomal recessive Hermansky-Pudlak syndrome, up to 10 different genes can have mutations that cause different subtypes. In this syndrome, which is accompanied by ocular albinism, platelets are normal in number and size, but the number of dense granules is severely decreased or even absent. Some patients with specific subtypes also develop severe pulmonary fibrosis, ophthalmologic complications, granulomatous colitis, and immune defects.

TABLE 159-4 SOME COMMON AGENTS CAUSING ACQUIRED PLATELET DYSFUNCTION

TYPE OF AGENT	EXAMPLES
Antiplatelet agents	Aspirin, clopidogrel, prasugrel, ticagrelor, ticlopidine, abciximab, eptifibatide, tirofiban
Nonsteroidal anti-inflammatory agents	Ibuprofen, naproxen, indomethacin diclofenac, tolmetin, piroxicam
Selective serotonin reuptake inhibitors	Fluoxetine, paroxetine, sertraline
Plasma expanders	Dextrans, hydroxyethyl starch
Antihistamines	Chlorpheniramine, diphenhydramine
Foods and supplements	Vitamin E, fish oil, omega-3-fatty acids, alcohol, garlic, Chinese black tree fungus, ginger, cumin, turmeric, onion, cloves
Phosphodiesterase inhibitors	Cilostazol, dipyridamole, caffeine, theophylline, aminophylline, sildenafil

Data from Casari C, Bergmeier W. Acquired platelet disorders. *Thromb Res*. 2016;141(Suppl 2):S73-S75.

In Chédiak-Higashi syndrome (Chapters 153 and 231), a disorder of platelet dense granules is associated with oculocutaneous albinism, neutropenia, and severe immune deficiency. Patients also have large neutrophilic cytoplasmic inclusions and can develop life-threatening lymphohistiocytosis.

The autosomal recessive gray platelet syndrome is characterized by a complete absence of α-granules. This syndrome is caused by recessive loss of function mutations in *NBEAL2*. The platelets appear gray on a peripheral smear, and the diagnosis is confirmed by transmission electron microscopy. Although the bleeding diathesis is usually mild to moderate, the syndrome can be associated with splenomegaly and bone marrow fibrosis later in life. Other rare syndromes associated with abnormal α-granules are associated with mutations in *FLI1*, *GFI1B*, *STIM1*, and *GATA1*.

Other Inherited Platelet Function Disorders

Over 75 genes have been associated with inherited platelet disorders. These disorders are typically diagnosed on gene panels. Some of these disorders (e.g., mutations in *RUNX1*, *ETV6*, and *ANKRD26*) are associated with an increased risk of malignancies.

Acquired Platelet Dysfunction

The most common cause of acquired platelet dysfunction[20] is antiplatelet medications (Chapter 70), including aspirin, the thienopyridines (clopidogrel, prasugrel), nonthienopyridines P2Y12 inhibitors (ticagrelor, cangrelor), and the GPIIbIIIa inhibitors (tirofiban, eptifibatide, and abciximab). However, other drugs (Table 159-4) and dietary supplements can inhibit platelet function and result in easy bruising or bleeding.

Hematologic disorders such as paraproteinemias (Chapter 173), myeloproliferative neoplasms, and myelodysplastic syndrome (Chapter 167) can cause functional platelet disorders, sometimes accompanied by thrombocytopenia. Patients with end-stage renal disease (Chapter 116) or with liver failure (Chapter 140) often develop platelet dysfunction. Immune thrombocytopenic purpura also can be associated with platelet dysfunction owing to having antibodies against specific platelet receptors. Transient platelet dysfunction is seen during cardiac surgery with cardiopulmonary bypass.

TREATMENT

In most patients with congenital or acquired platelet disorders, transfusion of donor platelets is the recommended treatment. Unfortunately, patients who receive multiple platelet transfusions can become resistant because of immunity to platelet-specific or HLA-related antigens. In Glazmann thrombasthenia, alloimmunization can lead to a refractoriness to platelet transfusions; as a result, many experts prefer activated recombinant factor VIIa as the first line of treatment and reserve platelet transfusions for life-threatening bleeding.

DDAVP is effective in treating uremic bleeding and platelet dysfunction and may provide some benefit when individuals with a storage pool defect and Bernard-Soulier syndrome develop mild to moderate bleeding. Administration of DDAVP may cause fluid retention and hyponatremia, so precautions must be taken to prevent electrolyte imbalances.

Recombinant factor VIIa is useful in individuals with congenital and acquired disorders of platelet function, particularly in patients in whom platelet

transfusion is ineffective. Recombinant factor VIIa increases the generation of thrombin at the site of damage to the vessel wall, thereby enhancing the recruitment of platelets. In individuals who have excessive mucocutaneous bleeding and in patients who are undergoing surgical procedures involving tissues of high fibrinolytic activity (e.g., nose, mouth, throat, and extraocular tissues), ε aminocaproic acid (5 g orally followed 1 hour later by 1 to 1.25 g/hour orally for 8 hours or until bleeding is controlled; maximum dose of 30 g/day), or tranexamic acid (15 to 25 mg/kg orally three times daily) can be useful.

HEREDITARY VASCULAR HEMORRHAGIC DISORDERS

HEREDITARY HEMORRHAGIC TELANGIECTASIA

Hereditary hemorrhagic telangiectasia, also known as Osler-Weber-Rendu syndrome, is an autosomal dominant disease with an estimated prevalence of approximately 1 in 5000. Hereditary hemorrhagic telangiectasia is characterized by vascular malformations involving the skin, nose, and gastrointestinal tract.

PATHOBIOLOGY

Sequence variations in a number of distinct genetic loci have been implicated in the pathogenesis of hereditary hemorrhagic telangiectasia. The affected genes encode proteins involved in regulating the signaling of the transforming growth factor (TGF-)β superfamily within endothelial cells.[21] A majority of patients (about 85%) have mutations of *ENG*, which encodes endoglin, or *ACVRL1*, which encodes activin receptor-like kinase (ALK1). Cumulatively, more than 500 different mutations of *ENG* or *ACVRL1* have been identified. Although all classical features can be seen in patients with either *ENG* (hereditary hemorrhagic telangiectasia type 1) or *ACVRL1* (hereditary hemorrhagic telangiectasia type 2) mutations, some genotype-phenotype correlations have been reported. For example, pulmonary and cerebral anterior venous malformations appear to be more common in type 1. Mutations affecting SMAD4 have also been described in a minority (2 to 3%) of patients and are associated with a concomitant precancerous state of juvenile polyposis.

CLINICAL MANIFESTATIONS

Vascular abnormalities are typically visible on the face and fingers (Fig. 159-3). Telangiectasia in the nose is associated with regular episodes of epistaxis that can be prolonged and severe in nature, and telangiectasia in the bowel can cause significant gastrointestinal bleeding (Chapter 121). As a result of recurrent bleeding, patients commonly have secondary iron-deficiency anemia (Chapter 145). The majority of patients with hereditary hemorrhagic telangiectasia also develop larger arteriovenous malformations within the brain, lungs, and liver. These malformations can contribute to pulmonary artery hypertension (Chapter 69), high-output heart failure (Chapter 45), and an increased risk for venous thrombosis.

DIAGNOSIS

Epistaxis and telangiectasias constitute the most common symptoms and signs of hereditary hemorrhagic telangiectasia and are part of standardized diagnostic criteria (Table 159-5). Telangiectasias and risk of gastrointestinal bleeding tend to become more apparent with aging, but the clinical diagnosis can be challenging in younger individuals, in whom genetic testing can be definitive.[22]

TABLE 159-5 DIAGNOSTIC CRITERIA FOR HEREDITARY HEMORRHAGIC TELANGIECTASIA

Recurrent spontaneous epistaxis
Multiple skin telangiectasias
Arteriovenous malformations (e.g., in lungs, brain, stomach, liver, intestines, spinal cord)
First-degree relative with the disease

Definitive disease = 3 or more criteria; possible disease = 2 criteria.

TREATMENT

Patients with epistaxis should use moisturizing topical therapies to humidify the nasal mucosa. Timolol gel (0.5 mL of 1% gel twice daily by syringe)[A2] and bevacizumab (7.5 mg/kg intravenously every 2 weeks)[A3] may be useful. Oral tranexamic acid (1 g three times daily) under expert guidance is effective, and local ablative therapies may be useful for significant epistaxis.[23] Patients with gastrointestinal bleeding require endoscopic evaluation (Chapter 120). Hemoglobin and ferritin levels should be closely monitored, and adequate iron replacement therapy must be given.

EHLERS-DANLOS SYNDROME

Ehlers-Danlos syndrome, which also can cause blood vessel rupture, is discussed in Chapter 239.

ACQUIRED VASCULAR HEMORRHAGIC DISORDERS

Patients with acquired vascular hemorrhagic disorders typically have no prior personal or family history of bleeding. Henoch-Schönlein purpura (Chapter 406) typically presents with a palpable lower extremity purpura, associated with arthralgias, abdominal pain, and renal injury. Scurvy (Chapter 199) typically presents with petechiae or bruising and with tiny perifollicular hemorrhages around corkscrew hairs. In senile purpura, diminished vascular support owing to aging and sun exposure result in easy bruising, especially on the dorsa of hands, forearms, and lower legs.

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For the General References and other additional features, please visit Elsevier eBooks+ at https://ebooks.health.elsevier.com.

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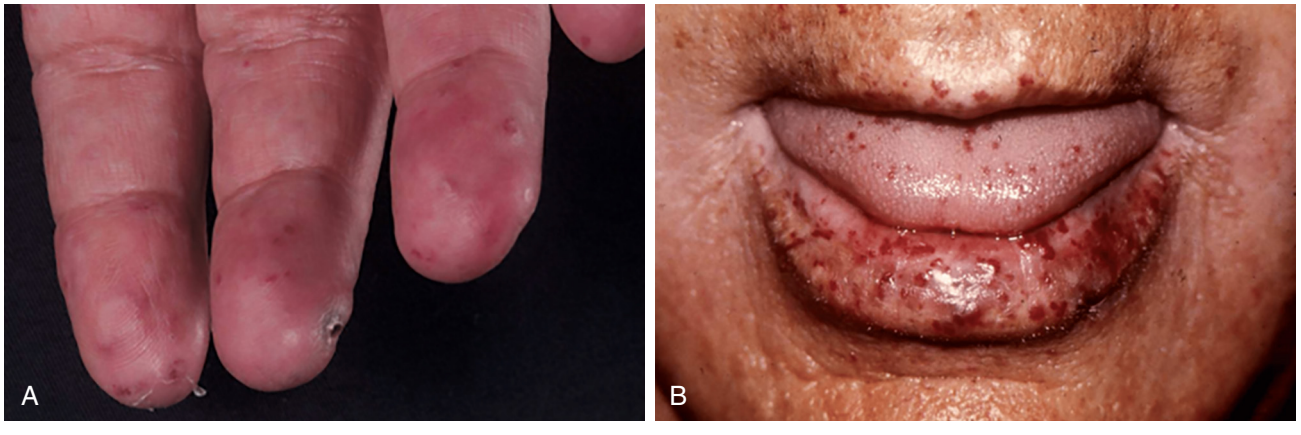

FIGURE 159-3. Hereditary hemorrhagic telangiectasia (HHT). Telangiectasias commonly occur on the fingers (A); face, lips, and tongue (B); and in other areas, including the nasal and gastrointestinal mucosa, and may develop in certain other internal organs. Skin or mucous membrane lesions typically blanch with pressure in contrast to petechiae, which do not. (A, Copyrighted and used with permission of the Mayo Foundation for Medical Education and Research, all rights reserved. B, Courtesy of Dr. Andrew Schafer.)

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160 COAGULATION FACTOR DEFICIENCIES

MARGARET V. RAGNI

COAGULATION DEFICIENCIES

Severe coagulation deficiencies, or coagulopathies, are typically characterized by spontaneous or provoked bleeding, such as during surgery or trauma, and may result in life- or limb-threatening complications. By contrast, moderate and mild coagulopathies may remain clinically silent until they are detected coincidentally on routine laboratory screening tests (e.g., prothrombin time [PT], activated partial thromboplastin time [aPTT]), or when these tests are ordered to evaluate the cause of abnormal bleeding or bruising.

In general, coagulopathies may result from inadequate synthesis of coagulation factor proteins or from inhibition of activated factor proteins by acquired antibodies or anticoagulant medications. Qualitative defects, either congenital or acquired, may also result in bleeding.

Much of the morbidity of coagulopathies can be minimized or avoided altogether by prophylactic replacement of the deficient clotting factor proteins. In contrast to the lifelong clinical manifestations of hereditary or congenital coagulopathies, acquired deficiencies usually appear acutely in previously asymptomatic individuals; they may not be suspected and often remit spontaneously or after eradication of an inciting disease state or withdrawal of an offending medication. Acquired coagulation disorders may be associated with more severe bleeding than congenital disorders, in part because of the delay in diagnosis.

HEREDITARY HEMOPHILIAS

DEFINITION

Hemophilia A and hemophilia B are caused by deficiencies or defects in clotting factor VIII (antihemophilic factor) and factor IX (antihemophilic factor B, or Christmas factor), respectively.[1] A deficiency of either of these intrinsic coagulation pathway proteins results in inadequate formation of thrombin at sites of vascular injury.

EPIDEMIOLOGY

Hemophilia A and B are sex-linked recessive disorders estimated to occur in 1 in 5000 and 1 in 30,000 male births, respectively. The higher incidence of hemophilia A may be due to the greater amount of DNA at risk for mutation in the large factor VIII gene (186,000 base pairs) compared with the factor IX gene (34,000 base pairs). Hemophilia A and B are observed in all racial and ethnic groups, and more than 20,000 individuals are affected in the United States. A substantial proportion (30%) of hemophilia cases arise as new, spontaneous mutations. Overall, the hemophilias are much more common than the autosomal recessive coagulation disorders (see later), which often affect progeny from consanguineous relationships and require the inheritance of two defective alleles for the bleeding manifestations to become evident.

PATHOBIOLOGY

Genetics

As with other sex-linked recessive diseases, the genes for factor VIII and factor IX are located on the long arm of the X chromosome. Males with a defective allele on their single X chromosome transmit this gene to all their daughters, who are then obligate carriers, but to none of their sons. Because the offspring of female carriers inherit one affected X chromosome, half of their sons develop the coagulation disorder, and half of their daughters are obligate carriers. Female carriers may manifest bleeding symptoms, particularly postpartum bleeding, if the alleles on the X chromosome are unequally inactivated (lyonization), if the defective hemophilic allele is expressed in preference to the normal allele, and if plasma factor VIII levels are below 50%. Female hemophilia may arise as a result of mating between a hemophilic male and a female carrier (homozygous for the defective factor VIII or IX gene) or in carrier females who have the 45,XO karyotype (Turner syndrome) and are hemizygous for the defective hemophilia gene.

No single mutation is responsible for the hemophilias. Many missense and nonsense point mutations, deletions, and inversions have been described. Severe molecular defects predominate, with 40 to 50% of all cases of severe hemophilia A evolving from a unique inversion of intron 22 (the largest of the factor VIII introns). This inversion results from the recombination and translocation of DNA within intron 22 of the factor VIII gene, with areas of extragenic but homologous "nonfunctional" DNA located at a distance from intron 22. Other less common severe molecular defects include large gene deletions (5 to 10% of cases) and nonsense mutations (10 to 15% of cases). The encoded proteins resulting from these mutations are defective and do not express any factor VIII activity. Mild or moderate hemophilia A is commonly associated with point mutations and deletions. In contrast, factor IX mutations are more diverse, and severe hemophilia B is more likely caused by large deletions. Mutated clotting factor genes responsible for the hemophilias may also encode for the production of defective nonfunctional proteins that circulate in the plasma and are detected at normal quantitative levels by immunoassays but not by functional activity assays. A listing of the mutations that cause the hemophilias can be accessed via the Human Gene Mutation Database (www.hgmd.org).

CLINICAL MANIFESTATIONS

Hemophilia A and hemophilia B are clinically similar, with clinical severity corresponding inversely to the circulating levels of plasma coagulant factor VIII or IX activity. However, hemophilia A is associated with a higher frequency of bleeding, a greater need for factor replacement therapy, and more frequent hospitalizations, thereby suggesting greater clinical severity than in hemophilia B. Individuals with less than 1% of normal factor VIII or IX activity are classified as having "severe" disease, which is characterized by frequent spontaneous bleeding events in joints (hemarthrosis) and soft tissues and by profuse hemorrhage with trauma or surgery. Although spontaneous bleeding is uncommon in mild deficiencies (>5% normal activity), excess bleeding typically occurs with trauma or surgery. A moderate clinical course is associated with factor VIII or IX levels between 1 and 5%. Approximately 60% of all cases of hemophilia A are clinically severe, whereas only 20 to 45% of cases of hemophilia B are severe.

Severe hemophilia is typically suspected and diagnosed during infancy in the absence of a family history. Among newborns, intracranial hemorrhage is the leading cause of morbidity and mortality, with a cumulative incidence of about 4%. Intracranial hemorrhage does not appear to be related to the mode of delivery, although half of such hemorrhages occur in the newborn period. Circumcision within days after birth is accompanied by excessive bleeding in less than half of severely affected boys. The first spontaneous hemarthrosis in severely affected hemophilic boys usually occurs between 9 and 18 months of age, when ambulation begins. In moderately affected individuals, it generally does not occur until 2 to 5 years of age. The knees are the most prominent sites of spontaneous bleeds, followed by the elbows, ankles, shoulders, and hips; wrists are less commonly involved. Female carriers may also sustain joint bleeding and hemarthrosis, often unrecognized until years later, with sports and/or trauma.

Acute hemarthroses (Fig. 160-1) originate from the subsynovial venous plexus underlying the joint capsule and produce a tingling or burning sensation, followed by the onset of intense pain and swelling. On physical examination, the joint is swollen, hot, and tender to palpation, with erythema of the overlying skin. Joint mobility is compromised by pain and stiffness, and the joint is usually maintained in a flexed position.

FIGURE 160-1. Acute hemarthrosis of the knee is a common complication of hemophilia. It may be confused with acute infection unless the patient's coagulation disorder is known, because the knee is hot, red, swollen, and painful. (From Forbes CD, Jackson WF. *Color Atlas and Text of Clinical Medicine*, 3rd ed. London: Mosby; 2003.)

ABSTRACT

Rare congenital and acquired bleeding disorders require an understanding of their coagulation pathways, clinical manifestations, and strategies for prevention and treatment of bleeding. Recombinant factor therapies, some with an extended half-life, and novel therapeutics are FDA approved or in clinical trials. Adeno-associated virus (AAV) gene therapy is achieving durable factor expression, and gene editing is underway in animal models. Both of these approaches could reduce or eliminate the need for the infusion of factors in the future.

KEYWORDS

hemophilia A
hemophilia B
rare congenital bleeding disorders
acquired bleeding disorders
coagulation factor treatment
lupus anticoagulant
antiphospholipid syndrome

Recurrent or untreated bleeds result in chronic synovial hypertrophy and, eventually, damage to the underlying cartilage, with subsequent subchondral bone cyst formation, bony erosion, and flexion contractures. Abnormal mechanical forces from weight bearing can produce subluxation, misalignment, loss of mobility, and permanent deformities of the lower extremities (Fig. 160-2). These changes are accompanied by chronic pain, swelling, arthritis, and disability. Plain radiographs and clinical examination of chronic hemarthroses often underestimate the extent of bone and joint damage; serial magnetic resonance imaging is the most sensitive technique to detect and monitor early and progressive disease, and early musculoskeletal ultrasound, performed in the office setting, may detect early joint disease even before symptoms occur.

Intramuscular hematomas account for about 30% of hemophilia-related bleeding events and are rarely life-threatening. Hematomas are usually precipitated by physical or iatrogenic trauma (e.g., after intramuscular injections) and may compromise sensory and motor function or arterial circulation if they entrap and compress vital structures in closed fascial compartments. The latter occurrence, termed *compartment syndrome*, presents with the rapid onset of swelling and severe pain in an extremity, unrelieved by factor infusion and standard analgesics, and is considered a medical emergency that may require fasciotomy to preserve tissue viability and provide pain relief. Retroperitoneal hematomas may be confused clinically with appendicitis or hip bleeds but should be suspected in a patient who is unable to stand erect due to the pain of muscle extension in the presence of hematoma. Immediate and aggressive treatment is required to prevent permanent anatomic deformity, such as flexion contracture, nerve damage, or pseudotumor formation (expanding hematomas that erode and destroy adjacent skeletal structures).

Bleeding from mucous membranes is not uncommon and when it involves the tongue or the retropharyngeal space, may threaten the airway. Gastrointestinal hemorrhage typically originates from anatomic lesions proximal to the ligament of Treitz and may be exacerbated by esophageal varices and/or thrombocytopenia secondary to cirrhosis and portal hypertension, or by the use of nonsteroidal anti-inflammatory drugs (NSAIDs) for the treatment of hemarthroses. Spontaneous bleeding in the genitourinary tract may arise from ureteral clots, renal stones, and/or less commonly, infection.

Intracranial bleeds occur in 10% of patients with a risk of 2% per year; they may be spontaneous or traumatic and are fatal in 30% of cases. Neuromuscular defects, seizure disorders, and intellectual deficits may ensue.

DIAGNOSIS

The diagnosis of hemophilia is suspected on the basis of a family and personal bleeding history and laboratory detection of prolongation of the aPTT (with normal PT). It is confirmed by significantly reduced plasma factor VIII or IX activity. As noted in Chapter 157, the aPTT is not a sufficiently sensitive screening test to be prolonged in mild hemophilia, where the factor VIII level is sometimes greater than 30% of normal. Severe hemophilia is usually recognized in infancy, with circumcision bleeding; by contrast, moderate or mild disease is recognized later in life after trauma or surgery. Hemophilia can be distinguished from von Willebrand disease (VWD; Chapter 159) by normal ristocetin cofactor and von Willebrand factor antigen levels. In type 2N VWD, the factor VIII level is significantly lower than ristocetin cofactor and von Willebrand factor antigen levels due to reduced factor VIII binding; this variant of VWD may require genotyping to distinguish it from hemophilia A. Other congenital intrinsic factor deficiencies (e.g., factor XI and XII) can be determined by coagulation factor–specific assays. Vitamin K deficiency (see later and Chapter 161) can be detected by the associated PT prolongation; deficiencies of factors II, VII, IX, and X; and resolution of the coagulation defect with vitamin K. The presence of heparin can be confirmed by correction of the aPTT after running the sample over a heparin absorption column. Failure of the aPTT to correct in a 1:1 mix with normal plasma suggests the presence of an inhibitor; specific inhibitors are associated with a single decreased factor level (usually factor VIII; see Alloantibody Inhibitors to Factors VIII and IX under Treatment), whereas blocking inhibitors cause nonspecific factor level changes associated with a positive hexagonal lipid assay (see Antiphospholipid Syndrome and Lupus Anticoagulant).

FIGURE 160-2. Severe chronic arthritis in hemophilia. The knee is the most commonly affected joint. Both knees are severely deranged in this patient. Note that the patient is unable to stand with both feet flat on the floor. (From Forbes CD, Jackson WF. *Color Atlas and Text of Clinical Medicine*, 3rd ed. London: Mosby; 2003.)

TREATMENT AND PREVENTION

General Care

Individuals with hemophilia cared for at hemophilia treatment centers have lower mortality and reduced costs of care compared with those receiving treatment elsewhere. The chronic care model practiced at hemophilia treatment centers emphasizes prevention to reduce joint disease and complications, optimization of factor dosing, counseling regarding safe sports, and the avoidance of aspirin and other drugs that inhibit platelet function, as well as management of surgical procedures and chronic transfusion-transmitted infections, including hepatitis C and HIV infection.

Treatment and Prevention of Bleeding

Replacement of Clotting Factors

Treatment and prevention of acute bleeding events in hemophilia A and B are based on replacement of the missing or deficient clotting factor protein to restore adequate hemostasis (Table 160-1). Use of factor on a prophylactic basis several times weekly to prevent bleeds can reduce or prevent joint bleeds and reduce joint arthropathy. All clotting factor concentrates available in the United States, whether plasma-derived or genetically engineered, are considered extremely safe; none has been implicated in the transmission of bloodborne viral pathogens or prions.

The goal of replacement therapy (see Table 160-1) is to achieve plasma factor VIII or IX activity levels that are sufficient to prevent spontaneous bleeds. As these events are individualized and vary by age, level of activity, and pharmacokinetics, the optimal level of treatment may vary among affected patients. In general, however, activity levels of 15% are sufficient to prevent spontaneous bleeding, whereas factor activity levels of 25 to 30% are recommended to treat minor spontaneous or traumatic bleeds (e.g., hemarthroses, persistent hematuria). At least 50% clotting factor activity levels are recommended for severe bleeds (e.g., major dental surgery, maintenance replacement therapy after major surgery or trauma), and 80 to 100% activity for any life-threatening or limb-threatening hemorrhagic event (e.g., major surgery, trauma). After major trauma or if visceral or intracranial bleeding is suspected, replacement therapy adequate to achieve 100% clotting factor activity should be administered immediately (within 5 to 10 minutes) *before* diagnostic procedures are initiated.

To calculate the initial dose of replacement factor, plasma factor VIII activity generally increases about 2% (0.02 IU/mL) for each unit of factor VIII administered per kilogram of body weight, and factor IX activity increases about 1% (0.01 IU/mL) for each unit of factor IX administered per kilogram of body weight. Therefore, a 70-kg individual with severe hemophilia A or B (factor VIII or IX activity <1% of normal) who requires replacement to 100% activity for major surgery should initially receive 3500 IU of factor VIII or 7000 IU of factor IX concentrate. The circulating half-lives of factors VIII and IX require subsequent dosing at half the initial dose every 8 to 12 hours for factor VIII and every 18 to 24 hours for factor IX, respectively. However, this empirical dosing should be individualized according to the patient's peak recovery and trough activity levels, using population pharmacokinetic modeling. The frequency of repeat dosing is also determined by the rapidity of pain relief, recovery of joint function, and resolution of active bleeding. Heterogeneity in the half-life of factor VIII concentrates is due to variability in clearance of von Willebrand factor.[2]

Replacement is usually maintained for at least 10 to 14 days after major surgery to allow proper wound healing and to avoid postoperative bleeding. In

TABLE 160-1 FDA-APPROVED COAGULATION PROTEINS AND REPLACEMENT THERAPIES AVAILABLE IN THE UNITED STATES

COAGULATION PROTEIN DEFICIENCY	INHERITANCE PATTERN	PREVALENCE	MINIMUM HEMOSTATIC LEVEL	REPLACEMENT SOURCES
Factor I (fibrinogen) Afibrinogenemia Dysfibrinogenemia	 Autosomal recessive Autosomal dominant or recessive	 Rare (<300 families) Rare (>300 variants)	50-100 mg/dL	Cryoprecipitate, FFP, fibrinogen concentrate
Factor II (prothrombin)	Autosomal dominant or recessive	Rare (25 kindreds)	30% of normal	FFP, factor IX complex concentrates
Factor V (labile factor)	Autosomal recessive	1 in 1 million births	25% of normal	FFP
Factor VII	Autosomal recessive	1 in 500,000 births	25% of normal	Recombinant factor VIIa (15-20 μg/kg), FFP, factor IX complex concentrates
Factor VIII (antihemophilic factor)	X-linked recessive	1 in 5000 male births	80-100% for surgery/life-threatening bleeds, 50% for serious bleeds, 25-30% for minor bleeds	Factor VIII concentrates (recombinant and recombinant extended-half-life factor VIII preferred)
Von Willebrand disease (also see Chapter 159) Type 1 and 2 variants Type 3	 Usually autosomal dominant Autosomal recessive	 1% prevalence 1 in 1 million births	>50% VWF antigen and ristocetin cofactor activity	DDAVP for mild to moderate disease (except type 2B; variable response in 2A); cryoprecipitate and FFP (not preferred, except in emergencies); plasma-derived factor VIII/VWF concentrate, viral attenuated, intermediate purity; recombinant VWF concentrate (the latter two proteins preferred for surgery, for disease unresponsive to DDAVP and for type 3)
Factor IX (Christmas factor)	X-linked recessive	1 in 30,000 male births	25-50% of normal, depending on extent of bleeding, surgery	Factor IX concentrates (recombinant and recombinant extended half-life factor IX preferred); FFP not preferred except in dire emergencies
Factor X (Stuart-Prower factor)	Autosomal recessive	1 in 500,000 births	10-25% of normal	Plasma-derived factor X concentrate, FFP, or factor IX complex concentrates
Factor XI (hemophilia C)	Autosomal dominant; severe type is recessive	4% of Ashkenazi Jews; 1 in 1 million general population	20-40% of normal	FFP or factor XI concentrate
Factor XII (Hageman factor), prekallikrein, high-molecular-weight kininogen	Autosomal recessive	Not available	No treatment necessary	—
Factor XIII (fibrin stabilizing factor)	Autosomal recessive	1 in 3 million births	5% of normal	Recombinant FXIII concentrate, FFP, cryoprecipitate, or viral-attenuated factor XIII concentrate

DDAVP = desmopressin; FDA = U.S. Food and Drug Administration; FFP = fresh-frozen plasma; VWF = von Willebrand factor.

the management of bleeds or surgical procedures in patients with hemophilia, either repetitive bolus injections, as described earlier, or continuous infusion can be used for delivery of clotting factor replacement. The latter can provide constant levels of the deficient coagulation factor and can be cost-effective. Extended half-life recombinant factor VIII and IX[3] (including pegylated, albumin-fusion, nonacog alfa [factor IX], or Fc-fusion [Fc domain of immunoglobulin G_1, IgG_1]) are also available for prophylaxis or treatment, as they are safe and effective in reducing bleed frequency and prolong half-life 1.5- to 2-fold for factor VIII and 2.5- to 5.0-fold for factor IX. These agents have also been used successfully in surgery, but they are costly and may not be available at many hospitals. The typical dose frequency for extended half-life recombinant factor VIII is twice weekly at a dose of 50 to 65 IU/kg; for extended half-life recombinant factor IX, the dose is once every 1 to 2 weeks at a dose of 100 IU/kg.

Other Approaches to Augment Clotting

Nonfactor therapeutics given by subcutaneous administration also can be used as prophylaxis to prevent clinical bleeding. Emicizumab, which is the only such agent currently FDA-approved, is a bispecific monoclonal antibody that bridges activated factor IX and factor X to replace the function of missing activated factor VIII, whether due to a factor VIII inhibitor or factor VIII deficiency in hemophilia A. Emicizumab prophylaxis (1.5 mg/kg subcutaneously weekly or 3.0 mg/kg every 2 weeks, or 6.0 mg/kg every 4 weeks) is effective in reducing clinical bleeding in hemophilia A among patients of all ages, with or without inhibitors.[A1–A3] However, emicizumab is effective only for prevention but not for the treatment of acute bleeds. For acute treatment of bleeds or surgery in patients receiving emicizumab, factor replacement is required urgently. A novel intravenous factor VIII fusion protein, efanesoctocog alfa, in which recombinant factor VIIIFc is fused to von Willebrand factor, results in a four-fold increase in the half-life of factor VIII, thereby suggesting the possibility of weekly intravenous dosing.[4]

Hemarthroses

For hemarthroses, immediate or early replacement of the deficient clotting factor to normal hemostatic levels rapidly reverses the pain, whereas delayed treatment results in excess pain, morbidity, and joint damage. Optimal management once a bleed occurs includes rest, ice, (factor) concentrate, and elevation,[5] as well as protective mechanotherapy for balanced and incremental rehabilitation of injured tissues.[6]

The moderate or severe pain that accompanies acute hemarthroses responds to immediate analgesic relief. Narcotic analgesics, such as codeine or synthetic derivatives of codeine, are avoided because of their addictive potential, and early consultation with pain service physicians is recommended. Chronic acetaminophen analgesia, although helpful in low doses, may be associated with hepatic toxicity as higher doses are used, especially in patients with chronic hepatitis. For some patients compliant with prophylaxis, nonsteroidal anti-inflammatory drugs (NSAIDs; Table 26-4) may be used provided that bleeding does not occur. Aspirin (ASA) is generally contraindicated as it irreversibly inhibits platelet aggregation.

Over 75% of children and about 50% of adults engage in prophylaxis (preventive) factor infusions several times a week to maintain factor VIII or IX levels above 1% to prevent joint bleeds and the development of chronic hemophilic arthropathy. However, prophylaxis must be initiated before 4 years of age, the earlier the better, and in the absence of obesity to preserve joint motion.[7] For

optimal outcomes, the patient and/or parent should be involved in decision making and the treatment plan.[8]

Although prophylaxis is the optimal strategy to prevent pain, reduced motion, and the disability of end-stage joint destruction, when prophylaxis has failed or was never initiated, surgery may be recommended. Synovectomy through open surgery or arthroscopy removes the inflamed tissue and may decrease pain and reduce recurrent bleeding, but usually only temporarily. Nonsurgical synovectomy (synoviorthosis), which involves the intra-articular administration of a radioisotope, may be considered in high-risk patients and for patients who have alloantibody inhibitors to factor VIII or IX (see later). Neither synovectomy nor synoviorthosis reverses joint damage, but both procedures may delay its progression. Non–weight-bearing exercises, such as swimming and isometrics, are important for periarticular muscle development and maintenance of joint stability for ambulation. Intractable pain and severe joint destruction secondary to repeated hemorrhage require prosthetic replacement. Chronic ankle pain responds best to open surgical or arthroscopic fixation and fusion (arthrodesis).

Genitourinary Bleeding

For genitourinary bleeding, clotting factor, fluid replacement, and, in children, a short course of steroids may be helpful to hasten resolution. However, genitourinary tract bleeding in patients with hemophilia may be worsened by the use of antifibrinolytic agents.

Alloantibody Inhibitors to Factors VIII and IX

Alloantibodies to infused factor VIII or, less frequently, to factor IX are usually detected in childhood after a median of 9 to 12 exposures to clotting factor. The prevalence of factor VIII alloantibodies among hemophilia A patients is 15 to 25%, whereas the prevalence of factor IX alloantibodies among hemophilia B patients is 1.5 to 3%.

Inhibitors are associated with hospitalization, cost, and early death. Inhibitors occur preferentially in patients who have a family history of inhibitors, patients who have large multidomain factor VIII and factor IX gene deletions, and in Black and Hispanic patients, but it is difficult to predict in whom inhibitors will develop. Among Black patients, gene sequence data suggest that mismatched factor VIII transfusions may account for the high risk of developing inhibitors. Nongenetic risk factors include early high-intensity or frequent daily exposure to factors to treat a bleed, trauma, or surgery. In previously untreated patients, the risk of developing inhibitors appears to be higher with recombinant than with plasma-derived factor.[A4]

Factor VIII–specific IgG1 antibodies appear first, followed by IgG3 and IgG4 antibodies. However, the appearance of factor VIII–specific IgG3 antibodies is always associated with the subsequent diagnosis of factor VIII inhibitors.[9]

The development of an alloantibody inhibitor is suspected when replacement therapy is ineffective in controlling bleeding symptoms. These antibodies completely neutralize clotting factor activity and prevent or reduce any increment in factor VIII or IX levels following bolus infusions of concentrate. Inhibitors are also associated with anaphylaxis and nephrotic syndrome.

Characterized as time and temperature dependent, inhibitors are quantitated in Bethesda units (BU). By definition, 1 BU is the amount of inhibitor that neutralizes 50% of the specific clotting factor activity in normal plasma. High responders, or patients with high-titer inhibitors (≥5 BU), mount an anamnestic antibody response to factor VIII clotting factor protein, usually within 5 to 7 days after subsequent exposure, and are no longer responsive to infused factor VIII. By contrast, low responders, or patients with low-titer inhibitors (<5 BU), do not manifest anamnesis, and such low-titer inhibitors can readily be overwhelmed by large amounts of human factor VIII or factor IX concentrate and can be successfully treated with three to four times the usual factor dose.

Management of patients with high-titer inhibitors[10] requires both assurance of hemostasis using bypass therapy and eradication of inhibitor formation (see Table 160-1). Bypass is typically accomplished with factor VIII inhibitor bypass activity (FEIBA; a plasma concentrate containing activated proenzymes of the prothrombin complex factors, prothrombin, and factors V11, IX and X). The usual treatment consists of one dose of FEIBA (75 IU/kg) or two doses of recombinant factor VIIa (90 to 270 μg/kg), although some patients may respond better to one agent than the other. Sequential use of FEIBA and recombinant factor VIIa (e.g., alternating every 6 hours) can improve hemostasis over single-agent treatment, but careful monitoring for thrombosis is necessary. The total dose of FEIBA should not exceed 20,000 IU in 24 hours.

Secondary prophylaxis in adults, with either recombinant factor VIIa, 90 μg/kg daily, 270 μg/kg daily, or FEIBA 85 IU/kg weekly, may significantly reduce bleeding rates as compared with on-demand treatment. Because neither agent is very effective alone and is limited by either total dose or dose frequency (VIIa must be given every 2 to 3 hours), these bypass agents may be alternated in selected patients (without cardiovascular risk, obesity, hypertension) every 3 hours for severe bleeds, surgery, or trauma. Alternatively, emicizumab prophylaxis (1.5 mg/kg subcutaneously weekly) may reduce bleeding events and improve quality of life compared with no prophylaxis in adults and children who have hemophilia A and have inhibitors.[A5,A6] By avoiding the need for factor VIII, inhibitor titers often decline.[11] Whether emicizumab and extended half-life agents such as recombinant factor VIIIFc will shorten the time to tolerance is currently uncertain. FEIBA should be avoided in patients who are receiving emicizumab because the combination increases the risk of thrombosis and thrombotic microangiopathy.

Eradication of inhibitors with immune tolerance induction is effective in about 75% of patients if initiated within 12 months of the detection of inhibitors. Immune tolerance induction regimens consist of daily factor concentrates (e.g., 200 IU/kg daily) to accomplish desensitization to infused factor. Immune tolerance induction is initiated as soon as the inhibitor is detected.[12] Maintenance of tolerance following induction usually, but not always, requires factor VIII or IX prophylaxis. Single or combination immunosuppressive agents (e.g., rituximab, mycophenolate, or cyclosporine) are variably effective. Other novel agents that promote thrombin generation by alternate pathways, including siRNA-antithrombin (fitusiran) and anti-TFPI, are in clinical trials to assess their safety and efficacy as potential bypass agents.[13] Preliminary data suggest bleeding frequency and factor use with these agents are reduced in inhibitor and noninhibitor patients.

Factor Concentrate–Transmitted Viral Infections

The prevalence of hepatitis C virus infection is about 90% in patients who were transfused from the late 1970s through the mid-1980s, and the prevalence of human immunodeficiency virus (HIV) infection is about 80% in patients who were transfused with factor VIII products and 50% in patients who were transfused with factor IX products from 1978 through the mid-1980s. Patients with HIV now can be controlled with highly active antiretroviral therapy (Chapter 357). Chronic hepatitis C infection (Chapter 135) remains the leading cause of death in hemophilia, in part because antiviral therapy does not prevent hepatocellular cancer in patients who have had long-standing chronic infection.

Ancillary and Other Therapies

Ancillary treatment strategies for the hemophilias include antifibrinolytic agents, such as ε-aminocaproic acid (50 mg/kg 3 to 4 times daily) or tranexamic acid (3 or 4 g orally daily in divided doses), to minimize mucous membrane bleeding, particularly in the oral cavity, and the application of fibrin glue to bleeding sites. Desmopressin (DDAVP) can be administered by nasal insufflation 30 minutes before a scheduled surgical procedure (one spray per nostril, to provide a total dose of 300 μg; or, in patients weighing less than 50 kg, 150 μg administered as a single spray). DDAVP may also be administered intravenously (dissolved in 50 mL normal saline) over 30 minutes at a dose of 0.3 μg/kg. DDAVP is especially useful in patients with mild hemophilia A because an adequate incremental rise in factor VIII activity can circumvent the use of clotting factor concentrates, and is generally available in most emergency department settings. Oral and intravenous fluid must be restricted to less than 1000 mL in any 24-hour period that DDAVP is administered whether to avoid hyponatremia and hyponatremic seizures. Other complications of DDAVP include facial flushing and tachyphylaxis (loss of response after three consecutive daily doses).

Gene Therapy for Hemophilia A and B

The hereditary hemophilias are model diseases for gene therapy[14] because they are caused by specific, well-defined gene mutations. A small, incremental rise in the synthesis of clotting factors can lead to substantially improved treatment and quality of life and inadvertent overexpression by successful gene transfer would not be detrimental.[15] Various adeno-associated (AAV) viral vectors carrying the Padua (FIX R338L) factor IX gain-of-function transgene in hemophilia B patients can achieve factor IX expression of 14 to 76% for up to 10 years.[16] In patients with severe hemophilia A, trials of AAV8-BDD-factor VIII and AAV5-BDD (B-domain deleted factor VIII)[17–19] have achieved factor VIII expression levels of 60% or higher for up to 3 years, but then waning to 20% or lower in some trials. These treatments resulted in a more than 90% reduction in annualized rate of bleeding events and use of factors in both hemophilia A and B. An immune response to the AAV capsid, associated with increases in liver aminotransferase levels, sometimes occurs but appears to be responsive to corticosteroids or possibly mycophenolate mofetil. Less immunogenic vectors, innovative delivery systems, and CRISPR gene editing are also being studied.

PREVENTION

Carrier Detection and Prenatal Diagnosis

Carrier detection and prenatal diagnosis have become technically feasible, very sensitive, and widely available. Noninvasive prenatal diagnosis by use of microfluidic digital PCR of maternal plasma DNA is based on the relative proportion of mutated versus normal alleles; it can detect an affected fetus as early as the eighth week of gestation. Because prenatal diagnosis requires the mother to have a known mutation, mothers are increasingly being tested in a nationwide hemophilia genotype program, MLOF (My Life, Our Future). However, at best only two thirds of carrier mothers will be identified because one third of new hemophilia cases arise as spontaneous mutations.

Early prenatal diagnosis is important to reduce intracranial bleeds in an infant with anticipated severe hemophilia by recommended caesarean delivery and to reduce circumcision-related bleeding by preventive factor treatment. Guidelines suggest caesarean section delivery be considered for any known male infants with severe hemophilia A. Vacuum extraction may increase cephalohematoma formation and is discouraged.

Early diagnosis is also important for the mother to reduce peripartum bleeding and advocate for genetic counseling regarding family planning. Next-generation sequencing, carrier testing, and prenatal diagnosis with genetic counseling are widely available in the United States through the network of federally funded hemophilia treatment centers. Fecundity rates remain high, and few confirmed carriers elect to terminate their pregnancies, even if an affected fetus is detected in utero. These decisions are influenced by the wide availability of safe and effective coagulation factor replacement concentrates and by the prospect of an eventual cure for the hemophilias through gene transfer or gene editing.

PROGNOSIS

The life expectancy of individuals with severe hemophilia is similar to that of the normal population. Although deaths from HIV and hepatitis C are declining, in part due to effective antiretroviral therapy for HIV (Chapter 357) and effective combination antiviral treatment for hepatitis C, patients with hemophilia and long-standing chronic hepatitis C infection prior to elective treatment still have a somewhat increased risk of hepatocellular carcinoma despite antiviral therapy.[20] Further, as patients with hemophilia live longer, malignancy and heart disease are becoming more common, and with them need for additional replacement during periods of chemotherapy-induced thrombocytopenia or antiplatelet therapy.[21] Among patients with alloantibody inhibitors, mortality rates are significantly higher than in other patients, so early diagnosis and early immune tolerance induction are recommended. Bleeding is also a leading cause of death, with a lifetime risk of intracranial hemorrhage of approximately 2 to 8%. Finally, the usual problems of aging are increasingly being recognized in those with hemophilia, including atherosclerosis, hypertension, hyperlipidemia, obesity, and diabetes. The impact of these conditions on the natural history of hemophilia, given several studies suggesting lower mortality from ischemic heart disease, remains to be seen.

ACQUIRED HEMOPHILIAS

EPIDEMIOLOGY AND PATHOBIOLOGY

Autoantibody inhibitors occur spontaneously in individuals with previously normal hemostasis. In contrast to alloantibody inhibitors in hemophilic men, which are directed against exogenous clotting factor, autoantibody inhibitors are directed against endogenous clotting factor, most commonly factor VIII. These autoantibodies typically arise in individuals with no past bleeding history, so the diagnosis may be missed until prolonged aPTT and aPTT mixed tests are obtained (Chapter 157). Although 50% of patients with autoantibody inhibitors have no obvious underlying cause, the other 50% are associated with autoimmune diseases, lymphoproliferative disorders, idiosyncratic drug reactions, pregnancy, and advanced age.

CLINICAL MANIFESTATIONS AND DIAGNOSIS

Massive hemorrhagic events, even more severe than in hemophilia patients with alloantibodies, and more commonly in soft tissues, may occur in those with autoantibodies because of a delay in diagnosis and treatment. The laboratory expression of autoantibodies is similar to that of alloantibodies, except that clotting factor activity is not completely neutralized. Residual clotting factor activities between 3 and 20% of normal are frequently observed in patients with autoantibodies.

TREATMENT

The same principles of replacement therapy for alloantibodies apply to these acquired autoantibody inhibitors.[22] The two goals of treatment are to stop the bleeding, assure hemostasis, and eradicate the inhibitor. For hemostasis, recombinant factor VIIa, activated prothrombin complex concentrate, or factor VIII bypass activity is commonly used, in similar doses used to achieve hemostasis with a success rate in over 90% of patients and thrombotic events in less than 5%. Emicizumab (3 mg/kg subcutaneously for 2 to 3 doses followed by 1.5 mg/kg every 3 weeks) can also be an effective prophylactic hemostatic therapy.[23]

Eradication of the inhibitor is significantly more successful (about 80%) in patients who are treated with corticosteroids (e.g., prednisone 1 mg/kg/day orally) and cyclophosphamide (150 mg/day orally or 500 to 750 mg/m^2 intravenous bolus every 3 to 4 weeks) than with corticosteroids alone (about 60%), with dose titration based on inhibitor levels and complicating cytopenias. Rituximab-based regimens (375 mg/m^2 intravenously weekly for 4 weeks) are also effective in about 60% of patients. High-dose intravenous immunoglobulin (IVIg)–based regimens under expert supervision may be effective in about 45% of patients. These agents are tapered and discontinued once the autoantibody has disappeared. The time to complete remission is about 5 weeks for corticosteroids plus cyclophosphamide, whereas rituximab-based regimens require twice as long to achieve remission.

PROGNOSIS

Patients with acquired hemophilia have a mortality rate of 15 to 25%, which is considerably higher than that observed with alloantibody factor VIII inhibitors. Survival in acquired hemophilia is influenced primarily by the achievement of a complete remission, age younger than 65 years at diagnosis, and any related diseases (malignancy vs. postpartum vs. others). Hemorrhagic complications are the primary cause of death, but about 15 to 20% of deaths are associated with sepsis, and about 70% of cases of sepsis arise as a complication of cyclophosphamide-induced neutropenia that may be avoided with future therapies.

VON WILLEBRAND DISEASE

The most common congenital bleeding disorder is von Willebrand disease, which is discussed in detail in Chapter 159.

FACTOR XI DEFICIENCY

EPIDEMIOLOGY

Factor XI deficiency has a prevalence of 1 in 1 million in the general population and 1 in 500 births in Ashkenazi Jewish families. The intrinsic pathway of coagulation of factor XI is the only contact-phase component that is associated with excessive bleeding complications when a deficiency exists.

PATHOBIOLOGY

Factor XI deficiency is predominantly an autosomal recessive trait, although some mutations may have a dominant transmission pattern. The factor XI gene (*FXI*) is located on chromosome 4, and the protein circulates as a homodimer, with each FXI monomer composed of four apple domains encoded by exons 3 through 10 and a protease domain encoded by exons 11 through 15. The Glu117 stop mutation in *FXI* is the most common cause of factor XI deficiency, due to poor secretion or stability of the truncated protein or decreased levels of messenger RNA. More than 170 mutations of *FXI* have been identified in factor XI–deficient patients (see www.factorxi.org), but close correlation between bleeding phenotype and genotype is lacking. Most mutations are missense or nonsense mutations and are located across all four apple domains and the serine protease region.

In Ashkenazi Jewish individuals, factor XI deficiency is common, with a heterozygote frequency of 8 to 10%; two predominant gene mutations occur with equal frequency and are designated type II (a stop codon in exon 5) and type III (a single base defect in exon 9). The most severe clinical disease is observed in patients who are homozygous for type II and who usually have less than 1% factor XI activity. Homozygous type III individuals also manifest severe symptoms, but typically less severe than those of type II patients; they have slightly higher factor XI levels of about 10 to 20%. Compound heterozygotes, type II/III, make up the bulk of factor XI–deficient patients; they have clinically mild disease, with factor XI levels between 30 and 50%.

In individuals of non-Ashkenazi Jewish ancestry, the mutations are more variable, although Cys128 stop has been described in several kindreds, and Cys38Arg has been found in several French Basque families. One third of patients who develop inhibitors are homozygous for Glu117 stop, which results in an absent *FXI*. Genotypic identification of affected patients is determined by measuring factor XI levels rather than by defining the specific gene defect.

CLINICAL MANIFESTATIONS

The clinical bleeding tendency in factor XI deficiency is less severe than that observed in severe hemophilia A or B and, in contrast to the hemophilias, does not correlate with the severity of the deficiency. Most individuals with less than 20% of normal factor XI activity experience excessive bleeding after trauma or surgery, but a few do not bleed. In contrast, bleeding has been observed in approximately 35 to 50% of mildly affected patients with factor XI levels between 20 and 50% of normal. Spontaneous hemorrhagic episodes, hemarthroses, and intramuscular and intracerebral bleeds are unusual; traumatic and surgical bleeds typically involve the mucous membranes. Patients undergoing tonsillectomy, prostatectomy, or dental extraction are at highest risk for bleeding unless replacement therapy is administered. Women may experience significant menorrhagia, and women with menorrhagia should be screened for both von Willebrand disease and factor XI deficiency. Patients with mild factor XI deficiency and coincident mild von Willebrand disease have an increased risk of bleeding.

DIAGNOSIS

Factor XI deficiency is diagnosed by a prolonged activated partial thromboplastic time (aPTt), normal prothrombin time (PT), and decreased factor XI activity ascertained in a specific quantitative clotting assay (normal range, 60 to 130%).

TREATMENT

Not all individuals with factor XI deficiency bleed, so it may be reasonable to monitor affected individuals with no treatment, especially if they have no family history of bleeding. For surgical or other major bleeding, fresh frozen plasma 15 to 20 mL/kg may be given, although potential complications include fluid overload and infection risk, which can be reduced with the use of pathogen-inactivated fresh frozen plasma,[24] if available. Use of factor XI concentrate, which is available in Europe but not the United States, may be complicated by thrombosis, which occurs in approximately 10% of patients, particularly in older individuals with preexisting cardiovascular disease or malignancy. Replacement dosing levels should not exceed 70% of factor XI activity. Repeat dosing with fresh frozen plasma or factor XI concentrate should take into consideration the long (60- to 80-hour) biologic half-life of factor XI in vivo.

The decision to treat heterozygotes with factor XI at levels greater than 20% is empirical and should be based on personal history of bleeding after trauma or surgery. There is no clear evidence that suggests any benefit of DDAVP. Because hemorrhagic complications originate most commonly from mucous membrane surfaces, antifibrinolytic agents such as ε-aminocaproic acid or tranexamic acid under expert supervision are frequently helpful as adjunctive therapy. In women with menorrhagia or postpartum hemorrhage, testing for von Willebrand disease is recommended because both diseases may be present, but testing should be postponed until 6 to 8 weeks after delivery to avoid hormone-induced increase in von Willebrand factor levels that may mask diagnosis.

Alloantibody inhibitors, which neutralize the hemostatic effects of exogenously administered factor XI replacement, can develop in patients with severe factor XI deficiency who have been exposed to plasma or factor XI concentrate. Recombinant factor VIIa can prevent bleeding during or after surgery in these patients.

DEFICIENCIES OF CONTACT ACTIVATION FACTORS

Although factor XI plays an important role in the activation of factor IX in the intrinsic pathway generation of thrombin, it is only one of the four components of the contact phase of coagulation (Chapter 157). Deficiencies in any of the other three factors (factor XII, prekallikrein, and high-molecular-weight kininogen) produce in vitro laboratory abnormalities. Even among those with severe factor XII deficiency (<1% activity), clinical bleeding does not occur. In fact, up to 8 to 10% with severe factor XII deficiency actually experience venous thromboembolic events, which are occasionally fatal. This finding has led to speculation that factor XII deficiency may lead to hypercoagulability through defective participation of the contact-phase proteins in the activation of fibrinolysis.

DIAGNOSIS

Deficiencies of each of these factors prolong the aPTT, often markedly, but it may normalize after prolonged incubation of the patient's plasma at 37° C with a negatively charged activator of the aPTT assay (i.e., kaolin or celite). Specific assays are also available to quantitate each of the contact factors.

TREATMENT

Deficiencies of the contact activation factors, however severe they are and however prolonged the associated aPTT may be, do not cause clinical bleeding problems, even in response to surgery or trauma. Therefore, no therapy is indicated for factor XII deficiency, prekallikrein deficiency, or high-molecular-weight kininogen deficiency. Routine anticoagulation regimens are used to treat thrombotic events.

FACTOR XIII (FIBRIN-STABILIZING FACTOR) DEFICIENCY

Factor XIII is a transglutaminase that is activated by thrombin and functions to cross-link fibrin to protect it from lysis by plasmin, the key enzyme of the fibrinolytic system. It is also involved in normal wound healing and tissue repair and seems to be crucial for maintaining a viable pregnancy. Homozygous severe deficiency states are rare and are inherited in an autosomal recessive manner, with a prevalence of 1 per 3 million births. Consanguinity is common. Most patients are deficient in the A-subunit (FXIII-A). Half of the molecular defects that account for A-subunit deficiency are missense mutations.

CLINICAL MANIFESTATIONS

Heterozygous carriers are usually asymptomatic, but homozygotes have lifelong bleeding that typically starts shortly after birth with persistent bleeding around the umbilical stump. Intracranial bleeding events, usually precipitated by minimal trauma, occur commonly enough in infants (25%) to justify the initiation of a primary prophylaxis regimen of replacement therapy. Delayed bleeding after surgery and trauma is the hallmark of the disease. However, easy bruising, poor wound healing with defective scar formation and dehiscence, and hemarthroses are also characteristic. Spontaneous abortions are increased in severely affected women.

DIAGNOSIS

The diagnosis is usually suspected on clinical grounds, given that factor XIII deficiency is not detected by conventional screening coagulation tests (i.e., aPTT, PT). Most laboratories use a rapid screening assay that assesses the ability of a fibrin clot to remain intact with incubation in 5 mol/L of urea or 1% monochloroacetic acid. With factor XIII levels less than 1% of normal, the clot dissolves within 2 to 3 hours. However, the clot solubility tests are not standardized and have a low sensitivity.[25]

TREATMENT

Normal hemostasis is achieved with a factor XIII level of only 5% of normal. Replacement therapy for prophylaxis or the treatment of acute bleeds in factor XIII deficiency can be accomplished by administering plasma-derived factor XIII concentrate, which is pasteurized for viral safety, or fresh frozen plasma. Recombinant factor XIII is safe and effective in preventing bleeds in factor XIII–deficient patients. The dose is 10 to 20 U/kg intravenously given every 3 to 4 weeks. Acquired alloantibody inhibitors can develop in severely affected individuals. Autoantibodies also occur, usually in association with systemic lupus erythematosus.

DYSFIBRINOGENEMIA AND AFIBRINOGENEMIA

Approximately 300 abnormal fibrinogens have been described, but few cause hemostatic symptoms. Abnormal fibrinogens are rare, autosomally inherited proteins. Quantitative fibrinogen deficiencies (afibrinogenemia and hypofibrinogenemia) may result from mutations affecting fibrinogen synthesis or processing, whereas qualitative defects (dysfibrinogenemia) are caused by mutations that lead to abnormal polymerization, defective cross-linking, or defective assembly of the fibrinolytic system.

The prevalence of dysfibrinogenemia in patients with a history of thromboembolic episodes approaches 0.8%. A high prevalence of dysfibrinogenemia has been reported among patients with chronic thromboembolic hypertension, thereby implicating changes in the molecular structure of fibrin in the development of this disorder. Clinically insignificant dysfibrinogenemias may be acquired in association with hepatocellular carcinoma.

CLINICAL MANIFESTATIONS

More than 50% of the dysfibrinogenemias are asymptomatic, 25% are associated with a mild hemorrhagic tendency (commonly caused by defective release of fibrinopeptide A), and 20% predispose individuals to thrombosis (usually caused by impaired fibrinolysis; Chapter 67). Concurrent bleeding and thrombosis also may occur. Women experience a high incidence of pregnancy-related complications, such as spontaneous abortion and postpartum thromboembolic events. Thrombin times and reptilase times (plasma-based clotting times with the substitution of reptilase snake venom for thrombin) are not helpful in predicting whether an abnormal fibrinogen will be prothrombotic, prohemorrhagic, or asymptomatic. However, clinical history, fibrinopeptide release studies, and fibrin polymerization studies may be useful.

In contrast to the hepatic synthesis of a qualitatively abnormal protein in dysfibrinogenemia, congenital afibrinogenemia is an autosomal recessive disorder that causes markedly deficient production of the normal protein. Severe life-threatening hemorrhagic complications can occur at any site, beginning at birth with umbilical bleeding. Intracranial hemorrhage is a frequent cause of death. Poor wound healing is characteristic.

DIAGNOSIS

Abnormalities are usually detected incidentally when routine coagulation screening assays reveal decreased fibrinogen concentrations and prolonged thrombin clotting times. On further evaluation, discordance between functional and immunologic fibrinogen levels (>50 mg/dL more antigenic than functional) is observed; clotting times using snake venom (reptilase or ancrod) are variably prolonged.

Afibrinogenemia is usually detectable by specific functional or immunologic assays. Platelet dysfunction may accompany afibrinogenemia and exacerbate bleeding.

TREATMENT

Deficiencies of fibrinogen can be corrected by the administration of cryoprecipitate or a viral-attenuated (pasteurized), plasma-derived fibrinogen concentrate.[26] The target replacement goal is 100 mg/dL, and given a circulating biologic half-life of at least 96 hours, treatment every 3 to 4 days is adequate.

Thrombosis is a potential complication of treatment. Primary prophylaxis regimens may be useful in afibrinogenemia, with on-demand or prophylactic replacement for trauma or surgery. Fibrinogen replacement may reduce not only bleeding but also thrombosis. Individuals with thrombophilic manifestations should receive anticoagulation long-term, depending on risk-benefit assessment. Solvent/detergent plasma, which is a pooled human plasma that reduces allergic reactions and transfusion-related acute lung injury, or psoralen-treated fresh frozen plasma may be alternatives.

FACTOR V DEFICIENCY

Factor V is a component of the prothrombinase complex that assembles factors Va and Xa on the phospholipid membrane of the platelet for prothrombin (factor II) activation to thrombin.

CONGENITAL FACTOR V DEFICIENCY

Deficiency of factor V is a rare, autosomal recessive disorder (1 in 1 million births). The factor V Leiden protein, which is responsible for resistance to activated protein C and thrombophilia, does not affect factor V coagulant activity. The severity of plasma factor V deficiency correlates less well with the risk of clinical bleeding than does the factor V content in platelet α-granules. This observation illustrates the critical role of the platelet in promoting adequate hemostasis at bleeding sites and explains why transfusions of normal platelets may be preferred over fresh frozen plasma for the treatment of hemorrhagic episodes secondary to congenital or acquired factor V deficiency. Hemostasis can be maintained without correcting plasma factor V activity (>25% of normal). Recombinant factor VIIa has also been used off-label to treat bleeding in factor V deficiency.

COMBINED DEFICIENCIES OF FACTORS V AND VIII

Factors V and VIII are structurally homologous proteins, and combined deficiencies of these factors occur as an autosomal recessive disorder with a prevalence of 1 in 100,000 births among Jews of Sephardic origin. The disorder is believed to be caused by defective secretion due to mutations in export proteins in the endoplasmic reticulum of endothelial cells. The severity of bleeding is determined by the levels of these factors, which usually range from 5 to 30% of normal. Replacement therapy should be aimed at normalizing both clotting protein activities.

ACQUIRED FACTOR V DEFICIENCY

Acquired factor V deficiency has been described in individuals exposed to bovine factor V, which contaminates the thrombin preparations used topically to control bleeding during cardiovascular surgery. This abnormality probably represents the development of anti–bovine factor V antibodies that cross-react with the human factor V protein. Profuse bleeding accompanies this complication.

DEFICIENCIES OF VITAMIN K–DEPENDENT COAGULATION

DEFICIENCIES OF FACTORS II, VII, AND X

PATHOBIOLOGY AND CLINICAL MANIFESTATIONS

Congenital deficiencies of factors II (prothrombin), VII, and X are rare, autosomally inherited disorders. Heterozygotes (with factor levels approximately 20% of normal) are typically asymptomatic except in the immediate newborn period, when physiologic vitamin K deficiency exacerbates the underlying clotting factor deficiency. Homozygotes with clotting factor levels less than 10% of normal manifest variable symptoms. As with other coagulopathies, these deficiencies are usually suspected after neonatal umbilical stump bleeding. Thereafter, unless replacement or prophylactic therapy is provided, these patients are subject to mucosal bleeding from epistaxis, menorrhagia, and dental extractions; hemarthroses and intramuscular hematomas; and bleeding after surgery or trauma.

Acquired factor VII deficiency has been associated with Dubin-Johnson and Gilbert syndromes (Chapter 133). Acquired factor IX deficiency has been associated with Gaucher disease, because factor IX binds to glucocerebroside. Acquired factor X deficiency and amyloidosis are discussed later.

DIAGNOSIS

In the coagulation laboratory, factor VII deficiency is associated with a prolonged PT and a normal aPTT. This pattern localizes the deficiency to the extrinsic pathway. In contrast, deficiencies of factors II (prothrombin) and X prolong both the PT and the aPTT, with the defects localized to the common pathway of coagulation. A Russell viper venom–based clotting test can differentiate between these two deficiencies; as a direct activator of factor X, the assay is prolonged with factor X deficiency but not with factor II deficiency. Mixing patient plasma with normal plasma results in a correction of these assays, and specific clotting assays using plasma deficient in the coagulation protein to be studied can confirm the diagnosis.

TREATMENT

Replacement therapy is indicated for acute symptomatic bleeds and for prophylaxis before surgery. Plasma-derived factor X is available to treat bleeding in factor X deficiency. Alternatively, factor IX complex concentrates can be administered to achieve hemostatic levels of any of these vitamin K–dependent factors (25 to 30% of normal).

Bleeding complications caused by acquired IgG autoantibodies directed against any coagulation factor protein can be reversed rapidly, albeit temporarily, by extracorporeal immunoadsorption over a Sepharose-bound polyclonal antihuman IgG or staphylococcal A column, with concomitant replacement therapy and initiation of immunosuppression. Recombinant factor VIIa is increasingly used for surgery in patients with rare congenital coagulation deficiencies and Glanzmann thrombasthenia, but typically at lower doses than with hemophilia inhibitors—generally 10 to 15 μg/kg per dose for up to several days.

FACTOR DEFICIENCY IN AMYLOIDOSIS

Severe acquired deficiency of factor X, often accompanied by deficiencies of other vitamin K–dependent factors, occasionally occurs in individuals with systemic amyloidosis (Chapter 174). Because amyloid fibrils in the reticuloendothelial system bind endogenous and exogenous sources of factor X, replacement therapy with FFP or factor IX complex concentrates, even in large quantities, may not be sufficient. Recombinant factor VIIa concentrate has been used to reverse acute bleeding. Splenectomy may ameliorate recurrent bleeding complications.

OTHER ACQUIRED COAGULATION ABNORMALITIES

ANTIPHOSPHOLIPID SYNDROME AND LUPUS ANTICOAGULANT

EPIDEMIOLOGY

The antiphospholipid antibody syndrome is associated with recurrent thrombosis or recurrent pregnancy loss with autoantibodies directed against phospholipids. Antiphospholipid antibodies may include lupus anticoagulant, anticardiolipin antibody (CL), or anti-β2-glycoprotein-I (anti-β2-GPI). Thrombocytopenia is also a common finding in this prothrombotic disorder. Rarely, multiorgan failure may arise from widespread thrombosis, a syndrome called catastrophic antiphospholipid antibody syndrome.

PATHOBIOLOGY

The prothrombotic effects of antiphospholipid antibodies may derive from their ability to complex with β2-GPI in vivo (thereby negating their modulatory phospholipid-binding function) or through inhibition of protein C activation, interference with antithrombin III activity, and/or disruption of the annexin V shield, thereby preventing normal clot breakdown (fibrinolysis). Although complement and inflammation play a role in fetal loss in a murine model of antiphospholipid antibody syndrome, the pathogenic mechanism of pregnancy loss remains unclear. Although non–β2-GPI antibodies detected by CL enzyme-linked immunosorbent assay (ELISA) may play a role in early obstetric antiphospholipid antibody syndrome, and anti-β2-GPI antibodies with lupus anticoagulant activity play a role in late miscarriage, additional studies are needed to classify, understand, and manage this syndrome.

CLINICAL MANIFESTATIONS

Lupus anticoagulants prolong coagulation in in vitro assays but are not generally associated with clinical bleeding. Rarely, clinical bleeding may occur when antiphospholipid antibody antibodies interact with factor II (prothrombin), producing an acquired prothrombin (factor II) deficiency associated with accelerated clearance of lupus anticoagulant–prothrombin complexes from the circulation. Bleeding tendencies also may arise when the lupus anticoagulant targets platelet membranes and produces quantitative or qualitative platelet abnormalities. Other clinical findings in the antiphospholipid antibody syndrome include livedo reticularis, valvular heart lesions, and nephropathy. Clinically, although both arterial and venous thrombosis may occur in the antiphospholipid antibody syndrome, the most relevant is venous thrombosis and stroke in young adults. A diagnostic evaluation in those with arterial thrombosis should include transesophageal echocardiography to exclude a cardiac source for arterial clots. In obstetric patients, other causes of miscarriage should be excluded. A history of recurrent spontaneous abortion associated with antiphospholipid antibody syndrome is a risk factor for subsequent venous thromboembolism in the long term. Nonpregnant individuals with antiphospholipid antibody syndrome–associated thrombotic manifestations have a 50% risk of experiencing recurrent events over a 5-year period. Typically, recurrent thrombotic episodes occur in a pattern consistent with the initial findings (e.g., venous recurrence following an initial deep vein thrombosis).[27]

DIAGNOSIS

The diagnosis of antiphospholipid antibody syndrome is based on both clinical and laboratory criteria. Clinical criteria include arterial, venous, or small-vessel thrombosis in any tissue or organ and pregnancy morbidity.[28] The latter includes one or more pregnancy losses before 10 weeks' gestation; one or more pregnancy losses before 34 weeks due to eclampsia, preeclampsia, or placental insufficiency; or three or more spontaneous abortions before 10 weeks. Antiphospholipid antibody syndrome may be suspected in the setting of recurrent spontaneous miscarriages or pregnancy-related thromboembolic events, with the detection of cerebral arterial thromboses in young adults, in those with systemic lupus erythematosus (20 to 40%; Chapter 245) or other autoimmune diseases or lymphoproliferative malignancies, in those receiving psychotropic medications (e.g., chlorpromazine), or when incidental coagulation assays reveal aPTT prolongation.

Laboratory criteria for antiphospholipid antibody syndrome include the detection of one or more high-titer antiphospholipid antibodies (lupus anticoagulant, CL, anti-β2-GPI) on at least two occasions at least 12 weeks apart. Antiphospholipid antibodies can be detected by three assays: the lupus anticoagulant assay, the CL ELISA assay, and the β2-GPI ELISA assay. The lupus anticoagulant assay includes a screening test, based on a prolonged phospholipid-dependent clotting time; a mixing test that distinguishes the inhibitor (fails to correct in a 1 : 1 mix) from a deficiency state (corrects in a 1 : 1 mix); and a confirmatory test based on platelet neutralization to demonstrate that the inhibitor is phospholipid dependent (clotting time corrects) or a modified aPTT reagent based on the binding of hexagonal-phase phospholipids to lupus anticoagulants. The CL ELISA measures antibodies in dilute sera that bind to CL-coated plates, including those that bind to CL alone or bound to bovine β2-GPI and both IgG and IgM, but it may miss CL bound to human β2-GPI. The β2-GPI ELISA detects antibodies that bind to β2-GPI–coated irradiated plates, but it has reduced specificity owing to binding by nonpathogenic antibodies. Positivity in multiple assays is strongly associated with thrombosis and miscarriage. The risk of first thrombosis among asymptomatic individuals positive for lupus anticoagulants, CL, and β2-GPI antibodies, so-called triple-positive patients, is about 5% per year. Of the three assays, the β2-GPI ELISA is most strongly associated with thrombosis and early recurrent miscarriage; the lupus anticoagulant assay is associated with venous thrombosis, stroke, and late miscarriage. The greatest weight is given to a positive lupus anticoagulant test. From a practical standpoint, testing for all three antibodies at diagnosis is recommended to guide follow-up, because oral anticoagulants may interfere with the lupus anticoagulant test.

TREATMENT

Because of the high risk of recurrent thromboembolism, patients with the antiphospholipid antibody syndrome should receive antithrombotic therapy. The approach is based on achieving a balance between thrombosis risk and bleeding complications, especially in those with thrombocytopenia. Recommendations for patients who have the antiphospholipid antibody syndrome emphasize the use of unfractionated heparin or low-molecular-weight heparin (LMWH), with a 4- to 5-day overlap with warfarin, for acute venous thromboembolism, followed by long-term warfarin to a target international normalized ratio (INR) of 2.0 to 3.0. In individuals with thrombocytopenia, more frequent monitoring of the INR may be warranted to avoid bleeding complications. The direct oral anticoagulant rivaroxaban, although effective in prevention of venous thrombosis, is not as effective as warfarin for arterial thrombosis,[A7] so warfarin remains the treatment of choice in patients who have the antiphospholipid antibody syndrome. The duration of anticoagulation is based on a balance between the risks of bleeding compared with the risks of recurrent thrombosis.

For women with the antiphospholipid antibody syndrome and a prior pregnancy loss but no past thrombosis, the goal is to prevent recurrent pregnancy loss. Based on randomized trials, recommendations generally include low-dose aspirin (81 mg daily) in combination with prophylactic heparin or LMWH in the antepartum period.[29,30]

In the setting of bleeding or when the inherent risk of bleeding exceeds the risk of bleeding with treatment among patients with antiphospholipid antibody syndrome–associated thrombocytopenia and a platelet count below 20,000 to 30,000/μL, management is similar to that for idiopathic thrombocytopenic purpura (see Chapter 158). Case reports indicate that danazol, dapsone, aspirin, or chloroquine may be helpful adjuncts under expert supervision. In pregnant women with antiphospholipid antibody syndrome–associated thrombocytopenia, treatment is advised before epidural anesthesia or cesarean section. In the latter case, early delivery under cover of intravenous immunoglobulin is recommended.

Treatment of antiphospholipid antibody syndrome–associated bleeding is dependent on the site and severity of bleeding. For patients who are taking anticoagulant therapy, the anticoagulant should be withheld and an antidote (e.g., protamine or vitamin K) should be given. For thrombocytopenic bleeding, platelet transfusions should be administered, with red blood cell transfusions if necessary. If both thrombosis and bleeding occur, treatment should be directed at the component that is most life-threatening. In patients with a high bleeding risk, anticoagulants should be withheld or given at a lower dosage; patients with a high thrombotic risk despite thrombocytopenia should be anticoagulated and given agents to boost the platelet count.

In the life-threatening multisystem complication of catastrophic antiphospholipid syndrome, which is characterized by histopathologic evidence of small vessel thrombosis and dysfunction of multiple organs (e.g., lung, brain, heart, kidneys, skin, or gastrointestinal tract) over a short period of time, maximal anticoagulation, plasma exchange, and immunosuppressive therapy have been used under expert supervision. Eculizumab, an inhibitor of terminal complement, was effective in a patient with recurrent catastrophic antiphospholipid syndrome.

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For the General References and other additional features, please visit Elsevier eBooks+ at https://ebooks.health.elsevier.com.

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161 DISSEMINATED INTRAVASCULAR COAGULATION AND BLEEDING IN LIVER FAILURE

ANDREW I. SCHAFER

DISSEMINATED INTRAVASCULAR COAGULATION

DEFINITION

Disseminated intravascular coagulation (DIC), also referred to as consumptive coagulopathy or defibrination, is caused by a wide variety of serious disorders (Table 161-1). In most patients, the underlying process dominates the clinical picture, but in some cases (e.g., occult malignant neoplasm, envenomation), DIC may be the initial or predominant manifestation of the disorder. DIC never occurs in isolation, without an inciting cause.

PATHOBIOLOGY

DIC is primarily a thrombotic process from a pathophysiologic perspective. However, its clinical manifestation may appear to be widespread hemorrhage in acute cases. The basic pathophysiologic mechanism (Fig. 161-1), regardless of cause, is entry into the circulation of procoagulant substances that trigger systemic activation of the coagulation system and platelets.[1] This results in disseminated deposition of fibrin-platelet thrombi within the microvasculature. In most cases, the procoagulant stimulus is tissue factor, a lipoprotein that is not normally exposed to blood. In DIC, tissue factor gains access to blood by tissue injury, its elaboration by malignant cells, or its expression on the surface of monocytes and endothelial cells by inflammatory mediators. Components of the inflammatory response and the coagulation system are reciprocally activated in some forms of DIC, such as sepsis. Tissue factor triggers generation of the coagulation protease thrombin, which induces fibrin formation and platelet activation. In some specific cases of DIC, procoagulants other than tissue factor (e.g., a cysteine protease or mucin in certain malignant neoplasms) and proteases other than thrombin (e.g., trypsin in pancreatitis, exogenous enzymes in envenomation) provide the procoagulant stimulus.

In acute, uncompensated DIC, coagulation factors are consumed at a rate in excess of the capacity of the liver to synthesize them, and platelets are consumed in excess of the capacity of bone marrow megakaryocytes to release them. The resulting laboratory manifestations under these circumstances are a prolonged prothrombin time (PT), a prolonged activated partial thromboplastin time (aPTT), and thrombocytopenia. Increased fibrin formation in DIC stimulates a heightened process of secondary fibrinolysis, in which plasminogen activators generate plasmin to digest fibrin (and fibrinogen) into fibrin(ogen) degradation products (FDPs). FDPs are potent circulating anticoagulants that further contribute to the bleeding manifestations of DIC. Intravascular fibrin deposition can cause fragmentation of red blood cells and lead to the appearance of schistocytes in blood smears (see Chapter 143); however, frank microangiopathic hemolytic anemia is unusual in DIC. Occlusive microvascular thrombosis in DIC can compromise the blood supply to some organs and lead to multiorgan failure, particularly when it is accompanied by systemic hemodynamic, inflammatory, and metabolic derangements.

TABLE 161-1 MAJOR CAUSES OF DISSEMINATED INTRAVASCULAR COAGULATION

INFECTIONS
Gram-negative bacterial sepsis
Other bacteria, fungi, viruses, Rocky Mountain spotted fever, malaria
IMMUNOLOGIC REACTIONS
Transfusion reactions (ABO incompatibility)
Organ transplant rejection
Hematopoietic stem cell transplantation
Chimeric antigen receptor (CAR) T-cell therapy
OBSTETRIC COMPLICATIONS
Amniotic fluid embolism
Retained dead fetus
Abruptio placentae
Toxemia, preeclampsia
Septic abortion
MALIGNANT NEOPLASMS
Pancreatic carcinoma
Adenocarcinomas
Acute promyelocytic leukemia
Other neoplasms
LIVER FAILURE
ACUTE PANCREATITIS
ENVENOMATION
RESPIRATORY DISTRESS SYNDROME
TRAUMA, SHOCK
Brain injury
Crush injury
Burns
Hypothermia or hyperthermia
Fat embolism
Hypoxia, ischemia
Surgery
VASCULAR DISORDERS
Giant hemangioma (Kasabach-Merritt syndrome)
Aortic aneurysm
Vascular tumors or malformations

Underlying Causes

DIC always has an underlying cause that must be identified and eliminated if the coagulopathy is to be managed successfully. The development of DIC in some of these disorders is associated with an unfavorable outcome. Infection is the most common cause of DIC. The syndrome is particularly associated with gram-negative or gram-positive sepsis (Chapter 94),[2] although it can be triggered by a variety of other bacterial, fungal, viral, rickettsial, and protozoal microorganisms. Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) with coronavirus disease 2019 (COVID-19) infection (Chapter 336) can also be associated with a picture of DIC.[3]

The placenta and uterine contents are rich sources of tissue factor and other procoagulants that are normally excluded from the maternal circulation; a spectrum of clinical manifestations of DIC may accompany obstetric complications when this barrier is breached, especially in the third trimester. These syndromes range from acute, fulminant, and often fatal DIC in amniotic fluid embolism to chronic or subacute DIC with a retained dead fetus. Other obstetric problems associated with DIC include abruptio placentae, toxemia, and septic abortion.

Chronic forms of DIC are caused by a variety of malignant neoplasms, particularly acute myeloid leukemia,[4] pancreatic cancer (Chapter 180), and mucin-secreting adenocarcinomas of the gastrointestinal tract (Chapter 179), in which thrombotic rather than bleeding manifestations predominate. Treatment with all-*trans*-retinoic acid has greatly reduced the incidence of severe DIC in patients with acute promyelocytic leukemia (Chapter 168). Up to 50% of patients develop coagulopathy following chimeric antigen receptor (CAR) T-cell therapy, often in the form of DIC. Likewise, coagulopathy with features of DIC can develop with hematopoietic stem cell transplantation (Chapter 163). It is not known whether liver failure (see later) can cause DIC or whether its coexistence merely exacerbates intravascular coagulation because of impaired clearance of activated clotting factors, plasmin, and FDPs. Snake venom contains a variety of substances that can affect coagulation and endothelial permeability. Bites from rattlesnakes and other vipers can induce profound DIC by introduction of these exogenous toxins and release of endogenous tissue factor through tissue necrosis.

The likelihood and degree of DIC caused by trauma, surgery, and shock (Chapter 92) are related to the extent of tissue damage and the organs involved. The brain is a particularly rich source of tissue factor, so traumatic brain injury (Chapter 368) can precipitate acute DIC.[5] Large aortic aneurysms (Chapter 63), giant hemangiomas, and other vascular malformations can cause subclinical or clinical chronic DIC that is initiated locally within the abnormal vasculature but can spill into the systemic circulation.[6]

CLINICAL MANIFESTATIONS

The clinical manifestations of DIC are determined by the nature, intensity, and duration of the underlying stimulus. The coexistence of liver disease

ABSTRACT

Mixed hemorrhagic disorders that involve deficiencies in multiple coagulation factors as well as platelets include disseminated intravascular coagulation (DIC) and the coagulopathy of liver failure. Vitamin K deficiency causes deficiencies of specific vitamin K–dependent coagulation factors II (prothrombin), VII, IX, and X, as well as specific vitamin K–dependent prothrombotic factors protein C and protein S, but does not involve platelets. DIC, also called consumptive coagulopathy, is a syndrome caused by a wide variety of disorders that all have in common their activation of the clotting system at different points in the coagulation cascade, leading to increased fibrin deposition in the microvasculature. So DIC is primarily a thrombotic disorder and may in fact present in its chronic form as thrombosis or occlusive organ dysfunction. The bleeding that more typically accompanies DIC, especially in acute cases, results from consumption of all clotting factors, consumption of platelets, and activation of the fibrinolytic system. The coagulopathy of liver failure is likewise a complex disorder that has both prothrombotic and antithrombotic components. Therefore, while most patients with liver failure have a bleeding diathesis, thrombosis can also occur depending on the balance of these opposing forces. Complete resolution of the coagulopathy of DIC and liver failure, which often coexist, depends on the ability to control the underlying disease.

KEYWORDS

disseminated intravascular coagulation
consumptive coagulopathy
coagulopathy of liver failure
vitamin K deficiency
thrombocytopenia
coagulation factor deficiencies

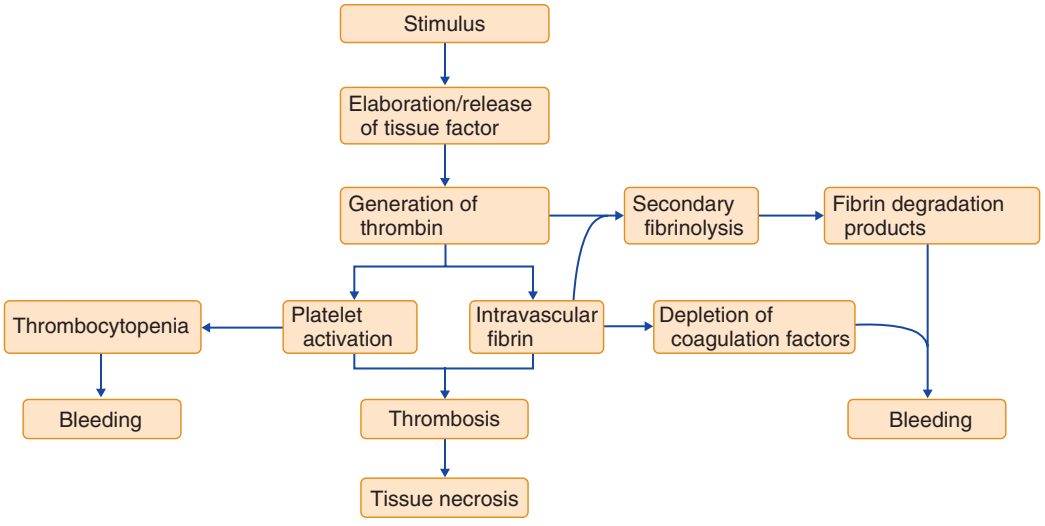

FIGURE 161-1. **Pathophysiologic process of bleeding, thrombosis, and ischemic manifestations in patients with disseminated intravascular coagulation.**

FIGURE 161-2. **Disseminated intravascular coagulation resulting from staphylococcal septicemia. Note the characteristic skin hemorrhage ranging from small purpuric lesions to larger ecchymoses. (From Forbes CD, Jackson WF. *Color Atlas and Text of Clinical Medicine,* 3rd ed. London: Mosby; 2003.)**

exacerbates DIC of any cause. Low-grade DIC is often asymptomatic and diagnosed only by laboratory abnormalities. Thrombotic complications of DIC occur most often with chronic underlying diseases, as exemplified by Trousseau syndrome in cancer (Chapter 67). The thrombotic phenotype of DIC, which occurs prototypically in association with solid tumor malignancies, can manifest as large vessel venous or arterial thrombosis, or as ischemic organ dysfunction due to microvascular thrombosis, or even as a thrombotic microangiopathy. DIC can present as acrocyanosis and gangrene of the digits in critically ill, hemodynamically compromised patients receiving vasopressors. Hemorrhagic necrosis of the skin (Fig. 161-2) and purpura fulminans may also be manifestations of DIC. Bleeding is the most common clinical finding in acute, uncompensated DIC. Bleeding can be limited to sites of intervention or anatomic abnormalities, but it tends to be generalized in more severe cases, including widespread ecchymoses and diffuse oozing from mucosal surfaces and orifices. In these cases, causes of which are exemplified by major trauma, abruptio placentae, or acute promyelocytic leukemia, the precipitating trigger is also a prothrombotic activation of the coagulation system but a fulminant, uncontrolled fibrinolytic response creates a bleeding or so-called fibrinolytic phenotype.

DIAGNOSIS

The laboratory diagnosis of fulminant acute DIC is not usually difficult.[7] Consumption and inhibition of the function of clotting factors cause prolongation of the PT, aPTT, and thrombin time. Consumption of platelets causes thrombocytopenia. Secondary fibrinolysis generates increased titers of FDPs, which can be measured by latex agglutination or D-dimer assays. Some schistocytes may be seen in the peripheral blood smear, but this finding is neither sensitive nor specific for DIC. Chronic or compensated forms of DIC are more difficult to diagnose, with highly variable patterns of abnormalities in "DIC screen" coagulation tests. Increased D-dimers and a prolonged PT are generally more sensitive measures than are abnormalities of the aPTT and platelet count. Overcompensated synthesis of consumed clotting factors and platelets in some chronic forms of DIC may actually cause shortening of the PT and aPTT or thrombocytosis (or both), even though elevated levels of D-dimers indicate secondary fibrinolysis in such cases. Elevated circulating D-dimers are nonspecific, but normal levels have a high negative predictive value for DIC.[8]

The most difficult differential diagnosis of DIC occurs in patients who have coexisting liver disease. The coagulopathy of liver failure (see the later section on liver failure) is often indistinguishable from that of DIC, partly because advanced hepatic dysfunction is in fact accompanied by a state of DIC. In liver failure, the combination of decreased synthesis of clotting factors, impaired clearance of activated clotting factors, secondary fibrinolysis, and thrombocytopenia from portal hypertension and hypersplenism may make the coagulopathy virtually impossible to differentiate from DIC. The coagulopathy associated with postpartum hemorrhage is rarely caused by DIC alone; there may also be varying proportions of dilutional coagulopathy, localized consumption, and increased fibrinolysis. Thrombotic microangiopathies including thrombotic thrombocytopenic purpura and hemolytic-uremic syndrome, the syndrome of "hemolysis, elevated liver enzymes, and low platelet count" (HELLP) in obstetric patients, and other forms of platelet consumption and thrombocytopenia (Chapter 158) are not accompanied by activation of clotting factors or secondary fibrinolysis; therefore, the PT, aPTT, thrombin time, and D-dimers are generally normal in these disorders. Schistocytes, often with frank hemolysis, are much more prominent in the peripheral smear in thrombotic thrombocytopenic purpura and hemolytic-uremic syndrome (Chapter 158) than in DIC. One situation where DIC and thrombotic microangiopathy can overlap and even coexist is in patients with cancer-associated thrombotic microangiopathy. These patients typically have bone marrow involvement and systemic microvascular metastases, either in the setting of known metastatic cancer or unexpectedly on presentation.

TREATMENT

Successful treatment of DIC (Table 161-2) requires that the underlying cause be identified and eliminated. All other therapies, including hemodynamic support, replacement of coagulation factors and platelets, and pharmacologic inhibitors of coagulation and fibrinolysis, are just temporizing measures. Because of the difficulty of testing this complex syndrome with multiple causes by controlled, randomized clinical trials, current guidelines for treatment are generally not based on high-grade evidence.[9]

In many patients with asymptomatic, self-limited DIC who have only laboratory manifestations of the coagulopathy, no treatment may be necessary. In patients with DIC who are actively bleeding or who are at high risk for bleeding, the blood component treatments of choice are transfusions of platelets to improve the thrombocytopenia and fresh-frozen plasma to replace all consumed coagulation factors and to correct the prolonged PT and aPTT. In the absence of robust evidence-based guidelines for the treatment of DIC, an

TABLE 161-2 TREATMENT OF DISSEMINATED INTRAVASCULAR COAGULATION

Identify and eliminate the underlying cause
No treatment if mild, asymptomatic, and self-limited
Hemodynamic support, as indicated, in severe cases
Blood component therapy
Indications: active bleeding or high risk for bleeding
Fresh-frozen plasma
Platelets
In some cases, consider cryoprecipitate, antithrombin III
Drug therapy
Indications: heparin for DIC manifested by thrombosis or acrocyanosis and without active bleeding; antifibrinolytic agents are generally contraindicated except with life-threatening bleeding and failure of blood component therapy

DIC = disseminated intravascular coagulation.

international consensus group recommended VTE prophylaxis in critically ill DIC patients, switching from pharmacologic to mechanical prophylaxis in the case of bleeding and maintaining platelets at greater than 20,000. For some patients who have particularly profound hypofibrinogenemia, the additional transfusion of cryoprecipitate, a plasma concentrate that is enriched in fibrinogen, may be useful. The theoretical concern that these blood products could "fuel the fire" and exacerbate the DIC has not been supported by clinical experience.

The use of pharmacologic inhibitors of coagulation and fibrinolysis in DIC is controversial. Heparin is of theoretical benefit because it blocks thrombin activity and quenches intravascular coagulation and the resultant secondary fibrinolysis. In practice, heparin might exacerbate the bleeding tendency in acute DIC. Heparin is usually reserved for special forms of DIC, including those manifested by thrombosis or acrocyanosis and forms that accompany cancer, vascular malformations, retained dead fetus, and possibly acute promyelocytic leukemia, in which active bleeding is not present. A meta-analysis of randomized controlled trials of anticoagulant therapy specifically in patients with sepsis and sepsis-induced DIC showed an increased risk of bleeding but significant reduction in mortality only in patients who had DIC.[A1] In cases of DIC in which thrombosis or acral ischemia predominates, unfractionated heparin should be used by continuous infusion because of its short half-life and reversibility in the event of increased bleeding. Monitoring the aPTT in the presence of DIC may be problematic, so heparin infusion in this setting should be followed mainly by clinical response and improvement in results of other tests of coagulation (e.g., thrombocytopenia). Antifibrinolytic agents, including ε-aminocaproic acid and tranexamic acid, are generally contraindicated in DIC. By blocking the secondary fibrinolytic response to DIC, these drugs cause unopposed fibrin deposition and may precipitate thrombosis. Antifibrinolytic agents may be effective in decreasing life-threatening bleeding in DIC, however, particularly in extreme cases in which aggressive blood component replacement fails to control the hemorrhage; in such situations, simultaneous infusion of low doses of heparin is needed to reduce the risk for thrombosis.

Antithrombin III and recombinant human soluble thrombomodulin[10] may have some efficacy in improving laboratory parameters of DIC, but neither reduces mortality significantly. Specific surgical treatments and pharmacotherapy may be required for treatment of DIC in patients with aortic aneurysm or vascular malformations.

LIVER FAILURE

Bleeding complications in patients with advanced liver disease (Chapters 139 and 140) can be severe and even fatal and directly account for about 20% of the deaths associated with hepatic failure. Procoagulant abnormalities often coexist. The extent of the bleeding tendency depends on the severity and type of liver disease involved. However, the hemostatic profile in liver failure is unrelated to the Model for End-stage Liver Disease (MELD) score (Table 139-2).[11] About one third of deaths in patients undergoing liver transplantation are attributable to perioperative hemorrhage.

PATHOBIOLOGY

The pathophysiologic mechanism of bleeding in liver failure is multifactorial. The complexity of the systemic coagulopathy of hepatic disease is not surprising inasmuch as the liver is the principal organ site for the synthesis of almost all the coagulation and fibrinolytic factors as well as their inhibitors. (Hepatocytes synthesize all the clotting factors except for von Willebrand factor [vWF], which serves as a physiologic "carrier" and stabilizer of factor VIII, so the elevated levels of vWF that are seen in liver disease can enable near-normal circulating levels of factor VIII despite diminished synthesis of the latter.) Thus, the abnormal hemostasis of liver failure is accompanied by opposing antithrombotic and prothrombotic alterations. Unfortunately, currently available laboratory tests of coagulation, with the possible future exception of thromboelastography (Chapter 157), cannot measure the net effect of the complex, incongruous hemostatic forces that are at work at any given time on clinical bleeding or thrombotic risk in a patient with liver disease. For example, the PT/international normalized ratio (INR) is still accepted as a valid prognostic marker of liver failure, but can no longer be considered a reliable indicator of bleeding tendency in these patients. Although the degree of prolongation of the PT/INR was commonly used in the past to guide treatment with fresh-frozen plasma (FFP) or prothrombin complex concentrate (PCC), it is now recognized that it is not a useful predictor of bleeding after surgery or an invasive procedure. This explains why having certain prolongations of the PT/INR and aPTT as a function of liver disease cannot be regarded as being functionally "auto-anticoagulated"; this notion is a seriously misleading fallacy.

The opposing hemostatic forces at work due to liver failure include (1) decreased *total* levels of circulating clotting factors (caused by consumption of the factors), (2) hypo- or dysfibrinogenemia, (3) enhanced fibrinolysis, and (4) increased levels of fibrin degradation products that act as circulating anticoagulants. All these forces promote bleeding, with simultaneously (1) increased levels of *activated* clotting factors (caused by impaired hepatic clearance), (2) decreased levels of the physiologic anticoagulant proteins antithrombin III (AT III), protein C and protein S (caused by consumption of those proteins), (3) elevated levels of von Willebrand factor and factor VIII, and (4) low plasminogen, all promoting thrombosis. Two factors that may tip the balance more toward a bleeding than a thrombotic phenotype in most of these patients are thrombocytopenia and anatomically vulnerable sites of bleeding in the GI tract, such as esophageal and gastric varices, gastritis (congestive gastropathy), and hemorrhoids.

There is an increased incidence of deep vein thrombosis and/or pulmonary embolism in patients with chronic liver disease (ranging from 0.5 to 6% in different studies). There is an even higher risk of portal vein thrombosis (ranging from 7 to 18% in different series; Chapter 129).[12]

Quantitative and qualitative abnormalities of platelets also contribute to the bleeding diathesis of liver failure. Congestive splenomegaly secondary to portal hypertension causes increased pooling of platelets in the spleen (hypersplenism). The resultant thrombocytopenia, the degree of which generally correlates with spleen size, rarely causes a reduction in the platelet count to less than 30,000/μL. In alcoholic patients, suppression of bone marrow thrombopoiesis by the acute toxic effects of alcohol or folate deficiency may contribute to the thrombocytopenia. Qualitative platelet abnormalities have also been described in patients with liver disease.

Liver transplantation (Chapter 140) poses special problems to the coagulation system. During the 2-hour or so anhepatic stage of surgery, defined as the time from physical removal of the liver from the recipient to recirculation of the graft, the complete cessation of synthesis of coagulation factors causes further prolongation of the PT and aPTT. Release of tissue plasminogen activator from the newly grafted liver leads to increased fibrinolysis and transient exacerbation of bleeding risk in the postoperative period.

CLINICAL MANIFESTATIONS

The most common hemorrhagic complication of liver disease is gastrointestinal bleeding, which is usually caused by anatomic abnormalities and exacerbated by the systemic coagulopathy of liver failure. Bleeding from other mucosal sites, extensive ecchymoses, or more serious hemorrhage into the retroperitoneum or central nervous system generally indicates more significant derangements of the coagulation system.

The severe coagulopathy in patients with liver disease makes liver biopsy a potentially hazardous procedure. The PT and platelet count may be the best guides to bleeding risk, but they lack reliability as predictors of risk of bleeding with liver biopsy. In general, liver biopsy can be performed safely if the platelet count is higher than 50,000/μL. The American Association for the Study of Liver Diseases has concluded that the bleeding risk-benefit ratio of liver biopsy must be carefully considered on a case-by-case basis.

DIAGNOSIS

Although the PT and aPTT are often prolonged in patients with advanced liver disease, the PT tends to be a more sensitive assay early in the course; a disproportionate prolongation of the aPTT should raise suspicion of a coexisting coagulation abnormality, such as a lupus anticoagulant or clotting factor inhibitor. A prolonged PT is also a useful prognostic indicator of poor outcome in patients with cirrhosis, acute acetaminophen hepatotoxicity, and acute viral

hepatitis; in acute viral hepatitis, it is a better index of prognosis than are serum albumin and transaminases. A disproportionate prolongation of the thrombin time should suggest the presence of dysfibrinogenemia. Hypersplenism (Chapter 154), possibly associated with nutritional folate deficiency or the acute toxic effects of alcohol on bone marrow, often causes mild to moderate thrombocytopenia in patients with liver disease. Thrombocytopenia in liver disease can also be due to impaired synthesis of thrombopoietin, the primary megakaryocytopoietic growth factor (Chapter 142). However, consideration should be given to other coexisting causes of thrombocytopenia if the platelet count is significantly less than 30,000/μL.

The coagulopathy of liver failure is often indistinguishable from that of DIC, in part because some degree of DIC is in fact a necessary accompaniment of advanced liver disease. In general, patients with DIC have more marked decreases in levels of factor VIII and increases in D-dimer than do patients with liver failure.

A combination of conventional coagulation tests usually does not provide an accurate overall assessment of in vivo hemostasis in patients with advanced liver disease at any given time. Global coagulation tests, such as thrombelastography (ROTEM), thrombin generation assay, and clot waveform analysis (Chapter 157), would seem to lend themselves ideally to assessing bleeding or thrombotic risk and monitoring the overall hemostatic state of a complex coagulopathy like the one encountered in patients with liver disease. While ROTEM is increasingly used perioperatively in liver transplantation, the clinical utility of these global coagulation assays in chronic liver disease has not yet been well validated. In a randomized study of patients with advanced cirrhosis with active coagulopathy and bleeding, a thromboelastography-guided transfusion strategy led to a significantly lower use of blood components compared with standard of care, without failure to control bleeding, failure to prevent rebleeding, or mortality.[A2]

TREATMENT

Simple clinical coagulation tests such as the PT/INR are of little value in predicting bleeding problems in patients with liver disease,[13] and there is a dearth of evidence that blood component transfusions can predictably avert bleeding complications based on certain cut-off values of PT/INR or platelet count. These observations have driven a significant movement toward more restrictive transfusion strategies in patients with liver disease. Restrictive transfusion policies are now widely used in liver transplantation and have led to significant reductions in intraoperative blood loss and red cell transfusion requirements. By reducing central venous pressures, and consequently portal pressures, performing intraoperative phlebotomy has decreased blood loss with liver transplantation.

Routine transfusion of FFP for prophylaxis of bleeding in coagulopathic liver disease patients is not recommended because patients are unlikely to benefit.[14] Response to FFP is unpredictable and usually does not fully normalize the PT/INR even when multiple units are transfused, in part because FFP and especially stored thawed plasma itself often does not have an INR of less than 1.3. Some institutional guidelines have recommended empirically giving an intravenous dose of vitamin K, which may slightly reduce the PT/INR in liver failure, as well as transfusing cryoprecipitate if the plasma fibrinogen is less than 100 mg/dL (as a concentrated source of fibrinogen) in patients with or without active bleeding who are undergoing invasive procedures. There is little experience with the efficacy of four-factor prothrombin complex concentrate (PCC, Kcentra), which is currently approved for urgent reversal of vitamin K antagonists. Therapeutic plasma transfusion (10 mL/kg) is usually reserved for patients who are actively bleeding despite other treatments, including platelet transfusions if indicated.

In addition to the uncertainty regarding platelet count thresholds for platelet transfusion in patients with liver disease, there are other considerations in those who have portal hypertension with congestive splenomegaly and hypersplenism. Normally, about one third of the total peripheral platelet pool is sequestered in the spleen at any given time. In a patient with hypersplenism, platelet sequestration in the spleen can expand to as much as 90%, depending on the size of the spleen. Much of this splenic platelet pool can be mobilized into the circulation with catecholamines. It is unknown whether this phenomenon also occurs in response to endogenous catecholamines, but it is plausible that the stress of a hemostatic challenge could induce a transient increase in platelet counts, making the baseline level of thrombocytopenia in these patients a significant underestimation of what actually occurs in vivo. Related to the potentially marked expansion of the splenic platelet pool with hypersplenism, transfusion of a given amount of platelets often does not produce the expected "bump" in platelet count, and more units of platelets might be needed to achieve a calculated recovery in peripheral blood. The use of a thrombopoietin-receptor agonist to increase the platelet count is contraindicated based on a randomized trial using eltrombopag to increase the platelet count of thrombocytopenic patients (platelets <50,000 per μL) with chronic liver disease, which was prematurely terminated because of an excess of cases of portal vein thrombosis in the treatment group.

Because of the increased risk of thrombosis, as well as bleeding, in patients with chronic liver disease, prophylactic anticoagulation, especially when hospitalized or immobilized, should not be withheld. Prophylactic doses of low-molecular-weight heparin are safe to use. If there is coexisting kidney disease that precludes its use, prophylactic doses of unfractionated heparin or warfarin can be substituted, although monitoring of the latter may be complicated by a preexisting prolonged INR. In patients who are actively bleeding or have a very low platelet count, mechanical thromboprophylaxis can be substituted for pharmacologic thromboprophylaxis.

VITAMIN K DEFICIENCY

Vitamin K is required for γ-carboxylation of glutamic acid residues of the procoagulant factors II (prothrombin), VII, IX, and X and the anticoagulant factors protein C and protein S via the enzyme, γ-glutamyl carboxylase (GGCX). This post-translational modification normally renders these proteins functionally active in coagulation. The PT is more sensitive than the aPTT in detecting vitamin K deficiency states because factor VII, the only vitamin K–dependent factor that is in the extrinsic pathway of coagulation, is the most labile of these proteins.

The two major sources of vitamin K are dietary intake and synthesis by the bacterial flora of the intestine. In the absence of malabsorption, nutritional deficiency alone rarely causes clinically significant vitamin K deficiency. However, when eradication of gut flora is combined with inadequate dietary intake, as commonly occurs when critically ill patients in intensive care units have no oral intake and are receiving broad-spectrum antibiotics for prolonged periods, clinically significant vitamin K deficiency can be observed. Vitamin K deficiency can also develop in patients receiving total parenteral nutrition unless the infusions are supplemented with vitamin K. Certain mutations of the gene encoding GGCX can also cause a bleeding diathesis.

Vitamin K is absorbed predominantly in the ileum and requires the presence of bile salts. Clinically significant vitamin K deficiency occurs with malabsorption of fat-soluble vitamins secondary to obstructive jaundice (Chapter 141) or with malabsorption caused by intrinsic small bowel diseases, including celiac sprue, short bowel syndrome, and inflammatory bowel disease (Chapters 126 and 127).

Warfarin acts as an anticoagulant by competitive antagonism of vitamin K. Rare cases of hereditary deficiency of the vitamin K–dependent coagulation factors may cause a lifelong bleeding tendency.

Correction of vitamin K deficiency, when it is clinically significant, can be achieved with oral supplementation, unless malabsorption is present, in which case parenteral vitamin K (10 mg subcutaneously daily) should be administered. Patients on vitamin K antagonist therapy who have a supratherapeutic INR between 4.5 and 10.0 without bleeding are not likely to benefit from vitamin K administration in addition to stopping the anticoagulant.[A3] Emergency treatment of bleeding caused by vitamin K deficiency is transfusion of fresh-frozen plasma or four-factor prothrombin complex concentrate.

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162 TRANSFUSION MEDICINE

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Blood transfusion can be lifesaving and is currently the safest it has ever been. However, blood transfusion is associated with multiple adverse outcomes, including both noninfectious and infectious complications. The benefits and risks of transfusion can be considered for each patient using evidence-based, multidisciplinary approaches to reduce unnecessary transfusions and improve patients' outcomes. As a result, the number of units of blood transfused has declined substantially in the United States and worldwide. In the United States, for example, about 10.6 million units of red blood cells (RBCs) are now transfused annually, a decrease from the high of 14.8 million units in 2008.[1]

BLOOD COMPONENTS

The majority of blood collections are whole blood, which can then be separated into plasma, platelets, and red blood cell (RBC) components. In the United States, 85% of RBC units are manufactured from whole blood and more than 90% of platelet components are collected by apheresis.

The majority of blood is transfused as component therapy, tailored to the need of a specific patient. Blood components such as RBCs, plasma, platelets, or granulocytes are obtained either from donation of whole blood or via apheresis (Table 162-1). Each component is stored under their respective optimal conditions; RBCs are refrigerated with additive solutions to improve long-term storage, plasma is frozen to preserve clotting factors, and platelets are stored at room temperature to preserve function and post-transfusion survival. As needed, components can be modified (e.g., irradiated) or selected (e.g., hemoglobin S negative) to meet specific patient requirements.

WHOLE BLOOD

Whole blood contains RBCs, platelets, and plasma. It is stored refrigerated unless used shortly after collection. The shelf-life depends on the storage conditions and preservation solution used. Whole blood provides oxygen-carrying capacity (RBCs) and coagulation support (plasma and platelets). Whole blood has largely been replaced by individual blood components because most patients only require one component (RBCs, platelets, or plasma).

However, whole blood can be useful particularly for trauma patients. The military uses a walking donor program for fresh whole blood, which is stored at 22° C for less than 24 hours. This product has addressed blood component shortages, particularly for platelet products, in austere environments. For civilian trauma, some institutions use cold stored (2° to 6° C) whole blood, which may or may not be leukoreduced (i.e., depleted of leukocytes).

RED BLOOD CELL COMPONENTS

RBC components are usually prepared from whole blood by removing 200 to 250 mL of plasma after centrifugation. RBC components can also be manufactured by apheresis, which can collect two components from a single donor. RBC components are stored at 1° to 6° C, which allows for 42-day storage. General characteristics of RBC components include 130 to 240 mL of RBCs, 50 to 80 g of hemoglobin, and 150 to 250 mg of iron per unit. The total volume (250 to 350 mL), and hematocrit (55 to 80%), vary depending on the volume of blood collected (450 versus 500 mL) and the specific preservative and additive solution used, which also determine its shelf life. RBCs have a hematocrit of 65 to 80% and a shelf life of 21 days when stored in citrate-phosphate-dextrose (CPD), a hematocrit of 65 to 80% and a shelf life of 35 days when stored in CPDA-1, and a hematocrit of 55 to 65% and a shelf life of 42 days when stored in additive solutions. In the United States, most RBC components are stored in additive solutions and contain small amounts of plasma, platelets, and leukocytes, unless the latter have been removed by leukoreduction filtration (which also removes platelets). Canada and many countries in Europe have a universally leukoreduced blood supply.

RED BLOOD CELL COMPONENT MODIFICATION

RBCs and other blood components can be modified to mitigate the complications of transfusion, such as transmission of infectious agents, and to enhance the preservation of rare components. Modified blood components include leukoreduced, irradiated, pathogen reduced, frozen (also known as cryopreservation), and washed components.

TABLE 162-1 BLOOD PRODUCT CHARACTERISTICS

PRODUCT	VOLUME	COMPOSITION	STORAGE CONDITIONS	STORAGE LENGTH	COMMENTS
Red blood cells	300-350 mL	200 mL RBCs, 30-40 mL plasma, 100-110 mL anticoagulant and additive solution	1-6° C	CPD: 21 days CPDA-1: 35 days AS: 42 days	• Leukoreduced: $<5 \times 10^6$ leukocytes • Red blood cells must be ABO compatible with patient plasma • D compatible for females with childbearing potential
Platelets	50 mL per whole blood derived platelet component; 200-400 mL/apheresis component	Platelets suspended in sufficient plasma or platelet additive solution	20-24° C with constant gentle agitation	5 days or 7 days with additional bacterial mitigation Pooled in an open system: 4 hrs	• Whole blood derived platelets: 5.5×10^{10} platelets/unit • Whole blood derived platelets into pools of 4-6 units • Apheresis platelets: 3×10^{11} platelets • Pool or apheresis, leukoreduced: $<5 \times 10^6$ leukocytes • ABO or D compatible is not required
Plasma	200-250 mL	One mL of plasma contains one unit of coagulation factor activity	−18° C; 1-6° C after thawing	Frozen shelf life: 1 yr FFP/FP24/PF24RT24 after thaw: 24 hrs Thawed plasma: 5 days	• FFP: Plasma frozen within 8 hrs of phlebotomy • FP24: Plasma frozen within 24 hrs of phlebotomy • PF24RT24: Plasma frozen within 24 hrs after phlebotomy held at room temperature up to 24 hrs after phlebotomy • Thawed plasma: FFP/FP24/FP24RT24 stored for up to 4 days beyond outdate • Plasma must be ABO compatible with patient RBCs • D compatible is not required
Cryoprecipitate	10-15 mL/unit	80-120 units Factor VIII, >150 mg Fibrinogen, Factor XIII, vWF	−18° C; room temperature after thawing	Frozen shelf life: 1 yr Thawed/pooled in an open system: 4 hrs Thawed/pooled in a closed system: 6 hrs	• ABO and RhD compatible cryoprecipitate is not required

AS = additive solution; CPD = citrate-phosphate-dextrose (anticoagulant); CPDA = citrate-phosphate-dextrose-adenine (anticoagulant); FFP = fresh frozen plasma; RBCs = red blood cells; vWf = von Willebrand factor.

ABSTRACT

Blood transfusion can be lifesaving and is currently the safest it has ever been. However, blood transfusion is associated with multiple adverse outcomes, including both noninfectious and infectious complications. Some mitigation strategies include donor testing and pathogen inactivation, irradiation, and leukoreduction of the products. The benefits and risks of transfusion must be considered for each patient for optimal outcome. Multidisciplinary blood management programs can reduce unnecessary transfusions and improve patients' outcomes. The management of massive bleeding continues to evolve with the use of whole blood, higher ratios of plasma and platelets to red blood cell units, thromboelastography testing, and use of tranexamic acid. Antigen-matched red blood cells can decrease the risk of alloimmunization in patients who require frequent transfusions.

KEYWORDS

transfusion medicine
red blood cells
platelets
plasma
granulocytes
patient blood management
transfusion
blood bank

Leukoreduction

To remove 99.9% of the white blood cells (yielding $<5 \times 10^6$ white blood cells per component), most RBC and platelet components transfused in the United States are leukoreduced. This process decreases the risk of febrile nonhemolytic transfusion reactions, transfusion-transmitted cytomegalovirus (CMV) and other leukocyte-transmitted infections, HLA alloimmunization, and a transient depression of the immune system after transfusion.

Irradiation and Cryopreservation

Irradiation of cellular blood components prevents transfusion-associated graft-versus-host disease (GVHD). Irradiation of RBCs shortens their storage period.

Freezing of RBCs extends their storage capability to 10 or more years. RBCs with rare phenotypes can therefore be frozen and banked for prolonged periods and be more readily available for patients who have antibodies to high-frequency antigens or rare combinations of antigens. After thawing, frozen RBCs must be washed to remove the cryoprotectant (glycerol). Because washed cellular blood components are depleted of plasma proteins, they are the preferred products for patients with a history of allergic, anaphylactoid, or anaphylactic reactions. Washed RBCs expire 24 hours after washing.

Pathogen Reduction

Pathogen reduction inactivates nucleic acids in viruses and bacteria and thus reduces the risk of transfusion-transmitted pathogens, both known and unknown. It also inactivates residual white blood cells, thereby eliminating the need for irradiation. Pathogen-reduced platelets[2] and plasma are used preferentially in some European countries and are increasingly being used in the United States. Pathogen-reduced plasma, particularly plasma treated with a solvent detergent, has a very low adverse event rate. RBC components derived from pathogen-reduced whole blood are approved in Europe, the Middle East, and Africa and are undergoing clinical trials for approval in other countries. Pathogen-reduced RBCs have a shortened shelf-life. In the United States, pathogen-reduced cryoprecipitate is approved for use in acquired fibrinogen deficiency or for replacement of factor XIII or von Willebrand factor when specific factor concentrates are not available.

PLATELET COMPONENTS

Platelet components can be produced from whole blood or apheresis collections and generally have a volume of approximately 300 mL. Platelets derived from whole blood are commonly referred to as *random donor platelets*, *platelet concentrates*, or *buffy coat platelets*. Each unit derived from whole blood contains approximately 0.5×10^{11} platelets. Typically 5 units are pooled to provide a therapeutic dose of 3.0×10^{11} platelets. Platelets collected by apheresis (or plateletpheresis) are referred to as *single donor platelets* or *apheresis platelets*. The required minimum content for a platelet component collected by apheresis is 3.0×10^{11} platelets, but many apheresis-derived platelet collections contain two or three times the required minimum and are therefore split to make multiple platelet components from a single collection. Outside the United States, platelets are made from whole blood using the buffy coat method. These are then pooled and stored in either platelet additive solution or a single donor's plasma. Platelet components can be stored for up to 7 days.

Platelet components are screened for the presence of bacteria to prevent septic transfusion reactions. Also, platelet and plasma components are prepared to reduce the risk of transfusion-related acute lung injury by selecting male or never-pregnant female donors or testing previously pregnant donors for HLA antibodies. Finally, platelets stored in platelet additive solutions have less plasma and thus are less likely to result in allergic reactions and hemolytic reactions due to ABO incompatibility between the donor and recipient.

Another product modification, cold-stored platelets, is emerging for use in trauma or during major bleeding. In the United States, cold-stored (1° to 6° C) platelets are approved with a 14-day shelf life when standard room temperature platelets are not available. These platelets remain in circulation less than 24 hours compared to 5 to 7 days for platelets stored at room temperature.

PLASMA COMPONENTS

Plasma components can be produced from whole blood after centrifugation and removal of RBCs or by apheresis. Notably, the following information applies to the United States, but other countries have simpler terms for their plasma components. *Fresh frozen plasma* (FFP) is frozen at −18° C or colder within 8 hours of collection. Plasma frozen at −18° C or colder within 24 hours of collection is referred to as *plasma frozen within 24 hours after phlebotomy. Plasma frozen within 24 hours after phlebotomy held at room temperature up to 24 hours after phlebotomy* prepared from apheresis collections is also available. Once frozen, plasma has a frozen shelf life of 1 year. Prior to transfusion, plasma must be thawed to 30° to 37° C, a process that takes 20 to 30 minutes. Thawed plasma should be transfused immediately or stored at 1° to 6° C for up to 24 hours. Thawed plasma can be stored for up to 4 additional days at 1° to 6° C to prevent wastage. FFP contains approximately 1 IU/mL of each clotting factor. From a clinical perspective, all plasma products are essentially equivalent.

Other plasma components which are less commonly used include *cryoprecipitate-reduced plasma* and *liquid plasma*. Cryoprecipitate-reduced plasma, which is the plasma remaining after cryoprecipitate is removed, is mostly deficient in factor VIII, fibrinogen, von Willebrand factor, factor XIII, and fibronectin. The sole clinical indication for cryoprecipitate-reduced plasma is in the treatment of thrombocytopenic thrombotic purpura (Chapter 158). Liquid plasma, stored at 1° to 6° C, is separated from whole blood and transfused no later than 5 days after the expiration date of the whole blood. This product contains viable lymphocytes, so it requires irradiation to prevent transfusion-associated graft-versus-host disease in high-risk recipients, such as patients who are immunocompromised.

CRYOPRECIPITATE

Cryoprecipitate is manufactured by thawing FFP at 1° to 6° C. During this thawing process, a precipitate forms (the cryoprecipitate), is separated, and is refrozen. Cryoprecipitate is selectively enriched in fibrinogen, fibronectin, factor VIII, von Willebrand factor, and factor XIII. Cryoprecipitate and its supernatant (cryoprecipitate-poor plasma) are separately refrozen and stored for up to 1 year after collection.

Each unit of cryoprecipitate contains at least 150 mg fibrinogen and 80 IU of factor VIII. A single 10 to 15 mL unit of cryoprecipitate should increase the fibrinogen concentration by approximately 50 mg/dL per 10 kg of body weight. Most blood centers provide prepooled cryoprecipitate, which typically consists of 5 units of cryoprecipitate and which is easier for the hospital transfusion service to prepare. For adult patients, the typical order is a dose of 5 to 10 units of cryoprecipitate.

GRANULOCYTES

Granulocytes have a 24-hour shelf life and are stored at room temperature without agitation. Mostly they are collected by apheresis using hydroxyethyl starch to improve collection. In order to increase the number of granulocytes collected, the donor may be stimulated with steroids to yield components with approximately 1×10^{10} granulocytes and donors stimulated with steroids and granulocyte colony-stimulating factor (G-CSF; Chapter 142) to yield components with approximately 1×10^{11} granulocytes. Apheresis granulocytes have approximately 200 mL volume, 10 to 50 mL of RBCs, 3×10^{11} platelets (equivalent to a platelet component), and plasma. All granulocytes should be irradiated, cannot be leukoreduced, and should be transfused as soon as possible.

PRETRANSFUSION TESTING

Routine pretransfusion testing of blood components includes receipt of an appropriately labeled patient specimen by the transfusion service, testing of the patient's specimen for ABO group and D type and for the presence of unexpected antibodies, and crossmatching of RBC components with the patient's sample.

In emergency situations and before crossmatch compatible blood components are available, group O RBCs and group AB plasma (some institutions use group A plasma) may be appropriately transfused.

Critical to safe blood transfusion is a properly labeled pretransfusion blood specimen from the intended transfusion recipient. Most hemolytic transfusion reactions are caused by misidentification or labeling errors in pretransfusion blood specimens. Radio-frequency identification technology improves the safety and efficiency.

A "type and screen" involves typing the patient's RBCs for ABO and Rh (also known as RhD or D) type, as well as screening the patient's plasma for clinically significant RBC antibodies. A "type and crossmatch" also includes the selection, crossmatching, and reserving of appropriate RBC components for the transfusion recipient. Many institutions have a maximum surgical blood order schedule, which indicates when a type and screen is ordered and how many components should be reserved for each type of surgical procedure.

RBC antibodies of clinical significance are formed in response to pregnancy or transfusion; they may cause hemolysis or shortened survival of transfused RBCs carrying the reciprocal antigen (i.e., acute or delayed hemolytic transfusion reaction). For this reason, the intended recipient's plasma is screened for

the presence of these unexpected antibodies prior to RBC transfusion. If a patient has a clinically significant antibody, the transfusion service will select and reserve the appropriate RBC components that do not carry the reciprocal antigen. The process of identifying a patient's RBC antibody and crossmatching the appropriate RBC components can take hours or even days, depending on the antibody or antibodies found. It can be particularly problematic when the intended recipient has autoantibodies (Chapter 146).

How far in advance a specimen can be drawn is determined by institutional policies. In patients with a negative antibody screen and no history of transfusion or pregnancy in the preceding 3 months, specimens may be drawn up to 1 month before surgery. However, if the patient has been transfused or has been pregnant in the preceding 3 months, a pretransfusion specimen is valid only for 3 days. Most hospitalized patients require a new specimen every 3 days.

ABO/D COMPATIBILITY

Individuals naturally have antibodies against the ABO groups they do not carry (i.e., group O individuals have anti-A and anti-B, group A individuals have anti-B, group B individuals have anti-A, and group AB individuals have none). RBC components must be major ABO compatible and usually D compatible. Group O is the universal RBC component because the RBCs carry no A or B group antigens, whereas group AB RBCs can only be transfused to group AB individuals, group A RBCs can only be transfused to group A or AB individuals, and group B RBCs can only be transfused to group B or AB individuals. Incompatible RBC transfusions may result in acute hemolytic transfusion reactions.

In contrast, D-negative individuals do not make anti-D unless exposed to D-positive RBCs through previous pregnancy or transfusion. D-negative females of childbearing potential must receive D-negative RBCs, unless unavailable in emergency situations, to prevent anti-D formation which may result in hemolytic disease of the fetus and newborn. If there is a shortage of D-negative RBCs, males and females not of childbearing potential (usually defined as age ≥50 years old) can receive D-positive components. The risk of anti-D formation from D-positive RBC unit is about 10 to 20%.

Plasma, which contains antibodies, should be minor ABO compatible such that group AB plasma is the universal product. Group A plasma can be transfused to group A or O individuals, group B to group B or group O individuals, and group O to group O individuals. Group A plasma is being used in massive transfusion settings due to the limited availability of group AB plasma (4% of the population is group AB). This practice appears safe, particularly given that these patients are receiving group O RBCs and are switched to type-specific components once the blood type is known. Plasma is not D-matched because no RBCs are in the product.

Platelets are typically transfused with ABO matching. ABO compatibility results in higher post-transfusion platelet count increment. To decrease the risk of hemolytic transfusion reactions from incompatible plasma, low titer (of anti-A) group O products are used. Risk of anti-D with D-positive to D-negative patients is less than 1%. Granulocytes should be major ABO compatible due to their contamination with RBC and subsequent risk of acute hemolytic transfusion reaction.

BLOOD SAFETY

Adverse events of blood transfusion occur in 0.2% of transfusions, and about 7% of these events are serious. Adverse events can be classified as acute (within hours) or delayed (days to years), and as noninfectious or infectious (Table 162-2 and Table 162-3).[3] Infectious risks include emerging infections, such as *Babesia*, and traditional infections, such as hepatitis B or C. With improvement in donor screening for transmissible diseases, more focus has been on reducing noninfectious transfusion reactions.[4,5]

TABLE 162-2 NONINFECTIOUS TRANSFUSION-ASSOCIATED EVENTS

TRANSFUSION-ASSOCIATED ADVERSE EVENT	RISK PER UNIT TRANSFUSED IN THE UNITED STATES
Acute hemolytic transfusion reaction	≈1 : 110,000 transfusions
Febrile nonhemolytic transfusion reaction	≈1 : 1100
Allergic transfusion reaction	≈1 : 1200 ≈1 : 15,500 severe
Transfusion-associated circulatory overload	≈1 : 9000
Transfusion-related acute lung injury	≈1 : 140,000
Hypotensive transfusion reactions	≈1 : 32,000
Transfusion-associated dyspnea	≈1 : 28,000
Delayed hemolytic transfusion reaction	≈1 : 32,000
Delayed serologic transfusion reaction	≈1 : 8000
Transfusion-associated graft-versus-host disease	<1 : 10,000,000
Post-transfusion purpura	≈1 : 10,000,000

TABLE 162-3 INFECTIOUS DISEASE WINDOW PERIOD AND RESIDUAL RISK

TEST	WINDOW PERIOD (DAYS)	RESIDUAL RISK OF TRANSFUSION
HIV MP-NAT	9	≈1 : 1,800,000
HIV EIA	21	
HCV MP-NAT	7	≈1 : 1,600,000
HCV EIA	51-58	
HBsAg	30-38	≈1 : 300,000
HBV NAT	40-50 (MP) and 15-34 (ID)	≈1 : 1,500,000
HTLV	80	≈1 : 3,300,000
Syphilis		1 reported case in the United States in the last 50 years
Chagas disease		7 reported cases in the U.S.; none since testing
WNV NAT		Last case in 2012
Bacterial contamination		1 : 200,000-1,000,000 with addition of multiple mitigation strategies

EIA = enzyme immunoassay; HBsAg = hepatitis B virus surface antigen; HBV NAT = hepatitis B virus nucleic acid test; HCV = hepatitis C virus; HIV = human immunodeficiency virus; HTLV = human T-cell leukemia-lymphoma virus; ID = individual donor nucleic acid testing; MP-NAT = mini-pool nucleic acid testing; WNV NAT = West Nile virus nucleic acid test.

NONINFECTIOUS ADVERSE EFFECTS OF BLOOD TRANSFUSION

ACUTE HEMOLYTIC TRANSFUSION REACTION

Acute hemolytic transfusion reactions occur when preformed recipient antibodies bind to transfused RBC antigens, thereby resulting in the formation of an antigen-antibody complex.[6] This complex activates the complement cascade and causes intravascular hemolysis. Most commonly, acute hemolytic transfusion reactions are severe reactions due to ABO incompatibility, usually because transfused RBC antigens are incompatible with the recipient's plasma (e.g., group A RBCs into group O recipient), and less commonly when transfused plasma contains antibodies against the recipient's RBC antigens (e.g., group O plasma into group A recipient). Acute hemolytic transfusion reactions can also be associated with antigen-antibody complexes outside of the ABO system. The destruction of RBCs also may result in mechanical hemolysis unrelated to the transfusion.

The incidence of acute hemolytic transfusion reactions is approximately 1 : 110,000 transfusions, and these rates have substantially decreased over time. About 70% of transfusion reactions are due to RBCs and 30% due to platelet transfusions. ABO-incompatible RBC transfusions most commonly occur with mistransfusion, when the patient receives an incorrect unit. Mistransfusion is usually caused by human error, including improper identification of the intended recipient during pretransfusion sample collection, improper ABO typing of the blood component or the intended recipient, or improper identification of the recipient or the blood component at the time of transfusion.

CLINICAL MANIFESTATIONS AND DIAGNOSIS

The signs and symptoms of acute hemolytic transfusion reactions are fever, chills/rigors, anxiety, chest and abdominal pain, flank and back pain, nausea, vomiting, dyspnea, hemoglobinuria, diffuse bleeding, and oliguria/anuria. If

an acute hemolytic transfusion reaction is suspected, the transfusion should be stopped immediately, the reaction should be reported to the transfusion service for investigation, and the unit should be returned to the blood bank. Diagnosis is based on laboratory evidence of hemolysis (e.g., decreased hemoglobin, decreased haptoglobin, hemoglobinuria, and elevated lactate dehydrogenase) and evidence of incompatible blood transfusion (e.g., positive direct antiglobulin test and incompatible crossmatch). Approximately 50% of ABO-incompatible RBC transfusions have no adverse effect, but 5% are fatal.

TREATMENT AND PREVENTION

Treatment includes saline infusion (and potentially the addition of low-dose dopamine) to maintain blood pressure and adequate urine output; a diuretic (e.g., furosemide) to increase renal blood flow; and plasma, cryoprecipitate, platelets, and heparin as needed for disseminated intravascular coagulopathy (Chapter 161).

Acute hemolytic transfusion reactions can be mitigated by decreasing the risk of ABO incompatible blood transfusion. Mislabeling of patient samples remains the major factor contributing to ABO incompatibility. Processes to address this problem include improved tracking and labeling of specimens, use of radiofrequency identification systems, and policies to require two separate blood draws for ABO typing prior to releasing type-specific RBC components.

Febrile Nonhemolytic Transfusion Reaction

Febrile nonhemolytic transfusion reaction, with an incidence of approximately 1 : 1100 transfusions, is defined as a temperature increase of 1° C or more or greater than 38° C and/or chills/rigors occurring within 4 hours of cessation of transfusion.[7] The incidence of febrile nonhemolytic transfusion reactions has significantly decreased with the widespread use of leukoreduction.

By definition, the temperature increase cannot be attributed to other etiologies. In platelet components, febrile nonhemolytic transfusion reactions are caused by leukocyte-derived cytokines that accumulate in the component during storage. With RBC components, these reactions are caused by donor leukocytes interacting with patient white blood cell antibodies.

If a febrile nonhemolytic transfusion reaction is suspected, the transfusion should be stopped and reported to the transfusion service to exclude a more serious transfusion-associated adverse event. Supportive care should be administered.

Allergic Transfusion Reaction

Allergic transfusion reactions have an overall incidence of approximately 1 : 1200 transfusions. Most allergic reactions are mild, but about 8% are severe. Platelet transfusions are the blood component most often associated with allergic reactions. Platelets stored in platelet additive solution have less plasma and thus a decreased allergic reaction rate of 0.3% compared with 0.8% for platelets stored in plasma. Solvent/detergent-treated plasma from pooled donors also has lower allergic reaction rates. Anaphylactic reactions (Chapter 233) may be secondary to anti-IgA, which can occur in patients with IgA deficiency.

Mild reactions consist of urticaria with or without generalized pruritus or flushing. More severe symptoms include hoarseness, stridor, wheezing, dyspnea, hypotension, gastrointestinal symptoms, and shock. Patients who have severe allergic reactions should be tested for IgA deficiency and the presence of anti-IgA.

TREATMENT AND PREVENTION

Mild reactions can be treated by temporarily stopping the transfusion and administering antihistamines, whereas severe reactions require discontinuation of the transfusion and treating with epinephrine, H1-receptor antagonists, and corticosteroids. (Chapter 233). Premedication with antihistamines decreases the incidence of allergic reactions, but is recommended only in patients who have a history of allergic reactions. If anti-IgA is identified, the patient should receive plasma components from IgA deficient donors or washed RBC and platelets components.

Transfusion-Associated Circulatory Overload

Transfusion-associated circulatory overload, with an incidence of approximately 1 : 9000 transfusions, results from circulatory overload following transfusion. Risk factors are age older than 70 years, a post-transfusion B-type natriuretic peptide (BNP) greater than 1000 pg/mL, a positive fluid balance of greater than 3 L, and more units transfused within 6 hours. Symptoms and signs include dyspnea, tachypnoea, decreased oxygen saturation, orthopnea, cough, chest tightness, cyanosis, hypertension, and headache. These signs and symptoms usually present at the end of transfusion but may occur up to 12 hours post-transfusion. Diagnosis is based on the presence of fluid overload and elevated levels of BNP or NT-pro BNP (Chapter 45). Management includes discontinuing the transfusion, diuretic therapy, oxygen supplementation, and sitting the patient upright (Chapter 46).

Transfusion-Related Acute Lung Injury

Transfusion-related acute lung injury (TRALI), with an incidence of approximately 1 : 140,000 transfusions, is noncardiogenic pulmonary edema that is associated with the transfusion and that occurs within 6 hours of cessation of transfusion.[8] The incidence of transfusion-related acute lung injury has substantially decreased[9] with the implementation of male-only, HLA antibody–negative, or nulliparous female plasma and platelet donors. Additionally, solvent/detergent-treated plasma has rarely been associated with cases of transfusion-related acute lung injury.

Transfusion-related acute lung injury is most commonly seen following platelet transfusions, and the majority of events are serious. Patient-related risk factors include higher IL-8 levels, liver surgery, chronic alcohol use disorder, shock, higher peak airway pressure while being mechanically ventilated, current smoking, positive fluid balance. Transfusion-related risk factors include the receipt of plasma from female donors and a higher volume of HLA class II human neutrophil antigen positive antibodies. Signs include hypoxemia with radiographic evidence of bilateral infiltrates. Transfusion-related acute lung injury is caused by neutrophil and pulmonary endothelial activation, usually a result of transfused donor white blood cell antibodies, including human leukocyte antigen (HLA) antibodies and human leukocyte antigen antibodies. These donor antibodies react with the recipient's white blood cells in the pulmonary vasculature, thereby causing leukoagglutination, activation of the complement cascade, cytokine release, and pulmonary edema. More rarely, transfusion-related acute lung injury is caused by the converse mechanism in which recipient white blood cell antibodies react against transfused donor white blood cells.

When hypoxemia occurs within 6 hours of transfusion in the absence of other risk factors for acute lung injury, the transfusion-related acute lung injury is called type 1, whereas it is called type 2 in patients who have such risk factors or already have at least mild preexisting acute respiratory distress syndrome or risk factors for it (e.g., pneumonia, inhalation injury, trauma, sepsis, drowning, pancreatitis, burn, shock, cardiopulmonary bypass, or drug overdose).

TREATMENT AND PROGNOSIS

In cases of suspected transfusion-related acute lung injury, the transfusion should be discontinued. Medical management is primarily supportive, commonly with supplemental oxygen and endotracheal intubation if needed. Diuresis is not indicated, and the role of corticosteroids is unclear. The majority of patients improve within 2 to 4 days, although transfusion-related acute lung injury has a 5 to 10% mortality rate.

Hypotensive Transfusion Reactions

Hypotensive transfusion reactions, with an incidence of approximately 1 : 32,000, are usually associated with transfusions of RBCs or platelets. These reactions appear to be related to the generation of bradykinin, thereby resulting in vasodilation and hypotension. Hypotensive reactions have most commonly been reported in association with the use of negatively charged bedside leukoreduction filters in patients being treated with angiotensin-converting enzyme inhibitors. The use of prestorage leukoreduction in lieu of bedside leukoreduction limits the incidence of these reactions. Hypotensive transfusion reactions typically resolve with cessation of transfusion.

Transfusion-Associated Dyspnea

Transfusion-associated dyspnea, with an incidence of approximately 1 : 28,000 transfusions, results in acute respiratory distress within 24 hours of transfusion cessation. It is a diagnosis of exclusion, when allergic reactions, transfusion-associated circulatory overload, and transfusion-related acute lung injury have been excluded.

Delayed Hemolytic and Serologic Transfusion Reaction

Delayed hemolytic transfusion reactions, with an incidence of approximately 1 : 32,000 transfusions, occur when RBC transfusion causes an alloantibody

response, thereby resulting in decreased RBC survival. If an alloantibody response is noted in the absence of RBC destruction, it is termed a delayed *serologic* transfusion reaction, which has an incidence of approximately 1 : 8000 transfusions. If alloantibodies are formed within days of transfusion, it is presumed to be an anamnestic alloantibody response in an individual who had previously formed antibodies, usually from an earlier transfusion or pregnancy. If alloantibodies are formed within weeks of transfusion, it is presumed to be a primary alloantibody response.

Delayed hemolytic transfusion reactions are characterized by an unexpected decrease or less than expected increase in the recipient's hemoglobin post-transfusion. Other signs and symptoms, which are typically much less severe than those associated with acute hemolytic transfusion reactions, include fever, chills, jaundice, malaise, back pain, and rarely renal failure. To prevent future reactions, the patient should receive antigen-negative RBCs for future transfusions. The primary mitigation strategy is prophylactic RBC antigen matching.

A severe form of delayed hemolytic transfusion reaction is hyperhemolytic transfusion reaction. This rare reaction, which is most often reported in patients who have sickle cell disease (Chapter 149) or thalassemia (Chapter 148), results in destruction of both donor and recipient RBCs, thereby leading to more severe anemia. Additionally, the patients usually have reticulocytopenia. RBC alloantibodies or autoantibodies may or may not be present. The pathophysiology remains unclear. Treatment includes erythropoietin, intravenous immunoglobulin, corticosteroids, rituximab, tocilizumab, and eculizumab under expert supervision. Future RBC transfusions should be administered cautiously.

Transfusion-Associated Graft-versus-Host Disease

Transfusion-associated graft-versus-host disease (GVHD), with an incidence of less than 1 : 10,000,000 transfusions, results from the engraftment of transfused viable donor lymphocytes in an immunosuppressed recipient. The donor lymphocytes subsequently mount an immune response against the recipient, thereby resulting in pancytopenia, an erythematous rash or even generalized erythroderma, liver dysfunction, and gastrointestinal symptoms. Unlike GVHD associated with hematopoietic progenitor cell transplantation (Chapter 163), transfusion associated-GVHD has a nearly 100% fatality rate due to the profound pancytopenia.

Patients at increased risk for transfusion associated-GVHD include individuals with congenital immunodeficiencies, Hodgkin disease, acute leukemia, or other hematologic malignancies, as well as patients undergoing hematopoietic progenitor cell transplantation. Patients who receive HLA-matched blood components or blood components from close relatives, granulocyte transfusions, intrauterine transfusions, or neonatal red cell exchange are also at increased risk. At-risk patients should receive irradiated or pathogen-reduced cellular blood components, which prevent leukocytes from engrafting.

Post-Transfusion Purpura

Post-transfusion purpura, with an incidence of approximately 1 : 10,000,000 transfusions, is an immune thrombocytopenia caused by antiplatelet alloantibodies, most often anti-HPA-1a (Chapter 158). All types of blood components have been implicated, with transfusion triggering an antibody response to platelet antigens.

Post-transfusion purpura is characterized by acute, profound thrombocytopenia (platelet count <10,000/μL), unexplained purpuric rash, bruising, or mucosal bleeding 1 to 3 weeks post-transfusion. Thirty percent of affected patients have major hemorrhage, and 10% of patients have fatal hemorrhage. Diagnosis is based on the clinical presentation and the identification of platelet-specific alloantibodies. The primary treatment for post-transfusion purpura is intravenous immunoglobulin under expert supervision.

INFECTIOUS COMPLICATIONS OF TRANSFUSION

Criteria for transfusion-transmission of pathogens include: an asymptomatic infectious phase in the donor; an agent's viability during storage; a seronegative recipient population; and an agent capable of causing disease post-transfusion. The transfusion-transmitted infection rate is about 1 : 225,000, and this rate has substantially decreased over time worldwide. Higher rates occur with platelet transfusions, and the majority are severe reactions. About 50% of the reactions are bacterial and about 50% are parasitic, with rare viral transmission.

Blood safety relies upon several measures, including careful donor screening by questionnaire, the use of good manufacturing practices, and donor and component screening for infectious diseases. Currently, in the United States, blood donors are screened for infection with hepatitis B virus, hepatitis C virus, HIV-1 and HIV-2, human T-cell lymphotropic viruses (HTLV) types I and II, West Nile virus (WNV), syphilis, and *Trypanosoma cruzi*. Additionally, donors may be screened for cytomegalovirus and *Babesia* in high epidemic areas of the United States. Platelet components are also screened for bacterial contamination unless they have been pathogen-reduced.

Bacterial Contamination

The risk of a septic reaction is approximately 1 : 200,000 to 1,000,000 transfusions, with the risk decreasing as additional platelet bacterial contamination mitigation strategies are implemented.[10] Platelet components are primarily associated with bacterial contamination due to their storage at room temperature. The implementation of multiple steps for platelet units, including skin cleansing, diversion pouch, and bacterial screening, has resulted in approximately two-thirds decrease in septic reactions. Pathogen reduction decreases bacteria loads by more than four logs for most organisms, although several septic reactions have been reported from pathogen-reduced platelet transfusion in the United States[11] Additional mitigation strategies implemented in the United States and other countries reduce septic reactions to less than 1 : 500,000 transfusions include delayed or repeat bacterial culture and use of point-of-issue bacterial screening.[12]

Septic reactions should be suspected if the transfused patient has fever (≥38° C with rise ≥1° C) with rigors, hypotension, shock, tachycardia, dyspnea, or nausea/vomiting. The transfusion should be promptly stopped, supportive care should be instituted, and blood samples should be drawn for culture (aerobic and anaerobic times two) prior to initiating antibiotics. Thrombocytopenic neutropenic patients are most at risk for septic reactions, mostly due to *Staphylococcal aureus*.

Virus

Hepatitis B (Chapter 134) virus has an estimated transfusion transmission risk of approximately 1 : 1,500,000 transfusions. In the United States, blood components are screened by testing for Hepatitis B surface antigen (HBsAg), anti-HBc, and HBV nucleic acid testing (NAT).

Hepatitis C has an estimated transfusion transmission risk of approximately 1 : 1,600,000 transfusions. In the United States, blood components are screened by testing for anti-HCV and HCV NAT.

Human immunodeficiency virus (HIV) has an estimated transfusion transmission risk of approximately 1 : 1,800,000 transfusions. HIV-2 is found mainly in West Africa. In the United States, blood components are screened by testing for anti-HIV-1/HIV-2 and HIV-1/HIV-2 NAT.

Human T-cell lymphotropic virus (Chapter 360) has an estimated transfusion transmission risk of approximately 1 : 3,300,000 transfusions. In the United States, blood components are screened for HTLV-I and HTLV-II by testing for anti-HTLV-I/II.

Donor screening has substantially reduced the number of transfusion-transmitted cases of West Nile virus (Chapter 352), with the most recent U.S. case being reported in 2012. In the United States, blood components are screened by West Nile virus NAT. To improve testing logistics and cost, testing is initially performed on pooled samples, and then this process continues until increased regional disease activity is detected, at which time testing is on individual samples.

Four suspected cases of transfusion-transmitted Zika virus (Chapter 352) have been reported, all in Brazil, and none were associated with clinical sequelae in the recipients. Zika NAT testing was performed in the United States from 2016 to 2021, but then the FDA determined that Zika virus is no longer a relevant transfusion-transmitted infection. Now, neither testing nor pathogen reduction is required.

Other Infections

In the United States, blood components are screened for syphilis (Chapter 295) by nontreponemal or treponemal tests. No transfusion-transmitted syphilis infections have been reported in the last several decades due to the spirochete's poor viability during storage.

In the United States blood components are screened for *T. cruzi*, which is the causative agent of Chagas disease (Chapter 318), by testing for anti–*T. cruzi* antibody. In the United States, donors are tested only at their first donation. Since the advent of screening, no transfusion-related cases have been reported.

Screening of blood donors for *Babesia* (Chapter 324) is performed using either NAT or pathogen reduction in high epidemic states to prevent transfusion-transmitted babesiosis. The implementation of screening has decreased the incidence of transfusion-transmitted *Babesia,* which is dependent on the donor's residence and travel.

Many other pathogens have been reported to be transfusion transmitted, including *Anaplasma phagocytophilum* (Chapter 324), parvovirus B19 (Chapter 342), hepatitis A (Chapter 134), Dengue virus (Chapter 352), variant Creutzfeldt-Jakob disease (Chapter 371), and malaria (Chapter 316). Donors are screened by donor history questionnaire for malaria in the United States. Plasma for further manufacturing is tested for parvovirus B19 and hepatitis A.

INDICATIONS FOR BLOOD TRANSFUSION (TABLE 162-4)

RED BLOOD CELL TRANSFUSIONS

RBC transfusions are used to treat anemia when patients require increased oxygen carrying capacity, based on their individual clinical status and coexisting medical conditions. In an average adult, one RBC component (unit) should increase the hemoglobin by about 1 g/dL and the hematocrit by about 3%.

Almost 50 randomized controlled trials[A1,A2,13] have compared restrictive (hemoglobin between 7.0 g/dL and 8.0 g/dL) versus liberal (hemoglobin between 9.0 g/dL and 10.0 g/dL) transfusion thresholds in a variety of clinical contexts, including medical and surgical adult patients. Transfusing at lower versus higher hemoglobin levels results in equivalent rates of mortality, myocardial infarction, stroke, pneumonia, thrombosis, and infection. Clinical situations in which a higher transfusion threshold (e.g., >8.0g/dL) should be considered are patients who have symptomatic anemia, an acute coronary syndrome, an acute myocardial infarction,[A3] severe thrombocytopenia, or who require chronic transfusions. The COVID-19 pandemic resulted in sustained blood shortages worldwide, particularly for RBC products, thereby resulting in the adoption of blood conservation strategies, including splitting products and altering transfusion practices.[14]

PLATELET TRANSFUSIONS

Platelet transfusions are given to prevent or treat bleeding in thrombocytopenic patients (Chapter 158). Platelet transfusion may also be considered in patients with qualitative defects in platelet function. The threshold to transfuse platelets is determined by the patient's platelet count combined with underlying disease and the presence of clinical bleeding.

To prevent bleeding in patients with low platelet counts, patients can be transfused platelets prophylactically.[15] Platelets are indicated in patients with therapy-induced hypoproliferative thrombocytopenia at a platelet count of 10,000/μL or less. Platelet transfusions are also indicated in patients who are having an elective central venous catheter placement with a platelet count of less than 20,000/μL, patients having elective diagnostic lumbar puncture or non-neuraxial surgery with a platelet count of less than 50,000/μL, and in patients having major elective neurosurgery with a platelet count of less than 100,000/μL.

TABLE 162-4 EVIDENCE-BASED TRANSFUSION TRIGGERS

BLOOD COMPONENT	COMMONLY ACCEPTED INDICATIONS	TYPICAL INCREASE
RBC	Hb <7.0 g/dL Hb< 8.0 g/dL acute coronary syndrome/myocardial infarction	Hb: 1 g/dL or Hct: 3% after one unit of RBC
Platelets	<10,000/μL hospitalized adult patients with therapy-induced hypoproliferative thrombocytopenia <20,000/μL if febrile/septic, central venous catheter, or other minor procedures <50,000/μL if surgery, lumbar puncture, invasive procedure, or active bleeding <100,000/μL neurosurgery or central nervous system bleeding	30-60,000/μL after one platelet dose (a single apheresis component or 4-6 whole blood derived platelet concentrates [3×10^{11} platelets])
Plasma	Massive transfusion (plasma : RBC: 1 : 2) INR >2.0 prior to invasive procedure Replacement fluid for plasma exchange for thrombotic thrombocytopenic purpura	10-15 mL/kg increases factor levels by ≈20%
Cryoprecipitate	Fibrinogen <150 mg/dL with bleeding	≈7 mg/dL increase in fibrinogen per unit

Hb = hemoglobin; Hct = hematocrit; ICH = intracranial hemorrhage; INR = international normalized ratio; PCC = prothrombin complex concentrate; RBC = red blood cell.

Platelets also are administered therapeutically in patients who have low platelet counts, generally less than 50,000/μL, and if they are actively bleeding. Platelet transfusions are also indicated in patients who have undergone cardiac surgery with cardiopulmonary bypass, exhibit perioperative bleeding, and are either thrombocytopenic or have evidence of platelet dysfunction. In patients who have a massive hemorrhage, platelets should be administered at an appropriate ratio to RBC transfusions. Platelet transfusion is not recommended for patients who have an intracranial hemorrhage while receiving antiplatelet therapy.[A4]

In adults, a typical platelet dose is a single apheresis component or four to six whole blood-derived platelet concentrates pooled (3×10^{11} platelets). Lower dose platelet transfusions (e.g., $1.1 \times 10^{11}/m^2$ or $2.2 \times 10^{11}/m^2$) result in similar bleeding outcomes but require more platelet transfusions per patient.

The response to platelet transfusion can be assessed by a decrease in clinical bleeding and by measuring the post-transfusion increment in platelet count about 15 to 60 minutes after transfusion. A typical dose of platelets should increase the patient's platelet count by 30,000 to 60,000/μL.

A more formal evaluation of the platelet increment can be performed using the corrected count increment, which accounts for both the patient's size (via body surface area) and the number of platelets in the transfused component. The corrected count increment is calculated as:

$$\frac{\text{Body surface area}(m^2) \times \text{Platelet count increment} \times 10^{11}}{\text{Number of platelets transfused}}$$

A 1-hour corrected count increment greater than 7.5 is considered acceptable, whereas a corrected count increment value less than 7.5 is suggestive of platelet refractoriness.

Many clinical conditions can decrease the expected post-transfusion increment in the platelet count, including fever, sepsis, disseminated intravascular coagulation, splenomegaly with hypersplenism, active bleeding, and platelet or HLA alloantibodies or autoantibodies. ABO-compatible transfusions result in higher post-transfusion increment than ABO-incompatible transfusions. Patients who have multiple platelet transfusions may develop antibodies that blunt the response of the platelet count, and evaluation of platelet refractoriness usually includes screening for HLA compatibility and platelet antibodies. In this situation, HLA epitope-matched platelet transfusions provide a better response than standard HLA antigen-matched transfusions, with each epitope mismatch reducing the platelet count response by about 15%.[A5]

PLASMA TRANSFUSIONS

Plasma transfusions are generally used either to prevent or treat bleeding in patients with acquired coagulopathies. For the majority of patients with congenital coagulopathies, the specific and appropriate clotting factor concentrate should be administered (Chapter 160), such as von Willebrand factor, factor VIII, factor IX, fibrinogen, factor X, factor VIIa, factor XIII, prothrombin complex concentrate, and C1 inhibitor concentrate. These factors are either purified and virally inactivated human or recombinant proteins. If the specific factor is not available, plasma should be transfused.

Plasma should be administered to massively hemorrhaging patients at an appropriate ratio to red blood cell transfusions. Plasma can also be used to treat or prevent major bleeding in patients with multiple coagulation factor deficiencies, including disseminated intravascular coagulopathy (Chapter 161) and liver failure (Chapter 140).

Plasma is also indicated as replacement fluid for plasma exchange in patients with thrombotic thrombocytopenic purpura (Chapter 158) and other diseases.[16] Plasma may also be used as part of the replacement fluid for patients at risk of coagulation factor depletion, particularly patients who are on daily plasma exchange with albumin as replacement fluid.

The only clinical indication for plasma cryoprecipitate-reduced and thawed plasma cryoprecipitate reduced is thrombotic thrombocytopenic purpura (Chapter 158). The only indication for liquid plasma is for initial treatment of patients undergoing massive transfusion.

Plasma transfusion is not recommended for warfarin-related serious hemorrhage unless prothrombin complex concentrate is not available. Prothrombin complex concentrate, specifically 4-factor (factors II, VII, IX, and X), should be used instead of plasma for the rapid reversal of warfarin in patients who experience bleeding or require urgent surgery (Chapter 161). Plasma is not recommended for reversal of novel oral anticoagulants (e.g., direct thrombin inhibitors and direct factor Xa inhibitors).

The typical dose of plasma is 10 to 15 mL/kg. Because each plasma component is 200 to 300 mL, an average adult dose is 3 to 5 plasma components

(units). Coagulation factors are expected to increase by approximately 20% immediately after plasma infusion.

CRYOPRECIPITATE TRANSFUSIONS

Cryoprecipitate is used for fibrinogen replacement when levels fall below 100 mg/dL in acquired hypofibrinogenemia with disseminated intravascular coagulopathy (Chapter 161), liver failure (Chapter 140), the anhepatic phase of liver transplantation (Chapter 161), and massive transfusion with dilution coagulopathy. Cryoprecipitate may also be used for management of intracranial bleeding related to thrombolytic therapy (tissue plasminogen activator). Pathogen-reduced cryoprecipitated fibrinogen concentrate, which is derived from pathogen-reduced plasma, is useful for the treatment and control of bleeding associated with fibrinogen deficiency.

GRANULOCYTE TRANSFUSIONS

Granulocytes are sometimes transfused in neutropenic patients with life-threatening infections (Chapters 153 and 260). However, their benefit in such patients is unproven.[A6]

INDICATIONS FOR COMPONENT MODIFICATION

LEUKOREDUCTION

The majority of RBC and platelet products are leukoreduced prior to storage. Leukoreduction removes white blood cells from the unit to mitigate febrile nonhemolytic transfusion reactions, HLA alloimmunization, CMV transmission, and transfusion-related immunomodulation. Thus, leukoreduction is indicated in patients at risk for these complications, such as potential transplant patients, patients with a history of febrile nonhemolytic transfusion reactions, pregnant patients, and immunocompromised patients.

CYTOMEGALOVIRUS SERONEGATIVE

For the mitigation of transfusion-transmitted cytomegalovirus, patients at risk for cytomegalovirus disease should receive leukoreduced, cytomegalovirus seronegative,[A7] or pathogen-reduced blood components. Such at-risk patients include transplant candidates, transplant recipients, patients undergoing chemotherapy, pregnant women, and immunocompromised patients.

IRRADIATION

Irradiation or pathogen reduction, which inactivates white blood cells so they cannot replicate, is used to prevent transfusion-associated graft-versus-host disease. Indications for irradiation include congenital immunodeficiency; stem cell transplantation; Hodgkin disease; use of purine analogue drugs, anti-CD32, or other drugs that alter T-lymphocyte function; intrauterine transfusion; neonatal exchange transfusion; leukemia; lymphoma; intense chemotherapy; congenital heart disease (DiGeorge syndrome); and aplastic anemia. Products from blood relatives, HLA match products, and granulocyte products should be irradiated.

PATHOGEN REDUCTION

Pathogen reduction mitigates the need for irradiation, cytomegalovirus seronegative blood products, testing for *Babesia*, and bacterial screening. Currently, this technology is mostly used in platelets and plasma. For plasma, solvent/detergent treated, pooled plasma product, or pathogen-reduced plasma product is available. The incidence of transfusion-related acute lung injury and allergic reactions with solvent detergent-treated pooled plasma is much lower than the risk with other plasma products.

For pathogen-reduced platelets data show: uncertainty as to whether pathogen-reduced platelets increase the risk of any bleeding, no evidence of difference in the incidence of clinically significant bleeding complications, probably no difference in all-cause mortality, probably no difference in serious adverse events, an increased risk of developing platelet refractoriness, an increased requirement for platelet transfusions, a shorter time interval between transfusions, and lower corrected platelet count increment compared with standard platelets.[A8]

SPECIFIC CLINICAL SETTINGS

Perioperative Alternatives to Allogeneic Transfusion

Autologous Donations

Patients may donate their own blood in the weeks prior to elective surgery. The advantages of such "preoperative autologous donation" include decreased risk of infectious disease transmission, decreased risk of alloimmunization to donor antigens, and the ready availability of compatible blood products if the patient requires rare RBC components. Its disadvantages include additional cost, potential adverse reactions associated with autologous blood donation, and the development of iatrogenic preoperative anemia associated with phlebotomy. These components are more expensive than allogeneic components because they are specially handled to ensure that they are transfused only to the intended recipient. Further concerns include bacterial contamination, transfusion-associated circulatory overload, and the potential for mislabeling. Additionally, the wastage rate for autologous components is about 60%, thereby suggesting that most autologous donations are unnecessary. As a result, routine use of autologous components is not recommended.

Directed Donors

Individuals who donate blood components for use by a specific patient, typically a family member or friend, are referred to as "directed donors." Although directed donors are typically motivated by compassion for the patient, components from directed donations are not safer than components from volunteer donations. Directed donors may intentionally or unintentionally omit information that might otherwise preclude them from donating, and this omission may compromise the safety of the resulting product. Nevertheless, directed donations from relatives may be medically desirable when a patient requires HLA-matched components or RBCs with a rare phenotype. All directed donations from blood relatives should be irradiated to prevent transfusion-associated-graft-versus-host disease.

Reinfusion of Recovered Blood

To salvage and reinfuse blood lost during a surgical procedure, intraoperative blood recovery is an option. The simplest approach is direct reinfusion of recovered blood without washing. In this method, recovered blood is collected, anticoagulant is added, and blood is reinfused. Recovered blood also can be washed with saline prior to reinfusion. Blood recovered by these methods must be reinfused within 4 hours or, if stored at 1° to 6° C, within 24 hours of the start of collection.

Cell salvage can be set up to meet the needs of patients who refuse blood transfusion, such as some Jehovah Witnesses. Potential contraindications to intraoperative blood recovery include a contaminated surgical site, blood collected from surgical procedures for cancer with the potential risk of tumor cell contamination, and blood collected in surgical sites that contain medications.

In the process of acute normovolemic hemodilution, intraoperative removal of whole blood into standard collection bags is replaced simultaneously with crystalloid or colloid of equal volume. Hemodilution reduces RBC loss because a bleeding patient with an iatrogenically lowered hematocrit loses fewer RBCs. The removed whole blood is stored in the operating room and reinfused in reverse order of collection. This approach allows for the components with the highest hematocrit to be transfused last, presumably when surgical bleeding has been controlled. The whole blood also has functioning platelets and coagulation factors. The iatrogenic anemia can compromise oxygen transport, but this problem is usually mitigated by the decrease in blood viscosity. If kept at room temperature, the collected components must be used within 8 hours of collection; if stored at 1° to 6° C, they must be used within 24 hours of collection.

Most patients tolerate the transfusion of autologous blood collected postoperatively from draining serosal cavities. Adverse effects can include respiratory distress, hypotension with anaphylaxis, and fever. Blood collected postoperatively must be used within 6 hours of collection.

MASSIVE TRANSFUSION

Massive transfusion is defined as transfusion of 10 or more RBC components (units) within 24 hours. Other definitions of massive transfusion include replacement of 50% of total blood volume within 3 hours or blood loss exceeding 150 mL per minute. Current practice is for a 1 : 1 : 1 or 1 : 1 : 2 ratio of plasma : platelets : RBCs during massive transfusion. In patients with severe trauma, a 1 : 1 : 1 ratio can reduce the rate of exsanguination within 24 hours and provide better hemostasis compared with a 1 : 1 : 2 ratio, but overall rates of complications and mortality are no different at 24 hours and 30 days.[A9] As a result, the 1 : 1 : 2 ratio remains the most commonly recommended transfusion ratio. Other options include the use of whole blood,[17] tranexamic acid, and the decision to transfuse guided by thromboelastography to assess clotting under expert supervision. Randomized trials have demonstrated improved survival with prehospital plasma transfusion when transport times are longer than 20 minutes.[A10]

HEMOGLOBINOPATHIES

Patients with hemoglobinopathies, such as thalassemia (Chapter 148) and sickle cell disease (Chapter 149), often require chronic transfusion. Patients who have sickle cell disease are at especially high risk of forming alloantibodies.

The use of prophylactic antigen matching has decreased alloimmunization rates from about 50% to 10% with limited matching (D, C, E, K antigens) and 5% with extended matching (D, C, E, K, Jk^b, Fy^a antigens). Additionally, individuals of African descent have variant Rh genes so may phenotype as positive but make alloantibodies to the antigen. As a result, genotyping for RBC antigens in this population is helpful to determine the appropriate antigen-negative component product. Providing units based on the patient's genotype has increased post-transfusion hemoglobin levels and transfusion intervals. Lastly, RBC units for sickle cell patients are hemoglobin S negative and labeled as such.

Patients with thalassemia (Chapter 148) may require chronic lifelong transfusion as frequently as every 2 to 5 weeks to maintain pretransfusion hemoglobin levels above 9 to 10.5 g/dL in order to promote normal growth and physical activity and suppress bone marrow activity. The predominant transfusion complication in these patients is iron overload.

PATIENT BLOOD MANAGEMENT

The goals of a patient blood management program include increasing awareness of evidence-based transfusion guidelines, reducing the likelihood of a transfusion, minimizing blood loss, improving blood utilization, continuously educating clinicians, and standardizing metrics. Implementation of patient blood management programs have decreased blood utilization, decreased cost, and improved patient care. Optimizing RBC mass includes the preoperative evaluation of anemia, the timing of surgery, and the optimization of postoperative erythropoiesis. Minimizing blood loss includes management of the risk of bleeding, meticulous surgical technique, blood sparing devices, blood conservation strategies, maintenance of normothermia, use of hemostatic agents, monitoring for postoperative bleeding, blood salvage, minimizing iatrogenic blood loss, managing anticoagulation, and prophylaxis for gastrointestinal hemorrhage. Optimizing physiologic anemia reserve includes estimating blood loss compared with the patient's tolerance, formulating a patient-specific blood management plan, optimizing cardiac output and oxygenation, optimizing anemia reserve, maximizing oxygen delivery, minimizing oxygen consumption, avoiding and treating infections, and using restrictive transfusion thresholds.

To decrease unnecessary use of blood products, general principles include:[18,19]

1. Do not transfuse more units than necessary. Transfuse using a restrictive threshold. Consider transfusing a single unit of RBCs in stable, nonbleeding hospitalized patients, and then checking the patient's hemoglobin and clinical status prior to further transfusions.
2. Do not proceed with elective surgery prior to evaluating and treating anemia.
3. Do not transfuse RBCs for iron deficiency if patients are hemodynamically stable. Iron-deficient patients should receive oral or intravenous iron.
4. Do not use blood products to reverse warfarin. Patients can generally be reversed with vitamin K alone. Prothrombin complex concentrates should be used in the setting of serious bleeding or the need for emergent surgery. Do not transfuse plasma to correct a mildly elevated INR (<1.8).
5. Do not perform serial blood counts on clinically stable patients. Repeat blood draws can result in iatrogenic anemia.
6. Do not transfuse O-negative blood except to O-negative patients and in emergencies for women of childbearing potential with unknown blood group. O-negative RBCs are in chronic short supply and should be restricted to patients who need them.
7. Do not transfuse AB plasma to non-AB patients except in emergency situations in which ABO blood type is unknown. Group A plasma can also be used for emergency transfusions.

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For the General References and other additional features, please visit Elsevier eBooks+ at https://ebooks.health.elsevier.com.

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163 HEMATOPOIETIC CELL TRANSPLANTATION

NELSON J. CHAO AND ARMAND KEATING

Hematopoietic cell transplantation is a procedure by which hematopoietic stem and progenitor cells are infused intravenously to restore hematopoiesis and immune function following a chemotherapy conditioning regimen, with or without radiation therapy, that ablates the endogenous hematopoietic and immune system.[1] Stem cells used for hematopoietic cell transplantation are of hematopoietic origin, in contrast to the more primitive pluripotent stem cells (i.e., embryonic stem cells) that are considered for regenerative therapy because of their ability to differentiate into virtually any somatic cell. Hematopoietic cell transplantation is now a standard treatment for many hematologic malignancies, immunodeficiency states, enzyme deficiencies (e.g., Hurler syndrome [Chapter 192]), and defective hematopoietic states (e.g., severe aplastic anemia [Chapter 151]).[2] In addition, hematopoietic cell transplantation can also treat hemoglobinopathies, immune deficiency states, and selected autoimmune diseases.[3] The infused hematopoietic stem/progenitor cells can give rise to all blood elements, including cells of the immune system, and they may be genetically modified to enhance their function. Furthermore, hematopoietic stem/progenitor cells may be manipulated ex vivo and used in the burgeoning field of regenerative medicine. Taken together, hematopoietic cell transplantation is a major component and foundation of the broader field of cellular therapy (Chapter 34).

The three cell sources for hematopoietic cell transplantation are syngeneic (i.e., cells from an identical twin), allogeneic (i.e., cells from a nonidentical donor), and autologous (i.e., reinfusion of one's own cells). The determination of the type of hematopoietic cell transplantation that a patient receives is based on the disease to be treated, the disease state (e.g., initial treatment vs. treatment of recurrent disease), the urgency with which the disease needs to be treated, the availability of a donor, and the time necessary to obtain hematopoietic stem/progenitor cells from a donor.

Hematopoietic stem/progenitor cells may be obtained from bone marrow (by serial aspirations from the posterior iliac crests while the donor is under general anesthesia), peripheral blood (after stimulation with hematopoietic growth factors such as granulocyte colony–stimulating factor [G-CSF] or plerixafor [a CXCR4 antagonist], followed by leukapheresis), or umbilical cord blood. In current practice, peripheral blood is the source for hematopoietic stem/progenitor cells in approximately 90% of autologous transplants and in approximately 70% of allogeneic transplants because of the relative ease of procurement and the donor's rate of hematopoietic recovery after infusion compared with cells derived from bone marrow.

Hematopoietic stem/progenitor cells may be infused fresh or after cryopreservation, which involves processing the cells in culture medium containing

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HEMOGLOBINOPATHIES

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Patients with thalassemia (Chapter 148) may require chronic lifelong transfusion as frequently as every 2 to 5 weeks to maintain pretransfusion hemoglobin levels above 9 to 10.5 g/dL in order to promote normal growth and physical activity and suppress bone marrow activity. The predominant transfusion complication in these patients is iron overload.

PATIENT BLOOD MANAGEMENT

The goals of a patient blood management program include increasing awareness of evidence-based transfusion guidelines, reducing the likelihood of a transfusion, minimizing blood loss, improving blood utilization, continuously educating clinicians, and standardizing metrics. Implementation of patient blood management programs have decreased blood utilization, decreased cost, and improved patient care. Optimizing RBC mass includes the preoperative evaluation of anemia, the timing of surgery, and the optimization of postoperative erythropoiesis. Minimizing blood loss includes management of the risk of bleeding, meticulous surgical technique, blood sparing devices, blood conservation strategies, maintenance of normothermia, use of hemostatic agents, monitoring for postoperative bleeding, blood salvage, minimizing iatrogenic blood loss, managing anticoagulation, and prophylaxis for gastrointestinal hemorrhage. Optimizing physiologic anemia reserve includes estimating blood loss compared with the patient's tolerance, formulating a patient-specific blood management plan, optimizing cardiac output and oxygenation, optimizing anemia reserve, maximizing oxygen delivery, minimizing oxygen consumption, avoiding and treating infections, and using restrictive transfusion thresholds.

To decrease unnecessary use of blood products, general principles include:[18,19]

1. Do not transfuse more units than necessary. Transfuse using a restrictive threshold. Consider transfusing a single unit of RBCs in stable, nonbleeding hospitalized patients, and then checking the patient's hemoglobin and clinical status prior to further transfusions.
2. Do not proceed with elective surgery prior to evaluating and treating anemia.
3. Do not transfuse RBCs for iron deficiency if patients are hemodynamically stable. Iron-deficient patients should receive oral or intravenous iron.
4. Do not use blood products to reverse warfarin. Patients can generally be reversed with vitamin K alone. Prothrombin complex concentrates should be used in the setting of serious bleeding or the need for emergent surgery. Do not transfuse plasma to correct a mildly elevated INR (<1.8).
5. Do not perform serial blood counts on clinically stable patients. Repeat blood draws can result in iatrogenic anemia.
6. Do not transfuse O-negative blood except to O-negative patients and in emergencies for women of childbearing potential with unknown blood group. O-negative RBCs are in chronic short supply and should be restricted to patients who need them.
7. Do not transfuse AB plasma to non-AB patients except in emergency situations in which ABO blood type is unknown. Group A plasma can also be used for emergency transfusions.

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For the General References and other additional features, please visit Elsevier eBooks+ at https://ebooks.health.elsevier.com.

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163 HEMATOPOIETIC CELL TRANSPLANTATION

NELSON J. CHAO AND ARMAND KEATING

Hematopoietic cell transplantation is a procedure by which hematopoietic stem and progenitor cells are infused intravenously to restore hematopoiesis and immune function following a chemotherapy conditioning regimen, with or without radiation therapy, that ablates the endogenous hematopoietic and immune system.[1] Stem cells used for hematopoietic cell transplantation are of hematopoietic origin, in contrast to the more primitive pluripotent stem cells (i.e., embryonic stem cells) that are considered for regenerative therapy because of their ability to differentiate into virtually any somatic cell. Hematopoietic cell transplantation is now a standard treatment for many hematologic malignancies, immunodeficiency states, enzyme deficiencies (e.g., Hurler syndrome [Chapter 192]), and defective hematopoietic states (e.g., severe aplastic anemia [Chapter 151]).[2] In addition, hematopoietic cell transplantation can also treat hemoglobinopathies, immune deficiency states, and selected autoimmune diseases.[3] The infused hematopoietic stem/progenitor cells can give rise to all blood elements, including cells of the immune system, and they may be genetically modified to enhance their function. Furthermore, hematopoietic stem/progenitor cells may be manipulated ex vivo and used in the burgeoning field of regenerative medicine. Taken together, hematopoietic cell transplantation is a major component and foundation of the broader field of cellular therapy (Chapter 34).

The three cell sources for hematopoietic cell transplantation are syngeneic (i.e., cells from an identical twin), allogeneic (i.e., cells from a nonidentical donor), and autologous (i.e., reinfusion of one's own cells). The determination of the type of hematopoietic cell transplantation that a patient receives is based on the disease to be treated, the disease state (e.g., initial treatment vs. treatment of recurrent disease), the urgency with which the disease needs to be treated, the availability of a donor, and the time necessary to obtain hematopoietic stem/progenitor cells from a donor.

Hematopoietic stem/progenitor cells may be obtained from bone marrow (by serial aspirations from the posterior iliac crests while the donor is under general anesthesia), peripheral blood (after stimulation with hematopoietic growth factors such as granulocyte colony–stimulating factor [G-CSF] or plerixafor [a CXCR4 antagonist], followed by leukapheresis), or umbilical cord blood. In current practice, peripheral blood is the source for hematopoietic stem/progenitor cells in approximately 90% of autologous transplants and in approximately 70% of allogeneic transplants because of the relative ease of procurement and the donor's rate of hematopoietic recovery after infusion compared with cells derived from bone marrow.

Hematopoietic stem/progenitor cells may be infused fresh or after cryopreservation, which involves processing the cells in culture medium containing

ABSTRACT

Hematopoietic cell transplantation is a procedure by which hematopoietic stem and progenitor cells are infused intravenously to restore hematopoiesis and immune function following a chemotherapy conditioning regimen, with or without radiation therapy, that ablates the endogenous hematopoietic and immune system. Stem/progenitor cells can be collected from a variety of sources, including bone marrow, peripheral blood, or umbilical cord blood.

The three types of hematopoietic cell transplantation are syngeneic (i.e., cells from an identical twin), allogeneic (i.e., cells from a nonidentical donor), and autologous (i.e., reinfusion of one's own cells). Because of better tissue typing, less intensive preparatory regimens, modern supportive measures, and expanded options for identifying qualified donors, the outcomes of hematopoietic cell transplantation have steadily improved. Hematopoietic cell transplantation is now used to treat blood cancers and other malignancies, enzyme deficiencies, hemoglobinopathies, and autoimmune disorders.

Complications associated with all forms hematopoietic cell transplantation include direct organ toxicities from the conditioning regimen as well as prolonged cytopenias that can result in infections and bleeding. Graft-versus-host disease (i.e., the donor rejecting the recipient) is a complication unique to allogeneic hematopoietic cell transplantation. Recurrence of malignancy remains the primary cause of treatment failure after both autologous and allogeneic hematopoietic cell transplantation.

KEYWORDS

hematopoietic cell transplantation
graft-versus-host disease
allogeneic
autologous
syngeneic
conditioning regimen

dimethyl sulfoxide (DMSO), placing them in specialized plastic bags, controlled freezing, and then storing in the vapor phase of liquid nitrogen until needed. Cord blood hematopoietic stem/progenitor cells are collected at the time of delivery, cryopreserved, and stored. For allogeneic donation, cells may also be infused on the day of collection. For autologous donation, cells are almost always cryopreserved.

ALLOGENEIC HEMATOPOIETIC CELL TRANSPLANTATION

The distinctive characteristics of allogeneic hematopoietic cell transplantation are that the stem cell graft allows for the establishment of a new immune system in addition to reconstitution of white blood cells, red blood cells, and platelets. The new immune system can be a major advantage if the immunologic response is directed against malignant cells, referred to as the graft-versus-leukemia or graft-versus-tumor effect, which potentially can eradicate disease and reduce the chance of disease relapse. However, if the immunologic response is directed against antigens present on normal tissues, the graft-versus-host response can result in the destruction of normal organs and is clinically described as graft-versus-host disease (GVHD). The risk for both graft rejection (host-versus-graft reaction) and GVHD rises with the degree of human leukocyte antigen (HLA) disparity between the donor and the recipient as well as the degree of immune suppression.

The clinical importance of the role that immunocompetent donor T cells play in mediating a graft-versus-tumor effect is exemplified by the increased rates of relapse in patients who receive allogeneic bone marrow grafts from which T cells had been removed (T-cell depletion), an inverse correlation between relapse and severity of GVHD, and increased rates of relapse after syngeneic or autologous hematopoietic cell transplantation in patients who have received similar conditioning regimens. However, the most compelling evidence for the importance of T cells mediating the graft-versus-tumor effect is the clinical observation that infusion of allogeneic T cells alone, termed a *donor lymphocyte infusion*, at a time remote from the transplant conditioning regimen can successfully eradicate leukemia that has persisted or recurred after allogeneic hematopoietic cell transplantation. Nevertheless, the clinical effectiveness of graft-versus-tumor can vary widely among different malignancies.

Because of the immunologic barriers that can result in graft rejection and GVHD, allogeneic hematopoietic cell transplantation requires that the donor and the recipient share as many key genes as possible. The most important of these are HLAs (Chapter 38), which are derived from the MHC located on chromosome 6. The HLA loci include HLA-A, HLA-B, HLA-C, DR, DP, and DQ. A single set of major histocompatibility complex (MHC) alleles, described as a haplotype, is inherited from each parent, thereby resulting in HLA pairs. A clinical "match" means that HLAs in the donor match the HLAs in the patient.

The choice of donor for an allogeneic hematopoietic cell transplantation takes into account several factors, including the patient's specific disease and disease state (i.e., remission vs. relapse) and the time that is required for obtaining hematopoietic stem/progenitor cells from a donor. A fully HLA-matched sibling is the preferred donor source because the risks for graft rejection and GVHD are lowest. The probability of having an HLA match with a single sibling is 25% and increases with the number of siblings within a specific family. This probability can be estimated using the following formula: chance of having an HLA-matched sibling $= 1 - (0.75)^n$, where n is the number of potential sibling donors. There is approximately a 1% chance of a crossover event (i.e., genetic material switched between chromosomes during meiosis), primarily between the HLA-A and the HLA-B loci. The clinical outcomes for allogeneic hematopoietic cell transplantation using a sibling with a single HLA mismatch are similar to those with a fully HLA-matched sibling.

For patients who lack an HLA-identical sibling donor, the alternative sources for allogeneic hematopoietic stem/progenitor cells include a fully HLA-matched volunteer unrelated donor, a fully or partially HLA-matched cord blood unit, or a partially HLA-matched first-degree family member. HLA genes are highly polymorphic, so the odds that any two unrelated individuals are HLA identical for main loci are less than 1 in 10,000. However, tens of millions of people worldwide are currently listed as potential volunteer donors, so a donor can be found for about 50% of all patients for whom a search is initiated. The probability of identifying a suitable volunteer donor is highly dependent on race because of varying degrees of HLA diversity. For example, for persons of northern European extraction, the probability of a match can be as high as 90%. In contrast, minority populations may have less than a 20% probability of a match because of fewer volunteer donors and a higher degree of genetic variation.

It usually takes about 2 to 4 months to locate and fully evaluate an unrelated donor, which may be too long for some patients with rapidly progressive malignancies. When a suitable volunteer is not available or a donor is needed more urgently, alternative sources can be considered, including partially HLA-matched ("haploidentical") relatives or umbilical cord blood. Haploidentical hematopoietic stem/progenitor cells are readily available but have increased risks for graft rejection and GVHD. These risks can be reduced by either ex vivo or in vivo T-cell depletion methods, but T-cell depletion may lead to delayed immune reconstitution and competency after transplantation, thereby increasing the risks for infection and recurrent disease. However, post-transplantation cyclophosphamide for GVHD prophylaxis has markedly increased the clinical use of haploidentical donors.

Umbilical cord blood hematopoietic stem/progenitor cells, which are taken at the time of delivery and stored in cord blood banks, are readily available within 2 to 4 weeks when needed. Because of the unique immature biology of lymphocytes in umbilical cord blood, these transplants are associated with less GVHD; consequently, the HLA-matching requirements are less strict, and two or three HLA mismatches may be acceptable. However, the small volume (50 to 150 mL) of cord blood that can be collected limits the number of hematopoietic stem/progenitor cells and often prohibits their use in adults because successful engraftment correlates with the number of cells per patient body weight. The limitation of cell dose can be overcome by the use of more than one cord blood unit and the ability to expand cord blood cells ex vivo, thereby resulting in engraftment rates similar to other cell sources. One significant disadvantage is that the use of a cord blood unit eliminates the probability of obtaining additional cells if the graft fails or if a donor lymphocyte infusion is required.

After a source of allogeneic stem cells has been identified, patients then receive a pretransplant regimen with the intent of "conditioning" or "preparing" them for the infusion (Fig. 163-1). These conditioning regimens are designed to be adequately immunosuppressive to overcome the host-versus-graft reaction and permit engraftment. They also are designed to eradicate the primary tumor in patients with an underlying malignancy. Most conditioning regimens use chemotherapy alone or a combination of total body irradiation or total nodal irradiation with chemotherapy. The doses of total body and total lymphoid irradiation vary between 200 and 1440 cGy. The most commonly used chemotherapy for conditioning regimens is an alkylating agent (e.g., cyclophosphamide, busulfan, thiotepa) combined with immunosuppressive drugs such as fludarabine. Conditioning regimens also may contain monoclonal antibodies that target T cells (e.g., antithymocyte globulin, alemtuzumab).

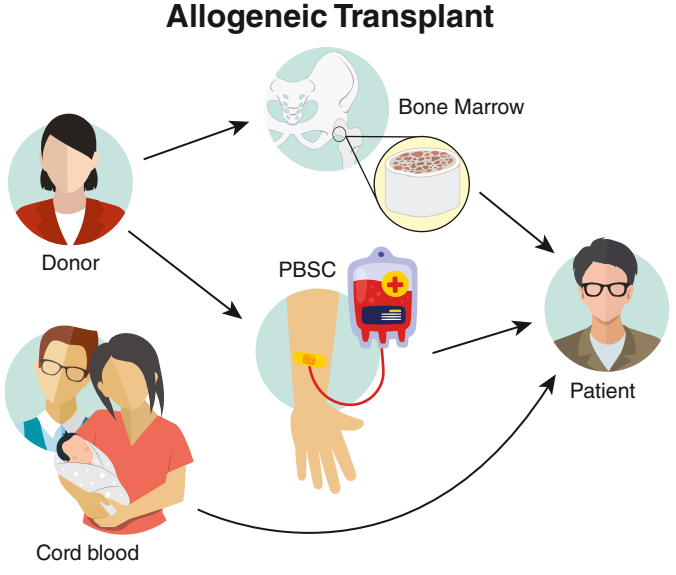

FIGURE 163-1. The process of allogeneic hematopoietic cell transplantation. (1) The patient receives a conditioning regimen of chemotherapy and/or radiation therapy that is used to both eliminate the underlying malignancy and suppress the immune system to prevent rejection of the allogeneic hematopoietic stem cells. (2) Allogeneic hematopoietic stem cells are then collected directly from the bone marrow or from the blood of a related or unrelated stem cell donor and infused intravenously into the donor. (3) After the infusion of the hematopoietic stem cells, the patient receives immunosuppressant drugs to help prevent the development of graft-versus-host disease (GVHD). PBSC = peripheral blood stem cells. (Image courtesy of the National Marrow Donor Program.)

The choice of a specific conditioning regimen depends on the disease being treated, and the doses of chemotherapy and radiation are highly variable. When the doses result in a degree of myelosuppression and immunosuppression that is nearly universally fatal without the infusion of hematopoietic stem/progenitor cells as a rescue product, they are referred to as myeloablative.

Allogeneic hematopoietic cell transplantation with myeloablative conditioning regimens has been performed successfully in patients older than age 60 years, but survival after transplantations declines with increasing age, thereby limiting the application of allogeneic transplantation to a minority of patients who potentially could benefit from this procedure. However, the demonstration that an immune-mediated graft-versus-tumor effect plays a central role in the therapeutic efficacy of allogeneic hematopoietic cell transplantation led to the development of less intensive conditioning regimens that are adequately immunosuppressive to permit the engraftment of donor cells but associated with decreased toxicities compared with myeloablative regimens. Another advantage of less intensive conditioning is that it can be delivered outside of the hospital setting, so that patients receive their care in the outpatient setting and are able to stay in a local apartment or their actual home if they live close to the center. Although the reduced doses of radiation and chemotherapy result in decreased antitumor activity and are associated with higher rates of recurrent disease after transplantation, these "nonmyeloablative" and "reduced-intensity" conditioning regimens have markedly increased the potential option of allogeneic hematopoietic cell transplantation for older patients and patients with preexisting comorbidities.

SYNGENEIC HEMATOPOIETIC CELL TRANSPLANTATION

The major advantage of a syngeneic hematopoietic cell transplantation from an identical twin is that it is not associated with GVHD or graft rejection, thereby resulting in a relatively low risk for treatment-related morbidity and mortality. Syngeneic hematopoietic cell transplantation, as with allogeneic transplantation, also avoids potential contamination with malignant cells. The major disadvantage of syngeneic transplantation is that it does not provide the graft-versus-leukemia effect associated with allogeneic transplantation. However, since far less than 1% of patients have an identical twin, syngeneic transplantation is rarely an option.

AUTOLOGOUS HEMATOPOIETIC CELL TRANSPLANTATION

The major rationale for autologous hematopoietic cell transplantation with the patient's own cells is that certain malignancies, such as leukemias and lymphomas, have a steep dose-response curve to chemotherapy and, to a relative degree, radiation. However, the associated limitation of higher doses of chemotherapy or radiation attenuates myelosuppressive effect. The infusion of autologous hematopoietic stem/progenitor cells (and for that matter, allogeneic and syngeneic cells) can restore hematopoiesis after the prior administration of high-dose chemotherapy, with or without radiation. The major advantages of autologous as compared with allogeneic transplantation are that the patient can serve as his or her own donor and that it may be performed in older patients with significantly lower morbidity and mortality because of the absence of GVHD. Although patients undergoing autologous hematopoietic cell transplantation have higher relapse rates than patients undergoing allogeneic transplantation, the lower rates of other complications seem to translate into similar long-term outcomes. Nevertheless, the higher conditioning doses of chemotherapy before autologous hematopoietic cell transplantation can be associated with more morbidity than conventional doses of chemotherapy.

INDICATIONS FOR TRANSPLANTATION

An estimated 90,000 hematopoietic cell transplantations are performed annually worldwide, primarily for the treatment of hematologic malignancies, bone marrow failure states, and immune and enzyme deficiencies (Fig. 163-2).

Acute Myeloid Leukemia

Allogeneic hematopoietic cell transplantation is capable of resulting in the long-term survival of 10% of patients with otherwise refractory acute myeloid leukemia (AML; Chapter 168).[4] By comparison, cure rates of 40 to 70% have been reported with hematopoietic cell transplantation performed during a first complete remission, and rates of 20 to 40% have been achieved in patients treated while in a second or subsequent complete remission. In randomized trials of patients with AML in first complete remission, both autologous and allogeneic hematopoietic cell transplantation provide improved leukemia-free survival compared with conventional chemotherapy. In terms of overall survival, however, meta-analyses demonstrate improvement with allogeneic hematopoietic cell transplantation compared with nonallogeneic treatments for AML in first complete remission in patients who have intermediate- and high-risk cytogenetics but not in patients who have good-risk AML.[A1] Data also indicate the importance of molecular mutations. For example, intermediate-risk AML with a normal karyotype represents a highly heterogeneous group with respect to prognosis based on molecular mutation status. Approximately one third of patients with normal-karyotype AML harbor the *FLT3*-internal tandem mutation, which carries a poor prognosis and may benefit from HLA-matched related hematopoietic cell transplantation, regardless of the presence of other mutations.

Acute Lymphoblastic Leukemia

Conventional chemotherapy provides excellent outcomes for childhood acute lymphoblastic leukemia (ALL), except for ALL associated with the Philadelphia chromosome (Chapter 168). In adults, however, remission, though frequently attained after intensive induction therapy, is commonly followed by relapse. Adverse prognostic factors include the presence of the Philadelphia chromosome, a high white blood cell count, advancing age, and the presence of minimal residual disease. Studies suggest that consolidation therapy including hematopoietic cell transplantation after initial chemotherapy improves overall survival compared with conventional chemotherapy alone, particularly for those who are Philadelphia chromosome–positive. For both pediatric and adult patients with relapsed ALL, the overall prognosis is relatively poor, and the general treatment strategy is to obtain a second complete remission and then proceed to an allogeneic hematopoietic cell transplantation.

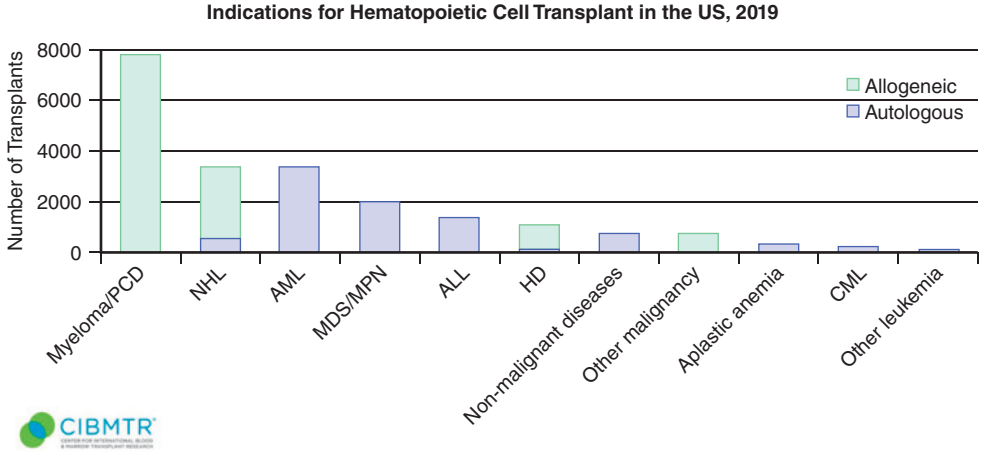

FIGURE 163-2. Indications for hematopoietic cell transplantation in the United States as reported to the Center for International Blood and Marrow Transplant Research. ALL = acute lymphocytic leukemia; AML = acute myeloid leukemia; CML = chronic myelogenous leukemia; HD = Hodgkin disease; MDS/MPN = myelodysplastic syndrome/myeloproliferative neoplasms; NHL = non-Hodgkin lymphoma. (Courtesy of the Center for International Blood and Marrow Transplant Research.)

Myelodysplastic Syndrome

The only known curative treatment for myelodysplastic syndrome (Chapter 167) is allogeneic hematopoietic cell transplantation. Unfortunately, the vast majority of patients are not considered candidates for this therapy for many reasons, including advanced age (the median age at diagnosis is in the seventh to eighth decade of life), comorbid diseases, the inability to identify a suitable donor, and the patient's preferences. The best results have been obtained in younger patients, who are earlier in their disease course and have not received any prior therapy. Increasing evidence suggests that reduced-intensity allogeneic hematopoietic cell transplantation may benefit even considerably older patients with myelodysplastic syndrome. A randomized trial of patients with myelodysplastic syndrome or secondary AML showed that a busulfan-based reduced-intensity conditioning regimen resulted in at least a 2-year relapse-free and overall survival, similar to that after a myeloablative conditioning regimen for allogeneic stem cell transplantation.[A2]

Chronic Myeloid Leukemia

In patients with chronic myeloid leukemia (CML; Chapter 170), hematopoietic cell transplantation is reserved for patients who are resistant to or intolerant of treatment with tyrosine kinase inhibitors, especially those who develop an accelerated phase or blast crisis CML. Although results of allogeneic hematopoietic cell transplantation are poor for accelerated-phase or blast-crisis disease, some patients may respond to tyrosine kinase inhibitors after transplantation.

Myeloproliferative Neoplasms

Myeloproliferative neoplasms, such as primary myelofibrosis, polycythemia vera, and essential thrombocythemia (Chapter 152), usually are chronic in nature but can progress to a "spent" phase and evolve into myeloid metaplasia, which is characterized by bone marrow fibrosis and a generally poor prognosis with transformation into acute leukemia and a median survival of less than 3 years. Conventional treatment options are limited at this stage, and the accepted standard of care for myeloid metaplasia/myelofibrosis is allogeneic hematopoietic cell transplantation, especially nonmyeloablative transplantation because of the older age of most patients with this condition.

Non-Hodgkin Lymphoma

Syngeneic, allogeneic, and autologous hematopoietic cell transplantation have all been reported to yield long-term, disease-free survival and an apparent cure for patients with advanced non-Hodgkin lymphoma (Chapter 171). Based on its risk-benefit ratio and availability, the standard of care for patients with primary refractory or chemotherapy-sensitive relapsed non-Hodgkin lymphoma of specific histologies (including diffuse large B-cell lymphoma) has been autologous hematopoietic cell transplantation. For mantle cell lymphoma, autologous hematopoietic cell transplantation appears to improve progression-free and possibly overall survival when used as part of front-line therapy, especially when combined with maintenance rituximab post-transplantation.[A3] The development of chimeric antigen receptor (CAR) T cells for lymphomas may challenge this sequence depending on the results of ongoing trials.

However, the graft-versus-tumor effect against various non-Hodgkin lymphoma histologies is very heterogeneous, and consensus is currently lacking regarding for which histology allogeneic hematopoietic cell transplantation is appropriate. For example, autologous transplantation can result in disease-free survival rates as high as 60% in patients with indolent follicular non-Hodgkin lymphoma,[A4] but late relapses after transplantation and the long overall survival observed with current medical therapy have reduced the role for hematopoietic cell transplantation despite its graft-versus-tumor effects.

Hodgkin Lymphoma

Based on a small prospective randomized trial conducted in the early 1990s, autologous hematopoietic cell transplantation has become the standard of care for patients with primary refractory and relapsed Hodgkin lymphoma (Chapter 172) whose disease nevertheless remains sensitive to chemotherapy. The usual approach is first to treat these patients with second-line chemotherapy and then with high-dose chemotherapy and autologous hematopoietic cell transplantation. Allogeneic transplantation has had a limited role because of the efficacy of autologous transplantation and the significant treatment-related toxicities associated with myeloablative allogeneic transplantation, but reduced-intensity allogeneic transplantation can be an option, especially in patients who relapse after autologous transplantation.

Multiple Myeloma

Although immunomodulatory derivatives and proteasome inhibitors are highly effective for the treatment of multiple myeloma (Chapter 173), early autologous hematopoietic cell transplantation, when feasible, remains the standard of care.[5] Prospective comparisons of single versus tandem autologous transplants give conflicting results, although overall survival rates appear similar. Single-arm and randomized trials support the use of a second autologous transplantation for patients who relapse after the first autologous transplantation, provided the duration of response was more than 1 year after the initial transplantation.

Solid Tumors

High-dose chemotherapy plus transplantation has had success in the treatment of some chemotherapy-sensitive solid tumors, including germ cell tumors and childhood cancers such as neuroblastoma and Wilms tumor. In patients who have germ cell tumors that are not cured by platinum-based chemotherapy regimens, high-dose chemotherapy and autologous hematopoietic cell transplantation has resulted in prolonged disease-free survival, even in patients with refractory disease.

Nonmalignant Conditions

Allogeneic hematopoietic cell transplantation can lead to long-term, disease-free survival in more than 50% of patients with severe aplastic anemia (Chapter 151). When compared with standard immunosuppressive therapy, allogeneic transplantation is more likely to produce a complete and durable reversal of the hematologic abnormalities. Patients with aplastic anemia who are less heavily transfused have better outcomes with allogeneic transplantation. For patients with less severe aplastic anemia, patients older than 40 years, and patients without a matched sibling donor, a trial of immunosuppression therapy is usually appropriate before consideration of allogeneic transplantation (Chapter 151).

Hematopoietic cell transplantation is also an effective treatment for other nonmalignant disorders, including thalassemia (Chapter 148), sickle cell disease (Chapter 149), immunodeficiency disorders, and enzyme deficiency states, primarily in children and young adults. Hemoglobinopathies can be cured by allogeneic hematopoietic cell transplantation, but new approaches such as gene therapy and the application of the clustered regularly interspaced short palindromic repeats (CRISPR) and CRISPR-associated protein 9 (CRISPR-Cas9) system may supplant hematopoietic cell transplantation (Chapter 34).[6] In thalassemia, the best transplant results have been obtained in pediatric patients with HLA-identical sibling donors. Adults tend to have more advanced disease with greater iron overload and more organ dysfunction; hence, they have high treatment-related mortality. Studies with nonmyeloablative regimens are ongoing. There is less experience with sickle cell disease (Chapter 149), partly because of reluctance to contemplate allogeneic hematopoietic cell transplantation in patients with an unpredictably variable clinical course.

For severe autoimmune disease, including systemic lupus erythematosus, rheumatoid arthritis, scleroderma, and multiple sclerosis, hematopoietic cell transplantation can reconstitute the immune system without the patient's native autoreactive T-cell clones. Trials have demonstrated clinically significant responses in patients with severe scleroderma (Chapter 246) and advanced multiple sclerosis (Chapter 380). In adults with severe scleroderma, for example, a randomized trial of myeloablative autologous hematopoietic cell transplantation showed long-term benefits, including improved event-free and overall survival, compared with 12 monthly infusions of cyclophosphamide.[A5]

COMPLICATIONS AFTER HEMATOPOIETIC STEM CELL TRANSPLANTATION

Improved supportive measures have led to a steady improvement in the outcomes of hematopoietic cell transplantation. Early complications, which are associated with all forms of hematopoietic cell transplantation, include direct organ toxicities from the conditioning regimen (e.g., mucositis) as well as prolonged cytopenias that can predispose to infections and bleeding.[7] Allogeneic hematopoietic cell transplantation also can be associated with acute and chronic GVHD. Long-term complications, particularly secondary malignancies, require that patients continue to be monitored for the remainder of their lives. A simple tally of the number of comorbid conditions can reliably predict nonrelapse mortality and survival and is useful for counseling patients before transplantation. Blood biomarkers may also

become useful for predicting complications after transplantation, including the future occurrence of GVHD and its responsiveness to therapy, as well as nonrelapse mortality.

GRAFT-VERSUS-HOST DISEASE (GVHD)

Around the time of engraftment, patients are at risk for the development of GVHD, which represents the most important clinical challenge with allogeneic hematopoietic cell transplantation.[8] GVHD occurs when donor T cells recognize recipient antigens as foreign and attack these cells/organs. The pathophysiology involves many other cell types, cytokines, and even an important interaction with the host's microbiome, primarily the gut microbiome.[9]

GVHD can be either acute,[10] generally presenting within the first 100 days after transplantation, or chronic,[11] generally presenting after the first 100 days. However, clinical features of both acute and chronic GVHD may be observed at any time following allogeneic hematopoietic cell transplantation, and clinical manifestations rather than time after transplantation may best determine whether the GVHD syndrome is considered acute or chronic.

The incidence of clinically significant GVHD (grades II to IV) in recipients of HLA-matched sibling grafts (T-cell replete) using tacrolimus and methotrexate for GVHD prophylaxis is approximately 30 to 40%. The incidence of grades II to IV GVHD in recipients of HLA-matched unrelated donor grafts is approximately 50 to 80%.

ACUTE GRAFT-VERSUS-HOST DISEASE (GVHD)

The broad category of acute GVHD includes "classic" acute GVHD, occurring within 100 days after transplantation or donor lymphocyte infusion, as well as "persistent," "recurrent," or "late" acute GVHD, occurring beyond 100 days after transplantation or donor lymphocyte infusion. Risk factors for acute GVHD include HLA mismatch, a female donor (particularly a multiparous donor), more advanced age of the patient and the donor, cytomegalovirus seropositivity of the donor or patient, use of an unrelated donor, or use of a T-cell-replete versus T-cell-depleted graft.

CLINICAL MANIFESTATIONS

Acute GVHD primarily affects the skin, gastrointestinal tract, and liver. The skin manifestations range from a maculopapular rash to generalized erythroderma or desquamation. The severity of gastrointestinal GVHD is based on the amount of diarrhea per day and the presence of an ileus. The severity of liver GVHD is scored on the basis of the bilirubin level. Organs may be involved in isolation or simultaneously.

DIAGNOSIS

Histologic confirmation can be valuable to exclude other possibilities, such as infection. Mild GVHD of the skin may demonstrate vacuolar degeneration and infiltration of the basal layer by lymphocytes. With more advanced disease, histologic findings of necrotic dyskeratotic cells with acantholysis may progress to frank epidermolysis. In the liver, early GVHD may be difficult to distinguish from hepatitis of other causes. A clinical grading system (Table 163-1) correlates with clinical outcome.

PREVENTION

The best approach to GVHD is prevention.[12] The prophylactic use of cyclosporine plus methotrexate is equivalent to the combination of tacrolimus plus sirolimus in terms of reducing the incidence and severity of acute GVHD and improving survival after allogeneic cell transplantation.[A6] In a nonrandomized study, the addition of sitagliptin, which inhibits dipeptidyl peptidase 4, reduced acute GVHD from its usual 30 to 40% incidence rate to less than 10%.[13]

Cyclosporine has significant toxicities, including hypertension, nephrotoxicity, hypomagnesemia, risk for seizures, hypertrichosis, gingival hyperplasia, tremors, and anorexia. Tacrolimus closely resembles cyclosporine in mechanism of action, spectrum of toxicities, and pharmacologic interactions. For allogeneic hematopoietic cell transplantation, prophylactic immunosuppression is not lifelong; when immunologic tolerance is established, immunosuppressive agents can be slowly withdrawn and discontinued.

Another strategy to prevent GVHD is to deplete the donor's T cells from the graft. The disadvantage of this approach is its association with increased rates of relapsed disease and infection. Furthermore, overall survival does not seem to be improved.

TABLE 163-1 CLASSIFICATION OF PATIENTS WITH ACUTE GRAFT-VERSUS-HOST DISEASE

	CLINICAL STAGING		
STAGE	**SKIN**	**LIVER**	**GUT**
+	Rash <25% BSA	Total bilirubin 2-3 mg/dL	Diarrhea 500-1000 mL/day
++	Rash 25%-50% BSA	Total bilirubin 3-6 mg/dL	Diarrhea 1000-1500 mL/day
+++	Generalized erythroderma	Total bilirubin 6-15 mg/dL	Diarrhea >1500 mL/day
++++	Desquamation and bullae	Total bilirubin >15 mg/dL	Pain, with or without ileus

	CLINICAL GRADING STAGE			
GRADE	**SKIN**	**LIVER**	**GUT**	**PS**
0 (none)	0	0	0	0
I	+ to ++	0	0	0
II	+ to +++	+	+	+
III	++ to +++	++ to +++	++ to +++	++
IV	++ to ++++	++ to ++++	++ to ++++	+++

BSA = body surface area; PS = performance status.

TREATMENT

Moderate to severe GVHD (grades II to IV) requires treatment, and the mainstay of therapy is corticosteroids. Methylprednisolone (1 to 2 mg/kg/day) achieves responses in 40 to 60% of patients, and higher doses of steroids are beneficial. For steroid-refractory GVHD, oral ruxolitinib (10 mg twice daily) can provide a durable 6-month response in 90% of patients and nearly double median overall survival from 6.5 months to 11.1 months as compared with alternative therapies,[A7] such as antithymocyte globulin or various monoclonal antibodies (e.g., daclizumab, infliximab). In general, acute GVHD of the skin is most responsive to treatment, whereas GVHD of the liver is least responsive. Unfortunately, the fatality rate for steroid-refractory acute GVHD may still be as high as 50%.

CHRONIC GRAFT-VERSUS-HOST DISEASE (GVHD)

Chronic GVHD, which occurs in 20 to 50% of long-term survivors, occurs most commonly between 100 days and 2 years after transplantation and has polymorphic features similar to a number of autoimmune diseases. Chronic GVHD is classified as classic chronic GVHD, which consists only of manifestations that can be ascribed to chronic GVHD, or as acute and chronic GVDH overlap syndrome, in which features of both acute and chronic GVHD appear together. These distinctions are clinically relevant because "late-onset" acute GVHD and overlap syndrome subsets have been associated with poor survival.

Chronic GVHD is most likely to develop in older patients who also had acute GVHD or received peripheral blood rather than bone marrow grafts. In 20% of cases of chronic GVHD, however, there is no history of prior acute GVHD.

CLINICAL MANIFESTATIONS

Common manifestations include the sicca syndrome (Chapter 247); lichen planus–like skin rash; scleroderma-like skin changes (Chapter 246);[14] esophageal, intestinal, and vaginal fibrosis; obstructive lung disease with or without pneumonitis; and an elevated alkaline phosphatase level with or without hyperbilirubinemia. Underlying immunologic deficiencies, including hypogammaglobulinemia, are common and place patients at increased risk for infectious events. Adverse prognostic factors include thrombocytopenia, a progressive clinical presentation, extensive skin involvement, and an elevated bilirubin level.

DIAGNOSIS

Historically, chronic GVHD has been considered as limited, with localized skin involvement and minimal or no liver involvement, or extensive, with generalized skin involvement with or without other organ involvement. Chronic GVHD is usually a clinical diagnosis although biopsy is sometimes needed. The severity of GVHD can be graded in transplant centers based on the severity of disease for each affected organ/site at any given time.

TREATMENT

Treatment of chronic GVHD, which is guided by the extent of disease, should be initiated before patients develop functional impairment. Treatment usually begins with corticosteroids (e.g., prednisone 0.5 to 1 mg/kg/day). Ruxolitinib (10 mg twice daily) can prolong median failure-free survival from about 6 months to more than 18 months in glucocorticoid-refractory disease.[A8] Belumosudil (200 mg daily) is another potential option with an overall response rate of about 75%.[15] Ibrutinib (420 mg twice daily)[16] and pomalidomide (0.5 to 2 mg daily)[A9] are other alternatives.[17] Ibrutinib is also useful for glucocorticoid-refractory chronic GVHD. Other potential therapies include extracorporeal photopheresis, cyclosporine, ultraviolet light treatments, monoclonal antibodies, and methotrexate. Given that the most common cause of death in patients with chronic GVHD remains infection, all patients with GVHD should receive prophylactic antibiotics (penicillin 500 mg twice daily) for encapsulated bacteria, with or without intravenous immunoglobulin, depending on serum levels.

Graft Rejection

Graft rejection occurs when immunologically competent cells of host origin destroy the transplanted cells of donor origin. This complication occurs more commonly in patients who receive transplants from alternative source such as cord blood or HLA-mismatched donors, in T-cell-depleted transplants, and in patients with aplastic anemia. Graft rejection also occurs if the conditioning regimen is not sufficiently immunosuppressive to facilitate engraftment of donor cells.

Infections

Infections are a major cause of morbidity and mortality after all forms of hematopoietic cell transplantation but especially following allogeneic transplantation (Chapter 260) because of prolonged use of immunosuppression for the prevention or treatment of GVHD.[18] Bacterial infections are frequently related to central venous catheters.

Among fungal infections, candida (Chapter 310) and aspergillus (Chapter 311) infections typically occur in patients receiving prolonged high-dose corticosteroids for the treatment of GVHD. In such patients, prophylactic antifungal treatment (e.g., fluconazole 400 mg daily) and anti–*Pneumocystis jirovecii* (e.g., one double strength trimethoprim-sulfamethoxazole tablet daily) is necessary.[19]

Viral infections include reactivation of cytomegalovirus (Chapter 347), human herpesvirus 6, BK virus (Chapter 341), and Epstein-Barr virus (Chapter 348) infections. Letermovir prophylaxis (480 mg orally daily through day 100) can significantly reduce the risk of cytomegalovirus reactivation.[A10] Varicella zoster vaccination (Chapter 346) can significantly reduce zoster reactivation[A11] in post-transplantation patients, but the live vaccine should not be used. These patients are also susceptible to seasonal respiratory viruses. Influenza vaccination (Chapter 332) and revaccination for common childhood infections (Chapter 15) are required after transplantation.[20] Vaccines for COVID-19 are recommended once blood counts and CD4 counts have recovered.

Cardiac Toxicity

Most transplant centers screen potential patients for underlying cardiac abnormalities that would place them at a potentially increased risk during the procedure. Despite this screening, however, a small number of patients experience a cardiac arrhythmia (Chapters 51 to 53), heart failure (Chapters 45 and 46), or cardiac ischemia (Chapter 57), either acutely during the transplantation or at a later time, often due to the large volumes of fluids administered during the procedure or from the added physiologic stress. A pericardial effusion (Chapter 62) can develop during or after transplantation, especially in patients with initial disease or radiation therapy near that area. An idiosyncratic cardiomyopathy, associated with the administration of high doses of cyclophosphamide, has been documented in a small number of patients. Viral cardiomyopathies (Chapter 47) also can be seen.

Engraftment Syndrome

Engraftment syndrome occurs when the neutrophil count recovers after either autologous or allogeneic hematopoietic cell transplantation. Engraftment syndrome consists of a constellation of symptoms and signs that may include fever, erythrodermatous skin rash, and noncardiogenic pulmonary edema. In its most extreme forms, patients also develop acute renal failure and diffuse alveolar hemorrhage. These clinical findings reflect the manifestations of increased capillary permeability and extensive release of cytokines. Corticosteroid therapy (typically prednisone at 0.5 mg/kg) is often dramatically effective for engraftment syndrome, particularly for its pulmonary manifestations.

Pulmonary Toxicities

Pulmonary toxicities are common during and after transplantation. Patients who receive certain chemotherapeutic agents, such as 1,3-bis (2-chloroethyl)-1-nitrosourea (BCNU; carmustine) have an increased incidence of chemotherapy-induced lung tissue damage, which usually occurs several weeks after transplantation and can be treated successfully with the prompt initiation of corticosteroid therapy (e.g., prednisone 1 mg/kg, with tapering initiated after response is achieved, usually within 2 weeks). In addition to these complications, patients who are undergoing allogeneic hematopoietic cell transplantation are at increased risk for pneumonitis, caused by cytomegalovirus (Chapter 347) and fungal infections, because of the patient's increased immunosuppression, and idiopathic adult respiratory distress syndrome (Chapter 90) or interstitial pneumonia (Chapter 80). Chronic GVHD also can manifest as bronchiolitis obliterans in the lung.

Liver Toxicity

The most common liver complication associated with transplantation is veno-occlusive disease/sinusoidal obstruction syndrome of the liver (Chapter 136). Symptoms associated with these complications include jaundice, tender hepatomegaly, ascites, and weight gain. Progressive hepatic and multiorgan system failure can develop in the most severe cases. Predisposing factors appear to be previous hepatic injury, use of estrogens, and high-dose intensity conditioning. Defibrotide (6.25 mg/kg every 6 hours for a minimum of 21 days) is approved by the FDA to treat advanced veno-occlusive disease in the setting of hematopoietic stem cell transplantation.

Renal Toxicity

Acute renal failure requiring dialysis occurs infrequently during transplantation, although patients with underlying renal dysfunction are at risk for this complication. An idiopathic or cyclosporine-induced hemolytic-uremic syndrome (Chapter 158) can be seen after allogeneic transplantation, can result in end-stage renal disease, and poses a high risk of mortality. Thrombotic microangiopathy also can lead to acute renal injury. Nephrotic syndrome and membranous nephropathy (Chapter 107) have been described in long-term survivors; these complications seem to be associated more commonly with chronic GVHD and nonmyeloablative conditioning.

Secondary Malignancies

One complication of chemotherapy, radiation therapy (especially total body radiation), or both used to treat malignancy and condition patients for hematopoietic cell transplantation is the development of a secondary malignancy. Secondary AML or myelodysplastic syndrome can occur after autologous transplantation. After allogeneic transplantation, the overall incidences of secondary malignancies are 2.2% at 10 years and 6.7% at 15 years. Solid malignancies occur in up to 15% of patients 15 years after hematopoietic cell transplantation with myeloablative conditioning, with no plateau in the incidence rates.[21] Within the first 1 to 2 years, the most common malignancies are Epstein-Barr virus–related lymphoproliferative disorders (Chapter 348)[22]; solid tumors are more likely to occur more than 3 years after transplantation. Risk factors include the use of antithymocyte globulin to treat GVHD, the use of a T-cell-depleted allogeneic graft, HLA incompatibility, and perhaps total body radiation. This high incidence stresses the importance of careful long-term follow-up.

Infertility and Hypogonadism

Many of the preparative regimens used for transplantation are associated with a high incidence of permanent sterility, especially regimens containing total body radiation. However, successful pregnancies have occurred in some patients after other regimens, particularly in younger patients. A reproductive endocrinologist should be consulted before transplantation when future fertility is important. Gynecomastia occasionally occurs in males.

Endocrine Dysfunction

Iatrogenic Cushing syndrome (Chapters 204 and 208) and diabetes (Chapter 210) can occur and are commonly due to long-term corticosteroid therapy for chronic GVHD. Particularly disabling are steroid-induced myopathy (Chapter 28), avascular necrosis of the hip (Chapter 229), and osteoporosis (Chapter 225). Because many patients take corticosteroids for many months, tapering can be associated with malaise, nausea, hypotension, and musculoskeletal pains. In these situations, slower tapering over several months or reintroduction of physiologic replacement doses (e.g., 7.5 to 10 mg/day of prednisone) is appropriate. Hypothyroidism (Chapter 207) is typically related to the use

of total body radiation or local radiation to the head and neck for lymphoma or other cancer.

Osteoporosis occurs in 50 to 60% of patients after hematopoietic cell transplantation. The major contributing causes include hypogonadism, secondary hyperparathyroidism caused by low serum calcium levels, and post-transplantation corticosteroid therapy. Bone mineral density should be evaluated before and after transplantation; osteopenia should be treated as appropriate with bisphosphonates, calcium, vitamin D, estrogen, and testosterone (Chapter 225).

FUTURE DIRECTIONS

There has been much progress in increasing the efficacy and safety of hematopoietic cell transplantation and in expanding the application of this treatment to more patients.[23] Areas currently under development that may further improve the use and efficacy of transplantation include continuous improvements in supportive care for transplant patients and the broadened use of alternative donors. Recurrence of disease remains the primary cause of treatment failure after both autologous and allogeneic hematopoietic cell transplantation in malignant diseases.[24] Better treatments are necessary for the treatment of GVHD and innovative studies are ongoing. Future progress depends on the ability to identify safer and better-targeted antitumor therapies that can be incorporated into transplantation regimens or given as maintenance therapy without increasing toxicity or attenuating graft-versus-tumor responses. Novel cellular therapies, including genetic modification of lymphocytes to enhance cancer-killing activity, such as chimeric antigen receptor (CAR) T cells (Chapter 34), hold considerable promise.

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164 APPROACH TO THE PATIENT WITH CANCER

JAMES H. DOROSHOW

INTRODUCTION TO THE CANCER PATIENT

Conveying or receiving an initial diagnosis of cancer, or the knowledge that cancer has recurred, is among the most difficult of human enterprises, and no amount of either specialized training or forewarning can adequately assuage the intensity of the emotions associated with these encounters. Patients often experience a storm of feelings that may limit useful discussion immediately following the receipt of a diagnosis of cancer. Even the most well-informed patient typically has difficulty processing the complexities of his or her individual situation, including the range of additional diagnostic tests that may be required and the potentially vast array of treatment options and outcomes that lie ahead. And yet, at some point prior to the initiation of treatment, the physician and the patient must discuss the diagnosis, its implications, and therapeutic alternatives. Because of the wide range of potential prognoses (from curable disseminated testicular cancer to the limited lifespan of patients with locally advanced gastric or pancreatic cancer), it is often useful for family members or close friends to be present in the consulting room when detailed discussions of the complexities of either disease or therapy are conducted, both to provide emotional support and to be another "set of ears" during the visit. It is helpful to ask patients directly: "What do you understand about your diagnosis and treatment?" Family members or close associates of the patient may also be especially helpful in developing a written or digital record of the questions posed to and answered by health care providers; many patients find such a record to be especially helpful for later reference.

If the physician is not familiar with the latest treatment options, prompt referral to a specialist, whether a surgical oncologist, radiation oncologist, or medical oncologist, is imperative. The generalist should not be a therapeutic nihilist unless she or he is intimately involved in the field and is well versed in the potential risks and benefits of currently available therapies and clinical trials.

DIAGNOSIS

Diagnostic possibilities are protean for the wide range of human malignancies that may be discovered either in the presence of nonspecific but foreboding symptoms or signs (severe weight loss [see Fig. 118-4], hematuria [see Fig. 100-3], jaundice [see Fig. 133-1]) or in asymptomatic individuals (e.g., during a routine physical examination).[1] The importance of the medical history and physical examination, however, must be emphasized *whether or not* a pathologic diagnosis of cancer has already been confirmed. One of the most important considerations that underlies the approach to both the diagnostic evaluation and choice of cancer treatment (surgical, radiation, and/or systemic therapy) is the patient's basic physiologic condition or "performance status" (Table 164-1). For example, a past medical history of prolonged tobacco smoking (Chapter 363) is not only relevant to a possible diagnosis of lung cancer but also to the ability of a patient to tolerate potentially curable multimodality treatment. Underlying evidence of excessive alcohol consumption (Chapter 364) may play a role in both the tolerance for and metabolism of systemic chemotherapeutic agents. Family histories of cancer can provide prognostic indicators as well as suggest molecularly guided treatment approaches in, for example, women with possible *BRCA1*-related breast or ovarian cancer. It is also critical to assess the environment of care, including the patient's support systems, which may be sorely tested by the experience of a cancer diagnosis and the interventions that ensue. Finally, the physical examination will define the extent of certain sites of measurable malignancy—for example, palpable lymph nodes or enlargement of the spleen or liver—as well as the patient's muscle strength, the presence of possible malignant effusions, and potential central or peripheral neuropathies reflective of metastatic disease or paraneoplastic syndromes. Most importantly, however, the evaluation provides the treating physician with an initial sense of the patient's well-being, or lack thereof, prior to the initiation of therapy.

TABLE 164-1 KARNOFSKY AND ZUBROD PERFORMANCE SCALES

KARNOFSKY PERFORMANCE STATUS SCALE

VALUE	LEVEL OF FUNCTIONAL CAPACITY
100	Normal, no complaints, no evidence of disease
90	Able to carry on normal activity, minor signs or symptoms of disease
80	Normal activity with effort, some signs or symptoms of disease
70	Cares for self, unable to carry on normal activity or to do active work
60	Requires occasional assistance but is able to care for most needs
50	Requires considerable assistance and frequent medical care
40	Disabled, requires special care and assistance
30	Severely disabled; hospitalization is indicated, although death is not imminent
20	Hospitalization is necessary; very sick, active supportive treatment necessary
10	Moribund; fatal processes progressing rapidly
0	Dead

EASTERN COOPERATIVE ONCOLOGY GROUP (ZUBROD) PERFORMANCE SCALE

PERFORMANCE STATUS	DEFINITION
0	Asymptomatic
1	Symptomatic; fully ambulatory
2	Symptomatic; in bed <50% of day
3	Symptomatic; in bed >50% of day
4	Bedridden

Diagnostic Procedures

After a lesion has been found, either on physical examination or following radiographic studies prompted by abnormal laboratory results, a percutaneous biopsy is often indicated for pathologic evaluation. The biopsy must be representative of the entire tumor and be robust enough in size that appropriate investigations (e.g., special immunohistologic stains, flow cytometry, cytogenetics, hormone assays, molecular testing) can be performed before treatment is initiated. If questions remain as to whether the lesion is benign or malignant or about its proper classification, consideration should be given to additional biopsies, and consultation with a reference pathologist may be indicated.

Molecular testing is increasingly useful for the early diagnosis of asymptomatic malignancy.[2] For example, a small number of cases of occult cancer may be subsequently diagnosed among pregnant women whose noninvasive prenatal testing results show discordance with the fetal karyotype.[3] Similarly, analysis of blood for circulating tumor cells (termed a liquid biopsy) can screen for some early cancers or a recurrence of tumor after treatment.

The wide range of molecularly targeted and immunotherapeutic agents active in solid tumors (see Table 164-2 for an abbreviated list of commonly used medications in cancer and https://www.cancer.gov/about-cancer/treatment/drugs/cancer-type for a full listing of all drugs approved by the U.S. Food and Drug Administration) has focused attention on obtaining sufficient tissue so that essential molecular studies (DNA sequencing, RNA expression analyses, FIH [fluorescence in situ hybridization], and immunologic profiling) are performed to guide choices among treatments. Although tumors removed by surgical resection are routinely of sufficient size to permit the full range of diagnostic examinations, active involvement of a skilled interventional radiologist or endoscopist is often required to produce both the size and number of tumor biopsies required for modern cancer therapeutic decision making. Emergent treatment is rarely required before appropriate pretreatment evaluations can be performed. For some tumor sites such as the colon (Chapter 179), one predominant histology is seen, but critical molecular features of the tumor (presence or absence of a mutant *Ras* oncogene) can define therapy. For other tumors, such as in the lung (Chapter 177), the distinction between

ABSTRACT

The care of the patient with cancer requires a broad knowledge of specific histologic diagnoses, an increasing appreciation of the biology and genetics of malignancy, an understanding of cancer immunology, and a broad appreciation of the pharmacology of the systemic agents, both cytotoxic and molecularly targeted, used to treat cancers in addition to standard surgical and radiotherapeutic approaches. The approach to the patient with cancer also requires a commitment to the critical psychosocial aspects of care that are essential for the optimal treatment of the multifaceted medical problems confronted by all cancer patients.

KEYWORDS

medical oncology
cancer therapy
immunotherapy
targeted therapy
systemic treatment

TABLE 164-2 U.S. FDA-APPROVED DRUGS COMMONLY USED FOR THE SYSTEMIC TREATMENT OF CANCER*

DRUG NAME	DRUG CLASS AND/OR MECHANISM	PHARMACOKINETICS/METABOLISM	TOXICITY	INDICATIONS†
Abiraterone acetate (Zytiga)	Inhibits androgen biosynthesis	Do not take with food; inhibits CYP2D6	Joint swelling or discomfort; edema; monitor liver enzymes	Metastatic prostate cancer
Acalabrutinib (Calquence)	Bruton kinase inhibitor	Avoid with proton pump inhibitors, strong CYP3A inhibitors or inducers, and patients with severe hepatic impairment	Opportunistic infection, cytopenias, atrial tachyarrhythmias, headache, diarrhea, musculoskeletal pain	CLL, small lymphocytic lymphoma, mantle cell lymphoma
Afatinib (Gilotrif)	Selective covalent inhibitor of EGFR, HER2, and HER4; inhibits wild-type and selected EGFR mutants	Interacts with P-gp inhibitors which may require dose reduction; dose reduction for moderate renal dysfunction	Acneiform eruption; hypokalemia; diarrhea, stomatitis, and nausea; altered liver function studies; decreased creatinine clearance	NSCLC first line with *EGFR* exon 19 deletions or exon 21 (L858R) mutation as detected by appropriate diagnostic test
Alectinib (Alecensa)	Tyrosine kinase inhibitor inhibiting *ALK* gene abnormalities and *RET* mutations; can inhibit certain *ALK* mutations that follow treatment with crizotinib	Hepatic metabolism by CYP3A4; excreted in the feces	Bradycardia; CK elevations; interstitial pneumonitis	ALK-positive metastatic NSCLC progressive on crizotinib
Amivantamab-vmjw (Rybrevant)	Human *EGFR* and *MET* bispecific antibody targeting *EGFR* exon 20 insertion mutations	Disrupts *EGFR* and *MET* signaling by blocking ligand binding and degrading *EGFR* and *MET*; terminal half-life of about 11 days	Rash; infusion reactions; paronychia; stomatitis; pruritus	NSCLC with *EGFR* exon 20 insertion mutations in patients who have progressed on platinum-based chemotherapy
Anastrozole (Arimidex)	Nonsteroidal aromatase inhibitor; blocks estrogen production selectively	Well absorbed from GI tract, maximum plasma levels within 2 hr; half-life is 50 hr; extensively metabolized in liver; despite hepatic and renal clearance being important, no adjustments needed for abnormal function of these organs because of the wide therapeutic index of this drug	Very well tolerated; asthenia, headache, and hot flashes occur in less than 15% of women; diarrhea, abdominal pain, anorexia, nausea, and vomiting occur in 10% or less; thrombophlebitis has been reported	As adjuvant therapy of breast cancer and for treatment of postmenopausal women with breast carcinoma who have progressed while being treated with tamoxifen
Apalutamide (Erleada)	Androgen receptor inhibitor	If no prior orchiectomy, prescribe a gonadotropin-releasing hormone analog concurrently	Ischemic cardiovascular events, fractures, fatigue, arthralgia, rash, decreased appetite, falls, weight decreased, hypertension, hot flush, diarrhea	Metastatic castration-sensitive prostate cancer or nonmetastatic castration-resistant prostate cancer
Arsenic trioxide (Trisenox)	Novel arsenical differentiating agent	Half-life of this compound is unknown; it is methylated in the liver and eliminated in the urine	The "differentiation syndrome" is dose limiting and includes leukocytosis, fever, dyspnea, chest pain, tachycardia, hypoxia, and sometimes death; corticosteroids seem to benefit this syndrome; QT prolongation is common; common adverse effects include rash, pruritus, headache, arthralgias, anxiety, bleeding, nausea, and vomiting; liver and renal toxicity are uncommon	Relapsed acute promyelocytic leukemia
L-Asparaginase (Elspar), colaspase	Naturally occurring enzyme derived from *Escherichia coli* or *Erwinia carotovora* that cleaves asparagine, an essential amino acid required by rapidly proliferating cells	After IV or IM injection, the drug is metabolized intravascularly by proteolysis; elimination half-life of 8-30 hr	Hypersensitivity can be life-threatening, requiring anaphylaxis precautions and a 2-unit test dose; coagulopathy is common and requires monitoring; nausea, vomiting, abdominal cramps, anorexia, elevated liver function tests, and transient renal insufficiency are common; lethargy, somnolence, fatigue, depression, and confusion are seen, as are pancreatitis and fever	ALL; also used in AML, late-stage CML, CLL, and non-Hodgkin lymphomas
Atezolizumab (Tecentriq)	Humanized monoclonal antibody that binds the programmed death ligand 1 (PD-L1) downregulating anti–T-cell function	No dosage adjustment for mild renal or hepatic insufficiency	Rash; endocrinopathies; immune hepatitis, pancreatitis, pneumonitis, colitis, adrenal insufficiency, diabetes; peripheral edema; fatigue; fever	NSCLC; small cell lung cancer; advanced urothelial cancer patients ineligible for or who have progressed after platinum-containing therapy; hepatocellular cancer; melanoma
Avelumab (Bavencio)	Programmed death ligand-1 (PD-L1) blocking antibody	Can cause fetal harm	Immune-mediated pneumonitis, hepatitis, colitis, endocrinopathies, nephritis; fatigue; musculoskeletal pain; rash; diarrhea	Adult and pediatric patients (12 yr of age and older) with metastatic Merkel cell carcinoma; renal cell carcinoma; urothelial carcinoma
Axitinib (Inlyta)	Avoid strong CYP3A inhibitors or reduce dose	Decrease dose 50% for CYP3A inhibitors, renal, hepatic impairment	Diarrhea, hypertension, fatigue, nausea	Advanced renal cell carcinoma after one treatment failure

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TABLE 164-2 U.S. FDA-APPROVED DRUGS COMMONLY USED FOR THE SYSTEMIC TREATMENT OF CANCER*—cont'd

DRUG NAME	DRUG CLASS AND/OR MECHANISM	PHARMACOKINETICS/METABOLISM	TOXICITY	INDICATIONS†
Azacytidine (Vidaza)	Antimetabolite; induces hypomethylation of DNA, either inducing apoptosis or restoring normal function; at higher doses, acts as a cytidine analog	Not orally bioavailable; metabolized by the liver and excreted in urine; elimination half-life of 4 hr	Myelosuppression is dose limiting; leukopenia, thrombocytopenia, and transient elevation of liver function tests are common; nausea and vomiting and abdominal pain are common	Myelodysplastic syndromes
Bacillus Calmette-Guérin (TICE BCG, TheraCys), BCG	Immunostimulant/vaccine; induces a cellular immune response at the site of instillation	BCG is a live, attenuated bacteria culture; it does not enter the body in viable form; it has no detectable pharmacokinetic fate; in rare cases, a clinical infection can result from treatment, indicating invasion of the body at site of administration into systemic circulation	Urinary symptoms predominate, including dysuria, hematuria, hesitancy, urgency, frequency, and secondary infection; other toxicities include fever, chills, malaise, myalgias/arthralgias, anorexia, nausea, vomiting, and anemia; clinical mycobacterial infection is rare and generally seen only in immunocompromised patients	Intravesical instillation for noninvasive bladder cancer after removal of papillary tumors; also used for some experimental vaccine programs as an adjuvant to the vaccine
Belinostat (Beleodaq)	Histone deacetylase inhibitor; results in accumulation of acetyl groups on histone and nonhistone proteins causing cell cycle arrest and apoptosis	Hepatic metabolism via *UGT1A1* and CYP2A6; excreted in urine	Myelosuppression; peripheral edema and prolonged QT interval; rash; nausea and vomiting; fatigue	Relapsed peripheral T-cell lymphoma
Bendamustine (Treanda)	Alkylating agent	Reduce dose for hematologic toxicity	Nausea, pyrexia, vomiting, hematologic abnormalities	CLL and B-cell non-Hodgkin lymphoma
Bevacizumab (Avastin)	Recombinant humanized monoclonal antibody that binds to all forms of VEGF, preventing binding to its receptors	Administered by IV infusion; half-life is 20 days; the fate of parent drug and metabolites is unknown	Asthenia, pain, nausea/vomiting, diarrhea, anorexia, stomatitis, dermatitis, hypertension, proteinuria; infusion-related reactions rare; hemoptysis, hemorrhage, delayed wound healing, GI perforations; increased risk of thromboembolic events can be severe or fatal	Metastatic colorectal cancer and NSCLC; renal cell carcinoma
Bicalutamide (Casodex)	Nonsteroidal antiandrogen	Well absorbed orally; highly protein bound; converted to inactive metabolites in liver via oxidation and glucuronidation; half-life of several days	Constitutional symptoms predominate, including hot flashes, decreased libido, depression, weight gain, edema, gynecomastia, early disease-site pain (flare reaction), and constipation; nausea, vomiting, anorexia, diarrhea, and dizziness are uncommon; dyspnea, anemia, fever, and rashes are rare	Stage D2 prostate cancer, in combination with an LHRH agonist agent
Binimetinib (Mektovi)	Mitogen-activated protein kinase 1 and 2 inhibitor	Reduce dose if moderate or severe hepatic impairment	Cardiomyopathy, retinopathy, interstitial lung disease, hepatotoxicity, rhabdomyolysis	Unresectable or metastatic melanoma with a *BRAF* V600E or V600K mutation
Bortezomib (Velcade)	Proteasome inhibitor	Metabolized in the liver by CYP2C19 and 3A4; dose reduction for hepatic dysfunction	Cardiovascular; peripheral neuropathy; skin rash; nausea and diarrhea	Multiple myeloma; mantle cell lymphoma
Brentuximab vedotin (Adcetris)	CD30-directed antibody conjugate	Monitor patients taking CYP3A inducers or inhibitors	Progressive multifocal leukoencephalopathy; peripheral neuropathy; neutropenia	Hodgkin lymphoma and anaplastic large cell lymphoma
Brigatinib (Alunbrig)	Multikinase inhibitor	Interacts with strong CYP3A inhibitors; requires dose reduction; avoid grapefruit juice	Hypertension; skin rash; fatigue; increased liver function tests	ALK-positive NSCLC for patients who have progressed on crizotinib
Capecitabine (Xeloda)	Oral antimetabolite prodrug	Readily absorbed by the GI tract, metabolized in vivo to fluorouracil in the liver by carboxylesterase and cytidine deaminase, and then in turn in the peripheral tissues and tumor tissue by thymidine phosphorylase	Myelosuppression and palmar-plantar erythrodysesthesia are dose limiting; diarrhea, fatigue, stomatitis, and hyperbilirubinemia are uncommon; nausea, vomiting, and rash are rare	Metastatic breast cancer and metastatic colorectal cancer; used also in head and neck squamous cell cancer
Cabazitaxel (Jevtana)	Microtubule inhibitor	Caution for patients taking strong CYP3A inducers or inhibitors	Neutropenia and hypersensitivity	Metastatic hormone refractory prostate cancer when docetaxel fails
Cabozantinib	Inhibits many receptor tyrosine kinases; anti-angiogenic	55-hour half-life; take without food	Perforations, fistulas, and hemorrhage	Metastatic medullary thyroid cancer; advanced renal cell carcinoma; advanced hepatocellular cancer

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Carboplatin (Paraplatin), Carbo, CBDCA	Atypical alkylator; produces intrastrand and interstrand cross-links in DNA via association bonds with the platinum molecule, leading to DNA strand breakage during replication	Rapidly cleared from the blood stream after IV infusion, with a terminal half-life of 2.5 hr; it is cleared largely as unchanged drug by the kidneys	Hemorrhage; thrombocytopenia	Ovarian cancer and used extensively in testicular cancer, squamous cell cancers of the head and neck and cervix, and lung cancer
Carfilzomib (Kyprolis)	Proteasome inhibitor	Drug-drug interactions unlikely; no adjustment for renal impairment; no experience with hepatic impairment	Fatigue, anemia, nausea, thrombocytopenia, dyspnea, diarrhea, and pyrexia; monitor for cardiac, pulmonary, tumor lysis, infusion reactions, thrombocytopenia	Multiple myeloma
Ceritinib (Zykadia)	Inhibitor of ALK tyrosine kinase as well as *ROS1*; also inhibits IGF-1R and the insulin receptor	Metabolized by CYP3A in the liver; dose reduction if concomitant strong CYP3A inhibitors are administered	Bradycardia; QTc prolongation; nausea, vomiting; hyperglycemia; interstitial pneumonitis	NSCLC that is *ALK* positive by an appropriate diagnostic test; demonstrated activity in crizotinib-resistant NSCLC xenograft models
Cetuximab (Erbitux)	Recombinant humanized monoclonal antibody, targeting *EGFR*; competitively inhibits growth factor binding; inhibits autophosphorylation and cell signaling	Metabolism poorly understood; half-life 5-7 days with minimal clearance by kidneys or liver	Infusion reaction, characterized by rapid-onset dyspnea, fever, chills, urticaria, flushing, angioedema, and hypotension, is seen in 40-50% of patients; acneiform rash is common; constitutional symptoms; hypomagnesemia; interstitial lung disease is rare	Metastatic colorectal cancer, head and neck cancer in combination with radiation
Cisplatin (Platinol)—cDDP, DDP, cisplatinum, cis-diamminedichloro-platinum (II)	Atypical alkylator; produces intrastrand and interstrand cross-links in DNA via association bonds with the platinum molecule, leading to DNA strand breakage during replication	After IV infusion, rapid distribution to tissues takes place, and the drug is over 90% protein bound	Nephrotoxicity is dose limiting for an individual dose, and neurotoxicity, especially painful peripheral neuropathy, is dose limiting for cumulative doses; myelosuppression is mild; nausea and vomiting are common but manageable, and anorexia and diarrhea are common; cumulative ototoxicity is also common; chronic renal magnesium and potassium wasting is common and sometimes not reversible; elevated liver transaminases can be seen, whereas alopecia and cardiac conduction abnormalities are rare; adequate renal perfusion and urine output are critical for minimizing renal toxicity; therefore prehydration and adequate posttreatment hydration are used, usually with normal saline solution with or without mannitol, potassium, and magnesium	Used for almost every class of solid tumor and lymphoma; FDA approved for testicular and ovarian cancer and transitional cell carcinoma
Cobimetinib (Cotellic)	Inhibitor of *MEK1* and *MEK2* in the MAPK cascade	Detoxified in the liver by CYP3A4 and UGT2B7; use of strong CYP3A4 inhibitors should be avoided; excreted in feces	Cardiotoxicity; rhabdomyolysis; rash; retinopathy; bleeding	Metastatic or unresectable melanoma for patients with *BRAF* V600E or V600K mutations in combination with vemurafenib
Copanlisib (Aliqopa)	PI-3 kinase inhibitor	Avoid concomitant strong CYP3A inducers and reduce dose of strong CYP3A inhibitors	Hyperglycemia, hypertension, neutropenia, thrombocytopenia, diarrhea, severe cutaneous reactions, nausea, lower respiratory tract infections	Relapsed follicular lymphoma after at least two prior systemic therapies
Crizotinib (Xalkori)	ALK kinase inhibitor; also inhibits *cMET*	Avoid strong CYP3A inhibitors, inducers, or substrates	Hepatotoxicity; pneumonitis; QT interval prolonged	*ALK*-positive NSCLC
Cyclophosphamide	Alkylating agent	Metabolized to its active alkylating species by mixed function oxidases in hepatic microsomes including CYP2A6 and 3A4; decreased activation to therapeutic species in the face of severe hepatic dysfunction	Myelosuppression; immunosuppression; hemorrhagic cystitis; myocarditis; pneumonitis; secondary malignancies; infertility; hyponatremia; veno-occlusive disease; nausea and vomiting; mucositis	Hodgkin and non-Hodgkin lymphoma; leukemias; ovarian cancer; breast cancer; retinoblastoma; neuroblastoma
Cytarabine	Antimetabolite that inhibits DNA polymerase after activation to its nucleotide triphosphate, is incorporated into DNA and RNA and blocks cell cycle progression from G1 to S phase	Metabolized in the liver and excreted by the kidney	Myelosuppression; immunosuppression; CNS, cardiac, and pulmonary toxicity; infection; fever, bone and chest pain and rash within hours of administration (Ara-C syndrome); nausea, diarrhea; mucositis; hepatic dysfunction	AML in adults and children

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TABLE 164-2 U.S. FDA-APPROVED DRUGS COMMONLY USED FOR THE SYSTEMIC TREATMENT OF CANCER*—cont'd

DRUG NAME	DRUG CLASS AND/OR MECHANISM	PHARMACOKINETICS/METABOLISM	TOXICITY	INDICATIONS†
Dabrafenib (Tafinlar)	BRAF kinase inhibitor; selectively inhibits BRAF V600E mutated kinase	Metabolized to active form by CYP isoforms in the liver; absorption delayed by a high-fat meal	Decreased LVEF; skin rash, alopecia, keratoacanthoma and squamous cell carcinoma, palmar-plantar erythrodysesthesia; hyperglycemia; diarrhea; lymphopenia and anemia; abnormal liver function tests	Metastatic or unresectable melanoma with BRAF V600 E mutation or in combination with trametinib if either BRAF V600E or V600K mutations present; NSCLC if BRAF V600E mutation detected by an approved test
Dasatinib (Sprycel)	Multikinase inhibitor including Bcr-Abl and Src	Use with caution in patients with hepatic impairment; CYP3A4 inhibitors: may increase dasatinib drug levels; avoid or monitor closely and consider reducing dose; CYP3A4 inducers: may decrease dasatinib drug levels; avoid or consider increasing dose; antacids: may decrease dasatinib drug levels; avoid simultaneous administration; if needed, administer the antacid at least 2 hr prior to or 2 hr after the dose; H2 antagonists/proton pump inhibitors: may decrease dasatinib drug levels; consider antacids in place of H2 antagonists or proton pump inhibitors	Myelosuppression, bleeding events, fluid retention, diarrhea, headache, musculoskeletal pain, and rash	(Ph+) chronic myeloid leukemia (CML) in chronic phase, or chronic, accelerated, or myeloid or lymphoid blast phase Ph+ CML with resistance or intolerance to prior therapy including imatinib, or Philadelphia chromosome–positive acute lymphoblastic leukemia (Ph+ ALL) with resistance or intolerance to prior therapy
Daunorubicin	Anthracycline antitumor antibiotic; pleiotropic effects including free radical formation, topoisomerase II inhibition; altered mitochondrial function	After IV bolus, widely distributed and metabolized in liver to active and inactive metabolites; half-life of the parent drug is 18 hr, and 25 hr for active metabolite daunorubicinol	Daunorubicin is a vesicant; precautions are necessary; myelosuppression is dose limiting; alopecia, nausea, vomiting, and stomatitis are common; diarrhea, rash, elevated liver function tests, and transient arrhythmias are uncommon; dose-related cardiomyopathy is uncommon below cumulative doses of 400-500 mg/m^2	AML and ALL
Decitabine (Dacogen)	Antimetabolite; inhibits DNA methyltransferase, causing hypomethylation of DNA; this may induce apoptosis or restore normal function to genes that control cellular differentiation and proliferation	Deaminated by cytidine deaminase, found in liver, granulocytes, gut, and blood; elimination half-life is 30 min	Myelosuppression; nausea, vomiting, abdominal pain; constitutional symptoms; elevated liver functions, blood sugar, low serum magnesium, low serum potassium; respiratory toxicity	Myelodysplastic syndromes
Denosumab (Xgeva)	Monoclonal antibody; RANK ligand inhibitor	No drug interaction studies; more hypocalcemia for creatinine clearance <30 mL/min	Use calcium and vitamin D to treat or prevent hypocalcemia; fatigue/asthenia, hypophosphatemia, and nausea; osteonecrosis of jaw	Bone metastases from solid tumors; not in multiple myeloma; giant cell tumor of bone
Dexrazoxane (Zinecard)—ADR-529, ICRF-187	Iron-chelating agent that serves as a free-radical scavenger/cytoprotectant; widespread and rapid	Metabolism is mostly hepatic; half-life is 3-4 hr; parent drug and metabolites are excreted by the kidneys; hepatic impairment not studied; renal impairment suggests 50% dose reduction	Dexrazoxane appears to worsen slightly the leukopenia induced by doxorubicin; mild nausea and vomiting are common; fever, stomatitis, fatigue, anorexia, and hypotension are uncommon; seizure, respiratory arrest, deep venous thrombosis, and significant liver toxicity are rare	Prevent doxorubicin-induced cardiomyopathy
Docetaxel (Taxotere), RP-56976	Docetaxel is a semisynthetic taxane, a class of compounds that inhibit the mitotic spindle apparatus by stabilizing tubulin polymers, leading to death of mitotic cells	After a 1-hr infusion, docetaxel is widely distributed, with elimination half-life of 1 hr and a terminal half-life of 18 hr; extent and by-products of metabolism are not well known; the main excretion route is biliary	Myelosuppression is universal and dose limiting; alopecia is also universal; edema and fluid accumulation, including pleural effusions and ascites, are common and can be dose limiting; fluid accumulation is partially preventable with corticosteroid treatment before and after each cycle of docetaxel; mild sensory or sensorimotor neuropathy is common; mucositis and diarrhea are common and usually mild; hypersensitivity reactions are uncommon and can largely be prevented through premedication with corticosteroids and antihistamines; rash and elevated liver function tests are uncommon	Metastatic breast cancer and first- and second-line NSCLC

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Doxorubicin (Adriamycin, Rubex), Adria, hydroxydaunorubicin	Anthracycline antitumor antibiotic; pleiotropic effects including free radical formation, topoisomerase II inhibition; altered mitochondrial function	After an IV dose, it is widely distributed in tissues and is 70% protein bound; it is metabolized in the liver to active and inactive forms; it has an elimination half-life of 18 hr or more; most of the drug and metabolites are excreted through the biliary route	Doxorubicin is a potent vesicant, and extravasation precautions are a must; myelosuppression is universal and usually dose limiting with each individual cycle; cardiotoxicity is common and can be dose limiting, although usually subclinical; chronic, cumulative cardiomyopathy is expected when the total dose exceeds 450 mg/m^2; this toxicity can be lessened by the addition of dexrazoxane or by longer infusions; acute cardiac effects, including arrhythmias, are less often seen and are unpredictable; nausea and vomiting are common but manageable; diarrhea and stomatitis are common but usually mild; alopecia, rash, and hyperpigmentation are common	Approved for a variety of cancers and used for many more; most commonly used for breast carcinoma, adult sarcomas, pediatric solid tumors, Hodgkin disease, non-Hodgkin lymphomas, and ovarian cancer
Doxorubicin, liposomal (Doxil)	Novel liposomal preparation of the anthracycline doxorubicin	Doxorubicin metabolized in the liver; significant plasma levels of the principal metabolite, doxorubicinol, not observed with the liposomal preparation, likely because of slow distribution of free doxorubicin to liver; half-life of liposomes in plasma is 55 hr	Myelosuppression is mild but dose limiting; palmar-plantar erythrodysesthesia is common and can occasionally be severe and dose limiting; stomatitis and nausea are common but usually mild; alopecia is uncommon; acute infusion reactions including chest pain, back pain, dyspnea, and wheezing can occur uncommonly	Recurrent metastatic ovarian cancer and AIDS-related Kaposi sarcoma; also used commonly in metastatic breast cancer and multiple myeloma
Durvalumab (Imfinzi)	Human monoclonal antibody that inhibits binding of PD-L1 to PD-1 and CD80, enhancing antitumor effects of T cells	May need to reduce dose or discontinue in the presence of treatment-related nephritis or hepatitis	Hepatotoxicity; renal toxicity; rash; endocrinopathies; colitis and diarrhea; infusion reactions; pneumonitis	Locally advanced or metastatic urothelial carcinoma following progression on platinum-based therapy; extensive stage small cell lung cancer; NSCLC
Enasidenib (IDHIFA)	Inhibitor of the enzyme isocitrate dehydrogenase (IDH2) targeting the R140Q, R172S, and R172K mutant variants of IDH2 to reduce 2-hydroxyglutarate levels and reestablish myeloid differentiation	Hepatic metabolism by way of multiple CYP isoforms and UGTs; primarily excreted in the feces; reduce dose for bilirubin >3 times ULN	Differentiation syndrome (black box warning): fever, respiratory distress, pleural and pericardial effusions, edema, multiorgan dysfunction—must be treated with corticosteroids; electrolyte imbalance; hepatotoxicity; nausea, vomiting, diarrhea; tumor lysis syndrome	AML patients with IDH2 mutations defined by an appropriate diagnostic test
Entrectinib (Rozlytrek)	Tropomyosin receptor kinase inhibitor	Avoid moderate and strong CYP3A inducers, reduce dose with moderate and strong CYP3A inhibitors	Heart failure, CNS side effects, skeletal fractures, hepatotoxicity, hyperuricemia, QT interval prolongation, vision disorders	Metastatic *ROS1*-positive NSCLC
Enzalutamide (Xtandi)	Androgen receptor signaling inhibitor	Take with or without food; 2C8 substrate; no other pathways need adjustments	Fatigue, musculoskeletal pain, dizziness, weakness	Metastatic castrate-resistant prostate carcinoma
Epirubicin (Ellence)	Anthracycline; pleiotropic effects including free radical formation, topoisomerase II inhibition; altered mitochondrial function	Metabolized primarily by liver; parent drug and metabolites glucuronidated and excreted in bile much more than via renal clearance; reduce doses for mild to moderate hepatic dysfunction; severe hepatic dysfunction is contraindicated; half-life is 30-35 hr	Myelosuppression is universal and dose limiting; alopecia is expected; this drug is a vesicant, and precautions must be taken to avoid extravasation into soft tissue around veins; nausea and vomiting are common but usually manageable; stomatitis is common; fatigue is common; detectable cardiac dysfunction at somewhat higher cumulative doses than doxorubicin; secondary leukemia is rare	Adjuvant therapy after optimal surgical treatment of localized breast cancer with involved axillary lymph nodes
Erdafitinib (Balversa)	FGFR kinase inhibitor	Avoid moderate CYP2C9 or strong CYP3A4 inhibitors, moderate or strong CYP2C9 or CYP3A4 inducers, CYP3A4 substrates, OCT2 substrates	Central serous retinopathy retinal pigment epithelial detachment, hyperphosphatemia, stomatitis, fatigue, increased creatinine level, diarrhea, dry mouth, palmar-plantar erythrodysesthesia syndrome	Locally advanced or metastatic urothelial carcinoma with FGFR3 or FGFR2 genetic alterations progressing despite chemotherapy
Eribulin mesylate (Halaven)	Microtubule inhibitor	Reduce dose in patients with hepatic impairment and moderate renal impairment	Neutropenia, peripheral neuropathy, monitor for QT prolongations, nausea, fatigue	Persons with metastatic breast cancer who have previously received at least two chemotherapeutic regimens for the treatment of metastatic disease; prior therapy should have included an anthracycline and a taxane in either the adjuvant or metastatic setting

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TABLE 164-2 U.S. FDA-APPROVED DRUGS COMMONLY USED FOR THE SYSTEMIC TREATMENT OF CANCER*—cont'd

DRUG NAME	DRUG CLASS AND/OR MECHANISM	PHARMACOKINETICS/METABOLISM	TOXICITY	INDICATIONS†
Erlotinib (Tarceva)	Targeted agent	Inhibits the tyrosine kinase domain of the EGFR, leading to inhibition of EGFR autophosphorylation and signaling	Acneiform rash; diarrhea; interstitial lung disease	Second- or third-line therapy of NSCLC; pancreatic cancer, in combination with gemcitabine
Erythropoietin (Epogen, Procrit), EPO, epoetin alpha	Hematopoietic growth factor; stimulates erythrocytic precursors	Detectable in plasma for 24 hr after dosing; distributed to volume approximating total blood volume; degraded by proteolysis within blood compartment; half-life is 4-27 hr; onset of therapeutic effect takes at least 7 days; excretion of intact peptide is negligible	Hypertension is common but usually mild and not dose limiting; injection site pain is common but mild; flulike syndrome and diaphoresis are uncommon; nausea and vomiting are rare; seizures have been reported in patients undergoing dialysis who receive the drug; iron deficiency anemia can occur after prolonged therapy, and concomitant iron dosing may increase effectiveness of erythropoietin; hematocrit values should be monitored closely during therapy to prevent polycythemia and hyperviscosity	The oncology indication is chemotherapy-induced anemia that is symptomatic; also used for anemia of chronic renal failure and HIV-associated anemia
Etoposide (Vespid), VP-16, epipodophyllotoxin; also available as etoposide phosphate (Etopophos)	Plant alkaloid; topoisomerase II inhibitor; partially cell cycle dependent	Etoposide phosphate is rapidly converted to etoposide after IV infusion; etoposide itself is extensively protein bound, is metabolized in liver, and has a half-life of about 10 hr; 50% of oral etoposide is absorbed via GI tract, requiring oral doses to be twice as high as parenteral doses; excreted both unchanged in urine and as metabolites in bile	Myelosuppression, primarily leukopenia, is universal and dose limiting; nausea and vomiting are common with PO administration but rare when the drug is given by IV; stomatitis and diarrhea are rare with normal doses but common with high doses; alopecia is mild or absent; hepatic toxicity and neurologic effects (peripheral neuropathy and CNS changes) are rare; hypotension can occur with rapid administration of etoposide but does not occur commonly when etoposide phosphate is infused over 5 min; secondary AML has been reported after etoposide	Germ cell tumors and SCLC; also used for lymphomas, AML, brain tumors, non-SCLC, and as high-dose therapy in the transplant setting for breast cancer, ovarian cancer, and lymphomas
Everolimus (Afinitor)	m-TOR inhibitor	Hepatic impairment: for advanced HR+ BC, advanced PNET, advanced RCC, or renal angiomyolipoma with TSC patients with hepatic impairment, reduce the starting dose. Strong CYP 3A4 inhibitors: avoid concomitant use. Moderate CYP 3A4 and/or PgP inhibitors: if combination is required, use caution and reduce dose. Strong CYP 3A4 inducers: avoid concomitant use. If combination cannot be avoided, increase dose.	Noninfectious pneumonitis: monitor for clinical symptoms or radiologic changes; fatal cases have occurred. Infections: increased risk of infections, some fatal. Monitor for signs and symptoms, and treat promptly. Oral ulceration: mouth ulcers, stomatitis, and oral mucositis are common. Cases of renal failure (including acute renal failure), some with a fatal outcome, have been observed. Laboratory test alterations: elevations of serum creatinine, blood glucose, and lipids may occur. Decreases in hemoglobin, neutrophils, and platelets may also occur. Monitor renal function, blood glucose, lipids, and hematologic parameters prior to treatment and periodically thereafter. Avoid live vaccines and close contact with those who have received live vaccines. Advanced HR+ BC, advanced PNET, advanced RCC: most common adverse reactions include stomatitis, infections, rash, fatigue, diarrhea, edema, abdominal pain, nausea, fever, asthenia, cough, headache, and decreased appetite. Renal angiomyolipoma with TSC: most common adverse reaction is stomatitis. SEGA with TSC: most common adverse reaction (incidence ≥30%) are stomatitis and respiratory tract infection.	Postmenopausal women with advanced hormone receptor-positive, HER2 negative breast cancer (advanced HR+ BC) in combination with exemestane after failure of treatment with letrozole or anastrozole. Adults with progressive neuroendocrine tumors of creatic origin (PNET) that are unresectable, locally advanced, or metastatic. Adults with advanced RCC after failure of treatment with sunitinib or sorafenib. Adults with renal angiomyolipoma and TSC not requiring immediate surgery. Pediatric and adult patients with TSC who have SEGA that requires therapeutic intervention but cannot be curatively resected.
Exemestane (Aromasin)	Hormonal agent, steroidal aromatase inhibitor	40% of oral exemestane is absorbed from GI tract and increased by a fatty meal; it is highly protein bound in plasma; exemestane is metabolized in liver by cytochrome P450 3A4 and aldoketoreductases	Although generally well tolerated, exemestane is expected to cause or exacerbate hot flashes or intermittent flushing in some women; fatigue and mild nausea are common; vomiting, headache, and dyspnea are uncommon; it is teratogenic and should not be used in premenopausal women	Estrogen-responsive metastatic breast cancer in postmenopausal women whose disease has progressed while undergoing prior hormonal therapy

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Filgrastim (Neupogen), G-CSF	Hematopoietic growth factor, relatively specific for the granulocyte lineage	After a bolus SQ injection, peak plasma levels of filgrastim occur in 2-6 hr, whereas the elimination half-life is generally 7 hr or less; metabolism is via proteolysis in the blood compartment; the intact molecule is largely absent from bile or urine	Mild bone pain is common; low-grade fever, myalgias, arthralgias, and transient hypotension are uncommon, as are hyperuricemia and elevations of lactate dehydrogenase and alkaline phosphatase; leukocytosis leading to hypoxia or capillary leak syndrome has been reported; anaphylaxis or allergic reaction is rare	Approved for minimization of granulocytopenia after myelosuppressive chemotherapy; also used to speed recovery of granulocytes in the setting of neutropenic fever after chemotherapy, for myelodysplastic syndromes, for congenital agranulocytosis, for cyclic neutropenia, and for mobilization of peripheral blood stem cells from patients or donors for transplant
Fludarabine (Fludara), FAMP	Purine nucleotide analog antimetabolite; only partially cell cycle–dependent	Fludarabine is available only by the parenteral route; after IV administration, the drug is metabolized to 2-fluoroara-A and widely distributed in tissues; it has an elimination half-life of 9-10 hr; the drug and metabolite are excreted primarily by the kidneys	Neurotoxicity, including cortical blindness, confusion, somnolence, coma, and demyelinating lesions, is dose limiting, but the lower doses that are conventionally used rarely produce these adverse effects; at these doses, mild myelosuppression is the most common toxicity, with cumulative lymphopenia being the most clinically important; nausea, vomiting, and other GI toxicities are rare; alopecia and rash are also rare	Approved for the treatment of CLL; also used for low-grade lymphomas and for AML
5-Fluorouracil (Adrucil, Efudex), 5-FU	Pyrimidine antimetabolite; inhibitor of thymidylate synthase; partially cell cycle dependent	80% of IV drug is metabolized to inactive dihydro-5-FU by dihydropyrimidine dehydrogenase in the liver; the rest of the drug is activated to fluorodeoxyuridine monophosphate in target cells; elimination half-life is 20 min; excretion is via the kidneys	GI toxicities, primarily mucositis for bolus injections and diarrhea for prolonged infusions, are dose limiting; rare patients with dihydropyrimidine dehydrogenase deficiency have excessive GI toxicity; myelosuppression is generally less with continuous infusion schedules; nausea and vomiting are uncommon and mild; dermatitis and other cutaneous toxicities, including hand-foot syndrome, are common; cerebellar ataxia and myocardial ischemia are rare	Approved for colon, rectum, gastric, pancreas, and breast carcinomas and used for a wide range of other neoplasms in combination regimens; used for intrahepatic arterial infusion for liver metastases from GI tumors; also used topically for various cutaneous neoplasms and disorders
Flutamide (Eulexin)	Nonsteroidal antiandrogen	Good oral bioavailability, with peak plasma levels after an oral dose at 1-2 hr; metabolized to active and inactive forms in the liver; half-life is 8-10 hr	Generally well tolerated; gynecomastia, galactorrhea, and impotence are common; nausea, vomiting, diarrhea, mild myelosuppression, myalgias, and elevated liver function tests are rare	Prostate carcinoma
Fulvestrant (Faslodex) estrogen receptor antagonist	Binds to the ER, leading to degradation and loss of ER from the cell	Peak plasma levels reached in 7 days, half-life is 40 days; metabolized by the liver microsomal P4503A4 systems	Constitutional symptoms, including hot flashes; peripheral edema; nausea, vomiting	ER+ metastatic breast cancer in postmenopausal women
Gemcitabine (Gemzar)	Antimetabolite; gemcitabine is a nucleoside analog that exhibits cell cycle–dependent and S-phase–specific cytotoxicity, likely because of inhibition of DNA synthesis	After IV infusion, the drug is rapidly distributed and has a half-life of less than 2 hr; it is metabolized throughout the body to inactive forms; parent drug and metabolite are excreted principally by the kidneys	Myelosuppression, including anemia, is mild but dose limiting; nausea and vomiting are mild but common; diarrhea and edema are sometimes seen; elevated transaminases are common, as is fever during drug administration; hematuria and proteinuria are uncommon; acute dyspnea and rash are uncommon; paresthesias and CNS depression are rare	Advanced pancreatic adenocarcinoma, NSCLC, and metastatic breast cancer; also extensively used in bladder cancer
Hydroxyurea (Hydrea)—hydroxycarbamide	Antimetabolite; inhibitor of ribonucleotide reductase, which converts nucleotides to the deoxyribose forms for DNA synthesis; cell cycle dependent	The drug is well absorbed; drug levels peak in the blood 2 hr after the dose is administered; half-life is 2-5 hr; metabolism to inactive forms in the liver; renal excretion is the route of elimination	Myelosuppression is common and dose limiting; other toxicities include rash, headache, fever, and hyperuricemia; nausea and vomiting are uncommon; liver toxicity and serious neurologic toxicity are rare	FDA approved for CML; commonly used for other myeloproliferative disorders; also used occasionally for metastatic melanoma, refractory ovarian carcinoma, and squamous cell carcinoma of the cervix and the head and neck
Ibrutinib (Imbruvica)	Irreversible inhibitor of Bruton tyrosine kinase altering B-cell receptor signaling	Hepatic metabolism by CYP3A and CYP2D6; dose reduction for hepatic dysfunction	Myelosuppression; cardiovascular; fatigue; skin rash; hyperuricemia; diarrhea, nausea; dry eyes; musculoskeletal pain	CLL and small lymphocytic lymphoma; mantle cell lymphoma; marginal zone lymphoma; Waldenström macroglobulinemia; chronic GVHD
Idelalisib (Zydelig)	Phosphatidylinositol 3-kinase delta inhibitor; results in apoptosis of malignant B cells	Metabolized in the liver by aldehyde oxidase and CYP3A	Hepatotoxicity; allergic reactions; myelosuppression; diarrhea; cutaneous reactions; infection; pneumonitis	Second-line therapy of CLL in combination with rituximab; follicular B-cell NHL; small lymphocytic lymphoma

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TABLE 164-2 U.S. FDA-APPROVED DRUGS COMMONLY USED FOR THE SYSTEMIC TREATMENT OF CANCER*—cont'd

DRUG NAME	DRUG CLASS AND/OR MECHANISM	PHARMACOKINETICS/METABOLISM	TOXICITY	INDICATIONS†
Ifosfamide (Ifex)	Classic alkylating agent; not cell cycle dependent	After an intravenous dose, ifosfamide is activated by hepatic microsomal enzymes; it is then converted to inactive metabolites in the liver; the active form of the drug is the same as that for cyclophosphamide; the elimination half-life of the drug is 7-15 hr; the metabolites and some unchanged drug are excreted in the urine	Myelosuppression, hemorrhagic cystitis, and CNS toxicity are all fairly common and can be dose limiting; hemorrhagic cystitis can largely be prevented by co-administration of the uroprotective agent mesna, and nausea and vomiting are minimized with modern antiemetic regimens; the CNS toxicity, including lethargy, stupor, coma, myoclonus, and seizures, is usually mild and completely reversible; it is worse with impaired renal function; renal dysfunction, usually reversible, is also seen with ifosfamide; hepatic toxicity, diarrhea, and rash are rare	Approved for the treatment of recurrent germ cell tumors; used for many other tumor types, including adult sarcomas, lymphoma, Hodgkin disease, breast cancer, and ovarian cancer
Imatinib (Gleevec)	Bcr-Abl tyrosine kinase inhibitor; also inhibits platelet-derived growth factor (PDGF), c-Kit, and stem cell factor (SCF)	Rapid oral absorption; metabolized in the liver by CYP3A4; AUC increased by severe hepatic dysfunction; dose reduction for renal dysfunction	Edema, ascites, chest pain; fatigue; skin rash; increased LDH; nausea, diarrhea; muscle cramps; increased serum creatinine and liver function tests	CML; ALL that is Philadelphia chromosome positive; gastrointestinal stromal tumors; myelodysplastic syndrome associated with PDGF receptor gene rearrangements
Infigratinib (Truseltiq)	Receptor tyrosine kinase inhibitor that blocks fibroblast growth factor receptors FGFR1, FGFR2, FGFR3; blocks FGFR signaling from activating receptor mutations and gene fusions	Metabolized by CYP3A4; excreted in feces. Steady-state concentrations increased by 50-100% in patients who have mild to moderate liver dysfunction, so the dose must be reduced. Avoid coadministration of proton pump inhibitor.	Hyperphosphatemia requiring monitoring and dose adjustment	Unresectable or locally advanced/metastatic cholangiocarcinoma with *FGFR2* fusion or other rearrangement
Ipilimumab (Yervoy)	Human CTLA-4–blocking antibody	No formal pharmacokinetic drug interaction studies have been conducted; no clinically important differences in clearance of ipilimumab were found between patients with renal impairment and patients with normal renal function; no clinically important differences in clearance of ipilimumab were found between patients with mild hepatic impairment and normal hepatic function	Immune-mediated adverse reactions; fatigue, diarrhea, pruritus, rash, and colitis	Unresectable or metastatic melanoma; NSCLC; mesothelioma; renal cell cancer; hepatocellular cancer; colorectal cancer (MSI-high)
Irinotecan (Camptosar)—CP T-11	Semisynthetic camptothecin, which functions as a topoisomerase I inhibitor; partly cell cycle dependent	Converted partially from active lactone form to inactive carboxylate form; active metabolite of irinotecan, SN-38, also exists in lactone and inactive carboxylate form in equilibrium in plasma; SN-38 is inactivated by glucuronidation in the liver; SN-38 is responsible for the majority of antitumor activity attributed to parent drug; half-life of irinotecan is 8 hr, whereas half-life of SN-38 is 12 hr	Myelosuppression, primarily neutropenia, is common and dose limiting; diarrhea is also common and can be dose limiting; diarrhea can occur as part of a cholinergic syndrome, along with cramping, nausea, and vomiting, during or immediately after drug administration or for several days after drug administration; anticholinergic and antidiarrheal agents will curtail the immediate diarrhea and other GI symptoms partially but are less effective in treating the delayed diarrhea; flushing, rash, and alopecia are common; significant hepatic, renal, neurologic, or pulmonary toxicities are rare	Irinotecan is FDA approved for refractory or recurrent metastatic colon cancer, and it has now been used in other malignancies, including lung cancer, ovarian cancer, and lymphoma
Ixabepilone (Ixempra)	Microtubule inhibitor	In combination with capecitabine, must not be given to patients with AST or ALT >2.5 × ULN or bilirubin >1 × ULN; dose reduction is recommended when administering ixabepilone as monotherapy to patients with hepatic impairment; no formal renal impairment study; inhibitors of CYP3A4 may increase plasma concentrations of ixabepilone; dose of ixabepilone must be reduced with strong CYP3A4 inhibitors; inducers of CYP3A4 may decrease plasma concentrations of ixabepilone; alternative therapeutic agents with low enzyme induction potential should be considered	Peripheral neuropathy: monitor for symptoms of neuropathy, primarily sensory; neuropathy is cumulative, generally reversible, and should be managed by dose adjustment and delays; myelosuppression: primarily neutropenia; monitor with peripheral blood cell counts and adjust dose as appropriate; hypersensitivity reaction: must premedicate all patients with an H1 antagonist and an H2 antagonist before treatment; fatigue/asthenia, myalgia/arthralgia, alopecia, nausea, vomiting, stomatitis/mucositis, diarrhea, and musculoskeletal pain	Combination with capecitabine is indicated for the treatment of metastatic or locally advanced breast cancer in patients after failure of an anthracycline and a taxane; as monotherapy is indicated for the treatment of metastatic or locally advanced breast cancer in patients after failure of an anthracycline, a taxane, and capecitabine

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Ixazomib (Ninlaro)	Inhibits 20 S proteasome	Absorption decreased by high-fat meals; hepatic metabolism; reduce dose for CrCl <30 mL/min and for total bilirubin >1.5 ULN	Myelosuppression; skin rash; peripheral neuropathy	Multiple myeloma in combination with lenalidomide and dexamethasone as second-line therapy
Lapatinib (Tykerb)	EGRF and HER2 tyrosine kinase inhibitor	Extensive metabolism spread over several enzymes	Hepatotoxicity; decreased left ventricular ejection fraction; diarrhea; some QT interval prolongation	HER2+ breast cancer, with capecitabine; treatment with anthracycline, taxane, trastuzumab failed
Larotrectinib (Vitrakvi)	Neurotrophic receptor tyrosine kinase inhibitor	Avoid strong CYP3A4 inhibitors, strong CYP3A4 inducers, and sensitive CYP3A4 substrates	Neurotoxicity, hepatotoxicity, nausea, vomiting, dizziness, cough, constipation, diarrhea	Metastatic or unresectable solid tumors with a neurotrophic receptor tyrosine kinase gene fusion
Lenalidomide (Revlimid)	Antiangiogenesis agent, immunomodulator	Mechanism of action not fully characterized; an immunomodulatory agent that inhibits angiogenesis in some cells; inhibits bone marrow secretion of IL-6, VEGF, and TNF-α	Myelosuppression; diarrhea, rash, fatigue; increased risk of DVT and PE	Transfusion-dependent anemia due to low- or intermediate-risk myelodysplasia with 5q deletion; multiple myeloma
Lenvatinib (Lenvima)	Multitargeted tyrosine kinase inhibitor *(VEGFR, FGFR, PDGFR, KIT, RET)*	Metabolized in the liver by CYP3A and aldehyde oxidase; dose reduction for hepatic insufficiency	Hypertension; alters thyroid suppression with TSH elevation and hypothyroidism; gastrointestinal toxicity and bowel fistula formation; hepatotoxicity; skin toxicity; hypocalcemia; renal toxicity	Renal cell carcinoma in combination with everolimus; differentiated thyroid cancer that is radioactive iodine refractory
Letrozole (Femara)	Nonsteroidal aromatase inhibitor	Letrozole has nearly 100% bioavailability, is metabolized in the liver, glucuronidated, and excreted by the kidneys; half-life is 2 days; with daily administration, steady-state plasma levels are reached in 2-6 wk	This drug is generally well tolerated; muscle aches and nausea are uncommon; hot flashes and fatigue are uncommon; weight change, urticaria, and dyspepsia are rare	Metastatic estrogen-responsive breast cancer in postmenopausal patients
Leucovorin calcium (Wellcovorin) citrovorum factor, folinic acid, FA, LV	Tetrahydrofolate derivative and enzyme cofactor for thymidylate synthase and other purine and pyrimidine synthesis steps; bypasses the dihydrofolate reductase step, which is inhibited by methotrexate and therefore can be used to "rescue" normal cells from the toxicity of methotrexate after high doses are administered; in addition, leucovorin potentiates the toxicity of fluoropyrimidines such as fluorouracil by strengthening the association of the drug	Leucovorin has excellent bioavailability by the oral or parenteral route; it is oxidized in cofactor reactions throughout the body and is also partly metabolized; it has an elimination half-life of 2-4 hr; excreted in the urine	Leucovorin is generally very well tolerated; it occasionally causes stomach upset or nausea, rash, diarrhea, and headache; allergic reactions have been reported	Used for rescue of high-dose methotrexate therapy for a variety of neoplasms and as a potentiator of fluoropyrimidines therapy in GI malignancies, particularly colorectal cancer
Leuprolide acetate (Lupron)—leuprorelin acetate	Gonadotropin-releasing hormone agonist, which serves to paradoxically shut down the pituitary release of gonadotropins with chronic exposure; this results in a dramatic decrease in gonadal estrogens and androgens and growth inhibition of hormone-dependent neoplasms	After an SQ injection, about 90% of the drug is eventually absorbed; the depot form of the drug is absorbed slowly over days, whereas the injectable solution is absorbed over several hours; the elimination half-life of the drug once in the serum is 3 hr; metabolism and excretion are not well delineated but are clinically unimportant	Usually well tolerated, but adverse effects can affect many systems, including endocrine (hot flashes, impotence, gynecomastia, breast tenderness, diminished libido, amenorrhea, atrophic vaginitis, increased cholesterol); GI (nausea, constipation, anorexia, diarrhea); hepatic (elevation of transaminases); dermatologic (rash, changes in body hair composition, pruritus); and neuropsychiatric (insomnia, depression, emotional lability, lethargy, memory loss); significant cardiac toxicity is rare	Approved for the treatment of hormone-dependent advanced prostate cancer; also used for breast cancer and endometriosis
Lurbinectedin (Zepzelca)	Alkylating agent	Avoid strong or moderate CYP3A inhibitors and strong or moderate CYP3A inducers	Myelosuppression, hepatotoxicity, increased creatinine level, hyperglycemia, nausea, musculoskeletal pain, constipation, dyspnea, decreased sodium level	Metastatic SCLC progressing despite platinum-based chemotherapy

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TABLE 164-2 U.S. FDA-APPROVED DRUGS COMMONLY USED FOR THE SYSTEMIC TREATMENT OF CANCER*—cont'd

DRUG NAME	DRUG CLASS AND/OR MECHANISM	PHARMACOKINETICS/METABOLISM	TOXICITY	INDICATIONS†
Methotrexate (Mexate, Folex, others)—MTX, amethopterin	Antifolate antimetabolite; interferes with nucleotide synthesis by inhibiting dihydrofolate reductase; cell cycle dependent	Good oral bioavailability at low doses; after oral or IV dosing, it is distributed throughout the body water compartment; it will accumulate in "third-space" fluid compartments and exhibit prolonged toxicity and therefore should be used with caution, if at all, in patients with significant pleural or peritoneal fluid; minimally metabolized in the liver; half-life is 3 hr; even low concentrations of drug after most of the drug is eliminated can contribute to significant toxicity; therefore dosing based on renal function is critical; excretion of this drug is mostly renal	Myelosuppression is expected and is usually dose limiting; stomatitis and diarrhea are common; nausea and vomiting are uncommon; renal toxicity is uncommon and usually reversible but can be severe; many types of skin reactions can occur but are uncommon; pulmonary fibrosis and hepatic fibrosis are rare; encephalopathy is rare with moderate- to low-dose therapy but is more common with high doses, intrathecal administration, or concomitant CNS radiation; it can be severe and permanent	Approved for a wide spectrum of malignant and nonmalignant diseases; most often used for acute leukemias, lymphomas, breast cancer, bladder cancer, squamous cell cancers, and sarcomas
Midostaurin (Rydapt)	Tyrosine kinase inhibitor targeting *FLT3, FLT3 ITD, KIT, PDGFR, VEGFR2,* and *PKC* family	Metabolized by CYP3A4 in the liver	Cardiovascular (edema and QTc prolongation); headache and fatigue; electrolyte abnormalities and hyperglycemia; nausea and vomiting; myelosuppression; abnormal liver function tests; infection	FLT3 mutation-positive AML in combination with cytarabine and daunorubicin; mast cell leukemia; systemic mastocytosis
Neratinib (Nerlynx)	Irreversible inhibitor of EGFR and HER2 kinases	Hepatic metabolism by CYP3A4; dose reduction for severe hepatic dysfunction	Severe diarrhea with dehydration; hepatic toxicity requiring careful monitoring of liver function	Adjuvant therapy of HER2-positive breast cancer following adjuvant trastuzumab-associated therapy
Nilotinib (Tasigna)	Kinase inhibitor including Bcr-Abl	Dose adjustment may be required for hematologic and nonhematologic toxicities and drug interactions; lower starting dose is recommended in patients with impairment (at baseline); do not consume food for at least 2 hr before the dose is taken and for at least 1 hr after	Prolongs QT interval; rash, pruritus, headache, nausea, fatigue, myalgia, nasopharyngitis, constipation, diarrhea, abdominal pain, vomiting, arthralgia, pyrexia, upper respiratory tract infection, back pain, cough, and asthenia; hematologic adverse drug reactions include myelosuppression: thrombocytopenia, neutropenia, and anemia	Newly diagnosed adult patients with Philadelphia chromosome–positive chronic myeloid leukemia (Ph+ CML) in chronic phase; also, the treatment of chronic and accelerated phase Ph+ CML in adult patients resistant to or intolerant to prior therapy that included imatinib
Niraparib (Zejula)	Poly (ADP-ribose) polymerase enzyme inhibitor	Metabolized by carboxylesterases and then glucuronidated	Hypertension; skin rash; fatigue; nausea and constipation; myelosuppression; weakness and back pain; hepatic dysfunction	Ovarian and primary peritoneal cancers in complete or partial response following platinum-containing chemotherapy
Nivolumab (Opdivo)	Human anti-PD-1 monoclonal antibody; releases PD-1 pathway inhibition to improve immune response	Prolonged (>20 day) half-life	Endocrinopathies; colitis; encephalitis; pneumonitis; hypophysitis; rash; if severe may require systemic corticosteroids; infusion reactions	Colorectal cancer with microsatellite instability-high (MSI-H) or mismatch repair deficient (dMMR) that is metastatic and has progressed following fluoropyrimidine, oxaliplatin, and irinotecan; head and neck squamous cell cancer that is recurrent or progressed on platinum-containing chemotherapy; Hodgkin lymphoma; metastatic melanoma; NSCLC; advanced renal cancer; advanced urothelial cancer; esophageal cancer or gastroesophageal junction adenocarcinoma; hepatocellular cancer; mesothelioma; squamous cancer of the head and neck
Obinutuzumab (Gazyva)	Anti-CD20 monoclonal antibody; upon binding to CD20 on B cells, initiates ADCC	No dosage adjustments for renal or hepatic dysfunction	Hypophosphatemia; hypocalcemia; hyperkalemia; blood count suppression; altered liver and kidney function; infection; cough	CLL previously untreated in combination with chlorambucil; follicular lymphoma in combination with bendamustine in patients refractory to rituximab-containing regimens

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Octreotide, octreotide long-acting (Sandostatin, Sandostatin LA), l-cysteinamide	Synthetic peptide analog of somatostatin; inhibits other GI peptide actions, such as serotonin, insulin, glucagon, and gastrin	Not orally bioavailable but rapidly absorbed after SQ administration; metabolized by hydrolysis throughout the body; no active metabolites; half-life of elimination is about 1.5 hr; intact drug is cleared via the kidneys	GI adverse effects are dose limiting and include abdominal pain, vomiting, loose stool, occasional fat malabsorption, bloating, and cholelithiasis; elevations of liver function tests can also occur, but frank hepatitis is rare; skin reactions, such as pain at the injection site or flushing, rash, or skin thinning, are sometimes seen; constitutional symptoms, including rhinorrhea, xerostomia, sweating, throat discomfort, and vertigo, can be bothersome; hyperglycemia or hypoglycemia can occur; cardiac side effects, including angina, congestive heart failure, and hypotension or hypertension, are uncommon; anxiety, depression, fatigue, and anorexia are uncommon, and seizures are rare	Approved for carcinoid tumors causing carcinoid syndrome and for vasoactive peptide–secreting tumors; also used for refractory diarrhea, either cancer related or treatment related, in patients with cancer
Olaparib (Lynparza)	Inhibitor of poly (ADP-ribose) polymerase enzyme; produces synthetic lethality in BRCA1/2-deficient tumor cells	Hepatic metabolism by CYP3A4; Cmax increased in patients with mild hepatic dysfunction; avoid concomitant use of CYP3A inhibitors	Peripheral edema; fatigue and headache; skin rash; nausea and abdominal pain; anemia and lymphopenia; myalgias; increased serum creatinine	*BRCA*-mutant ovarian cancer previously treated with three or more lines of therapy; maintenance therapy for ovarian cancer in complete or partial remission following platinum-based therapy
Osimertinib (Tagrisso)	Irreversible inhibitor of EGFR tyrosine kinase; binds to mutant forms of EGFR (*T970M, L858R*, exon 19 deletions); less active against wild-type EGFR	Metabolized by CYP3A and excreted in the feces; avoid concomitant use of strong CYP3A4 inducers	Bone marrow suppression; cardiotoxicity, decline in LVEF and prolongation of QTc; skin rash; impaired fertility; diarrhea; keratitis; pneumonitis	Metastatic NSCLC that is *T790M* mutation positive
Oxaliplatin (Eloxatin)	Platinating agent; DNA disrupted via intrastrand and interstrand cross-links with two strong platinum association bonds in the molecule, which induces apoptosis beyond a certain level of DNA damage in malignant cells	After IV administration, rapid distribution into tissues occurs, as well as rapid spontaneous conversion via hydrolysis into active drug and metabolites; the terminal half-life is long (>300 hr) but represents minimal plasma levels of the hydrolyzed drug; elimination of platinum metabolites is via the kidneys	Neurotoxicity, in the form of a transient neuropathy with each dose and a persistent, cumulative typical sensory polyneuropathy, is very common and dose limiting; myelosuppression is expected but mild and only sometimes dose limiting; fatigue and nausea are common but mild; diarrhea, stomatitis, edema, cough, hypersensitivity reactions, and extravasation injury are rare	Approved for metastatic colorectal cancer in combination with 5-FU/leucovorin
Paclitaxel (Taxol, Onxol)	Naturally occurring taxane molecule; inhibits depolymerization of tubulin in the spindle apparatus, thereby inducing apoptosis in dividing cells	After IV administration, the drug exhibits a large volume of distribution and undergoes metabolism in the liver; the elimination half-life is 15-50 hr; excretion of drug and metabolites is predominantly via the bile	Paclitaxel is an irritant or mild vesicant when extravasated into subcutaneous tissue; myelosuppression, predominantly neutropenia, is expected and is dose limiting; shorter infusions of the same dose produce less neutropenia; mucositis is also very common, particularly with longer infusions; peripheral neuropathy is common, usually mild, and increases with cumulative dose; acute neuromyopathy is also common and occurs for several days after each dose; this syndrome may require opiate analgesics to control pain; cardiovascular adverse effects, including hypertension, hypotension, premature contractions, and bradyarrhythmias, are common but rarely require intervention; hypersensitivity reactions to paclitaxel, including urticaria, wheezing, chest pain, dyspnea, and hypotension, are common but are reduced in frequency and severity by premedication with corticosteroids and histamine-1 and histamine-2 antihistamines (the recommended regimen is dexamethasone, 20 mg PO 12 and 6 hr prior to paclitaxel and diphenhydramine, 50 mg, and cimetidine)	Approved for salvage therapy in ovarian cancer and for breast cancer in both the metastatic and adjuvant settings; used also in persons with lung cancer, head and neck cancer, and bladder cancer
Paclitaxel, protein bound (Abraxane)	Taxane; an albumin-bound form of paclitaxel with a mean particle size of approximately 130 nanometers	No change in patients with mild to moderate hepatic dysfunction	Neutropenia, thrombocytopenia, anemia, hypersensitivity reactions, hypotension, cardiovascular events, dyspnea, cough, sensory neuropathy, arthralgias/myalgias, nausea/vomiting, asthenia	Metastatic breast cancer after failure of combination chemotherapy or relapse with 6 mo of adjuvant chemotherapy; also approved for NSCLC

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TABLE 164-2 U.S. FDA-APPROVED DRUGS COMMONLY USED FOR THE SYSTEMIC TREATMENT OF CANCER*—cont'd

DRUG NAME	DRUG CLASS AND/OR MECHANISM	PHARMACOKINETICS/METABOLISM	TOXICITY	INDICATIONS†
Palbociclib (Ibrance)	Reversible small molecule inhibitor of cyclin-dependent kinases 4 and 6 affecting cell cycle progression through the G1/S phase	Metabolized by the liver by CY3A and sulfotransferase; avoid simultaneous use of strong CYP3A inhibitors	Fatigue; alopecia and skin rash; nausea, stomatitis, diarrhea, infection; blood count suppression, infection	Advanced breast cancer that is ER positive, HER2 negative in combination with an aromatase inhibitor as initial therapy for postmenopausal women
Pamidronate (Aredia), APD, aminohydroxypropylidene diphosphonate	Organic bisphosphonate; inhibitor of bone resorption by osteoclasts	After IV administration, the drug concentrates in the bone, spleen, and liver; its metabolism is not well characterized; it has a terminal half-life of about 27 hr; 50% of the parent drug is eliminated in the urine	Pamidronate is usually quite well tolerated; hypotension, syncope, tachycardia, and even atrial fibrillation have been reported uncommonly during the infusion; hypocalcemia, hypophosphatemia, hypokalemia, and hypomagnesemia occur commonly but only rarely require intervention; nausea, vomiting, and somnolence are rare	Approved for malignancy-induced hypercalcemia; may lead to pain relief and even tumor shrinkage of bone metastases in multiple myeloma, breast cancer, and prostate cancer
Panitumumab (Vectibix)	Recombinant, fully humanized IgG2 kappa monoclonal antibody that binds specifically to EGFR, competitively inhibiting ligand binding to the receptor	Steady-state levels are reached by the third infusion; elimination half-life is about 7.5 days	Rash, which may be severe; diarrhea; infusion reactions; hypomagnesemia; pulmonary fibrosis	Previously treated EGFR-expressing metastatic colorectal cancer
Panobinostat (Farydak)	Histone deacetylase inhibitor, affects chromatin remodeling	Hepatic metabolism in part through CYP3A; reduce dose for hepatic dysfunction	ECG abnormalities; fatigue; electrolyte abnormalities; diarrhea; blood count suppression; infection; hyperbilirubinemia	Multiple myeloma in combination with bortezomib and dexamethasone in patients who have received 2 prior regimens
Pazopanib (Votrient)	Inhibits large number of tyrosine kinases	Take without food; reduce dose for mild to moderate hepatic impairment; avoid severe hepatic impairment; interacts with many metabolizing enzymes	Diarrhea, hypertension, nausea, anorexia, vomiting, hair color depigmentation	Renal cell carcinoma; also approved for soft tissue sarcoma
Pembrolizumab (Keytruda)	Human monoclonal antibody against programmed cell death-1 (PD-1) activity that inhibits negative immune regulation to enhance antitumor effects	Long half-life (22 days)	Peripheral edema; rash; fatigue; endocrinopathies; electrolyte abnormalities; hyperglycemia; nausea, diarrhea, colitis; abnormal liver function tests	Squamous cell cancers of the head and neck; Hodgkin lymphoma, melanoma, microsatellite instable (MSI-H) or mismatch repair deficient solid tumors and colorectal cancers that have no alternative treatment options; NSCLC first-line metastatic in patients with high (50%) PD-L1 expression that are EGFR or ALK negative and first-line therapy for metastatic nonsquamous NSCLC in combination with pemetrexed and carboplatin; urothelial carcinoma that has progressed on platinum-containing therapy; triple-negative breast cancer; cervical cancer; cutaneous squamous cell cancer; endometrial cancer that is MSI-high; esophageal, gastric, and gastroesophageal junction adenocarcinoma; hepatocellular cancer; Merkel cell carcinoma; renal cell cancer; primary large B-cell lymphoma
Pemetrexed (Alimta)	Antimetabolite; inhibits folate-dependent enzymes thymidylate synthetase, dihydrofolate reductase, and glycinamide ribonucleotide formyltransferase, which are involved in the de novo synthesis of thymidine and purine nucleotides, leading to inhibition of DNA and RNA synthesis and function; metabolized intracellularly to its highly active polyglutamated form	Excreted in urine with 90% of drug unchanged	Myelosuppression; nausea, vomiting, diarrhea; rash; dyspnea and fatigue	Mesothelioma and NSCLC

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Pertuzumab (Perjeta)	HER2/neu receptor antagonist antibody; HER2 testing: perform using FDA-approved tests by laboratories with demonstrated proficiency	Of 402 patients who received Perjeta in the randomized trial, 60 patients (15%) were 65 yr of age and 5 patients (1%) were 75 yr of age; no overall differences in efficacy and safety of Perjeta were observed between these patients and younger patients; based on a population pharmacokinetic analysis, no significant difference was observed in the pharmacokinetics of pertuzumab between patients <65 yr (n = 306) and patients ≥65 yr (n = 175)	Left ventricular dysfunction: monitor LVEF and withhold dosing as appropriate; reactions, hypersensitivity reactions/anaphylaxis: monitor for signs and symptoms; if a significant infusion-associated reaction occurs, slow or interrupt the infusion and administer appropriate medical therapies; in combination with trastuzumab and docetaxel: diarrhea, alopecia, neutropenia, nausea, fatigue, rash, and peripheral neuropathy	First-line HER2+ metastatic breast cancer
Pomalidomide (Pomalyst)	Immunomodulator, analog of thalidomide, decreases proliferation of myeloma cells, enhances T-cell–mediated immunity, and has antiangiogenic properties	Metabolized by CYP3A4 and CYP1A2; systemic exposure increased by hepatic dysfunction; avoid use with concomitant CYP1A2 inhibitors; reduce dose for renal or hepatic dysfunction	Thromboembolism; hematologic toxicity; hepatotoxicity; hypersensitivity; neurotoxicity; confusion; tumor lysis syndrome; fatigue; nausea; diarrhea; infection	Multiple myeloma in combination with dexamethasone as third-line therapy
Ponatinib (Iclusig)	Kinase inhibitor	For strong CYP3A inhibitors: reduce dose if co-administration cannot be avoided; renal or hepatic impairment not studied	Arterial thrombosis and hepatotoxicity have boxed warnings; nonhematologic adverse reactions (≥20%) were hypertension, rash, abdominal pain, fatigue, headache, dry skin, constipation, arthralgia, nausea, and pyrexia; hematologic adverse reactions included thrombocytopenia, anemia, neutropenia, lymphopenia, and leukopenia	CML and Philadelphia chromosome–positive acute ALL
Ramucirumab (Cyramza)	Monoclonal antibody targeting the vascular growth factor receptor 2, inhibiting endothelial cell proliferation and angiogenesis	Half-life 14 days	Infusion reaction; hypertension; proteinuria; arterial thrombosis; GI perforation; bleeding	Metastatic colorectal cancer in combination with FOLFIRI following progression on FOLFOX and bevacizumab; gastric cancer as a single agent or in combination with paclitaxel following progression on a fluoropyrimidine- or platinum-containing regimen; NSCLC in combination with paclitaxel for advanced disease after platinum-based treatment
Regorafenib (Stivarga)	Inhibits many membrane and intracellular kinases including *RET, VEGFR, KIT, PDGFR, FGF, TIE2, DDR2, TrkA, Eph2A, RAF-1, BRAF,* and *CSF1R*	Take with food; decreased exposure with strong inducers of CYP3A	Hepatotoxicity, fatigue, decreased appetite, hand-foot skin reaction	Previously treated metastatic colorectal cancer; gastrointestinal stromal tumor; hepatocellular carcinoma
Ribociclib (Kisqali)	Small molecule inhibitor of cyclin-dependent kinases 4 and 6; produces G1 cell cycle arrest; combined with aromatase inhibitors leads to enhanced tumor cell growth control	Metabolized in the liver by CYP3A4	Bone marrow suppression; hepatotoxicity with abnormal liver function; QT prolongation; peripheral edema; fatigue; alopecia; skin rash; hypokalemia; nausea and diarrhea; increased serum creatinine	Advanced breast cancer for patients with HR-positive, HER2-negative disease in combination with an aromatase inhibitor as initial endocrine therapy
Rituximab (Rituxan)	Monoclonal antibody directed against the B-cell surface antigen CD20	When given IV, it is taken up by B lymphocytes and then degraded throughout the body by proteolysis, with a wide-ranging serum half-life of 11-105 hr (mean 60 hr) with the first dose; there is no appreciable excretion of this polypeptide	Fever, chills, and malaise are common during administration, even with premedication with acetaminophen and diphenhydramine; other infusion-related symptoms include nausea, vomiting, flushing, urticaria, angioedema, hypotension, dyspnea, bronchospasm, fatigue, headache, rhinitis, and pain at disease sites; these symptoms are generally self-limited, improve with slowing of the infusion, and resolve after infusion; short-lived myelosuppression, abdominal pain, and myalgia are uncommon; arrhythmias and angina pectoris are rare	Relapsed or refractory low-grade or follicular, CD20-positive, B-cell lymphomas

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Rucaparib (Rubraca)	Inhibits poly (ADP-ribose) polymerase enzyme isoforms essential for DNA repair; increased cell killing in tumors deficient in BRCA1/2 repair pathway	Metabolized by CYP2D6 in the liver	Fatigue and dizziness; skin rash; increased cholesterol; nausea, constipation; diarrhea; blood count suppression; increased liver function tests; increased serum creatinine; weakness; dyspnea; fever	Advanced ovarian cancer in the presence of *BRCA* mutations (germline or somatic) detected by an approved diagnostic test as third-line therapy
Ruxolitinib (Jakafi)	Janus kinase signaling inhibitor	With or without food; reduce dose 50% with strong CYP3A inhibitors, moderate renal or hepatic impairment	Thrombocytopenia, anemia, bruising, dizziness, headache	Intermediate- or high-risk myelofibrosis
Sacituzumab govitecan-hziy (Trodelvy)	Trop-2–directed antibody and topoisomerase inhibitor conjugate	Individuals who are homozygous for the uridine diphosphate-glucuronosyl transferase 1A1 (UGT1A1)*28 allele are at increased risk for neutropenia	Neutropenia, severe diarrhea, hypersensitivity reactions, nausea, vomiting, anemia, alopecia, constipation, rash, abdominal pain	Metastatic triple-negative breast cancer despite at least two prior therapies
Selinexor (Xpovio)	Nuclear export inhibitor	95% protein bound; metabolized by liver	Thrombocytopenia, neutropenia, gastrointestinal toxicity, hyponatremia, serious infection, neurologic toxicity	With dexamethasone for relapsed or refractory multiple myeloma despite at least four prior therapies; or refractory diffuse large B-cell lymphoma, including disease arising from follicular lymphoma, after at least two lines of systemic therapy
Sonidegib (Odomzo)	Hedgehog pathway inhibitor that binds and inhibits Smoothened, a transmembrane protein essential for hedgehog signaling	Metabolized in the liver by CYP3A	Fatigue; alopecia; hyperglycemia; abnormal liver function tests; anemia; increased CK, muscle pain; increased serum creatinine	Locally advanced basal cell carcinoma recurrent after surgery or radiation therapy
Sorafenib (Nexavar)	Oral multikinase inhibitor that interacts with multiple intracellular (CRAD, BRAF) and cell surface kinases (KIT, FLT-3, VEGFR-2, and PDGFR); may inhibit angiogenesis	Metabolized in the liver; drug and metabolites are excreted primarily in the feces	Skin toxicity with rash and hand-foot syndrome; nausea, vomiting, anorexia, diarrhea; asthenia, pain, arthralgias; hypertension; bleeding events, especially in anticoagulated patients; cardiac ischemia; myelosuppression	Advanced renal cell carcinoma
Sotorasib (Lumakras)	Selective, orally active inhibitor that covalently binds to Cys12 of KRAS; inhibits signaling only in tumors that exhibit the KRAS-G12C mutation	Avoid proton pump inhibitors and histamine-2 receptor antagonists	Drug-induced hepatitis with increased ALT/AST requires monitoring of liver function tests; interstitial lung disease; diarrhea; musculoskeletal pain; nausea; fatigue	Adults with *KRAS-G12C*-mutated locally advanced or metastatic NSCLC
Sunitinib maleate (Sutent)	Inhibits PDGFR-A, PDGFR-B, and VEGFR1-3, stem cell factor receptor, FLT-3, CSF-1R, and the neurotrophic factor receptor; this inhibition inhibits tumor growth and metastases	Metabolized in the liver with elimination primarily in the feces; half-life is 40-60 hr for the drug and 80-110 hr for its primary metabolite	Cardiotoxicity—usually reversible; bleeding event, epistaxis most common; hypertension; myelosuppression; nausea, vomiting; rash; liver function test alterations	Advanced renal cell carcinoma; second-line therapy for GIST cell tumors; also approved for pancreatic neuroendocrine tumors
Talazoparib (Talzenna)	PARP inhibitor	Reduce dose if moderate renal impairment (creatinine clearance 30-59 mL/min)	Myelodysplastic syndrome, AML, myelosuppression, nausea, headache, vomiting, alopecia, diarrhea	Germline *BRCA*-mutated HER2-negative locally advanced or metastatic breast cancer
Tamoxifen (Nolvadex)	Nonsteroidal antiestrogen; cytostatic effects on estrogen-dependent and nondependent malignant cells	Tamoxifen has good oral bioavailability, is metabolized in the liver, and has an elimination half-life of about 7 days; neither tamoxifen nor its major metabolite is found in the bile or urine	Tamoxifen is usually very well tolerated; constitutional symptoms are most prevalent and usually dose limiting; hot flashes, sweating, mood changes, weight gain or loss, and stomach upset are most common; nausea, vomiting, diarrhea, and constipation are less common; menstrual changes, including significant vaginal bleeding, are uncommon; venous thromboembolism, myelosuppression, and retinopathy are rare	Approved for the treatment of breast cancer, generally in postmenopausal patients or those with ER+ tumors; the same dose has been approved for chemoprevention of breast cancer in high-risk individuals; higher doses are used for melanoma and pancreatic cancer
Tazemetostat (Tazverik)	Methyltransferase inhibitor	Avoid strong and moderate CYP3A inhibitors and strong and moderate CYP3A inducers	Fatigue, nausea, vomiting, constipation, upper respiratory tract infection, musculoskeletal pain, abdominal pain	Metastatic or unresectable locally advanced epithelioid sarcoma, relapsed or refractory follicular lymphoma with an EZH2 mutation or no alternative treatment options

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Temozolomide (Temodar)	Atypical alkylator (semiselective DNA methylator) drug sharing the same active metabolite as dacarbazine, MTIC but, unlike dacarbazine, is spontaneously converted to MTIC and also penetrates the blood-brain barrier effectively	Temozolomide had good bioavailability, enhanced by an empty stomach; after absorption into the blood stream, it is spontaneously converted to the active moiety MTIC; peak plasma concentrations occur in about 1 hr; the elimination half-life is about 1.8 hr; parent drug, MTIC, and other metabolites are eliminated in the urine	Myelosuppression is expected and dose-limiting; it may be cumulative; nausea is common but generally mild and treatable; headache and fatigue are common; rash or other cutaneous reactions are uncommon; infections are common in this population, and some are probably caused by immunosuppression that is known to occur with temozolomide	Approved for treatment of recurrent high-grade astrocytomas; used commonly for other gliomas and also for metastatic melanoma
Temsirolimus (Torisel)	Inhibitor of mTOR	Antihistamine pretreatment is recommended; dose reduction is required in patients with mild hepatic impairment; strong inducers of CYP3A4/5 and inhibitors of CYP3A4 may affect concentrations of the primary metabolite, sirolimus; if alternatives cannot be used, dose modifications are recommended	Hypersensitivity/infusion reactions (including some life-threatening and rare fatal reactions) can occur early in the first infusion; patients should be monitored throughout the infusion; monitor for symptoms or radiographic changes of ILD; if ILD is suspected, discontinue drug, and consider use of corticosteroids and/or antibiotics; bowel perforation may occur; evaluate fever, abdominal pain, bloody stools, and/or acute abdomen promptly; elderly patients may be more likely to experience certain adverse reactions, including diarrhea, edema, and pneumonia	Advanced renal cell carcinoma
Tepotinib (Tepmetko)	Tyrosine kinase inhibitor that blocks signaling through a *MET* exon 14 skipping mutation	Avoid use with strong CYP3A and P-gp inhibitors; metabolized in the liver and excreted in feces	Edema; fatigue; nausea; diarrhea; interstitial lung disease; hepatotoxicity	NSCLC with *MET* exon 14 skipping mutation
Tisagenlecleucel (Kymriah)	Anti-CD19 CAR–T-cell immunotherapy	No contraindications	Cytokine release syndrome; neurologic toxicity	ALL B-cell precursor type refractory to primary therapy
Topotecan (Hycamtin), hycamptamine	Semisynthetic camptothecin molecule; an inhibitor of topoisomerase I, which is required by cells for both transcription and replication	After IV administration, the drug is not extensively metabolized, and it has an elimination half-life of about 3 hr; a significant portion of the drug is excreted unchanged in the urine	Myelosuppression, especially leukopenia, is expected and dose limiting; thrombocytopenia and anemia are common but mild; nausea, vomiting, and diarrhea are common but usually not severe; headache, fever, fatigue, anorexia, malaise, and elevated liver function tests are also common; hypertension, tachycardia, urticaria, renal insufficiency, hematuria, neuropathy, and mucositis are uncommon	Approved for the treatment of refractory, relapsed ovarian carcinoma and for relapsed small cell lung cancer; also used in myeloid leukemias
Trabectedin (Yondelis)	Alkylating agent that binds the minor groove of DNA-producing adducts	Avoid strong CYP3A inhibitors or inducers	Neutropenic sepsis; rhabdomyolysis; hepatotoxicity; cardiotoxicity; fetal harm	Unresectable or metastatic liposarcoma or leiomyosarcoma after prior anthracycline therapy
Trametinib (Mekinist)	Selective inhibitor of mitogen-activated extracellular kinase (MEK) 1 and 2; decreases cellular proliferation; combination with BRAF inhibitors increases inhibition of MAPK pathway	Deacetylated and glucuronidated in liver; no dose adjustments for mild renal or hepatic dysfunction	Cardiovascular (hypertension, decreased LVEF); acneiform rash and palmar-plantar erythrodysesthesia; diarrhea; anemia; peripheral edema	Advanced melanoma in patients with *BRAF* V600E or V600K mutations alone or in combination with dabrafenib; metastatic NSCLC with *BRAF* V600E mutation in combination with dabrafenib
Aldo-trastuzumab emtansine (Kadcyla)	Antibody-drug conjugate targeting HER2; composed of trastuzumab covalently linked to a maytansine derivative (DM1) with microtubule inhibitory properties; after binding to HER2, it is internalized with release of DM1 and tubulin disruption	Metabolized in the liver by CYP3A4	Hepatotoxicity; left ventricular dysfunction; infusion reaction; pneumonitis; blood count suppression	HER2-positive metastatic breast cancer previously treated with trastuzumab and a taxane
Fam-trastuzumab deruxtecan-nxki (Enhertu)	HER2-directed antibody and topoisomerase inhibitor conjugate	Intravenous infusion only, but not with sodium chloride	Interstitial lung disease, neutropenia, left ventricular dysfunction, nausea, vomiting, fatigue, alopecia, constipation, anemia, diarrhea, thrombocytopenia	Unresectable or metastatic HER2-positive breast cancer despite two or more prior anti-HER2-based regimens

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TABLE 164-2 U.S. FDA-APPROVED DRUGS COMMONLY USED FOR THE SYSTEMIC TREATMENT OF CANCER*—cont'd

DRUG NAME	DRUG CLASS AND/OR MECHANISM	PHARMACOKINETICS/METABOLISM	TOXICITY	INDICATIONS†
Trastuzumab (Herceptin)	Genetically engineered humanized mouse monoclonal antibody directed against HER2/neu growth factor receptor that is overexpressed in many invasive breast carcinomas; mechanism of action for clinical activity in breast cancer is unknown but may be complement-mediated cell lysis, antibody-dependent cellular cytotoxicity, or induction of apoptosis	Binding studies show strong binding to cells overexpressing HER2/neu molecules; very little else is known regarding the distribution and metabolic fates of this molecule; half-life should be very short with minimal distribution outside the vascular compartment and minimal clearance by kidneys or liver (similar to other monoclonal agents)	Common toxicities include acute fever, chills, nausea, vomiting, and headache; trastuzumab seems to worsen leukopenia, anemia, and diarrhea when given with chemotherapy compared with chemotherapy alone; also, trastuzumab may have uncommon acute cardiotoxicity, which may add to the more common anthracycline-induced cardiotoxicity; therefore, the use of trastuzumab with doxorubicin is not indicated by the FDA	Approved for HER2/neu overexpressing metastatic or locally advanced breast cancer; has shown clinical benefit as a single agent and in conjunction with paclitaxel-based chemotherapy; also approved for gastric cancer
Tucatinib (Tukysa)	HER2 tyrosine kinase inhibitor	Avoid strong CYP3A inducers, moderate CYP2C8 inducers, strong CYP2C8 inhibitors, CYP3A substrates, and P-gp substrates	Diarrhea, hepatotoxicity	In combination with trastuzumab and capecitabine for advanced unresectable or metastatic HER2-positive breast cancer despite other anti-HER2 regimens
Umbralisib (Ukoniq)	Oral kinase inhibitor active against PI3K-delta and casein kinase CK1-epsilon	No dosage reduction required for mild renal or hepatic dysfunction; rapidly absorbed and excreted predominantly in feces	Neutropenia; diarrhea; noninfectious colitis; hepatotoxicity; cutaneous reactions	Marginal zone lymphoma relapsed or refractory following at least one prior anti–CD20-based regimen; follicular lymphoma relapsed or refractory after at least three lines of systemic therapy
Vandetanib (Caprelsa)	Kinase inhibitor	The concomitant use of known strong CYP 3A4 inducers may reduce drug levels of vandetanib and should be avoided. No clinically significant drug interaction was shown with vandetanib and the potent CYP 3A4 inhibitor, itraconazole. The administration of vandetanib with agents that may prolong the QT interval should be avoided. In total, 18% of medullary thyroid cancer patients treated with vandetanib were age 65 yr or older, and 3% were 75 yr and older. No overall differences in safety and efficacy were observed between elderly and younger patients. No adjustment in starting dose is required for patients over 65 yr of age. There are limited data for patients over the age of 75 yr. Limited data for renal or hepatic impairment point toward dose reductions	QT prolongation: sudden death has been reported. Monitor electrocardiograms and levels of serum potassium, calcium, magnesium, and TSH at baseline, 2-4 wk and 8-12 wk after starting treatment, and every 3 mo thereafter and following dose adjustments. Dose reduction as appropriate. Stevens-Johnson syndrome resulting in death has been observed. Severe skin reactions may prompt permanent discontinuation of the drug. Interstitial lung disease resulting in death has been reported. Interrupt dosing and investigate unexplained dyspnea, cough, and fever. Appropriate measures should be taken for ILD. Ischemic cerebrovascular events, hemorrhage, heart failure, diarrhea, hypothyroidism, hypertension, and reversible posterior leukoencephalopathy syndrome have been observed. Other common adverse events: diarrhea, rash, acne, nausea, hypertension, headache, fatigue, upper respiratory tract infections, decreased appetite, and abdominal pain. The most common laboratory abnormalities were decreased calcium, increased ALT, and decreased glucose	Thyroid cancer unresectable locally advanced or metastatic
Vemurafenib (Zelboraf)	Inhibits V600E serine-threonine and other kinases	Take with or without food; inhibits CYP1A2, 2D6; enhances CYP3A	Produces cutaneous squamous cell carcinoma, hypersensitive and dermatologic reagins, QT prolonged, liver lab abnormalities	Metastatic *BRAF*+ melanoma
Venetoclax (Venclexta)	BCL-2 inhibitor	Take with meal and water; prophylaxis for tumor lysis syndrome with anti-hyperuricemic agents and adequate hydration; do not use strong inhibitors of CYP3A at initiation and during ramp-up phase	Tumor lysis syndrome; neutropenia; fetal harm; diarrhea, nausea; anemia; upper respiratory tract infection	CLL with 17p deletion, per FDA-approved test, after at least one prior therapy

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Vinorelbine (Navelbine), 5′-noranhydrovinblastine, NVB	Semisynthetic vinca alkaloid; inhibitor of tubulin polymerization and thereby mitosis; G2-phase specific	Metabolized by the liver and has an elimination half-life of about 24 hr; excretion is predominantly in the bile	Vinorelbine is a mild vesicant, requiring extravasation precautions; myelosuppression, mostly leukopenia, is expected and dose limiting; significant nausea and vomiting are uncommon; neurotoxicity in the form of neuropathy is less common and milder than that seen with vincristine; tumor pain during administration has been reported; acute reaction such as dyspnea, chest pain, and wheezing have occurred during administration and may be prevented by premedication with corticosteroids	Approved for the treatment of relapsed metastatic breast cancer and for NSCLC as a single agent or combined with a platinating agent
Vismodegib (Erivedge)	Hedgehog pathway inhibitor	Safety and effectiveness have not been established for hepatic or renal impairment; absorption is saturable as evidenced by the lack of dose-proportional increase in exposure after a single dose of 270 mg or 540 mg vismodegib; may be taken without regard to meals because the systemic exposure of vismodegib at steady state is not affected by food	The most common adverse reactions (incidence of ≥10%) are muscle spasms, alopecia, dysgeusia, weight loss, fatigue, nausea, diarrhea, decreased appetite, constipation, arthralgias, vomiting, and ageusia. Advise patients not to donate blood or blood products while receiving vismodegib and for at least 7 mo after the last dose.	Metastatic basal cell carcinoma or locally advanced basal cell carcinoma that has recurred following surgery or patients who are not candidates for surgery and who are not candidates for radiation
Zoledronic acid (Zometa)	Bisphosphonate inhibitor of bone metastases	Zoledronic acid is poorly absorbed by the GI tract and is therefore given as an IV infusion; it is not metabolized and is excreted by the kidneys; it has a plasma terminal elimination half-life of about 150 hr	Zoledronic acid is generally well tolerated; the most common infusional adverse effect is fever, which is usually mild and treatable; nausea and constipation are also common; dyspnea, fatigue, diffuse pain, rash, and headache are uncommon; renal insufficiency is uncommon and generally reversible after discontinuation of the drug, but it is more likely with higher doses than with the approved and recommended 4-mg dose	Approved for treatment of hypercalcemia of malignancy and for prevention of pathologic fractures in multiple myeloma and solid tumors with known bone metastases

*Full listing of all FDA-approved agents appears online at https://www.cancer.gov/about-cancer/treatment/drugs/cancer-type.

†Note that indications may change based on the results of clinical trials and other data.

ABMT = autologous bone marrow transplantation; AC = accelerated phase; ADCC = antibody-dependent cell-mediated cytotoxicity; ADP = adenosine diphosphate; AIDS = acquired immunodeficiency syndrome; ALK = anaplastic lymphoma kinase; ALL = acute lymphoblastic lymphoma; ALT = alanine aminotransferase; AML = acute myelogenous leukemia; AST = aspartate aminotransferase; AUC = area under the curve; BC = breast cancer; BID = twice a day; CK = creatine kinase; CLL = chronic lymphocytic leukemia; CML = chronic myelogenous leukemia; CNS = central nervous system; CP = chronic phase; CTCL = cutaneous T-cell lymphoma; CTLA-4 = cytotoxic T-lymphocyte antigen 4; CYP = cytochrome; D5W = 5% dextrose in water; dATP = deoxyadenosine triphosphate; DMHHT = demethyl-homoharringtonine; DVT = deep vein thrombosis; ECG = electrocardiogram; EGFR = epidermal growth factor receptor; ER = estrogen receptor; FAMP = fludarabine monophosphate; FDA = Food and Drug Administration; 5-FU = 5-fluorouracil; FSH = follicle-stimulating hormone; G6PD = glucose-6-phosphate dehydrogenase; G-CSF = granulocyte-colony stimulating factor; GGT = gamma-glutamyltransferase; GI = gastrointestinal; GIST = gastrointestinal stromal tumor; GM-CSF = granulocyte-macrophage colony-stimulating factor; GnRH = gonadotropin-releasing hormone; GVHD = graft-versus-host disease; HDAC = histone deacetylase; HIV = human immunodeficiency virus; HMM = hexamethyl melamine; HR-positive = hormone receptor positive; HRT = hormone replacement therapy; HSC = hematopoietic stem cell; IFN = interferon; IGF = insulin-like growth factor; IgG2 = immunoglobulin G2; IL = interleukin; ILD = interstitial lung disease; IM = intramuscular; INR = International Normalized Ratio; IV = intravenous; LDH = lactate dehydrogenase; LH = luteinizing hormone; LHRH = luteinizing hormone–releasing hormone; LVEF = left ventricular ejection fraction; MAPK = mitogen-activated protein kinase; MDS = myelodysplastic syndrome; MET = mesenchymal epithelial transition factor receptor; MOPP = mechlorethamine, vincristine, procarbazine, and prednisone; MSI = microsatellite instability; MTIC = 5-(3-,ethyltriazen-1-yl)imidazole-4-carboxamide; mTOR = mammalian target of rapamycin; NHL = non-Hodgkin lymphoma; NSAIDs = nonsteroidal anti-inflammatory drugs; NSCLC = non–small cell lung cancer; PARP = poly (ADP-ribose) polymerase; PDGF = platelet-derived growth factor; PD-L1 = programmed death ligand 1; PE = pulmonary embolism; P-gp = P-glycoprotein; PI = phosphoinositide; PNET = progressive neuroendocrine tumor; PO = by mouth; PT = prothrombin time; RANK = receptor activator of nuclear factor–κB; RCC = renal cell carcinoma; SCLC = small cell lung cancer; SEGA = subependymal giant cell astrocytoma; SQ = subcutaneous; TID = three times a day; TNF = tumor necrosis factor; TSC = tuberous sclerosis; TSH = thyroid-stimulating hormone; UGTs = UDP-glucuronosyltransferases; ULN = upper limit of normal; VEGF = vascular endothelial growth factor.

As indicated throughout this chapter, the pace has accelerated for approvals of new drugs and new indications. Updated information should be checked on the FDA website (www.fda.gov/drugs) or other authoritative sources.

From Collins JM. Cancer pharmacology. In: Niederhuber JE, Armitage JO, Doroshow JH, Kastan MB, Tepper JE, eds. *Abeloff's Clinical Oncology*, 5th ed. Philadelphia: Churchill Livingston; 2014.

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small cell lung cancer and non–small cell lung cancer is critical for treatment. For breast cancer (Chapter 183), the treating physician is interested in a variety of factors, such as histology, tumor grade, the presence (and its degree) or absence of estrogen and progesterone receptor proteins, the presence of HER2/neu overexpression, and other molecular characteristics. The rapidly increasing sophistication of molecular diagnostics has also greatly improved the potential to localize cancers of unknown primary origin (see the section Cancer of Unknown Origin later in this chapter).

Staging and Multidisciplinary Evaluation

After a tissue diagnosis has been established, careful staging is required to determine the extent of disease. The American Joint Committee on Cancer staging system, which is the standard in the United States, is based on the TNM (tumor, node, metastasis) system that is anatomically and pathologically based. The approach to staging from a clinical perspective depends on the type of cancer, but it commonly includes computed tomography (CT), magnetic resonance imaging (MRI), and, increasingly, positron emission tomography (PET) and PET-CT. These studies are supplemented by routine hematologic and chemistry profiles, tumor markers, and molecular characterization (when appropriate), as well as by bone marrow aspiration and biopsy in some cases.

The goal of tumor staging is to define the extent of a patient's disease. Tumor stage provides critical prognostic information that will inform the therapeutic approach that is most appropriate. Accurate staging involves delineating the magnitude of the tumor determined by imaging procedures, as well as confirming the pathologic limits of disease spread from tissues removed at surgery. In essence, for most solid tumor patients, the tumor stage will establish whether the treatment will focus on a local (usually confined to an organ), regional, or disseminated pattern of malignancy and can determine whether the expected outcome of therapy is curative or palliative. Conversely, hematopoietic malignancies are often disseminated at diagnosis and demand their own prognostic classifiers.

The focus of the staging evaluation is to identify potential sites of metastases and to establish indicator lesions with which to monitor therapy. For most solid tumors, CT scans can accomplish both goals; however, in some circumstances, other imaging modalities are more appropriate for therapeutic monitoring (e.g., MRI when central nervous system [CNS] metastases are likely [e.g., small cell lung cancer], or combined PET/CT imaging to establish that a given lesion is likely to be metabolically active and malignant, or in diseases in which early metabolic responses to treatment can be confirmed [such as for gastrointestinal stromal tumors]). In patients with established advanced disease, indicator lesions for therapeutic monitoring should be carefully chosen prior to the initiation of treatment, be well documented in the medical record, and be evaluated with the minimum frequency of imaging procedures required for accurate follow-up, consistent with evidence-based medical practice or the clinical protocol on which the patient is entered.

The consulting medical oncologist may often be advised by a local tumor board composed of other medical, surgical, and radiation oncologists, pathologists, radiologists, and members of the cancer care team (oncology nurses, social workers, and palliative care specialists). In such a multidisciplinary environment, the patient's overall prognosis can be reviewed and alternatives for care, including standard therapy, possible clinical trials, a second opinion, or no treatment, can be considered. The outcome of such an evaluation is usually viewed by patients and families as an important component in the coordinated development of an overall plan for either further diagnostic procedures or therapy. Finally, many oncologists actively participate in clinical trials that may make investigational drugs or other investigational procedures available for patients, or they may suggest referral to a tertiary cancer center where disease-specific or molecularly defined clinical trials are available.

TREATMENT

Therapeutic Plan

Intention of Treatment

Based on the multidisciplinary evaluation of an accurately staged patient, the chosen intent of treatment may be curative or palliative. Whether or not this choice is made during a formal tumor board or multidisciplinary case conference, clarity must be reached regarding the specific choice of therapeutic options (and their potential risks and benefits, overall goals, and alternatives) when considered in the context of the wishes of the patient and family. This issue is particularly relevant when the side effects of treatment are substantial (such as for the multidisciplinary management of non–small cell lung cancer or esophageal cancer). For cancers that are amenable to surgery, resection is often an initial alternative if the patient is a suitable candidate for anesthesia and is otherwise in acceptable condition in terms of comorbid illnesses (Chapter 399). Determination of the patient's performance score (see Table 164-1) is a simple means of assessing functional status. If life expectancy is limited or if the patient is not a good candidate for surgery, more limited approaches to palliative radiation or systemic therapy may be appropriate. Substantial data indicate that the extent of surgery required for an optimal long-term outcome may be reduced for certain solid tumors through the use of presurgical, so-called "neoadjuvant" chemotherapy, often as part of an "organ-sparing" approach. Concomitant or sequential multimodality treatments also have the potential to produce long-term disease-free remissions. When the best therapeutic outcomes require the combined skills of surgical, radiation, and medical oncologists, the need for coordination of care among a variety of specialists becomes paramount and the use of predefined treatment regimens critical.

Therapeutic Paradigm and Therapeutic Index

The therapeutic paradigm in oncology, although still directed at improving the multidisciplinary care model, has begun to change from one focused on delivering treatments at the "maximally tolerated dose" for normal tissues to therapy that is personalized based on both the molecular characteristics of the patient's tumor as well as any individual germline features that could modify treatment tolerance (Chapter 166). Based on the rapid expansion of information regarding somatic mutations in human malignancies and the ability to produce therapeutic molecules that can target specific defects in tumoral DNA repair, growth factor signaling, energy balance, or immunocompetence, for example, the current approach to cancer therapeutics involves the use of predictive molecular markers ("biomarkers") whenever possible to guide all modalities of cancer care for the benefit of unique cancer patients. Hence, the focus of oncologists is on the elaboration of treatments that can be administered with a high therapeutic index, defined as the comparison of the amount of treatment that is effective as compared with the amount that causes toxicity. The goal of precision cancer medicine therapy is to minimize toxicity to normal tissues and to preserve quality of life by advancing therapies or procedures that are targeted only to the specific molecular dependencies of the patient's tumor.

Surgical Therapy

Surgery is used to biopsy a suspected lesion, remove the primary tumor, bypass obstructions, provide palliation, and prevent cancers in patients at very high risk because of genetic predispositions or chronic inflammatory states. Surgical staging also establishes the extent of disease. For example, patients with ovarian cancer (Chapter 184) benefit from surgical "debulking" to remove all visible disease, leave minimal residual tumor, and thereby enhance the effectiveness of systemic treatment. Placement of a venous access device at the time of surgery, if considered proactively, may eliminate the need for a second procedure.

Risk-reducing bilateral mastectomy and risk-reducing salpingo-oophorectomy are options for the primary prevention of breast (Chapter 183) and ovarian cancers in individuals who are genetically predisposed to these malignancies. Although these operations provide considerable efficacy in terms of cancer prevention, they can be associated with profound adverse physical and psychosexual effects. Decisions to proceed with such risk-reducing surgery are complex and emotionally charged. Patients require clearly understandable information and counseling, as well as adequate time and support to think through their options.[4]

Surgery remains the most common method to cure localized cancers such as breast cancer (Chapter 183), colorectal cancer (Chapter 179), and lung cancer (Chapter 177), but it is limited by the location of the tumor, its extension, and distant metastases.[A1] Even if a tumor cannot be removed, surgical biopsy provides confirmation of the diagnosis and additional tissue for molecular analysis. Occasionally, an obstructing lesion can be bypassed to provide palliation.

In specific circumstances when the primary tumor has been controlled, removal of a single metastasis (metastasectomy) can result in long-term survival; an example is resection of a solitary liver metastasis found at the time of colectomy for colorectal cancer (Chapter 179). A variety of surgical techniques, such as radiofrequency ablation or cryoablation, can also be used to treat hepatic metastases in carefully selected patients. Adjuvant chemotherapy is often given after surgery in this situation to treat microscopic metastases.

The careful application of reconstructive surgery after a disfiguring procedure is critical to long-term physical and emotional well-being. Examples include postmastectomy breast reconstruction (Chapter 183) and plastic surgical procedures to correct deformities following head and neck surgery (Chapter 176).

Radiation Therapy

Ionizing radiation (Chapter 18) can be delivered using beams of high-energy rays, known as *teletherapy*, via a linear accelerator; by brachytherapy, through the application of sealed radioactive implants, seeds, wires, or plaques; and intravenously by using radioisotopes, either directly or attached to antibodies or other targeting molecules.[5] Radiation interacts with water molecules to induce free radical species, including hydroxyl radicals, which damage DNA, proteins, and lipid membranes, thereby leading to cell death. As with chemotherapy, radiation therapy is most effective against rapidly dividing cells that are well oxygenated. Radiation-induced DNA damage may also increase sensitivity to chemo- or immunotherapy.

The utility of radiation therapy is limited by the inapparent extension of disease outside a local treatment field, by the location of tumors next to normal structures that must be preserved, and by the presence of distant metastases. Normal tissue tolerance, which varies across different organs and tissues, often prevents the use of radiation doses that could uniformly eradicate cancers. Radiation therapy is also limited by tumor hypoxia: large, bulky tumors are frequently relatively radioresistant, whereas well-oxygenated tumors can be more effectively treated at lower doses. In addition to acute radiation-related toxicities (Chapter 18), late effects of radiation therapy include second malignancies, such as breast cancers that may occur decades after administering thoracic radiation fields during curative treatment for Hodgkin disease.

Radiation therapy can be used as primary treatment, as part of multimodality therapy, in the adjuvant setting, and for palliation. As a single modality, radiation therapy can be curative for early-stage malignancies such as laryngeal cancer (Chapter 176), cervical cancer (Chapter 184), and prostate cancer (Chapter 186). Breast-conserving surgery (Chapter 183) requires the use of radiation to treat the remaining breast. Partial irradiation techniques using three-dimensional planning with external beam radiation can be used in selected patients with appropriately placed and sized breast cancers. For certain patients who have localized prostate cancer (Chapter 186), implanted radioactive seeds of gold or palladium offer an alternative to surgery or external beam radiation therapy.

Intensity-modulated radiation therapy (IMRT) permits more exact tailoring of the dose to the target, thereby reducing damage to the surrounding normal tissues. Stereotactic radiation therapy or gamma knife techniques allow the treatment of primary or metastatic brain tumors (Chapter 175) measuring up to 3 cm with enhanced accuracy, thereby minimizing damage to normal brain. An analogous approach may help patients whose primary tumor has been controlled and who have a limited number of metastatic lesions. Particle-based treatment with protons can deliver higher radiation doses locally. However, no randomized studies demonstrate its superiority over other approaches that use computational techniques (e.g., IMRT) to improve the specificity of the delivery of radiation. However, proton therapy is generally recommended for some uveal melanomas, base-of-skull tumors, and a few pediatric malignancies.

Low- to moderate-dose palliative radiation is used to ameliorate symptomatic cancer when cure is no longer the goal. For instance, radiation therapy can improve symptoms from brain metastases (Chapter 175), relieve pain from bone lesions (Chapter 187), relieve some obstructing lesions, and sometimes improve hemoptysis caused by lung cancer (Chapter 177) or bleeding from a gynecologic malignancy (Chapter 184). Bone-seeking radioisotopes of samarium, strontium, or radium may relieve pain from bone metastases in prostate cancer (Chapter 186) or breast cancer (Chapter 183).

Systemic Therapy

Cancer Pharmacology

Principles

The fundamental goal of cancer pharmacology is the development of treatments that can be matched to the intrinsic sensitivity of specific tumors and that can be delivered in concentrations that affect the molecular target of interest with an acceptable therapeutic index. Three properties of all cancer therapeutic agents underlie their clinical utility: pharmacogenetics of the drug (how the germline or somatic expression of genes alters normal tissue toxicity or antitumor efficacy); action of the drug (pharmacodynamics, or what the drug does to the tumor/body); and delivery of the drug (pharmacokinetics, or what the body does to the drug).

Pharmacogenetics

Pharmacogenetics, which is the study of inherited interindividual differences in drug disposition and effects, is important in cancer therapy because genetic polymorphisms in drug-metabolizing enzymes may be responsible for the variations in efficacy and toxicity that are observed with many chemotherapeutic agents. Drugs potentially affected by polymorphisms include the thiopurines, 5-fluorouracil, irinotecan, taxanes, and platinum agents. In patients who are heterozygous or homozygous for deficiencies in metabolizing enzymes, toxicity can be dramatically enhanced. Testing for pharmacogenetic variations that predict for altered normal tissue tolerance is currently available for thiopurines and irinotecan.

Molecular Targeting and Pharmacodynamics

Molecular diagnostic testing, which began with testing to predict the antitumor activity of hormonal and anti-HER2 therapeutics, is now relevant to a wider range of tumors for which molecularly targeted and immunotherapeutic anticancer agents are useful only after demonstration of specific molecular abnormalities.[6] Examples of such diagnostic/drug pairs include the prototypical *BCR-ABL* mutation in chronic myelogenous leukemia and imatinib; *EGFR* mutations in lung adenocarcinomas and erlotinib; *ALK* tyrosine kinase translocations in lung adenocarcinomas and crizotinib; $BRAF^{V600E}$ mutations in melanoma and vemurafenib, *NTRK* fusions and larotrectinib; and *KRAS* mutations in various solid tumors. Molecular targeting can also involve the expression of mismatch repair genes and immunologic checkpoint inhibitors.

Pharmacokinetics and Drug Delivery

Dose selection in oncology is a critical issue, primarily because anticancer agents have among the smallest therapeutic ratios in all of medicine. When tumors are responsive to treatment, higher doses may or may not be more effective but are likely to be more toxic to normal tissues. The clearance of a drug from both the systemic circulation and, potentially, from specific physiologic compartments (CNS, pleural, or peritoneal effusions), as evidenced by its systemic exposure, is the most important determinant of the recommended dose for a particular patient. Clearance, which is a composite of all the routes and mechanisms by which the drug can be eliminated from the body, determines dosing and dose adjustments in the face of changes in drug metabolism, transport, or altered organ function. Although a clear understanding of drug half-lives is important to establish initial dosing schedules, systemic exposure will be the actual determinant of the dose of drug that can be safely administered. Another aspect of drug delivery is the use of body surface area dosing versus flat dosing (using fixed amounts of a drug) in oncologic practice. Although dosing based on body surface area has a long history in oncology, very little data support this approach; for most agents in common use, empirically determined pharmacokinetic variability from patient to patient is far greater than what could reasonably be determined by dosing based on weight or surface area.

Routes of Drug Dosing

Although some agents require intravenous administration, oral agents that permit outpatient therapy are increasingly being used. The oral route of administration highlights drug delivery issues, such as adherence (does the patient take his/her medication), variability in absorption (due to food effects), emesis prior to drug absorption, first-pass metabolism in the liver or intestine, and difficulties in swallowing. For example, whether the orally administered anti-HER1/2 drug lapatinib is taken with food or on an empty stomach can alter its absorption by as much as 10-fold.

In addition to intravenous or oral dosing, anticancer drugs may be used for intrathecal delivery (to overcome the blood-brain barrier) in the treatment or prevention of meningeal spread of leukemia; for intravesicle therapy of early-stage bladder cancer; for intra-arterial delivery of fluoropyrimidines or other agents to treat hepatic metastases from colon cancer or hepatocellular carcinoma; and for intraperitoneal administration of drugs such as platinum agents for ovarian cancer therapy. In almost all cases, administration of anticancer agents by other than the oral or intravenous routes requires intimate involvement of an oncologic specialist.

Clinical Trials

Clinical trials in oncology are defined by the steps in which new diagnostic approaches, therapeutic agents, or procedures are tested to determine whether they will become part of the standard care for cancer patients. During interventional (rather than observational) clinical trials, specific treatments or procedures are assigned to participants, and the effects of the interventions are measured. For trials of new oncologic drugs, the U.S. Food and Drug Administration (FDA) recognizes several states in the drug development process. Exploratory studies of new drugs examined for the first time in humans (phase 0 trials) may be conducted in a limited number of patients to define a drug's mechanism of action or biodistribution and to guide subsequent dosing in larger studies. Phase I trials use a variety of dose-escalation strategies to define the maximum dose that can be safely administered to humans and the most appropriate schedule for drug administration, as well as the pharmacokinetic and pharmacodynamic profile of the drug. Phase II trials often enroll 50 to 150 subjects and focus on testing the drug to determine its effectiveness and side effect profile in a specific malignancy (or for a specific cancer-related molecular abnormality). If a drug demonstrates anticancer activity in a phase II study, phase III trials are performed to compare the usefulness of an investigational treatment to a control group of patients who receive the standard of care; patients in most phase III studies are randomly assigned to the new or standard treatment to avoid a biased assessment of the results of the study. Finally, after approval of a new drug by the FDA, usually based on the results of phase III studies, phase IV trials may be performed to collect safety information on larger patient populations to define the prevalence of side effects that may be rare but serious.

Traditionally designed phase II trials test one treatment at a time in heterogenous groups of patients and are therefore not an efficient use of clinical resources. Adaptive multigroup clinical trials have the potential to answer several questions simultaneously and more efficiently by matching targeted therapies to the cancer patients who are most likely to benefit from them. Some trials for breast cancer, for example, use a platform to compare up to 12 experimental therapies with a single, common control group in subgroups of breast cancer patients with 10 distinct biomarker signatures.[7] New drugs enter the platform as they emerge from phase I testing and exit the platform with an estimate of the chances of future success in a phase III trial of prespecified size. Despite some significant unresolved issues, the adaptive strategy is likely to become an important addition to the inventory of clinical trial designs. Another approach is so-called master protocols, which evaluate one or more agents against a specific molecular characteristic possessed by the tumor rather than its histology.[8]

Drug Interactions

Many drug interactions affect the toxicity profile of anticancer agents, usually because concomitant administration of a second drug changes the clearance of the cancer therapeutic, thereby potentially enhancing side effects if the clearance is decreased or diminishing efficacy because of reduced drug exposure.

Most often these interactions occur because one drug affects the metabolism of the other by inhibiting or enhancing the activity of cytochrome P-450 isoforms (such as CYP3A) in the liver. This interaction is particularly true for agents administered orally, such as imatinib, crizotinib, enzalutamide, pazopanib, and lapatinib. Concomitant drug-related as well as pharmacogenetic variations in proteins that affect the transport of anticancer agents across tumor and normal cell membranes, such as efflux pumps, also affect the sensitivity or resistance of many classes of cancer drugs. For example, certain drugs that are well-known inducers of hepatic metabolism (e.g., phenytoin and rifampin) also induce the expression of drug transport proteins.

Combination Therapy

Virtually all curative chemotherapy regimens developed for hematologic malignancies or solid tumors use combinations of active agents. Combination chemotherapy is usually superior to the use of single agents in adjuvant and neoadjuvant therapy as well. The improved results achieved by combination chemotherapy can be explained in several ways. Mechanisms of resistance to any particular single agent are almost always present in the tumor genome at diagnosis, even in clinically responsive tumors. Tumors that are initially "sensitive" to systemic therapy rapidly acquire resistance to single agents, either as a result of selection of a preexisting clone of resistant tumor cells or because of a variety of potential acquired molecular changes (e.g., increased drug efflux, enhanced DNA repair, insensitivity to apoptosis) that lead to clinical drug resistance. Combination therapy may address these phenomena by providing a broader range of mechanisms of drug action against initially resistant tumor cells, thereby preventing or slowing the selection of resistant clones.

The development of combination systemic therapy regimens follows a set of principles (Table 164-3). For standard cytotoxic agents, each drug in the combination must be active against the tumor, and all drugs must be given at an optimal dose and on an appropriate schedule. The drugs should have different mechanisms of antitumor activity as well as different toxicity profiles, and the drugs should be given at consistent intervals for the shortest possible treatment time. The use of molecularly targeted agents in combination requires that each agent engages its specific target and that the combination enhances the inhibition of the tumor's growth. Toxicities of targeted agents should be moderate to allow prolonged administration and maximum target inhibition.

Therapeutic Settings

Systemic therapy is used in a variety of settings with or without and before, during, or after surgery and radiation therapy (Table 164-4). Considerable experimental evidence suggests that cancers are most sensitive to chemotherapy during early stages of growth because of higher growth fractions and shorter cell cycle times. As a result, a given dose of a cytotoxic drug may exert a greater therapeutic effect against a rapidly growing tumor than against a larger quiescent tumor.

Neoadjuvant therapy, also called primary or induction systemic therapy, is used before surgery or radiation therapy to decrease the size of locally advanced cancers, thereby permitting a more complete surgical resection or eradication of undetectable metastases. Neoadjuvant therapy also affords an opportunity to evaluate the effectiveness of treatment by histologic and molecular analysis of resected tissue. This approach is most often used for locally advanced breast cancer (Chapter 183).

Organ-sparing therapy is another use of chemotherapy, radiation therapy, or both to salvage organs that would have been surgically removed if cure were the intended result. This technique is often effective in patients with cancers of the larynx (Chapter 176), esophagus (Chapter 178), and anus (Chapter 179).

Adjuvant chemotherapy is used in patients whose primary tumor and all visible evidence of cancer (e.g., regional lymph nodes) have been surgically removed or treated definitively with radiation, but in whom the risk of recurrence is high because of involved lymph nodes or certain morphologic or biologic characteristics of the cancer. Common examples include cancers of the breast (Chapter 183) and colon (Chapter 179). The typical end points of chemotherapy, such as shrinkage of measurable tumor on serial radiographic studies, are not available in this situation; instead, relapse-free survival and overall survival are the principal measures of a treatment's effect. The benefit of adjuvant therapy cannot be assessed in individual patients who receive it, so decisions about its use must be based on evidence from clinical trials.

Assessment of Response

Assessment of the response to therapy (usually performed using RECIST [Response Evaluation Criteria in Solid Tumors]) depends largely on the tumor's size, as determined by either direct measurement or diagnostic imaging studies, using predefined categories. The categories of response are "complete response," with total absence of tumor and correction of tumor-associated changes measured twice at least 4 weeks apart; "partial response," defined as 30% or greater reduction in the sum of the longest diameters of up to five target lesions per organ, confirmed by repeat measurement 4 weeks later; "progressive disease," characterized by either 20% or greater increase over the smallest sum of the longest diameters of target lesions or the development of new tumors; and "stable disease," defined as meeting criteria for neither partial response nor progressive disease. Leukemias are assessed by bone marrow biopsies and molecular diagnostic tests for residual disease, and multiple myeloma is typically assessed by the measurement of monoclonal proteins, peripheral blood counts, and percentages of malignant plasma cells in bone marrow samples, as well as imaging of bone lesions. Accurate assessment of response following systemic therapy is essential because of the tight relationship between the degree of response and the duration of disease control.

Classes of Therapeutic Agents

Cytotoxic Agents, Targeted Small Molecules, and Antibodies

An understanding of the pharmacologic properties and therapeutic indications of the most commonly used cytotoxic and molecularly targeted chemotherapeutic agents and antibodies approved by the FDA (see Table 164-2) is critical for prescribing physicians and is also important for physicians who participate in the patient's care. Current information should be sought from the manufacturer before therapy is initiated.

The administration of chemotherapy should be overseen by specifically trained individuals because of the dual acute risks of hypersensitivity reactions and extravasation. No doses or schedules are universally recommended because these agents are often used in combination, and the doses of each drug may need to be reduced when the compounds are combined, as well as when they are prescribed to patients who may have impaired liver or kidney function or a higher risk of adverse effects.

Unless otherwise specified, most cytotoxic chemotherapeutic agents may produce some degree of nausea and vomiting, myelosuppression, alopecia, mucositis, and/or diarrhea after treatment; many agents are also teratogenic, mutagenic, and carcinogenic. Specific drugs (see Table 164-2) often can be used to prevent agent-specific toxicities.

Small molecule anticancer agents with more precisely targeted mechanisms of action have become a standard part of oncologic practice (see Table 164-2). Although the molecular dependencies within the tumor cells against which these drugs are targeted are broad in scope, including tyrosine kinase growth factors or their receptors, they are functionally much more specific than prior generations of systemic cancer therapies. This specificity allows for a better appreciation of the clinical situations in which certain drugs might be beneficial, as well as the possibility of developing agents for use in specific tumors based on their genetic susceptibilities. The toxicity profiles of molecular targeted agents most often reflect alterations that are produced in biochemical pathways that control normal organ function, rather than a general pattern of toxicity consistent with injury to rapidly growing tissues, such as the bone marrow or gastrointestinal tract.

TABLE 164-3 PRINCIPLES OF COMBINATION THERAPY

CYTOTOXIC AGENTS	MOLECULARLY TARGETED DRUGS
Drugs are each active against the tumor	Agent has therapeutic effect on molecular pathway in vivo
Drugs have different mechanisms of action	Agents have complementary effects on the same target or other targets in the same pathway or pathways that cross-talk to control tumor growth
Drugs have different clinical toxicities to allow full doses of each to be administered	Toxicities do not overlap with cytotoxics and are moderate to low to allow prolonged administration. Consider physiologic consequences of target engagement in relation to toxicity profile
Intermittent intensive therapy is preferred to continuous treatment for cytoreduction and reducing immunosuppression	Schedule is chosen to maximize target inhibition

TABLE 164-4 COMMON EXAMPLES OF THERAPEUTIC SETTINGS

ADJUVANT THERAPY	NEOADJUVANT THERAPY	ORGAN-SPARING THERAPY	COMBINATION CHEMOTHERAPY
Stage I and II breast cancer Stage III colorectal cancer Stage II lung cancer	Stage III breast cancer	Anal cancer Laryngeal cancer Esophageal cancer	Metastatic solid tumors* Hematologic malignancies

*Usually palliative.

The development of monoclonal antibodies directed against proteins or other molecular determinants of cancer cells represents an additional approach to molecular targeting of systemic therapy. Examples include cetuximab (targeting the epidermal growth factor receptor), rituximab (targeting the B-cell CD20 surface antigen), and trastuzumab[A2] (which blocks HER2). These monoclonal antibodies can be used alone or in the form of recombinant bispecific or multispecific antibodies that provide multifunctional receptor targeting, they can be labeled with a radioactive molecule, or they can be conjugated to another cytotoxin to enhance cell killing. Radioimmunoconjugate approaches have been most effective in the treatment of non-Hodgkin lymphoma (Chapter 171) and chronic lymphocytic leukemia (Chapter 169). The effectiveness of monoclonal antibodies in specific tumor types is not identical to small molecules developed against the same target, in part because of the induction of immunologically mediated mechanisms of tumor cell killing that are unique to antibodies.

A major challenge with targeted therapy for malignancies is that drug resistance often develops. Cancers are characterized by extensive intratumor genetic heterogeneity, and resistance to molecularly targeted therapies can arise from the selected growth of preexisting subclones that are present within the bulk of the tumor and that carry drug-resistant mutations, which have a survival advantage for the tumor.[9]

Hormonal Therapies

Endocrine or hormonal therapy is almost entirely limited to breast cancer (Chapter 183) and prostate cancer (Chapter 186). Many premenopausal breast cancers are thought to be under the influence of ovarian estrogens, and hormonal deprivation (ablation) may produce long-term responses in properly selected patients (patients whose tumors express estrogen and/or progesterone receptors and who have predominantly soft tissue or bone disease). The antiestrogen tamoxifen is effective against breast cancer, and it may decrease the incidence of contralateral breast cancers in both premenopausal and postmenopausal women with breast cancer (Chapter 183). Tamoxifen also has an estrogen-like activity that is responsible for an increased rate of endometrial cancers. Postmenopausal women who are candidates for hormonal therapy may also respond to tamoxifen; however, aromatase inhibitors (e.g., anastrozole, letrozole, exemestane), which decrease the conversion of metabolites in fat and muscle into estrogen, are more effective than tamoxifen as first-line therapy in both the adjuvant and metastatic settings.

Prostate cancer (Chapter 186) is usually androgen-dependent, and androgen deprivation can produce meaningful responses. The recent introduction of more potent inhibitors of androgen biosynthesis (abiraterone) and androgen receptor-mediated signal transduction (enzalutamide) has further enhanced the range and effectiveness of androgen deprivation therapy for this disease.

The corticosteroids (Chapter 28), typically prednisone or dexamethasone, are widely used in the treatment of hematologic and oncologic cancers. In Hodgkin disease (Chapter 172), the non-Hodgkin lymphomas (Chapter 171), and multiple myeloma (Chapter 173), corticosteroids have antitumor activity. In solid tumor patients, they are used as antiemetics, for the symptomatic relief of cerebral edema in cases of CNS metastases (Chapter 175), or as an adjunct to radiation therapy for spinal cord metastases.

Epigenetic Therapies

Just as DNA mutations contribute to the progression of tumors, epigenetic alterations in the transcription of DNA also participate in the growth of tumors and their resistance to chemotherapy (Chapter 166). The two best characterized epigenetic mechanisms are DNA methylation and histone modification. DNA methylation is controlled by DNA methyltransferases, whereas histone modification (acetylation) is controlled by histone acetyltransferases. The DNA methyltransferase inhibitors (azacitidine and decitabine) produce durable responses and survival benefit in patients with myelodysplastic syndrome (Chapter 167) and acute myelogenous leukemia (Chapter 168). The histone deacetylase inhibitors (vorinostat and romidepsin) have clinical benefit for the treatment of cutaneous T-cell lymphoma (Chapter 171).

The DNA methyltransferase inhibitors also have an immune-based mechanism of action. Current clinical trials are testing the combination of epigenetic therapy plus immunotherapy in cancer treatment.[10]

Immunotherapy

Cancer immunotherapy blocks the processes by which tumors suppress the immune system. These agents have yielded dramatic clinical benefits for patients with a remarkably wide variety of advanced cancers, including melanoma, kidney, bladder, head and neck, esophageal, gastric, triple-negative breast, hepatocellular, and lung cancers, as well as Hodgkin and non-Hodgkin lymphoma. Immune checkpoint therapy targets regulatory pathways in T cells to enhance their antitumor immune responses. The goal of immune checkpoint blockade is not to activate the immune system to attack particular targets on tumor cells, but rather to remove inhibitory pathways that block effective antitumor T-cell responses. The survival of men and women with metastatic melanoma (Chapter 188) is significantly increased following treatment with antibodies (anti-CTLA-4 ipilimumab and anti-PD-1 nivolumab) that neutralize proteins that protect tumor cells against destruction by the immune system.[11] PD-1 antibodies also provide a survival benefit compared with platinum-based chemotherapy for patients with non–small cell lung cancer. Additional antibodies that target other immunologic checkpoint molecules (anti-PD-L1) provide substantive clinical benefits for patients with melanoma, renal cancer, non–small cell lung cancer, and a variety of other solid tumors and lymphomas. However, a broad range of toxicities can be associated with the use of checkpoint inhibitor therapy.[12]

Another approach to cancer immunotherapy is through adoptive cell transfer, which involves the engineering of the patient's own immune cells to recognize and attack their own tumors. In this form of treatment (CAR T-cell therapy),[13] T cells collected from a patient are genetically engineered to produce special receptors on their surface called "chimeric antigen receptors" (or "CARs"). Targeted CAR T cells have provided impressive responses in patients with B-cell malignancies and led to their FDA approval for an increasing number of indications despite a high risk of side effects, including cytokine release syndrome and acute neurologic complications.

Drugs for Prevention or Treatment of Toxicity

In addition to the hematopoietic growth factors used to reduce the adverse effects of systemic cancer therapies on the bone marrow (discussed later under Management of Complications), drugs have been developed to ameliorate important side effects of cytotoxic chemotherapy (see Table 164-2). These agents include dexrazoxane, which is an iron chelating agent that can prevent the cardiac toxicity of the anthracyclines (doxorubicin and daunorubicin); leucovorin, which can diminish the hematologic side effects of folic acid antagonists; and mesna, a thiol-containing compound that blocks damage to the bladder mucosa from metabolites of cyclophosphamide. Uridine triacetate is FDA-approved for the treatment of patients who receive an overdose of fluorouracil or capecitabine or who develop severe or life-threatening toxicities within 4 days of receiving them.

Bone Marrow or Hematopoietic Stem Cell Transplantation

Because the major dose-limiting toxicity of most chemotherapeutic agents is myelosuppression, pluripotent stem cells can be harvested from bone marrow, peripheral blood, or, less often, cord blood before marrow-damaging chemotherapy so that these stem cells can be reinfused later (Chapter 163). This technique is most effective for acute leukemias (Chapter 168), relapsed lymphomas (Chapter 171), and germ cell tumors (Chapter 185). The effectiveness of the approach is limited more by the inability to eradicate cancer cells than by the inability to achieve engraftment. Transplants may be syngeneic (from an identical twin), autologous (from oneself), allogeneic (from a matched donor such as a sibling or parent), or from a matched unrelated donor. Nonablative hematopoietic transplants that do not completely abolish myelopoiesis reduce toxicity and allow the treatment of older and medically infirm patients.

Special Treatment Populations

Obesity

Up to 40% of obese patients receive limited doses of chemotherapy that are not based on actual body weight. Concerns about toxicity or overdosing based on the use of actual body weight in obese patients with cancer are unfounded. Evidence-based practice guidelines recommend that full cytotoxic chemotherapy doses be used to treat obese patients with cancer, especially when the goal of treatment is cure.

Pregnancy

Cancer during pregnancy (Chapter 221) is not uncommon, with breast, cervical, ovarian, and thyroid cancers; melanoma; and hematologic malignancies being most frequent.[14] Cancer during pregnancy is an emotionally charged challenge, and clinical decision making is complicated by ethical, moral, cultural, and religious issues. If surgery can be safely accomplished, it may be the best course, even if it is only a temporizing measure. Radiation therapy carries the very real risk of radiation exposure to the fetus, and staging is almost always suboptimal and confined to ultrasound examinations. When the disease requires chemotherapy, both the mother and fetus must be taken into account. For example, drug clearance and gastrointestinal absorption are different during pregnancy, and placental transfer, fetal pharmacokinetics, and placental excretion can influence effective and safe drug dosing. Many commonly used chemotherapeutic drugs are classified by the FDA as category D (positive human fetal risk, but the benefits in pregnant women may be acceptable despite the risk) or category X (studies in humans and animals have shown fetal malformations or there is evidence of fetal risk based on human evidence). If the mother's condition permits, chemotherapy (including anthracyclines and taxanes) should be deferred during the first trimester and used to treat only life-threatening situations during the third trimester after extensive counseling with the parents.

The preservation of fertility is particularly challenging for women with newly diagnosed hematologic malignancies, breast cancer, sarcoma, and some pelvic cancers, for which combinations of alkylating agent chemotherapy, pelvic radiotherapy, and/or surgery are most likely to cause premature ovarian insufficiency. Options for the preservation of fertility include cryopreservation of embryos, mature oocytes, or ovarian tissue (Chapter 218).[15]

Geriatrics

An increasing proportion of cancers occur in an older population. The physiologic changes that develop with age (Chapter 23) include decreased excretion

of drugs and metabolites from the kidneys, decreased volume of distribution of water-soluble drugs, and increased susceptibility to myelosuppression, cardiomyopathy, and neuropathy, related in part to comorbid conditions (Chapter 24). As a general rule, the suitability of an older patient for therapy can be determined by a comprehensive geriatric assessment (Chapter 23) that evaluates the patient's function, comorbidity, nutrition, medications, and resources. Age itself is not a barrier to surgery; rather, the patient's performance status and the comprehensive geriatric assessment should determine the likelihood of a good recovery. Tolerance of radiation therapy seems to remain largely intact with increasing age. Chemotherapy decisions are also based on performance status and the comprehensive geriatric assessment. Dosage adjustments are also made, when appropriate, for glomerular filtration rates for patients ages 65 years and older. The use of lower chemotherapy doses based on age alone is not advisable and may result in ineffective treatment.

Organ Dysfunction

Alterations in drug clearance (Chapter 25) play a critical role in the safe administration of anticancer agents. Alterations in pharmacokinetic parameters per se may occur with or without important changes in toxicity. Where evidence exists, chemotherapeutic drug doses must be modified in the setting of renal or hepatic dysfunction (see Table 164-2).

Immunocompromised Patients

The increasing proportion of patients who survive long-term after hematopoietic cell transplantation or with hematologic malignancies are at risk of complications related to their markedly compromised immune systems. Such patients are less likely to develop protective antibodies after vaccination, are more likely to have a variety of infections (Chapter 260), and tend to become sicker with their infections. For example, patients who have hematologic malignancies have significantly lower rates of seroconversion following vaccination against SARS-CoV-2 and have higher rates of hospital admission and mortality following SARS-CoV-2 infection than do patients who have solid tumors.[16]

Management of Complications

Supportive Care

Nutritional Support

Nutrition is always a concern for patients who are newly diagnosed with cancer, even if they have not experienced weight loss. Significant weight loss is an adverse prognostic factor for several cancers, especially lung cancer.

Malnourished patients should be evaluated by a dietitian to determine whether they are ingesting sufficient calories (Chapter 198) and whether dietary supplements might be needed. Some patients, such as patients with head and neck cancers (Chapter 176) or esophageal cancers (Chapter 178), may require parenteral nutrition through a percutaneous gastrostomy tube. Total parenteral nutrition (Chapter 198) is rarely indicated.

Patients are often concerned about whether their diet contributed to development of the cancer and whether diet can influence the results of therapy. In most settings, neither of these scenarios is the case. Larger-than-recommended doses of vitamins are also not helpful and may be toxic (Chapter 199). Current or contemplated use of over-the-counter and/or alternative medications (Chapter 30) must be determined because they can have potentially important interactions with chemotherapeutic agents.

Psychosocial Support

Patients with a recent cancer diagnosis have increased risks of death from cardiovascular causes, especially during the first week after diagnosis. The associated anxiety, depression, and fear experienced by many patients commonly require substantial ongoing psychosocial support, which may exceed what the immediate family can provide. In this setting, patients often benefit from participation in support groups or from direct one-on-one counseling, as well as from efforts to improve communication across all levels of care and support systems.

Hematopoietic Growth Factors

Growth factors, such as granulocyte colony-stimulating factor (G-CSF) and granulocyte-macrophage colony-stimulating factor (GM-CSF), speed the recovery of the white blood cell count, thereby often permitting chemotherapy to be given on schedule, without reducing the dosage (Chapter 142).[A3] However, such therapy does not decrease hospitalizations or improve survival. Consensus guidelines[17] can help determine which individuals are at greatest risk for febrile neutropenia (Chapter 153) and are more likely to benefit from pre-emptive treatment. Correction of anemia with erythropoiesis-stimulating agents (epoetin alfa and darbepoetin alfa) may be associated with complications of adverse cardiovascular events and even potentially tumor progression (Chapter 144).[18]

Prevention of Pathologic Bone Fractures

Bisphosphonates (e.g., pamidronate and zoledronate) are very effective not only for the treatment of tumor-induced hypercalcemia but also to reduce pathologic fractures in bones with metastatic lesions (Chapter 187), particularly from breast cancer (Chapter 183), prostate cancer (Chapter 186), and myeloma (Chapter 173). Bisphosphonates are also used to treat osteoporosis caused by chemotherapy-induced premature menopause in young women with breast cancer (Chapter 225). Denosumab (a human monoclonal antibody that binds to RANK ligand, which is a protein that is found on osteoclasts and is involved in bone breakdown) is superior to zoledronic acid for the prevention of skeletal-related events in cancer patients with bone metastases.[A4] Compared with placebo, adjuvant denosumab administered subcutaneously every 6 months reduces the risk of clinical fracture in postmenopausal women whose breast cancer is being treated with aromatase inhibitors, without any added toxicity.[A5]

Symptom Management

Effective management of symptoms is critical to successful delivery of either curative or palliative treatment and maintenance of a patient's quality of life.

Nausea and Vomiting

Patients continue to fear chemotherapy because of the risk of nausea and vomiting. Antiemetics (Table 118-5), typically used in combination,[19] have made this side effect much less debilitating. Chemotherapeutic drugs can be ranked according to their probability of causing nausea and vomiting, with prophylactic treatment given accordingly. The availability of the serotonin 5-hydroxytryptamine type 3 (5-HT_3) receptor antagonists (dolasetron, granisetron, ondansetron) has dramatically improved the ability to control nausea and vomiting completely. More emetogenic regimens require combination therapy with a corticosteroid (usually dexamethasone), a 5-HT_3 antagonist, and a benzodiazepine (e.g., lorazepam) or the neurokinin-1 receptor antagonist aprepitant. Aprepitant is particularly useful for the treatment/prevention of delayed nausea and vomiting. The combination of a neurokinin-1 receptor antagonist with dexamethasone and a 5-HT3 receptor antagonist is even better to control carboplatin-induced emesis.

Pain Control

Oncologists use a variety of scales to evaluate pain control (Chapter 26), which can be accomplished with a variety combination of analgesics, both non-narcotic and narcotic. Pharmacologic treatment should start with nonsteroidal anti-inflammatory drugs (NSAIDs) such as aspirin or acetaminophen, progress through ibuprofen and related drugs (see Table 26-4), and then through combinations of NSAIDs and narcotics (see Table 26-6) to stronger narcotics.[20] Newer narcotics are available in both short-duration and long-duration forms; some dermal patches provide benefit for 72 hours and are ideal for patients who have severe pain and who are unable to take oral medications. Oral transmucosal fentanyl is more effective than standard-release morphine in this setting. Painful oral mucositis, a common complication of intensive therapy for hematologic malignancies, can be treated with local measures or with recombinant human keratinocyte growth factor (Chapter 393). Oral anti-*Candida* drugs that are absorbed or partially absorbed from the gastrointestinal tract can help prevent pain from oral candidiasis (Chapter 310); both pharmacologic and psychosocial interventions (e.g., relaxation training, cognitive-behavioral therapy, and other education- and skills-based approaches) are complementary approaches that have real but relatively modest effects on both the severity of pain and its interference with daily activities.

Malignant Effusions

Accumulations of fluid and malignant cells in the pleural (Chapter 86), peritoneal, or pericardial spaces (Chapter 62) are common complications of epithelial and hematopoietic malignancies that frequently produce a significant array of symptoms, either at the time of diagnosis or accompanying tumor progression. Malignant pleural effusions (Chapter 86) are most commonly associated with cancers of the lung and breast or lymphomas, may be the result of lymphatic obstruction or direct invasion of pleural membranes, and can produce significant degrees of dyspnea, cough, or pain that require therapy. Diagnostic thoracentesis of sufficient volume (>60 mL), with cytologic analysis of the pleural effusion, has a reasonably high diagnostic yield for malignancy (60 to 90%). In patients with previously untreated lymphoma, breast cancer, or small cell lung cancer, objective response to the initiation of systemic chemotherapy may provide long-term symptomatic relief. However, in patients with recurrent lung or breast cancer, for example, pleural effusions that are confirmed to contain malignant cells may present difficult ongoing therapeutic challenges. For symptomatic patients, therapeutic thoracentesis, usually under ultrasound guidance, is required and may need to be repeated to reduce dyspnea. When frequent thoracenteses over short intervals are needed, drainage of the pleural space is combined with a chest thoracostomy and the instillation of a sclerosing compound (talc, doxycycline) that will initiate an inflammatory response of sufficient magnitude to obliterate the pleural space (Chapter 86). Such pleurodesis is usually at least temporarily successful in preventing fluid recurrence in most patients. When it is no longer successful, placement of an indwelling pleural catheter may provide long-term symptomatic relief of dyspnea.

Malignant ascites (peritoneal effusion) occurs most frequently in patients with intra-abdominal malignancies (gastric, ovarian, pancreatic, and primary peritoneal cancers) but also can be observed in patients with advanced breast and lung cancers or lymphoma. Malignant ascites may be caused in part by increased permeability of the tumor vasculature as a result of overexpression of vascular endothelial growth factor, by the overproduction of inflammatory cytokines in the peritoneal space, or by lymphatic blockade secondary to carcinomatosis. Ultrasound-guided paracentesis provides relief of bloating, dyspnea, and the pain of abdominal distension. However, paracentesis must be repeated,

with an associated risk of dehydration, loss of protein, electrolyte imbalance, bleeding, infection, and kidney dysfunction. If paracentesis is required more often than once per week, prompt placement of a permanent catheter should be considered to allow self-drainage, even though these devices carry a significant risk of infection.

Malignant pericardial effusions (Chapter 62) are most commonly related to direct extension or metastatic spread from lung or breast cancers, melanomas, and hematologic malignancies. As is the case for other malignant effusions, image-guided pericardiocentesis with cytologic examination of the fluid that has been evacuated will frequently provide diagnostic confirmation of malignancy. Furthermore, the removal of even a relatively modest amount of fluid (<50 mL) may, at least partially, relieve the hemodynamic compromise produced by the effusion. The approach to a patient with malignant pericardial effusions is dictated by hemodynamic status (which can drive the choice between emergency pericardiocentesis or elective pericardiostomy) and by the predicted sensitivity of the inciting tumor to systemic therapy (e.g., untreated lymphoma versus chemotherapy-resistant lung cancer).

ENDOCRINE MANIFESTATIONS OF CANCER

Clinical syndromes associated with ectopic hormone production may pose special diagnostic dilemmas, can produce a significant degree of morbidity or even death in cancer patients, and may be difficult to treat (Table 164-5). Management of these syndromes involves the simultaneous treatment of both the cancer and the syndrome caused by excessive hormone production. Many of the endocrine manifestations of cancer[21] are caused by the production of small polypeptide hormones by tumors, some of which are derived from specific types of neuroendocrine cells. These cells are widely dispersed in a wide variety of organs, are often of neural crest origin, and can produce biogenic amines. The hormones produced from these tumors include adrenocorticotropic hormones (corticotropin, ACTH), calcitonin, vasoactive intestinal peptide, growth hormone–releasing hormone, corticotropin-releasing hormone (CRH), somatostatin, and other peptides. A second group of tumors, generally derived from squamous epithelium, produces parathyroid hormone–related proteins (PTHrP) and vasopressin.

TABLE 164-5 SOME CLINICAL SYNDROMES OF ECTOPIC HORMONE PRODUCTION

Humoral hypercalcemia
Parathyroid hormone–related protein
Squamous cell carcinoma
Breast cancer
Neuroendocrine tumors
Renal cell cancer
Melanoma
Prostate cancer
Increased calcitriol
Lymphoma
Benign conditions: sarcoid, berylliosis, tuberculosis, fungal infections
Corticotropin
Proopiomelanocortin
Small cell lung cancer
Pulmonary carcinoid
Medullary thyroid cancer
Islet cell tumor
Pheochromocytoma
Ganglioneuroma
Corticotropin-releasing hormone
Medullary thyroid cancer
Paraganglioma
Prostate cancer
Islet cell tumors
Human chorionic gonadotropin
Choriocarcinoma
Testicular embryonal cell carcinoma
Seminoma
Hypoglycemia
Insulinoma
Sarcomas or large retroperitoneal tumors
Inappropriate antidiuretic hormone secretion
Small cell lung cancer
Squamous cell head and neck cancer
Erythropoietin
Renal cell cancer
Hepatocellular carcinoma
Pheochromocytoma
Benign conditions: cerebellar hemangioblastoma, uterine fibroids

HYPERCALCEMIA OF MALIGNANCY

Humoral hypercalcemia (Chapter 227) is one of the most common endocrine syndromes related to an underlying malignancy. One of the most common causes of hypercalcemia of malignancy[22] is the ectopic production of parathyroid hormone–related protein, with resulting activation of the PTH receptor, an increase in the differentiation of osteoclasts, and increased bone resorption and consequent hypercalcemia. Ectopic parathyroid hormone–related protein (rather than PTH itself) can be produced by several different types of cancer, most characteristically squamous cell cancer, breast cancer, renal cell cancer, and prostate cancer, as well as by neuroendocrine tumors and melanoma (see Table 164-5). Increased production of calcitriol, which increases the absorption of calcium and suppresses levels of serum PTH, is another cause of malignant hypercalcemia, most commonly in patients with lymphoma. Bone metastases (Chapter 187), particularly in patients with breast cancer and myeloma, may produce hypercalcemia due to increased local production of PTHrP or other cytokines that increase bone resorption.

TREATMENT

The treatment of malignant hypercalcemia is similar to hypercalcemia that is caused by hyperparathyroidism (Chapter 227). The reversal of dehydration and the initiation of a saline diuresis should begin promptly; patients with a serum calcium in excess of 13 mg/dL should be treated with a bisphosphonate initially, with extended use of the bisphosphonate for the prevention of bone fractures and recurrence of hypercalcemia (Chapter 227).

OTHER ECTOPIC HORMONE SYNDROMES

Inappropriate secretion of ACTH is rare but resembles pituitary Cushing disease (Chapter 208). Tumors that produce corticotropin-releasing hormone include medullary thyroid cancer, prostate cancer, and islet cell neoplasms. Ectopic ACTH syndrome may manifest as classic Cushing syndrome, with easy bruisability, centripetal obesity, muscle wasting, hypertension, diabetes, and metabolic alkalosis. However, many patients with ectopic ACTH-producing cancers progress too quickly to develop prominent cushingoid manifestations clinically. Profound hypokalemia may predominate without the classic features of Cushing syndrome in patients with small cell lung cancer (Chapter 177).

Tumor-associated hypoglycemia (Chapter 211), although uncommon, may be the result of the overproduction of insulin by islet cell tumors; insufficient hepatic gluconeogenesis related to loss of functional hepatic mass by metastatic disease; or overexpression of insulin-like growth factor II, which can activate the insulin receptor in patients who have large retroperitoneal sarcomas or hepatocellular carcinomas. In each of these cases, treatment with frequent small feedings can be prescribed; however, successful symptomatic management of hypoglycemia may be difficult without control of the primary tumor mass or metastases.

The clinical syndrome of inappropriate secretion of antidiuretic hormone (Chapter 102) is caused by ectopic production of vasopressin, primarily in patients who have small cell lung cancer (Chapter 177) or squamous cancers of the head and neck (Chapter 176), and occasionally in patients with primary brain tumors (Chapter 175). This syndrome is characterized by hyponatremia, hypo-osmolality, excessive urine sodium excretion, and an inappropriately high urine osmolality for the low serum osmolality despite normal kidney, adrenal, and thyroid function. The hyponatremia in this condition is euvolemic. Fluid (free water) restriction can provide adequate short-term management of symptomatic hyponatremia, but treatment with demeclocycline, which blocks the effects of vasopressin on the kidney, provides more effective long-term therapy (Chapter 102).

PARANEOPLASTIC SYNDROMES

The term *paraneoplasia*, which means "alongside cancer," has been commonly used to denote a cancer's remote effects that cannot be attributed either to direct invasion or to distant metastases. These syndromes (Table 164-6)[23] affect up to 15% of patients with cancer; if patients with cachexia are excluded, however, the incidence probably drops to only a few percent.

Up to two thirds of paraneoplastic syndromes arise before an associated malignancy is diagnosed. In some cases, the paraneoplastic syndrome may be associated with relatively small tumors, and recognition of these associations may lead to earlier diagnosis and possibly more effective therapy. Furthermore, one of the hallmarks in defining a paraneoplastic syndrome is that the course of the syndrome generally parallels the course of the tumor. As a result, effective treatment of the underlying malignancy is often accompanied by improvement or resolution of the syndrome. Conversely, recurrence of the cancer may be heralded by the return of systemic symptoms.

TABLE 164-6 EVALUATION AND DIAGNOSIS OF PARANEOPLASTIC SYNDROMES

- Characterize abnormality; obtain laboratory studies and biopsy as necessary
- Carefully elicit any additional symptoms and signs
- Eliminate common causes
- If there is no obvious etiology, consider a paraneoplastic syndrome
- If findings are consistent with a known syndrome, screen for underlying malignancy
- If signs and symptoms are consistent with a known paraneoplastic syndrome, undertake a search for an unknown primary cancer or recurrence or progression of a known primary tumor
- Screening should include a careful physical examination including breast, gynecologic, and prostate evaluations; basic hematology, chemistry, and urine studies; chest radiograph; and mammogram
- Computed tomography (CT) of the abdomen and pelvis or positron emission tomography (PET) scan is indicated if there are any suspicious symptoms, signs, or laboratory abnormalities of cancer
- Antibody testing for paraneoplastic neurologic syndromes and/or skin biopsy should be performed as indicated
- Consider treatment of cancer and/or appropriate palliative treatment, including immunosuppressive therapy for paraneoplastic symptoms when possible

NEUROLOGIC PARANEOPLASTIC SYNDROMES

A variety of neurologic paraneoplastic syndromes[24] can complicate many different cancers, with small cell lung cancer (Chapter 177) being an especially common cause (Table 164-7). Lambert-Eaton myasthenic syndrome (Chapter 390) mimics myasthenia gravis clinically, with the exception that strength improves rather than deteriorates with sustained voluntary contraction. Paraneoplastic encephalitis, subacute sensory neuropathies (Chapter 388), and sensory ganglionopathies are also commonly associated with small cell lung cancer. Symptoms often include asymmetric numbness and paresthesias, as well as posterior column signs of loss of proprioception and vibratory sensation. Paraneoplastic cerebellar degeneration may be acute-onset and can mimic a cerebellar tumor (Chapter 175). Plasma cell dyscrasia and some lymphoproliferative neoplasms are associated with demyelinating peripheral neuropathies and with motor neuron symptoms that may mimic amyotrophic lateral sclerosis (Chapter 387). Polymyositis and dermatomyositis (Chapter 248) can be associated with a variety of tumors.

Paraneoplastic neurologic syndromes are more common with advanced tumors and are uncommonly the initial presenting manifestation, except perhaps with small cell cancers of the lung, plasma cell dyscrasias, and other

TABLE 164-7 PARANEOPLASTIC NEUROLOGIC SYNDROMES

NEUROLOGIC SYNDROME	CLINICAL MANIFESTATIONS	DIAGNOSIS	ANTIBODY AND ASSOCIATED MALIGNANCY
Lambert-Eaton myasthenic syndrome (Chapter 390)	Proximal lower limb weakness, with improvement in strength after several seconds of sustained voluntary contraction	Electromyogram showing *increased* muscle action potential with repeated nerve stimulation >10 Hz (opposite of myasthenia gravis)	Anti-VGCC or anti-SOX1 in small cell lung cancer (>80%)
Paraneoplastic encephalomyelitis/subacute sensory neuropathy (Chapter 383)	Subacute patchy or asymmetrical numbness, burning or aching paresthesias, and sensory ataxia with loss of proprioception and vibration sense	Clinical diagnosis supported by circulating antibodies and elevated cerebrospinal fluid protein levels with a lymphocytosis	Usually anti-Hu in small cell lung cancer; others include anti-SOX1 and anti-amphiphysin (small cell lung cancer, neuroblastoma), anti-Ma (small cell lung cancer, breast cancer), and anti-Trk (various carcinomas and lymphomas)
Paraneoplastic cerebellar degeneration	Often abrupt onset of dysarthria, ataxia, and oculomotor dysfunction	Clinical diagnosis supported by the presence of circulating antibodies, which also can be found in patients who have a variety of cerebellar disorders but no evidence of cancer; cerebrospinal fluid pleocytosis and elevated protein levels	Anti-Yo, anti-SOX1, or anti-Ri (breast, ovarian, and other gynecologic malignancies); anti-Hu (breast cancer); anti-Tr and anti-GluR (small cell lung cancer); and anti-Ma (Hodgkin lymphoma, various carcinomas)
Limbic encephalopathy (Chapter 383)	Subacute amnestic syndrome, affective disorder, seizures	Improvement common with treatment of underlying tumor	Anti-Hu, anti-amphiphysin, anti-SOX1, anti-VGKC, and anti-AMPA (small cell lung cancer); anti-Ta (testicular and breast cancers)
Stiff-person syndrome (Chapter 380)	Progressive muscle stiffness and rigidity, with intermittent and painful muscle spasms	Electromyogram showing continuous firing of motor unit potentials; may respond to muscle relaxants and improve with cancer therapy	Anti-amphiphysin (breast and small cell lung cancers) and anti-GAD (breast cancer)
Neuromyotonia (Chapter 390)	Diffuse muscle stiffness and cramps	Responds to treatment of tumor and immunosuppression	Anti-VGCC (thymoma)
Demyelinating neuropathies (including chronic demyelinating polyneuropathy, mononeuritis multiplex; Chapter 388)	Sensory more common than motor	IgM paraprotein may cross-react with myelin-associated glycoprotein, cryoglobulins	Plasma cell and lymphoproliferative neoplasms, osteosclerotic myeloma, POEMS, small cell lung cancer, other carcinomas
Necrotizing myelopathy	Symptoms associated with specific levels of spinal cord dysfunction; rapid deterioration and death		Variety of carcinomas and lymphomas
Motor neuron disease (Chapter 387)	Similar to amyotrophic lateral sclerosis with progressive weakness	Paraproteinemia	Plasma cell and lymphoproliferative neoplasms
Polymyositis/dermatomyositis (Chapter 248)	Proximal muscle weakness, skin lesions (Chapter 248)	May improve with treatment of cancer	Variety of carcinomas

AMPA = α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid; GAD = glutamic acid decarboxylase; GluR = glutamate receptor; IgM = immunoglobulin M; POEMS = polyneuropathy, organomegaly, endocrinopathy, monoclonal protein, and skin changes associated with osteosclerotic myeloma; VGCC = voltage-gated calcium channel; VGKC = voltage-gated potassium channel.

lymphoproliferative diseases. Paraneoplastic neurologic syndromes may show some response to effective treatment of the tumor, but they can also progress despite such therapy.

DERMATOLOGIC PARANEOPLASTIC SYNDROMES

Associations between cutaneous syndromes and underlying malignancies may be difficult to confirm. Generally, the skin condition and cancer follow a parallel course, and the two diagnoses should be made at about the same time. Some skin lesions are almost always associated with malignancy. Others, however, are nonspecific and are most commonly seen with nonmalignant conditions, thereby making it difficult or impossible to connect the skin disease with the underlying malignancy. In addition, biopsies of the skin lesion are usually nonspecific and show features identical to what are seen when the same lesion occurs without a malignant condition. The formation of tumor-related autoantibodies has rarely been associated with dermatologic paraneoplastic syndromes, although inflammatory cell infiltration may be seen.

Recognition of cutaneous manifestations of malignancy can be critical for the early diagnosis and successful treatment of cancer,[25] but some syndromes are seen only with advanced, incurable disease. Cutaneous manifestations include direct involvement of the skin with tumor as well as the remote effects of cancer. Both specific and nonspecific dermatologic adverse effects are also seen with cytotoxic chemotherapeutic agents, including alkylating agents, antimetabolites, anthracyclines, tyrosine kinase inhibitors, and immunotherapies.

One of the best-known paraneoplastic syndromes is acanthosis nigricans (Chapter 408 and Fig. 408-14), the pathogenesis of which is unclear. The tumor may produce factors that activate insulin-like growth factors or the insulin receptor in skin. Many tumors are known to produce transforming growth factor-α (TGF-α), which might activate epidermal growth factor receptors in the skin, causing hyperpigmentation and thickening. The skin lesions arise as velvety, verrucous hyperpigmentation of the neck, axilla, groin, and mucosal membranes, including the lips, periocular area, and anus. Although acanthosis nigricans clearly occurs as a benign entity associated with obesity and endocrinopathy, its appearance in older adults, especially when it includes mucosal lesions, is highly associated with malignancies of the gastrointestinal tract as well as with other adenocarcinomas. The lesions often regress with successful treatment of the underlying tumor.

RHEUMATOLOGIC PARANEOPLASTIC SYNDROMES

The possibility of an underlying occult malignancy should be considered[26] in patients who have rheumatic disorders with an atypical clinical presentation, particularly older patients, patients who have coexisting systemic symptoms, and patients who respond unexpectedly poorly to usual antirheumatic treatments. Chemotherapeutic agents can also cause rheumatic adverse effects.

One of the more common and specific rheumatologic paraneoplastic syndromes is hypertrophic osteoarthropathy,[27] which arises as an oligoarthritis or polyarthritis of the distal joints, with clubbing (Fig. 39-9), tender periostitis of the distal long bones, and noninflammatory synovial effusions (also see Chapter 254). Hypertrophic osteoarthropathy may affect up to 10% of patients with adenocarcinoma of the lung and is also seen with a variety of other pulmonary malignancies, including lung metastases from other primary sites. The etiology is unknown. Laboratory studies often reveal an elevation in the erythrocyte sedimentation rate; bone radiographs show linear ossification of the distal long bones separated by a radiolucent zone from the underlying cortex (Fig. 164-1).

TREATMENT

Treatment is symptomatic with anti-inflammatory agents. Successful treatment of the underlying tumor may also improve the signs and symptoms of this syndrome.

RENAL AND HEPATIC PARANEOPLASTIC SYNDROMES

The most common renal paraneoplastic syndrome is membranous glomerulonephritis, which can include nephrotic-range proteinuria, edema, hypertension, hypoalbuminemia, and microscopic hematuria (Chapter 100). The most common associated cancers include adenocarcinoma of the lung (Chapter 177), breast cancers (Chapter 183), and gastric adenocarcinomas (Chapter 178). Lymphoproliferative disorders, especially Hodgkin disease (Chapter 172), can cause minimal-change nephropathy. Renal microangiopathy can be seen with cryoglobulinemia associated with hepatitis C–related hepatocellular carcinoma (Chapter 181). Paraneoplastic hepatopathy with elevated liver enzymes and abnormal synthetic function can be seen with renal cell cancer (Chapter 182) without evidence of direct hepatic involvement by the tumor.

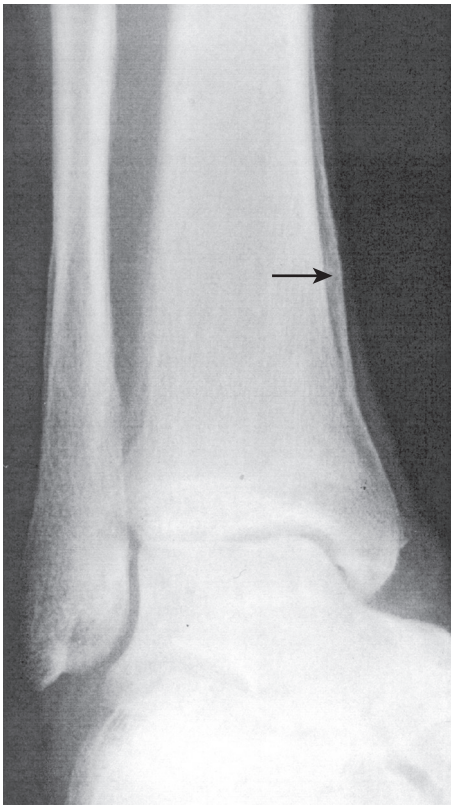

FIGURE 164-1. Hypertrophic pulmonary osteoarthropathy characterized by periosteal elevation of the tibia (*arrow*). (Courtesy Dr. Lynne S. Steinbach.)

HEMATOLOGIC PARANEOPLASTIC SYNDROMES

The most common immunologic paraneoplastic syndrome is thrombosis (Chapters 67 and 68). Some patients have hemorrhagic paraneoplastic syndromes, especially disseminated intravascular coagulation (Chapter 161), that can be seen in nearly all patients with acute promyelocytic leukemia (Chapter 168). Acquired von Willebrand disease (Chapter 159) may be seen in rare cases of lymphoproliferative and myeloproliferative disorders, and increased fibrinolysis can occur in patients with advanced prostate cancer (Chapter 186).

Anemia of chronic disease (Chapter 144) is a common finding in cancers of all types. Pure red cell aplasia (Chapter 151) is a rare condition associated with benign or malignant thymomas (Chapters 86 and 390).

Paraneoplastic hemolytic anemia (Chapter 147) can be seen with warm- or cold-reacting antibodies, especially in patients with chronic lymphocytic leukemia (Chapter 169). Microangiopathic hemolytic anemia (Chapter 147) with thrombocytopenia is a common complication of a variety of adenocarcinomas. Erythrocytosis is seen in tumors that produce erythropoietin, including renal cell cancers (Chapter 182), hepatocellular carcinomas (Chapter 181), and cerebellar hemangioblastomas (Chapter 175).

Patients with advanced cancer can develop leukocytosis caused by cytokines in the absence of infection. Eosinophilia (Chapter 156) can be seen with lymphoproliferative diseases, including Hodgkin disease. Paraneoplastic thrombocytosis (Chapter 152) is caused by tumors that produce interleukin-6 or thrombopoietin.

FEVER AND CACHEXIA

Fever (Chapter 260), night sweats, and cachexia are nonspecific symptoms that, when seen in the absence of infection or a known disorder, suggest the diagnosis of an underlying malignancy. Cytokines clearly play a pathogenetic role in inducing both fever and cachexia. TNF-α, interleukins (particularly IL-1 and IL-6), and interferon-γ, which result in a catabolic state, are produced directly by the tumor or by tumor-associated host inflammatory cells, such as macrophages. Cytokines may produce fever directly by acting at the level

of the hypothalamic thermoregulatory center. In addition to the burden of tumor and the production of cytokines, cachexia may be caused or worsened by the side effects of cancer treatment, by intestinal blockage or malabsorption caused by tumor infiltration, and by depression.

Fever is generally cyclic and may be associated with drenching night sweats. Symptoms resolve with successful treatment of the underlying tumor, and return of fever usually heralds relapse. When treatment of the tumor is not possible or is ineffective, NSAIDs (see Table 26-4) or corticosteroids given around the clock significantly improve quality of life. Although cancer-related fever is most commonly seen in association with malignant lymphoproliferative disease (Chapters 171 and 172), renal cell carcinoma (Chapter 182), and leukemias (Chapters 168 to 170), it may also occur with other cancers, particularly in the face of extensive hepatic metastases.

Cachexia, or cancer wasting syndrome, is probably the single most common paraneoplastic syndrome and eventually affects up to 80% of patients with cancer. Cachexia appears to be caused by a combination of protein wasting, malabsorption, immune dysregulation, and increased glucose turnover in the setting of tumor-induced increases in energy expenditure. This syndrome is characterized by anorexia, muscle wasting, loss of subcutaneous fat, and fatigue.

TREATMENT

Successful treatment of the underlying tumor reverses the process. By comparison symptomatic treatment for patients with advanced disease is modestly successful at best. Megestrol acetate given in high concentrations in liquid form (400 to 800 mg/day) can improve appetite and result in weight gain, but at the cost of fluid retention. Anamorelin, which is an oral ghrelin-receptor agonist with appetite-enhancing and anabolic activity (100 mg orally once daily), provides a favorable clinical response, including a significant increase in lean body mass.[A6,A7]

TUMOR LYSIS SYNDROME

Tumor lysis syndrome can be a major complication of the rapid response of hematologic malignancies and occasionally solid tumors to successful chemotherapy.[28] The sudden release of cellular contents (especially potassium, phosphate, and nucleic acids) can lead to deposition of uric acid and calcium phosphate in renal tubules. Clinical manifestations can include renal failure, seizures, and cardiac arrhythmias. Laboratory findings include elevated serum levels of uric acid, potassium, and phosphorus, with a decreased calcium level.

TREATMENT AND PROGNOSIS

The risks of complications from tumor lysis syndrome can be reduced by vigorous hydration and the prophylactic administration of allopurinol (300 mg daily), started at least 24 hours before chemotherapy and continued until uric acid levels normalize (Chapter 252). Another option is the therapeutic use of rasburicase (0.15 mg/kg intravenously, usually once, but it can be given daily for up to 5 days if needed).[29]

CANCER OF UNKNOWN PRIMARY ORIGIN

Some cancers present with biopsy-confirmed visceral or nodal metastases in the absence of an obvious primary lesion. Subsequent clinical evaluation, with a comprehensive history, physical examination, complete blood cell count, screening chemistries, chest and abdominal CT scans, and other radiologic studies directed by specific symptoms or signs can often identify the primary tumor site and clarify the extent of metastatic disease. When a primary tumor cannot be located despite such a clinical evaluation, the patient is classified as having *cancer of unknown primary origin*. Additional clinical, pathologic, and genetic evaluation can sometimes identify the primary site, but in up to 90% of patients a primary site may never be identified throughout their subsequent clinical course.

In patients whose primary cancer site remains undetectable, the primary site has presumably remained small or, less likely, regressed spontaneously. Approximately 4% of all cancer patients have metastatic disease without a known primary site, and autopsies identify a primary site in only about 50% to 70% of these patients. Cancer of unknown primary site increases with advancing age, but it occurs with about equal frequency in men and women.

DIAGNOSIS

The initial clinical, radiographic, and pathologic evaluations should focus not only on identifying a primary site but also on trying to identify tumors for which specific treatments may be most beneficial.

Biopsy and Pathologic Evaluation

The diagnosis of metastatic cancer should first be confirmed by biopsy of the most easily accessible lesion. A fine-needle aspiration is often adequate to confirm the diagnosis of cancer, but it will not provide adequate material for optimum pathologic evaluation. A larger surgical or core needle biopsy should be performed if technically feasible.

In about 60% of patients with cancer of unknown primary site, the initial microscopy will identify an adenocarcinoma. Other common light microscopy findings include poorly differentiated carcinoma (25%), squamous cell carcinoma (10%), and poorly differentiated neoplasm (inability to distinguish among carcinoma, lymphoma, sarcoma, and melanoma; 5%).

For poorly differentiated tumors, additional pathologic evaluation is required. An immunohistochemical stain usually can determine the lineage (e.g., carcinoma vs. lymphoma vs. sarcoma) of a "poorly differentiated neoplasm," and it sometimes can identify germ cell tumors or neuroendocrine carcinoma. More than 50% of such patients will have a lymphoma, for which treatment can be highly effective.

In patients with adenocarcinoma, immunohistochemical stains can narrow the diagnostic spectrum, particularly when interpreted in conjunction with clinical features. In several situations, immunohistochemical stains are quite specific, including prostate-specific antigen (PSA) for prostate cancer (Chapter 186), estrogen and progesterone receptors for breast cancer (Chapter 183), and leukocyte common antigen for non-Hodgkin lymphoma (Chapter 171). Other diagnoses suggested by immunoperoxidase staining include melanomas (Chapter 188), sarcomas (Chapter 187), and neuroendocrine tumors. Occasionally, electron microscopy or analysis for tumor-specific chromosomal abnormalities (i12p in germ cell tumors, Chapter 185; t11 : 22 in Ewing tumor; immunoglobulin gene rearrangements in non-Hodgkin lymphoma, Chapter 171) are useful in the evaluation of poorly differentiated tumors if results of other pathologic studies are inconclusive.

Since cancers usually retain gene expression profiles that are similar or even identical to their tissue of origin, modern molecular profiling can correctly predict the origin of more than 90% of metastatic cancers by finding such tissue-specific gene expression patterns.[30] Although the accuracy of genetic profiling is uncertain in patients with cancer of unknown primary origin, in part because most primaries never become manifest, current data suggest a similarly high accuracy rate. As a result, molecular tumor profiling is now a routine complement to pathologic evaluation and is indicated whenever a tissue of origin is not definitive on histologic examination.

Search for the Primary Site

After completion of the brief and focused evaluation needed to make the initial diagnosis of cancer of unknown primary origin, any additional diagnostic studies should be carefully targeted (Table 164-8). The value of positron emission tomography (PET) in identifying a primary site is unclear because it has not been shown to provide increased information above and beyond CT scanning.[31] Other routine radiologic and endoscopic evaluations of asymptomatic areas are rarely helpful for identifying a primary site and, as a result, are not recommended. Levels of serum tumor markers, including carcinoembryonic antigen, CA-125, CA-19-9, and CA-15-3, are frequently elevated in patients with carcinoma of unknown primary site, but such elevations are nonspecific and are not useful for inferring a primary site. They can, however, be useful to monitor a patient's response to treatment.

Specific clinical findings warrant additional diagnostic evaluation. In all men with metastatic adenocarcinoma, a serum PSA level should be measured. Mammography and breast MRI are routine components of the evaluation of women with metastatic adenocarcinoma, particularly if clinical features are consistent with metastatic breast cancer (e.g., axillary node involvement, pleural effusion, lytic or blastic bone metastases). In patients who are younger than age 50 years and who have poorly differentiated carcinoma, serum human chorionic gonadotropin and α-fetoprotein (AFP) levels are indicated to screen for germ cell tumors. If metastatic squamous carcinoma involves cervical lymph nodes, a thorough endoscopic head and neck evaluation, from the nasopharynx to the larynx, and biopsy of any suspicious areas are indicated (Chapter 176). In patients who have low cervical adenopathy but no identifiable primary site in the head or neck on endoscopic examination, fiberoptic bronchoscopy should also be considered. In patients with metastatic squamous carcinoma involving inguinal lymph nodes, all perineal structures should be carefully inspected, including by anoscopy, a urologic evaluation, and a pelvic examination in women.

TABLE 164-8 CANCER OF UNKNOWN PRIMARY ORIGIN: RECOMMENDED EVALUATION AFTER INITIAL LIGHT MICROSCOPIC DIAGNOSIS

DIAGNOSIS	CLINICAL EVALUATION*	SPECIAL PATHOLOGIC STUDIES
Adenocarcinoma (or poorly differentiated adenocarcinoma)	PET CT of the chest and abdomen Men: serum PSA Women: mammography, breast MRI Colonoscopy (patients with colon cancer "profile") Additional directed radiologic or endoscopic studies to evaluate abnormal symptoms, signs, laboratory values	Men: PSA stain Women: estrogen and progesterone receptor stains (if clinical features suggest metastatic breast cancer) Molecular tumor profiling
Poorly differentiated carcinoma	PET CT of the chest and abdomen Serum hCG and AFP Additional directed radiologic or endoscopic studies to evaluate abnormal symptoms, signs, and laboratory values	Immunoperoxidase staining Molecular tumor profiling Electron microscopy (if other studies are indeterminate or conflicting)
SCC, cervical nodes	PET Direct laryngoscopy with visualization; biopsy of the nasopharynx, pharynx, hypopharynx, and larynx Fiberoptic bronchoscopy (if laryngoscopy results are negative)	—
SCC, inguinal nodes	PET Complete examination of perineal area (including pelvic examination) Anoscopy Cystoscopy	—

*In addition to a history, physical examination, complete blood cell counts, chemistry profile, and chest radiograph.

AFP = α-fetoprotein; CT = computed tomography; hCG = human chorionic gonadotropin; MRI = magnetic resonance imaging; PET = positron emission tomography; PSA = prostate-specific antigen; SCC = squamous cell carcinoma.

From Hainsworth J, Greco FA. Approach to the patient with cancer. In: Goldman L, Schafer AI, eds. *Cecil Medicine,* 25th ed. Philadelphia: Elsevier; 2015.

TREATMENT AND PROGNOSIS

Site-Specific Therapy Directed by Molecular Tumor Profiling

Site-specific treatment of metastatic tumors, as characterized by their molecular profiling,[32] is the standard treatment (Table 164-9), and empiric chemotherapy should be reserved for the minority of patients whose tumors cannot be classified by molecular profiling. In general, the response to treatment and subsequent survival are consistent with the predicted types of cancer, and median survival is at least twice as long for patients who have more responsive tumors. Targeted treatment results in a median survival of 12.5 months, but some patients remain progression-free for more than 5 years.[A8]

Adenocarcinoma

Women with Axillary Lymph Node Metastases

Metastatic breast cancer should be suspected in any woman who has axillary lymph node involvement with adenocarcinoma, particularly if an alternative metastatic site is not evident. In these patients, pathologic evaluation of the initial lymph node biopsy should include staining for estrogen and progesterone receptors and for *HER-2* expression; elevated levels strongly suggest the diagnosis of breast cancer.

When no other metastases are identified, these women should be treated as if they had stage II breast cancer, which is potentially curable with appropriate therapy (Chapter 183). Modified radical mastectomy identifies a breast primary site in about 45 to 80% of women, even when the breast examination and mammographic findings are normal. Axillary lymph node dissection followed by radiation therapy to the breast appears to give results similar to those of mastectomy, although these two options for primary therapy have not been compared directly. Adjuvant systemic therapy should follow standard guidelines for treating women with stage II breast cancer.

Women with Peritoneal Carcinomatosis

Adenocarcinoma involving the peritoneum in women usually originates from the ovary (Chapter 184), although carcinomas arising in the gastrointestinal tract or breast can occasionally produce this syndrome. Diffuse peritoneal carcinomatosis can occasionally occur in women who have histologically normal ovaries or who have had previous bilateral oophorectomy. The peritoneum is frequently the only site of tumor involvement, and serum CA-125 levels are usually elevated. When histologic features suggest ovarian cancer, this syndrome has been called *peritoneal papillary serous carcinoma* or *primary extraovarian serous carcinoma*.

Even when the histologic features are not typical, women with adenocarcinoma of unknown primary site involving the peritoneum often have cancers that are biologically similar to ovarian cancer (Chapter 184). In such patients, treatment should follow guidelines for stage III ovarian cancer. A full laparotomy with maximal surgical cytoreduction should be performed when feasible, and it should be followed by combination chemotherapy with a taxane/platinum-containing regimen. Serial measurement of serum CA-125 levels can accurately assess the efficacy of treatment. Some patients may have complete responses and long-term survival, particularly when initial surgical cytoreduction leaves minimal residual disease. A similar syndrome of peritoneal carcinomatosis that is responsive to chemotherapy for ovarian cancer has rarely been reported in men.

Men with Skeletal Metastases or Elevated Serum Prostate-Specific Antigen Levels

Metastatic prostate cancer (Chapter 186) should be suspected in men who have an adenocarcinoma that predominantly involves bone, particularly if the metastases are blastic. An elevated serum PSA level or PSA tumor immunostaining confirms the diagnosis of prostate cancer. Occasionally, men who have adenocarcinoma of unknown primary site and metastatic patterns that are unusual for prostate cancer (e.g., lung metastases, mediastinal lymph node metastases) nevertheless have elevated serum PSA levels. Such patients should be treated according to guidelines for advanced prostate cancer. Androgen ablation produces excellent responses and substantial palliation in most patients.

Single Metastatic Lesion

Occasionally, a single metastatic lesion containing adenocarcinoma or poorly differentiated carcinoma is identified, and a complete evaluation reveals absolutely no other evidence of disease. Such single lesions may be a single lymph node, a subcutaneous site, or visceral lesions in liver, lung, bone, brain, or adrenal gland. One possibility is that an unusual primary tumor is mimicking a metastatic lesion (e.g., a subcutaneous nodule from a primary apocrine or sebaceous carcinoma rather than a metastasis). This possibility can usually be excluded on clinical or pathologic grounds, and PET scanning is useful to exclude other metastatic lesions.

In patients who have only a single identifiable lesion, definitive local therapy is recommended. Based on the site of the tumor, such therapy may include surgical resection, radiation therapy, or both. Although most such patients eventually have other evidence of metastatic disease, local treatment can provide substantial palliation, and some patients experience a significant disease-free period. The role of adding systemic chemotherapy to definitive local therapy is uncertain, but younger patients who have poorly differentiated carcinoma or adenocarcinoma are often treated with a short course of a taxane/platinum-based regimen.

Colon Cancer Profile

In a patient who has cancer of unknown primary origin, a colon cancer profile includes metastases seen predominantly in the liver, peritoneum, or both; an adenocarcinoma that has histologic features typical of gastrointestinal origin; and typical immunohistochemical staining (CK20 positive, CK7 negative, and CDX-2 positive). Patients who have such a profile should be treated according to guidelines for metastatic colorectal cancer (Chapter 179).

TABLE 164-9 CANCER OF UNKNOWN PRIMARY ORIGIN: SPECIFIC PATIENT SUBSETS AND RECOMMENDED TREATMENT

SUBSET-IDENTIFYING FEATURES		
HISTOLOGIC	**CLINICAL**	**TREATMENT RECOMMENDATIONS**
Adenocarcinoma	Women, isolated axillary adenopathy	Treat as stage II breast cancer
Adenocarcinoma, poorly differentiated carcinoma	Women, peritoneal carcinomatosis (occasionally men?)	Treat as stage III ovarian cancer
Adenocarcinoma	Men, elevated PSA or blastic bone metastases	Treat as advanced prostate cancer
Adenocarcinoma, poorly differentiated carcinoma	Single metastatic lesion	Definitive local therapy (resection or radiation therapy [or both]) with or without chemotherapy
Adenocarcinoma	Colon cancer profile	Treat as metastatic colorectal cancer
Squamous cell carcinoma	Cervical adenopathy	Treat as locally advanced head or neck cancer
Squamous cell carcinoma	Inguinal adenopathy	Definitive local therapy (node dissection with or without radiation therapy) with or without chemotherapy
Poorly differentiated carcinoma	Young men with midline tumor or elevated hCG or AFP	Treat as extragonadal germ cell tumor
Neuroendocrine carcinoma, poorly differentiated	Diverse clinical presentations	Treat as advanced stage small cell lung cancer
Neuroendocrine carcinoma, well differentiated	Usually liver metastases	Treat as metastatic carcinoid tumor

AFP = α-fetoprotein; hCG = human chorionic gonadotropin; PSA = prostate-specific antigen.
From Hainsworth J, Greco FA. Approach to the patient with cancer. In: Goldman L, Schafer AI, eds. *Cecil Medicine*, 25th ed. Philadelphia: Elsevier; 2015.

Squamous Cell Carcinoma

Squamous cell carcinoma of unknown primary site is relatively uncommon. Most patients are middle aged or elderly with a long history of substantial use of alcohol or tobacco or both.

Cervical Adenopathy

When the cervical lymph nodes, especially in the upper or midcervical area, are involved with squamous cell carcinoma, a primary site should be suspected in the head and neck region (Chapter 176). Nevertheless, a complete endoscopic evaluation will not identify a primary tumor in about 15% of such patients. When the endoscopic evaluation is negative, PET scanning can identify a primary head and neck lesion in about 25% of such patients, so it should be part of the initial evaluation.

In patients with a squamous cell carcinoma of unknown primary site, concurrent chemotherapy and radiation therapy are recommended as for locally advanced squamous cell carcinoma arising in the head and neck.[33] Combined modality therapy results in 50 to 60% 5-year disease-free survival rates. A node larger than 2 cm and the presence of multiple involved lymph nodes are adverse prognostic features (Chapter 176).

Inguinal Adenopathy

Metastatic squamous cell cancer occasionally can be found in an inguinal lymph node. In most such cases the primary site can be identified in the perineal or anorectal area. For the occasional patient in whom no primary site is identified, local therapy with inguinal lymph node dissection, with or without radiation therapy, can result in long-term survival. Combined-modality treatment with concurrent chemotherapy and radiation therapy has improved survival and even led to cure in patients with several types of squamous cell carcinomas that originate in this region (e.g., cervix, anus, bladder). Although data are incomplete, a reasonable approach is the addition of chemotherapy with a platinum–5-fluorouracil regimen, as used for locally advanced carcinoma of the cervix (Chapter 184).

Poorly Differentiated Carcinoma

Extragonadal Germ Cell Cancer Syndrome

Young men who have clinical features suggestive of extragonadal germ cell tumors, such as tumors that are located in the mediastinum or retroperitoneum or tumors that are associated with elevated serum levels of human chorionic gonadotropin (hCG) or alpha fetoprotein, should be treated according to guidelines for extragonadal germ cell tumors (Chapter 185). Some of these patients can be proven to have germ cell tumors by identifying an i12p chromosomal abnormality even when the diagnosis is not possible with other standard pathologic techniques. Approximately 30 to 40% of such patients achieve complete responses and long-term survival after chemotherapy with cisplatin, etoposide, and bleomycin as used for advanced germ cell tumors.

Anaplastic Lymphoma

An appropriate initial pathologic evaluation should identify most histologically atypical lymphomas. Occasionally, immunohistochemical staining for leukocyte common antigen is negative or cannot be adequately performed in patients with anaplastic lymphoma. In some of these patients, the type of tumor can be identified using other immunohistochemical stains (e.g., Ki-1, CD-30), molecular genetic analysis (detection of immunoglobulin gene rearrangements), or molecular tumor profiling. All patients whose lymphomas are identified by special pathologic studies should be treated using standard guidelines for aggressive non-Hodgkin lymphoma (Chapter 171).

Neuroendocrine Carcinoma

In approximately 10% of poorly differentiated carcinomas, neuroendocrine features are identified by either immunohistochemical staining or electron microscopy. Treatment of these patients is as described for neuroendocrine carcinoma (see later).

Other Poorly Differentiated Carcinomas

Most patients with poorly differentiated carcinoma have no clinical or pathologic features that can be used to identify a specific treatment. Such patients have a poor prognosis, similar to that of patients who have adenocarcinoma of unknown primary site, and their treatment should follow similar guidelines.

Neuroendocrine Carcinoma

Poorly Differentiated Neuroendocrine Carcinoma or Small Cell Anaplastic Carcinoma

High-grade neuroendocrine tumors can be reliably identified using readily available immunohistochemistry stains. Although the origin of these tumors is unknown, they frequently are very sensitive to combination chemotherapy. For example, platinum–etoposide chemotherapy, as prescribed for small cell lung cancer (Chapter 177), can provide an overall response rate in approximately 60% of patients, including complete responses in 15 to 20% of patients. In patients who have locoregional disease, post-chemotherapy radiation therapy is also reasonable. Peptide receptor radionuclide therapy with ^{177}lutethium dotatate is also useful for the treatment of neuroendocrine tumors.

Low-Grade (Carcinoid-Type) Neuroendocrine Tumors

Some low-grade neuroendocrine tumors present at a metastatic site, usually in the liver and usually with histologic features that suggest a carcinoid tumor (Chapter 213) or an islet cell tumor of gastrointestinal origin (Chapter 211). The clinical syndromes may be dominated by the secretion and action of vasoactive peptides (e.g., serotonin, vasoactive intestinal peptide, gastrin). As with other carcinoid tumors, these tumors often are relatively indolent, so patients can often survive for several years despite multiple liver metastases. Unlike poorly differentiated neuroendocrine tumors, however, these tumors tend to be relatively resistant to chemotherapy, so intensive combination regimens should usually be avoided. Treatment, which should follow guidelines for metastatic carcinoid tumors (Chapter 213), may include somatostatin analogues, local ablative procedures (e.g., surgical resection, radiofrequency ablation, chemoembolization), targeted agents (e.g., sunitinib, everolimus), or fluorouracil-based chemotherapy regimens.

Empiric Chemotherapy

A substantial proportion of patients with adenocarcinoma or poorly differentiated carcinoma of unknown primary site do not fit into a defined clinical subset for which targeted treatment is available. In such patients, empiric chemotherapy (usually taxane–platinum or gemcitabine–platinum combinations) can provide modest benefit, with response rates of 30 to 45% and a median survival of 9 to 11 months. However, empiric chemotherapy regimens are best avoided, and patients are better served by the best possible site-specific treatment, guided by the tumor's likely site of origin based on molecular tumor profiling.

SURVIVORSHIP AND FOLLOW-UP

Approximately 4% of the U.S. population (≈14 million people) is living with a history of cancer, and about 60% of cancer survivors are age 65 years or older. As a result, a large number of individuals are living longer as cancer survivors from the conclusion of active treatment to the time of recurrence or death from another condition. These patients have specific needs, including a defined program of surveillance to detect recurrence or second cancers and the late effects of cancer treatment; intervention to treat the consequences of the cancer and its treatment (such as lymphedema, fatigue, and psychosocial distress); prevention of new cancers by changes in diet, behavior, and physical activity[34,A9] (Chapter 165); and the institution of a coordinated program of care that may require a variety of specialty services.[35] Long-term follow-up can be optimized by the provision of a survivorship care plan that provides a comprehensive summary of all diagnostic and therapeutic procedures undergone, toxicities experienced, and therapeutic outcomes, as well as a specific program for stress management[36] and for individualized follow-up care.[A10] Although definitive follow-up regimens do not exist for most cancers, evidence-based templates for common malignancies have been developed by the American Society of Clinical Oncology and the National Comprehensive Cancer Network. In addition, issues of survivorship also affect caregivers, who often experience a high degree of psychological distress during and after the period of active treatment.

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165 EPIDEMIOLOGY OF CANCER

RULLA M. TAMIMI

CANCER BURDEN AND TRENDS

GLOBAL STATISTICS

Cancer is a major public health concern worldwide. The World Health Organization (WHO) estimates that cancer is the first or second leading cause of death before age 70 years in the majority of countries.[1] In 2020, 19.3 million new cases of cancer were diagnosed globally, and almost 10 million deaths were attributable to cancer (Fig. 165-1). Among women, breast cancer (24.5%) is the leading cause of incident cancer followed by colorectal cancer (9.4%), and breast cancer (15.5%) is the leading cause of cancer mortality followed by lung cancer (13.7%). Among men, lung cancer (14.3%) is the leading cause of incident cancer followed by prostate cancer (14.1%), and lung cancer (21.5%) is the leading cause of cancer mortality followed by liver cancer (10.5%). The burden of cancer varies substantially by geographic region and is impacted by factors such as the age of the population, the prevalence of cancer risk factors, screening and treatment practices, and a country's social and economic development. For example, the incidence and mortality of cervical cancer (Chapter 184) is quite low in high-income countries compared with low-income countries because of cervical cancer screening and vaccination for human papillomavirus.

UNITED STATES STATISTICS

In the United States, cancer is the second leading cause of death after heart disease. In 2020, more than 1.8 million new cases of cancer were diagnosed, and over 600,000 deaths were attributed to cancer. Over the past 50 years, the United States has experienced substantial changes in the incidence of several types of cancer as a reflection of patterns of exposure to risk factors as well as access to and utilization of cancer screening (Fig. 165-2).[2,3] For example, the dramatic increase in the incidence of prostate cancer (Chapter 186) in the 1990s reflected widespread prostate-specific antigen (PSA) testing in men and the resulting detection of asymptomatic disease. This increase was then followed by a dramatic decline in the reported incidence of prostate cancer in 2007 to 2014, largely attributable to changes in the screening guidelines of the United States Preventive Task Force (USPTF), which recommended against routine PSA screening because of concerns regarding overdiagnosis and overtreatment. Similar to prostate cancer, the incidence of breast cancer (Chapter 183) increased in the late 1980s with widespread adoption of mammographic screening. However, incidence rates for breast cancer have remained relatively stable, with slight increases observed in the last 20 years, thought to be attributable to continued increases in body mass index and trends in reproductive patterns (e.g., later age at first birth and lower parity). The incidence rates for colorectal cancer (Chapter 179) have been declining for both men and women since the mid-1980s, likely reflecting colorectal cancer screening practices that can detect precancerous lesions and prevent cancers from occurring. Incidence rates for lung cancer (Chapter 177) closely mirror smoking patterns in the population, although the decline in incidence rates is more pronounced in men than in women. Some of this sex difference may be related to differences in the initiation and cessation of smoking, but a greater percentage of lung cancers in women occur in nonsmokers.

By 2040, estimates suggest that breast cancer will be the most common cancer in the United States, followed by melanoma, lung cancer, and colorectal cancer. In terms of cancer death, lung cancer is projected to remain first, followed by pancreatic cancer, liver and biliary cancer, colon cancer, and breast cancer.[4]

CANCER RISK FACTORS

DEMOGRAPHIC FACTORS

Increasing age is an important risk factor for most cancers, with more than one-third of new cancers in the United States occurring in people age 75 years or older. Age likely represents the accumulation of biologic changes that influence carcinogenesis (Chapter 166). However, these biologic changes occur at different rates in different people depending on their underlying genetics and exposures across the life course. Additionally, cancers at different sites have unique patterns of incidence across the age continuum.

For cancers that occur in both men and women, cancer incidence rates tend to be higher in men (Fig. 165-2). At least some of these sex differences may be attributable to differences in the prevalence of relevant risk factors. For example, the prevalence of smoking has changed over time, but current smoking and smoking-related cancers continue to be higher in men in most countries.

Cancer incidence and mortality rates vary by race and ethnicity.[5] These differences are multifactorial and reflect differences in risk factors and access to high-quality preventive care, screening, and cancer treatments. Across all cancer sites, Black men in the United States have about a 20% higher cancer death rate than do White men. Similarly, Black women in the United States have about a 12% higher death rate than do White women, despite having a lower incidence rate. Black and Hispanic patients are often diagnosed at later stages of cancer, in part reflecting lower rates of screening. Overall cancer mortality rates mask disparities for specific cancers. For example, although Hispanic and Asian individuals have lower overall cancer mortality, their incidence and mortality of liver cancer are higher than in the White population.

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SURVIVORSHIP AND FOLLOW-UP

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165 EPIDEMIOLOGY OF CANCER

RULLA M. TAMIMI

CANCER BURDEN AND TRENDS

GLOBAL STATISTICS

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UNITED STATES STATISTICS

In the United States, cancer is the second leading cause of death after heart disease. In 2020, more than 1.8 million new cases of cancer were diagnosed, and over 600,000 deaths were attributed to cancer. Over the past 50 years, the United States has experienced substantial changes in the incidence of several types of cancer as a reflection of patterns of exposure to risk factors as well as access to and utilization of cancer screening (Fig. 165-2).[2,3] For example, the dramatic increase in the incidence of prostate cancer (Chapter 186) in the 1990s reflected widespread prostate-specific antigen (PSA) testing in men and the resulting detection of asymptomatic disease. This increase was then followed by a dramatic decline in the reported incidence of prostate cancer in 2007 to 2014, largely attributable to changes in the screening guidelines of the United States Preventive Task Force (USPTF), which recommended against routine PSA screening because of concerns regarding overdiagnosis and overtreatment. Similar to prostate cancer, the incidence of breast cancer (Chapter 183) increased in the late 1980s with widespread adoption of mammographic screening. However, incidence rates for breast cancer have remained relatively stable, with slight increases observed in the last 20 years, thought to be attributable to continued increases in body mass index and trends in reproductive patterns (e.g., later age at first birth and lower parity). The incidence rates for colorectal cancer (Chapter 179) have been declining for both men and women since the mid-1980s, likely reflecting colorectal cancer screening practices that can detect precancerous lesions and prevent cancers from occurring. Incidence rates for lung cancer (Chapter 177) closely mirror smoking patterns in the population, although the decline in incidence rates is more pronounced in men than in women. Some of this sex difference may be related to differences in the initiation and cessation of smoking, but a greater percentage of lung cancers in women occur in nonsmokers.

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CANCER RISK FACTORS

DEMOGRAPHIC FACTORS

Increasing age is an important risk factor for most cancers, with more than one-third of new cancers in the United States occurring in people age 75 years or older. Age likely represents the accumulation of biologic changes that influence carcinogenesis (Chapter 166). However, these biologic changes occur at different rates in different people depending on their underlying genetics and exposures across the life course. Additionally, cancers at different sites have unique patterns of incidence across the age continuum.

For cancers that occur in both men and women, cancer incidence rates tend to be higher in men (Fig. 165-2). At least some of these sex differences may be attributable to differences in the prevalence of relevant risk factors. For example, the prevalence of smoking has changed over time, but current smoking and smoking-related cancers continue to be higher in men in most countries.

Cancer incidence and mortality rates vary by race and ethnicity.[5] These differences are multifactorial and reflect differences in risk factors and access to high-quality preventive care, screening, and cancer treatments. Across all cancer sites, Black men in the United States have about a 20% higher cancer death rate than do White men. Similarly, Black women in the United States have about a 12% higher death rate than do White women, despite having a lower incidence rate. Black and Hispanic patients are often diagnosed at later stages of cancer, in part reflecting lower rates of screening. Overall cancer mortality rates mask disparities for specific cancers. For example, although Hispanic and Asian individuals have lower overall cancer mortality, their incidence and mortality of liver cancer are higher than in the White population.

ABSTRACT

Cancer is the first or second leading cause of death before age 70 years in the majority of countries. In 2020, 19.3 million new cases of cancer were diagnosed globally, and almost 10 million deaths were attributable to cancer. Among women, breast cancer (24.5%) is the leading cause of incident cancer and cancer mortality (15.5%). Among men, lung cancer (14.3%) is the leading cause of incident cancer and cancer mortality (21.5%). The burden of cancer varies substantially by geographic region and is impacted by factors such as the age of the population, the prevalence of cancer risk factors, screening and treatment practices, and social and economic factors. Tobacco use, in particular cigarette smoking, is associated with a number of cancer sites and is a leading cause of death from cancer. Excess body weight is also associated with cancer at multiple sites. Other cancer risk factors include diet, alcohol intake, physical activity, infectious agents, hormones, and ionizing radiation. This chapter also discusses the importance of molecular and genetic epidemiology, how the integration of molecular tools has allowed for robust insights into the causes of cancer, and how cancer control can reduce the burden of cancer in the population.

KEYWORDS

cancer burden
incidence rates
risk factors
obesity
tobacco
prevention

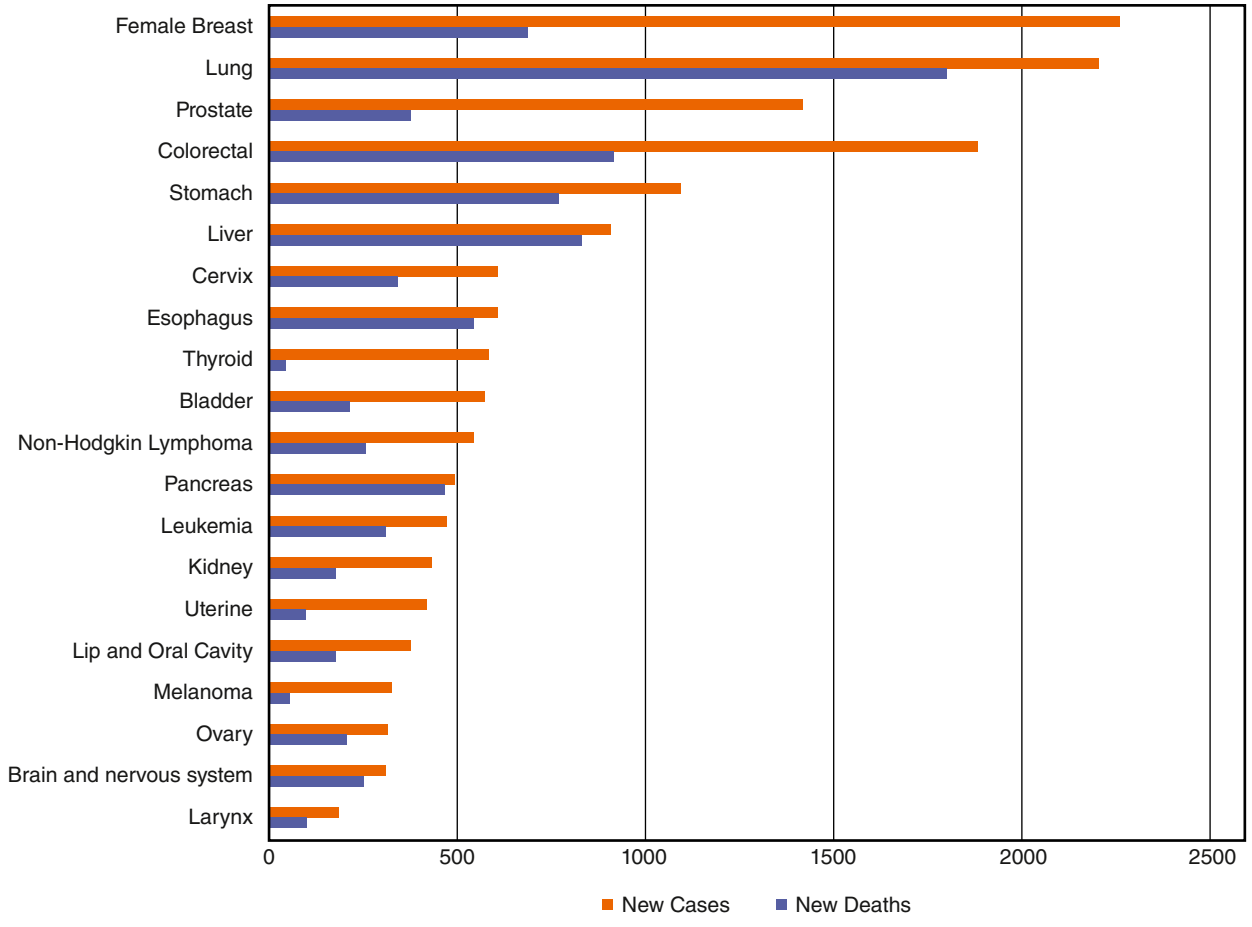

FIGURE 165-1. Rank order of the top 20 cancers worldwide. Worldwide cancer incidence and mortality in 2020. (Data from Sung H, Ferlay J, Siegel RL, et al. Global Cancer Statistics 2020: GLOBOCAN estimates of incidence and mortality worldwide for 36 cancers in 185 countries. *CA Cancer J Clin*. 2021;71:209-249.)

ENVIRONMENTAL AND LIFESTYLE FACTORS

Potentially modifiable environmental and lifestyle risk factors are major contributors to the development of cancer.[6,7]

Tobacco

Tobacco use (Chapter 363), and in particular cigarette smoking, is a leading cause of death from cancer. In the United States, almost 30% of cancer deaths are estimated to be attributable to tobacco smoking.[8] Strong evidence links tobacco smoking as a cause for a number of cancers, including lung, oral cavity, nasal cavity, nasopharynx, oropharynx, hypopharynx, larynx, esophagus, stomach, pancreas, liver, kidney, ureter, bladder, and cervix, as well as myeloid leukemia. Chewing tobacco also markedly increases the risk of oral and pharyngeal cancers. Significant advances in tobacco control have resulted in dramatic declines in the prevalence of smoking. Despite these successes, an estimated 22% of the global adult population smokes tobacco. Smoking rates vary widely by region and sex. China has the highest prevalence of adult male smoking (29%), whereas the United States has the highest prevalence of adult female smoking (10%).

Despite success in efforts to reduce cigarette smoking, the emergence of new tobacco products (e.g., vapes, sheesha, flavored tobacco products) has created new public health and equity issues. Additionally, tobacco control has been less successful in specific segments of the population, especially related to sexual orientation and gender identity (Chapter 215).

Obesity and Height

Consistent evidence links excess body weight (Chapter 201) with the risk of cancer at multiple sites. The risk is strongest (a three-fold increase in risk) for endometrial and esophageal cancers and more modest (relative risks of 1.5 to 3.0) for cancers of the kidney, liver, pancreas, and stomach, as well as for multiple myeloma and meningioma. The lowest relative risks (1.0 to 1.5) are for colorectal, postmenopausal breast, gallbladder, ovarian, and thyroid cancers.

The biologic mechanisms that have been proposed to underlie these associations include chronic inflammation, hyperinsulinemia/insulin resistance, insulin-like growth factor (IGF)-1 pathways, and the impact of obesity on circulating sex steroids. Given the strong association between adiposity and many cancers, maintaining a healthy body weight is an important recommendation for cancer prevention. For example, the marked weight loss after bariatric surgery is associated with a significant reduction in the incidence of cancer.[9]

Strong evidence links certain cancers with adult height independent of obesity. For example, adult height is positively associated with the risks of colorectal, ovarian, and breast cancer.[10] In a nationwide study in Sweden, every 10 cm increase in height was associated with about a 20% increased risk of cancer in women and about a 10% increased risk of cancer in men.[11] All cancer sites showed a positive association, with the strongest relative risk (35 to 40%) for malignant melanoma. Height may reflect a larger number of cells at risk of transformation, or adult height may reflect energy intake or exposures to growth factors early in life. For example, levels of IGF-1 in childhood are strongly correlated with height.

Diet and Alcohol

Although the association between adiposity and the risk of cancer is consistent across a number of cancer sites, the association between food groups and nutrients is not. Reasonable prevention recommendations specifically related to diet include: eat a diet rich in whole grains, vegetables, fruits, and beans; limit consumption of fast foods and/or other processed foods high in fat, starches, or sugars; limit consumption of red and processed meats;[12] and limit consumption of sugar-sweetened beverages (Chapter 13).

Alcohol (Chapter 364) is responsible for about 4% of cancers worldwide.[13] The magnitude of association is strongest for oral and pharyngeal cancers as well as esophageal squamous cell carcinoma, but alcohol is also associated with liver and colorectal cancer. For female breast cancer, the association is modest, with a relative risk of 1.6. No convincing evidence links alcohol to other common cancers such as prostate or lung cancers.

Most epidemiologic studies show a dose–response relationship, with increasing amounts of alcohol conveying higher risks regardless of the type of alcohol consumed. The primary hypothesized mechanism is via metabolites,

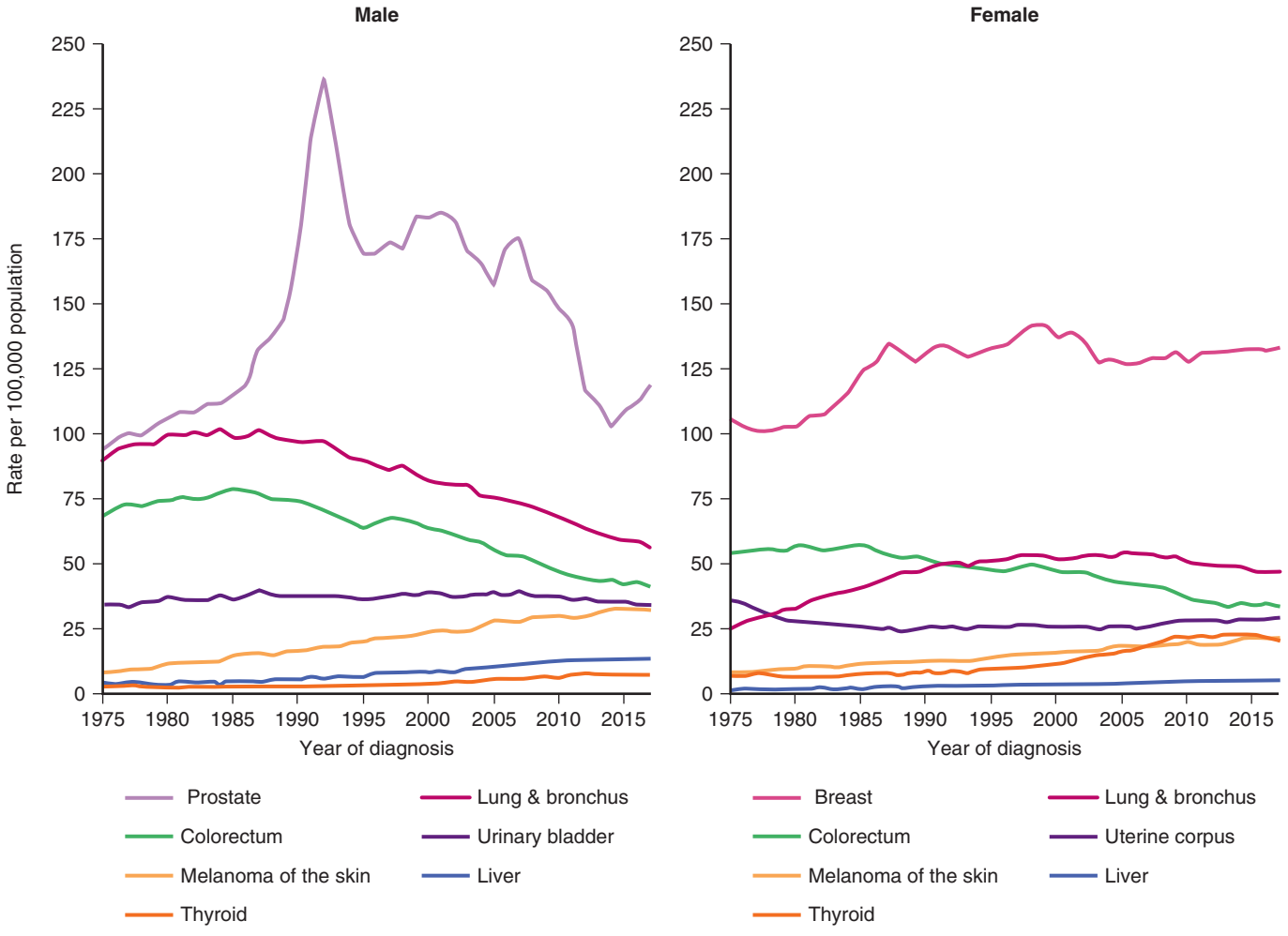

FIGURE 165-2. Trends in incidence rates for selected cancers by sex, United States, 1975-2017. (Reproduced from Siegel RL, Miller KD, Fuchs HE, et al. Cancer statistics, 2021. *CA Cancer J Clin*. 2021;71:7-33.)

such as acetaldehyde, which have carcinogenic and mutagenic properties. Alcohol's link to breast cancer probably is partly related to its association with increased levels of total and bioavailable estrogen in premenopausal women, as well as elevated plasma levels of estrogen and increased plasma estradiol levels in postmenopausal women. Additionally, alcohol consumption can indirectly impact the risk of cancer by its association with increases in body mass index.

Physical Activity

Physical activity (Chapter 14) has been hypothesized to reduce the risk of cancer, but the epidemiologic data are not entirely consistent, perhaps because of imperfect measurement of physical activity and the difficulty of separating the direct effects of physical activity from the effects of concomitant adiposity and obesity. The primary hypothesized mechanisms relate to the impact of physical activity on circulating hormones (e.g., sex steroids, insulin and insulin-like growth factors, adipokines), inflammation, immune function, and oxidative stress.

For example, pooled data suggest that higher levels of leisure time physical activity are associated with a reduced risk of 13 cancers,[14] with the strongest associations (>20% reduced risk when comparing the 90th percentile to the 10th percentile) for esophageal adenocarcinoma and cancers of the liver, lung, kidney, gastric cardia, and endometrium, as well as for myeloid leukemia. Moderate associations (10 to 20% reduced risk) are seen for colon, head and neck, rectal, bladder, and breast cancers, as well as for multiple myeloma. After adjusting for body mass index, endometrial, liver, and gastric cancer were no longer significantly associated with physical activity, whereas the relative risk for other cancer sites were only modestly reduced, thereby suggesting that physical activity is a risk factor independent of its relationship to body mass index. The relationship between increased physical activity and a reduced risk for breast cancer and colorectal cancer has also been confirmed using mendelian randomization analysis.[15]

Given the robust evidence and wide impact on reduced risk of several cancer sites, promoting physical activity should be a key component of cancer prevention efforts. For cancer prevention, adults should get at least 2.5 hours/week of moderate-intensity physical activity or 1.25 hours/week of vigorous-intensity physical activity.

Infectious Agents

Eleven infectious pathogens are classified as group 1 carcinogens (i.e., carcinogenic to humans), and an estimated 13% of all cancer cases worldwide are attributable to infections.[16]

The four agents with the greatest impact on cancer in rank order are *Helicobacter pylori* (non–cardia gastric adenocarcinoma; Chapter 178), high-risk human papillomavirus (Chapter 344; cervix, head and neck, and anal carcinoma), hepatitis B virus (Chapter 135), and hepatitis C virus. Almost all cervical cancers (Chapter 184) are attributable to high-risk subtypes of human papillomavirus. Hepatitis B virus is a DNA virus that can cause hepatocellular carcinoma; among carriers of hepatitis B virus, the lifetime risk of hepatocellular carcinoma (Chapter 181) is estimated to be 10 to 25%. Together, these four infectious agents explain >90% of all infection-related cancers globally. The age-standardized incidence rates for infection-attributable cancers vary considerably by geographic region. For example, although *H. pylori* is the most important infectious cause of cancer globally, the age-standardized incidence rates vary by more than five-fold from Eastern Asia, where they are highest, to North America, where they are lowest.

HORMONES

Endogenous Estrogens and Androgens

Several lines of evidence suggest that estrogens play a central role in the cause of female cancers. For example, the risk of breast cancer increases with increasing circulating levels of estrogen. Estrone, estrone sulfate, and free estradiol are similarly related to risk.

Androgens have been hypothesized to increase the risk of breast cancer either directly, by increasing the growth and proliferation of breast cancer cells, or indirectly, by their conversion to estrogen. In postmenopausal women, testosterone and other androgens have been positively associated with the risk of breast cancer. Among premenopausal women, data are much more limited, but statistically significant positive associations are also seen for testosterone, androstenedione, and dehydroepiandrosterone.[17]

Androgens are implicated in cancers of the prostate and breast. Total castration and androgen suppression are successful treatments for advanced prostate cancer,[18] but the association of circulating free testosterone with the risk of developing prostate cancer is more modest.[19]

Exogenous Hormones

Worldwide, the estimated 151 million women who use oral contraceptives represent 16% of women of reproductive age.[20] Most combined oral contraceptives contain ethinyl estradiol (or mestranol, which is metabolized to ethinyl estradiol; Chapter 220) plus a progestin. Patterns of use have changed considerably over time, with both increased duration of use and a trend toward younger age at first use.

The use of oral contraceptives is associated with a modest increased risk of breast cancer for current or recent users. Among women younger than age 50 years, the risk of breast cancer is about 20% higher in women who are current or recent users of hormonal contraceptives compared with nonusers, and a longer duration of use is associated with increased risk.[21] In contrast, the use of oral contraceptives has been associated with lower risks of colorectal, endometrial, and ovarian cancers.[22]

Some menopausal hormone therapies also increase the risk of breast cancer, but formulations and patterns of use have varied over time. The addition of a progestin to estrogen regimens has become increasingly common to minimize or eliminate the increased risk of endometrial hyperplasia and cancer associated with unopposed estrogens. Accumulating data suggest that the addition of a progestin increases the risk of breast cancer beyond that associated with estrogen alone, with stronger associations observed with longer durations of use. Furthermore, different formulations, routes of administration, and regimens may impact the association with breast cancer.[23] Postmenopausal hormonal therapy also appears to increase the risk of ovarian cancer.[24] By comparison, postmenopausal hormone therapies are associated with lower risks of colorectal, esophageal, and gastric cancers. Given the substantial evidence implicating postmenopausal hormone therapies in breast cancer, women and their physicians should carefully consider their risks and benefits (Chapter 222).

IONIZING RADIATION

Exposure to ionizing radiation (Chapter 18) causes somatic DNA mutations. The long-term effects of high levels of ionizing radiation on the risk of cancer is best estimated from people who were exposed to the atomic bombings in Japan in 1945 and to large nuclear disasters in Chernobyl and Fukushima. In atomic bomb survivors in Hiroshima and Nagasaki, excess cases of leukemia were observed by 3 years after exposure, and an excess risk of solid tumors was observed by 10 years after exposure. Sites of excess risk included bladder, breast (female), lung, brain, thyroid, colon, esophagus, ovary, stomach, and liver. For all of these types of cancer, the magnitude of risk increased as the radiation dose increased and as the age at exposure decreased.

MOLECULAR AND GENETIC EPIDEMIOLOGY

The integration of molecular tools in epidemiologic studies has allowed for robust insights into the causes of cancer. For example, aflatoxin is produced by a fungus, which can contaminate stored grain and nuts. Although animal studies demonstrated aflatoxin was carcinogenic, the association between the dietary intake of aflatoxin and liver cancer in humans was difficult to demonstrate until biomarkers of exposure (e.g., urinary metabolites of aflatoxin and DNA adducts reflecting exposure) were identified and showed strong evidence of a causal association.

The assessment of biomarkers for cancer epidemiologic research spans the continuum of disease from germline genetic susceptibility, markers of exposure (e.g., presence of cancer causing virus or cotinine), markers of internal dose (e.g., DNA adducts), markers of effective dose (e.g., somatic mutational patterns), or markers of tumor heterogeneity and prognosis (e.g., molecular subtypes). The landscape of molecular epidemiology has evolved over time as newer tools have demonstrated validity in stored biospecimens. Large-scale genome-wide association studies (GWAS) studies have led to the identification of single nucleotide polymorphisms (SNPs) that are associated with disease. Polygenic risk scores can incorporate multiple SNPs associated with a disease into a single score. Inclusion of a polygenic risk score to risk assessment models can significantly improve the ability to predict the development of breast and prostate cancer and may help develop more personalized cancer screening protocols.

CANCER CONTROL: PREVENTION AND TREATMENT

Cancer control refers to reducing the burden of cancer in the population, whether by reducing the incidence of and mortality from cancer or by improving the quality of life for patients who are being treated for and living with cancer (Fig. 165-3). Cancer prevention, screening, and early detection are critical for reducing the incidence and mortality from cancer.

PRIMARY PREVENTION

Primary prevention refers to strategies targeted at reducing exposure to established cancer risk factors. Cancer prevention efforts can be multifaceted by targeting individuals, medical recommendations, schools, neighborhood planning, and federal policies. Most notably, tobacco control efforts (Chapter 363) have had a substantial impact on the declining incidence and mortality rates attributable to lung cancer. Tobacco control efforts have included educational efforts to reduce the initiation of smoking and to increase the uptake of smoking cessation programs (Chapter 363). Policy changes have resulted in the implementation of tobacco-free public places, workplaces, and multiunit residential settings.

Vaccinations against carcinogenic infections are another successful approach for reducing the incidence of cancer. Vaccination programs for human papillomavirus (Chapter 344) and hepatitis B virus (Chapter 134) are two strategies to reduce the incidence rates of cervical and liver cancer,

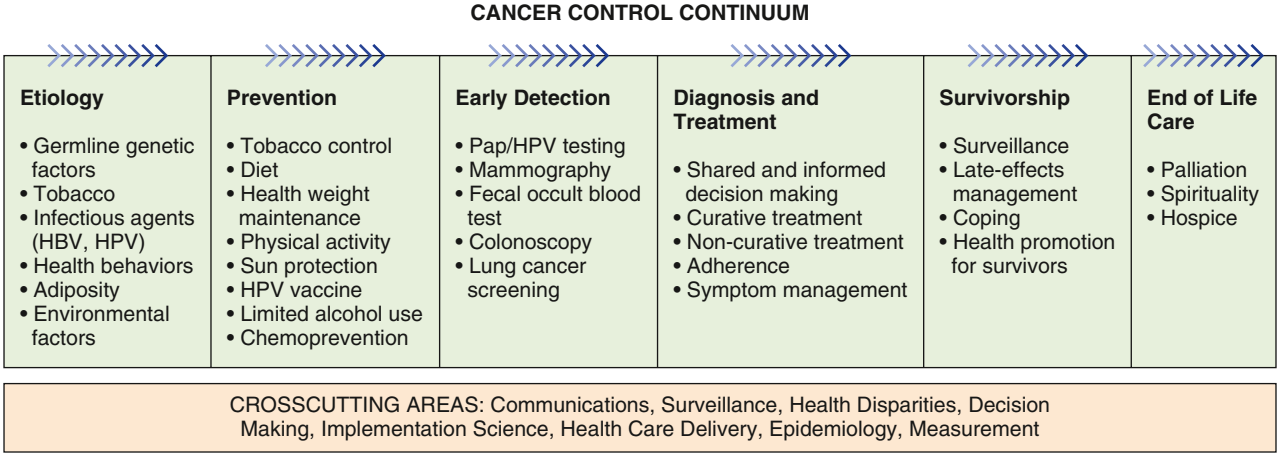

FIGURE 165-3. The Cancer Control Continuum. Examples and opportunities to impact cancer morbidity and mortality along the continuum. HBV = hepatitis B virus; HPV = human papillomavirus.

respectively. For example, a nationwide neonatal hepatitis B virus immunization program launched in Taiwan in 1984 reduced the incidence rate for hepatocellular carcinoma by 80%, and the mortality rate declined by over 90%.[25] Several clinical trials have demonstrated the efficacy and safety of vaccines for human papillomavirus,[A1] with data already showing reductions in cervical cancer[A2] and human papillomavirus–related oropharyngeal cancer.[A3] Because large-scale nationwide human papillomavirus vaccination programs were not initiated until 2007, it is too early to observe major declines in cancer incidence rates given the latency period, but widespread vaccination programs could lead to the elimination of cervical cancer. Major challenges that remain are related to the implementation of programs to improve both access and adherence.

Other established modifiable cancer risk factors include obesity (Chapter 201), physical inactivity (Chapter 14), poor diet (Chapter 13), and alcohol consumption (Chapter 364). Diets and behaviors aimed at maintaining healthy weights throughout life have the potential to reduce the risk of several cancers. Limiting alcohol consumption and being physically active also can reduce the risk of cancer.

SECONDARY PREVENTION

Secondary prevention refers to strategies aimed at reducing mortality from cancer. Screening is often a central part of secondary prevention because the goal of screening is to detect cancer in a presymptomatic state. Screening programs are well established for a number of cancers. For cervical cancer, initial success was observed with widespread screening using the Papanicolaou smear, and human papillomavirus–based screening strategies have demonstrated even greater efficacy when compared with cytology alone (Chapter 184).[A4] The incidence rates for colorectal cancer have been falling in the United States (see Fig. 165-2), largely due to the success of screening programs (with stool-based tests, sigmoidoscopy, and colonoscopy), which are now recommended to begin at ages 45 to 49 years (Chapters 12 and 179).[A5]

Widespread PSA testing for prostate cancer (Chapter 186) and mammography for breast cancer (Chapter 183) have resulted in dramatic increases in the reported incidence of these two cancers. Both approaches have also likely led to reductions in cancer-specific mortality, despite concerns about overdiagnosis and overtreatment of some of the lesions detected through these screening programs. Given concerns regarding harms related to PSA screening, the U.S. Preventive Services Task Force modified its recommendations in 2018 to advise that the decision to undergo PSA screening should be made at the individual level through shared decision making.[A6]

Lung cancer screening with low-dose computed tomographic scanning is beneficial for high-risk individuals, in whom it can reduce mortality by about 25 to 33% in the following 10 years.[A7,A8] The U.S. Preventive Services Task Force guidelines now recommend it for persons who are at high risk (e.g., adults ages 50 to 80 years with a >20 pack-year smoking history who either currently smoke or have quit within the past 15 years) of lung cancer (Chapters 12 and 177).[26] Unfortunately, the uptake of lung cancer screening has been slow, especially in diverse populations,[27] with <5% of eligible persons undergoing screening,[28] presumably reflecting a lack of awareness on the part of the physician and the patient, confusion regarding recommendations, limited access to screening, and the stigma associated with smoking and lung cancer.[29]

TREATMENT

The availability of cancer treatments, including surgery, radiation, and chemotherapy, varies significantly across the world, with fewer treatments in lower-income countries (Chapter 5) and by socioeconomic status and ethnicity even in higher-income countries (Chapter 4). Access to high-quality cancer care impacts patients' outcomes and survival. As treatment improves, the prevalence of cancer rises, thereby emphasizing the need to addresses cancer survivorship care (Chapter 164).

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166 CANCER BIOLOGY AND GENETICS

BEN HO PARK

INTRODUCTION

Cancer is a collection of many different diseases and is often not uniformly categorized by even the tissue of origin. For example, hormone receptor–positive breast cancers are distinct in biology, prognosis, and treatment compared with hormone receptor–negative breast malignancies. A unifying feature shared by all human cancers is that they have a genetic basis, even though familial cancer syndromes are relatively uncommon compared with sporadic cancers. However, both heritable and sporadic cancers require the accumulation of DNA mistakes or alterations that lead to a step-wise progression of events, ultimately resulting in cancer. These DNA alterations are typically classified as mutations, copy number changes, and gene rearrangements. Cancer also results when DNA undergoes epigenetic changes that do not involve alterations to the DNA sequence but produce modifications that result in either the silencing or activation of genes in an aberrant fashion.

CANCER IS A DISEASE OF CUMULATIVE DNA ALTERATIONS

When the balance of cell proliferation as compared with cell death or quiescence is perturbed, either due to abnormally increased proliferation or to decreased cell death or stasis, the initial steps of carcinogenesis have begun. Genes that mediate cell proliferation and cell death are often the early drivers of cancer, and many of these genes are mutated or altered in diverse types of cancer.

Two broad categories of cancer genes are termed *oncogenes* and *tumor suppressor genes*. Oncogenes, which are the accelerators of cancer growth, drive abnormal cell proliferation through various mechanisms. Common oncogenes that are often mutated or altered in human cancers include *KRAS*, *BRAF*, *PIK3CA*, and *ERBB2* (HER2). The functions of oncogenes are diverse, but many mutations and alterations that occur in oncogenes constitutively activate critical growth-promoting pathways that then drive cellular proliferation. Conversely, tumor suppressor genes act as the brakes of cell growth. Their normal function is to control cell cycling by monitoring and stopping proliferation when appropriate. Any disruption in the function of tumor suppressor genes would predictably lead to a net gain in cell numbers, possibly even without additional contributions of increased cell proliferation. Examples of tumor suppressor genes commonly mutated in human cancers include *TP53*, *CDKN2A*, *CDKN2B*, and others. Most cancers have genetic alterations involving both tumor suppressor genes and oncogenes, but the types of genetic alterations and consequences for therapies can vary dramatically between different malignancies.

DNA ALTERATIONS IN ONCOGENES AND TUMOR SUPPRESSOR GENES

Given the distinct yet complementary roles of oncogenes and tumor suppressor genes, it is perhaps not surprising that certain types of genetic alterations are associated more frequently with one or the other class of genes. Activating mutations within oncogenes, for example, tend to be heterozygous (i.e., only

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ABSTRACT

Cancer is a disease of DNA mutations and other alterations that promote the growth of cells at the expense of the host. In recent years, an explosion of knowledge has been realized due to massive efforts to sequence the genomes of many different human cancers. From these studies, a new understanding of cancers has emerged, leading to improved diagnostic testing and targeted therapies. In this chapter we will review the types of genes that drive cancer growth, as well as mutations and alterations that provide opportunities for therapeutic and diagnostic exploitation.

KEYWORDS

chromosomal instability
DNA
epigenetics
gene expression profiling
genetics
germline mutations
hallmarks of cancer
microsatellite instability
mutation
next-generation sequencing
oncogenes
somatic mutations
targeted therapies
tumor mutation burden
tumor suppressor genes
cancer

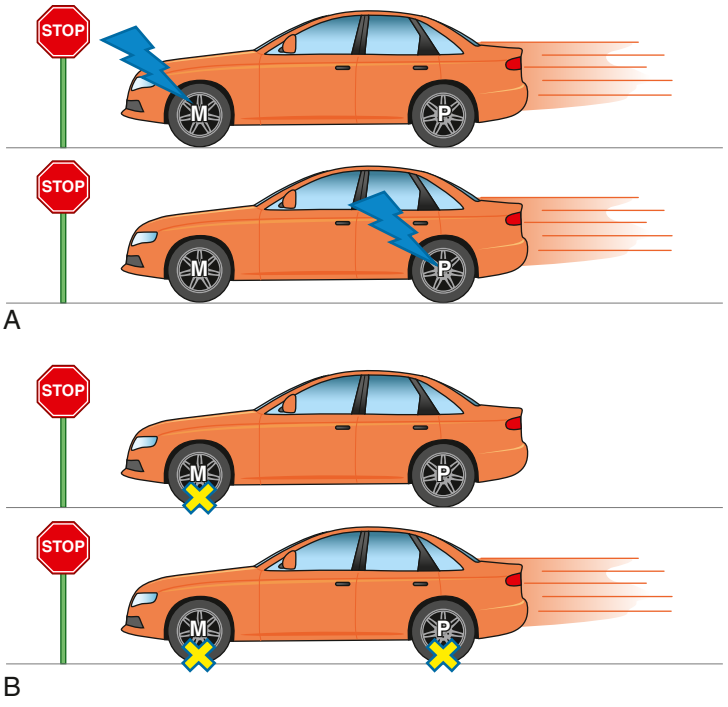

FIGURE 166-1. Oncogenes and tumor suppressor genes: the accelerators and brakes of cancer. A, Oncogenes act as the accelerators of cancer cells, driving forward even when the cell should stop (STOP sign). Oncogenic alterations such as mutations can occur in either the maternal allele (M front axle) or paternal allele (P rear axle) and will therefore cause the cell to continue to proliferate. In contrast (**B**), tumor suppressor genes are the brakes of the cell cycle. If a mutation or alteration disables only the front brakes or only the rear brakes (maternal allele; M front axle in figure), the cell can still obey stop signals. However, if both front (M axle) and rear (paternal allele; P rear axle) are disabled, the cell continues to go forward through normal stop signaling. Blue lightning bolts represent gain-of-function mutations in oncogenes; yellow X marks represent loss-of-function mutations in tumor suppressor genes.

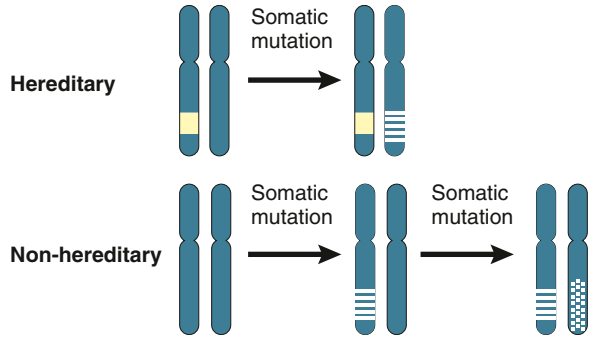

FIGURE 166-2. Knudson's two-hit model of cancer development. Biallelic inactivation (yellow band) is required for tumor initiation. In familial cancer syndromes, the first "hit" is inherited in the germline, requiring only a single somatic second "hit" (white stripes) to initiate carcinogenesis. In sporadic tumors, the first hit occurs in a single cell, and still requires the second somatic "hit" to occur in the same cell in order for tumor initiation to ensue. (Originally appearing in Jozwiak J, Jozwiak S, Wlodarski P. Possible mechanisms of disease development in tuberous sclerosis. *The Lancet Oncology*. 2008:Jan;9[1]:73-9.)

one allele is mutated) because a gain-of-function mutation would exert an effect even in the presence of the normal protein still being produced by the other wild-type allele (Fig. 166-1A). These mutations in oncogenes typically occur in regions that are known to regulate the corresponding protein's activity, such as kinase domain mutations that render the protein constitutively activated. An increased copy number of an oncogene can have a similar effect. Other examples are translocations and rearrangements, such as when the *BCR-ABL* translocation juxtaposes two genes so that the oncogene's normal function is in an "always on" state. In contrast, tumor suppressor genes generally require a loss-of-function genetic alteration, which by necessity usually requires alterations in both alleles of the cell (Fig. 166-1B). Accordingly, loss-of-function mutations observed in many tumor suppressor genes generally lead to premature truncation of the protein, such as nonsense mutations and insertion/deletion frameshift mutations. In addition, larger genomic alterations, such as deletions or loss of an entire gene or chromosome, are another mechanism for inactivating tumor suppression. Beyond these generalizations in the types of genetic alterations seen in oncogenes and tumor suppressor genes, exceptions also exist. For example, *TP53* is a tumor suppressor gene, yet the most frequent mutations found in human cancers are missense mutations, rather than frame shifts or deletions. These common missense mutations confer a dominant negative effect and prevent the p53 protein from forming tetramers, thereby usually resulting in a loss-of-function, although gain-of-function mutations in *TP53* have also been described. In contrast, certain deletions in the epidermal growth factor receptor (EGFR) gene (*ERBB1*) eliminate autoregulatory domains, thereby resulting in constitutive activation of this oncogene. Ultimately the nature and type of mutations in oncogenes and tumor suppressor genes are predicated on the domains of the protein that would readily lend themselves to activate or inactivate the gene, respectively.

GERMLINE VERSUS SOMATIC DNA ALTERATIONS IN CANCER

The human body is composed of trillions of cells, and each cell generally contains two copies (diploid) of the genome. Mature red blood cells and platelets are among the few cell types that are devoid of DNA, and gametes (i.e., ova and sperm) have only one copy of the genome (haploid), thereby allowing the zygote to inherit a haploid genome from each parent. DNA obtained from normal cells is often referred to as germline because it is derived from parental ova and sperm, which are also termed germ cells. By definition, germline DNA (sometimes also referred to as constitutional DNA) is heritable in that humans receive all their DNA from both parents. Any mutations that are present in a heterozygous fashion in germline DNA can be passed down to progeny, with a 50/50 chance of inheriting the mutant allele.

The majority of germline DNA alterations that lead to familial cancer syndromes are mutations in tumor suppressor genes.[1] In fact, the strictest genetic definition of a tumor suppressor is an alteration in a gene that predisposes to tumor formation. Indeed, pedigrees from families with hereditary predispositions to cancer have shed much light on the nature of tumor suppressor genes, including the "two-hit" hypothesis as well as the identification of key tumor suppressor genes such as *RB1, BRCA1, BRCA2* and *APC*. Since biallelic inactivation of a tumor suppressor is required to initiate cancer, familial cancer syndromes would be expected to follow an autosomal recessive pattern of inheritance. However, the majority of tumor suppressor genes are lethal to the embryo if two mutant copies are present in the zygote, so homozygosity is rarely seen in families with known mutations of a given tumor suppressor gene. Rather, a "second hit" (or inactivation of the second allele) occurs only in the cell or cells that are destined to become a tumor (Fig. 166-2). This second loss-of-function event can occur in a number of different ways, including loss of the gene, a new mutation, or epigenetic silencing. Regardless of the mechanism, because this second event occurs only in a single cell and therefore will not be present in gametes, these alterations are referred to as somatic changes. Because the human body has trillions of cells, the lifetime chance that any single cell in an individual who has inherited one mutant allele in a tumor suppressor gene will obtain a "second hit" is quite high; as a result, the pattern of inheritance for familial cancer syndromes is generally autosomal dominant. However, cancer is a result of the accumulation of many DNA alterations, so even the complete loss of function of a tumor suppressor gene is generally not sufficient to form a mass or tumor (Fig. 166-3). This requirement explains why, despite the autosomal pattern of inheritance, many familial cancer syndromes have incomplete penetrance (i.e., not all carriers will develop cancer).

Germline DNA alterations that predispose to tumor and cancer formation also explain the relatively earlier onset of diagnosis for familial cancers relative to sporadic counterparts. In the former, the initiation of cancer is accelerated because every diploid cell in the body has a lifelong functional loss of one of the two tumor suppressor genes. In the sporadic situation, by comparison, this "first hit" must occur somatically in any given cell.

With the advent of large cancer DNA sequencing, the complexity of human cancers has become apparent. Although these studies generally support the notion that most cancers arise from a stepwise accumulation of somatic genetic mutations and alterations that result in early proliferative changes, precancerous tumors, and then invasive disease, notable exceptions exist. For instance, pathogens such as viruses can initiate or predispose an individual to cancer. As an example, cells that are infected with human papillomaviruses (Chapter 344) can express proteins that inactivate key tumor suppressor genes such as p53 and RB. This suppression, which is to the advantage of the virus because cell proliferation is needed for viral replication, also establishes a situation akin

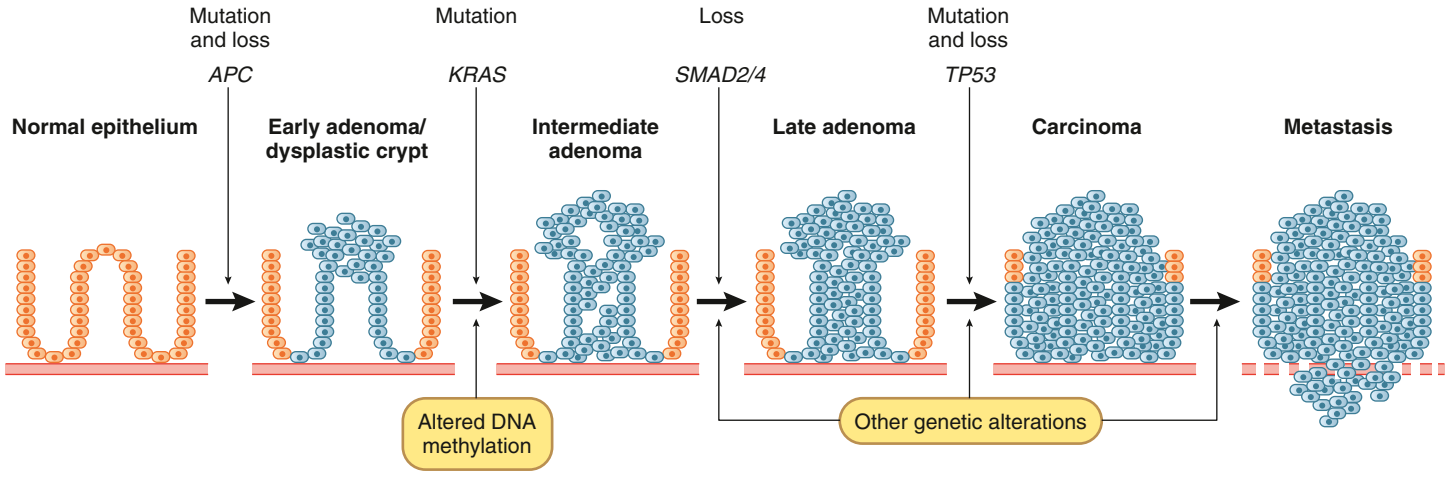

FIGURE 166-3. The stepwise progression from normal colonic epithelium to invasive cancer. Progression from normal epithelium through adenoma to colorectal carcinoma is characterized by accumulated genetic and epigenetic alterations of oncogenes and tumor suppressor genes, also known as "the Vogelgram" after Bert Vogelstein, MD. (From Davies RJ, Miller R, Coleman N. Colorectal cancer screening: prospects for molecular stool analysis. *Nature Reviews Cancer*. 2005;Mar;5[3]:199-209.)

to acquiring mutations within tumor suppressor genes. Similar to nonviral cancers, however, this suppression is an initiating event that is not sufficient to form a tumor because additional genetic events are required for a truly invasive cancer.

Sequencing studies have also shown that the number of mutations or genetic alterations required for carcinogenesis is highly variable, especially when considering the requirements for distant metastases. However, statistical analyses in pancreatic cancers suggest that two alterations may be sufficient.[2] Genomic and epidemiologic data suggest that increased cellular proliferation can be associated with an increased risk of cancer, but that the development of mutations, and therefore cancer, has a strong element of randomness or "bad luck."[3]

GENETIC INSTABILITY, CLONAL EVOLUTION, AND TUMOR HETEROGENEITY

When normal cells divide, surveillance and repair mechanisms within the cells ensure that any DNA errors are corrected prior to cytokinesis (i.e., cell division). This process ensures near-perfect fidelity and prevents the emergence of diseases, such as cancer, that are related to somatic alterations in DNA. In cancer cells, such fail-safe mechanisms are disabled, thereby allowing cells to accumulate DNA mutations, copy number changes, and genomic rearrangements. But even more daunting is that the lack of DNA repair mechanisms leads to a dynamic, ongoing process of Darwinian evolution. As cancer cells continue to divide, each resultant cell is slightly different from the next with regard to their genomes. Deleterious mutations or alterations will result in cell death, whereas advantageous changes will enable a clonal growth expansion, even as additional mutations and alterations are continually occurring within this clonal population. Although some rare cancers are exceptions to this model, modern sequencing studies of metastases support this notion, with many cancer cells within the same patient harboring so-called "private" mutations. Although some of these mutations may have no functional consequence and are therefore termed "passenger" mutations, these mutations along with other genomic alterations underscore the ongoing genetic instability of human cancers.

This continuing clonal evolution sets the stage for the development of cancer. Hallmarks (see Table 166-1) include angiogenesis, evasion of the immune system, escape from cell death and tumor suppressors, and a sustained proliferative capacity—all due to genetic alterations that directly or indirectly arise from genetic instability. Some of the mechanisms of genetic instability have been elucidated and can be classified into two broad categories. Chromosomal instability is a more common type of genetic instability in human cancers and is exemplified by copy number alterations and rearrangements. Cancers with chromosomal instability are therefore more likely to have amplifications, deletions, and aneuploidy. Conversely, genetic instability at the nucleotide level is also a much less common but well-described phenomenon, and sequencing has revealed that such cancers have thousands of mutations within their genomes and are often diploid or near diploid in contrast to tumors with chromosomal instability. This increase in mutations has been frequently referred to as high "tumor mutation burden." Several genes have been shown to mediate chromosomal instability, and many genes have also been shown to regulate an increase in tumor mutation burden. The most notable example of the latter is the mismatch repair genes and their regulation of a specific form of mutation burden termed microsatellite instability. Tumors with microsatellite instability generally have a high tumor mutation burden and a relatively diploid genome. The genetic defects that lead to microsatellite instability are the inactivation of DNA mismatch repair genes. In normal cells the presence of these mismatch repair proteins will ensure that any DNA mistakes occurring with cell replication will be corrected. The mismatch repair system is especially important for recognizing and correcting DNA mistakes that occur at base pair "repeat" sequences including mono-, di-, tri- and tetra-nucleotide sequences such as AAAAA, ATATAT, ATCATCATC, and ACGTACGTACGT, respectively. These areas of DNA repeats are scattered throughout the human genome and are termed microsatellite sequences. Tumors with microsatellite instability have difficulty repairing these microsatellite regions during DNA replication due to the lack of mismatch repair proteins. As a result, mismatch repair gene mutations, alterations, and epigenetic silencing occur in tumors with microsatellite instability. Most notably, right-sided colon cancers often have epigenetic silencing of mismatch repair proteins, with the two most frequently affected genes being *MLH1* and *MSH2*. Although not growth suppressors, *MLH1* and *MSH2* meet the definition of a tumor suppressor because germline mutations in either of these genes lead to hereditary nonpolyposis colorectal cancers and other malignancies, such as ovarian and endometrial cancers, also known as Lynch syndrome.[4] Examples of hereditary cancer risk syndromes are summarized in Table 166-2.

The genetic instability that drives tumor heterogeneity often makes cancers refractory to treatment and cure. Even though a therapeutic agent may be effective in the majority of cancer cells within a population, preexisting mutations and other alterations will then be selected as a new dominant population. In essence, the same Darwinian evolution that leads to cancer and metastases

TABLE 166-1 HALLMARKS OF CANCER

- Self-sufficiency in growth signals
- Insensitivity to anti-growth signals
- Evading apoptosis
- Limitless replicative potential
- Sustained angiogenesis
- Tissue invasion and metastasis
- Reprogramming energy metabolism
- Evading immune response
- Genome instability and mutation
- Tumor-promoting inflammation

Hanahan and Weinberg proposed in 2000 that there are six essential alterations in cell physiology ("hallmarks of cancer") that collectively dictate malignant growth, listed in the first six bullets. (Hanahan D, Weinberg RA. The hallmarks of cancer. *Cell*. 2000;100:57-70.) A decade later, they updated the list by adding four additional hallmarks, listed in the last four bullets. (Hanahan D, Weinberg RA. Hallmarks of cancer: the next generation. *Cell*. 2011;144:646-674.) There have been subsequent attempts to simplify the list by merging some of these core traits of most cancers. (Fouad YA, Aanel C. Revisiting the hallmarks of cancer. *Am J Cancer Res*. 2017;7:1016-1036.)

TABLE 166-2 COMMON FAMILIAL CANCER SYNDROMES

SYNDROME	GENE	ASSOCIATED TUMORS
TUMOR SUPPRESSOR MUTATIONS		
Cowden	*PTEN*	Breast, thyroid, endometrial, colorectal, kidney, melanoma
Familial adenomatous polyposis	*APC*	Colorectal, stomach, intestinal, hepatoblastoma, thyroid, pancreatic, adrenal, bile duct, medulloblastoma
Familial gastric carcinoma	*CDH1* (E-Cadherin)	Stomach, breast
Familial malignant melanoma	*CDKN2* ($p16^{INK4A}$ and $p14^{ARF}$), *CDK4*	Melanoma, pancreatic
Familial Wilms tumor	*WT1*	Wilms (kidney)
Hereditary leiomyomatosis and renal cell carcinoma	*FH*	Cutaneous leiomyomas, uterine leiomyomas (fibroids), renal cell carcinoma
Hereditary retinoblastoma	*RB1* (pRB)	Retinoblastoma
Hereditary paraganglioma	*SDHA, SDHB, SDHC, SDHD*, or *SDHAF2*(succinate dehydrogenase)	Paraganglioma, pheochromocytoma
Li-Fraumeni	*TP53* (p53)	Osteosarcoma, soft tissue sarcoma, leukemia, breast, brain, adrenal, melanoma, Wilms, stomach, colorectal, pancreatic, esophageal, lung, gonadal germ cells
Multiple endocrine neoplasia type 1	*MEN1*	Parathyroid, pituitary, islet cell, adrenal, carcinoid
Neurofibromatosis type 1	*NF1*	Neurofibroma, glioma, leukemia, breast, rhabdomyosarcoma, gastrointestinal stromal
Neurofibromatosis type 2	*NF2*	Neuromas, schwannomas, meningiomas, astrocytomas, gliomas
Peutz-Jeghers syndrome	*LKB1*	Colon, intestine, stomach, pancreas, cervix, ovary, testis, breast, thyroid
Von Hippel-Lindau	*VHL*	Kidney, adrenal, pheochromocytoma
DNA REPAIR GENE MUTATIONS		
Ataxia telangiectasia	*ATM*	Leukemia, lymphoma
Bloom	*BLM*	Leukemia, multiple solid tumors
Fanconi anemia	*FANCA, FANCC, FANCD2, FANCE, FANCF*, or *FANCG*	Leukemia, multiple solid tumors
Hereditary breast and ovarian cancer	*BRCA1* or *BRCA2*	Breast, ovary, pancreatic, fallopian tube
Lynch (hereditary nonpolyposis colon cancer)	*MLH1, MSH2, MSH6*, or *PMS2*	Colorectal, endometrial, stomach, breast, ovarian, intestinal, pancreatic, prostate, urinary tract, liver, kidney
MYH-associated polyposis	*MUTYH*	Colorectal, intestinal
Xeroderma pigmentosum	*XPA, XPC, ERCC2, ERCC3, ERCC4, ERCC5*, or *DDB2*	Skin (basal cells, squamous), melanoma, tongue, eye
ONCOGENE MUTATIONS		
Costello	*HRAS*	Papilloma, rhabdomyosarcoma, neuroblastoma
Noonan	*PTPN11, SOS1, KRAS, NRAS, RAF1*, or *BRAF* (Ras-Erk pathway regulators)	Leukemia, rhabdomyosarcoma, neuroblastoma
Familial malignant melanoma	*CDK4*	Melanoma
Multiple endocrine neoplasia type 2	*RET*	Thyroid, parathyroid, pheochromocytoma
Hereditary papillary renal cell carcinoma	*MET*	Type 1 papillary renal cell carcinoma

continues when the cancer is subjected to various chemotherapies and targeted therapies.

CANCER GENETICS AND TARGETED THERAPIES

A fundamental goal of translating genetic information about cancers is to use this knowledge for risk assessment, diagnosis, screening, and therapy. Targeted therapies are based on an understanding of how oncogenes and tumor suppressor genes drive cancer growth and then developing strategies to disrupt these mechanisms. One of the earliest examples is the *ERBB2* (HER2) oncogene and breast cancer. HER2 amplification occurs in 15 to 20% of breast cancers (Chapter 183) and is associated with an aggressive behavior and worse prognosis. The humanized monoclonal antibody, trastuzumab, was one of the first examples of a drug against a therapeutic target, because only patients with HER2 amplification/overexpression in their tumors appeared to derive benefit from this therapy. The successes of trastuzumab and additional HER2 targeted therapies (e.g., pertuzumab, neratinib, tucatinib, ado-trastuzumab, and trastuzumab deruxtecan) have changed the natural history of HER2-positive breast cancers such that they are now a highly favorable group with good prognosis (Chapter 183). This success serves as a strong reminder that understanding the underlying biology of cancer can lead to therapies that can have a dramatic impact on the disease.

Many other effective targeted therapies have shown noteworthy success (Table 166-3). Examples include imatinib, which inhibits the BCR-ABL fusion protein in chronic myelogenous leukemia (CML) (Chapter 170), thereby converting a once-fatal disease into a manageable chronic condition in which the majority of patients can now live out their natural lives.[5] In certain forms of lung cancer (Chapter 177), genomic alterations that occur with 1 to 10% frequency can be targeted with relatively specific drugs that can have a profound effect.[6]

The study of mechanisms of drug resistance has also led to an improved understanding of predictors of resistance and the development of targeted therapies that can overcome this resistance. For example, gefitinib and erlotinib are two small molecule inhibitors against certain activating mutations found within the EGFR oncogene in non–small cell lung cancers (Chapter 177). Remarkably, sequencing of tumors that developed resistance to these drugs revealed that many cancers acquired a specific recurrent mutation (i.e., T790M). Further laboratory research and clinical development led to approval of next-generation receptor tyrosine kinase inhibitors capable of overcoming cancers that harbored these mutations. Similar findings have also emerged for other diseases. As an example, accumulating evidence suggests that the emergence of resistance mutations in the estrogen receptor alpha (*ESR1*) gene's

TABLE 166-3 EXAMPLES OF TARGETED CANCER THERAPIES

THERAPEUTIC AGENT	TYPE	TARGET	DISEASE	INDICATION	COMPANION TEST
Imatinib Dasatinib Nilotinib	Small molecule	BCR-ABL	CML, ALL	Philadelphia chromosome–positive	Cytogenetic analysis, FISH, PCR
Ponatinib Bosutinib	Small molecule		CML and AML resistant to prior tyrosine kinase inhibitor therapy	Philadelphia chromosome–positive	Cytogenetic analysis, FISH, RT-PCR
Imatinib	Small molecule	c-Kit	Gastrointestinal stromal tumors	CD117 (c-Kit) positive	Immunohistochemistry (c-Kit PharmDx)
Cetuximab Panitumumab	Monoclonal antibody	EGFR	Colorectal cancer, head and neck	*KRAS* wild-type in colon cancer	PCR (*therascreen* KRAS RGQ Kit)
Gefitinib Erlotinib Afatinib Osimertinib	Small molecule	EGFR	NSCLC	Mutant EGFR	PCR (*therascreen* EGFR RGQ PCR Kit, cobas EGFR Mutation Test)
Trametinib/dabrafenib Cobimetinib/vemurafenib	Small molecule	MEK/BRAF	Melanoma	V600 mutant BRAF	PCR (THxID, cobas 4800 BRAF V600 Mutation Test)
Sotorasib	Small molecule	KRAS	Lung	G12C mutant KRAS	PCR (*therascreen* KRAS RGQ Kit) next-generation sequencing,
Trastuzumab Pertuzumab Trastuzumab emtansine (antibody drug conjugate of trastuzumab) Trastuzumab deruxtecan (antibody drug conjugate of trastuzumab)	Monoclonal antibody	HER2	Breast, stomach, gastroesophageal	HER2 positive	Immunohistochemistry (PATHWAY, InSite, Bond Oracle, HercepTest), FISH (Inform, PathVysion, SPOT-Light, HER2 CISH PharmDx)
Lapatinib Neratinib	Small molecule	HER2, EGFR	Breast	HER2 positive	HER2 testing as above
Bevacizumab	Monoclonal antibody	VEGF	NSCLC, metastatic colorectal, metastatic kidney, glioblastoma		
Ipilimumab	Monoclonal antibody	CTLA-4	Melanoma		
Pembrolizumab Nivolumab	Monoclonal antibody	PD-1	Melanoma, NSCLC, microsatellite instability–positive cancers, cancers with a high tumor mutation burden		Immunohistochemistry for PDL1, microsatellite testing, next-generation sequencing for high tumor mutation burden
Olaparib, rucaparib, talazoparib, niraparib	Small molecule	PARP1 (due to inactivation of BRCA pathway)	Breast, ovarian, prostate, pancreas	Germline and somatic *BRCA1* or *BRCA2* pathogenic variants	Next-generation sequencing of germline and/or tumor DNA

Companion tests in parentheses are U.S. Food and Drug Administration–stipulated tests for certain uses of the corresponding drug.
ALL = acute lymphoblastic leukemia; AML = acute myeloid leukemia; *BRCA1* = breast cancer gene 1; *BRCA2*; breast cancer gene 2; CML = chronic myelogenous leukemia; FISH = fluorescence in situ hybridization; NSCLC = non–small cell lung cancer; PARP = poly adenosine diphosphate-ribose polymerase; PCR = polymerase chain reaction; PDL1 = programmed death-ligand 1; RT-PCR = reverse transcription polymerase chain reaction.

ligand binding domain occur with relatively high frequency in patients whose metastatic hormone receptor-positive breast cancer (Chapter 183) is treated with aromatase inhibitors.[7] Strategies to overcome these *ESR1* mutations with newer combination endocrine therapies are being tested in clinical trials.

Although other resistance mutations have emerged through further sequencing efforts, additional clarity has been brought about with the understanding of gene mutations and their impact on signaling pathways. For example, given the sequence of events required for activation of the MAP kinase pathway (E-Fig. 166-1), it would be predicted that antibody therapies against EGFR would be ineffective in tumors that harbor an activating mutation in *KRAS*, because the activating "lesion" in this particular case is distal to EGFR. Therefore, inhibition of EGFR using a therapeutic monoclonal antibody would not yield any effect. This indeed was shown to be true and has led to the requirement for patients' tumors to be sequenced for *KRAS* prior to receiving anti-EGFR antibody therapies to ensure that only wild-type *KRAS* is present in the cancer.[8] The success and approval of mutation-specific KRAS inhibitors[9] may allow for future combination therapies.

Additional opportunities for therapeutic targeting have arisen through a better understanding of cancer genetics. "Synthetic lethality" is an idea originally based on the realization that the absence of the BRCA proteins would lead to a therapeutic vulnerability, which could be exploited because the noncancerous cells in the affected individual would still harbor 50% of a given BRCA protein due to the intact wild-type allele (Fig. 166-4). Hence, original laboratory studies demonstrated that poly adenosine diphosphate-ribose polymerase (PARP) inhibitors could effectively kill *BRCA* null cells but spare their wild-type counterparts.[10] These findings were rapidly translated into clinical trials that have led to the approval of PARP inhibitors for some ovarian (Chapter 184), breast (Chapter 183), pancreas (Chapter 180), and prostate (Chapter 186) cancers.

Although targeted therapies are generally initially approved in a single cancer tissue type, it is the target, not the particular cell type, that determines susceptibility to a targeted therapy. For example, HER2 amplified/overexpressing gastric cancers (Chapter 178) can respond to trastuzumab. Similarly, BRAF V600 oncogenic mutations generally respond to targeted

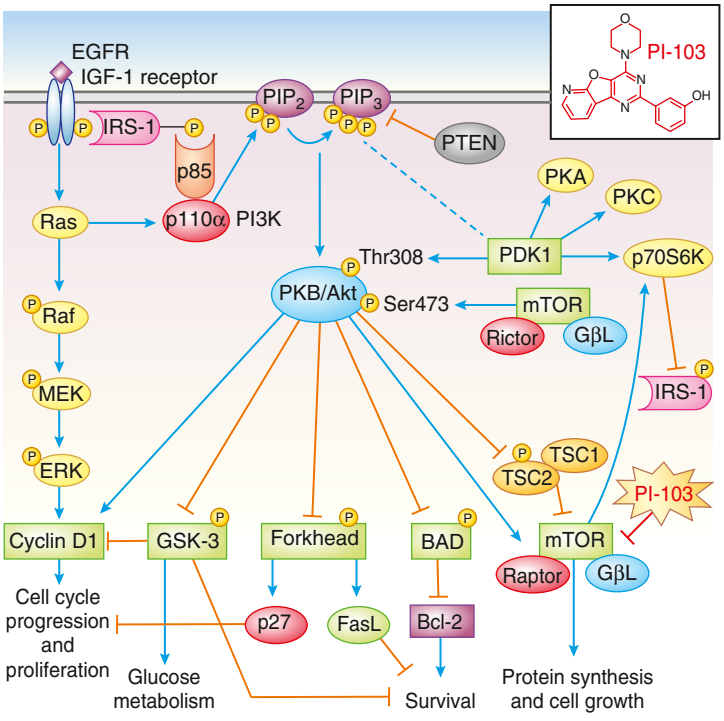

E-FIGURE 166-1. The MAP kinase and PI3 kinase/AKT signaling pathways. Shown are pathways starting from the receptor tyrosine kinase EGFR. (Adapted from Workman P, Clarke PA, Guillard S, et al. Drugging the PI3 kinome. *Nat Biotechnol*. 2006;24:794-796.)

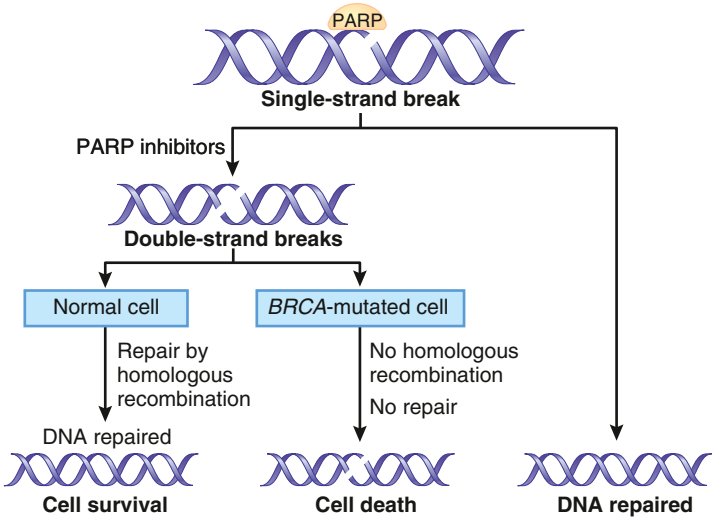

FIGURE 166-4. Poly(ADP-ribose) polymerase (PARP) inhibitors and synthetic lethality in BRCA null cells. PARP1 binds to DNA single-strand breaks that frequently occur during the cell cycle and recruits other enzymes to repair damaged DNA. Failure to repair DNA will eventually lead to further DNA damage and cell death. The BRCA pathway proteins can also repair this damaged DNA via homologous recombination. Because BRCA mediated cancers lack a BRCA protein, this ability to repair DNA via homologous recombination is lost. This is the basis for synthetic lethal and targeted therapy with PARP inhibitors in patients with BRCA-related cancers. DNA damage that occurs after inhibition of PARP activity cannot be repaired in BRCA null cancers, resulting in cell death. As BRCA proteins remain intact in noncancerous cells due to the retention of one functional copy of a *BRCA* gene, PARP inhibition selectively kills cancer cells. (From Sonnenblick A, de Azambuja E, Azim HA Jr, et al. An update on PARP inhibitors—moving to the adjuvant setting. *Nat Rev Clin Oncol*. 2015;12:27-41.)

therapies of V600 inhibitors, although colorectal cancers seem to be a notable exception.[11] Interestingly, suppression with BRAF V600 mutant inhibitors can lead to dysregulation of feedback networks in normal and cancerous cells. Combination therapies, including inhibitors of MEK, which is a molecule distal to BRAF in the MAP kinase pathway (E-Fig. 166-1), result in more efficacious therapy with fewer side effects. Another example of molecular targeted therapies is larotrectinib, which is an inhibitor of TRK proteins that have been made constitutively active via translocation of *TRK* genes with other genes, also known as fusion partners. This potent inhibitor has striking antineoplastic activity against a variety of tumor types, provided they have either a *TRK1*, *TRK2*, or *TRK3* translocation that leads to constitutive activation.[12] Both larotrectinib and entrectinib, which is another *TRK* inhibitor, are now FDA-approved for responsive cancer.

Research also led to the first approved antineoplastic therapy based upon the type of genetic instability. Melanomas and squamous cell lung cancers with high mutation burden are more likely to respond to immune check point inhibitors, in part because ultraviolet light and tobacco exposure, respectively, led to their high mutation burdens. Cancers with a high tumor mutation burden imparted by microsatellite instability have a significantly higher response rate to immune checkpoint inhibitor therapies, often even if such tumors have become refractory to all other therapies.[13]

CANCER GENETICS FOR DIAGNOSTICS

GENE EXPRESSION PROFILING FOR PROGNOSIS AND PREDICTION

The majority of RNA prognostic and predictive tests do not measure DNA alterations but instead assess relative levels of RNA within a tumor. These RNA levels are then used for various algorithms that have been validated for both prognostic information (i.e., the likelihood of recurrence and/or survival over a defined time frame) as well as predictive power (i.e., the likelihood of a patient benefitting from a given therapy). Several such tests have been validated in prospective trials[14] to help inform clinical decisions.

DIAGNOSTIC TESTS FOR TARGETED THERAPIES

Targeted therapies require genetic testing to select patients who will have the highest likelihood of responding to a given agent. For example, early studies of trastuzumab would likely have failed had patients not been preselected for HER2 amplification, given that the majority of breast cancers are HER2 negative. Next-generation sequencing (also see Chapter 33) involves generation of DNA "libraries" that are sequenced simultaneously (i.e., massively and in parallel), thereby generating terabytes or more of data. Redundant sequencing is needed to ensure that each nucleotide is sequenced enough times to differentiate true mutations from artifacts of the next-generation sequencing process. Each DNA molecule that is sequenced is then aligned against a reference genome to determine the presence or absence of mutations.

Because reference genomes are derived from a variety of sources, it is not always possible to distinguish a mutation from a normal variant that could exist within the population. As such, "germline sequencing and filtering" is becoming more commonplace for tumor sequencing. This technique entails obtaining a normal DNA sample from the patient whose tumor is being sequenced and subjecting the normal germline DNA to next-generation sequencing. After sequencing and alignment, the germline DNA is electronically subtracted from the tumor DNA to reveal only somatic mutations. Although this process can reduce the number of false-positive mutations, it also can potentially filter out important germline mutations that may have therapeutic relevance for a given cancer (e.g., *BRCA1*, *BRCA2*, *MLH1*, and *MSH2*). Newer bioinformatic methods may circumvent these issues by either not filtering germline mutations in key genes or identifying the likelihood of somatic versus germline mutations with the use of statistical algorithms.

Ongoing clinical trials are trying to exploit cancer DNA as a general diagnostic screening tool. For example, multitarget analysis of stool specimens using mutation testing, epigenetic markers, and a hemoglobin immunoassay has a relatively high sensitivity and specificity for detecting early-stage colorectal cancers,[15] and is now FDA-approved for colorectal cancer screening.

Next-generation sequencing has also brought to reality the concept of a "liquid biopsy," which is testing for circulating cell-free DNA for cancer diagnostics. All cells, cancerous and normal, shed DNA into the circulation.[16] This cell-free DNA can be isolated and analyzed by next-generation sequencing for a variety of purposes including identifying circulating tumor DNA using various substrates such as plasma, serum, urine, saliva, and others.[17,18] Next-generation sequencing, polymerase chain reaction testing, and other technologies have now become commonplace for detecting tumor mutations in the circulation.[19] Cell-free DNA is also being studied as a marker for residual cancer burden, response to therapies, and prognosis. In addition, asymptomatic clonal hematopoiesis, whereby precancerous stem cells accumulate genetic mutations that increase the risk of malignant transformation,[20] is another potential marker of prognosis. Interventions based on these new technologies have the potential to revolutionize how patients are treated for both early- and late-stage cancers, thereby allowing for precise knowledge of whether therapies are truly eradicating microscopic residual disease and effecting cures.

GENERAL REFERENCES

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167 MYELODYSPLASTIC SYNDROMES

RICHARD M. STONE

DEFINITION

The myelodysplastic syndromes include a heterogeneous group of bone marrow failure syndromes collectively characterized by ineffective hematopoiesis that results in peripheral blood cytopenias, most commonly anemia.[1] In some patients, the distinction between myelodysplastic syndrome and acute myeloid leukemia (AML; Chapter 168) may be challenging.[2] Although the dominant clinical feature of myelodysplastic syndromes is bone marrow failure, myelodysplastic syndromes are clonal disorders and therefore classified as hematopoietic neoplasms by the World Health Organization (WHO) and other organizations.

EPIDEMIOLOGY

The incidence and prevalence of myelodysplastic syndromes have been difficult to estimate accurately, in part because of varying definitions and

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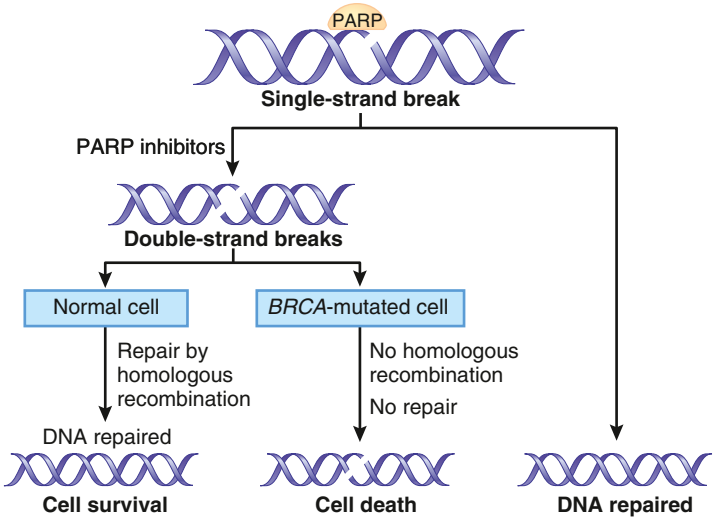

FIGURE 166-4. Poly(ADP-ribose) polymerase (PARP) inhibitors and synthetic lethality in BRCA null cells. PARP1 binds to DNA single-strand breaks that frequently occur during the cell cycle and recruits other enzymes to repair damaged DNA. Failure to repair DNA will eventually lead to further DNA damage and cell death. The BRCA pathway proteins can also repair this damaged DNA via homologous recombination. Because BRCA mediated cancers lack a BRCA protein, this ability to repair DNA via homologous recombination is lost. This is the basis for synthetic lethal and targeted therapy with PARP inhibitors in patients with BRCA-related cancers. DNA damage that occurs after inhibition of PARP activity cannot be repaired in BRCA null cancers, resulting in cell death. As BRCA proteins remain intact in noncancerous cells due to the retention of one functional copy of a *BRCA* gene, PARP inhibition selectively kills cancer cells. (From Sonnenblick A, de Azambuja E, Azim HA Jr, et al. An update on PARP inhibitors—moving to the adjuvant setting. *Nat Rev Clin Oncol*. 2015;12:27-41.)

therapies of V600 inhibitors, although colorectal cancers seem to be a notable exception.[11] Interestingly, suppression with BRAF V600 mutant inhibitors can lead to dysregulation of feedback networks in normal and cancerous cells. Combination therapies, including inhibitors of MEK, which is a molecule distal to BRAF in the MAP kinase pathway (E-Fig. 166-1), result in more efficacious therapy with fewer side effects. Another example of molecular targeted therapies is larotrectinib, which is an inhibitor of TRK proteins that have been made constitutively active via translocation of *TRK* genes with other genes, also known as fusion partners. This potent inhibitor has striking antineoplastic activity against a variety of tumor types, provided they have either a *TRK1*, *TRK2*, or *TRK3* translocation that leads to constitutive activation.[12] Both larotrectinib and entrectinib, which is another *TRK* inhibitor, are now FDA-approved for responsive cancer.

Research also led to the first approved antineoplastic therapy based upon the type of genetic instability. Melanomas and squamous cell lung cancers with high mutation burden are more likely to respond to immune check point inhibitors, in part because ultraviolet light and tobacco exposure, respectively, led to their high mutation burdens. Cancers with a high tumor mutation burden imparted by microsatellite instability have a significantly higher response rate to immune checkpoint inhibitor therapies, often even if such tumors have become refractory to all other therapies.[13]

CANCER GENETICS FOR DIAGNOSTICS

GENE EXPRESSION PROFILING FOR PROGNOSIS AND PREDICTION

The majority of RNA prognostic and predictive tests do not measure DNA alterations but instead assess relative levels of RNA within a tumor. These RNA levels are then used for various algorithms that have been validated for both prognostic information (i.e., the likelihood of recurrence and/or survival over a defined time frame) as well as predictive power (i.e., the likelihood of a patient benefitting from a given therapy). Several such tests have been validated in prospective trials[14] to help inform clinical decisions.

DIAGNOSTIC TESTS FOR TARGETED THERAPIES

Targeted therapies require genetic testing to select patients who will have the highest likelihood of responding to a given agent. For example, early studies of trastuzumab would likely have failed had patients not been preselected for HER2 amplification, given that the majority of breast cancers are HER2 negative. Next-generation sequencing (also see Chapter 33) involves generation of DNA "libraries" that are sequenced simultaneously (i.e., massively and in parallel), thereby generating terabytes or more of data. Redundant sequencing is needed to ensure that each nucleotide is sequenced enough times to differentiate true mutations from artifacts of the next-generation sequencing process. Each DNA molecule that is sequenced is then aligned against a reference genome to determine the presence or absence of mutations.

Because reference genomes are derived from a variety of sources, it is not always possible to distinguish a mutation from a normal variant that could exist within the population. As such, "germline sequencing and filtering" is becoming more commonplace for tumor sequencing. This technique entails obtaining a normal DNA sample from the patient whose tumor is being sequenced and subjecting the normal germline DNA to next-generation sequencing. After sequencing and alignment, the germline DNA is electronically subtracted from the tumor DNA to reveal only somatic mutations. Although this process can reduce the number of false-positive mutations, it also can potentially filter out important germline mutations that may have therapeutic relevance for a given cancer (e.g., *BRCA1*, *BRCA2*, *MLH1*, and *MSH2*). Newer bioinformatic methods may circumvent these issues by either not filtering germline mutations in key genes or identifying the likelihood of somatic versus germline mutations with the use of statistical algorithms.

Ongoing clinical trials are trying to exploit cancer DNA as a general diagnostic screening tool. For example, multitarget analysis of stool specimens using mutation testing, epigenetic markers, and a hemoglobin immunoassay has a relatively high sensitivity and specificity for detecting early-stage colorectal cancers,[15] and is now FDA-approved for colorectal cancer screening.

Next-generation sequencing has also brought to reality the concept of a "liquid biopsy," which is testing for circulating cell-free DNA for cancer diagnostics. All cells, cancerous and normal, shed DNA into the circulation.[16] This cell-free DNA can be isolated and analyzed by next-generation sequencing for a variety of purposes including identifying circulating tumor DNA using various substrates such as plasma, serum, urine, saliva, and others.[17,18] Next-generation sequencing, polymerase chain reaction testing, and other technologies have now become commonplace for detecting tumor mutations in the circulation.[19] Cell-free DNA is also being studied as a marker for residual cancer burden, response to therapies, and prognosis. In addition, asymptomatic clonal hematopoiesis, whereby precancerous stem cells accumulate genetic mutations that increase the risk of malignant transformation,[20] is another potential marker of prognosis. Interventions based on these new technologies have the potential to revolutionize how patients are treated for both early- and late-stage cancers, thereby allowing for precise knowledge of whether therapies are truly eradicating microscopic residual disease and effecting cures.

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167 MYELODYSPLASTIC SYNDROMES

RICHARD M. STONE

DEFINITION

The myelodysplastic syndromes include a heterogeneous group of bone marrow failure syndromes collectively characterized by ineffective hematopoiesis that results in peripheral blood cytopenias, most commonly anemia.[1] In some patients, the distinction between myelodysplastic syndrome and acute myeloid leukemia (AML; Chapter 168) may be challenging.[2] Although the dominant clinical feature of myelodysplastic syndromes is bone marrow failure, myelodysplastic syndromes are clonal disorders and therefore classified as hematopoietic neoplasms by the World Health Organization (WHO) and other organizations.

EPIDEMIOLOGY

The incidence and prevalence of myelodysplastic syndromes have been difficult to estimate accurately, in part because of varying definitions and

ABSTRACT

The myelodysplastic syndromes include a group of clonal hematopoietic stem cell disorders defined by marrow failure, dysplastic cell morphology, and a risk of clonal evolution including to acute myeloid leukemia (AML). Most cases arise de novo, but 10 to 20% are a consequence of prior cytotoxic chemotherapy or radiation therapy, and myelodysplastic syndromes due to a germline predisposition are increasingly recognized. More than 40 genes are recurrently mutated in association with myelodysplastic syndromes, including genes encoding factors important in epigenetic patterning, chromatin remodeling, mRNA splicing, signal transduction, transcription, and DNA repair. More than one half of patients have cytogenetic abnormalities in marrow cells, usually aneuploidy such as monosomy 7 or trisomy 8, or a deletion of the long arm of chromosomes 5 or 20. The most widely used myelodysplastic syndrome classification system is the 2016 World Health Organization criteria. Because the natural history of myelodysplastic syndromes is highly variable, risk stratification using tools such as the 2022 Molecular International Prognostic Scoring system is important for counseling patients and choosing appropriate therapy. Only allogeneic hematopoietic cell transplantation offers the possibility of cure, but most patients with myelodysplastic syndromes are not transplant candidates due to advanced age and comorbid conditions. Approved disease-modifying therapies include azacitidine, decitabine, decitabine/cedazuridine, and lenalidomide. Supportive care with erythropoiesis-stimulating agents, luspatercept, transfusions, and iron chelation are important for some patients. Enrollment in clinical trials is essential given the poor outcomes, especially patients who have been failed by hypomethylating agents.

KEYWORDS

myelodysplastic syndromes
clonal hematopoiesis
bone marrow failure
azacitidine
decitabine
lenalidomide
hematopoietic growth factors
allogeneic hematopoietic cell transplantation

imprecise terminology historically, and also because myelodysplastic syndrome cases are incompletely captured by cancer registries. About 10,000 to 12,000 new cases are officially diagnosed each year, but analysis of Medicare claims suggests that the actual incidence of myelodysplastic syndromes is much higher, with at least 40,000 new U.S. cases per year—more than twice the incidence of AML. In addition, many geriatric patients have mild cytopenias and may have myelodysplastic syndromes that have been incompletely evaluated (e.g., they do not undergo bone marrow aspiration) and never are specifically diagnosed.

The primary risk factor for development of a myelodysplastic syndrome is aging, with disease resulting as a consequence of cumulative acquisition of somatic mutations in marrow stem cells. In Asia and Eastern Europe, a myelodysplastic syndrome is typically diagnosed at younger ages than in the West; in the United States, the median age at which myelodysplastic syndromes are diagnosed is about 71 years, whereas in China it is closer to 50 years. Overall, males are slightly more affected than females.

The rate at which myelodysplastic syndromes are diagnosed is slightly increased in workers in certain industries such as the petroleum industry and agricultural sector, probably because of exposure to agents that favor expansion of mutant clones. Individuals who have been exposed to ionizing radiation or to certain types of cytotoxic chemotherapy (i.e., alkylating agents such as chlorambucil or melphalan, or topoisomerase II inhibitors such as etoposide or doxorubicin) have an increased risk for developing myelodysplastic syndromes. The peak incidence at which a myelodysplastic syndrome is diagnosed after exposure to an alkylating agent or radiation is 5 to 10 years later, whereas it is 1 to 3 years after exposure to a topoisomerase inhibitor. This increased risk never completely disappears; even 50 years after the Hiroshima and Nagasaki atomic bomb events in Japan, radiation-exposed individuals continued to be diagnosed with myelodysplastic syndromes at a higher rate than the unexposed population. Patients with a chemotherapy or radiation exposure history are said to have therapy-related myelodysplastic syndromes.

PATHOBIOLOGY

Myelodysplastic syndromes are clonal disorders, by which it is meant that one or several stem or progenitor cells in the marrow that bear somatic gene mutations proliferate at the expense of healthy stem cells, and these mutation-bearing progeny eventually come to dominate the bone marrow. Clones can acquire additional mutations that give rise to subclones, which can contribute to progression of disease if they have a greater proliferation potential than the original mutant clone. The process of somatic mutation acquisition may be accelerated through exposure to radiation or DNA-damaging chemicals, but more important, such exposures can also select for small *TP53* or *PPM1D* mutant preexisting clones. The marrow microenvironment (i.e., nonhematopoietic stromal cells) appears to play an important role in supporting neoplastic clones.

Marrow cellularity is usually normal or increased in myelodysplastic syndromes, but excessive apoptosis (i.e., programmed cell death) of hematopoietic cells within the bone marrow accounts for the peripheral blood cytopenias. Although excessive apoptosis within the marrow characterizes earlier phases of myelodysplastic syndromes, as the disease progresses toward AML, intramedullary apoptosis may decrease. In addition, hematopoietic differentiation, which is disordered but still can proceed in earlier stages of the disease, may become completely impaired later in the disease course such that most developing hematopoietic cells are arrested at the myeloblast stage.

Large gains and losses of chromosomal material within the disease cells, detectable by routine metaphase karyotyping, are present in one half of patients with de novo myelodysplastic syndromes and in more than 80% of patients with therapy-related myelodysplastic syndromes. Genetic techniques such as array-based comparative genomic hybridization can uncover cryptic chromosomal deletions in some patients whose myelodysplastic syndromes are associated with normal karyotyping results.

More than 40 genes are now known to be recurrently mutated in myelodysplastic syndromes,[3] but most of these mutations are also commonly detected in AML and other myeloid neoplasms, albeit at different frequencies.[4] No single mutation dominates; myelodysplastic syndromes are associated with considerable genetic heterogeneity (Table 167-1). More than 90% of patients with myelodysplastic syndromes have at least one detectable clonal somatic mutation, which influences the clinical presentation and prognosis. Mutations affecting epigenetic patterning through DNA methylation and chromatin conformation (e.g., histone-DNA interactions) are common.[5] In addition, mutations affecting pre-mRNA splicing are frequent,[6] especially in patients with ring sideroblasts (i.e., erythroid precursors with abnormal perinuclear iron-containing mitochondria visible with Perls Prussian blue reaction) (see Fig. 167-1C); the specific genes that are mis-spliced and give rise to a myelodysplastic syndrome phenotype are as yet unclear.

Genetic bone marrow failure syndromes such as Schwachman-Diamond and Fanconi anemia (Chapter 151) are associated with myelodysplastic syndrome in children.[7] Up to 20% of adults with myelodysplastic syndrome may have a germline predisposition, and inherited forms of myelodysplastic syndrome, such as Schwachman-Diamond, may present in the sixth decade of life or later.

A subset of patients with pathologic findings that resemble a myelodysplastic syndrome will have autoimmune hematopoietic suppression, which may be driven by an expanded autoreactive T-lymphocyte population. Patients are more likely to have an immune component to their marrow failure if they are younger than 55 years and have a hypocellular marrow similar to what is seen in aplastic anemia, a normal chromosome pattern or trisomy 8 (rather than a more complex karyotype), a paroxysmal nocturnal hemoglobinuria cell population detectable by flow cytometry (Chapter 146), and HLA DR15 tissue type. Such patients may respond to immunosuppressive anti-T-cell therapies.

CLINICAL MANIFESTATIONS

Most patients with myelodysplastic syndromes come to medical attention because they have anemia. Anemia is present in 95% cases and is often macrocytic, but about 50% of patients also have neutropenia, thrombocytopenia, or both at the time of diagnosis.

The clinical course in myelodysplastic syndromes is dominated by complications of the cytopenias, including mucosal bleeding, recurrent infections, and exertional dyspnea and fatigue. Fatigue correlates poorly with the degree of anemia and may be in part due to cytokine release by the abnormal clonal cells. Paraneoplastic manifestations, including neutrophilic dermatosis (Sweet syndrome, Chapters 406 and 407), inflammatory arthritis, and other rheumatologic syndromes, occur in 10 to 15% of patients. Repeated transfusions of red cells can lead to transfusional hemosiderosis and organ dysfunction, including hepatic and cardiac disease. The frequency with which complications of iron overload occur, as well as the importance of chelation therapy in myelodysplastic syndromes, are controversial topics.[8]

DIAGNOSIS

Myelodysplastic syndromes are usually suspected when an older patient is discovered to have cytopenias, especially macrocytic anemia that is not due to B_{12} or folate deficiency, medication effect (e.g., methotrexate or azathioprine), or alcohol abuse. The blood count abnormality may be an incidental finding, but most patients with myelodysplastic syndromes are symptomatic with fatigue, dyspnea, and other cytopenia-associated symptoms.

The peripheral blood exhibits characteristic "dysplastic" cell morphologic abnormalities. In the peripheral blood, these abnormalities include hypogranular neutrophils, hypolobated neutrophils such as the two-lobed pseudo-Pelger-Hüet cell (Fig. 143-20), increased platelet size and platelet hypogranularity, poorly hemoglobinized red cells, and circulating early myeloid cells including a small number of myeloblasts (Chapter 143).

A bone marrow aspirate is required to make the diagnosis, and bone marrow core (trephine) biopsy is also useful and can provide information about the marrow architecture and overall marrow cellularity.[9] Maturation abnormalities in the bone marrow include megaloblastoid erythroid changes, multinucleated erythroid cells, ring sideroblasts, nuclear karyorrhexis, left-shifted myelopoiesis, hypogranular white cells, micromegakaryocytes, large hypernucleated megakaryocytes, or hypolobated megakaryocytes (Fig. 167-1). A mild increase in reticulin fibrosis is common in myelodysplastic syndromes, but severe reticulin fibrosis and collagen fibrosis are rare. Extramedullary hematopoiesis is uncommon in myelodysplastic syndromes, and the presence of splenomegaly or hepatomegaly should prompt consideration of another diagnosis. Metaphase cytogenetics is essential, whereas fluorescence in situ hybridization (FISH) is only necessary if karyotyping fails because of unsuccessful marrow aspiration. FISH abnormalities are rarely detected in patients for whom at least 20 metaphases can be counted during karyotyping. Flow cytometric immunophenotyping can provide useful diagnostic and prognostic information but should not be relied on to count blast proportion.

Although not technically required to make the diagnosis, a next generation sequencing panel can provide adjunctive diagnostic information. Genetic-clinical correlations including a thrombocytopenic prodrome in RUNX1 mutant patients and the association of GATA2 mutations with mycobacterial infections, warts, or monocytopenia. Patients with a *TP53* mutation may warrant identification because of their poorer prognosis.[10]

TABLE 167-1 GENE MUTATIONS ASSOCIATED WITH MYELODYSPLASTIC SYNDROMES AND FUNCTIONAL CLASS OF THE ASSOCIATED PROTEIN

RECURRENTLY MUTATED GENES	MUTATION FREQUENCY IN MDS	ADDITIONAL NOTES
SPLICEOSOME COMPONENTS (ALTER PRE-mRNA SPLICING)		
SF3B1	20-25%	Strongly associated with the presence of ring sideroblasts (60-80% of MDS-RS cases), often co-occurs with *DNMT3A* mutations; associated with more favorable outlook
U2AF1	5-10%	Often co-occurs with del(20q)
SRSF2	5-10%	More frequent in CMML (25-30%) than in MDS without proliferative features, often co-occurs with *RUNX1* or *ASXL1* mutations
ZRSR2	3-5%	
U2AF2, SFRA1, PRPF40B, SF1	<2% each	
EPIGENETIC PATTERN AND CHROMATIN CONFORMATION MODIFIERS		
TET2	20-25%	More frequent in CMML (~40%)
DNMT3A	10-15%	Low variant allele frequency mutations are also commonly found in the healthy elderly population
SETBP1	5-10%	More common in CMML; associated with adverse prognosis in that setting
ASXL1	10-20%	More frequent in CMML (~40%)
**EZH2*	6%	More frequent in CMML (~12%)
KDM6A	<2%	Rare in MDS, more frequent in CMML
IDH1, IDH2	<2%	More frequent in AML than MDS; amenable to targeted therapy with novel agents
PHF6	<1%	
ATRX	Rare	Associated with acquired α-thalassemia (hemoglobin H inclusions in red blood cells)
TRANSCRIPTION FACTORS/DNA REPAIR		
**RUNX1*	10-15%	Germline mutations cause Familial Platelet Disorder with propensity to AML (FPD-AML)
ETV6	<5%	Translocations common in AML; formerly known as *TEL*
MYBL2	<1%	
GATA2	Rare	Germline mutations cause familial MDS with monocytopenia
CEBPA	Rare	More frequently mutated in AML, germline mutations cause familial AML without preceding dysplasia
WT1	Rare	More frequently mutated in AML
**TP53*	5-10%	Associated with very poor prognosis; associated with t-MDS and with complex karyotype
TYROSINE KINASE SIGNALING		As a group, these genes are more often mutated in myeloid malignancies with a proliferative component
NRAS, KRAS, BRAF	5-10% collectively	*NRAS* mutations more common in CMML and AML; first mutations described in MDS (1987)
JAK2	<5%	More frequent in MDS/MPN with ring sideroblasts and thrombocytosis (MDS/MPN-RS-T) (50%)
CBL, CBLB	<5%	More frequently mutated in CMML than MDS
FLT3, MPL, KIT	<1%	*MPL* mutated in (5%) of MDS/MPN-RS-T; *FLT3* and *KIT* mutations are rare in MDS and much more common in AML
NF1	<1%	Germline mutations cause neurofibromatosis type 1
PTPN11	<1%	Rare in MDS, more frequent in JMML (30%)
OTHERS		
NPM1	<2%	Much more frequently mutated in AML
GNAS	<1%	
BCOR, BCORL1	<1%	More common in aplastic anemia
PIGA	<1%	Associated with a *PNH* clone; more common in paroxysmal nocturnal hemoglobinuria
UMODL1	<1%	
ZSWIM4	<1%	
PPM1D	1-3%	Associated with t-MDS
Cohesins *(RAD21, STAG1, STAG2, SMC3, SMC1A)*	5-10%	Despite role in chromatid segregation, not associated with numerical chromosome abnormalities

*Mutations that appear to be independently associated with poor outcomes in myelodysplastic syndromes (MDS).

AML = acute myeloid leukemia; CMML = chronic myelomonocytic leukemia; JMML = juvenile myelomonocytic leukemia; MDS = myelodysplastic syndromes; MDS-RS = MDS with ringed sideroblasts; MDS/MPN-RS-T = MDS/myeloproliferative neoplasm overlap syndrome with ring sideroblasts and thrombocytosis; pre-mRNA = precursor-messenger RNA; t-MDS = therapy-related myelodysplastic syndrome.

Data based on Bejar R, Levine R, Ebert BL. Unraveling the molecular pathophysiology of myelodysplastic syndromes. *J Clin Oncol.* 2011;29:504-515; Bejar R, Papaemmanuil E, Haferlach T, et al. Somatic mutations in MDS patients are associated with clinical features and predict prognosis independent of the IPSS-R: analysis of combined datasets from the International Working Group for Prognosis in MDS-Molecular Committee. *Blood.* 2015;126:907; and others.

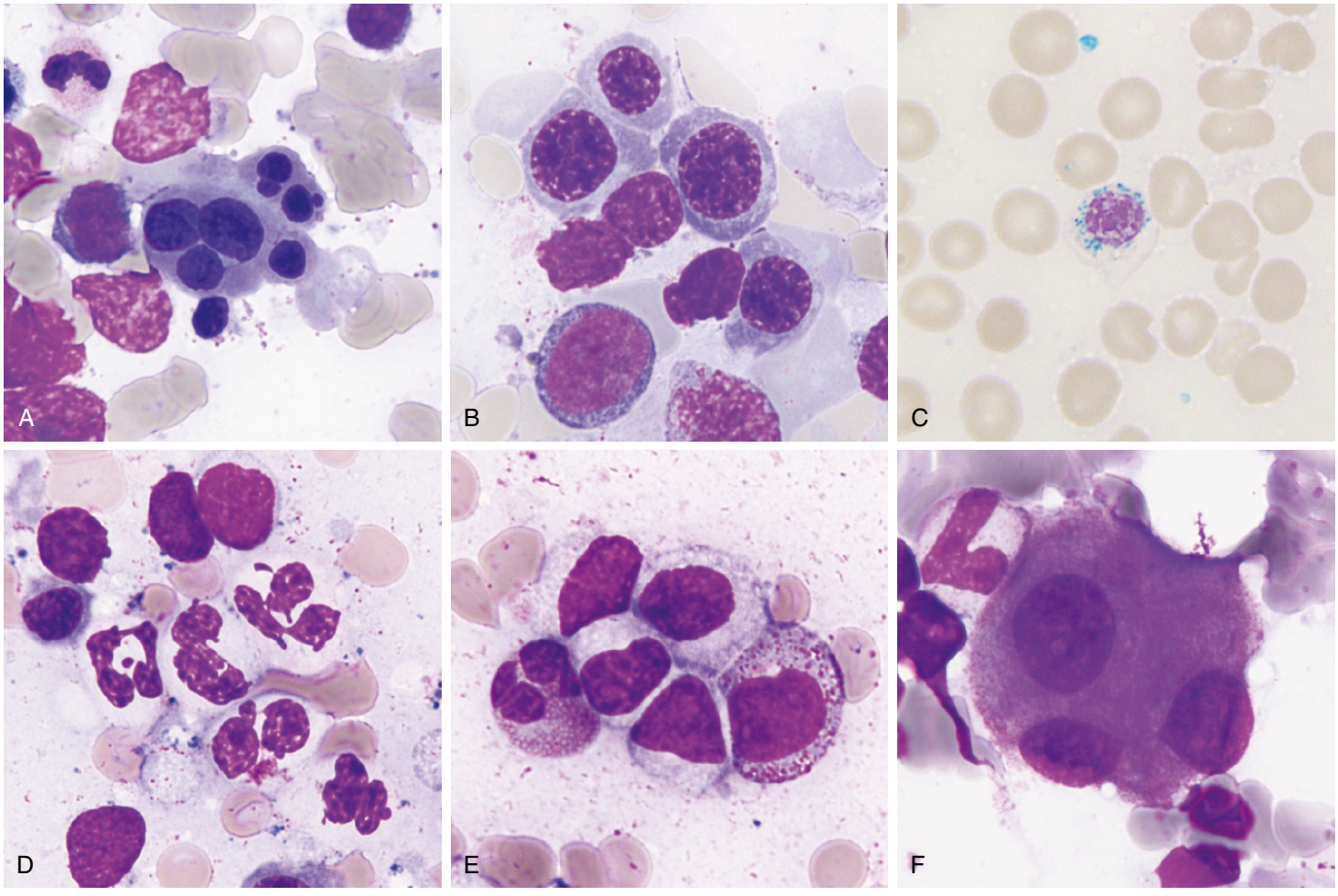

FIGURE 167-1. **"Dysplastic" cell morphologic abnormalities commonly observed in the peripheral blood or marrow patients with myelodysplastic syndromes. A,** Multinucleated erythroid precursor. **B,** Megaloblastoid maturation of erythroid precursors with "open" nuclear chromatin. **C,** Ring sideroblast (pathologic erythroid precursor with iron granules surrounding at least one third of the nucleus). **D,** Hypogranular neutrophils. **E,** Pseudo-Pelger-Huët anomaly (hypolobated neutrophil). **F,** Abnormal nuclear lobation in a megakaryocyte—a "pawn ball" cell with three separated nuclei/nuclear lobes. *A, B, D,* and *F* are Wright-Giemsa stained marrow aspirate; *C* is Perls' Prussian blue reaction of marrow aspirate; *E* is Wright-Giemsa stained peripheral blood. (Courtesy Elizabeth A. Morgan, MD, PhD, Brigham & Women's Hospital, Boston, MA.)

Diagnostic Criteria

Minimal diagnostic criteria for a myelodysplastic syndrome include the presence of one or more cytopenias, together with at least one additional feature. These features include: 5 to 19% marrow myeloblasts (although patients who have 10 to 19% marrow blasts may be classified as having myelodysplastic syndrome/acute myeloid leukemia);[11] an abnormal marrow karyotype with an acquired chromosome anomaly that is consistent with the diagnosis of a myelodysplastic syndrome;[12] or greater than 10% cells in any given hematopoietic linage that appears dysplastic (i.e., morphologically abnormal) in a patient in whom other causes of dysplastic cell morphology, such as nutritional deficiency or a drug effect, have been excluded.

Differential Diagnosis

Specific Other Diagnoses

Dysplastic hematopoiesis has a broad differential diagnosis, and other potential causes for cytopenias and morphologic abnormalities must be considered. This differential diagnosis includes nonclonal disorders such as B_{12} or folate deficiency (Chapter 150), copper deficiency (especially if ring sideroblasts are present), iron deficiency (Chapter 145), HIV infection, medication exposure (especially cytotoxic chemotherapy agents), or an immune disorder such as T-cell large granular lymphocyte (T-LGL) leukemia. In patients with isolated sideroblastic anemia (Chapter 145), it is important to exclude congenital sideroblastic anemias, including those due to germline mutations in *ALAS2*, which can present late in life.

Myelodysplastic syndromes must be distinguished from aplastic anemia (Chapter 151), which can be oligoclonal and associated with some of the same somatic mutations as myelodysplastic syndromes, but which is not typically associated with Pelger-Hüet cells or other morphologic abnormalities. The karyotype in aplastic anemia is usually (but not always) normal. Myelodysplastic syndromes can also be mistaken for a myeloproliferative neoplasm such as primary myelofibrosis (Chapter 152). Cases in which myelodysplastic syndrome features, such as cytopenias, overlap with myeloproliferative neoplasm features, such as leukocytosis and splenomegaly, include chronic myelomonocytic leukemia, which requires >1000 monocytes/μL in the blood to diagnose. The WHO categorizes myelodysplastic syndrome/myeloproliferative neoplasm overlap syndromes separately from myelodysplastic syndromes, and these cases have a distinct mutational spectrum.

Variants of Myelodysplastic Syndrome

Some patients with persistent cytopenias do not meet diagnostic criteria for a myelodysplastic syndrome, but no other diagnosis is apparent, even after detailed investigation.[13] This pattern has been termed *idiopathic cytopenias of undetermined significance* if a clonal somatic mutation is absent and *clonal cytopenias of undetermined significance* if a somatic myelodysplastic syndrome-associated mutation (e.g., *DNMT3A, TET2*) is present. Such patients should be followed over time because they have a risk for developing an overt myelodysplastic syndrome, especially if they have a clonal cytopenia of undetermined significance. More than 10% of the healthy population age 70 years or older have a somatic mutation in *DNMT3A, TET2*, or another myelodysplastic syndrome-associated gene; therefore, identification of a clonal mutation in the absence of any myelodysplastic syndrome feature (called *clonal hematopoiesis of indeterminate potential*) is not considered diagnostic of a myelodysplastic syndrome. If a patient has cytopenias even in the absence of characteristic myelodysplastic syndrome-associated morphologic abnormalities and a typical myelodysplastic syndrome-associated marrow cytogenetic abnormality (e.g., loss of chromosome 7 or deletion of the long arm of chromosome 5), the patient can be considered to have "unclassifiable

myelodysplastic syndrome" (Table 167-2). Patients with clonal hematopoiesis of indeterminate potential (Chapter 142) have an increased risk for developing a myelodysplastic syndrome or another hematologic malignancy, and they also have an increased risk for cardiovascular mortality.[14]

TREATMENT

Given the heterogeneity of myelodysplastic syndromes and the wide spectrum of functional status and comorbid conditions among patients with myelodysplastic syndromes, treatment must be individualized.[15–17] Currently, lack of a specific well-characterized molecular target in most patients with myelodysplastic syndromes precludes a true biologically based approach to therapy. Algorithms for treatment (Fig. 167-2) are based primarily on the patient's prognosis.

General Approach to the Patient

When choosing a potential therapy for a patient with a myelodysplastic syndrome, clinicians should consider the patient's age,[18] comorbid conditions, functional status, disease biology, and disease kinetics. Some patients with myelodysplastic syndromes have mild cytopenias and minimal or no symptoms, and they can reasonably be observed without therapy. For higher-risk patients (e.g., revised International Prognostic Scoring System high or very high risk [Fig. 167-3]), immediate therapy is usually indicated because such patients are usually severely cytopenic and have a life expectancy of less than 2 years. For lower-risk patients (very low risk or low risk on the revised International Prognostic Scoring System or the Molecular International Prognostic Scoring System [https://mds-risk-model.com]), a more cautious approach is appropriate.

The only curative modality for a myelodysplastic syndrome is allogeneic hematopoietic stem cell transplantation (Chapter 163), so this option should be considered in developing a therapeutic plan if the patient is young enough and lacks other major medical problems. If transplantation is not the goal, prolonged administration of hypomethylating agents is generally indicated. In lower-risk patients who have a chromosome 5 abnormality, the immunomodulatory agent lenalidomide is the treatment of choice. For other lower-risk patients, supportive care alone, hematopoietic growth factors, immunosuppressive therapy, immunomodulatory therapy, or hypomethylating agents can be considered, depending on the clinical situation.

Stem Cell Transplantation

Allogeneic hematopoietic stem cell transplantation (Chapter 163) should be considered promptly and generally be performed if feasible in all patients who have higher-risk myelodysplastic syndromes, who are approximately age 75 years or younger, and who lack major comorbid conditions. Allogeneic transplantation also may lead to better outcomes than medical therapy alone in higher-risk patients age 55 years or older.[19–21] The optimal conditioning regimen is unclear.[A1] Reduced-intensity conditioning stem cell transplantation is feasible in adults up to age 75 years, whereas myelosuppressive stem cell transplantation is generally reserved for patients younger than age 55 years.

Because most patients with myelodysplastic syndromes are older and uncommonly have a younger sibling who is a suitable stem cell donor, azacitidine or decitabine (see DNA Hypomethylating Agents) may be useful to stabilize a patient before transplantation while the search for an unrelated donor is ongoing.

The long-term outcome of patients undergoing stem cell transplantation varies widely according to disease and host features. Treatment-related mortality is as high as a 15 to 20% risk. Relapses are unfortunately common, but approximately 40% of patients will become long-term disease-free survivors.

Supportive Care

Hematopoietic Growth Factors and Other Approaches to Cytopenias

Because most patients with myelodysplastic syndromes are anemic, the erythropoiesis-stimulating agents epoetin and darbepoetin[A2] are often used under expert supervision, even though these agents are not specifically approved by the U.S. Food and Drug Administration (FDA) for treatment of myelodysplastic syndromes. The benefits of erythropoiesis-stimulating agents are generally modest and of limited duration. Patients with lower baseline serum erythropoietin levels (<500 U/L, and especially <100 U/L) are more likely to respond to erythropoiesis-stimulating agents than are patients with higher baseline serum erythropoietin levels. For patients with ring sideroblasts, the addition of low-dose granulocyte colony-stimulating factor (G-CSF) to the erythropoiesis-stimulating agent may potentiate the erythropoietic response.

In patients who have lower-risk myelodysplastic syndromes (>15% ring sideroblasts, or >5% ringed sideroblasts and an SF3B1 mutation) and who have high erythropoietin levels or have become refractory to or intolerant of

TABLE 167-2 WORLD HEALTH ORGANIZATION SUBTYPES OF MYELODYSPLASTIC SYNDROME (MDS)

MDS SUBTYPE	DYSPLASIA	BLAST COUNT	OTHER FINDINGS
MDS with single-lineage dysplasia (MDS-SLD)	• Present in only 1 lineage (>10% of cells in that lineage)	• Peripheral blood: <1% • Bone marrow: <5%	• Cases with bilineage cytopenias may be included in this category, but marrow dysplasia must be limited to 1 lineage • Ring sideroblasts represent <15% of erythroid precursors
MDS with ring sideroblasts (MDS-RS)	• Present in the erythroid lineage (>10% of erythroid precursors); subtypes with single-lineage dysplasia (MDS-RS-SLD) and with multilineage dysplasia (MDS-RS-MLD)	• Peripheral blood: none • Bone marrow: <5%	• Anemia (normocytic/macrocytic) • Ring sideroblasts comprise ≥15% of erythroid precursors or if *SF3B1* mutation is present ≥5% of erythroid precursors
MDS with multilineage dysplasia (MDS-MLD)	• Present in 2 or more lineages (>10% of cells in each affected lineage)	• Peripheral blood: <1% • Bone marrow: <5%	• One or more cytopenias • No Auer rods • If ≥15% of erythroid precursors or if *SF3B1* mutation is present in ≥5% of erythroid precursors, represents MDS-RS-MLD
MDS with excess blasts-1 (MDS-EB-1)	• Present in 1 or more lineages (>10% of cells in each affected lineage)	• Peripheral blood: <5% • Bone marrow: 5-9%	• One or more cytopenias • No Auer rods • 2-4% blasts in the peripheral blood → MDS-EB-1
MDS with excess blasts-2 (MDS-EB-2)	• Present in 1 or more lineages (>10% of cells in each affected lineage)	• Peripheral blood: 5-19% • Bone marrow: 10-19%	• One or more cytopenias • The presence of Auer rods for any blast count <20% → MDS-EB-2
MDS with isolated deletion of chromosome 5q (5q− syndrome)	• Increased numbers of megakaryocytes, many small and with hypolobated/nonlobated nuclei • Minimal or no dysplasia in granulocytic lineage	• Peripheral blood: no or rare blasts (<1%) • Bone marrow: <5%	• Anemia (often macrocytic) with or without other cytopenias/thrombocytosis • No Auer rods • Interstitial or terminal deletion of the long arm of chromosome 5 with no or one other cytogenetic abnormality
MDS, unclassifiable	• Unequivocal, but present in <10% of cells of one or more lineages	• Peripheral blood: ≤1% • Bone marrow: <5%	• May progress to a specific MDS • Can also include cases otherwise classified as: MDS-SLD or MDS-MLD but with 1% blasts in peripheral blood; MDS-SLD but with pancytopenia • Cases with an MDS-associated chromosome abnormality (other than loss of the Y chromosome or trisomy 8 or deletion of chromosome 20) but without dysplasia can be included in this category

Data based on the 2016 WHO classification of hematopoietic and lymphoid neoplasms (Arber D, Orazi A, Hasserjian R, et al. The 2016 revision to the World Health Organization classification of myeloid neoplasms and acute leukemia. *Blood* 2016:127:2391-2405), which was a minor revision of the 2008 classification. Familial myeloid neoplasms are classified separately, as are therapy-related myeloid neoplasia and myelodysplastic syndromes with myeloproliferative neoplasm features.

- Consider clinical trial enrollment for all patients
- Supportive care (e.g., transfusions and antimicrobials as needed) for all patients; consider chelation
- Risk stratification using the Revised International Prognostic Scoring System (see Table 167-2) supplemented by molecular testing

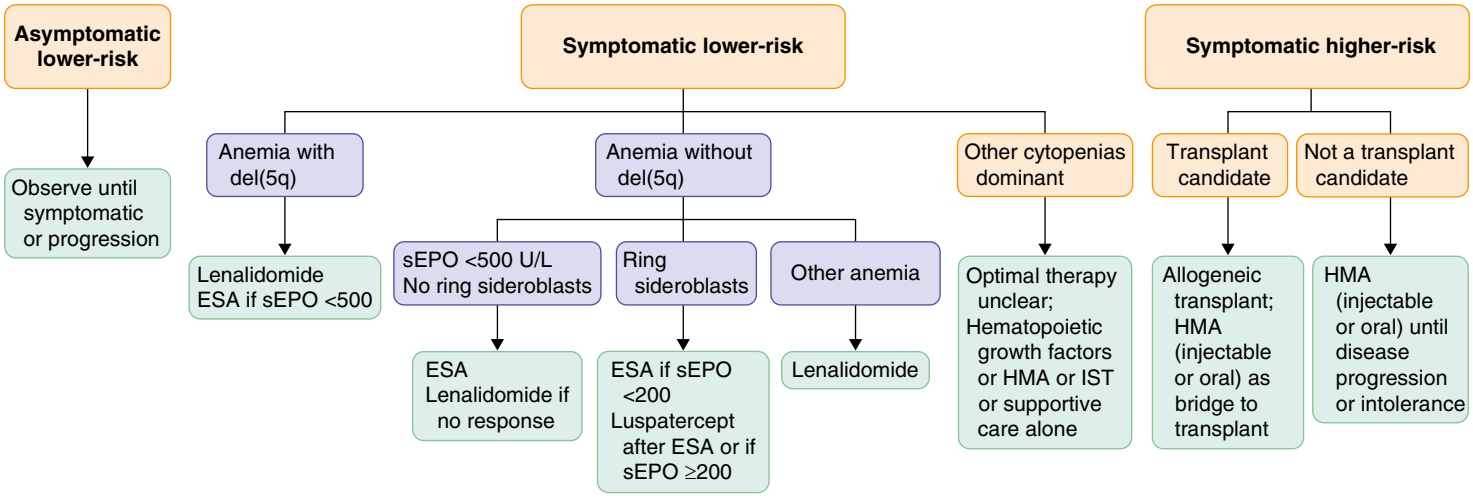

FIGURE 167-2. Treatment algorithm in myelodysplastic syndromes. EPO = erythropoietin; ESA = erythropoiesis-stimulating agent; HMA = DNA hypomethylating agent; IST = immunosuppressive therapy; sEPO = serum erythropoietin level. (Adapted from Steensma DP. Myelodysplastic syndromes current treatment algorithm 2018. *Blood Cancer J*. 2018;8:1-7.)

erythropoiesis-stimulating agents, luspatercept (1.0 to 1.75 mg/kg subcutaneously every 3 weeks) can reduce the severity of anemia by binding to cytokines that have a negative effect on erythropoiesis.[A3] A few patients will benefit from treatment with androgens, but the risk for prostate enlargement (in men) and other complications such as hepatotoxicity must be considered.

Myeloid growth factors such as G-CSF can ameliorate the neutropenia often seen in myelodysplastic syndrome patients but is not likely to reduce the risk for infections or provide other clinical benefits because of the frequency of neutrophil dysfunction in addition to neutropenia. Prophylactic antimicrobial agents have no clear role, but they can be considered in patients who have experienced recurrent infections or are at particularly high risk.

The thrombopoiesis-stimulating agents romiplostim and eltrombopag are not approved by the FDA for myelodysplastic syndromes and may induce progression to AML in some patients, but they may be useful in patients who have severe thrombocytopenia or clinically significant bleeding.[A4] Platelet transfusions should be used carefully in myelodysplastic syndrome patients because of the risk for alloimmunization. Prophylactic transfusion is appropriate only in patients with platelet counts less than 10,000/μL. Patients with mucosal bleeding and refractory thrombocytopenia may benefit from treatment with antifibrinolytic agents such as aminocaproic acid under expert supervision.

Iron Chelation Therapy

The multiple red blood cell (RBC) transfusions needed by some patients with myelodysplastic syndromes may cause iron overload and tissue injury, but the frequency with which this complication occurs is unclear. Furthermore, the toxicity and high cost of available chelators (e.g., deferasirox, deferiprone, or deferoxamine) makes their use controversial. A trial of iron chelation therapy is reasonable in patients with lower-risk disease and high transfusional burdens (e.g., more than 20 to 40 RBC units transfused).[A5]

Disease-Modifying Medical Therapy

DNA Hypomethylating Agents

Azacitidine and decitabine are two azanucleoside analogues that inhibit the enzyme DNA methyltransferase, thereby altering the cytosine methylation "epigenetic" status of DNA and changing gene expression. These agents have become the mainstay of therapy for most patients with higher-risk myelodysplastic syndromes, as well as for patients whose lower-risk myelodysplastic syndromes are refractory to other therapies.[22]

Azacitidine (75 mg/m^2 subcutaneously or intravenously daily for 7 days every month, given until disease progression or toxicity) can delay progression to AML, improve quality of life, and increase median survival from 15 to 24 months.[A6] Cytopenias and gastrointestinal symptoms are the most common adverse effects of this class of drugs.

Decitabine under expert supervision also can delay disease progression. Short courses of this agent may yield particular benefit in patients with lower-risk myelodysplastic syndrome.[A7] An oral formulation in combination with cedazuridine (i.e., a cytidine deaminase inhibitor that inhibits first-pass metabolism of the decitabine) provides responses similar to injectable decitabine.[23]

Although at least 50% of patients who receive a hypomethylating agent experience an improvement in at least one cytopenia, the risks of both neutropenia and thrombocytopenia are increased.[A8] These agents are not curative, and the median survival is less than 6 months when patients are unresponsive. No standard of care is available for patients whose disease worsens after treatment with hypomethylating agents. Options under study include[24] azacitidine with either magrolimab, venetoclax,[A9] or sabatolimab.

Immunomodulatory Agents

Patients with loss of chromosome 5q, either alone or in conjunction with other chromosomal abnormalities, have high response rates to lenalidomide, including a nearly 70% rate of transfusion independence and a greater than 30% rate of cytogenetic normalization persisting for a median of more than 2 years.[25] Lenalidomide (10 mg daily) is now the treatment of choice for lower-risk 5q– patients. In patients with lower-risk myelodysplastic syndromes without a chromosome 5 abnormality, the response rate to lenalidomide is approximately 35%; such responses persist for a median of 8 to 9 months.[26] In higher-risk myelodysplastic syndromes and AML with 5q–chromosomal abnormalities, however, it is less effective. Important adverse effects of lenalidomide include cytopenias, thrombosis, diarrhea, and rash.

Immunosuppressive Therapy

Patients who display a pathophysiology similar to aplastic anemia (e.g., T-lymphocyte-driven autoimmune attack against hematopoietic cells) may respond to anti-T-cell therapies, including antithymocyte globulin and calcineurin inhibitors under expert supervision. Younger patients with a normal karyotype, trisomy 8, paroxysmal nocturnal hemoglobinuria clones, or HLA DR15 status seem to have a higher likelihood of benefiting, but good predictive strategies for selecting patients for immunosuppressive therapy are lacking.

PREVENTION

At present there is no clear way by which myelodysplastic syndromes can be prevented, except avoiding known risk factors such as radiation exposure or alkylating agents. However, emerging clonal hematopoiesis following treatment for cancer or arising de novo can now be recognized at an early stage and may be amenable to intervention.[27]

PROGNOSIS

The natural history of myelodysplastic syndromes is highly variable. Approximately one half of patients will die of complications of the cytopenias, particularly infection due to neutropenia and functional neutrophil defects (i.e., impaired bactericidal activity due to hypogranularity). Among lethal infections in myelodysplastic syndromes, pneumonia and bacteremia are most common. Bleeding is the second most common disease-related cause of death. Anemia may exacerbate cardiovascular or cerebrovascular disease. Approximately 25% of patients will progress to AML, which is

Risk group	Included karyotypes	Median survival, years	25% of patients to AML, years	Proportion of patients in this group
Very good	del(11q), –Y	5.4	N/R	4%
Good	Normal, del(20q), del(5q) alone or with 1 other anomaly, del(12p)	4.8	9.4	72%
Intermediate	+8, del(7q), i(17q), +19, any other single or double abnormality not listed	2.7	2.5	13%
Poor	Abnormal 3q, –7, double abnormality include –7/del(7q), complex with 3 abnormalities	1.5	1.7	4%
Very poor	Complex with >3 abnormalities	0.7	0.7	7%

A

Parameter	Categories and associated scores				
Cytogenetic risk group	Very good	Good	Intermediate	Poor	Very poor
	0	1	2	3	4
Marrow blast proportion	≤2%	>2 – <5%	5 – 10%	>10%	
	0	1	2	3	
Hemoglobin	≥10 g/dL	8 – <10 g/dL	<8 g/dL		
	0	1	1.5		
Absolute neutrophil count	≥0.8 × 10^9/L	<0.8 × 10^9/L			
	0	0.5			
Platelet count	≥100 × 10^9/L	50 – 100 × 10^9/L	<50 × 10^9/L		
	0	0.5	1		

Possible range of summed scores: 0–10

B

Risk group	Points	% Patients (n = 7012; AML data on 6485)	Median survival, years	Median survival for patients <60 years	Time until 25% of patients develop AML, years
Very low	0–1.5	19%	8.8	Not reached	Not reached
Low	2.0–3.0	38%	5.3	8.8	10.8
Intermediate	3.5–4.5	20%	3.0	5.2	3.2
High	5.0–6.0	13%	1.5	2.1	1.4
Very high	>6.0	10%	0.8	0.9	0.7

C

FIGURE 167-3. The 2012 Revised International Prognostic Scoring System (IPSS-R) for myelodysplastic syndromes. A, Cytogenetic abnormalities. **B,** Table for calculation of IPSS-R risk group. **C,** Outcomes by risk group. AML = acute myeloid leukemia. (Data from Greenberg PL, Tuechler H, Schanz J, et al. Revised international prognostic scoring system for myelodysplastic syndromes. *Blood* 2012;120:2454-2465.)

usually a fatal complication.[28] Finally, because myelodysplastic syndromes are often diagnosed in elderly patients or people with a history of cancer, frailty and geriatric comorbid conditions contribute to death in at least one third of patients. The revised International Prognostic Scoring System (see Fig. 167-3) defines five different subgroups of myelodysplastic syndromes with varying risk for death and AML progression.

Molecular abnormalities (including mutations in *EZH2*, *TP53*, or *RUNX1*) are associated with poorer prognosis, and the Molecular International Prognostic Scoring System considers mutations in up to 17 genes to place patients into six prognostic categories.[29] Additionally, the presence of either a *TP53* or RAS pathway mutation predicts poor outcome after hematopoietic stem cell transplantation.

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168 THE ACUTE LEUKEMIAS

ROLAND B. WALTER AND FREDERICK R. APPELBAUM

DEFINITION

Normal hematopoiesis (Chapter 142) requires tightly regulated proliferation and differentiation of pluripotent hematopoietic stem cells that become mature blood cells. Acute leukemia begins as a clonal disease that is the result of a malignant event in an early hematopoietic cell. Over time, subsequent mutational events give rise to full-blown leukemia that may be composed of multiple subclones. Instead of proliferating and differentiating normally, the affected cells give rise to progeny that fail to differentiate normally but continue to proliferate in an uncontrolled fashion. As a result, immature myeloid cells in acute myeloid leukemia (AML) or lymphoid cells in acute lymphoblastic leukemia (ALL)—typically called blasts—rapidly accumulate and progressively replace other cells in the bone marrow, thereby diminishing the production of normal red cells, white cells, and platelets. This loss of normal marrow function, in turn, gives rise to the common clinical complications of acute leukemia: anemia, infection, and bleeding. With time, the leukemic blasts pour out into the blood stream and eventually occupy the lymph nodes, spleen, and other organs. If untreated, acute leukemia is often rapidly fatal; most patients die within several weeks to months after diagnosis. With appropriate therapy, however, the natural history of acute leukemia can be markedly altered, and many patients can be cured.

EPIDEMIOLOGY

Incidence

An estimated 20,000 or so new cases of AML and 6600 or so new cases of ALL occur annually in the United States.[1] This incidence of acute leukemia has remained relatively stable in the United States over the past three decades, but there is substantial variation in incidence among and within world regions.[2]

In the United States, the annual deaths are about 11,500 from AML and about 1400 from ALL. Although acute leukemia accounts for only about 2% of cancer deaths, the impact of leukemia is heightened because of the young age of some patients. For example, ALL has a maximum incidence between ages 2 and 10 years, is the most common cancer in children younger than age 15 years, and accounts for one third of all childhood cancer deaths. The incidence of AML gradually increases with age, with a median age at diagnosis of about 67 years and without an early peak.

Determinants

In most cases, acute leukemia develops for no known reason, but sometimes a possible cause can be identified.

Genetic Predisposition

The concordance rate is virtually 100% in identical twins if one twin develops leukemia during the first year of life. An increasing number of germline mutations (e.g., in *RUNX1, CEBPA, GATA2, DDX41, ETV6, IKZF1, PAX5,* and *SAMD9*) are recognized to cause rare syndromes that can lead to acute leukemia without other manifestations.[3] The incidence of acute leukemia is markedly increased in syndromes involving defective DNA repair, such as Fanconi anemia and Bloom syndrome, and in bone marrow failure syndromes associated with ribosomal abnormalities (Chapter 151), including Diamond-Blackfan anemia, Shwachman-Diamond syndrome, and dyskeratosis congenita. Germline mutations in *TP53* (Li-Fraumeni syndrome) and abnormalities in chromosome number, as in Down and Klinefelter syndromes (Chapters 32 and 214), are also associated with an increased incidence of acute leukemia.

Radiation

Ionizing radiation (Chapter 18) is leukemogenic. The incidences of ALL, AML, and chronic myeloid leukemia (CML) are increased in patients given therapeutic radiation and among survivors of the atomic bomb blasts at Hiroshima and Nagasaki. The magnitude of the risk depends on the dose of radiation, its distribution in time, and the age of the individual. Greater risk results from higher doses of radiation delivered over shorter periods to younger patients. In areas of high natural background radiation (often from radon), chromosomal aberrations are reportedly more frequent, but an increase in acute leukemia has not been consistently found. Although some investigations have raised concern about the possible leukemogenic effects of extremely low-frequency nonionizing electromagnetic fields emitted by electrical installations, findings have been inconsistent across studies; if any such effect exists at all, its magnitude is very small.

Oncogenic Viruses

The search for a viral cause of leukemia has been pursued intensely, but only two clear associations have been found. Human T-cell lymphotropic virus type I (HTLV-I), an enveloped, single-stranded RNA virus, is a causative agent of adult T-cell leukemia (Chapter 360), spread either horizontally by sexual contact or blood products or vertically from mother to fetus. This distinct form of leukemia is found within geographic clusters in southwestern Japan, the Caribbean basin, and Africa. Because HTLV-I seropositivity was found with increasing frequency among heavily transfused patients and intravenous drug users, screening of blood products for antibodies to HTLV-I is now routine practice in blood banks in the United States. Epstein-Barr virus (Chapter 348), the DNA herpes family virus that causes infectious mononucleosis, is associated with the endemic African form of Burkitt lymphoma/leukemia (Chapter 171).

Chemicals and Drugs

Heavy occupational exposure to benzene and benzene-containing compounds, such as kerosene and carbon tetrachloride, may lead to marrow damage, which can take the form of aplastic anemia, myelodysplasia, or AML. A link between leukemia and tobacco use (Chapter 363) has been reported.

With the increasing use of chemotherapy and radiotherapy to treat other malignancies, as much as 10% of AMLs and a smaller percentage of ALLs are likely the consequence of prior cancer therapy. Exposure to alkylating agents such as melphalan and the nitrosoureas is associated with a risk for secondary AML, which often manifests initially as a myelodysplastic syndrome (Chapter 167), frequently with abnormalities of chromosomes 5, 7, and 8 but with no distinct morphologic features. These secondary AMLs typically develop 4 to 6 years after exposure to alkylating agents, and their incidence may be increased with greater intensity and duration of drug exposure. Secondary AML associated with exposure to topoisomerase II inhibitors, including the epipodophyllotoxins (teniposide or etoposide) and doxorubicin, tends to have a shorter latency period (1 to 2 years), lacks a myelodysplastic phase, has a monocytic morphology, and involves abnormalities of the long arm of chromosome 11 (band q23) or chromosome 21 (band q22). Because patients frequently receive combination chemotherapy, it is often difficult to identify a single causative agent. On average, secondary leukemia responds less well to treatment than does de novo disease.

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168 THE ACUTE LEUKEMIAS

ROLAND B. WALTER AND FREDERICK R. APPELBAUM

DEFINITION

Normal hematopoiesis (Chapter 142) requires tightly regulated proliferation and differentiation of pluripotent hematopoietic stem cells that become mature blood cells. Acute leukemia begins as a clonal disease that is the result of a malignant event in an early hematopoietic cell. Over time, subsequent mutational events give rise to full-blown leukemia that may be composed of multiple subclones. Instead of proliferating and differentiating normally, the affected cells give rise to progeny that fail to differentiate normally but continue to proliferate in an uncontrolled fashion. As a result, immature myeloid cells in acute myeloid leukemia (AML) or lymphoid cells in acute lymphoblastic leukemia (ALL)—typically called blasts—rapidly accumulate and progressively replace other cells in the bone marrow, thereby diminishing the production of normal red cells, white cells, and platelets. This loss of normal marrow function, in turn, gives rise to the common clinical complications of acute leukemia: anemia, infection, and bleeding. With time, the leukemic blasts pour out into the blood stream and eventually occupy the lymph nodes, spleen, and other organs. If untreated, acute leukemia is often rapidly fatal; most patients die within several weeks to months after diagnosis. With appropriate therapy, however, the natural history of acute leukemia can be markedly altered, and many patients can be cured.

EPIDEMIOLOGY

Incidence

An estimated 20,000 or so new cases of AML and 6600 or so new cases of ALL occur annually in the United States.[1] This incidence of acute leukemia has remained relatively stable in the United States over the past three decades, but there is substantial variation in incidence among and within world regions.[2]

In the United States, the annual deaths are about 11,500 from AML and about 1400 from ALL. Although acute leukemia accounts for only about 2% of cancer deaths, the impact of leukemia is heightened because of the young age of some patients. For example, ALL has a maximum incidence between ages 2 and 10 years, is the most common cancer in children younger than age 15 years, and accounts for one third of all childhood cancer deaths. The incidence of AML gradually increases with age, with a median age at diagnosis of about 67 years and without an early peak.

Determinants

In most cases, acute leukemia develops for no known reason, but sometimes a possible cause can be identified.

Genetic Predisposition

The concordance rate is virtually 100% in identical twins if one twin develops leukemia during the first year of life. An increasing number of germline mutations (e.g., in *RUNX1, CEBPA, GATA2, DDX41, ETV6, IKZF1, PAX5,* and *SAMD9*) are recognized to cause rare syndromes that can lead to acute leukemia without other manifestations.[3] The incidence of acute leukemia is markedly increased in syndromes involving defective DNA repair, such as Fanconi anemia and Bloom syndrome, and in bone marrow failure syndromes associated with ribosomal abnormalities (Chapter 151), including Diamond-Blackfan anemia, Shwachman-Diamond syndrome, and dyskeratosis congenita. Germline mutations in *TP53* (Li-Fraumeni syndrome) and abnormalities in chromosome number, as in Down and Klinefelter syndromes (Chapters 32 and 214), are also associated with an increased incidence of acute leukemia.

Radiation

Ionizing radiation (Chapter 18) is leukemogenic. The incidences of ALL, AML, and chronic myeloid leukemia (CML) are increased in patients given therapeutic radiation and among survivors of the atomic bomb blasts at Hiroshima and Nagasaki. The magnitude of the risk depends on the dose of radiation, its distribution in time, and the age of the individual. Greater risk results from higher doses of radiation delivered over shorter periods to younger patients. In areas of high natural background radiation (often from radon), chromosomal aberrations are reportedly more frequent, but an increase in acute leukemia has not been consistently found. Although some investigations have raised concern about the possible leukemogenic effects of extremely low-frequency nonionizing electromagnetic fields emitted by electrical installations, findings have been inconsistent across studies; if any such effect exists at all, its magnitude is very small.

Oncogenic Viruses

The search for a viral cause of leukemia has been pursued intensely, but only two clear associations have been found. Human T-cell lymphotropic virus type I (HTLV-I), an enveloped, single-stranded RNA virus, is a causative agent of adult T-cell leukemia (Chapter 360), spread either horizontally by sexual contact or blood products or vertically from mother to fetus. This distinct form of leukemia is found within geographic clusters in southwestern Japan, the Caribbean basin, and Africa. Because HTLV-I seropositivity was found with increasing frequency among heavily transfused patients and intravenous drug users, screening of blood products for antibodies to HTLV-I is now routine practice in blood banks in the United States. Epstein-Barr virus (Chapter 348), the DNA herpes family virus that causes infectious mononucleosis, is associated with the endemic African form of Burkitt lymphoma/leukemia (Chapter 171).

Chemicals and Drugs

Heavy occupational exposure to benzene and benzene-containing compounds, such as kerosene and carbon tetrachloride, may lead to marrow damage, which can take the form of aplastic anemia, myelodysplasia, or AML. A link between leukemia and tobacco use (Chapter 363) has been reported.

With the increasing use of chemotherapy and radiotherapy to treat other malignancies, as much as 10% of AMLs and a smaller percentage of ALLs are likely the consequence of prior cancer therapy. Exposure to alkylating agents such as melphalan and the nitrosoureas is associated with a risk for secondary AML, which often manifests initially as a myelodysplastic syndrome (Chapter 167), frequently with abnormalities of chromosomes 5, 7, and 8 but with no distinct morphologic features. These secondary AMLs typically develop 4 to 6 years after exposure to alkylating agents, and their incidence may be increased with greater intensity and duration of drug exposure. Secondary AML associated with exposure to topoisomerase II inhibitors, including the epipodophyllotoxins (teniposide or etoposide) and doxorubicin, tends to have a shorter latency period (1 to 2 years), lacks a myelodysplastic phase, has a monocytic morphology, and involves abnormalities of the long arm of chromosome 11 (band q23) or chromosome 21 (band q22). Because patients frequently receive combination chemotherapy, it is often difficult to identify a single causative agent. On average, secondary leukemia responds less well to treatment than does de novo disease.

ABSTRACT

Acute leukemia begins as a clonal disease that is the result of a malignant event in an early hematopoietic cell. With time, subsequent mutational events give rise to full-blown leukemia that may be composed of multiple subclones. Instead of proliferating and differentiating normally, the affected cells give rise to progeny that fail to differentiate but continue to proliferate in an uncontrolled fashion. As a result, immature myeloid cells in acute myeloid leukemia (AML) or lymphoid cells in acute lymphoblastic leukemia (ALL)—called blasts—rapidly accumulate and progressively replace other cells in the bone marrow, thereby diminishing the production of normal red cells, white cells, and platelets. This loss of normal marrow function, in turn, gives rise to the common clinical complications of acute leukemia: anemia, infection, and bleeding. With time, the leukemic blasts pour out into the blood stream and eventually occupy the lymph nodes, spleen, and other organs. If untreated, acute leukemia is often rapidly fatal; most patients die within several weeks to months after diagnosis. With appropriate therapy, however, the natural history of acute leukemia can be markedly altered, and many patients can be cured.

KEYWORDS

acute myeloid leukemia
acute promyelocytic leukemia
acute lymphoblastic leukemia
Philadelphia chromosome
cytogenetic/molecular abnormality
immunophenotype
hematopoietic cell transplantation

PATHOBIOLOGY

Clonality and Cell of Origin

The acute leukemias are clonal disorders, and all leukemic cells in a given patient are descended from a common progenitor. The clonal nature of acute leukemia suggests that leukemic stem cells are capable of both self-renewal and proliferation. Leukemic stem cells in AML are rare among the leukemic mass, with a frequency of 0.2 to 10 per 10^6, and usually, but not invariably, are located within the primitive $CD34^{++}$ $CD38^{-}$ fraction. Less is known about the ALL stem cell.

Classification

The classification of acute leukemias is based on clinical, morphologic, immunophenotypic, cytogenetic, and molecular features (Table 168-1).

TABLE 168-1 WORLD HEALTH ORGANIZATION CLASSIFICATION OF ACUTE LEUKEMIAS (2016)

Acute Myeloid Leukemia (AML) and Related Neoplasms
AML with recurrent genetic abnormalities
AML with t(8;21)(q22;q22.1); *RUNX1-RUNX1T1*
AML with inv(16)(p13.1q22) or t(16;16)(p13.1;q22); *CBFB-MYH11*
APL with *PML-RARA*
AML with t(9;11)(p21.3;q23.3); *MLLT3-KMT2A*
AML with t(6;9)(p23;q34.1); *DEK-NUP214*
AML with inv(3)(q21.3q26.2) or t(3;3)(q21.3;q26.2); *GATA2, MECOM*
AML (megakaryoblastic) with t(1;22)(p13.3;q13.3); *RBM15-MKL1*
Provisional entity: AML with BCR-ABL1
AML with mutated NPM1
AML with biallelic mutations of *CEBPA*
Provisional entity: AML with mutated RUNX1
AML with myelodysplasia-related changes
Therapy-related myeloid neoplasms
AML, NOS
AML with minimal differentiation
AML without maturation
AML with maturation
Acute myelomonocytic leukemia
Acute monoblastic/monocytic leukemia
Pure erythroid leukemia
Acute megakaryoblastic leukemia
Acute basophilic leukemia
Acute panmyelosis with myelofibrosis
Myeloid sarcoma
Myeloid proliferations related to Down syndrome
Transient abnormal myelopoiesis (TAM)
Myeloid leukemia associated with Down syndrome
Blastic Plasmacytoid Dendritic Cell Neoplasm
Acute Leukemias of Ambiguous Lineage
Acute undifferentiated leukemia
Mixed phenotype acute leukemia (MPAL) with t(9;22)(q34.1;q11.2); *BCR-ABL1*
MPAL with t(v;11q23.3); *KMT2A* rearranged
MPAL, B/myeloid, NOS
MPAL, T/myeloid, NOS
B-Lymphoblastic Leukemia/Lymphoma
B-lymphoblastic leukemia/lymphoma, NOS
B-lymphoblastic leukemia/lymphoma with recurrent genetic abnormalities
B-lymphoblastic leukemia/lymphoma with t(9;22)(q34.1;q11.2); *BCR-ABL1*
B-lymphoblastic leukemia/lymphoma with t(v;11q23.3); *KMT2A* rearranged
B-lymphoblastic leukemia/lymphoma with t(12;21)(p13.2;q22.1); *ETV6-RUNX1*
B-lymphoblastic leukemia/lymphoma with hyperdiploidy
B-lymphoblastic leukemia/lymphoma with hypodiploidy
B-lymphoblastic leukemia/lymphoma with t(5;14)(q31.1;q32.3); *IL3-IGH*
B-lymphoblastic leukemia/lymphoma with t(1;19)(q23;p13.3); *TCF3-PBX1*
Provisional entity: B-lymphoblastic leukemia/lymphoma, BCR-ABL1–like
Provisional entity: B-lymphoblastic leukemia/lymphoma with iAMP21
T-Lymphoblastic Leukemia/Lymphoma
Provisional entity: Early T-cell precursor lymphoblastic leukemia
Provisional entity: Natural killer (NK) cell lymphoblastic leukemia/lymphoma

APL = acute promyelocytic leukemia; NOS = not otherwise specified.
Data from Arber DA, Orazi A, Hasserjian R, et al. The 2016 revision to the World Health Organization classification of myeloid neoplasms and acute leukemia. *Blood*. 2016;127:2391-2405.

Morphology

Leukemic blasts in AML are typically 12 to 20 µm in diameter, with discrete nuclear chromatin, multiple nucleoli, and cytoplasm that usually contains azurophilic granules (Fig. 168-1). Auer rods, which are slender, fusiform cytoplasmic inclusions that stain red with Wright-Giemsa stain, are virtually pathognomonic of AML (Fig. 168-2).

The leukemic cells in ALL tend to be smaller than AML blasts and relatively devoid of granules (see Fig. 168-1). ALL can be divided by French-American-British criteria based on size, nuclear chromatin appearance, nucleoli, and cytoplasm/granules. However, this morphologic classification scheme has been largely replaced by schemes that consider immunologic and cytogenetic characteristics.

Immunophenotyping

Immunophenotyping by multiparameter flow cytometry is used to determine lineage involvement of newly diagnosed acute leukemias and to detect aberrant immunophenotypes, thereby allowing quantification of measurable residual disease after therapy.

Acute Myeloid Leukemia

Most cases of AML express antigens seen on normal immature myeloid cells. The most immature forms of AML express CD34, CD117, and human leukocyte antigen (HLA)-DR, whereas more differentiated forms express CD13 and CD33. CD14, CD15, and CD11b are expressed by AMLs with monocytic features; erythroid leukemias express CD36, CD71, and CD235a (glycophorin A); and megakaryocytic AMLs express CD41 and CD61. In 10 to 20% of patients, otherwise typical AML blasts also express antigens usually restricted to B- or T-cell lineage (e.g., CD2, CD7, CD19, or CD56). Expression of a

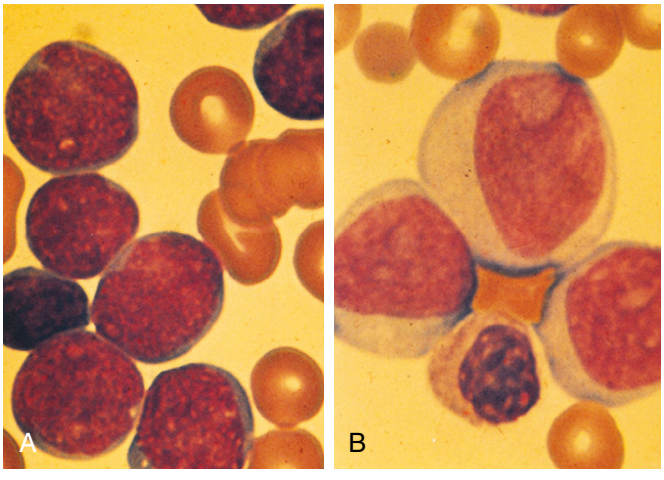

FIGURE 168-1. Acute leukemia. A, Acute lymphoblastic leukemia (ALL). **B**, Acute myeloid leukemia (AML). Lymphoblasts in ALL are smaller, with a higher ratio of nuclear to cytoplasmic material and less distinct nucleoli than in the myeloblasts in AML. The nucleoli in the myeloblasts are clear and "punched out."

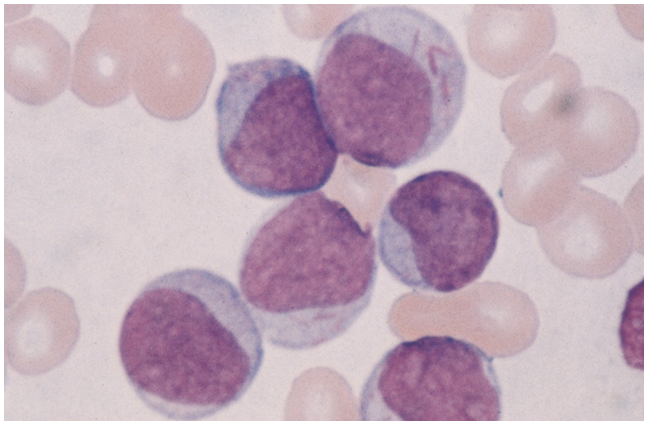

FIGURE 168-2. Acute myeloid leukemia. The myeloblasts in the smear show Auer rods as cytoplasmic inclusions.

single lymphoid antigen by AML cells does not change either the natural history or the therapeutic response of these leukemias.

Acute Lymphoblastic Leukemia

Approximately 75% of cases of ALL express B-lineage antigens and can be subdivided into four categories. The most immature group, previously called pro-B ALL, expresses the early B-cell antigens CD19 and/or CD22 but not CD10 and represents about 10% of cases of ALL. Approximately 50 to 60% of cases of ALL express CD19 and/or CD22 along with the common ALL antigen (CALLA, or CD10), a glycoprotein that is also found occasionally on normal early lymphocytes. CALLA-positive ALL is thought to represent an early pre–B-cell differentiation state. Approximately 10% of cases of ALL have intracytoplasmic immunoglobulin and were previously termed pre–B-cell ALL. The immunophenotypically most mature subset of B-cell ALL is signified by the presence of surface immunoglobulin and accounts for less than 5% of cases of ALL. In general, the best therapeutic outcomes among B-cell ALL types are with CALLA-positive ALL. The 25% of cases of ALL that express T-lineage antigens can be separated immunophenotypically into three groups: (1) those expressing CD7 but not CD1a or CD3 (currently recognized as early T-cell precursor lymphoblastic leukemia), (2) those expressing CD1a but not surface CD3 (previously termed thymic T-ALL), and (3) those expressing surface CD3 (previously termed mature T-ALL). In about 25% of patients with ALL, the leukemic cells may also express a myeloid antigen, but this antigen does not affect responses to current therapies. Although immunophenotyping remains important for ALL, the WHO currently classifies the ALLs largely based on cytogenetic and molecular features (see Table 168-1).

Acute Leukemia of Ambiguous Lineage

Acute leukemias of ambiguous lineage are rare cases with no evidence of lineage differentiation (i.e., acute undifferentiated leukemia) or with blasts that express definitive markers of more than one lineage (i.e., mixed phenotype acute leukemia). Mixed phenotype acute leukemia can contain either distinct blast populations of different lineages (bilineal) or a single population expressing features of both lineages (biphenotypic). In general, the prognosis of patients with acute undifferentiated leukemia or mixed phenotype acute leukemia is poor when treated with standard chemotherapy.

Cytogenetics and Molecular Biology

In most acute leukemias, an abnormality in chromosome number or structure is found. These abnormalities are (oligo)clonal, involving some or all of the malignant cells in a given patient; they are acquired and are not found in the patient's normal cells; and they are referred to as "nonrandom" because specific abnormalities are found in multiple cases and are associated with distinct morphologic or clinical subtypes of the disease. These abnormalities may simply entail the gain or loss of whole chromosomes, but more often they include chromosomal translocations, deletions, or inversions. When patients with acute leukemia and a chromosomal abnormality receive treatment and enter into complete remission, the chromosomal abnormality disappears; when relapse occurs, the abnormality often reappears. In many cases, these abnormalities have provided clues into the pathobiology of acute leukemia.

Acute Myeloid Leukemia

Translocations

The most common cytogenetic abnormalities seen in AML can be categorized according to their underlying biology and prognostic significance.[4,5] The translocation t(8;21) and the inversion inv(16) result in abnormalities of a transcription factor composed of core binding factor-α (CBF-α) and CBF-β. The translocation t(8;21) results in the fusion of CBF-α (*RUNX1*) on chromosome 21 with the *RUNXT1* gene on chromosome 8, whereas the inversion inv(16) results in the fusion of CBF-β (*CBFB*) on the q arm of chromosome 16 with the *MYH11* gene on the p arm. Both of these "core binding factor" AMLs (CBF-AMLs) are characterized by a high complete remission rate and relatively favorable long-term survival for the group as a whole. Comprehensive mutational profiling of CBF-AMLs does, however, reveal clinical prognostic as well as biologic heterogeneity within this pathogenetically unique category of patients.[6] An additional translocation with a favorable prognosis, t(15;17), involves two genes, *PML* and *RAR-α* (a gene encoding the α-retinoic acid receptor), and is invariably associated with acute promyelocytic leukemia. Other genetic alterations may cooperate with *PML-RARα* in the pathogenesis of acute promyelocytic leukemia. Translocations involving the *KMT2A* (previously: *MLL*) gene, located at chromosome band 11q23, are seen in 5 to 7% of AMLs. *KMT2A* is perhaps the most promiscuous oncogene partner in oncology, with more than 130 fusion partners identified. The prognosis of *KMT2A*-associated AML depends on the fusion partner, with t(9;11) predicting an intermediate prognosis but most others considered unfavorable. Trisomy 8 is among the most common nonrandom cytogenetic abnormalities seen in AML; it accounts for 9% of cases and carries an intermediate prognosis. Trisomies of chromosome 21, chromosome 11, and other chromosomes are sometimes seen as well. Deletions of part or all of chromosome 5 or 7 each account for 6 to 8% of cases of AML. These abnormalities are seen with greater frequency in older patients and in patients with AML secondary to myelodysplasia or prior exposure to alkylating agents, and they are associated with an unfavorable prognosis. The presence of multiple (three or more) cytogenetic abnormalities in individual cases of AML defines "complex cytogenetics" and also is associated with an unfavorable prognosis. Particularly unfavorable are cases with a monosomal karyotype (i.e., the presence of two or more distinct monosomies or one monosomy and another structural abnormality), at least partly because of their strong association with mutations in *TP53*.

TABLE 168-2 2017 EUROPEAN LEUKEMIANET CYTOGENETIC/MOLECULAR RISK STRATIFICATION OF AML

	SUBSET
Favorable	t(8;21)(q22;q22.1); *RUNX1-RUNX1T1* inv(16)(p13.1q22) or t(16;16)(p13.1;q22); *CBFB-MYH11* Mutated *NPM1* without *FLT3-ITD* or with *FLT3-ITD*^{low}* Biallelic mutated *CEBPA*
Intermediate	Mutated *NPM1* and *FLT3-ITD*^{high}* Wild-type *NPM1* without *FLT3-ITD* or with *FLT3-ITD*^{low}* (without adverse-risk genetic lesions) t(9;11)(p21.3;q23.3); *MLLT3-KMT2A*† Cytogenetic abnormalities not classified as favorable or adverse
	t(6;9)(p23;q34.1); *DEK-NUP214* t(v;11)(v;q23.3); *KTM2A* rearranged T(9;22)(q34.1;q11.2); *BCR-ABL1*
Adverse	inv(3)(q21.3q26.2) or t(3;3)(q21.3;q26.2); GATA2, MECOM (EVI1) −5 or del(5q); −7; −17/abnl(17p) Complex karyotype,‡ monosomal karyotype Wild-type *NPM1* and *FLT3-ITD*^{high}*
Adverse	Mutated *RUNX1*§ Mutated *ASXL1*§ Mutated TP53

*Low, low allelic ratio (<0.5); high, high allelic ratio (≥0.5).
†Takes precedence over rare, concurrent adverse-risk gene mutations.
‡Three or more unrelated chromosome abnormalities in the absence of one of the WHO-designated recurring translocations or inversions, that is, t(8;21), inv(16) or t(16;16), t(9;11), t(v;11)(v;q23.3), t(6;9), inv(3), or t(3;3).
§These markers should not be used as an adverse prognostic marker if they co-occur with favorable-risk AML subtypes.
AML = acute myeloid leukemia.

Mutations

Assaying for the status of genes that are frequently mutated in AML is slowly becoming standard, with increasing numbers of studies suggesting their utility both for prognosis (Table 168-2) and for the selection of treatment.[7] AML cells appear to carry, on average, about 10 to 15 mutations per cell, far less than found in epithelial cancers. Of these, on average five mutations are in genes recurrently mutated in AML (so-called driver mutations), with the remainder being considered as passenger mutations. Among the recurrently mutated driver mutations, several are of significant therapeutic and prognostic importance and thus are part of the standard evaluation of AML. *CEBPA*, a gene encoding a leucine zipper transcription factor involved in myeloid differentiation, is mutated in 4 to 15% of cases of AML. Biallelic mutations in *CEBPA* are associated with a more favorable prognosis. *NPM1* encodes a nucleolar phosphoprotein with multiple functions. Mutations in *NPM1* are found in approximately 30% of AML cases and are also associated with a more favorable prognosis. As for other genes, co-occurring mutations influence the prognostic significance of *NPM1* mutations. *FLT3* is a receptor tyrosine kinase and is mutated in 30 to 35% of AML patients, about one-fourth of the time as a point mutation and about three-fourths of the time as an internal tandem duplication. Mutations in *FLT3* are associated with a poorer clinical outcome, at least when found at a high allelic ratio. Other driver mutations recurrently mutated in AML include *DNMT3A, IDH1* and *2, NRAS* and *KRAS, RUNX1, TET2, ASXL1*, and *TP53*. Certain mutations (e.g., in *SRSF2, SF3B1, U2AF1*,

ZRSR2, *ASXL1*, *EZH2*, *BCOR*, or *STAG2*) are almost exclusively found in secondary AML and can be used to identify such cases molecularly.

Acute Lymphoblastic Leukemia

Translocations

The most common cytogenetic abnormality seen in adults with ALL is the Philadelphia chromosome, or t(9;22). This translocation results in fusion of the *BCR* gene on chromosome 22 to the *ABL1* tyrosine kinase gene on chromosome 9. The result is the constitutive activation of *ABL1*, but the precise mechanism by which this activity leads to leukemia is unclear. The *BCR-ABL1* fusion is associated with both ALL and CML (Chapter 170), with a difference in the breakpoint of *BCR* distinguishing the two. Specifically, a slightly smaller 190-kD fusion protein is usually found in ALL, whereas a larger 210-kD protein is characteristic of CML. The frequency of t(9;22) in ALL increases with age: it is found in approximately 5% of childhood cases and 25% of adults. Another translocation seen in adult B-cell ALL includes t(4;11), which is seen in 7% of cases, involves the *KMT2A* and *AF4* genes, and has a poor prognosis. t(8;14), which involves *MYC* and the immunoglobulin heavy chain gene, is the translocation associated with a leukemic variant of Burkitt lymphoma (Chapter 171). T-cell ALLs (Chapter 360) are frequently associated with translocations involving chromosomes 7 or 14 at the sites of T-cell receptor enhancer genes on these chromosomes. The other most common cytogenetic abnormalities seen in adult ALL include del(9p), seen in 5 to 9% of cases; del (6q), seen in 5 to 7%; and del(13q), seen in 3 to 5%.

Mutations

As in AML, directed and genome-wide evaluation of cases of ALL have revealed recurrent mutations in addition to those already identified through cytogenetics. Among the most common are mutations in *PAX5* and *IKZF1*, which are seen in 30 and 25% of cases of B-ALL, respectively, and mutations in *NOTCH1*, which are seen in 35% of cases of T-ALL. A poor-risk form of ALL termed Philadelphia chromosome–like ALL accounts for 20 to 25% of adult ALLs.[8] In this type of ALL, leukemia cells lack the classic *BCR-ABL1* translocation and, instead, have kinase-activating mutations in other genes in the same signaling pathway, including *CRLF2*, often in combination with mutations in *JAK2*.

CLINICAL MANIFESTATIONS

The signs and symptoms of acute leukemia, which result from decreased normal marrow function and invasion of normal organs by leukemic blasts, are usually rapid in onset, developing over a few weeks to a few months at most. Anemia, which is present at diagnosis in most patients, causes fatigue, pallor, headache, and, in predisposed patients, angina or heart failure. Thrombocytopenia is usually present, and approximately one third of patients have clinically evident bleeding at diagnosis, usually in the form of petechiae, ecchymoses, bleeding gums, epistaxis, or hemorrhage. Most patients with acute leukemia are significantly granulocytopenic at diagnosis. As a result, approximately one third of patients with AML and slightly fewer patients with ALL have significant or life-threatening infections, mostly of bacterial origin, when initially seen.

In addition to suppressing normal marrow function, leukemic cells can infiltrate other organs. In ALL, which tends to infiltrate normal organs more often than AML, enlargement of lymph nodes, liver, and spleen is common at diagnosis. Patients with T-ALL frequently have mediastinal masses. Bone pain, thought to result from leukemic infiltration of the periosteum or expansion of the medullary cavity, is a common complaint, particularly in children with ALL. Leukemic cells sometimes infiltrate the skin and result in a raised, nonpruritic rash—a condition termed *leukemia cutis*. Leukemic cells may infiltrate the leptomeninges and cause leukemic meningitis, typically manifested by headache and nausea. As the disease progresses, central nervous system (CNS) palsies and seizures may develop. Although less than 5% of patients with ALL have CNS involvement at diagnosis, the CNS is a frequent site of relapse, so CNS prophylaxis is an essential component of the treatment of ALL. Testicular involvement is seen in ALL, and the testicles are a frequent site of relapse.

In AML, collections of leukemic blast cells, often referred to as *chloromas* or *myeloblastomas* or *myeloid sarcomas*, can occur in virtually any soft tissue and appear as rubbery, fast-growing masses. Because the incidence of CNS disease is low in AML, there is no proven benefit of CNS surveillance or prophylaxis.

Certain clinical manifestations are unique to specific subtypes of leukemia. Patients with acute promyelocytic leukemia commonly have subclinical or clinically evident coagulation abnormalities, including disseminated intravascular coagulation (DIC; Chapter 161), caused by tissue thromboplastins released by the leukemic cells. AMLs with monocytic or myelomonocytic differentiation are most likely to have extramedullary involvement. Pure erythroid leukemia often has a long prodromal phase.

DIAGNOSIS

Abnormalities in peripheral blood counts are usually the initial laboratory evidence of acute leukemia, with anemia and thrombocytopenia being almost universal. Up to 25% of patients have severe thrombocytopenia (platelets <20,000/μL). Although most patients are granulocytopenic at diagnosis, the total peripheral white cell count is more variable; approximately 25% of patients have very high white cell counts (>50,000/μL), approximately 50% have white cell counts between 5000 and 50,000/μL, and about 25% have low white cell counts (<5000/μL). In most cases, blasts are present in the peripheral blood, although the percentage of blasts is quite low or absent in some patients.

The diagnosis of acute leukemia is typically established by marrow aspiration (or biopsy if an aspirate cannot be obtained), usually from the posterior iliac crest. Marrow aspirates and biopsy specimens are usually hypercellular and contain 20 to 100% blast cells, which largely replace the normal marrow (see Figs. 168-1 and 168-2). Occasionally, other abnormalities, such as marrow fibrosis (especially with acute megakaryoblastic leukemia) or bone marrow necrosis, are present in addition to the blast cell infiltrate. Marrow samples also should be evaluated for cytogenetic and molecular abnormalities, which are important for classification, prognostication, and guiding therapeutic decision making (see Table 168-2). A diagnostic lumbar puncture is generally recommended in all patients who have ALL but not in patients who have AML in the absence of CNS symptoms.

The prothrombin and partial thromboplastin times are sometimes elevated. In acute promyelocytic leukemia, reduced fibrinogen and evidence of DIC are often seen (Chapter 161). Other laboratory abnormalities frequently present include hyperuricemia, especially in ALL, and increased serum levels of lactate dehydrogenase. In cases of high cell turnover and cell death, evidence of *tumor lysis syndrome* (Chapter 164), including hypocalcemia, hyperkalemia, hyperphosphatemia, hyperuricemia, and renal insufficiency, may be noted at diagnosis. This syndrome, which is more commonly seen shortly after therapy is begun, can be rapidly fatal if untreated.

Differential Diagnosis

The diagnosis of acute leukemia is usually straightforward but can occasionally be difficult. Both leukemia and aplastic anemia (Chapter 151) can manifest with peripheral pancytopenia, but the finding of a hypoplastic marrow without blasts usually distinguishes aplastic anemia. An occasional patient has hypocellular marrow and a clonal cytogenetic abnormality, which establishes the diagnosis of myelodysplasia (Chapter 167) or hypocellular leukemia.

A number of processes other than leukemia can lead to the appearance of immature cells in the peripheral blood. Although other small round cell neoplasms can infiltrate the marrow and mimic leukemia, immunologic markers are effective in differentiating the two. *Leukemoid reactions* to infections such as tuberculosis can result in the outpouring of large numbers of young myeloid cells, but the proportion of blasts in marrow or peripheral blood almost never reaches 20% in a leukemoid reaction (Chapter 153). Infectious mononucleosis (Chapter 348) and other viral illnesses can sometimes mimic ALL, particularly if large numbers of atypical lymphocytes are present in the peripheral blood and the disease is accompanied by immune thrombocytopenia or hemolytic anemia.

TREATMENT AND PROGNOSIS

With the development of effective regimens of combination chemotherapy and advances in hematopoietic cell transplantation, many patients with acute leukemia can be cured. These therapeutic measures are complex and are best carried out at centers with appropriate support services and experience in treating leukemia. Because leukemia is often rapidly progressive, specific antileukemic therapy is typically started in a timely manner, usually within about 3 days of presentation. However, the time from diagnosis to treatment in AML is not related to survival, and it may be preferable to wait for a few extra days for genetic or other laboratory test results to become available in patients whose white blood cell counts are not rapidly increasing so that the best available treatment option can be determined. The goal of initial chemotherapy is to induce a complete remission with restoration of normal marrow function. In general, induction chemotherapy is intensive and is accompanied by significant toxicities. Therefore, patients should be stabilized to the extent possible before specific antileukemic therapy is begun.

Preparing the Patient for Therapy

The diagnosis of leukemia usually comes as a profound psychological shock to the patient and family. Therefore, in addition to stabilizing the patient hematologically and metabolically, it is worthwhile to have at least one formal conference in which the patient and family are advised about the meaning of the diagnosis and the consequences of therapy before treatment is initiated.

Severe bleeding usually results from thrombocytopenia, which can be reversed with platelet transfusions (Chapter 162). Once thrombocytopenic bleeding is stopped, continued prophylactic transfusions of platelets is warranted to maintain the platelet count higher than 10,000/μL. Occasionally, patients also have evidence of DIC (Chapter 161), usually associated with the diagnosis of acute promyelocytic leukemia. If acute promyelocytic leukemia is suspected as the cause, all-*trans*-retinoic acid should be started without waiting for molecular confirmation of the diagnosis (Table 168-3); the drug can be discontinued if the diagnosis is not confirmed. If active bleeding is due to DIC, low doses of heparin (50 U/kg) given intravenously every 6 hours can be of benefit. Platelets and fresh-frozen plasma (or cryoprecipitate) should be transfused to maintain the platelet count higher than 50,000/μL and the fibrinogen level greater than 100 mg/dL until the DIC abates. Whether heparin should be given prophylactically to patients with laboratory evidence of DIC but no active bleeding is an often debated but unsettled question.

In patients with fever and granulocytopenia, blood cultures should be obtained, and empiric broad-spectrum antibiotics should be started while awaiting guidance from the results of the blood cultures and sensitivities (Chapters 153 and 260). If the patient has an adequate granulocyte count, it is preferable to bring an infection under control before starting initial chemotherapy. However, patients often have infection but essentially no granulocytes; in this situation, delaying chemotherapy is unlikely to be beneficial.

Patients with very high blast counts may develop symptoms attributable to the effect of masses of these immature cells on blood flow (leukostasis). The role of leukapheresis and/or hydroxyurea in managing such patients is unclear. Randomized trials are lacking, but data in patients with AML and initial white cell counts greater than 100,000/μL show an early death rate of 20%, with neither leukapheresis nor hydroxyurea improving the outcome. Current guidelines thus suggest proceeding to cytoreductive treatment using planned induction therapy as soon as possible.

Before treatment, management in all patients should be aimed at preventing tumor lysis syndrome (Chapter 164). Patients should be hydrated and given allopurinol 100 to 600 mg orally or intravenously daily before chemotherapy is initiated. Allopurinol prevents the conversion of xanthine and hypoxanthine to uric acid but does not affect already formed uric acid. Patients who present with very high white cell counts may have uremia and anuria secondary to greatly increased serum uric acid levels and intratubular crystallization, even before starting therapy; these patients should be treated with intravenous rasburicase[9] under expert supervision to promote the catabolism of already-formed uric acid to allantoin. Urinary alkalinization is not recommended because it increases the possibility that xanthine and calcium phosphate will precipitate in the kidney.

Treatment of Acute Lymphoblastic Leukemia

After the patient's condition has been stabilized, antileukemic therapy should be started as soon as possible. Treatment of newly diagnosed ALL can be divided into three phases: induction of remission, postremission therapy, and CNS prophylaxis.[10]

Induction of Remission

The initial goal of treatment is to induce complete remission, defined as the reduction of leukemic blasts to undetectable levels and the restoration of normal marrow function. A number of different chemotherapeutic combinations can be used to induce remission; all include vincristine and prednisone, and most add L-asparaginase and daunorubicin, administered over a period of 3 to 4 weeks (Table 168-4). With such regimens, complete remission is achieved in 90% of children and 80 to 90% of adults. For adults age 18 to 59 years with CD20-positive, Philadelphia chromosome–negative ALL, the addition of rituximab (beginning with 375 mg/m^2 on days 1 and 7 and continuing for a total of 16 to 18 infusions) improves the outcome.[A1] Because vincristine, prednisone, and L-asparaginase are relatively nontoxic to normal marrow precursors, the disease often enters complete remission after a relatively brief period of myelosuppression. Failure to achieve complete remission is usually due to either the resistance of leukemic cells to the drugs or to progressive infection. These two complications occur with approximately equal frequency.

Postremission Chemotherapy

If no further therapy is given after induction of complete remission, relapse occurs in almost all cases, usually within several months. Chemotherapy after complete remission can be given in a variety of combinations, dosages, and schedules.

Consolidation chemotherapy refers to short courses of further chemotherapy, given in the hospital at doses similar to those used for initial induction. Consolidation chemotherapy usually involves different drugs than were successful for inducing the initial remission; alternatively, drug combinations can be rotated. Such drugs include high-dose methotrexate, cyclophosphamide, and cytarabine, among others. Most regimens include six to eight courses of intensive consolidation therapy. Maintenance involves the administration of low-dose chemotherapy on a daily or weekly outpatient basis for long periods. The most commonly used maintenance regimen in ALL combines daily 6-mercaptopurine and weekly or biweekly methotrexate. The optimal duration of maintenance chemotherapy is unknown, but it is usually given for 2 to 3 years. The use of more intensive regimens similar to those used in the treatment of pediatric ALL are tolerable in patients up to age 40 years and may improve outcomes compared with regimens initially developed for adults.

Central Nervous System Prophylaxis

Most chemotherapeutic agents that are given intravenously or orally do not penetrate the CNS well, and at least 35% of adults with ALL will develop CNS leukemia if no form of CNS prophylaxis is given. With prophylaxis, relapse in the CNS as an isolated event occurs in less than 10% of patients. Systemic chemotherapy with high-dose methotrexate (e.g., 200 mg/m^2 intravenously over 2 hours, followed by 800 mg/m^2 over 22 hours) and cytarabine (e.g., 3 g/m^2 over 2 hours every 12 hours for four doses) can achieve therapeutic drug levels within the CNS. Alternatives are intrathecal cytarabine, intrathecal methotrexate, intrathecal methotrexate combined with 2400 cGy radiation to the cranium, or 2400 cGy to the craniospinal axis.

Treatment of Burkitt-like ALL

Burkitt-like ALL (also called FAB L3 or mature B-cell ALL) is characterized by the presence of monoclonal surface immunoglobulin, cytogenetics showing t(8;14), and the constitutive expression of the *MYC* oncogene. Burkitt-like ALL, which accounts for 3 to 5% of adult cases of ALL, responds well to regimens that incorporate short, intensive courses of high-dose methotrexate (1.5 g/m^2 over 24 hours with leucovorin), cytarabine (3 g/m^2 over 2 hours every 12 hours for four doses), and cyclophosphamide (200 mg/m^2/day for 5 days); this regimen yields high rates of complete response and cures in about 50% of patients. The addition of rituximab may further improve outcomes.

Treatment of Philadelphia Chromosome–Positive ALL

Approximately 5% of pediatric cases and 25% of adult cases of ALL have cytogenetics showing t(9;22), the Philadelphia chromosome. The addition of a tyrosine kinase inhibitor such as imatinib, dasatinib, or ponatinib to conventional chemotherapeutic regimens can provide complete response rates equivalent to those seen in Philadelphia chromosome–negative ALL. Therapy with dasatinib (e.g., 70 mg twice daily for 84 days) and prednisone (e.g., 60 mg/m^2 per day for 24 days followed by a taper and discontinuing on day 32) alone without chemotherapy appears sufficient to allow the majority of older patients with Philadelphia chromosome–positive ALL to achieve an initial morphologic remission, but remissions typically are not durable.[11] However, subsequent treatment

TABLE 168-3 MANAGEMENT OF NEWLY DIAGNOSED ACUTE PROMYELOCYTIC LEUKEMIA

A. Induction—ATRA 45 mg/m^2 orally in divided doses daily plus arsenic trioxide 0.15 mg/kg daily until morphologic remission
B. Consolidation #1—oral arsenic trioxide 0.15 mg/kg/day 5 days/wk for 4 weeks every 8 weeks for total of 4 cycles, and ATRA 45 mg/m^2/day for 2 weeks every 4 weeks for total of 7 cycles

Or, if contraindications to arsenic:

A. Induction: Intravenous ATRA 45 mg/m^2 in divided doses daily plus idarubicin 12 mg/m^2 on days 2, 4, 6, 8
B. Consolidation: Intravenous ATRA 45 mg/m^2 × 15 days + idarubicin 5 mg/m^2 × 4 days × 1 cycle, then ATRA × 15 days plus mitoxantrone 10 mg/m^2 × 3 days × 1 cycle, then ATRA × 15 days + idarubicin 12 mg/m^2 × 1 day × 1 cycle

ATRA = all-*trans*-retinoic acid.

TABLE 168-4 MANAGEMENT OF NEWLY DIAGNOSED ADULT PHILADELPHIA CHROMOSOME–NEGATIVE ACUTE LYMPHOID LEUKEMIA UNDER EXPERT SUPERVISION

A. Induction (and courses 3, 5, 7)—cyclophosphamide 300 mg/m^2 over 3 hr q12h for 6 doses on days 1, 2, 3; doxorubicin 50 mg/m^2 on day 4; vincristine 2 mg/day on days 4 and 11; and dexamethasone 40 mg/day on days 1-4 and days 11-14
B. Consolidation (courses 2, 4, 6, 8)—MTX 200 mg/m^2 over 2 hr, followed by 800 mg/m^2 over 22 hr on day 1; high-dose cytarabine 3 g/m^2 over 2 hr q12h for 4 doses on days 2 and 3
C. Four intrathecal treatments of MTX 12 mg alternating with cytarabine 100 mg are given during the first four courses of systemic therapy

MTX = methotrexate.

with two cycles of blinatumomab (a bispecific antibody to CD19 on ALL cells and CD3 on T cells) can substantially increase the proportion of patients who achieve a molecular remission and is associated with survival expectations exceeding 90% at 18 months.[12]

Treatment of Relapsed ALL

Most relapses occur within 2 years after diagnosis, and most occur in the marrow. Occasionally, relapse is initially found in an extramedullary site such as the CNS or testes. Extramedullary relapse is usually followed shortly by systemic (marrow) relapse and should be considered part of a systemic recurrence. With the use of chemotherapeutic regimens similar to those used for initial induction, 50 to 70% of patients achieve at least a short-lived second remission. If the CNS or testes is the initial site of the relapse, specific therapy with chemotherapy and/or radiation to that site is also required along with systemic retreatment.

Because the prognosis of relapsed leukemia treated with standard chemotherapy alone is so poor, hematopoietic cell transplantation (Chapter 163) is usually recommended in this setting, especially if a morphologic remission is obtained with salvage therapy. Some alternatives to conventional multiagent salvage chemotherapy are available. For example, nelarabine when used as a single agent can induce complete remission in 30% of patients with recurrent T-ALL. The bispecific T-cell engager (BiTE) blinatumomab, which is composed of the single-chain variant fragments of anti-CD19 and anti-CD3 antibodies, improves disease-free and overall survival in patients with recurrent B-ALL[A2,A3] and in patients with B-ALL in first or second morphologic remission who have residual leukemia cells (i.e., measurable residual disease) quantified at more than 0.1%. Inotuzumab ozogamicin, which is a CD22 antibody conjugated to a highly toxic calicheamicin derivative, also can increase the complete remission rate, the duration of remission, and the progression-free survival in adults with relapsed or refractory B-ALL compared with standard intensive chemotherapy,[A4] but with an increased risk of sinusoidal obstruction syndrome (previously termed veno-occlusive disease; Chapter 129). Very high complete responses also have been reported in trials using chimeric antigen receptor T cells targeting CD19 or CD22[13,14] in B-ALL that is refractory or in second or later relapse. Cytokine release syndrome and neurologic toxicity are the most significant side effects.

Hematopoietic Cell Transplantation

The use of high-dose chemoradiotherapy followed by hematopoietic cell transplantation (Chapter 163) from a suitable donor can cure 20 to 40% of patients with ALL who fail to achieve an initial remission or who have a relapse after an initial complete remission; it can cure 50 to 60% of patients who undergo transplantation during a first remission. Despite considerable debate, several studies have reported improved survival when adults with high-risk or standard-risk ALL receive a hematopoietic stem cell transplant during a first remission rather than being treated with standard chemotherapy.[A5] The major limitations of transplantation are graft-versus-host disease, infections, and recurrent disease. If an HLA-identical sibling is not available, transplantation from a matched or partially matched unrelated donor or transplantation of cord blood from a partially matched unrelated donor can be conducted, with results that approach those seen with matched related donors.

Prognosis of ALL

A number of factors help predict the outcome in ALL, the most important of which are younger age, a lower white cell count at diagnosis, and favorable cytogenetics (Fig. 168-3). With currently available treatment regimens, 5-year survival has reached 90% for pediatric ALL. In adults, outcomes are less favorable, with 5-year survival rates of 65 to 75% in adolescents and young adults up to age 40 years, less than 20% in individuals older than age 60 years, and less than 45% overall.

Treatment of Acute Myeloid Leukemia

Remission Induction in Medically Fit Adults

Unless patients have contraindications to aggressive therapy, initial treatment generally includes a combination of an anthracycline and cytarabine (the latter at a dose of 100 to 200 mg/m^2/day for 7 days; Table 168-5) and leads to complete remission in 60 to 80% of patients.[15] Prospective randomized trials have demonstrated that for patients aged 65 years or less, idarubicin (10 to 12 mg/m^2/day for 3 days) or a higher dose of daunorubicin (60 to 90 mg/m^2/day for 3 days) is superior to the conventional daunorubicin dose of 45 mg/m^2/day for 3 days.[16] For acute myeloid leukemia with a mutation in isocitrate dehydrogenase 1, adding ivosidenib, which is an inhibitor of it, can prolong median overall survival from 8 months to 24 months.[A6] Profound myelosuppression always follows when these agents are used at doses capable of inducing complete remission. Approximately 50% of patients will have more than 5% blasts remaining in their marrow 1 week after completing the first cycle of induction. Many experts still recommend starting a second cycle in such circumstances, although the benefit of this approach has been questioned.

Persistence of blasts after the first cycle of induction appears to be associated with an increased risk of recurrent disease. In approximately 30% of cases, AML blasts will have mutations in *FLT3*. In such patients, the addition of the *FLT3* inhibitor midostaurin as part of induction (e.g., 50 mg twice daily on days 8 to 21), consolidation (e.g., 50 mg twice daily on days 8 to 21), and maintenance (e.g., 50 mg twice daily for 1 year) leads to improved disease-free and overall survival.[A7] The addition of the CD33 antibody-drug conjugate gemtuzumab ozogamicin to induction and, possibly, consolidation may reduce relapse and improve survival, particularly in patients with favorable-risk disease and, to a lesser extent, patients with intermediate-risk CD33-positive AML. Failure to achieve complete remission is usually due either to drug resistance or to fatal complications of myelosuppression. In older adults with therapy-related AML or AML with myelodysplasia-related changes, CPX-351, a liposomal formulation of cytarabine co-encapsulated with daunorubicin, leads to better survival than conventional chemotherapy.[A8] With the increasing availability of molecularly targeted agents and lower intensity regimens, a number of chemotherapeutic options are available for the initial therapy of AML in medically fit adults.[17]

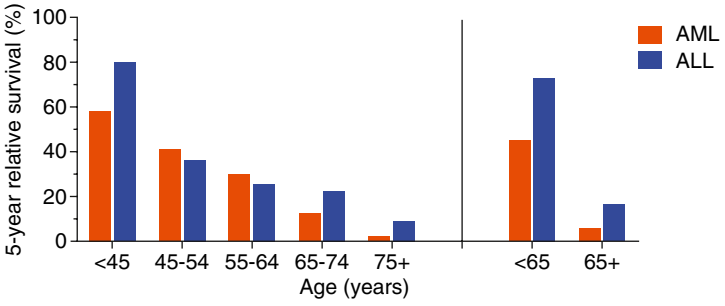

FIGURE 168-3. Shown are the 5-year survival rates (relative to age-matched controls) for adult patients with newly diagnosed acute myeloid leukemia (AML) on the left and acute lymphoblastic leukemia (ALL) on the right according to U.S. Surveillance, Epidemiology and End Results Program (SEER) data.

TABLE 168-5 MANAGEMENT OF NEWLY DIAGNOSED ACUTE MYELOID LEUKEMIA UNDER EXPERT SUPERVISION

A. Induction—daunorubicin 60-90 mg/m^2/day for 3 days (or idarubicin 10-12 mg/m^2/day for 3 days) and cytarabine 100-200 mg/m^2/day for 7 days
   1. At least for favorable-risk disease—add gemtuzumab ozogamicin 3 mg/m^2 (up to 4.5 mg) on days 1, 4, and 7
   2. For *FLT3*-mutated AML—add oral midostaurin 50 mg twice daily on days 8-21
   3. Older adults with therapy-related AML and AML with myelodysplasia-related changes—CPX-351 (100 mg/m^2 cytarabine, 44 mg/m^2 daunorubicin) on days 1, 3, and 5

B. Postremission
   1. Favorable risk—cytarabine 3 g/m^2 over 3 hr q12h on days 1, 2, and 3 every month for 4 months; may add gemtuzumab ozogamicin 3 mg/m^2 (up to 4.5 mg) on day 1 for first 2 cycles
   2. Intermediate risk—as for favorable risk; or, if HLA-matched related or unrelated donor exists, allogeneic hematopoietic cell transplantation
   3. Unfavorable risk—proceed to allogeneic transplantation if possible; if not, treat as for intermediate risk
   4. For *FLT3*-mutated AML—add oral midostaurin 50 mg twice daily on days 8-21
   5. Older adults with therapy-related AML and AML with myelodysplasia-related changes—CPX-351 (65 mg/m^2 cytarabine, 29 mg/m^2 daunorubicin) on days 1 and 3 for 1-2 cycles

AML = acute myeloid leukemia; CPX-351 = liposomal cytarabine-daunorubicin; *FLT3* = FMS-like tyrosine kinase 3; HLA = human leukocyte antigen.

Postremission Therapy

Intensive consolidation chemotherapy with repeated courses of daunorubicin and cytarabine at doses similar to those used for induction, high-dose cytarabine (1 to 3 g/m^2/day for 3 to 6 days), or other agents prolongs the average duration of remission and improves the chances for long-term, disease-free survival. The best results reported to date have generally been achieved with repeated cycles of high-dose cytarabine. Maintenance therapy with CC-486, an oral formulation of azacitidine, significantly improves median overall (from 15 to 25 months) and relapse-free (from 5 to 10 months) survival in older adults who are in remission after intensive induction/postremission therapy and cannot undergo allogeneic hematopoietic cell transplantation.[A9] In AML, recurrent leukemia occurs less often in the CNS (approximately 10% of cases) than in patients with ALL, most commonly in patients with monocytic or myelomonocytic differentiation of AML blasts. There is no evidence that CNS prophylaxis improves survival in AML.

Based on cytogenetics and molecular testing, the favorable outcomes after initial therapy are in patients who have t(8;21) or inv(16), patients who have

normal cytogenetics but biallelic mutated *CEBPA*, and patients who have mutated *NPM1* and either wild-type *FLT3* or low-allelic-ratio *FLT3*-ITD (see Table 168-2). Intermediate-risk patients have normal cytogenetics without mutations in *NPM1*, *CEBPA*, and *FLT3* (or *FLT3*-ITD with a low allelic ratio) or with high-allelic-ratio *FLT3*-ITD in combination with a mutation in *NPM1*. Also at intermediate risk are patients with t(9;11) or those with cytogenetic abnormalities not classified as favorable or unfavorable. Patients with an unfavorable prognosis have high-allelic-ratio inv(3), t(6;9), −5 or del5, or −7 or del7; a high-allelic-ratio *FLT3*-ITD, and wild-type *NPM1*; mutations in *RUNX1*, *ASXL1*, or *TP53*; or complex cytogenetics (three or more independent chromosome abnormalities).

Treatment of Recurrent AML

Patients in complete remission by morphologic criteria (i.e., ≤5% blasts in the bone marrow) may still have some residual leukemic disease not identified by light microscopy. Both multiparameter flow cytometry-based methods, which rely on identification of abnormal immunophenotypes, and molecular-based methods detecting chimeric fusion proteins or somatic mutations can detect and quantify residual disease, which identifies patients with a high risk of subsequent recurrent disease and worse overall survival.

About 50% of patients whose AML recurs after initial chemotherapy can achieve a second remission after retreatment with daunorubicin-cytarabine or high-dose cytarabine. The likelihood of achieving a second remission is predicted by the duration of the first remission: 70% in patients whose first remission persisted beyond 2 years, compared with less than 15% in those whose first remission lasted less than 6 months. Enasidenib and ivosidenib, oral targeted inhibitors of mutant *IDH2* and *IDH1*, respectively, have been approved for the treatment of patients with recurrent *IDH*-mutated AML based on nonrandomized studies. For the treatment of patients with recurrent *FLT3*-mutated AML, the tyrosine kinase inhibitor gilteritinib (120 mg daily) improves median survival by about 3.5 months compared with standard salvage chemotherapy.[A10]

Second remissions tend to be short-lived, however, and few patients in whom relapse occurs after first-line chemotherapy are cured by salvage chemotherapy. Therefore, hematopoietic cell transplantation is generally indicated, especially if a morphologic remission is obtained with salvage therapy.

Hematopoietic Cell Transplantation

For patients with AML in whom an initial remission cannot be achieved or for those who relapse after chemotherapy, hematopoietic cell transplantation (Chapter 163) from an HLA-identical sibling offers the best chance for cure. Allogeneic transplant is most effective when performed in AML patients who are in complete remission both morphologically and by measurable residual disease testing. Patients with measurable residual disease at the time of transplant are at increased risk for post-transplant relapse.[18]

Meta-analyses confirm that allogeneic transplantation from an HLA-matched sibling improves survival compared with chemotherapy in patients who are in a first remission with unfavorable-risk disease. By comparison, the benefits of hematopoietic cell transplantation are less clear in patients with intermediate-risk disease and probably do not extend to patients with favorable-risk AML in remission, especially if the cytogenetics are favorable. The major limitations of allogeneic hematopoietic cell transplantation are lack of a matched sibling donor, graft-versus-host disease, infections related to immunosuppression, and recurrent disease. Because transplant-related toxicities increase with patient age, some centers limit hematopoietic cell transplantation to patients 65 years of age or younger. However, recent studies of reduced-intensity allogeneic transplantation have shown encouraging results in patients with AML in remission at ages up to 75 years. Allogeneic transplantation using HLA-matched unrelated donors results in survival essentially equivalent to that seen using matched siblings, although there is a higher incidence of complications. In experienced centers, survival outcomes with HLA-haploidentical donors have also approached those seen with HLA-matched patients. Similarly, cord blood transplantation results in cure rates similar to those seen with HLA-matched unrelated transplants and may result in reduced relapse rates in patients with measurable residual disease at the time of transplant. Autologous hematopoietic cell transplantation offers an alternative for patients without matched siblings to serve as donors. In randomized trials, autologous transplantation after consolidation chemotherapy has significantly prolonged the duration of disease-free survival for patients with AML in first remission, but it has not altered overall survival compared with chemotherapy alone.

Treatment of AML in Patients Not Candidates for Intensive Therapy

The benefits of intensive chemotherapy are reduced in older, medically less-fit patients. Traditional alternatives to intensive chemotherapy include supportive care alone, low-dose cytarabine, or use of a DNA methyltransferase inhibitor (e.g., azacitidine or decitabine). For example, in patients age 65 years or older with newly diagnosed AML, azacitidine can increase median overall survival from 6.5 months to 10.4 months compared with conventional care regimens (best supportive care or standard induction chemotherapy or low-dose cytarabine), and its safety was consistent with its known safety profile in other trials.[A11] The oral BCL2 inhibitor venetoclax combined with azacitidine can double the complete remission rate from 18% to 37% and increase median survival from 14.7 to 20.5 months compared with azacitidine alone.[A12] As a result, the combination of venetoclax and azacitidine has become a new standard of care for medically less-fit adults with newly diagnosed AML. Venetoclax also can be used with low-dose cytarabine. For the same target patient population, the hedgehog signaling pathway inhibitor glasdegib has been approved for use together with low-dose cytarabine based on data from a randomized trial showing an increase in median survival from 4.9 to 8.8 months.[A13] Uncontrolled studies suggest that a 10-day course of decitabine may be superior to shorter courses, especially in patients with adverse-risk AML, including those with *TP53* mutations.

In older patients with AML who are ineligible for intensive chemotherapy, single-agent gemtuzumab ozogamicin, as compared with best supportive care (including hydroxyurea), modestly improves overall survival without excess serious adverse events.[A14]

Prognosis of AML

Among patients in whom complete remission is achieved, 20 to 40% remain alive in continuous complete remission for more than 5 years, suggesting a probable cure. As with ALL, younger patients (see Fig. 168-3) and those with a low white cell count at diagnosis have a more favorable outcome.

Fifteen percent of patients with refractory disease can be saved by hematopoietic cell transplantation. If the transplant is performed earlier, the outcome is better: 50 to 60% of patients are cured if hematopoietic cell transplantation is performed during the first remission, but only approximately 30% of patients who are treated with hematopoietic cell transplantation at first relapse or during second remission are cured.

Patients who have a preleukemic phase before their disease evolves into acute leukemia and those whose leukemia is secondary to prior exposure to chemotherapy also have a poorer prognosis. Any measurable residual disease following induction and consolidation greatly increases the risk of subsequent relapse.

Treatment and Prognosis of Other Acute Leukemias

Treatment of Acute Promyelocytic Leukemia

The combination of all-*trans*-retinoic acid (45 mg/m^2/day until complete remission is achieved) together with arsenic trioxide without any chemotherapy is superior to all-*trans*-retinoic acid plus an anthracycline for patients with low- to intermediate-risk acute promyelocytic leukemia (i.e., those who present with white blood cell counts <10,000/μL)[A15] and is preferred as first-line treatment.[19] For patients with high-risk disease, therapy with all-*trans*-retinoic acid/retinoic acid should be combined with either gemtuzumab ozogamicin or idarubicin, or all-*trans*-retinoic acid can be added to combination chemotherapy. Patients treated with all-*trans*-retinoic acid usually have their coagulation disorders corrected within several days. A unique toxicity of all-*trans*-retinoic acid in the treatment of acute promyelocytic leukemia is the development of hyperleukocytosis accompanied by respiratory distress and pulmonary infiltrates. This differentiation syndrome responds to temporary discontinuation of all-*trans*-retinoic acid and the addition of corticosteroids. In patients who have recurrent acute promyelocytic leukemia and who were not previously treated with all-*trans*-retinoic acid/arsenic trioxide or who have late relapse after all-*trans*-retinoic acid/arsenic trioxide therapy, arsenic trioxide (0.15 mg/kg/day until complete remission is achieved) ± all-*trans*-retinoic acid with or without an anthracycline or gemtuzumab ozogamicin is effective.

Treatment of Blastic Plasmacytoid Dendritic-Cell Neoplasm

Blastic plasmacytoid dendritic-cell neoplasm is a rare, aggressive malignancy with fewer than 1000 cases annually in the United States. With the newest WHO classification system, it is no longer considered a subtype of AML but, rather, considered a separate disease entity. In adults, it occurs primarily after age 60 years and in a 4:1 male:female ratio. The cause is the malignant proliferation of plasmacytoid dendritic cells that over-express CD123, the interleukin-3 receptor subunit alpha. In some patients, the disease can evolve from myelodysplastic syndrome (Chapter 167).

Bone marrow involvement typically presents as cytopenias. About 80% of patients have skin involvement, usually as brown to purple nodules, often accompanied by purpura. Lymphadenopathy, splenomegaly, and even central nervous system involvement can occur. Fatigue, fever, and night sweats are common. Skin or bone marrow biopsy shows immature plasmacytoid dendritic cells.

Tagraxofusp (SL-401) is an immunoconjugate consisting of IL-3 fused to a truncated diphtheria toxin (7 to 10 mg/kg on days 1 to 5 of each 21-day cycle)[20] that can result in remission in about 70% of cases. Hematopoietic cell transplantation is recommended during first remission. Chemotherapy regimens used for ALL and AML also can provide transient remission. In newly treated patients, about 50% survive for 2 or more years.

Management of Complications

Treatment of acute leukemia, especially AML, is accompanied by a number of complications, the two most serious and frequent being infection and bleeding. During the granulocytopenic period that follows induction and consolidation chemotherapy, the risk for bacterial infection is high. Antibiotic prophylaxis under expert supervision significantly decreases infection-related deaths in afebrile neutropenic patients, with the best results seen with quinolones. Despite

prophylaxis, many patients become febrile while neutropenic, and patients can still develop important infections. The most common bacterial species vary somewhat from medical center to medical center, but *Staphylococcus* (primarily *S. epidermidis*; Chapter 267) and *Enterococcus* species (Chapter 270) are the most frequent gram-positive organisms, whereas *Pseudomonas aeruginosa* (Chapter 282) and enteric organisms such as *Escherichia coli* (Chapter 280) and *Klebsiella* species (Chapter 281) are the most common gram-negative organisms isolated.

Even if no cause for fever is found, bacterial infection should be assumed, and, in general, all patients with fever and neutropenia should receive broad-spectrum antibiotics (Chapters 153 and 260). Monotherapy with an intravenous antipseudomonal agent, such as a carbapenem (e.g., imipenem-cilastatin), a cephalosporin (e.g., cefepime), or an antipseudomonal penicillin (e.g., piperacillin-tazobactam), is recommended as empirical therapy. Vancomycin should not be part of standard coverage in most patients but may be used in those with suspected catheter infections or severe mucositis and in patients with hemodynamic instability or altered mental status. Combination therapy with other gram-negative agents (e.g., aminoglycosides) may be needed. Once begun, antibiotics should be continued until patients recover their granulocyte counts, even if they become afebrile first. If documented bacteremia persists despite appropriate antibiotics, the physician should consider removal of indwelling catheters.

Invasive fungal infections are also common following chemotherapy for acute leukemia and are associated with significant morbidity and mortality. Antifungal prophylaxis is associated with a significant reduction in death from fungal infection in patients with AML receiving induction chemotherapy. Posaconazoles is often considered to be more effective than fluconazole or itraconazole. In addition to being granulocytopenic, patients undergoing induction chemotherapy for leukemia have deficient cellular and humoral immunity, at least temporarily, and therefore are subject to infections common in other immunodeficiency states, including *Pneumocystis jirovecii* infection and a variety of viral infections. *P. jirovecii* infection can be prevented by the prophylactic use of trimethoprim-sulfamethoxazole. In cytomegalovirus (CMV)–seronegative patients, CMV-seronegative or leukocyte-reduced blood products should be used to prevent primary infection (Chapter 347). Herpes simplex (Chapter 345) can often complicate existing mucositis and can be prevented with prophylactic acyclovir. Acyclovir is also useful for the prevention and treatment of herpes zoster (Chapter 346).

Myeloid growth factors (granulocyte or granulocyte-macrophage colony-stimulating factor; Chapter 142), if given shortly after the completion of chemotherapy, shorten the period of severe myelosuppression by, on average, 4 days. In most studies, this accelerated recovery has resulted in fewer days with fever and less use of antibiotics, but it has not improved the complete response rate or altered survival and is currently not recommended after induction chemotherapy.

The platelet count that signals a need for platelet transfusion has been the subject of debate. Platelet transfusions from random donors are recommended at a threshold to 10,000/μL in patients without active bleeding. In contrast, a no-prophylaxis strategy results in more days with bleeding and a shorter time to first bleeding episode and therefore is not recommended.[21] In 30 to 50% of cases, patients eventually become alloimmunized and require the use of HLA-matched platelets (Chapter 162). Transfusion-induced graft-versus-host disease (Chapter 162), manifesting as a rash, low-grade fever, elevated values in liver function tests, and decreasing blood counts, can be prevented by irradiating all blood products before transfusion.

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169 CHRONIC LYMPHOCYTIC LEUKEMIA

JENNIFER R. BROWN

DEFINITION

Chronic lymphocytic leukemia is a mature B-cell malignancy in which the neoplastic cells share an immunoglobulin gene rearrangement. The disease involves the blood, bone marrow, lymph nodes, spleen, liver, and often other organs at the time of presentation, but clinical manifestations range from asymptomatic disease that may not require therapy for decades to rapidly progressive disease that soon can be life-threatening. Recent therapeutic advances using targeted therapies can provide prolonged progression-free survival.[1]

EPIDEMIOLOGY

Chronic lymphocytic leukemia (CLL) is the most common leukemia in the Western Hemisphere. In the United States, the annual incidence is over 20,000 cases, the prevalence is nearly 200,000, and approximately 4400 individuals die from the disease each year.[2] The lifetime risk of developing chronic lymphocytic leukemia is approximately 0.6%. From 2006 to 2021, both the incidence and death rates declined.

The median age at diagnosis is 70 years, with approximately one third of patients under age 65 years and 10% under age 55 years. Approximately twice as many men as women are diagnosed with chronic lymphocytic leukemia. The disease is more common among Whites than Blacks or Native Americans and is rare among Asians and Pacific Islanders, even when the latter have moved to the Western Hemisphere.

The risk factors for chronic lymphocytic leukemia are not well defined. Up to 10% of individuals with chronic lymphocytic leukemia have a first-degree relative with the disease. Epidemiologic studies suggest a five- to eight-fold increased risk for chronic lymphocytic leukemia among individuals with one affected first-degree relative, and a 27-fold increase in risk with two affected first-degree relatives. Although families have been reported with Mendelian inheritance over multiple generations, no highly penetrant risk mutations have been identified. However, genome-wide association studies have identified over 40 common alleles of low penetrance, and data suggest that rare variants in the *ATM* gene may also contribute.

Epidemiologic studies suggest a possible increase in risk with exposure to pesticides or living on a farm, but the data are not definitive. Chronic lymphocytic leukemia is recognized as a service-connected illness among Vietnam War veterans who were exposed to Agent Orange. Studies of exposure to radiation at the Chernobyl atomic plant are suggestive, but most studies have not shown a definite association between radiation exposure and the risk of chronic lymphocytic leukemia.

PATHOBIOLOGY

In many patients who have chronic lymphocytic leukemia, lymphoid-primed hematopoietic stem cells give rise to mature B-cells that expand and can

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prophylaxis, many patients become febrile while neutropenic, and patients can still develop important infections. The most common bacterial species vary somewhat from medical center to medical center, but *Staphylococcus* (primarily *S. epidermidis*; Chapter 267) and *Enterococcus* species (Chapter 270) are the most frequent gram-positive organisms, whereas *Pseudomonas aeruginosa* (Chapter 282) and enteric organisms such as *Escherichia coli* (Chapter 280) and *Klebsiella* species (Chapter 281) are the most common gram-negative organisms isolated.

Even if no cause for fever is found, bacterial infection should be assumed, and, in general, all patients with fever and neutropenia should receive broad-spectrum antibiotics (Chapters 153 and 260). Monotherapy with an intravenous antipseudomonal agent, such as a carbapenem (e.g., imipenem-cilastatin), a cephalosporin (e.g., cefepime), or an antipseudomonal penicillin (e.g., piperacillin-tazobactam), is recommended as empirical therapy. Vancomycin should not be part of standard coverage in most patients but may be used in those with suspected catheter infections or severe mucositis and in patients with hemodynamic instability or altered mental status. Combination therapy with other gram-negative agents (e.g., aminoglycosides) may be needed. Once begun, antibiotics should be continued until patients recover their granulocyte counts, even if they become afebrile first. If documented bacteremia persists despite appropriate antibiotics, the physician should consider removal of indwelling catheters.

Invasive fungal infections are also common following chemotherapy for acute leukemia and are associated with significant morbidity and mortality. Antifungal prophylaxis is associated with a significant reduction in death from fungal infection in patients with AML receiving induction chemotherapy. Posaconazoles is often considered to be more effective than fluconazole or itraconazole. In addition to being granulocytopenic, patients undergoing induction chemotherapy for leukemia have deficient cellular and humoral immunity, at least temporarily, and therefore are subject to infections common in other immunodeficiency states, including *Pneumocystis jirovecii* infection and a variety of viral infections. *P. jirovecii* infection can be prevented by the prophylactic use of trimethoprim-sulfamethoxazole. In cytomegalovirus (CMV)–seronegative patients, CMV-seronegative or leukocyte-reduced blood products should be used to prevent primary infection (Chapter 347). Herpes simplex (Chapter 345) can often complicate existing mucositis and can be prevented with prophylactic acyclovir. Acyclovir is also useful for the prevention and treatment of herpes zoster (Chapter 346).

Myeloid growth factors (granulocyte or granulocyte-macrophage colony-stimulating factor; Chapter 142), if given shortly after the completion of chemotherapy, shorten the period of severe myelosuppression by, on average, 4 days. In most studies, this accelerated recovery has resulted in fewer days with fever and less use of antibiotics, but it has not improved the complete response rate or altered survival and is currently not recommended after induction chemotherapy.

The platelet count that signals a need for platelet transfusion has been the subject of debate. Platelet transfusions from random donors are recommended at a threshold to 10,000/μL in patients without active bleeding. In contrast, a no-prophylaxis strategy results in more days with bleeding and a shorter time to first bleeding episode and therefore is not recommended.[21] In 30 to 50% of cases, patients eventually become alloimmunized and require the use of HLA-matched platelets (Chapter 162). Transfusion-induced graft-versus-host disease (Chapter 162), manifesting as a rash, low-grade fever, elevated values in liver function tests, and decreasing blood counts, can be prevented by irradiating all blood products before transfusion.

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169 CHRONIC LYMPHOCYTIC LEUKEMIA

JENNIFER R. BROWN

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PATHOBIOLOGY

In many patients who have chronic lymphocytic leukemia, lymphoid-primed hematopoietic stem cells give rise to mature B-cells that expand and can

ABSTRACT

Chronic lymphocytic leukemia, which is a low-grade malignancy of mature B cells, has a widely variable clinical course that to some extent can be predicted by key biologic markers. Most newly diagnosed patients are followed without therapy, and a substantial fraction of patients never require any therapy. All patients are at increased risk of infection and secondary malignancies, so they should receive aggressive vaccination and cancer screening as part of their standard care. When patients require therapy, targeted therapies, particularly against Bruton tyrosine kinase and BCL-2, have revolutionized the landscape of the disease by providing effective, well-tolerated oral therapies.

KEYWORDS

chronic lymphocytic leukemia
monoclonal B-cell lymphocytosis
IGHV
TP53
FISH
iwCLL
ibrutinib
acalabrutinib
zanubrutinib
venetoclax
obinutuzumab
rituximab
FCR

become oligoclonal. The development and progression of one or more of these oligoclones is likely dependent on the acquisition of genetic events that lead to chronic lymphocytic leukemia. About 40% of patients with chronic lymphocytic leukemia carry what is called a stereotyped B-cell receptor, which has hundreds of types. These subgroups of B cell receptors are identical or almost identical to each other, a finding that strongly suggests a role for antigen stimulation in pathogenesis. Some stereotyped subsets of chronic lymphocytic leukemia lymphocytes with identical B cell receptors also carry the same genetic events.[3] Additionally, clones of chronic lymphocytic leukemia cells carry an epigenetic signature, which is similar to the developmental stage of the normal B-cell from which they arose. These genetic events, the B cell receptor structure, and the epigenetic signature all carry significant prognostic importance.

The B-Cell Receptor in Chronic Lymphocytic Leukemia

At the time when chronic lymphocytic leukemia is diagnosed, the population of B cells with a common immunophenotype by flow cytometry also carries and expresses a clonal, rearranged immunoglobulin heavy and light chain gene. Somatic hypermutation can be present, with up to 15% or more variations from germline.[4] Although the degree of somatic hypermutation is a continuum across chronic lymphocytic leukemia, the striking clinical observation is that the disease's behavior and outcome vary tremendously based on a dichotomous cutoff of 2% variation from germline. Patients whose chronic lymphocytic leukemia carries a mutated immunoglobulin heavy chain variable sequence that is more than 2% different from germline, called mutated IGHV, have an indolent course, sometimes not requiring therapy at all. By comparison, patients whose immunoglobulin heavy chain variable sequence is not mutated, defined as 2% or less different than germline and called unmutated IGHV, have higher risk disease. The biologic basis for this prognostic difference is unclear. The gene expression profile of both mutated and unmutated cells resembles a memory B cell and is more similar to each other than to any other normal or malignant B cell. Chronic lymphocytic leukemia with an unmutated immunoglobulin heavy chain variable sequence shows increased activation of the B-cell receptor, which drives survival and proliferation and is likely associated with increased clonal evolution over time. Most of the recurrently mutated cancer genes in chronic lymphocytic leukemia occur predominantly in cells with an unmutated immunoglobulin heavy chain variable sequence. In contrast, although chronic lymphocytic leukemias with mutated immunoglobulin heavy chain variable sequences have B cell receptors, activation is at a lower level, and these chronic lymphocytic leukemias are much less likely to have high risk cytogenetics and somatic mutations. Within a subset, chronic lymphocytic leukemia has similar clinical behavior, and some subsets have been associated with particular somatic mutations, thereby suggesting the possibility of codevelopment or crosstalk between B-cell receptor stimulation/selection and genetic abnormalities.[5]

Chromosomal Abnormalities

Chronic lymphocytic leukemia generally has a stable karyotype with few or no abnormalities, particularly at the time of diagnosis. In contrast to many other hematologic malignancies, balanced translocations are rare in chronic lymphocytic leukemia, which more commonly is associated with unbalanced deletions or amplifications but also usually has a quite stable karyotype. By fluorescence in situ hybridization (FISH) on interphase cells, the most common abnormalities in chronic lymphocytic leukemia are deletion 13q14, deletion 11q22, deletion 17p13, and trisomy 12.[6] Deletion 13q14, which is the most common abnormality in chronic lymphocytic leukemia, is seen in about 55% of patients and is the only abnormality that has been associated with favorable prognosis. In general, however, the prognosis of patients with deletion 13q14, trisomy 12, or normal cytogenetics follows what would be expected based on their *IGHV* mutation status. The highest risk abnormality is deletion 17p13, which deletes one copy of the *TP53* gene and is associated with the poorest prognosis. The second highest risk is deletion 11q22, which deletes one copy of the *ATM* gene. Both of these mutations are strongly associated with unmutated immunoglobulin heavy chain variable sequence, but mutated immunoglobulin heavy chain variable sequence mitigates the prognostic impact of the FISH abnormality. Other findings (e.g., deletion 6q22, trisomy 8, 8q gain, and 8p deletion) are relatively rare, especially at diagnosis, and have generally been associated with more aggressive disease. Cases with more than three to five abnormalities are associated with worse outcomes, but this information is not routinely used for determining prognosis.[7]

Recurrent Somatic Mutations

By next generation sequencing,[8] chronic lymphocytic leukemia has a relatively low mutation rate. Unlike Waldenstrom macroglobulinemia (*MYD88*; Chapter 173) and hairy cell leukemia (*BRAF*), chronic lymphocytic leukemia has no recurrent defining somatic mutation. The most common mutations in chronic lymphocytic leukemia occur in only 15 to 20% of patients and affect the *TP53* gene, *NOTCH1*, *SF3B1*, and *ATM*. Many other cancer genes are mutated in a few percent of cases, thereby making the disease genetically very heterogeneous. Some mutations can be clustered into affected pathways that are thought to be activated in most patients, either genetically or otherwise, and that may act cooperatively to induce disease.

Epigenetics

Methylation patterns in chronic lymphocytic leukemia correspond to the developmental pattern of the antecedent normal B cell and do not vary over the course of the disease.[9] The analysis of methylation patterns identifies three groups (low, intermediate, and high programmed chronic lymphocytic leukemia) that correspond to unmutated immunoglobulin heavy chain variable sequence, a mix of unmutated and mutated immunoglobulin heavy chain variable sequence, and mutated immunoglobulin heavy chain variable sequence.

Methylation can also silence genes that are sometimes deleted in chronic lymphocytic leukemia. For example, the most common recurrent genetic event in chronic lymphocytic leukemia is deletion 13q14, which removes the *miR-15* and *-16* genes that target *BCL-2*. When they are deleted, *BCL-2* is overexpressed. Interestingly, chronic lymphocytic leukemias that do not carry deletions of 13q14 typically have hypermethylation of that region, and the hypermethylation effectively silences *miR-15* and *-16*. This example of alternative mechanisms resulting in the same key pathogenetic event is believed to apply to other pathways in chronic lymphocytic leukemia (e.g., *NOTCH1* can be activated both mutationally or through stimulation by the microenvironment).

Immune Dysfunction

Patients with chronic lymphocytic leukemia display significant defects in immune function, including hypogammaglobulinemia and functional T-cell defects. Hypogammaglobulinemia can be present at diagnosis and progresses as the burden of disease increases. T cells show evidence of chronic stimulation, with exhaustion that also worsens with an increasing burden of disease. The number of T cells is often increased, but the cells are dysfunctional. Regulatory T cells are also increased. These defects do not always translate into infections in individual patients, but collectively patients with chronic lymphocytic leukemia have a substantially increased risk of infection.

CLINICAL MANIFESTATIONS

More than 75% of patients with chronic lymphocytic leukemia are asymptomatic at diagnosis. Diagnosis is most commonly made when a complete blood count obtained at the time of a routine physical examination or evaluation for an unrelated medical issue shows lymphocytosis. Alternatively, some patients may be identified when small lymph nodes (Chapter 154) are detected on a routine medical examination or sometimes on a mammogram.

Patients who present with symptomatic disease generally have larger lymph nodes, show signs or symptoms of splenomegaly (Chapter 154), have fatigue or dyspnea from anemia, or demonstrate petechiae or bruising from thrombocytopenia. Systemic (B) symptoms of fevers, chills, night sweats, or weight loss are very unusual except when chronic lymphocytic leukemia is very advanced.

Disease-Related Complications

Infectious Complications and Vaccination

Patients with chronic lymphocytic leukemia are immunosuppressed even at the time of diagnosis and are at increased risk of bacterial and viral infections, including reactivations of herpes virus and an increased mortality from coronavirus-2019 (COVID-19) infection. Sinus infections (Chapter 394) are particularly problematic.

Autoimmune Complications

Autoimmune complications, which can occur in up to 25% of patients with chronic lymphocytic leukemia, typically manifest as autoimmune hemolytic anemia (Chapter 146) or immune thrombocytopenia (Chapter 158), or very rarely autoimmune neutropenia (Chapter 153). Systemic autoimmune complications can occur but are also rare.

Autoimmune cytopenias can also arise as a complication of therapy, including purine analogues as well as newer targeted therapies, but they more commonly develop in the setting of progressive chronic lymphocytic leukemia. For many patients who develop an autoimmune complication, the problem is recurrent over the course of disease.

Secondary Malignancies

Additional cancers are common among people with chronic lymphocytic leukemia, probably related to immune suppression and perhaps genetic predisposition. Melanoma and non-melanoma skin cancers (Chapter 188) are especially increased, and non-melanoma skin cancers can be more invasive and more dangerous than in individuals without chronic lymphocytic leukemia. Common solid tumors including prostate (Chapter 186), breast (Chapter 183), colon (Chapter 179), and lung cancer (Chapter 177) are also increased.

Richter Transformation

Richter transformation, which is the development of an aggressive lymphoma in the context of underlying chronic lymphocytic leukemia, affects about 5% of patients,[10] especially heavily pretreated patients. The majority of lymphomas are diffuse large B-cell lymphomas (Chapter 171) that are clinically and genetically related to the underlying chronic lymphocytic leukemia. Patients commonly present with symptoms that include a rapidly enlarging lymph node, severe B symptoms, fatigue, and/or an elevated lactate dehydrogenase level. Biopsy is required to establish the diagnosis, and a positron emission tomographic (PET) scan is often helpful to target the area to biopsy. Diffuse large B-cell transformation that is clonally unrelated to the underlying chronic lymphocytic leukemia represents about 10 to 20% of cases and typically occurs in previously untreated patients.

DIAGNOSIS

The diagnosis of chronic lymphocytic leukemia should be suspected when an elevation of circulating lymphocytes leads to an elevated total white blood count, usually without any other associated abnormalities on the complete blood count. The peripheral blood smear typically shows an increase in mature appearing lymphocytes with smudge cells, which are an artifact when the fragile lymphocytes of chronic lymphocytic leukemia break open, thereby leaving the appearance of a smudge (Fig. 169-1 and E-Fig. 169-1). Higher numbers of smudge cells are associated with more indolent disease.

The most useful test for establishing a diagnosis of chronic lymphocytic leukemia is peripheral blood flow cytometry for lymphoid markers, which determine the immunophenotype of the circulating cells and often are definitive in establishing the diagnosis of chronic lymphocytic leukemia (Table 169-1). The classic immunophenotype in chronic lymphocytic leukemia includes expression of B-cell markers CD19 with dim CD20 and dim surface immunoglobulin; CD23; and the T-cell marker CD5.

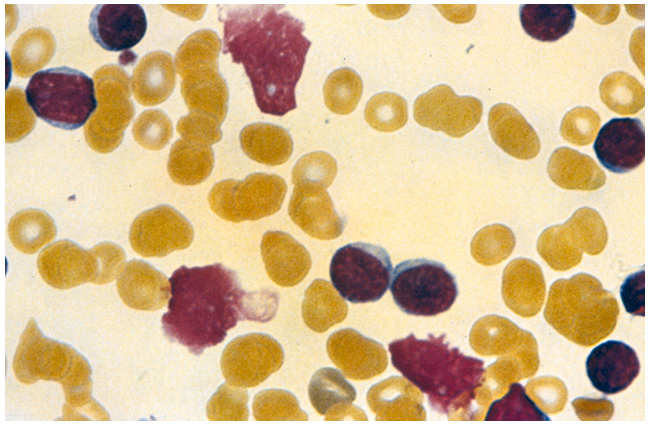

FIGURE 169-1. Chronic lymphocytic leukemia. Peripheral smear shows that the predominant leukocytes are "normal," mature-appearing lymphocytes, with occasional "smudge" cells. (Courtesy Andrew Schafer, MD.)

Differential Diagnosis

Infections such as Epstein-Barr virus (Chapter 348) and cytomegalovirus (Chapter 347) can present with marked lymphocytosis (Chapter 153). However, these and other reactive lymphocytoses are often more pleomorphic on the peripheral blood smear as compared with the lymphocytes of chronic lymphocytic leukemia. Furthermore, flow cytometry will be definitive in the occasional confusing case.

Small Lymphocytic Lymphoma

Small lymphocytic lymphoma (Chapter 171) also has the same immunophenotype as chronic lymphocytic leukemia and historically has been distinguished from chronic lymphocytic leukemia only because its initial presentation is with lymphadenopathy, with less than 5000/μL B lymphocytes in the blood. Currently, chronic lymphocytic leukemia and small lymphocytic lymphoma are considered the same disease and the choice of therapy is the same, so this distinction is of limited importance.

Monoclonal B-Cell Lymphocytosis

Essentially all patients diagnosed with chronic lymphocytic leukemia have had a preexisting subclinical phase called monoclonal B-cell lymphocytosis.[11] Monoclonal B-cell lymphocytosis is diagnosed when the circulating number of B lymphocytes is less than 5000/μL in the absence of cytopenias, lymphadenopathy, or splenomegaly. Many patients with this very low level of lymphocytosis have been told that they have chronic lymphocytic leukemia, when in fact they only meet criteria for monoclonal B-cell lymphocytosis. These monoclonal lymphocytic cells may be detected up to 77 months prior to the diagnosis of chronic lymphocytic leukemia. Although all patients with chronic lymphocytic leukemia have a pre-existing monoclonal B-cell lymphocytosis phase, most patients with monoclonal B-cell lymphocytosis will not progress to develop chronic lymphocytic leukemia.

Monoclonal B-cell lymphocytosis as detected by highly sensitive flow cytometry is very rare before age 40 years, but its prevalence increases to approximately 5% at age 60 years and as high as 45% at age 85 years. The incidence of monoclonal B-cell lymphocytosis is about twice as high among individuals in families with chronic lymphocytic leukemia compared with the general population of similar age.

Monoclonal B-cell lymphocytosis is divided into low-count (<500/μL monoclonal B-cells) disease, which is not detectable on a complete blood count and has a distinct pattern of B-cell receptor gene usage, and high-count (>500/μL but <5000μL monoclonal B-cell lymphocytosis) disease, which is usually identified on a complete blood count and has a B-cell receptor pattern gene usage that is similar to low-risk chronic lymphocytic leukemia.[12] High-count monoclonal B-cell lymphocytosis carries a 1 to 2% per year risk of progressing to chronic lymphocytic leukemia that requires therapy and about a 30% risk of becoming chronic lymphocytic leukemia over 7 years of follow-up, with the primary predictor of progression being a higher lymphocyte count at baseline. However, only 75% of high-count monoclonal B-cell lymphocytosis have a chronic lymphocytic leukemia phenotype, and careful clinical evaluation is warranted to exclude alternative diagnoses including non-Hodgkin lymphomas (Chapter 171).

Other Lymphoid Diseases

Other lymphoid diseases that can present with similar lymphocytosis on a blood smear include marginal zone lymphoma, lymphoplasmacytic lymphoma, mantle cell lymphoma, follicular lymphoma (Chapter 171), and hairy cell

TABLE 169-1 TYPICAL IMMUNOPHENOTYPE OF CHRONIC LYMPHOCYTIC LEUKEMIA COMPARED WITH OTHER B-CELL MALIGNANCIES

DISEASE	CD5	CD10	CD19	CD20	CD23	CYCLIN D1	SURFACE IMMUNOGLOBULIN
Chronic lymphocytic leukemia	+	–	+	+ (dim)	+	–	+ (dim)
Mantle cell lymphoma	+	–	+	+ (mod/bright)	–	+	+ (mod/bright)
Marginal zone lymphoma	–/+	–	+	+ (mod/bright)	–/+	–	+ (mod/bright)
B-prolymphocytic leukemia	–/+	–	+	+ (bright)	–	–	+ (bright)
Follicular lymphoma	–	+	+	+	+	–	

Adapted from Byrd J. Chronic lymphocytic leukemia. In: Goldman L, Schafer AI. *Goldman-Cecil Medicine*. 26th ed. Philadelphia: Elsevier; 2020.

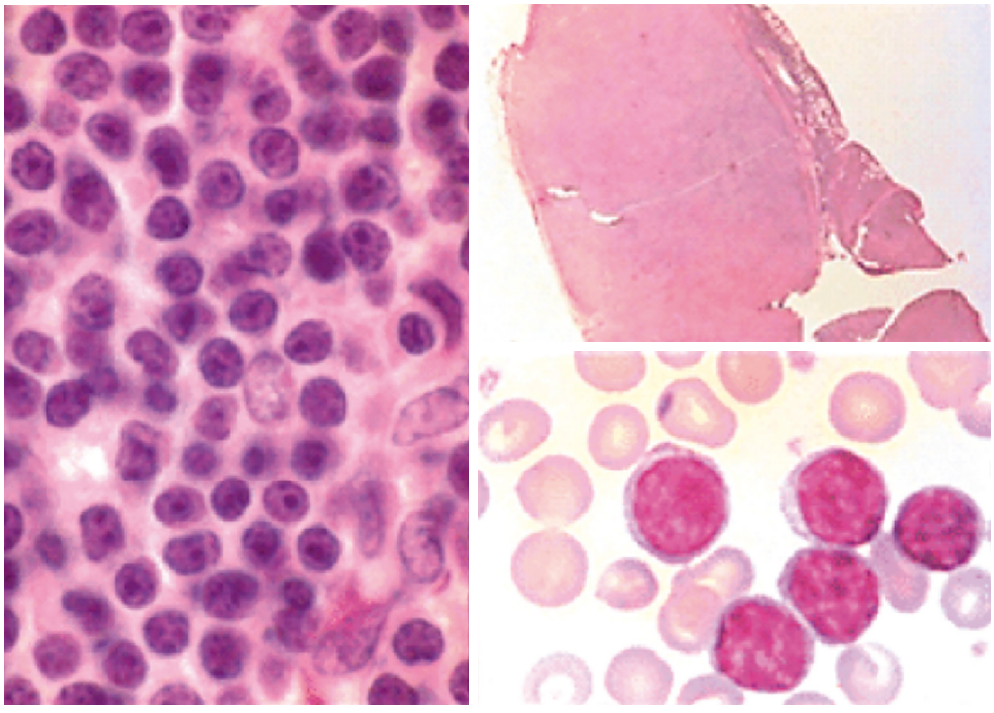

E-FIGURE 169-1. Chronic lymphocytic leukemia bone marrow, lymph node, and blood morphology. (Courtesy of Gerard Lozanski.)

leukemia. More aggressive B-cell lymphomas and mature T-cell leukemia/lymphoma (Chapter 171) can also circulate in the blood but are not difficult to distinguish morphologically from chronic lymphocytic leukemia.

Marginal zone lymphoma (Chapter 171) that is predominantly circulating or splenic is usually the most challenging disease to differentiate from chronic lymphocytic leukemia. Marginal zone lymphoma and lymphoplasmacytic lymphoma are typically negative for both CD5 and CD10, but they can sometimes express CD5 dimly. In these situations, clinical features and cytogenetic or mutational profiles (see Table 169-1) can help establish the most likely diagnosis, but some patients also exhibit features that span more than one diagnosis.

Among the low-grade B-cell diseases, CD5 positivity with CD10 negativity is a key differentiator that excludes follicular lymphoma, which is typically CD10 positive, and hairy cell leukemia, which is typically CD5 negative as well as positive for CD103, CD11c, and CD25. The other B-cell disease that expresses CD5 is mantle cell lymphoma, which can usually be distinguished from chronic lymphocytic leukemia because of the absence of CD23 and positivity for expression of cyclin D1 by immunohistochemistry and/or presence of t(11;14) juxtaposing the cyclin D1 gene with the immunoglobulin heavy chain gene.

Staging and Prognostic Factors

Chronic lymphocytic leukemia can be staged clinically using the Rai system (Table 169-2), which is based on the assessment of lymphadenopathy and organomegaly on physical examination as well as on the complete blood count. However, most patients are diagnosed with early-stage disease, and additional testing (Table 169-3) is useful to help inform prognosis. Among these risk factors, *TP53* aberration and immunoglobulin heavy chain variable mutational status are the most important.

TREATMENT

General Considerations

Very few patients with chronic lymphocytic leukemia require therapy at the time of diagnosis. Asymptomatic patients without cytopenias can be observed, sometimes for decades, and up to 30% of patients never require disease specific therapy. Nevertheless, referral to a specialist is important to confirm the diagnosis, to educate patients about complications, and to provide appropriate counseling and reassurance so patients can adjust to the diagnosis and to the possibility of not receiving therapy for a seemingly ominous condition.

Guidelines suggest the initiation of therapy when cytopenias reach a critical level (e.g., hemoglobin concentration <10 g/dL, platelet count <80-100,000/μL) or when patients develop bulky progressive or symptomatic lymphadenopathy (>10 cm), splenomegaly, significant disease-related symptoms, or difficult-to-control autoimmune hemolytic anemia or immune thrombocytopenic purpura.[13,14] The absolute lymphocyte count itself is not an indication for therapy, although its increase over time often correlates with slowly progressive anemia, thrombocytopenia, and increasing infections that can herald the need for therapy.

Before the initiation of therapy, a full-body computed tomographic scan should be considered in patients who have lymphadenopathy, and a bone marrow biopsy should be considered in patients who have cytopenias. Prognostic markers, such as del(17p), *TP53* mutation, and karyotype analysis, can evolve over time and should be reassessed before each new line of therapy (Table 169-3). Immunoglobulin heavy chain variable sequence mutation status remains stable and does not need to be repeated. If possible, any recommended vaccinations should be completed. Screening for prior hepatitis B infection is important because most therapies reactivate hepatitis B. Chronic active hepatitis B carriers should be on suppressive therapy (Chapter 135) with no detectable viral load before the initiation of any therapy.

Choosing among Medications

Classes of therapy in current use in chronic lymphocytic leukemia include Bruton tyrosine kinase inhibitors, venetoclax (a BCL-2 inhibitor), phosphatidylinositol 3-kinase inhibitors, chemotherapy, immunotherapy, chemoimmunotherapy, and cellular therapy (Table 169-4). Choices are generally determined by the patient's age and comorbid conditions, as well as their disease specific prognostic factors, particularly *TP53* alterations and immunoglobulin heavy chain variable mutation status (Fig. 169-2). Targeted therapies appear to be consistently superior to traditional chemotherapy for both initial treatment and treatment for relapsed or refractory disease (Table 169-5). Once therapy is required, most patients should receive targeted treatment with continuous Bruton tyrosine kinase inhibitor therapy with or without obinutuzumab, or time-limited therapy with venetoclax plus obinutuzumab. Young, fit patients who have favorable mutated immunoglobulin heavy chain gene (IgHV) mutation status and low-risk cytogenetics have the potential of cure with fludarabine/cyclophosphamide/rituximab chemoimmunotherapy.

Most patients are not diagnosed until after age 70 years and are even older by the time that treatment is initiated. Cardiac conditions and the possible need for anticoagulation should be considered prior to beginning treatment with Bruton tyrosine kinase inhibitors, whereas renal dysfunction is an important consideration before venetoclax therapy.[15]

Bruton Tyrosine Kinase Inhibitors

Chronic lymphocytic leukemia cells are dependent on signaling through the B-cell receptor for their growth and survival, and this signaling depends on Bruton tyrosine kinase. When Bruton tyrosine kinase is lost in the germline,

TABLE 169-2 THE RAI STAGING SYSTEM OF CHRONIC LYMPHOCYTIC LEUKEMIA

CLINICAL FEATURES	STAGE
Lymphocytosis only	0
Lymph node enlargement	1
Spleen or liver enlargement (by physical examination)	2
Anemia (hemoglobin <11 g/dL)	3
Thrombocytopenia (platelets <100,000/μL)	4

From Byrd J. Chronic lymphocytic leukemia. In: Goldman L, Schafer AI. *Goldman-Cecil Medicine*. 26th ed. Philadelphia: Elsevier; 2020.

TABLE 169-3 USEFUL TESTS IN THE EVALUATION OF PATIENTS WITH CHRONIC LYMPHOCYTIC LEUKEMIA

Immunophenotype (flow cytometry) – lymphoma markers
IGHV mutational status
Interphase FISH (deletion of 13q, 11q or 17p; trisomy 12)
Stimulated karyotype
TP53 mutation by next-generation sequencing
β_2-microglobulin level
Serum immunoglobulin levels

FISH = fluorescence in situ hybridization.

TABLE 169-4 THERAPIES USED IN CHRONIC LYMPHOCYTIC LEUKEMIA

THERAPY	MECHANISM OF ACTION
TARGETED THERAPIES	
Ibrutinib	Irreversible inhibition of BTK
Acalabrutinib	Second-generation irreversible inhibition of BTK
Zanubrutinib	Second-generation irreversible inhibition of BTK
Venetoclax	Inhibition of BCL-2 function
Idelalisib	Reversible inhibition of PI3Kδ
Duvelisib	Reversible inhibition of PI3Kδ,γ
BIOLOGIC THERAPIES	
Obinutuzumab	CD20-directed antibody with enhanced ADCC and direct killing
Rituximab	CD20-directed antibody with ADCC, CDC, and direct killing
Corticosteroids	Microenvironment effect and activation of the steroid receptor
CHEMOTHERAPY	
Chlorambucil	Alkylator/DNA damage
Cyclophosphamide	Alkylator/DNA damage
Bendamustine	DNA damage
Fludarabine	Purine analogue; inhibition of DNA and RNA synthesis and splicing

ADCC = antibody-dependent, cellular-mediated cytotoxicity; BTK = Bruton tyrosine kinase; CDC = complement-dependent cytotoxicity; PI3K = phosphoinositide 3-kinase.

patients lack mature B cells and have agammaglobulinemia as a result. The inhibitor of Bruton tyrosine kinase, ibrutinib (starting dose 420 mg orally daily), binds to Bruton tyrosine kinase covalently, thereby leading to its permanent inactivation.[16] Overall response rates are over 90%, most high-risk patients respond with at least somewhat durable responses, especially when the drug is continued as first-line therapy, and progression-free survival is improved compared with chemoimmunotherapy.[A1–A4]

Continuous therapy with ibrutinib is not possible in many patients because of significant side effects[17] related to the fact that it is not specific for Bruton tyrosine kinase but also potently inhibits 19 other kinases. Second-generation covalent Bruton tyrosine kinase inhibitors, which are more specific and better tolerated, include acalabrutinib (starting at 100 mg orally twice daily), which is FDA approved for the treatment of chronic lymphocytic leukemia at any stage of the disease based on randomized trials demonstrating over a 90% response rate[A5] and improved progression-free survival compared primarily to chemoimmunotherapy.[A6,A7] Zanubrutinib, which has a unique pharmacokinetic profile that maintains circulating drug levels throughout the dosing interval in addition to acting as a covalent inhibitor, is FDA approved for related B-cell malignancies and chronic lymphocytic leukemia. Both acalabrutinib and zanubrutinib[A8] are as efficacious and are substantially better tolerated than ibrutinib in relapsed chronic lymphocytic leukemia, with acalabrutinib showing significant reductions in the cumulative incidence of hypertension, arthralgia, bleeding, and diarrhea.[A9] Both acalabrutinib and zanubrutinib are tolerated by patients who have discontinued ibrutinib because of intolerance. Zanubrutinib also can improve progression-free survival compared with ibrutinib in relapsed CLL, with significantly fewer adverse events.[A10] In the United States, patients with chronic lymphocytic leukemia, particularly patients who are older or have comorbid conditions that put them at particular risk for complications of ibrutinib, should receive a second-generation Bruton tyrosine kinase inhibitor rather than ibrutinib.

With Bruton tyrosine kinase inhibitors, chronic lymphocytic leukemia cells are redistributed from lymph nodes, spleen, or bone marrow into peripheral blood, often resulting in an increase in the white count (called redistribution lymphocytosis) over the first few weeks of therapy, followed by stabilization and slow decline thereafter. Some patients will eventually achieve a normal white blood cell count, whereas other patients will have persistent stable elevation for years. Lymph nodes shrink rapidly and markedly, thereby allowing evaluation of response despite the increase in white count. Cytopenias also improve, sometimes rapidly but sometimes slowly over up to 6 months. Bruton tyrosine kinase inhibitors do not readily induce apoptosis in chronic lymphocytic leukemia cells, so they do not clear all disease. As a consequence, most patients have durable partial responses but the Bruton tyrosine kinase inhibitor must be continued indefinitely to sustain response.

Complications of Bruton tyrosine kinase inhibitors include a high incidence of cardiac side effects, particularly atrial fibrillation (in 10 to 20% of patients after 2 years on therapy) and hypertension (incidence ranging from 23 to 75% depending on the series), but ventricular arrhythmias, sudden death, conduction block, heart failure, and stroke can also occur. All of these side effects appear to be substantially less likely with acalabrutinib[A11] and zanubrutinib. All Bruton tyrosine kinase inhibitors can cause significant bruising and bleeding, so they must be discontinued for 7 days before and after any major surgical procedure and for 3 days before and after any minor procedure. The covalent Bruton tyrosine kinase inhibitors can be combined safely with single drug anti-platelet therapy (i.e., aspirin), but care must be taken if they are to be combined with anticoagulation, and dual anti-platelet therapy is usually best avoided. If anticoagulation is needed, warfarin is contraindicated and direct oral anticoagulants are preferred. Other side effects frequently leading to the discontinuation of ibrutinib include arthralgias, fatigue, infections, and cytopenias.

Venetoclax

Venetoclax inhibits BCL-2, which is universally overexpressed in chronic lymphocytic leukemia, and blocks apoptosis through direct binding and inhibition of pro-apoptotic proteins. Venetoclax, which is specific for BCL-2, is efficacious in patients with relapsed refractory chronic lymphocytic leukemia, in whom it can provide complete remissions. For example, 2 years of treatment with venetoclax plus rituximab is significantly better than bendamustine plus rituximab in terms of response rates, progression-free survival, and overall survival in heavily pretreated patients.[A12,A13] Even in previously untreated patients, 1 year of treatment with venetoclax plus obinutuzumab is superior to chlorambucil-obinutuzumab with

TABLE 169-5 REPORTED SUCCESS RATES FOR TREATMENT OF CHRONIC LYMPHOCYTIC LEUKEMIA

TREATMENT	PROGRESSION-FREE SURVIVAL	OVERALL SURVIVAL
PREVIOUSLY UNTREATED PATIENTS		
Fludarabine, cyclophosphamide, and rituximab	50% at 57 months	50% at 12.7 years
Bendamustine and rituximab	50% at 42 months	92% at 3 years
Chlorambucil and obinutuzumab	50% at 29 months	Not available
Acalabrutinib	78% at 48 months	88% at 48 months
Acalabrutinib and obinutuzumab	87% at 48 months	93% at 48 months
Venetoclax and obinutuzumab	74% at 48 months	85% at 48 months
Ibrutinib	70% at 5 years	83% at 5 years
RELAPSED OR REFRACTORY DISEASE		
Ibrutinib	50% at 52 months	55% at 7 years
Acalabrutinib	62% at 45 months	>90% at 16 months
Venetoclax	50% at 25 months	84% at 24 months
Venetoclax and rituximab	50% at 54 months	82% at 5 years

Adapted and updated from Burger JA. Treatment of chronic lymphocytic leukemia. *N Engl J Med.* 2020;383:460-473.

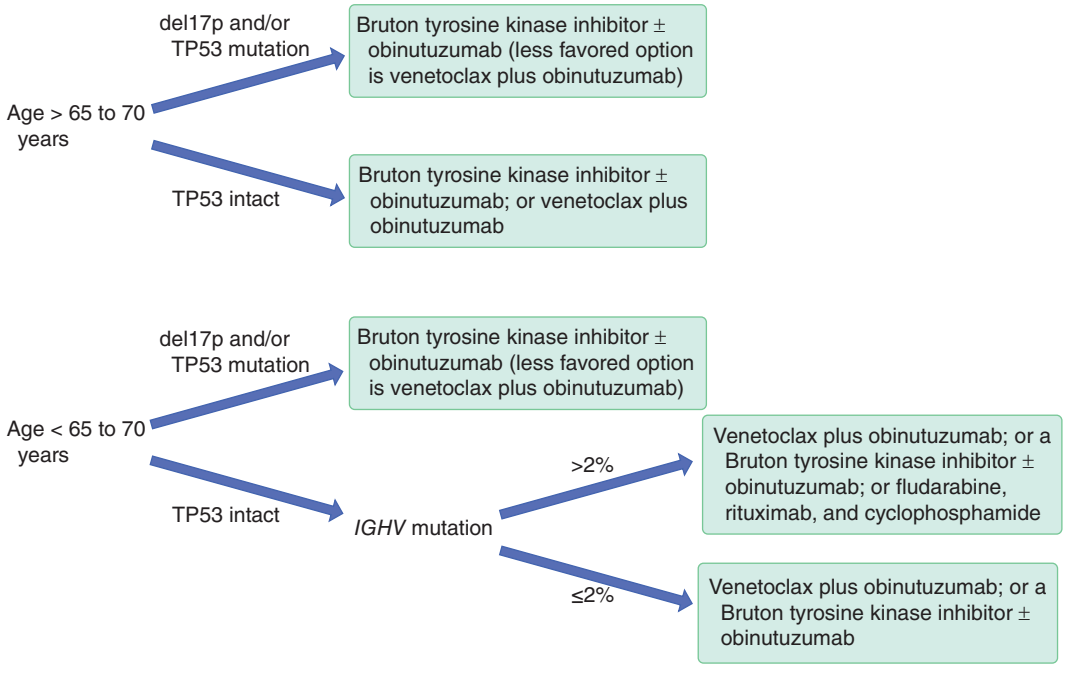

FIGURE 169-2. **Guide to the initial treatment of chronic lymphocytic leukemia.** *IGHV* = immunoglobulin heavy chain variable region.

marked improvement in progression-free survival and deep remissions without detectable residual disease in over 50% of patients,[A14] but all patients eventually relapse. Current investigations are focusing on combining venetoclax with Bruton tyrosine kinase inhibitors, also in time-limited regimens.[18,19] For example, 1 year of ibrutinib plus venetoclax is effective in older patients or patients with comorbid conditions.[A15] The goal of these time-limited regimens is to achieve deep remissions that allow patients substantial time without therapy, with the potential to resume therapy if and when relapse occurs. Venetoclax is also active in chronic lymphocytic leukemia patients whose disease has progressed on a prior Bruton tyrosine kinase inhibitor therapy, albeit with less durability than when it is used as frontline therapy or in patients at the time of first relapse.

The primary side effect of venetoclax is rapid induction of tumor cell death, thereby leading to potentially life-threatening tumor lysis syndrome (Chapter 164). As a result, approved administration starts at a low dose (20 mg orally daily) and is then increased weekly over 5 weeks to the full planned dose of 400 mg orally daily, with laboratory monitoring under expert supervision to avoid the tumor lysis syndrome. Venetoclax is very well tolerated, but other side effects include myelosuppression, nausea, vomiting, and diarrhea.

Immunotherapy

The most successful form of immunotherapy in chronic lymphocytic leukemia is monoclonal antibody therapy. CD20 is a B-cell specific antigen, so off-target effects are limited.

Obinutuzumab is a humanized, glycoengineered anti-CD20 antibody with antibody-dependent cellular cytotoxicity against tumor cells. Obinutuzumab provides better clinical responses and progression-free survival compared with rituximab, so it generally is the antibody of choice in chronic lymphocytic leukemia. For example, obinutuzumab is more potent than rituximab, however, and leads to a significant benefit in terms of progression-free survival when added to acalabrutinib.

The addition of rituximab to ibrutinib has no benefit for progression-free survival.[A16] Rituximab is now mostly used to treat autoimmune cytopenias or in combination with venetoclax.

Chemoimmunotherapy

The combination of CD20 antibodies with chemotherapy leads to synergistic benefit, with nearly universal overall response as well as a marked increase in rates of complete remission (30 to 70%) and durable remissions. For example, the addition of rituximab to chemotherapy with fludarabine plus cyclophosphamide increases overall response, complete response, progression-free survival, and overall survival. Patients with a mutated immunoglobulin heavy chain gene can achieve very prolonged progression-free survival with this regimen, with more than 50% still in remission at 12 years follow-up, thereby suggesting possible cure. Patients with unmutated immunoglobulin heavy chain genes generally experience relapse, but a subset with trisomy 12 can also have durable benefit. Fludarabine/cyclophosphamide/rituximab is preferred over bendamustine rituximab in terms of progression-free survival.[A17] The side effects of fludarabine/cyclophosphamide/rituximab include myelosuppression and a risk of secondary myeloid malignancy, both of which are worse with increasing age, thereby leading to the recommendation that fludarabine/cyclophosphamide/rituximab be considered only in young, fit patients with normal renal function.

Bendamustine plus rituximab can be used palliatively in older patients. Additionally, for older, less-fit patients, the combination of obinutuzumab plus chlorambucil is well tolerated and superior to chlorambucil alone. However, targeted therapy with a Bruton tyrosine kinase inhibitor or with venetoclax plus obinutuzumab provides better progression-free survival if it can be tolerated.[A18]

Phosphatidylinositol 3-kinase (PI3K) δ inhibitors

Like the Bruton tyrosine kinase inhibitors, the PI3Kδ inhibitors also inhibit B-cell receptor signaling downstream of the B-cell receptor. Options include idelalisib (150 mg orally twice daily) and duvelisib (25 mg orally twice daily). Because of substantial toxicity when used as front-line therapy (e.g., neutropenia, bacterial and opportunistic infections, severe colitis, pneumonitis, and elevated aminotransferase levels), these agents are limited to patients who have relapsed chronic lymphocytic leukemia after at least two prior regimens, both Bruton tyrosine kinase inhibitors and venetoclax, or who have comorbid conditions that preclude the use of these drugs.[20]

Refractory Disease

Patients with disease that has progressed despite continuous Bruton tyrosine kinase inhibitor therapy can respond to venetoclax, but durability is limited. Patients whose disease has progressed after both a Bruton tyrosine kinase inhibitor and venetoclax have limited treatment options, because neither PI3K inhibitors nor chemoimmunotherapy have established activity in this particular setting.

For refractory disease, allogeneic stem cell transplantation (Chapter 163) holds the promise of potential cure, but treatment-related mortality is 10 to 20%, and many patients have long-term chronic graft-versus-host disease. Furthermore, the efficacy of transplant is strongly dependent on the patient being in a deep remission, which is often not achievable.

Autologous chimeric antigen receptor (CAR) T-cell therapy is an emerging option for refractory disease. This treatment involves the engineering of the patient's own T cells with a chimeric T cell antigen receptor against a target on the B-cell malignancy, most commonly CD19. CAR T therapy has revolutionized the treatment of relapsed diffuse large B-cell lymphoma (Chapter 171), but results to date in chronic lymphocytic leukemia have been more modest. Possible explanations include the difficulty of collecting autologous T cells due to prior therapy, impaired function of collected T cells due to immune dysfunction, and impaired expansion of the CAR T cells either in vitro or in vivo after infusion, again due to the immune milieu related to chronic lymphocytic leukemia. The coadministration with Bruton tyrosine kinase inhibitors may mitigate some of these problems, but it is not known whether CAR T therapy has the same potential for cure that is offered by allogeneic stem cell transplantation.

Disease-Related Complications

Infections

Patients should be evaluated promptly for any fever, with a low threshold for antibiotic treatment with antimicrobial agents. Vaccination is strongly recommended, including yearly influenza vaccine, COVID-19 vaccine,[21] pneumococcal 20-valent conjugate vaccine followed at least 2 months later by pneumovax (which is then repeated every 5 years), and herpes zoster vaccination (Chapter 15). Studies generally demonstrate measurable but reduced response to these vaccines in patients with chronic lymphocytic leukemia, owing to their immune dysfunction. Patients with chronic lymphocytic leukemia should not receive live-attenuated vaccines because of the risk of disseminated disease arising from the vaccine. If patients have low IgG levels and develop recurrent bacterial infections, intravenous immune globulin replacement under expert supervision can substantially mitigate these infections. For sinus infections, regular sinus irrigation can help substantially.

Autoimmune Complications

When patients with chronic lymphocytic leukemia develop an autoimmune cytopenia, it can be treated with corticosteroids, the anti-CD20 antibody rituximab, or cyclosporine under expert supervision. When these complications develop in the setting of progressive disease, definitive therapy is required for the chronic lymphocytic leukemia.

Malignancy

Patients with chronic lymphocytic leukemia are advised to minimize exposure to ultraviolet light, use highly effective sunscreen, have regular dermatology examinations, and complete all other age-appropriate cancer screening. The treatment of any malignancies is generally the same as in other patients if it can be tolerated.

Richter Transformation

Diffuse large B-cell lymphoma (Chapter 171) can be cured with standard combination chemotherapy for lymphoma (Chapter 171) in previously untreated patients, but the median survival, even with aggressive therapy, is poor when the lymphoma occurs in previously heavily treated patients.

Hodgkin lymphoma (Chapter 172) is much less common. Hodgkin disease (Chapter 172) responds to standard combination chemotherapy for Hodgkin lymphoma and has a natural history like that of de novo disease.

PROGNOSIS

Deletion of 17p containing the *TP53* gene is associated with shorter time to needing treatment, poorer progression-free survival, and shorter overall survival. However, the era of targeted therapies has substantially improved outcome for these patients, with high response rates to targeted therapy albeit still generally shorter progression-free survivals.[22] Deletion 11q, which affects the *ATM* gene, is associated with a pattern of bulky lymphadenopathy, shorter time to treatment, and a shorter durability of remission; however, targeted therapies appear to mitigate this impact. *NOTCH1* mutation is another higher risk mutation that has been associated with an increased risk of Richter transformation. β_2 microglobulin is an extracellular protein component of the human leukocyte antigen (HLA) class 1 complex that associates with prognosis in many B-cell malignancies, most notably multiple myeloma but also chronic lymphocytic leukemia.

Immunoglobulin heavy chain variable sequence status similarly predicts shorter survival for early-stage patients, with older data from before the era of targeted therapy showing that unmutated *VH* genes predict an approximately 8-year survival compared with over 24 years for patients who have mutated *VH* genes. However, continuous Bruton tyrosine kinase inhibitor therapy can control disease for prolonged periods even in patients with unmutated immunoglobulin heavy chain variable sequence.

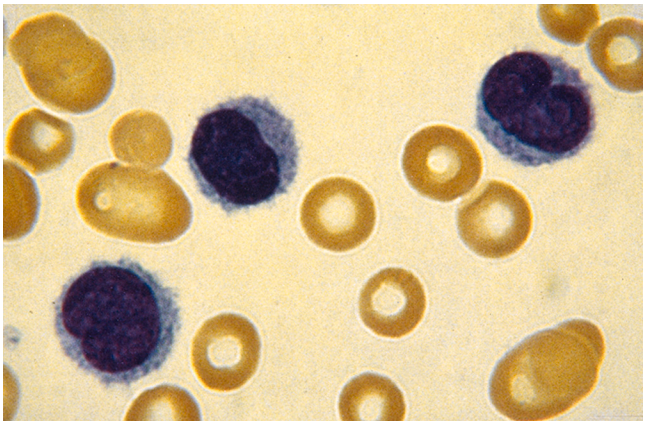

FIGURE 169-3. Hairy cell leukemia. Peripheral smear shows hairy cells with blue-gray cytoplasm; fine, hairlike projections (resembling ruffles); and oval or slightly indented nuclei with loose chromatin and indistinct nucleoli. (Courtesy Andrew Schafer, MD.)

OTHER CHRONIC LYMPHOCYTIC LEUKEMIAS

HAIRY CELL LEUKEMIA

Hairy cell leukemia, which is an indolent mature B-cell leukemia, is about five times more common in men than women and usually presents in patients aged 50 to 70 years. Most patients present with pancytopenia and marked splenomegaly without lymphadenopathy.[23] Typical mature hairy cells (which have thin cytoplasmic projections, a kidney-shaped nucleus, and one or two distinct nucleoli; Fig. 169-3) infiltrate the bone marrow, spleen, and liver. Because of a paucity of monocytes, tubercular and fungal infections are common. Diagnosis is based on finding the typical cells in the bone marrow. This leukemia is treated under expert supervision with purine analogues, which often lead to prolonged progression-free survival.[24] Vemurafenib, which is an oral BRAF inhibitor, combined with an anti-CD20 antibody also has substantial activity.[25]

PROLYMPHOCYTIC LEUKEMIA

In B-cell prolymphocytic leukemia, more than >55% of the circulating lymphocytes are prolymphocytes. These prolymphocytes are much larger than normal lymphocytes and have a typically round nucleus, with one clear punched-out nucleolus. Approximately 60% of patients have a translocation targeting *MYC*, and about 40% have a 17p deletion affecting *TP53*. B-cell prolymphocytic leukemia is quite rare as a presenting diagnosis, but some patients with chronic lymphocytic leukemia, typically patients with a 17p deletion, have a subset of cells that are similar to prolymphocytic leukemia cells. As the disease progresses, the distinction can pose a diagnostic dilemma, but the immunophenotype of B-cell prolymphocytic leukemia typically will differ from chronic lymphocytic leukemia by expressing surface immunoglobulin and CD20 brightly, not expressing CD23, and sometimes not expressing CD5. The targeted B-cell receptor pathway inhibitors that are effective in chronic lymphocytic leukemia also are effective for prolymphocytic leukemia, so the need to distinguish between these two diseases may be less important.

LARGE GRANULAR LYMPHOCYTIC LEUKEMIA

Large granular lymphocyte leukemia is discussed in Chapter 151.

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For the General References and other additional features, please visit Elsevier eBooks+ at https://ebooks.health.elsevier.com.

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170 CHRONIC MYELOID LEUKEMIA

JERALD RADICH

DEFINITION

Chronic myeloid leukemia (CML) is a hematopoietic stem cell disease caused by the reciprocal translocation of gene sequences from the breakpoint cluster region (*BCR*) gene on chromosome 22 with the tyrosine kinase sequences of the Abelson (*ABL*) gene on chromosome 9. On a cytogenetic level, this results in an elongated chromosome 9 and a shortened chromosome 22, the latter known as the Philadelphia (Ph) chromosome. The unique chimeric fusion protein, *BCR-ABL*, is a constitutively active tyrosine kinase that drives the pathogenesis of the disease. Thus, *BCR-ABL* represents the target for tyrosine kinase inhibitor therapy as well as a direct measure of disease burden. As described further below, there can be cases of "Ph-" CML, where the Ph chromosome is not detected, but other methods (fluorescence in situ hybridization [FISH], polymerase chain reaction [PCR]) can detect the chimeric *BCR-ABL*. There is no *BCR-ABL*-negative CML, and such diseases as "atypical" CML and chronic neutrophilic leukemia have distinct genetic features that identify them as unique disease entities (discussed briefly later).

CML is categorized in different phases (chronic, accelerated, and blast phases) based on bone marrow and peripheral blood blast counts, additional cytogenetic abnormalities besides the Ph chromosome, and clinical features such as fever. There are several classification schemes, including those proposed by the European Leukemia Network and the World Health Organization (WHO). The main difference between the European Leukemia Network and WHO classifications is the definition of accelerated phase and blast phase: the European Leukemia Network defines accelerated phase as peripheral or bone marrow blast counts of at least 15% to less than 30%, and blast phase as blasts counts greater than or equal to 30%, whereas in the WHO classification, these values are at least 10 to 20% and greater or equal to 20%, respectively. Of note, the WHO criteria are rarely used in clinical practice or clinical trials. More than 75% of CML cases in the developed world are diagnosed in the

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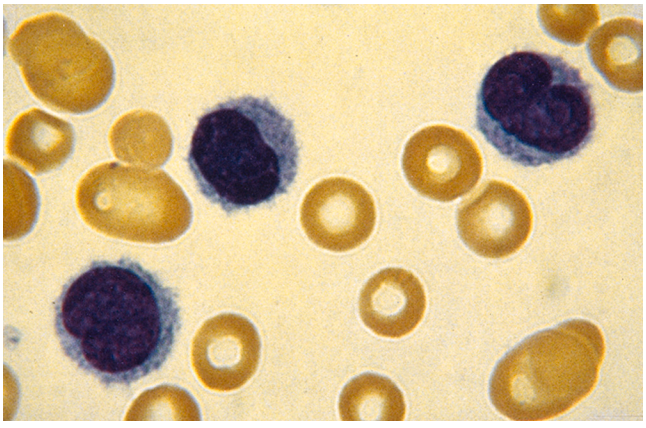

FIGURE 169-3. Hairy cell leukemia. Peripheral smear shows hairy cells with blue-gray cytoplasm; fine, hairlike projections (resembling ruffles); and oval or slightly indented nuclei with loose chromatin and indistinct nucleoli. (Courtesy Andrew Schafer, MD.)

OTHER CHRONIC LYMPHOCYTIC LEUKEMIAS

HAIRY CELL LEUKEMIA

Hairy cell leukemia, which is an indolent mature B-cell leukemia, is about five times more common in men than women and usually presents in patients aged 50 to 70 years. Most patients present with pancytopenia and marked splenomegaly without lymphadenopathy.[23] Typical mature hairy cells (which have thin cytoplasmic projections, a kidney-shaped nucleus, and one or two distinct nucleoli; Fig. 169-3) infiltrate the bone marrow, spleen, and liver. Because of a paucity of monocytes, tubercular and fungal infections are common. Diagnosis is based on finding the typical cells in the bone marrow. This leukemia is treated under expert supervision with purine analogues, which often lead to prolonged progression-free survival.[24] Vemurafenib, which is an oral BRAF inhibitor, combined with an anti-CD20 antibody also has substantial activity.[25]

PROLYMPHOCYTIC LEUKEMIA

In B-cell prolymphocytic leukemia, more than >55% of the circulating lymphocytes are prolymphocytes. These prolymphocytes are much larger than normal lymphocytes and have a typically round nucleus, with one clear punched-out nucleolus. Approximately 60% of patients have a translocation targeting *MYC*, and about 40% have a 17p deletion affecting *TP53*. B-cell prolymphocytic leukemia is quite rare as a presenting diagnosis, but some patients with chronic lymphocytic leukemia, typically patients with a 17p deletion, have a subset of cells that are similar to prolymphocytic leukemia cells. As the disease progresses, the distinction can pose a diagnostic dilemma, but the immunophenotype of B-cell prolymphocytic leukemia typically will differ from chronic lymphocytic leukemia by expressing surface immunoglobulin and CD20 brightly, not expressing CD23, and sometimes not expressing CD5. The targeted B-cell receptor pathway inhibitors that are effective in chronic lymphocytic leukemia also are effective for prolymphocytic leukemia, so the need to distinguish between these two diseases may be less important.

LARGE GRANULAR LYMPHOCYTIC LEUKEMIA

Large granular lymphocyte leukemia is discussed in Chapter 151.

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ABSTRACT

Chronic myeloid leukemia (CML) is a myeloproliferative disorder marked by the increased proliferation of a granulocytic cell line that retains the ability to differentiate. As many as 95% of patients with CML have the Philadelphia (Ph) chromosome caused by the reciprocal translocation of the long arms of chromosome 22 at the breakpoint cluster region (*BCR*) gene and chromosome 9 at the Abelson leukemia virus (*ABL*) gene (t[9;22]). As a result of this translocation, a *BCR-ABL* fusion gene is created that generates a chimeric protein with constitutively active tyrosine kinase activity. Tyrosine kinase inhibitor therapy has revolutionized the treatment of CML, giving patients with chronic phase disease a near-normal age-adjusted lifespan. For patients with chronic phase CML, the "first-generation" tyrosine kinase inhibitor imatinib gives a complete cytogenetic remission in roughly 60 to 70% of cases, a major molecular response (a three-log reduction of peripheral blood *BCR-ABL* mRNA) in 50 to 60% of cases, with overall survival rates of more than 90%. The "second-generation" tyrosine kinase inhibitors (e.g., dasatinib, nilotinib, and bosutinib) are more potent than imatinib and thus give higher short-term response rates and less progression to advanced phases of disease, although without a clear advantage in overall survival rates. Because of the success of tyrosine kinase inhibitors, CML will become a more prevalent oncologic diagnosis in the future, despite its relatively low incidence. CML is thus becoming an increasing part of most oncology practices, and an understanding of the pathobiology, monitoring, and treatment is important to optimize the management of CML patients.

KEYWORDS

chronic myeloid leukemia
BCR-ABL
Philadelphia chromosome
chronic phase
tyrosine kinase inhibitor
molecular monitoring

chronic phase, whereas the proportion of cases of advanced (accelerated and blast) phase disease is higher in the developing world. Untreated chronic phase CML will eventually progress to advanced phase within a mean period of approximately 3 to 5 years, and when disease reaches blast crisis, the natural history is survival of less than 1 year.

EPIDEMIOLOGY

The incidence of CML is fairly uniform throughout the world, affecting about 1 to 1.5 per 100,000 of the adult population each year.[1] In the Western industrialized world, CML represents approximately 15% of all adult and less than 5% of all childhood leukemias, with a median age of onset of about 65 years. The median age appears to be earlier in the developing world. As a result of the spectacular success of tyrosine kinase inhibitor therapy (see later), the prevalence of CML is increasing steadily because the average duration of the disease has lengthened appreciably.

There are no described "CML families." The greatest risk factor for CML is radiation exposure, particularly in Japanese atomic bomb blast survivors. Although *ABL* sequences are found in the Abelson murine leukemia retrovirus, no infectious agent for human CML has been described.

PATHOBIOLOGY

The Ph chromosome is an acquired cytogenetic abnormality present in all leukemic cells of the myeloid lineage and in some B cells and T cells in CML patients. It is formed as a result of a reciprocal translocation of genetic material of chromosomes 9 and 22 expressed as t(9;22)(q34;q11) (Fig. 170-1). The Ph chromosome is found in more than 90% of CML patients, whereas approximately 5% of cases have translocations that involve chromosomes 9, 22, and others as well. The remaining 5% of patients with clinical and hematologic features consistent with CML have undetectable Ph chromosome, but *BCR-ABL* can be detected by FISH (which detects the DNA fusion) or reverse transcription–polymerase chain reaction (RT-PCR), which detects the chimeric mRNA.

Three possible breakpoints in the *BCR* gene exist, including breaks in the *major* breakpoint cluster region (M-BCR) in the intron between exons e13 and e14 or in the intron between exons e14 and e15.[2] These breakpoints account for more than 95% of CML cases. The breakpoint in the *ABL* gene is varied and can occur broadly upstream of exon a2. Thus, the two possible common *BCR* breakpoints, merging with the *ABL* breakpoint, can yield two slightly different chimeric *BCR-ABL* genes, which yields a longer e13a2 or slightly smaller e14a2 transcript. Both transcripts are translated into a 210-kD BCR-ABL tyrosine kinase ($p210^{BCR-ABL}$) that has greatly enhanced tyrosine kinase activity compared with the normal ABL protein. Rarely in CML, the breakpoint *BCR* occurs 5′ to the common breakpoint between exons e1 and e2 in an area designated the *minor* breakpoint cluster region (m-bcr). This produces the e1a2 mRNA, yielding a smaller *BCR-ABL* fusion gene ($p190^{BCR-ABL}$). Curiously, although this genetic alteration is uncommon in CML, it accounts for roughly half of the cases of Ph chromosome–positive acute lymphoblastic leukemia (ALL).

Very rarely, a breakpoint in the so-called *micro* breakpoint cluster region (μ-bcr) results in e19a2 chimeric mRNA and a larger 230-kD BCR-ABL protein ($p230^{BCR-ABL}$). This molecular lesion appears to be associated with the rare Ph chromosome–positive chronic neutrophilic leukemia.

The normal ABL protein is a nonreceptor tyrosine kinase with important roles in signal transduction and the regulation of cell growth. Normal ABL protein migrates between the cytoplasm and nucleus. The chimeric BCR-ABL protein, however, associates with the cytoplasmic membrane and is constitutively active with increased kinase activity, causing activation of numerous signal transduction pathways, including MYC, RAS, STAT, JUN, and phosphatidylinositol-3 kinase. Unlike many multihit models of carcinogenesis, the single *BCR-ABL* lesion thus appears to influence cell cycling, differentiation, and apoptosis, causing DNA genetic instability and attenuation of the DNA damage response. In murine models, *BCR-ABL* can cause myeloproliferative diseases similar to human CML, although chronic phase has been difficult to simulate until recent sophisticated genetically engineered murine models coupled inducible *BCR-ABL* with the genetic scrambling of the Sleeping Beauty transposon. In vitro studies suggest that *BCR-ABL* expression allows cells to become cytokine independent, protects cells from apoptotic responses to DNA damage, and increases adhesion of hematopoietic cells to extracellular matrix proteins.

The progression to advanced phase disease will eventually occur in all cases not treated with a tyrosine kinase inhibitor or allogeneic transplantation, and advanced phase disease is not curable without transplant (even in the age of tyrosine kinase inhibitors). Progression is associated with a further block in differentiation, with death coming from the eventual absence of normal platelets (bleeding) or white blood cells (infection). Blast counts increase and new cytogenetic abnormalities accumulate. The most common cytogenetic changes in progression are an additional Ph chromosome, trisomy 8, isochrome i(17q), and trisomy 19. Gene expression profiling suggests that the bulk of the

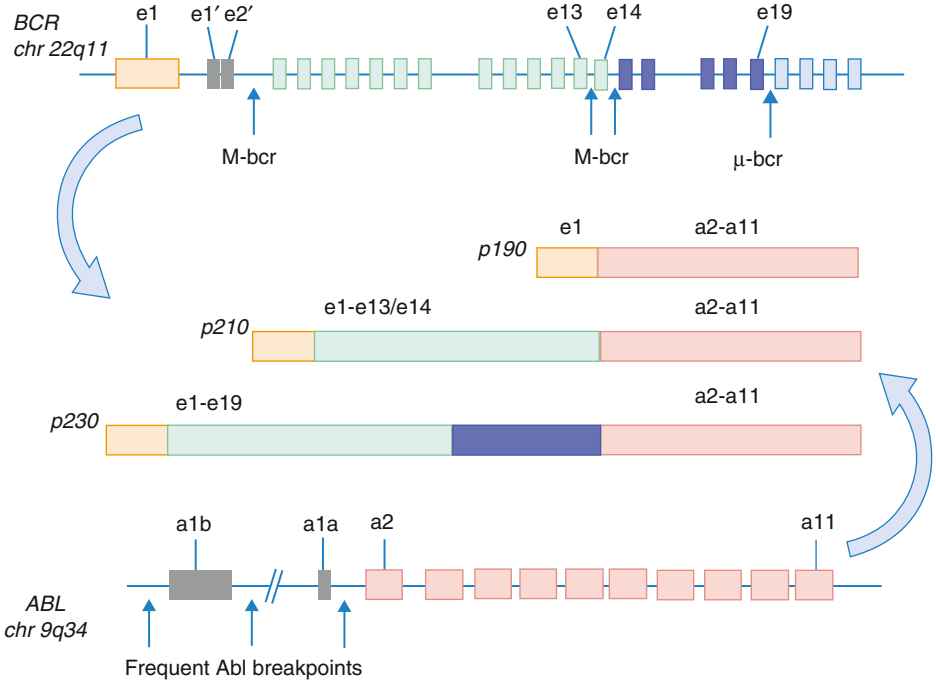

FIGURE 170-1. ***BCR* and *ABL* gene breakpoints.** The *BCR* gene (from chromosome 22) contains three primary breakpoint regions (denoted the "major breakpoint cluster" [M-bcr]; "minor breakpoint cluster" [*m-bcr*]; and "micro breakpoint cluster" [*μ-bcr*]). Gene rearrangement at the *M-bcr* site results in either of two p210 fusion proteins, composed of *BCR* exons 1-13 or exons 1-14 (*orange* and *green*) fused to *ABL* exons 2-11 (*pink*). Gene rearrangement at *m-bcr* site results in the p190 fusion protein, composed of *BCR* exon 1 (e1) (*orange*) fused to *ABL* exons 2-11 (a2-a11) (*pink*). Gene rearrangement at the *μ-bcr* site results in the p230 fusion protein, composed of *BCR* exons 1-19 (*orange*, *green*, and *purple*) fused to *ABL* exons 2-11 (*pink*). The *BCR* e1′ and e2′ are included in the fusion gene, but splicing events result in loss of RNA from the *BCR-ABL* transcript. Fusion transcripts may additionally include *ABL* exons 1a or 1a/1b with exons 2-11, depending on the *ABL* breakpoint region. Not to scale.

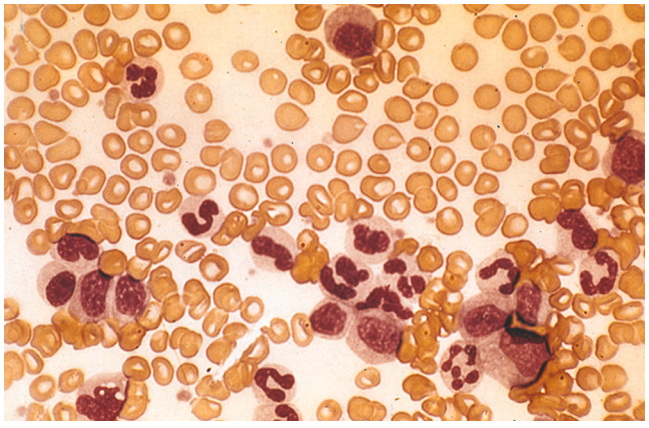

FIGURE 170-2. Chronic myeloid leukemia, chronic phase. Peripheral smear shows leukocytosis, with representation by the entire spectrum of leukocyte differentiation, ranging from myeloblasts to mature neutrophils. (Courtesy Andrew Schafer, MD.)

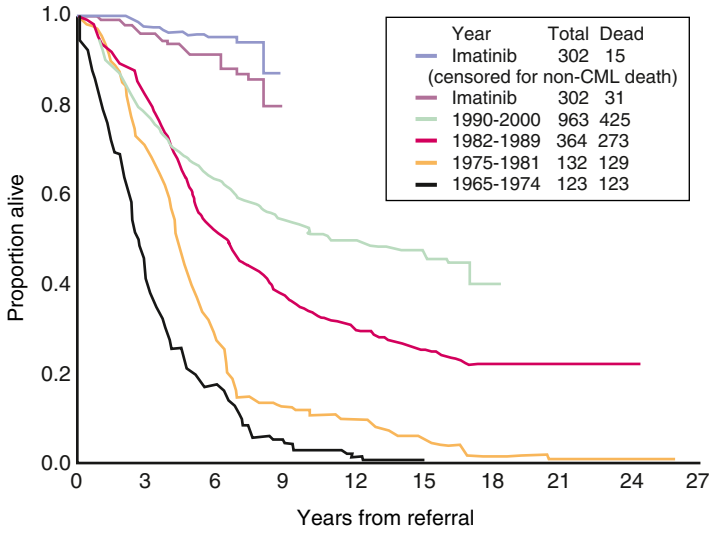

FIGURE 170-3. Survival of patients with Ph chromosome–positive chronic myeloid leukemia (CML) in chronic phase CML. In single-institutional studies, industry-sponsored trials, and national reports where tyrosine kinase inhibitor therapy has full penetration, the estimated 8- to 10-year survival rates are high. The survival rates are lower where tyrosine kinase inhibitor treatment penetration is not optimal. (From Bjorkholm M, Ohm L, Eloranta S, et al. Success story of targeted therapy in chronic myeloid leukemia: a population-based study of patients diagnosed in Sweden from 1973-2008. *J Clin Oncol*. 2011;29:2514-2520, and Chen Y, Wang H, Kantarjian H, et al. Trends in chronic myeloid leukemia incidence and survival in the United States from 1975-2009. *Leuk Lymphoma*. 2013;54:1411-1417.)

genetic changes triggering progression occur from the transition of chronic to accelerated phase, with relatively minor genetic changes occurring from accelerated to blast phase. In keeping with the stem cell origin nature of CML, in about 25% of blast phase cases, the predominant blast expansion is in the lymphoid, not myeloid, lineage.

CLINICAL MANIFESTATIONS

Most CML patients (>90%) present in chronic phase, often diagnosed incidentally during routine examination and blood cell counts. Symptoms, when present, usually include fatigue and abdominal discomfort from splenomegaly. More extreme constitutional symptoms of weight loss, bone pain, fever, and night sweats are more commonly associated with advancing disease. This has practical clinical relevance because although the tyrosine kinase inhibitors used to treat CML (discussed later) are generally well tolerated, compliance early in the treatment course can be challenging because the medications can make patients feel worse than they felt before they were diagnosed.

DIAGNOSIS

Patients generally present with leukocytosis, often accompanied by thrombocytosis and anemia (Fig. 170-2). Basophilia and eosinophilia are common. Without any other obvious explanation for a high white blood cell (WBC) count, the diagnosis of CML can be entertained.[3]

In CML, the diagnostic and monitoring target is the chimeric *BCR-ABL* gene, whether this is at the chromosome level (metaphase cytogenetics), at the DNA level (FISH), or by chimeric mRNA transcript (RT-PCR).

Diagnostic Work-Up

The diagnostic work-up for the suspected CML patient is fairly straightforward, and the goal is to establish both the diagnosis and the phase of disease. A bone marrow aspirate should be evaluated for, at minimum, morphology (to determine blast count) and cytogenetics (to look for the Ph chromosome and other cytogenetic abnormalities that would classify the patient as advanced phase). FISH can be used if the cytogenetic test fails and can be done on peripheral blood if need be. The RT-PCR assay of bone marrow or peripheral blood can be useful to define a "baseline" for later disease monitoring during therapy but is not required. Using peripheral blood RT-PCR testing for *BCR-ABL* can establish diagnosis, but initial diagnostic bone marrow is needed for staging.

TREATMENT

Tyrosine kinase inhibitors are the cornerstone of treatment for CML (Fig. 170-3).[4,5]

Frontline Tyrosine Kinase Inhibitors for CML

There are four FDA-approved tyrosine kinase inhibitors for newly diagnosed chronic phase CML, the "first-generation" tyrosine kinase inhibitor imatinib and three "second-generation" agents, dasatinib, nilotinib, and bosutinib (Table 170-1).[6–8] All work by competitively binding to the adenosine triphosphate (ATP)-binding pocket of BCR-ABL, thus blocking phosphate passage to other downstream signaling effector proteins. In addition, each tyrosine kinase inhibitor has a unique pattern of "off-target" kinase inhibition, which likely explains how the different toxicities of the agents can provide a 67% complete cytogenetic response compared with 7% in the control arm. After more than a decade of follow-up, the cumulative rate of complete cytogenetic response with imatinib is 80 to 85%, with an estimated freedom from progression to progressive disease and overall survival of 92% and 83%, respectively.[A1] Moreover, roughly half all patients with a complete cytogenetic response obtain a major molecular response.

However, the long-term follow-up studies showed that more than 40% of patients discontinue imatinib therapy. These failures of imatinib are roughly divided into thirds: primary resistance to tyrosine kinase inhibitors, intolerance, and resistance/progression after an initial response. Second-generation TKIs (nilotinib, dasatinib, and bosutinib; Table 170-2)[A2–A4] produce superior short-term responses, as measured by rate of complete cytogenetic response and major molecular response by 12 months of therapy. In addition, the second-generation tyrosine kinase inhibitors produce a higher proportion of "deep" molecular responses (which may influence the potential for tyrosine kinase inhibitor discontinuation, discussed later). Transformation to advanced phase disease is less frequent. However, long-term survival has not been significantly different between imatinib and the second-generation tyrosine kinase inhibitors.

Several trials have also compared standard (400 mg/day) to high-dose (600 to 800 mg/day) imatinib. These studies consistently show that high-dose imatinib can yield similar short- and long-term outcomes as the second-generation tyrosine kinase inhibitors. However, these higher doses are less well tolerated and are discouraged as initial therapy in newly diagnosed chronic phase cases.

Toxicities of Tyrosine Kinase Inhibitors

The common side effect of tyrosine kinase inhibitors is myelosuppression, which is less problematic in imatinib than the second-generation tyrosine kinase inhibitors (with grade 3 or 4 cytopenias occurring in roughly 10% vs. more than 20% for imatinib and the second-generation tyrosine kinase inhibitors, respectively). In addition, each tyrosine kinase inhibitor has a unique side-effect profile (see Table 170-1). The tyrosine kinase inhibitors tend to be "cross-tolerant" in that if a patient must change the tyrosine kinase inhibitor because of a particular side effect, it is unlikely that the same complication would be found with another tyrosine kinase inhibitor. Chronic fatigue (mostly correlated with musculoskeletal pain and muscular cramps) is especially problematic for imatinib users and is the side effect that most affects quality of life, although fluid retention is also a problem. Pleural effusion is an adverse event for dasatinib and can be found in about 20% of patients (as opposed to 1% with imatinib). In addition, reversible pulmonary arterial hypertension is a rare (about 5%) but serious side effect with dasatinib. Nilotinib can cause a prolongation of the QT interval and is associated with an increased risk for peripheral arterial occlusive disease. Bosutinib's primary toxicity is diarrhea, which can occur in up to 70% of patients. Ponatinib has a strong association with hypertension and carries a black box warning regarding hepatotoxicity and vascular occlusion. Indeed, arterial and venous thrombosis and occlusions occurred in approximately 30% of CML patients receiving the drug who had highly resistant disease, and these events happened in cases with and without cardiovascular risk factors. Peripheral and

TABLE 170-1 THERAPY OF CHRONIC MYELOID LEUKEMIA WITH OUTCOMES AND MOST FREQUENT SIDE EFFECTS

SETTING	DRUGS	CCyR (%)	SURVIVAL (%)	NOTABLE SIDE EFFECTS (TOP THREE)
Frontline	Imatinib	65% at 5 years	83% at 11 years	Muscle spasms (41%), edema (37%), hypophosphatemia (28%)
	Dasatinib	86% at 2 years	91% at 5 years	Neutropenia (29%), pleural effusion (28%), diarrhea (21%)
	Nilotinib	85% at 4 years	94% at 54 months	Rash (38%), headache (32%), fatigue (23%)
	Bosutinib	77% at 1 year	N/A	Diarrhea (70%), increased ALT (23%), thrombocytopenia (14%)
Second/third line	Dasatinib	50% at 5 years	71% at 6 years	
	Nilotinib		85% at 3 years	*For all TKIs given as third-line agents, same side effects occur with higher frequency*
	Bosutinib	40% at 2 years	92% at 2 years	
	Ponatinib	45% at 2 years	90% at 2 years	
	Omacetaxine	10% at 2 years	85% at 2 years	Cytopenias

ALT = alanine aminotransferase; TKI = tyrosine kinase inhibitor.

TABLE 170-2 TWELVE-MONTH RESPONSES IN THE ENESTND, DASISION, AND BOSUTINIB TRIALS

	ENESTND TRIAL			*DASISION TRIAL*		*BFORE TRIAL*	
RESPONSE	NIL300 BID	NIL400 BID	IM 400	DAS 100	IM 400	BOS 400	IM 400
CCyR	80%	78%	65%	83%	72%	77%	66%
MMR	44%	43%	22%	46%	28%	47%	37%
AP/BC	0.7%	0.4%	4.2%	1.9%	3.5%	2%	3%

AP/BC = patients progressing to accelerated phase and blast crisis; bid = twice daily; CCyR = complete cytogenetic remission; DAS = dasatinib; IM = imatinib; MMR = major molecular response; NIL = nilotinib.

coronary occlusion are seen to a lesser degree with bosutinib and are least likely in patients treated with imatinib.

Monitoring Tyrosine Kinase Inhibitor Therapy

The day-to-day management of tyrosine kinase inhibitor side effects is detailed extensively in the National Comprehensive Cancer Network guidelines.[9] The response to therapy must be carefully monitored and assessed. Many studies have shown that peripheral blood quantitative monitoring of mutant *BCR-ABL* transcript by RT-PCR is a sensitive and reliable measure of disease burden and correlates with short-term and long-term outcomes. Because of the exquisite sensitivity of the *BCR-ABL* assay (with an estimated detection limit of 1 CML cell in 10^5 normal cells), peripheral blood testing is the foundation of *monitoring* treatment (www.NCCN.org and www.leukemia-net.org). Indeed, quantitative PCR testing of *BCR-ABL* transcript is recommended as the only monitoring test needed during therapy. Follow-up bone marrow aspirates and cytogenetics are reserved for patients who fail to meet treatment milestones or relapse while on therapy (see later).

A complete hematologic response is the normalization of peripheral blood counts, and it occurs in more than 90% of patients within 3 months of starting tyrosine kinase inhibitor therapy. A cytogenetic response is based on the number of Ph chromosomes found on a metaphase preparation of at least 20 cells. A major cytogenetic response occurs when 0 to 35% of metaphases are positive for Ph chromosomes. A complete cytogenetic response is when no Ph chromosomes are found. Complete cytogenetic response correlates strongly with a high overall survival, and a peripheral blood value *BCR-ABL* allele burden of 1% correlates with a complete cytogenetic response.

A molecular response measures peripheral blood *BCR-ABL* as a ratio to a control (wild-type) gene (*BCR, ABL*, or *GUSB*, depending on the reference laboratory), set to an international scale (IS). A three-log reduction (0.1% IS) is termed a major molecular response and correlates with a superior progression-free survival and overall survival compared with patients with a lesser response. Deeper responses are based on the log reduction in the BCR-ABL load (e.g., MR4 represents a four-log reduction from baseline). The use of the terms "undetectable" and "negative" BCR-ABL is discouraged because the absence of BCR-ABL can be from either low actual disease burden or poor laboratory performance.

Discontinuation of Tyrosine Kinase Inhibitor Therapy

In in vitro studies, the "CML stem cell" appears impervious to tyrosine kinase inhibitor therapy, and therefore it was assumed that patients would have to remain on a tyrosine kinase inhibitor for life because discontinuation would simply allow the stem cell reservoir to proliferate, assuring certain relapse. However, about 40 to 50% of patients who have been without detectable *BCR-ABL* for several years remain in molecular remission for more than 2 years after tyrosine kinase inhibitor therapy is discontinued.[10,11] The minimum pre-discontinuation time appears to be at least 2 years of a deep response. Since about a year is required to obtain a deep response, most patients will have had at least 3 years of therapy. The rapidity of the BCR-ABL decline after initiating therapy ("halving time") and the detection of BCR-ABL by ultrasensitive techniques prior to discontinuation are associated with an increased or decreased chance of treatment-free remission, respectively.[12,13] Most (>90%) relapsing patients respond well and quickly to the reintroduction of therapy, although not all achieve similarly deep responses. Progression to advanced phase disease after discontinuation is exceedingly rare. However, the long-term consequences of discontinuation are unknown, and patients and physicians who wish to try discontinuation are advised to enroll in a clinical trial.

Which Tyrosine Kinase Inhibitor for Frontline Therapy?

Both the National Comprehensive Cancer Network and the European Leukemia Network are agnostic in regard to which tyrosine kinase inhibitor should be used as frontline therapy. Some practical considerations include:

1. *What are the treatment goals?* For an older patient, controlling the disease and extending survival without undue toxicity are primary goals, and these can be accomplished with imatinib. On the other hand, a younger patient may be interested in childbearing and/or discontinuation of tyrosine kinase inhibitor therapy. In this setting, starting with a second-generation tyrosine kinase inhibitor may be the best choice because the likelihood of a deep response is greater.
2. *What is the status of the disease?* Patients who present in chronic phase by morphologic and cytogenetic criteria may be in a high-risk group given a high WBC count and spleen size. In cases in which advancing phase disease is suspected, the use of the more potent second-generation tyrosine kinase inhibitor may have merit.
3. *What is the status of the patient?* Many patients may have comorbidities that can affect drug choice. Of the three agents available, imatinib has the longest track record and seems to be relatively free of long-term side effects. Nilotinib is associated with troublesome side effects in patients with the metabolic syndrome and has a higher incidence of vascular occlusive events compared with imatinib. Dasatinib has the highest risk for producing pleural effusions and is associated with pulmonary artery hypertension in a small subset of patients. Lastly, bosutinib can cause considerable diarrhea.

Resistance to Tyrosine Kinase Inhibition

Primary resistance to imatinib is defined as the failure to normalize peripheral blood counts (which typically occurs 1 to 3 months after initiating therapy). In clinical trials this occurs in less than 10% of cases. This can be confused with poor compliance for reasons noted previously because studies have shown that poor adherence significantly affects the likelihood of patients ever achieving a major molecular response or deeper response, or losing cytogenetic response; they have a nearly 30% chance of losing complete cytogenetic response compared with only about 2% in highly adherent patients. Beyond the strict definition of primary resistance, a failure to reach molecular response milestones

at 3 and 6 months bodes poorly (see later), and the fact that patients with a poor early response have a higher likelihood of early progression to advanced phase disease suggests a biologic relationship between primary resistance and progression.

Acquired or "secondary" resistance describes the phenomenon of an early response to therapy, with subsequent resistance and a rise in *BCR-ABL* transcript levels. In roughly 25 to 50% of cases, this is caused by a single base pair mutation in the *ABL* kinase domain, resulting in a change in protein conformation, with an alteration of the binding of tyrosine kinase inhibitors and the resulting inhibition of *BCR-ABL*. Thus far, more than 100 such mutations have been discovered. It is not clear whether these mutations are present at a very low level even at diagnosis and emerge under the selective pressure of the tyrosine kinase inhibitor, or whether they arise during therapy. In vitro methods have been used to describe the relative inhibitory effects of different tyrosine kinase inhibitors with different mutations, and this can be useful in selecting which tyrosine kinase inhibitor one should use as second-line therapy in cases of resistance. The detection of the T315I mutation is of special note because only one tyrosine kinase inhibitor (ponatinib) is effective with this particular mutation. The T315I mutation becomes more prevalent with increasing patterns of resistance and tyrosine kinase inhibitor substitution, so although unusual at the first signs of resistance, it is quite common in the setting of multiple tyrosine kinase inhibitor failure.

Treatment Milestones for Frontline Therapy in Chronic Phase CML

The National Comprehensive Cancer Network and the European Leukemia Network recommend a set of treatment milestones associated with survival outcomes (Table 170-3). The major prognostic milestones are (1) the achievement of a complete cytogenetic response (or its near equivalent, a *BCR-ABL* of ≤1% IS) should occur by 12 months of therapy; (2) thereafter, achievement of a major molecular response (*BCR-ABL* ≤0.1% IS) is desirable because this level of disease burden is associated with a very low rate of resistance and progression; and (3) deeper responses (MR4.0 and lower) that are sustained may allow for tyrosine kinase inhibitor discontinuation. The failure to reach milestones, or the loss of milestones, should prompt consideration of change to another tyrosine kinase inhibitor and mutation testing to inform the decision of which tyrosine kinase inhibitor to use as second-line therapy.

The treatment response of a complete cytogenetic response at 12 months of tyrosine kinase inhibitor therapy is a prognostic indicator of long-term survival with imatinib or second-generation tyrosine kinase inhibitors. For example, for chronic phase patients receiving either imatinib or second-generation tyrosine kinase inhibitors, the 3-year progression-free survival and overall survival rates for patients with and without a 12-month complete cytogenetic response were 98%/99% and 67%/94%, respectively. Achievement of a major molecular response is associated with continued complete cytogenetic response, less disease progression to advanced phases, and a better overall survival compared with patients without a major molecular response. For example, in the IRIS study, the 10-year overall survival rate was 91% for patients with a major molecular response at 12 months versus 85% in those without a major molecular response. Similar benefits of achieving a major molecular response are seen in patients receiving second-generation tyrosine kinase inhibitors.

Recent attention has shifted to even earlier assessment of disease burden as measured by peripheral blood *BCR-ABL* allele burden at 3 and 6 months of therapy (early molecular response, or EMR). The *BCR-ABL* cutoff of 10% IS or less (good prognosis) versus more than 10% IS (bad prognosis) has been evaluated after frontline therapy with imatinib, dasatinib, and nilotinib, and the early molecular response is consistently associated with short- and long-term outcomes across all tyrosine kinase inhibitors. A retrospective study of chronic phase CML patients treated with imatinib first-line therapy found that patients with 3-month BCR-ABL levels of 10% IS or less had overall survival and progression-free survival rates of 93% (both), whereas patients with more than 10% IS had inferior rates of 57% (both). This trend has been shown in several other retrospective and randomized trials. In addition, cytogenetic and molecular responses also differ based on early molecular response. For example, dasatinib-treated patients with good EMR had a 5-year complete cytogenetic response, a major molecular response, and MR4.5 rates of 94%, 87%, and 54%, whereas patients with poor early molecular response had rates of 41%, 38%, and 5%, respectively.

Second-Line Therapy—Tyrosine Kinase Inhibitors and Other Approaches

For second-line therapy, the second-generation tyrosine kinase inhibitors have quite similar efficacy.[A5,14,15] Single-arm studies suggest that these agents will yield a complete cytogenetic response in 30 to 50% of relapsed cases (much higher in cases in which a tyrosine kinase inhibitor switch was precipitated by a lack of tolerance to the first-line agent). The progression-free survival rate for second-line tyrosine kinase inhibitor therapy is more than 70% (see Table 170-1). At 5-year follow-up, however, only one third of patients remain on treatment. If or when subsequent relapse occurs, a third-line agent can be used, but in this setting, responses are unusual. The possible exception is ponatinib, which in the setting of multiple-resistant or T315I mutations, achieved a complete cytogenetic response of more than 70%, with 2-year progression-free survival rates of about 70%. The more frequent use of ponatinib for resistance has been constrained by its significant vascular side effects, however.

TABLE 170-3 DRUG FAILURE MILESTONES THAT SUGGEST NEED FOR A CHANGE IN TYROSINE KINASE INHIBITOR

TIME POINT AFTER INITIATION OF TKI THERAPY	RESPONSE MILESTONE
3 months	No CHR* Ph+ >95% *BCR-ABL* >10% IS†
6 months	*BCR-ABL* >10% IS Ph+ >35%
12 months	*BCR-ABL* >1% Ph+ >0%
Any time after 12 months	Loss of CHR Loss of CCyR Loss of MMR (*BCR-ABL* >0.1% IS) *ABL* kinase domain mutations New clonal cytogenetic abnormality

*Recommendations for milestones by the National Comprehensive Cancer Network and the European Leukemia Network.

†The National Comprehensive Cancer Network considers change for these patients if the patient has not had treatment interruptions from toxicity or adherence. The European Leukemia Network assesses early molecular response at 6 months.

CCyR = complete cytogenetic response; CHR = complete hematologic response; IS = international scale; MMR = major molecular response; Ph = Philadelphia chromosome; TKI = tyrosine kinase inhibitor.

In heavily pretreated CML patients with resistance to or unacceptable side effects from tyrosine kinase inhibitors, asciminib (10 to 200 mg once or twice daily), an allosteric inhibitor that binds a myristoyl site of the BCR-ABL1 protein, thereby locking BCR-ABL1 into an inactive conformation through a mechanism distinct from all other ABL kinase inhibitors, can provide a major molecular response in about 25 to 50% of patients.[16,A6]

A key question for patients with resistant disease who are placed on a salvage tyrosine kinase inhibitor regimen is when to judge efficacy because allogeneic stem cell transplantation would be the next strategy. Two different studies support an evaluation of response after 3 months of therapy. If a major cytogenetic response is not achieved, the progression-free survival is dramatically different compared with patients achieving a major cytogenetic response. If a patient is a transplantation candidate, a formal search can be initiated at the same time as the initiation of a second-line tyrosine kinase inhibitor because it usually requires 3 months to identify an unrelated donor. Thus, an assessment can be made as to adequacy of tyrosine kinase inhibitor response and availability of a donor at 3 months. If the patient has a good response, tyrosine kinase inhibitor therapy is continued; if the response is poor, the patient can move to transplantation.

Allogeneic Hematopoietic Stem Cell Transplantation

Before the advent of tyrosine kinase inhibitor therapy, allogeneic transplantation was the treatment of choice for newly diagnosed CML. Most centers reported survival rates of 75 to 85%, 25 to 40%, and 10 to 20% for chronic, accelerated, and blast phase disease, respectively. The results are similar for those with related and unrelated matched donors. Currently, transplantation is reserved for salvage therapy for those few patients who cannot tolerate tyrosine kinase inhibitors, patients with highly resistant disease, and those with advanced phase disease.[17,18] Several studies have shown that prior tyrosine kinase inhibitor therapy does not have an adverse effect on transplant-related mortality and that patients who undergo transplantation because of intolerance to tyrosine kinase inhibitors have survival rates similar to untreated historical controls. In additions, studies have shown that patients with T315I mutations have similar outcomes as historical controls.

Who Should Undergo Allogeneic Transplantation in the Era of Tyrosine Kinase Inhibitors?

Reasonable indications might include the following:

1. *Intolerance of tyrosine kinase inhibitors*. Tyrosine kinase inhibitors tend to be cross-tolerant, meaning that if a particular toxicity occurs with tyrosine kinase inhibitor "A," it is unlikely to occur with agent "B." However, rare patients cannot tolerate any tyrosine kinase inhibitors. For these patients, bone marrow transplantation is encouraged.
2. *Primary tyrosine kinase inhibitor failure* (e.g., failure to reach the National Comprehensive Cancer Network or European Leukemia Network guidelines, such as lack of a cytogenetic response by 3 to 6 months, less than major cytogenetic response by 12 months, or complete cytogenetic response by 18 months). These patients should receive a trial of a different tyrosine

kinase inhibitor, but it is prudent to make sure these patients are evaluated for transplantation and undergo HLA typing. Failure of the second agent in this setting would be a reasonable indication at least prompting evaluation for bone marrow transplantation.

3. *Secondary resistance*. When patients become resistant to a frontline agent, the probability of achieving a complete cytogenetic response with a second-line agent is 50% or less. In addition, the probability of such patients failing second-line therapy and developing progression or a T315I mutation is greatly increased compared with tyrosine kinase inhibitor-naïve patients.
4. *Patients with T315I mutation*. Ponatinib is highly effective in chronic phase patients with the T315I mutation, and most patients should initially be started on this agent. However, there is considerable risk for venous and arterial occlusive disease, so patients with a high risk for vascular events or who are young and might need to be on ponatinib for many years should consider the transplantation option. The protein synthesis inhibitor omacetaxine is also approved in this setting, although responses are few and short lived.
5. *Accelerated or blast phase disease*. The rare patients who present with accelerated phase respond well to tyrosine kinase inhibitor therapy and might not need transplantation (although it is worthwhile to begin looking for a donor early in these cases). Patients who present in blast crisis should get intensive therapy (often chemotherapy combined with a tyrosine kinase inhibitor) and move to transplantation when a donor is identified. Patients who progress to advanced phase disease while on a tyrosine kinase inhibitor have a median survival of less than 1 year and need transplantation in short order.
6. *Clonal abnormalities with myelodysplasia*. Clonal changes in Ph chromosome–negative cells occur in about 5% of patients in complete cytogenetic response. In most cases, these do not seem to affect the natural history. However, rare patients have a –5 or –7 abnormality associated with features of myelodysplastic syndrome and should consider bone marrow transplantation.

Treatment of Patients with Advanced Phase CML

It is rare for CML to present in advanced phase disease. Indeed, a patient who presents in lymphoid or myeloid blast crisis is difficult to distinguish from de novo ALL or acute myeloid leukemia (AML; Chapter 163).

Rarely, patients present with advanced phase disease defined by a modest increase in blast counts or the Ph chromosome with other clonal cytogenetic abnormalities. In this case, upfront treatment with a single-agent tyrosine kinase inhibitor regimen is often quite effective, yielding results similar to chronic phase disease. Results are different, however, in chronic phase CML, in which patients who progress to advanced phase disease while on tyrosine kinase inhibitors have a median survival of less than 1 year. Both dasatinib and bosutinib (but not nilotinib) are approved for the treatment of blast phase CML. In general, the blast phase of CML is treated with ALL- or AML-like chemotherapy (Chapter 163), with the addition of a tyrosine kinase inhibitor. Another potentially useful drug approved for chronic and accelerated phase disease is omacetaxine (also known as homoharringtonine), an inhibitor of protein synthesis. The major side effect is myelosuppression, and its role is generally as a bridge to allogeneic transplantation, which is the only potential curative therapy in patients with advanced phase disease in the face of tyrosine kinase inhibitor treatment. The survival rates after allogeneic transplantation are, roughly, for chronic phase more than 80%, accelerated phase 40 to 50%, and blast phase 10 to 20%.

PROGNOSIS

Several clinical and pathologic features at diagnosis or shortly thereafter are associated with long-term response. The strongest prognostic feature is the phase of disease.

Numerous risk scores have been used to predict long-term outcomes. Each combines clinical factors (e.g., age, spleen size) with laboratory values, and all work with a high degree of intrascore system correlation (Table 170-4). The scores typically divide patients into low-, intermediate-, and high-risk categories, with survival and progression correlating with risk group. The Sokal Index, developed in 1984 for chronic phase patients, is the most commonly used and places patients into risk categories based on age, blast count, spleen size, and platelet count. The Hasford score was developed from patients on interferon and adds peripheral blood counts to the Sokal measures. The more recently developed European Treatment and Outcome Study requires only an assessment of the spleen size and percent basophils in blood. All of these scores have online calculators for easy determination of score. At diagnosis, they prove a reasonable guide to predict outcome. These scores work similarly in cases treated with first- and second-generation tyrosine kinase inhibitors alike.

TABLE 170-4 CLINICAL SCORING SYSTEMS USED IN RISK-STRATIFYING CML PATIENTS

	SOKAL	HASFORD	EUTOS
Age	x	x	
Spleen size	x	x	x
Blast (peripheral)	x	x	
Basophilia		x	x
Eosinophilia		x	
Thrombocytosis	x	x	

EUTOS = European Treatment and Outcome Study for CML; Hasford = Hasford score for CML; Sokal = Sokal Index for CML (https://www.mdcalc.com/sokal-index-chronic-myelogenous-leukemia-cml).

Additional Cytogenetic Abnormalities

The presence of major additional chromosomal abnormalities (trisomy 8, isochromosome 17q, second Ph chromosome, and trisomy 19) at diagnosis is generally associated with negative prognostic impact on survival and disease progression to accelerated or blast phase. Patients with major route additional chromosomal abnormalities at the time of diagnosis have longer times to cytogenetic and molecular responses and shorter progression-free survival and overall survival than patients with t(9;22), t(v;22), loss of Y chromosome, or other minor additional chromosomal abnormalities. For example, 5-year survival rates are about 91%, 87%, 89%, 92%, and 52%, respectively, for patients with t(9;22), t(v; 22), loss of Y chromosome, minor route additional chromosomal abnormalities, and major route additional chromosomal abnormalities. Other studies have reported that some of the minor route additional chromosomal abnormalities, such as 11q23 and 3q26 rearrangements, are also associated with poor prognosis. Another study found that the presence of trisomy 8, loss of Y chromosome, or second Ph chromosome had no adverse impact on treatment response and survival, whereas the presence of isochromosome 17q, del7q, or 3q26.2 rearrangements was associated with lower response rates and inferior survival. The concurrent presence of two or more additional chromosomal abnormalities is associated with a poor prognosis.

Next-generation sequencing has shown that chronic phase patients who respond poorly to treatment and who progress to advanced phase disease have a higher prevalence of mutations in genes commonly associated with acute leukemia (e.g., *ASXL1, RUNX1, IZF1*). However, these markers are not currently used in routine clinical treatment algorithms.

Molecular Response

The peripheral blood monitoring of *BCR-ABL* transcripts has a very important role in CML management for the following reasons: (1) the depth of molecular responses is associated with outcomes (the achievement of a major molecular response is a "safe harbor" because disease resistance or progression is extremely rare after this low level of disease burden is achieved); (2) the kinetics of response appears to predict outcome because the rate of achieving the 3-month response is important and patients with a *BCR-ABL* of more than 10% IS at the 3-month mark do poorly compared with patients whose disease recedes more rapidly; and (3) deeper responses, beyond a major molecular response, are becoming increasingly more important as experience, trials, and treatment strategies move toward treatment discontinuation for those patients with a prolonged deep molecular response. Several studies have shown that a proportion of selected patients with persistently undetectable *BCR-ABL*, as defined by at least a 4- or 4.5-log read depth (the so-called "deep molecular response"), may discontinue tyrosine kinase inhibitor therapy without molecular relapse of their disease.

CHRONIC MYELOMONOCYTIC LEUKEMIA AND ATYPICAL CHRONIC MYELOPROLIFERATIVE DISEASES

DEFINITION AND EPIDEMIOLOGY

The chronic non-*BCR-ABL* leukemias are diseases that feature components of both myeloid dysplasia and proliferation. The WHO classifies chronic myelomonocytic leukemia (CMML), juvenile CMML, chronic neutrophilic leukemia (CNL), and atypical CML (aCML) among the myelodysplastic/myeloproliferative disorders (Chapters 152 and 167). Chronic neutrophilic leukemia and atypical CML are poorly named because they do not involve the *BCR-ABL* rearrangement. In CMML, there is an expansion of the monocytic

population in the peripheral blood and bone marrow, whereas in CNL, the neutrophil population is increased.

These diseases are quite rare, and indeed, their incidence is difficult to accurately estimate. CMML is estimated to have an incidence of less than 0.5/100,000, and aCML and CNL are even rarer. The median age at diagnoses for these diseases is approximately 65 to 75 years.

PATHOBIOLOGY

There is no singular distinguishing genetic feature of CMML. Clonal cytogenetic abnormalities are seen in about 30% of cases, and mutations in greater than 90%. The most common mutations are in genes associated with mRNA splicing (e.g., *SF3B1*), cytokine signaling (e.g., *NRAS*), and epigenetic modification (e.g., *TET2*). On the other hand, mutations in *CSF3R* are present in more than 60% of aCML and CNL patients, and this mutation is unusual in other myeloid leukemias and myelodysplastic syndrome. In addition, one fourth of cases of aCML will have a point mutation in the *SETBP1* gene.

CLINICAL MANIFESTATIONS AND DIAGNOSIS

Like CML, the signs and symptoms are often nonspecific. The first clue to the diagnosis is usually abnormal peripheral blood WBC counts, which in CMML would demonstrate monocytosis, and may include neutropenia, anemia, and thrombocytopenia. Splenomegaly is quite common in these diseases. The work-up will be negative for the Ph chromosome or molecular evidence of *BCR-ABL*. The bone marrow typically shows myeloid hyperplasia and dysplasia of the myeloid lineage (and sometimes other lineages).[19]

The WHO definition of CMML requires a persistent (at least 3 months) peripheral blood monocytosis of more than 1000/μL and more than 10% of the entire WBC differential. In addition, the peripheral blood and bone marrow myeloblasts plus monoblasts plus promyelocytes must be less than 20% of the total WBC differential; if it is higher, it is classified as AML. Chronic neutrophilic leukemia and atypical CML are not so strictly defined.

TREATMENT AND PROGNOSIS

The median survival for these diseases is less than 3 years, with death arising from either transition to acute leukemia or from complications of cytopenias. There is no curative therapy outside of allogeneic stem cell transplantation.[20] Patients with CMML may benefit from a trial of hypomethylating agents (with an overall response rate of ~30 to 40%) or opt for disease control (if they have a highly proliferative disease) with hydroxyurea under expert supervision.[21] For CMML there is a roughly 20% risk of transformation to acute myeloid leukemia (AML) after 3 years from diagnosis. If transition to AML occurs, induction therapy is often attempted, especially as a bridge to rapid transplantation. In atypical CML and chronic neutrophilic leukemia, mutations in *CSF3R* appear to cause aberrant signaling through SRC or JAK2, depending on where the mutation occurs. Thus, clinical trials are exploring targeted therapy inhibiting SRC and JAK in these rare patients.

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For the General References and other additional features, please visit Elsevier eBooks+ at https://ebooks.health.elsevier.com.

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171 NON-HODGKIN LYMPHOMAS

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DEFINITION

Lymphomas are solid tumors of the immune system. Increasing knowledge of the biology of the immune system has led to a corresponding increase in the understanding of these malignancies. In addition to better systems of classification and clinical evaluation, this new knowledge has led to the development of new therapies. Beneficial treatment is available for essentially every patient with non-Hodgkin lymphoma. The overall survival of lymphoma patients has increased steadily over the past 40 years, and many patients can be cured.

EPIDEMIOLOGY

In the United States, an estimated 80,000 or so new cases of non-Hodgkin lymphoma are diagnosed in annually, and about 20,000 patients to die of this disease each year. Non-Hodgkin lymphomas account for about 5% of new cancers in the United States and result in about 3% of cancer deaths. The U.S. lifetime risk for developing non-Hodgkin lymphoma is estimated to be 2.4% (1 in 42) for men and 1.9% (1 in 52) for women.[1] The incidence rate increases dramatically with age and is higher in Whites than in other ethnic groups.

Geographic differences in the incidence of non-Hodgkin lymphomas vary as much as five-fold. The highest rates are seen in the United States, Europe, and Australia, whereas lower rates are seen in Asia. Even more striking are geographic differences in the incidence of certain types of non-Hodgkin lymphoma, such as Burkitt lymphoma, follicular lymphoma, extranodal natural killer (NK)/T-cell nasal lymphoma, and adult T-cell leukemia/lymphoma.

In the United States the incidence rate for non-Hodgkin lymphomas increased by about 3 to 4% yearly from 1950 and the beginning of the 21st century, likely related to increased longevity, to the acquired immunodeficiency syndrome (HIV/AIDS) epidemic (Chapter 353), to occupational and environmental exposures (e.g., agricultural chemicals), to improvements in imaging techniques, and to improvements in the ability of pathologists to diagnose lymphoma. Since then, the incidence rate for non-Hodgkin lymphoma has reached a plateau, and the death rate from the disease has been declining.

PATHOBIOLOGY

For most cases of non-Hodgkin lymphoma, the cause is unknown, although genetic, environmental, and infectious agents have been implicated (Table 171-1).

Genetic Factors

Familial non-Hodgkin lymphoma clusters have been described, with a slightly higher risk for non-Hodgkin lymphoma among siblings and first-degree relatives of patients with lymphoma or other hematologic malignancies. The incidence of non-Hodgkin lymphoma has been associated with polymorphisms in a variety of genes related to immunity, including chemokines, tumor necrosis factor, interleukin-10 (IL-10), and lymphotoxin-α. Polymorphisms in other genes related to the cell cycle and apoptosis have also been associated with an increased risk for developing lymphoma.

Immune System Abnormalities

Several inherited disorders increase the risk for developing non-Hodgkin lymphoma as much as 250-fold (see Table 171-1). In some of these conditions, the lymphoma may be related to Epstein-Barr virus (Chapter 348). For example, patients with X-linked lymphoproliferative disorder have mutations in the *SH2D1A* gene, which encodes proteins that regulate the host immune response against Epstein-Barr virus–infected cells; individuals with this disorder may develop fatal infectious mononucleosis or non-Hodgkin lymphoma after primary exposure to Epstein-Barr virus. Acquired immunodeficiency states are also associated with an increased risk for non-Hodgkin lymphoma. For example, post-transplantation lymphoproliferative disorders (Chapter 348) occur in as many as 20% of solid organ transplant recipients, related to the proliferation of B lymphocytes that have been transformed during immunosuppressive therapy. The risk for non-Hodgkin lymphoma is also increased more than 100-fold in patients infected with the human immunodeficiency virus (HIV, Chapter 355). Almost all central nervous system (CNS) lymphomas

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population in the peripheral blood and bone marrow, whereas in CNL, the neutrophil population is increased.

These diseases are quite rare, and indeed, their incidence is difficult to accurately estimate. CMML is estimated to have an incidence of less than 0.5/100,000, and aCML and CNL are even rarer. The median age at diagnoses for these diseases is approximately 65 to 75 years.

PATHOBIOLOGY

There is no singular distinguishing genetic feature of CMML. Clonal cytogenetic abnormalities are seen in about 30% of cases, and mutations in greater than 90%. The most common mutations are in genes associated with mRNA splicing (e.g., *SF3B1*), cytokine signaling (e.g., *NRAS*), and epigenetic modification (e.g., *TET2*). On the other hand, mutations in *CSF3R* are present in more than 60% of aCML and CNL patients, and this mutation is unusual in other myeloid leukemias and myelodysplastic syndrome. In addition, one fourth of cases of aCML will have a point mutation in the *SETBP1* gene.

CLINICAL MANIFESTATIONS AND DIAGNOSIS

Like CML, the signs and symptoms are often nonspecific. The first clue to the diagnosis is usually abnormal peripheral blood WBC counts, which in CMML would demonstrate monocytosis, and may include neutropenia, anemia, and thrombocytopenia. Splenomegaly is quite common in these diseases. The work-up will be negative for the Ph chromosome or molecular evidence of *BCR-ABL*. The bone marrow typically shows myeloid hyperplasia and dysplasia of the myeloid lineage (and sometimes other lineages).[19]

The WHO definition of CMML requires a persistent (at least 3 months) peripheral blood monocytosis of more than 1000/μL and more than 10% of the entire WBC differential. In addition, the peripheral blood and bone marrow myeloblasts plus monoblasts plus promyelocytes must be less than 20% of the total WBC differential; if it is higher, it is classified as AML. Chronic neutrophilic leukemia and atypical CML are not so strictly defined.

TREATMENT AND PROGNOSIS

The median survival for these diseases is less than 3 years, with death arising from either transition to acute leukemia or from complications of cytopenias. There is no curative therapy outside of allogeneic stem cell transplantation.[20] Patients with CMML may benefit from a trial of hypomethylating agents (with an overall response rate of ~30 to 40%) or opt for disease control (if they have a highly proliferative disease) with hydroxyurea under expert supervision.[21] For CMML there is a roughly 20% risk of transformation to acute myeloid leukemia (AML) after 3 years from diagnosis. If transition to AML occurs, induction therapy is often attempted, especially as a bridge to rapid transplantation. In atypical CML and chronic neutrophilic leukemia, mutations in *CSF3R* appear to cause aberrant signaling through SRC or JAK2, depending on where the mutation occurs. Thus, clinical trials are exploring targeted therapy inhibiting SRC and JAK in these rare patients.

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171 NON-HODGKIN LYMPHOMAS

JULIE M. VOSE AND JAMES O. ARMITAGE

DEFINITION

Lymphomas are solid tumors of the immune system. Increasing knowledge of the biology of the immune system has led to a corresponding increase in the understanding of these malignancies. In addition to better systems of classification and clinical evaluation, this new knowledge has led to the development of new therapies. Beneficial treatment is available for essentially every patient with non-Hodgkin lymphoma. The overall survival of lymphoma patients has increased steadily over the past 40 years, and many patients can be cured.

EPIDEMIOLOGY

In the United States, an estimated 80,000 or so new cases of non-Hodgkin lymphoma are diagnosed in annually, and about 20,000 patients to die of this disease each year. Non-Hodgkin lymphomas account for about 5% of new cancers in the United States and result in about 3% of cancer deaths. The U.S. lifetime risk for developing non-Hodgkin lymphoma is estimated to be 2.4% (1 in 42) for men and 1.9% (1 in 52) for women.[1] The incidence rate increases dramatically with age and is higher in Whites than in other ethnic groups.

Geographic differences in the incidence of non-Hodgkin lymphomas vary as much as five-fold. The highest rates are seen in the United States, Europe, and Australia, whereas lower rates are seen in Asia. Even more striking are geographic differences in the incidence of certain types of non-Hodgkin lymphoma, such as Burkitt lymphoma, follicular lymphoma, extranodal natural killer (NK)/T-cell nasal lymphoma, and adult T-cell leukemia/lymphoma.

In the United States the incidence rate for non-Hodgkin lymphomas increased by about 3 to 4% yearly from 1950 and the beginning of the 21st century, likely related to increased longevity, to the acquired immunodeficiency syndrome (HIV/AIDS) epidemic (Chapter 353), to occupational and environmental exposures (e.g., agricultural chemicals), to improvements in imaging techniques, and to improvements in the ability of pathologists to diagnose lymphoma. Since then, the incidence rate for non-Hodgkin lymphoma has reached a plateau, and the death rate from the disease has been declining.

PATHOBIOLOGY

For most cases of non-Hodgkin lymphoma, the cause is unknown, although genetic, environmental, and infectious agents have been implicated (Table 171-1).

Genetic Factors

Familial non-Hodgkin lymphoma clusters have been described, with a slightly higher risk for non-Hodgkin lymphoma among siblings and first-degree relatives of patients with lymphoma or other hematologic malignancies. The incidence of non-Hodgkin lymphoma has been associated with polymorphisms in a variety of genes related to immunity, including chemokines, tumor necrosis factor, interleukin-10 (IL-10), and lymphotoxin-α. Polymorphisms in other genes related to the cell cycle and apoptosis have also been associated with an increased risk for developing lymphoma.

Immune System Abnormalities

Several inherited disorders increase the risk for developing non-Hodgkin lymphoma as much as 250-fold (see Table 171-1). In some of these conditions, the lymphoma may be related to Epstein-Barr virus (Chapter 348). For example, patients with X-linked lymphoproliferative disorder have mutations in the *SH2D1A* gene, which encodes proteins that regulate the host immune response against Epstein-Barr virus–infected cells; individuals with this disorder may develop fatal infectious mononucleosis or non-Hodgkin lymphoma after primary exposure to Epstein-Barr virus. Acquired immunodeficiency states are also associated with an increased risk for non-Hodgkin lymphoma. For example, post-transplantation lymphoproliferative disorders (Chapter 348) occur in as many as 20% of solid organ transplant recipients, related to the proliferation of B lymphocytes that have been transformed during immunosuppressive therapy. The risk for non-Hodgkin lymphoma is also increased more than 100-fold in patients infected with the human immunodeficiency virus (HIV, Chapter 355). Almost all central nervous system (CNS) lymphomas

ABSTRACT

The non-Hodgkin lymphomas represent no more than 5% of all new cancers, but they have a disproportionate importance because of the ability of therapy to cure a significant fraction of patients. For this reason, the management of lymphoma requires a meticulous approach to diagnosis and staging. A large number of histologic subtypes of lymphoma are recognized with differing clinical and microscopic appearances. Even when lymphomas appear morphologically similar, they may exhibit significant genetic and molecular heterogeneity. These differences, as well as individual patient differences, have ushered in an era of precision medicine for the treatment of lymphoma, with a large number of new chemotherapy agents, monoclonal antibodies, targeted agents, and immunotherapies. These new agents have improved the survival for many types of lymphoma.

KEYWORDS

lymphoma
non-Hodgkin lymphoma
lymphadenopathy
lymphoproliferative disorder
chemotherapy
monoclonal antibodies

TABLE 171-1 FACTORS ASSOCIATED WITH THE DEVELOPMENT OF NON-HODGKIN LYMPHOMA

Inherited immune disorders
Severe combined immunodeficiency disease
Common variable immunodeficiency disease
Wiskott-Aldrich syndrome
Ataxia-telangiectasia
X-linked lymphoproliferative disorder
Autoimmune lymphoproliferative syndrome
Acquired immune disorders
Solid organ transplantation
Acquired immunodeficiency syndrome (AIDS)
Rheumatoid arthritis and systemic lupus erythematosus
Sjögren syndrome
Hashimoto thyroiditis
Celiac disease
Drug related
Methotrexate for autoimmune disorders
JAK1/2 inhibitor for myelofibrosis
Azathioprine for autoimmune disorders
Anti–tumor necrosis factor agents (e.g., infliximab, adalimumab)
Infectious agents
Epstein-Barr virus
Human T-lymphotropic virus type 1
Human herpesvirus type 8
Hepatitis C virus
Helicobacter pylori
Borrelia burgdorferi
Chlamydia psittaci
Campylobacter jejuni
Coxiella burnetii
Occupational and environmental exposure
Herbicides
Organic solvents
Ultraviolet light
Diet
Smoking

and approximately 50% of other lymphomas in patients with the acquired immunodeficiency syndrome (AIDS) are related to Epstein-Barr virus. Some studies have shown a two-fold increase in the incidence of non-Hodgkin lymphomas among patients with rheumatoid arthritis (Chapter 243), and the risk for marginal zone lymphomas is increased approximately 30- to 40-fold in patients with Sjögren syndrome (Chapter 247). Increases in the incidence of thyroid lymphoma are seen in patients with Hashimoto thyroiditis (Chapter 207). Enteropathy-type T-cell lymphomas are associated with celiac disease (Chapter 126). Patients with the autoimmune lymphoproliferative syndrome, associated with mutations in the *FAS* gene, also appear to be at higher risk for developing lymphoma.

Infectious Agents

Epstein-Barr virus (Chapter 348) is associated with the majority of post-transplantation lymphoproliferative disorders and many HIV/AIDS-associated lymphomas. This viral genome is detectable in more than 95% of cases of endemic Burkitt lymphoma and in approximately 15 to 35% of cases of sporadic Burkitt lymphoma and AIDS-associated lymphomas. This virus is also associated with Epstein-Barr virus-positive diffuse large B-cell lymphoma of elderly people, plasmablastic lymphoma, and extranodal NK/T-cell lymphoma.

The human T-lymphotropic virus type 1 (HTLV-1; Chapter 360) is detectable in virtually all cases of adult T-cell leukemia/lymphoma. The risk for lymphoma is approximately 3% in patients infected with HTLV-1. In endemic areas, up to 50% of all non-Hodgkin lymphomas may be related to HTLV-1.

Human herpesvirus-8 (HHV-8, Kaposi sarcoma–associated herpesvirus; Chapter 359), which is associated with expansion of the B-cell population, is also associated with primary effusion lymphoma (see later) in immunocompromised patients and with multicentric Castleman disease. Patients with primary effusion lymphoma are often coinfected with Epstein-Barr virus.

Epidemiologic evidence has linked hepatitis C virus (Chapter 135) to lymphoplasmacytic lymphoma associated with type II cryoglobulinemia, nodal marginal zone lymphoma, and splenic marginal zone lymphoma. Chronic antigenic stimulation from this virus may lead to the emergence of malignant B-cell clones.

Helicobacter pylori is associated with gastric lymphoma (Chapter 178) of extranodal marginal zone/mucosa-associated lymphoid tissue (MALT). Colonized patients develop gastritis from chronic antigenic stimulation mediated by T cells, which respond to *H. pylori*–specific antigens and emergence of malignant B-cell clones. *Borrelia burgdorferi* (associated with Lyme disease, Chapter 296) has been associated with marginal zone B-cell lymphoma of the skin. Evidence also links *Chlamydia psittaci* (Chapter 294) with ocular adnexal lymphomas, *Campylobacter jejuni* with immunoproliferative small intestinal disease (Chapter 279), and *Coxiella burnetii* with diffuse large B-cell and follicular lymphoma.

Environmental and Occupational Exposure

Agricultural chemicals have been associated with an increased risk for developing non-Hodgkin lymphomas, and the strongest associations involve phenoxy herbicides such as 2,4-dichlorophenoxyacetic acid (2,4-D), which was also a component of Agent Orange. An increased risk has also been associated with ionizing radiation (Chapter 18), organic solvents, and nitrates in drinking water, although contradictory results have been reported. Some studies have also linked non-Hodgkin lymphomas to high-fat diets and ultraviolet radiation (Chapter 18). The risk for non-Hodgkin lymphoma is increased approximately 20-fold after treatment for Hodgkin lymphoma (Chapter 172). Heavy smokers (Chapter 363) have an increased risk for developing follicular lymphoma. Low levels of vitamin D have been associated with increased risk for recurrent lymphoma, as well as poor outcome. Anti–tumor necrosis factor (anti-TNF) agents might be associated with an increased risk for developing lymphoma, particularly hepatosplenic T-cell lymphoma. Breast implants also are associated with the development of anaplastic large cell lymphoma.

Pathology

Non-Hodgkin lymphomas are derived from cells of the immune system at varying stages of differentiation. In some cases, the cell of origin is directly linked to the morphology, immunophenotype, and clinical behavior of the lymphoma (E-Fig. 171-1 and Table 171-2).

The transformation of cells from the normal immune system into malignant lymphoma reflects the acquisition of specific genetic abnormalities. In many cases, cytogenetic studies can identify chromosomal translocations that underlie the development or progression of the lymphoma. In most cases of non-Hodgkin lymphoma, the activation of proto-oncogenes is the major abnormality, but occasionally chromosomal translocations can lead to fusion genes that code for chimeric proteins. In addition, some cases are associated with deletion of tumor suppressor genes. Specific genetic abnormalities are associated with some specific subtypes of non-Hodgkin lymphoma (Table 171-3). It is becoming clear that the tumor microenvironment from cells of the host immune system is important in tumor cell survival and response to therapy.

Classification

The updated 2016 World Health Organization (WHO) classification integrates genetic data into the clinicopathologic classification (Table 171-4). This classification divides lymphomas on the basis of B-cell or T/NK-cell origin and whether they are derived from primitive precursor cells or from more mature "peripheral" cells. Specific clinical and pathologic entities are recognized within each of these groupings. In the United States and Europe, 85 to 90% of non-Hodgkin lymphomas are B cell in origin.

The most frequent type is diffuse large B-cell lymphoma, which represents about 30% of all non-Hodgkin lymphomas worldwide. The next most frequent type is follicular lymphoma, which represents about 20% of cases. Follicular lymphoma is relatively more frequent in North America and Western Europe and less frequent in Asia. Less common types, each representing between 5 and 10% of all non-Hodgkin lymphomas, are extranodal marginal zone/MALT lymphomas, peripheral T-cell lymphomas, small lymphocytic lymphoma, and mantle cell lymphoma. Other types each represent less than 2% of non-Hodgkin lymphomas seen in the United States.

The non-Hodgkin lymphomas recognized in the WHO classification have clinically distinctive characteristics (Table 171-5), such that an experienced hematopathologist can accurately classify 85% or more of patients by WHO criteria when adequate material is available. Some diagnoses, such as follicular lymphoma, can be made with a high degree of accuracy without immunologic or genetic studies. The diagnosis of T-cell lymphomas cannot be made accurately without immunophenotyping. Cytogenetic studies and molecular genetic studies (fluorescence in situ hybridization, or FISH) can help resolve difficult differential diagnoses. For example, the presence of a t(8;14) translocation supports the diagnosis of Burkitt lymphoma, whereas a t(11;14) with cyclin D1 overexpression can confirm the diagnosis of mantle cell lymphoma (see Tables 171-2 and 171-3).

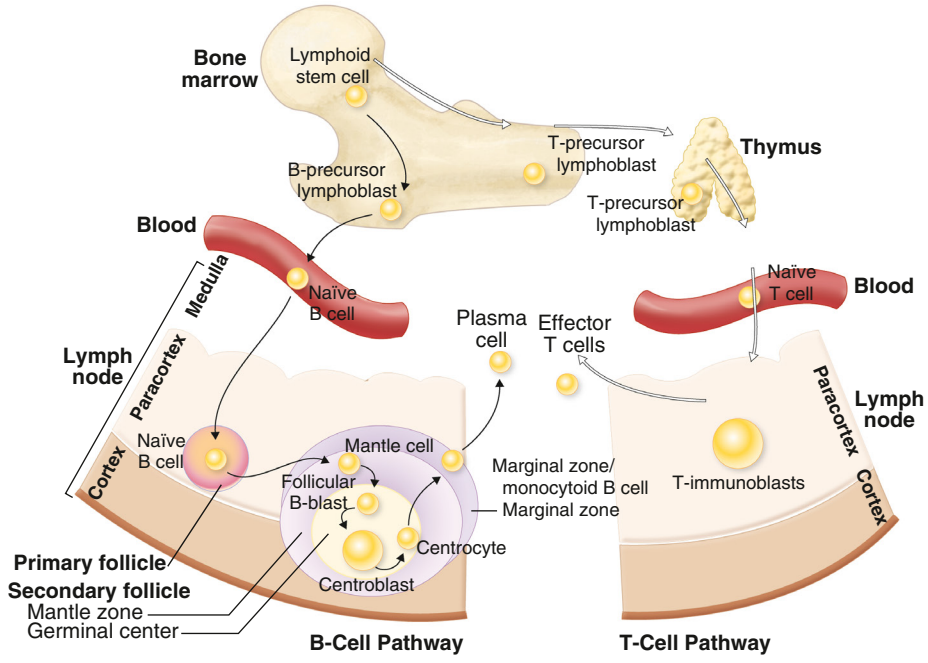

A

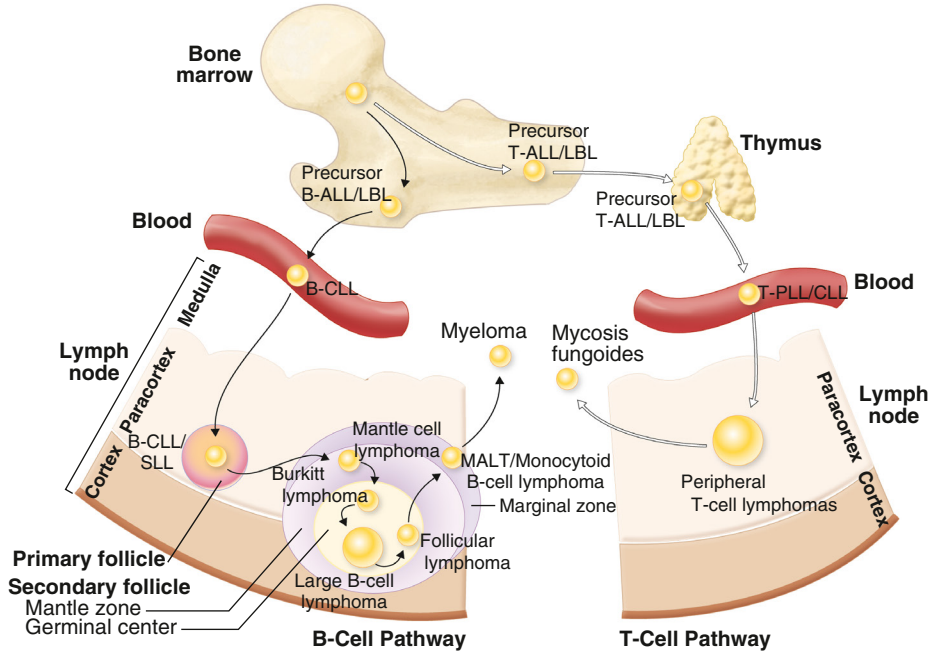

B

E-FIGURE 171-1. Postulated normal counterparts of currently recognized B- and T-cell malignancies. A, Schema of normal B- and T-cell differentiation. Bone marrow–derived lymphoid stem cells differentiate into committed B-cell precursors or into T-cell precursors that undergo further maturation in the thymus. These B- and T-cell precursors mature into naïve B or T cells that circulate to lymph nodes. After antigen exposure, normal B blasts proliferate and undergo further differentiation in the germinal center of the secondary follicle. The germinal center is surrounded by a mantle zone and a marginal zone. Antigen-specific B cells generated in the germinal center leave the follicle and reappear in the marginal zone. Thereafter, immunoglobulin-producing plasma cells accumulate in the lymph node medulla and subsequently exit to the periphery. Antigen-dependent T-cell proliferation occurs in the lymph node paracortex. After antigen exposure, mature T cells become immunoblasts and, subsequently, antigen-specific effector T cells that exit to the periphery. The postulated normal counterparts of many currently recognized T- and B-cell neoplasms are shown. **B,** T- and B-cell malignancies derived from the postulated normal counterparts shown in **A.** ALL = acute lymphoblastic leukemia; CLL = chronic lymphocytic leukemia; LBL = lymphoblastic lymphoma; MALT = mucosa-associated lymphoid tissue; PLL = prolymphocytic leukemia; SLL = small lymphocytic lymphoma.

TABLE 171-2 TYPICAL IMMUNOPHENOTYPES OF COMMON NON-HODGKIN LYMPHOMAS

LYMPHOMA	CD20	CD3	CD10	CD5	CD23	OTHER
Small lymphocytic	+	–	–	+	+	
Lymphoplasmacytic	+	–	–	–	–	Cytoplasmic immunoglobulin$^+$
Extranodal marginal zone MALT	+	–	–	–	–	
Nodal marginal zone	+	–	–	–	–	
Follicular	+	–	+	–		
Mantle cell	+	–	+	+		Cyclin D1$^+$
Diffuse large B cell	+	–				
Mediastinal large B cell	+	–				
Burkitt	+	–	+	–		TdT$^-$
Precursor T lymphoblastic	–	+/–				TdT$^+$, CD1a$^{+/-}$, CD7$^+$
Anaplastic large T cell	–	+/–				CD30$^+$, CD15$^-$, EMA$^+$, ALK$^{+/-}$
Peripheral T cell	–	+/–				Other pan-T variable

ALK = anaplastic lymphoma kinase; EMA = epithelial membrane antigen; MALT = mucosa-associated lymphoid tissue; TdT = terminal deoxynucleotidyl transferase.

Gene expression profiling has allowed the identification of distinct subsets of patients with diffuse large B-cell lymphoma (DLBCL). Patients with histologically identical lymphomas can be divided into those with gene expression patterns resembling normal germinal center B cells (GCBs), those whose tumors resemble activated post–germinal center B cells (ABCs), or those with patterns resembling that seen in Hodgkin lymphoma. The last pattern is most frequently found in young women who present with large mediastinal masses. Use of immunohistochemistry to subdivide diffuse large B-cell lymphoma into germinal center B cell subtype and activated post–germinal center B cell subtype is widely used but does not correlate perfectly with DNA microarray results. Using a combination of exome and transcriptome sequencing, array-based DNA copy-number analysis, and targeted amplicon resequencing of selected genes, diffuse large B-cell lymphoma can be further subtyped based on shared genomic abnormalities.

CLINICAL MANIFESTATIONS

The most common presentation of non-Hodgkin lymphoma is lymphadenopathy (Fig. 171-1; Chapter 154). In many cases, patients notice cervical, axillary, or inguinal adenopathy and seek a physician's advice. In general, lymph nodes containing lymphomas are firm, nontender, and not associated with a regional infection. In other patients, lymphadenopathy occurring in sites such as the mediastinum or retroperitoneum causes symptoms such as chest pain, cough, abdominal pain, and back pain. More extensive disease can also cause symptoms related to the superior vena cava syndrome, spinal cord compression, and renal insufficiency (associated with ureteral compression).

Non-Hodgkin lymphomas are often associated with systemic symptoms that may lead to the diagnosis. The most obvious symptoms, termed B symptoms, are fever, night sweats, and unexplained weight loss. Any of these symptoms without an obvious cause should lead a physician to consider the diagnosis of lymphoma. Other, less characteristic symptoms include fatigue, which is frequently present at the time of diagnosis if the patient is questioned carefully, and pruritus.

Non-Hodgkin lymphomas can involve essentially any organ in the body, and malfunction of that organ can cause symptoms that lead to the diagnosis. Examples include neurologic symptoms with primary brain lymphoma (Chapter 175), shortness of breath with MALT lymphomas in the lung, epigastric pain and vomiting with gastric MALT lymphomas or diffuse large B-cell lymphomas (Chapter 178), bowel obstruction with small bowel lymphomas (Chapter 179), testicular masses with diffuse large B-cell lymphoma (Chapter 185), and skin lesions with cutaneous lymphomas (Chapter 407). Many lymphomas involve the bone marrow and occasionally cause extensive myelophthisis (Chapter 151) and bone marrow failure. These patients may present with infections, bleeding, and anemia.

Non-Hodgkin lymphomas can also manifest with a variety of immunologic abnormalities. For example, autoimmune hemolytic anemia (Chapter 146) and immune thrombocytopenia (Chapter 158) can be the presenting manifestations of non-Hodgkin lymphoma, especially small lymphocytic lymphoma/chronic lymphocytic leukemia as well as other subtypes, including diffuse large B-cell lymphoma. Peripheral neuropathies (Chapter 388), often associated with overproduction of a monoclonal protein, can be seen in a variety of subtypes but are most characteristic of lymphoplasmacytic lymphoma; sometimes they are also seen with POEMS syndrome (polyneuropathy, organomegaly, endocrinopathy, M protein, skin changes; Chapter 173). Paraneoplastic neurologic complications of non-Hodgkin lymphoma include demyelinating polyneuropathy, Guillain-Barré syndrome, autonomic dysfunction, and peripheral neuropathy. Paraneoplastic syndromes (Chapter 164) associated with non-Hodgkin lymphoma can affect the skin (e.g., pemphigus), kidney (e.g., glomerulonephritis), and miscellaneous organ systems (e.g., vasculitis, dermatomyositis, cholestatic jaundice).

TABLE 171-3 CHROMOSOMAL TRANSLOCATIONS CHARACTERISTIC OF NON-HODGKIN LYMPHOMA

LYMPHOMA SUBTYPE	TRANSLOCATION	GENES INVOLVED	FREQUENCY (%)
Diffuse large B cell	t(3q27) t(14;18)(q32;q21) t(18;14)(q24;q32)	*BCL6* *IgH, BCL2* *MYC (c-Myc), IgH*	35 15-20 <5
Burkitt	t(8;14)(q24;q32) t(8;22)(q24;q11) t(2;8)(p12;q24)	*MYC, IgH* *MYC, IgL* *IgK, MYC*	100% have one of these, most commonly t(8;14)
Follicular	t(14;18)(q32;q21)	*IgH, BCL2*	~90
Mantle cell	t(11;14)(q13;q32)	*BCL1, IgH*	>90
ALCL	t(2;5)(p23;q35)	*ALK, NPM*	>80 of ALK+ ALCLs
MALT	t(11;18)(q21;q21) t(14;18)(q21;q32) t(1;14)(p22;q32)	*API2, MALT1* *IgH, MALT1* *BCL10, IgH*	35 20 10

ALCL = anaplastic large cell lymphoma; ALK = anaplastic lymphoma kinase; MALT = mucosa-associated lymphoid tissue.

DIAGNOSIS

Each new patient with a non-Hodgkin lymphoma should be thoroughly evaluated in a systematic manner (Table 171-6). The diagnosis of non-Hodgkin lymphoma must be considered in patients with compatible clinical presentations and then confirmed by an adequate biopsy read by an experienced hematopathologist. The diagnosis should never be inferred, and patients should not be treated until the diagnosis is confirmed by biopsy. Similarly, patients who achieve a complete remission with initial therapy should not be treated for presumed relapse on the basis of symptoms or abnormal images without a biopsy. Because subtle pathologic distinctions may alter therapy, the most important issue in managing non-Hodgkin lymphoma is to establish an accurate diagnosis.

The differential diagnosis in patients with non-Hodgkin lymphoma is broad. Any cause of lymphadenopathy or splenomegaly can potentially be confused with non-Hodgkin lymphoma (Chapter 154).[2] However, this confusion is resolved by an appropriate biopsy. Core needle biopsies can occasionally be used for a primary diagnosis if the specimen is handled properly. Fine-needle aspirates should not be used to diagnose lymphoma, because they preclude an accurate diagnosis of the specific subtype of non-Hodgkin lymphoma. In most cases, an excisional biopsy is necessary (and is always preferred) for the

TABLE 171-4 2016 REVISION OF THE WHO CLASSIFICATION OF NON-HODGKIN LYMPHOMA

MATURE B-CELL NEOPLASMS
Chronic lymphocytic leukemia/small lymphocytic lymphoma
Splenic marginal zone lymphoma
Hairy cell leukemia/lymphoma
Splenic B-cell lymphoma/leukemia, unclassifiable
Splenic diffuse red pulp B-cell lymphoma
Hairy cell leukemia-variant
Lymphoplasmacytic lymphoma
Waldenström macroglobulinemia
Extranodal marginal zone lymphoma of mucosa-associated lymphoid tissue (MALT)
Nodal marginal zone lymphoma
Follicular lymphoma
In situ follicular neoplasia*
Duodenal-type follicular lymphoma*
*Large B-cell lymphoma with IRF4 rearrangement**
Primary cutaneous follicle center lymphoma
Mantle cell lymphoma
In situ mantle cell neoplasia*
Diffuse large B-cell lymphoma (DLBCL), NOS
Germinal center B-cell type*
Activated B-cell type*
T-cell/histiocyte-rich large B-cell lymphoma
Primary DLBCL of the central nervous system (CNS)
Primary cutaneous DLBCL, leg type
EBV$^+$ DLBCL, NOS*
EBV$^+$ mucocutaneous ulcer*
DLBCL associated with chronic inflammation
Lymphomatoid granulomatosis
Primary mediastinal (thymic) large B-cell lymphoma
Intravascular large B-cell lymphoma
ALK$^+$ large B-cell lymphoma
Plasmablastic lymphoma
Primary effusion lymphoma
HHV8$^+$ DLBCL, NOS*
Burkitt lymphoma
High-grade B-cell lymphoma with *MYC* and *BCL2* and/or *BCL6* rearrangements
High-grade B-cell lymphoma, NOS*
B-cell lymphoma, unclassifiable, with features intermediate between DLBCL and HL
MATURE T AND NK NEOPLASIA
Chronic lymphoproliferative disorder of NK cells
Hydroa vacciniforme-like lymphoproliferative disorder*
Adult T-cell leukemia/lymphoma
Extranodal NK-/T-cell lymphoma, nasal type
Enteropathy-associated T-cell lymphoma
Monomorphic epitheliotropic intestinal T-cell lymphoma*
*Indolent T-cell lymphoproliferative disorder of the GI tract**
Hepatosplenic T-cell lymphoma
Subcutaneous panniculitis-like T-cell lymphoma
Mycosis fungoides
Sézary syndrome
Primary cutaneous CD30$^+$ T-cell lymphoproliferative disorders
Lymphomatoid papulosis
Primary cutaneous anaplastic large cell lymphoma
Primary γδ T-cell lymphoma
Primary cutaneous CD8$^+$ aggressive epidermotropic cytotoxic T-cell lymphoma
*Primary cutaneous acral CD8+ T-cell lymphoma**
Primary cutaneous CD4$^+$ small/medium T-cell lymphoproliferative disorder*
Peripheral T-cell lymphoma, NOS
Angioimmunoblastic T-cell lymphoma
*Follicular T-cell lymphoma**
*Nodal peripheral T-cell lymphoma with TFH phenotype**
Anaplastic large-cell lymphoma, ALK+
Anaplastic large-cell lymphoma, ALK$^-$
*Breast implant-associated anaplastic large-cell lymphoma**
POST-TRANSPLANT LYMPHOPROLIFERATIVE DISORDERS (PTLD)
Plasmacytic hyperplasia PTLD
Infectious mononucleosis PTLD
Florid follicular hyperplasia PTLD*
Polymorphic PTLD
Monomorphic PTLD (B- and T-/NK-cell types)

Provisional entities are listed in italics; *denotes changes from the 2008 classification (shown in Volume 25); ALK = anaplastic lymphoma kinase; EBV$^+$ = Epstein-Barr virus-positive; GI = gastrointestinal; HL = Hodgkin lymphoma; NK = natural killer; NOS = not otherwise specified; TFH = T follicular helper. This table does not include the lymphoid leukemias, plasma cell dyscrasia, and Hodgkin lymphoma (see Chapter 172).

Modified from Swerdlow SH, Campo E, Pileri SA, et al. The 2016 revision of the World Health Organization classification of lymphoid neoplasms. *Blood* 2016;127:2375-2390.

initial diagnosis. A second biopsy should be performed if sufficient material is not obtained with the first attempt.

Staging and Prognostic Systems

After diagnosis, a meticulous staging evaluation is necessary to estimate prognosis and determine therapy. Staging requires a careful history and physical examination; complete blood count; renal and hepatic function tests; serum lactate dehydrogenase (LDH) level; either computed tomography (CT) of the chest, abdomen, and pelvis or positron emission tomography (PET), which can often replace CT scanning when done on a combined PET/CT machine; and bone marrow biopsy (might not be necessary in patients with diffuse large B-cell lymphoma if the PET/CT scan showed bone marrow involvement). PET can identify initial sites of involvement and, after treatment, can distinguish persisting lymphoma from residual fibrosis in masses seen on CT. The most common staging system is the Ann Arbor classification, which separates patients into four stages based on anatomic sites of disease (Table 171-7). In addition, each stage is subdivided into A (no defined general symptoms) and B (unexplained weight loss >10% of body weight in the previous 6 months, unexplained temperature >38° C, or night sweats) categories. Known sites of disease can be re-evaluated after treatment to evaluate the response to therapy.

Although a wide variety of patient factors (e.g., age, symptoms, LDH level) and tumor factors (e.g., bulk, gene expression pattern, proliferation rate) can affect treatment outcomes, two prognostic systems can help in choosing therapy and determining an accurate prognosis. The International Prognostic Index (Table 171-8) is the most widely used method to predict treatment outcome and survival. This index is based on five adverse factors (age >60 years, performance status ≤2, elevated serum LDH level, two or more extranodal sites of disease, Ann Arbor stage III or IV), which are summed to give the score. This index was developed for patients with diffuse aggressive lymphoma (predominantly diffuse large B-cell lymphoma), but it can be used to predict treatment outcome with any subtype. For patients younger than 60 years, an abbreviated index that uses only reduced performance status, elevated serum LDH level, and high stage can be applied. Because patients with follicular lymphoma rarely have a reduced performance status or a large number of extranodal sites, an alternative index termed the Follicular Lymphoma International Prognostic Index was developed. It substitutes more than four nodal areas of involvement and a hemoglobin value less than 12 g/dL as staging criteria and is better for predicting the outcome of treatment for follicular lymphoma.

At the end of therapy, patients should undergo restaging, which involves repeating previously abnormal tests to prove the patient has achieved a complete remission. For most subtypes of lymphoma, the best definition of a complete remission is a PET/CT scan that has a score of Deauville 1, 2, or 3. The Deauville score uses the intensity of uptake in the mediastinum and liver as an internal control and is the most widely used system for documenting remission (Table 171-9).

TREATMENT

Lymphomas may behave in an indolent or an aggressive manner. The behavior of many of these neoplasms is distinctive, but within each category, behavior is frequently influenced by disease site, tumor bulk, and performance status of the patient. Some lymphomas can be managed, at least initially, with observation, whereas other situations are medical emergencies, such as spinal cord compression. Three questions should be considered before starting therapy: (1) Does treatment have curative potential? (2) Can treatment prolong survival? (3) Will treatment alleviate symptoms? When treatment is appropriate, genomic profiling is typically recommended to guide therapy and inform prognosis.[3]

SPECIFIC TYPES OF NON-HODGKIN LYMPHOMAS

PRECURSOR T-CELL AND B-CELL LYMPHOMAS

Precursor T-cell and B-cell lymphomas are nodal or other solid tissue infiltrates of cells that are morphologically and immunophenotypically identical to the immature cells seen in B-cell or T-cell acute lymphoblastic leukemia (Chapter 168). Patients who have predominantly nodal disease with minimal or no involvement of the bone marrow are frequently classified as having *lymphoblastic lymphoma*, whereas those with more than 25% neoplastic cells in the marrow are classified as having *lymphoblastic leukemia*. These distinctions are arbitrary and reflect the stage of disease rather than different diagnoses. These neoplasms are more common in children than in adults.

TABLE 171-5 PRESENTING CLINICAL CHARACTERISTICS OF COMMON NON-HODGKIN LYMPHOMA SUBTYPES

TYPE OF LYMPHOMA	MEDIAN AGE (yr)	MALE (%)	STAGE (%) I	STAGE (%) IV	B SYMPTOMS (%)	BONE MARROW INVOLVED (%)
B-CELL LYMPHOMAS						
Small lymphocytic	65	53	4	83	33	72
Lymphoplasmacytic	63	53	7	73	13	73
Extranodal marginal zone MALT	60	48	39	31	19	14
Nodal marginal zone	58	42	13	40	37	32
Follicular	59	42	18	51	28	42
Mantle cell	63	74	13	71	28	64
Diffuse large B cell	64	55	25	33	33	16
Mediastinal large B cell	37	34	10	31	38	3
Burkitt	31	89	37	38	22	33
PRECURSOR B/T-CELL LYMPHOMAS						
Precursor T lymphoblastic	28	64	0	75	21	50
T-CELL LYMPHOMAS						
Anaplastic large T cell	34	69	19	39	53	13
Peripheral T cell, NOS	61	55	8	65	50	36

B symptoms = fevers, night sweats, and weight loss; MALT = mucosa-associated lymphoid tissue; NOS = not otherwise specified.

Adapted from Armitage JO, Weisenburger DD, for the Non-Hodgkin Lymphoma Classification Project. New approach to classifying non-Hodgkin lymphomas: clinical features of the major histologic subtypes. *J Clin Oncol*. 1998;16:2780-2795.

FIGURE 171-1. Non-Hodgkin lymphoma. Despite the redness of the skin over the enlarged lymph node in this patient, the lesion was completely painless. (From Forbes CD, Jackson WF. *Color Atlas and Text of Clinical Medicine*, 3rd ed. London: Mosby; 2003.)

TABLE 171-7 STAGING OF NON-HODGKIN LYMPHOMA

STAGE	DESCRIPTION
I	Involvement of a single lymph node region (I) or a single extralymphatic organ or site (I_E)
II	Involvement of two or more lymph node regions on the same side of the diaphragm (II) or localized involvement of an extralymphatic organ or site and one or more lymph node regions on the same side of the diaphragm (II_E)
III	Involvement of lymph node regions on both sides of the diaphragm (III), which may also be accompanied by localized involvement of an extralymphatic organ or site (III_E) or by involvement of the spleen (III_S) or both (III_{SE})
IV	Diffuse or disseminated involvement of one or more extralymphatic organs or tissues with or without associated lymph node enlargement
Subtypes	
A	No B symptoms
B	B symptoms: unexplained weight loss ≥10% of body weight in prior 6 months, unexplained fever with temperature >38° C, or night sweats

Adapted from Carbone PP, Kaplan HS, Musshoff K, et al. Report of the Committee on Hodgkin Disease Staging Classification. *Cancer Res*. 1971;31:1860-1861.

TABLE 171-6 TYPICAL EVALUATION OF A PATIENT NEWLY DIAGNOSED WITH NON-HODGKIN LYMPHOMA

1. Biopsy to establish diagnosis
2. Careful history and physical examination
3. Laboratory evaluation
   - A. Complete blood count
   - B. Chemistry screen, including lactate dehydrogenase
4. Imaging studies
   - A. Computed tomography (CT) of chest, abdomen, and pelvis
   - B. Positron emission tomography (can often replace the CT scan)
5. Additional biopsies
   - A. Bone marrow
   - B. Any other suspicious site if results would change therapy (i.e., lumbar puncture)

B-cell precursor lymphomas frequently manifest as solid tumors with involvement of the skin and bones, whereas T-cell neoplasms typically manifest as a mediastinal mass in young males. Involvement of the CNS is common in T-cell lymphomas. Approximately 90% of patients who present with lymphoblastic lymphoma have a T-cell phenotype, whereas about 85% of patients who present with acute lymphoblastic leukemia have a B-cell phenotype.

TREATMENT AND PROGNOSIS

Patients with either T-cell lymphoblastic lymphoma or precursor B-cell lymphoblastic lymphoma are typically treated with regimens modeled after those used for acute lymphoblastic leukemia (Chapter 168). These regimens frequently contain cytarabine and high-dose methotrexate, and they often include maintenance therapy. CNS prophylaxis with intrathecal chemotherapy, high-dose methotrexate, or cranial irradiation is often a component of these regimens. Adverse prognostic characteristics include CNS involvement, stage IV disease, and an elevated LDH level.

TABLE 171-8 INTERNATIONAL PROGNOSTIC INDEX

CATEGORY	SCORE (NO. OF RISK FACTORS)
ALL PATIENTS*	
Low	0 or 1
Low intermediate	2
High intermediate	3
High	4 or 5
AGE-ADJUSTED INDEX, PATIENTS ≤60 YEARS†	
Low	0
Low intermediate	1
High intermediate	2
High	3

*Adverse factors for all patients: age >60 yr, ↑LDH, performance status 2-4, >1 extranodal site, Ann Arbor stage III or IV.
†Adverse factors for patients ≤60 yr: ↑LDH, performance status 2-4, Ann Arbor stage III or IV.
LDH = lactate dehydrogenase.
Adapted from Shipp M, Harrington D, Anderson J, et al. A predictive model for aggressive non-Hodgkin lymphoma. *N Engl J Med.* 1993;329:987-994.

TABLE 171-9 THE DEAUVILLE SCORE FOR ASSESSING POSITRON EMISSION TOMOGRAPHY/COMPUTED TOMOGRAPHIC SCANS TO MEASURE PATIENT RESPONSES TO THERAPY

CRITERIA

1. No uptake related to lymphoma
2. The highest uptake in any site of lymphoma is less than or equal to to the uptake by the mediastinum
3. The highest uptake by any site of lymphoma is greater than the uptake by the mediastinum, but less than or equal to the uptake by the liver
4. The uptake by any site of lymphoma is greater than the uptake by the liver
5. The presence of new sites of uptake or substantial increases in the standardized uptake value in previous sites of lymphoma, or both

MATURE B-CELL LYMPHOMAS

SMALL LYMPHOCYTIC LYMPHOMA AND CHRONIC LYMPHOCYTIC LEUKEMIA

Small lymphocytic lymphoma is defined as a lymph node or other tissue infiltrate that is morphologically and immunophenotypically identical to chronic lymphocytic leukemia (Chapter 169). Patients frequently are symptom free, and the diagnosis is often made when blood counts are performed for other reasons. Patients frequently have lymphadenopathy or splenomegaly. Fatigue is common. Hypogammaglobulinemia can occur and may lead to an increased susceptibility to infection.

TREATMENT AND PROGNOSIS

The median survival time is more than 10 years for patients without adverse characteristics, and these patients often can be managed initially with observation. Therapy is necessary for patients who develop extreme fatigue or have systemic symptoms, for those with rapidly progressive or symptomatic lymphadenopathy or splenomegaly, and for those who develop cytopenias. Management (Chapter 169) must be individualized because therapy is unlikely to be curative, and patients are often elderly.[4] Allogeneic hematopoietic stem cell transplantation may be curative, but few patients are candidates for this approach. Patients may develop autoimmune thrombocytopenia (Chapter 158), autoimmune neutropenia (Chapter 153), and red blood cell aplasia (Chapter 151). These disorders may respond to treatment with corticosteroids, intravenous immune globulin, anti-CD20 monoclonal antibodies such as rituximab or obinutuzumab, cyclosporine, or splenectomy, as used in patients without underlying lymphoma.

A poor prognosis is associated with advanced stage and systemic symptoms, unmutated immunoglobulin heavy chain genes, and genetic abnormalities such as del(17p) or *TP53* mutation. As many as 10% of patients exhibit transformation to diffuse large B-cell lymphoma (Richter syndrome), which is associated with a poor prognosis.

EXTRANODAL MARGINAL ZONE LYMPHOMA OF MUCOSA-ASSOCIATED LYMPHOID TISSUE (MALT LYMPHOMA)

The WHO classification of lymphomas recognizes three groups of marginal zone lymphomas (MZL): (1) splenic MZL, (2) nodal MZL, and (3) extranodal MZL of the MALT type (MALT lymphoma).[5] The marginal zone B cells in general are continuously exposed to exogenous antigens and have a physiologically reduced threshold for triggering proliferation, which may predispose them to malignant transformation. The first two types of marginal zone lymphomas are discussed later (section on "Rare Types of B-Cell Lymphoma"). They have different diagnostic criteria, behavior, and therapeutic implications.

MALT lymphomas are indolent lymphomas that originate in association with epithelial cells and are seen most commonly in the gastrointestinal tract, salivary glands, breast, thyroid, orbit, conjunctiva, skin, and lung. Gastric MALT lymphomas are frequently associated with infection by *H. pylori* (Chapter 125). The majority of cases are stage I or II at diagnosis, although in some series as many as 30% disseminate to bone marrow or other sites. These lymphomas tend to remain localized for extended periods.

TREATMENT AND PROGNOSIS

Local treatment with surgery or radiation therapy cures a high proportion of localized neoplasms. Even in patients who have more than one extranodal site, locations can sometimes be successfully treated with local therapy. Patients without symptoms can be monitored closely without therapy until symptoms progress. Patients with symptoms can be treated with rituximab, single-agent chemotherapy, or combinations similar to the treatment of follicular lymphoma (see later).[6]

About 75% of patients with gastric MALT lymphomas achieve remission after eradication of *H. pylori* (see Chapter 125), and more than 90% remain in remission for prolonged periods of time. Nonresponders are more likely to have submucosal invasion by endoscopic ultrasonography, lymph node metastases, or the t(11;18) chromosomal translocation. Approximately 25% of patients progress, of whom about 25% develop diffuse large B-cell lymphoma. Gastric MALT lymphoma that does not respond to antibiotics can be treated with radiation, rituximab as a single agent (similar to its use in follicular lymphoma), or several traditional combination chemotherapy regimens (see Table 171-10).

FOLLICULAR LYMPHOMA

Follicular lymphoma is derived from germinal center B cells. The hallmark t(14;18)(q32;q21) translocation of follicular lymphomas occurs early in B-cell development, caused by an error in VDJ ("variable," "diversity," and "joining" gene segments) recombination.[7] Follicular lymphoma is the most frequent of indolent or low-grade lymphomas in the United States. Follicular lymphoma is divided into three grades based on the proportion of large, transformed cells (centroblasts).

Patients with follicular lymphoma are frequently asymptomatic. The most common presenting complaint is painless lymphadenopathy. Some patients have cough or dyspnea related to pulmonary or mediastinal involvement or pleural effusions. Other patients have symptoms of abdominal pain or fullness related to subdiaphragmatic or splenic disease. A minority of patients have systemic symptoms of fevers, night sweats, or weight loss.

The clinical behavior and treatment of follicular lymphoma grades 1 and 2 are the same. Some grade 3 follicular lymphomas have a more aggressive clinical course and are treated similarly to diffuse large B-cell lymphoma (see later). This distinction between grade 3a (indolent behavior) and 3b (aggressive behavior) is based on the presence or absence of sheets of centroblasts, although this separation may not be reproducible among pathologists.

TREATMENT AND PROGNOSIS

Watch and Wait

A "watch and wait" approach is reasonable in asymptomatic elderly patients, patients with other medical illnesses, and in other selected patients who have low-grade follicular lymphoma and who are asymptomatic, have no disease involvement in sites that might be dangerous, and desire to avoid therapy as long as possible.[8] Such patients can sometimes be observed for long periods before treatment is required. However, modern treatment options may improve the survival of a large proportion of patients with follicular lymphoma.

TABLE 171-10 COMBINATION CHEMOTHERAPY REGIMENS FOR NON-HODGKIN LYMPHOMA

REGIMEN	DOSE	DAYS OF ADMINISTRATION	FREQUENCY
R-CHOP			**EVERY 21 DAYS**
Cyclophosphamide	750 mg/m^2 IV	1	
Doxorubicin	50 mg/m^2 IV	1	
Vincristine	1.4 mg/m^2 IV*	1	
Prednisone, fixed dose	100 mg daily PO	1-5	
Rituximab	375 mg/m^2 IV	1	
R-EPOCH†			**EVERY 21 DAYS**
Etoposide	50 mg/m^2/day IV‡	1-4	
Doxorubicin	10 mg/m^2/day IV‡	1-4	
Vincristine	0.4 mg/m^2/day IV‡	1-4	
Cyclophosphamide	750 mg/m^2 IV	5	
Prednisone	60 mg/m^2 bid PO	1-5	
Rituximab	375 mg/m^2 IV	1	
R-CVP			**EVERY 21 DAYS**
Cyclophosphamide	1000 mg/m^2 IV	1	
Vincristine	1.4 mg/m^2 IV*	1	
Prednisone, fixed dose	100 mg daily PO	1-5	
Rituximab	375 mg/m^2 IV	1	
B-R			**EVERY 28 DAYS**
Bendamustine	90 mg/m^2/day IV	1-2	
Rituximab	375 mg/m^2 IV	1	

*Vincristine dose is often capped at 2 mg total.
†Doses are adjusted based on myelosuppression with previous cycle.
‡Continuous infusion.
bid = twice daily; IV = intravenous; PO = oral.

Localized Disease

Approximately 5 to 15% of patients have localized disease (stage I or minimal stage II disease) at diagnosis. These lymphomas are typically treated with involved-field radiation, preferably with 24 Gy in 12 equal fractions,[A1] and most series report 10-year disease-free survival rates of approximately 50% and overall survival rates of about 50% at 20 years.[9]

Advanced Disease

Most patients with follicular lymphoma have extensive disease at diagnosis. The median survival time of these patients has improved after the addition of rituximab and is now 10 to 20 years. Spontaneous regression also has been described. However, as many as 30 to 50% of patients experience transformation to a more aggressive histology—usually diffuse large B-cell lymphoma. Transformation is frequently associated with new systemic symptoms, rapidly progressive lymphadenopathy, an aggressive clinical course, and a poor prognosis.

Most patients with follicular lymphoma eventually require treatment because of systemic symptoms, symptomatic or progressive lymphadenopathy, splenomegaly, effusions, or cytopenias. In elderly patients, patients who are poor candidates for intensive chemotherapy regimens, and patients who want to avoid the side effects of chemotherapy, single-agent rituximab (375 mg/m^2 intravenously, given weekly for 4 consecutive weeks) yields an objective response rate of well over 50%. The median duration of response is approximately 1 to 2 years for patients who receive no additional therapy, but the response can be extended with ongoing administration of rituximab once every 2 or 3 months or by repeating the initial four doses every 6 months.[10] When rituximab is combined with standard chemotherapy regimens (see Table 171-10) or with lenalidomide, the response rate, duration of response, and survival are increased compared with the chemotherapy regimen alone.[A2,A3] Maintenance rituximab extends the duration of remission but not overall survival.[A4] An alternative is obinutuzumab, which can provide longer progression-free survival but at the expense of more side effects, without improving overall survival.[A5]

Salvage Therapy

Most patients respond to initial chemotherapy. However, follicular lymphoma recurs in the majority of patients with advanced-stage disease. Patients who relapse usually respond to additional therapy, sometimes with the same agents, although the duration of response becomes progressively shorter with repeated courses of therapy.[11] For patients with disease that is refractory to rituximab, the combination of obinutuzumab plus bendamustine is preferable to bendamustine alone.[A6] Copanlisib, which is a pan-class PI3K inhibitor has also shown promising results when added to rituximab.[A7] Alternative therapies include lenalidomide with rituximab, or standard chemotherapies. Radiation therapy also may be useful for patients with a localized site of symptomatic disease.

Prolonged remissions have been observed after autologous hematopoietic stem cell transplantation. Allogeneic hematopoietic stem cell transplantation may cure some patients with relapsed follicular lymphoma but has more toxicity than autologous transplants. Chimeric antigen receptor (CAR) T-cell therapy (Chapter 164) has shown promise as salvage therapy in patients with relapsed or refractory B-cell lymphomas and is now FDA approved for patients whose follicular lymphoma has failed two prior therapies.[12]

MANTLE CELL LYMPHOMA

Mantle cell lymphoma is a B-cell neoplasm composed of small lymphoid cells that may resemble small lymphocytic lymphoma or follicular lymphoma. It is most common in elderly patients and is usually at an advanced stage at the time of diagnosis. Males are more frequently affected, and extranodal disease, especially involvement of the bone marrow, Waldeyer ring, and the gastrointestinal tract, is common. Mantle cell lymphoma is the most common cause of multiple lymphomatous polyposis, and many oncologists recommend that the gastrointestinal tract be evaluated with endoscopy during the initial evaluation.

Some patients present with involvement of the peripheral blood as well as the bone marrow, a clinical picture that resembles chronic lymphocytic leukemia (Chapter 169). The lymphocytes in both disorders are CD5$^+$, but the t(11;14) translocation[13] and overexpression of cyclin D1 seen in mantle cell lymphoma usually allow an accurate diagnosis.

TREATMENT AND PROGNOSIS

Occasional patients, particularly patients with a leukemic presentation, may have an indolent course without initial therapy. However, the median survival of mantle cell lymphoma has significantly improved with new therapies.[14] The combination of bendamustine plus rituximab and regimens that incorporate high-dose cytarabine are efficacious, as is the combination of lenalidomide plus rituximab. Ibrutinib added to rituximab plus bendamustine can significantly prolong remission-free survival[A8] and is commonly part of standard therapy. Substituting bortezomib (1.3 mg/m^2 on days 1, 4, 8, and 11) for vincristine (VR-CAP rather than R-CHOP) can improve the median progression-free survival seen with R-CHOP alone by about 40% (from 14 to about 25 months) in newly diagnosed patients.[A9] Maintenance rituximab seems to prolong the duration of remission.

Autologous hematopoietic stem cell transplantation is widely used for patients in their first remission. The Bruton tyrosine kinase inhibitors such as ibrutinib or acalabrutinib are very active and are part of standard therapy for relapsed disease.[15] If such therapy is not successful, anti-CD19 CAR T-cell therapy may provide a complete response in about 60% of patients.[16] Allogeneic transplantation can be curative but is associated with considerable morbidity and mortality.

The elderly comprise the majority of the patients with mantle cell lymphoma. For patients who are not too frail, 4-year overall survival of greater than 80% can be achieved with rituximab and moderate intensive chemotherapy such as R-CHOP followed by rituximab maintenance or R-bendamustine.

DIFFUSE LARGE B-CELL LYMPHOMA

Diffuse large B-cell lymphomas are the most common type of non-Hodgkin lymphoma, but their morphology and genetic features are heterogeneous. Signs and symptoms are similar to those of other subtypes, although patients are more likely to have B symptoms.[17]

The 2016 WHO classification of non-Hodgkin lymphomas has identified several variants and subtypes of diffuse large B-cell lymphoma (see Table 171-4). Many of these histologic or genetic subtypes or variants share the same standard treatment approach as used for diffuse large B-cell lymphoma. Other subtypes present unusual clinical syndromes or specific therapeutic problems.

TREATMENT

Localized Disease

As many as 30% of patients with diffuse large B-cell lymphoma have stage I or minimal stage II disease. These patients are occasionally cured with radiation therapy alone, but initial treatment with chemotherapy alone or combined with radiation therapy is more effective.[18] In the United States, most patients are treated with R-CHOP (see Table 171-10). Some patients can be treated with fewer courses of chemotherapy if radiotherapy is included. For patients with bulky disease, a complete course of chemotherapy is usually used with or without radiotherapy. Some physicians advocate the use of PET scans to shorten the duration of therapy or eliminate the need for radiotherapy in complete responders.

Advanced Disease

R-CHOP is still the most widely used regimen for adults of all ages with advanced-stage diffuse large B-cell lymphoma. Among patients older than age 60 years, 75% achieve a complete response, with a 10-year progression-free survival rate of about 35% and a 10-year overall survival rate of about 45%. In younger patients, the outcome is better. No advantage has been found for R-EPOCH over R-CHOP (see Table 171-10).[A10] Autologous stem cell transplantation in first remission may benefit very high-risk patients. Although not yet FDA approved for this purpose, the antibody-drug conjugate polatuzumab vedotin combined with R-CHP (rituximab-cyclophosphamide-doxorubicin-prednisone) can improve progression-free survival of diffuse large B-cell lymphoma patients compared with R-CHOP.[A11]

Salvage Therapy

A variety of chemotherapy regimens for patients who relapse after attaining a remission with initial chemotherapy commonly contain agents such as cisplatin, cytarabine, etoposide, carboplatin, and ifosfamide. Response rates exceeding 50% can be observed with these combinations, although no more than 10% of patients achieve long-term disease-free survival. High-dose therapy followed by autologous hematopoietic stem cell transplantation has become accepted therapy for patients with relapsed diffuse large B-cell lymphoma. Approximately 20 to 50% of these patients attain long-term disease-free survival, depending on their response to conventional salvage chemotherapy. Lenalidomide and ibrutinib seem to particularly benefit patients with activated B-cell (ABC) subtype. Other agents used as second- or third-line treatments include polatuzumab-vedotin plus bendamustine or rituximab or tafasitamab plus lenalidomide.[19,20] Autologous CD-19–directed, CAR T-cell therapy is now FDA approved for relapsed or refractory disease, especially with high-risk features.[21,A12]

Subtypes of Diffuse Large B-Cell Lymphoma

Approximately 30% of diffuse large B-cell lymphomas originate in extranodal sites. Presentation in certain extranodal sites is associated with unique clinical behaviors that may necessitate diagnostic studies or additional therapy beyond what is used for patients with nodal presentations.

Primary Mediastinal Large B-cell Lymphomas

Primary mediastinal large B-cell lymphomas originate in the thymus and are most common in young women. This subtype shares genetic features with classic Hodgkin lymphoma. This entity is distinguished by the presence of a mediastinal mass, which usually causes symptoms of cough, chest pain, or superior vena cava syndrome. A very large mass (>10 cm) or the existence of a malignant pleural effusion is associated with a worse prognosis.

TREATMENT AND PROGNOSIS

Mediastinal large B-cell lymphoma is treated with the same chemotherapy regimens used for diffuse large B-cell lymphoma, followed, in some cases, by consolidative radiation therapy.[22] R-EPOCH is more likely than R-CHOP (see Table 171-10) to achieve a durable remission without the need for radiotherapy. Relapses often occur in extranodal sites such as the CNS, lungs, gastrointestinal tract, liver, ovaries, and kidneys.

Intravascular Large B-cell Lymphoma

Intravascular large B-cell lymphoma is an aggressive lymphoma caused by cells that infiltrate the lumens of small blood vessels. Widespread extranodal involvement is common. Focal neurologic deficits and mental status changes are frequent. Cases are often diagnosed at autopsy, although durable responses to combination chemotherapy have been described.

Primary Effusion Lymphoma

Primary effusion lymphoma is associated with HHV-8 (Chapter 359) and is seen in HIV-infected and other immunosuppressed patients.[23] Effusions occur in serous body cavities. Peripheral lymphadenopathy is not seen. Prognosis is poor despite chemotherapy.

Primary CNS Lymphoma

Primary CNS lymphoma (Chapter 175) is increasing in incidence. Patients with primary CNS lymphoma (Chapter 175) commonly have ocular involvement, and all patients with this diagnosis should have a slit lamp examination.

TREATMENT AND PROGNOSIS

Surgical resection usually is not performed for primary CNS lymphoma, and the primary role of surgery is for diagnosis. Primary lymphomas of the CNS are very sensitive to corticosteroids, but some patients can be cured with chemotherapy regimens incorporating high-dose methotrexate (alone or in combination with other agents such as cytarabine, temozolomide, and rituximab) with or without autologous bone marrow transplant.[24] For primary CNS lymphoma, whole-brain radiotherapy is not as good as chemotherapy,[A13] does not add to the benefit achieved by chemotherapy alone, and is associated with increased neurologic toxicity.

Plasmablastic Lymphoma

Plasmablastic lymphoma is most often seen in patients with HIV infection and frequently presents with involvement of the head and neck. This tumor does not express CD20 and thus does not benefit from treatment with rituximab.

Primary Cutaneous Diffuse Large B-cell Lymphoma

Primary cutaneous diffuse large B-cell lymphoma of the leg (leg type) is one of two presentations of B-cell lymphoma in the skin.[25] This tumor occurs mostly in older patients and follows an aggressive course. This neoplasm must be distinguished from primary cutaneous follicle center lymphoma, which might also be diagnosed as a cutaneous diffuse large B-cell lymphoma but follows an indolent course and requires only local therapy.

Double-Hit, Triple-Hit, and Gray-Zone Lymphomas

Double-hit, triple-hit, and gray-zone lymphomas have rearrangements of *MYC* in combination with *BCL2* and/or *BCL6*. These tumors are now incorporated into an entity called high-grade B-cell lymphoma with rearrangements of *MYC* and *BCL2* and/or *BCL6*. Gray-zone lymphomas may have features intermediate between diffuse large B-cell lymphoma and Burkitt lymphoma or features intermediate between mediastinal diffuse large B-cell lymphoma and classic Hodgkin lymphoma.

TREATMENT AND PROGNOSIS

These lymphomas have a poor outcome when treated with standard chemotherapy regimens. More aggressive regimens such as DA-R-EPOCH (dose-adjusted etoposide, prednisone, vincristine, cyclophosphamide, and doxorubicin) may improve the outcome of the double- or triple-hit lymphomas.

Testicular, Gastric, and Intestinal Large B-Cell Lymphomas

Large B-cell lymphoma occasionally originates in the testis or gastrointestinal tract.

TREATMENT AND PROGNOSIS

Treatment of primary testicular lymphoma, the most common testicular cancer in men older than age 60 years (Chapter 185), usually consists of orchiectomy followed by combination chemotherapy. Relapse in the contralateral testicle is common, and radiation is usually given to the entire scrotal bed. CNS involvement is common, and prophylactic intrathecal chemotherapy is usually recommended. Late relapses occur frequently.

Diffuse large B-cell lymphoma of the stomach and gastrointestinal tract is treated differently from gastric MALT lymphoma, even if patients have is a history of prior MALT lymphoma. Patients can be cured with surgery and adjunctive radiation or chemotherapy, although surgery is rarely performed for gastric lymphomas because of the morbidity associated with gastric resection. Patients should be treated with chemotherapy regimens used for other diffuse large B-cell lymphomas. Radiation therapy is sometimes used after chemotherapy, although the role of combined-modality treatment is not defined.

BURKITT LYMPHOMA

Burkitt lymphoma is a highly aggressive B-cell lymphoma that is more common in children and immunosuppressed individuals than in healthy adults (see later).[26] Widespread extranodal involvement is common. The endemic form of Burkitt lymphoma is seen most frequently in children who reside in equatorial Africa. Involvement of bones of the jaw is common in this form. The sporadic form of Burkitt lymphoma is seen most commonly in children in the United States. Males are more frequently affected. Both children and adults frequently have bulky abdominal disease, sometimes with involvement of the kidneys, ovaries, and breasts. Bone marrow involvement is seen in about one third of cases.

TREATMENT

Tumors may progress extremely rapidly, so therapy should be started as soon as possible. Tumor lysis syndrome (Chapter 164) may occur because of the frequent presence of bulky disease, the high rate of tumor proliferation, and the extreme sensitivity of the tumor to chemotherapy. Patients are usually treated with specialized high-intensity regimens, including rituximab, of relatively short duration.[A14] Treatment with the R-CHOP regimen used for diffuse large B-cell lymphoma has a poor outcome, but excellent results have been described with R-EPOCH. CNS prophylaxis with intrathecal chemotherapy or high-dose methotrexate is required. Cure rates well in excess of 50% are typical with appropriate therapy.[27]

RARE TYPES OF B-CELL LYMPHOMA

Several rare types of lymphoma have distinct clinical features.

Lymphoplasmacytic Lymphoma

Lymphoplasmacytic lymphoma is an indolent lymphoma that frequently involves the bone marrow, peripheral blood, and spleen. Patients frequently have an immunoglobulin M (IgM) paraprotein that may lead to symptoms of hyperviscosity, autoimmune phenomena, or neuropathies. Plasmapheresis can reduce symptoms of hyperviscosity.

TREATMENT AND PROGNOSIS

Chemotherapy with alkylating agents, combination chemotherapy, or fludarabine all in combination with rituximab may be used. Ibrutinib and other Bruton tyrosine kinase (BTK) inhibitors have shown significant activity in lymphoplasmacytic lymphoma, and the combination of ibrutinib plus rituximab has resulted in significantly higher rates of progression-free survival than rituximab alone.[A15]

Splenic Marginal Zone Lymphoma

Splenic marginal zone lymphoma is an indolent lymphoma that usually manifests with splenomegaly and lymphocytosis. A monoclonal gammopathy is frequently seen. Peripheral lymphadenopathy is unusual. Anemia and thrombocytopenia may respond to splenectomy.

TREATMENT AND PROGNOSIS

Chemotherapy with single agents or anthracycline-based combinations may be useful, and when the lymphoma is associated with hepatitis C, antiviral therapy may be effective (Chapter 134 and 135). This lymphoma appears to be particularly responsive to rituximab with or without bendamustine. Bruton kinase inhibitors are also very useful for marginal zone lymphoma treatment.[28]

Nodal Marginal Zone B-cell Lymphoma

Nodal marginal zone B-cell lymphoma is an indolent disorder that is usually associated with generalized lymphadenopathy. The clinical course and prognosis are similar to those of follicular lymphoma, and it is usually treated in a similar manner.

Small Intestinal Immunoproliferative Disease

Small intestinal immunoproliferative disease, which is a disorder seen most frequently in the Middle East, begins as a polyclonal process and can progress to a large B-cell lymphoma. The process is often associated with *C. jejuni* infection (Chapter 279). Early in the disease, patients may respond to antibiotics, and frank lymphoma may respond to combination chemotherapy regimens.

MATURE T-CELL LYMPHOMAS (PERIPHERAL T-CELL LYMPHOMAS)

Peripheral (or mature) T-cell lymphomas are neoplasms of post-thymic T cells. These include relatively indolent disorders such as mycosis fungoides and $CD30^+$ cutaneous lymphoproliferative disorders, but most patients diagnosed with peripheral T-cell lymphoma have an aggressive neoplasm.[29] Peripheral T-cell lymphomas represent only 10% of the non-Hodgkin lymphomas occurring in the United States. Unfortunately, the treatment for these lymphomas has not progressed as rapidly as the treatments for B-cell lymphomas.

MYCOSIS FUNGOIDES

Mycosis fungoides (often referred to as *cutaneous T-cell lymphoma*) is an indolent malignancy that is most common in middle-aged and older adults.[30] The clinical course is usually a slow progression from isolated patches or plaques to thickened, more widespread plaques and then to multiple cutaneous tumors that may ulcerate (Chapter 407). A subset of patients presents with generalized erythroderma and circulating tumor cells, called *Sézary syndrome*. Lymph node and visceral involvement may occur late in the course of the disease.

TREATMENT

Cutaneous radiation therapy may be curative for patients with limited patch or plaque disease. Patients with early-stage disease (<10% body surface area) are frequently treated with skin-directed therapy that may include ultraviolet radiation, topical steroids, or topical nitrogen mustard.

Patients with more advanced disease frequently benefit from total skin electron beam therapy or extracorporeal photopheresis. Medical treatments include brentuximab vedotin, with[A16] or without[A17] standard chemotherapy, bexarotene (a selective retinoid X receptor agonist), interferon-α, retinoids, monoclonal antibodies, histone deacetylase inhibitors (vorinostat, romidepsin), and mogamulizumab (a monoclonal antibody directed against C-C chemokine receptor 4).[A18]

Unfortunately, treatments are usually only palliative.[31] Results with autologous hematopoietic stem cell transplantation are usually poor, although allogeneic stem cell transplantation has yielded promising results in some selected young patients.

ADULT T-CELL LYMPHOMA/LEUKEMIA

Adult T-cell lymphoma/leukemia, which is associated with HTLV-1 infection (Chapter 360), is most commonly seen in southern Japan and the Caribbean. Most infected patients are asymptomatic, and the lifetime risk for developing adult T-cell lymphoma/leukemia is approximately 3%.

Patients may have acute leukemia, aggressive lymphoma, or an indolent lymphoproliferative disease. Patients with aggressive disease present with generalized lymphadenopathy, hepatosplenomegaly, cutaneous infiltration, and hypercalcemia. Many patients have characteristic circulating tumor cells with a "flower" or "cloverleaf" nucleus.

TREATMENT

Patients with indolent disease can sometimes be monitored without therapy. Aggressive disease is usually treated with combination chemotherapy, but there is no consensus on the best regimen. Historically, the 5-year survival rate has been less than 10%, although recent trials have reported better outcomes.

$CD30^+$ CUTANEOUS LYMPHOPROLIFERATIVE DISORDERS

These disorders represent a spectrum of diseases that may have an identical histologic appearance and overlapping clinical manifestations. Treatment decisions are often based on the clinical behavior of the lesions. These lymphomas express CD30 but do not express the anaplastic lymphoma kinase (ALK) protein (see later).

Lymphomatoid Papulosis

Lymphomatoid papulosis is a "histologically malignant" clonal disorder consisting of erythematous or skin-colored papules that frequently undergo spontaneous ulceration and necrosis over a period of weeks. The prognosis is excellent, although patients may eventually develop lymphoma.

Primary Cutaneous Anaplastic Large Cell Lymphoma

Primary cutaneous anaplastic large cell lymphoma occurs most commonly in men and undergoes frequent spontaneous regression. The 5-year survival rate is greater than 90%. Treatment usually consists of local measures (surgery or radiation), although chemotherapy may be required.

PRIMARY SYSTEMIC ANAPLASTIC LARGE CELL LYMPHOMA

Anaplastic large cell lymphoma is an aggressive CD30$^+$ T-cell non-Hodgkin lymphoma that is seen most frequently in young males.[32] B-cell lymphomas with similar morphology can occur, but they have clinical features identical to other diffuse large B-cell lymphomas and are not considered part of this disease. A morphologically similar but biologically unrelated and clinically distinct neoplasm, primary cutaneous anaplastic large cell lymphoma, occurs predominantly in older adults and represents part of the spectrum of cutaneous CD30$^+$ lymphoproliferative disorders (see earlier). Primary systemic anaplastic large cell lymphoma frequently has a t(2;5) chromosomal translocation that leads to overexpression of ALK, a protein not normally detectable in lymphoid cells.

Patients usually have lymphadenopathy, and involvement of the skin, bone, and gastrointestinal tract may be observed.

A newly described entity of anaplastic large cell lymphoma of the breast is associated with breast implants. When localized, patients may be cured with surgery, including removal of the implant.

TREATMENT

Patients are usually treated with chemotherapy regimens such as CHOP with or without the addition of etoposide. Patients whose tumors express ALK have an excellent outcome, and 5-year survival rates of 70 to 90% have been observed. ALK-negative anaplastic large cell lymphoma is more common in older patients and is associated with an inferior response rate and shorter survival time. Autologous hematopoietic stem cell transplantation may be curative for patients who relapse. The anti-CD30 antibody-drug conjugate brentuximab vedotin is highly active for patients with relapsed disease and may be incorporated into primary therapy.[A19] Patients whose lymphomas express ALK usually respond to the ALK inhibitor crizotinib.

Anaplastic large cell lymphoma of the breast extends beyond the breast capsule. It is treated similarly to advanced-stage anaplastic large cell lymphoma.

PERIPHERAL T-CELL LYMPHOMAS, UNSPECIFIED

The largest group of patients with peripheral T-cell lymphomas is defined in the WHO classification as having "peripheral T-cell lymphoma, unspecified." These patients' signs and symptoms are similar to those of patients with aggressive B-cell lymphomas, although systemic symptoms (fevers, night sweats, and weight loss) and extranodal involvement are frequent. The diagnosis of peripheral T-cell lymphoma requires immunophenotyping to demonstrate the T-cell origin.

TREATMENT

Patients are generally treated with the same regimens used for diffuse large B-cell lymphomas (e.g., CHOP with or without etoposide), often in combination with upfront autologous hematopoietic stem cell transplantation, although the outcome is substantially worse. Belinostat is a histone deacetylase inhibitor that has some activity in peripheral T-cell lymphoma.[33] Patients who relapse after complete remission can sometimes be cured with hematopoietic stem cell transplantation.

UNUSUAL SUBTYPES OF T-CELL LYMPHOMA

Angioimmunoblastic T-cell Lymphoma

Angioimmunoblastic T-cell lymphoma is associated with generalized lymphadenopathy, fever, weight loss, skin rash, and polyclonal hypergammaglobulinemia. Results of therapy are similar to those for peripheral T-cell lymphoma, unspecified.

Extranodal NK/T-cell Lymphoma

Extranodal NK/T-cell lymphoma usually occurs in extranodal sites, especially the nose, palate, and nasopharynx. Involvement of the nose and face leads to the syndrome that was previously called lethal midline granuloma. This disorder is unusual in the United States, but it is frequent in Southeast Asia and Latin America. Patients with localized disease often can be cured with aggressive combination radiation therapy and chemotherapy.[34] Patients with widespread disease have a poor prognosis. These patients frequently respond to L-asparaginase.

Hepatosplenic T-cell Lymphoma

Hepatosplenic T-cell lymphoma is characterized by sinusoidal infiltration of the spleen, liver, and bone marrow, which leads to hepatosplenomegaly, systemic symptoms, and cytopenias. Lymphadenopathy is unusual. Hepatosplenic T-cell lymphoma is more commonly occurs in young men, and this disease can occur in the setting of immune dysfunction. The prognosis is poor.

Enteropathy-type T-cell Lymphoma

Enteropathy-type T-cell lymphoma is usually seen in patients with gluten-sensitive enteropathy (Chapter 126). Patients typically present with abdominal pain and diarrhea and sometimes with bowel perforation. Treatment of celiac disease with a gluten-free diet may reduce the risk for lymphoma. The prognosis in undernourished patients is poor, but more fit patients can sometimes be cured with intensive chemotherapy and autologous bone marrow transplant.

Subcutaneous Panniculitis-like T-cell Lymphoma

Subcutaneous panniculitis-like T-cell lymphoma manifests with multiple subcutaneous nodules and is often misdiagnosed as panniculitis. Patients with disseminated disease can have a syndrome consisting of fevers, weight loss, hepatosplenomegaly, pancytopenia, and phagocytosis of blood cells (hemophagocytic syndrome). Patients sometimes respond to combination chemotherapy regimens used for diffuse large B-cell lymphoma, interferon, and radiation therapy, but long-term disease-free survival is unusual.

SPECIAL CLINICAL SITUATIONS

The diagnosis and management of patients with the various types of non-Hodgkin lymphoma can be profoundly influenced by the site of origin of the lymphoma and by certain clinical characteristics of the individuals affected with the disease. Examples of the latter include lymphoma in patients who are severely immunosuppressed because of HIV infection or a prior transplant, elderly patients with lymphoma, and pregnant patients with lymphoma.

LYMPHOMA IN AIDS

Non-Hodgkin lymphoma is an AIDS-defining illness in HIV-infected individuals (Chapters 355 and 359), and the risk for developing a non-Hodgkin lymphoma is increased more than 150-fold after the diagnosis of another AIDS-defining illness.[35] Most cases are diffuse large B-cell lymphomas or Burkitt lymphomas. AIDS-associated lymphomas behave aggressively and frequently involve the CNS and other unusual sites, such as the gastrointestinal tract, anus, rectum, skin, and soft tissue. Factors associated with poor survival include low CD4 counts, poor performance status, older age, and advanced stage. The incidence of AIDS-associated non-Hodgkin lymphoma has declined, and the prognosis has improved considerably.

TREATMENT

Patients are generally treated in the same manner as nonimmunocompromised patients, and the prognoses are similar. Intrathecal prophylaxis is generally recommended because of a higher risk for CNS involvement.

POST-TRANSPLANT LYMPHOPROLIFERATIVE DISEASE

The risk for developing a non-Hodgkin lymphoma is also markedly increased in patients who have received a solid organ transplant. The histologic appearance of these lymphomas is variable, but they frequently resemble aggressive lymphomas in nonimmunocompromised patients. Epstein-Barr virus (Chapter 348) is almost always the causative agent. Similar disorders can be seen in patients who are treated with methotrexate and other drugs for autoimmune disorders and in recipients of allogeneic hematopoietic stem cell transplants, especially if the transplants are T-cell depleted. These post-transplantation lymphoproliferative disorders, which may develop within weeks after surgery, are more common in patients who receive aggressive immunosuppression after transplantation. Involvement of extranodal sites is common, and lymphoma frequently involves the transplanted organ.

TREATMENT

Post-transplantation lymphoproliferative disorders may respond to reduction or withdrawal of immunosuppression.[36] Acyclovir or ganciclovir can be considered, because these lymphomas are usually related to Epstein-Barr virus, but this practice is controversial. High response rates are also seen with rituximab. Other patients require treatment with combination chemotherapy regimens including rituximab.

NON-HODGKIN LYMPHOMA IN ELDERLY PATIENTS

More than 50% of patients who develop non-Hodgkin lymphomas are older than age 60 years, and the prognosis is generally worse for elderly patients. These poorer outcomes are related to increased toxicity of drug therapy, lower remission rates, increased rates of relapse, and higher death rates from cardiovascular disease and causes other than the lymphoma itself. Older patients are more likely to have other adverse prognostic characteristics (see Table 171-8), which also contribute to poorer outcomes. The practice of arbitrary dose reductions based solely on age should be discouraged if patients have a good performance status and no comorbid illnesses.

NON-HODGKIN LYMPHOMA AND PREGNANCY

Non-Hodgkin lymphoma in pregnancy involves major clinical and ethical issues, and a multidisciplinary approach is needed. Although chest radiographs are generally considered safe, ultrasound examination is usually used instead of CT for staging in the abdomen and pelvis.

TREATMENT

Treatment occasionally can be delayed until after delivery. However, most women have a lymphoma that is potentially curable, and delays in treatment may decrease the chance for cure. Other patients have conditions such as superior vena cava syndrome that require immediate treatment. After the first trimester, full-dose standard therapy such as R-CHOP may be used. Several studies indicate high probabilities of cure without significantly increased adverse long-term physical or intellectual deficits for the child. Although it is reasonable to offer therapeutic abortion for women in the first trimester, chemotherapy also may be successful in this situation. Regimens using methotrexate or abdominal radiation must be avoided.

DISEASES SOMETIMES CONFUSED WITH LYMPHOMA

A variety of conditions are associated with lymphadenopathy that can be confused with lymphoma. The most common atypical lymphoid proliferations that can be confused with lymphoma are florid reactions to immune stimulation. Follicular hyperplasia with diffuse proliferation of B cells and T cells can be seen in a variety of autoimmune diseases (e.g., Sjögren syndrome [Chapter 247], systemic lupus erythematosus [Chapter 245], rheumatoid arthritis [Chapter 243]) and infectious processes (e.g., Epstein-Barr virus [Chapter 348], cytomegalovirus [Chapter 247], cat-scratch disease [Chapter 291]). If the definitive diagnosis of lymphoma cannot be made even after immunologic and molecular studies, the patient should be closely observed. The clinical course or subsequent biopsies can usually resolve the confusion.

Castleman Disease

Castleman disease, or angiofollicular lymph node hyperplasia, usually appears with a hyaline vascular pattern of lymphoid proliferation, but a subset of patients has hyperplastic lymphoid follicles and sheets of plasma cells.[37] Patients with Castleman disease often present with a localized lymphoid mass, but some patients have a systemic illness with fevers, night sweats, weight loss, and fatigue. Frequently, the systemic symptoms of Castleman disease are related to excessive production of IL-6. Castleman disease in HIV-infected patients is frequently associated with HHV-8 (Chapter 358).

TREATMENT

Patients with disseminated and plasma cell–rich forms of Castleman disease may occasionally progress to lymphoma. Patients with localized Castleman disease can be treated with surgical removal, radiation therapy, or occasionally observation if asymptomatic.[38] Patients with systemic disease may respond to treatment with high-dose corticosteroids and/or rituximab. Patients with overexpression of IL-6 frequently benefit from treatment with an anti–IL-6 antibody. For example, siltuximab (a chimeric monoclonal antibody against interleukin 6 at 11 mg/kg intravenous infusion every 3 weeks) can provide durable responses in about one third of HIV-negative patients.[39] If other treatments fail, patients sometimes benefit from combination chemotherapy regimens, autologous or allogeneic hematopoietic stem cell transplantation, or both.[40] The mammalian target of rapamycin (mTOR) inhibitor sirolimus also is a potentially promising agent.

Sinus Histiocytosis with Massive Lymphadenopathy

Sinus histiocytosis with massive lymphadenopathy, also known as Rosai-Dorfman disease (Chapter 154), manifests as bulky lymphadenopathy in children and young adults. Extranodal sites such as the skin, upper airways, gastrointestinal tract, and CNS can be involved. The disease is usually self-limited, but it has been associated with autoimmune hemolytic anemia.

Kikuchi Disease (Histiocytic Necrotizing Lymphadenitis)

Kikuchi disease (histiocytic necrotizing lymphadenitis) is a disease of unknown origin that most commonly affects young women. Symptoms most commonly consist of painless cervical lymphadenopathy that is often accompanied by fever, flulike symptoms, and rash. Treatment is symptomatic, and manifestations usually resolve within weeks or months.

IgG4-related Disease

IgG4-related disease is a systemic immune-mediated fibrosing inflammatory disease in which various organs are infiltrated by IgG4-positive plasma cells (Chapter 254). Patients often have accompanying asymptomatic lymphadenopathy that usually responds to corticosteroids.

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172 HODGKIN LYMPHOMA

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DEFINITION

Hodgkin lymphoma, one of the B-cell lymphomas, consists of two major types: classic Hodgkin lymphoma, with a characteristic neoplastic cell, the Hodgkin-Reed-Sternberg cell; and the much less common (~10% of cases) nodular lymphocyte-predominant Hodgkin lymphoma, with a characteristic predominance of small lymphocytes. Both types have a distinct natural history, and most important, an excellent response to treatment, with the large majority of patients being cured. Highly effective multiagent chemotherapy is the cornerstone of treatment. Carefully selected patients may require the addition of radiation or, if the lymphoma recurs after primary treatment, high-dose chemoradiation therapy and autologous hematopoietic cell transplantation. The major challenge to clinicians managing this neoplasm is to cure the disease while minimizing long-term toxicity.

EPIDEMIOLOGY

The incidence of Hodgkin lymphoma varies substantially around the world. The highest rates occur in the United States, Canada, Switzerland, and northern Europe. Intermediate rates are seen in southern and eastern Europe and low rates in eastern Asia. No clear explanation for this variation has been found. Postulated reasons include differences in the age at onset or genotype of an associated Epstein-Barr virus infection; crowding during childhood as a result of lower socioeconomic status, predisposing to passage of an as-yet-undiscovered infectious vector; and intrinsic genetic differences in susceptibility.

Approximately 30,000 new cases are diagnosed annually in North America and Europe. The age-adjusted incidence of Hodgkin lymphoma declined modestly over the 20 years before 1990 but has leveled off since then at approximately 2.7 per 100,000. Age-adjusted annual mortality is 0.5 per 100,000. Hodgkin lymphoma occurs slightly more often in men and is seen more frequently in Whites than Blacks and much less frequently in Asian populations. Much of the difference in incidence between Whites and Blacks in North America can be attributed to the higher incidence seen in higher socioeconomic classes. The cumulative lifetime risk for Hodgkin lymphoma is approximately 1 in 250 to 1 in 300 in North America.

The incidence of Hodgkin lymphoma is bimodal in age distribution, rising from very low in childhood to an early peak in young adulthood (25 to 30 years) and a later peak in late adulthood (>50 years). In the Western world, only about 5% of cases occur in persons younger than 15 years of age and 5% in individuals older than 70 years of age. In contrast, the age distribution in the Indian subcontinent is strongly shifted into childhood.

PATHOBIOLOGY

The cause of Hodgkin lymphoma remains unclear. It is not associated with exposure to radiation, chemicals, biocidal agents, working in health care–related professions, or previous tonsillectomy. The leading suspect remains Epstein-Barr virus, based on much suggestive evidence but no definitive proof.[1]

Epstein-Barr Virus

Epstein-Barr virus is a large B-lymphocyte tropic herpesvirus (Chapter 348). Approximately 90% of the general population acquires infection by early adulthood. In the developing world, this infection usually occurs in childhood, but in developed countries, infection is often delayed into the teens, when it is associated with the syndrome of infectious mononucleosis in up to 30% of new cases. A history of infectious mononucleosis increases the likelihood for subsequent Hodgkin lymphoma three-fold. Antibodies to the viral capsid antigen reach higher levels in patients with Hodgkin lymphoma than in controls, and these higher levels appear several years before the neoplasm. In situ hybridization studies have demonstrated that the Hodgkin-Reed-Sternberg cells in approximately 50% of cases of Hodgkin lymphoma contain Epstein-Barr virus-encoded small RNA. In these cases, virtually all the Hodgkin-Reed-Sternberg cells are positive for the virus; the Epstein-Barr virus genome is amplified 50-fold or more in Hodgkin-Reed-Sternberg cells; and is monoclonal in an individual patient's Hodgkin-Reed-Sternberg cells. In some populations, virtually all cases of Hodgkin lymphoma occur in Epstein-Barr virus–positive individuals (<15 or >65 years of age; non-European ancestry; low socioeconomic status), but up to 50% of patients in developed countries do not have Epstein-Barr virus in their Hodgkin-Reed-Sternberg cells. Thus, although Epstein-Barr virus may play an important role in the development of Hodgkin lymphoma, that role is neither straightforward nor universal.

Genetic Factors

Circumstantial evidence for a genetic contribution to the etiology of Hodgkin lymphoma comes from studies showing that Hodgkin lymphoma is almost 100-fold more likely to develop in the monozygotic twin of an affected individual than in a dizygotic twin. First-degree relatives of individuals with the disease have up to a five-fold increased risk for development of the lymphoma. Genome-wide association studies have identified multiple genetic risk variants, which have been detected primarily in immune-related genes. For example, variants in *GATA3*, *IL13*, and genes controlling the expression of HLA class II molecules have been associated with the Epstein-Barr virus–negative nodular sclerosing subtype of classic Hodgkin lymphoma, which is seen predominantly in adolescents and young adults.

Polymerase chain reaction–based genotypic analysis has demonstrated the clonal derivation of Hodgkin-Reed-Sternberg cells, including identical *p53* mutations from multiple Hodgkin-Reed-Sternberg cells extracted from a single biopsy specimen, thereby unequivocally establishing clonality. The presence of clonal immunoglobulin gene rearrangements from multiple cells in the same biopsy specimen also confirms a B-cell origin.[2] Only a few rare cases with a T-cell genotype have been reported. Finally, identification of cells with identical immunoglobulin gene rearrangements, both at diagnosis and at relapse, verify that the B-cell clonality of the disease is preserved over time.

Aneuploidy and hyperploidy consistent with the multinucleated nature of Hodgkin-Reed-Sternberg cells are frequent, but no consistent chromosomal translocations have been detected. Several susceptibility loci for Hodgkin lymphoma have been localized to active chromatin with an overrepresentation of determinants of B-cell development and immune response.

Despite their B-cell origin, the neoplastic cells of Hodgkin lymphoma are incapable of making intact antibodies, perhaps because they lack the ability to make the transcription factors necessary to activate the immunoglobulin promoter. B cells that are incapable of manufacturing antibody should undergo apoptosis and immune destruction, but the Hodgkin-Reed-Sternberg cells avoid cell death by activating NFκB and thereby impeding apoptosis and inducing immune blockade by overexpressing checkpoint inhibitors such as programmed cell death ligands 1 and 2.

CLINICAL MANIFESTATIONS

Hodgkin lymphoma is usually manifested as lymphadenopathy (Chapter 154), typically in the cervical, axillary, or mediastinal areas for the predominant classic Hodgkin lymphoma, and only about 10% of patients present with nodal disease below the diaphragm. Although peripherally located nodes seldom reach large size, very large mediastinal masses or, less often, retroperitoneal masses can develop with only modest symptoms. Lymph node involvement in Hodgkin lymphoma is usually painless, but an occasional patient notes discomfort in involved nodal sites immediately after drinking alcohol.

Approximately 25% of patients with Hodgkin lymphoma have constitutional symptoms. The classic B symptoms—significant weight loss (>10% of baseline), night sweats, and persistent fever—usually signal widespread or locally extensive disease and imply a need for systemic treatment. Generalized pruritus, occasionally severe, can antedate the diagnosis of Hodgkin lymphoma by up to several years. Some patients have symptoms suggestive of a growing mass lesion, such as cough or stridor as a result of tracheobronchial compression from mediastinal disease or bone pain secondary to metastatic involvement. Because Hodgkin lymphoma can rarely involve the bone marrow extensively, an occasional patient presents with symptomatic anemia or incidentally noted pancytopenia. Paraneoplastic neurologic or endocrine syndromes (Chapter 164) have been reported with Hodgkin lymphoma but are rare.

DIAGNOSIS

The diagnosis of classic Hodgkin lymphoma is based on recognition of Hodgkin-Reed-Sternberg cells (Fig. 172-1) or Hodgkin cells (or both) in an appropriate cellular background in tissue sections from a lymph node or extralymphatic organ, such as bone marrow, lung, or bone. Fine-needle aspiration biopsy is not adequate for the diagnosis of Hodgkin lymphoma. Open biopsy and standard histochemical staining are required to establish the diagnosis unequivocally and to determine the histologic subtype.[3]

ABSTRACT

Approximately 30,000 new cases of Hodgkin lymphoma, an uncommon but frequently curable B-cell lymphoma, are diagnosed annually in North America and Europe. The etiology of Hodgkin lymphoma remains unknown, and it occurs with biphasic incidence peaking in adults in their mid-30s and again in those over the age of 50 years. Multiagent chemotherapy, occasionally complemented by therapeutic involved-field radiation, is the cornerstone of treatment and cures most patients. The 30% of patients with limited extent of disease require only brief chemotherapy, typically over 3 to 4 months; those with more extensive disease need more extended chemotherapy for 6 months. In both groups, functional imaging with fluorodeoxyglucose positron emission tomography helpfully separates the majority of patients who have had a complete remission from the minority with possible persistent localized lymphoma that may still be cured with the addition of radiation. If, despite optimal primary treatment, the lymphoma recurs, high-dose chemoradiation followed by autologous hematopoietic cell transplantation can cure approximately 50% of patients. Novel treatments with antibody-drug conjugates targeting unique cell surface characteristics on the malignant cells and immune checkpoint inhibitors that neutralize immune response-paralyzing factors produced by the malignant cells are highly effective for Hodgkin lymphoma and are undergoing clinical trials integrating their use into standard management. With most patients cured using current treatments, the major challenge to clinicians managing this neoplasm today is for the cure to be achieved while minimizing long-term toxicity.

KEYWORDS

Hodgkin lymphoma
multiagent chemotherapy
limited stage
advanced stage
positron emission tomography
hematopoietic stem cell transplantation
checkpoint inhibitor

Hodgkin lymphoma can typically be classified into well-described subtypes (Table 172-1), including a relatively new category of lymphocyte-rich classic Hodgkin lymphoma, which must be distinguished from nodular lymphocyte-predominant Hodgkin lymphoma. The most common subtype is nodular sclerosing, which has characteristic coarse bands of sclerosis surrounding nodules composed of typical Hodgkin-Reed-Sternberg cells in the usual background mixture of reactive and inflammatory cells.

In classic Hodgkin lymphoma, scattered large Hodgkin-Reed-Sternberg cells either are multinucleated or have large polyploid nuclei. Variations include mononuclear cells that are similar to the usual polylobated or multinuclear cells but have only one large nucleus with a prominent nucleolus, as well as lacunar cells, which are Hodgkin-Reed-Sternberg variants with abundant cytoplasm that has retracted as an artifact of formalin fixation. The infrequent Hodgkin-Reed-Sternberg cells are usually present in a background mixture of polyclonal lymphocytes, eosinophils, neutrophils, plasma cells, fibroblasts, and histiocytes. A high number of associated macrophages has been demonstrated to be a strong predictor of treatment resistance. Occasionally, granulomas form with a prominent histiocytic component. In contrast, in nodular lymphocyte-predominant Hodgkin lymphoma the cellular pattern predominantly consists of small lymphocytes and scattered histiocytes, epithelioid histiocytes, and characteristic large neoplastic lymphocytic cells ringed by non-neoplastic T lymphocytes.

The immunophenotype of the neoplastic cells in Hodgkin lymphoma can help identify the specific subtype. Typically, the Hodgkin-Reed-Sternberg cells stain positively for CD30 (90 to 100% of cases), CD15 (75 to 85% of cases), and B-cell-specific activating protein (BSAP), which is the product of the *PAX5* gene (>90% of cases). CD20, a generally reliable marker of B-cell lineage, is positive in about 40% of cases of classic Hodgkin lymphoma, but usually only in a minority of cells, and the staining can be weak. In contrast, nodular lymphocyte-predominant Hodgkin lymphoma almost always stains strongly positive for CD20 and for the specialized B-cell markers CD79a and CD45 but is negative for CD30 and CD15. Anaplastic large cell lymphoma (Chapter 171) is positive for CD30 but reliably negative for CD15, CD20, and CD79a.

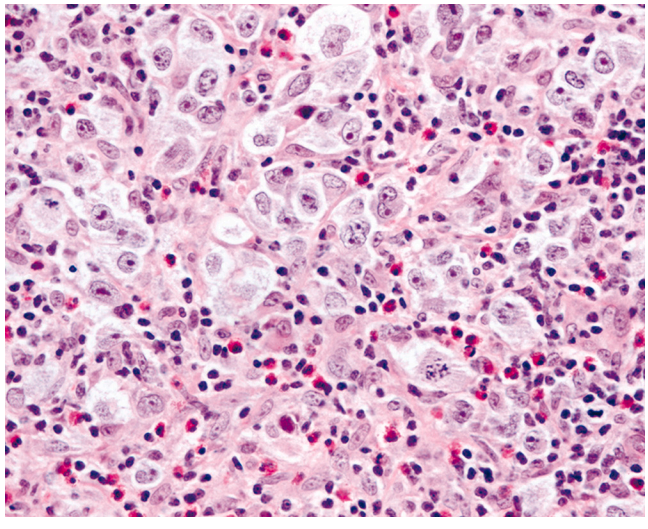

FIGURE 172-1. Nodular sclerosing Hodgkin lymphoma. This figure shows a typical case of classic nodular sclerosing Hodgkin lymphoma with many lacunar cells, occasional diagnostic Hodgkin-Reed-Sternberg cells, and the characteristic background of lymphocytes and eosinophils. (Photomicrograph courtesy of Randy D. Gascoyne, MD, British Columbia Cancer Agency.)

TABLE 172-1 WORLD HEALTH ORGANIZATION CLASSIFICATION OF HODGKIN LYMPHOMA SUBTYPES

SUBTYPE NAME	FREQUENCY (%)*
Classic Hodgkin lymphoma	
Nodular sclerosing	60
Lymphocyte rich	3
Mixed cellularity	9
Lymphocyte depleted	1
Nodular lymphocyte-predominant Hodgkin lymphoma	8
Hodgkin lymphoma, not otherwise classifiable	19

*Frequency based on all new cases (N = 2488) seen in British Columbia from January 1998, when the category of lymphocyte-rich classic Hodgkin lymphoma became well established, to December 2020.

Differential Diagnosis

Depending on the site of occurrence and associated symptoms, the differential diagnosis of Hodgkin lymphoma includes non-Hodgkin lymphoma (Chapter 171), primary mediastinal B cell lymphoma, mediastinal gray zone lymphoma, germ cell tumors (Chapters 184 and 185), thymoma (Chapter 390), sarcoidosis (Chapter 83), histiocytosis (Chapter 155), and tuberculosis (Chapter 299). However, the specific diagnosis is readily determined by obtaining an adequate biopsy specimen for review by an experienced hematopathologist. T-cell/histiocyte–rich B-cell lymphoma (Chapter 171) is distinguished from nodular lymphocyte-predominant Hodgkin lymphoma, which it otherwise closely resembles, by being CD30 negative but positive for IgD mantle cells and follicular dendritic cell networks. Proceeding to a biopsy early in the assessment of patients with lymphadenopathy (Chapter 154), especially of the mediastinum, often saves time and avoids delay in diagnosis. With appropriate biopsy procedures to investigate enlarged central thoracic or intra-abdominal lymph nodes, the diagnosis of Hodgkin lymphoma seldom presents difficulty. The immunophenotype helps distinguish Hodgkin lymphoma from other diseases. The combination of appropriate immunohistopathologic evaluation by an expert hematopathologist and clinical assessment has virtually eliminated difficulties with the differential diagnosis. Problems mostly arise when inadequate or improperly processed material is all that is available for diagnosis.

Staging

Physical Examination

The stage of Hodgkin lymphoma can be established by using readily available imaging and laboratory tests (Fig. 172-2 and Table 172-2). The evaluation should start with a careful history to search for the presence of localizing signs, such as bone pain, or the constitutional symptoms of fever, weight loss, or night sweats or comorbid conditions that may affect the safe delivery of planned treatment. The physical examination may identify lymphadenopathy or organomegaly.

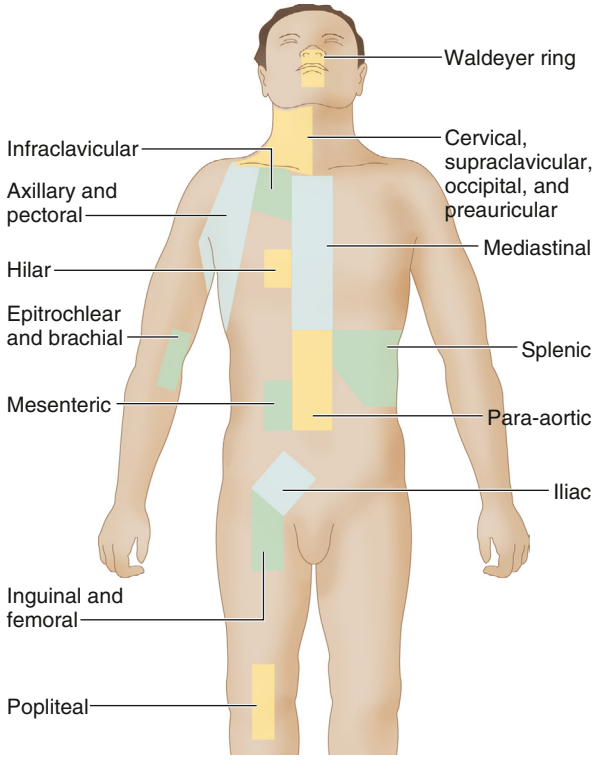

FIGURE 172-2. Anatomic definition of lymph node regions for staging of Hodgkin disease. (From Kaplan HS, Rosenberg SA. The treatment of Hodgkin disease. *Med Clin North Am*. 1966;50:1591-1610.)

TABLE 172-2 TESTS REQUIRED FOR STAGING OF HODGKIN LYMPHOMA

Complete history to search for B symptoms (fever, weight loss, night sweats) or other symptomatic problems suggesting more advanced disease
Physical examination for lymphadenopathy or organomegaly
Complete blood count
Serum creatinine, alkaline phosphatase, lactate dehydrogenase, bilirubin, and protein electrophoresis (including serum albumin level)
Chest radiograph, posteroanterior and lateral views
Computed tomography scan of the neck, thorax, abdomen, and pelvis
Fluorodeoxyglucose positron emission tomography with computed tomography (PET/CT)

TABLE 172-3 MODIFIED ANN ARBOR STAGING SYSTEM FOR HODGKIN LYMPHOMA

STAGE	INVOLVEMENT
I	Single lymph node region (I) or one extralymphatic site (I_E)
II	Two or more lymph node regions, same side of the diaphragm (II), or local extralymphatic extension plus one or more lymph node regions, same side of the diaphragm (II_E)
III	Lymph node regions on both sides of the diaphragm (III); may be accompanied by local extralymphatic extension (III_E)
IV	Diffuse involvement of one or more extralymphatic organs or sites
A	No "B" symptoms
B	Presence of at least one of the following: Unexplained weight loss >10% of baseline during 6 months before staging Recurrent unexplained fever >38° C Recurrent night sweats

Laboratory Testing

Laboratory testing should include blood cell counts and the erythrocyte sedimentation rate, assessment of liver and renal function, serum albumin level, serum protein electrophoresis, and serologic testing for human immunodeficiency virus (HIV) as well as hepatitis B and C. Bone marrow aspiration and biopsy have been rendered unnecessary by fluorodeoxyglucose positron emission tomography (PET).

Imaging

Imaging techniques to evaluate Hodgkin lymphoma continue to evolve (Fig. 172-3). All patients should undergo contrast-enhanced computed tomography (CT) scanning of the neck, thorax, abdomen, and pelvis with slices at intervals of 1 cm or less. Magnetic resonance imaging is occasionally useful when the extent of bone or soft tissue involvement must be determined precisely or for a patient with an absolute contraindication to the use of intravenous contrast agents.

Positron Emission Tomography

Fluorodeoxyglucose PET is more sensitive and specific than CT or gallium scanning both for staging and for assessment of residual masses after treatment, and it is now considered mandatory for staging and following patients with Hodgkin lymphoma.[4-6] For staging, PET imaging reliably detects Hodgkin lymphoma and therefore precludes the need for a bone marrow aspirate or biopsy and is very useful for the assessment of residual masses during or after planned treatment, thereby allowing better selection of patients who should receive altered or additional therapy, especially radiotherapy.

Staging System

The Ann Arbor staging system with the Cotswold modification (Table 172-3) categorizes patients into four stages. The spleen and the lymphoid tissue of the Waldeyer ring each count as nodal sites in this system. Stage IV is reserved for diffuse extranodal disease, which for all practical purposes is disease in the bone marrow, lung, bone, or liver. Hodgkin lymphoma at any other extranodal site should prompt questioning of the diagnosis or a search for HIV infection.

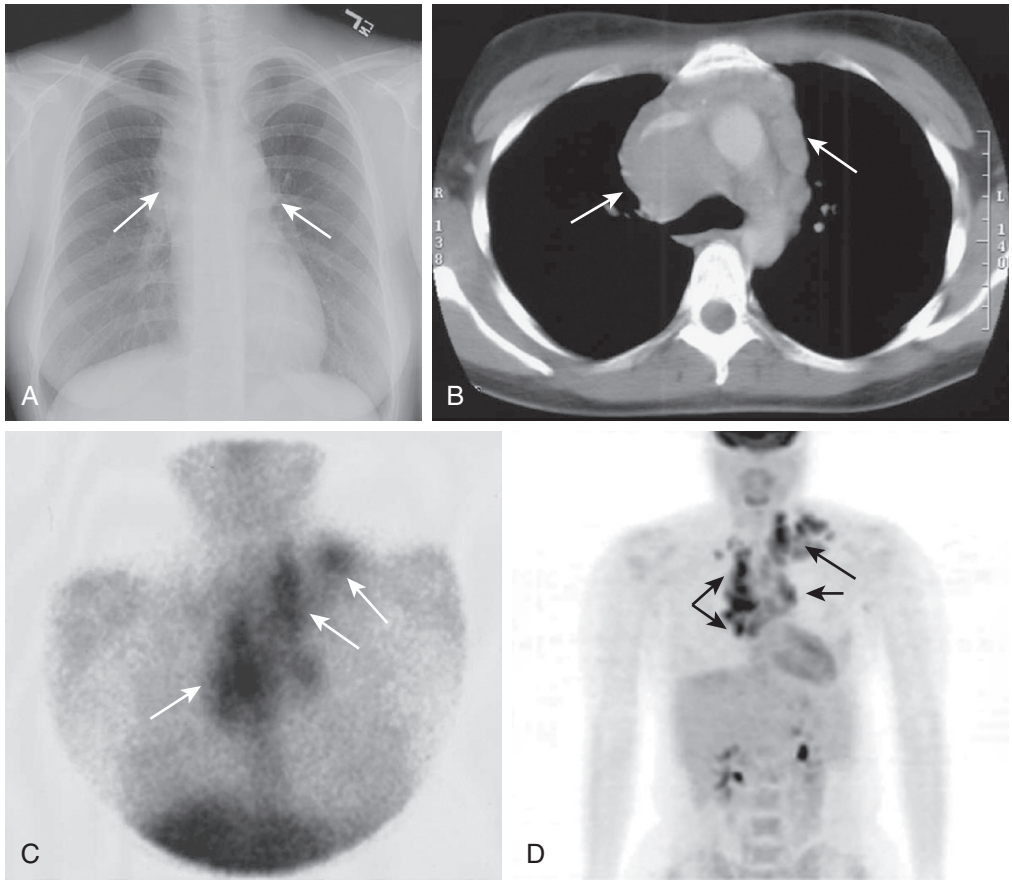

FIGURE 172-3. Imaging of Hodgkin lymphoma. Bulky Hodgkin disease as seen on chest radiograph (**A**), computed tomography (CT) of the chest (**B**), gallium scan (**C**), and positron emission tomography (PET) (**D**). The *arrows* indicate sites of disease. Note that the PET and CT scans provide more detailed information than the chest radiograph and gallium scan.

Bulky disease is defined as the presence of any tumor mass with the largest diameter of 10 cm or more. The E lesion designation identifies patients whose limited extranodal extension of Hodgkin lymphoma could be included in a reasonable involved field of irradiation. As part of staging, patients are further subdivided into those with or without fever, night sweats, or weight loss (B symptoms).

TREATMENT

Hodgkin lymphoma is usually cured.[7] Patients who are event-free at 2 years have an excellent outcome regardless of baseline prognostic factors, although they have an enduring increased risk of death from all causes compared with the general population.[8] Accurate diagnosis, staging, and delivery of appropriate combined-modality treatment and multiagent chemotherapy require a multidisciplinary team, including pathologists, experts in diagnostic imaging, medical and radiation oncologists, nurses, and support staff. The necessity to balance greater efficacy of initial treatment, which often requires an increase in intensity and therefore toxicity, against troublesome and occasionally fatal late complications has encouraged a long-term perspective and careful monitoring for late treatment-related side effects.

Patients with stage III or IV disease or bulky disease are defined as having advanced disease, whereas patients without these characteristics have limited-stage disease. In Europe, patients with limited disease are further subdivided into those with favorable and unfavorable outcomes. Cure rates exceed 90 to 95% for patients with nonbulky stage IA or IIA (limited) disease. However, for patients with advanced-stage disease, independent predictors of progression include sex, age, stage, hemoglobin level, white blood cell count, lymphocyte count, and serum albumin level. Current treatment results indicate a spread from 60 to 80% from the worst to best prognosis groups.[9] A straightforward plan of treatment for the 90% of patients in whom Hodgkin lymphoma is diagnosed between the ages of 16 and 70 years can be based on clinical stage, the presence of B symptoms, and bulk of the largest tumor mass (Table 172-4).

Treatment of Limited-Stage Hodgkin Lymphoma

More than 95% of the one third of patients with Hodgkin lymphoma initially found to have limited-stage disease can be cured regardless of the site of occurrence, the presence of disease above or below the diaphragm, or the histologic subtype. The challenge is to achieve this goal with the least toxicity and cost.[10]

Treatment with two cycles of ABVD (Adriamycin [doxorubicin], bleomycin, vinblastine, and dacarbazine under expert supervision) chemotherapy followed by involved-field or involved site irradiation cures nearly 95% of patients with limited-stage disease; nearly completely eliminates the risk for infertility, premature menopause, and leukemia; and minimizes cardiopulmonary toxicity.[11] However, three cycles of chemotherapy alone is a viable alternative for patients who have limited-stage Hodgkin lymphoma and who have a complete metabolic response, as documented by PET scan, because the reduction in the risks of exposure to radiation offset a slightly higher risk of progressive disease.[A1] For the minority whose lymphoma does not completely regress after three cycles as assessed by PET scanning, the addition of radiation is indicated.

In some European centers, limited-stage Hodgkin lymphoma is divided into favorable (lacking adverse prognostic factors) and unfavorable (bulky mediastinal mass, extranodal extension, elevated erythrocyte sedimentation rate, or involvement of three or more lymph node areas). Patients with limited-stage, favorable Hodgkin lymphoma are treated as described above, but more-intensive approaches have been tested for limited-stage but unfavorable Hodgkin lymphoma with these adverse prognostic factors. In such patients, two cycles of BEACOPP (bleomycin, etoposide, doxorubicin, cyclophosphamide, vincristine, procarbazine, and prednisone) followed by two cycles of ABVD under expert supervision plus involved-field radiotherapy significantly improves tumor control compared with four cycles of ABVD before involved-field radiotherapy, but long-term overall survival is not better.[A2] The addition of a checkpoint inhibitor (e.g., nivolumab or pembrolizumab) either before or concomitantly with four cycles of AVD under expert supervision appears to improve outcome for patients with limited stage, unfavorable Hodgkin lymphoma, in whom it can induce a progression-free survival of >98%,[12,13] but the role for checkpoint inhibitors awaits the results of ongoing clinical trials.

TABLE 172-4 TREATMENT PLAN FOR HODGKIN LYMPHOMA BASED ON STAGE

GROUP	STAGE	TREATMENT
Limited	IA or IIA, no bulky disease*	ABVD† × 2 + IRRT or ABVD × 3 If complete remission, no further treatment If partial remission, add IRRT or a checkpoint inhibitor × 8 doses + AVD × 4
Advanced	IB, IIB, or any stage III or IV or bulky disease, any stage	ABVD† × 6 or A+AVD × 6 or escalated BEACOPP† × 4-6
Refractory/ Relapsed	All stages	Second line chemotherapy followed by high-dose chemoradiation therapy and autologous hematopoietic cell transplantation

*Bulky refers to disease with the largest diameter of any single mass equal to or greater than 10 cm.
†See text for drugs in each regimen. Optimal dosing must be individualized.
A+AVD = brentuximab vedotin, doxorubicin, vinblastine, and dacarbazine; ABVD = Adriamycin [doxorubicin], bleomycin, vinblastine, and dacarbazine; BEACOPP = bleomycin, etoposide, doxorubicin, cyclophosphamide, vincristine, procarbazine, and prednisone; IRRT = involved region radiotherapy.

Treatment of Advanced-Stage Hodgkin Lymphoma

Formerly, in advanced-stage Hodgkin lymphoma (stages IIIA, IIIB, IVA, IVB, and in some cases bulky stage II), ABVD for six cycles under expert supervision had been the most widely used regimen.[14] If the PET scan had become negative after two cycles of ABVD, bleomycin could be safely omitted from the remaining four cycles.[A3] More recently, however, the addition of brentuximab vedotin, an anti-CD30 antibody-drug conjugate to doxorubicin, vinblastine, and dacarbazine (A+AVD), has been shown to improve both 5-year progression-free and overall survival compared with ABVD in previously untreated stage III or IV Hodgkin lymphoma and has become standard.[A4,A5] A negative PET scan at the end of chemotherapy distinguishes between residual fibrosis and persistent lymphoma and identifies the 75% of patients with a residual mass who do not require radiation therapy.[A6,A7]

An alternative to ABVD chemotherapy for advanced-stage Hodgkin lymphoma in patients less than 60 years of age is escalated BEACOPP (bleomycin, etoposide, doxorubicin, cyclophosphamide, vincristine, procarbazine, and prednisone under expert supervision; see Table 172-4), either by itself[15] or used only for patients with a positive interim PET scan after two cycles of ABVD. PET scan results also can guide the intensity of BEACOPP therapy and allow reductions in future doses in patients without detectable residual disease.[A8] Alternatively, BEACOPP may be switched to ABVD if the PET scan is negative after two cycles.[A9,A10] Assessing the appropriateness of escalated BEACOPP for advanced-stage Hodgkin lymphoma requires consideration of potential secondary treatments for those not cured by primary therapy. About 50% of such patients can be effectively treated with high-dose chemoradiation therapy and autologous hematopoietic cell transplantation (Chapter 163). Thus, although escalated BEACOPP offers better initial disease control, randomized trials have failed to demonstrate its superior overall survival compared with ABVD.[A11,A12]

Management of Refractory or Relapsed Hodgkin Lymphoma

For most patients whose Hodgkin lymphoma persists or recurs despite primary chemotherapy, high-dose chemoradiation therapy (e.g., BEAM [carmustine, etoposide, cytarabine, and melphalan] under expert supervision) and autologous hematopoietic cell transplantation is the recommended treatment, if feasible. Approximately one third of patients whose disease progresses during or within 3 months of initial multiagent chemotherapy (refractory Hodgkin lymphoma) and about two thirds of patients who relapse more than 3 months after multiagent chemotherapy (relapsed Hodgkin lymphoma) can be cured using high-dose chemoradiation therapy and autologous hematopoietic cell transplantation.[16] Two special subgroups may be exceptions. Patients who are initially stage I to III but who relapse solely in originally involved but unirradiated lymph nodes and without B symptoms or extranodal disease may obtain up to a 40 to 50% cure rate with wide-field irradiation, and patients who relapse without B symptoms more than 1 year after completion of primary chemotherapy also may achieve up to a 30 to 40% cure rate with additional chemotherapy with or without irradiation. However, these two subgroups may achieve up to an 80% 10-year disease-free survival rate after high-dose chemoradiation therapy and autologous hematopoietic cell transplantation. Thus, data suggest that patients with progressive Hodgkin lymphoma after primary chemotherapy for advanced-stage disease should undergo high-dose chemoradiation therapy and autologous hematopoietic cell transplantation regardless of the characteristics of the relapse. After high-dose chemoradiation therapy and autologous hematopoietic cell transplantation, the addition of consolidative brentuximab vedotin improves outcomes by eliminating approximately one third of the relapses that would have otherwise occurred.[A13,A14] For patients who relapse despite high-dose chemoradiation therapy and autologous hematopoietic cell transplantation, blockade of the programmed death 1 (PD-1) pathway with checkpoint inhibitors (e.g., nivolumab[A15] or pembrolizumab[A16,17]) can induce an objective response in more than 70% of patients.

Chimeric antigen receptor T-cells (CAR-T) directed against CD30 is being investigated for relapsed Hodgkin lymphoma. If efficacious, this approach may eventually become an alternative to high-dose chemoradiation therapy and autologous hematopoietic cell transplantation.[18]

Management of Complications

Follow-up and Late Complications of Treatment

Most adult patients with Hodgkin lymphoma are cured and experience minimal long-term toxicity from their treatment. However, the risk for certain late effects

TABLE 172-5 MONITORING AFTER SUCCESSFUL PRIMARY TREATMENT OF HODGKIN LYMPHOMA

RISK/PROBLEM	INCIDENCE/RESPONSE
Relapse	Ten to 30% of patients experience relapse. Careful attention should be directed to lymph node sites, especially if previously involved with disease and not treated with radiation. New persistent focal symptoms such as bone pain should be investigated with appropriate laboratory and imaging studies.
Dental caries	Neck or oropharyngeal irradiation may cause decreased salivation. Patients should have regular dental care and should make their dentist aware of the previous irradiation.
Hypothyroidism	After thyroid irradiation at doses sufficient to cure Hodgkin lymphoma, at least 50% of patients eventually become hypothyroid. All patients who have been exposed to neck irradiation should have an annual TSH level determined. Patients whose TSH level becomes elevated should be treated with lifelong thyroxine replacement in doses sufficient to suppress TSH levels to low normal (Chapter 207).
Cardiac complications	Coronary heart disease, especially in patients exposed to mediastinal radiation, anthracyclines, or both.
Infertility	ABVD is not known to cause permanent gonadal toxicity, although temporary oligospermia or irregular menses may persist for 1 to 2 years after treatment. Direct or scatter radiation to gonadal tissue may cause infertility, amenorrhea, or premature menopause, but this adverse event seldom occurs with the current fields used for the treatment of Hodgkin lymphoma. In general, women who continue menstruating are fertile, but men require semen analysis to provide a specific answer.
Secondary neoplasms	Although uncommon, certain secondary neoplasms occur with increased frequency in patients who have been treated for Hodgkin lymphoma: acute myelogenous leukemia; thyroid, breast, lung, gastric, pancreatic, colorectal, and cervical cancers; non-Hodgkin lymphoma; and melanoma. It is appropriate to "be vigilant" for these neoplasms for the remainder of the patient's life because they may have a lengthy induction period.

ABVD = doxorubicin (Adriamycin), bleomycin, vinblastine, and dacarbazine; TSH = thyroid-stimulating hormone.

warrants careful but not intrusive follow-up and selective intervention (Table 172-5). At the conclusion of treatment, a thorough reassessment of the initial sites of lymphoma should be completed to provide post-treatment baseline measurements. Patients should be seen by a specialist knowledgeable in the management of lymphoma, preferably about every 3 months for 2 years, after which follow-up can be switched to the patient's family physician every 6 months for 3 years, then annually. Patients should be strongly encouraged to refrain from smoking, to perform careful breast and skin examinations on a regular basis, and to undergo annual immunization for influenza, immunization for pneumococcus at diagnosis and 5 years after treatment, and immunization for diphtheria and tetanus every 10 years (Chapter 15). Patients who have received radiation to the head or neck area should follow a vigorous program of dental prophylaxis in anticipation of the deleterious effect of reduced saliva production and should have their thyroid-stimulating hormone (TSH) level checked annually in recognition of the 50% risk for eventual hypothyroidism.

Other potential long-term sequelae of the treatment of Hodgkin lymphoma include second malignancies. Radiation therapy–related solid tumors—most commonly nonmelanoma skin cancers, lung, breast, and colorectal malignancies—have a median latency period of more than 14 years after treatment. Chemotherapy-related myelodysplasia (Chapter 167) and acute myeloid leukemia (Chapter 168) are more likely to be caused by alkylating agents that are included in regimens like MOPP (mechlorethamine, vincristine, procarbazine, and prednisone) and BEACOPP, a risk minimized with ABVD, and have shorter latency periods (median of 3 years) after treatment. Despite the trend toward smaller radiation target volumes, lower radiation doses, and less toxic chemotherapy regimens, the risk of solid cancers has not appreciably changed among patients who were treated during the 1990s as compared with patients who were treated during earlier decades.[19] However, more recently treated female survivors of Hodgkin lymphoma appear to have a reduced risk of breast cancer, and the risk of hematologic malignancies has clearly decreased among 5-year survivors who were treated in the most recent study period, probably reflecting the declining use of alkylating agent–based chemotherapy.

Long-term (usually >10 years after treatment) cardiovascular complications include coronary artery disease (related to mediastinal irradiation) and cardiomyopathy (caused by the cardiotoxicity of anthracycline chemotherapy). The median interval between the initial treatment of Hodgkin lymphoma and the development of coronary artery disease is approximately 19 years. There is a linear, no-threshold relationship between mean heart dose of radiation therapy and development of coronary artery disease in survivors of Hodgkin lymphoma, so the reduced radiation exposure to the heart in current radiation therapy protocols should reduce cardiovascular risk in the future. Chemotherapy, particularly alkylating agents in MOPP and BEACOPP but not ABVD regimens, can cause permanent infertility. Long-term survivors of childhood Hodgkin lymphoma (median age at diagnosis of 15 years) are at increased risk for neurocognitive impairment.

Special Problems in the Management of Hodgkin Lymphoma

Hodgkin Lymphoma During Pregnancy

Between 0.5 and 1.0% of cases of Hodgkin lymphoma occur coincident with pregnancy (Chapter 221). When the lymphoma is discovered during pregnancy, it is almost always possible to keep it under control and allow the pregnancy to go to full term.

Standard staging tests (see Table 172-2) should be completed, except that imaging requiring radiation must be minimized. For example, abdominal ultrasonography can identify bulky retroperitoneal disease, and a single posteroanterior radiograph of the chest, with proper shielding, can identify bulky mediastinal disease.

Patients can often continue the pregnancy to term without any treatment of the lymphoma. If symptomatic or progressive disease develops, ABVD chemotherapy can be given in the second and third trimester with very low risk for injuring the fetus. An attractive alternative to multiagent chemotherapy is intermittent single-agent vinblastine, given in the lowest dose that can control symptoms until delivery, followed by a full course of six to eight cycles of multiagent chemotherapy after delivery.

Hodgkin Lymphoma and Acquired Immunodeficiency Syndrome

In patients with HIV infection, the incidence of Hodgkin lymphoma is increased as much as 5- to 10-fold, and the lymphoma manifests differently and pursues a more aggressive natural history (Chapter 359). Hodgkin lymphoma in HIV-positive individuals is almost always associated with Epstein-Barr virus within Hodgkin-Reed-Sternberg cells. The histology is much more likely to be mixed cellularity or lymphocyte depleted. The disease commonly involves extranodal sites, especially the bone marrow. More than 80% of patients have advanced-stage disease, and most patients have B symptoms.

Patients are prone to opportunistic infections, and the interaction of chemotherapeutic agents with other medications may compromise the patient's ability to tolerate treatment. Meticulous attention to drug-drug interactions is required to avoid drug toxicity and adverse pharmacokinetic effects that might compromise the potential for cure.[20] The best approach is a combination of highly active antiretroviral agents (Chapter 357); vigorous supportive care with antiherpetic agents (Chapter 345), antifungal agents (Chapter 307), and neutrophil-stimulating growth factors (Chapter 142); and standard multiagent chemotherapy. With appropriate supportive care, regimens such as ABVD can be delivered. However, more-severe-than-normal toxicity must be anticipated. With appropriate supportive care and careful choice of highly active antiretroviral therapy to avoid drug interactions that compromise delivery of full chemotherapy doses, cure rates and long term survival rates for Hodgkin lymphoma have become comparable to those seen in HIV-negative individuals.[21]

Hodgkin Lymphoma in the Elderly Population

Elderly patients with Hodgkin lymphoma have a worse outcome. For example, the 5-year overall survival rate falls from an average of about 80% in patients younger than age 65 years to less than 50% in patients older than age 65 years as a reflection of the impact of comorbid conditions that may lead to incomplete staging and inadequate adherence to standard treatment protocols. By comparison, elderly patients achieve outcomes equivalent to those of younger patients when they undergo complete staging and receive full doses of planned chemotherapy. The best approach for elderly patients is to attempt to treat them in a manner similar to younger patients, with vigorous supportive care and the addition of neutrophil growth factors such as filgrastim or pegfilgrastim under expert supervision if necessary to enable safe delivery of full doses. In patients over age 70 years or with preexisting pulmonary or cardiac disease, it might be necessary to reduce the dose of bleomycin or omit doxorubicin.

FUTURE DIRECTIONS

The ability to profile multigene expression patterns and identify genetic polymorphisms associated with specific malignancies may provide better insight into the molecular genesis of Hodgkin and other lymphomas. Molecular methods to monitor minimal residual disease, in addition to the current practice of

following only imaging and clinical evaluations, may transform treatment paradigms. Determining levels of circulating tumor DNA holds particular promise for such monitoring. The role of checkpoint inhibitors is likely to evolve as more trials are reported.[22] Therapeutic agents more specifically targeted at the malignant Hodgkin-Reed-Sternberg cells, such as those coupling an antibody to the CD30 antigen with a cellular toxin, hold substantial promise to improve treatment outcomes.

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173 PLASMA CELL DISORDERS

S. VINCENT RAJKUMAR

DEFINITION

Plasma cell disorders are neoplastic or potentially neoplastic diseases associated with the clonal proliferation of immunoglobulin-secreting plasma cells (Table 173-1). These disorders are characterized by the secretion of electrophoretically and immunologically homogeneous (monoclonal) proteins that represent intact or incomplete immunoglobulin molecules. Monoclonal proteins are commonly referred to as M proteins, myeloma proteins, or paraproteins.

Syndromes associated with plasma cell disorders and monoclonal proteins include premalignant disorders (monoclonal gammopathy of undetermined significance; MGUS), smoldering multiple myeloma, malignant neoplasms (multiple myeloma, Waldenström macroglobulinemia), as well as disorders primarily related to the unique properties of the secreted monoclonal protein (cryoglobulinemia, immunoglobulin light chain [AL] amyloidosis, light chain deposition disease; see Table 173-1).[1]

Serum Immunoglobulins

Intact immunoglobulins consist of two heavy (H) polypeptide chains of the same class and subclass and two light (L) polypeptide chains of the same type (Chapter 35). The heavy polypeptide chains are designated by Greek letters: γ in immunoglobulin G (IgG), α in immunoglobulin A (IgA), μ in immunoglobulin M (IgM), δ in immunoglobulin D (IgD), and ε in immunoglobulin E (IgE). The light chain types are kappa (κ) and lambda (λ). Both heavy chains and light chains have "constant" and "variable" regions with respect to the amino acid sequence. The class specificity of each immunoglobulin is defined by a series of antigenic determinants on the constant regions of the heavy chains (γ, α, μ, δ, and ε) and the two major classes of light chains (κ and λ). The amino acid sequence in the variable regions of the immunoglobulin molecule corresponds to the active antigen-combining site of the antibody.

In the majority of clonal plasma cell disorders, *intact* immunoglobulin molecules are secreted as monoclonal (M) proteins. In addition, there can also be abnormal secretion of excess monoclonal *free* light chains (FLCs) that are released without being bound to immunoglobulin heavy chains. In some patients, heavy chain expression is completely lost, and only monoclonal free light chains (commonly referred to as Bence Jones proteins) are secreted. Even less frequently, only heavy chains are secreted, resulting in heavy chain diseases (HCDs). Rare patients with multiple myeloma secrete no identifiable immunoglobulin ("nonsecretory myeloma").

Identification of Monoclonal Proteins

Protein electrophoresis of the serum and urine detects M protein as a narrow peak (like a church spire) on the densitometer tracing or as a dense, discrete band on agarose gel (Fig. 173-1). Electrophoresis also permits quantitation of M proteins. Monoclonal light chains (Bence Jones proteins) are rarely seen on serum electrophoresis but are easily detected on urine electrophoresis. Urine electrophoresis requires a 24-hour urine collection.

When a peak or band is first seen on protein electrophoresis, immunofixation of the serum and urine should be performed to identify the heavy and light chain type of the M protein. Immunofixation is also a more sensitive test than protein electrophoresis, and it should always be performed in conjunction with electrophoresis when multiple myeloma or related disorders are first suspected so as to detect small, unmeasurable M proteins that may be missed on electrophoresis. Immunofixation is particularly important in oligosecretory myeloma, primary amyloidosis, and solitary plasmacytoma, as well as after successful treatment of multiple myeloma or macroglobulinemia. In these instances, a small M protein can be concealed within the normal β or γ areas of the electrophoresis gel and may be overlooked. Mass spectrometry can be

TABLE 173-1 PLASMA CELL PROLIFERATIVE DISORDERS

I. Premalignant monoclonal gammopathies
  A. Monoclonal gammopathy of undetermined significance (MGUS)
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    2. Non-IgM MGUS
    3. Light chain MGUS
  B. Biclonal and triclonal gammopathies of undetermined significance
  C. Smoldering multiple myeloma
II. Malignant monoclonal gammopathies
  A. Multiple myeloma (IgG, IgA, IgD, IgE, and light chain only)
  B. Plasma cell leukemia
  C. POEMS syndrome
  D. Solitary plasmacytoma
  E. Solitary plasmacytoma with minimal marrow involvement
  F. Waldenström macroglobulinemia (IgM)
III. Heavy chain diseases (HCDs)
  A. γ-HCD
  B. α-HCD
  C. μ-HCD
IV. Cryoglobulinemia (types I, II, and III)
V. Immunoglobulin light chain amyloidosis

Ig = immunoglobulin; POEMS = polyneuropathy, organomegaly, endocrinopathy, monoclonal plasma cell disorder, and skin changes.

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  E. Solitary plasmacytoma with minimal marrow involvement
  F. Waldenström macroglobulinemia (IgM)
III. Heavy chain diseases (HCDs)
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IV. Cryoglobulinemia (types I, II, and III)
V. Immunoglobulin light chain amyloidosis

Ig = immunoglobulin; POEMS = polyneuropathy, organomegaly, endocrinopathy, monoclonal plasma cell disorder, and skin changes.

ABSTRACT

Plasma cell disorders encompass a wide spectrum of clinical conditions, including monoclonal gammopathy of undetermined significance (MGUS), smoldering multiple myeloma (SMM), multiple myeloma, solitary plasmacytoma, immunoglobulin light chain amyloidosis, and Waldenström macroglobulinemia. Almost all malignant plasma cell disorders start out as MGUS, which represents the premalignant stage. Although multiple myeloma remains an incurable disease, remarkable progress has been made in risk stratification and in treatment. Established treatments include alkylating agents (melphalan and cyclophosphamide), corticosteroids, immunomodulatory agents (thalidomide, lenalidomide, pomalidomide), proteasome inhibitors (bortezomib, carfilzomib, ixazomib), and monoclonal antibodies (daratumumab, elotuzumab, isatuximab). Major recent advances include chimeric antigen receptor T (CAR-T) cells (idecabtagene vicleucel; ide-cel), ciltacabtagene autoleucel (cilta-cel), bispecific antibodies, and exportin-1 inhibitors (selinexor). Autologous stem cell transplantation continues to be an important therapeutic option.

KEYWORDS

monoclonal gammopathy
multiple myeloma
plasmacytoma
amyloidosis
macroglobulinemia

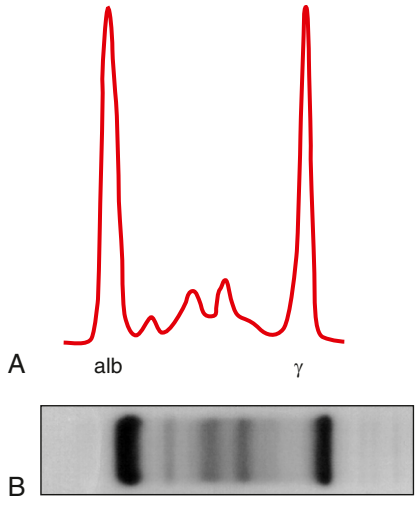

FIGURE 173-1. **Serum protein electrophoresis showing a monoclonal (M) protein. A,** Monoclonal pattern of serum protein as traced by a densitometer after electrophoresis on agarose gel: tall, narrow-based peak of γ mobility. alb = albumin. **B,** Monoclonal pattern from electrophoresis of serum on agarose gel (anode on the left): dense, localized band representing monoclonal protein of γ mobility. (From Kyle RA, Katzmann JA. Immunochemical characterization of immunoglobulins. In: Rose NR, Conway de Macario E, Folds JD, et al., eds. *Manual of Clinical Laboratory Immunology*, 5th ed. Washington, DC: ASM Press; 1997:156, with permission of the American Society for Microbiology.)

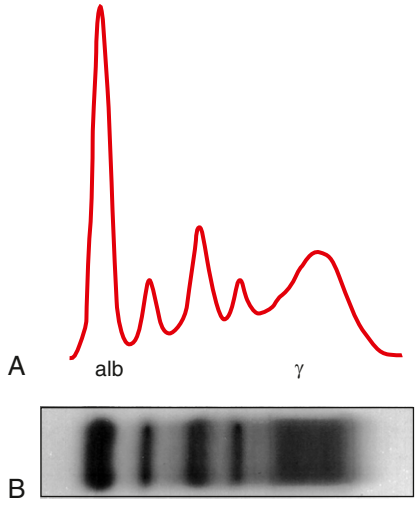

FIGURE 173-2. **Serum protein electrophoresis showing increased polyclonal immunoglobulins. A,** Polyclonal pattern from a densitometer tracing of agarose gel: broad-based peak of γ mobility. alb = albumin. **B,** Polyclonal pattern from electrophoresis of agarose gel (anode on the left). The band at the right is broad and extends throughout the γ area. (From Kyle RA, Katzmann JA. Immunochemical characterization of immunoglobulins. In: Rose NR, Conway de Macario E, Folds JD, et al., eds. *Manual of Clinical Laboratory Immunology*, 5th ed. Washington, DC: ASM Press; 1997:156, with permission of the American Society for Microbiology.)

used instead of immunofixation to identify the M protein more accurately (E-Figs. 173-1 and 173-2).

Monoclonal proteins must be distinguished from an excess of polyclonal immunoglobulins (one or more heavy chain types and both κ and λ light chains, usually limited to the γ region), which produce a broad-based peak or broad band (Fig. 173-2). This finding is associated with chronic infectious or inflammatory states.

Detection of Serum Free Light Chains

The serum free light chain assay measures the level of free κ and λ immunoglobulin light chains (i.e., light chains that are not bound to intact immunoglobulin). An abnormal κ/λ free light chain ratio (normal range, 0.26 to 1.65) indicates a significant excess of one light chain type versus the other and is interpreted as representing a monoclonal elevation of the corresponding light chain type. The serum free light chain assay is more sensitive than electrophoresis or immunofixation in detecting free monoclonal light chains and is useful in the diagnostic evaluation of plasma cell disorders and in risk stratification.

MONOCLONAL GAMMOPATHY OF UNDETERMINED SIGNIFICANCE

DEFINITION

Monoclonal gammopathy of undetermined significance (MGUS; formerly called *benign monoclonal gammopathy*) is a premalignant clonal plasma cell disorder characterized by the presence of a serum M protein in persons who lack evidence of multiple myeloma, macroglobulinemia, amyloidosis, or other related diseases. MGUS is defined by a serum M protein concentration lower than 3 g/dL, less than 10% clonal plasma cells in the bone marrow, and absence of myeloma-defining events. The main clinical significance of MGUS is its lifelong risk of transformation to myeloma or related malignancy at a fixed but unrelenting rate of 1% per year.[2] There are three major types of MGUS: IgM MGUS, non-IgM MGUS, and light chain MGUS (Table 173-2).

EPIDEMIOLOGY

Most patients in whom a serum M protein is detected have MGUS (E-Fig. 173-3). The prevalence of MGUS in the general population increases with age, from approximately 1% in persons 50 to 60 years old to greater than 5% in those older than 70 years. The age-adjusted prevalence is higher in males than in females and is twice as high in Blacks compared with Whites (E-Table 173-1). The prevalence of MGUS and of multiple myeloma is increased among blood relatives of individuals with monoclonal gammopathies.

PATHOBIOLOGY

The etiology of MGUS is unknown, but age, male gender, family history, immunosuppression, and exposure to certain pesticides are known risk factors. It is hypothesized that infection, inflammation, or other antigenic stimuli, acting in concert with the development of cytogenetic abnormalities in the plasma cells, are the initiating pathogenetic events in most patients. Approximately 40% of MGUS is associated with plasma cell translocations involving the immunoglobulin heavy chain (IgH) locus on chromosome 14q32 (IgH translocated MGUS), 40% with trisomies involving odd-numbered chromosomes (hyperdiploid MGUS), 15% with both trisomies and IgH translocations, and the remaining with other cytogenetic abnormalities. The primary IgH translocations seen in MGUS commonly involve one of five recurrent partner chromosome loci: 11q13 (*CCND1* [cyclin D1 gene]), 4p16.3 (*FGFR-3* and *MMSET*), 6p21 (*CCND3* [cyclin D3 gene]), 16q23 (*c-maf*), and 20q11 (*mafB*). On flow cytometry, normal plasma cells are preserved and reside alongside the clonal cells.

CLINICAL MANIFESTATIONS

MGUS is asymptomatic and is usually diagnosed incidentally on laboratory testing. Patients with MGUS progress to multiple myeloma or related malignancy at a rate of approximately 1% per year. Patients with IgM MGUS are at risk of progression to Waldenström macroglobulinemia, while patients with non-IgM MGUS and light chain MGUS are at risk of progression to multiple myeloma. All forms of MGUS carry a risk of progression to AL amyloidosis.

DIAGNOSIS

MGUS represents a limited, nonmalignant expansion of monoclonal plasma cells. MGUS is differentiated from multiple myeloma and smoldering multiple myeloma by the level of the M protein, the percentage of plasma cells in the bone marrow, and the presence or absence of anemia, renal failure, hypercalcemia, or lytic bone lesions (Table 173-2).[3] Because anemia and renal insufficiency are relatively common in the elderly population with MGUS, the causes of these conditions should be carefully investigated with adequate laboratory studies. Only patients with strong evidence of end-organ damage thought to be directly related to a plasma cell disorder can be considered to have myeloma or a related malignancy.

Although a reduction in the levels of the immunoglobulin classes other than M protein (i.e., the normal polyclonal or background immunoglobulins) is more frequently seen in multiple myeloma or Waldenström macroglobulinemia, such reductions also occur in almost 40% of patients with MGUS.

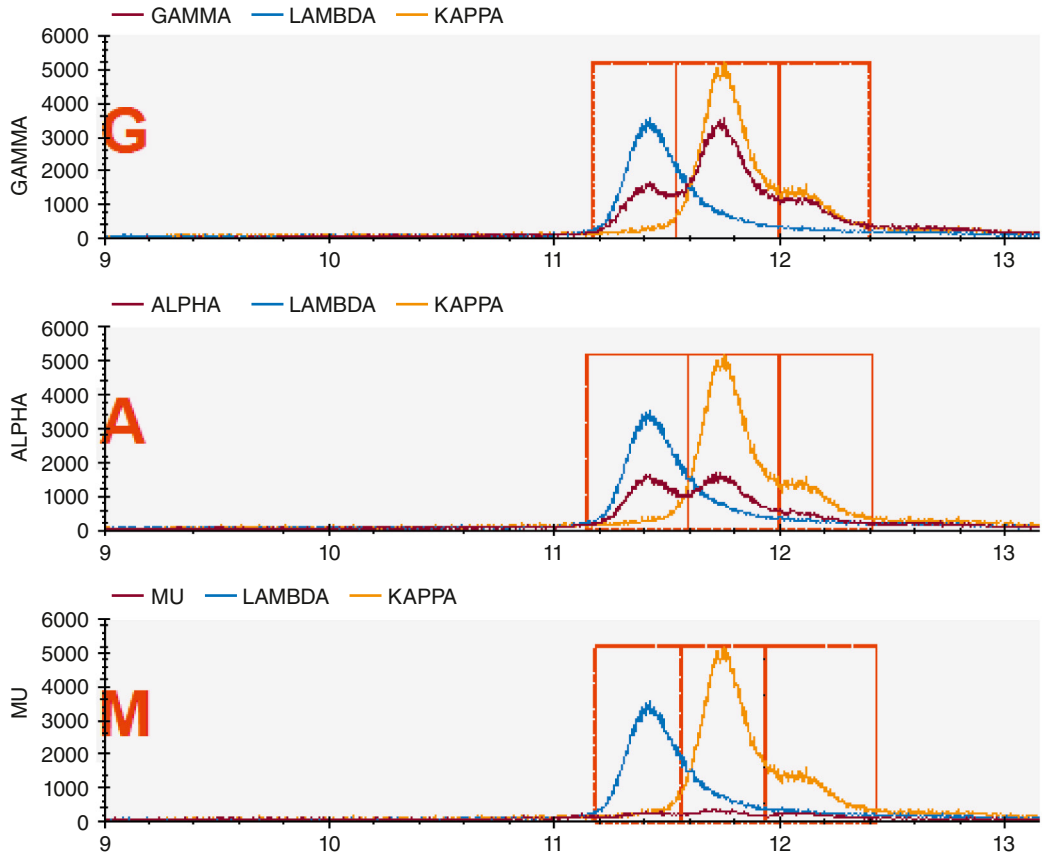

E-FIGURE 173-1. **Mass spectrometry to identify monoclonal protein.** Mass spectrometry shows normal results with total kappa light chain *(orange)* and total lambda light chain *(blue)* distribution repeated in all three spectra. The light chains associated with IgG *(top)*, IgA *(middle)*, and IgM *(bottom)* are displayed in red.

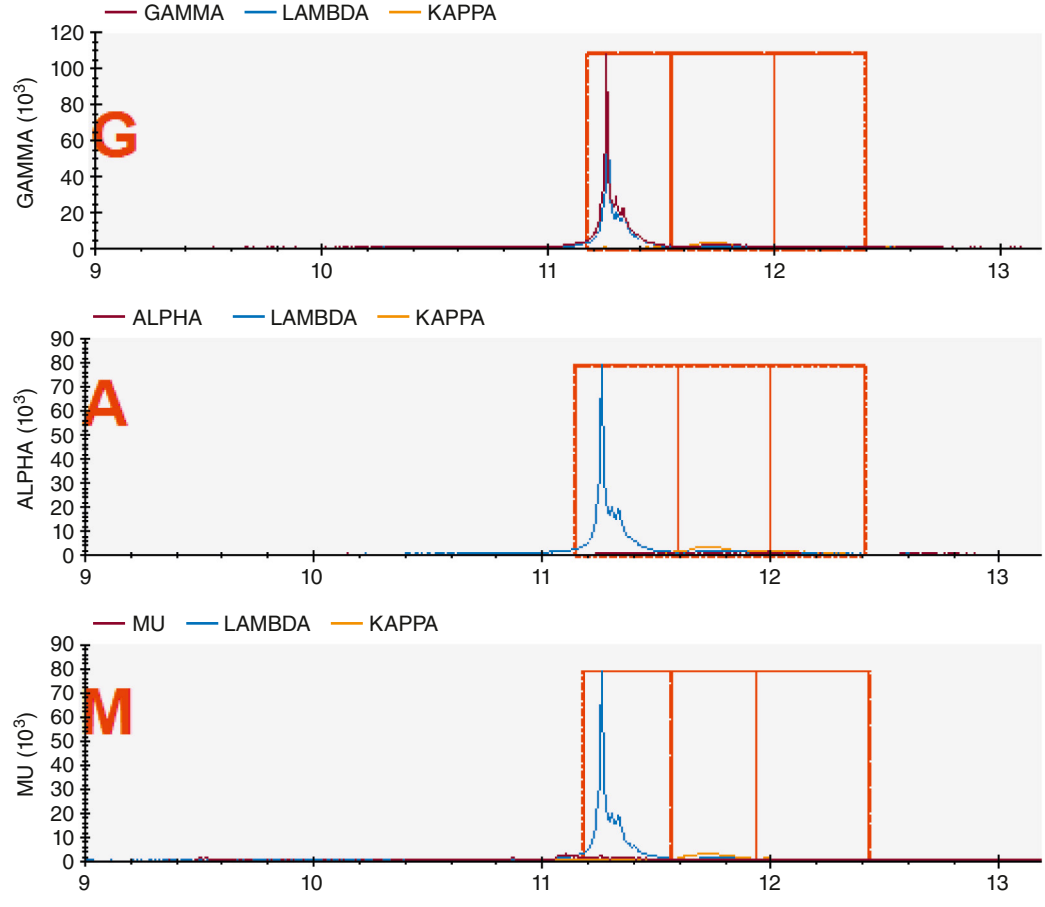

E-FIGURE 173-2. **Mass spectrometry to identify monoclonal protein.** Mass spectrometry showing overlapping peaks in the total lambda light chain distribution *(blue)* and in the light chains associated with IgG. This result is consistent with an IgG lambda paraprotein.

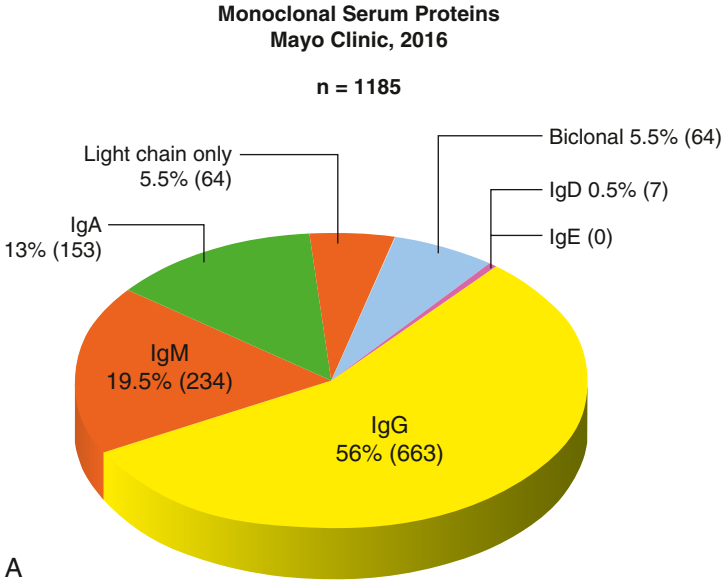

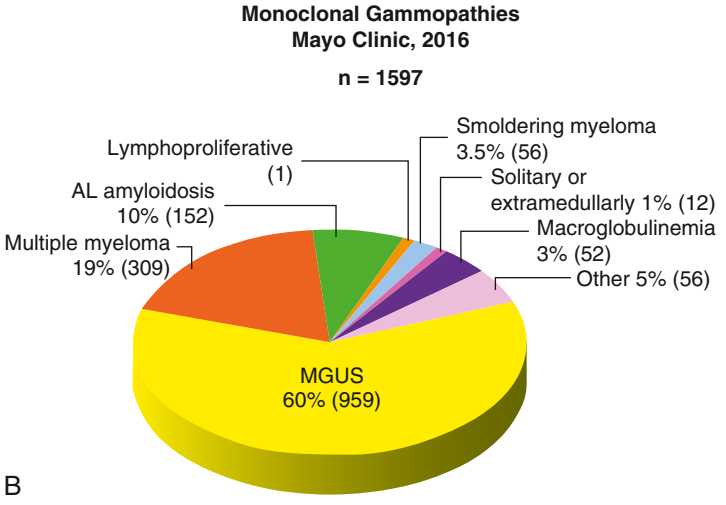

E-FIGURE 173-3. **Monoclonal gammopathy. A,** Distribution of serum monoclonal proteins in 1185 patients seen at the Mayo Clinic during 2016. Ig = immunoglobulin. **B,** Diagnoses in 1597 cases of monoclonal gammopathy seen at the Mayo Clinic during 2016. AL = amyloid light chain; Ig = immunoglobulin; MGUS = monoclonal gammopathy of undetermined significance.

E-TABLE 173-1 PREVALENCE OF MONOCLONAL GAMMOPATHY OF UNDETERMINED SIGNIFICANCE (MGUS) BY RACE/ETHNICITY AND AGE

AGE GROUP (YEARS)	BLACKS % (95% CI)	WHITES % (95% CI)	HISPANIC AMERICANS % (95% CI)	TOTAL POPULATION % (95% CI)
10-19	0.00 (NA)	0.0 (NA)	0.1 (0.0-0.8)	0.0 (0.0-0.1)
20-29	0.3 (0.1-0.8)	0.0 (NA)	0.00 (NA)	0.0 (0.0-0.1)
30-39	0.9 (0.4-1.5)	0.3 (0.1-1.0)	0.2 (0.1-0.8)	0.5 (0.3-0.9)
40-49	3.3 (2.0-5.2)	0.5 (0.2-1.4)	2.2 (1.2-4.0)	0.9 (0.5-1.5)
50-59	2.2(1.3-3.6)	1.0 (0.6-1.7)	0.9 (0.3-2.2)	1.2 (0.8-1.7)
60-69	3.5 (2.3-5.3)	2.4 (1.7-3.4)	2.4 (1.7-3.4)	2.5 (1.9-3.2)
70-79	5.7 (3.7-8.7)	3.4 (2.6-4.6)	2.5 (1.4-4.6)	3.4 (2.6-4.5)
80+	8.6 (4.9-14.5)	4.4 (3.3-5.9)	4.0 (1.3-11.2)	4.6 (3.5-5.9)

Modified from Landgren O, et al. Prevalence of myeloma precursor state monoclonal gammopathy of undetermined significance (MGUS) in 12,309 individuals 10 to 49 years old: a population-based study from the National Health and Nutritional Examination Survey. *Blood Cancer J.* 2017;7:e618.

TABLE 173-2 CRITERIA FOR THE DIAGNOSIS OF PLASMA CELL DISORDERS

DISORDER	DISEASE DEFINITION
IgM monoclonal gammopathy of undetermined significance (IgM MGUS)	All three criteria must be met: 1. Serum IgM monoclonal protein <3 g/dL 2. Bone marrow lymphoplasmacytic infiltration <10% 3. No evidence of anemia, constitutional symptoms, hyperviscosity, lymphadenopathy, or hepatosplenomegaly that can be attributed to the underlying lymphoproliferative disorder
Non-IgM monoclonal gammopathy of undetermined significance (MGUS)	All three criteria must be met: 1. Serum monoclonal protein (non-IgM type) <3 g/dL 2. Clonal bone marrow plasma cells <10%* 3. Absence of end-organ damage such as hypercalcemia, renal insufficiency, anemia, and bone lesions (CRAB) that can be attributed to the plasma cell proliferative disorder
Light chain MGUS	All criteria must be met: 1. Abnormal FLC ratio (<0.26 or >1.65) 2. Increased level of the appropriate involved light chain (increased κ FLC in patients with ratio >1.65 and increased λ FLC in patients with ratio <0.26) 3. No immunoglobulin heavy chain expression on immunofixation 4. Absence of end-organ damage that can be attributed to the plasma cell proliferative disorder 5. Clonal bone marrow plasma cells <10% 6. Urinary monoclonal protein <500 mg/24 h
Smoldering multiple myeloma	Both criteria must be met: 1. Serum monoclonal protein (IgG or IgA) ≥3 g/dL, or urinary monoclonal protein ≥500 mg per 24 h and/or clonal bone marrow plasma cells 10-60% 2. Absence of myeloma-defining events or amyloidosis

Multiple myeloma	Both criteria must be met:
	1. Clonal bone marrow plasma cells ≥10% or biopsy-proven bony or extramedullary plasmacytoma
	2. Any one or more of the following myeloma-defining events:
	• Evidence of end-organ damage that can be attributed to the underlying plasma cell proliferative disorder, specifically:
	  • Hypercalcemia: serum calcium >0.25 mmol/L (>1 mg/dL) higher than the upper limit of normal or >2.75 mmol/L (>11 mg/dL)
	  • Renal insufficiency: creatinine clearance <40 mL per minute or serum creatinine >177 μmol/L (>2 mg/dL)
	  • Anemia: hemoglobin value of >2 g/dL below the lower limit of normal or a hemoglobin value <10 g/dL
	  • Bone lesions: one or more osteolytic lesions on skeletal radiography, computed tomography (CT), or positron emission tomography-CT (PET-CT)
	• Clonal bone marrow plasma cell percentage ≥60%
	• Involved: uninvolved serum free light chain (FLC) ratio ≥100 (involved free light chain level must be ≥100 mg/L)
	• >1 focal lesions on magnetic resonance imaging (MRI) studies (at least 5 mm in size)

Solitary plasmacytoma	All four criteria must be met: 1. Biopsy-proven solitary lesion of bone or soft tissue with evidence of clonal plasma cells 2. Normal bone marrow with no evidence of clonal plasma cells 3. Normal skeletal survey and MRI (or CT) of spine and pelvis (except for the primary solitary lesion) 4. Absence of end-organ damage such as hypercalcemia, renal insufficiency, anemia, or bone lesions (CRAB) that can be attributed to a lymphoplasma cell proliferative disorder
Solitary plasmacytoma with minimal marrow involvement†	All four criteria must be met: 1. Biopsy-proven solitary lesion of bone or soft tissue with evidence of clonal plasma cells 2. Clonal bone marrow plasma cells <10% 3. Normal skeletal survey and MRI (or CT) of spine and pelvis (except for the primary solitary lesion) 4. Absence of end-organ damage such as hypercalcemia, renal insufficiency, anemia, or bone lesions (CRAB) that can be attributed to a lymphoplasma cell proliferative disorder

*A bone marrow can be deferred in patients with low-risk MGUS (IgG type, M protein <1.5 g/dL, normal free light chain ratio) in whom there are no clinical features concerning for myeloma.
†Solitary plasmacytoma with 10% or more clonal plasma cells is considered multiple myeloma.
FLC = free light chain; Ig = immunoglobulin; MRI = magnetic resonance imaging.
Reproduced from Rajkumar SV, Dimopoulos MA, Palumbo A, et al. International Myeloma Working Group updated criteria for the diagnosis of multiple myeloma. *Lancet Oncol* 2014;15:e538-e548.

Association of MGUS with Other Diseases

MGUS is associated with numerous diseases. However, because 3% of the general population older than 50 years has MGUS, it is often difficult to determine whether these reported associations are causal or coincidental. Associations that have been verified based on epidemiologic studies include peripheral neuropathy (Chapter 388), proliferative glomerulonephritis, deep vein thrombosis (Chapter 68), osteoporosis (Chapter 225), and lymphoproliferative disorders (Chapter 171). A secondary form of MGUS also occurs with immunosuppression after organ transplantation (Chapter 38) and autologous or allogeneic stem cell transplantation (Chapter 163). M proteins also occur in the sera of some patients with CLL (Chapter 169) but have no recognizable effect on the clinical course.

Approximately 5% of patients with sensorimotor peripheral neuropathy of unknown cause (Chapter 388) have an associated monoclonal gammopathy (monoclonal gammopathy–associated peripheral neuropathy).[4] Patients with IgM MGUS–associated peripheral neuropathy have a slowly progressive distal acquired demyelinating symmetric (DADS) presentation, with predominantly sensory symptoms beginning in the distal ends of the extremities and extending proximally. In contrast, non-IgM MGUS neuropathy may present similar to chronic inflammatory demyelinating polyneuropathy (CIDP) with both proximal and distal involvement and with more motor symptoms. A causal relationship between MGUS and peripheral neuropathy is usually assumed in younger patients and those without other conditions known to cause neuropathy in whom the neuropathy is severe and progressive. Therapeutic approaches include intravenous immunoglobulin or rituximab for IgM monoclonal proteins and plasmapheresis or prednisone for non-IgM monoclonal proteins.

Monoclonal gammopathy is also felt to be the underlying cause of approximately 50% of idiopathic proliferative glomerulonephritis (Chapter 107), including membranoproliferative glomerulonephritis and C3 glomerulopathy. Certain skin disorders are also known to be associated with MGUS. Lichen myxedematosus (papular mucinosis, scleromyxedema) (Chapter 407) is associated with an IgG γ protein. Pyoderma gangrenosum and necrobiotic xanthogranuloma are other associated skin disorders.

TREATMENT

No treatment is necessary for MGUS (Fig. 173-3).[5] A baseline bone marrow biopsy and bone imaging can be omitted in patients who appear clinically to have low-risk, uncomplicated MGUS, small IgM MGUS, or light chain MGUS with a free light chain ratio less than 8. Bone imaging can also be omitted in patients who have IgM MGUS and in whom bone disease is not suspected. Low-risk patients (Table 173-3) should be evaluated in 6 months and, if stable, require no further follow-up until symptoms suggestive of myeloma or related disorders occur. In all other patients with MGUS, electrophoresis, serum free light chains, complete blood count, and creatinine and calcium levels should be repeated at 6 months and, if stable, yearly thereafter.

PROGNOSIS

Differentiating a patient with MGUS in whom the disorder will remain stable for life from one in whom multiple myeloma, macroglobulinemia, or a related disorder will eventually develop is difficult when the M protein is first recognized. The size and type of the M protein at diagnosis of MGUS and an abnormal serum free light chain ratio are prognostic factors for progression (see Table 173-3).[6] Overall, about one third of patients progress to a symptomatic monoclonal gammopathy over 10 or more years.[7]

BICLONAL GAMMOPATHIES

Biclonal gammopathies occur in at least 5% of patients with clonal plasma cell disorders. A biclonal gammopathy of undetermined significance (analogous to MGUS) accounts for about two thirds of such patients. The remainder have multiple myeloma, macroglobulinemia, or other lymphoproliferative diseases. Rarely, triclonal gammopathies may occur.

MULTIPLE MYELOMA

DEFINITION

Multiple myeloma is a malignancy of plasma cells characterized by bone marrow infiltration and extensive skeletal destruction resulting in anemia, bone pain, and fractures. Multiple myeloma (commonly referred to as *myeloma*) is defined by the presence of 10% or more clonal plasma cells on bone marrow examination, M protein in serum or urine (except in the case of nonsecretory myeloma), and evidence of one or more myeloma-defining events (see Table 173-2). Patients with multiple myeloma must be differentiated from those with MGUS and smoldering multiple myeloma.[8]

EPIDEMIOLOGY

Multiple myeloma accounts for 1% of all malignant disease and slightly more than 10% of hematologic malignancies in the United States. The annual

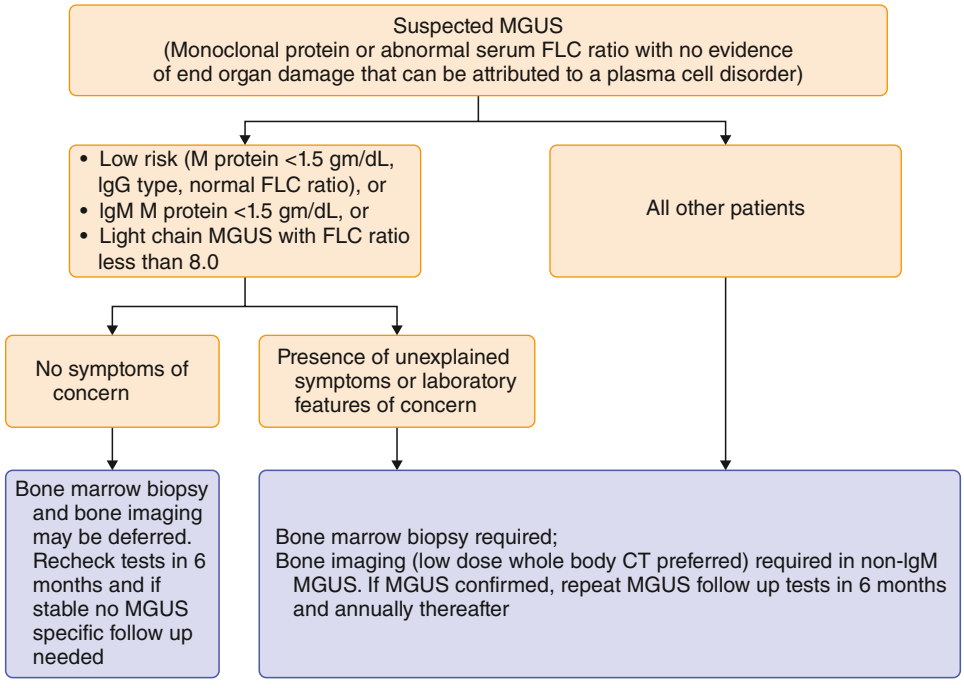

FIGURE 173-3. Approach to diagnosis and management of monoclonal gammopathy of undetermined significance. CT = computed tomography; FLC = free light chain ration; MGUS = monoclonal gammopathy of undermined significance.

TABLE 173-3 RISK OF PROGRESSION OF MONOCLONAL GAMMOPATHY OF UNDETERMINED SIGNIFICANCE TO MYELOMA OR RELATED DISORDERS

RISK GROUP	RELATIVE RISK	CUMULATIVE ABSOLUTE RISK OF PROGRESSION AT 20 YR (%)*	CUMULATIVE ABSOLUTE RISK OF PROGRESSION AT 20 YR ACCOUNTING FOR DEATH AS A COMPETING RISK (%)†
Low risk: serum M protein <1.5 g/dL, IgG subtype, normal free light chain ratio (0.26-1.65)	1	5	2
Low-intermediate risk: any one factor abnormal	5.4	21	10
High-intermediate risk: any two factors abnormal	10.1	37	18
High risk: all three factors abnormal	20.8	58	27

*Estimates in this column represent the risk of progression, assuming that patients do not die of other causes during this period.
†Estimates in this column represent the risk of progression calculated by using a model that accounts for the fact that patients can die of unrelated causes during this time.
Ig = immunoglobulin.
Adapted from Rajkumar SV, Kyle RA, Therneau TM, et al. Serum free light chain ratio is an independent risk factor for progression in monoclonal gammopathy of undetermined significance (MGUS). *Blood*. 2005;106:812-817.

incidence of multiple myeloma is approximately 4 per 100,000. The incidence of multiple myeloma in Blacks is almost twice that in Whites. Multiple myeloma is slightly more common in men than in women. The median age of patients at the time of diagnosis is about 65 years; only 2% of patients are younger than 40.

PATHOBIOLOGY

The cause of multiple myeloma is unclear. Exposure to radiation, benzene, and other organic solvents, herbicides, and insecticides may play a role. Multiple myeloma has been reported in familial clusters of two or more first-degree relatives and in identical twins.

Almost all cases of myeloma evolve from a premalignant MGUS phase, although the MGUS is clinically recognized before the diagnosis of myeloma in only a small minority of patients. The progression of MGUS to myeloma suggests a simple, random, two-hit genetic model of malignancy in which the risk of progression is fixed (approximately 1% per year) regardless of the duration of MGUS. Unfortunately, the precise mechanisms of progression are unknown, although several potentially pathogenetic abnormalities have been described in the clonal plasma cells. The two main events associated with progression of MGUS to multiple myeloma appear to be *RAS* mutations and *MYC* abnormalities. Deletions involving 17p and 1p and amplification of 1q occur with disease progression in multiple myeloma and are associated with adverse prognosis. These changes cause dysregulation of the NF-κB and other signaling pathways. Normal plasma cell differentiation is also affected. Changes in the bone marrow microenvironment likely play a major role in the pathogenesis, including induction of angiogenesis and abnormal paracrine loops involving cytokines such as interleukin-6 (IL-6), which serves as a major growth factor for plasma cells.

The lytic bone lesions, osteopenia, hypercalcemia, and pathologic fractures in patients with myeloma are a result of abnormal osteoclast activity induced by the neoplastic plasma cells, as well as inhibition of osteoblast differentiation. Osteoclasts are activated by stimulation of the transmembrane receptor RANK (receptor activator of nuclear factor κB), which belongs to the tumor necrosis factor (TNF) receptor superfamily. The ligand for this receptor (RANKL) also has a decoy receptor, osteoprotegerin (OPG). In myeloma, there is an increase in RANKL expression by osteoblasts (and possibly plasma cells), accompanied by a reduction in the level of OPG. The resultant increase in the RANKL/OPG ratio causes osteoclast activation and increased bone resorption and turnover (Chapter 225). Other factors that may play a role in osteoclast activation include increased levels of macrophage inflammatory protein–1-alpha (MIP-1-alpha), stromal derived factor alpha (SDF-alpha), IL (interleukin)-3, IL-1 beta, and IL-6. In addition to these changes that promote osteoclast activation, simultaneous suppression of osteoblasts is mediated by increased levels of IL-3, IL-7, and dickkopf 1 (DKK1). This combination leads to the pure osteolytic bone disease that is the hallmark of multiple myeloma.

Cytogenetic Abnormalities

As discussed earlier (see Pathobiology of MGUS), primary translocations involving the IgH loci (chromosome 14q32) are seen in up to 40% of patients with multiple myeloma (IgH-translocated or nonhyperdiploid myeloma). Approximately 40% of patients do not have IgH translocations but have evidence of trisomies (hyperdiploid myeloma), 15% have both IgH translocations and trisomies, and 5% have other abnormalities. Although IgH translocations and trisomies originate at the MGUS stage, the response to therapy and prognosis of myeloma are affected by the specific underlying abnormality (Table 173-4). Besides these primary cytogenetic abnormalities, other abnormalities (termed secondary cytogenetic abnormalities) occur as late events during the course of symptomatic myeloma; these include deletion of 17p, deletion of 1p, and amplification of 1q.

CLINICAL MANIFESTATIONS

Many patients are asymptomatic because they are detected early based on incidental laboratory testing. Smoldering (asymptomatic) multiple myeloma is defined by the presence of an M protein level greater than 3 g/dL in serum or 10 to 60% clonal plasma cells in bone marrow in the absence of anemia, renal insufficiency, hypercalcemia, or skeletal lesions. Clinically, patients with smoldering multiple myeloma are similar to patients who have MGUS but carry a much higher risk for progression to myeloma or a related malignancy: 10% per year for the first 5 years, 5% per year for the next 5 years, and 1 to 2% per year thereafter. Even patients who meet the full criteria for multiple myeloma may be asymptomatic and be detected only by an evaluation of laboratory abnormalities.

TABLE 173-4 STAGING AND PROGNOSTIC FACTORS IN MULTIPLE MYELOMA

STAGE/RISK FACTOR
Stage I (serum albumin >3.5, serum beta-2-microglobulin <3.5, no high-risk cytogenetics, and normal serum lactate dehydrogenase level)
Stage II (neither stage I nor stage III)
Stage III (serum beta-2-microglobulin >5.5 and either high-risk cytogenetics [t(4;14), t(14;16), or del(17p)] or elevated serum lactate dehydrogenase level)
High-risk myeloma (any one of the following): Translocations of t(14;16), t(14;20), t(4;14) Deletion of 17p Amplification of 1q p53 mutation
Standard-risk myeloma Translocations of t(11;14), t(6;14) Trisomies
Poor performance status
Increased circulating plasma cells
Plasmablastic morphology

History

Bone pain, particularly in the back or chest and less often in the extremities, is present at the time of diagnosis in more than two thirds of patients. The patient's height may be reduced by several inches because of vertebral collapse. Weakness and fatigue are common and are often associated with anemia. The incidence of infections is increased in patients with multiple myeloma. The propensity for infection results from impairment of the antibody response, deficiency of normal immunoglobulins, and neutropenia. Myeloma patients also have an increased risk of deep vein thrombosis, although some myeloma treatments (e.g., lenalidomide) may themselves cause thrombosis. Other symptoms may result from renal insufficiency, hypercalcemia, nephrotic syndrome, radiculopathy, or AL amyloidosis (Chapter 174).

Physical Examination

Pallor is the most frequent physical finding in patients with multiple myeloma. The liver is palpable in about 5% of patients and the spleen in only 1%. Tenderness may be noted at sites of bone involvement. Radiculopathy may be caused by spinal compression fractures. Occasionally, extramedullary plasmacytomas are palpable.

DIAGNOSIS

Laboratory Findings

A normocytic, normochromic anemia (Chapter 144) is present initially in approximately 75% of patients, but it eventually occurs in nearly every patient with multiple myeloma. Serum protein electrophoresis shows an M protein in 80% of patients. With the increased sensitivity of serum immunofixation, an M protein can be detected in 93% of patients. When these serum studies are combined with urine electrophoresis plus immunofixation, an M protein can be detected in 97% of patients with myeloma.[9] The serum free light chain assay is more convenient and can be used in place of urine studies in the diagnostic evaluation. The type of M protein is IgG in 52%, IgA in 21%, light chain only in 16%, IgD in 2%, and biclonal gammopathy in 2%; the light chain type is κ in 65% of cases and λ in 35%. In 3% of patients, no secreted M protein can be identified; these patients are considered to have nonsecretory myeloma.

In the bone marrow, clonal plasma cells account for greater than 10% of all nucleated cells in 96% of patients (Fig. 173-4 and E-Figs.173-4 and 173-5). In 4% of patients, bone marrow examination shows less than 10% plasma cells, even though the patient otherwise meets the criteria for myeloma; because bone marrow involvement in myeloma may be focal rather than diffuse, repeated bone marrow examinations or biopsy of a discrete bone or extramedullary lesion may be required. In most cases, the plasma cells in myeloma are cytoplasmic Ig^+, $CD38^+$, $CD45^-$, $CD138^+$, and CD 56^+. Only 20% express CD20. The clonality of the plasma cells is established using the κ/λ ratio by immunohistochemistry or flow cytometry (E-Fig. 173-6). The κ/λ ratio is abnormal in myeloma (either >4 : 1, indicating a clonal κ population, or <1 : 2, indicating a clonal λ population). This is helpful for differentiating monoclonal plasma cell proliferation in multiple myeloma from reactive plasmacytosis.

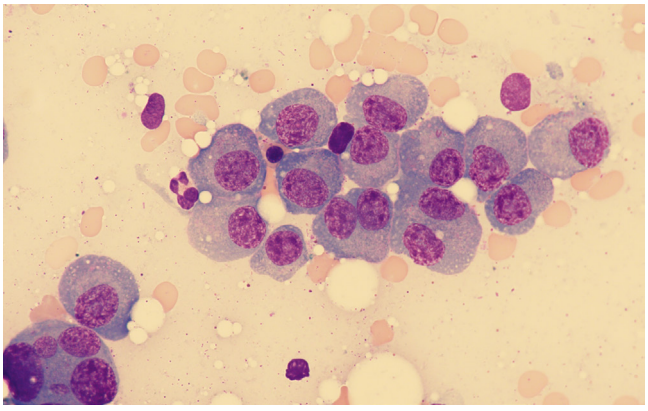

E-FIGURE 173-4. Wright-Giemsa stain of bone marrow aspirate at 600× magnification showing increased plasma cells in the bone marrow.

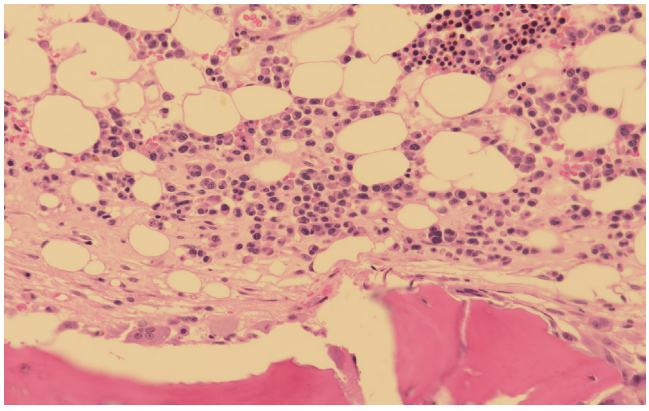

E-FIGURE 173-5. Bone marrow core biopsy. Hematoxylin-eosin stain at 200× magnification showing sheets of plasma cells.

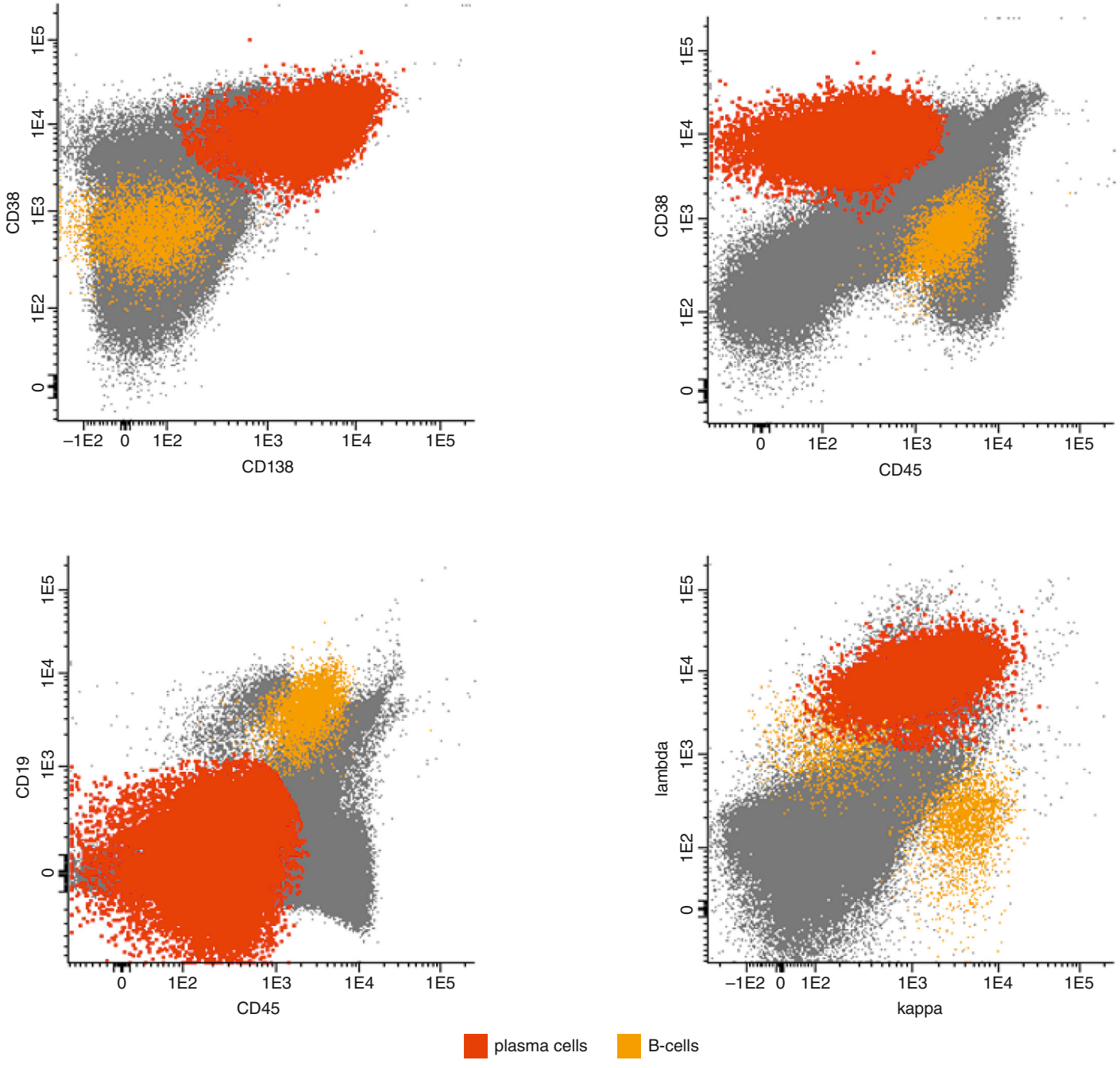

E-FIGURE 173-6. Flow cytometry of bone marrow in myeloma showing plasma cells that are CD38 and CD138 positive *(top left)*, CD38 positive and CD45 negative *(top right)*, CD19 and CD45 negative *(bottom left)*, and lambda positive and kappa negative *(bottom right)*.

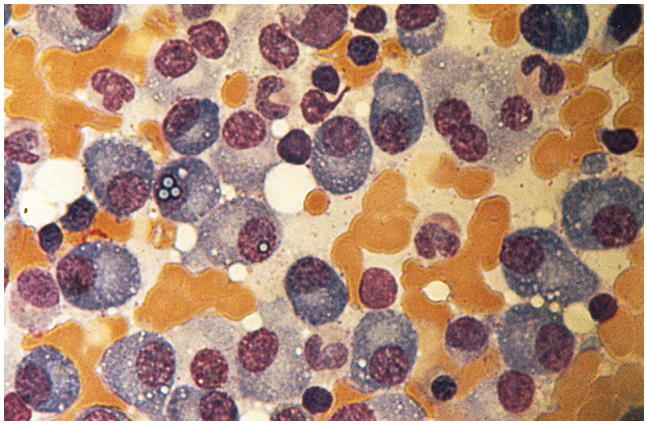

FIGURE 173-4. Multiple myeloma. A bone marrow aspirate shows a predominance of plasma cells.

FIGURE 173-5. Skull radiograph showing multiple lytic lesions.

Radiologic Findings

Conventional radiographic studies reveal abnormalities consisting of punched-out lytic lesions (Fig. 173-5), osteoporosis, or fractures in nearly 80% of patients. The vertebrae, skull, thoracic cage, pelvis, and proximal ends of the humerus and femur are the most frequent sites of involvement. Conventional radiographs are not sensitive, and low-dose whole body computed tomography and positron emission tomography (PET) are now the preferred imaging modalities to assess bone disease in multiple myeloma (Fig. 173-6).[10] Magnetic resonance imaging (MRI) is useful in patients in whom there is doubt about the magnitude of the disease burden and in those who have spinal involvement.

Organ Involvement

Renal

Renal insufficiency, defined as a creatinine level greater than 2 mg/dL, is observed in 20% of patients with multiple myeloma at diagnosis. The two major causes of renal insufficiency are light chain cast nephropathy *(myeloma kidney)* and hypercalcemia. Light chain cast nephropathy is characterized by the presence of large, waxy, laminated casts in the distal and collecting tubules. The casts are composed mainly of precipitated monoclonal light chains. The extent of cast formation correlates directly with the amount of free urinary light chain and with the severity of renal insufficiency. Hypercalcemia, which is present in 15 to 20% of patients initially, is a major and treatable cause of renal insufficiency. It results from destruction of bone. Other contributing factors include dehydration and hyperuricemia.

Besides light chain cast nephropathy and hypercalcemia, there are other mechanisms by which renal dysfunction can occur in myeloma and related plasma cell disorders. For example, light chain amyloidosis (Chapter 174) occurs in nearly 10% of patients with myeloma and may produce nephrotic syndrome, renal insufficiency, or both. Acquired Fanconi syndrome (Chapter 108), characterized by proximal tubular dysfunction, results in glycosuria, phosphaturia, and aminoaciduria. Deposition of monoclonal light chains in the renal glomerulus (light chain deposition disease) may also produce renal insufficiency and nephrotic syndrome. Monoclonal gammopathy–associated proliferative glomerulonephritis presents with hematuria and renal insufficiency.

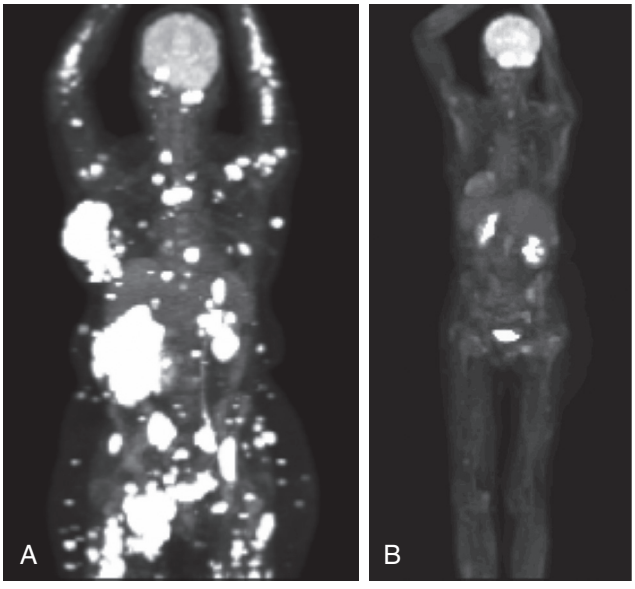

FIGURE 173-6. Positron emission tomography in multiple myeloma. A, Extensive bony and extramedullary disease. **B,** Significant improvement after systemic chemotherapy for myeloma.

Neurologic

Radiculopathy (Chapter 369), which is the single most frequent neurologic complication of multiple myeloma, usually occurs in the thoracic or lumbosacral area and results from compression of the nerve by the vertebral lesion or by the collapsed bone itself. Compression of the spinal cord occurs in up to 10% of patients. Peripheral neuropathy (Chapter 388) is uncommon in multiple myeloma and, when present, is generally caused by amyloidosis. Rarely, myeloma cells diffusely infiltrate the meninges. Intracranial plasmacytomas almost always represent extensions of myelomatous lesions of the skull. True involvement of the central nervous system is rare and is associated with poor prognosis.

Other Systemic Involvement

Hepatic infiltration, pleural effusions, or ascites suggests progression to plasma cell leukemia. Similarly the development of multiple extramedullary plasmacytomas is also a sign of more aggressive disease biology.

TREATMENT

Smoldering Multiple Myeloma

Treatment for patients with smoldering multiple myeloma depends on the risk of progression. Risk factors for progression include serum monoclonal protein greater than 2 gm/dL, serum free light chain ratio greater than 20, and bone marrow plasma cells greater than 20%. Patients with zero or one risk factor are considered to have low- or intermediate-risk smoldering multiple myeloma, respectively. Patients with two or three risk factors are considered to have high-risk smoldering multiple myeloma.[11]

Patients with low- or intermediate-risk smoldering multiple myeloma should not be treated until evidence of multiple myeloma develops (Fig. 173-7).[12,13] The standard of care for low- and intermediate-risk smoldering multiple myeloma is observation every 3 to 4 months. In patients with high-risk smoldering multiple myeloma, therapy for approximately 2 years with lenalidomide (25 mg on days 1 to 21 of a 28-day cycle) or with lenalidomide plus low-dose dexamethasone (40 mg once per week) can significantly reduce the risk of progression to symptomatic multiple myeloma, the development of end-organ damage,[A1] and overall mortality.[A2]

Multiple Myeloma

The approach to the treatment of multiple myeloma (Fig. 173-8) is increasingly targeted and personalized under expert supervision.[14] Response to therapy and minimal residual disease assessment is assessed using standard International

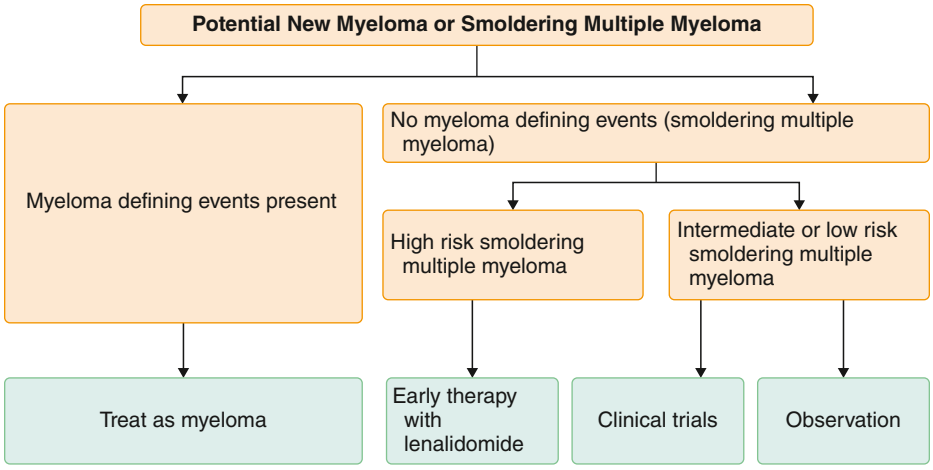

FIGURE 173-7. **Approach to the management of smoldering multiple myeloma.**

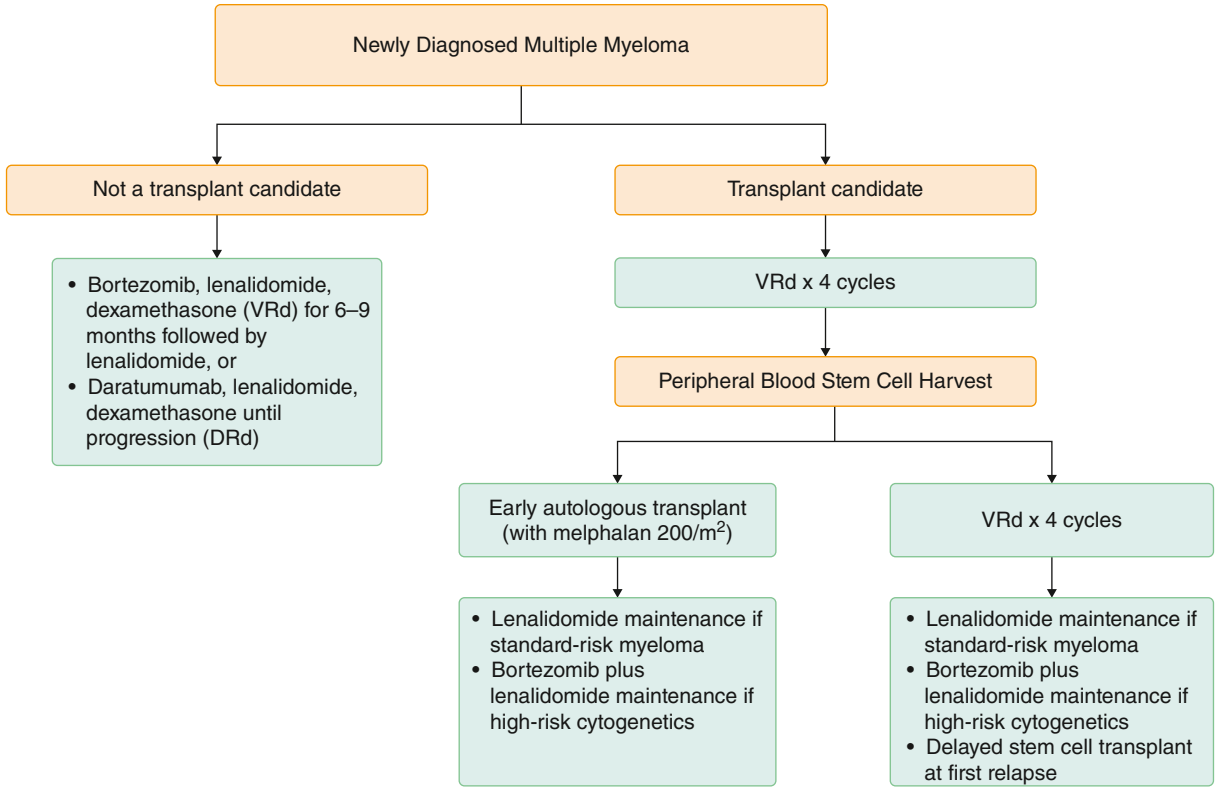

FIGURE 173-8. **Approach to newly diagnosed multiple myeloma.** DRd = daratumumab, lenalidomide, and dexamethasone; VRd = bortezomib-lenalidomide-dexamethasone.

Myeloma Working Group criteria.[15] Although achieving a minimal residual disease-negative state is associated with better survival, therapy usually is not changed based on the presence of minimal residual disease.

Initial Therapy of Patients Who Are Candidates for Autologous Stem Cell Transplantation

In the approximately 50% of patients with newly diagnosed multiple myeloma who are considered candidates for autologous stem cell transplantation based on good performance status, no or limited comorbid conditions, and younger physiologic age (<65 to 70 years), autologous peripheral blood stem cell transplantation (Chapter 163) with high-dose chemotherapy improves overall survival in comparison to conventional chemotherapy. Autologous transplantation is not curative, but it prolongs event-free and overall survival.[16]

Initial therapy typically consists of bortezomib, lenalidomide, and dexamethasone (VRd) for approximately 3 to 4 months followed by stem cell collection,[A3] but adding daratumumab may provide even better results[A4,A5] and can be considered in patients with high-risk myeloma. Alternative induction regimens include the combination of daratumumab, lenalidomide, and dexamethasone (DRd)[A6] or the combination of bortezomib, cyclophosphamide, and dexamethasone (VCD) (Table 173-5). Lenalidomide plus low-dose dexamethasone (40 mg once a week) is associated with superior overall survival compared with lenalidomide and high-dose dexamethasone (40 mg on days 1 to 4, 9 to 12, and 17 to 20). Toxicities of lenalidomide include deep vein thrombosis, and all patients must be treated with prophylactic aspirin or an anticoagulant.

After induction therapy, peripheral blood stem cells adequate for one to two stem cell transplants are collected with the use of granulocyte colony-stimulating factor with or without plerixafor or cyclophosphamide to aid in mobilization. Autologous stem cell transplantation (Chapter 163) is performed with melphalan 200 mg/m^2 as the conditioning regimen, followed by infusion of peripheral blood stem cells.

Early stem cell transplantation is often preferred[A7] because its mortality is low (<1%), and it avoids the inconvenience, cost, and potential side effects of prolonged chemotherapy. However, an equally good alternative approach in patients with standard-risk newly diagnosed myeloma is to delay transplantation until the first relapse.[A8] With this latter strategy, stem cells are collected and cryopreserved for future use after initial therapy. Patients then continue

TABLE 173-5 SELECTED REGIMENS FOR THE TREATMENT OF MULTIPLE MYELOMA

REGIMEN	USUAL DOSING SCHEDULE*
Bortezomib-cyclophosphamide-dexamethasone (VCd or CyBord)	Cyclophosphamide 300 mg/m^2 orally on days 1, 8, 15 and 22 Bortezomib 1.3 mg/m^2 intravenously on days 1, 8, 15, 22 Dexamethasone 40 mg orally on days on days 1, 8, 15, 22 Repeated every 4 wk
Bortezomib-lenalidomide-dexamethasone (VRd)	Bortezomib 1.3 mg/m^2 intravenous days 1, 8, 15 Lenalidomide 25 mg oral days 1-14 Dexamethasone 20 mg on day of and day after bortezomib (or 40 mg days 1, 8, 15, 22) Repeated every 3 wk
Carfilzomib-lenalidomide-dexamethasone (KRd)	Carfilzomib 20 mg/m^2 on cycle 1 and 27 mg/m^2 on subsequent cycles, intravenously on days 1, 2, 8, 9, 15, 16 Lenalidomide 25 mg oral days 1-21 Dexamethasone 20 mg on day of and day after bortezomib (or 40 mg days 1, 8, 15, 22) Repeated every 4 wk
Daratumumab-lenalidomide-dexamethasone (DRd)	Daratumumab 16 mg/kg intravenously weekly for 8 wk, and then every 2 wk for 4 mo, and then once monthly Lenalidomide 25 mg oral days 1-21 Dexamethasone 40 mg days 1, 8, 15, 22 Lenalidomide-dexamethasone repeated in usual schedule every 4 wk
Daratumumab-bortezomib-lenalidomide-dexamethasone (DVRd)	Daratumumab 16 mg/kg intravenously weekly × 8 wk, and then every 2 wk for 4 mo, and then once monthly Bortezomib 1.3 mg/m^2 intravenous days 1, 8, 15 Lenalidomide 25 mg oral days 1-14 Dexamethasone 40 mg days 1, 8, 15, 22 Bortezomib, lenalidomide, dexamethasone repeated every 3 wk
Elotuzumab-lenalidomide-dexamethasone (ERd)	Elotuzumab 10 mg/kg intravenously weekly × 8 wk, and then every 2 wk Lenalidomide 25 mg oral days 1-21 Dexamethasone 40 mg days 1, 8, 15, 22 Lenalidomide-dexamethasone repeated in usual schedule every 4 wk
Ixazomib-lenalidomide-dexamethasone (IRd)	Ixazomib 4 mg oral days 1, 8, 15 Lenalidomide 25 mg oral days 1-21 Dexamethasone 40 mg days 1, 8, 15, 22 Repeated every 4 wk
Daratumumab-bortezomib-dexamethasone (DVd)	Daratumumab 16 mg/kg intravenously weekly × 8 wk, and then every 2 wk for 4 mo, and then once monthly Bortezomib 1.3 mg/m^2 subcutaneously on days 1, 8, 15, 22 Dexamethasone 20 mg on day of and day after bortezomib or 40 mg days 1, 8, 15, 22 Bortezomib-dexamethasone repeated in usual schedule every 4 wk

*All doses need to be adjusted for performance status, renal function, blood counts, and other toxicities; doses of dexamethasone and/or bortezomib recommended have been reduced based on subsequent data showing lower toxicity and similar efficacy with reduced doses. Daratumumab can be given using a subcutaneous formulation instead of the intravenous route. Duration of therapy for all regimens varies under expert supervision depending on the disease phase.

Modified from Rajkumar SV. Multiple myeloma: 2020 update on diagnosis, risk-stratification, and management. *Am J Hematol*. 2020;95:548-567.

initial therapy for a few more months, followed by maintenance. Delayed stem cell transplantation is performed at the time of first relapse. The choice of early versus delayed transplantation is usually based on the patient's preferences and other clinical conditions, but early transplantation is often recommended.

Following stem cell transplantation, the long-term outcome is improved by lenalidomide maintenance (10 mg per day). In high-risk multiple myeloma, bortezomib maintenance is administered every 2 weeks in combination with lenalidomide (see Table 173-4 for definitions of standard and high-risk myeloma).

Allogeneic Bone Marrow Transplantation

Allogeneic transplantation for myeloma is best performed in the context of clinical trials or as second-line salvage therapy in selected high-risk patients who are willing to accept the high treatment-related mortality rate associated with the procedure.[17]

Initial Therapy of Patients Who Are Not Candidates for Transplantation

Approximately 50% of newly diagnosed patients are not considered candidates for stem cell transplantation either due to advanced age, poor performance status, or associated comorbidities. Initial therapy consists of either bortezomib/lenalidomide/dexamethasone (VRd) for approximately 9 months followed by lenalidomide maintenance, or daratumumab/lenalidomide/dexamethasone (DRd) given until disease progression. Ixazomib/lenalidomide/dexamethasone is used occasionally for high-risk patients who are unable to access parenteral therapy.[A9] Bortezomib/cyclophosphamide/dexamethasone (VCd) can be used as an alternative if lenalidomide is not available or in the setting of severe renal failure.

Treatment of Relapsed Refractory Myeloma

Almost all patients with multiple myeloma eventually relapse. The general goal is to select a regimen that contains more than two drugs that the patient has not received or to which the disease is or has become refractory. The duration of remission in relapsed multiple myeloma decreases with each regimen. All of the active agents discussed here can be used alone and in combination under expert supervision for the treatment of relapsed multiple myeloma.

The approach to therapy at relapse is complex, and a number of factors must be considered, including response to prior therapy, duration of prior remission, aggressiveness of the relapse, and eligibility for stem cell transplantation.[18] In general, if relapse occurs more than 6 months after stopping therapy, reinstitution of the initial chemotherapy regimen is reasonable. If patients have elected to undergo delayed transplant, then autologous transplantation should be considered. Similarly, eligible patients who have had a reasonable response to a prior autologous transplantation (>18 months without maintenance therapy or >36 months with maintenance therapy) may be considered for a second transplantation. In most patients, one of the triplet regimens (see Table 173-5) is used for the treatment of relapse, with each subsequent relapse treated with sequential regimens that contain drugs that are different than the ones used before. Patients with relapsed refractory myeloma should also be considered for clinical trials.

Specific Options for Relapsed Multiple Myeloma

Thalidomide, lenalidomide, and pomalidomide are closely related immunomodulatory drugs that form the backbone of numerous myeloma treatment regimens. Lenalidomide is better tolerated than thalidomide and has proven efficacy in relapsed myeloma. The starting dose of lenalidomide is 25 mg orally on days 1 to 21, every 28 days. Pomalidomide is a newer, more potent analogue of lenalidomide. All three drugs are associated with a risk of deep vein thrombosis, and therefore routine antithrombotic prophylaxis is needed.

Bortezomib, which is a selective proteasome inhibitor, is useful in relapsed multiple myeloma. The usual dose is 1.3 mg/m^2 administered subcutaneously on days 1, 8, 15, and 22 every 28 days. The once-weekly subcutaneous dosing is associated with significantly lower neuropathy than the twice-weekly intravenous schedule. The most common adverse events are gastrointestinal side effects, fatigue, and neuropathy. Newer proteasome inhibitors that have since been found to be effective in myeloma include carfilzomib and ixazomib.[A10,A11]

Both daratumumab and isatuximab (both of which target CD38) as well as elotuzumab (targeting SLAMF7) are monoclonal antibodies that are effective in the treatment of relapsed multiple myeloma.[A12–A14] Daratumumab can be

administered subcutaneously instead of intravenously without loss of efficacy and is better tolerated.[A15] Several triplet regimens using these agents have been developed for use in relapsed multiple myeloma.

Newer options for the treatment of relapsed refractory myeloma are teclistamab (bispecific antibody),[19] idecabtagene vicleucel (ide-cel; chimeric antigen receptor T [CAR-T] cell therapy),[20] and ciltacabtagene autoleucel (cilta-cel, which is another CAR-T product).[A16] These approaches target the B-cell maturation antigen that is almost universally expressed on the surface of plasma cells. The major toxicity with bispecific antibody and CAR-T therapies are cytokine release syndromes and neurologic complications. Venetoclax (a bcl-2 inhibitor) has significant activity against the t(11;14) subtype of myeloma but is not recommended in other cytogenetic types due to an adverse effect on overall survival.[A17] Other less commonly used options for relapsed myeloma include bendamustine and selinexor (exportin-1 inhibitor).[A18] In addition, traditional chemotherapeutic agents such as doxorubicin are also of benefit in selected patients. Promising investigational agents include newer bispecific antibodies (such as elranatamab, cevostamab, and talquetamab)[21] that target specific antigens expressed on myeloma cells.[22]

Role of Radiation Therapy

Palliative radiation in a dose of 20 to 30 Gy should be limited to patients who have multiple myeloma with disabling pain and a well-defined focal process that has not responded to chemotherapy and to patients with spinal cord compression from a plasmacytoma. Analgesics in combination with chemotherapy can usually control the pain (Chapter 26).

Management of Complications

Hypercalcemia

Hypercalcemia, which is present in 15 to 20% of patients at diagnosis, should be suspected in patients who have anorexia, nausea, vomiting, polyuria, polydipsia, constipation, weakness, confusion, or stupor. If hypercalcemia is untreated, renal insufficiency may develop. Hydration, steroids, and bisphosphonates (zoledronic acid or pamidronate) are recommended and will correct hypercalcemia in almost all patients (Chapter 227).

Renal Insufficiency

The most common cause of acute renal failure is light chain cast nephropathy in patients who have excess excretion of monoclonal protein in urine (myeloma kidney). Aggressive treatment of acute renal failure due to light chain cast nephropathy is critical for long-term overall survival. If the patient is not oliguric, intravenous fluids and furosemide are needed to maintain a high urine flow rate (100 mL/hour). Allopurinol (300 mg daily) is necessary if hyperuricemia is present. If the underlying cause is thought to be light chain cast nephropathy based on clinical findings (e.g., serum free light chains >150 mg/dL) or renal biopsy, plasmapheresis is recommended daily for 5 days to reduce the levels of circulating light chains.[23] Hemodialysis is necessary for symptomatic azotemia. The mainstay of therapy is aggressive treatment of myeloma with a combination regimen such as bortezomib/cyclophosphamide/dexamethasone or daratumumab/bortezomib/cyclophosphamide/dexamethasone or bortezomib/thalidomide/dexamethasone under expert oversight.

Infection

Prompt, appropriate therapy for bacterial infections is necessary. Prophylactic antibiotics such as trimethoprim-sulfamethoxazole should be considered in patients taking high-dose corticosteroids.[24] Acyclovir should be given as prophylaxis against herpes zoster in patients receiving bortezomib. Intravenously administered immunoglobulin is reserved for patients with hypogammaglobulinemia and recurrent severe infections. Pneumococcal and influenza immunizations (Chapter 15) should be given to all patients. COVID vaccination (Chapter 337) is recommended for all patients, and booster doses should also be given as needed.

Skeletal Lesions

Patients should be encouraged to be as active as possible but to avoid trauma. Zoledronic acid (4 mg intravenously over at least 15 minutes every 4 weeks) or pamidronate (90 mg infused intravenously over a 4-hour period every 4 weeks) is recommended for all patients with myeloma bone disease. These agents reduce the incidence of bone pain, pathologic fractures, and spinal cord compression and may improve overall survival. After 1 to 2 years the dosing can be reduced to once every 3 months in patients who are stable to minimize the risk of osteonecrosis of the jaw, which is a complication of long-term bisphosphonate therapy. Denosumab is an alternative agent that can be used in patients who are unable to tolerate zoledronic acid or pamidronate. Kyphoplasty is useful in selected patients with vertebral fractures.

Spinal cord compression from an extramedullary plasmacytoma (Chapter 369) should be suspected in patients who have severe back pain, weakness or paresthesia of the lower extremities, or bladder or bowel dysfunction. Initial treatment is with dexamethasone-based therapy and/or radiation therapy. If the neurologic deficit increases, surgical decompression is necessary.

Miscellaneous Complications

Symptomatic hyperviscosity (see later) is less common than in Waldenström macroglobulinemia. Anemia that persists despite adequate treatment of underlying myeloma often responds to erythropoietin (Chapter 144).

PROGNOSIS

Multiple myeloma is considered incurable at present, but survival has improved significantly in recent years. The median survival is approximately 6 to 7 years in patients who are older than age 65 years, and approximately 12 years in patients who are less than age 65 years and who are eligible for stem cell transplantation, but it varies widely according to clinical stage and risk stratification factors (Table 173-4). In some patients, an acute or aggressive terminal phase is characterized by rapid tumor growth, pancytopenia, soft tissue subcutaneous masses, decreased M protein levels, and fever; survival in this subset is generally limited to a few months.

VARIANT FORMS OF MULTIPLE MYELOMA

PLASMA CELL LEUKEMIA

Patients who have multiple myeloma with more than 5% plasma cells in the peripheral blood differential count and/or an absolute plasma cell count of 500/μL or greater are considered to have plasma cell leukemia.[25] Plasma cell leukemia is classified as primary when it is diagnosed in the leukemic phase (60%) or as secondary when there is leukemic transformation of a previously recognized multiple myeloma (40%). Patients with primary plasma cell leukemia are younger and have a greater incidence of hepatosplenomegaly and lymphadenopathy, a higher platelet count, fewer bone lesions, a smaller serum M protein component, and better survival than do patients with secondary plasma cell leukemia.

TREATMENT AND PROGNOSIS

Current treatments are generally unsatisfactory. An aggressive initial treatment regimen under expert supervision is a reasonable strategy. Options include bortezomib/dexamethasone/thalidomide/cisplatin/doxorubicin/cyclophosphamide/etoposide (VDT-PACE) or daratumumab plus bortezomib/lenalidomide/dexamethasone, followed by autologous stem cell transplantation and subsequent maintenance therapy with bortezomib plus lenalidomide. Nonetheless, the prognosis of primary plasma cell leukemia is significantly worse than high-risk multiple myeloma.

NONSECRETORY MYELOMA

Patients with nonsecretory myeloma have no M protein in either serum or urine and account for only 3% of cases of myeloma. To establish the diagnosis, the clonal nature of bone marrow plasma cells should be confirmed by immunoperoxidase, immunofluorescence, or flow cytometric methods. Treatment and survival are similar to those in patients with typical myeloma. The serum free light chain assay is abnormal in more than 60% of patients and can be used to monitor the response to therapy.

OSTEOSCLEROTIC MYELOMA (POEMS SYNDROME)

Osteosclerotic myeloma is characterized by polyneuropathy, organomegaly, endocrinopathy, M protein, and skin changes (POEMS).[26] Almost all patients have a λ-type M protein. The major clinical features are a chronic inflammatory-demyelinating polyneuropathy with predominantly motor disability and sclerotic skeletal lesions. The bone marrow usually contains less than 5% plasma cells, and hypercalcemia and renal insufficiency rarely occur. The diagnosis is confirmed by identification of monoclonal plasma cells obtained at biopsy of an osteosclerotic lesion.

If the lesions are in a limited area, radiation therapy substantially improves the neuropathy in more than 50% of patients. If the patient has widespread osteosclerotic lesions, treatment is with autologous stem cell transplantation or other systemic therapy similar to that used for myeloma.[27]

SOLITARY PLASMACYTOMA (SOLITARY MYELOMA) OF BONE

The diagnosis of solitary bone plasmacytoma is based on histologic evidence of a solitary tumor consisting of monoclonal plasma cells identical to those in multiple myeloma. In addition, PET-CT (or whole body CT) or MRI of the spine and pelvis must show no other lesions of myeloma, and the bone marrow aspirate must contain no evidence of clonal plasma cells. An M protein may be present in serum or urine at diagnosis, but persistence of the M protein after radiation therapy is associated with an increased risk for progression to

multiple myeloma. Treatment consists of radiation in the range of 40 to 50 Gy. Patients with an apparent solitary plasmacytoma who have limited (<10%) clonal marrow involvement are considered to have solitary plasmacytoma with minimal marrow involvement (Table 173-2). The risk of recurrence or progression to multiple myeloma within 3 years is approximately 10% in patients with solitary plasmacytoma versus 60% in patients with solitary plasmacytoma and minimal marrow involvement.

EXTRAMEDULLARY PLASMACYTOMA

Extramedullary plasmacytomas outside the bone marrow are most commonly found in the upper respiratory tract (80% of cases), especially in the nasal cavity and sinuses, nasopharynx, and larynx. Extramedullary plasmacytomas may also occur in the gastrointestinal tract, central nervous system, urinary bladder, thyroid, breast, testes, parotid gland, or lymph nodes. Extramedullary plasmacytomas may be solitary,[28] or they may occur in the context of existing myeloma. The diagnosis of solitary extramedullary plasmacytoma is based on detection of a plasma cell tumor in an extramedullary site, absence of clonal plasma cells on bone marrow examination, and absence of other bony or extramedullary lesions on radiographic studies. Treatment of solitary extramedullary plasmacytoma consists of either complete surgical resection or tumoricidal irradiation. The plasmacytoma may recur locally, metastasize to regional nodes, or, rarely, develop into multiple myeloma. Prognosis is generally better in patients with solitary extramedullary plasmacytoma, compared with solitary bony plasmacytoma.

WALDENSTRÖM MACROGLOBULINEMIA (PRIMARY MACROGLOBULINEMIA)

Waldenström macroglobulinemia is the result of the uncontrolled proliferation of lymphocytes and plasma cells in which an IgM M protein is produced. The median age of patients at the time of diagnosis is about 65 years, and approximately 60% are male. The cause is unknown, but familial clusters have been reported. A recurrent mutation of the *MYD88* gene (*MYD88 L265P*) is present in most patients with Waldenström macroglobulinemia and is thought to be relatively specific for this disease.

CLINICAL MANIFESTATIONS

Weakness, fatigue, and bleeding (especially oozing from the oronasal area) are common initial symptoms. Blurred or impaired vision, dyspnea, weight loss, neurologic symptoms, recurrent infections, and heart failure may occur. In contrast to multiple myeloma, lytic bone lesions, renal insufficiency, and amyloidosis are rare. Physical findings include pallor, hepatosplenomegaly, and lymphadenopathy. Retinal hemorrhages, exudates, and venous congestion with vascular segmentation ("sausage" formation) may occur. Sensorimotor peripheral neuropathy is common. Pulmonary involvement is manifested by diffuse pulmonary infiltrates and isolated masses.

Laboratory Evaluation

Almost all patients have moderate to severe normocytic, normochromic anemia. The serum electrophoretic pattern is characterized by a tall, narrow peak or dense band that is of the IgM type on immunofixation. Quantitative IgM levels are high. A monoclonal light chain is detected in the urine of 80% of patients, but the amount of urinary protein is generally modest.

The bone marrow aspirate is often hypocellular, but the biopsy is hypercellular and extensively infiltrated with lymphoid cells and plasma cells or lymphoplasmacytic cells. The number of mast cells is frequently increased. Rouleaux formation is prominent (Chapter 143), and the sedimentation rate is markedly increased. About 10% of cases may have an associated type I cryoglobulinemia (see later).

DIAGNOSIS

Diagnosis requires the combination of typical symptoms and physical findings, the presence of an IgM M protein, and 10% or greater lymphoplasmacytic infiltration of the bone marrow.[29]

Diagnostic Criteria and Differential Diagnosis

The diagnostic criteria are IgM monoclonal gammopathy (regardless of the size of the M protein), 10% or greater bone marrow infiltration (usually intertrabecular) by clonal lymphocytes that exhibit plasmacytoid or plasma cell differentiation, and a typical immunophenotype (e.g., surface IgM$^+$, CD5$^{+/-}$, CD10$^-$, CD19$^+$, CD20$^+$, CD23$^-$) that would satisfactorily exclude other lymphoproliferative disorders, including CLL (Chapter 169) and mantle cell lymphoma (Chapter 171).

Patients who meet the diagnostic criteria for Waldenström macroglobulinemia but who have less than 3 g/dL IgM protein at diagnosis have sometimes been classified as having "lymphoplasmacytic lymphoma with an IgM M protein" (Chapter 171). However, except for hyperviscosity, the clinical picture, therapy, and prognosis for these patients do not differ from those of patients with an IgM level of 3 g/dL or greater; thus, these patients are also considered to have Waldenström macroglobulinemia by the current definition.

Asymptomatic patients with 10% or greater lymphoplasmacytic infiltration of the bone marrow are considered to have smoldering Waldenström macroglobulinemia. Multiple myeloma, CLL, and MGUS of the IgM type must be excluded.

TREATMENT AND PROGNOSIS

Patients should not be treated unless they have anemia; constitutional symptoms such as weakness, fatigue, night sweats, or weight loss; hyperviscosity; or significant hepatosplenomegaly or lymphadenopathy. The most common regimens used as front-line therapy are the combination of ibrutinib plus rituximab,[A19] bendamustine plus rituximab, or dexamethasone/rituximab/cyclophosphamide.[30]

For relapse, the agents used as initial therapy can be given alone or in combination. Zanubrutinib, which is a more selective Bruton tyrosine kinase inhibitor, has comparable activity to ibrutinib and may be better tolerated.[A20] Autologous stem cell transplantation can be considered for eligible patients with relapsed disease. Other options under expert supervision include venetoclax, cladribine, or fludarabine (with or without rituximab); lenalidomide-based or bortezomib-based regimens; and other regimens used in the treatment of non-Hodgkin lymphoma (Chapter 171).

Spuriously low hemoglobin and hematocrit levels may occur because of the increased plasma volume from the large amount of intravascular M protein. Symptomatic hyperviscosity should be treated by plasmapheresis. The median survival of patients with macroglobulinemia is in excess of 5 to 7 years.

HYPERVISCOSITY SYNDROME

Hyperviscosity syndrome occurs when patients with Waldenström macroglobulinemia have high levels of serum IgM M protein (>5 g/dL) and occasionally in those with myeloma, especially of the IgA type. For any given level of paraprotein, IgM or IgA is more likely than IgG to cause hyperviscosity because the former circulate as pentamers or dimers, respectively, in contrast to monomeric IgG. Chronic nasal bleeding and oozing from the gums are the most frequent symptoms of hyperviscosity, but postsurgical or gastrointestinal bleeding may also occur. Retinal hemorrhages are common, and venous congestion with sausage-like segmentation and papilledema may be seen (Fig. 173-9). The patient occasionally complains of blurring or loss of vision. Dizziness, headache, vertigo, nystagmus, decreased hearing, ataxia, paresthesias, diplopia, somnolence, and coma may occur. Hyperviscosity can precipitate or exacerbate heart failure. Most patients have symptoms when the relative viscosity is greater than 4 cP, but the relationship between serum viscosity and clinical manifestations is not precise.

TREATMENT

Patients with symptomatic hyperviscosity should be treated with plasmapheresis and with chemotherapy to treat the underlying malignancy. Plasma exchange of 3 to 4 L with albumin should be performed daily until the patient is asymptomatic. Plasma exchange is rapidly effective (two to three exchanges) for IgM M proteins, which are primarily intravascular. For IgG M proteins, however, multiple attempts may be needed because a significant amount of IgG can exist in the extravascular space.

HEAVY CHAIN DISEASES

The heavy chain diseases are characterized by the presence of an M protein consisting of a portion of the immunoglobulin heavy chain in serum, urine, or both. These heavy chains are devoid of light chains and represent a lymphoplasma cell proliferative process. The three major types are γ-heavy chain disease, α-heavy chain disease, and μ-heavy chain disease.

γ-HEAVY CHAIN DISEASE

Patients with γ-heavy chain disease often initially have a lymphoma-like illness, but the clinical findings are diverse and range from an aggressive

FIGURE 173-9. Hyperviscosity syndrome. Right eye retinal image in a patient with Waldenström macroglobulinemia and hyperviscosity syndrome showing sausaging (focal venular dilations), intraretinal hemorrhages, microaneurysms, and peripapillary cotton-wool spots and disc swelling (papilledema).

lymphoproliferative process to an asymptomatic state. Hepatosplenomegaly and lymphadenopathy occur in about 60% of patients. Anemia is found in approximately 80% initially and in nearly all eventually. The electrophoretic pattern often shows a broad-based band more suggestive of a polyclonal increase than an M protein. The diagnosis depends on the identification of an isolated monoclonal γ-heavy chain on serum immunofixation, without evidence of either monoclonal κ or λ light chain expression.

TREATMENT AND PROGNOSIS

Treatment is indicated only for symptomatic patients and consists of chemotherapy with regimens used to treat non-Hodgkin lymphoma (Chapter 171), such as cyclophosphamide, vincristine, and prednisone. The prognosis of γ-heavy chain disease is variable and ranges from a rapidly progressive downhill course of a few weeks' duration to the asymptomatic presence of a stable monoclonal heavy chain in serum or urine.

α-HEAVY CHAIN DISEASE

α-Heavy chain disease, which is the most common form of heavy chain disease, occurs in patients from the Mediterranean region or the Middle East, generally in the second or third decade of life. About 60% of patients with α-heavy chain disease are men. Most commonly the gastrointestinal tract is involved, and severe malabsorption with diarrhea, steatorrhea, and weight loss is noted (Chapter 126). Plasma cell infiltration of the jejunal mucosa is the most frequent pathologic feature. Immunoproliferative small intestinal disease is restricted to patients with small intestinal lesions who have the pathologic features of α-heavy chain disease but do not synthesize α-heavy chains.

The serum protein electrophoretic pattern is normal in about 50% of cases. In the remainder, an unimpressive broad band may appear in the α_2 or β region. The diagnosis depends on identification of an isolated monoclonal α-heavy chain on serum immunofixation, without evidence of either monoclonal κ or λ light chain expression. The amount of α-heavy chain in urine is small.

TREATMENT AND PROGNOSIS

In the absence of therapy, α-heavy chain disease is typically progressive and fatal. The usual treatment consists of antibiotics, such as tetracyclines, and the eradication of any concurrent parasitic infection. Patients who do not respond adequately to antibiotics are given chemotherapy similar to that used to treat non-Hodgkin lymphoma, for example, the cyclophosphamide, hydroxydaunomycin, vincristine (Oncovin), and prednisone (CHOP) regimen (Chapter 171).

FIGURE 173-10. Skin infarction in cryoglobulinemia. The skin has a reticulated pattern as a result of leakage of red blood cells from damaged skin capillaries. Necrosis and ulceration have occurred in peripheral sites because of vessel blockage. This patient eventually required plastic surgery. (From Forbes CD, Jackson WF. *Color Atlas and Text of Clinical Medicine*, 3rd ed. London: Mosby; 2003.)

μ-HEAVY CHAIN DISEASE

μ-Heavy chain disease disease is characterized by the demonstration of an isolated monoclonal μ-chain fragment on serum immunofixation, without evidence of either monoclonal κ or λ light chain expression. The serum protein electrophoretic pattern is usually normal, except for hypogammaglobulinemia. Bence Jones proteinuria is found in two thirds of cases. Lymphocytes, plasma cells, and lymphoplasmacytoid cells are increased in the bone marrow. Vacuolization of the plasma cells is common and should suggest the possibility of heavy chain disease.

TREATMENT AND PROGNOSIS

Treatment is with corticosteroids and alkylating agents. The course of μ-heavy chain disease is variable, and survival ranges from a few months to many years.

CRYOGLOBULINEMIA

Cryoglobulins are plasma proteins that precipitate when cooled and dissolve when heated. They are designated as idiopathic or essential when they are not associated with any recognizable disease. Cryoglobulins are classified into three types: type I (monoclonal), type II (mixed monoclonal plus polyclonal), and type III (polyclonal).[31]

TYPE I CRYOGLOBULINEMIA

Type I (monoclonal) cryoglobulinemia is most commonly of the IgM or IgG class, but IgA and Bence Jones cryoglobulins have been reported. Most patients, even with large amounts of type I cryoglobulin, are completely asymptomatic from this source. Others with monoclonal cryoglobulins in the range of 1 to 2 g/dL may have evidence of vasculitis with pain, purpura, Raynaud phenomenon, cyanosis, and even ulceration and sloughing of skin and subcutaneous tissue (Fig. 173-10) on exposure to cold because their cryoglobulins precipitate at relatively high temperatures. Type I cryoglobulins are associated with macroglobulinemia, multiple myeloma, or MGUS.

TREATMENT

Therapy for patients with symptomatic type I cryoglobulinemia and significant symptoms is similar to that for Waldenström macroglobulinemia for the IgM type and multiple myeloma for the non-IgM type.

TYPE II CRYOGLOBULINEMIA

Type II (mixed) cryoglobulinemia typically consists of an immune complex of IgM M protein and polyclonal IgG, although monoclonal IgG or monoclonal IgA may also be seen with polyclonal IgM. Serum protein electrophoresis generally shows a normal pattern or a diffuse, polyclonal hypergammaglobulinemic pattern. The quantity of mixed cryoglobulin is usually less than 0.2 g/dL. Despite the monoclonal component, most patients do not have a clonal plasma cell disorder; rather, they have serologic evidence of infection with

hepatitis C virus (Chapter 135). At present, hepatitis C is thought to be the cause of most cases of type II cryoglobulinemia.

Most clinical manifestations are related to the development of vasculitis and include palpable purpura, livedo reticularis, polyarthralgias, and neuropathy. Involvement of the joints is symmetrical, but joint deformities rarely develop. Raynaud phenomenon, necrosis of the skin, and neurologic involvement may be present. In almost 80% of renal biopsy specimens, glomerular damage can be identified. Nephrotic syndrome may result, but severe renal insufficiency is uncommon.

TREATMENT

Treatment should target the underlying hepatitis C infection (Chapter 135). Administration of corticosteroids is often needed to control vasculitis. Agents to treat the monoclonal component, such as cyclophosphamide or rituximab, are used if there is no response. Plasmapheresis (with a warmed circuit) is helpful in the acute management of symptoms by removing circulating immune complexes.

TYPE III CRYOGLOBULINEMIA

Type III (polyclonal) cryoglobulinemia does not have a monoclonal component and is not associated with a clonal plasma cell proliferative disorder. Type III cryoglobulins are found in many patients with chronic infections or inflammatory diseases and are usually of no clinical significance unless associated with hepatitis C infection.

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174 AMYLOIDOSIS

MORIE A. GERTZ AND ANGELA DISPENZIERI

The amyloidoses are protein-misfolding diseases caused by a precursor protein that undergoes a conformational change, which in turn triggers the formation of amyloid fibrils that damage different organs. Amyloidosis can be either localized or systemic. In systemic amyloidosis (Table 174-1), amyloid deposition occurs at sites distant from where the precursor protein is formed.[1] In localized amyloidosis, the deposits form exclusively where the precursor protein is synthesized. Despite differences in structure and function, amyloid fibrils formed by all these various precursor proteins share a cross-β structure and form 2- to 5-nm-diameter filaments that either coil together or form laterally adherent fibrils with distinct intensities at 4.7 and 10 angstroms.

SYSTEMIC AMYLOIDOSIS

EPIDEMIOLOGY

The incidence of AL (formerly called primary) amyloidosis is about 12 per million persons per year. In one large series confirmed by mass spectroscopy, about 60% of cases were immunoglobulin amyloidosis, about 30% were transthyretin or TTR amyloidosis, and only about 3% were secondary amyloidosis. Familial amyloidosis mostly involves mutated transthyretin but also includes other rare mutations (Table 174-1). Wild-type TTR amyloidosis is often clinically unrecognized and is much more common than originally believed.

SYSTEMIC LIGHT CHAIN AMYLOIDOSIS

PATHOBIOLOGY

In rare cases, light chain amyloidosis can be familial, owing to a mutation in the light chain gene, rather than caused by a monoclonal plasma cell dyscrasia. Immunoglobulin light chain amyloidosis is characterized by a clonal population of bone marrow plasma cells that produces a monoclonal light chain of the κ or λ type, as either an intact molecule or a fragment. The light chain protein, instead of conforming to the α-helical configuration of most proteins, misfolds and forms a β-pleated sheet.[2] This insoluble protein is deposited in tissues and interferes with organ function. The β-pleated sheet configuration is responsible for the tinctorial properties; when the protein is stained with Congo red and viewed under polarized light, apple-green birefringence is demonstrated and is required for the diagnosis.

CLINICAL MANIFESTATIONS

The presenting symptoms can be diverse and are mimicked by far more common disorders (Table 174-2). The signs include tongue enlargement with dental indentations (Fig. 174-1) and "pinch" or periorbital purpura (Fig. 174-2), which is a result of vascular fragility. The signs are specific but lack sensitivity in that they are present in no more than 15% of patients.

Renal Involvement

The kidney is commonly involved in AL amyloidosis (58% of cases). The diagnosis should be suspected in any patient who presents with nondiabetic nephrotic-range proteinuria (Chapter 100).[3] One third of patients with AL amyloidosis have nephrotic syndrome that is manifested with dramatic increases in the blood cholesterol level (median, 270 mg/dL), and urinalysis for proteinuria should be done in patients with a sudden increase in the serum cholesterol

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174 AMYLOIDOSIS

MORIE A. GERTZ AND ANGELA DISPENZIERI

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PATHOBIOLOGY

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ABSTRACT

The amyloidoses are protein-misfolding diseases caused by a precursor protein that undergoes a conformational change, which in turn triggers the formation of amyloid fibrils that damage different organs. Amyloidosis can be either localized or systemic. The systemic amyloidoses can be manifested clinically in many organs, most notably the heart, kidneys, liver, peripheral nerves, skin, gastrointestinal tract, and the microvasculature of the brain. Diagnosis can be confirmed by mass spectrometry or immunoelectron microscopy (for unequivocal amyloid typing) of a Congo red–positive tissue biopsy of clinically involved organs or surrogate tissue, such as subcutaneous fat pad or bone marrow. The amyloidoses are not common and their presenting symptoms may be missed or confused with other clinical entities. For light chain amyloidosis, current therapy produces response rates of about 70% and median survival upward of 5 years.

KEYWORDS

amyloidosis
light chain
monoclonal immunoglobulin
nephrotic syndrome
restrictive cardiomyopathy
stem cell transplant

TABLE 174-1 SYSTEMIC AMYLOIDOSES

DISEASE	CAUSE	AFFECTED ORGANS
AL (Light chain) amyloidosis (formerly primary amyloidosis)	Immunoglobulin light chain	Heart, kidney, liver, nerve
AL (Heavy chain) amyloidosis	Immunoglobulin heavy chain	Kidney, liver, heart
TTRwt (formerly senile cardiac) amyloidosis	Accumulation of wild-type transthyretin	Heart, vessels, soft tissues (especially ligaments)
TTRm (formerly familial) amyloidosis	Hereditary mutation of transthyretin	Heart, kidney, peripheral nervous system
ALECT2	No mutation etiology not known	Kidney, liver
AA (Secondary) amyloidosis	Overproduction of serum amyloid A protein because of chronic inflammation	Kidney, liver, spleen
AB2 M wild-type (dialysis-related) amyloidosis	Acquired copper-triggered oligomerization of β_2-microglobulin	Musculoskeletal system
AB2 M variant amyloidosis	Hereditary variant of β_2-microglobulin	Autonomic nervous system
ALYS	Hereditary mutation of lysozyme	Kidney, liver, spleen
ApoAI amyloidosis	Hereditary mutation of apolipoprotein AI	Kidney, heart, liver
ApoAII amyloidosis	Hereditary mutation of apolipoprotein AII	Kidney
ApoAIV amyloidosis	Hereditary mutation of apolipoprotein AIV	Kidney
ApoCII amyloidosis	Hereditary mutation of apolipoprotein C II	Kidney
ApoCIII amyloidosis	Hereditary mutation of apolipoprotein C III	Kidney
AFib amyloidosis	Hereditary mutation of fibrinogen α chain	Kidney
AGel (Finnish hereditary) amyloidosis	Hereditary mutation of gelsolin	Cornea, facial and peripheral nerves, skin
ACys amyloidosis	Hereditary mutation of cystatin C	Peripheral nervous system, skin
ABri amyloidosis	Hereditary mutation of BriPP	Microvasculature of the brain

Apo = apolipoprotein; BriPP = Bri precursor protein; wtTTR = wild-type transthyretin.
Adapted from Blancas-Mejia LM, Ramirez-Alvarado M. Systemic amyloidoses. *Annu Rev Biochem*. 2013;82:745-774.

TABLE 174-2 SYMPTOMS, SIGNS, AND SYNDROMES OF SYSTEMIC AMYLOIDOSIS

SYMPTOMS AND SIGNS
Common symptoms: fatigue, edema, dyspnea, anorexia, paresthesias Rare symptoms: claudication, joint pain and stiffness, sicca syndrome Common signs: periorbital purpura, glossomegaly, hepatomegaly Rare signs: waxy infiltration of eyelids, shoulder pad sign
SYNDROMES
Nondiabetic nephrotic syndrome Nonischemic cardiomyopathy with an echocardiogram showing "hypertrophy" Hepatomegaly or increased alkaline phosphatase with no imaging abnormality Peripheral neuropathy with monoclonal gammopathy of undetermined significance or chronic inflammatory demyelinating polyneuropathy with autonomic features Atypical monoclonal gammopathy of undetermined significance or myeloma with monoclonal light chains and modest marrow plasmacytosis

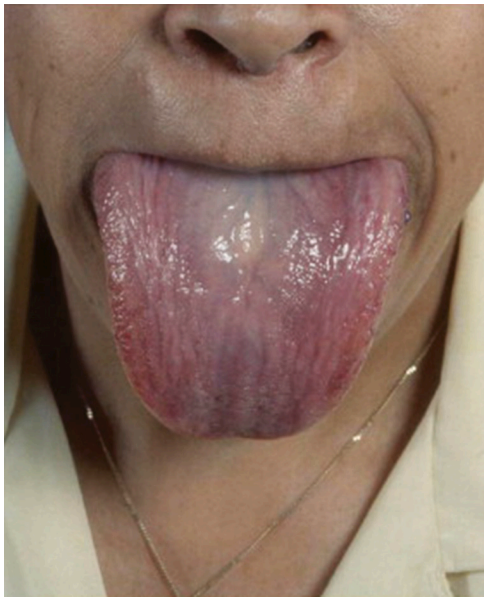

FIGURE 174-1. Macroglossia (or glossomegaly) in a patient with amyloidosis. (From Esplin BL, Gertz MA. Current trends in diagnosis and management of cardiac amyloidosis. *Curr Probl Cardiol*. 2013;38:53-96.)

FIGURE 174-2. Periorbital purpura in amyloidosis. (From Kitchens CS. Purpura and other hematovascular disorders. In: Kitchens CS, Konkle BA, Kessler CM, eds. *Consultative Hemostasis and Thrombosis*. 3rd ed. Philadelphia: Elsevier; 2012.)

level. Ten percent of renal biopsy specimens from patients with nondiabetic nephrotic syndrome are subsequently shown to be involved by amyloidosis. The incidence of bleeding after percutaneous renal biopsy is not increased in patients with AL amyloidosis.

Cardiac Involvement

The heart is involved in approximately 70% of patients with AL amyloidosis, and the presentation of disease is subtle because fatigue is often the only manifestation.[4] Because amyloid heart disease (Chapter 47) is a disorder of diastolic failure, the typical findings of cardiomyopathy (enlarged cardiac silhouette, depressed ejection fraction, and pulmonary vascular redistribution) are absent. The effect of amyloidosis on the heart is poor filling during diastole. Patients have low end-diastolic volume and, as a consequence, poor stroke volume, despite a completely normal ejection fraction.[5] Cardiac conduction abnormalities (Chapter 51) are common and can be a presenting clinical manifestation. Patients with amyloidosis rarely have symptoms of ischemic heart disease. Imaging is typically not helpful, and liver uptake is homogeneous. Liver biopsy is not associated with an increased rate of bleeding.

Neuropathy

The peripheral neuropathy (Chapter 388) associated with AL amyloidosis (seen in approximately 15% of patients) begins in the lower extremities, is symmetrical, and is generally sensory or mixed sensorimotor. When a monoclonal protein is recognized, frequent diagnoses are chronic inflammatory demyelinating polyneuropathy and neuropathy associated with monoclonal gammopathy of undetermined significance. Associated autonomic neuropathy occurs in approximately 4% of patients and can be characterized by orthostatic hypotension, which may be misattributed to cardiac failure.

Carpal tunnel syndrome (Chapter 384) occurs in approximately 10 to 15% of patients. It is not clinically distinguishable from the syndrome associated with repetitive stress injury but may fail to improve after surgical release.

Gastrointestinal/Liver

Autonomic dysmotility of the bowel is a common associated finding (Chapter 122). It can be upper intestinal, leading to pseudo-obstruction and recurrent emesis, or lower intestinal, characterized by alternating obstipation and fecal incontinence. Diarrhea caused by autonomic failure can be misdiagnosed as collagenous colitis when eosinophilic deposits are found in the bowel mucosa on hematoxylin-eosin staining in the absence of Congo red staining.

The liver is involved in 10 to 20% of patients with AL amyloidosis, and the typical presentation is hepatomegaly with an increased serum alkaline phosphatase value. Increased aminotransferase levels and hyperbilirubinemia are generally late signs. Many patients undergo evaluation for suspected malignant disease due to liver enlargement.

Other Symptoms

Rarely, patients present with spontaneous splenic rupture. Acquired deficiency of coagulation factor X (Chapter 160) is specific to AL amyloidosis and can be associated with severe hemorrhage. Interstitial lung disease, pseudoclaudication, periarticular deposits, and unexplained weight loss rarely are presenting symptoms.

DIAGNOSIS

AL amyloidosis is particularly difficult to diagnose. No single imaging procedure or laboratory study is diagnostic for AL amyloidosis. The clinician must therefore be aware of the possibility of amyloidosis, or it may be overlooked.[6]

In a patient with nondiabetic proteinuria, cardiomyopathy without ischemic risk factors, unexplained hepatomegaly, peripheral or autonomic neuropathy, or carpal tunnel syndrome, amyloidosis is not the most likely cause. The classic physical finding of periorbital purpura occurs in only 10% of patients, is often limited to petechial eruptions over the eyelids, and is easily overlooked. Enlargement of the tongue occurs in 10 to 15% of patients; therefore, although it is specific, it is not sensitive for the diagnosis. AL amyloidosis in patients with an enlarged tongue may be unrecognized, or these patients may be evaluated for acromegaly or undergo unnecessary tongue biopsies because of the suspicion of squamous cell cancer.

Initial Testing

When a patient presents with a compatible clinical syndrome, immunofixation of serum and a urine-free light chain assay should be completed before invasive diagnostic studies are performed (Fig. 174-3). Simple electrophoresis without immunofixation is inadequate because the monoclonal proteins are quantitatively very small in most patients and will not cause a detectable peak on serum protein electrophoresis. When these three diagnostic studies are used in combination, the sensitivity is 100%. The existence of a monoclonal protein, however, is not sufficiently specific to establish the diagnosis of AL amyloidosis.

With modern testing, a monoclonal component can be found in approximately 25% of patients with ATTRwt amyloidosis, so typing of the amyloid tissue is critical. If a monoclonal protein is not found, three possibilities exist: (1) the patient does not have amyloidosis; (2) if the patient is known to have amyloidosis, it may be localized rather than systemic; or (3) if the patient is known to have systemic amyloidosis, it may be ATTRwt (senile systemic) or ATTRm (familial type) rather than the light chain type (see later section on other forms of amyloidosis).

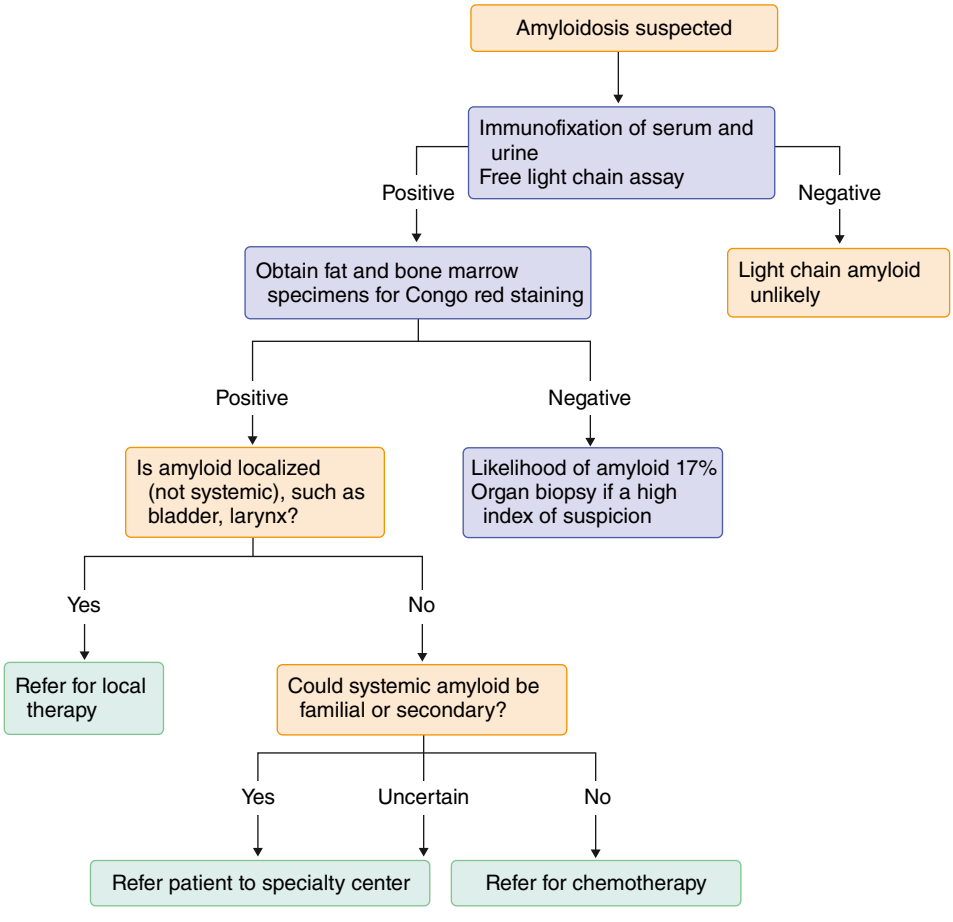

FIGURE 174-3. Algorithm for the cost-effective pursuit of a diagnosis of systemic light chain amyloidosis.

Differential Diagnosis

Systemic AL amyloidosis can be confused with early multiple myeloma (Chapter 174). Patients who present with vague symptoms of fatigue and edema are found to have a monoclonal protein in the urine, and a bone marrow biopsy specimen shows a clonal plasmacytosis with a median of 10% plasma cells in the bone marrow. These patients are often considered to have atypical multiple myeloma when the underlying amyloid syndrome is unrecognized. Taken together, a misdiagnosis of myeloma kidney or demyelinating neuropathy is made when an adequate diagnostic evaluation to exclude amyloidosis has not been performed.

Systemic AL amyloidosis also must be distinguished from systemic amyloidosis associated with inherited amyloid cardiomyopathies and neuropathies (familial amyloidoses) or cardiac amyloidosis caused by deposition of aberrant transthyretin. By definition, AL amyloidosis is a plasma cell dyscrasia (Chapter 174); therefore, virtually all patients have a detectable immunoglobulin abnormality by immunofixation of the serum or urine, or they have abnormal results on a serum immunoglobulin free light chain assay.

Definitive Testing

In view of the grave prognosis associated with AL amyloidosis, the diagnosis must be confirmed by biopsy (with Congo red staining) in all cases.[7] Subcutaneous fat aspiration is an outpatient procedure that has a 24-hour turnaround time, recognizes amyloid deposits in 70% of patients, and is the initial diagnostic test that should be performed to confirm AL amyloidosis. Bone marrow is a second convenient biopsy site, and this test is often required to exclude the possibility of associated multiple myeloma. Bone marrow biopsy is positive in 50% of patients. When both subcutaneous fat aspiration and bone marrow biopsy are combined, amyloid is detected in approximately 80% of patients. The remaining patients should have biopsy of the appropriate involved organ: the kidney when proteinuria is the presenting symptom, the heart when cardiomyopathy is recognized, the liver in patients who have hepatomegaly and an increased alkaline phosphatase value, or the nerve if sensorimotor functional loss is present. These latter procedures are quite invasive and often are not required for definitive diagnosis of AL amyloidosis.

Once amyloid deposits are detected in tissues, further diagnostic evaluation is required (Fig. 174-3). The presence of a monoclonal protein in the serum or urine and the presence of congophilic deposits in tissue do not verify that amyloidosis is light chain in origin. Further diagnostic studies are essential to classify the type of amyloid before therapy is initiated. Immunohistochemical studies on the tissue may be useful, but misfolding of the amyloid light chain often prevents epitopes from being recognized by commercial antisera; as a result, false-negative and false-positive results are common. Mass spectrometric analysis of the amyloid deposit can be performed on paraffin-embedded tissue and validates the type of amyloid by direct amino acid sequencing, thereby leaving no question about the origin of the amyloid protein as an immunoglobulin light chain. Alternatively, immunoelectron microscopy can be used to type the amyloid. Each of these tests have a specificity of nearly 100% for light chain amyloidosis.

When the heart is involved, electrocardiography frequently shows a pseudoinfarct pattern, which can be interpreted as demonstrating silent ischemic infarction; this finding can lead to coronary angiography, which is invariably negative (unless the patient has coincidental coronary artery disease). Echocardiography shows thickening of the heart walls and a hyperreflective granular texture (see Fig. 47-8) due to amyloid infiltration but can be misinterpreted as showing left ventricular hypertrophy. Enhancement on magnetic resonance imaging with gadolinium is delayed in approximately 70% of patients with cardiac amyloidosis. Myocardial enhancement is associated with increased ventricular mass and impaired left ventricular systolic function. Technetium pyrophosphate (Tc^{99} PYP) imaging of the heart can be supportive of a diagnosis of ATTR amyloidosis (see E-Fig. 44-4).

TREATMENT

AL amyloidosis was previously thought to be untreatable and invariably fatal. With current therapy,[8] complete response rates of over 50% are reported, and the median duration of survival is upward of 5 years.[9] Agents to reverse the misfolding of the protein and render it soluble would be ideal, but they are currently investigational. The source of the immunoglobulin light chain is the clonal plasma cell population in the bone marrow. All known therapies are directed at destruction of the plasma cell clone.

The two treatment choices are traditional-dose chemoimmunotherapy with or without high-dose chemotherapy with autologous stem cell transplantation. Most patients are not candidates for high-dose therapy because of age, advanced cardiac dysfunction, or renal insufficiency. High-dose melphalan is a feasible approach in selected patients with light chain amyloidosis and is associated with a high rate of hematologic and organ responses that lead to prolonged survival (Fig. 174-4). Current therapies include combinations of melphalan, cyclophosphamide, dexamethasone, bortezomib,[10] and lenalidomide. Treatment under expert oversight with a combination of daratumumab, which is a human monoclonal antibody against CD38 (1800 mg subcutaneously),[11] bortezomib (1.3 mg/m^2 weekly), cyclophosphamide (300 mg/m^2 orally weekly), and dexamethasone (40 mg weekly) can produce rapid and complete hematologic responses in the majority of patients with light chain amyloidosis with few side effects.[A1] Even without the daratumumab, the triplet of bortezomib, cyclophosphamide, and dexamethasone can result in slightly more than 50% of patients not requiring additional treatment for at least 7 years.[12] Effective plasma cell directed therapy has been associated with resolution of nephrotic syndrome, cardiac failure, and hepatomegaly.

For rescue therapy (Fig. 174-5), expert oversight is required. One option is pomalidomide plus dexamethasone.[13] Another option is to add daratumumab, which can provide a rapid hematologic response and a 2-year survival of about 75% as a single agent.[14,A2] Investigational venetoclax appears to have high activity in patients whose plasma cells express t(11;14).

For patients with chronic renal failure, kidney transplantation (Chapter 117) is an option.[15] Antibodies to amyloid fibrils are being tested.

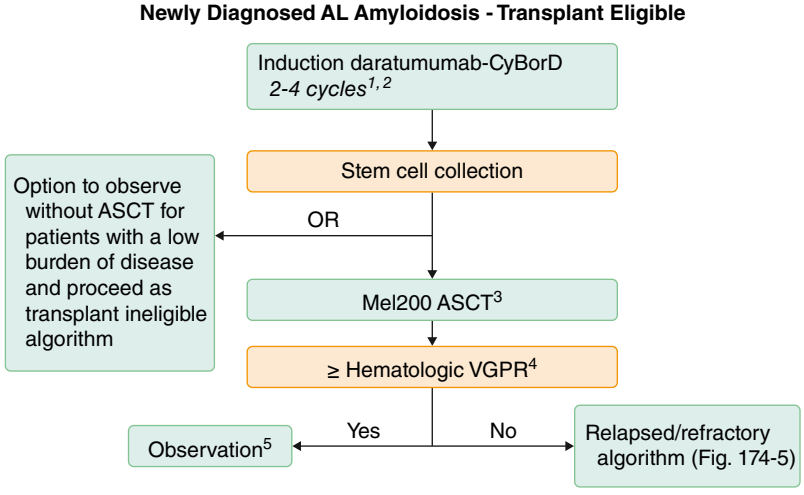

FIGURE 174-4. Treatment for newly diagnosed AL amyloidosis patients who are transplant-eligible. [1]Consider adding doxycycline for at least a year. [2]If daratumumab is not accessible, CyBorD is an acceptable alternative regimen (weekly bortezomib only). [3]For CrCl <30, use Mel 140 mg/m^2. [4]Decision to change therapy if in VGPR but < CR is based on a number of clinical factors, re-refer to amyloid center of excellence. [5]For patients with overt multiple myeloma, use myeloma-type maintenance; consider for BMPCs ≥20% and high-risk FISH (del 17p, t(4;14), t(14;16) and t(14;20)). Please refer for myeloma mSMART guidelines for choice of maintenance. https://www.mayoclinic.org/medical-professionals/cancer/news/msmart-a-clear-and-simple-guide-for-treating-patients-with-multiple-myeloma/mqc-20506750. ASCT = autologous stem cell transplant; BMPC = bone marrow plasma cells; CyBorD = cyclophosphamide, bortezomib, dexamethasone; Mel = melphalan; VGPR = very good partial remission.

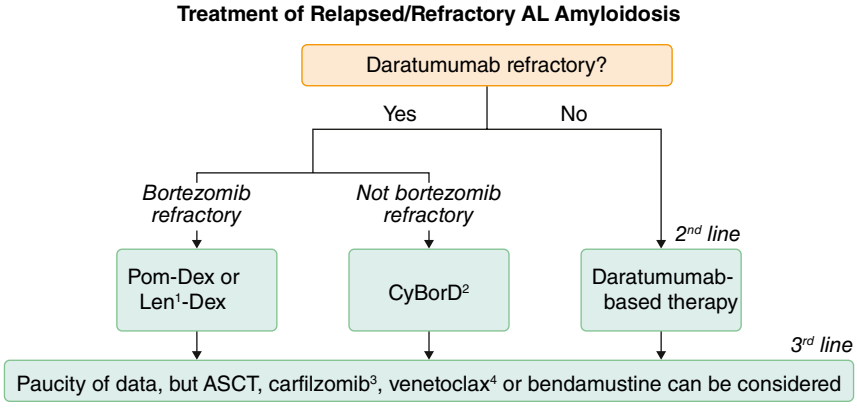

FIGURE 174-5. Treatment of relapsed/refractory AL amyloidosis. [1]Starting dose of lenalidomide should be no higher than 15 mg/d. [2]Melphalan-dexamethasone and ixazomib-dexamethasone are appropriate if patient has significant neuropathy. [3]Not recommended in patients with cardiac involvement. [4]For patients with t(11;14). Be cautious of infection risk. ASCT = autologous stem cell transplant; CyBorD = cyclophosphamide, bortezomib, dexamethasone; Dex = dexamethasone; Len = lenalidomide; Pom = pomalidomide.

PROGNOSIS

Patients who have AL amyloidosis and a baseline difference of less than 50 mg/L between circulating involved and uninvolved free light chain (i.e., low free light chain burden) have a better outcome.[16] This assay also can measure the therapeutic effect of interventions because the light chain level is quantifiable and reproducible.[17] Successful therapy is characterized by a 50% reduction in the abnormal free light chain level, but it is uncertain whether patients who do not achieve this level of response should be subjected to more intensive treatment in an effort to remove this pathogenic amyloid serum precursor.

The outcome of patients with light chain amyloidosis is highly dependent on the extent of cardiac involvement (Chapter 47), including myocardial dysfunction and arrhythmias. Doppler echocardiography allows quantitative measurements of diastolic function and reflects the slowing of blood flow into the ventricular chamber as the noncompliant left ventricle fills. This "stiffness," measured by the deceleration time, provides useful information and correlates well with survival.

Cardiac biomarkers are extremely sensitive measures of myocardial function, are reproducible, and can be used not only for prognosis but also to follow cardiac response after effective therapy.[18] The serum troponin value is a powerful predictor of survival in patients with amyloidosis, and the N-terminal pro–brain natriuretic peptide value also predicts survival. With the advent of routine hemodialysis, death due to renal failure is uncommon.

OTHER SYSTEMIC AMYLOIDOSES

ATTRwt AMYLOIDOSIS

ATTRwt amyloidosis (formerly known as senile systemic amyloidosis) results from the deposition of a normal serum protein, transthyretin, in the myocardium. Most patients are older than age 70 years.

The clinical presentation of ATTRwt is not distinguishable from that of cardiac light chain amyloidosis. The diagnosis of ATTRwt is supported when a cardiac technetium pyrophosphate scan is positive (see E-Fig. 44-4) in the absence of a monoclonal protein. ATTRwt is the only type of amyloid that can be made without a tissue diagnosis. When a monoclonal protein is present, however, confirmation of the type of amyloid requires analysis of the Congo red–positive tissues by mass spectrometry or immunoelectron microscopy.

TREATMENT AND PROGNOSIS

Tafamidis (61 mg once daily), an oral agent that prevents misfolding of TTR into amyloid configuration, is the only approved therapy for ATTRwt. Elevated levels of NT-pro-brain natriuretic peptide and/or troponin, a reduced eGFR, and a decreased left ventricular ejection fraction are adverse risk factors. The median survival is 3.6 years.

FAMILIAL AMYLOIDOSIS

Familial (or hereditary) amyloidosis is uncommon in the United States and represents only 3% of cases of systemic amyloidosis. The precursor protein of the amyloid determines the clinical phenotype (Table 174-1).

Among the 100 or more transthyretin point mutations, one important form of familial amyloidosis in the United States is a *TTR* allele in which isoleucine is substituted for valine at gene position 152 resulting in the TTR protein V122I. Approximately 4% of Black Americans are heterozygotes for *ATTRV122I*, which increases the risk of incident heart failure by 50% but not the risk of mortality.[19] The gene mutation *ATTRV50M* causes a late-onset transthyretin familial amyloid polyneuropathy. Less common causes of hereditary systemic amyloidoses include destabilizing mutations or deletions of lysozyme, apolipoprotein AI,[20] apolipoprotein AII, apolipoprotein AIV, fibrinogen α chain, gelsolin, and cystatin C.

CLINICAL MANIFESTATIONS AND DIAGNOSIS

Patients may present with the full clinical spectrum associated with amyloidosis, including cardiomyopathy, peripheral neuropathy, autonomic neuropathy, and/or proteinuria, depending on the precursor protein.[21] Diagnosis, typically by biopsy in the early stages, is essential to allow for timely treatment to prevent or delay disease progression. Myocardial radiotracer uptake on bone scintigraphy using technetium (Tc^{99}) pyrophosphate (PYP; see E-Fig. 44-4) or 3,3-diphosphono-1,2-propanodicarboxylic acid (DPD) is greater than 99% sensitive and 86% specific for cardiac mutant and wild-type ATTR cardiac amyloidosis, with false-positive results almost exclusively from uptake in patients with cardiac light chain amyloidosis.[22] Guidelines encourage genetic counseling and routine presymptomatic genetic testing.[23]

TREATMENT AND PROGNOSIS

Transthyretin amyloid cardiomyopathy is now a treatable condition.[24,25] Tafamidis (20 to 80 mg daily), which binds noncooperatively to the two thyroxine sites on the tetrameric form of transthyretin and thereby prevents its dissociation into monomers, can slow progression of transthyretin amyloid cardiomyopathy and reduce all-cause mortality.[A3] At 30 months, the 80-mg dose appears to be more efficacious, in terms of cardiac function as well as mortality.[A4] Patisiran (generally 0.3 mg/kg with a capped dose of 30 mg intravenously every 3 weeks) is a small interfering RNA drug that blocks the production of transthyretin; it can decrease ventricular wall thickness, reduce adverse cardiac outcomes,[A5] and slow the progression of the polyneuropathy.[A6] Similarly, inotersen (284 mg subcutaneously weekly) also can slow the progression of polyneuropathy and improve quality of life.[A7] Diflunisal (an FDA–approved generic nonsteroidal anti-inflammatory drug at 250 mg twice daily) can slow the rate of progression of the familial TTR amyloidosis–associated polyneuropathy.[26] Diflunisal complexes to the thyroxine binding sites on the tetrameric form of transthyretin, stabilizes it, and thus inhibits the release of the transthyretin monomer required for amyloidogenesis.

Because this disease is characterized by systemic accumulation of polymerized transthyretin in the peripheral nerves and systemic organs, liver transplantation stops the major production of amyloidogenic transthyretin. Selected patients with familial amyloidosis and polyneuropathy have benefited from liver transplantation. In the future, the availability of gene silencing therapy[27] may reduce the need for liver transplantation.

For transthyretin-related amyloidosis, the median historical survival was 5 to 15 years depending on the organs involved. The effect of newer medications on life expectancy is encouraging but uncertain. The estimated probability of 10-year survival in patients with familial amyloid polyneuropathy can be as high as 90 to 100%.

SECONDARY SYSTEMIC AMYLOIDOSIS

Systemic secondary amyloidosis is now the rarest form of amyloidosis in Western countries.[28] Previously, secondary amyloidosis was a well-recognized consequence of uncontrolled sustained inflammation, usually infectious, and causes included tuberculosis and osteomyelitis. Cystic fibrosis (Chapter 77), bronchiectasis (Chapter 78), decubitus ulcers, and skin abscesses related to subcutaneous injection of illicit drugs remain modern-day infectious causes. Secondary amyloidosis can also occur in patients with difficult-to-control inflammatory syndromes, including Crohn disease (Chapter 127), juvenile arthritis, and ankylosing spondylitis (Chapter 244). The number of patients who develop secondary amyloidosis related to rheumatic diseases has declined markedly, at least in part because of the use of disease-modifying antirheumatic therapy.[29] Familial forms of secondary amyloidosis are associated with familial periodic fever syndromes, the most common being familial Mediterranean fever (Chapter 254) due to mutations in the tumor necrosis factor receptor.

Organ damage results from the extracellular deposition of proteolytic fragments of the acute phase reactant serum amyloid A as amyloid fibrils. The distribution of deposits is mostly in the kidney, spleen, liver, and intestines.

Secondary amyloidosis patients typically present with proteinuria, nephrotic syndrome, or renal dysfunction. Diarrhea related to intestinal involvement (22%) and thyromegaly (9%) also occur.

TREATMENT

Suppression of the inflammatory process results in regression of tissue amyloid deposits. Therefore, monitoring of patients with chronic, active inflammatory disease by serial testing of serum amyloid A, C-reactive protein, microalbuminemia, proteinuria, and other indicators of amyloid development, as well as possibly determination of the *SAA1* genotype, can guide management. Anti–tumor necrosis factor-α agents have markedly reduced the incidence of secondary amyloidosis from inflammatory arthritis. Interleukin-1 inhibitors (e.g., anakinra) have been used successfully under expert oversight for patients who have inherited periodic fever syndromes (Chapter 254).

LOCALIZED AMYLOIDOSIS

Localized amyloidosis can be confused with systemic amyloidosis. However, patients with localized amyloidosis do not have a demonstrable monoclonal protein in the serum or urine and have a normal free light chain ratio. The location of the amyloid deposits also can be a clue to the localized nature.

Typical sites for localized amyloid deposition include the ureter, bladder, urethra, and prostate. Most forms of cutaneous amyloidosis are localized, although nodular cutaneous amyloidosis can occur in systemic light chain amyloidosis. Tracheobronchial and laryngeal amyloidosis and nodular pulmonary amyloidosis are localized and are not associated with a plasma cell dyscrasia. Nodular pulmonary amyloidosis is often diagnosed after thoracotomy or transcutaneous biopsy. Most cases of laryngeal amyloidosis are found when the patient presents to an otorhinolaryngologist with hoarseness and amyloid deposits are found on endoscopic biopsy. The localized amyloidosis found in Alzheimer disease (Chapter 371) is chemically unrelated to light chain amyloidosis, and patients with light chain amyloidosis do not have an increased risk of dementia.

TREATMENT AND PROGNOSIS

Management can be supportive or localized to the deposition, and patients generally do not require systemic therapy. For genitourinary amyloidosis, therapy entails cystoscopic resection or intravesical instillation of dimethyl sulfoxide. Laryngeal, tracheobronchial, and cutaneous amyloidosis can be treated with a variety of local agents under expert supervision with varying degrees of success. Overall, however, localized amyloidosis has a much better prognosis than does systemic amyloidosis.

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For the General References and other additional features, please visit Elsevier eBooks+ at https://ebooks.health.elsevier.com.

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175 TUMORS OF THE CENTRAL NERVOUS SYSTEM

INGO K. MELLINGHOFF AND LISA M. DEANGELIS

Central nervous system (CNS) tumors can involve the brain or the spinal cord, may be benign or malignant, and may be primary or metastatic. In the United States, about 80,000 new primary brain tumors and other nervous system tumors are diagnosed annually, and about one-third of primary CNS tumors are malignant. In contrast, intracranial metastases are five times more common than primary brain tumors.

Over 100 different types and subtypes of brain and spinal cord tumors arise from cells that make up the CNS (Table 175-1). Because CNS tumors grow within the CNS and rarely if ever metastasize to other organs, conventional tumor staging approaches are not applicable, so histopathologic and molecular features are used to categorize CNS tumors. Histopathologic features that suggest more aggressive growth include cytologic atypia, increased mitotic rate, microvascular proliferation, and regional necrosis. Tumors lacking these features are still able to grow within the CNS and to cause progressive neurologic disability, and they may acquire a more malignant phenotype over time. Tumor grading includes histologic features[1,2] as well as molecular information. In difficult cases, DNA methylation patterns can help assign a tumor subtype.

BRAIN TUMORS

Extra-axial primary brain tumors arise within the intracranial cavity but are not tumors of brain tissue. Although they produce neurologic symptoms and signs by compressing the underlying brain, almost all extra-axial tumors are benign. Since the brain is rarely invaded, complete surgical excision is often feasible.

In contrast, intra-axial primary brain tumors tend to invade brain tissue diffusely, and none can be completely excised surgically. Most primary intra-axial brain tumors are gliomas, including the astrocytomas, oligodendrogliomas, and ependymomas.

CLINICAL MANIFESTATIONS

A patient with a brain tumor can present with generalized and/or lateralizing symptoms and signs. Generalized symptoms, which include headache, lethargy, personality change, nausea, and vomiting, typically reflect the increased intracranial pressure that often accompanies cerebral tumors. Lateralizing symptoms, which reflect the specific location of the tumor, include hemiparesis, hemisensory deficits, aphasia, visual field impairment, and seizures (Table 175-2).

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SECONDARY SYSTEMIC AMYLOIDOSIS

Systemic secondary amyloidosis is now the rarest form of amyloidosis in Western countries.[28] Previously, secondary amyloidosis was a well-recognized consequence of uncontrolled sustained inflammation, usually infectious, and causes included tuberculosis and osteomyelitis. Cystic fibrosis (Chapter 77), bronchiectasis (Chapter 78), decubitus ulcers, and skin abscesses related to subcutaneous injection of illicit drugs remain modern-day infectious causes. Secondary amyloidosis can also occur in patients with difficult-to-control inflammatory syndromes, including Crohn disease (Chapter 127), juvenile arthritis, and ankylosing spondylitis (Chapter 244). The number of patients who develop secondary amyloidosis related to rheumatic diseases has declined markedly, at least in part because of the use of disease-modifying antirheumatic therapy.[29] Familial forms of secondary amyloidosis are associated with familial periodic fever syndromes, the most common being familial Mediterranean fever (Chapter 254) due to mutations in the tumor necrosis factor receptor.

Organ damage results from the extracellular deposition of proteolytic fragments of the acute phase reactant serum amyloid A as amyloid fibrils. The distribution of deposits is mostly in the kidney, spleen, liver, and intestines.

Secondary amyloidosis patients typically present with proteinuria, nephrotic syndrome, or renal dysfunction. Diarrhea related to intestinal involvement (22%) and thyromegaly (9%) also occur.

TREATMENT

Suppression of the inflammatory process results in regression of tissue amyloid deposits. Therefore, monitoring of patients with chronic, active inflammatory disease by serial testing of serum amyloid A, C-reactive protein, microalbuminemia, proteinuria, and other indicators of amyloid development, as well as possibly determination of the *SAA1* genotype, can guide management. Anti–tumor necrosis factor-α agents have markedly reduced the incidence of secondary amyloidosis from inflammatory arthritis. Interleukin-1 inhibitors (e.g., anakinra) have been used successfully under expert oversight for patients who have inherited periodic fever syndromes (Chapter 254).

LOCALIZED AMYLOIDOSIS

Localized amyloidosis can be confused with systemic amyloidosis. However, patients with localized amyloidosis do not have a demonstrable monoclonal protein in the serum or urine and have a normal free light chain ratio. The location of the amyloid deposits also can be a clue to the localized nature.

Typical sites for localized amyloid deposition include the ureter, bladder, urethra, and prostate. Most forms of cutaneous amyloidosis are localized, although nodular cutaneous amyloidosis can occur in systemic light chain amyloidosis. Tracheobronchial and laryngeal amyloidosis and nodular pulmonary amyloidosis are localized and are not associated with a plasma cell dyscrasia. Nodular pulmonary amyloidosis is often diagnosed after thoracotomy or transcutaneous biopsy. Most cases of laryngeal amyloidosis are found when the patient presents to an otorhinolaryngologist with hoarseness and amyloid deposits are found on endoscopic biopsy. The localized amyloidosis found in Alzheimer disease (Chapter 371) is chemically unrelated to light chain amyloidosis, and patients with light chain amyloidosis do not have an increased risk of dementia.

TREATMENT AND PROGNOSIS

Management can be supportive or localized to the deposition, and patients generally do not require systemic therapy. For genitourinary amyloidosis, therapy entails cystoscopic resection or intravesical instillation of dimethyl sulfoxide. Laryngeal, tracheobronchial, and cutaneous amyloidosis can be treated with a variety of local agents under expert supervision with varying degrees of success. Overall, however, localized amyloidosis has a much better prognosis than does systemic amyloidosis.

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175 TUMORS OF THE CENTRAL NERVOUS SYSTEM

INGO K. MELLINGHOFF AND LISA M. DEANGELIS

Central nervous system (CNS) tumors can involve the brain or the spinal cord, may be benign or malignant, and may be primary or metastatic. In the United States, about 80,000 new primary brain tumors and other nervous system tumors are diagnosed annually, and about one-third of primary CNS tumors are malignant. In contrast, intracranial metastases are five times more common than primary brain tumors.

Over 100 different types and subtypes of brain and spinal cord tumors arise from cells that make up the CNS (Table 175-1). Because CNS tumors grow within the CNS and rarely if ever metastasize to other organs, conventional tumor staging approaches are not applicable, so histopathologic and molecular features are used to categorize CNS tumors. Histopathologic features that suggest more aggressive growth include cytologic atypia, increased mitotic rate, microvascular proliferation, and regional necrosis. Tumors lacking these features are still able to grow within the CNS and to cause progressive neurologic disability, and they may acquire a more malignant phenotype over time. Tumor grading includes histologic features[1,2] as well as molecular information. In difficult cases, DNA methylation patterns can help assign a tumor subtype.

BRAIN TUMORS

Extra-axial primary brain tumors arise within the intracranial cavity but are not tumors of brain tissue. Although they produce neurologic symptoms and signs by compressing the underlying brain, almost all extra-axial tumors are benign. Since the brain is rarely invaded, complete surgical excision is often feasible.

In contrast, intra-axial primary brain tumors tend to invade brain tissue diffusely, and none can be completely excised surgically. Most primary intra-axial brain tumors are gliomas, including the astrocytomas, oligodendrogliomas, and ependymomas.

CLINICAL MANIFESTATIONS

A patient with a brain tumor can present with generalized and/or lateralizing symptoms and signs. Generalized symptoms, which include headache, lethargy, personality change, nausea, and vomiting, typically reflect the increased intracranial pressure that often accompanies cerebral tumors. Lateralizing symptoms, which reflect the specific location of the tumor, include hemiparesis, hemisensory deficits, aphasia, visual field impairment, and seizures (Table 175-2).

ABSTRACT

About 80,000 new primary tumors of the central nervous system are diagnosed annually in the United States, and five times as many intracranial metastases from a wide variety of other primary sites are diagnosed. Both types of tumors are addressed in this chapter. The new World Health Organization classification of primary brain tumors has incorporated some significant changes, particularly including molecular features in some categories of gliomas, ependymomas, and embryonal tumors in recognition of their prognostic value. Magnetic resonance imaging is far superior to computed tomography in diagnosis. The mainstays of therapy are surgery, radiation therapy, chemotherapy, and combinations of these modalities. Data from controlled clinical trials can often guide therapy, but experimental modalities are frequently tried in progressive cases.

KEYWORDS

glioma
glioblastoma
astrocytic tumors
oligodendroglial tumors
ependymal tumors
meningeal tumors
leptomeningeal
brain metastases

TABLE 175-1 WORLD HEALTH ORGANIZATION CLASSIFICATION (WHO) OF BRAIN TUMORS

GLIOMAS, GLIONEURONAL TUMORS, AND NEURONAL TUMORS
Adult-type Diffuse Gliomas
Astrocytoma, IDH-mutant
Oligodendroglioma, IDH-mutant, and 1p/19q-codeleted
Glioblastoma, IDH-wildtype
Pediatric-type Diffuse Low-grade Gliomas
Pediatric-type Diffuse High-grade Gliomas
Diffuse midline glioma, H3 K27-altered
Diffuse hemispheric glioma, H3 G34-mutant
Diffuse pediatric-type high-grade glioma, H3-wildtype and IDH-wildtype
Infant-type hemispheric glioma
Circumscribed Astrocytic Gliomas
Pilocytic astrocytoma
Pleomorphic xanthoastrocytoma
Subependymal giant cell astrocytoma
Glioneuronal and Neuronal Tumors
Ependymal Tumors
CHOROID PLEXUS TUMORS
EMBRYONAL TUMORS
Medulloblastoma
Other CNS embryonal tumors
PINEAL TUMORS (INCLUDING PINEOBLASTOMA, OTHERS)
CRANIAL AND PARASPINAL NERVE TUMORS (INCLUDING NEUROFIBROMA, SCHWANNOMA, OTHERS)
MENINGIOMAS
MESENCHYMAL, NON-MENINGOTHELIAL TUMORS
MELANOCYTIC TUMORS
HEMATOLYMPHOID TUMORS
Lymphomas, including Primary CNS Lymphoma
Histiocytic tumors
GERM CELL TUMORS
TUMORS OF THE SELLAR REGION
Craniopharyngioma
Pituitary adenoma/PitNET

CNS = central nervous system; IDH = isocitrate dehydrogenase; PitNET = pituitary neuroendocrine tumor. Abridged and modified from Louis DN, Perry A, Wesseling P, et al. The 2021 WHO classification of the tumors of the central nervous system: a summary. *Neuro Oncol*. 2021;23:1231-1251.

TABLE 175-2 FOCAL CLINICAL MANIFESTATIONS OF BRAIN TUMORS

FRONTAL LOBE	
Generalized seizures; focal motor seizures (contralateral); expressive aphasia (dominant side); behavioral changes; dementia; gait disorders; incontinence; hemiparesis (contralateral)	
BASAL GANGLIA	
Hemiparesis (contralateral); movement disorders (rare)	
PARIETAL LOBE	
Receptive aphasia (dominant side); spatial disorientation (nondominant side); cortical sensory dysfunction (contralateral); hemianopia (contralateral); agnosias	
OCCIPITAL LOBE	
Hemianopia (contralateral); visual disturbances (unformed)	
TEMPORAL LOBE	
Complex partial (psychomotor) seizures; generalized seizures; olfactory and complex visual auras; behavioral changes; visual field defect; language disorder (dominant side)	
CORPUS CALLOSUM	
Dementia (anterior); memory loss (posterior); asymptomatic (middle); behavioral changes	
THALAMUS	
Sensory loss (contralateral); language disorder (dominant side); behavioral changes	
MIDBRAIN/PINEAL	
Paresis of vertical eye; pupillary abnormalities; precocious puberty (boys)	
SELLA/OPTIC NERVE/PITUITARY	
Endocrinopathy; bitemporal hemianopia; monocular visual defects; ophthalmoplegia (cavernous sinus)	
PONS/MEDULLA	
Cranial nerve dysfunction; ataxia; nystagmus; spasticity; weakness; sensory loss	
CEREBELLOPONTINE ANGLE	
Deafness (ipsilateral); loss of facial sensation (ipsilateral); facial weakness (ipsilateral); ataxia	
CEREBELLUM	
Ataxia (ipsilateral or gait); nystagmus	

Symptoms of brain tumors can be produced by tumor that directly invades the brain parenchyma, when tumor and edema compress brain tissue, when obstruction to cerebrospinal fluid (CSF) is directly caused by the tumor or by a shift of brain tissue, and when herniation occurs. Invasion and compression typically produce lateralizing symptoms, whereas obstruction of the flow of cerebrospinal fluid and herniation typically produce generalized symptoms but can also cause false localizing signs, such as an abducens nerve palsy as a result of diffuse increased intracranial pressure.

Headache (Chapter 367) is a presenting symptom of approximately 35% of brain tumors. It is more common in younger than in older patients and more common in patients who have rapidly growing tumors than in patients whose tumors have evolved slowly. Local growth of the tumor may cause mental and cognitive abnormalities (e.g., aphasia, alexia, agnosia) or general impairment (e.g., lethargy, confusion, word finding difficulty, apathy).

Most patients have symptoms that progress during a week to a few months. A sudden intensification of symptoms may precipitate the patient's initial visit to the physician, but a careful history usually reveals symptoms that predated the acute deterioration and slowly worsened over time. Two exceptions are the new appearance of a seizure in a previously asymptomatic individual (Chapter 372) and sudden hemorrhage into a tumor.

Seizures (Chapter 372) affect approximately one-third of patients with brain tumors, and they are especially common as the presenting and only symptom of a low-grade tumor. The seizures, which are focal because they originate at the site of the tumor, may remain restricted (e.g., focal motor seizures), or they may generalize secondarily to produce loss of consciousness, sometimes so quickly that the focal signature is missed by the patient or even an observant witness.

DIAGNOSIS

A careful history and physical examination (Chapter 366) should assess cognitive function (Chapter 361) and search for any lateralizing signs. Routine hematologic and blood chemistry tests should be obtained to exclude a metabolic cause of mental status changes (Chapter 361). However, urgent brain imaging is required when the diagnosis of a brain tumor is suspected.

Brain Imaging

Magnetic resonance imaging (MRI) should be performed both without and with intravenous administration of gadolinium, preferably using a standardized brain tumor imaging protocol. A well-performed MRI identifies any intracranial tumor, and a normal MRI effectively excludes a neoplasm.

The MRI of some extra-axial tumors (e.g., acoustic neuromas, meningiomas) is so characteristic that histologic confirmation is not required. A non–contrast-enhancing infiltrative lesion that is visible primarily on T2-weighted or fluid-attenuated inversion recovery images is most consistent with a low-grade glioma (Fig. 175-1). A contrast-enhancing lesion with an area of central necrosis and surrounding edema is most likely to be a glioblastoma or possibly a brain metastasis.

MRI is far superior to computed tomography (CT) for the diagnosis of brain tumors and should be obtained in all patients with a suspected intracranial tumor. A CT scan, even with the administration of contrast material, may miss low-grade tumors and tumors in the posterior fossa, so a CT scan should be obtained only in patients who cannot undergo MRI.

In less clear cases, functional imaging techniques can be helpful to distinguish a brain tumor from other CNS lesions. Examples include cerebral blood volume (perfusion MRI), loss of tumor cellularity (diffusion-weighted MRI), the flow of contrast agent across a damaged blood-brain barrier (dynamic contrast-enhanced MRI), or the abundance of certain metabolites (MR spectroscopy).

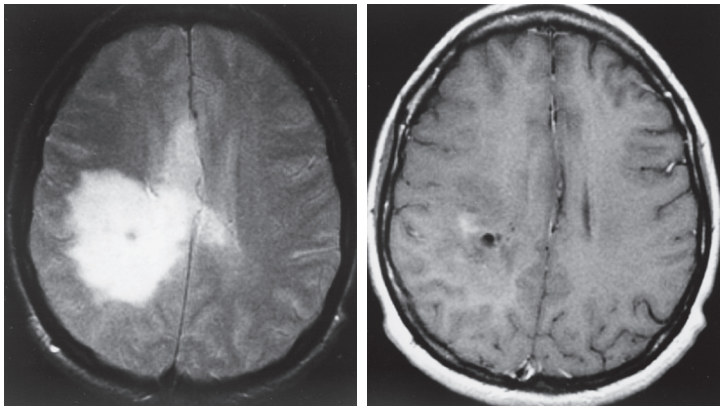

FIGURE 175-1. Glioma. Magnetic resonance imaging of a low-grade glioma. *Left*, T2-weighted image. *Right*, T1-weighted image, gadolinium contrast with minimum enhancement.

Malignant tumors, for example, are associated with an increased choline : *N*-acetylaspartate ratio and may contain areas with elevated levels of lactate and lipid. Functional MRI, which measures cerebral blood flow when areas of cortex are activated, may guide a safer and more complete surgical resection by localizing critical neurologic functions and their relationship to the tumor. Angiography no longer has a diagnostic role, but angiographic embolization is occasionally useful preoperatively to reduce the vascularity of some meningiomas, thereby making a complete resection safer.

Biopsy

Biopsy is typically part of a surgical procedure to remove the tumor to the greatest degree that is safe. However, most lesions that cannot be resected are still amenable to biopsy for diagnostic purposes. Stereotactic biopsy can reach lesions in almost any area of the brain with minimal morbidity. The risks of stereotactic biopsy include an inadequate tissue sample to make a diagnosis, a tissue sample that does not accurately reflect the most malignant grade of the tumor, and a procedure-related complication. Hemorrhage that causes neurologic impairment occurs in only 2% of stereotactic biopsies, typically in patients with glioblastomas. Unfortunately, some tumors, such as brain stem gliomas, are in such critical locations that biopsy should not be attempted.

Other Diagnostic Approaches

Electroencephalography (EEG) can be useful when a patient with a brain tumor has prolonged or unexplained confusion or stupor and for whom nonconvulsive status epilepticus is a consideration. Intraoperative monitoring is used frequently to help guide resection of epileptogenic cortex adjacent to or within the brain tumor tissue or to perform intraoperative mapping of critical functions to facilitate a safe, complete resection.

Cerebrospinal fluid analysis has a limited role in the diagnosis of most intracranial neoplasms. In primary CNS lymphoma (Chapter 171), however, the diagnosis may be established on cerebrospinal fluid cytologic examination in about 15% of patients. The sensitivity of cerebrospinal fluid cytology in the diagnosis of CNS lymphoma increases when it is combined with flow cytometry and is further enhanced by immunophenotypic and molecular genetic analyses of the cerebrospinal fluid. Rarely, a lumbar puncture is required to exclude inflammatory conditions or other processes that may be confused with a primary brain tumor. Lumbar puncture must be avoided in patients with cerebellar tumors because the release of pressure through the spinal needle may result in herniation of the cerebellar tonsils through the foramen magnum. The ability to detect tumor-derived DNA and circulating tumor cells in cerebrospinal fluid from some patients with CNS tumors may be helpful to monitor the tumor's evolution and response to therapy without the need for neurosurgical procedures.

Differential Diagnosis of Brain Tumors

Patients who present with symptoms of raised intracranial pressure or the new onset of central neurologic symptoms, such as hemiparesis or seizure, must be evaluated urgently. Prompt neuroimaging discloses a mass, and the radiographic features narrow the differential diagnosis (Table 175-3). Extra-axial tumors, such as a meningioma or acoustic neuroma, can be confused with a dural metastasis. Low-grade intra-axial tumors, which are nonenhancing on MRI, have been confused with infections such as herpes encephalitis (Chapter 383) when they involve the temporal lobe. Contrast-enhancing intra-axial tumors can be confused with a stroke (Chapter 376), brain abscess (Chapter 382), or focal plaque of demyelination (Chapter 380). Subacute infarction can show brisk contrast enhancement, usually in a gyral pattern, unlike brain tumors in which enhancement is primarily in the white matter; however, the two are occasionally indistinguishable radiographically. Brain abscesses (Fig. 382-1) typically have a thinner enhancing wall than a malignant tumor and have restricted diffusion. Despite careful evaluation, patients thought to have a malignant glioma occasionally are found at surgery to have a brain abscess. A single large plaque of demyelination can also be confused radiographically with a brain tumor and sometimes the diagnosis can be established only by biopsy.

When MRI suggests a primary brain tumor, an extensive systemic search for a possible source of metastasis is rarely required. Brain metastases are more common than primary brain tumors, but most occur in patients with known cancer, typically with active systemic disease. If an obvious systemic cancer is not revealed by a thorough physical examination, chest radiograph, routine blood tests, and urinalysis, the patient should proceed to craniotomy. Even if a brain metastasis is found at surgery, resection of a single brain metastasis is the appropriate treatment, and the pathologic examination of the lesion guides the subsequent search for the primary tumor.

TABLE 175-3 DIFFERENTIAL DIAGNOSIS OF INTRACRANIAL TUMORS

INFECTION
Brain abscess (Chapter 382)
Bacterial
Fungal
Parasitic (e.g., cysticercosis; Chapter 325)
Herpes encephalitis (Chapter 383)
VASCULAR DISEASE
Stroke (Chapter 376)
Intracranial hemorrhage (Chapter 377)
INFLAMMATORY CONDITIONS
Granuloma (sarcoid; Chapter 83)
Multiple sclerosis (Chapter 380): tumefactive single large lesion
VASCULAR MALFORMATIONS
Cavernous angiomas (Chapter 377)
Venous angiomas (Chapter 377)
CONGENITAL ABNORMALITIES
Cortical dysplasia (Chapter 385)
Heterotopia (Chapter 385)

TREATMENT

The treatment for all brain tumors can be divided into two main categories: symptomatic therapy and tumor-directed therapy (Table 175-4). Symptomatic treatment addresses cerebral edema, thromboembolic disease, and seizures, all of which can contribute substantially to clinical symptoms caused by the tumor.

Management of Symptoms

Corticosteroids (typically dexamethasone starting at 8 to 12 mg/day) decrease the vasogenic edema that often surrounds primary and metastatic brain tumors. Clinical improvement may begin within minutes, and patients frequently improve dramatically within 24 to 48 hours. This dose is then adjusted to find the lowest dose that alleviates neurologic symptoms. Once- or twice-daily dosing is preferred for maintenance therapy over more frequent dosing. After definitive treatment is instituted, many patients can be tapered off their corticosteroid completely. Chronic high-dose corticosteroid therapy is associated with substantial side effects (Chapter 28) and should be avoided if possible. Common side effects include insomnia, steroid myopathy, gastrointestinal complications, and opportunistic infections. Patients who will be taking corticosteroids for 6 weeks or longer should receive prophylaxis against *Pneumocystis jirovecii* (Chapter 313). Antibodies that block the effects of vascular endothelial growth factor (VEGF), such as bevacizumab, can be very effective in the management of symptomatic cerebral edema and can reduce corticosteroid requirements.

Venous thromboembolism affects about 25% of patients who have brain tumors. All patients undergoing neurosurgery should have pneumatic compression boots in the postoperative period to reduce the incidence of venous thromboembolism. Prophylactic anticoagulants (Chapter 68) also have been used successfully in the immediate postoperative period without increasing postoperative hemorrhage. Appropriately regulated anticoagulation (Chapter 70) is the optimal therapy for deep vein thrombosis and is not associated with an increased risk for intracerebral hemorrhage. Inferior vena cava filters can be used for patients who have deep vein thrombi or pulmonary emboli and who cannot be fully anticoagulated.

TABLE 175-4 TREATMENT OF BRAIN TUMORS

SYMPTOMATIC TREATMENT
Glucocorticoids
Antiepileptics
Venous thromboembolism prophylaxis and treatment
TUMOR-DIRECTED THERAPY
Surgery
Radiation therapy
Chemotherapy or other systemic therapy

Anticonvulsant medications (Chapter 372) are administered to any patient who has had a seizure, but prophylactic anticonvulsants should not be prescribed for patients who have never had a seizure, except in the immediate perioperative period. When used, the dose of antiepileptic agents generally should be tapered beginning 2 to 3 weeks after craniotomy.

Tumor-Directed Therapies

Surgery

Complete excision is the goal for a primary brain tumor. Surgical excision can often be accomplished for primary extra-axial tumors, such as meningiomas and acoustic neuromas, unless their intracranial location makes resection impossible. Tumors of the skull base are particularly difficult to remove, and partial resection for decompression is often performed to preserve neurologic function. The safe boundaries for resecting cortical lesions while preserving function often can be elucidated by preoperative functional MRI and intraoperative cortical mapping. However, lesions involving critical structures, such as the brain stem or thalamus, cannot be excised safely.

Complete excision can cure an extra-axial primary brain tumor and is associated with prolonged survival and better neurologic outcome, even in patients with primary intra-axial tumors. In patients with malignant and lower grade gliomas, gross total excision, as measured by postoperative neuroimaging, is associated with prolonged survival. However, most low-grade gliomas are not amenable to gross total excision, and only partial excision is usually feasible. In patients with high-grade gliomas, macroscopic tumor frequently can be removed completely, but microscopic disease that infiltrates surrounding brain tissue always remains.

Radiation Therapy

A course of external beam radiation therapy is delivered in small daily fractions to a total cumulative dose usually between 45 and 60 Gy. Dividing the treatment into small daily fractions permits sublethal repair in normal tissues and markedly reduces the neurologic toxicity that is associated with cerebral irradiation. External beam radiation, which is the most effective nonsurgical treatment of brain tumors, doubles median survival time of patients with malignant primary brain tumors or metastatic lesions. Radiation therapy can also be useful for recurrent meningiomas and acoustic neuromas. However, it only rarely cures any of these lesions, and most patients develop recurrent disease despite maximal radiation therapy.

Stereotactic radiosurgery delivers high fractions of focused radiation therapy that spare normal surrounding tissue. The technique is generally limited to tumors that are 3 cm in diameter or smaller and is less useful for malignant gliomas because of their infiltrative nature.

The neurologic complications of radiation therapy, which are usually observed months to years after completion of treatment, include radionecrosis, dementia, and leukoencephalopathy. The incidence is reported as less than 5%, and most patients die of their brain tumor before the delayed consequences of treatment can be observed. However, in long-term survivors (e.g., patients with lower grade glioma or children with medulloblastoma), the late consequences of radiation therapy are important. Dementia accompanying radiation-induced leukoencephalopathy can progress and result in severe neurologic impairment. Radionecrosis can mimic recurrent tumor with a large contrast-enhancing lesion on MRI. Corticosteroids under expert supervision can reduce the edema and sometimes are sufficient to treat small areas of radionecrosis. However, if the lesion is sufficiently large, resection may be required to decompress the mass and reduce the corticosteroid requirement. Laser interstitial thermal therapy is also a possible therapeutic approach for intractable radionecrosis.

Systemic Therapy

Systemic medical therapies vary depending on the type and grade of the tumor. Currently, all such regimens are palliative rather than curative, except for some patients who have CNS lymphomas.

SPECIFIC TYPES OF PRIMARY BRAIN TUMORS

MENINGIOMAS

EPIDEMIOLOGY AND PATHOBIOLOGY

Meningiomas are the most common primary CNS tumors and are usually benign. Between 10 and 15% of meningiomas are atypical or malignant variants with a more aggressive course.[3] Meningiomas are more common in women and may be multiple in about 10% of patients with sporadic meningioma.

FIGURE 175-2. Meningioma. Computed tomography scan with contrast enhancement of a meningioma in a patient who presented with mild cognitive deficits, illustrative of the size that a slow-growing tumor can attain in the brain. The tumor was completely resected.

Exposure to ionizing radiation elevates the risk for meningioma. Meningiomas are occasionally part of a familial syndrome and occur with increased frequency in patients with neurofibromatosis type 2 (NF2; Chapter 385). Inactivation of *NF2* is seen in approximately 50% of sporadic tumors. Other genes are also mutated frequently in meningioma (e.g., *SMO*, *AKT1*, *KLF4*, *TRAF7*), but the role of these alterations in the development or growth of meningioma remains to be defined.

CLINICAL MANIFESTATIONS AND DIAGNOSIS

Meningiomas grow slowly and produce symptoms that are insidious in onset and typically slowly progressive. Frequently, meningiomas are completely asymptomatic and are identified on neuroimaging done for another purpose, such as head trauma.

Tumors can reach a considerable size (Fig. 175-2), but they grow so slowly that the brain accommodates to the progressive compression. Meningiomas typically occur in specific locations: over the convexity, along the falx and parasagittal area, in the olfactory groove, at the base of the skull near the sphenoid bone, in the cavernous sinus (Fig. 175-3), in the cerebellopontine angle, and in the foramen magnum. Cortical and parasagittal tumors typically are manifested with seizures or progressive hemiparesis. Tumors in the anterior cranial fossa can cause slowly progressive cognitive and personality changes. Meningiomas at the base of the skull are manifested with cranial neuropathies and gait difficulties when the brain stem is compressed.

On MRI, meningiomas have a characteristic appearance consisting of a diffusely enhancing, dural-based lesion that is associated with a thin enhancing dural tail that extends from the tumor. The radiographic features are often so characteristic that biopsy is not required and surgery is performed for therapeutic purposes only. The radiographic differential diagnosis includes the less common hemangiopericytoma and dural metastasis. Most meningiomas are not accompanied by significant edema, but marked edema is seen with high-grade malignant lesions or the secretory variant.

TREATMENT AND PROGNOSIS

If small meningiomas are discovered in the absence of clinical symptoms or the symptoms are minor, lesions may be monitored with serial images because growth can be so slow. If treatment is indicated, complete resection is often curative, but even completely resected benign tumors may recur in as many as 20% of cases, so radiologic follow-up is essential. Tumors at the base of the skull often cannot be resected completely and tend to recur despite successive attempts at surgical resection. Stereotactic radiosurgery may be an alternative to surgery if the lesion is small or if patients have progressive or residual tumor.[4] External beam radiation therapy may slow progression of recurrent lesions and is essential for the treatment of malignant meningiomas.

DNA methylation profiling and determination of *CDKN2A/B* gene copy loss can provide prognostic information. No effective systemic therapy has been identified for recurrent meningioma.[5]

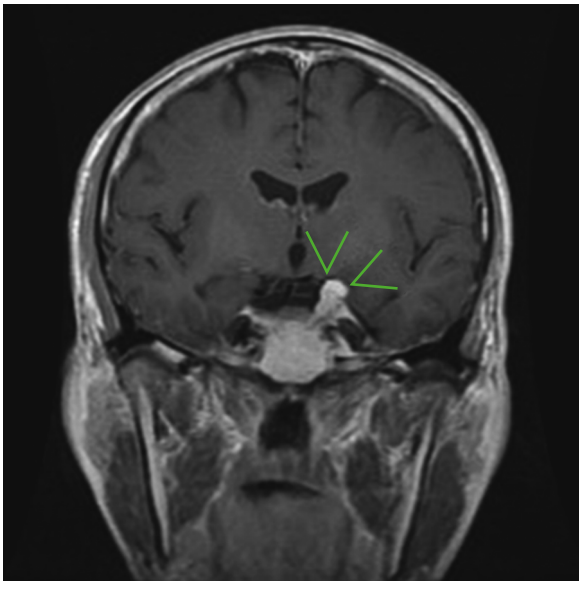

FIGURE 175-3. Skull base meningioma. A post-gadolinium coronal magnetic resonance image demonstrating a small left meningioma arising from the clinoid.

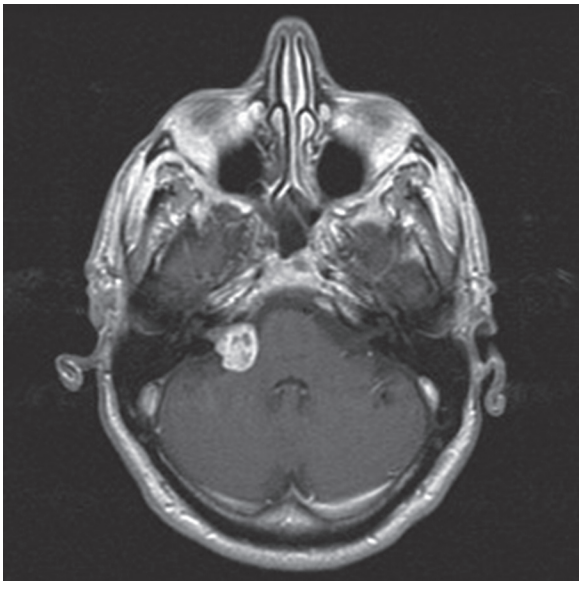

FIGURE 175-4. Vestibular schwannoma. A post-gadolinium magnetic resonance image demonstrating a large right vestibular schwannoma. The origin can be seen in the acoustic canal, but the tumor has grown into the cerebellopontine angle, where it is compressing the brainstem.

VESTIBULAR SCHWANNOMAS

Vestibular schwannomas, also called acoustic neuromas (Chapter 396), are benign tumors that arise from the eighth cranial nerve. Vestibular schwannomas are twice as common in women as in men, with a peak incidence between ages 40 and 60 years. Sporadic vestibular schwannomas are unilateral, whereas bilateral vestibular schwannomas are pathognomonic of neurofibromatosis type 2 (Chapter 385).

CLINICAL MANIFESTATIONS AND DIAGNOSIS

Vestibular schwannomas usually arise from the vestibular portion of the nerve and typically are manifest by unilateral hearing loss, sometimes preceded or accompanied by tinnitus and a sensation of dizziness or unsteadiness but not true vertigo (Chapter 396). The slow, progressive enlargement of the tumor produces ipsilateral facial numbness or weakness by compressing the fifth or seventh cranial nerve, respectively. Tumors originate within the internal auditory meatus but grow out of the acoustic canal and into the cerebellopontine angle, where they can compress the brain stem and cause ataxia and ipsilateral cerebellar signs.[6] Cranial MRI with gadolinium delineates even small acoustic neuromas with ease (Fig. 175-4).[7]

TREATMENT

Treatment is often surgical, but stereotactic radiosurgery is an effective alternative, especially for lesions smaller than 3 cm.[8] Tumors should be treated when they are small to preserve facial nerve function and hearing.

PITUITARY ADENOMAS

Pituitary adenomas are discussed in Chapter 205.

OTHER EXTRA-AXIAL PRIMARY BRAIN TUMORS

Pineal Tumors

Pineal region tumors include pineal parenchymal tumors, such as pineocytomas and the more aggressive pineoblastomas, and germ cell tumors, including germinomas and non-germinomatous germ cell tumors. Pineal region tumors all have a characteristic clinical presentation that includes Parinaud syndrome, which consists of paresis of upward gaze, poor pupillary reaction to light with brisk reaction on accommodation, impairment of convergence, and convergence-retraction nystagmus. Some of these lesions may also cause hydrocephalus and symptoms of increased intracranial pressure. Germinomas can be completely cured with focal radiation therapy, whereas non-germinomatous germ cell tumors are more aggressive and frequently relapse despite chemotherapy plus cranial irradiation.

Chordomas and Lipomas

Chordomas are rare tumors of residual notochordal tissue. They usually occur at the base of the skull, are locally invasive, and are characterized by multiple recurrences despite surgery and radiation therapy. Proton radiotherapy may be recommended for skull-based lesions that are adjacent to critical structures. Small molecule inhibitors of oncogenic signaling pathways (e.g., imatinib, sorafenib) have been reported to produce responses and clinical benefit in some patients with recurrent disease.

Lipomas are benign tumors that can occur in midline structures, particularly near the corpus callosum. They can be cured by complete removal.

Arachnoid Cysts

Arachnoid cysts are not tumors but can manifest with headache, seizures, or focal neurologic symptoms if they become large enough to compress underlying brain tissue. Many are completely asymptomatic and are found incidentally on neuroimaging. Only symptomatic cysts require removal.

GLIOMAS

DEFINITION

Gliomas comprise a heterogenous group of tumors.[9] Diffuse gliomas include types that primarily occur in adults and types that primarily occur in children. All diffuse astrocytic tumors with mutations in isocitrate dehydrogenase (IDH) 1 or 2 are considered a single type *(astrocytoma, IDH-mutant)* and then graded as grade 2 (previously called *diffuse astrocytoma, IDH-mutant*), grade 3 (previously called *anaplastic astrocytoma, IDH mutant*), or grade 4 (previously called *glioblastoma, IDH-mutant*). For IDH-wildtype diffuse astrocytic tumors, the diagnosis of glioblastoma, IDH-wildtype should be made if the tumor shows microvascular proliferation or necrosis or 1 or more of 3 genetic parameters: a *TERT* promoter mutation, *EGFR* gene amplification, or combined gain of chromosome 7 and loss of chromosome 10. All grade 2 to 4 gliomas are diffuse and infiltrate widely into the brain, and the lower grade lesions may progress to higher grade tumors over time. Grade 1 lesions such as the pilocytic astrocytoma are extremely low-grade focal tumors that have a separate designation; they are more common in children, may be associated with neurofibromatosis type 1, and are often cured by complete surgical excision.

EPIDEMIOLOGY

Gliomas occur at any age, but the peak is ages 20 to 30 years for grade 2 lesions, age 40 years for grade 3 tumors, and age 55 to 60 years for glioblastoma. For all grades of glioma, men are more frequently affected than women, and White persons are significantly more frequently affected than Black persons. Gliomas are typically single lesions, but multifocal disease is seen in approximately 5% of patients with high-grade tumors.

PATHOBIOLOGY

At least 95% of gliomas are sporadic, and only 5% occur in patients with a family history of brain tumor. Furthermore, patients with a familial history of glioma usually do not fall into a well-recognized hereditary syndrome.

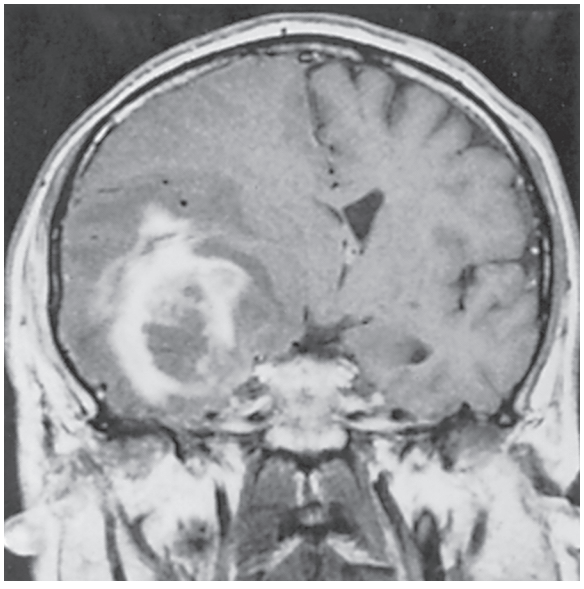

FIGURE 175-5. Temporal lobe glioblastoma. This T1-weighted gadolinium-enhanced magnetic resonance image shows a typical ring configuration of contrast material with central necrosis and marked mass effect.

Neurofibromatosis 1 (von Recklinghausen disease; Chapter 385) is associated with an increased incidence of gliomas, particularly in the optic pathway, hypothalamus, and brain stem. Gliomas also occur with increased frequency in Turcot and Lynch syndromes (Chapter 179), in which colorectal neoplasms are seen in association with a variety of CNS tumors. Somatic mutations of IDH1 and IDH2 have been identified in most lower grade gliomas.

CLINICAL MANIFESTATIONS AND DIAGNOSIS

Patients with gliomas often present with seizures, headache, and lateralizing signs such as hemiparesis, aphasia, or a visual field deficit. IDH-mutant astrocytomas and oligodendroglial tumors have a variable course, with the oligodendrogliomas being more indolent. These young adults often present with isolated seizures that can be controlled easily with antiepileptic agents.

On MRI, low-grade gliomas typically appear as diffuse, non-enhancing lesions with a propensity to occur in the frontal lobe and insular cortex (see Fig. 175-1). High-grade gliomas, which typically enhance with contrast material, occur in the cortical white matter and are accompanied by significant surrounding edema. Glioblastomas frequently have regions of central necrosis (Fig. 175-5), and hemorrhage can occur in 5 to 8% of patients.

TREATMENT AND PROGNOSIS

For all gliomas, treatment frequently involves surgery, radiation therapy, and chemotherapy.[10] The surgical goal of complete removal of all visible disease is often impossible; even when possible, residual tumor remains. The extent of resection can be optimized using intraoperative MRI guidance and fluorescence-guided resection using 5-aminolevulinic acid. The adequacy of resection is best assessed on a postoperative MRI, without and with gadolinium, performed within 24 to 96 hours after surgery. Glioma resections with intraoperative stimulation and cortical mapping are associated with fewer severe neurologic deficits and more extensive resection. Surgical removal usually improves neurologic function and reduces dependency on corticosteroids.

Age is the single most important clinical prognostic factor; younger patients live substantially longer than older patients. Tumors of any histology or grade with an IDH mutation have a significantly better prognosis than the identical tumor that is IDH-wildtype. Performance status, duration of symptoms, and whether a complete resection has been achieved are also strong predictors of improved outcome and prolonged survival.

Glioblastoma, IDH-Wildtype, Grade 4

All glioblastomas should be treated with postoperative radiation therapy to a dose of approximately 60 Gy. Hypofractionated radiotherapy is superior to standard radiation therapy in elderly patients with glioblastomas, especially in patients older than age 70 years.

The alkylating agent temozolomide (75 mg/m^2 daily orally), administered concurrently with radiation therapy and followed by adjuvant temozolomide (150 to 200 mg/m^2 for 5 consecutive days every 4 weeks for six cycles), can significantly improve median survival from 12.1 months to 14.6 months and more than double the 2-year survival rate to 26% compared with radiation therapy alone. Patients whose tumors contain a methylated promoter of the O6-methylguanine-DNA methyltransferase (MGMT) DNA repair gene benefit most from the addition of temozolomide.[11] In glioblastoma patients who have received standard radio-chemotherapy, the combination of maintenance temozolomide plus low-intensity alternating electric fields, which are delivered to the tumor through a portable medical device that is applied to the scalp, can improve progression-free survival and overall survival compared with maintenance temozolomide alone.[A1] The addition of bevacizumab, a monoclonal antibody that blocks vascular endothelial growth factor (VEGF), can be helpful to control cerebral edema, but it does not prolong survival and is not recommended for routine use in patients with newly diagnosed glioblastoma.

In almost all patients, the glioblastoma recurs following initial therapy. Recurrences can be treated with reoperation, stereotactic radiosurgery, tumor-treating fields, systemic agents, or a combination of approaches.[A2] Commonly used systemic therapies include temozolomide rechallenge, bevacizumab, and lomustine (alone or in combination with procarbazine and vincristine) under expert supervision.[12] A second course of radiation with concurrent bevacizumab is generally well tolerated and can prolong disease control.[A3] Chemotherapy is generally well tolerated and associated with minimal toxicity. Elderly patients, however, often do poorly, so alternative treatment approaches may be preferable. Since none of the currently available treatment approaches have been proven to prolong survival in recurrent glioblastoma, patients with recurrent glioblastoma should be encouraged to participate in a clinical trial whenever possible.

The median overall survival time for patients with glioblastoma is about 15 months. Key prognostic factors include patient age and performance status, as well as the presence or absence of *IDH* gene mutation and O6-methylguanine-DNA methyltransferase promoter methylation.

Astrocytomas, IDH Wildtype, Grade 2/3

No large randomized data exist to guide treatment decisions for patients with IDH-wildtype astrocytomas. Immediate postoperative radiation and chemotherapy, as described for the treatment of glioblastoma, are often used. However, close observation may be appropriate for young patients whose grade 2 tumors have undergone gross total resection.

Astrocytomas, IDH-Mutant, and All Oligodendrogliomas

For IDH-mutant astrocytomas and oligodendroglial tumors, resection should be performed at diagnosis. If a complete resection is achieved and the patient is younger than age 40 years, these patients have an excellent prognosis and may be followed with serial imaging alone to avoid long-term neurotoxicity from cranial irradiation.

For incompletely resected grade 2 tumors and for all grade 3 tumors, regardless of the degree of resection, however, immediate postoperative radiation plus adjuvant chemotherapy is recommended.[13] Postoperative radiation with adjuvant temozolomide is recommended for IDH-mutant astrocytomas.[A4] The combination of radiotherapy and chemotherapy with procarbazine, lomustine, and vincristine is superior to radiotherapy alone for patients with anaplastic oligodendroglial tumors.[A5]

Treatment is also instituted immediately after initial surgery in patients who have progressive neurologic symptoms or intractable seizures. It is also given at recurrence, sometimes following re-resection. Grade 2 tumors can transform to a higher-grade malignant neoplasm, a change that typically is associated with the appearance of contrast enhancement on MRI. Resection or a biopsy may be necessary in these patients to establish a change in grade, which often determines the appropriate dose of radiotherapy (60 Gy for high-grade lesions and about 54 Gy for low-grade tumors). Re-resection is followed by radiation therapy plus chemotherapy if patients have not received it previously. Salvage regimens include lomustine alone, bevacizumab, temozolomide (150 to 200 mg/m^2 for 5 days every 4 weeks for anywhere from 6 to 24 cycles), and carboplatin under expert supervision.

Optic and Brain Stem Glioma

Optic gliomas, which can involve the optic nerve or optic chiasm, are usually associated with neurofibromatosis type 1 (Chapter 385). Optic gliomas are typically pilocytic tumors that can have an indolent course, including rare spontaneous regression. Optic gliomas often are not amenable to surgical resection, and they can have a stuttering clinical course, with periods of visual loss punctuated by prolonged periods of visual stability. When necessary, radiation therapy or even chemotherapy may be useful under expert supervision, but often no treatment is required.

Brain stem gliomas usually involve the pons and less often the medulla or midbrain. Brain stem gliomas are most commonly seen in children in the first decade of life but can be found even in elderly people. Brain stem gliomas can have a low-grade or high-grade histology, but outcome is primarily determined by the location of the tumor. In general, most brain stem gliomas have a dismal

outcome, with survival of 1 year or less, but relatively benign variants occasionally occur, especially in adults with tumors in the medulla or midbrain.

Medulloblastoma

Medulloblastomas usually occur in the vermis of the cerebellum and principally affect children and young adults. Boys outnumber girls by about 2 : 1, and peak onset is age 7 years. Medulloblastoma in postpubertal patients and adults is rare and usually affects the cerebellar hemisphere.

Transcription profiles have identified four distinct subclasses that include the Wnt subtype (10% of tumors) driven by a stabilizing mutation in *CTNNB1* (β-catenin), which has an excellent prognosis; the SHH subtype (30% of tumors) with mutations in *PTCH1, SMO, GLI2,* or *SUFU,* which has an intermediate prognosis; group 3 (25% of tumors), which has an increased expression of *MYC* and has the worst prognosis; and group 4 (35% of tumors), which is characterized by isochromosome 17q and marked male predominance.[14] Medulloblastomas have a characteristic clinical presentation, with ataxia (due to cerebellar and brain stem involvement), headache, nausea, and vomiting (due to increased intracranial pressure from obstructive hydrocephalus).

TREATMENT AND PROGNOSIS

Aggressive surgery with complete excision is strongly associated with improved outcome. Surgery is always followed by craniospinal radiation therapy.

Adults with medulloblastoma should receive adjuvant multiagent chemoradiotherapy (e.g., vincristine, lomustine or cyclophosphamide, and cisplatin) under expert supervision. This treatment is associated with 5-year overall survival rates of up to 70% in adults with medulloblastoma despite its considerable toxicity.

Whether molecular subclasses should supersede clinical stratification or dictate the selection of treatment is unknown. The SHH-driven tumors may respond to Smo inhibitors.

Therapy of medulloblastoma often results in delayed complications in survivors, including intellectual deficits, growth impairment, and endocrinologic dysfunction. Late relapses and secondary neoplasms compromise long-term outcome.

Ganglioglioma

Gangliogliomas possess both a glial component and a neoplastic neural component (ganglion cell). Some low-grade gangliogliomas are indolent and do not require additional treatment after surgical extirpation. Patients with anaplastic tumors may fare better than patients with malignant gliomas, but recurrence is the rule despite surgery and radiation therapy. Gangliogliomas and other circumscribed astrocytic gliomas, glioneuronal, and neuronal tumors frequently harbor somatic mutations in the *BRAF* gene and respond to inhibitors of the RAF-MEK signaling axis.[15]

PRIMARY CENTRAL NERVOUS SYSTEM LYMPHOMA

Primary CNS lymphomas are associated with immunodeficiency states, particularly acquired immunodeficiency syndrome and organ transplantation, and are seen with increased frequency among the apparently immunocompetent population, in whom the median age at diagnosis is about 60 years. These tumors are usually diffuse large B-cell non-Hodgkin lymphomas identical to systemic diffuse large B-cell lymphoma (Chapter 171).

CLINICAL MANIFESTATIONS AND DIAGNOSIS

The tumor can involve the cerebrospinal fluid, eye, and brain, where it is multifocal in about 40% of patients at presentation (Fig. 175-6). Biopsy is usually the preferred surgical approach.

TREATMENT

In contrast to all other brain tumors, surgical resection may not be associated with improved survival and can cause significant neurologic morbidity. Chemotherapy is the primary treatment, and high-dose methotrexate (3 to 8 g/m^2 on alternate weeks for 3 to 12 months) is the most important chemotherapeutic agent.[16] In most patients, radiation therapy is avoided because the necessary whole brain irradiation causes significant cognitive impairment when it is combined with chemotherapy and does not prolong survival. Corticosteroids (e.g., dexamethasone 8 to 16 mg/day), which are frequently used as part of the chemotherapeutic regimen, not only help manage the associated cerebral edema but also can cause tumor regression. Ibrutinib, which is an inhibitor of Bruton tyrosine kinase, has antitumor activity in recurrent or refractory primary CNS lymphoma.

With the use of multiagent chemotherapy, with or without cranial irradiation, median survival is 3 to 5 years. Younger patients who receive high-dose chemotherapy and autologous stem cell transplantation may have a 60 to 70% chance of cure.[A6]

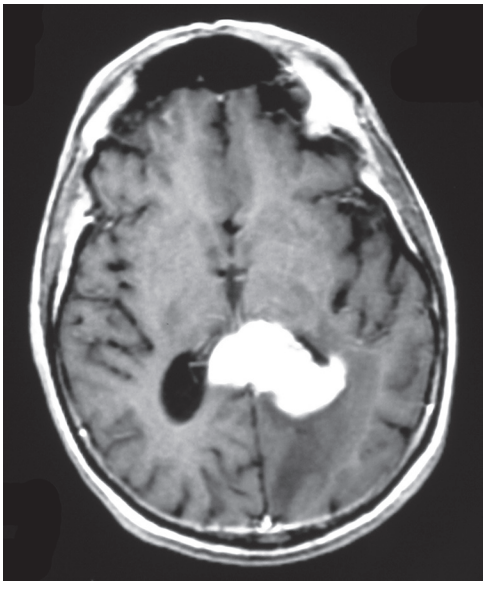

FIGURE 175-6. Primary central nervous system (CNS) lymphoma. A post-gadolinium magnetic resonance image demonstrating a diffusely enhancing splenial lesion. The periventricular location and absence of central necrosis are characteristic of primary CNS lymphoma.

OTHER INTRA-AXIAL PRIMARY BRAIN TUMORS

Rare, intra-axial cerebral tumors include ependymomas, which are optimally treated with surgical excision followed by radiation therapy.[17] Choroid plexus papillomas and carcinomas may be manifested with hydrocephalus or lateralizing signs. Resection may be sufficient for benign papillomas, but carcinomas rapidly recur even when postoperative radiation therapy is also used. Colloid cysts of the third ventricle are benign tumors that can cause obstructive hydrocephalus; they may be treated with a third ventriculostomy or with resection by use of an intraventricular endoscope.

Hemangioblastomas occur primarily in the cerebellum but can also occur in the spinal cord and the hemispheres. About 15% of patients with a hemangioblastoma have the autosomal dominant disorder von Hippel-Lindau disease (Chapter 385), which is characterized by hemangioblastomas in the CNS and retina, renal cell carcinoma, pheochromocytoma, endolymphatic sac tumors, and cysts in a variety of visceral organs. Hemangioblastomas are treated by surgical excision and require radiation therapy only for recurrence. Complete removal usually results in cure. The HIF-2α inhibitor belzutifan has shown promising antitumor activity against CNS hemangioblastomas in patients with von Hippel-Lindau disease.[18]

BRAIN METASTASIS

EPIDEMIOLOGY

Metastases are the most common intracranial tumors in adults. Every systemic cancer is capable of metastasizing to the brain. Melanoma (Chapter 188) has the greatest propensity to spread to the CNS, but the most common causes of CNS metastases are cancers of the lung (Chapter 177) and breast (Chapter 183). CNS metastases are being seen with greater frequency because patients with systemic cancers have prolonged survival with better treatments. In most patients with brain metastases, CNS disease develops late in the course of their illness, but a brain metastasis may be the initial presentation of a systemic cancer. In most of these patients, lung cancer is the primary site; in some, however, a primary site is never identified (Chapter 164).

CLINICAL MANIFESTATIONS AND DIAGNOSIS

Patients with brain metastases present with progressive neurologic symptoms and signs that typically include headache, seizures, and lateralizing signs. Metastases are best diagnosed by cranial MRI with gadolinium (Fig. 175-7). All lesions can be clearly seen by MRI, which is better than CT for visualizing the posterior fossa. Metastases, which are usually well-circumscribed lesions at the gray matter–white matter junction, are often associated with extensive edema. Hemorrhage into a metastasis occurs most frequently with metastases from melanoma, renal cancer, or thyroid cancer. Because brain metastases from lung cancer are so common, however, they are the most common hemorrhagic type. Sometimes, hemorrhage into a brain metastasis is best visualized by noncontrast head CT.

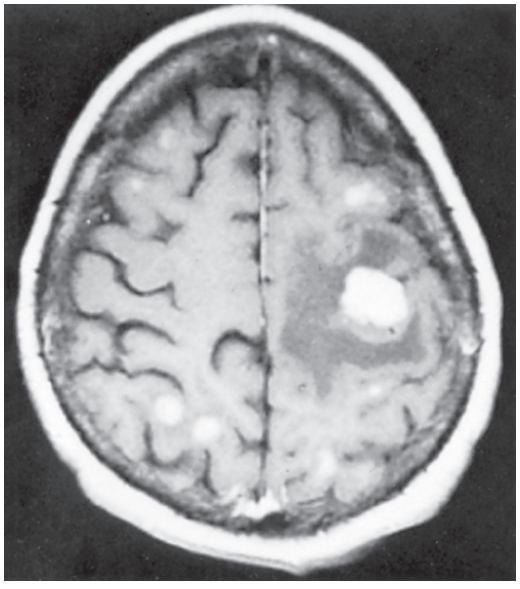

FIGURE 175-7. Brain metastasis. Multiple metastases from breast carcinoma are seen on this T1-weighted gadolinium-enhanced magnetic resonance image. The multiple smaller tumors were not visible on computed tomography, even after a contrast agent was given.

TREATMENT

The survival of patients with brain metastasis has been improved in recent decades by the increasingly individualized refinement of radiosurgical techniques and the development of more effective systemic therapies. Corticosteroids, especially dexamethasone (8 to 12 mg daily), are useful for symptomatic brain metastases. Anticonvulsant medications (Table 372-6) are required in patients who have seizures but are not recommended prophylactically in patients without seizures.[19]

Surgery

Because brain metastases do not widely infiltrate into brain tissue and tend to have a pseudo-capsule around them, they can be completely excised surgically. Complete removal of a single brain metastasis can substantially prolong life and maintain neurologic function. If multiple lesions can be completely resected, these patients do as well as patients in whom a single lesion has been removed.

Radiation Therapy

Postoperative whole brain radiation therapy significantly improves control of CNS disease after resection of a single brain metastasis, but it does not prolong survival because patients die of progressive systemic tumor.[20] The use of postoperative whole brain radiation therapy is frequently decided on an individual basis, but increasingly partial brain radiotherapy or stereotactic radiosurgery to the postoperative bed are used instead to avoid irradiating the entire brain. Nonetheless, many patients with multiple brain metastases are best treated with a course of whole brain radiation therapy, most commonly 3 Gy in 10 fractions for a total of 30 Gy. Stereotactic radiosurgery, with either a gamma knife that delivers gamma radiation from multiple cobalt sources or a linear accelerator that delivers x-rays to a highly focused area involving the tumor, has been effective for the treatment of patients with one to three brain metastases, resulting in less cognitive deterioration at 3 months, with no difference in overall survival compared with whole brain radiotherapy.[A7,A8] Growing evidence suggests the use of stereotactic radiosurgery for as many as 10 brain metastases.

Most patients tolerate radiosurgery without difficulty, but the procedure is occasionally complicated by seizures or acute swelling that causes more neurologic dysfunction. Approximately 20 to 30% of patients develop radiation necrosis, which may be indistinguishable clinically and on MRI from recurrent tumor. One advantage of stereotactic radiosurgery is that most of the normal brain is not exposed to the radiation.

Systemic Therapy

Chemotherapy is used to treat brain metastases from highly chemosensitive primary cancers, such as testicular cancer (Chapter 185), small cell lung cancer (Chapter 177), and, to a lesser extent, breast cancer (Chapter 183). Bevacizumab under expert supervision can be effective in progressive brain metastases or radionecrosis after stereotactic radiosurgery. Chemotherapy also has increasingly been used in asymptomatic patients in whom brain metastases are identified at diagnosis on a screening MRI examination and who require chemotherapy for their systemic disease. Brain metastases will frequently respond in a fashion comparable to other systemic sites of disease.

The choice of agents is based on the primary type of cancer and the patient's prior drug exposures under expert supervision. For patients with *BRAF*-mutant melanoma (Chapter 188), for example, the combination of BRAF plus MEK inhibition (dabrafenib plus trametinib) can achieve intracranial responses.[21] Similarly, systemic immunotherapy with nivolumab plus ipilimumab can provide clinically meaningful intracranial activity against asymptomatic melanoma brain metastases.[A9] Upfront systemic therapy with the combination of the HER2 kinase inhibitor tucatinib, capecitabine, and trastuzumab can be considered for the treatment of asymptomatic brain metastases in HER2-positive metastatic brain cancer patients (Chapter 183) who were previously treated with trastuzumab, pertuzumab, and trastuzumab-emtansine (T-DM1).[A10] Systemic therapy with newer-generation CNS-penetrant tyrosine kinase inhibitors, rather than radiation or surgery, is increasingly used for the initial treatment of lung cancer patients (Chapter 177) whose tumors harbor EGFR mutations, anaplastic lymphoma kinase (ALK) translocations, c-ROS oncogene 1 (ROS1)-rearrangements, RET fusions, or MET exon-14-skipping mutations.

FIGURE 175-8. Leptomeningeal metastases. Gadolinium-enhanced magnetic resonance imaging of the lumbosacral spine in a patient with leptomeningeal metastases from melanoma. Multiple enhancing nodules are seen on the cauda equina, and the conus medullaris and lower spinal cord are encased by tumor.

INTRACRANIAL LEPTOMENINGEAL METASTASIS

The brain is the most common intracranial site of metastases, but systemic cancer can spread to the dura and the leptomeninges as well. Dural metastases most commonly arise from breast (Chapter 183) or prostate (Chapter 186) cancer, frequently from a metastasis in the overlying calvaria.

CLINICAL MANIFESTATIONS AND DIAGNOSIS

Metastasis to the leptomeninges is often manifested as multifocal neurologic symptoms and signs. These metastases involve the cranial nerves to cause diplopia or bulbar palsy (E-Fig. 175-1); the cervical and lumbar roots to cause limb pain or weakness; and the intracranial space to cause headache, nausea, vomiting, and elevated intracranial pressure. The diagnosis is established by the presence of tumor cells in the cerebrospinal fluid, by cytologic examination or novel techniques to identify isolated cancer cells, or by neuroimaging that definitively outlines tumor in the subarachnoid space (Fig. 175-8).

TREATMENT

Treatment frequently involves radiation therapy to symptomatic sites. Intrathecal chemotherapy, usually through an intraventricular cannula (Ommaya reservoir), or systemic chemotherapy with agents or doses that penetrate into the cerebrospinal fluid are also used under expert supervision.

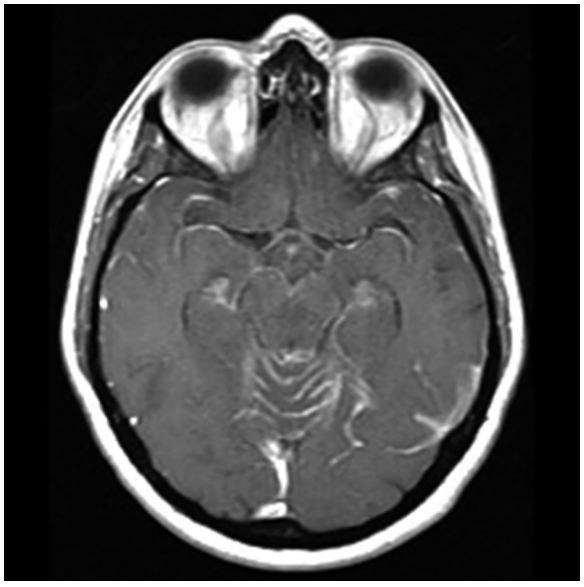

E-FIGURE 175-1. Leptomeningeal metastases. A post-gadolinium cranial magnetic resonance image demonstrating enhancement of all sulci of the cerebellar vermis representing tumor cells in the subarachnoid space of this patient with breast cancer.

TABLE 175-5 SPINAL TUMORS

EXTRADURAL
Metastasis
Primary bone tumors arising in the spine
Chordoma
Osteogenic sarcoma
Chondrosarcoma
Plasmacytoma
INTRADURAL EXTRAMEDULLARY
Meningiomas
Neurofibromas
Schwannomas
Lipomas
Arachnoid cysts
Epidermoid cysts
Metastasis
INTRAMEDULLARY
Ependymoma
Glioma
Hemangioblastoma
Lipoma
Metastasis

FIGURE 175-9. Multilevel epidural spinal cord compression. This patient with metastatic breast cancer has multiple areas of ventral epidural tumor seen throughout the thoracic spine on this post-gadolinium sagittal magnetic resonance image.

SPINAL TUMORS

Spinal tumors can be categorized according to the anatomic area they involve: extradural, intradural extramedullary, and intramedullary (Table 175-5). Extradural tumors typically arise from the bone elements of the spine and cause neurologic symptoms and signs by compressing the spinal cord. Intradural but extramedullary tumors arise from the pachy-meninges or nerve roots (meningiomas or schwannomas) and can cause either radicular symptoms or spinal cord compression. Most intradural extramedullary tumors are benign. Intramedullary spinal cord tumors are rare; they arise from the spinal cord parenchyma and have a biology that is similar to the biology of brain tumors.

EXTRADURAL TUMORS

Most extradural tumors originate from a metastasis to the bone elements of the spine, typically the vertebral body and occasionally the vertebral lamina or spinous process. Expansile growth of the bone tumor impinges on the spinal canal and, if untreated, compresses the spinal cord or the nerve roots as they exit the intervertebral foramina. Whereas most of these lesions arise from bone metastases, extradural tumors can also arise from paravertebral metastases that can grow through the intervertebral foramina and into the epidural space without affecting surrounding bone structures. Very rarely, a direct metastasis to the epidural space is also seen. The most common primary cancers that cause extradural metastases are prostate cancer (Chapter 186), breast cancer (Chapter 183), lung cancer (Chapter 177), and the lymphomas (Chapters 171 and 172). Hematologic malignant neoplasms may be associated with paravertebral disease that grows through the intervertebral foramina. Less common are primary tumors of the spine, including chordomas, osteogenic sarcomas, plasmacytomas, and chondrosarcomas.

CLINICAL MANIFESTATIONS

Extradural tumors cause neurologic symptoms and signs by compressing the spinal cord. Although the mass is a primary bone tumor or a metastasis from a distant source, 98% of patients present with pain that is usually localized to the site of the tumor. Because the spine has more thoracic than cervical or lumbar vertebrae, the tumor and pain are likely to be in the middle or high back, a site that is a less common site for benign pain (Chapter 369). Back pain often precedes the development of any other neurologic symptom or sign, frequently by weeks and occasionally by months. Motor impairment and sensory symptoms are present in about 50% of patients, whereas sphincter disturbances are found in only about 25% of patients.

DIAGNOSIS

Severe back pain in a patient with cancer should be evaluated by MRI, which does not require intravenous administration of contrast material. Plain films of the spine, bone scans, or even CT scans may show bone disease, but epidural tumor can only be seen only on MRI (Fig. 175-9). Furthermore, MRI is the only technique that can reveal paravertebral or direct epidural metastasis. Patients who cannot have an MRI study should be imaged by CT with sagittal reconstruction images.

The differential diagnosis of extradural tumors includes epidural abscess (Chapter 382), acute or subacute epidural hematomas (Chapter 369), herniated intervertebral discs (Chapter 369), spondylosis (Chapter 369), epidural lipomatosis, and, rarely, extramedullary hematopoiesis. On occasion, a percutaneous needle biopsy or decompressive laminectomy is required to make a definitive diagnosis.

TREATMENT

Epidural metastases require immediate treatment because patients can develop acute and unpredictable neurologic deterioration resulting in paraplegia.[22] Patients should be started on high-dose corticosteroids (usually >20 mg of intravenous dexamethasone), which rapidly relieve pain and may contribute to neurologic recovery.

Surgery followed by postoperative radiation therapy is superior to radiation therapy alone for preserving the ability to walk and may prolong survival in a wide population of patients with metastatic spinal cord compression. However, it may not benefit patients who are age 65 years and older.

Stereotactic radiosurgery is also an effective option to treat epidural metastases, either initially or at the time of relapse.[A11] It is much easier to preserve neurologic function than to reverse impairment, so clinically silent areas of extradural tumor that are detected on MRI should be treated before neurologic compromise develops. Patients with epidural metastasis can have a good neurologic outcome if they are treated before the onset of severe neurologic compromise, but their overall survival is usually short because of the presence of widespread metastatic disease.

Patients whose primary tumor arises in the spine, such as an osteogenic sarcoma (Chapter 187), should undergo definitive surgery. The need for postoperative radiation therapy is based on the tumor's histology.

INTRADURAL EXTRAMEDULLARY TUMORS

MENINGIOMAS

Spinal meningiomas are benign, slow-growing tumors that occur primarily in middle-aged women and are predominantly located in the thoracic region.

Back pain is a common symptom, but about 25% of patients have no pain and present with slowly progressive neurologic dysfunction, typically a gait disorder that has been progressing, frequently for years. Spinal MRI with gadolinium clearly delineates the lesion. Surgical resection is curative, and a complete resection can usually be accomplished easily.

NERVE SHEATH TUMORS

Nerve sheath tumors include schwannomas and neurofibromas. Both typically arise from the dorsal root, and the first symptom is often radicular pain that precedes symptoms of spinal cord compression by months or even years. Some patients with spinal neurofibroma or schwannoma have neurofibromatosis type 1 (Chapter 385), but most do not. The diagnosis is clearly established by gadolinium-enhanced MRI of the spine. The treatment is surgical, and complete removal results in cure.

METASTASES

Metastasis to the spinal leptomeninges can be manifested as an intradural extramedullary lesion. A single large tumor nodule can cause focal symptoms and signs referable to that spinal level. In most patients, however, multiple levels of the neuraxis are involved, and patients have multifocal neurologic symptoms and signs. Cervical and lumbosacral radicular pain, as well as sensory and motor loss, are seen in more than half of patients. The diagnosis is established by gadolinium-enhanced MRI showing multifocal nodules or sometimes a layer of cells coating the spinal cord or nerve roots (see Fig. 175-9). If imaging is negative, the diagnosis can be established by demonstrating tumor cells in the cerebrospinal fluid.

TREATMENT

Because of the diffuse nature of the disease, surgery is not an option. Treatment is complicated and frequently requires radiation therapy to symptomatic sites of disease, intrathecal chemotherapy best administered through an intraventricular cannula (Ommaya device) and occasionally systemic chemotherapy under expert guidance. Radiation therapy can ameliorate neurologic symptoms, particularly pain, but the disease often has a relentless progressive course, and results in death in 3 to 6 months despite aggressive therapy.

INTRAMEDULLARY TUMORS

Intramedullary spinal cord tumors are similar to neoplasms that arise in brain parenchyma. The most common spinal cord tumors are ependymomas and astrocytomas. Hemangioblastomas (particularly in association with von Hippel-Lindau disease), lipomas, and, rarely, intramedullary metastases are also seen.

CLINICAL MANIFESTATIONS AND DIAGNOSIS

All intramedullary tumors have a similar clinical presentation, and pain is a common initial symptom. Signs of spinal cord dysfunction subsequently ensue and reflect the location of the lesion. In addition, some intramedullary tumors are accompanied by a syrinx (Chapter 389), which can contribute to symptoms. The classic signs of intramedullary spinal cord lesions, such as dissociated sensory loss, sacral sparing, and early sphincter problems, are not sufficiently reliable to distinguish intramedullary from extramedullary lesions. The diagnosis is established by gadolinium-enhanced and T2-weighted MRI (Fig. 175-10).

TREATMENT

Surgery is the first therapeutic intervention, both to obtain a definitive diagnosis and to resect the lesion. Complete resection of spinal cord tumors is possible, particularly in the case of ependymomas and hemangioblastomas. However, spinal cord tumors are rare, and only neurosurgeons experienced in removal of this type of lesion should perform the procedure. High-grade gliomas and residual ependymomas should be treated with postoperative radiation therapy. Low-grade astrocytomas of the spinal cord can be treated with radiation therapy when the patient develops symptomatic neurologic impairment. Presymptomatic treatment does not prevent the development of impairment nor necessarily delay it. Intramedullary metastases do not require surgery because the diagnosis is usually straightforward. Radiation therapy provides limited benefit because these patients typically have other CNS metastases.

FIGURE 175-10. Spinal cord astrocytoma. T2-weighted sagittal magnetic resonance image demonstrating a lower cervical intramedullary low-grade astrocytoma; no enhancement was evident.

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176 HEAD AND NECK CANCER

JULIE E. BAUMAN

DEFINITION

Head and neck cancer arises from the mucosal linings of the upper aerodigestive tract, sinonasal cavities of the face, major or minor salivary glands, or the structures of the base of skull including cranial nerves. The dominant histology, squamous cell carcinoma, comprises more than 95% of cancers of the oral cavity, pharynx, larynx, and paranasal sinuses (Fig. 176-1). Due to the sun-exposed cutaneous surface area of the scalp and face, nonmelanomatous skin cancers, in particular basal cell carcinoma and squamous cell carcinoma, are also frequent within the head and neck. Other less common neoplasms occurring within the anatomic structures of the head and neck include sarcoma as well as cutaneous or mucosal melanoma, which are treated according to the principles for these mesodermal malignancies (Chapters 187 and 188, respectively).

Oral Cavity

The margins of the oral cavity extend superiorly from the skin-vermillion border of the upper lip to the junction of the soft and hard palates, inferiorly from the skin-vermillion border of the lower lip to the circumvallate papillae, and laterally to the anterior tonsillar pillars. The structures of the oral cavity include the mucosal lip, buccal mucosa, upper and lower alveolar ridges, retromolar trigone, floor of the mouth, hard palate, and oral or mobile tongue.

Nasopharynx

The margins of the nasopharynx start anteriorly at the posterior choana and extend along the superior, posterior, and lateral walls to a theoretical plane between the free edge of the soft palate and the posterior pharyngeal wall. The structures of the nasopharynx include the fossae of Rosenmüller, the superior surface of the soft palate, and the mucosal linings of the eustachian tube and choanal orifices.

Oropharynx

The margins of the oropharynx extend from the plane of the superior surface of the soft palate to the superior surface of the vallecula, or hyoid bone. The structures of the oropharynx include the base of the tongue (the lingular tonsil), the palatine tonsils, the glossotonsillar sulcus, the inferior surface of the soft palate and uvula, the anterior and posterior tonsillar pillars, and the continuity of the lateral and posterior pharyngeal walls. Oropharyngeal squamous cell carcinoma largely arises from the rich lymphoreticular tissue of the lingular and palatine tonsils.

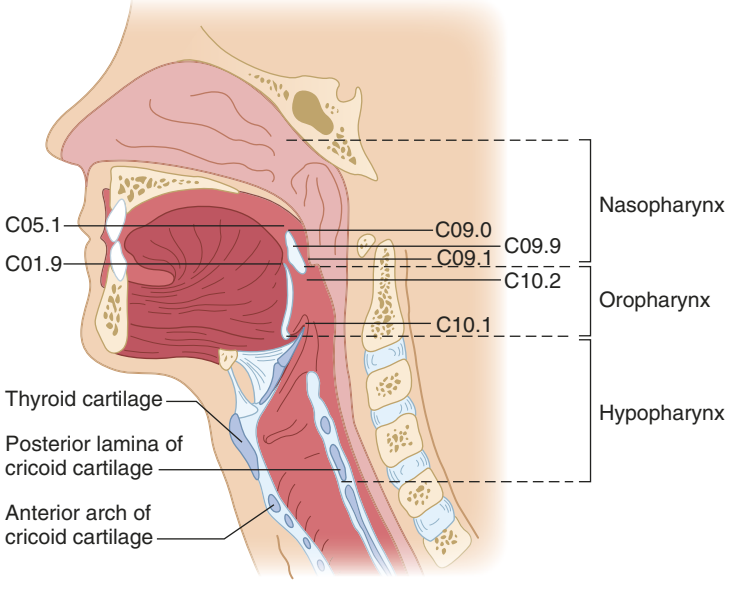

FIGURE 176-1. More than 95% of head and neck cancers arise from the mucosal surfaces of the upper aerodigestive tract. Specific anatomic sites are associated with unique etiologies, including environmental and viral risk factors, and underpin modern staging systems and treatment paradigms.

Hypopharynx

The margins of the hypopharynx extend from the plane of the superior border of the vallecula to the plane of the lower border of the cricoid cartilage. The structures of the hypopharynx include the pyriform sinuses, the lateral and posterior hypopharyngeal walls, and the postcricoid region.

Larynx

The margins of the larynx include anteriorly the anterior surface of the epiglottis, the thyroid cartilage, and the anterior arch of the cricoid cartilage; posterolaterally the aryepiglottic folds and arytenoids; superolaterally the tip and lateral borders of the epiglottis; and inferiorly the plane of the inferior border of the cricoid cartilage. The structures of the larynx include the epiglottis and false cords (supraglottic larynx), the true vocal cords (glottis), and the subglottis.

Salivary Glands

The salivary glands of the head and neck comprise the major salivary glands, which include the parotid, submandibular, and sublingual glands, as well as the minor salivary glands, which are scattered throughout the lining of paranasal sinuses, oral cavity, pharynx, and larynx. Approximately 6 to 8% of head and neck cancers arise from the salivary glands. Although the unified biologic function of salivary glands is the production and secretion of saliva, salivary gland tumors are histologically, genetically, and prognostically diverse. The three most common histologies are mucoepidermoid carcinoma, adenoid cystic carcinoma, and salivary duct carcinoma, which presents de novo or arises from a preexisting pleomorphic adenoma.

EPIDEMIOLOGY

Head and neck cancer is the seventh most common incident cancer worldwide. Among the more than 900,000 index cases of head and neck squamous cell carcinoma estimated in 2020, the substantial majority was caused by environmental carcinogenesis.[1]

Viruses

Human Papillomavirus

Oropharyngeal squamous cell carcinomas also can be caused by oncogenic human papillomaviruses (HPVs). Oral HPV 16 infection (Chapter 344) is responsible for about 80% of oropharyngeal cancers in the United States and is the cause of the ongoing epidemic of oropharyngeal squamous cell carcinoma predominantly occurring in males across all inhabited continents. Patients who are diagnosed with HPV-associated oropharyngeal squamous cell carcinoma have a lower median age at diagnosis, 58 years, than patients with environmental head and neck squamous cell carcinoma. The male:female incidence ratio is approximately 5 : 1.

Oral HPV infection is sexually transmitted and consistently associated with oral sexual behavior, including oral-oral, oral-genital, and oral-anal exposures. The prevalence of oral oncogenic HPV infection has two distinct peaks among males: between ages 25 and 30 years and 55 and 60 years, whereas the median age at diagnosis of HPV-associated oropharyngeal squamous cell carcinoma is 58 years. Thus, the estimated latency period between initial oral HPV infection and the development of oropharyngeal squamous cell carcinoma is approximately 10 to 30 years.

In the United States, the proportion of oropharyngeal squamous cell carcinoma cases infected with HPV has increased substantially. Furthermore, the incidence of human papillomavirus–associated oropharyngeal squamous cell carcinoma in the United States surpassed the incidence of cervical cancer in 2016. Incidence rates of HPV-associated oropharyngeal squamous cell carcinoma also have been rising in Europe, Australia, Asia, Brazil, and Peru, although large regional, racial, and ethnic variations exist as demonstrated by lower rates in Central Europe, some regions of Latin America, and among Blacks and Hispanics in the United States.

Epstein-Barr Virus

The dominant risk factor for nasopharyngeal carcinoma is infection with the Epstein-Barr virus (Chapter 348), which is an endemic cause of nasopharyngeal carcinoma in Southeast Asia, North Africa, and circumpolar indigenous populations, where the median age of diagnosis is age 50 years.[2] Head and

ABSTRACT

Head and neck cancer, the seventh most common cancer worldwide, primarily arises from the mucosal linings of the upper aerodigestive tract. Head and neck squamous cell carcinoma, the dominant histology, is caused either by environmental carcinogens such as tobacco and alcohol or by oncogenic viruses including human papillomavirus (HPV) and Epstein-Barr virus (EBV). Chronic exposure to environmental carcinogens causes the accumulation of structural and functional DNA damage, thereby leading to HPV-negative head and neck squamous cell carcinoma. Persistent infection with oral HPV is now recognized as a necessary cause for the epidemic of oropharynx cancer in the United States and Western Europe, whereas EBV has long been recognized as the cause of endemic nasopharynx cancer in Southeast Asia. The clinician must be aware of the ongoing epidemic of HPV-associated head and neck squamous cell carcinoma when evaluating a new, painless neck mass. The diagnosis of head and neck squamous cell carcinoma is established by biopsy of the primary or fine-needle aspirate of the neck mass. For oropharynx primaries, HPV status is determined by p16 immunohistochemistry. More than 90% of head and neck squamous cell carcinoma cases are stage I to IVb and can be treated with curative intent. A specialized multidisciplinary team composed of surgical, medical, and radiation oncologists optimizes oncologic and functional outcomes. Important advances in minimally invasive transoral surgical techniques, intensity-modulated radiation therapy, and molecular- and immune-directed systemic therapies improve both survival and survivorship.

KEYWORDS

head and neck cancer
squamous cell carcinoma
human papillomavirus
Epstein-Barr virus
environmental carcinogenesis
tobacco
molecular targeting
immunotherapy

neck cancer related to the oncogenic Epstein-Barr virus is also predominantly observed in males, with a male:female incidence ratio of approximately 3 : 1.

Human Immunodeficiency Virus (HIV)

The age-standardized incidence of HPV-associated and HPV-negative head and neck squamous cell carcinoma is three-fold higher in HIV-infected individuals than in the general U.S. population. Although the excess in tobacco-related cancers is decreasing in this population, likely due to declining tobacco use, the excess of HPV-associated head and neck squamous cell carcinoma is increasing. Unlike cervical cancer, HPV-associated oropharyngeal squamous cell carcinoma is not considered an AIDS-defining cancer. Nonetheless, the prevalence of oral HPV infection in HIV-infected people is inversely related to the $CD4^+$ T-cell count, thereby indicating that HIV-induced immunosuppression and the associated failure to control oncogenic HPV are major contributors to rising incidence rates.

Environmental Carcinogens

The risk of environmental head and neck squamous cell carcinoma increases with age, with diagnosis at a median age of 66 years. Environmental risk factors can be proximal, when modifiable individual behavior causes direct carcinogen exposure from tobacco, alcohol,[3] or the areca nut (Chapter 165). Depending upon the world region, approximately half of attributable risk for head and neck cancer is explained by such proximal environmental risk factors. Distal environmental risk factors also pose a substantial burden in developing countries when unavoidable exposures to secondhand smoke, industrial pollution, pestilence, or war are especially associated with low socioeconomic status. Incidence patterns for head and neck cancer caused by environmental carcinogenesis vary in relationship to exposure patterns. In the populations of the United States, Hong Kong, and the Republic of Korea, for example, the incidence of environmental head and neck squamous cell carcinoma is declining in parallel to decreased overall use of tobacco, whereas the incidence is rising in Taiwan, England, and Peru.[4]

Occupational exposures associated with head and neck cancer include the group 1 human carcinogen solvents, polycyclic aromatic hydrocarbons, and heavy metals. For head and neck cancer, the strongest data point to formaldehyde for nasopharynx cancer, polycyclic aromatic hydrocarbons for larynx cancer, chlorinated solvents for all head and neck squamous cell carcinoma anatomic sites, and wood dust for sinonasal cancer.

Leukoplakia

The minority of oral squamous cell cancers are preceded by precancerous lesions, termed *oral potentially malignant disorders*. Acquired potentially malignant disorders, including *leukoplakia* (mucosal white patches or plaques that cannot be rubbed off) and *erythroplakia* (a fiery red patch that cannot be characterized clinically or pathologically as any other diagnosis; Chapter 393), are associated with the consumption of tobacco and alcohol.[5] The presence of loss of heterozygosity within an oral potentially malignant lesion is associated with higher risk of progression to oral cancer within the lesion itself or at another site within the carcinogen-exposed epithelium and is useful for risk stratification.[6]

Sex and Genetic Risk Factors

Males demonstrate a significantly higher risk than females for head and neck squamous cell carcinoma, whether caused by environmental carcinogens or oncogenic viruses. The male:female ratio for HPV-unrelated head and neck squamous cell carcinoma parallels the sex-specific prevalence of tobacco, alcohol, or areca nut use in any geographic area. For instance, the age-adjusted incidence rate of oral cavity cancer among men ranges from 1 to 16 per 100,000 population as compared with 0 to 10 per 100,000 among women. Despite a similar prevalence of anogenital HPV infection between adult males and females, males have significantly higher rates of oral HPV infection. In a population-based, cross-sectional study in the United States, 1.6% of men versus 0.3% of women harbored oral HPV 16. The disparity in HPV oral infection is reflected in the incidence rate of HPV-associated oropharyngeal squamous cell carcinoma, in which the male:female ratio ranges from 2.7 to 5.7. Plausible biologic explanations for this disparity are two-fold: oral HPV infections are cleared more slowly by males, and the linear dose-response relationship between lifetime number of sexual partners and the prevalence of oral HPV infection exists uniquely among males, thereby suggesting that males less frequently develop protective anti-HPV antibodies when exposed to anogenital HPV than do females.[7]

Genetically inherited disorders associated with oral leukoplakia and high risk of progression to head and neck squamous cell carcinoma include the rare bone marrow failure syndromes dyskeratosis congenita, which is caused by aberrant telomere biology, and Fanconi anemia, which is caused by inherited mutations in DNA repair genes (Chapter 151).

Dietary Factors

A reduced risk for head and neck squamous cell carcinoma has been associated with diets rich in fruits and vegetables, in particular the *Brassica* genus of cruciferous vegetables. Crucifers are rich in isothiocyanates, which are phytochemicals that potently induce cytoprotective enzymes that could mitigate the impact of environmental carcinogens including benzene, polycyclic aromatic hydrocarbons, and mutagenic aldehydes found in tobacco smoke and air pollution. People with incident environmental head and neck squamous cell carcinoma have lower serum levels of several micronutrients, including vitamin A and beta carotene, which may be surrogates for lower intake of fruits and vegetables.

Ionizing Radiation

Ionizing radiation was first recognized as a risk factor for both benign and malignant salivary gland tumors among long-term survivors of the Hiroshima and Nagasaki, Japan, atomic bombs. Increased odds of salivary gland tumors are also observed in people treated with therapeutic radiation during childhood, with evidence of a dose-response relationship. Unlike head and neck squamous cell carcinoma, salivary gland tumors are not associated with tobacco exposure, with the single exception of the benign Warthin tumor.

PATHOBIOLOGY

Environmental Carcinogenesis

The transformation of oral epithelial cells by environmental carcinogens is based on the principle of multistep carcinogenesis, in which the accumulation of structural and functional DNA damage drives stepwise clonal evolution. Loss of heterozygosity, also known as allelic imbalance, has been quantified across the histopathologic spectrum of hyperplasia, dysplasia, and carcinoma in situ to model malignant transformation. In essence, environmentally induced head and neck squamous cell carcinoma is characterized by loss of function of tumor suppressor genes and genes that influence NOTCH signaling.[8] A central, early molecular event is loss of heterozygosity at 9p21, which is the locus of the *CDKN2A* gene. *CDKN2A* encodes p16, which is a tumor suppressor that regulates cell cycle traversal from the G1 to S-phase. Mutation of *TP53* is a later molecular event. Mutations of *CDKN2A* and *TP53* are the most common genetic alterations in HPV-negative head and neck squamous cell carcinoma and are observed in 57% and 84% of cases, respectively. Moreover, expression of p16 is lost due to epigenetic silencing in an additional 30% of tumors, thereby leading to the histopathologic classification of HPV-negative head and neck squamous cell carcinoma as "p16-negative." *PIK3CA*, which encodes the alpha subunit of phosphoinositide-3-kinase (PI3K), is the most commonly mutated oncogene in HPV-negative head and neck squamous cell carcinoma.[9] Nongenomic activation of the oncogenes epidermal growth factor receptor (EGFR) and cyclooxygenase-2 (COX2) is induced by tobacco smoke and also increases during oral epithelial transformation. Aberrant activation of PI3K, EGFR, and COX2 contributes to uncontrolled cellular proliferation while subverting an appropriate apoptotic response to DNA damage.

Viral Carcinogenesis

HPV, which is a member of the *Papillomaviridae* family, is an epitheliotropic, double-stranded, circular DNA virus with more than 170 distinct genotypes (Chapter 344). The viral life cycle is strictly dependent upon the cellular differentiation program of the keratinocyte, and viral oncogene expression is coordinated with cellular division and stratification. Members of the alpha genus infect mucosa, and high-risk anogenital genotypes, including HPV 16 and 18, are the established cause of cervical cancer. HPV genotype 16 also has a predilection for the lymphoid-rich mucosa of the oropharynx, and it comprises more than 95% of DNA isolated from oropharyngeal squamous cell carcinoma specimens. In particular, the early genes, E6 and E7, are transcribed in the basal and parabasal cell layers. The E6 and E7 oncoproteins degrade two critical tumor suppressors, p53 and retinoblastoma, respectively. Retinoblastoma is a nuclear protein that serves as the major G1 checkpoint in cell cycle regulation. The functional loss of retinoblastoma and p53 permit unbridled cellular proliferation. As the keratinocyte stratifies into the spinous epithelium, late viral genes are expressed, including the L1 and L2 capsid proteins. Ultimately, progenitor virions are encapsidated and released from the anuclear, cornified keratinocytes. In an HPV-transformed malignancy, late viral

gene expression is lost, and the virus fails to complete its life cycle. However, the E6 and E7 oncoproteins are preserved and necessary for maintenance of the transformed phenotype.

The mutational spectrum of HPV-associated oropharyngeal squamous cell carcinoma is distinct from that of HPV-negative disease. Although p53 dysfunction appears to be a universal requirement for squamous epithelial transformation, in HPV-associated oropharyngeal squamous cell carcinoma, this dysfunction is accomplished by the degradation of p53 protein by the E6 oncoprotein. Thus, in HPV-infected cells there is little selective advantage for *TP53* mutations, which are rarely identified in this setting. Likewise, genomic alterations in *CDKN2A* are not observed. In fact, as a consequence of negative feedback inhibition, p16 is upregulated as E7 degrades retinoblastoma, resulting in the histopathologic classification of HPV-positive oropharyngeal squamous cell carcinoma as "p16-positive." Diffuse nuclear and cytoplasmic immunohistochemical (IHC) staining for p16 is an accepted surrogate for HPV in oropharyngeal squamous cell carcinoma. The most common genomic alteration in HPV-associated oropharyngeal squamous cell carcinoma, found in approximately 50% of cases, is mutation or amplification of the oncogene *PIK3CA*. The selection for gain-of-function alterations in *PIK3CA* results in hyperactive PI3K pathway signaling, and the associated pro-proliferative, antiapoptotic phenotype may initially enhance the viral life cycle.

Immunology

Whether caused by environmental carcinogens or HPV oncogenes, head and neck squamous cell carcinoma demonstrates a markedly suppressive immune profile. Although immunogenic tumor antigens exist in head and neck squamous cell carcinoma, as confirmed by circulating T lymphocytes specific for p53 and the E6/E7 oncoproteins, head and neck squamous cell carcinoma evades recognition by selective loss of human leukocyte antigen I as well as antigen processing machinery. Head and neck squamous cell carcinoma also induces a tumor-permissive cytokine profile, in which immunosuppressive cytokines such as TGF-β, interleukin-6, and vascular endothelial growth factor predominate over immune-stimulatory cytokines such as IFN-γ or interleukin-12. Head and neck squamous cell carcinoma also demonstrates critical defects in immune effector cells. Tumor-infiltrating lymphocytes demonstrate low expression of costimulatory T-cell receptors, such as OX40 and CD137, and high expression of coinhibitory receptors, including the immune checkpoints cytotoxic T-lymphocyte–associated antigen 4 (CTLA-4) and programmed death 1 (PD-1).

Molecular Landscape of Salivary Gland Cancers

Approximately 90% of cases of mucoepidermoid carcinoma, which is the most common malignant salivary gland tumor, have the *MECT1-MAML2* gene fusion, which is now considered a genomic hallmark and used to establish pathologic diagnosis. Most adenoid cystic carcinomas harbor a gene rearrangement with the transcription factor *NFIB*, including *MYB-NFIB*, which is regulated by IGF1R in an AKT-dependent manner by overexpression of insulin growth factor receptor 1 (IGFR1). Secretory carcinoma, previously known as mammary analogue secretory carcinoma, is associated with *NTRK* gene fusions. Salivary duct carcinoma almost uniformly expresses the androgen receptor. Otherwise, salivary duct carcinoma demonstrates different genetic fingerprints depending upon whether it arises de novo or from a preexisting pleomorphic adenoma. De novo salivary ductal carcinoma frequently harbors somatic mutations in *HRAS, PIK3CA*, or both, whereas salivary ductal carcinoma from a preexisting pleomorphic adenoma is commonly enriched for HER2neu amplification.

CLINICAL MANIFESTATIONS

Oral Cavity Cancer

Proximal risk factors for oral cavity cancer include oral tobacco, tobacco smoke, areca nut (betel quid), alcohol, and poor dentition. Oral cavity cancers typically present at an early stage with the chief complaint of a persistent mouth sore, ulcer, or mass lesion.[10] Due to rich innervation, cancers of the mobile tongue are often painful and functionally interfere with the oral phase of eating. Dysarthria, but not hoarseness, can also be associated with larger lesions of the oral cavity.

HPV-Associated Oropharyngeal Squamous Cell Carcinoma

Risk factors for HPV-associated oropharyngeal squamous cell carcinoma include lifetime number of sexual partners and male sex. Although not pathognomonic, HPV-associated oropharyngeal squamous cell carcinoma typically presents with a small, asymptomatic T1-2 primary tumor and a persistent neck mass. Among squamous cell carcinomas of unknown primary metastatic to the cervical neck, the majority are p16-positive, and the primary is usually localized within the tonsil or base of the tongue. If an oropharynx tumor is more advanced, patients can present with globus sensation, throat pain, otalgia, dysphagia, odynophagia, or hemoptysis.

HPV-Unrelated Oropharyngeal Squamous Cell Carcinoma and Hypopharynx Cancer

Behavioral risk factors for HPV-unrelated oropharyngeal squamous cell carcinoma and hypopharynx cancer include tobacco smoke and alcohol. Due to occult anatomy, HPV-negative oropharynx and hypopharynx cancers often present with locally advanced T3-4 tumors that cause throat pain, dysphagia, or weight loss.

Larynx Cancer

Proximal risk factors for larynx cancer include tobacco smoking and alcohol use. Laryngeal cancers frequently present with hoarseness as early-stage T1-2 disease (Chapter 397). More advanced tumors can present with airway obstruction that requires emergent tracheostomy.

Nasopharyngeal Carcinoma

More than 70% of cases of nasopharyngeal carcinoma occur in Southeast Asia, although its incidence is declining worldwide. A painless cervical mass is the most common mode of presentation. Other associated symptoms include epistaxis, unilateral nasal obstruction, conductive hearing loss, and cranial nerve involvement.

Salivary Gland Tumors

Salivary gland tumors have a varied presentation depending upon the site of origin, with chief complaints including an uncomplicated parotid or submandibular mass, a new or growing oral or oropharyngeal lesion, dysphagia, cough, hoarseness, and even airway obstruction. A rare presentation is Bell palsy (Chapter 388) of cranial nerve VII, which courses through the deep parotid gland where occult tumors can be missed by routine inspection and palpation. The typical presentation of Bell palsy is acute, flaccid facial paralysis without an obvious parotid mass. If no mass is evident, cranial nerve VII palsy may initially be treated with steroids and antiviral therapy (Chapter 388), but follow-up for resolution is critical. An atypical presentation, such as a prodrome of unilateral facial twitching or spasm, slow progression over 1 month or more, or nonresolution after 4 months should trigger magnetic resonance imaging and referral to an otolaryngologist.

Other Head and Neck Tumors

Lymphomas frequently manifest either as neck nodes or in the lymphoid tissues of the ring of Waldeyer (Chapters 171 and 172). The tonsil is a preferred site for mantle cell and undifferentiated lymphomas. Solitary, extramedullary plasmacytoma (Chapter 173) can also occur in the nasopharynx or paranasal sinuses. Sarcomas (Chapter 187) in the head and neck include osteogenic sarcomas and nerve sheath tumors. Paragangliomas can be extensive, multicentric, and vascular. Rhabdomyosarcomas have a predilection for the orbit and sinuses. Melanomas and squamous cell cancers can be accompanied by neck adenopathy or parotid lesions.

DIAGNOSIS

Evaluation of a Neck Mass

In adults, particularly adults over age 40 years, a new neck mass requires a disciplined diagnostic approach with high suspicion for malignancy (Fig. 176-2). The mass, which can be a cystic mass, an enlarged lymph node, or a collection of lymph nodes (Chapter 154), should be considered cancer unless proved otherwise. In an adult male, HPV-associated oropharyngeal squamous cell carcinoma most commonly presents as a new painless neck mass. In endemic regions, Epstein-Barr virus–related nasopharyngeal carcinoma most commonly presents with a painless cervical neck mass, often in association with unilateral nasal obstruction and/or epistaxis. Supraclavicular masses usually are related to primary tumors below the clavicles, whereas submental, upper cervical, and midcervical neck masses almost always derive from head and neck tumors.

The differential diagnosis is framed by a detailed medical and social history, including assessment for time course; antecedent or current upper respiratory, dental, or sinus infection; epistaxis; dysphagia or odynophagia; otalgia; hoarseness; hemoptysis; B symptoms (fever, drenching night sweats, or weight loss); tobacco and alcohol habits; prior tobacco-related malignancy; prior

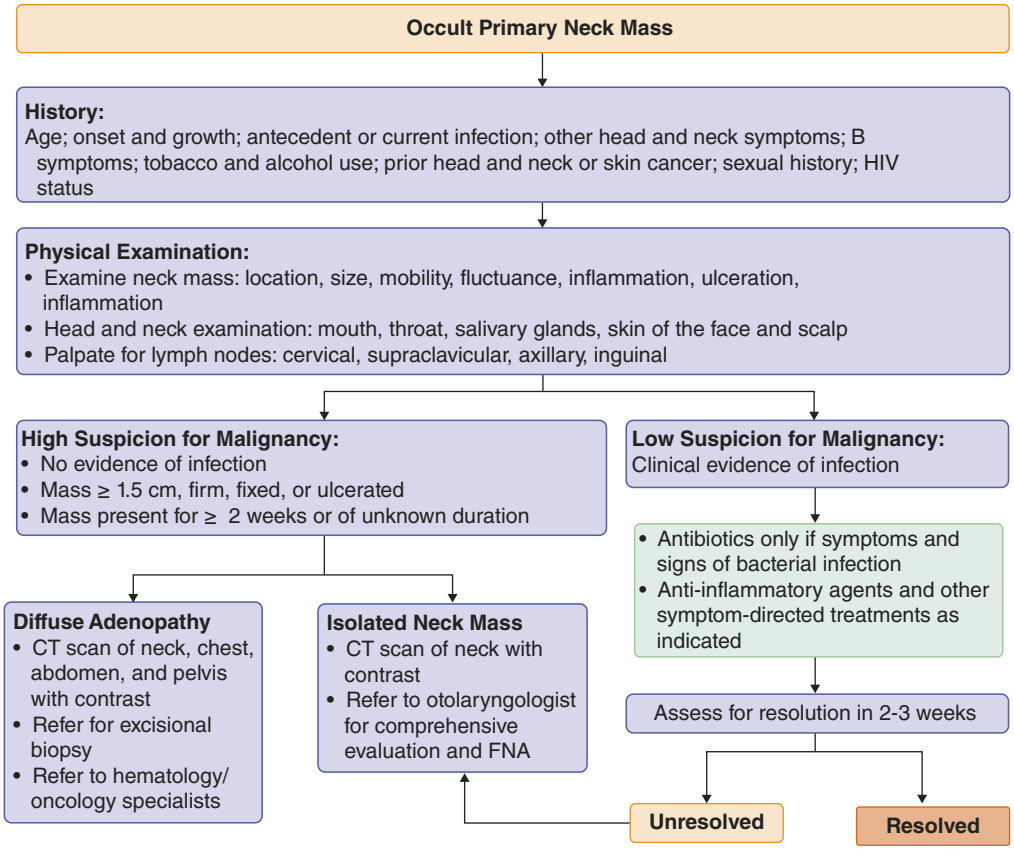

FIGURE 176-2. **Evaluation of an occult neck mass. B symptoms = fever, drenching night sweats, weight loss (>10% over 6 months); CT = computed tomography; FNA = fine needle aspiration; HIV = human immunodeficiency virus. (Adapted from Pynnonen MA, Gillespie MB, Roman B, et al. Clinical practice guideline: evaluation of the neck mass in adults. *Otolaryngol Head Neck Surg*. 2017;157[2 Suppl]:S1-S30.)**

skin cancer; sexual history; and HIV status. The physical examination should encompass the head and neck, including inspection and palpation of the oral cavity, oropharynx, and major salivary glands; inspection of the skin of the face and scalp; and a thorough examination of lymph nodes, including sites outside the neck.

The primary tumor site for an isolated upper cervical neck mass is most commonly found in the oropharynx (base of the tongue and tonsil), but salivary gland cancers, lymphomas, melanomas, and nonmelanoma skin cancers can also present in this manner. In East and Southeast Asia, a new neck mass also requires close examination of the nasopharynx.

Systemic symptoms or enlarged lymph nodes at other sites suggest lymphoma, whereas tenderness, warmth, and erythema suggest an infectious cause. Intraparotid nodes most commonly are metastases from skin malignancies. If the history and physical examination suggest reactive lymphadenopathy based on evidence of current or antecedent infection (Chapter 154), a brief course of observation or treatment with antimicrobial or anti-inflammatory medications is appropriate, but re-evaluation for resolution is critical. In all cases, a neck mass that persists for more than 3 weeks in an adult should prompt referral to an otolaryngologist to evaluate the patient for a potential malignancy.

Pathology

In the evaluation of a persistent neck mass, the initial test should be a fine needle aspiration (FNA) of the mass. Excisional biopsy is reserved for cases in which initial or repeat FNA is nondiagnostic and panendoscopy has identified no primary or when the baseline suspicion for lymphoma is very high due to extensive adenopathy outside of the neck (Chapter 154).

Ultimately, cytology or histology must confirm the diagnosis of head and neck squamous cell carcinoma. Environmental head and neck squamous cell carcinoma is associated with well to poorly differentiated cells, whereas well-differentiated tumors demonstrate unique features of keratinization including the presence of "keratin pearls" (Fig. 176-3 A and B). HPV-associated oropharyngeal squamous cell carcinoma is commonly associated with poorly differentiated or basaloid histology and lacks keratin pearls (Fig. 176-3 C and D). For oropharyngeal or unknown primary tumors, HPV status must be determined because it influences both staging and prognosis. The most widely used and accepted standard is immunohistochemistry for the cell cycle protein p16; diffuse nuclear and cytoplasmic staining in more than 70% of tumor cells signifies an HPV-positive tumor (Fig. 176-3E). Of note, p16 immunohistochemistry is not a direct measurement of the HPV 16 virus or its oncoproteins; rather, p16 overexpression confirms the presence of functionally relevant E7 oncoprotein. As such, p16 immunohistochemistry is not considered a surrogate for HPV infection outside of the oropharynx. Alternative methods for establishing the HPV status of oropharyngeal squamous cell carcinoma include in situ hybridization for HPV 16 DNA, multiplex polymerase chain reaction (PCR) for high-risk HPV genotypes, and detection of E6 and E7 mRNA by reverse transcription PCR.

Staging

Once a pathologic diagnosis of head and neck squamous cell carcinoma is established, the staging evaluation includes the following procedures:

- Complete head and neck examination with mirror or fiberoptic examination of the oropharynx, hypopharynx, larynx, and nasopharynx as indicated.
- Head and neck imaging. Locoregional staging is accomplished by a computed tomography (CT) or magnetic resonance imaging (MRI) scan of the primary and neck.
- Chest imaging. Less than 10% of patients with head and neck squamous cell carcinoma present with distant metastatic disease at diagnosis; however, distant metastases, when present, typically occur in the lungs. As a result, a diagnostic chest CT scan is a recommended component of staging; combined positron emission tomography (PET)/CT may also be considered, particularly in patients who have locally advanced tumors or nodal disease. Since patients with tobacco-related head and neck squamous cell carcinoma have a high risk for a second primary upper aerodigestive malignancy, including a head and neck, esophageal, or lung primary, a chest CT or PET/CT is also routinely indicated in such patients.
- The utility of panendoscopy under anesthesia with direct laryngoscopy, esophagoscopy, and bronchoscopy depends on expert consultation.

Each head and neck squamous cell carcinoma primary site has a staging system (Table 176-1). Staging for oral cavity tumors incorporates depth of invasion, tumor size, and invasion of adjacent structures. p16-positive (HPV-associated) oropharyngeal squamous cell carcinoma is distinguished from p16-negative oropharyngeal squamous cell carcinoma by a separate TNM staging system. p16-negative oropharyngeal squamous cell carcinoma is

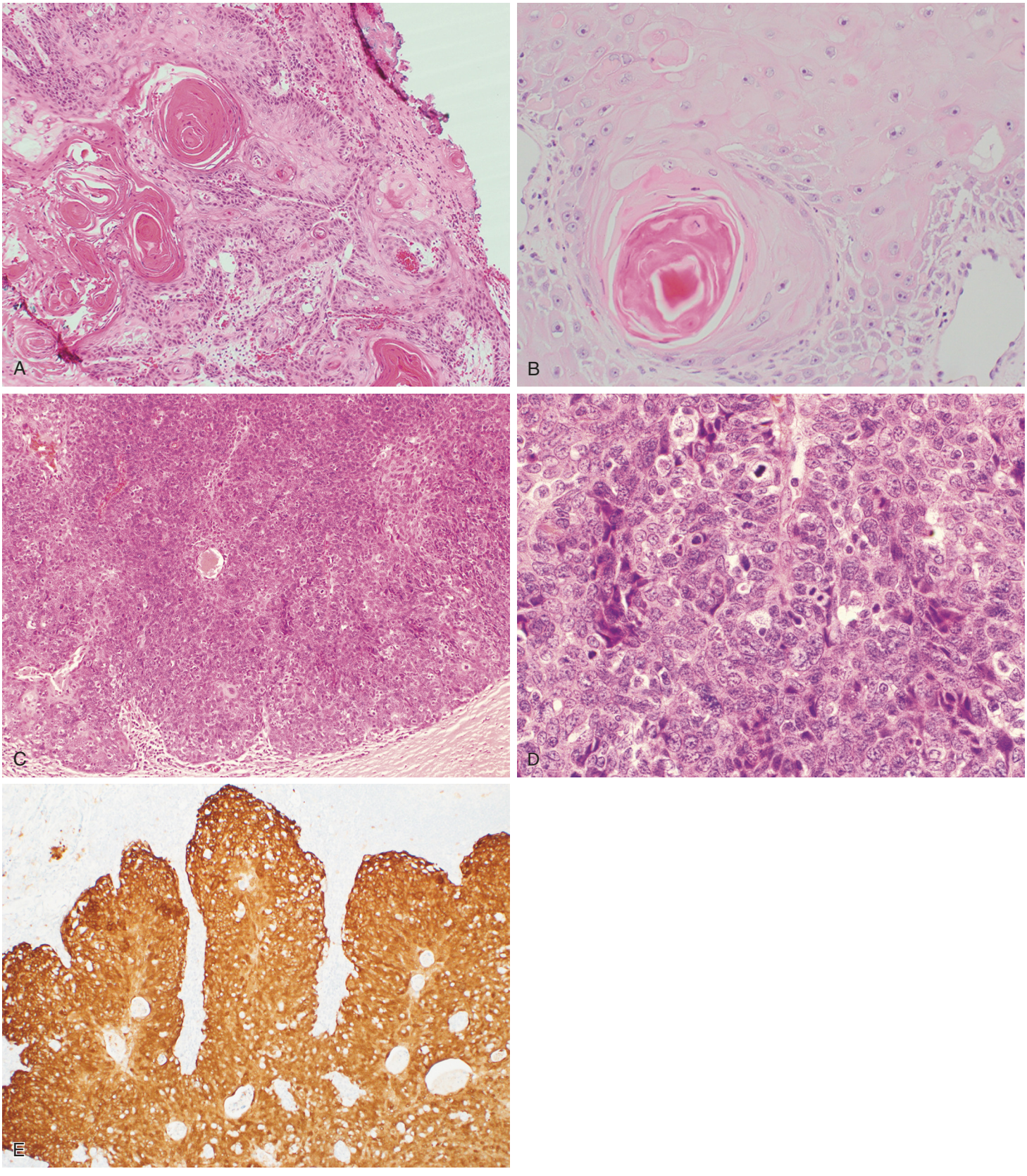

FIGURE 176-3. Head and neck squamous cell carcinoma histology and immunohistochemistry. A, The jagged outlines of well-differentiated squamous cell carcinoma tongues are associated with stromal desmoplastic reaction (low power). **B,** Keratin pearls, abnormal squamous cells forming concentric layers, are associated with well-differentiated squamous cell carcinoma (high power). **C,** Basaloid squamous cell carcinoma is frequently associated with human papillomavirus (HPV) infection, here demonstrating a highly infiltrative pattern of nests composed of poorly differentiated cells with pushing borders (low power). **D,** The basaloid squamous cell carcinoma cells demonstrate high nuclear to cytoplasmic ratios and numerous mitotic figures (high power). **E,** HPV-associated oropharyngeal squamous cell carcinoma shows poorly differentiated histology and diffuse nuclear and cytoplasmic staining for the p16 protein (high power).

grouped with hypopharynx cancers owing to the common etiology of environmental carcinogenesis, contiguous anatomy, and similarly poor prognosis. For hypopharynx and p16-negative oropharyngeal squamous cell carcinoma, tumor staging incorporates both size and invasion of adjacent structures. Staging of larynx cancer uniquely includes vocal cord mobility, where vocal cord fixation constitutes a T3 tumor irrespective of size. Due to distinct biology, patterns of spread, and natural history, nasopharyngeal carcinoma has its own staging system.

TABLE 176-1 CLINICAL PRIMARY TUMOR STAGING SYSTEM FOR HEAD AND NECK SQUAMOUS CELL CARCINOMA

TUMOR	LARYNX	LIP & ORAL CAVITY	HYPOPHARYNX	OROPHARYNX (p16-NEGATIVE)	OROPHARYNX (p16-POSITIVE)
T0	NA	NA	NA	NA	No primary identified
TX	Primary tumor cannot be assessed	Primary tumor cannot be assessed	Primary tumor cannot be assessed	Primary tumor cannot be assessed	NA
Tis	Carcinoma in situ	Carcinoma in situ	Carcinoma in situ	Carcinoma in situ	NA
T1	*Supraglottis*: Tumor limited to one subsite of supraglottis with normal vocal cord mobility *Subglottis*: Tumor limited to the subglottis *Glottis*: Tumor limited to the vocal cord(s) (may involve anterior or posterior commissure) with normal mobility	Tumor ≤2 cm, ≤5 mm depth of invasion (DOI) Note: DOI is depth of invasion and not tumor thickness	Tumor limited to one subsite of hypopharynx and/or ≤2 cm	Tumor ≤2 cm	Tumor ≤2 cm
T1a	*Glottis*: Tumor limited to one vocal cord				
T1b	*Glottis*: Tumor involves both vocal cords				
T2	*Supraglottis*: Tumor invades mucosa of more than one adjacent subsite of supraglottis or glottis or region outside the supraglottis (e.g., mucosa of base of tongue, vallecula, medial wall of pyriform sinus) without fixation of the larynx *Subglottis*: Tumor extends to vocal cord(s) with normal or impaired mobility *Glottis*: Tumor extends to supraglottis and/or subglottis, and/or with impaired vocal cord mobility	Tumor ≤2 cm, DOI >5 mm and ≤10 mm *or* tumor >2 cm but ≤4 cm, and ≤10 mm DOI	Tumor invades more than one subsite of hypopharynx or an adjacent site, or >2 cm but ≤4 cm without fixation of hemilarynx	Tumor >2 cm but ≤4 cm	Tumor >2 cm but ≤4 cm
T3	*Supraglottis*: Tumor limited to larynx with vocal cord fixation and/or invades any of the following: postcricoid area, preepiglottic space, paraglottic space, and/or inner cortex of thyroid cartilage *Subglottis*: Tumor limited to larynx with vocal cord fixation and/or invasion of paraglottic space and/or inner cortex of the thyroid cartilage *Glottis*: Tumor limited to the larynx with vocal cord fixation and/or invasion of paraglottic space and/or inner cortex of the thyroid cartilage	Tumor >4 cm *or* any tumor >10 mm DOI	Tumor >4 cm in greatest dimension or with fixation of hemilarynx or extension to esophagus	Tumor >4 cm or extension to lingual surface of epiglottis	Tumor >4 cm or extension to lingual surface of epiglottis
T4	Moderately advanced or very advanced	Moderately advanced or very advanced local disease	Moderately advanced or very advanced local disease	Moderately advanced or very advanced local disease	Moderately advanced local disease Tumor invades the larynx, extrinsic muscle of tongue, medial pterygoid, hard palate, or mandible or beyond Note: Mucosal extension to lingual surface of epiglottis from primary tumors of the base of the tongue and vallecula does not constitute invasion of the larynx
T4a	*Supraglottis*: Moderately advanced local disease. Tumor invades through the outer cortex of the thyroid cartilage and/or invades tissues beyond the larynx (e.g., trachea, soft tissues of neck including deep extrinsic muscle of the tongue, strap muscles, thyroid, or esophagus) *Subglottis*: Moderately advanced local disease. Tumor invades cricoid or thyroid cartilage and/or invades tissues beyond the larynx (e.g., trachea, soft tissues of neck including deep extrinsic muscles of the tongue, straps muscle, thyroid, or esophagus) *Glottis*: Moderately advanced local disease. Tumor invades through the outer cortex of the thyroid cartilage and/or invades tissues beyond the larynx (e.g., trachea, cricoid cartilage, soft tissues of neck including deep extrinsic muscle of the tongue, strap muscles, thyroid, or esophagus)	*Lip*: Tumor invades through cortical bone or involves the inferior alveolar nerve, floor of mouth, or skin of face (i.e., chin or nose) *Oral cavity*: Tumor invades adjacent structures only (e.g., through cortical bone of the mandible or maxilla, or involves the maxillary sinus or skin of the face) Note: Superficial erosion of bone/tooth socket (alone) by a gingival primary is not sufficient to classify a tumor as T4	Tumor invades thyroid/cricoid cartilage, hyoid bone, thyroid gland, or central compartment soft tissue Note: Central compartment soft tissue includes prelaryngeal strap muscles and subcutaneous fat	Tumor invades the larynx, extrinsic muscle of tongue, medial pterygoid, hard palate, or mandible Note: Mucosal extension to lingual surface of epiglottis from primary tumors of the base of the tongue and vallecula does not constitute invasion of the larynx	

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TABLE 176-1 CLINICAL PRIMARY TUMOR STAGING SYSTEM FOR HEAD AND NECK SQUAMOUS CELL CARCINOMA—cont'd

TUMOR	LARYNX	LIP & ORAL CAVITY	HYPOPHARYNX	OROPHARYNX (p16-NEGATIVE)	OROPHARYNX (p16-POSITIVE)
T4b	Tumor invades prevertebral space, encases carotid artery, or invades mediastinal structures	Tumor invades masticator space, pterygoid plates, or skull base and/or encases the internal carotid artery	Tumor invades prevertebral fascia, encases carotid artery, or involves mediastinal structures	Tumor invades lateral pterygoid muscle, pterygoid plates, lateral nasopharynx, or skull base or encases carotid artery	

CLINICAL REGIONAL LYMPH NODE STAGING

NX	Regional lymph nodes cannot be assessed	Regional lymph nodes cannot be assessed
N0	No regional lymph node metastases	No regional lymph node metastases
N1	Metastasis in a single ipsilateral lymph node, ≤3 cm and ENE(-)	≥1 ipsilateral lymph node, none >6 cm
N2	Assigned an N2 subcategory as identified below	Contralateral or bilateral lymph nodes, none >6 cm
N2a	Metastasis in a single ipsilateral lymph node >3 cm but <6 cm and ENE(-)	NA
N2b	Metastases in multiple ipsilateral lymph nodes, non >6 cm and ENE(-)	NA
N2c	Metastases in bilateral or contralateral lymph nodes, non >6 cm and ENE(-)	NA
N3	Assigned an N3 subcategory as identified later	Lymph node(s) >6 cm
N3a	Metastasis in a lymph node >6 cm and ENE(-)	NA
N3b	Metastasis in any node(s) and clinically overt ENE(+)	NA

OROPHARYNX (p16+) PROGNOSTIC STAGE GROUPS

M0*	T0	T1	T2	T3	T4
N0	I	I	I	II	III
N1	I	I	I	II	III
N2	II	II	II	II	III
N3	III	III	III	III	III

*When M1, the stage group is IV for any N and T.

LARYNX, LIP, AND ORAL CAVITY, HYPOPHARYNX, OROPHARYNX (p16–) PROGNOSTIC STAGE GROUPS

M0*	T1	T2	T3	T4a	T4b
N0	I	II	III	IVA	IVB
N1	III	III	III	IVA	IVB
N2	IVA	IVA	IVA	IVA	IVB
N3	IVB	IVB	IVB	IVB	IVB

*When M1, the stage group is IVC for any N and T.

ENE = extranodal extension; NA = not applicable.

AJCC Cancer Staging Manual, 8th ed. Chicago: American Joint Committee on Cancer and Springer; 2017.

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TREATMENT

Multidisciplinary Team

In head and neck squamous cell carcinoma, both the cancer itself and its treatment place patients at risk for acute and long-term compromise of critical human functions, including speaking, eating, and breathing. Treatment by a multidisciplinary team composed of a surgical, medical, and radiation oncologist with specific expertise in head and neck cancer optimizes both oncologic and functional outcomes. Early consultation with specialists in dental sciences, nutrition, and speech and language pathology is also optimal. Given the social and behavioral risk factors associated with HPV-negative head and neck squamous cell carcinoma, the integration of patient navigators, social workers, and behavioral medicine specialists into the clinical management team can be particularly beneficial for addressing social isolation, transportation barriers, housing and food security, treatment compliance, and addiction.

Because more than 90% of index head and neck squamous cell carcinoma diagnoses are stage I to IVb, initial treatment in the vast majority is curative in intent (see https://www.nccn.org/professionals/physician). The multidisciplinary team must optimally deploy and sequence three key modalities: surgery, radiation therapy, and systemic therapy.

Treatment Modalities

The primary curative modality for head and neck squamous cell carcinoma is either surgery or radiation therapy, whereas systemic therapy serves as an adjunct to radiation therapy.[11] The selection of a specific multimodality treatment plan is tailored to anatomic site, stage, organ preservation, and goals of care.[12,13]

Surgery

In head and neck surgery, the advent of minimally invasive endoscopic procedures incorporating transoral CO_2 laser microsurgery or robotic surgery has markedly limited the morbidity of surgical exposure to the oropharynx. Avoiding violation of the soft tissue framework of the head and neck, including muscles, ligaments, and bones, decreases hospital stay and enhances function and cosmesis compared to historical open procedures.[14]

Radiation Therapy

The dissemination of intensity-modulated radiation therapy techniques,[15] including image-guided radiation therapy, improves the precision and accuracy of delivery of radiation therapy to the tumor and regional nodes while sparing intricate and vulnerable head and neck structures. Intensity-modulated radiation therapy reduces the important long-term morbidity of xerostomia (dry mouth). Although hyperfractionated radiation therapy is superior to conventional fractionation and is an appropriate standard of care when concomitant chemotherapy is not indicated, the value of altered fractionation regimens is uncertain when concomitant chemotherapy is used.[A1]

Systemic Therapies

Systemic therapies used in head and neck cancer include cytotoxic chemotherapy, molecular targeted therapy, and immunotherapy under expert supervision. The core cytotoxic chemotherapies are cisplatin, 5-fluorouracil, and docetaxel. Cisplatin is used in both the primary setting, concurrent with radiation therapy, or as first-line treatment for recurrent/metastatic disease. 5-Fluorouracil and docetaxel are predominantly used in the recurrent/metastatic setting. Cetuximab, which is a murine-human chimeric IgG1 monoclonal antibody against EGFR, is used during definitive radiation therapy for patients who are not candidates for cisplatin and may be used in the recurrent/metastatic setting. Nivolumab and pembrolizumab, which are IgG4 monoclonal antibodies against PD-1, are indicated in the recurrent/metastatic setting and are under investigation for curative intent.

Oral Cavity Cancer

Cancers of the oral cavity are resistant to radiation and are preferably managed with primary surgery, which generally should include lymph node dissection at the time of the primary surgery.[16] The advancement of modern reconstruction techniques, including free tissue transfer with microvascular reconstruction, has enhanced functional and cosmetic outcomes. In the clinically negative (N0) neck, sentinel node biopsy provides equivalent survival and lower morbidity compared with modified radical neck dissection.[A2]

The recommendation for adjuvant radiation therapy is based on the presence of adverse pathologic features, including extension to extracapsular lymph nodes, positive surgical margins, a pT3-4 primary tumor, N2-3 nodal disease, and perineural or lymphovascular invasion. The addition of concurrent cisplatin chemotherapy to adjuvant radiation therapy under expert guidance improves locoregional control and survival in patients with pathologic high-risk head and neck squamous cell carcinoma, defined as the presence of extracapsular nodal extension or a positive surgical margin.

HPV-Unrelated Oropharyngeal Squamous Cell Carcinoma and Hypopharynx Cancer

The majority of patients with hypopharyngeal and p16-negative oropharyngeal squamous cell carcinoma present with locally advanced disease and are treated with an organ preservation approach (i.e., primary radiation therapy). In stage III or higher disease, concurrent systemic therapy with cisplatin or cetuximab under expert supervision increases locoregional control and survival compared with radiation therapy alone, with cisplatin generally being preferable to cetuximab. The decision to offer concurrent systemic therapy also depends upon physiologic fitness, because both acute and late toxicities are magnified in patients who are frail or have a low performance status. Although concurrent cisplatin improves locoregional control in people over age 70 years, it does not improve survival, probably because of competing comorbid conditions or late toxic effects such as aspiration pneumonia. Cetuximab has a more favorable systemic toxicity profile than cisplatin, with fewer renal, bone marrow, and otologic adverse events, so concurrent cetuximab-radiation therapy is an appropriate standard of care for locally advanced head and neck squamous cell carcinoma in patients who are unfit for cisplatin.[17]

HPV-Associated Oropharyngeal Squamous Cell Carcinoma

Patients with HPV-associated oropharyngeal squamous cell carcinoma have a markedly better prognosis than their HPV-negative counterparts, whether treated with primary surgery or radiation therapy. Treatment standards under expert supervision include definitive (chemo)radiation therapy or minimally invasive, transoral surgery followed by adjuvant (chemo)radiation therapy. When a definitive radiation approach is selected, cisplatin-radiation therapy is superior to cetuximab-radiation therapy and remains the standard of care.[A3,A4] Deintensification strategies under investigation include induction chemotherapy followed by lower-dose radiation therapy, minimally invasive surgery followed by lower-dose versus standard adjuvant radiation therapy,[A5] and lower-dose radiation therapy with either concurrent cisplatin or nivolumab.[A6]

Larynx Cancer

An important general principle for the treatment of larynx cancer is preservation of a functional larynx.[18] Maintaining the larynx without adequacy of its three key functions, airway patency, pharyngeal swallowing, and voice, is not an appropriate goal. For patients with early-stage T1-2 larynx cancer, single-modality treatment with either radiation therapy or larynx preservation surgery results in 90% long-term laryngectomy-free survival.

For patients with locally advanced larynx cancer, the combination of radiation therapy and chemotherapy under expert supervision is the preferred approach for organ preservation. The two evidence-based standards include cisplatin-based induction chemotherapy followed by definitive radiation therapy or concurrent cisplatin-radiation therapy.

Evidence also supports the feasibility of larynx preservation in appropriately selected patients with limited T4 disease. Patients who are likely to be more appropriate for up-front total laryngectomy include patients who have destructive tumors affecting both vocal cords, patients who are frail or have a poor performance status, and patients who are unlikely to adhere to a 7-week radiation therapy program that requires daily attendance.

Nasopharyngeal Carcinoma

Radiation therapy is the cornerstone of curative treatment for localized nasopharyngeal carcinoma. Radiation therapy alone is noninferior to chemoradiotherapy for low-risk localized disease,[A7] but induction chemotherapy with cisplatin and gemcitabine prior to concurrent cisplatin-radiation therapy significantly improves recurrence-free and overall survival compared with chemoradiotherapy alone in patients with locoregionally advanced disease.[A8] Neck dissection is recommended if locoregional treatment fails or disease recurs. For recurrent/metastatic disease, the addition of camrelizumab (an anti-PD-1 antibody) to gemcitabine plus cisplatin increases progression-free survival and is now a first-line standard.[19,A9]

Salivary Gland Malignancies

The primary curative-intent treatment for salivary gland malignancies is surgery, followed by reconstruction. Adjuvant radiation therapy is frequently offered for stage III-IVb disease. In recurrent or metastatic disease, platinum-based chemotherapy remains a palliative option, but its clinical activity is limited, and targeted molecular approaches are an increasingly utilized option under expert oversight. The TRK inhibitor larotrectinib can yield a response rate of 75% for tumors that harbor an *NTRK* gene fusion, including salivary gland cancers,[A10] and this agent compares favorably with cytotoxic chemotherapy. Combined androgen blockade can provide about a 40% overall response rate with excellent tolerability in patients who have advanced salivary duct carcinoma. HER2neu-enriched tumors may respond to ado-trastuzumab emtansine or other clinically available HER2 inhibitors.[20] The existence of multiple unique gene fusions within salivary gland cancers also raises the promise of immunotherapy against the peptide neoantigens translated from these fusion sites.

Recurrent/Metastatic Head and Neck Squamous Cell Carcinoma

For patients with locally advanced head and neck squamous cell carcinoma, the major cause of mortality is failure of locoregional control. In a minority of patients with isolated locoregional relapse, salvage surgery or re-irradiation can lead to durable long-term disease control but at the expense of substantial

morbidity.[21] For oligometastatic pulmonary disease, metastasectomy may occasionally be curative, particularly in patients who have HPV-associated cancer.

The majority of patients with locoregional recurrence and/or distant metastatic disease are candidates for palliative systemic therapy, depending upon performance status, comorbidities, and goals of care. The standard palliative systemic management of recurrent/metastatic head and neck squamous cell carcinoma is pembrolizumab (an anti-PD-1 monoclonal antibody), either as monotherapy or in combination with platinum and 5-fluorouracil[A11,A12] under expert supervision unless contraindicated by an autoimmune disorder. For the platinum-refractory disease, either nivolumab or pembrolizumab improves survival relative to single-agent chemotherapy or cetuximab.[A13] Treatment with PD-1 checkpoint blockade can provide long-term disease control in 10 to 20% of patients with recurrent/metastatic head and neck squamous cell carcinoma. HPV-specific immunotherapies under development include T cells engineered with a T-cell receptor targeting HPV-16 E7[22] and therapeutic HPV vaccines.[23]

Supportive and Palliative Care

Due to its anatomic location, head and neck squamous cell carcinoma and its treatment impact fundamental human functions, including voice, facial expression, eating, and breathing.[24] The care team must address both physical and psychological distress, often stemming from pain, nausea, malnutrition, fatigue, impaired communication, and social isolation. Even when cured from head and neck cancer, survivors experience a high burden of symptoms, including psychological distress and poor quality of life. Survivors have a high rate of suicide, almost twice that of survivors of cancers at other sites. In patients with recurrent/metastatic head and neck cancer, the burden of symptoms is particularly profound at the end of life, especially when locoregional disease is uncontrolled. The unique palliative challenges in this setting include the management of foul-smelling, ulcerative masses; decisions regarding the palliative role of enteral feeding tubes or tracheostomy; and preparation of the patient and caregivers for acute terminal events resulting from loss of airway or carotid exsanguination. Due to the unique burden of symptoms across the natural history of head and neck squamous cell carcinoma, early and continuous involvement of palliative care specialists is ideal.

PREVENTION

Environmental Head and Neck Squamous Cell Carcinoma

Patients with an index HPV-negative head and neck squamous cell carcinoma develop a second primary tumor of the upper aerodigestive tract at the alarming rate of 3 to 6% per year. The most important strategy for decreasing primary or secondary risk for head and neck squamous cell carcinoma is withdrawal of the offending carcinogen.[25] Although tobacco cessation reduces the incidence of second primary tumors, the risk is not reduced in the first 5 years and never returns to baseline. Although high-dose isotretinoin, a synthetic vitamin A analog, can reverse oral premalignant lesions and prevent second primary tumors following an index head and neck squamous cell carcinoma, isotretinoin is too toxic for chronic administration, and the risk returns to baseline upon its discontinuation. Ongoing investigations focus on whole plant-based interventions and on therapies aimed to reprogram the permissive immune microenvironment that tolerates oral epithelial transformation.

HPV-Associated Head and Neck Squamous Cell Carcinoma

HPV vaccination (Chapters 15 and 344) has an estimated 93% efficacy for preventing oral HPV[A14] and likely will prevent HPV-associated oropharyngeal cancer, although randomized clinical trials designed to demonstrate a reduction in HPV-associated oropharyngeal carcinoma are impractical because of the long latency period. HPV vaccination is recommended for all males and females ages 9 to 26 years and can be administered from ages 27 to 45 years after shared decision making.[26] The high risk of subsequent oropharyngeal cancers among persons who harbor oral HPV[27] raises the possibility of future minimally invasive screening protocols.

PROGNOSIS

Environmental Head and Neck Squamous Cell Carcinoma

The prognosis of HPV-negative head and neck squamous cell carcinoma is dependent upon stage and performance status. Although patients with stage I to II disease have an overall 5-year survival of 60 to 90%, the corresponding survival rate for patients who present with locally advanced stage III to IVb disease is only 30 to 50%. At the time of locoregional or distant metastatic relapse, median survival with modern palliative systemic therapy is 1 year.

HPV-Associated Head and Neck Squamous Cell Carcinoma

Patients with HPV-associated oropharyngeal squamous cell carcinoma have a more favorable prognosis than patients with HPV-negative cancer. Patients with stage I to II disease experience a 5-year overall survival of 72 to 89%. In nonsmokers with stage I to II disease, the 5-year overall survival rates approach 95%. Patients with stage III HPV-associated oropharyngeal squamous cell carcinoma have an intermediate prognosis, with a 5-year overall survival of 46 to 72%. When patients with HPV-associated oropharyngeal squamous cell carcinoma develop recurrent/metastatic disease, median survival is approximately 2 years, twice the survival rate for HPV-negative head and neck squamous cell carcinoma. This survival disparity in the recurrent/metastatic setting may be explained by better prognostic characteristics, including younger age and lower comorbidity scores, as well as the enhanced sensitivity of HPV-transformed cancers to chemotherapy.

Nasopharyngeal Cancer

Intensity-modulated radiation therapy can achieve locoregional control in >90% of stage I to II nasopharyngeal carcinomas. For locoregionally advanced disease, 5-year survival is about 85% with induction plus concurrent chemotherapy. Current median survival rates are about 29 months for metastatic disease.[28]

Salivary Gland Cancers

Prognosis is favorable in the setting of stage I to II disease, intermediate in the setting of stage III to IVb disease, and poor in the setting of stage IVc disease. For adenoid cystic carcinomas, the primary tumor is often well controlled following surgery and/or radiation, but the disease may relapse years later with involvement of cranial nerves and the base of the skull. Delayed lung metastases are also a common feature, so these patients are frequently followed for a decade or more by their treating oncologists.

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For the General References and other additional features, please visit Elsevier eBooks+ at https://ebooks.health.elsevier.com.

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177 LUNG CANCER AND OTHER PULMONARY NEOPLASMS

FADLO R. KHURI

Lung cancers grow from a single abnormal cell or small group of abnormal cells to develop into large macroscopic masses that may be several centimeters in diameter. Most lung cancers originate from the bronchial epithelium and are termed carcinomas. Primary noncarcinoma lung cancers are less common and include carcinoid, pulmonary blastomas (more common in younger patients), and sarcomas. Abnormal lung tissues range in histologic grade from mildly atypical cells to aggressive cancers. Lesions such as atypical adenomatous hyperplasia are considered preinvasive lesions, with a continuum of cellular atypia through adenocarcinoma.

BRONCHOGENIC LUNG CANCER

DEFINITION

Lung cancer, or bronchogenic carcinoma, is a proliferative malignant neoplasm arising from the primary respiratory epithelium. Lung cancer is generally divided into two major histologic groups: *non–small cell lung cancer* (NSCLC), which accounts for approximately 85% of all lung cancers, and *small cell lung cancer* (SCLC).

EPIDEMIOLOGY

Lung cancer is by far the leading cause of cancer-related mortality globally. An estimated 2.2 million new cases diagnosed worldwide each year account for nearly 11% of all cancers and cause an estimated 1.8 million annual deaths. Among men, lung cancer is the most common malignant neoplasm (worldwide incidence rate of 31.5 per 100,000), whereas in women, lung cancer incidence (14.6 per 100,000) trails breast, cervix, and colon cancers. The incidence and mortality related to lung cancer in men have declined during the last two decades in Western countries but continue to increase in the developing world.[1] In women, lung cancer deaths are increasing in most regions of the world. The most dramatic increases in lung cancer incidence and death globally are in China, which has experienced over a 4.5-fold increase in lung cancer–related deaths during the past 3 to 4 decades.

Risk Factors

Cigarette smoking is the most common risk factor for lung cancer, with roughly 85% of lung cancer patients having a tobacco-smoking history and approximately 50% being former smokers (defined as free from smoking for at least 12 months before diagnosis). The risk for developing lung cancer correlates with the number of cigarettes smoked per day and the cumulative duration of smoking time.[2] Patients with a smoking history of at least 20 to 30 pack-years (defined as one pack per day of cigarettes for 20 to 30 years) are at substantially increased risk for lung cancer.

Since the release of the first U.S. Surgeon General's Report on the Hazards of Smoking in 1964, the prevalence of cigarette smoking has declined considerably in the United States but continues to increase at an alarming rate in developing and third world countries. As a result, the number of cases of lung cancer diagnosed annually is likely to rise during the next few decades, and it is estimated that the majority of lung cancer cases will occur outside the United States and Europe by the year 2030. Smoking cessation is associated with a gradual reduction in risk of developing lung cancer, although it does not reach that of a never-smoker. Second-hand exposure to smoke is another risk factor that contributes to nearly 1% of all cases of lung cancer.

Because only about 11% of heavy smokers develop lung cancer, genetic susceptibility to lung cancer also appears to play a role. Patients with a family history of early lung cancer (before 60 years of age) have a two-fold higher risk for developing lung cancer. Women appear to be at a higher risk for lung cancer at the same smoking exposure level as that of men.

Occupational exposure to asbestos leads to an estimated four-fold higher risk of lung cancer, with cigarette smoking having an additive effect on risk. The latency between asbestos exposure and the development of lung cancer is several decades, and risk is related to the duration of exposure as well as to the quantity and the type of asbestos fiber. However, all forms of asbestos are carcinogenic.

Radon exposure has also been implicated in the development of 5 to 8% of lung cancer cases. Household exposure to radon, which results from the radioactive decay of uranium, is high in certain geographic regions. Exposure to ionizing radiation in the form of therapeutic radiation or frequent diagnostic radiographic tests is also associated with a higher risk for developing lung cancer. Similarly, exposures to metals (including arsenic, nickel, and chromium), silica, and general air pollution (including biomass fuels such as coal and wood smoke) are also associated with the risk of lung cancer but to a lesser degree compared with ionizing radiation. The human immunodeficiency virus is associated with a 3.6-fold increased risk of developing lung cancer.

PATHOBIOLOGY

Pathology

Lung cancer is broadly subdivided into NSCLC and SCLC on the basis of their distinct histopathology, biologic behavior, and response to therapies. NSCLC comprises *adenocarcinoma*, *squamous cell carcinoma*, and *large cell carcinoma* subtypes. In addition to morphologic features, immunohistochemical studies are important in establishing the histologic subtype of NSCLC.

Adenocarcinomas

Adenocarcinoma has increased in incidence over the past several decades and now represents over 50% of all lung cancers. Never-smokers who develop lung cancer most frequently have adenocarcinoma. Adenocarcinoma has a higher predilection for developing distant metastases compared with squamous cell lung cancers. Adenocarcinoma specimens usually stain positive for cytokeratin 7, thyroid transcription factor-1 (TTF-1), and Napsin-A, but they stain negative for cytokeratin 20.

Lung adenocarcinoma can be divided into preinvasive, minimally invasive, and invasive types. *Atypical adenomatous hyperplasia* refers to a localized proliferative lesion consisting of atypical type II pneumocytes or Clara cells and measuring less than 5 mm. *Adenocarcinoma in situ*, which refers to lesions that are smaller than 3 cm and that lack any invasive characteristics, was previously referred to as bronchioloalveolar carcinoma or noninvasive adenocarcinoma. Lesions 3 cm or smaller with a predominantly lepidic pattern and with invasion of less than 5 mm in greatest dimension are referred to as *minimally invasive adenocarcinoma*. Invasive adenocarcinoma represents nearly 90% of all cases of adenocarcinoma. Based on the predominant characteristic features, it is categorized as lepidic, acinar, papillary, micropapillary, or solid predominant with mucin production.

Squamous Cell Carcinoma

Squamous cell lung cancer is decreasing in incidence in the United States, most likely because of the changing smoking habits of the population. Squamous tumors of the lung are generally centrally located and are almost always seen in patients with a significant smoking history. Squamous dysplasia and squamous cell carcinoma in situ are preinvasive lesions that can develop into invasive cancers.

The majority of squamous cell tumors stain positive for p40 and p63, which are members of the p53 family of proteins, whereas adenocarcinomas occasionally stain positive for p63. On the basis of these findings, a panel of markers including TTF-1, p63, and p40 is frequently evaluated in diagnostic specimens of patients with lung cancer to identify the histologic subtype accurately (E-Table 177-1).

Large Cell Carcinoma

Large cell carcinoma represents 3 to 4% of NSCLC and is characterized by a high mitotic rate, necrosis, and morphologic features of NSCLC. Large cell tumors stain positively for neuroendocrine markers such as chromogranin A and synaptophysin. Large cell carcinoma is often difficult to diagnose accurately owing to an abundance of necrotic tissue and a poor degree of differentiation, so diagnosis requires an adequate tissue specimen. Large cell carcinoma is strongly associated with a history of prior smoking.

Small Cell Lung Cancer

SCLC is diagnosed in approximately 13% of lung cancer cases in the United States, and its incidence has gradually declined during the past several decades. SCLC is strongly associated with smoking and is rare in never-smokers. Pathologic diagnosis can be challenging because of an abundance of necrotic tissue but is established by characteristic features, such as a high degree of

ABSTRACT

Lung cancer is a common malignancy and the leading cause of cancer-related mortality globally, resulting in an estimated 1.8 million deaths each year worldwide. It is characterized by presentation at an advanced stage, aggressive disease course, and modest sensitivity to systemic therapies. Lung cancer is broadly subdivided into two major histologic types: non–small cell lung cancer (NSCLC) and small cell lung cancer (SCLC). NCSLC accounts for approximately 85% of all lung cancer cases and comprises adenocarcinoma, squamous cell carcinoma, and large cell carcinoma subtypes. Cigarette smoking is the most common risk factor for lung cancer, accounting for about 85% of all cases, although the number of never-smokers with lung cancer has increased in recent years. Specific molecular abnormalities in lung cancer include mutations in the epidermal growth factor receptor (EGFR) gene and rearrangements of the anaplastic lymphoma kinase (ALK) gene. Many of these molecular changes represent therapeutic targets and have led to the development of specific targeted therapies. Agents targeting the PD-1 pathway have led to a paradigm shift in the treatment of lung cancer. Increased understanding of disease biology, earlier detection, improved treatment agents and modalities, tumor sequencing, and improved supportive care measures are all rapidly changing the clinical landscape of lung cancer. The mortality related to lung cancer has decreased by 2 to 3% annually in the United States over the past few years.

KEYWORDS

non–small cell lung cancer (NSCLC)
small cell lung cancer (SCLC)
pathology
diagnosis
treatment
molecular
immunotherapy

E-TABLE 177-1 HISTOLOGIC MARKERS IN NON–SMALL CELL LUNG CANCER

	PERCENTAGE IHC-POSITIVE CASES AMONG HISTOLOGIC CARCINOMA SUBTYPES			*POSITIVE AND NEGATIVE PREDICTIVE VALUE OF ANTIBODY PANEL (%)*	
	ADENOCARCINOMA (n = 215)	**SQUAMOUS CELL CARCINOMA (n = 123)**	**LARGE CELL CARCINOMA (n = 22)**	**ADENOCARCINOMA**	**SQUAMOUS CELL CARCINOMA**
p63	7.0	99.2	52		88.9, 99.5
Cytokeratin 5/6	9.8	99.2	68		84.9, 99.5
TTF-1	83.5	3.4	23	97.7, 76.9	
Cytokeratin 7	97.2	23.5	77	88.4, 93.6	
Mucin	43.4	13.4	0		

IHC = immunohistochemically; TTF-1 = thyroid transcription factor-1.

Modified from Sterlacci W, Savic S, Schmid T, et al. Tissue-sparing application of the newly proposed IASLC/ATS/ERS classification of adenocarcinoma of the lung shows practical diagnostic and prognostic impact. *Am J Clin Pathol*. 2012;137:946-956.

mitosis and necrosis. The diagnostic evaluation of SCLC includes immunostaining for TTF-1, chromogranin, synaptophysin, and CD56. Approximately 15% of SCLC specimens have mixed morphology with components of NSCLC.

Molecular Pathology

Whole-genomic sequencing has revealed that the mutational burden in specimens of adenocarcinomas from the lungs of persons who have never smoked is a log order of magnitude lower than the mutational burden in the lungs of persons who have ever smoked. Characteristic cytosine-adenine (C→A) nucleotide transversions are associated with tobacco exposure and are seen predominantly in lung adenocarcinomas from smokers rather than from those who have never smoked. The cause of the increasing number of lung cancers among never-smokers is unclear, but affected individuals are more likely to harbor certain genetic alterations in the tumor, such as mutations in the gene encoding epidermal growth factor receptor (EGFR) and rearrangement in the gene encoding anaplastic lymphoma kinase (ALK).[3]

Oncogenes

In lung adenocarcinoma, nearly two thirds of patients harbor an oncogenic mutation that can potentially be targeted with specific agents (E-Fig. 177-1A).[4] The most common are mutations involving *KRAS*, *EGFR*, *BRAF*, *HER2*, *MET*, and *PIK3CA* and gene rearrangements involving *ALK*, *RET*, and *ROS1*. *KRAS* mutations are present in approximately 25% of lung adenocarcinomas and are usually associated with cigarette smoking. The most common sites of mutation in *KRAS* include codons 12, 13, and 61, where the resulting amino acid substitutions cause impaired GTPase activity and constitutive activation of RAS signaling.

Mutations in *EGFR* are observed in nearly 15% of White and almost 40% of Asian patients with lung adenocarcinomas. Deletion mutations in exon 19 and a point mutation in exon 21 are located in the tyrosine kinase–binding domain of the receptor and result in constitutive activation of the signaling pathway, thereby leading to proliferation, evasion of apoptosis, and enhanced angiogenesis. Patients with *EGFR*-activating mutations can derive robust and durable clinical benefit from treatment with EGFR tyrosine kinase inhibitors; however, most of the benefit is limited in duration and within 12 to 24 months, and nearly 60% of patients treated with first- or second-generation inhibitors will develop a secondary mutation in exon 20(T790M) that confers resistance to this therapy. In some patients with lung adenocarcinomas, this exon 20(T790M) mutation can also be found de novo along with an exon 19 or 21 mutation before exposure to EGFR tyrosine kinase inhibitor therapy. Another common mechanism of acquired resistance to EGFR tyrosine kinase inhibitor therapy is amplification of the growth factor receptor c-Met.

In approximately 5% of patients with lung adenocarcinomas, gene rearrangement involving *ALK* is observed. Clinical features associated with the *ALK* gene rearrangement include never-smokers, signet ring features on histopathologic evaluation, and younger age. The fusion gene results from inversion or translocation of portions of the *echinoderm microtubule-associated protein-like 4 (EML4)* with the *ALK* gene and leads to activation of downstream signals that can be inhibited by specific ALK kinase inhibitors such as crizotinib. The *ALK* gene rearrangement can be detected by fluorescence in situ hybridization or by immunohistochemistry. Other fusion abnormalities involving the *RET* and *ROS1* genes are each observed in 1% of lung adenocarcinoma specimens. It is noteworthy that *EGFR* and *KRAS* mutations and *ALK* gene rearrangements are usually mutually exclusive.

Squamous cell carcinoma has an entirely different spectrum of molecular abnormalities (E-Fig. 177-1B), including common mutations in *p53*, *PTEN*, *PIK3CA*, *KEAP1*, *DDR2*, and *RB1*. Amplification of the gene for *fibroblast growth factor receptor* (FGFR) is also noted in 10 to 20% of squamous cell lung cancers.

Tumor Suppressor Genes

The function of multiple tumor suppressor genes (e.g., *p53*, *Rb*, *LKB1*, and a number of genes found on the short arm of chromosome 3 [*3p*]) is frequently lost in lung cancer. Mutation or loss of *p53* correlates with cigarette smoking and is detected in some preneoplastic lesions of the lung. Mutations of *p53* are common in both NSCLC (≈50%) and SCLC (≈80%). Mutations in *LKB1* are also common in NSCLC. The *STK11/LKB1* gene, which encodes a *serine/threonine kinase*, regulates cell polarity and functions as a tumor suppressor. One of the earliest genetic abnormalities in lung cancer occurs during the deletion of genetic material on chromosome 3p (p14 to p23). The deletion occurs in approximately 50% of NSCLC and 90% of SCLC patients. The *FHIT* (fragile histidine triad) gene (3p14.2), which is abnormal in many lung cancers, may function as a tumor suppressor gene by limiting tumor growth and enhancing apoptosis. The Rb protein is not expressed in 90% of SCLC because of mutation or deletion. In NSCLC, Rb is normally expressed, but when Rb is phosphorylated, uncontrolled cell division can occur.

Epigenetics

Epigenetic modifications involving changes in DNA methylation are common in lung cancer and include hypomethylation, dysregulation of DNA methyltransferase I, and hypermethylation. Genes that are methylated in NSCLC include *p16*, *RARB*, *RASSFIA*, *MGMT* (methylguanine-methyltransferase), and death-associated protein kinase (DAP-kinase). Hypermethylation in lung cancer can often silence tumor suppressor genes, thereby promoting dysregulated cell growth. Silencing of tumor suppressor genes in histologically normal lymph nodes in patients with resectable NSCLC is associated with higher likelihood of disease relapse.

CLINICAL MANIFESTATIONS

Currently, only 15% of patients with lung cancer are asymptomatic when they are initially diagnosed. These early lung cancers often are manifested as a pulmonary nodule (defined as a rounded opacity, well or poorly defined, measuring up to 3 cm in diameter), first seen incidentally on a chest radiograph obtained for other reasons (e.g., a preoperative study) or on a screening computed tomographic (CT) scan.

Most patients have symptoms and signs that are caused by the pulmonary lesion itself: local tumor growth, invasion, obstruction, intrathoracic-regional tumor spread to lymph nodes and adjacent structures, distant extrathoracic spread of disease, or a paraneoplastic syndrome. Common presenting symptoms of lung cancer include cough, dyspnea, pain, hemoptysis, and weight loss. Anorexia occurs in about 30% of patients, fatigue in one third of patients, and anemia and fever in 10 to 20% of patients. More than 80% of patients initially have three or more symptoms or signs as a result of the lung cancer. Because the majority of patients with lung cancer have other tobacco-related cardiopulmonary diseases, such as chronic obstructive pulmonary disease (Chapter 76) and ischemic heart disease (Chapters 56 to 58), these overlapping symptoms often result in a delay in diagnosis of the underlying malignant disease. Symptoms that can result from local invasion or metastasis of the tumor include headache, bone pain, airway obstruction, cough, and hemoptysis. Paraneoplastic syndromes (Chapter 164) associated with lung cancer include the syndrome of inappropriate antidiuretic hormone (Chapter 102), hypercalcemia (Chapter 227), pulmonary hypertrophic osteoarthropathy (Chapter 254 and Fig. 254-1), Eaton-Lambert myasthenic syndrome (Chapter 390), and Cushing syndrome (Chapters 164 and 208). Hypercalcemia is common in squamous cell histology, whereas the syndrome of inappropriate antidiuretic hormone, Eaton-Lambert myasthenic syndrome, and Cushing syndrome are most commonly associated with SCLC.

DIAGNOSIS

Solitary Pulmonary Nodule

Asymptomatic solitary pulmonary nodules less than 3 cm in diameter with normal surrounding lung architecture are found incidentally in up to 0.2% of chest radiographs.[5] A solitary pulmonary nodule can be the first sign of early lung cancer, but about 95% of such lesions are noncancerous and most often are granulomas or intrapulmonary lymph nodes. Smaller nodules are likely to be benign. The potential for these lesions to be malignant increases with the patient's age, the size of the nodule, the nodule's rate of growth, a history of smoking, and any changes compared with prior imaging studies.

The evaluation (Fig. 177-1) begins with computed tomographic (CT) scanning. Nodules are categorized as small solid (<8 mm), large solid (≥8 mm), or subsolid. Subsolid nodules are divided into ground-glass nodules (no solid component) and part-solid nodules (both ground-glass and solid components). The likelihood of malignancy is <1% for nodules that are less than 6 mm and 1 to 2% for solid nodules that are 6 mm to 8 mm. These low-risk nodules can be monitored with serial CT scans. A pulmonary nodule that has not changed in size for more than 2 years is probably benign.

For larger nodules, which have a higher likelihood of malignancy, CT characteristics suggestive of malignancy include irregular margins, spiculation, invasion of adjacent structures, lymphadenopathy, and distant metastases.[6] Further imaging is warranted (e.g., positron emission tomography [PET]), and suspicious nodules should undergo definitive biopsy. For nodules that are partly solid, diagnostic strategies are typically guided by the size of the solid component.

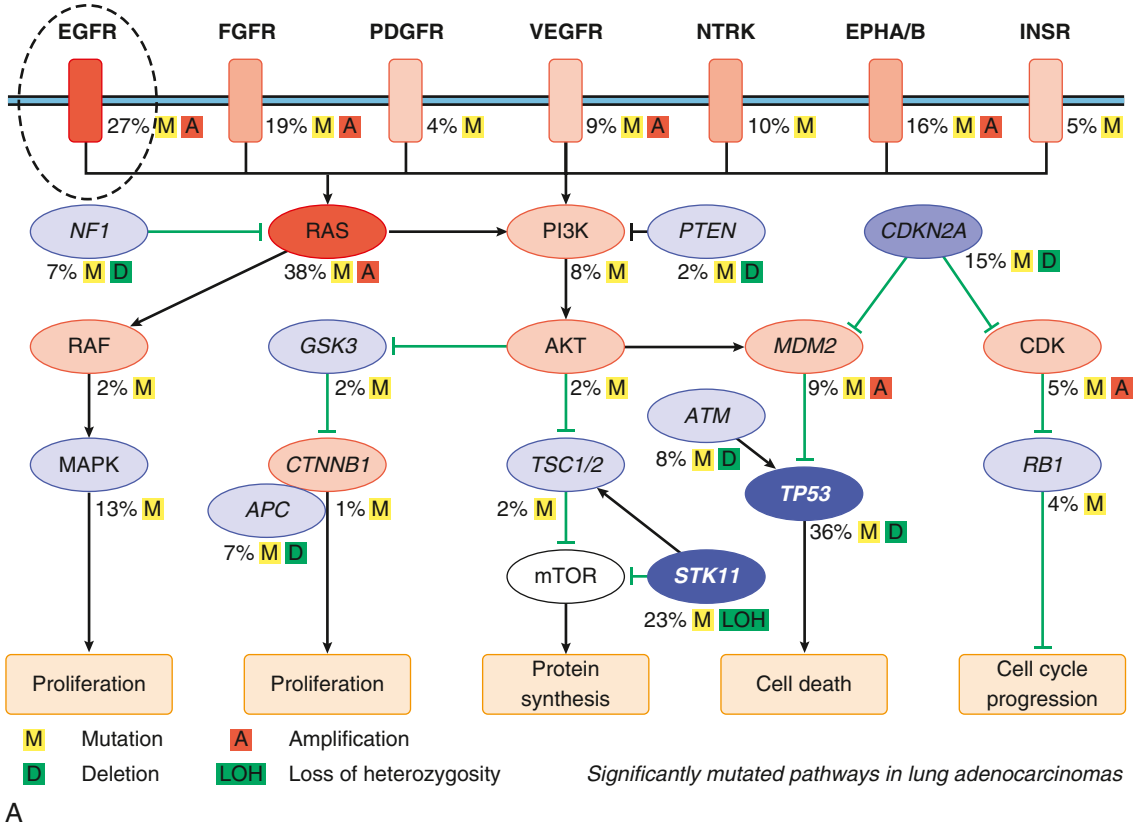

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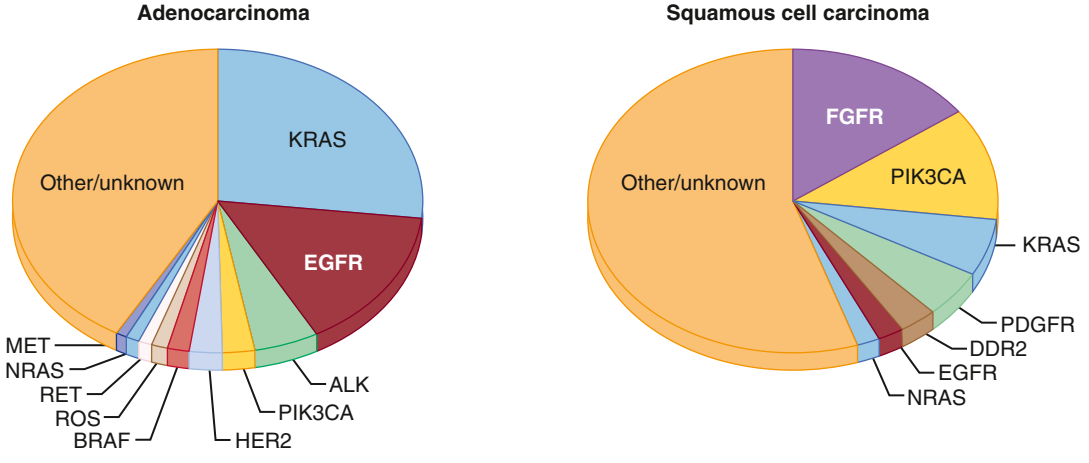

B

E-FIGURE 177-1. Altered signaling networks in lung cancer. A, Significantly mutated pathways in lung adenocarcinoma. AKT = AK strain transforming; *APC* = adenomatous polyposis coli; *ATM* = ataxia telangiectasia mutated; *CDKN2A* = cyclin dependent kinase inhibitor 2A; *CTNNB1* = catenin (cadherin-associated protein) beta 1; EGFR = epidermal growth factor receptor; EPHA/B = ephrin A/B; FGFR = fibroblast growth factor receptor; *GSK3* = glycogen synthase kinase 3 beta; MAPK = mitogen-activated protein kinase; *MDM2* = murine double minute 2 homolog; mTOR = mammalian target of rapamycin; *NF1* = neurofibromatosis type 1; NTRK = neurotrophic tyrosine kinase; PDGFR = platelet-derived growth factor receptor; PI3K = phosphatidylinositol-3-kinase; *PTEN* = phosphatase and tensin homolog; RAF = rapidly accelerated fibrosarcoma; RAS = rat sarcoma; *RB1* = retinoblastoma susceptibility gene; *STK11* = serine/threonine kinase 11; *TP53* = tumor protein 53 gene; *TSC1/2* = tuberous sclerosis complex 1/2; VEGFR = vascular endothelial growth factor receptor. (Modified from Ding L, Getz G, Wheeler DA, et al. Somatic mutations affect key pathways in lung adenocarcinoma. *Nature*. 2008;455:1069-1075.) **B**, Genetic profiles by histologic subtype. ALK = anaplastic lymphoma kinase; BRAF = B-Raf proto-oncogene, serine/threonine kinase; DDR2 = discoidin domain receptor 2; FGFR = fibroblast growth factor receptor; HER2 = human epidermal growth factor receptor 2; KRAS = Kristen rAt sarcoma virus; MET = metastatic; NRAS = neuroblastoma ras viral oncogene homolog; PDGFR = platelet-derived growth factor receptor; PIK3CA = phosphatidylinositol-4,5,-bisphosphate 3-kinase catalytic subunit alpha; RET = rearranged during transfection; ROS = reactive oxygen species. (From the Lung Cancer Mutation Consortium and modified from Sequist LV, Heist RS, Shaw AT, et al. Implementing multiplexed genotyping of non-small-cell lung cancers into routine clinical practice. *Ann Oncol*. 2011;22:2616-2624; Bergethon K, Shaw AT, Ou SH, et al. ROS1 rearrangements define a unique molecular class of lung cancers. *J Clin Oncol*. 2012;30:863-870; Weiss J, Sos ML, Seidel D, et al. Frequent and focal FGFR1 amplification associates with therapeutically tractable FGFR1 dependency in squamous cell lung cancer. *Sci Transl Med*. 2010;2:62ra93; Hammerman PS, Sos ML, Ramos AH, et al. Mutations in the DDR2 kinase gene identify a novel therapeutic target in squamous cell lung cancer. *Cancer Discov*. 2011;1:78-89.)

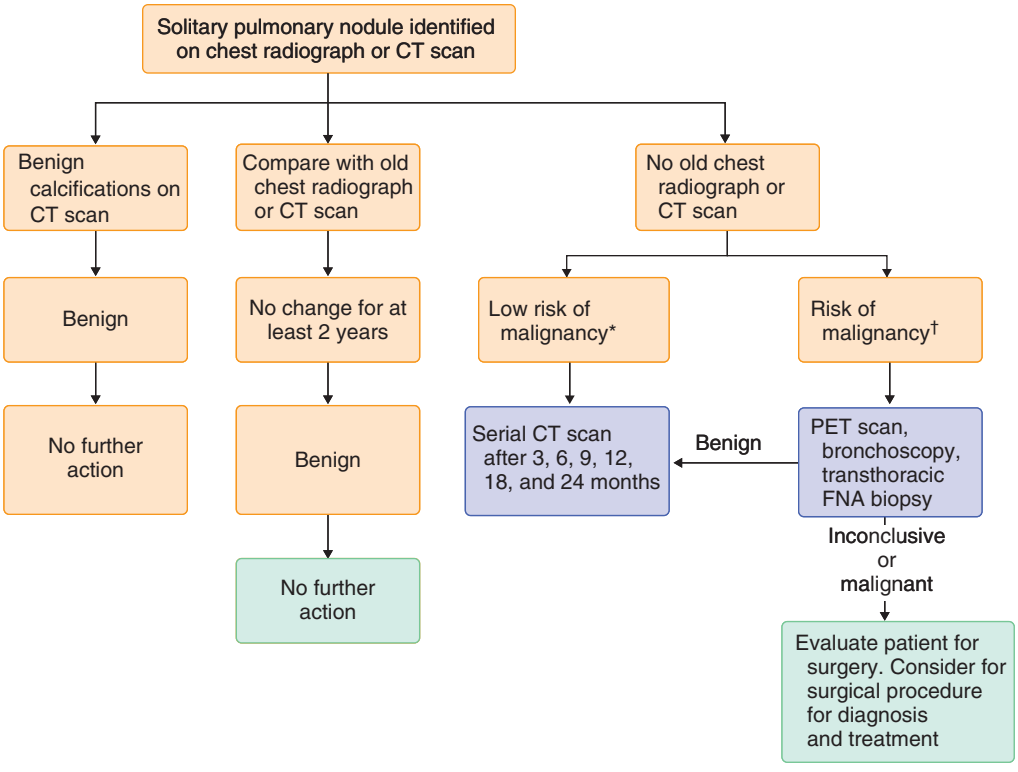

FIGURE 177-1. Evaluation of a patient with a solitary pulmonary nodule. *Patient with a minimal or absent history of smoking and other known risk factors for the development of lung cancer and a nodule 8 mm or smaller. †Patient with a history of smoking and other risk factors for the development of lung cancer and a nodule 8 mm or larger. CT = computed tomography; FNA = fine-needle aspiration; PET = positron emission tomography.

Noncancerous causes of a solitary pulmonary nodule include granulomatous diseases (e.g., sarcoidosis [Chapter 83] and histoplasmosis [Chapter 308], coccidiomycosis [Chapter 308], rheumatoid arthritis [Chapter 243]) and benign hematomas, as well as scars from prior pulmonary infections.

In screening studies, new solid nodules are detected at each round of screening in 5 to 7% of individuals. New nodules have a high probability of malignancy even when small, thereby suggesting more aggressive follow-up of new nodules that appear upon serial screening CT than for nodules that are detected at baseline imaging.

Initial Evaluation

With the advent of CT screening, a greater percentage of patients with lung cancer are being diagnosed before the onset of symptoms. In patients with clinical or radiographic findings suggestive of lung cancer, CT scans of the chest and abdomen are indicated to determine the location of the primary tumor, involvement of mediastinal lymph nodes (Fig. 177-2), and spread to other anatomic sites.

Invasive Diagnostic Procedures

Establishing the Diagnosis

Accurate diagnostic characterization of lung cancers is essential because the presence or absence of mediastinal nodal metastases is crucial in determining prognosis, assessing resectability, and selecting the appropriate treatment strategy for primary lung cancer.[7] For patients with localized lung tumors that are suggestive of cancer, it is reasonable to proceed with surgical resection without a diagnostic biopsy if all other potential causes are excluded. Commonly, however, a biopsy is necessary to establish the diagnosis of lung cancer and to define its histology before proceeding with surgery. The most accessible site with the least invasive method is the preferred approach to obtaining diagnostic tissue. Although a fine-needle aspiration procedure is often adequate to establish diagnosis and can be accomplished by a transthoracic approach or by bronchoscopy, the yield is often inadequate to conduct molecular studies. Therefore, a core needle biopsy to obtain sufficient tissue is recommended for patients with suspected lung cancer.[8]

For patients who present with pleural or pericardial effusions, transthoracic aspiration of fluid is typically sufficient for diagnosis and staging. Cell blocks prepared from the fluid can be used to conduct molecular studies, although the success rate depends on the number of viable cancer cells in the specimen. The diagnostic yield of pleural fluid in patients with malignant effusion is approximately 50 to 70%. In instances in which repeated aspiration of pleural fluid is nondiagnostic, a video-assisted thoracoscopy procedure might be necessary to establish diagnosis.

Staging Thoracic Disease

Enlarged lymph nodes identified by CT or positron emission tomography (PET) require histologic confirmation. Whether all patients require invasive mediastinal staging before surgical resection or other local treatment is uncertain because only 5 to 15% of patients who have peripheral T1 tumors and a negative mediastinum by CT or PET scanning have mediastinal nodal metastases.

Transbronchial needle aspiration allows staging of the mediastinum during diagnostic bronchoscopy. The sensitivity of transbronchial needle aspiration is dependent on the size and location of the lymph nodes (see Fig. 177-2) as well as on the size of the needle and is best suited for large, clinically positive lymph nodes. Endobronchial ultrasound can guide transbronchial fine-needle aspiration and provide an overall sensitivity approaching 90%. When combined with esophageal ultrasound-guided fine-needle aspiration (which provides access to lymph node stations 7, 8, and 9), the sensitivity can exceed 90%. Other diseases that are also associated with enlarged and metabolically active mediastinal lymph nodes include sarcoidosis, tuberculosis, and multiple infectious causes, generally of a fungal (e.g., histoplasmosis, coccidioidomycosis), atypical bacterial, or viral nature, so nodal tissue must be obtained.

Mediastinoscopy involves surgical assessment of mediastinal lymph nodes to determine tumor involvement. Cervical mediastinoscopy (which provides access to lymph nodes at stations 2, 4, 7, and often 10) has a complication rate of 2% but with few life-threatening complications. With video mediastinoscopy, sensitivity and specificity exceed 97%. Anterior mediastinotomy provides access to lymph node stations 5 and 6 (aortic and aortopulmonary window), which are generally not accessible with cervical mediastinoscopy.

Diagnostic Imaging

In conjunction with standard thoracic imaging procedures, additional sites of disease may require evaluation based on presenting complaints. The most common sites of lung cancer metastases include the contralateral lung, liver, adrenal gland, bones, and brain. Imaging of the brain is recommended to evaluate for metastasis in patients with suggestive symptoms and signs as well as in

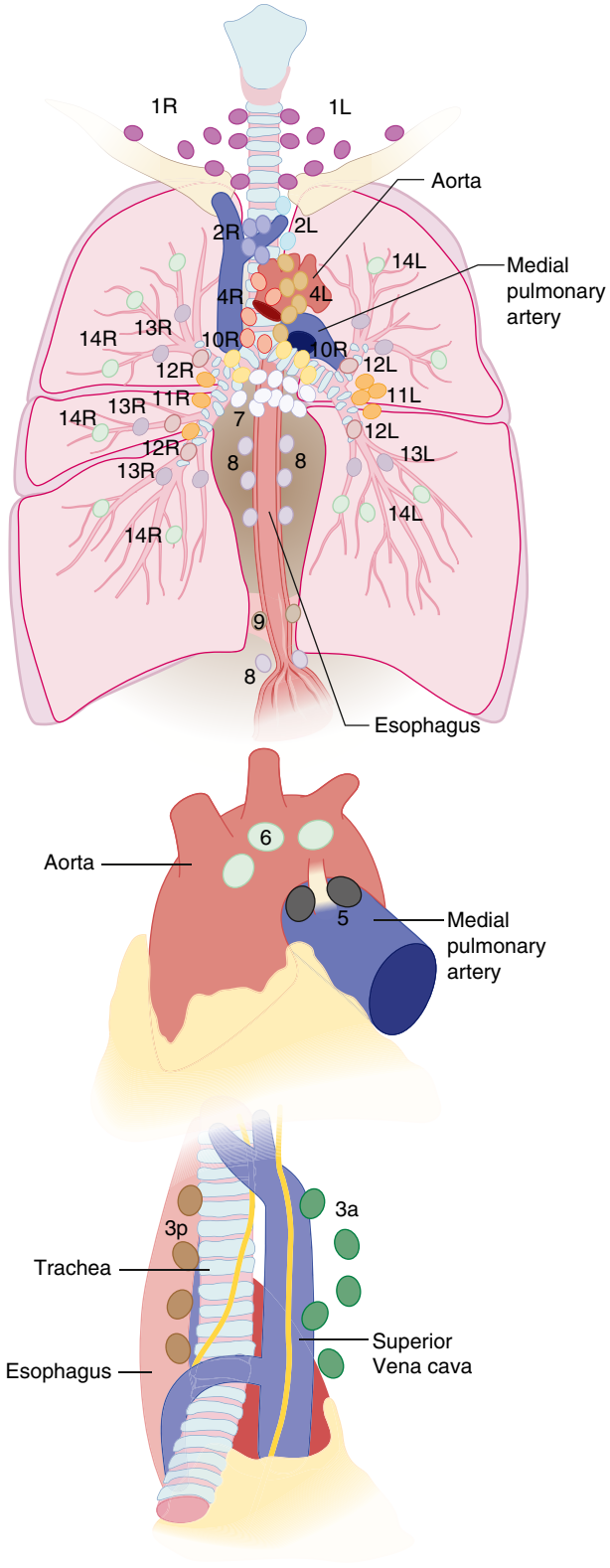

Supraclavicular zone

1 Low cervical, supraclavicular, and sternal notch nodes

Superior mediastinal nodes

Upper zone

2R Upper Paratracheal (right)

2L Upper Paratracheal (left)

3a Prevascular

3p Retrotracheal

4R Lower Paratracheal (right)

4L Lower Paratracheal (left)

Aortic nodes

Aortic-Pulmonary zone

5 Subaortic

6 Para-aortic (ascending aorta or phrenic)

Inferior mediastinal nodes

Subcarinal zone

7 Subcarinal

Lower zone

8 Paraesophageal (below carina)

9 Pulmonary ligament

N1 nodes

Hilar/Interlobar zone

10 Hilar

11 Interlobar

Peripheral zone

12 Lobar

13 Segmental

14 Subsegmental

FIGURE 177-2. The International Association for the Study of Lung Cancer (IASLC) lymph node map. Included is the proposed grouping of lymph node stations into "zones" for the purposes of prognostic analyses. (From Rusch VW, Asamura H, Watanabe H. The IASCL lung cancer staging project. A proposal for a new international lymph node map in the forthcoming seventh edition of the TNM classification for lung cancer. *J Thorac Oncol*. 2009;4:568-577.)

patients who have a lung adenocarcinoma larger than 3 cm and evidence of mediastinal nodal involvement. Magnetic resonance imaging (MRI) and CT scan with contrast enhancement are both acceptable modalities to evaluate for brain metastases, but MRI is preferred for its superior sensitivity. Radionuclide study of the bones is indicated in patients with bone pain or an unexplained elevation in serum alkaline phosphatase level.

PET scanning is part of staging in patients with localized lung cancer. MRI scan of the chest may be useful in determination of invasion of surrounding structures, such as the brachial plexus, in patients with tumors involving the superior sulcus of the lung, but its use in staging is generally restricted to preoperative settings.

Staging

Staging (Table 177-1) based on the size of the tumor, the presence of involved lymph nodes, and the presence of metastases guides therapeutic choices and is the most important determinant of prognosis in patients with lung cancer. The tumor size is categorized as less than 2, 2 to 3, 3 to 4, 4 to 5, 5 to 6, and then 7 cm. Currently, satellite nodules in the same lobe as the primary tumor

TABLE 177-1 TREATMENT BY AMERICAN JOINT COMMITTEE ON CANCER (AJCC) STAGE

	T	N	M	MEDICALLY FIT	MEDICALLY UNFIT
Stage IA and IB	1a, 1b, 1c, 2a	0	0	Surgery	SBRT
Stage IIA/B	T1-3	0/1	0	Surgery plus adjuvant chemotherapy	Thoracic radiation
Stage IIIA	X-3	1/2	0	Multimodality therapy	
	4	X	0		
Stage IIIB	X-4	2/3	0	Concurrent chemoradiation and immunotherapy	
Stage IIIC	1-4	3		Concurrent chemoradiation and immunotherapy	Sequential chemoradiotherapy
Stage IVA	X	X	1a/b	Systemic therapy	
Stage IVB	X	X	1c	Systemic therapy; radiation for palliation	

M = metastasis; N = node; SBRT = stereotactic body radiation therapy; T = tumor.
From *AJCC Cancer Staging Manual*, 8th ed. New York: Springer-Verlag; 2018.

are categorized as T3, and nodules in another lobe of the ipsilateral lung are characterized as T4. Malignant pleural or pericardial effusion constitutes M1 disease. Presence of metastases within the thorax constitutes M1a, and extrathoracic disease is classified as M1b because patients with M1a disease have a slightly better prognosis than those with M1b.

Molecular Testing

A full gene expression profile can improve the diagnostic accuracy of the biopsy for detecting lung cancer and is often helpful for therapeutic decisions. Guidelines recommend routine molecular testing for *EGFR* mutation and *ALK* translocation in all newly diagnosed patients with advanced-stage lung adenocarcinoma. For patients with tumors of squamous cell histology, routine molecular testing is not yet recommended, but randomized clinical trials using this approach are in progress.

TREATMENT

Non–Small Cell Lung Cancer

Treatment for non–small cell lung cancer includes surgery, radiation, and medications, depending on the stage of the tumor and the fitness of the patient.[9,10]

Surgery

Surgical management plays the major role in the treatment of patients with stage I, stage II, and selected stage III NSCLC. However, nearly 40% of patients with early-stage lung cancer are not candidates for surgery because of limiting comorbid conditions. The commonly used parameters for inoperability include pulmonary functions with baseline forced expiratory volume in the first second of expiration (FEV_1) of less than 40%, predicted postoperative FEV_1 of less than 30%, and severely limited diffusion capacity. Such patients are referred to as medically inoperable despite the presence of localized disease and may be candidates for stereotactic body radiation therapy.

Lobectomy is the standard surgical procedure for patients who have localized lung cancer and who are medically fit. If anatomic resection cannot be achieved with lobectomy, bilobectomy or pneumonectomy might be necessary. Sleeve resection refers to removal of the tumor along with the bronchus and anastomosis of the remaining ends of the bronchial tree. Surgical resection can be achieved by performing an open thoracotomy or by video-assisted thoracoscopic surgery (VATS; Chapter 87), which is associated with lower morbidity, faster recovery from surgery, and better ability to administer postoperative systemic therapy.[A1] The ability to achieve an R0 resection (defined as no gross or microscopic tumor at the resection margins) is critical, and surgery should not be attempted if this outcome is not deemed feasible based on the preoperative evaluation. For patients with positive surgical margins, re-resection should be attempted whenever it is feasible. If not, postoperative radiation therapy should be administered. Robotic resection of lung cancers, including robotic lobectomy and pneumonectomy, has increased in use but is not as widely used as are VATS approaches.

Sublobar resections are not recommended because of the higher risk of local recurrence. An exception to this rule is for patients with peripheral tumors smaller than 2 cm, for which studies have demonstrated excellent outcomes.[A2]

Tumors involving the superior sulcus are managed with preoperative chemoradiotherapy to enhance tumor resectability and to gain local and distant tumor control. The decision to perform surgery for these anatomically challenging tumors depends on the extent of local invasion, involvement of the brachial plexus, and mediastinal lymph node involvement.

For stage III NSCLC with mediastinal nodal involvement, surgery alone is associated with a poor outcome, and chemoradiotherapy followed by surgery does not improve survival compared with chemoradiotherapy alone. For patients with multistation N2 disease or bulky nodal disease, surgical resection is not recommended. Clearance of mediastinal nodes after induction therapy might be the most important predictor of benefit from surgical resection, which calls for restaging of the mediastinum after induction therapy if surgery is contemplated.

Surgery can be considered under certain situations in patients with oligometastatic disease.[11] Surgical resection of both the primary and a solitary brain metastasis can result in 5-year survival rates of approximately 20%. Limited data also suggest resection of oligometastatic disease to the adrenal glands, but similar approaches with solitary metastasis at other distant sites are not recommended. This approach cannot be recommended for patients with mediastinal nodal involvement. Spinal cord compression (Chapter 164) is often a surgical emergency.

Radiation Therapy

Radiation therapy is an important part of multimodality therapy for NSCLC. It plays a major role in curative therapy for stage I to III disease and palliation of stage IV disease.

Stage I and Stage II NSCLC

Stereotactic body radiation therapy, which involves the delivery of high-dose radiation to a limited tumor volume after stereotactic localization, is an effective treatment option for patients who have T1 and node-negative T2 tumors but who are medically inoperable because of comorbid illness.[A3] In such patients, radiation therapy over three to five fractions can provide local control in almost 90% of cases. Stereotactic body radiation therapy also has considerable efficacy for peripheral tumors. Radiation therapy is also indicated for patients with positive surgical margins after surgery for early-stage NSCLC but not for patients with negative surgical margins or with involved mediastinal nodes.

Stage III NSCLC

Whereas surgery is appropriate for patients with T3N1 disease, radiation therapy results in improved outcomes for patients who have involvement of mediastinal lymph nodes.[12] A subset of N2-positive patients might benefit from multimodality therapy involving neoadjuvant chemoradiation followed by surgical resection, including stage IIIA patients with single-station or microscopic lymph node involvement and disease amenable to resection with lobectomy or bilobectomy. Preoperative radiation generally consists of 45 Gy once daily, but a dose of 60 Gy also is associated with acceptable safety results.

For patients with unresectable stage III disease, thoracic radiation therapy to a dose of 60 to 66 Gy in once-daily fractions with concurrent (rather than sequential) chemotherapy is the recommended treatment and is associated with a 5-year survival rate of 20 to 25%. The main adverse events include esophagitis and pneumonitis (depending on the extent of normal lung tissue and the dose of radiation received by normal lung tissue) that can occur immediately after radiation therapy or 6 to 9 months later.

Hyperfractionated radiation administered as two or three fractions per day is preferable to once-daily fractionation, particularly in squamous cell carcinoma, but logistical constraints have limited the adoption of this approach. In stage III patients, prophylactic cranial radiation can significantly decrease the risk of developing symptomatic brain metastases but does not improve survival.[A4]

Stage IV NSCLC

In patients with advanced-stage NSCLC, radiation therapy can be effective for palliation of spinal cord compression, brain metastasis, airway obstruction, hemoptysis, and pain. Spinal cord compression is usually managed with 30 Gy of external beam radiation therapy plus high-dose corticosteroids, but surgical decompression should precede radiation therapy when neurologic compromise is early and the patient has well-controlled systemic disease (Chapter 164).

For multiple brain metastases or oligometastatic disease not amenable to surgical resection, whole-brain radiation therapy (30 to 37.5 Gy given in 10 to 15 fractions) can be administered. Stereotactic radiosurgery can be used instead of whole-brain radiation therapy when low-volume brain metastases are limited to one to three lesions and when-brain lesions progress after whole-brain radiation therapy.

A short course of radiation therapy can provide pain control at sites of bone metastases or chest wall involvement. Palliative radiation therapy is also administered at 30 to 45 Gy during 2 to 3 weeks before the initiation of systemic therapy in patients who have systemic disease and who present with hemoptysis or postobstructive pneumonia.

Systemic Therapy

Systemic therapy refers to the use of cytotoxic agents, molecularly targeted therapy, or immunotherapy. Although it was initially developed for patients with advanced-stage lung cancer, the high propensity for metastasis of lung cancer

TABLE 177-2 TARGETED AGENTS IN LUNG CANCER THERAPY

MOLECULAR TARGET	FDA-APPROVED AGENTS
EGFR	Erlotinib Gefitinib Afatinib Osimertinib Necitumumab Dacomitinib
ALK translocation	Crizotinib Ceritinib Alectinib Brigatinib Lorlatinib
ROS1 rearrangement	Crizotinib Entrectinib
VEGF	Bevacizumab Ramucirumab
B-Raf V600E	Dabrafenib/trametinib
NTRK gene fusion	Larotrectinib Entrectinib
MET exon 14 skip mutation	Capmatinib
RET gene fusion	Selpercatinib Pralsetinib

ALK = anaplastic lymphoma kinase; EGFR = epidermal growth factor receptor; MET = metastatic; NTRK = neurotrophic tyrosine kinase; RET = rearranged during transfection; ROS1 = c-ros oncogene 1; VEGF = vascular endothelial growth factor.

TABLE 177-3 CHEMOTHERAPY REGIMENS IN ADVANCED NON–SMALL CELL LUNG CANCER

FIRST-LINE THERAPY	SECOND-LINE THERAPY
Cisplatin/docetaxel Cisplatin/gemcitabine Cisplatin/pemetrexed (non-squamous tumors) Cisplatin/vinorlebine Cisplatin/paclitaxel Carboplatin/paclitaxel +/−bevacizumab Carboplatin/docetaxel Carboplatin/pemetrexed (non-squamous tumors) Carboplatin/vinorelbine Carboplatin/gemcitabine	Docetaxel +/− ramucirumab Pemetrexed (non-squamous tumors) Gemcitabine Vinorelbine

cells has extended the use of systemic therapy to patients with earlier stages of the disease. A number of effective and well-tolerated cytotoxic agents are now used for the routine care of patients with lung cancer. In addition, many targeted agents (Table 177-2) have replaced standard chemotherapy as first-line agents for patients with specific mutations, and others are under clinical investigation.

Systemic Therapy in Early-Stage NSCLC

Even in the setting of optimal surgery, patients with early-stage NSCLC remain at high risk for disease recurrence or metastases due to the presence of micrometastasis, which can increasingly be quantified by the evaluation of circulating tumor cells or circulating tumor DNA. In stage IA disease, the potential benefits of chemotherapy are largely outweighed by the risks, and the overall effect is detrimental. For stage IB disease, adjuvant therapy may improve survival in patients whose tumors are larger than 4 cm, but this observation has yet to be validated in prospective trials. Drug options include cisplatin/vinorelbine or newer and better tolerated agents such as taxanes, gemcitabine, and pemetrexed under expert supervision. For stage II and stage IIIA NSCLC, four cycles of adjuvant cisplatin-based two-drug combination regimens under expert supervision provide a 5 to 15% absolute improvement in 5-year survival rates and are the standard of care.

Consistent with the success of molecularly targeted therapies in advanced-stage NSCLC, osimertinib can prolong disease-free survival in patients whose EGFR-mutated tumors have been treated with surgery and adjuvant chemotherapy.[A5] Efforts are underway to evaluate ALK inhibitors and immune checkpoint inhibitors in the adjuvant and neoadjuvant settings.

Locally Advanced NSCLC

For patients whose stage III disease is not amenable to surgical resection, concomitant administration of cisplatin or carboplatin-based chemotherapy plus radiation therapy under expert supervision is superior to sequential therapy. With modern combined chemoradiotherapy regimens, cure rates of nearly 20 to 25% are achieved in locally advanced NSCLC, with esophagitis and pneumonitis being the main toxicities. The addition of 12 months of consolidation therapy with durvalumab (a PD-L1 inhibitor) can improve survival to 43% at 5 years[A6] in patients with nonprogressive disease following chemoradiotherapy, and this approach is now the standard of care.

Advanced-Stage NSCLC

In patients with advanced-stage NSCLC, platinum-based systemic therapy under expert supervision improves overall survival and quality of life compared with supportive care alone. Carboplatin is a better tolerated outpatient option, and its dose-limiting toxicity is thrombocytopenia. Cisplatin treatment may be slightly more efficacious but is associated with nausea, emesis, nephrotoxicity, and neurotoxicity, although the availability of highly effective antiemetic agents has greatly improved its tolerability. Two-drug combination regimens are superior to monotherapy, with survivals in the 10- to 11-month range, and are recommended. Options to add to platinum-based therapy under expert supervision include etoposide, vinblastine, vindesine, vinorelbine, taxanes, gemcitabine, irinotecan, and pemetrexed (Table 177-3), with the choices among them based on consideration of toxicity, the preference of the patient, schedule, and cost. Combinations of three cytotoxic agents are not recommended because of their higher toxicity without a meaningful incremental benefit.

Targeted Systemic Therapies

Although targeted agents have shown great efficacy against lung cancer, they are unfortunately not curative. Resistance is universal to these agents, and therapy is usually continued until the disease progresses or unacceptable toxicity develops.

In patients with an activating *EGFR* mutation, treatment with gefitinib or erlotinib is associated with improvements in progression-free survival and quality of life compared with platinum-based chemotherapy, and adding gefitinib to platinum-based therapy prolongs survival compared with gefitinib alone.[A7] Afatinib, which is an irreversible EGFR tyrosine kinase inhibitor, is superior to chemotherapy[A8] in patients who have an activating *EGFR* mutation. Dacomitinib and osimertinib, which are second- and third-generation agents, respectively, appear to be more efficacious than earlier agents.[A9,A10] Osimertinib is also associated with favorable effects against brain metastases, which are a common clinical problem in patients with EGFR-mutated NSCLC.

The VEGF antibody bevacizumab is useful for advanced NSCLC with non-squamous histology, in which it significantly improves overall survival and progression-free survival when added to carboplatin and paclitaxel chemotherapy. Notable adverse events include bleeding, hypertension, proteinuria, and neutropenia.

In *ALK*-positive advanced-stage NSCLC, second-generation ALK inhibitors (ceritinib,[A11] alectinib,[A12] brigatinib,[A13] and lorlatinib[A14]) are now preferred over crizotinib as first-line therapeutic options. Lorlatinib is also used for patients who develop acquired resistance to prior ALK inhibitors.

BRAF-V600E mutations are observed in 1 to 2% of NSCLC. The combination of dabrafenib plus trametinib can result in response rates of 60% or more.[13] *RET* fusions are also oncogenic drivers in 1 to 2% of patients with NSCLC, and a durable response with acceptable toxicity is seen with selpercatinib[14] in untreated and platinum-treated patients with *RET* fusion-positive NSCLC.

KRAS G12C mutations account for approximately 40% of all KRAS mutations in NSCLC. Sotorasib and adagrasib, which are inhibitors of the KRAS G12C mutation, can provide a 35% response rate and median progression-free survival of about 7 months in advanced-stage NSCLC.[15,16] In patients whose tumors express human epidermal growth factor receptor 2 (HER2), transtuzumab deruxtecan can provide durable benefit.[17]

Immunotherapy

Inhibition of the programmed death (PD-1) ligand pathway with monoclonal antibodies reverses T-cell exhaustion and results in activation of host antitumor immune responses. Nivolumab, pembrolizumab, and cemiplimab are monoclonal antibodies against the PD-1 receptor, whereas atezolizumab and durvalumab are monoclonal antibodies against its ligand (PD-L1). Pembrolizumab can provide superior overall survival when added to or used instead of platinum-based chemotherapy for first-line therapy.[A15] For patients with PD-L1 expression level >50%, pembrolizumab monotherapy is associated with a 5-year survival rate of 32%. Atezolizumab[A16] and cemiplimab[A17] are also effective as monotherapy for first-line treatment for patients with PD-L1 expression ≥50%. Toripalimab and atezolizumab are also incrementally beneficial in combination with standard chemotherapy.[A18,A19] Nivolumab is effective as neoadjuvant therapy for resectable NSCL[A20] and also improves survival when combined with ipilimumab as a first-line therapy, with improvement in overall survival compared with chemotherapy.[A21] Another approach involving two cycles of platinum-based chemotherapy in combination with nivolumab and ipilimumab has also shown superiority over chemotherapy alone regardless of PD-L1 expression level or histology. Sugemalimab has also shown benefit with or after chemotherapy as first-line[A22] or secondary[A23] treatment of NSCLC.

Based on these results, these agents are now front-line therapy of advanced NSCLC, thereby representing a major shift in the treatment paradigm for

advanced NSCLC. Specifically, for patients with PD-L1 >50%, which represents approximately 25 to 30% of NSCLC, immune checkpoint inhibitor monotherapy is the present standard of care; for PD-L1 <50% or negative disease, either the combination of chemotherapy with immunotherapy or the combination of ipilimumab and nivolumab is considered an acceptable first-line therapy option. In these patients, immunotherapy is used for a maximum duration of 2 years in patients who demonstrate clinical benefit. The main toxicity associated with these agents is autoimmune events, with pulmonary toxicity being the most serious; fortunately, the majority of these events are treatable with appropriate supportive and immunosuppressive therapy.

Role of Histology in Choice of Chemotherapy

Preferred chemotherapy regimens can vary for different histologic subtypes of NSCLC. For example, cisplatin-pemetrexed is preferred for nonsquamous advanced-stage NSCLC, whereas cisplatin-gemcitabine is preferred for squamous cell tumors. Nanoparticle albumin-bound paclitaxel (nab-paclitaxel) is associated with a favorable response rate in patients with advanced squamous NSCLC. Furthermore, the monoclonal antibody necitumumab added to gemcitabine and cisplatin is better than gemcitabine and cisplatin alone for patients with advanced squamous NSCLC.[A24]

Maintenance Therapy

Immunotherapy is now the major maintenance therapy, with the optional application of chemotherapy. Pemetrexed is the only cytotoxic agent that has specifically shown benefit as maintenance therapy. Single-agent maintenance therapy also is useful in patients who have a demonstrated clinical benefit from four cycles of platinum-based combination chemotherapy. Current therapeutic strategies employ either a "switch maintenance" approach, which uses an alternative cytotoxic or targeted agent that has not been previously administered, or "continuation maintenance," which involves continuing only the nonplatinum agent beyond four cycles.

Salvage Therapy

Virtually all patients with advanced NSCLC will eventually experience progressive disease regardless of the extent of benefit from first-line chemotherapy. Salvage therapy for these patients under expert supervision provides a modest but real improvement in survival. For patients who did not receive immune checkpoint inhibitors as part of first-line therapy, immune checkpoint inhibitors are the preferred salvage therapy, with a response rate of approximately 20%, an overall survival of 12 to 13 months, and a favorable toxicity profile. In patients who have received prior checkpoint inhibitor therapy, docetaxel (75 mg/m^2 every 3 weeks) improves survival compared with best supportive care or first-generation cytotoxic agents. Ramucirumab, a monoclonal antibody against VEGFR2 receptor, in combination with docetaxel provides a modest improvement in overall survival. Compared with docetaxel, pemetrexed has similar efficacy as salvage therapy and a more favorable toxicity profile, but its use is restricted to patients with nonsquamous histology. Overall, current salvage therapy options are associated with response rates of less than 10%, with a median progression-free survival of 3 months and overall survival of 8 months. Combinations of cytotoxic or targeted agents have not resulted in improved survival and are not recommended for salvage therapy.

Management of Special Populations of Patients

In the United States, the median age at diagnosis of lung cancer is 70 years, and elderly patients represent a growing subset of lung cancer patients. Aging is associated with a lower tolerance for systemic therapy, thereby making current physical function and prospective quality-of-life considerations important factors in the choice of systemic treatment.

For patients with a targetable mutation, appropriate targeted therapy can be administered regardless of the performance status in view of the greater potential for benefit. The use of immune checkpoint inhibitors, guided by PD-L1 expression level, is also appropriate for this patient population. However, bevacizumab is associated with a narrow therapeutic index in nonsquamous cancers in older patients, and it is recommended only with great caution.

Platinum-based combinations are superior to single-agent therapy for patients with a good performance status. Nevertheless, single-agent chemotherapy has a survival benefit compared with supportive care in elderly patients and is often more appropriate for selected patients with a poor performance status.

Small Cell Lung Cancer

For small cell lung cancer, the role of surgery is limited to the less than 5% of patients who present with peripheral lung lesions without mediastinal nodal involvement. Surgery may also be useful in the 10 to 15% of patients whose SCLC has a mixed histology with features of NSCLC.

For patients with limited-stage SCLC, radiation therapy (70 Gy on a once-daily fractioned schedule or 45 Gy on a twice-daily schedule) in combination with chemotherapy can achieve cure for approximately 20 to 30% of patients.[18] Earlier initiation of radiation therapy appears superior to a delayed approach, and twice-daily radiation therapy fractions are better than once-daily. Prophylactic cranial irradiation is associated with a modest improvement in 5-year survival for patients who have limited-stage SCLC and who achieve complete remission after combined modality therapy.

TABLE 177-4 SYSTEMIC THERAPY REGIMENS IN ADVANCED SMALL CELL LUNG CANCER

FIRST-LINE THERAPY	SECOND-LINE THERAPY
Cis- or carboplatin/etoposide	Platinum rechallenge
Cis- or carboplatin/irinotecan	Topotecan
Cis- or carboplatin/etoposide/durvalumab	Irinotecan
Carboplatin/etoposide/atezolizumab	Lurbinoctedin
	Nivolumab
	Pembrolizumab

However, approximately two thirds of patients present with extensive-stage SCLC, defined as having metastatic disease outside of the chest or having large-volume intrathoracic disease that cannot be cured with surgery or treated with radiation therapy.[19] SCLC is characterized by excellent initial sensitivity to systemic chemotherapy, although the disease commonly recurs regardless of the extent of the initial response.

Four to six cycles of cisplatin and etoposide under expert supervision is the standard chemotherapy. Carboplatin is an acceptable alternative in the treatment of extensive-stage disease. The addition of four to six cycles of immune checkpoint inhibitors (e.g., durvalumab, atezolizumab, and serplulimab) results in modest improvement in overall survival,[A25,A26] but disease recurs at a median of 4 to 6 months (Table 177-4).

Disease that progresses during or within 90 days of administration of cisplatin-based chemotherapy is referred to as refractory relapse. Topotecan can provide a response rate of 20% and improve the symptom profile but not overall survival in randomized studies. The combination of cisplatin, etoposide, and irinotecan can significantly improve overall survival compared with topotecan alone but with a higher incidence of febrile neutropenia.[A27] Other agents under study include lurbinectedin, which demonstrated a response rate of 35% in a phase 2 study of patients with relapsed/refractory SCLC.[20]

Surveillance and Follow-Up

The importance of smoking cessation cannot be overemphasized, given the high risk of enhanced complications of chemotherapy and the higher incidence of second primary tumors in lung cancer survivors. Patients should be provided with counseling and behavioral therapy and other treatment modalities to assist their efforts to discontinue smoking (Chapter 363).

CT scans are commonly used to follow patients who undergo surgical resection or chemoradiotherapy, but the relative merits of CT scan versus chest radiography, the frequency of evaluation, and the role of PET scans are unclear. For patients with advanced-stage disease, CT scans are used to assess response to therapy after every two or three cycles of treatment. In view of the proven role for salvage therapy, patients who are in follow-up after combination chemotherapy should be closely observed for development of new symptoms or clinical deterioration in addition to periodic radiographic studies.

Supportive Care

Respiratory therapy should be offered and strongly recommended to patients with dyspnea after surgery or chemoradiotherapy. Because a high proportion of these patients also have smoking-related pulmonary diseases, referral to a pulmonologist should be considered in symptomatic patients. Overall, a team approach that includes supportive care personnel, oncologic psychiatrists, nutritionists, oncologists, and appropriate additional specialists should be used to ensure the return of lung cancer survivors to normalcy to the fullest extent possible.

Because the cure rate for lung cancers is only 16%, even in the most advanced health care systems, early discussion and institution of palliative and supportive care (Chapter 3) are therefore critical to maximize quality of life. The early integration of supportive care not only helps maintain and improve quality of life but also may produce a meaningful impact on overall survival. Among family members of elderly patients who died with advanced-stage lung cancer, perceptions of better end-of-life care were associated with earlier enrollment in hospice care, avoidance of ICU admissions, death outside the hospital, and advanced care planning consistent with patients' preferences.

PREVENTION

Primary Prevention

Primary prevention of lung cancer focuses on ways to prevent individuals from smoking and promotion of smoking cessation (Chapter 363), which remain the most effective means to prevent lung cancer. The Environmental Protection Agency recommends that the household radon level be less than 4 picocuries/liter of air, and simple remedial methods are available to reduce radon exposures above this threshold. Trials of supplemental β-carotene, vitamin E, and selenium have been unsuccessful.

Secondary Prevention

Screening with annual low-dose CT scans in high-risk individuals is associated with a 20% reduction in lung cancer mortality and a 6.7% reduction in all-cause mortality. Nearly 80% of patients diagnosed with lung cancer with low-dose CT have stage I, II, or IIIA disease amenable to curative therapy. Among patients with a positive CT scan, 96.4% are deemed false positive after additional evaluation.[A28] Screening with low-dose CT is most beneficial among patients who are at highest risk and prevents very few deaths among those at lowest risk. These results have led to the adoption of low-dose CT for early detection of lung cancer by major health organizations, including the U.S. Preventive Services Task Force.[21] Because overly frequent screening has associated harms, increasing the interval between screens in persons with a negative low-dose CT result might be warranted.

PROGNOSIS

The use of targeted therapies has resulted in a substantial 50% decline in the annual mortality rate among patients diagnosed with NSCLC, and such patients now have a 35% chance of dying from a cause other than lung cancer.[22] Adenocarcinoma in situ and minimally invasive adenocarcinoma have a more than 95% 5-year survival rate when they are treated with surgical resection, thereby making the establishment of a precise pathologic diagnosis of great significance. Large cell carcinoma is often associated with an aggressive clinical course and poor survival rates, even when it is found in the setting of early-stage disease.

For SCLC, the median survival of untreated extensive-stage disease is less than 2 months, but platinum-based chemotherapy results in response rates of 50 to 70% and a median survival of 9 to 11 months. Survival for SCLC has not changed considerably over the past two decades.

OTHER PULMONARY NEOPLASMS

MALIGNANT MESOTHELIOMA

Malignant pleural mesotheliomas are generally related to asbestos exposure, with a peak risk for developing the disease 30 to 35 years after the initial exposure. Additional possible risk factors include radiation and the SV40 virus.

Mesothelioma is generally diagnosed in the fifth to seventh decade of life (median age 60 years), with a male-to-female preponderance of 5 : 1. Common symptoms include dyspnea (60%) and chest wall pain or discomfort (60%).

Chest radiographs and CT scan usually reveal pleural thickening (Fig. 86-6). Tumor progression and symptoms are generally the result of local progression, and symptomatic distant metastases are a late occurrence. Cytologic evaluation of pleural fluid to establish diagnosis is difficult and often inaccurate. The diagnosis is generally made by a biopsy procedure under CT guidance or thoracoscopically, including VATS if necessary. Several staging systems have been proposed, but none has achieved complete acceptance.

TREATMENT AND PROGNOSIS

Treatment, depending on the extent of disease, commonly includes surgery (thoracoscopy with sclerosis, pleurectomy, extrapleural pneumonectomy), radiation therapy, and, often, chemotherapy.[23] With rare exceptions, no single modality has significantly improved survival rates, and neither chemotherapy nor radiation therapy provides long-term palliation or relief of symptoms. Combination chemotherapy with pemetrexed and cisplatin can provide symptomatic relief in patients with advanced, unresectable malignant mesothelioma.

Immunotherapy with nivolumab[A29] or with nivolumab plus ipilimumab[A30] can improve overall survival, and the combination of chemotherapy with immune checkpoint inhibition has yielded promising results. The addition of bevacizumab to pemetrexed plus cisplatin can improve overall survival but just from 16.1 to 18.8 months and at the cost of manageable toxic effects.[A31]

NEUROENDOCRINE AND OTHER LUNG TUMORS

Carcinoid Tumors

Carcinoid tumors (Chapter 213) of the lung account for 1 to 2% of all lung neoplasms. These neuroendocrine tumors trace their origin to the Kulchitsky cell present in bronchial epithelium. Typical and atypical carcinoids differ in the number of mitoses (<2 per 10 high-power fields vs. 2 to 10 per 10 high-power fields, respectively), nuclear pleomorphism (absent vs. present), and regional lymph node metastases (5 to 15% vs. 20 to 28%). Distant metastases at initial evaluation are unusual (<20%). Carcinoid tumors are not associated with cigarette smoking, are twice as common in women as in men, usually occur in patients younger than age 40 years, and arise in the perihilar area of the lung. Treatment of bronchial carcinoid tumors is based on the stage of the disease. Mediastinal staging is usually followed by surgical resection. With mediastinal lymph node involvement, radiation therapy is recommended for typical carcinoid tumors if surgery cannot be performed. For atypical carcinoid or metastatic disease, chemotherapy (etoposide plus cisplatin every 3 weeks for four cycles) plus radiation therapy is commonly used, but there is no evidence for the benefit of one therapy over another. Patients with typical or low-grade carcinoid tumors usually live for many years, with a 10-year survival of >90%, whereas patients with atypical carcinoid tumors have a 5-year survival rate of about 60 to 90%.

Large Cell Neuroendocrine Carcinoma

Large cell neuroendocrine carcinoma is an aggressive neuroendocrine tumor that does not meet the criteria for carcinoid, atypical carcinoid, or SCLC. Treatment is usually with platinum agents and etoposide under expert supervision.

Salivary Gland Carcinomas

Salivary gland carcinomas (Chapter 176) include mucoepidermoid carcinoma and adenoid cystic carcinoma, which represent approximately 0.2% of lung cancers. These slow-growing neoplasms arise from the bronchial glands and are usually treated with surgery.

Primary Lung Sarcoma and Lymphoma

Primary sarcomas of the lung are very rare and include malignant fibrous histiocytoma, fibrosarcoma, leiomyosarcoma, rhabdomyosarcoma, epithelioid hemangioendothelioma, angiosarcoma, and liposarcoma (Chapter 187). The primary treatment is surgery. Depending on the size and grade of the tumor and whether the margins are clear, radiation therapy or chemotherapy may also be given. A subset of sarcomatoid carcinoma of the lung is likely to harbor MET 14 exon skipping mutations that could be amenable to targeted therapy.

Primary lymphomas of the lung are also very rare, accounting for approximately 0.3% of all primary lung cancers. The most common type is a low-grade small lymphocytic lymphoma, for which surgery and chemotherapy are the usual treatments (Chapter 171).

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For the General References and other additional features, please visit Elsevier eBooks+ at https://ebooks.health.elsevier.com.

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178 NEOPLASMS OF THE ESOPHAGUS AND STOMACH

ADAM J. BASS AND ANIL K. RUSTGI

NEOPLASMS OF THE ESOPHAGUS

DEFINITION

The esophagus (Chapter 124) is a hollow tubular organ with primary physiologic functions related to contraction to permit propulsion of solid and liquid food contents into the stomach. The mucosa is a stratified squamous epithelium that covers the submucosa and muscle; the latter is skeletal muscle in the proximal esophagus and smooth muscle in the mid-distal esophagus. Cancers of the esophagus may be classified broadly into epithelial versus nonepithelial cancers. Benign epithelial tumors are referred to as squamous cell papillomas. Malignant epithelial tumors are classified into two main subtypes: esophageal squamous cell carcinoma and esophageal adenocarcinoma. Other, less common, esophageal epithelium-derived cancers include verrucous squamous cell carcinoma, adenosquamous carcinoma, adenoid cystic carcinoma, and mucoepidermoid carcinoma. Benign nonepithelial tumors include leiomyoma, granular cell tumors, fibrovascular polyp, hemangioma, lymphangioma, lipoma, and fibroma. Malignant nonepithelial tumors include leiomyosarcoma and other sarcomas, metastatic carcinoma (e.g., originating from breast or lung), and lymphoma.

ESOPHAGEAL SQUAMOUS CELL CARCINOMA

EPIDEMIOLOGY

Esophageal squamous cell carcinoma is the more common type of esophageal cancer worldwide and is a major cause of cancer-related mortality.[1] Esophageal squamous cell carcinoma may have rates of up to 100 per 100,000 population in what is often termed the *Central Asian belt*, including regions around the Caspian Sea, Iran, India, and China; other areas of high incidence include some Mediterranean countries and Eastern Africa. In the United States, esophageal squamous cell carcinoma is more common among Black males than White males, with risks of 15.1 per 100,000 compared with 2.9 per 100,000, respectively. Rates are 2 to 3 times higher in men than in women. Although the U.S. incidence of esophageal squamous cell carcinoma is low in both men and women younger than age 50 years, the incidence increases with advancing age.

Risk Factors

Hereditary esophageal squamous cell carcinoma is exceedingly rare, and is associated with a desquamating condition termed *tylosis palmaris et plantaris*. This desquamation most dramatically affects the hands and feet but extends to the esophagus as well. Another uncommon condition, Plummer-Vinson syndrome or Paterson-Brown Kelly syndrome, entails glossitis, cervical esophageal webs, and iron deficiency anemia. In both conditions, it is likely that chronic inflammation triggers the cascade of events that culminate in esophageal squamous dysplasia and esophageal squamous cell carcinoma.

Most esophageal squamous cell carcinoma cases are related to cigarette smoking or alcohol consumption, especially in combination, because their deleterious effects appear to be synergistic. Chemical carcinogens that are present in both include *N*-nitroso compounds, polycyclic aromatic hydrocarbons, and aromatic amines. The relative risk for esophageal squamous cell carcinoma is 6.2-fold higher in persons who smoke more than 25 cigarettes daily. Cessation of cigarette smoking is helpful in attenuating risk after 10 years of abstinence. Cigarette smokers who drink beer and whiskey have a 10- to 25-fold enhanced risk of developing esophageal squamous cell carcinoma. Vitamins A, B_{12}, C, and E; folic acid; and certain minerals (zinc, selenium, molybdenum) exert direct or indirect antioxidant effects, and their deficiencies impair epithelial and tissue homeostasis and regeneration.

Other risk factors for esophageal squamous cell carcinoma (Table 178-1) include achalasia (Chapter 124), which is a disorder that involves aganglionosis of the Auerbach plexus, thereby resulting in dysphagia, chest pain, and weight loss, among other symptoms. The emergence of esophageal squamous cell carcinoma may be observed 10 to 20 years after the identification of achalasia. Because head and neck squamous cell carcinoma (Chapter 176) shares many of the same environmental and lifestyle risk factors with esophageal squamous cell carcinoma, particularly alcohol use and tobacco smoking, head and neck squamous cell carcinoma and esophageal squamous cell carcinoma may occur synchronously or metachronously. In different parts of the world, esophageal

TABLE 178-1 RISK FACTORS FOR ESOPHAGEAL CANCER

Esophageal squamous cell cancer
Tylosis palmaris et plantaris
Achalasia
Plummer-Vinson syndrome
Cigarette smoking
Alcohol
Chronic lye ingestion
Dietary deficiencies (minerals, vitamins)
Human papillomavirus (HPV) infection
Radiation injury
Celiac sprue
Esophageal adenocarcinoma
Gastroesophageal acid reflux
Bile reflux
Obesity
Barrett esophagus

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Risk Factors

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TABLE 178-1 RISK FACTORS FOR ESOPHAGEAL CANCER

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Tylosis palmaris et plantaris
Achalasia
Plummer-Vinson syndrome
Cigarette smoking
Alcohol
Chronic lye ingestion
Dietary deficiencies (minerals, vitamins)
Human papillomavirus (HPV) infection
Radiation injury
Celiac sprue
Esophageal adenocarcinoma
Gastroesophageal acid reflux
Bile reflux
Obesity
Barrett esophagus

ABSTRACT

Esophageal and gastric cancers are common worldwide. Esophageal cancer is subtyped into esophageal squamous cell carcinoma and esophageal adenocarcinoma, the latter of which is preceded typically by Barrett esophagus. The most common subtypes of gastric cancer are gastric adenocarcinoma followed by lymphoma. The pathobiology (especially genetics), clinical presentation, staging, diagnostic strategies, and therapeutic options often are different with each of these malignancies.

KEYWORDS

esophageal cancer
esophageal squamous cell carcinoma
Barrett esophagus
esophageal adenocarcinoma
gastric cancer
gastric adenocarcinoma
lymphoma

squamous cell carcinoma is also associated with chronic esophageal stricture due to lye ingestion, consumption of maté (a hot herb-based beverage), celiac sprue, infection with human papillomavirus (HPV) (especially genotypes HPV-16, HPV-18, and HPV-33), and radiation injury.

PATHOBIOLOGY

Esophageal squamous cell carcinoma involves the transition from normal squamous epithelium to squamous dysplasia to cancer. The initiation, progression, and metastatic potential of esophageal squamous cell carcinoma are associated with a number of genetic alterations, including overexpression of epidermal growth factor receptor (*EGFR*) and cyclin D1 oncogenes, as well as inactivation of *TP53*, *p16INK4A*, and p120-catenin (*p120ctn*) tumor suppressor genes. The frequency of these changes varies greatly based upon various studies, but the oncogenic alterations generally appear early in dysplasia and early esophageal squamous cell carcinoma, whereas the inactivation of tumor suppressor genes appears as later events in established primary and metastatic esophageal squamous cell carcinoma. From a genomic viewpoint, the SOX-2 transcription factor, which is important in the pluripotent capacity of somatic cells, is an important gene involved in the pathogenesis of esophageal squamous cell carcinoma. Conditional knockout of the *p120ctn* tumor suppressor gene in the esophagus of mice results in invasive esophageal squamous cell carcinoma. Deep DNA sequencing has confirmed these genetic alterations and revealed a lower frequency of other alterations, such as inactivation of chromatin-modifying enzymes.

CLINICAL MANIFESTATIONS

Symptoms and Signs

Although esophageal squamous dysplasia is typically not associated with symptoms, esophageal squamous cell carcinoma, which has a predilection for the proximal to mid-esophagus, may be associated with dysphagia, odynophagia, atypical or typical chest pain, gastrointestinal bleeding, nausea, vomiting, weight loss, and malnutrition. Esophageal squamous cell carcinoma may metastasize to local lymph nodes, lung, liver, and bone. Symptoms attributable to metastatic esophageal squamous cell carcinoma may include bone-related pain, dyspnea, and evidence of jaundice and liver failure, depending upon the extent of metastatic disease.

Physical Examination

Weight loss may result in general cachexia and muscle wasting. The patient should be evaluated for changes in hair, skin integrity, and nail beds as a reflection of malnutrition. Lymphadenopathy may be detected in the anterior cervical and supraclavicular regions. Hepatomegaly and complications of liver disease may herald metastatic disease to the liver.

Laboratory Studies

A progressive iron deficiency anemia may be due to chronic indolent upper gastrointestinal bleeding. Additional abnormalities may be reflected in metabolic disturbances, such as metabolic alkalosis due to vomiting and hypernatremia due to dehydration. Liver enzyme abnormalities, both hepatocellular and cholestatic, may reflect metastasis to the liver. Paraneoplastic hypercalcemia is uncommon. Esophageal squamous cell carcinoma has no specific markers, but an elevated carcinoembryonic antigen (CEA) level and levels of cell-free DNA from tumor cells may be used to aid in monitoring for recurrent disease after therapy.

DIAGNOSIS

An upper gastrointestinal contrast radiographic study can show a filling defect due to the mucosal lesion or impaired transit of contrast due to luminal growth (Chapter 119). However, definitive diagnosis involves direct visualization with upper endoscopy (Chapter 120). Once the mass is visualized, biopsies are necessary to confirm the diagnosis and to enable genomic studies. Fine-needle aspiration can provide a rapid diagnostic assessment in the procedure room. Esophageal squamous cell carcinoma may involve local lymph nodes, which are best detected by endoscopic ultrasound; as needed, samples can then be analyzed by cytopathology following fine-needle aspiration. Endoscopic ultrasound is routinely used also to gauge depth of invasion, which guides the use of neoadjuvant therapy in node-negative localized cases.

Evaluation of metastatic disease involves chest and abdominal computed tomography (CT) scans. Bone scan might be useful in patients who are symptomatic with bone-related pain. Positron emission tomography (PET) is increasingly used to assess metastatic disease. In totality, these diagnostic modalities also allow for staging of esophageal squamous cell carcinoma, which is important in guiding therapeutic options.

TREATMENT

Surgical Therapy

Surgery is the cornerstone of therapy for curative intent, but adjuvant chemotherapy or chemoradiation markedly improves outcomes.[2] Depending upon the location of the esophageal squamous cell carcinoma, either total esophagectomy or subtotal esophagectomy is pursued.[3] For the latter, jejunal or colonic interposition can be done.

Surgical techniques include transthoracic, transhiatal, and radical en bloc resections. Increasing surgical proficiency in performing esophagectomy improves short-term as well as long-term mortality results in esophageal cancer. In selected patients, minimally invasive esophagectomy[4] can provide equivalent or better perioperative mortality, morbidity, and oncologic outcomes compared with open surgery.[A1–A3]

In patients who are medically unfit for surgery or in whom surgery is likely to result in high morbidity (e.g., tumors in the cervical esophagus), definitive chemoradiation is often pursued as an alternative to surgical therapy. Salvage esophagectomy after definitive chemoradiotherapy can offer acceptable short- and long-term outcomes in selected patients whose esophageal cancers are treated at experienced centers.

Medical Therapy

Neoadjuvant or adjuvant combination chemoradiotherapy under expert supervision is more effective than surgery alone for improving the survival of patients with resectable esophageal cancer.[A4] For patients who have localized node-positive or more advanced esophageal cancer, outcomes are improved by neoadjuvant chemoradiation with about 40 Gy of radiation plus either carboplatin with paclitaxel[A5] or cisplatin with vinorelbine.[A6] Adjuvant nivolumab can enhance survival in patients who have residual disease despite chemoradiation and surgery.

In patients who have metastatic esophageal squamous cell carcinoma, first-line platinum-containing cytotoxic chemotherapy should be combined with immune checkpoint inhibition using nivolumab,[A7,A8] camrelizumab,[A9] toripalimab,[A10] or pembrolizumab.[A11] For patients who have unresectable or metastatic disease, palliative therapy includes endoscopically placed expandable prosthetic stents (to open the nearly obstructed lumen and to allow passage of food contents), percutaneous endoscopic gastrotomy tubes (to deliver nutrition to the stomach distal to the mass lesion), total parenteral nutrition, pain control, and systemic chemotherapy.[5]

PROGNOSIS

The 5-year survival for treated esophageal squamous cell carcinoma is dependent upon stage and types of therapies used. For stages T1 and T2 without lymph node involvement, surgery alone may be curative in more than 60% of cases. Major postoperative complications, which occur in about one third of patients, exert a long-lasting negative effect on health-related quality of life in patients who survive for 5 years after esophagectomy for cancer. Dyspnea, fatigue, eating restrictions, sleep difficulty, and gastroesophageal reflux progressively worsen more during follow-up in patients who suffer such major postoperative complications compared with patients without major surgical complications.

ESOPHAGEAL ADENOCARCINOMA

EPIDEMIOLOGY

Esophageal adenocarcinoma has an age-adjusted annual incidence of 1.3 per 100,000. It affects Whites more than Blacks, males much more than females (3:1 to 5.5:1), and increases in incidence after age 40 years. The incidence of esophageal adenocarcinoma is increasing dramatically in developed countries, especially in the United States (by 4 to 10% annually) and Western/Northern Europe.[6]

Risk Factors

Obesity (central) is an important risk factor for esophageal adenocarcinoma (see Table 178-1), perhaps because it is related to either mechanical factors that foster greater gastroesophageal reflux disease (GERD) or, more likely, the release of proinflammatory adipokines, cytokines, and chemokines that track to the esophagus. The major recognized precursor of esophageal adenocarcinoma is Barrett esophagus (Chapter 124), which is the replacement of

the normal stratified squamous epithelium by an incomplete small intestinal epithelium (metaplasia) that projects from the gastroesophageal junction into the distal esophagus in a distal-proximal gradient (Chapter 124). In turn, Barrett esophagus is fostered by GERD as well as by an admixture of bile acids in the acid refluxate. A small subset of patients with Barrett esophagus may progress to esophageal adenocarcinoma through intermediate stages of low-grade and high-grade dysplasia. In Barrett esophagus, one case of esophageal adenocarcinoma is estimated to arise in every 55 to 441 patient-years, a rate that corresponds to an approximately 125-fold increased risk for esophageal adenocarcinoma compared with the risk in the general population.

PATHOBIOLOGY

In Barrett esophagus, metaplasia in the distal esophagus results in a small intestinal epithelium with columnar enterocytes and secretory goblet cells, but without Paneth cells or enteroendocrine cells—hence the designation of incomplete intestinal metaplasia.[7] By itself, the metaplasia of Barrett esophagus cannot become esophageal adenocarcinoma. However, if and when Barrett esophagus transitions to low-grade and high-grade dysplasia, risk for esophageal adenocarcinoma increases dramatically. Barrett esophagus is associated with abnormal DNA ploidy as well as genetic alterations in epidermal growth factor receptor signalling, *TP53*, and *p16INK4A*. Emerging data demonstrate that markers, including mutation of TP53 and detection of aneuploidy, can identify patients whose Barrett esophagus has the greatest risk of progressing to cancer.

Esophageal adenocarcinoma can be distinguished from gastroesophageal adenocarcinomas (so-called gastroesophageal junctional cancer) and gastric cardia adenocarcinomas based on its location, although genomic data demonstrate remarkable similarity between esophageal and gastric adenocarcinomas. Whole-genome approaches show gains and losses of chromosomal regions that might lead to identification of known and previously unknown genes critical in the pathogenesis of esophageal adenocarcinoma.

CLINICAL MANIFESTATIONS

Symptoms and Signs

A small subset (about 5 to 15%) of patients who have gastroesophageal reflux disease may develop Barrett esophagus. However, millions of people are affected with gastroesophageal reflux disease, and most patients who have gastroesophageal reflux disease do not undergo upper endoscopy. Patients with Barrett esophagus may or may not have symptoms related to gastroesophageal reflux disease. Chronic gastroesophageal reflux disease with Barrett esophagus may be associated with distal esophageal strictures. Patients with esophageal adenocarcinoma may suffer from dysphagia, odynophagia, upper gastrointestinal bleeding, chest pain, nausea, vomiting, early satiety, weight loss, and malnutrition.

Physical Examination

Examination of the patient may reveal signs consistent with malnutrition and weight loss. Hepatomegaly may be present, and lymphadenopathy may be a sign of metastasis. Paraneoplastic syndromes are unusual with esophageal adenocarcinoma.

Laboratory Studies

Patients with esophageal adenocarcinoma may have iron deficiency anemia (from occult upper GI bleeding), metabolic derangements, and abnormal liver enzyme tests owing to metastatic disease. The CEA level may be elevated as a tumor serologic marker, although it is not a diagnostic test.

DIAGNOSIS

It is important to ensure that esophageal adenocarcinoma is not mistaken for a benign entity such as a primary esophageal motility disorder. Barium swallow radiography may lead to the suspicion of Barrett esophagus and can diagnose luminal mass lesions consistent with esophageal adenocarcinoma in the distal esophagus. However, the mainstay of diagnosis is upper endoscopy. If the extent of Barrett esophagus is 3 cm or less, it is termed *short-segment Barrett esophagus*; if it is more than 3 cm, it is referred to as *long-segment Barrett esophagus*. This distinction is important because the risk for esophageal adenocarcinoma in long-segment Barrett esophagus is greater than in short-segment Barrett esophagus. Unlike the pinkish-white hue of the normal esophageal mucosa, esophageal adenocarcinoma has a characteristic salmon-colored mucosa that can be visualized at the gastroesophageal junction, with frondlike projections in a proximal direction. Endoscopic mucosal biopsies from the Barrett esophagus region (with control biopsies from the normal esophagus and gastric cardia) are required for histopathologic diagnosis. Features of dysplasia are best appreciated in the absence of reflux-related esophagitis, which can lead to nuclear architectural distortion. Hence, gastric acid production should be suppressed with proton pump inhibitor therapy (Table 124-1) for 6 to 8 weeks prior to biopsy.

TREATMENT

The principles for surgical resection and neoadjuvant therapy after chemoradiation and surgical resection are similar to what is recommended for squamous cell esophageal carcinoma. However, the impact of neoadjuvant chemoradiation is more modest in esophageal adenocarcinoma. In the setting of residual disease despite chemoradiation and surgery, adjuvant nivolumab can improve survival.[A12]

Systemic therapies for advanced and metastatic esophageal adenocarcinomas are analogous to what are recommended for adenocarcinomas of the stomach, including immune checkpoint therapies in concert with chemotherapy for first-line treatment under expert supervision. For tumors that overexpress the HER2 protein, targeted therapies are recommended under expert oversight. Patients with esophageal cancers often have serious comorbid conditions (e.g., obesity, heart disease, emphysema, and malnutrition) that limit treatment options after first-line therapy. For advanced, unresectable tumors, self-expanding stents, often with localized brachytherapy, can provide palliation.[8]

PREVENTION

If the patient has Barrett esophagus metaplasia, upper endoscopy should be repeated every 3 years. However, low-grade dysplasia (with confirmation by an expert pathologist) requires surveillance endoscopy every 6 to 12 months. High-grade dysplasia, if properly evaluated by the pathologist, may require reconfirmation, but then leads to either medical (radiofrequency ablation or endoscopic mucosal resection) or surgical intervention because of the possibility of missed contiguous esophageal adenocarcinoma (Chapter 124). Radiofrequency ablation reduces the progression of low-grade dysplasia or possibly high-grade Barrett esophageal dysplasia to cancer. Endoscopic mucosal resection is used for Barrett esophagus–related high-grade dysplasia or Barrett esophagus associated with intramucosal (tumor stage T1a) esophageal adenocarcinoma.[9] Endoscopic ultrasound may be helpful in discriminating between high-grade dysplasia and esophageal intramucosal adenocarcinoma.

PROGNOSIS

Localized disease detected by careful follow-up of patients with residual Barrett esophagus can be cured. With localized disease, long-term survival can exceed 50%, with higher rates among patients with complete responses to neoadjuvant therapy. However, esophageal adenocarcinoma carries among the most dismal survival rates within oncology. The overall 5-year survival is about 20%, because the disease is diagnosed at an advanced stage, it has a propensity to relapse after surgical therapy, and the efficacy of chemoradiation is modest. Whether adjuvant immune checkpoint therapy and the introduction of new agents will substantially improve survival remains to be proven.

NEOPLASMS OF THE STOMACH

DEFINITION

Gastric neoplasms are predominantly malignant, and nearly 90 to 95% of these tumors are adenocarcinomas. Less frequently observed malignant diseases include lymphomas, especially non-Hodgkin lymphoma, and sarcomas such as leiomyosarcoma. Benign gastric neoplasms include leiomyomas, carcinoid tumors, and lipomas.

ADENOCARCINOMA OF THE STOMACH

EPIDEMIOLOGY

The great geographic variation in the incidence of gastric cancer worldwide indicates that environmental factors influence the pathogenesis of gastric carcinogenesis. Further support for this notion comes from observations that groups emigrating from high-risk to low-risk areas, such as Japanese individuals moving to Hawaii and Brazil, acquire the low risk of the area into which they emigrate, presumably because of adoption of the endogenous lifestyle and exposure to different environmental factors.[10]

TABLE 178-2 CONDITIONS PREDISPOSING TO OR ASSOCIATED WITH GASTRIC CANCER

ENVIRONMENTAL
Helicobacter pylori infection
Dietary: excess of salt (salted pickled foods), nitrates/nitrites, carbohydrates; deficiency of fresh fruit, vegetables, vitamins A and C, refrigeration
Low socioeconomic status
Cigarette smoking
GENETIC
Familial gastric cancer (rare)
Associated with hereditary nonpolyposis colorectal cancer
Blood group A
PREDISPOSING CONDITIONS
Chronic gastritis, especially atrophic gastritis with or without intestinal metaplasia
Pernicious anemia
Intestinal metaplasia
Gastric adenomatous polyps (>2 cm)
Postgastrectomy stumps
Gastric epithelial dysplasia
Ménétrier disease (hypertrophic gastropathy)
Chronic peptic ulcer

Gastric adenocarcinoma was the most frequently observed malignant disease in the world until the mid-1980s, and it remains extremely common among men in certain regions such as tropical South America, some parts of the Caribbean, and Eastern Europe. Regardless of gender, it remains one of the most common malignancies in Japan and China. Nevertheless, incidence is decreasing worldwide.[11,12]

Whereas gastric cancer was the most common cancer in the United States in the 1930s, its annual incidence has steadily decreased to fewer than 10,000 new cases per year. The U.S. incidence is about 1.8-fold higher in non-Whites and is highest among Korean Americans.[13] However, although the incidence of gastric adenocarcinoma localized to the distal stomach has declined, the incidence of proximal gastric and gastroesophageal junctional adenocarcinomas has been steadily increasing in the United States, a finding that perhaps reflects differences in pathogenic factors.

Typically, gastric cancer occurs between ages 50 and 70 years and is uncommon before age 30. The rates are higher in men than in women by 2:1. However, rates of the diffuse histologic form of gastric cancer are rising in younger women for reasons that are not understood. In the United States, gastric cancer is more common in Black men and women compared with White men and women.

Risk Factors

Risk factors for the development of gastric adenocarcinoma can be divided into environmental and genetic factors as well as precursor conditions (Table 178-2). For example, *Helicobacter pylori* infection is significantly more common in patients with noncardia gastric cancer than in matched control groups. Unlike distal gastric cancer emerging in the setting of intestinal metaplasia, where metaplasia is typically precipitated by *H. pylori*, adenocarcinomas near the gastroesophageal junction appear to be inversely associated with *H. pylori*. Epidemiologic studies of high-risk populations have also suggested that genotoxic agents such as *N*-nitroso compounds may play a role in gastric tumorigenesis. *N*-nitroso compounds can be formed in the human stomach by nitrosation of ingested nitrates, which are common constituents of the diet. High nitrate concentrations in soil and drinking water have been observed in areas with high death rates from gastric cancer. Atrophic gastritis (Chapter 125), with or without intestinal metaplasia, is observed in association with gastric cancer, especially in endemic areas. Pernicious anemia (Chapter 150) is associated with a several-fold increase in gastric cancer. Atrophic gastritis and intestinal metaplasia likely represent intermediary steps to gastric cancer. The achlorhydria associated with gastritis related to *H. pylori* infection, pernicious anemia, or other causes favors the growth of bacteria that are capable of converting nitrates to nitrites. At the same time, most patients with atrophic gastritis do not develop gastric cancer, a finding suggesting that neither atrophic gastritis nor achlorhydria alone is responsible.

Benign gastric ulcers do not appear to predispose patients to gastric cancer. However, patients who have a gastric remnant after subtotal gastrectomy for benign disorders have an increased relative risk for gastric cancer of 1.5 to 3.0 by 15 to 20 years after surgery.

PATHOBIOLOGY

Gastric adenocarcinomas can be divided into two types based on the Lauren classification[14]: intestinal and diffuse. The intestinal type (typically in the distal stomach with ulcerations and often preceded by premalignant lesions) is declining in incidence in the United States, but adenocarcinomas in the area of the cardia/gastroesophageal junction have increased. By contrast, the diffuse type involves widespread thickening of the stomach, especially in the cardia, and it often affects younger patients; this form may present as linitis plastica, which is a nondistensible stomach with the absence of folds and a narrowed lumen caused by infiltration of the stomach wall with tumor. Diffuse-type gastric cancers harbor mucin-producing cells. Other conditions that may result in linitis plastica include lymphoma (Chapter 171), tuberculosis (Chapter 299), syphilis (Chapter 295), and amyloidosis (Chapter 174).

Key histopathologic features of gastric cancer include the degree of differentiation, invasion through the gastric wall, lymph node involvement, and the presence or absence of signet ring cells within the tumor itself. Other pathologic manifestations include a polypoid mass, which may be difficult to distinguish from a benign polyp. Early gastric cancer, a condition that is common in Japan and has a relatively favorable prognosis, consists of superficial lesions with or without lymph node involvement. These lesions can be classified as group I, polypoid; group II, fungating ulcer with sharp raised margins; group III, ulcer with poorly defined infiltrative margins; and group IV, infiltrative, mostly intramural lesion, not well demarcated.

The leading hypothesis explaining the way in which *H. pylori* predisposes to gastric cancer risk is the induction of an inflammatory response, in which IL-1β may be pivotal. Chronic *H. pylori* infection also leads to chronic atrophic gastritis with resulting achlorhydria, which in turn favors bacterial growth that can convert dietary nitrates to nitrites. These nitrites, in combination with genetic factors, promote abnormal cellular proliferation, genetic mutations, and eventually cancer.

Genetics

Gastric cancer patients have a two- to three-fold higher family history of the disease, thereby suggesting a genetic contribution. Furthermore, germline or inherited mutations in the genes for E-cadherin and α-catenin, albeit rare, have been described in diffuse hereditary gastric cancer, which is seen in young patients. In addition, in Lynch syndrome (Chapter 179), patients have associated extracolonic cancers, including gastric cancer. Patients with familial adenomatous polyposis also have an increased risk of distal (antral) gastric adenocarcinoma. Blood group A is also associated with a higher incidence of gastric cancer, even in nonendemic areas.

Gene expression data have identified molecular subtypes linked to distinct patterns of molecular alterations that are associated with differences in disease progression and prognosis. Examples include Epstein-Barr virus–related tumors, tumors with microsatellite or chromosomal instability, and a diffuse histologic subtype that often has decreased genomic instability.[15] Gastric tumors with chromosomal instability bear striking similarity to esophageal adenocarcinomas. Both the activation of oncogenes and the inactivation of tumor suppressor genes can be promoted by processes including chromosomal instability, aberrant DNA methylation, and microsatellite instability. Loss of *p53* is common, especially in the chromosomal instability class of gastric cancers. The inactivation of *p53* in precancerous gastric lesions suggests that mutation of *p53* is an early event in gastric carcinogenesis.

CLINICAL MANIFESTATIONS

Symptoms and Signs

In its early stages, gastric cancer may be asymptomatic or produce only nonspecific symptoms that make early diagnosis difficult. Later symptoms include bloating, dysphagia, and epigastric pain. Early satiety or vomiting may suggest partial gastric outlet obstruction, although gastric dysmotility can contribute to the vomiting with nonobstructive tumors. Epigastric pain reminiscent of that associated with peptic ulcer occurs in about one fourth of patients, but the pain is not relieved by food or antacids in most patients with gastric cancer. Pain that radiates to the back may indicate that the tumor has penetrated the pancreas. When dysphagia is associated with gastric cancer, this symptom suggests a more proximal gastric tumor at the gastroesophageal junction or in the fundus.

Signs of gastric cancer include bleeding, which can result in iron deficiency anemia (Chapter 145) that produces weakness, fatigue, and malaise, as well as rare, more serious cardiovascular and cerebrovascular consequences. Perforation related to gastric cancer is unusual. Gastric cancer metastatic to the liver can lead to right upper quadrant pain, jaundice, and fever. Lung metastases can cause cough, hiccups, and hemoptysis. Peritoneal carcinomatosis can lead to malignant ascites unresponsive to diuretics. Gastric cancer can also metastasize to bone.

Physical Examination

In the earliest stages of gastric cancer, the physical examination may be unremarkable. At later stages, patients become cachectic, and an epigastric mass may be palpated. If the tumor has metastasized to the liver, hepatomegaly with jaundice and ascites may be present. Portal or splenic vein invasion and thrombosis can cause splenomegaly. Lymph node involvement in the left supraclavicular area is termed a Virchow node, and periumbilical nodal involvement is called a Sister Mary Joseph node. The fecal occult blood test may be positive. Metastasis to the ovary is termed Krukenberg tumor.

Paraneoplastic syndromes (Chapter 164) may precede or occur concurrently with gastric cancer. Examples include Trousseau syndrome (Chapter 67), which is recurrent migratory superficial thrombophlebitis indicative of a possible hypercoagulable state; acanthosis nigricans, which arises as raised and hyperpigmented skin lesions of the flexor areas, neck, axilla, groin, and mucosal membranes; neuromyopathy with involvement of the sensory and motor pathways; and central nervous system syndromes with altered mental status and ataxia.

Laboratory Studies

Laboratory studies may reveal iron deficiency anemia. Microangiopathic hemolytic anemia has also been reported. Abnormalities in liver tests generally indicate metastatic disease. Hypoalbuminemia is a marker of malnutrition. Protein-losing enteropathy is rare but can be seen in Ménétrier disease (Chapter 125), which is another predisposing condition. Serologic test results, such as CEA and CA72.4 (typically not used), may be abnormal. Although these tests are not recommended for initial diagnosis, they may be useful for monitoring disease after surgical resection.

DIAGNOSIS

The diagnostic accuracy of upper endoscopy with biopsy and cytologic examination approaches 95 to 99% for both types of gastric cancer. Cancer may arise as a small mucosal ulceration, a polyp, or a mass (Fig. 178-1). In some patients, gastric ulceration may first be noted in an upper gastrointestinal barium contrast study. A benign gastric ulcer is associated with a smooth, regular base, whereas a malignant ulcer is associated with a surrounding mass, irregular folds, and an irregular base. Although these and other radiographic characteristics historically helped to predict benign versus malignant disease, upper gastrointestinal endoscopy with biopsy and cytologic examination is mandatory whenever a gastric ulcer is found on a radiologic study, even if the ulcer has benign characteristics.

Endoscopic ultrasonography is very helpful in both the diagnosis and staging of gastric cancer. The extent of tumor, including gastric wall invasion and local lymph node involvement, can be assessed by endoscopic ultrasound (Fig. 178-2), which provides information complementary to that obtained from CT scans. Endoscopic ultrasound can help guide aspiration biopsies of lymph nodes to determine malignant involvement. CT of the chest, abdomen, and pelvis should be performed to document lymphadenopathy and extragastric organ (especially lung and liver) involvement. In some centers, staging of gastric cancer entails bone scans because of the proclivity of gastric cancer to metastasize to bone.

TREATMENT

Surgical Therapy

The primary chance for cure of gastric cancer is surgical resection, which is possible in 25 to 30% of cases.[16] If the tumor is confined to the distal stomach, subtotal gastrectomy is performed, with resection of lymph nodes in the porta hepatis and the pancreatic head. When early gastric cancer is confined to the mucosa, endoscopic mucosal resection may be an alternative. By contrast, tumors of the proximal stomach require total gastrectomy to obtain an adequate margin and to remove lymph nodes; distal pancreatectomy and splenectomy are usually also performed as part of this procedure, which carries higher mortality and morbidity rates. The addition of para-aorta nodal dissection does not improve survival. Even if a curative procedure is not possible because of metastasis, limited gastric resection may be necessary for patients with excessive bleeding or obstruction. However, gastrectomy followed by chemotherapy is no better than chemotherapy alone for advanced gastric cancer that is not surgically curable.[A13] If cancer recurs in the gastric remnant, limited resection may again be necessary for palliation. Most recurrences of either type of gastric cancer are in the local or regional area of the original tumor.

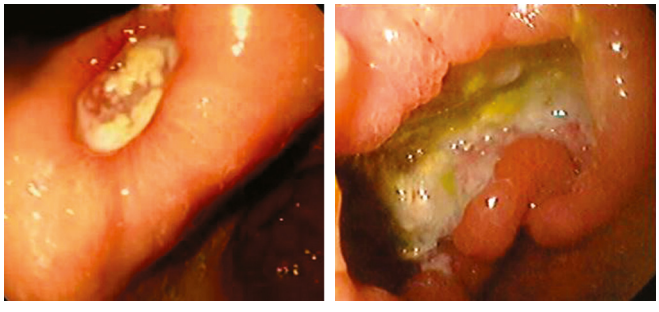

FIGURE 178-1. Benign (*left*) and malignant (*right*) gastric ulcer. Note the shaggy, thickened, and overhanging edges of the cancer. (Courtesy Pankaj Jay Pasricha, MD.)

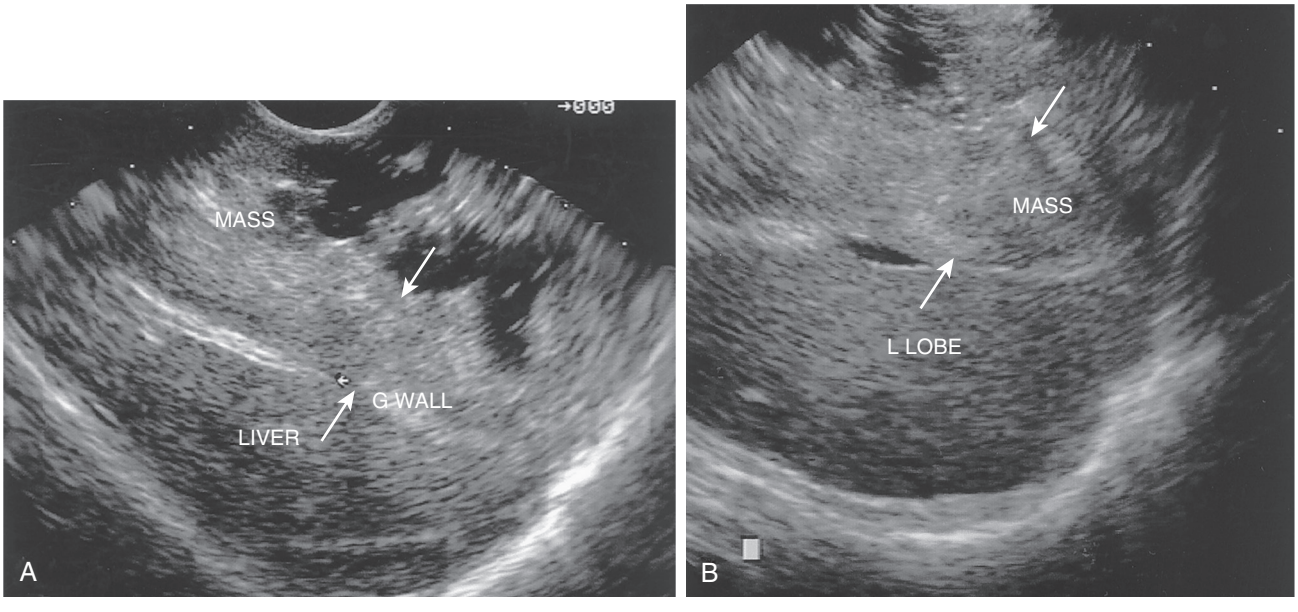

FIGURE 178-2. Gastric mass. Endoscopic ultrasonography depicting a large gastric mass that is compressing the liver and gallbladder wall (**A**) and, on a different view, the left lobe of the liver (**B**).

Medical Therapy

Gastric cancer is often responsive to chemotherapy.[17,18] Single-agent chemotherapy, which provides partial response rates of 20 to 30%, is reserved for patients with a poor performance status. Otherwise, combination chemotherapy increases overall survival compared with single-agent chemotherapy in metastatic disease as well as in the neoadjuvant and adjuvant treatment of nonmetastatic disease.[A14]

In patients who have gastric cancer and who undergo surgery with curative intent, the addition of perioperative chemotherapy can improve survival. For example, the combination of epirubicin, cisplatin, and fluorouracil, given both preoperatively and postoperatively, improves 5-year survival from 23 to 36% in patients with resectable gastroesophageal cancer. Perioperative therapy with a combination of fluorouracil, leucovorin, oxaliplatin, and docetaxel (Table 178-3) can extend median survival to 50 months and is increasingly used in medically fit patients.[A15] However, postoperative chemoradiotherapy does not improve overall survival compared with postoperative chemotherapy in patients whose resectable gastric cancers are treated with adequate preoperative chemotherapy and surgery.[A16]

For advanced or metastatic disease, combination regimens emphasize two-drug therapies, typically 5-fluorouracil or capecitabine with platinum. First-line therapy is now being increasingly supplemented with immune checkpoint inhibitors; their benefit is most notable in patients whose tumors express PD-L1,[A17] but patients whose tumors demonstrate microsatellite instability or are positive for Epstein–Barr virus may also be especially sensitive to PD-1 therapy.

Some gastric cancers have overexpression of the human epidermal growth factor receptor 2 (HER2, also called ERBB2). In patients with advanced gastric or gastroesophageal junction cancers showing overexpression of HER2, the addition of trastuzumab (a humanized monoclonal anti-HER2 antibody) to chemotherapy increases survival from 11.1 months to 13.8 months. The addition of the immune checkpoint inhibitor pembrolizumab is now approved in combination with trastuzumab and chemotherapy for first-line therapy in all ERBB2+ patients with metastatic disease.

Following resistance to first-line therapy, trastuzumab deruxtecan (which is an antibody-drug conjugate consisting of trastuzumab, a cleavable tetra-peptide-based linker, and a cytotoxic topoisomerase I inhibitor) can increase median survival by about 4 months and is now approved for second-line usage.[A18] The combination of ramucirumab (a VEGF receptor antagonist) plus paclitaxel can modestly increase median survival when compared with supportive care.

Empiric third-line chemotherapy in medically fit patients can include regimens utilized in other gastrointestinal cancers, such as irinotecan/5-fluorouracil. Radiation therapy alone is ineffective and is generally used only for palliative purposes in the setting of bleeding, obstruction, or pain.

Other Management

Critical in the management of the patient with gastric cancer is meticulous attention to nutrition (jejunal enteral feedings or total parenteral nutrition), correction of metabolic abnormalities that arise from vomiting or diarrhea, and treatment of infection from aspiration or spontaneous bacterial peritonitis. Patients with early gastric cancer who receive *H. pylori* eradication treatment have a reduced risk for metachronous gastric carcinoma.[A19] To maintain lumen patency, endoscopic laser treatment or prosthesis placement can be used in a palliative fashion.

TABLE 178-3 COMMON CHEMOTHERAPY REGIMENS FOR GASTRIC CANCER

NEOADJUVANT/PERIOPERATIVE THERAPY
For Medically Fit Patients: FLOT (5-fluorouracil, leucovorin, oxaliplatin, docetaxel) given as 4 preoperative and 4 postoperative 2-week cycles
METASTATIC CANCER FIRST LINE
5-fluorouracil and platinum chemotherapy backbone with immune checkpoint inhibitor (PD-1) for PD-L1+ (or can be used more broadly in PD-L1-); for ERBB2/HER2+ patients, add trastuzumab and pembrolizumab and consider addition of an anti-EGFR antibody

PREVENTION

In patients who have a family history of gastric cancer in a first-degree relative and who are infected with *H. pylori, H. pylori* eradication therapy reduces the risk of gastric cancer by about 75%.[A20] Such treatment also has reduced the incidence of gastric cancer by 40 to 50% in high-risk patients in Southern China[A21] and in patients who have precancerous lesions.[A22] Whether such treatment is equally effective in lower-risk populations is not known.[19]

PROGNOSIS

In aggregate, the overall 5-year survival rate of patients with gastric cancer is less than 10%. Approximately one third of patients who undergo a curative resection are alive after 5 years. In patients with early gastric cancer that is confined to the mucosa and submucosa, surgical resection can be curative and improves the 5-year survival rate to more than 50%.

Prognostic factors include anatomic location and nodal status. Distal gastric cancers without lymph node involvement have a better prognosis than proximal gastric cancers with or without lymph node involvement. Other prognostic factors include depth of penetration and tumor cell DNA aneuploidy. Linitis plastica and infiltrating lesions have a much worse prognosis than polypoid disease or exophytic masses.

LYMPHOMA OF THE STOMACH

EPIDEMIOLOGY

Gastric lymphoma represents about 5% of all malignant gastric tumors and is increasing in incidence. Most gastric lymphomas are non-Hodgkin lymphomas (Chapter 171), and the stomach is the most common extranodal site for non-Hodgkin lymphomas. Patients with gastric lymphoma are generally younger than patients with gastric adenocarcinoma, but the male predominance remains.

CLINICAL MANIFESTATIONS

Patients commonly present with symptoms and signs similar to those of gastric adenocarcinoma. Lymphoma in the stomach can be a primary tumor, or it can be secondary to disseminated lymphoma.

B-cell lymphomas (Chapter 171) of the stomach are most commonly large cell with a high-grade type. Low-grade variants in the setting of chronic gastritis and are termed mucosa-associated lymphoid tissue (MALT) lymphomas. MALT lesions are strongly associated with *H. pylori* infection.

DIAGNOSIS

Radiographically, primary gastric lymphomas usually arise as ulcers or exophytic masses; diffusely infiltrating lymphoma is more suggestive of secondary lymphoma. As a result, upper gastrointestinal contrast imaging usually shows multiple nodules and ulcers for a primary gastric lymphoma and typically has the appearance of linitis plastica (see earlier) with secondary lymphoma. As with gastric adenocarcinoma, however, upper endoscopy with biopsy and cytologic examination are required for diagnosis and have an accuracy of nearly 90%. Apart from conventional histopathologic analysis, immunoperoxidase staining for lymphocyte markers is helpful in diagnosis. As with gastric adenocarcinoma, proper staging of gastric lymphoma involves endoscopic ultrasound, chest and abdominal/pelvic CT scans, and bone marrow biopsy as needed.

TREATMENT

Treatment of gastric diffuse large B-cell lymphoma is best pursued with combination chemotherapy with or without radiation therapy (Chapter 171). For MALT lesions, eradication of *H. pylori* infection with antibiotics should be attempted[20] (Chapter 125), but patients with refractory lesions that are confined to the stomach can sometimes be cured with chemoradiotherapy (Chapter 171).

OTHER MALIGNANT TUMORS OF THE STOMACH

Leiomyosarcoma (Chapter 187), which constitutes approximately 1% of all gastric cancers, usually occurs as an intramural mass with central ulceration. Symptoms may include bleeding accompanied by a palpable mass. Leiomyosarcomas are often relatively indolent; surgical resection yields a 5-year survival rate of about 50%. Metastasis can occur to lymph nodes and the liver. Other gastric sarcomas include liposarcomas, fibrosarcomas, myosarcomas, and neurogenic sarcomas.

Most gastrointestinal stromal tumors (GISTs; Chapter 187) have been associated with activating mutations in the C-*kit* gene; a subset of such tumors is associated with mutations in the platelet-derived growth factor receptor (*PDGFR*) gene.[21] C-*kit* mutations are also found in chronic and acute myelogenous leukemia (Chapters 168 and 170), and approximately 50% of GISTs respond to imatinib mesylate (400 mg daily or 400 mg twice daily for *KIT* exon 9 mutant; Chapter 170), which is typically continued for at least 3 years.[A23] If imatinib is not successful, sunitinib increases survival. If both fail, regorafenib[A24] or ripretinib[A25] under expert supervision can prolong survival.[22] Pimitespib,

which is a heat shock protein 90 inhibitor, may be useful when tyrosine kinase inhibitors are no longer successful.[A26] Carcinoid tumors (Chapter 213) may begin in the stomach and are curable by removal if they have not yet spread to the liver.

Other primary tumors can spread to the stomach. In addition to lymphomas, primary lung (Chapter 177) and breast (Chapter 183) cancers as well as malignant melanoma (Chapter 188) can metastasize to the stomach.

LEIOMYOMAS AND BENIGN TUMORS

Leiomyomas (Chapter 187), which are smooth muscle tumors of benign origin, occur with equal frequency in men and women and are typically located in the middle and distal stomach. Leiomyomas can grow into the lumen, with secondary ulceration and consequent bleeding. Alternatively, they can expand to the serosa with extrinsic compression. Endoscopy may reveal a mass that has overlying mucosa or mucosa replaced by ulceration. On upper gastrointestinal imaging, leiomyomas are usually smooth with an intramural filling defect, with or without central ulceration. However, benign leiomyomas can be difficult to distinguish from their malignant counterparts radiographically or endoscopically, so tissue diagnosis is imperative. Symptomatic leiomyomas should be removed, but those without associated symptoms do not require therapy.

Other benign gastric tumors include lipomas, neurofibromas, lymphangiomas, ganglioneuromas, and hamartomas, the last associated with Peutz-Jeghers syndrome (Chapter 179) or juvenile polyposis (when restricted to the stomach).

ADENOMAS

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179 NEOPLASMS OF THE SMALL AND LARGE INTESTINE

EDWARD CHU

NEOPLASMS OF THE SMALL INTESTINE

EPIDEMIOLOGY

Small bowel malignancies are relatively rare and account for only approximately 3% of all cancers involving the gastrointestinal (GI) tract and less than 0.5% of all cancers in the United States. In 2022, an estimated 11,790 new cases of small bowel cancers will be diagnosed, and this disease accounts for nearly 1960 deaths annually.[1] The four major histologic subtypes, which make up over 90% of small bowel cancers, include carcinoid, adenocarcinoma, lymphoma, and gastrointestinal stromal tumors (GISTs). Over the past several decades, the incidence of small bowel tumors, and in particular carcinoid tumors, has increased significantly, in part because of improved diagnostic techniques.

For small bowel tumors, the mean age at diagnosis is 65 years. Sarcomas and lymphomas present at a slightly younger age, in the range of ages 60 to 62 years, whereas adenocarcinomas and carcinoid tumors present at a mean age of 68 years. These cancers are slightly more common in men compared with women and in Blacks compared with Whites.

PATHOBIOLOGY

Adenocarcinomas typically arise from adenomas, and the adenoma-carcinoma process is driven by specific genetic alterations.[2] Large-scale genomic analysis has identified distinct genomic differences between small bowel adenocarcinomas and colorectal cancers. *HER2* point mutations, microsatellite instability, and high tumor mutational load are more common in small bowel adenocarcinomas, and potentially targetable mutations in *PIK3CA* and *MEK1* also are seen. Small bowel adenocarcinomas comprise approximately 35 to 40% of all

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which is a heat shock protein 90 inhibitor, may be useful when tyrosine kinase inhibitors are no longer successful.[A26] Carcinoid tumors (Chapter 213) may begin in the stomach and are curable by removal if they have not yet spread to the liver.

Other primary tumors can spread to the stomach. In addition to lymphomas, primary lung (Chapter 177) and breast (Chapter 183) cancers as well as malignant melanoma (Chapter 188) can metastasize to the stomach.

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NEOPLASMS OF THE SMALL INTESTINE

EPIDEMIOLOGY

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For small bowel tumors, the mean age at diagnosis is 65 years. Sarcomas and lymphomas present at a slightly younger age, in the range of ages 60 to 62 years, whereas adenocarcinomas and carcinoid tumors present at a mean age of 68 years. These cancers are slightly more common in men compared with women and in Blacks compared with Whites.

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ABSTRACT

Neoplasms of the small intestine are relatively rare and only about 3% of primary gastrointestinal (GI) cancers arise in the small intestine. The most common small bowel cancers are adenocarcinomas, carcinoids, gastrointestinal stromal tumors (GIST), and GI lymphomas. Colorectal cancer is a major public health problem in the United States and globally. It is the third most common cancer in the United States and the second leading cause of cancer mortality. This chapter focuses on the key aspects and most updated developments relating to epidemiology, pathobiology, clinical manifestations, diagnosis, treatment, and prognosis for neoplasms of both the small and large intestine.

KEYWORDS

colon cancer
rectal cancer
small bowel
large bowel
risk factors
screening and early detection
systemic chemotherapy
biologic agents
immunotherapy

malignant small bowel tumors, and the duodenum is the most common site of presentation in the small bowel. The majority of these adenocarcinomas are moderately or well differentiated.

Small bowel carcinoids (Chapter 213) are derived from enterochromaffin cells in the crypts of Lieberkühn, and they account for up to 40 to 45% of cancers that arise in the small bowel. Carcinoids are typically well-differentiated cancers and, in contrast to adenocarcinomas, they tend to occur in the distal ileum. Up to 30% of cases are multifocal. Other less common small bowel neuroendocrine tumors include gastrinomas and somatostatinomas (Chapter 213). Small cell cancers occur rarely in the small bowel.

About 15% of small bowel cancers are malignant connective tissue tumors. GISTs, which are derived from the interstitial cells of Cajal, account for approximately 85% of the connective tissue tumors in the small bowel (Fig. 179-1). GISTs most commonly present in the duodenum, and they often resemble soft tissue sarcomas morphologically (Fig. 179-2). However, in contrast to classic sarcomas, GISTs express the c-Kit protein (CD117). Soft tissue sarcomas, such as leiomyosarcomas, present more commonly in the stomach and rarely in the small bowel (Chapter 187).

Primary GI lymphomas represent the most common location for extranodal lymphomas, and the second most common site in the GI tract is the small intestine. The non-Hodgkin histopathologic subtype is most commonly observed, and they account for nearly 10% of all small bowel cancers. The ileum is the most common region for these extranodal GI lymphomas, presumably because this region of the small intestine is rich in submucosal lymphoid follicles. These cancers may be low- or high-grade in nature. Although they are most commonly of B-cell origin (Chapter 171), they can also arise from precursor T lymphocytes.

The small intestine is also a site for metastatic spread of advanced solid cancers. Metastatic spread can occur via direct invasion, hematogenous spread, or extension of peritoneal metastases. For example, the small bowel is the most common GI site for metastatic malignant melanoma (Chapter 188). Ovarian (Chapter 184), breast (Chapter 183), lung (Chapter 177), and other GI cancers (Chapter 178) can also spread to the small bowel.

Benign tumors originating in the small bowel include adenomas, lipomas, and leiomyomas. Desmoids, hamartomas, and hemangiomas are other benign tumors but are relatively rare. These benign tumors usually present in the distal small bowel.

Predisposing Conditions

Age is an important risk factor for small bowel cancers as it is for colorectal cancer. These cancers occur in the older age population, with a mean age of 66 years. Chronic mucosal inflammatory conditions are linked to the development of small bowel adenocarcinomas and lymphoma. Inflammatory bowel disease (Chapter 127), in particular Crohn disease, is associated with an increased risk of adenocarcinoma within the involved region of the small intestine, and the risk of small bowel adenocarcinoma increases with extent and duration of small bowel involvement. Patients with chronic immunodeficiency states and autoimmune disorders, such as celiac disease (Chapter 126), are at increased risk for developing small bowel adenocarcinomas and small bowel lymphoma.

A number of dietary factors, including red meat, salt-cured and smoked food, refined sugar, and alcohol, are associated with an increased risk of small bowel adenocarcinomas. Although tobacco exposure and obesity may increase the risk of small bowel cancers, the data on the potential role of these two factors are conflicting.

Several familial polyposis syndromes are associated with small bowel neoplasms. Familial adenomatous polyposis syndrome is associated with a 100% risk of developing colorectal cancer, and patients with this familial colorectal cancer syndrome have a 4 to 12% lifetime risk of developing cancers in the duodenum or periampullary region. The risk of cancer is related to the number of polyps and to their size, histologic type, and degree of dysplasia. Hereditary nonpolyposis colon cancer is associated with an 80% lifetime risk of colorectal cancer and a 1 to 4% lifetime risk of small bowel cancer, which represents a 100-fold increased risk when compared with the general population. Hereditary nonpolyposis colorectal cancer–associated small bowel cancers tend to present 10 to 20 years earlier than the usual age of onset for small bowel cancer. Peutz-Jeghers syndrome is associated with a 57% lifetime risk of GI cancers, with colorectal cancer the most common tumor followed by small bowel adenocarcinoma.

CLINICAL MANIFESTATIONS

Small bowel malignant tumors are usually associated with symptoms, whereas benign tumors are asymptomatic in up to 50% of patients. The most common symptom is abdominal pain. Other symptoms include weight loss, nausea and vomiting, reduced appetite, fatigue, GI bleeding, and symptoms related to GI obstruction. Duodenal primary tumors, and especially tumors in the periampullary region, can be associated with obstructive jaundice.

Small bowel carcinoid tumors are usually asymptomatic. With advanced disease and especially in the presence of hepatic metastasis, they secrete bioactive amines that can lead to symptoms typically associated with the carcinoid syndrome: flushing, wheezing, diarrhea, and right-sided heart failure (related to valvular fibrosis) (Chapter 213). Systemic symptoms are more frequent with tumors that originate in the jejunum or ileum.

Patients with lymphoma may present with evidence of lymphadenopathy, hepatomegaly, and intestinal obstruction (e.g., abdominal distention and hyperperistalsis). GI lymphomas also may present with constitutional symptoms, such as fever, night sweats, and weight loss. Benign tumors usually are incidental findings, although larger tumors may eventually cause obstruction or bleeding.

DIAGNOSIS

The diagnosis of small bowel cancer is often delayed due to its rare and nonspecific presentation. The mean duration of symptoms prior to making a definitive diagnosis of small bowel cancer ranges from 8 to 10 months. In patients with small bowel tumors, the physical examination is typically unremarkable, although some patients develop a palpable mass, distended abdomen, or ascites. Patients with a primary duodenal tumor may present with scleral icterus and jaundice resulting from biliary obstruction.

The common laboratory findings may include iron deficiency anemia (Chapter 145) or elevations in hepatic enzymes (aspartate aminotransferase [AST], alanine aminotransferase [ALT], alkaline phosphatase). The serum bilirubin level can be elevated in patients who have liver metastases or biliary obstruction. In small bowel adenocarcinoma, serum levels of the carcinoembryonic antigen (CEA) may be elevated, especially in advanced cases, but this

FIGURE 179-1. Small bowel gastrointestinal stromal tumor with ulceration.

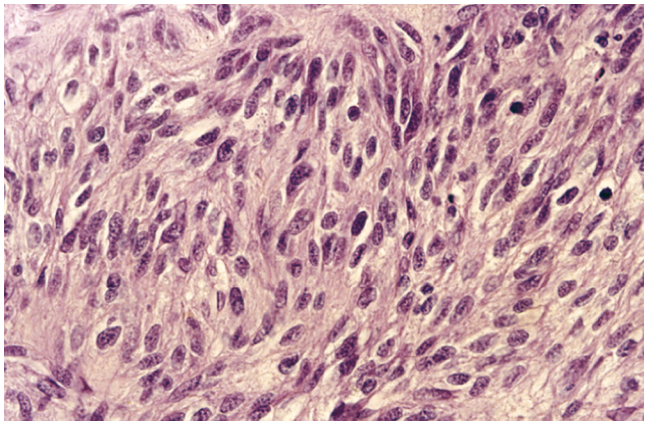

FIGURE 179-2. Histopathology of gastrointestinal stromal tumor (GIST).

marker is neither sensitive nor specific for routine diagnosis because several tumor types may present with elevated levels. In patients with neuroendocrine tumors, elevated levels of serotonin, chromogranin A, tumor-specific bioactive amines (e.g., gastrin), or urinary 5-hydroxyindoleacetic acid (5-HIAA) are commonly observed.

Imaging is required to diagnose and stage small bowel tumors, but no imaging modality is optimal.[3] Standard imaging techniques include upper GI series with small bowel follow-through, enteroclysis, transabdominal ultrasound, computed tomography (CT) scan, or magnetic resonance imaging (MRI). Enteroclysis is a double-contrast imaging study that is superior to an upper GI series with small bowel follow-through, and it has greater sensitivity to detect malignant small bowel tumors. A major limitation of enteroclysis is the inability to detect flat lesions. CT scanning of the abdomen is the most common imaging modality used in daily clinical practice, and this imaging modality is good for diagnosing primary tumors as well as metastatic disease. MRI appears to be superior to CT, especially as it relates to the detection of liver metastases as well as characterizing soft tissue sarcomas.

Carcinoids and primary neuroendocrine tumors are best imaged with nuclear medicine scans with indium-111 octreotide and/or meta-iodobenzylguanidine (MIBG). Over 90% of carcinoid tumors express somatostatin receptors, and the octreotide scan using the indium-111 tracer has high sensitivity (80 to 100%). A wide variety of small bowel cancers, including adenocarcinomas, lymphomas, and GISTs, may display uptake on positron emission tomograph (PET) scanning. However, PET is not useful for diagnosing carcinoid tumors because they are not typically FDG-avid.

Video capsule endoscopy (Chapter 120) uses a wireless endoscopic device to visualize the entire small bowel. The primary indication for video capsule endoscopy is to evaluate GI bleeding of an unknown source. In about 2 to 3% of patients who undergo capsule endoscopy for GI bleeding, a tumor is found. Capsule endoscopy can also assess the small intestine in patients who have familial adenomatous polyposis and Peutz-Jeghers syndrome, but its clinical utility as a routine screening test in such patients is unknown.

Deep enteroscopy techniques (Chapter 120) facilitate the intubation of the small bowel using long endoscopes. The small bowel may be examined antegrade (from the mouth) or retrograde (from the colon), thereby permitting direct examination of most of the small bowel. These methods are more invasive than capsule endoscopy but have the potential advantages for tissue biopsy, immediate polypectomy, and direct control of bleeding.

Staging

Staging for small bowel tumors varies by histology. Adenocarcinomas, GISTs, and neuroendocrine cancers are typically staged using specific classifications within the American Joint Committee on Cancer's (AJCC) TNM system. In contrast, non-Hodgkin lymphomas (Chapter 171) are staged in accordance with a modified Ann Arbor system originally used for the staging of Hodgkin disease (Chapter 172).

TREATMENT

Surgery

Surgical removal is the treatment of choice for localized small bowel tumors, with the extent of the surgical resection dependent on the tumor's histology and location. For adenocarcinomas in the first two portions of the duodenum, extensive pancreaticoduodenectomy is usually required, whereas small bowel carcinomas of the distal small intestine may require segmental or wide local resection of the tumor and the regional lymph nodes. En bloc resection is recommended for low-grade endocrine tumors, including regional lymph nodes. In contrast, GISTs do not require lymphadenectomy, unless the lymph nodes are grossly abnormal at the time of surgery. Surgery is not usually a primary treatment approach for lymphomas but can be considered for low-stage lymphomas. Surgery may also be required to treat complications such as bowel obstruction or perforation. Benign small bowel tumors, such as incidental lipomas, may simply be observed. Small adenomas can be removed by endoscopic polypectomy, but periampullary villous adenomas may require pancreaticoduodenectomy (Video 179-1).

Adjuvant Therapy

The role of adjuvant therapy depends on the specific type of small bowel cancer. Small bowel adenocarcinomas are generally treated similarly to colorectal cancer, with 6 months of fluoropyrimidine-based systemic chemotherapy under expert guidance for patients with lymph node involvement. Completely resected, moderately differentiated neuroendocrine cancers do not require adjuvant therapy.

For high-risk GISTs, postoperative imatinib reduces recurrence, and 3 years of treatment improves survival compared with 1 year of treatment, especially in patients with certain *Kit* exon 11 deletions as well as deletions that involve exon 11 codons 557 or 558. Emerging clinical data suggest that 5 years of adjuvant imatinib therapy may confer additional clinical benefit to patients with high-risk GISTs.[4] For other soft tissue sarcomas, adjuvant therapy has no definitive role following surgical resection. Postoperative systemic chemotherapy is recommended for both low- and high-grade lymphomas (Chapter 171).

Metastatic Disease

Metastatic small bowel carcinomas are generally treated with systemic chemotherapy regimens known to be effective against colorectal cancer, but no treatment regimen is standard.[5,6] For patients with metastatic GISTs, imatinib therapy yields median survival rates of nearly 4 years, with an estimated 10-year survival rate of about 20%.[A1] When resistance to imatinib develops, sunitinib and/or regorafenib are effective second-line treatments under expert guidance. For metastatic carcinoids that are surgically unresectable, somatostatin analogues, such as octreotide and lanreotide, are the main treatment options (Chapter 213), but agents such as 5-fluorouracil, streptozocin, and doxorubicin have been used with modest clinical activity (see Table 164-2).

PREVENTION

In patients with any of the various familial colon cancer syndromes (including familial adenomatous polyposis, hereditary nonpolyposis colorectal cancer, and Peutz-Jeghers syndrome), regular surveillance of the small intestine is required. Patients with familial adenomatous polyposis also should undergo regular screening esophagogastroduodenoscopy as part of their initial diagnostic evaluation and again at intervals of 1 to 5 years, depending on the presence and degree of duodenal polyposis. Patients with hereditary nonpolyposis colorectal cancer are also at increased risk for small bowel carcinomas, which may, in fact, be the first manifestation of their disease. Hereditary nonpolyposis colorectal cancer–associated small bowel cancer typically presents at a younger age (median, 39 years), and the duodenum is the most common site of disease (about 50% of cases). Screening should be started at age 30 years. Patients with sporadic small intestine adenomas and patients with carcinoid tumors should undergo colonoscopy given their higher risk of colonic neoplasia. Currently, no specific guidelines are available for the routine surveillance of patients with resected small bowel carcinomas.

PROGNOSIS

The overall prognosis for small bowel cancers depends on the specific pathologic subtype. For small bowel carcinomas, the 5-year survival is 50 to 85% for stage I to III patients but only 5% for stage IV. Tumor site is an important determinant of prognosis, with survival rates being worse for primary duodenal tumors compared with ileal or jejunal primary tumors. Other factors associated with poor prognosis include poor differentiation, lymph node involvement, distant metastases, and lymphovascular invasion. The tumor mutational burden and SMAD4 mutations may potentially be useful biomarkers for predicting the prognosis in small bowel cancers.[7]

Carcinoids (Chapter 213) are typically indolent, and 5-year survival rates range between 50 and 95% depending on the stage of disease. The prognosis of small intestine GISTs depends on the primary site (distal tumors have a worse prognosis), size, and mitotic activity, as well as the adequacy of surgical resection. However, 5-year survival rates approach 80% with imatinib therapy, even when complete surgical resection is not possible. For small intestinal lymphomas, the 5-year survival rate is over 60% but varies by histologic subtype.

NEOPLASMS OF THE LARGE INTESTINE

EPIDEMIOLOGY

In the United States, colorectal cancer is the third most common cancer, with an annual incidence of approximately 150,000. It is also the second-leading cause of cancer death, with approximately 53,000 deaths each year. Worldwide, an estimated 1.2 million new cases of colorectal cancer are diagnosed each year, and about 600,000 patients die from it. In the average individual, the lifetime risk of developing colorectal cancer is high, about 1 in 20.

About 75% of large bowel cancers arise in the proximal colon. Colorectal cancer is more common in the elderly, with a median age of approximately 73 years, but about 10% of cases are in patients younger than age 50 years. The overall incidence and mortality of colorectal cancer have declined significantly over the past 2 decades, especially for patients older than 50 years

of age. However, this decline has not occurred equally in all populations and varies according to age. For example, the incidence of colorectal cancer in adults younger than age 50 years has increased by more than 20% since 2000, and this rise has been driven by tumors in the distal colon and rectum.[8] The incidence in individuals between ages 20 and 49 years has also been increasing, with the largest increase, approaching 90%, in Hispanics ages 20 to 29 years.[9] The overall incidence of left-sided or distal colon cancer has decreased, likely because of effective distal large bowel screening, but the incidence of right-sided or proximal colon cancer has been steadily increasing in the United States.

Colorectal cancer is slightly more common in men than in women, and men, on average, develop the disease 5 to 10 years younger than women. The mortality associated with colorectal cancer is also 25% higher in men. Of all the ethnic groups in the United States, Blacks have the highest rates of colorectal cancer, and they are diagnosed an average of 5 to 10 years earlier than White patients, with an especially increased frequency under age 50 years. The mortality associated with this disease is 20% higher in Blacks than in Whites.

Risk Factors

Sporadic colorectal cancer accounts for 80 to 85% of cases, and the main risk factors include older age, male sex, African ancestry, family history, inflammatory bowel disease, obesity, diabetes mellitus and insulin resistance, tobacco use, and alcohol use. The consumption of red meat or processed foods and reduced intake of fiber, green leafy vegetables, and fruits also contributes to the risk of colorectal cancer. The presence of certain intestinal microbiota, including bacteria (*Streptococcus bovis*, *Fusobacterium*, and various *E. coli* strains) and viruses (human papillomavirus), may be risk factors. Factors associated with a reduced risk of colorectal cancer include greater physical activity and exercise; higher dietary intake of fiber, fruit, and vegetables; regular use of aspirin and nonsteroidal anti-inflammatory agents; and supplementation with folic acid, calcium, and vitamin D.

Age is the strongest risk factor for sporadic colorectal cancer, with risk increasing substantially starting at age 50 years. Nevertheless, 10 to 12% of colorectal cancers are diagnosed before age 50 years.[10] Family history is important, even in the absence of defined familial colon cancer syndromes. If a first-degree relative has colorectal cancer, a person's risk for developing colorectal cancer is two- to three-fold higher, with the risk rising to five- to six-fold when two first-degree relatives have colorectal cancer. Even if a first-degree relative has an adenoma, the risk of colorectal cancer is increased two-fold. Patients with a history of ulcerative colitis or Crohn disease (Chapter 127) have a 60% higher risk of colorectal cancer[11] compared with the general population, and the risk is related to the extent and duration of large bowel involvement.

PATHOBIOLOGY

Adenocarcinomas comprise more than 90% of colorectal cancers. Other relatively rare histologic subtypes include neuroendocrine cancers, epidermoid carcinomas, hamartomas, lymphomas, and sarcomas (including GISTs). Composite tumors are also observed, most commonly adenocarcinomas with neuroendocrine features.

Adenocarcinomas

Colorectal adenocarcinomas arise from the columnar glandular epithelium of the mucosa. Mucinous cancers make up the large majority of colorectal cancer, whereas only about 20% do not produce mucin. Mucinous cancers tend to develop in the right side of the colon. The medullary carcinoma subtype is characterized by large, eosinophilic cells and has a heavy infiltration of tumor-infiltrating lymphocytes. These tumors exhibit a high degree of microsatellite instability because they are deficient in one or more of the mismatch repair proteins. Medullary carcinomas arise more commonly on the right side of the colon, are seen in older women, and are less likely to spread to lymph nodes. Signet ring cancer is characterized by large numbers of single tumor cells with nuclear displacement by intracytoplasmic mucin.

Carcinogenesis for colorectal adenocarcinomas is caused by a multistep process when multiple genetic alterations occur over time (Fig. 179-3) in one or more of three pathways: chromosomal instability, microsatellite instability, and CpG island methylator phenotype. The chromosomal instability pathway, which accounts for up to 70% of cases of sporadic colorectal cancer, is most commonly related to mutations in the *APC* (tumor suppressor gene) and in the *KRAS* gene (proto-oncogene that regulates transduction of mitogenic signals across cell membranes). In familial adenomatous polyposis, germline mutations in *APC* are the result of chromosomal instability that leads to aneuploidy (imbalance in chromosome number), genomic amplifications, and loss of heterozygosity (cells have only one gene allele because of the loss of individual chromosomes during mitosis). Several other gene mutations lead to colorectal cancer, including the colon cancer (*MCC*) gene (a tumor suppressor gene), p53 (a key regulator of the cell cycle), *VEGF*, *MYC*, *MET*, *LYN*, and *PTEN*. Many of the mutational events have downstream effects on the Wnt signaling pathway.

The microsatellite instability pathway is a result of defects in DNA mismatch repair. Microsatellites are short repeating nucleotide sequences that are prone to errors because of their repetitive nature. Microsatellite instability–high tumors are caused by defects in the function of mismatch repair genes, especially *MLH1*, *MSH2*, *MSH6*, and *PMS2*. Germline mutations in these genes cause HNPCC (Lynch syndrome), but silencing of *MLH1* by hypermethylation is the most common molecular mechanism underlying mismatch repair defects in sporadic colorectal cancer. Microsatellite instability–high tumors are more

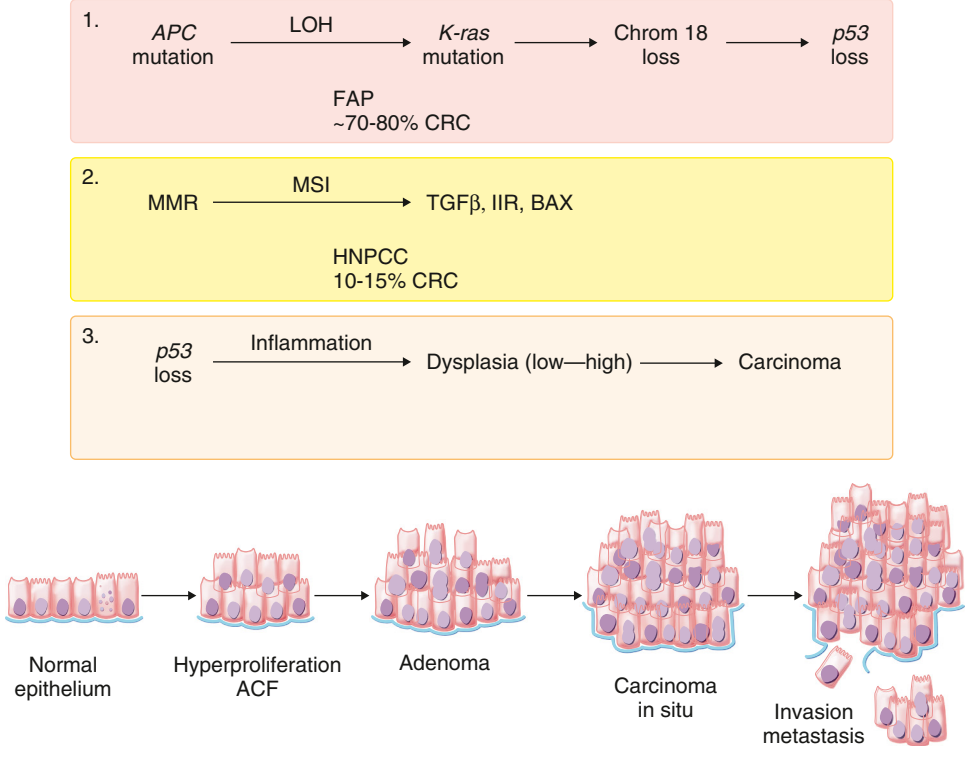

FIGURE 179-3. The molecular basis of colorectal cancer. Sequence-specific genetic alterations result in the transition from normal large bowel epithelium to invasive cancer. *Panel 1* demonstrates chromosomal instability, *Panel 2* illustrates microsatellite instability, and *Panel 3* shows the CpG island methylator phenotype. ACF = aberrant crypt foci; *APC* = adenomatous polyposis coli; BAX = apoptosis-related proteins; CRC = colorectal cancer; FAP = familial adenomatous polyposis; HNPCC = hereditary nonpolyposis colorectal cancer; IIR = type II receptor; LOH = loss of heterozygosity; MMR = mutation mismatch repair; MSI = microsatellite instability; TGF-β = transforming growth factor-β.

common in women and in the right colon, and they are often poorly differentiated and associated with a lymphocytic infiltration.

In the CpG island methylator phenotype pathway, hypermethylation of DNA promoter regions silences tumor suppressor genes, thereby leading to carcinogenesis. In colorectal cancer, hypermethylated genes include *APC*, *MCC*, *MLH1*, and *MGMT*. CpG island methylator phenotype-high tumors often have *BRAF* mutations, are poorly differentiated, have mucinous or signet ring morphology, and are microsatellite instability high. The precursor is likely to be a sessile serrated adenoma.

Neuroendocrine Cancers

Neuroendocrine cancers include carcinoid tumors (Chapter 213) and small cell carcinomas. Carcinoid tumors are the second most common colorectal neoplasms after adenocarcinomas, and are more common in non-Whites. In the distal bowel, carcinoids rarely are hormonally inactive.

Epidermoid Carcinomas

Epidermoid carcinomas are usually of the squamous cell subtype. They tend to be more common in women and Hispanic patients. More than 90% of epidermoid carcinomas are located in the rectum, and they tend to be moderately or poorly differentiated.

Lymphomas

Primary large intestinal lymphomas (Chapter 171) make up about 10 to 20% of all GI lymphomas but less than 1% of all colorectal cancers. The cecum is the most common site, and they are more common in males and in the elderly. The large majority of these large bowel lymphomas are of B-cell origin.

Sarcomas

Large bowel sarcomas are relatively rare, and a majority are leiomyosarcomas (Chapter 187). These tumors commonly present in the rectum, where they are usually localized at the time of diagnosis, regardless of their grade. GISTs and Kaposi sarcomas (Chapter 359) occur in the large bowel.

POLYPS OF THE COLON

A polyp is a grossly visible epithelial-cell mass that protrudes out from the intestinal mucosal surface into its lumen. A polyp may be flat, sessile, or pedunculated (attached by a stalk). Polyps can be non-neoplastic or neoplastic (adenomatous). Polyps usually are asymptomatic but can occasionally cause bleeding, prolapse, or obstruction. Non-neoplastic polyps are not premalignant, but neoplastic polyps can become a true cancer.

FAMILIAL COLORECTAL CANCER SYNDROMES

Several well-defined familial syndromes are associated with an increased risk for colorectal cancer. These syndromes include hereditary nonpolyposis colorectal cancer (HNPCC), Muir-Tore syndrome, familial adenomatous polyposis, Gardner syndrome, Turcot syndrome, *MUTYH*-associated polyposis, Peutz-Jeghers syndrome, and juvenile polyposis (Table 179-1).

Hereditary Nonpolyposis Colorectal Cancer

Hereditary nonpolyposis colorectal cancer (HNPCC), also known as Lynch syndrome, is the most common hereditary colorectal cancer syndrome and accounts for approximately 2% of all cases of colorectal cancers. The cause is a highly penetrant, autosomal dominant, loss-of-function germline mutation in genes (*MLH1, MSH2, MSH6*, and *PMS2*) that repair DNA base pair mismatches occurring during DNA replication.[12]

CLINICAL MANIFESTATIONS AND DIAGNOSIS

Although patients may have several adenomas, the diffuse polyposis characteristic of familial adenomatous polyposis is not typically observed. Synchronous and metachronous tumors are common. Colon cancers associated with HNPCC have a right-sided predominance (before the splenic flexure). These cancers are often poorly differentiated but generally have a better prognosis than typical sporadic colorectal cancers. Patients with HNPCC also have a higher risk for other solid tumors, especially endometrial cancer, as well as cancers of the ovary (Chapter 184), stomach (Chapter 178), small bowel, pancreas (Chapter 180), hepatobiliary tract (Chapter 181), and ureter (Chapter 182).

The median age for diagnosis of HNPCC is the mid-40s, which is 25 to 30 years younger than the age of presentation for sporadic colorectal cancer. Testing of patients for HNPCC includes testing the tumor for microsatellite instability and staining for the protein products of mismatch repair genes (*MLH1*, *MSH2*, *MSH6*, and *PSM2*).[13] A positive screen does not definitively diagnose HNPCC, because up to 15% of sporadic colorectal cancers may have these features. Germline testing of peripheral blood is generally preferred, but saliva or a buccal swab also can be tested to confirm the presence of mutations in one of the mismatch repair genes and to make the definitive diagnosis of HNPCC.

The Amsterdam criteria define HNPCC: (1) an HNPCC-associated cancer (colorectal cancer or cancers of the stomach, small bowel, renal pelvis, ureter, or endometrium) has been diagnosed in three or more relatives, one of whom is a first-degree relative of the other two, in the absence of familial adenomatous polyposis; (2) colorectal cancer has developed in at least two successive generations; and (3) one or more family members was diagnosed before age 50 years, with one being a first-degree relative of the other two. The revised Bethesda criteria define HNPCC when: (1) colorectal cancer is diagnosed in a patient younger than 50 years of age; (2) synchronous or metachronous colorectal cancer or other Lynch syndrome–associated tumors are diagnosed, regardless of age; (3) colorectal cancer has a high degree of microsatellite instability in a patient younger than 60 years of age; (4) colorectal cancer is diagnosed in one or more first-degree relatives with a Lynch syndrome cancer, with one of the cancers diagnosed at younger than 50 years of age; (5) colorectal cancer is diagnosed in two or more first-degree or second-degree relatives with a Lynch syndrome cancer, regardless of age.

Muir-Torre Syndrome

The Muir-Torre syndrome is a rare autosomal dominant syndrome that is an HNPCC subtype. Muir-Torre syndrome also arises from mutations in DNA mismatch repair genes (*hMLH1, hMSH2*, and *MSH6*), and patients present with colorectal cancer, genitourinary tract cancers, and skin lesions, including keratoacanthomas and sebaceous tumors.

TABLE 179-1 GENERAL FEATURES OF INHERITED COLORECTAL CANCER SYNDROMES

SYNDROME	POLYP HISTOLOGY	POLYP DISTRIBUTION	AGE OF ONSET	RISK OF COLON CANCER	GENETIC LESION	CLINICAL MANIFESTATIONS	ASSOCIATED LESIONS
Familial adenomatous polyposis	Adenoma	Large intestine, duodenum	16 yr (range, 8-34 yr)	100%	5q (*APC* gene)	Rectal bleeding, abdominal pain, bowel obstruction	Desmoids, CHRPE
Peutz-Jeghers syndrome	Hamartoma	Large and small intestine	First decade	Slightly above average	19p (*STK11*)	Possible rectal bleeding, abdominal pain, intussusception	Orocutaneous melanin pigment spots, other tumors
MUTYH-associated polyposis	Adenoma	Large intestine, duodenum	45-50 yr (range, 13-60 yr)	75% (range, 50-100%)	1p (*MUTYH* gene)	Rectal bleeding, abdominal pain, bowel obstruction	CHRPE, osteomas
Juvenile polyposis	Hamartoma (rarely adenoma)	Large and small intestine	First decade	≈9%	*PTEN*, *SMAD4*, *BMPR1*	Possible rectal bleeding, abdominal pain, intussusception	Pulmonary AVMs
Hereditary nonpolyposis colon cancer	Adenoma	Large intestine	40 yr (range, 18-65 yr)	30%	Mismatch repair genes*	Rectal bleeding, abdominal pain, bowel obstruction	Other tumors (e.g., ovary, uterus, pancreas, stomach)

*Including hMSH2, hMSH3, hMSH6, hMLH1, hPMS1, and hPMS2.
AVM = arteriovenous malformation; CHRPE = congenital hypertrophy of the retinal pigment epithelium.

Familial Adenomatous Polyposis

Familial adenomatous polyposis is an autosomal dominant condition with incomplete penetrance and is the result of a mutation in the adenomatous polyposis coli *(APC)* gene.[14] Patients have hundreds to thousands of adenomatous polyps (Fig. 179-4) that occur relatively evenly throughout the colon and that usually appear by early in the second decade of life. GI symptoms usually develop in the third or fourth decade, and nearly every untreated patient develops colorectal cancer by age 40 years. Small bowel adenomas, usually in the duodenum, are seen in 45 to 90% of cases, and periampullary duodenal cancer develops in about 10% of patients. Patients with an attenuated form of familial adenomatous polyposis have fewer than 100 colonic adenomas with a right colon predominance and develop colorectal cancer about 10 years later.

Gardner Syndrome

Gardner syndrome is a subtype of familial adenomatous polyposis and is also the result of mutations in the *APC* gene. It is characterized by extra-intestinal clinical features, including soft tissue tumors (e.g., lipomas, sebaceous cysts, and fibrosarcomas), supernumerary teeth, desmoid tumors, osteomas (particularly mandibular), mesenteric fibromatosis, and congenital hypertrophy of the retinal pigment epithelium. Gardner syndrome and familial adenomatous polyposis differ because of variations in the location of the *APC* mutation, modifying genes, and environmental factors. However, the adenomatous polyps in Gardner syndrome and in familial adenomatous polyposis have similar malignant potential, so screening and treatment recommendations also are similar.

Turcot Syndrome

Turcot syndrome is the combination of colorectal polyposis, colorectal cancer, and central nervous system malignancy. *APC* gene mutations cause two-thirds of cases, whereas the other one-third result from the same DNA mismatch repair gene mutations that are seen in HNPCC. The central nervous system malignancies include medulloblastomas, glioblastomas, and ependymomas.

MUTYH-Associated Polyposis

MUTYH-associated polyposis is an autosomal recessive syndrome caused by mutations in the *MUTYH* gene (also called MYH [mutY homologue]). Underlying defects in base excision repair as well as acquired mutations in the *APC* gene and other genes (e.g., *KRAS*) lead to colonic polyposis and an increased risk of developing colorectal cancer. About 0.4 to 0.7% of patients who develop colorectal cancer have a homozygous *MUTYH* mutation. The phenotype is similar to attenuated familial adenomatous polyposis. Patients have up to hundreds of adenomas throughout the colon and may also have multiple hyperplastic polyps as well as serrated adenomas. Compared with familial adenomatous polyposis, the colorectal cancers of *MUTYH*-associated polyposis are more likely to be right-sided, with an average age of onset at 45 to 50 years. Extra-colonic features include gastroduodenal polyps, duodenal carcinoma, breast cancer, ovarian cancer, bladder cancer, skin cancer, osteomas, and congenital hypertrophy of the retinal pigment epithelium.

Peutz-Jeghers Syndrome

Peutz-Jeghers syndrome is a rare but highly penetrant autosomal dominant syndrome caused by a mutation in the serine-threonine kinase *(STK11)* gene located on chromosome 19p. Nearly all patients have characteristic melanin spots on their lips, buccal mucosa, and skin. The average age at diagnosis is the third decade. The syndrome is characterized by benign hamartomatous polyps predominantly in the small intestine, stomach, and colon, occasionally accompanied by adenomatous and hyperplastic polyps. The most common symptoms are small bowel intussusception, obstruction, and GI bleeding. Nearly 50% of patients develop a malignancy by age 65 years, most commonly in the small intestine, stomach, colon, pancreas, testes, breast, ovary, cervix, or uterus. Because genetic testing is not widely available, first-degree relatives should be screened annually from birth, looking especially for melanotic spots, precocious puberty, and testicular tumors.

FIGURE 179-4. Resected colon of a patient with familial adenomatous polyposis.

Juvenile Polyposis

Familial juvenile (non-neoplastic, hamartomatous) polyposis is a rare (<1 in 100,000 births) syndrome in which patients develop 10 or more hamartomatous, non-neoplastic polyps (histologically distinct from those seen in Peutz-Jeghers syndrome) throughout their GI tract. This syndrome results from a highly penetrant autosomal dominant mutation in the *SMAD4*, *PTEN*, or *BMPR1A* gene. Symptoms and signs include abdominal pain, rectal bleeding, intestinal obstruction, and anemia by early adolescence. Pulmonary arteriovenous malformations are also seen. The risk of malignancy can be as high as 20%, with a median age of 37 years.[15]

NON-NEOPLASTIC POLYPS

About 50% of all large bowel polyps in average-risk individuals older than age 50 years are non-neoplastic (nonadenomatous) polyps. Nonadenomatous polyps can be hyperplastic, inflammatory, lymphoid, or juvenile. Hyperplastic polyps usually are caused by abnormal maturation of the mucosal epithelial cells. Hyperplastic polyps usually are small and seen mostly in the distal sigmoid colon and rectum. Hyperplastic polyps are not premalignant.

Patients with inflammatory bowel disease (Chapter 127) often have inflammatory pseudopolyps that are distinguished from neoplastic polyps only by biopsy. Lymphoid polyps contain exaggerated intramucosal lymphoid tissue. Juvenile polyps are focal hamartomatous malformations that are caused by abnormal development of the lamina propria and that are usually seen in the rectum of young children.

SERRATED POLYPS

Sessile serrated adenomas are neoplastic lesions with a right colon predominance and a high malignant potential.[16] Serrated polyps present with a disorganized and distorted crypt growth pattern. Because they are sessile or flat, they can be difficult to visualize on endoscopy. Their pathogenesis is via hypermethylation of CpG islands ("CIMP-high") and the *MLH1* mismatch repair gene, in the presence of *BRAF* mutations. As a result, serrated polyps exhibit a high degree of microsatellite instability.

Traditional serrated adenomas are rare and histologically distinct from sessile serrated adenomas. They commonly exhibit high-grade dysplasia and oftentimes carcinoma in situ.

ADENOMATOUS POLYPS

Adenomatous chronic polyps (adenomas) are benign glandular tumors with malignant potential. On pathologic examination, they can have evidence for low- or high-grade dysplasia. Adenomatous polyps have an anatomic distribution similar to colorectal adenocarcinoma, can vary in size, and may be sessile, flat, or pedunculated. Adenomatous polyps are the precursor lesions for colorectal adenocarcinoma. Furthermore, screening, early detection, and removal of adenomatous polyps substantially reduce the risk of subsequent colorectal cancer.

EPIDEMIOLOGY

Adenomatous polyps are relatively common and become more common with age: more than 15% of healthy women and more than 25% of healthy men over age 50 years have adenomas. The prevalence of adenomas tends to be higher in Western countries and wherever colorectal cancer is more common. In addition to defined genetic risks seen in familial colorectal cancer syndromes, sporadic adenomas have a familial component. For example, if a first-degree relative has an adenomatous polyp, an individual's risk is increased. In the United States, Blacks have a higher risk relative to Whites of European descent, whose risks, in turn, are similar to those of Asian and Hispanic individuals.

PATHOBIOLOGY

The epithelial cells in the large bowel undergo continuous self-renewal, with complete turnover every 3 to 8 days. Adenomatous polyps are caused by the sequence-specific acquisition of mutations that favor cell proliferation over cell death. Undifferentiated cells accumulate at the luminal surface, continue to divide, and eventually form an adenomatous tissue mass.

Adenomas can be tubular, villous, or tubulovillous. Most adenomas (70 to 85%) removed at colonoscopy are tubular; they typically are small, pedunculated, and composed of dysplastic glands that divide and branch out from the mucosal surface. Tubular adenomas rarely have high-grade dysplasia or carcinoma in situ. By comparison, villous adenomas (<5% of all adenomas) are usually large, sessile, and composed of dysplastic epithelium that projects into the intestinal lumen. Villous adenomas often have high-grade dysplasia or even carcinoma in situ. Tubulovillous adenomas (10 to 25% of all adenomas) include both tubular and villous components. An adenoma is considered "advanced" if it is at least 1 cm in size or has villous histology or high-grade dysplasia. Patients with advanced adenomas or three or more adenomas have a much higher risk of developing synchronous or metachronous colorectal cancer. In a patient who has a first documented adenoma, the risk of an additional adenoma is 30 to 50%.

CLINICAL MANIFESTATIONS

Most adenomatous polyps are asymptomatic and discovered only at the time of colorectal screening. Some patients, however, may present with an asymptomatic positive stool occult blood test or overt evidence of a lower GI bleed. Less than 5% of all adenomas will eventually develop into carcinomas: 1 to 3% of polyps smaller than 1 cm, 10% of polyps between 1 and 2 cm, and 40% of polyps larger than 2 cm. All adenomas contain some level of dysplasia, and higher-grade dysplasia carries a 30% risk of undergoing malignant transformation.

DIAGNOSIS

Colonic and rectal polyps and cancer can be diagnosed by several methods, including endoscopy, barium radiography, or CT colography (virtual colonoscopy). Colonoscopy is the preferred method because of its high accuracy and ability to perform a biopsy of and remove most polyps immediately. Nevertheless, colonoscopy may miss 6 to 12% of large (≥1 cm) polyps and 5% of cancers. By comparison, barium enemas miss about 50% of polyps that are larger than 1 cm. CT colography is sensitive for detecting large (>1 cm) polyps (>85%) and for detecting cancers (96%) but much less sensitive and specific for polyps smaller than 1 cm. Although CT colography is noninvasive and relatively quick, it still requires bowel preparation and exposes the patient to ionizing radiation. Nonpolypoid (flat and depressed) colorectal neoplasms, which are more likely to be carcinomatous than are polypoid lesions, are found on colonoscopy in almost 10% of asymptomatic and symptomatic adults but are much less likely to be diagnosed by barium radiography or CT colography.

Flexible sigmoidoscopy can be used to screen average risk asymptomatic individuals, but it detects only 50 to 60% of all polyps and cancers. Patients with polyps detected by barium radiography, CT colography, or flexible sigmoidoscopy should undergo colonoscopy to remove the lesion and to search for additional polyps or mass lesions. This need for subsequent colonoscopy underscores the attractiveness of using it as the initial screening modality.

TREATMENT

Neoplastic polyps should be removed endoscopically to reduce the risk of subsequent colorectal cancer. A pedunculated adenoma usually can be removed intact by snare polypectomy (Video 179-2), whereas sessile polyps may require piecemeal snare resection. Pathologic evaluation should assess the presence or absence of cancer; if malignant tissue is identified, it should be evaluated for its histologic grade, vascular and lymphatic spread, and adenoma-free margin. Unfavorable histopathologic factors that require prompt surgical resection after endoscopic polypectomy include poorly differentiated histology, vascular invasion, lymphatic invasion, and incomplete resection. Malignant pedunculated polyps can be treated with endoscopic resection alone if the cancer is confined to the submucosa and no unfavorable histologic features are present. When a malignant sessile polyp is removed endoscopically, the potential risk of recurrence or lymph node involvement must be weighed against the risks of definitive surgery in each individual patient.

PROGNOSIS

Patients who have undergone endoscopic removal of a previously diagnosed adenomatous or sessile serrated polyp are at increased risk for the subsequent development of adenomas and colorectal cancer. The recommended surveillance post-resection depends on the primary lesions, size, and histology, as well as the number of adenomas (Table 179-2).[17] If a low-risk patient has just 1 or 2 small tubular adenomas, surveillance colonoscopy can be delayed for 5 to 10 years. By comparison, patients who have multiple (>2) adenomas, large (≥1 cm) adenomas, adenomas with villous or high-grade histology, or numerous (>10) adenomas, should undergo repeat colonoscopy within 3 years. After removal of a large (≥2 cm) adenoma or the piecemeal resection of any adenoma, colonoscopy should be repeated within 6 months to determine whether the original resection was complete. For sessile serrated polyps smaller than 10 mm without dysplasia, surveillance colonoscopy is recommended at 5 years, but the recommended interval is 3 years if the serrated polyp showed high-grade dysplasia or was a traditional serrated adenoma (Video 179-3).

ADENOCARCINOMA OF THE COLON AND RECTUM

CLINICAL MANIFESTATIONS

Patients with early-stage colon cancer are typically asymptomatic, and the cancer is usually discovered upon routine screening. Symptoms usually arise when the tumor grows into the bowel lumen or when the tumor invades adjacent anatomic structures. Common symptoms related to colorectal cancer include lower abdominal pain, change in bowel function, GI bleeding (Chapter 121), anemia, and alterations in stool caliber. Anorexia, weight loss, and fatigue may develop, and liver metastases can be manifested by hepatomegaly, jaundice, abdominal fullness, or ascites.

Symptoms also depend on the primary site (Fig. 179-5). Proximal lesions more frequently present with iron deficiency anemia (Chapter 145) resulting from occult blood loss. For lesions that occur in the distal colon, the usual presenting symptoms include a change in bowel habits, such as constipation or diarrhea, and hematochezia. Tumors arising in the rectum usually present with changes in stool caliber, rectal bleeding, and rectal pain. In some cases when the rectal tumor involves sacral nerve plexi, significant neuropathic pain may be present.

TABLE 179-2 COLONOSCOPY SURVEILLANCE INTERVALS

MOST ADVANCED FINDING	INTERVAL
No polyps or small (<10 mm) hyperplastic polyps	10 yr
1-2 adenomas, <1 cm	5-10 yr
3-10 adenomas or adenoma with villous features, ≥1 cm, or with high-grade dysplasia	3 yr
>10 adenomas	<3 yr
Sessile adenoma ≥ 2 cm, piecemeal excision	2-6 mo
Serrated lesions:	
• <10 mm, no dysplasia	5 yr
• ≥10 mm or dysplasia	3 yr

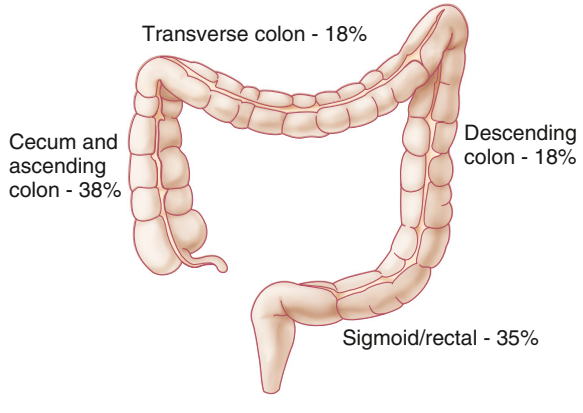

FIGURE 179-5. Sites of development of large bowel adenocarcinoma.

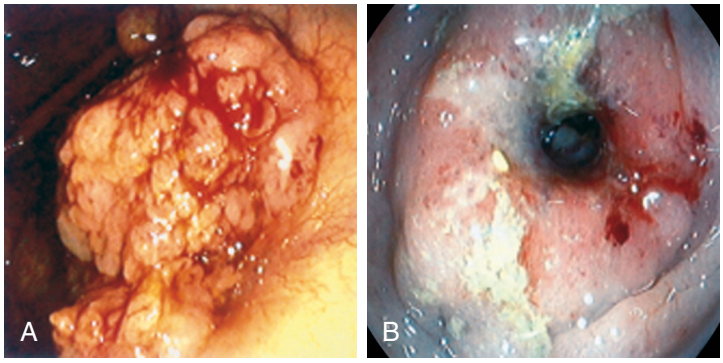

FIGURE 179-6. Colonoscopy appearance of large bowel adenocarcinomas. A, Exophytic growth within the bowel lumen. B, "Apple core" stricturing lesion.

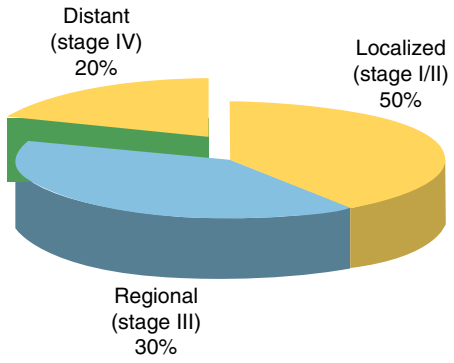

FIGURE 179-7. Stage of disease at time of initial presentation.

DIAGNOSIS

A careful history, physical examination, and radiologic evaluation are important in making the diagnosis. The patient should be questioned about a history of adenomatous polyps or colorectal cancer, a history of inflammatory bowel disease, and any family history of colorectal cancer or other solid tumors. On physical examination, extra-intestinal lesions characteristic of Peutz-Jeghers syndrome or Gardner syndrome may be noticed. Metastatic disease to the liver or lymph nodes may present with hepatosplenomegaly or lymphadenopathy, and abdominal fullness or ascites may reflect peritoneal involvement. Digital rectal examination may reveal a mass in the distal rectal region or spread of the tumor to the rectal shelf or pelvis. Examination of the stool may show frank or occult blood in up to 80% of advanced cases. Iron deficiency anemia and elevated liver enzymes (AST, ALT, and alkaline phosphatase) and serum bilirubin may aid in the diagnosis. The peripheral blood levels of the tumor markers (CEA and CA19-9) may be elevated, but these serum markers are relatively insensitive and can be elevated in other solid tumors.

The approaches for making the definitive diagnosis of colorectal cancer are similar to those used to detect adenomatous polyps. Colonoscopy is considered the standard for all patients with occult blood in their stools, unexplained iron deficiency anemia, or symptoms and signs suggestive of colorectal cancer (Fig. 179-6).

For rectal cancer, endoscopic ultrasound combines high-frequency ultrasonography with video endoscopy. This procedure is superior to CT to stage the tumor by accurately determining the degree of invasion as well as detecting and sampling any enlarged lymph nodes. Endoscopic ultrasound also is highly sensitive for detecting recurrent rectal cancer after a low anterior resection. MRI also can accurately stage rectal cancer and may be preferable to endoscopic ultrasound.

Consensus guidelines recommend CT scans of the chest, abdomen, and pelvis because advanced liver metastases or involvement of other sites often preclude immediate surgical resection of the primary tumor. PET scans can confirm systemic disease and are useful before resection of a solitary metastatic site and in patients who have a rising CEA or new symptoms suggestive of progressive disease, despite no change in their CT scans. PET scans also may be used to evaluate abnormal lesions seen on CT. However, PET has no specific role in the routine evaluation of patients with colorectal cancer. Plain chest radiographs are not sufficiently sensitive to detect the presence of metastatic lesions in the lungs, and plain abdominal films are useful only to aid in the diagnosis of bowel obstruction.

Histopathologic analysis is critical for making the diagnosis of colorectal cancer. Additional studies to evaluate immunohistochemical expression of certain key cellular proteins may be helpful in identifying adenocarcinomas of colorectal cancer origin. For example, cytokeratin 20 (CK20) and caudal-type homeobox 2 (CDX2) are two of the most sensitive and specific markers used to help diagnose colorectal cancer. Immunohistochemistry also can be helpful in making the diagnosis of defective mismatch repair by testing for the protein expression of the four main MMR genes: *MLH1, MSH2, PMS2*, and *MSH6*.

Staging

Accurate staging is critical for determining both prognosis and treatment. Colorectal cancer is staged according to the tumor, node, and metastasis (TNM) classification system based on the physical examination, radiography, endoscopy, surgery, and pathologic stage: stage I cancers penetrate into but not through the bowel wall (T1–2N0M0); stage II cancers penetrate through the bowel wall and can involve nearby organs but do not spread to regional lymph nodes; stage III cancers involve regional lymph nodes (Fig. 179-7); and stage IV disease spreads to the liver, lung, lymph nodes, and peritoneum. In the United States, about 50% of patients present with stage I or II disease, 30% with stage III disease, and 20% with advanced, metastatic disease. In general, primary tumors that arise in the colon follow an orderly spread to the regional lymph nodes, then to the liver, and then to the lungs and other distant sites. In contrast, because of the dual venous drainage of the rectum to the portal vein and inferior vena cava, primary rectal tumors may spread via hematogenous dissemination to the lungs before any liver involvement.

TREATMENT

Surgery

Surgical resection is the primary treatment for early-stage, locally confined colon cancer (stage 0 and stage I). Highly selected patients with site-limited metastatic disease (stage IV) also may undergo surgery with curative intent. Curative surgery aims to remove the primary tumor with tumor-free margins, as well as to remove the primary feeding arterial vessel and corresponding lymphatics en bloc. A minimum of 12 lymph nodes should be removed and examined microscopically for accurate staging. Synchronous colon cancers can be removed individually by subtotal colectomy. Any adjacent adherent structures should be resected en bloc. Prophylactic oophorectomy is not recommended, but if one ovary is grossly involved, the other should be removed as well given the risk of contralateral involvement. Laparoscopic resection is as safe and effective as open resection and requires a modestly shorter recovery time.[18]

For rectal cancer, the main goal of surgery is to preserve the function of the anal sphincter. For cancers involving the distal rectum, the recommendation is total mesorectal excision with en bloc removal of the lymphovascular and fatty envelope surrounding the rectum. For upper rectal tumors, by comparison, tumor-specific mesorectal excision (en bloc removal of the mesorectum 5 cm distal to the tumor) is sufficient. For minimal-risk (T1 disease, size <3 cm, well differentiated, within 8 cm of the anal verge, no lymphovascular invasion, and less than one third circumferential) low rectal cancers, local transanal excision is acceptable. Postoperatively, increased bowel frequency is common, and some patients develop fecal incontinence or evacuation dysfunction (Chapter 131). As such, the main focus in patients with rectal cancer is to preserve the function of the anal sphincter.

Obstructing tumors should be immediately resected with bowel re-anastomosis. Proximal diversion may be the only initial option for an advanced unresectable cancer, with future resection followed by ostomy closure if the primary tumor responds to the point where it can later be removed. Endoscopic stenting may sometimes relieve acute obstruction. Perforated bowel must be resected, with or without diversion, prior to re-anastomosis. In patients who present with synchronous colorectal cancer and unresectable metastases, an asymptomatic primary tumor can be treated safely with systemic medical therapy without surgery, with a low probability that serious complications will require immediate surgical intervention.

Post-Surgical Surveillance

Active surveillance is recommended after surgical resection of early-stage colon and rectal cancer because the risk for recurrent disease is highest within the first 2 to 3 years after surgery and adjuvant chemotherapy for patients with stage II or III cancer. The American Society of Clinical Oncology recommends a history and physical examination every 3 to 6 months for 5 years, annual chest and abdominal CT scans for 3 years after resection of high-risk primary tumors, and the addition of pelvic CT scanning for primary rectal cancer. However, CT plus CEA screening at 12 and 36 months appears to be as good as more frequent screening for stage II and III disease.[A2] Colonoscopy should be performed 1 year after the completion of adjuvant chemotherapy, and, if completely negative, every 5 years thereafter. Serum CEA levels should be measured every 3 to 6 months for 5 years.

Radiation Therapy

Radiation therapy is usually not considered as a treatment option for surgically resected early-stage colon cancer nor for the treatment of a primary colon cancer when metastatic disease is present. The major role for radiation therapy is in the combined modality treatment of locally advanced rectal cancer. Certain colorectal cancers are at high risk for locally recurrent disease, such as T4 tumors with penetration to a fixed structure especially within the pelvic region, may be considered for postoperative radiation therapy. However, no randomized clinical trials have documented benefit of radiation therapy in this setting. Palliative

radiation therapy also may be considered to control tumor-related symptoms when metastatic colon cancer spreads to bone, brain, liver, and lung.

Stereotactic radiation therapy can be useful for metastatic colorectal cancer patients with liver metastases. The 1- and 2-year local control rates are about 90%, with few reports of major toxicity. This approach is a reasonable and safe alternative for patients who have fewer than four liver metastatic lesions and who are unable to undergo surgery or any other treatment options.

Systemic and Combination Therapies

The backbone of the treatment of colorectal cancer, in both the adjuvant and metastatic disease settings, is 5-fluorouracil. Although 5-fluorouracil has modest activity as a single agent, its clinical efficacy is enhanced by prolonged infusion and by coadministration with the reduced folate leucovorin. Two other cytotoxic agents commonly used to treat metastatic colorectal cancer are irinotecan (a topoisomerase I inhibitor) and oxaliplatin (a third-generation platinum analogue; see Table 164-2). Biologic agents are available to target the vascular endothelial growth factor (VEGF) signaling pathway (bevacizumab, aflibercept, and ramucirumab), the epidermal growth factor receptor (EGFR) pathway (cetuximab and panitumumab), and tyrosine kinases that are involved in cell growth, proliferation, angiogenesis, invasion, and metastasis (regorafenib).

Patients with resected stage I colon cancer have an extremely high cure rate, approaching 95%, with surgery alone, and do not need adjuvant systemic therapy (Table 179-3).[A3] For stage II patients, the risk of relapse is higher (about 25% at 3 years), and combined treatment with 5-fluorouracil and leucovorin provides modest clinical benefit.[18] However, stage II tumors that express high levels of microsatellite instability have a better prognosis than tumors with microsatellite stable disease, and survival in such patients is worse when they are treated with 5-fluorouracil. Adjuvant chemotherapy is not recommended for stage II, microsatellite instability–high disease. For high-risk stage II disease (defined by obstruction, perforation, lymphovascular invasion, perineural invasion, and fewer than 12 lymph nodes in the surgical resection specimen), the benefit from adjuvant chemotherapy is similar to that seen for stage III colon cancer. Patients with high-risk stage II disease and good performance status should receive 6 months of adjuvant therapy with combination chemotherapy that includes 5-fluorouracil, leucovorin, and oxaliplatin (FOLFOX) or an alternative combination regimen of capecitabine and oxaliplatin (XELOX/CAPOX; Table 179-3) under expert supervision, with the decision potentially guided by the presence or absence of the circulating tumor DNA.[A4] Both FOLFOX and XELOX/CAPOX significantly prolong disease-free survival and overall survival compared with fluoropyrimidine monotherapy. For patients who have comorbid illnesses and who are unable to tolerate aggressive combination chemotherapy, fluoropyrimidine monotherapy with infusional 5-fluorouracil or oral capecitabine under expert supervision is a reasonable alternative.

In patients with stage III colon cancer, 5-year disease survival rates range from 25 to 85%, depending on the number of lymph nodes that are positive in the surgical resection specimen. The usual recommendation for patients with node-positive stage III disease is to receive adjuvant systemic therapy (E-Fig. 179-1). For patients with good performance status and no comorbid illnesses, aggressive treatment with the FOLFOX regimen significantly improves long-term survival rates and represents current standard care. XELOX/CAPOX appears to be as good as FOLFOX in patients of all ages. For patients who are not candidates for aggressive cytotoxic chemotherapy, fluoropyrimidine monotherapy with either infusional 5-fluorouracil or oral capecitabine is an appropriate option. Several randomized trials show that 3 months of adjuvant therapy is as good as 6 months of therapy in lower risk patients with T1 to T3 disease and only 1 to 3 positive lymph nodes. In contrast, for stage III patients with more than 4 lymph nodes, standard 6 months of adjuvant therapy provides greater clinical benefit than 3 months of therapy, albeit at a higher cost of adverse events. CAPOX rather than FOLFOX is now viewed as a preferred option for adjuvant therapy.

TABLE 179-3 TREATMENT OF EARLY-STAGE COLON CANCER ACCORDING TO DISEASE STAGE

STAGE	SURGICAL TREATMENT	ADJUVANT CHEMOTHERAPY
I	Colectomy with en bloc removal of regional lymph nodes	Observation
II (MSI-H/dMMR)	Colectomy with en bloc removal of regional lymph nodes	Observation
II (MSS/pMMR and no high-risk features)	Colectomy with en bloc removal of regional lymph nodes	Observation *OR* Consider capecitabine (6 months) or 5-FU/leucovorin (6 months)
II (MSS/pMMR and high-risk features)	Colectomy with en bloc removal of regional lymph nodes	FOLFOX (6 months) or CAPOX (3 months) *OR* Capecitabine (6 months) or 5-FU/leucovorin (6 months) for patients who cannot tolerate aggressive chemotherapy
III (low-risk)	Colectomy with en bloc removal of regional lymph nodes	CAPOX (3 months) or FOLFOX (3-6 months) *OR* Consider capecitabine (6 months) or 5-FU/leucovorin (6 months) for patients who cannot tolerate aggressive chemotherapy
III (high-risk)	Colectomy with en bloc removal of regional lymph nodes	CAPOX (3-6 months) or FOLFOX (6 months) *OR* Consider capecitabine (6 months) or 5-FU/leucovorin (6 months) for patients who cannot tolerate aggressive chemotherapy

MSI-H/dMMR = microsatellite instability-high/defective mismatch repair; MSS-H/pMMR = microsatellite stable/proficient mismatch repair.

Rectal Adenocarcinoma

The risk of local recurrence is much greater for rectal cancer, so the therapeutic approach for patients with primary rectal adenocarcinoma is distinct from that for primary colon cancer. Rectal cancer patients require accurate preoperative staging with endoscopic rectal ultrasound or rectal MRI for precise definition of the size, extent, and depth of invasion of the rectal tumor as well as lymph node involvement. For patients with stage I rectal cancer, surgical resection is sufficient with no need for additional adjuvant treatment with either radiation or chemotherapy. However, higher-risk patients (T2 disease, T1 with poorly differentiated histology, perineural or lymphovascular invasion, or close margins) should receive postoperative pelvic irradiation with or without 5-fluorouracil chemotherapy.

Radiation therapy is considered standard therapy for patients with locally advanced stage II and III rectal adenocarcinomas to decrease local relapse rates, improve the chance of sphincter preservation, and possibly improve survival. The major issues to consider relate to timing (preoperative or postoperative) and duration (short or long), as well as whether to combine it with fluoropyrimidine-based chemotherapy. Short-course 5-day preoperative irradiation without chemotherapy, as is practiced in certain countries in Europe, may be considered when tumor downsizing is not necessary. When short-course radiation is used, postoperative systemic adjuvant therapy is recommended with either a fluoropyrimidine alone (stage II) or a fluoropyrimidine-oxaliplatin combination regimen (node-positive disease).

For locally advanced rectal cancer, which includes lymph node involvement or large bulky tumors, a 5-day course of radiotherapy followed by either 6 cycles of CAPOX or 9 cycles of FOLFOX chemotherapy, can significantly reduce 3-year disease-related treatment failure[A5] and is now considered a standard treatment. With this neoadjuvant approach, induction systemic chemotherapy is administered first and followed by chemoradiation, with the goal of downstaging the primary tumor as well as reducing the risk of distant metastatic spread. Adjuvant chemotherapy is usually administered after surgical resection.

For stage II/III disease, however, the optimal chemotherapy regimen has yet to be determined. Fluoropyrimidine monotherapy with either infusional 5-fluorouracil or oral capecitabine is usually recommended if patients have no evidence of lymph node involvement in the surgical resection specimen and if the primary tumor has been significantly downstaged. If not, however, oxaliplatin-based chemotherapy regimens with either FOLFOX or XELOX/CAPOX are usually recommended.

Metastatic Colorectal Cancer

Metastatic colorectal cancer is treated with the same approach, regardless of the primary site of origin (colon versus rectum).[19,20] Metastatic colorectal cancer is becoming a chronic disease, and the key issue is to ensure that patients are treated in a continuum of care approach with exposure to all of the active agents within the therapeutic armamentarium. Current systemic cytotoxic chemotherapies in combination with various biologic agents (Chapter 29) have improved median overall survival to nearly three years (E-Fig. 179-1).[21]

First-Line Chemotherapy

For first-line treatment, the cytotoxic chemotherapy FOLFOX and FOLFIRI regimens provide virtually identical progression-free survival and overall survival,[A6] with a median overall survival of nearly 23 months. Interestingly, long-term results seem to be similar regardless of which drug (oxaliplatin or irinotecan) is combined first with 5-fluorouracil. However, the toxicity pattern varies, depending on which drug is given; irinotecan is commonly associated with GI side effects, whereas oxaliplatin treatment can lead to peripheral sensory neuropathy.

Biologic Therapy

ANTI–VASCULAR ENDOTHELIAL GROWTH FACTOR ANTIBODIES. In metastatic colorectal cancer patients with wild-type RAS, the addition of the anti-VEGF antibody bevacizumab or the anti-EGFR antibody cetuximab to cytotoxic chemotherapy (either FOLFOX or FOLFIRI) provides equivalent clinical

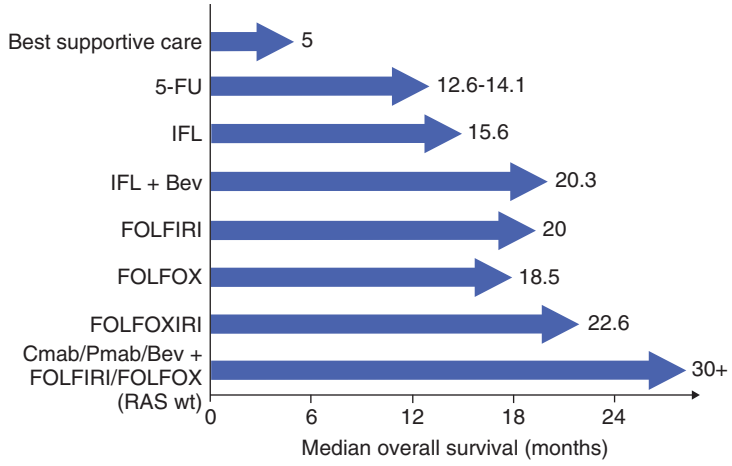

E-FIGURE 179-1. **Evolution of systemic therapy for metastatic colorectal cancer.** Bev = bevacizumab; Cmab = cetuximab; 5-FU = 5-flourouracil; FOLFIRI = 5-fluorouracil, folinic acid (leucovorin), irinotecan; FOLFOX = 5-fluorouracil, leucovorin, oxaliplatin; IFL = irinotecan, 5-fluorouracil, leucovorin; Pmab = panitumumab; RAS wt = RAS wild-type.

benefit, with a median progression-free survival of 10.6 months and a median overall survival of 30 months. If disease progresses, bevacizumab can be continued in combination with second-line cytotoxic chemotherapy. Aflibercept plus FOLFIRI improves survival compared with FOLFIRI alone in patients who progress despite oxaliplatin treatment. Ramucirumab is approved for use in combination with FOLFIRI in the second-line treatment of metastatic colorectal cancer. Cross-trial comparisons suggest equivalent clinical efficacy among bevacizumab, aflibercept, and ramucirumab, but aflibercept is significantly more toxic and ramucirumab is much more expensive than bevacizumab.

ANTI–EPIDERMAL GROWTH FACTOR ANTIBODIES. For epidermal growth factor receptor (EGFR) positive chemorefractory disease, two monoclonal antibodies (cetuximab and panitumumab) have nearly identical single-agent activity, and both agents can be effectively combined with FOLFIRI or FOLFOX chemotherapy in the first-line treatment setting to improve overall response rates and progression-free survival. However, these anti-EGFR antibodies should be used only in patients whose tumors express wild-type *RAS* and *BRAF*. Unfortunately, even in the setting of wild-type *RAS*, only about 30% of patients will respond to anti-EGFR therapy. Right-sided tumors derive little benefit from cetuximab, whereas left-sided tumors derive significantly greater clinical benefit from cetuximab compared with bevacizumab. Although bevacizumab is effective in both left- and right-sided tumors, its clinical efficacy is also much greater in left-sided tumors.[22]

Programmed Death 1 Blockade

Immunotherapy with an anti–programmed death 1 (PD-1) immune checkpoint inhibitor (pembrolizumab or nivolumab) is useful in patients who have metastatic disease that has progressed despite treatment with a fluoropyrimidine, oxaliplatin, and irinotecan.[23] These antibodies stimulate the T-cell immune response, thereby leading to T-cell activation and proliferation. For microsatellite instability–high or mismatch repair defective metastatic colorectal cancer,[A7] pembrolizumab is superior to 5-fluorouracil-based chemotherapy, regardless of whether patients are also receiving bevacizumab or cetuximab, with median progression-free survival doubled from 8.2 months to 16.5 months. Furthermore, patients who are treated with pembrolizumab immunotherapy have fewer treatment-related adverse events and a significantly improved health-related quality of life.[A8] The combination of nivolumab plus ipilimumab, an antibody that targets cytotoxic T-lymphocyte–associated protein 4 (CTLA4), is also associated with encouraging progression-free survival and overall survival at 12 months in patients with microsatellite instability–high or mismatch repair defective metastatic colorectal cancer, and this combination immunotherapy regimen appears to provide enhanced clinical efficacy when compared with anti-PD-1 monotherapy.[24]

BRAF *V600E Inhibition*

The 8% of patients whose metastatic cancer expresses the *BRAF* V600E mutation have an overall poor prognosis,[25] but a triplet combination of encorafenib (a *BRAF* inhibitor), cetuximab (an anti-EGFR antibody), and binimetinib (a MEK inhibitor) can improve survival compared with standard irinotecan-based chemotherapy plus cetuximab.[A9] This regimen is now considered standard of care for metastatic disease with this specific mutation.

Other Agents

Regorafenib (a multikinase inhibitor) and TAS-102 (a combination of trifluridine and tipiracil) are agents that have nearly identical clinical activity and improve median progression-free survival and overall survival in patients with progressive disease. In general, TAS-102 has a more manageable safety profile and does not require as many dose reductions or treatment delays. Sotorasib and adagrasib under expert supervision are options for solid tumors with the *KRAS*-G12C mutation.[26,27]

Locally Directed Treatment of Metastatic Disease

For select patients with metastatic colorectal cancer, complete resection of isolated hepatic or pulmonary metastases may provide long-term survival.[28] For hepatic metastasectomy, 5-year survival rates are in the 30 to 50% range. In patients initially deemed to have surgically unresectable metastatic disease, preoperative systemic therapy improves response rates. For patients with wild-type *RAS* disease, cytotoxic chemotherapy with FOLFOX or FOLFIRI in combination with cetuximab or panitumumab appears to offer the best chance for cytoreduction of the metastatic liver disease and successful surgical resection. In the setting of mutant *RAS* metastatic colorectal cancer, the anti-VEGF antibody bevacizumab combined with chemotherapy provides an objective response rate approaching 70% with successful surgical resection approaching 30%. In patients with initially unresectable *RAS* mutant colorectal liver metastases, bevacizumab combined with mFOLFOX6 can increase the resectability of liver metastases and improve survival compared with mFOLFOX6 alone.[A10] After patients have recovered from their surgical procedure, which usually requires 4 to 5 weeks, 6 months of adjuvant chemotherapy with FOLFOX is usually recommended.

Radio frequency ablation can be used for patients whose liver metastases are deemed to be surgically unresectable because of their anatomic location or because the patient is too debilitated to undergo hepatic resection. An alternative strategy is to administer fluoropyrimidine chemotherapy via the hepatic artery through an intraarterial catheter. Selective internal radiation therapy embolizes radiolabeled spheres into the hepatic artery for the treatment of liver metastases.[A11] Stereotactic body radiation therapy is also a reasonable and safe alternative for patients who have liver-limited metastatic colorectal cancer and who are unable to undergo surgery.

PREVENTION

Screening

The role of screening is to reduce colorectal cancer-related mortality by removing any precursor adenomas and by detecting true cancers at an earlier, more curable stage. For average-risk individuals, the relatively long latency between adenoma development and the development of cancer is of the order of 8 to 12 years, thereby making colorectal cancer a highly preventable disease using colonoscopy with polypectomy.[A12] For sporadic colorectal cancer, age is the major risk factor; for this reason, most patients should begin screening at age 45 years. The wide range of options for average-risk individuals (Table 179-4) can be divided into two distinct categories: stool tests for occult blood or abnormal DNA; and structural tests, which include colonoscopy, flexible sigmoidoscopy, CT colography, and double-contrast barium enema, used alone or in combination.[29] In asymptomatic adults age 50 to 69 years, one-time colonoscopy and fecal immunochemical testing are equally effective at identifying the presence of colorectal cancer, although a greater number of adenomas are identified by colonoscopy (Chapter 120). Current professional society guidelines recognize multiple screening options but recommend structural tests that can both detect and prevent colorectal cancer. For example, the American Cancer Society now recommends screening average-risk adults for colorectal cancer starting at age 45 years and high-risk individuals starting before age 40 years (or 10 years before the age when the youngest relative was diagnosed with colorectal cancer). Colonoscopy, flexible sigmoidoscopy, or a stool-based test are recommended for average-risk patients, but flexible sigmoidoscopy or colonoscopy is recommended for high-risk patients. For individuals in good health and expected to live at least more than 10 years, routine screening should continue up through age 75 years. Individuals between ages 76 to 85 years should consult with their primary health care provider as to whether screening should be continued.[30] The general recommendation is to discontinue colorectal cancer screening in individuals who are older than 85 years of age.

Patients with ulcerative colitis (Chapter 127) are 10 to 20 times more likely to develop colorectal cancer than the general population, with a 25-year cumulative incidence of about 12%. The risk is even higher in patients who have both primary sclerosing cholangitis (Chapter 141) and ulcerative colitis. If Crohn disease (Chapter 127) involves more than one-third of the colon, the risk of colorectal cancer risk is increased 6- to 8-fold. Patients with ulcerative colitis or extensive Crohn disease should have screening colonoscopy every 1 to 2 years, starting 8 to 10 years after the disease is first diagnosed. The main goal is to identify the presence of dysplasia. Multifocal low-grade dysplasia or any dysplasia that cannot be excised endoscopically is an indication for colectomy. In familial adenomatous polyposis, the *APC* gene mutation can be identified in up to 85% of affected individuals and is useful for screening.

Fecal occult blood testing detects the presence of hemoglobin from bleeding tumors. Guaiac-based testing decreases colorectal cancer mortality by 15 to 33%, with the mortality benefit persisting for 30 years. However, immunochemical-based tests have higher sensitivities and specificities than guaiac tests, and they identify 2.5-fold more advanced adenomas and colorectal cancers than do guaiac-based tests. Furthermore, they do not require any dietary restrictions and require only one stool specimen. As a result, immunochemical-based tests are now the preferred fecal occult blood test.[31] Fecal occult blood tests should be repeated on an annual basis, and any positive test should prompt colonoscopy.

TABLE 179-4 SCREENING METHODS FOR COLORECTAL CANCER*

TEST	INTERVAL
TESTS THAT DETECT ADENOMATOUS POLYPS OR CANCER	
Colonoscopy	Every 10 yr
Flexible sigmoidoscopy†	Every 5 yr
CT colography†	Every 5 yr
Double-contrast barium enema†	Every 5 yr
TESTS THAT DETECT PRIMARILY CANCER†	
Fecal occult blood tests	
• High-sensitivity guaiac-based fecal occult blood test	Annually
• Fecal immunochemical test	Annually
Stool DNA	Interval uncertain

*Beginning at age 45 for average-risk individuals.
†Positive test should prompt full colonoscopy.
CT = computed tomography.

The rationale for stool DNA tests is that both adenomas and carcinomas contain altered DNA, which is shed continuously in the stool. These stool DNA tests contain a panel designed to detect exfoliated DNA markers, including *KRAS* mutation, aberrant *NDRG4* and *BMP3* methylation, and beta-actin. Stool DNA testing identifies up to about 90% of patients with colorectal cancer and 40% of patients with advanced adenomas.[32] In a large colorectal cancer screening trial, the sensitivity of the multitarget stool DNA test for detecting colorectal cancer was 92% with stool DNA testing compared with 74% with fecal immunochemical testing, and the sensitivity for detecting advanced precancerous lesions and polyps with high-grade dysplasia was also significantly higher with stool DNA testing. However, stool DNA testing is more costly and associated with a higher false-positive rate. The optimal screening interval for stool DNA testing has not been clearly defined.

Flexible sigmoidoscopy (Chapter 120) is an endoscopic procedure that examines the rectum and distal colon up to the splenic flexure. It is performed with minimal bowel preparation, does not require sedation, and can be performed in the office by primary care doctors, nurses, or physician's assistants. This procedure detects distal cancers or polyps with the same accuracy as colonoscopy. If an adenoma is found on sigmoidoscopy, colonoscopy is required because of the high risk of synchronous polyps or cancer in the more proximal colon. Screening with flexible sigmoidoscopy (with subsequent colonoscopy as indicated) can reduce the incidence of both distal and proximal colorectal cancer by about 30%, with a significant 50% decrease in mortality from distal colorectal only. A single flexible sigmoidoscopy continues to provide significant protection against both incidental and fatal colorectal cancer for at least 15 to 17 years.[A13]

Colonoscopy (Chapter 120) allows complete visualization of the colon and removal of any visualized polyps. As such, colonoscopy is both diagnostic and preventive.[A14] Screening colonoscopy detects cancer in about 1% of patients, advanced adenoma (size >10mm, villous histology, or high-grade dysplasia) in 5 to 10% of patients, and 1 or more adenomas in at least 20% of patients. The major complication rate of screening colonoscopy is less than 3 per 1000, with more than half of such complications related to a polypectomy. After colonoscopic polypectomy, the incidence of colorectal cancer is reduced by 75 to 90%. In patients whose adenomas are detected and removed by colonoscopy, the subsequent risk of death from colorectal cancer is 50% lower than otherwise expected, with most of the benefit attributable to the removal of low-risk adenomas. The highest risk of subsequent colorectal cancer is in patients whose removed adenomas were 20 mm or greater in diameter or had high-grade dysplasia.[33] The benefit of colonoscopy is higher if it is performed by an experienced gastroenterologist. If the initial screening colonoscopy is completely normal, future screening can be deferred for 10 years. Re-screening is recommended more frequently in patients with positive findings (see Table 179-2).[34]

CT colography (virtual colonoscopy) obtains two- and three-dimensional images of the entire colon via multidetector CT scanning (Chapter 119). A rectal tube is used to infuse gas to distend the bowel for better imaging. The sensitivity is 85 to 92% for large polyps (≥10 mm), with a specificity of 83 to 89%, and about 65% for polyps 5 mm or larger. Its 96% sensitivity for detecting colorectal cancer is similar to colonoscopy. Because CT colography is less sensitive than colonoscopy for detecting lesions smaller than 10 mm and substantially less sensitive for detecting high-risk sessile serrated polyps, colonoscopy is the preferred screening procedure. Colon capsule endoscopy appears to be better than CT colography, but neither is as accurate as colonoscopy.[A15] If used, CT colography screening should begin at age 45 years and be repeated every 5 years. Discovery of a polyp larger than 5 mm requires colonoscopy.

Double-contrast barium enema (Chapter 119) can evaluate the mucosal surface of the entire colon. This test has a sensitivity of 85 to 97% for detecting colorectal cancers but only 48 to 73% for detecting large adenomas. Given this low sensitivity and the small but real risk of ionizing radiation, this imaging procedure is not recommended for routine screening.

Chemoprevention

NSAIDs[A16] and aspirin[A17,A18] reduce the formation of adenomas and inhibit the development of colon cancer by inhibiting cyclooxygenase and the subsequent generation of prostaglandin. In patients with familial adenomatous polyposis, sulindac (150 mg daily) and celecoxib can cause existing adenomas to regress and inhibit the formation of new adenomas. Aspirin also reduces the recurrence of adenomas by up to 20 to 40%, with pooled data suggesting up to a 70% reduction in the incidence of colorectal cancer when at least 75 mg of aspirin daily is taken for 5 or more years. Epidemiologic studies also show that regular users of NSAIDs have a lower risk of developing colorectal cancer. Calcium supplementation decreases the rate of metachronous adenomas by 20%, and total calcium intake greater than 1400 mg per day is associated with a significantly lower risk of colon cancer than an intake of less than 600 mg per day. Observational studies suggest that higher levels of 25-hydroxyvitamin D3 (25[OH]D) are associated with a reduced risk of colorectal cancer and also improved survival after its diagnosis. In patients with stage III colon cancer, adjuvant vitamin D supplementation is associated with a significant improvement in recurrence-free survival and overall survival. However, aspirin, NSAIDS, and calcium are not routinely recommended to prevent colorectal cancer, although they may be considered on an individual basis.

Dietary Prevention

Epidemiologic studies have identified a correlation of colorectal cancer with diets high in fat and low in fiber, green leafy vegetables, and fruits; physical inactivity; smoking; and excessive alcohol use. Increased fish consumption is associated with a lower incidence of colorectal cancer, and supplementation with the omega-3 fatty acid eicosapentaenoic acid can decrease the burden of polyps in familial adenomatous polyposis. However, randomized trials of modest dietary changes (10% less fat, 25 to 75% more fiber, 50% more fruits and vegetables) have not reduced the incidence of adenomas or colorectal cancers over 3 to 8 years of follow-up. It is possible that more prolonged dietary modification may be required to effect significant changes in the molecular events that mediate the development of adenomas and/or colorectal cancer.

PROGNOSIS

The overall prognosis for patients with colorectal cancer is mainly dependent on stage (Fig. 179-8), but up to 50% of patients who initially present with early-stage disease will recur with metastatic involvement. Five-year survival is approximately 90 to 95% for stage I disease and declines considerably to less than 10% for stage IV metastatic disease. The prognosis for stage III colorectal cancer can range from 65 to 70% for patients with only one or two lymph nodes and down to less than 25% for those with high-risk disease and more than four positive lymph nodes. Corresponding rates for rectal cancer are slightly inferior to those for colon cancer. In addition to stage, other factors that are associated with poorer outcomes in patients with early-stage colon cancer who undergo potentially curative resection include signet ring histology, high tumor grade, lymphovascular and perineural invasion, absence of host lymphoid response, evidence for obstruction or perforation preoperatively, high preoperative serum CEA levels, positive surgical margins, and microsatellite-stable disease.

Mucinous adenocarcinomas are associated with a worse overall prognosis than nonmucinous subtypes. By comparison, the medullary subtype has a relatively favorable prognosis.

Interestingly, the prognosis of colorectal cancers is not dependent on the size of the primary tumor. However, the location of the primary tumor is an important prognostic factor, with left-sided primary tumors associated with a significantly better prognosis compared with right-sided tumors. Moreover, the effect of tumor location is independent of other important clinical factors, including stage, race, and use of adjuvant chemotherapy.

Molecular biomarkers also correlate with the prognosis of all stages of colorectal cancer. *KRAS* mutations are present in 30 to 40% of colorectal cancer, and are associated with a worse prognosis. These mutations lead to constitutive

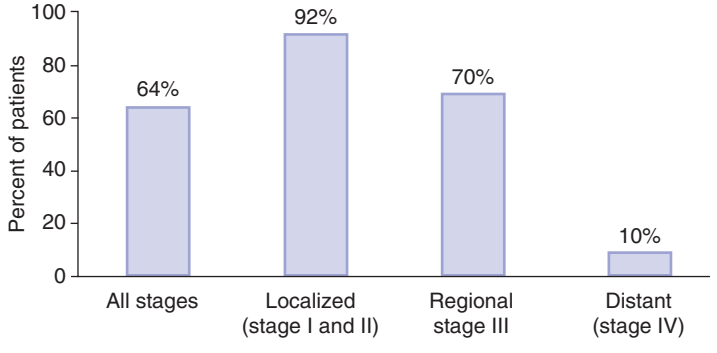

FIGURE 179-8. Five-year survival of colon cancer by disease stage.

activation of the RAS-RAF-MAPK signaling pathway downstream of EGFR, which render tumors resistant to anti-EGFR antibody therapy with cetuximab or panitumumab. *NRAS* mutations occur in only about 5% of colorectal cancer patients, and these mutations also confer resistance to anti-EGFR therapy. *BRAF* mutations, which are seen in 5 to 10% of colorectal cancer patients, are associated with poor prognosis and also predict resistance to anti-EGFR therapy.

More detailed molecular subtyping may be even more predictive. One approach groups colorectal cancers into four types—microsatellite instability immune, canonical, metabolic and mesenchymal—based on such profiling.

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180 PANCREATIC CANCER

DANIEL LAHERU

DEFINITION

More than 90% of pancreatic tumors are adenocarcinomas that arise from the ductal epithelium. Other major tumors of the pancreas include acinar cell, intraductal papillary mucinous neoplasm, mucinous cystic neoplasm, mixed histology, endocrine malignancies, carcinoid tumors, lymphomas, and a variety of rare sarcomas.

EPIDEMIOLOGY

Pancreatic ductal adenocarcinoma has one of the highest mortality-to-incidence ratios of any disease. Although it represents the tenth leading cause of cancer in the United States, it is the fourth leading cause of cancer-related deaths because most patients will die from their disease. By the year 2030, pancreatic cancer is expected to be the second leading cause of cancer-related death behind only lung cancer. Each year in the United States, approximately 50,000 individuals die from pancreatic adenocarcinoma or its complications.[1] The incidence of pancreatic cancer is slowly increasing based on the changing demographics of the U.S. population. In the United States, Blacks have a higher incidence and mortality from pancreatic cancer compared with Whites, although the incidence rate is not increasing as fast in Blacks as in Whites.[2] The risk of developing pancreatic adenocarcinoma increases with age, with a mean onset at age 71 years. The risk is equivalent in men and women, with an average lifetime risk for developing pancreatic adenocarcinoma of about 1 in 78. Globally, 70% of all pancreatic cancer cases occur in people living in advanced economies, with about 470,000 worldwide deaths in 2020.[3]

Smoking tobacco, as well as passive exposure to tobacco smoke in the environment, contributes significantly to the development of pancreatic adenocarcinoma and is also associated with a reduction in survival among patients with pancreatic cancer.[4] Occupational hazards that have been associated with an enhanced risk of developing pancreatic adenocarcinoma include exposure to chlorinated hydrocarbon solvents and heavy metals.

Most pancreatic adenocarcinoma cases are sporadic and occur without a history of the disease in first-degree relatives. Germline mutations in cancer susceptibility genes are commonly identified, even in patients without a significant family history of cancer.[5] Some pancreatic adenocarcinomas occur in association with other cancers or diseases, but most do not occur in association with a defined syndrome.

However, approximately 10% of pancreatic adenocarcinomas occur in families with a history of pancreatic adenocarcinoma.[6] In such families, the risk of developing pancreatic adenocarcinoma is increased seven-fold compared with the general population.[7] Premalignant cystic lesions of the pancreas also occur in families with pancreatic cancer. In addition to mutations of the *PALB2* gene in 3% of these families, mutations have also been identified in *ATM* or *BRCA2*, which are critical partners in the DNA damage repair pathway, as well as in *p16*.

Chronic pancreatic inflammation from alcohol misuse or genetic anomalies significantly increases the risk of being diagnosed with pancreatic adenocarcinoma. Pro-inflammatory cytokines contribute to the progression from premalignant lesion to advanced tumor.

New-onset insulin-dependent diabetes after age 50 years can be an indicator of pancreatic cancer.[8] Long-standing type 1 and type 2 diabetes mellitus may increase the risk of pancreatic adenocarcinoma. For example, the increase in obesity in the U.S. population and the concomitant increase in associated diabetes mellitus are strongly associated with an enhanced lifetime risk of developing pancreatic adenocarcinoma. Epidemiologic studies also note a relationship between type 3c diabetes (diabetes related to pancreatic disease and characterized by a severe deficiency of all glucoregulatory hormones) and the development of pancreatic adenocarcinoma. Patients with type 3c

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Most pancreatic adenocarcinoma cases are sporadic and occur without a history of the disease in first-degree relatives. Germline mutations in cancer susceptibility genes are commonly identified, even in patients without a significant family history of cancer.[5] Some pancreatic adenocarcinomas occur in association with other cancers or diseases, but most do not occur in association with a defined syndrome.

However, approximately 10% of pancreatic adenocarcinomas occur in families with a history of pancreatic adenocarcinoma.[6] In such families, the risk of developing pancreatic adenocarcinoma is increased seven-fold compared with the general population.[7] Premalignant cystic lesions of the pancreas also occur in families with pancreatic cancer. In addition to mutations of the *PALB2* gene in 3% of these families, mutations have also been identified in *ATM* or *BRCA2*, which are critical partners in the DNA damage repair pathway, as well as in *p16*.

Chronic pancreatic inflammation from alcohol misuse or genetic anomalies significantly increases the risk of being diagnosed with pancreatic adenocarcinoma. Pro-inflammatory cytokines contribute to the progression from premalignant lesion to advanced tumor.

New-onset insulin-dependent diabetes after age 50 years can be an indicator of pancreatic cancer.[8] Long-standing type 1 and type 2 diabetes mellitus may increase the risk of pancreatic adenocarcinoma. For example, the increase in obesity in the U.S. population and the concomitant increase in associated diabetes mellitus are strongly associated with an enhanced lifetime risk of developing pancreatic adenocarcinoma. Epidemiologic studies also note a relationship between type 3c diabetes (diabetes related to pancreatic disease and characterized by a severe deficiency of all glucoregulatory hormones) and the development of pancreatic adenocarcinoma. Patients with type 3c

ABSTRACT

Pancreatic cancer has one of the highest mortality-to-incidence ratios of any cancer. Risk factors for pancreatic cancer include cigarette smoking, a positive family history of pancreatic cancer, chronic pancreatitis, and diabetes mellitus (the latter having an unclear cause-and-effect relationship). The *KRAS* oncogene is mutated in more than 90% of pancreatic cancers. When a localized pancreatic cancer is suspected, a computed tomographic scan with oral and intravenous contrast and with thin cuts through the pancreas is the imaging modality of choice. Surgery followed by adjuvant chemotherapy offers the only chance to cure pancreatic cancer regardless of its stage. Neoadjuvant chemotherapy is commonly used even for patients whose disease appears to be resectable based on preoperative imaging criteria. For patients who present with metastatic cancer, chemotherapy can prolong survival.

KEYWORDS

pancreatic cancer
pancreatic ductal adenocarcinoma
cystic lesions of pancreas
adjuvant chemotherapy
low-molecular-weight heparin thromboprophylaxis

diabetes appear to have the highest associated risk of developing pancreatic adenocarcinoma, especially in the setting of coexisting chronic pancreatitis. Type 3c diabetes is also a consequence of pancreatic adenocarcinoma in approximately 30% of patients.

PATHOBIOLOGY

Pancreatic cancer is caused by inherited (germline) and acquired (somatic) mutations in cancer-causing genes. Oncogenes and tumor suppressor genes contribute to the growth of the tumor itself as well as to the surrounding microenvironment. A major advance in understanding the development of pancreatic cancer has been the appreciation that the majority of pancreatic adenocarcinomas progress sequentially from histologically normal ductal epithelium to low-grade pancreatic intraepithelial neoplasia, to high-grade pancreatic intraepithelial neoplasia, to invasive carcinoma. This process is associated with the accumulation of specific gene alterations (Fig. 180-1).

The *KRAS* oncogene, located on chromosome 12, is the most frequently mutated oncogene in pancreatic cancer in (>90% of tumors). It encodes a membrane-bound protein that has GTP-ase activity and is involved in signal transduction. When activated by mutation, typically a point mutation in codon 12, the functions of *KRAS* are independent of growth factor control, thereby leading to chronic activation of its downstream signaling partners (*PI3K*, *MAPK*, and *RAF*), the inhibition of apoptosis, the activation of the cell cycle, migration, angiogenesis, cytoskeletal remodeling, and unchecked proliferation. *KRAS* oncogenic dose variation plays an important role in pancreatic cancer tumorigenesis, progression, and metastasis.[9]

The tumor suppressor *CDKN2A/TP16*, which is a cell cycle control gene, is commonly inactivated in pancreatic cancer, with 80 to 95% loss of activity leading to increased cell cycle progression. *TP53* is activated by DNA damage to stop cell cycle progression and repair damaged DNA or initiate apoptosis. Mutations in this tumor suppressor gene are commonly found in 50 to 75% of pancreatic tumors. Inactivation of *SMAD4* (DPC4), which is involved in regulating cell cycle progression through the transforming growth factor (TGF)-β pathway, is observed in over 50% of pancreatic cancers and is associated with worse prognosis and the development of metastases. Inactivation of *RB1* (in <10% of pancreatic cancers) and *STK11* (responsible for Peutz-Jeghers syndrome) is also observed.

Several major signaling pathways are involved in pancreatic tumorigenesis. Hedgehog (Hh) signaling, critical in embryogenesis, regulates the cell cycle and apoptosis, aids in the formation of tumor stroma, and is often upregulated and abnormal in pancreatic cancers. The NOTCH pathway, which is also important in normal embryogenesis to prevent terminal differentiation of cells until appropriate, can be abnormally activated in pancreatic cancer, thereby allowing cells to remain in an undifferentiated state that contributes to tumor growth. When the Wnt pathway is activated, β-catenin is stabilized and migrates into the nucleus, where it activates its target genes. The epidermal growth factor receptor (EGFR), TGF-β, and JAK/STAT pathways are also abnormal in pancreatic cancer cells and lead to the promotion of cell growth, proliferation, differentiation, and survival. Epigenetic modification, the process by which gene expression is altered by mechanisms other than changes in the actual DNA sequence, also has a role in pancreatic cancer tumorigenesis.[10]

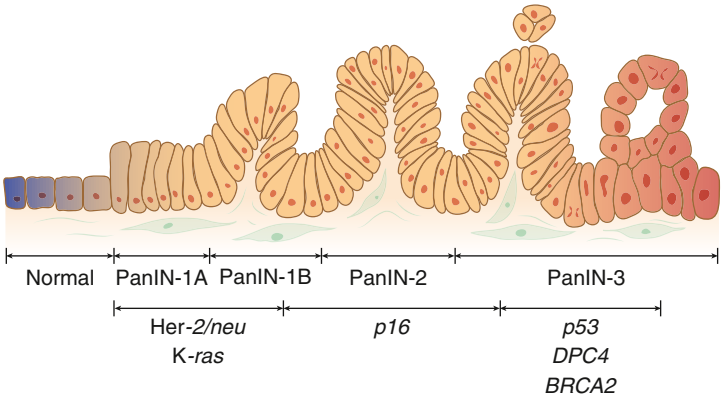

FIGURE 180-1. Genetic progression model of pancreatic adenocarcinoma. Molecular changes in the development of pancreatic ductal adenocarcinoma begin with early changes that include telomere shortening and development of mutations in *KRAS*; these are followed by loss of p16 function and expression of cyclin D1. Late changes include expression of p53 and loss of SMAD4/DPC4. PanIN = pancreatic intraepithelial neoplasia.

Shortening of telomeres and overexpression of microRNAs lead to chromosomal instability and dysregulation of gene expression, respectively.

In addition to cancer cells themselves, the tumor microenvironment is composed of stromal cells, inflammatory cells, and endothelial cells that all play a particularly important role in the growth of pancreatic cancer. Cancer cells secrete growth factors, including insulin-like growth factor (IGF)-1, fibroblast growth factor (FGF), TGF-β, vascular endothelial growth factor (VEGF), and platelet-derived growth factor (PDGF), that stimulate pancreatic stellate cells (also called myofibroblasts) to secrete excess amounts of extracellular matrix. In turn, the matrix and its stromal cells secrete cytokines and growth factors that promote the growth, invasion, and dissemination of cancer cells. This matrix also protects pancreatic cancer cells from apoptosis and generates a desmoplastic reaction that interferes with the delivery of chemotherapy to the tumor site. The local presence of TGF-β also leads to decreased activity of helper T-cells and thereby suppresses the body's immune reaction against pancreatic cancer cells.

CLINICAL MANIFESTATIONS

Many pancreatic tumors are asymptomatic when they are diagnosed by an imaging study obtained for an unrelated reason. The symptoms of early pancreatic adenocarcinoma are often subtle and include nonspecific gastrointestinal complaints (nausea, vague abdominal pain), fatigue, and weight loss of undetermined etiology. Epigastric pain and obstructive jaundice often prompt the initial diagnostic work-up of the biliary tree but are frequently late symptoms that are associated with advanced local or regionally disseminated disease. Because approximately 75% of pancreatic carcinomas are located in the head of the pancreas, clinical presentations are often related to compression or invasion of the biliary tree or pancreatic ducts. Deep or superficial venous thrombosis (Trousseau syndrome) is not infrequent, either early or late in the presentation of pancreatic adenocarcinoma. Observation of a palpably distended gallbladder (from obstruction of the distal common bile duct), or Courvoisier sign, is uncommon.

The laboratory abnormalities that accompany pancreatic adenocarcinoma at presentation include anemia and elevations of serum levels of bilirubin, alkaline phosphatase, and aminotransferases. A majority of patients eventually develop signs of obstructive jaundice as well as hyperglycemia, which reflects associated diabetes mellitus.

Early pancreatic intraepithelial neoplasia lesions are asymptomatic, and cystic lesions of the pancreas often remain asymptomatic. Some are discovered on abdominal imaging performed for other purposes, with some estimates that 2 to 15% of patients undergoing abdominal magnetic resonance imaging (MRI) may have unsuspected pancreatic cysts. Most small lesions do not cause symptoms and otherwise would remain undetected unless they later caused acute symptoms that would precipitate an abdominal computed tomographic (CT) scan. Large cysts may cause vague symptoms, but obstructive jaundice is uncommon. Most intraductal papillary mucinous neoplasms are asymptomatic, but some patients present with obstructive jaundice or with pancreatitis.

DIAGNOSIS

Differential Diagnosis

The differential diagnosis of pancreatic adenocarcinoma includes conditions that can present as a solid pancreatic mass, including acute (or an exacerbation of chronic) pancreatitis (Chapter 130), ampullary or distal cholangiocarcinomas (Chapter 181) with associated biliary obstruction and jaundice, and nonadenocarcinomatous cystic pancreatic neoplasms.

A high proportion of incidental cysts among patients without a history of pancreatitis are neoplastic. High-resolution CT may provide a presumptive diagnosis when characteristic features are present. MRI can identify any communication between the cyst and the pancreatic duct. Endoscopic ultrasonography can differentiate benign from malignant lesions if it finds a solid mass or invasive tumor.

Cystic Neoplasms

Cystic lesions of the pancreas can be categorized into non-neoplastic (e.g., pseudocysts; see Chapter 130) and neoplastic cystic lesions.[11] Cystic neoplasms can be subcategorized into mucin-producing and non-mucin-producing cystic neoplasms.[12] Cystic neoplasms that do not produce mucin include serous cystadenomas, which do not have increased risk of cancer, papillary cystic neoplasms, and cystic pancreatic neuroendocrine tumors.

Serous cystadenomas occur more commonly in women and are nearly always benign. Though usually asymptomatic, they can be symptomatic as

they enlarge. The pathology shows a well-circumscribed fibrous capsule containing numerous small fluid-filled cysts.

Mucinous cystic neoplasms, which nearly always occur in the pancreatic body or tail in women, comprise about 50% of pancreatic tumors removed in contemporary surgical series. About one third are discovered incidentally on radiographic imaging for other purposes, but patients also may present with pain, an abdominal mass, or weight loss. A thick fibrous capsule contains cysts lined by mucin-producing duct-like cells. About 30% of mucinous cystic neoplasms have evidence of invasive adenocarcinoma with a variable prognosis.

Intraductal papillary mucinous neoplasms are mucin-producing lesions that, unlike mucinous cystic neoplasms, communicate with the main pancreatic duct. Their intraductal dysplastic epithelium resembles colorectal villous adenomas, with papillae covered by columnar epithelium and the occasional goblet cell with extensive mucin production. These neoplasms often contain at least low-grade dysplasia and are always premalignant and require follow-up.

Imaging

A computed tomographic (CT) scan with oral and intravenous contrast and thin cuts through the pancreas is the imaging procedure of choice when pancreatic adenocarcinoma is suspected. CT scans can provide information regarding the presence of metastatic disease, vascular invasion, and potential for resection. Malignancy is more common when the cyst is greater than 3 cm, has a solid component, or is associated with a dilated pancreatic duct greater than 1 cm, but malignancy is less clearly associated with the rate of growth on serial imaging studies. Consensus recommendations[13] include MRI of pancreatic cysts identified on CT imaging; endoscopic ultrasonography and fine-needle aspiration for pancreatic cysts with concerning features on MRI; and cytologic and biomarker evaluation of aspirated fluid.[14]

Endoscopic ultrasound may provide additional information for preoperative assessment, including by guiding fine-needle aspiration biopsy. However, the typical desmoplastic reaction that can encase pancreatic adenocarcinomas increases the possibility of false-negative biopsy findings. Patients with locally advanced or metastatic disease should have their diagnosis confirmed pathologically by fine-needle biopsy of the primary site or of a metastasis.

Biomarkers and Screening

Analysis of cyst fluid can correctly identify up to 90% of pancreatic cysts that would not require surgery.[15] No serum- or tumor-based biomarkers or biomarker panels are both sensitive and specific enough for accurate early detection in clinical practice, but multianalyte blood tests that can detect and localize surgically resectable cancers, including pancreatic cancers, are promising.[16] CA19.9 is the most commonly used tumor biomarker for monitoring therapeutic progress in pancreatic adenocarcinoma, but the assay lacks specificity and cannot be used for early detection. Endoscopic ultrasound is useful for the evaluation of cystic lesions and permits sampling of cystic fluid for genetic markers associated with the development of pancreatic adenocarcinoma in cancer-prone families, as well as for cytologic studies. Some data suggest a potential benefit from annual screening using MRI, magnetic resonance cholangiopancreatography, or endoscopic ultrasound in asymptomatic adults who are carriers of the high-risk *CDNK2A* mutation.

TREATMENT

Pancreatic Cysts

Patients with pancreatic cysts that have concerning features (cyst ≥ 3 cm, a dilated main pancreatic duct > 1 cm, presence of an associated solid component or clinical symptoms such as jaundice) should be referred for fine-needle aspiration guided by endoscopic ultrasound. If the cytology is consistent with either high-grade dysplasia or invasive pancreatic cancer, these patients are commonly offered surgical resection (Table 180-1).[17] In contrast, patients whose features do not warrant resection should undergo MRI surveillance every 1 to 2 years for up to 5 years.[18]

Serous cystadenomas are benign abnormalities that do not connect to pancreatic ducts and warrant surgery only if symptomatic. Mucinous cystadenomas, which are precursors of pancreatic adenocarcinoma, are overtly malignant in 15% of patients and require surgical resection. Intraductal papillary mucinous neoplasms of the pancreas may contain malignant elements in about 40% of patients particularly in patients with concerning features, and should be removed surgically.

Pancreatic Cancer

Surgical Candidates

Surgery offers the only chance to cure pancreatic cancer.[19] Tumors are considered resectable if a clear fat plane is present around the celiac and superior mesenteric arteries and if the superior mesenteric and portal veins are patent. If the superior mesenteric vein and/or the portal vein is involved, that portion of the vein must be judged to be reconstructible. After surgery, the somatostatin analogue pasireotide (900 mg subcutaneously twice daily for 7 days beginning in the morning of surgery) may reduce the risk of a fistula leak with abscess. Unfortunately, tumor will recur in the majority of patients who undergo resection, including local recurrence in approximately 40% of patients.

Adjuvant and Neoadjuvant Therapy

Decisions regarding chemotherapy should be made in a multidisciplinary manner to achieve the most timely and coordinated therapy.[20] Participation in clinical research protocols should be encouraged.

Adjuvant therapy, typically started 1 to 2 months after surgery to allow the patient to recover from the complications associated with the underlying cancer as well as from the surgery itself, is indicated under expert oversight to decrease the risk and delay the onset of locoregional and metastatic recurrence. FOLFIRINOX (oxaliplatin, irinotecan, fluorouracil, and leucovorin) is the standard of care for patients who have a good performance status,[A1] but the rate of serious side-effects (including peripheral neuropathy) is higher compared with gemcitabine. If gemcitabine is chosen, adding capecitabine can increase survival by about 10 weeks.[A2] Another option for patients with resectable pancreatic cancers is neoadjuvant FOLFIRINOX or neoadjuvant nab-paclitaxel plus gemcitabine for 3 months preoperatively followed by 3 months postoperatively.[A3,A4]

Borderline Surgical Candidates

Neoadjuvant (presurgical) therapy can downstage 15 to 40% of borderline[A5] tumors, thereby allowing patients to undergo surgery with a higher likelihood of complete resection.[21] Neoadjuvant therapy also spares some patients the risks and stress of a complex surgical procedure, because rapidly developing metastatic disease may be detected by routine restaging following the completion of neoadjuvant treatment. Unfortunately, chemotherapy-resistant cancer can be demonstrated in 15 to 35% of patients initially considered for surgery in this setting.

The use of neoadjuvant treatment also guarantees that almost all patients will receive some form of chemotherapy or chemoradiation because they do not have any postoperative complications from which to recover. The chemoradiation component of neoadjuvant therapy also decreases local recurrence rates in patients who undergo surgery.

Local Recurrence

The complications associated with local recurrence include abdominal pain, risk for bowel obstruction, gastrointestinal bleeding, and recurrent biliary obstructions. Chemoradiation versus chemotherapy alone for locally advanced pancreatic cancer can decrease the risk for local recurrence but has not improved median survival compared with chemotherapy alone.[A6]

Unresectable or Metastatic Disease

First-line therapy for unresectable or metastatic pancreatic cancer is FOLFIRINOX or gemcitabine plus nab-paclitaxel (Table 180-2).[22] Nanoliposomal irinotecan in combination with fluorouracil and folinic acid extends survival with a manageable safety profile in patients with metastatic pancreatic adenocarcinoma who previously received gemcitabine-based therapy.[A7] Gemcitabine has also been combined with targeted therapies, such as the EGFR inhibitor erlotinib, but with a very modest improvement on overall survival.[23]

In the small percentage of patients with germline mutations in *BRCA1* or *BRCA2*, olaparib (300 mg twice daily) can prolong progression-free survival by about 3.5 months in patients who have been received a platinum-containing regimen for a minimum of 4 months and have been at least stable radiographically.[A8] In patients with KRAS G12C mutations, sotorasib is a promising experimental therapy.[24]

Thromboembolism

Advanced pancreatic cancer is associated with a high risk of venous thromboembolic complications. Current guidelines do not recommend routine thromboprophylaxis for all patients with active pancreatic cancer, but this prophylaxis

TABLE 180-1 GUIDELINES FOR ASYMPTOMATIC INCIDENTAL PANCREATIC CYSTS

CYST	MANAGEMENT STRATEGY
Either (a) a solid component and dilation of the main pancreatic duct of >5 mm or (b) suspicious EUS-guided FNA	EUS-guided FNA. Surgery if high-grade dysplasia or cancer, with follow-up MRI every 2 years after surgery; if benign, no follow-up required.
Size <3 cm, no solid component, no dilation of main pancreatic duct	MRI at 1, 3, and 5 years: if changes, EUS-guided FNA; if stable at 5 years, discontinue screening.

EUS = endoscopic ultrasound; FNA = fine needle aspiration; MRI = magnetic resonance imaging.
Vege SS, Ziring B, Jain R, et al. American Gastroenterological Association Institute guideline on the diagnosis and management of asymptomatic neoplastic pancreatic cysts. *Gastroenterology*. 2015;148:819-822.

TABLE 180-2 SELECTED METASTATIC PANCREATIC CANCER STUDIES

STUDY	CHEMOTHERAPY	MEDIAN SURVIVAL (MO)	1-YEAR SURVIVAL (%)
Burris (1997)* N = 126	5-FU vs. gem	4.4 vs. 5.6 ($P = .0025$)	2 vs. 18
Cunningham (2009)† N = 533	Gem ± capecitabine	7.4 vs. 6 ($P < .05$)	26 vs. 19
Conroy (2011)‡ N = 343	Gem v. FOLFIRINOX	6.8 vs. 11.1 ($P < .0001$)	17 vs. 36
Van Hoff (2013)§ N = 861	Gem ± nab-paclitaxel	8.5 vs. 6.7 ($P < .001$)	35 vs. 22 ($P < .001$)

*Burris H, Storniolo AM. Assessing clinical benefit in the treatment of pancreas cancer: gemcitabine compared to 5-fluorouracil. *Eur J Cancer*. 1997;33 Suppl 1:S18-S22.
†Cunningham D, Chau I, Stocken DD, et al. Phase III randomized comparison of gemcitabine versus gemcitabine plus capecitabine in patients with advanced pancreatic cancer. *J Clin Oncol*. 2009;27:5513-5518.
‡Conroy T, Desseigne F, Ychou M, et al. FOLFIRINOX versus gemcitabine for metastatic pancreatic cancer. *N Engl J Med*. 2011;364:1817-1825.
§Von Hoff DD, Ervin T, Arena FP, et al. Increased survival in pancreatic cancer with nab-paclitaxel plus gemcitabine. *N Engl J Med*. 2013;369:1691-1703.
5-FU = 5-fluorocil; FOLFIRINOX = combination chemotherapy with oxaliplatin, irinotecan, fluorouracil, and leucovorin; gem = gemcitabine; NR = not reported.

can be considered for patients who are at high risk.[25] Thromboprophylaxis with enoxaparin (Chapter 70) is feasible and effective.[A9] Another options is rivaroxaban (see Table 70-6).[A10]

Palliative Care

Because many patients suffer from biliary obstruction, diarrhea, pain, and malnutrition, palliative care (Chapter 3) can provide great benefit. Surgery can also play an important palliative role; patients whose tumors are unresectable may experience symptomatic improvement after a biliary or gastric bypass procedure, depending on the site of obstruction. Endoscopic placement of both biliary and duodenal stents may also improve pruritus, pain, or other complications of biliary tract obstruction. Palliative care for patients with pancreatic adenocarcinoma necessitates scrupulous attention to pain management (Chapter 26), often with a multidisciplinary approach, as well as maintenance of hydration and adequate nutrition.

Prevention

Even though premalignant intraductal papillary mucinous neoplasms or pancreatic mucinous neoplasms can be detected by imaging, screening is not currently recommended in asymptomatic adults.[26] However, consensus guidelines recommend that pancreatic cancer surveillance be considered for select high-risk individuals (based on family risk or germline mutation status) and that any evaluations should be conducted in a research protocol by experienced multidisciplinary teams.[27,28]

Prognosis

Among patients with a serous cystic neoplasm followed beyond 1 year, the size increases in about 40%, is stable in about 55%, and decreases in about 5%. Serous cystadenocarcinomas develop in only about 0.1% of patients at an average follow-up of 3 years.[29]

The overall 5-year survival for all patients with pancreatic cancer is less than 5%, because the cancer is advanced when clinically detected. Once patients are diagnosed, only 15 to 20% initially have resectable and potentially curable disease. In patients with early-stage disease, median survival has improved from 20 to 24 months to 54 months with adjuvant FOLFIRINOX. Patients with locally advanced (about 25 to 30% of patients at presentation) and metastatic (about 50 to 60% of patients at presentation) disease have median survivals of 8 to 14 months and 4 to 6 months, respectively. T-cell immunity has been linked to the exceptional outcome of the few long-term survivors, and neoantigen quality has been identified as a biomarker for immunogenic tumors.

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181 LIVER AND BILIARY TRACT TUMORS

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DEFINITION

Cancers arising from the liver and biliary tract include hepatocellular carcinoma, cholangiocarcinoma, and gallbladder adenocarcinoma, as well as other less common malignant histologies (E-Table 181-1, Fig. 181-1). Cholangiocarcinomas are further subclassified by their anatomic location along the biliary tract: intrahepatic (also known as peripheral) or extrahepatic, which includes hilar (also known as Klatskin tumors) and distal locations. These cancers collectively represent the third leading cause of cancer death worldwide and are rising in incidence.

The liver is also a frequent site of metastasis from other primary cancers. The diagnosis of liver tumors must distinguish metastatic disease from primary liver tumors.

EPIDEMIOLOGY

Hepatocellular Carcinoma

Hepatocellular carcinoma is the most common primary tumor of the liver and the third leading cause of cancer death worldwide.[1] It accounts for approximately 900,000 new cases and 830,000 deaths each year. More than 80% of hepatocellular carcinomas occur in developing countries (Fig. 181-2), owing to an increased prevalence of risk factors, particularly hepatitis B virus and hepatitis C virus (Chapter 134), but rates are also increasing in developed nations (E-Table 181-2).[2] Hepatitis B and hepatitis C viruses together account

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§Von Hoff DD, Ervin T, Arena FP, et al. Increased survival in pancreatic cancer with nab-paclitaxel plus gemcitabine. *N Engl J Med*. 2013;369:1691-1703.
5-FU = 5-fluorocil; FOLFIRINOX = combination chemotherapy with oxaliplatin, irinotecan, fluorouracil, and leucovorin; gem = gemcitabine; NR = not reported.

can be considered for patients who are at high risk.[25] Thromboprophylaxis with enoxaparin (Chapter 70) is feasible and effective.[A9] Another options is rivaroxaban (see Table 70-6).[A10]

Palliative Care

Because many patients suffer from biliary obstruction, diarrhea, pain, and malnutrition, palliative care (Chapter 3) can provide great benefit. Surgery can also play an important palliative role; patients whose tumors are unresectable may experience symptomatic improvement after a biliary or gastric bypass procedure, depending on the site of obstruction. Endoscopic placement of both biliary and duodenal stents may also improve pruritus, pain, or other complications of biliary tract obstruction. Palliative care for patients with pancreatic adenocarcinoma necessitates scrupulous attention to pain management (Chapter 26), often with a multidisciplinary approach, as well as maintenance of hydration and adequate nutrition.

Prevention

Even though premalignant intraductal papillary mucinous neoplasms or pancreatic mucinous neoplasms can be detected by imaging, screening is not currently recommended in asymptomatic adults.[26] However, consensus guidelines recommend that pancreatic cancer surveillance be considered for select high-risk individuals (based on family risk or germline mutation status) and that any evaluations should be conducted in a research protocol by experienced multidisciplinary teams.[27,28]

Prognosis

Among patients with a serous cystic neoplasm followed beyond 1 year, the size increases in about 40%, is stable in about 55%, and decreases in about 5%. Serous cystadenocarcinomas develop in only about 0.1% of patients at an average follow-up of 3 years.[29]

The overall 5-year survival for all patients with pancreatic cancer is less than 5%, because the cancer is advanced when clinically detected. Once patients are diagnosed, only 15 to 20% initially have resectable and potentially curable disease. In patients with early-stage disease, median survival has improved from 20 to 24 months to 54 months with adjuvant FOLFIRINOX. Patients with locally advanced (about 25 to 30% of patients at presentation) and metastatic (about 50 to 60% of patients at presentation) disease have median survivals of 8 to 14 months and 4 to 6 months, respectively. T-cell immunity has been linked to the exceptional outcome of the few long-term survivors, and neoantigen quality has been identified as a biomarker for immunogenic tumors.

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181 LIVER AND BILIARY TRACT TUMORS

ROBIN K. KELLEY AND ALAN P. VENOOK

DEFINITION

Cancers arising from the liver and biliary tract include hepatocellular carcinoma, cholangiocarcinoma, and gallbladder adenocarcinoma, as well as other less common malignant histologies (E-Table 181-1, Fig. 181-1). Cholangiocarcinomas are further subclassified by their anatomic location along the biliary tract: intrahepatic (also known as peripheral) or extrahepatic, which includes hilar (also known as Klatskin tumors) and distal locations. These cancers collectively represent the third leading cause of cancer death worldwide and are rising in incidence.

The liver is also a frequent site of metastasis from other primary cancers. The diagnosis of liver tumors must distinguish metastatic disease from primary liver tumors.

EPIDEMIOLOGY

Hepatocellular Carcinoma

Hepatocellular carcinoma is the most common primary tumor of the liver and the third leading cause of cancer death worldwide.[1] It accounts for approximately 900,000 new cases and 830,000 deaths each year. More than 80% of hepatocellular carcinomas occur in developing countries (Fig. 181-2), owing to an increased prevalence of risk factors, particularly hepatitis B virus and hepatitis C virus (Chapter 134), but rates are also increasing in developed nations (E-Table 181-2).[2] Hepatitis B and hepatitis C viruses together account

ABSTRACT

Malignancies arising from the liver parenchyma and biliary ductal epithelium are a heterogeneous group of cancers with generally poor prognosis. Risk factors include chronic liver injury from conditions such as viral hepatitis, alcohol, and nonalcoholic fatty liver disease, though some cases are idiopathic. These cancers collectively represent the third leading cause of cancer death worldwide and are rising in incidence. Hepatocellular carcinoma, the most common primary liver cancer that arises from the liver parenchyma, may be curable by surgery or transplantation if diagnosed at early stages. More advanced stages are treated with liver-directed therapies, such as chemoembolization, with systemic immunotherapy in combination with antiangiogenic therapy, or with multikinase inhibitors, (e.g., sorafenib, lenvatinib, regorafenib, and cabozantinib), all of which can prolong survival. Immunotherapy with the checkpoint inhibitors pembrolizumab or nivolumab alone or in combination with ipilimumab can provide durable tumor response.

Cholangiocarcinomas and gall bladder carcinomas arise from the biliary tract. These tumors, which are often complicated by biliary obstruction and infection, require multidisciplinary management. If diagnosed at early stages, biliary cancers sometimes can be cured by surgical approaches, but the risk of recurrence is high. Advanced or unresectable biliary cancers are treated with chemotherapy, with the combination of gemcitabine plus cisplatin as a standard first line regimen. Molecularly targeted therapies can benefit cholangiocarcinomas that harbor activating *FGFR2* translocations or mutations in *IDH1* or *BRAF*.

KEYWORDS

liver cancer
hepatobiliary cancer
hepatocellular carcinoma
cholangiocarcinoma
gall bladder cancer
bile duct cancer
biliary cancer

E-TABLE 181-1 PRIMARY MALIGNANT TUMORS OF THE LIVER AND BILIARY TRACT

TUMOR TYPE	APPROXIMATE ANNUAL INCIDENCE
Hepatocellular carcinoma	900,000 cases/yr worldwide*
Gallbladder carcinoma	220,000 cases/yr worldwide
Cholangiocarcinoma	10,000 cases/yr in United States†
Mixed hepatocellular-cholangiocarcinoma	Rare
Fibrolamellar hepatocellular carcinoma	Rare
Cystadenocarcinoma	Rare
Hepatic endothelioid hemangioendothelioma	Rare
Angiosarcoma and other sarcomas	Rare

*Includes cases of intrahepatic cholangiocarcinoma.
†Includes cases of gallbladder cancer and excludes cases of intrahepatic cholangiocarcinoma.

E-TABLE 181-2 RISK FACTORS FOR HEPATOCELLULAR CARCINOMA

RISK FACTOR	INCIDENCE OF HEPATOCELLULAR CARCINOMA*
Asian male HBV carriers over age 40	0.4-0.6%/yr
Asian female HBV carriers over age 50	0.3-0.6%/yr
HBV carrier with family history of HCC	Higher incidence than without family history
African/North American Blacks with HBV	HCC occurs at younger age
HBV carriers with cirrhosis	3-8%/yr
HCV cirrhosis	3-5%/yr
Stage 4 primary biliary cirrhosis	3-5%/yr
Hereditary hemochromatosis with cirrhosis	Unknown
α_1-Antitrypsin deficiency with cirrhosis	Unknown
Other-cause cirrhosis	Unknown

*Data from Marrero JA, Kulik LM, Sirlin CB, et al. Diagnosis, staging, and management of hepatocellular carcinoma: 2018 practice guidance by the American Association for the study of liver diseases. *Hepatology*. 2018;68:723-750.
HBV = hepatitis B virus; HCC = hepatocellular carcinoma; HCV = hepatitis C virus.
Modified from Marrero et al. Hepatology 2018;68:723-750.

for more than 80% of all hepatocellular carcinomas worldwide. Alcoholic cirrhosis is another classic predisposing factor.[3] However, nonalcoholic fatty liver disease has surpassed both viral hepatitis and alcoholic cirrhosis as the leading cause of hepatocellular carcinomas in the United States.[4]

Nonalcoholic fatty liver disease can lead to steatohepatitis, cirrhosis, and hepatocellular carcinoma.[5] When hepatocellular carcinoma develops in patients with nonalcoholic liver disease without preceding cirrhosis, it is more likely to present at an older age, with a larger tumor burden, and with higher rates of recurrent tumor compared with tumors that develop after patients already have cirrhosis.[6]

Hepatitis B virus is endemic in regions such as Asia and sub-Saharan Africa, and it can be vertically transmitted from mother to fetus in utero. Hepatitis C virus, which may be acquired by intravenous drug use or from blood transfusion (Chapter 134), is another important risk factor for hepatocellular carcinoma. In patients who have cirrhosis caused by hepatitis C virus, the estimated annual risk for developing hepatocellular carcinoma is 3 to 5% per year. Other risk factors for hepatocellular carcinoma include hepatitis D virus (which requires coinfection with hepatitis B virus to be pathogenic), hereditary hemochromatosis (Chapter 196), α_1-antitrypsin deficiency (Chapter 132), primary biliary cirrhosis (Chapter 141), autoimmune hepatitis (Chapter 135), male gender, and dietary exposure to fungal aflatoxins.

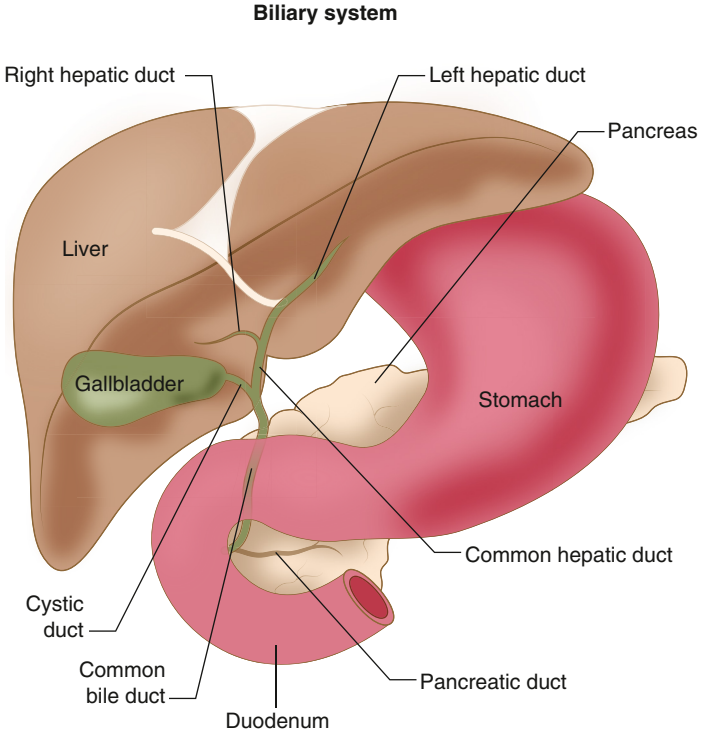

FIGURE 181-1. Anatomy of the liver and biliary tract. Hepatocellular carcinoma arises from liver parenchyma, and cholangiocarcinomas arise from the biliary ductal epithelium within (intrahepatic or peripheral) or outside of (extrahepatic) the liver. Tumors arising from the confluence of the right and left bile duct at the hepatic hilum are called hilar cholangiocarcinoma or Klatskin tumors.

Biliary Tract Cancers

Cholangiocarcinoma is the most common primary biliary tract malignancy and the second most common primary cancer of the liver after hepatocellular carcinoma. The incidence of intrahepatic cholangiocarcinoma appears to be increasing. Although most cases are sporadic, the risk for cholangiocarcinoma is increased in patients who have primary sclerosing cholangitis (Chapter 141), inflammatory bowel disease (Chapter 127), viral hepatitis (Chapter 135), congenital choledochal cysts or other structural abnormalities of the biliary tract, chronic pancreatitis (Chapter 130), obesity (Chapter 201), fluke infections (Chapter 326) and other causes of chronic cholangitis, bile duct adenomas, Caroli disease, and diabetes mellitus (Chapter 210).

Gallbladder adenocarcinomas are rare in the United States[7] but account for about 220,000 cases per year worldwide. The incidence varies geographically, with higher incidence rates reported in India and areas of South America and Asia. Risk factors for gallbladder adenocarcinoma include female gender, chronic cholelithiasis, chronic cholecystitis, history of gallbladder polyps, and abnormalities of the common bile duct (Chapter 141). Calcification of the gallbladder ("porcelain gallbladder") is often considered a risk factor, but it is only weakly associated with the development of cancer.

Other Primary Liver Cancers

Other primary tumors of the liver are much less common, with poorly understood risk factors. Chronic inflammatory conditions, including viral hepatitis, may be associated with the development of combined-histology liver tumors. Exposure to polyvinyl chloride has been implicated in the development of hepatic angiosarcomas. The fibrolamellar variant of hepatocellular carcinoma

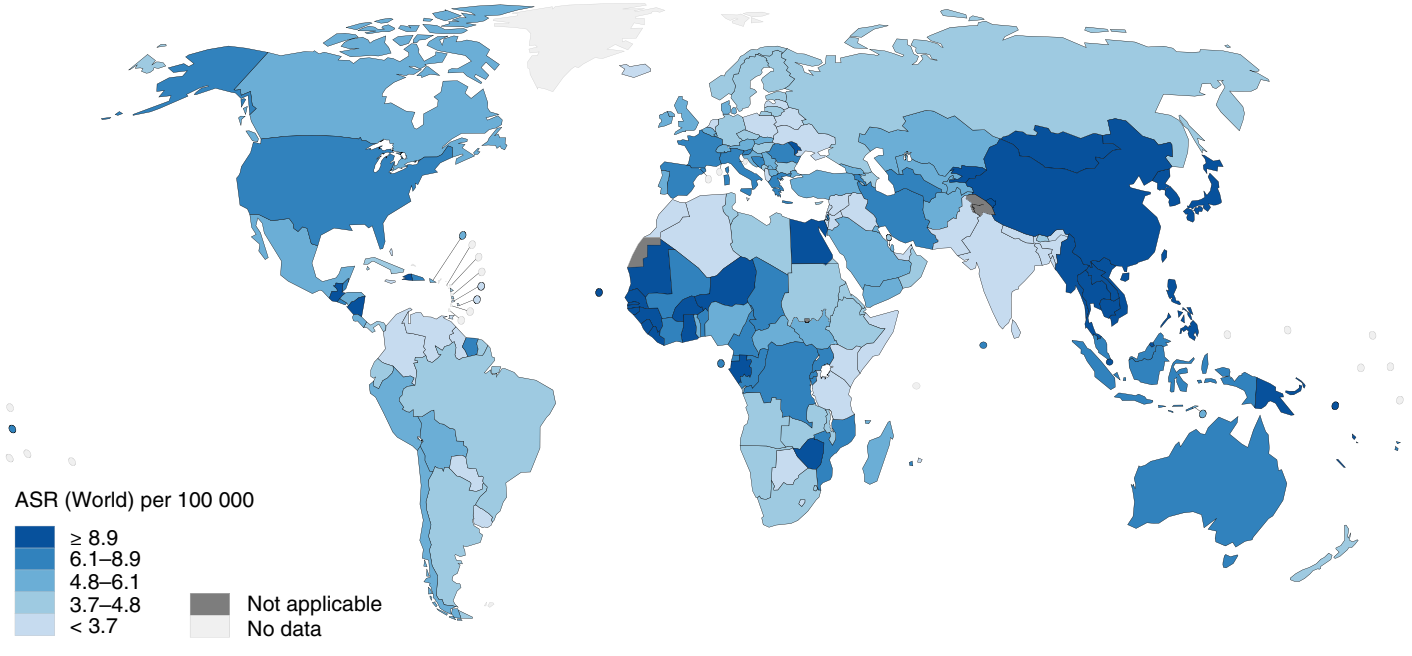

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Data source: GLOBOCAN 2020
Map production: IARC
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FIGURE 181-2. Estimated worldwide age-standardized incidence rates of liver cancer. The incidence rates are highest in Asia and parts of Africa.

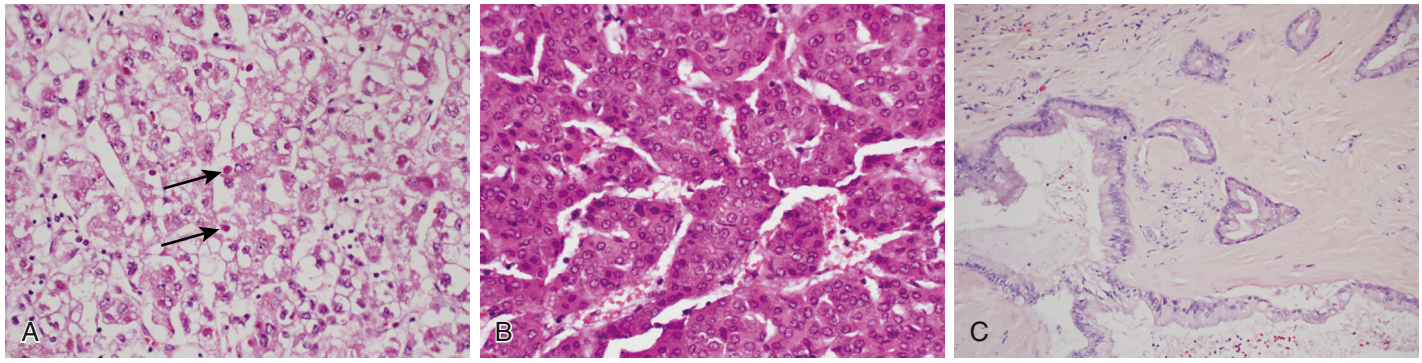

FIGURE 181-3. Histology of hepatocellular carcinoma and cholangiocarcinoma. A, Hepatocellular carcinoma (40×) with clear cell features and Mallory hyaline inclusions (*arrows*). **B,** Hepatocellular carcinoma (40×) with trabecular pattern and small cell change. **C,** Hilar cholangiocarcinoma (20×) with dense fibrous stromal reaction. (Courtesy Dr. Linda Ferrell, Department of Pathology, University of California, San Francisco.)

may occur more commonly in females. Hepatoblastoma tumors occur in infants and children, but almost never in adults.

PATHOBIOLOGY

Hepatocellular Carcinoma

Hepatocellular carcinoma is an epithelial neoplasm that arises from malignant transformation of liver hepatocytes (Fig. 181-3A and B). In the majority of cases, the pathogenesis of hepatocellular carcinoma is thought to be a multistep process triggered by underlying liver injury (such as from viral hepatitis, steatohepatitis, alcohol, iron overload, or exposure to aflatoxin). Subsequent inflammation, necrosis, regeneration, cell turnover, and proliferation[8] result in the progressive accumulation of genetic damage and somatic (acquired) mutations. Activation of oncogenes or inactivation of tumor suppressor genes, dysplasia, and subsequently carcinoma can arise. Promoter mutations that result in activation of the *TERT* gene, which encodes telomerase reverse transcriptase, are seen in approximately 45% of cases, inactivation of the tumor suppressor *TP53* is seen in about 30% of cases, and activation of the oncogene β-catenin (*CTNNB1*) gene is seen in about 25% of cases. Alterations in *Wnt*, cell cycle, and chromatin-remodeling pathways also have been described.

In hepatitis B-associated hepatocellular carcinoma, a unique mechanism of malignant transformation is direct integration of viral DNA into the host genome. This integration appears to favor specific loci, including activation of the *TERT* gene promoter.

Biliary Tract Cancers

Cholangiocarcinomas are a histologically diverse group of epithelial cancers that may arise from multiple different liver cell types, including biliary epithelial cells or hepatic progenitor cells, and are often surrounded by a dense stroma with cancer-associated fibroblasts (see Fig. 181-3C). Cholangiocarcinomas are associated with underlying inflammation and cholestasis, which activate growth factors and a proliferative response. Overexpression of *Notch1* and *AKT* has been implicated in a process by which hepatocytes are converted into the cholangiocytic precursors of intrahepatic cholangiocarcinoma. Molecular and genomic subtypes of biliary tract cancers can also be defined by mutational status and gene expression profiles.[9] For example, isocitrate dehydrogenase-1 (*IDH1*) gene mutations and fibroblast growth factor receptor-2 (*FGFR2*) gene fusions each occur in approximately 15% of intrahepatic cholangiocarcinomas.

CLINICAL MANIFESTATIONS

General Considerations

Liver masses, regardless of their cause, can be asymptomatic and may be detected during evaluation of abnormal liver chemistry tests (Chapter 133) or an imaging procedure obtained for an unrelated issue. In patients with known cirrhosis or other risk factors for hepatocellular carcinoma (see E-Table 181-2), an asymptomatic liver tumor also may be identified by surveillance imaging and/or monitoring of the serum alpha-fetoprotein (AFP) level.

Regardless of their histologic subtype, primary tumors of the liver can manifest with right upper quadrant pain, mass effect causing early satiety or obstructive symptoms, nausea, bleeding, and biliary obstruction. All of these tumors have metastatic potential, so they also can less commonly present with constitutional symptoms (e.g., weight loss, fevers, or night sweats) or signs or symptoms of metastatic disease (e.g., bone pain or a pathologic fracture). Paraneoplastic syndromes are rare in hepatobiliary cancers but can include the hypercalcemia of malignancy as well as erythrocytosis from the production of erythropoietin by tumor (Chapter 164).[10]

Hepatocellular Carcinoma

The clinical presentation of hepatocellular carcinoma can vary according to the extent of tumor and the degree of underlying liver dysfunction. Some patients may be asymptomatic, particularly when diagnosed by surveillance imaging and/or by an elevation in the AFP level. In cases with hepatic decompensation triggered by a growing tumor, patients present with symptoms of worsening liver function and portal hypertension (Chapter 139), including new ascites, encephalopathy, gastrointestinal bleeding, or jaundice, especially in the presence of associated portal vein thrombosis. In other cases, tumor involvement of the sensitive liver capsule can cause chronic progressive upper abdominal pain. The sudden onset acute pain suggests bleeding into the tumor or rupture. Constitutional symptoms such as cachexia, fatigue, and weight loss may be present with advanced stages.

On physical examination, patients with hepatocellular carcinoma may have an enlarged liver with tenderness, and a palpable mass lead to the diagnosis of hepatocellular carcinoma. A bruit may be auscultated over the liver surface, particularly with large and rapidly growing tumors. Ascites, jaundice, signs of portal hypertension (e.g., caput medusae and splenomegaly), and asterixis may be variably present if hepatic function has decompensated. The AFP level is elevated in approximately 70% of cases but is not diagnostic.

Biliary Tract Cancers

Extrahepatic cholangiocarcinomas most often manifest with signs and symptoms of biliary obstruction, such as jaundice, pruritus, pale stools, dark urine, anorexia, nausea, and weight loss. Intrahepatic cholangiocarcinomas can also cause obstruction, but generally only when extensive disease is present. Less commonly, complications such as biliary fistulas and hemobilia can occur.

Gallbladder cancers are often diagnosed incidentally during cholecystectomy, but some cases can be associated with right upper quadrant pain, biliary colic, or a tender and palpable mass. Biliary obstruction can lead to infections of the biliary tract (cholangitis), with symptoms including right upper quadrant pain, fever, chills, nausea, vomiting, and jaundice (Chapter 141). Cholangitis can lead to complications such bacteremia (most commonly with gram-negative enteric pathogens), sepsis, and abscess formation.

DIAGNOSIS

General Considerations

The approach to patients with a liver mass requires assessment of risk factors and extent of any underlying liver disease. The diagnostic evaluation, staging, and treatment options are guided by whether underlying liver disease is present as well as by its extent. The differential diagnosis for hepatocellular carcinoma and biliary tract cancers includes benign liver lesions (such as hemangiomas, adenomas, abscesses, and regenerative nodules), malignant tumors of other primary liver histologies, mixed-histology tumors, and metastatic disease.

Hepatocellular Carcinoma

Whether the patient has an asymptomatic liver mass or has a mass discovered because of symptoms, it must be evaluated promptly (see Fig. 132-6). Hepatocellular carcinoma is unique in oncology in that a diagnosis can be made radiographically without tumor tissue sampling in the appropriate clinical

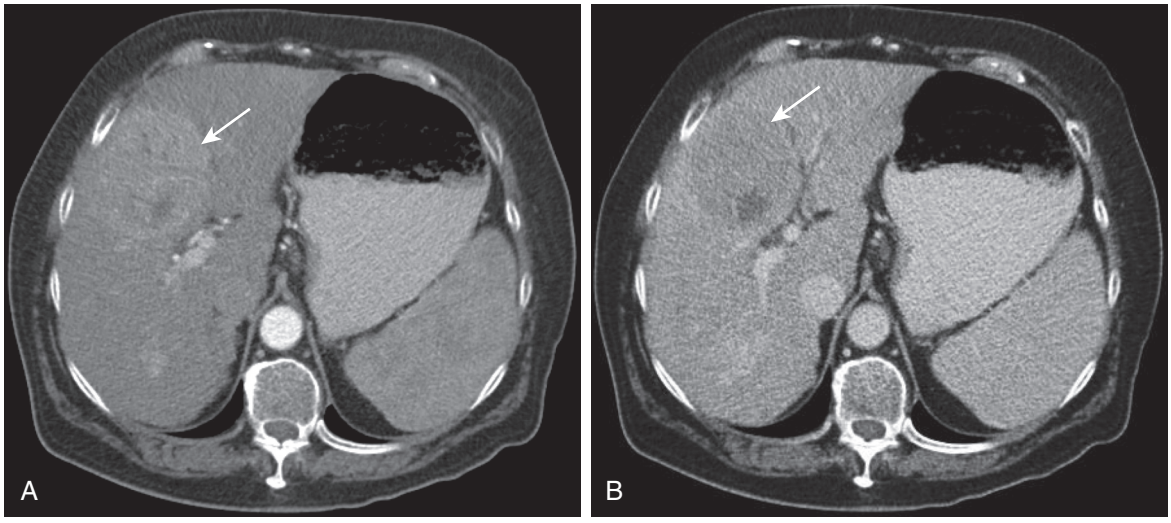

FIGURE 181-4. Imaging of hepatocellular carcinoma. In this contrast-enhanced computed tomography scan of the liver of a patient with hepatocellular carcinoma, a tumor in the right hepatic lobe demonstrates arterial phase enhancement (*arrow*, **A**) followed by "wash-out" in the portal venous phase (*arrow*, **B**). The bright arterial enhancement of hepatocellular carcinoma lesions on contrast-enhanced imaging studies is due to the propensity of this tumor to parasitize blood supply from the hepatic artery, whereas the normal hepatic parenchyma derives the majority of its blood supply from the portal vein.

context.[11] For the diagnostic evaluation of liver tumors, either magnetic resonance imaging (MRI) or computed tomography (CT) with multiple phases of contrast administration (including arterial, portal venous, and delayed phases) is recommended. In patients with risk factors for hepatocellular carcinoma (see E-Table 181-2), a nodule of at least 1 cm featuring arterial phase enhancement with decreased enhancement during the portal venous phase of contrast (known as "washout") is sufficient for a radiographic diagnosis (Fig. 181-4A and B).

A biopsy is warranted to confirm the diagnosis of hepatocellular carcinoma if diagnostic imaging criteria are not met. Because of the rare risk of seeding tumor along the needle track, biopsy should be performed at an expert center. When the first biopsy is inconclusive in patients whose liver nodules were found during the follow-up for chronic liver disease (e.g., fibrosis or no definitive focal lesion), a second biopsy of a suspicious lesion is indicated because its yield is as high as for the first biopsy.[12] An elevated AFP level is not sufficiently sensitive or specific for the diagnosis of hepatocellular carcinoma in cirrhotic patients with a liver mass.

Once a patient has been radiographically and/or pathologically diagnosed with hepatocellular carcinoma, the staging for extent of disease requires cross-sectional imaging of the chest, abdomen, and pelvis; an AFP measurement; and a bone scan if symptoms or signs of bone metastases (such as bone pain or markedly elevated alkaline phosphatase value) are present. Staging of hepatocellular carcinoma also requires a thorough assessment of underlying liver function, which affects prognosis and treatment options independent of the extent of the tumor.

Biliary Tract Cancers

For the diagnosis of biliary tract cancers, endoluminal approaches, such as by endoscopic retrograde cholangiopancreatography (ERCP) cytologic brushing or endoscopic ultrasound fine-needle aspiration, are preferred in patients whose early-stage disease may be amenable to curative surgery or transplantation. Cholangiography (by ERCP or magnetic resonance cholangiogram) may be indicated for both diagnostic and therapeutic purposes (such as stent placement), particularly if biliary obstruction is present. Staging of biliary tract and other rarer types of liver cancer generally includes cross-sectional imaging of the chest, abdomen, and pelvis. A mass in the gallbladder fossa suggests primary gallbladder cancer. Unlike hepatocellular carcinoma, cholangiocarcinomas characteristically display progressive enhancement during the portal venous phase of contrast imaging (Fig. 181-5). Biliary obstruction and ipsilateral hepatic lobe atrophy and contralateral hypertrophy may be present and can sometimes obscure identification of the actual tumor mass.

For biliary tract cancers, CA-19-9 and carcinoembryonic antigen (CEA) tumor markers may be elevated and can help to monitor response to treatment, although levels can be confounded if biliary obstruction and hyperbilirubinemia are present. Upper and lower endoscopy are indicated to exclude metastatic disease in patients who are diagnosed with likely intrahepatic cholangiocarcinoma, which otherwise can be difficult to discriminate from metastatic disease radiographically and histologically. Diagnostic laparoscopy should be considered to exclude peritoneal disease before undertaking a laparotomy for curative resection in patients with newly diagnosed gallbladder adenocarcinoma and cholangiocarcinoma because imaging may not detect peritoneal metastases, which would affect surgical decision making.

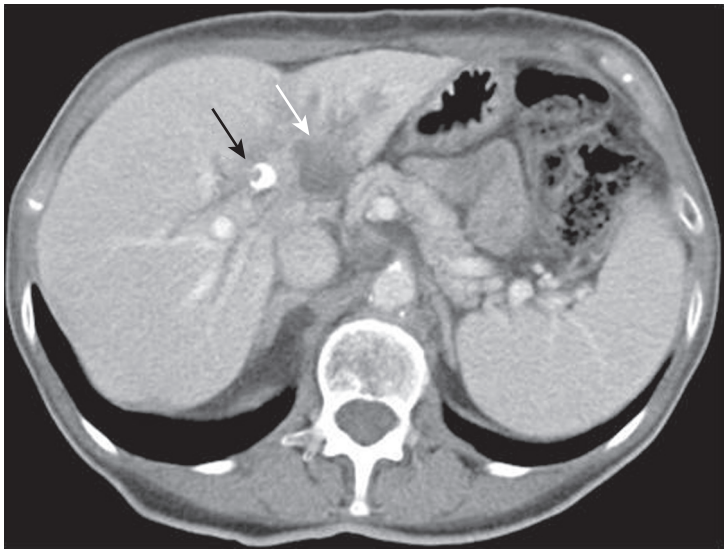

FIGURE 181-5. Imaging of cholangiocarcinoma. This computerized tomography image with contrast in portal venous phase depicts an infiltrative hilar cholangiocarcinoma (Klatskin tumor) extending into the left hepatic lobe (*white arrow*) with an endobiliary stent in place (*black arrow*).

TREATMENT

General Considerations

The treatment of patients with hepatobiliary cancers requires management of underlying liver disease or obstruction as well as the tumor itself. In patients with active hepatitis B virus infection or prior exposure, close monitoring of liver function and viral load is advisable; antiviral therapy (Chapter 135) may be required to prevent reactivation, which can occur with immunosuppressive therapy (Chapter 29). Management of liver tumors in patients with cirrhosis may necessitate treatment for complications of portal hypertension or liver dysfunction (Chapter 139). In patients with biliary tract cancers, biliary obstruction (Chapter 141) is a common complication that often requires endoscopic stent placement, percutaneous drainage, or antibiotic therapy if cholangitis develops. The doses of chemotherapy agents and of medications used for supportive care may require adjustment depending on the degree of liver dysfunction.

Hepatocellular Carcinoma

Surgery and Ablation

The treatment of early stages of hepatocellular carcinoma depends on the degree of liver dysfunction.[13] In patients who have localized hepatocellular carcinoma and preserved liver function without significant portal hypertension, surgical resection can be curative, with 5-year survival rates of approximately 60 to 80% in carefully selected patients. Among patients who have increasing degrees of portal hypertension, however, surgical outcomes are significantly poorer. For individuals with contraindications to surgery or inadequate projected future function of the liver remnant, ablation of small tumors (by radiofrequency, microwaves, or ethanol injection) can provide long-term control and is sometimes curative. Adjuvant systemic therapy does not improve outcomes after surgery or ablation for hepatocellular carcinoma.

If patients have one lesion 5 cm or smaller or up to three lesions 3 cm or smaller each without any evidence of vascular involvement or extrahepatic spread, and are not candidates for resection because of the tumor's location or inadequate hepatic reserve, orthotopic liver transplantation (Chapter 140) can provide long-term survival similar to that of patients undergoing transplantation for cirrhosis without cancer. Patients who have larger tumors may be accepted for transplantation at selected centers, often accompanied by liver-directed treatments such as embolization or ablation to control the tumor burden while awaiting transplant.

Embolization

When the hepatocellular carcinoma tumor burden exceeds criteria for transplantation or surgery but remains limited to the liver, liver-directed therapies can delay progression and prolong survival but are not likely to be curative. Transarterial chemoembolization, which delivers embolic material usually mixed with chemotherapeutic agents[A1] via arterial catheters directly to vascular tumors within the liver (Fig. 181-6), can prolong survival in patients who have intermediate-stage hepatocellular carcinoma. Radioembolization using yttrium-90 bound to glass or resin microspheres is another option.

Systemic Therapy for Advanced Disease

For patients with more advanced stage hepatocellular carcinoma, conventional cytotoxic chemotherapy agents do not improve survival. The combination of atezolizumab (a programmed death [PD]-L1 immune checkpoint inhibitor) and bevacizumab (a VEGF inhibitor) under expert supervision significantly improves progression-free survival, overall survival, and quality of life compared with sorafenib,[A2] which was the prior standard of care. As a result, it has become the standard of care for advanced hepatocellular carcinoma in patients with Child-Turcotte-Pugh A liver function (see Table 139-2).[14] Sorafenib also can significantly prolong survival, but tumors shrink in fewer than 5% of patients. Lenvatinib (a multikinase inhibitor that targets VEGFR and fibroblast growth factor receptors) is not inferior to sorafenib.[A3] The addition of other targeted therapies or chemotherapy to sorafenib has not improved outcomes over sorafenib monotherapy.

After progression on first-line therapy, the multikinase inhibitors regorafenib and cabozantinib improve survival compared with placebo.[A4,A5] The vascular endothelial growth factor receptor 2 inhibitor, ramucirumab, alco can improve survival in patients who have an elevated alpha-fetoprotein tumor marker greater than 400 ng/mL.[A6]

Monotherapy with either pembrolizumab and nivolumab can provide a durable objective tumor response in 15 to 20% of patients but has not improved overall survival.[15] The combination of nivolumab plus the ipilimumab can achieve objective responses in over 30% of patients,[16] but its impact on survival has not been established.

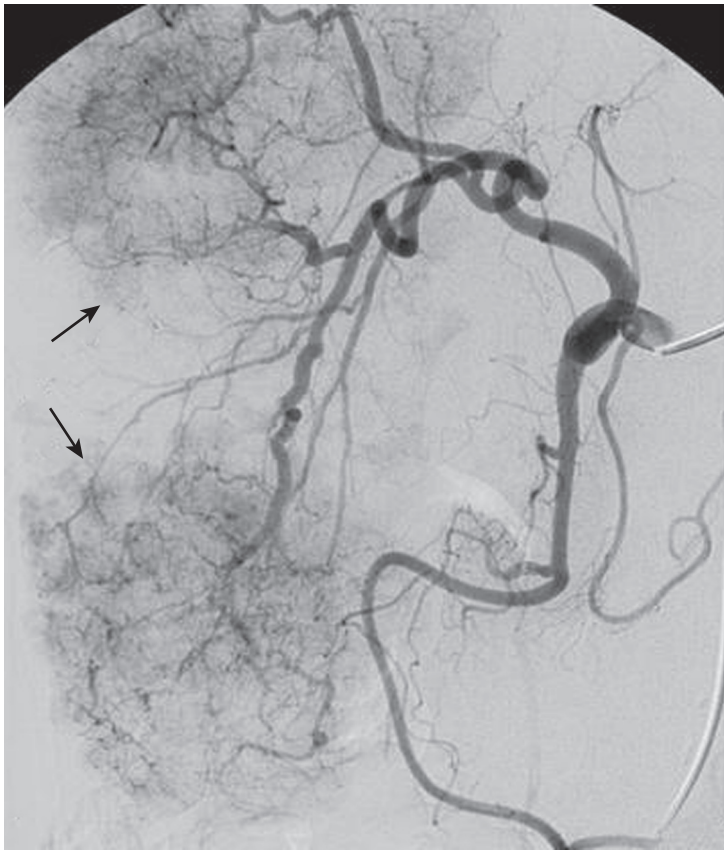

FIGURE 181-6. Transarterial chemoembolization of hepatocellular carcinoma. This common hepatic artery angiogram from a 42-year-old woman with hepatitis B shows two distinct areas of "tumor blush" corresponding to underlying hepatocellular carcinoma lesions (*arrows*) that were treated by transarterial chemoembolization. (Courtesy Dr. Nicholas Fidelman, Department of Interventional Radiology, University of California, San Francisco.)

Biliary Tract Cancers

Surgery

Surgical resection is the definitive therapy for patients with localized biliary tract cancers,[17,18] including gallbladder cancer.[19] For patients with distal cholangiocarcinoma, a Whipple pancreaticoduodenectomy may be required. Liver transplantation for early-stage hilar cholangiocarcinoma after neoadjuvant chemotherapy and/or chemoradiation may be an option at certain centers in highly selected patients.

For gallbladder cancer, cholecystectomy with en bloc hepatic resection and porta hepatis lymphadenectomy is recommended for patients with a gallbladder mass identified preoperatively on imaging or intraoperatively. A staging laparoscopy may be performed in advance to exclude occult peritoneal carcinomatosis. For patients with early-stage gallbladder cancer diagnosed incidentally on review of surgical pathologic findings after a cholecystectomy performed for benign causes, patients with tumors invading no deeper than the lamina propria (T1a) and negative surgical margins may be treated with observation only. If tumor invasion extends to the muscular layer (T1b) or beyond, patients should be referred to a specialized center for consideration of additional hepatic resection and lymphadenectomy.

Other Therapies

For patients with cholangiocarcinoma and gallbladder cancers, adjuvant chemotherapy, radiation, or chemoradiation can improve survival rates after surgical resection.[20] For example, the addition of adjuvant capecitabine for 6 months significantly prolongs overall survival and recurrence-free survival following resection of cholangiocarcinoma or gallbladder cancer and has become a standard adjuvant option.[A7]

In patients with advanced biliary tract cancers not amenable to resection, the addition of the immune checkpoint inhibitor durvalumab to combination chemotherapy (gemcitabine plus cisplatin) improves survival compared with chemotherapy alone.[A8] After progression on gemcitabine plus cisplatin chemotherapy, the combination of 5-fluorouracil plus oxaliplatin (FOLFOX) can improve survival compared with supportive care.[A9] Genomically targeted therapies, including *IDH1* and *FGRFR2* inhibitors, have shown benefit for mutation-defined subsets. For example, the IDH1 inhibitor ivosidenib improves progression-free survival in patients whose cholangiocarcinomas harbor *IDH1* mutations.[A10] The FGFR inhibitors pemigatinib and infigratinib can provide durable responses in patients whose cholangiocarcinomas are positive for *FGRF2* fusion.[21] For the rare subset of patients whose cholangiocarcinomas are mismatch repair (MMR) pathway–deficient, pembrolizumab can provide durable responses and prolongs survival.[22]

End-of-Life Care

Palliative care and end-of-life care (Chapter 3) play an integral role in management of patients who have primary hepatobiliary cancers because most patients progress and succumb to their cancer or to complications within a relatively short period of time. Palliative care specialists and social workers provide important ancillary services in the end-of-life care for patients with hepatobiliary cancers. Referral to hospice care (Chapter 3) may be appropriate when patients have progressed on standard anticancer therapies and/or are ineligible for further anticancer therapy because of extent of disease, liver dysfunction, poor performance status, or patient preferences.

As with most advanced cancers, pain control (Chapter 26), treatment of nausea (see Table 118-5) and constipation (see Table 122-3), and family and social support are essential. Pain management in patients with prior or active substance abuse disorder (Chapter 365) may be complicated by tolerance and/or dependency. In some cases, patients and caregivers may require providers' reassurance before using opiates or other analgesics for pain control because of

concerns about addiction. Bone metastases may require palliative radiation or stabilization procedures. Patients with advanced stages of hepatobiliary cancers, particularly hepatocellular carcinoma, are also at risk for developing complications of end-stage liver disease, such as intractable ascites, jaundice, pruritus, encephalopathy, infections, and gastrointestinal bleeding (Chapter 121). Diuretic therapy, therapeutic paracentesis, and endoscopic management of gastrointestinal bleeding may be required. In biliary tract cancers, biliary obstruction and recurrent cholangitis also may require endoscopic or percutaneous biliary drainage (Chapter 141)[23] and antibiotic therapy for palliation.

In the United States, hepatocellular carcinoma is associated with a high incidence of health disparities (Chapter 4) related to immigrant status, being a member of racial or ethnic minority, and lower socioeconomic status. Clinicians must have an awareness of cross-cultural issues surrounding disclosure of diagnosis, pain control, use of alternative therapies, and end-of-life care.

PREVENTION

Screening and surveillance for hepatocellular carcinoma is associated with improved outcomes in selected populations with cirrhosis,[24] but routine screening and surveillance remains controversial even for high-risk populations. Hepatitis B virus vaccination and treatment programs (Chapters 134 and 135) can reduce the incidence of hepatocellular carcinoma. Treatment of chronic hepatitis C infection my reduce the risk of hepatocellular cancer by about one-third, but the risk still appears to be perhaps 20-fold higher than in the general population. Prevention and treatment of alcohol-related disorders, obesity, and other conditions associated with nonalcoholic fatty liver disease are appropriate measures to mitigate risk factors and to minimize ongoing liver injury, but prospective evidence regarding any reduction in the risk of cancer is limited. Some data suggest that low-dose aspirin can significantly lower the risk of hepatocellular carcinoma and liver-related mortality in patients with chronic viral hepatitis.[25]

Limited evidence to support preventive measures or screening for biliary tract cancers. Patients who have primary sclerosing cholangitis (Chapter 141) are at increased risk for cholangiocarcinoma. Periodic screening by noninvasive imaging and serum CA-19-9 marker measurements may be considered, but supporting data are limited.

PROGNOSIS

The prognosis of patients with hepatocellular carcinoma and biliary tract cancers is generally poor. For patients with hepatocellular carcinoma or intrahepatic cholangiocarcinoma, the overall 5-year survival rate across stages is approximately 20%. Hepatocellular carcinomas associated with steatohepatitis and alcoholic liver disease have a similar clinical course, even though the characteristic features underlying these two diseases are different.

For the minority of patients whose hepatocellular carcinomas or intrahepatic cholangiocarcinomas are diagnosed at a localized stage of disease, the 5-year relative survival rate approaches 30%, but 5-year cause-specific survival rates generally approximate or exceed 60% when patients with early stages of disease undergo curative ablation, surgery, or transplantation. For patients who are diagnosed with metastatic hepatocellular carcinoma or cholangiocarcinoma, the 5-year survival rate is less than 5%, and the median overall survival is less than 1 year.

For patients with gallbladder adenocarcinoma, the overall 5-year survival rate ranges from approximately 50% for patients who have stage I tumors to less than 5% for patients who have metastatic disease. The rate of metastatic recurrence is high even among patients who have resectable gallbladder carcinoma. The prognosis of patients with rarer types of primary liver cancers such as fibrolamellar hepatocellular carcinoma, hepatic endothelioid hemangioendothelioma, or hepatic angiosarcoma is highly variable.

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182 TUMORS OF THE KIDNEY, BLADDER, URETERS, AND RENAL PELVIS

DEAN F. BAJORIN

RENAL CELL CARCINOMA

DEFINITION

Cancers of the kidney are a heterogeneous group of neoplasms, the majority of which are of epithelial origin and malignant. Renal cell carcinoma, classically referred to as clear cell carcinoma or hypernephroma, is not a single malignancy. Rather, renal cell carcinoma comprises a group of distinguishable entities (Table 182-1), each with a strong relationship between its morphologic and genetic features.[1] The metastatic potential depends on the histologic subtype and ranges from the most virulent conventional clear cell carcinomas (65% of total tumors but accounting for 90% of the metastases), to the more indolent papillary and chromophobe carcinomas (25% of the total but only 10% of the metastases), and to the benign oncocytomas (10% of all tumors).

EPIDEMIOLOGY

Over 75,000 new tumors of the kidney and renal pelvis are diagnosed in the United States annually, and they result in approximately 14,000 deaths each year. These cancers represent the sixth most common form of cancer in men and the ninth most common in women. The increase in incidence of renal cell cancers may be in part related to early detection as a consequence of computed tomography (CT) and magnetic resonance imaging (MRI) of the abdomen for other medical conditions. The ratio of males to females is approximately 2 : 1 to 3 : 1, and the incidence is highest in Black Americans and lowest in Asians and Pacific Islanders. The mean age at diagnosis is in the sixth to seventh decade of life. Aside from genetic predisposition, risk factors associated with renal cell carcinoma include cigarette smoking, obesity, hypertension, and the use of diuretics.[2] Obese persons have an increased risk for renal cell carcinoma, and the risk rises with increasing body mass index. The elevated risk associated with diuretic use is difficult to distinguish from the increased risk associated with hypertension. Renal cell carcinoma is more prevalent in patients with pre-existing renal injury,[3] such as polycystic kidney disease (Chapter 112), horseshoe kidney (Chapter 113), and chronic renal failure requiring hemodialysis (Chapters 116 and 117).

PATHOBIOLOGY

Renal Cell Carcinoma

Clear cell renal cell carcinoma constitutes approximately 65% of renal tumors (Table 182-2) and is believed to be derived from the proximal convoluted tubule. It is generally solitary and well circumscribed, with a golden yellow color that results from the abundant cytoplasmic lipid. Higher-grade tumors

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182 TUMORS OF THE KIDNEY, BLADDER, URETERS, AND RENAL PELVIS

DEAN F. BAJORIN

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Over 75,000 new tumors of the kidney and renal pelvis are diagnosed in the United States annually, and they result in approximately 14,000 deaths each year. These cancers represent the sixth most common form of cancer in men and the ninth most common in women. The increase in incidence of renal cell cancers may be in part related to early detection as a consequence of computed tomography (CT) and magnetic resonance imaging (MRI) of the abdomen for other medical conditions. The ratio of males to females is approximately 2 : 1 to 3 : 1, and the incidence is highest in Black Americans and lowest in Asians and Pacific Islanders. The mean age at diagnosis is in the sixth to seventh decade of life. Aside from genetic predisposition, risk factors associated with renal cell carcinoma include cigarette smoking, obesity, hypertension, and the use of diuretics.[2] Obese persons have an increased risk for renal cell carcinoma, and the risk rises with increasing body mass index. The elevated risk associated with diuretic use is difficult to distinguish from the increased risk associated with hypertension. Renal cell carcinoma is more prevalent in patients with pre-existing renal injury,[3] such as polycystic kidney disease (Chapter 112), horseshoe kidney (Chapter 113), and chronic renal failure requiring hemodialysis (Chapters 116 and 117).

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Renal Cell Carcinoma

Clear cell renal cell carcinoma constitutes approximately 65% of renal tumors (Table 182-2) and is believed to be derived from the proximal convoluted tubule. It is generally solitary and well circumscribed, with a golden yellow color that results from the abundant cytoplasmic lipid. Higher-grade tumors

ABSTRACT

Cancers of the kidney, ureters, and bladder include a broad spectrum of cancers with marked differences in etiology, cell of origin, surgical management, systemic therapy, and clinical outcomes. Clear cell cancer is the most common tumor that arises in the kidney. Urothelial cancer is the most common malignancy arising in the bladder, renal pelvis, ureters, and urethra. All stage 1 renal and urothelial cancers are characterized by very favorable cure rates when managed by either surgery alone or, in the case of bladder cancer, additional medications instilled directly in the bladder. Organ preservation approaches have been used in selected cases of both primary kidney and bladder cancers, either by partial nephrectomy for kidney cancer or trimodality therapy consisting of cystoscopic resection, radiation, and chemotherapy for bladder tumors. The management of stage 2 and 3 renal cell and urothelial cancer frequently includes both surgery and systemic treatment, such as adjuvant immunotherapy or tyrosine kinase inhibitor treatment for kidney cancer and either neoadjuvant or adjuvant chemotherapy or immunotherapy for urothelial cancers of the bladder, ureter, and renal pelvis. Systemic treatment with immunotherapy and tyrosine kinase inhibitors improves the clinical outcomes of patients with stage 4 kidney cancer and can sometimes achieve long-term cures. Multiagent chemotherapy and immunotherapy using checkpoint blockade inhibitors, both of which have demonstrated potential curability of metastatic disease, are standard treatments for urothelial cancers.

KEYWORDS

renal cell cancer
clear cell cancer
urothelial cancer
bladder cancer
upper tract urothelial cancer

TABLE 182-1 CLASSIFICATION OF RENAL CELL TUMORS ACCORDING TO THE 2016 WHO CLASSIFICATION

CURRENT RENAL CELL TUMOR SUBTYPES
Clear cell (conventional) renal cell carcinoma* (65-70%)
Papillary (chromophil) renal cell carcinoma* (15-20%)
Chromophobe renal cell carcinoma* (5-7%)
Collecting duct carcinoma*
Renal medullary carcinoma*
Mucinous tubular and spindle cell carcinoma*
RCC, unclassified*
Oncocytoma
Papillary (chromophil) adenoma
NEW RENAL CELL TUMOR SUBTYPES
Multilocular cystic renal neoplasm of low malignant potential
Mi T family translocation renal cell carcinoma*
Tubulocystic renal cell carcinoma*
Acquired cystic disease–associated renal cell carcinoma*
Clear cell papillary renal cell carcinoma*
Succinate dehydrogenase–deficient renal cell carcinoma*
Hereditary leiomyomatosis and associated renal cell carcinoma*

*Malignant.

Tumor subtypes comprising the percentages of all renal cell carcinomas (in parentheses), respectively.

Mi T = microphthalmia transcription factor; WHO = World Health Organization.

Adapted from Inamura K. Renal cell tumors: understanding their molecular pathological epidemiology and the 2016 WHO classification. *Int J Mol Sci*. 2017;18:2195. The revised 2016 WHO classification added the new tumor subtypes to the 2013 International Society of Urological Pathology (ISUP) Vancouver Classification of Renal Neoplasia (Srigley JR, Delahunt B, Eble JN, et al. *Am J Surg Pathol*. 2013;37:1469-1489).

TABLE 182-2 HISTOLOGIC SUBTYPES, GENETICS, AND SYNDROMES

HISTOLOGIC SUBTYPE	PERCENT	MAJOR GENETIC/ MOLECULAR DEFECTS	ASSOCIATED SYNDROMES
Conventional clear cell	75	LOH 3p mutation of 3p26 (*VHL*)	Von Hippel-Lindau hereditary renal cell carcinoma (RCC)
Papillary 1	5	*MET* gene mutation 7q34	Hereditary papillary renal cell carcinoma (HPRCC)
Papillary 2	10	Fumarate hydratase (*FH*)1q42.1	Hereditary leiomyomatosis renal cell carcinoma (HLRCC)
Chromophobe	5	Birt-Hogg Dubé 17p11.2 (*FLCN*)	Birt-Hogg Dubé
Oncocytoma	9.7	Birt-Hogg Dubé 17p11.2 (*FLCN*)	Familial oncocytoma Birt-Hogg Dubé
Collecting duct	0.4	−18, −Y	Renal medullary carcinoma

Modified from Zambrano N. Histopathology and molecular genetics of renal tumors. *J Urol*. 1999;162:1246-1258.

contain less lipid and glycogen. Approximately 50% of the tumors exhibit either a solid or acinar growth pattern that is characterized by solid sheets of tumor cells accompanied by a rich capillary vascular network.

Clear cell renal cell carcinoma is characterized by the loss of genetic material from the short arm of chromosome 3 (3p) and mutations in the von Hippel-Lindau (*VHL*) gene.[4] In patients with von Hippel-Lindau disease (Chapter 385), these losses and mutations occur in virtually all cases. The more common sporadic tumors also have somatic mutations and hypermethylation in the same region in approximately 75 to 80% of cases. Conventional clear cell tumors have a mutation in the *VHL* gene, which is inactivated by a point mutation or by epigenetic gene silencing by promoter methylation. The loss of *VHL*, which is responsible for ubiquination and degradation of the hypoxia-inducible factor (HIF), leads to upregulation of HIF-responsive genes responsible for angiogenesis and cell growth. Two of these upregulated genes are platelet-derived growth factor (PDGF) and vascular endothelial growth factor (VEGF), which are pro-angiogenic proteins that are thought to induce the neovascularity in both primary and metastatic clear cell cancers. Patients with von Hippel-Lindau disease more commonly develop tumors at an earlier age and frequently have multiple tumors. Other tumors associated with the syndrome include central nervous system hemangioblastomas, pancreatic neuroendocrine tumors, pheochromocytomas, retinal angiomas, and epididymal cystadenomas (Chapter 385). Molecular characterization of renal cell carcinoma shows alterations in genes responsible for maintenance of chromatin states such as *PBRM1*, the SWI/SNF chromatin remodeling complex including *ARID1A* and *SMARCA4*, and members of the P13K/AKT pathway.

Papillary Renal Cell Carcinomas

Papillary renal cell carcinomas comprise from 7 to 14% of primary epithelial renal neoplasms. The majority of patients present with unilateral tumors. Multifocality, either bilateral or multifocal lesions in the same kidney, is present in approximately 45% of cases. The majority of these tumors exhibit a broad morphologic spectrum, including papillary, papillary-trabecular, and papillary-solid areas; associated necrosis is a common finding. The classic papillary pattern is characterized by discrete papillary fronds lined by neoplastic epithelial cells and containing a central fibrovascular core, easily recognized on low magnification.

The majority of sporadic papillary renal cell carcinomas are characterized by trisomy of chromosomes 7 and 17 and loss of chromosome Y. Chromophobe renal cell cancers have genetic loss on chromosomes 1 and Y, as well as combined chromosomal losses affecting chromosomes 1, 6, 10, 13, 17, and 21. Hereditary papillary renal cell cancer is a result of germline mutations and activation of the *MET* proto-oncogene, which is located on chromosome 7q. These cells have aberrant hepatocyte growth factor receptors that are unable to deactivate after binding by the growth factor. Somatic *MET* gene amplifications also are observed in approximately 10% of cases of sporadic papillary renal cancer.[5]

These tumors are divided into type 1 and type 2 lesions, based on cytologic features and genetic differences. Comprehensive molecular characterization shows that type 1 and type 2 papillary renal cell carcinomas are clinically and biologically distinct.

Chromophobe Renal Cell Cancer

Chromophobe renal cancers account for 6 to 11% of renal epithelial tumors. Characteristically, these tumors are solitary and discrete but not encapsulated. The typical histologic findings consist of large round-to-polygonal cells with well-defined cell borders and pale basophilic cytoplasm admixed with a smaller population of polygonal cells with eosinophilic cytoplasm. These tumors may be quite large at diagnosis, with resectable tumors reported as big as 23 cm.

Other Renal Tumors

Hereditary leiomyomatosis renal cell carcinoma, which is characterized by alteration of the gene fumarate hydratase, is associated with uterine leiomyomas (more common) or leiomyosarcoma (rare), cutaneous nodules (leiomyomas), and type 2 papillary renal cell carcinoma, which is often solitary and frequently develops metastases. Birt-Hogg-Dubé syndrome is a rare disorder predominantly associated with chromophobe renal cancers but in which clear cell and chromophobe/oncocytic tumors can develop. Birt-Hogg-Dubé syndrome is characterized by fibrofolliculomas, pulmonary cysts, pneumothorax, and bilateral renal tumors. The gene associated with Birt-Hogg-Dubé syndrome has been mapped to 17p and expresses a novel protein, folliculin, whose function is not yet fully characterized.

CLINICAL MANIFESTATIONS

The majority of patients are asymptomatic at presentation, with about 50% of tumors detected by an abdominal ultrasound, a CT scan, or an MRI obtained for unrelated medical reasons. The next most common presentation is with asymptomatic hematuria, often microscopic. The classic presenting triad of hematuria, a palpable mass, and pain is now unusual, and less than 5% of patients have a palpable mass at presentation. The more common manifesting symptoms are anemia, weight loss, malaise, and anorexia (Table 182-3). Patients who present with renal cell carcinoma frequently have associated paraneoplastic syndromes (Chapter 164).[6] Hypercalcemia (Chapter 227) is observed in approximately 20% of patients and can be due to the secretion of parathyroid hormone, parathyroid hormone–like peptide, and interleukin-6 (IL-6), which stimulate osteoclastic bone resorption. Other associated syndromes include hypertension, erythrocytosis (from ectopic erythropoietin production), and the rare Stauffer syndrome, which is liver dysfunction without hepatic metastases and which resolves after surgical resection of the tumor.

TABLE 182-3 PRESENTING SYMPTOMS AND SIGNS OF RENAL CELL CARCINOMA (BOTH LOCALIZED AND METASTATIC DISEASE)

SYMPTOMS AND SIGNS	PERCENT
Anemia	52
Hepatic dysfunction	32
Weight loss	23
Hypoalbuminemia	20
Malaise	19
Hypercalcemia	13
Anorexia	11
Thrombocytosis	9
Night sweats	8
Fever	8
Hypertension	3
Erythrocytosis	4
Chills	3

Modified from Kim HI, Belldegrun AS, Freitas DG, et al. Paraneoplastic signs and symptoms of renal cell carcinoma: implications for prognosis. *J Urol.* 2003;170:1742-1746.

DIAGNOSIS

Ultrasonography, CT, and MRI can help distinguish benign from malignant lesions. Ultrasound can distinguish small simple cysts from solid lesions. For other renal cystic lesions, CT or MRI can define three categories: likely benign lesions that require no follow-up; lesions that are usually benign (generally smooth wall of no more than 3 mm with enhancing septa) but require repeat imaging at 6 months, 12 months, and then annually for 5 years; or thicker-walled or irregularly enhancing lesions that require biopsy.

CT is the most reliable method for evaluating solid lesions.[7] The preferred CT scan for renal masses can be divided into four phases, including the precontrast images, the arterial phase (~25 seconds after injection), the nephrographic phase (~90 seconds into the injection), and the excretory phase. The most important phases for imaging renal tumors are the precontrast and nephrographic images because renal lesions appear low in density in contrast to the uniformly enhanced renal parenchyma. The arterial phase is helpful for identifying renal arteries and small hypervascular masses. The excretory phase aids in assessing the collecting system and the renal pelvis. Lack of enhancement is consistent with a hemorrhagic or inflammatory cyst that can mimic a solid lesion. Macroscopic fat in a solid renal mass suggests an angiomyolipoma.

The complete evaluation for patients with suspected renal cell carcinoma should include a complete blood count, a chemistry profile, and a CT scan of the chest, abdomen, and pelvis. CT scan is also helpful for detecting regional metastases and for indicating when partial nephrectomy is feasible. MRI is useful for imaging tumors in patients who have poor renal function and in whom intravenous contrast may be contraindicated. MRI is also helpful for delineating any thrombi that may be extending into the renal vein or inferior vena cava, and magnetic resonance angiography can determine the number and location of renal arteries in patients who are candidates for partial nephrectomy. Once the evaluation is complete, the clinical stage is assessed using the Tumor, Node, Metastasis (TNM) system (Table 182-4). A bone scan is indicated for patients with clinically advanced disease, hypercalcemia, bone pain, and/or an elevated alkaline phosphatase level.

TABLE 182-4 TNM STAGING OF RENAL CELL CARCINOMA

TUMOR, NODE, AND METASTASIS CLINICAL CLASSIFICATION	
T—Primary Tumor	
TX	Primary tumor cannot be assessed
T0	No evidence of primary tumor
T1	Tumor 7 cm or less in greatest dimension, limited to the kidney
T1a	Tumor 4.0 cm or less in greatest dimension, limited to the kidney
T1b	Tumor more than 4 cm but not more than 7 cm in greatest dimension, limited to the kidney
T2	Tumor more than 7 cm in greatest dimension, limited to the kidney
T2a	Tumor more than 7 cm but less than or equal to 10 cm in greatest dimension, limited to the kidney
T2b	Tumor more than 10 cm, limited to the kidney
T3	Tumor extends into major veins or the perinephric tissues or into the ipsilateral adrenal gland and but not beyond the Gerota fascia
T3a	Tumor extends into renal vein or its segmental branches or pelvicalyceal system, or invades perirenal and/or renal sinus fat but not beyond the Gerota fascia
T3b	Tumor extends into the vena cava below the diaphragm
T3c	Tumor extends into the vena cava above the diaphragm or invades the wall of the vena cava
T4	Tumor invades beyond the Gerota fascia (including contiguous extension into the ipsilateral adrenal gland)
N—Regional Lymph Nodes	
NX	Regional lymph nodes cannot be assessed
N0	No regional lymph node metastasis
N1	Metastasis in regional lymph node(s)
M—Distant Metastasis	
Mx	Distant metastasis cannot be assessed
M0	No distant metastasis
M1	Distant metastasis
STAGE GROUPING	
Stage I	T1 N0 M0
Stage II	T2 N0 M0
Stage III	T1 N1 M0
	T2 N1 M0
	T3a N0 or N1 M0
	T3b N0 or N1 M0
	T3c N0 or N1 M0
Stage IV	T4 N0 M0
	T4 N1 M0
	Any T Any N M1

AJCC = American Joint Committee on Cancer.
Adapted from *AJCC Staging Manual*, 8th ed. New York: Springer International Publishing; 2017.

TREATMENT

Renal Cell Carcinoma

Localized Disease

The increasing prevalence of small tumors discovered incidentally on imaging has resulted in a marked increase in the use of partial nephrectomy rather than complete nephrectomy. For tumors of 7 cm or less, partial nephrectomy by the open or minimally invasive laparoscopic technique provides local tumor control and survival similar to radical nephrectomy. Partial nephrectomy preserves some renal function and reduces the risk for renal insufficiency over time. Partial nephrectomy is further supported by the fact that approximately 35% of renal cortical tumors are indolent papillary or chromophobe carcinomas.

Radical nephrectomy is generally preferred for large and centrally localized tumors that have effectively replaced the majority of the normal renal parenchyma, tumors associated with regional adenopathy (of benign or malignant etiology), tumors that extend into the inferior vena cava or right atrial vein, and even when metastatic disease is evident.[8] Radical nephrectomy can be performed laparoscopically or by an open technique through a flank, transperitoneal, or transthoracic approach. The ipsilateral adrenal gland is also removed, but a regional lymph node dissection is optional and controversial.

Renal cell carcinomas are resistant to both radiation therapy and cytotoxic chemotherapy, so neither modality is useful for adjuvant therapy after nephrectomy. However, sunitinib (a tyrosine kinase inhibitor that targets vascular endothelial growth factor [VEGF])[A1] and pembrolizumab (an antibody that inhibits programmed death-1 [PD-1] receptors)[A2] under expert oversight are effective as adjunctive treatment in patients at high risk for recurrence after nephrectomy.

Metastatic Disease

Surgery

Approximately 30% of patients with renal cell carcinoma present with metastatic disease, usually with pain from either an unresectable primary tumor or skeletal metastases, and an additional 20 to 30% of patients with surgically resected primary tumors will relapse with metastases.[9] Radiation therapy is

frequently used for palliation of bone metastases and for patients with multiple brain metastases. Palliative nephrectomy is sometimes used to provide symptomatic relief of pain. In other patients, surgical resection of the primary tumor can be considered, even in the presence of metastatic disease,[A3] but this approach is now less common with the advent of more effective systemic therapies. However, resection of metastatic sites of disease (metastasectomy) may extend survival in selected patients and may even cure a subset of patients.[10] The patients most likely to benefit from surgical resection of metastatic disease have a disease-free interval of greater than 1 year after nephrectomy, a solitary site of metastasis, and lung metastases.

Medications

Current consensus recommendations[11] are to use anti–PD-1 antibodies (nivolumab, pembrolizumab, or avelumab) in combination with either tyrosine kinase inhibitor therapy (e.g., axitinib, cabozantinib, lenvatinib, and sorafenib) or anti-CTLA antibodies (e.g., ipilumimab) under expert supervision for first-line treatment of metastatic clear cell carcinoma. Nivolumab in combination with either cabozantinib[A4] or ipilumimab[A5] provides significantly better progression-free and overall survival compared with sunitinib monotherapy, except perhaps for patients who have favorable risk factors. Pembrolizumab in combination with a tyrosine kinase inhibitor, either lenvatinib[A6] or axitinib,[A7,A8] is also superior to sunitinib monotherapy in terms of both progression-free and overall survival. Pembrolizumab plus either axitinib or lenvatinib is recommended in all patients irrespective of risk, whereas nivolumab plus ipilumimb is recommended in patients with intermediate and poor risk features. Common side effects with tyrosine kinase inhibitors include fatigue, diarrhea, hypertension, and hand-foot syndrome (a condition in which blisters appear at sites of physical contact).

Two drugs targeting the mammalian target of rapamycin (mTOR) pathway, everolimus and temsirolimus, are effective for the treatment of renal cell carcinoma. Everolimus, an oral mTOR inhibitor, is used most frequently based on clinical benefit in patients who have been previously treated with sunitinib or sorafenib. Belzutifan (a small molecule inhibitor of hypoxia-inducible factor-2) is useful for patients who have cancers associated with *VHL* mutations. Side effects include anemia, hypoxia, fatigue, increased glucose, headache, and nausea; both the anemia and the hypoxia can be severe.

Non–Clear Cell Cancer

For non–clear cell renal carcinoma, evidence supports sunitinib under expert supervision as the recommended treatment.[A9] Cabozantinib, as a single agent or in combination with immune therapy, is another potential agent.

PREVENTION

No interventions are proven to prevent renal cancers. However, the risk may decrease by 20 or so years after smoking cessation. Avoiding obesity also may decrease the risk. Whether controlling hypertension will reduce the risk is uncertain.

PROGNOSIS

Progression-free survival and overall survival rates for resected nonmetastatic renal cortical tumors substantially differ according to multiple factors, including age, size, grade, and pathologic state. Overall, 5-year survival rates are 90 to 95% for localized disease, 70% for disease with regional spread, and only 15% for disease with distant spread. Of the more common histologic subtypes of renal cell carcinoma, the prognosis of clear cell renal cell carcinoma is less favorable than that of papillary renal cell carcinoma; chromophobe renal cell carcinoma is the most favorable.

In patients with metastatic disease, clinical features associated with poorer natural history include low performance status, a hemoglobin concentration below 12 g/dL, an albumin-corrected calcium level above 10.2 mg/dL, an absolute neutrophil count above 7000/μL, a platelet count above 400,000/μL, and absence of prior nephrectomy. Survival directly correlates with the number of these pretreatment risk factors. For example, in patients who are treated with modern combination therapy, 85% of patients with zero risk factors survive for 30 months compared with about 70% for one risk factor, 60% for two risk factors, 40% for three risk factors, and 30% for four to six factors.[12] In patients who have solitary metastases after otherwise successful surgical therapy, long-term survival is seen after metastasectomy in the lung (up to 45%) and even in the brain (up to 20%) lesion.

BLADDER CANCER

DEFINITION

A spectrum of tumors arises from the urothelial lining of the bladder, renal pelvis, ureters, and urethra. The vast majority of tumors originate in the bladder, with a minority originating in the upper tracts (renal pelvis and ureters) and even fewer from the proximal urethra. Transitional cell carcinoma is the most common histologic type. Although transitional cell cancers possess a variable natural history, they have a proclivity for multifocality, high recurrence rates, and progression to higher pathologic stages. These tumors are generally grouped into the three broad categories of non–muscle-invasive, muscle-invasive, and metastatic disease, each of which differs in clinical behavior, prognosis, and primary management. For non–muscle-invasive tumors, the aim is to prevent recurrences and progression to a more advanced stage. In muscle-invasive disease, the medical challenge is to integrate the modalities of surgery, chemotherapy, and/or radiation to optimize cure and minimize morbidity. For metastatic disease, chemotherapy is used to palliate the symptoms of most patients, but there is a subset of patients for whom combination chemotherapy may result in long-term cure. Long-term cure is directly related to stage and grade, ranging from 99% for low-grade Ta tumors to up to 15% for metastatic disease.

EPIDEMIOLOGY

An estimated 80,000 or so new cases of bladder cancer are diagnosed in the United States annually, and approximately 17,000 patients die from this disease each year. The overall 77% 5-year survival rate for all stages results in a prevalence of more than 500,000 people living with bladder cancer in the United States. The ratio of males to females is 3:1, and bladder cancer is the fourth most common cancer in men. It is estimated that men have a 1 in 27 chance of developing this cancer in their lifetimes, whereas the risk is 1 in 89 for women. Bladder cancer is twice as prevalent in Whites as in Black Americans and is less frequently observed in Asians. The vast majority of patients (90%) are over age 50 years at diagnosis, with a median age of 73 years.

Carcinogens or their metabolites implicated in the carcinogenesis of bladder cancer are believed to be excreted in the urine, where they can act directly on the urothelial lining. The latency period from initial exposure to the development of cancer is almost 20 years, so it can be difficult to establish a definitive cause-and-effect relationship between a putative carcinogen and the development of disease. Cigarette smoking is the leading risk factor for bladder cancer and is believed to contribute to 50% of the cancers in men and 25% of the cancers in women.[13] A longer duration of exposure is associated with a higher risk than a more intense exposure (in cigarettes/day) over a shorter time period. Overall, smokers have a two-fold to four-fold higher relative risk for bladder cancer than nonsmokers. Smoking is associated with cellular atypia of the urothelium. Individuals who never smoke have atypia in only 4% of cases, whereas atypia is seen in 50% of smokers.

Polycyclic aromatic hydrocarbons such as 2-naphthylamine, 4-aminobiphenyl and benzidine, and benzene or exhausts from combustion gases are associated with an increased risk for bladder cancer. Occupations reported to be at higher risk include aluminum workers, dry cleaners, manufacturers of preservatives and polychlorinated biphenyls, and pesticide applicators. Arylamines, also implicated in carcinogenesis, are metabolically activated to electrophilic compounds by N-hydroxylation in the liver by cytochrome P-450 IA2 and detoxified by N-acetylation; studies suggest that individuals with a fast oxidizer and slow acetylator phenotype are at highest risk. Occupations associated with a higher exposure to arylamines, such as workers in the dye, rubber, or leather manufacturing industries, are believed to be at higher risk for developing bladder cancer. *Schistosoma haematobium* infection (Chapter 326) enhances formation of carcinogenic N-nitroso compounds and results in an increased risk for both squamous and transitional cell carcinomas of the bladder. An association has been observed between squamous cell carcinoma (but not transitional cell tumors) and the presence of chronic urinary tract infections seen in paraplegics and patients with chronic bladder stones and indwelling Foley catheters. The chemotherapy agent cyclophosphamide can increase the risk for bladder cancer nine-fold when used chronically, and phenacetin-containing compounds have been implicated in the development of tumors of the renal pelvis and ureters.

PATHOBIOLOGY

Urothelial tumors occur anywhere along the urinary tract, including the renal pelvis, ureters, bladder, and the urethra. Over 90% of tumors originate in the bladder, 8% in the renal pelvis, and the remaining 2% in the ureter and urethra. Transitional cell carcinomas comprise 90 to 95% of urothelial tumors; squamous cell (keratinizing) tumors (3%), adenocarcinomas (2%), and small cell tumors (1%) are the remainder. Mixed-histology tumors, consisting of predominantly transitional cell carcinoma with areas of squamous, adenocarcinomatous, or neuroendocrine elements, are frequently observed.[14] Squamous

cell tumors are more frequent in the distal urethra, and adenocarcinomas occur in the embryonal remnant of the urachus on the dome of the bladder and in periurethral tissues. In endemic areas of *S. haematobium* infections (such as Egypt; Chapter 326), 40% of tumors are squamous cell carcinomas. Rare tumors of the bladder include lymphoma (Chapter 171), sarcoma (Chapter 187), and melanoma (Chapter 188).

The majority (70 to 80%) of newly detected bladder cancers are classified as non–muscle-invasive tumors and include exophytic papillary tumors confined to the mucosa (Ta), tumors invading the lamina propria (T1), and carcinoma in situ (CIS). Non–muscle-invasive bladder tumors are typically graded according to the World Health Organization/International Society of Urologic Pathology (WHO/ISUP) grading system as low grade and high grade. If the grading system is not specified, a numeric system can be used: well differentiated (G1), moderately differentiated (G2), poorly differentiated (G3), and undifferentiated (G4). Grading is more important for noninvasive Ta tumors because almost all invasive bladder tumors (T1 or greater) are high grade. Primary carcinoma in situ without a concurrent Ta or T1 tumor constitutes 1 to 2% of new bladder cancer cases. More frequently, tumor in situ is found in the presence of multiple papillary tumors, either immediately adjacent to another lesion or involving remote mucosa in the bladder. Tumor in situ is, by definition, high-grade disease. T1 tumors are an aggressive, invasive malignancy. Virtually all T1 tumors are high grade, and 50% have associated tumors in situ. Disease recurs in 50% of patients by 1 year and in 90% within 5 years. At the time of diagnosis, a minority of primary tumors invade the muscularis propria (T2), extend to perivesicular fat (T3), or extend into immediately adjacent organs (T4); all primary tumors stage T2 or higher are high grade.

Genetic predisposition may also play a role in the development of urothelial cancer. About 15% of patients have germline variants in DNA-damage repair genes (e.g., *BRCA2*, *BRCA1*, *MSH2*, *CHEK2*, *ERCC3*, *NBN*, and *RAD50*), and about 40% of affected patients have biallelic inactivation.[15]

Recurrences may be clonal in origin. The epidermal growth factor receptor (EGFR) is highly expressed (~80%) in bladder cancers, whereas the HER2/Neu growth factor receptor is less frequently expressed (~50 to 70%). Studies suggest that higher expression of these receptors is associated with a more advanced and/or more aggressive phenotype of disease. Bladder cancer has a very high somatic mutation rate (7.7 per megabase) compared with that of other cancers, exceeded only by lung cancer and melanoma. Epigenetic modifying genes *MLL2, ARID1A, KDM6A,* and *EP300* are significantly mutated in bladder cancer; approximately 75% have at least one inactivating mutation. Genes that regulate the cell cycle are also frequently mutated, including *TP53* in 49% and *RB1* in 13% of tumors. Mutations and/or amplifications of *FGFR, ERBB2, MDM2,* and *EGFR* occur in a minority of tumors and represent potential therapeutic targets.

CLINICAL MANIFESTATIONS

Hematuria is the manifesting symptom in 80 to 90% of bladder cancers, but patients also may present with a urinary tract infection. Urinary frequency and nocturia may be present as a consequence of either irritative symptoms or a reduced bladder capacity. Pain, when present, typically reflects the location of the bladder tumor. Lower abdominal pain may occur as a result of a bladder mass, and rectal discomfort and perineal pain can result from tumors that invade the prostate or pelvis. Tumors of the renal pelvis, ureter, or bladder in which the ureteral orifice is obstructed can cause hydronephrosis, reduced renal function, and flank pain. Patients with more advanced disease can present with anorexia, fatigue, weight loss, or pain from a metastatic bone lesion. The physical examination is frequently unremarkable in patients who present with bladder tumors because the vast majority of patients have organ-confined tumors.

DIAGNOSIS

Individuals over age 40 years who develop hematuria should have an evaluation for the presence of urothelial cancer (Fig. 100-3), including urinary cytology, cystoscopy, and imaging of the urinary tract by either an ultrasound or CT scan. Urinary biomarkers currently are neither sufficiently sensitive nor specific for the diagnosis of bladder cancer,[16] and a small proportion of cases can be missed even if biomarkers are combined with urinary cytology.

The mainstay of diagnosis and staging is the cystoscopic evaluation under anesthesia to determine if a palpable mass (either mobile or not) is present. A nonmobile tumor mass is indicative of disease that invades the pelvic sidewall and that is unlikely to be resectable. Urine is obtained to evaluate for the presence of malignant cells. A cystoscope is inserted to inspect the bladder and detail the size, number, location, and growth pattern (papillary or solid) of all lesions.

All visible disease undergoes transurethral resection to determine the histologic subtype and depth of invasion. Adequate evaluation, particularly in large tumors that may be invasive, requires that muscle be identified in the pathologic specimen. Repeat biopsy of the resected area is occasionally required to ensure that no muscle invasion is present, because invasion into muscle requires consideration of surgical removal of the bladder rather than endoscopic resection of the tumor. Biopsies from any areas of erythema are performed to assess for carcinoma in situ. The urethra is inspected during withdrawal of the cystoscope, and biopsies are taken if clinically indicated. Patients with positive cytologic findings but no apparent tumor within the bladder undergo selective retrograde catheterization of the ureters up to the renal pelvices to determine whether upper tract disease is present.

The decision whether to obtain images of the abdomen and pelvis is based on the results of cystoscopy and the pathology of the tumor. Either CT or magnetic resonance urogram can evaluate the upper urinary tracts, and CT or MRI may distinguish whether a tumor extends to the perivesical fat (T3), prostate, or vagina (T4) and whether regional lymph nodes are involved (N+). For larger, invasive tumors, the presence or absence of distal metastases can be documented by physical examination, CT of the abdomen and pelvis, a chest radiograph, and radionuclide bone scan.

All patients with carcinoma of the bladder or related sites are staged using the TNM system (E-Table 182-1). The TNM system categorizes the depth of invasion of the primary tumor, nodal metastases in the pelvis (or retroperitoneum for upper tract disease) on the basis of the number and size of regional nodal involvement, other nonregional lymph node sites, and any visceral sites of disease.

TREATMENT

Non–Muscle-Invasive Disease

The standard treatment for non–muscle-invasive tumors is a complete endoscopic resection. Additional treatment in the form of adjuvant intravesical therapy depends on the number of lesions, the size, the depth of invasion, and the number of prior tumors in that individual. Immediate postresection intravesicular gemcitabine significantly reduces the risk of recurrence in patients who are at high risk of recurrence and progression because of multifocal or large lesions, high-grade papillary lesions, T1 tumors, carcinomas in situ, or a combination of these factors.[A10] Intravesical therapy is not warranted for Ta tumors that are low grade, and it is never advised for muscle-invasive tumors because agents instilled in the bladder do not penetrate beyond a few layers of cells. After allowing sufficient time for healing after the endoscopic resection, intravesical therapy is most frequently initiated with the immunologic agent bacillus Calmette-Guérin (BCG) weekly for 6 weeks, followed by a prolonged maintenance schedule.[17] BCG is highly effective for eradicating tumors in situ, with 70% of patients disease-free at 1 year and 40% at 10 years. Occasionally, other chemotherapeutic agents or cytokines are used under expert oversight when BCG is contraindicated. Bladder toxicity caused by urothelial irritation from BCG includes bladder irritability or spasms, hematuria, and pain on urination. A rare complication of BCG is development of a systemic tuberculosis infection requiring treatment with systemic antituberculosis agents (Chapter 299).

The majority of patients develop new tumors, 30% of which progress to a higher stage, so vigilant surveillance at 3-month intervals for the first year should include cystoscopy, urine cytology, and repeat transurethral resection when indicated. If disease persists, either a repeat course of BCG treatment or even an immediate cystectomy may be recommended. Pembrolizumab is useful for high grade, non–muscle-invasive bladder cancer that either does not respond to BCG or relapses within 12 months after BCG therapy.[18]

Selected tumors in the ureter or renal pelvis can be managed by ureteroscopic resection, sometimes accompanied by the instillation of BCG through the renal pelvis, or by nephroureterectomy. Tumors of the prostatic urethra are frequently managed by cystoprostatectomy, particularly if a complete resection cannot be accomplished.

Muscle-Invasive Tumors

For patients whose tumors are infiltrating the muscularis propria, the standard of care in the United States and Europe is a radical cystectomy and pelvic lymphadenectomy because of the high incidence of cancer extending into the perivesicular fat or into regional lymph nodes.[19,20] A prostatectomy is also performed in men; in women, the urethra, uterus, fallopian tubes, ovaries, and anterior vaginal wall are removed. Urinary flow can be directed through either a conduit diversion or a continent reservoir. With a conduit diversion, urine is drained directly from the ureters to a loop of small bowel that is anastomosed to the skin surface with no internal reservoir. Urine is collected in an external

appliance. Alternatively, a low-pressure continent reservoir can be created from a detubularized segment of bowel attached to the abdominal wall with a continent stoma that can be self-catheterized at regular intervals. Low-pressure reservoirs also can be anastomosed to the urethra, thereby creating an internal orthotopic neobladder that permits the patient to void via the normal urethra.[21] The standard pelvic lymphadenectomy includes the distal common iliac, external iliac, obturator, presacral, and hypogastric nodes; improved survival and decreased local recurrence are associated with removal of an increased number of lymph nodes. Radical cystectomy is effective at providing long-term disease control in 75 to 80% of patients with organ-confined disease, in approximately 50% of patients whose tumors extend into the perivesical tissues, and in up to one third of patients with regional lymph node involvement. Complications of cystectomy include recurrent urinary infections, hyperchloremic acidosis, oxalate stones, incontinence, and impotence.

For muscle-invasive bladder cancer, neoadjuvant chemotherapy with cisplatin-based combinations before cystectomy increases survival.[22] To be eligible, patients must have normal renal and cardiac function, as well as a good performance status. Immediate cystectomy followed by standard adjuvant chemotherapy is no better than neoadjuvant chemotherapy.[A11] However, nivolumab is recommended for 1 year after surgery for patients with pathologic features that carry a high risk of recurrence, even if they were treated with neoadjuvant chemotherapy.[A12]

Some patients prefer a nonsurgical, bladder-sparing approach using radiation treatment rather than a cystectomy. Radiation with chemotherapy sensitization (e.g., with cisplatin, gemcitabine, and mitomycin plus 5-fluorouracil) under expert supervision is preferred over radiation alone because of better tumor control. The best candidates for this approach are patients who have a solitary early-stage lesion and no evidence of hydronephrosis. This tri-modality treatment for bladder preservation first requires a successful, near-complete transurethral resection of tumor followed by concurrent chemotherapy and radiation. External beam treatments are typically delivered in five daily fractions per week, at conventional fractions of about 1.8 Gy to a total treatment dose of approximately 65 Gy. Toxicities include inflammation of the skin, impotence, fatigue, and irritative symptoms from the bladder and bowel, but persistent proctitis is rare. In this approach, cystectomy is reserved for patients whose disease failed to achieve complete response.

Metastatic Disease

Metastatic disease in the pelvic lymph nodes is very frequent despite a normal preoperative CT scan. Bilateral pelvic lymph node dissection in addition to cystectomy improves survival.

Patients with metastatic disease are treated with either platinum-based chemotherapy or immunotherapy with checkpoint blockade inhibitors targeting either PD-1 or PD-L1 under expert supervision.[23] Cisplatin-based chemotherapy is the standard first-line treatment based on the potential for cure. The two most commonly used regimens are either gemcitabine plus cisplatin or the four-drug regimen of methotrexate, vinblastine, doxorubicin, and cisplatin. The most frequently observed toxicities include anemia, thrombocytopenia, neutropenic fever, mucositis, and fatigue. The median survival of patients treated with either regimen is approximately 14 months, and the 5-year survival is 15% or less. Favorable prognostic factors include a good performance status and metastatic disease limited to the lymph nodes. When medical comorbid conditions preclude the use of cisplatin, immunotherapy with pembrolizumab can be considered instead of carboplatin-based chemotherapy if the tumor is positive for PD-L1.[24] After first-line chemotherapy, avelumab maintenance therapy can significantly prolong survival in patients whose disease did not progress during chemotherapy.[A13] Durable responses can also be obtained in patients with progressive disease by using pembrolizumab or nivolumab.[A14] The antibody-drug conjugate enfortumab vedotin can be considered for patients with progressive cancer despite chemotherapy and/or immunotherapy.[A15] Sacituzimab govitecan, another antibody-drug conjugate, is also useful for patients who were previously treated with chemotherapy and immunotherapy; myelosuppression is the most common toxicity.[25] For patients whose previously treated tumors harbor mutations or fusions in the fibroblast growth factor receptor (FGFR) 2 or 3 genes, the oral pan-FGFR inhibitor erdafitinib can be beneficial.[26] Common side effects include hyponatremia, stomatitis, and asthenia.

PREVENTION

Screening of asymptomatic individuals for hematuria increases the probability of diagnosing bladder cancer at an earlier stage but does not improve survival and is not routinely recommended.

PROGNOSIS

Cancer of the urinary bladder is a common but heterogeneous disease. The natural history of a urothelial tumor is to recur either at the same location or at a separate site in the urothelial tract and at the same or a more advanced stage. Non–muscle-invasive TaG1 lesions are easily treated with endoscopic resection alone and almost never progress.

Without treatment, about 60% of tumors in situ progress to more invasive disease within 5 years. Endoscopic resection plus intravesicular BCG immunotherapy can substantially reduce recurrence and progression, with 5-year disease-free survival rates of 60%.

Muscle-invasive disease is most frequently cured with an integrated approach of systemic chemotherapy for micrometastases followed by cystectomy and pelvic lymphadenectomy; cure rates for T2 tumors can be as high as 80% with this multimodality approach. Bladder-sparing approaches associated with an improved quality of life are possible using external beam radiation. The 5-year disease-free survival with this approach is approximately 50%, with the majority of surviving patients retaining a normally functioning bladder.

Metastatic urinary bladder cancer is a fast-growing and often lethal malignancy; despite aggressive chemotherapy, only about 15% of patients are disease-free at 5 years. Even in this chemotherapy-refractory setting, modern immunotherapy can potentially cure a subset of patients.

CANCERS OF THE RENAL PELVIS AND URETERS

Approximately 10% of transitional cell carcinomas are upper tract tumors that occur in the ureters and the renal pelvis. These tumors can arise either de novo or in the setting of prior tumors. The risk for developing an upper tract tumor approaches 25% by 10 years in patients who have multifocal carcinoma in situ of the bladder.

These tumors are morphologically similar to the tumors in the bladder and behave in a similar manner. Hematuria is the most common manifesting symptom, although patients with large tumors and/or ureteral obstruction can present with flank pain. A CT scan or MRI is used to stage the extent of primary disease and to detect regional metastases. Upper tract transitional cell carcinomas are staged according to the TNM system (see E-Table 182-1).

Low-grade tumors can be treated endoscopically, but high-grade tumors are most commonly treated with a nephroureterectomy. In contrast to bladder cancer, regional lymphadenectomy is not routinely performed. In renal pelvic tumors, the ureter is also removed because of the high risk for multifocal tumors along the entire upper tract and the inability to monitor the ureteral stump accurately postoperatively.

Adjuvant systemic chemotherapy under expert oversight with either cisplatin plus gemcitabine or carboplatin plus gemcitabine confers a survival advantage for patients whose tumors have pathologic features deemed at high risk for relapse.[A16] For advanced nonsurgical disease, treatment options include chemotherapy, immunotherapy, antibody drug conjugates, and targeted therapies similar to the approach used for primary bladder cancer. These upper tract urothelial tumors generally have the same responses to treatment and clinical outcomes as does bladder cancer.

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For the General References and other additional features, please visit Elsevier eBooks+ at https://ebooks.health.elsevier.com.

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E-TABLE 182-1 TNM DEFINITIONS FOR CANCERS OF THE BLADDER, URETER, AND RENAL PELVIS

PRIMARY TUMORS OF THE BLADDER (T)	
TX	Primary tumor cannot be assessed
T0	No evidence of primary tumor
Ta	Noninvasive papillary carcinoma
Tis	Carcinoma in situ (i.e., flat tumor)
T1	Tumor invades lamina propria (subepithelial connective tissue)
T2	Tumor invades muscularis propria
pT2a	Tumor invades non–muscle-invasive muscularis propria (inner half)
pT2b	Tumor invades deep muscularis propria (outer half)
T3	Tumor invades perivesical tissue
pT3a	Microscopically
pT3b	Macroscopically (extravesical mass)
T4	Tumor invades directly into any of the following: prostatic stroma, seminal vesicles, uterus, vagina, pelvic wall, abdominal wall
T4a	Extravesical tumor invades the prostatic stroma, uterus, vagina
T4b	Tumor invades the pelvic wall, abdominal wall

REGIONAL LYMPH NODES FOR UROTHELIAL TUMORS OF THE BLADDER (N)	
NX	Regional lymph nodes cannot be assessed
N0	No lymph node metastasis
N1	Single regional lymph node metastasis in the true pelvis (perivesical, obturator, external iliac, or sacral lymph node)
N2	Multiple regional lymph node metastases in the true pelvis (perivesical, obturator, external iliac, or sacral lymph node metastasis)
N3	Lymph node metastasis to the common iliac lymph nodes

PRIMARY TUMORS OF THE URETER AND RENAL PELVIS (T)	
TX	Primary tumor cannot be assessed
T0	No evidence of primary tumor
Ta	Papillary noninvasive carcinoma
Tis	Carcinoma in situ
T1	Tumor invades subepithelial connective tissue
T2	Tumor invades the muscularis
T3	(For renal pelvis only) Tumor invades beyond muscularis into peripelvic fat or the renal parenchyma
T3	(For ureter only) Tumor invades beyond muscularis into periureteric fat
T4	Tumor invades adjacent organs or through the kidney into perinephric fat

REGIONAL LYMPH NODES FOR UROTHELIAL TUMORS (N) OF URETER AND RENAL PELVIS	
NX	Regional lymph nodes cannot be assessed
N0	No regional lymph node metastasis
N1	Metastasis in a single lymph node, ≤2 cm in greatest dimension
N2	Metastasis in a single lymph node, >2 cm or multiple lymph nodes

DISTANT METASTASIS FOR BLADDER (M)	
MX	Distant metastasis cannot be assessed
M0	No distant metastasis
M1a	Distant metastasis limited to lymph nodes beyond the common iliacs
M1b	Non–lymph node distant metastases

DISTANT METASTASIS FOR UROTHELIAL TUMORS (M) OF URETER AND RENAL PELVIS	
MX	Distant metastasis cannot be assessed
M0	No distant metastasis
M1	Distant metastasis

AJCC STAGE GROUPINGS FOR BLADDER CANCER	
0a	Ta N0 M0
0is	Tis N0 M0
I	T1 N0 M0
II	T2a, N0 M0
	T2b N0 M0
III	T3a N0 M0
	T3b N0 M0
	T4a N0 M0
IVa	T4b any N M0
IVb	Any T any N M1a
	Any T any N M1b

AJCC STAGE GROUPINGS FOR CANCER OF THE RENAL PELVIS AND URETER	
0a	Ta N0 M0
0is	Tis N0 M0
I	T1 N0 M0
II	T2 N0 M0
III	T3 N0 M0
IV	T4 N0 M0
	Any T N1 M0
	Any T N2 M0
	Any T N3 M0
	Any T any N M1

AJCC = American Joint Committee on Cancer.
Adapted from *AJCC Staging Manual*, 8th ed. New York: Springer International Publications; 2017.

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183 BREAST CANCER AND BENIGN BREAST DISORDERS

NANCY E. DAVIDSON

BREAST CANCER

EPIDEMIOLOGY AND PATHOBIOLOGY

Invasive breast cancer, which is the most common nonskin cancer in women in the United States, is diagnosed in approximately 290,000 women annually and results in approximately 43,000 deaths each year.[1] Worldwide, about 2.25 million cases are diagnosed annually.[2] The incidence and mortality from breast cancer appear to be declining in the United States and parts of Western Europe, likely because of a decreased use of postmenopausal hormone replacement therapy (Chapter 222), early detection by screening mammography, and widespread use of adjuvant systemic therapy.

Breast cancer is largely a disease of women, but it occurs in men at an incidence of approximately 1% of the incidence seen in women. A second critical risk factor is age. Approximately 75% of breast cancer cases in the United States are diagnosed in women older than age 50 years.

Family history is a third critical risk factor (Table 183-1). Approximately 20% of breast cancers occur in women with a family history of breast cancer, and a diagnosis of breast cancer in first-degree relatives before age 50 years especially increases the risk. Of breast cancer cases, 5 to 8% occur in high-risk families. Familial breast cancer syndromes that are associated with known molecular abnormalities include the breast-ovarian cancer syndrome, which is linked to germline mutations in the breast cancer susceptibility genes, *BRCA1* and *BRCA2*. These mutations, which include specific breast cancer cluster regions within these genes, are inherited in an autosomal dominant fashion. Germline mutation in either of these *BRCA* genes is associated with a 50 to 85% lifetime risk for developing breast cancer.

Other hereditary cancer syndromes (Chapter 166) include the Li-Fraumeni syndrome (which is linked with germline mutations in the *p53* tumor suppressor gene), Cowden syndrome (which is associated with inherited mutations in the *PTEN* gene), and germline loss-of-function mutations in *PALB2, CHEK2*, and other DNA repair genes. In addition to these high-penetrance genetic susceptibility syndromes, low-penetrance genetic associations include single nucleotide polymorphisms in a variety of genes.

Reproductive risk factors that result in prolonged exposure of the breast to estrogen include early menarche, late menopause, nulliparity, and late first pregnancy. The association between postmenopausal obesity and breast cancer likely reflects estrogen exposure as well.

Certain types of preexisting breast pathology, including atypical hyperplasia and lobular carcinoma in situ, are also associated with increased risk of breast cancer. Breast density as assessed by mammography may also be a risk factor.

Exogenous environmental factors that may predispose to breast cancer include ionizing radiation during adolescence, prolonged use of combined estrogen plus progesterone hormone replacement therapy (but not estrogen therapy alone),[A1] ongoing use of oral contraceptives, and alcohol consumption. Large studies have failed to show any convincing association between breast cancer and exposure to estrogenic pesticides or to a high-fat diet.

CLINICAL MANIFESTATIONS

Breast cancer usually manifests as an asymptomatic abnormality on a screening mammogram. However, patients sometimes have a physical change in the breast, including a mass[3] or asymmetrical thickening, nipple discharge, or skin or nipple changes. These abnormalities are commonly first detected by the patient but also may first be noted on a routine physical examination by a clinician.[4]

A milky discharge is seldom associated with a malignant diagnosis, but a clear or bloody nipple discharge is of great concern, and a bloody discharge is frequently caused by an intraductal papilloma. Breast pain is common, especially as a premenstrual symptom in premenopausal women, but it may also be associated with an underlying malignancy.

Paget disease of the nipple is a form of adenocarcinoma that involves the skin and ducts and is manifested as nipple excoriation. Inflammatory breast cancer is characterized by a constellation of redness, warmth, and edema that often reflects infiltration of tumor cells into the dermal lymphatics of the breast, and can mimic simple mastitis.[5]

Although most breast cancers are localized or relatively localized at the time of diagnosis, metastatic disease can be seen at the time of presentation or up to decades later. Common metastatic sites include bone, with pain and pathologic fractures (Chapter 187); liver metastases, with elevations of liver enzymes and sometimes jaundice; pleura, with malignant effusions (Chapter 86); central nervous system, with space occupying lesions and spinal cord compression (Chapter 175); and pericardium, with effusions (Chapter 62). Breast cancer is also a common cause of a hypercoagulable state (Chapter 67) manifested by deep vein thrombosis of the legs and even thromboses of the upper extremity (Chapter 68).

DIAGNOSIS

Patients who have an asymptomatic mammographic abnormality or any of the clinical manifestations associated with breast cancer, whether initially noted by the patient or by an examining clinician, require a careful history and breast examination, including palpation for potentially suspicious axillary lymph nodes. A careful history should focus on family history and exposure to estrogens and hormone replacement therapy. The physical examination should

TABLE 183-1 RISK FACTORS FOR BREAST CANCER IN WOMEN

RELATIVE RISK >4.0
Age (65+ vs. <65 yr, although risk increases across all ages until age 80 yr)
Biopsy-confirmed atypical hyperplasia
Certain inherited genetic mutations for breast cancer, including *BRCA1, BRCA2, p53, CHEK2, PALB2, PTEN*
Ductal carcinoma in situ
Lobular carcinoma in situ
Mammographically dense breasts (compared with least dense)
Personal history of early-onset (<40 yr) breast cancer
Two or more first-degree relatives with breast cancer diagnosed at an early age
RELATIVE RISK 2.1-4.0
Personal history of breast cancer (40+ yr)
High endogenous estrogen or testosterone levels (postmenopausal)
High-dose radiation to chest
One first-degree relative with breast cancer
RELATIVE RISK 1.1-2.0
Alcohol consumption
Ashkenazi Jewish heritage
Diethylstilbestrol exposure
Early menarche (<12 yr)
Height (tall)
High socioeconomic status
Late age at first full-term pregnancy (>30 yr)
Late menopause (>55 yr)
Never breastfed a child
No full-term pregnancies
Obesity (postmenopausal)/adult weight gain
Personal history of endometrial or ovarian cancer
Proliferative breast disease without atypia (usual ductal hyperplasia and fibroadenoma)
Recent and long-term use of menopausal hormone therapy containing estrogen and progestin
Recent oral contraceptive use

Modified from American Cancer Society. *Breast Cancer Facts & Figures 2017-2018*. ACS; Atlanta, GA: 2017; Hu C, Hart SN, Gnanaolivu R, et al. A population-based study of genes previously implicated in breast cancer. *N Engl J Med*. 2021;384:440-451.

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NANCY E. DAVIDSON

BREAST CANCER

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Two or more first-degree relatives with breast cancer diagnosed at an early age
RELATIVE RISK 2.1-4.0
Personal history of breast cancer (40+ yr)
High endogenous estrogen or testosterone levels (postmenopausal)
High-dose radiation to chest
One first-degree relative with breast cancer
RELATIVE RISK 1.1-2.0
Alcohol consumption
Ashkenazi Jewish heritage
Diethylstilbestrol exposure
Early menarche (<12 yr)
Height (tall)
High socioeconomic status
Late age at first full-term pregnancy (>30 yr)
Late menopause (>55 yr)
Never breastfed a child
No full-term pregnancies
Obesity (postmenopausal)/adult weight gain
Personal history of endometrial or ovarian cancer
Proliferative breast disease without atypia (usual ductal hyperplasia and fibroadenoma)
Recent and long-term use of menopausal hormone therapy containing estrogen and progestin
Recent oral contraceptive use

Modified from American Cancer Society. *Breast Cancer Facts & Figures 2017-2018*. ACS; Atlanta, GA: 2017; Hu C, Hart SN, Gnanaolivu R, et al. A population-based study of genes previously implicated in breast cancer. *N Engl J Med*. 2021;384:440-451.

ABSTRACT

Breast cancer, which is the most common nonskin cancer in women in the world, includes a myriad of molecular subtypes. Screening mammography is an effective approach to early detection and can reduce the morbidity and mortality associated with advanced disease. Most patients present with early-stage disease and are treated in a personalized fashion with multimodality therapy, including surgery, radiotherapy, chemotherapy, endocrine therapy, and targeted therapy. Metastatic breast cancer can be managed as a chronic disease with sequential systemic therapies.

KEYWORDS

breast cancer
endocrine
HER2
BRCA
mammary

include inspection of the breasts for changes in shape, skin color, or dimpling with the patient's hands above their head and on the hips; palpation of the breasts in the upright and reclining positions using a standard approach of circles, wedges, or lines to cover the entire breast; and examination of the axillary, supraclavicular, and infraclavicular lymph nodes. If the abnormality was not detected by a screening mammogram, a mammogram should be obtained promptly.

If the breast examination and bilateral mammography are normal in patients who have localized noncyclic breast pain, ultrasound or magnetic resonance imaging (MRI) may be used to exclude the small possibility of a malignancy. Bilateral breast imaging is always recommended to identify any unsuspected lesions in the contralateral breast that may also require evaluation.

For both clinically occult and clinically apparent lesions, pathologic evaluation is mandatory to establish a diagnosis. An outpatient core needle biopsy should be guided by mammography, ultrasonography, or MRI if the lesion is not palpable. In patients who have clear or bloody nipple discharge, ductography and ductoscopy may help to identify the inciting lesion, but excisional biopsy may be required.

These technologies generally permit an accurate diagnosis that can be followed by definitive treatment, but the concordance among pathologists is only about 96% for the diagnosis of invasive carcinoma, about 85% for ductal carcinoma in situ or fully benign biopsies, and as low as 50% for atypia. Further expert evaluation is required when biopsy of a suspicious lesion yields equivocal diagnosis after needle aspiration or core biopsy.

Staging and Prognostic and Predictive Markers

Breast cancers are staged from I to IV, with stages I and II representing early-stage disease, stage III signaling more locally advanced disease, and stage IV denoting metastatic disease. Outcomes are highly correlated with stage of disease.

Anatomic staging (Table 183-2) considers just the tumor's size (T), nodal involvement (N), and metastases (M) and should only be used in global regions where biomarker tests are not routinely available. Most patients with breast cancer present with anatomic stage I or II disease in the absence of symptoms. In such patients, basic laboratory studies can be limited to blood counts, chemistry panel, and a chest radiograph, because more extensive radiologic evaluation is not warranted because of low yield. In contrast, women with clinical evidence of stage III or IV disease should undergo more intensive evaluation of common sites for metastases, including lung, liver, and bone, using computed tomography (CT) and positron emission tomographic (PET) radionuclide scanning.

TABLE 183-2 ANATOMIC STAGING OF BREAST CANCER

STAGE	DESCRIPTION
NONINVASIVE	
0	• Ductal carcinoma in situ; no invasion of the duct's basement membrane or adjacent normal tissue
INVASIVE	
1A	• Breast tumor ≤ 2 cm, no spread beyond the breast and no involved lymph nodes
1B	• No breast tumor, but microscopic (>0.2 mm to ≤2 mm) metastases in axillary lymph nodes OR • Tumor ≤ 2 cm in the breast plus involved lymph nodes
IIA	• No tumor in the breast, but macroscopic (>2 mm) tumor in one to three axillary lymph nodes OR • Tumor ≤ 2 cm in breast, with spread to axillary lymph nodes OR • Tumor > 2 cm to ≤5 cm in the breast, no spread to axillary lymph nodes
IIB	• Tumor > 2 cm but ≤5 cm in the breast, spread to one to three axillary lymph nodes OR • Tumor > 5 cm in the breast, no spread to axillary lymph nodes
IIIA	• Tumor > 5 cm in the breast, spread to axillary and/or internal mammary nodes • Metastases in four to nine axillary lymph nodes or in internal mammary nodes regardless of presence or size of tumor in the breast
IIIB	• Tumor spread to chest wall and/or skin of the breast regardless of size of tumor in the breast; may also be seen to axillary or internal mammary tumor nodes
IIIC	• Tumor of any size with spread to ≥10 axillary lymph nodes OR • Tumor spread to infraclavicular or supraclavicular lymph nodes OR • Tumor spread to both axillary lymph nodes and internal mammary nodes
METASTATIC	
IV	• Spread of tumor to other parts of the body such as liver, lung, or bone

However, all patients with invasive cancers (anatomic stage 1 A or higher) also should undergo pathological prognostic staging, which incorporates a number of biomarkers (including histologic grade, expression of estrogen and progesterone receptors and HER2 proteins, and sometimes multigene panels).[6] By integrating data derived from analysis by genomic DNA copy number arrays, DNA methylation, exome sequencing, messenger RNA arrays, microRNA sequencing, and reverse-phase protein arrays, breast cancers can be divided into at least four molecular subsets: luminal A and B, HER2, and basal. The luminal subtypes frequently express the estrogen receptor-α, but luminal A appears to be associated with a better prognosis and higher likelihood of response to endocrine therapy than luminal B. The basal subtype is dominated by tumors that lack expression of the estrogen receptor-α, the progesterone receptor, or HER2—the so-called triple-negative breast cancer that lacks a readily identified molecular target. Multigene assays can identify early-stage steroid receptor–positive breast cancers that will benefit from the addition of chemotherapy to endocrine therapy and may identify women with a poor prognosis.[A2] Whole-genome sequencing of the breast cancer also may help to pinpoint avenues for precise diagnostics and targeted therapy.

Germline testing for *BRCA1* and *BRCA2* mutations through a multigene panel should be part of the evaluation of women with clinical features suggestive of a hereditary breast cancer syndrome (e.g., a personal diagnosis of breast cancer at age 45 years or younger or of ovarian cancer at any age, a personal diagnosis of triple-negative breast cancer at age 60 years or younger, multiple family members with early-onset breast or ovarian cancer, bilateral breast cancer, or Ashkenazi Jewish heritage). Careful counseling about the implications of positive or negative results and about the limitations of testing is a prerequisite for testing.[7]

Less than 10% of women present initially with metastatic disease. Advanced disease is more commonly diagnosed in women who have a previous diagnosis of early breast cancer for which they have received treatment. Common sites for metastases include bone, soft tissues, lung, liver, and brain. If metastatic disease is suspected, relevant hematologic, biochemical, and radiographic evaluation is indicated to assess the location and severity of involvement. Because of the importance of the diagnosis, pathologic confirmation is preferred to verify recurrent disease, exclude other diagnoses, and reassess of biologic features such as the expression of estrogen receptors, progesterone receptors, and HER2. Elevation of tumor markers (e.g., CA-27-29, carcinoembryonic antigen) or the presence of circulating tumor cells or circulating free tumor DNA is not diagnostic of recurrent disease, although these markers may be useful adjuncts in the assessment of the effects of therapy.

TREATMENT

The treatment of breast cancer should be tailored to its stage and biology.[8] For example, tumors that express the estrogen receptor-α, the progesterone receptor, or both, are responsive to endocrine therapy, whereas tumors that lack both seldom respond to such therapy. Overexpression of the HER2 protein is associated with response to the HER2-targeted therapies.[9] Evidence that links expression of the estrogen receptor, the progesterone receptor, or HER2 to the efficacy of chemotherapy is equivocal.

In Situ Carcinoma

In countries where screening mammography is widely used, in situ carcinomas account for 20 to 25% of newly diagnosed cases of breast cancer (see Table 183-3).

Ductal Carcinoma In-Situ

Most in situ breast tumors are ductal carcinoma in situ (DCIS) lesions, which are associated with approximately a 30% risk for the development of subsequent invasive breast cancer in the same breast. The risk for metastatic breast cancer with a diagnosis of DCIS is extremely small. As a consequence, management decisions are centered on the involved breast, and axillary lymph node evaluation is not routinely performed. Total mastectomy has a high likelihood of cure, but lumpectomy with conservation of the breast is appropriate for many women with DCIS. Sufficient excision to obtain tumor-free margins is critical. Careful examination of the specimen and postexcision mammography are crucial to confirm that the DCIS has been adequately excised. The size and grade of the lesion are other important determinants of local outcome.

Radiotherapy plus lumpectomy decreases the likelihood of in situ or invasive recurrence compared with lumpectomy alone, but women who have favorable histologic findings and who are willing to undergo close surveillance are candidates for local excision alone. In addition, the use of oral tamoxifen (20 mg daily) or an aromatase inhibitor (e.g., oral anastrozole 1 mg daily) for 5 years can reduce the likelihood of recurrent ipsilateral breast cancer or a new contralateral breast cancer by approximately 50%.

Lobular Carcinoma In Situ

Controversy continues over whether lobular carcinoma in situ (LCIS) is truly a malignant lesion. LCIS is usually an incidental finding on a breast biopsy that

TABLE 183-3 CARCINOMA IN SITU: DUCTAL VERSUS LOBULAR

FEATURE	LOBULAR CARCINOMA IN SITU	DUCTAL CARCINOMA IN SITU
Age	Younger	Older
Palpable mass	No	Uncommon
Mammographic appearance	Not detected on mammography	Microcalcifications, mass
Immunophenotype	E-cadherin negative	E-cadherin positive
Usual manifestation	Incidental finding on breast biopsy	Microcalcifications on mammography or breast mass
Bilateral involvement	Common	Uncertain
Risk and site of subsequent breast cancer	25% risk for invasive breast cancer in either breast over remaining lifespan	At site of initial lesion; 0.5% risk/yr of invasive breast cancer in opposite breast
Prevention	Consider tamoxifen or raloxifene or aromatase inhibitor	Consider tamoxifen or aromatase inhibitor if estrogen receptor positive
Treatment	Yearly mammography and breast examination	Lumpectomy ± radiation; mastectomy for large or multifocal lesions

was performed for other indications, and it appears to be associated with a 25% risk for the development of invasive breast cancer in either breast. Women with LCIS are generally managed expectantly with regular breast examination and imaging. Bilateral total mastectomy is sometimes considered for women whose LCIS is associated with other risk factors for breast cancer or with extreme anxiety. Women with LCIS are candidates for tamoxifen (20 mg daily), raloxifene (60 mg daily), or an aromatase inhibitor (e.g., anastrozole 1 mg daily) as a risk-reduction strategy.

Early Stage Invasive Breast Cancer

Surgery

Breast conservation surgery with lumpectomy plus radiotherapy provides identical survival rates to modified radical mastectomy (removal of the breast and lymph nodes) for women with stages I and II breast cancer. Medical contraindications to breast conservation therapy include multifocal disease, previous radiotherapy, ongoing pregnancy that precludes the timely use of radiotherapy, poor cosmesis, and patient preference. Patients who undergo mastectomy should be counseled about the availability of autologous tissue and implant options for reconstruction, either at the time of surgery or any time thereafter.[10]

For women who have small tumors and a clinically negative axilla, no further local evaluation is needed. For adequate staging of larger tumors, however, the involvement of axillary lymph nodes must be determined. To minimize the incidence of postoperative lymphedema associated with lymph node dissection,[11] a radioactive tracer, blue dye, or both are injected into the area around the primary breast tumor and tracked to the dominant axillary lymph node (the sentinel node), which can be located and removed by the surgeon. If the sentinel node is tumor free or if the burden of disease in sentinel nodes is low, no further axillary surgery is required. Women who have palpable axillary nodes or who have extensively involved sentinel nodes should be counseled to undergo axillary dissection.

Adjuvant Radiotherapy

Women who have undergone lumpectomy alone have a breast cancer recurrence rate of up to 40%, whereas the rate of recurrence is less than 10% with whole-breast radiotherapy, often administered on an accelerated schedule.[12] Women who are older than age 65 years and who receive tamoxifen for low-risk estrogen receptor–positive tumors will have a lower rate of local recurrence but no benefit in terms of distant recurrence or survival.[A3] In women who have positive axillary nodes or high-risk characteristics despite negative nodes, radiation therapy appears to reduce recurrence rates but provides little if any overall survival benefit.

Women who have undergone mastectomy also likely gain a survival advantage from postoperative radiation therapy if they have more than three involved lymph nodes. For women who have involvement of one to three nodes, the potential benefit is smaller, and expert consultation is helpful.

Adjuvant Systemic Therapy

Neoadjuvant Chemotherapy

Women frequently receive several adjuvant interventions, including chemotherapy, radiotherapy, endocrine therapy, and/or anti-HER2 therapy. For clinically node-positive tumors or tumors larger than 2 cm, neoadjuvant preoperative checkpoint inhibitor therapy with pembrolizumab plus chemotherapy is standard treatment for triple-negative breast cancer, and neoadjuvant anti-HER2 therapy plus chemotherapy should be considered for HER2-positive breast cancer.[13] Otherwise, neoadjuvant chemotherapy improves the rate of breast conservation but does not enhance disease-free or overall survival.[A4]

TABLE 183-4 (NEO)ADJUVANT TREATMENT GUIDELINES FOR PATIENTS WITH EARLY-STAGE INVASIVE BREAST CANCER

PATIENT GROUP	TREATMENT
HORMONE RECEPTOR–POSITIVE (ER- AND/OR PR-POSITIVE) BREAST CANCER	
Low tumor burden	
≤0.5 cm pN0	Consider adjuvant hormonal therapy
0.6-1.0 cm well differentiated and no unfavorable features pN0	Consider adjuvant hormonal therapy
>1 cm	Adjuvant hormonal therapy ± adjuvant chemotherapy (may use genomic testing)
Intermediate or high tumor burden and unfavorable biology	
	Adjuvant hormonal therapy + adjuvant chemotherapy; may consider abemaciclib
HORMONE RECEPTOR–NEGATIVE (ER- AND PR-NEGATIVE) BREAST CANCER	
≤0.5 cm and pN0	No adjuvant therapy
All other tumors	(Neo)adjuvant chemotherapy; consider pembrolizumab
HER2 POSITIVE	
	Anti-HER2 therapy should be added to the suggested treatment above for all node-positive patients and considered for pN0 tumors that are >5 mm

Modified from National Comprehensive Cancer Network Guidelines and 2021 St. Gallen Conference. Available at http://www.nccn.org. and Ann Oncol 32:1216-1235, 2021.

Adjuvant Chemotherapy

After definitive local therapy for early breast cancer, adjuvant chemotherapy, endocrine therapy, biologic therapy, or a combination of these approaches aims to suppress or eradicate clinically occult micrometastases. Recommendations for adjuvant systemic therapy are based on menopausal status, lymph node status, tumor size, the extent of expression of the estrogen receptor, progesterone receptor, HER2 proteins in breast cancer cells, and certain multigene tests (Table 183-4).[14]

Adjuvant therapy results in a proportional reduction in risk for recurrence across all patients regardless of risk for recurrence, so the absolute benefit of adjuvant systemic therapy is greatest for patients who have the greatest risk for recurrence. However, women who have a high clinical risk but a low genomic risk for recurrence based on a 70-gene signature gain little benefit from adjuvant chemotherapy.

Adjuvant chemotherapy may be administered before or after radiotherapy. Adjuvant endocrine therapy should be delayed until after completion of chemotherapy. The benefit of trastuzumab for HER2-positive cancers appears to be optimized when it is coadministered with taxane chemotherapy rather than following completion of the taxane.

ADJUVANT ENDOCRINE THERAPY. Tamoxifen (20 mg/day for 5 to 10 years) improves outcomes in women of all ages with estrogen receptor– or progesterone receptor–positive breast cancer.[A5] Its side-effect profile includes an increased risk for thromboembolic events and uterine cancer, especially in postmenopausal women, because of its estrogen agonist properties. Potential benefits include promotion of bone density and lowering of cholesterol. Tamoxifen is the preferred adjuvant endocrine therapy for premenopausal women and for men.

Luteinizing hormone–releasing hormone (LHRH) agonists (e.g., leuprolide 3.75 mg intramuscularly monthly) can temporarily and reversibly suppress ovarian function when used in combination with an aromatase inhibitor (e.g., exemestane 25 mg daily) or tamoxifen (20 mg daily) and can improve disease-free survival in women who are premenopausal and are at sufficient risk for recurrence to warrant adjuvant chemotherapy.[A6] Administration of goserelin (a gonadotropin-releasing hormone agonist to protect ovarian function at 3.6 mg subcutaneously monthly) with chemotherapy may protect against permanent ovarian failure, thereby reducing the risk for early menopause and improving prospects for subsequent fertility.[A7]

In postmenopausal women, the primary source of estrogen is the conversion of androgens synthesized by the adrenal glands to estrogen through the activity of CYP19 or aromatase in peripheral tissues such as mammary and adipose tissues. The aromatase inhibitors (anastrozole 1 mg daily; letrozole 2.5 mg daily; and exemestane 25 mg daily) specifically inhibit this conversion, thereby leading to further estrogen deprivation in older women. Multiple trials suggest that an aromatase inhibitor is preferred over tamoxifen in postmenopausal women and in premenopausal women who are receiving an LHRH agonist for estrogen receptor–positive breast cancer because these inhibitors reduce recurrence rates by about 30% (proportionately) compared with tamoxifen.[A8,A9] Side effects include postmenopausal symptoms, osteoporosis, fractures, and arthralgias. Aromatase inhibitors are not useful for receptor-negative breast cancer, and they should not be used as monotherapy in premenopausal women or men with breast cancer. The simultaneous administration of aromatase inhibitor plus tamoxifen does not improve outcome over aromatase inhibitor alone, but the addition of abemaciclib (a CDK4/6 inhibitor) to an aromatase inhibitor can provide additional benefit for women who have high-risk early breast cancer.[A10]

The duration of endocrine therapy appears to be quite important. Five years of adjuvant endocrine therapy is associated with better outcomes than shorter periods, and 10 years of tamoxifen appears to be better than 5 years. However, the benefit of extending aromatase inhibitor therapy beyond 5 years is unproven.[A11] The greatest benefit of longer term therapy is probably prevention of contralateral breast cancer.

ADJUVANT ANTI-HER2 THERAPY. The transmembrane HER2/neu protein is overexpressed in approximately 15 to 20% of breast cancers, generally because of gene amplification. Adding 1 year of therapy with trastuzumab (a monoclonal antibody to HER2) to chemotherapy reduces the risk for recurrence by approximately 50% in women with high-risk or residual invasive HER2-positive early breast cancer.[A12] Questions remain regarding long-term risks and benefits, the use of trastuzumab in the absence of chemotherapy, and the role of other anti-HER2 agents such as lapatinib, pertuzumab, neratinib, and trastuzumab emtansine in addition to or in place of trastuzumab. Neratinib is beneficial when used as adjuvant therapy for 1 year after a year of trastuzumab-containing therapy, and emtansine is beneficial for women who have residual breast cancer after neoadjuvant chemotherapy.[A13]

ADJUVANT CHEMOTHERAPY. The benefit of conventional adjuvant chemotherapy varies by age and nodal status, with its greatest absolute benefit in women who are younger than age 50 years, in whom it decreases the 15-year risk of breast cancer mortality from 42 to 32%. Effective combination regimens may include anthracyclines, taxanes, antimetabolites, and cyclophosphamide, preferably for 3 to 6 months at standard doses under expert oversight. Careful use of colony-stimulating agents can minimize neutropenia, accelerate administration of chemotherapy, and improve responses,[A14] but current evidence argues against the use of erythroid-stimulating agents for chemotherapy-induced anemia. Acute side effects of therapy are nausea and vomiting, bone marrow suppression, and hair loss; all are reversible, and the first may be mitigated by the use of modern antiemetics. Induction of menopause is related to the type and duration of chemotherapy and the age of the patient; most women older than 40 years will suffer drug-induced menopause. Doxorubicin-related cardiomyopathy is noted in approximately 1% of women who receive doxorubicin-containing adjuvant chemotherapy. Use of standard adjuvant chemotherapy regimens results in a very small increase in the incidence of acute leukemia but not of other second tumors.

OTHER ADJUVANT APPROACHES. One year of the oral poly (ADP ribose) polymerase (PARP) inhibitor, olaparib, is indicated for adjuvant treatment of patients who have BRCA-mutated, HER2 negative, high-risk early breast cancer and who have been treated with neoadjuvant or adjuvant chemotherapy.[A15] The combination of pembrolizumab with chemotherapy in the neoadjuvant and adjuvant setting improves outcomes for early triple-negative breast cancer.[A16]

Follow-Up of Early-Stage Breast Cancer Survivors

Substantial evidence can guide follow-up of asymptomatic survivors of early-stage breast cancer (Table 183-5). More aggressive testing does not provide incremental value.

Stage III Breast Cancer

Approximately 10% of breast cancers present as locally advanced or inoperable stage III tumors that are characterized by large primary tumor, fixed tumor or lymph nodes, or neoplastic invasion of the skin or chest wall. Inflammatory breast cancers also are categorized as stage III. Because as many as one third of women with locally advanced breast cancer also have distant metastases at the time of diagnosis, an evaluation for metastatic disease is often indicated even in asymptomatic patients.

Combined-modality therapy is used under expert supervision to maximize control of local disease and distant micrometastases. Several months of preoperative endocrine therapy or chemotherapy can result in tumor regression in most patients, thereby allowing definitive breast surgery of some type to be performed. Postoperative radiotherapy is generally used to enhance local control, and some studies suggest that administration of further chemotherapy, hormone therapy, anti-HER2 therapy, or a combination thereof (depending on the features of the cancer) is then desirable.

TABLE 183-5 FOLLOW-UP GUIDELINES FOR PATIENTS WITH EARLY-STAGE BREAST CANCER: AMERICAN SOCIETY OF CLINICAL ONCOLOGY GUIDELINES

PROCEDURE OR TEST	FREQUENCY
History and physical examination* (eliciting of symptoms of breast cancer)	Every 3-6 mo for first 3 yr, every 6-12 mo for next yr, then yearly
MAMMOGRAPHY	
Mastectomy patients	Yearly
Lumpectomy patients	Yearly
Pelvic examination	Age appropriate
Breast self-examination	Monthly
Complete blood cell counts and chemistry studies	The literature does not support the use of these tests
Chest radiography, bone scans, PET scans, breast MRI, liver imaging, and tumor marker studies	Not recommended for routine follow-up in asymptomatic patients
Patient education regarding signs and symptoms of recurrence	Each visit

*Limited evaluation: assess for pain, dyspnea, weight loss, and other major changes in function. The limited examination should include an assessment of nodes, axillae, lumpectomy or mastectomy site, contralateral breast, chest, and abdomen. Patients should be instructed regarding symptoms of recurrence.

MRI = magnetic resonance imaging; PET = positron emission tomography.

Modified from Khatcheressian JL, Hurley P, Bantug E, et al. Breast cancer follow-up and management after primary treatment: American Society of Clinical Oncology clinical practice guideline update. *J Clin Oncol*. 2013;31:961-965.

Stage IV or Metastatic Breast Cancer

Whenever possible, biopsy of a putative metastatic lesion should be performed to confirm the diagnosis of metastatic breast cancer and assess biological markers to guide systemic therapy.[15] Although seldom curable, advanced breast cancer is a highly treatable illness. Palliation or prevention of symptoms without excess toxicity is the primary goal of treatment.

General Approach

The role of surgery in metastatic breast cancer is limited. However, surgery is useful in certain circumstances, such as resection of a chest wall nodule or solitary brain metastasis, or orthopedic stabilization to treat or prevent a long-bone fracture. Pleural (Chapter 86) and pericardial (Chapter 62) effusions should be drained percutaneously but often require more definitive local therapy.

Radiotherapy is a mainstay in the management of advanced disease. It may be used at any time during the patient's course to treat localized disease such as chest wall recurrence, brain metastases, or painful bony metastases.

Systemic treatment is the primary mode to manage disseminated disease. Key principles for the selection of therapy include maximal palliation of symptoms, minimization of treatment-related toxicity, and prevention of disease complications (Fig. 183-1).

Endocrine Therapy

Endocrine therapy under expert supervision is preferred as the first intervention for metastatic breast cancer whenever feasible because of its favorable therapeutic index. Factors that support the use of endocrine therapy include the expression of hormone receptors, a long disease-free interval, and absence of symptoms or visceral disease. More than 50% of women who meet these criteria respond to an initial course of hormone therapy, with a median response duration of 9 to 12 months. Length of response is a good predictor for the likelihood of response to a second course of endocrine therapy when the first agent fails. A second course of endocrine therapy is less likely to be successful, and the duration of response is shorter; again, duration of response predicts for likelihood of success with third-line therapy. In some women, this approach can result in good disease control with little toxicity for several years.

Several months of therapy are needed before the efficacy of a newly introduced endocrine therapy can be assessed. Patients and clinicians should be aware of the possibility of treatment-related tumor flare with worsening symptoms and increased circulating tumor markers within the first few weeks of treatment. This response is usually of short duration and should not be confused with progressive disease.

Available hormone therapies include the selective estrogen receptor modulator (SERM) tamoxifen, the selective estrogen receptor–degrading agent fulvestrant, the aromatase inhibitors, and ovarian suppression by oophorectomy or LHRH agonists. Selection under expert oversight is usually made on the basis of efficacy, toxicity, and menopausal status. Serial administration of agents is the norm, but the combination of the aromatase inhibitor anastrozole with fulvestrant is superior to anastrozole alone or to sequential anastrozole and

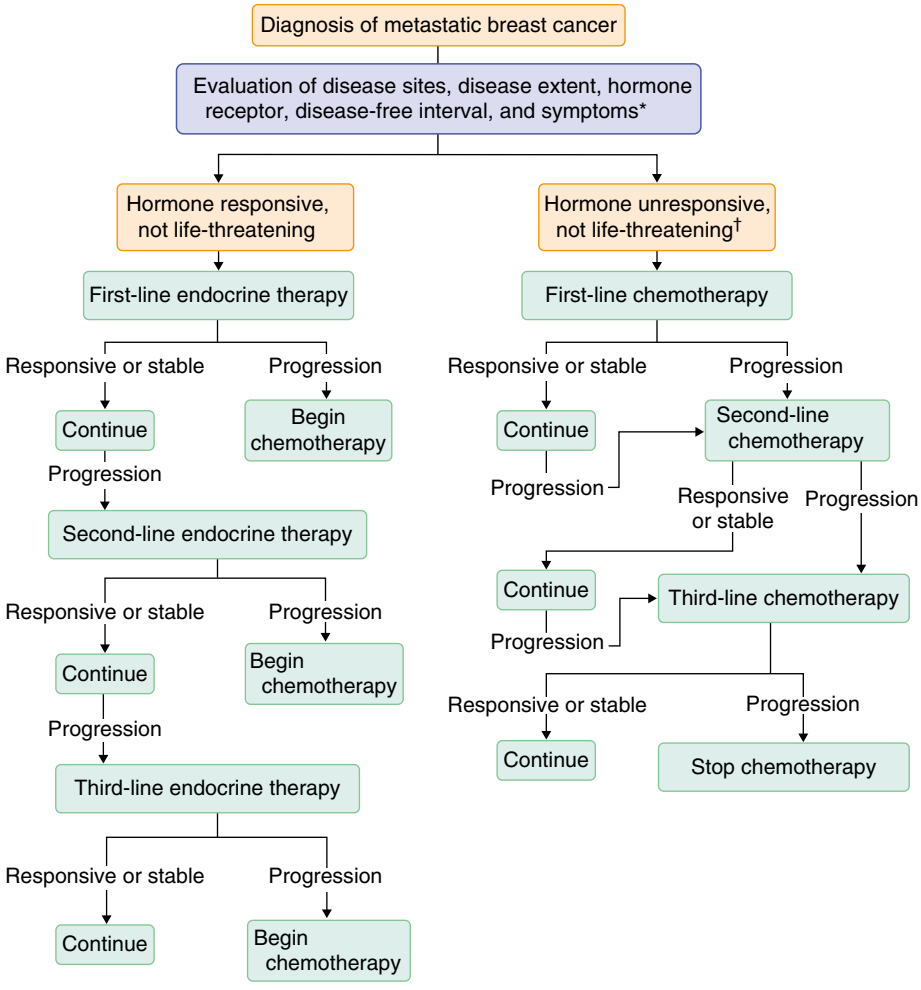

FIGURE 183-1. An algorithm used for the systemic treatment of stage IV breast cancer. *Consider use of bisphosphonate or denosumab if bone involvement and use of a CDK4/6 inhibitor with first-line endocrine therapy. †Consider integration of anti-HER2 therapy if the tumor overexpresses HER2 or pembrolizumab for triple-negative metastatic breast cancer.

fulvestrant.[A17] Other combination therapies (with the possible exception of ovarian suppression plus tamoxifen) do not improve outcomes.

Inhibitors of cyclin-dependent kinases 4 and 6 (e.g., palbociclib, ribociclib, and abemaciclib), which promote progression from the G1 phase to the S phase of the cell cycle, are now commonly used with endocrine therapy to improve outcomes. For example the combination of ribociclib plus letrozole increases survival[A18] in postmenopausal women with hormone-receptor-positive metastatic disease.

In patients who have PIK3CA-mutated hormone receptor–positive HER2-negative advanced breast cancer and who have previously received combination endocrine plus CDK4/6 inhibitor therapy, the addition of alpelisib (a PI3Kα-specific inhibitor) improves progression-free survival.[A19] Everolimus (but not temsirolimus) combined with an aromatase inhibitor can also improve progression-free survival compared with an aromatase inhibitor alone in patients with hormone receptor–positive advanced breast cancer previously treated with nonsteroidal aromatase inhibitors.

HER2-Expressing Tumors

Trastuzumab monotherapy under expert supervision can provide partial or complete tumor regression in about 30% of women who have metastatic HER2-overexpressing breast cancer. Concurrent trastuzumab with paclitaxel also increases the rate and duration of response as well as survival compared with paclitaxel alone for women with newly diagnosed HER2-overexpressing metastatic breast cancer. Seven other anti-HER2 agents now available for treatment of advanced breast cancer in the United States include the oral small molecule inhibitors (e.g., neratinib, tucatinib, and lapatinib), monoclonal antibodies (pertuzumab, which inhibits HER dimerization, as well as margetuximab-cmkb), and conjugates of a cytotoxic agent to trastuzumab (trastuzumab emtansine or trastuzumab deruxtecan).[16] The addition of pertuzumab to trastuzumab and docetaxel significantly improves outcomes in first-line treatment of metastatic HER2-positive breast cancer, whereas trastuzumab deruxtecan is preferred over trastuzumab emtansine in the second-line setting.[A20] Adding tucatinib to trastuzumab and capecitabine also can prolong survival in heavily pretreated patients.[A21]

Other Biologic Agents

The poly-ADP-ribose polymerase (PARP) inhibitors of DNA repair show activity in women with *BRCA* mutant breast cancer. Two inhibitors, olaparib[A22] and talzoparib,[A23] are now approved for use in women with germline *BRCA1*- or *BRCA2*-mutant advanced breast cancer.

Bevacizumab, which is a monoclonal antibody that targets the vascular endothelial growth factor, has only modest activity in metastatic breast cancer, whether used as monotherapy or in addition to taxane-based chemotherapy.

Chemotherapy

Most women with advanced breast cancer eventually become unresponsive to endocrine and other targeted therapies, at which time they become candidates for palliative chemotherapy. Serial chemotherapy under expert oversight is the norm. Patients receive two to four cycles of therapy and then are re-evaluated for stabilization or improvement. The duration of therapy varies depending on response, but quality of life is often better with continued therapy until the disease progresses, provided that side effects are tolerable.

Active agents include cyclophosphamide, doxorubicin, methotrexate, paclitaxel, docetaxel, vinorelbine, capecitabine, gemcitabine, carboplatin, ixabepilone, pegylated doxorubicin, eribulin, nano-albumin–bound paclitaxel, and sacituzumab govitecan-hziy. However, pembrolizumab may be combined with chemotherapy in patients who have advanced triple-negative breast cancer that expresses PD-L1.[A24]

As with endocrine therapy, response rates and duration diminish with each successive change in therapy. High-dose chemotherapy combined with autologous stem cell or bone marrow support is not of incremental benefit. A difficult question for patient and doctor is when to stop chemotherapy. No consensus guidelines indicate when to discontinue chemotherapy, but many patients and physicians move to a program of supportive care if two successive chemotherapy regimens fail to produce a tumor response or to stabilize the disease.

Supportive Care

Bone Health

Because palliation of symptoms and prevention of complications of metastatic disease are the primary goals of treatment for advanced breast cancer, careful attention to supportive care is vital. Bone is the most common site of metastasis in breast cancer, and bone disease can be a source of significant morbidity. The regular administration of a bisphosphonate such as zoledronate or pamidronate or the anti-RANKL monoclonal antibody denosumab (Chapter 225), in addition to endocrine therapy or chemotherapy, can reduce pain and the incidence of skeletal complications in

metastatic disease. Bisphosphonates are sometimes used as adjuvant therapy to try to reduce the rate of recurrent breast cancer in the bone and to improve breast cancer survival in early-stage postmenopausal patients, and denosumab (60 mg subcutaneously every 6 months) is another alternative in this setting.[A25]

Postmenopausal Symptoms

Postmenopausal symptoms (Chapter 222) are common in breast cancer survivors as a consequence of therapy or of natural aging. In general, hormone replacement therapy should be avoided in women with a history of breast cancer. A short course of treatment can be considered in patients who have early-stage breast cancer who have truly disabling symptoms. Topical estrogens are considered for women with vaginal dryness that does not respond to lubricants. Otherwise, vasomotor symptoms may be reduced by nonhormonal therapies (Chapter 222).

Lymphedema

Lymphedema develops in the ipsilateral arm in up to 15% of women after treatment for early breast cancer. Its incidence is lower with sentinel lymph node procedures and meticulous radiotherapy. Prevention includes avoidance of trauma and possibly exercises. Early recognition of symptoms is key. Affected patients should be referred to specialists for consideration of treatments such as manual drainage or the use of compression stockings or pumps.

Breast Cancer During Pregnancy

The risk for breast cancer is slightly increased during and just after pregnancy (Chapter 221). Suspicious breast findings during pregnancy should be investigated vigorously. Surgical therapy can be safely performed for breast cancer after the first trimester of pregnancy, but radiotherapy should be delayed until after delivery. Certain adjuvant chemotherapy regimens can be safely administered in the second and third trimesters of pregnancy under expert oversight. Administration of antimetabolites should be avoided because of the potential for damage to the placenta. Initiation of endocrine therapy is generally delayed until after delivery. Pregnancy after a diagnosis of early breast cancer does not appear to increase the risk for metastatic disease. The major considerations for women contemplating pregnancy should be its timing with regard to endocrine therapy, which may require 5 or more years to complete, as well as the underlying risk for recurrent breast cancer.

Breast Cancer in Men

Men account for not more than 1% of breast cancer cases.[17] Failure of the patient or health care provider to diagnose the disease means that it may be diagnosed at a later stage. Germline DNA repair gene mutations (especially *BRCA2*) are associated with breast cancer in men, and men with breast cancer should be offered genetic counseling and testing of relevant genes.[18] Most breast cancers in men express the estrogen receptor, and treatment recommendations for these men are generally similar to those for postmenopausal women.[19]

PREVENTION

Current strategies to prevent breast cancer include surgical, chemopreventive, and lifestyle modification approaches.

Prophylactic Mastectomy and Oophorectomy

Prophylactic mastectomy appears to reduce the risk for developing breast cancer by approximately 90% in individuals who are at high risk because of a strong family history or carriage of a germline *BRCA1* or *BRCA2* or related mutation. However, women who opt for prophylactic mastectomy must be counseled about the possibility that cancer may develop in remnants of breast tissue that persist after prophylactic mastectomy. In carriers of *BRCA* mutations, prophylactic oophorectomy can decrease the incidence of breast cancer by approximately 50%, presumably because of a reduction in ovarian steroids.

Chemoprevention

Tamoxifen (20 mg daily) reduces the risk of invasive breast cancer by about 40% in high-risk women (i.e., women who are age 60 years or older, have a diagnosis of lobular carcinoma in situ, or are ages 35 to 59 years with a constellation of risk factors that, when combined, result in a 1.67% or greater risk for breast cancer within 5 years).[20] Side effects include an increased risk for endometrial cancer and thromboembolic events in women over age 50 years. Raloxifene (60 mg daily) reduces the incidence of breast cancer in postmenopausal women who are at average risk of breast cancer but at elevated risk for cardiovascular disease, but it is less effective than tamoxifen for preventing invasive breast cancer in high-risk postmenopausal women. Raloxifene is associated with fewer uterine cancers but the same risk for thromboembolic events compared with tamoxifen. Other aromatase inhibitors (exemestane or anastrozole) also lower the incidence of breast cancer by approximately 50% in moderate- to high-risk postmenopausal women.[A26] Based on these data, the U.S. Preventative Services Task Force recommends tamoxifen, raloxifene, or aromatase inhibitors for women who have an increased risk of breast cancer and a low risk of adverse effects from these medications.[21,22]

TABLE 183-6 BREAST CANCER SCREENING IN WOMEN WITHOUT KNOWN GENETIC MUTATIONS (E.G., *BRCA1* OR *BRCA2*) OR FAMILIAL BREAST CANCER SYNDROME

TEST	ACS	USPSTF
Mammography	For average risk: Annual aged 45-54 yr Biennial (or annual) aged 55 yr and older if healthy and life expectancy ≥10 yr Option if 40-44 yr	Individual decision before age 50 Every 2 yr, aged 50-74 yr; insufficient evidence aged ≥75 yr
Clinical breast examination	Not recommended	Insufficient evidence to support
Breast self-examination	Not recommended	Not recommended

ACS = American Cancer Society; USPSTF = U.S. Preventive Services Task Force.

A vitamin A derivative, fenretinide, showed some impact as a chemopreventive agent for secondary prevention in premenopausal breast cancer survivors but has not found a place in routine practice. Finally, large epidemiologic studies have raised the possibility that aspirin or certain statins might also decrease breast cancer risk, but these agents have not yet been prospectively tested.

Lifestyle Modification

Regular exercise, especially during adolescence, may be associated with reduced risk of breast cancer. By extrapolation from the epidemiologic studies, abstinence from alcohol might slightly reduce the risk for breast cancer. A low-fat diet has not been shown to prevent breast cancer.

Screening

Conventional breast self-examination is not an effective screening tool, so many experts now promote breast awareness rather than regular breast self-examination. Breast examinations by a clinician have not been rigorously assessed, but the combination of examination plus mammography appears to decrease mortality from breast cancer by approximately 20% for average-risk women of all ages and by 25 to 30% in women over age 50 years. Considerable controversy continues over the value of screening mammography in women ages 40 to 50 years and women over age 70 years, as well as the optimal interval between mammograms for women ages 50 to 70 years. For example, a large randomized trial of annual mammography screening in women ages 40 to 49 years showed a 25% reduction in mortality from breast cancer at 10 years but no further reduction over the next 12 years.[A27] Currently, the American Cancer Society does not recommend clinical breast examination for cancer screening among average-risk women at any age, but it recommends annual screening mammography for women at standard risk for breast cancer starting at age 45 years (with opportunity to begin at age 40 years) and biennial screening (with opportunity to continue annual screening) beginning at age 55 years. In contrast, the U.S. Preventive Services Task Force and the American College of Physicians recommend that women between ages 40 and 50 years of age be counseled about the risks and benefits of screening mammography and that screening mammography can be used at 2-year intervals for women ages 50 to 74 years (Table 183-6). However, women ages 40 to 49 years with a two-fold increased risk for breast cancer have benefit-to-harm ratios for biennial screening mammography similar to average-risk women ages 50 to 74 years. In general, screening is unlikely to be worthwhile for women with a life expectancy of less than 10 years.

The survival benefits of mammography come at the cost of false-positive results that lead to anxiety and further evaluation.[23] By various estimates, more than 50% of women who are screened by mammography have false-positive results over 10 years of screening, and 7 to 9% are recommended for breast biopsy. Other studies have estimated an overdiagnosis rate of 3.3% for invasive cancer and from 18 to 32% for carcinoma in situ. The radiation exposure from mammography is estimated to cause 2 to 11 deaths per 100,000 screened women. Furthermore, some analysts suggest that the reduction in breast cancer mortality after the introduction of screening mammography is mostly a result of improved therapy rather than earlier diagnosis.

Screening mammography fails to diagnose approximately 10 to 15% of breast cancers, and screening MRI should be considered for women whose predicted risk for breast cancer exceeds 20%. MRI also can detect breast cancer in the

contralateral breast in 3% of women with a newly diagnosed breast cancer whose contralateral mammogram showed no abnormality.

For women with dense breasts, digital mammography may be more useful than conventional mammography. Another alternative is adjunctive ultrasonography, which similarly increases sensitivity and the detection rate of cancers but also has significantly more false positive results.

Supplemental MRI also increases the sensitivity for diagnosing cancer in women with extremely dense breasts.[A28] [A29] However, the use of MRI in the general population is limited by the fact that it is highly sensitive but lacks specificity. As a result, MRI has not translated into improved selection of surgical treatments or a reduction in the number of operations.

PROGNOSIS

Five-year life expectancy is 99% for localized disease and over 85% for regional disease. For stage III disease, multimodality therapy results in a 5-year disease-free survival rate of approximately 50%. The median survival after diagnosis of metastatic breast cancer is 2 to 3 years, although the range is great, and a small cadre of long-term survivors has been described. Poor prognosis is associated with high lymph node burden, poor histologic grade, large tumor size, absence of expression of estrogen receptors or progesterone receptors, and overexpression of HER2. Recent clinical trials document small improvements in survival with newer therapies.

BENIGN BREAST LESIONS

Benign breast disease includes mastalgia (pain and tenderness), mastitis (including infectious and noninfectious inflammatory conditions), trauma, and benign tumors.[24]

MASTALGIA

Mastalgia can be caused by trauma or by extramammary conditions, such as myocardial ischemia, pneumonia, pleural irritation, esophageal spasm, costochondritis, rib fracture, and varicella-zoster virus (preceding the skin eruption). After these conditions have been excluded, mastalgia is considered to be a benign condition that is self-limited. It can be cyclical or noncyclical in timing (where it is thought to be related to hormonal activity), and it may occur in postmenopausal women, even in the absence of hormone replacement therapy.

MASTITIS

Mastitis, which is caused by breast inflammation or infection, can occur in either nonlactating or lactating women. The typical presentation in nonlactating women is occurrence in their 40s with the acute onset of severe breast pain and tenderness followed by erythema and swelling that tends to be localized in the nipple-areolar area. In most cases, the cause is rupture of dilated subareolar ducts, followed by an inflammatory response to leakage of intraductal contents into periductal tissue. Infection is difficult to exclude, and patients are often treated with empirical antibiotics (e.g., oral cephalexin 250 mg every 6 hours or dicloxacillin 250 mg every 6 hours). If symptoms do not resolve within 7 to 10 days on antibiotics, ultrasound is required to exclude abscess.[25] If an abscess is found, incision and drainage are required. The most important differential diagnosis with mastitis is inflammatory carcinoma, and failure to improve with antibiotics or to find an abscess should lead to evaluation by a breast surgeon.

Mastitis in lactating women is often due to infection caused by a break in the skin of the nipple or milk stasis. *Staphylococcus aureus, Staphylococcus albus*, and sometimes *Escherichia coli, Corynebacteria*, or streptococci are the most common pathogens. Treatment requires antibiotics and removal of milk.

NONPROLIFERATIVE AND PROLIFERATIVE BENIGN BREAST LESIONS

The most common nonproliferative breast condition is fibrocystic breast disease, which is now more appropriately called *fibrocystic changes*. Fibrocystic changes are observed clinically in up to 50% of women and histologically in 90% of women. Lesions are composed of varying amounts of fibrosis and cysts, sometimes associated with calcifications and inflammation. Simple or complex cysts should be aspirated with ultrasound guidance and, when the fluid is not clear, sent for cytologic analysis.

Other nonproliferative benign breast lesions that can initially present as tumor-like processes include fibroadenomas (which are seen in about 25% of women and are usually solitary, sharply demarcated, smooth lesions in younger patients); phyllodes tumor (previously known as cystosarcoma phyllodes); and intraductal papillomas, which are solitary lesions that may be accompanied by bloody nipple discharge. Less-common nonproliferative benign breast lesions include inflammatory fat necrosis, which follows surgical or blunt trauma and generally resolves spontaneously; lymphocytic mastitis, which may be seen in diabetic patients; and granulomatous mastitis, which is associated with foreign body reactions (e.g., silicone and paraffin for breast augmentation and reconstruction after cancer surgery), sarcoid (Chapter 83), or certain infections.

Proliferative benign breast lesions include ductal or lobular hyperplasia. Atypical hyperplasias are associated with increased risk for breast cancer.

Overall, the relative risk for breast cancer for women with biopsy-proved benign breast disease is 1.5 to 1.6 compared with women in the general population, with this increased risk persisting for at least 25 years after the original biopsy. The relative risk for developing cancer is 4.24 with atypia, 1.9 with proliferative changes without atypia, and 1.3 with nonproliferative lesions. However, about 50% of the later cancers arise in the contralateral breast, thereby suggesting that these findings are more a marker than a cause of subsequent breast cancers.

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184 GYNECOLOGIC CANCERS

DEBORAH K. ARMSTRONG

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CERVICAL CANCER

EPIDEMIOLOGY

Cancer of the uterine cervix is the third most common gynecologic cancer in the United States. A more than 80% decrease in the incidence of cervical cancer since the 1950s is related to screening, initially for abnormal cervical cytology with the Papanicolaou (Pap) test and now for high-risk human papillomavirus (HPV) infection. These demographic trends are seen throughout the developed world, yet cervical cancer remains a major cause of cancer-related deaths in women worldwide, particularly in Central and South America and in Africa, owing to lack of access to screening and treatment. In the United States, over 14,000 new cases of cervical cancer and over 4000 cancer-related deaths occur annually.[1]

HPV infection is central to the development of preinvasive and invasive disease and is detected in more than 99% of cervical cancers.[2] Risk factors for cervical cancer (Table 184-1) are mostly related to increased risk of acquiring HPV or increased virulence of HPV infection.

Of the more than 200 strains of HPV (Chapter 344), about 40 infect the genital tract. Low-risk HPV causes genital warts, whereas high-risk HPV causes cancers of the anogenital tract, including cervical, vaginal, vulvar, anal, and penile cancers, as well as oral and throat cancers. Among the approximately one dozen high-risk HPVs, two types, HPV 16 and HPV 18, cause 70% of cervical cancers, and HPV types 31, 33, 45, 52, and 58 cause an additional 20% of cases. HPV is transmitted sexually through genital-genital or genital-oral contact, and the majority of sexually active individuals will be infected with HPV at some time, usually near the beginning of sexual activity, even though its transmission is significantly diminished with the use of condoms.

PATHOBIOLOGY

HPVs are small, nonenveloped, double-stranded DNA viruses protected by a capsid formed by late proteins, L1 and L2 (Chapter 344). The regulation of viral gene expression is complex and controlled by host cellular and viral transcription factors. HPV infection occurs at the basal cell layer of stratified squamous epithelial cells, thereby resulting in cellular proliferation, with pathologic findings from benign hyperplasia to dysplasia to invasive carcinoma. The E6 and E7 proteins of the high-risk HPV types act as viral oncoproteins that suppress normal, negative growth regulation. E6 binds to and degrades the tumor suppressor protein p53, thereby inhibiting normal apoptotic cell death, contributing to immortalization of HPV-infected cells. Similarly, E7 binds to and degrades the pRB tumor suppressor protein and targets cellular cyclins and cyclin-dependent kinases that are critical for cell cycle regulation. Both E6 and E7 have immunosuppressive effects that contribute to immune evasion and induction of peripheral tolerance in cytotoxic T lymphocytes.

HPV infects cutaneous and mucosal epithelial tissues with tropism for the anogenital tract. Most HPV infections are transient, asymptomatic, and without clinical consequences. They clear within 1 to 2 years. In about 10% of infected women, HPV DNA will continue to produce viral proteins, thereby resulting in persistent infection. In some cases, the HPV DNA is silenced, thereby resulting in latency of variable duration, but can be reactivated later. The persistence of HPV in a latent state requires maintenance of the viral genome in the infected cell, either as an episome or integrated into the host cell DNA. Persistent HPV infection is necessary for the development of precancerous cervical changes and, subsequently, cervical cancer.

TABLE 184-1 RISK FACTORS FOR CERVICAL CANCER

- Human papillomavirus
- Early onset of sexual activity
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- Lower socioeconomic status
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- Long-term use of oral contraceptive agents
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- In utero diethylstilbestrol (DES) exposure
- Hispanic and Black American women

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CLINICAL MANIFESTATIONS AND DIAGNOSIS

Early-stage cervical cancer is largely asymptomatic, and detection is generally made by colposcopy and biopsy for abnormalities that are detected by screening. Cervical cancer frequently spreads by local extension to the uterine corpus, vagina, bladder, and parametria. In advanced stages, patients may present with pain with intercourse, vaginal discharge or bleeding, pelvic pain, or abnormalities of bowel, bladder, or sexual function.

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TREATMENT AND PROGNOSIS

The treatment of cervical cancer is guided predominantly by the stage of the disease (Table 184-2). Survival from cervical cancer is higher when women are managed by a gynecologic oncologist, and prompt referral is important. In addition to clinical stage, treatment decisions must consider the patient's age, desire for fertility, and comorbid conditions, as well as the size of the tumor.

In some cases, a cervical cone biopsy (excision of a cone-shaped circumferential wedge from the cervix, the transformation zone, and at least a portion of the endocervical canal, called conization) or loop electrosurgical excision procedure (LEEP) may be sufficient for women with microscopic disease.[A1]

However, treatment of low-volume disease limited to the cervix is generally radical hysterectomy, although simple hysterectomy is an alternative in very-low-risk disease. In women undergoing radical hysterectomy, open surgery is indicated because it provides better disease-free survival compared with minimally invasive approaches (e.g., laparoscopic or robot-assisted laparoscopic).[A2] In limited situations in which the preservation of fertility is desired, a radical trachelectomy (removal of the cervix only) can be performed.

When hysterectomy reveals invasion of the lymphovascular space, deep cervical stromal involvement, larger-than-expected tumor size, positive surgical margins, parametrial involvement, or nodal involvement, adjuvant postoperative radiation therapy[A3] is typically recommended under expert supervision (see Table 184-2). Patients with stages IIB to IVA cancers should be treated with definitive chemoradiation therapy using radiation-sensitizing weekly cisplatin in combination with radiation therapy. Patients with persistent recurrent or metastatic cervical cancer are generally treated with systemic therapy containing a platinum taxane doublet. Bevacizumab, which is an antibody to vascular endothelial growth factor (VEGF), provides an incremental survival benefit when combined with initial chemotherapy for advanced cervical cancer.[A4] The immune checkpoint inhibitor pembrolizumab can be combined with chemotherapy, with or without bevacizumab, for patients whose tumors express PD-L1.[A5]

Highly selected patients with a central recurrence of cervical cancer may be candidates for pelvic exenteration, which is a very morbid procedure that cures 25 to 50% of patients. Otherwise, recurrent cervical cancer, though treatable, is usually not curable. Systemic chemotherapy under expert supervision is the usual approach. Palliative localized radiation may be used to manage symptoms.

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KEYWORDS

cervical cancer
endometrial cancer
ovarian cancer
human papillomavirus

TABLE 184-2 APPROACH TO CERVIX CANCER BY STAGE*

STAGE	BRIEF DEFINITION	USUAL TREATMENT
0	Carcinoma in situ	Conization, hysterectomy†
I	Cervical cancer confined to the uterus	
IA1	Microscopic stromal invasion <3 mm plus invasion of the lymphovascular space‡	Conization, hysterectomy† Radical hysterectomy or CRT
IA2	Microscopic stromal invasion 3 to 5 mm	Radical hysterectomy or CRT
IB1	Visible lesion ≤4 cm in greatest dimension§	Radical hysterectomy or CRT
IB2	Visible lesion >4 cm in greatest dimension	Radical hysterectomy or CRT
II	Limited cervical cancer spread beyond the uterus	
IIA	Tumor beyond the uterus, no parametrial involvement	
IIA1	Visible lesion ≤4 cm in greatest dimension	Radical hysterectomy or CRT
IIA2	Visible lesion >4 cm in greatest dimension	Radical hysterectomy or CRT
IIB	Parametrial extension	CRT
III	Pelvic extension of cervical cancer	
IIIA	Tumor involves lower third of the vagina but no pelvic wall extension	CRT
IIIB	Tumor extends to pelvic wall, hydronephrosis, or regional nodes	CRT
IVA	Involvement of mucosa of bowel or bladder	CRT
IVB	Distant metastatic disease	Chemotherapy¶

*Cervical cancer is staged clinically, radiographically, and pathologically. Staging may include findings at examination under anesthesia, imaging, and pathology, where available, to supplement clinical findings with respect to tumor size and extent, in all stages. Gynecologic cancers are most commonly staged using the FIGO (Fédération Internationale de Gynécologie et d'Obstétrique) staging system.

†If positive margins after cone, repeat cone or perform hysterectomy.

‡Hysterectomy recommended for lymphovascular space invasion.

§Chemoradiation therapy (CRT) includes weekly cisplatin treatment with definitive radiation therapy.

¶Initial chemotherapy for metastatic disease is generally a platinum taxane doublet with bevacizumab. Pembrolizumab can be added to chemotherapy for patients whose tumors express PD-L1.

TABLE 184-3 CERVICAL CYTOLOGY AND HISTOPATHOLOGY

Dysplasia	Very mild	CIN1	LSIL
	Mild		
	Moderate	CIN2	HSIL
	Severe	CIN3	
Carcinoma	In situ		
	Invasive		

CIN = cervical intraepithelial neoplasia; HSIL = high-grade squamous intraepithelial lesion; LSIL = low-grade squamous intraepithelial lesion.

PREVENTION

Human Papillomavirus Vaccine

Routine HPV vaccination should be given at ages 11 to 12 years, regardless of gender or gender identity, but can be given as early as age 9 years (Chapters 15 and 344). A two-dose series given 6 to 12 months apart is now recommended for any child who initiates vaccination before age 15 years. The vaccination is also indicated for previously unvaccinated adults up to age 45 years (see Table 344-2). Vaccination of males is critical not only to prevent the spread of HPV to female partners but also to prevent HPV-associated head and neck cancers (Chapter 176).

Pregnancy testing is not required before HPV vaccination, but vaccination should be delayed in pregnant women. Vaccination after treatment for cervical intraepithelial neoplasia types 2 and 3 may decrease the incidence of recurrence.

Three different HPV vaccines are approved by the FDA, but only the nine-valent vaccine is currently available in the United States. Trials of all three vaccines document a high level of safety.[A6] More than 97% of healthy vaccine recipients develop antibodies to HPV vaccine types after vaccination. All of the vaccines are highly effective in preventing sequelae of high-risk HPV in males and females, with 97% or greater efficacy.[A7] HPV vaccination also decreases invasive and pre-invasive cervical cancers in an age-dependent manner. The reduction in the incidence of cervical cancer and stage 3 cervical intraepithelial neoplasm is 87% for vaccination at ages 12 to 13 years, 62% for vaccination at age 14 to 16 years, and 34% for vaccination at ages 16 to 18 years compared with an unvaccinated cohort.[3]

A clinician's recommendation is one of the strongest drivers of adherence to vaccine recommendations. In the United States, about 75% of teens have received at least one dose of HPV vaccine, and nearly 60% are fully vaccinated, with rates slightly higher for females and in metropolitan areas. Lack of parental understanding about the necessity and safety of HPV vaccination appears to be the main reason why these rates are not higher. The U.S. Centers for Disease Control and Prevention (CDC) provides tools for clinicians to guide their recommendations, with an emphasis on cancer prevention.[4]

Screening Recommendations

The three options for cervical cancer screening are cervical cytology (Papanicolaou [Pap] test) alone, high-risk HPV testing, or cervical cytology and high-risk HPV testing together ("co-testing"). The U.S. Preventive Services Task Force and the American College of Obstetrics and Gynecology recommend cervical cytology every 3 years from ages 21 to 29 years, then cervical cytology every 3 years; high-risk HPV testing every 5 years from ages 30 to 65 years; or co-testing every 5 years from ages 30 to 65 years. The American Cancer Society recommends starting cervical cancer screening at age 25 years, with a high-risk HPV test alone every 5 years until age 65 years.

Adenocarcinoma may be better detected by HPV testing.[5,6] Screening is not recommended in women whose cervix has been removed, women younger than age 21 years, or women older than age 65 years who have previously been adequately screened. HPV vaccination status does not affect screening recommendations, so women who have been vaccinated against HPV should still follow these guidelines. Longer and more frequent screening are recommended for women who have had a positive Pap or HPV test, women who are at high risk for cervical cancer because of immunosuppression (e.g., HIV infection, organ transplantation, or long-term use of corticosteroids), or women who have had in utero exposure to diethylstilbestrol (DES).[7]

Interpretation of Screening Tests

Pap smear results are typically reported as normal, atypical squamous cells of undetermined significance (ASC-US), low-grade squamous intraepithelial lesion (LSIL), high-grade squamous intraepithelial lesion (HSIL), or atypical glandular cells. These cytologic findings generally correlate with subsequent histologic findings of varying degrees of dysplasia, cervical intraepithelial neoplasia (CIN), and carcinoma in situ or invasive carcinoma (Table 184-3). However, cytologic results may be associated with a subsequent histologic finding that is either more or less severe, so the results of cervical cytology are generally not used alone to make a definitive diagnosis or initiate treatment.

The recommended follow-up of an abnormal screening test follows an algorithm that incorporates current and prior test results, screening history, and age to estimate the risk of precancer. The finding of atypical squamous cells of undetermined significance conveys a low risk for progression to carcinoma. A low-grade squamous intraepithelial lesion, particularly in young women, is generally caused by a transient HPV infection. A high-grade squamous intraepithelial lesion is more likely to be associated with persistent HPV infection and a higher rate of progression to invasive cervical cancer. Colposcopy is recommended for most patients with positive HPV tests and abnormal Pap tests. The presence of atypical glandular cells on cervical cytology is a significant marker for premalignant disease of the cervix or endometrium, and evaluation should include testing of both these sites.

The colposcope is a lighted binocular microscope that magnifies the tissue of interest. Cervical colposcopy is used to examine the entire surface of the cervix, with emphasis on the squamocolumnar junction and transformation zones. Abnormal colposcopic findings are used to choose the sites to biopsy. In addition to cervical biopsy, repeat cervical cytology (with HPV testing, if indicated) and endocervical curettage may be obtained. The pathologic findings will guide follow-up and therapy, if necessary. Women with high-risk cytologic findings during pregnancy can still undergo colposcopy, although the endocervical curettage is omitted.

PROGNOSIS

Five-year survival rates are 92% for localized disease, about 60% for disease that has spread regionally, and about 20% for disease with distant spread. Cervical cancer survivors are also at risk for HPV-associated oropharyngeal (Chapter 176) and anal (Chapter 131) cancer.

The predominant site of recurrence for cervical cancer is locoregional at the vaginal apex or pelvic sidewall. Distant metastatic spread to lymph nodes, peritoneum, liver, lung, or bone can also be seen.

Median overall survival for individuals with advanced disease is less than 18 months. Death is usually associated with local recurrence and may also be associated with organ dysfunction such as hydronephrosis, bowel obstruction, and the formation of fistulas.

ENDOMETRIAL CANCER

Endometrial cancer arises from the inner epithelial lining of the uterus and is the most common gynecologic cancer in women in the United States. Most cancers are adenocarcinomas, but other rare histologic types include squamous cell, small cell, and transitional cell carcinomas.

EPIDEMIOLOGY

Endometrial cancer rates are rising in parallel with increasing obesity rates, with an estimated 67,000 new cases of endometrial cancer and 13,000 cancer-related deaths in the United States annually. Endometrial cancer is the fourth most common cancer in women after breast, lung, and colorectal cancers. Nearly 3% of women in the United States are expected to develop the disease. The average age of endometrial cancer diagnosis is 60 years, and it is rare in women before age 45 years. Endometrial cancer is more common in White women but has a higher mortality rate in Black women. A major factor for the development of endometrial cancer is estrogen exposure. Trends in the incidence of endometrial cancer may be largely explained by trends in exposure to endogenous estrogens and the use of exogenous estrogen in perimenopausal and postmenopausal women. Obesity is related to increased circulating estrogens due to increased aromatase activity in adipose tissue, thereby contributing to the conversion of adrenal androgens to estrogen (Table 184-4).

Women with a history of complex atypical hyperplasia have a nearly 30-fold risk for subsequently developing endometrial cancer. As the population ages, the incidence of endometrial cancer increases. The combination of improved life expectancy, decreasing parity, and rising rates of diabetes and obesity make endometrial cancer an increasing challenge in many developing and middle-income countries.

Most endometrial cancers are sporadic, but a small percentage (3 to 5%) of endometrial cancers are attributed to a genetic predisposition. Women with a family history of endometrial cancer are at a 1.5- to 2-fold increased risk for the disease. Lynch syndrome (also called *hereditary nonpolyposis colorectal cancer* [HNPCC; Chapter 179]) is the most common genetic syndrome associated with endometrial cancer and is caused by germline mutations in one of the DNA mismatch repair genes, *MLH1, MSH2, MSH6, PMS2*, or *EPCAM* (Chapter 166). Women with Lynch syndrome have up to a 80% lifetime risk for colorectal cancer and up to a 60% risk for developing endometrial cancer.

Cowden syndrome is a rare condition resulting from a mutation in the *PTEN* tumor suppressor gene. The lifetime risk for endometrial cancer is 13 to 20% in women with Cowden syndrome, a five-fold elevation compared with the general population.

PATHOBIOLOGY

More than 80% of endometrial cancers (type 1 endometrial cancers) are related to estrogen. The remaining 10 to 20% (type 2 endometrial cancers) are estrogen independent but share some risk factors with type 1 endometrial cancers, such as low parity, early age at menarche, and diabetes. The distinction between types 1 and 2 endometrial cancer is based on differences in histology and clinical outcomes, with type 2 having a poorer prognosis (Table 184-5). Type 1 malignancies tend to present with uterine-confined disease, generally have a better overall prognosis than the type 2 cancers, and often retain expression of hormone receptors. On a molecular level, type 1 tumors are more likely to be diploid, have loss of *PTEN*, retain wild-type *p53*, and be associated with microsatellite instability. Conversely, type 2 endometrial cancers are poorly differentiated; have serous, clear cell, or carcinosarcoma histology; often first present at advanced stages; and are at higher risk for disseminating. At the molecular level, type 2 endometrial cancers are higher grade, more frequently have aneuploidy, harbor mutations or loss of *p53*, and rarely express estrogen and progesterone receptors.

Endometrioid cancers include four subtypes (Fig. 184-1): *POLE* ultra-mutated, microsatellite instability hypermutated, copy number low (*TP53* wild-type), and copy number high (*TP53* mutated). In addition, about 25% of endometrioid tumors share characteristics with serous tumors, including extensive copy number alterations, few DNA methylation changes, low estrogen receptor and progesterone receptor expression, and frequent *TP53* mutations.

TABLE 184-4 RISK FACTORS FOR ENDOMETRIAL CANCER

- Complex atypical hyperplasia
- Unopposed estrogen exposure
- Obesity
- Increasing age
- Nulliparity
- Diabetes mellitus
- Early menarche, late menopause
- Tamoxifen use
- Family history of endometrial cancer
- Lynch syndrome (hereditary nonpolyposis colorectal cancer [HNPCC])
- Cowden syndrome

TABLE 184-5 TYPE 1 VERSUS TYPE 2 ENDOMETRIAL CANCERS

	TYPE 1 ENDOMETRIAL CANCERS	TYPE 2 ENDOMETRIAL CANCERS
Hormonal impact	Estrogen dependent	Estrogen independent
Histology	Endometrial adenocarcinoma	Clear cell or serous carcinosarcoma
Patient population	Younger, obese, perimenopausal	Older, thin, postmenopausal
Frequency	80-85%	15-20%
Prognosis	Lower grade; earlier stage; lower mortality rate	More aggressive; higher mortality rate
Molecular and genomic characteristics	ER/PR-positive; MSI	*P53* mutations; *ERBB2* overexpression

ER = estrogen receptor; MSI = microsatellite instability; PR = progesterone receptor.

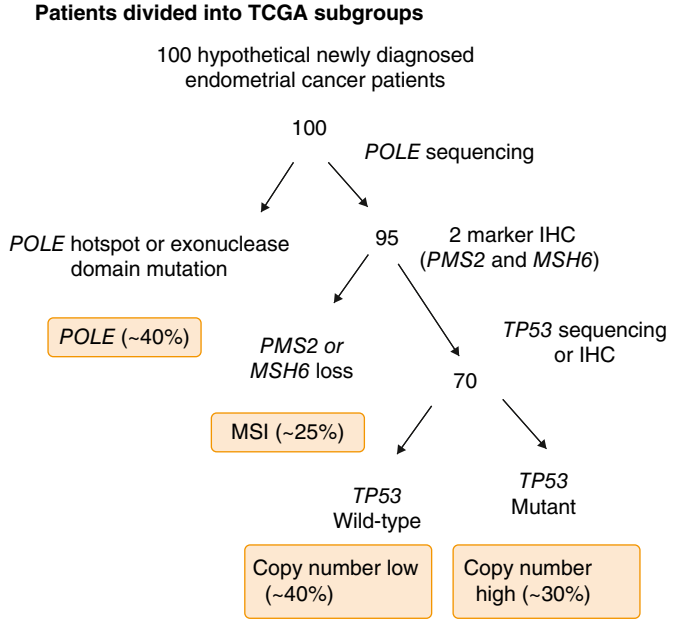

FIGURE 184-1. Suggested potential schema for molecular classification of endometrial cancer using sequencing and immunohistochemistry results to segregate patients into the molecular subtypes previously defined by The Cancer Genome Atlas (TCGA). IHC = immunohistochemistry; MSI = microsatellite instability; POLE = polymerase ε; TCGA = The Cancer Genome Atlas. (From MacKay HJ, Levine DA, Bae-Jump VL, et al. Moving forward with actionable therapeutic targets and opportunities in endometrial cancer: NCI clinical trials planning meeting report on identifying key genes and molecular pathways for targeted endometrial cancer trials. *Oncotarget*. 2017;8:84579-84594.)

About 30 to 40% of women with endometrioid endometrial cancer will have evidence of microsatellite instability, sometimes as a result of germline mutations in DNA mismatch repair genes (e.g., in Lynch syndrome), but more commonly from noninherited alterations, such as hypermethylation of the *MLH1* promoter or somatic mutations in the DNA mismatch repair genes that result in loss of protein expression. The proteins involved in mismatch repair correct errors that spontaneously occur during DNA replication, such as base mismatches or short insertions and deletions. Cells with deficient mismatch repair accumulate errors, creating novel microsatellite fragments. Mismatch repair–deficient cells have a marked increase in mutations: 1700 on average, compared with just 70 in a typical cancer cell. These mutations result in production of abnormal proteins that are recognized by the immune system as foreign.

CLINICAL MANIFESTATIONS AND DIAGNOSIS

The primary manifestation of endometrial cancer is postmenopausal vaginal bleeding (Chapter 218). Pap test results sometimes show signs of an abnormal endometrium. Any report of postmenopausal bleeding or of a suspicious finding on a Pap smear requires a thorough evaluation to exclude endometrial cancer. The initial approach to suspicious bleeding is pelvic examination, ultrasound imaging, and endometrial biopsy.

Special Considerations for Testing in Endometrial Cancer

Tumor tissue can be used to identify patients with abnormal DNA mismatch repair expression using immunohistochemistry for the four mismatch repair proteins. PCR to test for microsatellite instability requires tumor and normal tissue. Immunohistochemistry is frequently used because of the lower cost of this testing. In some cases, the etiology of loss of DNA mismatch repair protein expression can be identified by tumor tissue methylation testing. Tumors with deficient mismatch repair, regardless of site of origin, have a high response rate to immunotherapy with the PD-1 inhibitors pembrolizumab and dostarlimab, and an additional substantial fraction will have prolonged stable disease. All women who are diagnosed with endometrial cancer should undergo systematic clinical screening for Lynch syndrome (review of personal and family history) and/or molecular screening.

High-Risk Subtypes

Three high-risk histologic subtypes of endometrial cancer warrant special consideration: carcinosarcoma, serous carcinoma, and clear cell carcinoma. Uterine carcinosarcomas are rare, aggressive, biphasic neoplasms that contain high-grade malignant epithelial and mesenchymal elements. The mesenchymal component may resemble any one of a number of high-grade sarcomas. At the time of diagnosis, approximately one third of patients will have disease spread beyond the uterus. Uterine carcinosarcomas have frequent *TP53* mutations and are thus considered type 2 tumors. Uterine serous carcinomas are very aggressive neoplasms with a very high propensity for spread, including to distant sites in the upper abdomen, even when confined to the endometrium. Clear cell carcinomas are characterized by clear and often eosinophilic cells, and they are often aggressive.

TREATMENT

Fortunately, most women will have localized disease that is amenable to surgery. In almost all cases of pathologically confirmed endometrial cancer, hysterectomy with surgical staging is recommended. Minimally invasive surgery with a laparoscopic or robotic approach has largely replaced open surgical procedures for apparent uterine-confined disease. Total hysterectomy, bilateral salpingo-oophorectomy, peritoneal cytology (washings), and lymph node assessment are recommended. Visual inspection of the upper abdomen and pelvic surfaces is important to exclude extrauterine disease. Common sites of spread for endometrial cancer include the ovaries, pelvic or periaortic lymph nodes, and peritoneum. Sentinel node biopsy is an alternative at centers with expertise in these surgical methods. Comprehensive pathologic evaluation should include histologic subtype and grade, size and location of tumor, depth of myometrial invasion, presence or absence of cervical stromal involvement, involvement of the parametria, and assessment of lymphatic and vascular invasion.

For selected young women who have low-grade endometrial cancer and who desire to preserve fertility, or in women who are not medically fit for surgery, continuous progestin-based therapy with repeat endometrial sampling every 3 to 6 months can be considered. Radiation is another option for women with an absolute contraindication to surgical management.

Adjuvant Therapy

Surgical staging (Table 184-6) and identified risk factors guide recommendations for adjuvant, postoperative therapy. Risk factors include increasing age, invasion of the lymphovascular space, histology, tumor size, tumor grade, involvement of the lower uterine segment, or cervical stromal (glandular) involvement.[8,9]

For select women with uterine-confined disease, adjuvant, post-hysterectomy radiation with vaginal brachytherapy and/or external beam whole pelvic radiation therapy is sometimes considered.[A8] Systemic therapy has typically been with paclitaxel and carboplatin under expert supervision. Adjuvant treatment can reduce the risk for recurrence but may not have a significant impact on survival because of its toxicities. Numerous ongoing studies are evaluating the value of adding immunotherapy to initial chemotherapy.[10]

Advanced and Recurrent Disease

For women with adnexal, parametrial, or nodal involvement (stage III disease) or disseminated (stage IV) disease, systemic chemotherapy is as good as chemotherapy plus radiation.[A9] For women with distant metastases at the time of diagnosis, surgical debulking along with radiation for palliation is sometimes considered, but systemic chemotherapy is the standard of care.

For women with recurrent disease, systemic therapy is standard treatment. For low-grade tumors that are hormone receptor–positive, hormonal therapy under expert supervision can sometimes provide long-term treatment benefits. Progestational agents have traditionally been the backbone of hormonal treatment and can be used alone or with tamoxifen, but aromatase inhibitor therapy with everolimus or with palbociclib also has shown benefit.[A10]

Expert recommendations for systemic chemotherapy depend on prior treatment and time to recurrence. Bevacizumab alone or in combination with chemotherapy may be considered. In patients who have previously had chemotherapy, pembrolizumab or dostarlimab can be used for women who have a high tumor mutation burden or those whose tumor is deficient in the expression of DNA mismatch repair or has high microsatellite instability. Pembrolizumab in combination with lenvatinib can be used regardless of microsatellite status and is superior to second-line chemotherapy.[A11]

High-Risk Subtypes

High-risk subtypes (carcinosarcomas, serous carcinomas, and clear cell carcinomas) are more aggressive, have a higher propensity for advanced disease at diagnosis, and have a poorer overall prognosis. Systemic chemotherapy with or without radiation under expert supervision is recommended for almost all stages of these high-risk histologies. Uterine serous carcinomas and carcinosarcomas frequently overexpress ErbB2 (HER2), and HER2-directed therapy with trastuzumab should be added to chemotherapy when they do. For endometrial clear cell carcinomas, paclitaxel and carboplatin are considered standard therapy.

TABLE 184-6 APPROACH TO ENDOMETRIAL CANCER BY STAGE*

STAGE	BRIEF DEFINITION	TREATMENT
I	Tumor confined to the uterine corpus	
IA	<50% myometrial invasion	TH, BSO, ± vag brachy†
IB	≥50% myometrial invasion	TH, BSO, ± vag brachy†
II	Cervical stromal involvement	TH, BSO, EBRT ± vag brachy†
IIIA	Tumor involving uterine serosa and/or adnexa	TH, BSO, systemic therapy ± EBRT ± vag brachy
IIIB	Vaginal or parametrial involvement	TH, BSO, systemic therapy ± EBRT ± vag brachy§
IIIC1	Pelvic lymph node involvement	TH, BSO, systemic therapy ± EBRT ± vag brachy
IIIC2	Para-aortic lymph node involvement	TH, BSO, systemic therapy ± EBRT ± vag brachy
IVA	Tumor invades bladder or bowel	TH, BSO, systemic therapy ± EBRT ± vag brachy
IVB	Distant metastases, inguinal node involvement	TH, BSO, systemic therapy ± EBRT ± vag brachy

*Endometrioid histology.
†EBRT and systemic therapy can be considered for those with high-grade disease or adverse risk factors.
‡Systemic therapy can be considered for those with high-grade disease.
§Vaginal brachytherapy is recommended for stage IIIB.
BSO = bilateral salpingo-oophorectomy; EBRT= external beam radiation therapy; TH = total hysterectomy; vag brachy = vaginal brachytherapy.

PREVENTION

On reaching menopause, all women should be informed about the risks and symptoms of endometrial cancer and strongly encouraged to report any unexpected vaginal bleeding or spotting to their physicians. No standard endometrial cancer screening is recommended for the general population.

The identification of Lynch syndrome in women with endometrial cancer can lead to the prevention of a second cancer in the patient and prevention of new, incident cancers in family members by using risk-reducing strategies and heightened surveillance.[11] Women with Lynch syndrome should be offered endometrial cancer screening with transvaginal ultrasound and endometrial biopsy annually starting at age 35 years. Hysterectomy with bilateral salpingo-oophorectomy is recommended for women with Lynch syndrome after the completion of childbearing.

PROGNOSIS

Five-year survival rates are about 92% for tumors that are confined to the corpus of the uterus but fall to about 75% if the tumor invades the cervical stroma, 50% with local or regional spread, and only 15% if the tumor invades either the bladder or bowel. Typical sites of recurrent endometrial cancer include local pelvic disease and distant metastases to the upper abdomen or lung. The risk for local pelvic recurrence is lower in patients who have received radiation therapy.

Uterine serous carcinomas represent less than 10% of endometrial cancers but are responsible for more than 30% of endometrial cancer mortality. Uterine carcinosarcomas account for less than 5% of uterine malignancies but have a poor overall prognosis. Endometrial clear cell carcinomas are rare tumors that have an aggressive clinical behavior and a poor outcome.

Survivors of endometrial cancer are at higher risk for a number of long-term cardiovascular problems compared with their cancer-free counterparts, including thrombophlebitis, pulmonary heart disease, and atrial fibrillation. In survivors of endometrial cancer, obesity is associated with lower health-related quality of life.

OVARIAN AND FALLOPIAN TUBE CANCER

DEFINITION

The ovary has three types of cells, all of which can become malignant: the ovarian epithelial cells that form the surface of the ovary; the supporting stromal cells that provide structural support to the follicles, maintain cellular organization within the ovary, and differentiate into steroid-secreting cells necessary to promote oocyte development and ovulation; and the ova that are the female germ cells necessary for reproduction. *Ovarian cancers* refer to epithelial ovarian cancers, cancers of the fallopian tube, and primary peritoneal cancers. Tumors of the ovarian epithelium, along with the cells of the fallopian tube and cells that line the peritoneal cavity give rise to what is commonly referred to as *ovarian epithelial malignancies*.

EPIDEMIOLOGY

Approximately 20,000 new cases of ovarian cancer are diagnosed annually in the United States Unfortunately, most women have advanced disease at diagnosis, and 13,000 women die annually of their disease. As a result, ovarian cancer has the highest mortality rate of all gynecologic malignancies. Because the incidence of ovarian cancer is highest in developed countries where parity is lower, diets are higher in fat, and women have longer life expectancies, its incidence is highest in North America and Europe but lower in much of Asia and sub-Saharan Africa. The lifetime risk for ovarian cancer in women in the United States is 1:70, or 1 to 2%. The median age of onset for ovarian cancer is 60 to 65 years, although women with a genetic predisposition to ovarian cancer may develop the disease in their 40s or 50s.

Although risk factors for ovarian cancer have been identified (Table 184-7), the cause of most ovarian cancers is not known. More frequent lifetime ovulation is associated with increased risk, and factors that suppress ovulation (e.g., pregnancy, use of oral contraceptives, and prolonged lactation) are associated with a decreased risk. Most of these risk factors are modest, with the exception of genetic predisposition related to inherited germline mutations in cancer-predisposing genes.

The risk of ovarian cancer is lower in women who have had a tubal ligation, which may result in necrosis of the fallopian tube and death of tubal epithelial cells. A weak association with the use of powder in the genital area has been suggested by case-control studies but is controversial and not substantiated by cohort studies.[12,13]

Approximately 80% of ovarian cancers are sporadic, but about 15 to 20% can be linked to autosomal dominant germline mutations.[14] *BRCA1* and *BRCA2* are the most common mutations, identified in about 15% of patients with advanced ovarian cancer (Chapter 166). Inherited mutations in these genes are associated with a 5- to 30-fold increase in the lifetime risk of ovarian cancer and with a significantly increased risk for breast and other cancers (Table 184-8). In addition to *BRCA1* and *BRCA2*, other genes associated with an increased ovarian cancer risk include *ATM, BRIP1, PALB2, BARD1, RAD51C, RAD51D*, and the Lynch syndrome genes (*MSH2, MLH1, PMS2*, and *MSH6*).[15] These genes combined are responsible for the remaining 5% of advanced ovarian cancers with an identified germline mutation. Most of these genes have a lower penetrance and may increase the lifetime risk of ovarian cancer to 5 to 15% or less.

TABLE 184-7 RISK FACTORS FOR OVARIAN CANCER

Increasing age
Factors associated with increased lifetime ovulation
Early menarche
Late menopause
Nulliparity
Infertility
Use of ovulatory stimulating drugs
Family history of ovarian cancer
Genetic predisposition
BRCA1 and *BRCA2*
Lynch syndrome
Other genes
Decreased ovarian cancer risk
Use of oral contraceptives
Prolonged lactation
Increased parity
Tubal ligation

TABLE 184-8 *BRCA1* AND *BRCA2* PENETRANCE: CUMULATIVE LIFETIME CANCER RISK

	GENERAL POPULATION	*BRCA1*	*BRCA2*
Breast cancer	13%	50-72%	40-69%
Ovarian cancer	1-2%	35-60%	10-27%
Prostate cancer	11%	15-25%	15-25%
Pancreatic cancer	1-2%	Two-fold increase	Two- to five-fold increase

PATHOBIOLOGY

Histopathologic evaluation can identify several subtypes of epithelial ovarian cancer, the most common being serous, mucinous, clear cell, and endometrioid cancers. Endometrioid and clear cell carcinomas are much more common in early-stage ovarian cancer. By comparison, more than 80% of patients with advanced disease have high-grade, serous ovarian cancer, which is the best-understood ovarian cancer.

It is now clear that a significant portion, perhaps the majority, of serous ovarian cancers arise from the fallopian tube. The process of malignant transformation of the fallopian tube's epithelium is characterized by *p53* mutation, increased proliferation, cytologic atypia, detachment and exfoliation, metastasis, and implantation on peritoneal surfaces, including the ovary.[16]

CLINICAL MANIFESTATIONS AND DIAGNOSIS

Small adnexal masses are usually silent,[17] and most symptoms are related to disseminated disease within the abdomen and pelvis. The symptoms of dissemination include bloating, increased abdominal girth, early satiety, pelvic or abdominal pain, dyspareunia, and bowel or bladder complaints.

Ultrasonography or CT of the abdomen and pelvis will usually identify adnexal abnormalities and may also demonstrate ascites, lymphadenopathy, and omental or peritoneal involvement. Peritoneal fluid cytology can sometimes be diagnostic, but percutaneous biopsy of an apparently isolated adnexal mass is not recommended because of the potential for tumor spillage and spread of an otherwise localized tumor into the peritoneal cavity.

CA-125 is a glycoprotein encoded by the *MUC16* gene that is often significantly elevated in the serum of patients with ovarian cancer and can support the diagnosis of ovarian cancer. An elevated CA-125 alone is not diagnostic of ovarian cancer, because it can be elevated with other malignancies and with benign processes, especially conditions that affect the abdominal and peritoneal surfaces. It is also frequently normal when tumors are confined to the fallopian tube and/or ovary.

Ovarian cancer is often associated with inherited cancer-predisposing genes (Chapter 166). All women with ovarian cancer should undergo genetic counseling and consider genetic testing.

TREATMENT AND PROGNOSIS

Surgery and Neoadjuvant Therapy

In patients who are eligible, treatment of ovarian cancer starts with surgery, which should be performed by a gynecologic oncologist, preferably in a hospital with a high volume of ovarian cancer cases. Surgery makes the pathologic diagnosis and stages the patient's disease. Initial surgery should include an exploratory laparotomy, a total abdominal hysterectomy, bilateral salpingo-oophorectomy, omentectomy, removal of ascites or peritoneal washings, and, in certain circumstances, lymph node dissection. The diaphragm and upper abdomen should be inspected, and biopsies should be obtained. The goal of initial surgery, which may include peritonectomy and/or bowel resection, is to remove all visible disease. The improved outcome with resection of disseminated disease is somewhat unique to ovarian cancer and may reflect the propensity for peritoneal spread rather than lymphatic or hematogenous dissemination. If complete resection is not achievable, a maximal cytoreduction effort is still useful because of the direct correlation between volume of residual tumor and survival. Patients are characterized after initial surgery as R0 (zero visible residual disease) if no visible disease remains, optimally debulked when all visible disease is smaller than 1 cm, and suboptimally debulked if disease of 1 cm or greater remains at completion of surgery.

Primary cytoreductive surgery is recommended over neoadjuvant chemotherapy for women with a high likelihood of achieving optimal cytoreduction with acceptable morbidity.

However, if optimal debulking is not considered feasible because of the volume and location of disease, four or fewer cycles of neoadjuvant chemotherapy should precede debulking surgery.[A12] Outcomes for patients who are treated with neoadjuvant chemotherapy are not as good as for patients who can have all visible tumor removed or who can have optimal debulking before chemotherapy, their outcomes are similar to patients who have suboptimal initial debulking.

At the completion of primary surgery, the tumor's histology is identified, and the tumor is staged based on surgical and pathologic findings (Table 184-9). Up to 85% of patients have disease beyond the ovary at the time of diagnosis, and 75 to 80% will have stage III or IV disease. More than 85% of patients with advanced stages III and IV disease have serous histology, whereas clear cell and endometrioid histologies comprise approximately 50% of stages I and II disease.

For stage IA or IB, grade 1 tumors, disease recurs in less than 5% of patients, so postoperative observation without adjuvant chemotherapy is recommended. Grade 2 tumors are rare, and treatment recommendations for nonserous stage I, grade 2 tumors are individualized. Three to six cycles of chemotherapy (typically a platinum-taxane combination, but pegylated liposomal doxorubicin and carboplatin can also be considered) under expert oversight are recommended for stage I, grade 3 and stage IC disease. Six cycles are preferred for serous tumors, whereas three cycles may be sufficient for endometrioid, clear cell, and mucinous tumors.

For patients who have stage II disease or who have stage III disease with no residual tumor or with optimally debulked tumor after surgery, six cycles of platinum-based combined intravenous and intraperitoneal treatment can be considered. Patients who have suboptimal stage III or stage IV disease should receive intravenous platinum-based therapy with or without bevacizumab.

Advanced Disease

Most patients with advanced disease respond to initial therapy and enter a clinical remission, but the vast majority will eventually relapse. As a result, additional maintenance therapy should be considered under expert oversight after completion of initial chemotherapy. The most commonly used maintenance treatments are bevacizumab, which is used with and after initial chemotherapy, and poly-ADP-ribose polymerase (PARP) inhibitors.[18,19] PARP inhibitors (rucaparib, olaparib, or niraparib) for 2 to 3 years after platinum-based therapy can help maintain remission, with the greatest benefits seen in *BRCA*-associated homologous recombinant deficiency (HRD)–positive ovarian cancers.[A13,A14]

Patients who experience a recurrence more than 6 to 12 months after completion of initial platinum-based therapy are considered platinum-sensitive and are usually retreated with another platinum-containing doublet. Patients whose disease recurs less than 6 months after completion of prior platinum-based therapy are considered platinum-resistant and are typically treated with nonplatinum single-agent therapy. Bevacizumab added to treatment of platinum-sensitive or platinum-resistant disease can improve response to therapy and delay recurrence.[A15] In select patients with a late, platinum-sensitive recurrence, cytoreductive surgery followed by chemotherapy[20] is better than chemotherapy alone.[A16]

A much smaller fraction of familial ovarian cancers are linked to Lynch syndrome (HNPCC) or have microsatellite instability or somatic loss of DNA mismatch repair function. As in endometrial cancer, ovarian cancers that are deficient in mismatch repair will have a high rate of response to immune checkpoint inhibitor therapy with pembrolizumab.

TABLE 184-9 APPROACH TO OVARIAN CANCER BY STAGE

STAGE	BRIEF DEFINITION	TREATMENT
I	Tumor confined to the ovary or fallopian tube	
IA	No surface involvement	
	Grade 1/2	Staging laparotomy, observation*
	Grade 3	Staging laparotomy, 3-6 cycles IV chemotherapy
IB	Tumor confined to both ovaries or fallopian tubes	
	Grade 1/2	Staging laparotomy, observation
	Grade 3	Staging laparotomy, 3-6 cycles IV chemotherapy
IC	Surface involvement, positive ascites or washings	
	Capsule rupture or surgical spill	Staging laparotomy, 3-6 cycles IV chemotherapy
II	Disease spread limited to the pelvis	
IIA	Extension/Implants on the uterus, ovaries or fallopian tubes	Staging laparotomy, 3-6 cycles chemotherapy†,§
IIB	Extension to other pelvic tissues	Staging laparotomy, 3-6 cycles chemotherapy†,§
III	Tumor involving upper abdomen or regional nodes	
IIIA	Microscopic disease beyond the pelvis ± RP nodes	Staging laparotomy, 6 cycles IV or IVIP chemotherapy†,§
IIIB	≤2 cm disease beyond the pelvis ± RP nodes	Staging laparotomy, 6 cycles IV or IVIP chemotherapy†,§
IIIC	>2 cm disease beyond the pelvis ± RP nodes	Staging laparotomy, 6 cycles IV chemotherapy†,§
IVA	Pleural effusion, positive cytology	Staging laparotomy, 6 cycles IV chemotherapy†,§
IVB	Liver/spleen parenchyma, inguinal node involvement	
	Extraabdominal metastases	Staging laparotomy, 6 cycles IV chemotherapy‡,§

*Staging laparotomy includes exploratory laparotomy, a total abdominal hysterectomy with bilateral salpingo-oophorectomy, omentectomy, removal of ascites or peritoneal washings, and lymph node dissection.

†Combined intravenous and intraperitoneal chemotherapy can be considered for stage II patients and for R0 or optimally debulked stage III patients with less than 1 cm residual disease.

‡For patients unlikely to be successfully debulked with initial surgery, neoadjuvant chemotherapy with interval debulking can be considered.

§Maintenance PARP inhibitor therapy can be considered for responding patients with stage II-IV disease.

IV = intravenous; IVIP = intravenous/intraperitoneal; RP = retroperitoneal.

Less Common Histologies

A number of less common ovarian histologies have been identified (Table 184-10). Borderline tumors, also known as *low malignant potential tumors*, are a distinct group that is characterized by a lack of invasion (although it may spread within the peritoneal cavity), slow growth, and overall indolent behavior. These tumors tend to occur in younger women and are managed primarily with surgical resection as necessary. Low-grade ovarian cancers also have a lower growth fraction but have characteristics of invasion. These tumors have lower responses to chemotherapy and are more responsive to hormonal therapies. Mucinous cancers involving the ovary are commonly metastatic from a gastrointestinal primary that may be occult. Mucinous ovarian cancers are less responsive to standard ovarian chemotherapy regimens, and many require the use of agents used in treatment of gastrointestinal cancers (Chapter 179) under expert supervision.[21] As with endometrial carcinosarcomas, ovarian carcinosarcomas are biphasic neoplasms with malignant epithelial and mesenchymal elements. Carcinosarcomas are also less responsive to typical ovarian cancer treatments and may be more responsive to ifosfamide-based therapies under expert supervision. Clear cell carcinomas are frequently associated with endometriosis involving the ovary and are characterized by *ARID1A* driver mutations. These tumors are also less responsive to standard ovarian cancer therapies.

PREVENTION

Screening for ovarian cancer is not recommended in women who do not have symptoms. Neither serum CA-125 levels, alone or in combination with other markers, nor transvaginal ultrasound benefits the general population, and these tests are of limited value even in high-risk women.[A17]

TABLE 184-10 LESS COMMON OVARIAN HISTOLOGIES AND TREATMENT RECOMMENDATIONS

- **Borderline** (also known as low malignant potential [LMP]):
  - Observation
  - Complete surgical staging without invasive implants
- **Low-grade serous/endometrioid**
  - Hormonal therapy or
  - Chemotherapy ± hormonal therapy
- **Mucinous:**
  - Poor response to standard ovarian cancer chemotherapy, consider gastrointestinal-targeted therapies or regimens (5-fluorouracil, capecitabine, oxaliplatin)
- **Carcinosarcoma:**
  - Treated with standard ovarian cancer chemotherapy or an ifosfamide-containing regimen
- **Clear cell carcinoma:**
  - Associated with endometriosis, *ARID1A* driver mutations; less responsive to standard ovarian cancer chemotherapy

TABLE 184-11 OVARIAN CANCER: STAGE AND SURVIVAL

STAGE	PROPORTION OF PATIENTS		5-YR SURVIVAL
I	15%		90%
II	<5%		70%
III	70%	85%	25-50%
IV	10%		10-15%

Few strategies are available to prevent ovarian cancer. The use of oral contraceptive agents (Chapter 220) for 5 years or longer reduces the incidence of ovarian cancer by about 50%. For high-risk women, such as women with *BRCA1* or *BRCA2* mutations, prophylactic removal of the fallopian tubes and ovaries is recommended beginning at age 35 years and when childbearing is complete. Such surgery is the most effective approach to reduce the risk of ovarian cancer but is associated with complications of early menopause (Chapter 222). Given the role of the fallopian tube in ovarian carcinogenesis, the opportunistic removal of the fallopian tubes is increasingly recommended for primary prevention of epithelial ovarian malignancies.[22] This approach entails removal of the fallopian tubes in average-risk women undergoing pelvic surgery for another indication and allows preservation of the ovary without interruption of ovarian hormonal function. Common procedures that could potentially include opportunistic salpingectomy include hysterectomy for benign indications and in place of tubal ligation for women who desire sterilization.

PROGNOSIS

Recurrence and overall survival are related to stage of disease (Table 184-11). Ovarian cancer most commonly recurs at the prior sites of disease, typically in the abdominal or pelvic peritoneum or the pelvic and para-aortic nodes. Many patients with recurrent ovarian cancer will have significant bowel problems, including obstipation, constipation, and intermittent bowel obstruction.

Five-year survival rates for epithelial ovarian cancer are about 93% for localized disease, 75% for disease that has spread regionally, and 30% for disease with distant spread. Survival rates are reasonably similar for primary fallopian tube cancers and somewhat better for germ cell and stromal cell tumors. Women with *BRCA1/2*-mutated ovarian cancer survive longer than do women with sporadic ovarian cancer.

OTHER GYNECOLOGIC CANCERS

Malignant transformation can occur in every part of the müllerian tract. Other much less common types of gynecologic cancers include gestational trophoblastic disease, stromal and germ cell ovarian tumors, uterine sarcomas, and cancers of the vagina and vulva. Patients with these tumors should be referred to experts in the care and treatment of gynecologic cancer patients. Gestational trophoblastic disease is a group of pregnancy-related disorders resulting from a pathologic conceptus. The cells that form such tumors arise from trophoblastic tissue that will form the placenta. Gestational trophoblastic diseases range from benign hydatidiform moles to malignant choriocarcinoma. Ovarian germ cell tumors have strong homology with testicular cancer, including early age of onset, and a high cure rate with current therapies. Ovarian stromal tumors are typically early stage and usually cured with surgery alone but may require systemic therapy if advanced or recurrent.

The most common uterine sarcomas are leiomyosarcoma and endometrial stromal sarcoma. Leiomyosarcoma, which is a malignant tumor of smooth muscle, develops in the myometrium. Surgical resection is the treatment of choice. Neither adjuvant chemotherapy nor radiotherapy is useful for stage I disease, but recurrent leiomyosarcoma is most commonly treated with chemotherapy. Endometrial stromal sarcomas are commonly low grade and responsive to hormonal therapy, but when high grade, they are treated similarly to leiomyosarcomas. Cancers of the vagina and vulva are typically HPV-related cancers and are treated similarly to cervical cancer. Topical imiquimod is as effective as surgery for vulvar intraepithelial neoplasia.[A18]

Survivors of all forms of gynecologic cancers—whether of the cervix, endometrium, or ovary—are at risk for future sexual dysfunction as well as alterations of bowel and bladder function. They also must be counseled and often treated regarding the consequences of early menopause.

APPROACH TO SURVIVORS OF GYNECOLOGIC CANCERS

Survivors of gynecologic cancers are at continuous risk for both local and distant recurrences. Most gynecologic cancers that recur will do so within the first 5 years, but later recurrences can occur, particularly with low-grade disease. The treating oncology team will have primary responsibility for surveillance, but internists and primary care physicians may be called on to evaluate new symptoms, laboratory abnormalities, or physical examination findings.

Radical hysterectomy may disrupt the autonomic nervous system in the pelvis, thereby leading to bowel and/or bladder dysfunction. Pelvic lymphadenectomy, performed as part of many gynecologic cancer surgeries, can lead to lymphedema. Women treated with whole pelvic radiation therapy can suffer from bowel and bladder dysfunction and sexual dysfunction. Bladder problems may include urgency, incontinence, and chronic cystitis with loss of bladder elasticity and distensibility. Rectal problems include pain, diarrhea or constipation, rectal urgency, and incomplete stool evacuation or fecal incontinence. Radiation can also lead to pelvic insufficiency fractures with associated pain in up to 10% of patients.

Gynecologic cancer surgery and treatment are commonly associated with sexual dysfunction, which is multifactorial and related to fatigue from treatment, emotional and physical stresses of disease, surgery, and sequelae of systemic therapy. Vaginal stenosis, dryness, and dyspareunia are common. Resection of the upper vagina included in cervical cancer surgery may lead to a shortened vagina. Sexual dysfunction is increased after pelvic radiation but is also documented in women who have had surgery alone.

Most gynecologic cancer surgery will include removal of the ovaries. In premenopausal women, the result is abrupt menopause with its attendant short- and long-term sequelae (Chapter 222). In addition, even when the ovaries are preserved, as in younger cervical cancer patients, the ovarian blood supply may be compromised, thereby resulting in premature ovarian failure. For many gynecologic cancers, the use of hormone replacement therapy is contraindicated and should be used only after consultation with the oncology care team.

Cisplatin and paclitaxel, which are commonly used in all gynecologic cancers, can result in peripheral neuropathy, which can be permanent in many women. Cisplatin can also result in renal injury and renal electrolyte wasting, including loss of potassium, magnesium, and calcium. Bevacizumab is used in most gynecologic cancers, sometimes as prolonged maintenance in patients who are in remission. Bevacizumab toxicities, many of which are cumulative, include hypertension, proteinuria, bleeding or clotting, interference with wound healing, bowel perforation or fistula formation, and reversible posterior leukoencephalopathy syndrome. Patients whose ovarian cancer, especially BRCA-associated ovarian cancer, is treated with poly-ADP ribose polymerase (PARP) inhibitors are at increased risk for secondary hematologic malignancies, specifically myelodysplastic syndrome (Chapter 167) and acute myelogenous leukemia (Chapter 168). Persistent cytopenias or other unexplained abnormalities in blood counts in patients treated with this class of agents should prompt a thorough hematologic evaluation.

All gynecologic cancer survivors should be encouraged to adopt a healthy lifestyle, including increased physical activity (Chapter 14) and dietary modifications (Chapter 13). Fatigue, depression, and mood disorders are common in cancer survivors. These factors have a significant impact on quality of life and may persist many years, even decades, after treatment. Gynecologic cancer survivors may benefit from seeing a counselor or therapist to help with emotional issues associated with cancer treatment and recovery.

UTERINE FIBROIDS

The most common pelvic tumors in women are uterine fibroids, which are present in up to 40% of women during their reproductive years and up to 70 to 80% by 50 years of age.[23] Germline mutations in the *FH* (fumarate hydratase) gene are associated with early onset of uterine and cutaneous leiomyomas and renal cell cancer. Other implicated somatic mutations include the *MED12* gene on the X chromosome. Since fibroids require estrogen and progesterone, they can grow rapidly in early pregnancy but typically shrink after menopause.

Fibroids are usually asymptomatic. However, fibroids can cause pelvic discomfort and substantial uterine bleeding. Fibroids often can be detected by careful physical examination, but ultrasonography is confirmatory.

Fibroids themselves are benign and not premalignant. However, about 1 per 1100 to 1 per 1500 women under age 45 years may also have uterine cancer.

TREATMENT

The definitive treatment for fibroids is hysterectomy, but less invasive options are often preferable.[24] An anti-progesterone agent (e.g., oral mifepristone, 5 mg daily for 6 months or 10 mg daily for 3 months) or ulipristal acetate 5 or 10 mg per day for 13 weeks can effectively reduce fibroid size and symptoms.[A19] However, their benefits usually are transient. Oral gonadotropin-releasing hormone antagonists (e.g., elagolix at 300 mg twice daily[A20] or relugolix 40 mg once daily[A21]) combined with daily estradiol (1 mg) and norethindrone acetate (0.5 mg) can reduce fibroid-associated heavy menstrual bleeding and preserve bone density. Nonsteroidal anti-inflammatory drugs (e.g., naproxen or mefenamic acid) also are useful for discomfort. Hysteroscopic myomectomy can remove submucosal fibroids and preserve childbearing capacity, and myomectomy (open, laparoscopic, or hysteroscopic) provides better outcomes than uterine-artery embolization.[A22] For other symptoms, options include focused ultrasound surgery, radiofrequency ablation, and surgical myomectomy. Power morcellation has fallen out of favor because of the low but real chance of spreading malignant tissue that can appear as fibroids on imaging.

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185 TESTICULAR CANCER

LAWRENCE H. EINHORN

EPIDEMIOLOGY

Testicular cancer has an annual incidence of about 8700 cases per year in the United States and accounts for only 1% of all male malignancies.[1] Nevertheless, it is the most common carcinoma in men ages 15 to 35 years.[2] In the United States, testicular cancer is four to five times more common in White men compared with men of other ethnicities,[3] but incidence rates are rising in Asian/Pacific Islander and Hispanic men.[4] Men who have cryptorchidism have a 10- to 40-fold increased risk for the development of testicular cancer in the undescended testis, but even the normally descended testis in these men has a higher risk for malignancy. Testicular cancer is associated with drinking alcohol, overweight and obesity, and elevated blood lipid levels.[5]

PATHOBIOLOGY

More than 95% of testicular tumors are germ cell cancers.[6] Rare tumor types include lymphoma (especially in older men and often bilateral), Leydig cell, and Sertoli cell tumors. Non–germ cell tumors do not secrete serum α-fetoprotein or human chorionic gonadotropin and do not respond to platinum-based chemotherapy.

Of germ cell tumors, about half are seminomas and half are nonseminomas. Nonseminomas include embryonal cell carcinomas, yolk sac tumors, choriocarcinomas, and teratomas (with/without seminoma). Both seminomas and nonseminomas typically have amplification or aneuploidy with a gain of genetic information at the 12p position on the short arm of chromosome 12.[7]

CLINICAL MANIFESTATIONS

A testicular cancer may be first detected by the patient or a physician as a painless lump, often about the size of a pea. However, most patients present with unilateral pain or swelling of the testis or scrotum. Enlarging metastatic retroperitoneal nodes may cause flank pain as a presenting symptom. Less commonly, testicular cancer may be first suspected during a couple's evaluation for infertility when the male partner is found to have oligospermia. Pulmonary symptoms of chest pain, cough, or dyspnea are seen only with extensive hematogenous spread to the lungs. Significant elevation of the serum human chorionic gonadotropin level may produce gynecomastia.

Compared with nonseminomas, seminomas occur in men one to two decades older, never secrete α-fetoprotein,[8] have normal or modest elevation of human chorionic gonadotropin, and usually present with disease localized in the testis (stage I). Initial spread is lymphatic to ipsilateral retroperitoneal nodes, and hematogenous spread to lungs is rare.

DIAGNOSIS

Careful testicular examination is mandatory. With the patient standing or lying supine, the testes are gently palpated with the thumb and second or third fingers. Patients with a palpable mass or persistent orchialgia should be suspected of having testicular cancer. History of cryptorchidism or flank pain further raises the possibility of cancer. The differential diagnosis includes epididymitis, hydrocele (which may be secondary to cancer), torsion, or a varicocele.

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LAWRENCE H. EINHORN

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Testicular cancer has an annual incidence of about 8700 cases per year in the United States and accounts for only 1% of all male malignancies.[1] Nevertheless, it is the most common carcinoma in men ages 15 to 35 years.[2] In the United States, testicular cancer is four to five times more common in White men compared with men of other ethnicities,[3] but incidence rates are rising in Asian/Pacific Islander and Hispanic men.[4] Men who have cryptorchidism have a 10- to 40-fold increased risk for the development of testicular cancer in the undescended testis, but even the normally descended testis in these men has a higher risk for malignancy. Testicular cancer is associated with drinking alcohol, overweight and obesity, and elevated blood lipid levels.[5]

PATHOBIOLOGY

More than 95% of testicular tumors are germ cell cancers.[6] Rare tumor types include lymphoma (especially in older men and often bilateral), Leydig cell, and Sertoli cell tumors. Non–germ cell tumors do not secrete serum α-fetoprotein or human chorionic gonadotropin and do not respond to platinum-based chemotherapy.

Of germ cell tumors, about half are seminomas and half are nonseminomas. Nonseminomas include embryonal cell carcinomas, yolk sac tumors, choriocarcinomas, and teratomas (with/without seminoma). Both seminomas and nonseminomas typically have amplification or aneuploidy with a gain of genetic information at the 12p position on the short arm of chromosome 12.[7]

CLINICAL MANIFESTATIONS

A testicular cancer may be first detected by the patient or a physician as a painless lump, often about the size of a pea. However, most patients present with unilateral pain or swelling of the testis or scrotum. Enlarging metastatic retroperitoneal nodes may cause flank pain as a presenting symptom. Less commonly, testicular cancer may be first suspected during a couple's evaluation for infertility when the male partner is found to have oligospermia. Pulmonary symptoms of chest pain, cough, or dyspnea are seen only with extensive hematogenous spread to the lungs. Significant elevation of the serum human chorionic gonadotropin level may produce gynecomastia.

Compared with nonseminomas, seminomas occur in men one to two decades older, never secrete α-fetoprotein,[8] have normal or modest elevation of human chorionic gonadotropin, and usually present with disease localized in the testis (stage I). Initial spread is lymphatic to ipsilateral retroperitoneal nodes, and hematogenous spread to lungs is rare.

DIAGNOSIS

Careful testicular examination is mandatory. With the patient standing or lying supine, the testes are gently palpated with the thumb and second or third fingers. Patients with a palpable mass or persistent orchialgia should be suspected of having testicular cancer. History of cryptorchidism or flank pain further raises the possibility of cancer. The differential diagnosis includes epididymitis, hydrocele (which may be secondary to cancer), torsion, or a varicocele.

ABSTRACT

Testicular cancer is rare but is one of the most curable cancers in men. Most testicular tumors are germ cell cancers, which are divided into seminomas and nonseminomas. Patients with a palpable testicular mass or persistent orchialgia should be evaluated for testicular cancer by ultrasound. An intratesticular mass requires referral to a urologist for diagnosis and management. The treatment for testicular cancer depends on its histologic type and stage, and it may include surgery alone or with chemotherapy. Outcomes are excellent, but patients should be followed for recurrent disease and sequelae of therapy.

KEYWORDS

testicular cancer
germ cell cancer
seminoma
nonseminoma
α-fetoprotein (AFP)
human chorionic gonadotropin (hCG)

Testicular ultrasound is the diagnostic modality of choice in all suspicious cases.[9] A hypoechogenic intratesticular mass is almost always malignant and requires referral to a urologist (Fig. 185-1). Orchiectomy will diagnose the type of tumor. Embryonal cell carcinoma is positive for CD30, and seminoma is positive for CD117 and placental alkaline phosphatase. Most germ cell tumors are positive for OCT 3/4 and micro-RNA371.[10]

The evaluation for metastatic disease is dependent on signs, symptoms, and histology. In all cases, serum levels of human chorionic gonadotropin and α-fetoprotein should be obtained, and an abdominal computed tomographic (CT) scan should be performed.

Patients with testicular cancer are staged according to the anatomic extent of disease and presence or absence of detectable levels of serum human chorionic gonadotropin and α-fetoprotein post-orchiectomy. Lymphatic spread of a testicular germ cell cancer is detected on abdominal CT scanning with nodes more than 1 cm in the interaortocaval area for a right-sided primary tumor and left periaortic area for left-sided primary tumor. Nodal disease below the diaphragm constitutes stage II, and nodal spread above the diaphragm to posterior mediastinal or supraclavicular nodes is stage III. Hematogenous dissemination to lungs, or liver, bone, or brain is also classified as stage III. A chest radiograph or CT scan is routine for nonseminoma or for stage II seminoma. If a patient has cryptorchidism, scrotal violation, vasectomy, or prior inguinal hernia surgery, a pelvic CT scan also should be obtained. Head CT or magnetic resonance imaging is indicated only if the patient has signs or symptoms of central nervous system disease. Positron emission tomography is not indicated.

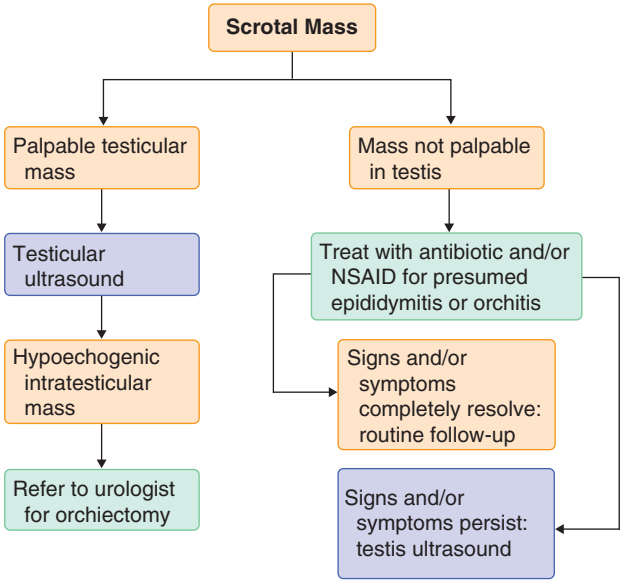

FIGURE 185-1. Management of a scrotal mass or orchialgia. NSAID = nonsteroidal anti-inflammatory drug.

TREATMENT

Initial treatment primarily depends on the stage of disease at presentation.[11,12]

Local and Regional Disease

Seminomas

Approximately 70% of seminomas are initially diagnosed with clinical stage I disease. Risk factors for micro-metastases include a primary tumor larger than 4 cm or involvement of the rete testis. Absence of either feature results in a 95% cure rate with orchiectomy alone. Presence of either adverse pathologic finding translates to an 80% cure rate with orchiectomy alone. A persistent or rising level of human chorionic gonadotropin indicates metastatic spread that requires chemotherapy, even in the absence of metastases on CT scans or physical examination. The half-life is 18 to 24 hours for human chorionic gonadotropin and 5 days for α-fetoprotein. As a result, the α-fetoprotein might require 6 weeks to normalize in a patient who had a preorchiectomy α-fetoprotein level of 1000 ng/mL even if stage I disease was cured with orchiectomy alone.

Although a single course of carboplatin or radiotherapy is an option,[13] the preferred recommendation for all clinical stage I seminomas is surveillance, with history and physical examination, serum levels of human chorionic gonadotropin and α-fetoprotein, and abdominal CT (with pelvic CT if indicated) every 4 months in year 1, every 6 months in year 2, and annually in years 3 to 5. Patients who relapse on surveillance still have a nearly 100% cure rate with either abdominal irradiation or cisplatin-based combination chemotherapy. Selected patients with early stage II disease can undergo retroperitoneal lymph node dissection to avoid late complications from chemotherapy or radiotherapy.

TABLE 185-1 DEFINITIONS OF POOR-RISK AND INTERMEDIATE-RISK DISEASE

POOR-RISK (ALL NONSEMINOMA)
hCG > 50,000 mIU/mL*
AFP > 10,000 ng/mL*
Nonpulmonary visceral metastases (e.g., bone, liver, or brain)
Primary mediastinal nonseminomatous germ cell tumor
INTERMEDIATE-RISK
Nonpulmonary visceral metastases in seminoma
hCG 5000-50,000 mIU/mL*
AFP 1000-10,000 ng/mL*

*Measured post-orchiectomy at start of chemotherapy.
AFP = α-fetoprotein; hCG = human chorionic gonadotropin.

Nonseminomatous Germ Cell Tumors

Patients who present with clinical stage I disease can be managed initially with orchiectomy alone and observation (surveillance), retroperitoneal lymph node dissection, or a single course of bleomycin/etoposide/cisplatin combination chemotherapy. All three options lead to an eventual 98 to 100% cure rate. Most relapses occur the first year and are detected by screening with a history, physical examination, and serum levels of human chorionic gonadotropin and α-fetoprotein every 2 months, as well as chest radiography plus an abdominal CT scan every 4 months. All studies should be repeated every 6 months during year 2 and annually in years 3 to 5. Risk factors for relapse on surveillance are vascular invasion in the orchiectomy specimen or embryonal carcinoma as the predominant cell type. Clinical small-volume stage II disease (1- to 3-cm nodes) is often managed by retroperitoneal lymph node dissection, which is best performed at a tertiary center with a nerve-sparing procedure to prevent retrograde ejaculation. Patients with bulky stage II or stage III disease are treated with cisplatin combination chemotherapy.

Chemotherapy for Disseminated Disease

Cisplatin combination chemotherapy under expert oversight can cure 70% of cases. Bleomycin/etoposide/cisplatin combination chemotherapy for three or four courses is the standard chemotherapy for disseminated testis cancer. About 60% of patients who require chemotherapy have good-risk metastatic disease.[14] Risk stratification, based on the amplitude of the serum human chorionic gonadotropin and α-fetoprotein levels and the presence of nonpulmonary visceral metastases, separates patients into good-risk (90% cure rate with three courses of chemotherapy), intermediate-risk (75% cure rate with three to four courses of chemotherapy), and poor-risk (50 to 60% cure rate with four courses of chemotherapy) (Table 185-1).

Second- or third-line therapy still has curative potential, either with standard-dose salvage chemotherapy (with ifosfamide/cisplatin plus either paclitaxel or vinblastine) or high-dose carboplatin/etoposide followed by peripheral blood stem cell transplantation under expert oversight.[15] Cure rates range from 25 to 85%, depending on second- versus third-line chemotherapy, the patient's characteristics, and the type of tumor. Selected patients with localized relapse are appropriate for salvage surgical procedures such as retroperitoneal lymph node dissection.

Late relapse beyond 2 years is uncommon but can occur in 2 to 3% of patients who have achieved a complete remission. Late relapse usually manifests by a rise in the serum α-fetoprotein level. The optimal approach is to identify the site of metastases and to perform surgical resection if feasible. Platinum-based chemotherapy without post-chemotherapy surgery can produce temporary remissions but few cures.

PREVENTION

Surgical correction of cryptorchidism before puberty reduces the risk of testicular cancer, but abnormalities in the testicle itself may explain both the cryptorchidism and the risk of cancer. Physicians should examine the testes carefully in men, especially men ages 15 to 40 years. Although self-examination has been associated with an earlier stage of diagnosis of testicular cancer,[16] the U.S. Preventive Services Task Force does not recommend it because of its limited accuracy for this rare condition and its tendency to generate needless testing.[17] However, patients who have been cured of their testis cancer have

a 2% probability of a second unrelated germ cell cancer in the contralateral testis. These high-risk individuals should be instructed in self-examination. Physician examination of the remaining testis should be a routine component of follow-up examinations.

PROGNOSIS

Testicular cancer is the most curable solid tumor, with 10-year survival rates of 95% for stages I to III and 80% for disseminated disease that requires chemotherapy. The amplitudes of serum levels of human chorionic gonadotropin and α-fetoprotein are independent prognostic variables for cure with cisplatin combination chemotherapy. However, potential sequelae in long-term survivors include a 2.5- to 3-fold increased risk of a second malignancy,[18] especially acute myeloid leukemia[19] and prostate cancer,[20] from chemotherapy or irradiation, cardiovascular disease, ototoxicity with tinnitus and high-frequency hearing loss, infertility, and psychosocial issues.[21] The great majority of survivors work full-time and lead healthy and productive lives. Patients with metastatic disease should not be denied curative platinum combination chemotherapy because of these late complications. Health maintenance, including exercise, abstinence from tobacco, avoidance of obesity, and management of the blood pressure and lipid profile, is crucial. Hypogonadism with low testosterone levels can increase the risk for the metabolic syndrome.

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186 PROSTATE CANCER

KATHLEEN A. COONEY AND ELISABETH I. HEATH

EPIDEMIOLOGY

Prostate cancer is the most common nonskin cancer that affects U.S. men, with approximately 270,000 new cases diagnosed annually and approximately 35,000 deaths each year. Worldwide, approximately 1.4 million cases of prostate cancer are diagnosed annually and lead to approximately 375,000 deaths each year. The disease is the most common cancer among men in much of Europe, North America, and Australia, but lower rates are observed in Asia. Higher mortality rates are observed in sub-Saharan Africa and the Caribbean, likely because of much lower rates of early detection.

In developed countries, the widespread use of screening with prostate-specific antigen (PSA) testing, beginning in the early 1990s, led to a rapid increase in the reported annual incidence of prostate cancer, mostly attributable to the identification of asymptomatic cases. Since 1992, however, the reported incidence rate of prostate cancer has fallen by 50%,[1] first because of an acceleration of diagnosis for early prevalent cases and subsequently because of more conservative recommendations regarding PSA screening.

The three well-recognized risk factors for prostate cancer are advanced age, ethnicity, and family history.[2] Prostate cancer is rarely diagnosed before age 40 years, and the average age of onset is approximately age 68 years. In the United States, non-Hispanic Black men have the highest incidence of prostate cancer (171.6 cases/100,000 population age adjusted) and the highest mortality (38.3/100,000) from the disease. In contrast, Asian/Pacific Islander men have the lowest incidence and mortality (53.8/100,000 and 8.8/100,000, respectively). About 10% of all prostate cancers in the United States are early onset, diagnosed at or before age 56 years; such men are more likely have a genetic component to their disease. The risk of prostate cancer is related to the number of affected family members, regardless of whether the first-degree relatives are affected, and the presence of early-onset disease in the pedigree. Familial clustering of prostate cancer appears to be related to genetic factors, with no evidence that shared environment contributes to familial clustering.[3] Other possible risk factors include high consumption of dietary fats, high intake of calcium, exposure to dioxin, and prior prostatitis.

PATHOBIOLOGY

Most prostate cancers are adenocarcinomas and arise from the epithelial cells that line the prostate gland. Prostate-specific antigen (PSA) is an androgen-regulated serine protease that is produced by epithelial cells in the prostate gland as well as by cancers that arise from these cells. High grade prostatic intraepithelial neoplasia and atypical small acinar proliferation are precursor lesions.

The PTEN protein is commonly lost in aggressive prostate cancers, generally through genomic deletion. Transposition of the transmembrane protease gene *TMPRSS2* to the ETS family member *ERG* gene, thereby creating the *TMPRSS2-ERG* fusion, is seen in 40 to 50% of prostate cancers, especially in White men. Other molecular abnormalities that are seen in cases without an ETS gene fusion include: overexpression of the serine peptidase gene *SPINK1*; recurrent point mutations in the transcriptional repressor gene *SPOP*; loss and/or mutations in the *CHD1* gene; and alterations in members of the RAS/RAF gene family. Metastatic and/or castrate-resistant prostate cancers often have aberrations in the androgen receptor, *TP53*, and *RB1* genes in addition to loss of PTEN.

Rare nonsynonymous mutations in the transcription factor *HOXB13* are associated with a three- to four-fold increased risk of prostate cancer.[4] Prostate cancer is also increased in carriers of *BRCA1* and *BRCA2* mutations. About 12% of men with metastatic prostate cancer have a germline mutation in a DNA repair gene.[5]

Histologies other than adenocarcinomas are reported in less than 5% of cases. Ductal and intraductal cancers may be related to germline DNA repair gene mutations.

CLINICAL MANIFESTATIONS

In the United States and most developed countries, the majority of men who are diagnosed with prostate cancer are asymptomatic and have tumors that are discovered by PSA screening. Men who have localized disease may complain of a variety of lower urinary tract symptoms, including urinary retention, frequency, and nocturia. Other symptoms may include hematuria and hematospermia. For men who present with metastatic disease, symptoms may include fatigue, weight loss, and bone pain. Spinal cord compression (Chapters 164 and 175) can be heralded by increasing and well-localized back pain that is associated with weakness and urinary retention. Some men with locally advanced prostate cancer may present with edema, hypertension, and renal failure. At the time of diagnosis, about 75% of men will have localized disease, about 15% will have regional disease, and about 10% will have distant disease.

DIAGNOSIS

An elevated PSA level is a nearly universal finding in patients who have prostate cancer.[6] However, an elevated PSA level can be caused by many noncancerous conditions including benign prostatic hypertrophy and prostatitis (Chapter 114). Most men undergo transrectal ultrasound-guided biopsy of the prostate gland to diagnose prostate cancer, but biopsy guided by magnetic resonance imaging (MRI) can improve the accuracy of the biopsy.[A1,A2] Since prostate cancer is often multifocal, usually 10 to 12 cores are obtained , but MRI-directed targeted biopsies of suspicious areas alone are an alternative.[A3] Infection is a risk of the procedure, and antibiotic prophylaxis (e.g., a single 750mg oral dose of ciprofloxacin or a single 160/800 mg oral dose of trimethoprim/sulfamethoxazole) is standard before the procedure. A routine urine culture can be obtained before the procedure to guide prophylactic prebiopsy and postbiopsy treatment if bacteria are detected (Chapter 263). Since bleeding is another procedural risk, anticoagulant and/or antiplatelet medications are ideally discontinued for the procedure and restarted afterwards.

Prostate cancers are graded by their Gleason score (Table 186-1), which grades the histology of the most frequent patterns on biopsy and then sums the two scores.

TABLE 186-1 GLEASON SCORING SYSTEM

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1	Prostate cancer is well differentiated, with small and well-formed glands that closely resemble normal prostate tissue
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3	A moderately differentiated carcinoma in which glands are recognizable but the cells are darker, have an infiltrative pattern, and are beginning to invade the surrounding tissue
4	A poorly differentiated carcinoma with few recognizable glands and cells that are invading the surrounding tissue in neoplastic clumps
5	Anaplastic carcinoma with few recognizable glands and with sheets of cells throughout the surrounding tissue

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5	Anaplastic carcinoma with few recognizable glands and with sheets of cells throughout the surrounding tissue

ABSTRACT

Prostate cancer is the most common nonskin cancer in men in North America and Europe. Three important risk factors for this disease are advanced age, race, and family history. In the United States and other high-resource countries, widespread testing for prostate-specific antigen (PSA) has increased the number of men diagnosed with localized disease. Treatment options for localized disease include observation, active surveillance, radiation therapy, and radical prostatectomy, with each option providing a 5-year survival of nearly 100%. Men with regional disease can also be managed with radiation and androgen deprivation therapy, with an excellent 5-year survival. Only 7% of men in the United States present with metastatic disease, commonly to bone, but some who present initially with localized or regional disease will progress to metastatic disease. Metastatic disease is highly treatable, with major improvements in survival and quality of life, but remains incurable.

KEYWORDS

prostatic neoplasm
adenocarcinoma
androgen deprivation therapy
prostatectomy
external beam radiation therapy

TABLE 186-2 STAGING OF PROSTATE CANCER

TUMOR (T)	NODES (N)	METASTASIS (M)	PSA (ng/mL)	GLEASON SCORE	STAGE
T1-T2	N0	M0	<10	6	I
T1-T2	N0	M0	≥10 to <20	6	IIA
T1-T2	N0	M0	<20	3+4=7	IIB
T1-T2	N0	M0	<20	4+3=7	IIC
T1-T2	N0	M0	<20	8	IIC
T1-T2	N0	M0	≥20	≤8	IIIA
T3-T4	N0	M0	Any	≤8	IIIB
Any T	N0	M0	Any	9-10	IIIC
Any T	N1	M0	Any	Any	IVA
Any T	Any	M1	Any	Any	IVB

M0 = no tumor spread to distant sites; M1 = tumor spread to distant sites; N0 = no tumor spread to regional lymph nodes; N1 = tumor spread to regional lymph nodes; PSA = prostate-specific antigen; T1 = tumor too small to be seen or felt on physical examination; T2 = tumor confined to the prostate gland; T3 = tumor invades the seminal vesicles or extends beyond the prostate gland; T4 = tumor extends to adjacent structures.
For Gleason score, see Table 186-1.

Atypical small acinar proliferation is observed in approximately 5% of prostate biopsies, and between 30 to 50% of individuals with this finding will have invasive cancer on repeat biopsy. Men whose biopsies show high-grade prostatic intraepithelial neoplasia or atypical small acinar proliferation are generally reevaluated at 6- to 24-month intervals and should be considered for biomarker tests or imaging to aid in cancer diagnosis if appropriate. Benign findings on a prostate biopsy include atrophy, adenosis, atypical adenomatous hyperplasia, and acute or chronic inflammation.

Staging

The initial risk stratification and staging of prostate cancer combines clinical and pathologic features as well as imaging results to establish the extent of cancer. Prostate cancer is staged based on the degree of elevation of the PSA level, the primary tumor's Gleason score and local extent, whether the tumor has spread to regional or distant lymph nodes or nearby structures, and whether it has spread to bone or distant organs (Table 186-2). Imaging studies are key to determine the extent of local disease as well as the presence of any metastatic disease. For local disease, transrectal ultrasound and magnetic resonance imaging (MRI) scans are preferred to determine the size of the prostate gland, to localize nodules, and to detect invasion into adjacent structures.[7] A bone scan and computed tomographic (CT) scan are preferred to assess metastatic disease. Positron emission tomography (PET)/CT scan can also assist not only in initial staging but also in assessing biochemically recurrent disease. The most common imaging tracers to detect small-volume disease in soft tissue and/or in bone are C-11 choline or F-18 fluciclovine rather than F-18 fluorodeoxyglucose (FDG), which is routinely used in other common cancers. Prostate-specific membrane antigen can be targeted using Ga-68 PSMA-11 and 18F-DCFPyl as tracers.[8]

Germline genetic testing is recommended for men who have prostate cancer and who have one or more of the following: high-risk, very-high-risk, regional, or metastatic prostate cancer; Ashkenazi Jewish ancestry; or a strong family history of prostate cancer or other epithelial cancers such as breast, ovarian, colorectal, or endometrial cancers.

TREATMENT

Prostate cancer exhibits extensive clinical heterogeneity, and some men may be treated aggressively for cancers that will never cause clinical symptoms. Treatment decisions are based not only on risk stratification and the stage of disease but also on the side effects of treatment (Table 186-3).[9,10]

Localized Disease

A number of treatment options are available for patients who have localized prostate cancer (Table 186-3).

Watchful Waiting and Active Surveillance

Observation (watchful waiting) is an option for men who have competing causes of death that are likely to shorten life-expectancy to less than 10 years.[A4] Another strategy is active surveillance, which includes PSA testing every 6 months, a digital rectal examination once a year, repeat prostate biopsies potentially every 12 months, and consideration of MRI spectroscopy.[11,A5] Ki-67 is a marker of proliferation, and high staining for Ki-67 and/or loss of PTEN may identify patients who may require more aggressive treatment.[12]

TABLE 186-3 TREATMENT OF PROSTATE CANCER

EXTENT OF CANCER	THERAPEUTIC OPTIONS
Stage I	Observation Active surveillance External-beam radiation therapy or brachytherapy Radical prostatectomy with or without pelvic lymph node dissection
Stage II	Active surveillance External-beam radiation therapy or brachytherapy Radical prostatectomy with or without pelvic lymph node dissection
Stage IIIA	Androgen-deprivation therapy plus either external-beam radiation therapy or brachytherapy Radical prostatectomy with pelvic lymph node dissection
Stage IIIB, IIIC, IVA, or IVB	External-beam radiation therapy, and/or brachytherapy plus androgen-deprivation therapy, and/or docetaxel Radical prostatectomy with pelvic lymph node dissection
Biochemical PSA relapse	Observation Salvage external-beam radiation therapy Salvage radical prostatectomy Androgen-deprivation therapy
Metastatic hormone-sensitive prostate cancer	Androgen-deprivation therapy, docetaxel, abiraterone, enzalutamide, apalutamide, darolutamide
Metastatic castration-resistant prostate cancer	Androgen-deprivation therapy, docetaxel, cabazitaxel, abiraterone, enzalutamide, darolutamide, sipuleucel-T, olaparib, rucaparib, radium 223, pembrolizumab, lutetium 177 vipivotide tetraxetan

Curative Therapy

Both radical prostatectomy and radiation therapy can achieve a high cure rate for early disease. The preferred option should consider the patient's wishes, experience, and expectations. Referral to the appropriate specialist or team is highly encouraged to provide a balanced explanation of the impacts of each option on bowel, bladder, and sexual function, as well as other systemic side effects.

Radical prostatectomy is an option for patients who have clinically localized disease and a life expectancy of more than 10 years.[A6] Laparoscopic and robot-assisted radical prostatectomy are commonly performed rather than open radical prostatectomy to reduce the length of hospital stay as well as blood loss, surgical complications, urinary incontinence, and erectile dysfunction.[A7] In patients in whom the probability of nodal involvement is high, a pelvic lymph node dissection should be performed, typically at the time of prostatectomy. An extended pelvic lymph node dissection removes all nodes in the external iliac vein, pelvic side wall, bladder wall, floor of the pelvis, and internal iliac artery.

Another curative treatment option for patients with clinically localized disease is radiation therapy,[A8] delivered either as external beam radiation therapy with photons or protons or by brachytherapy.[13] Intensity-modulated external beam radiation therapy (19 treatments of 3.4 Gy each rather than 39 treatments of 2.0 Gy each) or ultrafractionated therapy (7 treatments of 4.1 Gy each) provide

equivalent outcomes.[A9,A10] Three-dimensional image-guided radiation therapy localizes the tumor daily to ensure proper positioning, so as to localize therapy to the prostate and minimize the dose to the surrounding normal organs, such as the bladder and rectum. Proton therapy delivers highly conformal doses to the prostate with less radiation to the surrounding normal tissue, but it does not improve clinical outcomes despite its substantially higher costs.[14] Brachytherapy (seed implantation or interstitial radiation therapy), which delivers radioactivity directly to the prostate, can be used alone for patients who have early-stage, low-risk prostate cancer or in combination with external beam radiation therapy for patients who have higher-risk disease.[15]

High-Risk Disease

For patients who have high-risk stage II disease or have stage III disease, the higher risk of nodal and micrometastatic disease warrants radical prostatectomy, commonly followed by radiation therapy. For these high-risk patients, neoadjuvant androgen deprivation therapy[16] should precede surgery and radiation to increase the likelihood of achieving cure.[A11] High-intensity focal ultrasound, focal cryotherapy, and focal laser ablation are experimental approaches for localized disease, but they are associated with high recurrence rates and currently cannot be recommended for routine use.

Biochemical Recurrent Disease

Patients who undergo initial definitive therapy should undergo follow-up PSA testing every 6 to 12 months for the first 5 years and then annually thereafter. For patients who have lymph node–positive disease, PSA testing and a physical examination every 3 to 6 months are warranted. Imaging studies are not indicated as part of routine monitoring.

About 40% of men treated with definitive local therapy may experience biochemical recurrence within 10 years owing to residual or recurrent disease. After radical prostatectomy, the PSA level should be undetectable, and a biochemical recurrence is defined as a PSA level of 0.2 ng/mL or higher, confirmed at two different time points. In contrast to the immediate effect of surgery, the maximal effect of radiation therapy can occur up to 2 years later, and even then the PSA remains detectable because normal prostate cells continue to make PSA. After radiation therapy, recurrence is defined as a rising PSA level more than 2 ng/mL above its post-treatment nadir or a doubling of the PSA level within a 3-month period.

Salvage therapy should be initiated promptly for recurrent or residual disease after prostatectomy or radiation therapy. Depending on the degree of rise of the PSA level, on imaging results to search for local recurrence or distant disease, and on the type of prior definitive local therapy, options to treat recurrence vary but include PET/CT imaging guided radiation therapy[A12] and androgen deprivation therapy[A13] under expert supervision.

Androgen Deprivation Therapy

For patients with recurrent or advanced disease, the goal of systemic therapy is to reduce the testosterone level either surgically by bilateral orchiectomy or medically by androgen deprivation therapy (i.e., medical castration). Medical options under expert supervision include gonadotropin-releasing hormone (GnRH) agonists and antagonists. In the majority of patients treated with either class of agent, levels of serum testosterone decline to castration levels within 30 days of initial treatment.

GnRH agonists, which are synthetic analogs of GnRH, bind to the GnRH receptor in the anterior pituitary and can lead to a temporary surge of luteinizing hormone and hence in testosterone. As a result, patients who have significant metastatic disease can acutely deteriorate unless the amount of circulating testosterone is reduced by pretreatment with an antiandrogen or androgen receptor antagonist, such as oral flutamide, bicalutamide, or nilutamide. GnRH agonists, which are available either as injectables or implants, include leuprolide, goserelin, triptorelin, and histrelin.

GnRH antagonists, which are synthetic analogs of the gonadotropin-releasing hormone that is produced by the hypothalamus, prevent GnRH from binding to its receptors in the anterior pituitary. As a result, levels of luteinizing hormone are reduced, and then testosterone levels are reduced. Because GnRH antagonists have a direct mechanism of action, a flare response does not occur. Available GnRH antagonists under expert oversight, either as injectables or oral agents, are degarelix or relugolix.

Side effects with both GnRH agonists and antagonists reflect low testosterone levels. Common symptoms and signs for which patients should be monitored include hot flashes, weight gain, fatigue, osteoporosis, increased levels of serum cholesterol, loss of muscle mass, loss of libido, and increased blood pressure. The cumulative incidence of major adverse cardiovascular events (e.g., nonfatal myocardial infarction, nonfatal stroke, and all-cause death) is about 50% less with relugolix than with leuprolide.[A14]

Metastatic Prostate Cancer

Most metastatic prostate cancers are initially hormone-sensitive and respond to androgen deprivation, but nearly all tumors eventually become nonsensitive.[17]

Metastatic, Hormone-Sensitive Prostate Cancer

In patients who have metastatic disease, another systemic agent typically is added to androgen deprivation therapy because intensification of treatment with either docetaxel or a newer generation hormonal agent can significantly improve survival. For example, the addition of docetaxel to androgen-deprivation therapy in patients with hormone-sensitive disease extends median overall survival by 17 months compared with androgen therapy alone[A15] in patients who have high-volume disease, defined by presence of visceral metastasis or four or more bone lesions, including at least one beyond vertebral bodies and pelvis. In such patients, attaining a PSA level ≤ 0.2 ng/mL at 7 months is prognostic for longer overall survival.

Newer generation hormonal agents used under expert oversight include abiraterone, enzalutamide, apalutamide, and darolutamide, each of which blocks the androgen receptor and improves overall survival in both low- and high-volume disease when added to androgen deprivation therapy compared to androgen deprivation therapy alone.[A16–A19] Unlike abiraterone, treatment with enzalutamide and apalutamide does not require replacement glucocorticoid treatment.

Metastatic, Castration-Resistant Prostate Cancer

General Approach

Despite the success achieved by androgen deprivation and hormonal therapy, castration-resistant disease ultimately emerges, as evidenced by rising PSA levels despite testosterone levels that confirm castration. Under expert supervision, the treatment plan for patients with metastatic, castration-resistant prostate cancer should be guided by the location and burden of metastasis, the prior treatment that was received when disease was hormone-sensitive, symptoms, and molecular status. Single-agent treatment is usually preferred.

When PSA levels rise during treatment with androgen deprivation therapy and first-generation antiandrogens, androgen deprivation therapy (a GnRH agonist or antagonist) is generally continued indefinitely, but withdrawal of the antiandrogen may temporarily reverse the rise in PSA. If patients were treated with docetaxel, retreatment with docetaxel may be reasonable if the progression occurred more than 12 months after it was last used. If progression occurs quickly after docetaxel treatment in hormone-sensitive disease, cabazitaxel can be utilized. If patients received a newer-generation hormonal therapy, another similar agent should not be used. Instead, another agent with a different mechanism of action, such as docetaxel, should be considered. Abiraterone, enzalutamide, and darolutamide are FDA-approved agents in metastatic, castration-resistant prostate cancer, but apalutamide is not FDA-approved in this setting. The emergence of lethal and aggressive prostate cancer with neuroendocrine/small cell features requires treatment with combination chemotherapy (cisplatin/carboplatin and etoposide).

In addition to chemotherapy and novel hormonal therapy, other FDA-approved agents include immunotherapy, poly (ADP-ribose) polymerase (PARP) inhibitors, and bone-targeting agents such as radium-223. For patients whose tumors are microsatellite instability-high (MSI-H), mismatch repair deficient (dMMR), or tumor mutational burden-high (≥10 mutations/megabase cancer), pembrolizumab, a programmed death receptor-1 (PD-1) blocking antibody, is effective. Sipuleucel-T is an autologous cellular immunotherapy that is designed to induce an immune response targeted against prostatic acid phosphatase, which is an antigen that is expressed in prostate cancer. This agent is indicated for treatment of asymptomatic or minimally symptomatic metastatic, castration-resistant prostate cancer regardless of the type of prior therapy.[18] The toxicities related to sipuleucel-T are related to acute infusion reactions and include fatigue, fever, chills, and nausea.

Men with prostate cancer due to DNA repair gene mutations respond well to poly (ADP-ribose) polymerase (PARP) inhibitors. Men with prostate cancer in the setting of mutations in one of the mismatch repair genes associated with Lynch syndrome may benefit from immunotherapy. If the molecular profiling reveals a deleterious or suspected deleterious germline or somatic homologous recombination repair gene in patients who have progressed following prior treatment with chemotherapy and/or abiraterone or enzalutamide, treatment with PARP inhibitors (including olaparib and rucaparib) is useful.[A20,A21] The toxicities include anemia, pneumonitis, and diarrhea.

Radium 223, an α-particle-emitting radioactive therapeutic agent, is indicated for the treatment of patients with symptomatic bone metastasis and no known visceral metastatic disease. Similar to the other agents, the overall survival with this agent is nearly 4 months better compared with placebo. The toxicities from radium-223 include bone marrow suppression and an increased risk of fractures, but adding bone-strengthening agents may reduce the risk of fractures. Combination of radium-223 with other agents is not currently recommended.

Theranostics represent another therapeutic class of drugs. A targeted radioligand therapy, ^{177}Lu-PSMA-617, targets prostate specific membrane antigen, which is highly expressed in prostate cancer, as demonstrated by a positive prostate specific membrane antigen PET/CT scan.[A22]

Supportive Care

Optimization of quality of life requires careful management of the symptoms as well as the side effects of treatment. Goals of care in the management of patients with advanced or metastatic prostate cancer should be established early and revisited frequently by a multidisciplinary team of experts. For example, androgen deprivation therapy, whether given short or long term, has side effects that require collaboration with primary care physicians and

appropriate subspecialists, including cardiology, endocrinology, and/or orthopedics. Bone health also requires supplemental vitamin D and calcium as well as bisphosphonates, depending on bone density and the risk of fractures (Chapter 225). Fortunately, many therapeutic options and clinical trials are available.

PREVENTION

Screening

Randomized trials show that PSA screening can somewhat reduce prostate-cancer-specific mortality but probably not overall mortality despite the potential side-effects of biopsies and procedures.[A23,A24] Based on these data, the U.S. Preventive Services Task Force recommended against routine PSA screening in 2012 and now recommends that men ages 55 to 69 years be informed about the potential benefits and harms of PSA-based screening, so that they can make individualized decisions. For higher-risk men, such as men with a positive family history, screening probably should be encouraged. By comparison, routine screening is not recommended in men ages 70 years and older.[19]

PSA testing has a high sensitivity but low specificity because conditions such as benign prostatic hypertrophy and prostatitis (Chapter 114) can cause false-positive elevations. A PSA level above 4 ng/mL will detect 70 to 80% of tumors, but age-specific thresholds are 2.5 ng/mL for men ages 40 to 49 years, 3.5 ng/mL for men ages 50 to 59 years, 4.5 ng/mL for men ages 60 to 69 years, and 6.5 ng/mL for men ages 70 to 79 years. When the PSA is 4 to 10 ng/mL, a free PSA percentage below 25% can detect 95% of cancers while avoiding 20% of unnecessary biopsies. Another approach, especially for older men with concomitant benign prostatic hypertrophy, is to divide the PSA level in ng/mL by the size of the prostate in mL on ultrasonography; a value less than 0.09 ng/mL/cc is strongly suggestive of benign disease. When biopsy is being considered, magnetic resonance imaging guidance[A25] is generally preferred over ultrasonography-guided biopsy, and both are preferred over unguided biopsy.

Chemoprevention

Finasteride and dutasteride, which are 5α-reductase inhibitors that are commonly prescribed for benign prostatic hypertrophy (Chapter 114), reduce the risk of developing of prostate cancer.[A26] However, neither medication is FDA-approved to prevent prostate cancer because initial studies raised concerns that 5α-reductase inhibitors increased the risk of higher-grade prostate cancer. Interestingly, recent evidence from long-term follow-up studies of men with access to modern screening options questions this concern.[20]

PROGNOSIS

At the time of diagnosis, 5-year survival rates are 100% for localized disease, 100% for regional disease, and 30% for disseminated disease. However, 10-year PSA progression-free survival rates are lower: about 70 to 80% for well-differentiated tumors treated with either surgery or radiation therapy; 50 to 70% for intermediate-risk tumors; and 30% for high-risk tumors. The decrease in screening since the more conservative U.S. guidelines were promulgated has resulted in a small but real increase in the incidence of metastatic prostate cancer[21] and in prostate-cancer–specific mortality rates.[22]

Adverse prognostic markers include Gleason score at the time of prostatectomy, reappearance of PSA after complete prostatectomy, and the PSA doubling time. Bone metastases may be seen. For androgen-responsive metastatic disease, median survival generally ranges from 2 to 6 years depending on the tumor's characteristics. The median survival period for men with metastatic castration-resistant prostate cancer is about 3 years.

Rare ductal and intraductal tumors have a poorer prognosis. Small-cell or neuroendocrine carcinomas are characterized by lack of responsiveness to androgen deprivation as well as rapid progression, with lytic bone lesions and visceral disease.

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For the General References and other additional features, please visit Elsevier eBooks+ at https://ebooks.health.elsevier.com.

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187 MALIGNANT BONE TUMORS, SARCOMAS, AND OTHER SOFT TISSUE NEOPLASMS

ROBIN L. JONES

BONE TUMORS

Primary bone tumors include osteosarcomas, chondrosarcomas, and Ewing sarcoma. These rare tumors, which arise from the normal cellular components of bone and can potentially metastasize, have an incidence of 1.8 new cases per 100,000 population per year and account for only 0.2% of all cancers. Tumors that originate in other organs can metastasize to bone and represent the vast majority of bone cancers in adults.

CLINICAL MANIFESTATIONS AND DIAGNOSIS

Patients who have either primary malignant or benign bone tumors can present with pain, swelling, and sometimes pathologic fracture of the involved bone.

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At the time of diagnosis, 5-year survival rates are 100% for localized disease, 100% for regional disease, and 30% for disseminated disease. However, 10-year PSA progression-free survival rates are lower: about 70 to 80% for well-differentiated tumors treated with either surgery or radiation therapy; 50 to 70% for intermediate-risk tumors; and 30% for high-risk tumors. The decrease in screening since the more conservative U.S. guidelines were promulgated has resulted in a small but real increase in the incidence of metastatic prostate cancer[21] and in prostate-cancer–specific mortality rates.[22]

Adverse prognostic markers include Gleason score at the time of prostatectomy, reappearance of PSA after complete prostatectomy, and the PSA doubling time. Bone metastases may be seen. For androgen-responsive metastatic disease, median survival generally ranges from 2 to 6 years depending on the tumor's characteristics. The median survival period for men with metastatic castration-resistant prostate cancer is about 3 years.

Rare ductal and intraductal tumors have a poorer prognosis. Small-cell or neuroendocrine carcinomas are characterized by lack of responsiveness to androgen deprivation as well as rapid progression, with lytic bone lesions and visceral disease.

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187 MALIGNANT BONE TUMORS, SARCOMAS, AND OTHER SOFT TISSUE NEOPLASMS

ROBIN L. JONES

BONE TUMORS

Primary bone tumors include osteosarcomas, chondrosarcomas, and Ewing sarcoma. These rare tumors, which arise from the normal cellular components of bone and can potentially metastasize, have an incidence of 1.8 new cases per 100,000 population per year and account for only 0.2% of all cancers. Tumors that originate in other organs can metastasize to bone and represent the vast majority of bone cancers in adults.

CLINICAL MANIFESTATIONS AND DIAGNOSIS

Patients who have either primary malignant or benign bone tumors can present with pain, swelling, and sometimes pathologic fracture of the involved bone.

ABSTRACT

Primary bone tumors, including osteosarcomas, chondrosarcomas, and Ewing sarcoma, are rare. Metastatic tumors to bone are much more common and are seen especially with cancers of the breast, prostate, lung, thyroid, gastrointestinal tract, and kidney. Sarcomas are rare tumors of mesenchymal origin. Multidisciplinary care by an experienced team is vital to optimize outcomes for these patients.

KEYWORDS

sarcomas
osteosarcoma
leiomyosarcoma
rhabdomyosarcoma

Metastatic tumors to bone also can be similarly symptomatic but are often first suspected based on imaging tests that are obtained to stage the tumor. Imaging of a primary bone tumor includes plain radiographs, magnetic resonance imaging (MRI), and computed tomography (CT). On imaging, malignant tumors generally have irregular, poorly defined borders, a wide area of transition, evidence of cortical bone destruction, periosteal reaction, and soft tissue extension.

When imaging suggests a malignant primary bone tumor, the patient should be referred to an orthopedic oncologist to perform a diagnostic biopsy. An improperly performed biopsy can potentially change a tumor that is resectable by limb salvage to a tumor that requires amputation. Staging evaluation should include both a CT scan and a bone scan.

MAJOR PRIMARY MALIGNANT BONE TUMORS

OSTEOSARCOMA

Osteosarcoma, which is the most common bone sarcoma, accounts for approximately 35% of all primary bone tumors. Osteosarcomas have a bimodal age distribution, with the highest incidence before age 20 years and a second peak after age 60 years.[1] About 60% of cases occur in males. The most common primary sites in the younger age group are the metaphyses of long bones and the extremities, especially the distal femur, proximal tibia, and proximal humerus. In older adults, the primary anatomic sites are more varied.

Most osteosarcomas are sporadic, but the incidence is higher among families with germline gene mutations or deletions, such as retinoblastoma (about 60% of familial cases), *TP53* (Li-Fraumeni syndrome, about 40% of familial cases), or rarely the *RecQ DNA helicase* genes (Rothman-Thompson, Werner, or Bloom syndrome). Prior radiation and Paget disease (Chapter 228) are also risk factors, particularly for older individuals.

On histologic examination, osteosarcomas contain varying amounts of osteoid as well as cartilage and fibrous tissue. The typical radiologic appearance consists of a mixture of osteoblastic and osteolytic features with periosteal elevation.

TREATMENT

Management generally consists of neoadjuvant chemotherapy followed by surgical resection and then adjuvant chemotherapy.[2] Most patients can undergo limb salvage surgery rather than amputation. For patients under age 40 years, the most widely used chemotherapy schedule consists of methotrexate, doxorubicin, and cisplatin under expert supervision. Some patients with solitary or oligometastatic disease can undergo surgery with curative intent, but the evidence base is limited. A number of salvage chemotherapy schedules can be considered, including gemcitabine/docetaxel and ifosfamide/etoposide.

PROGNOSIS

With current multidisciplinary management, including complete surgical resection and multiagent chemotherapy, the overall survival of patients with osteosarcoma is on the order of 65%.[3] A higher percentage of tumor necrosis (>90%) following neoadjuvant chemotherapy portends a better prognosis. However, the outcome for patients with metastatic osteosarcoma is poor.

CHONDROSARCOMA

Chondrosarcomas, which are the second most common bone sarcoma (25% of cases), are characterized by malignant differentiation of hyaline cartilage.[4] The peak incidence is in the fifth to seventh decades. The pelvis, proximal femur, and proximal humerus are the most common primary sites, and patients can present with long-standing swelling and/or pain. Approximately 15% of chondrosarcomas arise from preexisting peripheral osteochondromas and harbor mutations in the exostosin (*EXT1 or EXT2*) gene. The other 85% arise in a central location, some in preexisting enchondromas. The majority of chondrosarcomas (90%) are low or intermediate grade, but the 10% of chondrosarcomas that are high-grade exhibit much more metastatic potential.

The pathologic distinction between low-grade chondrosarcoma and benign central enchondromas can be challenging, but size greater than 5 cm and axial location are very suggestive of malignancy. On imaging, chondrosarcomas often have a mixed sclerotic and lytic appearance.

TREATMENT AND PROGNOSIS

Complete surgical resection with clear margins is the mainstay of management for all grades of chondrosarcoma. The overall 5-year survival rate is about 75%, and most patients who survive for 4 years also survive for 10 years or longer.[5] Unfortunately, these tumors are relatively insensitive to radiation and chemotherapy, although these modalities may be considered in the palliative setting.

EWING SARCOMA

Ewing sarcoma, which accounts for approximately 15% of bone sarcomas, commonly has a characteristic translocation between *EWS* and *ETS* family transcription factors. The most common translocation [t(11;22)(q24;q12)] between *EWSR1* and *FLI1* occurs in approximately 85% of cases, but other fusion genes are also found. Although Ewing sarcoma most commonly presents in bone, it can also arise in soft tissue, in which case it is called extraosseous Ewing sarcoma.

The peak incidence for Ewing sarcoma is in the second decade, but about 20% of cases occur in older patients. This disease mainly occurs in Whites of European origin. Patients can present with a systemic illness, characterized by intermittent low-grade fever, leukocytosis, and anemia. Ewing sarcoma has a predilection for the diaphyseal region of long bones, pelvis, and ribs.

On imaging, these tumors frequently have associated soft tissue involvement and can also have a permeative or "moth-eaten" appearance and a multilayered "onion-skin" periosteal reaction. Special pathologic input is critical in establishing the diagnosis, particularly in distinguishing Ewing sarcoma from other small, round, blue cell tumors.

TREATMENT AND PROGNOSIS

Patients are generally treated with neoadjuvant chemotherapy followed by surgery/radiation and then adjuvant chemotherapy.[6] A commonly used combination under expert guidance is dose-intensive vincristine, doxorubicin, and cyclophosphamide alternating with ifosfamide and etoposide.[A1]

With multiagent chemotherapy, the 5-year event-free survival rate is about 70%. The outcome for patients with clinically detectable metastatic disease is poor. A number of salvage therapies can be used, including cyclophosphamide/topotecan, irinotecan/temozolomide, and gemcitabine/docetaxel.

METASTATIC TUMORS TO BONE

Metastatic bone disease from hematogenous spread[7] is an important cause of cancer-related morbidity. Breast cancer (Chapter 183) in women and prostate cancer (Chapter 186) in men are the most common tumors that metastasize to bone. Other tumors that often develop bone metastases include lung (Chapter 177), thyroid (Chapter 207), gastrointestinal tract (Chapter 179), and kidney (Chapter 182) cancers.[8]

A plain radiograph can show blastic (typical of prostate cancer) or lytic (e.g., myeloma; Chapter 173) lesions. However, most bone metastases have a mixed appearance. A radiologic survey should be performed in a patient who has known bony metastatic disease or who presents with bone pain to identify other possible metastatic lesions. CT scanning or MRI can help determine the risk of fracture. Radionuclide bone scans can also identify the extent of metastatic bone disease and evaluate response to treatment, but the bone scan may be negative in tumors such as myeloma that cause purely lytic lesions. If patients have no symptoms and a low risk of developing bone metastases, routine screening is not recommended.

TREATMENT

Pathologic fractures or lesions at imminent risk of fracture are generally treated with surgical fixation. Painful lesions with no risk of fracture are treated with external-beam radiation. Dexamethasone (two 4-mg dexamethasone tablets at least 1 hour before the start of radiation treatment and then every day for 4 days after radiotherapy) can reduce the risk of a radiation-associated flare of pain. Systemic palliative therapy for bone metastases[9] should follow standard guidelines for the specific tumor type, and treatment can include bisphosphonates (Chapter 225), denosumab, and endocrine and/or chemotherapy.

PREVENTION

Treatment with bisphosphonates under expert supervision can prolong the time to a first skeletal event in patients with breast cancer (Chapter 183), prostate cancer (Chapter 186), and myeloma (Chapter 173).[A2] The optimal schedule and duration of therapy remain to be defined.

PROGNOSIS

The prognosis of patients with metastatic cancer to bone depends on the specific type of tumor but typically is poor because it represents late-stage disease.

SOFT TISSUE SARCOMAS

DEFINITION

Sarcomas, which are malignant tumors of mesodermal origin, account for approximately 1% of all adult cancers. These tumors of connective tissue can occur in almost any anatomic location. In addition, they are very heterogeneous, with more than 100 different histologic subtypes, each with unique underlying biology and clinical behavior.[10]

EPIDEMIOLOGY

The incidence of soft tissue sarcomas in the United States is about 13,000 cases per year. Individuals who are at high risk for developing sarcomas include patients with Li-Fraumeni syndrome (Chapter 166), retinoblastoma (Chapter 391), neurofibromatosis (Chapter 385), malignant peripheral nerve sheath tumor, gastrointestinal stromal tumors (GISTs; Chapter 179), and familial polyposis (Chapter 179). Prior radiation treatment (e.g., for breast cancer, cervical cancer, or lymphoma) also increases the risk of developing a sarcoma in the radiation field. Occupational exposure to polyvinyl chlorides is associated with increased risk of hepatic angiosarcomas. Chronic lymphedema is also a risk factor for the development of angiosarcoma (Stewart-Treves syndrome). However, the vast majority of soft tissue sarcomas are sporadic with no known risk factor.

PATHOBIOLOGY

Soft tissue sarcomas can be divided into tumors with a complex karyotype (e.g., leiomyosarcoma, undifferentiated pleomorphic sarcoma, and angiosarcoma) and tumors with a simple karyotype. Tumors with simpler karyotypes include translocation-associated sarcomas (e.g., myxoid liposarcoma and synovial sarcoma), sarcomas with specific kinase mutations (notably gastrointestinal stromal tumors), tumors with simple genetic alterations (amplifications of *CDK4* and *MDM2* in dedifferentiated liposarcoma), and tumors with gene activation (e.g., *INI1* loss in rhabdoid tumors, *NF1* in malignant peripheral nerve sheath tumor, and *NTRK* fusions in soft tissue sarcomas).

CLINICAL MANIFESTATIONS AND DIAGNOSIS

The diversity of primary anatomic sites and the rarity as well as the heterogeneity of histologic subtypes can make the diagnosis and management of sarcomas challenging. Even within a particular subtype of sarcoma (e.g., leiomyosarcoma), clinical manifestations can be remarkably heterogeneous. Clinical behavior can range from an indolent tumor that can grow over decades (e.g., well-differentiated liposarcoma) to highly aggressive, life-threatening diseases (e.g., angiosarcoma). Sarcomas on the extremities often present with a slowly growing, nontender mass, but over 99% of such masses are benign soft tissue tumors of fat, muscle, fibrous or vascular tissue, or peripheral nerves rather than malignant sarcomas.[11]

The primary anatomic distribution of soft tissue sarcomas is approximately 40% on the lower extremities, 20% on an upper extremity, 20% in the abdomen or pelvis, 10% on the trunk, and 10% in the head and neck. The blood stream is the primary means of dissemination, and sarcomas very rarely spread to lymph nodes. Notable subtypes that can spread to lymph nodes include epithelioid, clear cell, and certain vascular sarcomas.

Initial investigation of a suspected sarcoma should include imaging of the primary site. MRI is preferred for sarcomas on the extremities, chest wall, head, or neck. CT scans are preferred to evaluate sarcomas of the abdomen and pelvis, as well as to define the possible presence of metastatic disease in the lungs and bone.

A core biopsy of the mass should be performed to make the histologic diagnosis. The biopsy tract should be in the direction of the future incision. Because of the challenges of histopathologic diagnosis, fine-needle aspiration is not performed except occasionally in gastrointestinal stromal tumors.

Because of their heterogeneous pathobiology, specialized pathologic review is needed to confirm the diagnosis of sarcoma. The most common histologic subtypes are gastrointestinal stromal tumor, undifferentiated pleomorphic sarcoma, leiomyosarcoma, and liposarcoma.

TREATMENT

Improperly performed surgical procedures can have a negative impact on outcome, so patients with a suspected sarcoma should be evaluated and treated by an experienced multidisciplinary team.[12]

Localized Sarcomas

The mainstay of management of localized sarcomas is limb-preserving complete surgical resection with clear margins plus radiation therapy. For large, high-grade soft tissue sarcomas of the extremities or trunk, preoperative neoadjuvant radiation is generally recommended over postoperative adjuvant radiation[13] because of its lower dose, smaller field size, and consequently reduced fibrosis and edema despite a higher wound complication rate than with adjuvant radiation.

For retroperitoneal sarcomas, an aggressive surgical approach, including resection of adjacent structures even in the absence of clear invasion, may improve local control. The role of neoadjuvant radiation in potentially operable retroperitoneal sarcomas is uncertain.

The role of neoadjuvant/adjuvant chemotherapy for soft tissue sarcomas other than large, high-grade tumors of the extremity and trunk remains controversial. Neoadjuvant/adjuvant chemotherapy provides a survival advantage in embryonal rhabdomyosarcoma and soft tissue Ewing sarcoma. If given under expert oversight, standard neoadjuvant chemotherapy (epirubicin/ifosfamide) is as good as histology-tailored chemotherapy.

Progressive or Metastatic Disease

Despite optimal management, about 50% of patients with high-grade localized soft tissue sarcomas progress to locally recurrent or metastatic disease. Such progression is usually within the first 3 years, but late spread can be seen with more indolent tumors. Some patients with low-volume, asymptomatic, and indolent disease may initially undergo active surveillance. For patients with solitary or oligometastatic disease, local therapy, including surgery, radiation, ablation, and embolization techniques, can be effective.[14]

However, the mainstay of management of metastatic disease is palliative chemotherapy. First-line palliative therapy generally consists of an anthracycline-based regimen, and the combination of doxorubicin plus trabectedin under expert supervision provides longer progression-free survival compared with doxorubicin alone.[A3] The combination of doxorubicin and ifosfamide is usually reserved for patients with symptomatic and rapidly progressive disease. Adding olaratumab (a monoclonal antibody that blocks subunit alpha of the platelet-derived growth factor receptor) to doxorubicin is of no incremental value.[A4] Pazopanib (a multitarget tyrosine kinase inhibitor) may be as effective and safe as doxorubicin for the initial treatment of patients over age 60 years.[A5]

For certain histologic subtypes, specific therapies can be considered under expert oversight. Examples include paclitaxel for angiosarcoma; aromatase inhibitors for endometrial stromal sarcoma and low-grade leiomyosarcoma; antiangiogenic agents (pazopanib/sunitinib) in alveolar soft part sarcoma and solitary fibrous tumor; tropomyosin receptor kinase inhibitors (e.g., larotrectinib or entrectinib) for sarcomas with *NTRK* fusions;[15] tazemetostat (a selective EZH2 inhibitor) for epithelioid tumors with a loss of INI1/*SMARCB1* expression;[16] and ALK inhibitors in *ALK*-mutated inflammatory myofibroblastic tumors.

For second-line systemic therapy, the combination of gemcitabine plus docetaxel or gemcitabine plus dacarbazine is preferred over single-agent therapy. Among patients with advanced pretreated liposarcoma and leiomyosarcoma, trabectedin can significantly prolong progression-free survival (median 4.2 vs. 1.5 months, respectively) but not overall survival compared with dacarbazine,[A6] whereas eribulin may prolong overall survival but not progression-free survival.[A7] In patients with pretreated advanced sarcomas, pazopanib can prolong median progression-free survival but not overall survival.

PROGNOSIS

Approximately 50 to 60% of patients with localized sarcoma are cured with optimal management. However, sarcomas encompass a range of different diseases with variable prognoses. The risk of recurrence varies depending on the tumor's grade, size, anatomic location, depth, and histologic subtype. Furthermore, the primary anatomic site can also be important; for example, the outcome following resection of a cutaneous sarcoma is excellent, whereas the prognosis of a cardiac sarcoma is poor.

The prognosis for patients with metastatic disease is limited, with a median overall survival between 12 and 18 months. However, prognosis varies depending on the volume of metastatic disease, histologic subtype, and location. For most sarcomas, however, current chemotherapeutic regimens have improved median survival from 12 months to approximately 18 to 20 months.

GASTROINTESTINAL STROMAL TUMORS

Gastrointestinal stromal tumors are the most common mesenchymal tumor of the gastrointestinal tract. About 85% of cases have activating mutations in *KIT* or *PDGFRA*.[17] Gain-in-function mutations in KIT and PDGFRA receptors lead to constitutive, ligand-independent activation of downstream signaling pathways. Most gastrointestinal stromal tumors express CD117 and DOG1, and CD34 is also expressed in about 70% of cases.[18]

Gastrointestinal stromal tumors occur throughout the gastrointestinal tract, most commonly in the stomach or small intestine. They typically are vascular tumors, frequently presenting with bleeding into the bowel or the abdominal cavity. Mass effects of gastrointestinal stromal tumors may cause abdominal pain or bowel obstruction, and they sometimes are palpable on physical examination. However, most gastrointestinal stromal tumors are detected by imaging, endoscopic screening for colon cancer, or surgical exploration.

TREATMENT

Surgery is the mainstay of management for localized disease,[19] but patients at high risk for progression should be treated with at least 3 years of adjuvant imatinib,[A8] which provides durable benefit in a high proportion of patients. For patients whose gastrointestinal stromal tumors recur or do not respond to imatinib, treatment with sunitinib, regorafenib, or ripretinib can provide sustained benefit (Chapter 178).[A9,A10]

DESMOID TUMORS/AGGRESSIVE FIBROMATOSIS

Desmoid fibromatosis is a very rare, monoclonal, fibroblastic proliferation. Between 80 and 95% of desmoid tumors harbor mutations in the β-*catenin* gene (*CTNNB1*), which leads to nuclear accumulation of β-catenin protein. This tumor lacks metastatic potential but is locally invasive, has a high local recurrence rate, and is characterized by an unpredictable clinical course.

TREATMENT

The general consensus is that a period of initial active surveillance is appropriate for most asymptomatic patients because spontaneous regressions can occur. Local treatment options include surgery, radiation, isolated limb perfusion, and ablation techniques under the expert oversight of an experienced multidisciplinary team. Sorafenib is of proven value for prolonging progression-free survival for advanced and refractory tumors.[A11] Other systemic therapies include tamoxifen/nonsteroidal anti-inflammatory drugs, liposomal doxorubicin, imatinib, navelbine, and methotrexate/vinorelbine.

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188 MELANOMA AND NONMELANOMA SKIN CANCERS

LYNN M. SCHUCHTER

MELANOMA

EPIDEMIOLOGY

The incidence of melanoma continues to rise rapidly worldwide, but mortality rates are declining. Each year in the United States, nearly 100,000 new cases of invasive melanoma are detected, and approximately 7000 patients die from melanoma.[1] Melanoma is the leading cause of death from cutaneous malignant disease, and it accounts for 1 to 2% of all cancer deaths in the United States.

The rising incidence is attributed to increasing sun exposure, especially early in life, as well as to more aggressive diagnosis[2] and even over-diagnosis.[3] Melanoma affects all age groups, with a median age at diagnosis of 63 years. Melanoma is largely a disease of Whites, with a very low incidence in Black Americans, Asians, and Hispanics.

Risk Factors

Risk factors for melanoma include family history of melanoma, prior melanoma or nonmelanoma skin cancer, inherited genetic susceptibility, and sun exposure. Artificial exposure to UV radiation by indoor tanning beds is likewise a risk factor for melanoma.[4] Individuals who have blond or red hair, blue eye color, and freckles have a tendency to burn rather than to tan and have higher rates of melanoma. The pattern of sun exposure may also be important; intermittent intense exposure, rather than chronic sun exposure, may carry a higher risk for melanoma.

Individuals with an increased number of typical or benign moles, atypical moles, or dysplastic nevi (Figs. 188-1 and 188-2) also have an increased risk for melanoma. Atypical moles or dysplastic nevi are important precursor lesions of melanoma and serve as markers for increasing risk. For example, individuals with dysplastic nevi have a 6% lifetime chance of developing melanoma, and this risk increases to as high as 80% in individuals who have dysplastic nevi and a strong family history of melanoma.

PATHOBIOLOGY

Exposure to sunlight, especially ultraviolet (UV) radiation (Chapter 18), is the major causative factor for the development of melanoma. Melanomas originate from melanocytes, which are located predominantly in the basal cell layer of the epidermis and use the enzyme tyrosinase to synthesize melanin pigment, which serves to protect against UV damage (Chapter 403). In persons of color, however, exposure to UV light may not be an important risk factor.[5]

Somatic mutations in primary and metastatic melanoma primarily involve the mitogen activated protein kinase pathway (MAPK). The point-mutation burden increases from benign through intermediate precursor lesions to melanoma, with strong genetic evidence of the effects of UV radiation detectable at all evolutionary stages. Activating mutations in the *BRAF* gene can be found in approximately 50% of melanomas, and 20% of melanomas are associated with a mutation in the *NRAS* gene. Distinct patterns of genetic alterations are found in primary melanomas based on anatomic location and extent of sun exposure.[6] For example, melanomas that originate on mucous membranes, acral skin (soles, palms), and skin with chronic sun damage (i.e., lentigo maligna melanoma) have frequent mutations in *KIT*. Uveal melanoma is associated with mutations in *GNAQ/GNA11*. Monosomy of chromosome 3 and somatic mutations in the gene encoding BRCA1-associated

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GASTROINTESTINAL STROMAL TUMORS

Gastrointestinal stromal tumors are the most common mesenchymal tumor of the gastrointestinal tract. About 85% of cases have activating mutations in *KIT* or *PDGFRA*.[17] Gain-in-function mutations in KIT and PDGFRA receptors lead to constitutive, ligand-independent activation of downstream signaling pathways. Most gastrointestinal stromal tumors express CD117 and DOG1, and CD34 is also expressed in about 70% of cases.[18]

Gastrointestinal stromal tumors occur throughout the gastrointestinal tract, most commonly in the stomach or small intestine. They typically are vascular tumors, frequently presenting with bleeding into the bowel or the abdominal cavity. Mass effects of gastrointestinal stromal tumors may cause abdominal pain or bowel obstruction, and they sometimes are palpable on physical examination. However, most gastrointestinal stromal tumors are detected by imaging, endoscopic screening for colon cancer, or surgical exploration.

TREATMENT

Surgery is the mainstay of management for localized disease,[19] but patients at high risk for progression should be treated with at least 3 years of adjuvant imatinib,[A8] which provides durable benefit in a high proportion of patients. For patients whose gastrointestinal stromal tumors recur or do not respond to imatinib, treatment with sunitinib, regorafenib, or ripretinib can provide sustained benefit (Chapter 178).[A9,A10]

DESMOID TUMORS/AGGRESSIVE FIBROMATOSIS

Desmoid fibromatosis is a very rare, monoclonal, fibroblastic proliferation. Between 80 and 95% of desmoid tumors harbor mutations in the β-*catenin* gene (*CTNNB1*), which leads to nuclear accumulation of β-catenin protein. This tumor lacks metastatic potential but is locally invasive, has a high local recurrence rate, and is characterized by an unpredictable clinical course.

TREATMENT

The general consensus is that a period of initial active surveillance is appropriate for most asymptomatic patients because spontaneous regressions can occur. Local treatment options include surgery, radiation, isolated limb perfusion, and ablation techniques under the expert oversight of an experienced multidisciplinary team. Sorafenib is of proven value for prolonging progression-free survival for advanced and refractory tumors.[A11] Other systemic therapies include tamoxifen/nonsteroidal anti-inflammatory drugs, liposomal doxorubicin, imatinib, navelbine, and methotrexate/vinorelbine.

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188 MELANOMA AND NONMELANOMA SKIN CANCERS

LYNN M. SCHUCHTER

MELANOMA

EPIDEMIOLOGY

The incidence of melanoma continues to rise rapidly worldwide, but mortality rates are declining. Each year in the United States, nearly 100,000 new cases of invasive melanoma are detected, and approximately 7000 patients die from melanoma.[1] Melanoma is the leading cause of death from cutaneous malignant disease, and it accounts for 1 to 2% of all cancer deaths in the United States.

The rising incidence is attributed to increasing sun exposure, especially early in life, as well as to more aggressive diagnosis[2] and even over-diagnosis.[3] Melanoma affects all age groups, with a median age at diagnosis of 63 years. Melanoma is largely a disease of Whites, with a very low incidence in Black Americans, Asians, and Hispanics.

Risk Factors

Risk factors for melanoma include family history of melanoma, prior melanoma or nonmelanoma skin cancer, inherited genetic susceptibility, and sun exposure. Artificial exposure to UV radiation by indoor tanning beds is likewise a risk factor for melanoma.[4] Individuals who have blond or red hair, blue eye color, and freckles have a tendency to burn rather than to tan and have higher rates of melanoma. The pattern of sun exposure may also be important; intermittent intense exposure, rather than chronic sun exposure, may carry a higher risk for melanoma.

Individuals with an increased number of typical or benign moles, atypical moles, or dysplastic nevi (Figs. 188-1 and 188-2) also have an increased risk for melanoma. Atypical moles or dysplastic nevi are important precursor lesions of melanoma and serve as markers for increasing risk. For example, individuals with dysplastic nevi have a 6% lifetime chance of developing melanoma, and this risk increases to as high as 80% in individuals who have dysplastic nevi and a strong family history of melanoma.

PATHOBIOLOGY

Exposure to sunlight, especially ultraviolet (UV) radiation (Chapter 18), is the major causative factor for the development of melanoma. Melanomas originate from melanocytes, which are located predominantly in the basal cell layer of the epidermis and use the enzyme tyrosinase to synthesize melanin pigment, which serves to protect against UV damage (Chapter 403). In persons of color, however, exposure to UV light may not be an important risk factor.[5]

Somatic mutations in primary and metastatic melanoma primarily involve the mitogen activated protein kinase pathway (MAPK). The point-mutation burden increases from benign through intermediate precursor lesions to melanoma, with strong genetic evidence of the effects of UV radiation detectable at all evolutionary stages. Activating mutations in the *BRAF* gene can be found in approximately 50% of melanomas, and 20% of melanomas are associated with a mutation in the *NRAS* gene. Distinct patterns of genetic alterations are found in primary melanomas based on anatomic location and extent of sun exposure.[6] For example, melanomas that originate on mucous membranes, acral skin (soles, palms), and skin with chronic sun damage (i.e., lentigo maligna melanoma) have frequent mutations in *KIT*. Uveal melanoma is associated with mutations in *GNAQ/GNA11*. Monosomy of chromosome 3 and somatic mutations in the gene encoding BRCA1-associated

ABSTRACT

Long-term exposure to sun and artificial exposure to ultraviolet radiation (e.g., indoor tanning beds) are established risk factors for both melanoma and nonmelanoma skin cancers. Somatic driver mutations in primary and metastatic melanoma include mutations in *BRAF, NRAS*, and *KIT*. Both checkpoint inhibitor immunotherapy and targeted therapy are standard treatments for melanoma. Nonmelanoma skin cancers (basal cell carcinoma and squamous cell carcinoma) are the most common malignancies in the United States. Both of these cancers can cause significant morbidity at the local site, but they almost always can be effectively treated and metastasize infrequently.

KEYWORDS

treatment of melanoma
basal cell skin cancer
squamous cell skin cancer
dysplastic nevi
sentinel lymph node
superficial spreading melanoma
lentigo maligna melanoma
nodular melanoma
ocular melanoma
mucosal melanoma
Mohs surgery

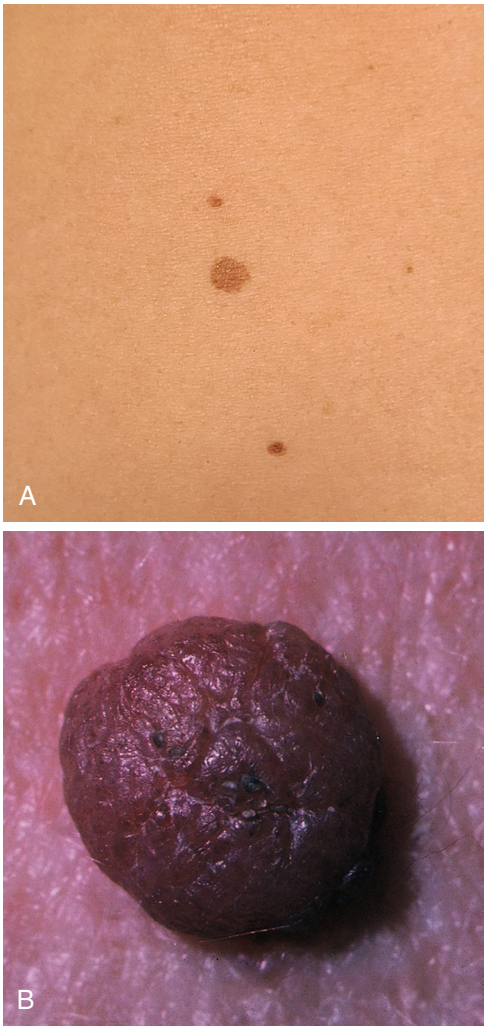

FIGURE 188-1. Nevi. A, Common benign nevus. B, Dermal nevus.

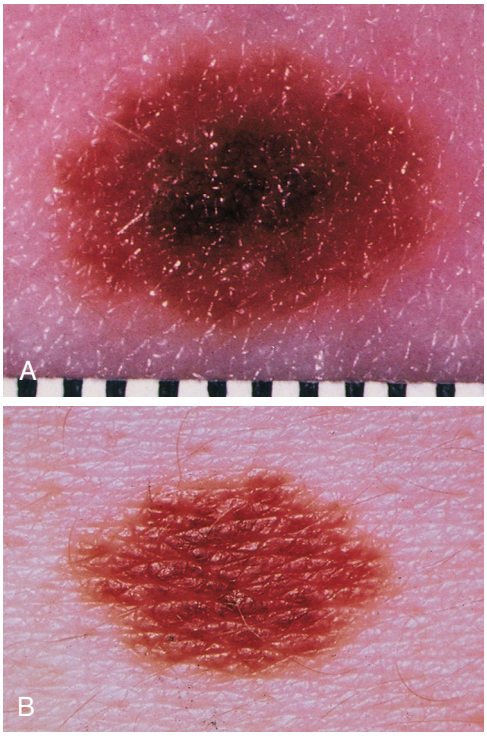

FIGURE 188-2. Dysplastic nevi. A and B, Examples of dysplastic nevi.

protein (BAP1) on chromosome 3 are associated with worse outcome and the development of metastatic melanoma. The discovery of somatic mutations in melanoma and associated aberrant signal transduction pathways has provided the basis for the development of molecularly targeted therapy for patients with advanced melanoma.[7]

Inherited Genetics

Approximately 10% of patients with melanoma have a family history of melanoma. Several chromosomal loci determine susceptibility to melanoma. The most important locus is *p16/CDKN2A*, which is on chromosome 9p21. This gene is a member of a class of molecules that play a central role in cell cycle regulation. Of the members of melanoma-prone families, 25 to 40% have mutations in this gene. The risk for developing cutaneous melanoma in an individual who is a *CDKN2A* carrier is between 30 and 90% by age 80 years and varies by geographic location.

Genetic variability in the melanocortin-1 receptor (MC1R) plays a key role in pigmentation of skin and hair, and this variability has been implicated in a predisposition to melanoma. Carriers of a pathogenic mutation in the *BRCA2* familial breast cancer gene have an increased risk of developing cutaneous melanoma. Germline mutations in *BAP1* gene are linked to the BAP1 tumor predisposition syndrome. Both uveal and cutaneous melanoma have been described in this syndrome, which is also associated with mesothelioma and renal cell cancer.

CLINICAL MANIFESTATIONS

Early detection and recognition of melanoma are key to improving survival. The signs of early melanoma are based on the clinical appearance of the pigmented lesion and a change in the shape, color, or surface of an existing mole. Most patients report a preexisting mole at the site of the melanoma. Itching, burning, or pain in a pigmented lesion should increase suspicion, although melanomas often are not associated with local discomfort. Bleeding and ulceration are signs of a more advanced melanoma. Most melanomas are varying shades of brown, but they may be black, blue, or pink. The ABCDEs for the recognition of melanoma are asymmetry, border irregularity, color variation, diameter greater than 6 mm, and evolution or a change in a skin lesion. The "ugly duckling" sign is recognizing a skin lesion that looks different from other skin lesions and is therefore suspicious.

Cutaneous melanoma has been divided into four subtypes. Superficial spreading melanoma, which accounts for 70% of all melanomas, can be located on any anatomic site (Fig. 188-3). Lentigo maligna melanoma, which represents 4 to 10% of all melanomas, tends to occur more commonly in chronically sun-exposed skin in older patients, frequently on the head and neck (Fig. 188-4); clinically, it appears as a macular (flat) lesion, with varying degrees of color, usually brown. Nodular melanoma (Fig. 188-5) accounts for 15 to 30% of melanomas and manifests as a rapidly enlarging, elevated, or polypoid lesion, often blue or black. These lesions can also be amelanotic and lack pigment and have more of a pink color. The ABCDE rule does not always apply as well to nodular melanomas. Acral lentiginous melanoma manifests as a darkly pigmented, flat to nodular lesion on the palm, on the sole, or subungually; sunlight is not thought to play a causative role in this form of melanoma. Histologic subtype does not directly correlate with clinical behavior. However, recent data suggest that histologic subtype may correlate with specific genetic abnormalities. For example, superficial spreading melanoma may be associated with *BRAF* mutation, and lentigo maligna melanoma may be associated with *KIT* mutation.[8]

Ocular melanomas arise from the pigmented layer of the eye. Uveal melanoma is the most common intraocular malignancy of adults. Melanomas can also arise from noncutaneous sites, including mucosal epithelium in the gastrointestinal tract, anorectal area, genitourinary tract, and nasal and nasopharyngeal mucosa. Melanomas of the vulva and vagina are relatively rare. In general, mucosal melanomas are diagnosed at a more advanced stage of disease. The mainstay of treatment is surgical.

DIAGNOSIS

Biopsy of the Primary Lesion

Any skin lesion suggestive of melanoma should be sampled by biopsy with complete excision, including a 1- to 2-mm margin of normal skin and some subcutaneous fat. Lesions that can be confused with melanoma include blue nevi, pigmented basal cell carcinoma, seborrheic keratosis, and hemangiomas (Table 188-1). Both molecular and cellular criteria can distinguish common nevi from dysplastic nevi.

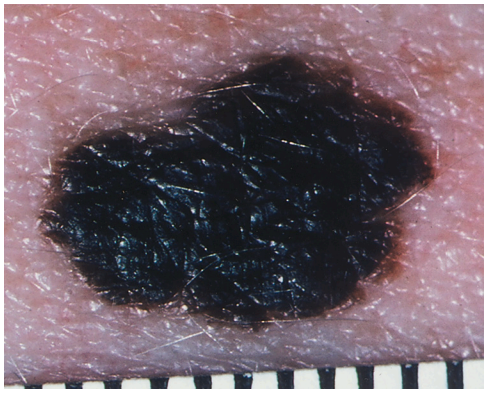

FIGURE 188-3. Superficial spreading melanoma.

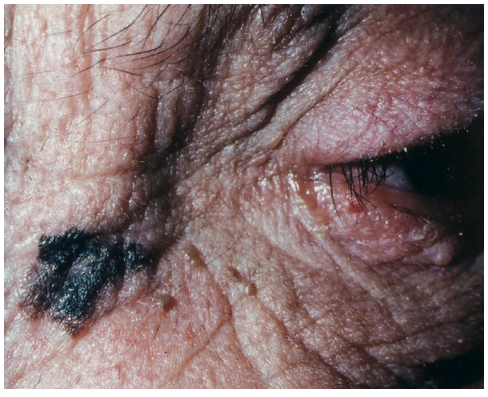

FIGURE 188-4. Lentigo maligna melanoma.

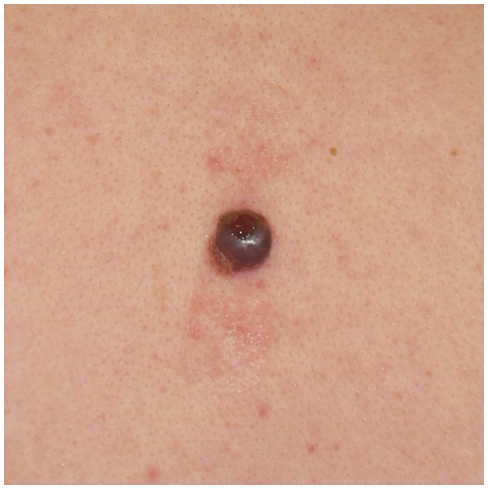

FIGURE 188-5. Nodular melanoma.

An incisional biopsy may be necessary for lesions that are too large for complete excision. Shallow shave biopsies, curettage, cryosurgery, laser, and electrodessication are contraindicated in lesions suggestive of melanoma.

Activating mutations in the *BRAF* gene are present in approximately 50% of melanomas, and all patients with advanced cutaneous melanoma should have their tumors assessed for the presence or absence of a *BRAF* mutation. Almost 80% of *BRAF* mutations are V600E, with most of the remainder consisting of V600K.

Sentinel Lymph Node Biopsy

Sentinel lymph node mapping is considered a critically important surgical staging tool[9] and should be performed whenever the melanoma is ulcerated or when the original biopsy reveals a melanoma with a depth of more than 1 mm or an increased mitotic rate (Fig. 188-6). For melanomas that are less than 1 mm thick, the likelihood of regional lymph node involvement is approximately 5%, so sentinel lymph node mapping is not routinely recommended for thin melanomas unless patients have adverse prognostic features such as ulceration and/or high mitotic count.

The sentinel lymph node biopsy is generally performed at the same time as the wide excision of the primary tumor and must be performed prior to the wide excision.[A1] The morbidity of sentinel lymph node biopsy is relatively low, and the staging information is critically valuable.

Sentinel lymph node biopsy accurately evaluates whether microscopic melanoma cells involve regional lymph nodes. The technique relies on the concept that specific regions of the skin drain specifically to an initial lymph node within the regional nodal basin through an organized pathway of afferent lymphatic channels. Sentinel lymph node biopsy is performed by injecting the primary melanoma site with blue dye (isosulfan blue), radiolabeled colloid, or both. When both modalities are used in combination, a sentinel node can be identified in 98% of patients; biopsy of the node accurately determines whether melanoma cells have metastasized to that specific lymph node basin.

TABLE 188-1 CLINICAL FEATURES OF COMMON NEVI, DYSPLASTIC NEVI, AND MELANOMAS

DISEASE	CHARACTERISTICS
Common acquired nevi (moles)	These tend to be small, flat, and round; the border is regular, smooth, and well defined; the color is homogeneous, usually no more than two shades of brown; any site is affected; lesions are usually <6 mm (see Fig. 188-1).
Dysplastic nevi (atypical moles)	These occur predominantly on the trunk; they tend to be large, usually >5 mm, with a flat component; the border is characteristically fuzzy and ill defined. The shape can be round, oval, or misshapen. The color is usually brown but can be mottled with dark brown, pink, and tan. Some individuals have only one to five moles; others have more than 100 (see Fig. 188-2).
Melanoma	The border is more irregular; lesions tend to be larger, often >6 mm; substantial heterogeneity of color is noted, which can be tan-brown, dark brown, black, pink, red, gray, blue, or white.

Staging

Staging and prognosis for melanoma are based on the TNM system, in which T refers to tumor, N to nodes, and M to metastasis.[10] Stages I (limited to the epidermis) and II (extending into the dermis) indicate clinically localized primary melanoma, stage III indicates regional involvement (lymph nodes or in-transit metastases), and stage IV is metastatic disease beyond the regional lymph nodes (i.e., lung, liver, brain).

Comprehensive Clinical Evaluation

The initial evaluation of a patient with melanoma should include a personal history, a family history, a total skin examination, and palpation of regional (draining) lymph nodes. The focus is to identify risk factors, signs, or symptoms of metastases, dysplastic nevi, and additional melanomas. A chest radiograph and liver enzyme tests may be performed at the discretion of the physician. Most patients who present with melanoma do not have distant metastatic disease at presentation, so extensive evaluations with computed tomography (CT) to search for distant metastases have an extremely low yield and are not indicated in asymptomatic patients. More extensive staging evaluation with CT or positron emission tomography (PET) can be considered in patients who have high-risk disease (primary melanoma >4 mm thick or node-positive disease), in whom the risk for distant metastatic disease is higher, or for mutations in *BRAC2*.

In patients who have a family history of melanoma, testing for mutations in the *p16/CDKN2A* locus can be informative. For patients or family members who are thought to be at risk for a hereditary cancer melanoma syndrome, referral to a genetic counselor should be considered to learn about the risks and benefits of genetic testing, the role of surveillance strategies, and their potential impact on medical management.

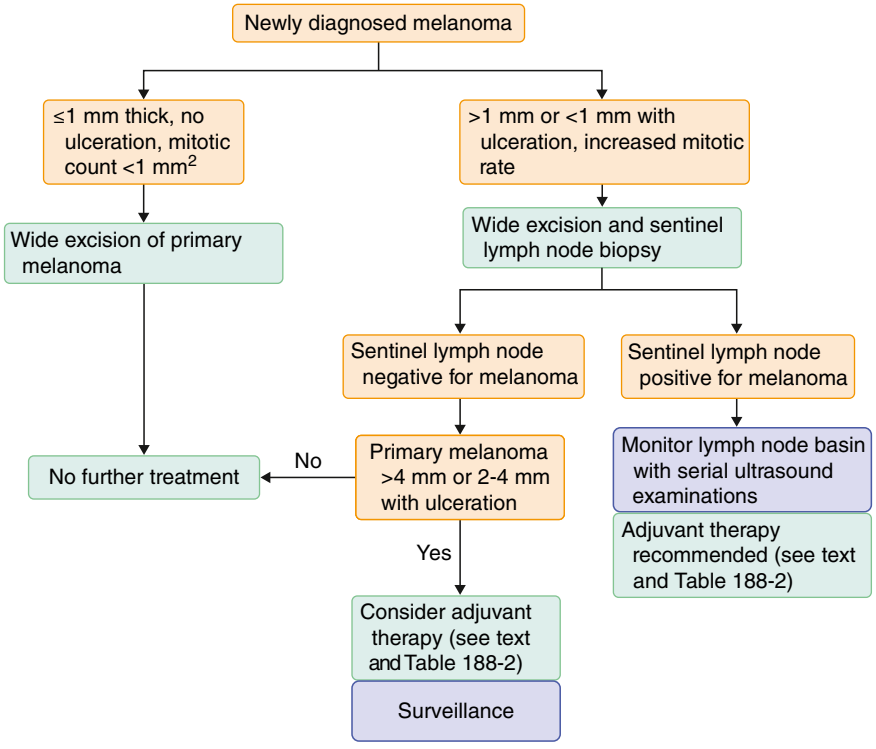

FIGURE 188-6. **Treatment algorithm for newly diagnosed melanoma.**

TREATMENT

Staging guides treatment decisions, including primary treatment, surveillance strategies, adjuvant therapy, and optimal management of patients with advanced melanoma.[11]

Primary Melanoma

After melanoma is diagnosed, the standard treatment is surgical excision of the primary lesion with consideration of an assessment of the regional nodal basin using sentinel lymph node mapping and biopsy (see Fig. 188-6). The extent of the surgery depends on the thickness of the primary melanoma, and most wide excisions can be performed with primary closure without skin grafting. For melanoma in situ, excision with a 0.5-cm border of clinically normal skin is sufficient. For melanomas less than 1 mm thick, a 1-cm margin is recommended. If the thickness is between 1 and 4 mm, a 1- to 2-cm margin is recommended. For melanomas thicker than 2 mm, a 2-cm resection margin also is sufficient and safe.[A2] In cosmetically sensitive areas (face) or anatomically difficult areas (ear, hands), the desired margin may be difficult to achieve, but at least a 1-cm margin should be obtained whenever possible.

Normal Regional Lymph Nodes

If the patient does not require a sentinel lymph node biopsy (see Fig. 188-6) or if the sentinel lymph node biopsy is negative for melanoma, no further lymph node surgery is required. For patients who have stage IIB (>2 to <4 mm thick with ulceration or >4 mm thick without ulceration) and stage IIC (>4mm thick with ulceration) node-negative melanoma, pembrolizumab under expert supervision can increase recurrence-free survival from 77 to 88% compared with placebo.[A3] The decision to offer adjuvant therapy to stage II melanoma patients requires expert consultation regarding its overall benefits and risks.

Stage III Disease

If the sentinel lymph node biopsy is positive for melanoma in a patient who does not otherwise have clinically apparent lymph node involvement, a completion lymph node dissection does not improve survival, and patients can be observed with ultrasonography monitoring.[A4] For patients with clinically enlarged regional lymph nodes, however, surgical (therapeutic) lymphadenectomy is the preferred treatment following pathologic confirmation of melanoma. The goal is to provide long-term, disease-free survival and reduce local morbidity of enlarged lymph nodes. In this patient population, neoadjuvant therapy or systemic therapy administered before surgery may be an appropriate option to consider, especially as part of a clinical trial.

Adjuvant Therapy for Stage III Melanoma

For patients who have completed surgical resection of the melanoma, the decision of whether to recommend adjuvant therapy is based upon characteristics of the primary tumor (thickness, mitotic count, ulceration status) and the involvement of regional lymph nodes. All patients with stage III melanoma should have their tumor assessed for the *BRAF* mutation. For patients with resected stage III (node positive) melanoma, adjuvant therapy with immunotherapy or targeted therapy under expert supervision is recommended to improve recurrence-free survival.[12] Options include adjuvant anti-PD-1 therapies (e.g., pembrolizumab or nivolumab), targeted therapy with dabrafenib and trametinib in *BRAF* mutant melanoma, or participation in a clinical trial. For example, anti-PD-1 antibody with nivolumab provides a higher rate of recurrence-free survival compared with ipilimumab (a CTLA4 inhibitor) and with much fewer adverse immune side effects.[A5,A6] Pembrolizumab can increase the 3-year rate of relapse-free survival from 44 to 64% compared with placebo.[A7]

For patients with BRAF V600 mutant melanoma, anti-PD-1 therapy is the preferred option, but another option under expert supervision is adjuvant targeted therapy with dabrafenib (BRAF inhibitor) plus trametinib (MEK inhibitor), which can increase the 5-year relapse-free survival from 36 to 52%.[A8]

Advanced Melanoma (Stage IV)

Melanoma can metastasize to virtually any organ, especially the lung, skin, liver, and brain. Treatment must be individualized under expert supervision based on the overall condition of the patient, the burden of disease, symptoms, prior treatment, a molecular analysis for the presence of a mutated *BRAF* gene, and eligibility for immunotherapy.[13] The initial focus of treatment is immunotherapy: either anti-PD-1 antibody monotherapy (nivolumab or pembrolizumab) or in combination with ipilimumab, even in patients with *BRAF* mutations. For patients with a *BRAF* mutation, another option is combination targeted therapy with *BRAF* and MEK inhibitors (vemurafenib and cobimetinib, dabrafenib and trametinib, or encorafenib and binimetinib) or immunotherapy (Table 188-2).[A9]

Immunotherapy

The overall response rate of metastatic melanoma to monotherapy with an anti-PD-1 antibody is about 25 to 35%. Responses are sometimes delayed, and disease may progress before it stabilizes or regresses. Nivolumab as first-line treatment is superior to dacarbazine[A10] or ipilimumab.[A11] Pembrolizumab also is superior to ipilimumab.[A12]

Treatment with PD-1 inhibitors is associated with immune-related adverse events including enterocolitis, hepatitis, dermatitis, and endocrinopathies such as hypopituitarism, hypothyroidism, and type 1 diabetes mellitus. Rare but serious immune-mediated pneumonitis or myocarditis can occur and requires careful monitoring. Tumor expression of PD-L1 may correlate with higher

TABLE 188-2 TREATMENTS FOR MELANOMA

AGENT	MECHANISM OF ACTION
Dabrafenib	BRAF inhibitor
Vemurafenib	BRAF inhibitor
Encorafenib	BRAF inhibitor
Binimetinib	MEK inhibitor
Trametinib	MEK inhibitor
Cobimetinib	MEK inhibitor
Pembrolizumab	Anti-PD-1 blocking antibody
Nivolumab	Anti-PD-1 blocking antibody
Ipilimumab	CTLA-4 inhibitor
Atezolizumab	Anti PD-L1 antibody
Nivolumab + relatlimab	Anti-PD-1 + Anti LAG 3
Talimogene laherparepvec	Oncolytic viral therapy

response rates but is not an adequate biomarker of response because patients may or may not have a response regardless of their PD-L1 expression status.[14]

The combination of anti-CTLA-4 and anti-PD-1 immunotherapy (dual-checkpoint blockade) under expert supervision is now the preferred approach for treatment of patients with stage IV melanoma when patients can tolerate its toxicity. In large trials of patients with either resected stage IV or metastatic melanoma, the combination of ipilimumab (which blocks CTLA-4) plus nivolumab is superior to either agent alone, with a median survival exceeding 5 years.[A13] Grades 3 to 4 treatment-related adverse events occur in about 50% of patients, including elevations of alanine aminotransferase levels, diarrhea, and colitis. Dose interruption of immunotherapy and corticosteroids are the mainstays of treatment for this side effect mediated by T-cell activation and proliferation.

Two immune checkpoint inhibitors, relatlimab (which targets LAG-3) and nivolumab, can be combined; compared with nivolumab alone, this combination can provide longer progression-free survival for patients who have advanced melanoma.[A14] Tumor-infiltrating lymphocyte therapy is another newer option for advanced melanoma.[A15]

BRAF Inhibitors and MEK Inhibitors

BRAF inhibitors can provide dramatic antitumor activity with an approximately 50% response rate. BRAF inhibitors (vemurafenib, dabrafenib, and encorafenib) and MEK inhibitors (trametinib, cobimetinib, and binimetinib) are indicated for *BRAF*-mutated melanoma but should not be used in *BRAF* wild-type tumors. Combination therapy with BRAF and MEK inhibition results in increased response rates, with improvement in progression-free and overall survival over monotherapy, and it is considered a standard treatment option (dabrafenib plus trametinib, vemurafenib plus cobimetinib, and encorafenib plus binimetinib).[A16] Although clinical activity of the selective BRAF inhibitors is impressive, complete responses are uncommon, and most patients develop progressive disease owing to acquired drug resistance.

The most common toxicities from *BRAF*-targeted therapy include fever, dermatologic complications (e.g., rash, photosensitivity, squamous cell carcinoma, keratoacanthoma, hyperkeratoses), arthralgia, fatigue, nausea, and diarrhea. The combination of encorafenib plus binimetinib is less likely to cause fever.[A17] Secondary tumors, including second primary melanomas, rapid expansion of chronic myelomonocytic leukemia, and mucosal cancers, have been reported.

Brain Metastases

Brain metastases occur in 10 to 50% of patients with advanced melanoma. Common symptoms include headache, seizures, or focal neurological symptoms. Nivolumab and ipilimumab[A18] have activity in the central nervous system and have improved prognosis for some of these patients. As a result, patients who have brain metastases should be considered for systemic therapy in addition to local measures, such as stereotactic radiotherapy or surgery. After such local measures, whole brain radiation does not add incremental benefit.[A19]

Surveillance and Follow-Up

Patients should be educated on the clinical characteristics of melanoma, the importance of safe sun exposure strategies, and the performance of monthly self-examinations of the skin. Patients should be followed regularly for evidence of local or regional recurrence, distant metastatic disease, and a second primary melanoma. The intensity of the surveillance and the extent of the investigation are influenced by risk for recurrence, with more frequent follow-up visits in patients who have thicker tumors or node-positive disease because these patients are at greater risk for recurrence.

For patients with low-risk melanoma (≤1 mm), visits are recommended every 6 months for 2 years and then annually. The surveillance guidelines for patients with high-risk melanoma include evaluation every 6 months for 5 years. After 5 years, patients are seen once a year. Patients are generally followed for 10 years. However, lifelong dermatologic examination is recommended, particularly for patients with dysplastic nevi or a family history of melanoma.

In general, a history and physical examination are performed at each visit. Periodic laboratory studies and other imaging studies are performed at the discretion of the treating physician. The physical examination should include a thorough skin examination because at least 3% of patients develop an additional primary cutaneous melanoma. Regional lymph nodes should be thoroughly examined, especially in patients without prior nodal surgery. The examination should also consider the frequency of metastases to lung, liver, and brain.

Follow-up studies may include a complete blood cell count and chemistry studies, including liver enzyme tests. An elevated lactate dehydrogenase level suggests metastatic melanoma. CT scans of chest/abdomen and pelvis or PET/CT scans are often performed every 6 months for 5 years after diagnosis in patients who have stage III melanoma.

PREVENTION

The most important measures to prevent melanoma are to reduce excessive sun exposure, particularly to the midday sun, and to avoid sunburns. Behavioral counseling should be encouraged[15] but is not of proven benefit.[A20] Sunscreen products with a sun protection factor (SPF) of 15 or greater and protective clothing are recommended. Data from some population studies support the use of sunscreen to prevent melanomas.[16] Sunscreens block primarily UVB rays, which are considered to be the major causative agent of cutaneous cancers. Newer sunscreen products also block UVA rays, which may contribute to the risk for melanoma. Use of these sunscreens has not been associated with reduction in bone mineral density or an increase in fractures in adults.[17]

Screening for skin cancer, whether by self-examination or by a health care provider, is controversial (Chapter 12)[18] and may lead to over-diagnosis and over-treatment.[19] Many public health experts do not recommend screening for adults in the general population, but some organizations do. On the basis of the type and number of nevi, family history of melanoma, prior melanoma, and history of severe sunburns, clinicians can identify patients who are at high risk for melanoma and who may benefit from screening programs. In several population studies, screening has detected melanomas at an earlier, curable stage. Physicians, other health care providers, and the public should be educated regarding the early signs of melanoma and the need for prompt biopsy of a suspicious pigmented lesion.

Patients with clinically atypical nevi (see Fig. 188-2), particularly patients who have a family history of melanoma, require a regular dermatologic surveillance program. Regular skin examinations should be performed every 6 to 12 months, preferably with the use of serial photography.

Numerous chemoprevention studies have been conducted aimed at reducing the development of melanoma, and none have proved effective.

PROGNOSIS

As with most malignancies, the outcome of melanoma depends on the stage and extent of disease at presentation. For localized melanoma, the most important prognostic factor is involvement of regional lymph nodes. The most important prognostic factor related to the primary tumor is the depth of invasion of the melanoma in millimeters. Increasing thickness is associated with an increased risk for recurrence, regional lymph node involvement, and death from melanoma. Patients whose melanomas are thinner than 1 mm have about a 99% 5-year survival and an 80 to 90% 10-year survival. For patients whose melanomas are thicker than 4 mm, the 10-year survival rate was 40 to 50% in the preimmunotherapy era but is improving. Other poor prognostic factors related to the primary melanoma include the presence of ulceration, an increasing level of invasion, a high mitotic rate, and the presence of microscopic satellites.

Regional lymph node involvement (stage III) has a major impact on survival, with 5-year survival rates of about 70%, depending on the number of involved lymph nodes. With modern treatment approaches, some patients with metastatic melanoma have a prolonged disease-free survival and a small subset of patients may be cured. Many have remarkable improvements in symptoms and quality and duration of life. The median overall survival of patients with disseminated melanoma has increased from 9 months before 2011 to almost 5 years now.

Patients with multiple primary melanomas may have a similar survival time as patients with single primary melanomas.[20] Melanomas that arise on the extremity tend to have a better prognosis, and women tend to do better than men.

BASAL AND SQUAMOUS CELL SKIN CANCER

Nonmelanoma skin cancer (basal and squamous cell carcinoma) is the most common malignant disease in the United States. Although national statistics are imprecise, an estimated 3.3 million Americans are diagnosed each year with basal cell or squamous cell skin cancer. Squamous cell carcinoma accounts for 20%, and most of the remainder are basal cell carcinoma.

EPIDEMIOLOGY

Overall, skin cancer incidence rates are rising[21] because of increased recreational sun exposure, longer life expectancy, and depletion of the ozone layer.[22] More than 99% of nonmelanoma skin cancers occur in Whites. These skin cancers are most often seen in elderly persons, especially individuals with fair skin and long-standing sun exposure. However, nonmelanoma skin cancers are increasingly being seen in people in their 30s and 40s. The lifetime risk for developing basal cell carcinoma is 30%.

PATHOBIOLOGY

Basal cell carcinoma arises from a pluripotential stem cell within the skin. Acquired mutations in the patched gene 1 (*PTCH1*), a tumor suppressor gene in the hedgehog signaling pathway, have been identified in cases of sporadic basal cell carcinoma. Sporadic basal cell carcinoma is also associated with mutations in the genes encoding p53 and RAS.

Squamous cell carcinoma of the skin is a malignant disease of epidermal keratinocytes. Many such carcinomas are derived from actinic keratosis, a precursor that appears as a rough, scaly, often erythematous papule, which often is more apparent on palpation than on visual examination. Estimates of the likelihood of progression of actinic keratosis to squamous cell carcinoma range from 0.025% to as high as 20%. Mutations in the gene encoding the p53 protein and in the RAS oncogene have been found in both actinic keratosis and squamous cell carcinomas. Mutations in *p16* have also been reported in squamous cell carcinomas.

Risk Factors

The most important risk factor is exposure to UV radiation from sunlight. The most clearly established association is with UVB radiation, but increasing evidence suggests that UVA is probably carcinogenic as well (Chapter 18). The timing and pattern of sun exposure are associated with different types of skin cancer. In general, squamous cell carcinoma is associated with cumulative sun exposure and occurs most frequently in areas maximally exposed to the sun (e.g., the face, back of hands, and forearms). Intermittent, intense exposure to the sun, particularly in childhood, is associated with an increased risk for basal cell carcinoma. Evidence suggests a dose-response relationship between artificial UV radiation exposure by use of tanning beds and the risk for skin cancers, especially basal cell carcinoma, and the association is stronger for individuals with a younger age at exposure. Individuals who have fair skin, light-colored eyes, red hair, a tendency to burn rather than tan, and a history of severe sunburns are at increased risk for nonmelanoma skin cancers. Other risk factors, primarily for squamous cell carcinoma, include chronic arsenic exposure, therapeutic radiation, chronic inflammatory skin conditions, psoralen plus UVA (PUVA) treatment for psoriasis and other diseases, as well as exogenous (e.g., after organ transplantation) or endogenous (e.g., chronic lymphocytic leukemia) immunosuppression. Long-term use of certain drugs with photosensitizing properties, including some antihypertensive agents (e.g., calcium-channel blockers, β-blockers), can also increase the risk for skin cancer. Most cases in Black American patients are associated with scarring or burns rather than UV exposure. Human papillomavirus infection (Chapter 344) has also been implicated in some squamous cell carcinomas, particularly in autosomal dominant epidermodysplasia verruciformis.

Basal cell carcinoma can be seen in association with several conditions, including the basal cell nevus syndrome (also called nevoid basal cell carcinoma syndrome or Gorlin syndrome), albinism, and xeroderma pigmentosum. The basal cell nevus syndrome is a rare autosomal dominant disorder caused by germline mutations in the patched gene (*PTCH*).

CLINICAL MANIFESTATIONS

Basal Cell Carcinoma

Approximately 90% of basal cell carcinomas occur on sun-exposed areas such as the face, neck, ears, scalp, and arms. The nose is the most common site. Typical basal cell carcinoma appears as slowly growing, shiny, skin-colored to pink translucent papules with telangiectasia and a "pearly," rolled border (Fig. 188-7). As the tumor grows, the center may become ulcerated and bleed, although usually without associated pain or tenderness.

Squamous Cell Carcinoma

Squamous cell skin cancer usually appears on areas of skin that are heavily damaged by sun exposure. The most common sites include the head, neck, back, forearms, and dorsum of the hand. Clinically, squamous cell carcinoma occurs as a discrete scaly erythematous papule on an indurated base that can develop on normal-appearing skin or on an actinic keratosis (Fig. 188-8). The lesion may grow over time and may become ulcerated, itchy, or painful and may bleed. Keratoacanthoma is a variant that is characterized by rapid growth and a crateriform appearance with a central plug. Bowen disease, or squamous cell carcinoma in situ, manifests as an erythematous, scaly, sharply defined plaque.

Untreated squamous cell carcinoma may cause significant local destruction. Most metastases develop in regional lymph nodes, although metastases may also occur in lung, liver, brain, skin, or bone. For patients with lymph node metastases, the 5-year survival rate is less than 50%.

DIAGNOSIS

The diagnosis of basal and squamous cell carcinoma is frequently suspected by inspection alone, but histologic confirmation is usually indicated. Either a shave or a punch biopsy technique is acceptable. Care should be taken to include the base of the lesion if a shave biopsy technique is used.

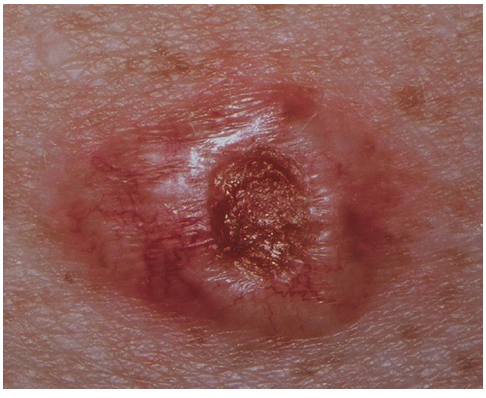

FIGURE 188-7. Basal cell carcinoma.

FIGURE 188-8. Squamous cell carcinoma of the skin.

TREATMENT

Basal Cell Carcinoma

Basal cell carcinomas are classified as low or high risk based on their clinical features, location, and histology.[23] Treatment options include cryotherapy (liquid nitrogen), electrosurgery (i.e., curettage and electrodessication), topical treatment (i.e., 5-fluorouracil, photodynamic therapy, or imiquimod),[A21] surgical excision, Mohs surgery, or radiation therapy. Mohs microsurgery involves serial excisions of a skin cancer with subsequent microscopic examinations for residual tumor, providing histologic control of the surgical margins to achieve the lowest recurrence rate while maximally preserving uninvolved tissue.[24] The procedure should be considered when treating recurrent cases; microscopically aggressive forms, such as the morpheaform subtype; lesions more than 2 cm in greatest diameter; and tumors of the ears, eyelids, nose, nasolabial folds, and lips.

For advanced and metastatic basal cell carcinomas, targeted therapy with vismodegib and sonidegib (which are inhibitors of the hedgehog signaling pathway) under expert supervision can provide objective tumor responses in 30 to 43% of patients and a complete response in 20% of patients. Side effects associated with therapy include muscle spasms, taste abnormalities, diarrhea, and fatigue. Patients often have an excellent long-term response after the drug is discontinued; if not, most patients respond when it is restarted. Immunotherapy with cemiplimab, which is an anti-PD-1 antibody, is also effective for patients who have locally advanced or metastatic basal cell carcinomas.[25]

Squamous Cell Carcinoma

As with basal cell carcinoma, squamous cell carcinoma can also be cured by traditional surgical excision or Mohs surgery, cryotherapy, topical therapies, and radiation therapy.[26] Topical 5-fluorouracil, photodynamic therapy, and imiquimod can also be useful for in situ squamous cell carcinoma. The optimal approach for a specific patient requires consideration of likelihood of the lesion recurring or metastatic potential, cosmetic factors, and the expertise of the treating physicians.

Mohs micrographic surgery provides the lowest recurrence rate, with cure rates greater than 90%. Mohs microsurgery is especially useful for recurrent tumors or lesions that have an increased risk for metastasis. Cemiplimab under expert supervision also can provide high response rates in patients with locally advanced or metastatic squamous cell carcinoma.[27] The PD-1 antibody pembrolizumab is also useful for patients with advanced squamous cell carcinoma,[28] provided that the squamous cell carcinoma was not a consequence of immunosuppression from organ transplantation. Cetuximab, a monoclonal antibody that targets epidermal growth factor receptor (EGFR), has some antitumor activity in patients with advanced squamous cell carcinoma of the skin.

PREVENTION

Primary prevention strategies are aimed at reducing long-term sun exposure. Public education and patient education should encourage the regular use of sunscreens with an SPF of 15 or greater, especially in childhood, and sun-protective clothing (e.g., a broad-brimmed hat). Avoidance of tanning salons and minimizing of total sun exposure, especially to the midday sun, is recommended. The thinning of the ozone layer has been linked to increased UV radiation and increases in the incidence of nonmelanoma skin cancers. Currently, no evidence indicates that total body skin examination is effective at reducing mortality or morbidity from nonmelanoma skin cancer. In one randomized trial of patients who had two or more nonmelanoma skin cancers in the prior 5 years, oral nicotinamide (vitamin B_3, 500 mg twice daily) safely reduced new nonmelanoma skin cancers and actinic keratosis by 20 to 30%.[A22]

PROGNOSIS

Basal cell carcinoma rarely metastasizes, and cure rates range from 90 to 99% with a variety of treatments. Although the mortality rate is low, these cancers may result in significant morbidity owing to invasive local growth with potential disfigurement and destruction of skin, bone, and cartilage.

Unlike basal cell carcinoma, squamous cell carcinoma carries a 0.5 to 5% risk for metastasis. Higher risk lesions are larger than 2 cm, are moderately or poorly differentiated, have perineural involvement, are located on the ear or the lip, arise in scars, or occur in immunosuppressed patients.

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For the General References and other additional features, please visit Elsevier eBooks+ at https://ebooks.health.elsevier.com.

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INDEX

Page numbers followed by "*f*" indicate figures, "*t*" indicate tables, and "*b*" indicate boxes.

A

AA amyloid, 788
AA (secondary) amyloidosis, 1306*t*
AB2 M variant amyloidosis, 1306*t*
AB2 M wild-type (dialysis-related) amyloidosis, 1306*t*
Abacavir, 2301*t*, 2319
Abaloparatide, for osteoporosis, 1643*b*–1646*b*, 1644*t*
Abatacept (Orencia)
  for rheumatoid arthritis, 1756*t*–1757*t*
  for total knee arthroplasty, 1830.*e*1*t*
Abciximab, 375*t*, 387*t*
Abdominal abscess, abdominal pain and, 854*t*
Abdominal actinomycosis, 2068
Abdominal aortic aneurysm
  clinical manifestations of, 436
  diagnosis of, 437–438, 438*f*
  epidemiology of, 436
  risk factors for, 436
  screening for, 53
  treatment of, 438*b*, 438.*e*1*f*
Abdominal compartment syndrome, 700*b*–703*b*
Abdominal distention, with ascites, 988
Abdominal emergencies, acute, characteristics of, 2270*t*
Abdominal examination, 31, 258
  in cardiovascular disease, 215
  in gastrointestinal disease, 851
  in liver disease, 988
Abdominal imaging, for liver disease, 990
Abdominal injuries, 700*b*, 701*f*
Abdominal pain, 854–858
  acute, 854–858
    clinical manifestations of, 854–857, 854*t*
    diagnosis of, 857–858, 858*f*
    history of, 854–857
    in hospital, 857
    imaging for, 857–858
    location of, 856, 856*f*
    physical examination for, 857, 857*t*
    special populations of, 857
    treatment of, 858*b*
  acute pancreatitis and, 969–970, 970
  chronic, 858, 859*f*
  chronic pancreatitis and, 974
  colon ischemia and, 964
  liver disease and, 986, 989*t*
  pathobiology of, 854
  from peptic ulcer, 1562–1563
  signs and symptoms of, approach to, 852*t*
Abdominal radiographs, description of, 866, 866*f*–868*f*, 867*f*, 868*f*
Abdominal ultrasonography, for acute pancreatitis, 971
Abelson *(ABL)* gene, 1272, 1273*f*
Abemaciclib, for breast cancer, 1369*b*–1373*b*
Abetalipoproteinemia, 939
Abiraterone acetate (Zytiga), 1215*t*
Ablation, for hepatocellular carcinoma, 1360*b*–1362*b*
Abnormal automaticity, 301
Abnormal thyroid function, 265*b*–278*b*
Abnormal uterine bleeding, 1597–1598, 1597*b*–1598*b*
ABO antigens, 205
Abortion, medical, 1617
  description of, 1610
  Paeniclostridium sordellii associated with, 1927
Abraxane. *See* Paclitaxel, protein bound
ABri amyloidosis, 1306*t*
Abscess
  amebic liver, 1022*t*, 1024–1025, 1025*b*, 1025*f*
  brain. *See* Brain abscess
  in Crohn disease, 945*b*–950*b*
Abscess *(Continued)*
  dental, pathogens and empirical therapy for, 2526*t*
  perianal, 978–979, 979*b*
  spinal epidural, 2527–2528, 2527*f*, 2527.*e*1*t*, 2528*b*
  subdural, 2528*f*
  temporal lobe, 2525
Absence seizures, 2428*t*, 2429–2430
Absolute hypovolemia, 735*b*, 735*t*
Absolute intensity, 61, 62*t*
Absolute refractoriness, 300
Absolute reticulocyte count, 1076*t*–1077*t*, 1076*t*
Absolute scarcity, 9
Abstainers, 2353
Abt-Letterer-Siwe disease, 1155
Abuse
  alcohol, 2353
  drugs of, 143
  in older adults, 118
Abused patient, management of, 1634*b*–1635*b*
Abusive patient, management of, 1634*b*
Acalabrutinib (Calquence), 1215*t*
  for chronic lymphocytic leukemia, 1269*t*–1270*t*, 1270*t*
Acamprosate
  for alcohol-associated liver disease, 1032*b*
  for alcohol use disorders, 2357*b*–2359*b*, 2358*t*–2359*t*
Acanthamoeba, 2150, 2150*t*
Acanthocytes, 1072*t*, 1074*t*
Acanthosis, 2241
Acanthosis nigricans, 987–988, 1239, 2745, 2746*f*, 2746*t*
Acarbose
  for orthostatic hypotension, 2559*t*
  for type 2 diabetes mellitus, 1541*t*
Accelerated gastric emptying, 890
Accelerated osteopenia, in liver disease, 987
Accessory pathway tachycardias, 324*f*, 326, 326*b*, 328*f*
Accidental infection, 2238
Accidents
  radiologic, 92, 92*t*
  "Swiss cheese" model of, 45
Accountability, medical profession, 4–5
Accutane. *See* Isotretinoin
ACE. *See* Angiotensin-converting enzyme
Acebutolol, 451*t*
Acetaminophen, *e*10*t*–*e*11*t*
  adverse reactions of, 132
  in blood pressure, 455
  for chronic pain, 138*t*
  toxicity, 686*t*, 690*t*, 1018, 1018.*e*1*f*
  for varicella, 2249*b*
Acetazolamide
  for action myoclonus, 2495*b*
  for altitude illness, 1889
  for Andersen-Tawil syndrome, 2585
  for high-altitude diseases, 593*t*
  for hypervolemia, 736*b*–737*b*
  for hypokalemia, 749, 749*t*, 752*b*
  for salicylate intoxication, 759
Acetoacetate, semiquantitative, *e*1*t*–*e*8*t*
Acetone, quantitative, *e*1*t*–*e*8*t*
Acetylcholine, 143, 2553
Acetylcholinesterase inhibitors, for Parkinson disease, 2487*t*
Acetylsalicylic acid
  for chronic pain, 138*t*
  pharmacokinetic parameters for, 127.*e*1*t*
Achalasia, 908, 908*b*, 908*f*, 908.*e*1*f*, 1337–1338
Achilles tendinosis, 1747–1749, 1748*b*
Achilles tendon rupture, 1748, 1748*b*
Achondroplasia, 1669–1670
Acid-base balance, kidney in, 754, 754.*e*1*f*
Acid-base disorders, 752–765
  clinical manifestations of, 755–756
  definition of, 752–756
  diagnosis of, 755, 755*f*, 756*t*
  epidemiology of, 752, 753*t*
  metabolic acidosis as, 756–762
  metabolic alkalosis as, 762–764
  pathobiology of, 752–755
  respiratory acidosis as, 765
  respiratory alkalosis as, 765
Acid maltase deficiency, 2586
Acid peptic disease, 913–923. *See also* Peptic ulcer
  anatomic diagnosis of, 917–918
  clinical manifestations of, 917
  definition of, 913–923
  diagnosis of, 917–919, 918*t*
  etiologic diagnosis of, 918–919
  Helicobacter pylori-associated, 920*f*
  hypersecretory syndromes causing, 918–919
  pathobiology of, 914–917
  physical examination of, 917
  prognosis for, 923
Acidemia, 752, 755*f*
Acidosis
  distal renal tubular, 749*t*
  hyperchloremic, 752*b*
  hypochlorhydric, 760
  lactic. *See* Lactic acidosis
  metabolic. *See* Metabolic acidosis
  respiratory. *See* Respiratory acidosis
  uremic, 757
Aciduria
  argininosuccinic, 1398*t*, 1402*t*
  glutaric, type I, 1398*t*, 1403*t*
  isobutyric, 1403*t*
  isovaleric, 1403*t*
  methylmalonic, 1398*t*, 1403, 1403*t*
  mevalonic, 1403*t*
  organic, 1403, 1403*f*, 1403*t*, 1404*b*
  propionic, 1398*t*, 1403, 1403*t*
Acinetobacter albensis, 1973.*e*3*t*
Acinetobacter apis, 1973.*e*3*t*
Acinetobacter baumannii, 1864*t*, 1973.*e*3*t*
Acinetobacter baylyi, 1973.*e*3*t*
Acinetobacter beijerinckii, 1973.*e*3*t*
Acinetobacter bereziniae, 1973.*e*3*t*
Acinetobacter bohemicus, 1973.*e*3*t*
Acinetobacter bouvetii, 1973.*e*3*t*
Acinetobacter calcoaceticus, 1973.*e*3*t*
Acinetobacter colistiniresistens, 1973.*e*3*t*
Acinetobacter courvalinii, 1973.*e*3*t*
Acinetobacter disperses, 1973.*e*3*t*
Acinetobacter genomospecies 6, 1973.*e*3*t*
Acinetobacter genomospecies 15BJ, 1973.*e*3*t*
Acinetobacter genomospecies 16BJ, 1973.*e*3*t*
Acinetobacter gerneri, 1973.*e*3*t*
Acinetobacter guillouiae, 1973.*e*3*t*
Acinetobacter haemolyticus, 1973.*e*3*t*
Acinetobacter johnsonii, 1973.*e*3*t*
Acinetobacter junii, 1973.*e*3*t*
Acinetobacter lwoffii, 1973.*e*3*t*
Acinetobacter nosocomialis, 1973.*e*3*t*
Acinetobacter parvus, 1973.*e*3*t*
Acinetobacter pittii, 1973.*e*3*t*
Acinetobacter radioresistens, 1973.*e*3*t*
Acinetobacter schindleri, 1973.*e*3*t*
Acinetobacter seifert, 1973.*e*3*t*
Acinetobacter spp., 1973–1975
  bacteremia caused by, 1973
  burn infection caused by, 1973
  clinical manifestations of, 1973–1974
  definition of, 1973
  diagnosis of, 1974
Acinetobacter spp. *(Continued)*
  epidemiology of, 1973
  pathobiology of, 1973
  pathogen causing, 1973, 1973.*e*3*t*
  prevention of, 1974
  prognosis of, 1974–1975
  representative members of, 1973.*e*3*t*
  skin and soft tissue infections caused by, 1973, 1974*f*
  treatment of, 1974*b*
  urinary tract infection caused by, 1973
  wound infection caused by, 1973
Acinetobacter tandoii, 1973.*e*3*t*
Acinetobacter tjernbergiae, 1973.*e*3*t*
Acinetobacter townerii, 1973.*e*3*t*
Acinetobacter ursingii, 1973.*e*3*t*
Acinetobacter variabilis, 1973.*e*3*t*
Acinetobacter venetianus, 1973.*e*3*t*
ACIP. *See* Advisory Committee on Immunization Practices
ACKD. *See* Acquired cystic kidney disease
Aclidinium bromide, 553*t*
ACLS. *See* Advanced cardiac life support
Acne, in women, medications for, 1608*t*
Acne keloidalis, 2744, 2745*f*
Acne vulgaris, 2722, 2722*b*, 2745*f*–2746*f*
Acoustic neuroma, 1312*b*–1313*b*, 2642
ACPA. *See* Anti-citrullinated peptide antibodies
Acquired angioedema
  clinical manifestations of, 1688*f*, 1690
  epidemiology of, 1690
  pathobiology of, 1690
  treatment and prevention of, 1690*b*–1691*b*
Acquired cystic kidney disease (ACKD), 808, 809*t*, 815, 815*b*
Acquired cystic lung diseases, 565
Acquired factor V deficiency, 1193
Acquired hemophilias, 1191, 1191*b*
Acquired hypogonadotropic disorders, 1584
Acquired hypoventilation syndrome, 536–537
  clinical manifestations of, 536–537, 537*f*
  definition of, 536
  epidemiology of, 535*t*, 536
  pathobiology of, 536
  prognosis for, 536*b*
  treatment of, 536*b*
Acquired immunodeficiency syndrome (AIDS). *See also* Human immunodeficiency virus
  candidiasis in, 2089
  cryptococcosis associated with, 2087
  cytomegalovirus in, 2251–2252
  epidemiology and diagnosis of, 2286–2291
  Hodgkin lymphoma and, 1292*b*–1293*b*
  immunization for, 65*t*–66*t*
  non-Hodgkin lymphoma and, 1287, 1287*b*
Acquired neuromyotonia, 2589*t*
Acquired platelet dysfunction, 1185, 1185*b*–1186*b*, 1185*t*
Acquired resistance, in Enterobacterales, 1965, 1966*t*
Acquired rhabdomyolysis, 714*t*, 715
Acquired von Willebrand disease, 1184, 1184*b*
Acral gangrene, plague and, 1991, 1991*f*
Acral lentiginous melanoma, 1391
Acrocyanosis, 474–475, 475*b*, 475*f*
Acrodermatitis chronica atrophicans, 2023, 2023*f*, 2025
Acrodermatitis verruciformis, 2729
Acrodynia, 103
Acrokeratosis neoplastica. *See* Bazex syndrome
Acromegaly, 1489–1490, 1489*b*–1490*b*, 1490*f*, 1823
Acroparesthesia, 1422
Acrylates, 88*t*

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Actemra. *See* Tocilizumab
ACTH. *See* Adrenocorticotropic hormone
ACTHoma, 1561*t*, 1566
Actigraphy, 2447*f*
Actinic keratoses, 2729, 2729*b*, 2730*f*
Actinobacillus actinomycetemcomitans, 2068
Actinomyces spp., 2066–2067
Actinomycetoma, 2110
Actinomycosis, 2066–2069, 2621*t*
  abdominal, 2068
  central nervous system infections and, 2068
  cervicofacial, 2067, 2067*f*
  clinical manifestations of, 2067–2068
  definition of, 2066–2069
  diagnosis of, 2068–2069
  epidemiology of, 2067
  pathobiology of, 2067
  pathogen that causes, 2066–2067
  pelvic, 2068
  prognosis of, 2069
  thoracic, 2067–2068, 2068*f*
  treatment for, 2069*b*
Action potential, 298–299
  cardiac, 223, 223*f*, 299–300, 299*f*, 333.e1*f*
  premature, 333.e1*f*
Action potential duration adaptation, 300
Action tremors, 2489
Actionability, of drugs, 167
Activated charcoal, for acute poisoning, 691*b*–693*b*
Activated partial thromboplastin time (APTT), *e8t*–*e9t*, 1166–1167, 1169, 1169*f*, 1195
Activated protein C resistance, 476
Activating *Kit* mutations, 1693
Activator protein-1 (AP1), 144
Active immunization, 64
Active myocarditis, 284–285
Active surveillance testing, for health care-associated infections, 1867–1868
Active tuberculosis, 2039–2040, 2040*b*–2043*b*
Activia, for irritable bowel syndrome, 896*t*
Activin, 1477
Activities of daily living (ADLs), 117
Acupuncture, 154
Acute abdominal emergencies, characteristics of, 2270*t*
Acute abdominal pain, 854
  clinical manifestations of, 854, 854*t*
  diagnosis of, 857, 858*f*
  history of, 854
  in hospital, 857
  imaging for, 857
  location of, 856, 856*f*
  physical examination for, 857, 857*t*
  special populations of, 857
  treatment of, 858*b*
Acute acalculous cholecystitis, 1053
Acute adrenal insufficiency, 1527, 1528*b*
Acute allograft rejection, 1049.e1*f*
Acute angle-closure glaucoma, 2608, 2608*f*
Acute aortic dissection
  diagnosis of, 440–441, 440*f*–441*f*
  evaluation for, 440*f*–441*f*
  high-risk characteristics for, 440*t*
  incidence of, 439
  management pathway for, 442*f*
  pathobiology of, 439
  prognosis of, 442.e1*f*, 443
  TEE findings, 440*f*
  type A, 441*b*–442*b*
  type B, 441*b*
Acute aortic regurgitation, 409
Acute aortic syndromes, 439–443, 439*f*
Acute bacterial prostatitis, treatment of, 825*b*
Acute bronchitis, 605–606, 605.e2*f*, 606*b*
Acute calcific periarthritis, 1815
Acute calculous cholecystitis
  clinical manifestations of, 1050, 1051*f*
  complications of, 1053
  pathobiology of, 1050
  treatment of, 1052*b*
Acute chest syndrome, in sickle cell disease, 1113
Acute cholecystitis, ultrasound of, 869*f*–870*f*
Acute compartment syndrome, causing envenomation, 705*b*–706*b*
Acute coronary syndrome, 370–380
  antiplatelet therapy for, 507
  clinical manifestations of, 371
  complications of, 374*t*–375*t*
  definition of, 370–380, 371*f*
  diagnosis of, 372–378
  differential diagnosis of, 373–378
Acute coronary syndrome *(Continued)*
  ECG findings, 372
  epidemiology of, 370
  initial treatment strategy, 378*t*
  integrated approach to, 374*t*
  non-ST elevation, 379*f*
  noninvasive testing for, 372
  pathobiology of, 370–371
  prognosis for, 378–380
  risk assessment in, 372, 373*f*, 375*t*
  risk score calculator in, 384.e1*f*
  serum biomarkers, 372
  symptoms, 371
  treatment of
    antianginal therapy, 374*t*
    strategies for, 375*t*
  triage for, 372, 373*f*
Acute cough, 512, 513*t*
Acute decompensated heart failure, 255, 255*t*
Acute dental infections, 2627
Acute diarrhea, 924–928
  clinical manifestations of, 924–928
  definition of, 923
  diagnosis of, 926, 927*f*
  epidemiology of, 925*t*
  prevention of, 928
  treatment of, 926*b*–927*b*
Acute disseminated encephalomyelitis, 2405, 2509
  Mycoplasma pneumoniae in, 2007
Acute dystonic reactions, 2495
Acute encephalitis, 2221
Acute exacerbation of COPD, in hypercapnic disease, 535*t*
Acute fatty liver, 998
  of pregnancy, 1625*t*, 1626, 1627*b*, 1627*t*
Acute febrile illness, 2030
Acute febrile neutrophilic dermatosis, 1857
Acute febrile syndrome, 590, 591*t*, 1869*t*
  clinical manifestations of, 590
  diagnosis of, 590
  treatment for, 591*b*
Acute fever, 2694*t*
Acute flaccid myelitis, 2258, 2258*b*
Acute flaccid paralysis, 1928, 2258, 2258*b*
Acute gallstone pancreatitis, 1055*b*
Acute generalized exanthematous pustulosis (AGEP), 2689*t*, 2722, 2723*f*, 2728
Acute glaucoma, characteristics of, 2270*t*
Acute glomerulonephritis, 783
Acute gouty arthritis, 1812*f*
Acute hemolytic transfusion reaction, 1201, 1202*b*
Acute hemorrhagic conjunctivitis, enteroviruses causing, 2260, 2260*b*
Acute hemorrhagic stroke, in sickle cell disease, 1113
Acute hepatic porphyrias, 1429, 1432
Acute hyperglycemic states, 1547–1549
  clinical manifestations of, 1547
  diagnosis of, 1547–1548
  epidemiology of, 1547
  pathobiology of, 1547, 1547*t*
  prevention of, 1549
  prognosis of, 1549
  treatment for, 1548*b*
Acute hypocalcemia, 1659*b*–1660*b*
Acute idiopathic interstitial pneumonias, 571*t*, 578–579
Acute infection, Whipple disease and, 2070
Acute injuries, occupational and environmental, 85–87, 86*t*
Acute intermittent porphyria (AIP), 1428*t*
Acute interstitial nephritis, 771, 771*t*
  biopsy of, 792, 792*t*, 793*f*
  causes of, 790*t*
  characteristics of, 790
  clinical manifestations of, 792–793, 792*t*
  diagnosis of, 792
  differential diagnosis of, 792
  drugs that cause, 790
  epidemiology of, 790
  granuloma formation in, 792
  prognosis for, 793
  proteinuria in, 792
  treatment of, 792*b*
Acute interstitial pneumonia, 566*t*, 567–568, 574*t*, 578, 579*f*
  clinical manifestations of, 568, 568*f*, 568.e1*f*
  definition of, 567–568
  diagnosis of, 568
  pathobiology of, 568
  treatment for, 568*b*
Acute ischemic stroke
  fibrinolytic therapy for, 509
  radiographic changes of, 2373–2374, 2373.e1*f*
  in sickle cell disease, 1113
Acute kidney injury (AKI), 725–726, 770–775
  categories of, 770*f*
  clinical manifestations of, 773
  critical care for, 636
  definition of, 770–775, 770*t*
  diagnosis of, 725–726, 773–774, 774*t*
  epidemiology of, 770–772
  imaging of, 726, 726*f*–727*f*
  intrarenal, 771*t*, 773–774
  intrinsic, 770–771, 771*t*
  laboratory testing of, 725–726
  pathobiology of, 772–773, 772*f*
  phases of, 775*f*
  postrenal, 771–774, 774
  prerenal, 772–773, 772*t*
  prevention of, 775
  prognosis of, 775
  rhabdomyolysis-induced, 717, 717*t*
  serum creatinine in, rapid resolution of, 771*f*
  in setting of SARS-CoV-2, 773
  in sickle cell disease, 1114
  treatment of, 774*b*–775*b*
  vascular disease in, 773
Acute leukemias, 1259–1266
  of ambiguous lineage, 1260*t*, 1261
  classification of, 1260, 1260*t*
  clinical manifestations of, 1262
  clonality and cell of origin of, 1260
  cytogenetics and molecular biology of, 1261–1262
  definition of, 1259–1266
  determinants of, 1259
    chemicals and drugs, 1259
    genetic predisposition, 1259
    oncogenic viruses, 1259
    radiation, 1259
  diagnosis of, 1260*f*, 1261*t*, 1262–1266
  differential diagnosis of, 1262–1266
  epidemiology of, 1259
  immunophenotyping of, 1260–1261
  incidence of, 1259
  management of complications of, 1262*b*–1266*b*
  morphology of, 1260, 1260*f*
  pathobiology of, 1260–1262
  treatment and prognosis of, 1262*b*, 1263*t*
Acute limb ischemia
  clinical categories of, 462*t*
  clinical manifestations of, 462
  diagnosis of, 462–463
  pathobiology of, 461–462
  treatment of, 464*b*–465*b*, 465*f*
Acute liver failure, liver transplantation for, 1044–1045
Acute lung injury, transfusion-related, 1200
Acute lymphoblastic leukemia (ALL), 1260*f*
  in adolescents, 111
  B-cell, 1260*t*
  Burkitt-like, 1262*b*
  cytogenetics and molecular biology of, 1262
  hematopoietic cell transplantation for, 1208
  immunophenotyping of, 1261
  morphology of, 1260
  mutations in, 1262
  peripheral blood smear of, 1073, 1073*f*–1074*f*
  Philadelphia chromosome-negative, 1263*t*
  Philadelphia chromosome-positive, 1262*b*
  prognosis of, 1262*b*, 1264*f*
  translocation in, 1262
  treatment of, 1262*b*, 1263*t*
Acute malnutrition, 1444, 1445.e1*f*, 1446*t*
Acute medical therapy, for aortic dissection, 443*t*
Acute mesenteric arterial occlusive disease, 960
Acute mesenteric ischemia, 959
  clinical manifestations of, 959
  diagnosis of, 960, 960*f*
  prognosis of, 960
  superior mesenteric artery embolism, 962, 962.e1*f*
  superior mesenteric artery thrombosis, 960
  treatment of, 960*b*, 961*f*
Acute motor axonal neuropathy (AMAN), 2564*t*
Acute motor sensory axonal neuropathy, 2571
Acute mountain sickness, 592*t*, 593*b*
Acute myeloid leukemia (AML), 1260*f*, 1260*t*
  cytogenetics and molecular biology of, 1261–1262
  mutations, 1261–1262, 1261*t*
Acute myeloid leukemia (AML) *(Continued)*
  translocations, 1261
  hematopoietic cell transplantation for, 1208–1209
  Hodgkin lymphoma and, 1292*b*
  immunophenotyping of, 1260–1261
  morphology of, 1260
  prognosis of, 1262*b*
  treatment of, 1262*b*, 1264*t*
Acute myocardial infarction, 395
  acute hospital phase, 384*b*–392*b*
  antiplatelet therapy for, 507
  causes of, 381*t*
  clinical manifestations of, 334–335
  coronary angioplasty for, 397*f*
  definition of, 380–392
  diagnosis of, 381–384
  early acute phase, 382
  echocardiographic findings, 242*t*
  electrocardiography in, 382–383, 382*f*
  evolved acute phase, 382–383
  hemodynamic subsets of, 389*t*
  pathobiology of, 380–381
  physical examination in, 381
  in presence of bundle branch block, 383
  ST-elevation, 380–393
    antiplatelet therapy for, 384*b*, 387*f*
    CABG for, 398
    clinical manifestations of, 381
    conditions that can mimic, 383*t*
    coronary intensive care for, 384*b*
    diagnosis of, 381
    differential diagnosis of, 383
    discharge, 384*b*
    echocardiography in, 384
    emergency department care for, 384*b*
    epidemiology of, 380–381
    general medical management of, 384*b*
    history in, 381
    hospital care for, 384*b*
    imaging in, 384
    late hospital phase, 384*b*
    management of complications of, 384*b*
    mechanical complications of, 384*b*
    patient education for, 384*b*
    physical examination in, 381
    post-hospital phase, 384*b*
    prehospital phase, 384*b*
    prognosis for, 392
    rehabilitation after, 384*b*
    reperfusion therapy for, 384*b*, 385*f*
    sample admission orders for, 388*t*
    secondary prevention of, 384*b*
    selection of ICD for, 389*f*
    thromboembolic complications of, 384*b*
    treatment of, 384*b*
Acute myopericarditis, 285*f*
Acute neurologic disorders, diagnosis and treatment of, 2369
Acute normovolemic hemodilution, 1205
Acute pain, 135, 1113
Acute pancreatitis, 969–973
  alcohol and, 969–970
  causes of, 970*t*
  clinical manifestations of, 970
  complications of, 972*t*
  definition of, 969
  determining severity of, 971–972, 972*f*
  diagnosis of, 970–972
  drugs, toxins, and metabolic factors, 970
  epidemiology of, 969
  etiology of, 971
  gallstones and, 969
  genetics of, 970
  imaging studies for, 971, 971*f*–972*f*
  infections and, 970
  laboratory tests for, 971
  pancreatic duct obstruction and, 970
  pathobiology of, 969–970
  prognosis of, 973
  risk stratification of, 972
  systemic complications of, 972*t*
  trauma and, 970
  treatment for, 972*b*–973*b*
Acute pericarditis, 423–425
  cardiac magnetic resonance image of, 427*f*
  clinical manifestations of, 423
  diagnosis of, 423
  diagnostic tests for, 425*t*
  electrocardiogram for, 426*f*
  epidemiology of, 423–425
  pathobiology of, 423

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Acute pericarditis *(Continued)*
prognosis for, 425
treatment of, 424*b*–425*b*
Acute peripheral vestibulopathy, 2644–2645
Acute phase response, 1712
Acute poisoning, 682–698
antidotes for, 691*b*, 693*t*
blood tests for, 690–691
cardiopulmonary effects of, 684
decontamination of, 691*b*
dermatologic signs of, 685
diagnosis of, 682–691
diagnostic tests for, 685–691, 689*t*–690*t*
elimination of, 691*b*
epidemiology of, 682–698
gastrointestinal effects of, 684–685
history of, 682
imaging for, 691
neurologic signs of, 683–684, 685*t*
physical examination for, 682–685, 683*t*
specific toxicants in, 685, 686*t*
stabilization of, initial, 691*b*
treatment of, 691*b*, 692*f*
vital signs for, 682–683
Acute progressive multiple sclerosis, 2501
Acute promyelocytic leukemia, 1262*b*, 1263*t*
Acute pulmonary edema, 273*f*
Acute radiation injury, 956
Acute radiation syndromes, 93, 94*f*
Acute radicular pain, 2398
Acute rejection, in renal transplantation, 845
Acute respiratory distress syndrome (ARDS), 591, 650–652, 700*b*
clinical manifestations of, 651
definition of, 650, 650*t*
diagnosis of, 651, 651*t*
disorders associated with, 650*t*
epidemiology of, 650
influenza and, 2200
mechanical ventilation for, 655–656
pathobiology of, 650–651
pathology of, 650
pathophysiology of, 651
prognosis of, 651–652
treatment of, 651*b*, 652*t*
Acute respiratory failure, 642–652
acute respiratory distress syndrome as, 650
chronic obstructive pulmonary disease as, 649–650
clinical evaluation of, 645, 645*t*
clinical manifestations of, 644
definition of, 642–645, 642*t*
diagnosis of, 643*t*, 644–645
pathobiology of, 642–644, 643*t*
pathophysiology of, 643–644, 644*f*
physiologic abnormalities in, assessment of, 645
treatment of, 647*b*–649*b*, 648*f*
without lung disease, 643*t*, 652
Acute respiratory tract infections, *Pseudomonas* infections causing, 1969
Acute retroviral syndrome, 2295
Acute rheumatic fever, *Streptococcus pyogenes* causing, 1917, 1917*b*, 1917*t*
Acute sarcoid arthritis, 602
Acute severe asthma, in hypercapnic disease, 535*t*
Acute sigmoid diverticulitis, with abscess, computed tomography of, 870*f*
Acute sinusitis, aspergillosis and, 2094
Acute spinal cord compression, 2369
Acute stress disorder, 2340*t*, 2344–2345, 2345*b*
Acute subdural hematoma, 2390
clinical manifestations of, 2391
diagnosis of, 2386*t*, 2387*f*, 2391
epidemiology of, 2390
pathobiology of, 2390
prognosis of, 2391*b*
treatment of, 2391*b*
Acute symptomatic hyponatremia, 741*b*–742*b*
Acute symptomatic seizures, 2434*b*–2436*b*
Acute telogen effluvium, 2748, 2748*b*, 2748*t*
Acute thyroiditis. *See* Infectious thyroiditis
Acute tubular injury (ATI), 773
Acute tubular necrosis (ATN), 773
Acute urticaria, 1674, 1687, 1689*b*, 2725
Acute viral hepatitis, 1002–1009, 1002*t*
clinical manifestations of, 1002–1003, 1003*f*, 1003*t*
diagnosis of, 1003, 1003*t*
general features of, 1002–1009
Acute viral hepatitis *(Continued)*
other types of, 1009
pathobiology of, 1002–1003
prognosis for, 1003
treatment of, 1003*b*
viruses that cause, 1002*t*
Acute viral respiratory illness, 585*t*
Acute watery diarrhea, 1869*t*
Acyclovir
for herpes simplex encephalitis, 2533*b*
for herpes simplex virus, 2521*b*
for herpes simplex virus infections, 2246
for herpesvirus infections, 2186, 2187*t*–2188*t*
for varicella, 2249*b*
for zoster, 2249*b*
Acyclovir-resistant varicella-zoster virus, treatment of, 2249*b*
ACys amyloidosis, 1306*t*
ADA2. *See* Adenosine deaminase-2
Adacel (Sanofi Pasteur), 81
Adalimumab (Humira)
description of, 151*t*
for inflammatory bowel disease, 945*b*, 946*t*
for rheumatoid arthritis, 1756*t*
for total knee arthroplasty, 1830.*e*1*t*
Adams forward bend test, 621
ADAMTS-13, *e*8*t*–*e*9*t*, 789, 1176–1177, 1180
Adapalene (Differin), 2698
Adaptive immune response, 192–195
Adaptive immune system, 182–191
cell differentiation of, 189–190
effector mediators of, 189
pathogenesis of disease and, 191
principles of activation of, 187–191
signaling pathways of, 189
Adaptive immunity, 671
ADC. *See* Apparent diffusion coefficient
Adcetris. *See* Brentuximab vedotin
Addiction
biology of, 142–143
definition of, 142
drug-induced neural plasticity relevant to, 143
neural substrate of, 142–143
in nicotine, complication of, 42
reward circuitry, 142, 143.*e*1*f*
risk factors for, 142
Addictive drugs, 142*t*, 143
Addison disease, in autoimmune polyglandular syndromes, 1560
Adefovir, for hepatitis B virus infections, 2181*t*–2182*t*, 2182*t*, 2183
Adenocarcinoma. *See also* Carcinoma
colon, 1349–1354
colorectal, 1346
diagnosis of, 1241*t*
esophageal, 1338–1339
gallbladder, 1358
gastric, 1339–1342
intraepidermal, 980
lung, 1329, 1329.*e*2*t*
pancreatic, 1354
rectal, 1350*b*–1352*b*
rectum, 1349
small bowel, 1343–1344
treatment of, 1241*b*–1242*b*, 1242*t*
Adenocarcinoma in situ, 1329
Adenoid cystic carcinoma, 2625
Adenomas
adrenal, 1522, 1524*b*
benign hepatocellular, 1615
hepatic, 991–992, 992*f*
large intestine, 1349
pituitary, 1524*b*
description of, 1486–1487, 1489
inherited syndromes of, 1487*t*
nonfunctioning, 1497–1498
prolactin-secreting, 1481
stomach, 1343
villous, 939
Adenomatoid malformation, congenital cystic, 565
Adenomatous polyposis coli *(APC)* gene, 1348
Adenomatous polyps, 1348–1349, 1349, 1349*b*, 1349*t*
Adenomyosis, 1054
Adenopathy, cervical, treatment of, 1241*b*
Adenosine, 325*t*
Adenosine deaminase-2 (ADA2), deficiency of, 1731*t*, 1733*t*, 1737
Adenosine deaminase deficiency, 174, 1676.*e*3*t*, 1678
Adenosine testing, 306
Adenosine triphosphatase, sodium-potassium, 745
Adenosine triphosphate (ATP), 2580
Adenoviral conjunctivitis, 2604, 2605*f*, 2605*t*
Adenoviral vectors, 175
Adenovirus
in acute bronchitis and tracheitis, 605
definition of, 2204
immunization for, 66*t*
manifestations of, 2205
pathobiology of, 2204
serotype distribution of, 2204.*e*2*f*
structure of, 2204*f*
subgroup of, 2204*t*
Adenovirus diseases, 2204–2206
clinical manifestations of, 2204–2205
definitions of, 2204–2205
diagnosis of, 2205
epidemiology of, 2204, 2204*f*, 2204.*e*1*f*
gastrointestinal tract infections, 2205
genitourinary tract infections, 2205
in immunocompromised patients, 2205
ocular infections, 2205
outbreaks of, 2204
pathobiology of, 2204
prevention of, 2205
prognosis of, 2205
respiratory tract infections, 2204–2205
treatment of, 2205*b*
Adenovirus vector vaccines, for COVID-19, 2219
Adenylate cyclase toxin, 1995
ADH. *See* Antidiuretic hormone
ADH1. *See* Autosomal dominant hypocalcemia type 1
ADH2. *See* Autosomal dominant hypocalcemia type 2
Adherence, drug, 265*b*
Adhesion molecules, 152
Adhesions, peritoneal, 957, 958*f*
Adhesive capsulitis. *See* Frozen shoulder
Adie pupil, 2555, 2600, 2617, 2617*f*
Adipocytes, 1464
Adipokines, 1464
Adiponectin, 1464
Adipose tissue
glucocorticoids metabolism in, 145
lipolysis of, 1465
Adjunctive antiandrogen therapy, for transgender women, 1578*b*–1580*b*
Adjunctive corticosteroids
for *Pneumocystis* pneumonia, 2103*b*
for tuberculosis, 2040*b*
Adjustment, in health delivery systems, 47, 48*f*
Adjuvant analgesics, 136*b*–141*b*
Adjuvant chemotherapy, for cancer, 1232*b*–1237*b*, 1234*t*
Adjuvant therapy
for melanoma, 1393*b*–1394*b*
for pain, in chronic pancreatitis, 975*t*
for systemic lupus erythematosus, 1772*b*–1775*b*
ADLs. *See* Activities of daily living
Admission orders, ICU, 637, 637*t*
Adnexal tumors, 2730
Adolescent(s), 110
approach to, 111–112
chronic illness and transition in, 113
confidentiality in, 111
eating disorders in, 113
health visit, 111–112
medical history of, 111
mental health of, 112–113
obesity in, 112
physical examination in, 111–112
physical growth and development of, normal, 110
preventive health care for, 111
primary malnutrition in, 1445*b*–1446*b*
psychosocial development of, normal, 110
sexual and reproductive health of, 112
substance use and substance use disorders in, 113
vital statistics of, 110–111
Adolescent medicine, 110–113
ADPKD. *See* Autosomal dominant polycystic kidney disease
Adrenal adenoma, 1522, 1524*b*
Adrenal cortex, 1520–1529, 1520*f*–1521*f*
anatomy of, 1520
disorders of, 1520–1529
adrenal incidentaloma, 1524
adrenal insufficiency. *See* Adrenal insufficiency
androgen excess, 1526, 1526*b*
Cushing syndrome. *See* Cushing syndrome
mineralocorticoid deficiency, 1529
mineralocorticoid excess, 1524–1526
function of, 1520
Adrenal cortical cancer, 1523
Adrenal cortical deficiency, complete, 750
Adrenal function, in HIV, 2317
Adrenal glands
histologic section of, 1521*f*
magnetic resonance imaging of, 1520*f*
weight of, 1520
Adrenal incidentaloma, 1524
Adrenal insufficiency, 1526–1529, 2665
acute, 1527, 1528*b*
ancillary tests for, 1527*t*
causes of, 1527*t*
chronic, 1527, 1528*b*
clinical manifestations of, 1527
diagnosis of, 1527–1528
differential diagnosis of, 1528
epidemiology of, 1526
glucocorticoids for, 1528*b*
pathobiology of, 1526–1527
primary, 1526, 1527*t*, 1528*f*
prognosis for, 1529
secondary, 1526–1527, 1527*t*, 1528*f*
treatment of, 1528*b*
Adrenal masses, 1591–1592
Adrenal medulla, 1529–1533
Adrenal steroidogenesis, 1569, 1569.*e*1*f*
Adrenal tissue, replacement of, 1526
Adrenal tumor or hyperplasia, 749*t*
Adrenalectomy, bilateral, role of, 1524*b*
Adrenarche, 110, 1581–1582, 1582*t*
α-Adrenergic blockers
for benign prostatic hyperplasia, 822*b*
clinical use of, 454–455
for hypertension, 454–455
for male lower urinary tract symptoms, 824*t*
mechanism of action of, 454
side effects of, 453*t*, 454
β-Adrenergic blockers, 264*b*
central nervous system effects of, 685*t*
for hypertension, 454
mechanism of action of, 454
side effects of, 453*t*, 454
toxicity, 686*t*
β_2-Adrenergic agents, for asthma, 541*b*–547*b*
β_3-Adrenergic receptor activator, for male lower urinary tract symptoms, 824*t*
Adrenergic toxidromes, 683*t*
Adrenocortical carcinoma, medical therapy for, 1524*b*
Adrenocorticotropic hormone (ACTH), *e*1*t*–*e*8*t*, 1492–1496
corticotropin-releasing hormone effects on, 1492
Cushing disease. *See* Cushing disease
deficiency of, 1481, 1492–1493, 1493*b*
definition of, 1492
ectopic, secretion of, 1523, 1523*t*, 1524*b*
endocrine diseases caused by, 1475*t*–1476*t*
excess of, 1523–1524
insufficiency tests of, 1484*t*
for multiple sclerosis, 2505*t*
Nelson syndrome, 1495–1496
plasma, 1496, 1522
pulsatile secretion of, 1492
reserve testing for, 1493
tests of, 1488*t*
24-hour secretion profile of, 1478.*e*1*f*
vasopressin and, 1499
Adrenoleukodystrophy, 1526, 2509
Adrenomyeloneuropathy, 2509, 2509*b*
Adriamycin. *See* Doxorubicin
Adrucil. *See* 5-Fluorouracil
ADTKD. *See* Autosomal dominant tubulointerstitial kidney disease
Adult inclusion conjunctivitis, 2604
Adult-onset diabetes, 1534
Adult-onset Still disease, 1731*t*, 1732
Adult polyglucosan body disease (APBD), 1416*b*–1418*b*, 1417*t*

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Adult T-cell leukemia/lymphoma, 2326–2327, 2327*t*
  clinical manifestations of, 2326, 2327*f*, 2327*t*
  diagnosis of, 2326, 2326*f*
  epidemiology and pathobiology of, 2326
  pathogenesis of, 2325, 2326*f*
  prognosis of, 2327
  treatment for, 2326*b*–2327*b*
Adult T-cell lymphoma/leukemia, 1286, 1286*b*
Adulterants, 2361
Adults
  congenital heart disease in, 347–356
  physical activity for, 62*t*, 63*b*–64*b*
  travel-related vaccines of, 1886*t*
Advanced cardiac life support (ACLS)
  for acute poisoning, 691*b*
  after cardiac arrest, 313*b*–316*b*, 315*f*–316*f*, 316*f*
Advanced endoscopy, 880–881
  combined procedures in, 881
  for creating anastomoses, 881
  esophageal varices in, 881, 881*f*
  imaging in, 880
  for remodeling organs, 881
  for surgical complications, 881
  tissue resection in, 880
Advanced gout, 1811–1812, 1812*f*
Adverse drug reactions, 131–133
  diagnosis and prevention of, 133
  epidemiology of, 131–132
  pathobiology of, 132–133
  predictable toxic responses, 132, 132*t*
  unpredictable toxic responses, 132–133
Adverse events, 45
Advisory Committee on Immunization Practices (ACIP), 76
Advocacy, in health delivery systems, 47, 48*f*
Aedes aegypti, 2266
Aedes albopictus, 90
Aerobic activity
  absolute intensity of, 62*t*
  for osteoarthritis, 1741*t*
Aerosols, 88*t*
Afatinib (Gilotrif), 1215*t*, 1251*t*
Afebrile neutropenia, 1147*b*–1148*b*
Affect, geriatric assessment of, 117
Afferent baroreflex failure, 2555
Afferent limb mechanisms, 734
Afferent visual system, examination of, 2615
AFib amyloidosis, 1306*t*
Afibrinogenemia, 1189*t*, 1192–1193, 1193*b*
Afinitor. *See* Everolimus
Aflatoxins, 59, 2093
Africa, arterial hypertension in, 445, 445.*e1f*
African Americans
  normal physical growth and development of, 110
  risks for atherosclerotic cardiovascular disease, 1*f*–2*f*
African drought, climate-related hazards, 91*t*
African sleeping sickness, 2123–2126
  clinical manifestations of, 2124–2125
  definition of, 2123–2126
  diagnosis of, 2125, 2125*f*
  East, 2124–2125
  epidemiology of, 2124, 2124.*e1f*
  pathobiology of, 2124
  pathogen of, 2123–2124
  prevention of, 2125–2126
  prognosis of, 2126
  treatment of, 2125*b*, 2125*t*
  West, 2124
African tick-bite fever, 2055*t*, 2057
African trypanosomiasis, 2115–2116. *See also* African sleeping sickness
  characteristics of, 2270*t*
  in travelers, 1889.*e1t*
Afterdepolarizations, 302
  delayed, 333, 333.*e1f*
  early, 333, 333.*e1f*
Afterload, 226
Agammaglobulinemia
  autosomal forms of, 1681*t*
  lack of B cells leading to, 1680
Agatston score, 249
Age, antimicrobial therapy affected by, 1843
Age-related changes
  cardiovascular disease and, 219
  cellular, 120
  molecular, 120
  physiologic system dysregulation, 120, 120.*e2f*
Age-related macular degeneration, 1731*t*, 2608, 2609*f*
  complement system and, 201*t*
AGel (Finnish hereditary) amyloidosis, 1306*t*
Agency for Healthcare Research and Quality (AHRQ), 41.*e1t*
  National Quality Measures Clearinghouse, 41–42
AGEP. *See* Acute generalized exanthematous pustulosis
Aggregatibacter aphrophilus, 2068
Aggressive fibromatosis, 1390, 1390*b*
Aggressive systemic mastocytosis, 1703, 1703*f*
Aging
  arterial hypertension and, 444, 444*f*
  bone loss related to, 1640–1641
  clinical manifestations of, 120
  clinical sequelae of, 120–124
    frailty, 122, 123*b*, 123*f*, 123*t*
    pressure sores, 122, 122*b*, 122*f*
    senile purpura, 121, 122*f*
  demography of, 114
  effects of, 121–123
  epidemiology of, 114–116, 120, 120*f*
  healthy, 115–116
  osteoarthritis and, 1738
  pathobiology of, 120
  pharmacology of, 122
  pubertal development and, 1581–1582
  pulse pressure and, 445.*e1f*
  responses to stressors, 226
  severe mental illness and, 2677–2678
α-Agonists, for alcohol withdrawal, 2358*t*
Agoraphobia, 2342*t*, 2343
Agranulocytosis, psychotropic medications and, 2678*t*
AHRQ. *See* Agency for Healthcare Research and Quality
Aicardi-Goutières syndrome, 1731*t*, 1735, 1768
AIDS. *See* Acquired immunodeficiency syndrome
AIDS-defining malignancies, 2315–2316
AIDS-defining non-Hodgkin lymphomas, 2315
AIHA. *See* Autoimmune hemolytic anemia
AIN. *See* Anal intraepithelial neoplasia
AIP. *See* Acute intermittent porphyria
Air bronchograms, 520
Air trapping, 530
AIRE-1. *See* Autoimmune regulator-1
Airway, radiofrequency ablation of, 541*b*
Airway clearance, for cystic fibrosis, 558*b*–559*b*
Airway closure, 654–655, 654.*e1f*
Airway obstruction, 513–515, 516*t*
  central, 630, 630*t*
    clinical manifestations of, 630, 630*f*–631*f*, 631*f*
    prognosis, 631
    treatment for, 630*b*
  congenital pulmonary malformations, 564–565
  diagnosis of, 513–515, 514*f*
  inflammation, 561*b*–562*b*
  mechanical ventilation for, 657
  prognosis for, 515*b*
  reversible, with heart failure, 265*b*
  treatment of, 515*b*
Airway responsiveness, assessing, 532
AJCC. *See* American Joint Committee on Cancer
Akathisia, 2495
Akinesia, in parkinsonism, 2484
Akinetic-rigid syndrome, 2486–2489
AL amyloid, 788
AL (heavy chain) amyloidosis, 1306*t*
AL (light chain) amyloidosis, 1306*t*
ALADP. *See* 5-Aminolevulinate dehydratase porphyria
Alafenamide, 2301*t*
Alanine aminotransferase (ALT), *e1t*–*e8t*, 998, 1017
Alastrim variola minor infection, 2238
Albendazole, 2112*t*, 2116–2117
  for ascariasis, 2172*b*
  for cystic echinococcosis, 2161
  for echinococcosis, 1029*b*
  for strongyloidiasis, 2173*b*
Albers-Schönberg disease, 1667
Albinism, 2742–2743
Albumin, *e1t*–*e8t*, 994
  description of, 1581
  in liver disease, 989–990
  urinary excretion of, 776
Albuminuria, 832–836, 834*t*, 836
Albuterol
  for asthma, 541*b*
  for hyperkalemia, 751*b*–752*b*
Alcohol
  acute pancreatitis and, 969
  cancer and, 1244–1245
  chronic pancreatitis and, 973
  consumption of, blood pressure and, 445
  coronary heart disease and, 58
  dietary guidelines for, 57.*e3t*
  folate deficiency and, 1120
  heart failure and, 265*b*
  intoxication levels, 2543
  liver cancer and, 59
  neuropathies, 2544–2545
  properties of, 142*t*
  rhabdomyolysis caused by, 715
Alcohol-associated liver disease, 1031–1033, 1031*t*, 1032*b*, 1032*f*
Alcohol intoxication, 2354
Alcohol-related cirrhosis, 2355
Alcohol-related diarrhea, 939
Alcohol-related disorders
  description of, 2543–2545
  hepatic encephalopathy, 2543
  liver toxicity, 2543
  neurologic disorders, 2537–2545
  seizures, 2543–2545, 2543*b*, 2543*f*
Alcohol-soluble protein fraction, of wheat gluten, 935
Alcohol use, 55
  in adolescents, 113, 113*t*
  in women, 1609
Alcohol use disorders, 2353–2359
  acute effects of, 2354
  cardiovascular disease and, 220
  chronic effects of, 2354–2356
  clinical manifestations of, 2354–2356
  complications of, 2355*t*
  criteria for, 2353*t*
  definition of, 2353–2359
  diagnosis of, 2356–2357, 2356*t*
  epidemiology of, 2353
  history of, 2356–2357
  laboratory findings in, 2357
  neurologic effects of, 2353–2354
  pathobiology of, 2353–2354, 2353*f*
  physical examination for, 2355*t*, 2357
  prevention of, 2357*b*
  prognosis of, 2359, 2359*t*
  treatment of, 2357*b*, 2358*t*, 2359*t*
Alcohol withdrawal syndrome, 2354, 2354*f*, 2357*b*, 2358*t*
Alcoholic cardiomyopathy, 287–288, 2355
Alcoholic ketoacidosis, 759
  clinical manifestations of, 759
  diagnosis of, 753*t*, 759
  epidemiology of, 759
  pathobiology of, 759
  prognosis of, 759–760
  treatment of, 759*b*
Alcoholic myopathy, 2544–2545
Alcoholic peripheral neuropathy, in liver disease, 987
Alcoholic steatohepatitis, 1031–1034
Alcoholism, 2353
Aldo-trastuzumab emtansine (Kadcyla), 1215*t*
Aldosterone, *e1t*–*e8t*, 732, 734
Aldosterone antagonists, 265*b*
  for hypertension, 451*t*
  for primary aldosteronism, 448*b*
Aldosterone paradox, 746
Aldosterone secretion, 1525
Aldosteronism, primary, 447–448, 1525*f*
Aldurazyme. *See* Laronidase
Alecensa. *See* Alectinib
ALECT2 amyloidosis, 1306*t*
Alectinib (Alecensa), 1215*t*
Alemtuzumab (Lemtrada)
  characteristics of, 152
  for multiple sclerosis, 2505*t*
  in renal transplantation, 845*t*
Alendronate, for osteoporosis, 1644*t*
Alendronic acid, for Paget disease, 1664*t*
Alexandrite lasers, 2701
Alexia, 2409–2410
Alfuzosin, 824*t*
Alginate, 1968
Alignment, in health delivery systems, 47, 48*f*
Alimta. *See* Pemetrexed
Aliphatic hydrocarbon-n-hexane, 88*t*
Aliqopa. *See* Copanlisib
Aliskiren, 451*t*
Aliskiren/HCTZ, 451*t*
ALK. *See* Anaplastic lymphoma kinase
Alkalemia, 752
Alkaline phosphatase, *e1t*–*e8t*, 999, 1010
  elevation, 1001, 1002*f*
  in liver disease, 989
Alkalosis
  metabolic. *See* Metabolic alkalosis
  postoperative, 2676
  respiratory. *See* Respiratory alkalosis
Alkaptonuria, 1825
Alkhurma hemorrhagic fever, 2265*t*, 2268*t*
Alkylamine, 2700*t*
Alkylating agents, 149
ALL. *See* Acute lymphoblastic leukemia
"All of Us" research program, 165–166
All-*trans*-retinoic acid (ATRA), for acute promyelocytic leukemia, 1262*b*, 1263*t*
Allelic imbalance, 1321
Allergen-specific IgE (sIgE), 1675
Allergens, anaphylaxis caused by, 1692–1693
Allergic *Aspergillus* sinusitis, 2095
Allergic asthma, 538, 1673*t*, 1674
Allergic bronchopulmonary aspergillosis, 541*b*
  clinical manifestations of, 2095
  diagnosis of, 2096, 2096*f*
  increased eosinophils counts in, 533
  pathobiology of, 2094
  treatment of, 2096
Allergic conjunctivitis, 1674, 2604, 2605*t*
Allergic contact dermatitis, 2704, 2729
  description of, 1674
  illustration of, 2691*t*, 2696*f*
Allergic disease
  approach to the patient with, 1672–1676
  definition of, 1672
  diagnosis of, 1675, 1675*t*
  epidemiology of, 1672
  IgE-mediated, 1672, 1672*f*, 1673*t*, 1673.*e1f*
  inborn errors of immunity, 1676
  laboratory evaluation of, 1675
  mixed, 1673*t*
  non-IgE mediated, 1672, 1673*t*
  pathobiology of, 1672–1673
  patient history of, 1675
  physical examination of, 1675
  prevention of, 1675*b*
  of skin, 1674
  treatment of, 1675*b*
Allergic reactions, 193
Allergic rhinitis, 1673*t*, 1674, 2193, 2631
Allergic transfusion reaction, 1202, 1202*b*
Allergy
  to antimicrobial therapy, 1842
  drug. *See* Drug allergy
  environmental, 1673
  food, 1673, 1673*t*
  gastrointestinal tract, 1674
  lower airway, 1674
  occupational, 1673
  upper airway, 1674
Allergy skin-prick tests, for sensitizer-induced occupational asthma, 586
Alloantibodies, 1171*b*–1173*b*
Alloantibody inhibitors
  for factor XI deficiency, 1192*b*
  for hemophilia, 1188*b*–1190*b*
Allodynia, 134
Allogeneic hematopoietic stem cell transplantation, 1207–1208, 1207*f*
  for aplastic anemia, 1126*b*
  for chronic myeloid leukemia, 1274*b*–1277*b*
  for myelodysplastic syndromes, 1255–1256
  for short telomere syndromes, 1129*b*
Allograft rejection, 205–206
AlloMap, 168
Allotransplants, 203
Allylamine. *See* Terbinafine
Almotriptan, 2380*t*
Alobar holoprosencephaly, 2547
Alogliptin, for type 2 diabetes mellitus, 1541*t*
Alongshan virus, 2282
Alopecia, 2747, 2747*t*
  androgenetic, 2748
  central centrifugal cicatricial, 2751, 2751*f*
  cicatricial, 2749–2750
  diffuse, 2747*t*, 2748
  frontal fibrosing, 2749–2750, 2750*f*
  marginal, 2747*t*
  patchy, 2747*t*, 2749–2750
  patterned, 2748

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Alopecia *(Continued)*
scarring, 2749
thallium and, 106, 106*b*
traction, 2751, 2751*f*
Alopecia areata, 2747*t*, 2749, 2749*b*, 2749*f*
Alosetron, for irritable bowel syndrome, 895*b*–898*b*, 896*t*
Alphacoronavirus, 2209*t*
Alphavirus, 2270*t*, 2278, 2520
Alprazolam, for anxiety disorders, 2344*t*
Alprostadil, for erectile dysfunction, 1589
ALPS. *See* Autoimmune lymphoproliferative syndrome
ALS. *See* Amyotrophic lateral sclerosis
ALT. *See* Alanine aminotransferase
Alteplase (t-PA), 386*t*, 509
Altered fat distribution, in HIV, 2317–2318, 2318*b*
Altered immunocompetence, immunization and, 76–77, 76.*e2t*
Altered mental status, severe mental illness and, 2683*t*
Altitude illness, in travelers, 1889
Altitude sickness, treatment of, 593*t*
Altruism, 4
Aluminum, *e*1*t*–*e*8*t*
dialysis dementia and, 101*t*–102*t*, 105, 105*b*
Alunbrig. *See* Brigatinib
Alveolar-arterial oxygen gradient, 639, 639*t*
Alveolar disease, 520
Alveolar filling disorders, 566–570, 566*t*, 582
acute interstitial pneumonia as, 567
classification of, 571*t*
definition of, 566
general approach to, 566*f*
invasive mucinous adenocarcinoma as, 569–570
lepidic predominant nonmucinous adenocarcinoma as, 569
pulmonary alveolar proteinosis as, 566–567
Alveolar hemorrhage, diffuse, 566*t*, 568–569
clinical manifestations of, 568, 568.*e*1*f*
definition of, 568
diagnosis of, 569, 569*f*, 569.*e*1*f*
pathobiology of, 568
prognosis of, 569
treatment for, 569*b*
Alveolar hydatid disease, 2162, 2162*b*
Alveolar hyperventilation, leading to respiratory alkalosis, 765
Alveolar macrophages, 2204
Alveolar proteinosis, 585*t*
Alveolar ventilation, 640–641
Alveolar volume, 530
ALYS amyloidosis, 1306*t*
Alzheimer disease, 2414–2417
amyloidosis and, 1310
anterograde amnesia in, 2408, 2416
clinical features of, 2485*t*
clinical manifestations of, 2415–2416
definition of, 2414
diagnosis of, 2416, 2416*t*, 2418*f*
epidemiology of, 2414
evidence-based treatments for, 2416*b*–2417*b*
genetics of, 2415
magnetic resonance imaging of, 2414–2415, 2415*f*
mortality from, 115
neuritic plaques in, 2414
neurofibrillary tangles in, 2414
pathobiology of, 2414–2415
pathophysiology of, 2414–2415
positron emission tomography of, 2416, 2417*f*–2418*f*, 2418*f*
posterior cortical atrophy caused by, 2410*f*
prevention of, 2416*b*
prognosis for, 2417
risk factors for, 2414
treatment of, 2416*b*
AMAN. *See* Acute motor axonal neuropathy
Amantadine, 2189–2190, 2189*t*, 2203*t*, 2487*t*
Amaurosis fugax, 2465
Ambient hypoxia, 1075
Ambiguous genitalia, surgery for, 1575*b*–1576*b*
Amblyomma americanum, 2025
Amblyopia, 2598
Ambulatory electrocardiography, 235
Ambulatory monitoring
in arrhythmias, 306–307
blood pressure, 446*t*, 447, 447.*e*1*f*
Ambulatory monitoring *(Continued)*
indications for, 212*t*
of psychiatric patient, 2683
Amebiasis, 2146–2150
asymptomatic intraluminal, 2147
characteristics of, 2270*t*
clinical manifestations of, 2147–2148
definition of, 2146–2150, 2147*f*
diagnosis of, 2148–2149, 2149*t*–2150*t*
diarrhea, 2147
dysentery or colitis, 2147–2148, 2148*f*
epidemiology of, 2146
liver abscess, 2148, 2149*f*
pathobiology of, 2146–2147
pathogen of, 2146
prevention of, 2149
prognosis of, 2150
thoracic, 2148
treatment of, 2149*b*, 2150*t*
Amebic dysentery, in travelers, 1891*t*
Amebic liver abscess, 1022*t*, 1024, 1025*b*, 1025*f*
Amebic trogocytosis, 2146
Amenorrhea, 1598–1600
biochemical evaluation of, 1599*f*
causes of, 1599*t*
clinical evaluation of, 1598–1600
diagnosis of, 1598–1600
hypergonadotropic, 1600, 1600*b*
laboratory findings of, 1599–1600
provocative testing of, 1598–1599
American Board of Internal Medicine, 41
American College of Radiology Thyroid Imaging, Reporting and Data System (ACR TI-RADS), 1516.*e*1*f*
American College of Rheumatology/European League Against Rheumatism (ACR/EULAR) classification criteria, 1755*f*
American human monocytic ehrlichiosis, 2060–2061, 2060*t*, 2061*b*, 2061*f*
American Joint Committee on Cancer staging system, 1232, 1333*t*
American Society of Anesthesiologist, 2661
American Spinal Injury Association Impairment Scale, 2390*t*
American Thoracic Society, 612*t*
American trypanosomiasis. *See* Chagas disease
Americas, cystic fibrosis in, 556
Amifostine, 597*b*
Amikacin, *e*10*t*–*e*11*t*
for bacterial meningitis, 2518*t*
dosage of, 1895*t*
for nontuberculous mycobacterial disease, 2046*t*
for pyelonephritis and urosepsis, 1877*t*
in renal failure, 129.*e*1*t*
Amiloride, 451*t*
for Gitelman syndrome, 817*b*
for hypervolemia, 736*b*, 737*t*
Amiloride/HCTZ, 451*t*
Amino acid solutions, in parenteral nutrition, 1450
Amino alkyl ether (ethanolamine), 2700*t*
Aminoglycosides
AUC exposures, 1894–1898, 1899*f*
for bacterial meningitis, 2518*t*
for cystic fibrosis, 1970*b*–1971*b*
dosage of, 1895*t*
for endocarditis, 419*t*
mechanism of action, 1895*t*
middle ear toxicity of, 1898
nephrotoxicity of, 1898
resistance mechanisms, 1893*t*
for *Stenotrophomonas maltophilia*, 1975*b*, 1976*t*
toxicities of, 1901*t*
for yersiniosis, 1994*b*
Aminohydroxypropylidene diphosphonate, 1215*t*
5-Aminolevulinate dehydratase porphyria (ALADP), 1428*t*, 1429, 1429.*e*1*f*
δ-Aminolevulinic acid (δ–ALA), *e*1*t*–*e*8*t*
Aminoquinolines, 2121*b*–2122*b*, 2698–2699
5-aminosalicylate, for inflammatory bowel disease, 945*b*, 946*t*
Aminotransferases, 998–999
asymptomatic abnormalities of, 1001, 1001*f*
Amiodarone, *e*10*t*–*e*11*t*, 325*t*
for advanced cardiac life support, 315*f*
for arrhythmias, 313*b*
for atrial fibrillation, 384*b*
Amiodarone *(Continued)*
for electrical storm, 338*b*–340*b*
induced hypothyroidism, 1507
for supraventricular arrhythmia, 282*b*–283*b*
thyroiditis caused by, 1514
Amitriptyline
for chronic pain, 138*t*–139*t*
for depression, 2340*t*
for irritable bowel syndrome, 896*t*
for tinnitus, 2643*b*
Amitriptyline + nortriptyline, *e*10*t*–*e*11*t*
Amivantamab-vmjw (Rybrevant), 1215*t*
AML. *See* Acute myeloid leukemia
Amlodipine, 451*t*
for acute STEMI, 384*b*
for ischemic heart disease, 470*b*
properties of, 367*t*
for Raynaud phenomenon, 473*b*
Amlodipine/benazepril, 451*t*
Amlodipine/olmesartan, 451*t*
Amlodipine/perindopril, 451*t*
Amlodipine/telmisartan, 451*t*
Amlodipine/valsartan, 451*t*
Ammonia, *e*1*t*–*e*8*t*, 88*t*, 999
Ammoniagenesis, 754
Ammonium, 755
Amnesic disorders, 2407–2408
Amnesic mild cognitive impairment, 2412*t*
Amnesic shellfish poisoning, 713
Amniotic fluid embolism, 492, 492*b*, 492.*e*1*f*
Amoebic encephalitis, 2112*t*, 2115
Amoxicillin
for cystitis, 1876*t*–1877*t*
dosage of, 1895*t*
for leptospirosis, 2031*b*
for Lyme disease, 2026*t*
pharmacokinetic parameters for, 127.*e*1*t*
Amoxicillin-clavulanate
for *H. influenzae* infections, 1954*b*
for *Moraxella catarrhalis* infections, 1955*b*
for peritonsillar abscess and deep space infections, 2649–2650
for *Streptococcus pneumoniae* pulmonary infections, 1912.*e*1*t*
for urinary tract infection, 1876*t*, 1877*t*
Amoxicillin-clavulanic acid
dosage of, 1895*t*
for pneumonia, 613*t*
AMP-activating protein kinase (AMPK), aging and, 115–116
AmpC β-lactamases, 1966
Amphetamines. *See also* Psychostimulants
central nervous system effects of, 685*t*
screening for, 689*t*
toxicity, 686*t*
Amphetamines, toxicity, 2363
clinical manifestations and diagnosis of, 2363
epidemiology of, 2363
pathobiology of, 2363
treatment of, 2363*b*
Amphotericin B
adverse effects of, 2078
drug interactions of, 2077
formulations and pharmacology of, 2077
for hepatosplenic candidiasis, 1024*b*
indications and dosage of, 2077
mechanism of action, 2077–2078
for mucormycosis, 2100*b*
for paracoccidioidomycosis, 2087*b*
preparations of, 2077–2078
for visceral leishmaniasis, 2132*b*–2133*b*
Amphotericin B deoxycholate, for cryptococcosis, 2088*b*
Ampicillin
for bacterial meningitis, 2518*t*
dosage of, 1895*t*
for endocarditis, 419*t*
for leptospirosis, 2031*b*
for listeriosis, 1938*b*
for vancomycin-resistant enterococci, 1922*t*
Ampicillin-sulbactam
for pneumonia, 613*t*
for pyogenic liver abscess, 1023*b*
AMPK. *See* AMP-activating protein kinase
Amplatzer devices, 250.*e*1*f*
Ampullary tumors, 1060, 1060.*e*1*f*
Ampyra. *See* Dalfampridine
Amsterdam criteria, for HNPCC, 1347
Amylase, *e*1*t*–*e*8*t*
in acute pancreatitis, 971
Amyloid, 2652, 2652.*e*2*f*
Amyloid arthropathy, 1822
Amyloidosis, 292, 1305–1310, 2560, 2560*b*, 2626
arthritis associated with, 1822
ATTRwt, 1309
cardiomyopathy with, 292
definition of, 1305
diagnosis of, 293, 294*f*
dialysis-associated, 842
epidemiology of, 292–293
of esophagus, 911
factor deficiency in, 1193
familial, 1306*t*, 1309
in familial Mediterranean fever, 1732
glomerular diseases in, 788
light chain, 2575–2576, 2576*b*
localized, 1310
pathobiology of, 292
prognosis for, 293*b*–294*b*
systemic, 1305, 1306*t*
light chain, 1305–1309
secondary, 1310
treatment of, 293*b*
β-Amyloidosis, 2414
Amyotrophic lateral sclerosis (ALS), 2543, 2562–2565, 2652
Awaji-Shima consensus criteria for, 2563*t*–2564*t*
clinical manifestations of, 2562–2563
definition of, 2561
diagnosis of, 2563, 2563*t*, 2564*t*
epidemiology of, 2562–2565
mimic syndromes of, 2564*t*
pathobiology of, 2562
pathology of, 2562
prognosis of, 2565
treatment of, 2563*b*–2565*b*
Anabolic agents, for osteoporosis, 1643*b*
Anabolic-androgenic steroids, 2365
Anaerobic bacteria, non-spore forming, 1938–1941
antimicrobial susceptibility patterns for, 1941*t*
bacteremia caused by, 1938
central nervous system infections caused by, 1938–1939
clinical manifestations of, 1938–1940
definition of, 1938–1941, 1939*f*, 1939*t*
diagnosis of, 1940–1941, 1940*t*
head infections caused by, 1939
intra-abdominal infections caused by, 1939
neck infections caused by, 1939
obstetric-gynecologic infections causing, 1939
osteomyelitis caused by, 1940
pathobiology of, 1938, 1938.*e*3*t*
pathogen that cause, 1938, 1938.*e*3*t*
prevention of, 1941
prognosis for, 1941
septic arthritis caused by, 1940
skin and soft tissue infections caused by, 1939–1940
taxonomy of, 1938.*e*3*t*
treatment of, 1940*b*, 1940*t*–1941*t*
Anagen effluvium, 2748
Anakinra (Kineret)
for cryopyrin-associated periodic syndromes, 1735*b*
description of, 150–151, 151*t*
for total knee arthroplasty, 1830.*e*1*t*
Anal cancer, 982
clinical manifestations of, 982
diagnosis of, 982
in HIV, 2316
treatment for, 983*b*
Anal dysplasia, 982
Anal endoscopic ultrasonography, 981
Anal fissure, 979–980, 979*f*
Anal fistula, 979, 979*b*–980*b*, 980*f*
Anal intraepithelial neoplasia (AIN), 982
Anal warts, 982, 982*b*, 982*f*
Analgesia
for critical care, 636
for postoperative pain, 1829
Analgesic nephropathy, 793, 794*f*
Analgesics
adjuvant, 136*b*, 138*t*
antipyretic, 136*b*, 138*t*
chronic interstitial nephritis caused by, 793
for common cold, 2193*b*
for fibromyalgia, 1819*b*–1820*b*

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Analgesics *(Continued)*
opioid, 136*b*, 138*t*, 141*t*
for pain, in chronic pancreatitis, 975*b*–976*b*, 975*t*
for skin diseases, 2699–2700
Anaphylatoxins, 201–202
distribution of, 202*t*
Anaphylaxis, 132–133, 1673*t*, 1674–1675, 1691–1695
allergens causing, 1692
aspirin causing, 1692–1693
clinical manifestations of, 1693
definition of, 1691–1695
diagnosis of, 1693–1694
differential diagnosis of, 1694
distinguishing features of, 515*t*
drugs associated with, 1698*t*
epidemiology of, 1691–1692
food allergy-associated exercise-induced, 1692
food causing, 1692
insect sting venom causing, 1692
latex causing, 1692
latex-induced, 1691–1692
medications causing, 1692
non-IgE-dependent agonists causing, 1692
nonsteroidal anti-inflammatory drugs causing, 1692
pathobiology of, 1692–1693
prevention of, 1694–1695
prognosis for, 1695
systemic
acute treatment of, 1694*f*
causes of, 1691*t*
diagnosing, 1693*f*
treatment of, 1694*b*
vaccines causing, 1692
Anaplasma phagocytophilum, 2025, 2060*t*, 2061
Anaplasmoses, 2060, 2060*t*
Anaplastic large cell lymphoma, 1287, 1287*b*
Anaplastic lymphoma, treatment of, 1241*b*
Anaplastic lymphoma kinase (ALK), lung cancer and, 1330
Anaplastic thyroid cancer, 1519, 1519*b*
ANAs. *See* Antinuclear antibodies
Anastomoses, endoscopy for, 881
Anastomotic ulceration, 916
Anastrozole (Arimidex), 1215*t*
for breast cancer, 1369*b*
Anatomic distribution, of disease, 523–524
ANCA. *See* Antineutrophil cytoplasmic antibodies; Antineutrophil cytoplasmic antibody
Ancylostoma duodenale, 2169
Andersen disease, 1417*t*
Andersen-Tawil syndrome, 2583.*e1t*, 2585
Andexanet alfa, 506*t*
Andres virus, 2265*t*
Androgen(s)
adrenal secretion of, 1572
biosynthesis, defects of, 1572
cancer and, 1245–1246
excess of, 1526, 1526*b*
Androgen insensitivity, 1573
Androgen receptor, 1384
Androgen replacement therapy, 1585*b*, 1585*t*
Androgen resistance, 1583
Androgenetic alopecia, 2747*t*, 2748, 2748*b*–2749*b*
Androstenedione, 1569, 1581
Anemia, 1074–1082
acute leukemias and, 1262
of aging, 1082
alcohol use disorders and, 2355
aplastic. *See* Aplastic anemia
associated with inadequate reticulocyte response, 1079–1080, 1080*t*, 1081*f*
associated with increased reticulocyte production, 1078, 1079*f*
blood loss causing, 1078
in chronic interstitial nephritis, 793
of chronic kidney disease, 836, 1080–1082, 1081*b*
clinical manifestations of, 1075–1076
Cooley, 1106
definition of, 1074
diagnosis of, 1076–1077
blood smear examination, 1077
bone marrow examination, 1077
complete blood counts, 1076–1077, 1076*t*, 1077*t*
medical history, 1076, 1076*t*, 1077*t*
physical examination, 1076–1077, 1077*t*
Anemia *(Continued)*
reticulocyte count, 1076*t*, 1077
dialysis-associated, 842
Diamond-Blackfan, 1127.*e1t*, 1129–1130, 1130*b*
differential diagnosis of, blood smear in, 1068–1070
of endocrine deficiency, 1081
Fanconi, 1127.*e1t*, 1129, 1129*b*, 1145
in heart failure, 265*b*
hemolysis causing, 1078, 1079*f*, 1079*t*–1080*t*, 1080*t*
hemolytic. *See* Hemolytic anemia
in HIV/AIDS, 2314, 2315*t*
of inflammation, 1079
initial laboratory approach to, 1078, 1078*t*
iron deficiency. *See* Iron deficiency anemia
of liver disease, 1081
macrocytic, 1079–1080, 1082–1086
malaria and, 2120
megaloblastic, 1080, 1117–1125
causes of, 1117*t*
clinical manifestations of, 1120–1122
complications of, 1120–1122, 1121*f*
definition of, 1117–1125, 1117*t*
diagnosis of, 1122–1123
epidemiology of, 1117–1118
pathobiology of, 1118–1120
peripheral blood smear of, 1069, 1072*t*
prevention of, 1124
prognosis of, 1124
treatment of, 1123*b*–1124*b*
methemoglobin and, 1075
microcytic, 1079
peripheral blood smear of, 1068–1069
normocytic, 1080
normocytic normochromic, peripheral blood smear of, 1069–1070
oxygen delivery and, 1074–1075, 1075*f*
pathobiology of, 1074–1078
pernicious
diagnosis of, 1123
incidence of, 1117
malabsorption of cobalamin and, 1119
physical findings of, 1076
physiologic, of pregnancy, 1081
postoperative, 2666, 2675
in pulmonary tuberculosis, 2035
regulation of red cell production in, 1075
in Rocky Mountain spotted fever, 2054
severe mental illness and, 2683*t*
sickle cell disease and, 1114*b*–1116*b*
sideroblastic, 1072*t*, 1084, 1086
acquired, 1086
clinical manifestations of, 1086
diagnosis of, 1086, 1086*f*
prognosis of, 1086*b*
treatment of, 1086*b*
symptoms of, 1075–1076
Anemia of chronic disease, 1085, 1086*b*
Anemia of inflammation, 1085, 1086*b*
Anergy, 207
Anesthesia, 2668–2672
airway assessment before, 2668
anaphylaxis in, 2669
dexmedetomidine for, 2670
diabetic ketoacidosis and, 2669
epidural, 2671
general, 2669, 2671
intraoperative management of, 2669–2671, 2669*t*
ketamine for, 2670
latex allergy and, 2669
malignant hyperthermia and, 2668, 2668*b*–2669*b*
medication reactions in, 2668–2669
midazolam for, 2670
monoamine oxidase inhibitors and, 2669
nausea and vomiting after, 2671
neuraxial, 2671
neuromuscular blockers for, 2670–2671
opioids for, 2670
in orthopedic patient, 1827
preoperative assessment, 2668
propofol for, 2669–2670
records of, in postoperative care, 2672
regional, 2671
serotonin toxicity and, 2669
for skin diseases, 2699–2700
sodium-glucose cotransporter-2 inhibitor and, 2669
spinal, 2671
volatile anesthetics for, 2670
Anetoderma, 2736–2737, 2737*f*
Aneuploidy, of sex chromosomes, 1574
Aneurysms
aortic, 436–439
abdominal, 436
clinical manifestations of, 436–437
definition of, 436–439, 437*t*
diagnosis of, 437–438
epidemiology of, 436
pathobiology of, 436
prognosis for, 438–439
risk factors of, 436
thoracoabdominal, 436
fusiform, 2478
hypothalamus and, 1480
left ventricular, 384*b*
mycotic, 2478
sinus of Valsalva, 352
visceral arterial, 969
Angina, 352
Angina pectoris, 211*t*, 356–370
in aortic stenosis, 400–404
chronic
diagnostic coronary angiography in, 363*t*
evaluation of, 361*f*
chronic stable, 398
definition of, 356–364
differential diagnosis of, 359
echocardiographic findings, 242*t*
epidemiology of, 356
exercise ECG in, 361
exercise test protocol for, 361–362
grading of, 356
history in, 357–358
microvascular, 369
noninvasive testing for, 359–363, 362*f*
pathobiology of, 356–357
Prinzmetal, 357, 368–369
prognosis for, 369
recommendations for myocardial revascularization in, 364*t*
rest or unstable, 211*t*
risk stratification of, 363–364
suspected, 360*f*
treatment of, 265*b*, 364*b*–368*b*, 364*t*, 365*f*
unstable, 370
in acute coronary syndrome, 370
definition of, 370, 371*f*
recurrent or refractory, 374*t*
treatment of, 374*t*
variant, 368
vasospastic, 357
Anginal equivalents, 357
Angioectasia, 965, 966*b*, 966*f*, 966.*e1*
Angioedema, 1674, 1687–1691
classification of, 1690*t*
clinical manifestations of, 1687, 1688*f*
definition of, 1687
hereditary, 1690–1691
visceral, 956
Angiography
in chronic stable angina, 361*f*
computed tomography
in atherosclerotic PAD, 463, 463*f*–464*f*
coronary, 249–250, 249.*e2f*, 250*f*
in coronary artery disease, 360–361
coronary
in acute coronary syndrome, 372–373, 375*t*
in chronic angina and stable ischemic heart disease, 363*t*
in coronary artery disease, 393
diagnostic, 363, 363*t*
technique, 395–396, 395*f*
digital subtraction, in atherosclerotic PAD, 463–465, 463*f*
in heart failure, 261
magnetic resonance, in atherosclerotic PAD, 463, 463*f*
subarachnoid hemorrhage on, 2476
Angioimmunoblastic T-cell lymphoma, 1287
Angiokeratomas, 1421*f*, 1422
Angioplasty
coronary
for acute MI, 397*f*
for atherosclerotic PAD, 467*b*
medical therapy *versus*, 397
percutaneous transluminal, 464.*e1f*, 468*b*
for fibromuscular dysplasia, 800*b*–801*b*
indications for, 385*t*
for renovascular hypertension, 449*b*
Angiosarcoma, 967, 2733–2734
Angiostrongyliasis, 2174*t*, 2175–2176, 2176*b*
Angiostrongylus cantonensis, 2175, 2524
Angiostrongylus costaricensis, 2175
Angiotensin, 730
Angiotensin-converting enzyme (ACE), *e1t*–*e8t*
Angiotensin-converting enzyme (ACE) inhibitors, 264*b*, 364*b*
for acute STEMI, 391*t*
for autosomal dominant polycystic kidney disease, 812*b*
for chronic interstitial nephritis, 795*b*
clinical benefits of, 265*b*
clinical use of, 452
for hypertension, 452–453
inducing angioedema, 1690–1691, 1690*b*
mechanism of action, 265*b*
mechanisms of action of, 452
practical use of, 265*b*, 266*t*
side effects of, 452–453, 453*t*
Angiotensin I, *e1t*–*e8t*
Angiotensin II, *e1t*–*e8t*, 730, 734
prostaglandins and, 734
Angiotensin receptor blockers (ARBs), 264*b*
for acute STEMI, 384*b*, 391*t*
clinical benefits of, 265*b*
clinical use of, 452
for hypertension, 451*t*, 452
mechanism of action of, 265*b*, 452
practical use of, 265*b*, 266*t*
side effects of, 452, 453*t*
Angiotensinogen, 730
Angle-closure glaucoma, 2608, 2608*f*
Angular cheilitis, 2624
Anhidrosis, 2555
Anhidrotic ectodermal dysplasia, with immunodeficiency, 1685, 1686*t*
Anidulafungin, 2078–2079
adverse effects of, 2079
drug interactions of, 2079
formulations and pharmacology of, 2078
for hepatosplenic candidiasis, 1024*b*
indications and dosage of, 2075*t*, 2078–2079
Anifrolumab (Saphnelo), for total knee arthroplasty, 1830.*e1t*
Anion gap, *e1t*–*e8t*
delta, 756–757
metabolic acidosis, 690–691, 757–760, 757*t*
Anisakiasis, 2173
Anisocytosis, peripheral blood smear of, 1067*f*
Ankle
disorders of, 1747–1749
fusion of, 1827
injury of, occupational, 86*t*
sprain, 1748
surgical treatment of, 1828–1829
Ankle-brachial index (ABI), 461, 461*f*
Ankylosing spondylitis, 622, 1708, 1717*t*, 1761–1762
clinical manifestations of, 622, 1761–1762, 1761*t*
diagnosis of, 622, 1762
differential diagnosis of, 1761*t*
epidemiology of, 622, 1761
exercise for, 1765*b*–1766*b*
HLA-B27 and, 1760, 1760*f*
imaging of, 1762, 1762*f*–1763*f*
interstitial lung disease associated with, 581
pathobiology of, 622, 1761
prognosis of, 622*b*, 1766–1767
treatment of, 622*b*, 1765*b*
Ankyrin, 1094
Anogenital warts, 2242
Anomalous pancreaticobiliary duct junction, 1058–1059, 1059.*e1f*
Anomalous pulmonary venous return, 247.*e1f*, 354
Anomia, 2408
Anorexia
abdominal pain and, 856
hypothalamic, 1481
liver disease and, 986
management of, approaches to, 13*t*
postoperative, 2673
signs and symptoms of, approach to, 852*t*
weight loss and, 860*t*
Anorexia nervosa
clinical manifestations of, 1461
definition of, 1461
hypogonadotropic hypogonadism and, 1584
hypothalamic chronic anovulation associated with, 1601
pathobiology of, 1461
prognosis of, 1462
treatment of, 1462*b*

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Anorgasmic state, 1590
Anovulatory bleeding, 1597
Anoxic brain injury, 591–592
Anserine bursitis. *See* Pes anserinus syndrome
Antalgic gait, 2373*t*
Anterior cerebral arteries, 2456–2457, 2458*f*
Anterior chamber, 2596
Anterior choroidal artery, 2457, 2459*f*, 2465, 2465*t*
Anterior communicating artery, 2463
Anterior cord syndrome, 2386, 2403
Anterior horn cell disease, 2581*t*
Anterior mediastinotomy, 1331
Anterior mediastinum, 527
Anterior pituitary, 1482–1498, 1482*f*
  adrenocorticotropic hormone. *See* Adrenocorticotropic hormone
  carcinomas of, 1498, 1498*f*
  definition of, 1482
  growth hormone. *See* Growth hormone
  insufficiency tests of, 1484*t*
  pathobiology of, 1482
  primary diseases of, 1483–1486
    empty sella, 1486, 1486*f*
    hypophysitis, 1483
    hypopituitarism. *See* Hypopituitarism
    pituitary apoplexy, 1485, 1485*t*–1486*t*, 1486*b*, 1486*t*
  prolactin. *See* Prolactin
  thyroid-stimulating hormone. *See* Thyroid-stimulating hormone
  tumors of, 1486–1488
    clinical manifestations of, 1487
    functioning, 1488*t*
    medical therapy for, 1487*b*
    pathobiology of, 1486–1488
    prognosis for, 1488
    radiation therapy for, 1487*b*
    surgery for, 1487*b*
    treatment of, 1487*b*
Anterior segment, 2596
Anterograde amnesia, 2407
  in Alzheimer disease, 2408
  clinical manifestations of, 2408
  residual deficit after, 2408
Anthelminthic drugs, 2116–2118
Anthracycline-induced dilated cardiomyopathy, 288
Anthralin, for psoriasis, 2698
Anthrax, 1930
  characteristics of, 2270*t*
  clinical manifestations of, 96–97, 1931
  cutaneous, 1932, 1932*b*
  description of, 96–97
  diagnosis of, 97
  epidemiology of, 96, 1930
  immunization for, 66*t*, 83–84
  inhalational, 1931, 1931*f*, 1932*b*
  pathobiology of, 96
  prevention of, 97
  prognosis of, 97
  treatment of, 97*b*
Anti-C5, 203
Anti-CD20 antibodies, 2701
Anti-citrullinated peptide antibodies (ACPA), 1750
Anti-cyclic citrullinated peptide antibody, 1707
Anti-endothelial cell antibodies, vasculitides and, 1794
Anti-epidermal growth factor antibodies, for colorectal cancer, 1350*b*
Anti-glomerular basement membrane (anti-GBM) disease, 784, 784*b*–785*b*, 784*f*, 784*t*, 1798
Anti-HER2 therapy, for breast cancer, 1369*b*
Anti-HMGCR myopathy, 1787–1789
Anti-IgA, 1202
Anti-IL2R monoclonal antibodies, in renal transplantation, 845*t*
Anti-infective therapy, principles of, 1840–1845. *See also* Antimicrobial therapy
Anti-inflammatory agents
  for acute STEMI, 384*b*
  for COVID-19, 2217
  for cystic fibrosis, 558*b*
  for radiation enteritis, 940*b*–941*b*
  for skin diseases, 2697–2699
Anti-ischemic therapies, for acute STEMI, 384*b*
Anti-La antibodies, 1715
Anti-La/SSB antibodies, in Sjögren syndrome, 1784
Anti-Parkinsonism medications, for Parkinson disease, 2486*b*
Anti-RNP antibodies, 1714
Anti-Ro antibodies, 1715
Anti-Ro/SSA antibodies, in Sjögren syndrome, 1784
Anti-*Saccharomyces cerevisiae* antibodies (ASCA), 945
Anti-Sm antibodies, 1714
Anti-tubular basement membrane disease, 790
Anti-tumor necrosis factor-α agents, for inflammatory bowel disease, 945*b*
Anti-vascular endothelial growth factor antibodies, for colorectal cancer, 1350*b*
Antianginal therapy, 374*t*
Antiarrhythmic drugs, 313*b*, 325*t*, 338*b*
  for acute STEMI, 384*b*
Antibacterial activity, synergism in, 1843–1844
Antibacterial chemotherapy, 1891–1902
  antibiotic selection, 1891–1892
  bacterial burden, 1893
  correct drug dose of, 1892
  culture, 1892
  dosages, 1891
  drug, classes and properties of, 1898–1900
  duration of therapy, 1900
  failure of, 1900–1902
  Gram stain, 1892
  infection site and, 1892, 1892*t*
  infection susceptibility to, 1892
  mechanism of action, 1894, 1895*t*
  pharmacokinetic of, changes of, 1894–1898, 1895*t*
  principles of, 1891
  resistance, 1892–1894, 1893*t*
  toxicities of, 1900, 1901*t*
Antibacterials, 1845*t*
  for skin diseases, 2699
Antibiotic(s)
  for acute bacterial prostatitis, 825*b*
  for acute bronchitis and tracheitis, 606*b*
  for acute mesenteric ischemia, 960*b*
  for asthma, 541*b*
  into cerebrospinal fluid, 2516*t*
  for common cold, 2193*b*
  for cystic fibrosis, 558*b*
  for diarrhea, 926*b*
  for diphtheria, 1935*b*
  for diverticulitis, 955*b*
  for *E. coli*, 1963*b*–1964*b*
  for esophagitis, 907*t*
  for inflammatory bowel disease, 945*b*
  for irritable bowel syndrome, 896*t*
  for malaria, 2121*b*
  for neutropenia, 1147*b*
  for perianal abscess, 979*b*
  for pyogenic liver abscess, 1023*b*
  reactions to, 1697–1698
  for relapsing fever, 2028*b*
  for shigellosis, 1981*b*–1982*b*
  for skin diseases, 2699
  for spondylitis, 1765*b*
  for *Stenotrophomonas maltophilia*, 1975*b*
  for *Streptococcus pneumoniae*, 1912*b*
  for viral hemorrhagic fevers, 2269*b*–2272*b*
Antibiotic-associated diarrhea, 926
Antibiotic resistance, mechanisms of, in Enterobacterales, 1965, 1966*t*
Antibodies, 152, 188, 192, 197
  for cancer, 1232*b*
  to citrullinated proteins, 1713
  monoclonal, for asthma, 541*b*
  specificities of, 188–189
Antibody deficiency, 1680–1682, 1681*t*
  clinical manifestations of, 1680–1682
  diagnosis of, 1682
  epidemiology and pathobiology of, 1680–1682, 1681*t*
  with normal immunoglobulins, 1682
  prognosis of, 1682
  treatment of, 1682*b*
Antibody-drug conjugates, 150*t*
Anticatabolic agents, for osteoporosis, 1643*b*
Anticholinergic agents
  central nervous system effects of, 685*t*
  toxidromes, 683*t*
Anticholinergic-antihistamine agents, for nausea and vomiting, 863*t*
Anticipatory anxiety, 2343
Anticoagulants, 364*b*, 501–506, 503*t*, 2666*t*, 2667*f*
  for giant cell arteritis, 1803*b*
  long-term use of, 487*b*–489*b*
  oral, 502*t*, 503–506
  parenteral, 501–503, 501*t*
  side effects of, 487*b*
Anticoagulation
  for acute coronary syndrome, 374*t*
  for acute STEMI, 384*b*, 387*f*
  for COVID-19, 2217
  in functional tests, 477–478
  for intracerebral hemorrhage, 2480*b*–2482*b*
  postoperative, 2667
  with warfarin, for portal vein thrombosis, 968*b*
Anticonvulsants
  central nervous system effects of, 685*t*
  for fibromyalgia, 1819*b*
  for myoclonus, 2493*b*–2494*b*
Antidepressants, 2679–2680, 2680*t*
  for anorexia nervosa, 1462*b*
  central nervous system effects of, 685*t*
  cyclic, toxicity, 686*t*
  in pregnancy, 1610
  tricyclic
    for chronic pain, 138*t*
    for depression, 2340*t*
    for fibromyalgia, 1819*b*
    screening for, 689*t*
Antidiarrheal agents, 940*b*, 941*b*
Antidiuresis, 1499
Antidiuretic hormone (ADH), *e*1*t*–*e*8*t*, 730–731, 738
Antidotes, for acute poisoning, 691*b*
Antidromic tachycardia, 323*t*, 326
Antiemetic regimens, for nausea and vomiting, 863*t*
Antiemetics, for intestinal pseudo-obstruction, 889*b*–890*b*
Antiepileptics, for alcohol withdrawal, 2358*t*
Antifibrinolytic agents, for disseminated intravascular coagulation, 1196*b*–1197*b*
Antifungal agents, 2074–2080, 2699
  amphotericin preparations as, 2077
  for aspergillosis, 2096
  azole, 2074–2077
    fluconazole as, 2075–2076
    indications and dosage of, 2075
    isavuconazole as, 2077
    itraconazole as, 2074–2075
    mechanisms of action, 2074
    posaconazole as, 2076–2077
    voriconazole as, 2076
  for coccidioidomycosis, 2085*b*
  dosing overview for, 2075*t*
  echinocandin, 2078–2079
    anidulafungin as, 2078
    caspofungin as, 2078
    mechanisms of action, 2078
    micafungin as, 2078
  flucytosine as, 2079
    adverse effects of, 2079
    drug interactions of, 2079
    formulation and pharmacology of, 2079
    indications and dosage of, 2075*t*, 2079
    mechanisms of action, 2079
  ibrexafungerp as, 2079
    adverse effects of, 2079
    drug interactions of, 2079
    indications and dosage of, 2075*t*, 2079
    mechanisms of action, 2079
  for mucormycosis, 2100*b*
  other, 2079
Antigen(s), 193*t*
  processing and presentation of, 188, 188*f*
  in transplantation, 203–205, 204*t*
Antigen-based testing, for COVID-19, 2214
Antigen detection, for malaria, 2120
Antigen-specific effector T cells, 193
Antigen-specific receptors, 188–189
Anti-glomerular basement membrane (anti-GBM), for glomerular syndromes, 727
Antihemophilic factor, 1189*t*
Antihistamines
  for acute bronchitis and tracheitis, 606*b*
  central nervous system effects of, 685*t*
  for rhinitis, 2632*b*–2634*b*
  for skin diseases, 2700, 2700*t*
Antihypertensive drugs, 1620*b*–1621*b*, 1621*t*
  classes of, 451–455
  interactions of, 455
  side effects of, 453*t*
  for specific condition, 454*t*
Antileukotrienes, 541*b*
Antimalarial drugs, 2698–2699
  for rheumatoid arthritis, 1755*b*–1758*b*
  for systemic lupus erythematosus, 1772*b*
Antimetabolites, for liver transplantation, 1048*t*
Antimicrobial resistance, 1834, 1965, 1966*t*
Antimicrobial therapy
  for *Acinetobacter* infection, 1974*b*
  administration of, 1844
  administrative aspects of, 1844–1845
  age and, 1843
  allergies to, 1842
  bactericidal activity of, 1842
  for bronchiectasis, 561*b*
  for *Campylobacter* infections, 1959*b*
  for cholera, 1956*b*–1957*b*
  combinations of, 1843
  definitive, 1841
  drug-drug interactions in, 1843
  drug resistance of, emergence of, 1843
  duration of, 1844
  empirical, 1840–1841
  failure of, 610*b*–611*b*, 1900
  for food poisoning, 1932*b*
  formularies for, 1844
  health care-associated infections and, 1863
  hepatic function in, 1843
  host factors, 1842–1844
  infection treated with, nature of, 1842
  pathogen of, identification of, 1841
  pharmacodynamic considerations in, 1844
  for plague, 1992*t*, 1993
  for pneumonia, 610*b*, 613*t*
  for polymicrobial infections, 1843
  in pregnancy, 1842–1843, 1842*t*
  renal function in, 1843
  resistance in, 1843
  route of administration, 1844
  selection of, 1840–1844
  for skin diseases, 2699
  stewardship for, 1844–1845, 1845*t*, 1865.*e*1*t*, 1867
  susceptibility testing of, 1836, 1840, 1916*b*
  toxicity of, 1843
Antimotility agents, for cholera, 1956*b*
Antimüllerian hormone, *e*1*t*–*e*8*t*, 1630
Antimuscarinics
  asthma and, 541*b*
  for benign prostatic hyperplasia, 822*b*
  for male lower urinary tract symptoms, 824*t*
Antineutrophil cytoplasmic antibodies (ANCA), 727, 1716, 1793–1794
Antineutrophil cytoplasmic antibody (ANCA)-associated vasculitis, 965, 1707–1708
Antineutrophil cytoplasmic antibody-associated vasculitides, 1796–1798
Antinuclear antibodies (ANAs), 727, 1714–1716, 1714*f*, 1785
  in pulmonary hypertension, 495
  systemic sclerosis, 1780
Antioxidants, 196, 975*t*
Antiparasitic therapy, 2111–2118, 2698
  for African trypanosomiasis, 2115
  for amoebic encephalitis, 2115
  for babesiosis, 2115
  for Chagas disease, 2116, 2128*b*
  for helminthic diseases, 2116–2118
  for intestinal protozoa, 2115
  for leishmaniasis, 2116
  for protozoal diseases, 2111–2116
  for skin diseases, 2699
  for toxoplasmosis, 2115
  for trypanosomiasis, 2115–2116
  for vaginal protozoa, 2115
Antiphospholipid antibody syndrome, 480–481, 481*b*, 1193, 1194*b*, 1715, 1770
Antiplatelet agents, 364*b*, 506–509, 506*t*, 2666–2667, 2666*t*, 2667*f*
  for acute coronary syndrome, 374*t*
  for acute STEMI, 384*b*, 387*f*
  for atherosclerotic PAD, 464*b*
  diabetes mellitus and, 1550
  for intracardiac procedures, 507–508
    adverse effects of, 508

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Antiplatelet agents *(Continued)*
combination of anticoagulant and, 508, 508*f*
pharmacology of, 507–509
α_1-Antiprotease, 548
Antipruritic agents, for skin diseases, 2700
Antipsychotics, 2679, 2680*t*
central nervous system effects of, 685*t*
Antipyretic analgesics, 136*b*
Antireflux surgery, 904*b*–905*b*
Antiretroviral therapy
corticosteroids and, 2317
for cryptosporidiosis, 2143*b*
gastrointestinal side effects of, 2319
for HIV infection, 2294, 2294*f*, 2297*b*, 2300–2305
for acute opportunistic infection, 2304–2305
available drugs for, 2300–2302, 2301*f*, 2301*t*
changing of, 2302–2303
for coinfection with hepatitis B, 2304
for coinfection with hepatitis C, 2304–2305
immunologic failure of, 2303
opportunistic infections associated with, 2307*b*–2308*b*
pregnancy and, 2305
recommended, 2303*t*–2304*t*
side effects and toxicity of, 2303–2304, 2304*t*
for special populations, 2304–2305
starting of, 2302
timing of, 2302, 2302*t*
toxic neuropathy caused by, 2313*b*
what to monitor, 2302
for *Pneumocystis* pneumonia, 2103*b*
to prevent sexual transmission, 2298–2299
Anti-SARS-CoV-2 monoclonal antibodies, 2216–2217, 2216*f*, 2219
Antiseizure medication
characteristics of, 2434*t*
discontinuation of, 2434*b*
selection of, 2433*t*, 2434*b*
Antisense oligonucleotides, 176–178
Antisocial personality disorder, 2348*t*
Antispasmodics, for irritable bowel syndrome, 895*b*, 896*t*
Antithrombin, 478*b*
Antithrombin III, *e8t*–*e9t*
deficiency, 475–476, 475*t*–477*t*
for disseminated intravascular coagulation, 1196*b*
for renal vein thrombosis, 802
Antithrombotic therapy, 501–509
for atherosclerotic PAD, 464*b*
for chronic kidney disease, 839*b*–840*b*
for gastrointestinal endoscopy, 875*t*
in-hospital dosing of, 387*t*
Antithyroid drugs, 1511*b*–1512*b*
α_1-Antitrypsin, *e1t*–*e8t*, 549, 551*b*–554*b*
α_1-Antitrypsin deficiency, 560, 993, 993*f*
Antituberculous agents, dosage of, 1895*t*
Antitumor cytotoxicity, 176
Antivenom, 708*b*–709*b*, 709*b*
for acute poisoning, 693*t*
for envenomation, 705*b*
for viperid bites, 708
Antiviral therapy, 2181–2191
for common cold, 2193*b*
for coronavirus infections, 2190–2191
for COVID-19, 2216–2217, 2217, 2217*f*
for cytomegalovirus, 2187*t*–2188*t*
for esophagitis, 907*t*
for hepatitis B virus infections, 2181–2183, 2181*t*
for hepatitis C virus infections, 2181*t*, 2182*t*, 2183–2186
for herpesvirus infections, 2186–2189, 2187*t*, 2188*t*
for influenza virus infections, 2189–2190, 2189*t*
for poxvirus infections, 2240*b*
for skin diseases, 2699
for varicella-zoster virus, 2187*t*
for viral hemorrhagic fevers, 2269*b*
Anton syndrome, 2616
Antral G-cell hyperplasia, 918
Anus
anatomy of, 977
diseases of, 977–983
anal fissure as, 979, 980*f*
anal fistula as, 979, 979*f*
Anus *(Continued)*
cancer as, 982
fecal incontinence as, 981, 981*f*
hemorrhoids as, 977–980, 978*f*
human papillomavirus as, 982–983
perianal abscess as, 978
pruritus ani as, 980
rectal prolapse as, 981*f*
sexually transmitted anorectal diseases, 983
warts as, 982, 982*f*
Anxiety
in adolescents, 112
chest pain in, 211*t*
management of, approaches to, 13*t*
in palliative care, 12
Anxiety disorders, 2337*t*, 2342–2343, 2683
clinical manifestations of, 2342–2343, 2343*t*
definition of, 2342–2343, 2342*t*
diagnosis of, 2343
epidemiology of, 2342
generalized, 2343
panic disorder, 2343
pathobiology of, 2342
phobias, 2343
prognosis of, 2343
social, 2343
treatment for, 2340*t*, 2343*b*, 2344*t*
in women, 1608*t*, 1609
Anxiolytic drugs, 926*b*, 2363, 2363*b*–2364*b*, 2679
Aorta
anatomy of, 437*f*
diseases of, 436
layers of, 436
normal, 436
Aortic aneurysm, 436
abdominal
clinical manifestations of, 436
diagnosis of, 437, 438*f*
epidemiology of, 436
risk factors for, 436
treatment of, 438*b*
clinical manifestations of, 436
definition of, 436, 437*t*
diagnosis of, 437
epidemiology of, 436
pathobiology of, 436
prognosis for, 438
risk factors of, 436
thoracic
diagnosis of, 438, 439*f*
treatment of, 438*b*
thoracoabdominal, 436
Aortic arch
anatomy of, 2454–2455, 2455*f*
magnetic resonance angiogram of, 2455*f*
Aortic diseases, 252, 253*f*
antihypertensive drug for, 454*t*
Aortic dissection, 211*t*, 439, 441*f*
acute. *See* Acute aortic dissection
acute medical therapy for, 443*t*
echocardiographic findings, 242*t*
stroke caused by, 2470.*e1t*
Aortic regurgitation, 240, 409–410
acute, 409, 410*b*
asymptomatic, with normal left ventricular function, 407*b*–408*b*
chronic, 410*b*
clinical manifestations of, 409–410
definition of, 409
diagnosis of, 410
echocardiographic findings, 410*f*
with left ventricular dysfunction, 410–411
noninvasive evaluation of, 410
pathobiology of, 409
physical examination of, 410
Aortic root dilation, 242*t*, 1725–1726
Aortic stenosis, 400
bicuspid, 400
clinical manifestations of, 402
congenital valvular, 351, 351*b*
diagnosis of, 402–403
Doppler echocardiogram from, 403*f*
epidemiology of, 400
exercise recommendations for, 355.*e2t*
low flow, low gradient, 403
measurement of, 239, 241*f*
medical therapy for, 405*b*–406*b*
pathobiology of, 400, 400.*e2f*
pathology of, 402*f*
prognosis for, 404
treatment of, 277*f*, 403*b*–404*b*
tricuspid, 400
Aortic valve, 224
bicuspid, 347
congenitally abnormal, 400
Aortic valve area (AVA), calculation of, 239
Aortic valve replacement, 402
transcatheter, 403*b*, 404*f*
Aortic vasculitis, 442.*e2f*, 443–444
Aortitis, asymptomatic, 2019
Aortoenteric fistulas, 967
Aortography, 463*f*
AP1. *See* Activator protein-1
Apalutamide (Erleada), 1215*t*
Apatite (basic calcium phosphate)-associated arthropathy, 1815, 1815*b*, 1815*t*
APBD. *See* Adult polyglucosan body disease
APBs. *See* Atrial premature beats
APECED. *See* Autoimmune polyendocrinopathy-candidiasis-ectodermal dystrophy
Aphasia
cause of, 2409
clinical manifestations of, 2408, 2409*f*
definition of, 2408
diagnosis of, 2408–2409
in frontotemporal lobar degeneration, 2421
language comprehension difficulties in, 2408
pathobiology of, 2408
primary progressive, 2409
treatment of, 2409*b*
Apheresis platelets, 1200
Aphthous stomatitis, 2620, 2621*f*, 2621*t*
Aphthous ulcer, oral, 2320*f*, 2322*t*
Apical lung disease, 524*f*
Apicomplexa species, 2141
Apixaban, 502*t*, 505, 505*t*
administration of, 506*t*
dosage and monitoring of, 505–506
for venous thromboembolism, 478*b*, 487*b*
Aplasia cutis, 2750
Aplastic anemia
Camitta criteria for, 1128*t*
clinical features of, 1127.*e1t*
drugs and toxins associated with, 1125.*e2t*
idiopathic, 1125–1126
large granular lymphocyte leukemia in, 1126–1128
myelodysplastic syndromes *versus*, 1255
paroxysmal nocturnal hemoglobinuria in, 1126
pure red cell aplasia in, 1128–1129, 1129*b*
related bone marrow failure states and, 1125–1130
Apnea, 2442–2443
Apo A lipoproteins, metabolism of, 1406, 1407*f*
ApoAI amyloidosis, 1306*t*
ApoAII amyloidosis, 1306*t*
ApoAIV amyloidosis, 1306*t*
ApoCII amyloidosis, 1306*t*
ApoCIII amyloidosis, 1306*t*
Apomorphine, for Parkinson disease, 2487*t*
Apoptosis, 671
Apparent diffusion coefficient (ADC), 1722
Apparent mineralocorticoid excess, 816*t*
Appearance, general, 212, 257–258
Appendectomy, 953*b*–954*b*
Appendiceal neuroendocrine neoplasms, 1566–1567
Appendicitis, 953
acute, abdominal pain and, 854*t*
clinical manifestations of, 953, 954*f*, 954*t*
differential diagnosis of, 953*t*
peritonitis caused by, 957
prognosis of, 953*b*
treatment of, 953*b*
Appetite, central nervous system regulation of, 1464.*e1f*, 1464.*e1t*
Applied energy, tissue effects of, 346
Apraxia
constructional, 989
oculomotor, 2619
Apremilast (Otezla), for total knee arthroplasty, 1830.*e1t*
Aprepitant, for nausea and vomiting, 863*t*
Aptamers, 177, 177*f*
aPTT. *See* Activated partial thromboplastin time
Aquagenic urticaria, 2725
Aquaporin 2, 730
Aqueous humor, 2607
Arachnia propionica, 2066
Arachnoid cysts, 1314
Arachnoiditis, 2398
Arava. *See* Leflunomide
Arboviruses, 2274–2284, 2520
characteristics of, 2270*t*
clinical manifestations of, 2274, 2275*t*–2276*t*, 2276*t*
definition of, 2274
diagnosis of, 2274
encephalitis syndrome and, 2280–2284
infectious process of, 2274
pathobiology of, 2274
phylogeny of, 2274
in travelers, 1890*t*
treatment of, 2276*b*
vector transmission of, 2274
ARBs. *See* Angiotensin receptor blockers
Arcanobacterium haemolyticum, 2649
Ardeparin, 503*t*
ARDS. *See* Acute respiratory distress syndrome
Area under the concentration-time curve, 1891–1892
Aredia. *See* Pamidronate
Arenaviruses, 2264
Argatroban, 501*t*, 503
Argentine hemorrhagic fever, 100*b*
Argininemia, 1398*t*, 1402*t*
Argininosuccinic aciduria, 1398*t*, 1402*t*
Argon, 88*t*
Argyll Robertson pupils, 2017, 2617
Argyria, 106, 106*b*, 106*f*
Arimidex. *See* Anastrozole
Aripiprazole
for psychotic disorders, 2346*t*
for Tourette syndrome, 2494*b*–2495*b*
ARISCAT Risk Index, 2664*t*
Aristolochic acid nephropathy, chronic interstitial nephritis caused by, 793
Armed spiders, envenomation of, 710
Armodafinil
description of, 2449*t*
for narcolepsy, 2446*b*
Aromasin. *See* Exemestane
Aromatase deficiency, 1573
Aromatase inhibitors, for breast cancer, 1369*b*
ARPKD. *See* Autosomal recessive polycystic kidney disease
Array-based comparative genomic hybridization, 164
Arrhythmias
alcohol use and, 2355
approach to, 303–312, 313*b*
bradyarrhythmias, 305, 318–319
cardiac, 301
causes of palpitations and syncope, 310*t*
clinical manifestations of, 303–312
diagnosis of, 305–309
diagnostic tests, 306–309
driving in patients with, 312*t*
life-threatening, 312–317, 313*b*
pharmacotherapy for, 313*b*
preoperative evaluation considerations, 2664
psychotropic medications and, 2678*t*
re-entrant, 301, 302.*e1f*
sinus, 318, 318*f*
supraventricular, 282*b*, 322
surgery for, 347
tachyarrhythmias, 305
treatment of, 264*b*
ventricular, 332–340, 333*f*–334*f*
Arrhythmogenesis, mechanisms of, 301–302
Arrhythmogenic right ventricular cardiomyopathy, 288–291, 337, 338*f*
clinical manifestations of, 289
definition of, 288
diagnosis of, 289–290, 289*f*, 290*t*
differential diagnosis of, 290
epidemiology of, 288
in first-degree relatives, 291*t*
pathobiology of, 288–289
pathology of, 288
prognosis of, 291
treatment of, 290*b*–291*b*
Arsenic toxicity, *e1t*–*e8t*, 87, 103–104, 690*t*
clinical manifestations of, 104
diagnosis of, 101*t*, 104
epidemiology of, 103–104
pathobiology of, 104
prognosis of, 104
treatment of, 102*t*, 104*b*
Arsenic trioxide (Trisenox), 1215*t*
Arsine gas, 104
Artemether-lumefantrine, 2112*t*, 2114, 2121*t*
Artemisinin, 2114, 2121*b*

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Arterial blood gases
in asthma, 540
in pulmonary function tests, 528*t*
systemic analysis of, 639, 639*f*
Arterial blood temperature, 678
Arterial CO_2 partial pressure ($Paco_2$), 642–643
Arterial dissection, 2464
Arterial gas embolism, 593–594, 594*b*
Arterial gas embolism syndrome, 593
Arterial hypertension, 439, 444–460
cardiovascular disease risk factors in, 447, 448*t*
clinical manifestations of, 445
definition of, 444–445
diagnosis of, 445, 446*f*
epidemiology of, 444–445
essential, 445, 448*t*
first-line drugs for, 451–454
identification and treatment of, 447–450, 448*t*, 450*b*
lifestyle modification for, 450, 450*t*
management of, 450*b*
medical therapy for, 450–455
pathobiology of, 445
secondary causes of, 450
Arterial oxygen content, 640
Arterial oxygenation, 644*f*
Arterial switch operation, 354
Arterial thromboembolism, 2667
Arteriovenous malformation, 2480*f*, 2482
Artery of Adamkiewicz, 2405
Artesunate, 2112*t*, 2114
Artesunate-amodiaquine (ASAQ), for malaria, 2121*t*
Arthralgia, 2274
arbovirus that cause, 2275*t*
arthritis *versus*, 1710
Whipple disease and, 2070
Arthritis, 1712–1713
acromegaly and, 1823
amyloidosis and, 1822
arthralgia *versus*, 1710
associated with treatments, for malignant diseases, 1823
autoimmune hepatitis and, 1820
carcinomatous polyarthritis and, 1823
diabetes mellitus and, 1822
enteropathic. *See* Enteropathic arthritis
epidemiology of, 1826
in familial Mediterranean fever, 1732
fungal, 1808
granulomatous, 1736
hemoglobinopathies and, 1822
in hemophilia, 1188, 1188*f*
hemophilia and, 1822
hyperlipoproteinemia and, 1823
hypertrophic osteoarthropathy and, 1823, 1824*f*–1825*f*
hypogammaglobulinemia and, 1822
inflammatory bowel disease and, 1821
leukemia and, 1823
Lyme, 1808, 2024
lymphoma and, 1823
Mycoplasma, 1808
in older adults, 115
osteoarthritis. *See* Osteoarthritis
pathobiology of, 1826, 1826*f*
perioperative, medication for, 1830, 1830.*e1t*
reactive. *See* Reactive arthritis
rheumatoid. *See* Rheumatoid arthritis
rheumatoid factor in, 1712–1713
septic, 1804–1807
systemic diseases associated with, 1820–1826, 1821*t*, 1824*f*, 1825*f*
thyroid disorders, 1822–1823
tuberculous, 1808
ureaplasma, 1808
viral, 1807
Whipple disease and, 2070
Arthrodesis, 1827
Arthrogryposis, 2589*t*
Arthropathy
apatite (basic calcium phosphate)-associated, 1815, 1815*b*, 1815*t*
hemochromatosis and, 1440, 1824*f*
Arthropods, 710–711
centipedes, 711
lice, 711
millipedes, 711
mites, 710–711
scorpion, 710
Arthropods *(Continued)*
ticks, 710
venomous, 710.*e1f*
Arthroscopy, 1827
Articular damage, 1751
Arylsulfatase B, for mucopolysaccharidosis type VI, 1420*t*
Asbestos, exposure to, 88*t*
lung cancer and, 1329
pleural effusions after, 626
Asbestos-related diseases, 589–590, 590*f*
Asbestosis, 590, 590*f*
ASCA. *See* Anti-*Saccharomyces cerevisiae* antibodies
Ascariasis, 2169–2170
clinical manifestations of, 2169–2170
diagnosis of, 2170
epidemiology of, 2169
pathobiology of, 2169, 2169*f*
prevention of, 2170
treatment of, 2170*b*, 2170*t*
Ascaris lumbricoides, 1026*t*, 2169
acute pancreatitis and, 970
treatment for, 2170*t*
Ascites, 736, 988, 988*f*, 989*t*, 990
in cancer, management of, 1232*b*
cirrhosis and, 1036, 1038
diagnosis of, 1039, 1040*t*
malignant, 957, 958*b*
treatment of, 1040*b*–1042*b*
Ascorbic acid, *e1t*–*e8t*, 1453*t*
ASCT. *See* Autologous stem cell transplant
ASDs. *See* Atrial septal defects
Asenapine, for psychotic disorders, 2346*t*
Aseptic meningitis
cerebrospinal fluid examination in, 2521
definition of, 2519
description of, 2030–2031
differential diagnosis of, 2521
enterovirus causing, 2520
epidemiology of, 2519–2520
herpes simplex virus causing, 2521
lymphocytic choriomeningitis causing, 2521
mumps causing, 2226, 2521
Mycoplasma pneumoniae in, 2007
noninfectious causes of, 2522
nonviral infectious causes of, 2522, 2522*t*
polymerase chain reaction for, 2521
prognosis for, 2522
Ash-leaf spots, of tuberous sclerosis, 2743
Asherman syndrome, 1598
Asia, HIV/AIDS in, 2289, 2289.*e2f*
Asian taeniasis, 2159
Ask-Tell-Ask approach, 12–13, 16*t*
Aspartate aminotransferase (AST), *e1t*–*e8t*, 998, 1017
Aspartylglucosaminuria, 1423–1424
Aspergilloma, 2094, 2095*f*
Aspergillosis, 2093
acute invasive, 2094
allergic forms of, 2095
caspofungin for, 2078
chronic pulmonary, 2094
classification of, 2094*t*
clinical manifestations of, 2094
definition of, 2093
diagnosis of, 2095
epidemiology of, 2093
extrapulmonary, 2094
invasive pulmonary, 2094
itraconazole for, 2075
pathobiology of, 2094
pathogens of, 2093
prevention of, 2097
prognosis of, 2098
treatment of, 2096
voriconazole for, 2076
Aspergillus flavus, 2093
Aspergillus fumigatus, 1857–1858, 2093
Aspergillus niger, 2093
Aspergillus spp.
endocarditis caused by, 417*t*
health care-associated infections caused by, 1865
otomycosis caused by, 2095
Aspergillus terreus, 2093
Asphyxia, psychotropic medications and, 2680
Aspiration, 597
distinguishing features of, 515*t*
psychotropic medications and, 2678*t*, 2680
Aspiration injury, 597–598
clinical manifestations of, 597
definition of, 597
diagnosis of, 597
pathobiology of, 597
prevention of, 598
prognosis of, 598
treatment of, 598*b*
Aspiration pneumonia, 615–616
clinical manifestations of, 615
diagnosis of, 615–616
epidemiology of, 615
pathobiology of, 615
prognosis of, 615, 616
treatment of, 616*b*
Aspirin, 387*t*, 506–507
for acute coronary syndrome, 374*t*
for acute STEMI, 384*b*, 391*t*
anaphylaxis caused by, 1692
for atherosclerotic PAD, 464*b*
for Fabry disease, 1423*b*
for frostbite, 474*b*
gastric ulcers and, 914–915
for homocystinuria, 1427
for ischemic heart disease, 470*b*
after PCI, 397
pharmacokinetic parameters for, 127.*e1t*
for postoperative care with substitute heart valves, 411–412
as preventive medications, 56
reactions to, 1698, 1698*t*
in renal failure, 129.*e1t*
Aspirin-exacerbated respiratory disease, 541*b*
Aspirin-induced asthma, 541*b*
Asplenia, immunization and, 76.*e2t*
Assessment, geriatric, 116–119
Assistance, in health delivery systems, 47, 48*f*
Assisted mechanical ventilation, 653
Assisted reproductive technologies
for infertility, 1603*b*–1604*b*
venous thromboembolism and, 481
Assisted suicide, 8–9
definition of, 8, 8*t*
empirical data for, 8–9
history of, 8
justification of, 8
practical considerations, 9
AST. *See* Aspartate aminotransferase
Asterixis, 989
Asthma, 537–547
allergic, 1673*t*, 1674
aspirin-induced, 541*b*
blood findings, 540
Chlamydia pneumoniae and, 2013
chronic obstructive pulmonary disease *versus*, 550
clinical manifestations of, 539
Crohn disease and, 943
cystic fibrosis and, 557
definition of, 537–547
diagnosis of, 539–541
differential diagnosis of, 541
ECG findings, 541
in emergency department, 541*b*
epidemiology of, 537–538
genetics of, 538
with heart failure, 265*b*
history in, 539
human microbiome and, 1840
increased eosinophils counts in, 533
laboratory findings of, 539–540
medications, 541*b*, 546*t*
obesity and, 533
occupational and environmental, 86, 86*t*
as occupational lung disease, 585*t*
pathobiology of, 538–539
physical examination of, 539
in pregnancy, 541*b*, 1619*t*
prevalence of, 538
prevention of, 541*b*
prognosis for, 547
pulmonary function findings, 539, 539*t*, 540*f*
with pulmonary infection, 541*b*
radiographic findings of, 540–541, 541*f*
rescue treatments for, 541*b*
in sickle cell disease, 1113–1114
sputum findings of, 541
treatment of, 541*b*, 542*f*
in women, medications for, 1608*t*
Astigmatism, 2598
Astra-Zeneca, 2219
Astrakhan fever, 2055*t*, 2057
Asymmetrical perfusion, 522–523
Asymptomatic bacteriuria, 1873, 1875*b*–1877*b*
Asymptomatic hyperuricemia, 1811
Asymptomatic hypoglycemia, 1546*t*
Asymptomatic infection, Whipple disease and, 2069
Asymptomatic intraluminal amebiasis, 2147
Asynchronous pubertal development, 1594
Asystole, 313*b*
At-risk drinking, 2353, 2353*t*
Ataxia
cerebellar, 2497–2498, 2497*b*, 2497*t*
Friedreich, 279–280, 2497
in multiple sclerosis, 2501
spinocerebellar, 2497
treatment of, 758*b*
Ataxia telangiectasia, 1250*t*, 2550*t*–2551*t*
Ataxia-telangiectasia, 1679, 1679*b*, 1679*t*
Ataxic breathing, 2438, 2439*t*
Atazanavir, 2301*t*, 2303, 2313
Atelectasis, 562–563, 563*b*, 563*f*
clinical manifestations of, 563
definition of, 562–563
diagnosis of, 563, 563*f*
epidemiology of, 563
pathobiology of, 563
rounded, 563, 563*f*
Atenolol, 451*t*
for alcohol withdrawal, 2358*t*
for premature ventricular contractions, 338*b*
for TSHomas, 1497*b*
Atenolol/chlorthalidone, 451*t*
Atezolizumab (Tecentriq), 1215*t*, 1394*t*
ATG16L1 gene, 942
Atheroembolic disease, 1142
Atherogenesis, 1406, 1407*f*
Atheromatous embolization, 469*t*–470*t*, 470*b*, 470*t*, 801, 801*b*, 802*f*
Atherosclerosis
cardiac risk factors associated with, 227
Chlamydia pneumoniae and, 2013
pathophysiology of, 227, 227.*e1f*
plaque activation of, 227, 227*f*, 227.*e1f*
regression of, 1406, 1406.*e1f*
Atherosclerotic cardiovascular disease (ASCVD), 1406, 1406.*e1f*, 1407*f*
prevention of, 1410
statin therapy for, 1411
Atherosclerotic peripheral arterial disease, 461–466
antiplatelet therapy for, 464*b*
antithrombotic therapy for, 464*b*
epidemiology of, 461
exercise therapy for, 464*b*
imaging of, 463–465, 463*f*, 464*f*
pathobiology of, 461–462
pharmacology of, 464*b*
prognosis for, 465
revascularization for, 464*b*, 464.*e1f*
risk factor modification for, 464*b*
Atherosclerotic renal artery stenosis, 800*b*, 800*t*
Atherosclerotic therapy, 227
Atherothrombosis, 2464
Athetosis, 2493
Athletes, electrocardiograms in, 234, 234*t*, 235*f*
Athlete's heart, 235*f*
ATI. *See* Acute tubular injury
ATN. *See* Acute tubular necrosis
Atomoxetine, for orthostatic hypotension, 2559*t*
Atopic asthma, 538
Atopic dermatitis, 1673*t*, 1674, 2702–2703, 2703*f*
Atopic diseases, 1672
Atopic keratoconjunctivitis, 1673*t*
Atorvastatin
for acute STEMI, 384*b*, 391*t*
for familial hypercholesterolemia, 1409*t*
for ischemic heart disease, 470*b*
Atovaquone, 2115
for amoebic encephalitis, 2112*t*
for babesiosis, 2112*t*, 2115, 2152*b*–2153*b*, 2152*t*
for *Pneumocystis* pneumonia, 2103*b*, 2106*t*, 2108*t*
for toxoplasmosis, 2112*t*, 2140*t*
Atovaquone-proguanil, 2115
for malaria, 1887–1888, 2112*t*, 2121*b*
ATRA. *See* All-*trans*-retinoic acid

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Atresia
  intestinal, 951
  tricuspid, 354–356
  vaginal, 1574
Atrial beats, complete heart block with, 321*f*
Atrial-esophageal fistulas, 912–913
Atrial fibrillation, 323*t*, 328–332, 328*f*
  antihypertensive drug for, 454*t*
  catheter ablation for, 346
  chronic persistent, 329*b*–332*b*
  clinical manifestations and diagnosis of, 329
  management of, 384*b*
  paroxysmal, 329*b*, 330*f*
  prognosis of, 331*t*, 332
  recent-onset, 329*b*, 330*f*
  renal infarction caused by, 802
  stroke caused by, 2464
  surgical ablation of, 347
  treatment of, 265*b*, 329*b*
  of uncertain duration, 329*b*, 330*f*
Atrial flutter, 323*t*, 326–327, 327*b*, 328*f*
Atrial myxoma, 2470.*e1t*
Atrial natriuretic peptide (ANP), 730, 734
Atrial premature beats (APBs), 322, 322*f*–323*f*
Atrial premature depolarizations, 328
Atrial septal defects (ASDs), 347
  classification of, 348–349
  color flow Doppler findings, 349.*e1f*
  diagnosis of, 349
  ECG findings, 349, 349*f*
  exercise recommendations for, 355.*e2t*
  prognosis for, 349*b*
  treatment of, 349*b*
Atrial tachycardias, 323*t*, 324, 324*f*
Atrioventricular (AV) block, 317*t*
  first-degree, 229, 320, 320*f*
  high-degree or advanced, 321, 321*f*
  Mobitz type I (Wenckebach), 306, 320, 320*f*
  third-degree, 321, 321*f*
Atrioventricular (AV) canal defect, 354
Atrioventricular (AV) conduction disturbances, 319–321, 321*b*
Atrioventricular (AV) dissociation, 321, 335
Atrioventricular nodal re-entrant tachycardia (AVNRT), 323*t*, 324, 324*b*, 324*f*, 327*f*
Atrioventricular (AV) node
  abnormalities, medications for, 319*t*
  two-to-one conduction in, 320*f*
Atrioventricular re-entrant tachycardia (AVRT), 323*t*, 326, 328*f*
Atrophic gastritis, 1340
Atrophic lesions, 2736–2737, 2737*f*, 2737*t*
Atrophic rhinitis, 2631
Atropine
  for acute poisoning, 693*t*
  for bradycardia, 313*b*, 316*f*, 384*b*
  for sinus node dysfunction and AV blocks, 321*b*
ATTRV50M, amyloidosis and, 1309
ATTRV122I, amyloidosis and, 1309
ATTRwt amyloidosis, 1306*t*, 1309, 1309*b*
Atypical absence seizures, 2430
Atypical adenomatous hyperplasia, 1329
Atypical bacterial pneumonia, characteristics of, 2270*t*
Atypical chronic myeloproliferative diseases, 1277–1278, 1278*b*
Atypical hemolytic-uremic syndrome, 201*t*, 1178
Atypical lymphocyte, 2253, 2254*f*
Atypical melanocytic nevi, 2733*f*
Atypical parkinsonism, 2486
Atypical squamous cells of undetermined significance (ASC-US), 1376
Aubagio. *See* Teriflunomide
Audiometry, for hearing loss, 2641
Auditory pathways, lesions within, localization of, 2641
Auditory system, disorders of, 2641–2643
  definition of, 2641–2643
  diagnosis of, 2641–2642
  epidemiology of, 2641
  pathobiology of, 2641
  tinnitus, 2643, 2643*b*, 2643*f*
  treatment of, 2642*b*
Auer rods, 1073, 1073*f*
Auerbach plexus, 887, 901
Augment clotting, for hemophilia, 1188*b*
Aura, 2376, 2378
Auscultation
  cardiac, 214, 215*f*, 216*t*
  lung, 512*t*
Auscultatory office blood pressure, 446–447, 446*t*
Autism spectrum disorders, 2548, 2548*b*, 2548*t*
Auto-PEEP, 654, 654.*e1f*
Autoantibodies, 194
  in rheumatic diseases, 1715*t*
  in systemic lupus erythematosus, 1768, 1768.*e2f*, 1772*t*
  in systemic sclerosis, 1776, 1777*t*
Autografts, 412*t*
Autoimmune acquired hypoparathyroidism, 1661
Autoimmune autonomic disorders, 2558–2560
Autoimmune conditions, in women, medications for, 1608*t*
Autoimmune cytopenias, in chronic lymphocytic leukemia, 1267
Autoimmune destruction, of adrenal gland, 1526
Autoimmune disease, 193
  bronchiectasis and, 560
  in pregnancy, 1619*t*
  treatment of, 1853*t*
Autoimmune encephalitis, 2535–2536
  clinical manifestations of, 2536
  diagnosis of, 2536
  epidemiology of, 2535–2536
  neural antigen targets and, 2536*t*
  pathobiology of, 2535
  prognosis of, 2536
  treatment of, 2536
Autoimmune ganglionopathies, 2554, 2554*t*
Autoimmune hemolytic anemia (AIHA), 1087–1089
  cold, 1088–1089, 1088*t*, 1090*f*
  corticosteroids for, 1089*b*–1091*b*
  diagnosis of, 1087–1089
  direct antiglobulin test for, 1087–1088
  epidemiology of, 1087
  folic acid supplementation for, 1089*b*
  laboratory test for, 1087
  pathobiology of, 1087
  rituximab for, 1089*b*
  signs and symptoms of, 1087
  splenomegaly associated with, 1152
  warm, 1087, 1089*t*
Autoimmune hepatitis, 1016–1017, 1017*b*
  acute manifestation of, 986
  arthritis associated with, 1820
  in pregnancy, 1625*t*
Autoimmune hypocalciuric hypercalcemia, 1658
Autoimmune hypophysitis, hypogonadotropic hypogonadism and, 1584
Autoimmune inner ear disease, 2645
Autoimmune lymphoproliferative syndrome (ALPS), 1684*t*
Autoimmune pancreatitis, 970, 970*t*
Autoimmune pericarditis, 424*t*, 432–433
Autoimmune polyendocrinopathy-candidiasis-ectodermal dystrophy (APECED), 1684*t*, 2090
Autoimmune polyglandular syndrome, 1559–1560
  clinical features of, 1559*t*
  type 1, 1559–1560, 1560*b*
  type 2, 1560, 1560*b*
  type 3, 1560, 1560*b*
  type 4, 1560, 1560*b*
Autoimmune regulator-1 (AIRE-1), 1559–1560
Autoimmune syndromes, chronic, 2510
Autoimmune testicular failure, 1584
Autoimmune thyroiditis, radiographic evaluation of, 1511*t*
Autoimmunity, 191, 1693
  complement system in, 197
  in systemic lupus erythematosus, 1768
  in systemic sclerosis, 1776
Autoinflammation, with arthritis and dyskeratosis, 1731*t*
Autoinflammation and PLCγ2-associated antibody deficiency and immune dysregulation (APLAID), 1731*t*
Autoinflammatory diseases, 1708
Autoinflammatory disorders, 1686
Autoinflammatory rheumatic diseases, 1708
Autologous hematopoietic cell transplantation, 1208
Autologous stem cell transplant (ASCT), for amyloidosis, 1308*f*–1309*f*
Autologous transplants, 203
Automated blood pressure machines, 33
Automated external defibrillators, 313*b*, 314*t*
Automatic junctional tachycardia, 323*t*
Automaticity, abnormal, 301
Autonomic disorders, 2553–2561
  autoimmune, 2558
  autonomic function tests for, 2556–2557
  classification of, 2554*t*
  clinical evaluation of, 2555–2556, 2556*f*, 2556*t*
  clinical manifestations of, 2554–2555
  definition of, 2553–2557
  diagnosis of, 2555–2557
  epidemiology of, 2553
  laboratory evaluation of, 2556, 2557*t*
  metabolic, toxic, and infectious causes of, 2560–2561
  pathobiology of, 2553–2554
  pathogenesis of, 2554, 2554*t*
  regional sympathetic dysfunction, 2561
  systemic, 2553–2557
  treatment for, 2557*b*–2558*b*
Autonomic failure, 2554–2555
Autonomic hyperactivity, 2555
Autonomic nervous system dysfunction, for tetanus, 1929*b*
Autonomic neuropathy
  in diabetes mellitus, 2577
  in HIV/AIDS, 2313
Autonomy, 4
Autosomal dominant hypocalcemia type 1 (ADH1), 1661
Autosomal dominant hypocalcemia type 2 (ADH2), 1661
Autosomal dominant hypophosphatemic rickets, 1648
Autosomal dominant inheritance, 160–161, 161*f*
Autosomal dominant polycystic kidney disease (ADPKD), 808–812
  clinical manifestations of, 811
  diagnosis of, 811–812, 811*f*
  gene products of, 810–811, 810.*e1f*
  genetics of, 808–810
  monitoring progressive renal disease in, 812
  pathobiology of, 808–811, 810*f*
  treatment of, 812*b*, 812.*e1f*
Autosomal dominant tubulointerstitial kidney disease (ADTKD), 795, 809*t*, 810*f*, 814, 814*b*, 818
Autosomal recessive inheritance, 161–162
Autosomal recessive polycystic kidney disease (ARPKD), 809*t*, 812–813
  clinical manifestations of, 813
  definition of, 812–813
  diagnosis of, 811*f*, 813
  epidemiology of, 812
  pathobiology of, 813
  prognosis of, 813
  treatment of, 813*b*
Autosomal recessive pseudohypoaldosteronism, type 1, 761–762
AV block. *See* Atrioventricular block
AV dissociation. *See* Atrioventricular dissociation
AV node. *See* Atrioventricular node
Avastin. *See* Bevacizumab
Avellis syndrome, 2465.*e2f*
Avelumab (Bavencio), 1215*t*
Avermectin, 2117
Avian influenza (H5N1), 2065*t*, 2199
AVNRT. *See* Atrioventricular nodal re-entrant tachycardia
Avoidant personality disorder, 2348*t*
Avoidant/restrictive food intake disorder, 1461, 1462*b*
Avonex. *See* Interferon Beta1*a*
AVRT. *See* Atrioventricular re-entrant tachycardia
Avulsion of flexor digitorum profundus, 1745–1746
Awaji-Shima consensus criteria, for amyotrophic lateral sclerosis, 2563*t*
Awareness, in health delivery systems, 47, 48*f*
Axial disease, 1710
Axillary buboes, 1991
Axillary lymph node metastases, treatment of, 1241*b*
Axitinib (Inlyta), 1215*t*, 1364*b*–1365*b*
Axonal injury, 2386, 2386.*e1f*
Azacitidine (Vidaza), 1215*t*, 1255
Azalides, mechanism of action, 1895*t*
Azathioprine, 148
  for Crohn disease, 945*b*, 946*t*
  for liver transplantation, 1048*t*
  for myocarditis, 286*b*
  in renal transplantation, 845*t*
  for rheumatoid arthritis, 1756*t*
  for systemic lupus erythematosus, 1772*b*
  for total knee arthroplasty, 1830.*e1t*
AZF. *See* Azoospermic factor
Azilsartan, 451*t*
Azilsartan/chlorthalidone, 451*t*
Azithromycin
  for acute bronchitis and tracheitis, 606*b*
  for babesiosis, 2112*t*, 2152*b*, 2152*t*
  for bronchiectasis, 561*b*
  for cat-scratch disease, 2003*b*
  for chancroid, 1951*b*
  for *Chlamydia trachomatis*, 2012*b*
  for cholera, 1956*b*
  for chronic obstructive pulmonary disease exacerbations, 555
  for COVID-19, 2217–2218
  for cystic fibrosis, 558*b*
  for diarrhea, 926*b*
  dosage of, 1895*t*
  for gonorrhea, 1948*b*
  for granuloma inguinale, 2004*b*
  for HIV/AIDS, opportunistic infections associated with, 2309*t*
  for legionnaires disease, 1999*t*
  for leptospirosis, 2031*b*
  for Lyme disease, 2026*t*
  for meningococcal disease, 1945*t*
  for nontuberculous mycobacterial disease, 2046*t*
  for pertussis, 1996
  for pneumonia, 613*t*
  for *Streptococcus pneumoniae* pulmonary infections, 1912.*e1t*
  for toxoplasmosis, 2140*t*
  for trachoma, 2010*b*
  for traveler's diarrhea, 1888, 1888*t*
  for typhoid fever, 1979*b*
  for urethritis, 1880*t*
  for yaws, 2021–2022, 2022*b*
Azole antifungal agents, 2074, 2085*b*
  fluconazole as, 2075
  indications and dosage of, 2075
  isavuconazole as, 2077
  itraconazole as, 2074
  mechanisms of action, 2074
  posaconazole as, 2076
  voriconazole as, 2076
Azoospermia, 1586
Azoospermic factor (AZF), 1586
Azotemia
  caused by amphotericin B, 2077
  postoperative, 2676
  severe mental illness and, 2683*t*
Aztreonam
  for bacterial meningitis, 2518*t*
  dosage of, 1895*t*
  for pneumonia, 613*t*
Azulfidine. *See* Sulfasalazine

B

B19 arthropathy, 2234. *See also* Parvovirus
B19 parvovirus, 2233, 2235*t*
Babesia, 1203
Babesia crassa, 2151
Babesia divergens, 2151
Babesia duncani, 2151
Babesia microti, 1026*t*, 2065*t*, 2151, 2152*f*–2153*f*
Babesia motasi, 2151
Babesia venatorum, 2151
Babesiosis, 1203, 2065*t*, 2115, 2151–2153
  clinical manifestations of, 2151
  diagnosis of, 2151–2152, 2152*f*, 2153*f*
  epidemiology of, 2151–2153
  pathobiology of, 2151
  prevention of, 2153
  prognosis of, 2153
  treatment of, 2112*t*, 2152*b*, 2152*t*
Baby boomers, 114
Bacillary angiomatosis, 2002–2003, 2002*f*, 2003*b*, 2003*t*
Bacillary dysentery, characteristics of, 2270*t*
Bacillus anthracis, infections caused by, 1930*f*, 2515*b*–2518*b*
  clinical manifestations of, 1931–1932, 1931*f*
  diagnosis of, 1932
  epidemiology of, 1930
  pathobiology of, 1931
  prevention of, 1932–1933
  treatment of, 1932*b*
Bacillus Calmette-Guérin (BCG) vaccine, 1215*t*, 2043, 2053

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Bacillus cereus, infections caused by, 1930
  clinical manifestations of, 1932
  diagnosis of, 1932
  pathobiology of, 1931
  prevention of, 1933
  treatment of, 1932*b*
Bacillus spp., infections caused by, 1930–1933
  clinical manifestations of, 1931–1932, 1931*f*
  definition of, 1930
  diagnosis of, 1932
  epidemiology of, 1930
  pathobiology of, 1931
  pathogen of, 1930, 1930*f*
  prevention of, 1932–1933
  prognosis of, 1933
  treatment of, 1932*b*
Bacillus thuringiensis, infections caused by, 1930
Bacitracin, for eye infection, 2605*t*
Back pain, 136*b*
Backwash ileitis, 944–945
Baclofen
  for chronic pain, 138*t*
  for spastic paraplegias, 2498*b*
Bacteremia, 2001*t*, 2002
  Acinetobacter causing, 1973
  anaerobic bacteria causing, 1938
  Campylobacter jejuni causing, 1959
  cellulitis caused by, 2740
  clinical manifestations of, 2002
  definition of, 669
  diagnosis of, laboratory methods for, 2003*t*
  in endoscopy, 876*t*
  enteric infections and, 1870*t*
  enterococci causing, 1921
  epidemiology and pathobiology of, 2002
  intraerythrocytic, 2000–2001, 2001*t*
  meningococcal, 1943*f*
  Pseudomonas infections causing, 1969, 1970*b*
  Salmonella causing, 1978
  Staphylococcus aureus causing, 1902, 1906*t*
  Streptococcus pyogenes causing, 1915
  systemic, hepatobiliary abnormalities affected by, 1023
  treatment of, 1921*b*–1924*b*, 1922*t*
Bacteria
  anaerobic. *See* Anaerobic bacteria
  peripheral blood smear of, 1074*t*
  in subarachnoid spaces, 2512
Bacterial ascites, in endoscopy, 876*t*
Bacterial conjunctivitis, 2604, 2605*f*, 2605*t*
Bacterial endocarditis, 2515, 2609, 2610*f*
  definitive therapy of, 419*t*
  pathogens and empirical therapy for, 2526*t*
  subacute, 195
Bacterial esophagitis, 912
Bacterial infections
  of liver, 1022–1023
  neutrophilia and, 1140–1141
  non-abscess hepatic, 1023
  of skin, 2739–2741, 2739*t*
    cellulitis as, 2739–2740, 2740*f*
    folliculitis as, 2739
    furuncles as, 2739, 2740*f*
    impetigo as, 2739, 2739*f*
    mycobacterial infections as, 2741
    Neisseria infections as, 2741, 2741*f*
    Pseudomonas infections as, 2741
    spirochetes as, 2741
    toxic erythemas as, 2740–2741
  in women, medications for, 1608*t*
Bacterial liver abscess, 1022*t*
Bacterial meningitis
  antimicrobial agents for, 2515*b*
  blood and respiratory tract cultures, 2514
  brain swelling in, 2515*b*
  cerebral blood flow in, 2512
  cerebrospinal fluid examination in, 2374*t*, 2513–2514, 2513*t*
  chemoprophylaxis for, 2519
  in children, 2511
  clinical manifestations of, 2512–2513
  coagulopathies associated with, 2518
  complications of, 2513, 2518
  corticosteroids for, 2515*b*
  definition of, 2510–2519
  diagnosis of, 2513–2519
  differential diagnosis of, 2514–2515
  epidemiology of, 2510–2511
  genetics of, 2512
  hypotension, 2515*b*
Bacterial meningitis *(Continued)*
  laboratory findings in, 2513–2514
  lactic acid in, 2514
  magnetic resonance imaging of, 2511
  neurologic findings in, 2513
  nosocomial, 2517*t*
  pathobiology of, 2511–2512
  pathogenesis of, 2511–2512
  pathology of, 2511
  physical findings in, 2512–2513
  prevention of, 2519
  prognosis for, 2519
  radiologic studies for, 2514
  recurrent, 2518–2519
  seizures in, 2513
  signs and symptoms of, 2512*t*
  supportive care for, 2515*b*
  surgery for, 2515*b*
  treatment of, 2519*b*
  vaccination for, 2519
Bacterial overgrowth
  antibiotics for, 889*b*
  gastrointestinal motility disorders and, 889
  intestinal, 932*t*, 934
    clinical manifestations of, 934
    diagnosis of, 931*t*–932*t*, 932*t*, 934
    treatment of, 934*b*
  tests for, 931*t*
Bacterial pericarditis, 426*t*, 431
Bacterial pneumonia, 566
  in left upper lobe, computed tomographic scan of, 521*f*
  in travelers, 1891*t*
Bacterial superinfection, of skin lesions, varicella and, 2248
Bacterial tonsillitis, 2649*t*
Bacterial vaginosis
  characteristics of, 1882
  organisms causing, 1879*t*
  treatment of, 1882*b*
Bactericidal, defined, 1894
Bactericidal antibiotics, for anthrax, 1932*b*
Bacteriology, for nocardiosis, 2073–2074
Bacteriostatic, defined, 1894
Bacteroides, 2068
Bacteroides fragilis, 1833
Bactrian. *See* Mupirocin
BAFF. *See* B-cell-activating factor
Bafiertam. *See* Monomethylfumarate
Baker cyst, 1752, 1752.*e*1*f*. *See also* Popliteal cysts
Balamuthia mandrillaris, 2150*t*
Balance activity, 63*b*
Balance training, 63*b*
Balancing professional responsibilities, 4–5
Balantidium coli, 2156, 2156*t*
Ballism, 2491–2492, 2492*t*
Balloon catheters, 395, 395*f*
Balloon-expandable coronary stents, 395.*e*1*f*
Balloon pumps, intra-aortic, 667*b*–669*b*
Baloxavir, for influenza, 2202*b*–2203*b*, 2203*t*
Baloxavir marboxil, for influenza virus infections, 2189, 2189*t*
Balsalazide (Colazal), for inflammatory bowel disease, 946*t*
Balversa. *See* Erdafitinib
Bamlanivimab/etesevimab, for coronavirus infections, 2190
Banana spiders, envenomation of, 710
BAP1. *See* BRCA1- associated protein
Barbiturates
  central nervous system effects of, 685*t*
  reactions to, 1698*t*
Bardet-Biedl syndrome, 809*t*
Bariatric surgery
  for obesity, 1467*b*–1469*b*
  for type 2 diabetes mellitus, 1540*b*–1544*b*
Baricitinib (Olumiant), 153*t*, 1755*b*, 1756*t*
  for total knee arthroplasty, 1830.*e*1*t*
Barium radiograph, of peptic stricture, 904*f*
Barlow type valve, 406.*e*1*f*
Barotrauma, 593
  clinical manifestations of, 594
  definition of, 593–594
  diagnosis of, 594
  epidemiology of, 593
  to middle ear, 2641
  pathobiology of, 594, 594.*e*1*f*
  prevention of, 594
  treatment of, 594*b*
Barrett esophagus, 905–906, 1338–1339
  clinical manifestations of, 905
  diagnosis of, 904*f*, 905–906
  epidemiology of, 905
  fluoroscopy of, 869*f*
  pathobiology of, 905
  prognosis of, 906
  treatment of, 904*t*, 906*b*, 906*f*
Barrier methods, for disseminated gonococcal infection, 1950
Barth syndrome, 1145
Bartonella alsatica, 2000, 2000*t*
Bartonella ancashensis, 2000, 2000*t*
Bartonella bacilliformis, 2000, 2000*t*
Bartonella clarridgeiae, 2000, 2000*t*
Bartonella elizabethae, 2000, 2000*t*
Bartonella grahamii, 2000, 2000*t*
Bartonella henselae, 1142, 1150, 2000, 2000*t*
Bartonella infections, 2000–2003
  bacillary angiomatosis as, 2002
  bacteremia and endocarditis as, 2002
  cat-scratch disease as, 2001–2002
  clinical manifestations of, 2000, 2001*t*
  definition of, 2000
  diagnosis of, 2002–2003
    alternative methods in, 2001*f*, 2002, 2003*t*
    mass spectrometry in, 2002
    molecular detection methods in, 2002
  differential diagnosis of, 2003
  endocarditis caused by, 417*t*
  epidemiology of, 2000, 2000*t*
  Oroya fever and trench fever as, 2000
  pathobiology of, 2000
  peliosis hepatis as, 2002
  prevention of, 2003
  prognosis of, 2003
  treatment for, 2003*b*
  verruga peruana as, 2002
Bartonella koehlerae, 2000, 2000*t*
Bartonella mayotimonensis, 2000, 2000*t*
Bartonella quintana, 2000, 2000*t*
Bartonella rochalimae, 2000, 2000*t*
Bartonella tamiae, 2000, 2000*t*
Bartonella vinsonii arupensis, 2000, 2000*t*
Bartonella vinsonii berkhoffii, 2000, 2000*t*
Bartonella washoensis, 2000, 2000*t*
Bartter syndrome, 749, 749*t*, 816*t*, 817, 817*b*, 817.*e*1*f*
Barttin, 817
Basal cell skin cancer, 1395–1396, 1395*f*, 1396*b*
Basal lung disease, 523–524, 523*t*
Basal metabolic rate (BMR), 1465
Basal pulmonary disease, 524*f*
Basaloid, 977
Basaloid squamous cell carcinoma, 1324*f*
Base excess, *e*1*t*–*e*8*t*
Basic calcium phosphate arthropathy, 1815, 1815*b*, 1815*t*
Basic life support (BLS), after cardiac arrest, 313*b*
Basilar artery, 2465
  anatomy of, 2456
  occlusion of, 2465
Basilar skull fracture, 2513
Basiliximab, in renal transplantation, 845*t*
Basophilic stippling
  conditions associated with, 1072*t*
  peripheral blood smear of, 1070*f*
Basophilopenia, 1148
Basophils, 183
Bat-borne viruses, 2264
Batteries, pacemaker, 342
Battering, 1633
Bavencio. *See* Avelumab
Bayes theorem, 38, 38.*e*1*t*
Baylisascariasis, 2065*t*, 2174
Baylisascaris spp., 2065*t*
Bazedoxifene, for osteoporosis, 1644*t*
Bazett's formula, 230
Bazex syndrome, 2710
B-cell(s), 204*t*
  development, 187, 187*f*
  differentiation of, 190
  stimulation and accessory molecules of, 189
B-cell-activating factor (BAFF), 151, 185–186
B-cell lymphoma
  diffuse large, 1279, 1284–1285, 1285*b*
    subtypes of, 1285, 1285*b*
  marginal, in Sjögren syndrome, 1785
  mature, 1283–1286
B-cell lymphoma *(Continued)*
  precursor, 1281–1282, 1282*b*
  primary mediastinal large, 1285
  rare types of, 1286
B-cell receptor
  in chronic lymphocytic leukemia, 1267
  genetic defects of, 1680, 1681*t*
BCG. *See* Bacillus Calmette-Guérin
B-complex vitamins, for malabsorption, 937*t*
Beau lines, 2752, 2752*f*, 2752*t*
Bebtelovimab, for coronavirus infections, 2190–2191
Becker disease, 2583.*e*1*t*
Becker muscular dystrophy, 2584, 2584*b*
Beclomethasone, 543*t*, 553*t*
Bedaquiline, dosage of, 1895*t*
Bedbugs, 711, 712*f*
Bedside radiography, 519
Beer potomania syndrome, 738
Behavior
  alcohol use disorders and, 2355*t*, 2356
  modification of, for obesity, 1467*b*
Behavioral determinants, of human blood pressure variation, 445
Behavioral intervention
  for alcohol use disorders, 2357*b*
  for disseminated gonococcal infection, 1950
  for urinary incontinence, 829*b*–830*b*
Behçet disease, 1731*t*, 1799, 2621*t*
  epidemiology of, 1793*t*
  of esophagus, 911
  intestinal ulcers associated with, 956
  prognosis of, 1799*b*
  treatment of, 1799*b*
Belatacept, in renal transplantation, 845*t*
Belching, 858
Beleodaq. *See* Belinostat
Belimumab (Benlysta), 1714, 1772*b*, 1830.*e*1*t*
Belinostat (Beleodaq), 1215*t*
Bell palsy, 1322, 2579, 2579*f*
Bempedoic acid, 1413
Benazepril, 451*t*
Benazepril/HCTZ, 451*t*
Bence Jones protein, 1294
Bendamustine (Treanda), 1215*t*
  for chronic lymphocytic leukemia, 1269*b*–1271*b*, 1269*t*, 1270*t*
  for mantle cell lymphoma, 1284*b*
Bendopnea, 256, 265*b*
Benedikt syndrome, 2465.*e*1*f*
Beneficence, 8
Benign asbestos disease, 589–590
Benign biliary strictures, 1056–1058, 1057*f*–1058*f*, 1058*f*
Benign breast lesions, 1374
Benign capillary hemangioma, 2731–2733, 2734*f*
Benign cramp-fasciculation syndrome, 2564*t*
Benign epidermal tumors, 2729–2730
Benign familial neutropenia, 1143
Benign hepatocellular adenoma, 1615
Benign migratory glossitis, 2623
Benign papules, of skin, 2729–2736
Benign paroxysmal positional vertigo, 2644, 2645*f*, 2647*t*
Benign prostatic hyperplasia (BPH), 821–823
  clinical manifestations of, 822
  definition of, 821, 821*f*
  diagnosis of, 822–823, 823*f*
  epidemiology of, 821
  laboratory findings of, 822–823
  management of, algorithm of, 824*f*
  pathobiology of, 821–822
  prognosis of, 823
  treatment of, 822*b*
Benign recurrent intrahepatic cholestasis, 997
Benlysta. *See* Belimumab
Benralizumab, for eosinophilic syndromes, 1164*b*
Benzathine penicillin G
  for nonsyphilitic treponematoses, 2019
  for yaws, 2022*b*
Benzene, 88*t*
Benzimidazoles, 2161*b*
Benznidazole, for Chagas disease, 2112*t*, 2116, 2128*b*
Benzodiazepines
  for alcohol withdrawal, 2358*t*
  for anxiety disorders, 2344*t*
  for catatonia, 2681*b*
  central nervous system effects of, 685*t*
  misuse, 2363

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Benzodiazepines *(Continued)*
for nausea and vomiting, 863*t*
for neuroleptic malignant syndrome, 2681*b*
screening for, 689*t*
for tetanus, 1929*b*
Benzoyl peroxide, for skin diseases, 2699
Benzyl alcohol, for lice, 711*b*
Benzyl benzoate, for scabies, 711*b*
Bepridil, 367*t*
Bereavement services, in hospice, 16
Berger disease, 969
Beri-beri, 2537
Bernard-Soulier syndrome, 1183*b*, 1184*f*, 1185
Bernoulli equation, simplified, 238
Beryllium, 88*t*
Beryllium disease, chronic, 589
Best Case/Worst Case communication framework, 15–16, 16.e1*f*
"Best-corrected visual acuity", 2615
"Best practices", 43–44
Betacoronavirus, 2209*t*
Betaine, 1427*b*
Betaseron. *See* Interferon Beta1b
Betaxolol, 451*t*
Bethesda criteria, for HNPCC, 1347
Bevacizumab (Avastin), 1186*b*, 1215*t*, 1251*t*, 1315*b*, 1369*b*
Bexarotene (Targretin), 2698
Bezlotoxumab, 1845*t*
Bicalutamide (Casodex), 1215*t*
Bicarbonate, *e1t–e8t*, 754
description of, 639
regulation of, 731–732, 731.e1*f*, 732*f*
for rhabdomyolysis, 717*b*, 717*t*
for salicylate intoxication, 759
Bicipital tendinosis, 1744, 1744*b*
Biclonal gammopathies, 1297
Bictegravir, 2301*t*
Bicuspid aortic valve, 347
Bifidobacterium dentium, 2066
Bifidobacterium infantis, for irritable bowel syndrome, 896*t*
Big-K channels, 746
Biguanides, for type 2 diabetes mellitus, 1541*t*
Bilateral primary adrenal disease, 1523
Bilateral subpulmonic pleural effusions, 525*f*
Bilateral violence, 1633
Bilateral vocal fold motion impairment, 2653
Bile, bilirubin in, 994
Bile acid diarrhea, 939, 939*b*
Bile acid sequestrants, 1413
for irritable bowel syndrome, 895*b*, 896*t*
Bile duct stones, 1054–1056. *See also* Choledocholithiasis
clinical manifestations of, 1054
complications of, 1055*b*, 1056*f*
diagnosis of, 1049.e1*f*, 1055, 1055*f*
pathobiology of, 1054
prevention of, 1056
treatment of, 1055*b*
Bile duct tumors, 1060
Bile salt, synthesis and delivery of, decreased, 933–934
Biliary and pancreatic ductal dilatation, magnetic resonance imaging of, 873*f*
Biliary cholangitis, 987
Biliary fistula, 1059
Biliary sphincterotomy, 1055*b*, 1056*f*
Biliary tract
anatomy of, 1358*f*
cystic fibrosis and, 556
Biliary tract cancers
clinical manifestations of, 1359
diagnosis of, 1360, 1360*f*
epidemiology of, 1358
pathobiology of, 1359, 1359*f*
prevention of, 1362
primary, 1357.e3*t*
prognosis of, 1362
treatment of, 1360*b*
Biliary tract disease, 996–1000, 998*f*
Bilirubin, 1429.e1*f*
acquired conjugation defects of, 997–998
in bile, 994
conjugated (direct), *e1t–e8t*
decreased uptake of, 995
excretion of, 994
genetic disorders of, 995
heme conversion to, 994
hepatic translocation of, 994
increased production of, 995
"indirect"-reacting, 994
Bilirubin *(Continued)*
liver deposition of, 994, 994.e1*f*
in liver disease, 986, 989
metabolism of, 994
plasma measurement of, 994–995
production of, 994, 994.e1*f*
total, *e1t–e8t*
unconjugated, 994
Biliverdin, 1429.e1*f*
Biliverdin reductase, 994
Binge drinking, 1609, 2353, 2543
Binge-eating disorder, 1461, 1462*b*
Binimetinib (Mektovi), 1215*t*, 1394*t*
Binocular vision loss, 2615
Bioassays, itraconazole, 2074–2075
Bioavailability, 126
Biochemical testing
for cobalamin and folate, 1122
for porphyrias, 1433–1434
Bioethics, in practice of medicine, 5–11
allocation of scarce medical resources, 9–10, 9*t*–10*t*, 10*t*
assisted suicide in, 8
euthanasia in, 8
financial conflicts of interest, 10–11
physician-patient relationship, informed consent in, 5–6
termination of medical interventions in, 6–7
Biologic agents, 149–153
adhesion molecules, 152
antibodies, 152
approved, 151*t*
B lymphocytes, 152
checkpoint molecules, 152
for chronic lymphocytic leukemia, 1269*t*
classes of, 150*t*
clinical applications of, 150*f*
complement, 152
costimulatory signals, 152
cytokines. *See* Cytokines
description of, 149–153
growth factor receptors, 152
for inflammatory bowel disease, 945*b*, 946*t*
for psoriatic arthritis, 1765*b*
specific types of, 151–153
for systemic lupus erythematosus, 1772*b*
T lymphocytes, 152
target cells, 152–153
targeted therapies as, 149
small molecule, 153
Biologic disease-modifying antirheumatic drugs, 1755*b*, 1756*t*
Biomarkers, for lysosomal storage diseases, 1419
Biopsy
for actinomycosis, 2068
for cancer of unknown primary origin, 1240
for chronic diarrhea, 930
for hepatocellular carcinoma, 1360
liver, 990
in α_1-antitrypsin deficiency, 993*f*
in hereditary hemochromatosis, 992, 993*f*
of lymph nodes, 1150
myocardial, 261
of pancreatic mass, 878*f*
of splenomegaly, 1153
Bioterrorism, 95–100
agents of concern, 96, 96*t*
epidemiologic clues to, 95–96, 96*t*
history of, 95
immunization against, 83–84
response to attack, 100
Biotin, 1453*t*
Biotin deficiency, 2541
Bipolar disorder, 2341–2342, 2341*b*–2342*b*, 2341*t*
Bipolar II disorder, 2342
Bipolar transurethral resection, for benign prostatic hyperplasia, 822*b*
Birt-Hogg-Dubé syndrome, 1363
Birthmark, 2743
Bismuth encephalopathy, 101*t*, 102*t*, 105, 105*b*
Bismuth subsalicylate
for diarrhea, 926*b*, 928
for traveler's diarrhea, 1888, 1888*t*
Bisoprolol
clinical use of, 451*t*
for heart failure, 267*t*
Bisoprolol/HCTZ, 451*t*
Bisphosphonates
for bone health, in breast cancer, 1369*b*
for esophagitis, 907*t*
for osteoporosis, 1608–1609, 1643*b*
for Paget disease of bone, 1664*b*–1665*b*, 1664*t*
Bitemporal hemianopia, 2616
Bites, 704–713
Crotalinae, 709*t*
snakebites
in Africa, 709
in Asia, 709
in Australia, 709
in Central America, 708–709
coral snake, 708, 708*b*
epidemiology of, 704–705
in Europe, 709
exotic, 710
in Mexico, 708
neurotoxic paralysis caused by, 707, 709.e1*t*
in New Guinea, 709
in North America, 708
signs of, 706*f*
in South America, 708
treatment of, in particular regions, 708–710, 708*b*
spider
envenomation of, 710
epidemiology of, 704
immunization for, 65*t*
signs of, 706*f*
viperid, 708
Bivalirudin, 387*t*, 501*t*, 503
for acute coronary syndrome, 374*t*
BK polyomavirus, 2228–2230, 2228*t*
hemorrhagic cystitis associated with, 2229, 2229*b*
nephropathy associated with, 2228–2229, 2229*b*, 2229.e1*f*
urothelial cancer associated with, 2229–2230, 2230*b*
Black Americans, 17–18
heart failure in, 254
hypertension in, 456
"Black box warning", 167
Black death, 96*t*, 1988
Black eschar, 1931, 1931*f*
Black skin, distinctive lesions in, 2744, 2744*t*
Black tar heroin, 1927
Blackheads, 2722
Bladder
neurogenic, 828
tumors of, 1362–1368
Bladder cancer, 1365–1367
clinical manifestations of, 1366
definition of, 1365
diagnosis of, 1366, 1367.e1*t*
epidemiology of, 1365
pathobiology of, 1365–1366
prevention of, 1367
prognosis of, 1367
treatment of, 1366*b*–1367*b*
Bladder diary, 829, 829.e1*f*
Bladder dysfunction, benign prostatic hyperplasia and, 822
Bladder exstrophy, 821, 821*b*
Bladder urgency, in multiple sclerosis, 2504*b*–2508*b*
Blast injury, 699*t*, 700, 700*f*
Blastic plasmacytoid dendritic cell neoplasm, 1260*t*, 1262*b*
Blastocystis hominis, 2156, 2156*t*
Blastomyces dermatitidis, 2080, 2080*f*, 2080*t*
Blastomyces spp., 2080
Blastomycosis, 2080–2081, 2080*t*, 2651
clinical manifestations of, 2080–2081
definition of, 2080
diagnosis of, 2081
disseminated infection in, 2081, 2081*f*
epidemiology of, 2080
pathobiology of, 2080
pathogen of, 2080, 2080*f*
prognosis of, 2081
pulmonary, 2080–2081
treatment of, 2081*b*
Blau syndrome, 1731*t*, 1736
Bleeding diathesis, of cyanotic congenital heart, 355.e1*f*
Bleeding disorder
alveolar hemorrhage and, 568
approach to, 1165–1170
in endoscopy, 876*t*
evaluation of, 1166–1169
history of, 1166, 1166*t*–1167*t*
laboratory screening for, 1166–1169
mechanisms of, 1165–1166
physical examination for, 1166
platelet
Bleeding disorder *(Continued)*
acquired, 1185
inherited, 1184–1185
preoperative evaluation of, 1169–1170
Bleeding score, 1166
Bleeding time, 1166, 1167
Blepharitis, 2601–2602, 2601*f*
Bloating
distention and, 859, 859*b*
gas and, 858–859
α-Blockers. *See* α-Adrenergic blockers
β-Blockers, 264*b*, 325*t*. *See also* β-Adrenergic blockers
for acute STEMI, 384*b*, 391*t*
for alcohol withdrawal, 2358*t*
for anxiety disorders, 2344*t*
for catecholaminergic polymorphic VT, 338*b*
clinical benefits of, 265*b*
clinical use of, 367*t*
for hypertension, 451*t*
mechanism of action, 265*b*
practical use of, 265*b*, 267*t*
Blocking anti-intrinsic factor antibodies, for pernicious anemia, 1123
Blood-borne viruses
health care-associated infections caused by, 1865, 1865.e1*t*
traveler exposure to, 1889
Blood-brain barrier, 2463
Blood cultures
for enteric infection, 1870*t*
for infection, 1834–1835
Blood-derived stem/progenitor cells, 172–174
Blood flow
coronary, 224
to digestive system, 959
Blood glucose concentration, abnormalities in, postoperative, 2676
Blood lipid levels, 219.e2*f*, 219–220
Blood pressure
abnormal, 34*t*
accurate measurement of, 445–447, 446*t*
aging and, 444*f*
ambulatory, 446*t*, 447, 447.e1*f*
cardiovascular disease and, 220
cardiovascular risk associated with, 444
control of
for chronic kidney disease, 839*b*
for diabetic nephropathy, 797*b*–798*b*
elevated, 35
in emergency department, 459–460
in heart failure, 257
low, 33*t*, 35, 455, 455.e1*t*
mean arterial pressure, 677*t*
measurement of, 29, 33, 461*f*
new-onset, evaluation of, 446*f*
normal range for, 32*t*
panic range for, 32*t*
stages of, 447*t*
systolic arterial pressure, 677*t*
variation
behavioral determinants of, 445
genetic determinants of, 445
Blood products, HIV transmission through, 2299
Blood-retinal barrier, 2596
Blood smears
for anemia, 1077
for malaria, 2120
Blood stream infections
central line-associated, 1862*t*, 1865–1866, 1865.e1*t*
Stenotrophomonas maltophilia and, 1975
Blood tests
for chronic diarrhea, 929–932, 929*f*
for Cushing disease, 1494
for gastrointestinal disease, 851–854
for toxicants, 690
Blood transfusion
ABO/D compatibility of, 1201
adverse effects of
allergic transfusion reaction, 1202, 1202*b*
Babesia transmission, 1203
bacterial contamination, 1203–1204
delayed hemolytic transfusion reaction, 1202–1203, 1203
delayed serologic transfusion reaction, 1202
febrile nonhemolytic transfusion reaction, 1202
hepatitis B virus transmission, 1203
hepatitis C virus transmission, 1203
human T-cell lymphotropic virus, 1203
hypotensive transfusion reactions, 1202

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Blood transfusion *(Continued)*
infectious complications of, 1203–1204
post-transfusion purpura, 1203
septic reactions, 1203
syphilis transmission, 1203
transfusion-associated circulatory overload, 1202, 1205
transfusion-associated dyspnea, 1202
transfusion-related acute lung injury, 1202, 1202*b*
Trypanosoma cruzi transmission, 1203
West Nile virus transmission, 1203
Zika virus transmission, 1203
allogeneic, 1205
autologous donation for, 1205
components of, 1199–1200, 1199*t*
directed donors, 1205
indications for, 1204–1205, 1204*t*
massive, 1205
safety of, 1201–1204, 1201*t*
for shock, 662*b*–665*b*
Blood urea nitrogen (BUN), 734
in acute kidney injury, 725
Blood volume, e8*t*–e9*t*
Bloody diarrhea, 1869*t*
Bloom syndrome, 1250*t*
BLS. *See* Basic life support
Blue nevi, 2730–2731, 2733*f*
Blue rubber bleb nevus syndrome, 969
Blunt injury, 699, 699*t*
B-lymphoblastic leukemia/lymphoma, 1260*t*
B lymphocytes, 152, 1784. *See also* B-cell(s)
BMAT. *See Brucella* microagglutination test
BMD. *See* Bone mineral density
BMI. *See* Body mass index
BMR. *See* Basal metabolic rate
Boceprevir, for hepatitis C infections, 2182*t*, 2185
Body fat, levels of, during adolescence, 110
Body fluid
osmolarity, 730–731, 732*f*
tonicity of
disorders of, 737–743
regulation of, 737–738, 737.e1*f*
Body lice, 711, 712*f*
Body mass index (BMI), 533, 1463
age and, 1582.e1*f*
of geriatric patient, 117
Body plethysmography, 530
Body temperature
abnormal, 34*t*
elevated, 34
low, 34
measurement, 33
measurement of, 29
normal, 32*t*, 34
panic range for, 32*t*
Body weight. *See also* Obesity
guidelines for management of, 63*b*
regulation of, 1464
Boerhaave syndrome, 912, 912*b*
Boils. *See* Furuncles
Bone
composition of, 803
glucocorticoids and, 145
peak mass, 1640, 1640.e1*f*–1640.e2*f*
remodeling of, 1640, 1640.e1*f*–1640.e2*f*
Bone densitometry, for celiac disease, 936*b*
Bone disorders
diffuse idiopathic skeletal hyperostosis, 1668
endosteal hyperostosis, 1666–1667, 1667*b*
fibrous dysplasia, 1668–1670, 1669*b*, 1669*f*
hereditary multiple exostoses, 1669
in HIV, 2318
hyperostosis, 1666–1668, 1666*t*
melorheostosis, 1668, 1668*b*
mixed sclerosing bone dystrophy, 1668
osteonecrosis, 1665
osteopathia striata, 1668
osteopetrosis, 1667, 1667*b*, 1668*f*
osteopoikilosis, 1668
osteosclerosis, 1665*f*, 1666, 1666*b*, 1666*t*
pachydermoperiostosis, 1667, 1667*b*
in sarcoidosis, 602, 604*t*
Bone edema, 1751
Bone infections, *Pseudomonas* infections causing, 1969, 1970*b*
Bone loss
aging-related, 1640
cause of, 1643
Bone loss *(Continued)*
drugs causing, 1641
mechanisms of, 1640–1641
secondary causes of, 1641, 1641*t*
Bone marrow
examination, for anemia, 1077
fibrosis, causes of, 1136*t*
myeloid maturation in, 1140*f*
transplantation, 1107*b*–1109*b*
Bone marrow-derived stem/progenitor cells, 172
Bone marrow failure defects, 1686
Bone marrow transplantation, for multiple myeloma, 1299*b*–1302*b*
Bone mass, regulation of, 1652*f*
Bone mineral density (BMD), 1638, 1642–1643, 1643.e1*f*–1643.e2*f*
Bone tumors, 1387–1389
chondrosarcoma, 1388, 1388*b*
clinical manifestations of, 1387–1388
diagnosis of, 1387
Ewing sarcoma, 1388, 1388*b*
metastatic, 1388–1389, 1388*b*
osteosarcoma, 1388, 1388*b*
primary, 1388
Bonferroni correction, 37
Bony osteonecrosis, 2621*t*
Boostrix (GlaxoSmithKline), 81
Borderline borderline leprosy, 2049, 2049*t*, 2049.e1*f*, 2050*f*
Borderline lepromatous leprosy, 2049, 2049*t*, 2050*f*, 2050.e1*f*
Borderline personality disorder, 2348*t*
Borderline tuberculoid leprosy, 2049, 2049*f*, 2049*t*
Bordetella ansorpii, 1994.e3*t*
Bordetella avium, 1994, 1994.e3*t*
Bordetella bronchiseptica, 1994, 1994.e3*t*
Bordetella hinzii, 1994, 1994.e3*t*
Bordetella holmesii, 1994.e3*t*
Bordetella parapertussis, 1994, 1994.e3*t*
Bordetella pertussis, 1994, 1994.e3*t*, 2649
Bordetella petrii, 1994.e3*t*
Bordetella species, 1994.e3*t*
Bordetella trematum, 1994.e3*t*
Borrelia afzelii, 2022
Borrelia burgdorferi, 1279, 2022, 2578, 2711
Borrelia duttonii, 2027
Borrelia garinii, 2022
Borrelia hermsii, 2027
Borrelia infections, relapsing fever as, 2027–2028
clinical manifestations of, 2028
definition of, 2027–2028
diagnosis of, 2028, 2028*f*
epidemiology of, 2027–2028
pathobiology of, 2028
prevention of, 2028
prognosis of, 2028
treatment for, 2028*b*
Borrelia miyamotoi, 2027
Borrelia parkeri, 2027
Borrelia turicatae, 2027
Borrelial lymphocytoma, 2024, 2024*f*
Bortezomib (Velcade), 1215*t*
for amyloidosis, 1308*b*
for multiple myeloma, 1299*b*, 1301*t*
Bosentan
for Eisenmenger syndrome, 355*b*
for Raynaud phenomenon, 473*b*
for systemic sclerosis, 1781*b*–1782*b*
Bosutinib, 1251*t*
for chronic myeloid leukemia, 1275*t*–1276*t*
Botulinum toxin, 1927
for achalasia, 908*b*
for anal fistula, 980*b*
Botulinum toxin A, for chronic pain, 138*t*
Botulism, 99, 1927–1928, 1928*b*, 2589*t*, 2592
clinical manifestations of, 99, 2592
diagnosis of, 99, 2592
immunization for, 65*t*
infant, 2571
pathobiology of, 2592
prognosis for, 99*b*, 2592*b*
treatment of, 99*b*, 2592*b*
Bourbon virus, 2065*t*
Bovine-associated vaccinia, 2238
Bowen disease, 980
Bowenoid papulosis, 2242
Box jellyfish, 712
Boyle's law, 594
BPH. *See* Benign prostatic hyperplasia
B-prolymphocytic leukemia, immunophenotype of, 1268*t*
Brachial plexopathy, 2368.e2*f*
Brachytherapy, for prostate cancer, 1385*b*–1387*b*
Bradyarrhythmias, 305, 313*b*, 318
Bradycardias, 34–35, 317–322, 317, 317*t*
acute poisoning and, 682
advanced cardiac life support response to, 316*f*
conditions associated with, 318*t*
definition of, 317–318
epidemiology of, 317
management of, 384*b*
pathobiology of, 317–318, 317.e3*f*
sinus, 319, 319*t*
Bradykinesia, 2484
Bradykinetic dysphagia, severe mental illness and, 2681*t*
Bradykinin-mediated hereditary angioedema, 1690, 1690*t*
clinical manifestations of, 1688*f*, 1690
diagnosis of, 1690–1691
epidemiology of, 1690
pathobiology of, 1690
prevention of, 1690*b*
prognosis of, 1691
treatment of, 1690*b*
BRAF inhibitors, for melanoma, 1393*b*
BRAF V600E inhibition, for colorectal cancer, 1350*b*
Brain, reward circuits, 143.e1*f*
Brain abscess, 2525–2530
clinical manifestations of, 2525
diagnosis of, 2525–2527
epidemiology of, 2525–2527
features of, 2525*t*
fungal, 2525
headache in, 2525
in immunocompromised host, 1861
magnetic resonance imaging of, 2526, 2526*f*
pathobiology of, 2525
pathogens that cause, 2526*t*
predisposing condition, 2525*t*
prognosis of, 2527
treatment of, 2526*b*
Brain death, 2437–2443, 2437*t*, 2442
clinical manifestations of, 2442–2443
diagnosis of, 2442, 2442*t*
epidemiology of, 2442
pathobiology of, 2442
tests for, 2442*t*
treatment of, 2443*b*
Brain infection, treatment of, 1970*b*
Brain malformations, 2547
Brain metastases, in melanoma, 1393*b*
Brain natriuretic peptide, 260, 403
Brain stem
abscess of, 2527*f*
blood supply to, 2458*f*
Brain stem auditory evoked responses, 2641
Brain stem dysfunction, *Mycoplasma pneumoniae* in, 2007
Brain stem encephalitis, 2531
Brain stem glioma, 1315–1316
Brain trauma, diabetes insipidus and, 1503
Brain tumors, 1310–1317
acoustic neuromas, 1312*b*
biopsy for, 1312
cerebrospinal fluid analysis of, 1312
chemotherapy for, 1313*t*
clinical manifestations of, 1310–1312, 1311*t*
diagnosis of, 1311–1312
differential diagnosis of, 1312, 1312*t*
electroencephalography of, 1312
extradural, 1318, 1318*b*
ganglioglioma, 1316
headache associated with, 1311
intra-axial, 1316
magnetic resonance imaging of, 1311, 1312*f*
medulloblastoma, 1316
meningiomas, 1313–1316
metastases, 1316–1317, 1317*b*, 1317*f*
pituitary adenomas, 1314
primary extra-axial, 1312*b*
radiation therapy for, 1312*b*
treatment of, 1312*b*
venous thromboembolism and, 1312*b*
Brainerd diarrhea, 932
Brainstem auditory evoked potentials, 2376
Brazilian purpuric fever, *H. influenzae* caused by, 1954
BRCA1- associated protein (BAP1), 1390–1391
BRCA1 mutations
in breast cancer, 1368, 1373
in ovarian cancer, 1379, 1379*t*
BRCA2 mutations
in breast cancer, 1369, 1373
in ovarian cancer, 1379, 1379*t*
Breakpoint cluster region *(BCR)* gene, 1272, 1273*f*
Breast
budding, 1591
development of, 1598, 1598*t*
female, 110.e2*f*
examination of, 30
Breast cancer, 1368–1375
adjuvant chemotherapy for, 1369*b*
anti-HER2 therapy for, 1369*b*
biologic agents for, 1369*b*
bone health in, 1369*b*
chemoprevention of, 1373
chemotherapy for, 1369*b*
clinical manifestations of, 1368
diagnosis of, 1368–1369
ductal, 1369, 1369*b*
early-stage, 1369*b*, 1370*t*–1371*t*, 1371*t*
endocrine therapy for, 1369*b*
epidemiology of, 1368–1374
hormone therapy for, 1369*b*
invasive, 1369*b*
lifestyle modification for, 1373
lobular, 1369*b*, 1370*t*
lymphedema associated with, 1369*b*
mammographic screening of, 1373–1374, 1373*t*
menopause associated with, 1630*b*–1631*b*
metastatic, 1369*b*
nutrition and, 59
pathobiology of, 1368
postmenopausal symptoms in, 1369*b*
in pregnancy, 1369*b*
prevention of, 1373–1374
preventive medications for, 56
prognosis for, 1374
prognostic and predictive markers of, 1369, 1369*t*–1370*t*
prophylactic mastectomy and oophorectomy for, 1373
radiotherapy for, 1369*b*
risk factors for, 1368*t*
screening for, 54, 1373, 1373*t*
selective estrogen receptor modifiers for, 1369*b*
stage III, 1369*b*
stage IV, 1369*b*, 1372*f*
staging of, 1369, 1369*t*
supportive care for, 1369
surgery for, 1369*b*
systemic therapy for, 1369*b*
tamoxifen for, 1369*b*
in women, 1607
Breast milk jaundice, 996
Breast pain, 1368
Breath sounds, bronchial, 512, 512*t*
Breathing
sleep-disordered, 257
spontaneous trial, 657
Brentuximab vedotin (Adcetris), 150, 1215*t*
Brief Pain Inventory, 12, 14*f*–15*f*
Brigatinib (Alunbrig), 1215*t*
Brill-Zinsser disease, 2055*t*, 2059
Brimonidine, for skin diseases, 2698
Bristol Stool Form Scale, 895*f*
Briumvi. *See* Ublituximab
Brivaracetam, for seizures, 2434*t*
Broad-spectrum antibiotic, for intestinal bacterial overgrowth, 934*b*
Brody disease, 2583.e1*t*, 2585
Bromocriptine
for hyperprolactinemia, 1491*b*–1492*b*
for neuroleptic malignant syndrome, 2681*b*
ovulation induction using, 1603*b*
for premenstrual syndrome, 1597*b*
Bronchial breath sounds, 512, 512*t*
Bronchial carcinoids, 1567
Bronchial thermoplasty, 630
Bronchiectasis, 560–562, 2327*t*
acute exacerbations of, 561*b*
anatomic causes of, 560
antimicrobial therapy for, 561*b*
central, 562*f*

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Bronchiectasis *(Continued)*
chronic obstructive pulmonary disease *versus*, 549–550
clinical manifestations of, 560
computed tomography findings of, 560, 560.e2*f*–560.e3*f*
cystic fibrosis with, 558, 558*f*
definition of, 560
diagnosis of, 560–561
diffuse, 522
distinguishing features of, 515*t*
epidemiology of, 560
"finger-in-glove" central bronchiectasis, 562*f*
genetics of, 560
imaging studies of, 560–561, 561*f*–564*f*, 561*f*, 562*f*, 563*f*, 564*f*
pathobiology of, 560
preventing exacerbations, 561*b*
prognosis for, 562
traction, 575, 575.e1*f*
treatment of, 561*b*, 562*t*
Bronchiolitis, 515*t*, 605, 2194
Bronchiolitis obliterans, 550
clinical manifestations of, 633
diagnosis of, 633
as occupational lung disease, 585*t*
pathobiology of, 633
prognosis for, 633–634
treatment for, 633*b*
Bronchiolitis obliterans organizing pneumonia of unknown cause, 578–579
Bronchioloalveolar cell carcinoma, 566*t*, 569
clinical manifestations of, 569
definition of, 569
diagnosis of, 569–570, 569.e1*f*, 570*f*
pathobiology of, 569
prognosis of, 570
treatment for, 570*b*
Bronchitis
acute, 605, 605.e1*f*, 606*b*
increased eosinophils counts in, 533
Bronchoalveolar lavage, 532–533
cellular constituents of, 533
fluid, 569.e1*f*
Bronchoconstriction, exercise-induced, 538
Bronchodilators, for cystic fibrosis, 558*b*
Bronchogenic carcinoma, 563.e1*f*
Bronchogenic cysts, 565
Bronchogenic lung cancer, 1329–1336
Bronchograms, air, 520
Bronchoscopy, 630–631
for acute interstitial pneumonia, 568
for alveolar filling disorders, 566*f*
for central airway obstruction, 630, 630*t*
for pulmonary alveolar proteinosis, 567
in surgical approach, 631
Bronzing, 1440
Brooke ileostomy, 945*b*
Brown classification, of drug reactions, 1696*t*
Brown fat, 1465
Brown-Séquard syndrome, 2386, 2404
Bruce protocol, 361
Brucella abortus, 1983
Brucella canis, 1983
Brucella endocarditis, 417*t*
Brucella melitensis, 1983
Brucella meningitis, 2515*b*
Brucella microagglutination test (BMAT), 1984
Brucella spp., 1804, 1983
Brucella suis, 1983
Brucellosis, 1983–1985
acute, 1889.e1*t*, 1984
clinical manifestations of, 1983–1984
clinical syndromes of, 1983–1984, 1984*t*
definition of, 1983–1985
diagnosis of, 1984
epidemiology of, 1983
immunity to, 1983
immunologic testing for, 1984
localized disease and complications of, 1984
pathobiology of, 1983
pathogen that causes, 1983
pathogenesis of, 1983
prevention of, 1985
prognosis of, 1985
relapsed infection of, 1985
strain-specific illness, 1983
subacute, 1984
subclinical illness of, 1983–1984
in travelers, 1891*t*
treatment of, 1984*b*, 1985*t*, 1987
Brudzinski sign, 2512
Brugada syndrome, 302–303, 303
cellular basis for, 302*f*
diagnosis of, 337–338, 338*f*
Bruns nystagmus, 2619–2620
Brush-border enzyme, mucosal malabsorption and, 934
Bruton tyrosine kinase inhibitors, 153, 1269*b*, 1284*b*
B-type natriuretic peptide (BNP), e1*t*–e8*t*
Bubonic plague, 1990*f*–1991*f*, 1990*f*, 1991, 1991*f*
Buckley-Job syndrome, 1679*t*, 1680
Budd-Chiari syndrome, 965*f*, 968, 968*b*, 986, 1170
Budesonide, 553*t*
for COVID-19, 2217
for ulcerative colitis, 945*b*, 946*t*
Budesonide MMX, for ulcerative colitis, 945*b*, 946*t*
Buerger disease, 468, 468*b*–469*b*, 469*f*, 1796
Bufadienolides, toxicity, 686*t*
Bulimia nervosa
clinical manifestations of, 1462
definition of, 1461
pathobiology of, 1461
prognosis of, 1462
treatment of, 1462*b*
weight loss and, 860*t*
Bulk-forming agents, 941*b*
Bulky Hodgkin disease, 1291*f*, 1292
Bullae, 2689*t*, 2696*f*
Bullectomy, 551*b*
Bullosis diabeticorum, 2720
Bullous impetigo, 2720, 2720*b*, 2720*f*
Bullous pemphigoid, 2689*t*, 2696*f*, 2717, 2717*b*, 2717*f*
Bumetanide, 451*t*, 737*t*
BUN. *See* Blood urea nitrogen
Bundle branch blocks, 231
diagnosis of acute MI in presence of, 383
left, 231, 231*t*, 232*f*–233*f*, 287.e1*f*
right, 231, 231*t*, 232*f*
Bundle branch re-entry, 334
Bunyavirales, 2274, 2279–2280, 2283–2284
Buprenorphine, 139*t*, 2362*b*–2363*b*
Bupropion
for depression, 2340*t*
for tobacco dependence, 2350*b*–2352*b*, 2351*t*
Burden of disease(s), global, 21*f*, 23
Burkholderia cepacia, 1972, 1972*b*
Burkholderia infections, 1972
Burkholderia mallei, 1972, 1972*b*
Burkholderia pseudomallei, 1972, 1972*b*
Burkholderia spp., cystic fibrosis and, 557
Burkitt-like acute lymphoblastic leukemia, 1262*b*
Burkitt lymphoma, 1286, 1286*b*, 2255, 2315
Burns
critical care of, 700*b*
early wound excision, 700*b*
infection, *Acinetobacter* causing, 1973
medical aspects of, 698–704
Pseudomonas infections causing, 1969
resuscitation formula, 702.e1*t*
Burosumab, for metabolic bone disease, 1639*b*
Bursae
definition of, 1804
infection of, 1804
superficial, 1804
Bursitis, 1747, 1747*b*
olecranon, 1804
septic, 1804
Bussuquara virus, 2275*t*
Busulfan, 1135*b*–1138*b*
Buthid scorpion venom, 710
Butorphanol, 136*b*, 139*t*
Bypass surgery. *See* Coronary artery bypass graft (CABG) surgery

C

C1 esterase inhibitor deficiency, 1694
C1-INH, 200*t*
C1 inhibitor deficiency, 1683, 1683*t*
C1*q* deficiency, 1683*t*
C1*r* deficiency, 1683*t*
C1*s* deficiency, 1683*t*
C2 deficiency, 1682, 1683*t*
C3 convertase, 199, 786
C3 deficiency, 1683*t*
C3 nephritic factor, 786
C3*a*, 201, 1768–1769
C3*a* receptor (C3*a*R), 202, 202*t*
C3*a*R. *See* C3*a* receptor
C4 deficiency, 1683*t*
C4*b*p (C4 binding protein), 200*t*
C5 convertase, 199
C5 deficiency, 1683*t*
C5*a*, 201
C5*a* receptor (C5*a*R), 202, 202*t*
C5*a*R. *See* C5*a* receptor
C5*b*-9, soluble, 200
C6 deficiency, 1683*t*
C7 deficiency, 1683*t*
C8 deficiency, 1683*t*
C9 deficiency, 1683*t*
Cabazitaxel (Jevtana), 1215*t*
Cabergoline
for acromegaly, 1489*b*
for Cushing syndrome, 1524*b*
ovulation induction using, 1603*b*
CABG. *See* Coronary artery bypass graft (CABG) surgery
Cabotegravir, 2301*t*
Cabozantinib, 1215*t*, 1364*b*
Cachexia
in cancer, 1239–1240, 1240*b*
cardiac, 257
management of, 13*t*
CACNA1A gene, 2376
Cadmium, e1*t*–e8*t*
Cadmium pneumonitis, 105
Cadmium toxicity, 88*t*, 104–105
chronic interstitial nephritis caused by, 794–795
clinical manifestations of, 105
diagnosis of, 101*t*, 105
epidemiology of, 104
pathobiology of, 104–105
prognosis of, 105
treatment of, 105*b*
Caffeine, e10*t*–e11*t*, 2449*t*
Caffeine halothane contracture test, 716
Calcific periarthritis, acute, 1815
Calcifications, in heart, 246, 247*f*
Calcified lesions, 2159
Calcineurin inhibitor-induced nephrotoxicity, in renal transplantation, 847
Calcineurin inhibitors, 148–149
for focal segmental glomerulosclerosis, 779*b*
for liver transplantation, 1048–1049, 1048*t*
in renal transplantation, 845*t*
for systemic lupus erythematosus, 1772*b*
Calcinosis cutis, in systemic sclerosis, 1777, 1779*f*
Calciphylaxis, 2735–2736
Calcipotriol, for skin diseases, 2698
Calcitonin, e1*t*–e8*t*
Calcitonin gene-related peptide (CGRP), 152
Calcitriol, 1650*t*–1651*t*, 1652
Calcium, 935, 937*t*
coronary artery scoring, 249, 249*f*
homeostasis of, 1652.e2*f*
intestinal actions of, 1654
ionized (iCa), e1*t*–e8*t*
metabolism of, 1652–1654
for narcolepsy, 2449*t*
for osteomalacia, 1651*t*
for osteoporosis, 1639*b*, 1643*b*
regulation of, 732, 732.e1*f*, 1652*f*
renal actions of, 1654
in sarcoidosis, 602
serum levels of, description, 1652
total, e1*t*–e8*t*
Calcium-channel blockers, 325*t*
for acute coronary syndrome, 374*t*
for acute STEMI, 384*b*
clinical use of, 452
for hypertension, 452
mechanism of action of, 452
properties of, 367*t*
for pulmonary hypertension, 496*b*–499*b*
side effects of, 452
Calcium channelopathies, 2585
Calcium channels, 300.e1*f*, 301, 305
Calcium deficiency, 288
Calcium gluconate, for arrhythmias, 313*b*
Calcium ion-sensing receptor, 817
Calcium oxalate crystals, 759–760
Calcium pyrophosphate dihydrate crystal deposition disease, 1713, 1717*t*, 1814, 1814*b*–1815*b*, 1815*f*
Calcium salt, for acute poisoning, 693*t*
Calcium-sensing receptor, 1652
Calcium stones, 803–804, 807*f*
California encephalitis virus, 2276*t*, 2283, 2284*b*
Caloric deprivation, 1430
Caloric test, 2646
Calquence. *See* Acalabrutinib
Calyceal diverticula, 819, 820*f*
Calymmatobacterium granulomatis, sexually transmitted anorectal diseases and, 983
Cameron ulcers, 916
Camitta criteria, for aplastic anemia, 1128*t*
Camptosar. *See* Irinotecan
Campylobacter concisus, 1960
Campylobacter fetus, 1960
Campylobacter hyointestinalis, 1960
Campylobacter infections, 1958–1960
clinical features of, 1959*t*
clinical manifestations of, 1959
definition of, 1958–1960
diagnosis of, 1959
differential diagnosis of, 1959
epidemiology of, 1958
gastroenteritis caused by, 1959
pathobiology of, 1958–1959
pathogen, 1958
prevention of, 1960
prognosis for, 1960
in travelers, 1889.e1*t*, 1891*t*
traveler's diarrhea caused by, 1888*t*
treatment of, 1959*b*
Campylobacter jejuni, 983, 1958
Campylobacter lari, 1960
Campylobacter upsaliensis, 1960
Camurati-Engelmann disease, 1666, 1666*b*
Canadian Association of Cardiology algorithm, 2662–2663, 2662.e1*f*
Canadian C-spine Rule, 2388, 2388*f*
Canadian Cardiovascular Society, angina grading scale, 356
Canadian Syncope Risk Score, 309*t*
Canagliflozin, for type 2 diabetes mellitus, 1541*t*
Canakinumab
description of, 151, 151*t*
for FMF, 1732*b*
for HIDS, 1734*b*
for TRAPS, 1734*b*
Canalithiasis, 2644
Canavan disease, 2510
Cancer
in adolescents, 111
anal. *See* Anal cancer
approach to, 1214–1243
biology, 1247–1252
breast. *See* Breast cancer
burden and trends, 1243
causes of death, 17
cell therapy, 175–176
cervical, 1375–1377, 1375*t*
clinical manifestations of, 1375
diagnosis of, 1375
epidemiology of, 1375, 2241
human papillomavirus and, 2241
loop electrosurgical excision procedure for, 1375*b*
pathobiology of, 1375
pelvic exenteration for, 1375*b*
prevention of, 1376
prognosis for, 1375*b*, 1377
risk factors for, 1375*t*
screening for, 1376, 1376*t*
treatment of, 1375*b*, 1376*t*
clonal evolution of, 1249–1250
colorectal. *See* Colorectal cancer
control, 1246, 1246*f*
diagnosis of, 1214–1232, 1214*t*
procedures for, 1214–1232, 1215*t*
staging and multidisciplinary evaluation for, 1232
diagnostic tests for, 1252
DNA alterations in, 1247–1250
ectopic hormone syndromes, 1237
endocrine manifestations of, 1237, 1237*t*
endometrial, 1377–1379
clinical manifestations, 1378
epidemiology, 1377
pathobiology, 1377–1378, 1377*f*, 1377*t*
prevention, 1379
prognosis, 1379
risk factors, 1377*t*
staging, 1378*t*
treatment, 1378*b*
epidemiology of, 1243–1247
fallopian tube, 1379–1381
clinical manifestations of, 1379–1380
definition of, 1379

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Cancer *(Continued)*
diagnosis of, 1379
epidemiology of, 1379, 1379*t*
pathobiology of, 1379
prevention of, 1380–1381
prognosis for, 1381, 1381*t*
risk factors for, 1379*t*
treatment of, 1380*t*–1381*t*, 1381*t*
familial cancer syndromes, 1250*t*
fever and cachexia in, 1239, 1240*b*
gene expression profiling, 1252
genetic instability of, 1249
genetics, 1247
germline DNA alterations in, 1248–1249, 1248*f*–1249*f*
global statistics, 1243, 1244*f*
hallmarks of, 1249*t*
head and neck, 1320–1328
hypercalcemia of, 1237, 1237*b*
lung. *See* Lung cancer
molecular and genetic epidemiology of, 1246
molecular diagnostics of, 166*t*
nutrition and, 58–60
obesity and, 1466
in older adults, 115
ovarian, 1379
clinical manifestations of, 1379
definition of, 1379
diagnosis of, 1379
epidemiology of, 1379, 1379*t*
pathobiology of, 1379
prevention of, 1380
prognosis for, 1381, 1381*t*
risk factors for, 1379*t*
treatment of, 1380*t*, 1381*t*
pancreactic. *See* Pancreatic cancer
prevention of, 1246–1247, 1246*f*
primary prevention of, 1246–1247
prostate. *See* Prostate cancer
of reproductive system, oral contraceptives and, 1615
risk factors of, 1243–1246
demographic factors, 1243, 1245*f*
environmental and lifestyle factors, 1244–1245
hormones, 1245–1246
ionizing radiation, 1246
secondary prevention of, 1247
somatic DNA alterations in, 1248, 1248*f*, 1249*f*
survivorship and follow-up in, 1243
systemic sclerosis and, 1780
targeted therapies for, 1250–1252, 1251*t*
therapeutic plan for, 1232*b*
thyroid. *See* Thyroid cancer
trajectories of, 12.*e1f*
treatment of, 1232*b*, 1234*t*, 1246, 1247*b*
adjuvant chemotherapy for, 1232*b*, 1234*t*
brachytherapy for, 1385*b*
combination therapy for, 1232*b*, 1234*t*
cytotoxic agents for, 1232*b*
diarrhea and, 926
epigenetic therapies for, 1232*b*
hematopoietic stem cell transplantation for, 1232*b*
hormonal therapies for, 1232*b*
immunotherapy for, 1232*b*
organ-sparing therapy for, 1232*b*, 1234*t*
targeted small molecules for, 1232*b*
tumor heterogeneity of, 1249
tumor lysis syndrome as, 1240, 1240*b*
United States statistics, 1243, 1245*f*
of unknown primary origin, 1240
biopsy and pathologic evaluation of, 1240
diagnosis of, 1240
search for, 1240, 1241*t*
treatment of, 1241*b*, 1242*t*
in women, 1607
Cancer antigen 15-3 (CA 15-3), *e1t*–*e8t*
Cancer antigen 19-9 (CA 19-9), *e1t*–*e8t*, 1356
Cancer antigen 125 (CA 125), *e1t*–*e8t*, 1379, 1591–1592
Cancer-associated venous thromboembolism, 487*b*
Cancer Genome Atlas, 167, 1377*f*
Cancer pharmacogenomics, 167
Candesartan, 451*t*
for heart failure, 266*t*
Candesartan/HCTZ, 451*t*
Candida albicans, 2089
Candida glabrata, 2089
Candida guilliermondii, 2089
Candida krusei, 2089
Candida lusitaniae, 2089
Candida parapsilosis, 2089, 2091
Candida tropicalis, 2089
Candidatus Neoehrlichia mikurensis, 2060*t*
Candidemia, 2090, 2091*f*
Candidiasis, 1882, 1882*b*, 1882*t*, 2650–2651, 2651*f*
caspofungin for, 2078
chronic disseminated, 2090, 2091*f*
chronic mucocutaneous, 2090
clinical manifestations of, 2090
definition of, 2089
diagnosis of, 2091
disseminated, 1861*f*
endophthalmitis caused by, 2091
epidemiology of, 2089
erythematous oral, 2623–2624, 2624*f*
of esophagus, 911, 912*f*
fluconazole for, 2075
hepatosplenic, 1023–1024, 1024*b*, 1024*f*, 2090
invasive, 2092
micafungin for, 2078
mucocutaneous, 2090, 2091
oral, 2320*f*, 2322*t*, 2623
oropharyngeal, 2090, 2090*f*
osteoarticular infections caused by, 2091
pathobiology of, 2089
pathogen that causes, 2089
peritonitis caused by, 2091
prevention of, 2093
prognosis for, 2093
treatment of, 2092*b*
urinary tract infections caused by, 2091
vulvovaginitis, 2090
CANDLE. *See* Chronic atypical neutrophilic dermatosis with lipodystrophy and elevated temperature
Cangrelor, 384*b*, 506*t*, 507
Canine monocytic ehrlichiosis, 2061
Canker sores, 2620, 2621*f*
Cannabidiol, for seizures, 2434*t*
Cannabinoids
for chronic pain, 136*b*
for nausea and vomiting, 863*t*
Cannabis sativa, 2364
Capecitabine (Xeloda), 1215*t*
for gallbladder cancer, 1054*b*
for gastric adenocarcinomas, 1341*b*–1342*b*
Capillaria hepatica, 1026*t*
Capillaria philippinensis, 2169, 2170*t*
Capillaritis, idiopathic pulmonary, 582
Capillary leak syndrome, 698
Capillary microcirculation, 1535
Caplacizumab, 152, 1177*b*–1178*b*
Capnocytophaga, 2068
Capnocytophaga canimorsus, characteristics of, 2270*t*
Capnometry, 640, 640.*e1f*
Caprelsa. *See* Vandetanib
CAPS. *See* Cryopyrin-associated periodic syndromes
Capsaicin, for skin diseases, 2699–2700
Capsule endoscopy, 880, 880*f*, 943, 1345
Captopril, 451*t*
for heart failure, 266*t*
for left ventricular dysfunction, 384*b*
Captopril/HCTZ, 451*t*
Caput medusae, 988*f*
CAR. *See* Chimeric antigen receptor
CAR-T cells. *See* Chimeric antigen receptor-T cells
Carbamates, toxicity, 88*t*, 686*t*
Carbamazepine, *e10t*–*e11t*
for action myoclonus, 2495*b*
for alcohol withdrawal, 2358*t*
for chronic pain, 138*t*
pharmacokinetic parameters for, 127.*e1t*
in renal failure, 129.*e1t*
for seizures, 2434*t*
toxicity, 690*t*
Carbapenem(s)
dosage of, 1895*t*
for pyogenic liver abscess, 1023*b*
toxicities of, 1901*t*
Carbapenem-resistant Enterobacterales, 1965
Carbapenem-resistant organisms, treatment of, 1966*b*–1967*b*
Carbapenemases, 1966
Carbohydrates
dietary guidelines for, 57.*e3t*
intestinal digestion and absorption of, 932.*e1f*
metabolism, disorders involving, 2586
Carbon-13 urea breath test, 918, 918*t*
Carbon-14 urea breath test, 918
Carbon dioxide
elimination of, by lung, 753–755
monitoring, 640
partial pressure (Pco_2), *e1t*–*e8t*
partial pressure of, 640
production of, 641
total (Tco_2), *e1t*–*e8t*
transcutaneous carbon dioxide measurement, 640
Carbon monoxide poisoning, 88*t*, 595–596, 596*b*, 700*b*
Carbonic acid, production of, 753
Carbonic anhydrase, 732
Carbonic anhydrase II deficiency, 816*t*, 1667
Carboplatin (Paraplatin), 1215*t*
Carboxyhemoglobin, toxicity, *e1t*–*e8t*, 690*t*
Carcinoembryonic antigen (CEA), *e1t*–*e8t*, 1360
Carcinogenesis
alcohol use disorders and, 2354
environmental, 1321
viral, 1321–1322
Carcinogens
of bladder cancer, 1365
environmental, 1321
Carcinoid heart disease, 1567
Carcinoid syndrome, 296, 1561*t*, 1567–1568
clinical manifestations of, 1567–1568
diagnosis of, 1567–1568
distinguishing features of, 515*t*
epidemiology of, 296
pathobiology of, 296
prognosis for, 296*b*
treatment of, 296*b*, 1568*b*
Carcinoid tumors, 1336
Carcinoma. *See also* Adenocarcinoma
bronchioloalveolar cell, 566*t*, 569
hepatocellular, 992*f*. *See also* Hepatocellular carcinoma
poorly differentiated, diagnosis of, 1241*t*
porphyrias and, 1432
renal cell, 1362–1365
squamous cell, of anus, 982
Carcinomatosis, peritoneal, treatment of, 1241*b*
Carcinomatous polyarthritis, 1823
Cardenolides, toxicity, 686*t*
Cardiac action potential, 223, 223*f*, 299, 299*f*, 333.*e1f*
Cardiac amyloidosis, 249, 249.*e2f*
Cardiac arrest, 312
AED rapid response to, 314*t*
bradycardic or asystolic, 316*f*
clinical manifestations of, 312–313
diagnosis of, 312
electrical mechanisms associated with, 313*f*
epidemiology of, 312–317
incidence of, 312
out-of-hospital, causes of, 313*t*
pathobiology of, 312
prognosis for, 316–317
sudden, 312
tachyarrhythmic, 313*b*
treatment of, 313*b*
Cardiac arrhythmias, 301
Cardiac cachexia, 257
Cardiac catheterization
for cardiovascular disease, 218
complications of, 393–395, 394*t*
contraindications to, 393, 394*t*
for mitral stenosis evaluation, 405
procedures performed in, 393.*e3t*
right-sided, in cardiogenic shock, 667
Cardiac cavities, extension of tumor into, 298
Cardiac cycle, 225, 225.*e1f*
filling phase, 225
pressure-volume loop, 225
Cardiac disease, in pregnancy, 1619*t*
Cardiac energetics, 225
Cardiac function, 223–227
Cardiac imaging
computed tomography, 249–251
echocardiography, 235–241
Cardiac imaging *(Continued)*
noninvasive, 244–254
radiography of, 244–247
stress MRI, 362–363
Cardiac implantable electronic devices, 340–345
Cardiac index, 677*t*
Cardiac inspection, 213–214
Cardiac masses
CMR imaging of, 252
echocardiographic findings, 242*t*
Cardiac output, 226, 677*t*
Cardiac resynchronization therapy (CRT), 265*b*, 344–345
complications of, 345
indications for, 345, 345*t*
Cardiac risk assessment, 2661–2664, 2662*t*, 2663*f*
Cardiac sarcoidosis, 249, 602, 603*b*–604*b*, 604*t*
Cardiac silhouette, 247
Cardiac syncope, 309*b*–311*b*
Cardiac syphilis, 2019
Cardiac tamponade
at cardiac catheterization, 429
echocardiography for, 426–427, 429*f*
treatment of, 427*b*–428*b*
Cardiac testing, noninvasive, 220–221
Cardiac toxicity, after hematopoietic cell transplantation, 1211
Cardiac transplantation, 265*b*
contraindication criteria for, 274*t*
heart-lung transplantation, 633
heart transplantation, 274*t*
Cardiac troponins, measured by a highly sensitive assay, 260.*e1t*
Cardiac tumors, 242*t*, 296–298, 297*f*, 297*t*
Cardioactive steroids, toxicity, 686*t*
Cardiogenic shock, 658–659, 659, 659*f*, 661*t*, 665–669
causes of, 666*t*
clinical manifestations of, 666, 666*f*, 667*t*
definition of, 665–669, 665*t*
diagnosis of, 665*t*, 666–667
epidemiology of, 665–666, 666*f*
inotropes for, 667*b*
management of, 384*b*
initial, 667*b*, 668*f*
vasopressors for, 667*b*
pathobiology of, 666
prognosis for, 669
Cardiology, nuclear, 247–249
in coronary artery disease, 362
in heart failure, 261
Cardiomyocytes, 224.*e1f*
Cardiomyopathy, 251–252, 253*f*
alcoholic, 287, 2355
arrhythmogenic right ventricular, 288, 337, 338*f*
causes of, 279.*e3t*
Chagas, 2127, 2127.*e1f*
chronic ischemic, 336*f*–337*f*
cirrhotic, 1037
classification of, 280*f*
CMR findings, 252
definition of, 279
dilated. *See* Dilated cardiomyopathy
genetic, causes of, 279.*e3t*
genetically inherited, 337
in HIV, 2317
Hodgkin lymphoma and, 1292*b*
hypertrophic, 279–284, 279.*e3t*, 337
apical, 281.*e1f*
echocardiographic findings, 242*t*
progressive, 281.*e2f*
hypertrophic obstructive, 282*f*
laboratory evaluation of, 287*t*
nonischemic dilated, 336–337
peripartum, 288, 1621–1622, 1622*b*, 1622*f*
psychotropic medications and, 2678*t*
rapidly reversing, 337
restrictive, 291–292
constrictive pericarditis *versus*, 429.*e1f*, 432*f*
differential diagnosis of, 433*t*
echocardiographic findings, 242*t*
overlap with dilated cardiomyopathy, 288
takotsubo (stress-induced), 294, 295*b*, 665
unclassified, 294–295
Cardiopulmonary arrest
electrical injury and, 703
lightning injury and, 704
Cardiopulmonary exercise tests, 532

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Cardiopulmonary resuscitation (CPR), after cardiac arrest, 313*b*
Cardiothoracic ratio, 244–245, 244*f*
Cardiotoxicity, psychotropic medications and, 2678*t*
Cardiovascular disease
  approach to, 210–218, 218
  atherosclerotic, 221.*e1f*
  autosomal dominant polycystic kidney disease and, 811
  in chronic kidney disease, 836
  complete medical history of, 212
  dialysis-associated, 842
  epidemiology of, 219–222
  future of, 221–222
  gene therapy for, 175
  global burden of, 219.*e2f*, 219
  hospitalization due to, 219
  hypertension and, 447, 448*t*
  laboratory studies, 216–218
  medical costs related to, 219
  molecular diagnostics and, 166*t*
  physical examination for signs, 212–218
  preoperative evaluation of, 2661, 2662*t*
  prevention of, 221
  rate of death due to, 219
  risk assessment, lifetime risk estimation, 221
  risk factors for, 219–222
    blood pressure, 439
    established, 219–220
    novel markers, 220–221
    screening for, 53
    short-term, 221
  in septic shock, 671–672
    clinical manifestations of, 672
    diagnosis of, 672–673, 673*f*
  severe mental illness and, 2677
  symptoms of, 212, 213*f*, 213*t*
    cardinal, 211*t*
    detection of, 210–212, 210*t*–211*t*
  US burden, 219
  in women, 1606–1607
Cardiovascular health, new paradigm for, 221, 222*t*
Cardiovascular magnetic resonance imaging (CMR), 251–253, 251*f*–252*f*
Cardiovascular risk, menopause associated with, 1632
Cardiovascular support, endocrine responses relevant to, 671
Cardiovascular syphilis, 2017, 2020*b*
Cardiovascular system
  age-related changes in, 121
  alcohol use disorders and, 2355, 2355*t*
  glucocorticoids and, 145
  metabolic regulation of, 224–225
  responses to stressors, 226, 226.*e1f*
  systemic lupus erythematosus manifestations of, 1769–1770
Cardioversion, transthoracic, 340
Caregivers, in heart failure management, 275*t*
Carfilzomib (Kyprolis), 1215*t*
Caribbean, HIV/AIDS in, 2289, 2289.*e4f*
Carney complex, 1487*t*, 1523, 1558, 1559*t*
Carnitine metabolism, disorders of, 1552*t*, 1555
Carnitine palmitoyltransferase I deficiency, 2586
Carnitine palmitoyltransferase II deficiency, 2586
Caroli disease, 990
β-Carotene, *e1t*–*e8t*, 59
Carotid body hypersensitivity, 306
Carotid duplex ultrasonography, 2468
Carotid endarterectomy, 2473
Carotid pulse, 30, 213, 215*f*
Carotid sinus massage, 324*b*
Carotid stenosis, 2473
Carpal tunnel syndrome, 1751, 1753*f*, 1779, 2579, 2579*b*
Carrier detection, for hemophilia, 1190–1191
Carrión disease, Oroya fever and, 2000–2001
Carteolol, 451*t*
Cartilage-hair hypoplasia, 1679*t*, 1680, 1680*b*
Cartilage-pannus junction, 1751
Carvajal syndrome, 288
Carvallo sign, 355
Carvedilol, 451*t*
  for acute STEMI, 384*b*, 391*t*
  for heart failure, 264*b*, 267*t*
Carvedilol phosphate, 451*t*
Case-control studies, 41
Case-mix adjustment methods, 41
Casirivimab/imdevimab, for coronavirus infections, 2191
Casodex. *See* Bicalutamide
Caspofungin
  adverse effects of, 2078
  drug interactions of, 2078
  formulations and pharmacology of, 2078
  for hepatosplenic candidiasis, 1024*b*
  indications and dosage of, 2075*t*, 2078
Cassava tubers (Konzo), 2541*t*
Cast nephropathy, in multiple myeloma, 794
Castleman disease, 1288, 1288*b*
Castration-resistant prostate cancer, 1385*b*
Casts, of urine, 722–724
Cat-scratch disease, 2001, 2003*b*, 2003*t*
Catabolism, 1429.*e1f*
Catalase, 196
Catamenial anaphylaxis, 1693
Cataract, 2606–2607
  congenital, 2612
  traumatic, 2604
Catastrophic antiphospholipid syndrome, 1770
Catathrenia, 2453*t*
Catatonia
  psychotropic medications and, 2681
  treatment for, 2681*b*
CATCH-22 syndromes, 347–348
Catecholamine(s), *e1t*–*e8t*, 1529, 1530.*e1f*
  half-life of, 1529
  synthesis of, 1529
  tyrosine synthesis of, 1529
Catecholamine-secreting tumors, 1529
  clinical manifestations of, 1530–1531
  complications of, 1533*b*
  definition of, 1529
  diagnosis of, 1531–1532, 1531*f*
  differential diagnosis of, 1531
  epidemiology of, 1530
  genetics of, 1530
  medical therapy for, 1533*b*
  pathobiology of, 1530
  signs and symptoms of, 1530*t*
  surgical therapy for, 1533*b*
  treatment of, 1533*b*
Catechol-*O* methyltransferase (COMT), 132*t*
Catheter ablation, 345–346, 345.*e1f*
  for atrial fibrillation, 329*b*, 346
  of supraventricular tachycardias, 346
  of ventricular arrhythmias, 346
  for ventricular tachycardia, 338*b*
Catheter-associated urinary tract infections, 1862*t*, 1866, 1873
Catheter-based adrenal ablation, for primary aldosteronism, 448*b*
Catheterization, cardiac
  for cardiovascular disease, 218
  complications of, 393, 394*t*
  contraindications to, 393, 394*t*
  for mitral stenosis evaluation, 405
  procedures performed in, 393.*e3t*
  right-sided, in cardiogenic shock, 667
Catheters, balloon angioplasty, 395, 395*f*
Cationic proteins, 183
Cationic trypsinogen gene *(PRSS1)*, mutations in, 970
Caucasian populations, cystic fibrosis in, 556
Cauda equina syndrome, 2402
Caudalization, 522
Causality, 37
Caustic injury, of esophagus, 907–908
Cavernous hemangioma, 2731
Cavernous sinus thrombosis, septic, 2528–2529
Cavitary disease, chronic, 2095
Cavitary lung diseases, 563–564, 564*b*, 564*t*
Cavitary tuberculosis, 2036*f*
Caya, 1611–1612
C-C chemokine receptor 2, 2089
CCKoma, 1561*t*, 1566
CCR5, 2291
CD4 cells, in opportunistic infections, 2306, 2306*f*
CD4 helper T (TH) cells, 2499
CD4+ T cells, 203–204, 204*t*
  depletion of, 2292–2293, 2292*f*
  micrographs of, 889.*e1f*
CD8+ T cells, 203, 204*t*
  micrographs of, 889.*e1f*
$CD8^+$T-cell-mediated hypersensitivity reaction, 2726
CD20, 152
$CD30^+$ anaplastic T-cell lymphoma, 2734
CD30+ cutaneous lymphoproliferative disorders, 1286
CD35, 200*t*
CD40 deficiency, 1681*t*
CD46, 200*t*
CD55, 200*t*
CD59, 200*t*
CD88, 202
CD207, 1154
CDC. *See* Centers for Disease Control and Prevention
CDKN2A, 1391
CEA. *See* Carcinoembryonic antigen
Cecal neuroendocrine neoplasms, 1566
Cefaclor, dosage of, 1895*t*
Cefadroxil, dosage of, 1895*t*
Cefazolin
  dosage of, 1895*t*
  for endocarditis, 422–423
Cefdinir, dosage of, 1895*t*
Cefditoren pivoxil, dosage of, 1895*t*
Cefepime
  for bacterial meningitis, 2518*t*
  dosage of, 1895*t*
  for pneumonia, 613*t*
  for pyelonephritis and urosepsis, 1877*t*
Cefiderocol, 1845*t*, 1970*b*
  Acinetobacter, 1974*b*
  dosage of, 1895*t*
Cefixime
  dosage of, 1895*t*
  for urinary tract infection, 1876*t*, 1877*t*
Cefotaxime
  for bacterial meningitis, 2518*t*
  dosage of, 1895*t*
  for *H. influenzae* infections, 1954*b*
  for meningococcal meningitis and meningococcemia, 1944*t*
  for pyelonephritis and urosepsis, 1877*t*
Cefotetan, for pelvic inflammatory disease, 1883*t*
Cefoxitin
  dosage of, 1895*t*
  for nontuberculous mycobacterial disease, 2046*t*
  for pelvic inflammatory disease, 1883*t*
Cefpodoxime proxetil
  for cystitis, 1876*t*
  dosage of, 1895*t*
Cefprozil, dosage of, 1895*t*
Ceftaroline
  for bacterial meningitis, 2518*t*
  dosage of, 1895*t*
  for pneumonia, 613*t*
  for *Streptococcus pneumoniae* pulmonary infections, 1912.*e1t*
Ceftazidime
  for bacterial meningitis, 2518*t*
  dosage of, 1895*t*
  for pneumonia, 613*t*
  for pyelonephritis and urosepsis, 1877*t*
  for *Stenotrophomonas maltophilia*, 1975*b*, 1976*t*
Ceftazidime-avibactam, dosage of, 1895*t*
Ceftibuten
  dosage of, 1895*t*
  for urinary tract infection, 1876*t*, 1877*t*
Ceftizoxime, dosage of, 1895*t*
Ceftolozane-tazobactam, dosage of, 1895*t*
Ceftriaxone
  for bacterial meningitis, 2518*t*
  disseminated gonococcal infection and, 1950*b*
  dosage of, 1895*t*
  for endocarditis, 419*t*
  for enteric fever, 1977
  for gonorrhea, 1948*b*
  for *H. influenzae* infections, 1954*b*
  for leptospirosis, 2031*b*
  for Lyme disease, 2026*t*
  for meningococcal disease, 1945*t*
  for meningococcal meningitis and meningococcemia, 1944*t*
  for pelvic inflammatory disease, 1883*t*
  for pneumonia, 613*t*
  for pyelonephritis and urosepsis, 1877*t*
  for *Streptococcus pneumoniae* pulmonary infections, 1912.*e1t*
  for urethritis, 1880*t*
  for Whipple disease, 2070*b*–2071*b*
Cefuroxime, dosage of, 1895*t*
Cefuroxime axetil
  dosage of, 1895*t*
  for Lyme disease, 2026*t*
  for urinary tract infection, 1876*t*, 1877*t*
Celecoxib
  for chronic pain, 138*t*
  for rheumatoid arthritis, 1756*t*
Celiac artery compression syndrome, 967, 967*f*
Celiac disease, 935, 1821
  clinical manifestations of, 935–936
  definition and epidemiology of, 935
  diagnosis of, 936, 936*f*
  osteomalacia and, 1649
  pathobiology of, 935
  prognosis of, 936–937
  treatment of, 936*b*
Cell-bound receptors, for immunoglobulin, 192
Cell count, in bacterial meningitis, 2514
Cell-free DNA, 1252
Cell therapy, 169–174
  definition of, 169–174
  for diabetes mellitus, 174
  disease application for, 174
  in mRNA anti-tumor vaccines, 177–178
  for neurodegenerative disorders, 174
  regenerative medicine approaches, 172–174, 173*f*
Cellular damage, in acute kidney injury, 773
Cellular immunity, in systemic sclerosis, 1776
Cellular mediators, 205
Cellular responses, 196
Cellulitis, 2739, 2740*f*
  Acinetobacter baumannii causing, 1973, 1974*f*
  H. influenzae causing, 1953
  Staphylococcus aureus causing, 1903
  Streptococcus pyogenes causing, 1915
Centers for Disease Control and Prevention (CDC), 41.*e1t*
  PulseNet, 1937
Centers for Medicare and Medicaid Services (CMS), 41.*e1t*, 44
Centipedes, 711
Central adiposity, 1629
Central Africa, HIV/AIDS in, 2289, 2289.*e1f*
Central Asia, HIV/AIDS in, 2289, 2289.*e2f*–2289.*e3f*
Central brain-gut neuromodulators, for irritable bowel syndrome, 895*b*, 896*t*
Central centrifugal cicatricial alopecia, 2751, 2751*f*
Central congenital hypoventilation syndrome, 534–536
  clinical manifestations of, 536
  definition of, 534
  epidemiology of, 534
  in hypercapnic disease, 535*t*
  pathobiology of, 534–536
  treatment of, 536*b*
Central cord syndrome, 2386, 2403
Central diabetes insipidus, 743
  clinical manifestations of, 1501, 1502*f*
  diagnosis of, 1502–1503
  pathobiology of, 1500
  treatment of, 1503*b*
Central Europe, HIV/AIDS in, 2289–2290, 2289.*e4f*, 2290.*e1f*
Central hearing disorders, 2641
Central hearing loss, 2642
Central hypothyroidism, 1497, 1497*b*
Central line-associated blood stream infections, 1862*t*, 1865, 1865.*e1t*
Central line bundle, 1866
Central nervous system (CNS)
  altered, irritable bowel syndrome and, 893
  brain tumors. *See* Brain tumors
  cobalamin deficiency of, 1124–1125
  glucocorticoids and, 145–146
  rhythms, 1478
  stimulants of, 2363
  toxicants and, 683
  tuberculosis, 2037
  tumors, 1310–1319, 1311*t*
  vasculitis, 1799–1800, 1800*t*
Central nervous system (CNS) infections
  actinomycosis and, 2068
  anaerobic bacteria causing, 1938
  cryptococcosis causing, 2087, 2088*b*
  enteroviruses causing, 2258–2259
  involvement, 2221
  nocardiosis and, 2073
  Pseudomonas infections causing, 1969
  Staphylococcus aureus causing, 1904
  subacute sclerosing panencephalitis, 2221
Central nervous system (CNS) lymphoma, 2255
  primary, 1316, 1316*b*, 1316*f*
Central neurogenic hyperventilation, 2438, 2439*t*
Central precocious puberty, 1481, 1582
Central retinal artery
  anatomy of, 2614
  occlusion, 2610, 2610*f*

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Central retinal vein occlusion, 2610, 2610*f*
Central sensitization, 134, 1816
Central sleep apnea, 534, 534*t*–535*t*, 2448, 2448.*e2f*
Central sympatholytics
  clinical use of, 455
  for hypertension, 455
  mechanism of action of, 455
  side effects of, 453*t*, 455
Central tendency, 36
Central venous catheter, in parenteral nutrition, 1450
Central venous pressure, 677*t*
Central venous thrombosis, in parenteral nutrition, 1450
Central vertigo, 2644
Centralization, 522
Centralized pain, 1816, 1817*t*
Centronuclear myopathy, 2585.*e1f*
CEP. *See* Congenital erythropoietic porphyria
Cephalexin
  for cellulitis, 2740*b*
  dosage of, 1895*t*
  for urinary tract infection, 1877*t*
Cephalic tetanus, 1928–1929
Cephalization, 522
Cephalosporins
  for bacterial meningitis, 2518*t*
  for chancroid, 1951*b*
  dosage of, 1895*t*
  for enteric fever, 1977
  for listeriosis, 1938*b*
  for *Moraxella catarrhalis* infections, 1955*b*
  toxicities of, 1901*t*
  for yersiniosis, 1994*b*
Cephradine, dosage of, 1895*t*
Cerebellar ataxia, 2373*t*, 2497, 2497*b*, 2497*t*
Cerebellar degeneration, 2544
Cerebellar hemorrhage, 2479
Cerebellopontine angle tumors, 2646
Cerebellum, infarction of, 2645–2646
Cerebral adrenoleukodystrophy, 1528
Cerebral amyloid angiopathy, 2419, 2478–2479
Cerebral aneurysms, 2476*f*
  autosomal dominant polycystic kidney disease and, 812
  description of, 2463
Cerebral arteries, 2465
Cerebral artery occlusion, 2465
Cerebral autosomal dominant arteriopathy with subcortical infarcts and leukoencephalopathy, 2419, 2472
Cerebral blood flow, 2459–2461
Cerebral edema, 2463–2464, 2464, 2511
  high-altitude, 592, 592*t*
Cerebral embolization, 2530
Cerebral hemorrhage, 2463
Cerebral infarct, 2530
Cerebral ischemia, 2462–2463
Cerebral malaria, 2120
Cerebral microbleeds, 2479*f*
Cerebral mucormycosis, 2099
Cerebral palsy, 2547, 2548*b*
Cerebral salt wasting, 739
Cerebral schistosomiasis, 2164
Cerebral venous thrombosis
  stroke caused by, 2471
  virally mediated, 2530
Cerebrospinal fluid (CSF)
  enteroviruses in, 2257–2258
  examination
    in bacterial meningitis, 2513, 2513*t*
    for cryptococcal meningitis, 2088
    for infection, 2110–2111
    lumbar puncture for, 2374, 2374*f*, 2374*t*
    in multiple sclerosis, 2503–2504
  in TB meningitis, 2040
Cerebrovascular diseases
  anatomy of
    anterior cerebral arteries, 2456, 2458*f*
    anterior choroidal artery, 2457, 2459*f*
    aortic arch, 2454, 2455*f*
    basilar artery, 2456
    circle of Willis, 2455.*e1f*, 2456
    external carotid arteries, 2455
    internal carotid arteries, 2455, 2456*f*
    middle cerebral artery, 2457, 2459*f*–2460*f*, 2460*f*
    posterior cerebral artery, 2457–2459
    venous system, 2459, 2461*f*–2462*f*
Cerebrovascular diseases *(Continued)*
    vertebral arteries, 2455–2456, 2457*f*
  approach to, 2454–2463
  blood-brain barrier, 2461
  cerebral ischemia, 2462
  cognitive impairment caused by
    clinical manifestations of, 2419
    definition of, 2417
    diagnosis of, 2419, 2419*t*
    epidemiology of, 2417–2418
    magnetic resonance imaging of, 2419*f*
    pathobiology of, 2418–2419
    prognosis for, 2420
    risk factors for, 2418
    treatment of, 2420*b*
  definition of, 2454–2461
  epidemiology of, 2454
  ischemic, 2464–2474
    clinical manifestations of, 2465–2466, 2465*t*
    diagnosis of, 2466–2469, 2466*f*
    differential diagnosis of, 2469
    epidemiology of, 2464
    pathobiology of, 2464
  neurovascular unit, 2461
  in older adults, 115
  pathobiology of, 2454–2461
  physiology of, 2459–2461
Cerebrovascular syncope, 306
Cerebrovascular syndrome, 93
Ceroid-lipofuscinoses, neuronal, 1420*t*, 1424
Certolizumab (Cimzia)
  for rheumatoid arthritis, 1756*t*
  for total knee arthroplasty, 1830.*e1t*
Certolizumab pegol
  description of, 151*t*
  for inflammatory bowel disease, 945*b*, 946*t*
Ceruloplasmin, *e1t*–*e8t*, 1436
Cerumen, impacted, 2641
Cervarix, 2243
Cervical adenopathy, treatment of, 1241*b*
Cervical artery dissection, 2470.*e1t*, 2471–2472
Cervical buboes, 1991
Cervical cancer, 1375, 1375*t*
  clinical manifestations of, 1375
  diagnosis of, 1375
  epidemiology of, 1375, 2241
  in HIV, 2316*b*
  human papillomavirus and, 1607, 2241, 2305–2306
  loop electrosurgical excision procedure for, 1375*b*
  oral contraceptives and, 1615
  pathobiology of, 1375
  pelvic exenteration for, 1375*b*
  prevention of, 1376
  prognosis for, 1375*b*, 1377
  risk factors for, 1375*t*
  screening for, 54, 112, 1376, 1376*t*
  treatment of, 1375*b*, 1376*t*
Cervical intraepithelial neoplasia, 1615, 2240, 2244
Cervical lymph nodes, nontuberculous mycobacteria causing, 2045
Cervical mediastinoscopy, 1331
Cervical mucus, in menstrual cycle, 1595
Cervical myelopathy, 2564*t*
Cervical neoplasia, organisms causing, 1879*t*
Cervical radiculopathy, 2394*t*, 2402–2403
Cervical spine, stenosis of, 2398*b*
Cervical spondylotic myelopathy, 2399–2401, 2401*b*, 2404*f*
Cervical squamous intraepithelial lesions, 2242–2243
Cervical vertebrae, 2392
Cervicitis, 1948
  characteristics of, 1883
  Chlamydia trachomatis causing, 2011
  clinical manifestations of, 1948, 1948*f*
  diagnosis of, 1948–1949, 1949
  organisms causing, 1879*t*
  treatment of, 1883*b*
Cervicofacial actinomycosis, 2067, 2067*f*
Cervix, menstrual cycle-related changes in, 1595
Cestodes, 2157
  cystic hydatid disease, 2161, 2161*b*, 2162*f*
  definition of, 2157
  Diphyllobothrium sp., 2157
  Dipylidium caninum, 2158, 2158*b*, 2158*t*
  Hymenolepis nana, 2157, 2158, 2158*b*
Cestodes *(Continued)*
  pathogens associated with, 2157
  Taenia asiatica, 2158*t*, 2159
  Taenia solium, 2158*t*, 2159, 2159*b*
Cetirizine, for mastocytosis, 1703*b*–1704*b*
Cetuximab (Erbitux), 1215*t*, 1251*t*
  for head and neck cancer, 1327*b*–1328*b*
CFTR. *See* Cystic fibrosis transmembrane conductance regulator
CFTR correctors, for cystic fibrosis, 558*b*
CFU. *See* Colony forming units
CGRP. *See* Calcitonin gene-related peptide
Chagas cardiomyopathy, 255, 2127, 2127.*e1f*
Chagas disease, 1203, 2065*t*, 2116, 2126–2130
  acute, 2127
  chronic, 2127
  clinical manifestations of, 2127–2128, 2127*t*
  constipation caused by, 890
  diagnosis of, 2127*t*, 2128, 2129*f*
  endemic, 2126
  epidemiology of, 2126
  infective myocarditis caused by, 284
  pathobiology of, 2126–2127, 2127*f*, 2127.*e1f*
  pathogen of, 2126
  prevention of, 2128
  prognosis of, 2129, 2129*t*
  symptomatic, management of, 2128*b*
  treatment of, 2128*b*
  in United States, 2126
  ventricular tachycardia in, 336–337
Chagoma, 2127
Chalazion, 2601, 2601*f*
Chamber hypertrophy, 233, 234*f*
Chancre, syphilitic, 1881, 2015
Chancroid, 1950–1952
  characteristics of, 1881
  clinical manifestations of, 1951, 1951*f*–1952*f*, 1952*f*
  definition of, 1950–1952
  diagnosis of, 1951
  epidemiology of, 1950–1951
  organisms causing, 1879*t*
  pathobiology of, 1951
  prevention of, 1952
  prognosis of, 1951–1952
  treatment of, 1881*b*, 1951*b*
Change, levers for, 44
Channelopathies
  description of, 2583.*e1t*
  genetically inherited, 333
Chapare virus, 2265*t*
Chaperones, 28–29
CHAPLE syndrome, 939
Charcot joint, 1822
Charcot-Leyden crystals, 2170
Charcot-Marie-Tooth disease, 2368.*e3f*, 2568–2570, 2570*b*, 2570*f*
Check for Safety: A Home Fall Prevention Checklist for Older Adults, 118
Checkpoint molecules, 152
Chédiak-Higashi syndrome, 1145, 1185, 1683, 1683.*e1t*, 1684*t*
Cheilitis, 943
Chelation therapy, for chronic poisoning of trace metals, 103*b*
Chemical injuries, to lung, 591–599
"Chemical" meningitis, 2515
Chemical peels, 2701
Chemical poisoning, industrial and agricultural, characteristics of, 2270*t*
Chemoimmunotherapy, for chronic lymphocytic leukemia, 1269*b*
Chemokine receptors, 184–185
Chemokines, hematopoiesis regulated by, 1065
Chemoprophylaxis, for common cold, 2193
Chemoradiotherapy, for anal cancer, 983*b*
Chemoreceptor proteins, 2639
Chemotherapy
  for brain metastases, 1317*b*
  for brain tumors, 1313*t*
  for breast cancer, 1369*b*
  for chronic lymphocytic leukemia, 1269*t*
  for cystic echinococcosis, 2161*b*
  for diffuse large B-cell lymphoma, 1285*b*
  for disseminated disease, 1383*b*, 1383*t*
  for esophagitis, 907*t*
  for Ewing sarcoma, 1388*b*
  neutropenia after, 1147*b*
  neutropenia induced by, 1854*t*
  reactions to, 1698
Chemotherapy *(Continued)*
  for schistosomiasis, 2165
  side effects of, 291
  ulcers associated with, 917
Chemotherapy-related myelodysplasia, Hodgkin lymphoma and, 1292*b*
Cherry hemangioma, 2731
Chest
  examination of, 30
  flail, 621–622, 621.*e1f*, 622*b*
  images of, evaluation of, 520–526
  injuries to, 700*b*
Chest pain, 210, 211*t*, 256–257, 394–395
  acute, 210
  cause of, 211*t*
  esophageal disease and, 902
  functional, 900–901
    clinical manifestations of, 900
    definition of, 900
    diagnosis of, 900
    differential diagnosis of, 901*t*
    epidemiology and pathobiology of, 900
    prognosis of, 901
    Rome IV diagnostic criteria for, 900*t*
    treatment of, 901*b*
  postoperative, 2673, 2673*t*
  recurrent, management of, 384*b*
  severe mental illness and, 2683*t*
Chest physical therapy, for viscid mucus, 558*b*
Chest radiography, 259, 358, 519
  of acute respiratory failure, 645, 645.*e1f*, 646*f*
  of apical lung disease, 524*f*
  of basal pulmonary disease, 524*f*
  of bilateral alveolar opacities
    with acute interstitial pneumonia, 568.*e1f*
    with diffuse alveolar hemorrhage, 568.*e1f*
  of bronchiectasis, 558*f*
  cardiac silhouette, 247
  of COVID-19, 520.*e1f*–520.*e2f*
  of cystic bronchiectasis, 557*f*–558*f*
  of cystic fibrosis with pulmonary hypertension and cor pulmonale, 558.*e1f*
  of diffuse alveolar damage, 520*f*
  of diffuse reticular lung disease, 522*f*
  double density sign, 245, 245*f*
  gooseneck sign, 247
  with implanted devices, 246
  in interstitial lung disease, 573–574, 573*t*
  of known transfusion reaction, 522*f*
  of left ventricular failure, 523*f*
  mediastinal findings on, 526–527, 526*f*–527*f*, 527*f*
  of multifocal pulmonary opacities, 524*f*
  of pleural effusion, 624, 624*f*
  pruned-tree sign, 246*f*
  of pulmonary alveolar proteinosis, 567, 567*f*
  of pulmonary arterial hypertension, 523*f*
  of pulmonary edema, 521*f*
  reversed figure-of-3 signs, 247
  scimitar sign, 247, 247.*e1f*
  of severe emphysema, 523*f*
  for signs of cardiovascular disease, 217
  of silicosis, 591*f*
  water-bottle sign, 245, 246*f*
Chest wall
  disorders of, 619*t*, 620–623
  imaging of, 519–527
Cheyne-Stokes breathing, 534, 534*b*, 534*t*, 2438, 2439*t*, 2448, 2448.*e1f*
Chiari I malformation, 2546, 2546*f*
Chiari II malformation, 2546
Chiari malformation, 2546, 2546*b*, 2546*f*
Chickenpox. *See also* Varicella
  immunization for, 65*t*, 82
  prophylaxis for, 2309*t*
Chigger mites, 711
Chikungunya virus, 1807, 2275*t*, 2278, 2278*b*, 2278.*e1f*
  in travelers, 1888, 1889.*e1t*, 1890*t*
Chilblains, 680, 1735
Childbirth, *Paeniclostridium sordellii* associated with, 1927
Children
  absence epilepsy in, 2432
  bacterial meningitis in, 2511
  cryptosporidiosis in, 2143
  histiocytosis X in, 2731
  meningococcal disease in, 1941
  obesity in, 1463–1464
  ovarian function in, 1591–1592

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Children *(Continued)*
primary malnutrition in, 1445*b*
recurrent parotitis in, 2626
reproductive axis development in, 1581–1582
Chills, caused by amphotericin B, 2078
Chimera, 162
Chimeric antigen receptor (CAR), 3, 207
Chimeric antigen receptor (CAR) T-cells
anticancer therapy uses of, 176, 176*f*
description of, 151
Chlamydia, 2649
definition of, 2009
developmental cycle of, 2009*f*
diseases caused by, 2009–2014
epidemiology of, 1879
pathobiology of, 2009
pathogens that cause, 2009
Chlamydia pneumoniae, 2010*t*
asthma and, 2013
atherosclerosis and, 2013
clinical manifestations of, 2013
description of, 2013
diagnosis of, 2013
epidemiology of, 2013
neurologic diseases and, 2013
prognosis of, 2013
treatment of, 2013*b*
Chlamydia psittaci, 2010*t*, 2013–2014, 2014*b*
Chlamydia trachomatis, 1879
annual screening for, 112
cervicitis caused by, 2011
conjunctivitis caused by, 2012
description of, 2009–2013
diagnosis of, 2010
diseases caused by, 2009–2014, 2010*t*
epididymitis caused by, 2011, 2012*b*
pelvic inflammatory disease caused by, 2011
in pregnancy, 2011–2012
prevalence of, 112
prevention of, 2012
proctitis caused by, 2012
prognosis of, 2012–2013
reactive arthritis caused by, 2012
serology of, 2012
sexually transmitted anorectal diseases and, 983
sexually transmitted infections caused by, 2010, 2011*f*
trachoma caused by, 2009
treatment of, 2012*b*
urethritis caused by, 2010–2011
Chlamydial conjunctivitis, 2604
Chlamydial infections, in adolescents, 112
Chlamydophila psittaci, 417*t*
Chlorambucil, for chronic lymphocytic leukemia, 1269*t*, 1270*t*
Chloramphenicol, e10*t*–e11*t*
for bacterial meningitis, 2518*t*
dosage of, 1895*t*
mechanism of action, 1895*t*
for meningococcal meningitis and meningococcemia, 1944*t*
for plague, 98*b*, 1992*t*
resistance mechanisms, 1893*t*
toxicities of, 1901*t*
Chlordiazepoxide
for alcohol withdrawal, 2358*t*
for anxiety disorders, 2344*t*
Chlorhexidine, reactions to, 1698*t*
Chlorhexidine-alcohol, for catheter-related infections, 1866
Chloride (Cl), e1*t*–e8*t*
Chloride channelopathies, 2585
Chloride-responsive metabolic alkalosis, 763
Chlorinated hydrocarbons, 88*t*
2-Chlorodeoxyadenosine (Mavenclad), for multiple sclerosis, 2505*t*
Chloromas, 1262
Chloroquine, 2114
for extraintestinal amebiasis, 2112*t*
for malaria, 1887, 2112*t*, 2121*b*
ocular effects of, 2613–2614
Chloroquine phosphate, for malaria, 2121*t*
Chlorpromazine, e10*t*–e11*t*, 2346*t*
Chlorthalidone, 451*t*
for hypervolemia, 737*t*
Cholangiocarcinoma, 1060
clinical manifestations of, 1359
definition of, 1357
histology of, 1359*f*
imaging of, 1360*f*
pathobiology of, 1359
Cholangiography, 1360
Cholangitis, 1055*b*
biliary, 987
in endoscopy, 876*t*
Cholecalciferol, 1650*t*
Cholecystectomy, 1052*b*, 1054*b*
Cholecystitis, acute
abdominal pain and, 854*t*
ultrasound of, 869*f*
Cholecystokinin, 1464–1465
Choledochal cysts, 1058, 1059*t*, 1059.e1*f*
Choledocholithiasis, 873*f*. *See also* Bile duct stones
Cholelithiasis, ultrasound of, 869*f*
Cholera, 1955–1957
clinical manifestations of, 1956
definition of, 1955
diagnosis of, 1956
epidemiology of, 1955, 1956*f*
immunization for, 66*t*, 83
pathobiology of, 1955–1956, 1957*t*
pathogen, 1955
prevention of, 1957
prognosis of, 1957
treatment of, 1956*b*, 1957*t*
vaccine, for traveler, 1886*t*, 1887
Cholescintigraphy, 1051
Cholesteatoma, 2641
Cholesterol, 1405, 1405*f*, 1405.e1*f*
dietary guidelines for, 57.e3*t*
dietary source of, 1405
metabolism of, 1406, 1407*f*
total, e1*t*–e8*t*
Cholesterol crystal embolization, 470
Cholesterol emboli, 2716, 2716*f*
Cholesterol gallstones, 1049
Cholesterol polyps, 1053–1054
Cholesterol reduction, 374*t*
Cholesteryl ester transfer protein, 1406
Cholestyramine, 941*b*, 1413, 1460*t*
for irritable bowel syndrome, 896*t*
for primary sclerosing cholangitis, 1058*b*
for small bowel rapid transit dysmotility, 890
Choline, 1451
Cholinergic urticaria, 2725
Cholinesterase, toxicity, 690*t*
Cholinesterase inhibitors
for Alzheimer disease, 2420*b*
for dementia with Lewy bodies, 2421*b*
Cholinomimetic toxidromes, 683*t*
Chondrocalcinosis, 1719, 1824
Chondrodystrophic myotonia, 2583.e1*t*
Chondrosarcoma, 1388, 1388*b*
Chordae tendineae, 224
Chordomas, 1314
Chorea
definition of, 2490–2492
differential diagnosis of, 2491*t*
Huntington disease, 2490–2491, 2490*b*–2491*b*, 2491*b*
Choreoathetosis, 2493
Choriomeningitis, lymphocytic, 2521
Chorionic gonadotropin, intact + beta subunit, e1*t*–e8*t*
Choroid, 2596
Choroid plexus papilloma, 1316
Choroidal dystrophy, 2611–2612
Christmas factor, 1189*t*
Chromaffin cells, 1529
Chromium, 88*t*, 1457*t*
Chromomycosis, 2109, 2109*f*, 2111*b*
Chromophobe renal cell cancer, 1363
Chromosomal aberrations, 164, 164.e1*f*
Chromosomal abnormalities, of chronic lymphocytic leukemia, 1267
Chromosomal deletions and duplications, 164
Chromosome 22q11.2 deletion syndrome, 1679*t*
Chronic abdominal pain, 854*t*, 858, 859*f*
Chronic actinic dermatitis, 2704–2705, 2704*f*
Chronic adrenal insufficiency, 1527, 1528*b*
Chronic adult T-cell leukemia/lymphoma, 2326, 2326*b*
Chronic alcohol use disorder, 1936
Chronic ambulatory peritoneal dialysis, 957
Chronic angina
coronary artery bypass graft for, 398
diagnostic coronary angiography in, 363*t*
Chronic anovulation, 1600–1602
causes of, 1601*t*
diagnosis of, 1601
endocrine causes of, 1602
hypothalamic, 1601–1602
Chronic anovulation *(Continued)*
inappropriate feedback causing, 1601
treatment of, 1601*b*
Chronic aortic regurgitation, 409
Chronic aspiration, cystic fibrosis *versus*, 558
Chronic atypical neutrophilic dermatosis with lipodystrophy and elevated temperature (CANDLE), 1731*t*, 1735
Chronic autoimmune syndromes, 2510
Chronic bacterial otomastoiditis, vertigo associated with, 2645
Chronic bacterial prostatitis, treatment of, 825*b*
Chronic beryllium disease, 589
clinical manifestations of, 589
diagnosis of, 589*b*, 589*f*
epidemiology of, 589
exposures to, 589*t*
pathobiology of, 589
treatment of, 589*b*
Chronic cavitary disease, 2095
Chronic coronary artery syndrome, antiplatelet therapy for, 507
Chronic cough, 512
diagnosis of, 512–513, 513*t*, 514*f*
management of, 514*f*
Chronic daily headache, 2378*t*, 2382, 2382*b*
Chronic diabetic kidney disease, 456
Chronic diarrhea, 928–932
causes of, 928*t*
clinical manifestations of, 928–932
diagnosis of, 928–932, 929*f*
Chronic disease
aging and, 120
prevention of, 57
Chronic disseminated candidiasis, 2092
Chronic dyspnea, 517*f*
Chronic eosinophilic pneumonia, 582
Chronic fatigue syndrome, 1816, 2372
Chronic fibrosing interstitial pneumonias, 571*t*, 575
Chronic granulomatous disease, 1683, 1683.e1*t*
Chronic hemodynamic monitors, 261
Chronic hemolytic anemia, 1072*t*
Chronic hepatitis B, 1010–1013
cirrhosis in, 1012–1013
clinical manifestations of, 1010–1011
diagnosis of, 1011, 1011*t*, 1012*f*
epidemiology of, 1010
pathobiology of, 1010
prevention of, 1011*b*–1012*b*, 1013*t*
prognosis for, 1012–1013
treatment of, 1011*b*, 1013*t*
Chronic hepatitis C, 1013–1014
clinical manifestations of, 1013–1014
diagnosis of, 1014
epidemiology of, 1013
human immunodeficiency virus and, 1014*b*
pathobiology of, 1013
prognosis for, 1014
recurrent, after liver transplantation, 1014*b*
treatment of, 1014*b*, 1015*t*
Chronic hepatitis D, 1015, 1015*b*
Chronic hepatitis E, 1016, 1016*b*
Chronic hypertension, in pregnancy, 1619*t*
Chronic hypocalcemia, 1659*b*
Chronic hyponatremia, 741*b*
Chronic idiopathic demyelinating polyneuropathy, 2564*t*
Chronic idiopathic neutropenia, 1146
Chronic idiopathic neutrophilia, 1141
Chronic idiopathic secretory diarrhea, 940
Chronic illness
in adolescents, 113
palliative care for, 11
Chronic immune demyelinating polyneuropathy (CIDP), immunization for, 65*t*
Chronic inflammation, neutrophilia and, 1141
Chronic inflammatory demyelinating polyneuropathy, 1296, 2313, 2375.e1*f*
Chronic inflammatory demyelinating polyradiculoneuropathy, 2572, 2572*b*
Chronic interstitial nephritis
analgesics causing, 793
anemia in, 793
cadmium toxicity causing, 794
causes of, 791*t*, 793–795
characteristics of, 790
clinical manifestations of, 793–795
diagnosis of, 793–795
granuloma formation in, 792
hypercalcemia causing, 794
lead toxicity causing, 794
Chronic interstitial nephritis *(Continued)*
myeloma causing, 794
obstruction causing, 794
pathology of, 791–792
primary, 790
vascular disease causing, 793
Chronic ischemic cardiomyopathy, 336*f*
Chronic ischemic heart disease, 336, 360*f*
Chronic kidney disease (CKD), 729, 729*f*, 831–840, 840
antihypertensive drug for, 454*t*
causes of, 831.e2*f*, 833*t*
clinical manifestations of, 834*t*, 836–837
conceptual model of, 831.e2*f*
criteria for, 837*t*
definition of, 831–840
diagnosis of, 837–839, 837*t*
disability-adjusted life years for, 831.e2*f*
epidemiology of, 831–832, 832*f*
evaluation of, 838*t*
cause, 839
duration, 837
glomerular filtration rate, 837–839, 839*t*
in hypertension, 448*t*
markers, 837
metabolic acidosis of, 757
pathobiology of, 832–836, 833*f*, 834*t*, 835*f*
porphyrias and, 1432
prevention of, 840.e1*f*, 840
prognosis of, 840
treatment of, 839*b*
Chronic limb ischemia, 462
Chronic limb ulceration syndrome, *H. ducreyi* and, 1951
Chronic liver failure, for liver transplantation, 1044
Chronic lower limb ischemia, 462*t*, 464*b*
Chronic lower respiratory disease
in adolescents, 110*t*
in older adults, 115
Chronic lung diseases, 1113–1114
occupational and environmental, 86
Chronic lymphocytic leukemia (CLL), 1266–1272, 1283, 1283*b*
autoimmune complications of, 1267, 1271
B-cell receptor in, 1267
chromosomal abnormalities in, 1267
clinical manifestations of, 1267–1268
definition of, 1266–1271
diagnosis of, 1268–1271, 1268*f*, 1268.e1*f*
differential diagnosis of, 1268–1269
disease-related complications of, 1267–1268, 1271
epidemiology of, 1266
epigenetics of, 1267
immunization for, 65*t*
pathobiology of, 1266–1267
peripheral blood smear of, 1074, 1074*f*
prognosis of, 1271
staging and prognostic factors of, 1269, 1269*t*
therapies used in, 1269*t*
treatment of, 1269*b*, 1270*f*, 1270*t*
Chronic medications, in preoperative evaluation, 2666–2667, 2666*t*
Chronic meningitis
infectious causes of, 2522–2524, 2523*t*–2524*t*
intermittent, 2524
noninfectious causes of, 2523–2524, 2524*t*
persistent, 2523*t*, 2524*t*
with predominantly neutrophilic pleocytosis, 2524, 2524.e1*t*
recurrent, 2523*t*
Chronic mesenteric ischemia, 916*f*, 963, 963*f*
clinical manifestations of, 963
diagnosis of, 963, 964*f*
treatment of, 964*b*
Chronic mitral regurgitation, asymptomatic, 407*b*
Chronic mountain sickness, 592, 592*t*, 593*b*
Chronic mucocutaneous candidiasis, 1686*t*, 2090
Chronic myelogenous leukemia (CML)
histamine hypersecretion, 917
neutrophilia and, 1142
Chronic myeloid leukemia (CML), 1272–1278
clinical manifestations of, 1274
cytogenetic abnormalities in, definition of, 1272–1277
diagnosis of, 1274, 1274*f*
epidemiology of, 1273
hematopoietic cell transplantation for, 1209
molecular response of, pathobiology of, 1273–1274, 1273*f*

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Chronic myeloid leukemia (CML) *(Continued)*
peripheral blood smear of, 1073, 1073*f*
prognosis of, 1277, 1277*t*
treatment of, 1274*b*, 1274*f*, 1275*t*, 1276*t*
Chronic myelomonocytic leukemia (CMML), 1277, 1278*b*
Chronic narcotic therapy, 534*t*
Chronic necrotizing pulmonary aspergillosis, 2095
Chronic neuropathy, porphyrias and, 1432
Chronic obstructive pulmonary disease (COPD), 547–556, 649, 2664
acute exacerbations of, 554–555
arterial blood gases of, 550
asthma *versus*, 550
bronchiectasis *versus*, 549
cigarette smoking and, 547
clinical manifestations of, 549, 649
computed tomography of, 548
cystic fibrosis and, 557
definition of, 547–554
diagnosis of, 549–550, 649
diagnostic testing of, 549–550, 550*t*
differential diagnosis of, 550
environmental air pollution and, 547–548
eosinophilic, 551*b*
epidemiology of, 547–548, 649
genetics of, 549
GOLD classification system for, 548*f*
history of, 549, 549*f*
in HIV, 2318
hospital management of exacerbations, 555*t*
imaging of, 550, 550*f*–551*f*, 551*f*
natural history of, 551*b*
as occupational lung disease, 585*t*, 588
in older adults, 114
oximetry of, 550
oxygen therapy for, 551*b*
pathobiology of, 548–549, 649
pathophysiology of, 548
pharmacotherapy for, 551*b*, 552*f*
physical examination of, 549, 549*f*
physical findings in, 549
prognosis of, 650
severe
contraindication for, 632*t*
decision guide for, 632*t*
indications for, 632, 632*t*
treatment of, 551*b*, 553*t*, 554*b*, 649*b*–650*b*, 649*t*
weight loss and, 860*t*
Chronic otitis media, 2526*t*, 2641
Chronic pain, 133
Chronic pancreatitis, 933, 973–976
abdominal pain and, 854*t*
alcohol and tobacco and, 973
causes of, 974
clinical manifestations of, 933, 974
definition of, 973
diagnosis of, 933, 974–975, 974*f*–975*f*, 974*t*, 975*f*
epidemiology of, 973
genetic of, 973
pancreatic duct obstruction and, 973–974
pathobiology of, 973–976
prevention of, 976
prognosis of, 976
treatment for, 975*b*, 975*t*
Chronic pelvic pain syndrome, treatment of, 825*b*
Chronic poisoning, of trace metals, 101–107
aluminum, 101*t*, 105, 105*b*
arsenic toxicity, 103
bismuth, 101*t*, 102*t*, 105, 105*b*
cadmium toxicity, 104
cobalt, 106, 106*b*
lead toxicity, 101
manganese, 101*t*, 107, 107*b*
mercury toxicity, 102–103
silver, 106, 106*b*, 106*f*
thallium, 106, 106*b*
zinc, 101*t*, 106, 107*b*
Chronic preexisting hypertension, 1620
Chronic progressive external ophthalmoplegia, 2586
Chronic Prostatitis Symptom Index, 826*f*
Chronic recurrent multifocal osteomyelitis (CRMO), 1731*t*
Chronic rejection, 206
in renal transplantation, 846
Chronic respiratory tract infections, *Pseudomonas* infections causing, 1969
Chronic rhinitis, 2627–2628
Chronic rhinosinusitis, 2628
cystic fibrosis and, 558
Chronic sarcoid arthritis, 602
Chronic sinusitis, 2627, 2633*t*
Chronic sleep-disordered breathing, 257
Chronic stable lower limb ischemia, 462
Chronic subdural hematoma, 2391, 2391*b*, 2391*f*
Chronic telogen effluvium, 2748
Chronic thromboembolic hypertension, 496*b*, 499.*e1f*
Chronic thromboembolic pulmonary hypertension, 490
Chronic tonsillitis, 2651
Chronic ulcerated herpes simplex, 2687.*e4t*
Chronic ulcerations, other, 2622
Chronic urate-lowering therapies, 1813*b*–1814*b*
Chronic urticaria, 1674, 1687, 2725
diagnosis of, 1688
diagnostic testing for, 1688
pathobiology of, 1687, 1687*f*
treatment of, 1689*b*
underlying causes of, 1688
Chronic viral hepatitis, 1009–1017
clinical manifestations of, 1009
definition of, 1009–1010
diagnosis of, 1010, 1010*t*
prognosis for, 1010*b*
treatment of, 1010*b*
Chronic wasting disease, 2422
Chronotropic incompetence, 319
Chrysotile asbestos, 589
Churg-Strauss syndrome, 2573. *See also* Eosinophilic granulomatosis with polyangiitis
Churg-Strauss vasculitis, 1142
Chvostek sign, 1648
Chylomicrons, 1405
Chylothorax, 626
Chylous effusions, 626–627, 626*b*
Cialis, 364*b*
CIAS1, 1734–1735
Cicatricial alopecia, 2749
Cicatricial pemphigoid, esophageal involvement in, 911
Cidofovir, 2187*t*, 2188*t*
for cytomegalovirus, 2252*b*
for molluscum contagiosum, 2240*b*
CIDP. *See* Chronic immune demyelinating polyneuropathy
Cigar-shaped elliptocytes, 1094*f*, 1097
Cigarette smoking, 2349–2352
behavioral treatment for, 2350*t*
bladder cancer and, 1365
blood pressure and, 445
cardiovascular disease and, 220
clinical manifestations of, 2349
COPD and, 547
definition of, 2349–2352
diagnosis of, 2349–2350
epidemiology of, 2349
lung cancer and, 1329
neutrophilia and, 1141
nicotine replacement therapy for, 2350*b*, 2351*t*
passive, 220
pathobiology of, 2349
pharmacologic treatment for, 2350*b*, 2351*t*
prevention of, 2352
prognosis for, 2352
psychosocial treatment for, 2350*b*, 2350*t*
second-hand, 220
treatment of, 2350*b*
vitamin levels affected by, 1459
in women, 1609
Ciguatera intoxication, in travelers, 1889.*e1t*
Ciguatera poisoning, 713
Ciguatoxin, 925
Ciliary body, 2596
Ciliary dyskinesia, primary, cystic fibrosis *versus*, 558
Cilofexor, for primary sclerosing cholangitis, 1058*b*
Cilostazol, 508–509
for atherosclerotic PAD, 464*b*
for ischemic heart disease, 470*b*
Cimzia. *See* Certolizumab
Ciprofloxacin
for anthrax, 97
for bacterial meningitis, 2518*t*
for *Campylobacter* infections, 1959*b*, 1960
for chancroid, 1951*b*
for cholera, 1956*b*
for cystoisosporiasis, 2112*t*
for diverticulitis, 955*b*
dosage of, 1895*t*
for eye infection, 2605*t*
for intestinal bacterial overgrowth, 934*b*
for lung disease, 558*b*
for meningococcal disease, 1945*t*
for nontuberculous mycobacterial disease, 2046*t*
for plague, 98*b*, 1992*t*
for skin diseases, 2699
for traveler's diarrhea, 926*b*, 1888, 1888*t*
for tularemia, 99*b*, 1987*b*–1988*b*
for urinary tract infection, 1876*t*, 1877*t*
for yersiniosis, 1994*b*
Circadian rhythm disorders
clinical manifestations of, 2452
definition of, 2451
diagnosis of, 2452
epidemiology of, 2451
graph of, 2452.*e1f*
pathobiology of, 2451
treatment of, 2452*b*
Circadian rhythms, 1478, 1478.*e1f*
description of, 2443–2444
Circle of Willis, 2455.*e1f*, 2456
Circulating vaccine-derived polioviruses, 2257
Circulation, 225
Circulatory support
for cardiogenic shock, 667*b*
mechanical, 265*b*
Circumcision
for chancroid, 1952
for HIV transmission prevention, 2298
male, 1884
Circumscribed hyperpigmentation, 2744, 2744*f*
Circumscribed hypopigmentation, 2743
Cirrhosis, 736, 988, 1035–1043, 1821
alcohol-related, 2355
causes of, 1036*t*
in chronic hepatitis B, 1013
clinical manifestations of, 1037–1038, 1037*f*
compensated, 1038, 1041*f*
complications of, 1036–1037, 1036*f*, 1039–1040
decompensated, 1014*b*, 1015*t*, 1038, 1041*f*
definition of, 1035–1043, 1035*f*
diagnosis of, 1038–1042
epidemiology of, 1035
with hepatocellular carcinoma, ultrasound of, 870*f*–871*f*
imaging studies for, 1039, 1039*f*
laboratory tests for, 1039
liver fibrosis and, 1035–1036
mesenteric venous thrombosis and, 963*t*
pathobiology of, 1035–1037
physical examination for, 1038–1039
portal pressure measurements for, 1039
prevention of, 1042
prognosis of, 1043
scoring systems in, 1038*t*
treatment of, 1040*b*, 1041*f*
weight loss and, 860*t*
in Wilson disease, 1436*f*–1437*f*
Cirrhotic cardiomyopathy, 1037
CISNE. *See* Clinical Index of Stable Febrile Neutropenia
Cisplatin (Platinol), 1215*t*
adverse reactions of, 132
for disseminated disease, 1383*b*
for head and neck cancer, 1327*b*
Cisternography, strengths and weaknesses of, 2373*t*
Citalopram
for depression, 2340*t*
for hot flashes, 1631*t*
for irritable bowel syndrome, 896*t*
Citrate, kidney stones, 803
Citrate-phosphate-dextrose, 1199
Citrullinated proteins, antibodies to, 1713
Citrulline, 1713
Citrullinemia, 1402*t*
CKD. *See* Chronic kidney disease
Cladribine, for multiple sclerosis, 2505*t*
Clarithromycin
dosage of, 1895*t*
for nontuberculous mycobacterial disease, 2046*t*
for pertussis, 1995*b*–1996*b*
Classic gout, 1811, 1812*f*
Classic heatstroke, 679*t*
Classic Hodgkin lymphoma, 1289–1290, 1290
Claude syndrome, 2465.*e1f*
Claudication
definition of, 462
intermittent, 465.*e1f*
Clear cell adenocarcinoma, of vagina, 1597
Clear cell renal cell carcinoma, 1363
Cleavage resistant RIPK1 induced autoinflammatory (CRIA) syndrome, 1731*t*
Clevidipine, for hypertensive emergencies, 460*t*
Climate change, 89–91
environmental impact from, 89
health care professionals and, 91.*e1f*, 91
how it affects health, 89–90, 90*f*, 91*t*
as occupational and environmental hazards, 87
recent evidence and projected impacts of, 90, 90*f*
research priorities for, 91
zoonoses and, 2064
Climate-related hazards, examples of, 91*t*
Climax, 1604
Clindamycin
for anthrax exposure, 97*b*
for babesiosis, 2112*t*, 2115, 2152*b*, 2152*t*
for cellulitis, 2740*b*
characteristics of, 1899–1900
dosage of, 1895*t*
for malaria, 2112*t*, 2121*t*
mechanism of action, 1895*t*
for peritonsillar abscess and deep space infections, 2649
for pneumonia, 616*b*
resistance mechanisms, 1893*t*
spectrum of activity, 1900
for *Streptococcus pneumoniae* pulmonary infections, 1912.*e1t*
toxicities of, 1901*t*
for toxoplasmosis, 2112*t*, 2140*t*
Clindamycin-primaquine, for *Pneumocystis* pneumonia, 2103*b*, 2106*t*
Clinical chemistry, reference intervals, *e1t*–*e8t*
Clinical decision support, 44, 169
Clinical genomics, 160–165
gene, 160–162, 161*f*
genetic test reports for, 165
genomic variations in, 162–165
assaying, 164–165
chromosomal aberrations in, 164, 164.*e1f*
copy number variants in, 164
deletion, insertion, and indels in, 163
structural aberrations in, 164
structural variants in, 164
tandem repeats in, 163–164
as normal part of medicine, 165
patterns of inheritance in, 160–162
mendelian inheritance, 160–162, 161*f*
mosaicism, 162, 163*f*
nonmendelian inheritance, 162
Clinical Index of Stable Febrile Neutropenia (CISNE), 1856*t*
Clinical pathways, 44
Clinical Pharmacogenomics Implementation Consortium, 167
Clinical syndromes, occupational and environmental, 85–87, 86*t*
Clinical transplantation, 203
Clitoromegaly, 1598
CLL. *See* Chronic lymphocytic leukemia
Clobazam, for seizures, 2434*t*
Clofazimine
for babesiosis, 2115
for leprosy, 2052*b*–2053*b*, 2053*t*
for nontuberculous mycobacterial disease, 2046*t*
Clomiphene citrate, for ovulation, 1603*b*
Clonal cytopenias, of undetermined significance, 1255
Clonal disorders, myelodysplastic syndromes as, 1253
Clonal expansion, in Enterobacterales, 1965, 1966*t*
Clonal hematopoiesis, 1064

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Clonazepam
for anxiety disorders, 2344*t*
for myoclonus, 2496*b*
Clonidine, 941*b*
for alcohol withdrawal, 2358*t*
for hot flashes, 1631*t*
oral, 451*t*
patch, 451*t*
perioperative cardiac events reduced using, 2662*b*–2663*b*
for small bowel rapid transit dysmotility, 890
for tobacco dependence, 2351*t*
for Tourette syndrome, 2494*b*
Clonorchiasis, 2166
Clonorchis, in travelers, 1889.*e1t*
Clonorchis sinensis, 1026*t*, 2166
Clopidogrel, 387*t*, 506*t*, 507
for acute coronary syndrome, 374*t*
for acute STEMI, 384*b*, 391*t*
for Fabry disease, 1423*b*
for stroke prevention, 397
Clorazepate, for anxiety disorders, 2344*t*
Closed pneumothorax, 526
Closed wet dressings, for skin diseases, 2697
Clostridial infections, 1924–1929
necrotizing, 1926–1927
botulism, 1927, 1928*b*
tetanus, 1928–1929, 1929*b*, 1929*t*
neurotoxic, 1927
Clostridial myonecrosis, 1926–1927, 1926*b*
Clostridioides difficile infection, 1833, 1839–1840, 1840.*e1f*, 1924–1926
antibiotic-induced, fever and, 1846
clinical manifestations of, 1925
colitis caused by, 1858–1859
definition of, 1924
diagnosis of, 1925
diarrhea caused by, 1836, 2673–2674
epidemiology of, 1924
health care-associated infections caused by, 1865
pathobiology of, 1924–1925
prevention of, 1925–1926
prognosis for, 1926
toxins A and B, 1927
treatment of, 1925*b*
Clostridioides difficile toxin A/B testing, for enteric infection, 1870*t*
Clostridium botulinum, 1833, 1927, 2592
Clostridium novyi infection, in injection drug users, 1927
Clostridium perfringens
cellulitis caused by, 2740
type A diarrhea, 1926, 1926*b*
type C enteritis, 1926, 1926*b*
Clostridium septicum, 1926
Clostridium tetani, 1833, 1928
Clot waveform analysis, 1169, 1198
Clotrimazole, for candidiasis, 2092*b*
Clotting factors, 1000, 1188*b*
Cloxacillin, dosage of, 1895*t*
Clozapine
for Parkinson disease, 2487*t*
for psychotic disorders, 2346*t*
weight gain and, 2680
CLPX-associated protoporphyria, 1428*t*
Clubbing, 216, 218*f*, 2752, 2752*f*
Cluster headache, 2377*t*, 2381–2382, 2381*t*, 2382*b*
Cluster randomized trials, 41
Clustered Regularly Interspaced Short Palindromic Repeats (CRISPR), 166
CML. *See* Chronic myeloid leukemia
CMML. *See* Chronic myelomonocytic leukemia
CMS. *See* Centers for Medicare and Medicaid Services
CMV. *See* Cytomegalovirus
CNS. *See* Central nervous system
CNS-acting drugs, for fibromyalgia, 1819*b*
Coagulase-negative staphylococci, 1909–1910
Coagulation, procoagulant response in sepsis, 671
Coagulation cascade, 1165*f*, 1167*f*
Coagulation disorders, 2470.*e1t*
Coagulation factor deficiencies, 1166*t*, 1167*t*, 1187–1194
coagulation abnormalities, 1193–1194
contact activation factors, deficiencies of, 1192, 1192*b*
dysfibrinogenemia and afibrinogenemia, 1192
factor V deficiency, 1193
factor XI deficiency, 1191
Coagulation factor deficiencies *(Continued)*
factor XIII, 1192, 1192*b*–1193*b*
hemophilias
acquired, 1191, 1191*b*
hereditary, 1187–1191
vitamin K-dependent coagulation, deficiencies of, 1193
von Willebrand disease, 1191
Coagulation factor IX, 476
Coagulation system, 1165
Coagulation tests, 999–1000
abnormal, evaluation of, 1169
albumin, 1000
for liver failure, 1198
prothrombin time, 999–1000
Coagulopathy
consumptive, 1195
cystic fibrosis and, 557
snake envenomation syndromes causing, 707
suspected, despite negative screening tests, 1167*f*, 1169
Coal, 88*t*
Coal workers' pneumoconiosis, 86
Coarctation of the aorta, 351–352, 352*b*, 352*f*, 450
evaluation of, 448*t*
exercise recommendations for, 355.*e2t*
Coarse atrial fibrillation, 328, 328*f*
Coartem, for malaria, 2121*t*
Cobalamin, 1117. *See also* Vitamin B_{12}
absorption of, 1117*t*, 1118–1119, 1118*f*
biochemical assays for, 1122
intracellular, metabolism pathway and defects of, 1425.*e2f*
malabsorption of, 1119
processes of, 1118*f*
processing of, 1425*t*–1426*t*
transport of, 1119, 1425*t*
Cobalamin deficiency, 2539–2540
of central nervous system, 1124
clinical manifestations of, 2539–2540
diagnosis of, 2540
due to drugs, 1119
epidemiology of, 1117, 1118*f*
megaloblastic anemia and, 1117*t*
metabolites for, 1124*t*
neurologic abnormalities due to, 1121–1122, 1122*f*
pathobiology of, 1118–1119
prevention of, 1124
prognosis for, 2540
treatment of, 1123*b*, 2540*b*
Cobalamins, 935
Cobalt, 1451
thyroid and cardiac toxicity, 106, 106*b*
toxicity, 88*t*
Cobb angle, 621, 621.*e1f*
Cobimetinib (Cotellic), 1215*t*, 1251*t*
for melanoma, 1394*t*
Cobra venom factor (CVF), 203
Cocaine. *See also* Psychostimulants
cardiomyopathy due to, 286
central nervous system effects of, 685*t*
screening for, 689*t*
toxicity, 2363, 2363*b*
Coccidian enteritis, 2155–2156
clinical manifestations of, 2155
diagnosis of, 2155–2156, 2155*f*
epidemiology of, 2155
pathobiology of, 2155
prevention of, 2156
prognosis of, 2156
treatment for, 2156*b*
Coccidioides immitis, 1024, 2083–2084
Coccidioides posadasii, 2083
Coccidioidomycosis, 2083–2085, 2084*t*, 2085*f*, 2651
clinical manifestations of, 2084
definition of, 2083–2084
diagnosis of, 2084–2085
epidemiology of, 2084
extrapulmonary dissemination in, 2084
pathobiology of, 2084
pathogen of, 2083–2084
pneumonia in, 520.*e2f*
primary pulmonary infections in, 2084
prognosis of, 2085
prophylaxis for, 2309*t*
treatment of, 2085*b*
Coccydynia, 1746, 1746*b*
Cochlear damage, 2641–2642
Cocoa, diet-related hyperoxaluria and, 806
Codeine, for hemarthroses, 1188*b*
Coenurosis, 2163
Coenzyme Q10 deficiency, 2586–2587
Coffin lid crystals, 723–724, 725*f*
Cogan syndrome, 1799, 1799*b*
Cognition, geriatric assessment of, 117
Cognitive behavioral therapy
for benzodiazepines, 2363*b*
for bulimia nervosa, 1462*b*
for drug use disorders, 2361*b*
for fibromyalgia, 1819*b*
Cognitive disorders, 2337*t*, 2548–2549
Cognitive dysfunction
amnesic disorders, 2407
in heart failure, 257
menopause associated with, 1630*b*
Cognitive impairments, 2412–2425
cerebrovascular disease causing
clinical manifestations of, 2419
definition of, 2417
diagnosis of, 2419, 2419*t*
epidemiology of, 2417
magnetic resonance imaging of, 2419*f*
pathobiology of, 2418
prognosis for, 2420
risk factors for, 2418
treatment of, 2420*b*
dementia. *See* Dementia
epidemiology of, 2412
management of, 2414
mild
amnesic, 2412*t*
cerebrospinal fluid findings in, 2416, 2417*f*
clinical manifestations of, 2415
diagnosis of, 2416, 2416*t*, 2418*f*
differential diagnosis of, 2416
genetics of, 2415
management of, 2414
prognosis for, 2417
neurologic diseases that cause, 2372–2373
in older adults, 114–115
screening for, 53
Cognitive psychotherapy, for depression, 2339*t*–2340*t*
Cohort studies, 41
Coitus interruptus, 1611
COL1A1, 1727
COL1A2, 1727
Colaspase, 1215*t*
Colazal. *See* Balsalazide
Colchicine
for acute pericarditis, 424*b*
for COVID-19, 2217
for pericardial constriction, 431*b*
for skin diseases, 2699
Cold agglutinin disease, 1087
Cold agglutinins, *Mycoplasma pneumoniae* in, 2007
Cold autoimmune hemolytic anemia, 1088, 1088*t*
Cold disorders, 678–682
Cold injury, 680–681
clinical manifestations and diagnosis of, 680, 681*f*, 681*t*
definition of, 680–681
epidemiology of, 680, 680*t*
factors predisposing to, 680*t*
as occupational and environmental hazards, 88*t*
prevention and treatment of, 681*b*, 681*t*
prognosis of, 681
Cold urticaria, 681, 2725
Colectomy, for ulcerative colitis, 945*b*
Colesevelam, for irritable bowel syndrome, 896*t*
Colistimethate, 2518*t*
Colistin, 1970*b*
Colitis
amebic, 2147, 2148*f*, 2149*t*, 2150*t*
cytomegalovirus, 2251
differential diagnosis of, 944*t*
hemorrhagic, *Escherichia coli* and, 1961, 1963
microscopic, 940
Collagen vascular disease
diffuse alveolar hemorrhage and, 568–569
treatment of, 1853*t*
Collagenomas, 2730
Collecting duct
disorder of, 817–818
diuretics, 736*b*
Collective dose, 91
Colloid cysts, 1316
Colloids, reactions to, 1698*t*
Colon
adenocarcinoma of, 1349
diverticulitis of, 954–955, 954.*e1f*, 955*b*, 955*f*
motility of, 887–888, 890–892
transit in, 887–888
Colon cancer
colonoscopy for, 879
human microbiome and, 1840
treatment of, 1241*b*
in ulcerative colitis, 945*b*
Colon ischemia, 964
algorithm of, 966*f*
clinical manifestations of, 964
conditions associated with, 964*t*
diagnosis of, 964, 965*f*, 965.*e1f*
medications associated with, 964*t*
treatment of, 965*b*
Colonoscopy, 879–880, 1349, 1349*t*, 1353
for colon ischemia, 965
indications for, 879, 879*f*–880*f*
instrument for, 879
for iron deficiency anemia, 887
for lower gastrointestinal bleeding, 885
preparation for, 879
procedure of, 879–880
Colony forming units (CFU), 1892
Colopathy, congestive, 967
Color blindness, 2598
Color flow Doppler imaging, 236
Colorado tick fever virus, 2276*t*, 2284, 2284*b*
Colorectal anastomotic leak, fluoroscopy of, 868*f*
Colorectal cancer, 1345–1346, 1346, 1346*f*
chemoprevention for, 1353
clinical manifestations of, 1349, 1349*f*
diagnosis of, 1350, 1350*f*
dietary prevention for, 1353
fecal occult blood tests for, 54
flexible sigmoidoscopy for, 54
follow-up for, 945*b*
in HIV, 2316
metastatic, 1350*b*, 1351.*e1f*
nutrition and, 59
prevention of, 1352–1353
prognosis of, 1353–1354, 1353*f*
screening for, 54, 1352–1353, 1352*t*
staging of, 1350, 1350*f*
stool DNA tests for, 54
treatment for, 1350*b*, 1351*t*
in women, 1607
Colostrum, for *E. coli*, 1963*b*
Colovesicular fistulas, in Crohn disease, 945*b*
Colpitis macularis, 1882–1883
Colposcope, 1376
Colposcopy, 2242
Coma, 2437
cause of, 2438*t*–2439*t*
clinical manifestations of, 2438
cranial nerve examination in, 2439
diagnosis of, 2438–2440, 2438*t*, 2439*t*
emergency management of, 2441*t*
epidemiology of, 2437, 2437*t*
grading of, 2440, 2440*t*
herniation causing, 2438
laboratory testing for, 2440
lightning injury and, 704
motor examination in, 2439–2440
pathobiology of, 2437–2438
prognosis for, 2440–2441, 2441*t*
treatment for, 2440*b*, 2441*t*
Comanagement, 2657*t*, 2658
Comatose patient, neurologic examination in, 2370
Combination dextroamphetamine/amphetamine, 2449*t*
Combination diuretic therapy, for hypervolemia, 736*b*
Combination T_4/T_3 therapy, for hypothyroidism, 1508*b*–1509*b*
Combination therapy
for cancer, 1232*b*, 1234*t*
for common cold, 2193*b*
for pulmonary hypertension, 496*b*, 499*f*
Combined resynchronization and cardioverter defibrillator therapy, 345
Common cold, 2192–2194
clinical manifestations of, 2192–2193
definition of, 2192–2194
diagnosis of, 2193
epidemiology of, 2192
pathobiology of, 2192
pathogens causing, 2192
prevention of, 2193–2194

Copyrighted material

Common cold *(Continued)*
prognosis of, 2194
treatment for, 2193*b*, 2193*t*
viruses associated with, 2192*t*
Common couple violence, 1633
Common variable immunodeficiency, 1681, 1681*t*, 1822
Common ventricle, 354
Commonwealth Foundation, 41.*e*1*t*
Commotio cordis, 700*b*
Communication, in psychiatric diseases, 2679
Community-acquired bacterial meningitis, 2516*t*
Community-acquired pneumonia, 606–613, 611*f*–612*f*, 612*f*, 1851*b*
antibiotic therapy for, 1912*b*
bacterial species that cause, 1892*t*
Staphylococcus aureus causing, 1904
Stenotrophomonas maltophilia and, 1975
Streptococcus pneumoniae causing, 1910
treatment of, 1998*b*–1999*b*
Comorbidity, heart failure and, 265*b*
Compartment syndrome, 716, 717*b*, 1188
Compensated cirrhosis, 1037–1038, 1038
Compensatory changes, in acid-base disorders, 755–756, 756*t*
Competency, geriatric assessment of, 117
Complement, 152, 1715–1716
activation of, 197–202, 202.*e*1*f*
alternative pathway of, 198–199, 198*f*–199*f*, 201*f*
classical pathway of, 197–198, 198*f*, 199*f*
lectin pathway of, 198, 198*f*, 199*f*
pathologic conditions associated with, 198*t*
regulators of, 197
tissue injury or degeneration and, 199*t*
levels, in nephritic syndrome, 778*t*
Complement C3, *e*1*t*–*e*8*t*
Complement C4, *e*1*t*–*e*8*t*
Complement disorders, 1682–1683, 1683*t*, 1731*t*
clinical manifestations of, 1683
diagnosis of, 1683
epidemiology of, 1682–1683
pathobiology of, 1682–1683
prognosis of, 1683
treatment of, 1683*b*
Complement fixation assays, for paracoccidioidomycosis, 2087
Complement inhibitors, 202–203
Complement-mediated membranoproliferative glomerulonephritis, 786, 786*t*
Complement receptor of the immunoglobulin superfamily (CRIg), 200*t*
Complement receptor type 1, 200*t*
Complement receptors, 184, 202
Complement system
in disease, 196–203, 201*t*
participation of, 198*t*
features of, 197*t*
function of, 197*f*
in host defense, 197*t*
regulating, 200*t*
Complementary and integrative medicine, 153–155
acupuncture, 154
definition of, 153–154
manual therapies, 154
meditation, 154
natural products, 154–155
for pain, 136*b*
tai chi, 154
traditional Chinese medicine, 154
use of, 154–155
yoga, 154
Complete blood counts, for anemia, 1076, 1076*t*, 1077*t*
Complete heart block, 321, 321*f*
Complex disorders, 533
Complex multimarker genomic tests, for disease diagnosis and prognosis, 168
Comportment, 2410–2411
Compound nevi, 2730
Comprehensive Environmental Response, Compensation, and Liability Act, 87
Compression-based ultrasound elastography, 1720
Compression-induced rhabdomyolysis, 715
Compression stockings, 490
Compression ultrasonography, description of, 484, 485*f*
Compressive focal motor neuropathies, 2564*t*
Compressive mononeuropathies, 2579
Compressive neuropathies, 2544
Compromised host
conditions and medical interactions in, 1853*t*
fever in, 1853–1861, 1854*b*–1855*b*
Computed tomographic pulmonary angiography, 484, 486*f*
Computed tomography (CT), 519
of acute kidney injury, 726, 727*f*
of acute mesenteric ischemia, 960
of acute pancreatitis, 969, 971, 971*f*
of bacterial pneumonia, 521*f*
of bronchiectasis, 558*f*
cardiac, 249
chronic obstructive pulmonary disease on, 548
of chronic pancreatitis, 974, 974*f*
of compensated cirrhosis, 1039, 1039*f*
of COVID-19, 520.*e*1*f*, 521*f*
of enterography, 871
in gastroenterology, 869–871, 870*f*, 871*f*
high-resolution, in interstitial lung disease, 574
of honeycombing, 522*f*
of hypoglycemia, 1557
of invasive mucinous adenocarcinoma, 569.*e*1*f*
of liver disease, 990
of lymphadenopathy, 1150
of mediastinum, 527
of metabolic bone disease, 1638–1639
of microscopic polyangiitis with pulmonary hemorrhage, 520.*e*1*f*
of mucormycosis, 520.*e*2*f*
of nephrolithiasis, 805, 805*f*
of neutropenic enterocolitis, 956, 956.*e*1*f*
of nocardiosis, 2073, 2073*f*–2074*f*, 2074*f*
of peritoneal carcinomatosis, 957*f*–958*f*, 958*f*
of primary coccidioidomycosis pneumonia, 520.*e*1*f*
of pulmonary alveolar proteinosis, 567, 567*f*
of pulmonary edema, 521*f*
of pyogenic liver abscess, 1022–1023, 1023*f*
of rheumatic disease, 1717–1718, 1719*f*
single-photon emission computed tomography. *See* Single-photon emission computed tomography
strengths and weaknesses of, 2373*t*
of stroke, 2464
Computed tomography angiography (CTA), 519, 870
in atherosclerotic PAD, 463, 463*f*
coronary, 249, 249.*e*2*f*, 250*f*
in coronary artery disease, 360
renal artery stenosis for, 800
Computed tomography colonography, 871, 871*f*, 1353
Computed tomography myelography, strengths and weaknesses of, 2373*t*
Computerized ECG readings, automated, 234
Concentration-mantra meditation, 154
Concussion, standardized assessment of, 2386*t*
Conditioning regimens, 1207, 1207*f*
Condoms, for HIV transmission prevention, 2298
Conduction, impulse, disorders of, 302
Conduction delays, management of, 384*b*
Conduction disorders, conditions associated with, 318*t*
Conduction system delays, 317
atrioventricular conduction disturbances, 319
conditions associated with, 318*t*
intraventricular blocks, 321–322, 322*b*
Conductive hearing loss, 2641
Condyloma, anal, 982*f*
Condylomata lata, 2014, 2015*f*, 2242, 2623
Cone snails, 713
Confabulation, 2539
Confidentiality, in adolescent medicine, 111
Confounding, 37
Confusion Assessment Method, 2331, 2331*f*
Confusional arousals, 2453*t*
Congenital abnormalities
of aortic valve, 400
cystic adenomatoid malformation of the lung, 565
of esophagus, 913
of pericardium, 433
pulmonary airway malformation, 565
Congenital adrenal hyperplasia, 1569–1572, 1569.*e*1*f*, 1594
description of, 749, 749*t*, 1520, 1526
diagnosis of, 1602
Congenital anomalies, in adolescents, 110*t*
Congenital cataract, 2612
Congenital coronary anomalies, 381*t*
Congenital disorders, cystic diseases, thoracic, 564
Congenital embryopathic disorders, 1478–1479
Congenital erythropoietic porphyria (CEP), 1428*t*, 1430, 1434*b*–1435*b*
Congenital factor V deficiency, 1193
Congenital heart disease, 253, 253*f*, 347
assessment of, 348*f*
clinical manifestations of, 348
CMR findings, 251, 251*f*, 252*f*
complex lesions, 353–356
echocardiographic findings, 242*t*
empirical therapy for, 2526*t*
epidemiology of, 347–348
exercise for, 355, 355.*e*2*t*
genetic determinants, 347–348
history of, 348
isolated shunt lesions, 348
laboratory investigations of, 348
pathobiology of, 347–348
physical examination for, 348
prognosis for, 355*b*
simple lesions, 348–353
treatment of, 347.*e*1*f*, 355*b*, 355.*e*1*f*
ventricular tachycardia in, 337
Congenital hyperinsulinemic hypoglycemia, 1554, 1557*b*–1558*b*
Congenital hypogonadotropic hypogonadism, 1584
Congenital infection, cytomegalovirus and, 2251
Congenital junctional ectopic tachycardia, 326
Congenital large hyperlucent lobe, 565
Congenital lobar emphysema, 565
Congenital muscular dystrophies, 2585–2587
Congenital myasthenic syndromes, 2591, 2591*b*
Congenital myopathies, 2585
Congenital neural tube defects, nutrition and, 60
Congenital nevus, 2692*t*
Congenital nonspherocytic hemolytic anemia, 1099
Congenital nystagmus, 2619
Congenital rubella syndrome, 2224
Congenital syndromes, with associated neutropenia, 1145
Congenital syphilis, 2018–2020, 2019, 2020*b*
Congenital thrombocytopenia, 1179
Congenital toxoplasmosis, 2136, 2138*t*, 2139
Congenital triangular alopecia, 2750
Congenital valvular aortic stenosis, 351, 351*b*
Congestion, 666
Congestive colopathy, 967
Congestive enteropathy, 967
Congestive gastropathy, 967
Congestive splenomegaly, 1152
Conidia, 2093
Conivaptan, for hypervolemia, 737*t*
Conjugate gaze disorders, 2619
Conjugated estrogen (Premarin), for genitourinary syndrome of menopause, 1632*t*
Conjunctiva
anatomy of, 2596
malignant melanoma of, 2612
Conjunctival suffusion, 2029–2030, 2030*f*
Conjunctivitis, 2600
acute hemorrhagic, enteroviruses causing, 2260, 2260*b*
adenoviral, 2604, 2605*f*, 2605*t*
allergic, 2604, 2605*t*
bacterial, 2604, 2605*f*, 2605*t*
Chlamydia trachomatis causing, 2012
chlamydial, 2604
follicular, 2009
Connective tissue, 1706
Connective tissue diseases, 1714, 1724–1729. *See also* Rheumatic diseases
clinical manifestations of, 1724–1725
cystic fibrosis *versus*, 558
diagnosis of, 1725
differential diagnosis of, 1725
Ehlers-Danlos syndromes, 1726–1727, 1727*b*, 1727*t*
interstitial lung disease associated with, 571*t*, 580–582
Marfan syndrome, 1725–1726, 1726*b*
mixed, 581
Connective tissue diseases *(Continued)*
mucopolysaccharidoses, 1724–1725, 1724*t*, 1725*b*
osteogenesis imperfecta, 1727–1729, 1728*b*, 1728*t*
pseudoxanthoma elasticum, 1729, 1729*b*
Connective tissue hyperplasia, 2624, 2625*t*
Consciousness, 2437, 2437*t*
Consolidation chemotherapy, 1262*b*
Constipation, 862
abdominal pain and, 856
algorithm for, 891*f*
diagnosis of, 890
epidemiology of, 890
evacuation disorder *versus*, 890*t*
irritable bowel syndrome in, 888
management of, 13*t*
pathobiology of, 890
psychotropic medications and, 2678*t*
severe mental illness and, 2683*t*
signs and symptoms of, approach to, 852*t*
slow-transit, 890
treatment of, 862*b*, 891*b*, 891*t*
Constitutional DNA, 1248
Constrictive pericarditis, 429.*e*1*f*, 431*f*–432*f*
Constructional apraxia, 989
Consultant, responsibilities of, 2658–2659
Consumer-based rhythm monitors, 308
Consumptive coagulopathy, 707, 1195
Contact activation factors, deficiencies of, 1192, 1192*b*
Contact activation (intrinsic) pathway, 1165
Contact dermatitis, 1673*t*, 2729
allergic
description of, 1674
illustration of, 2691*t*, 2696*f*
irritant, 2704
Contact hypersensitivity, 1692
Contemporary medical science, 2
Continence
geriatric assessment of, 118
physiology of, 888, 888*f*
Contingency management
for drug use disorders, 2361*b*
for stimulant use disorders, 2363*b*
Continuous data, 36
Continuous murmurs, 214
Contraception, 1610–1617
in adolescents, 112
barrier methods of, 1611–1613
diaphragm, 1611–1612
female condom, 1612–1613
intravaginal ring, 1615
male condom, 1612
oral contraceptives, 1613–1615
spermicides, 1611
transdermal patch, 1615
behavioral methods of, 1611
benefits of, 1611
contraindications for, 1611, 1616*t*
depot medroxyprogesterone acetate, 1615
emergency, 1615
hormonal (steroidal), 1613–1617
injectable steroid, 1615–1616
intrauterine devices for, 1617
natural method of, 1611
perfect use of, 1611, 1612*t*, 1613*f*
permanent, 1617
pregnancy and, 1772*b*
risks of, 1611
for sexually transmitted infections, 1884
sterilization for, 1617
subdermal implants for, 1616–1617
typical use of, 1611, 1612*t*, 1613*f*
unintended pregnancy and, 1611
vasectomy, 1617
venous thromboembolism and, 481
withdrawal method of, 1611
Contractile cells, 224
Contraction, 224, 224.*e*1*f*
Contraction coupling, 224.*e*1*f*
Contractures, 2370
Contrast echocardiography, 238, 240*f*
Contrast-induced acute kidney injury, 393–394
Contrast venography, 484
of venous thromboembolism, 490
Conus medullaris syndrome, 2404
Convalescent plasma, for COVID-19, 2216
Conventional angiography, strengths and weaknesses of, 2373*t*

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Conventional disease-modifying antirheumatic drugs, 1755*b*, 1756*t*, 1757*t*
Convergence, 2618, 2619*f*
Conversion disorder, 2346–2347, 2347*t*
Cooley anemia, 1106
COPA (coatamer subunit α) syndrome, 1731*t*
Copanlisib (Aliqopa), 1215*t*
Copaxone. *See* Glatiramer acetate
COPD. *See* Chronic obstructive pulmonary disease
Copeptin, 260.*e1t*
Copper, *e1t–e8t*, 1457*t*
  deficiency of, 2538*t*, 2541*t*, 2542
  for malabsorption, 937*t*
  toxicity, 88*t*
Coproporphyrinogen III, 1429.*e1f*
Coproporphyrinuria, 1434
Copy number variants, 164
Cor pulmonale, cystic fibrosis with, 558.*e1f*
Cor triatriatum, 354
Coral snake bites, 708, 708*b*
Corals, 713
Cord blood hematopoietic stem/progenitor cells, 1206–1207
Core myopathy, 2585.*e1f*
Core temperature, 33
Cori disease, 1417*t*
Cornea
  abrasion of, 2602–2603
  anatomy of, 2596
Cornea verticillata, 2614
Corneal reflex, 2439
Corneal stromal dystrophy, 2611
Cornell voltage criterion hypertrophy, 233
Coronary angiography
  in acute coronary syndrome, 372
  in chronic angina and stable ischemic heart disease, 363*t*
  computed tomography, 249, 249.*e2f*, 250*f*, 360
  in coronary artery disease, 393
  diagnostic, 363, 363*t*
  in heart failure, 261
Coronary angioplasty
  medical therapy *versus*, 397
  percutaneous transluminal, 464.*e1f*, 468*b*
  technique, 395*f*
Coronary arteriography, 393–395
Coronary artery
  anomalous origin of, 249.*e2f*, 352–353, 353*f*
  calcium scoring, 249, 249*f*
Coronary artery bypass graft (CABG) surgery, 265*b*, 397
  for acute STEMI, 398
  antiplatelet therapy for, 507
  for chronic stable angina, 398
  for coexisting cardiac disease, 399
  for failed PCI, 399
  indications for, 398–399
  for ischemic heart disease, 364*b*
  late outcomes, 399
  for multivessel coronary artery disease, 364*b*
  for myocardial infarction, 398
  PCI *versus*, 399
  perioperative risks, 398–399
  reoperations, 399
  for survival, 398–399
  for symptom relief, 398
  types of grafts, 397–398, 398*f*
Coronary artery disease, 312
  detection of, 248
  diagnose, 357*f*, 362*t*
  echocardiographic findings, 242*t*
  Hodgkin lymphoma and, 1292*b*
  interventional diagnosis and treatment of, 393–399
  predicted risk for, 221.*e1f*
  risk for, blood pressure and, 440–441
  thrombotic, 381*t*
Coronary artery fistulas, 352
Coronary artery injuries, 700*b*
Coronary artery surgery, 397–399
Coronary blood flow, 224
Coronary emboli, 381*t*
Coronary heart disease
  in HIV, 2316–2317
  menopause associated with, 1630*b*
  nutrition and, 58
  in women, 1607
Coronary intensive care, 384*b*
Coronary intervention, percutaneous, 265*b*
Coronary ostial occlusion, 381*t*
Coronary revascularization, 374*t*, 2662*b*
Coronary stenosis
  assessment of, 393, 394*f*
  coronary arteriography for, 393
Coronary stents, 395, 2662*b*
  balloon-expandable, 395.*e1f*
Coronary vascular disease, infiltrative and degenerative, 381*t*
Coronary vasculitis, 381*t*
Coronary vessels, 394*f*
Coronavirus 2019 (COVID-19), 17, 25, 46, 2213–2215, 2639
  acute respiratory distress syndrome and, 650
  chest radiograph of, 520.*e1f*
  classification of, 2209*t*
  clinical manifestations of, 2213–2214, 2214*f*, 2214*t*
  community prevention of, 2215
  computed tomographic scan of, 520.*e1f*, 521*f*
  diagnosis of, 2214–2215, 2215*f*
  encephalitis and, 2535
  epidemiology of, 2213–2215
  genome of, 2210, 2210*f*
  hypercoagulable states and, 481
  immune response of, 2212
  immunization for, 66*t*, 77–78, 78*f*
    adverse reactions of, 78
    indications for, 78
    schedule of, 76.*e1t*, 77*f*–78*f*
  in older adults, 115
  physical examination and, 28
  in pregnancy, 1628
  prognosis of, 2215
  thrombocytopenia and, 1175
  transmission of, 2213
  treatment of, 2216–2220
    for contacts of infected person, 2219
    general care for, 2218
    general principles of, 2216–2218, 2216*f*
    for hospitalized patients, 2217–2218
    for outpatients with mild to moderate, 2216–2217
    overview of, 2216, 2216*f*
  tuberculosis and, 2032
  vaccination for, 2218*t*, 2219
    adverse effects of, 2219
    policy of, 2219
  variants of, 2212
  virology and pathology of, 2209–2212
Coronaviruses, 2206*f*
  in acute bronchitis and tracheitis, 605
  antiviral therapy for, 2190
    bamlanivimab/etesevimab as, 2190
    bebtelovimab as, 2190
    casirivimab/imdevimab as, 2191
    imiquimod as, 2191
    molnupiravir as, 2190
    nirmatrelvir boosted with ritonavir as, 2190
    remdesivir as, 2190
    sotrovimab as, 2191
  Middle East respiratory syndrome. *See* Middle East respiratory syndrome
  pneumonia, 608
  pre-2019, 2206–2209
  seasonal, 2206–2207
  severe acute respiratory syndrome. *See* Severe acute respiratory syndrome
Corpus callosum, agenesis of, 1479, 2547, 2547*f*
Corrected count increment, 1204
Corrigan pulse, 410
Cortical collecting duct, 754, 754.*e1f*
Cortical thrombophlebitis, 2511
Corticobasal degeneration, 2485*t*
Corticomedullary cysts, 814
Corticosteroids
  for acute interstitial pneumonia, 568
  antiretroviral therapy and, 2317
  for aspergillosis, 2094
  for autoimmune hemolytic anemia, 1089*b*
  for Bell palsy, 2579*b*
  for blastomycosis, 2081*b*
  for cancer, 1232*b*
  for chronic lymphocytic leukemia, 1269*t*
  for COVID-19, 2217
  for Crohn disease, 945*b*, 946*t*
  for diffuse alveolar hemorrhage, 569*b*
  for focal segmental glomerulosclerosis, 779*b*
  for giant cell arteritis, 1803*b*
  for HAM/TSP, 2328*b*
Corticosteroids *(Continued)*
  for hearing loss, 2642*b*
  for immune thrombocytopenic purpura, 1175*b*–1176*b*
  for interstitial lung disease, 575*b*, 575*t*
  for listeriosis, 1938*b*
  for liver transplantation, 1048*t*, 1049
  for membranoproliferative glomerulonephritis, 786*b*
  for membranous nephropathy, 780*b*
  for minimal change disease, 778*b*
  for multiple sclerosis, 2504*b*
  for nausea and vomiting, 863*t*
  for pulmonary alveolar proteinosis, 567*b*
  for rapidly progressive glomerulonephritis, 785*b*
  for rhinitis, 2632*b*, 2634*t*
  for spondylitis, 1765*b*
  for uveitis, 2604
  for zoster, 2249*b*
Corticotroph adenoma, 1493
Corticotropin-releasing hormone (CRH)
  adrenocorticotropic hormone secretion affected by, 1492
  cortisol release by, 1520
  description of, 1477
  stimulation test, for Cushing disease, 1494
Cortisol, 746, 749
  free, *e1t–e8t*
  gluconeogenesis and, 1552–1553
  late-night salivary measurement of, 1494
  plasma, 1522
  production of, 1520
  total, *e1t–e8t*
Corynebacterium, infections caused by, 1933–1935
  clinical manifestations of, 1933–1935
  community-acquired, 1934*t*
  diagnosis of, 1935
  epidemiology of, 1933
  health care-associated, 1934*t*
  pathobiology of, 1933
  pathogen of, 1933
  prevention of, 1935
  prognosis of, 1935
  treatment of, 1935*b*, 1935*t*
Corynebacterium diphtheriae, infections caused by, 1933, 2578, 2649
  clinical manifestations of, 1933–1934
  diagnosis of, 1935
  epidemiology of, 1933
  pathobiology of, 1933
  prevention of, 1935
  prognosis of, 1935
  treatment of, 1935*b*
Corynebacterium jeikeium, 1934–1935
Corynebacterium minutissimum, cellulitis caused by, 2740
Corynebacterium pseudodiphtheriticum, 1934
Corynebacterium pseudotuberculosis, 1934
Corynebacterium ulcerans, 1934
Cosmetics, for skin cancers, 2701
Costello syndrome, 1250*t*
Costimulation blockade
  for allograft rejection, 207
  in renal transplantation, 845, 845*t*
Costimulatory signals, 152
Costochondritis, 359
Costs, quality and, 46
Cotellic. *See* Cobimetinib
Cotswold modification, 1291, 1291*t*
Cotton, 88*t*
Cough, 2192
  acute, 512
  by acute bronchitis, 605, 606*b*
  approach to, 512–513, 513*t*
  chronic, 512
    diagnosis of, 512, 513*t*, 514*f*
    management of, 514*f*
  cystic fibrosis and, 557
  Mycoplasma pneumoniae in, 2005–2006
  pulmonary alveolar proteinosis and, 567
  treatment of, 513*b*, 2193*b*
Cough-related syncope, 306
Counseling
  drug, 275*t*
  medication use, 265*b*
Counter-regulatory hormones, to hypoglycemia, 1552–1553, 1554*f*
Couples therapy, 1634*b*
Covariate, 36
COVID-19. *See* Coronavirus 2019
COVID-19-associated nephropathy, 789
COVID encephalitis, 2535, 2535*b*
Cowden syndrome, 1250*t*, 2729–2730, 2731*f*
Cowdry type A bodies, 2245
Cowpox, 2237–2239, 2238
Cox proportional hazards model, 37
Coxiella burnetii, 417*t*, 2054, 2062, 2064, 2065*t*
Coxiellae, 2055*t*
C-peptide, *e1t–e8t*
CPIC, 169.*e1t*
CPN-1 (carboxypeptidase-N), 200*t*
CPR. *See* Cardiopulmonary resuscitation
Crab lice, 711
Crackles, 30, 512–513, 512*t*
CRAFFT screening tool, for drug and alcohol use, in adolescents, 113, 113*t*
Cranial autonomic dysfunction, 2555
Cranial nerve examination, in coma, 2439
Cranial neuropathies, 2577
Cranial parasympathetic failure, 2554–2555, 2555
Craniopharyngiomas, 1479
Crazy paving, 567, 567*f*, 567.*e1f*, 598
C-reactive protein (CRP), *e1t–e8t*, 186, 1712
  by high-sensitivity method (hs-CRP), *e1t–e8t*
Cream, 2697
Creatine kinase (CK), *e1t–e8t*
  muscle isoform of, 2581
Creatinine, *e1t–e8t*
Creatinine clearance (Cl_{cr}), *e1t–e8t*, 129–130, 721, 721*t*
Creon, for exocrine pancreatic insufficiency, 975*t*
Crepitus, 1710
Crescendo thyrotoxicosis, 1511*b*
CREST syndrome
  ectasias and, 967
  florid features of, 987
Creutzfeldt-Jakob disease, 1204
  magnetic resonance imaging of, 2424*f*
  sporadic, 2422
CRH. *See* Corticotropin-releasing hormone
CRIA syndrome. *See* Cleavage resistant RIPK1 induced autoinflammatory syndrome
Cricoarytenoid joint, rheumatoid arthritis of, 1752
Cricopharyngeal bars, 909
CRIg. *See* Complement receptor of the immunoglobulin superfamily
Crigler-Najjar syndrome, 994–996, 995
  clinical features of, 997*t*
  type 1, 995
  type 2, 995
Crimean-Congo hemorrhagic fever, 99, 99.*e1t*, 2265*t*, 2266, 2268*t*, 2275*t*
Crisaborole, for skin diseases, 2698
CRISPR. *See* Clustered Regularly Interspaced Short Palindromic Repeats
Critical care
  analgesia in, 636
  approach to, 636–638
  long-term outcomes, 636–637
  oxygen intubation in, 636
  predictions, 638
  preferences for, 638
  prevention of complications, 637
  respiratory monitoring in, 639–641
  sedation in, 636
Critical care physicians, 636
Critical illness neuropathy, 2578
Critical illness-associated hypoglycemia, 1553, 1557*b*
Critical limb ischemia, 465.*e1f*
Crizanlizumab
  for hereditary angioedema, 152
  for sickle cell disease, 1116*t*
Crizotinib (Xalkori), 1215*t*
CRMO. *See* Chronic recurrent multifocal osteomyelitis
Crofelemer, 941*b*
Crohn colitis, 1056
Crohn disease
  abscesses in, 945*b*
  algorithm for, 947*f*
  asthma and, 943
  clinical characteristics of, 942*t*
  complications of, 945*b*
  corticosteroids for, 945*b*, 946*t*
  cystic fibrosis *versus*, 558
  definition of, 941
  endoscopy of, 944, 944*f*

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Crohn disease *(Continued)*
epidemiology of, 941
esophageal, 943
esophageal involvement in, 911
fistulae associated with, 943, 979, 979*f*
fistulizing, 945*b*
gastroduodenal ulcers associated with, 915–916
genetics of, 942
ileal disease and, 934
immunomodulators for, 945*b*
irritable bowel syndrome in, 889
medical therapy for, 945*b*
mild to moderate, 945*b*
moderate to severe, 945*b*
on MR enterography, 873*f*
obstruction in, 945*b*
pathology of, 942
perianal disease in, 945*b*
perianal fistulas associated with, 945*b*
physical examination in, 943
prognosis for, 950
radiology of, 945
rectovaginal fistulas associated with, 945*b*
serologic markers of, 945
surgical therapy for, 945*b*
symptoms of, 943
weight loss and, 860*t*
Crohn Disease Activity Index, 945.*e1t*
Cromolyn, 2632*b*
Cross-consultations, 2656
Cross-sectional studies, 41
Crotalinae bites, 709*t*
Crotamiton, for scabies, 711*b*
Croup, 2196
CRT. *See* Cardiac resynchronization therapy
Crush injury, 716
characteristics of, 699*t*, 700, 700*f*
management of, 717*b*
Crust, 2687.*e4t*
Crusted scabies, 2741–2742
Cryoglobulin, peripheral blood smear of, 1074*t*
Cryoglobulinemia, 681, 1304–1305, 1798, 1798*b*
essential mixed, 1716
mixed, 789, 1716
type I, 1304, 1304*b*, 1304*f*
type II, 1304–1305, 1305*b*
type III, 1305
Cryoglobulinemic vasculitis, 784*t*
Cryoglobulins, 1716
for glomerular syndromes, 727
Cryoprecipitate
HIV transmission through, 2299
transfusion, 1199*t*, 1200, 1205
Cryopyrin-associated periodic syndromes (CAPS), 1734–1735, 1735*b*
Cryopyrinopathies, 1734
Cryptic shock, 661
Cryptococcal meningitis
description of, 2087, 2523
fluconazole for, 2075–2076
Cryptococcal polysaccharide antigen (CRAG), 2088
Cryptococcosis, 2651
definition of, 2087
pathogens that cause, 2087
Cryptococcus neoformans, 1024, 1855–1857, 1861, 2087
Cryptogenic chronic liver disease, 1017
Cryptogenic fibrosing alveolitis, 2327*t*
Cryptogenic organizing pneumonia, 578–579
diagnosis of, 579–580, 579*f*–580*f*, 580*f*
increased lymphocyte counts in, 533
prognosis for, 579*b*
radiographic features of, 574*t*
treatment of, 579*b*
Cryptogenic stroke, 2472, 2472*f*
Cryptorchidism, surgical correction of, 1383–1384
Cryptosporidiosis, 2141–2143
childhood, 2143
clinical manifestations of, 2143
definition of, 2141–2143
diagnosis of, 2143
epidemiology of, 2141–2142
in immunocompetent host, 2143
in immunocompromised hosts, 2143
malabsorption and, 937
pathobiology of, 2142–2143
pathogen of, 2141, 2142*f*
Cryptosporidiosis *(Continued)*
prevention of, 2143
prognosis of, 2143
treatment for, 2143*b*
Cryptosporidium spp., 1026*t*
definition of, 2141
epidemiology of, 2141
life cycle of, 2141, 2142*f*
oocysts, 2141
outbreaks of, 925
pathobiology of, 2142
Crystal deposition diseases, 1810–1816
apatite (basic calcium phosphate)-associated arthropathy, 1815
calcium pyrophosphate dihydrate crystal deposition disease, 1814
gout, 1810–1813
hyperuricemia, 1810
Crystalline arthropathies, 1731*t*
Crystalline lens, 2596
Crystalloid solution, for shock, 662*b*
Crystals, of urine, 722, 724*f*–725*f*
CSF. *See* Cerebrospinal fluid
CT. *See* Computed tomography
CTA. *See* Computed tomography angiography
CTLA-4. *See* Cytotoxic T lymphocyte antigen-4
C-type lectin receptors, 183
Culture, of safety, 46
Culture-independent molecular stool testing, for enteric infection, 1870–1871, 1870*t*
Cultures, blood, for infection, 1834
Cumulative Deficit Frailty Model, in older adults, 123*t*
Cupula, 2644, 2646
Curbside consultation, 2657–2658
Cushing disease
blood tests for, 1494
clinical features of, 1493*t*, 1494*f*
clinical manifestations of, 1493–1494
CRH stimulation test for, 1494
definition of, 1493–1494
dexamethasone suppression testing for, 1494, 1495*t*
diagnosis of, 1494, 1495*f*
epidemiology of, 1493
inferior petrosal sinus sampling of, 1494
late-night salivary cortisol measurement for, 1494
magnetic resonance imaging for, 1494
pathobiology of, 1493
prognosis for, 1495*b*
treatment of, 1495*b*
24-hour urine for, collection of, 1494
Cushing reflex, 34
Cushing syndrome, 1520–1524
algorithm for, 1522*f*
clinical examination of, 1521
clinical manifestations of, 1520–1521
definition of, 1493
description of, 749, 749*t*, 1465
dexamethasone suppression tests for, 1522
diagnosis of, 1521–1524
differential diagnosis of, 1522–1524, 1523*f*
endogenous, 1522
epidemiology of, 1520
etiology of, 1522*t*
evaluation of, 448*t*
after hematopoietic cell transplantation, 1211–1212
hypercortisolism in, 1520–1521
laboratory findings in, 1521–1522
medical therapy for, 1524*b*
oligomenorrhea associated with, 1521
pathobiology of, 1520
prognosis for, 1524
pseudo-Cushing states *versus*, 1521*f*, 1522
radiation therapy for, 1524*b*
saliva cortisol measurements in, 1522
signs and symptoms of, 1520, 1521*t*
surgical therapy for, 1524*b*
treatment of, 1524*b*
urine free cortisol measurements in, 1522
Cutaneous anthrax, 1932, 1932*b*
Cutaneous atypical mycobacteria, in travelers, 1889.*e1t*
Cutaneous B-cell lymphoma, 2734
Cutaneous candidiasis, 2090
Cutaneous diphtheria, 1934
Cutaneous emboli, 2716, 2716*f*
Cutaneous human polyomavirus, 2232
Cutaneous infection, nocardiosis and, 2073
Cutaneous larva migrans, 2170, 2170*t*
in travelers, 1889.*e1t*
Cutaneous leishmaniasis, 2131
clinical manifestations of, 2133, 2134*f*
complex manifestations of, 2133–2135
diagnosis of, 2133
diffuse, 2133
disseminated, 2133
parasitology of, 2133, 2135*f*
prevention of, 2133
prognosis for, 2133–2135
recidivans, 2133
treatment of, 2133*b*, 2135*f*
Cutaneous lesions
blastomycosis and, 2081, 2081*f*
human immunodeficiency virus associated with, 2323*t*
Cutaneous leukocytoclastic angiitis, 1793*t*, 1799, 1799*b*
Cutaneous mastocytosis, 1699–1701, 1701
Cutaneous mucormycosis, 2099
Cutaneous mucosa-associated lymphoid tissue (MALT) lymphoma, 2734, 2734*f*
Cutaneous porphyrias, 1435, 2705, 2705*f*
Cutaneous psoriasis, 2705
Cutaneous T-cell lymphoma, 2686.*e2f*
Cutaneous ulcer, chancroid and, 1951, 1952*f*
CVF. *See* Cobra venom factor
CXCL4, 1065
CXCR2, 1065
CXCR4, 2291
Cyanide antidote kit, for acute poisoning, 693*t*
Cyanide poisoning, 596, 596*b*
Cyanosis, 215, 218*f*, 355, 639
CyberKnife stereotactic radiotherapy, for pituitary tumors, 1487*b*
CyBorD, for amyloidosis, 1308*f*
Cycad toxins, 2541*t*
Cyclic antidepressants, toxicity, 686*t*
Cyclic neutropenia, 1144, 1144*t*, 1683.*e1t*
Cyclizine, for nausea and vomiting, 863*t*
Cyclooxygenase-1 inhibitors, 914–915
Cyclooxygenase-2 inhibitors
description of, 914
for rheumatoid arthritis, 1755*b*
Cyclophosphamide, 149, 1215*t*
for amyloidosis, 1308*b*
cardiomyopathy due to, 288
for chronic lymphocytic leukemia, 1269*t*, 1270*t*
for granulomatosis with polyangiitis, 582
for membranous nephropathy, 780*b*
for rapidly progressive glomerulonephritis, 785*b*
for systemic lupus erythematosus, 1772*b*
for systemic sclerosis, 1781*b*
Cyclospora cayetanensis, 2155, 2155*f*, 2156*t*
Cyclosporiasis, 2155
Cyclosporine, 148–149
for acute graft-*versus*-host disease, 1210
for focal segmental glomerulosclerosis, 779*b*
hyperkalemic acidosis caused by, 751
for inflammatory bowel disease, 946*t*
for liver transplantation, 1048*t*
for membranous nephropathy, 780*b*
for minimal change disease, 778*b*
in renal transplantation, 845*t*
for total knee arthroplasty, 1830.*e1t*
Cyclosporine A, *e10t*–*e11t*
Cyclothymic disorder, 2342
CYP2B6 gene, 160*t*
CYP2C9 gene, 160*t*
CYP2C19 gene, 160*t*
CYP2D6 gene, 160*t*
CYP3A5 gene, 160*t*
CYP4F2 gene, 160*t*
Cyproterone acetate, for transgender women, 1579*t*
Cyramza. *See* Ramucirumab
Cyst(s)
benign pericardial, 433
bronchogenic, 565
echinococcal, 2161
hepatic, 990, 991*f*
thoracic, 564
Cystathionine β-synthase deficiency, 1425–1426, 1426*t*
Cystatin C, *e1t*–*e8t*, 260.*e1t*
Cysteamine bitartrate, 817*b*
l-Cysteinamide, 1215*t*
Cysteine proteinases, 227
Cystic bronchiectasis, chest radiograph of, 557*f*
Cystic diseases
adventitial, of lower extremity arteries, 467
congenital, of thorax, 564
Cystic echinococcosis, 2161, 2161*b*
Cystic fibrosis, 556–559, 993, 1825
associated variants of, 557*t*
classification of, 556*t*
clinical features of, 515*t*
clinical manifestations of, 557
definition of, 556–559
diagnosis of, 557–558, 557*f*, 558*f*, 558.*e1f*
differential diagnosis of, 558–559
epidemiology of, 556
gene therapy for, 177
genetics of, 556–557
in liver, 556
obstruction and, 532
in pancreas, 556
pathobiology of, 556–557
prevention of, 559
with pulmonary hypertension and cor pulmonale, 558.*e1f*
in sinuses and lungs, 556
in sweat glands, 556
treatment of, 558*b*, 1970*b*
Cystic fibrosis transmembrane conductance regulator (CFTR), 556, 1968
Cystic hydatid disease, 2161, 2161*b*, 2162*f*
Cystic kidney diseases, 808–815
acquired, 815, 815*b*
autosomal dominant polycystic kidney disease as, 808
autosomal dominant tubulointerstitial kidney disease as, 814
autosomal recessive polycystic kidney disease as, 812
clinical features of, comparison of, 809*t*
definition of, 808
epidemiology of, 808
gross pathology of, 808*f*
medullary sponge kidney as, 814, 814*b*
nephronophthisis as, 813–814
rare childhood syndromes as, 814, 815*b*
tuberous sclerosis as, 814, 814*b*
von Hippel-Lindau syndrome as, 814, 814*b*
Cystic medial necrosis, 1725
Cystic neoplasms, 1355–1356
Cysticercosis, 2158*t*, 2159
Cystine stones, 804–805, 815
Cystinosis, 815, 816*t*, 817*b*, 1420*t*, 1424
Cystinuria, 804–805, 815, 815*b*, 816*t*
Cystitis, 2091
antimicrobials for, 1876*t*
clinical manifestations of, 1874
description of, 1873
diagnosis of, 1876*t*
hemorrhagic, 2205
symptoms of, 1874*t*
treatment of, 1875*b*, 1876*t*
Cystoisospora belli, 2155, 2155*f*, 2156*t*
Cystoisosporiasis, 2155
Cystoscopy, for prostatitis, 825
Cytarabine, 1215*t*
Cytisine, for tobacco dependence, 2351*t*
Cytochrome oxidase inhibitors, central nervous system effects of, 685*t*
Cytochrome P-450 IIC (CYP2C), 132*t*
Cytochrome P-450 IID6 (CYP2D6), 132*t*
Cytochrome P-450 oxidoreductase deficiency, 1573
Cytogenetic abnormalities, of chronic myeloid leukemia, 1277
Cytogenomic microarray analysis, 158
Cytokine receptors, 184, 185*f*
Cytokines, 151–152, 189.*e1t*, 2079
in diabetic nephropathy, 796
interleukin-1, 151, 151*t*
interleukin-1β, 151
interleukin-2, 151
interleukin-4, 151
interleukin-5, 151
interleukin-6, 151, 151*t*
interleukin-12, 151
interleukin-13, 151
interleukin-17, 152
interleukin-23, 151
tumor necrosis factor-α, 151, 151*t*

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Cytolysin-hemolysin, 1920
Cytomegalovirus (CMV), 2250–2253, 2322*t*
  in acquired immunodeficiency syndrome, 2251
  antiviral therapy for, 2187*t*
  clinical manifestations of, 2251–2252
  colitis caused by, 2251
  congenital, 2251
  definition of, 2250–2253
  diagnosis of, 2252
  epidemiology of, 2250–2251
  of esophagus, 912
  gastrointestinal disease caused by, 1859
  hyperimmune globulin, 2252–2253
  immune response to, 2251
  immunization for, 65*t*
  in immunocompetent persons, 2251
  after lung transplantation, 633
  medications for, 2252*b*
  neonatal, 2251
  pathobiology of, 2251
  pathogen that causes, 2250
  pneumonia caused by, 2250*f*, 2251
  post-transplant, 2252*b*
  prevention of, 2252–2253
  prognosis for, 2253
  retinitis caused by, 2251, 2251*f*, 2307, 2606
  transfusion transmission of, 1200
  in transplant recipients, 2251
  treatment of, 2252*b*, 2252*t*
  ventriculitis, 2532*t*
Cytopenia, 2313–2314
  in hemophagocytic lymphohistiocytosis, 1160
Cytoplasmic nucleic acid sensors, 183, 184*f*
Cytotoxic agents
  for cancer, 1232*b*
  warm autoimmune hemolytic anemia treated with, 1089*b*
Cytotoxic T lymphocyte antigen-4 (CTLA-4), 152

D

D-dimer test, *e8t*–*e9t*, 483–484
D-Penicillamine, for Wilson disease, 1437*b*
Dabigatran, 502*t*, 504, 505*t*
  for atrial fibrillation, 397
  characteristics of, 487*b*
  for venous thromboembolism, 478*b*, 487*b*
Dabrafenib (Tafinlar), 1215*t*, 1251*t*
  for melanoma, 1394*t*
Daclatasvir, for hepatitis C infections, 2181*t*, 2182*t*, 2184–2185
Daclatasvir/asunaprevir, for hepatitis C infections, 2181*t*, 2185
Daclizumab, 151
Dacogen. *See* Decitabine
Dacrocytes, 1069*f*
Dactylitis, 1763
  in sickle cell disease, 1112–1113
DADA2. *See* Deficiency of adenosine deaminase-2
Dairy, dietary guidelines for, 57.*e3t*
Dalbavancin
  dosage of, 1895*t*
  mechanism of action, 1895*t*
  spectrum of activity, 1900
Dalfampridine (Ampyra), for multiple sclerosis, 2505*t*
Dalteparin, 503*t*
  for acute coronary syndrome, 374*t*
  for venous thromboembolism, 1624*t*
Damage-associated molecular patterns (DAMPs), 191, 192*f*
Damage control surgery, 700*b*
Damaged innervation, in lower urinary tract, 828
Damaging effectors, inhibitors of, 196
DAMPs. *See* Damage-associated molecular patterns
Danaparoid, 503*t*
Danazol
  for endometriosis, 1596*b*
  warm autoimmune hemolytic anemia treated with, 1089*b*
Danon disease, 1417*t*, 1418–1419
Dantrolene, for malignant hyperthermia, 679*b*–680*b*, 2668*b*
Dantrolene sodium, for malignant hyperthermia, 717*b*
Dapagliflozin
  for heart failure, 271*t*
  for type 1 diabetes mellitus, 1537*b*–1538*b*
  for type 2 diabetes mellitus, 1541*t*
Dapsone
  for HIV/AIDS, opportunistic infections associated with, 2309*t*
  hypersensitivity syndrome, 2052*b*
  for leprosy, 2052*b*, 2053*t*
  for *Pneumocystis* pneumonia, 2108*t*
  for skin diseases, 2699
  for toxoplasmosis, 2112*t*
Daptomycin
  for bacterial meningitis, 2518*t*
  characteristics of, 1900
  dosage of, 1895*t*
  for endocarditis, 419*t*
  mechanism of action, 1895*t*
  for methicillin-resistant *Staphylococcus aureus*, 1905
  resistance mechanisms, 1893*t*
  for vancomycin-resistant enterococci, 1922*t*
Daratumumab
  for amyloidosis, 1308*b*, 2560*b*
  for multiple myeloma, 1299*b*, 1301*t*
Darier sign, 2725
Darifenacin, 824*t*
Darunavir, 2301*t*
Dasatinib (Sprycel), 1215*t*, 1251*t*, 1275*t*
DASH. *See* Dietary Approaches to Stop Hypertension
DASH-sodium diet, for chronic kidney disease, 839*b*
Data
  characteristics, 36
  interpretation, 35–36
Daunorubicin, 1215*t*
Daycare diarrhea, 926
DCD. *See* Donation after cardiac death
DDAVP, for von Willebrand disease, 1183*b*
de Musset sign, 410
de Quervain tenosynovitis, 1745, 1745*b*, 1746*f*
de Quervain thyroiditis, 1513, 1514*b*
Dead space ventilation (V_D), 640–641
Deafness, hereditary, 2641
Death and dying
  causes of, in adolescents, 110, 110*t*
  in endoscopy, 876*t*
  leading causes of, 21, 22*f*, 57*t*
  in palliative care, 16
  sudden death, 282*b*
Deauville score, 1281
Debrisoquine-sparteine polymorphism, 132*t*
DEC. *See* Diethylcarbamazine
Decay-accelerating activity, 199
Decay-accelerating factor, 200*t*
Decision analysis, 39, 39.*e1f*
Decision making, 39
  aids to, 39
  decision analysis, 39, 39.*e1f*
  in geriatrics assessment, 117
  risk stratification with, 363*t*
  shared, 39
Decitabine (Dacogen), 1215*t*
  for myelodysplastic syndromes, 1255
Declarative episodic memory system, 2407
Decolonization therapy, for health care-associated infections, 1867
Decompensated cirrhosis, 1014*b*, 1015*t*, 1037, 1038
Decompression illness, 593
  clinical manifestations of, 594
  definition of, 593
  diagnosis of, 594
  epidemiology of, 593
  pathobiology of, 594, 594.*e1f*
  prevention of, 594
  treatment of, 594*b*
Decompression sickness, 593
  epidemiology of, 593
  type I, 593
  type II, 593
Decompressive surgery, 2401*b*
Decongestants, for rhinitis, 2632*b*
Decontamination, for acute poisoning, 691*b*
Decorticate posturing, 2439*t*, 2440
Decreased libido, 1587
Decubitus ulcers, spinal cord injury and, 2388*b*–2390*b*
Deep brain stimulation, for Parkinson disease, 2486
Deep enteroscopy techniques, 1345
Deep muscle necrosis, electrical injury and, 703
Deep mycoses, 2621*t*
Deep space infections, 2649–2650, 2650*f*
Deep venous thrombosis (DVT), 482
  algorithm for, 477*f*
  clinical manifestations of, 483, 483*f*
  diagnosis of, 483–487, 485*f*
  of lower extremities, 476
  in pregnancy, 1622
  therapy for, 478*b*
  treatment of, 487*b*
  of upper extremities, 490
Deescalation, in psychiatric diseases, 2679
DEET, 1889, 1988
Defecation, 888, 888*f*
Defecography, for rectal intussusception, 982
Deferiprone, chelation therapy with, 1822
Deferoxamine, for acute poisoning, 693*t*
Defibrillation, transthoracic, 340
Defibrination, 1195
Deficiency of adenosine deaminase-2 (DADA2), 1731*t*, 1733*t*
Deficiency of interleukin-1 receptor antagonist (DIRA), 1731*t*, 1735
Deficiency of the IL-36R antagonist (DITRA), 1731*t*, 1735
Degenerative disc disease, 1706*t*
Degos disease, 965, 969
Dehydrated hereditary stomatocytosis, 1097
Dehydration, signs of, 861
Dehydroascorbic acid, 1453*t*
Dehydroepiandrosterone (DHEA), 1520, 1581, 1585*b*, 1599–1600
  unconjugated, *e1t*–*e8t*
Dehydroepiandrosterone sulfate (DHEA-S), *e1t*–*e8t*
Dejerine syndrome, 2465.*e1f*
Delafloxacin, 1845*t*, 1895*t*
Delayed hemolytic transfusion reaction, 1202
Delayed puberty, 1593–1594, 1594*b*
Delayed serologic transfusion reaction, 1202
Delayed-type hypersensitivity reactions, 195, 2131
Deletion, 163, 207
Delirium, 2330–2336, 2336
  caregiver issues, 2334*b*–2335*b*
  clinical manifestations of, 2332–2334
  definition of, 2331–2336
  development of, 2332
  diagnosis of, 2334
  diagnostic criteria for, 2331*t*
  differential diagnosis of, 2334
  end-of-life care for, 2334*b*
  epidemiology of, 2331
  evaluation of, 2333*f*
  laboratory findings of, 2334
  management of, approaches to, 13*t*
  medical treatment, 2334*b*
  nonpharmacologic management, 2334*b*
  in older adults, 114, 2331
  in palliative care, 12
  pathobiology of, 2331–2332
  postoperative, 2674
  preoperative, 2665, 2665*b*, 2665*t*
  prevention of, 2335–2336, 2335*t*
  prognosis for, 2336
  treatment of, 2334*b*
Delta anion gap, 756
Delta check, 1067
Delta-delta, 756
Delusional disorder, 2345*t*–2346*t*, 2346
Dematiaceous fungal infections, 2108–2111
  associated diseases with, 2109*t*
  definition of, 2108–2111
  diagnosis of, 2110–2111
  differential diagnosis of, 2110–2111
  epidemiology of, 2108–2109
  pathobiology of, 2109
  pathogens causing, 2108
  prevention of, 2111
  prognosis for, 2111
  treatment of, 2111*b*
Dementia, 117, 2336, 2412, 2544
  clinical examination in, 2412–2413
  clinical manifestations of, 2412
  definition of, 2412, 2412*t*
  diagnosis of, 2412–2413, 2413*f*
  dialysis, 101*t*, 105, 105*b*
  differential diagnosis of, 2413, 2414*f*
  end-of-life care for, 2413
  epidemiology of, 2412
  HIV-associated, 2312
  multi-infarct, as arterial thrombotic complications, 481
  nutrition and, 60
Dementia *(Continued)*
  pathobiology of, 2412
  prognosis for, 2413
  rapidly progressive, 2424, 2424*t*
  semantic, 2421
  spectrum of mild cognitive impairment to, 2412–2413
  trajectories of, 12.*e1f*
Dementia with Lewy bodies, 2420–2421
  clinical manifestations of, 2420
  definition of, 2420
  diagnosis of, 2420–2421, 2420*t*
  differential diagnosis of, 2420–2421, 2485*t*
  epidemiology of, 2420
  pathobiology of, 2420
  prognosis of, 2421
  treatment of, 2421*b*
Demyelinating conditions, 2498–2510
  acute disseminated encephalomyelitis, 2509
  adrenoleukodystrophy, 2509
  adrenomyeloneuropathy, 2509, 2509*b*
  Canavan disease, 2510
  globoid cell leukodystrophy, 2510
  metachromatic leukodystrophy, 2509
  multiple sclerosis. *See* Multiple sclerosis
  neuromyelitis optica, 2508
  optic neuritis, 2500, 2508, 2508*b*
  Pelizaeus-Merzbacher disease, 2509
  transverse myelitis, 2406, 2508, 2509*b*
  vanishing white matter disease, 2510
Demyelinating neuropathies, 1238*t*
Demyelinating processes, monofocal and monophasic, 2508–2509
Dendritic cell-specific intracellular adhesion molecule-3 grabbing non-integrin (dendritic cell-SIGN), 183
Dendritic cells, 182
Dengue, 1*f*–2*f*, 2275*t*, 2277, 2277*b*, 2277.*e1f*
  in travelers, 1888, 1889.*e1t*, 1890*t*
Dengue hemorrhagic fever, 2268*t*
Dengue virus, 2265*t*, 2266
Denosumab (Xgeva), 1215*t*
  for osteoporosis, 1643*b*, 1644*t*
Dense connective tissue, 1707
Dent disease, 816*t*, 817, 817*b*
Dental abscess, pathogens and empirical therapy for, 2526*t*
Dental caries, Hodgkin lymphoma and, 1293*t*
Denture stomatitis, 2090
Denys-Drash syndrome, 1574
11-Deoxycortisol (compound S), *e1t*–*e8t*
Deoxyribonucleases (DNases), 1913
Department of Veterans Affairs, health care system in, 42
Dependent personality disorder, 2348*t*
Depot medroxyprogesterone acetate, 1615
Depression, 2337*t*
  in adolescents, 111–112, 112
  in heart failure, 265*b*
  intimate partner violence and, 1634
  management of, approaches to, 13*t*
  in palliative care, 12
  respiratory, psychotropic medications and, 2678*t*
  screening for, 53
  weight loss and, 860*t*
  in women, 1608*t*, 1609
Dermablend, 2701
Dermacentor andersoni, 1986, 2054
Dermacentor variabilis, 1986, 2054
Dermal depth, 2688*t*–2689*t*
Dermatitis, 1736
  allergic contact, 2704
  atopic, 2702, 2703*f*
  chronic actinic, 2704, 2704*f*
  disseminated gonococcal infection and, 1949
  irritant contact, 2704
  nummular, 2688*t*, 2702, 2702*f*
  occupational and environmental, 86*t*
  seborrheic, 2703, 2703*f*
Dermatitis herpetiformis, 2718, 2718*b*, 2718*f*
Dermatofibromas, 2730
Dermatofibrosis lenticularis disseminata, 1668
Dermatologic paraneoplastic syndromes, 1239
Dermatologic surgery, for skin cancers, 2701
Dermatomal zoster, 2248, 2249*f*
Dermatomes, 2395*f*
Dermatomyositis, 1238*t*, 2588*t*
  clinical features of, 1788*t*
  clinical findings of, 1788, 1790*f*
  cutaneous manifestations of, 1707
  diagnostic criteria for, 1790*t*

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Dermatomyositis *(Continued)*
epidemiology of, 1787
interstitial lung disease associated with, 581
pathobiology of, 1787
treatment of, 1790*b*
Dermatophytes, 2754
Dermatophytoses, 2710–2711, 2711*f*
Dermatoscopy, 2747
Dermographism, 1687, 1687*f*
Desensitization, for drug allergy, 1699*b*
Desipramine
for depression, 2340*t*
for irritable bowel syndrome, 896*t*
Desmoid tumors, 958, 1390, 1390*b*
Desmopressin
for central diabetes insipidus, 1503*b*
for gestational diabetes insipidus, 1503*b*
for subarachnoid hemorrhage, 2476*b*–2478*b*
Desquamative interstitial pneumonia, 578
diagnosis of, 578, 578*f*–579*f*, 578.e1*f*, 579*f*
prognosis for, 578*b*
radiographic features of, 574*t*
treatment of, 578*b*
Desvenlafaxine
for depression, 2340*t*
for hot flashes, 1631*t*
Detrusor hyperactivity with impaired contractility, 828
Detrusor overactivity, 827
Detrusor underactivity, 828
Deutetrabenazine, for tardive dyskinesia, 2496*b*
Developmental disorders, 2545–2553
Device-associated infections, 1865–1866, 1866
Dexamethasone
for bacterial meningitis, 2515*b*
for brain tumors, 1312*b*
for COVID-19, 2217
for *Haemophilus influenzae* type b meningitis, 1944*b*
for high-altitude diseases, 593*t*
for immune thrombocytopenic purpura, 1176*t*
for nausea and vomiting, 863*t*
Dexamethasone suppression testing
for Cushing disease, 1494, 1495*t*
for Cushing syndrome, 1522
Dexmedetomidine, 2670
Dexrazoxane (Zinecard), 1215*t*
Dextroamphetamine, 1460*t*, 2446*b*, 2449*t*
Dextrocardia, 354–355
DHEA. *See* Dehydroepiandrosterone
DHT. *See* Dihydrotestosterone
Diabetes foot, 1550, 1550*b*
Diabetes insipidus, 743–744, 1483, 1500–1504
central
clinical manifestations of, 1501, 1502*f*
diagnosis of, 1502
pathobiology of, 1500
treatment of, 1503*b*
clinical manifestations of, 1501
definition of, 1500
diagnosis of, 1501–1503, 1502*f*
epidemiology of, 1500
etiologic diagnosis of, 1502–1503
gestational
clinical manifestations of, 1501
pathobiology of, 1500
treatment of, 1503*b*
nephrogenic
clinical manifestations of, 1501
diagnosis of, 1503
pathobiology of, 1500
treatment of, 1503*b*
pathobiology of, 1500–1501
prognosis of, 1504.e1*f*, 1504
provocative testing for, 1501–1502
severe mental illness and, 2683*t*
Diabetes mellitus, 1534–1551, 1608*t*
acute hyperglycemic states, 1547
acute issues for individuals with, 1545–1549
antihypertensive drug for, 454*t*
arthritis associated with, 1822
autonomic neuropathies in, 2560
cardiomyopathy in, 294
cardiovascular disease and, 1550, 1550*b*
cell therapy for, 174
chronic complications of, 1549–1550
cystic fibrosis and, 557
definition of, 1534–1536, 1534*t*
diagnosis of, 1535–1536, 1536*t*
Diabetes mellitus *(Continued)*
diarrhea associated, 939
epidemiology of, 1549
gastroparesis associated with, 889
gestational, 1544–1545, 1624, 1624*b*
glomerular diseases in, 788
with heart failure, 265*b*
heart failure associated with, 262
after hematopoietic cell transplantation, 1211
in HIV, 2318, 2318*b*
hypoglycemia, 1545–1546
inpatient management of, 1538*t*, 1545
metabolic acidosis in, 747
microvascular complications of, 1549–1550
mucormycosis and, 2098
normal renal function and, 456
nutrition and, 60
pathobiology of, 1534–1535, 1534.e1*f*, 1535*f*, 1535*t*, 1549
in pregnancy, 1619*t*, 1624, 1624*b*
prevalence of, 18
screening for, 55
surgical risks associated with, 2665
type 1, 1534*t*, 1536–1539
clinical manifestations and diagnosis of, 1535*t*, 1536–1537, 1537*f*
diet and lifestyle treatment for, 1537*b*
epidemiology of, 1536–1539
insulin therapy for, 1537*b*, 1538*t*
pathobiology of, 1536
prevention of, 1538
prognosis of, 1539
treatment for, 1537*b*, 1538*t*
type 2, 1534*t*, 1539–1544
clinical manifestations of, 1540
diagnosis of, 1535*t*, 1539*t*, 1540
epidemiology of, 1539–1544
epigenetic risk of, 1539–1540
genetics of, 1539–1540
insulin action in, 1539
insulin secretion in, 1539
metabolic monitoring in, 1540*b*
obesity and, 1466, 1540
pathobiology of, 1539–1540, 1539*t*
pharmacologic therapy for, 1540*b*, 1541*t*, 1543*f*
polygenic risk of, 1539
prevention of, 1544, 1544*t*
prognosis of, 1544
self-management education and support for, 1540*b*
single-gene mutations, 1539
sleep deprivation and, 1540
smoking and, 1540
treatment for, 1540*b*
in women, 1607
Diabetic amyotrophy, 1822
Diabetic foot ulcer, 1892*t*
Diabetic ketoacidosis (DKA), 758
anesthesia and, 2669
clinical manifestations of, 758, 1547
diagnosis of, 758, 1547–1548, 1548*t*
epidemiology of, 758, 1547
pathobiology of, 758, 1547
prevention of, 1549
prognosis of, 758, 1549
treatment of, 758*b*, 1547*t*, 1548*b*
Diabetic lumbosacral radiculoplexus neuropathy, 2577
Diabetic nephropathy, 795–799, 1549
clinical manifestations of, 796
complications of, renal, 796
cytokines in, 796
diagnosis of, 796–797
epidemiology of, 795–799
genetics of, 796
hemodynamics in, 795–796
hormones in, 796
hyperglycemia in, 795
natural history of, 796
pathobiology of, 795–796
prognosis of, 798–799
renal biopsy for, 797
renal complications in, 796
stage I, 796, 797*f*
stage II, 796, 797*f*
stage III, 796, 797*f*
stage IV, 796, 797*f*
treatment of, 797*b*, 797*f*–798*f*
Diabetic neuropathy, 1550
acute focal neuropathies, 2577
definition of, 2577
diabetic lumbosacral radiculoplexus neuropathy, 2577
distal symmetrical and autonomic polyneuropathy, 2577, 2577*b*
epidemiology of, 2577
treatment-induced, 2577
Diabetic osteolysis, 1822
Diabetic retinopathy, 1549, 1549*b*, 1549*t*, 2609, 2609*f*
Diabetic stiff hand syndrome, 1822
Diagnostic and Statistical Manual of Mental Disorders, 5th edition (DSM-5)
on alcohol use disorders, 2353
on eating disorders, 1461
"Diagnostic dilemmas", 167
Dialysis
for acute kidney injury, 774*b*
for irreversible renal failure, 841–843
Dialysis dementia, 101*t*, 105, 105*b*
Dialysis-dependent chronic kidney disease, 842
Diamond-Blackfan anemia, 1127.e1*t*, 1129, 1130*b*
DIAPERS mnemonic, 828*t*
Diaphragm (contraceptive), 1611
Diaphragm (muscle), 619–620
Diaphragmatic disorders, 619–629
Diaphragmatic eventration, 620
Diaphragmatic weakness or paralysis, 619–620, 619*t*
causes of, 619*t*
chest radiography findings, 620, 620.e1*f*
clinical manifestations of, 619
diagnosis of, 619–620, 620*f*
epidemiology of, 619
pathobiology of, 619
sniff test for, 619–620
treatment of, 620*b*
Diarrhea, 865
abdominal pain and, 856
acute, 924
clinical manifestations of, 924
diagnosis of, 926
epidemiology of, 925*t*
prevention of, 928
alcohol-related, 939
amebic, 2147
approach to, 923–941
bile acid, 939, 939*b*
in carcinoid syndrome, 1567
chronic, 928
causes of, 928*t*, 932–938
clinical manifestations of, 928
diagnosis of, 924*t*, 927*f*, 928, 930*f*
chronic idiopathic secretory, 940
Clostridium perfringens type A, 1926, 1926*b*
congenital, 938–939
cryptosporidiosis and, 2143
definitions of, 923–924
diabetes mellitus-related, 939
in enteral nutrition, 1450
epidemiology of, 923–924
factitious, 940
in immunocompromised host, 1859
infectious, treatment of, 1872*t*
inflammatory, 924, 930*f*, 940
noninfectious, 1872*t*
pathobiology of, 924
persistent, 928
postoperative, 2673–2674
prolonged, 932
signs and symptoms of, approach to, 852*t*
treatment of, 926*b*, 941*b*
true secretory, 930*f*, 939–940
in VIPomas, 1564
watery, 760, 924, 930*f*, 939
Whipple disease and, 2070
in Zollinger-Ellison syndrome, 1563
Diarrheal syndromes, 1924–1926
Diastolic blood pressure
elevated, 33*t*
normal range for, 32*t*
panic range for, 32*t*
Diastolic ventricular function, 239
Diazepam
for alcohol withdrawal, 2358*t*
for anxiety disorders, 2344*t*
for diarrhea, 926*b*
Diazepam + nordiazepam, e10*t*–e11*t*
Diazoxide, for hypoglycemia, 1557*b*
DIC. *See* Disseminated intravascular coagulation
Dichlorphenamide, for hypokalemia, 752*b*
Diclofenac
for chronic pain, 138*t*
for dysmenorrhea, 1596*t*
for rheumatoid arthritis, 1756*t*
Dicloxacillin, dosage of, 1895*t*
Dicyclomine, for irritable bowel syndrome, 896*t*
Dientamoeba fragilis, 2156, 2156*t*
Diet. *See also* Nutrition
for arterial hypertension, 450*t*
behavioral interventions for, 55
cancer and, 1244
cardiovascular disease and, 220
for glycogen storage disease I, 1416*b*
for heart failure, 265*b*
for irritable bowel syndrome, 895*b*
micronutrient requirements, 1451
for obesity, 1467*b*
recommendations of, for chronic kidney disease, 839*b*
Dietary Approaches to Stop Hypertension (DASH) diet, 58, 59*t*, 450
Dietary deficiency, treatment of, 1123*b*
Dietary fat, intestinal digestion and absorption of, 932.e1*f*
Dietary Guidelines for Americans, 2020-2025, 57–58, 57.e3*t*, 58*t*
Dietary lipids, 932
Dietary oxaluria, 803
Dietary reference intakes, 57
Dietary Supplement Health and Education Act, 154
Dietary supplements, 60
Diethylcarbamazine (DEC), 2117–2118
for filariases, 2176*b*
for helminthic diseases, 2112*t*
for loiasis, 2179*b*–2180*b*
Dieulafoy lesion, 885*f*, 886, 918, 966, 967*f*
Dieulafoy ulcers, 913–914
Differential count, e8*t*–e9*t*
Differin. *See* Adapalene
Diffuse alopecia, 2747*t*, 2748
Diffuse alveolar damage, 650
chest radiograph of, 520*f*
Diffuse alveolar hemorrhage, 566*t*, 568
clinical manifestations of, 568, 568.e1*f*
definition of, 568
diagnosis of, 569, 569*f*, 569.e1*f*
pathobiology of, 568
prognosis of, 569
treatment for, 569*b*
Diffuse bronchiectasis, 522
Diffuse cutaneous leishmaniasis, 2133
Diffuse cutaneous systemic sclerosis, 1777, 1777*t*
Diffuse esophageal spasm, 909, 909*b*, 909*f*
Diffuse homogeneous opacities, 520–521
Diffuse hyperpigmentation, 2743
Diffuse hypoxic injury, 2462
Diffuse idiopathic skeletal hyperostosis (DISH), 1706*t*, 1815
Diffuse infiltrative lymphocytosis syndrome, 2323
Diffuse large B-cell lymphoma, 1279, 1284, 1285*b*, 2315
subtypes of, 1285, 1285*b*
Diffuse lung disease, 520–524
Diffuse pleural thickening, 526
Diffuse proliferative lupus nephritis, 787*f*–788*f*
Diffuse reticular lung disease, chest radiograph of, 522*f*
Diffuse-type gastric cancer, 1340
Diffusely adherent *E. coli*, 1961, 1962*t*
Diffusing capacity, in pulmonary function tests, 528*t*, 530–531, 531*f*
Diflunisal
for amyloidosis, 1309*b*, 2560*b*
for chronic pain, 138*t*
DiGeorge syndrome, 347, 1679–1680, 1679*b*, 1679*t*
hypoparathyroidism and, 1661
Digestive decontamination, for health care-associated infections, 1867
Digital rectal examination, for gastrointestinal disease, 851
Digital subtraction angiography, in atherosclerotic PAD, 463, 463*f*
Digitalis overdose, treatment of, 752*b*

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Digitoxin, e10t–e11t
Digoxin, e10t–e11t, 325t
  for atrial fibrillation, 384b
  for heart failure, 265b
  intoxication, immunization for, 65t
  toxicity, 686t, 690t
Digoxin-specific antibody fragments, for acute poisoning, 693t
Dihydroergotamine, 2378b–2379b
Dihydropyridines
  for hypertension, 451t
  side effects of, 453t
Dihydrotestosterone (DHT), 1581–1582
1,25-Dihydroxycholecalciferol, 732
1,25-Dihydroxyvitamin D, 1648–1649, 1652
Dilated cardiomyopathy
  acquired, 286
    clinical manifestations of, 287
    diagnosis of, 287
    prognosis for, 287–288
    treatment of, 287b
  characteristics of, 286–288
  definition of, 286
  echocardiographic findings, 242t
  epidemiology of, 286
  family screening for, 287b
  genetic, 286
  nonischemic, 265b, 336
  overlap with restrictive cardiomyopathy, 288
  pathobiology of, 286
Diloxanide furoate
  for amebiasis, 2150t
  for intestinal amebiasis, 2112t
Diltiazem
  for acute coronary syndrome, 374t
  for acute STEMI, 384b
  properties of, 367t
  for ventricular tachycardia, 338b
Diltiazem ER, 451t
Dilutional thrombocytopenia, 1179
Dimenhydrinate, for nausea and vomiting, 863t
Dimercaprol, for acute poisoning, 693t
Dimethylfumarate (Tecfidera), for multiple sclerosis, 2505t
Dipentum. See Olsalazine
Dipeptidyl peptidase 4 (DPP4), MERS and, 2208
Dipeptidyl peptidase 4 (DPP4) inhibitors, for type 2 diabetes mellitus, 1540b, 1541t
Diphenhydramine
  for intestinal pseudo-obstruction, 889b
  for nausea and vomiting, 863t
Diphenylhydantoin, e10t–e11t
Diphtheria, 1933
  clinical manifestations of, 1933
  cutaneous, 1934
  diagnosis of, 1935
  epidemiology of, 1933
  immunization for, 65t, 66t, 76.e1t, 77f, 78f, 82
  neuropathy associated with, 2578
  pathobiology of, 1933
  pathogen of, 1933
  prevention of, 1935
  prognosis of, 1935
  treatment of, 1935b, 1935t
  vaccinations, 1996
Diphtheria-tetanus-pertussis (DTaP) vaccine, 76
Diphtheria toxoid vaccine, 1935
Diphyllobothrium sp., 2157, 2158t
Dipylidium caninum, 2158, 2158b, 2158t
DIRA. See Deficiency of interleukin-1 receptor antagonist
Direct allorecognition, 205–206, 205f
Direct antiglobulin test, 1087
Direct factor Xa inhibitors, 505–506
  adverse effects of, 506
  anticoagulant effect, reversal of, 506, 506t
  dosage and monitoring of, 505–506
Direct fluorescent antibody test, of *Pneumocystis* pneumonia, 2105f
Direct/intrinsic hepatotoxicity, 1018–1019
  clinical manifestations of, 1018–1019, 1018.e2f
  diagnosis of, 1019, 1019t
  drugs and toxins that cause, 1018, 1019t
  pathobiology of, 1018
  prevention of, 1019
  prognosis of, 1019
  treatment for, 1019b
Direct MR arthrography, 1723
Direct oral anticoagulants (DOACs), 374t, 502t, 504–506, 505t
  for venous thromboembolism, 487b
Direct renin inhibitors, for hypertension, 452, 453t
Direct reprogramming, 173–174
Direct thrombin inhibitors, 502t, 504–505
  adverse effects of, 504
  anticoagulant effect of, reversal of, 504–505
  dosage and monitoring of, 504
  parenteral, 503
  vorapaxar as, 508–509
Direct-to-consumer genomic testing, 159
Dirofilaria immitis, 2180
Diroximel fumarate (Vumerity), for multiple sclerosis, 2505t
Dirty bomb, 92
Disability
  leading causes of, 21–23, 23f–24f, 24f
  in older adults, 115
Disaster management, in occupational and environmental medicine, 89
Discharge issues, 397
Discocyte, 1067f
Discoid lupus erythematosus, 2747t, 2750, 2750f
Disconjugate gaze-evoked nystagmus, 2619
Discordant thyroid tests, causes of, 1497t
Discrete data, 36
Discrimination, in health care, 42
Disease(s)
  anatomic distribution of, 523
  changing patterns of, 23
  complement system in, 196, 198t
  gene therapy for, 175–176
  genetic architecture of, 158, 158f
  global burden of, 21f, 23
  nutrition and, 57–60
  in older adults, 114–115
  stem cell-derived platforms for modeling of, 174
  trajectories of, 12.e1f
Disease-modifying antirheumatic drugs (DMARDs), 144, 1717, 1755b, 1756t, 1830.e1t
Disease-modifying medical therapy, for myelodysplastic syndromes, 1255
Disease-related malnutrition, 1447, 1447f
Disequilibrium dizziness, 2647t
DISH. See Diffuse idiopathic skeletal hyperostosis
Disoproxil fumarate, 2301t
Disopyramide, e10t–e11t, 283f, 325t
Dispersion, 36
Dissecting cellulitis, of scalp, 2750
Disseminated candidiasis, 1861f
Disseminated cutaneous leishmaniasis, 2133
Disseminated gonococcal infection, 1849, 1949–1950
  clinical manifestations of, 1949, 1949f
  diagnosis of, 1950
  prevention of, 1950
  prognosis of, 1950
  screening of, 1950
  treatment of, 1950b
Disseminated histoplasmosis, 2082, 2083b
Disseminated infections, 2090
Disseminated intravascular coagulation (DIC), 1178, 1195–1198
  causes of, 1195, 1195t
  clinical manifestations of, 1195–1196, 1196f
  definition of, 1195
  description of, 2696f
  diagnosis of, 1196
  management of, 2269b
  pathobiology of, 1195, 1196f
  treatment of, 1196b, 1197t
Disseminated mucormycosis, 2099
Disseminated nontuberculous mycobacterial disease, 2045
Distal acquired demyelinating symmetric neuropathy, 1296
Distal acquired demyelinating symmetric syndrome, 2576, 2576b
Distal acquired demyelinating syndrome, 2574, 2576b
Distal axonopathy, 683–684
Distal renal tubular acidosis, 749t, 761, 816t, 817, 818b, 818t
Distal subungual onychomycosis, 2754, 2754f
Distal symmetrical and autonomic polyneuropathy, 2577, 2577b
Distal symmetrical peripheral polyneuropathy, 2313
Distal tubule
  disorder of, 816t, 817
  diuretics, 736b
Distention
  abdominal pain and, 856
  bloating and, 859, 859b
Distinctive lesions, in black skin, 2744, 2744t
Distorted vision, 2599
Distributive shock, 658, 659, 659f, 661t
Disulfiram, for alcohol use disorders, 2357b, 2358t
DITRA. See Deficiency of the IL-36R antagonist
Diuretics
  for heart failure, 265b
  for hypertension, 454
  for hypervolemia, 736b, 736.e1f, 737t
  hypokalemia and, 749t
  for postpartum diuresis, 288b
Diverticular bleed, 884
Diverticular disease, 60, 954, 954.e1f, 955b, 955f
Diverticulitis, 955b, 955f
  abdominal pain and, 854t
  colitis, 956
  colonic, 954, 954.e1f, 955f
Diverticulosis, colonic, 954, 954.e1f, 955b, 955f
Dix-Hallpike test, 2646
Dizziness
  description of, 303, 2371, 2372f, 2646, 2647t
  evaluation of, 2646
  with palpitations, 303f
DKA. See Diabetic ketoacidosis
DMARDs. See Disease-modifying antirheumatic drugs
DNA hypomethylating agents, for myelodysplastic syndromes, 1255
DNA recombination, defects of, 1681t
DNA testing, 165
DNase, 625b
DOACs. See Direct oral anticoagulants
Dobrava-Belgrade virus, 2265t
Dobutamine
  for right ventricular infarction, 384b
  for shock, 664t, 667b, 672
Docetaxel (Taxotere), 1215t
  for head and neck cancer, 1327b
  for soft tissue sarcomas, 1389b
DOCK2 deficiency, 1678, 1678.e1t
DOCK8 deficiency, 1678, 1678.e1t
Docosanol, for herpesvirus infections, 2189
Doctoring, 3
Documented symptomatic hypoglycemia, 1546t
Doege-Potter syndrome, 526
Dofetilide, 325t
Döhle body, peripheral blood smear of, 1071f, 1072–1073
Dolasetron, for nausea and vomiting, 863t
Doll's eye test, 2646
Dolutegravir, 2301t
Domperidone, for intestinal pseudo-obstruction, 889b
Donabedian triad, 44, 44t
Donath Landsteiner test, 1088
Donation after cardiac death (DCD), 844
Donepezil
  for Alzheimer disease, 2416b
  for Parkinson disease, 2487t
Donor lymphocyte infusion, 1207
Donovanosis, 2004–2005, 2004b, 2004f
Dopa-responsive dystonia, 2493
Dopamine
  neurotransmitter, 143
  prolactin inhibition by, 1477–1478
  for shock, 662b, 664t, 673b–675b
  synthesis of, 1529
Dopamine agonist therapy, for Parkinson disease, 2486b
Dopamine receptor antagonists, for nausea and vomiting, 863t
Doppler echocardiography, 236–238
  color flow imaging, 236
  continuous-wave, 236
  modalities, 236
  principles of, 236
  pulsed, 236
  tissue, 236, 236.e1f
Doppler shift, 236
Doppler ultrasonography, 236
  continuous-wave, 236
  for gallbladder cancer, 1054
Doppler ultrasonography *(Continued)*
  pulsed, 236
  renal artery stenosis for, 800
Doravirine, 2301t
Doripenem
  dosage of, 1895t
  for pyelonephritis and urosepsis, 1877t
  for pyogenic liver abscess, 1023b
Dorsal midbrain syndrome, 2619
Dorsal root ganglionopathy, 2567t
Dot-in-circles sign, 2110–2111
Double-blinded controlled trial research design, 36
Double-contrast barium enema, 1353
Double density sign, 245, 245f
Double-hit and gray-zone lymphomas, 1285, 1285b
Double vision, 2598
Down syndrome, 164, 347, 2548f, 2549
  neutrophilia and, 1142
  treatment for, 2549b
Downbeat nystagmus, 2619
Doxazosin, 451t, 824t
Doxepin, 2452t
Doxepin + nordoxepin, e10t–e11t
Doxorubicin (Adriamycin, Rubex, Doxil), 1215t
Doxycycline, 2115
  for American monocytic ehrlichiosis, 2061b
  for anthrax exposure, 97
  for bacillary angiomatosis, 2003b
  for brucellosis, 1987b
  for cholera, 1956b, 1957t
  dosage of, 1895t
  for endocarditis, 2003b
  for granuloma inguinale, 2004b
  for intestinal bacterial overgrowth, 934b
  for leptospirosis, 2031b
  for Lyme disease, 2026t
  for malaria, 2112t, 2121t, 2123t
  for nontuberculous mycobacterial disease, 2046t
  for pelvic inflammatory disease, 1883t
  for plague, 98b, 1991b, 1992t
  for pneumonia, 613t
  for psittacosis, 2012b
  for Q fever, 2063b
  for relapsing fever, 2028b
  for rickettsialpox, 2060b
  for Rocky Mountain spotted fever, 2057b
  for scrub typhus, 2060b
  for syphilis, 2019
  for tick-borne rickettsioses, 2058b
  for total knee arthroplasty, 1830.e1t
  for tularemia, 99b
  for urethritis, 1880t
DPP4. See Dipeptidyl peptidase 4
DPYD gene, 160t
Dracunculiasis, 2180
DRB1*0301 allele, 204
DRESS. See Drug rash with eosinophilia and systemic symptoms
DRESS syndrome, 792
Dressings, for skin diseases, 2697
Dressler syndrome, 626
Driving, heart failure in, 265b
Dronabinol, for nausea and vomiting, 863t
Dronedarone, 325t
Droopy eyelid, 2600, 2600f
Droperidol, for nausea and vomiting, 863t
Dropped head syndrome, 2563
Drowning, 591–592, 592b
Droxidopa, for orthostatic hypotension, 2559t
Drug(s)
  absorption of, 126
  of abuse, 143
  acid peptic disease caused by, 917
  acquired platelet dysfunction caused by, 1185
  acute pancreatitis and, 970, 970t
  administration of, 126
  adverse reactions to, 131
  antiarrhythmic, 313b
  for atherosclerotic cardiovascular disease, 1410
  bioavailability of, 126
  bone loss as caused by, 1641
  classes of, 1898
  clearance, 127
  decreased excretion of, 131
  decreasing level of, 128
  determining accumulation of, 128, 128f
  distribution of, 126

Copyrighted material

Drug(s) *(Continued)*
altered, 131
volume of, 126–127, 126*f*, 127.*e1t*
dose
adjustments of, 129–130
increase on, effects of, 128, 129*f*
drug monitoring as guide to, 128–129, 129*f*
in elderly patients, 130, 130*t*
elimination of, 127
for esophageal disease, 904*t*
first-pass effect of, 126
gastric ulcers caused by, 917
half-life of, 127, 127*f*
hearing loss caused by, 2642
for heart failure with reduced left ventricular ejection fraction, 265*b*
hypercalcemia caused by, 1659
for hypertriglyceridemia, 1414*b*
loading dose, 127–128
maintenance dose, 128, 128*f*
metabolism of
decreased, 131
increased, 131
ocular effects of, 2613–2614, 2613*t*
for pain, 136*b*
pharmacodynamics of, 1892
potential interactions with, 155
primary testicular hypogonadism caused by, 1583–1584
principles of, 126–133
problems with interpreting concentration of, 129
properties of, 1898
for septic shock, 673*b*
stem cell-derived platforms for, 174
stroke caused by, 2472
usefulness of genomic data in, 133
vitamin levels affected by, 1459
Drug- and toxin-induced hypoglycemia, 1552*t*, 1555, 1555*t*
Drug addiction, 142
Drug adherence, 265*b*
Drug allergy, 1695–1699
Brown classification of, 1696*t*
classification of, 1695.*e2f*
clinical manifestations of, 1696–1698, 1696.*e1f*, 1697*f*, 1698*t*
definition of, 1695–1699, 1696*f*
description of, 1673
diagnosis of, 1698–1699
epidemiology of, 1695–1696
pathobiology of, 1696, 1697*f*
prognosis of, 1699, 1699*f*
risk factors for, 1695–1696
treatment of, 1699*b*
type A, 1695.*e2f*
type B, 1696*f*
Drug counseling, 275*t*
Drug desensitization, for drug allergy, 1699*b*
Drug exposure, fetus and, 1573
Drug fever, 1846
Drug-induced gingival hyperplasia, 2625*f*
Drug-induced immune hemolytic anemia, 1089
Drug-induced interstitial lung disease, 572*t*, 582
Drug-induced liver injury, 986, 1017–1021
clinical manifestations of, 1018.*e1f*
definition of, 1017–1018, 1018*t*
direct/intrinsic, 1018
epidemiology of, 1017–1018
idiosyncratic, 1019–1021
indirect, 1021
international consensus criteria for, 1018*t*
pathobiology of, 1018, 1018*t*
Drug-induced movement disorders, 2495–2496
Drug-induced neutropenia, 1145–1146, 1145*f*
Drug-induced pancreatitis, 970
Drug-induced parkinsonism, 2485*t*
Drug-induced thrombocytopenia, 1173–1174, 1174*b*, 1174*t*
Drug-induced thyroiditis, 1514, 1515*b*
Drug interactions, 130–131
diagnosis of, 131, 132*t*
pharmacodynamic, 131
pharmacokinetic, 131
prevention of, 131
Drug-metabolizing enzymes, 132*t*
Drug overdose, 130, 2270*t*
Drug paraphernalia, 2361
Drug rash(es), 2726–2729
clinical manifestations of, 2726, 2727*f*, 2727*t*
Drug rash(es) *(Continued)*
definition of, 2726
diagnosis of, 2726
pathobiology of, 2726
prognosis of, 2726*b*
specific syndromes of, 2726–2729
treatment of, 2726*b*
Drug rash with eosinophilia and systemic symptoms (DRESS), 1697, 2726–2727, 2727*b*, 2727*f*, 2727*t*
Drug reaction, 2621*t*
Drug-related pericarditis, 424*t*
Drug-resistant hypertension, 456–457, 456*t*, 457*f*
Drug response, germline genetic variants and, 167, 167.*e1t*
Drug sensitivity, characteristics of, 2270*t*
Drug testing, 685–690
Drug use
in adolescents, 113
pathogens and empirical therapy for, 2526*t*
Drug use disorders, 2360–2365
agent of, 2360
clinical manifestations of, 2361
definition of, 2360–2361
diagnosis of, 2361
DSM-5 criteria for, 2360*t*
environment of, 2360–2361
epidemiology of, 2360
host of, 2360
major drugs in, 2361–2365
anabolic-androgenic steroids as, 2365
cocaine and amphetamines as, 2363
hallucinogens as, 2364
marijuana as, 2364
opioids as, 2361–2362
phencyclidine as, 2364–2365
sedative-hypnotic and anxiolytic drugs as, 2363
medical complications related to, 2361
pathobiology of, 2360–2361
treatment of, 2361*b*
Drusen, 2608
Dry eye syndrome, 2596, 2602, 2603*f*
DSM-5. *See Diagnostic and Statistical Manual of Mental Disorders, 5th edition*
Dual energy x-ray absorptiometry (DXA), 1638
Dual-energy x-ray absorptiometry (DXA), 1608
Dubin-Johnson syndrome, 994, 996
Duchenne muscular dystrophy
characteristics of, 2583, 2583*b*, 2583.*e2f*
dilated cardiomyopathy in, 286
Ductal carcinoma in situ, 1369*b*, 1369*t*, 1370*t*
Duffy A-B- individuals, normal neutrophil count for, 1143
Duffy antigen receptor, 1162
Dulaglutide, for type 2 diabetes mellitus, 1541*t*
Duloxetine
for chronic pain, 138*t*
for depression, 2340*t*
for distal symmetrical and autonomic polyneuropathy, 2577*b*
for fibromyalgia, 1819*b*
Dumping syndrome, 890, 932, 1554, 1557*b*
Duodenal biopsies, for Whipple disease, 2070, 2070*f*–2072*f*, 2071*f*
Duodenal histology, for Whipple disease, 2070, 2072*f*
Duodenal ulcers
with bleeding visible vessel, 882*f*
description of, 913
endoscopy of, 913*f*–914*f*
epidemiology of, 914
malignant, 915
Dupilumab, 151
Duplication cysts, 913
Dupuytren contractures, 987, 1032*f*, 1822
Dural arteriovenous fistulas, 2482
Duroziez sign, 410
Durvalumab (Imfinzi), 1215*t*
Dusts, 87, 88*t*
Dutasteride, 824*t*
Duvelisib, for chronic lymphocytic leukemia, 1269*t*
DVT. *See* Deep venous thrombosis
DXA. *See* Dual energy x-ray absorptiometry
Dyes, reactions to, 1698*t*
Dynamic hyperinflation, 654
Dynamic International Prognostic Scoring System-Plus, 1137*f*, 1139
Dysbarism, 88*t*
Dysbiosis, 1852
Dyschondroplasia, 1669
Dysentery, amebic, 2147, 2148*f*
Dysfibrinogenemia, 1189*t*, 1192, 1193*b*
Dysfunctional bleeding, 1597
Dysgenesis, gonadal, 1600
Dysgerminomas, suprasellar, 1479
Dyshidrosis, 2702, 2702*f*–2703*f*
Dyskaryosis, 2241
Dyskeratosis congenita, 1129, 1129*b*, 1145
Dyskinetic dysphagia, severe mental illness and, 2681*t*
Dyslipidemia
diabetes mellitus and, 1550
obesity caused by, 1466
Dysmenorrhea, 1596, 1596*b*, 1596*t*
Dysmorphic erythrocytes, 723*f*
Dysostosis multiplex, 1724
Dyspepsia
approach to, 865, 865*f*
direct thrombin inhibitors and, 504
functional, 898–899
alarm symptoms associated with, 899*t*
algorithm for, 899*f*
definition and epidemiology of, 898
pathobiology of, 898
prognosis of, 899
Rome IV diagnostic criteria for, 898, 898*t*–899*t*, 899*t*
treatment of, 899*b*
nonulcer, abdominal pain and, 854*t*
Dysphagia, 852*t*, 865
esophageal disease and, 902
psychotropic medications and, 2678*t*, 2680
Dysphagia lusoria, 913
Dysphonia, 2653
Dysplasia, in ulcerative colitis, 945*b*
Dysplastic hematopoiesis, myelodysplastic syndromes *versus*, 1255
Dysplastic nevi, 1390, 1391*f*, 1392*t*
Dyspnea, 210, 256
acute pancreatitis and, 970
alveolar hemorrhage and, 568
approach to, 513, 516*t*
chronic, 517*f*
diagnosis of, 513, 514*f*
hepatic dysfunction and, 987
obesity and, 533
paroxysmal nocturnal, 256
postoperative, 2673, 2674*t*
of pregnancy, 1622
prognosis for, 515*b*
pulmonary alveolar proteinosis and, 567
refractory, oxygen in, 12
severe, 256
transfusion-associated, 1202
treatment of, 515*b*
Dysregulated stress responsiveness, in irritable bowel syndrome, 893
Dystonia, 2652
adult-onset idiopathic, 2493
classification of, 2492*t*
clinical manifestations of, 2493
definition of, 2492–2493
diagnosis of, 2493
dopa-responsive, 2493
heredodegenerative, 2492*t*
myoclonus, 2493
pathobiology of, 2492
primary, 2492*t*, 2493
secondary, 2492*t*
treatment of, 2493*b*
Dystonia-plus, 2492*t*, 2493
Dystonic gait, 2373*t*
Dystonic tremor, 2493
Dystrophic epidermolysis bullosa, esophageal involvement in, 911
Dystrophin, 2580
Dystrophin-sarcoglycan complex, 2580
Dystrophinopathies
Becker muscular dystrophy, 2584, 2584*b*
Duchenne muscular dystrophy, 2583, 2583*b*, 2583.*e1f*
DYT6, 2493

E

EAD. *See* Early afterdepolarizations
Eagle-Barrett syndrome, 821
Ear(s)
acute poisoning and, 683
examination of, 29
Ear infections, *Pseudomonas* infections causing, 1969, 1970*b*
Ear injury, occupational, 86*t*
Ear pain, 2636–2638
cause of, 2636*t*
clinical manifestations of, 2636, 2637*f*
definition of, 2636–2638
diagnosis of, 2636–2638
differential diagnosis of, 2637–2638, 2638*f*
imaging of, 2637
laboratory findings in, 2637
pathobiology of, 2636
physical examination of, 2636–2637, 2637*f*–2638*f*
treatment of, 2638*b*
Early afterdepolarizations (EAD), 333, 333.*e1f*
Early childhood gigantism, 1487*t*
Early gastric cancer, 1340
Early infectious syphilis, 2020*b*
Early-onset protein-losing enteropathy, and thrombosis, intestinal lymphangiectasia, and intestinal inflammation, 1731*t*
Early-onset sarcoidosis, 1731*t*
Early-stage breast cancer, 1369*b*, 1370*t*, 1371*t*
East African sleeping sickness, 2124
Eastern Africa, HIV/AIDS in, 2288–2289, 2288.*e1f*
Eastern equine encephalitis virus, 2276*t*, 2283, 2283*b*
Eastern Europe, HIV/AIDS in, 2289, 2289.*e1f*
Eating disorders, 1461–1463, 2346
in adolescents, 113
clinical manifestations of, 1461–1462
definition of, 1461–1463
diagnosis of, 1462
epidemiology of, 1461
pathobiology of, 1461
prevention of, 1462
prognosis of, 1462–1463
treatment of, 1462*b*
EBNAs. *See* Epstein-Barr nuclear antigens
Ebola virus, 99, 99.*e1t*, 100*b*, 2264, 2265*t*, 2268*t*, 2269*f*, 2273
immunization for, 66*t*, 84
Ebselen, 2643
Ebstein anomaly, 354
chest radiography findings, 247
exercise recommendations for, 355.*e2t*
EBV. *See* Epstein-Barr virus
Ecchymoses, 2714, 2715*f*
ECG. *See* Electrocardiography
Echinocandin antifungal agents, 2078
anidulafungin as, 2078
caspofungin as, 2078
mechanisms of action, 2078
micafungin as, 2078
Echinococcosis, 1025–1029, 1029*b*, 1029*f*
cystic, 2161, 2161*b*
Echinococcus granulosus, 1026*t*
description of, 2161, 2162*f*
Echinococcus multilocularis, 1026*t*, 2162, 2162*b*
Echinococcus oligarthrus, 2163
Echinococcus vogeli, 2163
Echinoderm microtubule-associated protein-like 4 (EML4), lung cancer and, 1330
Echo dropout, 236
Echocardiographic-guided percutaneous pericardiocentesis, 427*b*, 430*f*
Echocardiography, 235
approaches, 238–239, 238*t*–239*t*, 238*t*, 239*f*, 239*t*
in arrhythmia, 309
cardiac measurements, 236, 237*f*, 239–241
for cardiac tamponade, 426, 428*f*
in cardiogenic shock, 667
contrast, 238, 240*f*
Doppler, 236
examination with, 241
in heart failure, 260–261
imaging, 236, 236*f*
indication for, 241, 242*t*, 243*f*
in infective endocarditis, 416–417, 418*f*
integrating with clinical findings, 241
intracardiac, 239
limitations of, 236
normal findings, 241
point-of-care, 238, 239*t*

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Echocardiography *(Continued)*
principles of, 235
for pulmonary hypertension, 495
for signs of cardiovascular disease, 218
standard image planes, 236, 236*f*
stress, 238, 241*f*, 362
three-dimensional, 238, 240*f*–241*f*
transesophageal, 238, 238*t*, 239*f*
transthoracic, 238, 238*t*
E-cigarettes, in adolescents, 113
Ecologic model, intimate partner violence and, 1633
Ectasias, 967
Ecthyma, 1914–1915
Ecthyma gangrenosum, 1860*f*, 2239, 2741
Ectocervix, 2241
Ectoparasites
characteristics of, 1883
organisms causing, 1879*t*
of skin, 2739*t*, 2741–2742
Ectopia lentis, 1426
Ectopic ACTH secretion, 1523, 1523*t*, 1524*b*
Ectopic ACTH syndrome, Cushing disease *versus*, 1477
Ectopic atrial rhythm, 322, 323*f*
Ectopic hormone syndromes, 1237
Ectopic ureters, 819
Ectropion, 2601, 2601*f*
Eculizumab, for paroxysmal nocturnal hemoglobinuria, 1092*b*
Eczema, 2702–2704, 2702*t*
allergic contact dermatitis, 2704
atopic dermatitis, 2702, 2703*f*
dyshidrosis, 2702, 2702*f*, 2703*f*
irritant contact dermatitis, 2704
nummular dermatitis, 2702, 2702*f*
seborrheic dermatitis, 2703, 2703*f*
Eczema vaccinatum, 2238, 2240*b*
Edaravone, for amyotrophic lateral sclerosis, 2563*b*
Edema, 215
cerebral, 2464, 2511
high-altitude, 592*t*
due to heart failure, 258
postoperative, 2675
pulmonary
distinguishing features of, 515*t*
high-altitude, 592
subglottic, 2197*f*
wasting and, 1445
Edematous malnutrition, 1444–1445, 1445*f*
Edetate calcium disodium ($CaNa_2EDTA$), for acute poisoning, 693*t*
Edge Hill virus, 2275*t*
Edinburgh Hypoglycemia Scale, 1546*t*
Edmonton Symptom Assessment Scale, 12, 12.*e1f*
Edoxaban, 502*t*, 505*t*, 506
for venous thromboembolism, 478*b*, 487*b*
EDTA. *See* Ethylenediaminetetraacetic acid
Education, for heart failure, 265*b*
Edwards syndrome, 164
EEG. *See* Electroencephalography
Efavirenz, 2301*t*, 2303
for HIV/AIDS, 2312–2313
Effective dose, 91
Effector mechanisms, of rejection, 206
Effectors
of adaptive immune response, 192–193
damaging, inhibitors of, 196
of innate immune mechanisms, 191–192, 192*f*
Efferent limb mechanisms, 734–735
Effusion
in cancer, management of, 1232*b*
pericardial, 241, 243*f*, 425–428
causes of, 427*t*
chest radiography in, 245, 246*f*, 428*f*
clinical manifestations of, 425–426
diagnosis of, 426–427
epidemiology of, 425–428
management of, 429*f*
pathobiology of, 425
prognosis for, 428
treatment of, 427*b*
without tamponade, 427*b*
pleural, 623–625, 624*f*
Effusive-constrictive pericarditis, 431
Eflornithine, for African trypanosomiasis, 2112*t*, 2116, 2125*b*, 2125*t*
Efudex. *See* 5-Fluorouracil
EGAPP, 169.*e1t*
EGFR. *See* Epidermal growth factor receptor
eGFR. *See* Estimated glomerular filtration rate
Egg protein, in vaccines, 76
Egophony, 512
Ehlers-Danlos syndrome, 1186, 1726, 1727*b*, 1727*t*
esophageal involvement in, 911
type IV, 969
Ehrlichia canis, 2060*t*
Ehrlichia chaffeensis, 2060
Ehrlichia ewingii, 2060*t*
Ehrlichia muris-like, 2060*t*
Ehrlichia spp., 2061, 2061*b*
Ehrlichiae, 2055*t*
Ehrlichiosis, 2060, 2060*t*
American human monocytic, 2060, 2060*t*, 2061*b*, 2061*f*
characteristics of, 2270*t*
human granulocytic, 2060*t*, 2061, 2061*b*, 2062*f*
Japanese monocytic, 2060*t*
EIA. *See* Enzyme immunoassay
Eikenella corrodens, 2068
Eisenmenger complex, 350*b*
Eisenmenger syndrome, clinical manifestations of, 355, 355*b*
Ejaculatory failure, 1590, 1590*b*
Ejection, 225
Ejection fraction, 236
diminished, selection of ICD for, 389*f*
formula for, 236
preserved, heart failure with, 256, 256*t*
reduced, heart failure with, 255–256
three-dimensional echocardiography findings, 236, 237*f*
Elbow
disorders of, 1744–1745
injury of, occupational, 86*t*
surgical treatment of, 1828
Elderly. *See also* Older adults
epilepsies in, 2434*b*
gait disorder of, 2373*t*
non-Hodgkin lymphoma in, 1288
parainfluenza viral diseases in, 2196–2197
testosterone deficiency in, 1582, 1582*b*, 1582.*e1f*
urinary tract infection in, 1875*b*
Elective total hip, perioperative, medications for, 1830.*e1t*
Electrical alternans, 426, 428*f*
Electrical cells, 223
Electrical conduction
abnormalities, 231
of heart, 223–224, 228
Electrical injury, 699, 699*t*, 700*f*, 703
Electrical storm, treatment of, 338*b*
Electrocardiography (ECG), 228–235
abnormal, 231–233
in acute coronary syndrome, 372
in acute MI, 382, 382*f*
ambulatory, 235
approach to interpretation, 230–235, 231*t*
in arrhythmias, 306
in athletes, 234, 234*t*, 235*f*
automated computerized readings, 234
axes of electrical activation, 230, 230.*e1f*
axis deviation, 231, 231*t*, 232*f*
in chronic ischemic heart disease, 361–362
in COVID-19 disease, 234–235
exercise, 361
in heart failure, 258
leads, 230, 230.*e1f*
in narrow-complex tachycardia, 307*f*
normal, 228–231, 228*f*, 231, 231*f*
with pacemaker, 343*f*
resting, 358, 361*f*
screening, 235
standards, 228–229, 228*f*
waves, 228, 228*f*
in wide-complex tachycardia, 308*f*
Electroencephalography (EEG)
description of, 2374–2375, 2375*t*
for epilepsies, 2431
Electrolyte, intestinal transport of, 924, 924.*e1f*
Electromyography (EMG)
description of, 2375–2376, 2375*t*, 2399
muscle diseases on, 2581–2583
peripheral neuropathy evaluations, 2567
Electronic consultations, 2658
Electronic nicotine delivery systems (ENDS), 2352
Electrophysiologic procedures, 340–347
cardiac implantable electronic devices, 340
catheter ablation, 345, 345.*e1f*
of atrial fibrillation, 346
of supraventricular tachycardias, 346
of ventricular arrhythmias, 346
transthoracic cardioversion and defibrillation, 340
Electrophysiology, 298–302
in arrhythmia, 308–309
basic concepts of, 298–299
cardiac action potential, 299, 299*f*
impulse propagation, 300
ionic basis of, 299–300
molecular basis of, 300–301
calcium channels, 300.*e1f*, 301
gap junction channels, 300.*e1f*, 301
potassium channels, 300.*e1f*, 301
sodium channels, 300–301, 300.*e1f*
Elemental mercury, 103
Elephantiasis, 2177, 2177*f*
Eletriptan, 2380*t*
Elimination, enhanced, for acute poisoning, 691*b*
Elite controllers, 2294
Ellence. *See* Epirubicin
Elliptocyte
conditions associated with, 1072*t*
peripheral blood smear of, 1068*f*
Elliptocytosis, hereditary, peripheral blood smear of, 1068*f*
Eloxatin. *See* Oxaliplatin
Eltrombopag, 1175*b*, 2314*b*
characteristics of, 153
Elusive diarrhea, stool examination in, 931–932, 931*t*
Eluxadoline, for irritable bowel syndrome, 895*b*, 896*t*
Elvitegravir, 2301*t*
Embden-Meyerhof pathway
disorders of, 1099
of glycolysis, 1098–1099, 1098*f*
Embolic stroke, 2465, 2530
Embolism, superior mesenteric artery, 962, 962.*e1f*
Embolization
atheromatous, of renal arterial system, 801, 801*b*, 802*f*
for hepatocellular carcinoma, 1360*b*
Embryo, early, test of, 1603*b*
Embryopathic disorders, congenital, 1478
Emergency contraception, 1615
Emergency department care
for acute STEMI, 384*b*
psychiatric diseases in, 2679
Emergency Planning and Community Right-to-Know Act of 1986, 87
Emergency preparedness, in occupational and environmental medicine, 89
Emery-Dreifuss muscular dystrophy, 286, 302, 2584–2585
EMG. *See* Electromyography
Eminence-based medicine, 43
EML4. *See* Echinoderm microtubule-associated protein-like 4
EMLA. *See* Eutectic mixture of local anesthetic
Empagliflozin
for heart failure, 271*t*
for type 2 diabetes mellitus, 1541*t*
Empathic responses, in palliative care, 16
Emphysema, 548
congenital lobar, 565
severe, chest radiograph of, 523*f*
Empiric antibiotic therapy, for diarrhea and enteric infection, 1872*t*
Empiric chemotherapy, for cancer, 1241*b*
Empirical therapy
for community-acquired pneumonia, 1998*b*
for diffuse esophageal spasm, 909*b*
Empty sella, 1486, 1486*f*
Empyema, 625, 625*b*
subdural, 2528, 2528*b*
Emtricitabine, 2301*t*
Enalapril, 266*t*, 451*t*
Enalapril/HCTZ, 451*t*
Enalaprilat, for hypertensive emergencies, 460*t*
Enanthems, enteroviruses causing, 2259
Enasidenib (IDHIFA), 1215*t*
Enbrel. *See* Etanercept
Encephalitis, 2531–2536
acute, 2221, 2532
autoimmune, 2535
Encephalitis *(Continued)*
clinical manifestations of, 2536
diagnosis of, 2536
epidemiology of, 2535
neural antigen targets and, 2536*t*
pathobiology of, 2535
prognosis of, 2536
treatment of, 2536
brain stem, 2531
California, 2276*t*, 2283, 2284*b*
COVID, 2535, 2535*b*
definition of, 2531
diagnostic approach to, 2534*f*
eastern equine, 2276*t*, 2283, 2283*b*
enteroviruses causing, 2259, 2259*b*
granulomatous amebic, 2150
herpes simplex, 2247, 2247*b*, 2247*f*, 2520, 2532, 2532*t*, 2533*f*
Japanese, 66*t*, 83
limbic, 2532*t*
measles inclusion-body, 2221
mumps and, 2226*t*
Murray Valley, 2276*t*, 2283
neonatal, 2532*t*
parainfectious, 2532
rare viral causes of, 2535
relapsing, 2532*t*
specific viruses in, 2532–2535
St. Louis, 2276*t*, 2282, 2283*b*, 2520
subacute, 2221
tick-borne, 2276*t*, 2282, 2282*b*
toxoplasmic, 2136–2137, 2139, 2139*f*
Venezuelan equine, 2276*t*, 2283, 2283*b*
viral, 2531–2536
causes of, 2531*t*
cerebrospinal fluid findings in, 2374*t*
clinical manifestations of, 2531
diagnosis of, 2531–2532
differential diagnosis of, 2532
epidemiology of, 2531–2532
magnetic resonance imaging of, 2532
pathobiology of, 2531
prognosis for, 2532
rabies and, 2534, 2535*b*
spinal fluid analysis, 2532
tests for, 2532*t*
treatment of, 2532*b*
West Nile, 2532*t*
western equine, 2276*t*, 2283, 2283*b*
Encephalomyelitis
acute disseminated, 2509
description of, 2024–2025
paraneoplastic, 1238*t*
post-vaccination, 2238
Encephalopathy
bismuth, 101*t*, 102*t*, 105, 105*b*
cat-scratch disease and, 2001–2002
cirrhosis and, 1037–1038, 1038
coma and, 2438
diagnosis of, 1040–1042
hepatic, 986, 989*t*
hypertensive, 458
inborn errors of metabolism and, 1399
treatment of, 1040*b*
Enchondromatosis, 1669
Encorafenib, for melanoma, 1394*t*
End-diastolic pressure, 225
End-diastolic volume, 225
End-expiratory lung volume, 548
End-of-life care
for chronic kidney disease, 839*b*
in delirium, 2334*b*
for dementia, 2413
in heart failure, 278
for hepatobiliary cancers, 1360*b*
End-organ resistance, causes of, 1583*t*
End-plate development and maintenance, defects of, 2589*t*
End-stage heart failure, patients with, quality of life in, 12
End-stage liver disease, alcohol use disorders and, treatment of, 2357*b*
End-stage renal disease
in HIV/AIDS, 2313
renal transplantation for. *See* Renal transplantation
End-stage symptoms, treatment of, evidence for, 12
End-systolic volume, 225
Endemic countries, malaria in, 2118, 2122–2123

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Endemic mycoses, 2080–2087
blastomycosis as, 2080, 2080*t*
coccidioidomycosis as, 2083, 2084*t*, 2085*f*
histoplasmosis as, 2081–2083, 2081*t*
paracoccidioidomycosis as, 2086–2087
sporotrichosis as, 2085–2086
Endemic syphilis, 2021
Endobronchial sarcoidosis, 515*t*, 601
Endocannabinoids, 143
Endocardial diseases, 295
Endocarditis, 2001*t*, 2002, 2518
bacterial
definitive therapy of, 419*t*
subacute, 195
Candida, 2090
clinical manifestations of, 2002
continuing care for, 417*b*–422*b*
culture-negative, 416, 417*t*
diagnosis of, laboratory methods for, 2003*t*
echocardiographic findings, 242*t*
empiric therapy, 417*b*
empirical treatment of, 420*t*
in endoscopy, 876*t*
enterococci causing, 1921
epidemiology of, 2002
fungal, 416
glomerulonephritis with, 783–784
H. influenzae caused by, 1953–1954
indications for valve surgery in, 421*t*
infective, 413–423, 417*b*
Löffler fibroplastic endocarditis, 295
with negative blood cultures, 416
nonbacterial thrombotic, 296, 296*b*
pathobiology of, 2002
prophylaxis of, 355
prosthetic valve, 416, 416*t*
Q fever and, 2063
Staphylococcus aureus, 1903–1904
Stenotrophomonas maltophilia and, 1975
treatment of, 417*b*, 1921*b*, 1922*t*, 1970*b*, 2003*b*
zoonotic, 417*b*
Endocervix, 2241
Endocrine disease
approach to, 1472–1473
cardiomyopathy with, 288
genetic evaluation for, 1473
laboratory evaluation for, 1473
mechanisms of, 1474–1475, 1475*t*, 1476*t*
physical examination for, 1472, 1472*t*
in pregnancy, 1624–1625
response of, to treatment, 1473
surgical risks associated with, 2665
symptoms of, 1472, 1472*t*
thyroid disease, 2665
weight loss and, 860*t*
Endocrine dysfunction, after hematopoietic cell transplantation, 1211–1212
Endocrine insufficiency, chronic pancreatitis and, 975*b*
Endocrine system, age-related changes in, 121
Endocrinology, 1473–1476
Endocytosis, 730
Endodyogeny, 2136
Endofibrosis, iliac artery, 467, 468*b*
Endogenous acids, overproduction of, 757
Endogenous opioid peptides, 1478
Endoleaks, 438*b*, 438.*e*1*f*
Endometrial cancer, 1377
clinical manifestations of, 1378
epidemiology of, 1377
oral contraceptives and, 1615
pathobiology of, 1377, 1377*f*, 1377*t*
prevention of, 1379
prognosis for, 1379
risk factors for, 1377*t*
staging, 1378*t*
treatment of, 1378*b*
Endometrial clear cell carcinomas, 1378*b*
Endometriosis, 1596, 1596*b*, 1603*b*
Endometritis, 1949
Endometrium, menstrual cycle-related changes in, 1595–1596
Endomyocardial fibrosis, tropical, 296
Endophenotypes, 168
Endophthalmitis, 2604
Candida, 2091
fungal, 2606
Pseudomonas infections causing, 1969
Endoplasmic reticulum aminopeptidase gene, 1760
Endoscopic dilation, for peptic strictures, 905*b*
Endoscopic hemostasis, for upper gastrointestinal bleeding, 883*b*–884*b*
Endoscopic retrograde cholangiopancreatography (ERCP), 876–878
of acute pancreatitis, 970–971, 971
of benign biliary strictures, 1057*f*, 1058*f*
of chronic pancreatitis, 974, 975*f*
indications for, 878, 878*f*, 1000
instrument for, 876
preparation for, 876–878
procedure of, 878
Endoscopic therapy
for chronic pancreatitis, 975*b*
for obesity, 1467*b*
for pain, in chronic pancreatitis, 975*t*
for upper gastrointestinal bleeding, 883*b*, 883*t*
Endoscopic ultrasonography
of chronic pancreatitis, 974–975, 975*f*
of pancreatic cancer, 1355
Endoscopy
for chronic diarrhea, 930
Crohn disease on, 944, 944*f*
in emphysema, 632
gastritis on, 913*f*
gastrointestinal. *See* Gastrointestinal endoscopy
for gastrointestinal disease, 854
peptic ulcers on, 913, 913*f*, 914*f*
for pernicious anemia, 1123
Endosteal hyperostosis, 1666, 1667*b*
Endothelial injury, 671
Endothelin 1, 260.*e*1*t*
Endothelin B, 888
Endothelin receptor antagonists, for pulmonary hypertension, 496*b*
Endothelium, 670–671
Endovascular infections, *Pseudomonas* infections causing, 1969
Energy
balance, regulation of, 1464
depletion of, 1447*t*
requirements, estimation of, 1449
Energy expenditure, 1465
Energy intake, 1464–1465
Enfuvirtide, 2301*t*
Engineered cells, 150*t*, 151
Engraftment syndrome, after hematopoietic cell transplantation, 1211
Enhanced external counterpulsation, 364*b*
Enhertu. *See* Fam-trastuzumab deruxtecan-nxki
Enoxaparin, 387*t*, 503*t*
for acute coronary syndrome, 374*t*
for venous thromboembolism, 1624*t*
Entacapone, for Parkinson disease, 2487*t*
Entamoeba dispar infection, 2146
Entamoeba histolytica, 1024–1025, 1026*t*, 2146, 2147*f*
sexually transmitted anorectal diseases and, 983
in travelers, 1889.*e*1*t*, 1891*t*
Entecavir, for hepatitis B virus infections, 2181*t*, 2182–2183, 2182*t*
Enteral nutrition, 673*b*, 1449–1450
Enteral tube feeding, 1449, 1450*f*
Enteric fever
diagnosis of, 1978
differential diagnosis of, 1978
Salmonella causing, 1978
antimicrobial resistance of, 1977
asymptomatic intestinal carrier state of, 1977–1978
bacteremia caused by, 1978
carriers of, 1977–1978
clinical manifestations of, 1977–1978
contact with animals and their environments of, 1977
contact with infected persons of, 1977
contaminated animal products as source of, 1976–1977
in contaminated food and water, 1977
definition of, 1976–1980
diagnosis of, 1978
enterocolitis caused by, 1978
epidemiology of, 1976–1977
pathobiology of, 1977
pathogen description, 1976
prevention of, 1979
Enteric fever *(Continued)*
prognosis for, 1979–1980
treatment of, 1979*b*
in travelers, 1885–1886, 1889.*e*1*t*, 1890*t*
Enteric infection, 1868–1872
clinical manifestations of, 1869–1870, 1869*t*
complications and sequelae of, 1870*t*
definition of, 1868–1872
diagnosis of, 1870–1871
general approach, 1870
laboratory evaluation, 1870–1871, 1870*t*, 1871*f*
epidemiology of, 1868
etiology of, 1868, 1869*t*
pathobiology of, 1868–1869
prevention of, 1872
prognosis of, 1872, 1872*t*
treatment of, 1872*b*, 1872*t*
Enteric nervous system, 887
Enteric oxaluria, 803
Enteric protozoa, 2153–2157
amebiasis. *See* Amebiasis
coccidian enteritis, 2155
cryptosporidiosis. *See* Cryptosporidiosis
giardiasis. *See* Giardiasis
microsporidia, 2156
trichomoniasis, 2154–2155
Enteritis
Clostridium perfringens type C, 1926, 1926*b*
radiation, 940, 940*b*
in travelers, 1891*t*
Enteritis necroticans, 1926
Enteroaggregative *E. coli*, 1888*t*, 1961, 1962*t*
Enterobacterales, 1964–1967
carbapenem-resistant, 1965
clinical manifestations of, 1966
definition of, 1964–1967
diagnosis of, 1966
epidemiology of, 1964–1965
multidrug resistance, 1965, 1966*t*
pathobiology of, 1965–1966
pneumonia caused by, 1965
prevention of, 1967
prognosis for, 1967
treatment of, 1966*b*
Enterobiasis, 2172, 2172*b*
Enterobius vermicularis, 2169, 2170*t*
Enteroclysis, 951
Enterococcal infections, 1920–1924
bacteremia, 1921, 1922*t*
clinical manifestations of, 1920–1921
definition of, 1920–1924
diagnosis of, 1921
endocarditis caused by, 1921, 1922*t*
epidemiology of, 1920
intra-abdominal infections, 1921, 1921*b*
pathobiology of, 1920
pathogen associated with, 1920
primary prevention of, 1924
prognosis for, 1924
skin and soft tissue infections, 1921, 1921*b*
treatment of, 1921*b*, 1922*t*
urinary tract infections, 1920–1921, 1921*b*, 1922*t*
vancomycin-resistant enterococci
E. faecium causing, 1920
epidemiology, 1920
treatment, 1921*b*, 1922*t*
Enterococcus faecalis, 1920
Enterococcus faecium, 1864*t*, 1920
Enterocolitis, *Salmonella*, 1977
Enterocytozoon bieneusi, 2156
Enteroenteric fistulas, in Crohn disease, 945*b*
Enteroglucagon, pNEN secreting, 1561*t*
Enterohemorrhagic *E. coli*, 1961, 1962*t*
Enterohepatic circulations, 994
Enteroinvasive *E. coli*, 1961, 1962*t*
Enteropathic arthritis, 1763–1764
clinical manifestations of, 1764
diagnosis of, 1764
epidemiology of, 1763–1764, 1764*t*
pathobiology of, 1764
prognosis of, 1766
treatment of, 1765*b*
Enteropathogenic *E. coli*, 1961, 1962*t*
Enteropathy, congestive, 967
Enteropathy-type T-cell lymphoma, 1287
Enteroscopy, 878–879
Enterotoxigenic *E. coli*, 1868, 1888*t*, 1961, 1962*t*
Enterovesicular fistulas, in Crohn disease, 945*b*
Enteroviral meningitis, 2520–2521
Enteroviral myocarditis, 2257
Enteroviral pneumonia, 2260
Enteroviruses, 2256–2261
central nervous system infections caused by, 2258
classification of, 2256*t*
clinical manifestations of, 2257
clinical syndromes caused by, 2258–2261
definition of, 2256–2258
diagnosis of, 2257–2258
encephalitis caused by, 2259, 2259*b*
epidemiology of, 2257
ingestion of, 2257
meningitis caused by, 2259, 2259*b*, 2520
myopericarditis caused by, 2259, 2259*b*
myositis caused by, 2260
nonpolio, clinical manifestations of, 2258*t*
pathobiology of, 2257
pathogens that cause, 2256
prevention of, 2261
prognosis for, 2258*b*
respiratory tract syndromes caused by, 2260, 2260*b*
serotypes of, 2257*t*
in special populations, 2261
"summer cold" caused by, 2260
treatment of, 2258*b*
viral structure of, 2256
Enthesopathy, 1742
Entrectinib (Rozlytrek), 1215*t*
Entropion, 2601
Envenomation, 704, 2589*t*
acute coagulopathy associated with, 705*b*
antivenom for, 705*b*
arthropods, 710
centipedes, 711
lice, 711
millipedes, 711
mites, 710
scorpion, 710
ticks, 710
venomous, 710.*e*1*f*
clinical manifestations of, 704–705
diagnosis of, 704
epidemiology of, 704, 705*t*
first aid for, 705*b*
insects, 711–712
marine animals, 712–713, 712*b*
neurotoxic paralysis caused by, 707, 709.*e*1*t*
pathobiology of, 704
pressure bandage with immobilization for, 705*b*
signs of, 706*f*
snakebite. *See* Snakebites
spider bite. *See* Spider bites
syndromes of, 707–710
treatment of, 705*b*
Environmental carcinogenesis, 1321
Environmental carcinogens, 1321
Environmental contamination, health care-associated infections and, 1863
Environmental enteric dysfunction, 1444
Environmental enteropathy, enteric infections and, 1870*t*
Environmental head and neck squamous cell carcinoma, 1323, 1328
Environmental medicine
acute injuries in, 85, 86*t*
clinical implications of, 85–87
emergency preparedness and disaster management in, 89
hazards in, 88*t*
hierarchy of controls in, 87
history, salient features of, 1*f*–4*f*, 85
individual clinician in, role of, 89
medical surveillance in, 87
principles of, 84–89
regulatory environment of, 85
standards of, 87
syndromes in, 85, 86*t*
wellness and resiliency of, 87–89
work-related disability in, 85
worker's compensation in, 85
Environmental poisonings, diarrhea and, 925
Enzalutamide (Xtandi), 1215*t*
Enzootic cycle, of plague, 1988, 1990*f*

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Enzyme immunoassay (EIA)
for blastomycosis, 2081
for enteric infection, 1870*t*
for histoplasmosis, 2083
for paracoccidioidomycosis, 2087
Enzyme replacement therapy (ERT)
for Fabry disease, 1422*t*
for Gaucher disease, 1422*t*
for glycogen storage disease II, 1416*b*
for inborn errors of metabolism, 1401*b*
for mucopolysaccharidoses, 1424
Eosin-5-maleimide (EMA), 1095, 1096*f*
Eosinopenia, 1148
Eosinophil(s), 183, 538
acute inflammation and, 191–192
increased, 533
Eosinophilia, 1142
in mastocytosis, 1701
Eosinophilic cellulitis, 2737
Eosinophilic colitis, 1674
Eosinophilic esophagitis, 904*t*, 907, 907*b*, 907*f*, 907*t*
Eosinophilic fasciitis, 2737
Eosinophilic gastritis, 1674
Eosinophilic gastroenteritis, 940, 1674
Eosinophilic GI disorders, 1673*t*
Eosinophilic granuloma, 1155
Eosinophilic granulomatosis with polyangiitis, 573–574, 582, 1793*t*, 1797–1798, 1798*b*
Eosinophilic meningitis, 2523*t*, 2524
Eosinophilic myositis, 1788*t*
Eosinophilic pneumonia, chronic, 582
Eosinophilic pustular folliculitis, 2321, 2323*f*, 2723
Eosinophilic syndromes, 1162–1165
causes of, 1164*t*
clinical manifestations of, 1163
clinical subtypes of, 1163*t*
definitions of, 1162–1165
diagnosis of, 1163–1164
differential diagnosis of, 1163–1164, 1163*f*
epidemiology of, 1162
mutations in, 1163
pathobiology of, 1162–1163
prognosis of, 1165
treatment of, 1164*b*
Ependymoma, 1316
Ephedra alkaloids, central nervous system effects of, 685*t*
Ephedrine, *e*10*t*–*e*11*t*
Epidemic febrile polyarthritis, 2275*t*, 2279, 2279*b*
Epidemic influenza, 2199
Epidemic keratoconjunctivitis, 2205
Epidemic louse-borne typhus, 2059, 2059*b*
Epidemic typhus, 2055*t*
Epidermal depth, 2688*t*
Epidermal growth factor receptor (EGFR), 153
in bladder cancer, 1366
lung cancer and, 1330
Epidermal papules, 2729
Epidermis, 2686.*e*2*f*
Epidermodysplasia verruciformis, 2242
Epidermoid carcinomas, 1347
Epidermoid cyst, 2689*t*
Epidermolysis bullosa, 2621*t*
Epidermolysis bullosa acquisita, 2718, 2718*b*
Epidermolytic ichthyosis, 3*t*–4*t*
Epididymitis, *Chlamydia trachomatis* causing, 2011, 2012*b*
Epidural abscess, spinal, 2527, 2527*f*, 2527.*e*1*t*, 2528*b*
Epidural anesthesia, 2671
Epidural hematoma, 2391
Epigastric hernia, 952*b*–953*b*
Epigastric pain, 899*t*, 917, 917*t*
Epigenetics
for cancer, 1232*b*
of lung cancer, 1330
rheumatoid arthritis and, 1750
Epiglottitis, 2649*t*, 2651
description of, 2197*f*
distinguishing features of, 515*t*
H. influenzae caused by, 1953
Epilepsy, 2425–2436, 2547, 2547*b*
activity restrictions in, 2434*b*
childhood absence, 2432
definition of, 2425
diagnostic investigations of, 2431
in elderly, 2434*b*
electroencephalogram, 2431
Epilepsy *(Continued)*
epidemiology of, 2425–2427
with generalized tonic-clonic seizures alone, 2433
genetic testing for, 2431
genetics of, 2426–2427
headache associated with, 2425
idiopathic generalized, 2431–2433
imaging studies for, 2431, 2432*f*
incidence of, 2425
juvenile myoclonic, 2433
magnetoencephalography for, 2431
mesial temporal lobe, with hippocampal sclerosis, 2433
mortality risks, 2436
pathobiology of, 2426–2427
pathogenesis of, 2426
in pregnancy, 1619*t*
prevalence of, 2425
prognosis of, 2436
progressive myoclonus, 2433
reflex, 2433
risk factors for, 2425–2426
seizures *versus*, 2425
surgical treatment of, 2434*b*
syndromes, 2431–2433, 2431.*e*1*t*
temporal lobe, 2426*f*, 2646
treatment of, 2434*b*
Epinephrine
for pulseless electrical activity, 313*b*, 316*f*
for septic shock, 671
for shock, 664*t*
synthesis of, 1529
Epiphora, 2599–2600
Epiphrenic diverticula, 909–910, 910*f*
Epirubicin (Ellence), 1215*t*
Episcleritis, 2611
Epistaxis, 2635, 2635*f*–2636*f*, 2636*b*, 2636*f*
Epithelial cell apoptosis, 671
Epithelial cell infections, 1879*t*, 1881–1882
Epithelial sodium channel
activating mutations of, 749
description of, 746
Epitope spreading, in rheumatoid arthritis, 1750
Epizootic cycle, of plague, 1988, 1990*f*
Eplerenone, 451*t*
for Gitelman syndrome, 817*b*
for heart failure, 270*t*
for hypervolemia, 736*b*, 737*t*
Epley maneuver, 2645*f*
Epogen. *See* Erythropoietin
Eprosartan, 451*t*
Eprosartan/HCTZ, 451*t*
Epsilon-sarcoglycan gene, 2493
Epsilon waves, 338*f*
Epstein-Barr nuclear antigens (EBNAs), 2253
Epstein-Barr virus (EBV) infection, 1289, 2253–2256, 2650
acute infection of, 2253–2255
acute leukemias and, 1259
associated neoplasms with, 2256
Burkitt lymphoma and, 2255
central nervous system lymphoma and, 2255
chronic active, 2256
clinical manifestations of, 2253–2254, 2254*f*
clinical syndromes of, 2255–2256, 2256*b*
complications of, 2254
definition of, 2253
diagnosis of, 2254
epidemiology of, 2253
head and neck cancer and, 1320–1321
histiocytoses and, 2256
Hodgkin lymphoma and, 2255
lymphomatoid granulomatosis and, 2256
nasopharyngeal carcinoma and, 2256
non-Hodgkin lymphoma caused by, 1278–1279
oral hairy leukoplakia and, 2256
pathobiology of, 2253
post-transplant lymphoproliferative disorder and, 2255
prognosis of, 2255
related nasopharyngeal carcinoma, 1322
renal transplantation and, 847
treatment and prevention of, 2254*b*
X-linked lymphoproliferative syndrome and, 2254
Epstein-Barr virus pharyngitis, characteristics of, 2270*t*
Eptifibatide, 387*t*, 506*t*, 508
Epworth Sleepiness Scale, 2445, 2448*t*
Equalization, 522
Equilibrium, 2641–2647
Equivalent dose, 91
Eravacycline, 1845*t*, 1895*t*
Erbitux. *See* Cetuximab
ERCP. *See* Endoscopic retrograde cholangiopancreatography
Erdafitinib (Balversa), 1215*t*
Erdheim-Chester disease, 1155*f*, 1156–1157, 1157*b*
Erectile dysfunction, 1587–1589, 1589, 1589*t*, 1590*f*
Erectile physiology, 1581, 1581.*e*1*f*
Ergocalciferol, 1650*t*
Eribulin mesylate (Halaven), 1215*t*
Erivedge. *See* Vismodegib
Erleada. *See* Apalutamide
Erlenmeyer flask deformity, 1667
Erlotinib, 1251*t*
for pancreatic cancer, 1356*b*–1357*b*
Erosions, 913, 2687.*e*4*t*
Erosive gastritis, 913*f*
Errors, 45
ERT. *See* Enzyme replacement therapy
Ertapenem
dosage of, 1895*t*
for pneumonia, 616*t*
for pyelonephritis and urosepsis, 1877*t*
for pyogenic liver abscess, 1023*b*
Eructation, 858
ERV. *See* Expiratory reserve volume
Ervebo, 84
Erysipelas, 1903, 1915
Erysipeloid, 1936–1937, 1936*b*, 1936*f*
Erysipelothrix rhusiopathiae, 1936, 1936*b*, 1936*f*
Erythema, necrolytic migratory, 1564*f*
Erythema ab igne, 471*b*–472*b*, 472, 472*b*, 472*f*, 472.*e*1*f*
Erythema annulare centrifugum, 2711
Erythema chronicum migrans, 2711
Erythema elevatum diutinum, 2735
Erythema gyratum repens, 2711
Erythema induratum, 2735, 2736*f*
Erythema infectiosum, 2234, 2234*f*
Erythema marginatum, 2725, 2726*f*
Erythema migrans
clinical manifestations of, 2023–2025
differential diagnosis of, 2025
early localized infection associated with, 2023–2024, 2024*t*
illustration of, 2023*f*
laboratory tests for, 2025
single lesion, 2023–2024
treatment of, 2026*b*
Erythema multiforme, 2719, 2719*b*, 2719*f*, 2727–2728
description of, 2621*t*, 2691*t*
in parapoxvirus, 2239
prognosis of, 2728
treatment of, 2728*b*
Erythema nodosum, 601, 2688*t*, 2735, 2736*f*, 2736*t*
Erythema nodosum leprosum, 2050–2051, 2051.*e*1*f*
Erythema nodosum necroticans, 2050
Erythematotelangiectatic rosacea, 2722
Erythematous oral candidiasis, 2623, 2624*f*
Erythematous rashes, occupational and environmental, 87
Erythroblastosis fetalis, immunization for, 65*t*
Erythrocyte
disorders of, 724–725
dysmorphic, 723*f*
isomorphic, 723*f*
membrane of, 1093–1097, 1093*f*
disorders of, 1094–1097
function of, 1093–1094
lipids in, 1093–1094
proteins in, 1093–1094
metabolism of, 1098–1102
disorders of, 1099–1102
normal, 1098–1099
Erythrocyte count (RBC count), *e*8*t*–*e*9*t*
Erythrocyte sedimentation rate (ESR), 728, 1712
Westergren, *e*8*t*–*e*9*t*
Erythrocytosis, 355.*e*1*f*, 1134–1135, 1135*t*–1136*t*, 1135*t*, 1136*f*, 1136*t*
Erythrodermic mycosis fungoides, 2709–2710
Erythrodermic psoriasis, 2705–2706
Erythrogenic toxins, 1914
Erythromelalgia, 471, 471*f*, 471*t*, 480, 1133, 1133*f*
Erythromycin
for bacillary angiomatosis, 2003*b*
for bronchiectasis, 561*b*
for chancroid, 1951*b*
for *Chlamydia trachomatis*, 2012*b*
for cholera, 1956*b*, 1957*t*
dosage of, 1895*t*
for eye infection, 2605*t*
for intestinal pseudo-obstruction, 889*b*
for pertussis, 1995*b*
Erythrophagocytosis, conditions associated with, 1072*t*
Erythroplakia, 1321, 2623
Erythropoiesis, 2234
Erythropoietic porphyria, 1428
Erythropoietic protoporphyria, 1428*t*, 1430, 1433*f*, 2705
Erythropoietin (Epogen, Procrit), *e*1*t*–*e*8*t*, 1064–1065, 1215*t*
anemia and, 1075
for orthostatic hypotension, 2559*t*
pNEN secreting, 1561*t*
Escherichia coli, 1833
antimicrobial resistance of, 1864*t*
clinical manifestations of, 1963
definition of, 1960–1964
diagnosis of, 1963–1964
differential diagnosis of, 1963–1964
diffusely adherent, 1961, 1962*t*
enteric infections, 1960–1964, 1962*t*
enteroaggregative, 1961, 1962*t*
enterohemorrhagic, 1961, 1962*t*
enteroinvasive, 1961, 1962*t*
enteropathogenic, 1961, 1962*t*
enterotoxigenic, 1961, 1962*t*
epidemiology of, 1961
non-enterohemorrhagic, 1962*t*
pathobiology of, 1961–1963
pathogenesis of, 1961–1962
prevention of, 1964
prognosis for, 1964
septic bursitis caused by, 1804
shigatoxigenic, 1962*t*
traveler's diarrhea caused by, 1961
treatment of, 1963*b*
urinary tract infections caused by, 1873, 1965
Escitalopram
for depression, 2340*t*
for hot flashes, 1631*t*
Escobar syndrome, 2589*t*
Eslicarbazepine, for seizures, 2434*t*
Esmolol
for electrical storm, 338*b*
for hypertensive emergencies, 460*t*
Esomeprazole
for peptic ulcer disease, 921
for rheumatoid arthritis, 1756*t*
Esophageal adenocarcinoma, 1338
clinical manifestations of, 1339
diagnosis of, 1339
epidemiology of, 1338–1339
laboratory studies of, 1339
pathobiology of, 1339
physical examination for, 1339
prevention of, 1339
prognosis of, 1339
risk factors for, 1338–1339
symptoms and signs of, 1339
treatment for, 1339*b*
Esophageal atresia, 913
Esophageal Crohn disease, 943
Esophageal disease, 901–913
amyloidosis in, 911
anatomy and physiology of, normal, 901–902
bacterial esophagitis in, 912
Barrett esophagus as. *See* Barrett esophagus
candidiasis, 911, 912*f*
congenital abnormalities, 913
cricopharyngeal bars in, 909
cytomegalovirus in, 912
drug therapy for, 904*t*
esophageal diverticula, 909–910, 909*f*–910*f*
esophageal emergencies, 912–913
esophageal motor disorders as, 908–909
esophagitis as. *See* Esophagitis
gastroesophageal reflux disease as. *See* Gastroesophageal reflux disease
herpes simplex virus in, 911

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Esophageal disease *(Continued)*
hiatal hernia in, 910
human papillomavirus in, 912
peptic strictures as, 905
rings and webs, 910, 910*f*
scleroderma in, 911
skin disorders and, 911
symptoms of, 902
in systemic sclerosis, 1780
Esophageal diverticula, 909, 909*f*, 910*f*
Esophageal emergencies, 912
Esophageal fistula, 912–913
Esophageal functional testing, 901–902
Esophageal manometry, 904–905
Esophageal motor disorders, 908
achalasia in, 908
diffuse esophageal spasm in, 909
oropharyngeal dysfunction in, 908
Esophageal neoplasms, 1337–1339
adenocarcinoma, 1338
definition of, 1337
squamous cell carcinoma, 1337–1338
Esophageal reflux, 211*t*
Esophageal regurgitation, 852*t*, 865
Esophageal squamous cell carcinoma, 1337
clinical manifestations of, 1338
diagnosis of, 1338
epidemiology of, 1337–1338
laboratory studies for, 1338
medical therapy for, 1338*b*
pathobiology of, 1338
physical examination for, 1338
prognosis of, 1338
risk factors for, 1337–1338, 1337*t*
surgical therapy for, 1338*b*
symptoms and signs of, 1338
treatment for, 1338*b*
Esophageal varices, 912
endoscopy for, 881
Esophageal webs, 910, 910*f*
Esophagitis, 907–908
bacterial, 912
Candida, 2090
caustic injury, 907
clinical manifestations and diagnosis of, 907, 907*f*, 907*t*
eosinophilic, 907
pill-induced, 907, 907*t*
treatment and prognosis of, 904*t*, 907*b*
Esophagogastric junction outflow obstruction, 909
Esophagus, 901
alcohol use disorders and, 2355*t*
motor functions of, 901
Esotropia, 2598
ESR. *See* Erythrocyte sedimentation rate
Essential mixed cryoglobulinemia, 1716
Essential thrombocythemia, 1130–1139
anagrelide for, 1135*b*
aspirin for, 1135*b*
clinical manifestations of, 1133, 1133*f*
cytoreductive therapy for, 1135*b*
definition of, 1130–1139, 1130*t*
epidemiology of, 1130
erythromelalgia, 1133, 1133*f*
hydroxyurea for, 1135*b*
interferons for, 1135*b*
neutrophilia and, 1142
pathobiology of, 1130–1131, 1131*f*
ruxolitinib for, 1135*b*
treatment for, 1135*b*, 1136*t*
Essential tremor, 2490
Estimated glomerular filtration rate (eGFR), evaluation of, 837–839, 839*t*
Estradiol, 1581
for genitourinary syndrome of menopause, 1632*t*
by immunoassay, *e*1*t*–*e*8*t*
for transgender women, 1579*t*
Estradiol vaginal inserts (Imvexxy), for genitourinary syndrome of menopause, 1632*t*
Estradiol valerate, for transgender women, 1579*t*
Estrogen
cancer and, 1245
for osteoporosis, 1643*b*
for transgender women, 1578*b*, 1579*t*
Estrogen receptors, 1629
Estrogen replacement, hypertension associated with, 456
Eszopiclone, 2344*t*, 2452*t*
Etanercept (Enbrel)
description of, 150–151, 151*t*
for rheumatoid arthritis, 1756*t*
for total knee arthroplasty, 1830.*e*1*t*
Eteplirsen, 2583*b*
Ethacrynic acid, 451*t*
Ethambutol
dosage of, 1895*t*
for nontuberculous mycobacterial disease, 2046*t*
ocular effects of, 2614
for tuberculosis, 2040*b*, 2041*t*–2043*t*, 2041*t*, 2042*t*, 2043*t*
Ethanol, *e*10*t*–*e*11*t*
excess, 1072*t*
metabolism of, 2353*f*, 2354
toxicity, 690*t*
Ethanolamine. *See* Amino alkyl ether
Ethnic disparities, in health outcomes, 17–18
Ethnicity
age-adjusted drug overdose death rates by, 18*t*, 19*f*
arterial hypertension and, 444–445
Ethosuximide, *e*10*t*–*e*11*t*, 2434*t*
Ethylene glycol, 759–760
central nervous system effects of, 685*t*
toxicity, 686*t*, 690*t*, 698*t*
Ethylenediamine, 2700*t*
Ethylenediaminetetraacetic acid (EDTA), 1166–1167
Etodolac
for chronic pain, 138*t*
for rheumatoid arthritis, 1756*t*
Etopophos. *See* Etoposide phosphate
Etoposide (Vespid), 1215*t*
Etoposide phosphate (Etopophos), 1215*t*
Etoricoxib, for chronic pain, 138*t*
Etravirine, 2301*t*
Eulexin. *See* Flutamide
Eumycetoma, 2110
Europe
arterial hypertension in, 445, 445.*e*1*f*
Chagas disease in, 2126
European LeukemiaNet Cytogenetic/Molecular Risk Stratification of AML, 1261*t*
Eutectic mixture of local anesthetic (EMLA), for skin diseases, 2699
Euthanasia, 8, 8*t*
definition of, 8, 8*t*
empirical data for, 8
history of, 8
justification of, 8
practical considerations for, 9
safeguards, 8
Euthyroid sick syndrome, 1497
EV-A71, 2258
EV-D68, 2258
Evacuation disorder, constipation *versus*, 890, 890*t*
Event monitors, 307–308
Everolimus (Afinitor), *e*10*t*–*e*11*t*, 1215*t*
for liver transplantation, 1048*t*
in renal transplantation, 845*t*
Evidence-based medicine, 2
Evidence generation, 168–169, 168*t*
Evinacumab, 1413
Evoked potential tests
for multiple sclerosis, 2504
neurologic disease evaluations, 2376
Ewing sarcoma, 1388, 1388*b*
Ex vivo gene therapy, 175
Exanthems, 2712, 2712*t*
enteroviruses causing, 2259
macular, 2712–2716
papular, 2712
Excessive daytime sleepiness, 2444–2445, 2447*f*
Excitation-contraction coupling, 224.*e*1*f*
Excoriation, 2687.*e*4*t*
Executive cognitive dysfunction, 2410–2411, 2411*f*
Exemestane (Aromasin), 1215*t*
Exenatide, for type 2 diabetes mellitus, 1541*t*
Exercise
for atherosclerotic PAD, 464*b*
for congenital heart disease, 355, 355.*e*2*t*
definition of, 61
for heart failure, 265*b*, 275*t*
for osteoarthritis, 1741*t*
for pain, 136*b*
responses to stressors, 226
Exercise capacity, 261
Exercise electrocardiography, in angina pectoris, 361
Exercise-induced asthma, 541*b*
Exercise-induced bronchoconstriction, 538
Exercise-induced bronchospasm, 681
Exercise testing
in arrhythmia, 309
for hypoglycemia, 1557
for interstitial lung disease, 574
protocols, 212*t*
Exertional heat injury, 678.*e*2*f*
Exertional heatstroke, 678.*e*1*f*, 679*t*
Exertional rhabdomyolysis, 714, 715*t*
Exhaled nitric oxide, in asthma, 539–540
Exocrine insufficiency, chronic pancreatitis and, 975*b*
Exocytosis, 730
Exogenous hormones, cancer and, 1246
Exome sequencing, for inborn errors of metabolism, 1400
Exophthalmos, 2600, 2600*f*
Exotropia, 2598
Expanded volume, metabolic alkalosis with, 763–764
Expiratory flow, in pulmonary function tests, 528*t*
Expiratory reserve volume (ERV), 530
Exploding head syndrome, 2453*t*
Exposure Survey, 85, 85.*e*1*f*
Expressed genome, 168
complex multimarker genomic tests, for disease diagnosis and prognosis, 168
metabolic and protein profiling, 168
Expulsive therapy, for nephrolithiasis, 805*b*–806*b*
Exserohilum rostratum, 1865
Extavia. *See* Interferon Beta1*b*
Extended-spectrum β-lactamase-producing organisms, treatment of, 1966*b*
Extended-spectrum β-lactamases, 1966
Extensive urticaria, 1688*f*
External carotid arteries, 2455
External genitalia
abnormal differentiation of, 1572*f*
development of, 1569
Extra-axial brain tumors, 1313*t*
Extra-genital lesions, granuloma inguinale and, 2004
Extracellular fluid volume
control of, 733–734, 733*f*
depletion of, 738–739
disorders of, 733–736
pathobiology of, 733–735
regulation of, 730, 730.*e*1*f*
Extracellular pH, secretion, control of, 732
Extracellular vesicles, 172
Extracellular volume depletion, metabolic alkalosis with, 763
Extracorporeal photochemotherapy (photopheresis), 2701
Extracorporeal removal, for acute poisoning, 691*b*
Extracorporeal ultrafiltration, 736*b*
Extracranial carotid artery stenosis, 2464
Extradural brain tumors, 1318, 1318*b*
Extragenital lesions, chancroid and, 1951
Extraglandular disease, Sjögren syndrome and, 1785, 1786*b*–1787*b*
Extragonadal germ cell cancer syndrome, treatment of, 1241*b*
Extraintestinal infections, 2148
Extramedullary hematopoiesis, 527
pregnancy and, 1135*b*
in primary myelofibrosis, 1133
radiation therapy for, 1135*b*
Extramedullary plasmacytoma, 1303
Extranodal NK/T-cell lymphoma, 1287
Extrapulmonary aspergillosis, 2094
Extrapulmonary infections, legionellosis and, 1998
Extrapulmonary tuberculosis, 2035–2038, 2040, 2040*b*
Extrapyramidal symptoms, psychotropic medications and, 2678*t*
Extremities
due to heart failure, 258
for signs of cardiovascular disease, 215–216, 217*f*
Extrinsic allergic alveolitis, aspergillosis and, 2095
Extrinsic neuropathic disorders, 888
Extrinsic pathway, 1165
Exudates
characteristics of, 623–624
pleural
causes of, 626–627
fluid characteristics of, 625, 625*b*, 625*t*
Eye(s)
acute poisoning and, 683
anatomy of, 2597*f*
anterior chamber of, 2596
anterior segment of, 2596
ciliary body of, 2596
cornea of, 2596
crystalline lens of, 2596
examination of, 30
foreign body sensation in, 2599, 2600*f*
inflamed, 2599, 2599*t*
inflammatory disorders of, 2604
movements, examination of, 2618
onchocerciasis manifestations of, 2178
pain of, 2598–2599, 2599*t*
retina of, 2596
sclera of, 2596
syphilis involvement of, 2017
vision loss caused by, 2615
vitreous of, 2596
Eye disorders
Acanthamoeba keratitis, 2606
age-related macular degeneration, 2608, 2609*f*
autoimmune, 2611
in bacterial endocarditis, 2609, 2610*f*
cellulitis, 2604, 2605*f*
central retinal artery occlusion, 2610, 2610*f*
central retinal vein occlusion, 2610–2611, 2610*f*
choroidal dystrophy, 2611
conjunctivitis. *See* Conjunctivitis
corneal stromal dystrophy, 2611
cytomegalovirus retinitis, 2606
in diabetes mellitus, 2609, 2609*f*
endophthalmitis, 2604
fungal endophthalmitis, 2606
glaucoma. *See* Glaucoma
hemangioma of eyelid, 2612
herpes simplex keratitis, 2605, 2606*f*
herpes zoster ophthalmicus, 2605–2606
in hypertension, 2609, 2610*f*
idiopathic inflammatory, 2611
infectious, 2604–2606
keratoconjunctivitis sicca, 2611
lymphoma, 2613
pseudomonal keratitis, 2606
retinitis pigmentosa, 2612, 2612*f*
retinoblastoma, 2612
retinopathy of prematurity, 2612
in sarcoidosis, 601–602, 604*t*
scleritis, 2611
toxoplasmic retinitis, 2606
tuberculosis involvement, 2606
tumors, 2612–2613
uveitis, 2604
vascular abnormalities, 2610–2611, 2610*f*
Eye infections, *Pseudomonas* infections causing, 1969, 1970*b*
Eye injury, occupational, 85, 86*t*
Eyelids, 2596
abnormalities, 2601–2602
basal cell carcinoma of, 2602, 2602.*e*1*f*
benign neoplasms of, 2602
blepharitis of, 2601, 2601*f*
chalazion of, 2601, 2601*f*
ectropion of, 2601, 2601*f*
entropion of, 2601
hemangioma of, 2612
hordeolum of, 2601, 2601*f*
sebaceous carcinoma, 2602
squamous cell carcinoma of, 2602
twitching, 2600
Ezetimibe, 1413

F

Fabry disease, 787, 1398*t*, 1421–1423, 1825, 2560
cardiac involvement in, 282.*e*1*f*
clinical manifestations of, 1421*f*, 1422
definition of, 1421
diagnosis of, 1422–1423, 1422*t*
enzyme-specific treatments for, 1420*t*
epidemiology of, 1421

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Fabry disease *(Continued)*
female carriers of, 1422
pathobiology of, 1421–1422
stroke caused by, 2470.*e1t*
treatment of, 1423*b*
Face, examination of, 29
Facial injuries, in intimate partner violence, 1633–1634
Facial paralysis, 2579
Facioscapulohumeral dystrophy, 2368.*e3f*
Facioscapulohumeral muscular dystrophy, 2584, 2584*b*
Factitial dermatitis (dermatitis artefacta), 2687.*e4t*
Factitious diarrhea, 940
Factitious disorder, 2347, 2347*t*
Factor H, 200*t*
Factor I, description of, 200*t*
Factor II deficiency, 1189*t*, 1193, 1193*b*
Factor V deficiency, 1189*t*, 1193
Factor V Leiden, 476, 476*t*
Factor VII, 1000
Factor VII deficiency, 1189*t*, 1193
Factor VIII deficiency, 1189*t*
Factor IX deficiency, 1189*t*
Factor IX Padua, 476
Factor X deficiency, 1189*t*, 1193, 1193*b*
Factor XI deficiency, 1189*t*, 1191
clinical manifestations of, 1191
diagnosis of, 1191
epidemiology of, 1191
pathobiology of, 1191
treatment of, 1192*b*
Factor XI gene *(FXI)*, 1191
Factor XII deficiency, 1189*t*, 1192, 1192*b*, 1193*b*
Factor XIII deficiency, 1189*t*
Fainting. *See* Heat syncope
Fallopian tube cancer, 1379
clinical manifestations of, 1379
definition of, 1379
diagnosis of, 1379
epidemiology of, 1379, 1379*t*
pathobiology of, 1379
prevention of, 1380
prognosis for, 1381, 1381*t*
risk factors for, 1379*t*
treatment of, 1380*b*, 1380*t*, 1381*t*
Falls
frailty and, 123
multifactorial interventions for, 116
in older adults, 114
risk of, geriatric assessment, 118
Fam-trastuzumab deruxtecan-nxki (Enhertu), 1215*t*
Famciclovir
for herpes simplex virus infections, 2246
for herpesvirus infections, 2186, 2187*t*
for skin diseases, 2699
for zoster, 2249*b*
Familial adenomatous polyposis, 1250*t*, 1344, 1347*t*, 1348, 1348*f*
Familial amyloid polyneuropathy, 2560
description of, 2570–2571, 2570*b*
Familial amyloidosis, 1306*t*, 1309
clinical manifestations and diagnosis of, 1309
treatment and prognosis of, 1309*b*
Familial benign hypocalciuric hypercalcemia, 1658
Familial cancer syndromes, 1250*t*
Familial cholestasis syndromes, 997, 997.*e1t*
Familial cold autoinflammatory syndrome (FCAS), 1731*t*, 1733*t*
Familial cold urticaria, neutrophilia and, 1142
Familial colorectal cancer syndromes, 1347, 1347*t*
Familial combined hypercholesterolemia, 1409
Familial dysbetalipoproteinemia, 1409
Familial gastric carcinoma, 1250*t*
Familial hemophagocytic lymphohistiocytosis, 1159–1162, 1160*t*–1161*t*, 1161*b*–1162*b*, 1161*f*, 1161*t*, 1684*t*
Familial hypercholesterolemia, 160, 1398*t*, 1408
cascade screening for, 1409
clinical manifestations of, 1408
combined, 1409
diagnosis of, 1409
epidemiology of, 1408
pathobiology of, 1408
in pregnancy, 1409*b*
prognosis for, 1409
screening for, 1409
treatment of, 1409*b*, 1409*t*
Familial hypereosinophilic syndrome, 1162, 1163*t*
Familial hypokalemic periodic paralysis, 751–752
Familial hypomagnesemia with hypercalciuria, 816*t*
Familial intrahepatic cholestasis, 997
Familial isolated pituitary adenoma syndrome, 1487*t*
Familial juvenile polyposis, 1348
Familial keratosis lichenoides chronica, 1731*t*
Familial malignant melanoma, 1250*t*
Familial Mediterranean fever (FMF), 1730–1732, 1731*t*
clinical characteristics of, 1733*t*
clinical manifestations of, 1730–1732
definition of, 1730
diagnosis of, 1732
epidemiology of, 1730
pathobiology, 1730
prognosis for, 1732
treatment of, 1732*b*
Familial paraganglioma, 1530
Familial primary hyperparathyroidism, 1657
Familial pulmonary fibrosis, 570
Familial Wilms tumor, 1250*t*
Families
definition of, 12
in heart failure management, 275*t*
palliative care for, 12
Family history, 28, 2660
cardiovascular disease and, 220
Family screening, for dilated cardiomyopathy, 287*b*
Family testing, 2424–2425
Fanconi anemia, 1127.*e1t*, 1129, 1129*b*, 1145, 1250*t*, 1253
Fanconi-Bickel syndrome, 816*t*
Fanconi syndrome, 749*t*
in chronic interstitial nephritis, 793
Far-UVC radiation, 95
Farydak. *See* Panobinostat
Fascicular branch blocks, 231, 231*t*, 232*f*
Fasciculations, 2581*t*
Fasciola spp., 1026*t*
description of, 2166*t*
in travelers, 1889.*e1t*
Fascioliasis, 2165, 2168, 2168*b*
in travelers, 1891*t*
Fasciolopsis buski, 2166*t*
Faslodex. *See* Fulvestrant
FAST. *See* Focused abdominal sonography in trauma
Fasting
for hypoglycemia, 1556–1557, 1556*t*
rate of glucose during, 1552
Fasting glucose concentration, 1536*t*
Fasting hypertriglyceridemia, 1466
Fat
dietary guidelines for, 57.*e3t*
fecal, *e1t*–*e8t*
Fat atrophy, 2687.*e4t*
Fat embolism
in joint diseases, 1830
stroke caused by, 2472
Fat embolism syndrome, 491, 491.*e1f*
Fat-soluble vitamins, 1450–1451, 1451, 1453*t*
Fatal familial insomnia, 2423
Fatigue, 256
liver disease and, 986
management of, approaches to, 13*t*
multiple sclerosis and, 2501
neurologic diseases that cause, 2372
Fatty acid metabolism disorders, 2586, 2586*b*
Fatty acid oxidation, disorders of, 1404, 1404*b*, 1552*t*, 1555
Fatty acids
nonesterified, *e1t*–*e8t*
in parenteral nutrition, 1450
Favipiravir, 2202*b*, 2203*t*, 2269*b*
FBN1, mutations in, 1725
Fc receptors (FcRs), 184
FCAS. *See* Familial cold autoinflammatory syndrome
FcεR-bearing effectors, 193–194
FDA. *See* Food and Drug Administration
FDA Biomarkers, 169.*e1t*
18-FDG. *See* 18-Fluorine deoxyglucose
FDG-PET. *See* Fluorodeoxyglucose positron emission tomography
FDPs. *See* Fibrin degradation products
Febrile illnesses, 1851*b*
Febrile neutropenia, 1968–1969
syndrome of, 1855–1861
Febrile neutrophilic dermatosis. *See* Sweet syndrome
Febrile nonhemolytic transfusion reaction, 1202
Febrile seizures, prognosis after, 2436
Febrile syndromes, acute, 590, 591*t*
Fecal elastase-1 test, for malabsorption, 931*t*
Fecal incontinence, 865, 981
algorithm for, 981*f*
clinical manifestations and diagnosis of, 981
epidemiology and pathobiology of, 981
in older adults, 118
treatment for, 981*b*
Fecal microbiota transplantation, for *Clostridioides difficile*, 1925*b*
Fecal occult blood testing, 1352
Fecal transplantation, 1840
Fedratinib, 153*t*
Feeding, rate of glucose during, 1552
Feet, rheumatoid arthritis of, 1751
FEF. *See* Forced expiratory flow
Felodipine, 367*t*, 451*t*
Felty syndrome, 1146, 1152, 1754, 1755*b*
Female breast, development of, 110.*e1f*
Female condom, 1612
Female genital discharge, 1879*t*, 1882–1883
Femara. *See* Letrozole
Fenoldopam, for hypertensive emergencies, 460*t*
Fentanyl, 139*t*. *See also* Opioids
Fermentative *Corynebacteria*, 1934
Ferning, 1595
Ferric carboxymaltose, for iron deficiency anemia, 1085*t*
Ferric derisomaltose, for iron deficiency anemia, 1085*t*
Ferritin, *e1t*–*e8t*
Ferrous gluconate, for iron deficiency anemia, 1085*t*
Ferrous sulfate, for iron deficiency anemia, 1084*b*–1085*b*, 1085*t*
Fertility
in female, 1602
preservation of, in transgender individual, 1580
Fertility-awareness contraceptive method, 1611
Ferumoxytol, for iron deficiency anemia, 1085*t*
Fesoterodine, 824*t*
Fetal alcohol syndrome, 2545
Fetal hemoglobin, hereditary persistence of, 1106, 1107*f*
Fetal testicular regression syndrome, 1574
Fetal varicella syndrome, 2248
α-Fetoprotein (AFP), *e1t*–*e8t*
Fetor hepaticus, 1038
Fetus, maternal conditions affecting, 1573
FEV. *See* Forced expiratory volume
Fever
acute, 2694*t*
antibiotic therapy for, 1858*f*–1859*f*, 1859*f*
approach to, in normal host, 1845–1851
in cancer, 1239, 1240*b*
caused by amphotericin B, 2078
clinical manifestations of, 1846
in compromised host, 1853, 1854*b*
definition of, 1845–1846
diagnosis of, 1846–1847
drug, 1846
epidemiology of, 1846
in hemophagocytic lymphohistiocytosis, 1160
hepatosplenomegaly and, 1849
hospital-associated, 1846*t*
in immunocompromised host, 1851–1862
clinical manifestations of, 1854
definition of, 1851
diagnosis of, 1854
general concepts of, 1851–1852
treatment of, 1854*b*
infectious causes of, 1850*t*
in inpatients, 1846–1847
lymphadenopathy and, 1849, 1849*t*
management of, 1856*f*–1857*f*
musculoskeletal complaints and, 1849
in neutropenia, 1854
noninfectious causes of, 1851–1852
in outpatients, 1846
overview of, 1845–1847
pathobiology of, 1846
Pontiac, 1998–1999, 1999
postoperative, 1849, 2675
prolonged, in bacterial meningitis, 2518
Fever *(Continued)*
Q fever, 417*t*
rash and, 1847, 1848*t*
severe mental illness and, 2683*t*
syndromes, 1847–1851
travel associated with, 1890*t*
treatment of, 1851*b*
viral hemorrhagic, 99–100
vital signs in, 34
in women, medications for, 1608*t*
Fever of unknown origin (FUO), 1849–1850, 1850*f*, 1850*t*
Fexinidazole, for African trypanosomiasis, 2112*t*, 2115–2116, 2125*b*
FFP. *See* Fresh-frozen plasma
FGFR. *See* Fibroblast growth factor receptor
FHIT (fragile histidine triad) gene, lung cancer and, 1330
Fiber, dietary guidelines for, 57.*e3t*
Fibrates, for hypertriglyceridemia, 1414*b*
Fibrillary glomerulopathy-immunotactoid glomerulopathy, 788–789
Fibrin, 1165, 1165*f*
Fibrin degradation products (FDPs), *e8t*–*e9t*, 1195
Fibrin-stabilizing factor, 1189*t*, 1192, 1192*b*
Fibrinogen, *e1t*–*e8t*, *e8t*–*e9t*, 1167*t*, 1189*t*
Fibrinolysis, rare disorders of, 1169
Fibrinolytic therapy, 509
contraindications to, 487*t*
for STEMI, 384*b*, 386*t*
Fibroblast growth factor-23 (FG23), 732
Fibroblast growth factor receptor (FGFR), lung cancer and, 1330
Fibroblast-like synoviocytes, 1751
Fibrocystin, 813
Fibroelastomas, 296
Fibrogenesis imperfecta ossium, 1666
Fibromuscular dysplasia, 468, 468*f*
angioplasty for, 800*b*
clinical manifestations of, 468
diagnosis of, 468
epidemiology of, 799
renal artery stenosis caused by, 799
right renal arteriogram of, 801*f*
string of beads in, 449, 449*f*
"string of beads" lesion of, 468, 468*f*
treatment of, 800*b*
Fibromyalgia, 1708, 1769, 1816–1820, 2372
brain imaging studies for, 1817
clinical manifestations of, 1817–1818
comorbid, 1816
conditions that simulate, 1819*t*
definition of, 1816–1820, 1818*t*
diagnosis of, 1818–1819
epidemiology of, 1816
interventional therapies for, 1819*b*
nonpharmacologic therapies for, 1819*b*, 1819*t*
pain associated with
mechanistic characterization of, 1817*t*
processing, 1817
pathobiology of, 1816–1817
peripheral factors in, 1817
pharmacologic therapies for, 1819*t*
prognosis for, 1820
sensory processing in, 1817
stressors that cause, 1816, 1816*t*
symptom severity scale score for, 1818*f*
tricyclic agents for, 1819*b*
Fibronectin binding protein, 1913
Fibrosing mediastinitis, 629
Fibrosing mediastinitis, pulmonary histoplasmosis and, 2082
Fibrosis, in systemic sclerosis, 1776
Fibrous dysplasia, 1668, 1669*b*, 1669*f*
Fibrous tumors, of pleura, 526
FICA Spiritual Assessment Tool, 12, 16*t*
Fick equation, 640
Fidaxomicin, for *Clostridioides difficile*, 1925*b*
Fifth disease, 2234, 2234*f*
Figurate erythemas, 2711
Filamentous hemagglutinin, 1995
"Filarial dance sign", 2177
Filariases, 2176–2180, 2176*b*, 2176*t*
dracunculiasis, 2180
loiasis, 2179
lymphatics, 2176
Mansonella perstans, 2180
Mansonella streptocerca, 2180
onchocerciasis, 2178
in travelers, 1889.*e1t*
zoonotic, 2180

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Filgotinib, 153*t*
Filgrastim (Neupogen), 1215*t*
Fimbriae, 1913
Final menstrual period, 1628
Financial assessment, geriatric, 118
Financial conflicts of interest, in bioethics, 10
  definition of, 10, 10*t*
  empirical data for, 10–11
  history of, 10
  justification of, 10
  practical consideration for, 11
Finasteride, 824*t*
Fine-needle aspiration biopsy, for thyroid nodules, 1516, 1516*t*
Fingolimod (Gilenya), for multiple sclerosis, 2505*t*
FIP1L1-PDGFRA fusion gene, 295, 1142
First-degree atrioventricular block, 229
"First-order" process, 127
First-pass effect, of drugs, 126
FISH. *See* Fluorescence in situ hybridization
Fissure, 2687.*e4t*
Fistula
  anal, 979, 979*b*, 980*b*, 980*f*
  aortoenteric, 967
  coronary artery, 352
  Crohn disease and, 943
  esophageal, 912
  from hepatic artery, 969
  pulmonary arteriovenous, 350–351
Fitness, physical, 61
Fitzpatrick skin types, 2686.*e2t*
Fixed airway obstruction, 532
Fixed drug eruptions, 2728
Flaccid blisters, 2720
Flagyl. *See* Metronidazole
Flail arm syndrome, amyotrophic lateral sclerosis and, 2563
Flail chest, 621, 621.*e1f*, 622*b*
FLAIR. *See* Fluid-attenuated inversion recovery
Flat smallpox, 2237, 2237*t*, 2270*t*
Flat warts, 2242
Flatus, 858–859
Flavin adenine dinucleotide, 1530
Flaviviridae, 2274, 2276*b*, 2280–2283
Flaviviruses, in travelers, 1891*t*
Flavonoids, 116
Flax, 88*t*
Flea-borne spotted fever, 2055*t*, 2059
  in travelers, 1889.*e1t*
Flea-transmitted diseases, 2058–2059
Flecainide, *e*10*t*–*e*11*t*, 325*t*
Fleischer ring, 987
Flexibility activity, 63*b*
Flexible sigmoidoscopy, 1349, 1353
  for colorectal cancer, 54
Flinders Island spotted fever, 2055*t*
Floaters, 2599
"Floating teeth", 1154
Flour dust, 88*t*
Flow cytometry, for anemia, 1077
Flow-volume curve, 528, 529*f*
"Flowers of Lichtenberg", 704, 704*f*
Fluconazole, 2075, 2699
  adverse effects of, 2076
  for candidiasis, 2093
  for cryptococcosis, 2089
  drug interactions of, 2076
  formulations and pharmacology of, 2075
  for hepatosplenic candidiasis, 1024*b*
  for histoplasmosis, 2083*b*
  indications and dosage of, 2075–2076, 2075*t*
  for mycoses, 2076
  for paracoccidioidomycosis, 2087*b*
  for sporotrichosis, 2086*b*
  for vulvovaginal candidiasis, 1882*b*
Flucytosine, 2079
  adverse effects of, 2079
  for cryptococcosis, 2088*b*
  drug interactions of, 2079
  formulation and pharmacology of, 2079
  indications and dosage of, 2075*t*, 2079
  mechanisms of action, 2079
Fludara. *See* Fludarabine
Fludarabine (Fludara), 1215*t*
  for autoimmune hemolytic anemia, 1089
  for chronic lymphocytic leukemia, 1269*t*, 1270*t*
Fludarabine/cyclophosphamide/rituximab, for chronic lymphocytic leukemia, 1269*b*
Fludrocortisone
  for orthostatic hypotension, 2559*t*
  for septic shock, 673*b*
Fluid(s)
  for acute kidney injury, 774*b*
  intestinal transport of, 924, 924.*e1f*
  for resuscitation, 636
Fluid-attenuated inversion recovery (FLAIR), for epilepsies, 2431, 2432*f*
Fluid replacement, for diarrhea, 926*b*
Flukes
  intestinal, 2166*t*, 2167
    approach to, 2168
  liver
    approach to, 2168
    description of, 2165–2167
    fascioliasis, 2168
    opisthorchiasis, 2168
    paragonimiasis, 2168
  lung, 2166*t*, 2168
  pulmonary, 2167–2168
Flumazenil
  for acute poisoning, 693*t*
  for catatonia, 2681*b*
Flunisolide, 553*t*
Fluorescence in situ hybridization (FISH)
  for anemia, 1077
  for chronic lymphocytic leukemia, 1267
Fluorinated hydrocarbons, 88*t*
Fluorine, 1457*t*
18-Fluorine deoxyglucose (18-FDG), 1723
Fluorochrome stains, for tuberculosis, 2039
Fluorodeoxyglucose positron emission tomography (FDG-PET), 519
  for Hodgkin lymphoma, 1291
Fluoropolymers, 88*t*
Fluoroquinolones, 1893
  for anthrax, 1932*b*
  for bacterial meningitis, 2518*t*
  for *Campylobacter* infections, 1959*b*, 1960
  for enteric fever, 1979*b*
  for Oroya fever, 2003*b*
  reactions to, 1698*t*
  Streptococcus pneumoniae resistance to, 1912*b*
Fluoroscopy
  description of, 866–868, 868*f*–869*f*, 868*f*, 869*f*
  for rheumatic disease, 1717
  water-soluble contrast for, 866–867
5-Fluorouracil (Adrucil, Efudex), 1215*t*
  cardiomyopathy due to, 288
  for gastric adenocarcinomas, 1341*b*
  for head and neck cancer, 1327*b*
Fluoxetine
  for cataplexy, 2449*t*
  for depression, 2340*t*
  for hot flashes, 1631*t*
  for irritable bowel syndrome, 896*t*
Fluphenazine, for psychotic disorders, 2346*t*
Flurazepam, for anxiety disorders, 2344*t*
Flutamide (Eulexin), 1215*t*
Fluticasone, 553*t*
Fluvastatin, for familial hypercholesterolemia, 1409*t*
Fluvoxamine, for COVID-19, 2217
FMF. *See* Familial Mediterranean fever
Foam, 2697
Focal central nervous system disorders, 2561
Focal invasive candidiasis, 2091
Focal ischemic injury, 2463, 2463*f*
Focal nodular hyperplasia, 992, 992*f*
Focal oligemia, with vascular deficiency, 522
Focal segmental glomerulosclerosis, 778, 779*b*, 779*f*, 779*t*
Focal segmental ischemia, 962*f*
Focused abdominal sonography in trauma (FAST), 700*b*, 701*f*
FODMAPs, 859
Folate, *e*1*t*–*e*8*t*, 935, 1119–1120, 1427*b*, 1453*t*
  absorption of, 1119–1120
  biochemical assays for, 1122
  cycle, 1425.*e2f*
  functions of, 2540
  homocysteine and, 1459, 2540
  malabsorption of, 1120, 1123
  metabolism of, 1119, 2121*b*
  supplementation of, 1453*t*
  transport of, 1119
Folate deficiency
  alcohol and, 1120
  description of, 2538*t*, 2540, 2540*b*
Folate deficiency *(Continued)*
  drugs that cause, 1117*t*, 1120
  epidemiology of, 1117–1118
  megaloblastic anemia caused by, 1117*t*, 2540
  metabolites for, 1124*t*
  prevention of, 1124
  treatment of, 1123*b*
Folex. *See* Methotrexate
FOLFOX chemotherapy, for gallbladder cancer, 1054*b*
Folic acid, 1119–1120
  for malabsorption, 937*t*
  for neural tube defect prevention, 1452
  supplementation
    for autoimmune hemolytic anemia, 1089*b*
    for hearing loss in elderly, 2642*b*
Folinic acid, 1427*b*
  for acute poisoning, 693*t*
  for toxoplasmosis, 2140*t*
Follicle-stimulating hormone (FSH), 1496
  description of, 1580–1581
  gonadotropin-releasing hormone effects on, 1476
  insufficiency tests of, 1484*t*
  menopause and, 1629
  pathobiology of, 1496
  in puberty, 1591, 1591*f*
  secretion of, 1582
  subunits of, 1581
  tests of, 1488*t*
  tumors that produce, 1496, 1496*b*
Follicular B-cell lymphoma, 2734
Follicular conjunctivitis, 2009
Follicular lymphoma, 1268*t*, 1283, 1283*b*–1284*b*
Follicular maturation, hypothalamic-pituitary-ovarian axis in, 1596*f*
Follicular (differentiated) thyroid cancer, 1517, 1517*b*–1518*b*, 1517*t*, 1518*f*
Folliculitis, 1903, 2722–2723, 2739
  eosinophilic pustular, 2321, 2323*f*, 2723
  hot tub, 1970*b*
Folliculitis decalvans, 2747*t*, 2750, 2751*f*
Folliculogenesis, chronology of, 1595–1596
Follistatin, 1477
Follitropin (FSH), *e*1*t*–*e*8*t*
Fomepizole, for acute poisoning, 693*t*
Fomivirsen, 174, 2189
Fondaparinux, 387*t*, 501*t*, 502–503
  for acute coronary syndrome, 374*t*, 375*t*
Fontaine's clinical classification, 462*t*
Fontan operation, 355, 355.*e2t*
Food
  Acinetobacter in, 1973
  anaphylaxis caused by, 1692
  intake, alterations in, hypothalamic disease and, 1481
  obesity and, 1464
Food allergies
  description of, 1675*t*
  diarrhea and, 940
Food allergy-associated exercise-induced anaphylaxis, 1692
Food and Drug Administration (FDA), on antiretroviral therapy, 2300, 2302*t*
Food and exercise-induced anaphylaxis, 2725
Food-borne bacterial pathogens, *Campylobacter* infections and, 1958
Food-borne infectious diarrhea, 924–926, 925*t*
Food impaction, esophageal disease and, 902
Food poisoning, 1930
  diarrhea and, 925
Food protein-induced allergic proctocolitis, 1673*t*
Food protein-induced enterocolitis syndrome, 1673*t*
Food protein-induced enteropathy, 1673*t*
Foodborne botulism, 1927, 2592
Foot
  disorders of, 1747
  Pseudomonas osteomyelitis of, 1969
Foramen ovale, patent, 348, 349, 349*b*
Forbes disease, 1417*t*
Forced expiratory flow (FEF), 528
Forced expiratory volume (FEV), 528
Forced expiratory volume in 1 second, 547
  and severity of asthmatic attacks, 539
Forced vital capacity (FVC), 528
Forearm exercise test, for rhabdomyolysis, 716
Foreign bodies, in esophagus, 912
Foreign body sensation, 2599, 2600*f*
Formoterol, 553*t*
Fosamprenavir, 2301*t*
Fosaprepitant, for nausea and vomiting, 863*t*
Foscarnet
  for cytomegalovirus, 2252*b*
  for herpesvirus infections, 2187*t*, 2188, 2188*t*
  for zoster, 2249*b*
Fosfomycin, for vancomycin-resistant enterococci, 1922*t*
Fosfomycin trometamol, for cystitis, 1876*t*
Fosinopril, 451*t*
Fosinopril/HCTZ, 451*t*
Fostemsavir, 2301*t*
Fovea, 2614
Foville syndrome, 2465.*e1f*
Fractional flow reserve, 250.*e1f*, 393
Fractional lasers, for skin cancers, 2701
Fracture Risk Assessment Tool (FRAX), 1642–1643, 2318
Fractures
  cystic fibrosis and, 557
  multifactorial interventions for, 116
  osteoporotic, 1639
  proximal femur, 1639
Fragile X syndrome, 2549, 2549*b*
Fragmentation injury, 699*t*, 700, 700*f*
Frailty, 114, 115, 122, 123*b*, 123*f*, 123*t*
  geriatric assessment of, 118
  trajectories of, 12.*e1f*
Frailty measure, in older adults, 123*t*
Francisella tularensis, 1985, 2649
  rhabdomyolysis caused by, 715
Frank psoriasis, 2321
Frank-Starling law, 225–226, 226*f*
Frank-Starling mechanism, 406
Frasier syndrome, 1574
FRAX. *See* Fracture Risk Assessment Tool
FRC. *See* Functional residual capacity
Free fatty acids, 1465
Free-living amebae, 2150, 2150*t*
Fresh-frozen plasma (FFP), 1200, 2269*b*
  HIV transmission through, 2299
Frey syndrome, 2555
Fridericia formula, 230
Friedreich ataxia, 279, 2497
Frontal fibrosing alopecia, 2747*t*, 2749, 2750*f*
Frontal lobe, 2460*f*
Frontal lobe seizures, 2430–2431
Frontotemporal dementia, amyotrophic lateral sclerosis and, 2563
Frontotemporal lobar degeneration, 2421–2422
  clinical manifestations of, 2422
  definition of, 2421
  diagnosis of, 2422
  diagnostic criteria for, 2421*t*
  epidemiology of, 2421
  magnetic resonance imaging of, 2423*f*
  pathobiology of, 2421–2422
  prognosis of, 2422
  treatment of, 2422*b*
Frostbite, 474, 474*f*, 680
Frovatriptan, 2380*t*
Frozen shoulder, 1744, 1744*b*
Fructosamine, *e*1*t*–*e*8*t*
Fructose, diarrhea and, 939
Fruits, dietary guidelines for, 57.*e3t*
FSH. *See* Follicle-stimulating hormone
Fulminant influenza viral pneumonia, 2202*b*
Fulvestrant (Faslodex), 1215*t*, 1369*b*
Fumigants, 88*t*
Functional chest pain, 900
  clinical manifestations of, 900
  definition of, 900
  diagnosis of, 900
  differential diagnosis of, 901*t*
  epidemiology and pathobiology of, 900
  prognosis of, 901
  Rome IV diagnostic criteria for, 900*t*
  treatment of, 901*b*
Functional dyspepsia, 898
  alarm symptoms associated with, 899*t*
  algorithm for, 899*f*
  definition and epidemiology of, 898
  pathobiology of, 898
  prognosis of, 899
  Rome IV diagnostic criteria for, 898, 898*t*, 899*t*
  treatment of, 899*b*
Functional gallbladder disorder, 1053, 1054*t*
Functional GI disorders, 850

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Functional heartburn, 899–900
  clinical manifestations of, 900
  diagnosis of, 900
  epidemiology of, 900
  pathobiology of, 900
  prognosis of, 900
  Rome IV diagnostic criteria for, 900*t*
  treatment of, 900*b*
Functional incontinence, 828
Functional luminal imaging probe, 902
Functional neurologic symptom disorder. *See* Conversion disorder
Functional outlet obstruction, 890, 890*t*
Functional pancreatic neuroendocrine neoplasms, 1561*t*
Functional residual capacity (FRC), 530
Functional status, geriatric assessment of, 117
Fundoscopic examination, for toxoplasmosis, 2138*t*
Fungal arthritis, 1808
Fungal brain abscesses, 2525
Fungal endocarditis, 416
  noncandidal, 417*t*
  treatment of, 417*b*
Fungal endophthalmitis, 2606
Fungal infections, 2650–2651, 2651*f*
  amphotericin B for, 2077
  after hematopoietic cell transplantation, 1211
  liver, 1023–1024, 1024*b*
  predisposition to, 1686*t*
  of skin, 2736, 2739*t*, 2741
Fungal keratitis, 2602–2603
Fungal meningitis, cerebrospinal fluid findings in, 2374*t*
Fungal pericarditis, 432
Fungi
  health care-associated infections caused by, 1865
  as occupational and environmental hazards, 88*t*
  peripheral blood smear of, 1074*t*
Fungicides, 88*t*
Funguria, 1875*b*
Fungus ball, 607–608, 609*f*
Funnel web spiders, envenomation of, 710
FUO. *See* Fever of unknown origin
Furosemide, 451*t*
  for amyloidosis, 293*b*
  for hypervolemia, 737*t*
  hypokalemia and, 749*t*
Furuncles, 1903, 2739, 2740*f*
Fusiform aneurysms, 2478
Fusion proteins, 150, 150*t*
Fusobacterium, 2068
Fusobacterium necrophorum, 2648–2649
FVC. *See* Forced vital capacity

G

G protein-coupled receptor (GPCR), 1652, 2639
G6PD deficiency. *See* Glucose-6-phosphate dehydrogenase (G6PD) deficiency
G6PD gene, 160*t*
Gabapentin, *e*10*t*–*e*11*t*
  for chronic pain, 138*t*
  for distal symmetrical and autonomic polyneuropathy, 2577*b*
  for fibromyalgia, 1819*b*
  for hot flashes, 1631*t*
  for seizures, 2434*t*
  for zoster, 2249*b*
Gabapentin enacarbil, for restless legs syndrome, 2496*b*
Gabapentinoid, for restless legs syndrome, 2453
Gadolinium-enhanced MRI, for spinal epidural abscess, 2527
Gadolinium toxicity, 463
GAGs. *See* Glycosaminoglycans
Gain-of-function mutations, 1476*t*
Gait, 117
  antalgic, 2373*t*
  disorders of, 2371, 2373*t*
  dystonic, 2373*t*
  hemiparetic, 2373*t*
  hysterical, 2373*t*
  parkinsonian, 2373*t*
  spastic, 2373*t*
  steppage, 2373*t*
  waddling, 2373*t*
Galactorrhea, 1491, 1601
α-Galactosidase, 787
  for Fabry disease, 1420*t*
Galantamine, for Alzheimer disease, 2416*b*
Galectin-3, 260.*e*1*t*
Gallavardin phenomenon, 402
Gallbladder
  adenocarcinomas, 1358
  adenomas, 1054
  cancer, 1054
Gallbladder diseases, 211*t*, 1049–1061
  acute acalculous cholecystitis, 1053
  acute calculous cholecystitis, 1050. *See also* Acute calculous cholecystitis
  functional gallbladder disorder, 1053
  gallstone. *See* Gallstone(s)
  gallstones, 1049–1053
  tumors, 1053–1054
Gallbladder tumors, 1053
  benign, 1053–1054
  malignancy, 1054
  prevention and treatment of, 1054*b*
Gallstone(s), 1049
  acute pancreatitis and, 969, 970*t*
  bilirubinate, 1095
  clinical manifestations of, 1050
  diagnosis of, 1050–1051, 1051*f*–1052*f*
  epidemiology of, 1049
  formation of, 1049–1050, 1050*t*
  liver disease and, 986
  pathobiology of, 1049–1050
  prevention of, 1052–1053
  treatment of, 1052*b*, 1053*f*
Gallstone ileus, 1053
Gamekeeper's thumb, 1745
Gamma-glutamyl transpeptidase (GGT), 999
Gammopathy, monoclonal, 727
Ganciclovir
  for cytomegalovirus, 2252, 2252*b*
  for herpesvirus infections, 2186–2188, 2187*t*, 2188*t*
Ganglioglioma, 1316
Ganglion, 1745–1746, 1745*b*
Ganglionopathies, 2554*t*
Gap junction channels, 300.*e*1*f*, 301
Gardasil-9, 2243
Gardner syndrome, 1348
Gas, bloating and, 858
Gas gangrene, 1926, 1926*b*, 1939
Gastric acid, suppression of, for asthma, 541*b*
Gastric adenocarcinoma, 1339
  clinical manifestations of, 1340–1341
  diagnosis of, 1341, 1341*f*
  epidemiology of, 1339–1340
  genetics, 1340
  laboratory studies of, 1341
  medical therapy for, 1341*b*
  pathobiology of, 1340
  physical examination for, 1341
  prevention of, 1342
  prognosis of, 1342
  risk factors for, 1340, 1340*t*
  surgical therapy for, 1341*b*
  symptoms and signs of, 1340–1341
  treatment for, 1341*b*, 1342*t*
Gastric adenomas, 1343
Gastric angioectasia, 966.*e*1*f*
Gastric band bariatric surgery, abdominal radiographs of, 868*f*
Gastric cancer, fluoroscopy of, 868*f*
Gastric disease, in systemic sclerosis, 1780
Gastric electrical stimulation, 889*b*
Gastric emptying
  accelerated, 889*b*
  for acute poisoning, 691*b*
Gastric lymphoma, 1342
  clinical manifestations of, 1342
  diagnosis of, 1342
  epidemiology of, 1342
  Helicobacter pylori and, 1279
  treatment for, 1342*b*
Gastric mucosal biopsy, for *Helicobacter pylori*, 918
Gastric outlet obstruction, 923
Gastric ulcers, 1341*f*
  aspirin and, 914
  Cameron ulcers, 916
  classification of, 913
  malignant, 915
  nonsteroidal anti-inflammatory drugs and, 914
  prevention of, 921–923
Gastrin, *e*1*t*–*e*8*t*, 1566
Gastrinomas, 1561*t*, 1562
  clinical manifestations of, 1562–1563
  diagnosis of, 1563
  differential diagnosis of, 1563
  pathobiology of, 1562
  prognosis of, 1563
  treatment of, 1563*b*
Gastritis
  alcohol use causing, 917
  definition of, 913
  endoscopy of, 913*f*
  epidemiology of, 914
  erosive, 913*f*, 917
  Helicobacter pylori, 913
  hypertrophic, 913
  microbial causes of, 917
  nodular, 913
Gastroduodenal ulcers
  causes of, 915, 919
  malignant causes of, 915
  systemic inflammatory disorders that cause, 915–916
Gastroenteritis, 1869*t*
  acute, treatment of, 1963*b*
  Campylobacter jejuni and, 1959
  cryptosporidiosis and, 2143
Gastroenterology, 866–874
  abdominal radiographs, 866, 866*f*, 867*f*, 868*f*
  computed tomography, 869, 870*f*, 871*f*
  fluoroscopy, 866, 868*f*, 869*f*
  magnetic resonance imaging, 871–872, 872*f*–873*f*
  radiographic plain films, 866
  ultrasound, 869, 869*f*, 870*f*
Gastroesophageal junction, Mallory-Weiss tear at, 882*f*
Gastroesophageal reflux disease (GERD), 902–906
  abdominal pain and, 854*t*
  clinical manifestations of, 903, 903*f*
  definition of, 902–905
  diagnosis of, 903–905, 903*f*–904*f*
  epidemiology of, 902
  laryngopharyngeal reflux and, 2651
  obesity and, 1466
  pathobiology of, 902
  prognosis of, 905
  treatment of, 904*b*, 904*t*
  in women, medications for, 1608*t*
Gastrointestinal agents, for cystic fibrosis, 558*b*
Gastrointestinal anthrax, 1931, 1932*b*
Gastrointestinal bleeding, 852*t*, 864–865
  of acute pancreatitis, 972*t*
  direct thrombin inhibitors and, 504
  lower, 882, 884–885. *See also* Hematochezia
    colonoscopy for, 885
    definition of, 884
    diagnosis of, 884–885
    epidemiology of, 884
    treatment of, 885*b*
  obscure and occult, 885–887, 886*f*, 886*t*
  upper, 882–883
    acute management of, 883*b*
    clinical manifestations of, 882, 882*f*, 882*t*
    diagnosis of, 882–883
    endoscopic therapy for, 883*b*, 883*t*
    Glasgow-Blatchford score for, 883*b*, 883*t*
    management of, 884*f*
    medical therapy for, 883*b*
    peptic ulcer disease causing, 882
    treatment of, 883*b*
Gastrointestinal disease
  chronic, Chagas disease and, 2127–2128
  chronic, in travelers, 1891*t*
  cystic fibrosis and, 557
  functional, 892
  in pregnancy, 1625–1627
  Pseudomonas infections causing, 1969
Gastrointestinal disease, approach to, 850–865
  abdominal examination in, 851
  abdominal pain in. *See* Abdominal pain
  belching, 858
  bloating and distention, 859, 859*b*
  clinical history in, 850–854
  constipation, 862, 862*b*
  digital rectal and pelvic examinations in, 851
  family history in, 851
  fecal incontinence, 865
  flatus, 858
Gastrointestinal disease, approach to *(Continued)*
  gas and bloating, 858
  gastrointestinal bleeding, 864
  involuntary weight loss, 860–861, 860*t*
  laboratory studies in, 851–854
  nausea and vomiting, 861–862, 862*b*, 862*f*–863*f*
  nonabdominal examination in, 851
  other, 865, 865*f*
  past medical history in, 850
  physical examination in, 851
  signs and symptoms of, 850–854, 852*t*
  social history in, 850–851
Gastrointestinal endoscopy, 875–881
  advanced, 880
  antithrombotic therapy for, 875*t*
  capsule, 880
  colonoscopy in, 879
  complications of, 876*t*
  diagnostic, 875–881
  endoscopic retrograde cholangiopancreatography in, 876
  enteroscopy in, 878
  standard, adjuncts to, 875
  ultrasonography, 876
  upper, 875
Gastrointestinal hemorrhage, 882–887
  clinical manifestations of, 882, 882*t*
  liver disease and, 986–987
  mortality risks, 922
  prophylaxis for, 700*b*
  upper. *See* Upper gastrointestinal bleeding
Gastrointestinal motility
  definition of, 887–888
  disorders of, 887–892
Gastrointestinal motility disorders
  accelerated gastric emptying, 890
  constipation. *See* Constipation
  definition of, 887
  dumping syndrome, 890
  enteric neuropathic disorders, 888
  extrinsic neuropathic disorders, 888
  intestinal pseudo-obstruction. *See* Intestinal pseudo-obstruction
  intrinsic neuropathic disorders, 888
  pathobiology of, 887–888
  rapid transit dysmotility, 890
  smooth muscle disorders, 888–889
  weight loss and, 860*t*
Gastrointestinal mucormycosis, 2099
Gastrointestinal neuroendocrine neoplasms, 1562, 1566–1567
Gastrointestinal stromal tumors (GISTs), 1342–1344, 1390, 1390*b*
Gastrointestinal syndrome, 93
Gastrointestinal system
  age-related changes in, 121
  systemic lupus erythematosus manifestations of, 1770
Gastrointestinal tract
  alcohol use disorders and, 2355, 2355*t*
  allergy of, 1674
  fluid reabsorption in, 888
  infections of, 2205
  neuroenteric control of, 887
  physiology of, 887–888
  systemic sclerosis involvement of, 1778
  vascular diseases of, 959
    acute mesenteric ischemia as, 959
    angioectasia as, 965
    aortoenteric fistulas as, 967
    Budd-Chiari syndrome as, 968
    celiac artery compression syndrome as, 967, 967*f*
    chronic mesenteric ischemia as, 963, 963*f*
    colon ischemia as, 964, 964*t*, 965*f*
    Dieulafoy lesion as, 966
    ectasias as, 967
    hemangiomas as, 967
    hepatic and splenic, 968
    hepatic and splenic arterial disease as, 969
    hereditary hemorrhagic telangiectasia as, 967
    intestinal ischemia as, 959
    portal vein thrombosis as, 968, 968*b*
    radiation proctopathy as, 968, 968*f*
    splenic vein thrombosis as, 968
    superior mesenteric artery syndrome as, 967
    vascular anomalies and disorders as, 965
    vasculitis as, 965

Copyrighted material

Gastroparesis, 1778
  classification of, 888*t*
  clinical manifestations of, 888
  diagnosis of, 889
  differential diagnosis of, 889
  medical therapy for, 889*b*
  surgical therapy for, 891*b*
  treatment of, 889*b*
Gastroschisis, 951
Gastrostomy tube, for amyotrophic lateral sclerosis, 2563*b*
GATA1-associated CEP, 1428*t*
GATA2 deficiency, 1685–1686, 1686*t*
Gatifloxacin
  for bacterial meningitis, 2518*t*
  for eye infection, 2605*t*
Gaucher disease, 583, 1398*t*, 1420–1421
  clinical manifestations of, 1420–1421, 1421*f*
  definition of, 1420
  diagnosis of, 1421, 1421*f*, 1422*t*
  enzyme-specific treatments for, 1420*t*
  epidemiology of, 1420
  pathobiology of, 1420
  prognosis of, 1421*b*
  treatment of, 1421*b*, 1422*t*
Gaze-evoked nystagmus, 2619
Gazyva. *See* Obinutuzumab
Gefitinib, 1251*t*
Gels, 2697
Gemcitabine (Gemzar), 1215*t*
  for pancreatic cancer, 1356*b*
  for soft tissue sarcomas, 1389*b*
Gemzar. *See* Gemcitabine
Gender-affirming hormone therapy, 1578*b*
Gender identity, 1574–1575, 1577
Gender role, 1574
Gene, 160, 161*f*
Gene therapy, 174–178
  classification of, 175–178
  delivery methods, 175
  diseases treated by, 175
  ex vivo, 175
  for hemophilia, 1188*b*
  for herpes simplex virus infections, 2245
  human stem cell-based, 175–176
  indications for, 3
  liver involvement, 175
  mechanism of action, 175
  for sickle cell disease, 1114*b*
  suicide, 176
  for thalassemia, 1107*b*
  in vivo, 175
Gene transfer, horizontal, in Enterobacterales, 1965, 1966*t*
General advice, for heart failure, 275*t*
General anesthesia, 2669, 2671
General paresis, 2017
General risk assessment, 2661–2666
Generalized anxiety disorder, 2342*t*, 2343
Generalized morphea, 1782
Generalized pain syndromes, 1706
Generalized tetanus, 1928
Generalized vaccinia, 2238
Genetic bone marrow failure syndromes, 1253
"Genetic conditions", 158
Genetic counseling
  for cystic fibrosis, 559
  for inborn errors of metabolism, 1401*b*
Genetic dilated cardiomyopathy, 286
Genetic Information Nondiscrimination Act of 2008, 169
Genetic lipid disorders, 1408
Genetic polymorphisms, of drug-metabolizing enzymes, 132*t*
Genetic risk assessment, 159
Genetic test reports, 165
Genetic testing
  for endocrine disease, 1473
  for glomerular syndromes, 728, 728.*e1f*
  for monogenic common disorders, 159
  for porphyrias, 1434
Genetic Testing Registry, 169.*e1t*
Genetically inherited ventricular arrhythmias, 337–338
Genetics
  cystic fibrosis and, 556
  of diseases, 158, 158*f*
  principles of, 158–160
Genital herpes
  chancroid and, 1951
Genital herpes *(Continued)*
  characteristics of, 1880–1881, 2245–2246
  organisms causing, 1879*t*
  syphilis *versus*, 2019
Genital ulcers, 1880–1881
  organisms causing, 1879*t*
  treatment of, 1881*t*
Genital warts
  description of, 2242
  organisms causing, 1879*t*
Genitalia, male, examination of, 31
Genitourinary amyloidosis, 1310*b*
Genitourinary bleeding, hemophilia and, treatment of, 1188*b*
Genitourinary symptoms, of menopause, 1630, 1632*t*
Genitourinary tract infections
  adenovirus causing, 2205
  Pseudomonas infections causing, 1969
  Staphylococcus aureus causing, 1904–1905
Genome, expressed, 168
Genome editing, 178–179, 178*f*–179*f*
Genome sequencing, 158, 166–167
  of autoinflammatory syndromes, 1737
  cancer pharmacogenomics and, 167
  as driver of precision medicine, 166
  microbial, 167–168
  pharmacogenomics, 167, 167.*e1t*
  pre-conception carrier testing, 166
  prenatal diagnosis, 166
  for rare diseases and diagnostic dilemmas, 167
  for risk prediction, for common complex disease, 167
Genome-wide association studies (GWAS), 166
  description of, 159
  of rheumatoid arthritis, 1749
Genomic variations, 162
  assaying, 164
  chromosomal aberrations in, 164, 164.*e1f*
  copy number variants in, 164
  deletion, insertion, and indels in, 163
  single nucleotide, 162–163
  structural aberrations in, 164
  structural variants in, 164
  tandem repeats in, 163
Genomics, 1834
Gentamicin, *e10t*–*e11t*
  for bacterial meningitis, 2518*t*
  for bronchiectasis, 561*b*
  dosage of, 1895*t*
  for endocarditis, 417*b*, 419*t*
  for eye infection, 2605*t*
  for gonorrhea, 1948*b*
  for plague, 98*b*, 1992*t*
  for pyelonephritis and urosepsis, 1877*t*
  for trench fever, 2003*b*
  for tularemia, 99*b*, 1987*b*
Geographic tongue, 2623, 2623*f*
GERD. *See* Gastroesophageal reflux disease
Geriatric assessment, 116
  built and social environments in, 118
  cognition and competency in, 117
  continence in, 118
  financial assessment in, 118
  frailty in, 118
  function of, 116–118
  functional status in, 117
  goals and preferences of, 118–119
  hearing in, 117
  initial observation in, 117
  medication review in, 118
  mobility and life space in, 117–118
  mood and affect in, 117
  nutrition in, 117
  in practice, 119, 119*t*
  preventive services, 119, 119.*e1t*
  prognosis of, 118
  rationale of, 116
  risk of falls in, 118
  self-neglect and abuse in, 118
  sexuality in, 118
  social support in, 118
  vision in, 117
Geriatric Depression Scale, 2332*t*
Geriatric incontinence, 827
Geriatric syndromes, in older adults, 114
Germ cell tumors
  in adolescents, 111
  nonseminomatous, treatment of, 1383*b*
German measles. *See* Rubella
Germinomas, 1314
Germline DNA alterations, in cancer, 1248, 1248*f*, 1249*f*
Germline genetic variants, drug response and, 167, 167.*e1t*
Gerstmann-Sträussler-Scheinker syndrome, 2423
Gestational diabetes insipidus, 1501, 1503*b*
Gestational diabetes mellitus, 1544, 1545*b*
Gestational hypertension, 1620
Gestational rhinitis, 1618*t*–1619*t*
Gestational thrombocytopenia, 1178–1179
GFR. *See* Glomerular filtration rate
GFRomas. *See* Growth hormone-releasing factor secreting neuroendocrine neoplasms
GH. *See* Growth hormone
Ghon complex, 2034
Ghon focus, 2034
Ghrelin, 1477
Giant bullae, 631–632
Giant cell arteritis, 442.*e1f*, 443, 443*b*, 965, 1795, 1801–1804, 2383
  clinical manifestations of, 1801–1802, 1801*t*
  definition of, 1801–1803
  diagnosis of, 1802–1803
  differential diagnosis of, 1803
  epidemiology of, 1793*t*, 1801
  ischemic complications of, 1802
  ocular vascular abnormalities caused by, 2610
  pathobiology of, 1801
  prognosis for, 1803
  superficial temporal artery, assessment of, 1803
  survival rates for, 1803
  temporal artery biopsy for, 1803
  treatment of, 1803*b*
Giant cell myocarditis, 286
Giant platelets, 1073*f*
Giardia
  in travelers, 1889.*e1t*, 1891*t*
  traveler's diarrhea caused by, 1888*t*
Giardia lamblia infection, 937, 1858
  description of, 2144, 2144*f*
  sexually transmitted anorectal diseases and, 983
Giardiasis, 2115, 2144–2146
  characteristics of, 2270*t*
  clinical manifestations of, 2145
  diagnosis of, 2145
  epidemiology of, 2144
  pathobiology of, 2145
  pathogen that causes, 2144
  prevention of, 2146
  prognosis for, 2146
  treatment of, 2145*b*
Gigantism, 1489, 1489*b*
Gilbert syndrome, 994, 995, 997*t*, 2267
Gilenya. *See* Fingolimod
Gilotrif. *See* Afatinib
Gingival hyperplasia, 2624, 2625*f*
Gingival Kaposi sarcoma, 2320*f*, 2322*t*
Gingivostomatitis, characteristics of, 2245
GISTs. *See* Gastrointestinal stromal tumors
Gitelman syndrome, 749, 749*t*, 762–763, 816*t*, 817, 817*b*, 817.*e1f*
Give-way weakness, 2393
Glanders, 1972, 1972*b*
Glandular hypofunction, 1784
Glanzmann thrombasthenia, 1185
Glasgow-Blatchford score, for upper gastrointestinal bleeding, 883*b*, 883*t*
Glasgow Coma Scale, 2386, 2386*t*
Glatiramer acetate (Copaxone, Glatopa), for multiple sclerosis, 2505*t*
Glatopa. *See* Glatiramer acetate
Glaucoma, 2607–2608
  acute, characteristics of, 2270*t*
  angle-closure, 2608, 2608*f*
  drug-induced, 2613
  primary open-angle, 2607, 2607*f*
  secondary open-angle, 2607–2608
  visual loss caused by, 2615
Gleason scoring system, 1384*t*, 1387
Glecaprevir/pibrentasvir, 2181*t*, 2182*t*, 2184
Gleevec. *See* Imatinib
Gleich syndrome, 1162
Gliadins, 935
Glibenclamide, for type 2 diabetes mellitus, 1541*t*
Gliclazide, for type 2 diabetes mellitus, 1541*t*
Glimepiride, for type 2 diabetes mellitus, 1541*t*
Glinides, for type 2 diabetes mellitus, 1541*t*
Glioma, 1312*f*
  astrocytic, 1314
  brain stem, 1315
  clinical manifestations of, 1315–1316
  definition of, 1314
  diagnosis of, 1314–1316, 1315, 1315*f*
  epidemiology of, 1314
  optic, 1315
  pathobiology of, 1314–1315
  treatment of, 1315*b*
Glipizide, for type 2 diabetes mellitus, 1541*t*
Global coagulation laboratory, 1169
Global health, 21–25
  challenge, 23–25
  definition of, 21
  leading causes of deaths, 21, 22*f*
  leading causes of disabilities, 21, 23*f*, 24*f*
  leading underlying risk factors, 23, 24*f*
  life expectancy and, 21, 21*f*
Global ischemic injury, 2462
Global Partnership for Zero Leprosy, 2053
Global Registry of Acute Coronary Events (GRACE) risk score calculator, 373, 374*t*, 384.*e1f*
Global warming, 87
Globoid cell leukodystrophy, 2510
Globulin genes, 1113*f*
Globus pharyngeus, 2652
Glomerular basement membrane, 776
Glomerular capillaries, 729–730
Glomerular disorders/diseases, 776. *See also* Glomerulonephritis
  in amyloidosis, 788
  chronic kidney disease and, 833*t*
  clinical manifestations of, 776
  in COVID-19-associated nephropathy, 789
  definition of, 776
  in diabetes mellitus, 788
  diagnosis of, 776
  epidemiology of, 776
  in fibrillary glomerulopathy-immunotactoid glomerulopathy, 788
  with genetic defects, 786–787
  in human immunodeficiency virus-associated nephropathy, 789
  in light-chain deposition disease, 788, 788*f*
  in mixed cryoglobulinemia, 789
  in monoclonal gammopathy of renal significance, 788
  other, 787–789
  pathobiology of, 776
  proteinuria associated with, 776
  in systemic lupus erythematosus, 787–788, 787*b*–788*b*, 787*f*, 787*t*, 788*f*
  in thrombotic microangiopathies, 789
Glomerular filtration rate (GFR), *e1t*–*e8t*
  antiretroviral therapy and, 2302
  chronic kidney disease by, 833*t*, 835*f*
  complications of, treatment of, 839*b*
  evaluation of, 837, 839*t*
  plasma creatinine and, 721, 721*f*, 721*t*
  in sickle cell disease, 1114
Glomerular syndromes, 726–728
  diagnosis of, 727–728
  genetic testing for, 728, 728.*e1f*
  laboratory testing of, 727–728
  renal biopsy for, 728
  serologies for, 727–728
Glomerulonephritis, 736, 2164
  acute, 783
  Alport syndrome, 787
  complement-mediated membranoproliferative, 786, 786*t*
  immune complex, pneumonia with, 784*t*
  membranoproliferative, 785–786, 786*b*, 786*f*, 786*t*
  pauci-immune, 1716
  post-streptococcal, 783*b*, 1918, 1918*b*
  rapidly progressive, 784–786, 784*f*
    anti-glomerular basement membrane disease, 784, 784*b*, 784*f*, 784*t*
    classification of, 784*t*
    clinical manifestations of, 785
    diagnosis of, 785
    IgA nephropathy and, 781*b*
    immune complex, 785
    pauci-immune, 785–786
    prognosis for, 785
    treatment of, 785*b*, 785*f*
    vasculitis-associated, 785

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Glomerulosclerosis, focal segmental, 778, 779*b*, 779*f*, 779*t*
Glomerulus
  anatomy, 729
  renal pathologic processes that affect, 776
Glossomegaly, in amyloidosis, 1306*f*
Glossopharyngeal neuralgia, 2384
GLP-1. *See* Glucagon-like peptide-1
Glucagon
  for acute poisoning, 693*t*
  for hypoglycemia, 1557
  secretion of, 1552
Glucagon-like peptide-1 (GLP-1), 932
Glucagon-like peptide-1 (GLP-1) agonists, 262
  for chronic kidney disease, 839*b*
  for obesity, 1467*b*
  for type 2 diabetes mellitus, 1540*b*, 1541*t*
Glucagonomas, 1561*t*, 1563–1564, 1564*b*, 1564*f*
Glucocerebroside, for Gaucher disease, 1420*t*, 1421*b*
Glucocorticoid(s), 144*t*
  adipose tissue metabolism and, 145
  for adrenal insufficiency, 1528*b*
  bones and, 145
  cardiovascular system and, 145
  central nervous system and, 145
  clinical use of, 145–146
  endocrine diseases caused by, 1475*t*
  for eosinophilic syndromes, 1164*b*
  excess of, 1520
  history of, 144–146
  inflammation and, 144–145
  inhaled, for asthma, 541*b*
  liver metabolism and, 145
  monitoring of, 146
  muscle metabolism and, 145
  osteoporosis caused by, 145
  in pregnancy, 146
  for rheumatic diseases, 1712
  for rheumatoid arthritis, 1755*b*, 1756*t*
  for skin diseases, 2697–2698, 2698*t*
  systemic, for asthma, 541*b*
  tapering regimens for, 146
  toxicity of, 146
  withdrawal from, 146
Glucocorticoid deficiency, 739
Glucocorticoid-induced osteoporosis, 1643*b*
Glucocorticoid receptor, 144, 144*f*
Glucocorticoid-remediable hyperaldosteronism, 816*t*
Gluconeogenesis, hypoglycemia due to defects in, 1552*t*, 1555
Glucose, *e*1*t*–*e*8*t*, 1534–1535, 1534.*e*1*f*
  in bacterial meningitis, 2514
  blood, 1624
  cardiovascular disease and, 1550
  concentration of, 1551
  dipstick for, 722
  in parenteral nutrition, 1450
  physiology of, biochemical pathways in, 1553*f*
Glucose-6-phosphate dehydrogenase (G6PD), in erythrocytes, *e*8*t*–*e*9*t*
Glucose-6-phosphate dehydrogenase (G6PD) deficiency, 1100, 1398*t*
  adverse drug reactions and, 132
  clinical manifestations of, 1101–1102, 1101*t*
  diagnosis of, 1102
  epidemiology and pathobiology of, 1098*f*, 1100–1101
  features of, 1101*t*
  treatment of, 1102*b*
Glucose control, cardiovascular disease and, 220
Glucose intolerance, 1563
Glucose phosphate isomerase (GPI) deficiency, 1099–1100
Glucose tolerance test (GTT), *e*1*t*–*e*8*t*
Glucose transporter isotype 1 (Glut1), 2461
Glucose transporters (GLUT), 1415
α-1,4-Glucosidase, for Pompe disease, 1420*t*
α-Glucosidase inhibitor, for type 2 diabetes mellitus, 1540*b*, 1541*t*
GLUT. *See* Glucose transporters
γ-Glutamyl transpeptidase, 989, 1010
γ-Glutamyltransferase (GGT), *e*1*t*–*e*8*t*
Glutaric aciduria, type I, 1398*t*, 1403*t*
Glutathione metabolism, disorders of, 1102
Gluten-free diet, for celiac disease, 936*b*
Gluten-sensitive enteropathy, 1821
Glyburide, for type 2 diabetes mellitus, 1541*t*
Glycated hemoglobin (HbA1*c*), *e*1*t*–*e*8*t*, 1536*t*
Glycemic control
  for chronic kidney disease, 839*b*
  for diabetic nephropathy, 797*b*, 798*f*
Glycogen, 1415
  breakdown of, 1415, 1416*f*
  synthesis of, 1415
Glycogen storage diseases, 1415–1418
  clinical manifestations of, 1415, 1417*t*
  definition of, 1415–1418
  diagnosis of, 1415–1416
  differential diagnosis of, 1416
  epidemiology of, 1415
  pathobiology of, 1415, 1416*f*
  prognosis of, 1418
  treatment of, 1416*b*
  type Ib, 1145
Glycolic acid, 759
Glycolipids, 1093
Glycolysis, Embden-Meyerhof pathway of, 1098, 1098*f*
Glycophorin A, 1087
Glycophorins, 1094
Glycoprotein IIb/IIIa inhibitors, 374*t*
Glycopyrronium, 553*t*
Glycosaminoglycans (GAGs), 1724
Glycosylation defects, 2589*t*
Glycosylphosphatidylinositol, 1091
Glycylcyclines
  dosage of, 1895*t*
  mechanism of action, 1895*t*
  resistance mechanisms, 1893*t*
Glycyrrhizic acid, 749
GM-CSF. *See* Granulocyte-macrophage colony-stimulating factor
GNAS1 gene, 1661–1662
Gnathostoma spinigerum, 2176
Gnathostomiasis, 2176
  cutaneous or mucocutaneous, in travelers, 1889.*e*1*t*
GnRH. *See* Gonadotropin-releasing hormone
"God Committee", 9
Goiter, 1513*f*, 1515
  diagnosis of, 1508*f*, 1510*f*, 1515
  treatment for, 1515*b*
GOLD classification system, 548*f*
Golfer's elbow. *See* Medial epicondylitis
Goliath tarantula, 710
Golimumab
  description of, 151*t*
  for inflammatory bowel disease, 945*b*, 946*t*
  for rheumatoid arthritis, 1756*t*
Goltz syndrome, 1668
Gomori methenamine silver, for actinomycosis, 2068
Gonadal biopsies, 1575
Gonadal differentiation, 1569, 1571*f*
Gonadal dysgenesis, 1600
Gonadal steroidogenesis, 1569, 1569.*e*1*f*
Gonadotropin(s), 1496
  hypothalamic disease effects on, 1480–1481
Gonadotropin-releasing hormone (GnRH)
  description of, 1476–1477
  exogenous, 1477
  function of, 1476
Gonadotropin-releasing hormone (GnRH) agonists, for transgender women, 1578*b*, 1579*t*
Gonadotropin-releasing hormone (GnRH) analogs, for endometriosis, 1596*b*
Gonococcal keratitis, 2606
Gonococcal septic arthritis, 1807
  clinical manifestations of, 1807
  diagnosis of, 1807
  epidemiology of, 1807
  prognosis of, 1807
  treatment for, 1807*b*
Gonococcal urethritis, organisms causing, 1879*t*
Gonococcemia, 2741, 2741*f*
Gonorrhea, 2621*t*. *See also Neisseria gonorrhoeae*
  disseminated infection, 1949
    clinical manifestations of, 1949, 1949*f*
    diagnosis of, 1950
    prevention of, 1950
    prognosis of, 1950
    screening of, 1950
    treatment of, 1950*b*
  epidemiology of, 1879
  infectivity of, 1946
  in pregnancy, 1948–1949
Good syndrome, 1680, 1681*t*
Goodpasture syndrome, 784, 784*t*
  diffuse alveolar hemorrhage and, 568, 569
Gooseneck sign, 247
Gordon syndrome, 816*t*
Gorlin formula, 402–403
Goserelin acetate, for breast cancer, 1369*b*
Gout, 1708, 1717*t*, 1718*f*, 1810, 2689*t*
  advanced, 1811, 1812*f*
  alcohol use disorders and, 2356
  atypical presentations of, 1811*t*, 1812–1813
  classic, 1811, 1812*f*
  clinical manifestations of, 1811–1813
  definition of, 1810
  diagnosis of, 1813, 1813*f*
  epidemiology of, 1810
  flares of, 1811, 1813*b*
  monosodium urate monohydrate crystals and inflammation in, 1811
  pathobiology of, 1810–1811, 1810*t*–1811*t*, 1811*t*
  prevention of, 1813*b*, 1814*t*
  renal urate underexcretion in, 1810–1811, 1810.*e*3*f*
  treatment of, 265*b*, 1813*b*
  urate overproduction in, 1811
Gouty tophi, 1812*f*
Gowns, for HIV transmission prevention, 2300
GPCR. *See* G protein-coupled receptor
GPI. *See* Glucose phosphate isomerase
Graduate Medical Education (GME), 46
Graft rejection, after hematopoietic cell transplantation, 1211
Graft-*versus*-host disease (GVHD), 938, 1210–1212
  acute, 1210, 1210*b*, 1210*t*
  chronic, 1210, 1211*b*
  hematopoietic stem cell transplantation causing, 204–205, 1852–1853
  mechanisms of, 206
  strategies to prevent, 206–207
  transfusion-associated, 1203
Graft-*versus*-tumor (GVT), 206
Grafts, 397, 398*f*
Grains, dietary guidelines for, 57.*e*3*t*
Gram-negative bacillary meningitis, 2511, 2515*b*, 2519
Gram-negative organisms, 416, 419*t*
Gram-positive rod infections, 1930–1938
  caused by *Bacillus* species, 1930, 1930*f*, 1930*t*
  caused by *Corynebacterium*, 1933
  caused by *Erysipelothrix*, 1936
  caused by *Listeria monocytogenes*, 1937–1938
Gram stain, 1892
Gram-stained smear, in bacterial meningitis, 2513–2514
Granisetron, for nausea and vomiting, 863*t*
Granular cast, 722–723, 724*f*
Granulocyte colony-stimulating factor (G-CSF), 1065, 1200, 1206
  for febrile neutropenia, 1854*b*
Granulocyte-macrophage colony-stimulating factor (GM-CSF), pulmonary alveolar proteinosis and, 566–567
Granulocyte transfusion, 1200, 1205
Granuloma, 2033
  eosinophilic, 1155
  in sarcoidosis, 600
Granuloma inguinale, 2004
  chancroid and, 1951
  characteristics of, 1881
  clinical manifestations of, 2004, 2004*f*
  definition of, 2004–2005
  diagnosis of, 2004
  differential diagnosis of, 2004
  epidemiology of, 2004
  organisms causing, 1879*t*
  pathobiology of, 2004
  prognosis of, 2005
  treatment of, 1881*b*, 2004*b*
Granulomatosis with polyangiitis, 582, 1796–1797, 1797*f*, 2574*t*, 2652, 2652.*e*1*f*
  eosinophilic, 573, 582
  epidemiology of, 1793*t*
  flow-volume curve of, 529*f*
  pathologic characteristics of, 1793*t*
  prognosis of, 1797*b*
  treatment of, 1797*b*
Granulomatous amebic encephalitis, 2150
Granulomatous arthritis, 1736
Granulomatous disorders, 1659, 1659*b*, 2001*t*
Granulomatous liver diseases, 1029–1030, 1030*t*
Granulomatous lobular panniculitis, 2735
Granulomatous mediastinitis, pulmonary histoplasmosis and, 2082
Granulomatous meningitis, 2646
Granulomatous mycosis fungoides, 2734
Granulomatous myositis, 1788*t*
Granulomatous peritonitis, 957
Graves dermopathy, 1512
Graves disease, 1509
  clinical manifestations of, 1510*f*, 1512–1513
  diagnosis of, 1512
  hyperthyroidism and, 1472
  non-thyroid complications of, 1512
  radiographic evaluation of, 1511*t*
  treatment for, 1511*b*, 1511*t*, 1513*b*
Graves ophthalmopathy, 1510*f*, 1512
Gray platelet syndrome, 1185
Grazoprevir/elbasvir, for hepatitis C infections, 2181*t*, 2182*t*, 2185
Greater trochanter pain syndrome, 1746–1747, 1746*b*, 1746*f*
Greenhouse gas emission, 89
Griscelli syndrome II, 1145
Griseofulvin, 2699
Groin hernia, 952*b*
Gross hematuria, 856
Ground-glass opacities, 520
Group A β-hemolytic streptococci
  cellulitis caused by, 2739–2740
  impetigo caused by, 2739
Group A β-hemolytic *Streptococcus pyogenes*, causing pharyngitis, 2648
Group A streptococcus infections, 1913–1918
Growth differentiation factor-15, 260.*e*1*t*
Growth factors
  hematopoietic, 1064–1065
  receptors, 152
Growth hormone (GH), *e*1*t*–*e*8*t*, 1488–1490
  acromegaly and, 1489, 1489*b*, 1490*f*
  deficiency of, 1488–1489, 1489*b*
  endocrine diseases caused by, 1475*t*
  excess of, 1489, 1489*b*
  gigantism and, 1489, 1489*b*
  gluconeogenesis and, 1552
  hypothalamic disease effects on, 1480
  insufficiency tests of, 1484*t*
  metabolic effects of, 1488
  pathobiology of, 1488
  skeletal muscle functions of, 1488
  tests of, 1488*t*
Growth hormone-releasing factor secreting neuroendocrine neoplasms (GFRomas), 1561*t*, 1565, 1565*b*
Growth hormone-releasing hormone (GHRH), 1477
Growth hormone secretagogue receptor, 1477
Guanabenz, 451*t*
Guanarito virus, 2265*t*
Guanfacine, 451*t*
Guanylate cyclase stimulation, for pulmonary hypertension, 496*b*
Guillain-Barré syndrome, 106, 652, 2560
  botulism *versus*, 1928
  Campylobacter jejuni and, 1960
  cerebrospinal fluid findings in, 2374*t*
  clinical manifestations of, 2571
  definition of, 2571
  diagnosis of, 2571
  differential diagnosis of, 2571, 2572*t*
  enteric infections and, 1870*t*
  epidemiology of, 2571
  Mycoplasma pneumoniae in, 2007
  pathobiology of, 2571
  rhabdomyolysis *versus*, 716
  treatment of, 2571*b*
Gummas, 2017
Gummatous syphilis, 2014
Guselkumab (Tremfya), for total knee arthroplasty, 1830.*e*1*t*
Gustatory hyperhidrosis, 2555
Gut transit, irritable bowel syndrome and, 893
Guttate hypopigmentation, 2743, 2743*f*
Guttate psoriasis, 2705
GVHD. *See* Graft-*versus*-host disease
GVT. *See* Graft-*versus*-tumor
GWAS. *See* Genome-wide association studies
Gynecologic cancers, 1375–1382
  approach to survivors of, 1381
  cervical cancer, 1375, 1375*t*
  endometrial cancer, 1377, 1377*f*, 1377*t*, 1378*b*

Copyrighted material

Gynecologic cancers *(Continued)*
fallopian tube cancer, 1379
ovarian cancer, 1379
uterine fibrosis, 1382, 1382*b*

H

H_1-receptor antihistamines, for skin diseases, 2700
H1N1, in travelers, 1889.*e1t*
H2-histamine antagonists, 1460*t*
HA20. *See* Haploinsufficiency of A20
HACEK gram-negative organisms, 416
Haemophilus ducreyi, 983, 1950. *See also* Chancroid
Haemophilus influenzae, 1952–1954
acute bronchitis and, 605
bacteremia caused by, 1953
Brazilian purpuric fever caused by, 1954
cellulitis caused by, 1953
clinical manifestations of, 1953–1954
definition of, 1952, 1952*t*
endocarditis caused by, 1953
epidemiology of, 1952–1953
epiglottitis caused by, 1953
gynecologic and urologic infection caused by, 1953
infectious caused by, 2510
meningitis caused by, 1953
otitis media caused by, 1953
pathobiology of, 1953
pericarditis caused by, 1953
pneumonia caused by, 1953
prevention of, 1954
prognosis of, 1954
purulent conjunctivitis caused by, 1954
septic arthritis caused by, 1954
sinusitis caused by, 1953
site of colonization of, 1952*t*
tracheobronchitis caused by, 1953
treatment of, 1954*b*, 2515*b*
Haemophilus influenzae aegyptius, 1954
Haemophilus influenzae type B vaccine, 66*t*, 76.*e1t*, 77*f*, 78–79, 1954
Haemophilus parainfluenzae, 1954
Hageman factor, 1189*t*
Hailey-Hailey disease, 2687.*e4t*
Hair
normal, 2747
toxicants and, 685
Hair cells, 2644
Hair cycle, 2747
Hair disorders, 2747
in children, 2750–2751
excessive hair growth, 2751
racial differences and, 2751, 2751*f*
Hair follicles, 2747
Hair loss, 2747, 2747*t*
Hair shaft, 2747
Hair transplants, 2701
Hairy cell leukemia, 1272, 1272*f*
Hairy leukoplakia, 2623, 2623*f*
Halaven. *See* Eribulin mesylate
Hallucinogens
abuse of, 2364
clinical manifestations and diagnosis of, 2364
epidemiology of, 2364
pathobiology of, 2364
treatment of, 2364*b*
central nervous system effects of, 685*t*
Halogenated hydrocarbons, 88*t*
Haloperidol, *e10t*–*e11t*
for psychotic disorders, 2346*t*
Halos around lights, 2599
HAM/TSP. *See* HLTV-associated myelopathy/tropical spastic paraparesis
Hamartoma, hypothalamic, 1479
Hamman-Rich syndrome, 578
Hand-foot-and-mouth disease, 2259–2260, 2260*b*, 2520–2521
Hand-Schüller-Christian disease, 1155
Hands
disorders of, 1745–1746
injury of, occupational, 86*t*
rheumatoid arthritis of, 1751, 1752*f*
Handwashing, for common cold, 2194
Hansen disease. *See* Leprosy
Hantaan virus, 2265*t*
Hantavirus, 99, 99.*e1t*, 2264
Hantavirus pulmonary syndrome, 2268*t*
Haploinsufficiency of A20 (HA20), 1731*t*, 1736
Haplotype, 204
Haptoglobin, *e1t*–*e8t*
Harlequin syndrome, 2555
Hartnup disease, 816*t*
Hashimoto encephalopathy, 2536
Hashimoto-Pritzker disease, 1156
Hashimoto thyroiditis, 1507
HAV. *See* Hepatitis A virus
Hax-1, 1144
Hay fever, 2628
HAZ. *See* Height-for-age Z-score
HbA1*c*. *See* Glycated hemoglobin
HBeAg-negative chronic hepatitis B, 1011
HBGAs. *See* Histo-blood group antigens
HBO. *See* Hyperbaric oxygen
HBV. *See* Hepatitis B virus
HC-cobalamin complex, 1118–1119
HCG. *See* Human chorionic gonadotropin
HCN channels, 300–301
HCoVs. *See* Human coronaviruses
HCP. *See* Hereditary coproporphyria
HCV. *See* Hepatitis C virus
HDCV. *See* Human diploid cell vaccine
HDL cholesterol (HDLC), *e1t*–*e8t*
Head and neck, examination of, 29–30
Head and neck cancer, 1320
clinical manifestations of, 1322
definition of, 1320–1328, 1320*f*
diagnosis of, 1322–1324
dietary factors for, 1321
environmental, 1328
environmental carcinogens and, 1321
epidemiology of, 1320–1321
Epstein-Barr virus and, 1320
human immunodeficiency virus and, 1321
human papillomavirus and, 1320, 1328
human papillomavirus-related, 2622
hypopharynx, 1320
immunology of, 1322
ionizing radiation and, 1321
larynx, 1320
leukoplakia and, 1321
nasopharynx, 1320
occupational exposures associated with, 1321
oral cavity, 1320
oropharynx, 1320
pathobiology of, 1321–1322
pathology of, 1323, 1324*f*
prevention of, 1328
prognosis of, 1328
radiation therapy for, 1327*b*
recurrent/metastatic, 1327*b*
salivary glands, 1320
sex and genetic risk factors of, 1321
staging of, 1323–1324, 1325*t*
supportive and palliative care for, 1327*b*
surgery for, 1327*b*
systemic therapies for, 1327*b*
treatment for, 1327*b*
viral carcinogenesis in, 1321
viruses and, 1320–1321
Head infection, 1939
Head injuries, 700*b*
Head lice, 711, 711*b*
Head pain, neurologic diseases that cause, 2371–2372
Head-thrust test, 2646
Head tremors, 2489
Headaches, 2376–2385
in acromegaly, 1489
in brain abscess, 2525
in brain tumors, 1311
chronic daily, 2382, 2382*b*
clinical manifestations of, 2376, 2377*t*
cluster, 2381, 2381*t*, 2382*b*
definition of, 2376–2378
diagnosis of, 2376–2377, 2377*t*
epidemiology of, 2376
in epilepsies, 2425
glossopharyngeal neuralgia causing, 2384
intracranial hypertension causing, 2383, 2383*b*
intracranial hypotension causing, 2383, 2384*b*, 2384*f*
migraine, 2378–2380
pathobiology of, 2376
prevention of, 2377
prognosis for, 2377–2378
Headaches *(Continued)*
pseudotumor cerebri causing, 2383, 2383*b*
secondary cause of, 2382–2384
sinus, 2382
temporal arteritis causing, 2383
tension-type, 2380–2381, 2380*b*
treatment of, 2377*b*
trigeminal neuralgia causing, 2384, 2384*b*
in women, medications for, 1608*t*
Health
cardiovascular, new paradigm for, 221, 222*t*
climate change effects on, 89
environmental impact from, 89
health care professionals and, 91.*e1f*, 91
how it affects health, 89, 90*f*, 91*t*
recent evidence and projected impacts of, 90, 90*f*
research priorities for, 91
global, 21
challenge, 23
definition of, 21
leading causes of deaths, 21, 22*f*
leading causes of disabilities, 21, 23*f*, 24*f*
leading underlying risk factors, 23, 24*f*
life expectancy and, 21, 21*f*
measures of, 40–43, 40*t*
attributes of, 42*t*
as parts of a system, 42–43, 43*f*
selecting, based on evidence, 41
sources of, 41.*e1t*
types of, 40.*e2f*
uses of, 41*t*
population, determinants of, 42
Health Access and Quality of Care Index, 23–25
Health care
access to, 19, 19*f*–20*f*, 20*f*
barriers to, 1606
costs of, 40
measures of, 40, 40*t*
attributes of, 42*t*
as parts of a system, 42, 43*f*
selecting, based on evidence, 41
sources of, 41.*e1t*
types of, 40.*e1f*
uses of, 41*t*
Health care expenditures, for cardiovascular diseases, 219
Health care professionals, climate change and, 91.*e1f*, 91
Health care quality, measures of, 40, 40*t*, 40.*e1f*
Health care resources, measures of, 40, 40*t*, 40.*e1f*
Health care workers, HIV transmission to, 2299–2300
Health care-associated infections, 1862–1868
active surveillance testing for, 1867
antimicrobial stewardship for, 1865.*e1t*, 1867
blood-borne viruses causing, 1865, 1865.*e1t*
burden of, 1862–1868
catheter-associated urinary tract infections, 1862*t*, 1866
central line-associated blood stream infections, 1862*t*, 1865, 1865.*e1t*
Clostridioides difficile causing, 1865
coagulase-negative staphylococci causing, 1909
decolonization therapy for, 1867
definition of, 1862
device-associated infections, 1865, 1866
due to *Corynebacteria*, 1934*t*
enterococcal infections causing, 1920
epidemiology of, 1862, 1862*t*
fungi causing, 1865
health care delivery-related factors, 1863
health care-related factors, 1863
host-related factors, 1863
incentives and penalties for, 1868
interfacility and regional collaboration for, 1868
multidrug-resistant bacteria and, 1864–1865, 1864*t*
pathobiology of, 1862–1867
pathogen-related factors, 1863
pathogens in, 1863–1865
prevention of, 1865.*e1t*, 1867–1868
respiratory viruses causing, 1865
surgical site infections, 1862*t*, 1866–1867
ventilator-associated pneumonia, 1862*t*, 1866
viruses causing, 1865
Health care-associated pneumonia, 616*t*
Health delivery systems, activities of, 47, 48*f*
Health disparities, definition of, 17
Health-enhancing physical activity, 61
Health equity, 17
Health insurance coverage, 19
Health outcomes
ethnic disparities in, 17
racial disparities in, 17
socioeconomic disparities in, 18–19
Health-related physical fitness, 61
Health span, 116
Healthcare-associated infections, *Pseudomonas aeruginosa* and, 1968
Healthcare Effectiveness Data and Information Set, 41
Hearing, 2641
geriatric assessment of, 117
screening for, 55
Hearing aids, 116
Hearing loss
acoustic neuroma causing, 2642
bedside test for, 2641
central, 2642
cochlear damage causing, 2641
conductive, 2641
diagnosis of, 2641
differential diagnosis of, 2641–2642
drugs as caused of, 2642
epidemiology of, 2641
evaluation of, 2641, 2642*f*
mumps and, 2226*t*
noise-induced, 2642
presbycusis causing, 2642
prevalence, 2641
prevention of, 2643
prognosis for, 2643
sensorineural, 2641–2642
tinnitus, 2643, 2643*b*, 2643*f*
treatment of, 2642*b*
Heart
anatomy of, 224–225
boot-shaped, 247
conduction abnormalities, 231, 231*t*, 232*f*
conduction system of, 223–224, 224*f*, 228, 228*f*
development of, 223, 223.*e2f*
energetics of, 225
examination of, 30, 258
Frank-Starling law of, 225, 226*f*
function of, 223
functional measurement of, 239
inspection of, 213
ion channels expressed in, 300.*e1f*
normal activation of, 228, 228*f*
physiology of, 225–226
pressure-volume area, 225–226, 226*f*
regeneration of, 226
remodeling of, 301
structure of, 223–224, 223.*e1f*
ultrastructure of, 224
univentricular, 354
work of, 226
Heart block
complete, 321, 321*f*
functional, 302
management of, 384*b*
Heart defects, congenital, 347
Heart disease
acquired, 299
in adolescents, 110*t*
asymptomatic structural or functional, 264
causes of death, 17
chronic ischemic, 336
coexisting, 399
congenital, 347. *See also* Congenital heart disease
diagnosis of, 335*t*
echocardiographic findings, 242*t*
hemochromatosis and, 1440
hypertensive, 456
impulse conduction, disorders of, 302
impulse formation, disorders of, 301–302
prognosis for, 248–249, 248.*e1f*
in sarcoidosis, 602
structural, treatment of, 338*b*
valvular, 400–413
Heart failure, 226, 254–279, 262, 287.*e1f*
acute decompensated, 255, 255*t*
antihypertensive drug for, 454*t*
in aortic stenosis, 400
biomarkers, 260, 260.*e1t*

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Heart failure *(Continued)*
causes of, 254–255, 255*t*, 272*t*
classification of, 254, 254*f*
clinical manifestations of, 256–258, 257*f*, 257*t*
comorbidity and, 265*b*
coronary angiography findings, 261
definition of, 254–261
diagnosis of, 258–261
diastolic, 226
disparities, 254
drugs to use with caution in, 265*b*
ECG findings, 258, 259*f*–260*f*
education for, 265*b*
end-of-life considerations in, 278
epidemiology of, 254–255
evaluation of, 30, 262
fluid retention in, 735.*e1f*
hemodynamic monitoring in, 261
in HIV, 2317, 2317*b*
hypertrophic cardiomyopathy causing, 265*b*
hypervolemia and, 735–736
invasive diagnostics for, 261
laboratory findings, 259–260
on left ventricular ejection fraction, 264
left ventricular systolic dysfunction causing, 265*b*
practical use of ACEIs and ARBs for, 265*b*, 266*t*
practical use of β–blockers for, 265*b*, 267*t*
practical use of mineralocorticoid receptor antagonists for, 265*b*, 270*t*
practical use of SGLT2 inhibitors for, 265*b*, 271*t*
management of, 262, 384*b*
with mildly reduced left ventricular ejection fraction, 265*b*, 277*f*
misdiagnosis of, 261
nonischemic dilated cardiomyopathy causing, 265*b*
nuclear cardiology findings, 261
obstruction and, 532
outpatient follow-up for, 265*b*
pathobiology of, 255–256, 255*t*, 255.*e1f*
patterns of presentation, 258, 259*f*, 260*f*
physical findings, 257–258
pre-heart failure, 264
preoperative evaluation considerations, 2663
with preserved ejection fraction, 256, 256*t*
with preserved left ventricular ejection fraction, 265*b*, 278*f*
prognosis for, 278
with reduced left ventricular ejection fraction, 255, 264, 265*f*
second-line treatments for, 265*b*, 272*f*
refractory, 265*b*
risk factors for, 262–264
stages of, 262–278, 263*f*
subtypes of, 265*b*
symptomatic, 264–278
symptoms of, 256–257
therapies for, 262*t*
trajectories of, 12.*e1f*
treatment of, 264*b*
valvular heart disease causing, 265*b*
ventricular tachycardia in, 337
weight loss and, 860*t*
Heart-lung transplantation, 633
Heart murmurs, 214
cause of, 216*t*
systolic, bedside identification of, 216*t*
Heart rate, 226
abnormal, 34*t*
elevated, 33*t*, 34
measurement of, 33
normal, 318
normal resting, 229, 229*t*
Heart size, 244–245
Heart sounds, 258
first, 214, 215*f*
second, 214
tumor plop, 298
Heart transplantation
for Chagas disease, 2128*b*
indications for, 274*t*
Heart valves
location of, 249*f*
prosthetic
advantages and disadvantages of, 412*t*
choices among, 411, 412*f*
postoperative care of, 411
Heartburn, 852*t*, 865
esophageal disease and, 902
functional, 899
clinical manifestations of, 900
diagnosis of, 900
epidemiology of, 900
pathobiology of, 900
prognosis of, 900
Rome IV diagnostic criteria for, 900*t*
treatment of, 900*b*
gastroesophageal reflux disease and, 903, 903*f*
peptic strictures and, 905
in Zollinger-Ellison syndrome, 1563
Heartland viruses, 2065*t*, 2275*t*
Heat, 88*t*
Heat disorders, 678
Heat exhaustion, 679, 679*t*
Heat illness, 678–680
clinical manifestations of, 679, 679*t*
definition of, 678–680
epidemiology of, 678, 678*t*
factors predisposing to, 678*t*
management of, 679*t*
pathobiology of, 678, 678.*e1f*
prevention and treatment of, 679*b*, 679*t*
prognosis of, 680
Heat injury, 678.*e1f*, 679
Heat-labile toxin, of enterotoxigenic *E. coli*, 1962, 1962*t*
Heat rash. *See* Miliaria rubra
Heat-stable toxin, of enterotoxigenic *E. coli*, 1962, 1962*t*
Heat syncope, 679
Heatstroke, 679, 679*t*
characteristics of, 2270*t*
exertional, 678.*e1f*, 679*t*
α-Heavy chain disease, 1304, 1304*b*
γ-Heavy chain disease, 1303–1304, 1304*b*
μ-Heavy chain disease, 1304, 1304*b*
Heavy chain diseases, 1303–1304
Heavy drinking, 2353
HEEADSSS assessment, for adolescents, 111
Height, cancer and, 1244
Height-for-age Z-score (HAZ), 1445
Height vertigo, 2644
Heimlich maneuver, CPR and, 313*b*
Heinz bodies, 1100, 1100*f*, 1116
Helicobacter cinaedi, 1960
Helicobacter fennelliae, 1960
Helicobacter pylori
cancer and, 1245
carbon-13/-14 urea breath test for, 919
epidemiology of, 914
gastric adenocarcinoma and, 1340
gastric lymphoma and, 1279
gastric mucosal biopsy for, 918
histology of, 914*f*
pathobiology of, 914, 914*f*
prevention of, 921
serology testing for, 918
stool antigen test for, 918*t*
testing for, 918
triple therapy for, 919*b*–920*b*
ulcers associated with, 919*b*, 920*t*
Helium, 88*t*
Heller myotomy, for achalasia, 908*b*
HELLP syndrome, 998, 1178–1179, 1627
Helmet cells, 1068*f*
Helminth infections, of liver, 1025–1029
Helminthic infections, 2116
of liver, 1024–1029, 1025
treatment of, 2112*t*
Hemangioblastoma, 1316
Hemangioendotheliomas, 967
Hemangiomas, 967, 2731–2733, 2733*b*, 2734*f*
of eyelid, 2612
hepatic, 991, 992*f*
Hemarthroses, acute, hemophilia and, 1187, 1187*f*–1188*f*, 1188*b*
Hematemesis, 856, 864–865
Hematochezia, 882
with abdominal pain, 856
colonic sources of, 885*t*
management algorithm for, 885*f*
Hematocrit (HCT), *e8t*–*e9t*, 1074, 1076*t*
Hematologic disorders, mesenteric venous thrombosis and, 963*t*
Hematologic malignant neoplasms, characteristics of, 2270*t*
Hematologic paraneoplastic syndromes, 1239
Hematologic system, systemic lupus erythematosus manifestations of, 1770
Hematoma
epidural, 2391
post-traumatic, 2390–2392
subdural, 2390
Hematopoiesis, 1064–1066
clonal, 1064
definition of, 1064
extramedullary, 527
Hematopoietic cell expansion, 1064
Hematopoietic cell grafts, T-cell depletion of, 206
Hematopoietic growth factors, 1064
for cancer, 1232*b*
clinical uses of, 1065–1066
Hematopoietic progenitor cells, 1064
Hematopoietic stem cell transplantation (HSCT), 1206–1212
for acute leukemias, 1262*b*
allogeneic, 1207, 1207*f*
for aplastic anemia, 1126*b*
autologous, 1208
for cancer, 1232*b*
complications after, 1209–1212
for follicular lymphoma, 1283*b*
future directions of, 1212
for hemophagocytic lymphohistiocytosis, 1161*b*
human microbiome and, 1840
in immunocompromised host, 1852–1853, 1853*t*
indications for, 1208–1209, 1208*f*
for less severe T-and B-cell combined defects, 1678*b*
for multiple myeloma, 1299*b*
for primary myelofibrosis, 1135*b*
risk of, for GVHD and marrow graft failure, 204
for sickle cell disease, 1114*b*
syngeneic, 1208
for Wiskott-Aldrich syndrome, 1678*b*
Hematopoietic stem cells, 1064, 1206
Hematopoietic syndrome, 93
Hematopoietic system
age-related changes in, 121
alcohol use disorders and, 2355
Hematoxic snake bite envenomation, characteristics of, 2270*t*
Hematuria, 722, 723*f*, 1366
gross, 856
microscopic, 776
in sickle cell disease, 1114
Heme
bilirubin conversion of, 994
biosynthesis, 1429, 1429*f*
catabolism of, 1429.*e1f*
dipstick for, 722
regulation of, 1429
Heme deficiency, 1430
Heme oxygenase, 995
Hemiballism, 2491–2492
Hemicrania continua, 2377*t*, 2380
Hemifacial spasm, 2496–2497
Hemiparetic gait, 2373*t*
Hemiptera, 711
Hemiscorpius lepturus, 710
Hemispatial neglect, 2409–2410, 2410*f*
Hemisphere infarction, 2468*f*
Hemochromatosis, 1438–1442
arthritis and, 1824, 1824*f*
classification of, 1438*t*
clinical manifestations of, 1439–1440, 1439*t*
definition of, 1438–1442
diagnosis of, 1440–1441, 1441*f*
epidemiology of, 1438
hereditary, 294, 294*b*
pathobiology of, 1438, 1439*f*
physical findings in, 1440*t*
prognosis of, 1442
quantifying, 1441
screening for, 1441
symptoms and signs of, 1440, 1440*t*
treatment of, 1441*b*
Hemodialysis, 130, 841
access issues in, 842
complications of, 841
optimal dialysis access for, 842
in septic shock, 673*b*
toxicants removed by, 698*t*
Hemodynamic compromise, 654
Hemodynamic disease, drug dose adjustment in, 130
Hemodynamics, in heart failure, 261
Hemoglobin, *e8t*–*e9t*, 1074
globin genes, 1113*f*
sickle, 1110
Hemoglobin A_{1c}, 1624
Hemoglobin C
description of, 1116
homozygous, peripheral blood smear of, 1070*f*
Hemoglobin concentration, 1076*t*
Hemoglobin E, 1106
Hemoglobin E thalassemias, 1106
Hemoglobin electrophoresis, *e8t*–*e9t*
Hemoglobin F synthesis, stimulation of, 1107*b*
Hemoglobin H disease, 1104, 1107*b*
Hemoglobin S, 1068*f*, 1110*f*
Hemoglobinopathies
arthritis associated with, 1822
high-oxygen-affinity, 1116
transfusion for, 1206
types of, 1114
unstable, 1109, 1116
Hemoglobinuria, paroxysmal nocturnal, 480, 480*b*
Hemolysis, 1070
Hemolysis, elevated liver enzymes, and low platelet count (HELLP), 1196
Hemolytic anemia, 1078, 1079*f*, 1079*t*, 1080*t*
autoimmune, 1087
cold, 1088, 1088*t*, 1090*f*
corticosteroids for, 1089*b*
diagnosis of, 1087
direct antiglobulin test for, 1087
epidemiology of, 1087
folic acid supplementation for, 1089*b*
laboratory test for, 1087
pathobiology of, 1087
rituximab for, 1089*b*
signs and symptoms of, 1087
warm, 1087, 1089*t*
cause of, 1072*t*
definition of, 1086, 1087*t*
Heinz body, 1116
microangiopathic, in thrombotic thrombocytopenic purpura, 1177
peripheral blood smear of, 1070
red blood cell membrane and metabolic defects, 1093–1102
splenomegaly associated with, 1152
Wilson disease and, 1437
Hemolytic transfusion reactions, 1092
Hemolytic-uremic syndrome, 728, 1178, 1731*t*, 1961
clinical manifestations of, 1178
definition of, 1178
enteric infections and, 1870*t*
pathobiology of, 1178
prevention of, 1178*b*
treatment of, 1178*b*
Hemoperfusion, 130
Hemophagocytic lymphohistiocytosis, 1159, 1160*t*, 1161*b*, 1161*f*, 1161*t*, 1684
Hemophilia
acquired, 1191, 1191*b*
arthritis associated with, 1822
hereditary, 1187
Hemoptysis
alveolar hemorrhage and, 568
in alveolar hemorrhagic disorders, 566
approach to, 515–519
causes of, 518*t*
diagnosis of, 516–519, 518*f*
invasive mucinous adenocarcinoma and lepidic predominant nonmucinous adenocarcinoma and, 569
special evaluation for, 519*t*
treatment of, 519*b*
Hemorrhage
alveolar, 566*t*, 568
clinical manifestations of, 568, 568.*e1f*
definition of, 568
diagnosis of, 569, 569*f*, 569.*e1f*
pathobiology of, 568
prognosis of, 569
treatment for, 569*b*
cerebral, 2463
gastrointestinal. *See* Gastrointestinal bleeding
peptic ulcer causing, 921–922, 922*t*
splinter, 216
subarachnoid. *See* Subarachnoid hemorrhage

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Hemorrhagic cerebrovascular disease, 2474–2482
Hemorrhagic colitis, *Escherichia coli* and, 1961, 1963
Hemorrhagic cystitis, 2205
  BK polyomavirus-associated, 2229, 2229*b*
Hemorrhagic disorders, vascular
  acquired, 1186
  hereditary, 1186
Hemorrhagic fevers
  in travelers, 1890*t*
  viral, 99, 2264–2273
    antiviral therapy for, 2269*b*
    bat-borne viruses, 2264
    clinical management of, 2269*b*
    clinical manifestations of, 2267, 2268*t*
    contact tracing of, 2272
    definition of, 2264–2273
    diagnosis of, 2267–2269
    differential diagnosis of, 2270*t*
    epidemiology of, 2264–2266
    human-to-human transmission of, 2266
    infection prevention and control in, 2272
    laboratory testing for, 2269, 2271*t*
    maintenance in nature, 2264–2266
    mosquito-borne viruses, 2266
    nonspecific presentation of, 2268, 2272
    pathobiology of, 2266–2267
    pathogens that causes, 2264
    postexposure prophylaxis for, 2273
    in pregnancy, 2267, 2269*b*
    prevention of, 2272–2273
    prognosis for, 2273
    reservoir for, 2273
    ribavirin therapy for, 2272*t*
    rodent-borne viruses, 2264–2266
    sequelae of, 2273
    tick-borne viruses, 2266
    transmission to humans, 2264
    treatment of, 2269*b*
    vaccines for, 2272–2273
    vector control for, 2273
    viruses causing, 2265*t*
Hemorrhagic shock, 663*t*
  categorization of, 702*t*
  initial treatment of, 702*t*
Hemorrhagic smallpox, 2237, 2237*t*, 2270*t*
Hemorrhagic telangiectasia, hereditary, 1186, 1186*b*, 1186*f*, 1186*t*
Hemorrhoidectomy, operative, 978*b*
Hemorrhoids, 977
  clinical manifestations and diagnosis of, 977–978
  epidemiology and pathobiology of, 977
  external, 978, 978*f*
  internal, 977, 978*f*, 978*t*
  treatment for, 978*b*
Hemosiderinuria, 1092
Hemosiderosis, idiopathic pulmonary, 582
Hemostasis
  endoscopic, for upper gastrointestinal bleeding, 883*b*
  mechanisms of, 1165
  normal, 1165, 1165*f*
  point-of-care tests of, 1169
  screening tests of, 1166–1167, 1167*f*
    abnormal, 1167–1169, 1168*f*
Hemothorax, 626
Hemox-Analyzer, 1116
Hemp, 88*t*
Henderson-Hasselbalch equation, 639, 753
Hendra virus, 2065*t*
Henoch-Schönlein purpura, 965, 1798, 2715
  description of, 782
  pathologic characteristics of, 1793*t*
  treatment for, 1798*b*
Henry's law, 594
Heparin, 1165–1166
  for acute coronary syndrome, 374*t*
  bleeding caused by, 487*b*
  for disseminated intravascular coagulation, 1196*b*
  for hypercoagulable states, 477
  low-molecular-weight, 501*t*, 502, 503*t*
    for acute coronary syndrome, 374*t*
    in pregnancy, 1623*b*
  unfractionated, 501–502, 501*t*
    for acute coronary syndrome, 374*t*
    adverse effects of, 502
    dosage and monitoring of, 502
Heparin *(Continued)*
    effect of, reversing, 502
    in pregnancy, 1623*b*
  weight-based dosing of, 487*b*, 487*t*
Heparin-induced thrombocytopenia, 487*b*, 1174–1175
  clinical manifestations of, 1174–1175
  diagnosis of, 1174
  epidemiology of, 1174
  laboratory assays of, 1175*t*
  pathobiology of, 1174, 1174*f*
  prevention of, 1175*b*
  treatment of, 1175*b*
Heparin resistance, 478*b*
Hepatic adenomas, 991, 992*f*
Hepatic artery thrombosis, 969
Hepatic cirrhosis, in Wilson disease, 1436*f*
Hepatic cysts, 990, 991*f*
Hepatic disease, 968, 2246
Hepatic echinococcal cyst, 1029*f*
Hepatic encephalopathy, 986, 989*t*, 2544, 2544*b*
  alcohol causing, 2543
  cirrhosis and, 1037, 1038
  diagnosis of, 1040
  treatment of, 1040*b*
Hepatic fibrosis, autosomal recessive polycystic kidney disease and, 813
Hepatic glycogen release/storage, hypoglycemia due to, 1552*t*, 1555
Hepatic glycogenolysis, 1415
Hepatic hemangiomas, 991, 992*f*
Hepatic impairment, psychotropic medications and, 2678*t*
Hepatic mass, 989*t*
  approach to, 990–992, 991*f*
  solid, 990–992, 992*f*
Hepatic porphyria, 1428
Hepatic steatosis, with chemical shift imaging, 872*f*
Hepatitis
  acute, abdominal pain and, 854*t*
  acute viral. *See* Acute viral hepatitis
  autoimmune, 986, 1016, 1017*b*
Hepatitis A virus (HAV), 1004–1005
  clinical manifestations of, 1003*t*, 1004
  description of, 1002*t*, 1004
  diagnosis of, 1004, 1004*f*
  epidemiology of, 1004
  immunization for, 65*t*, 66*t*, 78*f*, 79
    adverse reactions of, 79
    indications for, 79
    schedule of, 76.*e*1*t*, 77*f*
    for traveler, 1886–1887, 1886*t*
  pathobiology of, 1004
  pathogen that cause, 1004
  prevention of, 1004
  prognosis of, 1004–1005
  prophylaxis for, 2309*t*
  in travelers, 1889.*e*1*t*
  treatment of, 1004*b*
Hepatitis B virus (HBV), 1245
  antiviral therapy for, 2181, 2181*t*
    adefovir as, 2183
    entecavir as, 2182
    interferons as, 2183
    lamivudine as, 2183
    telbivudine as, 2183
    tenofovir alafenamide as, 2181–2182
    tenofovir disoproxil fumarate as, 2181
  chronic, 1010
    cirrhosis in, 1012
    clinical manifestations of, 1010
    diagnosis of, 1011, 1011*t*, 1012*f*
    epidemiology of, 1010
    pathobiology of, 1010
    prevention of, 1011*b*, 1013*t*
    prognosis for, 1012
    treatment of, 1011*b*, 1013*t*
  clinical manifestations of, 1003*t*, 1005
  coinfection with, antiretroviral therapy for, 2304
  definition of, 1005
  description of, 1002*t*
  diagnosis of, 1005, 1005*t*, 1006*f*
  epidemiology of, 1005, 1358
  genotypes of, 1005
  immunization for, 65*t*, 66*t*, 78*f*, 79
    adverse reactions of, 79
    indications for, 76.*e*1*t*, 77*f*, 79
    schedule of, 76.*e*1*t*, 77*f*
    for traveler, 1886–1887, 1886*t*
Hepatitis B virus (HBV) *(Continued)*
  life cycle of, 1005
  pathobiology of, 1005
  pathogen that cause, 1005
  in pregnancy, 1626*b*
  prevention of, 1005–1006
  prognosis for, 1006
  prophylaxis for, 2309*t*
  screening for, 55
  transfusion-related transmission of, 1203
  transmission of, 1005
  treatment of, 1005*b*
Hepatitis C-associated cryoglobulinemia, 789
Hepatitis C virus (HCV)
  antiviral therapy for, 2181*t*, 2182*t*, 2183
    boceprevir as, 2185
    daclatasvir as, 2184
    daclatasvir/asunaprevir as, 2185
    glecaprevir/pibrentasvir as, 2184
    grazoprevir/elbasvir as, 2185
    ledipasvir/sofosbuvir as, 2184
    sofosbuvir as, 2185
    sofosbuvir/velpatasvir as, 2184
    sofosbuvir/velpatasvir/voxilaprevir as, 2184
  chronic, 986, 1013
    clinical manifestations of, 1013
    diagnosis of, 1014
    epidemiology of, 1013
    human immunodeficiency virus and, 1014*b*
    pathobiology of, 1013
    prognosis for, 1014
    recurrent, after liver transplantation, 1014*b*
    treatment of, 1014*b*, 1015*t*
  clinical manifestations of, 1007
  coinfection with, antiretroviral therapy for, 2304
  definition of, 1006
  description of, 1002*t*
  diagnosis of, 1007, 1007*f*, 1007*t*
  epidemiology of, 1006
  osteosclerosis associated with, 1668
  pathobiology of, 1007
  pathogen that cause, 1006
  in pregnancy, 1625–1626
  prevention of, 1008
  prognosis for, 1008
  screening for, 55
  transfusion-related transmission of, 1203
  transmission of, 1006
  treatment of, 1008*b*
Hepatitis D virus (HDV)
  chronic, 1015, 1015*b*
  clinical manifestations of, 1008
  definition of, 1008
  description of, 1002*t*
  diagnosis of, 1008
  epidemiology of, 1008
  pathobiology of, 1008
  pathogen that cause, 1008
  prevention of, 1008
  prognosis for, 1008
  treatment of, 1008*b*
Hepatitis E virus (HEV)
  chronic, 1016, 1016*b*
  clinical manifestations of, 1009
  definition of, 1008
  description of, 1002*t*
  diagnosis of, 1009
  epidemiology of, 1008–1009
  pathobiology of, 1008
  pathogen that cause, 1008
  prevention of, 1009
  prognosis for, 1009
  in travelers, 1889.*e*1*t*
  treatment of, 1009*b*
Hepatobiliary iminodiacetic acid (HIDA) scans, 1051
Hepatocellular carcinoma, 992, 992*f*, 1010, 1045
  clinical manifestations of, 1359
  diagnosis of, 1357.*e*3*t*, 1359–1360, 1360*f*–1361*f*, 1361*f*
  epidemiology of, 1357–1358
  hepatitis B virus causing, 1012
  magnetic resonance imaging of, 872*f*
  pathobiology of, 1359, 1359*f*
  risk factors for, 1357.*e*3*t*
  treatment of, 1360*b*
Hepatocellular necrosis, 1010
Hepatocyte dysfunction, 986
Hepatocytes, 986
Hepatojugular reflux, 215
Hepatomegaly
  diagnostic approach to, 989*f*
  glycogen storage disease *versus*, 1416
  hemochromatosis and, 1440
Hepatopulmonary syndrome
  cirrhosis and, 1038
  diagnosis of, 1040–1042
  treatment of, 1040*b*
Hepatorenal failure, 2031
Hepatorenal syndrome
  cirrhosis and, 1040
  treatment of, 1040*b*
Hepatosplenic candidiasis, 1023, 1024*b*, 1024*f*, 2090
Hepatosplenic T-cell lymphomas, 1287
Hepatosplenomegaly, fever and, 1849
Hepatotoxicity
  direct/intrinsic, 1018
  idiosyncratic, 1019
  indirect, 1021
Hepcidin, 1085, 1438, 1439*f*
Heptavalent botulinum antitoxin, 1928*b*
HER-2. *See* Human epidermal growth factor receptor 2
Herald patch, 2707, 2707*f*
Herald wave phenomenon, 2199
Herbicides, 88*t*
Herceptin. *See* Trastuzumab
Hereditary α-tryptasemia, 1693
Hereditary angioedema, 1690, 1731*t*
  acute attacks of, 1690*b*
  chronic therapy for, 1690*b*
  clinical manifestations of, 1688*f*, 1690
  complement system and, 201*t*
  diagnosis of, 1690
  epidemiology of, 1690
  pathobiology of, 1690
  prognosis of, 1691
  short-term prophylaxis for, 1690*b*
  treatment and prevention of, 1690*b*
Hereditary ATTR amyloidosis, 2560, 2560*b*
Hereditary breast cancer, 1250*t*
Hereditary coproporphyria (HCP), 1428*t*
Hereditary deafness, 2641
Hereditary elliptocytosis, 1096
  clinical manifestations of, 1097
  definition of, 1096
  epidemiology of, 1096
  pathobiology of, 1096–1097
  peripheral blood smear of, 1068*f*
Hereditary fructose intolerance, 816*t*
Hereditary hemochromatosis, 294, 294*b*, 992
Hereditary hemophilias, 1187
  clinical manifestations of, 1187–1188, 1187*f*, 1188*f*
  definition of, 1187
  diagnosis of, 1188
  epidemiology of, 1187
  genetics of, 1187
  pathobiology of, 1187
  prevention of, 1190–1191
  prognosis of, 1191
  treatment of, 1188*b*, 1189*t*
Hereditary hemorrhagic telangiectasia, 967, 1186, 1186*b*, 1186*f*, 1186*t*, 2550*t*
Hereditary leiomyomatosis, 1250*t*, 1363
Hereditary motor neuronopathy, 2565
Hereditary motor neuropathies, 2564*t*
Hereditary multiple exostoses, 1669
Hereditary nephropathies, 815–818, 816*t*
  cystinosis, 815
  cystinuria, 815
  Dent disease, 817
  distal renal tubular acidosis, 817, 818*b*, 818*t*
  distal tubule, 816*t*, 817
  Liddle syndrome, 817
  loop of Henle, 816*t*, 817
  proximal tubule, 815–817, 816*t*
Hereditary neutrophilia, 1141
Hereditary nonpolyposis colorectal cancer (HNPCC), 1250*t*, 1347, 1347*t*, 1377
Hereditary ovarian cancer, 1250*t*
Hereditary papillary renal cell carcinoma, 1250*t*
Hereditary paraganglioma, 1250*t*
Hereditary pyropoikilocytosis, 1094*f*, 1097
  diagnosis of, 1094*f*, 1097
  peripheral blood smear of, 1069*f*
  treatment of, 1097*b*

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Hereditary retinoblastoma, 1250*t*
Hereditary sensory and autonomic neuropathies, 2560
Hereditary spastic paraplegias, 2498, 2498*t*, 2564*t*
Hereditary spherocytosis, 1067*f*, 1094
  clinical manifestations of, 1095
  definition of, 1094, 1094*f*
  diagnosis of, 1094*f*, 1095–1096, 1095*t*, 1096*f*
  epidemiology of, 1094
  pathobiology of, 1094–1095
  treatment of, 1096*b*
Hereditary stomatocytosis, 1094*f*, 1097
Hermansky-Pudlak syndrome, 583
  type II, 1145
Hermaphroditism, true, 1574
Hernia, 952–953
  epigastric, 952*b*
  groin, 952*b*
  hiatal, 902, 910
  incisional, 952*b*
  inguinal, 952–953
  pelvic, 952*b*
  Spigelian, 953
  strangulated, abdominal pain and, 854*t*
  umbilical, 952*b*
Heroin. *See* Opioids
Herpangina, 2621*t*
  enteroviruses causing, 2259, 2260*b*
Herpes labialis, 2246*f*, 2621
Herpes simplex encephalitis, 1686*t*, 2247, 2247*b*, 2247*f*, 2408, 2532, 2532*t*, 2533*f*
Herpes simplex keratitis, 2605, 2606*f*
Herpes simplex virus (HSV) infections, 2244–2247, 2720, 2720*b*, 2721*f*
  aseptic meningitis caused by, 2521
  characteristics of, 2270*t*
  clinical manifestation of, 2245–2246
  definition of, 2244–2246
  diagnosis of, 2246
  of esophagus, 911
  gene therapy for, 2245
  genital, 2245
    characteristics of, 1880
    organisms causing, 1879*t*
    syphilis *versus*, 2019
  gingivostomatitis caused by, 2245
  in HIV, 2322*t*
  in immunocompromised hosts, 2246–2247, 2246*b*
  keratitis caused by, 2246, 2605, 2606*f*
  latency of, 2245, 2245.*e1f*
  meningitis caused by, 2246
  neonatal, 2247
  other cutaneous manifestations of, 2246
  pathobiology of, 2245
  pathogen that causes, 2244–2245
  pharyngitis and, 2650
  prevention of, 2246–2247
  primary, 2245.*e1f*, 2621*t*, 2622*f*
  primary prevention of, 2247
  recurrent, 2621*t*
  replication of, 2245.*e1f*
  secondary prevention of, 2246
  transmission of, 2245
  treatment of, 2246*b*
  type 1, 2532*t*
  type 2, 2532*t*
  virion of, 2245.*e1f*
Herpes zoster, 211*t*, 2689*t*, 2721, 2721*b*, 2721*f*
  immunization for, 66*t*
Herpes zoster ophthalmicus, keratitis caused by, 2605
Herpes zoster oticus, 2579
Herpesviridae, 2245
Herpesvirus infections, antiviral therapy for, 2186, 2187*t*, 2188*t*
  acyclovir as, 2186
  docosanol as, 2189
  famciclovir as, 2186
  fomivirsen as, 2189
  foscarnet as, 2188
  ganciclovir as, 2186
  letermovir as, 2188
  penciclovir as, 2186
  valacyclovir as, 2186
  valganciclovir as, 2186
Herpetic keratitis, 2246
Hers disease, 1417*t*
Heterochromia iridis, 2603
Heterosexual pubertal development, 1594
Heterotopic gastric mucosa, 913
Hexokinase deficiency, 1099
Hexose monophosphate shunt, 1098–1099
  disorders of, 1100
HFE mutations, 1438
Hiatal hernia, 902, 910
HIDA. *See* Hepatobiliary iminodiacetic acid
Hidradenitis suppurativa, 2723, 2723*b*, 2724*f*, 2745*f*
HIDS. *See* Hyperimmunoglobulinemia D with periodic fever syndrome
Hierarchy of hazard controls, 87
High-altitude diseases, 592–593
  clinical manifestations of, 593
  definition of, 592–593, 592*t*
  diagnosis of, 593
  epidemiology of, 592
  pathobiology of, 592–593
  prevention of, 593, 593*t*
  prognosis of, 593
  treatment of, 593*b*
High-altitude pulmonary edema, 592*t*
High-altitude retinal hemorrhage, 592*t*
High blood pressure, screening for, 53
High density lipoproteins, 1406, 1406.*e1f*
  high level of, 1410
  low level of, 1410
High-flow nasal oxygen, for acute respiratory failure, 647*b*
High-frequency ventilation, 653
High intensity statin, for acute STEMI, 391*t*
High-oxygen-affinity hemoglobinopathies, 1116
High-resolution computed tomography
  in interstitial lung disease, 574
  of lung parenchyma, 519
High-resolution esophageal manometry, 902
High-risk pulmonary embolism, 487*b*
High-throughput sequencing, 1169
Higher mental functions, 2407–2411
Hindbrain herniation, 2383
Hindgut neuroendocrine neoplasms, 1567
Hip
  disorders of, 1746–1747
  fractures of, osteoporosis and, 1607–1608
  injury of, occupational, 86*t*
  musculoskeletal anatomy of, 1743*f*
Hip, surgical treatment of, 1827–1828, 1828*f*
Hip fractures, surgery for, 1828
Hippocampal formation, 2407
Hippocampal sclerosis, mesial temporal lobe epilepsy with, 2433
Hirata disease, 1554
Hirschsprung disease, 862
  clinical manifestations of, 891–892
  definition of, 891
  diagnosis of, 892
  pathobiology of, 891
  treatment of, 892*b*
Hirsutism, 1598, 2751
Hispanic Americans, 18
  heart failure in, 254
Histamine, 193
  plasma, 1693–1694
Histamine-induced urticaria, 1687–1689, 1690*t*
Histiocyte, 1154
Histiocytoses, 1154–1162
  classification of, 1154*t*
  definition of, 1154
  Epstein-Barr virus and, 2256
  Erdheim-Chester disease, 1155*f*, 1156, 1157*b*
  hemophagocytic lymphohistiocytosis, 1159, 1160*t*, 1161*b*, 1161*f*, 1161*t*
  indeterminate cell, 1157
  Langerhans cell, 1154–1156
    clinical manifestations of, 1154–1156, 1155*f*, 1156*t*
    cutaneous features of, 1155*f*
    diagnosis of, 1156
    epidemiology of, 1154
    neurodegeneration associated with, 1156
    pathobiology of, 1154
    prognosis for, 1156
    treatment of, 1156*b*
  malignant, 1159, 1159*b*
  necrobiotic xanthogranuloma, 1158, 1158*b*
  Rosai-Dorfman disease, 1158, 1159*b*
Histiocytosis X, 1154
Histo-blood group antigens (HBGAs), noroviruses and, 2262
Histocompatibility antigens
  major, 203–205, 204*t*, 204.*e1f*, 204.*e1t*–204.*e2t*
  minor, 205
Histoid leprosy, 2051, 2052*f*
Histone deacetylase, 2701
Histoplasma capsulatum, 956, 1024
Histoplasma capsulatum var capsulatum, 2082
Histoplasmosis, 2081, 2081*t*, 2651
  acute pulmonary, 2082
  characteristics of, 2270*t*
  chronic pulmonary, 2082
  clinical manifestations of, 2082
  definition of, 2081–2082
  diagnosis of, 2082–2083
  disseminated, 2082
  epidemiology of, 2082
  identification of, 2082–2083, 2083*f*
  pathobiology of, 2082
  pathogen of, 2082
  prevention of, 2083
  prognosis of, 2083
  prophylaxis for, 2309*t*
  in travelers, 1889.*e1t*
  treatment of, 2083*b*
Histrionic personality disorder, 2348*t*
HIV. *See* Human immunodeficiency virus
HIV-1- specific antibodies, 2292
HIV-associated dementia, 2312
HIV-associated immune complex renal disease, 2313
HIV-associated lipodystrophy syndrome, 2317
HIV-associated nephropathy, 728, 2313
HIV-associated neurocognitive disorder, 2312
HLA. *See* Human leukocyte antigen
HLA-A gene, 160*t*
HLA-B gene, 160*t*
HLA-B27, 1760
HLA-DR3 allele group, 204
HLTV. *See* Human T-lymphotrophic virus
HLTV-associated myelopathy/tropical spastic paraparesis (HAM/TSP), 2327–2328
  clinical manifestations of, 2328
  diagnosis of, 2328
  epidemiology and pathobiology of, 2327–2328
  pathogenesis of, 2326
  prognosis of, 2328
  treatment for, 2328*b*
HNF1B nephropathy, 814
HNPCC. *See* Hereditary nonpolyposis colorectal cancer
Hoarseness, 2653
Hodgkin lymphoma, 1149, 1289–1294, 2255
  acquired immunodeficiency syndrome and, 1292*b*
  in adolescents, 111
  advanced-stage, 1292*b*
  classic, 1289, 1290
  clinical manifestations of, 1289
  definition of, 1289–1294
  diagnosis of, 1289–1292, 1290*f*
  differential diagnosis of, 1290
  in elderly population, 1292*b*
  epidemiology of, 1289
  Epstein-Barr virus and, 1289
  future directions of, 1293–1294
  genetic factors of, 1289
  hematopoietic cell transplantation for, 1209
  increased eosinophils counts in, 533
  limited-stage, 1292*b*
  management of complications of, 1292*b*, 1293*t*
  nodular lymphocyte-predominant, 1289, 1290
  nodular sclerosing, 1290, 1290*f*
  pathobiology of, 1289
  during pregnancy, 1291*t*, 1292*b*
  staging of, 1290–1291, 1291*t*
    imaging for, 1291, 1291*f*
    laboratory testing for, 1291
    physical examination for, 1290, 1290*f*, 1291*t*
    positron emission tomography for, 1291
  treatment for, 1292*b*, 1292*t*
  World Health Organization classification of, 1290*t*
"Holiday heart", 328
Holocarboxylase synthetase deficiency, 1403*t*
Holoprosencephaly, 2547
Holt-Oram syndrome, 302, 348
Holter monitors, 307
Home blood pressure, 446*t*, 447
Home HIV tests, 2297
Homicide, in adolescents, 110–111, 110*t*
Homocysteine, 1425
  folate and, 1459
  for megaloblastic anemias, 1122–1123, 1123
  metabolism of, 1425.*e1f*
Homocystinuria, 1402*t*, 1425–1427
  clinical manifestations of, 1425–1426
  definition of, 1425–1427, 1425.*e1f*
  diagnosis of, 1425*t*, 1426–1427, 1426*t*
  epidemiology of, 1425
  pathobiology of, 1425, 1425*t*, 1425.*e1f*
  prevention of, 1427
  prognosis of, 1427
  treatment of, 1427*b*
Homogeneous nucleation, 803
Homogeneous opacities, diffuse, 520
Homografts, advantages and disadvantages of, 412*t*
Homozygous acute porphyrias, 1433, 1433*f*
Homozygous cystathionine β-synthase deficiency, 479
Homozygous hemoglobin C, peripheral blood smear of, 1070*f*
Homozygous loss-of-function mutations, 939
Honeycombing, 522, 522*f*, 575.*e1f*
Hookworm
  clinical manifestations of, 2170*f*, 2171
  cutaneous larva migrans, 2170
  diagnosis of, 2171
  epidemiology of, 2170
  pathobiology of, 2171
  pathogen caused by, 2170, 2170*f*
  prevention of, 2171
  prognosis for, 2171
  treatment of, 2170*t*, 2171*b*
Hoover sign, 549
Hordeolum, 2601, 2601*f*
Hormonal change, in puberty, 1591, 1591*f*
Hormonal (steroidal) contraception, 1613
Hormonal therapies
  for cancer, 1232*b*
  menopausal
    discontinuation of, 1630*b*
    extended use of, 1630*b*
    vaginal symptoms and, 1630*b*
    venous thromboembolism and, 1630*b*
  for skin diseases, 2700
  for transgender men, 1578*b*, 1578*t*
  for transgender women, 1578*b*, 1579*t*
Hormone(s)
  cancer and, 1245
  in diabetic nephropathy, 796
  excess production of, hypoglycemia and, 1554
  exogenous, 1246
  mechanism of action, 1474, 1475*f*
  metabolism of, 1474
  synthesis and secretion of, 1474, 1474*f*
  transport of, 1474
Hormone deficiency, hypoglycemia due to, 1552*t*, 1555
Hormone insensitivity syndromes, 1573
Hormone replacement therapy
  for endocrine disease, 1473
  venous thromboembolism and, 481
Horner syndrome, 2555, 2618*f*, 2618*t*
Hospice, 16
Hospital-acquired pneumonia, 616*t*, 1965
  bacterial species that cause, 1892*t*
Hospital-associated fever, 1846*t*
Hospital-associated pneumonia, treatment of, 1970*b*
Hospitalist, medical consultations by, 2656
Hospitalization
  for cardiovascular disease, 219
  for pneumonia, 606
Host defense mechanisms, 191
Host-*versus*-graft (HVG), 203
Hot flashes, 1630*b*
Howell-Jolly bodies, 1152
  peripheral blood smear of, 1067*f*, 1074*t*, 1152
HPA axis. *See* Hypothalamic-pituitary-adrenal axis
HPV. *See* Human papillomavirus
HPV-associated oropharyngeal squamous cell carcinoma, 1320, 1322, 1324*f*, 1327*b*, 1328
HPV-unrelated oropharyngeal squamous cell carcinoma, 1322, 1327*b*
HSCT. *See* Hematopoietic stem cell transplantation
HSD3B2 gene, mutations in, 1571
HSV. *See* Herpes simplex virus
5-HT_3 receptor antagonists, for nausea and vomiting, 863*t*
HTLV-associated arthritis, 2327*t*
HTLV-associated myelopathy/tropical spastic paraparesis (HAM/TSP), 2327*t*
Human bone, 803

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Human chorionic gonadotropin (HCG), 1479
Human coronaviruses (HCoVs), 2206
  classification of, 2209, 2209*t*
Human cystic echinococcosis, 1025
Human diploid cell vaccine (HDCV), 82
Human epidermal growth factor receptor 2 (HER-2), 167
Human fetal tissue engraftment, 172–173
Human Gene Mutation Database, 1187
Human Genome Project, 165
Human granulocytic ehrlichiosis, 2060*t*, 2061, 2061*b*, 2062*f*
Human herpesvirus 6, 2532*t*
Human herpesvirus-8, 1279
Human immunodeficiency virus (HIV)
  acute, 2295–2297
    clinical manifestations, 2295–2297
    diagnosis of, 2296–2297
    infectivity, 2295–2296
    symptoms and signs of, 2295, 2295*t*
    in travelers, 1889.*e1t*
    viral load, 2295
  aging-related syndromes to, 2312
  antiretroviral therapy for, 2294, 2294*f*
    immune reconstitution using, 2307*b*
    toxic neuropathy caused by, 2313*b*
  associated with hypogonadism, 1583
  Campylobacter infections in, 1960
  candidiasis associated with, 2090
  cardiovascular manifestations of, 2316–2317
  chancroid and, 1950–1951
  characteristics of, 2270*t*
  chronic hepatitis C and, 1014*b*
  clinical consequences of, 2294
  cure for, 2305
  cutaneous lesions associated with, 2323*t*
  dermatologic manifestations of, 2321, 2323*t*
    approach to, 2323*t*
    inflammatory conditions, 2321
    pruritus, 2321
    skin malignancies, 2321
  diarrhea and, 937
  endocrine manifestations of, 2317–2318
  epidemiology and diagnosis of, 2286
  eradication of, 2294
  gastrointestinal manifestations of, 2319–2321, 2322*t*
    anorectal, 2321, 2322*t*
    biliary, 2321, 2322*t*
    esophageal, 2320, 2320*b*, 2322*t*
    gastric, 2322*t*
    hepatic, 2321, 2322*t*
    large bowel, 2320, 2320*b*–2321*b*, 2322*t*
    oral, 2319–2320, 2320*b*, 2322*t*
    small bowel, 2320, 2322*t*
  genes of, 2291, 2291.*e3f*
  global impact and response of, 2286–2288, 2286.*e3f*, 2287*f*–2288*f*, 2288*f*, 2288.*e1f*
  global statistics of, 2286, 2286*t*, 2286.*e2f*, 2287*f*
  head and neck cancer and, 1321
  hematology and, 2313–2316
    AIDS-defining malignancies, 2315
    anemia, 2314, 2315*t*
    cytopenia, 2313
    hypercoagulable state, 2315
    leukopenia, 2314
    thrombocytopenia, 2314, 2314*b*
    thrombotic microangiopathies, 2313
  HIV-1 replication, 2293–2294
  human papillomavirus and, 2241
  immune reconstitution inflammatory syndrome associated with, 2308–2313, 2311*b*, 2312*t*
  infected cells of, fate of, 2292–2293
  infertility associated with, 2318
  Leishmania donovani and, 2130
  Leishmania infantum and, 2133
  life cycle of, 2301*f*
  malaria and, 2121
  measles vaccination in, 2223
  meningitis caused by, 2521
  microbial complications of, 2305–2308
    clinical manifestations of, 2306–2307
    diagnosis of, 2307
    epidemiology of, 2305–2306
    pathobiology of, 2306
    prevention of, 2308, 2308.*e1f*
    treatment of, 2307*b*
Human immunodeficiency virus (HIV) *(Continued)*
  musculoskeletal manifestations of, 2321–2324
  nephropathy associated with, 789
  neuropsychiatric manifestations of, 2312–2313
  oncology and, 2313
    anal cancer, 2316
    cervical cancer, 2316*b*
    colorectal cancer, 2316
    Kaposi sarcoma, 2315, 2315*b*, 2316*f*
    lung cancer, 2316
    multicentric Castleman disease, 2316, 2316*b*
    non-AIDS-defining cancers, 2316, 2316*b*
    non-Hodgkin lymphoma, 2315
    prevention of, 2316
    primary effusion lymphoma, 2315
    screening for, 2316
  opportunistic infections associated with, 2305, 2306*t*
    antiretroviral therapy for, 2307*b*
    behavioral factors, 2306
    candidiasis, 2089
    CD4 cells in, 2306, 2306*f*
    clinical manifestations of, 2306
    cryptococcosis, 2087
    cytomegalovirus, 2307
    diagnosis of, 2307
    empiric management of, 2307*b*
    Mycobacterium tuberculosis, 2306
    natural histories of, 2306–2307
    pathobiology of, 2306
    prevention of, 2308, 2308.*e1f*
    prophylaxis for, 2309*t*
    treatment of, 2307*b*, 2307*t*
  oral lesions associated with, 2621*t*
  pathobiology of, 2291–2294
  pathogen that causes, 2291
  pharyngitis and, 2650
  physiology of, 2292–2294
  post-transcription events of, 2292.*e2f*
  preexposure prophylaxis for, 56, 1884
  prevention of, 2298–2300
    antiretroviral therapy for, 2298
    in blood products and other tissues, 2299
    development of, 2300
    in health care workers, 2299
    in injection drug users, 2299
    interventions in, 2300
    opportunities of, 2298*f*
    postexposure prophylaxis for, 2299, 2299*t*
    preexposure prophylaxis for, 2298–2299, 2299*t*
  pulmonary manifestations of, 2318–2319
  rapid tests and home testing options for, 2296–2297
  reactive arthritis and, 1763
  regional epidemics of, 2288–2291
    in Asia and the Pacific, 2289, 2289.*e1f*
    in Caribbean, 2289, 2289.*e1f*
    in Eastern and Southern Africa, 2288, 2288.*e1f*
    in Eastern Europe and Central Asia, 2289, 2289.*e1f*
    in Latin America, 2289, 2289.*e3f*
    in North Africa and the Middle East, 2289, 2289.*e1f*
    in United States, 2288*f*, 2290–2291, 2290*f*–2291*f*, 2291*f*
    in Western and Central Africa, 2289, 2289.*e1f*
    in Western and Central Europe and North America, 2289, 2289.*e1f*, 2290.*e1f*
  renal manifestations of, 2313
    end-stage renal disease, 2313
    immune complex renal disease, 2313
    nephropathy, 2313
    screening for, 2314*f*
    thrombotic microangiopathies, 2313
  replication of
    cycle, 2291–2292, 2292.*e1f*
    reverse transcription in, 2292, 2292.*e1f*
  RNA, 2292
  screening for, 55, 2297
  sexually transmitted infections and, 1880
  stages of early infection, 2296, 2297*t*
  syphilis and, 2017–2018
  systemic manifestations of, 2312–2324
Human immunodeficiency virus (HIV) *(Continued)*
  testing strategies, 2296, 2296*f*
  thrush in, 2090
  transcription of, 2292.*e1f*
  transmission
    modes of, 2298–2300, 2298*f*
    sexual, 2298–2299
  in travelers, 1889
  treated, 2294
  treatment of, 2297*b*
  tuberculosis and, treatment of, 2040*b*
  tubulointerstitial nephropathy in, 793
  untreated infection of, 2292–2294, 2293*f*
  virion structure of, 2291, 2291*f*
  weight loss and, 860*t*
  in women, 1609–1610
Human induced pluripotent stem cells (hiPSCs), 172, 172*f*
Human leukocyte antigen (HLA), 203
  associated with rheumatoid arthritis, 1749–1750, 1750.*e1t*
  diabetes mellitus and, 1536
  structural and functional features of, 1*t*–2*t*, 204
  two views of, 204.*e1f*
Human metapneumovirus, 2195, 2195*b*
Human microbiome, 1836–1840
  alteration of, 1837–1838, 1838*f*, 1838*t*
  definition of, 1836
  in developing precision medicine paradigm, 1840.*e2f*
  disease associations of, 1838–1840
    asthma, 1840
    C. difficile infection, 1839, 1840.*e1f*
    colon cancer, 1840
    hematopoietic stem cell transplantation, 1840
    inflammatory bowel disease, 1838–1839
    neurologic disorders, 1840
    obesity, 1838, 1839*f*
  environmental/iatrogenic factors of, 1838*t*
  establishment of, 1837, 1837*f*, 1837.*e1f*–1837.*e2f*
  host factors of, 1838*t*
  maternal factors of, 1837.*e1f*
  microbial factors of, 1838*t*
  postnatal factors of, 1837.*e1f*
  potential function of, 1838*f*
  structure and function relationships of, 1836
  studying of, 1837, 1837.*e1f*
  therapies targeting, 1840, 1840*t*
Human papillomavirus (HPV), 982
  anal cancer caused by, 2316
  cervical cancer and, 1375, 1607, 2241
  cervical carcinoma and, 2305
  characteristics of, 1881
  clinical manifestations of, 2241–2242
  definition of, 2240
  diagnosis of, 2242–2243
  epidemiology of, 2240–2241
  of esophagus, 912
  genital, 2240–2241, 2242*f*, 2244*f*
  genotypes of, 1881*b*
  head and neck cancer caused by, 1320, 2622
  human immunodeficiency virus and, 2241
  immune response to, 2241
  immunization for, 66*t*, 79
    adverse reactions of, 79
    indications for, 79
    schedule of, 76.*e1t*, 77*f*
  oncogenic risk of, 2241
  pathobiology of, 2241
  pathogen that causes, 2240
  plantar warts caused by, 2242
  prevention of, 2243–2244
  primary prevention of, 2243–2244, 2243*t*
  prognosis of, 2244
  prophylaxis for, 2309*t*
  secondary prevention of, 2244
  sexually transmitted, 1881
  treatment of, 2243*b*, 2243*t*
  vaccination for, 1376, 1884
  warts caused by, 2242
Human pluripotent stem cell lines, 174
Human polyomavirus, 2227–2228, 2228*t*
Human polyomavirus 6, 2232
Human polyomavirus 7, 2232
Human T-cell leukemia virus type 1, 2164
Human T-lymphotrophic virus (HLTV)
  -1, 2324, 2324*t*
  -2, 2324, 2324*t*
  adult-cell leukemia/lymphoma caused by, 2326
  associated diseases with, 2327*t*, 2328
  definition of, 2324–2326
  epidemiology of, 2324–2325
  pathobiology of, 2325–2326
  pathogens that cause, 2324
  prevention of, 2328
  transmission of, 2324–2325, 2324*t*
    by breast-feeding, 2324–2325
    by casual contact, 2325
    by coinfection with HIV, 2325
    by injection drug use, 2325
    sexual, 2324
    by solid organ transplantation, 2325
    by transfusion, 2325
  viral life cycle of, 2325
  virology of, 2325
Humira. *See* Adalimumab
Humoral hypercalcemia of malignancy, 1659
Humoral immunodeficiency, children with, 2261*b*
Hunt-Hess grading scale, 2477*t*
Hunter syndrome, 1724*t*
Huntington disease, 2411, 2416, 2420–2421, 2490, 2491*b*
Hurler syndrome, 1724*t*
Hutchinson sign, 2605–2606
HVG. *See* Host-*versus*-graft
Hyaline cast, 722, 724*f*
Hyaline thrombi, 1177
Hyaluronic acid capsule, 1913
Hyaluronidase, 1913–1914
Hycamptamine, 1215*t*
Hycamtin. *See* Topotecan
Hydatid cyst disease, 1025
Hydatid disease
  alveolar, 2162, 2162*b*
  cystic, 2161, 2161*b*, 2162*f*
Hydralazine, 451*t*
  for heart failure, 265*b*
  for preeclampsia, 1621*t*
Hydration
  for *E. coli*, 1963*b*
  for rhabdomyolysis, 717*b*
Hydrea. *See* Hydroxyurea
Hydrocalycosis, 819
Hydrocalyx, 819
Hydrocele, in bancroftian filariasis, 2177
Hydrocephalus, normal-pressure, 2421
Hydrochlorothiazide, 451*t*, 454
  for hypervolemia, 737*t*
Hydrocodone, 139*t*
Hydrocortisone
  for adrenocorticotropic hormone deficiency, 1493*b*
  for idiopathic pulmonary fibrosis, 576*b*
Hydrocytosis, 1094*f*, 1097
Hydrogen breath test, for malabsorption, 931*t*
Hydrogen cyanide, 88*t*
Hydrogen fluoride, 88*t*
Hydrogen ion concentration, in normal arterial blood pH, 753
Hydromorphone, 139*t*
  for erythromelalgia, 471*b*
  for frostbite, 474*b*
Hydrops fetalis, 1104, 1107*b*, 2235
Hydrostatic pulmonary edema, 566
Hydrothorax, in decompensated cirrhosis, 987
Hydroxocobalamin
  for acute poisoning, 693*t*
  for cyanide poisoning, 596*b*
α–Hydroxy acids, 2700
β-Hydroxybutyrate, e1*t*–e8*t*
γ-Hydroxybutyrate
  central nervous system effects of, 685*t*
  toxicity, 686*t*
Hydroxychloroquine, 2114
  for COVID-19, 2217
  development of, 146–147
  for malaria, 2112*t*
  ocular effects of, 2613
  for rheumatoid arthritis, 1755*b*, 1756*t*, 1757*t*
  for systemic lupus erythematosus, 1772*b*
Hydroxychloroquine, for total knee arthroplasty, 1830.*e1t*

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Hydroxydaunorubicin, 1215*t*
5-Hydroxyindole acetic acid (5-HIAA), *e1t–e8t*
11β–Hydroxylase deficiency, 1572
17α–Hydroxylase deficiency, 1571
21-Hydroxylase deficiency, 1571–1572, 1572*f*, 1593
Hydroxymethylbilane, 1429.*e1f*
17-Hydroxyprogesterone (17-OHP), *e1t–e8t*, 1593
3β–Hydroxysteroid dehydrogenase deficiency, 1571
Hydroxyurea (Hydrea), 1215*t*
  for essential thrombocythemia, 1135*b*
  for polycythemia vera, 1135*b*
  for sickle cell disease, 1114*b*
  sickle cell disease and, 1114*b*
25-Hydroxyvitamin D, 1453*t*, 1640–1641, 1648
Hydroxyzine, for mastocytosis, 1703*b*
Hymenolepis nana, 2157, 2158*t*
Hymenoptera, 522, 711
Hyoscyamine, for irritable bowel syndrome, 896*t*
Hyper-IgE syndrome, 1679*t*
Hyperacute rejection, 205, 845
Hyperaldosteronism, 746
Hyperaldosteronism, primary, 749, 1525, 1525*f*, 1525*t*
Hyperalgesia, 134
Hyperammonemia
  psychotropic medications and, 2678*t*
  severe mental illness and, 2683*t*
Hyperandrogenism, 1526, 1526*b*
Hyperbaric oxygen, 596*b*, 693*t*
Hyperbilirubinemia
  approach to, 995
  conjugated, 996, 997*t*
  definition of, 993–995
  differential diagnosis of, 996*t*
  intramedullary hemolysis and, 1121
  mixed, 996, 997*t*
  pathobiology of, 994–995
  postoperative, 2676
  unconjugated, 996
Hypercalcemia, 1652–1662, 1654
  autoimmune hypocalciuric, 1658
  causes of, 1655–1659, 1656*t*
  chromosomal locations of, 1653*t*
  chronic interstitial nephritis caused by, 794
  clinical features of, 1654*t*
  clinical manifestations of, 1654
  definition of, 1654
  diagnosis of, 1654, 1655*f*, 1656*t*
  drugs that cause, 1659
  endocrine causes of, 1658–1659
  epidemiology of, 1654
  familial benign hypocalciuric, 1658
  granulomatous disorders causing, 1659, 1659*b*
  of malignancy, 1237, 1237*b*, 1658–1659, 1659*b*
  pancreatic neuroendocrine neoplasms, 1561*t*
  pathobiology of, 1654
  in sarcoidosis, 603*b*
  symptomatic, 1654*b*–1655*b*, 1656
  thyrotoxicosis and, 1658
  treatment of, 1654
  Williams syndrome and, 1658
Hypercalcemia, for multiple myeloma, 1299*b*
Hypercalcemic disorders, nephrolithiasis and, 805*b*
Hypercapnia, 2461
  clinical manifestations of, 645*t*
  mechanisms of, 643*t*
Hypercapnic acute respiratory failure, causes of, 643*t*
Hypercapnic disease, 534, 535*t*
Hyperchloremic acidosis, 752*b*
Hyperchloremic metabolic acidoses, 753*t*, 760–762, 760*f*
  of nonrenal origin
    with hypokalemia, 760
    with normal or increased potassium level, 760
  of renal origin, with hyperkalemia, 761–762
Hypercholesterolemia, familial, 160, 1398*t*, 1408
  cascade screening for, 1409
  clinical manifestations of, 1408
  combined, 1409
  diagnosis of, 1409
  epidemiology of, 1408
  pathobiology of, 1408
  in pregnancy, 1409*b*
  prognosis for, 1409
  screening for, 1409
  treatment of, 1409*b*, 1409*t*
Hypercoagulable states, 475–482, 475.*e3f*, 2315
  evaluation of, 1166*t*, 1170, 1170*t*
  primary, 475–478, 475*t*, 476
    clinical manifestations of, 476–477, 476*t*, 477*t*
    diagnosis of, 477–478, 477*f*
    treatment of, 478*b*
  secondary, 478–482
    causes of, 479*t*
    definition of, 478
    prevention of, 480
    prognosis of, 480
    treatment of, 479*b*
Hypercortisolism, 1494, 1520
Hyperdynamic circulatory state, cirrhosis and, 1036, 1037*f*
Hyperemesis gravidarum, 1626, 1626*b*
Hypereosinophilic syndromes, 295–296, 296*b*, 1142, 1162
Hyperexplexia, 2495
Hyperfiltration, 795–796
Hyperfractionated radiation, for NSCLC, 1333*b*–1335*b*
Hyperfunctional neurologic disorders, 2652
Hypergastrinemia, peptic ulcers associated with, 916
Hyperglycemia, 795
  in acute pancreatitis, 971
  hypothalamic disease and, 1481
  in septic shock, 673*b*
  stroke-like symptoms associated with, 2467
Hyperglycinemia, nonketotic, 1398*t*
Hypergonadism, hypothalamic, 1481
Hypergonadotropic amenorrhea, 1600, 1600*b*
Hyperhemolytic transfusion reaction, 1203
Hyperhidrosis, 2555, 2557*b*
Hyperhistaminic syndromes, 917
Hyperhomocysteinemia, 479, 479.*e1f*, 1425, 1430–1433
  clinical manifestations of, 1425
  definition of, 1425, 1425.*e1f*
  diagnosis of, 1425*t*, 1426, 1426*t*
  epidemiology of, 1425
  pathobiology of, 1425, 1425*t*, 1425.*e1f*
  prevention of, 1427
  prognosis of, 1427
  treatment of, 1123*b*, 1427*b*
Hyperimmunoglobulin E syndrome, 1680, 1680*b*
Hyperimmunoglobulin M syndromes, 1681–1682, 1681*t*, 1686*t*
Hyperimmunoglobulinemia D with periodic fever syndrome (HIDS), 1731*t*, 1733–1734
  clinical characteristics of, 1733*t*
  clinical manifestations of, 1734
  prognosis for, 1734*b*
  treatment of, 1734*b*
Hyperinfection syndrome, 2173
Hyperinflation, dynamic, 654
Hyperinsulinemia, 1465
Hyperinsulinemic euglycemic therapy, for acute poisoning, 693*t*
Hyperinsulinemic hypoglycemia, 1552*t*
Hyperkalemia
  causes of, 750*t*
  in chronic kidney disease, 836
  chronic treatment of, 751*b*
  clinical manifestations of, 748
  definition of, 745
  disorders associated with, 750–751
  electrocardiographic manifestations, 748*f*
  emergent treatment of, 751*b*
  in hospitalized patients, 752
  hyperchloremic acidosis with, 761
  hypertensive syndromes, 751
  hypotensive syndromes, 750–751
  mortality associated with, 752
  normotensive syndromes, 750
  prognosis for, 752
  renin-angiotensin system inhibitors and, 453
  treatment of, 751*b*, 839*b*
Hyperkalemic periodic paralysis, 752*b*, 2583.*e1t*, 2585
Hyperlipidemia
  description of, 121
  in nephrotic syndrome, 777
  secondary cause of, 1408, 1408*t*
Hyperlipoproteinemia, 1823
Hyperlucent lungs, 565
Hypermagnesemia, 767, 767*b*
Hypermetabolic systemic response, to injury, 699
Hypernatremia, 733*t*, 742–743
  causes of, 743*t*
  clinical manifestations of, 742, 743*t*
  diagnosis of, 742
  prognosis of, 743
  severe mental illness and, 2683*t*
  treatment for, 743*b*
Hyperopia, 2598
Hyperosmolality, correction of, 1503*b*
Hyperosmolar hyperglycemic state
  clinical manifestations of, 1547
  diagnosis of, 1548
  epidemiology of, 1547
  pathobiology of, 1547
  prevention of, 1549
  prognosis of, 1549
  treatment for, 1547*t*, 1548*b*
Hyperosmolar nutrition solutions, 1450
Hyperostosis, 1666, 1666*t*
Hyperoxaluria, primary, 803
Hyperparathyroidism, 1655
  definition of, 1655
  magnesium deficiency and, 766
  primary, 1656
    clinical manifestations of, 1656
    description of, 1654
    diagnosis of, 1656–1657
    epidemiology of, 1656
    familial, 1657
    parathyroid surgery for, 1657*t*
    parathyroidectomy for, 1657*b*
    pathobiology of, 1656
    treatment of, 1657*b*
  secondary, 1658*t*
  uremic, 1657, 1658*b*
Hyperparathyroidism-jaw tumor syndrome, 1657
Hyperphosphatemia, 768–769
  causes of, 769*t*
  clinical manifestations of, 769
  diagnostic approach to, 769*f*
  dialysis-associated, 842
  pathobiology of, 768–769
  prognosis of, 769
  treatment of, 769*b*
Hyperpigmentation, 2742*t*, 2743–2744
  circumscribed, 2744, 2744*f*
  diffuse, 2743
  hemochromatosis and, 1440
  linear and reticulated, 2744
Hyperpolarization-activated cyclic nucleotide gated channels, 300
Hyperprolactinemia, 1479
  chronic anovulation caused by, 1601
  description of, 1491, 1491*b*, 1491*t*
  hypothalamic, 1481
  psychotropic medications and, 2678*t*
  treatment of, 1603*b*
Hyperpyrexia, severe, 1851
Hypersegmented neutrophils, 1072*f*
Hypersensitivity pneumonitis, 581, 581.*e1f*, 588
  chronic, 581.*e1f*
  classification of, 571*t*
  clinical features of, 581
  clinical manifestations of, 581, 588
  diagnosis of, 581, 588
  examples of, 588*t*
  increased lymphocyte counts in, 533
  pathobiology of, 581, 588
  prognosis for, 581*b*
  prognosis of, 589*b*
  treatment of, 581*b*, 589*b*
Hypersensitivity reactions, 193–195
  diarrhea and, 940
  type I, 193–194, 193*t*, 194*f*
  type II, 193*t*, 194, 194*f*
  type III, 193*t*, 194–195, 195*f*
  type IV, 193*t*, 195, 195*f*
  types I-IV, 1672*f*
  types of, 193*t*
Hypersensitivity vasculitis, 965. *See also* Cutaneous leukocytoclastic angiitis
Hypersomnia, 2444–2446
  diagnosis of, 2444–2445
  idiopathic, 2446
Hypersplenism, neutropenia due to, 1146
Hypertension, 220
  acute poisoning and, 683
  acute severe, 457–458, 458*b*–459*b*, 458*t*, 459*f*
  adrenocorticotropic hormone and, 1493
  arterial, 444
    cardiovascular disease risk factors in, 447, 448*t*
Hypertension *(Continued)*
    clinical manifestations of, 445
    definition of, 444
    diagnosis of, 445, 446*f*
    epidemiology of, 444
    essential, 445, 448*t*
    first-line drugs for, 451
    lifestyle modification for, 450, 450*t*
    management of, 450*b*
    medical therapy for, 450
    pathobiology of, 445
    secondary causes of, 450
  in Black Americans, 456
  chronic preexisting, 1620
  diabetes mellitus and, 1550
  drug-resistant, 456, 457*f*
  echocardiographic findings, 242*t*
  with estrogen replacement, 456
  gestational, 1620
  heart failure associated with, 262
  intracerebral hemorrhage related to, 2463
  intracranial, 2383, 2383*b*
  metabolic alkalosis with, 763
  nutrition and, 60
  obesity caused by, 1465
  ocular, 2609, 2610*f*
  with oral contraceptives, 456
  porphyrias and, 1432
  postoperative, 2674
  in pregnancy, 456
  preoperative evaluation considerations, 2664
  psychotropic medications and, 2678*t*
  pulmonary, 493–501
    arterial, in HIV, 2317, 2317*b*
    assessing response to therapy in, 496*b*, 500*t*
    background therapy for, 496*b*
    clinical classification of, 493*t*
    clinical manifestations of, 494–495
    collaborative care in, 496*b*
    complications of, 355
    cystic fibrosis with, 558.*e1f*
    definition of, 493–501, 493*t*
    diagnosis of, 495–496, 495*f*–499*f*, 496*f*, 497*f*, 498*f*, 499*f*
    differential diagnosis of, 359
    epidemiology of, 493–494
    history of, 494
    invasive therapies for, 496*b*
    medical therapy for, 496*b*, 500*t*
    pathobiology of, 494, 494.*e1f*
    physical examination for, 494–495
    primary lung disease, 493*t*, 496*b*
    prognosis for, 500–501
    special populations of, 496*b*
    thromboembolic hypertension, 493*t*, 496*b*, 499.*e1f*
    treatment of, 496*b*
    with unclear and/or multifactorial mechanisms, 493*t*
    venous hypertension, 496*b*
  renal artery causing, 799
  white coat and masked, 447, 447.*e1f*
  in women, medications for, 1608*t*
Hypertensive disorders of pregnancy, 1620–1621, 1620*b*, 1621*b*, 1621*t*
Hypertensive emergency, 35
Hypertensive encephalopathy, 458
Hypertensive nephrosclerosis, 839
Hypertensive peristalsis, 909
Hyperthermia, 34, 681–682
  acute poisoning and, 683
  malignant, 678, 715, 717*b*
  management of, 679*t*
  therapeutic, 682
Hyperthyroidism, 1509–1519
  cardiomyopathy with, 288
  clinical manifestations of, 1509–1510, 1510*f*
  definition of, 1509–1519
  diagnosis of, 1510–1512, 1510*f*, 1511*t*
  epidemiology of, 1509
  Graves disease and, 1472
  hypertension and, 450
  pathobiology of, 1506*t*, 1509
  subclinical, 1511*b*
  sustained, 1506*t*
  transient, 1506*t*
  treatment for, 1504.*e1f*, 1511*b*, 1511*t*
Hypertonic hyponatremia, 740
Hypertonic saline, for drowning, 592*b*
Hypertrichosis, 2751

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Hypertriglyceridemia, 1414, 1414*b*
  in acute pancreatitis, 971
  cause of, 1408
  diagnosis of, 1414
  drug therapy for, 1414*b*
  fasting, 1466
  severe, 1410
  statin therapy for, 1414*b*
  treatment of, 1410.*e1t*, 1414*b*
Hypertrophic cardiomyopathy, 281.*e1f*, 282
  apical, 281.*e1f*
  clinical manifestations of, 281
  definition of, 279
  diagnosis of, 281–282
  diagnostic criteria for, 282, 284*t*
  diagnostic testing of, 281
  echocardiographic findings, 281, 281.*e2f*
  epidemiology of, 279
  heart failure due to, 265*b*
  interventional therapy for, 282*b*
  management of, 283*f*
  medical therapy for, 282*b*
  pathobiology of, 279–281
  pathology of, 280–281
  pathophysiology of, 281
  prognosis for, 284, 284.*e1f*
  progressive, 281.*e2f*
  symptomatic management, 282*b*
  treatment of, 282*b*
  ventricular tachycardia in, 337
Hypertrophic gastritis, 913
Hypertrophic lichen planus, 2708
Hypertrophic obstructive cardiomyopathy, 282*f*
Hypertrophic osteoarthropathy, 1823, 1824*f*
Hyperuricemia, 1810–1813, 1810
  asymptomatic, 1811
  genetic causes of, 1811*t*
  nongenetic causes of, 1810*t*
  treatment of, 265*b*
Hyperuricosuria, 804
Hyperventilation
  vertigo and, 2646
  vital signs in, 34
Hyperviscosity symptoms, 355*b*
Hyperviscosity syndrome, 1303, 1303*b*, 1304*f*
Hypervolemia, 735–736, 735*t*
  clinical manifestations of, 736
  diagnosis of, 736
  pathobiology of, 735–736
  treatment for, 736*b*
Hypervolemic hypernatremia, 733*t*, 743
Hypervolemic hyponatremia, 733*t*, 741, 741*b*
Hyphae, 2093
Hyphema, 2603, 2604*f*
Hypnogram, 2443, 2444*f*
Hypnopompic hallucinations, 2446
Hypnotics, for insomnia, 2450*b*
Hypoadrenalism, 739
Hypoalbuminemia
  in nephrotic syndrome, 777
  postoperative, 2676
Hypoaldosteronism, 1529
  primary selective, 750, 750*t*
Hypocalcemia, 1652, 1659
  acute, 1659*b*
  in acute pancreatitis, 971
  causes of, 1658*t*, 1660–1662
  chromosomal locations of, 1653*t*
  chronic, 1659*b*
  clinical manifestations of, 1659, 1659*t*
  definition of, 1659
  diagnosis of, 1659, 1660*f*
  pathobiology of, 1659
  rhabdomyolysis and, 716
  treatment of, 1659*b*
Hypocapnia, 2461
  pulmonary embolism and, 487*b*
Hypochlorhydric acidosis, 760
Hypochondriasis, 2683
Hypochromia, 1067*f*
Hypocomplementemic urticarial vasculitis, 1798, 1798*b*, 2715
Hypodynamic variables, normal values, 677*t*
Hypofunctional neurologic disorders, 2652
Hypogammaglobulinemia
  arthritis associated with, 1822
  with B cells, 1681–1682
  immunization for, 65*t*
Hypoglycemia, 1545, 1551–1558
  causes of, 1552*t*, 1553–1555
Hypoglycemia *(Continued)*
  changes during fasting, 1552
  changes during feeding, 1552
  clinical manifestations of, 1546, 1546*t*, 1553
  counter-regulatory hormonal responses to, 1552, 1554*f*
  definition of, 1551–1558
  diagnosis of, 1546, 1546*t*, 1552*t*, 1555–1557, 1556*f*
  drug-and toxin-induced, 1552*t*, 1555, 1555*t*
  due to defects in gluconeogenesis, 1555
  due to defects in hepatic glycogen release/storage, 1555
  due to hormone deficiency, 1555
  epidemiology of, 1545, 1551, 1552*t*
  genetic studies for, 1557
  glycogen storage disease *versus*, 1416
  iatrogenic, 1546, 1546*t*
  insulin factitious, 1554
  metabolic diseases of, 1555
  nocturnal, 1546
  non-insulinoma pancreatogenous, 1554
  pathobiology of, 1545–1546, 1551–1553, 1553*f*
  prevention of, 1546
  prognosis of, 1546, 1558
  radiologic investigations of, 1557
  risk factors for, 1545*t*
  stroke-like symptoms associated with, 2467
  symptoms of, 1553
  treatment for, 1546*b*
  treatment of, 1557*b*
  tumor-associated, 1237, 1555
Hypogonadism, 1600
  definition of, 1582
  after hematopoietic cell transplantation, 1211
  hemochromatosis and, 1440
  hypogonadotropic, 1496, 1496*b*, 1573, 1584
    causes of, 1583*t*
    clinical manifestations of, 1584
    congenital, 1584
    diagnosis of, 1584–1585
    history of, 1584–1585
    laboratory studies in, 1584–1585
    physical examination of, 1584
    treatment of, 1585*b*
  hypothalamic, 1480–1481
  male, 1582–1585
    androgen preparations for, 1586*t*
    definition of, 1582–1585
    epidemiology of, 1582
    in HIV, 2318
    pathobiology of, 1583–1584
    testosterone delivery systems for, 1585*b*
    treatment of, 1585*b*
  primary testicular, 1583, 1583*t*
  systemic diseases associated with, 1584
Hypogonadotropic disorders, acquired, 1584
Hypogonadotropic hypogonadism, 1496, 1496*b*, 1573, 1584
  causes of, 1583*t*
  clinical manifestations of, 1584
  congenital, 1584
  diagnosis of, 1584
  history of, 1584
  isolated, 1601
  laboratory studies in, 1584
  physical examination of, 1584
  treatment of, 1585*b*
Hypokalemia
  causes of, 749, 749*t*, 750*f*
  clinical manifestations of, 747–748
  definition of, 745
  disorders associated with, 749–750
  electrocardiographic manifestations, 748*f*
  in Gitelman syndrome, 817*b*
  hyperchloremic metabolic acidoses with, 760
  hypertensive syndromes, 749
  hypomagnesemia and, 747
  hypotensive syndromes, 749–750
  mortality associated with, 752
  prognosis for, 752
  treatment of, 751*b*
Hypokalemic alkalosis, 749
Hypokalemic periodic paralysis, 751–752, 752*b*, 2583.*e1t*, 2585
Hypomagnesemia, hypokalemia and, 747
Hypomyelination, 2498
Hyponatremia, 733*t*, 738–742
  causes of, 739–740
  cirrhosis and, 1038
  clinical manifestations of, 738*t*, 740–741
  definition of, 738, 738*t*
  diagnosis of, 740, 740*f*
  epidemiology of, 738
  hypervolemic, 741
  hypovolemic, 741
  mechanisms of, 738*t*
  normovolemic, 741
  pathobiology of, 738–740, 738*t*
  prognosis of, 742
  psychotropic medications and, 2678*t*
  severe mental illness and, 2683*t*
  treatment of, 741*b*, 742*f*, 1040*b*
Hypoparathyroidism, 1658*t*, 1660–1661, 1823
  acquired forms of, 1660–1661
  autoimmune acquired, 1661
  in autoimmune polyglandular syndromes, 1560
  clinical manifestations of, 1662*t*
  complex syndromes associated with, 1661
  inherited of, 1661
  isolated, 1660–1661
  polyglandular autoimmune, 1661
  treatment of, 1661*b*
Hypoperfusion, 661
  epidemiology of, 770, 771*f*
Hypopharynx, 1320, 1320*f*, 2648
  cancer, 1322, 1325*t*, 1327*b*
Hypophosphatemia, 767–768
  cardiomyopathy with, 288
  causes of, 767*t*
  clinical manifestations of, 768
  diagnosis of, 768
  diagnostic approach to, 768*f*
  pathobiology of, 767–768
  prognosis of, 768
  treatment of, 768*b*
  X-linked, 1648
Hypophosphatemic rickets, 816*t*
Hypophysiotropic hormones
  corticotropin-releasing hormone, 1477
  functions of, 1476–1478
  gonadotropin-releasing hormone, 1476
  growth hormone-releasing hormone, 1477
  prolactin inhibitory factor, 1477–1478
  prolactin-releasing factor, 1478
  somatostatin, 1477
  thyrotropin-releasing hormone, 1476, 1477*f*
Hypophysitis, 1483
  clinical manifestations of, 1484
  diagnosis of, 1484
  empty sella causing, 1486, 1486*f*
  epidemiology of, 1483
  pathobiology of, 1483
  prognosis for, 1485*b*
  treatment of, 1485*b*
Hypopigmentation, 2742–2743, 2742*t*
  circumscribed, 2743
  congenital causes of, 2743
  guttate, 2743, 2743*f*
  linear, 2743
Hypopituitarism, 1482–1486
  acquired causes of, 1483*t*
  chronic anovulation caused by, 1601
  clinical manifestations of, 1483
  congenital causes of, 1483*t*
  diagnosis of, 1483
  epidemiology of, 1482–1483
  hormonal replacement therapy for, 1485*t*
  hypophysitis causing, 1483
  pathobiology of, 1482
  pituitary apoplexy causing, 1485, 1485*t*, 1486*b*, 1486*t*
  treatment of, 1483*b*
Hypopnea, 639
Hypotension
  acute pancreatitis and, 970
  acute poisoning and, 683
  in bacterial meningitis, 2515*b*
  intracranial, 2383, 2384*b*, 2384*f*
  orthostatic
    description of, 306
    psychotropic medications and, 2678*t*
  postoperative, 2675
  shock and, 660
Hypotensive transfusion reactions, 1202
"Hypothalamic" amenorrhea, 1480
Hypothalamic anorexia, 1481
Hypothalamic chronic anovulation, 1601
Hypothalamic hypergonadism, 1481
Hypothalamic hyperprolactinemia, 1481
Hypothalamic hypogonadism, 1480
Hypothalamic obesity, 1481
Hypothalamic-pituitary-adrenal (HPA) axis, 145, 1526–1527
Hypothalamic pituitary axis, 1483
Hypothalamic-pituitary axis, 1478
Hypothalamic-pituitary function, 1581–1582
Hypothalamic-pituitary-gonadal axis, 1580*f*
Hypothalamic-pituitary-ovarian axis, 1596*f*
Hypothalamic-pituitary thyroid axis, 1505, 1505.*e1f*
Hypothalamic-pituitary unit, failure of, 1601
Hypothalamic-pituitary axis, 2665
Hypothalamus
  disease of, 1478–1480
    congenital embryopathic disorders, 1478
    etiology of, 1479*t*
    gonadotropins affected by, 1480
    growth hormone affected by, 1480
    infiltrative, 1479–1480
    inflammatory, 1479
    irradiation affected by, 1480
    Langerhans cell histiocytosis, 1480, 1480*f*
    midline cleft syndromes, 1478
    optic nerve hypoplasia, 1478–1479
    on other neurometabolic functions, 1481
    pituitary function affected by, 1480–1481
    prolactin affected by, 1481
    sarcoidosis, 1479–1480
    thyroid-stimulating hormone affected by, 1476, 1481
    trauma and, 1480
    vascular, 1480
  dysfunction of, 1478
  lesions of, 1527
  neuroendocrine organization of, 1476*f*
  tumors of, 1479
Hypothermia, 34, 680, 681*f*
  acute poisoning and, 683
  stages and associated clinical manifestations of, 681*t*
  therapeutic, 681
  trauma, 681
  treatment of, 681*t*
Hypothermia thermometer, 33
Hypothermic syndromes, 681
Hypothesis testing, 36–37, 36*t*
Hypothyroidism, 739, 1465, 1506–1509, 2665
  cardiomyopathy with, 288
  central, 1497, 1497*b*
  clinical manifestations of, 1507
  definition of, 1506*t*
  diagnosis of, 1507–1508, 1508*f*
  epidemiology of, 1507
  Hodgkin lymphoma and, 1293*t*
  in older adults, 114
  overt, 1505, 1508*b*
  pathobiology of, 1506*t*, 1507
  primary, 1506–1507
  prognosis of, 1509
  subclinical, 1505, 1508*b*
  treatment for, 1508*b*, 1508*t*
Hypotonic hyponatremia, 740
Hypoventilation
  in acute respiratory failure, 643
  nocturnal, 619
  vital signs in, 34
Hypoventilation syndromes, 534–537, 534*t*, 535*f*, 535*t*
  acquired hypoventilation syndrome, 536
  central congenital hypoventilation syndrome, 534
  Cheyne-Stokes breathing, 534, 534*b*
Hypovolemia, 735
  absolute, 735*b*, 735*t*
  causes of, 735*t*
  clinical manifestations of, 735
  diagnosis of, 735
  relative, 735*t*
  signs of, 882
  treatment for, 735*b*
Hypovolemic hypernatremia, 733*t*, 743
Hypovolemic hyponatremia, 733*t*, 741
  treatment of, 741*b*
Hypovolemic shock, 658, 658–659, 659*f*, 661*t*

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Hypoxemia
and alveolar-arterial oxygen gradient, 639, 639*t*
clinical manifestations of, 645*t*
improving, methods for, 647*b*
mechanisms of, 643*t*
postoperative, 2675
pulmonary embolism and, 487*b*
severe mental illness and, 2683*t*
Hypoxemic acute respiratory failure, causes of, 643*t*
Hypoxemic respiratory failure, 596
Hypoxia, 595
ambient, 1075
tissue, 671
Hypoxia-induced factor (HIF) 1α, 1064
Hysterical gait, 2373*t*

I

I-cell disease, 1724, 1724*t*
IASLC. *See* International Association for the Study of Lung Cancer
Iatrogenic botulism, 1927
Iatrogenic hypoglycemia, 1546, 1546*t*
Iatrogenic interstitial lung disease, 572*t*
Iatrogenic perforation, 912
Ibalizumab, 2301*t*
for human immunodeficiency virus, 152
Ibandronate, for osteoporosis, 1644*t*
Ibrance. *See* Palbociclib
Ibrexafungerp, 2079
adverse effects of, 2079
drug interactions of, 2079
indications and dosage of, 2075*t*, 2079
mechanisms of action, 2079
Ibrutinib (Imbruvica), 1215*t*
for chronic lymphocytic leukemia, 1269*t*, 1270*t*
IBS. *See* Irritable bowel syndrome
Ibuprofen
for acute mountain sickness, 593
for chronic pain, 138*t*
for cystic fibrosis, 558*b*
for dysmenorrhea, 1596*t*
for patent ductus arteriosus, 350*b*
for pericardial constriction, 431*b*
for rheumatoid arthritis, 1756*t*
Ibutilide, 325*t*, 327*b*
ICDs. *See* Implantable cardioverter-defibrillators
Ichthyosis vulgaris, 2687.*e3t*
Iclusig. *See* Ponatinib
Icterus, 987, 987*f*–989*f*
Idarucizumab, 329*b*, 504–505
Idelalisib (Zydelig), 1215*t*
for chronic lymphocytic leukemia, 1269*t*
Ideomotor apraxia, 2408
Idiopathic and thrombotic thrombocytopenic purpura (ITP/TTP), characteristics of, 2270*t*
Idiopathic aplastic anemia, 1125
causes of, 1125*t*
clinical manifestations of, 1125
definition of, 1125–1126
diagnosis of, 1125, 1126*f*, 1127*t*
epidemiology of, 1125
pathobiology of, 1125
prognosis of, 1126
treatment of, 1126*b*
Idiopathic brachial plexitis, 2578
Idiopathic central apnea, 534*t*
Idiopathic cytopenias, of undetermined significance, 1255
Idiopathic generalized epilepsies, 2431
Idiopathic hypereosinophilic syndrome, 1162, 1163*t*
Idiopathic hypersomnia, 2446
Idiopathic megacolon, 890
Idiopathic nephrotic syndrome, 777–780, 777*t*
Idiopathic pulmonary arterial hypertension, 493
Idiopathic pulmonary capillaritis, 582
Idiopathic pulmonary fibrosis, 575
CT findings, 575.*e1f*
diagnosis criteria for, 577*t*
diagnosis of, 575–576, 576*f*
honeycombing in, 522*f*
as occupational lung disease, 585*t*
pathobiology of, 570
prognosis for, 577
radiographic features of, 574*t*
treatment of, 576*b*
Idiopathic pulmonary hemosiderosis, 582
Idiopathic thrombocytopenic purpura, 65*t*, 1770
Idiopathic tumoral calcinosis, 1815
Idiosyncratic hepatotoxicity, 1019
causes of, 1020*t*
clinical manifestations of, 1019*t*, 1019.*e1f*, 1020
diagnosis of, 1020–1021, 1021*t*
epidemiology of, 1019
factors that predispose to, 1020*t*
pathobiology, 1019–1020, 1019.*e1f*, 1020*t*
prevention of, 1021
prognosis of, 1021
treatment for, 1020*b*
Idioventricular rhythm, accelerated, 384*b*
Iduronate-2-sulfatase, for mucopolysaccharidosis type II, 1420*t*
α-l-Iduronidase, for mucopolysaccharidosis type I, 1420*t*
Ifex. *See* Ifosfamide
IFN-γ receptor 1 deficiency, 1686*t*
IFN-γ receptor 2 deficiency, 1686*t*
IFNL3 gene, 160*t*
Ifosfamide (Ifex), 1215*t*
cardiomyopathy due to, 288
IgA nephropathy. *See* Immunoglobulin A nephropathy
IgA vasculitis. *See* Immunoglobulin A (IgA) vasculitis
IgE. *See* Immunoglobulin E
IgE antibody, 193*t*
IGF-I. *See* Insulin-like growth factor-I
IgG4-related disease, 1288
IGNITE, 169.*e1t*
IGRA. *See* Interferon-gamma release assay
IL-1. *See* Interleukin-1
IL-1β. *See* Interleukin-1β
IL-2. *See* Interleukin-2
IL-4. *See* Interleukin-4
IL-5. *See* Interleukin-5
IL-6. *See* Interleukin-6
IL-12. *See* Interleukin-12
IL-13. *See* Interleukin-13
IL-17. *See* Interleukin-17
IL-23. *See* Interleukin-23
Ileal disease, 934
Ileal function, tests for, 931*t*
Ileitis, differential diagnosis of, 944*t*
Ileocecal syndrome, description of, 1860
Iliac artery endofibrosis, 467, 468*b*
Iliopectineal bursitis, 1746
Iliopsoas bursitis, 1746, 1747*b*
Iliotibial band syndrome, 1747, 1747*b*
Illness anxiety disorder, 2346, 2347*t*, 2683
Iloperidone, for psychotic disorders, 2346*t*
Iloprost, 468*b*, 473*b*
Imaging
cardiac, noninvasive, 244
myocardial perfusion, 248–249, 248*f*
pharmacologic stress myocardial perfusion, 248
speckle tracking strain imaging, 236, 236.*e1f*
of ventricular function, 249
Imatinib (Gleevec), *e10t*–*e11t*, 1215*t*, 1251*t*
for chronic myeloid leukemia, 1275*t*
for eosinophilic syndromes, 1164*b*
Imbruvica. *See* Ibrutinib
Imfinzi. *See* Durvalumab
Imidazole. *See* Ketoconazole
Imipenem, 1845*t*
for anthrax exposure, 97*b*
dosage of, 1895*t*
for nontuberculous mycobacterial disease, 2046*t*
for pneumonia, 613*t*
for *Stenotrophomonas maltophilia*, 1975*b*, 1976*t*
Imipenem-relebactam, dosage of, 1895*t*
Imipramine, for depression, 2340*t*
Imipramine + desipramine, *e10t*–*e11t*
Imiquimod, 2700
for anal warts, 982*b*
for coronavirus infections, 2191
Immature platelet fraction (IPF), *e8t*–*e9t*
Immature reticulocyte fraction (IRF), *e8t*–*e9t*
Immediate memory, 2407
Immobilization, thrombosis and, 481–482
Immune adherence or C4*b*/C3*b* receptor, 200*t*
Immune cells, 670
Immune checkpoint inhibitors, thyroiditis caused by, 1514
Immune complex glomerulonephritis, pneumonia with, 784*t*
Immune complex-mediated vasculitides, 1793, 1798
Immune complex rapidly progressive glomerulonephritis, 785
Immune complex renal disease, HIV-associated, 2313
Immune dysfunction, in chronic lymphocytic leukemia, 1267
Immune dysregulation syndromes, 1684–1685, 1684*t*
clinical manifestations of, 1685
diagnosis of, 1685
epidemiology of, 1684–1685
leading to colitis, 1684*t*
pathobiology of, 1684–1685
prognosis of, 1685
in systemic sclerosis, 1776
treatment of, 1685*b*
Immune globulin, defects of, 1680
clinical manifestations of, 1680
diagnosis of, 1682
epidemiology and pathobiology of, 1680, 1681*t*
prognosis of, 1682
treatment of, 1682*b*
Immune-mediated myocarditis, 286
Immune-mediated necrotizing myopathy, 1787, 1788, 1788*t*, 1790*t*
Immune-mediated thrombocytopenia, 1179
Immune neutropenia, 1146
Immune reconstitution inflammatory syndrome (IRIS), 2308, 2311*b*, 2312, 2312*t*
description of, 2088*b*
Immune-related adverse events, 1823
Immune response
to amebic infection, 2146
of COVID-19, 2212
innate, 670
Immune system
adaptive, 182
cell differentiation of, 189
effector mediators of, 189
pathogenesis of disease and, 191
principles of activation of, 187
signaling pathways of, 189
age-related changes in, 121
cells of, 182
components of, 1852*t*
evaluation of, approach to, 1676, 1677*f*, 1677*t*
in host defense, 182
innate, 182
activation of, 183–186
cell differentiation of, 185–186
cellular elements of, 182–183
effector mediators of, 185
localization of cells, 186
pathogenesis of disease and, 191
recognition receptors and triggers of, 183–186
role of, 186
signaling pathways of, 185
soluble products of, 185–186
transition to adaptive immune response, 186
in wound repair, 185*f*, 186
measles suppression of, 2220
overreactions of, 193
Immune therapies, for skin diseases, 2700–2701
Immune thrombocytopenic purpura (ITP), 1066, 1175, 1176*t*
Immune tolerance, 207
Immunity
adaptive, 671
inborn errors of, 1676
innate, 2108–2109
Immunization, 64–84. *See also* Vaccinations
active, 64
for adult, 66*t*, 76.*e1t*, 76.*e4t*
adverse reactions of, 76
altered immunocompetence in, 76, 76.*e2t*
for anthrax, 83
for chickenpox, 82
for cholera, 83
contraindications and precautions to, 75–76
for COVID-19, 77
for Ebola, 84
general characteristics of, 64–77
general considerations for, 76, 76.*e2t*, 77*f*, 78*f*
Haemophilus influenzae type b vaccine, 78
Immunization *(Continued)*
for heart failure, 275*t*
for hepatitis A, 79
adverse reactions of, 79
indications for, 79
for hepatitis B, 79
adverse reactions of, 79
indications for, 76.*e1t*, 77*f*, 79
for hepatitis B virus, 1006
for human papillomavirus, 79
adverse reactions of, 79
indications for, 79
for influenza, 79–80
adverse reactions of, 80
indications for, 79–80
for international travelers, 83
for Japanese encephalitis, 83
for measles, 80
for meningococcal disease, 80–81
adverse reactions of, 81
indications for, 80–81
for mumps, 81
passive, 64–75, 65*t*
pertussis, 1996
for pertussis, 81
for pneumococcal disease, 81
adverse reactions of, 81
indications for, 66*t*, 81
for poliomyelitis, 81–82
for possible bioterrorism agents, 83
for pregnancy, 76.*e2t*, 77
for rabies, 82
route and timing of, 75
for rubella, 82
schedule of, 76.*e1t*
for smallpox, 84
for tetanus and diphtheria, 82
for traveler
cholera, 1886*t*, 1887
description, 1885–1887
hepatitis A, 1886, 1886*t*, 1887
hepatitis B, 1886, 1886*t*, 1887
influenza, 1886*t*, 1887
Japanese encephalitis, 1886*t*, 1887
meningococcus, 1886*t*, 1887
polio, 1886*t*, 1887
rabies, 1886*t*, 1887
tetanus/diphtheria/acellular pertussis, 1886
typhoid, 1886*t*, 1887
update of, 1886–1887
varicella, 1886, 1886*t*
verification of, 1886
yellow fever, 1886*t*, 1887
for typhoid, 83
for varicella-zoster, 83
whooping cough, 1996
for yellow fever, 83
Immunocompetent donor T cells, role of, 1207
Immunocompromised hosts
adenovirus diseases in, 2205
approach to, 1852–1853
cutaneous syndromes in, 1855–1857, 1860*t*
diarrhea in, 1859
fever in, 1851, 1854*b*
gastrointestinal syndromes in, 1858–1860, 1860*t*
herpes simplex virus infections in, 2246, 2246*b*
infection in, 1851, 1854*b*
infectious syndromes in, 1860*t*
neurologic syndromes in, 1860*t*, 1861
noninfectious syndromes in, 1860*t*
parainfluenza viral diseases in, 2196
respiratory syncytial virus in, 2195
respiratory syndromes in, 1857–1858
sinopulmonary syndromes in, 1860*t*
Immunodeficiency, 191
autoinflammation, and amylopectinosis, 1731*t*
cystic fibrosis *versus*, 558
HLTV and, 2327*t*
inherited, 175
in solid organ transplant recipients, 1853
Immunoglobulin, intravenous, for autoimmune encephalitis, 2536
Immunoglobulin A (IgA), *e1t*–*e8t*
with IgG subclass deficiency, 1681*t*
Immunoglobulin A (IgA) nephropathy, 781, 783*f*
Immunoglobulin A (IgA) vasculitis, 782, 1798, 1798*b*, 2715
Immunoglobulin D (IgD), *e1t*–*e8t*
Immunoglobulin E (IgE), *e1t*–*e8t*, 1692

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Immunoglobulin G (IgG), *e1t–e8t*
antibody, 193*t*, 194
serologic tests, for toxoplasmosis, 2138*t*
subclass deficiency, 1681*t*, 1682
Immunoglobulin G4-related disease, 1825
Immunoglobulin G4-related interstitial nephritis, 793–794
Immunoglobulin-like domain-containing receptors, 183
Immunoglobulin-like killer inhibitory receptor (KIR), 183
Immunoglobulin M (IgM), *e1t–e8t*
antibody, 194
serologic tests, for toxoplasmosis, 2138*t*
Immunoglobulins
polyclonal, 1295, 1295*f*
serum, 1294
Immunologic disease, 1672
Immunologic failure, 2303
Immunologic testing, for brucellosis, 1984
Immunomodulatory drugs, 144–149, 146
azathioprine, 148
for Crohn disease, 945*b*, 946*t*
cyclophosphamide, 149
cyclosporine, 148
glucocorticoids, 144*t*
adipose tissue metabolism and, 145
bones and, 145
cardiovascular system and, 145
central nervous system and, 145
clinical use of, 145
history of, 144
inflammation and, 144
liver metabolism and, 145
monitoring of, 146
muscle metabolism and, 145
osteoporosis caused by, 145
in pregnancy, 146
tapering regimens for, 146
toxicity of, 146
withdrawal from, 146
hydroxychloroquine, 146
leflunomide, 147–148
6-mercaptopurine, 148
methotrexate, 147
mycophenolate mofetil, 147–148
for myelodysplastic syndromes, 1255
for retroperitoneal fibrosis, 1783*b*
sirolimus, 149
for skin diseases, 2700–2701
sulfasalazine, 146–147
tacrolimus, 148–149
Immunophilin-binding agents, 148
Immunoprophylaxis, for common cold, 2193
Immunosuppression
for acute kidney injury, 774*b*
Chagas disease and, 2128
for liver transplantation, 1048–1049, 1048*t*
net state of, 1853, 1853*t*
in renal transplantation, 844–845, 845*t*
reversal of, for aspergillosis, 2096
Immunosuppressive therapy, 147
for aplastic anemia, 1126*b*
for lung transplantation, 633
for myelodysplastic syndromes, 1255
for skin diseases, 2700
for systemic lupus erythematosus, 1772*b*
for systemic sclerosis, 1781*b*
Immunosuppressive therapy, warm autoimmune hemolytic anemia treated with, 1089*b*
Immunotherapy
for cancer, 1232*b*
for chronic lymphocytic leukemia, 1269*b*
for lung cancer, 1333*b*
for melanoma, 1393*b*
for rhinitis, 2634–2635
Impacted cerumen, 2641
Impaired lipolysis, 933
Impaired lymphatic drainage, 938
Impaired micelle formation, 933–934
Impaired mixing, 932
Impaired orgasm, 1590
Impetigo, 2687.*e4t*, 2720, 2739, 2739*f*
description of, 1903, 1914
Impingement syndrome. *See* Rotator cuff tendinosis
Implantable cardioverter-defibrillators (ICDs), 265*b*, 338*b*, 344
for acute STEMI, 384*b*
complications of, 345
Implantable cardioverter-defibrillators (ICDs) *(Continued)*
health care-associated infections and, 1866
indications for, 344, 344*t*
programming of, 344–345
pulse generators and leads for, 344, 344*f*, 344.*e1f*
selection of, 389*f*
Implantable electronic devices, cardiac, 340
Implantable loop recorders, 308
Impulse
conduction, disorders of, 302
formation, disorders of, 301
propagation, 300
Impulsivity, in eating disorders, 1461
IMRT. *See* Intensity-modulated radiation therapy
In vitro diagnostic multianalyte index assays, 168
In vitro fertilization (IVF), venous thromboembolism and, 481
In vivo gene therapy, 175
Inactivated hepatitis A vaccine, 66*t*
Inactivated Japanese encephalitis virus vaccine, 66*t*
Inactivated poliovirus vaccine (IPV), 66*t*, 81
Inactivated vaccine, 66*t*
Inactivated virus vaccine (IIV), 66*t*
Inborn errors of metabolism
approach to, 1398–1404
broad pathophysiologic mechanisms in, 1399*t*
characteristic signs of, 1399*t*
clinical manifestations of, 1399
definition of, 1398–1400
diagnosis of, 1399–1400, 1400*f*
epidemiology of, 1398, 1398*t*
fatty acid oxidation in, disorders of, 1404, 1404*b*
folate, 1120
micronutrients, 1452
pathobiology of, 1398–1399
protein metabolism in, disorders of, 1401–1404, 1402*t*
treatment of, 1401*b*, 1401*t*
Incidence, 35
"Incident reporting systems", 46
Incidental pulmonary nodule, as occupational lung disease, 585*t*
Incidentaloma, adrenal, 1524
Incisional hernia, 952*b*
Inclusion body myositis, 2368.*e4f*, 2564*t*, 2588*t*
clinical features of, 1788*t*
clinical manifestations of, 1789
diagnostic criteria for, 1790*t*
pathobiology of, 1787–1788
treatment of, 1790*b*
Incontinence
fecal, 865
stress. *See* Stress incontinence
urge. *See* Urge incontinence
urinary. *See* Urinary incontinence
Incontinentia pigmenti, 2550*t*
Indacaterol, 553*t*
Indapamide, 451*t*
Indels, 163
Indeterminate cell histiocytosis, 1157
Indian tick typhus, 2055*t*
Indinavir, 2301*t*, 2313
Indirect allorecognition, 205, 205*f*
Indirect euthanasia, 8*t*
Indirect hepatotoxicity, 1021, 1021*b*
Indirect magnetic resonance arthrography, 1722, 1722*f*
Individual clinician, role of, in occupational and environmental medicine, 89
Indolent systemic mastocytosis, 1703*b*
Indomethacin, for chronic pain, 138*t*
Inducible urticaria, chronic, 1687, 1690*t*
Induction therapy, in renal transplantation, 845
Industrial dusts, 88*t*
Inert gas dilution technique, 530
Infantile botulism, 1927, 2565
Infantile cystinosis, 816
Infantile febrile mucocutaneous lymph node syndrome, 965
Infants
with cystic fibrosis, 557
of diabetic mothers, 1464
micronutrient requirements for, 1452
Infection(s)
acute pancreatitis and, 970, 970*t*
of black skin, 2738–2742
blood cultures for, 1834
cancer and, 1245
cerebrospinal fluid testing for, 1835
chlamydial, in adolescents, 112
in chronic diseases, 1834–1836
in chronic lymphocytic leukemia, 1267
in chronic obstructive pulmonary disease, treatment of, 649*b*
coagulation response to, 671
and control, 2272
definition of, 1833
diagnosis of, 1834–1836
dialysis-associated, 843
early, 670
emerging, 1833–1834
in endoscopy, 876*t*
esophageal, 911–912
bacterial esophagitis in, 912
candidiasis in, 911, 912*f*
cytomegalovirus in, 912
herpes simplex virus in, 911
human papillomavirus in, 912
genetic susceptibility and response to, 1834
health care-associated, 1862
after hematopoietic cell transplantation, 1211
host reaction to, 1833
in immunocompromised host, 1851
clinical manifestations of, 1854
definition of, 1851
diagnosis of, 1854
general concepts of, 1851
treatment of, 1854*b*
in joints, 1717*t*
after lung transplantation, 633
microbiology testing of, 1834
nature of, antimicrobial therapy for, 1842
neutrophilia and, 1140–1141
occupational, 86*t*
parasitic, 515*t*
primary testicular hypogonadism caused by, 1583
prophylaxis for, 700*b*
pulmonary
and bronchiectasis, 560
pathogens and empirical therapy for, 2526*t*
Staphylococcus aureus causing, 1904
treatment of, 1970*b*
renal transplantation and, 846–847, 846*f*
respiratory specimen testing for, 1835–1836
sickle cell disease, 1114
stool testing for, 1836
treatment of, for cystic fibrosis, 558*b*
trematode, 2163–2168
urine testing for, 1836
Infection, periprosthetic joint, 1829
Infection-related neutropenia, 1145
Infections, extrapulmonary, legionellosis and, 1998
Infectious diseases
diagnostic testing for, 1834
historical description of, 1833
in pregnancy, 1627–1628
Infectious Diseases Society of America, guidelines for outpatient therapy for pneumonia, 612*t*
Infectious endocarditis, neurologic complications of, 2530, 2530*b*
Infectious enterocolitis, abdominal pain and, 854*t*
Infectious eruptions, 2712–2713
molluscum contagiosum, 2712–2713, 2713*f*
warts, 2713
Infectious myelopathy, 2406, 2406*b*
Infectious neuropathies, 2577–2578
Infectious pericarditis, 424*t*, 431–432
Infectious sacroiliitis, 1718, 1719*f*
Infectious sinusitis, 2631
Infectious thyroiditis, 1514, 1514*b*
Infective dermatitis, 2327*t*
Infective endocarditis, 413
causative organisms of, 415–416
clinical manifestations of, 414–415
complications of, 417*b*
definition of, 413–423
diagnosis of, 415–417, 415*t*
echocardiography in, 416, 418*f*
epidemiology of, 413–414
Infective endocarditis *(Continued)*
health care-associated, 414
history in, 414
incidence of, 413
laboratory findings of, 416
microbiology of, 415–416
modified Duke criteria for, 415, 415*t*
pathobiology of, 414
physical examination of, 414–415
predisposing conditions associated with increased risk of, 413*t*
prevention of, 422–423, 422*t*
prognosis of, 423
surgery for, 417*b*
Inferior petrosal sinus sampling, 1494, 1523–1524
Inferior vena cava filters, 487*b*
Infertility, 1580–1590
definition of, 1586
epidemiology of, 1586
female, 1602–1603
causes of, 1603*t*
definition of, 1602–1603
diagnosis of, 1602–1603
treatment of, 1603*b*
after hematopoietic cell transplantation, 1211
Hodgkin lymphoma and, 1293*t*
human immunodeficiency virus and, 2318
male, 1586
algorithm for, 1587*f*–1588*f*, 1588*f*
basic laboratory tests for, 1589*t*
clinical manifestations of, 1586
diagnosis of, 1586
treatment of, 1586*b*–1587*b*
pathobiology of, 1586
Infigratinib (Truseltiq), 1215*t*
Infiltrate, 520
Infiltrative cardiomyopathies, 249
Infiltrative disease, ventricular tachycardia in, 337
Inflamed eye, 2599, 2599*t*
Inflammasome, 183, 1735
Inflammation, 191
acute phase response, 1712
blood markers of, 220
glucocorticoids and, 144
markers of, 1712
in osteoarthritis, 1738
resolution of, 196, 196*f*
in sepsis, 670, 670.*e1f*–670.*e2f*
in systemic sclerosis, 1776
Inflammatory arthritis, pathobiology of, 1826, 1826*f*
Inflammatory bowel disease, 941–950
5-aminosalicylate for, 945*b*, 946*t*
antibiotics for, 945*b*
arthritis associated with, 1821
clinical manifestations of, 942–943
definition of, 941
diagnosis of, 943–945
diagnostic evaluation of, 943–945
differential diagnosis of, 944*t*
endoscopic evaluation of, 943
epidemiology of, 941
extraintestinal complications of, 943
extraintestinal manifestations of, 943, 943*t*
follow-up for, 945*b*
genetics of, 942
human microbiome and, 1838
laboratory findings in, 945
medical therapies for, 945*b*, 946*t*
nonsteroidal anti-inflammatory drugs and, 941
pathobiology of, 941–942
pathology of, 942
pathophysiology of, 942
physical examination of, 943
pregnancy in, 945*b*
prognosis for, 950
radiology of, 945
serologic markers of, 945
susceptibility gene in, 942
symptoms of, 943
treatment of, 945*b*
Inflammatory bowel disease-undetermined, 941
Inflammatory colitis, *E. coli* and, 1963
Inflammatory diarrhea, 924, 930*f*, 931, 940
Inflammatory disease, ventricular tachycardia in, 337
Inflammatory lung disorder, occupational and environmental, 86*t*
Inflammatory mediators, 183

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Inflammatory muscle diseases, 2587
Inflammatory myelopathy, 2406, 2406*b*
Inflammatory myopathies, 1787–1791, 2587.*e1t*, 2588*t*
  classification of, 1788*t*
  clinical manifestations of, 1788–1789
  definition of, 1787–1791
  diagnosis of, 1788
  diagnostic criteria for, 1790*t*
  epidemiology of, 1787
  pathobiology of, 1787–1788
  pathology of, 1789*f*
  prognosis for, 1791
  treatment of, 1790*b*, 1791*f*
Inflammatory myositis, 2260, 2260*b*
Inflammatory response
  adaptive, 192
  innate, 191–192, 192*f*
Inflammatory retiform purpura, 2715*t*, 2716, 2716*f*
Infliximab
  description of, 150, 151*t*
  for inflammatory bowel disease, 945*b*, 946*t*
  for rheumatoid arthritis, 1756*t*
  for sarcoidosis, 603*b*, 604*t*
Infliximab (Remicade), for total knee arthroplasty, 1830.*e1t*
Influenza, 2198–2203
  antigenic variation of, 2198–2199
  antiviral therapy for, 2189, 2189*t*
    amantadine, 2189
    baloxavir marboxil as, 2189
    oseltamivir as, 2189
    peramivir as, 2189
    rimantadine, 2189
    zanamivir as, 2189
  characteristics of, 2270*t*
  clinical manifestations of, 2200–2201
  definition of, 2198–2203, 2198.*e3t*
  diagnosis of, 2201
  epidemic, 2199
  epidemiology of, 2198–2199
  genetic variation of, 2198
  health care-associated infections and, 1865
  immunization for, 66*t*, 79
    adverse reactions of, 80
    indications for, 79
    schedule of, 76.*e1t*, 77*f*
  intrapandemic, 2199
  medications for chemoprophylaxis in, 2202, 2203*t*
  nonrespiratory complications of, 2200–2201
  pandemic, 2199
  pathobiology of, 2199–2200
  pathogen that causes, 2198, 2198.*e4f*, 2198.*e3t*
  precautions for, 2202
  prevention of, 2201–2202
  prognosis of, 2203
  respiratory complications of, 2200
  seasonal, 541*b*
  syndrome of, 2200, 2201*t*
  in travelers, 1889.*e1t*
  treatment for, 2201*t*, 2202*b*, 2203*t*
  vaccination, 2201–2202, 2201*t*, 2202.*e1t*
    prevention of, 555
    for traveler, 1886*t*, 1887
  virus structure, 2198.*e4f*
  zoonotic, 2199
Influenza A virus, 2198
  in acute bronchitis and tracheitis, 605
  antigenic subtypes of, 2198.*e3t*
  prophylaxis for, 2309*t*
  proteins of, 2198.*e3t*
Influenza B virus, 2198, 2309*t*
Influenza C virus, 2198
Influenza D virus, 2198
Information sharing, Ask-Tell-Ask, 12, 16*t*
Information technologies, advances in, 40
Informed consent, 5, 6*t*
Infradian rhythms, 1478
Infrapatellar bursa, 1747
Infrared radiation, 88*t*
Ingrowing toenails, 2754, 2755*f*
Inguinal adenopathy, treatment of, 1241*b*
Inguinal hernia, 952
Inhalation injury, 595–596, 703.*e1f*
  carbon monoxide poisoning, 595, 596*b*
  cyanide poisoning, 596, 596*b*
  e-cigarettes/vaping, 595
  oxygen toxicity, 596, 596*b*
  smoke inhalation, 595, 595*b*
  thermal injury, 595, 595*b*
Inhalational anthrax, 1931, 1931*f*, 1932*b*
Inhaled β-agonists, 551*b*
Inhaled glucocorticoids, 551*b*
Inhalers, 541*b*, 542*f*, 543*t*, 553*t*
Inheritance, patterns of, 160
  mendelian inheritance, 160, 161*f*
  mosaicism, 162, 163*f*
  nonmendelian inheritance, 162
Inherited autoinflammatory diseases, 1731*t*
Inherited bone marrow failure syndromes, 1129–1130
Inherited platelet bleeding disorder, 1184
Inherited renal tubular disorders, 815
Inherited rhabdomyolysis, 714*t*, 715
Inhibin, 1477
Inhibin B, 1586
Initiators
  of adaptive immune response, 192
  of innate immune mechanisms, 191, 192*f*
Injectable steroid contraceptives, 1615
Injection drug users
  Clostridium novyi infection in, 1927
  HIV transmission in, 2299
  infective endocarditis in, 413–414
Injury
  classes of, 699*t*
  clinical manifestations of, 699–703, 699*f*–700*f*, 699*f*, 700*f*
  critical care of, 700*b*, 703.*e1f*
  decompression procedures for, 700*b*, 702.*e1f*
  definitive surgical care for, 700*b*
  diagnosis of, 700*b*
  early response to, 698
  early systemic response to, 698
  emotional consequences of, 704
  epidemiology of, 698–703
  at extremes of age, 704, 704.*e1t*
  fluid resuscitation for, 700*b*
  initial evaluation for, 700*b*
  initial surgical care, 700*b*
  interhospital transport for, 700*b*
  late hypermetabolic systemic response to, 699
  late local response to, 698–699
  lung, 591
  pathobiology of, 698–699
  post-resuscitation metabolic issues, 700*b*, 703.*e1f*
  prehospital care of, 700*b*
  prevention, 55
  rehabilitation of, 700*b*, 703–704
  resuscitation for, 700*b*
  special considerations in, 703–704
  transfusion for, 700*b*
  treatment for, 700*b*
Inlet patches, 913
Inlyta. *See* Axitinib
Innate immune mechanisms, 191, 192*f*
Innate immune system, 182
  activation of, 183
  cell differentiation of, 185
  cellular elements of, 182
  effector mediators of, 185
  localization of cells, 186
  pathogenesis of disease and, 191
  recognition receptors and triggers of, 183
  role of, 186
  signaling pathways of, 185
  soluble products of, 185
  in systemic lupus erythematosus, 1768.*e2f*
  transition to adaptive immune response, 186
  in wound repair, 185*f*, 186
Innate immunity
  complement in, 196
  description of, 1834
Innate immunity, diseases of, 1685–1686, 1686*t*
  clinical manifestations of, 1685–1686
  diagnosis of, 1686
  epidemiology and pathobiology of, 1685–1686
  treatment and prognosis of, 1686*b*
Inorganic dusts, 88*t*
Inorganic mercury, 103
Inotersen, for amyloidosis, 1309*b*
Inotropes, 667*b*
Insects, envenomation of, 711
  anaphylaxis caused by, 1692
Insertion, 163
Insertional tendon. *See* Achilles tendon
Insoluble lipids, 938
Insomnia, 2450
  classification of, 2450*t*
Insomnia *(Continued)*
  clinical manifestations of, 2450
  definition of, 2450
  diagnosis of, 2450
  differential diagnosis of, 2451*f*
  epidemiology of, 2450
  medications for, 2452*t*
  nonpharmacologic therapies for, 2451*t*
  pathobiology of, 2450
  prognosis of, 2450
  treatment of, 2450*b*
Inspiratory capacity (IC), 530
Inspiratory hold maneuver, 640*f*
Inspiratory reserve volume (IRV), 530
INSTIs. *See* Integrase strand transfer inhibitors
Institute of Medicine (IOM), quality aims, 44*t*
Instrumental ADLs, 117
Insulin, *e1t*–*e8t*, 1534
  aging and, 115
  continuous infusion of, 1537*b*
  endocrine diseases caused by, 1475*t*
  intermittent subcutaneous, 1537*b*
  metabolic effects of, 1535*t*
  preparations, 1538*t*
  secretion of, 121
  in septic shock, 673*b*
  for type 1 diabetes mellitus, 1537*b*
  for type 2 diabetes mellitus, 1540*b*
Insulin antibodies, for hypoglycemia, 1557
Insulin autoimmune syndrome, 1554
Insulin deficiency, treatment of, 752*b*
Insulin-dependent diabetes, 1534
Insulin factitious hypoglycemia, 1554
Insulin-glucose, for acute poisoning, 693*t*
Insulin growth factor-1, aging and, 115
Insulin-like growth factor-I (IGF-I), 1474, 1477, 1488
Insulin-receptor mutations, hypoglycemia and, 1554
Insulin resistance
  HIV causing, 2318
  obesity and, 1465
  in pregnancy, 1624
Insulin secretagogues, for type 2 diabetes mellitus, 1534.*e1f*, 1540*b*, 1541*t*
Insulinoma, 1465, 1554, 1557*b*, 1561*t*
Insulitis, 1536
Insurance coverage, 19, 19*f*, 20*f*
Integral membrane proteins
  disorders, 1419*t*–1420*t*
  function, 1093–1094
Integrase strand transfer inhibitors (INSTIs), 2300–2302, 2303*t*, 2304*t*, 2319
Integrative medicine, complementary and, 153
Integumentary system, age-related changes in, 121–122
Intensity-modulated radiation therapy (IMRT), for cancer, 1232*b*
Intensive care
  admission orders, 637, 637*t*
  coronary, 384*b*
  long-term outcomes for survivors, 636
Intensivists, 636
Intentional injuries, in adolescents, 110–111, 110*t*
β-Intercalated cells, 754
Interdisciplinary team, in hospice, 16
Interferon (IFN)
  for hepatitis B virus infections, 2181*t*, 2182*t*, 2183
  thyroiditis caused by, 1514
  type I
    in COVID-19, 2212
    systemic lupus erythematosus and, 1768
Interferon-α
  cardiomyopathy due to, 288
  for chronic hepatitis B, 1011*b*
Interferon alfa-2*b*, 2701
Interferon-β, for COVID-19, 2217
Interferon beta1*a* (Avonex, Rebif), for multiple sclerosis, 2505*t*
Interferon beta1*a* pegylated (Plegridy), for multiple sclerosis, 2505*t*
Interferon beta1*b* (Betaseron, Extavia), for multiple sclerosis, 2505*t*
Interferon-gamma release assay (IGRA), 2039
  for nontuberculous mycobacteria, 2045
Interferon-related autoinflammatory syndromes, 1731*t*
Interferonopathies, 1731*t*, 1735–1736
  Aicardi-Goutières syndrome, 1731*t*, 1735
Interferonopathies *(Continued)*
  proteasome-associated autoinflammatory syndromes, 1731*t*, 1735–1736
  STING-associated autoinflammatory syndromes, 1736
Interleukin-1 (IL-1), 151, 151*t*
Interleukin-1 (IL-1) inhibitors, in familial Mediterranean fever, 1732
Interleukin 1 receptor associated kinase 4 (IRAK4), 1686*t*
Interleukin-1-related periodic fever syndromes, 1730–1735
Interleukin-1β (IL-β), 151
Interleukin-1-beta-related disorders, 1731*t*
Interleukin-2 (IL-2), 151
Interleukin-4 (IL-4), 151
Interleukin-5 (IL-5), 151
Interleukin-6 (IL-6), 151, 151*t*, 2217
Interleukin-6 (IL-6) receptor inhibitors, for rheumatoid arthritis, 1757*t*
Interleukin-7 (IL-7) deficiency, 1676.*e3t*
Interleukin-12 (IL-12), 151
Interleukin-12 (IL-12) receptor deficiency, 1686*t*
Interleukin-13 (IL-13), 151
Interleukin-17 (IL-17), 152
Interleukin-23 (IL-23), 151
Interleukin-23 (IL-23) receptor deficiency, 1686*t*
Intermediate density lipoproteins, 1405
Intermediate life support, 313*b*
Intermediate syndromes, hereditary stomatocytosis and, 1097
Intermittent claudication, 465.*e1f*
Intermittent infusions, 1449
Intermittent mandatory ventilation, 653
Internal carotid arteries, 2465
  anatomy of, 2455, 2456*f*
  bifurcation of, 2465
  magnetic resonance angiogram of, 2456*f*
International Association for the Study of Lung Cancer (IASLC), lymph node map, 1332*f*
International Cancer Genome Consortium, 167
International League Against Epilepsy Classification of Seizures, 2427*f*
International normalized ratio (INR), *e8t*–*e9t*
International Prognostic Index, 1281
International Prognostic Scoring System, for myelodysplastic syndromes, 1257–1258, 1258*f*
International Prostate Symptom Score (IPSS), 822, 823*f*
International travelers, vaccines for, 83
Internuclear ophthalmoplegia, 2500–2501, 2619, 2620*f*
Internuclear pathways, 2617–2618
Interpersonal behavior control, 2410, 2411*f*
Interpersonal psychotherapy, for depression, 2339*t*
Interprofessional team, in critical care, 636
Interrupted pregnancy, 1604
Interrupted time-series, 37
Interstitial cells of Cajal, 887
Interstitial disorder, occupational and environmental, 86*t*
Interstitial lung disease, 570–584
  chest radiograph in, 573, 573*t*
  classification of, 571*t*
  clinical manifestations of, 570–571
  connective tissue disease and, 571*t*, 580
  definition of, 570–575
  diagnosis of, 571–575, 572*f*
  drug-induced, 572*t*, 582
  epidemiology of, 570
  exercise testing for, 574
  forms of, 571*t*, 582–583
  high-resolution computed tomography in, 574
  history in, 572*f*
  iatrogenic, 572*t*
  incidence of, 570
  inherited disorders associated with, 583–584
  inherited forms of, 571*t*
  invasive evaluation of, 574–575
  laboratory testing for, 573
  noninvasive evaluation of, 573–574
  occupational, 582
  pathobiology of, 570
  physical examination for, 573
  prevalence of, 570
  pulmonary function tests for, 574
  pulmonary vasculitis and, 571*t*, 582
  respiratory bronchiolitis-associated, 574*t*, 577, 578*b*, 578*f*

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Interstitial lung disease *(Continued)*
in systemic sclerosis, 1779–1781, 1780, 1781*b*
treatment of, 575*b*, 575*t*
types of, 575–584
Interstitial nephritis, 790–795
acute
biopsy of, 792, 792*t*, 793*f*
causes of, 790*t*
characteristics of, 790
clinical manifestations of, 792, 792*t*
diagnosis of, 792
differential diagnosis of, 792
drugs that cause, 790
epidemiology of, 790
granuloma formation in, 792
prognosis for, 793
proteinuria in, 792
treatment of, 792*b*
characteristics of, 790
chronic
analgesics causing, 793
cadmium toxicity causing, 794
causes of, 791*t*, 793
characteristics of, 790
clinical manifestations of, 793
diagnosis of, 793
granuloma formation in, 792
hypercalcemia causing, 794
lead toxicity causing, 794
myeloma causing, 794
obstruction causing, 794
pathology of, 791
primary, 790
vascular disease causing, 793
definition of, 790–792
diagnosis of, 793
epidemiology of, 790
leptospirosis causing, 2029*f*
pathology of, 791–792
pathophysiology of, 790–791
prognosis of, 795
proteinuria in, 792
treatment of, 795*b*
Interstitial pneumonia
acute, 566*t*, 567, 574*t*, 578, 579*f*
clinical manifestations of, 568, 568*f*, 568.*e1f*
definition of, 567
diagnosis of, 568
pathobiology of, 568
treatment for, 568*b*
chronic fibrosing, 571*t*, 575
desquamative, 578
diagnosis of, 578, 578*f*, 578.*e1f*, 579*f*
prognosis for, 578*b*
radiographic features of, 574*t*
treatment of, 578*b*
honeycombing in, 522*f*
idiopathic, 575–580
acute, 571*t*, 578
radiographic features of, 574*t*
subacute, 571*t*, 578
lymphocytic, 579–580
diagnosis of, 580
prognosis for, 580*b*
radiographic features of, 574*t*
treatment of, 580*b*
lymphoid, 579, 580*b*, 580.*e1f*
nonspecific, 577
diagnosis of, 577, 577*f*
prognosis for, 577*b*
radiographic features of, 574*t*
treatment of, 577*b*
rare, 571*t*
smoking-related, 571*t*, 577
Interventional contrast pulmonary angiography, of venous thromboembolism, 486
Interventional procedures, 874
Interventional therapy, for aspergillosis, 2096
Interventricular septum, 224
Intestinal bacterial overgrowth, 932*t*, 934
clinical manifestations of, 934
diagnosis of, 931*t*, 932*t*, 934
treatment of, 934*b*
Intestinal diverticular disease, nutrition and, 60
Intestinal flukes, 2166*t*, 2167
Intestinal ischemia, 959
abdominal pain and, 854*t*
epidemiology of, 959
weight loss and, 860*t*
Intestinal metaplasia, 913
Intestinal perforation, enteric infections and, 1870*t*
Intestinal protozoa, 2112*t*, 2115
Intestinal pseudo-obstruction
clinical manifestations of, 888
diagnosis of, 889, 889*f*
medical therapy for, 889*b*
surgical therapy for, 889*b*
treatment of, 889*b*
Intestinal tuberculosis, 2037
Intestine
atresia, 951
blood flow to, 959
inflammatory diseases of, 951–959
malrotation, 951
Intimate partner violence (IPV), 1633–1636
abused patient, management of, 1634*b*
abusive patient, management of, 1634*b*
clinical manifestations of, 1633–1634
couples therapy in, 1634*b*
definition of, 1633–1636
diagnosis of, 1634–1635
epidemiology of, 1633
health care providers in, 1634*b*
pathobiology of, 1633, 1634*t*
prevention of, 1635–1636
prognosis of, 1636
treatment of, 1634*b*, 1635*t*
Intimate terrorism, 1633
Intoxication, 759
Intra-abdominal infections, 1921, 1921*b*
anaerobic bacteria causing, 1939
bacterial species that cause, 1892*t*
mesenteric venous thrombosis and, 963*t*
Pseudomonas infections causing, 1969, 1970*b*
Intra-abdominal testes, removal of, 1575*b*
Intra-aortic balloon pumps, 667*b*
Intra-axial brain tumors, 1316
Intracardiac echocardiography, 239
Intracardiac electrograms, 317.*e1f*
Intracavernosal injection, for erectile dysfunction, 1589
Intracavitary mycetoma, 607
Intracavitary tumors, 297–298
Intracerebral hemorrhage, 2479*f*
acute, 2481*t*
blood pressure control in, 2480*b*
causes of, 2479*t*
clinical manifestations of, 2479
definition of, 2478–2482
diagnosis of, 2479–2480, 2481*f*
epidemiology of, 2478–2482
hypertension-related, 2463
pathobiology of, 2478–2479
prevention of, 2480*b*
prognosis for, 2482
surgical treatment of, 2480*b*
treatment of, 2480*b*
Intracerebral Hemorrhage Score, 2481*t*
Intracerebral parenchymal brain hemorrhages, 2463
Intracranial aneurysm, autosomal dominant polycystic kidney disease and, 811
Intracranial epidural hematoma, 2391
clinical manifestations of, 2391
diagnosis of, 2387*f*, 2391
epidemiology of, 2391
pathobiology of, 2391
prognosis of, 2391*b*
treatment of, 2391*b*
Intracranial hypertension, 2383, 2383*b*
Intracranial hypotension, 2383, 2384*b*, 2384*f*
Intracranial leptomeningeal metastases, 1317, 1317*b*, 1317*f*, 1317.*e1f*
Intracranial plasmacytomas, 1299
Intracranial pressure, raised, treatment of, 2440*b*
Intradermal nevi, 2730
Intraductal papillary mucinous neoplasms, 1356
Intradural extramedullary tumors, 1318–1319, 1319*b*
Intraepidermal adenocarcinoma, 980
Intraepidermal blistering disorders, 2718
Intraepithelial neoplasia, cervical, oral contraceptives and, 1615
Intraepithelial neoplasias, 1376, 2242
Intraerythrocytic bacteremia, 2000, 2001*t*
Intrahepatic cholestasis of pregnancy, 1626, 1626*b*, 1627*t*
Intralesional bleomycin, 2700
Intraluminal digestion, impairment of, 932–934, 932.*e1f*
Intramedullary hemolysis, hyperbilirubinemia and, 1121
Intramedullary spinal cord tumors, 1319, 1319*b*, 1319*f*
Intramural hematoma, 439, 441*b*, 441*f*
Intramuscular hematomas, hemophilia and, 1188
Intramyocardial tumors, 298
Intraocular pressure, 2596
glaucoma and, 2607
Intrapandemic influenza, 2199
Intraperitoneal fibrosis, 1567
Intrarenal acute kidney injury, 773, 774
Intrathecal pumps, in palliative care, 12
Intrathecal tofersen, for amyotrophic lateral sclerosis, 2563*b*
Intrauterine devices (IUDs), for contraception, 1617
Intrauterine factors, 2641
Intravascular hemolysis, 1092
Intravascular large B-cell lymphoma, 1285
Intravenous access, for shock, 662*b*
Intravenous epoprostenol, 496*b*
Intravenous fluids
for cryptosporidiosis, 2143*b*
for shock, 662*b*
Intravenous gamma globulin, for systemic lupus erythematosus, 1772*b*
Intravenous GPIIb/IIIa receptor antagonists, 508
Intravenous hydration, for diarrhea and enteric infection, 1872*t*
Intravenous immunoglobulin, for Guillain-Barré syndrome, 2571*b*
Intravenous iron therapy, for iron deficiency anemia, 1084*b*
Intravenous medications, for hypertensive emergencies, 458*b*, 460*t*
Intraventricular blocks, 321, 322*b*
Intraventricular cysticerci, 2160*f*
Intraventricular hemorrhage, 2478
Intrinsic acute kidney injury, 770, 771*t*
Intrinsic factor, *e1t–e8t*
Intrinsic pathway, 1165
Intrinsic resistance, 1965, 1966*t*
Intubation, 654, 691*b*
Intussusception, 952, 952*b*
Invasive aspergillosis
clinical manifestations of, 2094
diagnosis of, 2095, 2095*f*
epidemiology of, 2094
treatment of, 2096
Invasive candidiasis, 2092
Invasive mucinous adenocarcinoma, 566*t*, 569, 569.*e1f*, 570*b*, 570*f*
Invasive procedures, diagnostic, 261
Inverse psoriasis, 2705
Involuntary active euthanasia, 8*t*
Involuntary bladder contraction, 827
Involuntary weight loss, 860
causes of, 860*t*
diagnosis of, 861, 862*f*
signs and symptoms of, 852*t*
Iodine, 1457*t*
for hyperthyroidism, 1511*b*
radioactive. *See* Radioactive iodine
Iodine deficiency, 1507, 2542–2543
Iodine-induced hyperthyroidism, 1511*t*
Iodine-induced thyrotoxicosis, 1514
Iodoquinol, for amebic liver abscess, 1025*b*
Ion channelopathies, 2585–2586
Ion channels, 223, 299*f*, 300
Ionizing radiation, 91–95
cancer and, 1246
definitions of, 91, 91*f*, 92*t*
exposure to, 88*t*
acute radiation syndromes, 93, 94*f*
clinical manifestations of, 93
diagnosis of, 93–94, 93*t*
epidemiology of, 91.*e1f*, 92
medical, 92
medical imaging of, 94–95
natural sources of, 92
organ-specific late effects after radiotherapy, 93, 93*t*
pathobiology of, 92
prevention of, 94–95
radiologic accidents, 92, 92*t*
Ionizing radiation *(Continued)*
radiologic terrorism, 92
stochastic effect, 93
head and neck cancer and, 1321
Ipilimumab (Yervoy), 1215*t*, 1251*t*
for melanoma, 1394*t*
for renal cell carcinoma, 1364*b*
Ipratropium bromide, 553*t*
IPSS. *See* International Prostate Symptom Score
IPV. *See* Intimate partner violence
Irbesartan, 451*t*
Irbesartan/HCTZ, 451*t*
Irinotecan (Camptosar), 1215*t*
IRIS. *See* Immune reconstitution inflammatory syndrome
Iris melanoma, 2612–2613, 2613*f*
Iritis, 2611
Iron, *e1t–e8t*, 1457*t*
for malabsorption, 937*t*
toxicity, 88*t*, 690*t*
Iron-binding capacity, total (TIBC), *e1t–e8t*
Iron bisglycinate, for iron deficiency anemia, 1085*t*
Iron chelation therapy, for myelodysplastic syndromes, 1255
Iron deficiency, 886
in heart failure, 265*b*
Iron deficiency anemia, 1082–1085
anemia of chronic disease *versus*, 1068–1069
cause of, 1083*t*
chronic hematuria as cause of, 1083–1084
clinical manifestations of, 1084
colonoscopy evaluations, 887
definition of, 1082
diagnosis of, 1084, 1084*f*, 1085*t*
differential diagnosis of, 1084
epidemiology of, 1082
gastrointestinal cause of, 1082–1083
pathobiology of, 1082–1084, 1083*f*, 1083*t*
prevention of, 1085
prognosis of, 1085
treatment of, 1084*b*
Iron overload, 1438
classification of, 1438*t*
clinical manifestations of, 1439, 1439*t*
definition of, 1438
diagnosis of, 1440, 1441*f*
epidemiology of, 1438
pathobiology of, 1438, 1439*f*
physical findings in, 1440*t*
prognosis of, 1442
quantifying, 1441
screening for, 1441
symptoms and signs of, 1440, 1440*t*
in thalassemia, 1107*b*
treatment of, 1441*b*
Iron saturation, *e1t–e8t*
Irradiation, hypothalamic disease effects on, 1480
Irregularly contracted cells, conditions associated with, 1072*t*
Irreversible renal failure, treatment of, 840–848
dialysis for, 841, 841*t*
hemodialysis for, 841
medical issues in, 842–843
peritoneal dialysis for, 841–842
prognosis of, 843, 843*t*
renal transplantation for, 843–848, 845*t*
Irritable bowel syndrome (IBS), 892–898
abdominal pain and, 854*t*
altered CNS processing and modulation in, 893
chronic diarrhea and, 928–929
clinical manifestations of, 893–894
definition of, 892
diagnosis of, 894–895
diagnostic criteria for, 895, 895*t*
dysregulated stress responsiveness in, 893
enteric infections and, 1870*t*
epidemiology of, 892
familial and genetic factors of, 892–893
gut transit and motility in, 893
increased visceral perception in, 893
pathobiology of, 892–893
peripheral gastrointestinal factors of, 893
postinfection, 893
prognosis of, 898
small bowel dysmotility in, 890
stressful life events and, 893

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Irritable bowel syndrome (IBS) *(Continued)*
symptom-based criteria for, 894–895, 894*f*, 894*t*
treatment of, 895*b*, 896*f*, 896*t*, 898*f*
weight loss and, 860*t*
Irritant contact dermatitis, 2704
Irritant dermatitis, 1692
Irritant exposure, 587–588
Irukandji syndrome, 712*b*
IRV. *See* Inspiratory reserve volume
Isavuconazole, 2077
adverse effects of, 2077
for aspergillosis, 2096
drug interactions of, 2077
formulations and pharmacology of, 2077
indications and dosage of, 2075*t*, 2077
for mucormycosis, 2100*b*
Ischemia
cerebral, 2462
colon, 964
algorithm of, 966*f*
clinical manifestations of, 964
conditions and medications associated with, 964*t*
diagnosis of, 964, 965*f*, 965.*e1f*
treatment of, 965*b*
focal segmental, 962*f*
intestinal, 959
epidemiology of, 959
pathobiology of, 959
limb
acute, 461, 462*t*, 465*f*
chronic, 462
lower limb
chronic, 462*t*, 464*b*
chronic critical, 462
chronic stable, 462
mesenteric
acute, 959
chronic, 963*f*
nonocclusive, 962, 962*f*
myocardial
differential diagnosis of, 424*t*
silent, 369
peptic ulcers caused by, 916
treatment of, 265*b*
Ischemic cardiomyopathy, chronic, 336*f*
Ischemic cerebrovascular disease, 2464
clinical manifestations of, 2465
definition of, 2464–2469
diagnosis of, 2466, 2466*f*
differential diagnosis of, 2469
epidemiology of, 2464
pathobiology of, 2464
physical examination of, 2466
Ischemic disease, end-stage, 242*t*
Ischemic heart disease
causes of, 358*t*
chronic, 356
blood tests in, 361*t*
epidemiology of, 356
noninvasive testing for, 359, 362*f*
pathobiology of, 356
symptoms of, 357*t*
diagnosis of, 358–364, 359*f*
diagnostic coronary angiography in, 363*t*
laboratory testing of, 358–359
physical examination of, 358
prognosis for, 369
risk stratification of, 363
stable, 356
treatment of, 364*b*
Ischemic nephropathy, 799
Ischemic optic neuropathy, 2615
Ischemic stroke
acute
fibrinolytic therapy for, 509
radiographic changes of, 2373, 2373.*e1f*
arterial hypertension in, 2471*f*
cerebral embolization causing, 2530
clinical manifestations of, 2465
definition of, 2464
diagnosis of, 2466
differential diagnosis of, 2469
endovascular therapy for, 2469*b*–2470*b*
epidemiology of, 2464
initial laboratory tests for, 2466–2469, 2467*t*
National Institutes of Health Stroke Scale, 2466, 2470*t*
physical examination of, 2466
recombinant tissue plasminogen activators for, 2469*b*, 2469*t*–2470*t*, 2469.*e1f*, 2470*t*
Ischemic stroke *(Continued)*
risk factors for, 2464*t*
treatment of, 2469*b*, 2469*t*
Ischial/ischiogluteal bursitis, 1747, 1747*b*
Isobutyric aciduria, 1403*t*
Isocarboxazid, for depression, 2340*t*
Isoimmune neonatal neutropenia, 1146
Isolated hypomagnesemia, 816*t*
Isolated hypoparathyroidism, 1660
Isomorphic erythrocytes, 723*f*
Isonatremia, 733*t*
Isoniazid, 1460*t*
dosage of, 1895*t*
for nontuberculous mycobacterial disease, 2046*t*
for tuberculosis, 2040*b*, 2041*t*, 2043*t*
Isopropyl alcohol, 760
Isoproterenol, 313*b*
Isosorbide-5-mononitrate, 368*t*
Isosorbide dinitrate, 265*b*, 368*t*
Isospora belli, sexually transmitted anorectal diseases and, 983
Isotonic hyponatremia, 740
Isotretinoin (Accutane), 2698, 2722*b*
Isovaleric aciduria, 1403*t*
Isovolumic contraction, 225
Isradipine, 367*t*, 451*t*
Israeli tick-bite fever, 2055*t*, 2057
Istradefylline, for Parkinson disease, 2487*t*
Ito cells, 1035–1036
Itraconazole, 2074, 2699
adverse effects of, 2075
for blastomycosis, 2081*b*
for chromomycosis, 2111*b*
drug interactions of, 2075
formulations and pharmacology of, 2074–2075
for histoplasmosis, 2083*b*
indications and dosage of, 2075, 2075*t*
for paracoccidioidomycosis, 2087*b*
for sporotrichosis, 2086*b*
Itraconazole + hydroxyitraconazole, *e*10*t*–*e*11*t*
IUDs. *See* Intrauterine devices
Ivabradine, 325*t*
for heart failure, 265*b*
for heart failure with reduced left ventricular ejection fraction, 265*b*
Ivermectin, 2117
for COVID-19, 2217
for helminthic diseases, 2112*t*
for lice, 711*b*
for onchocerciasis, 2179*b*
for strongyloidiasis, 2173*b*
IVF. *See* In vitro fertilization
Ixabepilone (Ixempra), 1215*t*
Ixazomib (Ninlaro), 1215*t*
Ixekizumab (Taltz), for total knee arthroplasty, 1830.*e1t*
Ixempra. *See* Ixabepilone
Ixodes dammini, 2151
Ixodes persulcatus, 2022
Ixodes ricinus, 2151
Ixodes scapularis, 2022, 2027
Ixodes spp., 710

J

J wave, 228, 229*f*, 680, 681*f*
J wave syndromes, 302, 302*f*
Jaccoud arthropathy, 1769
Jackhammer esophagus, 909
Jackson syndrome, 2465.*e1f*
Jacobsen/Paris-Trousseau syndrome, 1071
JAK inhibitors, for rheumatoid arthritis, 1757*t*
JAK2 V617f mutation, 1130–1131
JAK3 deficiency, 1676.*e3t*
Jakafi. *See* Ruxolitinib
JAKs. *See* Janus kinases
Jamestown Canyon virus, 2276*t*, 2283, 2284*b*
Janeway lesions, 216, 218*f*, 414–415, 414*t*
Janssen AD26 vector, 2218*t*, 2219
Janus kinase (JAK)-signal transducer, 185
Janus kinase-2, 1490
Janus kinase inhibitors
for COVID-19, 2217
for inflammatory bowel disease, 945*b*
Janus kinases (JAKs), 153, 153*t*
Japanese encephalitis, 2276*t*, 2280, 2280*b*
immunization for, 66*t*, 83
in travelers, 1891*t*
vaccine, for traveler, 1886*t*, 1887
Japanese monocytic ehrlichiosis, 2060*t*
Japanese spotted fever, 2055*t*, 2057
Jarisch-Herxheimer reactions
in leptospirosis, 2031*b*
in syphilis, 2020*b*
Jaundice
acute abdominal pain and, 856
approach to, 1000–1001, 1000*t*
cirrhosis and, 1037
definition of, 993
infectious causes of, 1849, 1850*t*
pathobiology of, 994
postoperative of, 998–1000
in pregnancy, 998
Jaw osteonecrosis, 1643*b*
JC polyomavirus, 2228*t*, 2230–2232, 2305
nephropathy associated with, 2231–2232
progressive multifocal leukoencephalopathy associated with, 2230–2231
Jejunostomy, nutritive, 1449
Jellyfish, 712
Jersey finger. *See* Avulsion of flexor digitorum profundus
Jervell and Lange-Nielsen syndrome, 348
Jet lag, traveler's, 1889
Jevtana. *See* Cabazitaxel
Johnson & Johnson's Janssen COVID-19 vaccine, 77–78
Joint(s)
infection of, 1804–1809
mobility and stability, for osteoarthritis, 1741*t*
rheumatoid arthritis of, 1751–1752, 1752.*e1f*, 1753*f*
Joint Commission, 46
Quality Check, 41.*e1t*
Joint diseases
in sarcoidosis, 602, 604*t*
surgical treatment of, 1826–1830
anesthesia in, 1827
complications of, 1829–1830
deciding upon, 1826–1827
epidemiology of, 1826
pathobiology of, 1826, 1826*f*
perioperative arthritis medication in, 1830, 1830.*e1t*
procedures for, 1827–1829
Joint fluid analysis, 1713, 1713*f*
Joint infections, *Pseudomonas* infections causing, 1969
Jugular veins, 212–213, 213*f*
distention of, 212–213, 214*f*
examination of, 30, 258, 259*f*, 260*f*
Jugular venous pressure, 212
Jumper's knee. *See* Patellar tendinitis
Junctional nevi, 2730, 2733*f*
Junctional premature beat, 322*f*
Junctional tachycardia, 324–326, 326*b*, 327*f*
Junin virus, 100*b*, 2265*t*
Juvenile myoclonic epilepsy, 2433
Juvenile-onset diabetes, 1534
Juvenile polyposis, 1347*t*, 1348
Juxtaglomerular apparatus, 734
Jynneos vaccine, 84

K

K complexes, 2443
Kadcyla. *See* Aldo-trastuzumab emtansine
Kallmann syndrome, 1480–1481, 1584, 1601
Kaplan-Meier analysis, 37
Kaposi sarcoma, 2624, 2733, 2734*f*
gingival, 2320*f*, 2322*t*
in HIV, 2315, 2315*b*, 2316*f*
Karnofsky and Zubrod performance scales, 1214*t*
Kawasaki disease, 965, 1793*t*, 1795, 1795*b*, 2712, 2712*b*
Kayser-Fleischer rings, 1436, 1437*f*, 2542
KDIGO. *See* Kidney Disease Improving Global Outcomes
KDPI. *See* Kidney Donor Profile Index
Kearns-Sayre syndrome, 2586
Keloids, 2730, 2744
Kennedy disease, 2564*t*, 2565–2566
Keratin pearls, 1323, 1324*f*
Keratinocyte, multinucleated, 2690.*e1f*
Keratitis
Acanthamoeba, 2606
gonococcal, 2606
herpes simplex, 2605, 2606*f*
herpetic, 2246
pseudomonal, 2606
Pseudomonas infections causing, 1969
Keratoconjunctivitis sicca, 1785, 1786*f*, 2327*t*, 2611
Keratoconus, 2598
Keratocytes, 1068*f*
Keratoderma blennorrhagicum, 1763
Keratolytics, 2700
Keraunoparalysis, 704
Kerley B lines, 245*f*, 405
Kerley lines, 521
Kernig sign, 2512
Kesimpta. *See* Ofatumumab
Ketamine
for anesthesia, 2670
for chronic pain, 138*t*
for erythromelalgia, 471*b*
properties of, 142*t*
Ketoacidosis
alcoholic, 759
cystic fibrosis and, 557
diabetic, 758
Ketoconazole, 2699
for Cushing syndrome, 1524*b*
for eumycetoma, 2111*b*
Ketolides
characteristics of, 1899
dosage of, 1895*t*
mechanism of action, 1895*t*
resistance mechanisms, 1893*t*
Ketone bodies, *e*1*t*–*e*8*t*
Ketone body synthesis/utilization, defects in, hypoglycemia and, 1552*t*
Ketoprofen
for chronic pain, 138*t*
for rheumatoid arthritis, 1756*t*
Ketorolac
for acute pericarditis, 424*b*
for chronic pain, 138*t*
17-Ketosteroid reductase deficiency, 1572
Keytruda. *See* Pembrolizumab
Kidney
in acid-base balance, 754, 754.*e1f*
agenesis, 818
calcium absorption by, 1652
development of, 818–821
dysfunction of
in septic shock, 673*b*
dysplasia, 818
ectopia, 819, 819*f*
function of, measuring, 720–721
hypoplasia, 818
malrotation, 819, 819*f*
potassium handling by, 746
production of acids and excretion by, 753
structure and function of, 729–733, 730*f*–731*f*, 730.*e1f*, 731*f*
body fluid osmolarity in, 730, 732*f*
extracellular fluid volume regulation in, 730, 730.*e1f*
plasma pH regulation in, 731, 731.*e1f*, 732*f*
plasma PO_4 and CA^{2+} in, 732, 732.*e1f*
plasma potassium regulation in, 732
systemic lupus erythematosus manifestations of, 1769
systemic sclerosis involvement of, 1779
transplantation. *See* Renal transplantation
tumors of, 1362
vascular disorders of, 728, 799–803
atheromatous embolization, of renal arterial system, 801, 801*b*, 802*f*
renal artery stenosis. *See* Renal artery stenosis
renal infarction, 801–802, 802*b*
renal vein thrombosis, 802, 802*b*
Kidney disease, drug dose adjustments in, 129–130, 129.*e1t*
loading dose in, 130
using clearance for, 130
Kidney Disease Improving Global Outcomes (KDIGO), on acute kidney injury, 770*t*
Kidney donation, in renal transplantation, 844
Kidney Donor Profile Index (KDPI), 844
Kidney failure, 738, 837
Kidney replacement therapy, for chronic kidney disease, 839*b*
Kidney stones, 803. *See also* Nephrolithiasis
Kikuchi disease, 1288, 1770
Kinase inhibitors, thyroiditis caused by, 1514
Kineret. *See* Anakinra
Kinesigenic, 2493
Kinetic tremor, 2484, 2489
Kisqali. *See* Ribociclib
Kissing bug, 2126

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Kisspeptin, 1477, 1592
Kisspeptin-neurokinin B-dynorphin neurons, 1580
KIT mutations, 1700
Klatskin tumors, 1357, 1360*f*
Klebsiella granulomatis, 2004
Klebsiella pneumoniae, 1022, 1965
  antimicrobial resistance of, 1864, 1864*t*
Klebsiella pneumoniae carbapenemase (KPC), 1966
Kleine-Levin syndrome, 2446
Klinefelter syndrome, 1574, 1582–1583
Klippel-Trenaunay syndrome, 969
Knee
  disorders of, 1747
  fusion of, 1827
  injury of, occupational, 86*t*
  surgical treatment of, 1828, 1828*f*–1829*f*, 1829*f*
Knudson's two-hit model of cancer development, 1248, 1248*f*
Koch-Weeks bacillus, 1954
Koilocytes, 2241
Koilocytosis, 2241
Koilonychia, 2751, 2752*f*
Koplik spots, 2220, 2221*f*, 2621
Korsakoff psychosis, 2539
Korsakoff syndrome, 2408, 2539
KPC. *See Klebsiella pneumoniae* carbapenemase
Krabbe disease, 2510
Krebs-Henseleit cycle, 999
Krukenberg tumor, 1341
Kupffer cells, 2204
Kussmaul sign, 384*b*, 428–429
Kwashiorkor, 1444, 1444*f*–1445*f*
Kyasanur Forest disease, 99.*e1t*, 2265*t*, 2268*t*
Kymriah. *See* Tisagenlecleucel
Kyphoplasty, 1643*b*
Kyphoscoliosis, 620–621
  clinical manifestations of, 621
  diagnosis of, 621
  epidemiology of, 620–621
  in hypercapnic disease, 535*t*
  pathobiology of, 620
  prognosis for, 621
  treatment of, 621*b*
Kyphosis, 622
Kyphotic deformity, 1642
Kyprolis. *See* Carfilzomib

L

L-carnitine, 693*t*, 1451–1452
L-glutamine, 1116*t*
La Crosse virus, 2276*t*, 2283, 2284*b*
Labetalol, 451*t*, 458*b*, 460*t*
  for preeclampsia, 1621*t*
Labile factor, 1189*t*
Laboratory testing
  anomalies, 3, 3.*e1t*
  cardiac catheterization. *See* Cardiac catheterization
Laboratory values, *e1*
  clinical chemistry, toxicology, and serology, *e1t*–*e8t*
  drugs: therapeutic and toxic, *e10t*–*e11t*
  hematology and coagulation, *e8t*–*e9t*
  prefixes and abbreviations, *e1t*
Labyrinthine concussion, 2645
Lacosamide, for seizures, 2434*t*
Lacrimal gland tumor, 2613
β-Lactamases
  AmpC, 1966
  extended-spectrum, 1966
  inhibitors, for multidrug-resistant Enterobacterales, 1967*t*
  narrow-spectrum, 1966
β-Lactams
  characteristics of, 1898–1900
  inhibitors of, for multidrug-resistant Enterobacterales, 1967*t*
  mechanism of action, 1895*t*
  reactions to, 1698*t*
  resistance mechanisms, 1893*t*
  for *Staphylococcus aureus*, 1909
  in *Stenotrophomonas maltophilia*, 1976*t*
Lactase deficiency, 935
L-Lactate, *e1t*–*e8t*
Lactate dehydrogenase (LDH), *e1t*–*e8t*, 999
Lactated Ringer solution, for cholera, 1956*b*
Lactation, familial hypercholesterolemia and, 1409*b*
Lactic acid, in bacterial meningitis, 2514
Lactic acidosis, 757
  causes of, 758*t*
  clinical manifestations of, 758
  diagnosis of, 758
  epidemiology of, 757–758
  pathobiology of, 757
  prognosis of, 758
  treatment of, 758*b*
Lactobacillus, for infectious gastroenteritis, 2263*b*–2264*b*
Lactobacillus acidophilus, 1882
Lactobacillus crispatus, 1882
Lactobacillus jensenii, 1882
Lactotrophs, 1490
Lactulose, for irritable bowel syndrome, 896*t*
Lacunar syndromes, 2465–2466, 2466*t*
Laguna Negra virus, 2265*t*
LAIV. *See* Live attenuated influenza virus
Lambert-Eaton myasthenic syndrome, 1238, 1238*t*, 2558–2560
Lambert-Eaton syndrome, 2589*t*, 2591
  clinical manifestations of, 2591
  diagnosis of, 2591
  pathobiology of, 2591
  prognosis of, 2591
  treatment for, 2591*b*
Lamellar ichthyosis, 2687.*e3t*
Lamivudine, 2181*t*, 2182*t*, 2183, 2301*t*
Lamotrigine, *e10t*–*e11t*
  for chronic pain, 138*t*
  for seizures, 2434*t*
Langerhans cell histiocytosis, 1154, 1480, 1480*f*, 2731, 2733*f*
  clinical manifestations of, 1154, 1155*f*, 1156*t*
  cutaneous features of, 1155*f*
  diagnosis of, 1156
  epidemiology of, 1154
  neurodegeneration associated with, 1156
  pathobiology of, 1154
  prognosis for, 1156
  pulmonary, 571, 582–583, 583.*e1f*
    clinical manifestations of, 583
    diagnosis of, 583
    prognosis for, 583*b*
    treatment of, 583*b*
  treatment of, 1156*b*
Lanifibranor, for nonalcoholic fatty liver disease, 1034*b*
Laninamivir, for influenza, 2203*t*
Lanreotide, for acromegaly, 1489*b*
Laparoscopic cholecystectomy, 1052*b*
Laparoscopic gastric banding, for obesity, 1467*b*
Laparoscopic ovarian surgery, for polycystic ovary syndrome, 1602*b*
Laparoscopy
  for endometriosis, 1596*b*
  for pelvic inflammatory disease, 1949
Lapatinib (Tykerb), 1215*t*, 1251*t*
Laplace equation, 400
Laplace's law, 225
LAR. *See* Lymphangitis-associated rickettsiosis
Large bowel adenocarcinoma, 1349*f*
Large bowel obstruction, abdominal pain and, 854*t*
Large bowel sarcomas, 1347
Large-cell B-cell lymphoma, 2613
Large cell carcinoma, 1329, 1329.*e2t*
Large cell neuroendocrine carcinoma, 1336
Large granular lymphocyte leukemia, 1126, 1272
  clinical manifestations of, 1127–1128
  definition and epidemiology of, 1126–1128
  diagnosis of, 1128, 1128*f*
  pathobiology of, 1126–1127
  prognosis of, 1128
  treatment of, 1128*b*
Large granular lymphocyte syndrome, 1146, 1754
Large intestine, neoplasms of, 1345–1354
  adenocarcinomas, 1346–1347, 1346*f*
  epidemiology of, 1345–1347
  epidermoid carcinomas, 1347
  lymphomas, 1347
  neuroendocrine cancers, 1347
  pathobiology of, 1346–1347
  risk factors of, 1346
  sarcomas, 1347
Large opacities, pulmonary, 520–521, 520*t*
Large pupil, 2600
Large vessel vasculitis, 965, 1792*t*, 1793, 1795, 2687.*e3t*
Laron dwarfism syndrome, 1488–1489
Laron-type dwarfism, IGF-I in, 1477
Laronidase (Aldurazyme), for mucopolysaccharidoses, 1725*b*
Larotrectinib (Vitrakvi), 1215*t*
Laryngeal amyloidosis, 1310
Laryngeal dystonia, severe mental illness and, 2681*t*
Laryngeal paralysis, 2653
Laryngeal stenosis, 2653
Laryngitis, 2651–2652
Laryngopharyngeal reflux, 2651–2653
Laryngotracheal injury, distinguishing features of, 515*t*
Larynx, 1320
  cancer, 1322, 1325*t*, 1327*b*
Lasers
  as occupational and environmental hazards, 88*t*
  for skin cancers, 2701
Lassa fever, 2268*t*, 2269*f*
Lassa virus, 99.*e1t*, 2265*t*
Late adolescence, 110
Late benign syphilis, 2017
Late neurologic Lyme disease, 2024–2025
Late-night salivary cortisol measurement, for Cushing disease, 1494
Late onset autoinflammatory disease, 1737
Late syphilis, 2017, 2017*t*
Latent syphilis, 2016
Latent tuberculosis, 2034
  skin testing for, 2038–2039
  treatment of, 2040*b*, 2041*t*
Lateral brain stem, infarction of, 2645
Lateral epicondylalgia, 1745, 1745*b*
Lateral flow analysis, 2088
Lateral sinus thrombosis, 2529–2530, 2529*b*, 2529*f*
Lateralization, of flow, 522
Latex allergy, 2669
Latex-induced anaphylaxis, 1691, 1692
Lathyrism, 2543
Latin America, HIV/AIDS in, 2289, 2289.*e1f*
Lauren classification, 1340
Laxatives
  for constipation, 862*b*
  for irritable bowel syndrome, 895*b*, 896*t*
LDL cholesterol. *See* Low-density lipoprotein cholesterol
Lead, *e1t*–*e8t*
Lead poisoning, 2564*t*
Lead toxicity, 87, 88*t*, 101, 690*t*
  chronic interstitial nephritis caused by, 794
  clinical manifestations of, 101
  diagnosis of, 101, 101*t*
  epidemiology of, 101
  pathobiology of, 101
  prognosis of, 101
  treatment of, 101*b*, 102*t*
Leading causes of death, 17, 18*t*
Leadless pacing system, 342, 342*f*
Lean or Six Sigma, 45
Leber hereditary optic neuropathy, 2586
Lecithin-cholesterol acyl transferase, 1406
Lectins, 197
Ledipasvir/sofosbuvir, for hepatitis C infections, 2181*t*, 2182*t*, 2184
Lefamulin, 1845*t*
  dosage of, 1895*t*
  mechanism of action, 1895*t*
  toxicities of, 1901*t*
Leflunomide (Arava), 147
  for rheumatoid arthritis, 1755*b*, 1756*t*, 1757*t*
  for total knee arthroplasty, 1830.*e1t*
Left anterior descending coronary artery, 397
Left anterior fascicular block, 231, 231*t*, 232*f*
Left atrial appendage, closure of, 347
Left bundle branch block, 231, 231*t*, 232*f*, 287.*e1f*
Left common carotid artery, 2454–2455
Left posterior fascicular block, 231, 231*t*, 232*f*
Left ventricular aneurysm, 384*b*
Left ventricular dysfunction
  aortic regurgitation with, 410
  management of, 384*b*
  mitral regurgitation with, 407
Left ventricular ejection fraction (LVEF)
  heart failure on, 264
  with mildly reduced, heart failure, 265*b*, 277*f*
  with preserved, heart failure, 265*b*, 278*f*
  with reduced, heart failure, 264, 265*f*
    second-line treatments for, 265*b*, 272*f*
  three-dimensional echocardiography of, 236, 237*f*
Left ventricular enlargement, 244, 245*f*
Left ventricular failure, chest radiograph of, 523*f*
Left ventricular hypertrophy, 233, 256–257
  concentric, 400
Left ventricular noncompaction, 294, 295*f*
Left ventricular outflow tract obstruction, 351–352, 351
Left ventricular stroke work index, 677*t*
Left ventricular systolic dysfunction, heart failure caused by, 265*b*
  ACEIs and ARBs for, 265*b*, 266*t*
  β–blockers for, 265*b*, 267*t*
  mineralocorticoid receptor antagonists for, 265*b*, 270*t*
  SGLT2 inhibitors for, 265*b*, 271*t*
Left ventricular thrombus, 242*t*
Left ventricular volume, 236, 237*f*
Legionella infections, 417*t*
Legionella pneumophila, epidemiology of, 1996.*e3f*, 1997
Legionella spp., 1996, 1998*f*
Legionellosis, 1996–1999
  clinical manifestations of, 1997–1998
  definition of, 1996–1999
  diagnosis of, 1998
  differential diagnosis of, 1998
  epidemiology of, 1996–1997, 1997.*e1f*
  pathobiology of, 1997, 1997.*e1f*
  pathogen of, 1996, 1996.*e1f*
  prevention of, 1999
  prognosis of, 1999
  in travelers, 1889.*e1t*
  treatment of, 1998*b*, 1999*t*
Legionnaires disease
  definition of, 1996
  pathology of, 1997.*e1f*, 1998
  treatment for, 1999*t*
Leiomyomas, 1343
Leiomyomatosis, hereditary, 1363
Leiomyosarcoma, 1342, 1389
Leishmania spp., 1026*t*, 2130
Leishmaniasis, 2116, 2130–2135
  characteristics of, 2130*t*
  cutaneous, 2131
    clinical manifestations of, 2133, 2134*f*
    complex manifestations of, 2133
    diagnosis of, 2133
    diffuse, 2133
    disseminated, 2133
    parasitology of, 2133, 2135*f*
    prevention of, 2133
    prognosis for, 2133
    recidivans, 2133
    treatment of, 2133*b*, 2135*f*
  cutaneous or mucocutaneous, in travelers, 1889.*e1t*
  definition of, 2130–2132
  epidemiology of, 2130–2131, 2130*t*, 2131*f*
  mucosal, 2133
  pathobiology of, 2131–2132
  pathogen that cause, 2130
  post-kala-azar dermal, 2131–2132, 2132
  treatment of, 2112*t*
  visceral, 2132
    antigen-based tests for, 2132
    clinical manifestations of, 2132
    complex manifestations of, 2132
    diagnosis of, 2132
    in immunodeficient patients, 2132*b*
    serologic tests of, 2132
    treatment of, 2132*b*
Leishmanin skin test, 2133
Lenalidomide (Revlimid), 1215*t*
  for multiple myeloma, 1299*b*
  for skin diseases, 2699
Lentigines, 2689*t*
Lentigo maligna melanoma, 1391, 1392*f*
Lentiviruses, 2291
Lenvatinib (Lenvima), 1215*t*
  for renal cell carcinoma, 1364*b*
Lenvima. *See* Lenvatinib

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Lepidic predominant nonmucinous adenocarcinoma, 566*t*, 569, 569.e1*f*, 570*b*, 570*f*
Lepromatous leprosy, 2049–2050, 2049*t*, 2050*f*–2051*f*, 2051*f*, 2734, 2735*f*
Leprosy, 1583, 2047–2053
  borderline borderline, 2049, 2049*t*, 2049.e1*f*, 2050*f*
  borderline lepromatous, 2049, 2049*t*, 2050*f*, 2050.e1*f*
  borderline tuberculoid, 2049, 2049*f*, 2049*t*
  classification of, 2048–2051, 2048*t*–2049*t*, 2049*t*
  clinical manifestations of, 2048–2051
  cutaneous or mucocutaneous, in travelers, 1889.e1*t*
  definition of, 2047–2053
  diagnosis of, 2052
  diagnostic criteria for, 2052
  drug resistance of, 2052*b*
  epidemiology of, 2047–2048
  global strategies for, 2053
  histoid, 2051, 2052*f*
  in immunocompromised hosts, 2051
  immunogenetics of, 2048
  immunotherapy for, 2052*b*
  laboratory testing for, 2052
  lepromatous, 2049, 2049*t*, 2050*f*, 2051*f*
  Lucio, 2051
  multibacillary, 2048, 2048*t*, 2048.e1*f*
  multidrug therapy for, 2052*b*, 2053*t*
  nerve damage in, pathogenesis of, 2048
  neuropathy caused by, 2578
  pathobiology of, 2048
  pathogen that causes, 2047
  pathogenesis of, 2048, 2048.e1*f*
  paucibacillary, 2048, 2048*t*, 2048.e1*f*
  pregnancy and, 2051
  prevention of, 2053, 2053*t*
  prognosis of, 2053
  pure neuritic, 2051
  reactions, 2050
  Ridley Jopling Classification of, 2048.e1*f*
  systemic involvement in, 2051
  treatment for, 2052*b*
  tuberculoid, 2048–2049, 2049*t*
  type 1 reactions, 2050, 2050.e1*f*
  type 2 reactions, 2050–2051, 2051.e1*f*
Leptin, 1464, 1475*t*
Leptomeningeal metastases, 1317, 1317*b*, 1317*f*, 1317.e1*f*, 2646
Leptospira interrogans, 2029, 2029*f*
Leptospirosis, 2029–2031, 2064
  aseptic meningitis associated with, 2030, 2522
  case definitions, 2030*t*
  characteristics of, 2270*t*
  clinical manifestations of, 2029–2030
  coagulation disorders associated with, 2029
  conjunctival suffusion associated with, 2029, 2030*f*
  definition of, 2029–2031
  diagnosis of, 2030–2031
  differential diagnosis of, 2031
  epidemiology of, 2029
  pathobiology of, 2029
  pathogen that causes, 2029, 2029*f*
  prevention of, 2031
  prognosis for, 2031
  signs and symptoms of, 2030*f*
  thrombocytopenia associated with, 2029
  in travelers, 1889.e1*t*, 1891*t*
  treatment of, 2031*b*
Letermovir, for herpesvirus infections, 2187*t*, 2188
Letrozole (Femara), 1215*t*
  for polycystic ovary syndrome, 1602*b*
Letterer-Siwe disease, 1155
Leucine sensitivity testing, for hypoglycemia, 1557
Leucovorin, for *Pneumocystis* pneumonia, 2108*t*
Leucovorin calcium (Wellcovorin), 1215*t*
Leukemia
  acute lymphoblastic. *See* Acute lymphoblastic leukemia
  acute myeloid. *See* Acute myeloid leukemia
  adult T-cell leukemia/lymphoma. *See* Adult T-cell leukemia/lymphoma
  arthritis associated with, 1823
  chronic myelogenous. *See* Chronic myelogenous leukemia
Leukemia *(Continued)*
  chronic myeloid. *See* Chronic myeloid leukemia
  peripheral blood smear of, 1073–1074, 1073*f*, 1074*f*
Leukemia cutis, 1262
Leukemoid reaction, 1140, 1141*f*, 1262–1266
Leukocoria, 2600, 2601*t*
Leukocyte, e8*t*–e9*t*
Leukocyte adhesion deficiency, 1142, 1683.e1*t*
Leukocyte count (WBC count), e8*t*–e9*t*
Leukocytoclastic vasculitis, 2714, 2715*f*, 2725, 2728
Leukocytosis, 1846
  due to expansion of other cell lines, 1142, 1143*t*
  peripheral blood smear of, 1072–1073
  postoperative, 2675
  psychotropic medications and, 2678*t*
  in pulmonary tuberculosis, 2035
Leukodystrophies, 2509
Leukoerythroblastic blood film, 1074*t*
Leukoerythroblastic reaction, 1141
Leukonychia, 2752–2753, 2753*f*
Leukopenia, 2314
  due to deficiency of other cell lines, 1148
  peripheral blood smear of, 1072
Leukoplakia, 1321, 2622–2623
Leukoreduction, 1200, 1205
Leukotriene modifiers, for rhinitis, 2632*b*
Leuprolide acetate (Lupron), 1215*t*
Levator ani muscle, 977
Levetiracetam, e10*t*–e11*t*
  for seizures, 2434*t*
Levitra, 364*b*
Levodopa, for Parkinson disease, 2486, 2486*b*
Levofloxacin
  dosage of, 1895*t*
  for *H. influenzae* infections, 1954*b*
  for legionnaires disease, 1999*t*
  for *Moraxella catarrhalis* infections, 1955*b*
  for plague, 98*b*, 1992*t*
  for pneumonia, 613*t*, 616*t*
  for *Streptococcus pneumoniae* pulmonary infections, 1912.e1*t*
  for urethritis, 1880*b*
  for urinary tract infection, 1876*t*, 1877*t*
Levoketoconazole, for Cushing syndrome, 1524*b*
Levorphanol, 139*t*
Lewy body dementia, 2558
Leydig cell agenesis, 1573
Leydig cells, steroid hormone synthesis of, 1581
LH. *See* Luteinizing hormone
Lhermitte sign, 2371, 2500
Li-Fraumeni syndrome, 1250*t*
Libido, decreased, 1587
Lice, 711, 2741
Lichen myxedematosus, 1296, 2737–2738, 2737*f*–2738*f*
Lichen nitidus, 2708, 2708*f*
Lichen planopilaris, 2747*t*, 2749, 2750*f*
Lichen planus, 2621*t*, 2707–2708
  characteristics of, 2623, 2623*f*, 2691*t*
  clinical manifestations of, 2708, 2708*f*
  diagnosis of, 2708
  epidemiology of, 2707
  esophageal involvement in, 911
  illustration of, 2687.e1*f*, 2687.e3*t*, 2688*t*
  pathobiology of, 2708
  treatment for, 2708*b*, 2708*t*
Lichen sclerosis et atrophicus, 2737
Lichen simplex chronicus, 2687.e3*t*, 2687.e4*t*
Lichenification, 2687.e4*t*
Lichenoid drug reaction, 2621*t*
Licorice, 749*t*
Liddle syndrome, 749*t*, 816*t*, 817
Lidocaine, e10*t*–e11*t*
  for electrical storm, 338*b*
Life expectancy, 17*f*, 21, 21*f*, 118, 118.e1*t*
Life-space mobility, 117
Life support, withdrawal of, 638, 638*t*, 638.e1*t*
Lifespan groups, for women's health, 1606, 1606*t*
Lifestyle modifications
  for arterial hypertension, 450, 450*t*
  for atherosclerotic cardiovascular disease, 1410, 1410*t*
  for chronic kidney disease, 839*b*
  drug use and, 2361
  for heart failure, 265*b*
  for heartburn, 900*b*
Lifestyle modifications *(Continued)*
  for hypertriglyceridemia, 1414*b*
  for ischemic heart disease, 366*f*
  for osteoporosis, 1643*b*
Ligamentous injury, spinal cord injury *versus*, 2388
Light chain amyloidosis, 2574
Light chain cast nephropathy, 1299
Light-chain deposition disease, glomerular diseases in, 788, 788*f*
Light chains, e1*t*–e8*t*
Light-near dissociation, 2616–2617
Light refraction, 2597, 2597*f*
Lightheadedness, 210*t*, 211–212, 211*t*
Lightning injury, 704
Likelihood ratio, 38
Limb-girdle muscular dystrophies, 2584
Limb ischemia
  acute
    clinical categories of, 462*t*
    clinical manifestations of, 462
    diagnosis of, 462
    pathobiology of, 461
    treatment of, 464*b*, 465*f*
  chronic, 463, 463*t*
  critical, 465.e1*f*
Limbic encephalitis, 2532*t*
Limbic encephalopathy, 1238*t*
Limbs, disorders of, occupational and environmental, 86*t*
Limited cutaneous systemic sclerosis, 1777, 1777*t*
Linaclotide, for irritable bowel syndrome, 895*b*, 896*t*
Linagliptin, for type 2 diabetes mellitus, 1541*t*
Lincosamides, dosage of, 1895*t*
Linear hypopigmentation, 2743
Linear immunoglobulin A bullous dermatosis, 2718, 2718*b*
Linezolid
  for bacterial meningitis, 97*b*, 2518*t*
  dosage of, 1895*t*
  mechanism of action, 1895*t*
  for nontuberculous mycobacterial disease, 2046*t*
  for pneumonia, 616*t*
  spectrum of activity, 1900
  for *Streptococcus pneumoniae* pulmonary infections, 1912.e1*t*
  for vancomycin-resistant enterococci, 1922*t*
Linkage disequilibrium, phenomenon of, 204
Lip cancer, 1325*t*
Lipase, e1*t*–e8*t*
  in acute pancreatitis, 971
Lipid(s)
  abnormal, screening for, 53
  blood levels, 219.e2*f*, 219
  insoluble, 938
  measurement of, 1407
  membrane, 1093
  metabolism of, 1405
    clinical disorder, 1408
Lipid disorders, 1404
  diagnosis, 1407
  genetic, 1408
  hyperlipidemia, 1408, 1408*t*
  pathobiology, 1405
  in women, medications for, 1608*t*
Lipid emulsion, for acute poisoning, 693*t*
Lipid-lowering therapy
  for acute MI, 384*b*
  for acute STEMI, 391*t*
  for chronic kidney disease, 839*b*
Lipid profile, fasting, 384*b*
Lipid storage disorders, 1419*t*
Lipoarabinomannan, 2040
Lipoatrophy, 2317
Lipoglycopeptides
  characteristics of, 1900
  resistance mechanisms, 1893*t*
  toxicities of, 1901*t*
Lipohypertrophy, 2318
Lipoid hyperplasia, 1571
Lipoid pneumonia, 598, 598*b*, 598*f*
Lipolysis, impaired, 933
Lipomas, 526, 1314
Lipophilic *Corynebacteria*, 1934–1935
Lipoproteins, 1406
  high density, 1406, 1406.e1*f*
  low density, 1405
  very low density, 1405
Liposomal amphotericin B, 2077, 2116
  indications and dosage of, 2075*t*
  for leishmaniasis, 2112*t*
Lipoteichoic acid, 1913
Liquid biopsy, 1252
Liraglutide
  for nonalcoholic fatty liver disease, 1034*b*
  for obesity, 1467*b*
  for type 2 diabetes mellitus, 1541*t*
Lirentelimab, 941*b*
Lisinopril, 451*t*
  for acute STEMI, 384*b*, 391*t*
  for heart failure, 266*t*
  for left ventricular dysfunction, 384*b*
Lisinopril/HCTZ, 451*t*
Lissencephaly, 2547
Listeria meningitis, 2515*b*
Listeria monocytogenes, 1861, 1937, 2510–2511
Listerial rhombencephalitis, 1937
Listeriosis, 1937
  clinical manifestations of, 1937
  definition of, 1937
  differential diagnosis of, 1937
  epidemiology of, 1937
  laboratory diagnosis of, 1937–1938
  pathobiology of, 1937
  pathogen of, 1937
  prevention of, 1938
  prognosis of, 1938
  treatment of, 1938*b*
Lithium, e10*t*–e11*t*
  causing hypothyroidism, 1507
  central nervous system effects of, 685*t*
  thyroiditis caused by, 1514
  toxicity, 686*t*, 690*t*, 698*t*
Lithium carbonate
  pharmacokinetic parameters for, 127.e1*t*
  in renal failure, 129.e1*t*
Lithotripsy, for chronic pancreatitis, 975*b*
Litifilimab, for cutaneous lupus erythematosus, 152
Live attenuated influenza virus (LAIV), 66*t*, 79
Live vaccinia virus, 66*t*
Live virus vaccine, 66*t*
  for measles, 2222
Livedo racemosa, 469–470, 469*f*, 470*b*, 2691*t*
Livedo reticularis, 469, 469*f*, 681, 2691*t*
Liver
  alcohol use disorders and, 2354–2355, 2355, 2355*t*
  anatomy of, 1358*f*
  cystic fibrosis and, 556
  examination of, 31
  function of, 986
  glucocorticoids metabolism in, 145
  infections of, 1022–1029
    bacterial, 1022
    helminthic, 1024, 1025
    parasitic, 1024, 1026*t*
    protozoal, 1024
  mass lesion in, approach to, 991*f*
  percussion of, 988
  ultrasound of, 1000
Liver abscess
  amebic, 1022*t*, 1024, 1025*b*, 1025*f*, 2148, 2149*f*, 2149*t*, 2150*t*
  bacterial, 1022*t*
  pyogenic, 1022–1023, 1023*b*, 1023*f*
Liver biopsy, 990
  for alcohol-associated liver disease, 1032, 1034*f*
  in α_1-antitrypsin deficiency, 993*f*
  for chronic viral hepatitis, 1010
  for hemochromatosis, 1441
  in hereditary hemochromatosis, 992, 993*f*
  indication of, 1001, 1001*f*
  Schistosoma mansoni on, 1029.e1*f*
Liver cancers
  epidemiology of, 1358–1359, 1358*f*
  nutrition and, 59
  prevention of, 1362
  primary, 1357.e3*t*
  prognosis of, 1362
Liver cirrhosis, mesenteric venous thrombosis and, 963*t*
Liver disease, 1072*t*, 2666
  abdominal examination in, 988, 988*f*
  abdominal imaging for, 990
  alcohol-associated, 1031
  approach to patient with, 986–993

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Liver disease *(Continued)*
bacterial, 1022
biliary tract disease and, 996
biopsy for, 990
diagnostic studies for, 989–990, 989*t*
drug dose adjustment in, 130
duration of, assessing, 987
family history of, 987
fungal, 1023, 1024*b*
general condition of, 987
granulomatous, 1029, 1030*t*
hematologic tests in, 1000
hemochromatosis and, 1440
hepatic mass in, approach to, 990, 991*f*
history of, 986–987
inherited, approach to, 992–993, 993*f*
laboratory studies for, 989–990
mucocutaneous findings in, 987–988, 987*f*, 988*f*
organ system review in, 987
parasitic, 1024
physical examination of, 987–989, 987*f*, 988–989, 988*f*, 989*f*
in pregnancy, 1625, 1625*t*
protozoal, 1025
risk factors for, 987
in sarcoidosis, 602, 604*t*
transjugular pressure in, measurement of, 990
Liver failure, 1043–1049, 1197–1198
acute, 1044
chronic, 1044
clinical manifestations of, 1043, 1197
diagnosis of, 1043, 1197–1198
epidemiology of, 1043
pathobiology of, 1043, 1197
prognosis for, 1044
treatment of, 1043*b*–1044*b*, 1198*b*
Liver fibrosis, cirrhosis and, 1035
Liver flukes
approach to, 2168
description of, 2165
fascioliasis, 2168
opisthorchiasis, 2168
paragonimiasis, 2168
Liver function tests
alkaline phosphatases, 999
aminotransferases, 998
hepatic enzymes, 999
hepatic synthetic function, 999–1000
metabolites and drugs, 999
for pulmonary hypertension, 495
Liver metastases, pancreatic neuroendocrine tumor with, magnetic resonance imaging of, 872*f*
Liver toxicity, after hematopoietic cell transplantation, 1211
Liver transplantation, 1044–1049, 1044*f*–1045*f*, 1045*f*
for acute liver failure, 1044
chronic, 1044
for chronic liver failure, 1044
for cirrhosis, 1040*b*
coagulation system and, 1043
complications of, 1047–1049, 1047*f*
contraindications to, 1046*t*
for hemochromatosis, 1441*b*
for hepatocellular carcinoma, 1045
immunosuppression for, 1048, 1048*t*
indications for, 1044–1045, 1045*f*
infectious complications of, 1047–1048, 1048*f*
listing for, 1046, 1048*t*
for liver failure, 1197
long-term management for, 1049
metabolic disorders associated with, 1045
for metastatic neuroendocrine tumor, 1568*b*
for porphyrias, 1434*b*
preoperative medical assessment for, 1046
preoperative psychosocial assessment for, 1046
for primary sclerosing cholangitis, 1058*b*
procedure, 1046–1047, 1046*f*–1047*f*
recurrent hepatitis C after, 1014*b*
rejection in, 1048, 1048*t*
selection for, 1045–1046, 1046*t*
surgical complications of, 1047
for Wilson disease, 1437*b*
Living donor lobar transplantation, 633
Living kidney donors, 844
Lixisenatide, for type 2 diabetes mellitus, 1541*t*
LMWHs. *See* Low-molecular-weight heparins
Loa loa, 2179
Loading dose, in renal insufficiency, 130
Lobar emphysema, congenital, 565
Lobar hemorrhages, 2479
Lobar holoprosencephaly, 2547
Lobar opacities, 520
Lobectomy, for lung cancer, 1333*b*
Lobular carcinoma in situ, 1369*b*, 1370*t*
Local tetanus, 1928
Localized amyloidosis, 1310, 1310*b*
Localized scleroderma, 1782
Locked-in syndrome, 2437*t*, 2442, 2465
Lockjaw, 1928–1929
Locoregional staging, of head and neck cancer, 1323
Loculated pleural effusions, 525, 525*f*
Locus heterogeneity, 1399
Loeys-Dietz syndrome, 1726
Löffler fibroplastic endocarditis, 295
Löfgren syndrome, 600, 604
Loiasis, 2179, 2179*f*
Lomentospora (Scedosporium) prolificans, infections by, voriconazole for, 2076
Lone Star tick, 2060
Long-acting β-agonists (LABA), for asthma, 541*b*
Long-chain fatty acids, 934–935
Long QT syndrome, 301, 303, 337, 338*f*
type 3 (LQT3), 300
Long-segment Barrett esophagus, 1339
Longevity, in older adults, 115–116, 116*t*
Longitudinal grooves and striations, of nails, 2752
Longitudinal melanonychia, 2754–2755, 2755*f*
Loop diuretics, 736*b*
for hypertension, side effects of, 453*t*
for hypervolemia, 737*t*
nephrolithiasis and, 805*b*
Loop electrosurgical excision procedure, 1375*b*
Loop of Henle disorder, 816*t*, 817
Loop recorders, implantable, 308
Loose anagen hair syndrome, 2750
Loose connective tissue, 1707
Loperamide
for diarrhea, 940
for irritable bowel syndrome, 895*b*, 896*t*
for small bowel rapid transit dysmotility, 890
for traveler's diarrhea, 1888, 1888*t*
Lopinavir/ritonavir, 2217, 2301*t*
Loratadine, for mastocytosis, 1703*b*
Lorazepam
for alcohol withdrawal, 2358*t*
for anxiety disorders, 2344*t*
for heatstroke, 679*b*
for nausea and vomiting, 863*t*
Losartan, 451*t*
for acute STEMI, 391*t*
for heart failure, 266*t*
Losartan/HCTZ, 451*t*
Loss of consciousness, transient, 305, 305*t*
Lotion, 2697
Louping ill virus, 2276*t*, 2282
Louse-borne epidemic relapsing fever, 2027
Lovastatin, for familial hypercholesterolemia, 1409*t*
Low back pain, 2393–2399
ancillary testing for, 2397
clinical examination of, 2396–2397
clinical manifestations of, 2395–2396
computed tomography of, 2397
corticosteroids for, 2398*b*
definition of, 2393
diagnosis of, 2396–2398, 2396*f*
differential diagnosis of, 2397–2398, 2397*t*, 2398*f*, 2403*t*
epidemiology of, 2393–2395
history-taking for, 2396
mechanical, 2399
medications for, 2398*b*
myocardial ischemia associated with, 2398
occupational and environmental, 86
pathobiology of, 2395
prognosis for, 2399
surgery for, 2398*b*
treatment of, 2398*b*
Low-density lipoprotein cholesterol (LDLC), *e*1*t*–*e*8*t*, 57–58
Low density lipoproteins, 1405
low level of, 1410
Low dietary solute, 738
Low-intensity vibration, 1643*b*
Low-molecular-weight heparins (LMWHs), 501*t*, 502, 503*t*
for acute coronary syndrome, 374*t*
in pregnancy, 1623*b*
weight-based dosing of, 487*b*
Low molecular weight iron dextran, for iron deficiency anemia, 1085*t*
Low-output states, management of, 384*b*
Lowe oculocerebrorenal syndrome, 817
Lowe syndrome, 816*t*
Lower abdominal pain, gonorrhea and, 1947
Lower airway allergy, 1674
Lower extremity, cystic adventitial disease of arteries in, 467
Lower gastrointestinal bleeding, 882, 884
colonoscopy for, 885
definition of, 884
diagnosis of, 884
epidemiology of, 884
treatment of, 885*b*
Lower gastrointestinal tract, systemic sclerosis involvement of, 1778
Lower limb ischemia, chronic
classification of, 462*t*
critical, 462
stable, 462
treatment of, 464*b*
Lower lobe predominant fibrosis, 575.*e*1*f*
Lower urinary tract, abnormalities of, 821
LRRK2, 2483
Lubiprostone, for irritable bowel syndrome, 895*b*, 896*t*
Lubrication, for skin diseases, 2700
Lucio leprosy, 2051
Lucio phenomenon, 2051
Lujo hemorrhagic fever, 2268*t*
Lujo virus, 2265*t*
Lumakras. *See* Sotorasib
Lumbar puncture
cryptococcal meningitis associated with, 2088
description of, 2374, 2374*f*, 2374*t*
stroke evaluations, 2468
subarachnoid hemorrhage evaluations, 2475
Lumbar radiculopathy, 2402
Lumbar spinal stenosis, 2399, 2399*b*
Lumbar vertebrae, 2392
Lumbosacral radiculopathy, 2394*t*
Lumefantrine, for malaria, 2121*b*
Lump, in throat, 2652
Lung(s)
congenital cystic adenomatoid malformation, 565
cystic fibrosis and, 556
examination of, 30, 258
hyperlucent, 565
imaging of, 519
shrinking, 580–581
systemic sclerosis involvement of, 1778–1779
Lung abscess, 1904
Lung auscultation, 512*t*
Lung cancer, 1329–1337
adenocarcinomas, 1329, 1329.*e*2*t*
bronchogenic, 1329
clinical manifestations of, 1330
definition of, 1329
diagnosis of, 1330–1335
diagnostic imaging for, 1331–1332
epidemiology of, 1329
epigenetics of, 1330
in HIV, 2316
initial evaluation, 1331–1332, 1332*f*
invasive diagnostic procedures, 1331
large cell carcinoma, 1329, 1329.*e*2*t*
metastatic, 631
molecular pathology of, 1330
molecular testing for, 1333–1335
non-small cell. *See* Non-small cell lung cancer
nutrition and, 59
as occupational lung disease, 585*t*, 591
oncogenes associated with, 1330, 1330.*e*1*f*
pathobiology of, 1329–1330
pathology of, 1329
pleural invasion by, 526
prevention of, 1335–1336
primary prevention of, 1335
prognosis of, 1336
risk factors for, 1329
screening for, 54–55, 1247
secondary prevention of, 1336
Lung cancer *(Continued)*
small cell, 1329–1330. *See also* Small cell lung cancer
solitary pulmonary nodule in, 1330–1331, 1331*f*
squamous cell carcinoma, 1329, 1329.*e*2*t*
staging of, 1332–1333, 1333*t*
supportive care for, 1333*b*
surgery for, 631
surveillance and follow-up for, 1333*b*
treatment for, 1333*b*
tumor suppressor genes associated with, 1330
in women, 1607
Lung disease
acute respiratory failure without, 652
apical, 524*f*
basal, 523, 523*t*
cystic fibrosis and, 557, 557*f*
diffuse, 520
interstitial. *See* Interstitial lung disease
interventional approaches to, 630–634
malignant, 631
surgery for, 631
occupational, 584–591
restrictive, cases of, 533
surgical approaches to, 630
Lung expansion maneuvers, 2664
Lung failure, trajectories of, 12.*e*1*f*
Lung flukes, 2165–2168
Lung function, 547.*e*3*f*
abnormality, common changes associated with, 532*t*
measures of, 528
Lung function tests, interpretation of, 531–532
Lung injury, 597–599
acute, transfusion-related, 598–599, 599*b*
aspiration injury, 597
chemical, 591
lipoid pneumonia, 598
physical, 591
radiation, 597, 597*b*
ventilator-induced, 655, 655.*e*1*f*
Lung neuroendocrine neoplasms, 1567
Lung transplantation, 551*b*, 632–634
acute rejection of, 633
bilateral, 632–633
chronic rejection of, 633
complications of, 633–634
for cystic fibrosis, 558*b*
decision guide for, 632*t*
heart-lung transplantation, 633
indications for, 632, 632*t*
living donor lobar transplantation, 633
post-transplantation issues, 633
prophylaxis after, 633
recipients, evaluation of, 633
single-lung, 633
survival estimates, 634.*e*1*f*
types of procedures, 632–633
Lung volume, 523
absolute, 530
body plethysmography for, 530
conditions associated with, 523*t*
inert gas dilution technique for, 530
nitrogen washout technique for, 530
in pulmonary function tests, 528*t*, 530, 530*f*
reduced, 533
Lung volume reduction, 551*b*
Lung volume reduction surgery, 631–632
decision guide for, 632*t*
inclusion and exclusion criteria for, 632*t*
mortality of, 631.*e*1*f*
Lupkynis. *See* Voclosporin
Lupron. *See* Leuprolide acetate
Lupus, during pregnancy, 1770
Lupus anticoagulant, 1193, 1715
clinical manifestations of, 1194
diagnosis of, 1194
epidemiology of, 1193
pathobiology of, 1193
treatment of, 1194*b*
Lupus erythematosus, 2621*t*
Lupus nephritis, 1769, 1771–1772, 1773*f*–1774*f*
classification of, 787–788, 787*t*
Lupus panniculitis, 2687.*e*4*t*, 2735
Lupus pernio, 601, 602*f*
Lurasidone, for psychotic disorders, 2346*t*
Lurbinectedin (Zepzelca), 1215*t*
Lutein, 1452

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Luteinization, 1595–1596
Luteinizing hormone (LH), *e1t–e8t*, 1496
  description of, 1580
  gonadotropin-releasing hormone effects on, 1476
  insufficiency tests of, 1484*t*
  pathobiology of, 1496
  in puberty, 1591
  secretion of, 1582
  subunits of, 1581
  syndrome, 1561*t*
  tests of, 1488*t*
  tumors that produce, 1496, 1496*b*
Lutembacher syndrome, 348
Luteogenesis, 1595–1596
Luteomas, of pregnancy, 1573
LVEF. *See* Left ventricular ejection fraction
17,20 Lyase deficiency, 1571
Lyme arthritis, 1808, 2024, 2026*b*
Lyme borrelia, 2022
Lyme borreliosis, 2022
Lyme disease, 286, 318–319
  Borrelia burgdorferi and, 1279
  cardiac, 2024, 2027
  chemoprophylaxis for, 2027
  chronic, 2027
  clinical manifestations of, 2023, 2023*f*
  coinfections, 2026*b*
  definition of, 2022–2027
  diagnosis of, 2025–2026, 2025*t*
  differential diagnosis of, 2025–2026
  early neurologic, 2024
  epidemiology of, 2022, 2023*f*
  extracutaneous, 2025–2026
  late, 2024–2025
  late neurologic, 2024
  neurologic manifestations of, 2024
  pathobiology of, 2022–2023
  pathogen that causes, 2022
  post-Lyme disease and syndrome, 2027
  in pregnancy, 2026*b*
  prevention of, 2026–2027
  prognosis of, 2027
  reinfection of, 2026*b*
  serologic testing for, 2027
  in travelers, 1889.*e1t*
  treatment of, 2026*b*
Lyme myocarditis, 2026*b*
Lymph nodes, 1148
  biopsy of, 1150
  on chest images, 524
  enlarged, 524, 524*t*
  enlargement of, 1148
  regional, treatment of, 1393*b*
Lymphadenitis
  acute, 2177
  chancroid and, 1951*f*
  tuberculosis, 2037
Lymphadenopathy, 1148–1151, 2001
  autoimmune disorders associated with, 1150
  biopsy of, 1151
  blood testing for, 1150
  clinical manifestations of, 1148
  computed tomography of, 1150
  diagnosis of, 1149–1151
  differential diagnosis of, 1149–1150, 1149*t*, 1150*f*
  evaluation of, 1151
  fever and, 1849, 1849*t*
  generalized, 1151
  history of, 1149
  imaging of, 1150–1151, 1150*f*
  localized, 1149–1150
  malignancy presenting as, 1150, 1150*f*
  in parapoxvirus, 2239
  physical examination of, 1149, 1149*t*
  in systemic lupus erythematosus, 1770
  treatment of, 1151*b*
  West African sleeping sickness and, 2124
Lymphangioleiomyomatosis, 583, 583*b*, 583.*e1f*
Lymphangitic carcinomatosis, distinguishing features of, 515*t*
Lymphangitis, in parapoxvirus, 2239
Lymphangitis-associated rickettsiosis (LAR), 2055*t*
Lymphatic drainage, impaired, 938
Lymphatic filariasis, 2176, 2177*b*–2178*b*, 2177*f*
Lymphatic system, examination of, 30
Lymphedema, 1369*b*
Lymphocutaneous disease, 2073
Lymphocutaneous sporotrichosis, 2086, 2086*f*
Lymphocyte apoptosis, defects in, 1685
Lymphocytes, 187–191
Lymphocytic choriomeningitis, 2521, 2535
Lymphocytic hypereosinophilic syndrome, 1162, 1163*t*
Lymphocytic hypophysitis, 1483–1484
Lymphocytic infundibuloneurohypophysitis, 1503
Lymphocytic interstitial pneumonia, 574*t*, 579, 580*b*
Lymphocytic interstitial pneumonitis, 2319
Lymphocytic phlebitis, 916
Lymphocytoma, borrelial, 2024
Lymphocytosis, 1142, 1143*t*
Lymphogranuloma venereum, 2012, 2019
  chancroid and, 1951
  characteristics of, 1881
  organisms causing, 1879*t*
Lymphohematopoiesis, hierarchical model of, 1064*f*
Lymphohistiocytosis, hemophagocytic, 1684
Lymphoid diseases, in chronic lymphocytic leukemia, 1268–1269
Lymphoid follicle, from airway submucosa, 556.*e3f*
Lymphoid interstitial pneumonia, 579, 580*b*, 580.*e1f*
Lymphoid polyps, 1348
Lymphoid tissue, 187
Lymphoma
  adult T-cell leukemia/lymphoma. *See* Adult T-cell leukemia/lymphoma
  arthritis associated with, 1823
  Burkitt, 1286, 1286*b*
  diffuse large B-cell, 1279, 1284, 1285*b*
  Hodgkin. *See* Hodgkin lymphoma
  non-Hodgkin. *See* Non-Hodgkin lymphoma
  peripheral blood smear of, 1073
  primary central nervous system, 1316, 1316*b*, 1316*f*
  primary lung, 1336
  Sjögren syndrome and, 1785
  stomach, 1342
Lymphomatoid granulomatosis, 2256
Lymphomatoid papulosis, 1286, 2734
Lymphoplasmacytic lymphoma, 1088–1089, 1279–1280, 1280, 1286, 1286*b*
Lymphoproliferative disorders, increased lymphocyte counts in, 533
Lymphoproliferative syndromes, 1684*t*
Lynch syndrome, 162, 1249, 1250*t*, 1377
Lynparza. *See* Olaparib
Lysinuric protein intolerance, 816*t*, 1398*t*
Lysis, osmotic, 199
Lysosomal acid lipase deficiency, 1420*t*, 1424
Lysosomal storage diseases, 1418–1424, 1419*t*
  aspartylglucosaminuria as, 1423
  classification of, 1419*t*
  clinical manifestations of, 1419, 1420*t*
  cystinosis as, 1420*t*, 1424
  diagnosis of, 1419
  epidemiology of, 1418–1419
  Fabry disease as, 1421
  Gaucher disease as, 1420
  lysosomal acid lipase deficiency as, 1420*t*, 1424
  metachromatic leukodystrophy as, 1423
  mucopolysaccharidoses as, 1420*t*, 1424
  neuronal ceroid-lipofuscinoses as, 1420*t*, 1424
  Niemann-Pick disease type C as, 1420*t*, 1423
  pathobiology of, 1418
  Pompe disease as, 1424
  prognosis of, 1419*b*
  Tay-Sachs disease as, 1423
  treatment of, 1419*b*, 1420*t*

M

M-BCR. *See* Major breakpoint cluster region
m-iodobenzylguanidine, 261
M proteins, 1913–1914
M-type immunoglobulins (IgM), 2005
MAC. *See* Membrane attack complex
Machine learning, 37
Machupo virus, 99.*e1t*, 2265*t*
Macro-ovalocytes, 1067*f*
Macroadenoma, 1523
Macrocyte, 1067*f*
Macrocytic anemia, 1079, 1082
  cause of, 1072*t*
  peripheral blood smear of, 1067*f*, 1069
Macrocytic hypochromic anemia, 1083*t*
Macrocytosis
  causes of, 1117*t*, 1120
  definition of, 1120
Macroglossia, in amyloidosis, 1306*f*
Macrolides
  for chancroid, 1951*b*
  characteristics of, 1899
  for cystic fibrosis, 558*b*
  dosage of, 1895*t*
  mechanism of action, 1895*t*
  resistance mechanisms, 1893*t*
  toxicities of, 1901*t*
Macrophage activation syndrome, 1159
Macrophage-derived cytokines, rheumatoid arthritis and, 1750–1751
Macrophages, 182–183, 191
Macroprolactin, 1490
Macroprolactinoma, 1492*f*
Macrovesicular steatosis, 1031, 1031*t*
Maculae ceruleae, 712*f*
Macular edema, 1549*t*
Macular exanthems, 2712
Macular purpura, 2713–2714, 2713*t*–2714*t*, 2714*f*–2715*f*
Maculatum rickettsiosis, 2065*t*
Macule, 2644, 2689*t*
Maculopapular exanthems, 1857
Maculopapular rash
  measles-related, 2220
  in rubella, 2224, 2224*f*
Maffucci syndrome, 1669
Magnesium, *e1t–e8t*
  deficiency, 766–767, 766*b*–767*b*, 766*t*
  deficiency of, 2538*t*
  depletion, 288
  diarrhea and, 939
  free, *e1t–e8t*
  for malabsorption, 937*t*
  metabolism, 766
  for narcolepsy, 2449*t*
  as occupational and environmental hazards, 88*t*
Magnesium ammonium phosphate stones, 804
Magnesium sulfate
  for advanced cardiac life support, 315*f*
  for arrhythmias, 313*b*
  for torsades de pointes, 338*b*
Magnetic coils, 519
Magnetic resonance angiography (MRA)
  in atherosclerotic PAD, 463, 463*f*
  description of, 872
  of renal artery stenosis, 800
  strengths and weaknesses of, 2373*t*
Magnetic resonance cholangiopancreatography (MRCP), 872, 1055
  for pancreatic duct obstruction, 970
  secretin-enhanced, for malabsorption, 931*t*
Magnetic resonance (MR) elastography, 872–873
Magnetic resonance (MR) enterography, description of, 872, 873*f*
Magnetic resonance imaging (MRI), 519
  acute MI on, 384
  acute pancreatitis on, 970–971, 971
  Alzheimer disease on, 2414, 2415*f*
  anterior pituitary on, 1483, 1484*f*–1485*f*, 1485*f*
  brain abscess on, 2526, 2526*f*
  brain tumors on, 1311, 1312*f*
  breast cancer screening uses of, 1373–1374
  cardiac
    in heart failure, 261
    stress, 362
  cardiovascular, 251, 251*f*
  cerebral microbleeds on, 2479*f*
  cervical spine on, 2401*f*
  chronic pancreatitis on, 974
  Creutzfeldt-Jakob disease on, 2424*f*
  Cushing disease on, 1494
  empty sella on, 1486*f*
  epilepsies on, 2431
  frontotemporal lobar degeneration on, 2423*f*
  gadolinium-enhanced, 2527
  in gastroenterology, 871, 872*f*, 873*f*
  herpes simplex encephalitis on, 2533, 2533*f*
  hippocampal formation on, 2407
  hypoglycemia on, 1557
  infectious endocarditis on, 2530
  liver disease on, 990
  lumbar spinal stenosis on, 2400*f*, 2402*f*
  macroprolactinoma on, 1492*f*
  meningiomas on, 1313, 1313*f*–1314*f*, 1314*f*
Magnetic resonance imaging (MRI) *(Continued)*
  metabolic bone disease on, 1638
  multiple sclerosis on, 2501–2503, 2502*f*–2503*f*, 2502*f*, 2502*t*, 2503*f*
  pancreatic duct obstruction on, 970
  paralytic rabies on, 2535
  pelvic inflammatory disease on, 1949
  pituitary tumors on, 1487
  rheumatic disease on, 1720–1723, 1721*f*–1722*f*
  strengths and weaknesses of, 2373*t*
  stroke on, 2467*f*, 2471*f*
  subdural empyema on, 2528, 2528*f*
  vasculitis on, 728, 729*f*
  venous thromboembolism on, 485–486
Magnetic resonance spectroscopy (MRS), strengths and weaknesses of, 2373*t*
Magnetoencephalography, for epilepsies, 2431
Magnocellular neurons, 1498
Mahvash disease, 1564
Major breakpoint cluster region (M-BCR), 1273
Major depressive disorder, 2337–2341
  clinical manifestations of, 2338, 2338*t*
  continuation and maintenance therapies for, 2338*b*–2341*b*
  definition of, 2337–2341
  diagnosis of, 2338
  epidemiology of, 2337–2338
  pathobiology of, 2338
  prognosis of, 2341
  symptoms/signs of, 2338*t*
  treatment for, 2338*b*, 2339*f*, 2339*t*, 2340*t*, 2346*t*
Major histocompatibility antigens
  class I deficiency, 1678, 1678.*e1t*
  class II deficiency, 1678, 1678.*e1t*
Major histocompatibility complex (MHC), 1*t*–2*t*, 203, 204*t*, 204.*e1f*, 204.*e2t*, 1760
Mal de débarquement syndrome, 2644
Malabsorption, 932, 932.*e1f*, 933*f*, 2145
  causes of, 928*t*
  clinical consequences of, 929*t*
  congenital, 938
  evaluation of, test for, 931*t*
  laboratory tests for, 930, 931*t*, 932*t*
  micronutrient deficiency caused by, 1452
  vitamin deficiency caused by, 2537
  weight loss and, 860*t*
Malaise, liver disease and, 986
Malakoplakia, 791
Malar rash, in systemic lupus erythematosus, 1770*f*
Malaria, 2065*t*, 2111–2115, 2118–2123
  anemia caused by, 2314
  characteristics of, 2270*t*
  chemoprophylaxis for, 1887–1888, 1890*t*, 2123*t*
  clinical features of, 2120
  clinical manifestations of, 2119–2120
  complications of, 2120
  definition of, 2118–2123
  diagnosis of, 2120–2121
  in endemic countries, 2118
  epidemiology of, 2118
  parasite of
    host immunity and genetics of, 2119
    life cycle of, 2118–2119, 2119*f*
    pathogenic features of, 2119
  pathobiology of, 2118–2119
  pathogen of, 2118
  prevention of, 2112*t*, 2122–2123
  prognosis of, 2123
  prophylaxis for, 2309*t*
  severe, 2120
  splenomegaly associated with, 1152
  transmission of, 2118
  in travelers, 2118
  treatment of, 2112*t*, 2121*b*, 2121*t*
  uncomplicated, 2119–2120
Malarone, for malaria, 2121*b*, 2121*t*, 2123*t*
Malassezia furfur, 2703
Malassezia globosa, 2711
Malathion
  for lice, 2742*b*
  for scabies, 711*b*
Maldigestion, micronutrient deficiency caused by, 1452
Male circumcision, 1884
Male condom, 1612
Male genitalia, examination of, 31

Copyrighted material

Male hypogonadism, 1582
androgen preparations for, 1586*t*
definition of, 1582
epidemiology of, 1582
in HIV, 2318
pathobiology of, 1583
testosterone delivery systems for, 1585*b*
treatment of, 1585*b*
Male infertility, 1586
algorithm for, 1587*f*, 1588*f*
basic laboratory tests for, 1589*t*
clinical manifestations of, 1586
diagnosis of, 1586
treatment of, 1586*b*
Male osteoporosis, 1646, 1646*b*
Male reproductive axis, 1580
Male reproductive physiology, 1580–1582, 1580*f*
Male senescence, 1582
Malignancy
in chronic lymphocytic leukemia, 1271
in chronic pancreatitis, 975*b*
hypercalcemia of, 1658, 1659*b*
Malignant ascites, 957, 958*b*
Malignant atrophic papulosis, 965, 969
Malignant diseases
arthritis associated with treatments for, 1823
in hypercoagulable states, 479–480, 479*b*, 480*f*
Malignant effusions, 625–626, 625*b*–626*b*
Malignant histiocytosis, 1159, 1159*b*
Malignant hyperthermia, 678, 715, 717*b*, 2583.*e1t*
anesthesia and, 2668, 2668*b*
Malignant melanoma, in adolescents, 111
Malignant mesothelioma, 1336
treatment and prognosis of, 1336*b*
Malignant neoplasms
in adolescents, 110*t*
alcohol use disorders and, 2355–2356
in renal transplantation, 847
with venous thromboembolism, 479, 480*f*
Malignant otitis externa, 1969
Malignant pericarditis, 432
Mallory-Weiss tear, 856, 882*f*, 912
Malnutrition
acute, 1444, 1445.*e1f*, 1446*t*
assessment and support for, 1446–1451
clinical manifestations of, 1447
common causes of, 1447*t*
definition of, 1446–1451
diagnosis of, 1447–1448, 1448*f*, 1449*t*
epidemiology of, 1446–1447
in older adults, 114
pathobiology of, 1447, 1447*f*
primary, in children and adolescents, 1445*b*
prognosis of, 1450–1451
screening for, 1447, 1448*t*
secondary, 1445, 1445*b*
severe, 1444–1446
clinical manifestations of, 1444–1445
definition of, 1444–1446
diagnosis of, 1445
epidemiology of, 1444
kwashiorkor, 1444, 1444*f*, 1445*f*
marasmus, 1444, 1444*f*
pathobiology of, 1444
prevention of, 1446
prognosis for, 1446
secondary, 1444
stunting, 1445
treatment of, 1445*b*
wasting, 1445
therapy for, 1448–1450, 1450*f*
vitamin deficiency caused by, 2537
MALT. *See* Mucosa-associated lymphoid tissue
Malta fever. *See* Brucellosis
Mammalian target of rapamycin (mTOR)
aging and, 115
inhibitors
for liver transplantation, 1048, 1048*t*
for renal transplantation, 845*t*
for renal cell carcinoma, 1364*b*
MammaPrint, 168
Mammillary bodies, 2407
Mammography, for breast cancer screening, 1373, 1373*t*
Mandatory consultations, 2658
Manganese, *e1t*–*e8t*, 1457*t*
hazards, 88*t*
parkinsonism and, 101*t*, 107, 107*b*
Manganism, 107
Mangled Extremity Severity Score, 717*b*
Mania, 2337*t*, 2341*t*
Manic-depressive illness, weight loss and, 860*t*
Mannitol
for drowning, 592*b*
for rhabdomyolysis, 717*b*, 717*t*
Mannose-binding lectin, 186
Mansonella ozzardi, 2180
Mansonella perstans, 2180
Mansonella streptocerca, 2180
Mantle cell lymphoma, 1284, 1284*b*
immunophenotype of, 1268*t*
Mantoux tuberculin skin test, 2039
Manual therapies, 154
MAOIs. *See* Monoamine oxidase inhibitors
MAP kinase pathway, 1251–1252, 1251.*e1f*
MAPK. *See* Mitogen activated protein kinase pathway
Maple syrup urine disease, 1398*t*, 1402*t*
Marasmus, 1444, 1444*f*
Maraviroc, 2301*t*
Marburg disease, 2501
Marburg virus, 99.*e1t*, 2264, 2265*t*, 2268*t*
March fracture. *See* Stress fracture
Marchiafava-Bignami syndrome, 2545
Marcus-Gunn pupil, 2500
Marfan syndrome, 210, 439, 1641
description of, 158, 1725, 1726*b*
Marginal alopecia, 2747*t*
Marginal micronutrient deficiencies, 1459–1460
Marginal ulcer, 913
Marginal zone lymphoma, 1268*t*, 1269, 1283, 1283*b*, 1284*t*
Margination, neutropenia due to, 1146
Marijuana, 2364
on cancer pain, 12
clinical manifestations and diagnosis of, 2364
epidemiology of, 2364
in palliative care, 16
pathobiology of, 2364
properties of, 142*t*
treatment of, 2364*b*
Marine animals, envenomation of, 712, 712*b*
Marine dinoflagellates, as source of food poisoning, 925
Marine omega-3 fatty acid, for hypertriglyceridemia, 1414*b*
Maroteaux-Lamy syndrome, 1724*t*
Marrow graft failure, hematopoietic cell transplantation and, 204
Marrow injury, neutropenia due to, 1145, 1145*f*
Marrow stimulation, neutrophilia and, 1141
MASCC Index. *See* Multinational Association for Supportive Care in Cancer Index
Masked hypertension, 447, 447.*e1f*
Masks, for HIV transmission prevention, 2300
Mass spectrometry, for *Bartonella* infection, 2002
Massage therapy, 154
Masses, mediastinal, 628–629
Massive pulmonary embolism, 487*b*
Massive transfusion, 1205
Mast cell(s), 183
acute inflammation and, 191
description of, 538
mediators released by, 1691
Mast cell activation syndrome, 1693
Mast cell leukemia, 1702
Mastalgia, 1374
Mastitis, 1374, 2226, 2226*t*
Mastocytomas, 1700–1701
Mastocytosis, 1699–1704
biopsy for, 1701–1702, 1702*f*
clinical manifestations of, 1700–1701
cutaneous, 1699, 1700, 1700*f*, 1701
cytoreductive therapy for, 1703*b*
definition of, 1699–1704, 1699*t*
diagnosis of, 1701–1703, 1701*f*
eosinophilia in, 1701
epidemiology of, 1700
gastrointestinal symptoms of, 1701
genetics of, 1700
hematologic manifestations of, 1701
medical therapy for, 1703*b*
musculoskeletal symptoms of, 1701
pathobiology of, 1700
prognosis for, 1704
protean clinical manifestations of, 1700
symptoms of, 1700, 1700*f*
systemic, 917, 1694, 1701–1703, 1703*f*
treatment of, 1703*b*
venom immunotherapy for, 1703*b*
Matrix-assisted laser desorption, for *Bartonella* infection, 2002
Matrix metalloproteinases, 227
Maturation arrest, 1143–1144
Maturity-onset diabetes of the young (MODY), 1539
Mavenclad. *See* 2-Chlorodeoxyadenosine
Maxi-K channels, 746
Maximal medical improvement, 85
Maximal mid-expiratory flow rate (MMEFR), 539, 539*t*
Maximal voluntary ventilation (MVV), 528, 531, 531*f*
Maximum surgical blood order schedule, 1200
May-Hegglin anomaly, 1071, 1179
Mayaro virus, 2275*t*, 2279, 2279*b*
Mayer-Rokitansky-Küster-Hauser (MRKH) syndrome, 1574
Mayzent. *See* Siponimod
Maze procedure, 329*b*
MC1R. *See* Melanocortin-1 receptor
McArdle disease, 1417*t*, 2586
McCune-Albright syndrome, 1487*t*, 1523, 1558, 1559*t*, 1668
MCH. *See* Mean corpuscular hemoglobin
MCHC. *See* Mean corpuscular hemoglobin concentration
McMahon Score Calculation, 717.*e1t*
MCP. *See* Membrane cofactor protein
MCTD. *See* Mixed connective tissue disease
MCV. *See* Mean corpuscular volume
MDI. *See* Methylene diphenyl diisocyanate
Mean arterial pressure, 677*t*
Mean corpuscular hemoglobin (MCH), *e8t*–*e9t*, 1076*t*
Mean corpuscular hemoglobin concentration (MCHC), *e8t*–*e9t*, 1076*t*, 1095
Mean corpuscular volume (MCV), *e8t*–*e9t*, 1076*t*, 1081*f*, 1095
Mean platelet volume (MPV), *e8t*–*e9t*
Meaningful Use standards, 46
Measles, 2220–2223, 2621*t*
characteristics of, 2270*t*
clinical manifestations of, 2221, 2222*f*
clinical progression of, 2221*f*
complications of, 2221
definition of, 2220–2223
diagnosis of, 2221–2222, 2223*t*
epidemiology of, 2220
German. *See* Rubella
global strategies, 2223
immunization for, 65*t*, 66*t*, 78*f*, 80
adverse reactions of, 80
indications for, 80
schedule of, 76.*e1t*, 77*f*
incidence of, 2220
Koplik spots associated with, 2220
pathobiology of, 2220–2221
prevention of, 2222–2223
prognosis for, 2223
rash associated with, 1847, 2221
in travelers, 1889.*e1t*
treatment of, 2222*b*
vaccination for, 2223
vaccine safety for, 2222–2223
vitamin A supplementation for, 2222*b*
Measles inclusion-body encephalitis, 2221
Measles-mumps-rubella (MMR) vaccine, 2225, 2249
Meat, dietary guidelines for, 57.*e3t*
Mebendazole, 2112*t*, 2117
Mecamylamine, for tobacco dependence, 2351*t*
Mechanical circulatory support, 265*b*, 667*b*
Mechanical load, in osteoarthritis, 1738
Mechanical reperfusion, for pulmonary embolism, 487*b*
Mechanical valves, 412*t*
Mechanical ventilation, 652–658
for acute respiratory distress syndrome, 655
assisted, 653
for chronic obstructive pulmonary disease, 649*b*
complications of, 654–655
discontinuation of, 657–658, 657*f*
high-frequency ventilation, 653
initiation of, 655, 655*t*
intermittent mandatory ventilation, 653
lung-protection strategies, 656
negative-pressure ventilators, 653
neurally adjusted ventilatory assist, 653
Mechanical ventilation *(Continued)*
noninvasive, 620.*e1t*
for obstructive airway disease, 657
positive end-expiratory pressure, 653–654
positive-pressure ventilators, 652–654
pressure-controlled ventilation, 653
pressure-support ventilation, 653
proportional assist ventilation, 653
for shock, 673*b*
specific common treatment scenarios, 655–657
for thermal injury, 595*b*
volume-controlled ventilation, 653
Meckel diverticulum, 951, 951*b*, 951*f*
Meclizine, for nausea and vomiting, 863*t*
Meclofenamate, for dysmenorrhea, 1596*t*
Medial epicondylitis, 1745, 1745*b*
Medial infarction, 2465.*e1f*
Median arcuate ligament syndrome, 967
Mediastinal masses, 628
anterior, 628–629
causes of, 628*t*
clinical manifestations of, 628, 628*f*
diagnosis of, 628–629
pathobiology of, 628
treatment of, 629*b*
Mediastinitis, 629
Mediastinoscopy, 1331
Mediastinum, 628–629
anterior compartment lesions, 628, 628*f*
compartments of, 527, 527*f*, 628.*e1f*
imaging of, 519, 526, 526*t*
techniques for, 526–527, 526*f*
pneumomediastinum, 629
Medicaid, 19
Medical abortion, 1617
description of, 1610
Paeniclostridium sordellii associated with, 1927
Medical care
coordination between, and community, 64
viewing, 42
Medical consultation
approach to, 2656
comanagement, 2657*t*, 2658
consultant in, 2658
curbside, 2657
electronic, 2658
impact of, on patient outcome, 2659
issues about, setting-specific, 2656–2657
mandatory, 2658
medical-medical consultations, 2656
postoperative surgical consultation, 2656
preoperative surgical consultation, 2656
principles of, 2656–2659
settings of, 2656
special consultative situations, 2657–2658
for special populations, 2656–2657
strategies for, 2657, 2657*t*
subspecialty, 2657, 2657*t*
telehealth, 2658, 2658*f*–2659*f*
Medical errors, in postoperative care, 2672
Medical exposures, of radiation, 92
Medical expulsive therapy, for nephrolithiasis, 805*b*
Medical history, 28, 29*t*, 2660–2661
complete, 212
family history, 28
history of the present illness, 28
past medical history, 28
review of systems, 28, 29*t*
surgical history, 28
Medical issues
alcohol use disorders and, 2356
in renal replacement therapy, 842
Medical marijuana
on cancer pain, 12
in palliative care, 16
Medical-medical consultations, 2656
Medical oncologist, 1232
Medical practice, changes in, 2
Medical profession, 4
Medical professionalism, 4
Medical resources, allocation of scarce, 9
definition of, 9
empirical data for, 10, 10*t*
ethical values for, 9*t*
history of, 9
justification of, 9
practical consideration for, 10

Copyrighted material

Medical rhythm control, for atrial fibrillation, 329*b*, 330*t*
Medical surveillance, 87
Medical therapy
  for chronic pancreatitis, 975*b*
  conventional, for systemic lupus erythematosus, 1772*b*
  for hypertension, 450
  for nephrolithiasis, 805*b*
  for pain, in chronic pancreatitis, 975*t*
  for pituitary tumors, 1487*b*
  for primary hyperparathyroidism, 1657*b*
  for upper gastrointestinal bleeding, 883*b*
  for Zollinger-Ellison syndrome, 1563*b*
Medical unit, psychiatric diseases in, 2679
Medicare, 19
  Value-based Purchasing program, 46
Medicare Hospice Benefit, 12
Medication-related diarrhea, 926
Medication review, in geriatric assessment, 118
Medication use counseling, 265*b*
Medicine
  accountability, 4
  anaphylaxis caused by, 1692
  approach to, 2–3, 3.e1*t*
  balancing professional responsibilities, 4
  changes in medical practice, 2
  clinical reasoning and decision-making, 3–4
  evidence-based, 2
  historic evolution of, 2–3
  incorporating a public health focus, 4
  internal, 2
  as learned and humane profession, 2–5
  new therapeutics, 3
  obesity caused by, 1465, 1466*t*
  psychiatry and, 2679
  social justice, 4
  societal implications, 3
  standard, 4
  teamwork, 4
  treatment, 3.e1*t*
  vitamin levels affected by, 1452, 1460*t*
Meditation, 154
Mediterranean diet, 58, 58*f*, 450
Mediterranean fever. *See* Brucellosis
Mediterranean spotted fever, 2055*t*, 2057
Mediterranean-type diet, for chronic kidney disease, 839*b*
Medium-chain acyl-CoA dehydrogenase deficiency, 2586
Medium vessel vasculitis, 965, 1792*t*, 1793–1794, 1795
Medullary collecting duct, 754, 754.e1*f*
Medullary sponge kidney, 814, 814*b*
Medullary stroke syndromes, 2465.e1*f*
Medullary thyroid cancer, 1518–1519, 1519*b*
Medulloblastomas, 1316, 1316*b*
Mees lines, 104
Mefenamic acid
  for chronic pain, 138*t*
  for dysmenorrhea, 1596*t*
Mefloquine, for malaria, 1887, 2112*t*, 2114, 2121*b*, 2121*t*, 2123*t*
Megacolon
  idiopathic, 890
  toxic, in ulcerative colitis, 945*b*
Megadisease, Chagas disease and, 2127
Megakaryoblasts, 1073
Megaloblastic anemia, 1080, 1117
  causes of, 1117*t*
  clinical manifestations of, 1120
  complications of, 1120, 1121*f*
  definition of, 1117, 1117*t*
  diagnosis of, 1122
  epidemiology of, 1117
  pathobiology of, 1118
  peripheral blood smear of, 1069, 1072*t*
  prevention of, 1124
  prognosis of, 1124
  treatment of, 1123*b*
Meibomian glands, 2596
Meigs syndrome, 626
Meissner plexus, 887, 901
MEK inhibitors, for melanoma, 1393*b*
Mekinist. *See* Trametinib
Mektovi. *See* Binimetinib
Melanocortin-1 receptor (MC1R), 1391
Melanocortin 4, endocrine diseases caused by, 1475*t*
Melanocytes, 1390
Melanocytic lesions, 2730–2731, 2733*f*
Melanoma, 1390–1395, 2691*t*
  acral lentiginous, 1391
  adjuvant therapy for, 1393*b*
  advanced, 1393*b*
  algorithm for, 1393*f*
  characteristics of, 1392*t*
  in chronic lymphocytic leukemia, 1268
  clinical manifestations of, 1391
  diagnosis of, 1391–1392
  dysplastic nevi associated with, 1390, 1391*f*, 1392*t*
  epidemiology of, 1390
  evaluation of, 1392
  follow-up for, 1393*b*
  immunotherapy for, 1393*b*
  inherited genetics of, 1391
  lentigo maligna, 1391, 1392*f*
  malignant, in adolescents, 111
  metastatic, 1393*b*
  mucosal, 1391
  nodular, 1391, 1392*f*
  ocular, 1391
  pathobiology of, 1390–1391
  prevention of, 1394
  primary, 1393*b*
  primary lesion in, biopsy of, 1391–1392
  prognosis for, 1394–1395
  regional lymph nodes and, 1393*b*
  risk factors for, 1390
  sentinel lymph node biopsy for, 1392
  somatic mutations in, 1390
  staging for, 1392
  superficial spreading, 1391, 1392*f*
  surveillance of, 1393*b*
  treatment of, 1393*b*, 1393*f*
Melanonychia, 2754–2755, 2755*f*
Melarsoprol, for African trypanosomiasis, 2112*t*, 2116, 2125*t*
Melasma, 2689*t*, 2744*b*
MELD. *See* Model for End-Stage Liver Disease; Model for End-stage Liver Disease
Melena, 864
Melioidosis, 1972, 1972*b*
  characteristics of, 2270*t*
  in travelers, 1889.e1*t*, 1891*t*
Melorheostosis, 1668, 1668*b*
Meloxicam, for chronic pain, 138*t*
Melphalan, for amyloidosis, 1308*b*
Memantine, for Alzheimer disease, 2416*b*
Membrane attack complex, 1091–1092
Membrane attack complex (MAC), 199–200
  activation of, 199.e1*f*, 201*t*
  regulation of, 200, 202*f*
Membrane cofactor protein (MCP), 200*t*
Membrane lipids, 1093
Membrane proteins, 1093
Membranoproliferative glomerulonephritis, 785, 786*b*, 786*f*, 786*t*
Membranous glomerulopathy, 781*f*
Membranous nephropathy, 727–728, 779–780
  clinical manifestations of, 780
  diagnosis of, 780, 780*f*–781*f*
  prognosis for, 780
  treatment of, 780*b*, 782*f*
Memory
  immune system and, 190–191
  loss of, neurologic diseases that cause, 2372
MEN. *See* Multiple endocrine neoplasia
MenACWY vaccine, 80
Menarche, 110
MenB vaccines, 80
Mendelian inheritance, 160, 161*f*
Mendelian Inheritance in Man, 158
Meniere disease
  hearing loss caused by, 2642
  treatment of, 2647*t*
  vertigo caused by, 2645
Meningiomas, 1313
  clinical manifestations of, 1313
  diagnosis of, 1313, 1313*f*, 1314*f*
  epidemiology of, 1313
  pathobiology of, 1313
  prognosis of, 1313*b*
  treatment of, 1313*b*
Meningitis, 2510–2524
  Acinetobacter causing, 1974
  Actinomyces causing, 2068
  anaerobic bacteria causing, 1938–1939
  anthrax and, 1931–1932, 1931
  aseptic
Meningitis *(Continued)*
  cerebrospinal fluid examination in, 2521
  definition of, 2519
  description of, 2030
  differential diagnosis of, 2521
  enterovirus causing, 2520
  epidemiology of, 2519
  herpes simplex virus causing, 2521
  lymphocytic choriomeningitis causing, 2521
  mumps causing, 2521
  noninfectious causes of, 2522, 2522*t*
  nonviral infectious causes of, 2522, 2522*t*
  polymerase chain reaction for, 2521
  prognosis for, 2522
  bacterial species that cause, 1892*t*
  by brain abscesses, 1937
  Brucella, 2515*b*
  Candida, 2091
  cerebral blood flow in, 2512
  cerebrospinal fluid findings in, 2374*t*
  "chemical", 2515
  chronic
    infectious causes of, 2522–2524, 2522, 2523*t*
    intermittent, 2524
    noninfectious causes of, 2523, 2524*t*
    persistent, 2523*t*, 2524*t*
    with predominantly neutrophilic pleocytosis, 2524, 2524.e1*t*
    recurrent, 2523*t*
  cryptococcal, 2087
  enteric infections and, 1870*t*
  enteroviruses causing, 2259, 2259*b*
  eosinophilic, 2523*t*, 2524
  gram-negative bacillary, 2515*b*
  H. influenzae caused by, 1953
  herpes, 2246, 2520
  in immunocompromised host, 1861
  Listeria, 2510, 2515*b*
  meningococcal, 1943, 1944*b*, 1944*t*, 2512, 2515*b*
  mumps and, 2226*t*
  nocardial, cerebrospinal fluid in, 2073
  non-nosocomial causes of, 2514*t*
  nosocomial, 2517*t*
  pneumococcal, 2511, 2514, 2515*b*
  purulent, 2516*t*
  staphylococcal, 2515*b*
  Staphylococcus aureus causing, 2511
  syphilitic, 2017
  in travelers, 1891*t*
  treatment of, 1970*b*
  viral, 2519–2522
    agents of, 2520*t*
    arboviruses causing, 2520
    cerebrospinal fluid findings in, 2521
    clinical manifestations of, 2520–2521
    definition of, 2519–2522
    differential diagnosis of, 2521
    enterovirus, 2520
    epidemiology of, 2519
    herpes simplex virus causing, 2521
    human immunodeficiency virus of, 2521
    lymphocytic choriomeningitis causing, 2521
    pathobiology of, 2520
    polymerase chain reaction for, 2521
  zoonotic, 2515*b*
Meningococcal colonization, initiation of, steps in, 1942.e1*f*
Meningococcal conjugate vaccines, 66*t*
Meningococcal disease, 2511
  chemoprophylaxis against, 1945*t*
  in children, 1941
  clinical manifestations of, 1943, 1943*f*
  epidemiology of, 1942*f*
  immunization for, 66*t*, 80
    adverse reactions of, 81
    indications for, 80
    schedule of, 76.e1*t*, 77*f*
  meningitis caused by, 1943, 1944*b*, 1944*t*, 2519
  necrotic purpura associated with, 1946
  polymerase chain reaction for, 1943–1944
  predisposing risk factor for, 1942
  prevention of, 1944–1945
  prognosis for, 1945–1946
  treatment of, 1944*b*, 1944*t*
  vaccination for, 1944–1945
Meningococcal septicemia, fulminant, 2512–2513
Meningococcemia, 1942, 2741, 2741*f*
  acute, 2695*f*
  characteristics of, 2270*t*
  treatment of, 1944*b*, 1944*t*
Meningococci, 1942
Meningococcus, vaccine, for traveler, 1886*t*, 1887
Meningoencephalitis, 2532*t*
  Chagas disease and, 2127
  definition of, 2531
  diagnosis of, laboratory methods for, 2003*t*
Meningovascular syphilis, 2017
Meniscal tears, 1747, 1747*b*
Menkes disease/syndrome, 1728–1729, 2542, 2550*t*
Menopausal hormone therapy
  discontinuation of, 1630*b*
  extended use of, 1630*b*
  vaginal symptoms and, 1630*b*
  venous thromboembolism and, 1630*b*
Menopausal transition, 1629
  bone health in, 1629
Menopause, 1628–1633
  breast cancer associated with, 1630*b*
  clinical manifestations of, 1629–1632
  cognitive dysfunction associated with, 1630*b*
  coronary heart disease associated with, 1630*b*
  definition of, 1628–1633
  diagnosis of, 1630
  epidemiology of, 1628–1629, 1628*t*–1629*t*
  final menstrual period, 1628
  genitourinary symptoms of, 1630, 1632*t*
  hormonal therapy for, 1630*b*
  mood disorders associated with, 1630, 1630*b*
  pathobiology of, 1629
  prevention of, 1632
  prognosis for, 1632
  restless legs syndrome associated with, 1630
  sleep disturbances in, 1630, 1630*b*
  treatment of, 1630*b*
  vasomotor symptoms of, 1629–1632, 1631*t*
  weight gain after, 1629
Menstrual attacks, porphyrias and, treatment of, 1434*b*
Menstrual cycle, 1595–1596
  cervical mucus, 1595
  cervix, 1595
  cytologic changes in, 1595, 1595*f*
  endometrium, 1595
  luteogenesis, 1595
  ovary changes in, 1595
  ovulation, 1595
  selection, 1595
  vagina in, 1595
Menstrual symptoms, 1596–1597
Mental health
  of adolescents, 112
  in pregnancy, 1623–1624, 1624*b*
Mental illnesses, severe
  health challenges for, 2677–2678
  population health for, 2677
  symptoms and findings in, approach to, 2681–2682, 2683*t*
Mental status, changes in, 2330–2336
  caregiver issues, 2334*b*
  clinical manifestations of, 2332
  definition of, 2331
  development of, 2332
  diagnosis of, 2334
  diagnostic criteria for, 2331*t*
  differential diagnosis of, 2330*t*, 2334
  end-of-life care for, 2334*b*
  epidemiology of, 2331
  evaluation of, 2330, 2330*t*, 2333*f*
  laboratory findings of, 2334
  medical treatment, 2334*b*
  nonpharmacologic management, 2334*b*
  in older adults, 2331
  pathobiology of, 2331
  prevention of, 2335, 2335*t*
  prognosis for, 2336
  treatment of, 2334*b*
Meperidine, 139*t*
Mephenytoin polymorphism, 132*t*
Mepolizumab, 541*b*, 1164*b*
6-Mercaptopurine, 148
  for inflammatory bowel disease, 945*b*, 946*t*
Mercury toxicity, e1*t*–e8*t*, 102, 690*t*
  clinical manifestations of, 103
  diagnosis of, 101*t*, 103
  epidemiology, 102

Copyrighted material

Mercury toxicity *(Continued)*
as hazard, 88*t*
pathobiology of, 102–103
treatment of, 102*t*, 103*b*
Merkel cell carcinoma, 2232, 2232*b*, 2233*f*, 2730, 2732*f*
Merkel cell polyomavirus, 2228*t*, 2231
Meropenem, 1845*t*
Acinetobacter, 1974*b*
for bacterial meningitis, 97*b*, 2516*t*
dosage of, 1895*t*
for meningococcal meningitis and meningococcemia, 1944*t*
for pneumonia, 613*t*, 616*t*
for pyelonephritis and urosepsis, 1877*t*
for pyogenic liver abscess, 1023*b*
Meropenem-vaborbactam, dosage of, 1895*t*
Merozoites, 2141
MERS. *See* Middle east respiratory syndrome
Mesalamine, 945*b*, 946*t*
Mesenchymal stromal cells, 172, 1640
Mesenteric arterial occlusive disease, acute, 960
Mesenteric cysts, 958
Mesenteric fibromatosis, 958
Mesenteric ischemia
acute, 959
clinical manifestations of, 959
diagnosis of, 960, 960*f*
prognosis of, 960
specific, 960
treatment of, 960*b*, 961*f*
chronic, 963, 963*f*
clinical manifestations of, 963
diagnosis of, 963, 964*f*
treatment of, 964*b*
nonocclusive, 962, 962*f*
Mesenteric panniculitis, 958
Mesenteric venous thrombosis, 962, 963*f*, 963*t*
Mesentery, anatomic diseases of, 958, 958*t*
Mesial temporal lobe epilepsy, with hippocampal sclerosis, 2433
Mesial temporal sclerosis, 2433
Mesocardia, 354
Mesonephric duct, 818
Mesothelioma, 590, 627
clinical manifestations of, 627
computed tomography of, 627*f*
diagnosis of, 627
epidemiology of, 627
pathobiology of, 627
prognosis of, 627*b*
treatment of, 627*b*
Messenger RNA-based therapeutics, 177
MET level requirements, 61*t*
Meta-analysis, 37
Metabolic acidosis, 754–762, 756
anion gap, 757, 757*t*
in chronic kidney disease, 836
clinical manifestations of, 757
epidemiology of, 756–757
expected compensation of, 755, 756*t*
hyperchloremic, 760, 760*f*
pathobiology of, 756
potassium levels affected by, 747
prognosis of, 762
treatment of, 762*b*
Metabolic alkalosis, 753*t*, 762
associated with extracellular volume depletion, 763
associated with normal or expanded volume, 763
associated with volume depletion, 762–763
associated with volume expansion and hypertension, 763
clinical manifestations of, 763
diagnosis of, 753*t*, 763–764, 764*f*
epidemiology of, 762
expected compensation of, 755–756, 756*t*
pathobiology of, 762
treatment of, 764*b*
Metabolic bone disease, 1638–1639
diagnosis of, 1638–1639
dialysis-associated, 842
laboratory and radiologic investigation of, 1638–1639
physical examination of, 1638
treatment of, 839*b*, 1639*b*
Metabolic disease
cardiomyopathy with, 288
hypoglycemia due to, 1555
Metabolic equivalents (METs), 61, 1465
Metabolic myelopathy, 2406, 2406*b*
Metabolic myopathies, 2583.*e2t*, 2586–2587
Metabolic pericarditis, 424*t*
Metabolic profiling, 168
Metabolic syndrome
in obesity, 60
psychotropic medications and, 2680
severe mental illness and, 2683*t*
Metabolism, 1447
cardiovascular, 224
of magnesium, 766
microbiota and, 1839*f*
of phosphorus, 767
Metabolomics, 168
Metachromatic leukodystrophy, 1423, 2509
Metals
as occupational and environmental hazards, 87, 88*t*
trace, chronic poisoning, 101
Metamorphopsia, 2599
Metamyelocyte, 1140*f*
Metastases
bone tumors, 1388, 1388*b*
brain, 1316, 1317*b*, 1317*f*
breast cancer, 1369*b*
ocular, 2613
to spinal leptomeninges, 1318*f*, 1319
Metastatic differentiated thyroid cancer, 1511*t*
Metastatic disease
of bladder, treatment of, 1366*b*
in lungs, 631
on positron emission tomography/computed tomography, 874*f*
of renal cell carcinoma, treatment of, 1364*b*
in Zollinger-Ellison syndrome, treatment of, 1563*b*
Metastatic extraintestinal infection, enteric infections and, 1870*t*
Metastatic neuroendocrine tumor, computed tomography of, 871*f*
Metastatic spinal cord compression, 2406, 2406*b*
Metformin, 1460*t*
for polycystic ovary syndrome, 1602*b*
for type 2 diabetes mellitus, 1540*b*, 1541*t*
Methacrylates, 88*t*
Methadone, 139*t*
for opioid use disorders, 2362*b*
Methanol, 760
central nervous system effects of, 685*t*
toxicity, 686*t*, 690*t*, 698*t*
Methemoglobin, toxicity, *e1t–e8t*, 690*t*
Methemoglobin reductase deficiency, adverse drug reactions and, 132
Methemoglobinemia, 215, 1075, 1075*t*
Methicillin-resistant *Staphylococcus aureus* (MRSA), 1865, 1902, 1902.*e3t*
Methimazole
for Graves disease, 1511*t*
for hyperthyroidism, 1511*b*
Methionine, oral, 1427*b*
Methotrexate (Mexate, Folex), *e10t–e11t*, 147, 1215*t*
for Crohn disease, 945*b*, 946*t*
for rapidly progressive glomerulonephritis, 785*b*
for rheumatoid arthritis, 1755*b*, 1756*t*, 1757*t*, 1765*b*
for systemic lupus erythematosus, 1772*b*
for systemic sclerosis, 1781*b*
for total knee arthroplasty, 1830.*e1t*
1-Methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP), 2483
Methyl conjugation polymorphism, 132*t*
Methyl mercury, 102
Methyl-tetrahydrofolate, 1118
Methyldopa, 451*t*
Methylene blue, for acute poisoning, 693*t*
Methylene diphenyl diisocyanate (MDI), 588
5,10-Methylenetetrahydrofolate reductase (MTHFR) deficiency, 1425, 1426*t*
Methylmalonic acid, for megaloblastic anemias, 1122
Methylmalonic aciduria, 1398*t*, 1403, 1403*t*
Methylphenidate, 2446*b*, 2449*t*
Methylphenidate ER, 2449*t*
Methylprednisolone
for acute rejection, 633
for diffuse alveolar hemorrhage, 569*b*
for idiopathic pulmonary fibrosis, 576*b*
Methylprednisolone *(Continued)*
intravenous, for autoimmune encephalitis, 2536
for membranous nephropathy, 780*b*
for *Pneumocystis* pneumonia, 2106*t*
for rapidly progressive glomerulonephritis, 785*b*
in renal transplantation, 845*t*
for status asthmaticus, 541*b*
for ulcerative colitis, 945*b*, 946*t*
for vestibular neuritis, 2647*b*
Metoclopramide
for intestinal pseudo-obstruction, 889*b*
for nausea and vomiting, 863*t*
Metolazone, 451*t*
for hypervolemia, 736*b*, 737*t*
Metoprolol, 460*t*
for acute STEMI, 384*b*, 391*t*
for aortic dissection, 441*b*
for arrhythmias, 313*b*
for atrial fibrillation, 384*b*
for heart failure, 267*t*
for premature ventricular contractions, 338*b*
Metoprolol succinate, 451*t*
Metoprolol succinate/HCTZ, 451*t*
Metoprolol tartrate, 451*t*
Metoprolol tartrate/HCTZ, 451*t*
Metronidazole (Flagyl), 2115
for amebiasis, 2150*t*
for amebic liver abscess, 1025*b*
for *Clostridioides difficile*, 1925*b*
dosage of, 1895*t*
for giardiasis, 2145*b*
for intestinal amebiasis, 2112*t*
for intestinal protozoa, 2112*t*
mechanism of action, 1895*t*
toxicities of, 1901*t*
for trichomoniasis, 2154*b*
for urethritis, 1880*t*
METs. *See* Metabolic equivalents
Metyrapone, for Cushing syndrome, 1524*b*
Mevalonate kinase deficiency (MKD), 1731*t*, 1733
Mevalonic acid, 1734
Mevalonic aciduria, 1403*t*
Mexate. *See* Methotrexate
Mexiletine
for amyotrophic lateral sclerosis, 2563*b*
for erythromelalgia, 471*b*
MHC. *See* Major histocompatibility complex
MHC class I-related chain A (MICA), 205
MI. *See* Myocardial infarction
MIC. *See* Minimal inhibitory concentration
Micafungin, 2078
adverse effects of, 2078
drug interactions of, 2078
formulations and pharmacology of, 2078
indications and dosage of, 2075*t*, 2078
Micelle formation, impaired, 933
Micro breakpoint cluster region (μ-bcr), 1273
Microalbuminuria, 722
Microangiopathic hemolytic anemia
hemolytic-uremic syndrome causing, 1178
in thrombotic thrombocytopenic purpura, 1177
Microbial disease, 1833–1836
Microbial prophylaxis, for disseminated gonococcal infection, 1950
Microbial sequencing, 167
Microbiome, human, 1836
alteration of, 1837, 1838*f*, 1838*t*
definition of, 1836
in developing precision medicine paradigm, 1840.*e2f*
disease associations of, 1838
asthma, 1840
C. difficile infection, 1839, 1840.*e1f*
colon cancer, 1840
hematopoietic stem cell transplantation, 1840
inflammatory bowel disease, 1838
neurologic disorders, 1840
obesity, 1838, 1839*f*
environmental/iatrogenic factors of, 1838*t*
establishment of, 1837, 1837*f*, 1837.*e1f*
host factors of, 1838*t*
maternal factors of, 1837.*e1f*
microbial factors of, 1838*t*
postnatal factors of, 1837.*e1f*
potential function of, 1838*f*
Microbiome, human *(Continued)*
structure and function relationships of, 1836
studying of, 1837, 1837.*e1f*
therapies targeting, 1840, 1840*t*
Microconidia, inhalation of, 2082
Microcyte, 1067*f*
Microcytic anemia, 1079
peripheral blood smear of, 1068
β_2-Microglobulin, *e1t–e8t*
Micronodular abscesses, with minimal capsular formation, 2073
Micronutrients, 1451
depletion of, malnutrition and, 1447*t*
dietary requirements for, 1451
medications, 1452, 1460*t*
older adults, 1452
pathophysiologic, 1452–1459
pharmacologic, 1452
toxins, 1459
women of childbearing age, 1452
function of, 1451–1452, 1453*t*
optimal intake of, 1451, 1452*t*
trace elements, 1451
types of, 1451
Micropenis, 1570*t*
MicroRNa (miRNA) inhibitors, 177
MicroRNa (miRNA) mimics, 177
Microsatellite instability, 1377
Microscopic colitis, 940
Microscopic polyangiitis, 520.*e2f*, 1797, 1797*b*
Microsomal transfer protein, 1405
Microsporidia, 1026*t*, 2156, 2156*b*, 2156*t*
Microtophi, 1811
Microvesicular steatosis, 1031, 1031*t*
Mid-esophageal diverticula, 909
Midazolam, for anesthesia, 2670
Midbrain stroke syndromes, 2465.*e1f*
Middle adolescence, 110
Middle cerebral artery
anatomy of, 2457, 2459*f*, 2460*f*
occlusion of, 2465
Middle East, HIV/AIDS in, 2289, 2289.*e1f*
Middle East respiratory syndrome (MERS), 2207–2209
clinical manifestations of, 2208
diagnosis of, 2208
epidemiology of, 2207*t*, 2208
pathobiology of, 2208
prevention of, 2208–2209
prognosis of, 2209
treatment for, 2208*b*
Middle mediastinum, 527
Midline cleft syndromes, 1478
Midline (lethal) granuloma, 2621*t*
Midodrine, for orthostatic hypotension, 2559*t*
Midostaurin (Rydapt), 1215*t*
Mifepristone, 1524*b*, 1610, 1617
Miglustat, for Niemann-Pick disease type C, 1423
Migraine headaches, 2378, 2464
clinical manifestations of, 2378
definition of, 2378–2380
description of, 2599, 2645
diagnosis of, 2377*t*, 2378, 2379*f*
differential diagnosis of, 2377*t*
pathobiology of, 2378
prevention of, 2379–2380
prognosis for, 2380
treatment of, 2378*b*, 2378*t*
Migrating motor complex, 887, 887.*e3f*
Mild hypothermia, 681*t*
Miliaria rubra, 679
Miliary tuberculosis, 2035, 2037*f*
Military service, history of, 29*t*
Millard-Gubler syndrome, 2465.*e1f*
Millennials, 114
Miller-Fisher syndrome, 2571
Millipedes, 711
Milnacipran, for fibromyalgia, 1819*b*
Milrinone, 667*b*
for shock, 664*t*
Miltefosine, 2116
for amoebic encephalitis, 2112*t*
for leishmaniasis, 2112*t*
for visceral leishmaniasis, 2132*b*
Milwaukee shoulder, 1815
Minamata disease, 103
Mind and body practices, 154–155
Mindfulness-based cognitive therapy, 154
Mineral supplementation, 56

Copyrighted material

Mineral supplements, 155
Mineral toxicity, 2541*t*
Mineralocorticoid receptor antagonists (MRAS)
  clinical benefits of, 265*b*
  mechanism of action, 265*b*
  practical use of, 265*b*, 270*t*
Mineralocorticoids
  deficiency of, 1529
  excess of, 1524
    algorithm for, 1525*f*
    causes of, 1525*t*
    clinical manifestations of, 1525
    description of, 749, 749*t*
    diagnosis of, 1525–1526
    differential diagnosis of, 1525–1526
    epidemiology of, 1524
    pathobiology of, 1525
    treatment of, 1526*b*
Mini-Cog test, 117, 2331*t*
Mini Nutritional Assessment - Short Form score, 1447
Minimal change disease, 777, 778*b*, 778*f*
Minimal inhibitory concentration (MIC), 1892, 1892*f*
Minimally conscious state, 2437*t*, 2441–2442, 2442*b*, 2442*t*
Minimally invasive adenocarcinoma, 1329
Minimally symptomatic patients, 541*b*
Minocycline
  dosage of, 1895*t*
  for rheumatoid arthritis, 1755*b*, 1756*t*
Minor histocompatibility antigens, 205
Minoxidil, 451*t*
Minute ventilation, 640
Mirabegron, 824*t*
Mirtazapine, 2340*t*, 2452*t*, 2696*b*
Misoprostol, 1610, 1617, 1756*t*
Mites
  description of, 710
  as vectors of zoonotic disease, 2064
Mitochondrial DNA depletion syndromes, 2586
Mitochondrial encephalomyopathy with lactic acidosis and strokelike episodes (MELAS), 2586
Mitochondrial myopathies, 2583.*e2t*
Mitochondrial oxidative phosphorylation disorders, 2586
Mitogen activated protein kinase pathway (MAPK), 1390
Mitoxantrone (Novantrone), for multiple sclerosis, 2505*t*
Mitral regurgitation, 240
  acute, severe, 406
  asymptomatic
    chronic, 407*b*
    with left ventricular dysfunction, 407*b*
    with normal left ventricular function, 407*b*
  chronic symptomatic, 407*b*
  echocardiography in, 407, 407*f*
  functional (secondary), 409
  pathophysiology of, 406, 406*f*
  primary (organic)
    clinical manifestations of, 407
    diagnosis of, 407
    epidemiology of, 406
    medical therapy for, 407*b*
    pathobiology of, 406–407
    surgical therapy for, 407*b*
  secondary (functional), 409
    clinical manifestations of, 409
    definition of, 409
    diagnosis of, 409
    epidemiology of, 409
    pathobiology of, 409
    prognosis of, 409*b*
    treatment of, 409*b*
  treatment of, 265*b*
Mitral stenosis, 404–405, 404.*e1f*
  clinical manifestations of, 404–405
  diagnosis of, 405, 405*f*
  epidemiology of, 404
  evaluation of, 239–240
  invasive evaluation of, 405
  mechanical therapy for, 405*b*
  medical therapy for, 405*b*
  pathobiology of, 404
  physical examination of, 404–405
Mitral valve, 224
Mitral valve prolapse, 408–409
  definition of, 408
  diagnosis of, 408–409
Mitral valve prolapse *(Continued)*
  history in, 408
  noninvasive evaluation of, 408–409
  physical examination of, 408
  prognosis for, 409
  treatment of, 409*b*
Mitral valve regurgitation, 1918
Mitral valve repair, 245*f*, 407*b*, 408*f*
Mitral valve replacement, transcatheter, 407*b*
Mixed connective tissue disease (MCTD), 581, 1782, 1782*b*
Mixed cryoglobulinemia, 789, 1716
Mixed cryoglobulins, 1798
Mixed disorder, 533
Mixed gonadal dysgenesis, 1574, 1594
Mixed incontinence, 829
Mixed-meal test, for hypoglycemia, 1557, 1557*t*
Mixed neuroendocrine-non-neuroendocrine neoplasms, 1567
Mixed pain, 134–135, 135*t*
Mixed sclerosing bone dystrophy, 1668
MKD. *See* Mevalonate kinase deficiency
MMR vaccine. *See* Measles-mumps-rubella
Mobile cardiac outpatient telemetry, 307
Mobility, geriatric assessment of, 117
Mobitz type I AV block (Wenckebach block), 306, 320
Modafinil, 2446*b*, 2449*t*
Model for End-stage Liver Disease (MELD) score, 1032*b*, 1197, 2666
Moderate aplastic anemia, 1125
Moderate drinking, 2353
Moderate hypothermia, 681*t*
Moderna COVID-19 vaccine, 77, 2218*t*, 2219
Modified acid-fast staining, for enteric infection, 1870*t*
Modified Ann Arbor staging system, 1291, 1291*t*
Modified barium swallow, 868
Modified Bruce protocol, 212*t*
Modified Fisher CT rating scale, 2478*t*
Modified Harris-Benedict equation, 703.*e1t*
Modified smallpox, 2237, 2237*t*
MODY. *See* Maturity-onset diabetes of the young
Moexipril, 451*t*
Moexipril/HCTZ, 451*t*
Mogamulizumab, for adult T-cell leukemia/lymphoma, 2326*b*
Mohs surgery
  for skin cancers, 2701
  for squamous cell skin cancer, 1396*b*
Moisturizers, 2700
Molds, 87
Molecular detection methods, for *Bartonella* infection, 2002
Molecular imaging, 1717
Molecular technologies, 165–169
  continuum from health to disease, 165–166, 166*f*, 166*t*
  expressed genome in, 168
  genomes, disease, and treatment, 166–168
  precision medicine, 168–169, 168*t*
Molecular testing, for cancer, 1214
Molecular tumor profiling, site-specific therapy directed by, 1241*b*
Moles, characteristics of, 1392*t*
Mollaret meningitis, 2524
Molluscipoxvirus, epidemiology of, 2237
Molluscum contagiosum, 1882, 2242, 2712, 2713*f*, 2729, 2731*f*
  clinical manifestations of, 2239
  diagnosis of, 2239
  epidemiology of, 2237
  organisms causing, 1879*t*
  prevention of, 2240*b*
  treatment of, 2240*b*
Mollusks, venomous, 712–713
Molnupiravir
  for coronavirus infections, 2190
  for COVID-19, 2216
Molybdenum, 1457*t*
Mometasone, 553*t*
Monge disease, 592
Monkeypox, 2236, 2238, 2239*f*
Monoamine oxidase inhibitors (MAOIs)
  anesthesia and, 2669
  central nervous system effects of, 685*t*
  for depression, 2340*t*
Monoarthritis, 1710
  joint fluid analysis for, 1713
Monobactams, dosage of, 1895*t*
Monoblasts, 1073
Monoclonal antibodies, 150, 150*t*
  anti-SARS-CoV-2, 2216, 2216*f*, 2219
  anti-spike, for SARS-CoV-2, 153
  for asthma, 541*b*
  for COVID-19, 2217
  reactions to, 1698
  therapeutic targets engaged by, 152–153
Monoclonal B-cell lymphocytosis, in chronic lymphocytic leukemia, 1268
Monoclonal gammopathy, 727
Monoclonal gammopathy of renal significance, 788
Monoclonal gammopathy of undetermined significance (MGUS), 1295–1297, 2574–2575
  clinical manifestations of, 1295
  definition of, 1295–1297, 1296*t*
  diagnosis of, 2575
  diseases associated with, 1296
  epidemiology of, 1295, 1295.*e2f*, 1295.*e2t*, 2574
  multiple myeloma *versus*, 1295
  pathobiology of, 1295, 2575
  prevalence of, 1295.*e2t*
  prognosis of, 1297
  smoldering multiple myeloma *versus*, 1295
  treatment of, 1297*b*, 1297*f*, 1297*t*, 2575*b*
Monoclonal proteins
  identification of, 1294–1295, 1295*f*, 1295.*e1f*
  polyclonal immunoglobulin *versus*, 1295, 1295*f*
  serum protein electrophoresis of, 1294, 1295*f*
Monocytes, 182
Monocytopenia, 1148
Monocytosis, 1142, 1143*t*
Monogenic defects, 1684–1685
Monogenic disorders, 158
  high-penetrance, 158
  inborn errors of metabolism as, 1399
  versions of common disorders, 159
Monomethylfumarate (Bafiertam), for multiple sclerosis, 2505*t*
Monomorphic ventricular tachycardia, in myocardial infarction, 334*f*
Mononeuritis multiplex, 2313, 2567, 2567*t*, 2573
Mononucleosis, 2650
Monosodium urate monohydrate crystals, 1811
Monosomy X, 164
Monosulfiram, for scabies, 711*b*
Monotherapy, for hepatocellular carcinoma, 1360*b*
Monoxide, carbon, 595, 596*b*
Montreal classification, of gastroesophageal reflux disease, 903*f*
Montreal Cognitive Assessment, 2332*f*
Mood, geriatric assessment of, 117
Mood disorders, 257, 2337
  bipolar disorder, 2341, 2341*b*, 2341*t*
  major depressive disorder, 2337
  menopause associated with, 1630, 1630*b*
Mood stabilizers, 2679
Mooren ulcer, 2611
Moraxella catarrhalis, 1954–1955
  clinical manifestations of, 1955
  definition of, 1954
  epidemiology of, 1954–1955
  infections, 1954
  pathobiology of, 1954
  as pathogen, 1954, 1954*t*
  prognosis of, 1955
  sites of colonization of, 1954*t*
  treatment of, 1955*b*
Moraxella lacunata, 1954*t*, 1955
Morbidity
  causes of, in women's health, 1609–1610
  changes in, 23
  of older adults, 114–115
Morbilliform eruptions, 1857, 2712, 2712*t*, 2713*f*
Morning stiffness, 1751
Morphea, 1782, 2737, 2738*f*
Morphine, e10*t*–e11*t*, 139*t*. *See also* Opioids
Morphine sulfate, for left ventricular dysfunction, 384*b*
Morquio syndrome, 1724*t*
Mortality
  causes of, in women's health, 1606–1609
  changes in, 23
  of older adults, 114*t*, 115, 115*f*
  socioeconomic disparities in, 18
Morton neuroma, 1748, 1748*b*, 1749*f*
Mosaicism, 162, 163*f*
Mosquito-borne viruses, 2266
Mosquito protection, 1889
Motility
  colonic, 887
  defects of, 1683, 1683.*e1t*
  gastric, 887
  of irritable bowel syndrome, 893
  small bowel, 887, 888*f*
Motion sickness, 2644
Motivational enhancement therapy, for drug use disorders, 2361*b*
Motivational incentive, for drug use disorders, 2361*b*
Motor examination, in coma, 2439
Motor neuron diseases, 1238*t*, 2561–2566
  amyotrophic lateral sclerosis. *See* Amyotrophic lateral sclerosis
  classification of, 2562*t*
  definition of, 2561
Motor unit, 2580
Mounier-Kuhn syndrome, 560
Mountain sickness
  acute, 592, 592*t*
  chronic, 592, 592*t*
Mouse spiders, envenomation of, 710
Mouth, examination of, 29
Movement disorders, 2489–2498
  akathisia, 2495
  cerebellar ataxia, 2497, 2497*b*, 2497*t*
  clinical manifestations of, 2489
  definition of, 2489
  diagnostic approach to, 2489
  hyperkinetic, 2489, 2489*t*
  hypokinetic, 2489
  neuroleptic malignant syndrome, 2496
  painful legs and moving toes, 2496
  spastic paraplegias, 2498*b*, 2498*t*
  tardive dyskinesia, 2496, 2496*b*
Moxidectin, for helminthic diseases, 2112*t*, 2117
Moxifloxacin
  for bacterial meningitis, 2518*t*
  dosage of, 1895*t*
  for eye infection, 2605*t*
  for *H. influenzae* infections, 1954*b*
  for *Moraxella catarrhalis* infections, 1955*b*
  for nontuberculous mycobacterial disease, 2046*t*
  for plague, 98*b*, 1991*b*, 1992*t*
  for pneumonia, 613*t*, 616*t*
  for *Streptococcus pneumoniae* pulmonary infections, 1912*b*
Moyamoya disease, 2470.*e1t*
Mozambique cyclones, climate-related hazards, 91*t*
MPO-ANCA, 1716
MRA. *See* Magnetic resonance angiography
MRAS. *See* Mineralocorticoid receptor antagonists
MRCP. *See* Magnetic resonance cholangiopancreatography
MRI. *See* Magnetic resonance imaging
MRKH. *See* Mayer-Rokitansky-Küster-Hauser
mRNA anti-tumor vaccines, 177
MRS. *See* Magnetic resonance spectroscopy
MRSA. *See* Methicillin-resistant *Staphylococcus aureus*
MTHFR. *See* 5,10-methylenetetrahydrofolate reductase
mTOR. *See* Mammalian target of rapamycin
Mucin cysts, 2730
Mucinous cancer, 1346
Mucinous cystadenomas, 1355
Mucinous cystic neoplasms, 1356
Muckle-Wells syndrome (MWS), 1731*t*, 1733*t*
Mucoceles, 2625
Mucocutaneous candidiasis, 1560, 2090
Mucocutaneous lymph node syndrome. *See* Kawasaki disease
Mucoid impaction, 522
Mucolipidoses, 1419*t*, 1724, 1724*t*
Mucopolysaccharidoses, 1419*t*, 1420*t*, 1424, 1724, 1724*t*, 1725*b*
Mucorales fungi, 2098
Mucormycosis, 2098, 2695*f*
  adjunct treatments for, 2100*b*
  antifungal therapy for, 2100*b*
  clinical manifestations of, 2098
  clinical specimens of, 2099
  computed tomographic scan of, 520.*e1f*
  culture of, 2100
  definition of, 2098

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Mucormycosis *(Continued)*
diagnosis of, 2100*f*
disseminated, 2099
epidemiology of, 2098
gastrointestinal, 2099
histopathology of, 2099, 2100*f*
management of comorbidity of, 2100*b*
pathobiology of, 2098
prognosis of, 2101
pulmonary, 2099, 2100*f*
radiology of, 2099, 2100*f*
rare clinical presentations of, 2099
rhinocerebral, 2099
skin and soft tissue, 2099
surgery for, 2100*b*
treatment of, 2100*b*, 2101*f*, 2523
Mucosa, 901
Mucosa-associated lymphoid tissue (MALT) lymphoma, 1283, 1283*b*, 1284*t*, 1342
Mucosal disease, tests for, 931*t*
Mucosal leishmaniasis, 2116, 2133
Mucosal malabsorption, impairment of, 934–938
Mucosal melanomas, 1391
Mucosal telangiectasia, 880*f*
Mucositis, 2621–2622, 2695*f*
Mucous membrane pemphigoid, 911, 2621*t*, 2624, 2717–2718, 2718*b*, 2718*f*
Mucous membranes, 1769
Mucus retention cyst, 2631–2632
Muehrcke lines, 2753*f*
Muir-Torre syndrome, 1347
Müllerian ducts, anomaly of, 1594
Multibacillary leprosy, 2048, 2048*t*, 2048.*e1f*
Multicentric Castleman disease, 2316, 2316*b*
Multicentric reticulohistiocytosis, 1824, 2734
Multidrug hypersensitivity, 1695–1696
Multidrug resistance, mechanisms of, Enterobacterales and, 1965, 1966*t*
Multidrug-resistant bacteria, health care-associated infections and, 1864, 1864*t*
Multifactorial disorders, 159
Multifocal atrial tachycardia, 324, 324*b*, 326*f*
Multifocal motor neuropathy, 65*t*, 2564*t*, 2572–2573, 2573*b*
Multifocal patchy opacities, 520
Multifocal pulmonary opacities, chest radiograph of, 524*f*
Multilevel spinal cord and root compression, 2564*t*
Multimarker genomic tests, for disease diagnosis and prognosis, 168
Multimineral supplementation, 1460
Multimorbidity, of older adults, 114, 114*t*
Multinational Association for Supportive Care in Cancer (MASCC) Index, 1854*b*, 1855*t*
Multiple chemical sensitivities, occupational and environmental, 86*t*
Multiple comparisons, 37
Multiple endocrine neoplasia (MEN), 1530
pituitary adenomas and, 1487*t*
type 1 (MEN 1), 1250*t*, 1558, 1559*t*
type 2 (MEN 2), 1250*t*, 1558, 1559*t*
type 4 (MEN 4), 1558, 1559*t*
type 5 (MEN 5), 1558, 1559*t*
Multiple enzyme deficiency disorders, 1419*t*
Multiple erythema migrans skin lesions, 2024
Multiple gadolinium-enhanced brain lesions, caused by Nocardia infection, 2074*f*
Multiple myeloma, 1297–1302
allogeneic bone marrow transplantation for, 1299*b*
autologous stem cell transplantation for, 1299*b*, 1301*t*
clinical manifestations of, 1298
complications of, 1299*b*
cytogenetic abnormalities of, 1298
diagnosis of, 1298–1299
epidemiology of, 1298
hematopoietic cell transplantation for, 1209
history of, 1298
hypercalcemia associated with, 1299*b*
infections and, 1299*b*
laboratory findings of, 1298, 1298.*e1f*, 1299*f*
monoclonal gammopathy of undetermined significance *versus*, 1295
neurologic involvement, 1299
neuropathies associated with, 2574–2576
pathobiology of, 1298
physical examination of, 1298
prognosis for, 1298*t*, 1302
Multiple myeloma *(Continued)*
radiation therapy for, 1299*b*
radiologic findings of, 1299, 1299*f*
relapsed refractory, 1299*b*
renal insufficiency associated with, 1299*b*
renal involvement, 1299
skeletal lesions and, 1299*b*
smoldering
monoclonal gammopathy of undetermined significance *versus*, 1295
treatment of, 1299*b*, 1300*f*
treatment of, 1299*b*, 1300*f*
variant forms of, 1302–1303
Multiple nodules, as occupational lung disease, 585*t*
Multiple parenchymal cysticerci, 2159
Multiple pterygium, 2589*t*
Multiple sclerosis, 2411, 2498–2508, 2564*t*, 2652
acute progressive, 2501
ataxia in, 2501
behavioral symptoms of, 2501
bladder urgency in, 2504*b*
cerebrospinal fluid in, examination of, 2503
clinical manifestations of, 2500–2501
cognitive symptoms of, 2501
corticosteroids for, 2504*b*
definition of, 2498–2508
diagnosis of, 2501–2504
diagnostic criteria for, 2502*t*
differential diagnosis of, 2504
disease-modifying treatments for, 2504*b*
epidemiology of, 2498–2499
evoked potential tests for, 2504
fatigue associated with, 2501
genetics of, 2499
incidence of, 2498–2499
magnetic resonance imaging of, 2501, 2502*f*, 2502*t*, 2503*f*
medications for, 2505*t*
motor symptoms of, 2501
optic neuritis caused by, 2615
optical coherence tomography for, 2504, 2504.*e1f*
organ dysfunction in, 2501
pathobiology of, 2499–2500
pathogenesis of, 2500
pathology of, 2499–2500
plaques associated with, 2499
in pregnancy, 2501
presenting symptoms of, 2499*t*–2500*t*, 2500, 2500*t*
prevention of, 2504*b*
primary progressive, 2501
prognosis for, 2508
relapsing-remitting, 2501
secondary progressive, 2501
sensory abnormalities of, 2500
sexual dysfunction in, 2504*b*
spasticity in, 2504*b*
systemic symptoms of, 2501
treatment of, 2504*b*
types of, 2501
vertigo caused by, 2646
visual effects of, 2500–2501
well-being in, 2504*b*
Multiple self-healing palmoplantar carcinoma, 1731*t*
Multiple sleep latency test, 2444
Multiple system atrophy (MSA), 2485*t*, 2558, 2652
Multislice CT scanners, S19
Multisystem inflammatory syndrome, with COVID-19, 2218
Multivariable statistics, 37
Multivitamin supplementation, 1460
Mumps, 2225–2227
aseptic meningitis caused by, 2521
clinical manifestations of, 2226, 2226*f*, 2226*t*
definition of, 2225–2227
description of, 1583
diagnosis of, 2226–2227
encephalitis caused by, 2535
epidemiology of, 2225–2226
immunization for, 66*t*, 76.*e1t*, 77*f*, 78*f*, 81
pathobiology of, 2226
pathogen of, 2225
prevention of, 2227
prognosis of, 2227
in travelers, 1889.*e1t*
treatment of, 2227*b*
Munchausen syndrome. *See* Factitious disorder
Mupirocin (Bactrian), for skin diseases, 2697, 2699
Mural thrombosis, 384*b*
Murine typhus, 2055*t*, 2058, 2059*b*
Murphy sign, 988
Murray Valley encephalitis virus, 2276*t*, 2283
Muscarinic antagonists, 551*b*
Muscle(s)
fiber structure of, 2580
glucocorticoids metabolism in, 145
strength testing of, 2581, 2582*t*
structure of, 2580.*e2f*
Muscle biopsy, for rhabdomyolysis, 716
Muscle cramps, 2581
Muscle diseases, 2580–2588
assessment of, 2583*t*
classification of, 2580*t*
clinical manifestations of, 2580–2581
definition of, 2580–2583
diagnosis of, 2581–2583
electromyography of, 2581
epidemiology of, 2580
genetic testing of, 2582
history-taking for, 2580–2581
inherited, 2583
muscle biopsy of, 2582–2583
physical examination of, 2581, 2582*f*
Muscle-invasive tumors, of bladder, treatment of, 1366*b*
Muscle pain, 2370–2371, 2580–2581
Muscle strengthening, 61
Muscle stretch reflexes, 2370
Muscle symptoms, statins and, 1412, 1412*t*
Muscle tension dysphonia, 2652
Muscle wasting, 2587
Muscular dystrophies, 2583–2584
Becker, 2584, 2584*b*
congenital, 2585
Duchenne, 2583, 2583*b*, 2583.*e1f*
Emery-Dreifuss, 2584
facioscapulohumeral, 2584, 2584*b*
limb-girdle, 2584
oculopharyngeal, 2585
types of, 2583.*e1t*
Muscular rings, 910
Musculoskeletal conditions
chest pain, 211*t*
fever and, 1849
Musculoskeletal disorders, occupational and environmental, 86–87, 86*t*
Musculoskeletal injuries
in intimate partner violence, 1633
occupational, 86*t*
Musculoskeletal system
age-related changes in, 122
examination of, 31
systemic lupus erythematosus manifestations of, 1769
systemic sclerosis complications of, 1779
Mustard or Senning repair, exercise recommendations for, 355.*e2t*
Mutation, 162–164
MUTYH-associated polyposis, 1347*t*, 1348
MVV. *See* Maximal voluntary ventilation
MWS. *See* Muckle-Wells syndrome
Myasthenia gravis, 2589–2591, 2589*t*, 2652
clinical manifestations of, 2590, 2590*f*
complement system and, 201*t*
diagnosis of, 2590
pathobiology of, 2589–2590, 2589.*e1f*
prognosis of, 2591
treatment for, 2590*b*
Mycetoma, 2108
clinical manifestations of, 2110, 2110*f*
diagnosis of, 2110
differential diagnosis of, 2110
epidemiology of, 2108
intracavitary, 607
pathobiology of, 2109
predominant agents of, 2109.*e1f*
prevention of, 2111
prognosis for, 2111
treatment of, 2111*b*
Mycobacterial infections, 1686*t*, 2651, 2741
Mycobacterium abscessus, 2044, 2044*t*
Mycobacterium africanum, 2031
Mycobacterium avium, 2044, 2044*t*
Mycobacterium avium complex, 2307, 2309*t*
Mycobacterium bovis, 2031
Mycobacterium canettii, 2031
Mycobacterium caprae, 2031
Mycobacterium celatum, 2044*t*
Mycobacterium chelonae, 2044*t*, 2741
Mycobacterium fortuitum, 2044*t*, 2045
Mycobacterium genavense, 2044, 2044*t*
Mycobacterium gordonae, 2044*t*
Mycobacterium haemophilum, 2044*t*
Mycobacterium kansasii, 2044*t*, 2045
Mycobacterium leprae, 2047, 2651. *See also* Leprosy
Mycobacterium malmoense, 2044*t*
Mycobacterium marinum, 1861*f*, 2044*t*
Mycobacterium marinum, infections with, 2741
Mycobacterium massiliense, 2044
Mycobacterium microti, 2031
Mycobacterium neoaurum, 2044*t*
Mycobacterium pinnipedii, 2031
Mycobacterium scrofulaceum, 2044*t*
Mycobacterium simiae, 2044*t*
Mycobacterium smegmatis, 2044*t*
Mycobacterium szulgai, 2044*t*
Mycobacterium terrae, 2044*t*
Mycobacterium tuberculosis, 1145, 2031. *See also* Tuberculosis
intestinal ulcers associated with, 956
prophylaxis for, 2309*t*
pulmonary infection caused by, 1855
septic bursitis caused by, 1804
tuberculosis caused by, 2306
Mycobacterium ulcerans, 2044*t*
Mycobacterium xenopi, 2044*t*
Mycophenolate, e10*t*–e11*t*
Mycophenolate mofetil, 147
for liver transplantation, 1048*t*
for systemic lupus erythematosus, 1772*b*
for total knee arthroplasty, 1830.*e1t*
Mycophenolic acid, 147, 845, 845*t*
Mycoplasma arthritis, 1808
Mycoplasma fermentans, 2008, 2008*t*
Mycoplasma genitalium, 2008, 2008*b*, 2008*t*
Mycoplasma hominis, 1808, 2008, 2008*b*, 2008*t*
Mycoplasma orale, 2008*t*
Mycoplasma pneumoniae, 2005–2008, 2649
cardiovascular complications of, 2007
clinical manifestations of, 2005–2007
definition of, 2005
dermatologic involvement of, 2006–2007, 2007*f*
diagnosis of, 2007
epidemiology of, 2005
extrapulmonary involvement of, 2006–2007
hematologic complications of, 2007
musculoskeletal complications of, 2007
neurologic complications of, 2007
pathobiology of, 2005, 2006*f*
prevention of, 2008
prognosis of, 2008
renal complications of, 2007
as respiratory infection, 2005–2006, 2006*f*
treatment of, 2007*b*
Mycoplasma salivarium, 2008, 2008*t*
Mycoses, endemic, 2080
blastomycosis as, 2080
coccidioidomycosis as, 2083, 2085*f*
histoplasmosis as, 2081
paracoccidioidomycosis as, 2086
sporotrichosis as, 2085
Mycosis fungoides, 1286, 1286*b*, 2686.*e1f*, 2709–2710, 2710*f*, 2710*t*, 2734
Mycotic aneurysms, 2478, 2530
Mydriasis, 684*f*
Mydriatic drugs, 2617
Myelin, diseases of, 2499*t*, 2508–2510
Myelin-associated glycoprotein, 2568
Myeloblastomas, 1262
Myeloblasts, 1073, 1140*f*
Myelocele, 2545, 2545*f*
Myelocyte, 1140*f*
Myelodysplastic syndromes, 1072*t*, 1252–1259, 1259
clinical manifestations of, 1253
definition of, 1252–1258
diagnosis of, 1253–1256
diagnostic criteria for, 1255
differential diagnosis of, 1255–1256
epidemiology of, 1252–1253
gene mutations associated with, 1254*t*
hematopoietic cell transplantation for, 1209

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Myelodysplastic syndromes *(Continued)*
International Prognostic Scoring System for, 1258*f*
pathobiology of, 1253, 1255*f*
prevention of, 1259
prognosis of, 1257–1258
treatment of, 1255, 1257*f*
variants of, 1255–1256, 1256*t*
Myelofibrosis, primary, 1130, 1130*t*
allogeneic hematopoietic stem cell transplantation for, 1135*b*
clinical manifestations of, 1133–1134
definition of, 1130, 1130*t*
diagnostic criteria for, 1134–1135, 1134*t*
Dynamic International Prognostic Scoring System-Plus for, 1137*f*, 1139
epidemiology of, 1130
extramedullary hematopoiesis in, 1133
pathobiology of, 1130, 1131*f*
peripheral blood smear of, 1134–1135
in pregnancy, 1135*b*
prognosis for, 1138–1139
ruxolitinib for, 1135*b*, 1138*f*
splenomegaly in, 1134
survival in, 1139, 1139*f*
treatment of, 1135*b*, 1136*t*
Myeloid dendritic cells, 182–183
Myeloid hypereosinophilic syndrome, 1162, 1163*t*
Myeloid maturation, in bone marrow, 1140*f*
Myeloid sarcomas, 1262
Myelokathexis, neutropenia of, 1145
Myeloma defining events, 1300*f*
Myelomeningocele, 2545, 2545*f*, 2546*b*
Myelopathy
causes of, 2403*t*
in HIV/AIDS, 2313, 2313*b*
infectious, 2406, 2406*b*
inflammatory, 2406, 2406*b*
metabolic, 2406, 2406*b*
necrotizing, 1238*t*
vascular, 2405, 2406*b*
Myelophthisis, 1141
Myeloproliferative neoplasms, 480, 480*b*, 1130
genotype-phenotype correlations, 1131
hematopoietic cell transplantation for, 1209
molecular abnormalities in, 1131, 1132*t*
neutrophilia and, 1142
risk factors of, 1130
Myelosuppression, for chronic myeloid leukemia, 1274*b*
Myenteric plexus, 888
MYH-associated polyposis, 1250*t*
Myiasis, cutaneous or mucocutaneous, in travelers, 1889.*e1t*
Myocardial biopsy, 261
Myocardial contractility, 226
Myocardial contusion, 700*b*
Myocardial depression, 287–288
Myocardial disease, 279–295, 280*t*, 281.*e3f*
Myocardial infarction (MI), 211*t*
acute
acute hospital phase, 384*b*
antiplatelet therapy for, 507
causes of, 381*t*
clinical manifestations of, 334
coronary angioplasty for, 397*f*
definition of, 380
diagnosis of, 381
early acute phase, 382
electrocardiography in, 382, 382*f*
evolved acute phase, 382
hemodynamic subsets of, 389*t*
key echocardiographic findings, 242*t*
pathobiology of, 380
physical examination in, 381
in presence of bundle branch block, 383
ST-elevation, 380
chronic phase, 383
complications of, 380, 384*b*
differential diagnosis of, 424*t*
discharge medication checklist after, 391*t*
epidemiology of, 380
left circumflex patterns, 383
monomorphic ventricular tachycardia in, 334*f*
neutrophilia and, 1141
non-ST-elevation, 380
nonfatal, 221.*e1f*
oral contraceptives and, 1614–1615
pathobiology of, 380–381
post-myocardial infarction pericarditis, 426*t*
post-myocardial infarction ventricular tachycardia, 336
Myocardial infarction (MI) *(Continued)*
postoperative, 2673*t*
risk stratification after, 384*b*
true posterior, 383
universal definition of, 374*t*
Myocardial ischemia, differential diagnosis of, 424*t*
Myocardial necrosis
pathobiology of, 380
serum cardiac biomarkers of, 383
Myocardial perfusion imaging, 248, 248*f*
clinical applications of, 248–249
determination of, 249
imaging agents for, 248
SPECT, 248–249
Myocardial revascularization, 364*b*, 364*t*
Myocardial tumors, 296
Myocarditis
active, 284–285
borderline, 284
causes of, 284*t*
definition of, 284
enteroviral, 2257
epidemiology of, 284
giant cell, 286
immune-mediated, 286
pathobiology of, 284–285
patterns of, 284
persistent, 284
psychotropic medications and, 2678*t*
resolving or resolved, 284
toxoplasmosis, 286
treatment of, 286*b*
viral, 285–286
Myoclonic epilepsy with ragged-red fibers (MERRF), 2586
Myoclonic seizures, 2428*t*, 2430
Myoclonus, 2495, 2495.*e1t*, 2652
Myoclonus dystonia, 2493
Myofibrillar myopathies, 2584, 2584.*e1f*
Myofibrils, 2580
Myoglobinuria, rhabdomyolysis and, 716
Myokymia, 2501
Myonecrosis, *Streptococcus pyogenes* causing, 1915
Myopathies
centronuclear, 2585.*e1f*
classification of, 2580*t*
clinical findings of, 2581*t*
congenital, 2583.*e1t*, 2585
core, 2585.*e1f*
definition of, 2580
flow-volume curve of, 529*f*
in HIV/AIDS, 2313, 2313*b*
inclusion-body myositis, 2588*t*
inflammatory, 1787, 2587.*e1t*, 2588*t*
classification of, 1788*t*
clinical manifestations of, 1788
definition of, 1787
diagnosis of, 1788
diagnostic criteria for, 1790*t*
epidemiology of, 1787
pathobiology of, 1787
pathology of, 1789*f*
prognosis for, 1791
treatment of, 1790*b*, 1791*f*
metabolic, 2583.*e2t*, 2586
mitochondrial, 2583.*e2t*
myofibrillar, 2584, 2584.*e1f*
necrotizing autoimmune, 2588*t*
nemaline rod, 2585.*e1f*
pathobiology of, 2580
polymyositis, 2588*t*
prevalence of, 2580
steroid-induced, 2587
toxic, 2587, 2587*t*
Myopericarditis, 433
acute, 285*f*
enteroviruses causing, 2259, 2259*b*
Myopia, 2597–2598, 2597*f*
Myositis, 1849, 2260
Myotonia, 2581
Myotonic dystrophies, 2581, 2582*f*, 2584–2585, 2584*b*
Myotonic dystrophy, 1600, 2368.*e3f*
MyPlate, 60, 61*f*
Myxedema coma, hypothyroidism and, 1508*b*
Myxoma, 297
clinical manifestations of, 297–298
definition of, 297
diagnosis of, 298
epidemiology of, 297
treatment of, 298*b*

N

N-acetyl cysteine (NAC)
for acetaminophen overdose, 1019*b*
for acute poisoning, 693*t*
N-acetyl-p-benzoquinone imine (NAPQI), 1018
N-acetylation polymorphism, 132*t*
N-acetyltransferase (NAT2), 132*t*
NAATs. *See* Nucleic acid amplification tests
Nabilone, for nausea and vomiting, 863*t*
Nabumetone, for chronic pain, 138*t*
Nadolol, 451*t*
for torsades de pointes, 338*b*
Nadroparin, 503*t*
Naegleria fowleri, 2150, 2150*t*
Nafcillin
for bacterial meningitis, 2518*t*
dosage of, 1895*t*
NAFLD. *See* Nonalcoholic fatty liver disease
Nail
normal, 2751
pigmentation, 2754
toxicants and, 685
Nail disorders, 2751–2755
Beau lines, 2752, 2752*f*, 2752*t*
clubbing, 2752, 2752*f*
ingrowing toenails, 2754, 2755*f*
koilonychia, 2751, 2752*f*
leukonychia, 2752, 2753*f*
longitudinal grooves and striations, 2752
melanoma, 2755, 2755*f*
melanonychia, 2754, 2755*f*
nail pigmentation, 2754
onycholysis, 2753, 2754*f*
onychomadesis, 2752, 2752*f*, 2752*t*
onychomycosis, 2754, 2754*b*, 2754*f*
paronychia, 2753–2754
pitting, 2752, 2753*f*
splinter hemorrhages, 2753, 2753*t*
yellow nail syndrome, 2753, 2753*f*
Nail-patella syndrome, 787
Na^+,K^+-ATPase, 745–746, 746
Nalbuphine, 136*b*, 139*t*
Nalmefene, for alcohol-associated liver disease, 1032*b*
Naloxone, for acute poisoning, 693*t*
Naltrexone
for alcohol-associated liver disease, 1032*b*
for alcohol use disorders, 2357*b*, 2358*t*
for opioid use disorders, 2362*b*
for tobacco dependence, 2351*t*
NAPQI. *See* N-acetyl-p-benzoquinone imine
Naproxen
for chronic pain, 138*t*
for rheumatoid arthritis, 1756*t*
Naproxen sodium, for dysmenorrhea, 1596*t*
Naratriptan, 2380*t*
Narcissistic personality disorder, 2348*t*
Narcolepsy, 2371, 2445–2446, 2449*t*
Narcotic analgesics, for hemarthroses, 1188*b*
Narcotic overdose, in hypercapnic disease, 535*t*
Narrow-spectrum β-lactamases, 1966
Nasal and face mask oxygen, for acute respiratory failure, 647*b*
Nasal calcitonin, 1643*b*
Nasal congestion, treatment for, 2193*b*
Nasal obstruction, 2192
Nasal polyps, 2629, 2629*f*–2630*f*, 2630*f*, 2635, 2635*b*, 2635*f*
NASH. *See* Nonalcoholic steatohepatitis
Nasolacrimal duct, 2596
Nasopharyngeal carcinoma, 1322, 1327*b*, 1328, 2256
Nasopharynx, 1320, 1320*f*, 1942.*e1f*, 2648
Natalizumab (Tysabri)
definition of, 152
for inflammatory bowel disease, 945*b*, 946*t*
for multiple sclerosis, 2505*t*
Nateglinide, for type 2 diabetes mellitus, 1541*t*
National Academy of Medicine, 17
National Clinicians' Post-Exposure Prophylaxis Hotline, 2300
National Committee for Quality Assurance, 41
National Healthcare Safety Network, 1863
National Human Genome Research Institute's Undiagnosed Diseases Program, 167
National Institute of Occupational Safety and Health (NIOSH), 87
National Institutes of Health (NIH)
Chronic Prostatitis Symptom Index, 826*f*
Patient Reported Outcomes Measurement Information System, 41
National Quality Forum (NQF), 41, 41.*e1t*
National Surgical Quality Improvement, 2661
National Vaccine Injury Compensation Program, 76
Natriuretic medications, 737*t*
Natriuretic peptide levels, postoperative, 2676
Natural killer (NK) cells, 182, 204*t*, 205, 206.*e2f*
Natural products, 154
Naughton protocol, 212*t*
Nausea and vomiting, 861
abdominal pain and, 856
acute pancreatitis and, 969, 970
after anesthesia, 2671
in cancer, management of, 1232*b*
diagnosis of, 861–862, 863*f*
in enteral nutrition, 1449–1450
management of, approaches to, 13*t*
signs and symptoms of, approach to, 852*t*
treatment of, 862*b*, 863*t*
Navelbine. *See* Vinorelbine
Naxos disease, 288
NDM. *See* New Delhi metallo-β-lactamase
Near-drowning, 591
Near-faint dizziness, 2647*t*
Nebivolol, 267*t*, 451*t*
Necator americanus, 2169
Neck
examination of, 30
infection, 1939
mass, 1322–1323, 1323*f*
rheumatoid arthritis of, 1752, 1752*f*
Neck pain, 2393
ancillary testing for, 2397
clinical examination of, 2396
clinical manifestations of, 2395
computed tomography of, 2397
definition of, 2393
diagnosis of, 2396, 2396*f*
differential diagnosis of, 2397, 2397*t*
epidemiology of, 2393
history-taking for, 2396
medications for, 2398*b*
myocardial ischemia associated with, 2398
pathobiology of, 2395
surgery for, 2398*b*
treatment of, 2398*b*
Necrobiosis lipoidica, 2688*t*
Necrobiotic xanthogranuloma, 1158, 1158*b*
Necrolytic acral erythema, 2710, 2710*f*
Necrolytic migratory erythema, 1564, 1564*f*
Necrosis
in pancreatitis, 969
papillary, 728–729
Necrotizing autoimmune myopathy, 2588*t*
Necrotizing clostridial infection, 1926
botulism, 1927, 1928*b*
tetanus, 1928, 1929*b*, 1929*t*
Necrotizing fasciitis, 1847, 1903, 1915, 2740
Necrotizing myelopathy, 1238*t*
Necrotizing pulmonary aspergillosis, chronic, 2095
Necrotizing sialometaplasia, 2621*t*
Negative blood cultures
endocarditis with, 416
Negative concordance, 335
Negative predictive value, 38
Negative-pressure ventilators, 653
Negative selection, 204
Neisseria gonorrhoeae, 1946–1950, 2649. *See also* Gonorrhea
annual screening for, 112
cervicitis caused by, 1948, 1948*f*
clinical manifestations of, 1946–1947
definition of, 1946–1947
diagnosis of, 1947, 1947*f*
epidemiology of, 1946
keratitis caused by, 2606
pathobiology of, 1946
pelvic inflammatory disease due to, 1949, 1949*b*
pharyngitis caused by, 1948
in pregnancy, 1948
prevalence of, 112
proctitis caused by, 1948
septic arthritis caused by, 1807
sexually transmitted anorectal diseases and, 983
urethritis caused by, 1947, 1947*f*
Neisseria infections, 2741, 2741*f*
Neisseria lactamica, 1943

Copyrighted material

Neisseria meningitidis, 1941–1946
bacteremia, 1847, 1891*t*
clinical manifestations of, 1943, 1943*f*
definition of, 1941–1946
description of, 1880
diagnosis of, 1943–1944
epidemiology of, 1941–1942, 1942*f*
pathobiology of, 1942–1943, 1942.*e*1*f*
prevention of, 1944
prognosis for, 1945
recurrent, 2518–2519
serogroups of, 1941
in sub-Saharan Africa, 1941
treatment of, 1944*b*, 1944*t*
Nelfinavir, 2301*t*
Nelson syndrome, 1495
Nemaline rod myopathy, 2585.*e*1*f*
Nematodes, 2169–2180
angiostrongyliasis, 2175
anisakiasis, 2173
ascariasis, 2169
baylisascariasis, 2174
Capillaria philippinensis, 2173
definition of, 2169
enterobiasis, 2172
gnathostomiasis, 2176
pathogen caused by, 2169, 2169*f*
prognosis for, 2170
strongyloidiasis, 2172–2173
tissue, 2173–2180
toxocariasis, 2174, 2174*b*, 2174*t*
treatment of, 2170*t*
trichinellosis, 2174–2175
Trichostrongylus, 2173
trichuriasis, 2171–2172
NEMO deleted exon 5 autoinflammatory syndrome (NDAS), 1731*t*
Neoadjuvant chemotherapy, for muscle-invasive bladder cancer, 1366*b*
Neoadjuvant therapy, for cancer, 1232*b*, 1234*t*
Neodymium:yttrium-aluminum-garnet, 2701
Neonatal alloimmune thrombocytopenia, 1179
Neonatal encephalitis, 2532*t*
Neonatal herpes simplex virus infection, 2247
Neonatal infection, cytomegalovirus and, 2251
Neonatal-onset multisystem inflammatory disease (NOMID), 1731*t*, 1733*t*
Neonatal onset pancytopenia, autoinflammation, rash, and hemophagocytic lymphohistiocytosis (NOCARH syndrome), 1731*t*
Neonatal tetanus, 1929
Neoplasms
distinguishing features of, 515*t*
esophagus, 1337
large intestine, 1345
pulmonary, 1329
small intestine, 1343
stomach, 1339–1343
Neoplastic disease, patients with, 1852–1853, 1853*t*
Neoplastic pericarditis, 424*t*
Neorickettsia sennetsu, 2060*t*
Neovascularization, 2608, 2609*f*
Nephrectomy, for autosomal dominant polycystic kidney disease, 812*b*
Nephritic syndrome, 780–784
clinical manifestations of, 781
complement levels in, 778*t*
diagnosis of, 781
epidemiology of, 780–781
mechanisms of, 782*f*
pathobiology of, 780
Nephritis
interstitial. *See* Interstitial nephritis
nephrotic syndrome *versus*, 777*t*
Nephrocalcinosis, 794, 803
Nephrogenic diabetes insipidus, 744, 816*t*
clinical manifestations of, 1501
diagnosis of, 1503
gestational, 1501
pathobiology of, 1500
treatment of, 1503*b*
Nephrogenic sclerosing dermopathy, 463
Nephrogenic syndrome of inappropriate antidiuresis, 739
Nephrogenic systemic fibrosis, 463, 1782, 2737, 2737*f*
Nephrolithiasis, 803–808
calcium stones, 803
clinical manifestations of, 804*f*, 805
cystine stones, 804
diagnosis of, 805, 805*f*
epidemiology of, 803–808
pathobiology of, 803–805
prevention of, 806–807, 807*f*
prognosis of, 808
struvite stones, 804
treatment of, 805*b*, 806*t*
uric acid stones, 804
Nephron, 729, 731*f*
Nephronophthisis, 809*t*, 813, 814*b*
Nephropathy
BK polyomavirus-associated, 2228, 2229*b*
HIV-associated, 2313
human immunodeficiency virus-associated, 789
immunoglobulin A, 781, 783*f*
membranous, 727, 779
clinical manifestations of, 780
diagnosis of, 780, 780*f*, 781*f*
prognosis for, 780
treatment of, 780*b*, 782*f*
in systemic sclerosis, 1781
Nephrosclerosis, hypertensive, 839
Nephrotic-range proteinuria, 792
Nephrotic syndromes, 726, 736, 776–780
causes of, 777*t*
clinical manifestations of, 777
definition of, 776–777
diagnosis of, 777
epidemiology of, 776–777
focal segmental glomerulosclerosis, 778, 779*b*, 779*f*, 779*t*
idiopathic, 777, 777*t*
membranous nephropathy, 779
minimal change disease, 777, 778*b*, 778*f*
nephritis *versus*, 777*t*
pathobiology of, 777
primary, 777
renal diseases associated with, 784*t*
salt retention in, 777
secondary, 777*t*
treatment of, 777*b*
volume retention in, 777
warfarin in, 777*b*
Nephrotoxicity, calcineurin inhibitor-induced, in renal transplantation, 847
Neprilysin, inhibition of, 265*b*
Neratinib (Nerlynx), 1215*t*, 1251*t*
Neridronate, for Paget disease, 1664*t*
Nerlynx. *See* Neratinib
Nernst equation, 299
Nerve biopsy, for peripheral neuropathy, 2567–2568
Nerve blocks, 136*b*, 975*t*
Nerve conduction study, 2375, 2375*t*, 2375.*e*1*f*
Nerve root disorders, 2401–2403, 2402*f*, 2403*b*
Nerve sheath tumors, 1319
Nervous system, alcohol use disorders and, 2355, 2355*t*
Nesiritide, intravenous, for heart failure, 265*b*
Netherlands, euthanasia and physician-assisted suicide in, 8
Netilmicin, dosage of, 1895*t*
NETs. *See* Neutrophil extracellular traps
Netupitant, for nausea and vomiting, 863*t*
Neupogen. *See* Filgrastim
Neural antigen targets, autoimmune encephalitis and, 2536*t*
Neural crest cell tumors, 2730, 2732*f*
Neural tube defects, 2545–2547
congenital, nutrition and, 60
folic acid supplementation for, 1452
Neuralgic amyotrophy, 2578
Neurally adjusted ventilatory assist, 653
Neuraxial anesthesia, 2671
Neuregulin 1, 260.*e*1*t*
Neuritis, leprosy and, 2050
Neuro-ophthalmology, 2614–2620
oculomotor control, 2617–2620, 2618.*e*1*t*
pupillary control, 2616–2617
vision, 2614–2616
Neurobrucellosis, 2515*b*, 2522
Neurocardiogenic syncope, 305–306, 309*b*
Neurocognitive disorders, 2312–2313, 2337*t*
Neurocutaneous disorders, 2549–2553, 2550*t*
Neurocutaneous melanosis, 2550*t*
Neurocysticercosis
description of, 2159
in travelers, 1889.*e*1*t*
Neurodegenerative disorders, 174
Neurodegenerative synucleinopathies, 2554, 2558
Neurodermatitis, 2687.*e*4*t*
Neuroendocrine neoplasms, 1347, 1561–1568
clinical manifestations of, 1562
definition of, 1561–1562
epidemiology of, 1561
of gastrointestinal tract and thorax, 1566
metastatic, principles for controlling growth of, 1568
molecular pathogenesis of, 1562
pancreatic, 1561*t*, 1562
pathobiology of, 1561–1562
pathology/classification of, 1561–1562
treatment of, 1241*b*, 1242*t*, 1562*b*
type 2, 1566
type 3, 1566
Neuroendocrine system, 1476–1481
central nervous system rhythms, 1478
disease of, 1478–1481
endogenous opioid peptides, 1478
feedback loops of, 1476
function of, 1478
hypophysiotropic hormones
corticotropin-releasing hormone, 1477
functions of, 1476
gonadotropin-releasing hormone, 1476
growth hormone-releasing hormone, 1477
prolactin inhibitory factor, 1477
prolactin-releasing factor, 1478
somatostatin, 1477
thyrotropin-releasing hormone, 1476, 1477*f*
regulation by, 1476–1478
Neuroendocrinology, 1476
Neurofibrillary tangles, 2414
Neurofibromas, 2730, 2732*f*
Neurofibromatosis, 583, 1530
stroke caused by, 2472
type 1, 1250*t*, 2550, 2550*t*, 2551*f*–2552*f*, 2552*f*
treatment for, 2550*b*, 2552*t*
type 2, 1250*t*, 2550*t*, 2551, 2552*f*
treatment for, 2551*b*
Neurogenic bladder, 828
Neurogenic tumors, 526
Neurokinin-1 receptor antagonists, for nausea and vomiting, 863*t*
Neuroleptic malignant syndrome, 678, 2496
characteristics of, 2682*t*
psychotropic medications and, 2681
treatment for, 2681*b*
Neuroleptics, for chronic prostatitis/chronic pelvic pain syndrome, 825*b*
Neurologic disease, 2368–2376
acute, diagnosis and treatment of, 2369
clinical manifestations of, 2368
complaints commonly caused by, 2370–2373
cognitive impairment, 2372
dizziness, 2371, 2372*f*
episodic weakness, 2371
fatigue, 2372
gait disorders, 2371, 2373*t*
head pain, 2371
intermittent weakness, 2371
memory loss, 2372
muscle pain, 2370
pain, 2371
sensory symptoms, 2371
spontaneous movements, 2370
weakness, 2371
cytomegalovirus and, 2252*b*
diagnosis of, 2368–2369
electroencephalography, 2374, 2375*t*
electromyography, 2375, 2375*t*
imaging, 2373–2374, 2373*t*
lumbar puncture, 2374, 2374*f*, 2374*t*
nerve conduction study, 2375, 2375*t*, 2375.*e*1*f*
repetitive stimulation study, 2375
history of, 2368–2369
human microbiome and, 1840
hyperfunctional, 2652
hypofunctional, 2652
neurologic examination for, 2369–2370
neurologic findings for, 2368.*e*5*f*
in sarcoidosis, 602, 602*t*
symptoms of, 2368
of throat, 2652, 2652*t*
Neurologic examination, 2369
Neurologic Lyme disease, 2026*b*
Neurologic paraneoplastic syndromes, 1238–1239, 1238*t*
Neurologic syndromes, 2222
Neurologic testing, 309
Neurologic toxicity, diphtheria and, 1934
Neurological syncope, 309*b*
Neurolytic blocks, in palliative care, 12
Neuromodulators, central brain-gut, for irritable bowel syndrome, 895*b*, 896*t*
Neuromuscular and balance exercises, for osteoarthritis, 1741*t*
Neuromuscular blockers
for anesthesia, 2670
reactions to, 1698*t*
Neuromuscular disorders, 620.*e*1*f*
in hypercapnic disease, 535*t*
preoperative, 2664–2665
Neuromuscular junction disease, 2581*t*
Neuromuscular transmission, disorders of, 2588–2593
definition of, 2588–2589, 2589*t*
drugs that worsen or induce, 2592*t*
epidemiology of, 2588
pathobiology of, 2588–2589, 2588.*e*2*f*
Neuromyelitis optica, 2508
Neuromyelitis optica spectrum disorder, 201*t*, 2560
Neuromyotonia, 1238*t*, 2591–2592
acquired, 2589*t*
clinical manifestations of, 2591–2592
definition and epidemiology of, 2591
description of, 2585–2586
diagnosis of, 2592
pathobiology of, 2591
prognosis of, 2592
treatment for, 2592*b*
Neuronal ceroid-lipofuscinoses, 1420*t*, 1424
Neuronal migration, disorders of, 2547, 2547*b*
Neuropathic arthropathy, 1822
Neuropathic pain, 134, 135*t*, 136, 1817*t*
Neuropathy
amyloidosis and, 1307
associated with monoclonal gammopathies, 2574
critical illness, 2578
herpes zoster-related, 2578
HIV-associated, 2577–2578
infectious, 2577
leprosy-associated, 2578
Lyme disease-associated, 2578
peripheral. *See* Peripheral neuropathy
thallium and, 106, 106*b*
toxic, 2578
Neurophysins, 1498, 1499*f*
Neuropsychiatric lupus, 1772
Neuropsychiatric syncope, 306
Neuroretinitis, cat-scratch disease and, 2001
Neurosarcoidosis, 602, 602*t*, 603*b*, 604*t*
Neurosyphilis, 1881, 2017, 2019, 2020*b*
Neurotoxic clostridial infections, 1927
Neurotoxic paralysis, 707, 709.*e*1*t*
Neurotoxic poisoning, in travelers, 1889.*e*1*t*
Neurotoxic shellfish poisoning, 713
Neurotoxins, 2589*t*, 2592–2593, 2592*t*
Neurovascular unit, 2461
Neutropenia, 1142–1148
afebrile, 1147*b*
after chemotherapy, 1147*b*
chemotherapy-induced, 1854*t*
chronic idiopathic, 1146
clinical manifestations and diagnosis of, 1146–1147, 1147*f*
congenital syndromes with, 1145
cyclic, 1144
cytotoxic therapy causing, 1065–1066
differential diagnosis of, 1144*t*
drug-induced, 1145, 1145*f*
due to increased margination and hypersplenism, 1146
due to nutritional deficiency, 1146, 1146*f*
epidemiology and pathobiology of, 1143–1148
febrile, 1855, 1968
fever in, 1854
immune, 1146
infection-related, 1145
management of, 1856*f*, 1857*f*
peripheral blood smear of, 1073

Copyrighted material

Neutropenia *(Continued)*
primary causes of, 1143–1145
psychotropic medications and, 2678*t*
secondary causes of, 1145–1146
severe congenital, 1143–1144, 1144*t*
treatment of, 1147*b*
Neutropenic enterocolitis
description of, 1860, 1926
intestinal ulcers associated with, 956, 956.*e1f*
Neutrophil differentiation, defects of, 1683.*e1t*
Neutrophil elastase (ELANE), 1144
Neutrophil extracellular traps (NETs), 1811
Neutrophil gelatinase-associated lipocalin, 260.*e1t*
Neutrophil production system, 1065*f*
Neutrophilia, 1140–1142
chronic idiopathic, 1141
clinical manifestations and diagnosis of, 1142, 1143*f*
differential diagnosis of, 1140*t*
epidemiology and pathobiology of, 1140–1142
hereditary, 1141
primary causes of, 1141–1142
secondary causes of, 1140–1141
Neutrophilic drug reactions, 2728, 2728*f*
Neutrophils, 182–183
acute inflammation and, 191
hypersegmented, 1072*f*
increased, 533
normal, dynamics of, 1140, 1140*f*
Nevi, 2730
Nevirapine, 2301*t*, 2303
Nevus
benign, 1391*f*
characteristics of, 1392*t*
dermal, 1391*f*
dysplastic, 1390, 1391*f*, 1392*t*
Nevus anemicus, 2743
Nevus depigmentosus, 2743
New Delhi metallo-β-lactamase (NDM), 1966
New-onset diabetes, in renal transplantation, 847
Newborn screening, 166, 1404
Nexavar. *See* Sorafenib
Next-generation sequencing, 164–165
for hereditary spherocytosis, 1096
for inborn errors of metabolism, 1400
NF-kappa-B-related autoinflammatory syndromes, 1731*t*
NFAT. *See* Nuclear factor of activated T cells
Niacin, 1413, 1453*t*
for hypertriglyceridemia, 1414*b*
Nicardipine
for hypertensive emergencies, 460*t*
properties of, 367*t*
Nicardipine SR, 451*t*
Nickel, *e1t–e8t*, 88*t*
Niclosamide
for *Diphyllobothrium*, 2157*b*, 2158*t*
for helminthic diseases, 2118
Nicotine, *e10t–e11t*
addiction, complication of, 42
dopaminergic activity and, 2679
properties of, 142*t*
Nicotine adenine dinucleotidase, 1913
Nicotine gum, 2350*b*
Nicotine inhaler, 2350*b*, 2351*t*
Nicotine lozenge, 2350*b*, 2351*t*
Nicotine metabolite (Cotinine), *e10t–e11t*
Nicotine nasal spray, 2350*b*, 2351*t*
Nicotine replacement therapy, 1609
Nicotine vaccine, for tobacco dependence, 2351*t*
Niemann-Pick disease, 583
type C, 1420*t*, 1423
Nifedipine
for high-altitude diseases, 593*t*
for livedo reticularis, 470*b*
for preeclampsia, 1621*t*
properties of, 367*t*
for Raynaud phenomenon, 473*b*
Nifedipine LA, 451*t*
Nifurtimox
for African trypanosomiasis, 2112*t*, 2125*b*, 2125*t*
for Chagas disease, 2116, 2128*b*
Night blindness, 2500, 2599
Nightmares, 2453, 2453*t*
NIH. *See* National Institutes of Health
Nilotinib (Tasigna), 1215*t*, 1251*t*
for chronic myeloid leukemia, 1274*b*, 1275*t*
Ninlaro. *See* Ixazomib
NIOSH. *See* National Institute of Occupational Safety and Health
Nipah virus, 2065*t*
Nipple discharge, 1368
Niraparib (Zejula), 1215*t*, 1251*t*
Nirmatrelvir
boosted with ritonavir, for coronavirus infections, 2190
for COVID-19, 2216
Nisoldipine, 367*t*, 451*t*
Nitazoxanide, 2115
for amebiasis, 2150*t*
for amebic liver abscess, 1025*b*
for cryptosporidiosis, 2112*t*, 2143*b*
for giardiasis, 2112*t*, 2145*b*
for helminthic diseases, 2118
for infectious gastroenteritis, 2263*b*
for tapeworm infections, 2158*t*
Nitrates, 357, 368*t*
Nitrendipine, 367*t*
Nitric oxide, 1581
Nitrofurantoin
for complicated urinary tract infection, 1875*b*
for cystitis, 1875*b*, 1876*t*
dosage of, 1895*t*
for urinary tract infection, 1877*t*
Nitrogen, 88*t*
Nitrogen washout technique, 530
Nitroglycerin, 368*t*
for acute coronary syndrome, 374*t*
for acute STEMI, 384*b*, 391*t*
for hypertensive emergencies, 460*t*
Nitroimidazoles, for amebiasis, 2149*b*
Nitroprusside, for hypertensive emergencies, 460*t*
Nitrous oxide
for anesthesia, 2670
for homocystinuria, 1427
Nivolumab (Opdivo), 1215*t*, 1251*t*
for melanoma, 1394*t*
for renal cell carcinoma, 1364*b*
NK. *See* Natural killer
NKCC2. *See* Sodium-potassium-2 chloride cotransporter
NLR. *See* Nucleotide-binding oligomerization domain (NOD)-like receptor
NLRP3, 1734, 1735
NMDA-receptor, autoimmune encephalitis and, 2536
NNRTIs. *See* Non-nucleoside analogue reverse transcriptase inhibitors
No-reflow phenomenon, 2463
Nocardia spp., 1855, 2072
Nocardial meningitis, cerebrospinal fluid in, 2073
Nocardiosis, 2072–2074
central nervous system infection and, 2073
clinical manifestations of, 2073
cutaneous infection and, 2073
definition of, 2072–2074
diagnosis of, 2073–2074
bacteriology for, 2073
procedure, 2073
radiology for, 2073, 2073*f*, 2074*f*
epidemiology of, 2072–2073
pathobiology of, 2073
pathogen causing, 2072
prognosis of, 2074
pulmonary, 2073
treatment for, 2074*b*
NOCARH syndrome. *See* Neonatal onset pancytopenia, autoinflammation, rash, and hemophagocytic lymphohistiocytosis
Nociceptive pain, 134, 135*t*, 1817*t*
Nociplastic pain, 134, 135*t*, 1817*t*
Nocturia, autosomal dominant polycystic kidney disease, 811
Nocturnal dyspnea, paroxysmal, 256
Nocturnal hypoglycemia, 1546
Nocturnal hypoventilation, 619
NOD2/CARD15, 942
Nodal marginal zone B-cell lymphoma, 1286
Nodular gastritis, 913
Nodular lymphocyte-predominant Hodgkin lymphoma, 1289, 1290
Nodular melanoma, 1391, 1392*f*
Nodular pulmonary amyloidosis, 1310
Nodular sclerosing Hodgkin lymphoma, 1290, 1290*f*
Nodular vasculitis, 2735
Nodules, 2689*t*
of skin, 2729, 2729*t*
Noise
hazard, 88*t*
hearing loss caused by, 2642
Noise-induced hearing loss, 2642
Nolvadex. *See* Tamoxifen
Non-abscess hepatic bacterial infections, of liver, 1023
Non-AIDS-defining cancers, 2316, 2316*b*
Non-enterohemorrhagic *E. coli*, 1962*t*
Non-group A β–hemolytic streptococcal infections, causing acute pharyngitis, 2648
Non-Hispanic White Americans, 17
Non-Hodgkin lymphoma, 1150, 1278–1288, 2315
in adolescents, 111
in AIDS patients, 1287, 1287*b*
B-cell lymphomas
diffuse large, 1279, 1284, 1285*b*
mature, 1283
precursor, 1281, 1282*b*
primary mediastinal large, 1285
rare types of, 1286
Burkitt lymphoma, 1286, 1286*b*
clinical manifestations of, 1280, 1282*f*
definition of, 1278–1281
diagnosis of, 1280–1281, 1282*t*
diseases confused with, 1288
in elderly patient, 1288
environmental exposure causing, 1279
epidemiology of, 1278
factors associated with development of, 1279*t*
familial, 1278
follicular lymphoma, 1283, 1283*b*
gastric mucosa-associated lymphoid tissue lymphomas, 1283, 1283*b*, 1284*t*, 1285*b*
genetic factors, 1278–1279
hematopoietic cell transplantation for, 1209
immunologic abnormalities, 1278–1279, 1279*t*
infectious agents associated with, 1279
occupational exposure causing, 1279
pathobiology of, 1278–1280, 1279*t*
pathology of, 1279, 1279.*e1f*, 1280*t*
posttransplant, 1287, 1287*b*
in pregnancy, 1288, 1288*b*
prognostic systems for, 1281, 1283*t*
Sjögren syndrome and, 1785
staging of, 1281, 1282*t*
T-cell lymphomas, 1281, 1282*b*
treatment, 1281*b*
World Health Organization classification of, 1279–1280, 1281*t*–1282*t*, 1282*t*
Non-homologous end-joining, 178
Non-IgE-dependent agonists, anaphylaxis caused by, 1692
Non-insulin-dependent diabetes, 1534
Non-insulinoma pancreatogenous hypoglycemia syndrome, 1554
Non-ionizing radiation, 91, 95
clinical manifestations of, 95
pathobiology of, 95
prevention of, 95
FAR-UV radiation, 95
radiofrequency radiations, 95.*e1f*, 95
ultraviolet radiation, 95
Non-muscle-invasive disease, of bladder, treatment of, 1366*b*
Non-neoplastic polyps, 1348
Non-nucleoside analogue reverse transcriptase inhibitors (NNRTIs), 2300, 2304*t*
Non-replicating adenovirus vector vaccine, 66*t*
Non-small cell lung cancer (NSCLC), 1329
chemotherapy regimens in, 1334*t*
histologic markers in, 1329.*e2t*
treatment for, 1333*b*
Non-spore forming anaerobic bacteria, 1938
antimicrobial susceptibility patterns for, 1941*t*
bacteremia caused by, 1938
central nervous system infections caused by, 1938
clinical manifestations of, 1938
definition of, 1938, 1939*f*, 1939*t*
diagnosis of, 1940, 1940*t*
head infections caused by, 1939
intra-abdominal infections caused by, 1939
neck infections caused by, 1939
obstetric-gynecologic infections causing, 1939
osteomyelitis caused by, 1940
pathobiology of, 1938, 1938.*e3t*
pathogen that cause, 1938, 1938.*e3t*
prevention of, 1941
prognosis for, 1941
septic arthritis caused by, 1940
skin and soft tissue infections caused by, 1939
taxonomy of, 1938.*e3t*
treatment of, 1940*b*, 1940*t*, 1941*t*
Nonabdominal examination, for gastrointestinal disease, 851
Nonacute porphyrias, 1429–1430
Nonalcoholic fatty liver disease (NAFLD), 986, 1033–1034, 1358
alanine aminotransferase levels in, 999
clinical manifestations of, 1033, 1033*f*–1034*f*
definitions of, 1033
diagnosis of, 1033–1034, 1033*f*, 1034*f*
epidemiology of, 1033
pathobiology of, 1033
prevention of, 1034
prognosis of, 1034
risk factors of, 1031*t*
treatment for, 1034*b*
Nonalcoholic steatohepatitis (NASH), 1031, 1466
Nonallergic rhinitis with eosinophilia syndrome, 2630*f*–2632*f*, 2631
Nonarteritic ischemic optic neuropathy, 2611
Nonarticular pain syndromes
definition of, 1742*t*
diagnosis of, 1742
epidemiology of, 1742
by region, 1742*t*
sports medicine injuries, 1742, 1744*t*
treatment of, 1742*b*
Nonarticular rheumatism, 1742
Nonbacterial thrombotic endocarditis, 414
Noncarbonic acids, 753
Noncardiogenic interstitial pulmonary edema, bilateral, 2267
Noncaseating granulomas, 942
Noncatastrophic disability, 115
Noncognitive psychiatric syndrome, 2336
Nonconvulsive status epilepticus, ECG findings in, 2429, 2429*f*
Noncoronary sinus, 352
Nondihydropyridines, for hypertension, 451*t*, 453*t*
Nonexercise activity thermogenesis, 1465
Nonfermentative *Corynebacteria*, 1934
Nonfunctional pancreatic neuroendocrine neoplasms, 1565–1566, 1566*b*
Nonfunctional PPoma, 1561*t*
Nongonococcal septic arthritis, 1805
clinical manifestations of, 1805
diagnosis of, 1805–1806, 1806*f*
differential diagnosis of, 1806
epidemiology of, 1805
pathobiology of, 1805, 1805*t*
prevention of, 1807
prognosis of, 1807
treatment for, 1806*b*, 1807*t*
Nongonococcal urethritis, organisms causing, 1879*t*
Nonhematologic malignancy, neutrophilia and, 1141, 1141*f*
Noninfectious pericarditis, 424*t*
Noninfectious pharyngitis, 2651–2653
Noninfectious recombinant vaccine, 66*t*
Noninferiority trials, 37
Noninflammatory retiform purpura, 2715*t*, 2716
Noninvasive mechanical ventilation, 620.*e1f*
Noninvasive positive-pressure ventilation, 620*b*, 653–654
Nonischemic dilated cardiomyopathy, 265*b*, 336
Nonketotic hyperglycinemia, 1398*t*
Nonmaleficence, 5
Nonmalignant conditions, hematopoietic cell transplantation for, 1209
Nonmelanoma skin cancers, 1390–1396
basal cell skin cancer, 1395, 1395*f*, 1396*b*
squamous cell skin cancer, 1395, 1395*f*, 1396*b*
Nonmendelian inheritance, 162
Nonocclusive mesenteric ischemia, 962, 962*f*
Nonpalpable purpura, 2713–2714
Nonparoxysmal junctional tachycardia, 323*t*, 326
Nonpneumococcal streptococcal infections, 1913–1919
Streptococcus agalactiae, 1918, 1918*b*
Streptococcus anginosus, 1919, 1919*b*
Streptococcus canis, 1919
Streptococcus dysgalactiae subspecies *equisimilis*, 1919, 1919*b*
Streptococcus gallolyticus, 1919
Streptococcus iniae, 1919
Streptococcus milleri, 1919
Streptococcus pyogenes, 1913
acute infections, 1913–1917
acute rheumatic fever caused by, 1917, 1917*b*, 1917*t*
bacteremia caused by, 1915

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Nonpneumococcal streptococcal infections *(Continued)*
cell wall of, 1913
cellulitis caused by, 1915
clinical manifestations of, 1914–1916
definition of, 1913
deoxyribonucleases, 1913
diagnosis of, 1914
ecthyma caused by, 1914
epidemiology of, 1913
erysipelas caused by, 1915
fibronectin binding protein, 1913
fimbriae, 1913
hyaluronic acid capsule, 1913
hyaluronidase, 1913
impetigo caused by, 1914
lipoteichoic acid, 1913
M proteins, 1913
myonecrosis caused by, 1915
necrotizing fasciitis caused by, 1915
nicotine adenine dinucleotidase, 1913
pathobiology of, 1913–1914
pharyngitis caused by, 1914, 1914*f*, 1914*t*
pneumonia caused by, 1916
post-streptococcal glomerulonephritis caused by, 1918
prevention of, 1917
prognosis for, 1916*b*
puerperal sepsis caused by, 1915
pyrogenic exotoxins, 1914, 1914*f*
rheumatic heart disease caused by, 1917–1918
scarlet fever caused by, 1914
streptolysin O, 1913
streptolysin S, 1913
treatment of, 1916*b*
Nonproliferative benign breast lesions, 1374
Nonproliferative diabetic retinopathy (NPDR), 1549*t*
Nonreplicative persister, 1900
Nonsecretory myeloma, 1302
Nonseminomatous germ cell tumors, treatment of, 1383*b*
Nonspecialist, in management
in rare genetic disorders, 158
role of, 159
Nonspecific building-related illness, occupational and environmental, 86*t*
Nonspecific immunosuppression, for allograft rejection, 207
Nonspecific interstitial pneumonia, 577
diagnosis of, 577, 577*f*
prognosis for, 577*b*
radiographic features of, 574*t*
treatment of, 577*b*
Nonsteroidal anti-inflammatory drugs (NSAIDs), 1460*t*
for acute pancreatitis, 972*b*
anaphylaxis caused by, 1692
in blood pressure, 455
for dysmenorrhea, 1596*t*
for esophagitis, 907*t*
for fibromyalgia, 1819*b*
gastric ulcers associated with, 914
hyponatremia and, 739–740
inflammatory bowel disease and, 941
for osteoarthritis, 1740*b*–1741*b*
in palliative care, 12
peptic ulcers caused by, 918, 919*b*
for postoperative pain, 1829
reactions to, 1698, 1698*t*
for rheumatoid arthritis, 1755*b*, 1756*t*
for skin diseases, 2698
for spondyloarthritis, 1765*b*
Nonsteroidal mineralocorticoid antagonism, for diabetic nephropathy, 797*b*
Nonstreptococcal bacterial pharyngitis, 2648–2649, 2649*f*
Nonsyphilitic treponematoses
definition of, 2021
pathogens that cause, 2021
Nontuberculous mycobacteria, 2040, 2044–2047
cervical lymph nodes in, 2045
clinical manifestations of, 2045
definition of, 2044–2047
diagnosis of, 2045–2046
diagnostic criteria for, 2046
disseminated disease in, 2045
epidemiology of, 2044
pathobiology of, 2044–2045, 2045.*e1f*
Nontuberculous mycobacteria *(Continued)*
pathogens that cause, 2044, 2044*t*
prevention of, 2047
prognosis of, 2047
pulmonary disease in, 2045
radiology for, 2045–2046, 2045*f*
rapidly growing, 2044*t*
skin and soft tissue disease, 2045
slowly growing, 2044*t*
treatment for, 2046*b*–2047*b*, 2046*t*
Nonulcer dyspepsia, abdominal pain and, 854*t*
Nonvariceal hemorrhage, treatment of, 883*b*
Nonviral vectors, 175
Nonvoluntary active euthanasia, 8*t*
Noonan syndrome, 348, 1250*t*
5'-noranhydrovinblastine, 1215*t*
Norepinephrine, 2553
for septic shock, 671
for shock, 662*b*, 664*t*, 667*b*
synthesis of, 1529
Norfloxacin
for cholera, 1956*b*
for urinary tract infection, 1876*t*, 1877*t*
Normal-pressure hydrocephalus, 2421, 2485*t*
Normocytic anemia, 1080
Normocytic normochromic anemia, peripheral blood smear of, 1069
Normothermia, 681*t*
Normovolemic hyponatremia, 733*t*, 741, 741*b*
Noroviruses, 1868, 2261–2264
clinical manifestations of, 2263
definition of, 2261–2264
diagnosis of, 2263
epidemiology of, 2262, 2262*t*
pathobiology of, 2262
as pathogen, 2261
prevention of, 2263
traveler's diarrhea caused by, 1888*t*
treatment of, 2263*b*
North Africa, HIV/AIDS in, 2289, 2289.*e1f*
North America, HIV/AIDS in, 2289, 2289.*e1f*, 2290.*e1f*
North American blastomycosis, 2080
Northern Europe, cystic fibrosis in, 556
Nortriptyline
for chronic pain, 138*t*
for depression, 2340*t*
for erythromelalgia, 471*b*
for irritable bowel syndrome, 896*t*
for tobacco dependence, 2351*t*
for zoster, 2249*b*
Norwalk virus, 2261
Nose
acute poisoning and, 683
examination of, 29
Nosocomial hospital diarrhea, 926
Nosocomial infections, 1997
suspected, 1851
Nosocomial meningitis, 2517*t*
Novantrone. *See* Mitoxantrone
Novavax, 77, 2218*t*, 2219
Novichok, 2592
Noxious gases, 88*t*
NPDR. *See* Nonproliferative diabetic retinopathy
NQF. *See* National Quality Forum
NRTIs. *See* Nucleoside analogue reverse transcriptase inhibitors
NSAIDs. *See* Nonsteroidal anti-inflammatory drugs
NSCLC. *See* Non-small cell lung cancer
NT-pro-BNP, *e1t*–*e8t*
Nuclear cardiology, 247
in coronary artery disease, 362
in heart failure, 261
Nuclear factor κ light chain enhancer of activated B cells (NF-κB) pathway, 185
Nuclear factor-kappa B (NF-κB)
activation of, autoinflammatory disease associated with, 1736
regulation, disorders of, 1736
transcription factor complex, 1730
Nuclear factor of activated T cells (NFAT), 148
Nuclear medicine, 872–874, 874*f*
Nuclear pathways, 2617–2618
Nucleation, 803
Nucleic acid amplification tests (NAATs)
for *Chlamydia trachomatis*, 2012
for *Clostridioides difficile*, 1925
for COVID-19, 2214
description of, 1834
Nucleic acid amplification tests (NAATs) *(Continued)*
for influenza, 2201
for sexually transmitted infections, 1879
Nucleoside analogue reverse transcriptase inhibitors (NRTIs), 2300, 2304*t*
Nucleoside analogues, for chronic hepatitis B, 1011*b*
Nucleoside reverse transcriptase inhibitors, 2577
Nucleosome, 1714
5'-Nucleotidase, 999
Nucleotide-binding oligomerization domain (NOD)-like receptor (NLR), 183
Nucleus accumbens, of brain, 142–143
NUDT15 gene, 160*t*
Nuedexta, for amyotrophic lateral sclerosis, 2563*b*
Null hypothesis, 36
Nummular dermatitis, 2687.*e3t*, 2702, 2702*f*
Nursing homes, death in, 16
Nusinersen, for spinal muscular atrophy, 2565*b*
Nutrient deficiency, 2542–2543
Nutrition, 57–61
breast cancer and, 59
for cancer, 58, 1232*b*
cardiovascular disease and, 57
colorectal cancer and, 59
congenital neural tube defects and, 60
coronary heart disease and, 58
dementia and, 60
diabetes mellitus and, 60
dietary change, translating evidence into, 60
dietary guidelines, 57, 57.*e3t*, 58*t*
dietary requirements in, 57, 57*t*
dietary supplements, 60
diseases and, 57
geriatric assessment of, 117
for heart failure, 265*b*
hypertension and, 60
for inborn errors of metabolism, 1401*b*
influence of, on mortality and morbidity, 57–60
intestinal diverticular disease and, 60
liver cancer and, 59
lung cancer and, 59
obesity and, 60
osteoporosis and, 60
pancreas cancer and, 59
prostate cancer and, 59
in renal replacement therapy, 842
Nutrition Risk Screening 2002, 1447, 1448*t*
Nutritional assessment, 1448
Nutritional deficiency, neutropenia due to, 1146, 1146*f*
Nutritional folate deficiency, causes of, 1120
Nutritional neurologic disorders, 2537
Nutritive jejunostomy, 1449
Nuts, diet-related hyperoxaluria and, 806
Nyctalopia, 2500
Nystagmography, 2646
Nystagmus, 2619–2620, 2620*t*

O

Obesity, 623, 1446, 1463–1470
in adolescents, 111, 112
blood pressure and, 445
body mass index and, 1463
body weight regulation, 1464
cancer and, 59, 1232*b*, 1244, 1466
cardiomyopathy and, 288
cardiovascular disease and, 220
in children, 1463
cholesterol gallstones and, 1049
classification of, 1463*t*
constitutional influences on, 1464
definition of, 1463–1470
diabetes and, 1540
diabetes mellitus and, 60
diagnosis of, 1466
dyslipidemia causing, 1466
endocrine manifestations of, 1466
energy balance regulation, 1464
energy expenditure and, 1465
energy intake and, 1464
environmental contributors to, 1464, 1464*t*
epidemiology of, 1463
evaluation of, 1466
flow diagram for, 1467*f*
food and, 1464
Obesity *(Continued)*
genetic aspects of, 1463–1464
human microbiome and, 1838, 1839*f*
hypertension caused by, 60, 1465
hypothalamic, 1481
increased intra-abdominal fat associated with, 902
insulin resistance and, 1465
kidney stone and, 803
medications causing, 1465, 1466*t*
metabolic complications of, 1465–1466
mortality rates for, 1463
nutrition and, 60
in older adults, 114, 117
osteoarthritis and, 1738
pathobiology of, 1463–1466
physical activity and, 1464, 1467*b*
prevalence of, 1463
prevention of, 1470
prognosis for, 1470
pulmonary function in, 533
secondary causes of, 1465
sleep apnea and, 1466
systemic complications of, 1466
testosterone affected by, 1583
treatment of, 1467*b*
bariatric surgery, 1467*b*
behavior modification, 1467*b*
diet, 1467*b*
endoscopic treatment, 1467*b*
laparoscopic gastric banding, 1467*b*
pharmacotherapy, 1467*b*, 1468*t*
physical activity, 1467*b*
very low calorie diets, 1467*b*
type 2 diabetes mellitus and, 1466
in women, 1609
Obesity-hypoventilation syndrome, in hypercapnic disease, 535*t*
Obeticholic acid
for nonalcoholic fatty liver disease, 1034*b*
for primary biliary cholangitis, 1058*b*
Obinutuzumab (Gazyva), 1215*t*
for chronic lymphocytic leukemia, 1269*b*, 1269*t*, 1270*t*
Object agnosia, 2409
Objective tinnitus, 2643
Obscure gastrointestinal bleeding, 885, 886*f*, 886*t*
Observation, 257–258
Observational studies, 41
Obsessive-compulsive disorder (OCD), 2343–2344, 2344*t*, 2348*t*
prognosis of, 2344*b*
treatment of, 2340*t*, 2344*b*, 2346*t*
Obstetric-gynecologic infections, 1939
Obstructive airway disease, 657
Obstructive jaundice, cholestatic liver disease *versus*, 1000*t*
Obstructive shock, 658, 659, 659*f*, 661*t*
Obstructive sleep apnea
characteristics of, 2448
clinical manifestations of, 2448
polysomnography of, 2444, 2445*f*
treatment of, 2449*b*
Occipital lobe, 2460*f*
Occlusive hydrocolloid dressing, for skin diseases, 2697
Occult gastrointestinal bleeding, 885, 886*f*, 886*t*
Occupational asthma, 541*b*
Occupational interstitial lung diseases, 582
Occupational lung disease, 584
acute febrile syndromes as, 590, 591*t*
asbestos-related diseases as, 589, 590*f*
cancer as, 591
chronic beryllium disease as, 589
chronic obstructive pulmonary disease as, 588
epidemiology of, 584
examples of, 585*t*
hypersensitivity pneumonitis as, 588
pneumoconioses as, 590, 590*t*, 591*f*
silicosis, 590, 590*t*, 591*f*
specific, 584–588
work-related asthma as, 585–588, 586*t*, 587*f*
Occupational medicine
acute injuries in, 85, 86*t*
clinical implications of, 85
clinical syndromes in, 85, 86*t*
emergency preparedness and disaster management in, 89
hazards in, 88*t*

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Occupational medicine *(Continued)*
hierarchy of controls in, 87
history, salient features of, 85, 85.*e1f*
individual clinician in, role of, 89
medical surveillance in, 87
principles of, 84
safety standards of, 87
wellness and resiliency in, 87
work-related disability in, 85
worker's compensation in, 85
Occupational Safety and Health Administration (OSHA), 87
OCD. *See* Obsessive-compulsive disorder
Ochronosis, 1825
Ocrelizumab (Ocrevus), for multiple sclerosis, 152, 2505*t*
Ocrevus. *See* Ocrelizumab
Octopus species, 712–713
Octreotide, 941*b*, 1215*t*
for acromegaly, 1489*b*
for acute poisoning, 693*t*
for carcinoid syndrome, 1568*b*
for GFRomas, 1565*b*
for glucagonomas, 1564*b*
for intestinal bacterial overgrowth, 934*b*
for intestinal pseudo-obstruction, 889*b*
for orthostatic hypotension, 2559*t*
Ocular adenovirus infection, 2205
Ocular allergies, 1674
Ocular bobbing, 2439, 2620
Ocular dysmetria, 2620
Ocular flutter, 2620
Ocular hypertension, 2607
Ocular infections, adenovirus causing, 2205
Ocular larva migrans, 2174
Ocular melanomas, 1391
Ocular metastases, 2613
Ocular myoclonus, 2620
Ocular rosacea, 2722
Ocular syphilis, 1881, 2017, 2020*b*, 2606
Ocular toxoplasmosis, 2136
diagnosis of, 2138*t*, 2139, 2139*f*
treatment for, 2140*b*, 2140*t*
Ocular trauma, 2603–2604
Oculomotor apraxia, 2619
Oculomotor control, 2617, 2618*t*
Oculopharyngeal muscular dystrophy, 2585
Odomzo. *See* Sonidegib
Odynophagia, 852*t*, 865
Ofatumumab (Kesimpta), for multiple sclerosis, 2505*t*
"Off-the-midline" fissures, 980
Ofloxacin, for eye infection, 2605*t*
OGTT. *See* Oral glucose tolerance test
Ointment, 2697
Olanzapine
for nausea and vomiting, 863*t*
for psychotic disorders, 2346*t*
weight gain and, 2680
Olaparib (Lynparza), 1215*t*, 1251*t*
Older adults. *See also* Elderly
cancer in, treatment of, 1232*b*
congenital heart disease in, 355–356
delirium in, 2331
dietary requirements for, 1452
disease and disability in, 114
frail, 122–123, 123*f*
frailty in, 114*t*, 115
geriatric syndromes in, 114
health expectancy in, 116*t*
life expectancy in, 116*t*
mental status change in, 2331
morbidity in, 114
mortality of, 115, 115*f*
multimorbidity in, 114
obesity in, 114
pain management in, 136*b*
physical activity for, 63*b*
psychosocial and physiologic considerations in, 704.*e1t*
subclinical disease in, 114
Olecranon bursitis, 1744–1745, 1745*b*, 1745*f*
Olfactogenital dysplasia, 1601
Olfactory dysfunction, 2640*b*
Olfactory receptors, 2639
Oligoarthritis, peripheral, 1762
Oligodendrogliomas, 1315*b*
Oligomeganephronia, 818
Oligomenorrhea, 1598
in Cushing syndrome, 1521
Oligosaccharidoses, 1419*t*
Oligozoospermia, 1586
Ollier disease, 1669
Olmesartan, 451*t*, 926
Olmesartan/amlodipine/HCTZ, 451*t*
Olmesartan/HCTZ, 451*t*
Olodaterol, 553*t*
Olsalazine (Dipentum), for inflammatory bowel disease, 946*t*
Olumiant. *See* Baricitinib
Omacetaxine, for chronic myeloid leukemia, 1275*t*
Omadacycline, 1845*t*, 1895*t*
Omalizumab
for asthma, 541*b*
description of, 152
dosing calculators, 541*b*
Omega-3 polyunsaturated fatty acids, for heart failure, 265*b*
"Omega" sign, 951, 952*f*
Omental cysts, 958
Omentum, anatomic diseases of, 958, 958*t*
Omeprazole
for acute pericarditis, 424*b*
for functional chest pain, 901*b*
Omphalocele, 951
Omsk hemorrhagic fever, 99.*e1t*, 2265*t*, 2268*t*, 2275*t*
Onchocerca volvulus, 2178
Onchocerciasis, 2178
Onchodermatitis, 2178
Oncogenes, 1247
DNA alterations in, 1247–1248, 1248*f*
in lung cancer, 1330, 1330.*e1f*
Oncogenic osteomalacia, 768
Oncogenic viruses, 1259
Ondansetron
for infectious gastroenteritis, 2263*b*
for nausea and vomiting, 863*t*
Ondine's curse, 534
"One-hand, two-feet syndrome", 2710–2711
Onxol. *See* Paclitaxel
Onycholysis, 2753, 2754*f*
Onychomadesis, 2752, 2752*f*, 2752*t*
Onychomycosis, 2754, 2754*b*, 2754*f*
Candida, 2090
O'nyong-nyong virus, 2275*t*, 2278, 2279*b*
Oocytes, 1591
Oophorectomy, 1373
Oophoritis, 1949
mumps and, 2226, 2226*t*
Opdivo. *See* Nivolumab
Open-angle glaucoma
primary, 2607, 2607*f*
secondary, 2607
Open pneumothorax, 526
Operative hemorrhoidectomy, 978*b*
Ophthalmologic examination, 212
Ophthalmoplegia, supranuclear, Whipple disease and, 2070
Opiates, 941*b*
Opicapone, for Parkinson disease, 2487*t*
Opioid peptides, endogenous, 1478
Opioids
abuse of, 2361
clinical manifestations and diagnosis of, 2362
epidemiology of, 2361
medical complications of, 2362
pathobiology of, 2361
physical dependence on, 2362
treatment of, 2362*b*
for anesthesia, 2670
central nervous system effects of, 685*t*
for irritable bowel syndrome, 895*b*, 896*t*
in palliative care, 12
properties of, 142*t*
reactions to, 1698*t*
screening for, 689*t*
toxicity, 686*t*
toxidromes, 683*t*
Opisthorchiasis, 2166, 2166*t*, 2168
Opisthorchis felineus, 2166
Opisthorchis spp, 1026*t*
Opisthorchis viverrini, 2166
Opportunistic infections
associated with candidiasis, 2089
cryptococcosis, 2087
description of, 1857
in HIV/AIDS, 2305, 2306*t*
antiretroviral therapy for, 2304, 2307*b*
behavioral factors, 2306
CD4 cells in, 2306, 2306*f*
Opportunistic infections *(Continued)*
clinical manifestations of, 2306
cytomegalovirus, 2307
diagnosis of, 2307
empiric management of, 2307*b*
Mycobacterium tuberculosis, 2306
natural histories of, 2306
pathobiology of, 2306
prevention of, 2308, 2308.*e1f*
prophylaxis against, 2304
prophylaxis for, 2309*t*
treatment of, 2307*b*, 2307*t*
Opsoclonus, 2620
Opsonization, 202
Optic chiasm, 2616
Optic disc abnormalities, 30
Optic glioma, 1315
Optic nerve, 2596
arteries of, 2614
vision loss caused by, 2615–2616
Optic nerve hypoplasia, 1478
Optic neuritis, 2500, 2508, 2508*b*, 2615
Optic neuropathy, 2542, 2544
Optic tract, 2616
Optical coherence tomography, for multiple sclerosis, 2504, 2504.*e1f*
Opticospinal multiple sclerosis, 2509
OPV. *See* Oral poliovirus vaccine
Oral allergy syndrome, 1673*t*
Oral anticoagulants, 503
Oral aphthous ulcer, 2320*f*, 2322*t*
Oral candidiasis, 2320*f*, 2322*t*
Oral cavity
anatomy of, 1320
cancer of, 1322, 1325*t*, 1327*b*
Oral contraceptives, 1613
for abnormal uterine bleeding, 1597*b*
benign hepatocellular adenoma and, 1615
cancer and, 1246
cervical cancer and, 1615
combined, 1614
complications of, 1614–1615
contraindications for, 1610, 1615, 1616*t*
endometrial cancer and, 1615
formulations of, 1613–1614, 1614*t*
hypertension associated with, 456
management of, 1615
missed, 1615
myocardial infarction and, 1614
for polycystic ovary syndrome, 1602*b*
reproductive system cancers and, 1615
rheumatoid arthritis and, 1750
risk factors for, 1614
side effects, 1614
stroke and, 1614
thrombosis caused by, 1614
venous thromboembolism and, 481
Oral-facial digital syndrome-1, 809*t*
Oral glucose tolerance test (OGTT), 1535, 1536*t*
Oral hairy leukoplakia, 2256, 2319*f*, 2322*t*
Oral iron supplement, for iron deficiency anemia, 1084*b*
Oral lichen planus, 2708, 2708*f*
Oral mucosal diseases
angular cheilitis, 2624
candidiasis, 2623
erythema multiforme, 2622
erythematous oral candidiasis, 2623, 2624*f*
geographic tongue, 2623, 2623*f*
hairy leukoplakia, 2623, 2623*f*
lichen planus, 2623, 2623*f*
mucocutaneous diseases, 2624
pigmentations associated with, 2624, 2624*t*
squamous cell carcinoma, 2622
ulcers, 2621*t*
viral ulcers, 2621
white lesions, 2622–2623
Oral poliovirus vaccine (OPV), 81
Oral potentially malignant disorders, 1321
Oral rehydration salts solution, for infectious gastroenteritis, 2263*b*
Oral rehydration therapy
for cholera, 1956*b*
for cryptosporidiosis, 2143*b*
for diarrhea and enteric infection, 1872*t*
Oral soft tissue tumors, 2624–2625, 2625*t*
connective tissue hyperplasia, 2624, 2625*t*
epithelial proliferations, 2625
mucoceles, 2625
papillary epithelial tumors, 2625*f*
reactive hyperplasias, 2625, 2625*t*
Oral temperature, 29, 33
Orbit, 2596
metastases to, 2615
pseudotumor, 2611
tumors, 2613
Orbital floor, 2597
Orbital restrictive disease, 2618–2619
Orchitis, 1583
mumps and, 2226, 2226*t*
Order sets, 44
Ordinary confluent smallpox, 2237, 2237*t*
Ordinary discrete smallpox, 2237, 2237*t*
Ordinary semiconfluent smallpox, 2237, 2237*t*
Oregon, physician-assisted suicide in, 8
Orencia. *See* Abatacept
Organ dysfunction, cancer and, treatment of, 1232*b*
Organ-restricted eosinophilic disease, 295
Organ-sparing therapy, for cancer, 1232*b*, 1234*t*
Organ support, during critical illness, with COVID-19, 2218
Organ transplantation, for inborn errors of metabolism, 1401*b*
Organic acidurias, 1403, 1403*f*, 1403*t*, 1404*b*
Organic compounds, 88*t*
Organic mercury, 103
Organophosphate poisoning, 88*t*, 2592
Organophosphorus compounds
central nervous system effects of, 685*t*
toxicity, 686*t*
Orgasm, 1604
impaired, 1590
Oriental cholangiohepatitis, 1056
Oriental rat flea, plague and, 1988
Orientia tsutsugamushi. *See also* Scrub typhus
diseases caused by, 2054–2060
in travelers, 1889.*e1t*, 1891*t*
Oritavancin
dosage of, 1895*t*
mechanism of action, 1895*t*
spectrum of activity, 1900
Orlistat, 1467*b*, 1609
Ornidazole
for amebiasis, 2150*t*
for amebic liver abscess, 1025*b*
Ornithine transcarbamylase deficiency, 1398*t*, 1402*t*
Ornithodoros hermsii, 2027–2028
Oropharyngeal candidiasis, 2090, 2090*f*
Oropharyngeal dysfunction, 908
Oropharyngeal infection, 2012
Oropharyngeal squamous cell carcinoma
HPV-associated, 1320, 1322, 1324*f*, 1327*b*, 1328
HPV-unrelated, 1322, 1327*b*
Oropharynx, 1320, 1320*f*, 2648
Acinetobacter in, 1973
cancer, 1325*t*
Oroya fever, 2000, 2001*f*, 2003*b*, 2003*t*
Orthodromic AV re-entrant tachycardia, 323*t*, 326
Orthopnea, 256
Orthopoxvirus
clinical manifestations of, 2237–2239
cowpox, 2237, 2238
diagnosis of, 2239–2240
epidemiology of, 2236
monkeypox, 2236, 2238, 2239*f*
prevention of, 2240*b*
smallpox, 2236–2240. *See also* Smallpox
treatment of, 2240*b*
vaccination for, 2240*b*
vaccinia
bovine-associated, 2238
clinical manifestations of, 2238
epidemiology of, 2236
generalized, 2238
post-vaccination, 2238
progressive, 2238
Orthopoxvirus variola, smallpox caused by, 2236
Orthostatic hypotension, 2554–2555
description of, 306
psychotropic medications and, 2678*t*
treatment for, 2557*b*, 2559*f*, 2559*t*
Orthostatic intolerance, without autonomic failure, 2554*t*, 2555
Orthostatic vital signs, 33
Osborne wave, 680, 681*f*
Oscillometric office blood pressure, 446*t*, 447
Oscillopsia, 2500, 2645

Copyrighted material

Oseltamivir
for influenza, 2189, 2189*t*, 2202*b*, 2203*t*
for pneumonia, 613*t*
OSHA. *See* Occupational Safety and Health Administration
Osilodrostat, for Cushing syndrome, 1524*b*
Osimertinib (Tagrisso), 1215*t*, 1251*t*
Osler nodes, 216, 414, 414*t*, 415*f*
Osler-Weber-Rendu disease, 348, 967, 1186
Osmolality, *e*1*t*–*e*8*t*
regulation of, vasopressin and, 1499
volume regulation and, interaction of, 1499
Osmolarity, body fluid, 730, 732*f*
Osmoreceptor dysfunction
clinical manifestations of, 1501
pathobiology of, 1499*f*, 1500
treatment of, 1503*b*
Osmostat, 1499
Osmotic demyelination, 741*b*, 2544*f*, 2545, 2545*b*
Osmotic diuresis, 744
Osmotic lysis, 199
Osmotic pressure, 737
Ospemifene, for genitourinary syndrome of menopause, 1632*t*
Osteitis fibrosa cystica, 1823
Osteoarthritis, 1706*t*, 1717*t*, 1718*f*, 1737–1741, 1751–1752, 1751*f*–1752*f*, 1753*f*
aging and, 1738
clinical manifestations of, 1739
comprehensive assessment of, 1740*t*
definition of, 1737–1741
diagnosis of, 1739–1740
disease-modifying drugs for, 1740*b*
endotypes of, 1739
epidemiology of, 1737–1738, 1826
exercises and physical activities for, 1741*t*
genetic contribution to, 1738–1739
holistic evaluation of, 1740, 1740*t*
imaging of, 1740
incidence of, 1738*f*
joint injury and, 1738
natural history of, 1739.*e*1*f*
nonsteroidal antiinflammatory drugs for, 1740*b*
obesity and, 1738
in older adults, 114
pain in, etiology of, 1739, 1739.*e*1*f*
pathobiology of, 1738–1739, 1826, 1826*f*
phenotypes of, 1739, 1739.*e*1*f*
prevention of, 1741
prognosis for, 1741
risk factors of, 1738–1739, 1739*f*
signaling pathways and structural changes in, 1738.*e*1*f*
signs of, 1739
symptoms of, 1739
treatment of, 1740*b*
in women, 1609
Osteoarticular candidiasis infections, 2091
Osteoarticular sporotrichosis, 2086
Osteoarticular tuberculosis, 2037, 2038*f*
Osteocartilaginous exostoses, 1669
Osteocytes, 1640
Osteogenesis imperfecta, 1641, 1727, 1728*b*, 1728*t*
Osteomalacia, 1453*t*, 1647–1651
cause of, 1647*t*
celiac disease and, 1649
clinical manifestations of, 1648
definition of, 1647–1651
diagnosis of, 1648–1651
differential diagnosis of, 1648*f*, 1649–1651
epidemiology of, 1647
hypophosphatemia causing, 1648, 1650*b*–1651*b*
oncogenic, 768
pathobiology of, 1647–1648, 1648*f*
prevention of, 1651
prognosis for, 1651
pseudofractures associated with, 1649
radiographic findings of, 1649, 1649*f*
treatment of, 1650*b*
tumor-induced, 1649
vitamin D deficiency causing, 1647, 1647*t*, 1650*b*, 1650*t*, 1651*t*
Osteomyelitis, 1809, 1849
Acinetobacter causing, 1973–1974
anaerobic bacteria causing, 1940
blastomycosis and, 2081
Osteomyelitis *(Continued)*
clinical manifestations of, 1809
definition of, 1809
diagnosis of, 1809
epidemiology of, 1809
microorganisms responsible for, 1805*t*
pathobiology of, 1809
prevention of, 1809
prognosis of, 1809
Pseudomonas, of foot, 1969
Staphylococcus aureus causing, 1904–1905
treatment for, 1807*t*, 1809*b*
vertebral, 1904, 1904*f*
Osteonecrosis, 1665, 1665*f*, 1665*t*, 1666*b*
of jaw, 1643*b*
pathobiology of, 1826
Osteopathia striata, 1668
Osteopenia, 1639
cystic fibrosis and, 557
Osteopetrosis, 1667, 1667*b*, 1668*f*, 1729
Osteopoikilosis, 1668
Osteoporosis, 1639–1647, 1706*t*, 1755*b*
anabolic agents for, 1643*b*
anticatabolic agents for, 1643*b*
antiresorptive and anabolic agents for, 116
bisphosphonates for, 1643*b*
bone loss mechanisms, 1640
bone mineral density
definition, 1639
measurement, 1642, 1643.*e*1*f*
testing of, 1638
calcium for, 1643*b*
clinical manifestations of, 1642
computed tomography of, 1641, 1641*f*
cystic fibrosis and, 557
definition of, 1639–1646
denosumab for, 1643*b*
diagnosis of, 1642–1646, 1642*f*
epidemiology of, 1639, 1640*f*
estrogen for, 1643*b*
exercise for, 1643*b*
femoral fracture caused by, 1643*b*
fractures associated with, 1639
fragility fractures in, 1641, 1641*f*
glucocorticoid-induced, 145, 1643*b*
hip fractures associated with, 1639
in HIV, 2318
laboratory workup of, 1638*t*
lifestyle modifications for, 1643*b*
male, 1646, 1646*b*
medications for, 1643*b*
menopause associated with, 1632
nutrition and, 60
pathobiology of, 1639–1641
prevention of, 1643*b*
prognosis, 1646
screening for, 55
secondary causes of, 1641, 1641*t*
selective estrogen receptor modulators for, 1643*b*
treatment of, 1639*b*, 1643*b*, 1643*t*–1644*t*
vertebral fractures associated with, 1642
vitamin D for, 1643*b*
Wilson disease and, 1437
in women, 1607–1609
Osteoprotegerin, 1298, 1640, 1654
Osteosarcoma, 1388, 1388*b*
Osteosclerosis, 1666
Osteosclerotic myeloma, 1302
Osteotomy, 1827
Otalgia, 2636
cause of, 2636*t*
clinical manifestations of, 2636, 2637*f*
definition of, 2636
diagnosis of, 2636
differential diagnosis of, 2637, 2638*f*
imaging of, 2637
laboratory findings in, 2637
pathobiology of, 2636
physical examination of, 2636, 2637*f*, 2638*f*
treatment of, 2638*b*
Otezla. *See* Apremilast
Otic barotrauma, 594
Otic syphilis, 2017
Otitis externa
malignant, 1969
treatment of, 2638*b*
Otitis media
chronic, 2641
Otitis media *(Continued)*
chronic suppurative, 1972
H. influenzae caused by, 1953
Otosclerosis, 2641
Ottawa Subarachnoid Hemorrhage Rule, 2475*f*
OTULIN deficiency (otulipenia), 1731*t*
Otulipenia. *See* OTULIN deficiency
Out-of-hospital cardiac arrest, causes of, 313*t*
Outpatient ambulatory setting, for fever, 1851*b*
Output-selective disorders, 2554*t*
Ova and parasite examination, for enteric infection, 1870*t*
Oval macrocytes
conditions associated with, 1072*t*
peripheral blood smear of, 1067*f*
Ovarian cancer, 1379
clinical manifestations of, 1379
definition of, 1379
diagnosis of, 1379
epidemiology of, 1379, 1379*t*
pathobiology of, 1379
prevention of, 1380
prognosis for, 1381, 1381*t*
risk factors for, 1379*t*
treatment of, 1380*b*, 1380*t*, 1381*t*
in women, 1607
Ovarian cysts, 1591
Ovarian epithelial malignancies, 1379
Ovarian function, in HIV, 2318
Ovaries, 1591–1594
definition of, 1591–1592
development, 1569
menstrual cycle-related changes in, 1595
pathobiology of, 1591–1592
Overactive bladder, 827
Overflow incontinence, 828, 830*t*
Overhydrated hereditary stomatocytosis, 1097
Overlap hypereosinophilic syndrome, 1162
Overlap syndromes, 1788, 1788*t*
Overt hypothyroidism, 1505, 1508*b*
Overt shock, 660
Overweight
cardiovascular disease and, 220
classification of, 1463*t*
flow diagram for, 1467*f*
Ovotesticular disorder, of sexual development, 1574
Ovulation
clomiphene citrate for, 1603*b*
in menstrual cycle, 1595
Oxacillin
for bacterial meningitis, 2518*t*
dosage of, 1895*t*
Oxalate crystals, *e*1*t*–*e*8*t*, 725*f*
Oxalate nephropathy, 795
Oxalate renal stones, 934
Oxaliplatin (Eloxatin), 1215*t*
Oxalyl diaminopropionic acid, 2541*t*
Oxamniquine, for schistosomiasis, 2165*b*
Oxantel pamoate, for helminthic diseases, 2117
Oxaprozin, for chronic pain, 138*t*
Oxazepam, for anxiety disorders, 2344*t*
Oxazolidinones
characteristics of, 1899
dosage of, 1895*t*
Oxcarbazepines, *e*10*t*–*e*11*t*
for chronic pain, 138*t*
for seizures, 2434*t*
Oximetry, pulse, 640
5-Oxoprolinuria, 759
Oxybutynin, 824*t*
Oxycodone, 139*t*
Oxygen
alveolar-arterial oxygen gradient, 639
arterial content, 640
myocardial requirements, 381*t*
partial pressure of, *e*1*t*–*e*8*t*, 639
normal values, 639
venous content, 640
Oxygen consumption, 677*t*
Oxygen consumption index, 677*t*
Oxygen delivery
normal value, 677*t*
systemic, 640
Oxygen delivery index, 677*t*
Oxygen extraction ratio, 677*t*
Oxygen intubation, 636
Oxygen saturation, *e*1*t*–*e*8*t*
abnormal, 34*t*
decreased, 35
Oxygen saturation *(Continued)*
low, 33*t*
measurement of, 33
normal range for, 32*t*
panic range for, 32*t*
Oxygen therapy, for carbon monoxide poisoning, 596*b*
Oxygen toxicity, 596
clinical manifestations of, 596
definition of, 596
diagnosis of, 596
pathobiology of, 596
prognosis of, 596
treatment of, 596*b*
Oxygen transport, systemic, 640
Oxygenation
therapy for, 647*b*
for viral hemorrhagic fevers, 2269*b*
Oxyhemoglobin association-dissociation curve, 643*f*, 1075*f*
Oxymetazoline hydrochloride, for skin diseases, 2698
Oxymorphone, 139*t*
Oxytocin, 1500
Ozanimod (Zeposia)
for inflammatory bowel disease, 945*b*, 946*t*
for multiple sclerosis, 2505*t*

P

P. falciparum erythrocyte membrane protein-1 (PfEMP-1), 2119
p-aminosalicylic acid, for actinomycosis, 2068
P values, 36
P wave, 228*f*, 229, 229*t*
p16, 1391
Pacemaker
complications of, 343–344
dual-chamber, 342*f*
electrocardiogram with, 343*f*
leadless, 342*f*
permanent, indications for, 341, 341*t*
programming of, 342–343
Pachydermoperiostosis, 1667, 1667*b*
Pachygyria, 2547
Pacific, HIV/AIDS in, 2289, 2289.*e*1*f*
Pacific Coast tick fever, 2055*t*, 2065*t*
Pacing
modes, 342
permanent, 341–343
indications for, 341, 341*t*
synchronous biventricular, 342, 342*f*
systems of, 341–342, 342*f*
temporary, 341
Paclitaxel (Taxol, Onxol), 1215*t*
protein bound (Abraxane), 1215*t*
PACNS. *See* Primary angiitis of the central nervous system
Paeniclostridium sordellii, 1927, 1927*b*
Paget disease of bone, 1662–1665
arthritis associated with, 1823
bisphosphonates for, 1664*b*, 1664*t*
clinical manifestations of, 1663–1664
definition of, 1662–1665
diagnosis of, 1663*f*, 1664
drug therapy for, 1664*b*
epidemiology of, 1662
monitoring disease activity of, 1664*b*
pathobiology of, 1662–1663, 1662.*e*1*f*, 1663*f*
prognosis for, 1665
surgery for, 1664*b*
treatment of, 1664*b*
Paget disease of nipple, 1368
Pain, 133–141
acute, 135, 1113
back pain, 136*b*
biopsychosocial model of, 133, 134*f*
in cancer, management of, 1232*b*
categorization of states, 135*t*
centralized, 1816, 1817*t*
chest, 210, 211*t*
chronic, 133, 1113
in chronic pancreatitis, treatment for, 975*b*, 975*t*
chronic widespread, 1816
clinical manifestations of, 135–136
definition of, 133–141
diagnosis of, 135
diagnostic tests, 136
ear, 2636

Copyrighted material

Pain *(Continued)*
epidemiology of, 133
eye, 2598, 2599*t*
fibromyalgia and
mechanistic characterization of, 1817*t*
processing, 1817
history of, 135–136
management of, approaches to, 13*t*
mixed, 134, 135*t*
nature *versus* nurture, 134–135
neurologic diseases that cause, 2371
neuropathic, 134, 135*t*, 1817*t*
nociceptive, 134, 135*t*, 1817*t*
nociplastic, 134, 135*t*, 1817*t*
in osteoarthritis, etiology of, 1739, 1739.*e1f*
pathobiology of, 133–135, 134*f*
pathologic, 133–134
physical examination of, 136
postoperative, in joint diseases, 1829
psychologic assessment of, 136, 136*t*
severe mental illness and, 2683*t*
in sickle cell disease, 1113, 1114*b*
somatic, 134, 135*t*
treatment of, 136*b*, 137*f*
visceral, 134, 135*t*
Pain management
combination therapy, 136*b*
complementary and alternative medical (CAM) therapy, 136*b*
future developments of, 141
interventional therapy, 136*b*
in older adults, 136*b*
pharmacologic therapy, 136*b*
psychologic treatment, 136*b*
in women, medications for, 1608*t*
Pain-related symptoms, treatment for, 2193*b*
Pain syndromes, 1708
Painful hunger, 917
Painful legs and moving toes, 2496
Pakistan monsoon flooding, climate-related hazards, 91*t*
Palbociclib (Ibrance), 1215*t*
for breast cancer, 1369*b*
Paliperidone, for psychotic disorders, 2346*t*
Palivizumab, 153
for respiratory syncytial virus, 2195
Palliative care, 11–17, 638
domains of, 12–16
for hepatobiliary cancers, 1360*b*
questions to address, 12
Palliative radiation, for cancer, 1232*b*
Pallor, anemia and, 1076
Palmar erythema, 987, 988*f*
Palmar fasciitis and arthritis syndrome, 1823–1824
Palmoplantar psoriasis, 2705
Palonosetron, for nausea and vomiting, 863*t*
Palpable purpura, 2690*f*, 2692*t*, 2714, 2714*f*, 2714*t*, 2715*f*
Palpation
cardiac, 213
skin, 2687
Palpitations, 210–212, 212*t*
anemia and, 1075–1076
definition of, 303–304
Palytoxin poisoning, 713
Pamidronate (Aredia), 1215*t*
for Paget disease, 1664*t*
PAMPs. *See* Pathogen-associated molecular patterns
pANCA. *See* Perinuclear antineutrophil cytoplasmic antibodies
Pancreas, alcohol use disorders and, 2354, 2355, 2355*t*
Pancreatic cancer, 1354–1357
adenocarcinomas, 1354
biomarkers of, 1356
clinical manifestations of, 1355
definition of, 1354–1357
diagnosis of, 1355–1357
differential diagnosis of, 1355
epidemiology of, 1354–1355
hypercoagulability and, 479
imaging of, 1356
metastatic, 1356*b*, 1357*t*
neoadjuvant therapy for, 1356*b*
nutrition and, 59
palliative care for, 1356*b*
pathobiology of, 1355, 1355*f*
prevention of, 1357
prognosis for, 1357
screening of, 1356
treatment of, 1356*b*, 1356*t*
Pancreatic cancer *(Continued)*
tumorigenesis of, 1355
unresectable, 1356*b*, 1357*t*
Pancreatic duct, obstruction of
acute pancreatitis and, 970, 970*t*
chronic pancreatitis and, 973
Pancreatic enzyme replacement therapy
chronic pancreatitis, 975*b*, 975*t*
for cystic fibrosis, 558*b*
Pancreatic function tests, 931*t*, 975
Pancreatic insufficiency, cystic fibrosis and, 557
Pancreatic islet cell transplantation, for type 1 diabetes mellitus, 1537*b*
Pancreatic neuroendocrine neoplasms (pNENs), 1561*t*, 1562
ACTHomas as, 1566
carcinoid syndrome as, 1567
functional, 1562–1563
glucagonomas as, 1563
growth hormone-releasing factor secreting neuroendocrine neoplasms as, 1565, 1565*b*
nonfunctional, 1565, 1566*b*
somatostatinomas as, 1565
VIPoma syndrome as, 1564–1565
Zollinger-Ellison syndrome as, 1562
Pancreatic neuroendocrine tumor, with liver metastases, magnetic resonance imaging of, 872*f*
Pancreatic panniculitis, 1821–1822
Pancreatic pseudocyst, 975*b*
Pancreatic structure, tests of, 974–975, 974*f*, 975*f*
Pancreatic tumors, hypoglycemia and, treatment of, 1557*b*
Pancreatitis, 969–977
acute, 969
abdominal pain and, 854*t*
causes of, 970*t*
clinical manifestations of, 970
complications of, 972*t*
definition of, 969
determining severity of, 971, 972*f*
diagnosis of, 970
epidemiology of, 969
etiology of, 971
imaging studies for, 971, 971*f*, 972*f*
laboratory tests for, 971
pathobiology of, 969
prognosis of, 973
treatment for, 972*b*
autoimmune, 970, 970*t*
chronic, 933, 973
clinical manifestations of, 933, 974
definition of, 973
diagnosis of, 933, 974, 974*f*, 974*t*, 975*f*
epidemiology of, 973
pathobiology of, 973
prevention of, 976
prognosis of, 976
treatment for, 975*b*, 975*t*
in endoscopy, 876*t*
mumps and, 2226*t*
pleural effusions in, 626–627, 626*b*
weight loss and, 860*t*
Pancreatitis-arthritis syndrome, 1821–1822
Pancreaze, for exocrine pancreatic insufficiency, 975*t*
Pandemic, quality and safety during, 46
Pandemic influenza, 2199
Panencephalitis, subacute sclerosing, 2221
Panhypopituitarism, 1479, 1483
Panic attacks, 2342
Panic disorder, 2342*t*, 2343
Panitumumab (Vectibix), 1215*t*, 1251*t*
Panmyelosis, neutrophilia and, 1142
Panniculitis, 2735–2736
Panobinostat (Farydak), 1215*t*
Pansystolic murmurs, 214
Pantothenic acid deficiency, 1453*t*
Panuveitis, 793
PAPA. *See* Pyogenic arthritis with pyoderma gangrenosum and acne
Papillary muscle, 224
Papillary necrosis, 728
Papillary renal cell carcinomas, 1363
Papillary (differentiated) thyroid cancer, 1517
clinical manifestations of, 1517
epidemiology of, 1517
pathobiology of, 1517
prognosis of, 1518–1519, 1518*f*
risk for persistence/recurrence of, 1517*t*
treatment for, 1517*b*
Papilledema, 2513, 2609, 2610*f*, 2616, 2616*t*
Papillomatosis, 2241
Papillomaviruses, 2240–2244
Pappenheimer bodies, peripheral blood smear of, 1069*f*
Papular eruptions, 2712–2713
Papular exanthems, 2712
Papule, 2689*t*
Papulopustular rosacea, 2722
Papulosis, malignant atrophic, 965, 969
Papulosquamous diseases, 2705–2711, 2705*t*
Bazex syndrome, 2710
dermatophytoses, 2710, 2711*f*
lichen nitidus, 2708, 2708*f*
lichen planus, 2707
mycosis fungoides, 2709, 2710*f*, 2710*t*
necrolytic acral erythema, 2710, 2710*f*
parapsoriasis, 2709, 2709*f*
pityriasis lichenoides, 2709
pityriasis rosea, 2707
pityriasis rubra pilaris, 2707
psoriasis, 2705–2706
secondary syphilis, 2709, 2709*f*
Paracellular pathway, 730
Paracetamol. *See* Acetaminophen
Paracoccidioides brasiliensis, 1024
Paracoccidioides spp., 2086
Paracoccidioidomycosis, 2086, 2087*b*, 2651
Paradoxical vocal fold movement, distinguishing features of, 515*t*
Paraesophageal hernia, 910
Parafibromin, 1657
Paraganglioma
epidemiology of, 1530
familial, 1530
hypertension and, 450, 450*b*
metastatic, 1533
pheochromocytoma *versus*, 1529–1533
in von Hippel-Lindau disease, 1530
Paragonimiasis, 2167
Paragonimus spp., 2166*t*
Paragonimus westermani, 524
Parainfectious encephalitis, 2532
Parainfectious encephalomyelitis, 2646
Parainfluenza viral diseases, 2196–2198
in acute bronchitis and tracheitis, 605
clinical manifestations of, 2196–2197
diagnosis of, 2197
in elderly, 2196
epidemiology of, 2196–2198
in immunocompromised patients, 2196
pathobiology of, 2196
prevention of, 2198
primary infection, 2196
prognosis of, 2198
reinfection of, 2196
treatment of, 2197*b*–2198*b*
Paralysis, diaphragmatic, 619, 620.*e1f*
Paralysis ticks, 710
Paralytic rabies, 2535
Paralytic shellfish, 713
Paralytic shellfish poisoning, in travelers, 1889.*e1t*
Parameningeal infections, 2515, 2523, 2525
cerebral venous thrombosis, virally mediated, 2530
infectious endocarditis, neurologic complications of, 2530, 2530*b*
sinus thrombosis
lateral, 2529, 2529*b*, 2529*f*
septic cavernous, 2528, 2529*b*
septic sagittal, 2530, 2530*b*
venous, 2528–2530
spinal epidural abscess, 2527, 2527*f*, 2527.*e1t*
clinical manifestations of, 2527
definition of, 2527–2528
diagnosis of, 2527
epidemiology of, 2527
pathobiology of, 2527
prognosis of, 2528
treatment of, 2528*b*
subdural empyema, 2528, 2528*b*
Paramyxoviridae family, 2225
Paraneoplastic cerebellar degeneration, 1238*t*
Paraneoplastic encephalomyelitis, 1238*t*
Paraneoplastic hypercalcemia, pancreatic neuroendocrine neoplasm, 1566
Paraneoplastic neuropathies, 2576–2577
Paraneoplastic pemphigus, 2718
Paraneoplastic syndromes, 1237–1240, 2564*t*
dermatologic, 1239
diagnosis of, 1238*t*
Paraneoplastic syndromes *(Continued)*
evaluation of, 1238*t*
hematologic, 1239
hepatic, 1239
neurologic, 1238, 1238*t*
renal, 1239
rheumatologic, 1239, 1239*b*, 1239*f*
Paranoid personality disorder, 2348*t*
Paraplatin. *See* Carboplatin
Parapoxvirus, 2239, 2240*b*
Parapsoriasis, 2709, 2709*f*
Parasites
peripheral blood smear of, 1074*t*
of skin, 2739*t*, 2742
Parasitic infections
distinguishing features of, 515*t*
of liver, 1024, 1026*t*
treatment of, 2112*t*
Parasomnias, 2452–2453, 2453*b*
Paraspinal region, of mediastinum, 527
Parathyroid disorders
arthritis associated with, 1823
chromosomal locations of, 1653*t*
hypercalcemia. *See* Hypercalcemia
Parathyroid glands, 1652
Parathyroid hormone, 1652–1654, 1652.*e1f*
actions of, 1653–1654
extracellular fluid calcium regulated by, 1652*f*
intact, *e1t*–*e8t*
PTH gene and, 1652–1654
skeletal actions of, 1654
Parathyroid surgery, for primary hyperparathyroidism, 1657*t*
Parathyroidectomy, for primary hyperparathyroidism, 1657*b*
Paraventricular nucleus, 1477*f*
Paravertebral compartment, of mediastinum, 527
Parenchymal disorder, occupational and environmental, 86*t*
Parenchymal lung disease, 494
Parenteral anticoagulants, 501, 501*t*
Parenteral nutrition, 1445*b*, 1450, 1450*f*, 1451*t*
Parietal lobe, 2460*f*
Parinaud oculoglandular syndrome, cat-scratch disease and, 2001
Parinaud syndrome, 1314, 2619
Parkinson disease, 173*f*, 174, 2483–2486, 2558
deep brain stimulation of, 2486
diagnosis of, 2484–2485
differential diagnosis of, 2485*t*
drugs for, 2487*t*
epidemiology of, 2483
late-stage, 2484*t*
levodopa for, 2486, 2486*b*
motor symptoms, 2483–2484
pathobiology of, 2483
pathology of, 2483
pramipexole for, 265*b*
signs and symptoms of, 2484*t*
Parkinsonian gait, 2373*t*
Parkinsonism, 2483–2489
akinesia in, 2484
clinical manifestations of, 2483–2484
complications of, 2484
definition of, 2483
differential diagnosis of, 2483*t*
drug-induced, 2485*t*
manganese and, 101*t*, 107, 107*b*
postural disturbances in, 2484
prognosis of, 2486
resting tremor of, 2484
rigidity associated with, 2484
secondary, 2483*t*
treatment of, 2486*b*
Paromomycin
for amebiasis, 2150*t*
for amebic liver abscess, 1025*b*
for cryptosporidiosis, 2112*t*
for giardiasis, 2145*b*
for intestinal amebiasis, 2112*t*
for visceral leishmaniasis, 2132*b*
Paronychia, 1969, 2753
Parotid gland, swelling of, 987
Parotitis
of childhood, 2626
mumps, 2521
mumps and, 2226
Paroxetine, *e10t*–*e11t*
for depression, 2340*t*
for irritable bowel syndrome, 896*t*
Paroxetine mesylate, for hot flashes, 1631*t*
Paroxysmal atrial fibrillation, 329*b*, 330*f*

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Paroxysmal hemicrania, 2377*t*, 2381
Paroxysmal hypothermia, 681
Paroxysmal nocturnal dyspnea, 256
Paroxysmal nocturnal hemoglobinuria (PNH), 480, 480*b*, 1091–1092, 1126
  clinical manifestations of, 1092
  complement system and, 201*t*
  definition of, 1091–1092
  epidemiology of, 1091
  pathobiology of, 1091–1092
PARP. *See* Poly(ADP-ribose) polymerase
Partial pressure of carbon dioxide ($PaCO_2$), 639
Partial pressure of oxygen (PaO_2), *e*1*t*–*e*8*t*, 639
  normal values of, 639
Particulate matter, 87
Parvoviridae, 2233
Parvovirus, 2233
  B19 arthropathy caused by, 2234
  clinical manifestations of, 2234–2235
  definition of, 2233
  diagnosis of, 2235
  epidemiology of, 2233
  fifth disease caused by, 2234, 2234*f*
  hydrops fetalis caused by, 2235
  other syndromes of, 2235
  pathobiology of, 2234
  persistent infection in, 2235
  prevention of, 2235
  prognosis of, 2236
  pure red cell aplasia caused by, 2235*f*
  transient aplastic crisis caused by, 2234, 2235*t*
  treatment of, 2235*b*
PASC. *See* Post-Acute Sequelae of SARS-CoV-2
Pasireotide, 1356*b*, 1489*b*
"Passenger" mutations, 1249
Passive euthanasia, 8*t*
Passive immunity, 64, 65*t*
  for COVID-19, 2216, 2216*f*, 2217
Passive oral immunotherapy, for infectious gastroenteritis, 2263*b*
Past medical history, 28
Paste, 2697
Pastia lines, 1914
Patau syndrome, 164
Patch, 2689*t*
Patchy alopecia, 2747*t*, 2749
Patellar tendinitis, 1747
Patent ductus arteriosus (PDA), 350
  anatomy of, 350.*e*1*f*
  diagnosis of, 350
  exercise recommendations for, 355.*e*2*t*
  prognosis for, 350*b*
  treatment of, 350*b*
Patent foramen ovale, 348, 349, 349*b*
Paterson-Brown Kelly syndrome, 1337
Pathogen-associated molecular patterns (PAMPs), 182, 183, 191, 192*f*
Pathogen lipid shuttling, 670.*e*1*f*
Pathologic bone fractures, prevention of, in cancer, 1232*b*
Pathologic fractures, bone tumors and, 1388*b*
Pathologic myopia, 2598
Pathologic pain, 133
Patient autonomy, 4
Patient blood management, 1206
Patient communication
  advances in, 40
  Ask-Tell-Ask, 12, 16*t*
  core skills for, 16*t*
Patient education, for acute STEMI, 384*b*
Patient Health Questionnaire-9 (PHQ-9), 54*t*, 257
Patient-level measures, 40
Patient-physician interaction, 4
Patient safety, 45–46
  epidemiology of, 45
  improvement of, 45–46
  modern approach to, 45
Patiromer, for hyperkalemia, 751*b*
Patisiran, for amyloidosis, 1309*b*
Pattern reversal visual evoked potentials, 2376.*e*1*f*, 2376
Patterned alopecia, 2748
Patterns of inheritance, 160
  mendelian inheritance, 160, 161*f*
  mosaicism, 162, 163*f*
  nonmendelian inheritance, 162
Pauci-immune glomerulonephritis, 1716
Pauci-immune rapidly progressive glomerulonephritis, 785, 1716
Paucibacillary leprosy, 2048, 2048*t*, 2048.*e*1*f*
Pay for performance, 44–45
Pazopanib (Votrient), 1215*t*
PBC. *See* Primary biliary cholangitis
PBGD. *See* Porphobilinogen deaminase
PCECV. *See* Purified chick embryo cell vaccine
PCFT. *See* Protein-coupled folate transporter
PCI. *See* Percutaneous coronary intervention
PCOS. *See* Polycystic ovary syndrome
PCP. *See Pneumocystis* pneumonia
PCR. *See* Polymerase chain reaction
PCSK9 monoclonal antibodies, 1413, 1413*t*
PCT. *See* Porphyria cutanea tarda
PDA. *See* Patent ductus arteriosus
PDR. *See* Proliferative diabetic retinopathy
Peak bone mass, 1640, 1640.*e*1*f*
Peak expiratory flow rate (PEFR), 539, 539*t*
Pearson syndrome, 2586
Pectus excavatum, 621, 621*b*, 622*f*
Pediatric autoimmune neuropsychiatric disorders associated with streptococcal infections (PANDAS), 1918
Pediculus humanus, 2027, 2059
Pedunculated polyps, 1343
Peficitinib, 153*t*
PEG. *See* Percutaneous endoscopic gastrostomy
Pegvisomant, for acromegaly, 1489*b*
Pegylated interferon-alfa-2*a*
  for chronic hepatitis B, 1011*b*
  for hepatitis C infections, 2181*t*
Pegylated interferon-alfa-2*b*, for hepatitis C infections, 2181*t*, 2182*t*, 2185–2186
Pegylated interferon lambda, for COVID-19, 2217
Pelger-Huët anomaly, 1071*f*, 1141–1142
Peliosis hepatis, 2002, 2003*b*, 2003*t*
Pelizaeus-Merzbacher disease, 2509
Pellagra, 2541
Pelvic examination
  description of, 31
  for gastrointestinal disease, 851
Pelvic exenteration, for cervical cancer, 1375*b*
Pelvic hernia, 952*b*
Pelvic infection, actinomycosis and, 2068
Pelvic inflammatory disease (PID), 1949
  characteristics of, 1883
  Chlamydia trachomatis causing, 2012
  clinical manifestations of, 1949
  diagnosis of, 1949
  organisms causing, 1879*t*
  prognosis for, 1883, 1949
  treatment of, 1883*b*, 1883*t*, 1949*b*
Pelviureteral abnormalities, 818–819, 820*f*
Pembrolizumab (Keytruda), 1215*t*, 1251*t*
  for melanoma, 1394*t*
  for renal cell carcinoma, 1364*b*
Pemetrexed (Alimta), 1215*t*
Pemphigoid gestationis, 2717, 2717*b*, 2717*f*
Pemphigus, 2651–2652, 2718, 2718*b*–2719*b*
Pemphigus foliaceus, 2687.*e*3*t*, 2718
Pemphigus vulgaris, 194, 2718, 2719*f*
  description of, 2621*t*, 2624
  esophageal involvement in, 911
Penbutolol, 451*t*
Penciclovir, for herpesvirus infections, 2186
Pencil cells, 1068, 1068*f*
Penetrating aortic ulcer, 439, 441*b*, 441*f*
Penetrating injury, 699*f*, 699*t*
Penetrating trauma, pathogens and empirical therapy for, 2526*t*
Penicillamine, 1460*t*
Penicillin
  adverse reactions of, 132
  dosage of, 1895*t*
  for endocarditis, 419*t*, 422
  for Oroya fever, 2003*b*
  for streptococcal infections, 2648
  for *Streptococcus pneumoniae* pulmonary infections, 1912.*e*1*t*
  for syphilis, 2020*b*, 2020*t*
  toxicities of, 1901*t*
Penicillin allergy, delabeling, 1699.*e*1*f*, 1699*b*
Penicillin-binding proteins, 1898
Penicillin G
  for actinomycosis, 2069*b*
  for bacterial meningitis, 2518*t*
  dosage of, 1895*t*
  for erysipeloid, 1936*b*
  for meningococcal meningitis and meningococcemia, 1944*t*
Penicillin V, dosage of, 1895*t*
Penicilliosis, prophylaxis for, 2309*t*
Penile prostheses, for erectile dysfunction, 1589
Pentamidine
  for African trypanosomiasis, 2112*t*, 2125*b*, 2125*t*
  for *Pneumocystis* pneumonia, 2103*b*, 2106*t*, 2108*t*
  for visceral leishmaniasis, 2132*b*
Pentazocine, 136*b*, 139*t*
Pentose phosphate pathway, 1098
Pentoxifylline
  for ischemic heart disease, 470*b*
  for nonalcoholic fatty liver disease, 1034*b*
PEP. *See* Postexposure prophylaxis
Peppermint oil, for irritable bowel syndrome, 895*b*, 896*t*
Peptic strictures, 905
  clinical manifestations and diagnosis of, 904*f*, 905
  prognosis of, 905
  treatment of, 904*t*, 905*b*
Peptic ulcer(s), 211*t*
  abdominal pain from, 1562
  at anastomoses, 916
  "clean base", 922
  clinical presentation of, 919
  complicated, 917*t*
  complications of
    hemorrhage, 921, 922*t*
    intractability, 923
    perforation, 922–923, 922*f*
    stenosis, 923
  definition of, 913
  diagnosis of, 917, 918*t*
  differential diagnosis of, 919
  endoscopy of, 918, 922*t*
  Helicobacter pylori associated with, 914
  Helicobacter pylori-negative, non-NSAID, 915
  hypergastrinemic syndromes causing, 916
  hypersecretory syndromes causing, 918
  ischemia causing, 916
  malignant, 915
  nonsteroidal anti-inflammatory drugs causing, 918
  pathobiology of, 914
  perforation of, 922, 922*f*
  prevention of, 921
  prognosis for, 923
  rebleeding of, 922
  signs and symptoms of, 917*t*
  uncomplicated, 917*t*
Peptic ulcer disease
  abdominal pain and, 854*t*
  differential diagnosis of, 915*t*
  etiologic diagnosis of, 918
  idiopathic, 915, 919*b*
  physical examination of, 917
  prevention of, 921
  upper gastrointestinal bleeding caused by, 882
Peptide-binding cleft, 204.*e*1*f*
Peptide hormone receptors, 1475*f*
Peptide receptor radionuclide therapy, for metastatic neuroendocrine tumor, 1568*b*
Pepto-Bismol, for diarrhea, 926*b*
Per-oral myotomy, 880
Peramivir, for influenza, 2189, 2189*t*, 2202*b*, 2203*t*
Perampanel, for seizures, 2434*t*
Percussion, of liver, 988
Percutaneous coronary intervention (PCI), 265*b*, 395–397
  advantages of, 384*b*
  antiplatelet therapy for, 507
  complications of, 395–396
  coronary artery bypass grafting *versus*, 399
  disadvantages of, 384*b*
  discharge issues of, 397
  failed, 399
  indications for, 384*b*
  for ischemic heart disease, 364*b*
  mechanisms of, 395–397, 395.*e*1*f*, 396*f*
  for multivessel coronary artery disease, 364*b*
  for myocardial infarction, 384*b*, 385*t*
  procedural success of, 395
  recommendations for, 364*t*
  restenosis after, 396
  selection of patients for, 395
  technical considerations of, 395, 395.*e*1*f*, 396*f*
  thrombosis after, 396
Percutaneous endoscopic gastrostomy (PEG), 1449
Percutaneous pericardiocentesis, echocardiographic-guided, 427*b*, 430*f*
Percutaneous transhepatic cholangiography, 1000
Percutaneous transluminal angioplasty, 464.*e*1*f*, 468*b*
Perfectionism, in eating disorders, 1461
Perforation
  in endoscopy, 876*t*
  iatrogenic, 912
Perfusion, asymmetrical, 522
Perfusion imaging, myocardial, 248, 248*f*
Perianal abscess, 978, 979*b*
Perianal disease, in Crohn disease, 945*b*
Perianal fistulas, Crohn disease associated with, 945*b*
Perianal warts, 2242
Pericardial constriction, 428–431
  clinical manifestations of, 428–429
  diagnosis of, 429–430
  differential diagnosis of, 429–430, 433*t*
  epidemiology of, 428–430
  pathobiology of, 428
  treatment of, 431*b*
Pericardial cysts, benign, 433
Pericardial diseases, 423–433
  CMR findings, 252, 253*f*
  echocardiographic findings, 242*t*
  in HIV, 2317, 2317*b*
  specific forms of, 431–433
Pericardial effusion, 241, 243*f*, 425
  in cancer, management of, 1232*b*
  causes of, 427*t*
  chest radiography in, 245, 246*f*, 428*f*
  clinical manifestations of, 425
  diagnosis of, 426
  epidemiology of, 425
  management of, 429*f*
  pathobiology of, 425
  prognosis for, 428
  treatment of, 427*b*
  tuberculosis, 2040
  without tamponade, 427*b*
Pericardial tamponade, 425
  clinical manifestations of, 425
  diagnosis of, 426
  epidemiology of, 425
  pathobiology of, 425
  prognosis for, 428
  treatment of, 427*b*
Pericardial tumors, 296–297
  clinical manifestations of, 296
  diagnosis of, 297
  prognosis for, 297
  treatment of, 297*b*
Pericardiocentesis, echocardiographic-guided percutaneous, 427*b*, 430*f*
Pericarditis, 211*t*, 1769
  acute, 423
    cardiac magnetic resonance image of, 427*f*
    characteristics of, 359
    clinical manifestations of, 423
    diagnosis of, 423
    diagnostic tests for, 425*t*
    electrocardiogram for, 426*f*
    epidemiology of, 423
    pathobiology of, 423
    prognosis for, 425
    treatment of, 424*b*
  autoimmune, 424*t*, 432
  bacterial, 426*t*, 431
  causes of, 424*t*
  constrictive, 429.*e*1*f*, 431*f*
  drug-related, 424*t*
  effusive-constrictive, 431
  fungal, 432
  H. influenzae caused by, 1953
  infectious, 424*t*, 431
  initial management of, 427*f*
  malignant, 432
  metabolic, 424*t*
  neoplastic, 424*t*
  noninfectious, 424*t*
  post-myocardial infarction, 426*t*
  presentation of, 426*t*
  Staphylococcus aureus causing, 1904
  traumatic, 424*t*
  tuberculous, 426*t*, 431, 2037
  uremic, 426*t*, 431
  viral, 426*t*

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Pericardium, congenital abnormalities of, 433
Perihilar opacities, 520
Perilymphatic fistula, 2642
Perindopril, 451*t*
Perinephric abscess, 1875*b*
Perinuclear antineutrophil cytoplasmic antibodies (pANCA), 945
Periodic fever with aphthous stomatitis, pharyngitis, and cervical adenopathy (PFAPA), syndrome of, 1731*t*
Periodic fever with immunodeficiency and thrombocytopenia (PFIT), syndrome of, 1731*t*
Periodic paralysis, 2583.*e1t*, 2585, 2585*t*
Periodontal disease, 2627
Perioperative anaphylaxis, reactions to, 1698
Periorbital purpura, in amyloidosis, 1305, 1306*f*
Periorbital xanthelasma, 1155*f*
Periorificial dermatitis, 2722, 2722*f*
Periostitis, 1667
Peripartum cardiomyopathy, 1621, 1622*b*, 1622*f*
Peripheral arterial disease (PAD), 467–475
  antiplatelet therapy for, 507
  approach to suspected, 466*f*
  atherosclerotic, 461
  cilostazol for, 508
  lower extremity, 461
  in older adults, 114
  patients at risk for, 461*t*
  prognosis for, 468*b*
Peripheral arthritis, 1710
Peripheral autonomic neuropathies, 2560–2561
Peripheral blood smear, 1066–1074
  acute lymphoblastic leukemia on, 1073, 1073*f*
  anisocytosis on, 1067*f*
  basophilic stippling on, 1070*f*
  chronic lymphocytic leukemia on, 1074, 1074*f*
  chronic myeloid leukemia on, 1073, 1073*f*
  clinically significant abnormalities in, incidental detection of, 1074, 1074*t*
  Döhle body on, 1071*f*, 1072
  elliptocyte on, 1068*f*
  "flags" on, 1066–1067
  hemolytic anemia on, 1070
  hereditary elliptocytosis on, 1068*f*
  hereditary pyropoikilocytosis on, 1069*f*
  hereditary spherocytosis on, 1067*f*
  homozygous hemoglobin C on, 1070*f*
  of Howell-Jolly bodies, 1067*f*, 1074*t*
  interpretation of, 1066
  leukemias on, 1073, 1073*f*, 1074*f*
  leukocytosis on, 1072
  leukopenia on, 1072
  lymphomas on, 1073
  macrocyte on, 1067*f*
  macrocytic anemia on, 1067*f*, 1069
  megaloblastic anemia on, 1069
  microcytic anemia on, 1068
  neutropenia on, 1073
  normal, 1066*f*
  normocytic normochromic anemia on, 1069
  Pappenheimer bodies on, 1069*f*
  Pelger-Huët anomaly, 1071*f*
  platelet morphology assessment, 1070–1072
  poikilocytosis on, 1067*f*
  polychromasia on, 1067*f*
  polychromatic cells on, 1067*f*
  polychromatic macrocytes on, 1067*f*
  reasons for performing, 1066–1068, 1071*t*
  red cell on
    agglutination, 1070*f*
    fragmentation, 1068*f*
  rouleaux formation on, 1070*f*
  sickle cells on, 1068*f*
  target cells on, 1068*f*, 1074*t*
  teardrop poikilocytes on, 1069*f*
  thalassemia minor on, 1067*f*
  thrombocytopenia assessment, 1070
  thrombocytosis assessment, 1070
  toxic granulation on, 1071*f*
Peripheral cold injuries, 680
Peripheral cutaneous T-cell lymphomas, 2734
Peripheral edema, anemia and, 1076
Peripheral lung disease, 523, 524*t*
Peripheral membrane proteins, 1094
Peripheral nerve entrapment syndromes, 1754
Peripheral nerve injuries, in joint diseases, 1829
Peripheral neuropathy, 2554*t*, 2564*t*
  alcoholism causing, 2544
  anatomic pattern of, 2568*t*
  characteristics of, 2581*t*
  Charcot-Marie-Tooth disease, 2568, 2570*b*, 2570*f*
Peripheral neuropathy *(Continued)*
  clinical manifestations of, 2566–2567
  definition of, 2566
  diagnosis of, 2567–2568, 2569*f*
  epidemiology of, 2566–2568
  familial amyloid polyneuropathy, 2570, 2570*b*
  in HIV/AIDS, 2313, 2313*b*
  inborn errors of metabolism and, 1399
  laboratory testing of, 2568
  in Lyme disease, 2025
  in multiple myeloma, 1299
  nerve biopsy of, 2567, 2569*f*–2570*f*
  nerve conduction studies for, 2571
  pathobiology of, 2566
  prevalence of, 2566
  skin biopsy of, 2567, 2569*f*, 2570*f*
Peripheral oligoarthritis, 1762
Peripheral polyneuropathy, 2566, 2567*t*, 2578
Peripheral spondyloarthritis, 1765–1767
Peripheral T-cell lymphomas, 1286–1287
Peripheral vertigo, 2644
Periprosthetic joint infection, 1829
Perisinusoidal cells, 1035
Peristalsis, defense mechanisms based on, 902
Peritendinitis, 1742
Peritoneal adhesions, 957, 958*f*
Peritoneal carcinomatosis, 957, 958*b*, 958*f*, 1241*b*
Peritoneal dialysis
  chronic ambulatory, 957
  for irreversible renal failure, 841
Peritoneum
  anatomic disease of, 951
  inflammatory diseases of, 951
Peritonitis, 956–958, 1949
  abdominal pain and, 854*t*, 856
  Candida, 2091
  chronic ambulatory peritoneal dialysis as cause, 957
  clinical manifestations of, 957, 957*f*
  diagnosis of, 957
  primary, 956–957
  prognosis for, 957*b*
  secondary, 957
  spontaneous bacterial, cirrhosis and, 1036–1038
  treatment of, 957*b*
  tuberculous, 957, 2037
Peritonsillar abscess, 2649, 2649*t*, 2650*f*
Perjeta. *See* Pertuzumab
Permanent contraception, 1617
Permanent partial disability, 85
Permanent total disability, 85
Permethrin
  for lice, 2742*b*
  for scabies, 711*b*
Pernicious anemia, 1340
  cobalamin malabsorption and, 1119
  diagnosis of, 1123
  incidence of, 1117
Pernio, 473–474, 474*f*
  lupus, 601, 602*f*
  proposed diagnostic criteria of, 473.*e1f*, 474*t*
Peroral endoscopic myotomy, for achalasia, 908*b*
Perphenazine, *e*10*t*–*e*11*t*, 2346*t*
Persistent infectious diarrheas, 932
Persistent müllerian duct syndrome (PMDS), 1573
Personal behavior control, 2410
Personal hygiene, shigellosis and, 1982
Personality disorders, 2346*t*, 2347, 2347*b*, 2348*t*
Personality pathology, 2337*t*
Personalized medicine, 174
Pertussis, 1994
  immunization for, 66*t*, 78*f*, 81
    schedule of, 76.*e1t*, 77*f*
  in travelers, 1889.*e1t*
Pertuzumab (Perjeta), 1215*t*, 1251*t*
Pertzye, for exocrine pancreatic insufficiency, 975*t*
Pes anserinus syndrome, 1747, 1747*b*
Pesticides, 88*t*
PET. *See* Positron emission tomography
PET/CT. *See* Positron emission tomography/computed tomography
Petechiae, 414, 414*f*, 1172*f*, 2713, 2713*t*, 2714*f*
Petrolatum (Vaseline), for skin diseases, 2697
Peutz-Jeghers syndrome, 1250*t*, 1344, 1347*t*, 1348
PFAPA. *See* Periodic fever with aphthous stomatitis, pharyngitis, and cervical adenopathy
PFIT. *See* Periodic fever with immunodeficiency and thrombocytopenia
Pfizer BioNTech COVID-19 vaccine, 77, 2218*t*, 2219
pH, *e*1*t*–*e*8*t*
  Henderson-Hasselbalch equation, 639
  kidney and, 731
  secretion, control of, 732
  of urine, 721–722
Ph chromosome, 1273
pH-sensitive intracellular processes, 752
PHACE syndrome, 2550*t*
Phaeohyphomycosis, 2109–2110, 2111*b*
Phagocytic defects, 1683–1684, 1683.*e1t*, 1684*b*
Phalen sign, 2578–2579
Pharmacodynamics
  changes with age, 130
  drug interactions, 131
Pharmacogenetic syndromes, 132
Pharmacogenetic testing, 159–160, 160*t*
Pharmacogenomics, 167
Pharmacokinetics
  changes with age, 130
  clinical application of, 127–128
  drug interactions, 131
  principles, 126–127
Pharmacology, of aging, 122
Pharmacotherapy
  for irritable bowel syndrome, 895*b*
  for obesity, 1467*b*, 1468*t*
  for resistant arrhythmias, 313*b*
  for urinary incontinence, 829*b*
PharmGKB, 169.*e1t*
Pharyngitis, 1948, 2648–2651
  clinical manifestations of, 1948
  diagnosis of, 1948
  management of, guidelines for, 2649*t*
  noninfectious, 2651
  Streptococcus pyogenes causing, 1914, 1914*f*, 1914*t*
  viral, sore throat and, 2649*t*
Pharynx, 2648, 2648*f*
Phase 2 re-entry, 302, 302*f*
Phencyclidine, 2364, 2365*b*
  properties of, 142*t*
  screening for, 689*t*
Phenelzine, for depression, 2340*t*
Phenobarbital, *e*10*t*–*e*11*t*
  for primary sclerosing cholangitis, 1058*b*
  for seizures, 2434*t*
  toxicity, 690*t*, 698*t*
Phenothiazine, 2700*t*
Phenotypes, 1674
Phenoxybenzamine, 451*t*, 1533*b*
Phentermine, for obesity, 1467*b*
Phentolamine, for hypertensive emergencies, 460*t*
Phenylephrine, 747
  for cardiogenic shock, 667*b*
  for shock, 664*t*
Phenylketonuria, 1398*t*, 1402, 1402*b*, 1402*t*
Phenytoin
  free, *e*10*t*–*e*11*t*
  pharmacokinetic parameters for, 127.*e1t*
  in renal failure, 129.*e1t*
  for seizures, 2434*t*
  total, *e*10*t*–*e*11*t*
  toxicity, 690*t*
Pheochromocytoma
  cardiomyopathy associated with, 1531
  clinical manifestations of, 1530, 1530*t*
  complications of, 1533*b*
  definition of, 1529
  diagnosis of, 1531, 1531*f*
  differential diagnosis of, 1531
  epidemiology of, 1530
  evaluation of, 448*t*
  in familial paraganglioma, 1530
  genetic testing of, 1532
  genetics of, 1530
  hypertension and, 450, 450*b*
  laboratory findings for, 1531, 1532*f*, 1532*t*
  localization of tumor in, 1531–1532
  medical therapy for, 1533*b*
  metastatic, 1533
  in multiple endocrine neoplasia, 1530
  in neurofibromatosis, 1530
  paraganglioma *versus*, 1529
  pathobiology of, 1530
  in pregnancy, 1533
  prognosis for, 1533
  signs and symptoms of, 1530*t*
  surgical therapy for, 1533*b*
  treatment of, 1533*b*
  in von Hippel-Lindau disease, 1530
Philadelphia chromosome-negative acute lymphoblastic leukemia, 1263*t*
Philadelphia chromosome-positive acute lymphoblastic leukemia, 1262*b*
Phlebitis, in hyperosmolar nutrition solutions, 1450
Phlebotomus, 90, 2280, 2280*b*
Phlebotomus fever virus, 2275*t*
Phlebotomy, for hemochromatosis, 1441*b*
Phosphate
  inorganic, *e*1*t*–*e*8*t*
  for osteomalacia, 1651*t*
  regulation of, 732, 732.*e1f*
Phosphate economy, regulation of, 1652*f*
Phosphatidylinositol 3-kinase (PI3K) δ inhibitors, for chronic lymphocytic leukemia, 1269*b*
Phosphatidylinositol glycan *(PIG-A)* gene, 1091
Phosphodiesterase 4 inhibitors, 551*b*
Phosphodiesterase inhibition, 508
  clinical uses of, 508
  pharmacology of, 508
Phosphodiesterase type 5 inhibitors
  for benign prostatic hyperplasia, 822*b*
  for erectile dysfunction, 1589
  for male lower urinary tract symptoms, 824*t*
  for pulmonary hypertension, 496*b*
Phospholamban, 224
Phospholipids, 1093, 1715
Phosphorus
  metabolism, 767
  for osteomalacia, 1639*b*
Phosphorylase deficiency, 2586
Photoallergy, 2705, 2705*t*
Photochemotherapy, for mastocytosis, 1703*b*
Photodermatoses, 2704–2705, 2704*t*
  chronic actinic dermatitis, 2704, 2704*f*
  cutaneous porphyrias, 2705, 2705*f*
  photoallergy, 2705, 2705*t*
  phototoxicity, 2705, 2705*t*
  polymorphic light eruption, 2704, 2704*f*
Photodynamic therapy, for skin cancers, 2701
Photophobia, 2599
Photopsia, 2599
Photosensitivity, 1430, 1433
Photosensitivity and withdrawal reactions, 2728, 2729*t*
Phototherapy, for skin cancers, 2701
Phototoxicity, 2705, 2705*t*
Phymatous rosacea, 2722
Physical abuse, neurologic diseases and, 2369
Physical activity, 61–64
  behavioral interventions for, 55
  cancer and, 1245
  definition of, 61
  dose-response, 62–63, 63*f*
  energy expenditure of, 1465
  guidelines
    for adults, 62*t*, 63*b*
    for older adults, 63*b*
    for weight management, 63*b*
  health-enhancing, 61
  health risks, 63*b*
  levels of, 62
  mechanisms of effect, 62, 63*f*
  for obesity, 1464, 1467*b*
  for osteoarthritis, 1741*t*
  preventive health benefits in adults, 62
  recommendations
    for clinical settings, 63*b*
    tailoring, 63*b*
  risk management of, 63*b*
  therapeutic health benefits of, 63*b*
  types of, 61
  volume of, 61
Physical change, in puberty, 1591, 1591*f*
Physical examination, 28–32, 28
  of abdomen, 31
  for acute poisoning, 682, 683*t*
  for adolescents, 111
  for alcohol use disorders, 2355*t*, 2357
  of breast, 30
  chaperones, 28
  of chest, 30
  for cirrhosis, 1038
  for endocrine disease, 1472
  findings on, as health measures, 40
  future directions for, 32
  for gastrointestinal disease, 851
  of head and neck, 29
  of heart, 30
  of liver, 31
  for liver disease, 988

Copyrighted material

Physical examination *(Continued)*
lungs, 30
of male genitalia, 31
of musculoskeletal system, 31
pelvic examination, 31
of rectum, 31
of respiratory system, 639
for signs of cardiovascular disease, 212
of skin, 31
of spleen, 31
summarizing findings for patients, 32
vital signs, 29
Physical fitness, health-related, 61
Physical frailty, in older adults, 123*t*
Physical inactivity, cardiovascular disease and, 220
Physical injuries, to lung, 591
Physical stimuli, 1693
Physical symptoms, management of, approaches to, 13*t*
Physician-assisted suicide, 8, 8*t*
definition of, 8, 8*t*
empirical data for, 8
history of, 8
justification of, 8
practical considerations for, 9
safeguards, 8
state laws regarding, 16
Physician-patient relationship, informed consent, 5, 6*t*
Physicians, in health resources, 43
Physiologic anisocoria, 2617
Physiologic system dysregulation, 120, 120.e1*f*
Physiologic tremor, enhanced, 2489–2490
Physiologic vertigo, 2644
Physiology
of circulatory control, 225
of heart, 225
Physostigmine, for acute poisoning, 693*t*
PI3 kinase/AKT signaling pathways, 1251.e1*f*
Pibrentasvir, for hepatitis C virus, 1008*b*
Pica, 1075, 1084, 1461, 1462*b*
Pick disease, 2421–2422
PID. *See* Pelvic inflammatory disease
Piebaldism, 2743
Pigmentary retinal degeneration, 2615
Pigmentation, disorders of, 2742–2744, 2742*t*
Pigmented granular casts, 722, 724*f*
Pill-induced esophagitis, 907, 907*t*
Pimavanserin, 2487*t*
Pindolol, 451*t*
Pineal gland tumors, 2617
Pinguecula, 2602, 2603*f*
Pink disease, 103
Pinta, 2021
Pinworm, 2172
Pioglitazone, for type 2 diabetes mellitus, 1541*t*
Piperacillin-tazobactam
for pyelonephritis and urosepsis, 1877*t*
for pyogenic liver abscess, 1023*b*
for *Stenotrophomonas maltophilia*, 1975*b*
Piperacillin/tazobactam
dosage of, 1895*t*
for pneumonia, 613*t*, 616*t*
Piperazine, 2700*t*
Piperidine, 2700*t*
Pirfenidone, 576*b*
Piroxicam
for chronic pain, 138*t*
for dysmenorrhea, 1596*t*
Pit vipers, 708
Pitavastatin, for familial hypercholesterolemia, 1409*t*
Pitolisant, 2449*t*
Pitting, 2752, 2753*f*
Pittsburgh Sleep Quality Index, 2444
Pituitary adenomas, 1314, 1524*b*
description of, 1486, 1489
inherited syndromes of, 1487*t*
nonfunctioning, 1497
Pituitary apoplexy, 1485, 1485*t*, 1486*b*, 1486*t*
Pituitary axis, 1482
Pituitary carcinomas, 1498, 1498*f*
Pituitary gland
intrinsic rhythm of, 1478
lesions of, 1527
neuroendocrine organization of, 1476*f*
Pituitary macroadenoma, 1485*f*
Pituitary tumors, 1486
clinical manifestations of, 1487
Pituitary tumors *(Continued)*
functioning, 1488*t*
hypogonadotropic hypogonadism and, 1584
medical therapy for, 1487*b*
pathobiology of, 1486
prognosis for, 1488
radiation therapy for, 1487*b*
surgery for, 1487*b*
treatment of, 1487*b*
Pityriasis (tinea), 2744
Pityriasis lichenoides, 2709
Pityriasis lichenoides chronica (PLC), 2709
Pityriasis lichenoides et varioliformis acuta (PLEVA), 2709
Pityriasis rosea, 2687.e3*t*, 2707, 2707*b*, 2707*f*
Pityriasis rubra pilaris, 2692*t*, 2707, 2707*b*, 2707*f*
Pityrosporum folliculitis, 2723
Pivmecillinam, for cystitis, 1876*t*
PKD1, 810
PKD2, 810
Placenta, 1569
Plague, 1988–1994, 2065*t*
bioterrorism uses of, 98–99
bubonic, 1990*f*, 1991, 1991*f*
clinical manifestations of, 98, 1991
definition of, 1988
diagnosis of, 98, 1991
differential diagnosis of, 1991
ecology and transmission of, 1990*f*
epidemiology of, 98, 1988–1989, 1988.e3*f*, 1989*f*–1990*f*
pathobiology of, 98, 1989–1991, 1990*f*
pathogen that causes, 1988, 1988*f*
pneumonic, 1990*f*, 1991
prevention of, 99, 1992–1993
prognosis of, 99, 1993
septicemic, 1991
treatment of, 98*b*, 1991*b*, 1992*t*
Plain radiographs, for acute mesenteric ischemia, 960
"Plan, do, study, act" (PDSA), 45
Plantar fasciitis, 1748, 1748*b*
Plantar warts, 2242, 2242*f*
Plaque, 2499
atherosclerotic, 227.e1*f*, 370
rupture, 370–371
skin, 2689*t*
Plasma, 1581
bilirubin measurement in, 994
pH regulation, 731, 731.e1*f*, 732*f*
potassium regulation, 732
transfusion, 1200, 1204–1205, 1204*t*
Plasma cell disorder, 1294–1305
definition of, 1294–1295, 1294*t*
heavy chain diseases, 1303
hyperviscosity syndrome, 1303, 1303*b*, 1304*f*
monoclonal gammopathy of undetermined significance. *See* Monoclonal gammopathy of undetermined significance
multiple myeloma. *See* Multiple myeloma
syndromes associated with, 1294
Waldenström macroglobulinemia. *See* Waldenström macroglobulinemia
Plasma cell leukemia, 1302, 1302*b*
Plasma exchange, for thrombotic thrombocytopenic purpura, 1177*b*
Plasma volume, *e8t*–*e9t*
Plasmablastic lymphoma, 1285, 2315
Plasmapheresis, 2701
for systemic lupus erythematosus, 1772*b*
for thrombotic thrombocytopenic purpura, 1177*b*
Plasminogen activator, tissue, for frostbite, 474*b*
Plasmodial parasites, 2120
Plasmodium brasilianum, 2118
Plasmodium falciparum, 2118. *See also* Malaria
malaria caused by, 2111
in travelers, 1889.e1*t*
Plasmodium knowlesi, 2065*t*, 2118
Plasmodium ovale, 2118
Plasmodium simium, 2118
Plasmodium spp, 1026*t*
Plasmodium vivax
malaria caused by, 2111
in travelers, 1889.e1*t*
Plastics, 88*t*
Plateau airway pressure, 652*t*
Plateau pressure, 640*f*, 655
Platelet(s)
activation, 1165
adhesion, 1165
aggregation of, 370
blood smear, 1071, 1072*f*
decreased production of, 1171
destruction of, 1171, 1171*t*
HIV transmission through, 2299
immune-mediated destruction of, 1171
morphology of, peripheral blood smear assessment of, 1070
sequestration of, 1171
Platelet-activating factor, 1694
Platelet concentrates, 1204
Platelet count, *e8t*–*e9t*, 1070–1071, 1166, 1173*t*
abnormalities in, postoperative, 2675
Platelet dysfunction, acquired, 1185, 1185*b*, 1185*t*
Platelet function, disorders involving, 1184–1185
Platelet granule defects, 1185
Platelet $P2Y_{12}$ receptor antagonists, 507
Platelet plugs, 371
Platelet-poor plasma (PPP), 1169
Platelet receptor defects, 1184
Platelet-rich plasma (PRP), 1169
Platelet transfusions
alloantibodies, 1171*b*
complications of, 1171*b*
components of, 1200
indications for, 1204, 1204*t*
prophylactic, 1171*b*, 1204
for thrombocytopenia, 1171*b*
for von Willebrand disease, 1183*b*
Platelet-vascular disorders, 1166*t*
Platinol. *See* Cisplatin
Plazomicin, 1845*t*, 1899
dosage of, 1895*t*
PLC. *See* Pityriasis lichenoides chronica
Plecanatide, for irritable bowel syndrome, 895*b*, 896*t*
Plegridy. *See* Interferon Beta1*a* pegylated
Pleomorphic adenoma, 2625
Plethysmography, body, 530
Pleura, 623–627
Pleural disease, 525–526
Pleural effusion, 623
clinical manifestations of, 624
conditions that cause, 623*t*
diagnosis of, 624–625, 624*f*
epidemiology of, 623–624
malignant, 625, 625*b*
Mycoplasma pneumoniae in, 2006
as occupational lung disease, 585*t*
parapneumonic, 625, 625*b*
pathobiology of, 623
recumbent studies on, 519
in systemic inflammatory disorders, 626
tuberculous, 626, 626*b*
Pleural empyema, *Staphylococcus aureus* causing, 1904
Pleural exudates, 626
Pleural fluid
disease characteristics, 625*t*
mechanisms that promote accumulation of, 623*t*
normal turnover, 623
Pleural friction rub, 512
Pleural plaques, 525–526, 525*f*
Pleural tuberculosis, 2035, 2036*f*
Pleural tumors, 526
Pleurisy, 211*t*, 1730–1732
Pleurodynia, enteroviruses causing, 2260, 2260*b*
Pleuropulmonary infections, 1939
PLEVA. *See* Pityriasis lichenoides et varioliformis acuta
Plicatic acid, 88*t*
Plummer-Vinson syndrome, 1084, 1337
Pluripotent stem cells, induced, 170*f*–172*f*, 171–172
PMA. *See* Progressive muscular atrophy
PMR. *See* Polymyalgia rheumatica
PMS. *See* Premenstrual syndrome
pNENs. *See* Pancreatic neuroendocrine neoplasms
Pneumatic dilation, for achalasia, 908*b*
Pneumatosis, 867*f*, 960*f*
Pneumococcal conjugate vaccine, 66*t*, 81, 612–613
Pneumococcal disease, immunization for, 66*t*, 81
adverse reactions of, 81
indications for, 66*t*, 81
schedule of, 76.e1*t*, 77*f*
Pneumococcal meningitis, 2511, 2514
Pneumococcal pneumonia
antimicrobial therapy for, 1912*t*
clinical manifestations of, 1911
complications of, 1911
diagnosis of, 1911
incidence of, 1910
prevention of, 1912
radiographic findings, 609
risk factors for, 1910
treatment of, 1912*b*
Pneumococcal polysaccharide vaccine (PPSV23), 66*t*, 81, 612
Pneumoconioses, 88*t*, 590, 590*t*, 591*f*
Pneumocystis jirovecii
definition of, 2101
as pathogen, 2101
Pneumocystis pneumonia (PCP), 520, 2101
adjunctive corticosteroid therapy for, 2103*b*
algorithm for, 2105*f*
alternative antimicrobial for, 2103*b*
antiretroviral therapy for, 2103*b*
clinical manifestations of, 2102, 2103.e1*f*
definition of, 2101
diagnosis of, 2103, 2104*f*, 2105*f*
drug regimens for, 2106*t*
epidemiology of, 2102
histopathology of, 2102.e1*f*, 2103.e1*f*
HIV/AIDS patients, 2106, 2107*t*
non-HIV patients, 2106, 2108*t*
pathobiology of, 2102, 2102.e1*f*
pathogen, 2101
prevention of, 2106
prognosis of, 2107
prophylaxis for, 2309*t*
treatment for, 2103*b*, 2106*t*
Pneumomediastinum, 541*f*, 629
Pneumonia, 700*b*, 1911*f*
Acinetobacter causing, 1973
acute interstitial, 566*t*
antimicrobial therapy for, 613*t*
in-hospital regimens, 610*b*
outpatient regimens, 610*b*
aspiration, 615
bacterial, 566, 610*b*
bronchiolitis obliterans organizing pneumonia of unknown cause, 578
causative agent of, 608–609, 609*t*
causes of, 610*t*
chronic eosinophilic, 582
clinical manifestations of, 607
community-acquired, 606, 611*f*, 612*f*, 1851*b*
antibiotic therapy for, 1912*b*
bacterial species that cause, 1892*t*
Staphylococcus aureus causing, 1904
Stenotrophomonas maltophilia and, 1975
Streptococcus pneumoniae causing, 1910
treatment of, 1998*b*
cryptogenic organizing, 578
diagnosis of, 579, 579*f*, 580*f*
prognosis for, 579*b*
radiographic features of, 574*t*
treatment of, 579*b*
curb-65 scoring system for, 610*t*
cytomegalovirus, 2250*f*, 2251
definition of, 606
diagnosis of, 607–610
differential diagnosis of, 609–610
Enterobacterales causing, 1965
enteroviral, 2260
epidemiology of, 606–607
H. influenzae caused by, 1953
health care-associated, 616*t*
hospital-acquired, 613–615, 615*b*, 616*t*
with immune complex glomerulonephritis, 784*t*
in immunocompromised hosts, 616–619, 617*b*, 617*t*, 618*f*
interstitial
acute, 574*t*, 578, 579*f*
chronic fibrosing, 571*t*, 575
desquamative, 578
idiopathic, 575
lymphocytic, 579
lymphoid, 579, 580*b*, 580.e1*f*
nonspecific, 577
rare, 571*t*
smoking-related, 571*t*, 577
laboratory testing of, 609
legionellosis and, 1997–1998, 1998*f*

Copyrighted material

Pneumonia *(Continued)*
lipoid, 598, 598*b*, 598*f*
as occupational lung disease, 585*t*
overview of, 606–619
patchy, 608*f*
pathobiology of, 607
physical examination of, 607
with pleurisy, 211*t*
Pneumocystis, 2101
prevention of, 612–613, 615
prognosis for, 613, 615
radiology of, 607–608, 608*f*
Streptococcus pyogenes causing, 1916
treatment of, 610*b*
ultrasonography for, 520
unusual causes of, 609
ventilator-associated, 614*t*, 1862*t*, 1866, 1969, 1970*b*
viral, 607
Pneumonia Severity Index, 611*t*
Pneumonic plague, 1990*f*, 1991, 2270*t*
Pneumonic tularemia, 1987
Pneumonitis, hypersensitivity, 581, 581.*e1f*, 588
chronic, 581.*e1f*
classification of, 571*t*
clinical features of, 581
clinical manifestations of, 581
diagnosis of, 581
pathobiology of, 581
prognosis for, 581*b*
treatment of, 581*b*
Pneumonitis, in HIV, 2319
Pneumoperitoneum, abdominal radiographs of, 867*f*
Pneumothorax, 526, 526.*e1f*, 627
clinical manifestations of, 627
diagnosis of, 627, 627*f*
epidemiology of, 627
pathobiology of, 627
right-sided, 624*f*
spontaneous, 211*t*, 631
surgery for, 631
tension, 627
treatment of, 628*b*
ultrasonography for, 520
PNH. *See* Paroxysmal nocturnal hemoglobinuria
PNH II erythrocytes, 1091
PNH III erythrocytes, 1091
PNP. *See* Purine nucleoside phosphorylase
Podocytes, 729, 779–780
Podophyllin, topical, for anal warts, 982*b*
POEMS syndrome, 2316, 2575, 2575*b*, 2575*f*, 2575*t*, 2743, 2743*t*
Poikilocytes, teardrop, 1069*f*
Poikilocytosis, peripheral blood smear of, 1067*f*
Poikilothermy, 1481
Point-of-care echocardiography, 238, 239*t*
Point-of-care tests, 1169
Poison ivy dermatitis, 2691*t*
Poisoning, 759–760, 2589*t*
acute, 682
antidotes for, 691*b*, 693*t*
blood tests for, 690
cardiopulmonary effects of, 684
decontamination of, 691*b*
dermatologic signs of, 685
diagnosis of, 682
diagnostic tests for, 685, 689*t*, 690*t*
elimination of, 691*b*
epidemiology of, 682
gastrointestinal effects of, 684
history of, 682
imaging for, 691
neurologic signs of, 683, 685*t*
physical examination for, 682, 683*t*
specific toxicants in, 685, 686*t*
stabilization of, initial, 691*b*
treatment of, 691*b*, 692*f*
vital signs for, 682
arsenic, 103
cadmium, 104
carbon monoxide, 595, 596*b*
cyanide and other gases, 596, 596*b*
lead, 101
by marine animals, 713
mercury, 102
trace metals, 101
Policymakers, criteria for, 42*t*
Polio, vaccine, for traveler, 1886*t*, 1887
Poliomyelitis, 2257
immunization for, 66*t*, 76.*e1t*, 81
Polioviruses, circulating vaccine-derived, 2257
Poly(A)-binding protein, 2585
Polyangiitis, granulomatosis with, 582
eosinophilic, 573, 582
Polyarteritis nodosa, 965, 1795, 1797*f*, 2716*f*, 2735
epidemiology of, 1793*t*
pathologic characteristics of, 1793*t*
prognosis of, 1795*b*
treatment of, 1795*b*
Polychondritis
flow-volume curve of, 529*f*
relapsing, 2652, 2652.*e1f*
Polychromasia, peripheral blood smear of, 1067*f*
Polychromatic cells, peripheral blood smear of, 1067*f*
Polychromatic macrocytes, peripheral blood smear of, 1067*f*
Polyclonal immunoglobulins, 1295, 1295*f*
Polycystic kidney diseases (PKDs)
autosomal dominant. *See* Autosomal dominant polycystic kidney disease
autosomal recessive. *See* Autosomal recessive polycystic kidney disease
Polycystic liver disease, 990
Polycystic ovary syndrome (PCOS), 1594, 1601, 1602*b*, 1608*t*
Polycystin-1 (PC1), 810.*e1f*
Polycystin-2 (PC2), 810.*e1f*
Polycythemia vera, 1130
anagrelide for, 1135*b*
aspirin for, 1135*b*
clinical manifestations of, 1133, 1133.*e1t*
definition of, 1130, 1130*t*
diagnostic criteria for, 1134, 1134*t*
epidemiology of, 1130
gender-stratified features, 1133.*e1t*
genotype-phenotype correlations, 1131
hydroxyurea for, 1135*b*
interferons for, 1135*b*
neutrophilia and, 1142
pathobiology of, 1130, 1131*f*
prognosis for, 1138
ruxolitinib for, 1135*b*
survival in, 1138–1139, 1138.*e1t*
treatment of, 1135*b*, 1136*t*
Polydipsia, primary
clinical manifestations of, 1501
diagnosis of, 1503
pathobiology of, 1500
treatment of, 1503*b*
Polyethylene glycol, for irritable bowel syndrome, 895*b*, 896*t*
Polygenic risk scores, 159, 159*f*, 167
Polyglandular autoimmune hypoparathyroidism, 1661
Polyglandular disorders, 1558–1560
autoimmune, 1559
clinical features of, 1559*t*
type 1, 1559
type 2, 1560, 1560*b*
type 3, 1560, 1560*b*
type 4, 1560, 1560*b*
definition of, 1558
epidemiology of, 1558
neoplastic, 1558–1559, 1559*b*, 1559*t*
Polymerase chain reaction (PCR), 1834, 1835*f*
for acute bronchitis and tracheitis, 605
for amebiasis, 2148
for anemia, 1077
for *Bartonella* infection, 2002
for *Campylobacter jejuni*, 1958–1959
for COVID-19, 2214, 2215*f*
for granuloma inguinale, 2004
for legionellosis, 1998
for meningococcal disease, 1943
for mumps, 2226
for nocardiosis, 2073
for relapsing fever, 2028
for toxoplasmosis, 2138*t*
for varicella-zoster virus, 2249
for Whipple disease, 2070
Polymicrobial endobronchial colonization, in cystic fibrosis, 557
Polymicrobial infections, for antimicrobial therapy, 1843
Polymicrogyria, 2547
Polymorphic light eruption, 2704, 2704*f*
Polymyalgia rheumatica (PMR), 1801
algorithm for, 1802*f*
clinical manifestations of, 1801
definition of, 1801
Polymyalgia rheumatica (PMR) *(Continued)*
diagnosis of, 1709, 1802
differential diagnosis of, 1803
epidemiology of, 1801
pathobiology of, 1801
prognosis for, 1803
superficial temporal artery, assessment of, 1803
survival rates for, 1803
treatment of, 1803*b*
Polymyositis, 1238*t*, 2327*t*, 2588*t*
clinical features of, 1788*t*
diagnosis of, 1788
diagnostic criteria for, 1790*t*
epidemiology of, 1787
interstitial lung disease associated with, 581
pathobiology of, 1787
treatment of, 1790*b*
Polymyxin B (Polypore)
for *Acinetobacter*, 1974*b*
for bacterial meningitis, 2518*t*
for skin diseases, 2697
for *Stenotrophomonas maltophilia*, 1975*b*
Polyomavirus, 2227–2233
Polypharmacy, 118
Polyploidies, 164
Polypoid lesion, CT colonography for, 871*f*
Poly(ADP-ribose) polymerase (PARP) inhibitors, 1251, 1252*f*
Polyps, 1347–1349
adenomatous, 1348
colonic, 1347
lymphoid, 1348
nasal, 2629, 2629*f*, 2630*f*, 2635, 2635*b*, 2635*f*
non-neoplastic, 1348
serrated, 1348
Polyradiculoneuropathy, chronic inflammatory demyelinating, 2572, 2572*b*
Polyradiculopathy, 2567*t*
Polysomnography
indications for, 2446*t*
for obstructive sleep apnea, 2444, 2445*f*
Polyunsaturated fatty acids, omega-3, for heart failure, 265*b*
Polyuria, 743–744, 743*t*, 744*b*, 744*f*
Pomalidomide (Pomalyst), 1215*t*
Pomalyst. *See* Pomalidomide
POMC. *See* Proopiomelanocortin
Pompe disease, 282*b*, 1417*t*, 1420*t*, 1424
Ponatinib (Iclusig), 1215*t*, 1251*t*, 1275*t*
Ponesimod (Ponvory), for multiple sclerosis, 2505*t*
Pontiac fever, 1998, 1999
Pontine hemorrhage, 2479
Pontomedullary and pontine stroke syndromes, 2465.*e1f*
Ponvory. *See* Ponesimod
Poor self-esteem, adolescents with, 113
Popliteal artery entrapment syndrome, 467, 467*b*, 467*f*
Popliteal cysts, 1747, 1747*b*
Population health, 47–49
management, 47
on severe mental illnesses, 2677
social determinants of health
activities of health delivery systems to address social needs and, 48*f*
interventions focused on, 47
relative contribution of clinical care, individual behaviors, 48*f*
Population screening, 159
Porcelain gallbladder, 1052*b*
Pork tapeworm, 2159
Porphobilinogen (PBG), *e1t*–*e8t*
Porphobilinogen deaminase (PBGD), 1428*t*, 1429, 1429.*e1f*
Porphyria cutanea tarda (PCT), 1428*t*, 1434*b*, 2705, 2705*f*, 2719–2720, 2719*b*, 2719*f*
Porphyrias, 1428–1435, 1428*t*, 2564*t*
acquired, somatic mutations resulting in, 1430
acute attack of, 1430, 1431*f*
clinical manifestations of, 1430–1432, 1431*f*
diagnosis of, 1433
differential diagnosis of, 1434
prognosis of, 1435
treatment of, 1434*b*
acute hepatic, 1429
clinical manifestations of, 1430
congenital erythropoietic, 1430
definition of, 1428–1435
diagnosis of, 1433–1434
Porphyrias *(Continued)*
differential diagnosis of, 1434
epidemiology of, 1428–1429
genetic testing for, 1434
nonacute, 1429
pathobiology of, 1429–1430, 1429*f*
pathogenesis of, 1430
prevention of, 1435
prognosis of, 1435
recurrent attacks, 1432, 1434*b*
treatment of, 1434*b*
Porphyrogenic medication, 1430
Portal hypertension, cirrhosis and, 1036, 1037*f*
Portal vein, 986
Portal vein thrombosis, 968
clinical manifestations and diagnosis of, 968
prognosis of, 968
treatment of, 968*b*
Portopulmonary hypertension, cirrhosis and, 1037, 1040
Posaconazole, 2076
adverse effects of, 2077
drug interactions of, 2076
formulations and pharmacology of, 2076
for hepatosplenic candidiasis, 1024*b*
for histoplasmosis, 2083*b*
indications and dosage of, 2075*t*, 2076
for mucormycosis, 2100*b*
for sporotrichosis, 2086*b*
Positive concordance, 335
Positive end-expiratory pressure, 653
for acute respiratory distress syndrome, 656, 656*f*
auto-PEEP, 654, 654.*e1f*
Positive predictive value, 38
Positive-pressure ventilation, 652
noninvasive, 620*b*, 653
Positive selection, 204
Positron emission tomography (PET), 519
for Hodgkin lymphoma, 1291
for lung cancer, 1331
for rheumatic diseases, 1723
strengths and weaknesses of, 2373*t*
Positron emission tomography/computed tomography (PET/CT), metastatic disease on, 874*f*
Post-Acute Sequelae of SARS-CoV-2 (PASC), 2208
Post-herpetic neuralgia, zoster and, 2248–2249
Post-kala-azar dermal leishmaniasis, 2131, 2132
Post-myocardial infarction ventricular tachycardia, 336
Post-polio syndrome, 2564*t*
Post-radiotherapy sequelae, 94
Post-splenectomy, neutrophilia and, 1142
Post-streptococcal glomerulonephritis, 783, 783*b*, 783*f*, 1918, 1918*b*, 2270*t*
Post-streptococcal immunologic phenomena, 1917–1918
Post-thrombotic syndrome, 490
Post-transfusion purpura, 1203
Post-transfusion thrombocytopenia, 1179
Post-transplant lymphoproliferative disorder (PTLD), 1287, 1287*b*, 2255
clinical manifestations of, 2255
diagnosis of, 2255
epidemiology of, 2255
pathobiology of, 2255
treatment and prevention of, 2255*b*
Post-traumatic hematoma, 2390
Post-traumatic stress disorder (PTSD), 2344
history of, 29*t*
intimate partner violence and, 1634
prognosis of, 2345*b*
treatment of, 2340*t*, 2345*b*
Post-traumatic vertigo, 2645
Post-vaccination encephalomyelitis, 2238
Post-vaccination vaccinia, 2238
Postanoxic action myoclonus, 2495*b*
Postbulbar ulcers, 913
Postconcussion syndrome, 2645
Posterior cerebral artery, 2457
Posterior choroidal melanoma, 2613*f*
Posterior cortical atrophy, 2410, 2410*f*
Posterior leukoencephalopathy syndrome, 2616
Posterior pituitary, 1498–1504
anatomy of, 1498–1500, 1499*f*
hormone synthesis in, 1498
oxytocin in, 1500
vasopressin in, 1499
Posterior reversible encephalopathy syndrome, 1861

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Posterior tibial tendinitis, 1748, 1748*b*
Posterior tibialis tendon rupture, 1748, 1748*b*
Posterior urethral valves, 821
Postexposure prophylaxis (PEP), to prevent sexual transmission, 2299, 2299*t*
Post-Lyme disease, 2027
Postmenopausal hormone therapy, 56
Postmenopausal osteoporosis, 1644*f*
Postnasal drip syndrome, distinguishing features of, 515*t*
Postoperative care, 2672–2673
  checking orders in, 2672
  effective teamwork in, 2672
  focusing on recovery, 2672
  future prevention in, 2673
  overview of, 2672
  patterns of mistake in, 2672
  reading anesthesia records, 2672
  recommended prophylaxis for, 2672–2673
Postoperative complications, 2673–2677
  abnormal serum potassium concentration, 2676
  abnormal sodium concentration, 2675–2676
  abnormalities in blood glucose concentration, 2676
  abnormalities in platelet count, 2675
  aftermath of, 2677
  alkalosis, 2676
  ambiguity of, 2676–2677
  anemia, 2675
  anorexia, 2673
  azotemia, 2676
  chest pain, 2673, 2673*t*
  delirium, 2674
  diarrhea, 2673
  dyspnea, 2673, 2674*t*
  edema, 2675
  fever, 2675
  hyperbilirubinemia, 2676
  hypertension, 2674
  hypoalbuminemia, 2676
  hypotension, 2675
  hypoxemia, 2675
  laboratory, 2675–2676
  leukocytosis, 2675
  multiplicity of, 2676
  redundancy of, 2676
  seizures, 2674
  setting priorities, 2677
  signs of, 2674–2675
  special situations, 2676–2677
  symptoms of, 2673–2674
  tachycardia, 2675
  troponin and natriuretic peptide levels, 2676
  vomiting, 2673
  weakness, 2674
Postoperative diuresis, 1501
Postoperative fever, 1849
Postoperative surgical consultation, 2656
Postpartum thyroiditis, 1513, 1513*b*, 1513*f*
Postpericardiotomy syndrome, 431
Postpoliomyelitis muscle atrophy, 2258*b*
Postprandial distress syndrome, 899*t*
Postprandial hypoglycemia, 1554, 1557*b*
Postradiation pericarditis, 432
Postrenal acute kidney injury, 771, 773, 774
Postural disturbances, in parkinsonism, 2484
Postural hypotension, 306
Postural tachycardia syndrome (POTS), 2555
Potassium, *e*1*t*–*e*8*t*
  adaptation of, 745
  balance of, 745
  body amount of, 745
  in cortical collecting duct, 746.*e*1*f*
  deficiency of, 2538*t*
  definition of, 745
  depletion of, 745
  excess of, 745
  excretion of, 745–747
  external balance of, 747
  function of, 746
  hormonal effects of, 747
  importance of, 745
  internal balance of, 747, 747*t*
  level of, 745
  metabolic acidosis on, effects of, 747
  for narcolepsy, 2449*t*
  regulation of, 726*f*
  renal handling of, 746
  secretion of, 746
Potassium *(Continued)*
  secretory channels of, 746
  tubular flow rate of, 746
Potassium channels, 300.*e*1*f*, 301
Potassium chloride, 313*b*
Potassium citrate
  for hypercalciuria, 806
  for hypokalemia, 751*b*
Potassium disorders, 745–752
  clinical manifestations of, 747–748
  definition of, 745–752
  diagnosis of, 748–751
  epidemiology of, 745
  pathobiology of, 745–747
  prognosis for, 752
  treatment of, 751*b*, 752*b*
Potassium hydroxide, 2690.*e*1*f*
Potassium-sparing diuretics
  for hypertension, 451*t*, 454
  for hypervolemia, 737*t*
  side effects of, 453*t*, 454
Potentiators, for cystic fibrosis, 558*b*
POTS. *See* Postural tachycardia syndrome
Pott disease, 2038*f*
Potter phenotype, 818
Powassan virus, 2276*t*, 2282, 2282*b*
Powder, 2697
Power analysis, 36
Poxvirus infections, 2236
  clinical manifestations of, 2237–2239
  definition of, 2236
  diagnosis of, 2239
  epidemiology of, 2236
  molluscipoxvirus, epidemiology of, 2237
  molluscum contagiosum virus. *See* Molluscum contagiosum
  orthopoxvirus. *See* Orthopoxvirus
  parapoxvirus, 2239, 2240*b*
  pathobiology of, 2237
  pathogens that causes, 2236
  prevention of, 2240*b*
  prognosis for, 2240
  taxonomy of, 2236*t*
  treatment of, 2240*b*
  yatapoxvirus, 2237, 2239
PP interval, 229
PPNAD. *See* Primary pigmented nodular adrenocortical disease
PPP. *See* Platelet-poor plasma
PR interval, 229, 229*t*
PR3-ANCA, 1716
PRAAS. *See* Proteasome-associated autoinflammatory syndromes
Practice guidelines, 44
Pralidoxime chloride, for acute poisoning, 693*t*
Pramipexole
  for Parkinson disease, 265*b*, 2487*t*
  for restless legs syndrome, 2453, 2496*b*
Pramlintide, for type 1 diabetes mellitus, 1537*b*
Pramoxine hydrochloride, for skin diseases, 2700
Prasterone, for genitourinary syndrome of menopause, 1632*t*
Prasugrel, 387*t*, 506*t*, 507
  for acute coronary syndrome, 374*t*, 375*t*
  for acute MI, 397
  for acute STEMI, 384*b*, 391*t*
Pravastatin, for familial hypercholesterolemia, 1409*t*
Praziquantel, 2117
  for *Diphyllobothrium*, 2157*b*
  for helminthic diseases, 2112*t*
  for schistosomiasis, 2165*b*
  for tapeworm infections, 2158*t*
Prazosin, 451*t*
Pre-2019 coronaviruses, 2206
  definition of, 2206
  Middle East respiratory syndrome, 2208
  pathogen causing, 2206, 2206*f*
  seasonal coronavirus, 2206
  severe acute respiratory syndrome, 2208
Pre-conception carrier testing, 166
Pre-heart failure, 264
Pre-mutation, 163–164
Pre-rheumatoid arthritis, 1750
Prebiotics, 155
Precision medicine, 168, 168*t*
  data ownership, privacy, and sharing in, 168*t*, 169, 169.*e*1*t*
  evidence generation in, 168, 168*t*
Precision medicine *(Continued)*
  implementation of, in health care systems, 168–169, 168*t*
  participant engagement and trust in, 168*t*, 169
Precision Medicine Initiative, 165
Precocious puberty, 1592–1593
  in boys, 1481, 1582
  clinical manifestations of, 1593
  definition of, 1592
  diagnosis of, 1582, 1593
  diagnostic tests for, 1593
  epidemiology of, 1592
  pathobiology of, 1592
  peptide hormones in, 1593
  steroid hormones in, 1593
  treatment of, 1582*b*, 1593*b*, 1594*t*
Precordial thump, 313*b*
Prediction rules, 39
Prednisolone
  for alcohol-associated liver disease, 1032*b*
  for myocarditis, 286*b*
Prednisone
  for acute pericarditis, 424*b*
  for autoimmune hemolytic anemia, 1089*b*
  for focal segmental glomerulosclerosis, 779*b*
  for giant cell arteritis, 443*b*
  for granulomatosis with polyangiitis, 582
  for immune thrombocytopenic purpura, 1175*b*, 1176*t*
  for liver transplantation, 1048*t*
  for membranous nephropathy, 780*b*
  for minimal change disease, 778*b*
  for *Pneumocystis* pneumonia, 2106*t*
  for radiation lung injury, 597*b*
  for rapidly progressive glomerulonephritis, 785*b*
  in renal transplantation, 845, 845*t*
  for respiratory bronchiolitis-associated interstitial lung disease, 578*b*
  for retroperitoneal fibrosis, 1783*b*
  for rheumatoid arthritis, 1755*b*, 1756*t*, 1757*t*
  for sarcoidosis, 603*b*, 604*t*
  for systemic lupus erythematosus, 1772*b*
  for ulcerative colitis, 945*b*, 946*t*
  for vasculitis neuropathy, 2572*b*
  for zoster, 2249*b*
Predominant febrile illness, 1869*t*
Preeclampsia, 1178–1179, 1618, 1621*t*
Preexposure prophylaxis (PrEP), to prevent sexual transmission, 2298, 2299*t*
Pregabalin
  for chronic pain, 138*t*
  for distal symmetrical and autonomic polyneuropathy, 2577*b*
  for erythromelalgia, 471*b*
  for restless legs syndrome, 2453
  for zoster, 2249*b*
Preganglionic neurons, 2553
Pregnancy
  antidepressant medications in, 1610
  antihypertensive drug for, 454*t*
  antimicrobial therapy in, 1842, 1842*t*
  aplastic anemia during, 1126*b*
  asthma in, 541*b*
  cancer and, treatment of, 1232*b*
  cardiopulmonary resuscitation in, 1619–1620, 1619.*e*1*f*
  Chlamydia trachomatis in, 2011
  congenital rubella syndrome and, 2224
  contraception and, 1772*b*
  endocrine disorders in, 1624
  extramedullary hematopoiesis and, 1135*b*
  familial hypercholesterolemia and, 1409*b*
  gastrointestinal and liver diseases unique to, 1626
  general principles of, 1618–1620
  glucocorticoids in, 146
  gonorrhea in, 1948
  HIV in, antiretroviral therapy for, 2305
  Hodgkin lymphoma during, 1291*t*, 1292*b*
  hypercoagulable states in, treatment of, 478*b*, 481
  hypertension in, 456
  hypertensive disorders unique to, 1620, 1621*b*, 1621*t*
  hyperthyroidism and, 1511*b*
  hypothyroidism and, 1508*b*
  immunization and, 76.*e*2*t*, 77
  infectious disease in, 1627
  in inflammatory bowel disease, 945*b*
Pregnancy *(Continued)*
  interrupted, 1604
  jaundice in, 998
  laboratory test results in, 1619, 1620*t*
  lupus during, 1770
  luteomas of, 1573
  Lyme disease in, 2026*b*
  medical issues in, 1618–1628, 1618.*e*2*f*
    acute fatty liver of pregnancy, 1626, 1627*b*, 1627*t*
    asthma, 1619*t*
    deep vein thrombosis, 1622
    diabetes mellitus, 1624, 1624*b*
    eclampsia, 1620
    hyperemesis gravidarum, 1626, 1626*b*
    hypertensive disorders, 1620–1621, 1620*b*, 1621*t*
    intrahepatic cholestasis of, 1626, 1626*b*
    liver disease, 1625, 1625*t*
    thrombophilia, 1622
    venous thromboembolism, 1619*f*, 1622–1623, 1623*b*, 1623*f*, 1624*t*
    viral hepatitis, 1625, 1626*b*
  medications for, 1618–1620, 1619*t*
  mental health in, 1623, 1624*b*
  multiple sclerosis in, 2501
  non-Hodgkin lymphoma in, 1288, 1288*b*
  pheochromocytoma in, 1533
  physiologic changes in, 1618, 1618*f*
  polycystic ovary syndrome in, 1602*b*
  prolactin levels in, 1490
  radiation exposure in, 1618, 1618*t*, 1619*t*
  relapsing fever in, 2028
  renin-angiotensin system inhibitors and, 452–453
  seizures in, 2434*b*
  sickle cell disease in, 1114, 1114*b*
  syphilis in, 2020*b*
  in thrombocytopenia, 1178–1179
  tubal, 1604
  undernutrition in, 1464
  unintended, 1611
  urinary tract infection in, 1878
  venous thromboembolism in, 487*b*
  in viral hemorrhagic fevers, 2267
Preload, 226
Premature action potential, 333.*e*1*f*
Premature atherosclerotic disease, 1775
Premature ovarian failure, X chromosome mutation in, 1600
Premature ventricular contractions (PVCs), 333
Premenstrual dysphoric disorder, 2342
Premenstrual syndrome (PMS), 1596–1597, 1597*b*, 1597*t*
Premenstrual tension, 1596
Prenatal diagnosis, 166
Preoperative evaluation, 2659–2668
  anesthesiologist and, 2667
  assessing risk in, 2661
  cardiovascular diseases, 2663–2664
  cardiovascular risk assessment, 2661, 2662*t*
  endocrine conditions, 2665
  general principles of, 2659–2660, 2660*t*
  hematologic problems, 2666
  history of, 2660
  liver disease, 2666
  neurologic problems, 2664–2665
  perioperative medications, 2666–2667
  physical examination of, 2660
  prognostic impact of, 2660
  pulmonary risk assessment, 2664, 2664*t*
  renal disorders, 2666
  tests, 2661, 2662*t*
  timing of surgery, 2660, 2661*f*
Preoperative surgical consultation, 2656
PrEP. *See* Preexposure prophylaxis
Prepatellar bursitis, 1747
Prerenal acute kidney injury, pathobiology of, 772, 772*t*
Prerenal azotemia
  diagnosis of, 772*f*, 774
  epidemiology of, 770, 771*f*
  for hypokalemia, 751*b*
Presbycusis, 117
  hearing loss caused by, 2642
Presbyopia, 2598
Presenilin 1, 2415
Presenilin 2, 2415
Preseptal cellulitis, 2596, 2604, 2605*f*

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Pressure-assisted ventilation, for acute respiratory failure, 647*b*
Pressure bandage with immobilization, for envenomation, 705*b*
Pressure-controlled ventilation, 653
Pressure sores, 122, 122*b*, 122*f*
Pressure-support ventilation, 653
Pressure ulcers, in older adults, 114
Pressure-volume area, 225
Pressure-volume loop, 225, 225*t*, 225.*e1f*
Pressure-volume relationships, 225, 226*f*
Presyncope (dizziness), 304–305, 304*t*
Presystemic effect, of drugs, 126
Pretibial myxedema. *See* Graves dermopathy
Pretomanid, 1845*t*
Pretomanid, dosage of, 1895*t*
Prevalence, 35, 38
Preventive health care
  for adolescents, 111
  visit, 52
    asymptomatic risk factors, 52–55, 52*t*–53*t*
    behavioral interventions, 55
    history of, 52
    immunizations, 55–56
    preventive medications and supplements, 56
    risk assessment of, 52
    screening for early disease, 52, 52*t*, 53*t*
Preventive services, geriatric assessment, 119, 119.*e1t*
Priapism, 1114
Primaquine
  for malaria, 2112*t*, 2114, 2121*b*, 2121*t*, 2123*t*
  for *Pneumocystis* pneumonia, 2106*t*
Primary adrenal disorders, 1522–1523
Primary adrenal insufficiency, 1526, 1527*t*, 1528*f*
Primary aldosteronism, 447, 448*b*, 448*t*, 1525*f*
Primary amenorrhea, 1598
Primary amyloidosis. *See* AL (light chain) amyloidosis
Primary angiitis of the central nervous system (PACNS), 1799–1800, 1800*b*, 1800*t*
Primary biliary cholangitis (PBC), 1059, 1821
  clinical manifestations of, 1059
  diagnosis of, 1059
  epidemiology of, 1059
  pathobiology of, 1059
  prognosis of, 1059–1060
  treatment of, 1059*b*
Primary biliary cirrhosis. *See* Primary biliary cholangitis
Primary bone tumors, 1388
Primary carnitine deficiency, 2586
Primary central nervous system lymphoma, 1316, 1316*b*, 1316*f*, 2315
Primary ciliary dyskinesia, 560
Primary CNS lymphoma, 1285, 1285*b*
Primary coenzyme Q10 deficiency, 2586
Primary cutaneous anaplastic large cell lymphoma, 1286
Primary cutaneous diffuse large B-cell lymphoma, 1285
Primary debulking surgery, for metastatic neuroendocrine tumor, 1568*b*
Primary dystonia, 2492*t*, 2493
Primary effusion lymphoma, 1285, 2315
Primary extra-axial brain tumors, 1312*b*
Primary hyperaldosteronism, 749, 1525, 1525*f*, 1525*t*, 1526*b*
Primary hyperoxaluria, 807
Primary hyperparathyroidism, 1656
  clinical manifestations of, 1656
  description of, 1654
  diagnosis of, 1656
  epidemiology of, 1656
  familial, 1657
  parathyroid surgery for, 1657*t*
  parathyroidectomy for, 1657*b*
  pathobiology of, 1656
  treatment of, 1657*b*
Primary hypodipsia, 742
Primary immunodeficiency diseases, 1676, 1676–1686
  autoinflammatory disorders as, 1686
  bone marrow failure defects as, 1686
  C1 inhibitor deficiency as, 1683
  categories of, 1676*t*
  complement disorders as, 1682, 1683*b*, 1683*t*
  immune dysregulation syndromes as, 1684, 1684*t*, 1685*b*
Primary immunodeficiency diseases *(Continued)*
  immune globulin and antibody production in, defects of, 1680, 1681*t*, 1682*b*
  intrinsic and inate immunity in, diseases of, 1685, 1686*b*, 1686*t*
  phagocytic defects as, 1683, 1683.*e1t*, 1684*b*
  T-and B-cell combined defects as
    less, 1678, 1678.*e1t*
    severe, 1676–1678, 1676.*e3t*, 1678*b*
    with syndromic features, 1678–1680, 1678*b*, 1679*t*
Primary junctional tachycardia, 324
Primary large intestinal lymphomas, 1347
Primary lateral sclerosis, 2564*t*
Primary lesion, biopsy of, 1391
Primary lung disease, 496*b*
Primary lung sarcoma, 1336
Primary mediastinal large B-cell lymphoma, 1285
Primary myelofibrosis, 1130, 1130*t*
  allogeneic hematopoietic stem cell transplantation for, 1135*b*
  clinical manifestations of, 1133
  definition of, 1130, 1130*t*
  diagnostic criteria for, 1134, 1134*t*
  Dynamic International Prognostic Scoring System-Plus for, 1137*f*, 1139
  epidemiology of, 1130
  extramedullary hematopoiesis in, 1133
  pathobiology of, 1130, 1131*f*
  peripheral blood smear of, 1134
  in pregnancy, 1135*b*
  prognosis for, 1138
  ruxolitinib for, 1135*b*, 1138*f*
  splenomegaly in, 1134
  survival in, 1139, 1139*f*
  treatment of, 1135*b*, 1136*t*
Primary open-angle glaucoma, 2607, 2607*f*
Primary ovarian insufficiency, 1600
Primary peritonitis, 956
Primary pigmented nodular adrenocortical disease (PPNAD), 1487*t*, 1523
Primary polydipsia, 738, 1503*b*
Primary progressive aphasia, 2409, 2422
Primary progressive multiple sclerosis, 2501
Primary sclerosing cholangitis, 1056
  clinical manifestations of, 1057
  definition of, 1056
  diagnosis of, 1057, 1058*f*
  epidemiology of, 1056
  pathobiology of, 1056
  prognosis of, 1058
  treatment of, 1058*b*
Primary selective hypoaldosteronism, 750, 750*t*
Primary Sjögren syndrome, 2558
Primary syphilis, 2015, 2015*f*
Primary testicular hypogonadism, 1583, 1583*t*
Primary thyroid lymphoma, 1519, 1519*b*
Primary vesicoureteral reflux, 819–820, 820*b*
Primidone + phenobarbital, *e*10*t*–*e*11*t*
Prinzmetal angina, 357
Prion diseases
  clinical manifestations of, 2422–2423
  diagnosis of, 2423
  other classic, 2422–2423
  pathobiology of, 2422
  prevention of, 2423
  prognosis of, 2423
  treatment of, 2423
"Private" mutations, 1249
Pro-adrenomedullin, mid-regional (MR-proADM), 260.*e1t*
Pro-oxytocin, 1498
Probiotics, 155
  for *E. coli*, 1963*b*
  for irritable bowel syndrome, 895*b*, 896*t*
  for microbiota, 1840
Problem-solving therapy, for depression, 2339*t*
Procainamide, *e*10*t*–*e*11*t*, 325*t*
  for advanced cardiac life support, 315*f*
  for arrhythmias, 313*b*
Procainamide + N-Acetyl (NAPA), *e*10*t*–*e*11*t*
Procalcitonin, *e*1*t*–*e*8*t*, 1851*b*
Processed food, dietary guidelines for, 57.*e3t*
Prochlorperazine, for nausea and vomiting, 863*t*
Procrit. *See* Erythropoietin
Proctitis, 1948
  Chlamydia trachomatis causing, 2012
  clinical manifestations of, 1948
  description of, 943
  diagnosis of, 1948
  treatment of, 945*b*
Proctopathy, radiation, 968, 968*f*
Proctosigmoiditis, description of, 943
Professionalism, 4*t*
Profound hypothermia, 681*t*
Progenitor cells, 172
Progestogen hypersensitivity, 1693
Proglottids, 2157
Prognostication, 12
Prograf. *See* Tacrolimus
Programmed death 1 (PD-1) blockade, for colorectal cancer, 1350*b*
Progressive diaphyseal dysplasia, 1666, 1666*b*
Progressive external ophthalmoplegia, 2618
Progressive multifocal leukoencephalopathy, 1861, 2230, 2230*b*–2231*b*, 2231*f*, 2532*t*
Progressive muscular atrophy (PMA), 2564*t*
Progressive myoclonus epilepsies, 2433
Progressive supranuclear palsy, 2411, 2416, 2485*t*, 2652
Progressive systemic sclerosis, interstitial lung disease associated with, 580
Progressive vaccinia, 2238
Proguanil, 2115
Proinsulin, intact, *e*1*t*–*e*8*t*
Prolactin, *e*1*t*–*e*8*t*, 1490–1491, 1498, 1500
  deficiency of, 1491
  hyperprolactinemia and, 1491, 1491*b*, 1491*t*
  hypothalamic disease effects on, 1481
  insufficiency tests of, 1484*t*
  lactotroph regulation of, 1490
  pregnancy levels in, 1490
  tests of, 1488*t*
Prolactin inhibitory factor, 1477
Prolactin receptor, 1490
Prolactin-releasing factor, 1478
Prolactin-secreting adenoma, 1481
Prolactinomas, 1487, 1491, 1584
Proliferative benign breast lesions, 1374
Proliferative diabetic retinopathy (PDR), 1549*t*
Prolonged infectious diarrheas, 932
Prolymphocytic leukemia, 1272
Promethazine, for nausea and vomiting, 863*t*
Promyelocyte, 1140*f*
Proopiomelanocortin (POMC), 1478, 1492
Propafenone, 325*t*
Propensity score, 37
Properdin, 1942
Prophylactic mastectomy, 1373
Prophylaxis, recommended, in postoperative care, 2672
Propionibacterium acnes, 2722
Propionic aciduria, 1398*t*, 1403, 1403*t*
Propofol, for anesthesia, 2669
Proportional assist ventilation, 653
Propoxyphene, 139*t*
Propranolol, *e*10*t*–*e*11*t*
  for alcohol withdrawal, 2358*t*
  for anxiety disorders, 2344*t*
  for arrhythmias, 313*b*
  for hyperthyroidism, 1511*b*
  for hypertrophic cardiomyopathy, 282*b*
Propranolol IR, 451*t*
Propranolol LA, 451*t*
Proprotein convertase subtilisin kexin type 9 antibodies, 227
Proprotein convertase subtilisin kexin type 9 gene, 221–222
Proptosis, 2600, 2600*f*
Propylene glycol, 760
Propylthiouracil
  for Graves disease, 1511*t*
  for hyperthyroidism, 1511*b*
Prostacyclin, 468*b*
Prostaglandin synthetase inhibitors, 1595
Prostaglandins, angiotensin II and, 734
Prostanoids, for pulmonary hypertension, 496*b*
Prostate cancer, 1384–1387
  androgen receptor expression by, 1385*b*
  brachytherapy for, 1385*b*
  castration-resistant, 1385*b*
  chemoprevention for, 1387
  clinical manifestations of, 1384
  diagnosis of, 1384–1385, 1384*t*
  epidemiology of, 1384–1387
  Gleason score for, 1384*t*
  localized, 1385*b*
  metastasis, 1385*b*, 1385*t*
  nutrition and, 59
  pathobiology of, 1384
  prevention of, 1387
  prognosis for, 1387
Prostate cancer *(Continued)*
  prostate-specific antigen screening for, 1384
  radiation therapy for, 1385*b*, 1385*t*
  recurrent, 1385*b*
  screening for, 54, 1387
  staging of, 1385, 1385*t*
  supportive care for, 1385*b*
  treatment of, 1385*b*, 1385*t*
Prostate gland, 821, 821*f*
Prostate-specific antigen (PSA), *e*1*t*–*e*8*t*, 1384
Prostatic hyperplasia, benign, 821
  clinical manifestations of, 822
  definition of, 821, 821*f*
  diagnosis of, 822, 823*f*
  epidemiology of, 821
  laboratory findings of, 822
  management of, algorithm of, 824*f*
  pathobiology of, 821
  prognosis of, 823
  treatment of, 822*b*
Prostatic obstruction, in heart failure, 265*b*
Prostatitis, 823–826
  bacterial species that cause, 1892*t*
  classification of, 825*t*
  clinical manifestations of, 823
  diagnosis of, 823–825, 826*f*
  epidemiology of, 823
  laboratory evaluation for, 825
  pathobiology of, 823
  prognosis of, 825–826
  treatment of, 825*b*
Prosthetic heart valves
  advantages and disadvantages of, 412*t*
  choices among, 412*f*
  echocardiographic findings, 242*t*
  postoperative care for, 411
Prosthetic joint infection, 1808
  clinical manifestations and diagnosis of, 1808
  prevention of, 1808–1809
  treatment for, 1808*b*
Prosthetic valve endocarditis, 416
  causes of, 416*t*
  Staphylococcus aureus causing, 1903–1904
Protease inhibitors, 196, 2319
  for HIV, 2300, 2304*t*
Proteasome-associated autoinflammatory syndromes (PRAAS), 1731*t*, 1735
Protectin, 200*t*
Protective eyewear, for HIV transmission prevention, 2300
Protein
  in bacterial meningitis, 2514
  depletion of, 1447*t*
  dietary guidelines for, 57.*e3t*
  dipstick for, 722
  intestinal digestion and absorption of, 932.*e1f*
  membrane, 1093
  requirements, estimation of, 1449
Protein binding, 129
Protein-bound cobalamin malabsorption, 1119
Protein C deficiency, 476, 476*t*
Protein-energy malnutrition, acute malnutrition and, 1444
Protein F, 1913
Protein-losing gastroenteropathy, 940
Protein metabolism, disorders of, 1401, 1402*t*
Protein profiling, 168
Protein S, 200*t*
  deficiency, 476, 476*t*
Protein sensitivity, for hypoglycemia, 1557
Protein subunit vaccine, 66*t*
Protein tyrosine phosphatase nonreceptor 22 (PTPN22), functional polymorphism in, 1750
Protein-coupled folate transporter (PCFT), 1119
Proteinosis, pulmonary alveolar, 566, 566*t*, 585*t*
  clinical manifestations of, 567
  diagnosis of, 567, 567*f*, 567.*e1f*
  epidemiology of, 566
  pathobiology of, 566–567
  treatment for, 567*b*
Proteinuria, 727, 832, 833*f*
  glomerular disorders and, 776
  nephrotic-range, 792
Proteoglycans, 1724
Proteomics, 168
Proteus mirabilis, 804, 1874, 1965
Prothrombin, 1189*t*
Prothrombin complex concentrates, 1204
Prothrombin G20210A mutation, 476, 476*t*

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Prothrombin time (PT), 999, 1166, 1167, 1167*f*, 1167*t*, 1169*f*, 1195, 1453*t*
  one-stage, *e8t*–*e9t*
Prothrombotic factors, increased, 475*t*
Prothrombotic states, mesenteric venous thrombosis and, 963*t*
Proton pump inhibitors, 1460*t*
  for Barrett esophagus, 906*b*
  for peptic ulcer disease, 921
  reactions to, 1698*t*
  for upper gastrointestinal bleeding, 883*b*
Protoporphyria, 1428*t*, 1432–1433, 1432*f*, 1434*b*
Protoporphyrin IX, 1429.*e1f*
Protoporphyrinogen IX, 1429.*e1f*
Protozoal diseases, treatment of, 2111
Protozoal liver diseases, 1025
Protracted diarrhea, 1869*t*
Protriptyline, *e10t*–*e11t*
  for cataplexy, 2449*t*
Provasopressin, 1498
Providers, criteria for, 42*t*
Provocative testing, 532
  for diabetes insipidus, 1501
Proximal femur fractures, 1639
Proximal renal tubular acidosis, 761, 816*t*
Proximal subungual onychomycosis, 2754
Proximal tubular dysfunction, Wilson disease and, 1437
Proximal tubule, 731.*e1f*, 754, 754.*e1f*
Proximal tubule disorder, 815, 816*t*
Proximal tubule diuretics, 736*b*
PRP. *See* Platelet-rich plasma
Prune-belly syndrome, 821
Pruned-tree sign, 246*f*
Prurigo nodularis, 2321
Pruritus, 2690–2696, 2694*t*, 2697*t*, 2726
  in HIV, 2321
  West African sleeping sickness and, 2124
Pruritus ani, 980, 980*b*
Prussian blue staining, for anemia, 1077
Pseudo-Cushing states, Cushing syndrome *versus*, 1521*f*, 1522
Pseudo-delta wave, 335
Pseudo-Hurler polydystrophy, 1724*t*
Pseudo-hypoglycemia, 1546*t*
Pseudo-obstruction
  classification of, 888*t*
  description of, 888
Pseudo-osteoarthritis, 1814
Pseudo-precocious puberty, 1582
Pseudo-pseudogout, 1815
Pseudoaldosteronism, 817
Pseudoappendicitis, enteric infections and, 1870*t*
Pseudobulbar palsy, 2562, 2652
Pseudoclaudication, 2399
Pseudocyst, 971–972, 972*f*
Pseudofractures, osteomalacia in, 1649
Pseudogout, calcium pyrophosphate dihydrate crystals in, 1713
Pseudohemoptysis, 515
Pseudohyperkalemia, 748
Pseudohyperphosphatemia, 768–769
Pseudohypoaldosteronism
  autosomal recessive, type 1, 761
  type 1, 816*t*
  type 2, 816*t*
Pseudohyponatremia, 738
Pseudohypoparathyroidism, 1661, 1662*t*
Pseudomembranous candidiasis, 2623
Pseudomembranous colitis, 1865, 1925
Pseudomonal keratitis, 2606
Pseudomonas aeruginosa, 1968
  antimicrobial resistance of, 1864*t*
  community-acquired, 1968
  cystic fibrosis and, 557
  description of, 1894
  epidemiology of, 1968
  keratitis caused by, 2606
  multidrug-resistant, 1968
  treatment of, 1970*b*
  urinary tract infection and, 1874
  virulence factors in, 1968.*e2t*
Pseudomonas fluorescens, 1970
Pseudomonas folliculitis, 2723, 2723*f*
Pseudomonas infections, 1968–1972, 2741
  acute respiratory tract infections caused by, 1969
  bacteremia caused by, 1969, 1970*b*
  bacterial factors in, 1968
  bone infections caused by, 1969, 1970*b*
Pseudomonas infections *(Continued)*
  central nervous system infections caused by, 1969
  chronic respiratory tract infections caused by, 1969
  clinical manifestations of, 1968–1970
  cystic fibrosis and, 556
  definition of, 1968–1972
  diagnosis of, 1970
  ear infections caused by, 1969, 1970*b*
  endophthalmitis caused by, 1969
  endovascular infections caused by, 1969
  epidemiology of, 1968
  eye infections caused by, 1969, 1970*b*
  in febrile neutropenia, 1968
  gastrointestinal infections caused by, 1969
  genital tract infections caused by, 1969
  intra-abdominal infections caused by, 1969, 1970*b*
  joint infections caused by, 1969
  keratitis caused by, 1969
  pathobiology of, 1968
  pathogenesis of, 1968
  pathogens, 1968
  pathology of, 1968
  pathophysiology of, 1968
  prevention of, 1971–1972
  prognosis for, 1972
  skin and soft tissue infections caused by, 1969, 1970*b*
  treatment of, 1970*b*
  uncommon, 1969
  urinary tract infections caused by, 1969, 1970*b*
  ventilator-associated pneumonia caused by, 1969, 1970*b*
  virulence factors in, 1968.*e2t*
Pseudomonas stutzeri, 1970
Pseudopolyps, 942
Pseudoporphyria, 2720
Pseudopropionibacterium propionicum, 2066
Pseudothrombocytopenia, 1166
Pseudotumor cerebri, 2383, 2383*b*
Pseudotumors, 624
Pseudoxanthoma elasticum, 1729, 2550*t*, 2609, 2730
Psittacosis, 2013
Psoriasiform dermatitis, 2321
Psoriasis, 1707, 2689*t*, 2705
  clinical manifestations of, 2705–2706, 2706*f*
  description of, 2687.*e3t*, 2692*t*
  diagnosis of, 2706
  epidemiology of, 2705
  pathobiology of, 2705
  pustular, 2722, 2723*f*
  regional involvement of, 2745*f*
  therapies for, 2698
  treatment for, 2706*b*–2707*b*, 2706*t*
Psoriasis vulgaris, 2705
Psoriatic arthritis, 1717*t*, 1764
  clinical manifestations of, 1764
  diagnosis of, 1764, 1765*f*
  differential diagnosis of, 1764
  epidemiology of, 1764
  pathobiology of, 1764
  prognosis of, 1766
  radiographs of, 1764
  treatment of, 1765*b*
Psychedelics, in palliative care, 16
Psychiatric diseases
  aging and, 2677
  alcohol use disorders and, 2355*t*, 2356
  ambulatory medical care for, 2683
  cardiovascular disease and, 2677
  giving recommendations in, 2682–2683, 2683*t*
  health challenges with, 2677, 2678*t*
  medical care for, 2677–2684
  population health for, 2677
  providing care in different settings for, 2678–2679
  substance use disorders and, 2678
  symptoms and findings of, approach to, 2681, 2683*t*
  treatments for, medical complications of, 2679–2681, 2680*t*
Psychiatric disorders, 2336–2349
  acute stress disorder, 2344
  anxiety disorders, 2342
  bipolar disorder, 2341
  categories of, 2337*t*
Psychiatric disorders *(Continued)*
  causes of, 2336*t*
  comorbid conditions in, 2337
  definition of, 2336
  delusional disorder, 2346
  eating disorders, 2346
  evaluation for, 2347–2348, 2348*t*
  major depressive disorder, 2337
  obsessive-compulsive disorder, 2343, 2344*t*
  personality disorders, 2347
  post-traumatic stress disorder, 2344
  schizophrenia, 2345–2346
  somatic symptom and related disorders, 2346–2347, 2347*t*
  suicide, 2347, 2348*t*
  treatments in, 2337
Psychiatric evaluation, 31
Psychiatric illness
  substance use disorder and, 2360
  weight loss and, 860*t*
Psychiatric unit, consultations to, 2679
Psychiatry, medicine and, 2679
Psychodynamic psychotherapy, for depression, 2339*t*
Psychogenic dizziness, 2646, 2647*t*
Psychogenic eating disorders, weight loss and, 860*t*
Psychogenic nonepileptic seizures, 2431
Psychological symptoms, management of, approaches to, 13*t*
Psychological therapies, for irritable bowel syndrome, 895*b*
Psychomotor speed, 2411
Psychopathology, intimate partner violence and, 1633
Psychosocial issues
  alcohol use disorders and, 2355*t*, 2356
  in heart failure, 275*t*
Psychosocial support
  for cancer, 1232*b*
  for sexual development, 1575*b*
Psychostimulants, properties of, 142*t*
Psychotherapy, for pain, 136*b*
Psychotic disorders, 2337*t*, 2345–2346
Psychotropic medications
  brief overview of, 2679–2680
  cardiovascular complications of, 2678*t*, 2680, 2680*t*
  regimens, continue outpatient, 2679
  respiratory complications of, 2680
PT. *See* Prothrombin time
Pterygium, 2602, 2603*f*
PTH gene, parathyroid hormone and, 1652
PTH-related peptide (PTHrP), 1653
PTHrP. *See* PTH-related peptide
PTLD. *See* Post-transplant lymphoproliferative disorder
Ptosis, 2600, 2600*f*
PTSD. *See* Post-traumatic stress disorder
Pubarche, premature, 1593
Pubertal development, 1591
Pubertal maturation, Tanner stages during, 1598*t*
Puberty, 110
  aberrations in, 1592–1594, 1592*t*
  adrenarche and, 1581, 1582*t*, 1593
  asynchronous development, 1594
  breast budding in, 1591
  central precocious, 1582
  delayed, 1582, 1582*b*, 1593, 1594*b*
  in girls, 1591
  heterosexual development, 1594
  hormonal changes of, 1591, 1591*f*
  ovarian function in, 1591
  physical changes at, 1591, 1591*f*
  precocious, 1592
    in boys, 1481, 1582
    clinical manifestations of, 1593
    definition of, 1592
    diagnosis of, 1582, 1593
    diagnostic tests for, 1593
    epidemiology of, 1592
    pathobiology of, 1592
    peptide hormones in, 1593
    steroid hormones in, 1593
    treatment of, 1582*b*, 1593*b*, 1594*t*
  pseudo-precocious, 1582
  reproductive axis development in, 1581
  timing of, aberrations of, 1582
  weight gain, 110
Pubic hair
  development of, 110.*e2f*
  at puberty, 1573
  Tanner stages of, 1598*t*
Pubic lice
  organisms causing, 1879*t*
  treatment of, 1884*t*
Puerperal sepsis, 1915
Puerto Rican, 583
Pulmonary airway malformation, congenital, 565
Pulmonary alveolar proteinosis, 566, 566*t*
  clinical manifestations of, 567
  diagnosis of, 567, 567*f*, 567.*e1f*
  epidemiology of, 566
  pathobiology of, 566
  treatment for, 567*b*
Pulmonary arterial hypertension, 211*t*, 493*t*
  chest radiograph of, 523*f*
  echocardiographic findings, 242*t*
  group 1, 493*t*, 494
  group 2, 493–494, 493*t*
  group 3, 493*t*, 494
  group 4, 493*t*, 494
  in HIV, 2317, 2317*b*
  in systemic sclerosis, 1779, 1781*b*
Pulmonary arteriovenous fistulas, 350
Pulmonary artery obliterative vasculopathy, 1776.*e1f*
Pulmonary artery occlusion pressure, 677*t*
Pulmonary artery pressure
  normal value, 677*t*
  systolic, 240–241
Pulmonary artery wedge pressure, 677*t*
Pulmonary atresia, 247.*e1f*
Pulmonary atypical mycobacteria, in travelers, 1889.*e1t*
Pulmonary barotrauma, 594
Pulmonary capillaritis, idiopathic, 582
Pulmonary chest infections, as occupational lung disease, 585*t*
Pulmonary congestion, 256, 256.*e1f*, 394
Pulmonary cryptococcal infection, 2088, 2088*b*
Pulmonary disease
  basal, 524*f*
  chronic obstructive, 541*b*
  imaging in, 519–527
  nontuberculous mycobacteria causing, 2045
Pulmonary edema, 245*f*, 265*b*
  acute, 273*f*
  distinguishing features of, 515*t*
  hydrostatic, 566
  interstitial, 245*f*
  photographic negative of, 582
  ultrasonography for, 520, 521*f*
Pulmonary embolism, 211*t*
  algorithm for, 477*f*
  chronic, 246*f*
  classic electrocardiogram findings with, 486*f*
  definition of, 482
  differential diagnosis of, 424*t*
  distinguishing features of, 515*t*
  high-risk, 487*b*
  hypocapnia and, 487*b*
  hypoxemia and, 487*b*
  low-risk, 487*b*
  massive, 487*b*
  mechanical reperfusion for, 487*b*
  nonthrombotic, 491–492
  in pregnancy, 1622, 1624*t*
  severe, 487*t*
Pulmonary emphysema, 246*f*
Pulmonary examination, 258
Pulmonary fibrosis
  idiopathic, 575
    CT findings, 575.*e1f*
    diagnosis criteria for, 577*t*
    diagnosis of, 575, 576*f*
    pathobiology of, 570
    prognosis for, 577
    radiographic features of, 574*t*
    treatment of, 576*b*
  as occupational lung disease, 585*t*
Pulmonary flukes, 2167
Pulmonary function tests, 528, 528*t*, 2664
  bronchoalveolar lavage in, 532
  cardiopulmonary exercise tests in, 532
  for complex disorders, 533
  diffusing capacity in, 530
  for interstitial lung disease, 574
  lung volumes in, 530, 530*f*

Copyrighted material

Pulmonary function tests *(Continued)*
maximal respiratory pressures in, 531, 531*f*
in obesity, 533
provocative testing in, 532
reference equations in, 530
spirometry in, 528
of ventilation, 528
Pulmonary hemorrhage, 2029
microscopic polyangiitis with, 520.*e1f*
Pulmonary hemosiderosis, idiopathic, 582
Pulmonary histoplasmosis
acute, 2082
chronic, 2082
complications of, 2082
treatment of, 2083*b*
Pulmonary hypertension, 211*t*, 493
assessing response to therapy in, 496*b*, 500*t*
background therapy for, 496*b*
chronic thromboembolic, 490
clinical classification of, 493*t*
clinical manifestations of, 494
collaborative care in, 496*b*
complications of, 355
cystic fibrosis with, 558.*e1f*
definition of, 493, 493*t*
diagnosis of, 495, 495*f*–499*f*
differential diagnosis of, 359
epidemiology of, 493
history of, 494
invasive therapies for, 496*b*
medical therapy for, 496*b*, 500*t*
pathobiology of, 494, 494.*e1f*
physical examination for, 494
primary lung disease, 493*t*, 496*b*
prognosis for, 500
in sickle cell disease, 1113
special populations of, 496*b*
in systemic sclerosis, 1781
thromboembolic hypertension, 493*t*, 496*b*
treatment of, 496*b*
with unclear and/or multifactorial mechanisms, 493*t*
venous hypertension, 496*b*
Pulmonary infections
and bronchiectasis, 560
pathogens and empirical therapy for, 2526*t*
Staphylococcus aureus causing, 1904
treatment of, 1970*b*
Pulmonary Langerhans cell histiocytosis, 571, 582, 583*b*, 583.*e1f*
Pulmonary lymphocyte alveolitis, 2327*t*
Pulmonary mucormycosis, 2099, 2100*f*
Pulmonary neoplasms, 1329
Pulmonary nocardiosis, 2073
Pulmonary nodules
on chest images, 524, 524*f*
solitary
description of, 1330, 1331*f*
surgery for, 631
Pulmonary opacities, 520
alveolar pattern of, 522
bronchial patterns of, 522
honeycombing, 522, 522*f*
linear patterns of, 521, 522*f*
nodular patterns of, 521
reticular patterns of, 522, 522*f*
vascular patterns of, 522–523, 523*f*
Pulmonary pressures, 240
Pulmonary rehabilitation, 551*b*
Pulmonary risk assessment, 2664*t*
Pulmonary sarcoidosis, 603*b*
Pulmonary sequestration, 565, 565*f*
Pulmonary stenosis (PS)
exercise recommendations for, 355.*e2t*
valvular, 351, 351*b*
Pulmonary system, systemic lupus erythematosus manifestations of, 1770
Pulmonary toxicities, after hematopoietic cell transplantation, 1211
Pulmonary toxoplasmosis, 2136
Pulmonary tuberculosis
clinical manifestations of, 2034–2035, 2036*f*
diagnosis of, 2039–2040
Pulmonary valve, 224
Pulmonary vascular resistance, 677*t*
Pulmonary vascular resistance index, 677*t*
Pulmonary vasculature, 246, 247*f*
Pulmonary vasculitis, interstitial lung disease associated with, 571*t*, 582
Pulmonary venous hypertension, 496*b*
Pulmonary venous return, anomalous, 247.*e1f*, 354–355
Pulmonic stenosis, 411
Pulse
abnormalities of, 214*t*
carotid, 30, 213, 215*f*
Corrigan, 410
irregular rapid, 33*t*
low, 33*t*, 34–35
measurement of, 33
normal range for, 32*t*
panic range for, 32*t*
Quincke, 410
Pulse oximetry, 32, 640, 683
Pulse pressure
aging and, 444, 445.*e1f*
narrow, 257
Pulsed Doppler, 236
Pulseless disease. *See* Takayasu arteritis
Pulseless electrical activity, 313*b*, 316*f*
Pulseless ventricular tachycardia, 315*f*
Pulsus alternans, 257
Punctate basophilia, 1070*f*
Pupil(s)
abnormalities of, 2617
Argyll Robertson, 2017, 2617
dilated, 2618*f*
examination of, 2616–2617
Pupillary control, 2616
Pupillary pathways, 2616, 2617*f*
Pure gonadal dysgenesis, 1600
Pure neuritic leprosy, 2051
Pure red cell aplasia, 1128, 1129*b*, 2235, 2235*f*
Pure tone testing, 2641
Purified chick embryo cell vaccine (PCECV), 82
Purine inhibitors, 147–148
Purine nucleoside phosphorylase (PNP) deficiency, 1679*t*
Purine synthesis inhibitors
in renal transplantation, 845*t*
for systemic lupus erythematosus, 1772*b*
Purpura
causes of, 2687
Henoch-Schönlein, 2715
inflammatory retiform, 2715*t*, 2716, 2716*f*
macular, 2713, 2713*t*, 2714*f*
noninflammatory retiform, 2715*t*, 2716
nonpalpable, 2713
palpable, 2690*f*, 2692*t*, 2714, 2714*f*, 2714*t*, 2715*f*
retiform, 2715–2716, 2715*t*
solar, 2690*f*, 2714, 2715*f*
steroid, 2714
Purpura fulminans, 2716*f*
Purpuric eruptions, 2713–2716, 2713*t*, 2714*f*, 2714*t*
Purulent conjunctivitis, *H. influenzae* caused by, 1954
Purulent meningitis, 2516*t*
Pustular eruptions, 2722
Pustular lesions, of smallpox, 2238*f*
Pustular psoriasis, 2722, 2723*f*
Pustular psoriasis of von Zumbusch, 2705, 2706*f*
Pustule, 2689*t*
Puumala virus, 2265*t*
PVCs. *See* Premature ventricular contractions
Pyelonephritis, 2091
antimicrobials for, 1877*t*
characteristics of, 2270*t*
clinical manifestations of, 1874
description of, 1873
diagnosis of, 1876*t*
in pregnancy, 1627–1628, 1628*b*
symptoms of, 1874*t*
treatment of, 1875*b*, 1876*t*
Pyknodysostosis, 1668, 1668*b*, 1729
Pyoderma gangrenosum, 2735
Pyogenic arthritis, 2518
Pyogenic arthritis with pyoderma gangrenosum and acne (PAPA), syndrome of, 1731*t*, 1736–1737
Pyogenic liver abscess, 1022, 1023*b*, 1023*f*
Pyogenic meningitis, 2513–2514
Pyomyositis, 1903
Pyrantel pamoate, 2112*t*, 2117
Pyrazinamide
dosage of, 1895*t*
for tuberculosis, 2040*b*, 2041*t*–2043*t*
Pyrethrins, 88*t*
Pyridostigmine, for orthostatic hypotension, 2559*t*
Pyridoxal-5-phosphate, 1453*t*
Pyridoxine
for acute poisoning, 693*t*
Pyridoxine *(Continued)*
deficiency of, 2540–2541, 2540*b*
toxicity, 2540
for type 1 primary hyperoxaluria, 807
for Wilson disease, 1437*b*
Pyrimethamine
for cystoisosporiasis, 2112*t*
for *Pneumocystis* pneumonia, 2108*t*
for toxoplasmosis, 2112*t*, 2115, 2140*t*
Pyrimidine 5′-nucleotidase deficiency, 1100, 1100*f*
Pyrimidine inhibitors, 147
Pyrogenic exotoxins, 1914, 1914*f*
Pyronaridine, for malaria, 2121*b*
Pyrophosphate arthropathy, 1814
Pyropoikilocytosis, hereditary, peripheral blood smear of, 1069*f*
Pyruvate kinase deficiency, 1099, 1099*b*, 1100*f*
Pyruvic acid, *e1t*–*e8t*
Pyuria, 722, 724*t*
urinary tract infection and, 1875

Q

Q fever, 417*t*, 2062–2063, 2065*t*
characteristics of, 2270*t*
clinical manifestations of, 2062–2063, 2062*t*
diagnosis of, 2063
epidemiology of, 2062–2063
pathobiology of, 2062
prevention of, 2063
prognosis of, 2063
treatment of, 2063*b*
Q-switched lasers, 2701
QRS complex, 228*f*, 229–230, 229*t*
QRS voltage, low, 233, 234*t*
QT interval, 230
corrected, 230
long QT syndrome, 337, 338*f*
Qualitative stool fat test, for malabsorption, 931*t*
Quality, changing environment for, 44–45
Quality-adjusted life years (QALYs), 39
Quality improvement, strategies, 45
Quality measures, 44*t*
Quality of care, 19–20, 43–45
Quality-related problems, epidemiology of, 44
Quantitative culture, of small intestinal aspirate, for malabsorption, 931*t*
Quantitative proteomics, 168
Quantitative stool fat test, for malabsorption, 931*t*
Quasi-experimental study designs, 37
Queensland tick typhus, 2055*t*
Quetiapine
for Parkinson disease, 2487*t*
for psychotic disorders, 2346*t*
Quinapril, 451*t*
Quinapril/HCTZ, 451*t*
Quincke pulse, 410
Quinidine, *e10t*–*e11t*, 325*t*
Quinidine gluconate, 2112*t*, 2114–2115
Quinine, 2114–2115
for babesiosis, 2152*b*, 2152*t*
for malaria, 2121*b*, 2121*t*
Quinine sulfate, 2114
for babesiosis, 2112*t*
for malaria, 2112*t*
Quinolones, 1899
for chancroid, 1951*b*
for cholera, 1957*t*
dosage of, 1895*t*
mechanism of action, 1895*t*
resistance mechanisms, 1893*t*
toxicities of, 1901*t*
Quinupristin, resistance mechanisms, 1893*t*
Quinupristin-dalfopristin
characteristics of, 1900
dosage of, 1895*t*
mechanism of action, 1895*t*

R

Rabies
encephalitis caused by, 2534, 2535*b*
immunization for, 65*t*, 66*t*, 82
in travelers, 1889.*e1t*, 1891*t*
vaccine, for traveler, 1886*t*, 1887
Rac 2 deficiency, 1683.*e1t*
Race
age-adjusted drug overdose death rates by, 18*t*, 19*f*
arterial hypertension and, 444
Racecadotril, for infectious gastroenteritis, 2263*b*
Racial differences, in cardiovascular disease, 219
Racial disparities, in health outcomes, 17
Radiation
acute leukemias and, 1259
marrow injury and, 1146
as occupational and environmental hazards, 87
Radiation biodosimetry, 94
Radiation carcinogenesis, 93
Radiation cataractogenesis, 93
Radiation enteritis, 940, 940*b*
intestinal ulcers associated with, 956
Radiation injury, 91–95
ionizing radiation in
clinical manifestations of, 93
diagnosis of, 93, 93*t*
ionizing radiation in, 91
medical imaging of, 94
pathobiology of, 92
prevention of, 94
lung, 597, 597*b*
non-ionizing, 95
Radiation myelopathy, 2564*t*
Radiation pneumonitis, increased lymphocyte counts in, 533
Radiation proctopathy, 968, 968*f*
Radiation therapy
for brain tumors, 1312*b*
for breast cancer, 1369*b*
for cancer, 1232*b*
for Cushing syndrome, 1524*b*
for extramedullary hematopoiesis, 1135*b*
for multiple myeloma, 1299*b*
for NSCLC, 1333*b*
organ-specific late effects after, 93, 93*t*
for pituitary tumors, 1487*b*
for prostate cancer, 1385*b*, 1385*t*
sequelae, treatment of, 94*b*
Radical nephrectomy, for renal cell carcinoma, 1364*b*
Radio frequency coils, 519
Radioablation, for ventricular tachycardia, 338*b*
Radioactive iodine
for Graves disease, 1511*t*
for hyperthyroidism, 1511*b*
Radioactivity, 91
Radiocontrast media, reactions to, 1698*t*
Radiofrequency radiation, 88*t*, 95.*e1f*, 95
Radiography
bedside, 519
chest, 519
in gastroenterology, 866
of heart, 244
for rheumatic disease, 1717, 1717*t*, 1718*f*
Radiologic accidents, 92, 92*t*
Radiologic terrorism, 92
counter measures after, 94
Radiology
for gastrointestinal disease, 854
for nocardiosis, 2073, 2073*f*, 2074*f*
Radionuclide imaging, in acute MI, 384
Radium 223, 1385*b*
Radon, exposure to, lung cancer and, 1329
Rales, 512
Raloxifene
for breast cancer, 1373
for osteoporosis, 1608
Raltegravir, 2301*t*
Ramelteon, 2452*t*
Ramipril, 451*t*
for acute STEMI, 384*b*, 391*t*
for heart failure, 266*t*
Ramsay Hunt syndrome, 2646
Ramucirumab (Cyramza), 1215*t*, 1341*b*
Randall plaques, 803–804
Random donor platelets, 1200
Randomized research design, 36
RANK ligand, 145
RANKL, 151
Ranolazine, 364*b*
Rapid bacteriologic diagnosis, in bacterial meningitis, 2514
Rapid intestinal transit, 939
Rapid plasma reagin test, 2018
Rapid ultrasound in shock (RUSH) protocol, 661*t*
Rapidly progressing myopia, 2597–2598
Rapidly progressive dementia, 2424, 2424*t*
Rapidly progressive glomerulonephritis, 784, 784*f*
anti-glomerular basement membrane disease, 784, 784*b*, 784*f*, 784*t*

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Rapidly progressive glomerulonephritis (*Continued*)
classification of, 784*t*
clinical manifestations of, 785
diagnosis of, 785
IgA nephropathy and, 781*b*
immune complex, 785
pauci-immune, 785
prognosis for, 785
treatment of, 785*b*, 785*f*
vasculitis-associated, 785
Rapidly reversing cardiomyopathy, 337
Rare childhood syndromes, 814, 815*b*
Rasagiline, for Parkinson disease, 2487*t*
Rash
acute, 2694*t*
fever and, 1847, 1848*t*
infectious entities associated with, 1849*t*
in Rocky Mountain spotted fever, 2054
Rate control, for atrial fibrillation, 329*b*
RaTG13, 2210
Rathke cleft cyst, 1479
Rationale, for heart failure, 275*t*
Raxibacumab, 97, 153
Raymond syndrome, 2465.e1*f*
Raynaud phenomenon, 472–473, 472*t*–473*t*, 681
bilateral, 473.e1*f*
in *Mycoplasma pneumoniae*, 2007
in systemic lupus erythematosus, 1770
in systemic sclerosis, 1776–1778
unilateral, 473*f*
RBBB. *See* Right bundle branch block
RBC. *See* Red blood cell
RBC size distribution width (RDW), 1076*t*
RCVS. *See* Reversible cerebral vasoconstriction syndrome
RDW. *See* RBC size distribution width
Re-entrant arrhythmias, 301, 302.e1*f*
Re-entry, 302, 302*f*
Reactivation pneumonitis, 1858
Reactive airways dysfunction syndrome, 587
Reactive arthritis, 1750, 1762–1763
Chlamydia trachomatis causing, 2012
clinical manifestations of, 1763, 1763*f*
definition of, 1762–1763
diagnosis of, 1763, 1764*f*
enteric infections and, 1870*t*
epidemiology of, 1762
human immunodeficiency virus and, 1763
pathobiology of, 1763
prognosis of, 1766
treatment of, 1765*b*
Reactive hyperplasias, 2625, 2625*t*
Ready-to-use therapeutic food (RUTF), for severe acute malnutrition, 1445*b*, 1446*t*
Rebif. *See* Interferon Beta1*a*
Rebound nystagmus, 2619
Receiver operator characteristic (ROC) curve, 38, 39*f*
Receptor activator of nuclear factor-κB ligand, 1640, 1640.e1*f*
Receptor editing, 187
Receptor-mediated signaling pathways, 185–186
Recidivans cutaneous leishmaniasis, 2133
Recluse spiders, envenomation of, 710
Recombinant human von Willebrand factor (rVWF), 1183*b*
Recombinant meningococcal B protein vaccines, 66*t*
Recombinant proteins, 149, 150*t*
Recombinant S protein vaccine, for COVID-19, 2219
Recombinant tissue plasminogen activators (rtPA), for ischemic stroke, 2469*b*, 2469*t*, 2469.e1*f*, 2470*t*
Recombinant zoster vaccine (RZV), 66*t*, 83
Recommended dietary allowances, 57, 1451
Rectal adenocarcinoma, 1349, 1350*b*
Rectal bleeding, 978
Rectal infection, diagnosis of, 1949
Rectal neuroendocrine tumors, 1567
Rectal prolapse, 981–982, 981*f*, 982*b*
Rectal temperature, 33, 678
Rectovaginal fistulas, Crohn disease-related, 945*b*
Rectum
anatomy of, 977
diseases of, 977
anal fissure as, 979, 980*f*
anal fistula as, 979, 979*f*
Rectum (*Continued*)
cancer as, 982
fecal incontinence as, 981, 981*f*
hemorrhoids as, 977, 978*f*
human papillomavirus as, 982
perianal abscess as, 978
pruritus ani as, 980
rectal prolapse as, 981, 981*f*
sexually transmitted anorectal diseases, 983
warts as, 982, 982*f*
distention of, 888
examination of, 31
Recurrent artery of Heubner, 2456–2457
Recurrent corneal erosion, 2602
Recurrent pregnancy loss, in hypercoagulable states, 476
Recurrent somatic mutations, in chronic lymphocytic leukemia, 1267
Recurrent unstable angina, 374*t*
Recurrent venous thromboembolism, 490
Red blood cell (RBC), 1076*t*
packed, HIV transmission through, 2299
transfusion of, 1199–1200
cryopreservation of, 1200
indications for, 1204
irradiation of, 1200, 1205
leukoreduction, 1205
modification of, 1199–1200, 1205
pathogen reduction in, 1200, 1205
for septic shock, 673*b*
Red cell agglutination
conditions associated with, 1072*t*
peripheral blood smear of, 1070*f*
Red cell distribution width, coefficient of variation (RDW-CV), e8*t*–e9*t*
Red cell distribution width (RDW), 1076–1077
Red cell fragmentation
conditions associated with, 1072*t*
peripheral blood smear of, 1068*f*
Red cell indices, 1076, 1076*t*
Red cell release, increasing, 1107*b*
Red cell volume, e8*t*–e9*t*
Red eye, 2599, 2599*t*
Red lesions, 2622*t*, 2623–2624
"Red man syndrome", 1692
5α-Reductase deficiency, 1572
5α-Reductase inhibitors
for benign prostatic hyperplasia, 822*b*
for male lower urinary tract symptoms, 824*t*
Refeeding syndrome, 1450
Reference intervals, e1
clinical chemistry, toxicology, and serology, e1*t*–e8*t*
drugs: therapeutic and toxic, e10*t*–e11*t*
hematology and coagulation, e8*t*–e9*t*
prefixes and abbreviations, e1*t*
Referred pain, 2393
Reflex epilepsies, 2433
Reflux, esophageal, 211*t*
Refractoriness
absolute, 300
dispersion of, 302
relative, 300
Refractory angina, 364*b*
Refractory disease, treatment of, 1269*b*
Refractory dyspnea, oxygen in, 12
Refractory heart failure, 265*b*
Refractory/relapsed Hodgkin lymphoma, management of, 1292*b*
Refractory unstable angina, 374*t*
Regenerative medicine, 169–179
Regional anesthesia, 1827, 2671
Regional dermatoses, 2745, 2745*f*, 2746*f*, 2746*t*
Regional pain syndrome, 1708
Regional rheumatic pain syndromes, 1742
Regional sympathetic dysfunction, 2561
Regional therapy, for metastatic neuroendocrine tumor, 1568*b*
Regorafenib (Stivarga), 1215*t*
for colorectal cancer, 1350*b*
Regulators of complement activation, 197
at C3 and C5 steps, 199
Regulatory cell therapy, 207
Regurgitation
esophageal disease and, 902
gastroesophageal reflux disease and, 903, 903*f*
peptic strictures and, 905
Rehabilitation, for acute STEMI, 384*b*
Rehydration, for cholera, 1956*b*
Reifenstein syndrome, 1573
RELA haploinsufficiency, 1731*t*, 1736
Relapsing encephalitis, 2532*t*
Relapsing fever, 2027, 2059
characteristics of, 2270*t*
clinical manifestations of, 2028
definition of, 2027
diagnosis of, 2028, 2028*f*
epidemiology of, 2027
pathobiology of, 2028
prevention of, 2028
prognosis of, 2028
in travelers, 1889.e1*t*, 1891*t*
treatment for, 2028*b*
Relapsing pancreatitis, prevention of, 972*b*
Relapsing polychondritis, 1825, 2652, 2652.e1*f*
Relapsing-remitting multiple sclerosis, 2501
Relapsing syphilis, 2016
Relative hypovolemia, 735*b*, 735*t*
Relative intensity, 61
Relative refractoriness, 300
Relative scarcity, 9
Relatlimab, for melanoma, 1394*t*
Relaxation, isovolumic, 225
Release reaction, 1165
Relebactam, 1845*t*
REM. *See* Rapid eye movement
REM sleep behavior disorder, 2420, 2452, 2453*t*
Remdesivir, 2190, 2216–2217
Remethylation disorders, 1425*t*, 1426
Remicade. *See* Infliximab
Remodeling organs, endoscopy for, 881
Renal acidification, mechanisms of, 754.e1*f*
Renal agenesis, 818
Renal allograft dysfunction
causes of, 847*t*
evaluation of, 847*t*
Renal arterial system, atheromatous embolization of, 801, 801*b*, 802*f*
Renal arteriography, for vasculitis, 728
Renal artery stenosis, 749*t*, 799–801
atherosclerosis causing, 799
atherosclerotic, 800*b*, 800*t*
clinical manifestations of, 800
definition of, 799
diabetes and, 796
diagnosis of, 800, 800*f*
epidemiology of, 799
fibromuscular dysplasia causing, 799
pathobiology of, 799
prognosis for, 801
Renal biopsy
for acute interstitial nephritis, 792, 792*t*, 793*f*
for diabetic nephropathy, 797
for glomerular syndromes, 728
Renal cell carcinoma, 1362
classification of, 1363*t*
clinical manifestations of, 1363, 1364*t*
definition of, 1362
diagnosis of, 1364
epidemiology of, 1362
pathobiology of, 1362–1363, 1363*t*
prevention of, 1365
prognosis of, 1365
TNM staging of, 1364*t*
treatment of, 1364*b*
Renal colic, evaluation of, algorithm of, 804*f*
Renal dialysis, 673*b*, 677*f*
Renal disease
acute kidney injury as, 725
approach to, 720–729, 720*f*
diagnosis of, 720–725
measuring kidney function in, 720, 721*f*
pathobiology of, 720–725
chronic kidney disease as, 729, 729*f*
glomerular syndromes as, 726
papillary necrosis as, 728
in pregnancy, 1619*t*
sickle cell disease and, 1114*b*
tubulointerstitial diseases as, 728, 728*t*
vasculitis and vascular diseases of kidney as, 728
Renal drug clearance, 129
Renal dysfunction
for septic shock, 673*b*, 677*f*
treatment of, 265*b*
Renal dysplasia, 818
Renal failure
bleeding and, 1166
chronic, weight loss and, 860*t*
drug dose adjustments in, 129.e1*t*
Renal function, normal, diabetes and, 456
Renal glycosuria, 816*t*
Renal hypoplasia, 818
Renal hypouricemia, 816*t*
Renal infarction, 801, 802*b*
Renal insufficiency
drug dosage in, 130
loading dose in, 130
psychotropic medications and, 2678*t*
Renal interstitium, injury to, 771
Renal involvement, in sarcoidosis, 602
Renal malrotation, 819, 819*f*
Renal nerves, 734–735
Renal osteodystrophy, 1657–1658
Renal outer medullary potassium channel (ROMK), 746
Renal parenchymal hypertension, 449, 449*b*
Renal pelvis, cancers of, 1367
Renal replacement therapy, 840–841, 841*t*
for diabetic nephropathy, 797*b*
hemodialysis. *See* Hemodialysis
peritoneal dialysis. *See* Peritoneal dialysis
Renal sodium, imbalances in, 724–725
Renal syndrome, hemorrhagic fever with, 2268*t*
Renal system, systemic lupus erythematosus manifestations of, 1769
Renal toxicity, after hematopoietic cell transplantation, 1211
Renal transplantation, 843
allocation of, 844
antihypertensive drug for, 454*t*
candidate for, 844
complications of, 846–847
epidemiology of, 843–844
immunosuppression in, 844, 845*t*
kidney donation in, 844
management after, 847
prognosis of, 847–848, 847*t*
rejection of, treatment of, 845–846
success rates of, 844
Renal tubular acidosis (RTA)
causes of, 761*t*
clinical manifestations of, 762
diagnosis of, 762
distal, 749*t*, 761
prognosis of, 762
proximal, 761
treatment of, 762*b*
Renal tubular disorders
cystinuria, 815
inherited, 815
Renal tumors, 1363
Renal vein thrombosis, 802, 802*b*
Renin, e1*t*–e8*t*, 730, 734, 1561*t*
Renin-angiotensin II-aldosterone, 734
Renin-angiotensin system, 225
Renin-angiotensin system inhibitors, for hypertension, 452
Renin-secreting tumor, 749*t*
Renomegaly, autosomal dominant polycystic kidney disease and, 811
Renova, for acne, 2698
Renovascular disease, hypertension and, 448*t*, 449, 449*b*, 449*f*
Reoviridae, 2274, 2284
Repaglinide, for type 2 diabetes mellitus, 1541*t*
Reperfusion injury, rhabdomyolysis and, 715
Reperfusion therapy
for acute STEMI, 384*b*, 385*f*
for shock, 667*b*
Repetitive stimulation study, 2375
Repetitive transcranial magnetic stimulation (rTMS), for fibromyalgia, 1819*b*
Repetitive use syndromes, 1742
Repolarization abnormalities, 233, 234*t*
Reproductive axis development, in childhood and puberty, 1581
Reproductive endocrinology, 1595–1604
abnormal uterine bleeding and, 1597, 1597*b*
amenorrhea and, 1598
chronic anovulation and, 1600
dysmenorrhea and, 1596, 1596*b*, 1596*t*
endometriosis and, 1596, 1596*b*, 1603*b*
menstrual cycle, 1595
premenstrual syndrome and, 1596, 1597*b*, 1597*t*
Reproductive health, of adolescents, 112
Reproductive issues
cystic fibrosis and, 557
in women, 1610

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Reproductive system
cancers of, 1615
syndromes affecting, 1570*t*
Reproductive tracts, male and female, development of, 1569, 1571*f*
Reprogramming, direct, 173
Reserpine, 451*t*
Residual volume (RV), 528
Resiliency, in occupational and environmental medicine, 87
Reslizumab, for eosinophilic syndromes, 1164*b*
Resource Conservation and Recovery Act, 87
Respiration, assessment of, 30
Respiratory acidosis, 765
clinical manifestations of, 765
diagnosis of, 765
expected compensation of, 756, 756*t*
toxicants and, 691*b*
treatment of, 765*b*
Respiratory alkalosis, 765
clinical manifestations of, 765
diagnosis of, 765
epidemiology of, 765
expected compensation of, 756, 756*t*
pathobiology of, 765
treatment of, 765*b*
Respiratory bronchiolitis-associated interstitial lung disease, 574*t*, 577, 578*b*, 578*f*
Respiratory burst, defects of, 1683.*e1t*
Respiratory cancers, occupational and environmental, 86
Respiratory compliance
measurement of, 641
static (Crs), 641
Respiratory depression, psychotropic medications and, 2678*t*
Respiratory diphtheria, 1933–1934
Respiratory disease, 512–519, 512*t*
aspirin-exacerbated, 541*b*
chronic lower, in adolescents, 110*t*
Respiratory drive, measurement of, 641
Respiratory failure
hypoxemic, 596
obesity and, 533
Respiratory function, testing, 528–533
Respiratory infections
cryptosporidiosis and, 2143
Mycoplasma pneumoniae in, 2005, 2006*f*
prevention of, in travelers, 1889
Respiratory monitoring, in critical care, 639
Respiratory muscle strength, measurement of, 641
Respiratory rate
abnormal, 34*t*
decreased, 35
increased, 35
measurement of, 33
normal, 639
normal range for, 32*t*
panic range for, 32*t*
Respiratory specimen testing, for infection, 1835
Respiratory support
for acute poisoning, 691*b*
for shock, 662*b*
Respiratory syncytial virus, 2194–2195
in acute bronchitis and tracheitis, 605
clinical manifestations of, 2194–2195
definition of, 2194
diagnosis of, 2195
epidemiology of, 2194
pathobiology of, 2194
pathogen that causes, 2194
prevention of, 2195
prognosis for, 2195
treatment of, 2195*b*
Respiratory system
age-related changes in, 121
disease, in sarcoidosis, 600–601, 601*f*, 601*t*
physical examination of, 639
Respiratory tract, cancer of, occupational and environmental, 86*t*
Respiratory tract infections
adenovirus causing, 2204
Stenotrophomonas maltophilia in, 1975
Respiratory tract syndromes, enteroviruses causing, 2260, 2260*b*
Respiratory viruses
health care-associated infections caused by, 1865
in travelers, 1891*t*
Rest, for heart failure, 275*t*
Resting membrane potential, 299
Resting metabolic rate (RMR), 1465
Resting tremor, 2484, 2489
Restless legs syndrome, 1630, 2496
anemia and, 1075
characteristics of, 2453
clinical manifestations of, 2496
diagnosis of, 2496
epidemiology of, 2496
pathobiology of, 2496
Restrictive cardiomyopathy, 291
causes of, 291*t*
clinical manifestations of, 291
constrictive pericarditis *versus*, 429.*e1f*, 432*f*
definition of, 291
diagnosis of, 291–292, 292.*e1f*, 293*f*
differential diagnosis of, 433*t*
epidemiology of, 291
idiopathic, 292*f*
overlap with dilated cardiomyopathy, 288
pathobiology of, 291
prognosis of, 292
treatment of, 292*b*
Restrictive disorder, 530
Resuscitation
postresuscitation care, 313*b*
for shock, 662*b*
RET defects, 888
Reteplase (r-PA), 386*t*
Reticular activating system, 2443, 2443.*e3f*
Reticulate macular erythema, 2713*f*
Reticulocyte count, *e8t–e9t*
absolute, *e8t–e9t*
Reticulocyte hemoglobin, *e8t–e9t*
Reticulocyte percentage, 1076*t*
Reticulocyte production index (RPI), 1076*t*, 1077
Retiform purpura, 2687, 2715, 2715*t*
Retin-A, for acne, 2698
Retina, 2596
arteries of, 2614
tears of, 2615
Retinal artery occlusion, as arterial thrombotic complications, 481
Retinal detachment, 2596, 2608
Retinal dystrophy, optic nerve edema, splenomegaly, anhidrosis, migraine headache (ROSAH) syndrome, 1731*t*
Retinal involvement, 2091*f*
Retinal necrosis, zoster and, 2249
Retinitis
diagnosis of, laboratory methods for, 2003*t*
Retinitis, cytomegalovirus, 2251, 2251*f*
Retinitis pigmentosa, 2612, 2612*f*
Retinoblastoma, 2612
Retinoic acid inducible gene I (*RIG-1*), influenza and, 2199–2200
Retinoids, for skin diseases, 2698
Retinopathy, diabetic, 2609
Retinopathy of prematurity, 2612
Retrocalcaneal bursitis, 1748
Retroperitoneal fibrosis, 1567, 1782–1783, 1783*b*
Retroperitoneal sarcomas, 1389*b*
Retropharyngeal abscess, distinguishing features of, 515*t*
Retrotracheal region, of mediastinum, 527
Retroviral vectors, 175
Retroviruses, 2324–2328
Rett syndrome, 2548, 2549*b*
Reverse transcriptase inhibitors, 2319
Reverse transcription polymerase chain reaction (RT-PCR)
for noroviruses, 2263
for rotaviruses, 2263
for rubella virus, 2224
Reversed figure-of-3 signs, 247
Reversible airway obstruction, with heart failure, 265*b*
Reversible cerebral vasoconstriction syndrome (RCVS), 1800, 1800*b*, 1800*t*, 2384
Reversible posterior leukoencephalopathy syndrome, 2616
Review of systems, 28, 29*t*, 2660
Revised Cardiac Risk Index (RCRI), 2661, 2662*t*
Revised El Escorial criteria, for amyotrophic lateral sclerosis, 2563*t*
Revlimid. *See* Lenalidomide
Reward, operational definition of, 142
Reward circuitry, 142, 143.*e1f*
Reye syndrome, influenza and, 2200–2201
Rhabdomyolysis, 714–717
acquired, 714*t*, 715
Rhabdomyolysis *(Continued)*
clinical manifestations of, 716
compression-induced, 715
creatinine kinase levels in, 716
definition of, 714–717, 2581
diagnosis of, 716
differential diagnosis of, 716
drugs and toxins causing, 714–715
epidemiology of, 714, 714*t*
exertional, 714, 715*t*
Guillain-Barré syndrome *versus*, 716
hydration for, 717*b*
infections causing, 715
inherited, 714*t*, 715
laboratory tests for, 716
Mycoplasma pneumoniae in, 2007
myoglobin testing for, 716
pathobiology of, 714–716
pathophysiology of, 714–715, 714.*e2f*
periodic paralysis *versus*, 716
prevention of, 716, 717*t*
prognosis of, 717, 717.*e1t*
statin-induced, 714
trauma causing, 715–716, 715*t*
treatment for, 717*b*, 717*t*
treatment of, 705*b*
Rhabdomyosarcoma, chemotherapy for, 1389*b*
Rheumatic diseases, 1706–1712
autoimmune, 1708
classification of, 1706, 1706*t*
clinical manifestations of, 1707–1709
crepitus associated with, 1710
cutaneous manifestation of, 1707–1708
definition of, 1706–1712
degenerative, 1708
diagnosis of, 1709–1712, 1709*t*, 1711*f*
epidemiology of, 1706–1707
glucocorticoid for, 1712
imaging studies in, 1711–1712, 1717–1723
computed tomography, 1717, 1719*f*
magnetic resonance imaging, 1720, 1721*f*, 1722*f*
radiographic evaluation, 1717, 1717*t*, 1718*f*
scintigraphy, 1723, 1723*f*
ultrasonography, 1718–1720, 1719*f*–1720*f*
joint symptoms associated with, 1707, 1708*f*
laboratory testing for, 1712–1716
anti-DNA, 1714
anti-La antibodies, 1715
anti-RNP antibodies, 1714
anti-Ro antibodies, 1715
anti-Sm antibodies, 1714
antibodies to citrullinated proteins, 1713
antibodies to phospholipids, 1715
antineutrophil cytoplasmic antibodies, 1716
antinuclear antibodies, 1714, 1714*f*
complement, 1715
cryoglobulins, 1716
erythrocyte sedimentation rate, 1712
joint fluid analysis, 1713, 1713*f*
to manage therapy, 1716
rheumatoid factor, 1712
laboratory testing in, 1711
medical history of, 1709–1710
nonspecific clinical presentation of, 1707
pain associated with, 1708–1709
pathobiology of, 1707
pattern of onset, 1710
physical examination of, 1710
range of motion assessment, 1710
specific joint symptoms and, 1710
stiffness associated with, 1710
systemic manifestations of, 1708
treatment of, 1712*b*
Rheumatic fever, 1913
acute, *Streptococcus pyogenes* causing, 1917, 1917*b*, 1917*t*
Rheumatic heart disease, *Streptococcus pyogenes* causing, 1917
Rheumatic valvular heart disease, 400
Rheumatoid arthritis, 1717*t*, 1718*f*, 1721*f*, 1749–1758
articular manifestations of, 1751–1752, 1751*f*, 1752*f*
cardiovascular involvement in, 1753
classification of, 1754, 1755*f*
clinical features of, 2574*t*
clinical manifestations of, 1751–1754
cutaneous manifestations of, 1707
cystic fibrosis *versus*, 558
definition of, 1749–1758
Rheumatoid arthritis *(Continued)*
diagnosis of, 1754–1758
differential diagnosis of, 1755–1758, 1755*t*
epidemiology of, 1749
etiology of, 1750, 1750.*e1f*
extra-articular manifestations of, 1752–1754, 1753*t*
of feet, 1751
Felty syndrome, 1754
gender predilection of, 1709
genetics of, 1749–1750, 1750.*e1t*
of hands, 1751, 1752*f*
hoarseness in, 2652
human leukocyte antigens and, 1750.*e1t*
hydroxychloroquine for, 146
initiation of, 1750.*e1f*
interstitial lung disease associated with, 580, 580*f*
juvenile, 2611
laboratory findings in, 1754–1755, 1755*t*
of large joints, 1751, 1752.*e1f*, 1753*f*
of neck, 1752, 1752*f*
neurologic manifestations of, 1754
ophthalmologic manifestations of, 1753
of other joints, 1752
pathobiology of, 1749–1751
pathogenesis and tissue pathology of, 1750–1751, 1750.*e2f*
pattern of onset, 1710
prognosis of, 1759
pulmonary manifestations of, 1753, 1754*f*
skin involvement in, 1752–1753, 1753*f*–1754*f*
splenomegaly associated with, 1152
treatment of, 1755*b*, 1756*t*–1757*t*, 1758*f*
of wrists, 1751, 1753*f*
Rheumatoid factor, 1712, 1751, 1754
in pleural fluid, 626
Rheumatoid nodules, 1752–1753, 1753*f*
Rheumatoid nodulosis, 1754*f*
Rheumatoid synovitis, 1750, 1750.*e1f*
Rheumatologic paraneoplastic syndromes, 1239, 1239*b*, 1239*f*
Rhinitis, 2627–2635
antihistamines for, 2632*b*
cause of, 2628*t*
characteristics of, 2628
chronic, 2627
clinical manifestations of, 2628–2629
corticosteroids for, 2632*b*, 2634*t*
cromolyn for, 2632*b*
decongestants for, 2632*b*
definition of, 2627
diagnosis of, 2629–2632
differential diagnosis of, 2630*f*, 2631, 2633*t*
epidemiology of, 2627
gestational, 1618*t*
imaging of, 2630–2631, 2630*f*–2632*f*
infectious, 2632*b*
laboratory findings in, 2630
leukotriene modifiers for, 2632*b*
medical therapy for, 2632*b*
nonallergic, with eosinophilia syndrome, 2630*f*, 2631
pathobiology of, 2627–2628
physical examination of, 2629–2630, 2629*f*–2630*f*
treatment of, 2632*b*, 2634*t*
Rhinocerebral mucormycosis, 2099
Rhinorrhea, 2193*b*, 2519
Rhinosinusitis, 2628
chronic, 2627, 2628
chronic, cystic fibrosis and, 558
definition of, 2627
diagnosis of, 2629
differential diagnosis of, 2631, 2633*t*
epidemiology of, 2627
imaging of, 2630, 2630*f*, 2631*f*, 2632*f*
laboratory findings in, 2630
pathobiology of, 2627
physical examination of, 2629, 2629*f*, 2630*f*
symptoms of, 2628*t*
Rhinoviruses, 605, 609, 2192
Rhonchus, 512, 512*t*
Rhythm disturbances, management of, 384*b*
Rhythmic movement disorder, 2452
Rib-pelvis distance, 1638*f*
Ribavirin
for hepatitis C, 1014*b*, 2182*t*, 2185
for respiratory syncytial virus, 2195*b*
for viral hemorrhagic fevers, 2272*t*

Copyrighted material

Ribociclib (Kisqali), 1215*t*
for breast cancer, 1369*b*
Riboflavin, *e*1*t*–*e*8*t*, 1453*t*
Richter syndrome, 1283*b*
Richter transformation, in chronic lymphocytic leukemia, 1268, 1271
Rickets, 1453*t*, 1647
definition of, 1647
epidemiology of, 1647
Wilson disease and, 1437
Rickettsia akari, 2060
Rickettsia felis, 2058–2059
Rickettsia parkeri, 2065*t*
Rickettsia philipii 364D, 2065*t*
Rickettsia prowazekii, 2054
Rickettsia rickettsii, 1847
Rickettsia spp., diseases caused by, 2054
Rickettsia typhi, 2058
in travelers, 1889.*e*1*t*
Rickettsiae, 2055*t*
Rickettsial infections, 2054–2063
definition of, 2054
ehrlichioses and anaplasmoses, 2060–2062, 2060*t*
flea-transmitted diseases, 2058
genetic classification of, 2055*t*
in human beings, 2055*t*
louse and mite infections, 2059–2060
pathogens of, 2054
Q fever, 2062
rickettsioses, 2054
Rickettsialpox, 2055*t*, 2060, 2060*b*
Rickettsioses, 2054
lymphangitis-associated, 2055*t*
tick-borne, 2054–2058, 2055*t*
Riedel thyroiditis, 1515, 1515*b*
Rifabutin
for nontuberculous mycobacterial disease, 2046*t*
for tuberculosis, 2040*b*
Rifampicin
for leprosy, 2052*b*, 2053, 2053*t*
for primary sclerosing cholangitis, 1058*b*
Rifampin
for bacterial meningitis, 2518*t*
dosage of, 1895*t*
for endocarditis, 417*b*
for *H. influenzae* type B disease, 1954
mechanism of action, 1895*t*
for meningococcal disease, 1945*t*
for nontuberculous mycobacterial disease, 2046*t*
resistance mechanisms, 1893*t*
for tuberculosis, 2040*b*, 2041*t*–2042*t*, 2043*t*
Rifamycin, 1845*t*
Rifapentine, for tuberculosis, 2040*b*, 2041*t*
Rifaximin
for bloating, 859*b*
for irritable bowel syndrome, 895*b*, 896*t*
for traveler's diarrhea, 1888, 1888*t*
Rift Valley fever, 99, 99.*e*1*t*, 2265*t*, 2266, 2268*t*, 2275*t*, 2279, 2280*b*
RIG-1. *See* Retinoic acid inducible gene I
Right atrial pressure, 240
Right bundle branch block (RBBB), 231, 231*t*, 232*f*, 334
Right ventricular enlargement, 245
Right ventricular failure, 494
Right ventricular hypertrophy, 233
Right ventricular infarction
ECG findings, 383
management of, 384*b*
Right ventricular outflow tract obstruction, 351
Rigidity, in parkinsonism, 2484
Rilonacept, description of, 151, 151*t*
Rilpivirine, 2301*t*
Riluzole, for amyotrophic lateral sclerosis, 2563*b*
Rimantadine, for influenza, 2189, 2189*t*, 2203*t*
Ringed sideroblasts, 1086, 1086*f*
Rings, esophageal, abnormalities of, 910, 910*f*
Rinne test, 2641
Rinvoq. *See* Upadacitinib
Riociguat, for pulmonary hypertension, 496*b*
Rippling muscle disease, 2583.*e*1*t*, 2585
Risankizumab, for inflammatory bowel disease, 945*b*, 946*t*
Risdiplam, for spinal muscular atrophy, 2565*b*
Risedronate
for osteogenesis imperfecta, 1728*b*
for osteoporosis, 1644*t*
for Paget disease, 1664*t*
Risk assessment
cardiovascular, 2661, 2662*t*, 2663*f*
general, 2661
genetic, 159
Risk factors, 28
Risk prediction, for common complex disease, 167
Risk-reducing bilateral mastectomy, for cancer, 1232*b*
Risk stratification, 363
for decision making, 363*t*
after myocardial infarction, 384*b*
Risperidone, 2346*t*, 2496*b*
Ristocetin cofactor activity, 1181
Ritonavir, 2301*t*
Rituxan. *See* Rituximab
Rituximab (Rituxan), 1215*t*
for autoimmune hemolytic anemia, 1089*b*
for chronic lymphocytic leukemia, 1269*t*, 1270*t*
description of, 152
for immune thrombocytopenic purpura, 1175*b*, 1176*t*
for minimal change disease, 778*b*
for rapidly progressive glomerulonephritis, 785*b*
for rheumatoid arthritis, 1756*t*
for systemic lupus erythematosus, 1772*b*
for total knee arthroplasty, 1830.*e*1*t*
Rivaroxaban, 502*t*, 505, 505*t*
administration of, 506*t*
description of, 364*b*
dosage and monitoring of, 505
for venous thromboembolism, 478*b*, 487*b*
Rivastigmine
for Alzheimer disease, 2416*b*
for Parkinson disease, 2487*t*
Rizatriptan, 2380*t*
RMR. *See* Resting metabolic rate
RMSF. *See* Rocky Mountain spotted fever
RNA-based therapeutics, 176–178
RNA interference (RNAi), 176–177
Ro60, 1768
Robotic-assisted cholecystectomy, 1052*b*
Robotic resection, of lung cancer, 1333*b*
Rocio virus, 2276*t*, 2283
Rock of Gibraltar sign, 525
Rocky Mountain spotted fever (RMSF), 2054, 2055*t*
clinical manifestations of, 2054, 2057*f*
diagnosis of, 2054–2057
epidemiology and pathobiology of, 2054
prevention of, 2057, 2057*f*
prognosis of, 2057
reported cases of, 2056*f*
treatment of, 2057*b*
Rodent-borne viruses, 2264
Rodent flea, plague and, 1988, 1990*f*
Roflumilast, 553*t*
Rokitansky-Aschoff sinuses, 1054
Rolapitant, for nausea and vomiting, 863*t*
Romano-Ward syndrome, 348
Romhilt-Estes criteria, 233
Romiplostim, 1175*b*, 2314*b*
ROMK. *See* Renal outer medullary potassium channel
Romosozumab, for osteoporosis, 1643*b*, 1644*t*
Ropinirole
for Parkinson disease, 2487*t*
for restless legs syndrome, 2453, 2496*b*
Rosacea, 2722, 2722*b*, 2722*f*
ROSAH syndrome. *See* Retinal dystrophy, optic nerve edema, splenomegaly, anhidrosis, migraine headache syndrome
Rosai-Dorfman disease, 1158, 1159*b*
Rosiglitazone, for type 2 diabetes mellitus, 1541*t*
Ross River virus, 2275*t*, 2279, 2279*b*
in travelers, 1889.*e*1*t*
Rosuvastatin
for acute STEMI, 391*t*
for familial hypercholesterolemia, 1409*t*
for ischemic heart disease, 470*b*
lipid metabolism affected by, 364*b*
Rotational thromboelastometry (ROTEM), 1169
Rotator cuff tear, 1744, 1744*b*
Rotator cuff tendinosis, 1743–1744, 1743*f*, 1744*b*
Rotaviral NSP4, 2262–2263
Rotaviruses, 2261
clinical manifestations of, 2263
definition of, 2261
diagnosis of, 2263
epidemiology of, 2262, 2262*t*
pathobiology of, 2262–2263
as pathogen, 2261
prevention of, 2263–2264
traveler's diarrhea caused by, 1888*t*
treatment of, 2263*b*
vaccination, 928
ROTEM. *See* Rotational thromboelastometry
Roth spots, 2610*f*
Rotigotine
for Parkinson disease, 2487*t*
for restless legs syndrome, 2453
Rouleaux formation, peripheral blood smear of, 1070*f*
Roussel Uclaf Causality Assessment Method (RUCAM), 1020, 1021*t*
Roux-en-Y gastric bypass, 1467*b*
Rozlytrek. *See* Entrectinib
RPI. *See* Reticulocyte production index
R-protein, 1118
RR interval, 229, 229*t*
RT-PCR. *See* Reverse transcription polymerase chain reaction
RTA. *See* Renal tubular acidosis
rTMS. *See* Repetitive transcranial magnetic stimulation
rTPA. *See* Recombinant tissue plasminogen activators
Rubella, 2224–2225
characteristics of, 2270*t*
clinical manifestations of, 2224, 2224*f*, 2225*t*
definition of, 2224–2225
diagnosis of, 2224
epidemiology of, 2224
immunization for, 66*t*, 78*f*, 82
schedule of, 76.*e*1*t*, 77*f*
pathobiology of, 2224
pathogen of, 2224
prevention of, 2225
prognosis of, 2225
in travelers, 1889.*e*1*t*
treatment of, 2224*b*
Rubex. *See* Doxorubicin
Rubivirus, 2224
Rubraca. *See* Rucaparib
Rubulavirus, 2225
Ruby, 2701
RUCAM. *See* Roussel Uclaf Causality Assessment Method
Rucaparib (Rubraca), 1215*t*, 1251*t*
Rufinamide, for seizures, 2434*t*
Rumination disorder, 1461, 1462*b*
Runner's diarrhea, 926
Ruptured viscus, abdominal pain and, 854*t*
RUSH. *See* Rapid ultrasound in shock
Russell viper venom, 707–708
RUTF. *See* Ready-to-use therapeutic food
Rutherford's clinical classification, 462*t*
Ruxolitinib (Jakafi), 153, 153*t*, 1135*b*, 1138*f*, 1161*b*, 1215*t*
RV. *See* Residual volume
Ryanodine receptor 2, 224
Rybrevant. *See* Amivantamab-vmjw
Rydapt. *See* Midostaurin
RZV. *See* Recombinant zoster vaccine

S

S1PR1. *See* Sphingosine-1-phosphate receptor
Sabiá virus, 2265*t*
Saccades, 2618, 2618.*e*1*t*
Saccular aneurysms, 2475*f*
Sacituzumab govitecan-hziy (Trodelvy), 1215*t*
Sacral nerve modulation, for fecal incontinence, 981*b*
Sacral promontory, 977
Sacroiliitis, 1708
Sacubitril/valsartan, 265*b*, 269*t*, 451*t*
Safety
and cost, 46
culture of, 46
patient, 45
Safety data sheet (SDS), in occupational and environmental medicine history, 85
Safety factor, 300
Safinamide, for Parkinson disease, 2487*t*
Sail sound, 354
Salicylate intoxication, 686*t*, 690*t*, 698*t*, 758
clinical manifestations of, 759
diagnosis of, 759
epidemiology of, 758–759
pathobiology of, 758
prognosis of, 759
treatment of, 759
Salicylates, *e*10*t*–*e*11*t*
central nervous system effects of, 685*t*
Saliva cortisol, measurements of, 1522
Salivary gland, 1320
cancer, 1322, 1328
malignancies, 1327*b*
tumors of, 1322
Salivary gland carcinomas, 1336
Salivary gland diseases
enlargement, causes of, 2626*t*
impaired, without gland enlargement, 2626, 2626*b*
primary, 2625
secondary, 2625–2626
secretion, causes of, 2626*t*
sialolithiasis, 2625
Warthin tumor, 2625
Salmeterol
description of, 553*t*
for high-altitude diseases, 593*t*
Salmonella
nontyphoidal, in travelers, 1891*t*
in travelers, 1891*t*
traveler's diarrhea caused by, 1888*t*
Salmonella enterica, 1833
Salmonella enteritis, in travelers, 1889.*e*1*t*
Salmonella paratyphi, in travelers, 1887, 1891*t*
Salmonella sp.
antimicrobial resistance of, 1977
asymptomatic intestinal carrier state of, 1977
bacteremia caused by, 1978
carriers of, 1977
clinical manifestations of, 1977
contact with animals and their environments of, 1977
contact with infected persons of, 1977
contaminated animal products as source of, 1976
in contaminated food and water, 1977
definition of, 1976
diagnosis of, 1978
enterocolitis caused by, 1978
epidemiology of, 1976
pathobiology of, 1977
pathogen description, 1976
prevention of, 1979
prognosis for, 1979
treatment of, 1979*b*
Salmonella typhi, in travelers, 1891*t*
Salp15, 2023
Salpingitis, 1883, 1949
Salt retention, in nephrotic syndrome, 777
Salvage, for lung cancer, 1333*b*
Salvage antifungal therapy, for aspergillosis, 2096
Salvage esophagectomy, for esophageal squamous cell carcinoma, 1338*b*
Sanfilippo syndrome, 1724*t*
Sanofi Pasteur, 2219
SAPHO. *See* Synovitis acne pustulosis hyperostosis osteitis syndrome
Sappinia, 2150*t*
Saquinavir, 2301*t*
Sarcocystis spp, 2155
Sarcocystosis, 2155
Sarcoid arthropathy, 1824
Sarcoidosis, 292, 292*b*, 582, 599–604, 1029–1030, 1030*b*, 1150, 2611, 2652, 2734, 2735*f*
bone and joint involvement, 602
calcium metabolism in, 602
cardiac disease, 602
cardiomyopathy with, 292
central nervous system involvement of, 1479
chest CT findings of, 600*f*
chest radiography of, 600*f*
clinical manifestations of, 600–602, 600*f*
definition of, 599–604
description of, 1824–1825, 1825*f*
diagnosis of, 602–603
drug-induced, 603
endobronchial, distinguishing features of, 515*t*
epidemiology of, 599–600
eye disease, 601

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Sarcoidosis *(Continued)*
hepatic, 603
illustration of, 2688*t*, 2692*t*
increased lymphocyte counts in, 533
intestinal ulcers associated with, 956
liver disease, 602
neurologic disease, 602, 602*t*
obstruction and, 532
as occupational lung disease, 585*t*
pathobiology of, 600, 600.*e1f*
prognosis for, 604
renal involvement, 602
respiratory system disease, 600, 601*f*, 601*t*
skin disease, 601, 602*f*
splenic, 602
steroid-dependent, 603*b*
treatment for, 603*b*, 604*t*
Sarcoma, 2733–2734, 2734*f*
chondrosarcoma, 1388, 1388*b*
Ewing, 1388, 1388*b*
Kaposi, 2315, 2315*b*, 2316*f*, 2624
large bowel, 1347
leiomyosarcoma, 1389
osteosarcoma, 1388, 1388*b*
retroperitoneal, 1389*b*
rhabdomyosarcoma, 1389*b*
soft tissue, 1389, 1389*b*
Sarcomeres, 224, 224.*e1f*, 2580
Sarcopenia, 2587
Sarcoplasmic reticulum calcium ATPase, 175
Sarcoptes mite, 2741
Sarcoptes scabiei, 710
Sarecycline, 1845*t*
Sarilumab, description of, 151, 151*t*
SARS. *See* Severe acute respiratory syndrome
SARS-CoV-2. *See* Severe acute respiratory syndrome coronavirus-2
SAT. *See* Standard (tube) agglutination test
Satiation, 1464
Satiety, 1464
Saturated fats, dietary guidelines for, 57.*e3t*
Saturated solution of potassium iodide (SSKI), for sporotrichosis, 2086*b*
Savage syndrome, 1600
SAVI. *See* STING-associated vasculopathy with onset in infancy
Saxagliptin, 262
for type 2 diabetes mellitus, 1541*t*
Scabies, 710, 711*b*, 711*f*, 2687.*e1t*, 2741, 2742*f*
organisms causing, 1879*t*
treatment of, 1884*t*
Scalded skin syndrome, 1908
Scalp eschar, neck lymphadenopathy after tick bite (SENLAT), 2055*t*
Scalp psoriasis, 2747*t*
Scarlatina, 1914
Scarlatiniform eruptions, 2712, 2712*t*
Kawasaki disease, 2712
Scarlet fever, 2712
toxic shock syndrome, 2712
Scarlet fever, 1914, 2712
Scarpa ganglion, 2644
Scarring alopecia, 2749
Scavenger receptors, 183
SCC. *See* Squamous cell carcinoma
Scedosporium apiospermum, infections by, voriconazole for, 2076
Schamberg disease, 2713
Schatzki ring, 910, 910*f*
Scheie syndrome, 1724*t*
Schiff-Sherrington phenomenon, 2386
Schistocytes
conditions associated with, 1072*t*
peripheral blood smear of, 1068*f*
Schistosoma haematobium, 2163–2164, 2165*t*
Schistosoma intercalatum, 2165*t*
Schistosoma japonicum, 1029, 2163, 2164, 2165*t*
Schistosoma mansoni, 1029, 1029.*e1f*, 2163*f*, 2164, 2165*t*
Schistosoma mekongi, 2165*t*
Schistosoma spp., 1026*t*
etiology of, 2163–2164
life cycle of, 2163, 2163*f*
in travelers, 1891*t*
Schistosomes
dermatitis caused by, 2164
description of, 1029
Schistosomiasis, 1029, 1029*b*, 1029.*e1f*
acute, 2164
chronic, 2164
clinical manifestations of, 2164
Schistosomiasis *(Continued)*
definition of, 2163–2165
diagnosis of, 2164–2165, 2165*t*
epidemiology of, 2163–2164
pathobiology of, 2164
pathogen that causes, 2163
prevention of, 2165
prognosis of, 2165
in travelers, 1889.*e1t*
treatment of, 2165*b*
Schizoaffective disorder, 2340*t*, 2345*t*, 2346, 2346*t*
Schizoid personality disorder, 2348*t*
Schizonts, 2141
Schizophrenia, 2345
definition of, 2345
diagnosis of, 2345, 2345*t*
epidemiology of, 2345
pathobiology of, 2345
prognosis of, 2345–2346
symptoms and signs of, 2345*t*
treatment for, 2345*b*, 2346*t*
Schizotypal personality disorder, 2348*t*
Schnitzler syndrome, 1731*t*
Schwannoma, 2730, 2732*f*
Schwartz-Jampel syndrome, 2583.*e1t*
Sciatica, 2402
Scimitar sign, 247
Scintigraphy, for rheumatic disease, 1723, 1723*f*
SCLC. *See* Small cell lung cancer
Sclera, 2596
Scleral icterus, 987, 987*f*, 2030*f*
Scleritis, 2611
Scleroderma, 888, 2737. *See also* Systemic sclerosis
of esophagus, 911
florid features of, 987
Scleroderma, ectasias and, 967
Scleroderma renal crisis, 1779, 1781, 1781*b*
Sclerosing thyroiditis, 1515, 1515*b*
Sclerosis, 2737
multiple. *See* Multiple sclerosis
systemic. *See* Systemic sclerosis
tuberous, 583
Sclerostin, 1643*b*
Sclerotic lesions, 2737–2738, 2737*f*, 2738*f*
SCN4A gene, 2585
SCN5A gene, 337
Scoliosis, 620–621
Scombroid poisoning, in travelers, 1889.*e1t*
Scopolamine patch, for nausea and vomiting, 863*t*
Scorpion, envenomation of, 65*t*, 710
Screening
for abdominal aortic aneurysm, 53
cancer
breast, 1373, 1373*t*
cervical, 1376, 1376*t*
colorectal, 54
pancreatic, 1356
prostate, 1387
skin, 1394
electrocardiograms, 235
family, 287*b*
newborn, 166, 1404
Scrub typhus, 2055*t*, 2059, 2060*b*. *See also* *Orientia tsutsugamushi*
SDS. *See* Safety data sheet
Sea anemone stings, 713
Sea urchins, 713
Seafood, as source of food poisoning, 925
Seasonal allergic rhinitis, 1674
Seasonal coronavirus, 2206
clinical manifestations of, 2207
diagnosis of, 2207
epidemiology of, 2206, 2207*t*
pathobiology of, 2206, 2207*t*
prevention of, 2207
prognosis of, 2207
treatment for, 2207*b*
Seasonal influenza vaccination, 541*b*
Sebaceous carcinoma, of eyelids, 2602
Sebastian syndrome, 1179
Seborrheic blepharitis, 2602
Seborrheic dermatitis, 2321, 2687, 2687.*e3t*, 2703, 2703*f*, 2745*f*, 2747*t*
Seborrheic keratoses, 2602, 2688*t*, 2689*t*, 2729, 2730*f*
Secnidazole, 1845*t*, 2150*t*
Second-line agents, for eosinophilic syndromes, 1164*b*
"Second-wind" phenomenon, 2586
Secondary adrenal insufficiency, 1492, 1526, 1527*t*, 1528*f*
Secondary amenorrhea, 1598
Secondary autoimmune neutropenia, 1146
Secondary dystonia, 2492*t*
Secondary gonadal insufficiency, 1584
Secondary hyperaldosteronism, 1525*t*
Secondary hyperparathyroidism, 1658*t*
Secondary hypocortisolism, 1492
Secondary malignancies
in chronic lymphocytic leukemia, 1268
after hematopoietic cell transplantation, 1211
Secondary malnutrition, 1445, 1445*b*
Secondary open-angle glaucoma, 2607
Secondary parkinsonism, 2483*t*
Secondary peritonitis, 957
Secondary progressive multiple sclerosis, 2501
Secondary syphilis, 2015–2016, 2016*f*, 2709, 2709*f*
Secondary systemic amyloidosis, 1310, 1310*b*
Secretin, 1561*t*
Secretin stimulation test, for malabsorption, 931*t*
Secukinumab (Cosentyx)
for psoriatic arthritis, 1765*b*
for total knee arthroplasty, 1830.*e1t*
Sedation, 636
Sedative-hypnotics, 2363, 2363*b*
central nervous system effects of, 685*t*
toxidromes, 683*t*
Sedentary behavior, 63*b*
Sediment, *e1t–e8t*
^{75}SeHCAT test, for malabsorption, 931*t*
Seizures, 306
absence, 2428*t*, 2429
acute symptomatic, 2434*b*
alcohol-related, 2543, 2543*b*
atonic, 2428*t*, 2430
autonomic, 2428*t*
in bacterial meningitis, 2513
causes of, 2426*t*
classification of, 2427*f*
clinical manifestations of, 2427–2430
clonic, 2428*t*
cognitive, 2428*t*
convulsive, 2429
definition of, 2425–2436
diagnosis of, 2430–2433
differential diagnosis of, 2430*t*
drug-resistant, 2434*b*
dystonic, 2428*t*
emotional, 2428*t*
epilepsies *versus*, 2425
febrile, prognosis after, 2436
focal, 2427–2429, 2428*t*
frontal lobe, 2430
generalized, 2425, 2428*t*, 2429
gustatory, 2428*t*
impaired awareness, 2428*t*
inborn errors of metabolism and, 1399
myoclonic, 2428*t*, 2430
olfactory, 2428*t*
postoperative, 2674
in pregnancy, 2434*b*
prognosis of, 2436
psychogenic nonepileptic, 2431
psychotropic medications and, 2678*t*
severe mental illness and, 2683*t*
single, 2431
single unprovoked, 2434*b*, 2436
somatosensory, 2428*t*
after subarachnoid hemorrhage, 2476*b*
surgical treatment of, 2434*b*
syncope *versus*, 2430*t*
tonic, 2428*t*, 2430
tonic-clonic, 2428*t*, 2429
treatment of, 2434*b*
type of, antiseizure medication selection by, 2433*t*, 2434*b*
vestibular, 2428*t*
visual, 2428*t*
in women, medications for, 1608*t*
Selective estrogen receptor modulators
for breast cancer, 1369*b*
for osteoporosis, 1643*b*
Selective IgA deficiency, 1681*t*, 1682, 1822
Selective oropharyngeal decontamination, in health care-associated infections, 1867
Selective serotonin reuptake inhibitors (SSRIs)
for anorexia nervosa, 1462*b*
central nervous system effects of, 685*t*
for depression, 2340*t*
for fibromyalgia, 1819*b*
in pregnancy, 1610
toxicity, 686*t*
Selegiline
for depression, 2340*t*
for Parkinson disease, 2487*t*
Selenium, *e1t–e8t*, 1457*t*
Selexipag, for pulmonary hypertension, 496*b*
Self-help groups, for alcohol use disorders, 2357*b*
Self-identified race, 219
Self-neglect, geriatric assessment of, 118
Selinexor (Xpovio), 1215*t*
Semaglutide
for nonalcoholic fatty liver disease, 1034*b*
for type 2 diabetes mellitus, 1541*t*
Semantic dementia, 2422
Semen analysis, 1589*t*
Semidirect allorecognition, 205, 205*f*
Seminomas, treatment of, 1383*b*
Semont maneuver, 2645*f*
Senile cardiac amyloidosis. *See* ATTRwt amyloidosis
Senile purpura, 121, 122*f*
SENLAT. *See* Scalp eschar, neck lymphadenopathy after tick bite
Senolytics, 116
Sensitivity, 38
Sensitization, central, 134
Sensitizer-induced occupational asthma, 585
clinical manifestations of, 585–586
diagnosis of, 586
epidemiology of, 585
pathobiology of, 585
prevention of, 586*b*
prognosis of, 586
treatment of, 586*b*
Sensorineural hearing loss, 2641
occupational and environmental, 86, 86*t*
Sensory, age-related changes in, 122
Sensory ataxia, 2373*t*
Sensory neuronopathy, 2567*t*
Sensory receptor, 2639
"Sentinel events", 46
Sentinel lymph node biopsy, for melanoma, 1392
Sepsis
definition of, 669
immunodepression in, 671.*e2f*
lactate and, 757
mesenteric venous thrombosis and, 963*t*
procoagulant response in, 671.*e1f*
screening for, 670*t*
severe, 669
shock syndromes related to, 669–677
thrombocytopenia and, 1175
Septic abortion, characteristics of, 2270*t*
Septic arthritis, 1804
anaerobic bacteria causing, 1940
definition of, 1804–1805
gonococcal, 1807, 1807*b*
H. influenzae caused by, 1954
microorganisms responsible for, 1805*t*
nongonococcal, 1805
clinical manifestations of, 1805
diagnosis of, 1805, 1806*f*
differential diagnosis of, 1806
epidemiology of, 1805
pathobiology of, 1805, 1805*t*
prevention of, 1807
prognosis of, 1807
treatment for, 1806*b*, 1807*t*
Staphylococcus aureus causing, 1904–1905
Septic bursitis, 1804
clinical manifestations of, 1804
definition of, 1804
diagnosis of, 1804
differential diagnosis of, 1804
epidemiology of, 1804
pathobiology of, 1804
prevention of, 1804
prognosis of, 1804
treatment for, 1804*b*, 1805*t*, 1807*t*
Septic cavernous sinus thrombosis, 2528, 2529*b*
Septic emboli, 2741
Septic embolization, 1904*f*
Septic sagittal sinus thrombosis, 2530, 2530*b*
Septic shock, 658–659, 659
antibiotics for, 673*b*, 675*t*
cardiovascular dysfunction in, 671

Copyrighted material

Septic shock *(Continued)*
circulatory therapy for, 673*b*
definition of, 669
differential diagnosis of, 673
drugs for, 673*b*
endocrine response and therapies in, 671.*e1f*
epidemiology of, 669–670
intensive insulin therapy for, 673*b*
pathobiology of, 670–672
prevention of, 676
prognosis for, 676
respiratory therapy for, 673*b*
tissue hypoxia in, 671
Septic thrombophlebitis, 2650
Septicemia, meningococcal fulminant, 2512
Septicemic plague, 1991, 2270*t*
Septo-optic dysplasia, 2547
Serologic tests
for COVID-19, 2214–2215
for malaria, 2120
for toxoplasmosis, 2138*t*
Serology
for *Bartonella* infection, 2002
for glomerular syndromes, 727
for histoplasmosis, 2083
reference intervals, *e1t–e8t*
for rubella virus, 2224
Seronegative arthritis, 1721*f*
Serotonin and norepinephrine reuptake inhibitors (SNRIs)
central nervous system effects of, 685*t*
for depression, 2340*t*
for fibromyalgia, 1819*b*
Serotonin re-uptake inhibitors (SRIs)
central nervous system effects of, 685*t*
toxicity, 686*t*
Serotonin syndrome, 1921*b*
characteristics of, 2682*t*
psychotropic medications and, 2681
treatment for, 2681*b*
Serotonin toxicity, anesthesia and, 2669
Serous cystadenomas, 1355–1356
Serovar Typhi, *Salmonella*, in travelers, 1891*t*
SERPINA1 Z allele, 556
Serrated polyps, 1348
Sertraline, *e10t–e11t*
for depression, 2340*t*
for irritable bowel syndrome, 896*t*
Serum aminotransferases, in liver disease, 989
Serum-ascites albumin, 1039, 1040*t*
Serum-ascites albumin gradient, 990
Serum cardiac biomarkers, 383
Serum creatinine, 721, 721*f*
Serum ferritin, in gastrointestinal disease, 851–854
Serum free light chain assay, 1295
Serum immunoelectrophoresis, for glomerular syndromes, 727
Serum potassium concentration, abnormal, postoperative, 2676
Serum protein electrophoresis, of monoclonal proteins, 1294, 1295*f*
Serum sickness, 195, 705*b*, 1694
Serum trypsinogen, in chronic pancreatitis, 974
Serum tryptase, 1675, 1693
Serum TSH, 1505
SeSAME syndrome (EAST syndrome), 816*t*
Severe acute respiratory syndrome (SARS), 2208
clinical manifestations of, 2208
diagnosis of, 2208
epidemiology of, 2207–2208, 2207*t*
pathobiology of, 2208
prevention of, 2209
prognosis of, 2209
treatment for, 2208*b*
Severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2), 286, 2213
acute kidney injury in, 773, 774*t*
acute respiratory distress syndrome and, 650
in adolescents, 111
clinical manifestations of, 2213, 2214*f*, 2214*t*
community prevention of, 2215
diagnosis of, 2214, 2215*f*
epidemiology of, 2213
functional domains of, 2211*f*
hypercoagulable states and, 481
infection of cells in, 2210–2211, 2210*f*
myocarditis and, 2259
nail signs of, 2752*t*
Severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2) *(Continued)*
origin of, 2210
prognosis of, 2215
rapid identification of, 40
schematic drawing of, 2210*f*
spill-back infections of wildlife, 2212
transmission electron micrograph of, 2209*f*
transmission of, 2213
in travelers, 1888
variants of, 2212, 2212*t*
virus and genome of, 2209–2210, 2209*t*
in women, 1610
Severe aplastic anemia, 1125, 1128*f*
Severe combined immunodeficiency
gene therapy, 174
X-linked, 175
Severe congenital neutropenia, 1143, 1144*t*, 1683.*e1t*
Severe fever with thrombocytopenia syndrome virus, 2275*t*
Severe hyperpyrexia, 1851
Severe hypoglycemia, 1546*t*
Severe malnutrition, 1444
clinical manifestations of, 1444
definition of, 1444
diagnosis of, 1445
epidemiology of, 1444
kwashiorkor, 1444, 1444*f*, 1445*f*
marasmus, 1444, 1444*f*
pathobiology of, 1444
prevention of, 1446
prognosis for, 1446
secondary, 1444
stunting, 1445
treatment of, 1445*b*
wasting, 1445
Severe parenchymal lung disease, in hypercapnic disease, 535*t*
Sex
arterial hypertension and, 444
in travelers, 1889
Sex chromosomes, aneuploidy of, 164, 1574
Sex hormone-binding globulin, 1581, 2318
Sex-linked inheritance, 162
Sex steroids, 1591
Sexual activity, heart failure in, 265*b*
Sexual assault, survivors of, regimen for, 1884*t*
Sexual development, 1569–1576
definition of, 1569
differences of, 1569–1573, 1570*t*
considerations related to sex assignment, 1575*b*
diagnosis of, 1575
initial medical management of, 1575*b*
surgical management of, 1575*b*
treatment of, 1575*b*
fetus in, maternal conditions affecting, 1573
hormone insensitivity syndromes, hormone deficiencies and, 1573
ovotesticular disorder of, 1574
Sexual differentiation
normal, 1569
prenatal, course of, 1571*f*
Sexual dysfunction, 1587–1590, 1604, 1604*b*
decreased libido, 1587
ejaculatory failure, 1590, 1590*b*
erectile dysfunction, 1587, 1589, 1589*t*, 1590*f*
impaired orgasm, 1590
in multiple sclerosis, 2504*b*
Sexual function, 1581, 1604
Sexual health, of adolescents, 112
Sexual maturity ratings (SMRs), 110, 110.*e1f*
Sexual orientation, 1574
Sexual transmission, of human immunodeficiency virus, 2298, 2298*f*
Sexuality, geriatric assessment of, 118
Sexually transmitted infections (STIs), 1878–1885
in adolescents, 112
bacterial vaginosis, 1882
barrier methods for, 1884
behavioral interventions for, 1883–1884
candidiasis, 1882, 1882*b*, 1882*t*
chlamydia, epidemiology of, 1879
Chlamydia trachomatis, 1879, 2010, 2011*f*
contraception for, 1884
counseling for, 1883–1884
definition of, 1878–1880
diagnosis of, 1879–1880
donovanosis as, 2004
Sexually transmitted infections (STIs) *(Continued)*
epidemiology of, 1878–1879
epithelial cell infections, 1881
general approach to, 1880*b*
genital herpes, 1880
genital ulcers, 1880
HIV infection and, 1880
human papillomavirus, 1881
lymphogranuloma venereum, 1881
male circumcision and, 1884
partner services for, 1884
pathobiology of, 1879
pelvic inflammatory disease, 1883
postexposure prophylaxis for, 1884, 1884*t*
preexposure interventions for, 1884
prevention of, 1883–1884
screening for, 55
screening of, for adolescents, 112
syndromes of, 1879*t*, 1880–1883
syndromic strategies to, 1879–1880
syphilis. *See* Syphilis
in travelers, 1889
treatment of, 1880*b*
trichomoniasis, 1882–1883, 1883*b*
urethritis, 1880
SGLT2. *See* Sodium-glucose cotransporter-2
Shared care, 2656
Shared decision making, 39
Shared epitope, 1749, 1750.*e1t*
Shear wave elastography, 1720
Shellfish poisoning, 713
in travelers, 1889.*e1t*
Shiga toxin-producing E. coli, 1178
Shigatoxigenic *E. coli*, 1962*t*
Shigella, 1980
epidemiology of, 1980
sexually transmitted anorectal diseases and, 983
transmission of, 1980
in travelers, 1889.*e1t*, 1891*t*
traveler's diarrhea caused by, 1888*t*
virulence of, 1981
Shigella boydii, 1980
Shigella dysenteriae, 1980
Shigella flexneri, 1980
Shigella sonnei, 1980
Shigellosis, 1980–1982
antibiotics for, 1981*b*
clinical manifestations of, 1981
complications of, 1981*t*
definition of, 1980–1982
diagnosis of, 1981
diarrhea caused by, 1981*t*
epidemiology of, 1980
incidence of, 1980
pathobiology of, 1980–1981
pathogen that causes, 1980
prevention of, 1982
prognosis of, 1982
treatment of, 1981*b*, 1982*f*
Shock, 658–665, 2518
blood and blood products for, 662*b*
body positioning for, 662*b*
cardiogenic, 659, 665
causes of, 666*t*
clinical manifestations of, 666, 666*f*, 667*t*
definition of, 665, 665*t*
diagnosis of, 665*t*, 666
epidemiology of, 665, 666*f*
inotropes for, 667*b*
management of, 384*b*
pathobiology of, 666
prognosis for, 669
cardiovascular pathophysiology of, 658–659
cellular pathobiology of, 659–660
clinical manifestations of, 660–661
cryptic, 661
definition of, 658–665, 659*f*
diagnosis of, 660*t*, 661–665
differential diagnosis of, 661
distributive, 659
early manifestations of, 660
emergency procedures for, 662*b*
epidemiology of, 658
genetic susceptibility of, 660
hemorrhagic, 663*t*
hypovolemic, 658
intravenous access for, 662*b*
intravenous fluids for, 662*b*
obstructive, 659
Shock *(Continued)*
organ pathobiology of, 659
overt, 660, 660*t*
pathobiology of, 658–660
physical examinations and laboratory signs in, 660*t*
prevention of, 665
prognosis of, 665
progression of treated or partially treated, 661
respiratory support for, 662*b*
resuscitation for, 662*b*
septic, 669
supportive care for, 662*b*
treatment of, 662*b*, 662*f*
type of, 661–665, 661*t*
untreated, 661
vasoactive agents for, 662*b*
vasopressors for, 662*b*, 664*t*
Short-acting β-adrenergic agents (SABA), for asthma, 541*b*, 544*t*
Short anagen syndrome, 2751
Short-bowel syndrome, 937*t*, 938, 938*b*
Short Nutritional Assessment Questionnaire (SNAQ), 1447, 1448*t*
Short Portable Mental Status Questionnaire, 2334*t*
Short-segment Barrett esophagus, 1339
Short telomere syndromes, 584, 1127.*e1t*, 1129, 1129*b*
Short unilateral headache, with conjunctival injection and tearing, 2377*t*, 2381
Shortness of breath
alveolar hemorrhage and, 568
invasive mucinous adenocarcinoma and lepidic predominant nonmucinous adenocarcinoma and, 569
management of, approaches to, 13*t*
after surgery, 2673
Shoulder
disorders of, 1742–1744
surgical treatment of, 1828
Shwachman-Diamond syndrome, 1145, 1253, 1683, 1683.*e1t*
SIADH. *See* Syndrome of inappropriate antidiuretic hormone secretion
Sialadenosis, 2626
Sialolithiasis, 2625
Sialorrhea
psychotropic medications and, 2678*t*
severe mental illness and, 2681*t*
Sialosis, 2626
Siberian tick typhus, 2055*t*, 2057
Sicca syndrome, 1786*b*
Sick building syndrome, 87
Sick sinus syndrome, 319
Sickle cell(s)
conditions associated with, 1072*t*
peripheral blood smear of, 1068*f*
Sickle cell anemia, 1113
genetics of, 1112*t*
laboratory features of, 1112*t*
Sickle cell carrier, 1111–1112
Sickle cell disease, 1109–1116
acute chest syndrome in, 1113
acute hemorrhagic stroke associated with, 1113
acute ischemic stroke associated with, 1113
acute kidney injury in, 1114
anemia associated with, 1113
asthma in, 1113
blood tests for, 1114
blood transfusion for, 1114*b*
cardiorespiratory complications of, 1113–1114
carriers of, 1111
chronic sickle lung disease in, 1113
clinical manifestations of, 1111–1114
complications of, 1112*t*
crizanlizumab for, 1116*t*
dactylitis associated with, 1112
definition of, 1109
diagnosis of, 1111*f*, 1114
epidemiology of, 1109–1110
gene therapy for, 1114*b*
genetics of, 1112*t*
glomerular filtration rate in, 1114
hematopoietic stem cell transplantation for, 1114*b*
high-pressure liquid chromatography of, 1111*f*, 1114

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Sickle cell disease *(Continued)*
hydroxyurea for, 1114*b*
infection, 1114
infection prophylaxis in, 1114*b*
laboratory features of, 1112*t*
multiorgan disease associated with, 1112–1113
Mycoplasma pneumoniae in, 2007
pain associated with, 1113
pathobiology of, 1110–1111
pathophysiology of, 1110*f*
in pregnancy, 1114
prevalence of, 1110
prevention of, 1114*b*
priapism in, 1114, 1114*b*
primary stroke prevention in, 1112
prognosis for, 1116
pulmonary hypertension in, 1113
red flags for, 1114*t*
renal complications of, 1114
screening of, 1114
silent cerebral infarction in, 1113
sleep-disordered breathing in, 1113
stem cell therapy for, 1114*b*
stroke caused by, 2470.*e1t*, 2472
transfusion for, 1114*b*, 1206
treatment of, 1114*b*
urologic complications of, 1114
vaso-occlusive crises associated with, 1113
Sickle cell trait, 1110*f*, 1111
Sickle hemoglobin, 1110
Sideroblastic anemia, 1072*t*, 1084, 1086
acquired, 1086
clinical manifestations of, 1086
diagnosis of, 1086, 1086*f*
prognosis of, 1086*b*
treatment of, 1086*b*
Signal aliasing, 236
Signal transduction, 1474
Signaling inhibitors, 149, 153
clinical applications of, 150*f*
Janus kinases, 153, 153*t*
Signaling pathways, genetic defects of, 1680, 1681*t*
Signet ring abnormality, 560.*e2f*
Sildenafil, 364*b*, 824*t*
for erectile dysfunction, 1589
for idiopathic pulmonary fibrosis, 576*b*
Silent cerebral infarction, in sickle cell disease, 1113
Silent gallstones, 1052*b*
Silent myocardial ischemia, 358, 369
Silica, 88*t*
Silicosis, 590, 590*t*, 591*f*
Silver, argyria and, 106, 106*b*, 106*f*
Silver deposition, 106, 106*f*
Simple cysts, 809*t*
Simple virilizers, 1572
Simvastatin, for familial hypercholesterolemia, 1409*t*
Sin Nombre virus, 2265*t*
Sindbis virus, 2275*t*, 2279, 2279*b*
Single-lung transplantation, 633
Single metastatic lesion, treatment of, 1241*b*
Single nucleotide variants, 162
Single-organ vasculitides, 1792*t*, 1799–1800
Single-photon emission computed tomography (SPECT)
for epilepsies, 2431, 2432*f*
myocardial perfusion imaging, 248, 249.*e1f*
strengths and weaknesses of, 2373*t*
Single seizures, 2431
Single stripe sign, 965.*e1f*
Single unprovoked seizures, 2434*b*, 2436
Single ventricle, 354
Sinoatrial block, 320*f*
Sinus arrhythmia, 318, 318*f*
Sinus bradycardia, 319, 319*f*, 319*t*
Sinus headache, 2382
Sinus histiocytosis with massive lymphadenopathy, 1288
Sinus node dysfunction, 317*t*, 319
treatment of, 321*b*
Sinus node inhibitors, for heart failure with reduced left ventricular ejection fraction, 265*b*
Sinus node re-entry, 323*t*, 324
Sinus of Valsalva aneurysms, 352
Sinus of Valsalva anomalies, 352–353
Sinus tachycardia, 323–324, 323*t*, 324*b*, 324*f*
Sinus thrombosis
lateral, 2529, 2529*b*, 2529*f*
septic cavernous, 2528, 2529*b*
septic sagittal, 2530, 2530*b*
venous, 2528
Sinuses, cystic fibrosis and, 556
Sinusitis. *See also* Rhinosinusitis
allergic *Aspergillus*, 2095
H. influenzae caused by, 1953
pathogens and empirical therapy for, 2526*t*
Sinusoidal obstruction syndrome, 1019
Siponimod (Mayzent), for multiple sclerosis, 2505*t*
Sirolimus (Rapamycin), e10*t*–e11*t*, 149
for liver transplantation, 1048*t*
for lymphangioleiomyomatosis, 583*b*
in renal transplantation, 845*t*
Sirtuins, aging and, 115
Sister Mary Joseph node, 1341
Sitagliptin, for type 2 diabetes mellitus, 1541*t*
Site-specific therapy, directed by molecular tumor profiling, 1241*b*
Sitosterolemia, 1410
Six Sigma, 45
6-minute walk test, 532
Sixth nerve palsy, 2618
Sjögren syndrome, 1783–1787, 2327*t*, 2564*t*
anti-La/SSB antibodies in, 1784
anti-Ro/SSA antibodies in, 1784
clinical manifestations of, 1707, 1707*t*, 1784–1785
cystic fibrosis *versus*, 558
definition of, 1783–1787
diagnosis of, 1785, 2626
differential diagnosis of, 1785
epidemiology of, 1783
extraglandular disease and, 1785, 1786*b*
genetics of, 1783
glandular (sicca) features of, 1784
glandular manifestations of, 1786*t*
immune mechanisms of, 1784
interstitial lung disease associated with, 581
labial salivary glands in, histopathology of, 1784.*e2f*
laboratory testing for, 1785
lymphoma and, 1785
pathobiology of, 1783–1784
prognosis for, 1787
rheumatology classification for, 1785*t*
sensory neuropathy of, 2573
treatment of, 1786*b*
Skeletal metastases, treatment of, 1241*b*
Skeletal muscle
composition of, 2580
growth hormone effects on, 1488
Skier's thumb. *See* Gamekeeper's thumb
Skin
allergic disease of, 1674
atrophy of, 2687.*e4t*
Candida infection of, 2090
color of, 2687
complicated, bacterial species that cause, 1892*t*
configuration of, 2687, 2691*t*
diagnostic tests of, 2688*t*, 2690, 2692*t*
examination of, 31, 2686–2687, 2686.*e3f*–2686.*e4f*, 2687*f*
Fitzpatrick types, 2686.*e1f*
function of, 2686
fungal infections of, 2736
granulomatous diseases of, 2734, 2735*f*
history, 2687, 2694*t*
inflammatory diseases of, 2734, 2734*f*
inflammatory lesion and nodules of, 2734–2735, 2735*f*
life-threatening emergencies of, 2687–2690
morphology of, 2687, 2689*t*
observational checklist, 2686*t*
onchocerciasis manifestations of, 2178
pruritus of, 2690, 2694*t*
secondary changes of, 2687
structure of, 2686
systemic lupus erythematosus manifestations of, 1769
systemic sclerosis involvement of, 1777, 1781*b*
toxicants and, 685
ulcers, 2738
Skin and soft tissue infections
Acinetobacter causing, 1973
anaerobic bacteria causing, 1939
enterococcus causing, 1921, 1921*b*
Pseudomonas infections causing, 1969, 1970*b*
Staphylococcus aureus causing, 1903
Skin biopsy, for peripheral neuropathy, 2567, 2569*f*, 2570*f*
Skin cancer
basal cell, 1395, 1395*f*, 1396*b*
screening for, 1394
squamous cell, 1395, 1395*f*, 1396*b*
Skin cancers, treatment for, 2701
cosmetics, 2701
dermatologic surgery, 2701
phototherapy and laser, 2701
sunscreen, 2701
Skin diseases
approach to, 2686–2697, 2696*t*
associated with immediate photosensitivity, 1432–1433
atrophy of, 2687.*e4t*
color of, 2687
configuration of, 2687, 2691*t*
diagnostic tests of, 2688*t*, 2690, 2692*t*
esophageal diseases and, 911
examination of, 2686, 2686.*e1f*, 2687*f*
Fitzpatrick types, 2686.*e1f*
function of, 2686
history, 2687, 2694*t*
life-threatening emergencies of, 2687
morphology of, 2687, 2689*t*
observational checklist, 2686*t*
porphyrias *versus*, 1434
protection against, in travelers, 1889
pruritus of, 2690, 2694*t*
in sarcoidosis, 601, 602*f*, 604*t*
secondary changes of, 2687
structure of, 2686
therapy for, 2697–2701
anti-inflammatory agents, 2697
antibacterials, 2699
antifungals, 2699
antihistamines, 2700*t*
antimalarial and antiparasitic drugs, 2698
antimicrobial agents, 2699
antiparasitics, 2699
antipruritic or anesthetic agents, 2699
antivirals, 2699
brimonidine and oxymetazoline hydrochloride, 2698
calcipotriol, 2698
colchicine, 2699
dapsone, 2699
glucocorticoids, 2697, 2698*t*
hormonal therapies, 2700
immune therapies, 2700
immunomodulatory therapies, 2700
immunosuppressive agents, 2700
keratolytics, 2700
moisturizers, 2700
nonsteroidal anti-inflammatory agents, 2698
psoriasis therapies, 2698
retinoids, 2698
soaks and dressings, 2697
thalidomide and lenalidomide, 2699
topical, 2697
topical analgesics, 2699
treatment of, 1434*b*
Skin infections, 2738, 2739*t*
bacterial, 2739
cellulitis as, 2739, 2740*f*
ectoparasites in, 2741, 2742*f*
folliculitis as, 2739
fungal, 2741
furuncles as, 2739, 2740*f*
impetigo as, 2739, 2739*f*
mycobacteria infections as, 2741
Neisseria infections as, 2741, 2741*f*
parasites in, 2742
Pseudomonas infections as, 2741
spirochetes as, 2741
toxic erythemas as, 2740
viral, 2741
Skin lesions, 2686*t*
of bacillary angiomatosis, 2002, 2002*f*
SENLAT with, diagnosis of, laboratory methods for, 2003*t*
Skin malignancies, in HIV, 2321
Skin manifestations
occupational, 86*t*
occupational and environmental, 87
Skin necrosis, warfarin-induced, 478*b*, 478*f*
Skin pigmentation, hemochromatosis and, 1440
Skin rash, drug allergy and, 1695
Skin tags, 2602
Skin testing, for latent TB infection, 2038
Skull fracture, 2513
"Slapped cheek" rash, 2234, 2234*f*
SLC3A1, 815
SLCO1B1 gene, 160*t*
SLE. *See* Systemic lupus erythematosus
Sleep
age-related changes in, 122
definition of, 2443
diary, 2445*f*
graph of, 2444.*e1f*
hypnogram of, 2443
NREM, 2448.*e1f*, 2452
pathobiology of, 2443–2444
REM, 2443, 2443.*e3f*, 2444*t*
stage N1, 2444*t*
stage N2, 2443, 2444*t*
stage N3, 2444*t*
Sleep apnea, 2446–2449
central, 2448, 2448.*e1f*
in heart failure, 265*b*
obesity and, 1466
Sleep-disordered breathing, 257
in sickle cell disease, 1113
Sleep disorders, 2443–2454
clinical manifestations of, 2444
definition of, 2443–2444
diagnosis of, 2444
with heart failure, 257
pathobiology of, 2443
Sleep disturbances, menopause and, 1630, 1630*b*
Sleep hypoventilation syndromes, 534*t*
Sleep-related breathing disorders
circadian rhythm disorders. *See* Circadian rhythm disorders
description of, 2446–2453
parasomnia, 2452, 2453*b*
Sleep-related eating, 2453*t*
Sleep-related hypoventilation, 2448
Sleep spindles, 2443
Sleep terrors, 2453*t*
Sleep transition apneas, 534*t*
Sleeping sickness. *See* African trypanosomiasis
Sleepwalking, 2453*t*
Slit lamp biomicroscope, 2597
Slow-transit constipation, 890
Sly syndrome, 1724*t*
SM1 gene, 2164
SMA. *See* Spinal muscular atrophies
Small bowel
adenocarcinomas, 1343
biopsy, for malabsorption, 931*t*
functions of, 888
motility of, 887, 887.*e1f*
neuroendocrine neoplasms of, 1566, 1566*b*
slow-transit disorders involving pathobiology of, 888
Small bowel carcinoids, 1344
Small bowel obstruction
abdominal pain and, 854*t*
abdominal radiographs of, 866*f*
computed tomography of, 870*f*
Small cell lung cancer (SCLC), 1329
treatment for, 1333*b*, 1335*t*
Small congenital nevi, 2730, 2733*f*
Small fiber neuropathies, 2554
Small interfering RNA (siRNA), 176, 177*f*
Small intestinal immunoproliferative disease, 1286
Small intestinal ulcers, 955–956, 956*f*, 956*t*
Small intestine, neoplasms of, 1343
adjuvant therapy for, 1345*b*
clinical manifestations of, 1344
diagnosis of, 1344–1345
epidemiology of, 1343–1345
metastatic disease of, 1345*b*
pathobiology of, 1343–1344, 1344*f*
predisposing conditions of, 1344
prevention of, 1345
prognosis of, 1345
staging of, 1345
surgery for, 1345*b*
treatment for, 1345*b*
Small lymphocytic lymphoma, 1268, 1283, 1283*b*
Small molecule targeted therapies, 153
Small opacities, pulmonary, 521–523, 521*t*
Small pupil, 2600
Small vessel vasculitis, 784*t*, 965, 1753, 1754*f*, 1792*t*, 1793
Smallpox, 97–98, 98*f*, 2236
clinical manifestations of, 97, 2237–2238
diagnosis of, 97, 2239
epidemiology of, 97, 2236
flat, 2237, 2237*t*
hemorrhagic, 2237, 2237*t*
immunization for, 66*t*, 84
modified, 2237, 2237*t*

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Smallpox *(Continued)*
ordinary confluent, 2237, 2237*t*
ordinary discrete, 2237, 2237*t*
ordinary semiconfluent, 2237, 2237*t*
Orthopoxvirus variola causing, 2236
pathobiology of, 97, 2237
prevention of, 97–98
prognosis for, 98
pustular lesions of, 2238*f*
treatment of, 97*b*
types of, 2237*t*
SMCHD1 gene, 2584
Smell, 2639–2640, 2640*b*, 2640*t*
Smith-Lemli-Opitz syndrome, 1573
SMN. *See* Survival motor neuron
Smoke inhalation, 595
Smoking
cessation of, 384*b*
heart failure in, 265*b*
history of, obtaining, 2679
rates of, 18, 18*f*
rheumatoid arthritis and, 1750
vitamin levels affected by, 1459
in women, 1609
Smoking-related interstitial pneumonias, 571*t*, 577
Smoldering adult T-cell leukemia/lymphoma, 2326, 2326*b*
Smoldering multiple myeloma
monoclonal gammopathy of undetermined significance *versus*, 1295
treatment of, 1299*b*, 1300*f*
Smooth muscle, airway, 541*b*
Smooth pursuit, 2618, 2618.e1*t*
SMV thrombosis. *See* Superior mesenteric vein thrombosis
Snake handlers, 710
Snakebites
in Africa, 709
in Asia, 709
in Australia, 709
in Central America, 708
coral snake, 708, 708*b*
envenomation syndromes of, 707–708
clinical manifestations of, 707–708, 707.e1*t*
coagulopathy associated with, 707
Colubridae, 707.e1*t*
Crotalinae, 707.e1*t*
Elapidae, 707.e1*t*
hematologic effects of, 708
Hydrophiinae, 707.e1*t*
Lamprophiidae, 707.e1*t*
local tissue injury associated with, 707
myotoxicity associated with, 707
Natricidae, 707.e1*t*
treatment of, 708*b*
Viperinae, 707.e1*t*
epidemiology of, 704
in Europe, 709
exotic, 710
immunization for, 65*t*
in Mexico, 708
neurotoxic paralysis caused by, 707, 709.e1*t*
in New Guinea, 709
in North America, 708
signs of, 706*f*
in South America, 708
treatment of, in particular regions, 708, 708*b*
venomous, 708.e1*f*
SNAQ. *See* Short Nutritional Assessment Questionnaire
Snellen eye chart, 117
"Sniff test", 619
SNRIs. *See* Serotonin and norepinephrine reuptake inhibitors
Soaks, for skin diseases, 2697
Social anxiety disorder, 2342*t*, 2343
Social determinants of health
activities of health delivery systems to address social needs and, 48*f*
interventions focused on, 47
relative contribution of clinical care, individual behaviors, 48*f*
Social environments, geriatric assessment of, 118
Social history, 28, 85
Social justice, 4
Social learning theory, intimate partner violence and, 1633
Social phobia, 2342*t*
Social support, geriatric assessment of, 118
Societal implications, 3
Socioeconomic disparities
in health outcomes, 18
magnitude of, 19
Socioeconomic factors, 21
Sodium, e1*t*–e8*t*
dietary guidelines for, 57.e3*t*
reabsorption of, 746
regulation of, 730, 730.e1*f*
Sodium bicarbonate
for acute poisoning, 693*t*
for hyperkalemia, 751*b*
for lactic acidosis, 758*b*
for postresuscitation care, 313*b*
for pulseless electrical activity, 316*f*
Sodium channelopathies, 2585
Sodium channels, 300, 300.e1*f*
Sodium concentration
abnormal, postoperative, 2675
of body fluids, 737
Sodium disorders, 733–744
epidemiology of, 733, 733*t*
pathobiology of, 733
Sodium-glucose cotransporter-2 (SGLT2) inhibitors
anesthesia and, 2669
for chronic kidney disease, 839*b*
clinical benefits of, 265*b*
mechanism of action, 265*b*
practical use of, 265*b*, 271*t*
for type 2 diabetes mellitus, 1540*b*, 1541*t*
Sodium-iodide symporter, 1504, 1504.e3*f*
Sodium nitrite, 596*b*
Sodium oxybate, 2446*b*, 2449*t*
for narcolepsy, 2449*t*
Sodium phenylbutyrate, for amyotrophic lateral sclerosis, 2563*b*
Sodium phosphate, diarrhea and, 939
Sodium-potassium adenosine triphosphatase, 300.e1*f*
Sodium thiosulfate, 596*b*, 693*t*
Sodium-potassium-2 chloride cotransporter (NKCC2), 746
Sofosbuvir, for hepatitis C, 1008*b*, 2181*t*, 2182*t*, 2185
Sofosbuvir/velpatasvir, for hepatitis C infections, 2181*t*, 2182*t*, 2184
Sofosbuvir/velpatasvir/voxilaprevir, for hepatitis C infections, 2181*t*, 2184
Soft tissue diseases, 1742
Soft tissue sarcomas, 1389, 1389*b*
SOJIA. *See* Systemic-onset juvenile idiopathic arthritis
Sokolow-Lyon criterion, 233
Solar purpura, 2690*f*, 2714, 2715*f*
Solar urticaria, 2725
Solid organ transplant recipients, in immunocompromised host, 1852, 1853*t*
Solid tumors, hematopoietic cell transplantation for, 1209
Solifenacin, 824*t*
Solitary plasmacytoma, 1302–1303
Solitary pulmonary nodule
description of, 1330, 1331*f*
surgery for, 631
Solriamfetol, 2449*t*
Soluble C5b-9, 200
Soluble fiber, for irritable bowel syndrome, 895*b*
Soluble guanylate cyclase stimulator, for heart failure with reduced left ventricular ejection fraction, 265*b*
Soluble mediators, 196
Soluble transferrin receptor, 1084
Solute diuresis, 743*t*
Solutions, 2697
Somatic DNA alterations, in cancer, 1248, 1248*f*, 1249*f*
Somatic mutations
in autoinflammatory disease, 1737
in melanoma, 1390
in pancreatic neuroendocrine neoplasms, 1562
resulting in acquired porphyria, 1430
Somatic pain, 134, 135*t*
Somatic sequencing, of tumor DNA, 167
Somatic symptom and related disorders, 2337*t*, 2346, 2347*b*, 2347*t*
Somatoform disorders. *See* Somatic symptom and related disorders
Somatosensory evoked potentials, 2376
Somatostatin, 1477
Somatostatin analogs
for acromegaly, 1489*b*
for glucagonomas, 1564*b*
for metastatic neuroendocrine tumor, 1568*b*
Somatostatinomas, 1561*t*, 1565, 1565*b*
Somatotrophs, 1487
Somatotropin release-inhibiting factor. *See* Somatostatin
Sonidegib (Odomzo), 1215*t*
Sorafenib (Nexavar), 1215*t*
Sorbitol, diarrhea and, 939
Sore throat, common conditions arising as, clinical differentiation of, 2649*t*
Sotalol, 325*t*
Sotatercept, for pulmonary hypertension, 496*b*
Sotorasib (Lumakras), 133, 1215*t*, 1251*t*
Sotrovimab, for coronavirus infections, 2191
South Africa, HIV/AIDS in, 2288, 2288.e1*f*
South American blastomycosis, 2086
South American hemorrhagic fever, 2268*t*
Southern tick-associated rash illness (STAR), 2025
Sowda, 2178
Space sickness, 2644
Spastic gait, 2373*t*
Spastic paraplegias, 2498*b*, 2498*t*
Spasticity, in multiple sclerosis, 2504*b*
Special populations, consultations for, 2656
Specialized acute care unit, 16
Specific gravity, e1*t*–e8*t*, 721
Specificity, 38
Specificity spillover, 1474–1475
Speckle tracking strain imaging, 236, 236.e1*f*
SPECT. *See* Single-photon emission computed tomography
Spectinomycin, dosage of, 1895*t*
Spectrin, 1094
Speech discrimination test, 2641
Speech reception threshold, 2641
Spermatogenesis, 1496, 1581
Spermicides, 1611
SPF. *See* Sun protection factor
Spherocytes
conditions associated with, 1072*t*
peripheral blood smear of, 1067*f*
Spherocytosis, hereditary, 1067*f*, 1094
clinical manifestations of, 1095
definition of, 1094, 1094*f*
diagnosis of, 1094*f*, 1095, 1095*t*, 1096*f*
epidemiology of, 1094
pathobiology of, 1094
treatment of, 1096*b*
Spheroschistocytes, 1068*f*
Sphincter muscle, external, 977
Sphincter of Oddi dysfunction, 1060
Sphincter relaxants, topical, for anal fistula, 980*b*
Sphingolipidoses, 1419*t*
Sphingosine-1-phosphate receptor (S1PR1), 153
Spider bites
envenomation of, 710
epidemiology of, 704
immunization for, 65*t*
signs of, 706*f*
Spider nevi, on face and thorax, 987
Spigelian hernia, 953
Spin-lattice relaxation (T1), in MRI, 1720, 1721*f*
Spina bifida, 2545, 2545*f*, 2546*b*
Spinach, diet-related hyperoxaluria and, 806
Spinal anesthesia, 2671
Spinal cord
anatomy of, 2393*f*
astrocytoma, 1319*f*
blood supply of, 2405*f*
compression of, metastatic, 2406, 2406*b*
fiber tracts of, 2404*f*
segments of, 2392–2393
Spinal cord disorders, 2403–2406
ancillary testing for, 2404
clinical manifestations of, 2403–2404
definition of, 2403–2405
diagnosis of, 2404–2405
differential diagnosis of, 2404–2405
epidemiology of, 2403
overview of, 2403
pathobiology of, 2403
prognosis of, 2405*b*
treatment of, 2405*b*
Spinal cord injury, 2385–2392
clinical manifestations of, 2386
decubitus ulcers and, 2388*b*
diagnosis of, 2387–2388
epidemiology of, 2385
ligamentous injury *versus*, 2388
pathobiology of, 2385–2386
primary injury phase of, 2385
prognosis of, 2390
secondary injury phase of, 2386
spine imaging for, 2388
thromboembolic disease and, 2388*b*
treatment for, 2388*b*
ventilatory support for, 2388*b*
visceral function and nutrition for, 2388*b*
Spinal cord ischemia, 2406*b*
Spinal cord lesions, 2371
Spinal cord stimulation, 136*b*
Spinal dural arteriovenous fistulas, 2405
Spinal epidural abscess, 2527, 2527*f*, 2527.e1*t*, 2528*b*
Spinal fluid analysis, for herpes simplex encephalitis, 2533
Spinal fluid PCR analyses, for viral encephalitis, 2532*b*
Spinal malformations, 2545–2547
Spinal manipulation, 154
Spinal meningiomas, 1318–1319
Spinal muscular atrophies (SMA), 2564*t*, 2565, 2565*b*
Spinal nerves, 2392
Spinal poliomyelitis, 2258*b*
Spinal stenosis, 1706*t*
cervical, 2399, 2401*b*, 2401*f*
lumbar, 2399, 2399*b*
Spinal tumors
classification of, 1318–1319, 1318*t*
intramedullary, 1319, 1319*b*, 1319*f*
Spine
anatomy of, 2393*f*
injuries, 700*b*
pain, 2397*t*
surgical treatment of, 1829
Spine disorders, 2392
clinical manifestations of, 2393
diagnosis of, 2393
pathobiology of, 2392–2393
Spinobulbar muscular atrophy, 2565, 2566*b*
Spinocerebellar ataxia, 2497
Spiny venomous fish, 712
Spiramycin, for toxoplasmosis, 2112*t*, 2115, 2140*t*
Spiritual distress, management of, approaches to, 13*t*
Spirituality, in palliative care, 12
Spirochetes, 2027, 2028*f*, 2741
Spirometry, 528
Spironolactone, 265*b*, 270*t*, 451*t*
for hypervolemia, 736*b*, 737*t*
for transgender women, 1578*b*, 1579*t*
Spironolactone/HCTZ, 451*t*
Spitting cobra venom, 709*b*
Spleen, 1151
examination of, 31
in hereditary spherocytosis, 1095
platelet sequestration in, 1171
red pulp of, 1151
white pulp of, 1151
Splenectomy
for autoimmune hemolytic anemia, 1089*b*
for immune thrombocytopenic purpura, 1176*t*
laparoscopic, 1089*b*
Splenic disease, 968
in sarcoidosis, 602
Splenic marginal zone lymphoma, 1286, 1286*b*
Splenic vein thrombosis, 968
Splenomegaly, 988, 1151–1153
autoimmune disorders associated of, 1152
biopsy of, 1153, 1153*t*
clinical manifestations of, 1151
congestive, 1152
diagnosis of, 1151–1153
differential diagnosis of, 1151*t*, 1152
evaluation of, 1152, 1152*f*
Gaucher disease and, 1421
history of, 1152
imaging of, 1152–1153, 1153*f*
infectious causes of, 1152
physical examination of, 1152
primary myelofibrosis in, 1134

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Splenomegaly *(Continued)*
prognosis for, 1153
in sarcoidosis, 602
in systemic lupus erythematosus, 1770
treatment of, 1153*b*
Splinter hemorrhages, 216, 414, 2753, 2753*t*
Spondyloarthritis, 1760–1767
biologic therapies for, 1765*b*
clinical manifestations of, 1760
corticosteroids for, 1765*b*
definition of, 1760–1761, 1760*f*
diagnosis of, 1760–1761, 1761*t*
epidemiology of, 1760
genetic susceptibility of, 1760
nonsteroidal anti-inflammatory drugs for, 1765*b*
pathobiology of, 1760
sulfasalazine for, 1765*b*
treatment of, 1765*b*, 1766*f*
Spondyloarthropathies, 1708
ankylosing spondylitis. *See* Ankylosing spondylitis
enteropathic arthritis. *See* Enteropathic arthritis
psoriatic arthritis. *See* Psoriatic arthritis
undifferentiated, 1710
Spondylosis
cervical, 2399
description of, 2395, 2402
Spontaneous bacterial peritonitis
cirrhosis and, 1036, 1038
diagnosis of, 1040
treatment of, 1040*b*
Spontaneous nystagmus, 2619
Spontaneous subarachnoid hemorrhage, 2474–2478
clinical manifestations of, 2475
diagnosis of, 2475–2476, 2476*f*
epidemiology of, 2474–2478
Hunt-Hess grading scale for, 2477*t*
laboratory testing for, 2475–2476
prevention of, 2478
prognosis for, 2478
"thunderclap" headache associated with, 2475
Spontaneous tension hydropneumothorax, 526*f*
Spontaneous urticaria, chronic, 1687, 1690*t*
Spoon nails, 2751, 2752*f*
Sporadic colorectal cancer, 1346
Sporadic inclusion body myositis, 2327*t*
Sporadic painless thyroiditis, 1513, 1513*b*, 1513*f*
Sporothrix spp., 2085
Sporotrichoid disease, 2073
Sporotrichosis, 2085, 2086*f*
Sports medicine injuries, 1742, 1744*t*
Spotted fever rickettsiosis, 2065*t*
characteristics of, 2270*t*
in travelers, 1889.*e1t*, 1891*t*
Spray, 2697
S protein, 2210
Sprycel. *See* Dasatinib
Spurling maneuver, 2396
Squamocolumnar junction, 1375
Squamous cell carcinoma (SCC), 2621*t*
of anus, 982
diagnosis of, 1241*t*
esophageal, 1337
of eyelids, 2602
lung, 1329, 1329.*e2t*
oral, 2622, 2622*f*
skin, 1395, 1395*f*, 1396*b*
treatment of, 1241*b*
Squamous intraepithelial lesion, 982
Src homology (SH)2 domains, 1065
SRH. *See* Stigmata of recent hemorrhage
SRIs. *See* Serotonin re-uptake inhibitors
SSKI. *See* Saturated solution of potassium iodide
SSRIs. *See* Selective serotonin reuptake inhibitors
St. John's wort, 155
St. Jude valve, 250.*e1f*
St. Louis encephalitis, 2276*t*, 2282, 2283*b*, 2520
ST segment, 228, 228*f*, 233
ST_2, 260, 260.*e1t*
Stable de-repression, 1894
Stable ischemic heart disease, antihypertensive drug for, 454*t*
Staging hypertension, 447, 447*t*
Standard (tube) agglutination test (SAT), for brucellosis, 1984
Standard exposure history, in occupational and environmental medicine history, 85, 85.*e1f*
Standards, medical profession, 4
Staphylococcal bullous impetigo, 2687.*e4t*
Staphylococcal food poisoning, 1906, 1906*b*
Staphylococcal infections, 1902–1910
Staphylococcal meningitis, 2515*b*
Staphylococcal scalded skin syndrome, 2720, 2720*b*, 2720*f*
Staphylococcal septicemia, disseminated intravascular coagulation from, 1196*f*
Staphylococcal toxic shock syndrome, 1906
Staphylococcemia, characteristics of, 2270*t*
Staphylococcus aureus, 416
antimicrobial resistance of, 1864*t*
bacteremia caused by, 1903
biofilm formation in, 1903
blepharitis caused by, 2601–2602
cellulitis caused by, 1903
clinical manifestations of, 1903–1905
CNS infections, 1905
cystic fibrosis and, 557
decolonization procedures for, 1908–1909
definition of, 1902–1909
diagnosis of, 1905
endocarditis, 783
epidemiology of, 1902
in exit site and tunnel infections, 843
genitourinary infections caused by, 1904, 1905
host defenses against, 1903
infections caused by, 1903
mechanisms of disease of, 1903
methicillin-resistant, 1902, 1902.*e3t*
orthopedic device-related infections, 1904–1905, 1905
osteomyelitis caused by, 1904, 1905
pathobiology of, 1902–1903
pericarditis caused by, 1904
pneumonia caused by, 606, 1905
prevention of, 1908–1909
prognosis of, 1909
prosthetic valve endocarditis caused by, 1903
pulmonary infections caused by, 1904
scalded skin syndrome, 1908, 1908*f*
septic arthritis caused by, 1904, 1905
septic bursitis caused by, 1804
skin and soft tissue infections caused by, 1903
spinal epidural abscess and, 2527
susceptibility testing for, 1905
toxin-mediated syndromes caused by, 1903
treatment of, 1905*b*–1906*b*, 1907*t*
virulence factors of, 1902–1903, 1902.*e3t*
Staphylococcus epidermidis, 1909
Staphylococcus lugdunensis, 1909
Staphylococcus saprophyticus, 1874
Starch blockers, for type 2 diabetes mellitus, 1541*t*
Stasis dermatitis, regional involvement of, 2745*f*
STAT proteins, 1065
Statin-induced rhabdomyolysis, 714
Statins, 1411
for acute coronary syndrome, 375*t*
hepatotoxicity, 1018
for hypertriglyceridemia, 1414*b*
indication for, 1411, 1411*f*
monitoring of, 1411.*e1f*, 1413
for nonalcoholic fatty liver disease, 1034*b*
rhabdomyolysis caused by, 715
risk estimation for, 1411, 1412*t*
safety of, 1412
Statistical interpretation of data, 35–39
causality in, 37
confounding in, 37
data characteristics in, 36
hypothesis testing in, 36, 36*t*
incidence in, 35
interpreting data in, 35
machine learning in, 37
noninferiority trials in, 37
prevalence in, 35
statistical approaches and challenges in, 37
study design in, 36–37
theories and principles for decision making, 38–39, 38*f*–39*f*, 39*f*
time to event data in, 37
using data for clinical decision making, 37–39, 38*t*
Status asthmaticus, 541*b*
Status epilepticus
alcohol-related, 2543, 2543*b*
nonconvulsive, ECG findings in, 2429, 2429*f*
treatment of, 2434*b*
Steatohepatitis
alcoholic, 1031
nonalcoholic, 1031, 1466
Steatorrhea
infants with, 558
signs and symptoms of, approach to, 852*t*
Stelara. *See* Ustekinumab
Stem cell(s), 170–172, 170*f*, 1206
adult (postnatal), 170–172, 170*f*
delivery of, 172
embryonic, 171, 171*f*, 172*f*
pluripotent
ex vivo differentiation of, 173
induced, 171, 171*f*
for sickle cell disease, 1114*b*
tissue-specific, 172
Stem cell transplantation
hematopoietic. *See* Hematopoietic stem cell transplantation
for inborn errors of metabolism, 1401*b*
for myelodysplastic syndromes, 1255
for neutropenia, 1147*b*
Stenotrophomonas maltophilia, 1969, 1975–1976
clinical manifestations and diagnosis of, 1975
definition of, 1975
epidemiology of, 1975
pathobiology of, 1975
prevention of, 1976
prognosis of, 1976
resistance in, mechanisms of, 1976*t*
risk factors for, 1975*t*
treatment of, 1975*b*
Stents/stenting
for atherosclerotic renal artery stenosis, 800*t*
choices related to, 396–397
Steppage gait, 2373*t*
Stepped wedge design, 37
Stereotactic body radiation therapy, for NSCLC, 1333*b*
Sterilization, 1617
Steroid acute regulatory protein, 1581, 1581.*e1f*
Steroid-dependent sarcoidosis, 603*b*
Steroid hormone receptor, 1475*f*
Steroid-induced myopathies, 2587
Steroid purpura, 2714
Steroidal contraception, 1613
Steroidogenesis
adrenal, 1569, 1569.*e1f*
defects of, 1569–1573, 1573
gonadal, 1569, 1569.*e1f*
hypothalamic-pituitary-ovarian axis in, 1596*f*
Steroids
for acute pericarditis, 424*b*
anabolic-androgenic, 2365
ranking of, 2698*t*
in renal transplantation, 845*t*
Stevens-Johnson syndrome, 1847, 2303, 2727
Mycoplasma pneumoniae in, 2007, 2007*f*
prognosis of, 2728
psychotropic medications and, 2678*t*
treatment of, 2728*b*
Stibogluconate sodium, 2112*t*, 2116
Stiff-person syndrome, 1238*t*
Stiffness, in rheumatic diseases, 1710
Stigmata of recent hemorrhage (SRH), endoscopic, for peptic ulcer bleeds, 883*t*
Still disease, adult-onset, 1731*t*, 1732
Stimulants, for narcolepsy, 2449*t*
Stimuli, of intestinal secretion, 924*t*
STING-associated autoinflammatory syndromes, 1736
STING-associated vasculopathy with onset in infancy (SAVI), 1731*t*
Stingrays, venomous, 712
Stings, 704
sea anemone stings, 713
spiny venomous fish, 712
venomous stingrays, 712
STIs. *See* Sexually transmitted infections
Stivarga. *See* Regorafenib
STK11/LKB1 gene, lung cancer and, 1330
Stomach
alcohol use disorders and, 2355*t*
slow-transit disorders involving
gastroparesis. *See* Gastroparesis
intestinal pseudo-obstruction. *See* Intestinal pseudo-obstruction
pathobiology of, 888
systemic sclerosis involvement of, 1778
Stomach neoplasms, 1339
adenocarcinoma, 1339
adenomas, 1343
benign tumors, 1343
definition of, 1339
Stomach neoplasms *(Continued)*
leiomyomas, 1343
lymphoma, 1342
malignant tumors, 1342–1343
Stomach neuroendocrine tumors, 1566
Stomatocyte
conditions associated with, 1072*t*
peripheral blood smear of, 1069*f*
Stomatocytosis, 1069*f*
hereditary, 1094*f*, 1097
Stool cultures, for enteric infection, 1870*t*
Stool DNA testing, 1353
Stool examination
in elusive diarrhea, 931, 931*t*
for gastrointestinal disease, 854
for infection, 1836
Storage diseases, 1150
Strabismus, 2598, 2618–2619, 2619*f*
Strangulated hernia, abdominal pain and, 854*t*
"Strawberry cervix", 1882
Strawberry hemangioma, 2731
Strengthening, for osteoarthritis, 1741*t*
Streptococcal infections, 2648, 2649*t*
glomerulonephritis after, 783, 783*b*, 783*f*
Streptococcal pharyngitis, characteristics of, 2270*t*
Streptococcal toxic shock syndrome, 1914–1916, 1915, 1915*t*
Streptococcus
classification of, 1913
group A, 1913
severe, 1915–1916
group B, 1918
group C, 1919*b*
group G, 1919*b*
identification of, 1913
nutritionally variant, 417*t*
viridans group, 415–416, 1919
zoonotic, 1919
Streptococcus agalactiae, 1918, 1918*b*
Streptococcus anginosus, 1919, 1919*b*
Streptococcus canis, 1919
Streptococcus dysgalactiae subspecies *equisimilis*, 1919, 1919*b*
Streptococcus gallolyticus, 1919
Streptococcus iniae, 1919
Streptococcus milleri, 1919
Streptococcus pneumoniae, 1910–1912, 1953
antibiotics for, 1912*b*
blood cultures of, 1911
clinical manifestations of, 1911
community-acquired pneumonia caused by, 1910
definition of, 1910–1912
diagnosis of, 1911
drug-resistant, 1912*b*
epidemiology of, 1910
Gram stain of, 1910*f*
immunochromatography of, 1911
pathobiology of, 1910–1911
pathogen, 1910
prognosis of, 1912
prophylaxis for, 2309*t*
rhabdomyolysis caused by, 715
sputum Gram stain for, 1911
transmission of, 1910–1911
treatment of, 1912*b*, 2516*t*
Streptococcus pyogenes, 1913
acute infections, 1913
acute rheumatic fever caused by, 1917, 1917*b*, 1917*t*
bacteremia caused by, 1915
cell wall of, 1913
cellulitis caused by, 1915
clinical manifestations of, 1914
definition of, 1913
deoxyribonucleases, 1913
diagnosis of, 1914
ecthyma caused by, 1914
epidemiology of, 1913
erysipelas caused by, 1915
fibronectin binding protein, 1913
fimbriae, 1913
hyaluronic acid capsule, 1913
hyaluronidase, 1913
impetigo caused by, 1914
lipoteichoic acid, 1913
M proteins, 1913
myonecrosis caused by, 1915
necrotizing fasciitis caused by, 1915
nicotine adenine dinucleotidase, 1913

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Streptococcus pyogenes (Continued)
pathobiology of, 1913
pharyngitis caused by, 1914, 1914*f*, 1914*t*
pneumonia caused by, 1916
post-streptococcal glomerulonephritis caused by, 1918
prevention of, 1917
prognosis for, 1916*b*
puerperal sepsis caused by, 1915
pyrogenic exotoxins, 1914, 1914*f*
rheumatic heart disease caused by, 1917
scarlet fever caused by, 1914
streptolysin O, 1913
streptolysin S, 1913
treatment of, 1916*b*
Streptococcus suis, 1919, 2515*b*
Streptococcus viridans endocarditis, 783
Streptokinase (SK), 386*t*
Streptolysin O, 1913
Streptolysin S, 1913
Streptomycin
for nontuberculous mycobacterial disease, 2046*t*
for plague, 98*b*, 1991*b*, 1992*t*
for tularemia, 1987*b*
for verruga peruana, 2003*b*
Stress
dysregulation of responses, 120, 120.*e1f*
hypogonadotropic hypogonadism and, 1584
neutrophilia and, 1141
responses to stressors, 226, 226.*e1f*
Stress cardiac magnetic resonance imaging, 362
Stress echocardiography, 238, 241*f*, 362
Stress fracture, 1748–1749, 1749*b*
Stress incontinence, 827–828
clinical manifestations of, 829
in men, 830
treatment of, 829*b*, 830*t*
in women, 1609
Stress-induced (takotsubo) cardiomyopathy, 665
Stress syndromes, 1747, 1747*b*
Stress testing
for chronic stable angina, 359–360, 361*f*
for signs of cardiovascular disease, 218
Stress ulcers, 916
Stressful life events, irritable bowel syndrome and, 893
Stridor, 512, 512*t*
Stroke
acute ischemic
fibrinolytic therapy for, 509
radiographic changes of, 2373, 2373.*e1f*
in sickle cell disease, 1113
as arterial thrombotic complications, 481
as asymptomatic carotid stenosis, 2473
atrial fibrillation causing, 2464
brain imaging of, 2467–2468, 2468*f*
carotid duplex ultrasonography of, 2468
catheter angiography of, 2469
cerebral venous thrombosis causing, 2471
cervical artery dissection causing, 2470.*e1t*
coagulation disorders causing, 2470.*e1t*
computed tomography of, 2464
cryptogenic, 2472, 2472*f*
devices for, 2473
differential diagnosis of, 2469
disabling deficits, 2473.*e1t*
endovascular therapy for, 2469*b*
epidemiology of, 2454
Fabry disease causing, 2470.*e1t*
fat embolism causing, 2472
history of, 2466
in HIV/AIDS, 2313
hyperviscosity causing, 2470.*e1t*
incidence of, 284
ischemic
arterial hypertension in, 2471*f*
cerebral embolization causing, 2530
clinical manifestations of, 2465
definition of, 2464
differential diagnosis of, 2469
endovascular therapy for, 2469*b*
epidemiology of, 2464
initial laboratory tests for, 2466, 2467*t*
prevention of, 2473
primary prevention of, 2473
risk factors for, 2464*t*
sickle cell disease causing, 2470.*e1t*, 2472
lumbar puncture of, 2468
mortality rates for, 2474
Stroke *(Continued)*
oral contraceptives and, 1614
postoperative, 2664
predicted risks for, 221.*e1f*
prevalence of, 2454
procedures for, 2473
prognosis for, 2473–2474
rare genetic causes, 2472
recovery/rehabilitation from, 2469*b*
risk for, 2454
secondary prevention after, 456, 2473
sickle cell disease causing, 1114*b*, 2470.*e1t*, 2472
after transient ischemic attack, 2473
unusual causes of, 2470–2474, 2470.*e1t*
vasculitis causing, 2470.*e1t*, 2472
Stroke volume, 238
calculation of, 238
formula of, 238
Strongyloides spp., 2172
in travelers, 1889.*e1t*, 1891*t*
Strongyloides stercoralis, 1026*t*, 2170*t*
Strongyloidiasis, 2172, 2173*b*
Strontium ranelate, for osteoporosis, 1643*b*
Structural aberrations, 164
Structural lesion, of bulbar region, 2564*t*
Structural variants, in genomics, 164
Struvite stones, 804
prevention of, 807
Stuart-Prower factor, 1189*t*
Study design, 36
Stunting, 1445
Stupor, cause of, 2437*t*
Sturge-Weber syndrome, 2550*t*, 2551–2552, 2552*b*, 2552*f*
Stuttering, 2408
Stye, 2601, 2601*f*
Subacromial bursa, 1743*f*
Subacute encephalitis, 2221
Subacute idiopathic interstitial pneumonias, 571*t*, 578
Subacute sclerosing panencephalitis, 2221
Subacute sensory neuropathy, 1238*t*, 2576, 2577*b*
Subacute thyroiditis, 1513, 1514*b*
Subarachnoid cysticerci, 2160, 2160*f*
Subarachnoid hemorrhage
angiography for, 2476
bacterial meningitis *versus*, 2515
causes of, 2476
cerebrospinal fluid findings in, 2374*t*
definition of, 2463
fusiform aneurysms causing, 2478
hydrocephalus after, 2476*b*
management of, 2477*t*
medical complications of, 2476*b*
mycotic aneurysms causing, 2478
non-aneurysmal causes of, 2475*t*
seizures after, 2476*b*
spontaneous, 2474
clinical manifestations of, 2475
diagnosis of, 2475, 2476*f*
epidemiology of, 2474
Hunt-Hess grading scale for, 2477*t*
laboratory testing for, 2475
prevention of, 2478
prognosis for, 2478
"thunderclap" headache associated with, 2475
treatment of, 2476*b*
Subclavian artery stenosis, 306
Subclinical disease, in older adults, 114
Subclinical hyperthyroidism, 1511*b*
Subclinical hypothyroidism, 1505, 1508*b*
Subcutaneous fat, 2688*t*
Subcutaneous nodules, 2178
Subcutaneous onchocercomas, 2178
Subcutaneous panniculitis-like T-cell lymphoma, 1287
Subcutaneous phaeohyphomycosis, 2110
Subcutaneous tophus, 1812
Subcutaneous treprostinil, for pulmonary hypertension, 496*b*
Subdermal implants, for contraception, 1616
Subdural abscess, 2528*f*
Subdural effusions, 2511
Subdural empyema, 2528, 2528*b*
Subdural hematoma, 2390
acute, 2390
chronic, 2391
Subfrontal craniotomy, 1487*b*
Subglottic edema, 2197*f*
Subglottic stenosis, 2653
Subjective tinnitus, 2643
Sublobar resections, of lung cancer, 1333*b*
Submersion incidents, 591, 592*b*
Subpleural reticulations, 575.*e1f*
Subpulmonic pleural effusions, 525, 525*f*
Subspecialty consultations, 2657, 2657*t*
Substance abuse
neurologic diseases and, 2369
psychiatric disorders and, 2337
weight loss and, 860*t*
Substance use
in adolescents, 113
in women, 1609
Substance use disorder, 2360
in adolescents, 113
agent of, 2360
clinical manifestations of, 2361
definition of, 2360
diagnosis of, 2361
DSM-5 criteria for, 2360*t*
environment of, 2360
epidemiology of, 2360
history of, obtaining, 2679
host of, 2360
major drugs in, 2361
anabolic-androgenic steroids as, 2365
cocaine and amphetamines as, 2363
hallucinogens as, 2364
marijuana as, 2364
opioids as, 2361
phencyclidine as, 2364
sedative-hypnotic and anxiolytic drugs as, 2363
medical complications related to, 2361
pathobiology of, 2360
severe mental illness and, 2678
treatment of, 2361*b*
Substituted judgment, 6
Substrate reduction therapy, for Gaucher disease, 1421*b*
Succimer, for acute poisoning, 693*t*
Succinate dehydrogenase, 1530
Succinylcholine
for anesthesia, 2670–2671
toxicants and, 691*b*
Sudden cardiac arrest, 312
prevention of, 316
Sudden cardiac death, 333
Sudomotor dysfunction. *See* Sweating disorders
Sufentanil, 139*t*
Sugammadex, reactions to, 1698*t*
Sugar, dietary guidelines for, 57.*e3t*
Sugar cane, 88*t*
Sugar monomers, 938
Suicide, 2347, 2348*t*
in adolescents, 110, 110*t*
assisted, 8
Suicide genes, 176
Sulbactam, for pneumonia, 616*t*
Sulfadiazine
dosage of, 1895*t*
for toxoplasmosis, 2112*t*, 2115, 2140*t*
Sulfamethoxazole, dosage of, 1895*t*
Sulfamethoxazole-trimethoprim, for granuloma inguinale, 2004*b*
Sulfasalazine (Azulfidine), 146
for inflammatory bowel disease, 945*b*, 946*t*
for psoriatic arthritis, 1765*b*
for rheumatoid arthritis, 1755*b*, 1756*t*, 1757*t*
for total knee arthroplasty, 1830.*e1t*
Sulfate, diarrhea and, 939
Sulfhemoglobin, *e1t–e8t*
Sulfonamides
dosage of, 1895*t*
mechanism of action, 1895*t*
reactions to, 1698
resistance mechanisms, 1893*t*
toxicities of, 1901*t*
for toxoplasmosis, 2115
Sulfonylureas, for type 2 diabetes mellitus, 1541*t*
Sulindac, for chronic pain, 138*t*
Sumatriptan, 2380*t*
Sun protection factor (SPF), 2701
Sunitinib maleate (Sutent), 1215*t*
Sunitinib monotherapy, for renal cell carcinoma, 1364*b*
Sunscreen, for skin cancers, 2701
Superantigen model, vasculitides and, 1794
Superficial bursae, 1804
Superficial phaeohyphomycosis, 2109–2110
Superficial spreading melanoma, 1391, 1392*f*
Superficial temporal artery, assessment of, 1803
Superficial vein thrombosis, 490–491
Superior mesenteric artery embolism, 962, 962.*e1f*
Superior mesenteric artery syndrome, 967
Superior mesenteric artery thrombosis, 960
Superior mesenteric vein thrombosis, computed tomography for, 871*f*
Superior sulcus sign, 627
Superior vena cava obstruction, 628, 628*f*
Superoxide dismutase, 196
Supersaturation, 803
Supine hypertension, 2554
Supportive care
for acute kidney injury, 774*b*, 775*f*
for acute pancreatitis, 972*b*
for acute respiratory failure, 647*b*
for cancer, 1232*b*
for myelodysplastic syndromes, 1255
Suppression, 207
Suppurative thyroiditis. *See* Infectious thyroiditis
Suprachiasmatic nucleus, 1478
Supraglottic stenosis, 2652.*e2f*
Supraglottitis, 2651
Supranuclear ophthalmoplegia, Whipple disease and, 2070
Supranuclear pathways, 2618
Suprasellar dysgerminomas, 1479
Supraventricular arrhythmias, 291
with normal rate, 322, 322*f*, 323*b*, 323*f*
Supraventricular ectopy, 322–332
Supraventricular tachyarrhythmias, 323–332, 323*t*, 384*b*
Supraventricular tachycardia (SVT)
catheter ablation of, 346
differential diagnosis of, 335, 335*t*
Suramin
for African trypanosomiasis, 2112*t*, 2125*b*, 2125*t*
Surface electrocardiogram, 317.*e1f*
Surface functions, agents for, 2700
Surgery, 340
for ambiguous genitalia, 1575*b*
for aortic regurgitation, 409
aortic valve replacement, 403*b*
for arrhythmia, 347
for aspergillosis, 2096
for benign prostatic hyperplasia, 822*b*
for biliary tract cancers, 1360*b*
for brain tumors, 1312*b*
for breast cancer, 1369*b*
for bronchiectasis, 561*b*
bronchoscopic approaches, 630
coronary artery, 397. *See also* Coronary artery bypass graft (CABG) surgery
for gastrointestinal stromal tumors, 1390*b*
for heart failure, 265*b*
for hepatocellular carcinoma, 1360*b*
for infective endocarditis, 417*b*
for lung disease, 631
minimally invasive approaches, 631
open approaches, 631
lung volume reduction, 631
decision guide for, 632*t*
inclusion and exclusion criteria for, 632*t*
for malignant lung disease, 631
for mitral regurgitation, 407*b*
mitral valve, 407*b*
for nephrolithiasis, 805*b*
for Paget disease of bone, 1664*b*
patient treated with, 136*b*
for pectus excavatum, 621*b*
for pheochromocytoma, 1533*b*
for pituitary tumors, 1487*b*
for primary lung cancer, 631
for renal cell carcinoma, 1364*b*
for sickle cell disease, 1114*b*
video-assisted thoracoscopic, 631
Surgical floor, psychiatric diseases in, 2679
Surgical history, 28
Surgical procedures, for urinary incontinence, 829*b*
Surgical resection, for coccidioidomycosis, 2085*b*
Surgical revascularization, for atherosclerotic renal artery stenosis, 800*t*
Surgical site infections, 1862*t*, 1866
Staphylococcus aureus causing, 1903

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Surgical therapy
Acinetobacter, 1974*b*
for cancer, 1232*b*
for chronic pancreatitis, 975*b*
for cirrhosis, 1040*b*
for Cushing syndrome, 1524*b*
for pain, in chronic pancreatitis, 975*t*
for premenstrual syndrome, 1597*b*
for Zollinger-Ellison syndrome, 1563*b*
Surgical total thyroidectomy, for Graves disease, 1511*t*
Survival motor neuron *(SMN)*, 2565
Suspected infection, approach to, in normal host, 1845
fever, 1845
nosocomial, 1851
Sutent. *See* Sunitinib maleate
Suvorexant, 2452*t*
SVT. *See* Supraventricular tachycardia
Sweat glands, cystic fibrosis and, 556
Sweating disorders, 2555
Sweet syndrome, 1857, 2724, 2724*b*, 2724*f*, 2734–2735, 2735*f*
Swimmer's itch, 2742
Swine H3N2 viruses, 2199
"Swiss cheese" model of accidents, 45
Switch maintenance, for lung cancer, 1333*b*
Swollen belly syndrome, 2173
Swyer-James-McLeod syndrome, 522
Swyer-James syndrome, 565
Swyer syndrome, 1574
Sydenham chorea, 2491
Sylvatic typhus, 2059
Sympathetic ophthalmia, 2611
Sympathoadrenal system, 747
Sympatholytics, central, for hypertension, 455
Symptom temporality, in occupational and environmental medicine history, 85
Symptomatic gallstones, 1052*b*
Symptomatic hypercalcemia, 1654*b*, 1656
Symptomatic hyponatremia, 741*b*
Symptomatic therapies, for diarrhea and enteric infection, 1872*t*
Symptoms
as health measures, 40
review of, 28
Synchronous biventricular pacing, 342, 342*f*
Syncope, 210*t*, 211, 211*t*, 304, 304*t*
in aortic stenosis, 400
cardiac, 309*b*
causes of, 304*t*
cerebrovascular, 306
cough-related, 306
neurocardiogenic, 305, 309*b*
neurological, 309*b*
neuropsychiatric, 306
prognosis of, 311–312
seizures *versus*, 2430*t*
treatment of, 309*b*, 310*t*
vasovagal, 304*t*
Syndrome of inappropriate antidiuretic hormone secretion (SIADH), 739, 1500
causes of, 739*t*
criteria for the diagnosis of, 739*t*
Syndromes, 3
Synergism, in antibacterial activity, 1843
Syngeneic hematopoietic cell transplantation, 1208
Synovectomy, 1827
Synovial cysts, 1752, 1752.*e1f*
Synovial hypertrophy, chronic, bleeds in, 1188
Synovitis, 1718, 1719*f*
Synovitis acne pustulosis hyperostosis osteitis syndrome (SAPHO), 1731*t*
Synthetic lethality, in BRCA null cells, 1251, 1252*f*
α-Synuclein, 2420
Syphilis, 1808, 2014–2021
algorithm for, 1881.*e1f*
cardiovascular, 2017
chancres associated with, 1881, 2015
chancroid and, 1951
characteristics of, 1881
chemiluminescence immunoassays for, 2018
clinical manifestations of, 2015–2018
condylomata lata associated with, 2015*f*, 2016
congenital, 2018, 2019
cutaneous manifestations of, 2015
dark-field examination for, 2018
definition of, 2014
diagnosis of, 2018–2019
differential diagnosis of, 2019
Syphilis *(Continued)*
early infectious, 2020*b*
endemic, 2021
enzyme immunoassays for, 2018
epidemiology of, 1879, 2014
false-positive serologic test results for, 2019
follow-up examinations for, 2021
gummatous, 2014
incidence of, 2014
Jarisch-Herxheimer reactions, 2020*b*
late, 2017, 2017*t*
late benign, 2017
latent, 2016
meningovascular, 2017
more than 1 year in duration, 2020*b*
natural history of, 2015
neurosyphilis, 1881, 2017, 2019
nontreponemal tests for, 2018
ocular, 1881, 2017, 2606
organisms causing, 1879*t*
otic, 2017
pathobiology of, 2014–2015
pathogen that causes, 2014
penicillin for, 2020*b*, 2020*t*
in pregnancy, 2020*b*
prevention of, 2019–2020
primary, 2015, 2015*f*, 2621*t*
prognosis for, 2021
prophylaxis for, 2309*t*
rapid plasma reagin test for, 2018
relapsing, 2016
screening for, 2019
secondary, 2015, 2016*f*, 2623
serologic tests for, 2018–2019, 2018*t*
tabes dorsalis, 2017, 2019
transfusion-related transmission of, 1203
treatment of, 2020*b*
treponemal tests for, 2018–2019
Syphilitic lesions, 2741
Syphilitic meningitis, 2017
Syringomyelia, 2546*f*, 2547, 2547*b*
Systemic amyloidosis, 1305, 1306*t*
Systemic anaphylaxis
acute treatment of, 1694*f*
causes of, 1691*t*
diagnosing, 1693*f*
Systemic antifungal agents, 2074
amphotericin preparations as, 2077
adverse effects of, 2078
drug interactions of, 2077
formulations and pharmacology of, 2077
indications and dosage of, 2077
mechanism of action, 2077
azole, 2074
fluconazole as, 2075
indications and dosage of, 2075
isavuconazole as, 2077
itraconazole as, 2074
mechanisms of action, 2074
posaconazole as, 2076
voriconazole as, 2076
dosing overview for, 2075*t*
echinocandin, 2078
anidulafungin as, 2078
caspofungin as, 2078
mechanisms of action, 2078
micafungin as, 2078
flucytosine as, 2079
adverse effects of, 2079
drug interactions of, 2079
formulation and pharmacology of, 2079
indications and dosage of, 2075*t*, 2079
mechanisms of action, 2079
ibrexafungerp as, 2079
adverse effects of, 2079
drug interactions of, 2079
indications and dosage of, 2075*t*, 2079
mechanisms of action, 2079
other, 2079
Systemic autoinflammatory diseases, 1730–1737, 1731*t*
adenosine deaminase-2, deficiency of, 1731*t*, 1733*t*, 1737
associated with activation of NF-$_{\kappa}$B, 1736
associated with *NLRC4* mutations, 1731*t*
clinical characteristics of, 1733*t*
cryopyrin-associated periodic syndromes, 1734, 1735*b*
deficiency of interleukin-1 receptor antagonist, 1731*t*, 1735
deficiency of the IL-36R antagonist, 1731*t*, 1735
Systemic autoinflammatory diseases *(Continued)*
definition of, 1730
discovery of, 1737
familial cold autoinflammatory syndrome, 1731*t*, 1733*t*
familial Mediterranean fever, 1730, 1731*t*
clinical characteristics of, 1733*t*
clinical manifestations of, 1730
definition of, 1730
diagnosis of, 1732
epidemiology of, 1730
pathobiology, 1730
prognosis for, 1732
treatment of, 1732*b*
genome sequencing of, 1737
hyperimmunoglobulinemia D with periodic fever syndrome, 1731*t*, 1733
clinical characteristics of, 1733*t*
clinical manifestations of, 1734
prognosis for, 1734*b*
treatment of, 1734*b*
inherited, 1731*t*, 1736–1737
innate immune pathways in, 1737
interferon-related, 1731*t*
late onset, 1737
Muckle-Wells syndrome, 1731*t*, 1733*t*
neonatal-onset multisystem inflammatory disease, 1731*t*, 1733*t*
proteasome-associated autoinflammatory syndromes, 1731*t*, 1735
pyogenic arthritis with pyoderma gangrenosum and acne, syndrome of, 1731*t*, 1736
somatic mutation in, 1737
tumor necrosis factor receptor-associated periodic syndrome, 1731*t*, 1733*t*, 1734
diagnosis of, 1734
epidemiology of, 1734
pathobiology of, 1734
prognosis for, 1734
treatment of, 1734*b*
type I interferon-associated, 1735
Systemic autonomic disorders, 2553
autonomic function tests for, 2556
clinical evaluation of, 2555, 2556*f*, 2556*t*
clinical manifestations of, 2554
definition of, 2553
diagnosis of, 2555
epidemiology of, 2553
laboratory evaluation of, 2556, 2557*t*
pathobiology of, 2553
pathogenesis of, 2554, 2554*t*
treatment for, 2557*b*
Systemic circulation, nutrient delivery to, impairment of, 924.*e1f*, 938
Systemic diseases
arthritis and, 1820, 1821*t*, 1824*f*, 1825*f*
of hemostasis, 1166*t*
inflammatory, with pleural effusions, 626
of throat, 2651
Systemic glucocorticoids, for skin diseases, 2698
Systemic inflammation, hypercoagulable states and, 481
Systemic inflammatory disorders, weight loss and, 860*t*
Systemic light chain amyloidosis, 1305
cardiac involvement in, 1306
clinical manifestations of, 1305–1307, 1306*f*, 1306*t*
definitive testing for, 1307*f*, 1308
diagnosis of, 1307–1308
differential diagnosis, 1308
gastrointestinal/liver and, 1307
initial testing for, 1307, 1307*f*
neuropathy and, 1307
pathobiology of, 1305–1309
prognosis of, 1309
renal involvement and, 1305–1306
treatment for, 1308*b*, 1308*f*, 1309*f*
Systemic lupus erythematosus (SLE), 195, 784*t*, 965, 1767–1775
adjunctive therapies for, 1772*b*
alkylating agents for, 1772*b*
anti-DNA, 1714
antinuclear antibody test for, 1768
antiphospholipid antibody syndrome in, 1770
autoantibodies associated with, 1768, 1768.*e1f*, 1772*t*
biologic therapies for, 1772*b*
cardiovascular system manifestations of, 1769
classification of, 1770–1771, 1771*t*, 1772*f*
clinical manifestations of, 1769–1770, 1769*t*
Systemic lupus erythematosus (SLE) *(Continued)*
complement associated with, 1768–1769
constitutional symptoms of, 1769
conventional medical therapy for, 1772*b*
cutaneous membranes involvement, 1769
definition of, 1767–1775
diagnosis of, 1770–1772
differential diagnosis of, 1771
diffuse alveolar hemorrhage and, 568
discoid skin lesions in, 1769
environmental triggers of, 1768
epidemiology of, 1767
of esophagus, 911
flares of, 1768
gastrointestinal system manifestations of, 1770
gender predilection of, 1709
genetics of, 1768
genomic region of, 1768.*e1t*
glomerular diseases in, 787, 787*b*, 787*f*, 787*t*, 788*f*
hematologic system manifestations of, 1770
immune complexes associated with, 1768
immunologic triggers of, 1768
immunosuppressive therapies for, 1772*b*
innate immune system of, 1768.*e1f*
intravenous gamma globulin for, 1772*b*
laboratory findings in, 1771
lupus nephritis, 1769, 1771, 1773*f*, 1774*f*
lymphadenopathy in, 1770
malar rash associated with, 1770*f*
mucous membranes involvement, 1769
musculoskeletal system manifestations of, 1769
neuropsychiatric involvement in, 1770
ocular manifestations of, 2611, 2624
organ-system disease in, management of, 1772*b*
pathobiology of, 1767–1769
plasmapheresis for, 1772*b*
in pregnancy, 1619*t*
prevalence of, 1767
prognosis for, 1775
pulmonary involvement, 580–581
pulmonary system manifestations of, 1770
Raynaud phenomenon in, 1770
renal system manifestations of, 1769
skin manifestations of, 1769
splenomegaly associated with, 1152
splenomegaly in, 1770
symptoms and signs of, 1769–1770
treatment of, 1772*b*
type I interferon and, 1768
vasculopathy in, 1769
Systemic mastocytosis, 917, 1694, 1701
Systemic-onset juvenile idiopathic arthritis (SOJIA), 1731*t*
Systemic sclerosis, 1775–1783
antinuclear autoantibodies in, 1780
autoantibodies associated with, 1776, 1777*t*
B cells in, 1776
calcinosis cutis in, 1777, 1779*f*
cancer and, 1780
cardiac involvement in, 1779, 1781
cellular immunity in, 1776
classification of, 1777*t*, 1780*t*
clinical manifestations of, 1777–1780
conditions associated with, 1780*t*
definition of, 1775–1782
diagnosing systemic involvement in, 1780–1781
diagnosis of, 1780–1781
epidemiology of, 1706–1707, 1775
facial features in, 1778*f*
fibrosis in, 1776
gastrointestinal complications in, 1781*b*
gastrointestinal tract involvement in, 1778
genetic factors, 1775–1776
humoral immunity in, 1776
immune dysregulation in, 1776
immunosuppressive agents for, 1781*b*
incidence of, 1707*t*
initial clinical presentation of, 1777
interstitial lung disease in, 1779, 1780, 1781*b*
kidney involvement in, 1779
laboratory features of, 1780
lower gastrointestinal tract involvement in, 1778
lung involvement in, 1778
microangiopathy of, 1780
mortality ratios for, 1782
musculoskeletal complications in, 1779
occupational exposure for, 1775

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Systemic sclerosis *(Continued)*
organ involvement in, 1777–1780
pathobiology of, 1775–1776
pathogenesis of, 1776.e1*f*
prevention of, 1781*b*
prognosis for, 1782
progressive, interstitial lung disease associated with, 580
pulmonary arterial hypertension in, 1779, 1781*b*
Raynaud phenomenon in, 1776, 1777
skin involvement in, 1777, 1781*b*
treatment of, 1781*b*
upper gastrointestinal tract involvement in, 1778
vascular complications of, 1778*f*
vasculopathy in, 1776
Systemic therapy
for cancer, 1232*b*
for hepatocellular carcinoma, 1360*b*
for lung cancer, 1333*b*, 1334*t*
Systemic vascular resistance, 677*t*
Systemic vascular resistance index, 677*t*
Systemic vasculitides, 1791–1800. *See also* Vasculitides
Systems thinking, 45
Systolic blood pressure
in industrialized societies, 444
normal range for, 32*t*
panic range for, 32*t*
Systolic hypertension, in elderly patients, 455, 455.e2*f*
Systolic murmurs, quiet, 30
Systolic thrill, 30
Systolic ventricular function, 239

T

T-and B-cell combined defects
less severe, 1678, 1678.e1*t*
severe, 1676, 1676.e3*t*, 1678*b*
with syndromic features, 1678, 1678*b*, 1679*t*
T-cell(s), 152, 186–187
development of, 186, 186*f*
differentiation of, 189–190, 189.e1*t*
homeostasis of, 190
regulatory, 190
stimulation and accessory molecules of, 189
T-cell depletion, 1207
disadvantage of, 206, 206.e2*f*
of hematopoietic cell grafts, 206, 206.e1*t*
T-cell lymphoma
adult, 1286, 1286*b*
anaplastic large cell lymphoma, 1287
angioimmunoblastic, 1287
enteropathy-type, 1287
extranodal NK/T-cell lymphoma, 1287
hepatosplenic, 1287
mature, 1286
mycosis fungoides, 1286, 1286*b*
precursor, 1281, 1282*b*
subcutaneous panniculitis-like, 1287
T-cell receptor chain defects, 1676.e3*t*, 1678
T-cell receptor excision circles (TRECs), 1679
T-cell receptors (TCRs), 188–189, 206
specificities of, 188
T-cell trafficking, role of, 206
T cell-depleting antibodies, in renal transplantation, 845*t*
T-lymphoblastic leukemia/lymphoma, 1260*t*
T lymphocytes, 152
t-PA. *See* Alteplase
T-regulatory cells, genetic defects of, 1684*t*, 1685
T wave, 228, 228*f*, 233
Tabes dorsalis, 2017, 2019
Tachy-brady syndrome, 319, 319*f*
Tachyarrhythmia, 34, 305, 322
supraventricular, 323, 323*t*, 384*b*
Tachyarrhythmic cardiac arrest, 313*b*
Tachycardia, 34
accessory pathway, 326, 326*b*, 328*f*
acute pancreatitis and, 970
in acute poisoning, 682
antidromic, 323*t*, 326
atrial, 323*t*, 324, 324*f*
atrioventricular nodal re-entrant, 323*t*, 324, 324*f*, 327*f*
atrioventricular re-entrant, 323*t*, 326, 328*f*
automatic junctional, 323*t*
monomorphic wide-complex, 335
postoperative, 2675
Tachycardia-induced cardiomyopathy, atrial fibrillation and, 329
Tachypnea, 35
acute pancreatitis and, 970
caused by amphotericin B, 2078
Tacrolimus (Prograf), e10*t*–e11*t*, 148, 2700
for focal segmental glomerulosclerosis, 779*b*
hyperkalemic acidosis caused by, 751
for liver transplantation, 1048*t*
for membranous nephropathy, 780*b*
for minimal change disease, 778*b*
in renal transplantation, 845, 845*t*
for total knee arthroplasty, 1830.e1*t*
Tactile fremitus, 512
Tadalafil, 364*b*, 824*t*
for erectile dysfunction, 1589
for high-altitude diseases, 593*t*
Taenia asiatica, 2158*t*
Taenia saginata, 2158, 2158*t*, 2159*b*
Taenia solium, 2158*t*, 2159
Taeniasis, 2158, 2159*b*
Tafamidis, for amyloidosis, 1309*b*, 2560*b*
Tafenoquine, 2114
for malaria, 2112*t*, 2121*b*, 2121*t*, 2123*t*
Tafinlar. *See* Dabrafenib
Tagrisso. *See* Osimertinib
Tai chi, 154, 1741*t*
Takayasu arteritis, 442.e1*f*, 443–444, 1795, 1796*f*
epidemiology of, 1793*t*
pathologic characteristics of, 1793*t*
prognosis of, 1795*b*
treatment of, 1795*b*
Takayasu disease, 965
Takayasu retinopathy, 1795
Takotsubo cardiomyopathy, 665
Talaromyces (Penicillium) marneffei, 2065*t*
Talaromycosis, 2065*t*, 2309*t*
Talazoparib (Talzenna), 1215*t*, 1251*t*
Talcott group classification, 1856*t*
TALENs. *See* Transcription activator-like effector nucleases
Talimogene laherparepvec, for melanoma, 1394*t*
Taltz. *See* Ixekizumab
Talzenna. *See* Talazoparib
Tamm-Horsfall proteins, 794
Tamoxifen (Nolvadex), 1215*t*
for breast cancer, 1369*b*
Tamponade, pericardial, 425
clinical manifestations of, 425
diagnosis of, 426
epidemiology of, 425
pathobiology of, 425
prognosis for, 428
treatment of, 427*b*
Tamsulosin, 824*t*
Tanapox virus, 2237
Tandem repeats, in genomics, 163
Tanner stages, 110
Tanycytes, 1476
Tapentadol, 136*b*, 139*t*
Tapeworm infections
Diphyllobothrium sp., 2158, 2158*b*, 2158*t*
Dipylidium caninum, 2158
Hymenolepis nana, 2158, 2158*b*, 2158*t*
Taenia asiatica, 2158*t*, 2159
Taenia saginata, 2158, 2159*b*
Taenia solium, 2158*t*, 2159, 2159*b*
treatment of, 2157*b*
Tarantula, goliath, 710
Tardive dyskinesia, 2496, 2496*b*
Target cells
conditions associated with, 1072*t*
peripheral blood smear of, 1068*f*, 1074*t*
Targeted small molecules, for cancer, 1232*b*
Targeted synthetic disease-modifying antirheumatic drugs, 1755*b*, 1756*t*
Targeted therapies
as biologic agents, 149
for chronic lymphocytic leukemia, 1269*t*
for eosinophilic syndromes, 1164*b*
for pulmonary hypertension, 496*b*
small molecule, 153
Targretin. *See* Bexarotene
Tarui disease, 1417*t*
TAS-102, for colorectal cancer, 1350*b*
Tasigna. *See* Nilotinib
Taste, 2639, 2640*b*, 2640*t*
Taste bud, 2639
Taste pathways, 2640*f*
Taurursodiol, for amyotrophic lateral sclerosis, 2563*b*
Taxol. *See* Paclitaxel
Taxotere. *See* Docetaxel
Tay-Sachs disease, 1399, 1423
Tazarotene (Tazorac), 2698
Tazemetostat (Tazverik), 1215*t*
Tazorac. *See* Tazarotene
Tazverik. *See* Tazemetostat
TB. *See* Tuberculosis
TBK1 deficiency, 1731*t*
Tc-MDP. *See* Technetium-99*m* methylene diphosphate
TCAs. *See* Tricyclic antidepressants
TCD. *See* Transcranial Doppler
TCRs. *See* T-cell receptors
Teamwork, medical profession, 4
Teardrop poikilocytes, 1069*f*
Tecentriq. *See* Atezolizumab
Tecfidera. *See* Dimethylfumarate
Technetium-99*m* methylene diphosphate (Tc-MDP), 1723
Tecovirimat, 2240*b*
Tedizolid
dosage of, 1895*t*
mechanism of action, 1895*t*
spectrum of activity, 1900
Tegaserod, for irritable bowel syndrome, 896*t*
Teicoplanin, mechanism of action, 1895*t*
Telangiectasia, 1778*f*, 2738
hereditary hemorrhagic, 967
Telangiectasia macularis eruptiva perstans, 1701
Telavancin
dosage of, 1895*t*
mechanism of action, 1895*t*
spectrum of activity, 1900
Telbivudine, for hepatitis B virus infections, 2181*t*, 2182*t*, 2183
Telehealth
consultations, 2658, 2658*f*, 2659*f*
for COVID-19, 31–32
for quality of care, 42
Teletherapy, 1232*b*
Telithromycin, dosage of, 1895*t*
Telmisartan, 451*t*
Telmisartan/HCTZ, 451*t*
Telogen effluvium, 2748
acute, 2748, 2748*b*, 2748*t*
chronic, 2748
Temazepam, 2344*t*, 2452*t*
Temodar. *See* Temozolomide
Temozolomide (Temodar), 1215*t*
Temperature
definition of, 1845–1846
regulation, 678, 1481
Temporal arteritis, 1801, 2383
Temporal artery biopsy, for giant cell arteritis, 1803
Temporal bone fracture, 2645
Temporal lobe
anatomy of, 2460*f*
epilepsy, 2426*f*, 2646
herniation of, 2511
Temporary partial disability, 85
Temporary total disability, 85
Temsirolimus (Torisel), 1215*t*
Ten Commandments, for effective consultations, 2657, 2657*t*
Tenapanor, for irritable bowel syndrome, 895*b*, 896*t*
Tendinitis, 1747, 1747*b*. *See also* Tendinosis
Tendinosis, 1742
Tendon rupture, of knee, 1747, 1747*b*
Tenecteplase (TNK-t-PA), 386*t*
Tennis elbow. *See* Lateral epicondylalgia
Tenofovir, 2301*t*
for chronic hepatitis B, 1011*b*
Tenofovir alafenamide, for hepatitis B virus infections, 2181, 2181*t*, 2182*t*
Tenofovir disoproxil fumarate
for chronic hepatitis B, 1011*b*
for hepatitis B, 1006, 2181, 2181*t*, 2182*t*
nephrotoxicity caused by, 2313
Tenosynovial giant cell tumor, diffuse type of, 1825–1826
Tenosynovitis, 1742
Tenosynovitis, disseminated gonococcal infection and, 1949
TENS. *See* Transcutaneous electrical nerve stimulation
Tension pneumothorax, 526, 627
Tension-type headache, 2377*t*, 2380, 2380*b*
Tepmetko. *See* Tepotinib
Tepotinib (Tepmetko), 1215*t*
Terazosin, 451*t*, 824*t*
Terbinafine, 2111*b*, 2699
Teriflunomide (Aubagio), for multiple sclerosis, 2505*t*
Teriparatide, for osteoporosis, 1643*b*, 1644*t*
Terminal follicles, 2747
Termination of medical interventions, 6
definition of, 6–7
empirical data for, 7
history of, 6
justification of, 6
practical considerations for, 7, 7*t*
Terrorism
bioterrorism, 95
radiologic, 92
Tesamorelin, 2318*b*
Testicular cancer, 1382–1384
clinical manifestations of, 1382
diagnosis of, 1382–1383, 1383*f*
epidemiology of, 1382–1384
pathobiology of, 1382
prevention of, 1383–1384
prognosis of, 1384
treatment of, 1383*b*, 1383*t*
Testicular feminization syndrome, 1573
Testicular ultrasound, for testicular cancer, 1383
Testis, 1580
irradiation to, 1583
physiology of, 1580
trauma to, 1583
Testosterone, 2365
benefits and risks of, 1585*b*
deficiency of, in elderly, 1582, 1582*b*, 1582.e1*f*
delivery systems for, 1585*b*
description of, 1496*b*
free, e1*t*–e8*t*
plasma proteins and, 1581
at puberty, 1573
secretion of, 1581
total, e1*t*–e8*t*
transdermal delivery for, 1585*b*
for transgender men, 1578*t*
Testosterone buccal patch, for transgender men, 1578*t*
Testosterone cypionate, for transgender men, 1578*t*
Testosterone enanthate, for transgender men, 1578*t*
Testosterone gel, for transgender men, 1578*t*
Testosterone patch, for transgender men, 1578*t*
Testosterone undecanoate, for transgender men, 1578*t*
Tetanospasmin, 1928
Tetanus
description of, 1928, 1929*b*, 1929*t*
immunization for, 65*t*, 66*t*, 78*f*, 82
schedule of, 76.e1*t*, 77*f*
Tetanus/diphtheria/acellular pertussis (Tdap) vaccination
description of, 1996
for traveler, 1886
Tetanus immune globulin, 1929
Tetanus toxoid vaccination, 1929
Tetany, 2581
Tethered spinal cord, 2546, 2546*b*
Tetrabenazine
description of, 2491
for tardive dyskinesia, 2496*b*
Tetracyclines, 2115
characteristics of, 1899
dosage of, 1895*t*
for intestinal bacterial overgrowth, 934*b*
mechanism of action, 1895*t*
resistance mechanisms, 1893*t*
spectrum of activity, 1900
for *Streptococcus pneumoniae* pulmonary infections, 1912.e1*t*
toxicities of, 1901*t*
Tetrahydrocannabinol, screening for, 689*t*
Tetralogy of Fallot (TOF), 353–354
chest radiography findings, 247.e1*f*
exercise recommendations for, 355.e2*t*
incidence and prevalence of, 347
repair of, 353, 353*f*
Tetrathiomolybdate, for Wilson disease, 1437*b*
Tetrodotoxin poisoning, 713

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TGF-β receptor, 185
T_H1-mediated hypersensitivity reactions, 195
α-Thalassemia, 1102–1104, 1103*t*, 1104
  minor, 1104
β-Thalassemia, 1103*t*, 1104–1106
  clinical classification of, 1105*f*
  genetics of, 1112*t*
  intermedia, 1104–1106
  laboratory features of, 1112*t*
  major, 1106
  minor, 1104
  pathophysiology of, 1106*f*
δβ-Thalassemia, 1103*t*, 1106, 1107*f*
Thalassemia(s), 1102–1109, 1103*t*
  clinical manifestations of, 1104–1106
  definition of, 1102–1107
  diagnosis of, 1106–1107
  diagnostic approach to, 1108*f*
  epidemiology of, 1102
  genetics of, 1102–1103
  hemoglobin E, 1106
  molecular basis of, 1103–1104
  pathobiology of, 1102–1104
  prognosis of, 1107*b*
  transfusion for, 1206
  treatment of, 1107*b*
  unstable hemoglobinopathies, 1109
Thalassemia intermedia, 1104, 1107*b*
Thalassemia major, 1104, 1107*b*
Thalassemia minor, 1107*b*
  peripheral blood smear of, 1067*f*
Thalidomide, for skin diseases, 2699
Thallium
  neuropathy and alopecia, 106, 106*b*
  toxicity, 690*t*
Theophylline, *e*10*t*–*e*11*t*
  for asthma, 541*b*
  toxicity, 690*t*
Therapeutic hyperthermia, 682
Therapeutic hypothermia, 681, 2462
Therapeutic index, 128–129, 1232*b*
Therapeutic paradigm, in oncology, 1232*b*
Therapeutic window, 128
Thermal disorders, 471–475, 471*f*
Thermal injury, 699, 699*f*, 699*t*
  to lungs, 595
  to upper airway
    clinical manifestations, 595
    diagnosis, 595
    pathogenesis, 595
    prognosis, 595
    treatment, 595*b*
Thermometers, 29
Thermoplasty, bronchial, 630
Thiamin, 1453*t*
Thiamine, *e*1*t*–*e*8*t*
  for alcoholic ketoacidosis, 759*b*
  deficiency of
    cardiomyopathy with, 288
    description of, 2537–2539, 2538*t*
Thiazide diuretics, 736*b*
  for hypercalciuria, 806
  for hypertension, 451*t*
  for hypervolemia, 737*t*
  hypokalemia and, 749*t*
  side effects of, 453*t*
Thiazide-induced hyponatremia, 739, 741
Thiazide-sensitive NaCl cotransport, 746–747
Thiazolidinediones
  description of, 262
  for nonalcoholic fatty liver disease, 1034*b*
  for type 2 diabetes mellitus, 1540*b*, 1541*t*
Thick ascending limb, 754.*e*1*f*, 817.*e*1*f*
Thioridazine, for psychotic disorders, 2346*t*
Thiothixene, for psychotic disorders, 2346*t*
Third nerve palsy, isolated, 2618
Thomsen disease, 2583.*e*1*t*
Thoracic actinomycosis, 2067, 2068*f*
Thoracic amebiasis, 2148
Thoracic aortic aneurysm, 437, 438*b*, 439*f*
Thoracic cysts, 564
Thoracic kyphosis, 1638
Thoracic radiation therapy, for NSCLC, 1333*b*
Thoracic radiculopathy, 2394*t*
Thoracic vertebrae
  anatomy of, 2394*f*
  description of, 2392
Thoracoabdominal aortic aneurysms, 436
Thoracoscopic surgery, video-assisted, 631
Thorax, neuroendocrine tumors of, 1566
Three-dimensional echocardiography, 238, 240*f*
Throat
  acute poisoning and, 683
  lump in, 2652
  neurologic disorders affecting, 2652, 2652*t*
  systemic diseases of, 2651
Throat disorders, 2648–2653
  clinical differentiation of, 2649*t*
  epiglottitis as, 2651
  laryngopharyngeal reflux as, 2651
  pharyngitis as, 2648
    chronic tonsillitis, 2651
    fungal infections, 2650, 2651*f*
    management of, guidelines for, 2649*t*
    mycobacterial infections, 2651
    noninfectious, 2651
    nonstreptococcal bacterial, 2648, 2649*f*
    peritonsillar abscess and deep space infections, 2649, 2650*f*
    streptococcal infections, 2648
    viral infections, 2650, 2650*f*
Thrombelastography, for liver failure, 1198
Thrombi, 2716
Thrombin, 1165
Thrombin generation tests, 1169
Thrombin time, *e*8*t*–*e*9*t*, 1166
Thromboangiitis obliterans, 468, 468*b*, 969
Thrombocytopenia, 1166, 1170–1179, 1196, 2314, 2314*b*
  clinical manifestations of, 1171
  congenital, 1179
  COVID-19 and, 1175
  definition of, 1170–1171
  diagnosis of, 1171, 1172*f*
  dilutional, 1179
  disorders that cause of, 1171*t*
  drug-induced, 1173, 1174*b*, 1174*t*
  epidemiology of, 1170–1171
  gestational, 1178
  heparin-induced, 487*b*, 1174, 1174*f*, 1175*b*, 1175*t*
  immune, 1179
  immune thrombocytopenic purpura, 1175
  in leptospirosis, 2029
  neonatal alloimmune, 1179
  pathobiology of, 1171
  peripheral blood smear of, 1070
  platelet transfusions for, 1171*b*
  post-transfusion, 1179
  in pregnancy, 1178
  psychotropic medications and, 2678*t*
  Q fever and, 2063
  sepsis causing, 1175
  thrombotic thrombocytopenic purpura, 1176–1177, 1177*b*, 1177*f*
  treatment of, 1171*b*
  vasculitis causing, 1179
Thrombocytopenic purpura, idiopathic, immunization for, 65*t*
Thrombocytosis, 1134, 1135*t*, 1136*f*, 1136*t*
  peripheral blood smear of, 1070
Thromboelastography, 1169
Thromboembolic disease
  in pregnancy, 1619*t*
  spinal cord injury and, 2388*b*
Thromboembolic prophylaxis, for atrial fibrillation, 329*b*, 331*f*, 331*t*
Thromboembolism
  atrial fibrillation and, 329
  in nephrotic syndrome, 777
  vision loss caused by, 2616*t*
Thrombolysis, 384*b*
Thrombolysis in Myocardial Infarction (TIMI) risk algorithm, 373
Thrombophilias, 476*t*, 477*f*
Thrombophlebitis, septic, 2650
Thrombopoietin, 1066
  description of, 1065
  for immune thrombocytopenic purpura, 1176*t*
Thrombopoietin receptor agents, for immune thrombocytopenic purpura, 1176*t*
Thrombosis, 1138.*e*1*t*, 1139, 1139*f*
  in acute coronary syndrome, 370
  approach to, 1165
  central venous, in parenteral nutrition, 1450
  deep vein, 482
  evaluation of, preoperative, 1169
  hepatic artery, 969
  history and physical examination for, 1166, 1166*t*, 1167*t*
  laboratory testing for, 1166
  mechanisms of, 1165
Thrombosis *(Continued)*
  mesenteric venous, 962, 963*f*, 963*t*
  oral contraceptives and, 1614
  pathogenesis of, general scheme of, 475.*e*1*f*
  after PCI, 396
  portal vein, 968, 968*b*
  postoperative, 481
  prototypical systemic inflammatory states and, 481*t*
  in superficial veins, 482
  superior mesenteric artery, 960
  traveler's, 1889
Thrombosis threshold, 482.*e*3*f*
Thrombospondin type-1 domain containing 7A, 779
Thrombotic coronary artery disease, 381*t*
Thrombotic disorders, hypercoagulable states, 475
Thrombotic endocarditis, nonbacterial (marantic), 296
Thrombotic microangiopathies, 728, 789, 2313
Thrombotic thrombocytopenic purpura, 728, 1176, 1177*b*, 1177*f*
Thrombus formation, in acute coronary syndrome, 371
Thrush, 2090, 2090*f*
Thymic stromal lymphopoietin (TSLP), 152
Thymocytes, 204
Thymoglobulin, in renal transplantation, 845*t*
Thymus neuroendocrine neoplasm, 1567
Thyroglobulin (Tg), *e*1*t*–*e*8*t*
Thyroglobulin antibodies, *e*1*t*–*e*8*t*
Thyroid acropachy, 1822–1823
Thyroid cancer, 1517
  in adolescents, 111
  anaplastic, 1519
  medullary, 1518
  papillary and follicular, 1517
  primary thyroid lymphoma, 1519
Thyroid disease/disorders, 1504–1505
  arthritis associated with, 1822
  clinical manifestations of, 1505
  diagnosis of, 1505
  differential diagnosis of, 1505, 1506*t*
  goiter, 1515
  in HIV, 2317
  hyperthyroidism, 1509
  hypothyroidism, 1506
  imaging for, 1505
  laboratory testing for, 1505, 1506*t*
  pathobiology of, 1504
  physical examination for, 1505
  in pregnancy, 1619*t*, 1624, 1625*b*
  preoperative evaluation, 2665
  psychotropic medications and, 2678*t*
  screening for, 55
Thyroid gland, 1504–1519
  abnormal function, 265*b*
  examination of, 30
  follicular cells, 1504, 1504.*e*1*f*
Thyroid hormone
  endocrine diseases caused by, 1475*t*
  set points of, 1505, 1505.*e*1*f*
  synthesis and secretion of, 1504, 1504.*e*1*f*
  transport and metabolism of, 1504, 1504.*e*3*f*
Thyroid nodules, 1515
  diagnosis of, 1515–1516, 1516*f*
  fine-needle aspiration biopsy for, 1516, 1516*t*
  imaging for, 1516
  treatment for, 1517*b*
Thyroid-stimulating hormone (TSH), 1505
  in amenorrhea, 1599
  central hypothyroidism, 1497, 1497*b*
  function of, 1497
  hypothalamic disease effects on, 1476, 1481
  insufficiency tests of, 1484*t*
  tests of, 1488*t*
  tumors that secrete, 1497, 1497*b*, 1497*t*
Thyroid storm, 1511*b*
Thyroiditis, 1513
  drug-induced, 1514
  infectious, 1514
  postpartum, 1513
  sclerosing (Riedel), 1515
  sporadic painless, 1513
  subacute (de Quervain), 1513
Thyrotoxicosis, 1509, 2564*t*
  assessment of, 1510*f*
  hypercalcemia and, 1658
  radiographic evaluation of, 1511*t*
Thyrotropin (hTSH), *e*1*t*–*e*8*t*
Thyrotropin-releasing hormone (TRH)
  description of, 1476, 1477*f*
  prolactin secretion regulated by, 1490–1491
Thyroxine, 1497, 1504
  free (FT_4), *e*1*t*–*e*8*t*
  for hypothyroidism, 1508*b*, 1508*t*
  total (T_4), *e*1*t*–*e*8*t*
Thyroxine-binding globulin (TBG), *e*1*t*–*e*8*t*
Tic douloureux. *See* Trigeminal neuralgia
Ticagrelor, 387*t*, 506*t*, 507
  for acute coronary syndrome, 375*t*
  for acute STEMI, 384*b*, 391*t*
Ticarcillin/clavulanate, dosage of, 1895*t*
Tick-bite hypersensitivity reactions, 2025
Tick-borne encephalitis, 2276*t*, 2282, 2282*b*
  in travelers, 1891*t*
Tick-borne relapsing fever, 2027
Tick-borne rickettsioses, 2054, 2055*t*, 2057, 2058*b*, 2058*f*
Tick-borne viruses, 2266
Tickover, 198
Ticks
  description of, 710
  as vectors of zoonotic disease, 2064
  viruses caused by, 2266
Tics
  clinical manifestations of, 2494
  diagnosis of, 2494
  epidemiology of, 2494
  etiology of, 2494*t*
  pathobiology of, 2494
  Tourette syndrome causing, 2494–2495
Tidal volume (TV), 530, 652*t*
Tigecycline
  Acinetobacter, 1974*b*
  dosage of, 1895*t*
  for nontuberculous mycobacterial disease, 2046*t*
Tilt table testing, 308
Time to event data, 37
Time Up and Go approach, 118
Timolol, 451*t*
Tin, 88*t*
Tinea capitis, 2747*t*
Tinea corporis, 2686.*e*2*f*, 2687.*e*3*t*, 2710
Tinea cruris, 2710, 2711*f*
Tinea manuum, 2710
Tinea pedis, 2710
Tinea versicolor, 2687.*e*3*t*, 2692*t*, 2711, 2711*f*
Tinel sign, 2578
Tinidazole (Tindamax), 2115
  for amebiasis, 2150*t*
  for amebic liver abscess, 1025*b*
  for giardiasis, 2112*t*, 2145*b*
  for intestinal amebiasis, 2112*t*
  for trichomoniasis, 2112*t*, 2154*b*
  for urethritis, 1880*t*
Tinnitus, 2643, 2643*b*, 2643*f*
Tinzaparin, 503*t*
  for venous thromboembolism, 1624*t*
Tiotropium bromide, 553*t*
Tipranavir, 2301*t*
TIPS. *See* Transjugular intrahepatic portosystemic shunt
Tirofiban, 375*t*, 387*t*, 506*t*, 508
Tirzepatide, for type 2 diabetes mellitus, 1540*b*, 1541*t*
Tisagenlecleucel (Kymriah), 1215*t*
Tissue cestode (cyst) infection, 2159, 2160*b*
Tissue damage, mediators of, 1162–1163
Tissue Doppler, 236, 236.*e*1*f*
Tissue engineering, 174
Tissue factor (extrinsic) pathway, 1165
Tissue hypoxia, in septic shock, 671
Tissue injury, 191–196
Tissue plasminogen activator, for frostbite, 474*b*
Tissue repair, 191
Tissue-resident macrophages, 182
Tissue-specific stem/progenitor cells, 172
TLC. *See* Total lung capacity
TLR. *See* Toll-like receptor; Toll-like receptors
TLR-4. *See* Toll-like receptor 4
TLRs. *See* Toll-like receptors
TMP-SMX. *See* Trimethoprim-sulfamethoxazole
TNF-α. *See* Tumor necrosis factor-α
TNF receptor-associated death domain (TRADD), 185
TNK-t-PA. *See* Tenecteplase
Tobacco history, 28
Tobacco smoking, 55, 2349
  behavioral treatment for, 2350*t*

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Tobacco smoking *(Continued)*
cancer and, 1244
chronic pancreatitis and, 973
clinical manifestations of, 2349
definition of, 2349
diagnosis of, 2349
epidemiology of, 2349
nicotine replacement therapy for, 2350*b*, 2351*t*
pathobiology of, 2349
pharmacologic treatment for, 2350*b*, 2351*t*
prevention of, 2352
prognosis for, 2352
psychosocial treatment for, 2350*b*, 2350*t*
treatment of, 2350*b*
in women, medications for, 1608*t*
Tobramycin, *e10t–e11t*
for bacterial meningitis, 2518*t*
for bronchiectasis, 561*b*
dosage of, 1895*t*
for eye infection, 2605*t*
for pulmonary infection, 1970*b*
for pyelonephritis and urosepsis, 1877*t*
in renal failure, 129.*e1t*
Tocilizumab (Actemra)
for COVID-19, 2217
description of, 151, 151*t*
for giant cell arteritis, 1803*b*, 2383
for rheumatoid arthritis, 1756*t*
for total knee arthroplasty, 1830.*e1t*
α-Tocopherol, 1453*t*
TOF. *See* Tetralogy of Fallot
Tofacitinib (Xeljanz), 153*t*
for inflammatory bowel disease, 945*b*, 946*t*
for psoriatic arthritis, 1765*b*
for rheumatoid arthritis, 1755*b*, 1756*t*
for total knee arthroplasty, 1830.*e1t*
Togaviridae, 2224, 2274, 2278–2279, 2283
Tolbutamide, for type 2 diabetes mellitus, 1541*t*
Tolcapone, for Parkinson disease, 2487*t*
Tolerable upper limits, 1451
Tolerance, 129
immune system and, 190–191
Tolerance signatures, 207
Toll-like receptor 4 (TLR-4), activation of, 1942
Toll-like receptors (TLR), 183–185, 191, 1801
Tolmetin, for rheumatoid arthritis, 1756*t*
Tolterodine, 824*t*
Tolvaptan
for autosomal dominant polycystic kidney disease, 812*b*
for hypervolemia, 737*t*
Tonicity, 737
Tonsillitis
bacterial, 2649*t*
chronic, 2651
Topical analgesics, for skin diseases, 2699
Topical corticosteroid, 474*b*
Topical cytotoxic drugs, for skin diseases, 2700
Topical decolonization therapy, for health care-associated infections, 1867
Topical podophyllin, for anal warts, 982*b*
Topical sphincter relaxants, for anal fistula, 980*b*
Topical therapy, principles of, 2697
Topiramate
for obesity, 1467*b*
for seizures, 2434*t*
Topotecan (Hycamtin), 1215*t*
Torisel. *See* Temsirolimus
Torsades de pointes, 302, 336*f*
diagnosis of, 335
pathobiology of, 334
treatment of, 338*b*
Torsemide, 451*t*, 737*t*
Toscana virus, 2276*t*
Total energy, dietary guidelines for, 57.*e3t*
Total hip replacement, 1827–1828, 1828*f*
Total iron-binding capacity, 1457*t*
Total joint arthroplasty, 1827–1829
Total knee replacement, 1828, 1828*f*, 1829*f*, 1830.*e1t*
Total lung capacity (TLC), 528
Total peripheral resistance (TPR), 226
Total protein, *e1t–e8t*
Tourette syndrome, 2494, 2494*b*
Touton cells, 1157
Toxic adenoma, 1511*t*
Toxic epidermal necrolysis, 1847, 2695*f*, 2727, 2728*f*
prognosis of, 2728
treatment of, 2728*b*
Toxic erythemas, 2740
Toxic granulation, peripheral blood smear of, 1071*f*
Toxic megacolon
enteric infections and, 1870*t*
in ulcerative colitis, 945*b*
Toxic multinodular goiter
radiographic evaluation of, 1511*t*
treatment for, 1511*b*
Toxic myopathies, 2587, 2587*t*
Toxic neuropathy, 2313*b*, 2568*t*, 2578
Toxic pneumonitis, acute, 589
Toxic shock syndrome, 2695*f*, 2712
clinical manifestations of, 2712
influenza and, 2200
staphylococcal, 1906–1908, 1908*b*
streptococcal, 1914, 1915, 1915*t*
treatment for, 2712*b*
Toxic shock syndrome toxin-1, 1906
Toxicant-induced bilateral miosis, 683, 684*f*
Toxicants, 682, 683*t*
removed by hemodialysis, 698*t*
Toxicology, reference intervals, *e1t–e8t*
Toxidromes, 682, 683*t*
Toxin(s)
acute pancreatitis and, 970, 970*t*
primary testicular hypogonadism caused by, 1583
vitamin levels affected by, 1459
Toxin-mediated disease
diphtheria and, 1934
Staphylococcus aureus causing, 1906–1908
Toxocara canis, 2174
Toxocara cati, 2174
Toxocara spp., 1026*t*, 2174
Toxocariasis, 2174
Toxoid, administration of, 64
Toxoplasma gondii, 1026*t*, 2136, 2137*f*
prophylaxis for, 2309*t*
retinitis caused by, 2606
Toxoplasmic encephalitis, 2136, 2139, 2139*f*
Toxoplasmic retinitis, 2606
Toxoplasmosis, 2136–2141
clinical manifestations of, 2137–2138, 2138*t*
congenital infection in, 2137–2138
definition of, 2136–2141
diagnosis of, 2138–2139, 2138*t*
epidemiology of, 2136
human pathology findings of, 2136–2137
in immunocompetent patients, 2137, 2139
in immunocompromised patients, 2137, 2139, 2141
after organ transplantation, 2137, 2141
pathobiology of, 2136–2137
pathogen that causes, 2136, 2137*f*
in patients on immunosuppressive medications, 2137
in patients with HIV/AIDS, 2137
in pregnant women, 2140*b*
prevention of, 2140–2141
in primary infection, 2140–2141
prognosis of, 2141
reactivation disease, 2141
serologic tests for, 2138*t*
treatment of, 2112*t*, 2140*b*, 2140*t*
TPMT gene, 160*t*
Trabectedin (Yondelis), 1215*t*
Trace elements, 1451, 1457*t*
Trace metals, chronic poisoning of, 101
aluminum, 101*t*, 105, 105*b*
arsenic toxicity, 103
bismuth, 101*t*, 102*t*, 105, 105*b*
cadmium toxicity, 104
cobalt, 106, 106*b*
lead toxicity, 101
manganese, 101*t*, 107, 107*b*
mercury toxicity, 102
silver, 106, 106*b*, 106*f*
thallium, 106, 106*b*
zinc, 101*t*, 106, 107*b*
Tracheal plateau, 529*f*, 532
Tracheal stenosis, 532
flow-volume curve of, 529*f*
Tracheitis, 605, 605.*e1f*, 606*b*
Tracheobronchial amyloidosis, 1310
Tracheobronchitis, 700*b*
H. influenzae caused by, 1953
Tracheoesophageal fistulas, 913
Tracheostomy tubes, *Acinetobacter* in, 1973
Trachoma
clinical manifestations of, 2010
diagnosis of, 2010
epidemiology of, 2009–2010
prevention of, 2010
Traction alopecia, 2751, 2751*f*
Traction bronchiectasis, 575, 575.*e1f*
TRADD. *See* TNF receptor-associated death domain
Traditional Chinese medicine, 154
Tramadol, 136*b*, 138*t*, 139*t*
Trametinib (Mekinist), 1215*t*, 1251*t*
for melanoma, 1394*t*
Trandolapril, 266*t*, 451*t*
Trandolapril/verapamil, 451*t*
Tranexamic acid, for von Willebrand disease, 1183*b*
Trans fats, 57
dietary guidelines for, 57.*e3t*
Trans-sulfuration, 479.*e1f*, 1425*t*
Transabdominal ultrasound, 1050, 1051*f*
Transbronchial needle aspiration, 1331
Transcobalamin, 1426*t*
Transcortin (corticosteroid-binding globulin), *e1t–e8t*
Transcranial Doppler (TCD), strengths and weaknesses of, 2373*t*
Transcription activator-like effector nucleases (TALENs), 166, 178
Transcutaneous bilirubinometry, 994
Transcutaneous carbon dioxide measurement, 640
Transcutaneous electrical nerve stimulation (TENS), for fibromyalgia, 1819*b*
Transdermal nicotine patch, 2350*b*, 2351*t*
Transdiaphragmatic pressure, 620
Transduction, 175
Transepithelial transport, 730
Transesophageal echocardiography, 238, 238*t*, 239*f*
in aortic dissection, 440, 440*f*, 441*f*
in infective endocarditis, 416–417
Transfer factor, 530
Transferrin, *e1t–e8t*
Transfusion(s), 1199–1206
ABO/D compatibility of, 1201
adverse effects of
allergic transfusion reaction, 1202, 1202*b*
Babesia transmission, 1203
bacterial contamination, 1203
delayed hemolytic transfusion reaction, 1202
delayed serologic transfusion reaction, 1202
febrile nonhemolytic transfusion reaction, 1202
hepatitis B virus transmission, 1203
hepatitis C virus transmission, 1203
human T-cell lymphotropic virus, 1203
hypotensive transfusion reactions, 1202
post-transfusion purpura, 1203
septic reactions, 1203
syphilis transmission, 1203
transfusion-associated circulatory overload, 1202
transfusion-associated dyspnea, 1202
transfusion-related acute lung injury, 1202, 1202*b*
Trypanosoma cruzi transmission, 1203
West Nile virus transmission, 1203
Zika virus transmission, 1203
blood components of, 1199, 1199*t*
cryoprecipitate, 1199*t*, 1200, 1205
cytomegalovirus transmission via, 1200
granulocytes, 1200, 1205
for hemoglobinopathies, 1206
indications for, 1204, 1204*t*
massive, 1205
patient blood management, 1206
plasma, 1199*t*, 1200, 1204, 1204*t*
platelet
alloantibodies, 1171*b*
complications of, 1171*b*
components, 1200
indication, 1204, 1204*t*
prophylactic, 1171*b*
for thrombocytopenia, 1171*b*
red blood cell, 1199
cryopreservation of, 1200
indications for, 1204, 1204*t*
irradiation for, 1200, 1205
Transfusion(s) *(Continued)*
leukoreduction, 1205
modification of, 1199, 1205
pathogen reduction in, 1200, 1205
for septic shock, 673*b*
safety of, 1201, 1201*t*
for sickle cell disease, 1114*b*, 1206
whole blood, 1199
Transfusion-associated circulatory overload, 1202
Transfusion-associated dyspnea, 1202
Transfusion-associated graft-*versus*-host disease, 1203
Transfusion reactions
allergic, 1202, 1202*b*
delayed hemolytic, 1202
febrile nonhemolytic, 1202
hemolytic, 1092
hyperhemolytic, 1203
hypotensive, 1202
Transfusion-related acute lung injury (TRALI), 598, 599*b*, 1200, 1202, 1202*b*
Transgender, 1575
Transgender medicine, 1577–1580
clinical manifestations of, 1577
definition of, 1577–1580, 1577*t*
diagnosis of, 1577
epidemiology of, 1577
pathobiology of, 1577
prognosis for, 1580
treatment in, 1578*b*
Transgender men
hormone therapy for, 1578*b*, 1578*t*
surgeries for, 1578*b*
Transgender women
hormone therapy for, 1578*b*, 1579*t*
surgeries for, 1578*b*
Transient aplastic crisis, 2234
Transient elastography, for hepatic fibrosis, 990
Transient global amnesia, 2408
Transient incontinence, 827, 828*t*
Transient infection, Whipple disease and, 2070
Transient ischemic attack
as arterial thrombotic complications, 481
definition of, 2464
pathobiology of, 2464
prognosis of, 2473
secondary prevention after, 2473
stroke after, 2473
Transient neonatal myasthenia, 2589*t*
Transient receptor potential vanilloid 5 (TRPV5), 1654
Transjugular intrahepatic portosystemic shunt (TIPS), 1041*f*
Transjugular pressure, measurement of, 990
Translocator protein, 1581, 1581.*e1f*
Transmembrane cytoplasmic protein 43 gene, 288
Transplantation
bone marrow, for multiple myeloma, 1299*b*, 1301*t*
for bronchiectasis, 561*b*
Chagas disease and, 2128
of ex vivo differentiated human pluripotent stem cells, 173
heart-lung transplantation, 633
liver, 1044, 1044*f*, 1045*f*
for acute liver failure, 1044
for chronic liver failure, 1044
coagulation system and, 1043
complications of, 1047, 1047*f*
contraindications to, 1046*t*
for hepatocellular carcinoma, 1045
immunosuppression for, 1048, 1048*t*
indications for, 1044, 1045*f*
infectious complications of, 1047, 1048*f*
listing for, 1046, 1048*t*
long-term management for, 1049
metabolic disorders associated with, 1045
preoperative medical assessment for, 1046
preoperative psychosocial assessment for, 1046
procedure, 1046, 1046*f*, 1047*f*
recurrent hepatitis C after, 1014*b*
rejection in, 1048, 1048*t*
selection for, 1045, 1046*t*
surgical complications of, 1047
for Wilson disease, 1437*b*
lung, 632
bilateral, 632

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Transplantation *(Continued)*
complications of, 633
contraindication for, 632*t*
decision guide for, 632*t*
heart-lung transplantation, 633
indications for, 632, 632*t*
living donor lobar transplantation, 633
post-transplantation issues, 633
prophylaxis after, 633
recipients, evaluation of, 633
single-lung, 633
survival estimates, 634.*e1f*
types of procedures, 632
Transplantation immunology, 203–208
antigens in, 203, 204*t*
major, 1*t*–2*t*, 203, 204*t*, 204.*e1f*, 204.*e2f*, 204.*e2t*
minor, 205
other, 205
definition of, 203
graft-*versus*-host disease in
mechanisms of, 205
prevention of, strategies, 206, 206.*e2f*, 206.*e1t*
rejection in
mechanisms of, 205
prevention of, strategies, 207
Transportasome, 1810
Transposition of the great arteries
complete, 354, 355.*e2t*
congenitally corrected transposition, 354
Transsphenoidal hypophysectomy, 1487*b*
Transthoracic cardioversion and defibrillation, 340
Transthoracic echocardiography, 238, 238*t*, 416
Transthyretin (prealbumin), *e1t*–*e8t*
Transthyretin amyloid cardiomyopathy, 1309*b*
Transudates, 624–625
Transverse myelitis, 2406, 2508, 2509*b*, 2615
incomplete, 2500
Mycoplasma pneumoniae in, 2007
Transverse relaxation time (T2), in MRI, 1720, 1721*f*
Transverse sinuses, 2459
Trantas dots, 1674
Tranylcypromine, for depression, 2340*t*
TRAPS. *See* Tumor necrosis factor receptor-associated periodic syndrome
Trastuzumab (Herceptin), 167, 1215*t*, 1251*t*
for breast cancer, 1369*b*
cardiomyopathy due to, 288
for gastric adenocarcinomas, 1341*b*
Trastuzumab deruxtecan, 1251*t*, 1341*b*
Trastuzumab emtansine, 150, 1251*t*
Trauma, 381*t*
acute pancreatitis and, 970, 970*t*
causing subarachnoid hemorrhages, 2478
hypothalamic diseases associated with, 1480
hypothermia, 681
medical aspects of, 698
ocular, 2603
penetrating, pathogens and empirical therapy for, 2526*t*
severe mental illness and, 2683*t*
thrombosis and, 481
Traumatic brain injury, 2385
biomarkers for, 2387
clinical manifestations of, 2386, 2386*t*
diagnosis of, 2386–2387, 2386*t*
epidemiology of, 2385
imaging for, 2387, 2387*f*, 2387*t*
mild, 2388*b*, 2389*t*, 2390
moderate to severe, 2388*b*, 2390
pathobiology of, 2385
primary injury phase of, 2385
prognosis of, 2390
secondary injury phase of, 2386, 2386.*e1f*
treatment for, 2388*b*, 2389*t*
Traumatic pericarditis, 424*t*
Traumatic spinal epidural hematoma, 2391–2392, 2392, 2392*f*
Traumatic ulcers, 2621*t*
Travel
approach to the patient before and after, 1885–1891
travel-related vaccines, 1886*t*, 1887
fever associated with, 1890*t*
heart failure in, 265*b*
problems of, non-infectious, 1889
Travel-related vaccines, 1886*t*, 1887
Travelers
altitude illness in, 1889
blood-borne pathogen exposure risks, 1889
Travelers *(Continued)*
Chikungunya virus in, 1888, 1889.*e1t*, 1890*t*
Dengue fever in, 1888, 1889.*e1t*, 1890*t*
enteric fever in, 1885, 1889.*e1t*, 1890*t*
food precautions for, 1889
gastrointestinal diseases in, chronic, 1891*t*
HIV infection in, 1889
immunization for
cholera, 1886*t*, 1887
description, 1885
hepatitis A, 1886, 1886*t*, 1887
hepatitis B, 1886, 1886*t*, 1887
influenza, 1886*t*, 1887
Japanese encephalitis, 1886*t*, 1887
meningococcus, 1886*t*, 1887
polio, 1886*t*, 1887
rabies, 1886*t*, 1887
tetanus/diphtheria/acellular pertussis, 1886
typhoid, 1886*t*, 1887
update of, 1886
varicella, 1886, 1886*t*
verification of, 1886
yellow fever, 1886*t*, 1887
jet lag in, 1889
malaria chemoprophylaxis in, 1887, 1890*t*
malaria in, 2118, 2122
post-travel care for, 1889–1891
pretravel consultation for, 1885*t*
preventive behaviors for, 1888–1889
respiratory infections in, prevention of, 1889
SARS-CoV 2 in, 1888
sexually transmitted infections in, 1889
skin diseases in, protection against, 1889
swimming by, 1889
thrombosis in, 1889
water exposure by, 1889
water precautions for, 1889
Zika virus in, 1888, 1890*t*
Traveler's diarrhea, 925–926, 1888, 1888*t*
Escherichia coli and, 1961
Trazodone, for depression, 2340*t*
Treadmill testing, 362
Treanda. *See* Bendamustine
Treatment-induced neuropathy of diabetes, 2577
Treatment-related tumor flare, 1369*b*
TRECs. *See* T-cell receptor excision circles
TREM. *See* Triggering receptors expresses by myeloid cells
TREM2 gene, 2415
Trematode
clonorchiasis, 2166
fascioliasis, 2165, 2166*t*, 2168
infections, 2163
opisthorchiasis, 2166
paragonimiasis, 2167
Tremor
action, 2489
clinical manifestations of, 2489
definition of, 2489–2490
differential diagnosis of, 2490*t*
dystonic, 2493
essential, 2490
head, 2489
kinetic, 2489
physiologic, enhanced, 2489
postural, 2489
resting, 2484, 2489
vocal, 2652
Trench fever, 2000, 2001*f*, 2003*b*, 2003*t*, 2059
Trench foot, 680
Treponema carateum, 2021
Treponema pallidum, 2014, 2649
chancroid and, 1951
sexually transmitted anorectal diseases and, 983
Treponemal tests, 2018
Tretinoin, 2698
TRH. *See* Thyrotropin-releasing hormone
Triad syndrome, 821
Triamterene, 451*t*
for hypervolemia, 736*b*, 737*t*
Triamterene/HCTZ, 451*t*
Triazolam, for anxiety disorders, 2344*t*
Trichiasis, 2601
Trichinella spiralis, 2175
Trichinellosis, 2174
definition of, 2174–2175
diagnosis of, 2175
epidemiology of, 2175
pathobiology of, 2175, 2175*f*
prevention of, 2175
prognosis for, 2175
in travelers, 1889.*e1t*
treatment of, 2175*b*
Trichodynia, 2748
Trichodysplasia spinulosa polyomavirus, 2228*t*, 2232
Trichoepitheliomas, 2730
Trichomonas vaginalis, 1879, 1882, 2154, 2154*f*
Trichomoniasis, 1882, 1883*b*, 2154, 2154*b*
Trichostrongylus spp., 2170*t*, 2173
Trichotillomania, 2747*t*, 2749, 2750*f*
Trichrome staining, for enteric infection, 1870*t*
Trichuriasis, 2171, 2172*b*
Trichuris trichiura, 2170*t*, 2172
Triclabendazole, for helminthic diseases, 2112*t*
Tricuspid atresia, 354
Tricuspid regurgitation, 410–411
definition of, 410–411
diagnosis of, 411
prognosis of, 411*b*
treatment of, 265*b*, 411*b*
Tricyclic antidepressants (TCAs)
for chronic pain, 138*t*
for depression, 2340*t*
for fibromyalgia, 1819*b*
screening for, 689*t*
Trifluoperazine, for psychotic disorders, 2346*t*
Trigeminal autonomic cephalalgias, 2381
Trigeminal neuralgia, 2384, 2384*b*, 2578–2579
Trigeminocervical complex, 2376
Trigger finger, 1745, 1745*b*, 1746*f*
Triggering receptors expresses by myeloid cells (TREM), 183
Triglycerides, *e1t*–*e8t*, 970, 1405, 1405*f*, 1405.*e1f*, 1410.*e1t*
Triiodothyronine, 1497, 1504
free (FT_3), *e1t*–*e8t*
total (T_3), *e1t*–*e8t*
Trimethobenzamide, for nausea and vomiting, 863*t*
Trimethoprim
dosage of, 1895*t*
mechanism of action, 1895*t*
resistance mechanisms, 1893*t*
for urinary tract infection, 1876*t*, 1877*t*
Trimethoprim-dapsone, for *Pneumocystis* pneumonia, 2106*t*
Trimethoprim-sulfamethoxazole (TMP-SMX)
for bacterial meningitis, 2518*t*
for cellulitis, 2740*b*
for HIV/AIDS, opportunistic infections associated with, 2309*t*
for nocardiosis, 2072–2073, 2074*b*
for plague, 1991*b*, 1992*t*
for *Pneumocystis* pneumonia, 2106*t*, 2108*t*
for *Stenotrophomonas maltophilia*, 1975*b*
for *Streptococcus pneumoniae* pulmonary infections, 1912.*e1t*
toxicities of, 1901*t*
for toxoplasmosis, 2112*t*, 2140*b*, 2140*t*
for urinary tract infection, 1876*t*, 1877*t*
Tripeptide thyrotropin-releasing hormone (TRH), 1505
Triple-negative breast cancer, 1369
Triple phosphate stones, 804
Tripod sign, 639, 639.*e2f*
Trisenox. *See* Arsenic trioxide
Trismus, 1928
Trisomy 21. *See* Down syndrome
Trisomy X, 1600
Trochanteric bursitis. *See* Greater trochanter pain syndrome
Trochlear nerve palsy, 2618
Trodelvy. *See* Sacituzumab govitecan-hziy
Trogocytosis, amebic, 2146
Tropheryma whipplei, 417*t*, 1821, 2069
Trophozoites, 2141
Tropical endomyocardial fibrosis, 296
Tropical fever virus, 2275*t*
Tropical myositis, 1903
Tropical sprue, 937, 1870*t*
Troponin(s)
elevated, 383, 383*t*
in heart failure, 260
measured by a highly sensitive assay (hs-cTn), 260.*e1t*
postoperative, 2676
Troponin-I, *e1t*–*e8t*
Troponin-T, *e1t*–*e8t*
Trospium, 824*t*
Trousseau syndrome, 1170, 1341, 1355, 1648
TRPV5. *See* Transient receptor potential vanilloid 5
True secretory diarrhea, 930*f*, 939
Truncal radiculopathy, 2577
Trunk, disorders of, occupational and environmental, 86*t*
Truseltiq. *See* Infigratinib
Trypanosoma brucei, 2126
Trypanosoma brucei gambiense, 2124
Trypanosoma brucei rhodesiense, 2123–2124, 2124, 2125*f*
Trypanosoma cruzi, 1203, 2065*t*, 2126, 2127*f*
Trypanosomiasis, 2115
in travelers, 1891*t*
treatment of, 2112*t*
Tryptase, serum, 1675, 1693
α-Tryptasemia, hereditary, 1693
TSH. *See* Thyroid-stimulating hormone
TSH-secreting pituitary adenoma, 1497
radiographic evaluation of, 1511*t*
TSH-suppressive levothyroxine, for thyroid cancer, 1517*b*
TSHomas, 1497
TSLP. *See* Thymic stromal lymphopoietin
Tubal pregnancy, 1604
Tube feeding, 1445*b*
Tuberculin skin test, 2039
Tuberculoid leprosy, 2048, 2049*t*
Tuberculoma, in travelers, 1889.*e1t*
Tuberculosis (TB), 2031–2044, 2621*t*
active, 2039, 2040*b*
cavitary, 2036*f*
central nervous system, 2037
characteristics of, 2270*t*
clinical manifestations of, 2034–2038
cystic fibrosis *versus*, 558
definition of, 2031–2043
diagnosis of, 2038–2040
drug-resistant, treatment of, 2040*b*
epidemiology of, 2032–2033, 2032*f*
extrapulmonary, 2035, 2040, 2040*b*
genitourinary, 2037
human immunodeficiency virus and, treatment of, 2040*b*
immunologic manifestations of, 2038
intestinal, 2037
latent, 2034
skin testing for, 2038
treatment of, 2040*b*, 2041*t*
lymphadenitis, 2037
miliary, 2035, 2037*f*
ocular involvement of, 2606
osteoarticular, 2037, 2038*f*
outcomes after, spectrum of, 2035*f*
pathobiology of, 2033, 2034*f*
pathogen of, 2031–2032
pericarditis, 2037
peritonitis, 2037
pleural, 2035, 2036*f*
prevention of, 2043
primary, 2034, 2036*f*
prognosis of, 2043
pulmonary
clinical manifestations of, 2034, 2036*f*
diagnosis of, 2039
risk factors for, 2033*t*
in travelers, 1889.*e1t*
treatment of, 2040*b*, 2041*t*, 2042*t*, 2043*t*
weight loss and, 860*t*
Tuberculous arthritis, 1808, 1808*b*
Tuberculous meningitis
cerebrospinal fluid findings in, 2374*t*
in travelers, 1889.*e1t*
Tuberculous pericarditis, 426*t*, 431
Tuberculous peritonitis, 957
Tuberculous pleural effusion, 626, 626*b*
Tuberous sclerosis, 583, 809*t*, 814, 814*b*
ash-leaf macule of, 2692*t*
Tuberous sclerosis complex, 2549, 2549*b*, 2550*t*, 2551*f*, 2551*t*
Tubular adenomas, 1349
Tubular cell cast, 722
Tubular necrosis, 720
Tubulointerstitial disease, 720, 728, 728*t*
autosomal dominant, 791
chronic kidney disease and, 833*t*
interstitial nephritis. *See* Interstitial nephritis
Tubulointerstitial nephritis, with uveitis syndrome, 793
Tubulointerstitial nephropathy, in human immunodeficiency virus infection, 793
Tubulovillous adenomas, 1349
Tucatinib (Tukysa), 1215*t*
Tukysa. *See* Tucatinib
Tularemia, 99, 1985–1988
characteristics of, 2270*t*
clinical manifestations of, 99, 1986–1987

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Tularemia *(Continued)*
definition of, 1985–1988
diagnosis of, 99, 1987
differential diagnosis of, 1987
epidemiology of, 1986, 1986.e1*f*
glandular disease caused by, 1986
oculoglandular disease caused by, 1986
oropharyngeal disease caused by, 1986
other clinical presentations, 1987
pathobiology of, 1986
pathogen of, 1985–1986
pneumonic disease caused by, 1986–1987
prevention of, 1988
prognosis for, 99*b*, 1988
treatment of, 99*b*, 1987*b*
typhoidal disease caused by, 1986
ulceroglandular disease caused by, 1986, 1987*f*
vectors of, 1986
Tumor(s)
cardiac, 296, 297*f*, 297*t*
of hypothalamus, 1479
intracavitary, 297
intramyocardial, 298
myocardial, 296
orbital, 2613
of skin, 2729, 2729*t*
Tumor-associated hypoglycemia, 1237, 1555
Tumor genetics, drug development and, 133
Tumor-induced osteomalacia, 1649
Tumor lysis syndrome, 1240, 1240*b*, 1262
Tumor mutation burden, 1249
Tumor necrosis factor-α (TNF-α), 151, 151*t*, 184–185
Tumor necrosis factor (TNF) inhibitors, for rheumatoid arthritis, 1757*t*
Tumor necrosis factor receptor-associated periodic syndrome (TRAPS), 1731*t*, 1733*t*, 1734, 1734*b*
Tumor plop, 298
Tumor suppressor genes, 1247
DNA alterations in, 1247, 1248*f*
in lung cancer, 1330
Tungiasis, cutaneous or mucocutaneous, in travelers, 1889.e1*t*
Tuning fork tests, 2641
Turcot syndrome, 1348
Turf toe, 1748, 1748*b*
Turner syndrome, 347, 967, 1574, 1600
TV. *See* Tidal volume
24-hour urine, collection of, for Cushing disease, 1494
Tykerb. *See* Lapatinib
Tylosis palmaris et plantaris, 1337
Tympanic membrane thermometer, 33
Type I interferon-associated autoinflammatory diseases, 1735
Type II error, 36
Typhlitis, description of, 1860
Typhoid fever
azithromycin for, 1979*b*
characteristics of, 2270*t*
immunization for, 66*t*, 83
vaccine, for traveler, 1886*t*, 1887
Tyrosine, catecholamine synthesis from, 1529
Tyrosine kinase inhibitors
cardiomyopathy due to, 288
for chronic myeloid leukemia, 1274*b*
toxicities of, 1274*b*, 1275*t*
Tyrosinemia
type I, 816*t*, 1398*t*, 1402*t*
type II, 1398*t*, 1402*t*
Tysabri. *See* Natalizumab
Tzanck smear, 2690

U

U wave, 228
Ublituximab (Briumvi), for multiple sclerosis, 2505*t*
"Ugly duckling" sign, 1391
UGT1A1 gene, 160*t*, 995
Ukoniq. *See* Umbralisib
Ulcer(s), 2738
anastomotic, 913
chancroid and, 1951
diabetic foot, 1892*t*
marginal, 913
pressure, in older adults, 114
Ulceration, 2687.e4*t*
Ulcerative colitis
acute flare of, 945*b*
algorithm for, 948*f*
budesonide for, 945*b*, 946*t*
budesonide MMX for, 945*b*
clinical characteristics of, 942*t*
colectomy for, 945*b*
colon cancer in, 945*b*
complications of, 945*b*
definition of, 941
diagnosis of, 943
dysplasia in, 945*b*
early, 942
endoscopy of, 944–945, 944*f*
epidemiology of, 941
extensive, 945*b*
maintenance therapy for, 945*b*
medical management of, 945*b*
medical therapy for, 945*b*
pathology of, 942
prognosis for, 950
radiology of, 945
severe, 945*b*
surgical therapy for, 945*b*
symptoms of, 943
Ulcerative jejunoileitis, 955
Ulcerative lesions, of granuloma inguinale, 2004, 2004*f*
Ulceroglandular disease, 1986, 1987*f*
Ulesfia lotion, 711*b*
Ultradian rhythms, 1478
Ultrasonography, 520
abdominal, for acute pancreatitis, 971
for abdominal pain, 857–858
for acute kidney injury, 726, 726*f*
for acute pancreatitis, 970
for autosomal dominant polycystic kidney disease, 811–812, 811*f*
for chronic kidney disease, 837
compression, 484, 485*f*
Doppler, 236
continuous-wave, 236
pulsed, 236
endobronchial, 630, 630.e2*f*
endoscopic, 876, 974
for gallbladder cancer, 1054
in gastroenterology, 869, 869*f*, 870*f*
for kidney stones, 805
for liver disease, 990
for pelvic inflammatory disease, 1949
for rheumatic disease, 1718, 1719*f*, 1720*f*
strengths and weaknesses of, 2373*t*
testicular, for testicular cancer, 1383
for thyroid disease, 1505
Ultrasound elastography (USE), 1720
Ultraviolet radiation, 95
as hazard, 88*t*
for skin cancers, 2701
Umbilical cord blood hematopoietic stem/progenitor cells, 1207
Umbilical hernia, 952*b*
Umbralisib (Ukoniq), 1215*t*
Umeclidinium, 553*t*
Uncal herniation, 2385
Uncinaria stenocephala, 2170
Unconjugated bilirubin, 994
Unconjugated hyperbilirubinemia, 996
Undervirilization, 1570*t*
Undervirilized male, biochemical evaluation of, 1575
Undifferentiated inflammatory polyarthritis, 1710
Undifferentiated spondyloarthropathy, 1710
Undulant fever. *See* Brucellosis
Unfractionated heparin, 387*t*, 501, 501*t*
adverse effects of, 502
dosage and monitoring of, 502
effect of, reversing, 502
in pregnancy, 1623*b*
Unilateral obstruction, of pulmonary artery, 522
Unilateral vocal fold paralysis, 2653
Unintended pregnancy, 1611
Unintentional injuries, in adolescents, 110, 110*t*
Unipolar disorders, 2337
United States
acute pancreatitis in, 969
amebiasis in, 2146
arterial hypertension in, 444–445
cardiovascular disease burden, 219
Chagas disease in, 2126
United States *(Continued)*
demographic changes in, 17
endoscopy in, 875
HIV/AIDS in, 2288*f*, 2290, 2290*f*, 2291*f*
routine newborn screening for cystic fibrosis in, 557–558
tuberculosis in, 2032
United States Preventive Services Task Force
on preventive health care, 111
preventive services for older adults, 119, ~~119.e1*t*~~
Univentricular heart, 354
Universal screening, 117
Unresponsive wakefulness syndrome, 2441
clinical manifestations of, 2441
diagnosis of, 2441, 2441*t*
epidemiology of, 2441
pathobiology of, 2441
treatment of, 2441*b*
Unstable hemoglobinopathies, 1116
Upadacitinib (Rinvoq), 153*t*
for inflammatory bowel disease, 945*b*, 946*t*
for rheumatoid arthritis, 1756*t*
for total knee arthroplasty, 1830.e1*t*
Upper aerodigestive tract
anatomy of, 2648, 2648*f*
infectious diseases of, 2648–2651
Upper airway
allergy of, 1674
irritation, occupational and environmental, 86*t*
thermal injury
clinical manifestations, 595
diagnosis, 595
pathogenesis, 595
prognosis, 595
treatment, 595*b*
Upper gastrointestinal bleeding, 882
acute management of, 883*b*
AIMS65 scoring system for, 921*t*
Blatchford system for, 921*t*
clinical manifestations of, 882, 882*f*, 882*t*
diagnosis of, 882
endoscopic therapy for, 883*b*, 883*t*
Glasgow-Blatchford score for, 883*b*, 883*t*
management of, 884*f*
medical therapy for, 883*b*
peptic ulcer disease causing, 882
Rockall scoring system for, 921*t*
treatment of, 883*b*
Upper gastrointestinal tract, systemic sclerosis involvement of, 1778
Upper GI endoscopy, 875
indications for, 875, 876*t*
instrument for, 875
preparation for, 875
procedure for, 875, 877*f*
Upper mesenteric ischemia, 916, 916*f*
Upper zone lung disease, 523, 523*t*
Upshaw-Schulman syndrome, 1177
Urapidil, for hypertensive emergencies, 460*t*
URAT1, 1810
Urate, 1810
crystals, 723, 725*f*, 1813*f*
overproduction of, 1811
renal, underexcretion in, 1810, 1810.e1*f*
Urea, for hyponatremia, 741*b*
Urea cycle, disorders of, 1402, 1403*f*
clinical manifestations of, 1402
diagnosis of, 1402
prognosis of, 1403
treatment of, 1402*b*
Urea nitrogen, e1*t*–e8*t*
Urea nitrogen/creatinine ratio, e1*t*–e8*t*
Ureaplasma arthritis, 1808
Ureaplasma spp., 2008, 2008*b*, 2008*t*
Uremic acidosis, 757
Uremic hyperparathyroidism, 1657, 1658*b*
Uremic lung, 784*t*
Uremic pericarditis, 426*t*, 431
Uremic syndrome, 836
Uremic toxins, 841
Ureteric anomalies, 819
Ureterocele, 819
Ureteropelvic junction obstruction, 818
Ureterosigmoidostomies, 760
Ureters, cancers of, 1367
Urethral obstruction, 828
Urethritis, 1947
characteristics of, 1880
Chlamydia trachomatis causing, 2010
Urethritis *(Continued)*
clinical manifestations of, 1880, 1947, 1947*f*
diagnosis of, 1880, 1947–1948, 1948
gonococcal, organisms causing, 1879*t*
nongonococcal, organisms causing, 1879*t*
treatment of, 1880*b*, 1880*t*
Urge incontinence, 827
bladder relaxant agents for, 831*t*
clinical manifestations of, 828
treatment of, 829*b*, 830*t*
in women, 1609
Uric acid, e1*t*–e8*t*, 1810
secretion, regulation of, 754–755
stones, 804
Uridine 5'-diphospho-glucuronosyltransferase, 995
Urinalysis
for benign prostatic hyperplasia, 822
chronic interstitial nephritis findings, 793
for prostatitis, 825
for renal disease, 721–724, 722*t*
Urinary alkalinization, for acute poisoning, 691*b*
Urinary antigen testing, for legionellosis, 1998
Urinary buffers, 754
Urinary histamine, 1693
Urinary incontinence, 827–831
clinical evaluation of, 829*t*
definition of, 827–831
diagnosis of, 829–830
epidemiology of, 827
functional incontinence, 828
lower urinary tract and, 827–828
in men, 830
mixed incontinence, 829
in older adults, 114, 118
pathobiology of, 827–828
prevention of, 830
prognosis for, 831
transient incontinence, causes of, 827, 828*t*
treatment of, 829*b*
in women, 1609
Urinary obstruction, 1875*b*
chronic interstitial nephritis caused by, 794
Urinary oxalate, 803
Urinary retention
psychotropic medications and, 2678*t*
severe mental illness and, 2683*t*
Urinary sediment, e1*t*–e8*t*
Urinary system, age-related changes in, 121
Urinary tract
abnormalities of, 818
development of, 818
lower
abnormalities of, 821
causes of established incontinence related to, 827
Urinary tract infection (UTI), 1873–1878
Acinetobacter causing, 1973
bacterial species that cause, 1892*t*
candidiasis causing, 2091
catheter-associated, 1862*t*, 1866, 1873
clinical manifestations of, 1874
clinical presentation of, 1873
complicated, 1873, 1873*t*, 1875*b*
control of, 1877–1878
definition of, 1873–1878
diagnosis of, 1874–1875
differential diagnosis of, 1875
in elderly, 1875*b*
enterococcus causing, 1920
Escherichia coli causing, 1873, 1965
etiology of, 1874, 1874*t*
follow-up for, 1875*b*
imaging of, 1875
laboratory findings of, 1874–1875
pathobiology of, 1873–1874
in pregnancy, 1878
prevention of, 1877–1878, 1877*t*
prognosis for, 1878
Pseudomonas infections causing, 1969, 1970*b*
pyuria associated with, 1875
risk factors for, 1873
screening for, 1877
symptoms of, 1874*t*
treatment of, 1875*b*, 1876*f*, 1921*b*, 1922*t*, 1966*b*
uncomplicated, 1873
urine culture for, 1875*t*

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Urine
  macroscopic appearance of, 722*t*
  sediment of, 722–724
  specific gravity of, 721
  testing of, for infection, 1836
Urine culture, for urinary tract infection, 1875*t*
Urine dipstick, for renal disease, 721–722
Urine free cortisol, in Cushing syndrome, 1522
Urine immunoelectrophoresis, for glomerular syndromes, 727
Urine porphobilinogen testing, for porphyrias, 1433
Urine sediment, evaluation of, 837
Urodynamic methods, for prostatitis, 825
Urogenital sinus, 1572*f*
Urolithiasis, 1874
Urologic disease, sickle cell disease and, 1114*b*
Urologic infection, *H. influenzae* caused by, 1953
Uroporphyrinogen III, 1429.*e1f*
Urorectal fold, 818
UROS-associated CEP, 1428*t*
Urosepsis
  antimicrobials for, 1877*t*
  clinical manifestations of, 1874
  description of, 1873
  symptoms of, 1874*t*
  treatment of, 1875*b*
Urothelial cancer, BK polyomavirus-associated, 2229, 2230*b*
Urothelial tumors, 1365–1366
Ursodeoxycholic acid, for primary sclerosing cholangitis, 1058*b*
Urticaria, 1673*t*, 1687, 2692*t*, 2724–2725
  accompanied by angioedema and anaphylaxis, 2725*t*
  classification of, 1690*t*
  clinical manifestations of, 1687, 1688*f*, 2725
  definition of, 1687, 2724–2725, 2725*f*, 2725*t*
  diagnosis of, 1688, 1689*f*, 2725, 2726*f*
  epidemiology of, 1687, 2724
  familial cold, neutrophilia and, 1142
  histamine-induced, 1687
  illustration of, 2691*t*
  like eruptions and reactive erythemas, 2725*t*
  pathobiology of, 1687, 2724–2725
  prevention of, 1689
  prognosis of, 1689
  treatment of, 1689*b*, 2726*b*, 2726*t*
Urticaria pigmentosa, 1700*f*, 2725
Urticarial vasculitis, 2715
  hypocomplementemic, 1798
U.S. hurricane Katrina, climate-related hazards, 91*t*
USE. *See* Ultrasound elastography
Ustekinumab (Stelara), 151
  for inflammatory bowel disease, 946*t*
  for psoriatic arthritis, 1765*b*
  for total knee arthroplasty, 1830.*e1t*
Usutu virus, 2276*t*
Uterine carcinosarcomas, 1378
Uterine fibroids, 1382, 1382*b*
Uterine serous carcinomas, 1379
UTI. *See* Urinary tract infection
Utility, 39
Uveal tract, malignant melanoma of, 2612
Uveitis, 1736, 2327*t*, 2604
  diagnosis of, laboratory methods for, 2003*t*
  in sarcoidosis, 601–602

V

V2 vasopressin receptor, endocrine diseases caused by, 1475*t*
Vaborbactam, 1845*t*
Vaccinations. *See also* Immunization
  bacterial meningitis, 2519
  for cancer, 1246–1247
  for COVID-19, 2218*t*, 2219
  for disseminated gonococcal infection, 1950
  for heart failure, 275*t*
  for hepatitis A, 1004
  for hepatitis B, 1006
  hesitancy, 2223
  for human papillomavirus, 2243
  for influenza, 2201, 2201*t*, 2202.*e1t*
  for measles, 2223
  for meningococcal disease, 1944
  for mumps, 2227
  for older adults, 119
  for orthopoxvirus, 2240*b*
  pneumococcal, 541*b*
  for rubella, 2225
Vaccinations *(Continued)*
  for seasonal influenza, 541*b*
  tetanus toxoid, 1929
Vaccine Adverse Event Reporting System, 76
Vaccine-derived polioviruses, circulating, 2257
Vaccines
  administration of, 64
  for amebiasis, 2149
  anaphylaxis caused by, 1692
  for certain destinations, 1887
  consideration of, for world travelers, 1886–1887
  for human papillomavirus, 1884
  for international travelers, 83
  for possible bioterrorism agents, 83
  reactions to, 1698, 1698*t*
  travel-related, 1886*t*, 1887
Vaccinia
  autoinoculation, of eye, 2238*f*
  bovine-associated, 2238
  clinical manifestations of, 2238
  epidemiology of, 2236
  generalized, 2238
  immunization for, 65*t*
  post-vaccination, 2238
  progressive, 2238
Vaccinia immune globulin (VIG), 2240*b*
VACTERL syndrome, 818
Vacuolated lymphocytes, 1074*t*
Vacuoles, E1 ligase, X-linked, autoinflammatory, somatic (VEXAS) syndrome, 1731*t*
Vagal impairment, 2554
Vagina
  atresia, 1574
  menstrual cycle-related changes in, 1595
Vaginal protozoa, 2112*t*, 2115
Vaginal ring, 1615
Vaginal symptoms, 1630*b*, 1632*t*
Vaginismus, 1604
Vaginitis
  characteristics of, 1882–1883
  organisms causing, 1879*t*
Vagus nerve, 2553
Valacyclovir
  for herpes simplex virus infections, 2246
  for herpesvirus infections, 2186, 2187*t*
  for skin diseases, 2699
  for zoster, 2249*b*
Valganciclovir
  for cytomegalovirus, 2252, 2252*b*
  for herpesvirus infections, 2186, 2187*t*, 2188*t*
Valproate, for seizures, 2434*t*
Valproic acid, e10*t*–e11*t*
  toxicity, 690*t*, 698*t*
Valsartan, 451*t*
  for acute STEMI, 384*b*, 391*t*
  for heart failure, 266*t*
Valsartan/amlodipine/HCTZ, 451*t*
Valsartan/HCTZ, 451*t*
Value, 46
Valvular heart disease, 400, 2663
  echocardiographic findings, 242*t*
  heart failure due to, 265*b*
  rheumatic, 400
  severe, 401*t*
Valvular pulmonary stenosis, 351, 351*b*
Valvular regurgitation
  echocardiographic findings, 242*t*
  evaluation of, 240
Valvular stenosis
  echocardiographic findings, 242*t*
  measurement of, 239–240, 241*f*
Van Buchem disease, 1666–1667
Vanadium pentoxide, 88*t*
Vancomycin, e10*t*–e11*t*
  for anthrax exposure, 97*b*
  for bacterial meningitis, 2518*t*
  characteristics of, 1900
  for *Clostridioides difficile*, 1925–1926, 1925*b*
  dosage of, 1895*t*
  mechanism of action, 1895*t*
  for methicillin-resistant *Staphylococcus aureus*, 1905
  pharmacokinetic parameters for, 127.*e1t*
  for pneumonia, 613*t*, 616*t*
  reactions to, 1698*t*
  in renal failure, 129.*e1t*
  resistance mechanisms, 1893*t*
  for *Streptococcus pneumoniae* pulmonary infections, 1912.*e1t*
  toxicities of, 1901*t*
Vancomycin-resistant enterococci
  E. faecium causing, 1920
  epidemiology, 1920
  treatment of, 1921*b*
Vandetanib (Caprelsa), 1215*t*
Vanillylmandelic acid (VMA), *e1t*–*e8t*
Vanishing bile duct syndromes, 1059–1060
Vanishing white matter disease, 2510
Vaping, in adolescents, 113
Vaping-associated lung disease (E-VALI), 2352
Vapor inhaler, for tobacco dependence, 2351*t*
Vaptans
  for hypervolemia, 737*t*
  for hyponatremia, 741*b*
Vardenafil, 364*b*
  for erectile dysfunction, 1589
Varenicline
  for spinocerebellar ataxia, 2497*b*
  for tobacco dependence, 2351*t*
Varenicline tartarate, for tobacco dependence, 2350*b*
Variability, 36
Variable-vessel vasculitides, 1792*t*, 1798–1799
Variant angina, 368
Variant-specific proteins (VSPs), 2144
Variceal hemorrhage
  cirrhosis and, 1036, 1038, 1038*t*
  diagnosis of, 1039
  treatment of, 883*b*, 1040*b*, 1041*f*
Varicella, 2720–2721, 2721*b*, 2721*f*
  diagnosis of, 2249
  epidemiology of, 2248
  immunization for, 65*t*, 66*t*, 76.*e1t*, 77*f*, 78*f*
  pathobiology of, 2248
  postexposure prophylaxis, 2250
  prevention of, 2249–2250
  prophylaxis for, 2309*t*
  treatment of, 2249*b*
  vaccination for, 1886, 1886*t*, 2249
Varicella immune globulin. *See* VariZIG
Varicella-zoster virus, 2247–2250, 2532*t*, 2621*t*
  antiviral therapy for, 2187*t*
  characteristics of, 2270*t*
  clinical manifestations of, 2248–2249
  definition of, 2247–2250
  diagnosis of, 2249
  disseminated, 2695*f*
  epidemiology of, 2248
  immunization for, 76.*e1t*, 77*f*, 78*f*, 83
  pathobiology of, 2248
  as pathogen, 2247
  prevention of, 2249–2250
  prognosis of, 2250
  treatment of, 2249*b*
Varices
  cirrhosis and, 1036
  diagnosis of, 1039
  treatment of, 1040*b*
Varicose veins, 491*f*, 2692*t*
Variegate porphyria (VP), 1428*t*
Variola major, 98
Variola minor, 98
Variola sine eruptione, 2237, 2237*t*
VariZIG, 2250
Vascular diseases
  in acute kidney injury, 773
  chronic kidney disease and, 833*t*
  of gastrointestinal tract, 959
    acute mesenteric ischemia as, 959
    angioectasia as, 965
    aortoenteric fistulas as, 967
    Budd-Chiari syndrome as, 968
    celiac artery compression syndrome as, 967, 967*f*
    chronic mesenteric ischemia as, 963, 963*f*
    colon ischemia as, 964, 964*t*, 965*f*
    Dieulafoy lesion as, 966
    ectasias as, 967
    hemangiomas as, 967
    hepatic and splenic, 968
    hepatic and splenic arterial disease as, 969
    hereditary hemorrhagic telangiectasia as, 967
    intestinal ischemia as, 959
    portal vein thrombosis as, 968, 968*b*
    radiation proctopathy as, 968, 968*f*
    splenic vein thrombosis as, 968
    superior mesenteric artery syndrome as, 967
    vascular anomalies and disorders as, 965
    vasculitis as, 965
  of kidney, 728
  in systemic sclerosis, treatment of, 1781*b*
Vascular endothelial growth factor (VEGF), 152
Vascular hemorrhagic disorders
  acquired, 1186
  hereditary, 1186
Vascular injury, platelet activation at, 1165
Vascular insufficiency, 2645–2646
Vascular lesions, 2731–2734
Vascular malformations, brain, 2482, 2482*b*
Vascular myelopathy, 2405, 2406*b*
Vascular parkinsonism, 2485*t*
Vasculitic neuropathies, 2573–2574, 2574*b*, 2574*t*
Vasculitides, 1791
  antineutrophil cytoplasmic antibody-associated, 1796
  associated with probable etiology, 1792*t*
  associated with systemic disease, 1792*t*
  of central nervous system, 1799, 1800*t*
  classification of, 1791–1792
    considerations in, 1791–1792, 1792*t*
    by vessel size, 1791–1792, 1792*t*
  definition of, 1791–1795, 1792*t*
  diagnosis of, 1794, 1794*t*
  epidemiology of, 1792, 1793*t*
  immune complex-mediated, 1793, 1798
  large-vessel, 1792*t*, 1793, 1795
  medium-vessel, 1792*t*, 1793, 1795
  pathobiology of, 1792–1794, 1793*t*
  pathophysiology of, 1792–1794
  prognosis of, 1795
  selected single-organ, 1799
  single-organ, 1792*t*
  small-vessel, 1792*t*, 1793, 1796–1798
  treatment for, 1794*b*
  variable-vessel, 1792*t*, 1798
Vasculitis, 728, 965, 1708, 2714, 2715*f*, 2734
  aortic, 442.*e1f*, 443
  diagnosis of, 2714–2715, 2714*t*, 2714.*e1f*
  large vessel, 965
  medium vessel, 965
  small vessel, 965
  stroke caused by, 2470.*e1t*, 2472
  thrombocytopenia and, 1179
  treatment for, 2715*b*
  vision loss caused by, 2616*t*
Vasculitis-associated rapidly progressive glomerulonephritis, 785
Vasculopathy
  in systemic lupus erythematosus, 1769
  in systemic sclerosis, 1776
Vasculoproliferative disease, 2001*t*, 2002
Vasectomy, 1617
Vaso-occlusive crises, 1113
Vasoactive agents, for shock, 662*b*
Vasoactive intestinal peptide (VIP), prolactin secretion regulated by, 1490
Vasodilators
  mechanism of action of, 455
  side effects of, 453*t*, 455
Vasomotor tone, shock and, 658
Vasopressin, 730
  adrenocorticotropic hormone and, 1499
  for advanced cardiac life support, 315*f*
  osmotic and volume regulation in, interaction of, 1499
  pressure and, 1499
  regulation of osmolality and, 1499, 1499*f*, 1499.*e1f*
  for shock, 662*b*, 664*t*
  volume regulation and, 1499
Vasopressors
  for cardiogenic shock, 667*b*
  for shock, 662*b*, 664*t*
Vasospasm, vision loss caused by, 2616*t*
Vasospastic (or Prinzmetal) angina, 357
Vasovagal hypotension, 394
Vasovagal syncope, 304, 1694
VDRL test. *See* Venereal Disease Research Laboratory test
Vectibix. *See* Panitumumab
Vedolizumab, 152, 945*b*, 946*t*
Vegetable dusts, 88*t*
Vegetables, dietary guidelines for, 57.*e3t*
Vegetative state, 2441
  clinical manifestations of, 2441
  diagnosis of, 2441, 2441*t*
  epidemiology of, 2441
  pathobiology of, 2441
  treatment of, 2441*b*
VEGF. *See* Vascular endothelial growth factor
Velcade. *See* Bortezomib

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Vellus follicles, 2747
Velocardiofacial syndrome, 1679*t*
Velocity-time integral, 238
Vemurafenib (Zelboraf), 133, 1215*t*, 1251*t*, 1394*t*
Venclexta. *See* Venetoclax
Venereal Disease Research Laboratory (VDRL) test, 1881
Venereal infections, 2622
Venetoclax (Venclexta), 1215*t*
  for chronic lymphocytic leukemia, 1269*b*, 1269*t*, 1270*t*
Venezuelan equine encephalitis virus, 2276*t*, 2283, 2283*b*
Venlafaxine
  for cataplexy, 2449*t*
  for chronic pain, 138*t*
  for depression, 2340*t*
  for hot flashes, 1631*t*
Veno-occlusive disease. *See* Sinusoidal obstruction syndrome
Venom
  clinical effects of, 707*t*
  description of, 704
  immunotherapy, for mastocytosis, 1703*b*
Venomous arthropods, 710.*e1f*
Venomous insects, 711–712
Venomous mollusks, 712
Venomous snakes, 708.*e1f*
Venomous stingrays, 712
Venous air embolism, 491–492, 492*b*
Venous oxygen content (Cvo_2), 640
Venous pressure, abnormalities of, 214*t*
Venous sinus thrombosis, 2528
Venous sinuses, 2529*f*
Venous system, 2459, 2461*f*, 2462*f*
Venous thromboembolism (VTE), 1170
  anticoagulation for, 487*b*
  blood tests of, 486
  brain tumors, 1312*b*
  cancer-associated, 487*b*
  clinical manifestations of, 483, 483*f*, 483*t*
  compression ultrasonography of, 484, 485*f*
  computed tomographic pulmonary angiography of, 484, 486*f*
  contrast venography of, 484, 486*f*
  D-dimer tests for, 483
  definition of, 482
  diagnosis of, 483, 484*t*
  diagnostic approach to, 477, 477*f*
  direct oral anticoagulants for, 487*b*
  echocardiographic findings in, 487
  epidemiology and risk of, 476*t*
  epidemiology of, 482
  in HIV, 2318–2319, 2319*b*
  hormonal therapy and, 1630*b*
  interventional contrast pulmonary angiography of, 486
  in joint diseases, 1829–1830
  long-term complications of, 489–490
  magnetic resonance imaging of, 485
  pathobiology of, 482–483
  post-thrombotic syndrome caused by, 490
  in pregnancy, 1619*f*, 1622, 1623*b*, 1623*f*, 1624*t*
  prevention of, 491
  prognosis for, 489
  recurrent, 490
  of upper extremities, 490
  ventilation-perfusion lung scanning for, 484–485, 486*f*
Venous ulcers, 490
Ventilation, 657
  alveolar ventilation (Va), 640
  assessment of, 639
  dead space (Vd/Vt), 640
  measurement of, 640
  mechanical, 652
    assisted, 653
    negative-pressure ventilators, 653
    positive end-expiratory pressure, 653
    positive-pressure ventilators, 652
    pressure-controlled ventilation, 653
    volume-controlled ventilation, 653
  minute (V_E), 640
  for viral hemorrhagic fevers, 2269*b*
Ventilation-perfusion mismatch, in acute respiratory failure, 643
Ventilation-perfusion scanning, for venous thromboembolism, 484, 486*f*
Ventilator-associated pneumonia, 616*t*, 1862*t*, 1866
  antibacterial chemotherapy for, 1900
  Pseudomonas infections causing, 1969, 1970*b*
Ventilator-induced lung injury, 655, 655.*e1f*
Ventilatory control disorder, 534–537
Ventilatory maneuvers, for acute respiratory failure, 647*b*
Ventral epidural hematoma, 2392*f*
Ventral induction, disorders of, 2547
Ventral lateral preoptic nucleus, 2443.*e3f*
Ventral tegmental area, of brain, 142
Ventricular arrhythmias, 332, 333*f*
  catheter ablation of, 346
  causes of, 335–336
  clinical manifestations of, 334–335
  definition of, 332–340
  diagnosis of, 335–338
  epidemiology of, 333
  genetically inherited, 337
  management of, 384*b*
  pathobiology of, 333–334
  prognosis for, 340
  treatment of, 338*b*
Ventricular contractility, 226
Ventricular cysticerci, 2159
Ventricular empyema, 2511
Ventricular fibrillation (VF), 333*f*
  ACLS response to, 315*f*
  acute management of, 338*b*
  AED rapid response to cardiac arrests caused by, 314*t*
  definition of, 333
  diagnosis of, 313, 338
  late, 384*b*
  prognosis for, 340
  treatment of, 338*b*
Ventricular function
  diastolic, 239
  imaging of, 249
  systolic, 239
Ventricular septal defect (VSD), 347, 349–350
  diagnosis of, 349–350, 349
  exercise recommendations for, 355.*e2t*
  prognosis for, 350*b*
  treatment of, 350*b*
Ventricular tachycardia, 333.*e1f*, 336.*e1f*
  acute management of, 338*b*
  definition of, 332–333
  diagnosis of, 313, 335*t*
  differential diagnosis of, 335, 335*t*
  electrocardiographic parameters, 336*t*
  genetically acquired, treatment of, 338*b*
  iatrogenic, 338, 338*b*
  idiopathic, 336.*e1f*, 338*b*
  monomorphic, 333, 333*f*, 334*f*, 336*f*, 337*f*
  pleomorphic, 333
  polymorphic, 333, 334*f*
  post-myocardial infarction, 336
  prognosis for, 340
  pulseless, 315*f*
  surgery for, 347.*e1f*, 347
  sustained, 332
Ventriculitis, 2511
  cytomegalovirus, 2532*t*
Ventriculoperitoneal shunting, 1725*b*
VEPs. *See* Visual evoked potentials
Verapamil, 367*t*
  for acute coronary syndrome, 375*t*
  for hypertrophic cardiomyopathy, 282*b*
Verapamil IR, 451*t*
Verapamil SR, 451*t*
Verapamil-delayed-onset ER, 451*t*
Vericiguat, for heart failure with reduced left ventricular ejection fraction, 265*b*
Verner-Morrison syndrome. *See* VIPomas
Vero cell, vaccine, for traveler, 1886*t*
Verruca plana, 2242
Verrucae, 2699, 2741
Verruga peruana, 2002, 2003*b*, 2003*t*
Vertebral arteries, 2465
  anatomy of, 2455, 2457*f*
Vertebral fractures, 1642
Vertebral osteomyelitis, 1904, 1969
Vertebrobasilar insufficiency, 2645
Vertebroplasty, 1643*b*
Vertigo, 2371
  bedside tests for, 2646
  benign paroxysmal positional, 2644, 2645*f*, 2647*t*
Vertigo *(Continued)*
  caloric test for, 2646
  causes of, 2644–2645
  central, 2644
  central causes of, 2646
  description of, 2647*t*
  doll's eye test for, 2646
  evaluation of, 2644*f*
  head-thrust test for, 2646
  height, 2644
  hyperventilation and, 2646
  Meniere disease causing, 2645
  migraine and, 2645
  nystagmography of, 2646
  peripheral causes of, 2645–2646
  physiologic, 2644
  positional tests for, 2646
  post-traumatic, 2645
  prognosis for, 2647
  treatment of, 2647*b*, 2647*t*
  vascular insufficiency causing, 2645
  vestibular rehabilitation exercises for, 2647*b*
Very low calorie diets, 1467*b*
Very low density lipoproteins, 1405
Very severe aplastic anemia, 1125
VES-13. *See* Vulnerable Elders Survey
Vesicle, 2689*t*, 2696*f*
Vesicoureteral reflux, 791, 818–820, 819, 820*b*
Vesiculo-erosive skin disease, porphyrias and, 1432
Vesiculobullous diseases, 2716–2721, 2717*t*
  hypersensitivity reactions causing blisters, 2719
  immunologically mediated blistering diseases, 2716–2717
  infectious diseases causing blisters, 2720–2721
  intraepidermal blistering disorders, 2718
  metabolic disorders causing blisters, 2719
  mucous membrane pemphigoid, 2717, 2718*f*
  pemphigoid gestationis, 2717, 2717*f*
  subepidermal blistering disorders, 2717
Vespid. *See* Etoposide
Vestibular neuritis, 2644, 2647*t*
Vestibular rehabilitation exercises, 2647*b*
Vestibular schwannomas, 1314, 1314*b*, 1314*f*
Vestibular system, anatomy and physiology of, 2644
Vestibulo-ocular reflex, 2439, 2618
Vestibulospinal function, 2646
VEXAS syndrome. *See* Vacuoles, E1 ligase, X-linked, autoinflammatory, somatic syndrome
VF. *See* Ventricular fibrillation
VHL. *See* von Hippel-Lindau disease
Viagra (sildenafil), 364*b*
Vibegron, 824*t*
Vibration, 88*t*
Vibrio cholerae, 1955
  nontoxigenic, 1958
Vibrio infections, 1957–1958
  in travelers, 1889.*e1t*
Vibrio parahaemolyticus, 90, 1958
Vibrio vulnificus, 1958
Vicenza bleeding score, 1166
Vidaza. *See* Azacitidine
Video-assisted thoracoscopic surgery, 631
Video capsule endoscopy, 1345
VIG. *See* Vaccinia immune globulin
Vilazodone, for depression, 2340*t*
Vildagliptin, for type 2 diabetes mellitus, 1541*t*
Villous adenomas, 939, 1349
Villous atrophy, inflammation and, 935
Vinorelbine (Navelbine), 1215*t*
Vinyl chloride, 88*t*
Viokace, for exocrine pancreatic insufficiency, 975*t*
VIP. *See* Vasoactive intestinal peptide
Viperid bites, 708
VIPomas, 1561*t*, 1564, 1565*b*
Viral arthritis, 1807
Viral carcinogenesis, 1321
Viral conjunctivitis, 2604, 2605*f*
Viral encephalitis, 2531
  causes of, 2531*t*
  cerebrospinal fluid findings in, 2374*t*
  clinical manifestations of, 2531
  diagnosis of, 2531
  differential diagnosis of, 2532
  epidemiology of, 2531
  magnetic resonance imaging of, 2532
  pathobiology of, 2531
Viral encephalitis *(Continued)*
  prognosis for, 2532
  rabies and, 2534, 2535*b*
  spinal fluid analysis, 2532
  tests for, 2532*t*
  treatment of, 2532*b*
Viral hemorrhagic fevers, 99, 2264
  antiviral therapy for, 2269*b*
  bat-borne viruses, 2264
  clinical management of, 2269*b*
  clinical manifestations of, 99–100, 2267, 2268*t*
  contact tracing of, 2272
  definition of, 2264
  diagnosis of, 100, 2267
  differential diagnosis of, 2270*t*
  epidemiology of, 99, 2264
  human-to-human transmission of, 2266
  infection prevention and control in, 2272
  laboratory testing for, 2269, 2271*t*
  maintenance in nature, 2264
  mosquito-borne viruses, 2266
  nonspecific presentation of, 2268, 2272
  pathobiology of, 99, 2266
  pathogens that causes, 2264
  postexposure prophylaxis for, 2273
  in pregnancy, 2267, 2269*b*
  prevention of, 100, 2272
  prognosis of, 100, 2273
  reservoir for, 2273
  ribavirin therapy for, 2272*t*
  rodent-borne viruses, 2264
  sequelae of, 2273
  tick-borne viruses, 2266
  transmission to humans, 2264
  treatment of, 100*b*, 2269*b*
  vaccines for, 2272
  vector control for, 2273
  viruses causing, 99.*e1t*, 2265*t*
Viral hepatitis
  acute, 986
  characteristics of, 2270*t*
Viral infections, 2650, 2650*f*
  of skin, 2739*t*, 2741
Viral meningitis
  agents of, 2520*t*
  arboviruses causing, 2520
  cerebrospinal fluid findings in, 2374*t*, 2513*t*
  clinical manifestations of, 2520
  definition of, 2519
  differential diagnosis of, 2521
  enterovirus, 2520
  epidemiology of, 2519
  herpes simplex virus causing, 2521
  human immunodeficiency virus causing, 2521
  lymphocytic choriomeningitis causing, 2521
  pathobiology of, 2520
  polymerase chain reaction for, 2521
Viral myocarditis, 285
  clinical manifestations of, 285
  diagnosis of, 285–286
  prognosis for, 286
  specific causes of, 286
Viral pericarditis, 426*t*
Viral pneumonia, 607
Viral rhinitis, 2631
Viral vectors, 175
Virchow node, 1341
Viremia, zoster and, 2248
Viridans group streptococci, 415, 1919
Virilization, 1570*t*
Virilized female, biochemical evaluation of, 1575
Virologic failure, 2302–2303
Virtual colonoscopy, 1353
Viruses, health care-associated infections caused by, 1865
Visceral abscesses, glomerulonephritis with, 783
Visceral angioedema, 956
Visceral arterial aneurysms, 969
Visceral compartment, 527
Visceral larva migrans, 2174
  in travelers, 1889.*e1t*
Visceral leishmaniasis, 2116, 2132
  antigen-based tests for, 2132
  clinical manifestations of, 2132
  complex manifestations of, 2132
  diagnosis of, 2132
  in immunodeficient patients, 2132*b*
  serologic tests of, 2132
  in travelers, 1889.*e1t*
  treatment of, 2132*b*

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Visceral pain, 134, 135*t*
Visceral perception, increased, irritable bowel syndrome and, 893
Viscid mucus, clearance of, 558*b*
Viscosity, *e1t–e8t*
Vision
  change in, 2598, 2599*t*
  geriatric assessment of, 117
  loss of
    binocular, 2614–2615
    eye causing, 2615
    optic chiasm lesions causing, 2616
    optic nerve causing, 2615
    transient monocular, 2616*t*
  screening for, 55
Vismodegib (Erivedge), 1215*t*
Visual axis, 2596
Visual evoked potentials (VEPs)
  in multiple sclerosis, 2504
  pattern reversal, 2376.*e1f*, 2376
Visual fields, 2615, 2615*f*
Visual function disorders, 2409, 2410*f*
Visual pathways, lesions of, 2614–2615
Visual radiations, 2616
Visual-sensitive seizures, 2433
Visual system diseases, 2596–2614
  amblyopia, 2598
  anatomy of, 2597*f*
  astigmatism, 2598
  clinical manifestations of, 2597
  color vision change, 2598
  common clinical conditions of, 2597–2604
  conjunctivitis, 2600
  corneal abrasion, 2602
  diplopia, 2598
  dry eyes, 2602, 2603*f*
  endophthalmitis, 2604
  esotropia, 2598
  excessive tearing, 2599
  exotropia, 2598
  floaters, 2599
  foreign body sensation, 2599, 2600*f*
  functional evaluation of, 2597, 2597*f*, 2597*t*, 2597.*e1f*
  halos around lights, 2599
  hyperopia, 2598
  hyphema, 2603, 2604*f*
  keratoconus, 2598
  leukocoria, 2600, 2601*t*
  myopia, 2597
  night blindness, 2599
  ocular surface abnormalities, 2602–2604
  pain, 2598, 2599*t*
  photophobia, 2599
  photopsia, 2599
  pinguecula, 2602, 2603*f*
  presbyopia, 2598
  proptosis, 2600, 2600*f*
  pterygium, 2602, 2603*f*
  ptosis, 2600, 2600*f*
  recurrent corneal erosions, 2602
  red eye, 2599, 2599*t*
  strabismus, 2598
  uveitis, 2604
Vital capacity (VC), 530
Vital signs
  abnormal
    approach to patient with, 32–35
    differential diagnosis, 34
    multiple, 34
    in patients who appear to be ill, 33–34, 34*t*
    in patients who complain of systemic illness but do not appear to be very ill, 33
    in patients without systemic complaints, 33
    requiring rapid evaluation, 33*t*
    single, 34
    that require urgent evaluation, 34*t*
    treatment options, 34
  for acute poisoning, 682
  in asthma, 539
  as health measures, 40
  in heart failure, 257
  importance of, 32, 32*t*
  measurement of, 29
  measuring, 33
  normal ranges for, 32*t*
  panic ranges for, 32*t*
  predictive value, 32
  role of, 33–35, 33*t*
  as symptoms, 32
Vital statistics, of adolescent, 110
Vitamin(s)
  fat-soluble, 1451
  for inborn errors of metabolism, 1401*b*
  as supplements, 56, 155
  water-soluble, 1451
Vitamin A, *e1t–e8t*
  characteristics of, 1453*t*
  deficiency of, 1453*t*, 2222*b*, 2538*t*, 2542
  for malabsorption, 937*t*
  toxicity, 2541*t*
Vitamin B_1, *e1t–e8t*
  characteristics of, 1453*t*
  deficiency of, 1453*t*, 2538*t*, 2578
Vitamin B_2, *e1t–e8t*
  characteristics of, 1453*t*
  deficiency of, 1453*t*, 2541
Vitamin B_3
  characteristics of, 1453*t*
  deficiency of, 1453*t*, 2538*t*, 2541
  toxicity, 2541*t*
Vitamin B_5, deficiency of, 2538*t*, 2541
Vitamin B_6, *e1t–e8t*, 1427*b*
  characteristics of, 1453*t*
  deficiency, 1453*t*
  deficiency of, 2538*t*, 2540–2541
  toxicity, 2541*t*
Vitamin B_{12}, *e1t–e8t*, 1427*b*
  characteristics of, 1453*t*
  deficiency, 1453*t*
  deficiency of, 2538*t*, 2539
  for malabsorption, 937*t*
Vitamin C, *e1t–e8t*
  characteristics of, 1453*t*
  deficiency, 1453*t*
Vitamin D
  characteristics of, 1453*t*
  deficiency of, 1453*t*, 2538*t*, 2541–2542, 2542*b*
    causes of, 2541
    characteristics of, 2538*t*
    in HIV, 2318
    osteomalacia and, 1647, 1647*t*, 1650*b*, 1650*t*, 1651*t*
  1,25-dihydroxy, total, *e1t–e8t*
  endocrine diseases caused by, 1475*t*
  function of, 2541
  25-hydroxy, total, *e1t–e8t*
  for malabsorption, 937*t*
  for osteoporosis, 1639*b*, 1643*b*
  toxicity, 2541*t*
  in women, 1607
Vitamin D_3, excretion of, 732, 732.*e1f*
Vitamin deficiencies
  clinical manifestations of, 2537
  fat-soluble vitamins, 2541–2542
  thiamine, 2537, 2538*t*
  types of, 2538*t*
  water-soluble vitamins, 2537–2541
Vitamin E, *e1t–e8t*
  characteristics of, 1453*t*
  deficiency of, 1453*t*, 2538*t*, 2541, 2541*b*
  for malabsorption, 937*t*
  for nonalcoholic fatty liver disease, 1034*b*
  toxicity, 2541*t*
Vitamin K, 999–1000
  for acute poisoning, 693*t*
  characteristics of, 1453*t*
  deficiency of, 1198, 1453*t*, 2538*t*, 2542
  for malabsorption, 937*t*
Vitamin K antagonists, 503–504
  adverse effects of, 504
  anticoagulant effect of, reversing, 504, 504*t*
  dosage and monitoring of, 502*t*, 503–504, 504*t*
Vitamin K-dependent coagulation, deficiencies of, 1193
Vitamin K-dependent coagulation factors, 1167*t*
Vitamin K epoxide reductase C1, 503
Vitiligo, 2743, 2743*f*, 2745*f*
Vitrakvi. *See* Larotrectinib
Vitreous, 2596
Vitronectin, 200*t*
V(D)J recombination, defects of, 1676.*e3t*, 1678
VKORC1 gene, 160*t*
Vocal cord dysfunction syndrome, distinguishing features of, 515*t*
Vocal tremor, 2652
Voclosporin (Lupkynis), for total knee arthroplasty, 1830.*e1t*
Vogt-Koyanagi-Harada syndrome, 2524
Volanesorsen, for hypertriglyceridemia, 1414*b*
Volatile acid, 753
Volatile anesthetics, 2670
Volume-controlled ventilation, 653
Volume depletion
  management of, 384*b*
  metabolic alkalosis with, 762
Volume expansion, metabolic alkalosis with, 763
Volume-limited ventilation, 653
Volume regulation
  osmotic and, interaction of, 1499
  vasopressin and pressure and, 1499
Voluntary active euthanasia, 8*t*
Volvulus, 951
  clinical manifestations of, 951
  colonic, 952*b*
  diagnosis of, 951, 952*f*
  prognosis of, 951*b*–952*b*
  treatment of, 951*b*
Vomiting. *See also* Nausea and vomiting
  acute pancreatitis and, 969, 970
  in cancer, management of, 1232*b*
  characteristics of, 888
  in enteral nutrition, 1449
von Gierke disease, 1417*t*
von Hippel-Lindau disease (VHL), 1530, 1558, 1559*t*, 2552–2553, 2553*b*
von Hippel-Lindau syndrome, 809*t*, 814, 814*b*, 1250*t*
von Recklinghausen disease, 583
von Willebrand disease, 1180–1186, 1189*t*, 1191
  acquired, 1184, 1184*b*
  classification of, 1180*t*
  clinical assessment of, 1181, 1181*f*, 1182*t*
  clinical manifestations of, 1180–1181
  definition of, 1180–1184
  desmopressin for, 1180, 1182*t*
  diagnosis of, 1180*t*, 1181–1183
  epidemiology of, 1180
  factor replacement therapy for, 1183*t*
  laboratory evaluation of, 1181–1183, 1181*f*
  pathobiology of, 1180
  treatment of, 1183*b*
von Willebrand factor, 1180, 1183*t*
von Willebrand factor activity, *e8t–e9t*
von Willebrand factor antigen, *e8t–e9t*
Vorapaxar, 506*t*, 508
Voriconazole, *e10t–e11t*, 2076
  adverse effects of, 2076
  for aspergillosis, 2096
  for candidiasis, 2092*b*
  for chromomycosis, 2111*b*
  for cryptococcosis, 2088*b*
  drug interactions of, 2076
  formulations and pharmacology of, 2076
  for hepatosplenic candidiasis, 1024*b*
  indications and dosage of, 2075*t*, 2076
  for mycoses, 2076
  for paracoccidioidomycosis, 2087*b*
Vortioxetine, for depression, 2340*t*
Votrient. *See* Pazopanib
Voxelotor, for sickle cell disease, 1116*t*
Voxilaprevir, 2182*t*
VSD. *See* Ventricular septal defect
VSPs. *See* Variant-specific proteins
VT. *See* Ventricular tachycardia
VTE. *See* Venous thromboembolism
Vulnerability, in older adults, 122, 123*f*
Vulnerable Elders Survey (VES-13), in older adults, 123*t*
Vulvovaginal candidiasis, 1882
Vulvovaginitis, 2090
Vumerity. *See* Diroximel fumarate

W

Waddling gait, 2373*t*
Waist circumference, 1466
Wakefulness, 2443, 2443.*e1f*, 2444*t*
Wakefulness test, 2444
Waldenström macroglobulinemia, 1088, 1303, 2713–2714
  clinical manifestations of, 1303
  diagnosis of, 1303
  diagnostic criteria of, 1303
  differential diagnosis of, 1303
  laboratory evaluation of, 1303
  prognosis for, 1303*b*
  treatment of, 1303*b*
Walking pneumonia, 2006
Wallenberg syndrome, 2465.*e1f*
Wandering atrial pacemaker, 322, 323*f*
Warfarin, *e10t–e11t*, 502*t*, 503, 504*t*
  anticoagulation uses of, 487*b*
  for hypercoagulable states, 477, 478*b*
  in nephrotic syndrome, 777*b*
  parenteral anticoagulation after, 487*b*
  for portal vein thrombosis, 968*b*
  in pregnancy, 487*b*, 487*t*
  skin necrosis, 2716
  for vitamin K deficiency, 1198
Warfarin-induced skin necrosis, 478*b*, 478*f*
Warm autoimmune hemolytic anemia, 1087, 1089*t*
Warm sitz baths, for chronic prostatitis/chronic pelvic pain syndrome, 825*b*
Warthin tumor, 2625
Warts, 2713, 2713*f*, 2741
  anal, 982, 982*b*, 982*f*
  genital, 2242
  human papillomavirus causing, 2242
  plantar, 2242, 2242*f*
Warty lesions, 2729–2730, 2731*f*
WASP. *See* Wiskott-Aldrich syndrome protein
Wasting, 1445
Water
  hazards, 87
  imbalances in, 724
Water-based exercises, for osteoarthritis, 1741*t*
Water-based lubricants, for HIV transmission prevention, 2298
Water-borne infectious diarrhea, 924
Water-bottle sign, 245, 246*f*
Water content, regulation of, 730, 732*f*
Water disinfection, for *Legionella*, 1999
Water disorders, 733, 733*t*
Water diuresis, 743*t*
Water-soluble vitamins, 935, 1450, 1451, 1453*t*
Waterhouse-Friderichsen syndrome, 1944*b*
Watery diarrhea, 760, 924
  laboratory tests for, 930, 931*t*
WBC. *See* White blood cell count
WBC casts, 722
Weakness
  diaphragmatic, 619
  neurologic causes of, 2371, 2371*t*
  postoperative, 2674
Weapons of mass destruction, 96, 96*t*. *See also* Bioterrorism
Weaver's bottom. *See* Ischial/ischiogluteal bursitis
Weber syndrome, 2465.*e1f*
Weber test, 2641
Webs, esophageal, 910, 910*f*
Wegener granulomatosis, 727. *See also* Granulomatosis with polyangiitis
Weibel-Palade bodies, 1180
Weight loss
  causes of, 1447–1448
  energy intake reduction for, 1467*b*
  goals for, 1609
  hypogonadotropic hypogonadism and, 1584
  involuntary, 860
    causes of, 860*t*
    diagnosis of, 861, 862*f*
    in older adults, 117
    signs and symptoms of, 852*t*
Weil disease, 2030
Wellcovorin. *See* Leucovorin calcium
Wellness, in occupational and environmental medicine, 87
Wells syndrome. *See* Eosinophilic cellulitis
Wenckebach AV block. *See* Mobitz type I AV block
Werdnig-Hoffman disease, 2565
Wernicke encephalopathy, 2537, 2539*b*, 2539*f*, 2545
West African sleeping sickness, 2124
West Nile encephalitis, 2532*t*
West Nile virus, 1203, 2276*t*, 2281, 2281*f*, 2282*b*
  in travelers, 1889.*e1t*
Western Africa, HIV/AIDS in, 2289, 2289.*e1f*
Western equine encephalitis virus, 2276*t*, 2283, 2283*b*
Western Europe, HIV/AIDS in, 2289, 2289.*e1f*, 2290.*e1f*
Wet age-related macular degeneration, 2608, 2609*f*
Wet-to-dry dressings, for skin diseases, 2697
Wheat gluten, alcohol-soluble protein fraction of, 935
Wheezes, 512, 512*t*, 513, 513*b*, 513.*e1f*, 515*t*, 539, 557

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WHIM syndrome, 1145
Whiplash, 2395
Whipple disease, 417*t*, 937, 1821, 2069–2071
  classical, 2070, 2070*t*
  clinical manifestations of, 2069–2070
  definition of, 2069–2071
  diagnosis of, 2070, 2070*f*, 2071*f*, 2072*f*
  epidemiology of, 2069
  pathobiology of, 2069
  pathogen that causes, 2069
  prevention of, 2071
  prognosis of, 2071
  treatment for, 2070*b*
Whisper test, 117
White blood cell count (WBC), ranges of, 1140
White coat hypertension, 447
White heads, 2722
White superficial onychomycosis, 2754, 2754*f*
WHO. *See* World Health Organization
WHO/ISUP. *See* World Health Organization/International Society of Urologic Pathology
Whole blood, HIV transmission through, 2299
Whole-body exposure syndromes, treatment of, 94*b*, 94*f*
Whole bowel irrigation, for acute poisoning, 691*b*
Whole-lung lavage, for pulmonary alveolar proteinosis, 567*b*, 567.*e1f*
Whole pancreas transplantation, for type 1 diabetes mellitus, 1537*b*
Whooping cough
  chemoprophylaxis for, 1996
  clinical manifestations of, 1995
  complications of, 1995
  definition of, 1994–1996
  diagnosis of, 1995
  epidemiology of, 1994–1995
  immunizations for, 1996
  pathobiology of, 1995
  pathogens that cause, 1994
  prevention of, 1996
  prognosis for, 1996
  treatment of, 1995*b*
Widow spiders, envenomation of, 710
Wiggers diagram, 225.*e1f*
Williams syndrome, 348, 1658
Wilson disease, 816*t*, 993, 999, 1398*t*, 1436–1437
  clinical manifestations of, 1436–1437, 1436*f*, 1437*f*
  definition of, 1436–1437
  diagnosis of, 1437
  dystonia *versus*, 2493
  epidemiology of, 1436
  pathobiology of, 1436
  in pregnancy, 1625*t*
  prognosis of, 1437
  treatment of, 1437*b*
Wiskott-Aldrich syndrome, 1071, 1144, 1179, 1678–1679, 1678*b*, 1679*t*
Wiskott-Aldrich syndrome protein (WASP), 1736–1737
Withdrawal of life support, 638, 638*t*, 638.*e1t*
WNK kinases, 746
Wnt signaling pathway, 1640
Wohlfart-Kugelberg-Welander disease, 2565
Wolbachia bacteria, 2061–2062
Wolff-Parkinson-White syndrome, 229, 306, 326
Women's health, 1606–1610
  alcohol use, 1609
  anxiety disorders, 1608*t*, 1609
  cancer, 1607
  cardiovascular disease, 1606
Women's health *(Continued)*
  depression, 1608*t*, 1609
  health disparities in, 1606
  human immunodeficiency virus, 1609
  incontinence, 1609
  lifespan groups for, 1606, 1606*t*
  medications for, 1608*t*
  morbidity causes, 1609
  mortality causes, 1606
  obesity, 1609
  osteoarthritis, 1609
  osteoporosis, 1607
  risks for atherosclerotic cardiovascular disease, 221.*e1f*
  severe acute respiratory syndrome coronavirus 2, 1610
  smoking, 1609
  substance use, 1609
  type 2 diabetes, 1607
  urinary tract infection in, prophylactic regimens for, 1877*t*
Women's Health Initiative, 1630*b*
Wood alcohol, 760
Work-exacerbated asthma, 586
  clinical manifestations of, 586–588
  diagnosis of, 586*b*
  epidemiology of, 586
  treatment of, 586*b*
Work of breathing, 641, 641*f*
Work-related asthma, 585
  clinical evaluation of, 587*f*
  management of, 587*f*
  occupations at risk for, 586*t*
Work-related disability, 85
Workers' compensation, 85
World Health Organization (WHO)
  classification of Hodgkin lymphoma, 1290*t*
  mastocytosis
    classification of, 1699*t*
    disease categories, 1702, 1702*t*
  on myelodysplastic syndromes, 1252
  non-Hodgkin lymphoma, 1279
  rubella, 2224
  sexually transmitted infection estimates, 1879
  on tuberculosis, 2032
World Health Organization/International Society of Urologic Pathology (WHO/ISUP), 1366
Wound
  botulism of, 1927
  infection
    Acinetobacter causing, 1973
    in endoscopy, 876*t*
  tetanus prophylaxis in, 1929*t*
Wrist
  disorders of, 1745
  fractures of, osteoporosis and, 1607
  rheumatoid arthritis of, 1751, 1753*f*
  surgical treatment of, 1828
Wuchereria bancrofti, 2176

X

X chromosome mutation, in premature ovarian failure, 1600
X-inactivation, 162
X-linked agammaglobulinemia, 1681*t*
X-linked hypophosphatemia, 1648
X-linked ichthyosis, 2687.*e3t*
X-linked lymphoproliferative syndrome, 2254
X-linked proliferative disorder (XLP), 1684
X-linked protoporphyria (XLP), 1428*t*, 1433
X-linked severe combined immunodeficiency, 175, 1676.*e3t*, 1678
X-linked thrombophilia, 476
Xalkori. *See* Crizotinib
Xanthelasma, 987, 2692*t*
Xanthine oxidase, 1810
Xanthogranuloma family, 1157–1158, 1158*b*
Xanthogranulomatous pyelonephritis, 791
Xanthoma disseminatum, 1157
Xanthomas, 216, 216.*e1f*, 1823
Xeljanz. *See* Tofacitinib
Xeloda. *See* Capecitabine
XEN402, 471*b*
Xenografts, 203
Xenopsylla cheopis, 1988
Xenotransplantation, of genetically modified animals, 172
Xerocytosis, 1097
Xeroderma pigmentosum, 1250*t*
Xerostomia, 2626
Xgeva. *See* Denosumab
Xpovio. *See* Selinexor
Xtandi. *See* Enzalutamide
XX male syndrome, 1574
XY female syndromes, 1574

Y

Yatapoxvirus, 2237, 2239
Yaws, 2021
Yellow fever, 99.*e1t*, 2275*t*, 2276
  clinical manifestations of, 2277
  definition of, 2276
  description of, 2265*t*, 2266, 2268*t*
  diagnosis of, 2277
  epidemiology of, 2276
  immunization for, 66*t*, 83
  pathobiology of, 2277
  treatment of, 2277*b*
  vaccine, for traveler, 1886*t*, 1887
Yellow nail syndrome, 2753, 2753*f*
Yersinia enterocolitica, 1993
Yersinia frederiksenii, 1988
Yersinia intermedia, 1988
Yersinia pestis, 1150, 1988, 1988*f*, 2065*t*. *See also* Plague
Yersinia pseudotuberculosis, 1993
Yersiniosis, 1993–1994
  clinical manifestations of, 1993–1994
  definition of, 1993
  diagnosis of, 1994
  epidemiology of, 1993
  pathobiology of, 1993
  pathogens that cause, 1993
  prevention of, 1994
  prognosis of, 1994
  treatment for, 1994*b*
Yervoy. *See* Ipilimumab
Yoga, 154
  for osteoarthritis, 1741*t*
Yondelis. *See* Trabectedin
Young modulus, 1720

Z

Z discs, 2580
Zafirlukast, 541*b*
Zaleplon, 2344*t*, 2452*t*
Zanamivir, for influenza, 2189, 2189*t*, 2202*b*, 2203*t*
Zanubrutinib, for chronic lymphocytic leukemia, 1269*t*
ZAP-70 deficiency, 1678, 1678.*e1t*
Zeaxanthin, 1452
Zejula. *See* Niraparib
Zelboraf. *See* Vemurafenib
Zenker diverticulum, 909, 909*f*
Zenpep, for exocrine pancreatic insufficiency, 975*t*
Zeposia. *See* Ozanimod
Zepzelca. *See* Lurbinectedin
Zidovudine, 2301*t*, 2303
  toxic myopathy caused by, 2313
Zika virus, 1203, 2065*t*, 2275*t*, 2278, 2278*b*, 2571
  in travelers, 1888, 1890*t*
Zileuton, 541*b*
Zinc, *e1t–e8t*, 1457*t*
  for malabsorption, 937*t*
  myelopathy and, 101*t*, 106, 107*b*
  toxicity, 88*t*
Zinc finger nucleases, 178
Zinc oxide, for pruritus ani, 980*b*
Zinc protoporphyrin, *e1t–e8t*
Zinc supplementation, for infectious gastroenteritis, 2263*b*
Zinecard. *See* Dexrazoxane
Ziprasidone, for psychotic disorders, 2346*t*
Zirconium cyclosilicate, for hyperkalemia, 751*b*
Zoledronate, for osteoporosis, 1644*t*
Zoledronic acid (Zometa), 1215*t*
  jaw osteonecrosis caused by, 1643*b*
  for osteoporosis, 1643*b*
  for Paget disease, 1664*t*
Zollinger-Ellison syndrome, 763, 1561*t*, 1562
  clinical manifestations of, 1562
  description of, 917
  diagnosis of, 918, 1563
  diarrhea associated with, 917
  differential diagnosis of, 1563
  pathobiology of, 1562
  prognosis of, 1563
  treatment of, 1563*b*
Zolmitriptan, 2380*t*
Zolpidem, 2344*t*, 2363, 2452*t*
Zometa. *See* Zoledronic acid
Zonisamide, *e10t–e11t*
  for myoclonus, 2495*b*
  for seizures, 2434*t*
Zoonoses, 2063–2066
  clinical manifestations of, 2064
  definition of, 2063–2066
  diagnosis of, 2065
  emerged and reemerging, examples of, 2065*t*
  epidemiology and pathobiology of, 2063–2064, 2064*f*, 2066*f*
  prevention of, 2065–2066
  prognosis of, 2066
  transmission of, 2064
  treatment of, 2065*b*
Zoonotic endocarditis, 417*b*
Zoonotic filarial infections, 2180
Zoonotic influenza, 2199
Zoonotic malaria, 2065*t*
Zoonotic spillover, 2063–2064
Zoster, 2248–2249, 2249*f*
  diagnosis of, 2249
  epidemiology of, 2248
  neuropathies associated with, 2578
  pathobiology of, 2248
  prevention of, 2250
  prophylaxis for, 2309*t*
  treatment of, 2249*b*
Zoster vasculopathy, zoster and, 2248
Zydelig. *See* Idelalisib
Zytiga. *See* Abiraterone acetate

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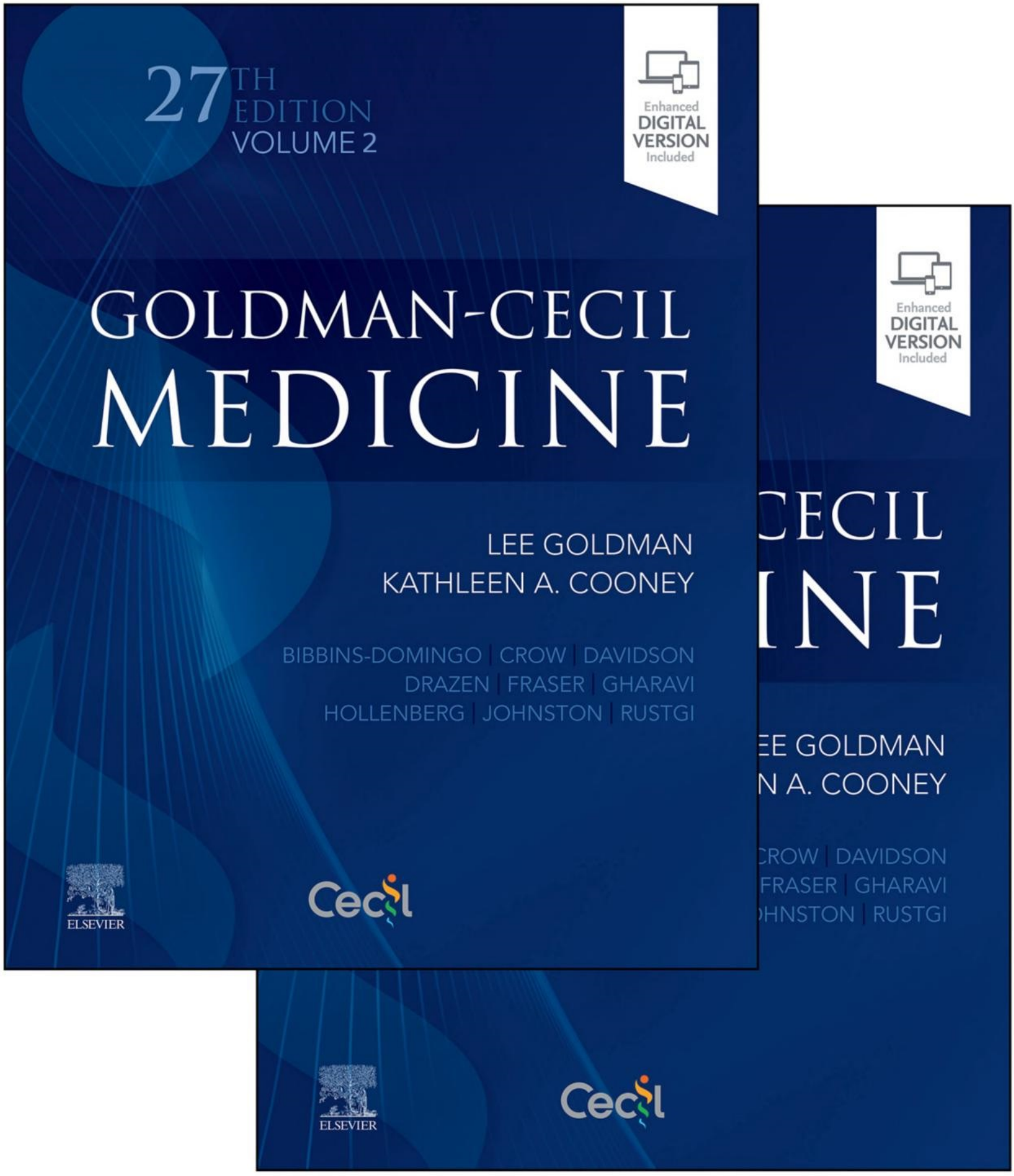

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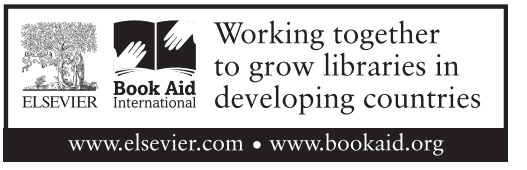

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PREFACE

In the more than 95 years since the first edition of the *Cecil Textbook of Medicine* was published, almost everything we know about internal medicine has changed. Progress in medical science is now occurring at an ever-accelerating pace, and it is doing so within the framework of transformational changes in biomedical science, clinical practice, and the delivery of health care at individual, societal, and global levels. This textbook and its associated electronic products incorporate the latest medical knowledge in multiple formats that should appeal to students and seasoned practitioners, regardless of how they prefer to access this rapidly changing information.

Even as *Cecil*'s specific information has changed, however, we have remained true to the tradition of a comprehensive textbook of medicine that carefully explains the *why* (the underlying genetics, genomics, and pathobiology of disease) and the *how* (now expected to be evidence-based from randomized controlled trials and meta-analyses). Descriptions of physiology and pathophysiology include the latest genetic advances in a practical format that strives to be useful to the nonexpert so that care can truly be as precise and personalized as possible.

Medicine has entered an era when the acuity of illness and the limited time available to evaluate a patient threaten the ability of physicians to satisfy their intellectual curiosity. As a result, the acquisition of information, quite easily achieved in this era, is often confused with knowledge. We have attempted to address this dilemma with a textbook that not only informs but also stimulates new questions and gives a glimpse of the future path to new knowledge. Grade A evidence is specifically highlighted in the text and referenced at the end of each chapter.

In addition to the information provided in the printed textbook and its electronic version, *Cecil* is commonly accessed on Elsevier's electronic Clinical Key platform. *Cecil* content and graphics are specifically organized to optimize not only its readability but also the searchability and utility of these electronic versions, which are continuously updated to incorporate new Grade A references and other evidence.

The section for each organ system begins with a chapter that summarizes an approach to patients with suspected or known dysfunction of that organ system. As summarized in E-Table 1-1, the text specifically provides clear, concise information regarding how a physician should approach more than 150 common symptoms, signs, and laboratory abnormalities, usually with a flow diagram, a table, or both for easy reference. In this way, *Cecil* remains a comprehensive text to guide diagnosis and therapy, not only for patients with suspected or known diseases, but also for patients who may have undiagnosed symptoms or signs that require an initial evaluation.

Just as each edition brings new authors, it also reminds us of our gratitude to past editors and authors. Previous senior editors of *Cecil* include a short but remarkably distinguished group of leaders of American medicine: Russell Cecil, Robert Loeb, Paul Beeson, Walsh McDermott, James Wyngaarden, Lloyd H. Smith, Jr., Fred Plum, J. Claude Bennett, Dennis Ausiello, and Andrew Schafer. As we welcome a group of outstanding new editors—Kathleen A. Cooney, Kirsten Bibbins-Domingo, Victoria J. Fraser, Ali G. Gharavi, Anthony N. Hollenberg, and S. Claiborne Johnston—we also express our appreciation to Robert C. Griggs, Donald W. Landry, Wendy Levinson, W. Michael Scheld, Allen M. Spiegel, and other associate editors from previous editions on whose foundation we continue to build. Our returning associate editors—Mary K. Crow, Nancy E. Davidson, Jeffrey M. Drazen, Anil K. Rustgi—continue to make critical contributions to the selection of authors and the review and approval of all chapters in their respective sections.

The tradition of *Cecil* is that all chapters are written by distinguished experts in each field. All told, our 409 chapters and the Appendix are written by approximately 570 individual authors. Steven A. Seifert, an author of the chapter on "Envenomation, Bites, and Stings," passed away after submitting his chapter, and we deeply mourn his passing.

The editors are most grateful for the superb editorial assistance of Maribel Lim, who expertly coordinated a team that included Caroline Davidson, Pamela Ehn, Julie Mangoff, and Joan Dupont, and without whose dedication, perseverance, and attention to detail this book never would have been possible. At Elsevier, we are most indebted to Dolores Meloni, Laura Schmidt, Daniel Fitzgerald, and Maggie Reid—dedicated professionals who have been critical to the planning and production of this edition.

This edition of *Goldman-Cecil Medicine* includes many new authors. We would also like to thank outgoing authors, who often provided figures that are included in this edition as well as tables that have been included or modified for this edition. Furthermore, because of the templated format and extensive editing that are characteristic of *Goldman-Cecil Medicine*, some new chapters incorporate principles, concepts, and organizational aspects from those prior chapters, often revised extensively prior to publication. Prior authors whose 26th edition coauthors have revised and updated their chapters include: Jeffrey L. Anderson, Gerald B. Appel, David Atkins, Richard L. Barbano, Stephen G. Baum, Hasan Bazari, George A. Beller, Paul D. Berk, Philip J. Bierman, Michael R. Bishop, William A. Blattner, William Bonnez, David M. Buchner, Edgar M. Carvalho, Troy E. Daniels, W. Lawrence Drew, George L. Drusano, David O. Freedman, John N. Galgiani, Jeffrey S. Ginsberg, Colleen Hadigan, Frederick G. Hayden, Douglas C. Heimburger, Edward W. Hook, III, Michael R. Jaff, Alain Joffe, Sian Jones, Carol A. Kauffman, Anthony E. Lang, Geoffrey S.F. Ling, Kieren A. Marr, Eric L. Matteson, William J. McKenna, Theodore E. Nash, Lindsay E. Nicolle, David L. Paterson, Srinivasa N. Raja, Daniel E. Rusyniak, George Sakoulas, Robert A. Salata, William Schaffner, W. Michael Scheld, Harry Shamoon, Richard M. Siegel, David P. Steensma, Raymond A. Strikas, and Ronald B. Turner. Special thanks also to Morton J. Kern, Gary S. Firestein, and Stephanie M. Stanford, whose excellent chapters were eliminated to save space, with their key information shortened and incorporated into other chapters. We also thank other non-returning authors from the 26th edition, many of whom had contributed to multiple editions: Grover C. Bagby, Thomas P. Bleck, Olaf A. Bodamer, Patrick J. Bosque, Lucy Breakwell, John C. Byrd, Clara Camaschella, Jane A. Cauley, William P. Cheshire, Jr., Arun Chockalingam, Steven L. Cohn, David S. Cooper, Joseph Craft, Mark R. Cullen, Stephen C. Dreskin, Thomas D. DuBose, Jr., Herbert L. DuPont, George M. Eliopoulos, Jerrold J. Ellner, Joel D. Ernst, Gregory T. Everson, Amelia Evoli, Martyn A. French, Susan I. Gerber, Dale N. Gerding, Matthew R. Golden, Richard M. Gore, Leslie C. Grammer, M. Lindsay Grayson, Lev M. Grinberg, Rajesh Gupta, H. Hunter Handsfield, David J. Hunter, Karen R. Jacobson, Stuart Johnson, Jacqueline Jonklaas, Gerald T. Keusch, Alexander Kratz, Virginia Byers Kraus, Frank A. Lederle, William M. Lee, James E. Leggett, Glenn N. Levine, Marc S. Levine, Bennett Lorber, Daniel R. Lucey, Peter Manu, Xavier Mariette, Thomas J. Marrie, Emeran A. Mayer, Stephan A. Mayer, Graeme Meintjes, Jonathan W. Mink, William E. Mitch, Bruce A. Molitoris, José G. Montoya, Daniel M. Musher, Stanley J. Naides, Anne T. Neff, Anne B. Newman, Gaetane Nocturne, James R. O'Dell, Pablo C. Okhuysen, Pankaj Jay Pasricha, Manisha Patel, Michael A. Pesce, James D. Ralston, Adam J. Ratner, Susan E. Reef, David B. Reuben, Karen Rosene-Montella, Renato M. Santos, Sam Schulman, Wun-Ju Shieh, Michael S. Simberkoff, Eric J. Small, Magdalena E. Sobieszczyk, Roland W. Sutter, Ronald G. Victor, Angela Vincent, Tonia L. Vincent, Edward H. Wagner, John T. Watson, David A. Weinstein, Anita K.M. Zaidi, Sherif Zaki, and Thomas Ziegler. We also thank Peter S. Aronson, who contributed to the chapter on "Acid-Base Disorders"; Ghada Hijazi, who contributed to the chapter on "Glycogen Storage Diseases"; Alexander Hillel, who contributed to the chapter on "Throat Disorders"; and Jason Pan, who contributed to the chapter on "Hepatic Failure and Liver Transplantation." Chapters written by public employees reflect recommendations and conclusions of

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Laboratory Testing in the Rheumatic Diseases

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Tumors of the Central Nervous System

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Interventional and Surgical Approaches to Lung Disease

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Microcytic and Hypochromic Anemias

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COVID-19: Epidemiology, Clinical Manifestations, Diagnosis, Community Prevention, and Prognosis; Prevention of Human Immunodeficiency Virus Infection

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Approach to the Patient with Neurologic Disease

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Systemic Antifungal Agents

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Rhabdomyolysis

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Aplastic Anemia and Related Bone Marrow Failure States

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Diabetes Mellitus

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Principles of Drug Therapy

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Nematode Infections

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Headaches and Other Head Pain

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Syphilis and Nonsyphilitic Treponematoses

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Von Willebrand Disease and Hemorrhagic Abnormalities of Platelet and Vascular Function

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Amyloidosis

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Approach to the Patient with Cancer

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Approach to Medicine, the Patient, and the Medical Profession: Medicine as a Learned and Humane Profession; Asthma

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Approach to the Patient with Urinary Tract Infection

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Clostridial and Clostridioides *Infections*

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Urinary Incontinence

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Zoonoses

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Effects of Climate Change on Health

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Parainfluenza Viral Disease

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Venous Thrombosis and Embolism

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Testicular Cancer

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Diseases of the Myocardium and Endocardium

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Bioethics in the Practice of Medicine

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Pseudomonas *and* Burkholderia *Infections*

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Diseases of the Esophagus

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ST-Elevation Acute Myocardial Infarction and Complications of Myocardial Infarction

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Haemophilus *and* Moraxella *Infections*

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Intimate Partner Violence

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Interventional and Surgical Approaches to Lung Disease

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Streptococcus pneumoniae *Pulmonary Infections*

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Principles of Electrophysiology

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Arterial Hypertension

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Approach to the Patient with Suspected Enteric Infection

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Pancreatitis

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Rickettsial Infections

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Infective Endocarditis

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Rotaviruses, Noroviruses, and Other Gastrointestinal Viruses

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Approach to Medicine, the Patient, and the Medical Profession: Medicine as a Learned and Humane Profession; Introduction to Microbial Disease: Pathophysiology and Diagnostics; Legionella *Infections*

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Approach to Women's Health

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Chronic Poisoning: Trace Metals and Others

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Hemolytic Anemias: Red Blood Cell Membrane and Metabolic Defects

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COVID-19: Epidemiology, Clinical Manifestations, Diagnosis, Community Prevention, and Prognosis

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COVID-19 Treatment and Vaccination

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Ventricular Arrhythmias

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Cirrhosis and Its Sequelae

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Diseases Caused by Chlamydiae

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Amyloidosis

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Approach to Medicine, the Patient, and the Medical Profession: Medicine as a Learned and Humane Profession; Approach to the Patient with Renal Disease

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Interstitial Nephritis

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Whooping Cough and Other Bordetella *Infections*

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Applications of Molecular Technologies to Clinical Medicine

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Systemic Manifestations of HIV/AIDS

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Herpes Simplex Virus Infections

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Mycoplasma *Infections*

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Approach to Medicine, the Patient, and the Medical Profession: Medicine as a Learned and Humane Profession; Approach to the Patient with Possible Cardiovascular Disease; Bradycardias and Conduction System Delays; Supraventricular Ectopy and Tachyarrhythmias

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Approach to Cerebrovascular Diseases; Ischemic Cerebrovascular Disease

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Shock Syndromes Related to Sepsis

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Cholera and Other Vibrio *Infections*

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Rotaviruses, Noroviruses, and Other Gastrointestinal Viruses

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Coma, Disorders of Consciousness, and Brain Death

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Hereditary Nephropathies and Developmental Renal/Urinary Abnormalities

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Approach to Medicine, the Patient, and the Medical Profession: Medicine as a Learned and Humane Profession; Approach to the Patient with Neurologic Disease

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Diseases of the Mouth and Salivary Glands

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Vascular Diseases of the Gastrointestinal Tract

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Overview of Pneumonia

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Mucormycosis; Mycetoma and Dematiaceous Fungal Infections

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Professor of Clinical Neurology (Emeritus), New York Medical College, Valhalla, New York
Nutritional and Alcohol-Related Neurologic Disorders

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Professor of Medicine, Washington University School of Medicine in St. Louis, St. Louis, Missouri
Approach to the Patient with Jaundice or Abnormal Liver Tests

Bruce R. Korf, MD, PhD
Wayne H. and Sara Crews Finley Endowed Chair in Medical Genetics, Distinguished Professor of Genetics, and Associate Dean for Genomic Medicine, University of Alabama at Birmingham Heersink School of Medicine, Birmingham, Alabama
Principles of Genetics

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Professor of Preventive Medicine and Medicine and Vice President for Research, Uniformed Services University of the Health Sciences, Bethesda, Maryland
Bioterrorism

Anita A. Koshy, MD
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Toxoplasmosis

Shyamasundaran Kottilil, MD, PhD
Professor of Medicine and Chief of Infectious Diseases, University of Maryland School of Medicine, Baltimore, Maryland
Antiviral Therapy (Non-HIV)

Joseph A. Kovacs, MD
Senior Investigator, Critical Care Medicine Department, National Institutes of Health Clinical Center, Bethesda, Maryland
Pneumocystis *Pneumonia*

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Professor of Medicine, David Geffen School of Medicine at UCLA, Los Angeles, California
Gastrointestinal Hemorrhage

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Professor of Medicine, Elson S. Floyd College of Medicine, and Director, Liver Institute Northwest, Washington State University, Seattle, Washington
Iron Overload (Hemochromatosis)

Monica Kraft, MD
Murray M. Rosenberg Professor and System Chair, Samuel Bronfman Department of Medicine, Icahn School of Medicine at Mount Sinai and Mount Sinai Health System, New York, New York
Approach to the Patient with Respiratory Disease

Christopher M. Kramer, MD
George A. Beller MD/Lantheus Medical Imaging Distinguished Professor of Cardiovascular Medicine and Chief, Cardiovascular Division, University of Virginia School of Medicine, Charlottesville, Virginia
Noninvasive Cardiac Imaging

Donna M. Krasnewich, MD, PhD
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Lysosomal Storage Diseases

William E. Kraus, MD
Richard and Pat Johnson Distinguished University Professor, Duke University School of Medicine, Durham, North Carolina
Physical Activity

Peter J. Krause, MD
Senior Research Scientist, Yale University School of Public Health and Yale University School of Medicine, New Haven, Connecticut
Babesiosis and Other Protozoan Diseases

Andrew T. Kroger, MD, MPH
Medical Officer, National Center for Immunization and Respiratory Diseases, Centers for Disease Control and Prevention, Atlanta, Georgia
Immunization

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Professor, Vice Chair of Strategic Initiatives and Faculty Development, and Director of Pediatric Dermatology, Department of Dermatology, Duke University School of Medicine, Durham, North Carolina
Macular, Papular, Purpuric, Vesiculobullous, and Pustular Diseases

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Professor of Medicine, Virginia Commonwealth University School of Medicine, Richmond, Virginia
Inflammatory and Anatomic Diseases of the Intestine, Peritoneum, Mesentery, and Omentum

Ernst J. Kuipers, MD, PhD
Professor of Medicine, Erasmus MC University Medical Center, Rotterdam, Netherlands
Acid Peptic Disease

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Professor of Medicine, University of Colorado School of Medicine, Aurora, Colorado
Palliative Care

Daniel Laheru, MD
Ian T. MacMillan Professorship in Clinical Pancreatic Research, Johns Hopkins University School of Medicine, Baltimore, Maryland
Pancreatic Cancer

Rachel Lampert, MD
Professor of Medicine, Yale University School of Medicine, New Haven, Connecticut
Cardiac Arrest and Life-Threatening Arrhythmias

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Professor and Chair of Medicine, University of Alabama at Birmingham Heersink School of Medicine, Birmingham, Alabama
Geriatric Assessment

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Prevention of Human Immunodeficiency Virus Infection

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Approach to the Patient with Renal Disease

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Acute Coronary Syndrome: Unstable Angina and Non–ST Elevation Myocardial Infarction

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John Romano Professor and Chair, Department of Psychiatry, University of Rochester School of Medicine & Dentistry, Rochester, New York
Psychiatric Disorders in Medical Practice

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Influenza

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Professor of Medicine and Dr. Gerald J and Dorothy R Friedman Professor Emeritus, Tufts University School of Medicine; Chief Emeritus, Division of Nephrology, Tufts Medical Center, Boston, Massachusetts
Chronic Kidney Disease

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Alveolar Filling Disorders

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Inflammatory Bowel Disease

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Shirlee and Bernard Brown Professor and Vice Chair, Department of Ophthalmology, Columbia University Vagelos College of Physicians and Surgeons, New York, New York
Diseases of the Visual System

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Professor of Medicine, Falk Chair in Ambulatory Medicine, and Chief, Division of General Internal Medicine, University of Pittsburgh School of Medicine, UPMC Health System, Pittsburgh, Pennsylvania
Drug Use Disorders

Henry W. Lim, MD
Former Chair, Department of Dermatology; Senior Vice President for Academic Affairs, Henry Ford Health, Detroit, Michigan
Eczemas, Photodermatoses, Papulosquamous (Including Fungal) Diseases, and Figurate Erythemas

Aldo A.M. Lima, MD, PhD
Professor, Institute of Biomedicine, Federal University of Ceara, Fortaleza, Ceará, Brazil
Cryptosporidiosis

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Professor of Medicine and Director, Solid Organ Transplant Infectious Disease Program, Departments of Medicine and Laboratory Medicine, Division of Allergy & Infectious Diseases, University of Washington, Seattle, Washington
Cytomegalovirus

Nita A. Limdi, PharmD, PhD, MSPH
Ray L Watts Heersink Endowed Chair and Professor, Departments of Neurology and of Epidemiology; Director, Translational Pharmacogenomics Program and Associate Director, Hugh Kaul Precision Medicine Institute, University of Alabama Birmingham Heersink School of Medicine, Birmingham, Alabama
Principles of Genetics

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Electrocardiography

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Professor, Vaccine and Infectious Disease Division, Fred Hutchinson Cancer Center; Professor of Medicine, University of Washington, Seattle, Washington
Staphylococcal Infections

Donald M. Lloyd-Jones, MD, ScM
Eileen M. Foell Professor of Heart Research; Professor of Preventive Medicine, Medicine, and Pediatrics; Chair, Department of Preventive Medicine; Northwestern University Feinberg School of Medicine, Chicago, Illinois
Epidemiology of Cardiovascular Disease

Fred A. Lopez, MD
Richard Vial Professor and Vice Chair, Department of Medicine, Louisiana State University Health Sciences Center-New Orleans, New Orleans, Louisiana
Tularemia and Other Francisella *Infections*

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Professor of Medicine, Molecular Genetics and Microbiology and Associate Director, Institute for Therapeutic Innovation, University of Florida College of Medicine, Orlando, Florida
Antibacterial Chemotherapy

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President and CEO, American Board of Psychiatry & Neurology, Deerfield, Illinois; Professor Emeritus of Psychiatry, University of Rochester School of Medicine & Dentistry, Rochester, New York
Psychiatric Disorders in Medical Practice

C. Ronald MacKenzie, MD
C. Ronald MacKenzie Chair in Ethics and Medicine, Hospital for Special Surgery; Professor of Clinical Medicine and Medical Ethics, Weill Medical College of Cornell University, New York, New York
Surgical Treatment of Joint Diseases

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Shigellosis

Harriet L. MacMillan, CM, MD, MSc
Chedoke Health Chair in Child Psychiatry and Distinguished University Professor of Psychiatry & Behavioural Neurosciences and of Pediatrics, Offord Centre for Child Studies, McMaster University Michael G. DeGroote School of Medicine, Hamilton, Ontario, Canada
Intimate Partner Violence

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Diseases of the Rectum and Anus

Jacquelyn Maher, MD
William and Mary Ann Rice Distinguished Professor of Medicine and Director of UCSF Liver Center, University of California, San Francisco School of Medicine, San Francisco, California
Alcoholic and Nonalcoholic Steatohepatitis

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Physical and Chemical Injuries of the Lung

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Pathobiology of Human Immunodeficiency Viruses

Atul Malhotra, MD
Peter C Farrell Presidential Chair and Professor of Medicine, Research Chief of Pulmonary and Critical Care Medicine, and Director of Sleep Medicine, University of California, San Diego, School of Medicine, La Jolla, California
Disorders of Ventilatory Control

Mark J. Manary, MD
Helene B. Roberson Professor of Pediatrics, Washington University, St. Louis, Missouri
Severe Malnutrition

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Associate Professor of Medicine and Director of the Tick-Borne Disease Center, Division of Infectious Diseases, Department of Medicine; Department of Microbiology and Immunology, Renaissance School of Medicine at Stony Brook University, Stony Brook, New York
Trematode Infections

Ariane J. Marelli, MD, MPH
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Congenital Heart Disease in Adults

Andrew R. Marks, MD
Wu Professor and Chair, Department of Physiology and Cellular Biophysics, Director, Helen and Clyde Wu Center for Molecular Cardiology, Columbia University Vagelos College of Physicians and Surgeons, New York, New York
Cardiac and Circulatory Function

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Professor of Medicine, Washington University School of Medicine in St. Louis, St. Louis, Missouri
Legionella *Infections*

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Mandel Chair in Gastroenterology and Chief, Division of Digestive Health and Liver Diseases, University of Miami Miller School of Medicine, Miami, Florida
Approach to the Patient with Liver Disease

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Bruce Webster Professor of Internal Medicine, Weill Medical College of Cornell University; Chief, Division of Pulmonary and Critical Care Medicine, Weill Medical College of Cornell University/NY Presbyterian Hospital, New York, New York
Interstitial Lung Disease

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Vitamins, Trace Minerals, and Other Micronutrients

Henry Masur, MD
Chief, Critical Care Medicine Department, Clinical Center, National Institutes of Health, Bethesda, Maryland
Microbial Complications of HIV/AIDS

Amy J. Mathers, MD
Associate Professor of Medicine and Pathology, Associate Director of Clinical Microbiology, and Medical Director Antimicrobial Stewardship, University of Virginia School of Medicine, Charlottesville, Virginia
Enterobacterales: Non-Enteric Infections and Multidrug Resistance

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Professor of Medicine and Anesthesia, University of California, San Francisco School of Medicine, San Francisco, California
Acute Respiratory Failure

F. Dennis McCool, MD
Professor of Medicine, Warren Alpert Medical School of Brown University, Providence, Rhode Island
Diseases of the Diaphragm, Chest Wall, Pleura, and Mediastinum

Iain B. McInnes, PhD
Vice-Principal and Head of College of Medical, Veterinary and Life Sciences, Muirhead Chair of Medicine/Versus Arthritis Professor of Rheumatology, University of Glasgow, Glasgow, United Kingdom
Rheumatoid Arthritis

Vallerie McLaughlin, MD
Kim A. Eagle MD Endowed Professor of Cardiovascular Medicine, Professor of Medicine, and Director, Pulmonary Hypertension Program, University of Michigan Medical School, Ann Arbor, Michigan
Pulmonary Hypertension

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Professor of Dermatology, Wake Forest School of Medicine, Winston-Salem, North Carolina
Infections, Pigmentation Disorders, Regional Dermatology, and Distinctive Lesions in Black Skin

John J.V. McMurray, MB ChB, MD
Professor of Medical Cardiology, British Heart Foundation Cardiovascular Research Centre, University of Glasgow; Honorary Consultant Cardiologist, Queen Elizabeth University Hospital Glasgow, Glasgow, Scotland, United Kingdom
Heart Failure: Treatment and Prognosis

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Professor of Clinical Medicine and Vice-Chair, Department of Medicine, University of California, San Francisco School of Medicine; Chief of the Medical Service, San Francisco Veterans Affairs Medical Center, San Francisco, California
Approach to the Patient with Gastrointestinal Disease

Paul S. Mead, MD, MPH
Chief, Bacterial Diseases Branch, Division of Vector-Borne Diseases, Centers for Disease Control and Prevention, Fort Collins, Colorado
Plague and Other Yersinia *Infections*

Robert T. Means, Jr., MD
Professor of Internal Medicine and Clinical Professor of Pathology, East Tennessee State University James H. Quillen College of Medicine, Johnson City, Tennessee
Approach to the Anemias

Michael T. Melia, MD
Associate Professor of Medicine, Johns Hopkins University School of Medicine, Baltimore, Maryland
Approach to Fever or Suspected Infection in the Normal Host

Ingo K. Mellinghoff, MD
Chair, Department of Neurology, Memorial Sloan Kettering Cancer Center; Professor of Neurology and of Neuroscience, Weill Medical College of Cornell University, New York, New York
Tumors of the Central Nervous System

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Professor of Surgery, University of Minnesota Medical School, Minneapolis, Minnesota
Diseases of the Rectum and Anus

Samuel T. Merrick, MD
Professor of Clinical Medicine, Weill Medical College of Cornell University, New York, New York
Systemic Manifestations of HIV/AIDS

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Clinical Professor of Infectious Diseases and Internal Medicine, University of Michigan Medical School, Ann Arbor, Michigan
Endemic Mycoses

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Professor and Head of the Department of Internal Medicine and Clinical Immunology, Henri Mondor University Hospital, Assistance Publique Hopitaux de Paris, Université Paris-Est Créteil, Creteil, France
Autoimmune and Intravascular Hemolytic Anemias

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Chief Strategy Officer, Population Health, and Professor of Health Metrics Sciences, Department of Health Metrics Sciences, Institute of Health Metrics and Evaluation, University of Washington, Seattle, Washington
Global Health

Ernest Moy, MD, MPH
Executive Director, Office of Health Equity, Veterans Health Administration, Washington D.C.
Measuring Health and Health Care

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Acute Coronary Syndrome: Unstable Angina and Non–ST Elevation Myocardial Infarction

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Approach to the Patient with Nose, Sinus, and Ear Disorders

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Professor of Medicine, Cardiovascular Genetics, and Physiology, Department of Medicine, University of Miami Miller School of Medicine, Miami, Florida
Cardiac Arrest and Life-Threatening Arrhythmias

Kari C. Nadeau, MD, PhD
John Rock Professor of Climate and Population Studies and Chair, Department of Environmental Health, Harvard T.H. Chan School of Public Health, Boston, Massachusetts
Approach to the Patient with Allergic or Immunologic Disease

Avindra Nath, MD
Chief, Section of Infections of the Nervous System, National Institutes of Neurological Diseases and Stroke, National Institutes of Health, Bethesda, Maryland
Meningitis: Bacterial, Viral, and Other; Brain Abscess and Parameningeal Infections

Genevieve Neal-Perry, MD, PhD
Robert A. Ross Distinguished Professor and Chair, Department of Obstetrics and Gynecology, University of North Carolina School of Medicine, Chapel Hill, North Carolina
Menopause

Eric G. Neilson, MD
Vice President for Medical Affairs, Lewis Landsberg Dean, and Professor of Medicine and of Cell and Developmental Biology, Northwestern University Feinberg School of Medicine, Chicago, Illinois
Interstitial Nephritis

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Medical Officer, Bacterial Diseases Branch, Division of Vector-Borne Diseases, Centers for Disease Control and Prevention, Fort Collins, Colorado
Plague and Other Yersinia *Infections*

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Gillette Professorship of Obstetrics and Gynecology, Dedman Family Scholar in Clinical Care, Associate Professor of Obstetrics and Gynecology and Chief, Division of Maternal-Fetal Medicine, University of Texas Southwestern Medical Center, Dallas, Texas
Medical Issues in Pregnancy

Lewis S. Nelson, MBA, MD
Professor and Chair, Department of Emergency Medicine; Director, Division of Medical Toxicology, Rutgers New Jersey Medical School, Newark, New Jersey
Acute Poisoning

Eric J. Nestler, MD, PhD
Nash Family Professor of Neuroscience and Director, Friedman Brain Institute, Icahn School of Medicine at Mount Sinai, New York, New York
Biology of Addiction

Kathleen M. Neuzil, MD, MPH
Myron M. Levine Professor of Medicine and Pediatrics and Director, Center for Vaccine Development and Global Health, University of Maryland School of Medicine, Baltimore, Maryland
COVID-19 Treatment and Vaccination

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Senior Investigator, Diabetes, Endocrinology and Obesity Branch, National Institute of Diabetes and Digestive and Kidney Diseases, National Institutes of Health, Bethesda, Maryland
Approach to the Patient with Endocrine Disease; Adrenal Cortex; Polyglandular Disorders

Alexander S. Niven, MD
Professor of Medicine, Mayo Clinic College of Medicine and Science, Rochester, Minnesota
Respiratory Testing and Function

Christopher M. O'Connor, MD
Adjunct Professor of Medicine, Duke University School of Medicine, Durham, North Carolina; CEO, Inova Heart and Vascular Institute, Fairfax, Virginia
Heart Failure: Epidemiology, Pathobiology, and Diagnosis

Francis G. O'Connor, MD, MPH
Professor of Military and Emergency Medicine and Medical Director, Consortium for Health and Military Performance, Uniformed Services University of the Health Sciences, Bethesda, Maryland
Disorders Due to Heat and Cold; Rhabdomyolysis

Patrick G. O'Connor, MD, MPH
Dan Adams and Amanda Adams Professor of Medicine and Chief, General Internal Medicine, Yale University School of Medicine, New Haven, Connecticut
Alcohol Use Disorders

Anne E. O'Donnell, MD
The Nehemiah and Naomi Cohen Chair in Pulmonary Disease Research, Georgetown University School of Medicine; Chief, Division of Pulmonary, Critical Care and Sleep Medicine, Georgetown University Medical Center, Washington, D.C.
Bronchiectasis, Atelectasis, Cavitary, or Cystic Lung Diseases

James S. O'Donnell, MD, PhD
Professor, Irish Centre for Vascular Biology, Royal College of Surgeons in Ireland, Dublin, Ireland
Von Willebrand Disease and Hemorrhagic Abnormalities of Platelet and Vascular Function

Jae K. Oh, MD
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Pericardial Diseases

Michael S. Okun, MD
Professor and Chair of Neurology, Fixel Institute for Neurological Diseases, University of Florida College of Medicine, Gainesville, Florida
Parkinsonism; Other Movement Disorders

Sean T. O'Leary, MD, MPH
Professor of Pediatrics, University of Colorado School of Medicine, Aurora, Colorado
Papillomavirus

Jeffrey E. Olgin, MD
Gallo-Chatterjee Distinguished Professor and Chief of Cardiology, University of California, San Francisco School of Medicine, San Francisco, California
Approach to the Patient with Suspected Arrhythmia

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Professor of Medicine, University of North Carolina at Chapel Hill, Chapel Hill, North Carolina
The Nontuberculous Mycobacteria

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Professor of Cardiovascular Medicine, Meyer Children's Hospital IRCCS, University of Florence, Florence, Italy
Diseases of the Myocardium and Endocardium

Nancy J. Olsen, MD
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Biologic Agents and Signaling Inhibitors

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Professor of Medicine, Pediatrics, Epidemiology & Global Health, Emory University School of Medicine; Associate Director, Emory Vaccine Center, Atlanta, Georgia
Immunization

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Professor of Medicine and Pathology and Chief, Division of Hematology, Duke University School of Medicine, Durham, North Carolina
Antithrombotic and Antiplatelet Therapy

John J. O'Shea, MD
Scientific Director, National Institute of Arthritis and Musculoskeletal and Skin Diseases, National Institutes of Health, Bethesda, Maryland
Biologic Agents and Signaling Inhibitors

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Infections of Bursae, Joints, and Bones

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Parkinsonism; Other Movement Disorders

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Mucormycosis

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Echocardiography

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Measles

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Professor of Medicine, Mayo Clinic College of Medicine and Science, Rochester, Minnesota
Rubella (German Measles)

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Professor of Medicine, University of Alabama at Birmingham Heersink School of Medicine, Birmingham, Alabama
Candidiasis; Mycetoma and Dematiaceous Fungal Infections

Ben Ho Park, MD, PhD
Benjamin F. Byrd, Jr Chair in Oncology and Professor of Medicine, Vanderbilt University School of Medicine; Director, Vanderbilt-Ingram Cancer Center, Vanderbilt University Medical Center, Nashville, Tennessee
Cancer Biology and Genetics

Robin Patel, MD
Elizabeth P. and Robert E. Allen Professor of Individualized Medicine and Professor of Medicine and of Microbiology; Director, Infectious Diseases Research Laboratory and Vice Chair Education, Department of Laboratory Medicine and Pathology, Mayo Clinic College of Medicine and Science, Rochester, Minnesota
Introduction to Microbial Disease: Pathophysiology and Diagnostics

Thomas F. Patterson, MD
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Aspergillosis

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Acute Viral Hepatitis; Chronic Viral and Autoimmune Hepatitis

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Professor of Medicine and Professor of Biomedical Informatics and Medical Education, University of Washington School of Medicine; Adjunct Professor of Health Systems and Population Health, University of Washington School of Public Health, Seattle, Washington
Statistical Interpretation of Data for Clinical Decision Making

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Professor of Medicine, Boston University Chobanian & Avedisian School of Medicine, Boston, Massachusetts
Thyroid

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Professor Emeritus of Medicine, University of Virginia School of Medicine, Charlottesville, Virginia
Antiparasitic Therapy

Trish M. Perl, MD, MSc
Professor of Medicine and H. Ben and Isabelle T. Decherd Chair in Internal Medicine in Honor of Henry M. Winans, Sr., M.D., University of Texas Southwestern Medical Center, Dallas, Texas
Enterococcal Infections

Brett W. Petersen, MD, MPH
Deputy Branch Chief, Poxvirus and Rabies Branch, Centers for Disease Control and Prevention, Atlanta, Georgia
Smallpox, Monkeypox, and Other Poxvirus Infections

William A. Petri, Jr., MD, PhD
Wade Hampton Frost Professor of Epidemiology and Vice Chair for Research, Department of Medicine, University of Virginia School of Medicine, Charlottesville, Virginia
Relapsing Fever and Other Borrelia *Infections; African Sleeping Sickness; Amebiasis*

Marc A. Pfeffer, MD, PhD
Distinguished Dzau Professor of Medicine, Harvard Medical School; Senior Physician, Brigham and Women's Hospital, Boston, Massachusetts
Heart Failure: Treatment and Prognosis

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Theodore and Bertha Bryan Professor of Medicine and Molecular Microbiology and Co-Director, Division of Infectious Diseases, Washington University School of Medicine in St. Louis, St. Louis, Missouri
Tuberculosis

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Professor of Medicine and Immunology, Duke University School of Medicine; Medical Research Service, VA Medical Center, Durham, North Carolina
Laboratory Testing in the Rheumatic Diseases

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Approach to the Patient with Nose, Sinus, and Ear Disorders

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Pre-2019 Coronaviruses

Gregory A. Poland, MD
Lowell Leary Emeritus Mary Professor of Medicine and Director, Vaccine Research Group, Mayo Clinic College of Medicine and Science, Rochester, Minnesota
Rubella (German Measles)

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Disorders of Ventilatory Control

Reed E. Pyeritz, MD, PhD
William Smilow Professor of Medicine and Genetics, Emeritus, University of Pennsylvania Perelman School of Medicine, Philadelphia, Pennsylvania
Inherited Diseases of Connective Tissue

Thomas C. Quinn, MD, MSc
Professor of Medicine and Pathology and Director, Center for Global Health, Johns Hopkins University School of Medicine; Associate Director for International Research, National Institute of Allergy and Infectious Diseases, National Institutes of Health, Baltimore, Maryland
Epidemiology and Diagnosis of Human Immunodeficiency Virus Infection and Acquired Immunodeficiency Syndrome; Acute Clinical Manifestations and Diagnosis of HIV

Vincent Racaniello, PhD
Higgins Professor of Microbiology & Immunology, Columbia University Vagelos College of Physicians and Surgeons, New York, New York
COVID-19: Virology and Pathology

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Professor of Medicine, Columbia University Vagelos College of Physicians and Surgeons; Clinical Director, Division of Nephrology, Columbia University Irving Medical Center, New York, New York
Disorders of Sodium and Water; Glomerular Disorders and Nephrotic Syndromes

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Chronic Myeloid Leukemia

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Pseudomonas *and* Burkholderia *Infections*

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Interstitial Lung Disease

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Coagulation Factor Deficiencies

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Spondyloarthritis

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Plasma Cell Disorders

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Paget Disease of Bone

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Bartonella *Infections; Rickettsial Infections*

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Gram-Positive Rod Infections

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Bacterial, Parasitic, Fungal, and Granulomatous Liver Diseases

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Postoperative Care and Complications

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Occupational Lung Disease

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Chronic Obstructive Pulmonary Disease

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Associate Professor of Medicine, Duke University School of Medicine, Durham, North Carolina
Zoonoses

Hilary E.L. Reno, MD, PhD
Professor of Medicine, Washington University in St. Louis, St. Louis, Missouri
Diseases Caused by Chlamydiae

Neil M. Resnick, MD
Thomas Detre Professor of Medicine, University of Pittsburgh School of Medicine; Chief, Division of Geriatric Medicine and Gerontology, University of Pittsburgh Medical Center, Pittsburgh, Pennsylvania
Urinary Incontinence

Louis B. Rice, MD
Joukowsky Family Professor and Chair of Medicine, Professor of Molecular Microbiology and Immunology, Warren Alpert Medical School of Brown University, Providence, Rhode Island
Principles of Anti-Infective Therapy

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Systemic Antifungal Agents

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Nonpneumococcal Streptococcal Infections and Rheumatic Fever

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Glomerular Disorders and Nephrotic Syndromes

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Myelodysplastic Syndromes

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Approach to the Patient with a Sexually Transmitted Infection

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Neisseria gonorrhoeae *Infections*

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Interventional Diagnosis and Treatment of Coronary Artery Disease

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Babesiosis and Other Protozoan Diseases

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Disorders of Magnesium and Phosphorus

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CONTENTS

VOLUME 1

SECTION I: SOCIAL AND ETHICAL ISSUES IN MEDICINE

1 Approach to Medicine, the Patient, and the Medical Profession: Medicine as a Learned and Humane Profession 2
LEE GOLDMAN, KATHLEEN A. COONEY, KIRSTEN BIBBINS-DOMINGO, MARY K. CROW, NANCY E. DAVIDSON, JEFFREY M. DRAZEN, VICTORIA J. FRASER, ALI G. GHARAVI, ANTHONY N. HOLLENBERG, S. CLAIBORNE JOHNSTON, AND ANIL K. RUSTGI

2 Bioethics in the Practice of Medicine 5
EZEKIEL J. EMANUEL

3 Palliative Care 11
ROBERT M. ARNOLD AND JEAN S. KUTNER

4 Disparities in Health and Health Care 17
JOHN Z. AYANIAN

5 Global Health 21
ALI H. MOKDAD

SECTION II: PRINCIPLES OF EVALUATION AND MANAGEMENT

6 History and Physical Examination 28
DAVID L. SIMEL

7 Approach to the Patient with Abnormal Vital Signs 32
DAVID L. SCHRIGER

8 Statistical Interpretation of Data for Clinical Decision Making 35
THOMAS H. PAYNE

9 Measuring Health and Health Care 40
CAROLYN M. CLANCY AND ERNEST MOY

10 Quality, Safety, and Value 43
ROBERT M. WACHTER AND KAVEH G. SHOJANIA

11 Population Health 47
KIRSTEN BIBBINS-DOMINGO

SECTION III: PREVENTIVE AND ENVIRONMENTAL ISSUES

12 The Preventive Health Visit 52
MARY B. BARTON AND TRACY A. WOLFF

13 Diet and Nutrition 57
DONALD D. HENSRUD

14 Physical Activity 61
WILLIAM E. KRAUS

15 Immunization 64
ANDREW T. KROGER AND WALTER A. ORENSTEIN

16 Principles of Occupational and Environmental Medicine 84
JUDITH GREEN-MCKENZIE

17 Effects of Climate Change on Health 89
JEREMY HESS AND KRISTIE EBI

18 Radiation Injury 91
DAVID J. BRENNER

19 Bioterrorism 95
MARK G. KORTEPETER AND THEODORE J. CIESLAK

20 Chronic Poisoning: Trace Metals and Others 101
LOUISE W. KAO, LAURA TORMOEHLEN, AND BLAKE A. FROBERG

SECTION IV: AGE-SPECIFIC AND GERIATRIC MEDICINE

21 Adolescent Medicine 110
DEBRA K. KATZMAN AND S. TODD CALLAHAN

22 Epidemiology of Aging 114
LOUISE ARONSON

23 Geriatric Assessment 116
C. SETH LANDEFELD

24 Common Clinical Sequelae of Aging 120
JEREMY D. WALSTON

SECTION V: CLINICAL PHARMACOLOGY

25 Principles of Drug Therapy 126
ROBERT B. DIASIO

26 Pain 133
STEVEN P. COHEN

27 Biology of Addiction 142
ERIC J. NESTLER

28 Immunomodulatory Drugs 144
ANNE R. BASS AND INEZ ROGATSKY

29 Biologic Agents and Signaling Inhibitors 149
NANCY J. OLSEN AND JOHN J. O'SHEA

30 Complementary and Integrative Medicine 153
FREDERICK M. HECHT

SECTION VI: GENETICS

31 Principles of Genetics 158
BRUCE R. KORF AND NITA A. LIMDI

32 Clinical Genomics—Genome Structure and Variation 160
LESLIE G. BIESECKER

33 Applications of Molecular Technologies to Clinical Medicine 165
GEOFFREY S. GINSBURG

34 Regenerative Medicine, Cell Therapy, and Gene Therapy 169
LIOR GEPSTEIN AND KARL SKORECKI

SECTION VII: PRINCIPLES OF IMMUNOLOGY AND INFLAMMATION

35 The Innate and Adaptive Immune Systems 182
MARY K. CROW

36 Tissue Injury and Repair 191
JANE E. SALMON

37 Complement System in Disease 196
JOHN P. ATKINSON AND V. MICHAEL HOLERS

38 Transplantation Immunology 203
MEGAN SYKES

SECTION VIII: HEART DISEASES

39 Approach to the Patient with Possible Cardiovascular Disease 210
LEE GOLDMAN

40 Epidemiology of Cardiovascular Disease 219
DONALD M. LLOYD-JONES

41 Cardiac and Circulatory Function 223
ANDREW R. MARKS

Copyrighted material

42 Electrocardiography 228
LEONARD GANZ AND MARK S. LINK

43 Echocardiography 235
CATHERINE M. OTTO

44 Noninvasive Cardiac Imaging 244
CHRISTOPHER M. KRAMER, VASKEN DILSIZIAN, AND KLAUS D. HAGSPIEL

45 Heart Failure: Epidemiology, Pathobiology, and Diagnosis 254
JOSEPH G. ROGERS AND CHRISTOPHER M. O'CONNOR

46 Heart Failure: Treatment and Prognosis 262
JOHN J.V. MCMURRAY AND MARC A. PFEFFER

47 Diseases of the Myocardium and Endocardium 279
PERRY M. ELLIOTT AND IACOPO OLIVOTTO

48 Principles of Electrophysiology 298
GLENN I. FISHMAN

49 Approach to the Patient with Suspected Arrhythmia 303
JEFFREY E. OLGIN

50 Cardiac Arrest and Life-Threatening Arrhythmias 312
ROBERT J. MYERBURG AND RACHEL LAMPERT

51 Bradycardias and Conduction System Delays 317
PETER ZIMETBAUM AND LEE GOLDMAN

52 Supraventricular Ectopy and Tachyarrhythmias 322
PETER ZIMETBAUM AND LEE GOLDMAN

53 Ventricular Arrhythmias 332
HASAN GARAN

54 Electrophysiologic Procedures and Surgery 340
PETER A. SANTUCCI AND DAVID J. WILBER

55 Congenital Heart Disease in Adults 347
JUDITH THERRIEN AND ARIANE J. MARELLI

56 Angina Pectoris and Chronic Ischemic Heart Disease 356
WILLIAM E. BODEN

57 Acute Coronary Syndrome: Unstable Angina and Non–ST Elevation Myocardial Infarction 370
RICHARD A. LANGE AND DEBABRATA MUKHERJEE

58 ST-Elevation Acute Myocardial Infarction and Complications of Myocardial Infarction 380
FREDERICK G.P. WELT AND JAMES C. FANG

59 Interventional Diagnosis and Treatment of Coronary Artery Disease 393
PAUL S. TEIRSTEIN AND AJAY J. KIRTANE

60 Valvular Heart Disease 400
BLASE A. CARABELLO AND SUSHEEL KODALI

61 Infective Endocarditis 413
VANCE G. FOWLER, JR., ARNOLD S. BAYER, AND LARRY M. BADDOUR

62 Pericardial Diseases 423
BRIAN D. HOIT AND JAE K. OH

SECTION IX: VASCULAR MEDICINE

63 Diseases of the Aorta 436
JOSHUA A. BECKMAN

64 Arterial Hypertension 444
JOHN M. FLACK

65 Atherosclerotic Peripheral Arterial Disease 461
CHRISTOPHER J. WHITE

66 Other Peripheral Arterial Diseases 467
JOHN R. BARTHOLOMEW

67 Thrombotic Disorders: Hypercoagulable States 475
ANDREW I. SCHAFER

68 Venous Thrombosis and Embolism 482
JEFFREY I. WEITZ AND JOHN W. EIKELBOOM

69 Pulmonary Hypertension 493
MARIUS M. HOEPER AND VALLERIE MCLAUGHLIN

70 Antithrombotic and Antiplatelet Therapy 501
RICHARD C. BECKER AND THOMAS L. ORTEL

SECTION X: RESPIRATORY DISEASES

71 Approach to the Patient with Respiratory Disease 512
MONICA KRAFT

72 Imaging in Pulmonary Disease 519
PAUL STARK

73 Respiratory Testing and Function 528
PAUL D. SCANLON AND ALEXANDER S. NIVEN

74 Disorders of Ventilatory Control 534
ATUL MALHOTRA AND FRANK POWELL

75 Asthma 537
JEFFREY M. DRAZEN AND ELISABETH H. BEL

76 Chronic Obstructive Pulmonary Disease 547
JOHN REILLY

77 Cystic Fibrosis 556
HARTMUT GRASEMANN

78 Bronchiectasis, Atelectasis, and Cavitary or Cystic Lung Diseases 560
ANNE E. O'DONNELL

79 Alveolar Filling Disorders 566
STEPHANIE M. LEVINE

80 Interstitial Lung Disease 570
GANESH RAGHU AND FERNANDO J. MARTINEZ

81 Occupational Lung Disease 584
SUSAN M. TARLO AND CARRIE A. REDLICH

82 Physical and Chemical Injuries of the Lung 591
DAVID C. CHRISTIANI AND LISA A. MAIER

83 Sarcoidosis 599
MICHAEL C. IANNUZZI

84 Acute Bronchitis and Tracheitis 605
GONZALO M. BEARMAN AND RICHARD P. WENZEL

85 Overview of Pneumonia 606
LINDSEY R. BADEN, MARIE R. GRIFFIN, AND MICHAEL KLOMPAS

86 Diseases of the Diaphragm, Chest Wall, Pleura, and Mediastinum 619
F. DENNIS MCCOOL

87 Interventional and Surgical Approaches to Lung Disease 630
DAVID J. FELLER-KOPMAN AND MALCOLM M. DECAMP

SECTION XI: CRITICAL CARE MEDICINE

88 Approach to the Patient in a Critical Care Setting 636
DEBORAH J. COOK

89 Respiratory Monitoring in Critical Care 639
JAMES K. STOLLER AND NICHOLAS S. HILL

90 Acute Respiratory Failure 642
MICHAEL A. MATTHAY AND LORRAINE B. WARE

91 Mechanical Ventilation 652
LAURENT BROCHARD AND ARTHUR S. SLUTSKY

92 Approach to the Patient with Shock 658
DEREK C. ANGUS

93 Cardiogenic Shock 665
STEVEN M. HOLLENBERG AND CLYDE W. YANCY

94 Shock Syndromes Related to Sepsis 669
ANTHONY C. GORDON AND JAMES A. RUSSELL

95 Disorders Due to Heat and Cold 678
MICHAEL N. SAWKA AND FRANCIS G. O'CONNOR

96 Acute Poisoning 682
LEWIS S. NELSON AND DIANE P. CALELLO

97 Medical Aspects of Trauma and Burns 698
ROBERT L. SHERIDAN

98 Envenomation, Bites, and Stings 704
STEVEN A. SEIFERT, RICHARD C. DART, AND JULIAN WHITE

99 Rhabdomyolysis 714
FRANCIS G. O'CONNOR AND PATRICIA A. DEUSTER

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SECTION XII: RENAL AND GENITOURINARY DISEASES

100 Approach to the Patient with Renal Disease 720
ALI G. GHARAVI AND DONALD W. LANDRY

101 Structure and Function of the Kidneys 729
QAIS AL-AWQATI AND JONATHAN BARASCH

102 Disorders of Sodium and Water 733
QAIS AL-AWQATI AND JAI RADHAKRISHNAN

103 Potassium Disorders 745
JULIAN LAWRENCE SEIFTER

104 Acid-Base Disorders 752
JULIAN LAWRENCE SEIFTER

105 Disorders of Magnesium and Phosphorus 766
ALAN S.L. YU

106 Acute Kidney Injury 770
ANUPAM AGARWAL AND JONATHAN BARASCH

107 Glomerular Disorders and Nephrotic Syndromes 776
JAI RADHAKRISHNAN AND M. BARRY STOKES

108 Interstitial Nephritis 790
CYBELE GHOSSEIN AND ERIC G. NEILSON

109 Diabetes and the Kidney 795
RAYMOND C. HARRIS

110 Vascular Disorders of the Kidney 799
THOMAS M. COFFMAN AND STEPHEN R. SMITH

111 Nephrolithiasis 803
DAVID A. BUSHINSKY

112 Cystic Kidney Diseases 808
M. AMIN ARNAOUT

113 Hereditary Nephropathies and Developmental Renal/Urinary Abnormalities 815
LISA M. GUAY-WOODFORD

114 Benign Prostatic Hyperplasia and Prostatitis 821
STEVEN A. KAPLAN

115 Urinary Incontinence 827
NEIL M. RESNICK AND CATHERINE E. DUBEAU

116 Chronic Kidney Disease 831
ANDREW S. LEVEY AND MARK J. SARNAK

117 Treatment of Irreversible Renal Failure 840
DAVID COHEN AND ANTHONY MICHAEL VALERI

SECTION XIII: GASTROINTESTINAL DISEASES

118 Approach to the Patient with Gastrointestinal Disease 850
KENNETH R. MCQUAID

119 Diagnostic Imaging Procedures in Gastroenterology 866
LAURA R. CARUCCI

120 Gastrointestinal Endoscopy 875
KENNETH K. WANG

121 Gastrointestinal Hemorrhage 882
THOMAS O. KOVACS AND DENNIS M. JENSEN

122 Disorders of Gastrointestinal Motility 887
MICHAEL CAMILLERI

123 Irritable Bowel and Functional Upper Gastrointestinal Syndromes 892
LIN CHANG

124 Diseases of the Esophagus 901
GARY W. FALK AND DAVID A. KATZKA

125 Acid Peptic Disease 913
ERNST J. KUIPERS

126 Approach to the Patient with Diarrhea and Malabsorption 923
CAROL E. SEMRAD

127 Inflammatory Bowel Disease 941
GARY R. LICHTENSTEIN

128 Inflammatory and Anatomic Diseases of the Intestine, Peritoneum, Mesentery, and Omentum 951
JOHN F. KUEMMERLE

129 Vascular Diseases of the Gastrointestinal Tract 959
CHARLES J. KAHI

130 Pancreatitis 969
CHRIS E. FORSMARK

131 Diseases of the Rectum and Anus 977
ROBERT D. MADOFF AND GENEVIEVE B. MELTON

SECTION XIV: DISEASES OF THE LIVER AND BILIARY SYSTEM

132 Approach to the Patient with Liver Disease 986
PAUL MARTIN

133 Approach to the Patient with Jaundice or Abnormal Liver Tests 993
KEVIN M. KORENBLAT

134 Acute Viral Hepatitis 1002
JEAN-MICHEL PAWLOTSKY

135 Chronic Viral and Autoimmune Hepatitis 1009
JEAN-MICHEL PAWLOTSKY

136 Drug-Induced Liver Injury 1017
PAUL B. WATKINS

137 Bacterial, Parasitic, Fungal, and Granulomatous Liver Diseases 1022
K. RAJENDER REDDY

138 Alcoholic and Nonalcoholic Steatohepatitis 1031
NAGA P. CHALASANI AND JACQUELYN MAHER

139 Cirrhosis and Its Sequelae 1035
GUADALUPE GARCIA-TSAO

140 Liver Failure and Transplantation 1043
ROBERT J. FONTANA

141 Diseases of the Gallbladder and Bile Ducts 1049
EVAN L. FOGEL AND STUART SHERMAN

SECTION XV: HEMATOLOGIC DISEASES

142 Hematopoiesis and Hematopoietic Growth Factors 1064
KENNETH KAUSHANSKY

143 The Peripheral Blood Smear 1066
BARBARA J. BAIN

144 Approach to the Anemias 1074
ROBERT T. MEANS, JR.

145 Microcytic and Hypochromic Anemias 1082
THOMAS G. DELOUGHERY

146 Autoimmune and Intravascular Hemolytic Anemias 1086
MARC MICHEL

147 Hemolytic Anemias: Red Blood Cell Membrane and Metabolic Defects 1093
PATRICK G. GALLAGHER

148 The Thalassemias 1102
MARIA DOMENICA CAPPELLINI

149 Sickle Cell Disease and Other Hemoglobinopathies 1109
JO HOWARD

150 Megaloblastic Anemias 1117
SALLY P. STABLER

151 Aplastic Anemia and Related Bone Marrow Failure States 1125
AMY E. DEZERN AND ROBERT A. BRODSKY

152 Polycythemia Vera, Essential Thrombocythemia, and Primary Myelofibrosis 1130
JASON GOTLIB

153 Leukocytosis and Leukopenia 1140
NANCY BERLINER

154 Approach to the Patient with Lymphadenopathy or Splenomegaly 1148
JANE N. WINTER

155 Histiocytoses 1154
BARRETT J. ROLLINS AND NANCY BERLINER

156 Eosinophilic Syndromes 1162
AMY D. KLION

Copyrighted material

157 Approach to the Patient with Bleeding or Thrombosis 1165
ANDREW I. SCHAFER

158 Thrombocytopenia 1170
CHARLES S. ABRAMS

159 Von Willebrand Disease and Hemorrhagic Abnormalities of Platelet and Vascular Function 1180
JORGE DI PAOLA AND JAMES S. O'DONNELL

160 Coagulation Factor Deficiencies 1187
MARGARET V. RAGNI

161 Disseminated Intravascular Coagulation and Bleeding in Liver Failure 1195
ANDREW I. SCHAFER

162 Transfusion Medicine 1199
BETH H. SHAZ AND CHRISTOPHER D. HILLYER

163 Hematopoietic Cell Transplantation 1206
NELSON J. CHAO AND ARMAND KEATING

SECTION XVI: ONCOLOGY

164 Approach to the Patient with Cancer 1214
JAMES H. DOROSHOW

165 Epidemiology of Cancer 1243
RULLA M. TAMIMI

166 Cancer Biology and Genetics 1247
BEN HO PARK

167 Myelodysplastic Syndromes 1252
RICHARD M. STONE

168 The Acute Leukemias 1259
ROLAND B. WALTER AND FREDERICK R. APPELBAUM

169 Chronic Lymphocytic Leukemia 1266
JENNIFER R. BROWN

170 Chronic Myeloid Leukemia 1272
JERALD RADICH

171 Non-Hodgkin Lymphomas 1278
JULIE M. VOSE AND JAMES O. ARMITAGE

172 Hodgkin Lymphoma 1289
JOSEPH M. CONNORS AND KERRY J. SAVAGE

173 Plasma Cell Disorders 1294
S. VINCENT RAJKUMAR

174 Amyloidosis 1305
MORIE A. GERTZ AND ANGELA DISPENZIERI

175 Tumors of the Central Nervous System 1310
INGO K. MELLINGHOFF AND LISA M. DEANGELIS

176 Head and Neck Cancer 1320
JULIE E. BAUMAN

177 Lung Cancer and Other Pulmonary Neoplasms 1329
FADLO R. KHURI

178 Neoplasms of the Esophagus and Stomach 1337
ADAM J. BASS AND ANIL K. RUSTGI

179 Neoplasms of the Small and Large Intestine 1343
EDWARD CHU

180 Pancreatic Cancer 1354
DANIEL LAHERU

181 Liver and Biliary Tract Tumors 1357
ROBIN K. KELLEY AND ALAN P. VENOOK

182 Tumors of the Kidney, Bladder, Ureters, and Renal Pelvis 1362
DEAN F. BAJORIN

183 Breast Cancer and Benign Breast Disorders 1368
NANCY E. DAVIDSON

184 Gynecologic Cancers 1375
DEBORAH K. ARMSTRONG

185 Testicular Cancer 1382
LAWRENCE H. EINHORN

186 Prostate Cancer 1384
KATHLEEN A. COONEY AND ELISABETH I. HEATH

187 Malignant Bone Tumors, Sarcomas, and Other Soft Tissue Neoplasms 1387
ROBIN L. JONES

188 Melanoma and Nonmelanoma Skin Cancers 1390
LYNN M. SCHUCHTER

VOLUME 2

SECTION XVII: METABOLIC DISEASES

189 Approach to Inborn Errors of Metabolism 1398
WILLIAM J. CRAIGEN

190 Disorders of Lipid Metabolism 1404
JENNIFER G. ROBINSON

191 Glycogen Storage Diseases 1415
PRIYA S. KISHNANI

192 Lysosomal Storage Diseases 1418
DONNA M. KRASNEWICH AND ELLEN SIDRANSKY

193 Homocystinuria and Hyperhomocysteinemia 1425
MANUEL SCHIFF AND HENK J. BLOM

194 The Porphyrias 1428
RICHARD J. HIFT

195 Wilson Disease 1436
MICHAEL L. SCHILSKY

196 Iron Overload (Hemochromatosis) 1438
KRIS V. KOWDLEY

SECTION XVIII: NUTRITIONAL DISEASES

197 Severe Malnutrition 1444
MARK J. MANARY AND INDI TREHAN

198 Malnutrition: Assessment and Support 1446
TOMMY E. CEDERHOLM AND INGVAR G. BOSAEUS

199 Vitamins, Trace Minerals, and Other Micronutrients 1451
JOEL B. MASON AND SARAH L. BOOTH

200 Eating Disorders 1461
EVELYN ATTIA, MARIAN TANOFSKY-KRAFF, AND B. TIMOTHY WALSH

201 Obesity 1463
MICHAEL D. JENSEN AND DANIEL H. BESSESEN

SECTION XIX: ENDOCRINE DISEASES

202 Approach to the Patient with Endocrine Disease 1472
DAVID R. CLEMMONS AND LYNNETTE K. NIEMAN

203 Principles of Endocrinology 1473
ALLEN M. SPIEGEL

204 Neuroendocrinology and the Neuroendocrine System 1476
ROY E. WEISS

205 Anterior Pituitary 1482
ROY E. WEISS

206 Posterior Pituitary 1498
JOSEPH G. VERBALIS

207 Thyroid 1504
ELIZABETH N. PEARCE AND ANTHONY N. HOLLENBERG

208 Adrenal Cortex 1520
LYNNETTE K. NIEMAN

209 Adrenal Medulla, Catecholamines, and Pheochromocytoma 1529
WILLIAM F. YOUNG, JR.

210 Diabetes Mellitus 1534
KETAN K. DHATARIYA, GUILLERMO E. UMPIERREZ, AND JILL P. CRANDALL

211 Hypoglycemia 1551
KHALID HUSSAIN

212 Polyglandular Disorders 1558
LYNNETTE K. NIEMAN AND ALLEN M. SPIEGEL

213 Neuroendocrine Neoplasms 1561
EDWARD M. WOLIN AND ROBERT T. JENSEN

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214 Sexual Development 1569
PERRIN C. WHITE

215 Transgender Medicine 1577
JOSHUA D. SAFER

216 The Testis and Male Hypogonadism, Infertility, and Sexual Dysfunction 1580
RONALD S. SWERDLOFF AND CHRISTINA WANG

217 Ovaries and Pubertal Development 1591
WILLIAM H. CATHERINO

218 Reproductive Endocrinology and Infertility 1595
WILLIAM H. CATHERINO

SECTION XX: WOMEN'S HEALTH

219 Approach to Women's Health 1606
KAREN M. FREUND

220 Contraception 1610
BEVERLY WINIKOFF AND DANIEL GROSSMAN

221 Medical Issues in Pregnancy 1618
CATHERINE Y. SPONG AND DAVID B. NELSON

222 Menopause 1628
NANETTE SANTORO AND GENEVIEVE NEAL-PERRY

223 Intimate Partner Violence 1633
GENE FEDER AND HARRIET L. MACMILLAN

SECTION XXI: DISEASES OF BONE AND MINERAL METABOLISM

224 Approach to the Patient with Metabolic Bone Disease 1638
THOMAS J. WEBER

225 Osteoporosis 1639
THOMAS J. WEBER

226 Osteomalacia and Rickets 1647
ROBERT S. WEINSTEIN

227 The Parathyroid Glands, Hypercalcemia, and Hypocalcemia 1652
RAJESH V. THAKKER

228 Paget Disease of Bone 1662
STUART H. RALSTON

229 Osteonecrosis, Osteosclerosis/Hyperostosis, and Other Disorders of Bone 1665
MICHAEL P. WHYTE AND KATHRYN M. DAHIR

SECTION XXII: DISEASES OF ALLERGY AND CLINICAL IMMUNOLOGY

230 Approach to the Patient with Allergic or Immunologic Disease 1672
KARI C. NADEAU

231 Primary Immunodeficiency Diseases 1676
CHARLOTTE CUNNINGHAM-RUNDLES

232 Urticaria and Angioedema 1687
SARBJIT S. SAINI

233 Anaphylaxis 1691
LAWRENCE B. SCHWARTZ AND MARIANA CASTELLS

234 Drug Allergy 1695
MARIANA CASTELLS

235 Mastocytosis 1699
CEM AKIN

SECTION XXIII: RHEUMATIC DISEASES

236 Approach to the Patient with Rheumatic Disease 1706
VIVIAN P. BYKERK AND MARY K. CROW

237 Laboratory Testing in the Rheumatic Diseases 1712
KEVIN D. DEANE AND DAVID S. PISETSKY

238 Imaging Studies in the Rheumatic Diseases 1717
RONALD S. ADLER

239 Inherited Diseases of Connective Tissue 1724
REED E. PYERITZ

240 The Systemic Autoinflammatory Diseases 1730
DANIEL L. KASTNER

241 Osteoarthritis 1737
DAVID J. HUNTER

242 Bursitis, Tendinopathy, Other Periarticular Disorders, and Sports Medicine 1742
JOSEPH J. BIUNDO AND JUAN J. CANOSO

243 Rheumatoid Arthritis 1749
IAIN B. MCINNES

244 Spondyloarthritis 1760
ROBERT D. INMAN AND PROTON RAHMAN

245 Systemic Lupus Erythematosus 1767
MARY K. CROW

246 Systemic Sclerosis (Scleroderma) 1775
JOHN VARGA

247 Sjögren Syndrome 1783
E. WILLIAM ST. CLAIR

248 Inflammatory Myopathies 1787
STEVEN A. GREENBERG

249 The Systemic Vasculitides 1791
JOHN H. STONE

250 Giant Cell Arteritis and Polymyalgia Rheumatica 1801
ROBERT SPIERA

251 Infections of Bursae, Joints, and Bones 1804
DOUGLAS R. OSMON

252 Crystal Deposition Diseases 1810
N. LAWRENCE EDWARDS

253 Fibromyalgia 1816
DANIEL J. CLAUW

254 Systemic Diseases in Which Arthritis Is a Feature 1820
STERLING G. WEST AND S. LOUIS BRIDGES, JR.

255 Surgical Treatment of Joint Diseases 1826
C. RONALD MACKENZIE AND EDWIN P. SU

SECTION XXIV: INFECTIOUS DISEASES

256 Introduction to Microbial Disease: Pathophysiology and Diagnostics 1833
ROBIN PATEL AND VICTORIA J. FRASER

257 The Human Microbiome 1836
VINCENT B. YOUNG

258 Principles of Anti-Infective Therapy 1840
LOUIS B. RICE

259 Approach to Fever or Suspected Infection in the Normal Host 1845
MICHAEL T. MELIA

260 Approach to Fever and Suspected Infection in the Immunocompromised Host 1851
COSTI D. SIFRI

261 Prevention and Control of Health Care–Associated Infections 1862
DAVID P. CALFEE

262 Approach to the Patient with Suspected Enteric Infection 1868
JAMES M. FLECKENSTEIN

263 Approach to the Patient with Urinary Tract Infection 1873
DIMITRI DREKONJA

264 Approach to the Patient with a Sexually Transmitted Infection 1878
HEIDI SWYGARD AND MYRON S. COHEN

265 Approach to the Patient Before and After Travel 1885
LIN H. CHEN

266 Antibacterial Chemotherapy 1891
ARNOLD LOUIE

267 Staphylococcal Infections 1902
CATHERINE LIU, BO SHOPSIN, AND HENRY F. CHAMBERS

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THOMAS MCDONALD FILE, JR.

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DENNIS L. STEVENS, AMY E. BRYANT, AND MELISSA M. HAGMAN

270 Enterococcal Infections 1920
PATRICE SAVARD AND TRISH M. PERL

271 Clostridial and *Clostridioides* Infections 1924
MARK H. WILCOX AND ERIK R. DUBBERKE

272 Gram-Positive Rod Infections 1930
ROSE KIM, HEATHER CLAUSS, AND ANNETTE C. REBOLI

273 Diseases Caused by Non–Spore-Forming Anaerobic Bacteria 1938
ITZHAK BROOK

274 *Neisseria meningitidis* Infections 1941
DAVID S. STEPHENS

275 *Neisseria gonorrhoeae* Infections 1946
JEFFREY D. KLAUSNER AND STEPHANIE N. TAYLOR

276 Chancroid 1950
STANLEY M. SPINOLA

277 *Haemophilus* and *Moraxella* Infections 1952
MONICA M. FARLEY

278 Cholera and Other *Vibrio* Infections 1955
EDUARDO GOTUZZO AND CARLOS SEAS

279 *Campylobacter* Infections 1958
BAN MISHU ALLOS

280 *Escherichia coli* Enteric Infections 1960
THEODORE S. STEINER

281 Enterobacterales: Non-Enteric Infections and Multidrug Resistance 1964
AMY J. MATHERS

282 *Pseudomonas* and *Burkholderia* Infections 1968
MATTHEW E. FALAGAS AND PETROS I. RAFAILIDIS

283 Diseases Caused by *Acinetobacter* and *Stenotrophomonas* Species 1973
KEITH S. KAYE AND ROBERT A. BONOMO

284 *Salmonella* Infections (Including Enteric Fever) 1976
JOHN A. CRUMP

285 Shigellosis 1980
CALMAN A. MACLENNAN

286 Brucellosis 1983
EDSEL MAURICE T. SALVANA

287 Tularemia and Other *Francisella* Infections 1985
KAREN C. BLOCH AND FRED A. LOPEZ

288 Plague and Other *Yersinia* Infections 1988
PAUL S. MEAD AND CHRISTINA A. NELSON

289 Whooping Cough and Other *Bordetella* Infections 1994
CHRISTOPHER J. GILL AND ERIK L. HEWLETT

290 *Legionella* Infections 1996
JONAS MARSCHALL AND VICTORIA J. FRASER

291 *Bartonella* Infections 2000
JEAN-MARC ROLAIN AND DIDIER RAOULT

292 Granuloma Inguinale (Donovanosis) 2004
WALTER BELDA, JR.

293 *Mycoplasma* Infections 2005
DAVID L. GOLDMAN

294 Diseases Caused by Chlamydiae 2009
HILARY E.L. RENO AND WILLIAM M. GEISLER

295 Syphilis and Nonsyphilitic Treponematoses 2014
JODIE A. DIONNE AND KHALIL G. GHANEM

296 Lyme Disease 2022
GARY P. WORMSER

297 Relapsing Fever and Other *Borrelia* Infections 2027
WILLIAM A. PETRI, JR.

298 Leptospirosis 2029
DAVID A. HAAKE

299 Tuberculosis 2031
THOMAS C. BAILEY AND JENNIFER A. PHILIPS

300 The Nontuberculous Mycobacteria 2044
STEVEN M. HOLLAND AND KENNETH N. OLIVIER

301 Leprosy (Hansen Disease) 2047
SUNIL DOGRA

302 Rickettsial Infections 2054
PIERRE-EDOUARD FOURNIER AND DIDIER RAOULT

303 Zoonoses 2063
MEGAN E. RELLER AND J. STEPHEN DUMLER

304 Actinomycosis 2066
ITZHAK BROOK

305 Whipple Disease 2069
THOMAS RUDOLF SCHNEIDER

306 Nocardiosis 2072
FREDERICK S. SOUTHWICK

307 Systemic Antifungal Agents 2074
DAVID W. DENNING AND DAVID A. STEVENS

308 Endemic Mycoses 2080
GEORGE R. THOMPSON, III, AND MARISA H. MICELI

309 Cryptococcosis 2087
SHARON C-A CHEN

310 Candidiasis 2089
PETER G. PAPPAS

311 Aspergillosis 2093
THOMAS J. WALSH AND THOMAS F. PATTERSON

312 Mucormycosis 2098
DIMITRIOS P. KONTOYIANNIS AND LUIS OSTROSKY-ZEICHNER

313 *Pneumocystis* Pneumonia 2101
JOSEPH A. KOVACS

314 Mycetoma and Dematiaceous Fungal Infections 2108
PETER G. PAPPAS AND DIMITRIOS P. KONTOYIANNIS

315 Antiparasitic Therapy 2111
PHILIP J. BUDGE AND RICHARD D. PEARSON

316 Malaria 2118
PHILIP J. ROSENTHAL AND MOSES R. KAMYA

317 African Sleeping Sickness 2123
WILLIAM A. PETRI, JR.

318 Chagas Disease 2126
LOUIS V. KIRCHHOFF

319 Leishmaniasis 2130
PIERRE A. BUFFET, SIMON L. CROFT, AND MITALI CHATTERJEE

320 Toxoplasmosis 2136
ANITA A. KOSHY

321 Cryptosporidiosis 2141
CIRLE A. WARREN AND ALDO A.M. LIMA

322 Giardiasis 2144
DAVID R. HILL

323 Amebiasis 2146
WILLIAM A. PETRI, JR.

324 Babesiosis and Other Protozoan Diseases 2151
SAM R. TELFORD, III, AND PETER J. KRAUSE

325 Cestodes 2157
A. CLINTON WHITE, JR., AND ENRICO BRUNETTI

326 Trematode Infections 2163
LUIS A. MARCOS

327 Nematode Infections 2169
DAVID J. DIEMERT

328 Antiviral Therapy (Non-HIV) 2181
JOHN H. BEIGEL AND SHYAMASUNDARAN KOTTILIL

329 The Common Cold 2192
BRUCE BARRETT

Copyrighted material

330 Respiratory Syncytial Virus and Human Metapneumovirus 2194
H. KEIPP TALBOT AND EDWARD E. WALSH

331 Parainfluenza Viral Disease 2196
GEOFFREY A. WEINBERG AND KATHRYN M. EDWARDS

332 Influenza 2198
MICHAEL G. ISON AND NELSON LEE

333 Adenovirus Diseases 2204
MICHAEL G. ISON

334 Pre-2019 Coronaviruses 2206
FIONA P. HAVERS, HANNAH KIRKING, AND IAN D. PLUMB

335 COVID-19: Virology and Pathology 2209
VINCENT RACANIELLO

336 COVID-19: Epidemiology, Clinical Manifestations, Diagnosis, Community Prevention, and Prognosis 2213
CARLOS DEL RIO, MONICA GANDHI, AND MYRON S. COHEN

337 COVID-19 Treatment and Vaccination 2216
RAJESH T. GANDHI AND KATHLEEN M. NEUZIL

338 Measles 2220
MARTIN G. OTTOLINI

339 Rubella (German Measles) 2224
GREGORY A. POLAND, INNA G. OVSYANNIKOVA, AND RICHARD B. KENNEDY

340 Mumps 2225
JENNIFER B. ROSEN AND JANE R. ZUCKER

341 Polyomaviruses 2227
HANS H. HIRSCH

342 Parvovirus 2233
NEAL S. YOUNG

343 Smallpox, Monkeypox, and Other Poxvirus Infections 2236
BRETT W. PETERSEN AND INGER K. DAMON

344 Papillomavirus 2240
SEAN T. O'LEARY AND JOHN M. DOUGLAS, JR.

345 Herpes Simplex Virus Infections 2244
RICHARD J. WHITLEY AND JOHN W. GNANN, JR.

346 Varicella-Zoster Virus (Chickenpox, Shingles) 2247
JEFFREY COHEN

347 Cytomegalovirus 2250
GUY BOIVIN AND AJIT P. LIMAYE

348 Epstein-Barr Virus Infection 2253
ROBERT T. SCHOOLEY AND UPTON D. ALLEN

349 Enteroviruses 2256
JOSÉ R. ROMERO

350 Rotaviruses, Noroviruses, and Other Gastrointestinal Viruses 2261
MANUEL A. FRANCO AND HARRY B. GREENBERG

351 Viral Hemorrhagic Fevers 2264
DANIEL G. BAUSCH AND LAURENT KAISER

352 Arboviruses Causing Fever, Rash, and Neurologic Syndromes 2274
J. DAVID BECKHAM

SECTION XXV: RETROVIRUSES

353 Epidemiology and Diagnosis of Human Immunodeficiency Virus Infection and Acquired Immunodeficiency Syndrome 2286
LARRY W. CHANG AND THOMAS C. QUINN

354 Pathobiology of Human Immunodeficiency Viruses 2291
JOEL N. BLANKSON, ROBERT F. SILICIANO, AND FRANK MALDARELLI

355 Acute Clinical Manifestations and Diagnosis of HIV 2295
THOMAS C. QUINN AND LARRY W. CHANG

356 Prevention of Human Immunodeficiency Virus Infection 2298
RAPHAEL J. LANDOVITZ, CARLOS DEL RIO, AND MYRON S. COHEN

357 Antiretroviral Treatment of Human Immunodeficiency Virus Infection 2300
ROY M. GULICK

358 Microbial Complications of HIV/AIDS 2305
HENRY MASUR

359 Systemic Manifestations of HIV/AIDS 2312
SAMUEL T. MERRICK AND MARSHALL J. GLESBY

360 Retroviruses Other Than Human Immunodeficiency Virus 2324
CHARLES R.M. BANGHAM AND LUCY B.M. COOK

SECTION XXVI: BEHAVIORAL MEDICINE

361 Delirium and Changes in Mental Status 2330
SHARON K. INOUYE

362 Psychiatric Disorders in Medical Practice 2336
JEFFREY M. LYNESS AND HOCHANG B. LEE

363 Nicotine and Tobacco 2349
TONY P. GEORGE

364 Alcohol Use Disorders 2353
PATRICK G. O'CONNOR

365 Drug Use Disorders 2360
ROGER D. WEISS AND JANE M. LIEBSCHUTZ

SECTION XXVII: NEUROLOGY

366 Approach to the Patient with Neurologic Disease 2368
GABRIELE C. DE LUCA, ROBERT C. GRIGGS, AND S. CLAIBORNE JOHNSTON

367 Headaches and Other Head Pain 2376
KATHLEEN B. DIGRE

368 Traumatic Brain Injury and Spinal Cord Injury 2385
JEFFREY J. BAZARIAN

369 Mechanical and Other Lesions of the Spine, Nerve Roots, and Spinal Cord 2392
J.D. BARTLESON

370 Regional Cerebral Dysfunction: Higher Mental Functions 2407
DAVID S. KNOPMAN

371 Cognitive Impairment and Dementia 2412
DAVID S. KNOPMAN

372 The Epilepsies 2425
SAMUEL WIEBE

373 Coma, Disorders of Consciousness, and Brain Death 2437
DAVID M. GREER AND JAMES L. BERNAT

374 Sleep Disorders 2443
BRADLEY V. VAUGHN AND ROBERT C. BASNER

375 Approach to Cerebrovascular Diseases 2454
LARRY B. GOLDSTEIN

376 Ischemic Cerebrovascular Disease 2464
LARRY B. GOLDSTEIN

377 Hemorrhagic Cerebrovascular Disease 2474
SEEMANT CHATURVEDI AND MAGDY SELIM

378 Parkinsonism 2483
JILL L. OSTREM AND MICHAEL S. OKUN

379 Other Movement Disorders 2489
MICHAEL S. OKUN AND JILL L. OSTREM

380 Multiple Sclerosis and Demyelinating Conditions 2498
PETER A. CALABRESI

381 Meningitis: Bacterial, Viral, and Other 2510
AVINDRA NATH

382 Brain Abscess and Parameningeal Infections 2525
AVINDRA NATH AND JOSEPH R. BERGER

383 Encephalitis 2531
ALLEN J. AKSAMIT, JR.

384 Nutritional and Alcohol-Related Neurologic Disorders 2537
BARBARA S. KOPPEL, LOUIS H. WEIMER, AND MICHAEL DARAS

385 Developmental and Neurocutaneous Disorders 2545
E. STEVE ROACH

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386 Autonomic Disorders 2553
EDUARDO E. BENARROCH AND ROY FREEMAN

387 Amyotrophic Lateral Sclerosis and Other Motor Neuron Diseases 2561
PAMELA J. SHAW AND MERIT E. CUDKOWICZ

388 Peripheral Neuropathies 2566
A. GORDON SMITH AND MICHAEL E. SHY

389 Muscle Diseases 2580
DUYGU SELCEN

390 Disorders of Neuromuscular Transmission 2588
HENRY J. KAMINSKI

SECTION XXVIII: EYE, EAR, NOSE, AND THROAT DISEASES

391 Diseases of the Visual System 2596
GEORGE A. CIOFFI AND JEFFREY M. LIEBMANN

392 Neuro-Ophthalmology 2614
ROBERT W. BALOH AND JOANNA C. JEN

393 Diseases of the Mouth and Salivary Glands 2620
RICHARD C. JORDAN

394 Approach to the Patient with Nose, Sinus, and Ear Disorders 2627
ANDREW H. MURR AND STEVEN D. PLETCHER

395 Smell and Taste 2639
ROBERT W. BALOH AND JOANNA C. JEN

396 Hearing and Equilibrium 2641
ROBERT W. BALOH AND JOANNA C. JEN

397 Throat Disorders 2648
PAUL W. FLINT

SECTION XXIX: MEDICAL CONSULTATION

398 Principles of Medical Consultation 2656
GERALD W. SMETANA AND BARBARA A. SLAWSKI

399 Preoperative Evaluation 2659
ANDREW D. AUERBACH

400 Overview of Anesthesia 2668
JEANINE P. WIENER-KRONISH AND LEE A. FLEISHER

401 Postoperative Care and Complications 2672
DONALD A. REDELMEIER

402 Medical Care of Patients with Psychiatric Diseases 2677
MARSHA N. WITTINK AND S. RYAN GREYSEN

SECTION XXX: SKIN DISEASES

403 Approach to Skin Diseases 2686
CHRISTINE J. KO

404 Principles of Therapy of Skin Diseases 2697
VICTORIA P. WERTH AND APRIL W. ARMSTRONG

405 Eczemas, Photodermatoses, Papulosquamous (Including Fungal) Diseases, and Figurate Erythemas 2702
HENRY W. LIM AND JOEL M. GELFAND

406 Macular, Papular, Purpuric, Vesiculobullous, and Pustular Diseases 2712
DANIELA KROSHINSKY

407 Urticaria, Drug Hypersensitivity Rashes, Nodules and Tumors, and Atrophic Diseases 2724
MADELEINE DUVIC AND SUSAN Y. CHON

408 Infections, Pigmentation Disorders, Regional Dermatology, and Distinctive Lesions in Black Skin 2738
JEAN BOLOGNIA AND AMY MCMICHAEL

409 Diseases of Hair and Nails 2747
ANTONELLA TOSTI

APPENDIX

Reference Intervals and Laboratory Values e1
JORGE SEPULVEDA

Index I-1

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VIDEO CONTENTS

This icon appears throughout the book to indicate chapters with accompanying video available on Elsevier eBooks+.

HEART DISEASES

Standard Echocardiographic Views: Long Axis Image Plane
Chapter 43, Video 1A – CATHERINE M. OTTO

Standard Echocardiographic Views: Short Axis Image Plane
Chapter 43, Video 1B – CATHERINE M. OTTO

Standard Echocardiographic Views: Short Axis Image Plane
Chapter 43, Video 1C – CATHERINE M. OTTO

Standard Echocardiographic Views: Four-Chamber Image Plane
Chapter 43, Video 1D – CATHERINE M. OTTO

Dilated Cardiomyopathy: Long Axis View
Chapter 43, Video 2A – CATHERINE M. OTTO

Dilated Cardiomyopathy: Short Axis View
Chapter 43, Video 2B – CATHERINE M. OTTO

Dilated Cardiomyopathy: Apical Four-Chamber View
Chapter 43, Video 2C – CATHERINE M. OTTO

Three-Dimensional Echocardiography
Chapter 43, Video 3 – CATHERINE M. OTTO

Stress Echocardiography: Normal Reaction
Chapter 43, Video 4A – CATHERINE M. OTTO

Stress Echocardiography: Proximal Stenosis of the Left Anterior Descending Coronary Artery
Chapter 43, Video 4B – CATHERINE M. OTTO

Pericardial Effusion: Parasternal Long Axis
Chapter 43, Video 5A – CATHERINE M. OTTO

Pericardial Effusion: Parasternal Short Axis
Chapter 43, Video 5B – CATHERINE M. OTTO

Pericardial Effusion: Apical Four-Chamber Views
Chapter 43, Video 5C – CATHERINE M. OTTO

Secundum Atrial Septal Defect
Chapter 55, Video 1 – ARIANE J. MARELLI

Perimembranous Ventricular Septal Defect
Chapter 55, Video 2 – ARIANE J. MARELLI

Coronary Stent Placement
Chapter 59, Video 1 – PAUL S. TEIRSTEIN

Guidewire Passage
Chapter 59, Video 2 – PAUL S. TEIRSTEIN

Delivering the Stent
Chapter 59, Video 3 – PAUL S. TEIRSTEIN

Inflating the Stent
Chapter 59, Video 4 – PAUL S. TEIRSTEIN

Final Result
Chapter 59, Video 5 – PAUL S. TEIRSTEIN

RESPIRATORY DISEASES

Wheezing
Chapter 75, Video 1 – RAYMOND MURPHY

Inhaler Use
Chapter 75, Video 2 – LESLIE HENDELES, GENE L. COLICE, AND ROBERT J. MEYER

VATS Wedge Resection
Chapter 87, Video 1 – MALCOLM M. DECAMP

CRITICAL CARE MEDICINE

Ventilation of an Ex Vivo Rat Lung
Chapter 91, Video 1 – ARTHUR S. SLUTSKY, GEORGE VOLGYESI, AND TOM WHITEHEAD

GASTROINTESTINAL DISEASES

Ulcerative Colitis, Moderately Severe
Chapter 127, Video 1 – GARY R. LICHTENSTEIN

CMI Stents
Chapter 129, Video 1 – CHARLES J. KAHI

DISEASES OF THE LIVER AND BILIARY SYSTEM

Endoscopic Ultrasound of Biliary Ascariasis, Endoscopic Retrograde Cholangiopancreatography of Biliary Ascariasis, and Extraction of the Helminthic Worm
Chapter 137, Video 1 – K. RAJENDER REDDY

ONCOLOGY

Laparascopic Assisted Double Balloon Enteroscopy with Polypectomy of a Jejunal Adenoma Followed by Surgical Oversew of the Polypectomy Site
Chapter 179, Video 1 – SHABANA PASHA

Snare Polypectomy of a Colon Adenoma
Chapter 179, Video 2 – JONATHAN LEIGHTON

Endoscopic Mucosal Resection Using Saline Lift Polypectomy of a Colon Adenoma, Followed by Closure of the Mucosal Defect with Clips
Chapter 179, Video 3 – WAJEEH SALAH

ENDOCRINE DISEASES

Pituitary Surgery
Chapter 205, Video 1 – IVAN CIRIC

BEHAVIORAL MEDICINE

Confusion Assessment Method
Chapter 361, Video 1 – SHARON K. INOUYE

NEUROLOGY

Focal Seizure Disorder - Temporal Lobe Epilepsy
Chapter 366, Video 1 – GABRIELE C. DE LUCA, ROBERT C. GRIGGS, AND S. CLAIBORNE JOHNSTON

Generalized Seizure Disorder - Myoclonic Epilepsy
Chapter 366, Video 2 – GABRIELE C. DE LUCA, ROBERT C. GRIGGS, AND S. CLAIBORNE JOHNSTON

Pronator Drift
Chapter 366, Video 3 – GABRIELE C. DE LUCA, ROBERT C. GRIGGS, AND S. CLAIBORNE JOHNSTON

Parkinsonism
Chapter 366, Video 4 – GABRIELE C. DE LUCA, ROBERT C. GRIGGS, AND S. CLAIBORNE JOHNSTON

Internuclear Ophthalmoplegia
Chapter 366, Video 5 – GABRIELE C. DE LUCA, ROBERT C. GRIGGS, AND S. CLAIBORNE JOHNSTON

Spastic-Ataxic Gait
Chapter 366, Video 6 – GABRIELE C. DE LUCA, ROBERT C. GRIGGS, AND S. CLAIBORNE JOHNSTON

Sustained Clonus
Chapter 366, Video 7 – GABRIELE C. DE LUCA, ROBERT C. GRIGGS, AND S. CLAIBORNE JOHNSTON

Fasciculations (Tongue and Lower Limb)
Chapter 366, Video 8 – GABRIELE C. DE LUCA, ROBERT C. GRIGGS, AND S. CLAIBORNE JOHNSTON

Brachial Plexopathy
Chapter 366, Video 9 – GABRIELE C. DE LUCA, ROBERT C. GRIGGS, AND S. CLAIBORNE JOHNSTON

Length-Dependent Peripheral Neuropathy
Chapter 366, Video 10 – GABRIELE C. DE LUCA, ROBERT C. GRIGGS, AND S. CLAIBORNE JOHNSTON

Fatigable Ptosis, Dysarthria, and Dysphonia
Chapter 366, Video 11 – GABRIELE C. DE LUCA, ROBERT C. GRIGGS, AND S. CLAIBORNE JOHNSTON

Myotonic Dystrophy
Chapter 366, Video 12 – GABRIELE C. DE LUCA, ROBERT C. GRIGGS, AND S. CLAIBORNE JOHNSTON

Facioscapulohumeral Muscular Dystrophy
Chapter 366, Video 13 – GABRIELE C. DE LUCA, ROBERT C. GRIGGS, AND S. CLAIBORNE JOHNSTON

Cervical Provocation
Chapter 369, Video 1 – J.D. BARTLESON

Spurling Maneuver
Chapter 369, Video 2 – J.D. BARTLESON

Cervical Distraction Test
Chapter 369, Video 3 – J.D. BARTLESON

Straight Leg Raise
Chapter 369, Video 4 – J.D. BARTLESON

Contralateral Straight Leg Raise
Chapter 369, Video 5 – J.D. BARTLESON

Seated Straight Leg Raise
Chapter 369, Video 6 – J.D. BARTLESON

Discectomy
Chapter 369, Video 7 – J.D. BARTLESON

Typical Absence Seizure
Chapter 372, Video 1 – SAMUEL WIEBE

Left Rolandic Seizure
Chapter 372, Video 2 – SAMUEL WIEBE

Left Temporal Focal Impaired Awareness Seizure
Chapter 372, Video 3 – SAMUEL WIEBE

Left Temporal Focal Impaired Awareness Seizure, Postictal Confusion
Chapter 372, Video 4 – SAMUEL WIEBE

Left Temporal Focal Impaired Awareness Seizure
Chapter 372, Video 5 – SAMUEL WIEBE

Supplementary Sensory-Motor Seizure
Chapter 372, Video 6 – SAMUEL WIEBE

Right Posterior Temporal Seizure—Dramatic Hyperkinetic Semiology
Chapter 372, Video 7 – SAMUEL WIEBE

Right Mesial Frontal Hyperkinetic Seizure
Chapter 372, Video 8 – SAMUEL WIEBE

Generalized Nonconvulsive Status Epilepticus
Chapter 372, Video 9 – SAMUEL WIEBE

GTC Seizure Tonic Phase
Chapter 372, Video 10 – SAMUEL WIEBE

GTC Seizure Clonic Phase
Chapter 372, Video 11 – SAMUEL WIEBE

Myoclonic Facial Seizure
Chapter 372, Video 12 – SAMUEL WIEBE

Tonic Seizure Lennox Gastaut
Chapter 372, Video 13 – SAMUEL WIEBE

Atonic Seizure Lennox Gastaut
Chapter 372, Video 14 – SAMUEL WIEBE

Reflex Auditory Seizure
Chapter 372, Video 15 – SAMUEL WIEBE

Early Parkinson's Disease
Chapter 378, Video 1 – JILL L. OSTREM AND MICHAEL S. OKUN

Freezing of Gait in Parkinson's Disease
Chapter 378, Video 2 – JILL L. OSTREM AND MICHAEL S. OKUN

Gunslinger Gait in Progressive Supranuclear Palsy
Chapter 378, Video 3 – JILL L. OSTREM AND MICHAEL S. OKUN

Supranuclear Gaze Palsy in Progressive Supranuclear Palsy
Chapter 378, Video 4 – JILL L. OSTREM AND MICHAEL S. OKUN

Applause Sign in Progressive Supranuclear Palsy
Chapter 378, Video 5 – JILL L. OSTREM AND MICHAEL S. OKUN

Apraxia of Eyelid Opening in Progressive Supranuclear Palsy
Chapter 378, Video 6 – JILL L. OSTREM AND MICHAEL S. OKUN

Cranial Dystonia in Multiple System Atrophy
Chapter 378, Video 7 – JILL L. OSTREM AND MICHAEL S. OKUN

Anterocollis in Multiple System Atrophy
Chapter 378, Video 8 – JILL L. OSTREM AND MICHAEL S. OKUN

Stridor in Multiple System Atrophy
Chapter 378, Video 9 – JILL L. OSTREM AND MICHAEL S. OKUN

Alien Limb Phenomenon in Corticobasal Syndrome
Chapter 378, Video 10 – JILL L. OSTREM AND MICHAEL S. OKUN

Myoclonus in Corticobasal Syndrome
Chapter 378, Video 11 – JILL L. OSTREM AND MICHAEL S. OKUN

Levodopa-Induced Dyskinesia in Parkinson's Disease
Chapter 378, Video 12 – JILL L. OSTREM AND MICHAEL S. OKUN

Essential Tremor
Chapter 379, Video 1 – MICHAEL S. OKUN AND JILL L. OSTREM

Huntington's Disease
Chapter 379, Video 2 – MICHAEL S. OKUN AND JILL L. OSTREM

Hemiballism
Chapter 379, Video 3 – MICHAEL S. OKUN AND JILL L. OSTREM

Blepharospasm
Chapter 379, Video 4 – MICHAEL S. OKUN AND JILL L. OSTREM

Oromandibular Dystonia
Chapter 379, Video 5 – MICHAEL S. OKUN AND JILL L. OSTREM

Cervical Dystonia
Chapter 379, Video 6 – MICHAEL S. OKUN AND JILL L. OSTREM

Writer's Cramp
Chapter 379, Video 7 – MICHAEL S. OKUN AND JILL L. OSTREM

Embouchure Dystonia
Chapter 379, Video 8 – MICHAEL S. OKUN AND JILL L. OSTREM

Sensory Trick in Cervical Dystonia
Chapter 379, Video 9 – MICHAEL S. OKUN AND JILL L. OSTREM

Generalized Dystonia
Chapter 379, Video 10 – MICHAEL S. OKUN AND JILL L. OSTREM

Tics
Chapter 379, Video 11 – MICHAEL S. OKUN AND JILL L. OSTREM

Tardive Dyskinesia
Chapter 379, Video 12 – MICHAEL S. OKUN AND JILL L. OSTREM

Hemifacial Spasm
Chapter 379, Video 13 – MICHAEL S. OKUN AND JILL L. OSTREM

Eye Movements (Nystagmus) of Wernicke Encephalopathy
Chapter 384, Video 1 – BARBARA S. KOPPEL

Eye Movements (Nystagmus) of Wernicke Encephalopathy
Chapter 384, Video 2 – BARBARA S. KOPPEL

Eye Movements (Slow Dysconjugate Horizontal Movements) of Osmotic Demyelination Syndrome
Chapter 384, Video 3 – BARBARA S. KOPPEL

Limb Symptoms and Signs in ALS
Chapter 387, Video 1 – PAMELA J. SHAW

Bulbar Symptoms and Signs in ALS
Chapter 387, Video 2 – PAMELA J. SHAW

Video Fluoroscopy of Normal Swallowing and of Swallowing in an ALS Patient with Bulbar Dysfunction
Chapter 387, Video 3 – PAMELA J. SHAW

Charcot-Marie-Tooth Disease Examination and Walk
Chapter 388, Video 1 – A. GORDON SMITH AND MICHAEL E. SHY

EYE, EAR, NOSE, AND THROAT DISEASES

Skin Testing
Chapter 394, Video 1 – LARRY BORISH

Nasal Endoscopy
Chapter 394, Video 2 – LARRY BORISH

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189 APPROACH TO INBORN ERRORS OF METABOLISM

WILLIAM J. CRAIGEN

OVERVIEW

DEFINITION

The definition of inborn errors of metabolism includes not only enzyme deficiencies but also any condition in which perturbation of a biochemical pathway is intrinsic to the pathobiology of the disorder. Inborn errors of metabolism can be classified as disorders that result in the accumulation or deficiency of small molecules, thereby leading to intoxication disorders; the abnormal accumulation or deficiency of complex molecules such as glycogen, sphingolipids, or glycosaminoglycans; and disorders of energy deficiency.[1–3] Inborn errors of metabolism can be the result of defects in membrane transporter proteins, chaperone proteins, transcription factors, assembly factors, or other classes of proteins and nucleic acids. The more than 1400 inborn errors of metabolism include autosomal recessive, autosomal dominant, X-linked, and matrilineal (mitochondrial DNA [mtDNA]) inheritance.[4]

The clinical phenotypes associated with inborn errors of metabolism can occur across all ages,[5] with the more severe disorders having an onset in infancy or in utero. Clinically, a disorder can be episodic and fluctuating, stationary, or inexorably progressive, such as in neurodegenerative diseases, depending on organ system involvement. Disorders of intermediary metabolism, such as aminoacidopathies, often exhibit an acute or chronic intoxication and encephalopathy, whereas disorders of complex molecules, such as glycosaminoglycans or organelles such as peroxisomes, have a more chronic and progressive course, depending on the specific organ system that is involved. Disorders of energy production, such as mitochondrial respiratory chain disorders, may have both acute and chronic manifestations.

EPIDEMIOLOGY

Inborn errors of metabolism are individually rare but collectively have an incidence as high as 1 per 800. The specific incidence of any given disorder depends in part on the severity of the condition, the presence of founder mutations in a particular population (e.g., Old Order Amish), and the degree of consanguinity in the population (e.g., Saudi Arabia). Although some inborn errors of metabolism are relatively more common (Table 189-1) across diverse populations, genetic counseling and carrier screening should be tailored to different populations, such as small and/or consanguineous populations, when the frequency of disease alleles is known. In developed countries where consanguinity is rare, most affected individuals are compound heterozygous, and the clinical phenotype is generally determined by the milder allele.

PATHOBIOLOGY

Understanding of the genetic architecture of human populations is incomplete but growing due to the development of low-cost DNA sequencing and other technologies. Databases such as gnomAD (https://gnomad.broadinstitute.org/) that aggregate exome (the protein coding regions of the genome) and, increasingly, genome sequences obtained from hundreds of thousands of individuals from diverse populations provide valuable information on polymorphic DNA variants in humans, whether single nucleotide variants, insertion/deletion (indels) variants, or copy number variants. Most of these variants are benign, but they may be low-impact disease variants for common diseases or more rare, highly penetrant monogenic alleles. The genetic interactions of these variants affect many different biologic processes commonly referred to as the proteome, transcriptome, methylome, and other "-omics". This complexity and the effects on the mechanisms of disease are increasingly understood because of advances in protein, lipid, and carbohydrate analytic techniques, single-cell RNA and DNA sequencing technologies, computational biology, and studies in model organisms. Epigenetic methylation of DNA and histones as well as acetylation or other covalent modifications also can lead to epigenetic disorders that typically are syndromic in nature, with effects on growth, organogenesis, cognition, and the risk of cancer. Finally, copy number variants and chromosomal rearrangements are much more frequent than de novo single nucleotide variants (Chapter 32), with potential effects on gene

TABLE 189-1 SELECTED INBORN ERRORS OF METABOLISM

DISORDER	FUNCTIONAL DEFECT	INHERITANCE	CLINICAL PHENOTYPE
Argininemia	Arginase	Autosomal recessive	Hyperammonemia, fibrotic liver disease, progressive spasticity
Argininosuccinic aciduria	Argininosuccinate lyase	Autosomal recessive	Hyperammonemia, liver cirrhosis, hypertension, hypokalemia
Nonketotic hyperglycinemia	Glycine cleavage enzyme	Autosomal recessive (multiple loci)	Glycine encephalopathy, seizures, apnea, severe intellectual disability
Maple syrup urine disease	Branched-chain α-keto acid dehydrogenase complex	Autosomal recessive (multiple loci)	Encephalopathy, ataxia, brain herniation
Ornithine transcarbamylase deficiency	Ornithine transcarbamylase	X-linked	Severe hyperammonemia, occasional liver failure in females
Phenylketonuria	Phenylalanine hydroxylase	Autosomal recessive	Intellectual disability, hypopigmentation, seizures
Tyrosinemia type I	Fumaryl acetoacetate hydrolase	Autosomal recessive	Acute or chronic liver failure, tubulopathy, liver cancer
Tyrosinemia type II	Tyrosine aminotransferase	Autosomal recessive	Corneal lesions, hyperkeratosis of the skin, mild intellectual disability
Lysinuric protein intolerance	Lysine, ornithine, arginine transporter SLC7A7	Autosomal recessive	Hyperammonemia, anemia, osteoporosis, lung disease, growth failure
Glutaric acidemia type I	Glutaryl-CoA dehydrogenase	Autosomal recessive	Macrocephaly, dystonia, seizures, developmental delay
Methylmalonic aciduria	Methylmalonyl-CoA mutase, defects in vitamin B_{12} metabolism	Autosomal recessive (multiple loci)	Hyperammonemia, metabolic acidosis, renal failure, pancreatitis, optic atrophy, and neurologic abnormalities
Propionic aciduria	Propionyl-CoA carboxylase	Autosomal recessive (two loci)	Neonatal metabolic acidosis and hyperammonemia, developmental delay, dystonia, autism, cardiomyopathy
Fabry disease	α-Galactosidase	X-linked	Neuropathy, paresthesia, cardiomyopathy, renal failure, angiokeratoma, anhidrosis
Gaucher disease	Glucocerebrosidase	Autosomal recessive	Hepatosplenomegaly, anemia, thrombocytopenia, osteoporosis, fractures, neuropathy
Wilson disease	*ATP7B* copper transporter	Autosomal recessive	Liver failure, neurologic and psychiatric features
G6PD deficiency	Glucose-6-phosphate dehydrogenase	X-linked	Acute or chronic hemolytic anemia, drug-induced hemolytic anemia
Familial hypercholesterolemia	LDL receptor	Autosomal dominant and recessive	Elevated LDL cholesterol levels, premature or early onset coronary heart disease, tendon xanthomas

LDL = low density lipoprotein.

ABSTRACT

Inborn errors of metabolism are genetic disorders that affect the intrinsic metabolic pathways because of deficiencies of enzymes, membrane transporter proteins, transcription factors, chaperone or assembly proteins, or structural proteins. The resulting clinical phenotypes cause manifestations that may be stationary, progressive, or fluctuating in nature and may become symptomatic at any age. Although any inborn error of metabolism can, in principle, present during adolescence or adulthood, the more severe manifestations of these disorders are typically recognized during infancy and childhood. The use of newborn screening and the development of biochemical analytic and genomic technologies have improved the early diagnosis and treatment of these conditions. As a result, an increasing number of patients with inborn errors of metabolism now reach adulthood.

KEYWORDS

inborn errors of metabolism biochemical
metabolic
gene
phenylketonuria
urea cycle
organic acidurias
fatty acid oxidation disorders
enzyme replacement therapy

regulation or expression over considerable chromatin distances. For example, copy number variants of cytochrome P450 enzymes in diverse populations influence rates of xenobiotic elimination.

Inborn errors of metabolism are generally monogenic disorders, with the majority exhibiting autosomal recessive inheritance due to complete or partial loss of function. However, autosomal dominant conditions can occur, either due to haploinsufficiency, dominant negative alleles, or occasionally overactive enzymes. Both recessive and dominant inheritance can be observed at a single locus, often with distinct or overlapping phenotypes. For X-linked disorders, the pattern of X inactivation can have an impact on the severity of disease, as is seen with the clinical variability of ornithine transcarbamoylase deficiency in females. Postulated genetic modifiers may explain intrafamilial variability, but identifying these modifiers has been challenging. Certain disorders, such as Tay-Sachs disease (caused by mutations in *HEXA*), appear not to be influenced by environmental modifiers, whereas other conditions (e.g., glucose 6 phosphate dehydrogenase deficiency [Chapter 147] or hemochromatosis [Chapter 196]) are heavily influenced by diet or other environmental effects. Disorders of mitochondrial DNA can either be mendelian in inheritance or matrilineal if they involve one or more of the 37 genes encoded in mitochondrial DNA. In the latter case, the proportion of mutated mitochondrial molecules (termed heteroplasmy) and the distribution across tissues are major determinants of the severity of disease. In general, the mendelian forms of disorders of mitochondrial DNA occur more commonly in infancy or childhood, with primary disorders such as MELAS syndrome (mitochondrial encephalopathy, lactic acidosis, strokelike episodes; commonly due to c.3243A>G) occurring in older children and adults. Late-onset forms of childhood disease typically occur due to milder alleles (hypomorphs), an example being Pompe disease (acid glucosidase deficiency; Chapter 191), in which the classic picture is one of an infantile onset of a lethal cardiomyopathy and hypotonia, in contrast to a slowly progressive cardiomyopathy and respiratory failure in adults in whom the correct diagnosis may be missed. Similarly, propionic acidemia is typically detected by newborn screening and is symptomatic with hyperammonemia and refractory acidosis in infancy, but mild forms of the disease may manifest as isolated heart failure in older adults. Glycogen storage disorder type IV (glycogen branching enzyme deficiency, *GBE1*; Chapter 191) may be severe enough to cause lethal hydrops fetalis or more mild cases and cause the adult-onset neurologic disorder polyglucosan body disease, depending on the residual enzyme activity.

A number of pathophysiologic mechanisms (Table 189-2) may act individually or in combination to cause symptoms, and the organ system involvement can be cell type–specific or may affect multiple cell types and organs, either due to shared function or because of circulating toxic metabolites. The accumulation of enzyme substrates may lead to toxicity or to the increase of a toxic byproduct; alternatively, the loss of the enzyme reaction product may cause disease. Similarly, deficiencies of vitamin cofactors (e.g., vitamin B_{12}, which is required for the metabolism of homocysteine [Chapter 193] and methylmalonic acid) or allosteric regulators (e.g., N-acetylglutamate, needed to activate carbamoylphosphate synthetase of the urea cycle) may also mimic an enzyme deficiency.

Locus heterogeneity, by which more than one gene can cause the same clinical phenotype, can also be a feature of inborn errors of metabolism. For example, defects in the synthesis of tetrahydrobiopterin (BH4) lead to elevated levels of phenylalanine, as does a defect in the chaperone protein DNAJC12 or in phenylalanine hydroxylase. Defects in catabolic pathways, such as amino acid degradation, may be more readily detected because of the accumulation of substrates, but disorders in the synthesis of metabolites, such as defects in serine biosynthesis, are increasingly recognized.

CLINICAL MANIFESTATIONS

The clinical features and natural history of inborn errors of metabolism are highly diverse owing to the large number of entities and varying degrees of protein dysfunction.[6] Neurologic manifestations, which are the most common feature, include neurodevelopmental delay, encephalopathy, seizures, neurodegeneration, and peripheral neuropathy. Psychiatric manifestations are also observed in over 100 inborn errors of metabolism. However, essentially any organ system may be involved (Table 189-3). Disorders of intermediary metabolism can broadly affect acid/base balance, the excretion of nitrogen, and glucose homeostasis, or they can cause isolated neurometabolic conditions, such as glutaric aciduria type I. A subset of disorders also affects fetal development, thereby leading to a variety of birth defects such as congenital heart disease, brain malformations, limb defects, and genitourinary anomalies.

DIAGNOSIS

Most inborn errors of metabolism can be diagnosed by biochemical analysis of small molecules such as metabolites, peptides, and hormones in various body fluids, including serum or plasma, urine, or cerebrospinal fluid (CSF) (Fig. 189-1).[7]

TABLE 189-2 BROAD PATHOPHYSIOLOGIC MECHANISMS IN INBORN ERRORS OF METABOLISM

MECHANISM	DISORDER
Accumulation of toxic substrates through primary blockage of catabolic pathway	Organic acidurias (MMA, PA, glutaric aciduria type I) MSUD, tyrosinemia type 1
Accumulation of nontoxic macromolecules through blockage of catabolic pathways	Lysosomal storage disorders (MPS, Pompe disease)
Energy failure through primary blockage of pathway relevant for ATP synthesis	Fatty acid oxidation defects Glycogen storage disorders Respiratory chain enzyme deficiencies
Impairment of post-translational glycosylation	Congenital disorders of glycosylation
Deficiency of end product through primary blockage of anabolic pathway	Albinism, orotic aciduria, disorders of serine synthesis, creatine deficiency
Lack of detoxification through primary blockage of catabolic pathway	Urea cycle defects
Enzyme overactivity leading to substrate depletion and/or excess product	Glutamate dehydrogenase overactivity; hyperinsulinism and hyperammonemia, PRPP synthetase overactivity; gout

ATP = adenosine triphosphate; MMA = methylmalonic aciduria; MPS = mucopolysaccharidoses; MSUD = maple syrup urine disease; PA = propionic aciduria; PRPP = phosphoribosylpyrophosphate.
Adapted from Bodamer OA. Approach to inborn errors of metabolism. In: Goldman L, Schafer AI, eds. *Goldman-Cecil Medicine,* 26th ed. Philadelphia: Elsevier; 2020:1352-1355.

TABLE 189-3 CLINICAL CHARACTERISTIC SIGNS OF INBORN ERRORS OF METABOLISM

ORGAN	CLINICAL SIGN	DISORDER
Eye (cornea)	Corneal clouding, corneal dystrophy	MPS (Hurler, Maroteaux-Lamy, Sly disease), Fabry disease
Skeletal system	Ochronosis, black urine	Alkaptonuria
Connective tissue	Carpal tunnel syndrome, contractures	MPS I, II, VI, and VII
Central nervous system	Ataxia, intellectual disability, seizures, peripheral neuropathy	Respiratory chain enzyme deficiency, congenital disorders of glycosylation
Heart	Cardiomyopathy	Fabry disease, long chain fatty acid oxidation disorders, glycogen storage disease
Lung	Interstitial lung disease, obstructive or restrictive disease	Gaucher disease, MPS I, II, VI
Muscle	Hypotonia, rhabdomyolysis	Infantile Pompe disease, respiratory chain enzyme deficiency, long chain fatty acid oxidation disorders
Liver	Hepatomegaly/splenomegaly, fibrosis/cirrhosis	MPS I, II, VI, and VII; GSD I, III, IV, IX; Gaucher disease, Niemann-Pick disease, transaldolase deficiency
Kidney	Renal insufficiency, proteinuria	Cystinosis, Fabry disease, MMA
Skin	Angiokeratomata, hypopigmentation	Fabry disease, fucosidosis, phenylketonuria, tyrosinase deficiency

GSD = glycogen storage disease; MMA = methylmalonic aciduria; MPS = mucopolysaccharidosis.
Adapted from Bodamer OA. Approach to inborn errors of metabolism. In: Goldman L, Schafer AI, eds. *Goldman-Cecil Medicine,* 26th ed. Philadelphia: Elsevier; 2020:1352-1355.

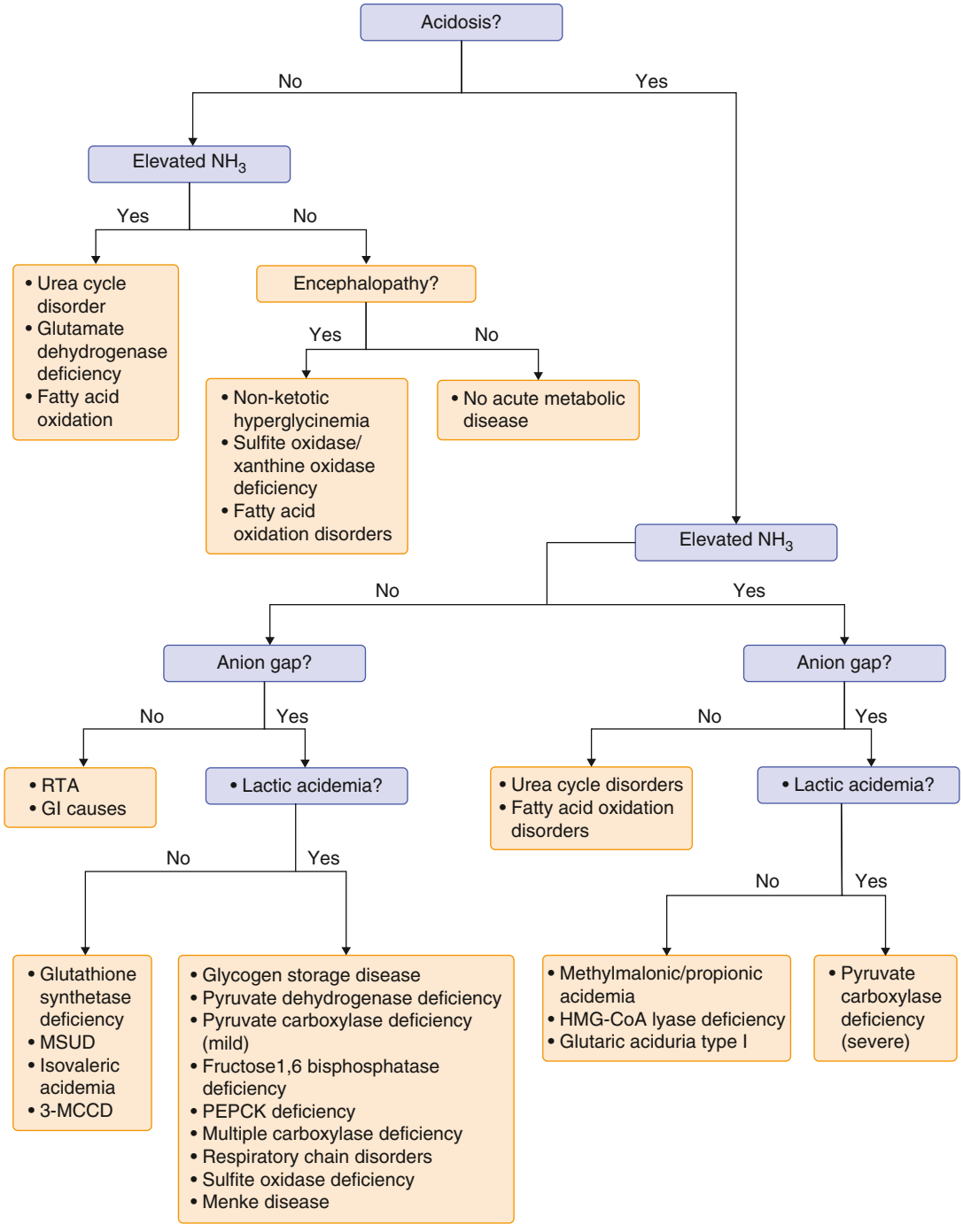

FIGURE 189-1. Diagnostic evaluation for metabolic disorders. 3-MCCD = 3-methyl-crontonyl-CoA carboxylase deficiency; CoA = coenzyme A; GI = gastrointestinal; HMG-CoA = hydroxy-methyl-glutaryl-CoA; MSUD = maple syrup urine disease; NH_3 = ammonia; PEPCK = phosphoenoylpyruvate carboxykinase; RTA = renal tubular acidosis.

DNA sequencing has largely replaced tissue biopsies for histology, histochemistry, or enzymatic analysis. Untargeted analyses of hundreds of metabolites can be performed on single samples of blood, urine, or CSF using multiple analytic platforms—an approach commonly referred to as metabolomics. This approach has been shown to improve diagnostic rates when compared with more traditional analytic testing, in part by identifying rare diagnostic compounds not typically detected by prior analytic approaches.[8,9] This technology is also useful in conjunction with DNA-based exome or genome analysis to provide metabolic confirmation of novel variants in known disease genes.[10]

DNA-based molecular confirmation (Chapters 32 and 33) is warranted to provide genotype-phenotype information that is useful in clinical prognostication and treatment, genetic counseling, identification of other potentially affected family members, carrier screening, and prenatal or preimplantation diagnosis. Next-generation sequencing is performed as part of diagnostic gene panels, exome sequencing, or genome sequencing. Gene panels have the advantage of avoiding variants in genes unrelated to the clinical phenotype and are typically less expensive. Exome and genome sequencing cast a large net and are developing into first-line testing. Ideally, a "trio" (parents and patient) should be subject to testing due to the observation that in about 50% of solved cases, the variant in the disease gene is a de novo change not seen in the parents. Examining parents also allows for the "phasing" of two variants in the patient, that is, determining if any two variants in a gene are on the same or opposite chromosomes. Exome sequencing in adults leads to a lower but still significant diagnostic rate compared to pediatric cases, and reanalysis of exome or genome data yields additional diagnoses as more disease genes are identified.[11]

In some settings, however, biochemical analyses may be followed by testing for enzyme activities in tissues or specific cells such as dried whole blood, lymphocytes, leukocytes, fibroblasts, or liver or muscle tissue. Selected metabolic tests used for the diagnosis of inborn errors of metabolism include analysis of amino acids in plasma, urine, and CSF; organic acids in urine and occasionally plasma; specific acylcarnitine species in plasma and dried blood spots; analysis of total and free carnitine in plasma and urine; succinylacetone (a diagnostic metabolite observed in tyrosinemia type I) in dried blood spots and urine; purines and pyrimidines in plasma and urine; sterols and bile acids in plasma and urine; and the pyrimidine intermediate orotic acid in urine.

TABLE 189-4 EXAMPLES OF THERAPEUTIC STRATEGIES FOR INBORN ERRORS OF METABOLISM

LEVEL	THERAPEUTIC APPROACH	DISORDER
Gene	Solid organ transplantation	Urea cycle defects, maple syrup urine disease, tyrosinemia type I
	Stem cell transplantation	Adrenoleukodystrophy, mucopolysaccharidosis I
	Gene therapy	Mucopolysaccharidoses I and II, VI, VII, phenylketonuria, urea cycle disorders
	Stop codon read-through therapy	Glycogen storage disease 1A
	Modified mRNA	Duchenne muscular dystrophy, cystic fibrosis, ornithine transcarbamylase deficiency, methylmalonic acidemia
Enzyme	Recombinant enzyme replacement	Gaucher disease, Pompe disease, Fabry disease; mucopolysaccharidoses I, II, IVa, and VI, phenylketonuria
	Chaperone	Fabry and Pompe diseases
Substrate	Substrate reduction	Phenylketonuria, maple syrup urine disease
	Substrate inhibition	Gaucher disease, Tay-Sachs disease, Niemann-Pick type C
	Substrate diversion	Urea cycle disorders

mRNA = messenger RNA.

TREATMENT

Strategies for treating inborn errors of metabolism (Table 189-4) include: (1) dietary interventions to reduce the deleterious substrate, (2) administration of vitamin cofactors to enhance residual enzyme activity, (3) provision of a missing cofactor, (4) chaperone therapy to stabilize an unfolded or mistargeted protein, (5) direct enzyme replacement therapy, (6) inhibiting an upstream enzyme to reduce a substrate, (7) small molecule inhibition of a toxic metabolite, (8) replacement of an affected organ, (9) stem cell transplantation, (10) "read-through" of premature termination codons, or (11) gene replacement therapy. For example, in patients with primary hyperoxaluria (characterized by oxalosis, nephrocalcinosis, nephrolithiasis, and kidney failure),[12] lumasiran, which reduces oxalate formation by blocking glycolate oxidase, can lead to normal or near-normal oxalate levels.[A1] Other therapeutic approaches, including modified mRNA therapies and gene correction strategies (e.g., CRISPR), are currently in clinical trials.

A curative approach is preferred whenever possible, such as may be achieved with various transplantation or gene delivery strategies. In conditions with central nervous system manifestations, however, the blood-brain barrier may limit the effectiveness of larger molecules, such as enzymes, that are not directly administered to the brain parenchyma.

Unfortunately, curative interventions often are not possible or are potentially hazardous. Individuals with inborn errors of metabolism often require a multidisciplinary team of biochemical geneticists, internists, genetic counselors, and other subspecialists.

Nutritional Therapy

The therapeutic goal for nutritional therapy under expert guidance is to correct the metabolic imbalance by reducing the accumulation of substrate, promoting protein synthesis through anabolism, and preventing episodes of metabolic decompensation in conditions such as urea cycle disorders or organic acidurias. Appropriate medical foods are low in protein or have a specific composition of amino acids or fatty acids. In addition, supplementation of a deficient product may be needed, as in the case of most urea cycle disorders in which provision of citrulline or arginine is required.

Enzyme Replacement Therapy

Intravenous enzyme replacement therapy with glucocerebrosidase is the treatment for type I Gaucher disease (Chapter 191). Enzyme replacement therapy (Chapters 191 and 192) is also available for Pompe disease (α-glucosidase), mucopolysaccharidosis type I (α-iduronidase; Hurler/Scheie disease), mucopolysaccharidosis type II (α-iduronate sulfatase; Hunter disease), mucopolysaccharidosis type IVa (galactosamine-6-sulfatase; Morquio disease), mucopolysaccharidosis type VI (arylsulfatase B; Maroteaux-Lamy disease), and Fabry disease (α-galactosidase). Enzyme therapies also exist for late infantile neuronal ceroid lipofuscinosis type 2 (CLN2) caused by deficiency of tripeptidyl peptidase 1 (administered directly into the brain) and phenylketonuria (a recombinant phenylalanine ammonia lyase that is pegylated to improve its stability and administered daily as a subcutaneous injection). A variety of other enzyme products are in different phases of clinical trials.

Another approach is to reduce the accumulation of toxic substrate by inhibiting the reverse enzyme reaction that leads to its synthesis. This strategy can reduce glucosylceramide levels in Gaucher disease type I (Chapter 191).

Enzyme therapy can also use small molecules to increase endogenous enzymatic activity. For example, individuals with tetrahydrobiopterin-responsive phenylketonuria have improved tolerance to phenylalanine and lower blood and tissue levels of phenylalanine when they take pharmacologic doses of tetrahydrobiopterin.

Vitamin Therapy

A number of inborn errors of metabolism affect transport or metabolism of vitamins. Patients who have these conditions typically benefit from supraphysiologic doses of vitamins. One example is when riboflavin transporter deficiencies, caused by pathogenic variants in *SLC52A2* or *SLC52A3*, result in Brown-Vialetto-Van Laere syndrome or Fazio-Londe syndrome and lead to a progressive neuropathy, optic atrophy, deafness, ataxia, and respiratory insufficiency. Treatment with 10 to 70 mg/kg/day of riboflavin can stabilize the progression of disease and sometimes reverse it. Other vitamin deficiencies include disorders of thiamin, biotin, nicotinamide adenine dinucleotide, and folic acid metabolism.

Organ and Stem Cell Transplantation

Liver transplantation is often performed in patients who have defects in the urea cycle, late-diagnosed tyrosinemia type 1, methylmalonic aciduria, propionic aciduria, maple syrup urine disease, and glycogen storage diseases that affect the liver. The benefits of liver transplantation in these disorders include improved metabolic control, restoration of normal liver function, and avoidance of malignant transformation. However, liver transplantation typically does not correct the intrinsic defect in other tissues. For example, liver transplantation in mitochondrial diseases associated with liver failure does not protect the individual from progressive neurologic disease. In contrast, liver transplantation appears to protect individuals with propionic acidemia from cardiomyopathy.

Kidney transplantation may be required for disorders that impair kidney function, as seen in methylmalonic acidemia, hyperoxaluria, or cystinosis. Stem cell transplantation may benefit selected patients with inborn errors of metabolism, such as presymptomatic bone marrow or stem cell transplantation in X-linked adrenoleukodystrophy, severe mucopolysaccharidosis type I (Hurler disease), or metachromatic leukodystrophy.

Genetic Counseling

Genetic counseling by board-certified genetic counselors is important for the evaluation and management of patients with any genetic disorder,[13] including an inborn error of metabolism. A multigenerational family history and thorough medical history are needed for an appropriate clinical and diagnostic evaluation. The limitations and implications of genetic testing and the resultant diagnosis are communicated to the patient and the family by genetic counselors in a language appropriate for the family. Individuals who have inborn errors of metabolism that put them at risk for acute metabolic decompensation, such as fatty acid oxidation disorders, urea cycle disorders, and organic acidurias, should be provided with an "emergency letter" detailing their diagnosis and the required emergency treatment, as well as contact information for the treating metabolic center.

SELECTED ERRORS OF METABOLISM

Some inborn errors of metabolism are part of broader families of disorders (e.g., glycogen storage disorders [Chapter 191] and lysosomal storage disorders [Chapter 192]) or are well-recognized adult conditions (e.g., porphyrias [Chapter 194] and disorders of metal metabolism [Chapters 195 and 196]). Others, however, most commonly present in infancy or childhood, and they are now seen in adults only because of successful pediatric interventions.

DISORDERS OF PROTEIN METABOLISM

A variety of disorders of protein metabolism can cause hyperammonemia, neurologic dysfunction, and other manifestations (Table 189-5).

TABLE 189-5 DISORDERS OF PROTEIN METABOLISM

DISORDER	ENZYME DEFECT	METABOLITE(S)	CLINICAL PHENOTYPE
Argininemia	Arginase	Arginine	Hyperammonemia, neurologic disease
Argininosuccinic aciduria	Argininosuccinate lyase	Argininosuccinate	Hyperammonemia, liver cirrhosis
Citrullinemia	Argininosuccinate synthetase	Citrulline, orotic acid*	Hyperammonemia, liver cirrhosis
Homocystinuria	Cystathionin β-synthase	Homocysteine, methionine	Marfanoid habitus, intellectual disability, lens dislocation
Maple syrup urine disease	Branched-chain α-keto acid dehydrogenase complex	Alloisoleucine,* leucine, valine, isoleucine	Encephalopathy, ataxia, metabolic decompensation
Ornithine transcarbamylase deficiency	Ornithine transcarbamylase	Orotic acid,* citrulline, arginine	Severe hyperammonemia, X-linked inheritance
Phenylketonuria	Phenylalanine hydroxylase	Phenylalanine	Intellectual disability,† seizures†
Tyrosinemia type I	Fumaryl acetoacetate hydrolase	Succinylacetone,* tyrosine	Acute liver failure, renal tubulopathy
Tyrosinemia type II	Tyrosine aminotransferase	Tyrosine, phenylalanine	Corneal lesions, hyperkeratosis of the skin, mild intellectual disability

*Diagnostic compound.
†If untreated.
Adapted from Bodamer OA. Approach to inborn errors of metabolism. In: Goldman L, Schafer AI, eds. *Goldman-Cecil Medicine,* 26th ed. Philadelphia: Elsevier; 2020:1352-1355.

PHENYLKETONURIA

Phenylketonuria[14] is caused by reduced activity or loss of function of phenylalanine hydroxylase, which normally converts the amino acid phenylalanine to tyrosine. The incidence is about 1 in 10,000 to 15,000 newborns in the United States, Europe, and among Native Americans, but it is much less common in other populations. In addition to protein synthesis, the tyrosine product of the tetrahydrobiopterin-dependent phenylalanine hydroxylase is required to synthesize neurotransmitters, melanin, and thyroid hormone. Phenylalanine is transported via a large neutral amino acid transporter (LAT1, *SLC7A5*) and thus competes for uptake into the brain with eight other amino acids. Hence, increasing the phenylalanine concentration by 20- to 30-fold, as occurs in classic untreated phenylketonuria, leads to a tissue deficit of other amino acids, thereby affecting the synthesis of proteins and neurotransmitters. The degree of hyperphenylalaninemia varies considerably among affected individuals and is primarily determined by the patient's genotype at the *PAH* locus.

CLINICAL MANIFESTATIONS AND DIAGNOSIS

The defect, if untreated, results in elevated blood and urine concentrations of phenylalanine and its metabolites and can lead to seizures, neurocognitive defects, and psychiatric disease. Diagnosis is by newborn screening, which is mandated in infants during the first 3 days of life in the United States, to detect an elevated blood level of phenylalanine. However, many countries do not have screening programs, so the disease can present later in such countries or in immigrants from such countries.

Approximately 1000 variants in phenylalanine can occur (https://www.ncbi.nlm.nih.gov/clinvar/) and expert interpretation is often required. Phenylketonuria also exhibits genetic locus heterogeneity, and defects in the enzymes involved in the synthesis of tetrahydrobiopterin also cause hyperphenylalaninemia and require a different treatment strategy beyond phenylalanine restriction. In fact, tetrahydrobiopterin deficiency is the leading cause of hyperphenylalaninemia in Saudi Arabia.

TREATMENT

Treatment with a protein-restricted, tyrosine-supplemented diet avoids the long-term complications of substantial intellectual disability,[15] but more subtle deficits may still occur.[16] However, other treatment strategies include supplementation with other large neutral amino acids to compete for transport; pharmacologic doses of tetrahydrobiopterin, which can raise the residual activity of phenylalanine hydroxylase in up to a third of patients[A2]; and enzyme replacement therapy.[A3,A4] Gene therapy trials are currently underway.

PROGNOSIS

With effective dietary treatment, most affected individuals live normal lives. However, adherence is difficult, so many adult patients have poor dietary control and raised phenylalanine levels that can lead to psychiatric morbidities such as anxiety and depression. Interventions such as focused educational instruction to empower caregivers can improve long-term dietary adherence.[A5]

DISORDERS OF THE UREA CYCLE

The urea cycle is a mechanism for the excretion of nitrogen that is generated by the oxidation of amino acids so as to avoid the accumulation of ammonium by forming urea (Fig. 189-2). The entire cycle is present in the liver, whereas the proximal portion of the cycle is present in the intestines (as a means for generating citrulline), and the distal portion of the cycle (but lacking arginase activity) is present in the kidney to generate arginine from circulating citrulline. The proximal portion of the cycle (N-acetylglutamate synthetase, carbamoylphosphate synthetase, and ornithine transcarbamoylase) is located in mitochondria, whereas the distal portion (argininosuccinate synthetase, argininosuccinate lyase, and arginase) resides in the cytosol. The first two enzymes of the distal portion, arginosuccinate synthetase and arginosuccinate lyase, link the urea cycle to the Krebs cycle via the metabolites oxaloacetate, aspartic acid, and fumarate. Both enzymes are also expressed in additional cell types and are central to the synthesis of nitric oxide and the conversion of arginine to citrulline. Transporters that are required for the intracellular shuttling, in particular the aspartate/glutamate exchanger, are additional disease loci.

CLINICAL MANIFESTATIONS AND DIAGNOSIS

Mutated citrin can present as cholestasis and failure to thrive in infancy or altered mental status and hyperammonemia in adults.[17] Affected individuals will often exhibit aversion to dietary protein, with complaints of headache, diplopia, abdominal pain, and vomiting prior to metabolic decompensation. A coagulopathy and other evidence of liver failure may also be seen. Although most cases are diagnosed in infancy, the age of onset can be quite broad, with many late-onset cases reported in adults, in particular females with deficiency in ornithine transcarbamylase due in part to variation in the pattern of X inactivation. Symptoms of encephalopathy and liver disease are typically brought on by intercurrent illness or metabolic stress, such as childbirth in females with ornithine transcarbamylase deficiency.

Currently, newborn screening detects disorders of the distal portion of the cycle (arginosuccinate synthetase, arginosuccinate lyase, and arginase) but not the proximal portion. Ammonia levels must be measured directly, and more specific testing, such as levels of plasma amino acids and urine orotic acid, can generally determine the site of the metabolic block. With the exception of X-linked *OTC*, all disorders are inherited in an autosomal recessive manner, so a correct diagnosis is essential for family counseling.

TREATMENT

Treatment involves aggressive restriction of dietary protein and provision of the enzyme product, such as citrulline or arginine. Medications that are used to provide an alternate means of nitrogen excretion, such as benzoate and phenylacetate, are termed nitrogen scavenging agents.[18] For acute hyperammonemia, emergency treatment with nitrogen scavenging agents or hemodialysis is required to prevent brain edema and death. Liver transplantation may be curative, and trials of modified mRNA and gene therapy are underway.

PROGNOSIS

Most patients survive through adolescence. A higher blood ammonia level at diagnosis portends a worse prognosis, especially if above 360 μmol/L, as does the duration of hyperammonemia.[19]

ORGANIC ACIDURIAS

Organic acidurias are a heterogenous group of inborn errors of metabolism that are primarily due to defects in the degradation of certain amino acids. The pathophysiology of these disorders is complicated. Available evidence suggests hyperammonemia is a consequence of inhibition of N-acetyl glutamate synthetase, which is the first enzyme of the urea cycle, by metabolites of propionate (see Fig. 189-2).

For propionic acidemia, no clear relationship between metabolic instability and the risk of cardiomyopathy is apparent. A founder variant in *PCCB* (p.N536D) in the Amish population has been associated with both childhood metabolic decompensation and adult-onset cardiomyopathy in the absence of metabolic events.

Methylmalonic acidemia provides an example of extreme locus heterogeneity, with pathogenic variants in the mitochondrial enzyme methylmalonyl-CoA mutase as well as defects in the generation of an active form of vitamin B_{12}, adenosylcobalamin. Lack of active forms of vitamin B_{12} may be due to genetic defects in the absorption, transport, or cellular uptake of dietary vitamin B_{12} or its intracellular processing from the lysosome to activation and transport to mitochondria. Depending on the affected protein in the pathway of vitamin B_{12} activation, patients may be deficient in methylcobalamin, which is required for the conversion of homocysteine to methionine, adenosylcobalamin, or both. The most common of these disorders is methylmalonic acidemia with homocystinuria due to pathogenic variants in *MMACHC*, in which both levels of homocysteine and methylmalonic acid are elevated. With the exception of 3-hydroxy-2-methylbutyryl-CoA dehydrogenase deficiency, which is an X-linked semi-dominant condition, and methylmalonic acidemia and homocysteinemia type CblX, an X-linked transcription factor that impacts *MMACHC* expression, organic acidurias are inherited in an autosomal recessive manner.

CLINICAL MANIFESTATIONS AND DIAGNOSIS

These acidurias can cause hyperammonemia, anemia, and a high anion gap acidosis, as well as more chronic ailments such as recurrent pancreatitis, renal failure, cardiomyopathy, optic atrophy, seizures, strokelike episodes, movement disorders, and intellectual disabilities (Table 189-6).[20] The disease spectrum

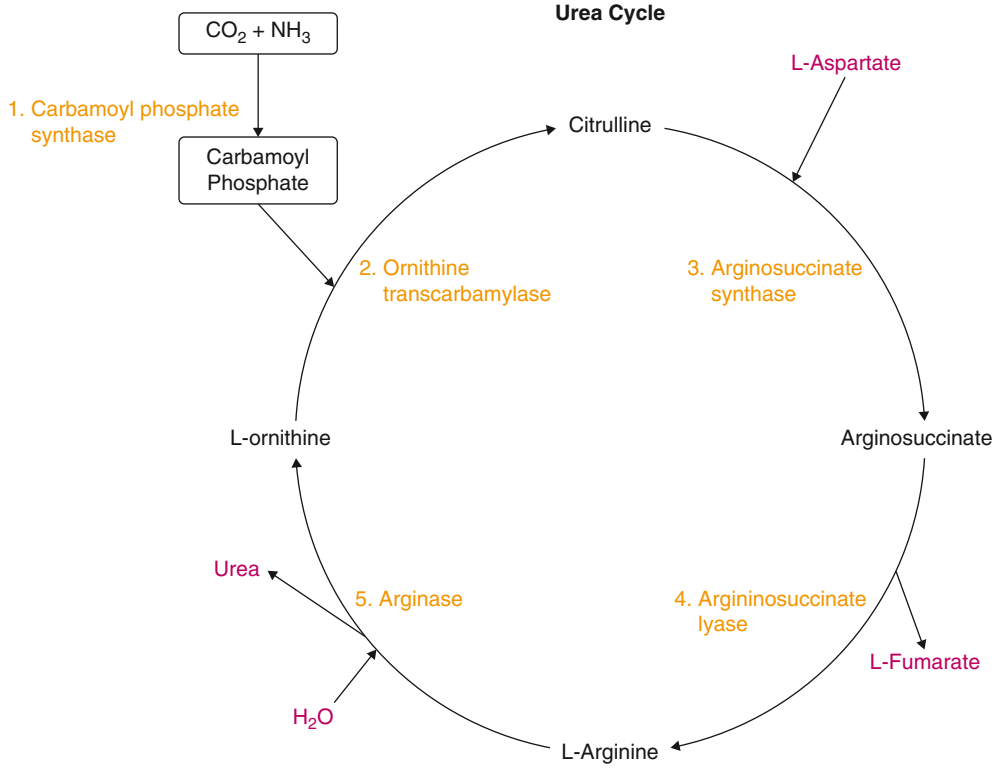

FIGURE 189-2. The urea cycle. The liver converts ammonia to less toxic urea. The urea is then transported to the kidneys and excreted in urine.

TABLE 189-6 ORGANIC ACIDURIAS

DISORDER	ENZYME DEFECT	INHERITANCE	URINE METABOLITES
Glutaric aciduria type I	Glutaryl-CoA dehydrogenase	Autosomal recessive	3-Hydroxyglutaric acid, glutaric acid
Holocarboxylase synthetase deficiency	Holocarboxylase synthetase	Autosomal recessive	β-Hydroxyisovaleric acid, β-methylcrotonylglycine, β-hydroxypropionic acid, 3-methycitrate
Isobutyric aciduria	Isobutyryl-CoA dehydrogenase	Autosomal recessive	Isobutyric acid
Isovaleric aciduria	Isovaleryl-CoA dehydrogenase	Autosomal recessive	Isovaleric acid
Methylmalonic aciduria	Methylmalonyl-CoA dehydrogenase	Autosomal recessive	Methylmalonic acid
Mevalonic aciduria	Mevalonate kinase	Autosomal recessive	Mevalonic acid
Propionic aciduria	Propionyl-CoA carboxylase	Autosomal recessive	3-Methycitrate, propionic acid, 3-hydroxypropionic acid

CoA = coenzyme A.
Adapted from Bodamer OA. Approach to inborn errors of metabolism. In: Goldman L, Schafer AI, eds. *Goldman-Cecil Medicine*, 26th ed. Philadelphia: Elsevier; 2020:1352-1355.

varies from apparently benign elevations in metabolites, such as is seen in a common variant of isovaleric acidemia, to neonatal decompensation with severe hyperammonemia and acidosis. Brain damage is common, with the basal ganglia being particularly vulnerable to strokelike events, likely reflecting the toxicity of accumulating metabolites on mitochondrial respiratory chain function. Late-onset forms of milder cobalamin-C deficiency may have the onset of psychiatric symptoms or encephalopathy, as well as transverse myelitis in adolescence or adulthood.

An elevated glycine level is a common feature of propionic acidemia and methylmalonic acidemia. The more common forms are now identified by newborn screening through the quantitative measurement of acyl-carnitine species for which each organic aciduria has a signature, although not unique, profile. However, not all organic acidurias are detectable by this strategy and may require alternative technologies for diagnosis, for example D- or L-2-hydroxyglutaric acidurias. Several disorders identified by newborn screening have no apparent pathology, such as 3-methylcrotonyl-CoA carboxylase deficiency and 2-methylbutyryl-CoA dehydrogenase deficiency, the latter being common in the Hmong population of Southeast Asia.

TREATMENT

Treatment of organic acidurias under expert consultation is disease-dependent but typically involves protein restriction to reduce the offending amino acids in conjunction with medical foods that provide a source of nonrestricted amino acids and additional calories. Providing an alternative source of N-acetyl glutamate relieves the inhibition of the urea cycle and reduces ammonia levels, thereby serving as an effective strategy for acutely ill patients. Supplemental carnitine is provided to promote the excretion of the accumulated abnormal metabolite. For disorders of vitamin B_{12} metabolism, daily doses of up to 30 mg of hydroxycobalamin given subcutaneously may be needed in conjunction with betaine (trimethylglycine) (up to 18 grams/day) to promote the synthesis of methionine from homocysteine.

DISORDERS OF FATTY ACID OXIDATION

Fatty acid β-oxidation is a major source of energy for heart and skeletal muscle. Each cycle of β-oxidation generates acetyl-coenzyme A (CoA) that can be used for tricarboxylic acid cycle function and the production of ketone bodies. Ketone bodies produced in the liver can be used for energy by tissues such as the brain when the supply of glucose is limited. Fatty acid β-oxidation occurs in mitochondria, thereby requiring a mechanism for the import of long-chain fatty acids across the outer and inner mitochondrial membranes. Long-chain fatty acids entering the cell are esterified with carnitine via the mitochondria outer membrane enzyme carnitine-palmitoyltransferase I before being transported across the mitochondrial membranes through a series of reactions known as the carnitine cycle. The free acyl-coenzyme A esters can then undergo β-oxidation in the mitochondrial matrix. Medium- and short-chain fatty acids do not require this pathway for import. Disorders that interfere with any of these steps limit the production of energy in the heart and skeletal muscle and reduce the ability of other tissues, such as the brain, to tolerate a low-glucose milieu during episodes of increased energy demand. All the known fatty acid β-oxidation disorders are inherited in an autosomal recessive manner.

CLINICAL MANIFESTATIONS AND DIAGNOSIS

Fatty acid β-oxidation disorders can present at any age, with the age of onset largely dependent on the residual activity of the defective enzyme. Complete or near-complete deficiencies are typically symptomatic in infancy or early childhood and associated with hypoketotic hypoglycemia, rhabdomyolysis, cardiomyopathy, and occasionally liver failure, whereas onset in adolescence and adulthood is usually associated with recurrent rhabdomyolysis (Chapter 99) without hypoglycemia.[21] Long-chain fatty acid β-oxidation disorders often involve the heart, whereas medium- and short-chain disorders typically do not.

Newborn screening detects many of these conditions, but the diagnostic analytes used for newborn screening may be only transiently elevated, especially in milder forms. As a result, follow-up testing often relies on DNA-based analyses. To date, 22 genes involved in fatty acid β-oxidation have been definitively associated with human disease, with the most common disorders being medium-chain acyl-coenzyme-A dehydrogenase (*ACADM*) deficiency and very long-chain acyl-acetyl-coenzyme-A dehydrogenase (VLCAD encoded by *ACADVL*) deficiency. However, a common and quite severe allele of *ACADM* (p.K304E) is found in Northern European populations, with a homozygous birth incidence of 1 per 10,000 in Germany. VLCAD deficiency has a birth incidence of about 1 per 50,000 in the United States but can be as high as 1 per 3000 in one region of Saudi Arabia.[22]

TREATMENT

Treatment depends on the specific deficiency.[23] Long-chain fatty acid β-oxidation disorders may be treated with medium-chain triglycerides under the supervision of a specially trained dietician or the odd-chain triglyceride triheptanoin (approximately 30% of total daily calories).[A6] Medium-chain acyl-coenzyme-A dehydrogenase deficiency is typically managed with anticipatory guidance concerning fasting and illness, as well as carnitine supplementation (10 to 100 mg/kg/day) due to a secondary carnitine deficiency observed in many patients.

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190 DISORDERS OF LIPID METABOLISM

JENNIFER G. ROBINSON

Disorders of lipid metabolism are an increasingly common consequence of modern industrial lifestyles. With increasing prosperity, the spread of Western-style diets and sedentary habits is resulting in dramatic rises in obesity in countries around the world. Poor lifestyle habits coupled with genetic predisposition commonly result in dyslipidemia, which is characterized by higher levels of the atherogenic cholesterol- and triglyceride-rich apolipoprotein (apo) B-100 lipoproteins, higher levels of triglyceride-rich apo B-48 lipoproteins, and lower levels of apo A lipoproteins. In the office setting, these apolipoproteins are reflected in levels of low-density lipoprotein (LDL) cholesterol, triglycerides, high-density lipoprotein (HDL) cholesterol, and non-HDL-cholesterol.

The most common clinical manifestation of lipid disorders is atherosclerotic cardiovascular disease (ASCVD) that results from elevated levels of apo B-100 lipoproteins.[1] In the United States, 44% of adults have elevated non-HDL cholesterol levels above 130 mg/dL.[2,3] Apo A lipoproteins have a smaller role in the development of (or protection from) ASCVD. Severe hypertriglyceridemia is primarily associated with an increased risk of pancreatitis.

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varies from apparently benign elevations in metabolites, such as is seen in a common variant of isovaleric acidemia, to neonatal decompensation with severe hyperammonemia and acidosis. Brain damage is common, with the basal ganglia being particularly vulnerable to strokelike events, likely reflecting the toxicity of accumulating metabolites on mitochondrial respiratory chain function. Late-onset forms of milder cobalamin-C deficiency may have the onset of psychiatric symptoms or encephalopathy, as well as transverse myelitis in adolescence or adulthood.

An elevated glycine level is a common feature of propionic acidemia and methylmalonic acidemia. The more common forms are now identified by newborn screening through the quantitative measurement of acyl-carnitine species for which each organic aciduria has a signature, although not unique, profile. However, not all organic acidurias are detectable by this strategy and may require alternative technologies for diagnosis, for example D- or L-2-hydroxyglutaric acidurias. Several disorders identified by newborn screening have no apparent pathology, such as 3-methylcrotonyl-CoA carboxylase deficiency and 2-methylbutyryl-CoA dehydrogenase deficiency, the latter being common in the Hmong population of Southeast Asia.

TREATMENT

Treatment of organic acidurias under expert consultation is disease-dependent but typically involves protein restriction to reduce the offending amino acids in conjunction with medical foods that provide a source of nonrestricted amino acids and additional calories. Providing an alternative source of N-acetyl glutamate relieves the inhibition of the urea cycle and reduces ammonia levels, thereby serving as an effective strategy for acutely ill patients. Supplemental carnitine is provided to promote the excretion of the accumulated abnormal metabolite. For disorders of vitamin B_{12} metabolism, daily doses of up to 30 mg of hydroxycobalamin given subcutaneously may be needed in conjunction with betaine (trimethylglycine) (up to 18 grams/day) to promote the synthesis of methionine from homocysteine.

DISORDERS OF FATTY ACID OXIDATION

Fatty acid β-oxidation is a major source of energy for heart and skeletal muscle. Each cycle of β-oxidation generates acetyl-coenzyme A (CoA) that can be used for tricarboxylic acid cycle function and the production of ketone bodies. Ketone bodies produced in the liver can be used for energy by tissues such as the brain when the supply of glucose is limited. Fatty acid β-oxidation occurs in mitochondria, thereby requiring a mechanism for the import of long-chain fatty acids across the outer and inner mitochondrial membranes. Long-chain fatty acids entering the cell are esterified with carnitine via the mitochondria outer membrane enzyme carnitine-palmitoyltransferase I before being transported across the mitochondrial membranes through a series of reactions known as the carnitine cycle. The free acyl-coenzyme A esters can then undergo β-oxidation in the mitochondrial matrix. Medium- and short-chain fatty acids do not require this pathway for import. Disorders that interfere with any of these steps limit the production of energy in the heart and skeletal muscle and reduce the ability of other tissues, such as the brain, to tolerate a low-glucose milieu during episodes of increased energy demand. All the known fatty acid β-oxidation disorders are inherited in an autosomal recessive manner.

CLINICAL MANIFESTATIONS AND DIAGNOSIS

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Treatment depends on the specific deficiency.[23] Long-chain fatty acid β-oxidation disorders may be treated with medium-chain triglycerides under the supervision of a specially trained dietician or the odd-chain triglyceride triheptanoin (approximately 30% of total daily calories).[A6] Medium-chain acyl-coenzyme-A dehydrogenase deficiency is typically managed with anticipatory guidance concerning fasting and illness, as well as carnitine supplementation (10 to 100 mg/kg/day) due to a secondary carnitine deficiency observed in many patients.

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190 DISORDERS OF LIPID METABOLISM

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ABSTRACT

Disorders of lipid metabolism are an increasingly common consequence of modern industrial lifestyles. The most common clinical manifestation of lipid disorders is atherosclerotic cardiovascular disease (ASCVD) that results from elevated levels of apo B-100 lipoproteins. Despite tremendous advances in prevention and treatment, ASCVD remains the leading cause of death in almost every developed country in the world. Statins are the first-line lipid-modifying therapy for ASCVD risk reduction based on extensive clinical trial data that they reduce fatal and nonfatal ASCVD events and overall mortality. When the response to statins is insufficient, an increasing number of effective options are now available.

KEYWORDS

cholesterol
apolipoproteins
triglycerides
atherosclerosis
cardiovascular prevention
statins
lipid-lowering drug therapy

LIPID METABOLISM

PATHOBIOLOGY

Cholesterol and Triglycerides

Cholesterol, which is an essential component of all animal cell membranes, functions as a precursor to fat-soluble vitamins and steroid hormones such as cortisol, estradiol, progestins, and testosterone. Plants utilize sterols rather than cholesterol as structural components of the cell membrane. Triglycerides are composed of three fatty acid chains attached to a glycerol molecule. Triglycerides are a source of energy, particularly in the fasting state. Both cholesterol and triglycerides are insoluble in water, so they require lipoprotein particles to transport them in plasma (Fig. 190-1). Apolipoproteins, which are amphipathic molecules that are located on the surface of the lipoprotein particle and serve as biochemical keys to specific receptors or binding sites, allow delivery, entry, or modification of cholesterol (E-Fig. 190-1).

Cholesterol and triglycerides are either synthesized or absorbed from the intestine. Adults synthesize about 100 mg of cholesterol per day. The liver synthesizes about 25% of cholesterol, but the brain, reproductive organs, adrenal glands, and intestines synthesize it. Cholesterol is synthesized via multiple steps from acetyl CoA and acetoacetyl-CoA. The rate-limiting step in cholesterol synthesis is the reduction to mevalonate by 3-hydroxy-3-methyl-glutaryl-CoA (HMG-CoA) reductase, which is the target of statins. Downstream metabolites of mevalonate include several bioactive molecules, which have been implicated in some adverse effects of statins.

Diet provides 300 to 500 mg cholesterol per day. Bile acids provide about two thirds of daily cholesterol (800 to 1200 mg) and sloughed intestinal cells about 300 mg. Nonesterified cholesterol is secreted from the liver in bile acids, which are stored in the gallbladder and secreted into the small intestine, where they solubilize dietary fats and enhance fatty acid, lipid, and fat-soluble vitamin absorption. Bile acids are largely reabsorbed from the distal ileum and transported back to the liver via the enterohepatic circulation.

Dietary fats and animal products are broken down in the intestine, and the constituents are transported into enterocytes, where they are re-esterified into cholesteryl ester and triglycerides. Cholesterol is absorbed from the intestine via the Niemann-Pick C1-Like 1 (NPC1L1) receptor, which can be inhibited with ezetimibe.

Chylomicrons

In the enterocyte, triglycerides and cholesterol are packaged with apo B48 as well as apo CII and CIII and other apolipoproteins for secretion into the blood as triglyceride-rich chylomicrons (see Fig. 190-1). Chylomicrons undergo progressive hydrolysis of triglycerides into fatty acids by lipoprotein lipase in the capillary endothelium, which binds apo CII as well as other apolipoproteins. The fatty acids can be stored in adipose tissue or used as fuel by muscle tissue. Chylomicrons are converted into chylomicron remnants, which are relatively enriched in cholesteryl esters. Chylomicrons, which are the largest lipoproteins, are unlikely to contribute to atherosclerosis; they are not soluble in plasma, cause a "tomato soup" appearance to freshly drawn plasma, and rise to the top of the serum after overnight refrigeration to cause a "cream" layer. The smaller chylomicron remnants, which can enter the subendothelial space to be taken up by macrophages, may be the mechanism through which postprandial hypertriglyceridemia contributes to atherogenesis.

Chylomicrons and chylomicron remnants are also taken up by the liver by the LDL receptor–related protein, which interacts with apo E, and to a lesser extent by the LDL receptor and cell surface glycosaminoglycans. The liver breaks down the chylomicron particles, which can be stored as cholesteryl ester and triglycerides that are assembled into very-low-density lipoprotein (VLDL) particles for secretion into the blood, or the cholesteryl esters can be incorporated into bile acids for secretion into the intestine.

VLDL, IDL, LDL

The liver assembles a VLDL particle from one apolipoprotein B100 molecule, cholesteryl esters, triglycerides, and a number of other apolipoproteins and lipids. Triglycerides are the rate-limiting step in the synthesis of VLDL. Microsomal transfer protein (MTP) transfers triglycerides to the growing apo B peptide. Drugs such as lomitapide that inhibit MTP can cause intrahepatic accumulation of triglyceride. Mipomersen, which is a drug that is no longer available in the United States, inhibits apo B synthesis and can also increase the intrahepatic accumulation of triglyceride, increase hepatic fat content, and cause hepatic steatosis.

Nascent VLDL is secreted into the blood, where it acquires apo E, apo CII, and apo CIII. Apo CIII and angiopoietin-like protein 3 activate lipoprotein lipase to hydrolyze the VLDL triglycerides into fatty acids for transport into tissues. As VLDL continues to deliver cholesterol and triglycerides to tissues, VLDL is transformed into increasingly cholesteryl-rich intermediate density lipoproteins (IDL) and ultimately into LDL (see Fig. 190-1). LDLs, which comprise the largest fraction of circulating lipoproteins, contain about 60 to 70% of total cholesterol in the circulation.

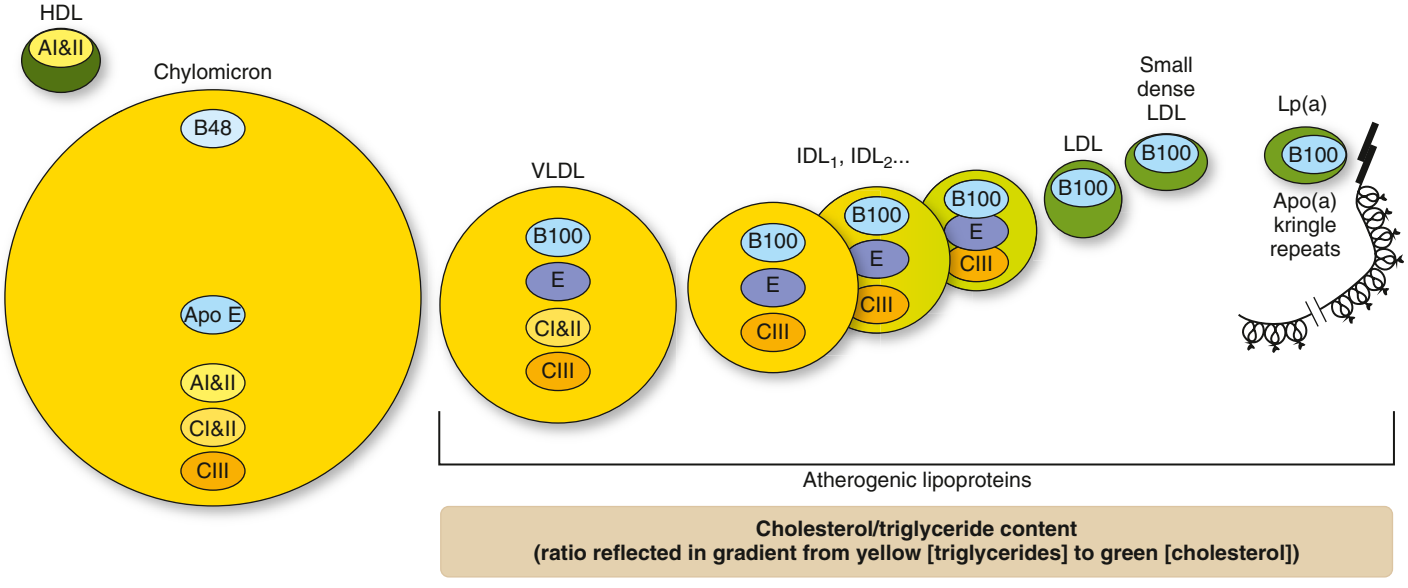

FIGURE 190-1. **Relative size (not to scale) of triglyceride *(yellow)* and cholesterol *(green)* composition, major apolipoproteins, and atherogenicity of circulation lipoproteins.** HDL = high-density lipoprotein; IDL = intermediate-density lipoprotein; LDL = low-density lipoprotein; VLDL = very-low-density lipoprotein. (Adapted from Robinson J. *Clinical Lipid Management*. West Islip, NY: Professional Communications, Inc; 2016.)

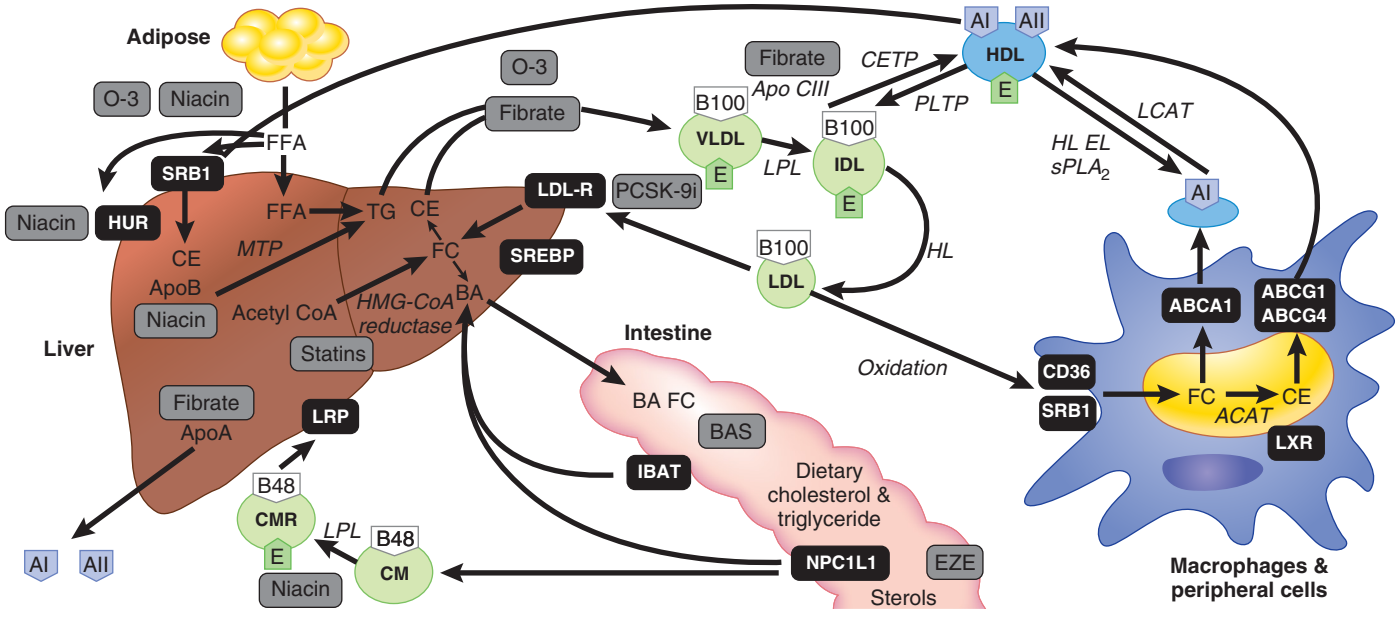

E-FIGURE 190-1. **Overview of cholesterol, triglyceride, and apolipoprotein B lipoprotein metabolism and sites of drug action. Statins** inhibit the rate-limiting step in cholesterol synthesis, 3-hydroxy-3-methylglutaryl coenzyme A reductase (HMG-CoA reductase) which binds acetyl CoA to free cholesterol to create cholesterol esters. Reduction in intrahepatic free cholesterol (FC) increases the number of LDL receptors (LDL-R) on the cell membrane, facilitating removal of LDL-cholesterol from plasma. **Bile-acid sequestering agents (BAS)** and **ezetimibe (EZE)** lower plasma LDL-cholesterol by lowering intracellular free cholesterol levels. BAS bind bile acids via the intestinal bile acid transporter (IBAT), interrupting the enterohepatic circulation of bile acid FC. EZE acts on the Niemann-Pick C1-Like 1 (NPC1L1) transporter at the intestinal wall to prevent absorption of dietary and biliary cholesterol. EZE also blocks uptake of plant sterols. **Dietary sterols/stanols** competitively inhibit the uptake of cholesterol in the intestine. The efficacy of all three intestinally active agents is limited because there is a compensatory increase in hepatic cholesterol synthesis. **Niacin** acts through unknown and known mechanisms, including partially inhibiting the release of free fatty acids (FFA) from adipose; increasing lipoprotein lipase (LPL) activity, thereby enhancing removal of chylomicron (CM) triglyceride from plasma; decreasing apolipoprotein B (apo B) synthesis, which lowers very-low-density lipoprotein cholesterol (VLDL-C) and intermediate-density lipoprotein cholesterol (IDL-C), and thus plasma triglycerides; and increasing high-density lipoprotein cholesterol (HDL-C) levels through decreased hepatic uptake, likely through the holo-uptake receptor (HUR) and catabolism. Increased levels of HDL-cholesterol may increase reverse cholesterol transport from peripheral cells to the liver. **Fibrates** lower triglyceride levels by decreasing VLDL secretion and increasing catabolism of triglyceride-rich particles via several mechanisms, including reduced apolipoprotein C (apo C) production, which upregulates lipoprotein-lipase-mediated lipolysis and increases cellular FFA uptake as well as increasing FFA catabolism. Fibrates increase HDL-cholesterol–induced apolipoprotein AI and AII synthesis via the liver X receptor/retinoid X receptor heterodimer (LXR). **Omega-3 fatty acids (O-3)** reduce the rate of VLDL synthesis through a number of putative mechanisms, inhibiting release of FFA from adipose, inhibiting FFA synthesis, and increasing apo B degradation. ABC = ATP-binding cassette; ABCA1, ABCG1, ABDG4 = ATP-binding cassette subfamily A or G transporter; ACAT = acyl coenzyme A: cholesterol acyltransferases; B48 or B100 = apolipoprotein B48 or B100; CD36 = cluster of differentiation 36; CE = cholesteryl ester; CETP = cholesterol ester transfer protein; CMR = CM remnant; E = apolipoprotein E; EL = endothelial lipase; FFA = free fatty acid; HL = hepatic lipase; LDL = low-density lipoprotein; LPL = lipoprotein lipase; LRP = LDL receptor-related protein 1; MTP = microsomal transfer protein; PLTP = phospholipid transport protein; PTPL = phospholipase transfer protein; $sPLA_2$ = secretory phospholipase A_2; SRB-1 = steroid receptor binding protein. (From Robinson J. *Clinical Lipid Management*. West Islip, NY: Professional Communications; 2016.)

LDL is removed from the blood predominantly by the LDL receptor. The expression of the LDL receptor is regulated by proprotein convertase subtilisin/kexin type 9 (PCSK9). In response to decreased intracellular cholesterol levels, sterol regulator element-binding proteins (SREBP) 1 and 2 upregulate the hepatic synthesis of both LDL receptors and PCSK9. LDL receptors travel to the cell surface, where they bind LDL particles from the blood. The LDL particle–LDL receptor complex is then taken up into vesicles, where the LDL particle undergoes degradation while the LDL receptor remains intact. The LDL receptor is then recirculated intact back to the cell surface to continue to remove LDL particles from the blood.

At the same time that the LDL receptor is traveling to the cell surface, the PCSK9 molecule is secreted into the blood, where it can bind the LDL-LDL receptor complex, tagging both the LDL receptor and the LDL particle for degradation. Inhibition or decreased levels of PCSK9 thus permit more LDL receptor to circulate and enhance removal of the LDL particles from the circulation.

The only hypertriglyceridemic polymorphisms that influence cardiovascular risk are those influencing VLDL levels. The atherogenicity of large VLDL particles is unclear, but smaller VLDL particles, IDL, and LDL are clearly atherogenic.

Lp(a)

The liver assembles lipoprotein(a) (Lp[a]) from an apo(a) moiety connected to the apo B of an LDL-like particle (see Fig. 190-1). Apo(a) isoforms are quite variable owing to the number of kringle repeats as determined by the apo(a) gene. The size of apo(a), which is inversely related to its Lp(a) concentration, is thought to result from the longer assembly time of an apo(a) isoform with a large number of kringle repeats. The liver removes Lp(a) from the circulation. This process and the function of Lp(a) are not well understood. Polymorphisms causing very elevated Lp(a) levels are associated with increased cardiovascular risk, and Lp(a) levels correlate with the risk of developing ASCVD independent of LDL-cholesterol levels.[4] Although Lp(a) can be reduced pharmacologically (e.g., with a hepatocyte-derived antisense oligonucleotide),[A1] it is unknown whether such therapy will reduce cardiovascular events.

HDL

HDL is the smallest and densest of the circulating lipoproteins (see Fig. 190-1). HDL carries apos AI and AII rather than apo B-100 or apo B-48. HDL is synthesized in the liver from apos AI, AII, and phospholipids to form nascent HDL or pre-β HDL (E-Fig. 190-2). As this particle circulates through the body and interacts with peripheral cells, it acquires cholesterol and additional phospholipid by binding to adenosine triphosphate-binding cassette protein (ABC1) through a process called "reverse cholesterol transport."

HDL carries about 30% of blood cholesterol. Inside the HDL particle, unesterified cholesterol is esterified by lecithin-cholesterol acyl transferase (LCAT). Esterified cholesterol can be removed from HDL via the scavenger receptor B1 (SR-B1) in the liver. In the blood, esterified cholesterol can be exchanged for triglycerides from apo B lipoproteins via the cholesteryl ester transfer protein (CETP) in the plasma. Phospholipid transfer protein transfers phospholipids from apo B lipoproteins to HDL. Lipoprotein lipase hydrolyzes triglycerides from VLDL and chylomicrons to HDL. Hepatic lipase removes triglycerides from HDL.

The functionality of HDL as measured by in vitro reverse cholesterol assays has been associated with reduced cardiovascular risk, independent of HDL-cholesterol levels. An uncommon apo AI mutation, apo AI-Milano, causes low HDL-cholesterol levels but is associated with reduced cardiovascular risk that is thought to be mediated by more efficient reverse cholesterol transport.

In epidemiologic studies, low levels of HDL, HDL-cholesterol, and apo AI are associated with increased cardiovascular risk. However, low HDL-cholesterol, which is often accompanied by elevated triglyceride levels, does not clearly appear to be a direct cause of cardiovascular disease but rather a marker of impaired glucose metabolism and insulin resistance. For example, mendelian randomization studies have failed to find an association between HDL-cholesterol–raising genes and cardiovascular risk. Several genetic polymorphisms that markedly increase HDL-cholesterol levels are associated with increased cardiovascular risk, HDL-cholesterol levels above 80 mg/dL are associated with an increased risk of coronary heart disease events,[5] and apo AII is associated with increased cardiovascular risk through unknown mechanisms. In randomized trials, HDL-cholesterol–raising drugs have not reduced cardiovascular events.[A2]

Apo B Lipoproteins, Cholesterol, and Atherogenesis

The accumulation of cholesterol and triglyceride-rich apo B lipoproteins in the arterial subendothelium is the pathologic initiating factor in the development of an atherosclerotic plaque (Chapter 41 and Fig. 190-2). Apolipoproteins with up to approximately 70-nm diameter (LDL, IDL, smaller VLDL, remnant chylomicron particles, and Lp[a]) more efficiently cross the endothelium. High plasma concentrations increase the probability that these particles will enter the subendothelial space of the artery. This size limitation is likely why very high plasma levels of the large apo B-48 chylomicrons in lipoprotein lipase deficiency do not cause atherosclerosis.

Normally, few apo B lipoproteins are retained in the subendothelium, and most return to the circulation. The key initiating factor of atherogenesis is the subendothelial retention of apo B lipoproteins, a process that is influenced by cardiovascular risk factors and genetic susceptibility. The presence of atherosclerotic plaque increases endothelial permeability to apo B lipoproteins, thereby accelerating their accumulation and the growth of plaque. Treatment of hyperlipidemia results in rapid decreases in endothelial permeability and increased fractional degradation of the LDL entering the plaque; as a result, plaque can stabilize and even regress.

In the earliest stages of atherogenesis, negatively charged proteoglycans in the extracellular matrix of the arterial intima trap the positively charged apo B-100 and apo B-48 moieties. Other characteristics of the LDL molecule that may affect atherogenicity by influencing apo B binding or proteoglycan interactions include the composition of surface core lipids. Apo E mediates binding to arterial glycosaminoglycans but also facilitates hepatic disposal of apo B lipoproteins. Conversely, apo CIII increases both the affinity of LDL for arterial wall proteoglycans and decreases hepatic uptake of apo B lipoproteins, thereby promoting retention of the cholesterol and triglyceride-rich apo B lipoproteins.

Atherogenesis begins in childhood and may progress to advanced plaque by late adolescence or early adulthood, a process that is accelerated in the presence of other cardiovascular risk factors and genetic predisposition. Apo B lipoproteins, as measured by total, LDL-cholesterol, and non-HDL-cholesterol levels, predict ASCVD risk in all ages, genders, races/ethnicities, and regions. Mendelian randomization studies have consistently found that genetic polymorphisms that increase LDL-cholesterol or non-HDL-cholesterol increase cardiovascular risk and that the converse is true for those that cause lower LDL-cholesterol or HDL-cholesterol levels. The increase in the relative risk of ASCVD per increment increase in total or LDL-cholesterol depends on age and the level and duration of exposure (Fig. 190-3). Cumulative exposure to LDL-cholesterol levels greater than 100 mg/dL or non-HDL-cholesterol levels greater than 130 mg/dL since adolescence or early adulthood markedly increases the lifetime risk of ASCVD.[6] Elevated cholesterol levels remain a risk factor into old age, although the relative contribution to risk is attenuated.

Stabilization and Regression of Atherosclerosis

Reducing LDL and other apo B lipoprotein levels can regress atheroma. Markedly lowering apo B lipoprotein levels results in reduced subendothelial uptake and retention, as well as decreased recruitment of monocytes and macrophages (E-Fig. 190-3). Reducing the toxic input of apo B lipoproteins allows the normal scavenger and phagocytic clearance mechanisms to clear the overload of apo B lipoproteins. Reverse cholesterol transport mechanisms mobilize cholesterol out of the foam cells, which decrease owing to emigration into adventitial lymphatics and transmigration into the lumen. More effective efferocytosis clears apoptotic cells and necrotic core. Inflammatory cells out-migrate, and smooth muscle cells migrate into the subendothelium; collagen synthesis falls, and fibrosis resolves. In animal models, very low LDL-cholesterol levels of less than 20 to 40 mg/dL completely regress early atheroma and normalize vascular function. In more advanced atheroma, substantial regression can occur, but residual stabilized plaque remains.

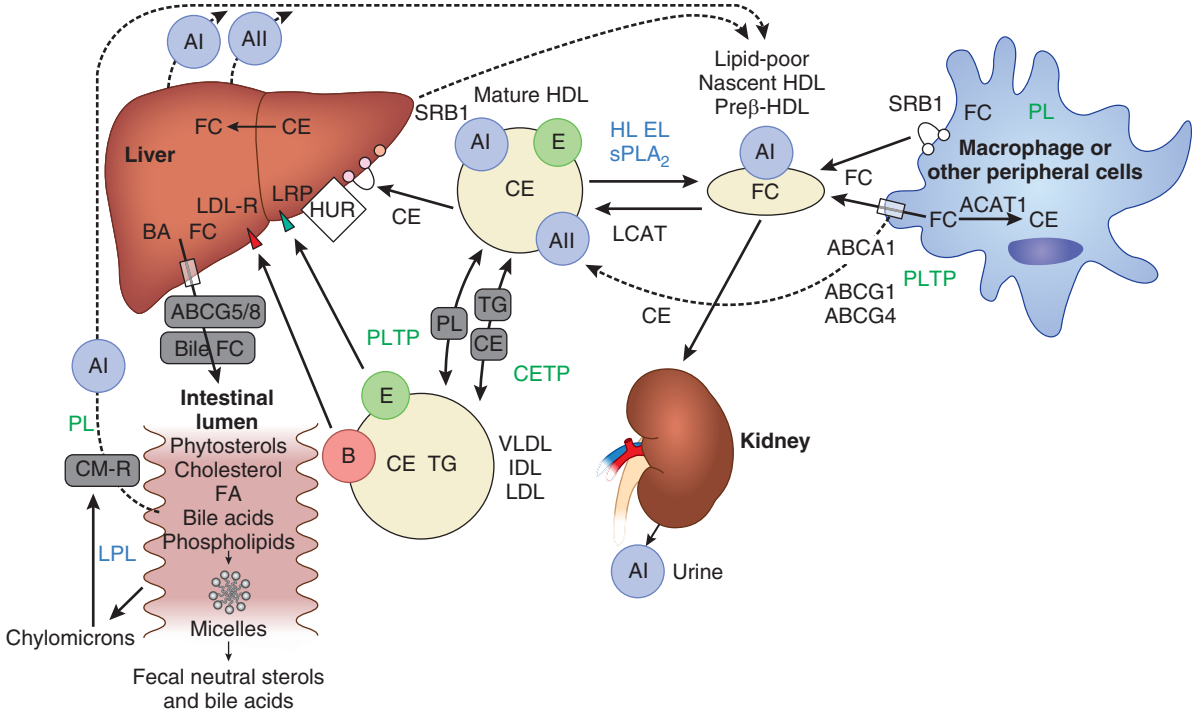

E-FIGURE 190-2. **Overview of HDL metabolism and sites of drug action.** ABC = ATP-binding cassette; AI or AII = apolipoprotein AI or AII; BA = bile acids; CE = cholesterol ester; CETP = cholesterol ester transport protein; CM-R = chylomicron remnant; E = apolipoprotein E; EL = endothelial lipase; FC = free cholesterol; HL = hepatic lipase; HUR = holo-uptake receptor; IDL = intermediate-density lipoproteins; LCAT = lecithin-cholesterol acyltransferase; LDL = low-density lipoprotein cholesterol; LDL-R = LDL receptor; LPL = lipoprotein lipase; LRP = LDL receptor-related protein; PL = phospholipids; PLTP = phospholipid transport protein; SRB1 = scavenger receptor B type 1; TG = triglyceride. (From Robinson JG, Davidson MH. Investigational drugs targeting HDL-C metabolism and reverse cholesterol transport. *Future Lipidol*. 2007;2:285-301.)

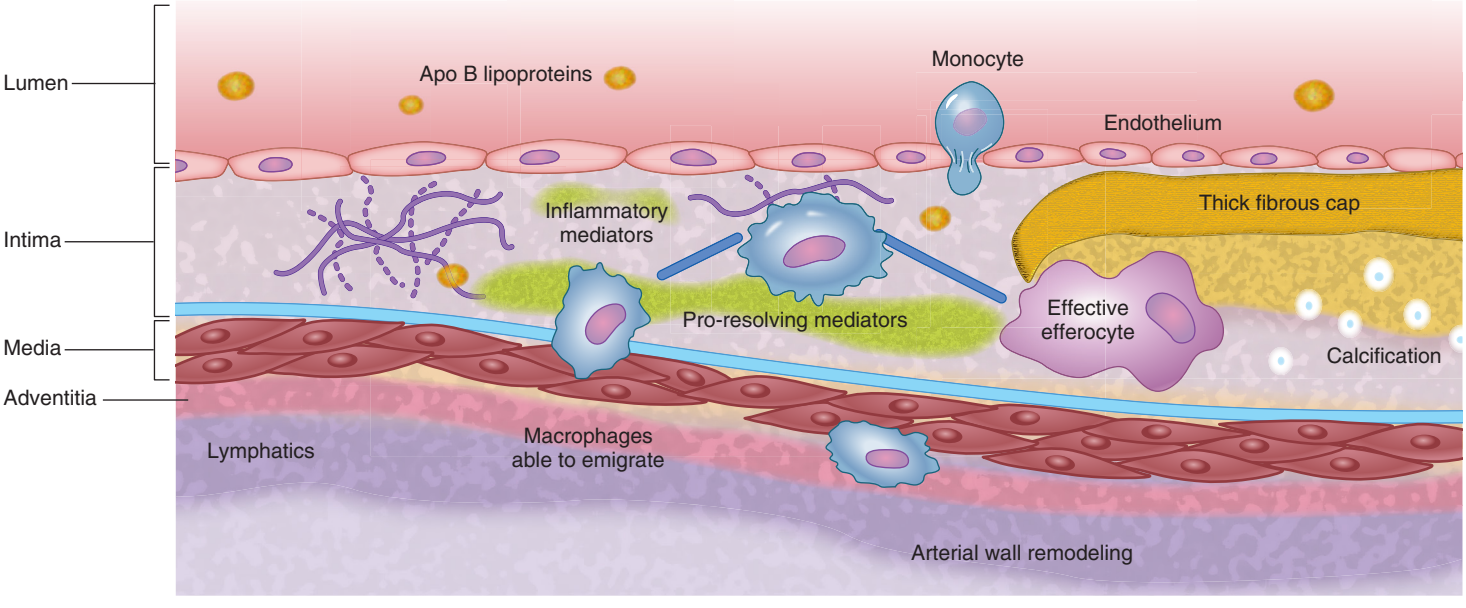

E-FIGURE 190-3. **Mechanisms of regression following apo B lipoprotein reduction.** Dramatic reduction in plasma concentrations of LDL-cholesterol and other apo B lipoproteins leads to decreased subendothelial entry and retention. Decreased levels of "toxic" apo B lipoproteins allows normal phagocytic and inflammation resolving mechanisms to "heal" the plaque. Decreased foam cell formation in the intima allows macrophages to migrate into adventitial lymphatics. Increased in-migration of monocytes that become healthy macrophages results in effective efferocytosis to remove necrotic debris. apo = apolipoprotein; LDL = low-density lipoprotein. (From Robinson J, Williams K, Gidding SS, et al. Eradicating the burden of atherosclerotic cardiovascular disease by lowering apolipoprotein B lipoproteins earlier in life. *J Am Heart Assoc*. 2018;7:e009778.)

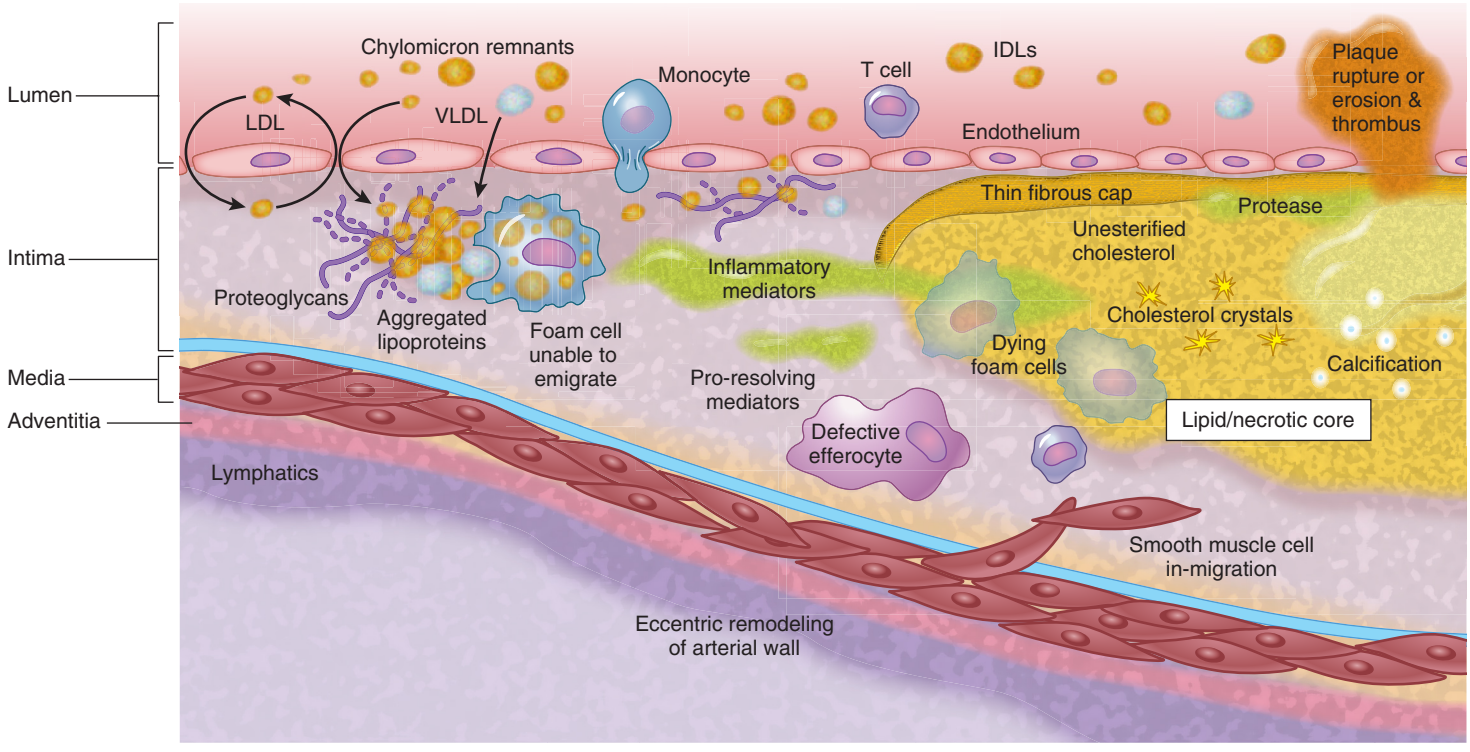

FIGURE 190-2. Apo B lipoprotein response-to-retention model of atherosclerosis initiation and progression. High plasma concentrations of apo B lipoproteins (LDL, IDL, VLDL, chylomicron remnants, Lp[a]) increase entry into intima and retention. Apo B lipoproteins bind to proteoglycans and begin aggregating, a process that accelerates once plaque begins. Retention is influenced by particle composition and diet. Retention leads to a maladaptive cellular response leading to increased inflammation, fibrosis, and necrosis. The lipid/necrotic core forms when normal phagocytotic processes and efferocytosis are overwhelmed by continued retention and accumulation of "toxic" apo B lipoproteins. Plaque rupture or erosion can lead to formation of overlying thrombus, which can precipitate an acute clinical event. apo = apolipoprotein; IDL = intermediate lipoprotein; LDL = low-density lipoprotein; Lp(a) = lipoprotein (a); VLDL = very-low-density lipoprotein. (From Robinson JG, Williams KJ, Gidding S, et al. Eradicating the burden of atherosclerotic cardiovascular disease by lowering apolipoprotein B lipoproteins earlier in life. *J Am Heart Assoc*. 2018;7:1-12.)

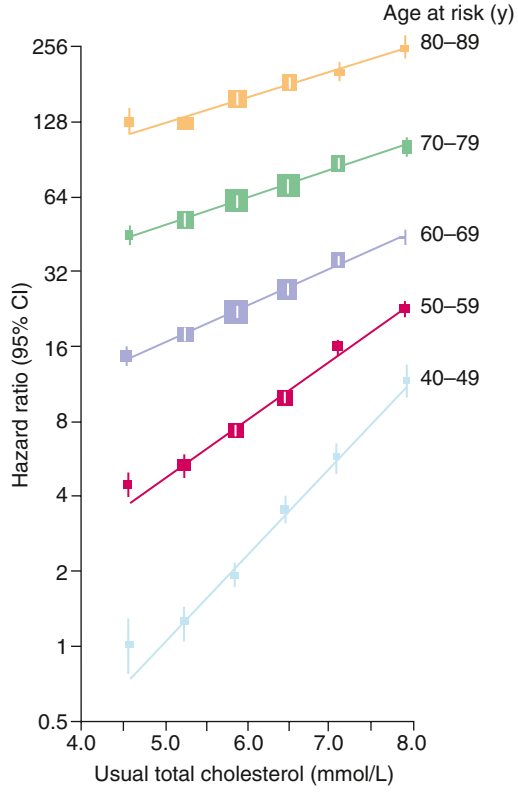

FIGURE 190-3. Age-specific association of atherosclerotic coronary heart disease mortality and total cholesterol level. CI = confidence interval. (From Prospective Studies Collaboration; Lewington S, Whitlock G, Clarke R, et al. Blood cholesterol and vascular mortality by age, sex, and blood pressure: a meta-analysis of individual data from 61 prospective studies with 55,000 vascular deaths. *Lancet*. 2007;370:1829-1839.)

DIAGNOSIS

Lipid Measurement

In the clinical laboratory, lipoprotein particles are usually not measured directly but rather by density ultracentrifugation, which separates them into bands based on their cholesterol and triglyceride content and reports levels of triglycerides, total cholesterol, LDL-cholesterol, and HDL-cholesterol. Patients who have high triglyceride levels have elevated numbers of chylomicrons, chylomicron remnants, or VLDL particles, or they have increased triglyceride content in VLDL. Triglycerides do not exist as independent entities in the blood, so blood triglyceride levels reflect the triglyceride content of the lipoprotein particles. High blood cholesterol levels reflect either increased numbers of LDL, VLDL, IDL, or Lp(a) particles circulating in the blood or an increased cholesteryl content in these particles.

On fasting or nonfasting samples (≥8 hours), LDL-cholesterol is usually calculated by the Friedewald equation when the triglyceride level is lower than 400 mg/dL.

$$\text{LDL-cholesterol} = \text{Total cholesterol} - \text{HDL-cholesterol} - \text{triglycerides}/5$$

Calculated LDL-cholesterol is not accurate in the presence of type III hyperlipidemia (see later) or when cholesteryl ester transfer protein inhibitors are used.

More recently developed methods facilitate more accurate indirect estimation of LDL-cholesterol when triglyceride levels are elevated as high as 800 mg/dL.[7] LDL-cholesterol also can be measured directly. Direct LDL-cholesterol levels are 5 to 10 mg/dL lower than calculated LDL-cholesterol levels unless corrected for the Lp[a] level. HDL-cholesterol levels are measured directly using a number of methods, the results of which may vary to modest extent.

On nonfasting or fasting samples when triglycerides are greater than 500 mg/dL, non-HDL-cholesterol (non-HDL-C) can be calculated as:

$$\text{non-HDL-cholesterol} = \text{Total cholesterol} - \text{HDL-cholesterol}$$

Thus, non-HDL-cholesterol represents the atherogenic apo B lipid component (see Fig. 190-1). Non-HDL-cholesterol is generally about 30 mg/dL higher than LDL-cholesterol.

Measurement of Lp(a) has been problematic due to interindividual variation in the number of kringles in the apo(a) moiety. Several methods are available, but no standardized method has been used consistently. Large variations by race support the need to develop better reference ranges.

Advanced lipid testing can measure apo B and apo A directly, but the clinical utility of such testing is not clearly established. The vast majority of patients can be managed with calculated LDL-cholesterol or non-HDL-cholesterol levels, which is the least expensive and widely available method. Apo B measurement may be helpful in select patients with hypertriglyceridemia.

CLINICAL DISORDERS OF LIPID METABOLISM

SECONDARY CAUSES OF HYPERLIPIDEMIA

All patients with a newly identified LDL-cholesterol level of 160 mg/dL or higher or a triglyceride level of 500 mg/dL or higher should be evaluated for secondary causes of hyperlipidemia (Table 190-1). The most common causes of secondary hypercholesterolemia include obesity (Chapter 201), high intake of saturated or trans fats, and glucocorticoids. The most common causes of hypertriglyceridemia are poorly controlled diabetes (Chapter 210), obesity (Chapter 201), and high dietary intake of refined carbohydrates, alcohol, or fat. After secondary causes are addressed or stabilized, a repeat fasting lipid panel can be used to guide therapy.

GENETIC LIPID DISORDERS

Blood levels of LDL-cholesterol, non-HDL-cholesterol, triglycerides, and HDL-cholesterol are influenced by genetics, lifestyle habits, medications, and medical conditions. Secondary causes of hyperlipidemia should be identified and treated. Severe primary elevations in LDL-cholesterol (≥190 mg/dL), non-HDL-cholesterol (≥220 mg/dL), or triglycerides (≥1000 mg/dL) almost always occur in the setting of a significant genetic disorder. However, treatment approaches are guided by LDL-cholesterol or non-HDL-cholesterol levels unless triglyceride levels are higher than 1000 mg/dL.

In the United States, individuals with LDL-cholesterol higher than 190 mg/dL have a five-fold higher lifetime risk of ASCVD, and individuals with familial hypercholesterolemia have a 20-fold higher lifetime risk. In the Netherlands, where nationwide efforts to identify patients with familial hypercholesterolemia have resulted in earlier treatment, patients with familial hypercholesterolemia who receive statins have an ASCVD risk similar to that of the nonfamilial hypercholesterolemia population. Therefore, all patients older than 20 years with a primary elevation in LDL-cholesterol higher than 190 mg/dL should receive high-intensity statin therapy unless a contraindication is present.

FAMILIAL HYPERCHOLESTEROLEMIA

EPIDEMIOLOGY

Familial hypercholesterolemia[8] is a common genetic disorder, affecting about 1 in 250 persons in populations around the world. Familial hypercholesterolemia may be more common in some populations such as Ashkenazi Jews, some Lebanese groups, French Canadians, and other populations with frequent consanguineous marriages. Homozygous familial hypercholesterolemia or compound heterozygous familial hypercholesterolemia is present in about 1 in 500,000 adults.

PATHOBIOLOGY

Heterozygous familial hypercholesterolemia is characterized by LDL-cholesterol levels higher than 190 mg/dL and a family history of severe LDL-cholesterol elevations, or premature cardiovascular disease, and/or a genetic familial hypercholesterolemia mutation. About 60 to 75% of individuals with heterozygous familial hypercholesterolemia have a monogenetic autosomal dominant mutation, and the remainder have a polygenic disorder. The most common familial hypercholesterolemia mutations result in loss of function in the LDL receptor. Uncommon mutations are *PCSK9* gain-of-function mutations, which result in more rapid degradation of the LDL receptor, and mutations that alter the apo B LDL receptor binding site.

CLINICAL MANIFESTATIONS

Homozygous familial hypercholesterolemia manifests with ASCVD events in childhood. Heterozygous familial hypercholesterolemia is a common cause of premature atherosclerotic coronary heart disease in the 30s and 40s in men and 40s and 50s in women. The first sign or symptom can be sudden death in younger adults, thereby leaving no opportunity for prevention.

TABLE 190-1 SECONDARY CAUSES OF HYPERLIPIDEMIA

SECONDARY CAUSE	ELEVATED LDL-CHOLESTEROL OR NON-HDL-CHOLESTEROL	ELEVATED TRIGLYCERIDES
Diet	**Saturated or trans fats, large weight gain** , anorexia	**Large weight gain**, high fat intake, **high refined carbohydrate intake, excessive alcohol intake**, very-low-fat diets if high in refined carbohydrates
Drugs	**Glucocorticoids**, cyclosporine, anticonvulsants, oral contraceptives, anabolic steroids, diuretics, sirolimus, amiodarone	**Glucocorticoids**, oral estrogens, anabolic steroids, bile acid sequestrants, highly active retroviral therapy, retinoic acid (isotretinoin), sirolimus, tacrolimus, raloxifene, tamoxifen, β-blockers (not carvedilol), thiazides, cyclophosphamide, L-asparaginase, second-generation antipsychotics (clozapine and olanzapine)
Diseases	Biliary obstruction, nephrotic syndrome, monoclonal gammopathy	**Proteinuria**, nephrotic syndrome, chronic renal failure, glomerulonephritis, Cushing syndrome, HIV, lipodystrophies, monoclonal gammopathy, systemic lupus erythematosus, autoimmune chylomicronemia, chronic idiopathic urticaria
Disorders and altered states of metabolism	**Obesity**, hypothyroidism, pregnancy*	**Diabetes (poorly controlled), obesity**, lipodystrophy, hypothyroidism, pregnancy,* polycystic ovarian syndrome

*Cholesterol and triglycerides rise progressively throughout pregnancy.

Common causes of secondary hyperlipidemia (most common causes in **bold**; leading causes **underlined**).

Secondary causes of hyperlipidemia should be evaluated in patients with:

- Newly identified LDL-cholesterol ≥160 mg/dL or non-HDL-cholesterol ≥190 mg/dL
- Newly identified triglycerides ≥500 mg/dL
- Worsening LDL-cholesterol, non-HDL-cholesterol, or triglyceride levels despite adherences to lifestyle and drug therapy

Initial laboratory tests should include:

- Fasting glucose or hemoglobin A_{1C} (HbA_{1C})
- Thyroid-stimulating hormone (TSH)
- Alkaline phosphatase, bilirubin, and alanine aminotransferase (ALT)
- Creatinine/glomerular filtration rate (GFR)
- Urinary albumin

Additional tests include:

- Total protein
- Women of childbearing age—beta human chorionic gonadotropin (βhCG)

HDL = high-density lipoprotein; HIV = human immunodeficiency virus; LDL = low-density lipoprotein.

Used with permission of author: Robinson JG. *Clinical Lipid Management*. West Islip, NY: Professional Communications Inc; 2015.

DIAGNOSIS

Screening

Because heterozygous familial hypercholesterolemia is a common and completely reversible genetic disorder if treated early, universal screening with a fasting or nonfasting lipid panel is recommended between the ages of 8 and 11 years. Screening should occur at an even earlier age if there is family history of an LDL-cholesterol level higher than 190 mg/dL or onset of ASCVD before age 55 in a male first-degree relative or age 65 in a first-degree female relative. All adults should be screened with a lipid panel by no later than age 20 years.

Cascade Screening

Once an index case of familial hypercholesterolemia is identified, all first-degree relatives should be screened with a fasting lipid panel. As an autosomal dominant genetic disorder, 50% of first-degree relatives will likely have familial hypercholesterolemia and benefit from early treatment.

TREATMENT AND PREVENTION

Treatment of Familial Hypercholesterolemia

Smoking avoidance and risk factor control are imperative for patients with familial hypercholesterolemia. All familial hypercholesterolemia patients should adhere to healthy lifestyle habits, but almost all will need pharmacologic therapy owing to the impaired removal of LDL-cholesterol from the blood. Moderate-intensity statin therapy is recommended for children and adolescents with LDL-cholesterol greater than 160 mg/dL after a trial of lifestyle change to healthy habits. High-intensity statin therapy (Table 190-2) is recommended after age 20 years for adults with familial hypercholesterolemia and an LDL-cholesterol greater than 190 mg/dL. Some individuals will have milder cases of familial hypercholesterolemia with LDL-cholesterol levels of 160 to 189 mg/dL. Because of their exposure to elevated LDL-cholesterol levels since birth, these patients also benefit from early statin treatment, especially if risk factors are present.

TABLE 190-2 HIGH-, MODERATE-, AND LOW-INTENSITY STATIN THERAPY*

	DAILY DOSE		
STATIN THERAPY	**HIGH INTENSITY† ↓LDL-C ≥50%**	**MODERATE INTENSITY‡ ↓LDL-C 30-<50%**	**LOW INTENSITY§ ↓LDL-C <30%**
Atorvastatin	(**40**[áC–])-**80 mg**	**10** (*20*) **mg**	
Rosuvastatin	**20** (*40*) **mg**	(*5*) **10 mg**	
Simvastatin		**20-40 mg**¶	*10 mg*
Pravastatin		**40** (*80*) **mg**	**10-20 mg**
Lovastatin		**40 mg**	**20 mg**
Fluvastatin		*80 mg (Fluvastatin XL)*	*20*-**40 mg**
Fluvastatin		**40 mg****	
Pitavastatin		**2-4 mg**	*1 mg*

*Individual responses to statin therapy varied in randomized, controlled trials and vary in clinical practice. A less-than-average response may have a biologic basis. Statins and dosages in bold were reduced in major cardiovascular events in randomized, controlled trials. Statins and doses in italics were approved by the FDA but were not tested in randomized, controlled trials.

†Daily dose decreases LDL-C levels by an average of ≥50%.

‡Daily dose decreases LDL-C levels by an average of 30 to <50%.

§Daily dose decreases LDL-C levels by an average of <30%.

áC–Evidence from 1 randomized, controlled trial only; down-titration if patient is unable to tolerate atorvastatin, 80 mg.

¶Although simvastatin, 80 mg, was evaluated in randomized, controlled trials, the FDA recommends against initiation of or titration to 80 mg of simvastatin because of increased risk for myopathy and rhabdomyolysis.

**Twice daily.

FDA = U.S. Food and Drug Administration; LDL-C = low-density lipoprotein cholesterol; XL = extended-release.

Reprinted with permission of the authors: Stone NJ, Robinson JG, Lichtenstein AH, et al. 2013 ACC/AHA guideline on the treatment of blood cholesterol to reduce atherosclerotic cardiovascular risk in adults: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines. *J Am Coll Cardiol*. 2014;63(25, Part B):2889-2934.

A high-intensity statin on average lowers LDL-cholesterol by about 50%. Many patients with familial hypercholesterolemia may achieve LDL-cholesterol levels around 100 mg/dL with a high-intensity statin plus ezetimibe (see later), in addition to healthy lifestyle habits. For primary prevention of younger patients with familial hypercholesterolemia, an LDL-cholesterol level of 100 mg/dL along with non-HDL-cholesterol levels around 130 mg/dL are likely sufficient to prevent significant progression of atherosclerosis. However, patients who have more severe familial hypercholesterolemia or clinically evident ASCVD benefit from the addition of a PCSK9 inhibitor or bempedoic acid to achieve greater reductions in LDL-cholesterol levels (see later). Bile acid sequestrants are infrequently used in patients with familial hypercholesterolemia owing to problems with tolerability and only modest efficacy. LDL apheresis under the direction of a lipid specialist may be an option for patients who are intolerant of or insufficiently responsive to lipid-lowering medications.

Pregnancy and Lactation

Statins and PCSK9 monoclonal antibodies are contraindicated during pregnancy and lactation owing to potential effects on the fetus and infant. Therefore, early treatment may be helpful for a woman with familial hypercholesterolemia, because she may more comfortably discontinue statin therapy once she contemplates pregnancy and lactation. Statin therapy can then be resumed once childbearing is complete.

PROGNOSIS

Untreated men and women with heterozygous familial hypercholesterolemia have a 20-fold higher lifetime risk of ASCVD and death owing to their genetic disorder. In individuals who also have other cardiovascular risk factors, clinical ASCVD is markedly accelerated, and death in the 20s and 30s is not uncommon if the LDL-cholesterol remains untreated. In patients who have with heterozygous familial hypercholesterolemia, initiation of statin therapy in adolescence or early adulthood is associated with clinical ASCVD rates that are similar to the rates in unaffected first-degree relatives.

FAMILIAL COMBINED HYPERCHOLESTEROLEMIA

Familial combined hypercholesterolemia is relatively common polygenic cholesterol disorder that often runs in families, although in a less distinct pattern than that of autosomal dominant familial hypercholesterolemia. The genetic predisposition of familial combined hypercholesterolemia is expressed with advancing age and increasing adiposity. Most typically, non-HDL-cholesterol is elevated to higher than 220 mg/dL and accompanied by elevated triglyceride levels of 200 to 600 mg/dL. Familial combined hypercholesterolemia also can be expressed as pure elevations of LDL-cholesterol or triglycerides. Onset of clinical ASCVD is somewhat later than in familial hypercholesterolemia, with clinical ASCVD typically developing in the 50s in men and 60s in women if the LDL-cholesterol remains untreated. Screening and treatment is as for familial hypercholesterolemia, with an emphasis on lifestyle, weight control, and statin therapy. Additional LDL-cholesterol lowering with ezetimibe, PCSK9 inhibitors, or bempedoic acid may be needed, especially if clinical ASCVD is present and greater LDL-cholesterol reduction is indicated. If triglyceride levels remain elevated above 1000 mg/dL after lifestyle and maximal statin therapy, triglycerides should be treated as outlined in the Hypertriglyceridemia section.

FAMILIAL DYSBETALIPOPROTEINEMIA

Familial dysbetalipoproteinemia is an uncommon (1 in 10,000) but extremely high-risk genetic disorder for premature coronary heart disease.[9] These patients have two copies of apo E2, which results in impaired clearance of VLDL through the VLDL receptor. However, two copies of apo E2 are insufficient to cause severe hyperlipidemia in the absence of conditions that slow VLDL clearance, such as obesity, diabetes, or hypothyroidism. LDL-cholesterol levels are usually over 190 mg/dL and non-HDL-cholesterol levels are over 220 mg/dL. Triglyceride levels higher than 500 mg/dL are common and are caused by impaired lipolysis of VLDL remnants, in addition to the higher levels of circulating VLDL. Patients with familial dysbetalipoproteinemia respond well to fibrates, but a statin should be added to lower LDL-cholesterol and non-HDL-cholesterol levels to reduce ASCVD risk.

OTHER RARE MONOGENETIC LIPID DISORDERS

Low LDL-Cholesterol

Individuals who are homozygous for mutations in the gene encoding microsomal triglyceride transfer protein can have abetalipoproteinemia, a rare disease characterized by the absence of circulating apo B, VLDL-cholesterol, IDL-cholesterol, and LDL-cholesterol. Fat-soluble vitamins (vitamins A, D, E, K) cannot be transported in the absence of apo B, and patients with abetalipoproteinemia suffer from multiple disorders, including severe neurologic dysfunction and retinopathy beginning early in life.

Individuals homozygous for mutations that result in abnormal or decreased apo B synthesis have hypobetalipoproteinemia with low but not absent levels of circulating apo B, VLDL-cholesterol, IDL-choleseterol, and LDL-cholesterol levels. These individuals appear to be healthy.

Loss-of-function *PCSK-9* mutations result in no breakdown of LDL receptors and enhanced removal of LDL from the blood. Depending on the degree of loss of function, heterozygotes have lower than average LDL-cholesterol levels and reduced risk of cardiovascular disease.[10] Rare homozygotes have LDL-cholesterol levels of 10 to 15 mg/dL and appear to be healthy.

Low and High HDL-Cholesterol

HDL-cholesterol levels have a U-shaped association with mortality, with both low and extremely high HDL-cholesterol levels (>115 mg/dL in men and >135 mg/dL in women) associated with increased mortality. The mechanism is unclear but is consistent with the lack of benefit observed in trials of raising HDL levels.

Sitosterolemia

Beta sitosterolemia results from increased intestinal absorption of plant and shellfish sterols, which are normally excreted back into the intestine by ABCG5 and ABCG8. Patients may present with high cholesterol levels and xanthomas, and they have a markedly increased risk of developing ASCVD. A few laboratories measure sitosterol levels, and genetic testing can confirm the diagnosis. A diet low in shellfish, vegetable oils, nuts, seeds, and chocolate is recommended. Ezetimibe lowers blood sitosterol levels by blocking its intestinal absorption. Bile acid sequestrants may need to be added to achieve normal blood sitosterol levels.

Severe Hypertriglyceridemia

Severe hypertriglyceridemia (>1000 mg/dL) is due to rare monogenetic lipid disorders, typically unmasked in the presence of secondary causes of hypertriglyceridemia (see Table 190-1). Treatment of hypertriglyceridemia is outlined in the Hypertriglyceridemia section.

PREVENTION OF ASCVD

Despite tremendous advances in prevention and treatment, ASCVD remains the leading cause of death in almost every developed country in the world.[11] Lipid-modifying drugs[12] that predominantly lower LDL-cholesterol and/or non-HDL-cholesterol levels are the first-line approach to reduce the risk of a first or recurrent cardiovascular event.[A3–A5] HDL-cholesterol raising has not been shown to reduce cardiovascular events after accounting for the reduction in LDL-cholesterol or non-HDL-cholesterol levels. Reduction of elevated triglyceride-rich lipoproteins may also be beneficial in selected patients.[13]

Lifestyle is the foundation of all cardiovascular risk reduction efforts. However, most individuals are at increased risk of cardiovascular events during their lifetime, due to genetic predisposition, unhealthy lifestyle habits, or both. Statins are overwhelmingly the first choice for cardiovascular prevention, based on an enormous amount of data in support of their efficacy and safety in a wide variety of populations around the world. However, patients who remain at high risk after maximizing statin therapy benefit from the addition of a nonstatin cholesterol-lowering therapy to reduce their cardiovascular risk further.[14]

Randomized clinical trial evidence provides the basis in support of the 2018 AHA/ACC Multispecialty Guideline on the Management of Blood Cholesterol.[15,16] Guidelines from the U.S. Preventive Services Task Force and National Institutes for Clinical Excellence, among others, have taken a similar approach by focusing on treatment in patients who are most likely to benefit.

By comparison, some specialty groups and the European Society of Cardiology continue to recommend titrating the medication dose to a target LDL-cholesterol level.

The guidelines also recommend periodically monitoring LDL-cholesterol levels after initiating statin therapy to evaluate treatment response and adherence, but they do not rely on a treat-to-target approach for several reasons. First, clinical trial evidence is based on drug regimens, not titration to a specific cholesterol level. Second, titration to a goal does not account for the potential net benefit, which is a function of both the benefit of further lowering cholesterol as well as the harms from the added therapy. Harms include not only the potential for adverse effects from the drug but also diminished adherence to evidence-based therapy and increased costs. Being "at goal" may mean a patient does not receive evidence-based statin therapy or receives a suboptimal intensity of statin therapy. Treat to goal also means a patient with cholesterol slightly above goal is treated, whereas the patient with slightly below goal is not, despite an identical risk of ASCVD. The 2018 AHA/ACC guidelines use LDL-cholesterol (or non-HDL-cholesterol) levels as thresholds for triggering consideration of the potential for added therapy to provide net benefits, which depend on the absolute risk of ASCVD, the relative risk reduction from the added therapy, and the potential for harm.[17]

LIFESTYLE

Healthy lifestyle habits throughout the lifespan are associated with lower cardiovascular risk, and lifestyle remains the foundation of all cardiovascular risk reduction efforts (Chapter 40). Unfortunately, by adulthood, less than 5 to 10% of individuals in industrialized societies remain in a state of ideal cardiovascular health as characterized by healthy diet (Chapter 13), regular physical activity (Chapter 14), smoking avoidance (Chapter 363), and desirable levels of cholesterol, blood pressure (Chapter 64), and blood glucose (Chapter 210).[18]

Lifestyle modifications can reduce LDL-cholesterol levels by about 10 mg/dL (Table 190-3). Referral to a dietician can be helpful for motivated patients who are seeking to improve their dietary habits (Chapter 13). Weight loss by a Mediterranean diet,[19] a low-fat or low-carbohydrate diet,[20] or alternate-day fasting[21] can reduce LDL-cholesterol levels.

DRUG THERAPY

Several classes of drugs have been shown to reduce cardiovascular events when used as monotherapy.[22] Based on an extensive body of randomized trial evidence, statins are overwhelmingly the first choice for reducing ASCVD events, cardiovascular mortality, and all-cause mortality.[23,A6] Ezetimibe[A7] and

TABLE 190-3 2013 ACC/AHA LIFESTYLE GUIDELINE RECOMMENDATIONS

DIET
Consume a dietary pattern that: • Emphasizes intake of vegetables, fruits, and whole grains • Includes low-fat dairy products, poultry, fish, legumes, nontropical vegetable oils, and nuts • Limits intake of sweets, sugar-sweetened beverages, and red meats • Adapts to appropriate calorie requirements, personal and cultural food preferences, and nutrition therapy for other medical conditions (including diabetes mellitus) • Follows plans such as the DASH dietary pattern, the USDA Food Pattern, or the AHA Diet
Aim for a dietary pattern that achieves 5 to 6% of calories from saturated fat
Reduce percent calories from saturated fat
Reduce percent calories from trans fat
PHYSICAL ACTIVITY
In general, advise adults to engage in aerobic physical activity to reduce LDL-C and non-HDL-C • Three to four sessions per week • Lasting on average 40 minutes per session • Involving moderate to vigorous physical activity

ACC/AHA = American College of Cardiology/American Heart Association; DASH = Dietary Approaches to Stop Hypertension; HDL-C = high-density lipoprotein cholesterol; LDL-C = low-density lipoprotein cholesterol; USDA = U.S. Department of Agriculture.

From Stone NJ, Robinson JG, Lichtenstein AH, et al. 2013 ACC/AHA guideline on the treatment of blood cholesterol to reduce atherosclerotic cardiovascular risk in adults: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines. *J Am Coll Cardiol.* 2014;63(25Pt B):2889-2934.

E-TABLE 190-1 COMPARISON OF TRIGLYCERIDE-LOWERING DRUG EFFICACY

DRUG	EFFICACY (%)
Double statin dose	−2 to −12
Moderate- vs. high-intensity statin	−26
Fenofibrate 145 mg Fenofibric acid 135 mg	Mixed dyslipidemia: −15 to 36
Gemfibrozil 600 mg bid	Isolated hypertriglyceridemia: −46 to −62
Marine omega-3 fatty acids (dose dependent)	Mixed dyslipidemia: −19 to −44 Isolate hypertriglyceridemia: −26 to −52
Niacin extended-release 2 g	Mixed dyslipidemia: −5 to −38
Ezetimibe 10 mg	−9
Alirocumab 75 mg q2wk; increase to 150 mg q2wk if LDL-cholesterol ≥ 70 mg/dL	0 to −13
Alirocumab 150 mg q2wk	−17
Evolocumab 140 mg q2wk or 420 mg q4wk	−4 to −23
CONTRAINDICATED WHEN TRIGLYCERIDES > 300 mg/dL	
Bile acid binding agents Colestipol 2 scoops (6 g) Cholestyramine 2 scoops (8 g) Colesevelam 6 tabs or suspension (3.75 g)	0 to +23

LDL = low-density lipoprotein.

From Robinson J. *Clinical Lipid Management*. West Islip, NY: Professional Communications Inc; 2016.

PCSK9 monoclonal antibodies[A8] can further reduce cardiovascular events when added to background statin therapy in high-risk patient populations. The relative reduction in ASCVD risk from all of these drugs is proportional to the magnitude of the lowering of LDL-cholesterol or non-HDL-cholesterol.[A9] Each 39 mg/dL (1 mmol/L) reduction in LDL-cholesterol is associated with a 22% reduction in cardiovascular events.

STATIN THERAPY

Statins inhibit HMG-CoA reductase, which is the rate-limiting step in cholesterol synthesis. The resulting lower level of intrahepatic cholesterol stimulates the synthesis of LDL-cholesterol receptors, thereby increasing uptake of LDL particles from the blood.

Indications for Statins

With the exception of patients with class II to IV heart failure or receiving hemodialysis, all patient groups in the clinical trials benefited from statin therapy. The 2018 AHA/ACC cholesterol guideline identified four groups of patients for high-intensity statin therapy (unless safety concerns) and at least a 50% reduction in LDL-cholesterol levels (Fig. 190-4):

1. Clinical ASCVD
2. LDL-cholesterol higher than 190 mg/dL
3. Higher risk diabetes (high-risk characteristics or ≥7.5% 10-year ASCVD risk)
4. Primary prevention with at least 20% 10-year ASCVD risk

Based on a high level of clinical trial evidence, two groups of patients were identified for moderate-intensity statin therapy following a clinician–patient discussion:

1. Lower risk diabetes (no risk factors or <7.5% 10-year ASCVD risk)
2. Primary prevention with 7.5 to less than 20% 10-year ASCVD risk

Because the margin of benefit may be less, a clinician–patient discussion is recommended to consider the potential for an ASCVD risk reduction benefit, potential for adverse effects, and patient preferences. There is also moderate evidence from one trial of benefit from statins in primary prevention patients with 5 to less than 7.5% 10-year ASCVD risk.

Statins, whose primary effect is on LDL-cholesterol and non-HDL-cholesterol levels, are categorized by intensity (see Table 190-2). Based on extensive clinical trial evidence that high-intensity statins reduce cardiovascular events more than moderate-intensity statins and that the relative reduction in cardiovascular risk is proportional to the magnitude of LDL-cholesterol reduction, high-intensity statins are recommended for higher risk patients. Moderate-intensity statins are recommended for primary prevention in lower-risk patients, patients older than age 75 years, or patients who have safety concerns such as the potential for drug-drug interactions.

In patients who have heart failure with reduced ejection fraction attributable to ischemic heart disease, who have a reasonable life expectancy, and who are not already on a statin because of ASCVD, clinicians may consider initiation of moderate-intensity statin therapy to reduce the occurrence of ASCVD events. In patients requiring hemodialysis, statins are not routinely recommended but can be continued if already initiated.

Risk Estimation for Primary Prevention

The ASCVD risk calculator (http://tools.acc.org/ascvd-risk-estimator-plus/#!/calculate/estimate/) estimates the risk of an incident of fatal or nonfatal myocardial infarction or stroke over 10 years. It performs well in the general U.S. population of non-Hispanic White and African American women and men. However, the risk estimate may be adjusted upward or downward based on other characteristics (Table 190-4). In populations outside the United States, country-specific risk calculators may be available, for example, the

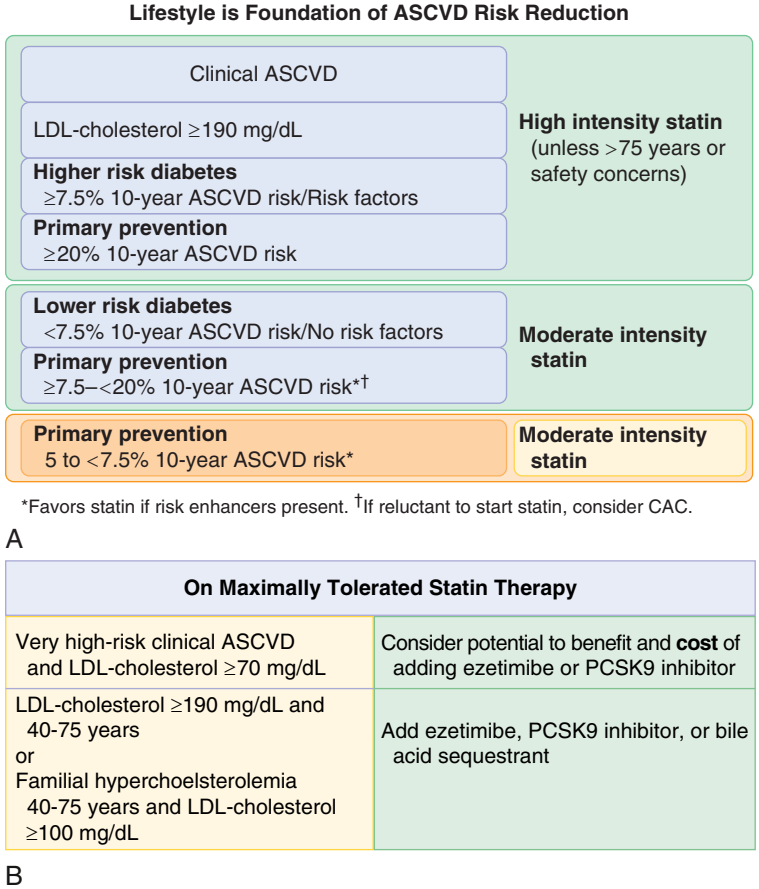

FIGURE 190-4. **Summary of 2018 American College of Cardiology/American Heart Association cholesterol guideline recommendations for statin and nonstatin therapy.** Background color denotes class and level of evidence: Blue = class I (strong) recommendation; yellow = reasonable recommendation; green = high level of evidence; orange = moderate level of evidence. ASCVD = atherosclerotic cardiovascular disease; CAC = coronary artery calcium; LDL = low-density lipoprotein.

Moderate-intensity statin treatment

Assumes a 35% relative risk reduction in ASCVD from moderate-intensity statin treatment number needed to treat (NNT) to prevent 1 ASCVD event varies by baseline estimated 10-year ASCVD risk. NNH based on 1 excess case of incident diabetes per 100 individuals* treated with statins for 10 years.

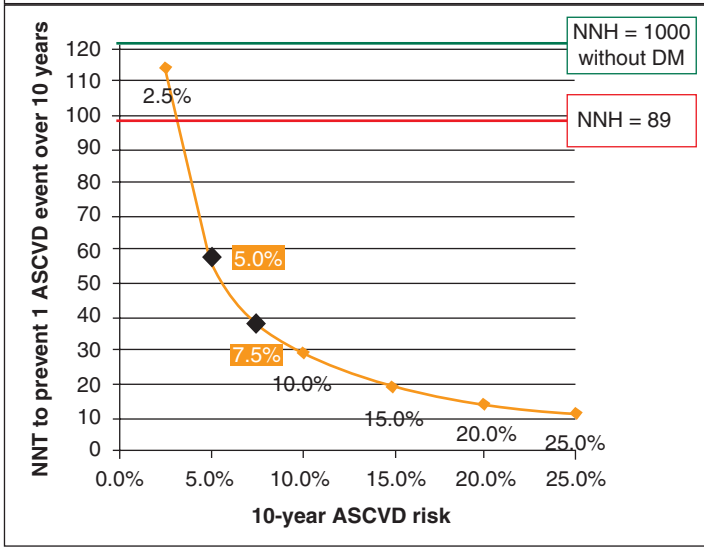

High-intensity statin treatment

Assumes a 45% relative risk reduction in ASCVD from high-intensity statin treatment; NNT to prevent 1 ASCVD event varies by baseline estimated 10-year ASCVD risk. NNH based on 3 excess cases of incident diabetes* per 100 individuals treated with statins for 10 years.

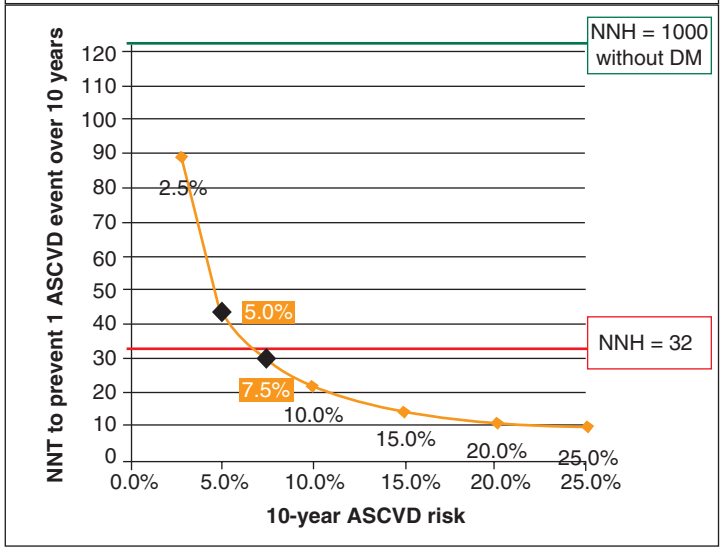

*A conservative estimate of adverse events includes excess cases of incident diabetes, myopathy, and hemorrhagic stroke. The number needed to harm (NNH) is dominated by excess cases of diabetes, with minimal contribution by myopathy (approximately 0.01 excess case per 100) and hemorrhagic stroke (approximately 0.01 excess case per 100 for hemorrhagic stroke) (90,114,116)

E-FIGURE 190-4. Comparison of the number needed to treat to prevent one ASCVD event (NNH) and the number needed to treat to cause one adverse event (harm; NNH) across the range of 10-year ASCVD risk for moderate- and high-intensity statin therapy. If the excess risk of diabetes is excluded, the NNH is 1000 based on the excess risk of serious myopathy and hemorrhagic stroke. ASCVD = atherosclerotic cardiovascular disease; DM = diabetes mellitus. (Adapted from Stone N, Robinson J, Lichtenstein A et al. 2013 ACC/AHA guideline on the treatment of blood cholesterol to reduce atherosclerotic cardiovascular risk in adults. *Circulation*. 2014;129[Suppl 2]:S1-S45. Full Report online supplement.)

TABLE 190-4 RISK-ENHANCING FACTORS FAVORING STATIN INITIATION

These characteristics may confer increased ASCVD risk as a result of genetic or adverse cardiometabolic risk factors:
Family history of premature ASCVD (males, age < 55 years; females, age < 65 years)
Metabolic syndrome
CKD (eGFR 15-59 mL/min/1.73 m^2 ± albuminuria; no dialysis or transplantation)
Chronic inflammatory conditions (e.g., psoriasis, rheumatoid arthritis, HIV/AIDS)
Premature menopause (before age 40 years)
Pregnancy-associated conditions that increase later ASCVD risk (e.g., preeclampsia)
High-risk race/ethnicities (e.g., South Asian ancestry)
Ankle-brachial index < 0.9
LDL-cholesterol 160-189 mg/dL (4.1-4.8 mmol/L)
Non-HDL-cholesterol 190-219 mg/dL (4.9-5.6 mmol/L)
Persistently elevated, primary hypertriglyceridemia (≥175 mg/dL)
Lp(a) ≥ 50 mg/dL or ≥125 nmol/L
apo B ≥ 130 mg/dL
hs-CRP ≥ 2.0 mg/L

AIDS = acquired immunodeficiency syndrome; Apo = apolipoprotein; ASCVD = atherosclerotic cardiovascular disease; CKD = chronic kidney disease; HDL = high-density lipoprotein; HIV = human immunodeficiency virus; hs-CRP = high-sensitivity C-reactive protein; LDL = low-density lipoprotein.
Robinson JG. Disorders of Lipid Metabolism. In: Goldman L, Schafer A, eds. *Goldman-Cecil Medicine*. 26th ed. Philadelphia: Elsevier; 2020.

TABLE 190-5 APPROACH TO PATIENTS WITH SYMPTOMS DURING STATIN THERAPY

Mild-moderate symptoms	1. Stop statin 2. Wait until symptoms resolve 3. Rechallenge with lower dose of same statin, or another statin, per the patient's preference 4. Increase statin dose/interval as tolerated
Severe muscle pain or weakness	1. Stop statin 2. Check creatine kinase (CK), creatinine/glomerular filtration rate (GFR), urine myoglobin 3. Admit and carefully hydrate if CK >10 × ULN and elevated/worsened creatinine or myoglobinuria 4. Evaluate for predisposing factors and treat 5. If considering restarting statin, refer to lipidologist
Jaundice or persistent hepatic transaminases >5×	1. Stop statin 2. Evaluate for other causes of hepatitis 3. Consider statin reinitiation once condition resolves
Diabetes mellitus	1. Continue statin 2. Encourage weight loss and regular physical activity 3. Treat diabetes

ULN = upper limit of normal.

SCORE equations (https://www.escardio.org/Education/Practice-Tools/CVD-prevention-toolbox/SCORE-Risk-Charts) are recommended in Europe, and the QRISK equations (https://www.qrisk.org/) are recommended in the United Kingdom. Since the lifetime burden of hypercholesterolemia is important, earlier reductions in LDL cholesterol can save more years of life (Chapter 40).[24]

In patients who remain reluctant to initiate statin therapy for primary prevention after estimating their atherosclerotic risk, coronary artery calcification (Chapter 44) can be measured in selected patients. In patients who do not smoke or have diabetes, a family history of premature atherosclerotic disease, or an LDL-cholesterol level of 130 mg/dL or higher, a calcium score of zero indicates low atherosclerotic risk over the next 3 to 5 years.

Statin Safety

Statins have an excellent margin of safety in all populations, including the elderly. However, statins are contraindicated during pregnancy and lactation, and women with childbearing potential should be appropriately counseled.

Moderate-intensity statins slightly increase, and high-intensity statins modestly increase, the risk of diabetes in individuals already at risk for diabetes. However, this risk is not of clinical concern because the diagnosis is accelerated by only about 2 months, and the benefits of statins for ASCVD risk reduction far exceed the slight excess duration of diabetes.[25] Patients who receive statins should be encouraged to adhere to healthy lifestyle habits (Chapter 40). Patients who have glucose intolerance or risk factors for diabetes should be counseled to lose weight and engage in regular physical activity to prevent progression to diabetes.

Statins have no hepatotoxic effects. Elevations in serum aminotransferase levels are commonly observed in clinical practice but are not due to statin therapy. If baseline hepatic aminotransferase levels are less than two times the upper limit of normal, no further monitoring is needed following statin initiation. If aminotransferase levels are two to three times the upper limit of normal, then the alanine aminotransferase level can be retested in 3 months as reassurance of continued statin safety. In patients with aminotransferase levels that are more than three times the upper limit of normal, other causes of hepatoxicity or infection should be investigated prior to initiating or continuing statins, and the potential benefit and safety of statin therapy should be assessed. If symptoms of hepatitis develop during statin therapy or if aminotransferase levels are more than five times the upper limit of normal persist on retest, the statin should be stopped until the patient's condition has improved.

Muscle Symptoms While Taking a Statin

Many patients have symptoms during statin therapy. Overall, statin therapy causes a small excess of mostly mild muscle pain,[A10] but more than 90% of muscle symptom reports are not due to the statin. The challenge is to determine if the symptoms are caused by the statin.

Placebo-controlled trials have found that about 75 to 80% of patients reporting intolerance to two or more statins can tolerate atorvastatin 20 mg when received as blinded therapy. In a N-of-1 trial of patients who reported intolerance to statins and were randomly allocated to 12 1-month treatment periods of atorvastatin 20 mg, matching placebo, or no pills, similar rates of mild muscle symptoms were observed in the atorvastatin and placebo groups and even fewer symptoms during the no-pill intervals.[A11] Two thirds of patients in this and other studies were able to restart statin therapy successfully. Therefore, patients' expectations of adverse effects, the "nocebo" effect, may play a large role in reported symptoms during statin therapy.

The most straightforward approach in patients with mild to moderate symptoms is to stop the statin, wait until symptoms resolve, and rechallenge with the same statin at a lower dose or another statin at least once a week, depending on the patient's preferences after being informed of the benefits of statins (heart attack, stroke, and death reduction; Table 190-5). If symptoms do not resolve within 2 months, the statin is not the cause, and alternative etiologies should be investigated and treated. When treated, up to 80 to 90% of patients will be able to resume statin therapy. After the statin has been tolerated for 3 months, up-titration is desirable.

Severe myopathy and rhabdomyolysis (Chapter 99) during statin therapy are very rare, but patients with severe muscle pain or weakness or dark urine should be evaluated for the possibility of rhabdomyolysis. Symptomatic creatine kinase elevations of more than 10 times the upper limit of normal, elevated creatinine levels, and myoglobinuria are indicative of rhabdomyolysis. In such cases, the statin should be stopped, and the patient should be admitted to the hospital for hydration, close observation, and evaluation for other causes of severe muscle damage. After any predisposing conditions are addressed, the safety and potential benefits of reinitiating statin therapy need to be carefully considered. Referral to a lipid specialist is advisable.

Special Populations

Many groups of patients were excluded from the randomized trials due to concerns regarding safety or the potential to benefit. Little clinical trial evidence is available for *primary* prevention in patients older than 75 years of age,[A12] but pooled data from primary and secondary randomized trials show benefits of similar proportion to what is seen in younger patients.[A13] As a result, the initiation of statin therapy should be individualized in *primary* prevention for patients older than age 75 years based on a patient's risk, preferences, and severity of other comorbid conditions. Statins should be prescribed for *secondary* prevention regardless of age, although moderate-intensity rather than high-intensity statins are recommended for patients with clinical atherosclerotic disease if they are ages 75 years or older.

Patients with inflammatory or chronic infectious conditions may be at increased cardiovascular risk and may meaningfully benefit from statin therapy. However, these patients also may be at increased risk of drug-drug interactions owing to immunosuppressive or antiviral therapy. Consultation with

a pharmacist may be helpful for identifying a statin and dose with the least likelihood of drug-drug interactions.

Monitoring Statin Therapy

The 2018 AHA/ACC cholesterol guideline recommends periodically monitoring LDL-cholesterol levels after initiating statin therapy to evaluate the response to treatment and adherence to lifestyle and drug therapy. Routine monitoring of creatine kinase levels is not recommended. The risks of rhabdomyolysis, severe myopathy, and hemorrhagic stroke events are rare and outweighed by the benefits of cholesterol reduction (E-Fig. 190-4).

NONSTATIN THERAPY

Once statin therapy and lifestyle are optimized, selected high-risk patients may benefit from further therapy to lower LDL-cholesterol.[26]

Ezetimibe

Ezetimibe acts in the small intestine to block cholesterol uptake by the Niemann-Pick C1-Like 1 receptor. The resulting lower level of intrahepatic cholesterol stimulates the synthesis of LDL-cholesterol receptors, thereby increasing the uptake of LDL particles from the blood. Ezetimibe 10 mg daily lowers LDL-cholesterol by 14% as monotherapy and an additional 20 to 25% when added to statin therapy, with similar percent reductions in non-HDL-cholesterol.

In a large randomized trial, ezetimibe 10 mg *daily* further reduced cardiovascular events by 10% when added to moderate-intensity statin therapy in patients with acute coronary syndromes and at least one additional high-risk characteristic.[A14] The greatest reductions occur in patients who have diabetes, polyvascular ASCVD, multiple high-risk characteristics, or are over age 75 years.

Ezetimibe is very safe and can be combined with moderate-intensity statin therapy to provide lipid-lowering in excess of what can be achieved with high-intensity statin therapy.[A15] Otherwise, it usually is of marginal benefit and should be reserved for patients who have familial hypercholesterolemia, cannot tolerate statin therapy, or have clinical ASCVD and an LDL-cholesterol greater than 70 mg/dL despite maximal statin therapy.[27] Ezetimibe has no known significant adverse effects but should be avoided during pregnancy and lactation.

PCSK9 Monoclonal Antibodies

PCSK9 monoclonal antibodies inactivate PCSK9, which allows the LDL receptor to be recirculated to the cell surface to continue to remove LDL from the blood. Alirocumab (75 to 150 mg every 2 weeks or 300 mg every 4 weeks) lowers LDL-cholesterol by 45 to 65% as monotherapy or when added to background statin therapy. Evolocumab (140 mg every 2 weeks or 320 mg every 4 weeks) lowers LDL-cholesterol by 50 to 70%. Fairly similar reductions in non-HDL-cholesterol occur. These drugs also lower Lp(a) by 25 to 30%, but the significance of this effect is unclear.

When added to high- or moderate-intensity statin therapy in patients with cardiovascular disease and additional high-risk characteristics, evolocumab can reduce ASCVD events by 20% over 2.2 years.[A16] In another trial, alirocumab further reduced cardiovascular events in patients who survived an acute coronary syndrome and were being treated with high-intensity or moderate-intensity statin therapy,[A17] with the majority of the ASCVD risk reduction occurring in patients who had baseline LDL-cholesterol levels of 100 mg/dL or higher.

In the various studies of evolocumab and alirocumab, reductions in ASCVD events here paralleled reductions in LDL-cholesterol levels,[A18] with each 39 mg/dL reduction in LDL-cholesterol associated with a 22% reduction in cardiovascular events when the pretreatment LDL-cholesterol was 120 mg/dL or higher. However, when baseline LDL-cholesterol levels are less than 100 mg/dL, further reducing LDL-cholesterol is of diminishing benefit for primary prevention[A19] but still likely of clinical value for secondary prevention[28,29]

PCSK9 monoclonal antibodies have been well tolerated over a period of up to 3 years, even when LDL-cholesterol is reduced to below 25 mg/dL. The most common adverse effect is mild, transient injection site reactions, which occur in less than 5% of patients. Evolocumab and alirocumab have no drug interactions. Both antibodies are contraindicated during pregnancy and lactation.

The acquisition price of PCSK9 monoclonal antibodies has limited their use. As a result, the 2018 AHA/ACC cholesterol guidelines and others recommend the consideration of PCSK9 monoclonal antibodies principally as secondary prevention in patients with ASCVD or primary prevention in patients with familial hypercholesterolemia when LDL-cholesterol levels remain greater than 70 mg/dL despite maximally tolerated statin and ezetimibe therapy (Table 190-6).

TABLE 190-6 TARGETED USE OF PCSK9 MONOCLONAL ANTIBODIES

LDL-C ≥ 70 MG/DL AND EXTREME HIGH RISK (>40% 10-YEAR ASCVD RISK)	LDL-C ≥ 100 MG/DL AND VERY HIGH RISK (30-39% 10-YEAR ASCVD RISK)	LDL-C ≥ 130 MG/DL AND HIGH RISK (20-29% 10-YEAR ASCVD RISK)
• For example, extensive or active ASCVD, usually with extremely high risk and poorly controlled cardiometabolic risk factors • Less extensive ASCVD and extremely high risk cardiometabolic risk factors	• For example, less extensive ASCVD and poorly controlled cardiometabolic risk factors	• For example, less extensive ASCVD and well-controlled cardiometabolic risk factors • Primary prevention for familial hypercholesterolemia or severe hypercholesteremia with LDL-C > 220 mg/dL and other poorly controlled risk factors

ASCVD = atherosclerotic cardiovascular disease; LDL-C = low-density lipoprotein cholesterol.
Adapted from Robinson JG, Jayanna MB, Brown A, et al. Enhancing the value of PCSK9 monoclonal antibodies by identifying patients most likely to benefit. *J Clin Lipidol.* 2019;13:525-537.

Other Nonstatin Therapies

Inclisiran

Inclisiran, which is a small interfering RNA that inhibits the hepatic synthesis of PCSK9, can reduce LDL-cholesterol levels by 40 to 50% when administered subcutaneously every 6 months, with sustained effects over at least 18 months.[A20,A21] A cardiovascular outcomes study is ongoing.

Bempedoic Acid

Bempedoic acid is a once-daily oral pro-drug that is activated in the liver and that inhibits adenosine triphosphate (ATP)-citrate lyase, an enzyme upstream of HMG-CoA reductase. Bempedoic acid (180 mg once daily) reduces LDL-cholesterol by about 20% compared with placebo in patients who are taking statins and in patients who are intolerant to statins, with about a 12% reduction in subsequent cardiovascular events.[A22] Since this risk reduction is commensurate with the reduction in LDL-cholesterol levels, bempedoic acid in combination with ezetimibe should be considered in statin-intolerant patients.

Evinacumab

Evinacumab is a fully humanized monoclonal antibody that inhibits angiopoietin-like protein 3 (ANGPTL3), which affects the hydrolysis of triglycerides and phospholipids via lipoprotein lipase and endothelial lipase. Given subcutaneously, it can lower LDL-cholesterol by more than 50% in patients with homozygous familial hypercholesterolemia[A23] or refractory hypercholesterolemia.[A24] Evinacumab is FDA-approved for use in patients with homozygous familial hypercholesterolemia.

Bile Acid Sequestering Agents

Cholestyramine, colestipol, and colesevelam bind bile acids in the intestinal lumen, thereby interrupting the enterohepatic recirculation of the cholesterol-rich bile acids. Decreased intracellular cholesterol levels upregulate LDL-cholesterol receptor synthesis, thereby enhancing removal of LDL from the blood. Bile acid sequestrants are not absorbed and are excreted in the feces. At the full recommended doses, the three bile acid sequestering agents reduce LDL-cholesterol by 15 to 20% and can reduce the risk of ASCVD events in proportion to their cholesterol-lowering effect. Their poor tolerability, their modest LDL-cholesterol lowering effects, and the availability of other medications have essentially eliminated the use of these agents except in highly specialized situations.

Niacin

Niacin, or nicotinic acid, raises HDL-cholesterol and also lowers LDL-cholesterol, triglycerides, and Lp(a) in a dose-dependent manner. Although monotherapy with 2 g daily of immediate-release niacin showed a modest benefit for the secondary prevention of nonfatal coronary heart disease events, niacin combined with the antiflushing agent laropiprant showed no cardiovascular benefit and increased the risk of adverse events. Because of safety concerns and poor tolerability, niacin no longer has any clinical indications except in very unusual patients treated in highly specialized centers.

Other Drugs

Lomitapide, which is an orphan drug that has significant hepatotoxicity, is approved for use only in patients with homozygous familial hypercholesterolemia. It should be used only under the direction of a lipid specialist.

HYPERTRIGLYCERIDEMIA

Reported triglyceride levels reflect the triglycerides in the triglyceride-rich lipoproteins as well as their remnants, predominantly chylomicrons, VLDL, IDLs, and to some extent, LDL[30] (see Fig. 190-1). Since both cholesterol and triglycerides are carried in apo B–containing lipoproteins, genetic variants associated with elevated blood triglyceride levels due to elevated triglyceride-rich lipoproteins are associated with increased ASCVD risk. Since the increased cardiovascular risk does not appear to be due to triglyceride levels per se,[31] but rather to the cholesterol- and triglyceride-rich lipoproteins, cardiovascular risk reduction efforts should focus primarily on reducing the levels of LDL-cholesterol and the triglyceride- and cholesterol-rich lipoproteins that constitute non-HDL-cholesterol.

Mild to moderate hypertriglyceridemia (150 to 499 mg/dL) is common in patients with cardiovascular risk factors, diabetes, or cardiovascular disease.[32] Small effects from a number of common and rare genetic variants contribute to triglyceride levels of 175 to 899 mg/dL. Triglyceride levels over 900 mg/dL usually result from a large-effect monogenetic disorder. Hypertriglyceridemia gene expression is modified by stimuli from the diet, excess adiposity, poorly controlled diabetes, physical inactivity, drugs, and other factors. Because hypertriglyceridemia clusters in families owing to shared genetic and environmental stimuli, screening and counseling of family members is recommended when severe hypertriglyceridemia (>500 mg/dL) is identified. The risk of pancreatitis is increased when fasting triglyceride levels exceed 1000 mg/dL, thereby suggesting that such patients should benefit from therapy targeted specifically at lowering triglyceride levels. Familial chylomicronemia syndrome and familial partial lipodystrophy are severe autosomal recessive triglyceride disorders that are associated with significant noncardiovascular morbidity from diabetes, pancreatitis, and hepatic steatosis.

DIAGNOSIS

Triglyceride levels should be measured in a fasting state. If triglycerides are elevated above 500 mg/dL after lifestyle changes (see later), secondary causes should be sought and treated (see Table 190-1). The most common secondary cause of hypertriglyceridemia is undiagnosed or inadequately treated diabetes mellitus (Chapter 210). Other common causes include a large weight gain, excessive intake of alcohol or sugar, drugs (estrogen, glucocorticoids, protease inhibitors, retinoic acid), pregnancy, and renal disease.

TREATMENT

Patients should be retested after at least a 12-hour fast to confirm fasting hypertriglyceridemia. Reductions in severely elevated triglyceride levels may benefit selected patients by reducing the risk of pancreatitis. Lowering of LDL-cholesterol and non-HDL-cholesterol are also indicated to reduce atherosclerotic risk, which is particularly elevated when both LDL-cholesterol and triglyceride levels are high.[33]

Lifestyle

Successful lifestyle modification often has dramatic effects in hypertriglyceridemic patients. All patients with triglycerides above 150 mg/dL should be counseled on a healthy diet, with an emphasis on avoiding refined carbohydrates and processed foods, as well as intake of the saturated, trans, and overall fats. Increased omega-3–rich fish intake may also be beneficial. Regular physical activity and modest weight loss are also helpful. Alcohol should be avoided. Patients whose fasting triglyceride levels remain over 1000 mg/dL should also be referred to a dietician for counseling on a very-low-fat diet.

Drug Therapy To Lower Triglyceride Levels

Although elevated triglyceride levels are associated with increased cardiovascular risk, drug therapy to lowering triglyceride levels has not been shown to reduce cardiovascular events.[A25] Patients with triglyceride levels over 1000 mg/dL or a history of hypertriglyceridemic pancreatitis may benefit from drug therapy to lower triglycerides to decrease the risk of pancreatitis (E-Table 190-1). Low-intensity to moderate-intensity statin therapy should be intensified because high-intensity statins further reduce triglyceride levels by about 25%.

Statins

Hypertriglyceridemic patients who are at increased atherosclerotic risk should receive statins (see Table 190-2) as first-line therapy to reduce the risk of ASCVD. A direct LDL-cholesterol level or an alternative calculated LDL-cholesterol measurement should be obtained when triglyceride levels exceed 500 mg/dL.

Marine Omega-3 Fatty Acids

Four grams daily of icosapent ethyl, which is a highly purified ester, reduces ASCVD events in moderately hypertriglyceridemic (fasting levels 135 to 499 mg/dL), high-risk patients with ASCVD or diabetes plus an additional risk factor.[A26] Combinations of eicosapentaenoic acid and docosahexaenoic acid (DHA) reduce triglyceride levels but do not reduce ASCVD events.[A27]

It is probably safer for patients on high-intensity statin therapy to add omega-3 fatty acids with at least 3.4 mg of marine omega-3 fatty acids rather than adding a fibrate. This amount of omega-3 fatty acids, which can be obtained from four capsules containing 850 mg omega-3 fatty acids per 1000 mg marine oil capsule, can be taken in divided doses. Lower doses (1000 mg daily) can reduce triglyceride levels but do not appear to reduce cardiovascular events in statin-treated patients.[A28]

Fibrates

As monotherapy, gemfibrozil and fenofibrate reduce cardiovascular events in selected populations with moderate hypertriglyceridemia. However, they are less effective than statins for this purpose and should be considered for ACSVD risk reduction only if additional triglyceride lowering is needed after maximizing lifestyle, statin therapy, and adding icosapent ethyl. Fenofibrate lowers triglyceride levels by 15 to 35%. However, fenofibrate increases the risk of serious myopathy five-fold in patients who are also treated with moderate-intensity statins, with little safety data on use with high-intensity statins. Fenofibrate also can sometimes raise LDL-cholesterol levels and creatinine levels, without affecting renal function, and it needs dose adjustment when the glomerular filtration rate is below 60 mL/min/1.73 m^2. Gemfibrozil increases the risk of serious myopathy and rhabdomyolysis 30-fold in statin-treated patients and should be avoided. In pregnant women, the benefits of fenofibrate and gemfibrozil therapy should be carefully weighed against the risks; fibrates should not be used in nursing mothers.

Other Lipid Drugs

Volanesorsen is an antisense oligonucleotide that targets the messenger RNA for apo C-III. This orphan drug may be useful for some patients who have severe genetic triglyceride disorders. In such patients, it can reduce triglyceride levels to below 750 mg/dL in about 75% of treated patients.[A29]

Niacin has modest triglyceride-lowering effects, but it may exacerbate hyperglycemia, and its other significant adverse effects limit its use. Ezetimibe and PCSK9 monoclonal antibodies have no significant triglyceride-lowering effects. Bile acid sequestrants should be avoided when triglycerides are over 300 mg/dL because they have been known to cause hypertriglyceridemic pancreatitis.

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For the General References and other additional features, please visit Elsevier eBooks+ at https://ebooks.health.elsevier.com.

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PRIYA S. KISHNANI

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Glycogen is a glucose polymer that is found predominantly in the liver and muscle. In the liver, glycogen maintains glucose homeostasis during periods of fasting. In the muscle, glycogen produces energy during exercise. Tissues other than the liver and skeletal muscle contain lesser amounts of glycogen. Postprandially, blood glucose levels increase, and as a result the expression of glucose transporters (GLUT) is upregulated in response to either the exposure to increased blood glucose levels (GLUT2 in the liver) or insulin release by the pancreas (GLUT4 in the skeletal muscle). GLUT2 and GLUT4 facilitate the transport of glucose into the cells. Intracellular glucose can be used to produce energy (ATP) or to synthesize glycogen[1,2] (Fig. 191-1).

Glycogen Synthesis

The synthesis of glycogen occurs mainly in the liver and muscle, where intracellular glucose is used to synthesize glycogen that is then stored to be used at times of need. The first step in glycogen synthesis is the phosphorylation of glucose into glucose-6-phosphate by the enzyme glucokinase in the liver and hexokinase in muscle. Next, phosphoglucomutase converts glucose-6-phosphate into glucose-1-phosphate, which then reacts with uridine triphosphate (UTP) to form the nucleotide sugar UDP-glucose. An autoglycosylating protein known as glycogenin then transfers the glucose from UDP-glucose to form an oligosaccharide primer chain, which is then used to form glycogen. Glycogen synthase, which is the primary regulatory enzyme in the synthesis of glycogen, and branching enzyme extend the oligosaccharide primer chain by adding more glucose molecules through α-1,4 and α-1,6 glycosidic bonds, respectively.

Glycogen Breakdown

Hepatic glycogenolysis (see Fig. 191-1) is activated by fasting, which leads to an increase of counter-regulatory hormones such as glucagon, cortisol, and adrenaline. In the muscle, the increase of cAMP during exercise stimulates the breakdown of glycogen. A small amount of glycogen is catabolized in the lysosomes, but the majority of catabolism occurs in the cytosol via a process called glycogenolysis. Glycogenolysis requires the coordinated action of phosphorylase kinase, phosphorylase, and debranching enzyme. Phosphorylase kinase is responsible for activating muscle and liver phosphorylase via phosphorylation. Next, activated phosphorylase releases glucose-1-phosphate from the glycogen branch. This process continues until there are four glucose residues from the α-1,6 branch point. At this point, the debranching enzyme continues the breakdown of glycogen through its two independent catalytic activities: amylo-1,6-glucosidase and 4-α-glucanotransferase. The 4-α-glucanotransferase catalyzes the transfer of three glycosyl residues from one outer branch to another, thereby exposing a single glucose residue that is linked by an α-1,6-glycosidic bond. The α-1,6-glucosidase breaks the α-1,6-glycosidic bond and releases a free glucose molecule.

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Glycogen storage diseases are divided into two main clinical phenotypes. Hepatic glycogen storage diseases, which present with hepatomegaly and fasting hypoglycemia, include types 0a, I, III (a and b), IV, VI, and IX (α2, γ2, and β) and Fanconi-Bickel syndrome (GSD XI). Muscle glycogen storage diseases, which manifest as exercise intolerance, progressive myopathy, and/or cardiomyopathy include types 0b, II, IIIa, IV, V, VII, IX (α1, γ1, and β), and XII-XV.[3] In some instances, patients can have involvement of liver, muscle, and other organs as well. Each glycogen storage disease has its own characteristic clinical manifestations (Table 191-1).

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ABSTRACT

The glycogen storage diseases are caused by the aberrant synthesis or degradation of glycogen. Liver glycogen storage disease manifests as fasting hypoglycemia, whereas the muscle forms of the disease cause a myopathy. Despite current treatment, long-term complications can still occur.

KEYWORDS

glycogen storage disease
complications
treatment
cornstarch
hypoglycemia
myopathy

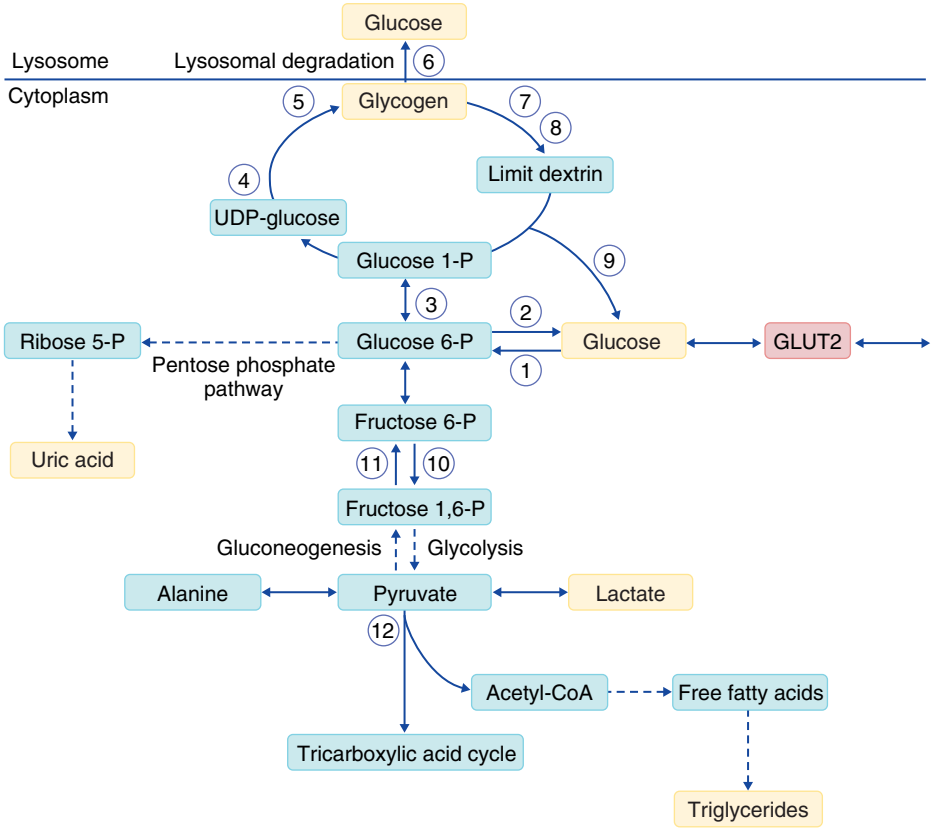

FIGURE 191-1. Simplified scheme of glycogen synthesis and degradation in the liver. Note that in skeletal muscle, glucose transporter type 4 (GLUT4) transports glucose across the cell membrane and glucose-6-phosphatase is absent. 1, hexokinase/glucokinase; 2, glucose-6-phosphatase; 3, phosphoglucomutase; 4, glycogen synthase; 5, branching enzyme; 6, lysosomal acid α-glucosidase (GAA); 7, phosphorylase kinase; 8, glycogen phosphorylase; 9, debranching enzyme; 10, phosphofructokinase; 11, fructose-1,6-bisphosphatase; 12, pyruvate dehydrogenase. CoA = coenzyme A; UDP-glucose = uridine diphosphoglucose. (Modified from Weinstein D. Glycogen storage diseases. In: Goldman L, Schafer AI., eds. *Goldman-Cecil Medicine*. 26th ed. Philadelphia: Elsevier; 2020:Chapter 196.)

The diagnosis of glycogen storage diseases is established by identifying two pathogenic variants in the gene of interest in autosomal recessive conditions and one disease-causing variant in the X-linked diseases by molecular genetic testing. Molecular genetic testing, which may be gene targeted (serial single-gene testing, multigene panel) or comprehensive (exome sequencing, genome sequencing), has become the primary recommended method of diagnosis. Deficient enzyme activity in the relevant tissue of involvement, such as the liver, muscle, or skin fibroblasts, is another approach to diagnosis and is very important in situations in which genetic testing is not conclusive.

Differential Diagnosis

Hypoglycemia (Chapter 211) and hepatomegaly are the hallmarks of hepatic glycogen storage diseases. Although these conditions present similarly, biochemical and radiological findings can help differentiate among them. For example, glycogen storage disease III can be distinguished from glycogen storage disease I by higher levels of liver aminotransferases, the presence of cardiomyopathy and myopathy with increased creatine kinase levels, and the absence of lactic acidosis, hyperuricemia, and renomegaly. Other disorders that present with hypoglycemia are glycogen storage disease 0a, VI, IX, and XI, as well as fructose-1,6-bisphosphatase deficiency. In glycogen storage disease IV, hypoglycemia is a late finding and is most likely secondary to liver failure rather than to the primary enzymatic defect.

Patients with glycogen storage disease V and glycogen storage disease VII can present with rhabdomyolysis and markedly increased plasma creatine kinase levels. Glycogen storage disease VII can be differentiated from glycogen storage disease V by the presence of hyperbilirubinemia secondary to hemolytic anemia. A distinguishing feature of glycogen storage disease V is the "second-wind" phenomena, in which patients who rest shortly after the start of exercise can continue exercising for longer periods with less myalgia. Fatty oxidation defects such as very long-chain acyl-CoA dehydrogenase, carnitine palmitoyl transferase II, long-chain 3-hydroxyacyl-CoA dehydrogenase, and mitochondrial trifunctional protein deficiencies (Chapter 389) can present similarly and must be excluded.

A large number of genetic disorders can present with cardiomyopathy and/or myopathy. Spinal muscular atrophy 1 (Chapter 387) can present with findings that are similar to Pompe disease (glycogen storage disease II), although the lack of cardiomyopathy can distinguish it from infantile Pompe disease. An X-linked disorder, Danon disease, which is caused by the deficiency of lysosomal-associated membrane protein 2 (LAMP2), presents with cardiomyopathy and myopathy in hemizygous males and heterozygous females. Danon disease can be distinguished from Pompe disease by the presence of intellectual disability and retinopathy. Patients with mutations in the PRKAG2 gene (PRKAG2 syndrome or adenosine monophosphate–activated protein kinase γ_2 deficiency, AD) can present similarly to infantile Pompe disease.

TREATMENT

With the exception of glycogen storage disease II (Pompe disease),[4] definitive treatment is currently not available for glycogen storage diseases. Gene therapy is in clinical trials.[5] Liver transplantation, which is indicated for advanced liver disease, hepatocellular carcinoma, and multiple hepatic adenomas, typically is curative for the hepatic phenotype of glycogen storage diseases such as types I, III, IV, and IX. However, liver transplantation has no effects on the progression of extrahepatic manifestations such as myopathy and cardiomyopathy.

Most glycogen storage diseases involve multiple body systems and special diets,[6] so they require supportive care by a multidisciplinary team approach to reduce the burden of the disease and improve quality of life. The main goal of treatment for hepatic glycogen storage disease is to maintain euglycemia with dietary therapy. In the muscular glycogen storage diseases, physical therapy and preventive measures to avoid rhabdomyolysis are standard care for patients who have myopathy.

TABLE 191-1 THE MOST COMMON GLYCOGEN STORAGE DISEASES: ENZYMES, PHENOTYPES, AND TREATMENT OPTIONS

TYPE OF GLYCOGEN STORAGE DISEASE	AFFECTED ENZYME/ GENE	CLINICAL FEATURES	TREATMENT OPTIONS
0a	Hepatic glycogen synthase/*GYS2*	Fasting ketotic hypoglycemia, postprandial hyperglycemia and hyperlactatemia, hyperalaninemia, no hepatomegaly	Diet: Complex carbohydrates (e.g., UCCS and high-protein diet)
Ia *von Gierke disease*	Glucose-6-phosphatase/*G6PC1*	Hepatomegaly, hypoglycemia, lactic acidosis, hyperuricemia, hyperlipidemia, growth retardation, nephromegaly with proteinuria, and risk of kidney failure	Diet: UCCS during the day and night or continuous overnight intragastric feeding. Extended-release cornstarch at bedtime in some patients
Ib *von Gierke disease*	Glucose 6-phosphate transporter/*SLC37A4*	Same phenotypes as type Ia with neutropenia, recurrent bacterial infections, and inflammatory bowel disease	Same as type Ia with granulocyte colony-stimulating factor, mesalamine, SGLT2 inhibitors, and vitamin E supplementation
II *Pompe disease*	Lysosomal acid alfa glucosidase/*GAA*	**Infantile form:** Hypotonia, muscle weakness, and hypertrophic cardiomyopathy leading to cardiorespiratory failure in infancy **Late onset form:** Slowly progressing myopathy with early involvement of the diaphragm as the primary clinical manifestations, can present as early as first year of life to late adulthood; distinguishing feature from infantile-onset Pompe disease is the absence of cardiomyopathy in the first year of life	Intravenous enzyme replacement with recombinant human acid α-glucosidase Gene therapy currently in clinical trials
III *Cori or Forbes disease*	Debranching enzyme/*AGL*	Hepatomegaly, ketotic hypoglycemia, liver fibrosis/cirrhosis, (with hepatocellular carcinoma in some patients), proximal and distal muscle weakness and wasting, hypertrophic cardiomyopathy (IIIa) Hepatic phenotype, no muscle or cardiac disease (IIIb)	Diet: High-protein diet with low-dose UCCS and anaplerotic agents such as medium-chain triglycerides
IV *Andersen disease/Adult polyglucosan body disease (APBD)*	Glycogen branching enzyme/*GBE1*	A clinically heterogeneous disorder. **Hepatic:** Liver disease in early childhood may progress to lethal cirrhosis or hepatocellular carcinoma. Patients with hepatic GSD IV can develop hepatocellular carcinoma and/or extrahepatic manifestations; e.g., myopathy and cardiomyopathy. Some patients have a more slowly progressive form **Neuromuscular:** Distinguished by age of onset into four groups: fatal perinatal, congenital, childhood/juvenile, and adult (adult polyglucosan body disease) **APBD:** Muscle weakness, neurogenic bladder, spastic paraparesis, central and peripheral nervous system involvement	Liver transplantation for hepatic subtypes, (extrahepatic manifestations can occur despite liver transplant), symptomatic treatment for neuromuscular subtypes
V *McArdle disease*	Muscle glycogen Phosphorylase/*PYGM*	Symptoms usually begin in adolescence or early adulthood with exercise intolerance, fatigue, myalgia, muscle cramps, and "second-wind" phenomenon. Exercise-induced rhabdomyolysis may occur. Later in adult life, persistent and progressive muscle weakness and atrophy with fatty replacement; serum creatine kinase level is increased	Carbohydrate-rich diet Oral sucrose or carbohydrate-rich meal before exercise may be beneficial Low-dose creatine, aerobic exercise programs, avoidance of strenuous exercise
VI *Hers disease*	Hepatic glycogen Phosphorylase/*PYGL*	Hepatomegaly, ketotic hypoglycemia, growth retardation, increased serum levels of aminotransferases, cholesterol, and triglycerides; some patients can develop progressive liver fibrosis; cirrhosis	Diet: UCCS, high-protein diet, and frequent feedings to prevent hypoglycemia
VII *Tarui disease*	Muscle phosphofructokinase/*PFKM*	Fatigue, muscle cramps, exercise intolerance, rhabdomyolysis and myoglobinuria with strenuous exertion, "out-of-wind" phenomenon, increased serum creatine kinase level; may have mild hemolytic anemia, hyperbilirubinemia, and hyperuricemia	No specific treatment; ketogenic diet, avoid strenuous exercise, carbohydrate meals, and glucose infusions Unlike GSD V, pre-exercise ingestion of sucrose is harmful
IX	Phosphorylase kinase/ Liver: *PHKA2*,* *PHKG2* Muscle: *PHKA1*,* *PHKG1*† Liver and muscle: *PHKB*	**Liver:** Hepatomegaly; ketotic hypoglycemia; growth retardation; increased serum transaminases, cholesterol, and triglycerides; liver fibrosis; cirrhosis **Muscle:** Exercise intolerance, muscle cramps, and weakness	Diet: UCCS, high-protein diet, and frequent feedings to prevent hypoglycemia
Danon disease	Lysosome-associated membrane protein 2/*LAMP2*	Hypertrophic cardiomyopathy, skeletal myopathy, and intellectual disability	Symptomatic treatment

*X-linked recessive disease; all others are autosomal recessive diseases.
†No reported mutations.
GSD = glycogen storage disease; SGLT2 = sodium glucose transport protein 2; UCCS = uncooked cornstarch.

Glycogen Storage Disease I

Dietary therapy under the guidance of a metabolic dietitian is the primary treatment for patients who have glycogen storage disease I.[7] Frequent feedings and use of uncooked cornstarch, including extended-release cornstarch preparations, are the key dietary treatments to maintain normoglycemia. The consumption of sucrose, fructose, and galactose should be avoided or severely limited. Dietary supplements should include multivitamins, calcium, and vitamin D. Obesity and insulin resistance are well-known complications of over-treatment.

Patients with advanced kidney disease may require kidney transplantation. Some patients may develop hepatic adenomas, for which ethanol injection, radiofrequency ablation, or partial liver resection may be helpful. Liver transplantation is required in the setting of multiple adenomas, a rapid increase in size and or number or adenomas, recurrent adenomas, or adenomas with risk for malignant transformation. Liver transplant also markedly improves metabolic control.[8]

Patients with glycogen storage disease Ib have an increased risk of inflammatory bowel disease (Chapter 127) and can benefit from mesalamine. Granulocyte colony-stimulating factor therapy (Chapter 153) can increase the neutrophil count and decrease the risk of life-threatening infections. Empagliflozin (starting at 5 mg daily, increased to 10 mg daily in the second week, and then to as high as 20 mg daily 1 month later) is an inhibitor of the sodium glucose cotransporter 2 and can reduce recurrent infections and symptoms of inflammatory bowel disease by decreasing the accumulation of 1,5-anhydroglucitol-6-phosphate (1,5AG6P) and enhancing neutrophilic function.[9]

Glycogen Storage Disease II

Enzyme replacement using alglucosidase alfa (a recombinant acid α-glucosidase) has been the standard treatment for Pompe disease,[10] but some patients may develop antibodies that decrease its efficacy. Avalglucosidase alfa, a second-generation recombinant acid α-glucosidase replacement therapy with a significantly higher number of mannose 6 phosphate tags,[11] can provide significant benefit over alglucosidase alfa.[A1] Administration of cipaglucosidase alfa plus oral miglustat can improve motor function and disease biomarkers to the same extent as alglucosidase alfa.[A2] Treatment requires a multidiscipline team approach, including physical therapy and speech therapy. Some patients require assistive mobility devices, including a wheelchair, and noninvasive or invasive ventilation.

Glycogen Storage Disease III

Complex carbohydrates, often in the form of uncooked cornstarch, and frequent feedings can prevent hypoglycemia in younger patients. In adults, a diet containing a restricted amount of complex carbohydrates (<50% of total calories) is recommended to decrease the amount of accumulated glycogen. In some patients with glycogen storage disease IIIa,[12] a high-protein diet (up to 3 g/kg/day) with supplementation of fat and medium-chain triglycerides can take advantage of intact gluconeogenesis in patients with glycogen storage disease IIIa and IIIb. This dietary modification improves cardiac and skeletal myopathy in some patients with glycogen storage disease IIIa. Liver transplantation can be considered in patients with advanced hepatic cirrhosis or hepatocellular carcinoma, and heart transplantation can be considered in patients with decompensated cardiomyopathy. Unfortunately, muscle weakness progresses after liver and cardiac transplantation.

Glycogen Storage Disease IV and Adult Polyglucosan Body Disease

Glycogen storage disease IV and adult polyglucosan body disease represent a disease continuum due deficiency of glycogen branching enzyme.[13] Treatment is symptomatic.[14] Liver transplantation cures the hepatic disease, but extrahepatic manifestations including cardiomyopathy and neuromuscular manifestations may progress.[15] Dietary therapy is of uncertain benefit.[16] For the adult polyglucosan body disease, symptomatic treatment, anticholinergic drugs, and bladder catheterization (either intermittent catheterization or an indwelling catheter) are recommended.

Other Glycogen Storage Diseases

For glycogen storage disease V, preventive measures include avoiding strenuous exercise. Preexercise ingestion of oral sucrose can reduce the risk of rhabdomyolysis. Diets rich in carbohydrates and protein, aerobic exercise programs, and low-dose creatine under expert supervision can improve exercise tolerance.[17]

For glycogen storage disease VII, avoidance of strenuous exercise and of a high-carbohydrate diet are key because an increase in blood glucose levels inhibits lipolysis as well as the formation of free fatty acids and ketone bodies that are needed as the source of energy to generate ATP in muscles. A ketogenic diet may be helpful.[18]

Both glycogen storage disease VI and IX are treated with a high-protein diet and complex carbohydrates to prevent hypoglycemia.[19] Patients with the myopathic glycogen storage disease IX subtype may benefit from physical therapy, but some patients with the hepatic glycogen storage disease IX subtype may require liver transplantation.

PROGNOSIS

For Pompe disease, enzyme replacement therapy is life-saving and leads to an improvement or stabilization of muscle disease. In infants, the cardiomyopathy can reverse. However, some manifestations of the disease, such as muscle weakness, respiratory insufficiency, cardiac arrhythmias, and neurologic manifestations (e.g., central, peripheral, and autonomous nervous system involvement, sensorineural hearing loss, foot-slapping gait, bulbar weakness with dysarthria and oropharyngeal dysphagia, small fiber neuropathy, and white matter hyperintense foci), persist or in some cases may progress despite enzyme replacement therapy.[20]

In patients with other glycogen storage diseases, treatment options such as dietary interventions, physical therapy, and other preventive measures increase life expectancy and improve the quality of life. Nevertheless, the diseases often progress, and complications can still occur. Definitive treatments such as gene therapy, enzyme replacement therapy, or small-molecule therapy will be needed to correct the underlying causes.

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192 LYSOSOMAL STORAGE DISEASES

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The lysosomal storage diseases encompass a group of more than 70 different inherited disorders, all sharing a defect in lysosomal function. Lysosomes are acidic, membrane-bound organelles that are located in the cytoplasm and contain enzymes that degrade macromolecules. Lysosomal storage disorders ensue when one or more of the hydrolytic enzymes are deficient or when essential lysosomal transporters, receptors, cofactors, or protective proteins are defective or lacking. Typically, complex macromolecules, including glycolipids, mucopolysaccharides, and glycoproteins, are delivered to the lysosome, where they undergo sequential modification by a series of hydrolases. An enzymatic deficiency becomes clinically important when macromolecules accumulate due to inadequate degradation. Different categories of defects result in the various forms of lysosomal dysfunction that are encountered in the lysosomal storage disorders (Table 192-1).

EPIDEMIOLOGY AND PATHOBIOLOGY

Although most lysosomal storage disorders are rare, with the incidence of individual diseases ranging from 1 in 50,000 to 1 in 250,000 live births, as a group their frequency is estimated to be 1 per 7000 to 8000 live births. These percentages are undoubtedly an underestimate because milder or attenuated forms of these disorders are often not identified. Each of the disorders has an autosomal recessive pattern of inheritance, except for Fabry disease and Hunter syndrome (mucopolysaccharidosis II), which are X-linked recessive, and Danon disease, which is caused by deficiency of the lysosome-associated membrane protein 2 (LAMP-2) and is inherited in an X-linked dominant manner. All lysosomal storage disorders are characterized by a broad spectrum of oftentimes subtle manifestations, so they may evade diagnosis when the focus is on an individual organ system. Many of these disorders were traditionally classified into infantile, juvenile, and adult types, based on the patient's age at the onset of manifestations, but such age-based distinctions can

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EPIDEMIOLOGY AND PATHOBIOLOGY

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ABSTRACT

The lysosomal storage diseases encompass a group of more than 70 inherited disorders, all sharing a defect in lysosomal function. Lysosomes are acidic, membrane-bound organelles that contain enzymes that degrade macromolecules, including glycolipids, mucopolysaccharides, and glycoproteins. Lysosomal storage occurs when one or more of the hydrolytic enzymes are deficient or when essential lysosomal transporters, receptors, cofactors, or protective proteins are defective or lacking. This storage results in an array of clinical manifestations of varying severity in different organs. Lysosomal disorders may present at different ages, from infancy to adulthood, and should be considered in the differential diagnosis of organomegaly, cardiomyopathy, renal disease, bony involvement, and neurodegeneration. Each disorder has varying degrees of severity, many ranging from early lethality to a normal life expectancy. Two of the more common lysosomal storage disorders that may present in adulthood, Gaucher disease and Fabry disease, have implications relevant to other more common diseases. Heterozygous and homozygous mutations in the Gaucher glucocerebrosidase gene are a common genetic risk factor for the development of Parkinson disease and related synucleinopathies, whereas Fabry mutations are identified in patients with hypertrophic cardiomyopathies. Several treatment strategies are available, including enzyme replacement and substrate reduction. However, new therapeutic approaches that cross the blood-brain barrier are needed for neuronopathic manifestations of lysosomal storage diseases.

KEYWORDS

lysosome
enzyme deficiency
Gaucher disease
Fabry disease
enzyme replacement therapy
genotype-phenotype correlation
heterogeneity
neurodegeneration

TABLE 192-1 CLASSIFICATION OF LYSOSOMAL STORAGE DISORDERS BASED ON THE TYPE OF DEFECT*

SPHINGOLIPIDOSES
Fabry disease (α-galactosidase)
Farber disease (ceramidase)
GM_1 gangliosidosis/ (β-galactosidase)
GM_2 gangliosidosis/Tay-Sachs disease (β-hexosaminidase A)
GM_2 gangliosidosis/Sandoff disease (β-hexosaminidase B)
Gaucher disease (glucocerebrosidase)
Niemann-Pick disease, types A and B (sphingomyelinase)
Metachromatic leukodystrophy (arylsulfatase A)
Globoid cell leukodystrophy/Krabbe disease (β-galactocerebrosidase)
Metachromatic leukodystrophy (arylsulfatase A and prosaposin)
Niemann-Pick disease type C (NPC1 protein, intracellular cholesterol transporter)
LIPID STORAGE DISORDERS
Wolman disease (lysosomal acid lipase)
Ceroid-lipofuscinosis, adult type, Kufs/Parry (heterogeneous, with 13 enzymes involved in lysosomal, endoplasmic reticular, and cytoplasmic vesicular transmembrane proteins)
MUCOPOLYSACCHARIDOSES
Type I/Hurler disease (α-L-iduronidase)
Type II/Hunter disease (iduronate-2-sulfatase)
Type III/Sanfilippo disease (four different enzymes in the degradation of heparan sulfate defining types A-D)
Type IV/Morquio disease (*N*-acetylgalactosamine 6-sulfatase-type IVA, β-galactosidase-type IVB)
Type VI/Maroteaux-Lamy disease (arylsulfatase B)
Type VII/Sly disease (β-glucuronidase)
OLIGOSACCHARIDOSES
Aspartylglucosaminuria (aspartylglucosaminidase)
Fucosidosis (α-fucosidase)
α and β Mannosidosis (α-mannosidase or β-mannosidase)
Schindler disease (α-*N*-acetylgalactosaminidase)
Sialidosis I (sialidase)
Sialidosis II/mucolipidosis I (sialidase)
MUCOLIPIDOSES
Mucolipidosis I/sialidosis (neuraminidase)
Mucolipidosis II/I-cell disease (*N*-acetylglucosaminylphosphotransferase)
Mucolipidosis III/pseudo-Hurler (*N*-acetylglucosaminylphosphotransferase)
Mucolipidosis IV (mucolipin TRP cation channel 1/*MCOLN1* mutation)
LYSOSOMAL GLYCOGEN STORAGE DISORDERS
Glycogenosis type II/Pompe disease (α-1,4-glucosidase or acid maltase)
INTEGRAL MEMBRANE PROTEIN DISORDERS
Sialic acid storage disease/Salla disease (sialin/SLC17A5)
Cystinosis (cystine transporter/CTNS)
Niemann-Pick disease, type C (intracellular cholesterol transport)
Danon disease (LAMP2)
MULTIPLE ENZYME DEFICIENCY DISORDERS
Galactosialidosis (β-galactosidase and sialidase)
Multiple sulfatase deficiency/Austin disease (sulfatases)

*Full chapters describing each of these disorders are available in Valle D, Beaudet AL, Vogelstein B, et al., eds. *The Online Metabolic and Molecular Bases of Inherited Disease*. http://www.ommbid.com/OMMBID.

be misleading. Among the factors that contribute to this phenotypic diversity are the amount of residual enzyme activity, the cellular localization of the enzyme, the genotype, and the genetic background of the affected individual, as well as other environmental and epigenetic influences.[1]

CLINICAL MANIFESTATIONS AND DIAGNOSIS

With the advent of new therapies for some of the lysosomal storage disorders, early establishment of the diagnosis is paramount. Suggestive clinical findings include coarse facial features; organomegaly; specific eye findings, including corneal clouding or a cherry red spot (of the macula); cardiac involvement; cytopenia; neurologic involvement, including psychiatric symptoms or delay or progressive loss of developmental skills; and skeletal abnormalities, notably dysostosis multiplex (Table 192-2). The index of suspicion should be heightened whenever these features occur in concert, the findings are progressive, developmental milestones are missed, new psychiatric features appear, or the affected individual appears dissimilar to other family members.

The diagnostic evaluation includes a careful history, with analysis of the family pedigree and assessment of developmental milestones in childhood and adolescence. A family history of consanguinity, other affected siblings, multiple miscarriages, or early deaths can aid in making the diagnosis. Ethnicity can be a helpful clue because some of the lysosomal disorders occur with increased incidence in specific populations, such as Ashkenazi Jews (Gaucher disease type 1, Tay-Sachs disease, mucolipidosis type IV) and Scandinavians (mannosidosis, sialic acid storage disease, aspartylglucosaminuria, Gaucher disease type 3).

On physical examination, special attention should be paid to head circumference (microcephaly or macrocephaly); facial appearance (coarse facies); enlargement of the tongue; hepatosplenomegaly; skeletal manifestations, including kyphosis, broadening of the long bones, and stiffness of the joints; and behavior and development. Evaluations by multiple specialists are often helpful to define related manifestations across all organ systems. Skin evaluation may reveal angiokeratoma, especially around the umbilicus and in skin creases, seen in Fabry disease, fucosidosis, sialidosis, galactosialidosis, and GM_1 gangliosidosis. The eye evaluation should include a funduscopic and slit lamp examination to screen for storage material within the retina (cherry red spots), seen in sialidosis, galactosialidosis, and GM_1 and GM_2 gangliosidosis, as well as an assessment for atypical eye movements, which may be pathognomonic for disorders such as neuronopathic Gaucher disease and Niemann-Pick disease type C. Unexplained cardiomyopathy and cryptogenic stroke may be the initial presentation of Fabry disease. A careful neurologic and cognitive evaluation can be fruitful, because the later presentations of some lysosomal disorders include dementia and psychiatric manifestations. Regression of developmental milestones can provide an early diagnostic clue in some disorders, whereas developmental delay occurs in others.

Physicians' increased awareness of the range of manifestations and presentations of lysosomal disorders may lessen the lengthy delays in diagnosis that patients frequently experience. Preliminary clinical diagnostic studies include urine or blood chromatography screens for storage material, blood count with smear for vacuolated white blood cells, skeletal radiography, and ophthalmologic examination.

The diagnosis of a specific lysosomal storage disorder can be established by sequencing the specific gene or by an enzyme assay. DNA sequence analysis is typically more successful when a mutation has already been identified in a family or when specific mutations are known to be common in a given ethnic group. In addition, when clinical signs point to several different disorders, diagnostic testing based on DNA sequencing of panels of genes implicated in lysosomal storage disease is available. Next-generation sequencing at times can also reveal the diagnosis, although the identification of new variants of unknown significance can introduce uncertainty. The expanded use of next-generation DNA sequencing has led to the identification of lysosomal storage disorders in patients who do not have classic manifestations of their storage disease. Newborn screening in some states may also include specific lysosomal storage disorders to optimize early identification and treatment.

Enzymatic activity may be assayed in a blood sample using a lysosomal panel that evaluates the activities of multiple lysosomal enzymes from the same sample. A tissue biopsy, most often of the bone marrow or liver, can confirm the diagnosis but now is rarely indicated.

Biomarkers also can be suggestive of a specific disorder. For example, elevated levels of the lipid glucosylsphingosine (lysoGb1) are highly suggestive of Gaucher disease.

TREATMENT AND PROGNOSIS

Patients with lysomal storage disorders should receive disease-specific care via specialized centers, where improved care and enzyme-specific therapeutic modalities (Table 192-3) under expert supervision have transformed the natural history of several of these disorders. With patients' increased longevity, diseases that were once encountered only by pediatricians are now seen by adult physicians. Moreover, many of the classic complications are now avoided by early therapeutic interventions.[2] In some instances, however, prolonged survival has unmasked unanticipated clinical consequences such as myopathy in cystinosis and learning disabilities in Gaucher disease type 3.

TABLE 192-2 MANIFESTATIONS ENCOUNTERED IN DIFFERENT LYSOSOMAL STORAGE DISORDERS

FINDING	DISORDERS
Hepatosplenomegaly	GM_1 gangliosidosis, Niemann-Pick disease, Gaucher disease, Wolman disease, Schindler disease, fucosidosis, Pompe disease, mannosidosis, galactosialidosis, multiple sulfatase deficiency, sialidosis, sialic acid storage disease, several mucopolysaccharidoses, aspartylglucosaminuria
Coarse facies	GM_1 gangliosidosis, fucosidosis, mannosidosis, sialidosis, galactosialidosis, multiple sulfatase deficiency, sialic acid storage disease, several mucopolysaccharidoses, mucolipidosis II and III, aspartylglucosaminuria
Skeletal findings	GM_1 gangliosidosis, Gaucher disease, fucosidosis, mannosidosis, sialidosis, galactosialidosis, several mucopolysaccharidoses, mucolipidosis II and III
Cherry red spot (retina)	Infantile forms of GM_1 gangliosidosis, Sandhoff disease, Tay-Sachs disease, Niemann-Pick disease, sialidosis, galactosialidosis, I-cell disease
Corneal clouding	GM_1 gangliosidosis, several mucopolysaccharidoses, mannosidosis, I-cell disease, mucolipidosis III and IV, multiple sulfatase deficiency, galactosialidosis
Brain involvement	GM_1 gangliosidosis, GM_2 gangliosidosis, Sandhoff disease, Tay-Sachs disease, Niemann-Pick disease, Gaucher disease type 2, Fabry disease, Schindler disease, fucosidosis, mannosidosis, multiple sulfatase deficiency, sialidosis, galactosialidosis, several mucopolysaccharidoses, sialic acid storage disease, aspartylglucosaminuria, I-cell disease, mucolipidosis III and IV, Krabbe disease, metachromatic leukodystrophy, neuronal ceroid lipofuscinosis, Danon disease
Peripheral nervous system findings	Metachromatic leukodystrophy, Fabry disease, Sandhoff disease
Cardiac	Mucopolysaccharidosis (I, II, IV, and VII), mucolipidosis I and II, Fabry disease, Farber disease, galactosialidosis, Pompe disease
Hematologic	Anemia, thrombocytopenia in Gaucher disease; eosinophil abnormalities in multiple sulfatase deficiency, GM_1 gangliosidosis, Salla disease, foam cell in GM_1 gangliosidosis, Niemann-Pick disease, Gaucher disease, acid lipase deficiency, fucosidosis
Granulated or vacuolated white blood cells	Several mucopolysaccharidoses, sialidosis, galactosialidosis, neuronal ceroid-lipofuscinosis, Niemann-Pick disease, Wolman disease, fucosidosis, mannosidosis, aspartylglucosaminuria, I-cell disease, mucolipidosis III, multiple sulfatase deficiency
Psychiatric or behavioral manifestations	Several mucopolysaccharidoses (especially Sanfilippo), sialidosis, galactosialidosis, Fabry disease, mannosidosis, neuronal ceroid-lipofuscinosis, metachromatic leukodystrophy, Tay-Sachs disease, Niemann-Pick disease (type C)
Newborn presentations	Gaucher disease (type 2), GM_1 gangliosidosis, Krabbe disease, Niemann-Pick disease, (types A and C), mucopolysaccharidosis (I, IVA, VII), Pompe disease, sialidosis (types I and II), mucolipidosis (types I and II), Schindler disease, Wolman disease, infantile sialic acid storage disease, sialuria, Salla disease, galactosialidosis, multiple sulfatase deficiency, prosaposin deficiency

TABLE 192-3 APPROVED ENZYME-SPECIFIC TREATMENTS FOR LYSOSOMAL STORAGE DISEASES

DISEASE	DEFICIENT ENZYME	ENZYME REPLACEMENT THERAPY	OTHER DISEASE-MODIFYING DRUGS (SUBSTRATE REDUCTION THERAPY)
Gaucher disease	Glucocerebrosidase	Imiglucerase, velaglucerase alfa, taliglucerase alfa	Miglustat, eliglustat
Fabry disease	α-Galactosidase	Agalsidase alfa, agalsidase beta	Migalastat
Pompe disease	α-1,4-Glucosidase	Alglucosidase alfa, avalglucosidase alfa	
Mucopolysaccharidosis type I	α-L-Iduronidase	Laronidase	
Mucopolysaccharidosis type II	Iduronate-2-sulfatase	α-L-Iduronidase, JR-141	
Mucopolysaccharidosis type VI	Arylsulfatase B	Galsulfase	
Niemann-Pick C			Miglustat

GAUCHER DISEASE

DEFINITION

Gaucher disease is divided into three types based on the absence or presence and the rate of progression of neurologic involvement.[3] Type 1, the non-neuronopathic form, is the most common type in the Western world and can manifest at any age. Type 2, the acute neuronopathic form, manifests before or shortly after birth and has a rapid and progressive course. Type 3 is the subacute neuronopathic form. The spectrum of manifestations encountered in this disorder ranges from asymptomatic octogenarians to infants who succumb in utero. Some patients defy classification into one of the three types.

EPIDEMIOLOGY AND PATHOBIOLOGY

Gaucher disease is a pan-ethnic disorder. Type 1 Gaucher disease is more frequent among Ashkenazi Jews, in whom the carrier frequency is about 1 in 16, whereas the carrier frequency in the general population is approximately 1 in 100.

Gaucher disease, the autosomal recessively inherited deficiency of the lysosomal enzyme glucocerebrosidase, is a disorder primarily of the reticuloendothelial system. Lysosomes within macrophages become engorged with the substrate glucocerebroside, thereby giving rise to the characteristic Gaucher cells, which have a wrinkled-paper appearance that results from the intracytoplasmic deposition of glucocerebroside. The accumulated glycolipids, glucocerebroside and glucosylsphingosine, result from the degradation of senescent leukocytes or erythrocyte membranes.

The gene encoding glucocerebrosidase, *GBA1,* is located on chromosome 1q21. More than 600 different mutations have been found, several of which are encountered with increased frequency in specific types. For example, mutation N370S (p.N409S), which is the most common allele among Ashkenazi Jews, is seen only in type 1 Gaucher disease. Homozygosity for L444P (p.L483P) is most often associated with type 3 Gaucher disease. Oftentimes, however, identified mutations cannot be used to predict the clinical phenotype.

CLINICAL MANIFESTATIONS

Commonly encountered symptoms in all types of Gaucher disease include easy bruisability, hepatomegaly, splenomegaly, chronic fatigue, and bone pain or pathologic fractures. Laboratory findings include anemia, thrombocytopenia, and elevations of ferritin, acid phosphatase, angiotensin-converting enzyme, and, at times, liver enzymes. Levels of lyso-Gb1 are massively elevated, and assays for this lipid are increasingly used as a biomarker of disease.[4] About 50% of patients develop polyclonal gammopathy, and about 30% develop monoclonal gammopathy (Chapter 173).[5] Altered macrophage function, complement processing, elevated

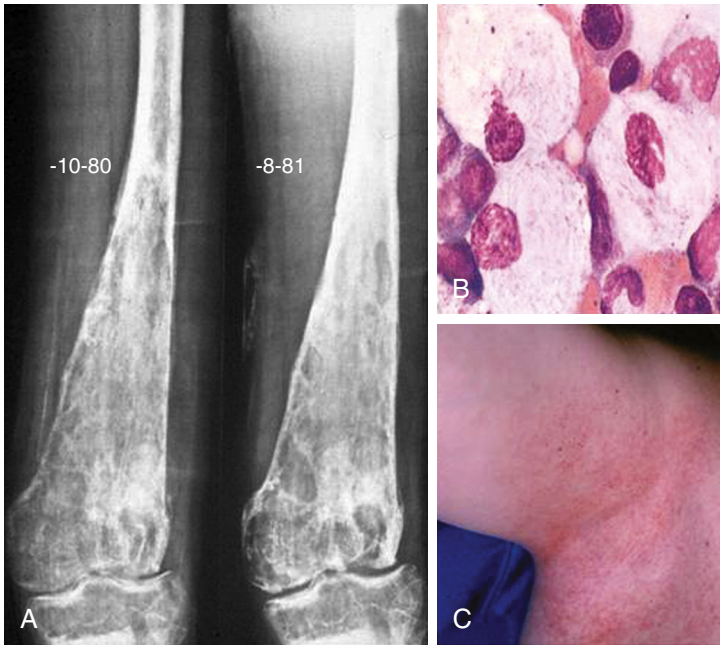

FIGURE 192-1. **A, Radiographic image showing the Erlenmeyer flask deformity in Gaucher disease. There is cortical thinning and widening of the medullary cavity of the metaphysis and adjacent diaphysis. B, Gaucher cells—reticuloendothelial cells storing abnormal amounts of lipid. C, Angiokeratomas, the nonblanching punctate skin lesion in Fabry disease.**

cytokine levels, and an increased risk for multiple myeloma (Chapter 173) have been reported.

Painless splenomegaly is the most common presentation in patients with Gaucher disease type 1, and the spleen can be massively enlarged.[6] Thrombocytopenia and/or anemia are frequent. Occasional patients have pulmonary involvement or pulmonary hypertension. Bone involvement, which is a significant cause of morbidity, can manifest with extreme bone pain or pathologic fractures. Most patients have radiologic evidence of skeletal involvement, including the classic Erlenmeyer flask deformity of the distal end of the femur and osteopenia (Fig. 192-1A). Pathologic fractures (especially of the hip, ribs, or spine), lytic bone lesions, and osteoporosis may occur. Painful bone crises, which are episodes of bone infarction, can persist for weeks and may require aggressive pain management.

An important association exists between the presence of pathologic variants in *GBA1* and parkinsonism[7] (Chapter 378). Both patients with Gaucher disease as well as heterozygous carriers have a higher incidence of Parkinson disease and Lewy body disorders. Studies in large Parkinson cohorts around the world reveal a 5- to 10-fold increased frequency of *GBA1* mutations, thereby rendering this the most common genetic risk factor for parkinsonism identified to date. However, the majority of patients with Gaucher disease and carriers of a *GBA1* mutation do not develop Parkinson disease, and this reduced penetrance remains unexplained.

Type 2 Gaucher disease, which is rare, is characterized by a rapid neurodegenerative course with extensive visceral involvement, and it is associated with failure to thrive, laryngospasm, strabismus, and seizures. Death occurs within the first years of life.

Type 3 disease is clinically variable and is often noted in childhood. In addition to organomegaly and bone involvement, patients have abnormal horizontal eye movements, and some develop myoclonic epilepsy or neurodegeneration. A subgroup of patients have cardiac calcifications, hydrocephalus, and other atypical manifestations. Patients with this specific Gaucher phenotype (Gaucher disease type 3C) are homozygous for the *GBA1* variant D409H (p.D448H).

DIAGNOSIS

Gaucher disease should be considered in the differential diagnosis when patients of any age have unexplained organomegaly, easy bruisability, or bone pain (Table 192-4). Measurement of the biomarker LysoGbl, performed on dried blood spots or serum, is increasingly being used as a diagnostic screen. Elevated levels can then be confirmed by enzymatic or DNA analyses to establish the definitive diagnosis.

The diagnosis can be made by demonstrating deficient glucocerebrosidase activity in leukocytes or cultured cells. In some populations, particularly Ashkenazi Jews, screening for specific mutations can be diagnostic because mutation N370S accounts for about 70% of mutant alleles. Generally, sequencing of the entire *GBA1* gene is required for an accurate molecular diagnosis. Since the presence of a highly homologous pseudogene sequence nearby can complicate molecular analysis, diagnostic laboratories must be knowledgeable about the gene. Bone marrow and liver biopsies show pathologic changes (see Fig. 192-1B) but are not indicated for diagnosis. Carrier identification is best achieved by DNA testing when the mutant allele is known. Prenatal diagnosis is possible by determining the enzymatic activity or specific mutations in chorionic villi or cultured amniotic fluid cells.

TREATMENT AND PROGNOSIS

Two treatment approaches to reduce the pathologic accumulation of glucocerebroside are enzyme replacement therapy and substrate reduction therapy. Asymptomatic and mildly symptomatic adults do not always require treatment.

Enzyme replacement with recombinant glucocerebrosidase (see Table 192-2) is available for the treatment of symptomatic patients with types 1 and 3 Gaucher disease (Table 192-5).[8] Anemia, thrombocytopenia, and organomegaly are reversed within 12 to 36 months with enzyme doses between 15 and 60 IU/kg given every other week. The treatment is ongoing, administered intravenously, and extremely expensive. The enzyme does not cross the blood-brain barrier and does not alter the neurologic progression of patients who have neuronopathic forms of Gaucher disease, but it can still be useful in alleviating visceral manifestations.

Substrate reduction therapy uses eliglustat, which is a ceramide analogue[9] and a potent specific inhibitor of glucosylceramide synthase, which reduces glucosylceramide production to match its impaired rate of degradation. Eliglustat, which is administered orally under expert supervision, significantly improves spleen and liver volumes, hemoglobin levels, and platelet counts.[A1] Currently eliglustat is being used instead of enzyme replacement therapy in some adults who prefer an oral alternative. CYP2D6 status should be evaluated before use to determine both eligibility for the drug and the appropriate dosing. Ultrarapid CYPRD6 metabolizers should not receive eliglustat, whereas normal or intermediate metabolizers should receive a dose of 84 mg twice daily, and poor metabolizers should be treated with 84 mg once daily.

Currently available therapies appear to have a positive effect on bone disease[10] but do not prevent the development of parkinsonism. Efforts are ongoing to develop alternative therapies, including brain-penetrant enzyme replacement and substrate reduction therapies, chemical chaperones, and gene therapy.

Useful supportive therapies include bisphosphonates for osteoporosis, orthopedic surgery for bone fractures, and palliative therapy and hydration for bone crises. Total or partial splenectomy is now rarely indicated. Hematopoietic stem cell transplantation (Chapter 163) can improve systemic but not neurologic manifestations; it has been performed in patients who have severe organomegaly and cytopenia in countries where other options are not available.

FABRY DISEASE

DEFINITION

Fabry disease, an X-linked inherited deficiency of the lysosomal enzyme α-galactosidase A, has intermediate penetrance in females and is considered a systemic vascular disorder.

EPIDEMIOLOGY

Based on pilot newborn screening studies and the implementation of next-generation sequencing strategies in patients with cardiovascular disease, Fabry disease is now considered to be more common than previously recognized. Mutations associated with classic Fabry disease features are present in approximately 1 : 22,000 to 1 : 40,000 males and mutations associated with atypical presentations are present in about 1 : 1000 to 1 : 3000 males and 1 : 6000 to 1 : 40,000 females. As many as 3 to 12% of adults with hypertrophic cardiomyopathy (Chapter 47) may have Fabry disease.

PATHOBIOLOGY

Fabry disease is caused by a defect in the hydrolytic cleavage of the terminal molecule of galactose from glycolipids. The result is lysosomal

TABLE 192-4 SUGGESTIVE DIAGNOSTIC FEATURES IN ADULTHOOD FOR GAUCHER DISEASE AND FABRY DISEASE

GAUCHER DISEASE	FABRY DISEASE
Family member with Gaucher disease	Family history of Fabry disease
Hepatomegaly, splenomegaly (sometimes massive)	Cutaneous lesions of capillaries (angiokeratoma)
Frequent epistaxis	Corneal and lenticular opacities
Easy bruising	Hypohidrosis or heat intolerance
Abnormal saccadic eye movements	Intermittent severe extremity pain (acroparesthesias)
Thrombocytopenia or anemia	Left ventricular hypertrophy of unknown etiology in young adulthood
Painful bone crisis	Stroke of unknown etiology in young adulthood
Erlenmeyer flask deformity of the distal femur, aseptic necrosis of the femoral heads	Chronic kidney disease of unknown etiology in young adulthood
Pathologic fractures, unexplained rib fracture	Multiple renal sinus cysts
Multiple myeloma	Female carriers may have more variable and less severe symptoms with later onset
Parkinsonism	
Elevated serum ferritin, glucosylsphingosine, angiotensin-converting enzyme, or tartrate-resistant acid phosphatase	

TABLE 192-5 THERAPIES INCLUDING ENZYME REPLACEMENT THERAPY (ERT) FOR GAUCHER DISEASE AND FABRY DISEASE

GAUCHER DISEASE	FABRY DISEASE
ERT is a costly but effective intravenous therapy, generally administered every other week for life.	ERT is a costly but effective intravenous therapy, generally administered every other week for life.
An oral substrate reduction drug eliglucerase also successfully reverses disease manifestations.	An oral pharmacologic chaperone (migalastat) can now be used instead of ERT in patients with amenable genetic variants.
Decreased splenic and hepatic volumes and increases in hemoglobin levels and platelet counts are expected in the first year of treatment.	Hemizygous males with a low or undetectable level of α-galactosidase A should be treated with ERT (or migalastat) whether or not clinical features are present.
Asymptomatic and mildly symptomatic adults do not always require treatment.	Current trials suggest that female carriers and atypically affected males with clinical features of Fabry disease (renal, neurologic, cardiovascular) should be treated with ERT or, if appropriate, migalastat.
ERT and eliglustat do not cross the blood-brain barrier and do not correct neurologic features of neuronopathic forms of Gaucher disease.	In patients with end-stage renal disease due to Fabry disease, ERT should be considered on an individual basis, potentially to reduce other organ involvement.
ERT will not prevent the development of parkinsonism.	

accumulation of globotriaosylceramide and galabiosylceramide in many types of cells.

Lysosomal inclusions or lipid deposits can be seen in vascular cells, including both endothelial and smooth muscle cells; cardiac cells, such as endocardial cells, cardiomyocytes, and cardiac valves; kidney epithelial cells, including tubular and glomerular cells and podocytes; and nerve cells, including dorsal root ganglia and some central nervous system neurons.

The gene encoding α-galactosidase A, *GLA*, is located on Xq22.1. Over 1000 mutations in *GLA* have been described, including missense/non-sense mutations, small deletions, large deletions, splice defects, and complex rearrangements. Most affected individuals have 2 to 25% of residual enzymatic activity, but the most severe form of Fabry disease has been correlated with complete absence of α-galactosidase A activity.

CLINICAL MANIFESTATIONS

Clinically, angiokeratomas (nonblanching, punctate, blue-black skin lesions), debilitating pain, and corneal opacities can occur in childhood and may lead to the diagnosis. Progressive renal and cardiac deterioration may develop. Affected adults have a propensity for ischemic stroke, sometimes in their 20s but more commonly in the fourth and fifth decades of life. As with many metabolic disorders, the spectrum of presentations can mimic more common disorders, and many patients are undiagnosed.[11]

Fabry disease typically manifests in childhood in classically affected males with episodes of extremity pain. Angiokeratomas develop in adolescence, followed by advancing renal disease during adulthood. The progressive cardiac and cerebrovascular involvement accounts for most of the deaths associated with Fabry disease in adulthood. X-linked inactivation and the penetrance of this X-linked disorder are reflected in the fact that approximately 90% of females carrying the mutation have symptoms, although they frequently go undiagnosed. Affected males tend to show more significant clinical manifestations at an earlier age than do heterozygous females.

Although variable, the clinical manifestations of Fabry disease often occur in a predictable order; acroparesthesia, angiokeratoma, proteinuria, polyuria, polydipsia, heat, cold, exercise intolerance, hypohidrosis or hyperhidrosis, lymphadenopathy, abdominal pain and diarrhea, with increasing risk in adulthood of progressive cardiac and central nervous system involvement. Atypical (late-onset) variants, including the hypertrophic cardiomyopathy cardiac variant (Chapter 47), can present in the third to seventh decades of life.

The majority of patients experience acroparesthesia, or a "Fabry crisis," characterized by excruciating, burning pain that may be either continuous or episodic, often as the initial clinical manifestation. The pain typically affects the feet first, followed by the hands, and may be triggered by exercise, stress, and extremes in environmental temperatures. Abdominal or flank pain, simulating renal colic, may occur.

Angiokeratomas (see Fig. 192-1C) are often an early sign of Fabry disease and may be accompanied by hypohidrosis. These classic skin lesions increase in number and size over time and are typically most dense between the umbilicus and the knees; however, they may occur anywhere, including the buccal mucosa. Ophthalmologic findings include conjunctival and retinal tortuosity and corneal opacities (cornea verticillata). Characteristic lenticular lesions are observed during slit lamp examination and are present in affected males and female heterozygotes. Progressive hearing loss may also occur.

Renal involvement is seen in approximately 50% of affected males by age 35 and 20% of affected females, initially manifesting with proteinuria, followed by progressive renal insufficiency, with birefringent "Maltese crosses" sometimes seen in the urinary sediment. Chronic kidney disease is part of the natural history, and end-stage renal disease may develop in the second to fourth decades. Fabry disease should be considered when multiple renal sinus cysts are seen on an imaging study. As affected men and women age, cardiovascular findings may include ventricular hypertrophy, conduction defects, coronary artery disease, aortic and mitral valve insufficiency, and aortic root dilation.[12] Furthermore, atypical Fabry disease can manifest with concentric left ventricular hypertrophy and no other disease findings. Cerebrovascular involvement, leading to transient ischemic attacks and stroke, occurs in approximately 25% of patients, with a mean age at onset of 40 years.

Female Carriers

Female carriers of this X-linked disorder may show any or all clinical signs of Fabry disease, but they are more variable and less severe, with a later age at onset. As the women age, they may develop cardiac involvement and cerebrovascular disease, including transient ischemic attacks and strokes. Kidney disease occurs less frequently in affected women than men; however, if renal disease does develop, it progresses at the same rate as in affected males. The onset of cardiomyopathy in affected women is generally 10 years later than the classic presentation in men and may be the only manifestation of Fabry disease. Twenty percent of affected women develop major cardiac, cerebrovascular, or kidney complications by age 46.

DIAGNOSIS

Fabry disease should be considered in individuals with acroparesthesia, angiokeratoma, hypohidrosis, and corneal lesions, as well as in individuals with cryptogenic strokes, idiopathic left ventricular hypertrophy, arrhythmias (especially in young adults), or renal disease (see Table 192-4). Men and women with left ventricular hypertrophy without any other explanation or with a family history of renal, cardiovascular, cerebrovascular, or skin issues

should be screened for Fabry disease. Angiokeratoma should be differentiated from Fordyce disease, benign angiokeratomas of the scrotum, and angiokeratoma circumscriptum. Angiokeratomas are also seen in other lysosomal disorders, including mannosidosis, fucosidosis, sialidosis, and β-galactosidase and β-hexosaminidase deficiency. The corneal abnormalities resemble those seen secondary to the use of chloroquine or amiodarone. Exposure to silicone dust can result in similar renal findings.

Mutational analysis of *GLA*, the gene that encodes α-galactosidase, is the gold standard for confirming the diagnosis in males and females. The diagnosis also can be established by finding low α-galactosidase activity in leukocytes or cultured skin fibroblasts. Levels below 20% of normal are considered diagnostic, and levels up to 35% of normal should be considered suggestive. However, *GLA* mutation analysis is critical for confirmation in atypically presenting males and heterozygote females because random X chromosome inactivation may lead to only slightly reduced or normal enzyme activity. Plasma and urine lysoGb3 levels, if elevated, may help to confirm the diagnosis of Fabry disease among patients with a *GLA* gene variant of uncertain significance.

TREATMENT

Symptomatic treatment of the clinical manifestations of Fabry disease should follow standard medical care.[13] Antiplatelet agents such as aspirin (81 mg daily) or clopidogrel (75 mg daily) should be used for the prevention of strokes. Angiotensin-converting enzyme inhibitors and angiotensin receptor blockers are appropriate to manage hypertension and to preserve renal function (Chapter 64). Kidney transplantation (Chapter 117) is effective in individuals with end-stage renal disease. Neuropathic pain can be treated with gabapentin or other anticonvulsants (Table 26-5). Opioids should be avoided if possible, as should nonsteroidal anti-inflammatory agents, which can cause renal toxicity.

Specific Fabry therapy is indicated for classically affected males, symptomatic females, and males with atypical disease (see Table 192-5).[14] Enzyme replacement therapy (see Table 192-3) can modify the natural course of the disease.[A2] Migalastat hydrochloride, which is an oral pharmacologic chaperone of mutated α-galactosidase A, may be useful when the α-galactosidase A leukocyte activity level is less than 35% of normal and the patient's mutation is known to be responsive to miglustat therapy.[A3] Migalastat should not be used in patients who have low glomerular filtration rates.

OTHER LYSOSOMAL DISORDERS SEEN IN ADULTS

METACHROMATIC LEUKODYSTROPHY

Metachromatic leukodystrophy, which is the deficiency of arylsulfatase A (or in rarer cases, prosaposin), results in the accumulation of sulfatides in the central and peripheral nervous systems, thereby leading to demyelination of axons and peripheral nerves. This condition has a spectrum of manifestations, divided into childhood, juvenile, and adult-onset variants.[15] In the childhood form, peripheral neuropathy is often the presenting feature. Gallbladder involvement is common, with manifestations that include hyperplastic polyps and possibly an increased risk of gallbladder carcinoma. Presentation of the juvenile onset form is heterogeneous, with intellectual impairment, behavioral difficulties, gait disturbances, ataxia, upper motor neuron signs, and peripheral neuropathy. The adult form typically presents with dementia and behavioral disturbances, often mistakenly resulting in a diagnosis of psychosis.

Metachromatic leukodystrophy is a recognized underlying cause of psychiatric illness in adults, and prominent features include auditory hallucinations, bizarre delusions, behavioral changes, personality changes, disinhibition and disorganization in daily life, and catatonic posturing. Other neurologic manifestations, such as dysarthria and spasticity, develop later as the disease progresses. The diagnosis can be especially difficult in these individuals.[16]

Metachromatic leukodystrophy should be considered in individuals with the combined findings of reduced nerve conduction velocity and elevated cerebrospinal fluid protein levels. The diagnosis is made by demonstration of low arylsulfatase A activity. However, because there can be a pseudodeficiency, the diagnosis must be confirmed by molecular testing or the demonstration of the excretion of sulfatides in urine. Data suggest that allogeneic hematopoietic cell transplantation can slow the progression of the disease. Preliminary evidence suggests that gene therapy[17] with the *ARSA* gene or gene therapy combined with hematopoietic stem cell transplantation can slow the progression of the disease, but complications remain a concern.

TAY-SACHS DISEASE

Tay-Sachs disease (or GM_2 gangliosidosis), which is caused by β-hexosaminidase A deficiency, is characterized by an excessive accumulation of the fatty acid derivative ganglioside GM_2 in neurons. Although the more common pathogenic variants in *HEXA* have been described in individuals of Ashkenazi Jewish background, other populations have variants spread throughout the *HEXA* gene.

There are three clinical variants based on the age at onset: type 1, infantile acute; type 2, subacute (2 to 18 years); and type 3, late onset.[18] The main features of the disease are neurologic and cognitive deterioration, as well as blindness, a macular cherry red spot, and deafness. In patients with late-onset GM_2 gangliosidosis, the typical presentation is with subtle motor deficits. In some patients, psychiatric signs may manifest years before the appearance of significant motor findings. The most common psychiatric signs include acute psychosis, mania, and depression without psychosis. Either recurrent progressive psychosis, consistent with schizophrenia-hebephrenia, or major depression followed by psychotic features may occur. Dysarthria and progressive speech loss are also common.

The disorder is diagnosed by measurement of β-hexosaminidase A activity in the serum or white blood cells in the presence of normal or elevated activity of the β-hexosaminidase B isoenzyme. *HEXA* variants can cause pseudodeficiency in the enzyme assay with no clinical symptoms, so enzyme testing is required. The diagnosis is made when enzyme levels are 0 to 15% of normal values. In pregnant women or those taking oral contraceptives, the enzyme assay should be performed only in leukocytes.

Community-based screening efforts in the high-risk Ashkenazi Jewish population have vastly decreased the incidence of this disorder.

NIEMANN-PICK DISEASE TYPE C

Niemann-Pick disease type C results from an error in cellular trafficking of exogenous cholesterol, thereby leading to lysosomal accumulation of unesterified cholesterol. The disease is linked to mutations in *NPC1* (95% of cases) and *NPC2* (5% of cases) genes.

Affected individuals present with a spectrum of features ranging from a rapidly progressive, fatal neonatal phenotype to an adult-onset chronic, neurodegenerative course. In adults, the presentation may include progressive ataxia, vertical supranuclear ophthalmoplegia, and dystonia. Dementia, depression, bipolar symptoms or schizophrenia may be the presenting features. Systemic involvement of liver, spleen, or lung is present in more than 85% of cases and often precedes the development of neurologic findings.

When the disease is suspected,[19] the first-line screening test is measurement of oxysterols, specifically cholestane triol (see Table 192-2). The diagnosis is confirmed by genetic testing with mutations in either *NPC1* (95% of cases) or *NPC2* genes.

Miglustat (*N*-butyldeoxynojirimycin) has been shown in clinical trials to stabilize, but not prevent or reverse, key neurologic findings.[20] Decisions about starting this therapy typically involve the team of physicians, parents, and caregivers of the affected individual. Other small-molecule drugs, including arimoclomol, are thought to function by stimulating a normal cellular protein repair pathway through chaperones[A4] and have shown promising results.

ASPARTYLGLUCOSAMINURIA

Aspartylglucosaminuria, which is particularly seen in Finland, is caused by an autosomal recessive defect in glycoprotein degradation with subsequent lysosomal storage of the undegraded compounds. Affected individuals generally have a slow or progressive delay in development. The speech delay and motor defects are often accompanied by repeated upper respiratory infections. Patients typically achieve the developmental competency of a 5- to 6-year-old child at around puberty; subsequent progressive deterioration may result in the severe cognitive impairment seen in adulthood. The characteristic coarse facial features, thick calvaria, and osteoporosis result from mild connective tissue transformation. During the later stages of the disease, about 20% of patients experience seizures that result primarily from abnormalities in the differentiation between gray and white matter and delayed myelination.

The diagnosis is made by the detection of elevated urine oligosaccharides, deficient aspartylglucosaminidase activity in leukocytes, or sequence analysis of the *AGA* gene.[21]

NEURONAL CEROID-LIPOFUSCINOSES

The neuronal ceroid-lipofuscinoses were historically divided into four major groups—infantile, classic late infantile, juvenile, and adult (Kufs disease)—to reflect the age of onset of symptoms and the appearance of autofluorescent ceroid lipopigments in the brain and other tissues. To date, mutations causing neuronal ceroid-lipofuscinoses have been found in 13 human genes. The associated clinical phenotypes are numerous, but all include progressive neurologic disease and, in most cases, retinal disease, in association with intracellular storage of material that is morphologically characterized as ceroid lipofuscin. In children and adolescents, clinical manifestations include visual impairment that leads to blindness, gait abnormalities, seizures, and early death. The two major clinical phenotypes in adults are progressive myoclonic epilepsy with dementia, ataxia, and late occurring parkinsonian symptoms and behavioral changes and dementia, with motor dysfunction, ataxia, and extrapyramidal and brain stem involvement.

The diagnosis is based on diminished enzyme activity, molecular genetic testing, and, in some cases, clinical findings and electron microscopy of biopsied tissues. Distinguishing among the clinical phenotypes can be challenging because of the wide variation in both the age of onset and disease progression, so molecular testing is necessary for optimal classification. Intrathecal recombinant cerliponase alfa therapy (see Table 192-2) may slow the decline in motor and language function.[22–24]

LYSOSOMAL ACID LIPASE DEFICIENCY

Lysosomal acid lipase deficiency (Wolman disease in infants or cholesterol ester storage disease in adults) is an autosomal recessive storage disease caused by mutations in the *LIPA* gene. Clinical manifestations are due to the lysosomal accumulation of cholesteryl esters and triglycerides, which lead to reduced free cholesterol, increased production of apolipoprotein B–containing lipoproteins, and reduced formation of high-density lipoprotein cholesterol. In infants, progression of the disease is rapid, typically occurring within 6 months of age. Adults typically have dyslipidemia, hepatomegaly, liver cell damage, and elevated serum aminotransferase levels, with progression to hepatic fibrosis and cirrhosis. Because each of these manifestations can be caused by many other diseases, lysosomal acid lipase deficiency is an under-recognized condition, and many affected individuals are not diagnosed or receive the incorrect diagnoses of heterozygous familial hypercholesterolemia, familial combined hyperlipidemia (Chapter 190), or nonalcoholic steatohepatitis (Chapter 138).

When the diagnosis is suspected based on clinical or laboratory findings, confirmation can be made by sequence analysis of the *LIPA* gene or by enzyme assay. Enzyme replacement with sebelipase-alfa therapy is an FDA-approved therapy (see Table 192-2)[25] to reduce hepatic and lipid abnormalities in children and adults.[A5] Hematopoietic stem cell therapy is under study.

POMPE DISEASE

Pompe disease is discussed in Chapters 191 and 389.

MUCOPOLYSACCHARIDOSES

The mucopolysaccharidoses are a group of disorders that result from defective lysosomal degradation and storage of glycosaminoglycans. These chronic, progressive storage disorders show clinical manifestations that vary by type.[26] Findings may include growth impairment, coarse facial features, dysostosis multiplex, organomegaly, and neurologic manifestations with regression. Affected individuals may develop ophthalmologic, cardiovascular, musculoskeletal, neurologic, gastrointestinal, and auditory complications. All types are inherited in an autosomal recessive pattern except for mucopolysaccharidosis II (Hunter syndrome), which is X-linked. With the advent of enzyme replacement therapy, improved management strategies, and the recognition of milder forms, more patients are now surviving into adulthood.

Clinical features of each type have similarities and distinctions. For example, patients with mucopolysaccharidosis type IS (Scheie syndrome) may present with normal to short stature, normal intelligence, degenerative joint disease, corneal opacities, and cardiac valve lesions. Patients with mucopolysaccharidosis II share the symptoms of mucopolysaccharidosis I but are more prone to have airway involvement, and their corneas are clear. Patients with mucopolysaccharidosis III (Sanfilippo) have primarily central nervous system manifestations, with mild somatic involvement; they develop progressive speech impairment as well as severe behavioral and sleep disturbances, and they later experience an unrelenting loss of skills and deterioration into a vegetative state, with death often in the third decade. Individuals with mucopolysaccharidosis IV have severe skeletal dysplasia, with normal intelligence in type A and a degenerative course in type B.

Screening is available by measuring urinary glycosaminoglycan concentration, fractionation, and analysis of oligosaccharides. Definitive diagnosis requires assay of enzyme activity in leukocytes and confirmation by molecular analysis.

Treatment is available in the form of enzyme replacement therapy for mucopolysaccharidosis I, mucopolysaccharidosis II, mucopolysaccharidosis IV, VI, and VII (see Table 192-3). In general, attention should focus on optimizing joint mobility and function by physical therapy and managing airway involvement that, if present, results from progressive storage in the soft tissue of the upper airway. Patients with mucopolysaccharidosis I, II, and VI should be monitored for the development of cervical myelopathy, which is due to dural thickening and which may have an impact on endurance, before ascending paralysis becomes apparent. Gene therapy is a promising experimental approach for mucopolysaccharidosis type I (Hurler disease)[27] and type VI.[28]

CYSTINOSIS

Cystinosis (Chapter 113) is a lysosomal storage disorder with three clinical phenotypes: the most common infantile or nephropathic form, an intermediate or juvenile-onset form, and a more benign form typically seen in adults and affecting primarily the eyes. Lysosomal cystine accumulation results from mutations in the *CTNS* gene that codes for cystinosin, which is a lysosomal carrier protein. Individuals with the nephropathic form have lysosomal accumulation of cystine that leads to multiorgan system involvement, including progressive renal disease, corneal crystals, and abnormalities of the thyroid gland, gonads, pancreas, muscle, and central nervous system. The adult form has only corneal crystals.

Diagnosis can be made by either finding elevated cystine in peripheral blood leukocytes or fibroblasts, observing cystine corneal crystals on slit lamp examination, or identifying pathologic variants in *CTNS*. Treatment includes oral cysteamine (see Table 192-2), to decrease the accumulation of cystine, as well as supportive care for renal, growth, and eye manifestations.[29] Cysteamine hydrochloride eyedrops dissolve corneal crystals and relieve photophobia.[30]

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For the General References and other additional features, please visit Elsevier eBooks+ at https://ebooks.health.elsevier.com.

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193 HOMOCYSTINURIA AND HYPERHOMOCYSTEINEMIA

MANUEL SCHIFF AND HENK J. BLOM

DEFINITION

Homocysteine, which is a nonprotein amino acid, is a key metabolic branch point metabolite between the trans-sulfuration and remethylation pathways of methionine metabolism. The many conditions associated with high homocysteine levels encompass a wide range of clinical manifestations. The normal level of plasma total homocysteine is below 15 μM. However, the threshold of total homocysteine above which a disorder of homocysteine metabolism should be suspected and a specific therapy should be initiated is about 50 μM. These metabolic conditions mainly include genetic recessively inherited disorders of homocysteine metabolism but also include acquired severe nutritional deficiencies in cobalamin (cbl, vitamin B_{12}) or folate.

Inherited disorders of homocysteine metabolism (E-Figs. 193-1 and 193-2) comprise disorders of the trans-sulfuration pathway with cystathionine β-synthase deficiency (or classical homocystinuria), and disorders of remethylation of homocysteine to methionine. The latter include 5,10-methylenetetrahydrofolate reductase (MTHFR) deficiency and inherited disorders of cobalamin absorption, transport, or intracellular metabolism,[1] as well as the very rare congenital folate malabsorption disorder. Intracellular remethylation defects share defective methionine synthesis as a common feature, MTHFR deficiency impairs 5-methyltetrahydrofolate (5-methylTHF) synthesis, cobalamin F and cobalamin J defects result in the defective lysosomal release of cobalamin. Cobalamin C and cobalamin D defects result in the abnormal cytosolic reduction and transport of hydroxocobalamin. Cobalamin F, cobalamin J, cobalamin C, and cobalamin D all impair the synthesis of both methyl- and adenosylcobalamin. Isolated deficiencies of methionine synthase (cobalamin E and cobalamin G) are associated with defective methyl cobalamin synthesis as well as the cobalamin D-homocysteine (cblD-Hcy) variant.

In cystathionine β-synthase deficiency, severe elevations of total homocysteine are accompanied by increased levels of plasma methionine. In remethylation disorders, however, the increased total homocysteine is associated with a low (or low-normal) plasma level of methionine owing to the ineffective conversion (remethylation) of homocysteine to methionine. Among the remethylation disorders, the cobalamin C defect (the most frequent inherited disorder of intracellular cobalamin metabolism) and MTHFR deficiency are by far the most frequent.

EPIDEMIOLOGY

Prevalence and Incidence

The worldwide incidence of cystathionine β-synthase deficiency is estimated to be about 0.038/100,000, with a higher incidence in Europe (about 0.72/100,000) and Latin America (about 0.45/100,000) and a lower incidence in Africa (about 0.20/100,000) and Asia (about 0.02/100,000).[2] Studies from the Saudi Arabian countries have shown incidence rates as high as 1 in 1800 live births. The incidence of severe homocysteine remethylation defects has never been evaluated but may be less than 1 in 500,000 live births.

PATHOBIOLOGY

The homocysteine that accumulates in both cystathionine β-synthase deficiency and remethylation defects is a well-known multisystem toxic agent. It exerts its effects either directly or indirectly via conversion to S-adenosylmethionine (AdoHcy) (see E-Fig. 193-1), which potentially inhibits many essential methyltransferases. Direct cellular homocysteine toxicity is found with endothelial damage and neuronal cell death. Homocysteine's effects on vascular endothelium predispose to thrombosis that may occur at any age and involve arteries and/or veins of any size. Specifically in cystathionine β-synthase deficiency, accumulation of homocysteine and/or cysteine deficiency induces modification of connective tissue proteins, possibly causing the skeletal and ocular manifestations of the disease. These effects are probably related to fibrillin, which is rich in cysteine and is a component of the periosteum, perichondrium, and zonular fibers of the ocular lens. The structure of fibrillin can be affected by the linking of homocysteine to cysteine; as a result, some clinical features of homocystinuria overlap with the fibrillin mutations seen in Marfan syndrome (Chapter 239).

Remethylation defects (cobalamin C and MTHFR) not only result in severe elevations of homocysteine but also in depletion of methionine that is required for the synthesis of proteins and of s-adenosylmethionine. The result is a reduction of cellular methylation capacity and accumulation of S-adenosylhomocysteine, especially in the central nervous system (CNS). The cobalamin C defect is an inborn error of intracellular cobalamin metabolism due to a mutation in *MMACHC*, the gene that encodes methylmalonic aciduria and homocystinuria type C protein. In the absence of normal MMACHC, neither methylcobalamin (the cofactor of methionine synthase) nor adenosylcobalamin (the cofactor of methylmalonyl-CoA mutase) is functional, and the result is secondary defects in methionine synthase (remethylation defect) and methylmalonyl-CoA mutase (methylmalonic acid accumulation), respectively (see E-Fig. 193-2). In MTHFR deficiency, the methyl donor 5-methylTHF cannot be produced, which secondarily reduces methionine synthase function and subsequent remethylation. The pathogenesis of MTHFR deficiency can be ascribed to homocysteine toxicity as well as depletion of cellular methionine. In addition, 5-methylTHF (the circulating form of folate) formation is hampered, thereby causing in particular cerebral folate deficiency. One unique mechanism in cobalamin defect is the trapping of 5-methylTHF owing to dysfunction of methionine synthase. Because MTHFR activity is irreversible, 5-methylTHF accumulates. Because this form of folate is not available for metabolism in the cobalamin C defect, it results in cellular folate deficiency. All these disorders are inherited in an autosomal recessive manner (Table 193-1).

CLINICAL MANIFESTATIONS

Cystathionine β-synthase Deficiency

As an autosomal recessive condition, cystathionine β-synthase deficiency can clinically affect homozygous or compound heterozygous individuals. Affected individuals are normal at birth after an uneventful pregnancy and delivery. If untreated, they progressively develop the core clinical symptoms of cystathionine β-synthase deficiency, which involve four major organ systems. The time of onset of clinical symptoms is extremely variable, and symptoms may first manifest during adulthood or even up to 60 years of age.[3]

TABLE 193-1 GENETIC DEFECTS ASSOCIATED WITH HOMOCYSTINURIA

FUNCTIONAL DEFECT	COMMON NAME	ENZYME DEFECT	GENE	CHROMOSOME LOCUS
Trans-sulfuration	"Classical" homocystinuria	Cystathionine β-synthase	*CBS*	21q22.3
Remethylation	Folate-dependent homocystinuria	Methylenetetrahydrofolate reductase	*MTHFR*	1p36.3
	cblE	Methyltransferase reductase	*MTRR*	5p15.2-p15.3
	cblG	Methionine synthase	*MTR*	1q43
Cobalamin transport	TC-II	Transcobalamin	*TCN2*	22q11.2-qter
	cblF	Lysosomal B_{12} translocase	*LMBRD1*	6q13
Cobalamin processing	cblC	Intracellular cobalamin chaperone?	*MMACHC*	1p34.1
	cblD	Cobalamin reductase?	*MMADHC*	2q23.2
	cblJ	Cobalamin processing?	*ABCD4*	14q24.3

ABSTRACT

In all inherited homocystinurias, accumulation of homocysteine causes subsequent neurotoxicity. The two distinctive clinical entities are: classical homocystinuria owing to deficiency in cystathionine β-synthase and rare inborn errors of cobalamin and folate metabolism. In the latter group, remethylation disorders of homocysteine to methionine (mainly cblC defect and 5,10-methylenetetrahydrofolate reductase [MTHFR] deficiency) are by far the most frequent. The natural history of cystathionine β-synthase deficiency is relatively well known and described. Similarly, clinical presentations of remethylation defects are becoming better recognized and reported. Thromboembolic disease is the leading feature shared by all homocystinurias. In cystathionine β-synthase deficiency, patients also exhibit eye, skeletal, and neuropsychiatric abnormalities. In remethylation defects, patients typically exhibit neuropsychiatric issues as well as hematological findings (i.e., megaloblastic bone marrow failure). The diagnosis is suggested by high total homocysteine plasma levels, with high methionine levels in cystathionine β-synthase and normal-low methionine levels in remethylation defects with methylmalonic acidemia/uria. Confirmatory diagnosis relies on molecular testing. Treatment aims at lowering (albeit not to normal levels) plasma total homocysteine with a low-protein diet and/or vitamin B_6, as well as betaine in cystathionine β-synthase deficiency. In remethylation defects, betaine is given in association with vitamin B_{12} and/or B_9, either orally or intramuscular depending on the site of the defect.

KEYWORDS

homocystinuria
homocysteine
remethylation defects
cblC
inborn errors of metabolism
methionine
betaine
hydroxocobalamin
vitamin B_{12}
folates

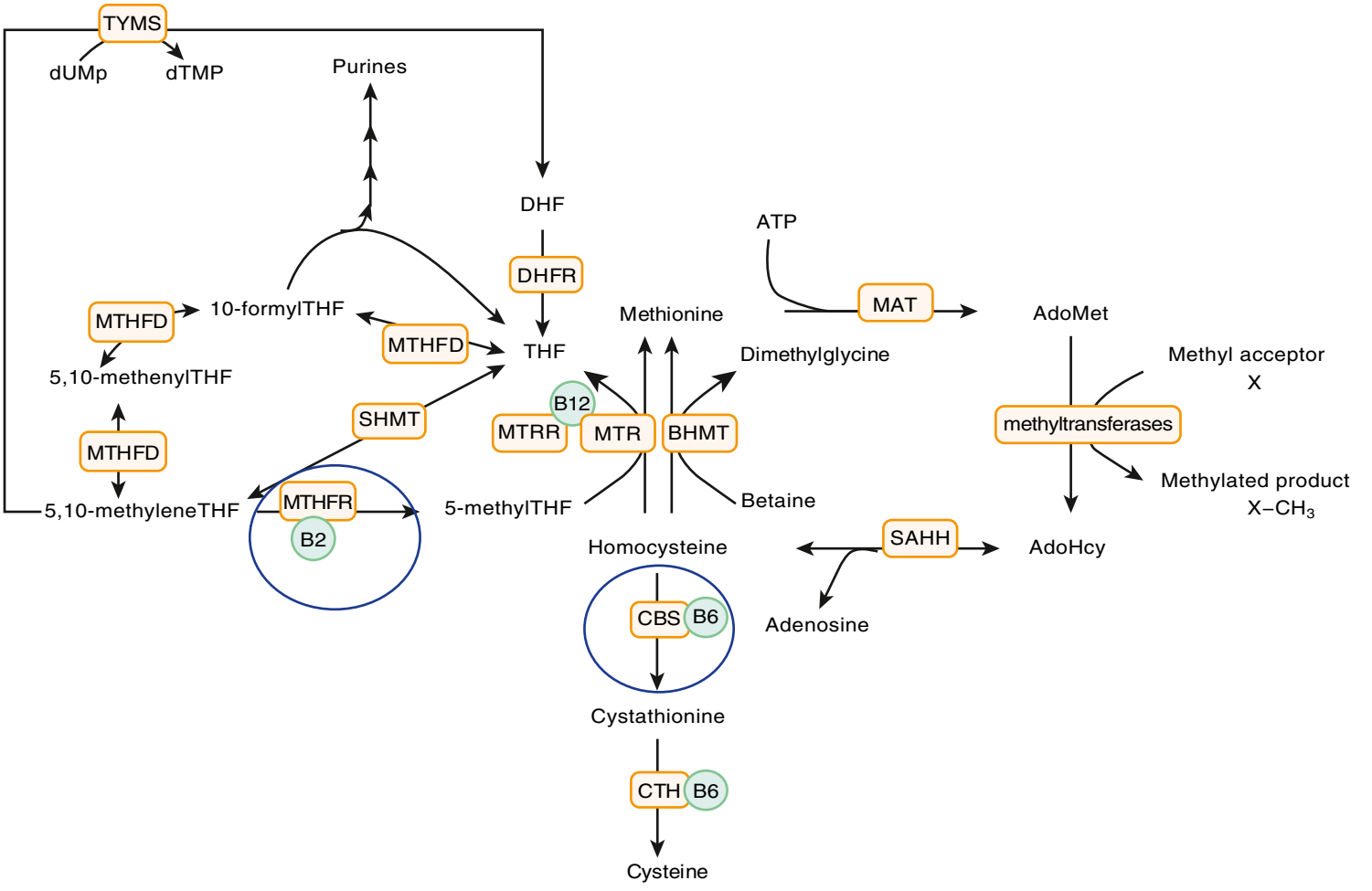

E-FIGURE 193-1. Homocysteine metabolism and the folate cycle. AdoHcy = S-adenosylhomocysteine; AdoMet = S-adenosylmethionine; ATP = adenosine triphosphate; BHMT = betaine-homocysteine methyltransferase; CBS = cystathionine β-synthase; CTH = cystathionine γ-lyase; DHF = dihydrofolate; DHFR = dihydrofolate reductase; dUMP = deoxyuridine monophosphate; dTMP = deoxythymidine monophosphate; FAICAR = formyl-AICAR; MAT = methionine-adenosyltransferase; MTHFD = methylenetetrahydrofolate dehydrogenase/methenyltetrahydrofolate cyclohydrolase/formyltetrahydrofolate synthetase; MTHFR = methylenetetrahydrofolate reductase; MTR = methionine synthase; MTRR = methionine synthase reductase; SAHH = S-adenosylhomocysteine; SHMT = serine-hydroxymethyltransferase; THF = tetrahydrofolate; TYMS = thymidylate synthase. The two conditions leading to accumulation of homocysteine (CBS and MTHFR) are surrounded by a blue circle.

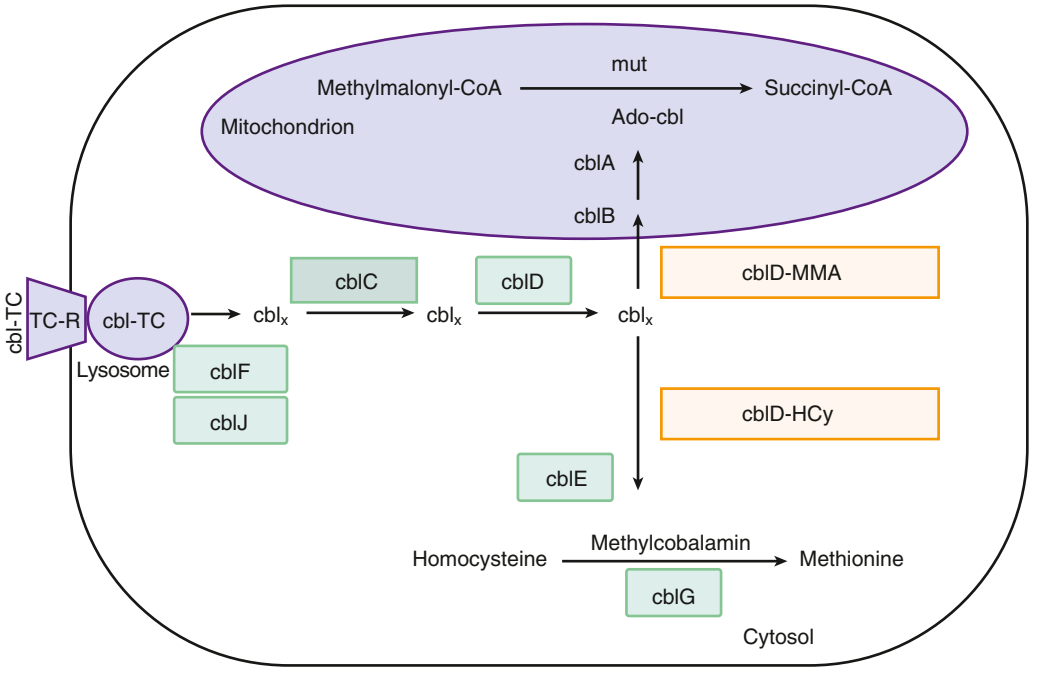

E-FIGURE 193-2. Intracellular cobalamin metabolism pathway and its defects. To date, 10 complementation-group defects of the cobalamin pathway have been described. After binding to transcobalamin receptor (TC-R), cobalamin bound to TC enters the cell via lysosome-mediated endocytosis and is released through proteolysis. Export from the lysosome into the cytoplasm is defective in patients with the cobalamin F and recently described cobalamin J defects. The steps in the cytosol after lysosomal release are defined by the complementation groups cobalamin C and cobalamin D. The exact form of cobalamin at this stage is unclear (as indicated by "cblx"). In the cytosol, cobalamin is reductively methylated by methionine synthase reductase (cobalamin E) to methylcobalamin, the cofactor for methionine synthase (cobalamin G). After its transport into the mitochondrion, cobalamin is converted to adenosylcobalamin, the cofactor for methylmalonyl-coenzyme A (CoA) mutase (mut), by cobalamin adenosyltransferase (cobalamin B). Cobalamin D defect can cause isolated methylmalonic aciduria (cobalamin D-MMA complementation group), isolated homocystinuria (cobalamin D-homocysteine), or both (cobalamin D). In all the above-mentioned conditions with defective remethylation (TC and TC-R deficiency, cobalamin F, cobalamin J, cobalamin C, cobalamin D, cobalamin D-homocysteine, cobalamin E, and cobalamin G defects), there is homocysteine accumulation due to dysfunction in methionine synthesis. Ado-cbl = adenosylcobalamin; cbl = cobalamin; cblC = cobalamin C; cblD = cobalamin D; cblE = cobalamin E; cblF = cobalamin F; cblG = cobalamin G; CoA = coenzyme A; Hcy= homocysteine; MMA = methylmalonic acid; mut = methylmalonyl-CoA mutase; TC = transcobalamin; TC-R = transcobalamin receptor.

Central Nervous System

Developmental delay and mental retardation affect about 60% of the patients to a variable degree of severity. Seizures, electroencephalogram abnormalities, and psychiatric disturbances occur in approximately half of the cases. Focal neurologic signs may be a consequence of cerebrovascular accidents. IQ in individuals with untreated homocystinuria ranges widely, from 10 to 138. In B_6 (pyridoxine)-responsive untreated individuals, the mean IQ is 79 versus 57 for those who are B_6-nonresponsive. Neuropsychiatric symptoms can include schizophrenia or autism-like features.

Eye

Dislocation of the ocular lens (ectopia lentis), myopia, and glaucoma are frequent, severe, and characteristic complications.[4] Adults can present with isolated quick loss of diopter, which is the most common symptom before diagnosis. Retinal detachment and degeneration, optical atrophy, and cataracts may eventually appear. Myopia often precedes lens dislocation. Ectopia lentis is detected in most untreated patients from 5 to 10 years of age and in nearly all untreated patients by the end of the fourth decade. Once ectopia lentis has occurred, a peculiar trembling of the iris (iridodonesis) following eye or head movement may be observed.

Skeleton

Individuals are often tall and slender with a marfanoid habitus and are prone to osteoporosis (Chapter 225), which is almost invariable. Frequent consequences are scoliosis and a tendency toward pathologic fractures and vertebral collapse. Homocystinuric patients tend to be tall, with thinning and elongation (dolichostenomelia) of long bones near puberty, enlarged metaphyses and epiphyses, especially at the knees, and arachnodactyly, present in about half of the patients. Other bone deformities include genu valgum, pes cavus, and pectus carinatum or excavatum. Restricted joint mobility, particularly at the extremities, contrasts with the joint laxity observed in Marfan syndrome.

Vascular System

The main acute manifestation in adulthood is thromboembolic disease, which can occur in arteries and veins[5] of all parts of the body. Thromboembolism constitutes the major cause of morbidity and mortality in affected individuals.

Remethylation Disorders

Clinical signs of remethylation defects are mainly neurologic, but isolated arterial and venous occlusive disease may present at any age. Neonatal and early-onset patients exhibit acute neurologic distress. In childhood, patients exhibit nonspecific developmental delay often associated with acquired microcephaly. Adolescents and adults exhibit, after a period of normal development or mild developmental delay, a rapid mental or psychiatric deterioration. In adults, neuropsychiatric abnormalities include ataxia, cognitive impairment, and psychosis.[6] Patients may typically have signs of subacute combined degeneration of the spinal cord or present with isolated stroke.

In cobalamin C disease, hematologic signs (megaloblastic bone marrow leading to macrocytic anemia or pancytopenia) are common. Severe and occasionally fatal multisystem complications owing to a thrombotic microangiopathy may include hemolytic uremic syndrome, cardiomyopathy, and interstitial pneumonia. Pulmonary hypertension has also been reported. In addition, a peculiar and poorly understood retinopathy with nystagmus is often present, especially in early onset severe presentations. Hydrocephalus is also a complication in remethylation disorders.

DIAGNOSIS

If homocystinuria is suspected clinically, initial laboratory testing should include a complete blood count with blood smear (to look for characteristics of vitamin B_{12}/folate deficiency; Chapter 150), as well as blood levels of folate, vitamin B_{12}, and total plasma homocysteine. Metabolic biomarkers (plasma methionine and methylmalonic acid) can then be obtained selectively to differentiate among the various forms of homocystinuria (Table 193-2).[7] If total homocysteine is below 50 μM, the probability of a disorder of homocysteine metabolism is very low but not excluded. If the methionine level is elevated or high-normal with low cysteine level, cystathionine β-synthase deficiency is most likely, whereas decreased or low-normal methionine level plus elevated total homocysteine points to remethylation defects. In cobalamin C disease, patients have megaloblastic bone marrow failure with normal vitamin B_{12} and folate blood levels. Nutritional vitamin B_{12} or folate deficiencies and other genetic causes of cobalamin and folate metabolism should also be considered. The plasma methylmalonic acid level is a useful diagnostic clue in remethylation disorders: it is elevated in patients who have a cobalamin C defect or disorders of cobalamin intake, absorption, and transport, whereas it is normal in MTHFR and disorders that solely affect methionine synthase function

TABLE 193-2 CLINICAL FEATURES OF HOMOCYSTINURIAS

	BIOCHEMICAL FEATURES			*CLINICAL FEATURES*	
CLASS	**TOTAL PLASMA HOMOCYSTEINE**	**PLASMA METHIONINE**	**METHYLMALONIC ACID URINE OR PLASMA**	**SYSTEM**	**SIGNS**
Cystathionine β-synthase deficiency	↑	↑	–	Ocular	Ectopia lentis, myopia, glaucoma, optic atrophy, retinal detachment
				Skeletal	Elongated and thinned bones, arachnodactyly, genu valgum, pectus malformation, scoliosis
				Vascular	Thromboembolic events (arterial or venous)
				Neurologic	Mental retardation in untreated cases, cerebrovascular thromboses, seizures
					Psychiatric disorders, personality disorder
5,10-Methylenentetrahofolate reductase (MTHFR) deficiency	↑	↓	–	Vascular	Thromboses
				Neurologic	Variable: psychiatric to severe neurologic
Transcobalamin	↑	–/↓	+	Hematologic	Early-onset pancytopenia, macrocytosis
Cobalamin F, cobalamin J	↑	–/↓	+	Pansystemic	Methylmalonic acid urine or plasma, macrocytosis, stomatitis, congenital heart defects
Cobalamin C, cobalamin D	↑	↓	+	Hematologic	Pancytopenia
				Neuropsychiatric	
				Systemic (cobalamin C)	Hemolytic uremic syndrome
Cobalamin E, cobalamin G	↑	↓	–	Vascular	Thromboses
				Hematologic	Pancytopenia
				Neurologic	
				Ocular	Retinopathy (macular involvement) in early onset cobalamin deficiency

HUS = hemolytic uremic syndrome; Meth = plasma methionine; MMA = methylmalonic acid urine or plasma; tHcy = total plasma homocysteine.

(mainly cobalamin E and cobalamin G defects). Cystathionine β-synthase deficiency can cause secondary vitamin B_{12} and folate deficiency, and remethylation defects can cause secondary folate deficiency. In MTHFR, folate levels (serum, red blood cells, CSF) are usually low. Definitive diagnosis can be confirmed at the molecular level by sequence analysis of the putative gene or direct homocystinurias panel sequencing (see Table 193-1).[8] If the molecular studies are not conclusive, functional studies can be performed in fibroblasts or lymphocytes.

TREATMENT

The general therapeutic goal is to reduce total homocysteine accumulation and, for remethylation disorders, to bypass the remethylation defect, thereby maintaining normal methionine and folate concentrations. Published treatment guidelines are not evidence-based because of the rarity of these disorders.[9] Although normalization of plasma total homocysteine levels is difficult if not impossible to achieve, treatment prevents further thromboembolic events even when the total homocysteine levels remain clearly above the normal range. Decreasing total homocysteine to 50 to 100 μM is a reasonable goal in many patients with cystathionine β-synthase deficiency, whereas 50 to 70 μM should be the goal for remethylation disorders.

For remethylation disorders, treatment is combined supplementation of vitamin B_{12}, vitamin B_9 (folate), vitamin B_6, betaine, and methionine, although the dosage and route of administration may vary with the type of defect. For cystathionine β-synthase deficiency, therapy is based on: increasing residual cystathionine β-synthase activity with the use of vitamin B_6 (in B_6-responsive patients); decreasing the load on the affected pathway and replacing the deficient products with a low methionine diet, limitation of natural proteins, methionine-free amino acid mixture, special low-protein foods, and supplementation of cystine to increase cysteine; and increasing remethylation to methionine with folate, vitamin B_{12}, and betaine to reduce the total accumulation of homocysteine.

Vitamin B_{12}

In remethylation disorders, initial treatment includes daily parenteral administration of hydroxocobalamin (1 mg/day). If MTHFR deficiency is confirmed, treatment can be switched to oral hydroxocobalamin (1 mg/day to 1 mg/week), but lifelong high-dose intramuscular hydroxocobalamin injections are needed in the cobalamin C defect. In cystathionine β-synthase deficiency, hydroxocobalamin may be given orally (1 mg/day to 1 mg/week) according to the serum B_{12} level to prevent cobalamin deficiency (Chapter 150).

Folate

For folate supplementation, folinic acid is the preferred form because it is the most stable and because folic acid may exacerbate cerebral CH_3-tetrahydrofolate deficiency, especially in MTHFR deficiency. In MTHFR deficiency, folinic acid should be given orally at 5 to 30 mg daily or higher under expert guidance. In cystathionine β-synthase deficiency, folinic acid should be given orally at 1 to 5 mg/day. Moreover, such folate repletion may be necessary to permit a pyridoxine (B_6) response, which means that pyridoxine responsiveness should always be tested after correction of the depletion of folate. In cobalamin C defect, the daily dose varies from 5 to 30 mg.

Vitamin B_6

In remethylation disorders, B_6 might theoretically enhance homocysteine removal and may be given at a low dose (50 to 100 mg/day). In cystathionine β-synthase-deficient patients, vitamin B_6 (or pyridoxine) is given orally at 10 mg/kg/day (500 mg/day, maximum adult dose) for 4 to 6 weeks, after which total homocysteine is determined to evaluate whether B_6 administration has been effective in lowering (or even normalizing) total homocysteine levels. Patients who achieve plasma total homocysteine levels below 50 μM on pyridoxine are responsive and do not need any other treatment. If the level falls by more than 20% but remains above 50 μM, additional treatment should be considered (i.e., diet and/or betaine). If total homocysteine level falls by less than 20% on pyridoxine, the patient is likely to be unresponsive.[10] B_6 should always be combined with folinic acid and vitamin B_{12}. In B_6-responsive patients, long-term therapy with pyridoxine and folate prevents further deterioration.

For pyridoxine-responsive cystathionine β-synthase-deficient patients, pyridoxine should be kept at the lowest dosage needed (no more than 500 mg/day) to achieve adequate metabolic control so as to avoid high-dose pyridoxine toxicity on the peripheral nervous system. In pyridoxine-nonresponsive patients, a daily dosage of 50 to 100 mg of pyridoxine can be added to the treatment in an attempt to enhance the low residual cystathionine β-synthase activity.

Betaine

Betaine, which is derived from choline and is a substrate for the enzyme betaine-homocysteine methyltransferase, acts as a methyl donor and decreases homocysteine levels. Doses have ranged from 150 to 250 mg/kg/day in children and 5 to 10 g/day in adults, usually given in divided doses two or three times daily.[A1]

In remethylation disorders, betaine increases systemic methionine levels, especially in patients with MTHFR deficiency. In cystathionine β-synthase deficiency, betaine usually increases plasma methionine and lowers plasma total homocysteine levels. Methionine levels should be kept below 1000 μM because of the risk of brain edema at higher levels. In B_6-nonresponsive early-treated patients, a low-methionine diet alone can be sufficiently successful that betaine may not be needed in highly adherent patients. In poorly adherent patients, however, the total plasma homocysteine may not decrease sufficiently with low-methionine diet alone; in this situation, betaine (5 to 10 g/day) is needed.

Oral Methionine

For patients with remethylation defects, methionine depletion is rarely corrected by betaine therapy alone. The combination of oral methionine (50 to 100 mg/day) plus betaine (5 to 10 g/day) usually corrects methionine depletion.

PREVENTION

Low-dose aspirin (50 to 100 mg daily) is recommended to prevent thrombosis in cystathionine β-synthase deficiency. Smoking and oral contraceptive agents should be avoided in all homocystinurias.

In all homocystinurias, nitrous oxide is contraindicated because it inhibits methionine synthase. In cystathionine β-synthase deficiency, surgery poses serious risks and should be avoided if possible, especially when the total homocysteine level is above 50 μM. However, it can be performed safely if the total homocysteine level is below 50 μM (or has been lowered to such levels after a few days of an emergency dietary regimen) provided that the patient is well hydrated (1.5 times IV maintenance) and treated with low-molecular-weight heparin.

PROGNOSIS

If MTHFR-deficient patients are treated in the neonatal period, the outcome is good.[11] If undiagnosed or untreated or late treated, patients have a very poor outcome with severe impairments. Early-onset cobalamin C-defective patients have a poor long-term outcome, with multisystem involvement, thrombotic microangiopathy, and retinopathy.

In cystathionine β-synthase deficiency, pyridoxine responsiveness generally correlates with higher residual enzyme activity, and the outcome is significantly better than for unresponsive cases, with or without treatment. Skeletal, ocular, vascular, and neurologic risks are all reduced with successful treatment. Without the early institution of treatment, the median IQ in a large outcome study was 57 for unresponsive patients and 78 for responsive patients. With early treatment, pyridoxine-unresponsive patients have a nearly normal median IQ. For patients who are responsive and adherent to treatment, the prognosis for intellectual development is very good, especially with diet alone. However, in cases of poor adherence, significant elevations in total homocysteine generally persist, and some increased risk for vascular complications probably remains.

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194 THE PORPHYRIAS

RICHARD J. HIFT

DEFINITION

The porphyrias, which are a group of disorders that arise from disturbances in heme synthesis, are characterized by the accumulation of porphyrins or their precursors on the heme biosynthetic pathway. Most porphyrias are genetic and heritable, except for the sporadic form of porphyria cutanea tarda and rare instances of porphyria arising from acquired somatic mutations.

Approximately 90% of heme biosynthesis occurs within the erythron, where it leads to the production of heme for incorporation into hemoglobin. The remainder is synthesized in all other nucleated cells of the body, thereby producing heme for incorporation into hemoproteins. The liver is the predominant site of nonerythroid heme synthesis, with much of the product being incorporated into enzymes of the cytochrome P450 (CYP) system.

The porphyrias may be classified into two categories: the erythropoietic and hepatic porphyrias. Disturbances in erythroid heme biosynthesis give rise to congenital erythropoietic porphyria and protoporphyria. Disturbances in nonerythroid heme biosynthesis give rise to five forms of hepatic porphyria: acute intermittent porphyria, variegate porphyria, porphyria cutanea tarda, hereditary coproporphyria, and 5-aminolevulinate dehydratase porphyria.

A clinical classification divides the porphyrias into a further two cross-cutting groups (Table 194-1). The acute porphyrias are characterized by the potential to develop a fatal acute attack (acute intermittent porphyria, variegate porphyria, hereditary coproporphyria, and 5-aminolevulinate dehydratase porphyria), whereas the nonacute porphyrias (porphyria cutanea tarda, congenital erythropoietic porphyria, erythropoietic protoporphyria, and X-linked protoporphyria) present with cutaneous manifestations alone.

EPIDEMIOLOGY

The reported prevalence of disease-associated mutations in Europe is 9.2 per million for erythropoietic protoporphyria, 5.9 per million for acute intermittent porphyria, and 3.2 per million for variegate porphyria. Hereditary coproporphyria has a lower prevalence, whereas congenital erythropoietic porphyria and 5-aminolevulinate dehydratase porphyria are very rare. The figures for North America are believed to be similar.

The clinical penetrance of the porphyrias is low, and the prevalence of asymptomatic carriers exceeds the prevalence of clinically affected patients. Penetrance is higher, about 23%, in affected relatives of clinically expressed patients. As a result of this low penetrance, the prevalence of potentially pathogenic mutations is thought to be much higher. For acute intermittent porphyria, for example, the prevalence of mutations has been estimated to be 50 per million. The prevalence of porphyria cutanea tarda in Europe is variously estimated at 40 to 200 per million. Founder effects have led to a

TABLE 194-1 SUMMARY OF THE PORPHYRIAS

PORPHYRIA	PROTEIN OR ENZYME	KEY CLINICAL FEATURES AND LONG-TERM COMPLICATIONS	INHERITANCE
ACUTE PORPHYRIAS			
More Common			
Acute intermittent porphyria (AIP)	Hydroxymethylbilane synthase *(HMBS), also known as porphobilinogen deaminase (PBGD)*	Acute attacks Hypertension Chronic kidney disease Hepatocellular carcinoma	Autosomal dominant
Variegate porphyria (VP)	Protoporphyrinogen oxidase *(PPOX)*	Vesiculo-erosive skin disease Acute attacks Hepatocellular carcinoma	Autosomal dominant
Less Common			
Hereditary coproporphyria (HCP)	Coproporphyrinogen oxidase *(CPOX)*	Vesiculo-erosive skin disease Acute attacks	Autosomal dominant
Rare			
5-Aminolevulinate dehydratase porphyria (ALADP)	Porphobilinogen synthase *(PBGS), also known as aminolevulinate dehydratase (ALAD)*	Acute attacks Neuropathy	Autosomal recessive
NONACUTE PORPHYRIAS			
More Common			
Porphyria cutanea tarda (PCT)	Uroporphyrinogen decarboxylase *(UROD)*	Vesiculo-erosive skin disease Associated with iron-loading, alcoholic liver disease, hepatitis C, HIV infection, renal failure, and other disorders	Acquired, sometimes on a background of an inherited mutation
*Protoporphyria			
Erythropoietic protoporphyria (EPP) (>90%)	Ferrochelatase *(FECH)*	Immediate photosensitivity Cholelithiasis, liver disease	Autosomal recessive; usually as a pathogenic mutation in trans to a common *FECH* polymorphism
X-linked protoporphyria (XLP) (<10%)	5-Aminolevulinate synthase *(ALAS)*	Immediate photosensitivity Cholelithiasis, liver disease	X-linked
CLPX-associated protoporphyria (rare)	Caseinolytic mitochondrial matrix peptidase chaperone subunit X *(CLPX)*	Immediate photosensitivity Cholelithiasis, liver disease	Autosomal dominant
Rare			
*Congenital erythropoietic porphyria (CEP)		Immediate photosensitivity Cholelithiasis, liver disease	
UROS-associated CEP (>99%)	Uroporphyrinogen III synthase *(UROS)*	Vesiculo-erosive skin disease Severe photomutilation	Autosomal recessive
GATA1-associated CEP (<1%)	GATA-binding factor 1 *(GATA1)*		X-linked

*Erythropoietic porphyrias. The remainder are classified as hepatic porphyrias.
HIV = human immunodeficiency virus.

ABSTRACT

The porphyrias are a group of disorders that arise from disturbances in heme synthesis and are characterized by the accumulation of porphyrins or their precursors. Most porphyrias are genetic and heritable. They are classified as acute and nonacute. The acute porphyrias (acute intermittent porphyria, variegate porphyria, hereditary coproporphyria, and 5-aminolevulinate dehydratase porphyria) are characterized by the acute attack: a metabolic crisis associated with severe abdominal pain, autonomic overactivity, metabolic disturbance, and neurologic dysfunction. Acute attacks are often induced by drugs that increase the requirement for heme. The nonacute porphyrias are characterized by vesiculo-erosive skin disease in sun-exposed areas (porphyria cutanea tarda and congenital erythropoietic porphyria) or immediate photosensitivity (erythropoietic protoporphyria and X-linked protoporphyria). Porphyria cutanea tarda is typically an acquired disorder, arising from an enzyme inhibition in association with factors such as iron overload, alcohol, estrogens, and renal failure. The porphyrias are diagnosed by demonstrating characteristic patterns of the accumulation of porphyrins in urine, stool, plasma, and erythrocytes. Patients should then be tested to determine the underlying molecular defect, which can then be sought in family members. The acute attack is treated with a hemin infusion. Givosiran may be used to prevent recurrent attacks. The prognosis is usually good. Recognized long-term complications of the acute porphyrias include recurrent attacks, painful neuropathy, hypertension, chronic kidney disease, and hepatocellular carcinoma. Skin disease is treated symptomatically, with sun avoidance and sun protection. Protoporphyria responds well to afamelanotide.

KEYWORDS

porphyria
porphyrin
acute attack
photosensitivity
aminolevulinate
porphobilinogen
porphyrogenic
heme
heme arginate
givosiran

high prevalence of acute intermittent porphyria in northern Sweden (23 per million) and of variegate porphyria among the Dutch-descended immigrant population of South Africa (1.2 per thousand in this population).

PATHOBIOLOGY

The initial step in the heme biosynthetic pathway (Fig. 194-1) is the synthesis of 5-aminolevulinate, catalyzed by the enzyme 5-aminolevulinate synthase. The nonerythroid enzyme, 5-aminolevulinate synthase 1 (ALAS1), is strongly expressed in the liver and is encoded by the *ALAS1* gene. The erythroid form, 5-aminolevulinate synthase 2 (ALAS2), is encoded by the *ALAS2* gene on the X chromosome. The two genes share 73% homogeneity. The remaining genes are common to both systems.

Regulation of Heme Biosynthesis

The synthesis of 5-aminolevulinate is typically the rate-limiting step in the pathway. ALAS1 and ALAS2 are regulated by different mechanisms, and mutations in regulatory genes (*GATA1* and *CLPX*) can result in phenotypically expressed porphyria in the absence of a defect within the primary enzymes of the heme biosynthetic pathway.

Transcription of *ALAS1* in the liver is upregulated in response to a reduction of heme within the hepatocyte and conversely is suppressed by heme replenishment. ALAS2 is not subject to repression by exogenous hemin, nor is it induced by factors responsible for induction of hepatic ALAS1. Instead, ALAS2 is primarily regulated by the availability of iron. When the intracellular iron pool is reduced, iron regulatory proteins IRP1 and IRP2 bind to an iron-responsive element in the 5′ region of the *ALAS2* mRNA, thereby preventing translation and blocking the synthesis of ALAS2.

Heme Biosynthetic Pathway

After 5-aminolevulinate synthase–mediated synthesis, 5-aminolevulinate is converted into porphobilinogen, which has a monopyrrolic ring structure (E-Fig. 194-1). Four porphobilinogen molecules are then combined to form the linear tetrapyrrole hydroxymethylbilane, which is then enzymatically cyclized by the enzyme uroporphyrinogen-III synthase, thereby resulting in the tetrapyrrolic macrocycle, uroporphyrinogen-III. Sequential modification of the porphyrinogen side chains of uroporphyrinogen-III results in the production of a sequence of porphyrinogens and their oxidized counterparts, the porphyrins. In the final step, iron is incorporated into the tetrapyrrolic macrocycle, thereby resulting in the functional heme molecule. The enzymes 5-aminolevulinate synthase, coproporphyrinogen oxidase, protoporphyrinogen oxidase, and ferrochelatase are all mitochondrial, whereas the remaining enzymes are cytosolic. Heme synthesis therefore begins and ends in the mitochondrion, with intermediate metabolism occurring in the cytoplasm.

Characteristics of the Porphyrins

5-Aminolevulinate and porphobilinogen are classified as porphyrin precursors, whereas the subsequent tetrapyrrolic structures are known as the porphyrins. The porphyrin precursors and the initial porphyrins in the pathway (5-aminolevulinate, porphobilinogen, uroporphyrin, and coproporphyrin) are water-soluble, circulate freely in the plasma, and are largely excreted in urine. Protoporphyrin is hydrophobic, may be protein bound in the plasma, and is subject to biliary excretion, eventually being excreted in the stool. Coproporphyrin has intermediate water solubility and is found in both urine and stool. The acute attack is always associated with elevations in the precursors in urine and plasma, whereas skin disease is characteristic of the disorders in which substantial amounts of porphyrin accumulate in plasma and skin, as well as variably in urine and feces.

Acute Hepatic Porphyrias

Acute intermittent porphyria, variegate porphyria, and hereditary coproporphyria are inherited as autosomal dominant disorders. 5-Aminolevulinate dehydratase porphyria is autosomal recessive and rare. The dominant porphyrias are associated with numerous family-specific mutations. Rare cases of homozygous acute intermittent porphyria variegate porphyria, and hereditary coproporphyria have been described.

Nonacute Porphyrias

In approximately 75% of patients with porphyria cutanea tarda, the *UROD* gene is normal, and symptoms result from the inhibition of UROD enzymatic activity by uroporphomethene, which is an oxidative product of the normal substrate uroporphyrin. Porphyria cutanea tarda is associated with hepatic iron overload, significant alcohol use, hepatitis C virus infection, HIV infection, estrogen treatment, renal failure, lymphoma, systemic lupus erythematosus, and exposure to toxins such as hexachlorobenzene. In the other 25%, an inherited mutation results in reduced UROD activity (familial porphyria cutanea tarda). Since this mutation is insufficient on its own to cause symptoms, clinically expressed patients with familial porphyria cutanea tarda frequently will be found to have one or more of the precipitating conditions listed above.

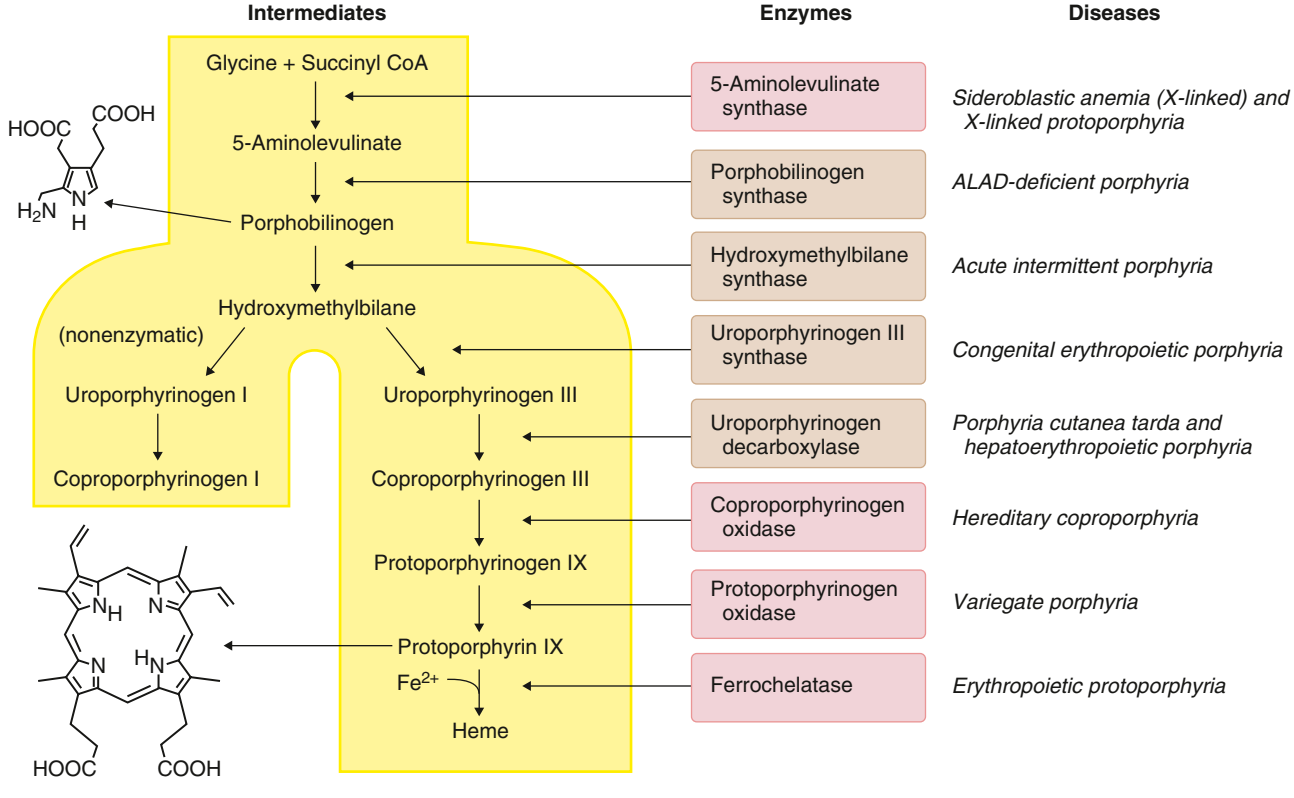

FIGURE 194-1. The heme biosynthetic pathway. Heme is synthesized via a series of porphyrin precursor and porphyrin intermediates, catalyzed by the enzymes listed on the *left* of the figure. The form of porphyria associated with abnormal enzyme function is shown on the *right*.

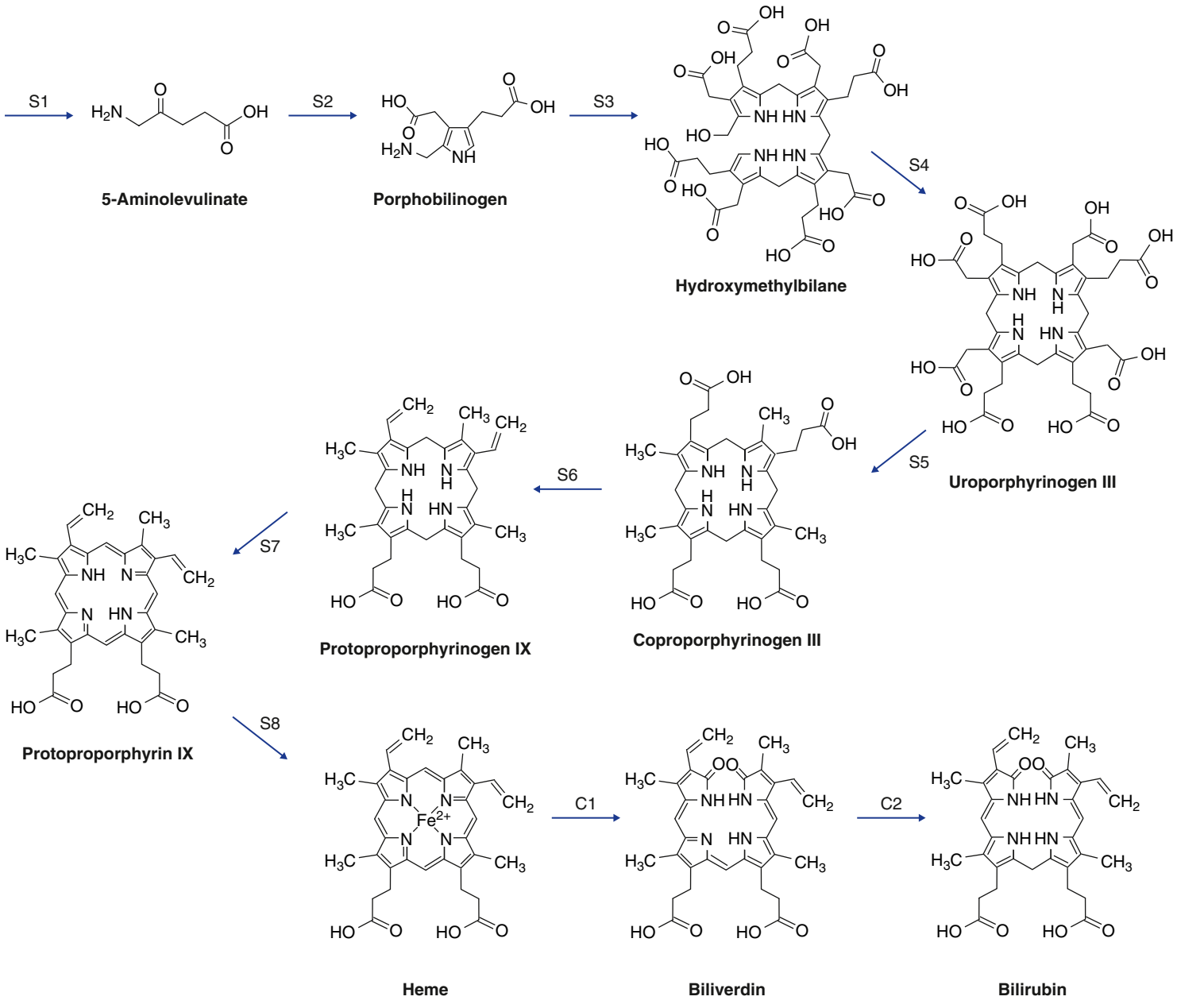

E-FIGURE 194-1. **Heme biosynthesis and catabolism.** *S1-S3. Synthesis of the porphyrin precursors and the first tetrapyrrole.* S1. 5-Aminolevulinate is synthesized from glycine and succinyl-CoA, catalyzed by the mitochondrial enzyme 5-aminolevulinate ALA synthase. S2. Two molecules of 5-aminolevulinate condense to form a cyclic pyrrole, porphobilinogen, catalyzed by the cytosolic enzyme porphobilinogen synthase. S3. Four molecules of porphobilinogen are combined to form an open tetrapyrrole, hydroxymethylbilane, catalyzed by the cytosolic enzyme hydroxymethylbilane synthase. *S4-S8. Sequential modification of tetrapyrrolic porphyrinogens, porphyrins, and heme.* S4. The cytosolic enzyme uroporphyrinogen III synthase (UROS) catalyzes ring closure, thereby forming a closed macrocycle and the series 3 isomer of the first porphyrin, uroporphyrinogen III. In the absence of the enzyme, spontaneous cyclization occurs, thereby giving rise to uroporphyrinogen I. This nonphysiologic isomer is not available for further enzymatic conversion. S5. Uroporphyrinogen III undergoes four sequential decarboxylation reactions all catalyzed by the cytosolic enzyme uroporphyrinogen decarboxylase (UROD), producing sequentially heptacarboxylic porphyrinogen, hexacarboxylic porphyrinogen, pentacarboxylic porphyrinogen (not shown), and coproporphyrinogen. S6. Coproporphyrinogen-III re-enters the mitochondrion and is oxidized to protoporphyrinogen-IX by coproporphyrinogen oxidase (CPOX). S7. Protoporphyrinogen IX is oxidized to protoporphyrin IX by the mitochondrial enzyme protoporphyrinogen oxidase (PPOX). S8. Elemental iron is inserted into the macrocycle by the mitochondrial enzyme ferrochelatase (FECH), forming heme. *C1-C2. Heme catabolism.* C1. Catalyzed by heme oxygenase (HO), the tetrapyrrolic macrocycle is opened, thereby releasing iron and carbon monoxide and forming biliverdin. C2. A reduction step catalyzed by biliverdin reductase (BVR) results in bilirubin, which is bound to albumin and other plasma proteins and excreted.

Iron loading may be secondary to known causes (Chapter 196), and the C282Y mutation in the *HFE* gene commonly found in Caucasian patients with hereditary hemochromatosis is overrepresented in porphyria cutanea tarda. Alcohol, toxins, and hepatitis C virus infection may induce porphyria cutanea tarda via the downregulation of hepcidin and oxidative stress. Rare cases of homozygous porphyria cutanea tarda, known as hepatoerythropoietic porphyria, have been described.

Erythropoietic Protoporphyria

Erythropoietic protoporphyria is associated with at least three gene variants. The classic form, which accounts for approximately 90% of cases, is a recessive disorder associated with ferrochelatase mutations. Of these 90%, approximately 5% of cases are homozygous, whereas the remaining 95% carry a disease-associated mutation on one allele and have inherited the common *FECH**IVS3-48C polymorphism on the other.[1] The summative effect of the family-specific mutation and low-expression allele is sufficient to reduce ferrochelatase activities to a level below approximately 35%. The final step in heme biosynthesis, the incorporation of iron into protoporphyrin, is therefore retarded, and ALAS2 may be induced; excessive amounts of iron-free protoporphyrin accumulate in the plasma and are subsequently taken up into the hepatocyte. The prevalence of the low-expression polymorphism in the population varies from 1% in West African to 12% in European and 47% in Japanese populations. As a result of the high prevalence of the polymorphism in Caucasian populations, erythropoietic protoporphyria presents clinically more frequently than is expected of a recessive disorder, and its inheritance has been described as "pseudo-dominant."

Approximately 5% of families with erythropoietic protoporphyria have normal *FECH* genes but carry X-linked mutations in the *ALAS2* gene. These gain-of-function mutations cause an increased flux of porphyrins through the erythroid heme biosynthetic pathway. Ferrochelatase and iron availability then become rate-limiting, such that substantial amounts of protoporphyrin cannot be further metabolized to heme but are diverted to the plasma, thereby replicating the erythropoietic protoporphyria phenotype. The penetrance of this form of protoporphyria is near 100%.

A third variant of erythropoietic protoporphyria is associated with mutations in the *CLPX* gene, which tightly regulates vertebrate erythroid heme synthesis. The result can be both upregulation of heme synthesis and inhibition of the terminal enzymes of the pathway, thereby leading to accumulation of protoporphyrin.[2]

Congenital Erythropoietic Porphyria

Congenital erythropoietic porphyria is an autosomal recessive disorder associated with homozygosity or compound heterozygosity for mutations in the *UROS* gene. A number of patients with congenital erythropoietic porphyria have normal *UROS* but carry a mutation in the X-linked gene that encodes the GATA1 transcription factor, thereby causing a reduction in gene expression.

Somatic Mutations Resulting in Acquired Porphyria

Very rarely, non–germline tissue-specific mutations may result in manifest porphyria. Cases of congenital erythropoietic porphyria, erythropoietic protoporphyria, and variegate porphyria have been described in neoplastic and paraneoplastic settings such as myelodysplasia (Chapter 167), myeloproliferative disorders (Chapter 152), and hepatocellular carcinoma (Chapter 181).

Pathogenesis

Heme Deficiency

Reduced heme production does not appear to result in direct clinical adverse effects in patients with the porphyrias. However, a high incidence of hyperhomocysteinemia is reported in patients with acute intermittent porphyria,[3] possibly resulting from reduced heme availability for the heme-dependent enzyme cystathionine-beta-synthase. A further exception may be the homozygous forms of acute hepatic porphyria, which are accompanied by a range of developmental abnormalities that may possibly be heme-dependent.

The principal consequence of heme deficiency in the hepatic porphyrias is the induction of *ALAS1,* which upregulates heme biosynthesis with a consequent increase in the flux of porphyrins through the pathway. If this throughput exceeds the capacity of a secondary, downstream rate-limiting step (in most cases, a mutant or inhibited enzyme), porphyrins, their precursors, or both will accumulate, thereby potentially precipitating symptoms. This mechanism is the key to understanding the porphyrias.

Photosensitivity

In porphyrias associated with skin disease, porphyrins are found in high concentrations in plasma, skin, and blister fluid. Porphyrins are fluorescent. Stimulation by light results in an excitation of the porphyrin molecules, the promotion of electrons to a higher energy state, and the production of singlet oxygen. Relaxation to the ground state is accompanied by loss of energy manifesting as a radiation of red light. In the skin, this energy may be transferred to biologic molecules, and the resulting oxidation of membrane lipids, polypeptides, and nucleic acids leads to phototoxic skin damage. The most potent wavelengths for porphyrin excitation lie within the ultraviolet spectrum, between 400 and 410 nm, but additional absorption bands are present in the range 500 to 700 nm, so even visible light, against which most topical sunscreen preparations are ineffective, is harmful to the skin in subjects with a cutaneous porphyria. Pathologic examination suggests that the blood vessels of the dermis may be the principal target for light-induced injury.

The Acute Attack

Elevated concentrations of the heme precursors 5-aminolevulinate and porphobilinogen are always present during the acute attack in patients with acute intermittent porphyria, variegate porphyria, and hereditary coproporphyria, and remission is commonly accompanied by a reduction in these concentrations. The rare acute 5-aminolevulinate dehydratase porphyria manifests with elevation of 5-aminolevulinate alone, since it is the following step in synthesis that is affected.

The onset of the acute attack is associated with induction of *ALAS1*. In patients with acute intermittent porphyria, hydroxymethylbilane synthase becomes rate-limiting, thereby resulting in increased concentrations of 5-aminolevulinate and porphobilinogen. In variegate porphyria and hereditary coproporphyria, the accumulation of coproporphyrinogen and protoporphyrinogen secondarily inhibits hydroxymethylbilane synthase with the same consequences. Evidence also points to a direct role for 5-aminolevulinate in causing the symptoms of the acute attack.

Many drugs will induce ALAS1 as part of their metabolism. Such drugs are termed *porphyrogenic,* and exposure to porphyrogenic medication is a common cause of the acute attack. The most powerfully porphyrogenic compounds include multifunctional inducers, which induce multiple hepatic microsomal autosomal enzymes, drugs that induce the CYP3A and CYP2C9 subclasses, and drugs that are associated with irreversible mechanism-based inhibition of CYP. Such inhibition results in destruction of the enzyme and the release of heme, which is then catabolized by heme oxygenase, thereby leading to a reduction in the free heme pool, and consequently to *ALAS1* induction. However, patients who carry a gene for an acute porphyria do not respond uniformly or predictably to specific drug exposures.

Caloric deprivation induces porphyrin synthesis and potentially the acute attack, whereas glucose administration has a suppressive effect. Women with acute intermittent porphyria may show a pattern of regularly recurring attacks associated with the luteal phase of the menstrual cycle. Endogenous hormone production is sufficient to induce 5-aminolevulinate synthase and cause an acute attack. Smoking, stress, and infection also are possible inducers of acute attacks.

Hyperhomocysteinemia

Patients with acute intermittent porphyria have an increased risk of hyperhomocysteinemia, with levels appearing to correlate with expression of the porphyria and reduced levels of ALAS1. Hyperhomocysteinemia may be a manifestation of heme deficiency, possibly following reduced activity of the heme-dependent enzyme cystathionine β-synthase.

CLINICAL MANIFESTATIONS

Patients with congenital erythropoietic porphyria and erythropoietic protoporphyria and patients with the homozygous forms of the acute porphyrias usually present in childhood, but occasional patients with milder expression may present in adult life. Porphyria cutanea tarda and the acute porphyrias are not expressed until after puberty, most commonly in the third decade.[4]

The Acute Attack

The cardinal manifestation of the acute hepatic porphyrias is the acute attack. Although there is a degree of variation in symptomology, the attack tends to evolve through a set of characteristic phases (Fig. 194-2).

After a brief prodrome of mild behavioral disturbance, anxiety, and restlessness, patients develop a characteristic picture of severe, generalized abdominal pain, felt throughout the abdomen and sometimes in the lower back, buttocks, and thighs.[5] The pain is severe and requires opioids for relief. It is not associated with signs of peritonitis, and typically the abdominal examination is normal. Autonomic overactivity may manifest as hypertension, tachycardia, gastrointestinal dysfunction, vomiting, and constipation. Occasionally

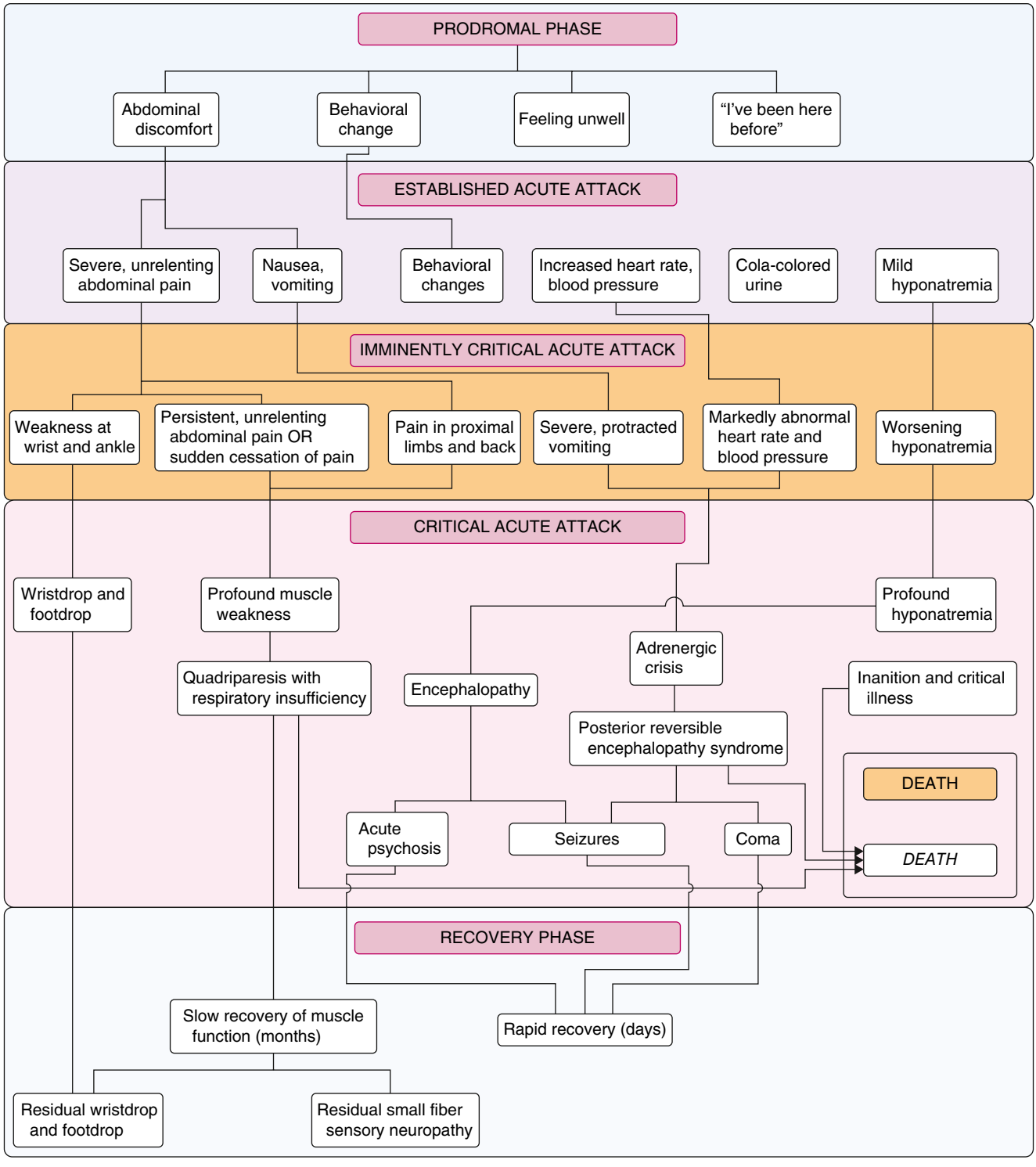

FIGURE 194-2. Schematic representation of the clinical features of an acute attack of porphyria. No causal relationship is intended, and not all of these features may be present. The **prodromal phase** is marked by abdominal discomfort, a feeling of being unwell, and sometimes mild behavioral changes. Patients who have previously suffered acute attacks usually recognize this prodrome as heralding the onset of an acute attack. ("I've been here before.") The **established acute attack** is marked by severe, unrelenting abdominal pain that requires opioids for relief. Behavioral change, nausea, vomiting, and a slight increase in heart rate and blood pressure may be noted. The urine becomes dark, and mild hyponatremia is frequent. A number of warning signs may portend transition to an **imminently critical acute attack**, which may be life-threatening. These warning signs include persistent abdominal pain, pain spreading to the limbs and back, weakness of dorsiflexion at the wrists and ankles, markedly abnormal heart rate and blood pressure, and worsening hyponatremia. Occasionally the abrupt disappearance of abdominal pain (in contrast with the normal gradual improvement which accompanies settling of the acute attack) heralds the onset of paralysis. The **critical acute attack** is accompanied by two major clinical features: rapid onset of motor neuropathy, which may progress to quadriplegia and respiratory insufficiency requiring ventilation, and encephalopathy, which is marked by seizures, confusion, possible psychosis, and coma. Patients may demonstrate the posterior reversible encephalopathy syndrome, which is often precipitated by an adrenergic crisis marked by profound hypertension and tachycardia. Significant hyponatremia may be present. Death may follow respiratory failure, severe autonomic and metabolic disturbance, and any complication applicable to the critically ill patient. In patients subject to recurrent attacks, death may follow a downhill spiral of recurrent attacks, worsening neuropathy and severe inanition. In the **recovery phase**, metabolic derangement, pain, and encephalopathy recover very quickly as the attack settles, often over the course of 24 to 48 hours. Established neuropathy usually requires 8 to 12 months of rehabilitation. There is, however, substantial recovery, although some residual weakness, particularly footdrop and wristdrop, frequently persists.

autonomic overactivity is so severe as to resemble a pheochromocytoma crisis (Chapter 209).

A severe acute attack may be complicated by a rapid-onset motor neuropathy, usually developing 24 or more hours after the onset of the abdominal pain. Rarely, a patient will present with an acute-onset neuropathy with a history of minimal or no abdominal pain. The neuropathy is typically symmetrical and predominantly affects proximal muscles; it may progress to quadriparesis and respiratory paralysis requiring ventilation. Though motor signs predominate,

there may be some sensory involvement in a central, "bathing-suit" distribution. Once established, the recovery of motor function is typically slow, but usually near-complete. Cranial nerve or cerebellar involvement is occasionally noted. Patients with severe acute attacks may develop the posterior reversible encephalopathy syndrome with radiologic evidence of reversible cerebral ischemia (Chapter 260). Rhabdomyolysis (Chapter 99), acute renal failure, and potentially fatal cardiac arrhythmias can complicate the acute attack.

Occasionally patients manifest a short-lived psychotic episode, which reverses completely with remission of the attack. A statistical association with chronic anxiety and depression in patients with acute intermittent porphyria has been shown but may not differ from that encountered in other chronic disorders. Schizophrenia and bipolar illness may be more common in families with acute intermittent porphyria, but these associations are weaker than initially reported.

The acute attack is more common in females than males, is rare before puberty, and becomes uncommon from the sixth decade onward. Acute attacks are more prevalent in patients with acute intermittent porphyria and more likely to be associated with hormonal factors than variegate porphyria. Occasional patients experience more frequent attacks during pregnancy, but pregnancy is usually uncomplicated; it is associated with good maternal outcomes and only a slightly increased risk of fetal loss in patients who experience recurrent attacks.

The most characteristic laboratory disturbance is hyponatremia (Chapter 102), which may be present in up to 40% of cases. It may be severe, associated with encephalopathy, seizures, and coma. The pattern of electrolyte excretion frequently suggests renal salt-wasting, sometimes associated with marked urinary losses of potassium, calcium, and magnesium. Typically, the urine darkens on standing owing to the nonenzymatic conversion of porphobilinogen to the colored molecules porphobilin and uroporporphyrin-I. Hematologic parameters are usually normal.

Chronic Phase of Acute Hepatic Porphyrias

Recurrent Attacks

Approximately 3 to 5% of patients, typically young women with acute intermittent porphyria, show a course characterized by recurrent acute attacks, sometimes with a clear relationship to the menstrual cycle. A range of debilitating symptoms, including abdominal pain, muscle pain, insomnia, nausea, fatigue, and mood disorders can occur with or without overt acute attacks.[6] The worst-affected patients show evidence of accumulating neuronal damage, become debilitated and cachectic, and may ultimately die.[7]

Chronic Neuropathy

Patients who have had severe or recurrent attacks may develop a persistent small-fiber neuropathy that presents with generalized dysesthesia and hyperalgesia.[8] Electromyography initially shows a pattern of denervation, with widespread fibrillation, later replaced by a pattern of reinnervation marked by polyphasic motor unit potentials with increased amplitude and duration. It may be difficult to distinguish a recurrent acute attack from a flare in neuropathic pain centered on the abdomen.

Skeletal muscle may show neurogenic atrophy. Nerve conduction studies show a characteristic pattern of axonal necrosis with little evidence of demyelination. Upper limbs may be affected more than the lower limbs.

Hypertension and Chronic Kidney Disease

At least 40% of patients with acute intermittent porphyria will develop chronic hypertension, possibly due in part to chronic activation of the sympathetic nervous system. Many patients with symptomatic acute intermittent porphyria develop a chronic tubulointerstitial nephropathy or focal cortical atrophy secondary to reabsorption of 5-aminolevulinate.

Carcinoma

A strong association between both acute intermittent porphyria and variegate porphyria and noncirrhotic hepatocellular carcinoma (Chapter 181) has been reported,[9] especially in females. For patients with acute intermittent porphyria older than age 50 years, the risk may be increased more than 80-fold. The risk also may be increased in variegate porphyria. One study in Norway also suggested that acute hepatic porphyrias are associated with kidney and endometrial cancers.

Vesiculo-erosive Skin Disease

The vesiculo-erosive skin disease of variegate porphyria, hereditary coproporphyria, porphyria cutanea tarda, and congenital erythropoietic porphyria presents as blistering and erosions, typically in response to minor skin trauma, in sun-exposed areas, particularly the dorsal surfaces of the hands and forearms, the face, and the back of the neck. There is no immediate photosensitivity, and changes develop insidiously, so patients frequently fail to recognize the association between sun exposure and skin damage. The lesions heal slowly, leaving a residuum of scarring and areas of hypopigmentation or hyperpigmentation (Fig. 194-3). Milia may be present, particularly on the dorsal surfaces of the hands and in the digital clefts. The most severe skin disease, which is seen in congenital erythropoietic porphyria and hepatoerythropoietic porphyria, is characterized by photomutilation, including loss of skin appendages such as the nose, ears, and lips. Patients with homozygous variegate porphyria and hereditary coproporphyria may show lesser changes.

Porphyria cutanea tarda usually presents in middle-aged and older subjects who develop characteristic vesiculo-erosive skin lesions in sun-exposed areas (Figs. 405-12 and 406-17). Patients may develop thickening of the skin of the fingers and hands (so-called pseudosclerodermoid changes), which may lead to a misdiagnosis of scleroderma. Other common features are facial hypertrichosis, skin darkening, and alopecia. A precipitating factor such as hepatic iron overload, liver dysfunction, alcohol misuse, estrogen use, or renal failure is usually present.

Congenital erythropoietic porphyria is usually severely mutilating. Patients typically demonstrate scarring; loss of skin appendages such as ears, nose, and lips; loss of fingernails and digits; ulcerative keratitis; and corneal scarring. Patients may show erythrodontia, osteodystrophy, a hypercellular bone marrow, hemolytic anemia, and splenomegaly. The skin deteriorates progressively with age. Impact on quality of life and psychosocial consequences may be severe. There is a variable genotype-phenotype correlation, and some patients are less severely affected. The features most predictive of a severe course are early age of onset and the presence of hematologic complications, particularly severe anemia and thrombocytopenia.

Skin Disease Associated with Immediate Photosensitivity

Protoporphyria

Patients with erythropoietic protoporphyria, X-linked protoporphyria, and the protoporphyria associated with *Clpx* mutations do not manifest the vesiculo-erosive skin disease, but instead develop a characteristic pattern of immediate photosensitivity. After a short period of sun exposure, patients develop severe discomfort and pain in sun-exposed areas, sometimes associated with erythema and edema. The discomfort may persist for 24 to 48 hours after cessation of sun exposure. Photosensitivity is often sufficiently severe to markedly impair quality of life and to restrict the patient's choice of occupation and recreational activity.

The onset of the illness is usually in childhood. Chronic skin changes are minimal and are usually limited to the development of a waxy thickening and grooving of the skin, typically over the bridge of the nose and over the

FIGURE 194-3. The hands in variegate porphyria. The characteristic lesions are bullae, shallow erosions that develop scabs and heal slowly, leaving areas of hypopigmentation and hyperpigmentation. The skin disease of porphyria cutanea tarda and hereditary coproporphyria is similar.

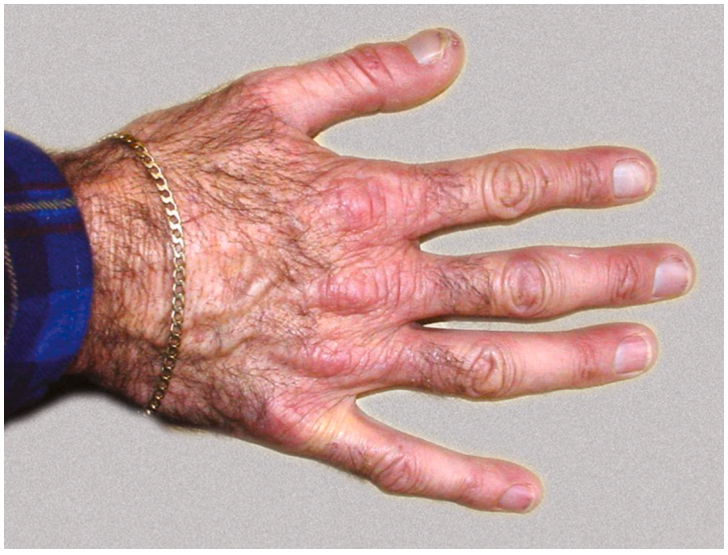

FIGURE 194-4. The hands in erythropoietic protoporphyria. There is thickening and grooving of the skin over the knuckles.

FIGURE 194-5. The hands of a patient with a homozygous form of variegate porphyria, termed hepatoerythropoietic porphyria. In addition to the characteristic vesiculo-erosive skin lesions, there is marked brachydactyly, representing both photo-osteolysis and a skeletal developmental defect.

knuckles (Fig. 194-4). A late-onset form of inherited erythropoietic protoporphyria has been described.

A mild microcytic hypochromic anemia may be present. Cholelithiasis associated with pigment stones is common. Patients are at low risk of developing a severe cholestatic hepatitis with liver failure.[10]

X-linked Protoporphyria

X-linked protoporphyria and erythropoietic protoporphyria cannot for practical purposes be distinguished clinically. Iron deficiency is common as the consequence of the increased demand for iron needed to chelate the excessive amounts of protoporphyrin produced in the bone marrow. Patients may report a correlation between iron deficiency and the severity of symptoms, with symptoms improving on iron replacement therapy. Patients with X-linked protoporphyria, particularly males, tend to have higher protoporphyrin levels than patients with erythropoietic protoporphyria and appear to be at higher risk of hepatopathy.

Immediate Photosensitivity in Other Settings

A transient immediate acute photosensitivity, sometimes associated with acute loss of fingernails, is occasionally observed in patients with variegate porphyria as they emerge from an acute attack. Patients with congenital erythropoietic porphyria may manifest immediate photosensitivity in addition to the characteristic vesiculo-erosive skin response. Immediate photosensitivity is observed in patients treated with 5-aminolevulinate or synthetic porphyrin analogues as part of photodynamic therapy for cancer.

Homozygous Acute Porphyrias

Patients with homozygous acute intermittent porphyria present with severe neurodevelopmental abnormalities,[11] and the disease is usually fatal in childhood. 5-Aminolevulinate dehydratase deficiency porphyria is an extremely rare recessive disorder that may present in either childhood or adulthood, depending on the severity of the phenotype, typically with chronic neuropathy, other neurologic symptoms, and acute attacks.

The skin disease of homozygous variegate porphyria is marked by vesiculo-erosive skin changes, alopecia, skeletal dysmorphism, resorption of digits (Fig. 194-5), nystagmus, seizures, sensory neuropathy, and cognitive impairment. Acute attacks do not occur, and the phenotype appears to be significantly less severe than that of homozygous acute intermittent porphyria, with most patients surviving into adulthood with a reasonable quality of life.

Homozygous hereditary coproporphyria takes two forms. The first resembles homozygous variegate porphyria with small stature, photosensitivity, psychomotor retardation, and neurologic defects. The second presents at birth with hemolytic anemia and severe jaundice.

DIAGNOSIS

Delayed diagnosis may result in impaired quality of life and a potentially fatal acute attack. Physicians must recognize the acute attack early and should be particularly alerted by the presence of hyponatremia, dark urine, or muscle weakness in the patient with severe abdominal pain.[12,13]

Conversely it is not unusual for patients to be erroneously diagnosed as having porphyria. A diagnosis should never be based on clinical presentation alone, and an accurate laboratory diagnosis is essential in all cases.

Biochemical Testing

No single test or specimen can provide all the information needed to diagnose the type and activity of each type of porphyria. Clinicians who suspect the diagnosis should request advice from the hospital laboratory and provide sufficient clinical information for the laboratory to select the most appropriate testing regimen.[14] It is highly recommended that diagnostic testing for porphyria be restricted to national reference laboratories that analyze sufficient cases to develop expertise.

Acute Attack

Biochemical analysis is the essential step for diagnosis and evaluation of the porphyrias. The acute attack in all the acute porphyrias other than 5-aminolevulinate synthase deficiency porphyria is always associated with significantly elevated urine porphobilinogen concentrations, typically at least five times the upper limit of normal for that laboratory. When an acute attack is suspected, it is sufficient to submit a spot urine sample for measurement of porphobilinogen. If urine porphobilinogen concentrations are normal after correcting for the creatinine concentration, an acute attack is essentially excluded. For immediate use in the emergency setting, semiquantitative test kits are available.

No defined urinary porphobilinogen diagnostic threshold reliably distinguishes acute intermittent porphyria in the acute phase from acute intermittent porphyria in remission, so recurrent attacks must be diagnosed clinically. In both variegate porphyria and hereditary coproporphyria however, porphobilinogen concentrations return to normal once the acute attack has resolved.

General Diagnosis

Urine porphobilinogen testing, although essential for the diagnosis of the acute attack, is not suitable as a stand-alone test for the general diagnosis of porphyria. Plasma fluorescence scanning is a useful initial screening test for porphyria that is suitable for most laboratories. When subjected to ultraviolet light, porphyrins carried in the plasma in high concentrations will fluoresce with a typical pattern in terms of the emission maximum, or peak wavelength of the emitted light. A plasma sample will typically demonstrate an emission peak at approximately 630 nm in erythropoietic protoporphyria, 625 nm in variegate porphyria, and 619 nm in acute intermittent porphyria, hereditary coproporphyria, and porphyria cutanea tarda. The fluorescence emission peak in acute intermittent porphyria may be transient, and a negative test does not exclude the diagnosis.

Definitive diagnosis, however, requires quantifications of the various porphyrin species using a high-performance liquid chromatographic separation technique with fluorometric detection of the porphyrins. The isomer profile is important in diagnosis, particularly in hereditary coproporphyria. The erythropoietic porphyrias are diagnosed by measuring erythrocyte porphyrin concentrations. Accordingly, a full diagnostic workup may require examination of urine, stool, plasma, and erythrocyte porphyrins, although the diagnostic approach is predicated on the clinical presentation.

Coproporphyrinuria is a relatively common finding in patients with liver disease, in which it is essentially irrelevant but may be misdiagnosed as porphyria. It is characterized by an isolated elevation of urinary coproporphyrin and results from a diversion of coproporphyrin excretion from bile to urine.

Genetic Testing

Once a biochemical diagnosis of porphyria has been made, the underlying mutation should be identified. No standard test exists for the diagnosis of porphyria, and clinicians should be guided by their local reference laboratory in requesting and interpreting tests. No mutation-specific diagnostic test will exclude any form of porphyria other than the one specifically associated with that gene and that mutation. Conversely, detection of a mutation in the gene does not establish the diagnosis because it may represent an incidental polymorphism. Predicting whether such a mutation is indeed associated with a risk of disease rather than being an incidental finding requires expertise. Furthermore, unlike biochemical testing, genetic testing provides no information on the degree of activity of the porphyria at the time of testing.

Where there is a very high prevalence of a single mutation because of a founder effect, screening for that specific mutation may prove useful in preliminary assessment. This situation is seen in South Africa, where a single *PPOX* mutation, the R59W mutation, accounts for over 95% of all cases of variegate porphyria.

Differential Diagnosis

Acute Attack

The differential diagnosis of an acute attack includes any cause of severe abdominal pain (Table 118-2; Fig. 118-2). About 40% of children with hereditary tyrosinemia type I may develop a syndrome closely resembling the acute attack. Lead poisoning (Chapter 20) also may be accompanied by an acute abdominal crisis, and both these conditions may be distinguished from an acute porphyria by demonstrating isolated elevation of the urinary 5-aminolevulinate level with a normal porphobilinogen concentration.

The more closely the presentation resembles the typical syndrome (see Fig. 194-2), the more likely it is to be an acute attack. Atypical presentations can occur, however, and rapid urine porphobilinogen testing is critical in every case. Neurologic presentations, which are often preceded by abdominal pain, can be misdiagnosed as Guillain-Barré syndrome (Chapter 388) or autoimmune encephalitis (Chapter 383),[15] but neurophysiologic testing in acute porphyria will show a pattern of axonal necrosis rather than demyelination.

Skin Disease

The differential diagnosis of the typical vesiculo-erosive pattern of porphyria skin disease includes other chronic bullous diseases (Chapter 406). Epidermolysis bullosa is not restricted to sun-exposed areas. Pseudoporphyria, which is a vesiculo-erosive disease resembling porphyria, is associated with end-stage renal or liver disease, with tanning bed use, or as drug-induced skin reactions, particularly in response to nonsteroidal anti-inflammatory drugs, tetracycline, sulfur-containing diuretics, systemic retinoids, cyclosporine, and dapsone. In pseudoporphyria, porphyrin profiles are normal, and the pathogenetic mechanism is unknown.

TREATMENT

The Acute Attack

Patients should be managed by or in consultation with a physician experienced in the management of porphyria.[16] Pain is severe and requires opioid analgesia (Table 26-6). All porphyrogenic drugs (e.g., rifampin, thiopental, and ritonavir but also many others) must be discontinued, and no medication should be administered unless its safety in porphyria has been checked (http://www.drugs-porphyria.org). Patients may require antiemetics (Table 118-5).

Electrolyte balance requires careful monitoring. Though carbohydrate loading with enteral glucose suppresses porphyrin synthesis, its effect is minimal in comparison with hemin therapy.

Specific Therapy

Hemin, which is a stable form of heme incorporating ferric iron complexed with a coordinating chloride ligand, inhibits 5-aminolevulinate synthase 1, thereby leading to a rapid reduction in the synthesis of porphyrin, reduction of symptoms within 24 hours, and the prevention of neurologic complications. Options include lyophilized human hemin (a powder that is reconstituted with sterile water for injection and infused intravenously in a dose of 1 to 4 mg per kilogram per day) and heme arginate (available in Europe and other areas, but not the United States; administered intravenously at 3 mg/kg in human serum albumin or in sodium chloride daily for 4 days). The patient can usually be discharged after the fourth dose.

Patients may rarely present with an adrenergic crisis marked by severe hypertension, tachycardia, and encephalopathy, which may manifest as coma, seizures, and the posterior reversible encephalopathy syndrome. A combined α- and β-adrenergic blocker such as an intravenous infusion of labetalol (beginning at 50 mg per hour and increasing as necessary to achieve autonomic control) is useful for controlling the autonomic overactivity while the attack is aborted with hemin. Intravenous magnesium sulfate (an initial bolus of 1 to 2 g followed by a continuous infusion of 1 to 2 g per hour) may provide incremental benefit. Recovery from such a crisis is usually rapid and complete once the attack is brought under control.

Recurrent Attacks

Recurrent acute attacks are uncommon and affect only about 3 to 8% of all symptomatic patients. Medications should be reviewed and potentially porphyrogenic medication stopped. Smoking and alcohol should be discouraged. Under the care of an experienced physician or team, arrangements should be made to ensure that hemin will be available when required. Anesthesia is safe in acute hepatic porphyria, provided that nonporphyrogenic anesthetic agents and ancillary drugs are used.

Reducing Recurrent Acute Attacks

Patients must avoid all potentially porphyrogenic medication. Anyone with an acute porphyria-associated mutation, whether clinically expressed or not, must consult a drug safety database (http://www.drugs-porphyria.org) before taking any medicinal agent, and no physician should prescribe medication for such individuals without doing the same. Sudden reductions in caloric intake should also be avoided.

Monthly subcutaneous injections of givosiran (2.5 mg/kg), which inhibits the synthesis of ALAS1, are highly effective in preventing recurrent attacks of acute intermittent porphyria,[A1] with approximately 80% of patients becoming attack-free on therapy. Side effects include injection site reactions, usually mild increases in serum creatinine and hepatic aminotransferase levels,[17] and elevations in serum homocysteine concentrations.[18] Long-term efficacy and safety data are not yet available, and the cost of givosiran has limited its use in many settings.[19]

If givosiran is not tolerated or available, recurrent acute attacks may respond to prophylactic hemin administered under expert oversight weekly, monthly or 3-monthly, or on demand at the earliest onset of symptoms. Frequent administration is associated with a high incidence of thrombophlebitis, so a permanent indwelling central venous catheter is usually required. Hemin, which contains 9% iron by weight, can cause iron overload, so ferritin levels should be measured at regular intervals and phlebotomy undertaken if necessary. Hemin may also induce the catalytic enzyme heme oxygenase, thereby leading to rapid destruction of heme and a vicious cycle.

Menstrual Attacks

Female patients may experience frequent attacks coinciding with the luteal phase of the menstrual cycle, typically two or three days before the onset of menstruation. Such patients may respond to gonadotrophin-releasing hormone analogues, givosiran, or prophylactic hemin given just before the luteal phase of the menstrual cycle. Attempts to provide estrogen supplementation to suppress gonadotropins have variable success and should be tried only in specialized centers.

Some patients may experience acute attacks during pregnancy. Hemin therapy is regarded as safe during pregnancy, whereas the safety of givosiran is not yet established.

Liver Transplantation

Orthotopic liver transplantation, which prevents further acute attacks of both acute intermittent porphyria and variegate porphyria, should be considered in patients who have severe repetitive acute attacks, particularly when there is incomplete recovery between attacks, progressive disability, or severely impaired quality of life despite medical therapy. Five-year survival is approximately 80%, which is similar to the transplant experience for other metabolic diseases.[20] Combined liver and kidney transplantation may be necessary when acute intermittent porphyria is accompanied by chronic kidney disease.

Managing Chronic Pain

Following resolution of a severe acute attack, patients may develop chronic neuropathic pain, particularly in the abdomen and proximal limbs. Hyperesthesia is often prominent. Failure to recognize the nature of the problem frequently leads to patients being erroneously diagnosed as having recurrent attacks and receiving repeated courses of hemin, which is of no benefit in the situation. Chronic pain should be treated similarly to other illnesses accompanied by neuropathic pain (Chapter 26), using analgesics and neuro-active agents such as anticonvulsants and antidepressants (Chapter 362), usually assisted by a specialist in pain management.

Skin Disease

Treatment begins with reducing sun exposure using clothes and sunscreen. Zinc or titanium-based sunscreens are indicated because they block ultraviolet A, ultraviolet B, and visible light wavelengths. For vesiculo-erosive skin disease, sun avoidance is critical, but no specific therapy is available. Trauma to exposed areas should be minimized. Aseptic lancing of bullae may hasten resolution, and established lesions should be carefully cleaned with nonastringent antiseptics.

Porphyria Cutanea Tarda

Porphyria cutanea tarda will usually remit following the removal of the precipitating factors. Once attained, remission is usually maintained for many years, though occasionally retreatment may be necessary.

Alcohol use (Chapter 364) should be severely restricted. Treating concurrent hepatitis C infection (Chapter 135) will induce long-term remission. Elevated iron stores should be reduced. Oral chloroquine (typically 125 mg twice weekly), which releases porphyrins from the liver into the plasma so they can be eliminated by the kidneys, is effective in inducing remission in porphyria cutanea tarda. Patients with porphyria cutanea tarda should be screened for hemochromatosis-associated mutations (Chapter 196).

Given the deleterious effects of iron overload, it is often prudent to combine treatment of hepatitis C or the use of chloroquine with iron-lowering therapy. Although iron chelation therapy is effective (Chapter 196), a 500-mL venesection every 2 weeks until the serum ferritin is in the low-normal range is more efficient, typically requiring about 8 to 12 sessions. Patients who are anemic, such as patients with renal failure, may require concurrent erythropoietic medications to maintain an adequate hemoglobin concentration.

Protoporphyrias

In addition to reducing sun exposure, afamelanotide is standard care. This agent is a synthetic melanocyte-stimulating hormone analogue that induces the synthesis of both pheomelanin and eumelanin, which together absorb and reflect radiation over a wide light spectrum. Afamelanotide is administered as a subcutaneous implant every 4 months by a specialist.[A2] Dersimelagon (an oral selective melanocortin-1 receptor agonist that increases the production of melanin in the skin in the absence of ultraviolet radiation) is an experimental approach for both erythropoietic and X-linked protoporphyria. For the acute pain of erythropoietic protoporphyria, no intervention has shown consistent benefit.

In patients with X-linked protoporphyria, anemia and iron deficiency are common. It is appropriate to provide iron replacement therapy with careful monitoring of both the clinical response and plasma protoporphyrinogen levels. Some patients will report reduced photosensitivity following treatment.

Patients who have protoporphyria-associated hepatopathy require the care of a hepatologist, but no evidence-based therapies are available other than orthotopic liver transplantation for severely affected patients. Protoporphyrin will reaccumulate in the transplanted liver, so combined bone marrow and liver transplantation should be considered.

Congenital Erythropoietic Porphyria

Reduction in light exposure and protection against exposure for both skin and eyes is essential. In addition to avoiding sun exposure, fluorescent lighting should be replaced with other forms of illumination, and transparent film should be applied to windows, spectacles, and windshields to exclude short wavelengths. Afamelanotide has shown benefit in a single case. Some patients require chronic transfusion for anemia and may benefit from splenectomy. Early allogeneic stem cell transplantation, which will prevent further disfigurement and its psychosocial consequences in severely affected individuals, should be offered before mutilating disease becomes established in patients with severe disease or a mutation known to be associated with a severe phenotype.

Investigational Therapies for the Porphyrias

Treatments under study[21] include gene replacement therapy and the transplantation of hepatocytes, molecular chaperones, and potential regulators of heme-dependent biologic pathways.[22] Since ALAS1 is central to the pathogenesis of the acute attack, ALAS1 downregulation is a potential target for therapeutic intervention.

PREVENTION

Given that most of the porphyrias are genetically determined, there is currently no practical way in which these illnesses may be prevented. Genetic counseling and education of patient and family, as well as access to appropriate literature resources for patient support, are important. Screening of family members[23] can be targeted to the mutation in the proband. For acute porphyrias, asymptomatic carriers can practice risk avoidance. Diagnosis in utero using molecular methods to identify family-specific mutations is possible. The conditions most likely to result in severely impaired quality of life are congenital erythropoietic porphyria, hepatoerythropoietic porphyria, and the homozygous acute porphyrias.

PROGNOSIS

With few exceptions, the prognosis of the porphyrias is favorable.

Acute Porphyrias

Patients may expect a normal lifespan provided that acute attacks are avoided and, if experienced, effectively treated. The prognosis for the individual attack is good if the patient receives adequate treatment, particularly with hemin, before the onset of neuropathy. Even where the patient has developed quadriparesis, the prognosis for ultimate recovery is good provided the patient receives high-quality care, including assisted ventilation if necessary. Typically, the patient may be weaned off the ventilator within 4 months and is usually fully ambulant and independent by 8 months. Recovery is usually near-complete by 12 months, although residual footdrop and wristdrop frequently persist. It is important to avoid further acute attacks during the period of convalescence and to treat recurrent attacks promptly.

The prognosis is less benign in patients who have recurrent acute attacks that are poorly responsive to therapy, but givosiran may change this prognosis. Patients with homozygous acute intermittent porphyria are prone to severe developmental abnormalities and may die in childhood. By contrast, there appears to be no early mortality in patients with homozygous variegate porphyria, though the photomutilation and neurodevelopmental effects may have psychosocial and educational consequences.

Patients should be screened at regular intervals for hypertension, chronic kidney disease, and hepatocellular carcinoma. Renal disease is slowly progressive and may result in end-stage kidney disease requiring dialysis or renal transplantation. The outcome of transplantation is good, and appears to be accompanied by substantial decrease in the activity of the disease.[24]

Cutaneous Porphyrias

The skin disease of porphyria is not life threatening. Patients with congenital erythropoietic porphyria are subject to severe photomutilation with serious psychosocial consequences and should be assessed for allogeneic stem cell transplantation. Porphyria cutanea tarda is treatable, and remission is expected once the precipitating factors, including iron overload, have been corrected. A small proportion of patients with protoporphyria will develop hepatopathy, which may prove fatal. The majority will, however, have a normal lifespan.

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For the General References and other additional features, please visit Elsevier eBooks+ at https://ebooks.health.elsevier.com.

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195

WILSON DISEASE

MICHAEL L. SCHILSKY

DEFINITION

Wilson disease is an autosomal recessive disorder of copper transport. Affected individuals accumulate toxic levels of copper in the liver and later in the brain as a consequence of mutations in both alleles of the Wilson disease gene (*ATP7B*). The gene encodes a copper-transporting ATPase expressed primarily in hepatocytes in the liver, where its major function is excretion of hepatic copper into the biliary tract.

EPIDEMIOLOGY

The incidence of Wilson disease, defined as the occurrence of new cases, is approximately 1 in 30,000 to 40,000 live births. For special populations in which consanguinity is common, the incidence is higher. In the general population, the prevalence of heterozygous gene carriers (defined as the ratio of all individuals with one mutant *ATP7B* allele to the population at large) is estimated to be 1 in 90 to 1 in 180, although this incidence may be an underestimate.

PATHOBIOLOGY

Individuals normally consume 1 to 3 mg of dietary copper daily, 50% of which is absorbed through the gastrointestinal tract. Most diets contain adequate amounts of copper, and certain foods (e.g., shellfish, liver, mushrooms, chocolate, nuts) contain higher quantities. In normal homeostasis, copper is absorbed from the stomach and duodenum, where absorption at the apical surface of the enterocyte is mediated by a specific copper transporter, hCTR1. *ATP7A*, which encodes a copper-transporting ATPase protein with high homology to the one encoded by *ATP7B*, transports copper from intestinal epithelial cells into the portal blood stream, where it is bound by albumin or amino acids, carried to the liver (which can avidly extract the copper) and to other organs and tissues, or excreted by the kidney. Renal copper excretion represents a minor pathway for copper balance, and adults normally excrete only up to 40 µg of copper per day in the urine.

Within the liver, copper may be (1) incorporated into ceruloplasmin, a multifunctional 132-kD α_2-glycoprotein enzyme containing six or seven copper atoms per molecule; (2) used in the synthesis of other copper-requiring enzymes; (3) bound by metallothionein, a low-molecular-weight, cysteine-rich protein that provides an intracellular storage and detoxification depot for copper and other trace metal elements; or (4) excreted into the bile. *ATP7B*, the gene that is mutated in Wilson disease, is expressed primarily in hepatocytes and encodes the copper-transporting protein that facilitates the removal of excess hepatic copper through the bile.[1] Biliary copper does not undergo enterohepatic recirculation, so fecal loss of copper normally represents a major pathway for copper excretion.

In Wilson disease, copper excretion is impaired owing to the impaired function or absence of the ATPase copper transporter encoded by the mutant *ATP7B* gene. The result is initially hepatic copper overload before copper accumulates in other organs.[2] Wilson disease can be associated with more than 500 known disease-specific mutations, about 97% of which are on coding exons or intronic sequences, and most patients have different mutations on each allele.[3] With untreated hepatic copper overload, excess copper enters the circulation, and copper subsequently deposits in other tissues. In the brain, which is particularly sensitive to perturbations in trace metal homeostasis, copper deposits especially in the basal ganglia.

In Wilson disease, the acquisition of copper by ceruloplasmin is usually reduced as a reflection of impaired transport of copper into the trans-Golgi compartment, where glycoprotein processing and the incorporation of copper by apoceruloplasmin occur. The result is low circulating levels of holoceruloplasmin (the protein with its full complement of copper) owing to the instability of the apoprotein (without copper) in the circulation. Because copper in ceruloplasmin accounts for 90% of circulating copper, total serum copper is low in most patients with Wilson disease despite even massive hepatic accumulation of copper.

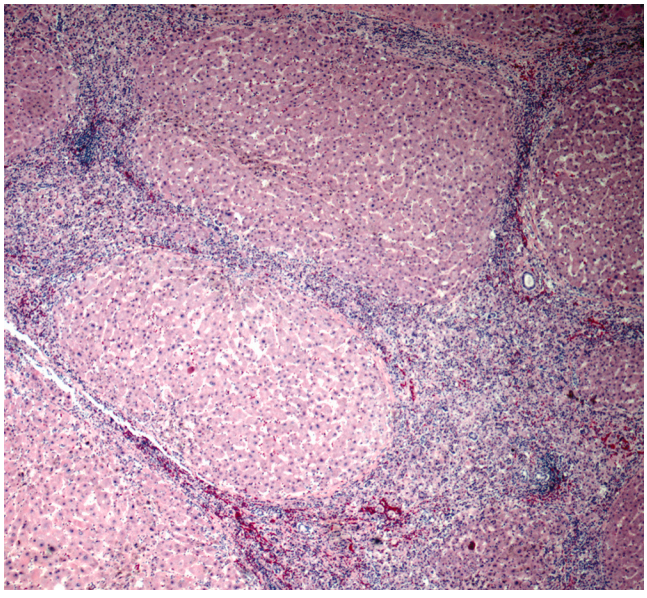

FIGURE 195-1. Hepatic cirrhosis in Wilson disease. (Image courtesy Kisha A. Mitchell, MD.)

CLINICAL MANIFESTATIONS

Presenting clinical features of Wilson disease include nonspecific liver disease (Fig. 195-1), neurologic abnormalities, psychiatric illness, hemolytic anemia, renal tubular Fanconi syndrome, and various skeletal abnormalities.[4,5]

Clinical presentation and phenotype in Wilson disease can vary considerably.[6] About 50% of adult patients with Wilson disease present with neurologic and psychiatric symptoms, about 20% with neurologic and hepatic symptoms, and about 20% with purely hepatic symptoms. Liver disease is more often the presenting abnormality in patients under age 30 years and sometimes can even present in the first or second decades of life. By contrast, patients who present with neurologic or psychiatric signs typically do so after age 20 years. Regardless of clinical presentation, some degree of liver disease is invariably present.

In hepatic presentations, signs and symptoms include fatigue, jaundice, hepatomegaly, edema, and ascites. Secondary endocrine effects of liver disease may include delayed puberty or amenorrhea. Viral hepatitis and autoimmune hepatitis (Chapter 135) are often initial diagnostic considerations in individuals with Wilson disease, especially in younger patients. Rare patients have Wilson disease concurrent with another liver disorder, and the diagnosis of Wilson disease is often delayed in these individuals as a consequence.

Wilson disease is primarily a movement disorder, and Parkinson disease or other movement disorders may be mistakenly diagnosed (Chapters 378 and 379). Abnormalities include speech difficulty (dysarthria), dystonia, rigidity, tremor or choreiform movements, abnormal gait, uncoordinated handwriting, and (rarely) a combined motor and sensory peripheral neuropathy.[7]

In psychiatric presentations,[8] changes in personality (irritability, anger, poor self-control), depression, and anxiety are common symptoms. Psychosis or bipolar disorder may also occur. Patients who present with psychiatric symptoms are typically in their late teens or early twenties, a period during which substance abuse (Chapter 365) and schizophrenia are also prime diagnostic considerations. Wilson disease should be considered and formally excluded in all young adults with new-onset psychiatric symptoms, especially if results of liver function tests are abnormal or a family history of Wilson disease is noted.

In addition to brain and liver, copper deposition in the eye produces a benign but characteristic sign, the Kayser-Fleischer ring (Fig. 195-2),[9] owing to annular deposition of copper in the periphery of the cornea. Approximately 95% of patients with neurologic or psychiatric signs have Kayser-Fleischer rings compared with approximately 50 to 65% of those with hepatic presentations. This important diagnostic sign first appears as a golden-colored superior crescent, then develops inferiorly, and ultimately becomes circumferential. In the early stage, a slit-lamp examination or optical tomography of the cornea may be needed to detect the copper deposits. Copper can also accumulate in the lens and produce "sunflower" cataracts.

ABSTRACT

Wilson disease is an autosomal recessive disorder of copper metabolism due to mutation of the *ATP7B* gene encoding a copper transporting ATPase present in hepatocytes. The pathologic accumulation of copper in the liver and then at other sites in the body, in particular in the central nervous system, is responsible for the disease that is progressive if untreated. The diagnosis is established by a combination of clinical and laboratory testing or by identification of two disease-specific mutations of *ATP7B* on each allele. Most younger patients present with liver disease, whereas neuropsychiatric manifestations typically occur later in life. About 5% of patients present with acute liver failure and require urgent liver transplantation for survival. Treatment is lifelong with medical therapy (e.g., chelating drugs or zinc) or liver transplantation. Gene therapy for Wilson disease is under investigation.

KEYWORDS

copper
ceruloplasmin
Kayser-Fleischer ring
hepatolenticular degeneration
ATP7B
chelation therapy

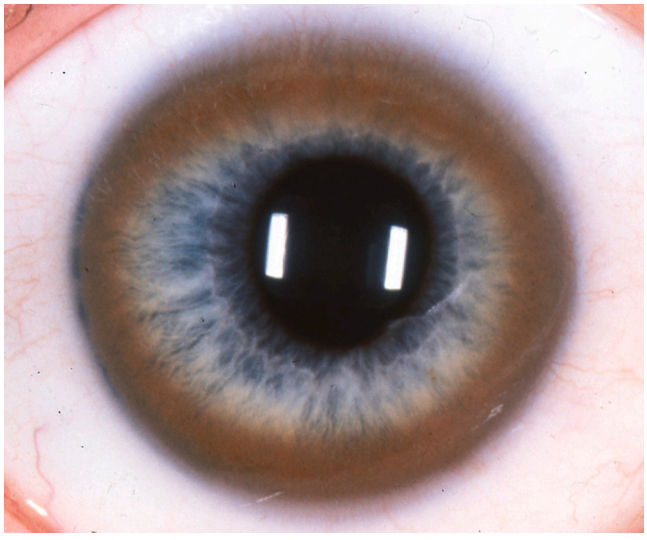

FIGURE 195-2. Kayser-Fleischer ring in a newly diagnosed patient with Wilson disease.

Hemolytic anemia (Chapter 147) can be a result of the direct toxic effects of copper on red blood cell membranes. Hemolysis is usually associated with the release of massive quantities of hepatic copper into the circulation, a phenomenon that can be sudden and catastrophic due to the development of acute (fulminant) liver failure. On occasion, hemolytic anemia may occur without liver failure.

Proximal tubular dysfunction (Chapter 108) can lead to abnormal losses of amino acids, electrolytes, calcium, phosphorus, uric acid, and glucose. This effect is presumably related to direct renal tubular copper toxicity or toxicity of copper complexes with metallothionein.

Osteoporosis (Chapter 225) and rickets (Chapter 226) in Wilson disease may be attributable to renal losses of calcium and phosphorus. Osteoarthritis (Chapter 241), primarily affecting the knees and wrists, may be the result of excess copper deposition in bone and cartilage.

DIAGNOSIS

Wilson disease should be considered in patients who have liver disease without a clear cause; acute liver failure with associated hemolysis; neurologic and psychiatric disease, especially if there is concomitant liver disease; and in first-degree relatives of identified patients. Clinical signs of the disease include the stigmata of chronic liver disease, neurologic signs and symptoms, and Kayser-Fleischer rings, which often require a slit-lamp examination to be detected.

Other laboratory findings supporting the diagnosis include low levels of serum copper, elevated urine copper excretion (>100 µg/24 hours), elevated hepatic aminotransferase levels, low serum albumin, an elevated international normalized ratio, aminoaciduria, low uric acid levels, and direct antiglobulin test (Coombs)–negative hemolytic anemia.

The most efficient approach to diagnosis is a serum ceruloplasmin level below 11.5 mg/dL followed by genetic testing for *ATP7B* mutations.[10–12] A blood spot assay for quantitatively detecting lower levels of *ATP7B* peptides in affected individuals with Wilson disease may also be useful in the future.[13]

Percutaneous needle liver biopsy for quantitative measurement of hepatic copper remains a useful test for the diagnosis of Wilson disease when other data are insufficient to establish the diagnosis (e.g., when Kayser Fleischer rings are absent, only one pathogenic *ATP7B* mutation is detected, or ceruloplasmin values are normal). Hepatic copper values higher than 250 µg/g of dry weight (normal, 20 to 50 µg/g dry weight) are characteristic of Wilson disease, although rare patients may have levels as low as 75 µg/g dry weight liver.

TREATMENT

D-Penicillamine (usually starting at 250 mg two times daily and then titrating the dose under expert supervision to 15 to 20 mg/kg in two to four doses) binds copper and greatly enhances its urinary excretion, thereby preventing copper overload and its toxic effects.[14] Pyridoxine (vitamin B_6) should be prescribed concomitantly to counter the vitamin B_6 deficiency that may develop with long-term D-penicillamine administration. About 20% of patients cannot tolerate D-penicillamine. Significant side effects include hypersensitivity; nephrotoxicity; hematologic abnormalities; and a distinctive rash, elastosis perforans serpiginosa, that often involves the neck and axilla. Furthermore, in some patients with neurologic presentations, D-penicillamine treatment induces paradoxical worsening of the neurologic disease.

In patients who cannot tolerate D-penicillamine, oral zinc acetate and triethylene tetramine dihydrochloride, which decrease copper absorption in the intestine, under expert supervision are suitable alternative agents with somewhat less side-effect profiles.[15] Zinc monotherapy is particularly useful in young, presymptomatic patients and in pregnant patients, given the possible fetal teratogenic effects of other compounds. Whereas most patients do well with zinc therapy, 10 to 20% experience dyspepsia, and a higher incidence of hepatic decompensation has been observed with long-term zinc therapy compared with chelation therapy. Another drawback to zinc is the relatively long time (4 to 6 months) needed to restore proper copper balance if zinc monotherapy is used as initial treatment.

Tetrathiomolybdate, which is an experimental treatment for Wilson disease, forms stable tripartite complexes with albumin and copper and promotes biliary copper excretion. It is fast acting and can restore normal copper balance within several weeks, compared with the several months required with other copper chelators or with zinc. Tetrathiomolybdate may be especially appropriate for the initial treatment of patients with neurologic presentations.[A1] Trientine tetrahydrochloride under expert supervision is noninferior to D-penicillamine for copper maintenance therapy in patients who have stable Wilson disease.[A2]

Regardless of the specific regimen chosen, dietary copper restriction (especially of copper-rich shellfish, liver, nuts, and chocolate) is recommended.[16] Drinking water should be tested for copper concentration and avoided if levels approach 1.3 mg/L. Treatment of Wilson disease is lifelong. Noncompliance eventually leads to symptomatic disease or liver failure.

Liver transplantation cures Wilson disease, but should be considered mainly for patients whose acute liver failure or end-stage, irreversible liver disease is unlikely to respond to medical therapy. Long-term outcomes after transplantation are excellent, and the disease does not recur.[17] Phase I/II trials of adeno-associated virus gene therapy are ongoing.[18]

Newly diagnosed patients with neurologic manifestations frequently need speech therapy, physical therapy, or occupational therapy. Treatment for tremor or dystonia (Chapter 379) and for psychological evaluation may be required.

Genetic counseling is recommended regarding family screening.

PROGNOSIS

The prognosis in Wilson disease is generally favorable. Current therapeutic approaches can prevent, stabilize, or reverse most of the significant clinical signs and symptoms.[19] Copper chelation therapy, zinc treatment, and liver transplantation cause fading and disappearance of Kayser-Fleischer rings and also often improve the renal disturbances.

If treatment is stopped, however, recurrence of symptoms and potentially fatal liver damage inevitably occur. In part because of late diagnosis and noncompliance, long-term mortality is almost three-fold higher than in the general population.[20]

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For the General References and other additional features, please visit Elsevier eBooks+ at https://ebooks.health.elsevier.com.

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196 IRON OVERLOAD (HEMOCHROMATOSIS)

KRIS V. KOWDLEY

DEFINITION

Hereditary hemochromatosis is an inherited disorder that leads to iron overload due to excessive absorption of dietary iron because of a deficiency of hepcidin, which is an iron regulatory peptide hormone.[1] A homozygous C282Y mutation in *HFE* is responsible for the vast majority of hereditary cases. However, iron overload due to hyperabsorption of dietary iron may result from other genetic mutations, chronic anemias associated with ineffective erythropoiesis (e.g., thalassemia; Chapter 148), chronic liver disease, and iatrogenic causes (see Table 196-1).

EPIDEMIOLOGY

Three common *HFE* mutations (C282Y, H63D, and S65C) have been described in the general population, but only the homozygous C282Y and the C282Y/H63D compound heterozygous mutations have been associated with the hemochromatosis phenotype in the absence of another contributing factor for iron overload. A North American study that screened almost 100,000 patients found an estimated prevalence of C282Y homozygosity in 0.44% of non-Hispanic Whites, 0.11% of Native Americans, 0.027% of Hispanics, 0.014% of Blacks, 0.12% of Pacific Islanders, and 0.000039% of Asians.[2,3] The H63D mutation is associated with phenotypic hemochromatosis only when present along with the C282Y mutation, whereas the S65C mutation is considered a polymorphism and has not been shown to contribute to iron overload. The true prevalence of these other, nonclassic forms 2 to 4 are unknown.

PATHOBIOLOGY

Dietary iron absorption is regulated by body iron needs.[4] Under circumstances of iron deficiency, iron absorption is increased until body iron stores are replete, at which time iron absorption decreases to basal levels. Iron from the diet is absorbed in the proximal duodenum either as inorganic iron or as heme iron (Fig.196-1). Iron balance in humans is regulated primarily at the level of intestinal absorption because the body does not have a mechanism to excrete iron other than by the physiologic loss of desquamated cells or by menses. Hepcidin, which is a 25–amino acid peptide hormone synthesized mainly in the liver and secreted into the blood, is considered the master regulator of iron homeostasis.[5] Hepcidin acts by blocking iron absorption from the intestine and blocking iron release from reticuloendothelial cell storage sites, which are mainly within the liver (see Fig. 196-1). Genetic iron overload disorders are caused when mutations in iron regulatory genes result in reduced production and inappropriately low levels of hepcidin in response to stored and circulating levels of iron, the net effect of which is lifelong hyperabsorption of dietary iron. Progressive iron loading of various organs can eventually cause the characteristic tissue injuries of the hemochromatosis phenotype.

Absorption of inorganic iron follows a coordinated process beginning with conversion of iron from the ferric form to the ferrous form by the duodenal cytochrome b–related ferric reductase (dcytb) that is present on the luminal surface of duodenal enterocytes. Ferrous iron then traverses the apical membrane of enterocytes via the divalent metal transporter 1. The absorbed iron may be utilized for intracellular processes, stored as ferritin in enterocytes, or converted back to ferric iron by hephaestin, thereby allowing it to be transferred across the basolateral membrane of enterocytes into circulating plasma via the iron export protein, ferroportin. Iron is bound to transferrin at the transferrin receptor (TfR1) in the circulation. Hepatocytes take up transferrin-bound iron via the receptors TfR1 and possibly TfR2, as well as by non–receptor-mediated mechanisms. Hepatocytes may also absorb free iron from the circulation when transferrin becomes highly saturated. In contrast, reticuloendothelial system cells (Kupffer cells in the liver) take up iron primarily by phagocytosis of senescent erythrocytes or possibly apoptotic hepatocytes. Kupffer cells can also sequester transferrin-bound iron via TfR1.

Mutations in the *HFE*, *TfR2*, and *HJV* genes result in markedly depressed hepcidin levels, thereby permitting persistently increased absorption of iron from a normal diet. Mutations in the *HAMP* (hepcidin) gene may likewise lead to inappropriately low levels of hepcidin, thereby resulting in iron overload. Parenchymal iron overload may also be caused by mutations in the ferroportin gene.

TABLE 196-1 CLASSIFICATION OF IRON OVERLOAD SYNDROMES

HEREDITARY HEMOCHROMATOSIS
Type 1-*HFE* Related Autosomal Recessive
C282Y/C282Y
C282Y/H63D
Other mutations
Type 2-4-Non–*HFE* Related
Hemojuvelin (*HJV*) mutations (autosomal recessive)
Hepcidin (*HAMP*) mutations (autosomal recessive)
Transferrin receptor 2 (*TFR2*) mutations (autosomal recessive)
Ferroportin (*SLC40A1*) mutations (autosomal dominant)
Aceruloplasminemia
Divalent metal transporter 1 (*SLC11A2*) mutations (rare)
Atransferrinemia
Miscellaneous
African iron overload
Neonatal iron overload (rare)
SECONDARY IRON OVERLOAD
Anemia Caused by Ineffective Erythropoiesis
Thalassemia major
Sideroblastic anemias
Congenital dyserythropoietic anemias
Liver Disease
Alcoholic liver disease
Chronic viral hepatitis B and C
Porphyria cutanea tarda
Nonalcoholic steatohepatitis
After portacaval shunt
Miscellaneous
Transfusional iron overload
Excessive parenteral iron administration

Classical (*HFE*) hemochromatosis is defined as type 1 hemochromatosis, whereas other rare types of hereditary hemochromatosis are now classified as types 2 to 4.[6,7] Juvenile hemochromatosis, which is a severe form of hemochromatosis that is associated with severe iron overload and that presents in the second to third decade of life, consists of type 2A and type 2B forms. Type 2A is caused by a mutation in the hemojuvelin (*HJV*) gene, which is located on chromosome 1 and which encodes the hemojuvelin protein. Type 2B is caused by a mutation in the hepatic antimicrobial protein (*HAMP*) gene, which encodes hepcidin. Type 3 is due to a mutation in the transferrin receptor 2 (*TFR2*) gene that is located on the long arm of chromosome 7; *TFR2* is similar to *TFR1* but expressed predominantly in the liver. Type 4 is caused by dominant gain-in-function mutations in the ferroportin (*SLC40A1*) gene, which is located on chromosome 2, thereby leading to hepcidin resistance. A different mutation resulting in loss of function in ferroportin has been termed "ferroportin disease" because its clinical, biochemical, and histologic features are very different from other forms of hereditary hemochromatosis.[8]

Population-based screening studies have shown that the penetrance and clinical expressivity of the homozygous C282Y mutation is low, especially in women. A number of factors may be associated with phenotypic expression, such as physiologic blood loss due to menses or factors leading to increased iron absorption (e.g., excess alcohol intake or other liver diseases such as chronic hepatitis C or steatohepatitis) and increased intake of ascorbic or citric acid.

Iron overload is associated with reduced function in immune cells. It is also associated with altered regulation of CD8 T lymphocytes from both *HFE* patients and *Hfe*-null mice. Siderophilic microbes grow rapidly in niches where iron is more available, and these organisms may cause severe infections in patients with iron overload. The putative mechanisms for diabetes include direct damage to pancreatic beta cells by iron, with some component of insulin resistance in the liver due to the organ's iron loading. Hypothyroidism is thought to be due to direct iron toxicity in the thyroid gland, whereas rare hypogonadotropic hypogonadism and adrenal insufficiency in hereditary hemochromatosis may be due to iron deposition in the anterior pituitary. Arthropathy is believed to be caused by the deposition of calcium pyrophosphate crystals in joint spaces, thereby leading to inflammation, joint space narrowing, chondrocalcinosis, formation of subchondral cysts, and osteopenia.

ABSTRACT

Hereditary hemochromatosis is one of the most common inherited disorders among persons of Northern European descent. Screening should be conducted with serum levels of iron and total iron binding capacity, and patients with a transferrin-iron saturation greater than 45% should have repeat fasting measurements of serum iron and total iron binding capacity as well as serum ferritin and hepatic enzymes. Serum transferrin-iron saturation should also be measured in patients with liver disease. Patients who have a repeat transferrin-iron saturation greater than 45% should undergo *HFE* gene testing. Patients who have the homozygous C282Y genotype have type 1 hereditary hemochromatosis and should undergo subsequent testing for hepatic fibrosis by magnetic resonance imaging, transient elastography, serum markers of fibrosis, or liver biopsy. In patients who have iron overload but who are not C282Y homozygotes, other causes of iron overload should be sought, such as fatty liver disease, excess alcohol consumption, or chronic viral hepatitis. Family screening using iron studies is important for all patients with known or suspected hereditary hemochromatosis. Therapeutic phlebotomy remains the most effective therapy for most patients, although small-molecule therapies to block iron absorption are being studied and may have a role in the future.

KEYWORDS

iron overload
hemochromatosis
HFE gene
hereditary
hepcidin
ferroportin
phlebotomy

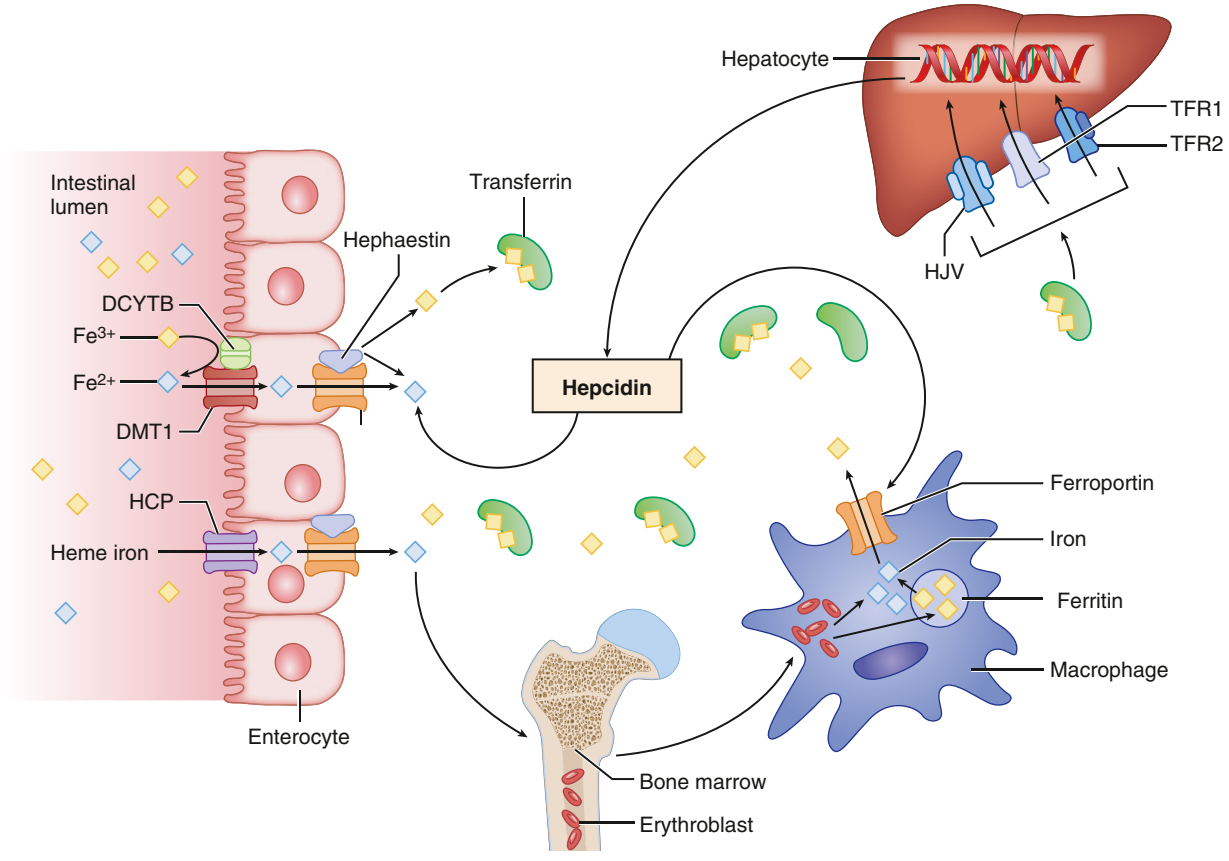

FIGURE 196-1. Hepcidin, the master regulator of iron absorption and secretion. Plasma iron levels are controlled primarily at the level of absorption by duodenal enterocytes and reticuloendothelial system (RES) macrophages. Heme-iron can also be directly absorbed from the gastrointestinal tract through a carrier protein, possibly heme carrier protein. Non-heme (inorganic) iron is absorbed via divalent metal transporter 1 after conversion from ferric (Fe 3+) to ferrous (Fe 2+) iron through duodenal cytochrome b–related ferric reductase. RES macrophages acquire iron through erythrophagocytosis. Efflux of iron from both enterocytes and RES macrophages occurs through the iron export protein ferroportin. Fe 2+ is reduced back to ferric iron (Fe 3+) through hephaestin before being transported out of the enterocyte. Iron is bound to transferrin as it enters the plasma and then travels through the circulation, where it is taken up by various organs and used in the development of erythrocytes and other biologic processes. The principal regulator of iron levels is the hormone hepcidin, which is produced by hepatocytes. As iron stores increase, hepcidin inhibits iron efflux from both duodenum enterocytes and RES macrophages through downregulation of ferroportin. Serum iron levels influence hepcidin expression through the interaction of the HFE protein with TFR1/TFR2 along with BMP6 and HJV. BMP = bone morphogenic protein; DCYTB = duodenal cytochrome b–related ferric reductase; DMT1 = divalent metal transporter 1; HCP = heme carrier protein; HJV = hemojuvelin; TFR1 = transferrin receptor 1; TFR2= transferrin receptor 2. (From Kowdley KV, Gochanour EM, Sundaram V, et al. Hepcidin signaling in health and disease: ironing out the details. *Hepatol Commun*. 2021;5:723-735.)

TABLE 196-2 THE TYPES OF HEREDITARY HEMOCHROMATOSIS AND CLINICAL FEATURES

TYPE	AGE	MUTATION/GENE	INHERITANCE	COMMON CLINICAL FEATURES
1A	Middle-age	C282Y+/+ *HFE*	AR	Arthropathy, diabetes, hypothyroidism, hypogonadism, adrenal insufficiency, liver disease, endocrine dysfunction, cardiomyopathy, skin discoloration
1B	Middle-age	C282Y/H63D *HFE*	AR	
2A	<30 years	G3290V/*HJV*	AR	Hypogonadism, cardiomyopathy
2B	<30 years	Several/*HAMP*	AR	
3	Intermediate	Several/*TfR2*	AR	May have juvenile hereditary hemochromatosis or type 2 features
4	Variable	Several/ *SLC40A1*	AD	Hepcidin resistance, fatigue, joint pain

AD = autosomal dominant; AR = autosomal recessive.

CLINICAL MANIFESTATIONS

The clinical features vary among the different forms of genetic hemochromatosis (Table 196-2). Many patients who carry *HFE* mutations, whether heterozygous or homozygous, do not express the clinical phenotype of iron overload disease (Tables 196-3 and 196-4) or even biochemical evidence of iron overload (increased serum transferrin-iron saturation, ferritin), and the majority of patients with the homozygous C282Y mutation may never develop end-organ damage from iron overload. For example, among C282Y homozygotes with normal serum ferritin values at diagnosis, less than 15% develop ferritin values >1000 ng/mL over 12 years of follow-up. An estimated 50% of female and 25% of male adults who are homozygous for the C282Y mutation have normal serum ferritin levels and will never require phlebotomy therapy. However, about 1 in 10 male C282Y homozygotes will eventually develop liver disease if hemochromatosis is not diagnosed early, usually by screening, and treated.[9]

Furthermore, the H63D mutation does not result in iron overload unless present in compound heterozygous form with C282Y. In addition, the S65C mutation is now recognized to be a polymorphism that is not associated with iron overload.

Based on genetics, phenotypic expression, and long-term natural history, hereditary hemochromatosis may be classified into three clinical stages, as shown:

- Stage 1: genetic predisposition for hereditary hemochromatosis without evidence for increase in iron stores (normal serum iron studies)
- Stage 2: genetic predisposition for hereditary hemochromatosis and some phenotypic characteristics of iron overload in the absence of organ damage

TABLE 196-3 SYMPTOMS IN PATIENTS WITH HEREDITARY HEMOCHROMATOSIS

ASYMPTOMATIC
Abnormalities of serum iron studies on routine screening chemistry panel
Abnormal liver test results
Identified by family screening
Identified by population screening
NONSPECIFIC SYSTEMIC SYMPTOMS
Weakness
Fatigue
Lethargy
Apathy
Weight loss
SPECIFIC ORGAN-RELATED SYMPTOMS
Abdominal pain (hepatomegaly)
Arthralgias (arthritis)
Symptoms of diabetes mellitus (pancreas)
Amenorrhea (cirrhosis)
Loss of libido, impotence (pituitary, cirrhosis)
Heart failure symptoms (heart)
Arrhythmias (heart)

From Bacon BR. Chapter 212. Iron overload (hemochromatosis). In: *Goldman-Cecil Medicine*. 25th ed. Philadelphia: Elsevier; 2016.

TABLE 196-4 PHYSICAL FINDINGS IN PATIENTS WITH HEREDITARY HEMOCHROMATOSIS

ASYMPTOMATIC
No physical findings
Hepatomegaly
SYMPTOMATIC
Liver
Hepatomegaly
Cutaneous stigmata of chronic liver disease
Splenomegaly
Signs of liver failure: ascites, encephalopathy
Joints
Arthritis
Joint swelling
Heart
Dilated cardiomyopathy
Congestive heart failure
Skin
Increased pigmentation
Endocrine
Testicular atrophy
Hypogonadism
Hypothyroidism

From Bacon BR. Chapter 212. Iron overload (hemochromatosis). In: *Goldman-Cecil Medicine*. 25th ed. Philadelphia: Elsevier; 2016.

- Stage 3: genetic predisposition for hereditary hemochromatosis accompanied by evidence for iron overload with tissue injury or organ damage

Symptoms and Signs Associated with Hereditary Hemochromatosis

General Health

Fatigue is a nonspecific but common symptom in hereditary hemochromatosis patients. Because of altered T-cell function,[10] patients with hereditary hemochromatosis also have an increased risk of infections with *Listeria monocytogenes* (Chapter 272), *Yersinia enterocolitica* (Chapter 288), *Cunninghamella bertholletiae* (Chapter 312), *Aeromonas hydrophila*, and *Vibrio vulnificus* (Chapter 278).

Arthropathy

Arthropathy occurs in 20 to 60% of patients with hereditary hemochromatosis,[11] especially patients with higher erythrocyte mean corpuscular volumes.[12] The second and third metacarpophalangeal joints and knees are most commonly involved, but other joints may be affected in a monoarticular or polyarticular arthritis. The axial skeleton can be involved with associated deformities. The features may overlap osteoarthritis (Chapter 241) and calcium pyrophosphate deposition disease (Chapter 252). The classic physical sign is "pain on handshake," reflecting inflammatory changes of the second and third metacarpophalangeal joints. Plain radiography can differentiate hereditary hemochromatosis–associated arthritis from calcium pyrophosphate deposition disease by the finding of specific involvement of the second and third metacarpophalangeal joints and "hook-shaped" osteophytes of the metacarpal heads.

Liver Disease

Hepatomegaly is frequently present and may be asymptomatic or be associated with right upper quadrant pain from distension of the liver capsule.[13] Progressive iron accumulation in the liver can lead to hepatic fibrosis and cirrhosis. Advanced fibrosis and even cirrhosis may occur in the absence of inflammation, so serum aminotransferase levels are not useful to identify patients with advanced hepatic fibrosis.

Heart Disease

Cardiac manifestations of hereditary hemochromatosis are uncommon, but they are the second leading cause of disease-related death. Cardiac iron overload in hereditary hemochromatosis is associated with conduction defects, which may lead to supraventricular tachyarrhythmias (Chapter 52) or heart block (Chapter 51).[14] Patients may initially present with exertional dyspnea due to diastolic dysfunction that creates restrictive hemodynamics and elevated filling pressures (Chapters 45 and 47). Manifestations of dilated cardiomyopathy and left ventricular systolic dysfunction occur later.[15]

Endocrine Manifestations

Endocrine manifestations are common with advanced disease.[16] In type 1 hereditary hemochromatosis, the prevalence of diabetes (Chapter 210) is estimated to be approximately 13 to 23%, but it is higher in juvenile hereditary hemochromatosis (type 2) and possibly type 4.

Hypogonadism (Chapters 216 and 218), which is the second most common endocrine complication of hereditary hemochromatosis after diabetes mellitus, is an especially predominant feature of juvenile hereditary hemochromatosis (type 2). Clinical manifestations in men include loss of libido, impotence, and early osteoporosis. Amenorrhea, loss of libido, or premature menopause is seen in women. The prevalence of hypothyroidism is 80 times higher in hereditary hemochromatosis than in the general population. Absolute or relative adrenal insufficiency (Chapter 208) can also occur.

Skin Pigmentation

Hyperpigmentation of the skin in hereditary hemochromatosis is mostly due to primary adrenal insufficiency, which leads to increased melanin production that results in the characteristic metallic or slate gray hue commonly referred to as bronzing. Hyperpigmentation is most pronounced in the face, neck, and extremities. Increased pigmentation can also appear on the hard palate and retina. Epidermal and dermal atrophy can be seen.

DIAGNOSIS

The evaluation for suspected hereditary hemochromatosis should begin with serum iron, total iron binding capacity, calculation of transferrin-iron saturation, and a serum ferritin level (Fig. 196-2).[17] A transferrin-iron saturation greater than 45% or an elevated serum ferritin level should prompt *HFE* gene testing.[18] Patients found to be C282Y homozygous can be confirmed to have hereditary hemochromatosis.

Routine clinical genetic testing is limited to the C282Y, H63D, and S65C mutations, but testing can be obtained for types 2, 3, and 4 through specialized laboratories. In addition, because the C282Y mutation is present primarily in White populations, *HFE* gene testing is less likely to be positive in persons of non-White descent. Therefore, patients who have clinical or laboratory evidence of iron overload but who do not have a mutation of the *HFE* gene that is associated with classical (type 1) hereditary hemochromatosis may have a non-*HFE* form of hereditary hemochromatosis.

Furthermore, patients who are not C282Y homozygous are more likely to have an additional explanation for hepatic iron overload compared with C282Y homozygotes. Patients with the C282Y/H63D compound heterozygous mutation and other *HFE* genotypes are more likely to have portal or lobular inflammation and steatosis on liver biopsy than are C282Y homozygotes, thereby suggesting that patients with *HFE* genotypes should be evaluated

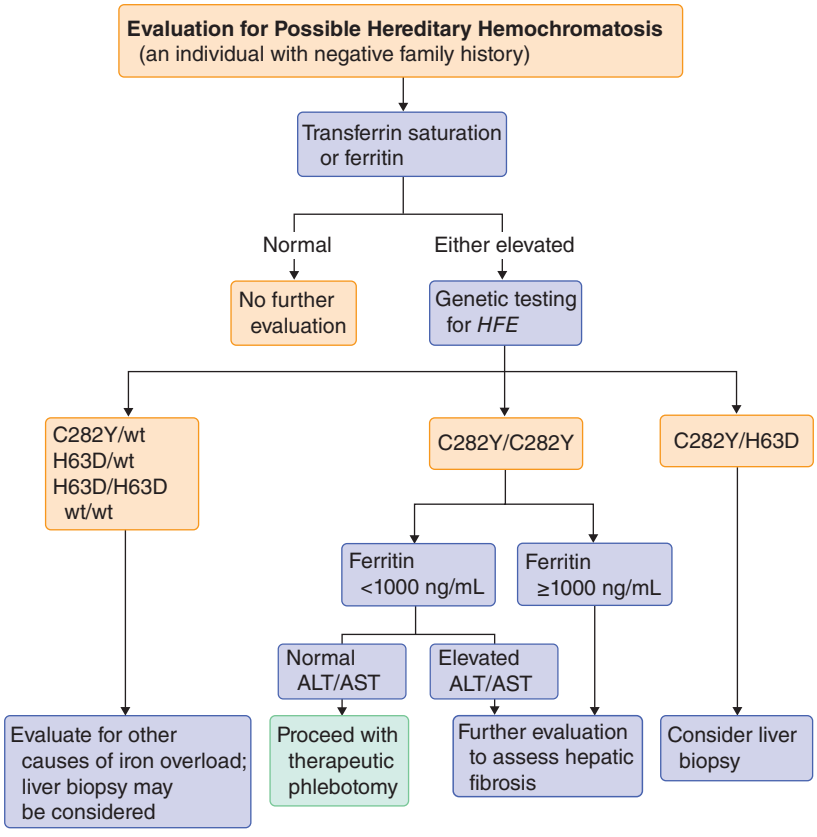

FIGURE 196-2. Proposed algorithm for diagnosis and management of hereditary hemochromatosis. ALT = alanine aminotransferase; AST = aspartate aminotransferase; wt = wild-type (normal).

for the presence of concomitant liver disease such as hepatitis or fatty liver disease. Conversely, patients with advanced liver disease from another cause, particularly hepatitis C and alcohol, may have increased serum-transferrin saturation and ferritin levels as well as increased hepatic iron content even in the absence of hereditary hemochromatosis. *HFE* genotyping is necessary to establish the diagnosis in this setting, although genetic testing may not be helpful in patients with non-HFE hereditary hemochromatosis (types 2 to 4). Phenotypic analysis of hereditary hemochromatosis caused by one of the 70 different mutations identified to date in the *HJV*, *HAMP*, and *TFR2* genotypes has shown that these patients have an earlier age of onset and a more severe clinical course than *HFE* hereditary hemochromatosis, with cardiomyopathy and hypogonadism being particularly prevalent.[19]

Liver biopsy, which had been the gold standard for confirming the diagnosis of hereditary hemochromatosis, for measuring the amount of hepatic iron, and for determining the degree of hepatic fibrosis, can be reserved for establishing the phenotypic diagnosis when *HFE* genotyping is negative. For secondary iron overload (e.g., transfusional iron overload), the pattern of iron distribution within the liver is similar to that observed in type 4 hereditary hemochromatosis, with iron deposition primarily localized in Kupffer RES cells, a scarcity of iron in hepatocytes, and the lack of a periportal to pericentral iron gradient.

Quantifying Iron Overload

Once the diagnosis has been established, the next steps are to assess the degree of hepatic iron overload, the possibility of advanced hepatic fibrosis, and extrahepatic manifestations. Additional measures to evaluate the degree of hepatic fibrosis include serum hyaluronic acid levels, transient elastography, or magnetic resonance elastography.[20] Patients with a serum ferritin level over 1000 ng/mL have up to a 40% risk of advanced hepatic fibrosis or cirrhosis and should be evaluated for advanced hepatic fibrosis. Magnetic resonance (MR) imaging (T2*-weighted) is the most available sensitive and specific imaging modality to diagnose and quantify iron overload in patients with hereditary hemochromatosis.[21] For advanced hepatic fibrosis, noninvasive methods to detect liver stiffness (which is a marker of severe iron deposition, the likelihood of cirrhosis, and the risk of progression to hepatocellular carcinoma) include MR elastography or vibration-controlled transient elastography.[22]

Screening

Routine screening is not recommended because hemochromatosis is sufficiently infrequent. However, first-degree relatives of patients with genotypically confirmed hereditary hemochromatosis should be screened with *HFE* mutational analysis as well as measurement of transferrin saturation and ferritin level. Relatives of patients with *HFE*-related hereditary hemochromatosis who are negative for *HFE* mutations do not require further testing, whereas relatives who are positive should be monitored annually for serum ferritin levels, and phlebotomy should be started when clinical iron overload appears.

TREATMENT

The cornerstone of therapy of hereditary hemochromatosis with a serum ferritin level of 300 ng or more[A1] is one unit of therapeutic phlebotomy at regular intervals, with a goal of reducing the serum ferritin level to less than 100 ng/mL.[23] Each unit of whole blood (450 to 500 mL) contains about 200 to 250 mg of iron, and most patients tolerate frequent phlebotomies (weekly or biweekly) until they have depleted their total body iron stores. Erythrocytapheresis selectively removes red cells, is more efficient, and leads to faster iron depletion than simple phlebotomy, but it requires apheresis equipment and expertise. Because the rate of iron mobilization may vary among patients, serum ferritin levels and hemoglobin levels must be monitored.

Phlebotomy should be suspended or the schedule modified if the hemoglobin level drops to less than 11 g/dL. After reaching the target serum ferritin level of 50 to 100 ng/mL, maintenance phlebotomy should be continued every 2 to 4 months because of ongoing hyperabsorption and reaccumulation of iron. Oral deferiprone[24] or deferasirox or parenteral deferoxamine may be used under expert supervision in patients whose anemia makes them unable to undergo therapeutic phlebotomy.[25]

A diet with little or no red meat reduces iron intake and may reduce phlebotomy requirements.[26] Proton pump inhibitors may somewhat reduce iron absorption and phlebotomy requirements,[A2] but their long-term use is not currently recommended for this purpose because their marginal benefits are small. The future development of hepcidin agonists holds promise.

Liver transplantation can be performed for end-stage liver disease or hepatocellular carcinoma. In theory, liver transplantation should cure the disease, since the liver is the primary location of the deficient *HFE* gene that results in impaired production of hepcidin. However, patients with hereditary hemochromatosis may be at increased risk of infectious or cardiac complications after liver transplantation, and attempts should be made to reduce cardiac iron overload prior to liver transplantation.[27]

PROGNOSIS

Patients who have HFE mutations without phenotypic hemochromatosis or whose iron overload is treated before end-organ damage develops have a normal life expectancy. Fatigue may improve with iron depletion. Unfortunately, iron depletion by phlebotomy does not reliably improve joint symptoms.

The presence of coincidental liver disease, particularly steatohepatitis (alcoholic or nonalcoholic) and chronic hepatitis C, may increase the level of hepatic iron overload and the likelihood of cirrhosis in patients with hereditary hemochromatosis. Patients with cirrhosis have a significantly increased risk of hepatocellular carcinoma, especially in the presence of another coexisting form of liver disease. Liver disease is the most common cause of mortality in *HFE*-associated hereditary hemochromatosis.

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197 SEVERE MALNUTRITION

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DEFINITION

Severe malnutrition encompasses at least three distinct clinical syndromes. The first and most common, stunting, occurs throughout the developing world. It is a consequence of chronic macronutrient and micronutrient deficiency prenatally and during early childhood and is manifested as low birthweight and irreversible cognitive and physical stunting, including below normal weight and short stature in the first few years of life. A second manifestation takes the form of acute malnutrition, a primarily macronutrient deficiency that can also occur in adults. In its most severe forms, it includes kwashiorkor (edematous malnutrition), marasmus (severe wasting), and the mixed form of marasmic kwashiorkor. The third syndrome is the wasting that occurs secondary to acute or chronic underlying medical or surgical illnesses. In clinical practice, these syndromes often overlap significantly on both a population basis and within a given individual, particularly stunting and acute malnutrition in children in impoverished settings.

EPIDEMIOLOGY

Despite a worldwide pandemic of obesity (Chapter 201), severe malnutrition[1,2] still causes a global epidemic of stunting, mostly in rural populations in poor countries.[3] Approximately 22% of children younger than 5 years are stunted worldwide, and another 6.7% suffer from wasting.[4] An estimated 15% of the worldwide under-5 mortality is attributable to stunting and another 12% to wasting.

Rates of secondary severe malnutrition among patients with medical and surgical illnesses vary widely and are a function of underlying disease processes, comorbid conditions, nutritional status before illness, and level of financial resources and social support. In elderly outpatients, the prevalence of malnutrition can exceed 10%.[5] Among hospitalized patients, malnutrition rates of 25 to 60% are common (Chapter 198).

PATHOBIOLOGY

Most stunting in children occurs during the critical 1000 days between conception and 2 years of age. Maternal undernutrition contributes to low birthweight, which persists as underweight, short stature, and cognitive stunting. Stunting also places children at elevated risk for acute malnutrition when challenged by food shortages or acute infections. Even children without prenatal stunting are at high risk for stunting and acute malnutrition when raised in impoverished environments. HIV infection and exposure, diarrhea, pneumonia, measles, and malaria lead to anorexia with decreased dietary intake, increased energy expenditure, and poor nutrient absorption, placing the child at risk for stunting and acute malnutrition. The end of exclusive breast-feeding (whether prematurely or at the recommended 6 months of age) and the introduction of complementary feeding also represent a high-risk period as the child ingests a variety of environmental pathogens and often suffers a relative loss of high-quality protein, lipids, and micronutrients.

Aside from chronic food insecurity and repeated gastrointestinal infections, two major pathobiologic factors contribute significantly to the development of severe malnutrition in children. The first is environmental enteric dysfunction, which is endemic in children and adults throughout the developing world.[6] Environmental enteric dysfunction is characterized by blunted and atrophied intestinal villi, hyperplasia of the crypts, and lymphocytic infiltration of the lamina propria, histologically similar in many ways to celiac disease (Chapter 126). The net effect of environmental enteric dysfunction is an increase in intestinal permeability with translocation of bacteria and toxins, owing to loss of tight junction integrity, changes in the small intestinal microbiota, impaired immune function, and malabsorption. Environmental enteric dysfunction is generally subclinical, predisposes children to poor growth, and makes them more susceptible to developing acute malnutrition.[7]

Secondary severe malnutrition that occurs in the context of an underlying illness often results from a triad of decreased energy intake, malabsorption, and catabolic stressors. Virtually any chronic and/or critical illness can precipitate protein-energy malnutrition, but among the most common are cancer,[8] HIV/AIDS (Chapter 359), tuberculosis (Chapter 299), inflammatory bowel disease (Chapter 127), chronic kidney disease (Chapter 116), chronic liver disease (Chapter 139), and rheumatologic illnesses (Chapter 236). The patient is in a state of net negative energy balance manifested by decreased weight and metabolic rate, accompanied to varying degrees by muscle wasting, depletion of fat stores, reduced cardiorespiratory capacity, skin thinning with easy breakdown and ulceration, hypothermia, immunodeficiency with impaired wound healing, and apathy.

The specific pathobiologic etiologies and risk factors for the development of secondary protein-energy malnutrition are numerous. Primary among them is poor dietary intake from nausea, anorexia, depression, poor dentition, and oral-motor weakness accompanying the underlying illness. Even nutrients that are ingested may not be absorbed for reasons such as reduced bile salt secretion that leads to steatorrhea, pancreatic insufficiency, and damage to the intestinal mucosa in Crohn disease. The systemic inflammation and oxidative stress that are common in conditions such as critical illness, cirrhosis, HIV/AIDS infections, and hemodialysis contribute to a catabolic state. In patients with chronic renal disease, altered amino acid homeostasis by the kidney, resistance to growth hormone and insulin-like growth factor-1, low testosterone levels, insulin resistance, and altered insulin signaling are all important factors in protein-energy wasting. Patients with chronic liver disease often suffer from severe malnutrition owing to a combination of altered gut motility, dyspepsia, cholestasis with poor absorption of fat-soluble vitamins, small intestine bacterial overgrowth, a hypermetabolic state, inadequate hepatic protein synthesis, lack of glycogen reserves, and blood loss from varices.

CLINICAL MANIFESTATIONS

Stunting manifests as short stature and underweight for age. Brain development, and thus head circumference, may also be small for age, although brain size usually is relatively proportional to overall body size.

Acute malnutrition manifests in at least three different forms. Patients with wasting are emaciated and weak, having suffered significant weight loss in a relatively short period. The wasting often first manifests in the axilla and groin, progresses to the thighs and buttocks, and eventually becomes visible in the face, taking on an appearance like an old man. Wasting may be mild, moderate, or severe (marasmus) (Fig. 197-1).

The second form of acute malnutrition is edematous malnutrition, or kwashiorkor.[9] Bilateral peripheral edema begins in the most dependent areas of the

FIGURE 197-1. Kwashiorkor and marasmus in brothers. The younger brother, on the left, has kwashiorkor with generalized edema, skin changes, pale reddish yellow hair, and an unhappy expression. The older child, on the right, has marasmus, with generalized wasting, spindly arms and legs, and an apathetic expression. (From Peters W, Pasvol G, eds. *Tropical Medicine and Parasitology*, 5th ed. London: Mosby; 2002, Fig. 986.)

ABSTRACT

Severe malnutrition includes growth stunting among impoverished populations that begins in childhood and continues into adulthood. Acute malnutrition can occur at any age and often complicates the care of patients with acute illnesses worldwide. All forms of severe malnutrition lead to an array of pathophysiologic changes in multiple organ systems that may not recover fully, even when the patient's nutritional status appears be clinically restored. Effective interventions to reverse growth stunting are relatively lacking, and preventive approaches focus on improved sanitation, attention to acute and chronic infections, and increased intake of complete dietary protein. Uncomplicated cases of acute malnutrition can generally be treated as outpatients using ready-to-use therapeutic food; cases complicated by severe infection or anorexia require inpatient treatment. Patients with malnutrition concomitant with an acute illness will benefit from nutritional rehabilitation in addition to therapies directed at their primary underlying disease(s). The consequences of stunting and acute malnutrition in childhood persist for life and place survivors at increased risk for the metabolic syndrome and obesity.

KEYWORDS

severe malnutrition
kwashiorkor
stunting
wasting
ready-to-use therapeutic food
double burden

FIGURE 197-2. Edematous malnutrition (kwashiorkor).

body and progresses cephalad as it worsens. Despite what can be a relatively profound edema, patients generally do not have ascites, nor is it clear whether their illness is a result of hepatic insufficiency or hypoalbuminemia.[10] The skin may have patchy areas of "flaky paint" depigmentation, commonly with areas of breakdown and resultant infection (Fig. 197-2).

Severe malnutrition in patients with severe or chronic underlying disease generally presents as low body mass index (BMI) or with progressive weight loss. Virtually every organ system is starved of energy in all forms of severe malnutrition and tries to adapt to the decreased energy that is available. Within days, fat replaces glucose as the body's primary fuel source, and ketosis quickly develops. Marked changes in glucose production and protein breakdown are associated with decreased urea production and urinary fluid losses. The basal metabolic rate declines, accompanied by hypothermia and easy fatigue. As starvation continues, nearly all of the body's fat stores are depleted, and lean muscle tissue may be cut in half. Hypokalemia leads to rapid muscle fatigue. In cardiac muscle, the metabolic changes can lead to bradycardia, decreased stroke volume, hypotension, and poor tissue perfusion. Intravascular volume may be diminished at the same time that cellular and capillary leakage increases, thereby leading to generalized edema, particularly in kwashiorkor.

Pulmonary capacity is adversely affected by decreased respiratory muscle mass and electrolyte disturbances. The skin and hair often atrophy, depigment, and break down, thereby leaving the patient susceptible to cutaneous infections. Insulin and thyroid hormone levels decrease, and cortisol concentrations increase. A state of immunodeficiency, which develops as lymphoid tissues atrophy and cell-mediated immunity becomes impaired, places the malnourished patient at high risk for opportunistic infections. Pancytopenia can occur due to bone marrow suppression. Prolonged malnutrition leads to deterioration of all portions of the gastrointestinal system, including atrophy and blunting of the intestinal villi (thereby complicating therapeutic feeding), impaired exocrine pancreatic function, and decreased gastric and biliary secretions. Hepatomegaly and fatty liver infiltration are seen. Except in cases in which renal pathology is the inciting pathway, kidney function is relatively well preserved until late in the course. Although the brain is preserved longer than other organs, cerebral atrophy is seen in acute malnutrition, and delayed cognitive development is a profound complication with lifelong consequences among survivors.

DIAGNOSIS

Careful measurement of height, weight, and mid-upper arm circumference can accurately evaluate any individual for severe malnutrition.

Stunting

Children and adults are considered stunted when the height-for-age Z-score (HAZ) is 2 or more standard deviations (SDs) below the median.[11] Familial short stature, hypothyroidism (Chapter 207), growth hormone deficiency (Chapter 205), and micronutrient deficiency (Chapter 199) are all in the differential diagnosis for a stunted child, but these causes are relatively rare compared with nutritional stunting in the relevant epidemiologic context.

Wasting

Wasting may be diagnosed based on a weight-for-height Z-score (WHZ) or BMI-for-age Z-score (BMIZ) more than 2 SDs below the median. The mid-upper arm circumference can also be used to diagnose wasting in children under 5, in pregnant women, and in adults. Congenital heart disease (Chapter 55), severe diarrhea (Chapter 126) and dehydration, malabsorption syndromes due to intestinal parasites, malaria (Chapter 316), HIV/AIDS (Chapter 359), tuberculosis (Chapter 299), and malignancy should be considered in the differential diagnosis of a patient presenting with wasting.

The presence of edema in the appropriate epidemiologic context, regardless of other anthropometric parameters, should prompt serious consideration of the diagnosis of kwashiorkor. The usual physiologic causes of edema, including underlying cardiac (Chapter 46), hepatic (Chapter 140), and renal diseases (Chapter 116), should be considered in the differential diagnosis. In rural impoverished populations where kwashiorkor is endemic, routine health care is also generally limited; thus, the possibilities of congenital or rheumatic heart disease, nephrotic syndrome (Chapter 107), profound anemia (from primary iron deficiency, severe malaria, or hookworm, among other causes), and tuberculosis should be considered. Nevertheless, for the majority of children presenting with edema in these populations, kwashiorkor remains the leading diagnosis (E-Fig. 197-1).

Secondary Malnutrition

Secondary malnutrition due to underlying illness also requires careful anthropometry, with a BMI of less than 18.5 kg/m^2 representing moderate malnutrition and a BMI of less than 15 kg/m^2 representing severe malnutrition.[12] Even without a BMI this low, any significant weight loss, especially if associated with lean muscle loss in addition to depletion of fat stores, should prompt consideration of severe malnutrition and necessitates an investigation into an underlying illness if one has not been previously identified. No reliable diagnostic tests are available to identify those with severe malnutrition because serum markers such as albumin, prealbumin, and C-reactive protein are themselves acute-phase reactants and nonspecific for this purpose. Diminished grip strength is perhaps the best single clinical measure to assess the degree of malnutrition in this context.

TREATMENT

Primary Malnutrition in Children and Adolescents

Relatively little can be done to reverse stunting because the physical and cognitive growth faltering suffered in the first 1000 days is due to a confluence of environmental factors not likely amenable to medical therapies. Children and adolescents remain at high risk for further stunting, although some degree of catch-up growth is possible. Attention should be directed to an overall improvement in dietary quality and diversity, particularly with respect to increased complete protein intake. Routine health care, including immunizations, vitamin A supplementation, and periodic deworming, should be ensured. HIV testing and treatment should be sought. Improvements in sanitary living conditions are likely to be the most beneficial.

Children and adolescents with uncomplicated severe acute malnutrition can be treated as outpatients using ready-to-use therapeutic food (Table 197-1), most often a fortified peanut paste, if they are successfully able to ingest approximately 30 g of ready-to-use therapeutic food under directly observed therapy (see E-Fig. 197-1). The inclusion of a week of empiric oral antibiotic therapy decreases mortality, improves nutritional recovery, and decreases the need for hospitalization.[A1]

Children and adolescents with complicated severe acute malnutrition should be managed as inpatients, with initial attention focused urgently on the infections, hypoglycemia, hypothermia, and dehydration that lead to early mortality. A microbiota-directed complementary food prototype can change the intestinal microbiome (Chapter 257) and significantly improve weight gain.[A2]

Mortality and nutritional recovery outcomes from community-based programs are generally superior to those achieved by inpatient care, even for infants under 6 months of age.[13] As a result, community-based care is the current international standard of care and has relegated inpatient care only to patients who have anorexia or medical complications or who are in an area where ready-to-use therapeutic food is not available.

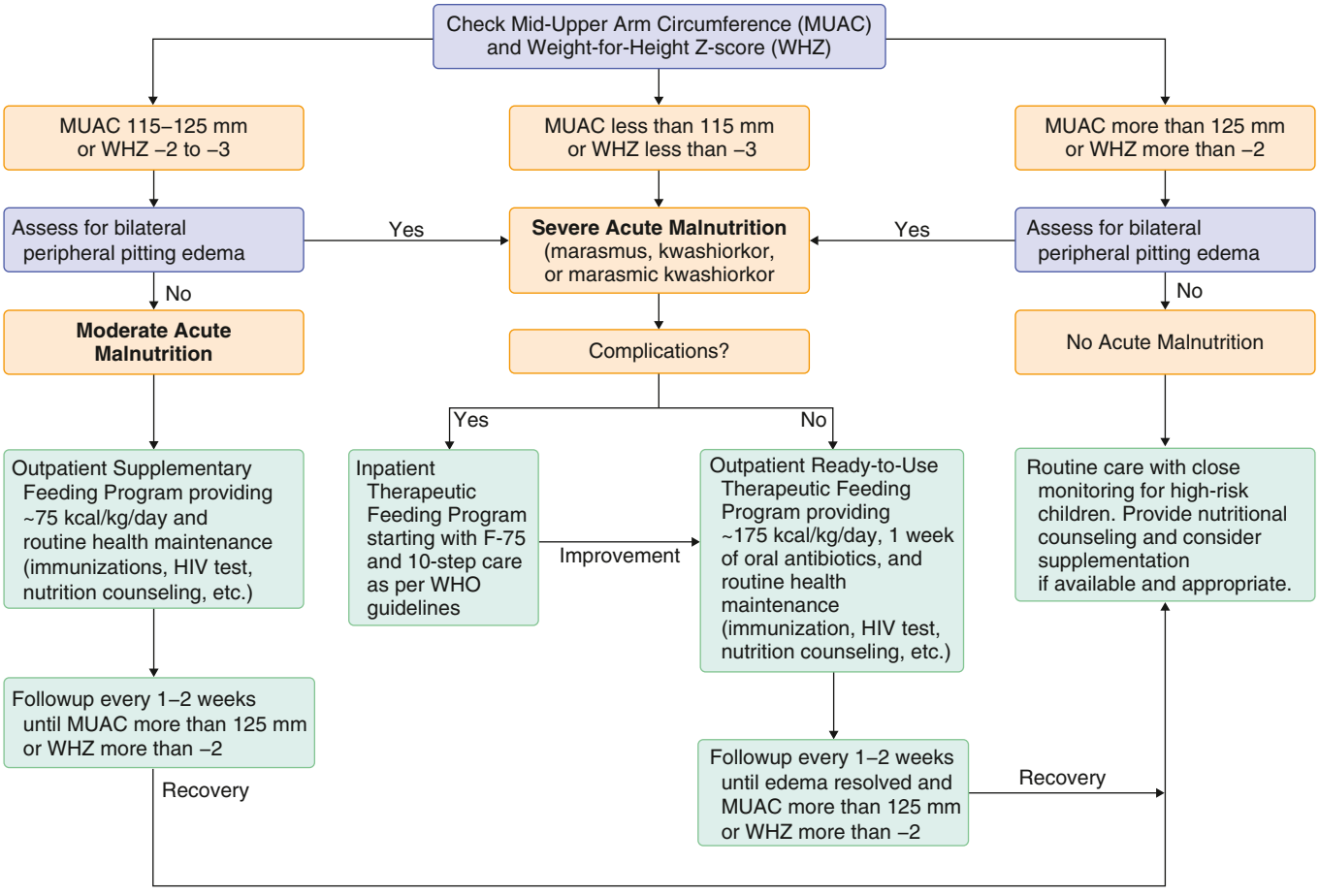

E-FIGURE 197-1. Diagnostic and treatment algorithm for acute malnutrition in children 6 to 59 months of age. Mid-upper arm circumference (MUAC) is only to be used for children 6 to 59 months of age. For details of diagnosis and management, see Trehan I, Manary MJ. Management of severe acute malnutrition in low-income and middle-income countries. *Arch Dis Child*. 2015;100:283-287. HIV = human immunodeficiency virus; WHO = World Health Organization.

TABLE 197-1 NUTRITIONAL COMPOSITION OF THERAPEUTIC FOODS FOR SEVERE ACUTE MALNUTRITION

	F-75 (100 mL)	F-100 (100 mL)	RUTF (100 mg)
Energy (kcal)	75	100	543
Protein (g)	0.9	2.9	13.6
Lactose (g)	1.3	4.2	
Potassium (mg)	156	246	1111
Sodium (mg)	14	44	189
Magnesium (mg)	10.5	17.7	92
Zinc (mg)	2	2.3	14
Copper (mg)	0.25	0.25	1.78
Osmolarity (mOsm/L)	413	419	
% of total energy from protein	5	12	10-12
% of total energy from fat	36	53	45-60

RUTF = ready-to-use therapeutic food.

Secondary Malnutrition

Patients with secondary severe malnutrition should, first and foremost, have their underlying illness addressed because this approach is most likely to lead to long-term recovery of their nutritional status. Concomitantly, nutritional rehabilitation should be undertaken to prevent further energy losses and allow for recovery of damaged organic pathways. Oral supplements[14] and dietary counseling can significantly improve nutrition in at-risk community-dwelling older adults.[A3] In inpatients, fluid, electrolyte, and acid-base status should be corrected cautiously. In general, enteral nutrition (Chapter 198) is preferred over parenteral, assuming the gastrointestinal tract is functioning adequately.[A4] Frequent small feedings or slow drip feedings may be necessary. Aggressive tube feeding or parenteral nutrition (Chapter 198) should be avoided in the early stages of rehabilitation because the refeeding syndrome is a real danger in patients who are malnourished. Hypophosphatemia, hypokalemia, hypomagnesemia, hyperglycemia, fluid overload, muscular weakness, cardiac arrhythmias, and diarrhea are all risks associated with aggressive refeeding. Fluid status, glycemic status, and electrolyte levels should be monitored closely throughout refeeding.

PREVENTION

Prevention of stunting and acute malnutrition remains one of the most challenging and elusive goals in global health, especially given the intergenerational effects of maternal malnutrition. Adherence to exclusive breast-feeding for the first 6 months and continued breast-feeding for at least the first 2 years is beneficial, as is early diagnosis and treatment of HIV in mothers and their infants. Addressing sanitation, food insecurity, spotty vaccination coverage, protein intake,[A5] and limited access to medical care may provide the most benefit to decreasing severe malnutrition during childhood and adolescence, as well as its adult consequences.

Close attention to the nutritional status of medical and surgical patients, with risk stratification based on BMI and weight trajectory, is necessary to limit the risk for protein-energy malnutrition in these patients as they are treated for their underlying illnesses. Optimizing nutritional status will aid in recovery from their primary conditions, and similarly, recovery from the primary condition will improve benefit to overall nutritional status. Efforts to empirically provide extra protein, calories, and micronutrients during times of particular oxidative stress and catabolism will help limit weight loss and its adverse effects.

PROGNOSIS

The prognosis for stunted adolescents generally remains poor because the physical and cognitive deficits they suffer are mostly carried with them throughout life.[15,16] Individuals who recover from an episode of severe acute malnutrition remain more susceptible to further episodes over the next several months than their peers; those with underlying illnesses such as HIV or tuberculosis remain at significantly elevated risk. The best recovery rates in severe acute malnutrition treatment programs peak at approximately 90%, with about 4 to 5% mortality. Mortality rates are substantially higher in children and adolescents who require hospitalization. Untreated episodes of severe wasting carry an estimated 10 to 20% mortality risk per month.

Early childhood severe malnutrition is linked to an increased risk for the metabolic syndrome in adults, as part of the double epidemic of childhood undernutrition and adult obesity being increasingly observed worldwide. Thus, although the predominant burden of severe malnutrition occurs in young childhood, its intergenerational effects and lifelong consequences make an assessment of nutritional challenges during childhood and adolescence an important consideration when caring for any adult patient with a vulnerable background. In older adults, severe malnutrition is associated with frailty, failure to thrive, and increased in-hospital mortality.[17]

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198 MALNUTRITION: ASSESSMENT AND SUPPORT

TOMMY E. CEDERHOLM AND INGVAR G. BOSAEUS

DEFINITION

Malnutrition is the result of an interplay between food deprivation and catabolic processes that are linked to acute and chronic diseases as well as to aging.[1] Disease-related malnutrition should be distinguished from starvation-related malnutrition (food insecurity), which is linked to poverty, warfare, and natural catastrophes (Chapter 197). Obesity, which is also a manifestation of improper nutrition, is discussed in Chapter 201.

Acute and chronic diseases that affect most organ systems may have profound effects on appetite, food intake, and metabolism. The result can be tissue catabolism, which leads to wasting syndromes, micronutrient deficiencies, and weight loss, which can be minor or pronounced. Malnutrition may manifest as changes in body composition (e.g., reductions in muscle mass and deficiencies in micronutrients) rather than as underweight per se. Weight loss and body composition are better indicators of malnutrition than weight itself.

The sequelae of disease-related malnutrition include disability, morbidity, and eventually mortality. Morbidity includes catabolic syndromes, such as sarcopenia and frailty (Chapter 24), that require specific therapies because they have both nutritional and non-nutritional components.

EPIDEMIOLOGY

The incidence and prevalence of malnutrition vary greatly by underlying disease, stage of disease, age of the patient,[2] and settings (e.g., community, nursing home, or hospital). Overall estimates of the prevalence of malnutrition in older populations (>65 years of age) are 5 to 10% in community-dwelling older individuals, 20 to 40% in older hospitalized patients, and up to 50% in residents of nursing homes. With some malignant diseases, especially cancers of the upper gastrointestinal tract, patients develop malnutrition early in the course of disease.[3] With other tumors, such as of the breast, lung, and kidney, patients become malnourished and lose weight later in the course of their disease. Thus, the prevalence of malnutrition ranges from 0 to up to 50% in

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198 MALNUTRITION: ASSESSMENT AND SUPPORT

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ABSTRACT

Malnutrition is a complex condition that usually results from a combination of insufficient intake of vital nutrients and increased disease-related catabolism. Altered body composition, especially decreased muscle mass and body cell mass, leads to clinical manifestations that include diminished physical and mental function, increased susceptibility to infections, organ dysfunction, and mortality. Adults hospitalized or in long-term care facilities should be screened for their risk of malnutrition and, when indicated, receive counseling as well as oral, enteral, or parenteral nutrition. Individuals should generally receive 20 to 30 kcal/kg body weight and 0.8 to 1.5 g protein/kg body weight depending on the clinical situation. Effective interventions can supply nutrient needs but may not reverse the conditions that initially may have led to the malnutrition.

KEYWORDS

malnutrition
weight loss
nutritional assessment
nutrition support
enteral nutrition
parenteral nutrition
refeeding syndrome

patients with cancer depending on the type and stage. Severe trauma, burns (Chapter 97), and acute infections trigger inflammatory and catabolic processes that rapidly degrade fat and muscle mass, as well as other organ tissues. In malabsorptive gastrointestinal diseases (e.g., Crohn disease [Chapter 127] or celiac disease [Chapter 126]), weight loss and malnutrition are major manifestations of the underlying disease, and essentially all patients will eventually become malnourished if treatment is not provided.

Most patients with chronic disorders of major organ systems eventually develop malnutrition at the end stages of the disease. Mechanisms vary, but homeostatic inflammatory activity is invariably abundant. In patients with chronic obstructive pulmonary disease (Chapter 76),[4] heart failure (Chapter 45), liver cirrhosis (Chapter 139), or chronic kidney failure (Chapter 116), 20 to 50% of patients have signs of malnutrition. Patients with neurologic diseases, especially post-stroke (Chapter 375) or with Parkinson disease (Chapter 378) with dysphagia, have a similar risk of malnutrition. With a major depressive disorder (Chapter 362), up to 50% of patients lose weight, but one third may gain weight. Eating disorders are discussed in Chapter 200.

PATHOBIOLOGY

Malnutrition develops when the intake of energy and/or other nutrients is sufficiently lower than the expenditure for a sufficient period of time so as to deplete body stores. When metabolism is adapted to use stored energy for fuel, the structure (i.e., lower mass) and function of most organ systems will eventually be adversely affected.

Disease-related malnutrition develops through two parallel pathways (Fig. 198-1), depending on the presence and degree of systemic inflammation. In noninflammatory conditions, the main problem is that the intake (or uptake) of energy and nutrients is too low in relation to requirements. In this situation, metabolism adapts to the starving condition. Resting energy expenditure, defined as the basal metabolic rate (Chapter 201), decreases, mediated by neuroendocrine mechanisms that alter the functions of multiple organs, typically causing reductions in heart rate and body temperature. Behavioral changes, which also are common, include less spontaneous physical activity, muscular atrophy, and mood changes.

Metabolism also switches to use available substrates for fuel. Carbohydrate stores are limited; for example, glycogen in liver and muscle is consumed within 1 to 2 days of total starvation. Body fat depots are used as the main energy source, but the breakdown of protein in muscle and other organs also provides amino acids that are oxidized for energy. In the absence of inflammation, both synthesis and breakdown of protein decrease so as to minimize the net loss of protein. These adaptive changes contribute to the ability to survive prolonged starvation. The use of body stores to fuel energy metabolism is reflected in loss of body weight. The change in weight adjusted for height, usually expressed as body mass index (BMI; weight in kilograms divided by height in meters squared), may then reflect the degree of depletion of body energy stores.

When the underlying disease is accompanied by an inflammatory response, the problem becomes more complex. Inflammatory conditions often suppress appetite, thereby decreasing food intake and resulting in negative energy balance. Inflammation is also associated with maladaptive catabolism beyond what is needed to compensate for the gap in nutrient intake. Unlike simple starvation, inflammatory catabolism increases resting energy expenditure, often in proportion to the degree of metabolic stress. The resting heart rate and body temperature are usually elevated. The breakdown of protein in skeletal muscle is increased, and amino acids are used for fuel, for the production of glucose by neoglucogenesis, and for the synthesis of other proteins, such as acute phase reactants. Protein turnover is not nutritionally regulated but rather continues even if sufficient energy is supplied. The net result is a loss of muscle mass.

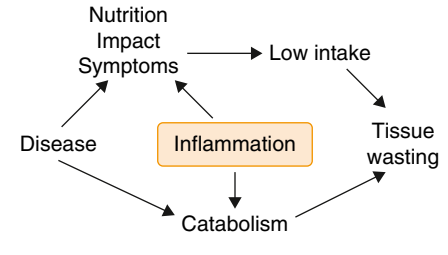

FIGURE 198-1. **Disease-related malnutrition develops through two parallel pathways. In the absence of inflammation, low intake symptoms dominate. With inflammation, catabolism increases tissue loss while concurrent loss of appetite may also decrease intake.**

CLINICAL MANIFESTATIONS AND DIAGNOSIS

The classic clinical manifestation of malnutrition is underweight or weight loss. Underweight for height, defined as a BMI below 20 in younger individuals or below 22 in older (i.e., age >70 years and over) individuals, raises a suspicion for malnutrition. In patients with various acute or chronic illnesses, weight loss and malnutrition can be caused by a variety of mechanisms (Table 198-1).

Screening for Malnutrition

All patients who see a health care clinician or who use elderly care services should be screened for possible malnutrition within the first 24 to 48 hours and then at regular intervals thereafter. Screening tools attempt to identify patients who have or are at high risk for developing malnutrition. For hospitalized patients, the Nutrition Risk Screening 2002 (Table 198-2) can provide a rapid assessment of nutritional status and the likelihood of needing nutritional intervention. For nonhospitalized patients, the clinical setting and local preferences may guide toward which tool to apply. The Short Nutritional Assessment Questionnaire (SNAQ; Table 198-3) can estimate the future likelihood of a significant involuntary weight loss. For older persons, the Mini Nutritional Assessment–Short Form score (https://www.nestle.com/asset-library/documents/library/events/2010-malnutrition-in-older-people/mna_mini_english.pdf)[5] can quickly estimate current nutritional status.

DIAGNOSIS

When screening identifies subjects at risk for malnutrition, the clinician should assess whether the patient meets diagnostic criteria for malnutrition (Fig. 198-2),[6] based on at least one of three phenotypic criteria (weight loss, low body mass index, or reduced muscle mass) and at least one of two etiologic criteria (reduced food intake/food assimilation or high disease burden as reflected by persistent or recurring inflammation).[7] The severity of these conditions can be graded as moderate or severe (Table 198-4) and categorized according to etiology: disease-related malnutrition with inflammation, disease-related malnutrition with no perceived inflammation, or malnutrition/undernutrition without disease (i.e., starvation).

Causes of Weight Loss

Weight loss can be caused by a myriad of medical disorders[8] that affect essentially every organ system. The first step in diagnosis is to exclude a specifically

TABLE 198-1 COMMON CAUSES OF MALNUTRITION WITH PROTEIN, ENERGY, AND MICRONUTRIENT DEPLETION IN MEDICAL PATIENTS WITH ACUTE OR CHRONIC ILLNESSES

- Decreased spontaneous food intake due to anorexia from chronic or acute illness, gastrointestinal symptoms (e.g., nausea, vomiting, abdominal pain), depression/anxiety
- Restricted food intake required for surgical operations or diagnostic/therapeutic procedures and gastrointestinal dysfunction that follows them
- Abnormal macronutrient and micronutrient losses from the body due to malabsorption (e.g., celiac sprue, short-gut syndrome, inflammatory bowel disease, cystic fibrosis, diarrhea), maldigestion (e.g., pancreatitis), emesis, polyuria (e.g., in diabetes), wound drainage, or renal replacement therapy
- Periods of increased energy expenditure (calorie needs), protein requirements, and micronutrient needs (e.g., critical illness, increased inflammation)
- Catabolic effects of counter-regulatory hormones (e.g., cortisol, catecholamines, glucagon), release of pro-inflammatory cytokines from stimulated immune cells and endothelial and epithelial cells (interleukins 1, 6, and 8 and tumor necrosis factor-α), and peripheral tissue resistance to the anabolic hormones insulin and insulin-like growth factor-I
- Bedrest, decreased ambulation, and chemical paralysis during mechanical ventilation (skeletal muscle wasting due to impaired protein synthesis)
- Administration of drugs that induce skeletal muscle breakdown, gastrointestinal injury, or electrolyte and water-soluble vitamin losses (e.g., corticosteroids, chemotherapeutic agents, diuretics, and antirejection regimens)
- Socioeconomic deprivation, inadequate caregiving, ambulation difficulties in the home setting
- Inadequate provision of calories, protein, and essential micronutrients (vitamins, minerals, and trace elements) during hospitalization

From Ziegler T. Malnutrition: assessment and support. In: Goldman L, Schafer AI, eds. *Goldman-Cecil Medicine*, 26th ed. Philadelphia: Elsevier; 2020:1401-1405.

TABLE 198-2 NUTRITIONAL RISK SCREENING 2002 FOR HOSPITALIZED PATIENTS

1. If the patient has any of the following characteristics:	Has a BMI <20.5 kg/m^2 Has lost >5% of body weight in past 3 months Has reduced dietary intake in the past week or is in an ICU	
2. Ask the following questions:		
A. Nutritional impairment	None	0
	Mild: weight loss >5% in 3 months or food intake <50 to 75% of normal in the past week	+1
	Moderate: weight loss >5% in 2 months or BMI 18.5 to 20.5 plus impaired general condition or food intake 25 to 60% of normal in past week	+2
	Severe: weight loss >5% in 1 month (>15% in 3 months) or BMI < 18.5 plus impaired general condition or food intake 0 to 25% of normal in past week	+3
B. Severity of disease	Normal nutritional requirement	0
	Hip fracture, chronic illness (may have acute complications; e.g., cirrhosis or COPD), chronic dialysis, diabetes, cancer	+1
	Major abdominal surgery, stroke, severe pneumonia, hematologic malignancy	+2
	Head injury, bone marrow transplant, ICU patient with APACHE > 10	+3
C. Age	< 70 years	0
	≥ 70 years	+1
3. Add up the score:	Score 0-3 = low risk; rescreen weekly Score 4 = at risk; start nutritional planning Score 5-7 = high risk; initiate nutritional intervention	

APACHE = Acute Physiology and Chronic Health Evaluation score; BMI = body mass index; COPD = chronic obstructive pulmonary disease; ICU = intensive care unit.

Based on Kondrup J, Rasmussen HH, Hamberg O, et al. Nutritional risk screening (NRS 2002): a new method based on an analysis of controlled clinical trials. *Clin Nutr*. 2003;22:321-336.

TABLE 198-3 THE SIMPLIFIED NUTRITIONAL APPETITE QUESTIONNAIRE (SNAQ)

ASSESSING APPETITE TO PREDICT WEIGHT LOSS		POINTS*
A. My appetite is:	Very poor	1
	Poor	2
	Average	3
	Good	4
	Very good	5
B. When I eat:	I feel full after eating only a few mouthfuls	1
	I feel full after eating about a third of a meal	2
	I feel full after eating over half a meal	3
	I feel full after eating most of the meal	4
	I hardly ever feel full	5
C. Food tastes:	Very bad	1
	Bad	2
	Average	3
	Good	4
	Very good	5
D. Normally I eat:	Less than one meal a day	1
	One meal a day	2
	Two meals a day	3
	Three meals a day	4
	More than three meals a day	5

*If the sum of the four answers is 14 or less, the patient is at significant risk of a loss of 5% or more of body weight in the next 6 months.

Based on Wilson M-MG, Thomas DR, Rubenstein LZ, et al. Appetite assessment: simple appetite questionnaire predicts weight loss in community-dwelling adults and nursing home residents. *Am J Clin Nutr*. 2005;82:1074-1081.

treatable cause (see Fig. 118-4). Involuntary weight loss of 5% or more of body mass over a period of 6 to 12 months raises the possibility of a major underlying condition such as an occult malignancy or a chronic inflammatory

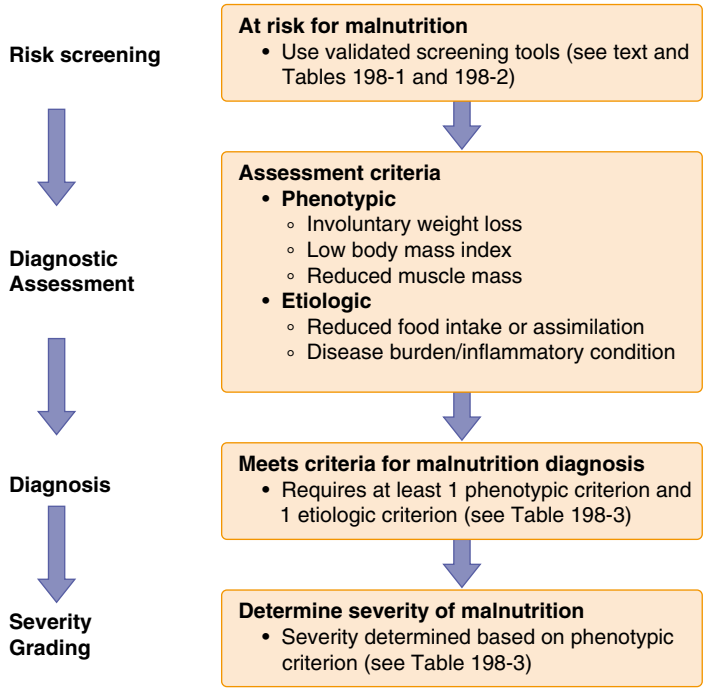

FIGURE 198-2. Global Leadership Initiative on Malnutrition diagnostic scheme for screening, assessment, diagnosis, and grading of malnutrition. (From Cederholm T, Jensen GL, Correia MITD, et al. GLIM criteria for the diagnosis of malnutrition: a consensus report from the global clinical nutrition community. *Clin Nutr*. 2019;38:1-9.)

or infectious process, depression (Chapter 362), or a primary eating disorder (Chapter 200).

Nutritional Assessment

The nutritional assessment, which provides the basis for understanding the underlying mechanisms and how to tailor nutritional treatment, should include:

1. A detailed medical history, focusing on potential comorbid medical and psychiatric conditions that are associated with poor nutrition, to understand the underlying diseases or conditions of the state of malnutrition.
2. Social and psychological history, with an emphasis on living conditions, loneliness, and depression.
3. Nutritional history, including limitations in food intake (e.g., due to dental status or dysphagia), and a food log that includes specific foods and amounts eaten over several days.
4. A careful physical examination of all organ systems, including an estimation of muscle and fat mass, as well as an estimation of frailty and sarcopenia (Chapter 23).
5. A record of food intake and observations of a patient while eating, including direct observation of the patient's ability to chew and swallow.
6. Laboratory testing, including routine hematology and chemistry testing, as well as tests of renal and liver function, lipid levels, and biomarkers of inflammation and catabolic activity (e.g., serum levels of albumin and C-reactive protein). The hemoglobin level may correlate with the severity of malnutrition, and a serum insulin-like growth factor-1 may indicate anabolic activity. The serum pre-albumin level may monitor changes in nutritional status better than an albumin level because of its shorter half-life. The serum creatinine level may reflect muscle mass when renal function is intact. The serum cholesterol usually decreases with malnutrition.

THERAPY

Nutrients can be provided as a regular oral diet, a modified therapeutic diet (e.g., fortified food and/or oral nutritional supplements), via enteral tube feeding, or as parenteral nutrition. Oral intake of food and drink is preferred and should be based on a dietician's evaluation of the patient's current intake and ability to ingest food.

In patients who have an underlying disease that causes functional impairment, energy expenditure from physical activity is usually reduced. As a result, energy requirements may be lower, but requirements of other nutrients are generally unchanged or increased, depending on the underlying disease.

Appetite is often reduced, and oral food should be modified to accommodate the amount of nutrients needed in a lower food volume.

In many patients with malnutrition, the ability to increase oral food intake is insufficient to counteract the catabolic process. In such patients, individualized medical nutritional therapy is required with a fortified diet and nutritional supplements.[A1] If that approach is inadequate or impractical, alternative food delivery (enteral or parenteral nutrition) is required based on the patient's ability to ingest, absorb, and metabolize food.[A2] The goal is to meet energy and nutrient needs and, over time, restore depleted stores of body nutrients in as simple and safe a way as possible, recognizing that the goal may be met by a combination of foods and routes. However, permissive underfeeding (70 to 80% of caloric requirements) and trophic feeding (25% of caloric requirements) can be equivalent to full feeding for critically ill adults during the first week or two of hospitalization[A3] unless the patient has preexisting malnutrition.

Enteral tube feeding delivers nutrients directly into the gastrointestinal tract, whereas parenteral nutrition delivers nutrients directly into the blood stream. These treatment modalities must be individually tailored, weighing the benefits compared with the risks, and monitored to avoid complications. The general indication for enteral or parenteral feeding is inadequate intake due to prolonged disease of 1 week or more.

When the gastrointestinal tract is functional, enteral nutrition is always the preferred choice,[A4,A5] if tolerated (Fig. 198-3), recognizing that gastrointestinal function often varies over the course of a disease and delivery of nutrition therapy must adapt to such changes. Enteral nutrition is associated with an improved gut barrier function[9] as well as fewer infectious and metabolic complications compared with parenteral nutrition. If gastrointestinal function is insufficient, the residual amount of nutrients and energy should be delivered parenterally, but only a small percentage of patients need total parenteral nutrition.

Estimation of Energy and Protein Requirements

After assessing nutritional status, the clinician should estimate energy requirements, because therapy must address the gap between these two figures.[10] Energy requirements are preferably measured by indirect calorimetry but are usually estimated based on the patient's size and sex. For example, the Harris-Benedict equation can be used to estimate basal 24-hour caloric expenditures as

$$66 + (13.7 \times \text{kg body weight}) + (5.0 \times \text{height in cm}) - (6.8 \times \text{age in years})$$

in men and as

$$655 + (9.6 \times \text{kg body weight}) + (1.8 \times \text{height in cm}) - (4.7 \times \text{age in years})$$

in women. Ambulatory individuals require about 1.3 times those amounts. Energy requirements also can be approximated as 25 kcal/kg/day in bedridden patients and 30 kcal/kg/day in mobile patients with limited physical activity.

On average, protein needs are in the range from 0.8 g/kg/day in healthy adults but are 1.2 to 1.5 g/kg/day in acutely ill or postoperative well-nourished patients and can be 1.5 g/kg/day or even higher in patients who have catabolic conditions or who are already protein-depleted. However, needs are lower in patients who have difficulty handling protein, such as patients with hepatic or kidney failure. Micronutrient requirements should be determined according to prevailing recommendations and the clinical condition (Chapter 199). Although clinicians should have an understanding of nutritional needs and the components of tube feedings, specific details should be guided by dietician services.

Systematic monitoring of clinical and laboratory parameters is part of appropriate management with all forms of nutritional therapy. In acute care and in metabolically unstable patients, frequent measurements of blood glucose levels and serum electrolytes may be warranted, as well as daily body weight measurements for fluid balance. In stable patients, weekly assessment of body weight (for long-term tissue repletion), oral and total intake (when applicable), and selected laboratory parameters is a common procedure. In patients on parenteral nutrition, liver function tests are usually monitored.

Enteral Nutrition

Enteral nutrition can be deferred for the first 24 to 48 hours in critically ill patients without adverse effects.[A6,A7] Enteral nutrition is delivered through a tube, which is either passed per orally through a nostril and the esophagus and into the stomach or proximal small bowel or placed directly as a nutritive stoma into the gastrointestinal tract by an endoscopic or operative procedure. A nasogastric tube is often used initially and when a short-term course of therapy (up to a few weeks) is expected. Tolerability is often limited in conscious patients, mainly due to symptoms from the nose and throat. Thin, soft tubes are preferable, but no single design is clearly superior. When enteral tube feeding is required for a prolonged period of time (more than a few weeks), most patients prefer and tolerate a nutritive stoma better than a nasogastric tube, but this choice should be weighed against the operative risk, especially in older frail patients. The most common nutritive stoma is a percutaneous endoscopic gastrostomy (PEG), which is inserted through the abdominal wall into the stomach by an endoscopic procedure. A nutritive jejunostomy is sometimes performed, most commonly as part of a major operative procedure on the upper abdomen. When enteral nutrition is delivered directly into the proximal small bowel, the normal regulation of gastric emptying is bypassed, so care should be taken to ensure a controlled slow, smooth delivery (by pump).

Enteral nutrition, especially if infused directly into the small bowel, is best delivered by continuous flow from a container attached to the feeding tube, with or without pump control over 20 to 24 hours per day. The infusion rate is adapted to the patient's needs and tolerance, often not exceeding 125 mL/hour directly into the small bowel. When delivery is into a functioning stomach, administration can be in intermittent doses adapted to the size of the enteral products, usually 500 mL. Intermittent infusions can allow the patient to be more mobile between infusions, but continuous infusion is generally preferred in critically ill adults.[A8] At the initiation of therapy, slow infusion rates may be needed to avoid gastrointestinal symptoms, such as nausea and diarrhea. One approach is to begin at 40 to 50 mL per hour and advance up to 125 mL per hour, but starting doses as low as 15 to 20 mL per hour may be preferable in patients with a history of prolonged starvation, in the early postoperative phase, and in the intensive care unit (ICU).

Enteral Formulas

Enteral formulas, which should be able to provide all essential nutrients, have a sufficiently low viscosity to allow flow through a thin feeding tube. Standard formulas usually have an energy density of 1 kcal/mL (4.2 kJ/mL) and an osmolality close to that of plasma. High-protein and energy-rich formulas,[A1] which provide about 1.5 kcal/mL, are used when the volumes needed to meet energy needs are not tolerated. Energy-rich formulas may prolong gastric emptying, and care must be taken to ensure fluid needs are met so that patients do not become dehydrated.

Complications

Gastrointestinal symptoms are common with enteral tube feeding, especially at the initiation of the therapy. Nausea and vomiting are almost always associated with impaired gastric emptying. Feeding must be reduced or stopped quickly to reduce the risk of pulmonary aspiration of gastric contents. A slower infusion

TABLE 198-4 DIAGNOSIS OF MODERATE AND SEVERE MALNUTRITION BY PHENOTYPIC CRITERIA

	CRITERIA (ANY ONE OF THESE IS DIAGNOSTIC)		
	WEIGHT LOSS (%)	**BODY MASS INDEX**	**MUSCLE MASS**
Moderate Malnutrition	5 to 10% within the past 6 months or 10 to 20% beyond 6 months	<20 if <70 years old; <22 if ≥70 years old	Mild to moderate reduction*
Severe Malnutrition	>10% within the past 6 months or >20% beyond 6 months	<18.5 if <70 years old; <20 if ≥70 years old	Severe reduction*

*By body composition testing, dual-x-ray absorptiometry, bioelectric impedance analysis, computed tomography, magnetic resonance imaging, physical examination, or circumference of the mid-arm or calf. Adapted from Cederholm T, Jensen GL, Correia MITD, et al. GLIM criteria for the diagnosis of malnutrition: a consensus report from the global clinical nutrition community. *Clin Nutr*. 2019;38:1-9; and Compher C, Cederholm T, Correia MITD, et al. *JPEN* 2022 Apr 19. https://doi.org/10.1002/jpen.2366. Online ahead of print.

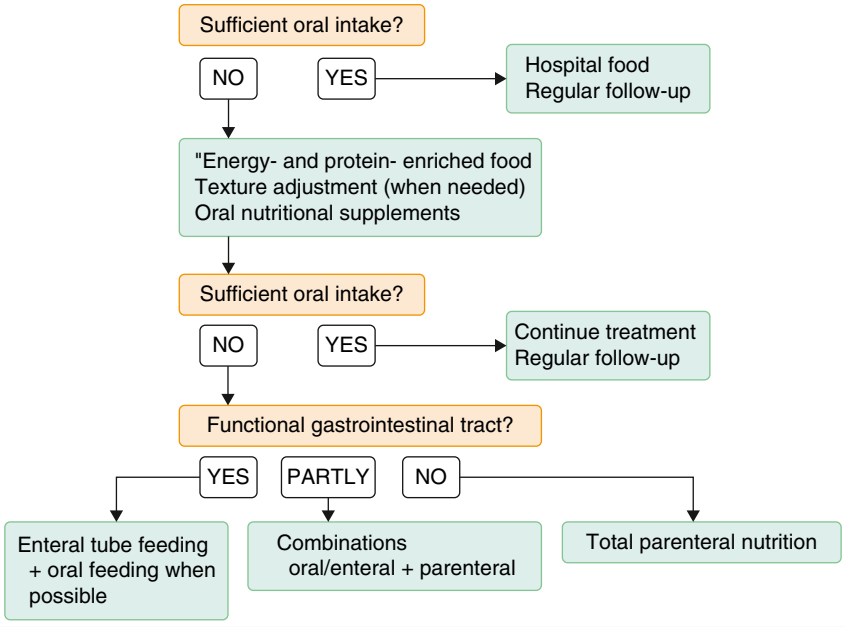

FIGURE 198-3. **Flow diagram illustrating principles for nutrition support.**

rate may alleviate symptoms, and prokinetic drugs (e.g., metoclopramide 10 mg twice daily for a maximum 5 days) should be considered.

Diarrhea, which is the most common complication of enteral tube feeding, is typically due to factors such as concomitant antibiotic treatment, rapid administration of enteral feeding, or use of hyperosmolar solutions. Patients who have intrinsic bowel disease or severe hypoalbuminemia also may develop diarrhea. Metabolic complications of enteral tube feeding include fluid imbalances, hyperglycemia, electrolyte abnormalities, and occasionally refeeding syndrome (see later). Patients who receive enteral tube feeding as their sole source of nutrition for prolonged periods (months to years) should be monitored for possible deficiencies of micronutrients (Chapter 199).

Parenteral Nutrition

When gastrointestinal function is insufficient to enable uptake of nutrients and/or fluids to meet nutritional requirements, parenteral nutrition is the only option.[11] In patients who have had major abdominal surgery, beginning supplemental parenteral nutrition on postoperative day 3 appears to be better than delaying until postoperative day 8.[A9]

Parenteral nutrition is first-line therapy only in patients who have chronic intestinal failure. However, relatively few patients need total parenteral nutrition, since most patients can tolerate some degree of enteral nutrition (Fig. 198-3).[12]

Vascular Access

Parenteral nutrition is administered into the blood stream through a venous catheter that can be placed in a peripheral or central vein. A peripheral catheter is technically simpler but has limitations in capacity to deliver nutrients, especially for a prolonged period of time. Hyperosmolar nutrition solutions tend to induce phlebitis, and tolerance in thin, peripheral veins with low blood flow is usually limited. Peripheral parenteral nutrition also requires removal of the catheter after infusion and rotation of venous access points. As a result, a central venous catheter usually is the method of choice when parenteral nutrition is required for a longer period of time (more than a few weeks) or when the patient requires a central venous access for other reasons (e.g., major surgery or intensive care).

A central venous catheter carries risks, including blood stream infection and thrombosis, so rigorous adherence to safety procedures is required. For long-term use in chronic intestinal failure, a central venous catheter is tunneled subcutaneously from the venous access point to a skin exit on the anterior chest. Peripherally inserted central catheters (PICC lines) into a central vein are commonly used.

Parenteral Nutrition Solutions

Parenteral nutrition must meet basal glucose needs, provide adequate energy, and deliver amino acids that can be used for protein synthesis.

For glucose, approximately 125 g glucose per day is usually sufficient, but up to about 200 g per day may have protein-sparing effects. Glucose solution concentrations up to 100 mg/mL can be administered via a peripheral vein, but higher concentrations require central venous access. Blood glucose levels should be monitored.

Requirements for essential fatty acids can be covered by about 200 g of lipid emulsion per week, but usually up to half of nonprotein energy is provided from lipids.

Amino acid solutions, which are used as the source of protein, should provide 0.10 to 0.15 g/kg/day as basal replacement but should provide 0.15 to 0.20 g/kg/day in inflammatory and hypermetabolic conditions. Sometimes, however, increased protein losses cannot be met by increased delivery, so the goal is to minimize net losses. Serum urea levels should be monitored.

Fat- and water-soluble vitamins and trace elements should be added to all solutions to provide a complete nutrient solution.

Complications

Complications of parenteral nutrition may be related either to the central venous access or to metabolic complications. Infections dominate, mainly catheter-related blood stream infections but also local exit-site infections. A catheter-related infection should always be suspected if a patient develops a fever or unexplained biochemical signs of inflammation (e.g., an increased C-reactive protein level). Central venous thrombosis with occlusion of central vein(s) is less common.

Metabolic complications (Table 198-5) are quite common and are usually related to the rate of infusion. Elevated blood glucose levels and alterations in blood electrolytes dominate, but azotemia, hypertriglyceridemia, and hepatic steatosis can occur. Longer-term parenteral nutrition is sometimes complicated by hepatic dysfunction, often with cholestasis; maintaining some degree of oral or enteral intake probably decreases these hepatobiliary risks.

Refeeding syndrome may develop at the start of therapy when parenteral glucose increases insulin levels and reduces blood levels of phosphate, potassium, and magnesium, which are shifted intracellularly; levels of these electrolytes must be carefully monitored. The demand for thiamine increases during the transition from starvation to feeding, and thiamine deficiency with cerebral symptoms (Wernicke syndrome; Chapter 384) may develop unless thiamine supplementation is provided. Treatment is to reduce caloric delivery and then slowly advance to cover requirements.[13]

PROGNOSIS

Patients who are malnourished or who require in-hospital nutritional support are generally sicker, more frail, and have a poorer prognosis[14] than patients with similar primary diagnoses but who are well-nourished. There is a vicious cycle of nutrient deficiency and disease combined that augment tissue catabolism, leading to further depressed organ functions and compromised immune functions. Increased care burden and substantially prolonged hospital stays increase costs for health care. Outpatient nutritional support services are critically important for patients who are on home enteral or parenteral nutrition.[15,16]

TABLE 198-5 COMMON METABOLIC COMPLICATIONS OF PARENTERAL NUTRITION

PARENTERAL NUTRITION PRESCRIPTION PROBLEM	METABOLIC/CLINICAL CONSEQUENCES
Excess kcal, CHO, fat	Abnormal liver function tests
Excess kcal, CHO, fat	Hepatic steatosis
Excess CHO	Hypercapnia
Excess fluid, kcal, CHO, fat	Respiratory insufficiency
Excess amino acids	Azotemia
Excess sodium and fluid	Sodium and fluid retention
Excess CHO, inadequate insulin	Hyperglycemia-mediated immune cell dysfunction, infection
Inadequate or excessive electroylytes	Abnormal blood electrolyte levels
Excess fluid, kcal, sodium, CHO, inadequate electrolytes	Heart failure, arrhythmias
Excess CHO, inadequate electrolytes, thiamine	Refeeding syndrome

CHO = carbohydrate; kcal = calories.

From Ziegler T. Malnutrition: assessment and support. In: Goldman L, Schafer AI, eds. *Goldman-Cecil Medicine,* 26th ed. Philadelphia: Elsevier; 2020:1401-1405.

For malnourished patients, thorough nutritional care plans and provision of nutrition support improve clinical outcomes, including survival.[17]

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199 VITAMINS, TRACE MINERALS, AND OTHER MICRONUTRIENTS

JOEL B. MASON AND SARAH L. BOOTH

MICRONUTRIENTS IN NUTRITIONAL SCIENCE

DIETARY REQUIREMENTS

Micronutrients are a diverse array of dietary components that are necessary to sustain health. The physiologic roles of micronutrients are as varied as their composition. Some micronutrients are used in enzymes as either coenzymes or prosthetic groups, some are biochemical substrates or hormones; in some instances, functions are not well defined. Under normal circumstances, the average daily dietary intake required to sustain normal physiologic functions for each micronutrient is measured in milligrams or smaller quantities. In this manner, micronutrients are distinguished from macronutrients, which encompass carbohydrates, fats, and proteins, as well as macrominerals such as calcium, magnesium, phosphorus, sodium, potassium, and chloride (Chapter 13).

OPTIMAL INTAKE

For orderly homeostasis to proceed, most dietary nutrients must be ingested in quantities that are neither too small nor too great, because disorders may arise when intake regularly falls either below this physiologic window because of poor diet (Chapter 198) or above this physiologic window, often because of the iatrogenic or self-selected administration of large quantities. The dietary requirement for a particular micronutrient is determined by many factors (Table 199-1). The U.S. National Academy of Medicine periodically issues *recommended dietary allowances* (RDAs) that state the quantity of each micronutrient that is "adequate to meet the known nutrient needs of practically all healthy persons" (Tables 199-2 and 199-3), as well as *tolerable upper limits* (TULs), which are the "maximal daily levels of oral intake likely to pose no adverse health risks." *Adequate intake*, the amount necessary to prevent a deficiency state, is not necessarily synonymous with *optimal intake*. Since habitual dietary habits as well as the intake of specific nutrients play important roles in determining the risk of common degenerative diseases, ongoing efforts are trying to determine levels of nutrient intake that can ameliorate the risk of chronic disease.

TYPES AND FUNCTION OF MICRONUTRIENTS

VITAMINS

Vitamins are categorized as either fat soluble (A, D, E, K) or water soluble (all the others; see Table 199-2). Fat-soluble vitamins rarely serve as coenzymes, whereas most of the functions of the water-soluble vitamins are as coenzymes. Intestinal absorption of the fat-soluble vitamins is primarily through a micellar phase, and pathophysiologic conditions that are associated with fat malabsorption frequently are also associated with selective deficiencies of fat-soluble vitamins. In contrast, water-soluble vitamins are not absorbed through the lipophilic phase in the intestine and are not linked to the absorption of fats.

TRACE ELEMENTS

Fifteen trace minerals (iron, zinc, copper, chromium, selenium, iodine, fluorine, manganese, molybdenum, cobalt, nickel, tin, silicon, vanadium, and arsenic; see Table 199-3) are essential for health, but only the first 10 of these have compelling evidence to indicate that they are essential nutrients in humans. Cobalt appears to be essential solely as a component of vitamin B_{12}, but an isolated deficiency state has never been described. Only under exceptional circumstances, such as long-term reliance on total parenteral nutrition (Chapter 198), have deficiencies of some of these trace minerals (e.g., selenium) been observed.

The biochemical functions of trace elements appear to be as components of prosthetic groups (i.e., tightly bound units required for the biologic function of some proteins) or as cofactors for enzymes (i.e., units bound to an apoenzyme by noncovalent binding). With the exception of iron, blood levels of these trace elements frequently do not correlate well with levels in the target tissues, and accurate functional tests are not available.

ADDITIONAL COMPOUNDS WITH NUTRITIONAL RELEVANCE

Humans also appear to have an absolute requirement for the dietary component choline, which is a necessary precursor for acetylcholine and phospholipids and also is needed to sustain normal levels of biologic methylation. Deficiency is extremely rare, although pregnancy, and particularly lactation, increases the apparent requirement. The most significant adverse effect of dietary inadequacy is hepatic inflammation. Individuals whose long-term nutritional requirements are solely derived from total parenteral nutrition appear to be susceptible to choline deficiency. Both an RDA (425 mg, women; 550 mg, men) and a TUL (3.5 g) have now been established.

L-Carnitine is a dietary component that facilitates the transport of fatty acids into mitochondria, and a deficit therefore limits the fatty acid β-oxidation

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199 VITAMINS, TRACE MINERALS, AND OTHER MICRONUTRIENTS

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MICRONUTRIENTS IN NUTRITIONAL SCIENCE

DIETARY REQUIREMENTS

Micronutrients are a diverse array of dietary components that are necessary to sustain health. The physiologic roles of micronutrients are as varied as their composition. Some micronutrients are used in enzymes as either coenzymes or prosthetic groups, some are biochemical substrates or hormones; in some instances, functions are not well defined. Under normal circumstances, the average daily dietary intake required to sustain normal physiologic functions for each micronutrient is measured in milligrams or smaller quantities. In this manner, micronutrients are distinguished from macronutrients, which encompass carbohydrates, fats, and proteins, as well as macrominerals such as calcium, magnesium, phosphorus, sodium, potassium, and chloride (Chapter 13).

OPTIMAL INTAKE

For orderly homeostasis to proceed, most dietary nutrients must be ingested in quantities that are neither too small nor too great, because disorders may arise when intake regularly falls either below this physiologic window because of poor diet (Chapter 198) or above this physiologic window, often because of the iatrogenic or self-selected administration of large quantities. The dietary requirement for a particular micronutrient is determined by many factors (Table 199-1). The U.S. National Academy of Medicine periodically issues *recommended dietary allowances* (RDAs) that state the quantity of each micronutrient that is "adequate to meet the known nutrient needs of practically all healthy persons" (Tables 199-2 and 199-3), as well as *tolerable upper limits* (TULs), which are the "maximal daily levels of oral intake likely to pose no adverse health risks." *Adequate intake*, the amount necessary to prevent a deficiency state, is not necessarily synonymous with *optimal intake*. Since habitual dietary habits as well as the intake of specific nutrients play important roles in determining the risk of common degenerative diseases, ongoing efforts are trying to determine levels of nutrient intake that can ameliorate the risk of chronic disease.

TYPES AND FUNCTION OF MICRONUTRIENTS

VITAMINS

Vitamins are categorized as either fat soluble (A, D, E, K) or water soluble (all the others; see Table 199-2). Fat-soluble vitamins rarely serve as coenzymes, whereas most of the functions of the water-soluble vitamins are as coenzymes. Intestinal absorption of the fat-soluble vitamins is primarily through a micellar phase, and pathophysiologic conditions that are associated with fat malabsorption frequently are also associated with selective deficiencies of fat-soluble vitamins. In contrast, water-soluble vitamins are not absorbed through the lipophilic phase in the intestine and are not linked to the absorption of fats.

TRACE ELEMENTS

Fifteen trace minerals (iron, zinc, copper, chromium, selenium, iodine, fluorine, manganese, molybdenum, cobalt, nickel, tin, silicon, vanadium, and arsenic; see Table 199-3) are essential for health, but only the first 10 of these have compelling evidence to indicate that they are essential nutrients in humans. Cobalt appears to be essential solely as a component of vitamin B_{12}, but an isolated deficiency state has never been described. Only under exceptional circumstances, such as long-term reliance on total parenteral nutrition (Chapter 198), have deficiencies of some of these trace minerals (e.g., selenium) been observed.

The biochemical functions of trace elements appear to be as components of prosthetic groups (i.e., tightly bound units required for the biologic function of some proteins) or as cofactors for enzymes (i.e., units bound to an apoenzyme by noncovalent binding). With the exception of iron, blood levels of these trace elements frequently do not correlate well with levels in the target tissues, and accurate functional tests are not available.

ADDITIONAL COMPOUNDS WITH NUTRITIONAL RELEVANCE

Humans also appear to have an absolute requirement for the dietary component choline, which is a necessary precursor for acetylcholine and phospholipids and also is needed to sustain normal levels of biologic methylation. Deficiency is extremely rare, although pregnancy, and particularly lactation, increases the apparent requirement. The most significant adverse effect of dietary inadequacy is hepatic inflammation. Individuals whose long-term nutritional requirements are solely derived from total parenteral nutrition appear to be susceptible to choline deficiency. Both an RDA (425 mg, women; 550 mg, men) and a TUL (3.5 g) have now been established.

L-Carnitine is a dietary component that facilitates the transport of fatty acids into mitochondria, and a deficit therefore limits the fatty acid β-oxidation

ABSTRACT

Dietary nutrients whose daily requirements to sustain health are measured in milligram or smaller quantities are called micronutrients. These nutrients encompass a diverse array of vitamins, trace minerals, and other compounds that support a wide range of metabolic functions, which in some cases remain poorly understood. The amount of any particular nutrient that is required to sustain health is defined by a number of physiologic, pathologic, and pharmacologic factors. A common query posed by patients is whether routine supplementation with one or more micronutrients is beneficial; present evidence suggests there is little benefit for the generally healthy adult population in high-income countries. Nevertheless certain segments of the population, such as older adults and individuals with certain chronic illnesses, may realize genuine benefits from targeted supplementation.

KEYWORDS

vitamin
trace mineral
recommended daily allowance
nutrient deficiency
nutrient supplementation

TABLE 199-1 FACTORS THAT DETERMINE DIETARY REQUIREMENT OF A MICRONUTRIENT

PHYSIOLOGIC FACTORS
Bioavailability: the proportion of an ingested micronutrient that is capable of being assimilated and used for physiologic purposes
Quantity required to fulfill physiologic roles
Extent to which the body can reuse the micronutrient
Distribution of nutrient in the body: storage compartments
Gender
Stage of life cycle: intrauterine development, childhood, adulthood, elder adulthood, pregnancy, lactation
PATHOPHYSIOLOGIC AND PHARMACOLOGIC FACTORS
Inborn errors of metabolism: variously affect assimilation, utilization, or excretion of micronutrients
Acquired disease states that alter the amounts required to sustain homeostasis (e.g., malabsorption, maldigestion, states that increase utilization)
Lifestyle habits: smoking, ethanol consumption
Drugs: may alter bioavailability or utilization

that occurs in those organelles. Although no evidence exists for a dietary requirement in healthy children or adults, individuals undergoing chronic hemodialysis (Chapter 117) develop diminished plasma and muscle levels. Controlled clinical trials in hemodialysis patients who suffer from cardiomyopathy, intradialytic hypotension, or anemia refractory to erythropoietin have shown improvements in these parameters with intermittent parenteral supplementation.[A1] Individuals on long-term total parenteral nutrition may also be susceptible to the clinical consequences of L-carnitine depletion, but convincing evidence is lacking.

Lutein and zeaxanthin are two carotenoids that are not precursors of vitamin A but appear to play a role in age-related macular degeneration (Chapter 391). Low plasma lutein and zeaxanthin concentrations or dietary intake are associated with a low density of macular pigment and an increased risk of macular degeneration. A combination supplement that includes lutein, zeaxanthin, vitamin C, vitamin E, zinc oxide, and cupric oxide significantly diminishes the progression of macular degeneration.[A2]

CONDITIONS THAT INCREASE REQUIRED DIETARY INTAKE

Many physiologic, pathophysiologic, and pharmacologic factors increase the dietary requirements for micronutrients (see Table 199-1), thereby enhancing the risk for development of a deficiency state.

PHYSIOLOGIC FACTORS

Stages of the life cycle frequently have a significant impact on the requirements of nutrients. Phases of rapid growth and development, such as in utero development, infancy, adolescence, and pregnancy, are associated with increases in the utilization of certain micronutrients on a per-kilogram basis.

PREGNANCY

Requirements for most micronutrients are increased in pregnancy,[1] but, proportionately, the observed increases in the maternal requirements for iron and folate are particularly great and are related to the rapid proliferation of placental and fetal tissues. Periods of lactation are similarly associated with remarkable increases in requirements; a lactating woman experiences disproportionately large increases in her requirements for zinc and vitamins A, E, and C to meet the metabolic demands incurred by milk production in addition to the aforementioned needs observed in pregnancy.

WOMEN OF CHILDBEARING AGE

Aside from its general role in supporting the rapid proliferation of placental and fetal tissues, folate plays a specific role in the prevention of particular birth defects. A 20 to 85% reduction in births complicated by neural tube defects (i.e., spina bifida and anencephaly) has been realized by providing women of childbearing age with a daily supplemental folic acid in the form of vitamin supplements as well as fortified foods. However, many women do not receive the recommended daily intake of folate from diet alone, even with fortified bread. All women who are planning or at risk of pregnancy should take a daily supplement of 0.4 to 0.8 mg (400-800 micrograms) of folate because the nascent neural tube closes on about day 20 after conception, too soon for folate to be started after pregnancy is confirmed.

The ability to maintain adequate iron status from menarche through menopause is compromised in women by the additional losses incurred by menstruation, pregnancy, and lactation. Clinicians must maintain a heightened index of suspicion for iron deficiency in women in this age range.

OLDER ADULTS

Several specific dietary recommendations are different for adults over 65 years because aging has an impact on the need for and absorption of certain micronutrients.[2] Vitamin B_{12} status declines significantly with aging, in large part because of the high prevalence of atrophic gastritis and its associated impairment in the absorption of protein-bound vitamin B_{12}. Since 10 to 20% of the elderly population is at risk for clinically significant vitamin B_{12} deficiency, older adults should consume some of their vitamin B_{12} requirement in the crystalline form rather than solely from the naturally occurring protein-bound forms found in food. Older adults also require greater quantities of vitamins B_6 and D to maintain health compared with younger adults, as reflected in the new RDAs (see Table 199-2). The increased need for vitamin D appears to result from less consumption of vitamin D, diminished cutaneous synthesis of the vitamin by senile skin, and from decreased sun exposure, which is a particularly important factor in elders residing in institutional facilities. The need for crystalline vitamin B_{12} and for a quantity of vitamin D that is difficult to achieve without resorting to a supplement questions whether use of a daily supplement containing these nutrients might benefit older adults, although they are not currently recommended by the U.S. Preventive Services Task Force. Widespread use of a multivitamin that contains a broad spectrum of micronutrients is more controversial, in part because of concerns about subtle toxicity. For example, elders with chronic renal insufficiency and renal failure (stages 3 and above; Chapter 116) appear to have a vulnerability to vitamin A toxicity, thereby suggesting that use of supplements containing this vitamin is contraindicated in these individuals.

PATHOPHYSIOLOGIC AND PHARMACOLOGIC FACTORS

DISEASES OF THE GASTROINTESTINAL TRACT

Malabsorption and maldigestion (Chapter 126) predispose to multiple micronutrient deficiencies. Both fat- and water-soluble micronutrients (except vitamin B_{12}) are absorbed predominantly in the proximal small intestine. Therefore, diffuse mucosal diseases affecting the proximal portion of the gastrointestinal tract are likely to result in deficiencies of multiple micronutrients. Even in the absence of mucosal disease of the proximal small intestine, extensive ileal disease, small bowel bacterial overgrowth, and chronic cholestasis can each interfere with the maintenance of adequate intraluminal conjugated bile acid concentrations and thereby impair absorption of fat-soluble vitamins. Maldigestion, which is usually the result of chronic pancreatitis (Chapter 130), frequently causes malabsorption and deficiencies of fat-soluble vitamins.

INBORN ERRORS OF METABOLISM

Myriad rare inborn errors of metabolism impair an individual's ability to assimilate, to use, or to retain a particular micronutrient (Chapter 189). Such defects are usually partial and can often be overcome, to a certain extent, by administering doses that are several orders of magnitude greater than usually required. Suspicion for such defects should be entertained if a known defect exists in the family, a deficiency syndrome arises at birth or during infancy, or the deficiency syndrome is present despite adequate dietary intake and the absence of any disease that would impair the ability to assimilate the nutrient.

MEDICATIONS

Long-term administration of many drugs may adversely affect micronutrient status (Table 199-4).[3] Some drugs exert their therapeutic effects by specifically inhibiting the actions of a micronutrient. For example, coumarin derivatives (Chapter 70) inhibit γ-carboxylation reactions mediated by vitamin K, and methotrexate (Chapter 164) binds tightly to dihydrofolate reductase, thereby inhibiting folate metabolism.

Text continued on p. 1459

TABLE 199-2 VITAMINS AND THEIR FUNCTIONS

	BIOCHEMISTRY AND PHYSIOLOGY	DEFICIENCY [RDA*]	TOXICITY [TUL†]	ASSESSMENT OF STATUS
FAT-SOLUBLE VITAMINS				
Vitamin A	A family of retinoid compounds, each member having biologic activity qualitatively similar to retinol. Carotenoids are structurally related to retinoids. Some carotenoids, most notably β-carotene, are metabolized into compounds with vitamin A activity and are therefore considered to be provitamin A compounds. Vitamin A is an integral component of rhodopsin and iodopsins, light-sensitive proteins in rod and cone cells in the retina. Additional functions: induction and maintenance of cellular differentiation in certain tissues; signal for appropriate morphogenesis in the developing embryo; maintenance of cell-mediated immunity. 1 μg of retinol = 3.33 IU of vitamin A.	Follicular hyperkeratosis and night blindness are early indicators. Conjunctival xerosis, degeneration of the cornea (keratomalacia), and dedifferentiation of rapidly proliferating epithelia are later indications of deficiency. *Bitot spots* (focal areas of the conjunctiva or cornea with foamy appearance) are an indication of xerosis. Blindness, due to corneal destruction and retinal dysfunction, ensues if left uncorrected. Increased susceptibility to infection is also a consequence. [F: 700 μg; M: 900 μg]	In adults, >150,000 μg may cause *acute* toxicity: fatal intracranial hypertension, skin exfoliation, and hepatocellular necrosis. *Chronic* toxicity may occur with habitual daily intake of >10,000 μg: alopecia, ataxia, bone and muscle pain, dermatitis, cheilitis, conjunctivitis, pseudotumor cerebri, hepatocellular necrosis, hyperlipidemia and hyperostosis are common. Single, large doses of vitamin A (30,000 μg) or habitual intake of >4500 μg/day in early pregnancy can be teratogenic. Excessive intake of carotenoids causes a benign condition characterized by yellowish discoloration of the skin. [3000 μg]	Retinol concentration in the plasma and vitamin A concentrations in the milk and tears are reasonably accurate measures of adequate status. Toxicity is best assessed by elevated levels of retinyl esters in plasma. A quantitative measure of dark adaptation for night vision and electroretinography are useful functional tests.
Vitamin D	A group of sterol compounds whose parent structure is cholecalciferol (vitamin D_3). Cholecalciferol is formed in the skin from 7-dehydrocholesterol (provitamin D_3) by exposure to UVB radiation. A plant sterol, ergocalciferol (provitamin D_2), can be similarly converted into vitamin D_2 and has similar vitamin D activity. The vitamin undergoes sequential hydroxylations in the liver and kidney at the 25 and 1 positions, respectively, producing the most bioactive form of the vitamin, 1,25-dihydroxy vitamin D. Vitamin D maintains intracellular and extracellular concentrations of calcium and phosphate by enhancing intestinal absorption of the two ions and, in conjunction with PTH, promoting their mobilization from bone mineral. It retards proliferation and promotes differentiation in certain epithelia. Purported actions of vitamin D as an antidiabetes, anti-inflammatory, and cancer preventive agent remain controversial and are under investigation. 1 μg = 40 IU.	Deficiency results in decreased mineralization of newly formed bone called rickets in childhood and osteomalacia in adults. Deficiency also contributes to osteoporosis and increased fracture risk in later life. Commonly appears following gastric bypass procedures. Expansion of the epiphyseal growth plates and replacement of normal bone with unmineralized bone matrix are the cardinal features of rickets; the latter feature also characterizes osteomalacia. Deformity of bone and pathologic fractures occur. Decreased serum concentrations of calcium and phosphate may occur. [15 μg, ages 19-70 yr; 20 μg, age >70 yr]	Excess amounts result in abnormally high concentrations of calcium and phosphate in the serum; metastatic calcifications, renal damage, and altered mentation may occur. [100 μg for ages ≥9 yr]	The serum concentration of the major circulating metabolite, 25-hydroxyvitamin D, is the best indicator of systemic status except in advanced kidney disease (stages 4 and 5), in which the impairment of renal 1-hydroxylation results in disassociation of the mono- and dihydroxyvitamin concentrations. Measurement of the serum concentration of 1,25-dihydroxyvitamin D is then necessary. Also, measuring free 25-hydroxyvitamin D rather than including protein-bound forms may minimize artifacts created by liver disease, sex hormones, kidney function, and genetic background.
Vitamin E	A group of at least eight naturally occurring compounds, some of which are tocopherols and some of which are tocotrienols. At present, the only dietary form that is thought to be biologically active in humans is α-tocopherol. Vitamin E acts as an antioxidant and free radical scavenger in lipophilic environments, most notably in cell membranes. It acts in conjunction with other antioxidants, such as selenium.	Deficiency due to dietary inadequacy is rare. It is usually seen in premature infants, individuals with fat malabsorption, and individuals with abetalipoproteinemia. Red blood cell fragility occurs and can produce a hemolytic anemia. Neuronal degeneration produces peripheral neuropathies, ophthalmoplegia, and destruction of posterior columns of the spinal cord. Neurologic disease is frequently irreversible if deficiency is not corrected early enough. May contribute to the hemolytic anemia and retrolental fibroplasia seen in premature infants. Reported to suppress cell-mediated immunity. [15 mg]	Depressed levels of vitamin K–dependent procoagulants and potentiation of oral anticoagulants have been reported, as has impaired WBC function. Doses of 800 mg/day have been reported to increase slightly the incidence of hemorrhagic stroke. [1000 mg]	Plasma or serum concentration of α-tocopherol is most commonly used. Additional accuracy is obtained by expressing this value per milligram of total plasma lipid. RBC peroxide hemolysis test is not entirely specific but is a useful functional measure of the antioxidant potential of cell membranes.

TABLE 199-2 VITAMINS AND THEIR FUNCTIONS—cont'd

	BIOCHEMISTRY AND PHYSIOLOGY	DEFICIENCY [RDA*]	TOXICITY [TUL†]	ASSESSMENT OF STATUS
Vitamin K	A family of naphthoquinone compounds with similar biologic activity. Phylloquinone (vitamin K_1) is derived from plants; a variety of menaquinones (vitamin K_2) are derived from bacterial and animal sources. Vitamin K serves as an essential cofactor in the post-translational γ-carboxylation of glutamic acid residues in many proteins. These proteins include several circulating procoagulants and anticoagulants as well as proteins in a variety of tissues.	Deficiency syndrome is uncommon except in breast-fed newborns, in whom it may cause "hemorrhagic disease of the newborn," especially among newborns whose parents refuse prophylactic administration of vitamin K at birth. Also occurs in adults with fat malabsorption or who are taking drugs that interfere with vitamin K metabolism (e.g., coumarin, phenytoin, broad-spectrum antibiotics) and in individuals taking large doses of vitamin E and anticoagulant drugs. Excessive hemorrhage is the usual manifestation. [F: 90 µg; M: 120 µg]	Rapid intravenous infusion of K_1 has been rarely associated with dyspnea, flushing, and cardiovascular collapse; this is likely related to the dispersing agents in the solution. Supplementation may interfere with coumarin-based anticoagulation. Pregnant women taking large amounts of the provitamin menadione may deliver infants with hemolytic anemia, hyperbilirubinemia, and kernicterus. [No TUL established.]	Prothrombin time is typically used as a measure of functional K status; it is neither sensitive nor specific for vitamin K deficiency. Determination of fasting plasma vitamin K is an accurate indicator of status. Undercarboxylated plasma prothrombin is also an accurate metric, but only for detecting the deficient state, and is less widely available than plasma vitamin K.
WATER-SOLUBLE VITAMINS				
Thiamin (vitamin B_1)	A water-soluble compound containing substituted pyrimidine and thiazole rings and a hydroxyethyl side chain. The coenzyme form is thiamin pyrophosphate (TPP). Thiamin serves as a coenzyme in many α-ketoacid decarboxylation and transketolation reactions. Inadequate thiamin availability leads to impairments of these reactions, resulting in inadequate adenosine triphosphate synthesis and abnormal carbohydrate metabolism, respectively. It may have an additional role in neuronal conduction independent of the aforementioned actions.	Classic deficiency syndrome (beriberi) remains endemic in Asian populations consuming a polished rice diet. Globally, alcoholism, chronic renal dialysis, and persistent nausea and vomiting after bariatric surgery are also common precipitants. High carbohydrate intake increases need for B_1. Mild deficiency: irritability, fatigue, and headaches. More severe deficiency: combinations of peripheral neuropathy, cardiovascular dysfunction, and cerebral dysfunction. Cardiovascular involvement (wet beriberi): congestive heart failure and low peripheral vascular resistance. Cerebral disease: nystagmus, ophthalmoplegia, and ataxia (Wernicke encephalopathy); hallucinations, impaired short-term memory, and confabulation (Korsakoff psychosis). Deficiency syndrome responds within 24 hr to parenteral thiamin but is partially or wholly irreversible after a certain stage. [F: 1.1 mg; M: 1.2 mg]	Excess intake is largely excreted in the urine, although parenteral doses of >400 mg/day are reported to cause lethargy, ataxia, and reduced tone of the gastrointestinal tract. [TUL not established.]	The most effective measure of B_1 status is the erythrocyte transketolase activity coefficient, which measures enzyme activity before and after addition of exogenous TPP; RBCs from a deficient individual express a substantial increase in enzyme activity with addition of TPP. Thiamin concentrations in blood or urine are also used.
Riboflavin (vitamin B_2)	Consists of a substituted isoalloxazine ring with a ribitol side chain. Riboflavin serves as a coenzyme for a diverse array of biochemical reactions. The primary coenzymatic forms are flavin mononucleotide and flavin adenine dinucleotide. Riboflavin holoenzymes participate in oxidation-reduction reactions in myriad metabolic pathways.	Deficiency is usually seen in conjunction with deficiencies of other B vitamins. Isolated deficiency of riboflavin produces hyperemia and edema of nasopharyngeal mucosa, cheilosis, angular stomatitis, glossitis, seborrheic dermatitis, and a normochromic, normocytic anemia. [F: 1.1; M: 1.3]	Toxicity is not reported in humans. [TUL not established.]	The most common method of assessment is to determine the activity coefficient of glutathione reductase in RBCs (the test is invalid for individuals with glucose-6-phosphate dehydrogenase deficiency). Measurements of blood and urine concentrations are less desirable methods.

TABLE 199-2 VITAMINS AND THEIR FUNCTIONS—cont'd

	BIOCHEMISTRY AND PHYSIOLOGY	DEFICIENCY [RDA*]	TOXICITY [TUL†]	ASSESSMENT OF STATUS
Niacin (vitamin B_3)	Refers to nicotinic acid and the corresponding amide, nicotinamide. The active coenzymatic forms are composed of nicotinamide affixed to adenine dinucleotide, forming NAD or NADP. More than 200 apoenzymes use these compounds as electron acceptors or hydrogen donors, either as a coenzyme or as a co-substrate. The essential amino acid tryptophan is a precursor of niacin; 60 mg of dietary tryptophan yields approximately 1 mg of niacin. Dietary requirements thus depend partly on tryptophan intake. Requirement is often determined on basis of calorie intake (i.e., niacin equivalents/1000 kcal). Large doses of nicotinic acid (1.5-3 g/day) effectively lower low-density lipoprotein cholesterol and elevate high-density lipoprotein cholesterol.	*Pellagra* is the classic deficiency syndrome and is often seen in populations in which corn is the major source of energy; it is still endemic in parts of China, Africa, and India. Diarrhea, dementia (or associated symptoms of anxiety or insomnia), and a pigmented dermatitis that develops in sun-exposed areas are typical features. Glossitis, stomatitis, vaginitis, vertigo, and burning dysesthesias are early signs. It is reported occasionally to occur in carcinoid syndrome because tryptophan is diverted to other synthetic pathways. [F: 14 mg; M: 16 mg]	Human toxicity is known largely through studies examining hypolipidemic effects. Includes vasomotor phenomenon (flushing), hyperglycemia, parenchymal liver damage, and hyperuricemia. [35 mg]	Assessment of status is problematic; blood levels of the vitamin are not reliable. Measurement of urinary excretion of the niacin metabolites *N*-methylnicotinamide and 2-pyridone is thought to be the most effective means of assessment at present.
Vitamin B_6	Refers to several derivatives of pyridine, including pyridoxine, pyridoxal, and pyridoxamine, which are interconvertible in the body. The coenzymatic forms are pyridoxal-5-phosphate (PLP) and pyridoxamine-5-phosphate. As a coenzyme, B_6 is involved in many transamination reactions (and thereby in gluconeogenesis), in the synthesis of niacin from tryptophan, in the synthesis of several neurotransmitters, and in the synthesis of δ-aminolevulinic acid (and therefore in heme synthesis). It also has functions unrelated to coenzymatic activity: pyridoxal and PLP bind to hemoglobin and alter oxygen affinity; PLP also binds to steroid receptors, inhibiting receptor affinity to DNA and thereby modulating steroid activity.	Deficiency is usually seen in conjunction with other water-soluble vitamin deficiencies. Stomatitis, angular cheilosis, glossitis, irritability, depression, and confusion occur in moderate to severe depletion; normochromic, normocytic anemia has been reported in severe deficiency. Abnormalities on electroencephalography and, in infants, convulsions have also been observed. Some sideroblastic anemias respond to B_6 administration. Isoniazid, cycloserine, penicillamine, ethanol, and theophylline can inhibit B_6 metabolism. [Ages 19-50 yr: 1.3 mg; >50 yr: 1.5 mg for women, 1.7 mg for men]	Long-term use with doses exceeding 200 mg/day (in adults) may cause peripheral neuropathies and photosensitivity. [100 mg]	Many useful laboratory methods of assessment exist. The plasma or erythrocyte PLP levels are most common. Urinary excretion of xanthurenic acid after an oral tryptophan load and activity indices of RBC alanine or aspartate transaminase are functional measures of B_6-dependent enzyme activity.
Folate	A group of related pterin compounds. More than 35 forms of the vitamin are found naturally. The fully oxidized form, folic acid, is not found in nature but is the pharmacologic form of the vitamin used in supplements and fortification programs. All folate functions relate to its ability to transfer one-carbon groups. It is essential in the de novo synthesis of nucleotides and in the metabolism of several amino acids; it is an integral component for the regeneration of the "universal" methyl donor, *S*-adenosylmethionine. Inhibition of bacterial and cancer cell folate metabolism is the basis for the sulfonamide antibiotics and chemotherapeutic agents, such as methotrexate and 5-fluorouracil, respectively.	Women of childbearing age are most likely to be deficient. Classic deficiency syndrome: megaloblastic anemia, diarrhea. The hematopoietic cells in bone marrow become enlarged and have immature nuclei, reflecting ineffective DNA synthesis. The peripheral blood smear demonstrates macro-ovalocytes and polymorphonuclear leukocytes with an average of more than 3.5 nuclear lobes. Megaloblastic changes also occur in other epithelia that proliferate rapidly (e.g., oral mucosa and gastrointestinal tract, producing glossitis and diarrhea, respectively). Sulfasalazine and diphenytoin inhibit absorption and predispose to deficiency. [400 μg of dietary folate equivalents (DFE); 1 DFE = 1 μg food folate = 0.6 μg folic acid]	Doses >1000 μg/day may partially correct the anemia of B_{12} deficiency and may therefore mask (and perhaps exacerbate) the associated neuropathy. Large doses are also reported to lower seizure threshold in individuals prone to seizures. Parenteral administration is rarely reported to cause allergic phenomena, which is probably due to dispersion agents. [1000 μg]	Serum folate measures short-term folate balance, whereas RBC folate is a better reflection of tissue status. Serum homocysteine rises early in deficiency but is nonspecific because B_{12} or B_6 deficiency, renal insufficiency, and older age may also cause elevations.

TABLE 199-2 VITAMINS AND THEIR FUNCTIONS—cont'd

	BIOCHEMISTRY AND PHYSIOLOGY	DEFICIENCY [RDA*]	TOXICITY [TUL†]	ASSESSMENT OF STATUS
Vitamin C (ascorbic and dehydroascorbic acid)	Ascorbic acid readily oxidizes to dehydroascorbic acid in aqueous solution. Dehydroascorbic acid can be reduced in vivo, so it possesses vitamin C activity. Total vitamin C is therefore the sum of ascorbic and dehydroascorbic acid content. Vitamin C serves primarily as a biologic antioxidant in aqueous environments. Biosyntheses of collagen, carnitine, bile acids, and norepinephrine, as well as proper functioning of the hepatic mixed-function oxygenase system, depend on this property. Vitamin C in foodstuffs increases the intestinal absorption of nonheme iron.	Overt deficiency is uncommon in developed countries. The classic deficiency syndrome is *scurvy:* fatigue, depression, and widespread abnormalities in connective tissues, such as inflamed gingivae, petechiae, perifollicular hemorrhages, impaired wound healing, coiled hairs, hyperkeratosis, and bleeding into body cavities. In infants, defects in ossification and bone growth may occur. Tobacco smoking lowers plasma and leukocyte vitamin C levels. [F: 75 mg; M: 90 mg; increase requirement for cigarette smokers by 35 mg/day]	≥500 mg/day (in adults) may cause nausea and diarrhea. >1 g/day modestly increases risk for oxalate kidney stones. Supplementation may interfere with laboratory tests based on redox potential (e.g., fecal occult blood testing, serum cholesterol, and glucose). Withdrawal from chronic ingestion of high doses of vitamin C supplements should be done gradually because accommodation appears to occur, raising a concern of "rebound scurvy." [2 g]	Plasma ascorbic acid concentration reflects recent dietary intake, whereas WBC levels more closely reflect tissue stores. Women's plasma levels are approximately 20% higher than men's for any given dietary intake.
Vitamin B_{12}	A group of closely related cobalamin compounds composed of a corrin ring (with a cobalt atom in its center) connected to a ribonucleotide through an aminopropanol bridge. Microorganisms are the ultimate source of all naturally occurring B_{12}. The two active coenzyme forms are deoxyadenosylcobalamin and methylcobalamin. These coenzymes are needed for the synthesis of succinyl CoA, which is essential in lipid and carbohydrate metabolism, and for the synthesis of methionine. The synthesis of methionine is essential for amino acid metabolism, for purine and pyrimidine synthesis, for many methylation reactions, and for the intracellular retention of folates.	Dietary inadequacy is a rare cause of deficiency except in strict vegetarians. Most deficiencies arise from loss of intestinal absorption, which may occur with pernicious anemia, pancreatic insufficiency, atrophic gastritis, small bowel bacterial overgrowth, or ileal disease. Megaloblastic anemia and megaloblastic changes in epithelia (see Folate) are the result of sustained depletion. Demyelination of peripheral nerves, posterior and lateral columns of the spinal cord, and nerves within the brain may occur. Altered mentation, depression, and psychoses occur. Hematologic and neurologic complications may occur independently. Folate supplementation, in doses of 1000 µg/day, may partly correct the anemia, thereby masking (or perhaps exacerbating) the neuropathic complication. [2.4 µg]	A few allergic reactions have been reported to crystalline B_{12} preparations and are probably due to impurities, not the vitamin. [TUL not established.]	Serum or plasma B_{12} concentrations are generally accurate, although subtle deficiency with neurologic and/or hematologic complications can occur with levels in the low-normal range (148-258 pmol/L or 200–350 pg/mL). In this setting deficiency can be established by concurrently measuring the concentration of plasma B_{12} and serum methylmalonic acid, which is a sensitive indicator of cellular deficiency. This subtle deficiency state has been increasingly recognized among older populations. Serum holotranscobalamin is another metric, although it is not clearly superior to plasma B_{12}.
Biotin	A bi-cyclic compound consisting of a ureido ring fused to a substituted tetrahydrothiophene ring. Endogenous synthesis by intestinal flora may contribute significantly to biotin nutriture. Most dietary biotin is linked to lysine, a compound called biotinyl lysine, or biocytin. The lysine must be hydrolyzed by an intestinal enzyme called biotinidase before intestinal absorption occurs. Biotin acts primarily as a coenzyme for several carboxylases; each holoenzyme catalyzes an adenosine triphosphate–dependent carbon dioxide transfer. The carboxylases are critical enzymes in carbohydrate and lipid metabolism.	Isolated deficiency is rare. Deficiency in humans has been produced by prolonged total parenteral nutrition lacking the vitamin and by ingestion of large quantities of raw egg white, which contains avidin, a protein that binds biotin with such high affinity that it renders it biounavailable. Alterations in mental status, myalgias, hyperesthesias, and anorexia occur. Later, a seborrheic dermatitis and alopecia develop. Deficiency is usually accompanied by lactic acidosis and organic aciduria. [30 µg]	Toxicity has not been reported in humans with doses as high as 60 mg/day in children. [TUL not established.]	Plasma and urine concentrations of biotin are diminished in the deficient state. Elevated urine concentrations of methyl citrate, 3-methylcrotonylglycine, and 3-hydroxyisovalerate are also observed in deficiency.

TABLE 199-2 VITAMINS AND THEIR FUNCTIONS—cont'd

	BIOCHEMISTRY AND PHYSIOLOGY	DEFICIENCY [RDA*]	TOXICITY [TUL†]	ASSESSMENT OF STATUS
Pantothenic acid	Consists of pantoic acid linked to β-alanine through an amide bond. Pantothenic acid is an essential component of CoA and phosphopantetheine, which are essential for synthesis and β-oxidation of fatty acids as well as for synthesis of cholesterol, steroid hormones, vitamins A and D, and other isoprenoid derivatives. CoA is also involved in the synthesis of several amino acids and δ-aminolevulinic acid, a precursor for the corrin ring of vitamin B_{12}, the porphyrin ring of heme, and of cytochromes. CoA is also necessary for the acetylation and fatty acid acylation of a variety of proteins.	Deficiency is rare; it has been reported only as a result of feeding of semisynthetic diets or consumption of an antagonist such as calcium homopantothenate (which has been used to treat Alzheimer disease). Experimental, isolated deficiency in humans produces fatigue, abdominal pain, vomiting, insomnia, and paresthesias of the extremities. [5 mg]	In doses of 10 g/day, diarrhea is reported to occur. [TUL not established.]	Whole blood and urine concentrations of pantothenate are indicators of status; serum levels are not thought to be accurate.

*Recommended daily allowance (RDA) established for female (F) and male (M) adults by the U.S. Food and Nutrition Board, 1999-2001 (updated in 2010 for vitamin D and calcium). In some instances, insufficient data exist to establish an RDA, in which case the adequate intake (AI) established by the board is listed.

†Tolerable upper limit (TUL) established for adults by the U.S. Food and Nutrition Board, 1999-2001.

CoA = coenzyme A; F = female; M = male; NAD = nicotinamide adenine dinucleotide; NADP = nicotinamide adenine dinucleotide phosphate; PLP = pyridoxal phosphate; PTH = parathyroid hormone; RBC = red blood cell; TUL = tolerable upper limit; UVB = ultraviolet B; WBC = white blood cell.

TABLE 199-3 NUTRITIONAL TRACE ELEMENTS AND THEIR CLINICAL IMPLICATIONS

	BIOCHEMISTRY AND PHYSIOLOGY	DEFICIENCY [RDA*]	TOXICITY [TUL†]	ASSESSMENT OF STATUS
Chromium	Dietary chromium consists of both inorganic and organic forms. Its primary function in humans is to potentiate insulin action. It accomplishes this function as a circulating complex called *glucose tolerance factor*, thereby affecting carbohydrate, fat, and protein metabolism.	Deficiency in humans has been described only in long-term total parenteral nutrition (TPN) patients receiving insufficient chromium. Hyperglycemia or impaired glucose tolerance occurs. Elevated plasma free fatty acid concentrations, neuropathy, encephalopathy, and abnormalities in nitrogen metabolism are also reported. Whether supplemental chromium may improve glucose tolerance in glucose-intolerant individuals remains controversial. [F: 25 μg; M: 35 μg]	Toxicity after oral ingestion is uncommon and seems confined to gastric irritation. Airborne exposure may cause contact dermatitis, eczema, skin ulcers, and bronchogenic carcinoma. [No TUL established.]	Plasma or serum concentration of chromium is a crude indicator of chromium status; it appears to be meaningful when the value is markedly above or below the normal range.
Copper	Copper is absorbed by a specific intestinal transport mechanism. It is carried to the liver, where it is bound to ceruloplasmin, which circulates systemically and delivers copper to target tissues in the body. Excretion of copper is largely through bile and then into the feces. Absorptive and excretory processes vary with the levels of dietary copper, providing a means of copper homeostasis. Copper serves as a component of many enzymes, including amine oxidases, ferroxidases, cytochrome *c* oxidase, dopamine β-hydroxylase, superoxide dismutase, and tyrosinase.	Dietary deficiency is rare; it has been observed in premature and low-birthweight infants fed exclusively a cow's milk diet and in individuals on long-term TPN lacking copper. It has also been described after gastric bypass surgery and with chronic zinc supplementation. Clinical manifestations include depigmentation of skin and hair, myelopathy and other neurologic lesions, leukopenia, anemia, and skeletal abnormalities. Anemia arises from impaired utilization of iron and therefore often is manifested as a sideroblastic anemia. The peripheral smear and bone marrow may mimic myelodysplasia. A deficiency syndrome is also observed in Menkes disease, a rare inherited condition associated with impaired copper utilization. [900 μg]	Acute copper toxicity has been described after excessive oral intake and with absorption of copper salts applied to burned skin. Milder manifestations include nausea, vomiting, epigastric pain, and diarrhea; coma and hepatic necrosis may ensue in severe cases. Toxicity may be seen with doses as low as 70 μg/kg/day. Chronic toxicity is also described. Wilson disease is a rare, inherited disease associated with abnormally low ceruloplasmin levels and accumulation of copper in the liver and brain, eventually leading to damage to these two organs. [10 mg]	Practical methods to detect marginal deficiency are not available. Marked deficiency is reliably detected by diminished serum copper and ceruloplasmin concentrations as well as by low red blood cell superoxide dismutase activity.

TABLE 199-3 NUTRITIONAL TRACE ELEMENTS AND THEIR CLINICAL IMPLICATIONS—cont'd

	BIOCHEMISTRY AND PHYSIOLOGY	DEFICIENCY [RDA*]	TOXICITY [TUL†]	ASSESSMENT OF STATUS
Fluorine	Known more commonly by its ionic form, fluoride. Fluorine is incorporated into the crystalline structure of bone, thereby altering its physical characteristics. Fluoridation of water has reduced incidence of caries in communities with fluoridation programs.	Intake of <0.1 mg/day in infants and <0.5 mg/day in children is associated with an increased incidence of dental caries. Optimal intake in adults is between 1.5 and 4 mg/day. [F: 3 mg; M: 4 mg]	Acute ingestion of >30 mg/kg body weight is likely to cause death. Excessive chronic intake (0.1 mg/kg/day) leads to mottling of teeth (dental fluorosis), calcification of tendons and ligaments, and exostoses and may increase the brittleness of bones. [10 mg]	Estimates of intake and clinical assessment are used because no good laboratory test exists.
Iodine	Iodine is readily absorbed from the diet, concentrated in the thyroid, and integrated into the thyroid hormones thyroxine and triiodothyronine. These hormones circulate largely bound to thyroxine-binding globulin. They modulate resting energy expenditure and, in the developing human, growth and development.	In the absence of supplementation, populations relying primarily on food from soils with low iodine content have endemic iodine deficiency. Maternal iodine deficiency leads to fetal deficiency, which produces spontaneous abortions, stillbirths, hypothyroidism, cretinism, and dwarfism. Permanent cognitive deficits may result from iodine deficiency during the first 2 years of life. In the adult, compensatory hypertrophy of the thyroid (goiter) occurs along with varying degrees of hypothyroidism. [150 µg]	Large doses (>2 mg/day in adults) may induce hypothyroidism by blocking thyroid hormone synthesis. Supplementation with >100 mg/day to an individual who was formerly deficient occasionally induces hyperthyroidism. [1.1 mg]	Iodine status of a population can be estimated by the prevalence of goiter. Urinary excretion of iodine is an effective laboratory means of assessment. Thyroid-stimulating hormone blood level is an indirect and therefore not entirely specific means of assessment.
Iron	Conveys the capacity to participate in redox reactions to a number of metalloproteins, such as hemoglobin, myoglobin, cytochrome enzymes, and many oxidases and oxygenases. The primary storage form of iron is ferritin and, to a lesser degree, hemosiderin. Intestinal absorption is 15-20% for "heme" iron and 1-8% for iron contained in vegetables. Absorption of the latter form is enhanced by the ascorbic acid in foodstuffs; by poultry, fish, or beef; and by an iron-deficient state. It is decreased by phytate and tannins.	Iron deficiency is the most common micronutrient deficiency in the world. Women of childbearing age are the group at highest risk because of menstrual blood losses, pregnancy, and lactation. The classic deficiency syndrome is hypochromic, microcytic anemia. Glossitis and koilonychia ("spoon" nails) are also observed. Easy fatigability often is an early symptom, before anemia appears. In children, mild deficiency of insufficient severity to cause anemia is associated with behavioral disturbances and poor school performance. [postmenopausal F and M: 8 mg; premenopausal F: 18 mg]	Iron overload typically occurs when habitual dietary intake is extremely high, intestinal absorption is excessive, repeated parenteral administration occurs, or a combination of these factors exists. Excessive iron stores usually accumulate in the reticuloendothelial tissues and cause little damage (hemosiderosis). If overload continues, iron eventually begins to accumulate in tissues such as the hepatic parenchyma, pancreas, heart, and synovium, causing hemochromatosis (Chapter 196). Hereditary hemochromatosis results from homozygosity of a common recessive trait. Excessive intestinal absorption of iron is seen in homozygotes. [45 mg]	Negative iron balance initially leads to depletion of iron stores in the bone marrow; a bone marrow biopsy and the concentration of serum ferritin are accurate indicators of early depletion. As the severity of deficiency proceeds, serum iron (SI) decreases and total iron-binding capacity (TIBC) increases; an iron saturation (SI/TIBC) of <16% suggests iron deficiency. Microcytosis, hypochromia, and anemia ensue. Elevated levels of serum ferritin or an iron saturation of >60% suggests iron overload, although systemic inflammation elevates serum ferritin regardless of iron status.
Manganese	A component of several metalloenzymes. Most manganese is in mitochondria, where it is a component of manganese superoxide dismutase.	Manganese deficiency in the human has not been conclusively demonstrated. It is said to cause hypocholesterolemia, weight loss, hair and nail changes, dermatitis, and impaired synthesis of vitamin K–dependent proteins. [F: 1.8 mg; M: 2.3 mg]	Toxicity by oral ingestion is unknown in humans. Toxic inhalation causes hallucinations, other alterations in mentation, and extrapyramidal movement disorders. [11 mg]	Until the deficiency syndrome is better defined, an appropriate measure of status will be difficult to develop.
Molybdenum	A cofactor in several enzymes, most prominently xanthine oxidase and sulfite oxidase.	A probable case of human deficiency is described as being secondary to parenteral administration of sulfite and resulted in hyperoxypurinemia, hypouricemia, and low sulfate excretion. [45 µg]	Toxicity not well described in humans, although it may interfere with copper metabolism at high doses. [2 mg]	Laboratory means of assessment are not meaningful until the deficiency syndrome is better described.

TABLE 199-3 NUTRITIONAL TRACE ELEMENTS AND THEIR CLINICAL IMPLICATIONS—cont'd

	BIOCHEMISTRY AND PHYSIOLOGY	DEFICIENCY [RDA*]	TOXICITY [TUL†]	ASSESSMENT OF STATUS
Selenium	Most dietary selenium is in the form of an amino acid complex. Nearly complete absorption of such forms occurs. Homeostasis is largely performed by the kidney, which regulates urinary excretion as a function of selenium status. Selenium is a component of several enzymes, most notably glutathione peroxidase and superoxide dismutase. These enzymes protect against oxidative and free radical damage of various cell structures. The antioxidant protection conveyed by selenium apparently operates in conjunction with vitamin E because deficiency of one seems to potentiate damage induced by a deficiency of the other. Selenium also participates in the enzymatic conversion of thyroxine to its more active metabolite, triiodothyronine.	Deficiency is rare in North America but has been observed in individuals on long-term TPN lacking selenium. Such individuals have myalgias or cardiomyopathies. Populations in some regions of the world, most notably some parts of China, have marginal intake of selenium. In these regions *Keshan disease*, a condition characterized by cardiomyopathy, is endemic; it can be prevented (but not treated) by selenium supplementation. [55 µg]	Toxicity is associated with nausea, diarrhea, alterations in mental status, peripheral neuropathy, and loss of hair and nails; such symptoms were observed in adults who inadvertently consumed 27-2400 mg. [400 µg]	Erythrocyte glutathione peroxidase activity and plasma or whole blood selenium concentrations are the most commonly used methods of assessment. They are moderately accurate indicators of status.
Zinc	Intestinal absorption occurs by a specific process that is enhanced by pregnancy and corticosteroids and diminished by coingestion of phytates, phosphates, iron, copper, lead, or calcium. Diminished intake of zinc leads to an increased efficiency of absorption and decreased fecal excretion, providing a means of zinc homeostasis. Zinc is a component of more than 100 enzymes, among which are DNA polymerase, RNA polymerase, and transfer RNA synthetase.	Zinc deficiency has its most profound effect on rapidly proliferating tissues. Mild deficiency: growth retardation in children. More severe deficiency: growth arrest, teratogenicity, hypogonadism and infertility, dysgeusia, poor wound healing, diarrhea, dermatitis on the extremities and around orifices, glossitis, alopecia, corneal clouding, loss of dark adaptation, and behavioral changes. Impaired cellular immunity is observed. Excessive loss of gastrointestinal secretions through chronic diarrhea and fistulas may precipitate deficiency. *Acrodermatitis enteropathica* is a rare, recessively inherited disease in which intestinal absorption of zinc is impaired. [F: 8 mg; M: 11 mg]	Acute zinc toxicity can usually be induced by ingestion of >200 mg of zinc in a single day (in adults). It is manifested by epigastric pain, nausea, vomiting, and diarrhea. Hyperpnea, diaphoresis, and weakness may follow inhalation of zinc fumes. Copper and zinc compete for intestinal absorption: long-term ingestion of >25 mg/day of zinc may lead to copper deficiency. Long-term ingestion of >150 mg/day has been reported to cause gastric erosions, low high-density lipoprotein cholesterol levels, and impaired cellular immunity. [40 mg]	No accurate indicators of zinc status exist for routine clinical use. Plasma, red blood cell, and hair zinc concentrations are often misleading. Acute illness, in particular, is known to diminish plasma zinc levels, in part by inducing a shift of zinc out of the plasma compartment and into the liver. Functional tests that determine dark adaptation, taste acuity, and rate of wound healing lack specificity.

*Recommended daily allowance (RDA) established for female (F) and male (M) adults by the U.S. Food and Nutrition Board, 1999-2001. In some instances, insufficient data exist to establish an RDA, in which case the adequate intake (AI) established by the board is listed.
†Tolerable upper limit (TUL) established for adults by the U.S. Food and Nutrition Board, 1999-2001.

TOXINS

Tobacco smoking (Chapter 363) alters the metabolism of several vitamins, including folate and vitamins C and E. Diminished plasma levels of folate and ascorbic acid also have been observed in chronic smokers. Smoking is also associated with diminished levels of folate in cells of the oral mucosa, diminished ascorbic acid levels in leukocytes, and decreased concentrations of vitamin E in the alveolar fluid, thereby indicating that its effects do not simply represent a shift of these micronutrients out of the plasma compartment.

CONTROVERSIES REGARDING MARGINAL MICRONUTRIENT DEFICIENCIES

In a number of circumstances, micronutrient supplementation can improve a physiologic measurement but not to provide overall clinical benefit, especially when used in supraphysiologic doses. For example, gram quantities of niacin can reduce low-density lipoprotein (LDL) cholesterol levels but may marginally increase all-cause mortality.[A3,4]

Examples of the complexities in redefining the criteria for vitamin deficiencies and vitamin requirements are two water-soluble vitamins, folate and B_{12}. Degrees of deficiency that are not sufficiently severe to cause anemia (Chapter 150) may still disturb normal biochemical and physiologic homeostasis and, in some instances, cause clinical disease.

For example, women who take folic acid supplements at the time of conception have a markedly lower chance of delivering a baby with a neural tube defect compared with women who are not taking folate supplements, even if they have a folate level within the conventionally accepted normal range. Less-than-optimal intake of folate is also evidenced by an increase in the serum level of homocysteine, which is an amino acid that is normally metabolized by a folate-dependent pathway (Chapter 193). Before the federally mandated fortification of flour, the median intake of folate among adults was half of the present RDA, and a substantial minority of Americans had significantly elevated serum homocysteine levels. An elevated homocysteine level (Chapter 193), which is associated with the development of occlusive vascular disease and accelerated cognitive decline, can be reduced with supplemental folate, vitamin B_{12}, and vitamin B_6. A moderate level of evidence indicates supplemental folate may decrease the risk of stroke, but the risks of coronary artery and peripheral vascular disease are not diminished.

A compelling body of rigorously performed epidemiologic studies has demonstrated that habitually low consumption of folate is associated with a substantially increased risk of colorectal cancer, and mechanistic animal studies support true causality. The optimal folate intake in regard to cancer prevention is unclear, but epidemiologic studies suggest the value is about 500 µg per day. The question of optimal intake is further confounded by

TABLE 199-4 DRUG-MEDIATED EFFECTS ON MICRONUTRIENT STATUS: EXAMPLES

DRUG	NUTRIENT	MECHANISM OF INTERACTION
Dextroamphetamine, levodopa	Potentially all micronutrients	Induces anorexia
Proton pump inhibitors, H2-histamine antagonists	Vitamin B_{12}	Modest bacterial overgrowth, decreases gastric acid, impairs absorption
Metformin	Vitamin B_{12}	Impairs absorption
Isoniazid	Vitamin B_6	Impairs utilization of B_6
Nonsteroidal anti-inflammatory drugs	Iron	Gastrointestinal blood loss
Penicillamine	Zinc	Increases renal excretion
Cholestyramine and related drugs	Vitamin D, folate	Adsorbs nutrient, decreases absorption

observations that doses of supplemental folic acid exceeding 1000 µg/day may mask B_{12} deficiency and may paradoxically enhance the risk of colorectal cancer, thereby underscoring the potential for harm produced by taking a nutrient outside of its physiologic window.[5] Presently, the recommended daily intake of folate is 400 µg/day, and women capable of becoming pregnant should consume an additional 400 µg/day in the form of supplements or fortified food. The tolerable upper limit is 1000 µg/day, and continuing research efforts will hopefully clarify any potential role for what constitutes ideal folic acid consumption and levels

For vitamin B_{12} (see Chapter 150), a plasma level between 200 and 350 pg/mL, which is at the lower end of the normal range in most laboratories, may not exclude neuropsychiatric complications, even in the absence of any indications of megaloblastic anemia, especially in older adults who have a higher prevalence of atrophic gastritis and use of medications (gastric acid suppressants and metformin) that reduce B_{12} absorption.[6] In such individuals, an elevated serum level of methylmalonic acid is both a sensitive and a specific indicator of cellular vitamin B_{12} deficiency, and vitamin B_{12} repletion (see Chapter 150) should be prescribed to lower the methylmalonic acid level to normal. However, routine vitamin B_{12} supplementation in individuals with an adequate B_{12} status has no effect on cognitive function, depressive symptoms, or fatigue.[A4]

IS ROUTINE MULTIVITAMIN AND MULTIMINERAL SUPPLEMENTATION BENEFICIAL?

In recent surveys of U.S. adults, use of supplements, including vitamins and minerals, remains high: about 60% of adults ages 20 years and older report use of a supplement in the past month, and the percentage is about 75% among adults ages 60 years and over. Among this older cohort, 25% of individuals report the use of four or more supplements. Despite the absence of unanimous consensus about whether regular use of a multivitamin or multimineral supplement assists in the maintenance of health, the weight of current evidence indicates little or no benefit from micronutrient supplementation in the general adult North American population in terms of preventing common chronic degenerative diseases such as vascular disease, cancer, and dementia.

Poor dietary patterns are often observed among individuals of lower socioeconomic status. Moreover, in many regions of the world, there continues to be a high prevalence of marginal micronutrient status among the general adult population, and in such areas widespread supplementation may be indicated.

The elderly frequently cannot achieve recommended intakes of vitamin D and calcium to optimize bone health with diet alone, and a plasma 25-hydroxy vitamin D level below 20 ng/L has been associated with increased mortality.[7] Targeted supplementation with vitamin D (400 to 800 IU daily) plus calcium (1000 mg) can reduce the risk of fractures[A5] and is often indicated for this purpose (see Chapter 225).[8] However, meta-analyses of randomized trials of vitamin D supplementation have shown no benefit for preventing cancer or cardiovascular events,[A6] depression,[A7] tuberculosis infection,[A8] or the outcomes of critically ill patients who are vitamin D deficient.[A9] Whether vitamin supplementation retards the progression from pre-diabetes to diabetes remains a matter of controversy.[9,A10] Routine screening for vitamin deficiency is not recommended by the U.S. Preventive Services Task Force,[10] but a vitamin D level should be obtained in high-risk individuals, including whenever a pathologic fracture has occurred.

Although daily supplementation at the levels found in most multivitamin preparations probably presents no risk of harm, vitamin and mineral supplements are of no proven benefit for preventing cardiovascular disease or cancer.[A11,11] Vitamin C supplementation is of no benefit for adults with sepsis[A12] or severe infection.[A13]

Furthermore, adverse health effects have been observed in several rigorously performed clinical trials of long-term supplementation with micronutrients at levels that exceed the RDA (or conventional levels of dietary intake) by several-fold. For example, an increased incidence of prostate cancer was observed when vitamin E was administered at a dose of 400 IU/day, and β-carotene supplementation resulted in an increased incidence of lung cancer among heavy smokers in doses of 20 to 30 mg/day.

Nevertheless, health benefits are likely in individuals whose dietary intake is chronically inadequate or in patients whose medical conditions are predictably complicated by micronutrient deficiencies, such as patients on chronic renal dialysis (Chapter 116), individuals with marginally controlled intestinal malabsorption (Chapter 126), and pregnant women.

New biochemical functions of vitamins are increasingly being recognized, and the quantities of each micronutrient that are required to optimize such functions may need to be considered. Also, future efforts to refine appropriate dietary goals for each micronutrient will have to consider whether the level of consumption that conveys health benefits to one segment of the population is beneficial, or even appropriate, for all segments of society, thereby underscoring the importance of personalized medicine.

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200 EATING DISORDERS

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DEFINITION

Feeding and eating disorders are characterized by a persistent disturbance of eating or eating-related behavior that results in the altered consumption or absorption of food and that significantly impairs physical health or psychosocial functioning.[1] The *Diagnostic and Statistical Manual of Mental Disorders*, 5th edition (DSM-5)[2] provides formal criteria defining anorexia nervosa, bulimia nervosa, binge-eating disorder, and avoidant/restrictive food intake disorder. Presentations that do not meet criteria for any of these specific diagnoses but that cause significant distress or impairment can be described as other feeding or eating disorders.

Anorexia Nervosa

The salient feature of anorexia nervosa is the restriction of caloric intake, thereby resulting in a significantly low body weight. Individuals with anorexia nervosa experience an intense fear of gaining weight or becoming fat, are overly concerned with weight or shape, and often do not recognize the seriousness of their low body weight. Anorexia nervosa has two subtypes, restricting and binge-eating/purging.

Bulimia Nervosa

Bulimia nervosa is characterized by recurrent episodes of binge eating (i.e., the consumption of an unambiguously large amount of food given the context), accompanied by a sense of loss of control over eating. Episodes of binge eating are followed by behaviors intended to compensate for energy consumed and to prevent weight gain, such as self-induced vomiting and laxative abuse. Binge-eating and compensatory behaviors must occur, on average, at least once a week for 3 months. The self-esteem of individuals with bulimia nervosa is excessively influenced by their body weight and shape.

Binge-Eating Disorder

Individuals with binge-eating disorder engage in recurrent episodes of binge eating but in the absence of the inappropriate compensatory behaviors that characterize bulimia nervosa. The binge episodes are accompanied by at least three associated indicators of loss of control, such as eating very rapidly and eating until feeling uncomfortably full. Individuals experience marked distress surrounding the binge episodes, and the binge-eating episodes occur, on average, at least once a week for 3 months.

Avoidant/Restrictive Food Intake Disorder

Individuals with avoidant/restrictive food intake disorder significantly restrict their food intake but do not have the major concerns about body shape and weight that are seen in individuals with anorexia nervosa. Individuals may avoid food generally or may avoid foods with specific characteristics, such as color or texture.

Pica

Pica refers to the persistent and age-inappropriate consumption of nonfood substances, such as dirt, paper, or soap.

Rumination Disorder

Rumination disorder is characterized by the repeated regurgitation of food after eating. The food may then be re-chewed, re-swallowed, or spit out.

EPIDEMIOLOGY

The lifetime prevalence of anorexia nervosa is approximately 0.8%, with higher rates among women (1.4%) compared with men (0.12%). The lifetime prevalence of bulimia nervosa appears to be about 0.3%, with higher rates among women (5%) than men (0.1%). The lifetime prevalence of binge-eating disorder is estimated at 1.3% for women and 0.4% for men. Contrary to the view that eating disorders afflict only non-Hispanic White, affluent females, individuals of all races, ethnicities, and cultures are impacted by these diagnoses. Female sex, age, presence of eating disorders in siblings and comorbid disorders in family members, pediatric overweight, inappropriate concerns about body shape and weight, sexual abuse, trauma, and mood disorders are risk factors for eating disorders.

Personality-related variables, such as impulsivity and perfectionism, also appear to be linked to eating disorders. Internalization of the "thin ideal" (a sociocultural emphasis on shape and weight and a marked preference for a thin body type) and resulting weight and shape concerns have been proposed to contribute to eating disorder development, particularly among adolescents who are under strong influence from their peer and family environments. For example, parental over-concern about eating, shape, and weight, as well as weight-related teasing by family members, confers risk for eating disorders. Teasing and bullying are specific risk factors for bulimia nervosa and binge-eating disorder

PATHOBIOLOGY

A detailed understanding of the relationship between brain structural and functional abnormalities and the development, severity, and course of eating disorders is lacking.[3] Most research on the neurobiology of eating disorders has focused on anorexia nervosa and bulimia nervosa. Structural brain imaging has found that patients with anorexia nervosa have reduced volumes of gray and white matter, which generally normalize with restoration of weight. Several studies have described decreased cortical thickness in frontal and parietal regions, with suggestions that decreased cortical thickness is associated with greater disturbances in eating behavior.

Individuals with anorexia nervosa tend to show decreased brain responses to images of food and to sweet tastes compared with healthy controls, but precisely how such differences are related to the core disturbance in eating behavior is less clear. When making decisions about what to eat, individuals with anorexia nervosa engage the dorsal striatum, an area associated with habitual behavior, more than healthy controls. Neurocognitive tasks indicate deficiencies in inhibitory control mechanisms, particularly to food cues.

Anorexia nervosa, bulimia nervosa, and binge-eating disorder aggregate in families,[4] with estimates from twin studies suggesting that 40 to 60% of vulnerability for eating disorders is genetic. The most extensive genetic studies have focused on anorexia nervosa, for which eight loci have been identified, but the number of loci is expected to increase as more studies are performed.

CLINICAL MANIFESTATIONS

Anorexia Nervosa

Anorexia nervosa typically manifests during adolescence, although the disorder can develop prior to puberty. Individuals with anorexia nervosa may develop a wide range of physical symptoms and signs largely related to starvation.[5] Individuals with anorexia nervosa frequently present with symptoms of other psychiatric disorders (Chapter 362), including obsessionality, anxiety, and depression, as well as with high rates of suicidal ideation and behavior. Symptoms include fatigue, constipation, and intolerance to cold. Hypogonadism with amenorrhea (Chapter 218) is nearly universal in females. In addition to wasting, the physical examination may reveal lanugo hair and hypercarotenemia.

Health problems associated with malnutrition impact the cardiovascular, gastrointestinal, reproductive, hematologic, and endocrine systems.[6] Hypotension and sinus bradycardia are characteristic findings. However, patients with anorexia nervosa can also develop arrhythmias, prolongation of the QTc interval on the electrocardiogram, sudden cardiac death, and structural changes in the heart such as left ventricular atrophy and cardiac fibrosis.

Patients with anorexia nervosa can have markedly slowed gastric emptying (Chapter 122), manifested by early satiety, nausea, abdominal pain, and bloating. Superior mesenteric artery syndrome, resulting in chronic intermittent or acute duodenal obstruction (which can be complete or partial), can result from the loss of fatty tissue that normally maintains the angle between the superior mesenteric artery and the aorta, thereby leading to extrinsic compression of the duodenum by the superior mesenteric artery. Normochromic, normocytic anemia and leukopenia are commonly observed owing to deficiencies in iron and vitamins as well as to gelatinous transformation of the bone marrow. Slight elevations of liver aminotransferase levels are common. Levels of thyroid-stimulating hormone and thyroxine may be slightly low, and levels of reverse triiodothyronine are usually elevated. Reduced bone density may auger the onset of premature osteopenia and osteoporosis.

ABSTRACT

The feeding and eating disorders encompass anorexia nervosa, bulimia nervosa, binge-eating disorder, avoidant/restrictive food intake disorder, pica, and rumination disorder. All are associated with significant impairments of physical health and psychosocial functioning. The neurobiology underlying these disorders is under study. Risk factors have been identified. The clinical manifestations of eating disorders are protean, can be caused directly or indirectly by the eating disorder, and can vary in severity to include potentially fatal outcomes. Cognitive behavioral therapy and interpersonal psychotherapy are most effective for bulimia nervosa and binge-eating disorder. Severely underweight patients with anorexia nervosa may require inpatient medical monitoring and supervised nutritional rehabilitation.

KEYWORDS

anorexia nervosa
bulimia nervosa
binge-eating disorder
avoidant/restrictive food intake disorder
psychotherapy
malnutrition
comorbid psychiatric disorders

Bulimia Nervosa

Bulimia nervosa frequently develops during late adolescence or early adulthood. Individuals with bulimia nervosa present with signs and symptoms most commonly associated with purging behavior. These problems include erosion of dental enamel owing to vomiting; gastrointestinal symptoms, including gastric acid reflux that can lead to dyspepsia and dysphagia; salivary gland hypertrophy; and potentially dangerous disturbances in electrolytes and in acid-base balance. For example, individuals who purge via self-induced vomiting may develop hypokalemic alkalosis.[6] Metabolic acidosis with the loss of bicarbonate from the bowel can occur in patients who are abusing laxatives as a result (Chapter 104).

Binge-Eating Disorder

Binge-eating disorder often manifests in adulthood, but adolescents also present with the disorder. The weights of individuals with binge-eating disorder are frequently in the overweight or obese range.[7] Compared with similar adults without binge-eating disorder, individuals with the disorder experience significant impairment in a number of domains of psychosocial functioning, including a poorer quality of life and more impaired functioning in their home and social lives. Individuals with binge-eating disorder often have higher levels of disability, health problems, and impairment of work productivity compared with similar individuals without binge eating.

The most common psychiatric comorbidities (Chapter 362) in binge-eating disorder are major depressive disorder, anxiety disorders, substance use disorders, and disruptive behavioral disorders. The presence of binge eating following bariatric surgery may impact the outcome (Chapter 201), thereby resulting in less weight loss or more weight regain.

Other Eating Disorders

Avoidant/restrictive food intake disorder, pica, and rumination disorder most frequently present during childhood but may also develop in adults. Individuals with avoidant/restrictive food intake disorder are at risk for a range of nutritional deficiencies that reflect the specific nature of their dietary disturbance.[8] When affected individuals are significantly underweight, they may develop physical complications similar to those seen in individuals with anorexia nervosa. Pica is sometimes associated with deficiencies in vitamins or minerals (e.g., zinc, iron) and, in youth, is often associated with intellectual disability. Pica can result in the development of serious medical complications, including poisoning, intestinal obstruction, and the formation of bezoars. As with pica, rumination disorder is often seen in children with intellectual disabilities. Extreme cases may be associated with emaciation.

DIAGNOSIS

Although a number of structured, well-validated assessments (e.g., www.EDA.org) exist for the diagnosis of eating disorders, eating disorders are typically diagnosed by review of the patient's history, symptoms, and behaviors in an interview format. Information should be gathered on interpersonal relationships, history of sexual and physical abuse, self-harm, and suicidal ideation or behavior. Family involvement is crucial, particularly for younger patients. A complete physical examination is recommended for all patients to assess body composition, vital signs, and cardiovascular function. Laboratory testing should include a complete blood count with differential and a platelet count, as well as blood chemistries (including electrolytes and tests of liver, renal, and thyroid function).

TREATMENT

The approach to the eating disorder shares some similarities, but syndrome-specific treatments vary.[9,10]

Anorexia Nervosa

The first goal of treatment for anorexia nervosa is to restore weight. For severely underweight patients, inpatient medical monitoring and supervised nutrition rehabilitation are required,[11] and higher calorie refeeding is superior to lower calorie refeeding acutely[A1] and at 1 year.[A2] For other patients, the optimal setting (inpatient vs. residential vs. outpatient treatment) is unclear,[A3] and consideration of the costs of the various options plays an important role in determining the choice of treatment. However, for pediatric patients, family-based psychotherapy, particularly during the early phases of the disorder, has demonstrated effectiveness.[A4] This treatment involves both joint family sessions and simultaneous, but independent, patient/family intervention. Antidepressants (e.g., selective serotonin reuptake inhibitors) have not been found to be effective, but the atypical antipsychotic olanzapine (2.5 to 10 mg/d) has been associated with a modest increase in weight gain.[A5] The treatment potential of neuromodulative techniques such as transcranial direct current stimulation, repetitive transcranial magnetic stimulation, and deep brain stimulation are currently being explored. Results with cannabinoids as an appetite stimulant have been inconclusive.[A6]

Bulimia Nervosa

Cognitive-behavioral therapy is the treatment of choice for bulimia nervosa. Interpersonal psychotherapy is also effective, particularly for patients who are nonresponsive to cognitive-behavioral therapy.[12] Antidepressants, especially selective serotonin reuptake inhibitors (Chapter 362), are modestly effective for reducing binge eating in bulimia nervosa over the short term and long term, and fluoxetine (60 mg/day) is approved by the U.S. Food and Drug Administration (FDA) for this purpose.[13] Topiramate (25 to 400 mg/day) has consistently been shown to decrease binge eating in bulimia nervosa, but cognitive side effects limit its usefulness.

Binge-Eating Disorder

Psychological treatment for binge-eating disorder aims to reduce binge eating, reduce concerns about body weight and shape, and prevent excess weight gain and/or induce modest weight loss. Cognitive-behavioral therapy, interpersonal psychotherapy, and behavioral weight loss are first-line treatments, but cognitive-behavioral therapy–guided self-help approaches are also useful, especially when specialist care is not available. However, face-to-face cognitive-behavioral therapy leads to quicker and greater reductions in the number of objective binge-eating episode days, better abstinence rates, and better eating disorder psychopathologic findings and may be generally a better initial treatment option than Internet-based guided self-help.[A7] Lisdexamfetamine (50 or 70 mg/day), which can reduce binge-eating episodes and is associated with modest weight loss, is currently the only FDA-approved medication for binge-eating disorder in adults.[A8] Selective serotonin reuptake inhibitors (e.g., fluoxetine 60 mg/day) and topiramate (25 to 400 mg/day) can also reduce the frequency of binge eating relative to placebo in short-term trials, but topiramate is frequently associated with cognitive side effects.

Avoidant/Restrictive Food Intake Disorder, Pica, and Rumination Disorder

Few controlled trials have evaluated treatments for avoidant/restrictive food intake disorder, pica, and rumination disorder. Current approaches are based on behavioral interventions.[14–16] Weight restoration is indicated for underweight individuals.

PREVENTION

The U.S. Preventive Services Task Force found insufficient data[A9] to recommend for or against screening adolescents and adults who are not known to be at high risk for eating disorders,[17] but some professional societies recommend such screening as part of a comprehensive evaluation.[18] Currently available data indicate that interactive, multisession programs with adolescent girls are more effective than universal, didactic, heterogeneous programs for reducing the risk factors that are associated with eating disorders. For example, dissonance-based programs, in which participants are encouraged to challenge the notion that being thinner will lead to being happier, aimed at reducing risk factors for eating disorder in adolescent girls have demonstrated effectiveness, especially for reducing binge eating.

PROGNOSIS

Eating disorders tend to exhibit a remitting and relapsing natural course across the lifespan and with high rates of diagnostic crossover. Outcome data indicate that patients with anorexia nervosa tend to transition to bulimia nervosa or an unspecified eating disorder, whereas patients with bulimia nervosa and binge-eating disorder may migrate from one to the other.

Anorexia Nervosa

The outcome of anorexia nervosa is extremely variable. Many individuals, especially those with brief mild illnesses, completely remit with resolution of signs, symptoms, and at least some of the associated psychological issues. Conversely, anorexia nervosa has one of the highest mortality rates among all psychiatric diagnoses due to suicide, nutritional deficits, cardiac complications, and substance abuse. Between these extremes, most individuals may remain chronically underweight or gain weight and develop bulimia nervosa.

Bulimia Nervosa

Most individuals with bulimia nervosa (70% or greater) who receive treatment fully remit when assessed 5 to 20 years later, but remission rates are much lower (27 to 28%) at 1-year follow-up. If individuals with bulimia nervosa do not achieve remission within 5 years, however, they are likely to exhibit a chronic course. Diagnostic crossover from bulimia nervosa to anorexia nervosa is relatively rare. However, the more frequent diagnostic crossover between bulimia nervosa and binge-eating disorder suggests possible common psychological and/or biological processes.

Other Eating Disorders

A paucity of data exists on the long-term outcomes for binge-eating disorder patients, but upward of 80% of patients may remit at 1 year following outpatient treatment. Little information is currently available on the long-term course of avoidant/restrictive food intake disorder, pica, and rumination disorder.

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201 OBESITY

MICHAEL D. JENSEN AND DANIEL H. BESSESEN

Obesity is the most common nutritional disorder in the United States, and it directly or indirectly accounts for a significant portion of health-related expenses. Lifestyle change, antiobesity medications, and bariatric surgery are evidence-based treatment options, but each requires training and time to implement.

DEFINITION

Obesity, which is a degree of excess adiposity that can predispose to adverse health consequences, is a disease of body weight regulation, much as diabetes is a disease of glucose regulation.[1] Body mass index (BMI), calculated as weight in kilograms divided by height squared in meters, is the most commonly used screening tool to assess the health risks related to weight.

EPIDEMIOLOGY

More than 1.9 billion adults worldwide are overweight, and over 650 million are obese.[2] Obesity causes an estimated 4.7 million deaths worldwide. In the United States, over 70% of adults are overweight, and the prevalence of obesity is about 42% in women and 44% in men.[3] BMI rises between ages 20 and 60 years and falls slightly thereafter.[4] Severe obesity is inversely associated with urbanization,[5] with a significantly greater prevalence of obesity and severe obesity among adults living in nonmetropolitan areas compared with large metropolitan statistical areas.[6] Black American women and Mexican Americans of both sexes have the highest rates of overweight and obesity in the United States. Women in lower socioeconomic classes are much more likely than those in higher socioeconomic classes to be obese, an association that reduces, but does not eliminate, the racial differences in the prevalence of obesity. Whether the remaining racial differences in the prevalence of obesity are due to genetic, constitutional, or social and environmental factors is not yet known.

The health risks associated with increased adiposity increase continuously as BMI exceeds 25 (Table 201-1). Lower BMI values of 23 to 24 are recommended for Asian populations, who are at risk for the typical metabolic complications of obesity at lower BMI and waist circumferences than are individuals of other ethnicities. Risks associated with being overweight are modest but are higher in the presence of central obesity. Some persons who are overweight (BMI of 25.0 to 29.9) may have increased muscle mass rather than increased body fat; these individuals are not difficult to identify clinically and do not have an elevated waist circumference. The prevalence of comorbid conditions and risk of new morbid conditions increase considerably at a BMI of more than 30, which is the definition of obesity. Obesity is divided into three classes, also depending on BMI (see Table 201-1).

Young adults, who accumulate greater exposure to metabolic and mechanical damage from being overweight or obese throughout their lives, are at increased risk for chronic health conditions such as coronary heart disease and type 2 diabetes mellitus. By comparison, the increase in mean BMI with age, though deleterious, is not as much of a threat to population health as is a similar increase in the BMI of younger populations.

The lowest mortality rates for young adults have historically been for a BMI in the normal range (20.0 to 24.9), whereas the BMI associated with the lowest mortality rates is somewhat above 25 kg/m^2 for adults in their 60s and 70s.[7] Data also suggest that the optimal BMI may be about 27.0 for older adults given current life expectancy data.

PATHOBIOLOGY

Genetic and constitutional susceptibility to obesity are heavily influenced by the environment. Studies of twins adopted into different families indicate that within a given environment, a significant portion of the variation in weight is genetic. However, the growing prevalence of obesity is related to changes in environment, not human genetics.

Genetic Aspects of Human Obesity

Variants in the fat mass and obesity-associated (FTO) gene, which are relatively common (16% of adults are homozygous for the predisposing allele), account for only a few percent of the differences in body weight. Large genome-wide association studies have identified over 100 loci that associate with BMI, but together these genes account for less than 3% of the variance in BMI. The majority of the genes associated with BMI are expressed in the central nervous system, thereby suggesting effects on ingestive behavior. Genome-wide association studies have also identified about 50 loci that are associated with waist-to-hip ratio after adjusting for BMI, but these loci combined account for only 1 to 2% of the variance in waist-to-hip ratio. Most of these genes are preferentially expressed in adipose tissue, thereby implying that hereditary differences in body fat distribution are driven by genetic factors.

Genetic obesity is seen in a variety of childhood-onset conditions, including autosomal dominant Prader-Willi (Chapter 214) and Albright hereditary osteodystrophy, as well as autosomal recessive Laurence-Moon-Biedl, Cohen, Carpenter, Alstrom, and Tubby syndromes. Virtually all monogenic obesity syndromes cause hyperphagia by disrupting parts of appetite regulation pathways. For example, children with homozygous or compound heterozygous loss-of-function mutations in the genes encoding leptin (LEP) and the leptin receptor (LEPR) develop intense hyperphagia that results in severe obesity. Congenital leptin deficiency results in undetectable serum leptin concentrations, whereas leptin concentrations are not unusually increased

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ABSTRACT

The epidemiology and biology of obesity are best understood as they relate to energy expenditure, the regulation of appetite, and their medical/mechanical complications. The primary treatments of obesity include dietary intervention, increased physical activity, and behavioral modalities. Antiobesity medications, endoscopic treatments, and bariatric surgery are indicated for difficult-to-treat cases.

KEYWORDS

adipose tissue
energy expenditure
diet
bariatric surgery
appetite
physical activity

TABLE 201-2 ENVIRONMENTAL FACTORS PROMOTING OBESITY

DIETARY	ACTIVITY
↑ Energy density of foods	↑ Sedentary behavior
↑ Portion size	↓ Activities of daily living
↑ Variety*	↓ Employment-related physical activity
↑ Palatability	
↑ Availability	
↓ Cost	
↑ Caloric beverages (sugar-sweetened beverages)	

*Variety of sweets, snacks, and entrees.

in those with LEPR deficiency. Approximately 5% of patients with severe, early-onset obesity have been reported to have heterozygous loss-of-function MC4R mutations, which appear to be inherited in a codominant manner. The features of MC4R deficiency include hyperphagia, hyperinsulinemia, and increased linear growth. Homozygous or compound heterozygous mutations in proopiomelanocortin (POMC) can result in hyperphagia and early-onset obesity, isolated adrenocorticotropic hormone (ACTH) deficiency (due to lack of adrenocorticotrophin), and hypopigmentation of skin and hair (due to lack of signaling through the melanocortin 1 receptor). Humans lacking prohormone convertase 1 also develop severe, early-onset obesity and ACTH deficiency due to impaired processing of POMC.

Constitutional Influences on Obesity

Environmental factors can result in long-term, epigenetic effects that affect body weight regulation and the susceptibility to obesity-related health problems. For example, undernutrition in the last trimester of pregnancy and in the early postnatal period decreases the risk of adult obesity, although the low birthweight associated with undernutrition (or smoking) in late pregnancy also increases the risk of adulthood hypertension, abnormal glucose tolerance, and cardiovascular disease. In contrast, undernutrition limited to the first two trimesters of pregnancy is associated with an increased probability of adult obesity. Infants of diabetic mothers tend to be fatter than those of nondiabetic mothers, and children of diabetic mothers have a greater prevalence of obesity when they are 5 to 19 years old, independent of whether their mother is obese. Finally, intrauterine exposure to the diabetic environment results in an increased risk of diabetes mellitus and obesity in the offspring.

Environmental Contributors to Obesity

Dramatic changes in the environment of developed and even developing countries over the past 50 years include reduced demands for physical activity and alterations in the food supply (Table 201-2). These changes in the food supply help explain why the reduced energy expenditures by persons in the industrial and postindustrial eras have not been accompanied by a decrease in energy intake.

Food

The consumption of energy-dense foods results in greater energy intake because adults tend to respond to food volume rather than to the energy content. Many high-fat foods are also energy dense and contribute to weight gain. The consumption of sugar-sweetened beverages, such as soft drinks and fruit juices, is not accompanied by a decrease in food intake to offset the extra energy intake and promotes weight gain. The larger portion size of food and beverages also increases food intake. Food variety can also affect energy intake, and the ready availability of an increased variety of entrees, sweets, snacks, and carbohydrates is associated with an increase in food intake and body fatness. In contrast, an increase in the variety of vegetables available does not appear to increase energy intake and is not associated with increased body fatness. Other factors include the reduced costs of food, increased availability, and palatability. Psychological factors such as dietary restraint or disinhibition, as well as the social context in which the food is present, can influence how food properties affect energy intake.

Physical Activity

Physical activity (Chapter 14) levels have been decreasing in the United States and worldwide, as reduced activity at work is not replaced, on average, by increased leisure activity. The result is decreased energy expenditure, estimated to be over 100 calories/day, at a time when the food supply has led to sustained or increased caloric consumption. The amount of time spent in sedentary pursuits is associated with an increased risk of overweight and obesity, likely independent of participation in traditional exercise activities.

Regulation of Body Weight and Energy Balance

The typical U.S. adult will take in and expend approximately 2000 to 3000 kcal/day. Consistent errors of even 1% in excess food consumption can result in body fat gain of 25 to 30 pounds in 10 years, assuming no change in energy expenditure, so adults who do not gain weight must regulate their average energy balance with greater than 1% precision. This balanced regulation of energy intake and energy expenditure requires both conscious and unconscious processes.

The excess energy consumed by adults is generally stored as triglycerides in adipocytes. Humans continuously recruit new adipocytes from a large preadipocyte pool to replace dying adipocytes. Although the primary means by which abdominal adipose tissue mass expands is by increasing the size of existing fat cells (adipocyte hypertrophy), this process can store only a limited amount of fat. Adults who gain leg fat accumulate more rather than larger adipocytes on average, thereby resulting in a net increase in the number of adipocytes. Some adults recruit new adipocytes more readily than others, and their body fat is more related to adipocyte hyperplasia (increased fat cell number) than adipocyte hypertrophy. Adults who gain fat primarily via adipocyte hypertrophy are more likely to be insulin resistant.

In addition to its role in storing excess energy as triglyceride, adipose tissue secretes a large number of hormones (termed adipokines), the most prominent of which is leptin. Leptin has a role in regulating appetite, and very low leptin concentrations result in increased hunger. The other well-known adipokine is adiponectin, which is thought to have metabolic protective properties. The functions of scores of other adipokines have not yet been clearly identified in humans.

Energy Intake

Signals can affect hunger, which is the compelling need or desire for food; satiation, which is the state of being satisfactorily full and unable to consume more; and satiety, which is the sense of no longer being hungry. The hypothalamus is a key component of the regulation of the intake of food (E-Fig. 201-1). Hypothalamic arcuate nucleus neurons synthesize neuropeptide Y (NPY) and agouti-related protein (AgRP) and are activated under energy-deficit conditions by reduced levels of insulin and leptin, thereby resulting in the drive to eat (orexigenic response). When energy intake is sufficient, POMC neurons in the arcuate nucleus generate responses that reduce appetite (anorectic responses). The neurons that express POMC also express cocaine- and amphetamine-related transcript (CART). POMC is processed to the melanocortin (MSH) peptides alpha, beta, and gamma MSH, which are melanocortin 3 and 4 receptor (MC4R) agonists. These arcuate nucleus neurons project to MC4R-expressing neurons in the paraventricular nucleus, where activation of MC4R generates the anorectic response. In conditions of energy deficit, the MC4R receptor is inhibited by AgRP. Neurons in the paraventricular nucleus also express NPY receptors, which, when activated, cause hunger. The balance among these numerous signals plays an important role in the desire to eat. Perhaps the most obvious example of how this pathway can be disrupted is the increase in hunger in response to high-dose, exogenous corticosteroids; suppression of POMC neurons by corticosteroids results in unopposed activity of NPY on paraventricular nucleus neurons.

Satiety, which is the sense of no longer being hungry, is a complex set of postprandial events that affect the interval to and/or the amount consumed at the next meal. The leptin receptor is highly expressed in the hypothalamus. When it is activated by leptin, which is secreted by adipocytes, the expression of POMC increases, thereby leading to reduced food intake. Gut peptides that can influence food intake are secreted in response to mechanical stimuli (e.g., the fullness of the stomach) and/or the presence of nutrients in the jejunum and ileum. These peptides include peptide YY 36 (PYY), glucagon-like peptide 1 (GLP-1), and oxyntomodulin (OXM) that, like leptin and insulin, inhibit neurons that express NPY and AgRP. In contrast, ghrelin activates NPY and AgRP neurons, thereby generating a sensation of hunger, an effect that is exacerbated by prolonged fasting, possibly because leptin secretion decreases out of proportion to the loss of body fat.

In addition to the hypothalamic energy balance system, other central nervous system responses have important effects on food intake (E-Table 201-1).

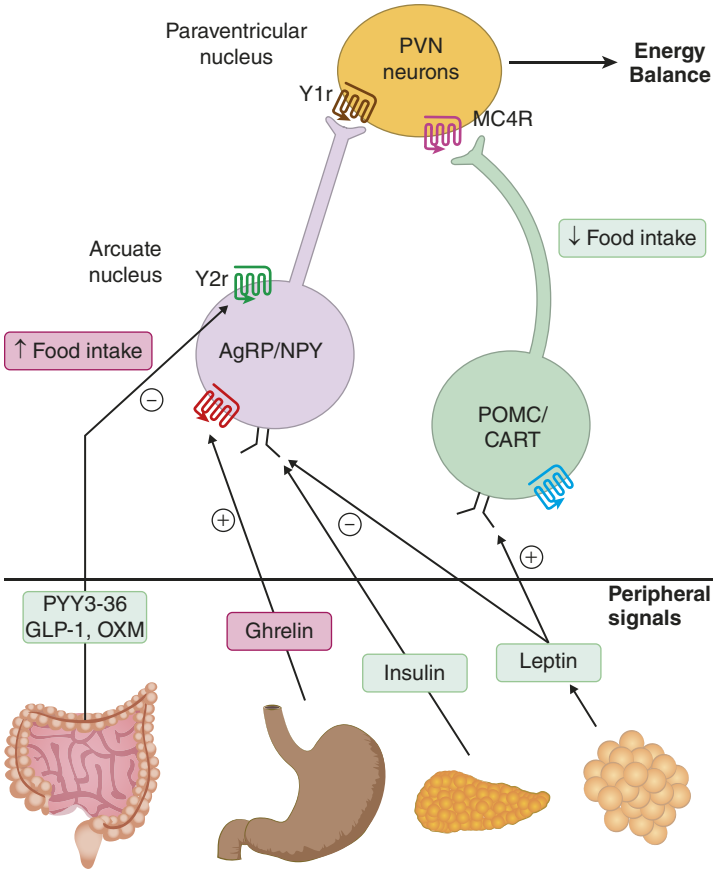

E-FIGURE 201-1. Central appetite regulation pathways. AgRP = agouti-related protein; CART = cocaine- and amphetamine-related transcript; GLP-1 = glucagon-like peptide 1; MC4R = melanocortin 4 receptor; NPY = neuropeptide Y; OXM = oxyntomodulin; POMC = proopiomelanocortin; PVN = paraventricular nucleus; PYY3-36 = peptide tyrosine tyrosine 3-36.

E-TABLE 201-1 CENTRAL NERVOUS SYSTEM REGULATION OF APPETITE

Brain region	Functions	Neurotransmitters
Hypothalamus	Energy homeostasis	Norepinephrine, GABA, POMC, CART, AgRP, NPY
Ventral striatum	Reward aspects of food intake	Dopamine
Prefrontal cortex	Executive function, impulse control	Norepinephrine, dopamine, glutamate
Brainstem, vagus nerve	Signals from GI tract	GLP-1
Cortex	Social meaning of eating	

AgRP = agouti-related protein; CART = cocaine- and amphetamine-related transcript; GABA = γ-aminobutyric acid; GI = gastrointestinal; GLP-1 = glucagon-like peptide 1; NPY = neuropeptide Y; POMC = proopiomelanocortin.

Relevant structures include the ventral striatum, where the reward aspects of food intake are determined; the prefrontal cortex, where executive function and impulse control take place; the brain stem, where vagal inputs from the gastrointestinal tract modulate food intake; and the cortex, where the social meaning of eating is interpreted. Other factors that have been shown to affect food intake include cholecystokinin, which causes satiation but has no effect on satiety, and pancreas-derived amylin, which acts on the gastrointestinal tract and the hypothalamus to inhibit appetite.

Signals of energy availability from the small intestine, stomach, pancreas, and adipose tissue are relayed to the hypothalamus via the circulation. In the arcuate nucleus of the hypothalamus, neurons that express NPY and AgRP are activated under energy deficit conditions and drive feeding (orexigenic) responses by signaling to NPY1 receptor (Y1r) neurons in the paraventricular nucleus (PVN). Ghrelin activates NPY and AgRP neurons, whereas PYY, GLP-1, OXM, insulin, and leptin inhibit these neurons. In the arcuate nucleus of the hypothalamus, neurons that express POMC generate anorectic signals under conditions of energy surplus. POMC neurons coexpress CART. Anorectic peptides (PYY, GLP-1, and OXM) activate POMC neurons. In the paraventricular nucleus, melanocortin melanocyte-stimulating hormone (α-MSH), which is a product of POMC cleavage, activates the MC4R, which generates a feeling of satiety. Depending on energy needs versus availability, the balance between activating NPY/AgRP as compared with POMC/CART neurons is thought to drive hunger and satiety.

Energy Expenditure

Daily energy expenditures in adults can range from less than 1400 kcal/day to more than 5000 kcal/day, with larger, more physically active individuals having the greatest energy needs. Typically, daily energy expenditure is divided into resting (or basal) metabolic rate, the thermic effect of food, and physical activity energy expenditure.

Basal Metabolic Rate

The basal metabolic rate (BMR) is the energy expenditure of lying still, at rest, awake, and in the fasting state. Most formulas calculate BMR as strictly measured, and BMR is considered the foundation of daily energy expenditure. Under most clinical circumstances, however, the resting metabolic rate (RMR) is measured because of the difficulty in measuring BMR; RMR is not necessarily measured before arising from bed and may not be in the fasting state, so it may be greater than BMR. For most sedentary adult Americans, BMR represents the major portion of energy expended during the day and may range from less than 1200 to more than 3000 kcal/day. Most (~80%) of the variability in BMR can be explained by the amount of lean and fat tissue. In addition, BMR is slightly lower in women than in men and in older than in younger adults even after accounting for the amount of lean and fat tissue. Heritable factors may account for as much as 10% of the interindividual differences in BMR. With an energy-restricted diet, BMR may decline out of proportion to the loss of fat-free mass. Reductions in the production of triiodothyronine from thyroxine and the sympathetic nervous system drive are thought to contribute to this phenomenon. Likewise, during brief periods of overfeeding, BMR increases slightly above that which would be expected for the amount of lean tissue present. Formulas to estimate BMR (available through numerous online calculators: https://www.calculators.org/health/bmr.php.) on the basis of height, weight, age, and sex are accurate to within 10% in approximately 90% of adults with BMIs of 18.5 to 45 kg/m^2.

Muscle accounts for only 25% of BMR but can account for 80 to 90% of energy expenditure during exercise. Adipose tissue requires only about 3 kcal/kg of body fat per day, so it is a minor contributor to daily energy expenditure.

Brown fat is adipose tissue that expresses large amounts of uncoupling protein-1 (a protein that allows a mitochondrial membrane proton leak).[8] When activated, this process results in the release of heat as opposed to chemical work from adenosine triphosphate—"uncoupling" of substrate oxidation from chemical or mechanical work. This thermogenic tissue, which exists only in small amounts in adults, might become a target for future interventions to reduce adiposity. Methods used to detect brown fat largely rely on ^{18}F-fluorodeoxyglucose positron emission tomography scanning of humans exposed to cold.

Physical Activity Energy Expenditure

The energy expenditure of physical activity is a product of the amount of work done and the work efficiency of the individual. Work units are expressed as metabolic equivalents (METs; see Table 14-1), a multiple of the RMR. If an individual's RMR is 1 kcal/minute (1440 kcal/day), a workload of 5 METs would be 5 kcal/minute. Although most sedentary individuals can work for only a limited amount of time at relatively low workloads, highly trained athletes can work at extremely high METs (>16) for extended periods.

Nonexercise activity thermogenesis is the energy expense of performing all activities other than exercise- or employment-related activity. Such activities may include tasks as mundane as getting up to walk 50 feet to the water fountain or spending 8 hours cleaning one's living space. The range of observed nonexercise activity thermogenesis varies from less than 100 to more than 800 kcal/day. On average, about 10% of the energy content of food (ranging from a low of about 3% to a high of about 15%) is expended in the process of digestion, absorption, and metabolism of nutrients. The energy expended from a physically demanding job or volitional exercise may or may not be offset by reductions in spontaneous (nonemployment) activity.

Secondary Causes of Obesity

A number of medications cause weight gain in some or most of the patients for whom they are prescribed (Table 201-3). Awareness of the medications that have this potential can facilitate weight loss treatment in some patients.

Less than 1% of obese patients have an underlying systemic disease that can explain the development of their obesity. Endocrinopathies, which are the most common secondary cause of obesity, include Cushing syndrome (Chapter 208), hypothalamic damage that results in overeating (most commonly after pituitary surgery), insulinoma (Chapter 211), and hypothyroidism (Chapter 207). With hypothyroidism, the weight gain is largely due to fluid retention rather than to the accumulation of fat.

Sexual, physical (Chapter 223), and emotional abuse, especially in women, can result in long-term adverse consequences, including obesity. Abused women may be severely obese, suffer from chronic depression, and experience a number of psychosomatic symptoms, particularly chronic gastrointestinal distress. Identifying these issues before initiating weight loss programs is important because successful weight loss may actually aggravate the distress experienced by these women.

Metabolic Complications of Obesity

A central or upper body fat distribution is more predictive than total fat mass of the metabolic complications of obesity. The release of free fatty acids and glycerol from adipose tissue into the circulation by lipolysis provides 50 to 100% of daily energy needs. Adipose tissue lipolysis is regulated primarily by insulin (inhibition) and catecholamines (stimulation), although growth hormone, cortisol, and atrial natriuretic peptide also stimulate lipolysis. Upper body obesity is associated with a higher postprandial release of free fatty acids, and this abnormality is particularly evident in type 2 diabetes.

Insulin Resistance

Insulin resistance (Chapter 210) refers to a diminished ability of insulin to promote glucose uptake and to inhibit the release of glucose into the circulation. Skeletal muscle is the primary site of insulin-stimulated glucose uptake, oxidation, and storage, whereas the liver is the primary site of glucose production. Insulin resistance initially leads to hyperinsulinemia and may eventually lead to the development of type 2 diabetes if β-cells become exhausted (Chapter 210), although many obese individuals with insulin resistance do not develop diabetes.

The ability of insulin to promote glucose uptake, oxidation, and storage in muscle and to suppress plasma free fatty acid concentrations is reduced in upper body obesity. High plasma free fatty acid concentrations can induce a state of insulin resistance both in the muscle (glucose uptake) and in the liver (glucose release), independent of obesity (Chapter 210).

Hypertension

In obesity, increased circulating blood volume, abnormal vasoconstriction, decreased vascular relaxation, and increased cardiac output may all contribute to hypertension (Chapter 64). The effect of hyperinsulinemia to increase renal sodium absorption may contribute to hypertension through increased circulating blood volume. Abnormalities of vascular resistance also contribute to the pathophysiologic process of obesity-related hypertension. Some obese adults have increased sympathetic nervous system activity, which could contribute to obesity-associated hypertension. Finally, angiotensinogen (also produced by adipocytes) is a precursor of the vasoconstrictor angiotensin II and is proposed to contribute to elevated blood pressure.

TABLE 201-3 PHARMACOLOGIC INFLUENCES ON WEIGHT GAIN AND ALTERNATIVE THERAPIES

DRUGS THAT MAY PROMOTE WEIGHT GAIN	ALTERNATIVE TREATMENTS: WEIGHT NEUTRAL OR WEIGHT LOSS
PSYCHIATRIC AND NEUROLOGIC MEDICATIONS Antipsychotics: olanzapine, clozapine, risperidone, quetiapine, aripiprazole Antidepressants Tricyclics: imipramine, amitriptyline Triazolopyridines: trazodone Serotonin reuptake inhibitors: paroxetine, fluoxetine, citalopram Tetracyclics: mirtazapine Monoamine oxidase inhibitors Antiepileptic drugs: gabapentin (higher doses), valproic acid, carbamazepine, divalproex Mood stabilizers: lithium, carbamazepine, lamotrigine, gabapentin (higher doses)	**ALTERNATIVE PSYCHIATRIC AND NEUROLOGIC MEDICATIONS** Ziprasidone Nortriptyline, bupropion, nefazodone, fluvoxamine, sertraline, duloxetine Topiramate, zonisamide (weight loss), lamotrigine (less weight gain)
STEROID HORMONES Progestational steroids Corticosteroids Hormonal contraceptives	**ALTERNATIVES TO STEROID HORMONES** Barrier methods, intrauterine device Nonsteroidal anti-inflammatory drugs
ANTIDIABETES AGENTS Insulin (most forms) Sulfonylureas Thiazolidinediones	**ALTERNATIVE ANTIDIABETES AGENTS** Metformin Acarbose, miglitol Exenatide Dipeptidyl peptidase 4 inhibitors Liraglutide Sodium-glucose cotransporter 2 inhibitors
ANTIHISTAMINES Commonly reported with older agents; also oxatomide, loratadine, and azelastine	**ALTERNATIVES TO ANTIHISTAMINES** Decongestants, mast cell stabilizers, antagonists of endogenous mediators of inflammation
ANTIHYPERTENSIVE AGENTS α-Adrenergic and β-adrenergic receptor blockers Calcium channel blockers: nisoldipine	**ALTERNATIVE ANTIHYPERTENSIVE AGENTS** Angiotensin-converting enzyme inhibitors Angiotensin receptor blockers Calcium channel blockers: most other agents Diuretics
HIGHLY ACTIVE ANTIRETROVIRAL THERAPY	

Dyslipidemia

Upper body obesity and type 2 diabetes mellitus are associated with increased concentrations of triglycerides, decreased concentrations of high-density lipoprotein (HDL) cholesterol, and a high proportion of small, low-density lipoprotein (LDL) particles (Chapter 190). This dyslipidemia contributes to the increased cardiovascular risk observed in metabolic syndrome. Fasting hypertriglyceridemia is caused by increased hepatic very low density lipoprotein (VLDL) secretion, which may be driven by increased delivery of free fatty acids to the liver from both visceral fat and upper body subcutaneous fat. The reduced HDL cholesterol concentrations and the increased small, dense LDL particle concentrations associated with upper body obesity are likely an indirect consequence of elevated triglyceride-rich VLDL. Genetic influences play a significant role in the expression of these lipid abnormalities. Polymorphisms in the genes for apolipoprotein E, lipoprotein lipase, apolipoprotein B-100, and apolipoprotein A-II are correlated with increased triglycerides and decreased HDL.

Endocrine Manifestations of Obesity

Obesity is associated with abnormalities of the endocrine system, including polycystic ovary syndrome (Chapter 218), which is characterized by mild hirsutism and irregular menses or amenorrhea with anovulatory cycles. The insulin resistance associated with obesity may trigger the development of polycystic ovary syndrome in susceptible individuals. Obese men may suffer from mild to severe hypothalamic hypogonadism (Chapter 216), which improves with weight loss.

Systemic Complications of Obesity

The excess body weight associated with obesity is thought to be responsible for the increased prevalence of lower extremity degenerative joint disease (Chapter 241). Severely obese individuals may also have problems with venous stasis (Chapter 68), which is occasionally aggravated by right-sided heart failure.

Sleep apnea (Chapter 374) is common in severely obese patients and is more prevalent in men and in women with an upper body/visceral obesity. Sleep apnea is most likely explained by enlargement of upper airway soft tissue, resulting in collapse of the upper airways during inspiration while sleeping. The obstruction leads to apneas, with hypoxemia, hypercarbia, and high levels of catecholamines and endothelins. The frequent arousals to restore breathing result in poor sleep quality. Sleep apnea is associated with an increased risk of hypertension, and if sleep apnea is severe, it can lead to right-sided heart failure and sudden death.

Obesity is associated with an increased risk of at least 13 different types of cancer (breast, esophageal, liver, gallbladder, stomach, pancreas, colorectal, ovarian, uterine, renal cell, thyroid, meningioma, and multiple myeloma),[9] likely due to higher levels of insulin-like growth factor and estrogens. Obese individuals have a greater prevalence of gastroesophageal reflux disease (Chapter 124) and gallstones (Chapter 141). Fatty liver and nonalcoholic steatohepatitis (Chapter 138) are strongly associated with overweight, obesity, and the metabolic syndrome.

DIAGNOSIS

Evaluation of Obesity

In the office practice, obtaining height and weight allows calculation of BMI. (https://www.nhlbi.nih.gov/health/educational/lose_wt/BMI/bmicalc.htm). A review of the patient's lifestyle, including an assessment of physical activity level (Chapter 14) and eating habits (Chapter 13), may help provide information about why the patient is obese. A family history of obesity, or long-standing obesity, provides evidence against a secondary cause of obesity. A careful medication history, including over-the-counter medications, and social history may help the clinician identify precipitating factors that can be modified.

For patients with a BMI above 25 and below 35, measuring waist circumference is recommended to help with the treatment decision-making process. In persons of European and African descent, waist circumference cut points of more than 102 cm (40 inches) for men and more than 88 cm (35 inches) for women are indicators of increased metabolic risk. Adults with waist circumferences above the cut points deserve further evaluation to detect other cardiovascular disease risk factors. Adults with class II or class III obesity are at sufficiently high risk that waist circumference information does not add valuable information.

Blood pressure should be measured, with a large blood pressure cuff, if needed. A suspicion for sleep apnea should prompt a referral for an overnight sleep test (Chapter 374).

Routine blood testing for persons with a BMI 25 to 35 kg/m^2 and an elevated waist circumference should include a fasting glucose concentration and a lipid panel. Other laboratory tests (thyroid and liver function studies) may be indicated if symptoms or signs warrant.

TREATMENT

General Considerations

Before a patient enters a weight management program, the clinician should try to ensure that the patient is interested and ready to make lifestyle changes and has realistic goals and expectations. Patients who expect to lose large amounts of weight in a short time are virtually doomed to disappointment. Medical treatment programs, even if they include pharmacotherapy, struggle to achieve a sustained weight loss of more than 10%. Although this amount of weight loss is sufficient to markedly reduce the medical complications of obesity, disappointment with "only" 10% weight loss may cause patients to abandon a medically successful program. Helping the patient to accept that lifestyle changes resulting in achievable (10%) weight loss is a reasonable, initial goal can be challenging for a physician.

It is sometimes necessary to delay entry into any treatment program if a patient is not ready to make lifestyle changes. Every form of treatment currently available requires some degree of lifestyle accommodation, and patients who are uninterested in doing so should be advised to reconsider their goals at a later date. A reasonable strategy is to remind the patient of the health benefits of improved activity and eating habits at each visit and to reconsider efforts once a willingness to make changes is apparent.

Treatment approaches may differ for individuals who are overweight and for different classes of obesity. Simply making a diagnosis of obesity is associated with patients taking action to lose weight.[10]

Lifestyle treatment is appropriate for individuals who are overweight or obese, and pharmacotherapy can be an adjunct treatment for any class of obesity, even if medical complications are not present, and may be considered in patients who have a BMI above 27 plus a weight-related comorbid condition. Patients with class II obesity (BMI of 35.0 to 39.9) may be considered for bariatric surgery if medical treatments have failed and if serious, weight-related comorbid conditions are present. Class III obesity (BMI > 40) is one feature that might prompt consideration of a patient for bariatric surgery when medical treatments have failed.

Obesity is a chronic disease, so its treatment (Fig. 201-1) must be considered a long-term issue. Although severe dietary calorie restriction can result in substantial weight loss, body fat is invariably regained without approaches to ensure behavioral changes. Patients must learn how to make permanent changes in eating and activity behaviors to achieve permanent weight loss. Behavior modification approaches,[11] which can help patients recognize and circumvent environmental cues for sedentary behavior and overeating, can increase the likelihood that patients will accomplish these lifestyle changes,[A1] and intensive lifestyle intervention is associated with fewer hospitalizations, fewer medications, and lower health care costs in overweight or obese adults with type 2 diabetes.

Reducing energy intake is the most efficient and effective means to lose weight. For example, creating a 500 kcal/day deficit by reduced food intake will initially theoretically result in the loss of 1 pound of fat per week. It is more

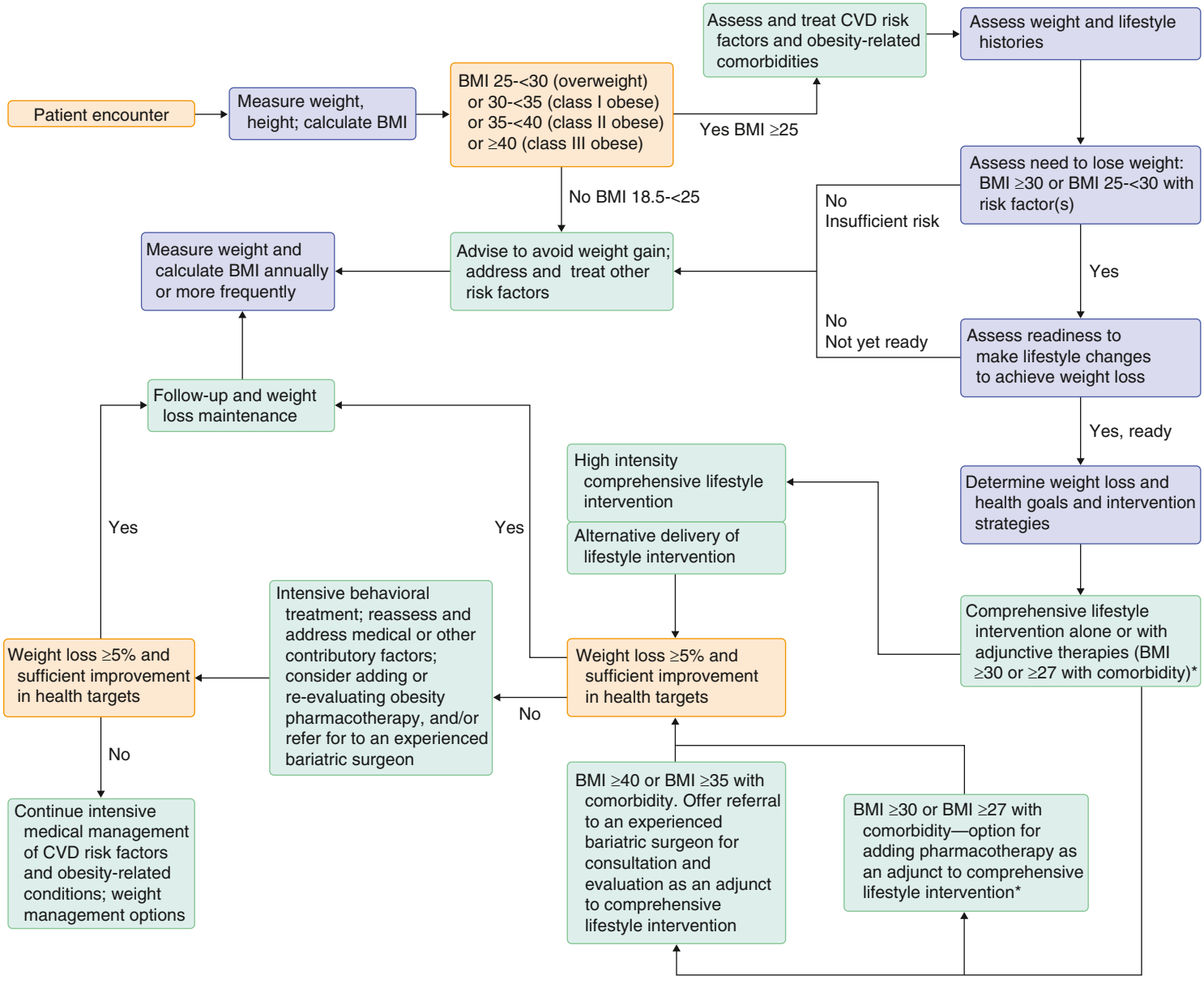

FIGURE 201-1. Flow diagram for the evaluation and management of overweight and obesity. BMI = body mass index; CVD = cardiovascular disease. *BMI cutpoint determined by the U.S. Food and Drug Administration (FDA) and listed on the package inserts of FDA-approved obesity medications. (Modified from Jensen MD, Ryan DH, Apovian CM, et al. 2013 AHA/ACC/TOS guideline for the management of overweight and obesity in adults: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines and The Obesity Society. *J Am Coll Cardiol*. 2014;63:2985-3023.)

difficult to increase energy expenditure by 500 kcal/day through exercise. Greater amounts of physical activity can prevent weight gain (or weight regain after weight loss). Some patients are able to change eating and activity habits on their own, given the proper information, whereas others require formal or informal behavior modification interventions (see later) to help make these changes. In some instances, pharmacotherapy, endoscopic obesity treatments, or bariatric surgery may be needed to treat obesity.

Diet

Changes in eating habits must be permanent if weight loss is to be maintained. An experienced registered dietitian can be helpful to evaluate a patient's eating habits and to provide the needed education. The diet history may identify eating behaviors that result in excess energy intake. Although it is important to address specific adverse eating behaviors, patients must also understand general dietary principles. Reducing the energy density of food (most commonly accomplished by reducing dietary fat) can allow patients to feel satiated while consuming fewer calories. A consensus recommendation is to prescribe a 1200 to 1500 kcal/day diet for women and a 1500 to 1800 kcal/day diet for men. Alternatively, diets that produce an energy deficit of 500 to 750 kcal/day can be recommended. Because no single diet appears to be clearly superior (e.g., low-carbohydrate compared with low-fat) over another with regard to weight loss,[A2] clinicians should prescribe any evidence-based diet that restricts selected types of food (e.g., high-carbohydrate foods, low-fiber foods, or high-fat foods) to create an energy deficit by reducing food intake. To address dyslipidemia, diabetes, and hypertension, a Mediterranean-type diet is preferred (see Fig. 13-1).[A3] Patients should be informed that consuming foods high in water and fiber (fruits, vegetables, legumes, and soups) can provide satiety without excess calories. Patients also should be counseled to reduce the intake of beverages containing substantial calories, most often sugar-sweetened beverages. Finally, a regular pattern of eating should be encouraged.

New diets are continually being promoted with the promise of easy weight loss. A common feature of these diets is the claim that special properties of certain foods help people lose weight or are the cause of obesity. If followed, most of these diets result in weight loss because of a reduced energy intake. The reduced intake can often be explained by the monotony of the diet, and no diets have been documented to cause persons to lose weight out of accordance with physiologic principles. Although a number of dietary approaches can be successful in promoting weight loss, any diet without peer-reviewed evidence for safety and success should be reviewed by a dietitian for nutritional safety.

Contrary to expectations, however, the opportunity to choose what diet to follow does not necessarily improve weight loss. More than 95% of patients embarking on self-diets or fad diets fail to maintain a significant weight loss for a time that would have meaningful health benefits.

Very low calorie diets (<800 calories per day) can achieve accelerated weight loss under expert supervision. Because the long-term results of these diets are no better and sometimes worse than the results from the standard low-calorie diet combined with behavior modification, these diets are not commonly used. Intermittent or alternate-day fasting and time-restricted eating are no better than standard weight-loss diets[A4,A5] and are not advocated as primary strategies because of inadequate evidence.

Commercial weight-loss programs (Weight Watchers, Jenny Craig, Nutrisystem) generally result in 2 to 4% more weight loss than usual education and counseling. The average weight loss is 4.8 to 6.6 kg at 6 months when conventional foods are consumed and 6.6 to 10.1 kg at 12 months when prepared food is provided. Comprehensive weight management programs delivered at academic medical centers that employ behavior modification, dietary instruction, and physical activity can achieve equally or more impressive results.

Measurement of BMR is sometimes helpful for evaluating patients who insist that they are unable to lose weight despite following a diet that contains less than 1000 kcal/day. Almost without fail, BMR measured with a reliable instrument is substantially greater than the reported food intake, thereby confirming that patients must be eating as much as, if not more, than their energy expenditure. This finding underscores the fact that most adults are unreliable in assessing their own food intake.

Physical Activity

A long-term increase in physical activity, either through the activities of daily living or through regular exercise, is key to sustained, long-term weight loss.[A6] Although exercise (fitness- and sports-related activities) is a component of thermogenesis, most adults do not exercise at high levels or for a sufficient duration to expend a large amount of energy, so focusing solely on "exercise" as the main component of physical activity will miss significant opportunities for improving energy balance. In addition, only about 100 kcal are expended by a 70-kg adult walking 1 mile. Losing weight solely by increasing exercise is impractical for most patients. However, increasing physical activity as a means of maintaining weight loss is an attainable goal for most patients.

Successful maintenance of weight loss usually entails maintaining a daily energy expenditure approximately 80 to 90% above BMR, a considerable increase for most patients. For example, someone with a BMR of 1500 kcal/day would need to expend about 1000 kcal/day in physical activity to meet this target. Activities other than exercise are important means to achieve this goal. Options for increasing physical activity include exercise (sports or fitness pursuits) and use of lifestyle approaches, such as habitually increasing the amount of walking throughout the day.

Persuading obese patients to become more active is not easy. Physicians can begin by asking patients about their current and past activity habits as well as what barriers they see to increasing physical activity. If patients agree to begin an exercise or physical activity program, they will need to set realistic goals for the amount of exercise they are going to achieve and to monitor their activity. Unlike highly fit individuals, obese sedentary adults often become so uncomfortable that they cannot continue exercising at what might be considered moderate levels of activity because their lactate threshold (the level of work that causes blood lactate concentrations to increase dramatically) is low. Even walking as slow as 3 miles per hour may exceed the lactate threshold for adults who are obese with type 2 diabetes. The ready availability of step counters and electronic activity monitoring devices built into many "smartphones" offers a practical means for patients to track physical activity throughout the day and to assess the effects of changes in lifestyle on their activity level. Many Americans take as few as 4000 to 5000 steps per day, whereas it may take as many as 15,000 to 17,000 steps per day for patients who have lost significant amounts of weight to maintain that lower weight. Gradually increasing the number of steps regularly taken during the day through a series of changes in habits (e.g., parking farther away, walking during work breaks) is more likely to result in long-term success for most persons than setting aside 2 hours or more for continuous walking. Gradual increases in physical activity also will improve fitness and eventually allow for sufficient energy expenditure to help maintain weight loss.

Behavior Modification

Patients who are unable to make changes in eating activity habits on their own or with informal office counseling may benefit from referral to an interventionist or commercial program that provides weight-loss–specific behavioral therapy.[12] The goals are to help patients modify their eating, activity, and thinking habits that predispose to obesity and focus on specific pathways to achieve the goals. As part of this process, patients are taught the benefits of and how to self-monitor (food intake, activity, environmental cues); set goals (realistic short-, medium-, and long-term goals that are specific, measurable, attainable, relevant, and time-limited); identify and leverage personal strengths to change behavior; create a healthy external environment (stimulus control—identify and modify the environmental stimuli that thwart changes in eating/activity habits); manage stress if it causes extra eating or reduces planned activity; manage emotional triggers that may cause someone to eat so as to feel better); be more mindful about eating and enjoy food more, so as to limit the amount eaten while still feeling satisfied; leverage social/community support to begin and maintain behavior change; maintain perspective; and reduce all-or-nothing thinking as a way to maintain motivation and prevent relapse.

The best weight loss results are provided by in-person, high-intensity (≥14 sessions in 6 months) comprehensive behavioral interventions, which average an 8-kg (5 to 10% of body weight) loss in 6 months, even in underserved populations.[A7] Approaches that provide electronically delivered counseling (telephone or Internet),[A8,A9] including some commercial programs, can also achieve weight loss, but generally less than with in-person approaches. Commercial programs that have published their results in peer-reviewed journals are preferred. Physicians who refer patients to programs that offer intensive, comprehensive lifestyle interventions are encouraged to obtain outcomes data from those programs.

Pharmacotherapy

Drugs to help patients lose weight[13] should be used in concert with a comprehensive lifestyle intervention by knowledgeable clinicians (Table 201-4). Antiobesity medications may be considered in patients who have not reached a weight loss goal with lifestyle treatment alone or who have a BMI greater than 30

TABLE 201-4 INDICATIONS FOR PHARMACOLOGIC TREATMENT OF OBESITY

Body mass index > 27 kg/m^2
One or more complications or conditions that are likely to improve with weight loss
Previous failure of conservative treatment with behavioral intervention, diet, and exercise
Agree to 2- to 4-wk trial of making initial changes in diet and exercise before starting pharmacotherapy
Agree to continue treatment with comprehensive lifestyle attempts while receiving support with pharmacologic treatment
Agree to periodic follow-up
Premenopausal women (able to have children) must use some form of contraception
Consider a pregnancy test on initiation of treatment if there is any possibility of pregnancy
No contraindications to the specific drug used for pharmacologic treatment

in the absence of a weight-related comorbidity or a BMI of 27-30 in the presence of a weight-related comorbidity. Weight loss achieved with medications varies substantially, with some people losing almost nothing and others occasionally losing more than 15% of their starting weight. A weight loss of 5% within 3 to 6 months of initiating therapy is considered a clinically significant response. If a person loses less than this amount, the medication should be stopped. If a person loses weight with an antiobesity medication, the benefit will likely be sustained only while they take the medication, so long-term continuous or intermittent use is required to maintain long-term benefits.

The available medications vary in cost, effectiveness, side effect profile, and associated benefits. Health insurance plans often do not cover these medications. None of these medications have been shown to be safe in pregnancy, and so women of reproductive age must be on an effective form of contraception. Knowledge of these factors for each medication will allow the provider to tailor therapy to the individual patient.

Currently Available Medications

The medications currently available for long-term use either reduce appetite or cause fat malabsorption by inhibiting pancreatic lipase. All are better than placebo for achieving weight loss.[A10]

Orlistat

Orlistat (120 mg three times daily with meals by prescription or 60 mg three times daily over the counter) causes about 30% of dietary fat to be malabsorbed, results in weight loss of about 3 to 5%, and is the safest option of the available antiobesity medications. Adverse gastrointestinal side effects, such as oily spotting, abdominal pain, excess flatus, fecal urgency, and fatty or oily stools may occur but generally decrease over time; the concomitant use of bulk-forming laxatives (e.g., psyllium, methylcellulose) can reduce these symptoms. A daily multivitamin is recommended in patients who receive long-term orlistat therapy.

Phentermine

Phentermine is the most commonly prescribed antiobesity medication (doses ranging from 8 mg to 37.5 mg per day), but it is approved as monotherapy only for short-term (3 months) use. Phentermine may increase cardiovascular morbidity by increasing pulse and blood pressure in some patients, so it should not be prescribed in patients who have uncontrolled hypertension or known coronary artery disease, or who are at high risk for cardiac ischemia.

The combination of phentermine and topiramate (7.5 mg phentermine/46 mg extended-release topiramate, or 15 mg /92 mg) can be used chronically, with the higher dose resulting in an average of an 8% weight loss at 2 years, with slightly more than half of patients achieving a 10% weight loss and 15% of patients achieving a 20% weight loss. The most common side effects are constipation, paresthesia, sinusitis, and dry mouth; the incidence of individual adverse effects diminishes significantly after the first year.

Glucagon-Like Peptide 1 Antagonists

Glucagon-like peptide-1 agonists, which are effective for diabetes (Chapter 210), are also effective for the treatment of obesity.[14] Liraglutide (3 mg per day subcutaneously) can reduce weight by an average of about 6% more than lifestyle alone, but semaglutide (2.4 mg per week subcutaneously) is more effective than liraglutide[A11] and can reduce weight by 10 to 12% more than diet and exercise alone.[A12–A14] Tirzepatide, which is a dual glucose-dependent insulinotropic polypeptide and glucagon like peptide-1 receptor agonist, can lead to substantial weight loss averaging 5.5 kg at a 5 mg subcutaneous weekly dose and nearly 9 kg at a dose of 15 mg weekly.[A15,A16] Side effects are generally similar to semaglutide.[A17] Cagrilintide, an amylin analog, is an investigational once-weekly subcutaneous drug that appears to be quite effective.[A18]

Other Options

The combination of bupropion and naltrexone results in an average weight loss of 4 to 5% more than lifestyle alone, with relatively few side effects and no abuse potential. The cardiovascular risk of this combination remains uncertain.[A19] Gelesis100 is a nonsystemic, superabsorbent hydrogel whose particles expand in the stomach after ingestion to create a sense of fullness. One capsule twice daily before meals produces about a 2% weight loss.

Choosing Among Alternatives

Each of these approved medications has advantages, side effects, and cost considerations. Physicians should consider their patients' comorbid conditions and preferences to tailor treatment for each individual. For example, semaglutide is the most effective currently available agent, but is injectable and expensive. Phentermine/topiramate is the least expensive option and the most effective oral medication, but it can have cognitive side effects and is subject to limited prescribing periods in some states. Orlistat is the lowest risk, but it has gastrointestinal side effects. Liraglutide and bupropion/naltrexone are intermediate in side effects, efficacy, and cost.

Endoscopic Treatment of Obesity

Endoscopic approaches to treating obesity include space-occupying devices in the stomach (intragastric balloons),[15] gastroesophageal stents that exert pressure on the gastric cardia to create a sensation of fullness, and gastric remodeling techniques that reduce the gastric reservoir by creating a tubular sleeve along the greater curvature of the stomach and aspiration therapy. Intragastric balloons can result in significantly more weight loss than lifestyle modifications alone[A20] and are a reasonable option in patients with a BMI over 30. Endoscopic small bowel interventions, such as excluding the proximal small intestine using impermeable polymer duodenojejunal bypass liners and ablative duodenal resurfacing techniques that regenerate the proximal small intestinal mucosal barrier in hopes of modifying ingestive behavior, are under investigation. Another approach is to insert self-assembling magnets that create a dual-path enteral bypass between the proximal jejunum or duodenum and the ileum, with the goal of diverting bile to the terminal ileum. Data currently are insufficient to guide when, if ever, these endoscopic options should be recommended.

Bariatric Surgery

Bariatric surgery, which almost always results in more weight loss than lifestyle or antiobesity medications, can be considered in patients who have a BMI of 35 to 40 plus serious weight-related comorbid conditions, especially uncontrolled type 2 diabetes, assuming prior attempts at medical treatments have failed,[16,A21] or a BMI higher than 40. The benefits of bariatric surgery compared with medical treatment include long-term reduced risks of obesity-related comorbidity; improvement or remission of type 2 diabetes, hypertension, and dyslipidemia; and a likely reduction in long-term mortality,[A22–A24] including obesity-associated cancer and cancer-related mortality.[17] However, these benefits must be balanced against a small (<0.5%) risk of death, potential surgical complications, and longer-term risks for nutritional deficiencies, new-onset depression, treatment with opioids, and the need for additional surgical procedures.

Laparoscopic approaches are routinely used for bariatric surgery because they reduce the length of hospitalization and the risk of incisional hernias compared with open procedures. Contraindications to surgery include active substance abuse, defined noncompliance or inability to comply with medical care, and schizophrenia, borderline personality disorder, or uncontrolled depression.

A multidisciplinary team (including a physician, dietitian, psychologist or psychiatrist, and experienced surgeon) is important for optimal outcome. Most successful patients will achieve weight losses of 25 to 35% of body weight but are not likely reach their ideal body weight. Follow-up to support the necessary changes in long-term behavior is recommended to optimize weight loss outcomes.

Among the available bariatric surgical techniques, procedures that only modify the capacity of the stomach (laparoscopic gastric banding) are much less effective than Roux-en-Y gastric bypass in terms of long-term weight loss. Procedures that both reduce stomach size and modify other stomach properties (e.g., sleeve gastrectomy) appear to be almost as effective as Roux-en-Y gastric bypass in terms of long-term weight loss and outright surgical success, with durable benefits in terms of type 2 diabetes, hypertension, and dyslipidemia.[A25,A26] The partial pancreaticobiliary bypass, the very long limb Roux-en-Y gastric bypass, and the duodenal switch procedures create malabsorption that results in greater weight loss than with the standard Roux-en-Y gastric bypass. Unfortunately, the incidence of severe and even fatal vitamin and mineral deficiencies (Chapter 199) is much higher with these procedures.

Surgical mortality and morbidity (e.g., infection, anastomotic leak, wound dehiscence) are low in centers with expertise, despite the high-risk population. Laparoscopic gastric banding is rarely used now because of the inferior long-term weight loss results and late complications of band slippage, erosion, and weight regain.

After surgery, approximately 70% of patients achieve success, with almost all of the weight loss occurring during the first 1 to 2 years. Long-term (>5 year) success rates are outstanding in good programs. Up to two thirds of patients regain 20% or more of their maximum weight loss in the years following the weight nadir, so postoperative weight regain remains an important clinical challenge. Despite this regain, weight remains substantially below preoperative levels for most patients.

Careful long-term follow-up is needed to ensure adequate protein, calorie, vitamin, and mineral nutrition. Supplemental vitamin B_{12}, iron, and calcium are routinely added to standard multivitamins. The most common nutritional consequences of malabsorptive procedures are disorders of calcium and vitamin D metabolism, although many severely obese patients have low vitamin D levels even before surgery (Chapter 226). An increase in the bone alkaline phosphatase level may signal deficiency of calcium or vitamin D. Low plasma vitamin D levels and low urinary calcium excretion should prompt aggressive replacement therapy. Iron deficiency, other fat-soluble vitamin deficiencies, and copper deficiency can occur more than 5 to 10 years after surgery.

Pancreatogenous hypoglycemia can develop after bariatric surgical procedures; symptoms are primarily postprandial and can be quite severe. Medical management by specialists in this field is the best approach for these patients.

PREVENTION

The dramatic increase in the prevalence of obesity during the past few decades strongly suggests that preventive strategies are needed. Public health approaches that emphasize education have been almost uniformly unsuccessful at preventing weight gain or producing weight loss. Public health strategies that virtually impose behavior change are more successful in this regard. Unless widespread efforts are made to address the problem of obesity, it is likely that its prevalence and complications will become an ever-increasing health burden.

PROGNOSIS

On a population basis, life expectancy declines as BMI rises within the obese range. The loss of life is about 3 years for a BMI of 30 to 39, 7 years for a BMI of 40 to 44, 9 years for a BMI of 45 to 49, 10 years for a BMI of 50 to 54, and 14 years for a BMI of 55 to 59. Data are insufficient to estimate life expectancy of patients who lose weight. In markedly obese patients, however, bariatric surgery is associated with about a 6-year increase in life expectancy compared with current medical management,[18] but life expectancy still remains less than in the general population.[19]

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202 APPROACH TO THE PATIENT WITH ENDOCRINE DISEASE

DAVID R. CLEMMONS AND LYNNETTE K. NIEMAN

Most endocrine disorders are due to either an excess or a deficiency of a hormone that is transported in the systemic circulation and therefore result in multiorgan manifestations. Since individual hormones commonly have multiple sites of action, patients rarely present with a single set of symptoms or signs isolated to only one organ system. Generalized nonspecific symptoms such as weakness, difficulty concentrating, lack of energy, and change in appetite are common. Any single symptom evaluated in isolation is rarely helpful, and a constellation of findings is typically required to point to the correct diagnosis (Table 202-1).

To diagnose an endocrinologic condition, a careful longitudinal history is critical. The duration of hormone excess or deficiency often dictates the severity of symptoms, and the characterization of progressive symptoms over time can be very helpful in selecting diagnostic tests, substantiating the need for treatment, and choosing the optimal treatment. The physical examination helps to confirm the likelihood of a diagnosis; for example, the presence of a symmetrically enlarged thyroid gland indicates that Graves disease is the most likely cause of hyperthyroidism (Chapter 207). Even if endocrine disorders are diagnosed by biochemical screening in the absence of symptoms or signs of overt disease (e.g., hyperparathyroidism; Chapter 227), a thorough history and physical examination are still important to determine whether the patient is truly in the asymptomatic phase of the disease and whether observation or therapy is the preferred option. A careful temporal history of a symptomatic change may also assist with the differential diagnosis—for example, whether a thyroid mass is due to a hemorrhagic cyst (i.e., occurring suddenly) or is an adenoma that evolved over an extended period. A thorough general history and physical examination may identify diseases associated with endocrinologic abnormalities, such as cancers that secrete ectopic hormones.

An accurate family history can indicate a need for genetic testing[1] or familial screening. A thorough evaluation of medication use is also mandatory. Some medications can mask the symptoms of overt endocrine disease, such as β-blockers in hyperthyroidism, and others can exacerbate the findings, such as use of a thiazide diuretic in hyperparathyroidism. Medications also may confound laboratory evaluation, such as diuretics in patients with hyperaldosteronism or acetaminophen in patients screened for pheochromocytoma; in such situations medications may need to be discontinued before testing. Finally, it may be difficult to obtain an accurate history of certain complaints. For example, in evaluating male sexual dysfunction (Chapter 216), a corroborating history from his partner may be needed.

The off-target effects of treatments provide another example of the importance of a complete medical history. A variety of medical treatments also may cause either hormone excess or deficiency. For example, administration of high-dose glucocorticoid therapy for immune suppression can result in Cushing syndrome,[2] and abrupt discontinuation of such therapy can cause acute adrenal insufficiency because of suppression of the pituitary-adrenal axis (Chapter 208). Immunotherapy with checkpoint inhibitors (Chapter 164) may cause both endocrine excess and deficiency, most commonly involving the thyroid gland. Many traditional chemotherapies adversely affect reproductive endocrine function, and radiation therapy (Chapter 18) of tumors may cause endocrine deficiencies.

TABLE 202-1 SYMPTOM CONSTELLATIONS SUGGESTING SPECIFIC ENDOCRINE DISORDERS

SYMPTOM CONSTELLATION	DIAGNOSIS
Weakness, fatigue, anorexia, loss of appetite, postural hypotension	Adrenal insufficiency
Cold intolerance, dry skin, constipation, weight gain	Hypothyroidism
Fatigue, easy bruising, striae, proximal muscle weakness, weight gain, hypertension, acne	Cushing syndrome
Weight loss, increased appetite, palpitations, tremor, emotional lability, diffuse hair thinning	Hyperthyroidism
Galactorrhea, amenorrhea, headaches	Prolactinoma
Weight loss, anorexia, loss of pubic and axillary hair	Hypopituitarism
Episodic palpitations, tremor, anxiety, headaches, sweating, weight loss	Pheochromocytoma
Episodic flushing, palpitations, abdominal cramping, and diarrhea	Carcinoid syndrome

COMMON SYMPTOMS OF ENDOCRINOLOGIC DISEASE

Signs and symptoms common to many endocrine disorders and the general population without endocrine disorders include weakness and fatigue, abnormal menstrual function, constipation or diarrhea (Chapters 122 and 126), generalized hair loss or male pattern balding (Chapter 409), recurrent or episodic headaches (Chapter 367), altered libido (Chapters 216 and 219), polyuria and nocturia, weight gain or loss[3] (Chapters 164 and 201), depression (Chapter 362), altered mood, acne (Chapter 406), dry skin, and vitiligo (Chapter 408). By contrast, pain is not common except in an acute endocrine emergency such as diabetic ketoacidosis or adrenal crisis, although chronic bone pain is seen in hyperparathyroidism (Chapter 227) and osteomalacia (Chapter 226).

PHYSICAL EXAMINATION

The physical examination can confirm or refute findings ascertained by a medical history (Table 202-2). Thyroid disease is often first suspected based on the physical examination. Endocrinopathies lead to skin changes that may occur early in the illness and progress over time and may assist in identifying the diagnosis. For example, striae (Chapter 208), plethora, easy bruisability, acanthosis nigricans, and hyperpigmentation may suggest Cushing syndrome.

Edema may be an early sign of hormone-producing tumors that result in salt retention, including Cushing syndrome and hyperaldosteronism (Chapter 208). Measurement of upper trunk to leg-length ratios and arm span is helpful in establishing the timing and onset of puberty in primary gonadal disorders.

On pelvic examination, palpation may identify polycystic ovaries (Chapter 217) or suggest the absence of ovarian tissue. The absence of a uterus is important in the differential diagnosis of pseudohermaphroditism, and the evaluation of external genitalia can be important in establishing the presence of congenital adrenal hyperplasia. Vaginal dryness and breast atrophy are signs of severe estrogen deficiency.

Mental status changes (Chapter 361) occur frequently with extreme hypercalcemia, Cushing syndrome, and hyperthyroidism. Many primary endocrine disorders are associated with characteristic psychiatric manifestations (Chapter 362).

TABLE 202-2 PHYSICAL SIGNS THAT SUGGEST SPECIFIC ENDOCRINE DISORDERS

Hyperpigmentation of palms, extensor surfaces, and buccal mucosa	Adrenal insufficiency
Facial plethora, moon facies, striae, purpura, proximal muscle weakness	Cushing syndrome
Skin tags, acral enlargement, prognathism, orthodontia, cardiomegaly, increased size of hand/foot/tongue	Acromegaly
Proptosis, lid lag, symmetrically diffuse thyroid enlargement, abnormal extraocular movements	Graves disease
Hyperreflexia, moist skin, thin hair, tachycardia, wide pulse pressure, flow murmur, bruit over thyroid, tremor	Hyperthyroidism
Hyperkeratosis, myxedema, hyporeflexia, coarse hair	Hypothyroidism
Retinal microaneurysms, macular edema, motor nerve defect, inability to detect monofilament or vibratory sensation	Diabetic retinopathy/ neuropathy
Short stature, web neck, loss of tears, coarctation of the aorta	Turner syndrome
Shield-like chest, short fourth metacarpal	Primary ovarian failure
Bowing of the legs	Hypophosphatemic rickets
Orthostatic blood pressure	Pheochromocytoma
Galactorrhea	Hyperprolactinemia
Purple-hued flushing	Midgut carcinoid

ABSTRACT

Endocrine disorders can be classified as states in which there is too much or too little of one or more hormones. Since many hormones have multiple sites of action, a deficiency or excess of a hormone can cause many possible symptoms and signs, not all of which may be present, particularly in early stages of the disease. Thus, a very complete history and physical examination are often required to determine whether these entities are the cause of the patient's complaints. Laboratory evaluation is usually needed to validate the clinical clues, except when the disorders are severe and clinically unmistakable. The treatment of endocrine excess disorders is generally directed to resection of the causative (overactive) tissue, whereas the treatment of endocrine deficiency is generally directed to replacement of the missing hormones with a satisfactory exogenous substitute.

KEYWORDS

endocrinopathy
physical examination
diagnosis
treatment
laboratory evaluation

LABORATORY EVALUATION

Asymptomatic endocrine diseases are frequently diagnosed because of abnormalities on radiologic or hormonal tests. The most common radiologic conundrums occur in patients who are noted incidentally to have small pituitary, thyroid, or adrenal masses. Evaluation for a functionally active tumor is usually necessary, even though only a minority will test positive. For pituitary tumors (Chapter 205), testing includes measurement of a baseline serum prolactin level and, in cases with suggestive symptoms, of 24-hour urine cortisol and growth hormone after glucose suppression. In patients with incidentally found adrenal masses ("incidentalomas"; Chapter 208),[4,5] the tumor heterogeneity, size (>4 cm) and density (>10 Hounsfield units), hypertension or hypokalemia, and symptoms and signs of Cushing syndrome should be evaluated. If any of these are present, the patient must be evaluated for Cushing syndrome, adrenal cortical carcinoma, hyperaldosteronism, and pheochromocytoma[6] (Chapters 208 and 209).

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ABSTRACT

The principles of endocrinology are presented: what is a hormone; regulation of hormone synthesis and secretion; hormone transport and metabolism; mechanism of hormone action; endocrine diseases caused by mutations in signaling components, by mutations leading to neoplasia, and by autoimmune destruction; new approaches to the study of endocrine disease.

KEYWORDS

hormone
signal transduction
genetic disorders
steroid hormone receptor
G protein–coupled receptor
tyrosine kinase receptor

REGULATION OF HORMONE SYNTHESIS AND SECRETION

Two broad categories of hormone synthesis are responsible for the synthesis of peptide hormones and steroid hormones, including the active form of vitamin D, thyroid hormones, catecholamines, and other nonpeptide hormones. In the former category, hormone structure is encoded genetically, and mRNA translation yields a protein precursor (pre-prohormone) that is generally cleaved through successive steps to yield the mature secreted product. Some protein precursors such as proopiomelanocortin contain multiple hormonal products, in this case adrenocorticotropic hormone (ACTH), melanocyte-stimulating hormone (MSH), and endorphins. In certain situations, inappropriate secretion of immature hormones creates a pathologic condition (e.g., excessive proinsulin secretion by insulinomas). Post-translational modifications occur for some hormones, such as disulfide bond formation for vasopressin and insulin; C-peptide cleavage for insulin; and glycosylation of the pituitary glycoprotein hormones, thyroid-stimulating hormone (TSH), follicle-stimulating hormone (FSH), and luteinizing hormone (LH). Mutations in genes that encode peptide hormones can lead to disruption of normal hormone synthesis or secretion, a rare cause of hormone deficiency. Peptide hormones are typically stored in secretory granules, and they are secreted by an exocytosis process that is regulated by calcium (Ca^{2+}) and other factors. For steroids and other nonpeptide hormones, hormone synthesis is accomplished by a series of enzymatic steps that act on precursors (cholesterol for steroid hormones; aromatic amino acids for thyroid hormones, catecholamines, and related compounds). Mutations in genes encoding enzymes responsible for one or more steps in hormone synthesis can lead to hormone deficiency and/or excess of another hormone, as in congenital adrenal hyperplasia (Chapter 214).

Negative feedback regulation is the general principle that governs normal hormone synthesis and secretion. For endocrine glands whose growth and hormone secretion are stimulated by pituitary trophic hormones (gonads, adrenal cortex, thyroid), the hormone secreted by the gland acts directly on cognate pituitary trophic cells (e.g., cortisol acting on ACTH-secreting pituitary corticotrophs) to suppress hormone secretion (Fig. 203-1). Conversely, a physiologically meaningful reduction in target gland hormone secretion leads to increased pituitary trophic hormone secretion. In many other cases, negative feedback regulation operates without the pituitary as an intermediate (e.g., PTH secretion from the parathyroid glands regulates extracellular Ca^{2+} homeostasis, and Ca^{2+} feeds back directly on parathyroid cells via a Ca^{2+} sensing receptor to regulate PTH secretion). Chronic hormone deficiency with resultant loss of negative feedback can lead to hypersecretion of the cognate trophic hormone and even to neoplastic proliferation of trophic hormone–secreting cells. Examples include Nelson syndrome (Chapter 205) in which corticotroph tumors form after adrenalectomy,[4] and tertiary hyperparathyroidism in which parathyroid adenomas occur in the setting of chronic hypocalcemia (Chapter 227). In some adrenal cortical disorders, hormone deficiency leads to loss of negative feedback of trophic hormone secretion, which in turn causes pathologic hypersecretion of alternative steroid hormones. The various forms of congenital adrenal hyperplasia (Chapter 214)[5] are caused by mutations in one of the several enzymes in the cortisol biosynthetic pathway. The most common such mutation, which is 21-hydroxylase deficiency, can lead to virilization in female infants, with excessive adrenal androgen secretion caused by ACTH stimulation in the face of inability to synthesize cortisol. Inhibition of enzymatic steps in hormone synthesis, such as aromatase inhibitors to decrease estrogen formation in estrogen receptor–positive forms of breast cancer (Chapter 183), may be an important therapeutic target.

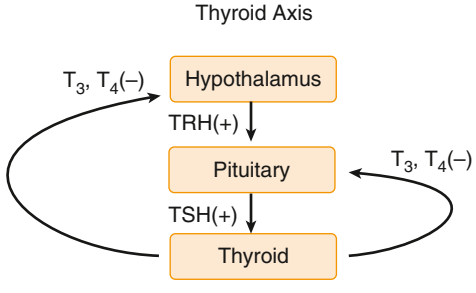

FIGURE 203-1. Hypothalamic-pituitary-thyroid axis illustrating negative feedback regulation. Following thyroid-stimulating hormone (TSH) secretion by the pituitary, the thyroid gland secretes triiodothyronine (T_3) and thyroxine (T_4), which feed back on the hypothalamus and pituitary to suppress further increases in thyrotropin-releasing hormone (TRH) and TSH secretion.

Hormone hypersecretion syndromes, in which excessive hormone secretion occurs in the face of "normal" levels of the factor that ordinarily suppresses the cognate hormone, are by definition caused by some intrinsic defect in negative feedback suppression. This defect may be caused by neoplastic proliferation of hormone-secreting cells, so that "basal" hormone secretion from the increased mass of cells exceeds physiologic levels. This defect also may be due to alterations in the intrinsic "set-point" for negative feedback suppression of hormone secretion. In practice, it may be impossible to differentiate between these two mechanisms, and they are not mutually exclusive.

Hormone secretion is subject to many additional forms of regulation beyond simple negative feedback suppression. These regulatory mechanisms include metabolic, neural, and other internal and environmental inputs. The temporal pattern of hormone secretion is often related to diurnal rhythms, as classically seen for cortisol, and also pulsatility. Changes in gonadotropin secretion during the menstrual cycle (Chapter 218) and during the course of puberty (Chapter 214) are striking examples of complex regulation of temporal patterns of hormone secretion.

HORMONE TRANSPORT AND METABOLISM

Most peptide hormones circulate as the free peptide, but insulin-like growth factor-I (IGF-I) uniquely binds to a number of specialized binding proteins. Steroid and thyroid hormones are lipophilic molecules that circulate largely in protein-bound form. Specialized binding proteins for cortisol, androgens, estrogens, and thyroid hormones are selective for their cognate hormone. The free circulating hormone concentration is only a small fraction of the total hormone measured by routine analytic methods. Binding protein abnormalities can occur in liver disease because most are synthesized by the liver. Thus, the determination of free as opposed to total plasma hormone concentration may be critical to accurate diagnosis in certain clinical conditions.

Hormone metabolism is another critical determinant of action for some hormones. For testosterone (Chapter 216), thyroxine (Chapter 207), and vitamin D (Chapter 199), enzymatic conversion to more potent hormones—dihydrotestosterone formation in target tissues such as skin by 5-α reductase, thyroxine conversion to triiodothyronine by deiodinases, and 1,25 dihydroxyvitamin D formation by sequential hydroxylations in the liver and kidney—are all critical to normal hormone action. Defects in these metabolic steps leads to impaired hormone action. Even some peptide hormones such as angiotensin must undergo enzymatic conversion from secreted precursor form to generate the active hormone.

MECHANISM OF HORMONE ACTION

A hormone circulating in the blood stream in minute concentrations must be recognized by its specific target cells so it can regulate physiologic processes within them. Receptors, which are proteins in these target cells, bind their cognate hormones with high affinity and specificity. Two broad classes of receptors are cell surface receptors that typically span the plasma membrane one or more times (Fig. 203-2) and nuclear receptors that either reside in the nucleus or reside initially in the cytoplasm but then subsequently translocate into the nucleus (Fig. 203-3).

Hormones regulate cellular physiologic processes such as secretion of hormones, enzymes, and other compounds; muscle contraction; growth; and proliferation. Signal transduction is the general term for the biochemical steps between when the hormone binds to the receptor and the resulting alterations in cellular physiology. Most peptide and protein hormones (e.g., insulin, growth hormone, ACTH) bind to cell surface receptors that can be classified according to the mechanism of signal transduction to which they are coupled (e.g., G protein–coupled,[6] receptor tyrosine,[7] or serine kinase, JAK/STAT coupled; see Fig. 203-2). Cell surface receptors may generate "second messengers," which in turn regulate a kinase cascade. The activation of the receptor may result in rapid effects, such as exocytosis of secretory granules, but longer-term actions involving gene regulation may also be a consequence of the activation of second messengers and the resulting kinase cascade. Steroid and thyroid hormones and vitamin D bind to members of the nuclear receptor family; the latter act as "ligand-regulated" transcription factors to regulate gene expression (see Fig. 203-3).[8]

MECHANISMS OF ENDOCRINE DISEASE

Endocrine disease may be caused by acquired or inherited errors in signal transduction. "Specificity spillover" is a clinically important phenomenon in which supraphysiologic concentrations of a hormone lead to binding to and activation of a noncognate receptor for a related hormone. Examples include: hypoglycemia with nonislet cell tumors that secrete IGF-II, which binds to the insulin receptor; skin hyperpigmentation in patients with

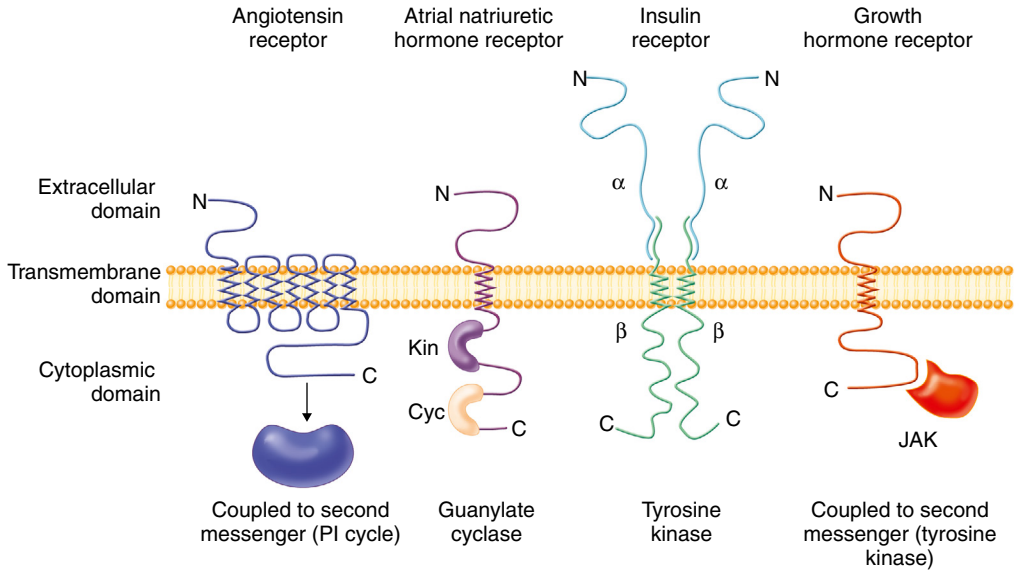

FIGURE 203-2. Structures of different types of peptide hormone receptors. PI = phosphoinositide.

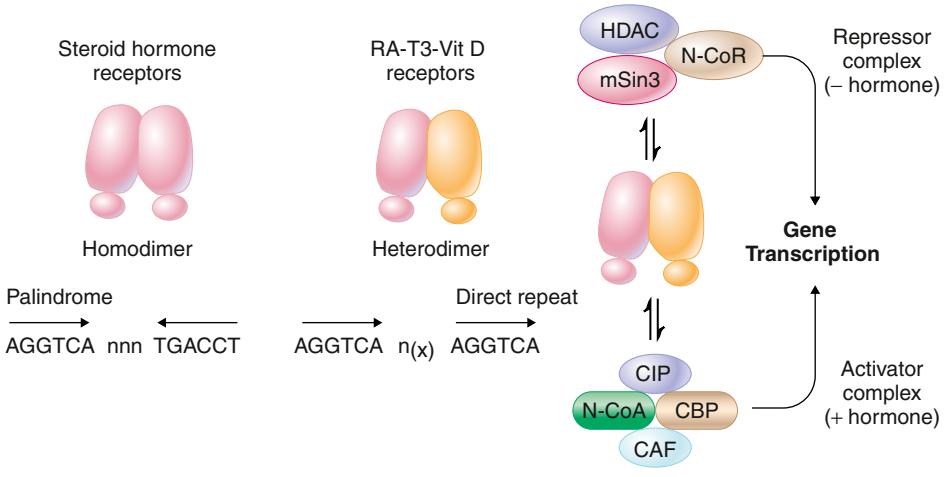

FIGURE 203-3. How steroid hormone receptors function. *Left*, Glucocorticoid receptor family members bind as homodimers to palindromic DNA sites. Thyroid hormone receptor family members bind primarily as heterodimers with retinoid X receptor to direct repeat DNA sites separated by varying numbers of base pairs. *Right*, As a result of hormone binding, repressor complexes dissociate and activator complexes bind to nuclear receptors. Repressor complexes contain histone deacetylase (HDAC), and activator complexes contain histone acetylase (CAF). CBP = CREB binding protein (CREB = cAMP response element binding protein); CIP = cyclin-dependent kinase interacting protein; mSin3 = mammalian homologue of the yeast *SIN3* gene; N-CoA = nuclear receptor coactivator protein; N-CoR = nuclear receptor corepressor protein; RA-T3-Vit D = retinoic acid–triiodothyronine-vitamin D.

Addison disease (Chapter 208), in whom excessive ACTH secretion activates the melanocortin receptor in melanocytes that are normally regulated by MSH; and hyperthyroidism (Chapter 207) in pregnant women whose high human chorionic gonadotropin (HCG) concentrations activate the TSH receptor.

Mutations in one component of a signal transduction pathway can lead either to hormone "resistance" or hormone-independent activation. In the former, patients present with an apparent hormone deficiency, but direct hormone measurement reveals high concentrations of bioactive hormone that fails to act owing to target organ resistance. In the latter, patients present with apparent endocrine hyperfunction, but direct measurement reveals suppressed hormone concentration owing to intact negative feedback. Receptor-inactivating mutations that lead to hormone-resistance diseases[9] have been identified for both the cell surface and nuclear classes of receptors (Table 203-1). Mutations that constitutively activate G protein–coupled receptors have been identified in many endocrine diseases (Table 203-2).

Benign and malignant forms of endocrine neoplasia are caused by somatic and germline mutations in genes that regulate cell proliferation (Chapter 213). Autoimmune destruction of endocrine glands and the resulting deficiencies in hormone secretion may be caused by inherited mutations in immune regulatory genes (Chapter 212) or can be acquired, particularly owing to treatment of cancer with immune checkpoint inhibitors.[10,11]

TABLE 203-1 ENDOCRINE DISEASES CAUSED BY HORMONE RECEPTOR LOSS-OF-FUNCTION MUTATIONS

RECEPTOR	DISEASE	INHERITANCE
V2 vasopressin	Nephrogenic diabetes insipidus	X-linked
ACTH	Familial ACTH resistance	Autosomal recessive
Melanocortin 4	Early onset obesity	Autosomal recessive
Leptin	Early onset obesity	Autosomal recessive
Growth hormone	Laron dwarfism	Autosomal recessive
Insulin	Severe insulin resistance	Autosomal recessive or dominant
Glucocorticoid	Glucocorticoid resistance	Autosomal dominant or recessive
Thyroid hormone	Thyroid hormone resistance	Autosomal dominant or recessive
Vitamin D	Rickets and alopecia syndrome	Autosomal recessive

ACTH = adrenocorticotropic hormone.

TABLE 203-2 ENDOCRINE DISEASES CAUSED BY RECEPTOR GAIN-OF-FUNCTION MUTATIONS

RECEPTOR	DISEASE	INHERITANCE
LH	Familial male precocious puberty	Autosomal dominant
TSH	Sporadic hyperfunctional thyroid nodules	Noninherited (somatic)
Ca^{2+} sensing	Familial hypocalcemic hypercalciuria	Autosomal dominant

Ca^{2+} = calcium; LH = luteinizing hormone; TSH = thyroid-stimulating hormone.

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204

NEUROENDOCRINOLOGY AND THE NEUROENDOCRINE SYSTEM

ROY E. WEISS

NEUROENDOCRINE REGULATION

Neuroendocrinology is the interactions between the nervous system and the endocrine system's metabolic and hormonal homeostatic activities. One role the nervous system has is to connect the environment with the body. The most important environmental factors are temperature and light, which fluctuate in a predictable way each day. Humans have a circadian clock (Chapter 374) to assure that physiology and behavior are attuned to the time of day.[1] The nervous system senses temperature and light, and it uses them as clues to guide eating, activity, sleep, and other essential life functions. The microbiome (Chapter 257) may also influence complex feeding behaviors via the neuroendocrine axis. The neurohypophysial neurons originate from the paraventricular and supraoptic nuclei and traverse the hypothalamic-pituitary stalk to the posterior pituitary, where nerve endings release vasopressin and oxytocin. Hypophysiotropic neurons are localized to specific hypothalamic nuclei, from which they project their axons to the median eminence, where they secrete hormones, which in turn stimulate or inhibit the release of peptides and bioamines into the proximal hypothalamic-pituitary vessels (Fig. 204-1). The blood supply of the median eminence comes from the superior hypophysial artery and its richly arborized capillary beds that extend into the median eminence and then coalesce to form the portal veins that traverse the pituitary stalk and terminate in the pituitary gland. The neuroendocrine system relies on a series of feedback loops, which regulate pituitary hormones as well as the levels of target organ hormones. The target organ hormones regulate both the hypothalamus and the pituitary gland to complete the feedback loop. Perturbations in feedback loops can be altered by factors such as circadian rhythms (circadian periodicity), physiologic and psychological stress, nutritional status, and response to systemic illness.

Hypophysiotropic Hormones

The hypophysiotropic hormones regulate the secretion of pituitary hormones. Some feedback loops are redundant, and some hypophysiotropic hormones exert effects on more than one pituitary hormone. Furthermore, the hypophysiotrophic hormones themselves are regulated by signals higher in the brain, such as the thalamus and the molecular clocks.

Thyrotropin-Releasing Hormone

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Gonadotropin-Releasing Hormone

Gonadotropin-releasing hormone (GnRH) is a 10–amino acid peptide. The neurons that produce GnRH originate outside the central nervous system in the epithelium of the medial part of the olfactory placode. This location is relevant to Kallmann syndrome (Chapter 214),[2] in which GnRH deficiency is associated with congenital agenesis of the olfactory bulbs. One of its genetic forms is caused by a loss of anosmin, which is a protein that facilitates the embryologic migration of these GnRH-producing neurons.

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Once the GnRH neuron migrates to the hypothalamus, a GnRH pulse generator is activated. In early postnatal life, GnRH secretion increases, thereby leading to temporary activation of gonadal hormone production, referred to as "minipuberty." During childhood, the gonads respond to exogenous LH and FSH stimulation but remain quiescent because the endogenous pulsatile GnRH release is suppressed until puberty.

GnRH results in the differential secretion of LH and FSH owing to variable sensitivity of the feedback loop for steroid and peptide hormones, as well as variable sensitivity to GnRH. The pulsatile secretion of GnRH directly increases its own receptor, whereas continuous administration of GnRH is associated with a decrease. In women, positive and negative regulation of steroid hormone feedback in the hypothalamic-pituitary-gonadal axis occurs at both the hypothalamic and pituitary levels. The hypothalamic effects depend on the amplitude and frequency of the pulsed release of GnRH, whereas the pituitary effects are modulated by the gonadotropin response to GnRH. In males, testosterone decreases pulsatile GnRH secretion, with a resulting

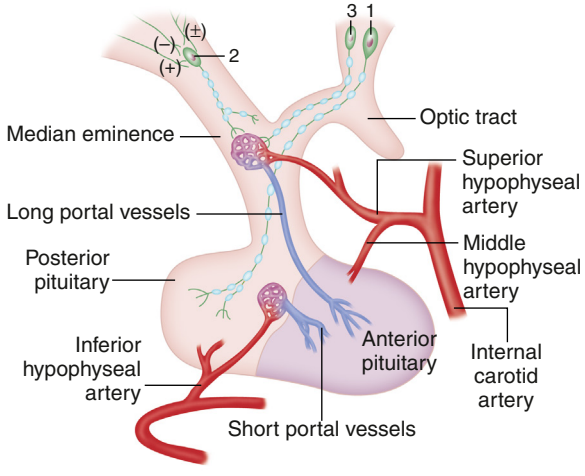

FIGURE 204-1. Neuroendocrine organization of the hypothalamus and pituitary gland. The posterior pituitary is fed by the inferior hypophyseal artery and the hypothalamus by the superior hypophyseal artery, both branches of the internal carotid artery. Most of the blood supply to the anterior pituitary is venous by way of the long portal vessels, which connect the portal capillary beds in the median eminence to the venous sinusoids in the anterior pituitary. Hypophysiotropic neuron 3 in the parvocellular division of the paraventricular nucleus and neuron 2 in the arcuate nucleus are shown to terminate in the median eminence on portal capillaries. These neurons of the tuberoinfundibular system secrete hypothalamic-releasing and -inhibiting hormones into the portal veins for conveyance to the anterior pituitary gland. Neuron 2 is innervated by monoaminergic neurons. Note that the multiple inputs to such neurons, using neuron 2 as an example, can be stimulatory, inhibitory, or neuromodulatory, in which another neuron may affect neurotransmitter release. Neuron 1 represents a peptidergic neuron originating in the magnocellular division of the paraventricular nucleus or supraoptic nucleus and projecting directly to the posterior pituitary by way of the hypothalamic-neurohypophyseal tract. (From Gay VL. The hypothalamus: physiology and clinical use of releasing factors. *Fertil Steril*. 1972;23:50-63, with permission of the American Society for Reproductive Medicine.)

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TABLE 203-2 ENDOCRINE DISEASES CAUSED BY RECEPTOR GAIN-OF-FUNCTION MUTATIONS

RECEPTOR	DISEASE	INHERITANCE
LH	Familial male precocious puberty	Autosomal dominant
TSH	Sporadic hyperfunctional thyroid nodules	Noninherited (somatic)
Ca^{2+} sensing	Familial hypocalcemic hypercalciuria	Autosomal dominant

Ca^{2+} = calcium; LH = luteinizing hormone; TSH = thyroid-stimulating hormone.

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204

NEUROENDOCRINOLOGY AND THE NEUROENDOCRINE SYSTEM

ROY E. WEISS

NEUROENDOCRINE REGULATION

Neuroendocrinology is the interactions between the nervous system and the endocrine system's metabolic and hormonal homeostatic activities. One role the nervous system has is to connect the environment with the body. The most important environmental factors are temperature and light, which fluctuate in a predictable way each day. Humans have a circadian clock (Chapter 374) to assure that physiology and behavior are attuned to the time of day.[1] The nervous system senses temperature and light, and it uses them as clues to guide eating, activity, sleep, and other essential life functions. The microbiome (Chapter 257) may also influence complex feeding behaviors via the neuroendocrine axis. The neurohypophysial neurons originate from the paraventricular and supraoptic nuclei and traverse the hypothalamic-pituitary stalk to the posterior pituitary, where nerve endings release vasopressin and oxytocin. Hypophysiotropic neurons are localized to specific hypothalamic nuclei, from which they project their axons to the median eminence, where they secrete hormones, which in turn stimulate or inhibit the release of peptides and bioamines into the proximal hypothalamic-pituitary vessels (Fig. 204-1). The blood supply of the median eminence comes from the superior hypophysial artery and its richly arborized capillary beds that extend into the median eminence and then coalesce to form the portal veins that traverse the pituitary stalk and terminate in the pituitary gland. The neuroendocrine system relies on a series of feedback loops, which regulate pituitary hormones as well as the levels of target organ hormones. The target organ hormones regulate both the hypothalamus and the pituitary gland to complete the feedback loop. Perturbations in feedback loops can be altered by factors such as circadian rhythms (circadian periodicity), physiologic and psychological stress, nutritional status, and response to systemic illness.

Hypophysiotropic Hormones

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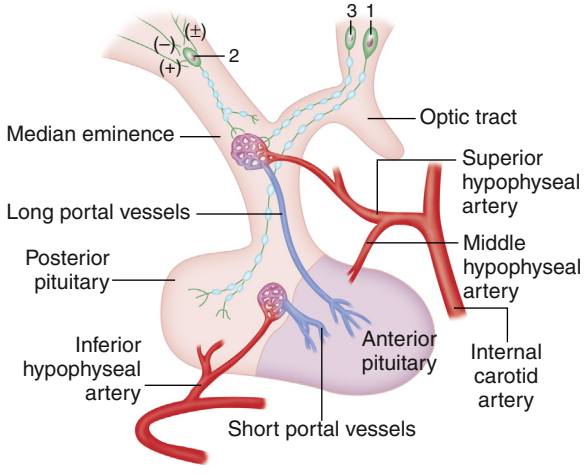

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ABSTRACT

Neuroendocrinology refers to the area of endocrinology in which the nervous system interacts with the endocrine system to link neural activity with metabolic and hormonal homeostatic activity. Neuroendocrine diseases include congenital disorders, tumors, inflammatory and infiltrative diseases, trauma, and irradiation.

KEYWORDS

neuroendocrine
hypothalamus
hypophysiotropic hormones
rhythms
puberty

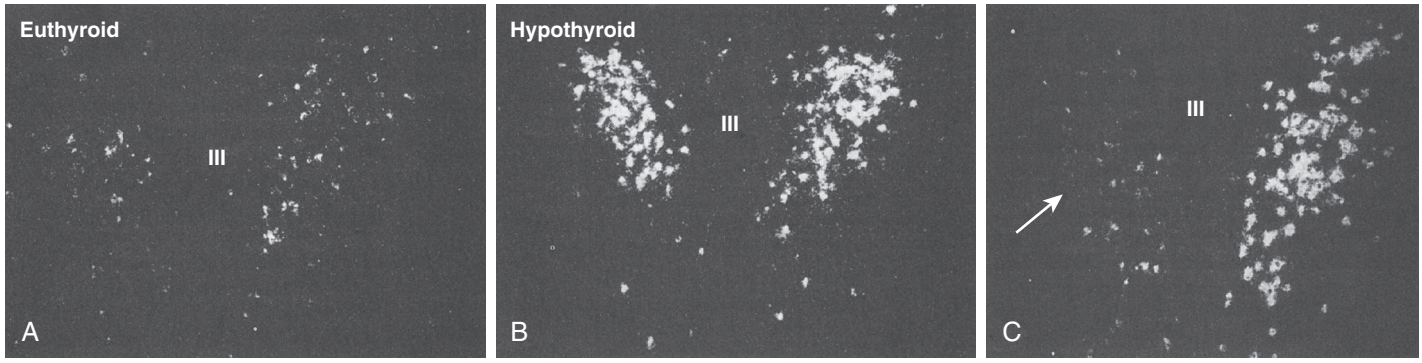

FIGURE 204-2. In situ hybridization autoradiographs of proTRH mRNA in the paraventricular nucleus of (A) euthyroid and (B) hypothyroid rats. Note the marked increase in hybridization signal in (B). C shows the effect of stereotaxic placement of a thyroid hormone implant adjacent to one side of the paraventricular nucleus in a hypothyroid animal. Marked asymmetry of hybridization signal is apparent with diminished signal on the side of the implant (*arrow* III, 3rd ventricle). (From Lechan RM, Hollenberg A. Thyrotopin releasing hormone [TRH]. In: Henry H, Norman AW. *Encyclopedia of Hormones*. Academic Press: Amsterdam; 2003:519.)

decrease in the amplitude and frequency of the gonadotropin pulse as well as a decreased gonadotropin response to exogenous GnRH.

In addition to pulsatility and regulation of GnRH receptors, kisspeptin may indirectly stimulate LH and FSH release by stimulating GnRH neurons. Kisspeptin levels rise just before puberty. Mutations in the kisspeptin gene have been associated with hypothalamic hypogonadism and impaired pubertal development, thereby demonstrating its role in the reproductive axis.

The negative feedback effects of inhibin, a peptide produced by testicular Sertoli cells and ovarian granulosa cells, are predominantly on FSH at the pituitary level, where inhibin causes a decrease in the sensitivity of gonadotrophs to GnRH. A related ovarian protein, activin, stimulates the basal and GnRH-stimulated synthesis and release of FSH from the pituitary, but its primary effect is to promote the response of ovarian granulosa cells to FSH. Another gonadal peptide, follistatin, inhibits the GnRH-induced rise in FSH that follows oophorectomy, primarily by binding to activin. These ovarian peptides are also found in the pituitary; therefore they may have additional local effects on gonadotropin secretion.

Pulsatile administration of exogenous GnRH is very successful for restoring normal sexual function and fertility in patients who have hypogonadotropic hypogonadism (Chapter 216) secondary to GnRH deficiency. Long-acting GnRH agonists also are useful to downregulate GnRH receptors and gonadotropin secretion in a variety of conditions, including precocious puberty (Chapter 214), prostate cancer (Chapter 186), breast cancer (Chapter 183), uterine fibroids (Chapter 184), and endometriosis (Chapter 218). Direct GnRH antagonists, which competitively bind to the GnRH receptor, are used for similar conditions.

Somatostatin

Somatostatin (also known as somatotropin release–inhibiting factor) inhibits the secretion of growth hormone. The interactions between somatostatin and growth hormone–releasing hormone (GHRH) and their effects on the secretion of growth hormone are complex. Growth hormone secretory episodes are associated with increased secretion of GHRH, often accompanied by low somatostatin levels. By comparison, basal or trough levels of growth hormone are associated with lower levels of GHRH and more elevated levels of somatostatin. Somatostatin also inhibits both the basal and stimulated TSH secretion. However, growth hormone is about 10-fold more sensitive to inhibition by somatostatin than is TSH, thereby suggesting that the physiologic role of somatostatin in inhibiting TSH secretion is limited. Other tissues with somatostatin include the gut mucosa, D cells of the pancreatic islets, and the myenteric neural plexus. By its paracrine and endocrine actions, somatostatin suppresses the secretion of insulin, glucagon, gastrin, secretin, cholecystokinin, vasoactive intestinal polypeptide (VIP), and other gastrointestinal hormones, which in turn regulate functions such as gastric acid secretion, gastric emptying, gallbladder contraction, and splanchnic blood flow. Somatostatin analogs are used to treat acromegaly (Chapter 205), carcinoid tumors (Chapter 213), VIP-secreting tumors (Chapter 213), TSH-secreting pituitary tumors (Chapter 205), and islet cell tumors (Chapter 211).[3]

Corticotropin-Releasing Hormone

Corticotropin-releasing hormone (CRH) stimulates the release of equimolar amounts of adrenocorticotropic hormone (ACTH), β-endorphin, β-lipotropin, melanocyte-stimulating hormone (MSH), and other peptides that are generated from proopiomelanocortin. CRH and vasopressin have synergistic effects on the release of ACTH. For example, the release of ACTH in response to stress is mediated 75% via CRH and 25% by vasopressin. However, since the releases of CRH and vasopressin are not always coordinated, stress can selectively activate the vasopressin-containing subset of CRH neurons. In a feedback loop, cortisol decreases ACTH secretion at both the hypothalamic and the pituitary levels. ACTH and β-endorphin also feed back negatively to decrease the release of CRH by the hypothalamus. Central bioamines, opioids, and peptides also influence the secretion of CRH. Inflammatory monokines, including interleukin (IL)-1, IL-6, and tumor necrosis factor (TNF)-α, stimulate the synthesis and release of CRH and vasopressin from the hypothalamus. The resulting increase in cortisol then reduces the intensity of the inflammatory response and the related release of monokines, thereby completing the feedback loop. CRH receptors, which are widely distributed in the brain, are activated by the sympathetic nervous system and suppressed by the parasympathetic nervous system. CRH may also help regulate body weight, because overfeeding increases leptin levels, which stimulate CRH, which in turn inhibits appetite and increases energy expenditure.

Biosynthetic human CRH is helpful for differentiating Cushing disease from ectopic ACTH syndrome (Chapter 208), with the finding that patients with Cushing disease respond with a greater than 35% increment, whereas those with ectopic ACTH secretion have a lesser response. If the results are equivocal, CRH testing during bilateral inferior petrosal sinus sampling for ACTH often provides additional discriminatory information.

Growth Hormone–Releasing Hormone

GHRH dose-dependently stimulates growth hormone secretion. Repetitive administration of GHRH can release enough growth hormone in children with GHRH deficiency to increase insulin-like growth factor (IGF)-I levels and accelerate growth. The negative feedback of both IGF-I and growth hormone on the secretion of growth hormone decreases GHRH and increases somatostatin. This feedback effect is clinically relevant, as evidenced by high circulating growth hormone levels in IGF-I–deficient states such as renal insufficiency (Chapter 116) and cirrhosis (Chapter 139). In children in whom mutations in the growth hormone receptor make them unresponsive to growth hormone (also known as Laron-type dwarfism), IGF-I levels are very low and levels of growth hormone are correspondingly elevated.

A separate growth hormone–stimulating system involves a distinct receptor, termed the *growth hormone secretagogue* receptor, which interacts with a 28–amino acid peptide called ghrelin, which initially was isolated from the stomach. Both growth hormone secretagogue receptor and ghrelin messenger RNA are present in the human hypothalamus and pituitary. The physiologic interaction of ghrelin with GHRH and somatostatin is complex. In addition to a direct stimulatory effect on the pituitary, ghrelin amplifies secretion of growth hormone by indirect hypothalamic actions. However, ghrelin appears to be more important for the regulation of appetite and food intake.

Prolactin Inhibitory Factor

The inhibitory component of hypothalamic regulation of prolactin secretion predominates over the stimulatory component. Dopamine is the major factor that inhibits prolactin in most physiologic circumstances (e.g., lactation), such as when a rising prolactin level is accompanied by a simultaneous fall in dopamine, as well as a rise in prolactin-releasing factors such as VIP. When endogenous dopamine receptors are blocked by drugs, such as the antipsychotic agents, prolactin levels rise. Lesions that interrupt the basal hypothalamic neuronal pathways that carry dopamine to the median eminence

or interrupt portal blood flow (e.g., craniopharyngiomas or other large mass lesions) decrease the amount of dopamine that reaches the pituitary and can cause hyperprolactinemia.

Prolactin-Releasing Factor

Hypothalamic peptides other than TRH also have prolactin-releasing factor activity. VIP stimulates the synthesis and release of prolactin in hypothalamic-pituitary portal blood. Within the VIP precursor, another similarly sized peptide (peptide histidine methionine) also has prolactin-releasing factor activity. Prolactin-releasing peptide, which is a hypothalamic factor with main effects on the brain, participates in the regulation of food intake and energy expenditure.

Endogenous Opioid Peptides

Endogenous opioid peptides, which have a common 5–amino acid sequence at their amino terminals (Tyr-Gly-Gly-Phe-Met [or Leu]), bind to endogenous opioid receptors. The opioid μ-receptor mediates most of the opioid endocrine effects and analgesia (Chapter 26). Its primary peptide ligand is β-endorphin, which is derived from proopiomelanocortin. For the opioid δ-receptor, which mediates behavioral, analgesic, and endocrine effects, the principal peptide ligands are met- and leu-enkephalins that are derived from proenkephalin A. Naloxone is not as effective for blocking the δ-receptor as for blocking the μ-receptor. The κ-receptor, which mediates sedation and ataxia, binds principally to dynorphin and the neoendorphins. A fourth receptor, which is partly homologous with the δ-receptor, binds to nociception, an endogenous 17–amino acid peptide.

Proopiomelanocortin, which is a 31-kD precursor peptide, contains ACTH, β-lipotropin, and β-endorphin. Its major cleavage products in the anterior pituitary are ACTH and β-lipotropin, and much of the latter is then processed into β-endorphin. In the intermediate lobe of the pituitary, the major products are α-melanocyte stimulating hormone (α-MSH), corticotropin-like intermediate peptide, β-endorphin, and γ-lipotropin. In the brain, however, proopiomelanocortin is processed primarily to β-endorphin, γ-lipotropin, and ACTH, with most of the ACTH then further processed to corticotropin-like intermediate peptide and α-MSH. The pentapeptide enkephalins are derived from the 28-kD precursor proenkephalin A. Neuronal perikarya containing the enkephalins are widely distributed in the brain. Dynorphin is a 17–amino acid peptide that is derived from a 28-kD precursor called proenkephalin B or prodynorphin. This peptide, as well as shorter peptides called α-neoendorphin (with 10 amino acids) and β-neoendorphin (with 9 amino acids), react almost exclusively with the κ-receptor. Nociceptin, which is a 17–amino acid peptide that is derived from a κ precursor called pronociceptin, and its receptor, which also is present in the hypothalamus as well as in other areas of the brain, are sources of monoamine neurotransmitters. Nociceptin appears to have an antiopioid or antinociceptive effect. Opioid peptides that influence hormone secretion in the anterior pituitary are produced through modulation of hypothalamic bioamines and hypophysiotropic factors.

The various opioid peptides and their receptors are linked to a number of bodily functions, including stress, mental illness, narcotic tolerance and dependence, pregnancy, eating, drinking, gastrointestinal function, learning, memory, reward, cardiovascular responses, respiration, thermoregulation, locomotor activity, seizures, brain electrical activity, and neuroimmune activity. Endogenous opioids inhibit gonadotropin secretion via their action on GnRH secretion. The exogenous administration of analogues of β-endorphin or enkephalin increase serum levels of growth hormone and prolactin, but blocking endogenous opioid pathways with naloxone does not alter basal or stimulated levels of growth hormone or prolactin. Opioids provide negative feedback on the secretion of ACTH and β-endorphin, and naloxone increases basal and stimulated levels of ACTH. Overall, the effects of the endogenous opioids on the normal physiologic regulation of the various pituitary hormones in humans is minimal. However, exogenous opioids in pharmacologic doses can impair the secretion of GnRH and gonadotropin, thereby causing hypogonadism (reduced libido, sexual function, and fertility) and adrenal insufficiency (by impairing the secretion of CRH and ACTH).

Central Nervous System Rhythms and Neuroendocrine Function

Pituitary hormones are secreted in a pulsatile fashion but in the context of underlying rhythms. A pituitary hormone's pulse amplitude reflects the amount of releasing hormone as well as factors that alter the pituitary's sensitivity to that releasing hormone. The pulse amplitude will be reduced by inhibitory factors (e.g., GHRH versus somatostatin), feedback from target organ hormones, nutritional factors, and prior stimulation that can deplete the releasable hormone pool. Pulse frequency is driven by the frequency at which the hypophysiotropic factor is released, which in turn is regulated by the hypothalamic pulse generator system.

The pituitary has an intrinsic rhythm of small amplitudes at a frequency of every 2 to 10 minutes. The pulsatile release of hypophysiotropic-releasing factors is superimposed on this intrinsic rhythm with or without the withdrawal of a corresponding inhibitory factor. Ultradian rhythms are less than 1 day, circadian rhythms have a periodicity of about 24 hours (synchronized by an environmental cue such as the light-dark cycle), and infradian rhythms have a periodicity of more than 24 hours. The suprachiasmatic nucleus functions as a circadian pacemaker and receives light-induced electrical impulses from the retina and then transmits these impulses to the pineal gland, where they are converted to hormonal signals. Infradian rhythms include the gravitational influence of the moon, which guides the menstrual cycle.

Circadian and infradian rhythms are modulated by the sleep-wake cycle. For example, the secretion of growth hormone, prolactin, ACTH, and pubertal LH are linked more to the sleep-wake cycle than to the dark-light cycle (E-Fig. 204-1). Each of these hormones increases to its maximal level after the onset of sleep. The marked diurnal variation in ACTH and cortisol is often an indication of whether this system is functioning normally. Loss of this diurnal rhythm occurs when the regulation of CRH is abnormal, which may occur with depression, excessive alcohol intake, or autonomous secretion of ACTH in Cushing disease (Chapter 208). In fact, a diagnostic test for Cushing syndrome is the presence of a disrupted diurnal cortisol rhythm.

Hypothalamic-pituitary axes are blunted with aging. Furthermore, changes in the hormonal milieu associated with sleep deprivation and disruption of the axes result in significant metabolic sequelae, such as hypertension and impaired glucose tolerance.

NEUROENDOCRINE DISEASE

DISEASES OF THE HYPOTHALAMUS

Diseases that cause localized hypothalamic changes include generalized central nervous system diseases (e.g., neurosarcoidosis [Chapter 83]) and processes (e.g., hydrocephalus) (Table 204-1). Systemic illnesses also can alter hypothalamic regulation.

Axons that project to the median eminence contain the various hypophysiotropic factors that are concentrated in the basal portion of the hypothalamus. Thus, lesions located within this final common pathway can decrease secretion of some or all of the pituitary hormones except prolactin, which may increase because its tonic inhibition by dopamine is eliminated. Diabetes insipidus (Chapter 206) may also occur. Symptoms of hypothalamic dysfunction also correlate with the size of the lesion, the involved area of the hypothalamus, and the rapidity at which the lesion grows. Slowly growing lesions typically cause gradual hormone dysregulation rather than sudden symptoms. However, slowly growing but large lesions also can cause acute symptoms if a slight increment in growth eliminates the remaining vestiges of vasopressin or ACTH secretion. The best way to diagnose structural hypothalamic lesions is magnetic resonance imaging (MRI) with gadolinium enhancement, although computed tomographic (CT) scanning with intravenous contrast is also effective. Visual field testing may detect an impingement on the optic chiasm and nerves by hypothalamic lesions. Detailed hypothalamic-pituitary function testing may reveal functional hypothalamic disruption that is not otherwise clinically evident.

CONGENITAL EMBRYOPATHIC DISORDERS

The most common embryopathic disorders that affect the hypothalamus are the midline cleft syndromes, which cause varying defects of midline structures, especially the optic and olfactory tracts, the septum pellucidum, the corpus callosum, the anterior commissure, the hypothalamus, and the pituitary. The clinical features of midline cleft defects vary from cyclopia to cleft lip and from isolated hypothalamic hormone defects to panhypopituitarism.

Optic nerve hypoplasia involves a spectrum of anatomic malformations and clinical manifestations ranging from isolated hypoplasia of one or both optic nerves, with a variable degree of visual impairment, to extensive brain malformations, hypothalamic-pituitary dysfunction, neurocognitive disability, and autism spectrum disorders (Chapter 385). It is the second leading cause

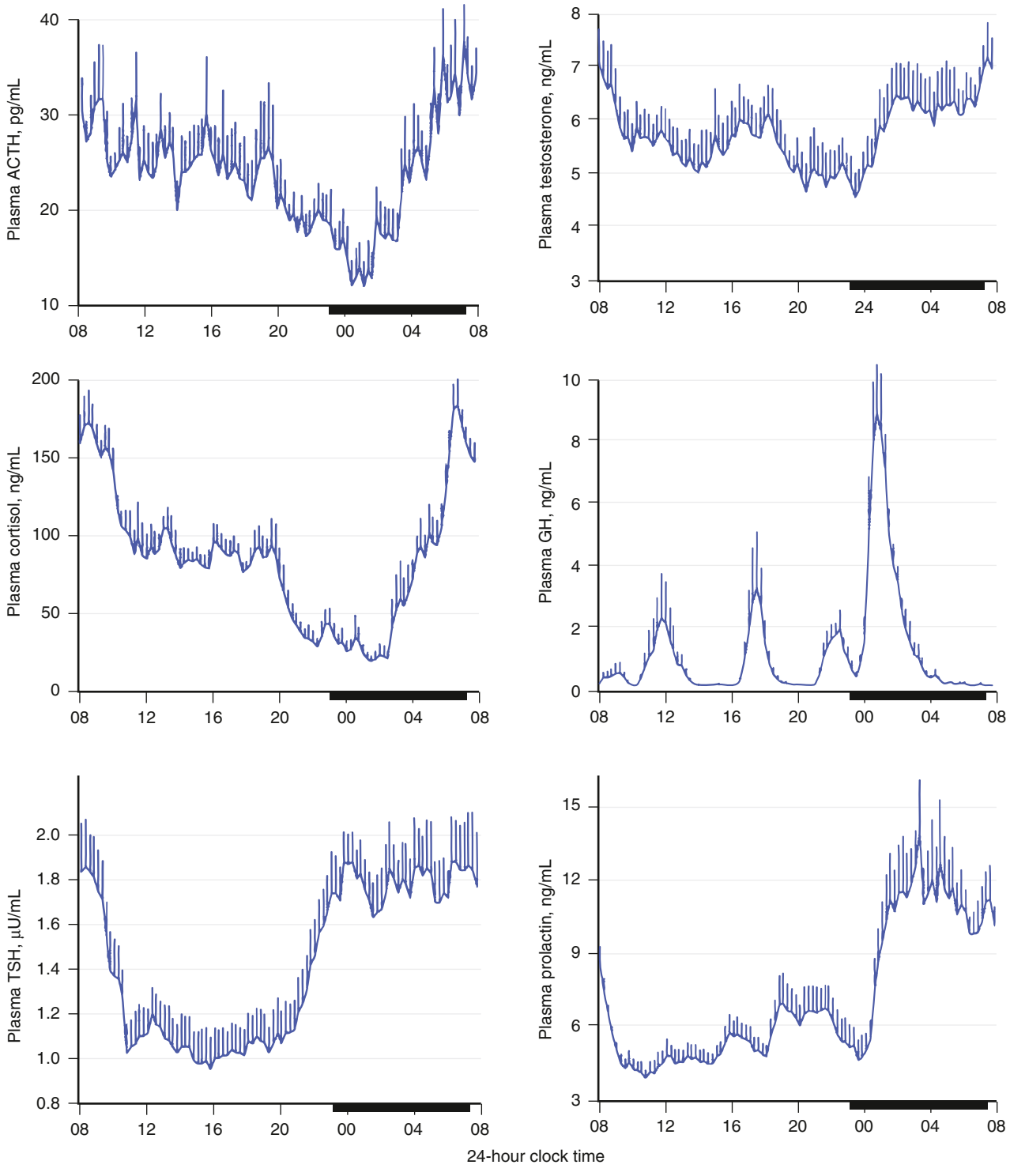

E-FIGURE 204-1. Hormonal circadian rhythms. Mean (+SEM) profiles of plasma levels of adrenocorticotropic hormone (ACTH), cortisol, thyroid-stimulating hormone (TSH), testosterone, growth hormone (GH), and prolactin from a group of 8 to 12 normal men studied at 15-minute intervals for 24 hours. The sleep times are indicated by black bars. (Redrawn with permission from Van Cauter E. Diurnal and ultradian rhythms in human endocrine function: a minireview. *Horm Res*. 1990;34:45-53.)

TABLE 204-1 ETIOLOGY OF HYPOTHALAMIC DISEASE BY AGE OF PRESENTATION

NEONATES
Congenital embryopathic disorders: agenesis of the corpus callosum, cleft palate (*HESX1*)
Congenital disorders: isolated hormone and receptor mutations, combined pituitary hormone deficiency (*PIT1, PROP1*), Laurence-Moon-Bardet-Biedl syndrome, Prader-Labhart-Willi syndrome
Tumors: glioma, hemangioma
Trauma
Hydrocephalus, hydranencephaly, kernicterus
1 MONTH TO 2 YEARS
Tumors: glioma, especially optic glioma, hemangiomas
Infiltrative disease: Langerhans cell histiocytosis, meningitis
Hydrocephalus
2-10 YEARS
Tumors: craniopharyngioma, glioma, dysgerminoma, hamartoma, leukemia, ganglioneuroma, ependymoma, medulloblastoma
Infiltrative disease: Langerhans cell histiocytosis, meningitis, tuberculosis, encephalitis
Irradiation: for nasopharyngeal tumors, intracranial tumors, leukemia
Functional: psychosocial deprivation
10-25 YEARS
Congenital disorders: Kallmann syndrome, gonadotropin-releasing hormone receptor defects
Tumors: craniopharyngioma, pituitary tumors, glioma, hamartoma, dysgerminoma, dermoid, lipoma, neuroblastoma
Trauma: subarachnoid hemorrhage, vascular aneurysm, arteriovenous malformation
Infiltrative diseases: Langerhans cell histiocytosis, sarcoidosis, tuberculosis, meningitis, encephalitis, leukemia
Chronic hydrocephalus or increased intracranial pressure
Functional: hypogonadotropic hypogonadism associated with weight loss, exercise
25-50 YEARS
Tumors: pituitary tumors, meningioma, craniopharyngioma, Rathke cleft cyst, glioma, lymphoma, angioma, colloid cysts, ependymoma
Infiltrative diseases: sarcoidosis, Langerhans cell histiocytosis, tuberculosis, viral encephalitis
Subarachnoid hemorrhage, vascular aneurysms, arteriovenous malformation
Irradiation: for pituitary adenoma, nasopharyngeal tumors, intracranial tumors
Nutritional: Wernicke disease
Functional: hypogonadotropic hypogonadism associated with weight loss, exercise
50 YEARS AND OLDER
Tumors: pituitary tumors, meningioma, craniopharyngioma, sarcoma, glioblastoma, lymphoma, colloid cysts, ependymoma
Vascular: infarct, subarachnoid hemorrhage, pituitary apoplexy, aneurysm
Irradiation: for pituitary adenoma, nasopharyngeal tumors, intracranial tumors
Infiltrative diseases: encephalitis, sarcoidosis, meningitis
Nutritional: Wernicke disease

Modified from Plum F, Van Uitert R. Non-endocrine diseases of the hypothalamus. In: Reichlin S, Baldessarini RJ, Martin JB, eds. *The Hypothalamus*. New York: Raven Press; 1978:415.

of congenital visual impairment, superseded only by cortical visual impairment. Some such patients have precocious puberty (Chapter 214), presumably because they lack other inhibitory influences but have intact GnRH-producing structures.

Nearly 50% of patients with "idiopathic" growth hormone deficiency will have an absent infundibulum detectable on MRI. Mutations in *HESX1*, *SOX2*, *SOX3*, and *OTX2* transcription factor genes cause agenesis of the corpus callosum and panhypopituitarism. The diagnosis is made by finding anosmia and low gonadotropin levels, and MRI will show absence or hypoplasia of the olfactory bulbs.

TUMORS

The most common tumors that affect the hypothalamus are pituitary adenomas with significant suprasellar extension. Such tumors typically either disturb the pituitary stalk and the mediobasal hypothalamus or compress the normal pituitary.[4]

Tumors cause symptoms because their mass effects precipitate headache, vomiting, visual disturbance, seizures, hypopituitarism, and polyuria. Some patients have galactorrhea, amenorrhea, and hyperprolactinemia suggestive of a prolactinoma. Careful endocrine testing reveals varying degrees of hypopituitarism in 50 to 75% of cases, modest hyperprolactinemia in 25 to 50%, and often diabetes insipidus. A normal or elevated prolactin level indicates the hypothalamus or stalk as the site of the lesion, and normal pituitary function often returns following therapy. Diabetes insipidus (Chapter 206) is rarely caused by pituitary adenomas.

Craniopharyngiomas, which arise from remnants of the Rathke pouch, are the next most common tumors affecting the hypothalamus. Microscopically, craniopharyngiomas consist of cysts alternating with stratified squamous epithelium. The cyst's fluid is usually dark and thick, and the lesion is often calcified. A Rathke cleft cyst is a closely related lesion that develops from the space between the anterior and rudimentary intermediate lobes. These cysts are lined with cuboidal (as opposed to squamous) epithelium, and their fluid is usually white and mucoid. Craniopharyngiomas most commonly arise during childhood but can occur in adults and even the elderly.[5]

Transsphenoidal surgery is the preferred treatment if the hypothalamus is not involved.[6] Unfortunately, surgical extirpation of craniopharyngiomas commonly worsens pituitary function; often results in complete panhypopituitarism and diabetes insipidus; and may damage the hypothalamic centers that regulate thirst, body temperature, and food intake, thereby resulting in severe obesity.[7] Hypothalamic-sparing surgery may cause less obesity without increasing recurrence rates. If a craniopharyngioma cannot be removed completely, postoperative radiation reduces the risk of recurrent symptoms. Rathke cleft cysts are less likely to recur.

Suprasellar dysgerminomas[8] arise from primitive germ cells, which are structurally identical to germ cell tumors and which migrated during fetal development. The tumors occur most commonly in children, in whom they decrease growth because of hypopituitarism, and also cause diabetes insipidus and visual problems. Hyperprolactinemia occurs in more than 50% of affected children, and 10% have precocious puberty because of the production of human chorionic gonadotropin (HCG) by the tumor. The finding of an elevated HCG level in the spinal fluid may be diagnostic. As compared with craniopharyngiomas, these tumors are very radiosensitive, and radiation therapy combined with chemotherapy is the preferred treatment.

A hypothalamic hamartoma[9] is a nodule of hypothalamic neurons, glia, and fiber bundles. It is attached to the hypothalamus by a pedicle between the tuber cinereum and the mammillary bodies, and it extends into the basal cistern. Asymptomatic hamartomas can be identified in up to 20% of routine autopsies. These lesions rarely may enlarge and disrupt hypothalamic function because they compress adjacent tissues. Less commonly, they may cause seizures, especially gelastic seizures. Some hamartomas can be associated with other congenital anomalies and mutations in the transcription factor gene *GLI3*. A choristoma (or gangliocytoma) is a hamartomatous variant composed of similar tissue in the anterior pituitary but not attached to the hypothalamus. These neuronal tumors cause precocious puberty, acromegaly, or Cushing syndrome when they produce GnRH. Surgery can be risky. Treatment with a long-acting GnRH analogue can be used to suppress gonadotropin secretion and may be preferred if the hamartoma does not cause mass effects.

Other tumors and space-occupying lesions in the suprasellar area include arachnoid cysts, meningiomas (Chapter 175), gliomas (Chapter 175), astrocytomas, chordomas, infundibulomas, cholesteatomas (Chapter 396), neurofibromas (Chapter 385), lipomas, and metastatic cancer (especially from the breast and lung). Such lesions can cause varying degrees of hypopituitarism, diabetes insipidus, and hyperprolactinemia. Unfortunately, surgical therapy often worsens the hormonal deficit and may cause other hypothalamic damage.

INFLAMMATORY AND INFILTRATIVE DISORDERS

Sarcoidosis (Chapter 83) involves the central nervous system clinically in 1 to 5% of patients and in up to 16% of patients at autopsy. Isolated central nervous system sarcoidosis, however, is uncommon. When sarcoidosis involves the central nervous system, it affects the hypothalamus in 10 to 20% of cases. Sarcoid granulomas can be seen in the hypothalamus, pituitary, or stalk, either as an infiltrative process or as a mass lesion.[10] The most common endocrinologic sequelae are varying degrees of hypopituitarism, diabetes insipidus, and hyperprolactinemia. Obesity can also result from hypothalamic involvement by sarcoidosis. Examination of cerebrospinal fluid usually shows pleocytosis, elevated protein levels, low glucose levels, and variable elevations of angiotensin-converting enzyme. In a patient who has isolated central nervous system sarcoidosis, the diagnosis may be extremely difficult to establish, and biopsy

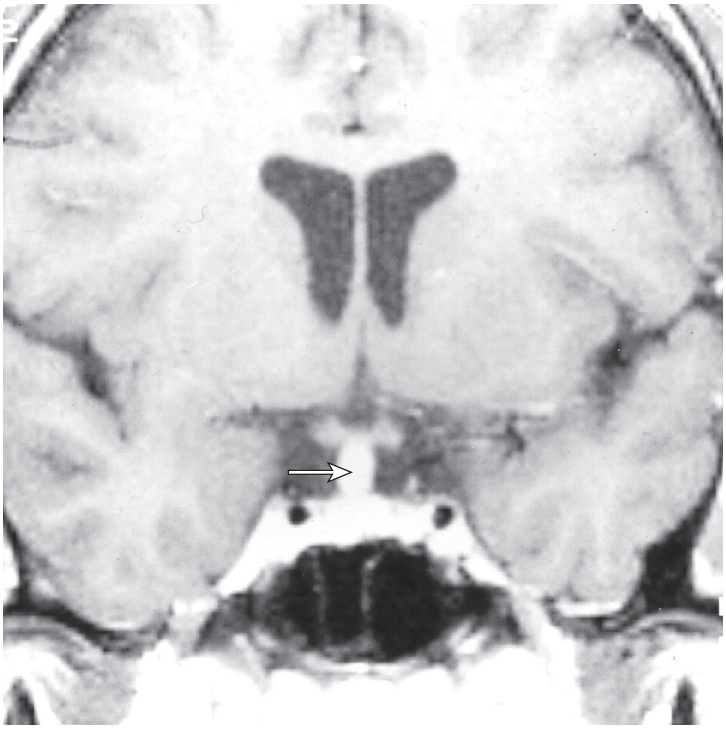

FIGURE 204-3. Thickened pituitary stalk in Langerhans cell histiocytosis. Magnetic resonance image of patient with Langerhans cell histiocytosis who manifested initially with amenorrhea, galactorrhea, and diabetes insipidus. *Arrow* points to the thickened pituitary stalk. (Reproduced with permission from Purdy LP, Molitch ME. Sudden onset of diabetes insipidus in an adolescent. *Endocr Trends*. 1998;5:1-7.)

is often required. Corticosteroid therapy can at least partially reverse the thirst disorders, but deficits in anterior pituitary hormones usually do not improve.

Langerhans cell histiocytosis (Chapter 155) of the hypothalamus can cause diabetes insipidus, varying degrees of hypopituitarism, and hyperprolactinemia.[11] It is the most common cause of diabetes insipidus in children. This infiltration usually thickens the pituitary stalk, but it may cause a mass lesion of the hypothalamus or pituitary (Fig. 204-3). Osteolytic lesions may be seen on radiographs of the jaw or mastoid. Therapy consists of surgery, focal irradiation, or chemotherapy with alkylating agents and high-dose corticosteroids.

Other infiltrative diseases that can cause progressive alteration in the hypothalamic regulation of the secretion of pituitary hormones include tuberculosis (Chapter 299), lymphomas (Chapters 171 and 172), and fungal diseases.

VASCULAR DISEASE

An enlarging aneurysm (Chapter 377) may present as a mass lesion in the hypothalamic-pituitary area, where it can cause visual field defects and hypopituitarism. Tumors and aneurysms may also coexist, and careful MRI evaluation is critical. Vascular infarction very rarely causes hypothalamic disease, but almost 50% of cases of subarachnoid hemorrhage (Chapter 377) may be associated with varying degrees of hypopituitarism. Diabetes insipidus is an uncommon complication.

TRAUMA

Traumatic brain injury (Chapter 368) can cause a variety of hormonal perturbations that range from isolated ACTH deficiency to panhypopituitarism with diabetes insipidus.[12] With frontal injuries, the brain travels backward, but the pituitary cannot move; as a result, the pituitary stalk is avulsed, with interruption of the portal vessels. The paraventricular and supraoptic nuclei and median eminence are particularly involved with microhemorrhages, hence the high frequency of panhypopituitarism with diabetes insipidus. Most patients with head injury are hyperprolactinemic, which clinically confirms that the primary site of injury is the hypothalamus or stalk. Blood levels of growth hormone, ACTH, TSH, LH, and prolactin may actually be elevated. These levels subsequently fall, and then pituitary function either may return to normal or hypopituitarism may develop.[13] Overall, about 25% of surviving patients develop hypopituitarism after major traumatic brain injury, but significant hypothalamic, pituitary stalk, or anterior pituitary damage is seen in about 85% of fatal cases. Deficiencies in ACTH (and hence cortisol) may be life-threatening, so cortisol levels should be monitored carefully in the hours and days after major brain trauma. Hypocortisolism must be treated with stress doses of glucocorticoids (Chapter 28). However, hypopituitarism should not be confused with prolonged stress-related endocrine alterations.

IRRADIATION

Whole-brain irradiation frequently causes hypothalamic dysfunction, with resulting endocrine abnormalities and behavioral changes. The loss of pituitary function is so frequent that all patients who have had their pituitary and hypothalamic areas irradiated must be monitored periodically to detect the most common abnormality, which is hyperprolactinemia, as well as hypopituitarism that occurs, especially when the radiotherapy is targeted to the hypothalamic area.[14] However, such deficiencies may occur many years later, so annual testing is recommended for up to 20 years. Stereotactic gamma knife irradiation and external beam radiation of pituitary and other parasellar tumors appear to carry a similar risk of subsequent hypopituitarism.

EFFECTS OF HYPOTHALAMIC DISEASE ON PITUITARY FUNCTION

Hypothalamic disease can cause both pituitary hyperfunction and hypofunction of varying degrees of severity. Although severe disease can cause absolute deficiencies of the various hormones, milder disease may cause subtle alterations, such as the loss of menstrual cycling and subsequent "hypothalamic" amenorrhea (Chapter 218). Furthermore, these hypothalamic defects may be interrelated. A rather common phenomenon is when hyperprolactinemia owing to hypothalamic dysfunction causes a hypogonadotropic hypogonadism that can be reversed when the elevated prolactin levels are normalized. Oftentimes MRI does not reveal a structural lesion, so a functional defect is presumably related to altered neurotransmitter regulation.

GROWTH HORMONE

Loss of normal secretion of growth hormone is the most common hormonal defect caused by structural hypothalamic disease. About 75% of patients with congenital idiopathic growth hormone deficiency respond normally to exogenous GHRH, thereby implying that the problem is probably disordered hypothalamic regulation (Chapter 205). A rare form of growth hormone deficiency is caused by a mutation in the GHRH receptor. Reversible idiopathic growth hormone deficiency, which can be caused by inadequate parental care and affection, is termed emotional deprivation syndrome or psychosocial dwarfism. The disordered regulation of growth hormone is probably caused by psychogenic alterations in the balance of neurotransmitters needed for normal secretion of GHRH and somatostatin. Restoration of proper care promptly normalizes the secretion of growth hormone and subsequent growth. Treatment of systemic illnesses that also may decrease the secretion of growth hormone will correct the growth abnormality.

GONADOTROPINS

Hypothalamic Hypogonadism

The primary defect in hypothalamic hypogonadism (Chapter 216) is when the diminished secretion of GnRH impairs the secretion of pituitary gonadotropin and gonadal function.[15] The cause may be congenital or acquired. Depending on the age of onset, these conditions may be manifested as either delayed development or loss of adult gonadal function. Hormonal deficiencies may be isolated to GnRH or involve other hormones as well. Primary growth hormone deficiency is the most common cause. Hypothalamic structural damage is the second most common cause, but a substantial portion of these defects are caused by hyperprolactinemia and are reversible if the hyperprolactinemia is corrected.

In children with isolated disorders of GnRH and gonadotropins, growth and development are normal until puberty, when the expected growth spurt does not occur. About 50% of males with GnRH deficiency have undescended testes, probably secondary to the absence of gonadotropins during fetal development. The most common congenital lesion causing prepubertal GnRH deficiency is Kallmann syndrome. In patients with GnRH deficiency, subcutaneous replacement of GnRH every 2 hours via a portable pump (beginning with a dose of 25 ng/kg per bolus and adjusting upward until there is a rapid increase of FSH and LH so that testosterone levels rise to normal) restores

normal spermatogenesis. Similar approaches in women restore the ovulatory cycles in 80% of patients. In men, comparable results can be obtained with a more practical administration of human chorionic gonadotropin (2000 units 3 times per week subcutaneously under the abdominal skin or intramuscularly into the buttocks) to normalize the serum testosterone within 1 to 2 months. In patients with GnRH receptor mutations, GnRH therapy is not successful; testosterone replacement (intramuscular testosterone cypionate 100 to 200 mg every 2 weeks or 50 to 100 mg every week; or topical gel 1% or 1.62% 50 to 100 mg daily) alone induces adequate androgenization but does not increase testicular size or generate spermatogenesis.[16]

Acquired loss of previously normal GnRH secretion in adulthood may be caused by structural hypothalamic damage (e.g., a tumor), a functional change without a detectable anatomic lesion, or hyperprolactinemia. A CT or MRI is indicated to evaluate possible structural disease. Most cases of functional hypogonadotropic hypogonadism occur in women, especially related to weight loss, excessive exercise with reduced body fat even if body weight is unchanged, psychogenic stress, or systemic illness, but idiopathic forms also are seen. Pulsatile gonadotropin secretion is usually lost, but the gonadotropin response to injected GnRH is normal. Weight gain and reduced exercise can restore normal gonadal function. Furthermore, experimental leptin administration may also restore the normal pulsatile secretion of gonadotropins and subsequent ovulation, thereby confirming that leptin has a critical mediating influence on reproductive function. Postpuberty hyperprolactinemia can also decrease GnRH as well as the pulsatile secretion of LH and FSH, thereby resulting in anovulation with oligomenorrhea and amenorrhea in women and impotence and infertility in men.

In the idiopathic form, spontaneous resolution does not occur. The treatment of idiopathic functional hypogonadotropic amenorrhea focuses on restoration of a normal estrogen status to promote well-being, to prevent osteoporosis, and to facilitate ovulation. The first two usually can be achieved with cyclic estrogen and progesterone (Chapter 218), whereas the latter may require clomiphene, GnRH, or gonadotropin therapy. In men, similar goals may be achieved with testosterone, GnRH, or gonadotropins (see Chapter 216).

Hypothalamic Hypergonadism (Precocious Puberty)

Precocious puberty (Chapter 217) is defined when puberty begins before 8 years of age in girls or 9 years of age in boys.[17] Central (GnRH-dependent) precocious puberty is characterized by hormonal changes similar to what occurs at the time of normal puberty (i.e., an increase in the pulsatile release of LH, an increase in the gonadotropin response to GnRH, and an increase in gonadal steroid secretion). Pseudoprecocious puberty results from peripheral (gonadal or adrenal) causes.[18]

In girls, hypothalamic hamartomas account for only about 15% of cases, other central nervous system lesions for 14%, and McCune-Albright syndrome (polyostotic fibrous dysplasia [Chapter 212]) for 6%; the remaining 65% are idiopathic. GnRH-dependent precocious puberty can be related to premature activation of the GnRH pulse generator by a variety of lesions, or it may also be idiopathic.

Boys represent only about 10% of cases of central precocious puberty, but they often have more serious underlying causes (Chapter 216). For example, hypothalamic hamartomas account for about 40% of boys who have central GnRH-dependent precocious puberty, another 30% are caused by central nervous system lesions, familial disease accounts for about 25% of cases, and the remainder are idiopathic.

The treatment of central GnRH-dependent precocious puberty emphasizes surgical removal of the tumor or medical therapy with a long-acting GnRH analogue, either as monthly injections or yearly implants (see Chapters 216 and 217). When therapy is discontinued at the time of normal puberty, sex steroid levels increase, secondary sexual characteristics again develop, growth increases, and regular menses appear spontaneously.

PROLACTIN

Hypothalamic Hyperprolactinemia

Structural or infiltrative hypothalamic lesions can decrease how much dopamine reaches the lactotrophs and thereby cause modest hyperprolactinemia (usually <100 ng/mL). A nonsecreting pituitary adenoma with extensive suprasellar extension can cause elevated prolactin levels that must be distinguished from a prolactin-secreting adenoma, which usually elevates prolactin levels 5 to 50 times higher (Chapter 205). In patients with very large tumors, the prolactin level should be measured undiluted and at 1 : 100 dilution to avoid spurious findings. A number of medications, especially antipsychotic agents, can cause hyperprolactinemia, primarily by interfering with central catecholamines.

THYROID-STIMULATING AND ADRENOCORTICOTROPIC HORMONE

Hypothalamic hypothyroidism (Chapter 207) is caused by a central lesion that impairs the secretion of TRH, usually along with the loss of other hormones.[19] It occurs considerably less commonly than hypothalamic deficiencies in growth hormone and gonadotropins. Molecular causes of central hypothyroidism include mutations in the TRH receptor and the TSH beta gene that encodes for the TSH β-glycoprotein. In these patients, TSH is less biologically active than normal, so it binds less well to the TSH receptor. Treatment is with L-thyroxine (Chapter 207), and patients should be monitored with free thyroxine (T_4) levels rather than TSH levels.

Hypothalamic lesions rarely cause ACTH deficiency.

EFFECTS OF HYPOTHALAMIC DISEASE ON OTHER NEUROMETABOLIC FUNCTIONS

Other functions that are regulated, at least in part by the hypothalamus include food intake, carbohydrate metabolism, temperature control, sleep, and behavior.

ALTERATIONS IN FOOD INTAKE

Hypothalamic Obesity

Destruction of the mediobasal hypothalamus can suppress the phenomenon of satiety, thereby resulting in hyperphagia and hypothalamic obesity.[20] Because of the location of the lesions, hypopituitarism and diabetes insipidus often coexist. Whether the obesity seen in rare patients with Prader-Willi (Chapter 214) and Laurence-Moon-Biedl-Bardet (Chapter 214) syndromes is caused by hypothalamic dysfunction is unproven.

Hypothalamic Anorexia

Very rare bilateral lesions of the lateral hypothalamus can destroy nigrostriatal dopaminergic fibers that pass through this area, suppress appetite, increase peripheral norepinephrine turnover, and raise the metabolic rate. By comparison, the hormonal changes seen in patients with anorexia nervosa (Chapter 200) are a result of the weight loss, with no evidence for a primary preexisting hypothalamic abnormality.

HYPERGLYCEMIA

The hypothalamic response to stress can release growth hormone, ACTH, and prolactin, which then stimulate gluconeogenesis, lipolysis, and insulin resistance, thereby resulting in elevation of blood glucose levels. This hypothalamic response also activates the sympathetic nervous system, which releases catecholamines that inhibit insulin secretion and stimulate glycogenolysis.

TEMPERATURE REGULATION

Although input regarding body temperature comes from a variety of feedback signals,[21] these signals appear to converge on a common set of neurons in the preoptic area of the hypothalamus. The anterior hypothalamus and preoptic area contain temperature-sensitive neurons that respond to internal temperature changes by initiating the thermoregulatory responses that are needed to restore and maintain a constant temperature. Measures that dissipate heat include cutaneous vasodilation, sweating, and panting; measures that increase body heat include increasing metabolic heat production, shivering, and cutaneous vasoconstriction.

Poikilothermy results from an inability to dissipate or generate heat to keep the body temperature constant in the face of varying ambient temperatures. This condition results from bilateral lesions, possibly due to ischemia, in the posterior hypothalamus and rostral mesencephalon, which are the areas responsible for the final integration of thermoregulatory neural efferents. Patients with this condition are not bothered by temperature changes and typically are unaware that they have such a problem. Depending on the ambient temperature, they may experience life-threatening hypothermia or hyperthermia.

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205 ANTERIOR PITUITARY

ROY E. WEISS

DEFINITION

The pituitary is located in the sella turcica, which is a part of the sphenoid bone of the skull. It is attached to the base of the brain by a stalk, known as the infundibulum, and is contained in a capsule that is continuous with the dura mater, thereby placing it technically outside of the blood-brain barrier. The gland itself is composed of two parts, the anterior pituitary (adenohypophysis) and the posterior pituitary (neurohypophysis). The adenohypophysis has three anatomic components: the pars distalis (where the hormone-secreting cells are situated); the pars tuberalis (which hugs the infundibulum); and the pars intermedia, which is present in children but essentially absent in adulthood. The infundibulum has direct neural fibers that connect to the neurohypophysis, and, in a network of blood vessels, the infundibulum communicates with the adenohypophysis. The inferior border of the pituitary rests on the floor of the sella turcica, and the superior border is located just under the optic chiasm. Growth of the pituitary inferiorly can lead to erosion of the floor of the sella turcica and invasion into the sphenoid bone and sphenoid sinus, whereas the cavernous sinus and carotids are found laterally. Abnormal superior growth of the pituitary explains the visual problems encountered when the pituitary is enlarged by tumor, bleeding, or infiltration because of impingement on the optic chiasm.

The superior and inferior hypophyseal arteries provide the main arterial supply to the anterior and posterior pituitary, respectively (Fig. 205-1). These vessels are branches from the internal carotid arteries. The superior hypophyseal artery forms the primary plexus of the hypophyseal portal system at the origin of the infundibulum. Blood from this plexus flows down the portal vessels. The pars distalis receives very little blood from the internal carotid and instead is mainly supplied by the venous system—long portal veins from the plexus and from the neurohypophysis through short portal vessels. This anatomy allows the pars distalis to be exposed to hormones from the hypothalamus, posterior pituitary, and the general blood circulation. Lack of direct arterial supply to the pars distalis makes it vulnerable to ischemia secondary to hypovolemia and hypotension. For the anterior pituitary, venous drainage is by the hypophyseal veins; for the posterior pituitary, it is via the short portal and hypophyseal veins to the cavernous sinus. The cavernous sinus drains into the inferior petrosal sinuses and then the internal jugular vein.

PATHOBIOLOGY

The Pituitary Axis

The pituitary gland secretes adrenocorticotropic hormone (ACTH), thyroid-stimulating hormone (TSH), luteinizing hormone (LH), follicle-stimulating hormone (FSH), and growth hormone, largely regulated by signals from the hypothalamus (Chapter 204), and it also secretes prolactin, largely regulated by dopamine as well as by thyrotropin-releasing hormone (see Fig. 205-1). The multitude of effects that the hormones of the pituitary have on the physiology and metabolism of the entire body provides exquisite control of hormone secretion regulated via multiple feedback loops and stimuli, not only from the hypothalamus, but also from higher in the brain and in the environment. All pituitary hormones are regulated and secreted with a highly reproducible diurnal variation and with superimposed episodic secretion throughout the day and night and influenced by sleep and wakefulness (Chapter 204). Therefore, measurement of hormone levels must account for the episodic secretion of the hormones, and a single point in time may not reflect the overall activity of the axis. For example, the stress and pain (although minimal) of phlebotomy itself can be sufficient to cause an increase in prolactin and cortisol.

One example of axis regulation is the release of thyroid hormone from the thyroid under the control of thyroid-stimulating hormone from the pituitary thyrotrophs. The more TSH stimulates the TSH receptors on the thyroid cells (thyrocytes), the more thyroid hormone is released. The thyroid hormone then feeds back to the pituitary to downregulate further secretion of TSH, which then turns off thyroid hormone release from the thyrocytes. Superimposed on this process is the hypothalamus, which secretes TRH (thyrotropin-releasing hormone) and stimulates the release of TSH. However, thyroid hormone also provides feedback to the hypothalamus and, independent of TSH, turns off TRH secretion. Therefore the pituitary's thyrotrophs need to integrate the positive stimulation of TRH and at the same time the inhibition by the thyroid hormone levels in order to modulate the level of TSH release. The story is still not complete, because dopamine and other neurotransmitters from centers in the brain above the hypothalamus can stimulate and inhibit TRH, thereby providing an additional level of control over thyroid hormone secretion. Similar multilevel feedback control mechanisms can be described for cortisol from the adrenal gland as well as other pituitary hormones such as the gonadotropins, prolactin, and growth hormone. Understanding the basis for hypothalamic-pituitary-target endocrine gland axis regulation is essential for the diagnosis of abnormalities at specific levels of the axis as interpreted from provocative and suppressive tests used clinically to assess the pituitary axes.

HYPOPITUITARISM

EPIDEMIOLOGY AND PATHOBIOLOGY

Hypopituitarism is a deficiency of one or more pituitary hormones. The prevalence is between 290 and 455 cases per million, with an incidence of 42 cases per million per year. Hypopituitarism can be congenital (with known and unknown genetic causes)[1] and acquired (Table 205-1).[2] Panhypopituitarism refers to a defect in all pituitary hormone lines.

The most common cause of hypopituitarism is a tumor, specifically a macroadenoma in the sella. Tumor enlargement within the confines of the bony sella turcica can compress the normal pituitary cells, thereby resulting in their failure to function. Irradiation of the pituitary, pituitary infarction (such as

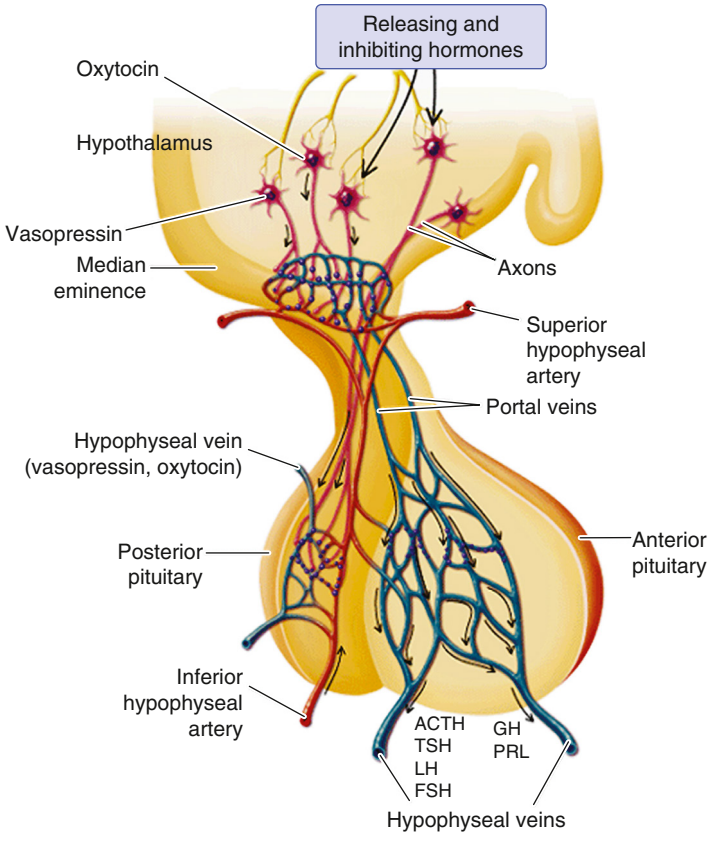

FIGURE 205-1. Structural-functional, humoral, endocrine, and neuroendocrine relationships within the hypothalamic-pituitary unit emphasize the unique and intimate interdependence of neural structures and hormone secretion with the circulation. Oxytocin and vasopressin neuron bodies located in the hypothalamus send axons through the pituitary stalk that terminate in the posterior pituitary, where they release oxytocin and vasopressin into blood vessels within the posterior pituitary. Hypothalamic neurons that produce growth hormone–releasing hormone, corticotropin-releasing hormone, thyrotropin-releasing hormone, and gonadotropin-releasing hormone send their axons through the median eminence to terminate and release their hormones into the hypophyseal-portal circulation. This network of blood vessels is located at the median eminence, which surrounds the pituitary stalk and penetrates into the anterior lobe of the pituitary. These hypothalamic neurohormones stimulate responsive anterior pituitary cells to secrete growth hormone (GH), adrenocorticotropic hormone (ACTH), thyroid-stimulating hormone (TSH), luteinizing hormone (LH), and follicle-stimulating hormone (FSH), respectively. Dopamine neurons reaching the median eminence are responsible for tonic inhibition of prolactin (PRL) secretion from the anterior pituitary, whereas somatostatin released from somatostatinergic neurons inhibits the release of GH and thyrotropin-releasing hormone. (From Melmed S. *The Pituitary,* 3rd ed. London: Elsevier; 2011.)

ABSTRACT

The anterior pituitary, which is the command center for the majority of endocrine organs, regulates the adrenal, thyroid, and gonads as well as being responsible for the release of growth hormone and prolactin. Diseases of the anterior pituitary can result in abnormally low or high secretion of one or more of the hormones. Diagnosis of these conditions requires astute clinical skills to suspect the syndromes of hormone deficiency or excess, as well as rational provocative testing, based on the physiology, and selective imaging. Treatment either replaces the deficient hormones or uses medical or surgical intervention to correct hypersecretory states.

KEYWORDS

adenoma
hypopituitarism
Cushing
acromegaly
transsphenoidal adenomectomy
hypogonadism
stimulation testing

TABLE 205-1 CONGENITAL AND ACQUIRED CAUSES OF HYPOPITUITARISM

CONGENITAL EMBRYOPATHIC DEFECTS
Anencephaly
Midline cleft defects: septo-optic dysplasia, basal encephalocele, cleft lip and palate
Pituitary aplasia
Kallmann syndrome (GnRH defect with anosmia)
ACQUIRED DEFECTS
Tumors: pituitary adenomas, craniopharyngiomas, dysgerminomas, meningiomas, gliomas, metastatic tumors, hamartomas, Rathke cleft cysts
Irradiation
Trauma: surgery, external blunt trauma (Chapter 368)
Empty sella syndrome
Vascular
Pituitary apoplexy
Sheehan syndrome
Internal carotid aneurysm
Vasculitis (Chapter 249)
Subarachnoid hemorrhage (Chapter 377)
Inflammatory and infiltrative diseases
Sarcoidosis (Chapter 83)
Histiocytosis (Chapter 155)
Tuberculosis (Chapter 299), syphilis (Chapter 295)
Granulomatosis with polyangiitis (Chapter 249)
Meningitis (Chapter 381)
Lymphocytic hypophysitis, infundibulohypophysitis
Metabolic defects
Hemochromatosis (Chapter 196)
Amyloidosis (Chapter 174)
Critical illness (Chapter 88)
Malnutrition (Chapter 197 and 198)
Anorexia nervosa (Chapter 200)
Psychosocial deprivation
Idiopathic

GnRH = gonadotropin-releasing hormone.

Sheehan syndrome, which is caused by severe postpartum bleeding[3]), surgical intrusion, and infiltrative disease also can compromise normal pituitary functioning.

Genetic defects have been reported at every level of the hypothalamic pituitary axis, including defects in the hypothalamic factors, receptors for the hypothalamic factors, and the genes for the pituitary hormones. Defects in the genes coding for the specific hormone almost always result in a low serum concentration of the hormone.

Although congenital hypopituitarism may involve deficiency of a single or multiple pituitary hormones, acquired types of hypopituitarism usually simultaneously involve more than one of the pituitary hormones. Defects in genes encoding for factors such as the *PIT1* and *PROP1* genes may impair pituitary cell differentiation. Furthermore, the pituitary hormone receptor in the respective glands may be defective, thereby resulting in resistance to the action of the pituitary hormones. Finally, genetic defects in the gene coding for the hormone or the hormone's receptor can result in profound hormone deficiency.

Functional causes of defective pituitary function can be seen in severe malnutrition (Chapter 197), in anorexia nervosa (Chapter 200), or in critically ill patients who are in a state of severe calorie deprivation. In these situations, central (hypothalamic and higher) mechanisms and molecular mediators (e.g., cachexins and tumor necrosis factor) inhibit the release of pituitary hormone. This form of hypopituitarism is generally reversible when the caloric situation improves.

Traumatic brain injury (Chapter 368) is an increasingly recognized cause of hypopituitarianism.[4] Deposition and infiltration of amyloid protein in amyloidosis (Chapter 174), iron in hemochromatosis (Chapter 196) or granulomas (in sarcoidosis [Chapter 83], tuberculosis [Chapter 299], or granulomatosis with polyangiitis [Chapter 249]) also can cause hypopituitarism. Invasion of the hypothalamus and pituitary by histiocytosis (Chapter 155) or metasteses from breast cancer, lung cancer, melanoma, and rarely, colon cancer can impair pituitary function. Hypopituitarism is also a rare complication of infection with human immunodeficiency virus (HIV) or severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2).

In addition to congenital and acquired pituitary defects, hypopituitarism may result from a hypothalamic disorder (Chapter 204). Concurrent diabetes insipidus, which is indicative of dysfunction of the posterior pituitary (Chapter 206), usually suggests combined hypothalamic and pituitary defects. Hyperprolactinemia, which suggests interruption of the hypothalamic dopaminergic inhibition of prolactin, also can be a result of hypothalamic defects.

CLINICAL MANIFESTATIONS

Congenital defects are usually noted soon after birth when an absent pituitary hormone results in growth retardation or failure to develop. Patients may also present with congenital failure of a specific pituitary function and manifest with early-onset growth defects, delayed puberty, or hypothyroidism.

Acquired hypopituitarism presents earlier in its course in women of reproductive age because any perturbation in the hypothalamic pituitary milieu will likely result in an abnormality of the menstrual cycle (Chapter 218), which requires orchestration of multiple hormones that are exquisitely sensitive to changes in the pituitary hormones. By comparison, males of all ages and women of postreproductive age usually have hypopituitarism for several years before the diagnosis is made. In such patients, the symptoms can be nondescript (e.g., fatigue, decreased muscle strength and muscle mass, and increased body fat) and not appreciated for many years after the onset of hypopituitarism.

Although growth hormone deficiency can exist in up to 60% of patients with hypopituitarism, such deficiency in an adult is not likely to cause the same remarkable symptoms as the short stature that is seen in children. When multiple hormones are deficient, the manifestations in adulthood may be as subtle as skin changes, decreased sexual functioning, decreased muscle mass, and increased fat mass.

DIAGNOSIS

Diagnosis of hypopituitarism in patients with secreting or nonsecreting pituitary masses usually involves a combination of static and stimulatory blood tests (Table 205-2) beginning with morning fasting level of ACTH, TSH, FSH, LH, growth hormone, and prolactin. If multiple deficiencies are found, panhypopituitarism is likely. Isolated deficiencies in only one pituitary hormone can occur, but if two or more are deficient, it is likely that all are deficient. Testing (Table 205-2) often depends on the age of the patient and the clinical setting. Oftentimes, no single gold-standard test is available for each hormone, so equivocal results on one test may require another test. For example, growth hormone reserve in children is usually best documented with an arginine stimulation test, whereas an insulin tolerance test would be more appropriate in an adult in whom the ACTH axis should be evaluated at the same time. Sometimes multiple tests may be performed if results of one test are equivocal.

The next diagnostic imperative is to image the pituitary to determine the cause. Magnetic resonance imaging (MRI) is the preferred radiologic method for anatomic definition of the pituitary and its surrounding structures. The normal pituitary is less than 1 cm in height, and a small tumor (microadenoma) can be as small as 1 mm, so high-quality imaging is necessary. Sagittal and coronal images are the most useful to obtain (Fig. 205-2). Intravenous contrast can enhance MRI images because normal pituitary generally enhances more than tumors. When the use of a contrast agent is not contraindicated, T2 images may be helpful to distinguish normal pituitary from a tumor (Fig. 205-3). In such cases, helical computed tomography (CT) also can be useful with noncontrast and immediate postcontrast imaging.

TREATMENT

Treatment includes replacement of the deficient hormones (Table 205-3) but also must address the underlying cause (see Table 205-1), such as hypophysitis, empty sella syndrome, pituitary apoplexy, infiltrating diseases, malnutrition, and pituitary tumors.

PRIMARY DISEASES OF THE ANTERIOR PITUITARY

HYPOPHYSITIS

EPIDEMIOLOGY AND PATHOBIOLOGY

Inflammation of the pituitary is known as hypophysitis and can be classified clinically as primary hypophysitis when isolated inflammation of the pituitary is not associated with other inflammatory conditions, infections, or medications, including checkpoint inhibitors.[5] Lymphocytic hypophysitis,

TABLE 205-2 TESTS TO DIAGNOSE PITUITARY INSUFFICIENCY

HORMONE	TEST	INTERPRETATION
Growth hormone (GH)	*Insulin tolerance test:* Regular insulin (0.05-0.15 U/kg) is given IV, and blood is drawn at −30, 0, 30, 45, 60, and 90 min for measurement of glucose and GH.	If hypoglycemia occurs (glucose <40 mg/dL), GH should increase to >5 µg/L*
	Arginine-GHRH test: GHRH 1 µg/kg IV bolus followed by 30-min infusion of L-arginine (0.5 g/kg up to 30 g)	Normal response is GH >4.1 µg/L
	Glucagon test: 1 mg IM with GH measurements at 0, 60, 90, 120, 150, and 180 min	Normal response is GH >3 µg/L
	Arginine-L-DOPA test: L-DOPA 500 mg PO at start of arginine 30 g in 10% solution IV infusion over 30 min, blood sampled at 30, 60, 90, 120 min	Normal response is GH >1.5 µg/L
Adrenocorticotropic hormone (ACTH)	*Insulin tolerance test:* Regular insulin (0.05-0.15 U/kg) is given IV, and blood is drawn at −30, 0, 30, 45, 60, and 90 min for measurement of glucose and cortisol.	If hypoglycemia occurs (glucose <40 mg/dL), cortisol should increase by >7 µg/dL or to >20 µg/dL
	CRH test: 1 µg/kg ovine CRH IV at 8 AM, with blood samples drawn at 0, 15, 30, 60, 90, and 120 min for measurement of ACTH and cortisol	In most normal individuals, the basal ACTH increases two- to four-fold and reaches a peak (20-100 pg/mL). ACTH responses may be delayed in cases of hypothalamic dysfunction. Cortisol levels usually reach 20-25 µg/dL
	ACTH stimulation test: $ACTH_{1-24}$ (cosyntropin), 0.25 mg IM or IV. Cortisol is measured at 0, 30, and 60 min.	A normal response is cortisol >18 µg/dL. In suspected hypothalamic-pituitary deficiency, a low-dose (1-µg) test may be more sensitive
Thyroid-stimulating hormone (TSH)	*Basal thyroid function tests:* free T_4, free T_3, TSH	Low free thyroid hormone levels in the setting of TSH levels that are not appropriately increased
Luteinizing hormone (LH), follicle-stimulating hormone (FSH)	*Basal levels of LH, FSH, testosterone, estrogen*	Basal LH and FSH should be increased in postmenopausal women. Low testosterone levels in conjunction with low or low-normal LH and FSH are consistent with gonadotropin deficiency
Prolactin	*Basal level of Prolactin*	The low range of prolactin levels in men and women is not established and depends on the assay. If prolactin is undetectable, deficiency is likely. Levels lower than 10 ng/mL indicate a possible deficiency

*Values are with polyclonal assays.
ACTH = adrenocorticotropic hormone; CRH = corticotropin-releasing hormone; FSH = follicle-stimulating hormone; GH = growth hormone; GHRH = growth hormone–releasing hormone; IM = intramuscularly; IV = intravenously; LH = leutinizing hormone; PO = orally; T_3 = triiodothyronine; T_4 = thyroxine; TSH = thyroid-stimulating hormone.

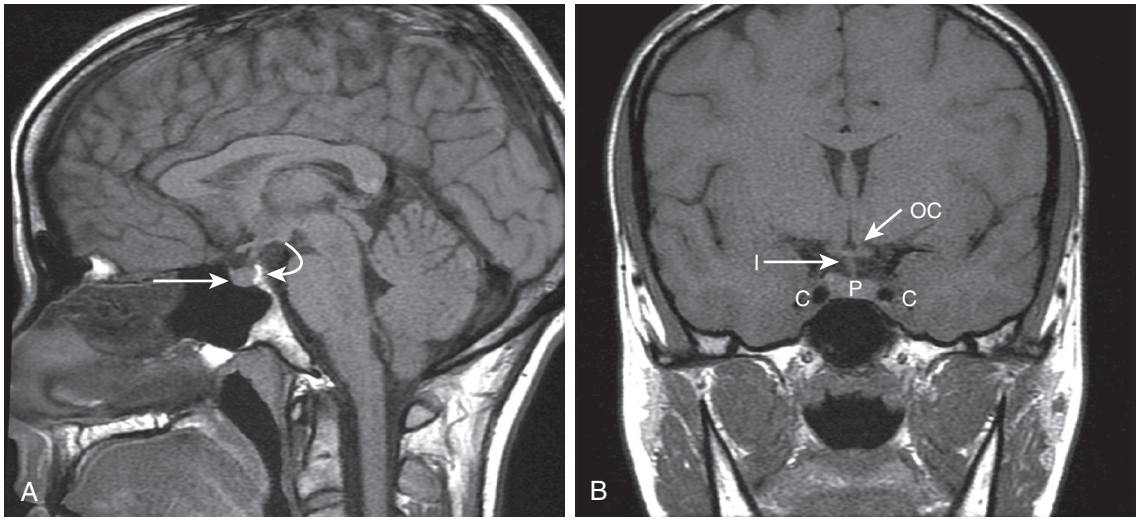

FIGURE 205-2. Magnetic resonance image of normal pituitary. A, Sagittal postcontrast. Normal anterior pituitary (*long arrow*), posterior pituitary (*curved arrow*). **B**, Coronal postcontrast image shows homogeneously enhancing gland (P) and stalk (I). Note the carotid arteries (C), easily depicted by their flow voids. Optic chiasm (OC) is the cranial nerves within the cavernous sinuses.

which is the most common form of this rare condition, occurs three times more frequently in women, typically in the fourth decade and often related to the end of pregnancy or the first few months after delivery. Lymphocytic hypophysitis is also seen in about 3 to 8% of patients treated with immune checkpoint inhibitors, specifically with the anti–CTLA-4 class of inhibitors, with peak onset at a median of 2.3 months after starting therapy.[6] The other histologic types, granulomatous and xanthomatous hypophysitis, are not associated with pregnancy although they are more common in females. The least common form, plasmacytic or IgG4-related hypophysitis, occurs in males in a 2:1 ratio, usually presents in the seventh decade, and may include orbital inflammation, hypertrophic pachymeningitis, and central nervous system parenchymal disease.

CLINICAL MANIFESTATIONS AND DIAGNOSIS

Patients with hypophysitis usually present with headaches and multiple deficiencies of anterior pituitary hormones. Diabetes insipidus (Chapter 206) is reported in about 50% of patients, and most have associated mild hyperprolactinemia.

On MRI, hypophysitis usually causes diffuse pituitary enlargement and thickening of the midline stalk, with a normal sellar size, but MRI cannot reliably differentiate hypophysitis from a pituitary adenoma.

Definitive diagnosis is usually made by biopsy. A clinical diagnosis can, however, be inferred based on radiologic and clinical characteristics during or just after pregnancy or if there is a proximal history of use of anti–CTLA-4 agents several months prior to the onset of symptoms (headaches and weakness).

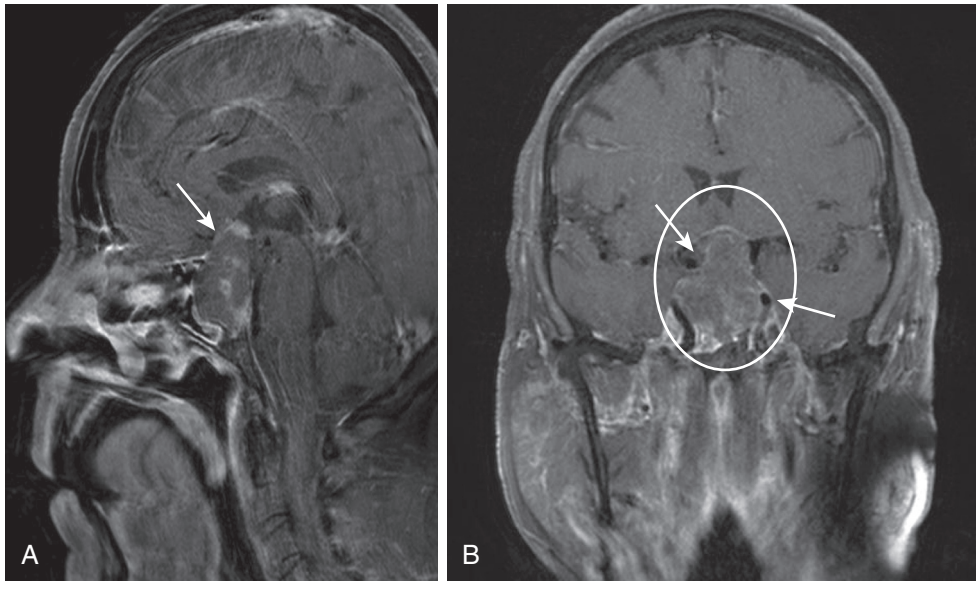

FIGURE 205-3. **Magnetic resonance image of a large pituitary macroadenoma. A**, Sagittal postcontrast. Note the extension of the tumor (*arrow*) below and above the sella. **B**, Coronal postcontrast. Large tumor is encircled with displacement of the carotid arteries (*arrow*), erosion of the floor of the sella turcica, and extension into the sinuses.

TABLE 205-3 HORMONAL REPLACEMENT THERAPY IN HYPOPITUITARISM*

PITUITARY AXIS	HORMONAL REPLACEMENTS
Growth hormone (GH)	In children, GH (0.25 mg/kg) SQ daily. In adults, GH (0.3-1.2 mg) SQ daily. Titrate dose to achieve IGF-I levels in middle to upper part of normal range. Women receiving oral estrogens require higher doses.
Prolactin	None; although not clinically available, human recombinant prolactin has been used
Adrenocorticotropic hormone–cortisol	Hydrocortisone (10-15 mg PO q AM; 5-10 mg PO q PM) or prednisone (2.5 mg PO q AM; 2.5 mg PO q PM). Dose adjusted on clinical basis. Stress dosing: 50-75 mg hydrocortisone IV q8h
Thyroid-stimulating hormone–thyroid	L-thyroxine (0.075-0.15 mg) PO daily
Gonadotropins–gonads	FSH and LH (or HCG) can be used to induce ovulation in women. HCG alone or with FSH can be used to induce spermatogenesis in men. In men, testosterone enanthate (100-300 mg) IM q1-3 wk or testosterone cyclopentylpropionate (100-300 mg) IM q1-3 wk. Testosterone transdermal patches can also be used (5 mg daily). Testosterone gel 5-10 g daily† In women, conjugated estrogens (0.625-1.25 mg) PO days 1-25 each month, cycled with medroxyprogesterone acetate (5-10 mg) PO days 15-25 each month. Low-dose contraceptive pills may also be used. Estrogen-containing transdermal patches are also available.
Posterior pituitary	Desmopressin, 0.05-0.2 mL (5-20 µg) intranasally once or twice daily, or tablets (0.1-0.4 mg q8-12h), or 0.5 mL (2 µg) SQ

*Replacement therapy is dictated by the types of hormone deficiencies and by the clinical circumstances. In each case, the recommended preparations and doses are representative but need to be adjusted for individual patients. Other hormonal preparations are also available.

†Several oral formulations of testosterone undecanoate have recently been approved by the FDA based on single arm trials in hypogonadal men. (https://secure.medicalletter.org/TML-article-1662b.)

FSH = follicle-stimulating hormone; GnRH = gonadotropin-releasing hormone; HCG = human chorionic gonadotropin; IGF-I = insulin-like growth factor-I; IM = intramuscularly; LH = luteinizing hormone; PO = orally; SQ = subcutaneously.

TREATMENT AND PROGNOSIS

Surgery is indicated when a biopsy is needed for diagnosis or if there is a mass effect. Careful pituitary function testing and repletion of physiologic hormone levels[7] are mandatory, even in patients who do not undergo surgery because they might otherwise die from undiagnosed adrenocortical insufficiency. Stress doses of corticosteroids (e.g., 50 to 75 mg hydrocortisone IV every 8 hours) are indicated perioperatively.

The prognosis is unclear, but both the structural and functional abnormalities can occasionally resolve spontaneously. Glucocorticoids in physiologic doses may have a direct effect on limiting the lymphocytic invasion in lymphocytic hypophysitis, but there are no prospective treatment trials.

TABLE 205-4 PREDISPOSING CONDITIONS ASSOCIATED WITH PITUITARY APOPLEXY

- Pituitary Tumor
  - Nonfunctioning pituitary macroadenoma
  - Certain functional tumors
- Hypertension and/or hypotension
- Surgery
  - Cardiac surgery (heart lung bypass; coronary artery grafts)
  - Major orthopedic procedures
- Drugs
  - Cabergoline
  - Bromocriptine
  - Endocrine stimulation tests (thyrotropin-releasing hormone stimulation; insulin tolerance test)
  - Anticoagulants
  - Estrogen
- Head Trauma
- Pregnancy and delivery (when significant hemorrhage and hypovolemia occurs, called Sheehan syndrome)
- Infections
  - Dengue fever
  - Hypophysitis
- Radiation therapy
- Diabetes, poorly controlled
- Sickle cell anemia

PITUITARY APOPLEXY

The pituitary can be involved with hemorrhage, infarction, or both. When abrupt, and sometimes catastrophic, hemorrhagic infarction occurs in the pituitary, it is defined as apoplexy.[8]

EPIDEMIOLOGY AND PATHOBIOLOGY

Certain conditions predispose a patient to pituitary apoplexy (Table 205-4). Although all large pituitary tumors are at risk for hemorrhagic infarction, certain functional pituitary tumors, such as those in Cushing disease or acromegaly, may be particularly prone. In women who have microprolactinomas treated with dopamine agonists, stopping the agonist while pregnant can precipitate pituitary apoplexy.[9] Nearly 25% of all patients with apoplexy have inadequately treated hypertension. The main symptoms and consequences of apoplexy are due to the increased pressure present within the bony walls of the sella turcica in which the pituitary resides. A sudden increase in the sellar contents, due to blood and edema, results in increased pressure. This increased pressure and meningeal irritation are responsible for the neurologic symptoms, including the increased pressure in the cavernous sinus and the cranial nerve palsies, as well as bitemporal hemianopsia. Extravasation of blood into the subarachnoid space causes meningeal irritation. Asymptomatic hemorrhage and infarction into a pituitary tumor can occur in 10 to 25% of patients, but true apoplexy occurs in only 2 to 10% of pituitary tumor patients.

CLINICAL MANIFESTATIONS

The most common presenting complaint, headache, can present variably from retro-orbital to unilateral to bilateral temporal headaches during the acute phase of apoplexy. The constellation of headache, vomiting, visual impairment, and altered consciousness with hemodynamic instability is not specific for pituitary apoplexy but raises suspicion for the diagnosis (Table 205-5). Often, this dramatic presentation is the first time the patient is aware of a potential pituitary tumor. As the hemorrhagic infarction resolves, the patient often is left with hypopituitarism.

DIAGNOSIS

Prompt recognition of patients presenting with the triad of headache, vomiting, and visual disturbances is required to prevent death or irreversible neurologic impairment. Clinical evaluation of the patient should begin with a thorough history from the patient, if sufficiently conscious to give one, or from family members. A history of a pituitary tumor should raise the suspicion of apoplexy. More subtle abnormalities associated with pituitary dysfunction (hypofunctioning of thyroid, adrenal, or gonadal systems) may be helpful.

The cornerstone for diagnosis is urgent MRI T2-weighted images. A CT scan can be useful when an MRI is not available or possible.

Urgent measurement of blood chemistries, including electrolytes, kidney function, liver function, complete blood count with platelets, and prothrombin time, can be useful. Because more than 80% of patients will have endocrine dysfunction, urgent measurement of free T_4, TSH, prolactin, and random cortisol can be helpful. Less rapidly available and helpful (and less important in the initial diagnosis and management) are other pituitary hormones such as LH, FSH, estradiol or testosterone, growth hormone, and IGF-I.

Examination of cerebrospinal fluid (CSF) is usually not diagnostic and is unnecessary if the diagnosis of apoplexy is certain. However, if there is bleeding into the CSF as a result of the apoplexy, red blood cells as well as an elevated protein level and xanthochromia can be seen.

TABLE 205-5 SIGNS AND SYMPTOMS OF PITUITARY APOPLEXY

SYMPTOM	APPROXIMATE INCIDENCE
Headache	95%
Vomiting	70%
Vision Defects:	
Visual field defect	65%
Decreased visual acuity	50%
Diplopia (CN III, IV, V, and VI)	40-100%
Hemiplegia	Rare
Meningismus	Rare
Hypotension (cardiovascular collapse)	95%

CN = cranial nerves.

The differential diagnosis of pituitary apoplexy should include other conditions that result in the symptoms of headache, vomiting, visual disturbances, and hemodynamic instability such as infection (meningitis [Chapter 381]), cavernous sinus thrombosis (Chapter 376), migraine (Chapter 367), Rathke cyst hemorrhage (Chapter 377), and hyperemesis gravidarum (Chapter 221). Each of these conditions is itself a medical emergency that requires specific treatment.

TREATMENT

The initial management is stabilization of the hemodynamic status with intravenous 0.9% NaCl boluses to maintain normal tissue perfusion, usually accompanied by high-dose parenteral glucocorticoids (100 mg hydrocortisone every 8 hours intravenously). Emergent surgical decompression may be required in patients who have progressive visual or neurologic impairment.

Although 80% of patients have residual hypopituitarism following apoplexy (with or without surgical decompression), some patients do not display immediate evidence of hypopituitarism. A month after discharge from the hospital and recovery from the acute event, patients should have repeat endocrine testing to determine if the endocrine defect persists. Repeat testing will confirm whether the patient needs to remain on lifelong hormone replacement therapy.

Recurrent apoplexy can occur. MRI of the pituitary should be obtained at 3- to 6-month intervals until the anatomy is stable and then yearly for 5 years.

EMPTY SELLA

Empty sella is a radiologic diagnosis that refers to the observation on imaging of the presence of CSF in the sella turcica accompanied by a flattened pituitary gland (Fig. 205-4). An empty sella is usually noted as an incidental finding when an MRI or CT scan of the skull is performed because of problems unrelated to the pituitary. It can be primary or acquired when a defect in the diaphragma sella allows the arachnoid membrane to herniate into the sella.[10] Patients with acquired empty sella may have a prior history of an infarcted pituitary, surgery, or radiation. If the herniation has been present for years, the sella enlarges, probably owing to persistent exposure to intracranial pressure. Primary empty sella is more frequent in women and may be accompanied by benign intracranial hypertension (Chapters 175 and 367).

In asymptomatic patients, there is no need to measure hormone levels unless there is suspicion of a clinical abnormality related to the pituitary. Pituitary function is usually normal, but about 10% of patients also have mild hyperprolactinemia, probably owing to stretching of the pituitary stalk. Because pituitary function is usually normal, no specific treatment is required. However, if there is concern about possible hypopituitarism, investigation as outlined earlier for hypopituitarism (see Table 205-2) should be undertaken.

PITUITARY TUMORS

EPIDEMIOLOGY AND PATHOBIOLOGY

Pituitary adenomas have an incidence of about 4 to 7 cases per 100,000 and a prevalence of about 1/1000 population.[11] Clonal proliferation of any of the different cell types in the pituitary result in the formation of tumors. Pituitary

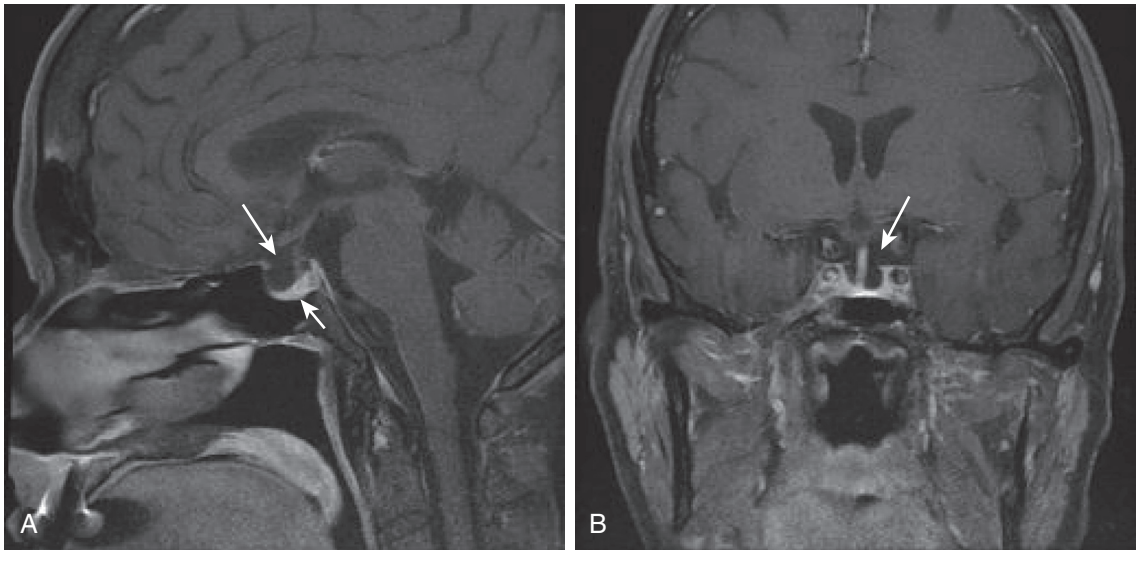

FIGURE 205-4. **Magnetic resonance image of an empty sella. A,** Sagittal postcontrast. Note the void in the sella (*large arrow*) with compression of the normal pituitary against the sella turcica (*small, thin arrow*). **B,** Coronal postcontrast. Sella filled with cerebrospinal fluid and appears as empty.

tumors are classified clinically as functioning if they produce one or more hormones in excess or nonfunctioning if they do not produce excess hormone in blood.[12] Because most functional tumors do not have appropriate physiologic feedback owing to their oncologic nature, they usually cause the clinical syndrome of the excess hormone. However, some functional tumors do not result in excess blood levels of the hormone, owing to a defect in intracellular processing or release.

Prolactinomas, which may account for up to 50% of pituitary tumors, are likely caused when proliferation of the lactotroph results in excess prolactin, with subsequent galactorrhea and hypogonadism. Somatotrophs producing growth hormone, corticotrophs making ACTH, and gonadotrophs making LH and FSH together account for 10 to 20% of adenomas. Nonfunctioning tumors, which mainly cause a mass effect or hypopituitarism, account for 10 to 25%. In addition to functioning and nonfunctioning, tumors are classified by their anatomy based on imaging studies. Microadenomas are less than 10 mm in diameter, whereas macroadenomas are greater than 10 mm in diameter (and typically with extrasellar extension).

Pituitary adenomas are monoclonal and can be locally invasive, but they are rarely malignant. The somatic mutations causing most pituitary tumors remain unknown, but at least six types of inherited predispositions to pituitary tumors are recognized (Table 205-6). When macroadenomas are found in children or when there is a family history of pituitary adenomas, genetic testing is warranted so that appropriate monitoring can occur before the patient is symptomatic. Local expansion of the tumor can cause headaches. The mass effect of the tumor is also responsible for the temporal visual field defects associated with macroadenomas that expand into the suprasellar region and abut against the optic chiasm.

CLINICAL MANIFESTATIONS

The clinical manifestations of pituitary tumors depend in large part on whether they are functional and whether their size compromises the normal function of the pituitary gland and thereby results in clinical symptoms of hypopituitarism.[13] In general, the diagnosis of a tumor due to excess or diminishing hormone secretion presents the greater clinical challenge.

The size of the tumor usually is proportional to the amount of hormone it produces when functioning. Certain tumors are usually diagnosed sooner and therefore are usually smaller on diagnosis than others. For example, gonadotropinomas are usually diagnosed as macroadenomas because their symptoms are usually more subtle than TSH-secreting tumors, in which the symptoms present early so the tumors are usually smaller at the time of diagnosis.

As is true for hypopituitarism of all causes, pituitary tumors have historically been diagnosed more frequently in women of reproductive age because even a slight perturbation in hormonal milieu will disrupt the multiple hormone interactions necessary for a normal menstrual period (Chapter 219). In men or postmenopausal women, slight perturbations in hormone levels (either excess or deficiency) are usually not noticed for several years. More recently, the diagnosis of pituitary adenomas is often an incidental finding on an imaging study obtained for unrelated reasons (e.g., a motor vehicle accident, headaches, or a nonpituitary intracerebral mass effect), and a pituitary microadenoma is an incidental finding. These findings are referred to as "incidentalomas" that otherwise would have avoided clinical detection because they are either silent or subclinical. Incidentalomas can be found in up to 10% of some autopsy series, so they are more common than pituitary tumors found during life. Even after careful endocrine evaluation of patients with incidental tumors, hyper- or hyposecretion of pituitary hormones is found in only a small percentage, and such incidental tumors usually do not increase in size over time.[14]

Other than hormonal effects, reasons for suspicion of a pituitary mass are headaches and visual field abnormalities. A reported 33 to 72% of patients with a pituitary lesion have headaches, a percentage that is greater than the 22% of women and 11% of men in the general population who complain of headaches (Chapter 367), but discerning which patients have a headache from the pituitary lesion and which ones have an unrelated cause for the headache is challenging. Headaches due to pituitary lesions are more common in females and in patients with Rathke cleft cysts and apoplexy.

Severely impaired visual fields can be revealed on examination by confrontation testing. The superior and temporal visual fields are most affected.

MRI is the cornerstone of diagnosis for nonfunctioning tumors and key for the evaluation of functioning tumors. If there is any evidence on MRI that the tumor is close to or abuts the chiasm, formal visual field testing should be performed. Specific diagnosis of pituitary adenomas that are actively secreting a hormone is based on basal hormone levels followed by provocative testing (Table 205-7).

TREATMENT

Surgery

The first line of therapy for pituitary tumors that require treatment is surgery (Video 205-1). The major exception is for prolactinomas (even those that are macroadenomas and result in visual field cuts, headaches, and evidence of selected hypopituitarism), for which medical therapy is the first mode of treatment. Indications for surgery include decompression of mass effects, prevention of further tumor expansion, and normalization of hormone levels. The endoscopic transsphenoidal approach is the standard for decompression or extirpation. Subfrontal craniotomy is reserved for tumors requiring extensive extrasellar exploration. Transsphenoidal surgery is effective, with a less than 5% complication rate and 1% mortality rate in experienced centers, but potential sequelae include sinusitis, hemorrhage, CSF leak, hypopituitarism, and optic nerve injury. About 5% of patients develop transient postoperative diabetes insipidus that rarely persists. About 80 to 90% of microadenomas and only 30 to 60% of macroadenomas are completely cured by transsphenoidal hypophysectomy, but most other patients substantially improve in terms of their hormone levels.

Radiation Therapy

Irradiation (typically 45 Gy) can be adjunctive therapy after surgery or used in combination with medical therapy after curative surgery has failed, based on radiographic or endocrine testing, or when surgery is unable to remove the tumor completely. CyberKnife stereotactic radiotherapy can deliver the same total dose in one treatment as would be provided by traditional external beam radiotherapy over 5 weeks. CyberKnife therapy spares critical radiosensitive structures, but the response can take months up to several years. Proton beam therapy may be performed for intrasellar lesions but is not widely available. Irradiation provides complete remission, and it is most useful for nonfunctioning macroadenomas and for patients who have some residual postoperative tumor or visible tumor. Complications are generally dose related and include partial or complete hypopituitarism (50 to 70% of patients), second tumors in the radiation field (about 2% of patients over a 20-year period), cognitive dysfunction, damage to the optic nerve, and stroke. Stereotactic radiotherapy appears to cause similar complication rates of hypopituitarism but less stroke compared with conventional external beam therapy.

Medical Therapy

Medical therapy varies by the type of tumor (see later for details). Medical therapy is the primary treatment for prolactinomas but is a secondary option when surgery is not curative or is contraindicated by other pituitary tumors.

TABLE 205-6 INHERITED SYNDROMES OF PITUITARY ADENOMAS

SYNDROME	PITUITARY TUMOR	MOLECULAR PATHOGENESIS	MODE OF INHERITANCE	OTHER MANIFESTATIONS
McCune Albright	F/NF	*Gsα SU*	Somatic mutation	Ovary, bone, thyroid dysfunction
Multiple endocrine neoplasias*	F (30% PRL)/NF	Menin (*MEN1*) and MEN4 (*CDKN1B*)	AD	Parathyroid and pancreas tumors
Familial isolated pituitary adenoma (FIPA) syndrome*	F/NF	Arylhydrocarbon receptor interacting protein (*AIP*)	AD with variable penetrance	None
Carney complex (with or without PPNAD)	1/3 with Cushing	Type 1A regulatory subunit of protein kinase A (*PRKARIA*)	AD	Atrial myxomas, spotty skin pigmentation, schwannomas
Primary pigmented nodular adrenocortical disease (PPNAD)	Cushing	Succinate dehydrogenase subunit (*SDH*)	AD	Pheochromocytomas, paragangliomas
Early childhood gigantism	GH	*CD40LG, ARHGEF6, RBMX, GPR101*	X-linked	Gigantism

*Tumors are generally more aggressive and occur at a younger age.

AD = autosomal dominant; F = functioning; GH = growth hormone; NF = nonfunctioning; PPNAD = primary pigmented nodular adrenocortical disease; PRL = prolactin.

TABLE 205-7 SELECTED TESTS TO CONFIRM EXCESS PITUITARY FUNCTION

HORMONE	TEST	INTERPRETATION
Growth hormone (GH)	*Basal IGF-I*	Elevated IGF-I levels are consistent with acromegaly when interpreted in the context of age and nutritional status.
	Oral glucose suppression test: after 75-g glucose load, GH is measured at −30, 0, 30, 60, 90, 120 min.	GH should be suppressed to <1 μg/L in normal persons with polyclonal radioimmunoassays; <0.4 μg/L with two-site monoclonal assays. GH may paradoxically increase in acromegaly.
Prolactin	*Basal prolactin levels*	Elevated prolactin (>200 μg/L) is consistent with a prolactinoma. When prolactin levels are between 20 and 200 μg/L, other causes of hyperprolactinemia should be considered.
Adrenocorticotropic hormone (ACTH)	*Measurement of 24-hr urine free cortisol*	Elevated level is suggestive of Cushing syndrome, but it has several other causes as well.
	Midnight salivary cortisol: special tubes with cotton pledgets available to collect saliva at 11 PM to midnight	In normal persons, the midnight salivary cortisol is very low because of the normal diurnal variation. In patients with Cushing syndrome, the salivary cortisol is elevated.
	Overnight dexamethasone suppression test: dexamethasone (1 mg) PO at midnight, followed by 8 AM plasma cortisol	In normal persons, AM cortisol should be suppressed to <5 μg/dL. Normal test excludes Cushing syndrome. Other disorders can cause failure to suppress normally.
	CRH test: ovine CRH (1 μg/kg) is administered IV, and ACTH and cortisol are drawn at −15, 0, 15, 30, 60, 90, and 120 min.	In Cushing disease, there is usually a 50% increase in ACTH and a 20% increase in cortisol. Adrenal adenoma is associated with suppressed ACTH. Ectopic ACTH is associated with high basal ACTH and cortisol levels that are not affected by CRH.
	Petrosal sinus ACTH sampling: the inferior petrosal sinus is catheterized bilaterally, and plasma ACTH is compared with simultaneous peripheral samples. The sampling can be done in conjunction with CRH or vasopressin stimulation.	In Cushing disease, the ratio of ACTH in the petrosal sinus to the periphery is at least 2 basally and at least 3 after CRH. In ectopic ACTH, the ratio of petrosal sinus to peripheral level is <1.5.
Thyroid-stimulating hormone (TSH)	*Basal thyroid function tests*	An inappropriate normal or elevated TSH in the setting of increased free thyroid hormone levels is consistent with a TSH-producing tumor or other causes of inappropriate TSH secretion.
	Free α-subunit level	Elevated levels associated with inappropriately elevated TSH are suggestive of a TSH-producing tumor.
Follicle-stimulating hormone (FSH), luteinizing hormone (LH)	*Basal FSH, LH, testosterone*	Increased LH and testosterone levels in males are consistent with LH-secreting tumors. Elevated FSH and low-normal testosterone are suggestive of an FSH-producing tumor if primary gonadal failure is not present. In females, assessment of excess hormone secretion is difficult because of changes during the menstrual cycle and at menopause.

CRH = corticotropin-releasing hormone; IGF = insulin-like growth factor; TRH = thyrotropin-releasing hormone.

PROGNOSIS

In general, the sooner treatment is initiated to decompress the chiasm (with surgery, or in the case of a medically responsive prolactinoma, with appropriate medication), the more likely vision will be restored; however, visual improvement has been noted even after months of visual field impairment. Even after apparent surgical cure, about 10 to 20% of tumors recur within several years, as manifested by oversecretion of their hormones, and recurrence is more likely if the tumor extended into the suprasellar space or fragmented upon removal.

GROWTH HORMONE

PATHOBIOLOGY

Growth hormone is the main regulator of the growth of bone and other tissues. The human growth hormone gene, along with four other related genes, is located at the growth hormone locus on chromosome 17 where, by gene duplication, these genes are interspersed in the same transcriptional orientation. The five genes not only have a high degree of sequence identity but also exist as multiple isoforms based on variable splicing. The variant expressed in the somatotrophs of the pituitary gives rise to two isoforms. Growth can occur in the fetus and early postnatal state independent of growth hormone; but soon after birth, growth hormone controls growth, and its deficiency results in dwarfism.

Growth hormone is a peptide hormone whose receptor is located on the cell surface. Growth hormone promotes the dimerization of two growth hormone receptors and activates JAK2 by phosphorylation of tyrosine residues. The activated JAK2 in turn activates STAT and an entire cascade of signal factors, thereby resulting in nuclear activation.

The metabolic effects of growth hormone are both direct, by interaction with its tissue receptors, as well as mediated by a serum factor secreted by the liver (somatomedin or insulin-like growth factor-I [IGF-I]). IGF-I in turn acts on a variety of tissues to stimulate body growth. IGF-I is also produced in a variety of tissues including smooth muscle, skin, lung, bone, and cartilage. However, in addition to IGF-I production in the various tissues, growth hormone causes hydrolysis of triglycerides in adipose tissue. In skeletal muscle, growth hormone enhances uptake of amino acids and retention of nitrogen, similar to what would be expected in exercising muscle. Growth hormone also stimulates glycogenolysis and gluconeogenesis.

GROWTH HORMONE DEFICIENCY

PATHOBIOLOGY

Growth hormone deficiency in children may be due to hypothalamic defects in the production, release, or sensing of growth-hormone-releasing hormone (GHRH). Deficiency also can be caused by any congenital disorder of pituitary gland development or from central nervous system defects such as tumors (craniopharyngioma, germinoma, ependymoma, pituitary adenoma, meningioma, medulloblastoma, glioma, Rathke cleft cyst, and arachnoid cyst). Postsurgical disruption of the hypothalamic pituitary axis, trauma, radiation, or infiltration also can cause growth hormone deficiency. Isolated growth hormone deficiency, which is the most common form of nonfamilial deficiency, is responsible for most cases of hypopituitarism in children. Growth hormone deficiency also can occur in combination with other pituitary hormone defects, as discussed earlier.

CLINICAL MANIFESTATIONS

In children, growth hormone deficiency is primarily manifested by slow growth. Due to redundancy of other hormones and factors on growth, children usually are not small for gestational age at birth but can manifest hypoglycemia due to the counter-regulatory effect of growth hormone. There is an increase in body fat, which may result in an appearance that the child is younger than the stated age, and hypogonadism or small genitalia may variably be present. Children usually are diagnosed when found to be shorter than their peers—at well-baby visits, when they enter school, or at puberty.

DIAGNOSIS

In children, the diagnosis of isolated growth hormone deficiency is most reliably made by careful growth measurements, a thorough medical history to exclude other causes of growth failure (renal tubular acidosis [Chapter 104], thyroid disease [Chapter 207], Turner syndrome in girls, or other chronic disease), or combined hormone deficiencies. Because growth hormone is secreted

episodically, measurements of serum growth hormone, IGF-I, and insulin-like growth factor binding protein-3 (IGFBP-3) are also helpful to confirm the diagnosis. Growth hormone levels are typically low, but growth hormone levels are high in the Laron dwarfism syndrome, owing to failure of IGF-I stimulation caused by mutations in the growth hormone receptor. Growth hormone secretion declines with aging, and elderly individuals often have mild and apparently asymptomatic reductions in basal growth hormone levels.[15]

Unless a pituitary disorder has already been confirmed, provocative tests are usually necessary to diagnose growth hormone deficiency that is sufficient to warrant replacement therapy[16] (see Table 205-2). Children with the diagnosis of idiopathic growth hormone deficiency should be retested as adults if they were inadequately diagnosed or had a mild form that resolved in adulthood. If an adult is deficient in three pituitary hormones and has an IGF-I level below the lower limit of normal, provocative testing is not required.

TREATMENT

The treatment of isolated growth hormone deficiency in childhood is replacement of growth hormone. Lonapegsomatropin (0.24 mg/kg/week) is recommended over somatropin (20 to 35μg/kg/week subcutaneously, divided into 6 or 7 daily doses).[A1] The average growth is 9 to 10cm in the first year of treatment, and then it begins to slow down to 6 to 7 cm per year for the next 2 years. At the time of puberty, the dose is often increased to 70 μg/kg/day while monitoring serum IGF-I and IGFBP-3 levels to be sure they are not greater than 2 standard deviations above the upper limit of normal. If growth slows, thyroid function should be checked because hypothyroidism develops in some children who are treated with growth hormone.

Treatment of adult-onset growth hormone deficiency is with human recombinant growth hormone at 2.0 to 5.0 μg/day subcutaneously. The goal is to start with low doses and gradually increase the dose to achieve a serum IGF-1 concentration in the mid-normal range for age. In women who are premenopausal or taking oral estrogen replacement, the dose is 3.0μg/day. The dose is usually given in the evening to mimic the diurnal variation in growth hormone secretion in the physiologic state. Assessment of fat and muscle mass, as well as objective assessment of quality of life, can be helpful to monitor treatment. Although generally safe, complications of treatment include fluid retention (resulting in lower extremity edema or carpal tunnel syndrome) and mild glucose intolerance. Contraindications for treatment include known malignancy, intracranial hypertension, and proliferative retinopathy. The duration of treatment is usually long-term. Lonapegsomatropin, which is the long-acting formulation of growth hormone, may also be efficacious in adults,[A2] but currently has not been approved for weekly treatment in adult-onset growth hormone deficiency.

GROWTH HORMONE EXCESS: ACROMEGALY AND GIGANTISM

Acromegaly is a disease of excessive growth and metabolic derangements caused by proliferation of pituitary somatotrophs and excessive secretion of growth hormone. If left untreated, it results in gross acral and facial disfigurement, cardiac disease, cancer, metabolic abnormalities including diabetes, and increased mortality.

EPIDEMIOLOGY AND PATHOBIOLOGY

The incidence of acromegaly is between 0.2 and 1.1 cases per 100,000 population, with a prevalence of between about 8 and 14 cases per 100,000. The median age at diagnosis is in the fifth decade after a diagnostic delay of about 5 years.

The hypothalamic factor, somatotropin release–inhibiting factor, inhibits the release of growth hormone, whereas growth hormone–releasing hormone stimulates both its synthesis and release. Other growth hormone secretagogues, such as ghrelin in the gastrointestinal tract, directly bind to growth hormone–stimulating receptors in the hypothalamus and induce the release of growth hormone. Furthermore, growth hormone's action is mediated by hepatic IGF-I, which inhibits growth hormone synthesis by stimulating somatotropin release–inhibiting factor in the hypothalamus and pituitary. Acromegaly therefore can be due to pituitary adenomas that produce excessive and uncontrolled amounts of growth hormone, to ectopic production of growth hormone by islet cell tumors (Chapter 211) or lymphomas (Chapters 171 and 172), or to ectopic production of growth hormone–releasing hormone in bronchial carcinoid tumors (Chapter 177), small cell cancers of the lung (Chapter 177), medullary thyroid cancers (Chapter 207), or pheochromocytomas (Chapter 209).

The *MEN1* gene, which codes for menin, is associated with defects in histone methylation, syndromic acromegaly, hyperplastic parathyroid glands, and adenomas of the endocrine pancreas and anterior pituitary. Pituitary adenomas develop in 50% of these patients, and 10% of their tumors secrete growth hormone. Activating mutations in the Gs alpha subunit result in ligand-independent Gs activity, thereby causing elevated cAMP levels and growth hormone hypersecretion.

CLINICAL MANIFESTATIONS

When first encountering patients with excess growth hormone, the handshake by a large, enveloping doughy hand and a rough, resonant voice may be the first hints of acromegaly. Symptoms associated with growth hormone hypersecretion are often not recognized for 10 or more years after their often-subtle onset. The classic coarse facial features are usually not immediately apparent but are recognized in retrospect and after looking at past photographs (Fig. 205-5). Because these pituitary tumors are usually diagnosed only years after the onset of symptoms,[17] they are usually macroadenomas by the time of presentation (75%). Headaches are an initial symptom in up to 60% of the patients, and 10% present with the classic temporal hemianopsia. Tall stature may be present depending on when the growth hormone excess began, with younger age of onset correlating with taller stature.

The effects are most apparent in the bones and soft tissue with bony overgrowth. A protruding lower jaw, splayed teeth, malocclusion, mandibular overbite, and macroglossia are frequently noted. Overgrowth of soft tissues of the pharynx may result in sleep apnea (Chapter 374). Enlargement of the nose and facial bones results in frontal bossing. Enlargement of bones and soft tissue likewise account for the changes patients may observe in ring, shoe, or hat size. Soft tissue growth, including multiple skin tags, is often associated with premalignant colonic polyps and colon cancer (Chapter 179). Hyperhidrosis at rest is very common. Neuropathy, such as carpal tunnel syndrome (Chapter 388), can be seen secondary to nerve entrapment. Increased risks of hypertension, diabetes mellitus, and myocardial hypertrophy predispose patients to ischemic heart disease and heart failure.

DIAGNOSIS

Because growth hormone is secreted in a pulsatile manner and at high amplitudes (>50 ng/mL), random measurements are not very useful for diagnosing or excluding acromegaly. A better way to screen for acromegaly is to measure IGF-I levels (which correlate well with daily secretion of growth hormone and with the activity of the disease) after a 2-hr, 75-g oral glucose tolerance test (Table 205-7). In acromegaly, glucose administration will not suppress growth hormone levels to below 1 ng/mL by a polyclonal antibody immunoassay or below 0.4 ng/mL by a chemiluminescent immunoradiometric assay. Co-secretion of prolactin should be measured, since a significant percentage of tumors co-secrete growth hormone and prolactin, and these findings have implications for medical therapy with dopamine agonists.

After the diagnosis of acromegaly is made based on a full endocrine evaluation, an MRI should be obtained to determine the extent of tumor growth. Although 90% of patients have a visible pituitary adenoma on MRI, 10% of the patients have an empty sella. The rare nonpituitary causes of acromegaly include hypothalamic tumors that make excess growth hormone–releasing hormone or nonendocrine tumors that secrete ectopic growth hormone. Occasionally, selective venous sampling over tumor beds identified radiologically can identify sources of secreted IGF-I or similar compounds.

TREATMENT

The goals of therapy, which is best administered as a multidisciplinary approach with experienced neurosurgeons and endocrinologists,[18–20] are to shrink the tumor, normalize growth hormone and IGF-I levels, prevent tumor mass effects, prevent recrudescence, and avoid precipitating hypopituitarism, thereby reducing the long-term morbidity and mortality that result from excess production of growth hormone. Cure usually is defined by the normalization of random blood levels as well as of IGF-I levels after an oral glucose tolerance test. Transsphenoidal surgery can reduce growth hormone levels below 2.5 ng/mL in 80 to 90% of microadenomas. Macroadenomas have tumor cure rates less than 30%, but the growth hormone level usually is substantially reduced. Radiation is not an effective primary treatment because it will not reduce growth hormone levels until 5 to 10 years later and carries a high risk of hypopituitarism and other complications. However, adjunctive radiation therapy, especially stereotactic radiotherapy, may benefit patients whose macroadenomas persist despite transsphenoidal surgery and medical therapy.

Medical therapies are used as adjunctive therapy if surgery does not cure the tumor or as primary therapy when a surgical cure is not possible, such as when the tumor has invaded the cavernous sinus. Intramuscular somatostatin analogues given every 4 weeks almost always reduce growth hormone and IGF-I levels, and they normalize IGF-I levels in about 50 to 60% of cases. Pasireotide LAR (either 40 mg or 60 mg intramuscularly once every 28 days) is superior to

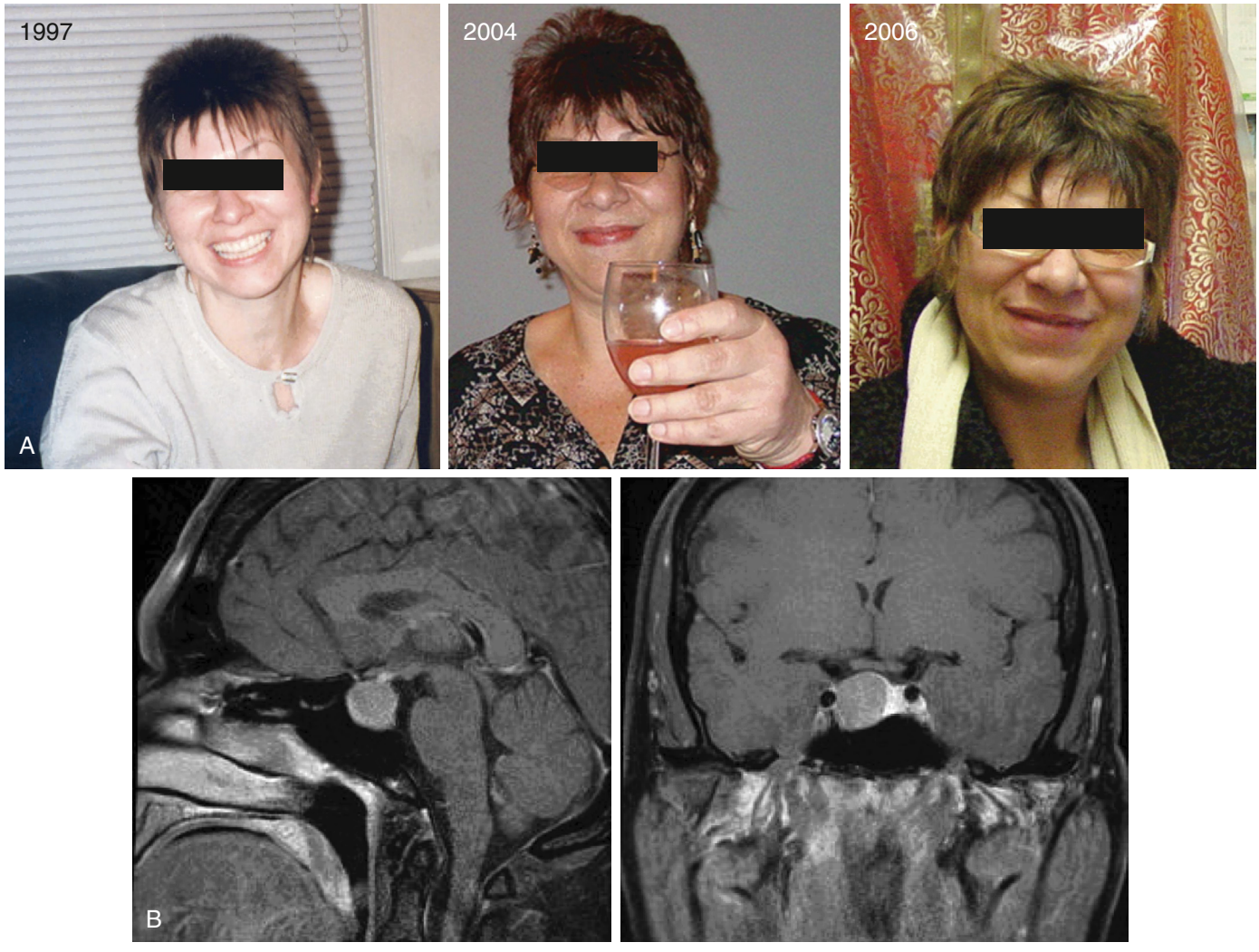

FIGURE 205-5. **Clinical features of acromegaly. A**, Serial photographs of a woman with acromegaly. Over a 9-year period, there is a progressive coarsening of facial features, including enlargement of the nose and lips and development of prognathism. She also experienced hypertension, arthropathy, and enlargement of the hands. **B**, Magnetic resonance image of patient's pituitary adenoma at the time of presentation.

other somatostatin analogues for reducing growth hormone secretion.[A3] Tumor size is reduced modestly in about 50% of cases, and about 10 to 20% of patients who achieve normal levels of growth hormone and IGF-I can eventually be successfully withdrawn from treatment after several years. Side effects of somatostatin analogues include diarrhea and cholelithiasis, although cholecystitis and subsequent cholecystectomy are rare. Oral octreotide (40 mg/day given as 20 mg capsules twice per day 1 hour before meals or 2 hour after meals) is useful in patients who have demonstrated complete or partial biochemical response to injectable octreotide or lanreotide. Oral octreotide should be initiated at the time of the previously scheduled octreotide injection, with the dose up-titrated by 20 mg every 2 to 4 weeks based on the IGF-1 level and clinical symptoms.

Some patients experience additive benefit when other medications are added or combined in low doses to diminish adverse effects. Cabergoline (0.5 to 1 mg 2 times per week), which is a dopamine agonist, often can reduce levels of growth hormone and IGF-I, but levels return to normal in only about 30% of patients when it is used alone. Pegvisomant, which is a biosynthetic analogue of growth hormone, prevents growth hormone from binding to its receptor. When given by daily injection (an initial dose of 40 mg subcutaneously on day 1 followed by 10 to 30 mg daily, with a 5 mg/day adjustment every 4 to 6 weeks based on the goal of normalizing IGF-1 levels), IGF-I levels normalize in greater than 90% of patients,[A4] but it does not affect the size of the tumor itself. It can be reserved for patients who do not respond to other therapies, be used as initial medical therapy for small tumors, or be combined with somatostatin analogues. The most common adverse effect of pegvisomant is an increase in liver enzyme levels.

PROGNOSIS

Treatment can markedly improve symptoms as well as the diabetes and other metabolic derangements,[21] although the arthropathy of acromegaly may progress in about one-third of patients.[22] Patients with larger tumors or higher growth hormone levels are less likely to achieve remission after surgery and more likely to require continued medical treatment.

Patients with acromegaly have a mortality similar to the general population if they achieve growth hormone suppression to less than 1 ng/mL during an oral glucose tolerance test and normal IGF-I levels, especially with ongoing use of somatostatin analogs as adjuvant therapy. However, they have a higher lifetime risk of death due to cancer.

PROLACTIN

Both prolactin and growth hormone have similar amino acid sequences and are present in all vertebrates. During pregnancy, prolactin concentrations increase and, in conjunction with the other hormones of pregnancy, stimulate the breast epithelium to produce milk. Lactotrophs, which are the cells that secrete prolactin, represent 20 to 50% of the anterior pituitary cell population and are the most likely to give rise to pituitary tumors. Prolactin is now implicated not only in lactation but also in inhibition of reproductive function (by suppression of gonadotropins) and support of maternal behavior. A prolactin variant, "big prolactin" or macroprolactin, is a high-molecular-weight variant due to the tendency of prolactin to aggregate and form intermolecular disulfide bridges spontaneously or with IgG. Despite their immunoreactivity, these prolactin variants usually have decreased biologic activity.

Prolactin binds to the prolactin receptor, which is a member of the type 1 cytokine receptor family. Janus kinase-2 mediates prolactin's effect in the target cells. The prolactin receptor is also the receptor for placental lactogens, which are hormones synthesized during pregnancy.

Regulation of prolactin secretion by lactotrophs is primarily under the inhibition of dopamine, which acts through the D_2-type receptors on lactotrophs. Inhibition of the dopamine ("inhibiting the inhibitor") results in a release of prolactin as is seen in nonsecreting pituitary tumors or trauma that disrupts

TABLE 205-8 CAUSES OF HYPERPROLACTINEMIA

DRUG CAUSES	EXAMPLES	MECHANISM	SERUM PRL RANGE PG/ML
Antiemetics	Metoclopramide, domperidone, prochlorperazine	Dopamine receptor blockade	
Antipsychotics	First generation: fluphenazine; haloperidol, others Second generation: paliperidone, risperidone	Dopamine receptor blockade	20-70
Antidepressants, cyclic	Clomipramine	Unknown	20-70
Narcotics	Methadone, morphine, others	Indirect effect of opioid mu receptor activation	20-70
Estrogen	Oral contraceptives	Stimulates PRL at transcription	20-70
NONDRUG CAUSES			
Stress		Hypothalamic	20-70
Pregnancy		Estrogen	20-500
Pituitary adenoma			Macro: 200->10,000 Micro: 20-250
Hypothyroidism		Increase in TRH	Moderate; <100
Chronic renal failure, cirrhosis		Decreased clearance and central effect	Moderate; <100
Chest wall injury, nipple stimulation		Unknown	20-70

PRL = prolactin; TRH = thyrotropin releasing hormone.

the pituitary stalk, thereby preventing dopamine from inhibiting prolactin release. Estrogen is a potent stimulator of lactotroph proliferation and raises the possibility that exogenous estrogen could increase the growth of prolactinomas, although clinical evidence suggests this phenomenon may be true only for macroprolactinomas. Thyrotropin-releasing hormone (TRH) and vasoactive intestinal peptide (VIP) also stimulate the release of prolactin, so when hypothyroidism increases TRH release from the hypothalamus, it causes hyperprolactinemia. In addition to hypothalamic control, prolactin secretion gradually declines at night and rises overnight to reach its highest level in the morning. In addition stress, chest wall stimulation, and pregnancy stimulate the release of prolactin. During pregnancy, high levels of estrogen and progesterone inhibit lactation, and their postpartum decline permits lactation accompanied by the secretion of oxytocin in response to suckling.

PROLACTIN DEFICIENCY

The normal concentration for prolactin is less than 15 to 20 pg/mL in women and less than 10 to 15 pg/mL in men. Low serum levels of prolactin, which can be seen in hyperthyroidism because TRH is suppressed, may prevent adequate lactation in nursing mothers and may be a reliable marker for hypopituitarism when seen with deficiencies in other pituitary hormones. Lactation is not completely absent because nipple stimulation may be sufficient to start milk production. No cases of isolated prolactin deficiency have been reported in men.

HYPERPROLACTINEMIA

EPIDEMIOLOGY AND PATHOBIOLOGY

Hyperprolactinemia occurs in less than 1% of the general population but can be as common as 14% in women with abnormal menses. Among causes of elevated levels of prolactin (Table 205-8) are medications that antagonize dopamine action or increase the activity of endorphins or serotonin. These mechanisms result in mild hyperprolactinemia (<100 pg/mL), but the most common cause of hyperprolactinemia greater than 100 pg/mL is a prolactinoma.

CLINICAL MANIFESTATIONS

Although rare in children (<2 to 3% of intracranial tumors), prolactinomas are usually detected and have clinical symptoms when they become macroadenomas and cause neurologic symptoms (visual problems, headaches), delay puberty, or retard growth. The latter two signs may be due to the direct effects of the tumor on other cell lines or to the effect of excess prolactin on the release of growth hormone and reduced gonadotropin response.

In adult premenopausal females, the typical presentation is galactorrhea and oligomenorrhea. Because galactorrhea is enabled by estrogen, postmenopausal women, who are generally deficient in estrogen, do not develop galactorrhea despite elevated prolactin levels. Prolactin can also suppress GnRH, and therefore LH and FSH, and in turn, estrogen. As a result, symptoms of hyperprolactinemia may also be manifestations of low estrogen levels, such as infertility, decreased libido, and vaginal dryness. Oral contraceptive agents (Chapter 220) can overcome the perturbations in GnRH and induce normal menses even in the presence of elevated prolactin levels. Osteopenia (Chapter 225) may be a direct effect of an elevated prolactin level on the bone as well as its indirect effects on estrogen. If the prolactinoma grows large enough, neurologic symptoms (e.g., vision changes and headaches) can appear even before endocrine manifestations.

In adult men, prolactinomas are usually detected late because a large mass is necessary to cause neurologic or endocrine manifestations. However, excess prolactin inhibits GnRH, thereby lowering testosterone and resulting in decreased libido, impotence, reduced muscle mass, and increased fat mass. In rare situations when men have elevated estrogen levels (e.g., cirrhosis), high prolactin levels can induce gynecomastia and even galactorrhea. In men with osteopenia (Chapter 225), prolactin should be measured because elevated levels decrease testosterone and osteoblasts. Because dopamine inhibits prolactin, nonprolactin–secreting pituitary or hypothalamic tumors that compress the pituitary stalk can also cause an increase in prolactin by disrupting the flow of dopamine to the lactotrophs.

DIAGNOSIS

The diagnosis of hyperprolactinemia[23] is based on a straightforward measurement of elevated blood prolactin by immunoassay. Levels above 100 pg/mL are consistent with an adenoma. When an occasional macroprolactinoma causes a prolactin level higher than 1000 pg/mL, falsely low values may be reported because the high level "overwhelms" the antibody and artificially reduces the measured value. Conversely, prolactin can dimerize with itself ("big prolactin") or complex with circulating IgG ("big big prolactin") to form "macroprolactin" complexes that are not biologically active but may result in elevated prolactin values on some immunoassays.

A brain MRI is recommended in any patient who has a prolactin level >100 ng/mL or is symptomatic (e.g., galactorrhea or amenorrhea) from the elevated prolactin level. In patients who have mildly elevated prolactin levels (<100 pg/mL) but no tumor seen on MRI, the cause may be macroprolactin, a microadenoma too small to be seen on MRI, or "idiopathic" hyperprolactin owing to hypothalamic dysfunction.

Prolactin values slightly above normal but less than 70 pg/mL are usually caused by medications. Other causes include stimulation of the chest wall secondary to chest surgery, pregnancy, lactation, and renal failure as well as prolactin-secreting adenomas.

TREATMENT AND PROGNOSIS

The goals of therapy are to restore normal gonadal function and to shrink the tumor to alleviate any anatomic or neurologic mass effects. The dopamine agonist cabergoline (starting at 0.5 mg orally twice weekly) is effective and relatively well-tolerated (Fig. 205-6). The dose should be titrated to the lowest dose that reduces the serum prolactin level to less than 10 pg/mL. In general, patients with macroprolactinomas require higher doses, usually greater than 2.0 mg/week.

Between 80 and 90% of patients with macroprolactinomas have a greater than 50% decrease in tumor size, and visual field defects can improve within the first week. Patients who cannot tolerate cabergoline due to nausea and dizziness may respond better to bromocriptine (2.5 to 15 mg orally daily), which can be inserted vaginally in women at the same dose. Alternatively, estradiol along with a

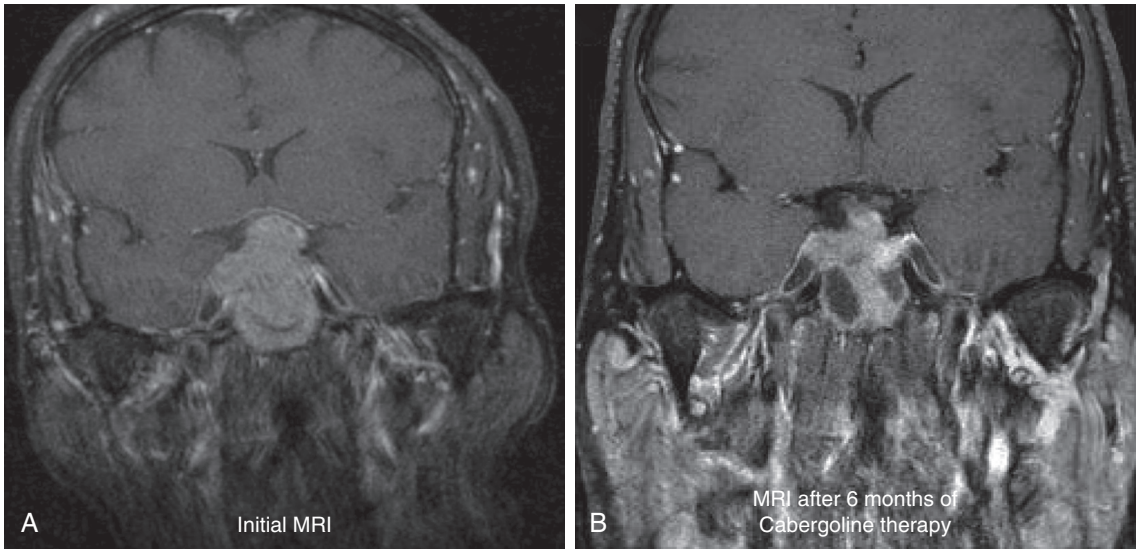

FIGURE 205-6. Magnetic resonance image of a macroprolactinoma before (A) and after (B) commencing cabergoline therapy. A 43-year-old man presented with headaches for 4 weeks and normal vision. Magnetic resonance image (MRI) revealed the large mass. Prolactin on presentation was 8000 ng/dL (normal <20). After 2 doses of cabergoline (0.5 mg orally at night), the serum prolactin level was 2086; after 6 months of treatment, the prolactin level was 15 ng/dL, and repeat MRI showed a significant decrease in the size of the tumor.

progestin (see Table 220-2) can be given in women with microprolactinomas who cannot tolerate dopamine agonists. Because of the concern that these agents could damage heart valves,[24] it is reasonable to perform yearly echocardiograms in patients who have known valvular heart disease or who require long-term therapy at doses greater than 5 mg/week.

Patients who respond well—with suppression of prolactin levels, disappearance of their tumor, and resolution of symptoms for at least a year—should reduce their dose or stop it completely. Prolactin levels and MRI should be repeated at 3 months after stopping the medication, then at 6 months, and then yearly until it is certain there is no recurrence. Macroprolactinomas are more likely to recur than microprolactinomas. If cabergoline is restarted, it should be prescribed at the lowest dose necessary to keep the serum prolactin less than 10 pg/mL.

After a woman is on treatment and her prolactin values normalize, ovulation may be possible. Pregnant patients should discontinue medical therapy. Their prolactin levels should be monitored, acknowledging that pregnancy alone causes prolactin levels to increase. About 25% of macroprolactinomas grow during pregnancy, as evidenced by symptoms of headache and visual field abnormalities, so visual fields should be measured at each trimester. If visual fields are normal, the pregnancy can progress without medication. If visual fields change, discussion should take place about restarting bromocriptine because of more experience with it during pregnancy.

A clear second choice, and usually only in patients in whom pharmacologic intervention is not successful, is transsphenoidal tumor resection. Although cure rates are not as impressive as for medication, prolactin normalizes in 65 to 85% of microadenomas[25] and 30 to 40% of macroadenomas, with recurrent rates of 20% over 10 years. Radiotherapy is rarely used.

ADRENOCORTICOTROPIC HORMONE (ACTH)

INTRODUCTION

ACTH is a 39–amino acid peptide synthesized as part of a precursor polypeptide, proopiomelanocortin (POMC; 241 amino acids). In humans, the *POMC* gene is located at 2p23 on the short arm of chromosome 2 and is composed of three exons. The first exon is the leader sequence and binds the ribosome. The second exon contains the signal sequence, which enables the protein to be translocated to the endoplasmic reticulum and codes for the initial part of POMC. The third exon codes for the mature protein and the polyA tail. In humans, there are three RNA transcripts. The T1 transcript is the form found in the corticotroph cells of the pituitary as well as the hypothalamus. The T2 transcript arises from the 5′ end of exon 3 and is found primarily in peripheral tissues, and the T3 transcript has promoter elements upstream of exon 1 and is expressed in ACTH-secreting tumors, such as small cell lung cancer. POMC undergoes proteolytic cleavage to generate pro-ACTH and β-lipotropin. ACTH is cleaved into corticotropin-like intermediate lobe peptide and α-melanocyte stimulating hormone.

In extrapituitary tumors, the processing of POMC is variable, and a number of intermediates are produced. Therefore, tumors that produce ectopic ACTH usually are accompanied by detectable blood levels of other POMC intermediates that are not seen when a pituitary adenoma causes excess ACTH.

The most important stimulator of ACTH secretion is hypothalamic corticotropin-releasing hormone (CRH). Chronic CRH stimulation causes hyperplasia of corticotroph cells, which rarely can be seen in neuroendocrine tumors that secrete CRH. However, other neurotransmitters and brain peptides (including various cytokines that synergize with hypothalamic hormones, leukemia inhibitor factor, and CRH) also traverse the hypothalamic portal axis and stimulate the corticotroph to release ACTH. In addition, hypoglycemia, stress (as from sepsis, surgery, acute illness), and depression can stimulate the peripheral and hypothalamic cytokines that activate the hypothalamic-pituitary-adrenal axis. Cortisol inhibits the release of ACTH, blunts the response of ACTH to CRH, and inhibits the production of CRH. After prolonged administration of exogenous glucocorticoids and the resulting suppression of the hypothalamic-pituitary-adrenal axis, the recovery of endogenous CRH secretion, which appears to be the rate-limiting step for a return to normal function, can take several months.

ACTH is released in an ultradian pulsatile manner, with 10 to 12 pulses each day, thereby resulting in plasma levels that range from less than 10 to 80 pg/mL. Values are highest around 8 AM and spike with meals. The nadir is usually around 1 to 2 AM. Even the stress of a venipuncture can increase plasma ACTH concentrations. Pulse release combined with a short half-life (minutes) explains why random measurement of ACTH is generally unhelpful except when the random level is very high, as can be seen in primary adrenal insufficiency (low cortisol).

Trauma and infection increase the secretion of CRH, ACTH, and, as a result, cortisol levels. Analogous adjustments in the doses of cortisol replacement therapy are required in seriously ill patients.

ADRENOCORTICOTROPIC HORMONE DEFICIENCY: SECONDARY HYPOCORTISOLISM

EPIDEMIOLOGY AND PATHOBIOLOGY

Secondary adrenal insufficiency refers to states of low cortisolism due to inappropriately low levels of CRH or ACTH. Any congenital or acquired disease that disrupts normal pituitary function can disrupt the formation and release of ACTH.

ACTH deficiency is most often caused when exogenous glucocorticoid treatment suppresses the hypothalamic-pituitary-adrenal axis. Because of the lack of ACTH stimulation, the sudden discontinuation of exogenous glucocorticoids or an unmet increased need for them because of intervening severe stress can cause symptoms and signs of glucocorticoid deficiency.

When ACTH deficiency otherwise occurs in adults, it is almost always accompanied by deficiencies in other pituitary hormones, especially in women who have lymphocytic hypophysitis. Isolated primary ACTH deficiency is

rare,[26] though it can be seen in defects of transcription factors (T-Box19 and pituitary restricted transcription factor), proopiomelanocortin expression, or CRH gene expression.

CLINICAL MANIFESTATIONS

Symptoms of fever, nausea, vomiting, weakness, and fatigue are typically accompanied by relative or absolute hypotension. Abnormal laboratory test findings can include hypoglycemia, hyponatremia, and eosinophilia. Primary adrenal insufficiency (Chapter 208) usually causes more severe cortisol deficiency and associated mineralocorticoid deficiency, whereas secondary adrenal insufficiency is often not as severe and is not accompanied by mineralocorticoid deficiency, because the mineralocorticoids are controlled primarily through the renin-angiotensin system rather than ACTH-dependent mechanisms. As a result, volume depletion is less pronounced in ACTH deficiency, and hyperkalemia is not a part of the clinical syndrome. Another differentiating feature is that MSH levels are low when ACTH levels are low, so hyperpigmentation is not a feature of primary adrenal insufficiency. In women, a reduction in adrenal androgens can reduce libido and lead to loss of hair in the axillary and pubic areas.

DIAGNOSIS

ACTH reserve is usually assessed by the controlled induction of hypoglycemia with intravenous insulin via an insulin tolerance test that directly tests the hypothalamic-pituitary-adrenal axis by stimulating the brain to release cytokines and CRH, which in turn stimulate ACTH release (see Table 205-2). The insulin tolerance test is performed following an overnight fast by administering 0.1 U insulin/kg/body weight intravenously (or 0.05 U if there is high suspicion of ACTH deficiency) using 0.9% NaCl to maintain IV access. The blood glucose level is measured every 15 minutes, monitoring for a glucose level less than 40 mg/dL or when symptoms of hypoglycemia appear (whichever is first). Patients with ACTH deficiency may not rebound from the hypoglycemia and may need to receive 50 mL of 50% dextrose solution to normalize their blood sugar. A normal test would be a cortisol level greater than 18 μg/dL at or soon after confirmed hypoglycemia. The insulin tolerance test should be conducted cautiously in patients with seizure disorders because hypoglycemia may lower the seizure threshold.

Another way to determine ACTH reserve when ACTH deficiency is suspected is to administer CRH (1 μg/kg) intravenously at time "zero," with cortisol measurements at 5, 10, 15, and 30 minutes following the injection. This test, which is not as well standardized as the insulin tolerance test, bypasses the hypothalamus.

TREATMENT

ACTH deficiency responds to glucocorticoid replacement. In general, isolated ACTH deficiency requires only hydrocortisone, usually 20 mg in the morning and 10 mg in the afternoon, to mimic the physiologic profile of cortisol release. Such doses are usually doubled during mild to moderate stress. Emergency hydrocortisone injection kits are worthwhile in case vomiting prevents oral dosing. Stress doses of steroids (e.g., 50 to 75 mg every 8 hours for severe stress) are required for acute illness. Patients who have been taking long-acting, potent glucocorticoids (e.g., prednisone) for months for chronic inflammatory diseases (e.g., asthma [Chapter 75], systemic lupus erythematosus [Chapter 245], or inflammatory bowel disease [Chapter 127]) can be liberated from chronic glucocorticoid treatment if the hypothalamic-pituitary-adrenal axis is stimulated by switching to shorter-acting glucocorticoids (e.g., hydrocortisone) in gradually diminishing doses, oftentimes slowly titrated over many months. However, if the underlying disease for which the steroids were given is still active, other immunosuppressive drugs must be substituted, or the underlying disease will flare.

CUSHING DISEASE

Cushing syndrome reflects excessive tissue exposure to glucocorticoids. The syndrome can be ACTH-dependent or ACTH-independent, but the most common cause is when excess cortisol is produced by the unmitigated release of ACTH from a pituitary adenoma; the term Cushing *disease* is reserved for this specific cause of Cushing *syndrome*. Other causes of ACTH-dependent Cushing syndrome are discussed in Chapter 208.

EPIDEMIOLOGY AND PATHOBIOLOGY

Cushing disease is rare, with an annual incidence of 1.2 to 2.4/million in the population. Approximately 60 to 70% of all cases of Cushing syndrome represent Cushing disease caused by a solitary corticotroph adenoma, although rare cases are caused by corticotroph hyperplasia or, even more rarely, a corticotroph carcinoma. Cushing disease occurs 8 to 10 times more frequently in women than in men. Most tumors are small when they are identified because of the profound biologic effects of excess cortisol, but 10 to 15% present as macroadenomas. Relatively constant high levels of cortisol do not follow the physiologic diurnal variation. The molecular pathology of most corticotroph adenomas is unknown.

CLINICAL MANIFESTATIONS

The symptoms that lead most patients to seek medical care are decreased libido, weight gain, sleep disturbances, emotional lability, and the typical physical changes associated with glucocorticoid excess (see Table 208-1).[27] Most patients experience depression, and some even have suicidal ideation if left untreated. In menstruating females, the first perturbations can be oligomenorrhea and amenorrhea. Patients may also note proximal muscle weakness when entering or exiting an automobile or even brushing their hair. Occasional patients complain of headaches and vision loss depending on the size of the pituitary adenoma. Women can also present with hirsutism and worsening acne. Because of their immunocompromised state, the initial presentation also can be with life-threatening infections and sepsis. The associated hypercoagulable state can result in deep venous thrombosis or pulmonary embolism (Chapter 68).

Common findings on physical examination include central obesity, owing to muscle wasting. Hypertension, which is common, is caused by the direct ability of ACTH to stimulate the secretion of mineralocorticoids as well as glucocorticoids. Large, wide, violaceous striae ("stretch marks") are also seen on the abdomen, under the breasts, in the axillae, and in the upper inner thighs. Compared with the stretch marks in pregnancy, Cushing striae are usually wider than a fingerbreadth, purple in color, and can have subcutaneous bleeding that contributes to their pigmentation. Abnormal adipose tissue is usually seen between the scapulae ("buffalo hump") or in the supraclavicular space. In the face, fat deposition causes "moon facies," and the increased hematocrit contributes to facial plethora (ruddy cheeks) (Table 205-9). Hair growth is increased in an androgen-dependent distribution, and male-pattern baldness develops in women (Fig. 205-7). Multiple ecchymoses on the trunk and extremities can be seen due to bruising from capillary fragility.

TABLE 205-9 CLINICAL FEATURES OF CUSHING DISEASE

GENERAL
Obesity (centripetal distribution)
"Moon facies" and mild proptosis
Increased supraclavicular fat and "buffalo hump"
Hypertension
SKIN
Hyperpigmentation
Facial plethora
Hirsutism
Violaceous striae and thin skin
Capillary fragility and easy bruising
Acne
Edema
Female balding
MUSCULOSKELETAL
Muscle weakness (proximal)
Osteoporosis and back pain
REPRODUCTIVE
Decreased libido
Oligomenorrhea and amenorrhea
NEUROPSYCHIATRIC
Depression
Irritability and emotional lability
Psychosis
Disrupted sleep
METABOLIC
Hypokalemia and alkalosis
Hypercalciuria and renal stones
Glucose intolerance or diabetes mellitus
Impaired wound healing
Impaired resistance to infection
Granulocytosis and lymphopenia
Hypercoagulable state—Pulmonary embolus, deep vein thrombosis
TUMOR MASS EFFECTS
Headache
Visual field loss
Hypopituitarism and mass effect of tumor

FIGURE 205-7. Clinical features of Cushing disease before (A, C) and after (B, D) transsphenoidal resection of an ACTH-secreting pituitary adenoma. An 18-year-old male presented with lower back pain secondary to vertebral fractures, depression, and 20-pound weight gain over a 2-year period. Note the "moon facies" and facial plethora (**A**) and abdominal obesity with thin extremities as well as violaceous striae (**C**). One year after pituitary tumor removal the patient had weight loss, and while the striae remained as scar tissue, they were less violaceous. Muscle mass increased and abdominal obesity decreased. WWW.BOOKBAZ.IR

An additional finding in ACTH-dependent Cushing disease is hyperpigmentation owing to the melanocyte-stimulating hormone (MSH) that is secreted along with ACTH from the adenoma. Although the hyperpigmentation is not as marked as seen in Addison disease (where ACTH levels are usually 10- to 100-fold greater) or as in ectopic hypercortisolism, it is certainly more than seen in ACTH-independent causes of Cushing syndrome.

Patients can have mild glucose intolerance or flagrant diabetes depending on the absolute elevation of the cortisol level as well as its chronicity. The mineralocorticoid excess also commonly leads to kaliuresis and hypokalemia.

DIAGNOSIS

Most patients with obesity, hypertension, and glucose intolerance or diabetes do not have Cushing syndrome, but the presence of the classic physical findings may suggest the need for further investigation. No single diagnostic test can confirm Cushing disease, but a constellation of test results is usually determinative.[28] The first and often most difficult step is to document hypercortisolism. The second step is to determine whether it is caused by elevated ACTH, and if so, the third step is to identify whether the ACTH is coming from the pituitary or an ectopic source (Fig. 205-8).

Blood Tests

Testing usually begins with blood tests of ACTH and cortisol. A morning cortisol level can confirm hypercortisolism, but a random serum cortisol level is unreliable, because of the episodic secretion of cortisol and because 90% of circulating cortisol is bound to cortisol-binding globulin or to albumin. ACTH values above 15 pg/mL are consistent with an ACTH-secreting tumor, either in the pituitary or ectopically. By comparison, very high values (e.g., above 100 pg/mL) are commonly seen in primary adrenal insufficiency. Nearly undetectable plasma ACTH concentrations in the setting of hypercortisolism suggest a primary adrenal source (an adrenal adenoma making cortisol or congenital adrenal hyperplasia).

Late-Night Salivary Cortisol Measurement

An alternative to blood tests is late-night (23:00 to 24:00 hour) salivary cortisol testing. Saliva is collected after refraining from drinking, smoking, eating, or use of oral hygiene products for at least 30 minutes prior to collecting saliva onto an absorbent tube, which is then compressed into a collection tube and brought to the laboratory the next morning. Cortisol is measured by liquid chromatography and tandem mass spectroscopy. Cortisol values greater than 0.09 ug/uL indicate hypercortisolemia. This test has a sensitivity of 80 to 90% for diagnosing Cushing syndrome, but its specificity is lower (70 to 90%). Nevertheless, its excellent sensitivity makes it a good screening test. Salivary cortisol is a measure of free cortisol in the blood and is not affected by elevated cortisol binding globulin, as in serum cortisol measurements.

24-Hour Urine

A properly collected 24-hour urine specimen showing an elevated urine free cortisol level in an unstressed patient with normal renal function is usually sufficient to diagnose Cushing syndrome. Conversely, a normal result is strong evidence against that diagnosis. However, biologic variation and technical challenges hamper the use of this test for the initial screening of Cushing syndrome.

Dexamethasone Suppression Testing

Among the various versions of dexamethasone suppression testing, perhaps the most practical option is a single dose of 1 mg dexamethasone administered at 11 PM, with blood obtained by 8 AM the following morning. A normal response is a serum cortisol concentration of less than 1.8 µg/dL. An alternative cut point, less than 5 µg/dL, is more specific but less sensitive. If the cortisol level is greater than 10 µg/dL, the likelihood of hypercortisolism is high, but the cause could be an unsuppressed pituitary adenoma, an ectopic source of ACTH, or a primary adrenal tumor (Table 205-10).

Patients with corticotroph-secreting macroadenomas or very active tumors may have urine free cortisol levels greater than 1000 µg/dL after 1 mg of dexamethasone and require higher doses of dexamethasone (up to 8 mg q6h for 2 days) to confirm suppressibility and exclude ectopic ACTH production.

CRH Stimulation Test

The CRH stimulation test is one of the most sensitive (93%) and specific (100%) ways to determine if there is an abnormality in the hypothalamic-pituitary-adrenal axis and for diagnosing the etiology of hypercortisolism in ACTH-dependent Cushing disease. The mean ACTH concentrations at 15 and 30 minutes after administrating CRH (1 ug/kg up to 70 ug IV) should increase by at least 35% above the mean basal value in patients with Cushing disease but not in patients with ectopic ACTH secretion.

MRI

The best next step in the evaluation of patients with documented hypercortisolism (i.e., nonsuppression with low-dose dexamethasone and CRH hyperstimulation) is MRI to confirm the presence of a pituitary mass. Unfortunately, 10% of all normal individuals may have slight MRI abnormalities of their pituitary glands, and many patients with Cushing disease may have tumors that are too small to be seen on MRI. However, subjecting a patient to surgical pituitary exploration in the absence of a demonstrable mass is likely to result in an unsuccessful surgery.

Inferior Petrosal Sinus Sampling

If dexamethasone suppression testing and CRH testing are equivocal, inferior petrosal sinus sampling should be performed to confirm the pituitary as the source of the ACTH. Although this test is less reliable in lateralizing the ACTH source (i.e., left vs. right) than it is in confirming that the ACTH source is central in origin, it can exclude ectopic ACTH production by a tumor. However, it usually cannot distinguish an ectopic CRH-secreting tumor from true Cushing disease.

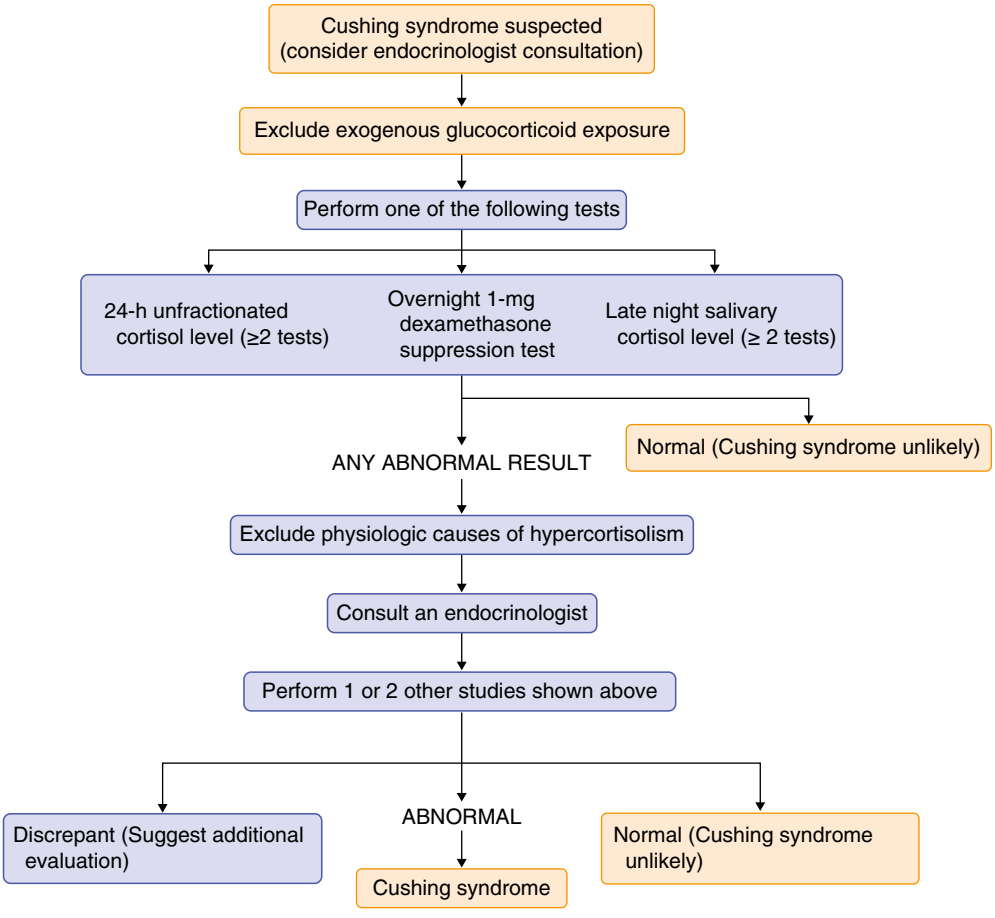

FIGURE 205-8. Approach to testing for suspected Cushing syndrome. Diagnostic criteria that suggest Cushing syndrome are an unfractionated cortisol level greater than the normal range for the assay, a serum cortisol greater than 1.8 μg/dL (50 nmol/liter) after a 1 mg dexamethasone suppression test, and late-night salivary cortisol greater than 145 ng/dL (4 nmol/liter). (Adapted from Nieman LK, Biller BM, Findling JW, et al. The diagnosis of Cushing's syndrome: an Endocrine Society Clinical Practice Guideline. *J Clin Endocrinol Metab*. 2008;93:1526-1540.)

TABLE 205-10 INTERPRETING RESULTS OF PROVOCATIVE TESTING FOR CUSHING SYNDROME

Cause of hypercortisolism	Plasma ACTH	"Low Dose" oral dexamethasone 0.5 mg q6h for 2 days (measure 24 h urine cortisol)	"High Dose" oral dexamethasone 2.0 mg q6h for 2 days (measure 24 h urine cortisol)	Corticotropin-releasing hormone stimulation test (measure response of ACTH and cortisol at 15 and 30 minutes after injection)
Adrenal adenoma	Undetectable	No suppression	No suppression	No stimulation
Pituitary adenoma	>15 ng/dL	No Suppression	Suppression	Stimulation
Ectopic ACTH-secreting tumor	>100 ng/dL	No suppression	No Suppression	No stimulation
Pseudocushings (obesity, drugs, alcohol)	Normal	Suppression	Suppression	Not indicated

To ensure patient compliance with dexamethasone administration and determine whether there is abnormal metabolism of the dexamethasone, the serum level of dexamethasone can be (but is not usually) measured.
ACTH = adrenocorticotropic hormone.

TREATMENT AND PROGNOSIS

The best chance of curing an ACTH-secreting adenoma is transsphenoidal surgery (Fig. 205-7). Recurrences are seen in 7% of cases when the immediate postoperative plasma cortisol is less than 3 μg/dL compared with 100% when the postoperative plasma cortisol is 3 to 8 μg/dL. In patients with Cushing disease and macroadenomas, only about one third of patients have long-term remission. When initial surgery fails, a second pituitary surgery has a success rate of only about 50%. If postoperative cortisol levels drop below 1 ug/dL, the surgery was likely successful. Although glucocorticoids are not started preoperatively or given postoperatively, the serum cortisol level should be monitored every 4 hours in the first postoperative day. If the cortisol level drops below 5 ug/dL, glucocorticoid replacement should be started. However, several weeks later it should be held in the evening and the following morning to see if the pituitary adrenal axis has recovered. Patients should be closely followed by an endocrinologist with a quarterly urine free cortisol level or late-night salivary cortisol level to assure continued remission.

Pituitary irradiation or bilateral adrenalectomy may be recommended in patients who have a recurrence, in whom surgery is contraindicated (large tumor with invasion of carotid or cavernous sinus), or when a skilled neurosurgeon is not available. Pituitary radiation can take up to 2 to 5 years to be effective, and panhypopituitarism usually results. If a pituitary tumor cannot be demonstrated with certainty, bilateral laparoscopic adrenalectomies will cure the hypercortisolism, but lifetime postoperative steroid replacement is then required.

Medical therapies to inhibit ACTH release from the corticotroph, to block the synthesis of cortisol by the adrenal glands, or to inhibit the action of cortisol at the tissue level are neither particularly well tolerated nor easy to monitor. These therapies are used as last resorts and only by experts. Perhaps the most promising is chemical adrenalectomy with osilodrostat (1 to 30 mg twice daily), which is an inhibitor of 11ß-hydroxylase and can normalize cortisol levels in about 80% of patients,[A5] but with substantial side effects. The glucocorticoid receptor antagonist mifepristone (300 mg once daily, increased in 300 mg increments at 2- to 4-week intervals to a maximum dose of 1.2 grams daily, based on tolerability and control of symptoms) can treat hyperglycemia and can improve quality of life. However, patients may become severely adrenally insufficient because of the receptor blockade, despite very high cortisol and ACTH levels. Other such options (including ketoconazole, mitotane, metapyrone, or etomidate) can be difficult to titrate to normal adrenal function.

NELSON SYNDROME

Nelson syndrome is a rare condition of uncontrolled growth of an ACTH-secreting pituitary adenoma, usually within 3 years after bilateral adrenalectomy has been performed to treat Cushing disease.[29] The incidence of Nelson syndrome following bilateral adrenalectomy can be as high as 43% in patients with macroadenomas, high plasma concentrations of ACTH, and visible pituitary tumors prior to adrenalectomy. Other risk factors for Nelson syndrome

include longer duration of Cushing disease before diagnosis and treatment, younger patients, inadequate glucocorticoid replacement, and tumors with higher mitotic indices.

All patients have high plasma ACTH levels following bilateral adrenalectomy, even those without prior Cushing disease. Such patients should have their hormones measured prior to administration of the AM dose of steroid or 1 hour thereafter. Some experts recommend follow-up MRI every 6 months for several years in patients who have undergone bilateral adrenalectomy after failed transsphenoidal pituitary adenomectomy. Treatment of Nelson syndrome is usually with the same modalities used for ACTH-secreting pituitary adenomas. Despite treatment, some patients have progressive disease.[30]

GONADOTROPINS (FOLLICLE-STIMULATING HORMONE AND LUTEINIZING HORMONE)

PATHOBIOLOGY

The three pituitary glycoprotein hormones—FSH, LH, and TSH—have a common α-subunit and a hormone-specific β-subunit that are combined together to form the hormone. Chorionic gonadotropin (hCG), which is structurally very similar to LH, is made in the placenta. These peptides interact with their cognate receptors located in the cell membrane of their target cells. These transmembrane receptors classically have an extracellular domain that binds the hormone, an intramembranous domain, and an intracellular domain that transduces the hormone signal to the cell. Mutations in the extracellular or intracellular domain can cause constitutive activation of the receptor even in the absence of the ligand. The result is the appearance of a hormone-rich state in the absence of the hormone (e.g., precocious puberty due to the constitutive activation of the FSH receptor). Similarly, mutations in the receptor can make it insensitive to the ligand, so that even high hormone levels are not recognized by the receptor. Lastly, due to the similarity of the α-subunit among these glycoprotein hormones, there can be some promiscuity of ligand stimulation when ligand levels are high. During pregnancy, for example, the hCG level is very high and can stimulate the TSH receptor as if TSH were present.

Gonadotropins regulate sexual differentiation, the production of sex steroids, and gametogenesis. In males, FSH receptors are located on Sertoli cells and seminiferous tubules, where they stimulate sperm maturation, whereas LH receptors on Leydig cells in the testis stimulate the production of androgen. Together, FSH and LH induce spermatogenesis (Chapter 216). In females, ovarian FSH receptors on granulosa cells induce the biosynthesis of estrogen, whereas LH receptors on ovarian thecal cells stimulate the synthesis of ovarian androgens and steroid precursors that granulosa cells aromatize into estrogens. The secretion of FSH and LH regulate the menstrual cycle (Chapters 217 and 218).

HYPOGONADOTROPIC HYPOGONADISM

EPIDEMIOLOGY AND PATHOBIOLOGY

Hypogonadotropic hypogonadism or secondary hypogonadism is defined as failure of gonadal function due to pituitary or hypothalamic abnormalities that result in acquired or congenital reductions in LH, FSH, or GnRH.[31] Congenital forms of hypogonadotropic hypogonadism can be due to at least 18 different genes involved in the migration of the GnRH neurons and stimulation of GnRH signaling. Selective deficiency of LH or FSH can rarely be due to inactivating mutations of the β-subunit. Acquired forms can be due to a tumor that interferes with the normal production of LH or FSH, such as Rathke pouch cysts, craniopharyngiomas, or other brain tumors. Functional gonadotropin deficiency can be transient, as seen in chronic illness, starvation, Cushing syndrome, anorexia nervosa (Chapter 200), or alcoholism (Chapter 364). Other causes of acquired hypogonadotropic hypogonadism include infection (tuberculosis [Chapter 299], HIV [Chapter 359], syphilis [Chapter 295]), trauma, infiltrative diseases (e.g., hemochromatosis [Chapter 196] and sarcoidosis [Chapter 83]), as well as medications such as opioids and anabolic steroids.

CLINICAL MANIFESTATIONS AND DIAGNOSIS

The clinical presentation of hypogonadotropic hypogonadism (Chapter 216) depends on the onset (acquired or congenital), the severity of the defect, and any associated conditions. In congenital forms, patients classically present in the second or third decade of life with poorly or absent sexual characteristics, failure to enter puberty, and primary amenorrhea or infertility. In acquired forms, hypogonadotropic hypogonadism is usually the first manifestation of any process that interferes with normal pituitary function because reductions in FSH and LH usually cause symptoms before reductions in other inhibitory hormones.

The endocrine diagnosis of hypogonadotropic hypogonadism is rather straightforward when men have low levels of testosterone or women have low levels of estradiol in the presence of low or normal levels of gonadotropins. Occasionally, baseline testing is equivocal, so a provocative test is necessary to confirm hypogonadotropic hypogonadism and to distinguish hypothalamic from pituitary disease. In such instances, leuprolide is administered (10 μg/kg subcutaneously), and then LH and FSH are measured at −10, 0, 30, 60, 90, 180, 240, and 1440 minutes later, with estradiol (or testosterone) also measured at baseline and 1440 minutes. In patients with pituitary disease, leuprolide will not stimulate baseline LH or FSH, so levels of testosterone or estradiol will remain flat. In patients with hypothalamic disease, by comparison, the intact pituitary will respond to the leuprolide by increasing levels of LH and FSH and, thereby, levels of testosterone or estradiol.

TREATMENT

Replacement of gonadal hormones is usually the best treatment. In females who have not yet started puberty, estrogen should be initiated at low doses to promote breast development. When breakthrough bleeding occurs about 6 months later, cyclical therapy can be started by adding a progestogen and then increasing estrogen doses gradually over a 2- to 3-year period (Chapter 214). Vitamin D replacement (Chapter 225) should also be provided. Chapter 218 provides guidance for inducing ovulation for women who hope to become pregnant.

In men, transdermal testosterone (50 mg each morning to the surface of the skin, with the dose adjusted monthly to keep the free testosterone in the mid-normal range) is usually preferred because of ease of administration. Alternatively, intramuscular injections at 2- to 4-week intervals (e.g., testosterone cypionate 200 mg every 2 weeks) are effective (see Table 216-6). Doses should be adjusted based on peak and trough testosterone levels (1 week after and just before the next dose) and self-reported libido. Men over age 50 or those that have a family history of prostate cancer or are African American should be screened for prostate cancer before starting treatment. Prostate specific antigen blood levels are expected to increase with therapy, but if the PSA increases more than 1.4 ng/mL in any one year or to >4 ng/mL, a urologic consultation is recommended. If the hematocrit increases to >54%, the hematocrit should be repeated in 2 months, and if still elevated the testosterone should be reduced or discontinued. Several oral preparations of testosterone undecanoate have recently been approved by the FDA.

TUMORS PRODUCING FOLLICLE-STIMULATING HORMONE AND LUTEINIZING HORMONE

PATHOBIOLOGY

A majority of pituitary tumors are classified clinically as nonsecreting or nonfunctional adenomas, but the majority (70 to 80%) secrete small amounts of either the α-subunit or β-subunit of LH or FSH (which have no clinical manifestations) or rarely an intact LH or FSH with both α-and β-subunits. FSH is more common than LH, and free α-subunits are more common than β-subunits. Little is known about the molecular basis of these tumors.

CLINICAL MANIFESTATIONS

Most gonadotrophinomas are clinically silent except when their size results in neurologic findings such as visual field problems or headaches. Patients usually present with hypogonadism because secreted gonadotropins are ineffective for stimulating the gonads. Premenopausal females may have ovarian cysts and menstrual disorders. Men commonly are hypogonadal because of low testosterone levels but also develop testicular enlargement from FSH-secreting tumors. In rare tumors that secrete LH, males have elevated testosterone and hemoglobin levels.

DIAGNOSIS

No clinical syndrome is uniquely associated with these tumors. Some patients may have nonspecific moderate elevations of prolactin, but almost all cases are diagnosed postoperatively when the surgical specimen is analyzed.

TREATMENT

Because the major symptoms of the gonadotropin-producing tumors or nonfunctioning adenomas are related to local mass effects and extrasellar extension, the goal of treatment is to reduce the size of the tumor. Transsphenoidal surgery usually can completely or partially reverse any hypopituitarism and visual field impairment but is rarely curative because the tumors are large. Postoperative radiation therapy may benefit patients who have minimal residual tumor. If no tumor is seen on a postoperative MRI, annual monitoring with visual field testing plus CT or MRI is indicated. Tumor markers such as LH and FSH also can monitor tumor activity. For growing tumors, repeat surgery, radiation therapy, or both are indicated. Medical therapy (e.g., dopamine agonists and somatostatin analogues) usually is not helpful.

THYROID-STIMULATING HORMONE

Thyroid function (Chapter 207) and growth are controlled by the action of TSH. Similar to LH and FSH, TSH is composed of a common α-subunit and a β-subunit that is unique to thyrotrophs. Regulation of TSH secretion is by the hypothalamic TRH (Chapter 204) and by thyroid hormone itself. Feedback by thyroid hormone is dependent on intranuclear thyroid hormone receptors, which bind T_3.

T_4 enters the portal-hypophyseal plexus and is deiodinated into T_3 where it then effects pituitary thyrotroph release. TSH acts on thyroid cells via a specific TSH membranous receptor, which contains extracellular, intramembranous, and intracellular domains. Large quantities of hormones similar to TSH, such as hCG, can stimulate the TSH receptor, and thereby the thyroid gland, in the absence of TSH. Furthermore, most thyroid-hormone secreting ("toxic" or "hot") thyroid nodules are due to constitutive activating mutations in the *TSHR* gene.

TSH is secreted in a pulsatile and diurnal variation; but, unlike other pituitary hormones, random measurements of morning serum TSH are consistent enough so that measurement of TSH is clinically useful in determining the extent of thyroid hormone production. Whereas the range of TSH in the normal population is generally between 0.4 and 4.0 mU/L, each person has an individual "thyroid thermostat" set at a specific level. In general, screening for thyroid disease is best done by TSH measurement and, if outside the normal range, confers a high likelihood of thyroid dysfunction (see Chapter 207). Alternatively, when thyroid hormone levels are high and the TSH is not suppressed, secondary hyperthyroidism, of which TSH-secreting pituitary adenomas are in the differential diagnosis (see later), is likely.

CENTRAL HYPOTHYROIDISM

PATHOBIOLOGY

Failure of the pituitary to produce TSH in response to low levels of thyroid hormone is consistent with central or secondary hypothyroidism. An isolated TSH defect is relatively rare and usually related to a genetic factor necessary for thyrotroph differentiation. Pituitary masses that impinge on the thyrotrophs also cause failure to produce sufficient amounts of TSH in the setting of low thyroid hormone levels. However, reduced TSH secretion is usually a late-stage result of pituitary masses, which tend to affect other pituitary hormones first.

CLINICAL MANIFESTATIONS AND DIAGNOSIS

The clinical signs and symptoms of central hypothyroidism are indistinguishable from primary thyroid disease, except that the thyroid is nonpalpable. When the thyroid hormone levels are low and the TSH is normal or low, central hypothyroidism is suggested. However, another cause of the constellation of thyroid tests consistent with central hypothyroidism (Table 205-10) is euthyroid sick syndrome (Chapter 207) or nonthyroidal illness, in which cytokines inhibit the release of hypothalamic and pituitary hormones. Euthyroid sick syndrome is also characterized by an increase in serum reverse T_3, which is formed by 5′ deiodination of T_4 and is not biologically active. The same test results are seen in starvation due to activation of the deiodinase. Because isolated TSH deficiency is rare, testing for deficiencies in other pituitary hormones is always recommended.

TREATMENT

Treatment of secondary hypothyroidism is straightforward with a physiologic replacement dose of thyroid hormone (e.g., levothyroxine starting at 1.6 mg/kg and titrated to serum T_4 levels at the upper end of normal if not slightly elevated; see Chapter 207). TSH is not a useful marker of adequate replacement because the thyrotroph is not responsive to the thyroid hormone concentration. In general, titration of thyroxine replacement involves a combination of monitoring the serum T_4 concentration and listening to the patient. The patient should take the thyroxine without food, iron, calcium, or fibrates, all of which can impair its intestinal absorption.

TUMORS THAT SECRETE THYROID-STIMULATING HORMONE

Rarely, pituitary adenomas known as TSHomas or TSH-secreting pituitary adenomas can produce TSH. These tumors account for less than 1% of all cases of hyperthyroidism.

TABLE 205-11 CAUSES OF DISCORDANT THYROID TESTS

LOW TH AND NORMAL OR LOW TSH
Secondary hypothyroidism
Pituitary dysfunction
TRH mutation
TSH mutation
Low TBG or other binding proteins (free T_4 would be normal)
Nonthyroidal illness
Medications
HIGH TH AND NORMAL OR HIGH TSH
TSHoma
Thyroid hormone receptor β resistance to thyroid hormone
Elevated binding proteins (e.g., elevated TBG, familial dysalbuminemic hyperthyroxinemia)
Thyroid hormone habituation
Selenocysteine deficiency syndrome (elevated T_4 due to inability to convert T_4 to T_3)
MCT8-deficiency (elevated T_3 and normal TSH with low T_4)

MCT8 = monocarboxylase transporter 8; T_3 = triiodothyronine; T_4 = thyroxine; TBG = thyroid-binding globulin; TH = thyroid hormone; TRH = thyroid-releasing-hormone; TSH = thyroid-stimulating hormone.

CLINICAL MANIFESTATIONS AND DIAGNOSIS

In addition to classic findings of hyperthyroidism, clinical findings in TSHoma include a diffuse goiter, visual field defects, headache, and menstrual irregularities in women. Occasionally, patients do not have hyperthyroid symptoms, most likely due to habituation to the mildly elevated hormone concentrations.

A diagnosis of TSHoma should be considered when patients present with high serum levels of thyroxine and triiodothyronine as well as a normal or elevated TSH level (see Table 205-11). In postmenopausal women, elevated serum levels of the α-subunit of the TSH molecule and nonsuppressed TSH can be seen. Other causes of elevated T_4 and T_3 in the presence of nonsuppressed TSH are shown in Table 205-10.

The diagnosis is rarely straightforward. A combination of tests (e.g., repeat thyroid tests in another laboratory, α-subunit, other pituitary hormones) can confirm the diagnosis, but no single test is diagnostic. In the absence of any history or testing suggestive of a pituitary adenoma, and given the difficulty in distinguishing patients with TSH-secreting tumors from resistance to thyroid hormone, consideration should be given to performing (when available) an analysis for mutations in the thyroid hormone receptor-β gene in patients with elevated free T_4 and T_3, nonsuppressed TSH, and a normal serum α-subunit.

TREATMENT

The goal of treatment is to reduce the size of the tumor with surgery or radiation and to control the hyperthyroidism. In patients with TSH-secreting pituitary tumors, medical or surgical thyroidectomy can cause growth of the tumor. Outcomes are similar to those for gonadotropin-producing adenomas (see earlier).

A β-blocker such as propranolol (80 to 160 mg daily) or atenolol (25 to 50 mg daily) can be given to ameliorate some of the symptoms and signs of hyperthyroidism (Chapter 207). Long-term antithyroid drug therapy or thyroid ablation with radioiodine or surgery is not indicated because sustained reductions in thyroid hormone secretion would be expected to increase TSH secretion and stimulate the tumor's growth. However, if euthyroidism cannot be achieved with somatostatin analogs or dopamine agonists, short-term administration of a thionamide (for example, methimazole 10 mg twice a day; see Chapter 207) is necessary to restore euthyroidism prior to neurosurgery.

NONFUNCTIONING PITUITARY ADENOMAS

Nonfunctioning pituitary adenomas do not cause hormonal excess,[32] although hyperprolactinemia can occur if the pituitary stalk is sufficiently compressed. As a result, these tumors are usually detected when their size causes neurologic symptoms, especially visual field abnormalities, headaches, and ophthalmoplegias. Elevated prolactin levels from stalk compression are much lower than the levels seen with a macroprolactinoma, usually 50 to 100 ng/mL.

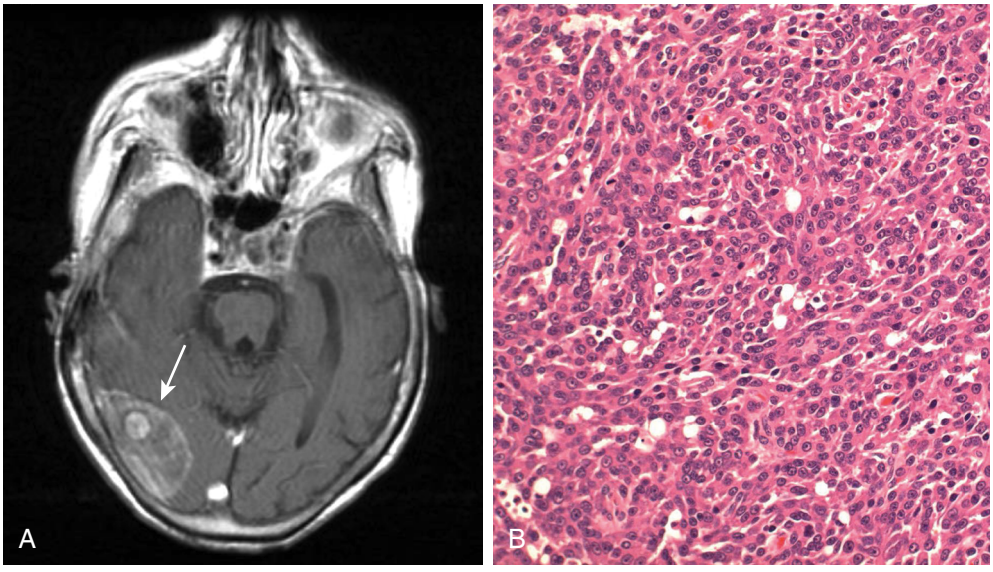

FIGURE 205-9. Pituitary carcinoma. Magnetic resonance image of a cerebral mass in a 43-year-old male patient with an aggressive adenoma that was secreting thyroid-stimulating hormone (**A**). The patient presented with seizures. Biopsy of a brain lesion revealed sheaths of disorganized pituitary cells (**B**).

Oftentimes a nonfunctioning pituitary adenoma is found incidentally when a pituitary mass is discovered in a patient who has a brain imaging study for an unrelated reason. Evaluation (Table 205-7) reveals no hormone excess. Nonfunctioning pituitary adenomas that cause neurologic symptoms require surgical removal, preferably transsphenoidal. Asymptomatic nonfunctioning pituitary adenomas can be monitored by hormonal testing, to assure that no abnormal abnormalities develop, and by MRI, to evaluate the tumor's potential growth. About 50% of tumors grow, and about 20% may require treatment within 7 years.[33]

PITUITARY CARCINOMAS

With few exceptions, pituitary tumors are adenomas that can grow around the sella and invade the carotids and sphenoid sinuses but that do not metastasize. The term *pituitary carcinoma* is restricted to 0.1 to 0.2% of the pituitary tumors that metastasize beyond the immediate vicinity of the sella to the craniospinal region or systemically. Ki-67 is a nuclear protein, and staining tissue for this protein gives the pathologist a marker of the tumor's proliferation index. If the Ki-67 proliferation index is greater than 3%, it suggests a more aggressive pituitary tumor. Approximately half of these tumors produce either ACTH or prolactin, and the remainder are nonsecreting. Surgical debulking, either by a transsphenoidal or open approach depending on its size and the other structures involved by it (e.g., cavernous sinus invasion or attachment to the optic nerve), is the standard therapy, but radiotherapy and temozolomide chemotherapy[34] also have been used because pituitary tumors can have multiple recurrences and be resistant to standard treatments.[35] These aggressive tumors generally have a high mortality rate (over 50%), with a median life expectancy of about 10 months after diagnosis (Fig. 205-9).[36]

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206 POSTERIOR PITUITARY

JOSEPH G. VERBALIS

ANATOMY AND HORMONE SYNTHESIS

Vasopressin and oxytocin, which are hormones of the posterior pituitary, are synthesized in specialized neurons of the hypothalmus. These neurons, notable for their large size, are termed *magnocellular neurons*. In the hypothalamus, the magnocellular neurons are clustered in the paired paraventricular and supraoptic nuclei (Fig. 206-1). Vasopressin and oxytocin are also synthesized in parvocellular (i.e., small cell) neurons of the paraventricular nuclei,[1] and vasopressin (but not oxytocin) is also synthesized in the suprachiasmatic nucleus.

Transcription of vasopressin and oxytocin messenger RNA and translation of the vasopressin and oxytocin prohormones occur entirely in the cell bodies of the neurohypophyseal neurons. The prohormones, provasopressin and pro-oxytocin, are packaged along with processing enzymes into neurosecretory granules that are transported out of the perikaryon of the neurohypophyseal neurons via microtubules and down the long axons that form the supraopticohypophysial tract, which terminates in the posterior pituitary. During transport, the processing enzymes cleave provasopressin into vasopressin (9 amino acids), vasopressin-neurophysin (95 amino acids), and vasopressin glycopeptide, or copeptin (39 amino acids). Pro-oxytocin is similarly cleaved to oxytocin (which differs from vasopressin by only two of nine amino acids) and oxytocin-neurophysin. The neurophysins form neurophysin-hormone complexes that stabilize the hormones. Stimulatory (e.g., glutamatergic, cholinergic, and angiotensin) neurotransmitter terminals and inhibitory (e.g., γ-aminobutyric acid and noradrenergic) neurotransmitter terminals control the release of vasopressin through the activity of synaptic contacts on the neurohypophyseal cell bodies. Physiologic release of vasopressin or oxytocin into the general circulation occurs at the level of the posterior pituitary. Although each of the other prohormone fragments are released into the circulation, vasopressin and oxytocin are the only known biologically active components of the prohormones. Factors that stimulate the release of neurohypophyseal hormones also stimulate their synthesis. Because synthesis is delayed, maintenance of a large store of hormone in the posterior pituitary is essential to enable the instantaneous release of each hormone that is necessary following acute hemorrhage (vasopressin) or during parturition (oxytocin). Sufficient vasopressin is stored in the posterior pituitary to support maximal antidiuresis for several days and to maintain baseline levels of antidiuresis for weeks.

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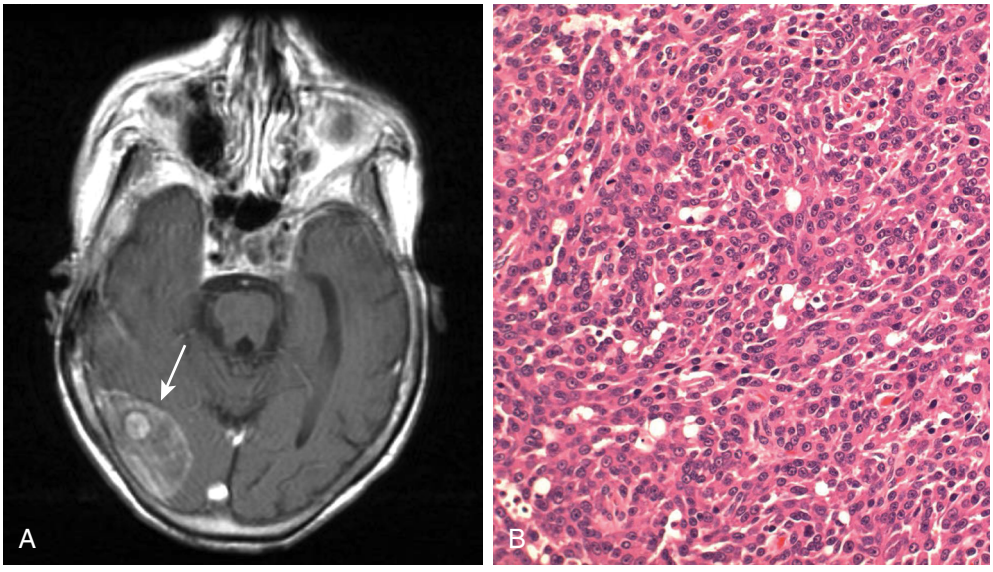

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206 POSTERIOR PITUITARY

JOSEPH G. VERBALIS

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ABSTRACT

Vasopressin and oxytocin, which are the hormones of the posterior pituitary, are synthesized in the hypothalamus and transported to the posterior pituitary, where they are released in response to specific stimuli. The primary physiologic action of vasopressin is its function as a water-retaining hormone. In response to conditions of reduced body water, vasopressin is secreted to maximize urine concentration and reduce urine volume losses. Diabetes insipidus can result from either inadequate vasopressin secretion (central) or inadequate renal response to vasopressin (nephrogenic). Central diabetes insipidus is caused by a variety of acquired or congenital anatomic lesions that disrupt the neurohypophysis. Nephrogenic diabetes insipidus is most commonly congenital, but therapy with drugs such as lithium can cause an acquired form sufficient to warrant treatment. Regardless of the etiology of the diabetes insipidus, the end result is a water diuresis due to an inability to concentrate urine appropriately. Patients develop polyuria and secondary polydipsia from the stimulation of thirst, unless they also have osmoreceptor dysfunction, which impairs thirst. Treatment, which depends on the type of diabetes insipidus, can consist of replacement of vasopressin via synthetic vasopressin analogues in central diabetes insipidus or treatments to reduce polyuria in nephrogenic diabetes insipidus. In all cases, achievement of normal water homeostasis with reduction of polyuria and polydipsia is the goal.

KEYWORDS

oxytocin
vasopressin
diabetes insipidus
osmolality
water homeostasis
polyuria
polydipsia

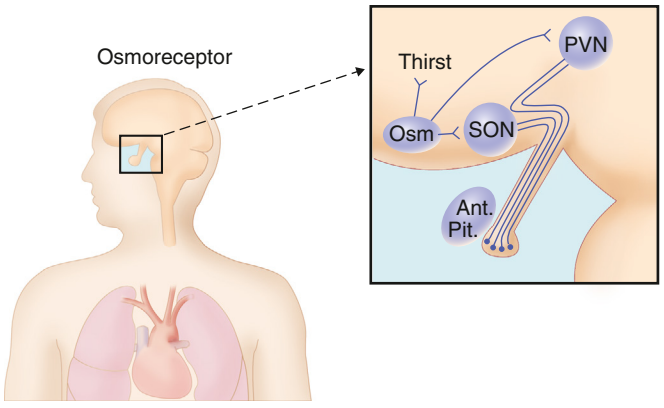

FIGURE 206-1. Sagittal view of the head, demonstrating the position of the neurohypophysis. The magnocellular neurons are clustered in two paraventricular nuclei (PVN) and two supraoptic nuclei (SON). Only one nucleus of each pair is illustrated. The supraoptic nuclei are lateral to the edge of the optic chiasm, whereas the paraventricular nuclei are central along the wall of the third ventricle. The axons of the four nuclei combine to form the supraopticohypophysial tract as they course through the pituitary stalk to their storage terminals in the posterior pituitary. The osmostat (Osm) is in the hypothalamus anterior to the third ventricle; the thirst center (Thirst) is distributed across different brain areas. Ant. Pit. = anterior pituitary. (From Buonocore CM, Robinson AG. Diagnosis and management of diabetes insipidus during medical emergencies. *Endocrinol Metab Clin North Am*. 1993;22:411-423.)

VASOPRESSIN

Vasopressin and Regulation of Osmolality

The primary physiologic action of vasopressin is its function as a water-retaining hormone. The central sensing system (osmostat) for controlling the release of vasopressin is anatomically discrete, located in a small area of the hypothalamus just anterior to the third ventricle (see Fig. 206-1). The osmostat controls the release of vasopressin to allow water retention and also stimulates thirst to cause water repletion.

Osmotic regulation of vasopressin release and osmotic regulation of thirst are usually tightly coupled, but they can be dissociated under pathologic conditions. The primary extracellular osmolyte to which the osmoreceptor responds is sodium. Although basal osmolality in normal individuals ranges between 280 and 295 mOsm/kg H_2O, extracellular fluid osmolality for each individual is maintained within narrow ranges. Increases in plasma osmolality as small as 1 to 2% are sufficient to stimulate vasopressin release. Basal plasma levels of vasopressin are generally 0.5 to 2 pg/mL, a level that maintains urine osmolality above plasma osmolality and urine volume in the range of 1 to 3 L/day. When vasopressin levels are suppressed below 0.5 pg/mL, urine osmolality decreases to below 100 mOsm/kg H_2O, and a free water diuresis (or "aquaresis") ensues at levels that approach 800 to 1000 mL/hour (18 to 24 L/day). Increases in plasma osmolality cause a linear increase in plasma vasopressin and a corresponding linear increase in urine osmolality. At a plasma osmolality of approximately 295 mOsm/kg H_2O, urine osmolality is maximally concentrated to 1000 to 1200 mOsm/kg H_2O. As a result, the entire physiologic range of urine osmolality is accomplished by relatively small changes in plasma vasopressin levels of 0 to 5 pg/mL (E-Fig. 206-1).

Thirst is not stimulated until a somewhat higher plasma osmolality (5 to 10 mOsm/kg H_2O) above the threshold for release of vasopressin. Most humans derive sufficient water from habitual fluid intake and catabolism of food to maintain plasma osmolality below the threshold that activates thirst. Therefore, under normal physiologic conditions, water balance (and hence plasma osmolality) is regulated more by secretion of vasopressin than by thirst. However, with severe degrees of dehydration, thirst is essential to restore body water deficits.

Vasopressin acts on the V_2 subtype of vasopressin receptors in the collecting duct principal cells of the kidney. Vasopressin V_2 receptors activate adenylate cyclase, and the subsequent increased intracellular levels of cyclic adenosine monophosphate (cAMP) initiate the movement of aquaporin-2 (AQP2) water channels to the apical (luminal) membrane of the collecting duct cells. These channels allow facilitated rapid transport of water from the collecting duct lumen into the principal cell along osmotic gradients. The water then exits the cell through the basolateral membrane into the kidney medullary circulation through constitutively expressed aquaporin-3 and aquaporin-4 water channels. This entire process is termed *antidiuresis*.[2] In the absence of vasopressin, the AQP2 channels are reinternalized from the apical membrane into subapical vesicles. This process prevents active reabsorption of water from the collecting duct lumen, thereby resulting in diuresis. In addition to this rapid shuttling of the AQP2 channels to regulate water reabsorption on a minute-to-minute basis, vasopressin acts through the V_2 receptors to regulate long-term stores of AQP2. The absence of vasopressin results in decreased synthesis of AQP2. The hypertonic medullary interstitium is the determinant of the maximal concentration of the urine, which is in equilibrium with the osmolality of the inner medulla of the kidney under conditions of maximal antidiuresis (Chapter 101).

Vasopressin and Pressure and Volume Regulation

High-pressure baroreceptors are located in the aorta and carotid sinus, and low-pressure baroreceptors are located in the right and left atria. Decreases in blood pressure or intravascular volume stimulate the release of vasopressin, whereas situations that increase blood volume or left atrial pressure (e.g., negative-pressure breathing) decrease the secretion of vasopressin.[3] The release of vasopressin in response to changes in volume or pressure is much less sensitive than the release in response to osmoreceptors; generally a 10 to 15% reduction in blood volume or pressure is needed to stimulate the release of vasopressin. However, once arterial pressure falls below this threshold, the stimulated response is exponential, thereby resulting in plasma levels of vasopressin that are markedly greater than those resulting from osmotic stimulation.

The pressor effects of vasopressin are mediated through a separate vasopressin receptor subtype, the V_{1a} receptors, located on vascular smooth muscle. However, the renin-angiotensin-aldosterone system (Chapter 208) is more important for controlling extracellular and blood volume than is the regulation of water homeostasis. Nevertheless, the pressor effects of vasopressin to increase blood pressure can become prominent when other blood pressure regulatory systems are deficient (e.g., autonomic neuropathy [Chapter 386] or blockade of the renin-angiotensin-aldosterone system with medication) or in states of pathologic vasodilation (e.g., liver cirrhosis [Chapter 139], septic shock [Chapter 94]).

Vasopressin and Adrenocorticotropic Hormone

Vasopressin stimulates secretion of adrenocorticotropic hormone (ACTH) via stimulation of the vasopressin V_{1b} receptor subtype that is located on anterior pituitary corticotroph cells. Although the major regulator of ACTH secretion is corticotropin-releasing hormone (Chapter 205), vasopressin activates a different signal transduction system in the corticotrophs, so these hormones have synergistic effects on the secretion of ACTH.

Interaction of Osmotic and Volume Regulation

The vasopressin system optimizes water homeostasis. Water is consumed as available in the absence of stimulated thirst, and vasopressin secretion then regulates water excretion to maintain plasma osmolality. Thirst serves as a reserve mechanism if dehydration becomes excessive. Because pressure-volume regulation of vasopressin is less sensitive, modest changes in pressure or volume, which are exacerbated by upright posture, do not interfere with the regulation of osmolality. Yet the pressor effect of high vasopressin levels serves to maintain blood pressure if volume depletion or hypotension becomes excessive. Usually, the physiologic regulation of osmolality and pressure-volume is synergistic. Dehydration causes an increase in plasma osmolality and a decrease in blood volume, both of which stimulate the release of vasopressin. Conversely, excess fluid administration causes a decrease in plasma osmolality and an expansion of blood volume, both of which inhibit vasopressin secretion.

With volume expansion, the secretion of vasopressin decreases. During pregnancy, plasma osmolality decreases by approximately 10 mOsm/kg H_2O as a result of a resetting of the osmostat for vasopressin secretion, and the osmostat for thirst is reset downward in parallel. These effects appear to be mediated by the placental hormone relaxin.

Abnormalities in water and electrolyte balance are common in the elderly, in part owing to age-related changes in body volume (as much as a 50% decrease in total body water occurs in those older than 75 years) and renal function. The elderly also have a decreased sense of thirst. Despite a normal or even increased ability to secrete vasopressin with age, the ability to achieve either maximal urine concentration to retain water or maximal dilution of urine to excrete water is diminished. Consequently, the elderly are particularly prone to both hypernatremia and hyponatremia (Chapter 102) when faced with diseases or medications that affect water balance.

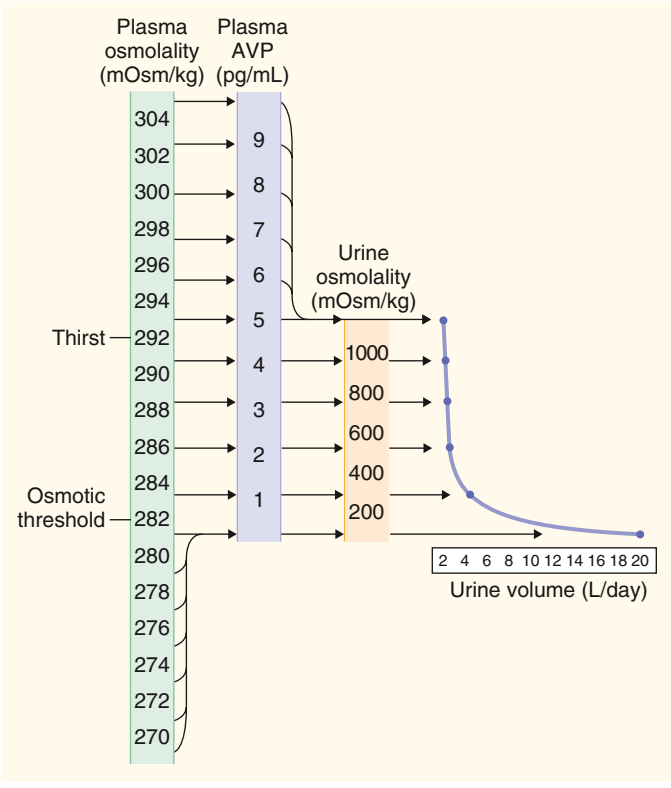

E-FIGURE 206-1. Idealized schematic of the normal physiologic relationships among plasma osmolality, plasma vasopressin (AVP), urine osmolality, and urine volume. The entire physiologic range of urine osmolality occurs with plasma vasopressin levels from 0 to 5 pg/mL. Increases in plasma osmolality above approximately 290 to 295 mOsm/kg H_2O result in increases in plasma vasopressin but no further concentration of the urine, which is limited by the maximal osmolality in the inner medulla. The relation of volume (calculated on the basis of a constant osmolar load) is inversely exponential to the other parameters. Because of this relationship, urine volume does not change substantially until there is nearly absent vasopressin secretion, after which urine volume increases dramatically. (Calculated from formulas presented in Robertson GL, Shelton RL, Athar S. The osmoregulation of vasopressin. *Kidney Int*. 1976;10:25-37. Figure drawn by J.G. Verbalis, Georgetown University, Washington, DC.)

OXYTOCIN

Prolactin is the main hormone necessary for milk production, but oxytocin is essential for milk secretion. Suckling stimulates tactile receptors in the nipple, thereby producing an afferent signal to the hypothalamus that causes a synchronized release of oxytocin from the posterior pituitary. Oxytocin binds to oxytocin receptors in the breast and induces the alveoli and ductules to eject milk. Upregulation of uterine oxytocin receptors also dramatically increases uterine smooth muscle contractions at the end of pregnancy, when it induces uterine contraction to inhibit blood loss after delivery. No pathologic syndromes of either increased or decreased secretion of oxytocin have yet been defined, although oxytocin is clearly important for maternal and affiliative behaviors. However, because of their structural similarity, at high plasma levels oxytocin can activate vasopressin receptors, and vasopressin can activate oxytocin receptors.

SYNDROME OF INAPPROPRIATE ANTIDIURETIC HORMONE SECRETION

Excess secretion of vasopressin can be caused by abnormally regulated secretion from the posterior pituitary or by ectopic synthesis and secretion of vasopressin by tumors. Osmotically inappropriate secretion of vasopressin causes renal water retention and volume expansion, with consequent dilutional hyponatremia. This disorder, called the syndrome of inappropriate antidiuretic hormone secretion (SIADH), is discussed in Chapter 102.

DIABETES INSIPIDUS

DEFINITION

Diabetes insipidus is the excretion of a large volume of hypotonic insipid (tasteless) urine, usually manifested by polyuria (increased urination) and polydipsia (increased thirst).[4] The large urine volume, usually in excess of 50 to 60 mL/kg/day, must be distinguished from an increased frequency of small urine volumes and from large volumes of isotonic or hypertonic urine, both of which have different clinical significance.

EPIDEMIOLOGY

Diabetes insipidus is a rare disease with a reported prevalence of 1:25,000. Less than 10% of diabetes insipidus can be attributed to hereditary forms such as X-linked nephrogenic diabetes insipidus, which represents 90% of cases of congenital nephrogenic diabetes insipidus and occurs with a frequency of 4 to 8 per 1 million male live births. No sex difference has been reported for the other forms.

PATHOBIOLOGY

Five pathophysiologic mechanisms must be considered in the differential diagnosis of diabetes insipidus.

Central Diabetes Insipidus

Central diabetes insipidus is caused by the inability of the hypothalamus-posterior pituitary to secrete (and usually to synthesize) vasopressin in response to increased osmolality. Central diabetes insipidus can be inherited as an autosomal dominant disease that is typically characterized by an asymptomatic infancy and an onset later in childhood. Most genetic defects are either in the signal peptide of the pre-prohormone or in the neurophysin portion of the prohormone. Most cases are believed to result from disruption of cleavage from the signal peptide or abnormal folding of the neurophysin, which slows trafficking of the mutant prohormone through the endoplasmic reticulum, thereby leading to neuronal cell dysfunction or death.[5] Because this is a cumulative process, this explains the later onset of central diabetes insipidus with these types of mutations.

As few as 10 to 15% of the normal number of vasopressinergic neurons in the hypothalamus is sufficient to maintain an asymptomatic urine volume, but the further loss of just a small number of these neurons produces a rapid increase in urine volume and symptomatic polyuria. The dilute glomerular filtrate is not concentrated in the renal collecting duct, and consequently, a large volume of hypotonic (i.e., dilute) urine is excreted. The result is a secondary increase in serum osmolality, with stimulation of thirst and secondary polydipsia. Levels of vasopressin in plasma are unmeasurable or inappropriately low for the plasma osmolality. Most cases are acquired, for example, from tumors, neurosarcoidosis of the hypothalamus (Chapter 83), tuberculous meningitis (Chapter 299), multiple sclerosis (Chapter 380), histiocytosis (Chapter 155), or brain trauma (Chapter 368), particularly neurosurgical resection of pituitary adenomas,[6] but some are idiopathic, and a small proportion are genetic.

Osmoreceptor Dysfunction

Osmoreceptor dysfunction is a variant of central diabetes insipidus in which the neurohypophysis is intact, but the osmoreceptive cells in the anterior hypothalamus have been damaged (see Fig. 206-1). Because the osmoreceptor cells are necessary for osmotically stimulated vasopressin secretion, the patient manifests polyuria. When such patients are euvolemic, an increase in plasma osmolality produces neither secretion of vasopressin nor a sensation of thirst. When baroreceptors are stimulated by hypovolemia or hypotension, stored vasopressin in the posterior pituitary results in the prompt secretion of vasopressin.

Because the osmoreceptor cells also control thirst, these patients do not have polydipsia. As a result, patients are characterized by elevated serum sodium levels and plasma osmolalities. For this reason, this disorder has also been called essential hypernatremia and adipsic diabetes insipidus, in recognition of the profound thirst deficits found in most of the affected patients.

Lesions that cause osmoreceptor dysfunction are similar to lesions that can cause central diabetes insipidus, but in contrast to central diabetes insipidus, these lesions usually occur more rostrally in the hypothalamus, consistent with the anterior hypothalamic location of the primary osmoreceptor cells. One lesion that is unique to this disorder is an anterior communicating cerebral artery aneurysm (Chapter 377), particularly following clipping or resection of the aneurysm.

Nephrogenic Diabetes Insipidus

Nephrogenic diabetes insipidus is caused when mutations of the vasopressin V_2 receptor or the vasopressin-induced water channel AQP2, or impairments in the signal transduction system linking V_2 receptor activation and AQP2 membrane insertion, make an otherwise normal kidney unable to respond to vasopressin. Familial nephrogenic diabetes insipidus is a rare, X-linked recessive disease, most cases of which (>90%) are due to more than 100 different mutations of the V_2 receptor.[7] In less than 10% of patients, mutations of the AQP2 water channel on chromosome 12 cause autosomal recessive disease. Nephrogenic diabetes insipidus can also be acquired when drugs (such as demeclocycline, which can be used to treat SIADH [Chapter 102], or lithium carbonate, used to treat bipolar disorders [Chapter 362]) or electrolyte abnormalities (such as severe hypokalemia [Chapter 103] and hypercalcemia [Chapter 227]) decrease the synthesis and/or function of AQP2.

As in hypothalamic (central) diabetes insipidus, the dilute glomerular filtrate entering the collecting duct is excreted as a large volume of hypotonic urine. The rise in plasma osmolality stimulates thirst and produces polydipsia. Unlike central diabetes insipidus, however, measured levels of vasopressin in plasma are high or appropriate for plasma osmolality.

Gestational Diabetes Insipidus

Gestational diabetes insipidus is a rare condition produced by elevated levels or activity of placental cysteine aminopeptidase (oxytocinase or vasopressinase) during pregnancy.[8] The rapid destruction of vasopressin produces diabetes insipidus with polyuria and secondary stimulation of thirst with polydipsia. Because of the circulating vasopressinase, plasma vasopressin levels usually cannot be measured.

Primary Polydipsia

Primary polydipsia is a disorder of excess fluid ingestion rather than of vasopressin secretion or activity. Primary polydipsia is sometimes due to a severe mental illness (Chapter 362), such as schizophrenia, mania, or obsessive-compulsive disorder, in which case it is called psychogenic polydipsia. The prevalence in psychiatric hospitals can be as high as 40%, and there is no obvious explanation for the polydipsia. Dipsogenic diabetes insipidus is caused by increased fluid intake that is not due to underlying psychiatric disease. It is usually idiopathic, but it can also be secondary to organic structural lesions in the hypothalamus as for central diabetes insipidus. Primary polydipsia is also sometimes caused by a high fluid intake for valid (e.g., recurrent nephrolithiasis) or unsubstantiated health reasons. These patients lack overt signs of mental illness, but they also deny thirst and usually attribute their polydipsia to habits acquired from years of adherence to a drinking regimen.

Excessive ingested water produces a mild decrease in plasma osmolality, that shuts off the secretion of vasopressin. In the absence of vasopressin action on the kidney, urine does not become concentrated, and a large volume of hypotonic urine is excreted. The amount of vasopressin in plasma is unmeasurable or low but is appropriate for the low plasma osmolality.

Postoperative Diuresis

Sometimes a postoperative water diuresis occurs as a result of water retention during the surgical procedure. During recovery, vasopressin levels fall, and a diuresis of the retained fluid occurs. Persistent polyuria can be mistaken for diabetes insipidus, but if the patient receives intravenous fluids to match urine output, the serum sodium level is almost always normal.

CLINICAL MANIFESTATIONS

Central Diabetes Insipidus

The sudden appearance of hypotonic polyuria after transcranial surgery in the area of the hypothalamus or after head trauma with basal skull fracture and hypothalamic damage strongly suggests the diagnosis of central diabetes insipidus.[9] Central diabetes insipidus occurs commonly in patients with severe brain ischemia and is often indicative of brain death. Transient hyponatremia without preceding or subsequent diabetes insipidus has been reported with surprisingly high frequency after transsphenoidal surgery for pituitary microadenomas, and it is a common cause of hospital readmission after pituitary surgery.[10]

However, even in patients with more insidious progression of a specific disease or in patients with idiopathic central diabetes insipidus, the onset of polyuria is often relatively abrupt and occurs over several days or weeks. Most patients do not notice polyuria until urine volume exceeds 3 to 4 L/day (Fig. 206-2); urine volume does not exceed 4 L/day until the ability to concentrate the urine is severely limited and plasma vasopressin is nearly absent. Urine volume seldom exceeds the amount of dilute fluid delivered to the collecting duct (≈18 to 24 L in humans). Patients often express a preference for cold liquids, which are more effective in assuaging thirst. Both thirst and increased urine output persist through the night, thereby impairing sleep.

Patients with partial central diabetes insipidus have some ability to secrete vasopressin, but this secretion is markedly attenuated at normal levels of plasma osmolality. Therefore, these patients often have urine volume and symptoms similar to those of patients with complete central diabetes insipidus.

Because most patients with central diabetes insipidus have sufficient thirst to drink fluid to match urine output, few laboratory abnormalities are present at the time of initial evaluation. The serum sodium level can be in the high-normal range, whereas the urine sodium level is usually low secondary to the large urine volume. Uric acid is relatively high because of the modest intravascular volume contraction and lack of action of vasopressin on V_{1a} receptors in the kidney, which stimulate the clearance of uric acid. Uric acid levels greater than 5 mg/dL can help to differentiate diabetes insipidus from primary polydipsia. Both myxedema (Chapter 207) and adrenal insufficiency (Chapter 208) impair the ability to excrete free water by renal mechanisms. The simultaneous occurrence of either of these diseases with central diabetes insipidus (as can occur with a tumor of the hypothalamus or pituitary) can decrease an otherwise large urine output, thereby masking the symptoms of diabetes insipidus. Replacement treatment for the anterior pituitary deficiency, especially glucocorticoids, can then cause a sudden and massive excretion of dilute urine. Similarly, the onset of either hypothyroidism or adrenal insufficiency during the course of diabetes insipidus can decrease the need for vasopressin replacement and in some cases can even cause hyponatremia.

Osmoreceptor Dysfunction

Because patients lack thirst, they are chronically dehydrated, often with markedly increased serum sodium levels (hypovolemic hypernatremia). The volume of urine output depends on the degree of dehydration-induced secretion of vasopressin. If sufficient fluid replacement is given to return extracellular fluid volume to normal, these patients are unable to regulate vasopressin by osmolality and again become polyuric, thereby manifesting their underlying central diabetes insipidus.

Nephrogenic Diabetes Insipidus

Symptoms of the X-linked mutations are noted only in affected males, who often present with vomiting, constipation, failure to thrive, fever, and polyuria during the first week of life. Hypernatremia with a hypotonic urine is typically present. Consanguinity and a family history of the disease in both men and women are common in the autosomal recessive form. However, most adult outpatients with nephrogenic diabetes insipidus are not hypernatremic, because the polydipsia produced by a normal thirst response is generally sufficient to maintain water homeostasis. Instead, adults present with polyuria, polydipsia, and a normal sodium level (unlike children, who cannot increase fluid intake and frequently present with severely symptomatic hypernatremia).

Gestational Diabetes Insipidus

In pregnancy, gestational diabetes insipidus causes polyuria, which stimulates thirst and subsequent polydipsia. In general, diabetes insipidus does not persist after the pregnancy ends and does not recur in subsequent normal pregnancies. Polyuria during pregnancy can also manifest in patients who have limited vasopressin reserve (partial central diabetes insipidus) or who respond poorly to vasopressin action (compensated nephrogenic diabetes insipidus).

Primary Polydipsia

Excessive fluid intake also causes hypotonic polyuria and, by definition, polydipsia. This disorder must be differentiated from the various causes of diabetes insipidus. Despite normal pituitary and kidney function, patients share many characteristics of both central diabetes insipidus (vasopressin secretion is suppressed as a result of decreased plasma osmolality) and nephrogenic diabetes insipidus (kidney AQP2 expression is decreased as a result of suppressed plasma vasopressin levels).[11] These patients usually deny true thirst and attribute their polydipsia to bizarre motives, such as a need to cleanse the body of poisons. Primary polydipsia can also be caused by an abnormality in the osmoregulatory control of thirst, in which case it is called dipsogenic diabetes insipidus.[12] These patients have no overt psychiatric illness and invariably attribute their polydipsia to a nearly constant thirst. In primary polydipsia, laboratory studies are generally normal, although the serum sodium concentration is sometimes at the low end of the normal range, and the level of uric acid is generally lower than in patients with other forms of diabetes insipidus.

DIAGNOSIS

Diabetes insipidus should be considered in all patients who present with significant polyuria, defined as urine output greater than 50 mL/kg/day. If the urine volume is lower (or lower than 3 L/day), diabetes insipidus is excluded (Fig 206-2). Although osmotic diuresis secondary to hyperglycemia, intravenous contrast agents, or renal injury is a more common clinical cause of polyuria, the medical history, an isotonic urine osmolality, and routine clinical laboratory tests generally distinguish these disorders from diabetes insipidus.

After polyuria is confirmed, the urine osmolality should be measured.[13] The diagnosis of diabetes insipidus can be made when urine osmolality is inappropriately low in the presence of an elevated plasma osmolality as a result of an increased serum sodium concentration. A urine osmolality <800 mOsm/kg confirms hypotonic polyuria, whereas an osmolality above this value excludes diabetes insipidus. A low serum sodium level and a low plasma osmolality level can then identify primary polydipsia. Otherwise, a plasma copeptin level should be obtained; a very high level (≥21.4 pmol/L) confirms partial or complete nephrogenic diabetes insipidus, a very low level (<2.6 pmol/L) identifies complete central diabetes insipidus, and an intermediate level requires further evaluation with either a water deprivation test or a hypertonic saline infusion test (see Fig. 206-2).

Provocative Testing

The hypertonic saline infusion test measures plasma copeptin levels after 2 hours of infusing hypertonic (3%) NaCl to achieve a serum sodium level of at least 150 mmol/L.[14] However, because some patients may not be acceptable candidates for increasing the serum sodium level to ≥150 mmol/L, another alternative measures copeptin after an arginine infusion, with a level below 3.5 pM at 60 minutes confirming diabetes insipidus.

A water deprivation test should be performed only under controlled observation in the hospital or an appropriately equipped outpatient area.[15] The patient is weighed at the beginning of the test, and all subsequent fluids are withheld. The volume and osmolality of all excreted urine are measured, and the patient is reweighed after each liter of urine output. When two to three consecutive urine samples have an osmolality differing by no more than 10% and the patient has lost at least 2% of body weight, a blood sample is obtained to measure serum osmolality, serum sodium, and plasma vasopressin levels. The patient is then given 2 μg of desmopressin intravenously or subcutaneously and observed for an additional 2 hours. Adults with normal vasopressin secretion concentrate their urine to greater than 800 mOsm/kg H_2O and have less than a 10% increase in urine osmolality in response to the administered desmopressin. Patients with complete central diabetes insipidus have minimal concentration of the urine with dehydration and a marked increase in urine osmolality (usually >50%) in response to administered desmopressin. Patients with nephrogenic diabetes insipidus usually have no increase in urine concentration in response to administered desmopressin. In patients with partial central diabetes insipidus and patients with primary polydipsia, the urine is often somewhat concentrated in response to dehydration but not to the maximum of a normal person. When

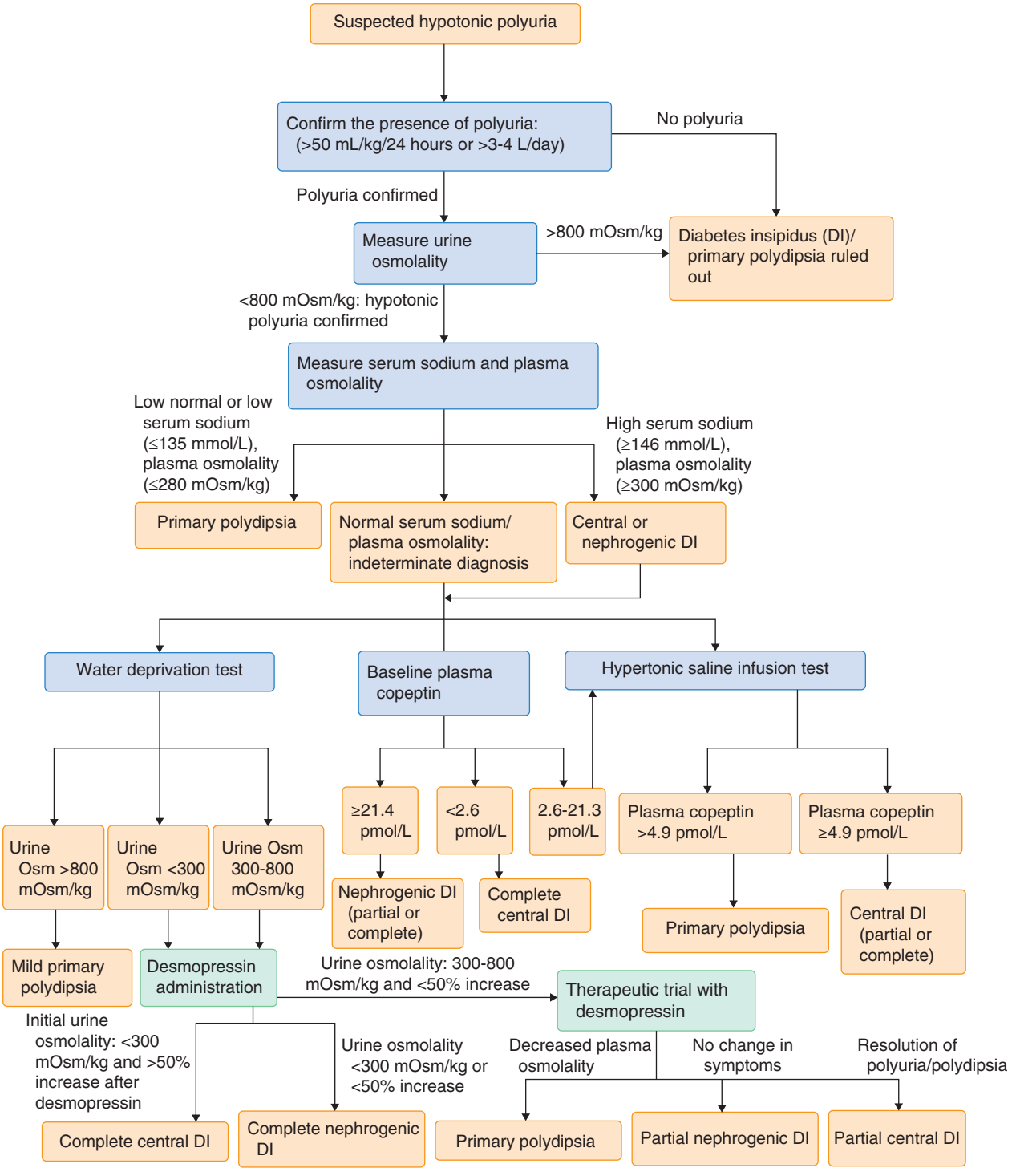

FIGURE 206-2. Algorithm for diagnosis of the various types of polyuria polydipsia syndromes. DI = diabetes insipidus. (Adapted from Gubbi S, Hannah-Shmouni F, Koch CA, et al. Diagnostic testing for diabetes insipidus. [Updated 2019 Feb 10]. In: Feingold KR, Anawalt B, Boyce A, et al., eds. Endotext [Internet]. South Dartmouth: MDText.com, Inc.; 2000. Available from: https://www.ncbi.nlm.nih.gov/books/NBK537591/.)

desmopressin is administered, patients with partial central diabetes insipidus have a further increase (usually >10% but <50%) in urine osmolality, whereas most patients with primary polydipsia have no further increase (i.e., <10%).

In some difficult cases, a decrease in polyuria and thirst with maintenance of normal serum sodium concentration after treatment with a vasopressin agonist can be used to distinguish partial central diabetes insipidus from primary polydipsia. If this approach is used, however, the serum sodium level must be checked within several days to avoid severe hyponatremia in patients with primary polydipsia.

Etiologic Diagnosis

Once the diagnosis of diabetes insipidus has been confirmed physiologically, the next step is to determine its cause.[16,17]

Central Diabetes Insipidus

If testing confirms that inadequate vasopressin secretion is responsible for the polyuria, the underlying cause of central diabetes insipidus must then be determined by magnetic resonance imaging (MRI) of the immediate suprasellar region of the hypothalamus, the pituitary stalk, and the posterior pituitary within the sella turcica.[18] To cause central diabetes insipidus, tumors in the hypothalamic area immediately above the sella must be either sufficiently large to destroy 80 to 90% of the vasopressin cells or be located where the paths of the four nuclear groups converge at the origin of the pituitary stalk, just above the diaphragm sella, and typically thick (i.e., >2 mm) on MRI.

On T1-weighted MRI, the vasopressin and oxytocin stored in neurosecretory granules in the posterior pituitary are visualized as a bright spot in the sella turcica. Most normal subjects have this bright spot (it is absent more

frequently in elderly and dehydrated patients), whereas the bright spot is absent in most patients with central diabetes insipidus. Thickening of the stalk and absence of the bright spot are therefore especially suggestive of a hypothalamic disease process.[19]

Tumors that cause central diabetes insipidus are most often benign primary intracranial tumors such as craniopharyngiomas,[20] ependymomas (suprasellar germinoma), and pinealomas, which arise in the third ventricle. Primary tumors of the anterior pituitary (Chapter 205) cause diabetes insipidus only when substantial suprasellar extension is present. However, rapidly growing intrasellar lesions, such as metastases from carcinomas of the lung, breast, and melanoma or hemorrhage into pituitary adenomas, can cause diabetes insipidus because of insufficient time for the vasopressin axons to adapt by releasing vasopressin from the hypothalamus. Metastases to the hypothalamus can also destroy the supraopticohypophysial tract and produce diabetes insipidus.

Brain trauma (Chapter 368), especially when severe, can also cause diabetes insipidus. In particular, deceleration injuries can cause a shearing of the pituitary stalk at the level of the diaphragm sella. Patients with basilar skull fractures should always be evaluated for possible accompanying diabetes insipidus.

Granulomatous diseases, such as Langerhans cell histiocytosis (Chapter 155), sarcoidosis (Chapter 83), tuberculosis (Chapter 299), and leukemic infiltrates (Chapters 168, 169, and 170) and lymphomas (Chapters 171 and 172) of the hypothalamus (Chapter 204), can cause diabetes insipidus by destroying vasopressin cells.[21] In such patients, the diagnosis is usually suspected on the basis of peripheral manifestations of the respective diseases.

Lymphocytic infundibuloneurohypophysitis is an autoimmune disease, similar to lymphocytic hypophysitis of the anterior pituitary (Chapter 205), in which lymphocytes infiltrate the neurohypophysis to produce diabetes insipidus. The hallmarks of this process are a thickened pituitary stalk and an absence of the pituitary bright spot in a patient with the abrupt onset of polyuria and polydipsia, particularly a postpartum female. When no specific cause is identified, most such cases are probably caused by an autoimmune disease, such as hypophysitis.[22]

A family history suggestive of diabetes insipidus should be investigated with genetic testing for inherited mutations in the vasopressin or vasopressin receptor genes depending on the site of the defect. When no cause is obvious, cerebrospinal fluid may reveal tumor cells or abnormal biomarkers (e.g., elevated angiotensin-converting enzyme levels with neurosarcoidosis, elevated β-HCG levels with germinomas).

Spontaneous (i.e., nontraumatic) diabetes insipidus should not be considered idiopathic until at least 4 years of follow-up. During this interval, annual computed tomography or MRI is indicated to search for a tumor or infiltrative process that may not have been detected at the initial examination.

Nephrogenic Diabetes Insipidus

Other diseases of the kidney can produce polyuria and inability to concentrate the urine secondary to altered renal medullary blood flow or to disorders that inhibit maintenance of the hyperosmolar concentrating gradient in the inner medulla. Renal manifestations of such disorders (e.g., sickle cell disease, sarcoidosis, pyelonephritis, multiple myeloma, analgesic nephropathy) are discussed in Chapter 107.

Primary Polydipsia

All polydipsic patients should be evaluated with MRI of the brain before it is concluded that excessive water intake is due to an idiopathic or psychiatric cause. Primary polydipsia can also be produced by diseases or drugs that cause a dry mouth (Chapter 393) or by any peripheral disorder causing marked elevations of renin or angiotensin II.

TREATMENT

Because excess excretion of water is the primary manifestation of diabetes insipidus, water replacement in adequate quantities avoids the metabolic complications of all forms of this disease. However, oral or intravenous administration of the volume of fluid required to replace the often large urinary losses in diabetes insipidus is difficult and inconvenient. The goal is therapy targeted[23,24] to reduce the amount of polyuria and polydipsia to a tolerable level while avoiding overtreatment, which can produce water retention and hyponatremia.

Central Diabetes Insipidus

The best therapeutic agent for the treatment of central diabetes insipidus is the vasopressin agonist desmopressin, which is available as tablets for oral administration and in either a spray bottle (which delivers a fixed dose of 10 μg in 100 μL) or a bottle with a rhinal catheter (which can deliver 50 to 200 μL [5 to 20 μg]) for intranasal administration. It is generally best to begin therapy with a low dose (e.g., half of a 0.1-mg tablet, 5 μg by the rhinal tube, or a single 100-μL spray of 10 μg) at bedtime and then determine the duration of action by quantifying the polyuria the next day. The duration of action of a single dose varies from 6 to 24 hours; most patients can achieve a good therapeutic response on an every-12-hour schedule for the nasal spray or an 8- or 12-hour schedule for the tablets. The standard therapy for diabetes insipidus in hospitalized adults is parenteral desmopressin (1 to 2 μg every 8 to 12 hours). With any form of administration, serum sodium levels should be monitored regularly to prevent the development of hyponatremia.[25]

With post-traumatic or post-surgical diabetes insipidus, recovery often occurs within the first year of the injury, so allowing the patient to hold a dose of desmopressin once weekly can allow assessment of the need for ongoing therapy. Some patients who have autoimmune neurohypophysitis or granulomatous disease can recover sufficient vasopressin secretion to resolve symptomatic diabetes insipidus after a course of high-dose glucocorticoids under expert guidance (see Chapter 204). Most genetic causes do not recover.

Osmoreceptor Dysfunction

Patients with osmoreceptor dysfunction respond to desmopressin, as do patients with central diabetes insipidus. However, because of their thirst defect, they also must be given a "prescription" for the amount of fluids to be consumed each 24 hours. This prescription must be individualized to each patient, because overconsumption of fluid coupled with desmopressin can produce severe hyponatremia. Daily body weight on an accurate scale can guide hydration, but frequent monitoring of serum sodium levels is usually necessary as well.

Nephrogenic Diabetes Insipidus

Some patients with nephrogenic diabetes insipidus may partially respond to high doses (e.g., 10 to 20 μg) of subcutaneous desmopressin or of intranasal desmopressin (e.g., 100 to 200 μg, which is difficult to administer), but most patients will require additional therapy. Symptomatic nephrogenic diabetes insipidus is usually treated with a thiazide diuretic (e.g., hydrochlorothiazide 12.5 to 25 mg daily),[26] which is enhanced by coadministration of the potassium-sparing diuretic amiloride (5 to 10 mg daily). Some patients benefit from addition of prostaglandin E inhibitors (e.g., indomethacin) that increase cAMP generation by vasopressin and by non–vasopressin-mediated pathways in the kidney. Careful attention should be paid to the possibility that the induced dehydration may increase the concentration of other drugs.

For drug-induced nephrogenic diabetes insipidus, the most direct therapy is discontinuation of the offending agent, if possible. Amiloride (5 to 10 mg daily) can be especially beneficial in cases of nephrogenic diabetes insipidus induced by lithium, because the drug decreases the entrance of lithium into cells in the distal tubule.

Gestational Diabetes Insipidus

Desmopressin, as for central diabetes insipidus, is the drug of choice. During pregnancy, normal serum sodium decreases by approximately 10 mOsm/kg H_2O because of a reset osmostat, so pregnant patients with diabetes insipidus require only enough desmopressin to maintain the plasma osmolality at this lower level. Treatment may be required only during the pregnancy, and the patient often returns to her previous baseline function without the need for therapy when the pregnancy ends. Less commonly, central diabetes insipidus of another cause first becomes symptomatic during pregnancy and then persists afterward, following the usual course of diabetes insipidus.

Primary Polydipsia

For primary polydipsia, treatment commonly focuses on the underlying psychiatric issues (Chapter 362). Preliminary data suggest that the glucagon-like peptide-1 agonist dulaglutide (1.5 mg weekly) can significantly reduce thirst and fluid intake in patients with primary polydipsia[A1] and could therefore be a treatment option for these patients.

Correction of Hyperosmolality

Rarely, severe hypernatremia (Chapter 102) can develop acutely, when patients with diabetes insipidus are unable to drink or are given a hypertonic solution. If the hypernatremia persists for a longer time, the neurons accommodate by producing organic osmolytes (previously called idiogenic osmoles), which limit the amount of brain shrinkage. Once this adaptation has occurred, a too-rapid lowering of osmolality in the extracellular fluid, especially in children, will produce a shift of water into the brain and cause cerebral edema. In this situation in children, desmopressin can be administered to produce constant antidiuresis, and the amount of water given can be regulated to decrease osmolality by no more than approximately 12 mEq/L every 24 hours. By comparison, adults do not require slow correction of hypernatremia.

Postoperatively or after head trauma, diabetes insipidus can be transient (see Prognosis), and the need for long-term antidiuretic maintenance therapy cannot be immediately established.

PROGNOSIS

The prognosis of properly treated diabetes insipidus is excellent. If nephrogenic diabetes insipidus is diagnosed and treated early, kidney damage is only mild to moderate.[27] When central diabetes insipidus is secondary to an invasive disease process, that disease generally determines the ultimate prognosis.

Diabetes insipidus after surgical or traumatic injury to the neurohypophysis can follow any of several well-defined patterns (E-Fig. 206-2). In some patients, polyuria develops 1 to 4 days after injury and resolves spontaneously. Less often, the diabetes insipidus is permanent. Other patients have a triphasic diabetes insipidus, with the first phase of hours or several days of axon shock and lack of function of the damaged neurons, followed by a 2- to 14-day antidiuretic phase that is due to the uncontrolled release of vasopressin from the disconnected and degenerating posterior pituitary or from the remaining severed neurons. Overly aggressive administration of fluids during the second phase does not suppress the uncontrolled vasopressin release from the damaged neurohypophysis and can lead to hyponatremia. This phase is followed by a third phase, in which diabetes insipidus recurs after depletion of vasopressin from the degenerating posterior pituitary gland.

If postoperative diabetes insipidus persists more than several weeks, recovery is less common, and recovery is uncommon after 1 year of continued diabetes insipidus; however, well-documented cases of recovery as long as 10 years after the initiating event have been reported.

Once a deficiency of vasopressin secretion has been present for more than a few weeks, however, it rarely improves, even if the underlying cause of the neurohypophyseal destruction is eliminated. The major exceptions are gestational and postoperative diabetes insipidus, in which spontaneous resolution is the rule.

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207 THYROID

ELIZABETH N. PEARCE AND ANTHONY N. HOLLENBERG

OVERVIEW OF THYROID DISEASE

The thyroid gland synthesizes both T_4 and T_3, which are essential for normal human growth and development and for normal physiologic function during adult life. Thyroid hormone levels are genetically set in each individual and are regulated by a negative feedback loop that allows for exquisite control. Disorders of thyroid hormone production, including both hypothyroidism and hyperthyroidism, have diverse causes, are exceedingly common, and present important therapeutic challenges for clinicians who are caring for these patients. Patients who have goiters can be hypothyroid, hyperthyroid, or euthyroid. Thyroid nodules, which have the potential to be malignant, are extremely common in the general population. A systematic approach is critical to discern which nodules must be evaluated further but also to avoid unnecessary therapy, including thyroid surgery.

PATHOBIOLOGY

The thyroid gland is an essential endocrine organ whose principal function is to secrete two thyroid hormones: 3,5,3′,5′–l-tetraiodothyronine (also known as thyroxine or T_4) and 3,5,3′–l-triiodothyronine (also known as T_3) from thyroid follicular cells. The gland itself also contains parafollicular or C cells that produce the hormone calcitonin, which plays little role in normal human physiology but can be used pharmacologically to treat hypercalcemia. T_4 and T_3 are absolutely required for normal development of the human fetus, and lack of thyroid hormones either early in utero or immediately after birth has severe neurologic consequences. After birth, thyroid hormone is critical for normal growth and development through adulthood and is also responsible for the control of many aspects of normal physiologic function, including cardiac contractility and heart rate, free water clearance, and regulation of body weight and energy expenditure.

T_3 is the principal biologic congener of the thyroid hormones, whereas T_4 functions as a pro-hormone that is converted to T_3. The actions of T_3 are mediated by a family of thyroid hormone receptors that exert their actions primarily in the cell nucleus to regulate physiology by changing gene expression.

The thyroid gland develops in the first trimester of pregnancy from the anterior endoderm. Mutations in key transcription factors that are responsible for this development can lead to congenital hypothyroidism, which is found in 1 per 3500 births. Thyroid follicular cells, which are derived from embryonic stem cells, also can be derived from induced pluripotent stem cells.[1] The thyroid gland weighs approximately 10 to 20 grams in adults and is shaped like a butterfly, with a right lobe and left lobe that are each approximately 4 cm in height and 2 cm in width with an isthmus that bridges the two lobes. In a small percentage of patients, a vestigial pyramidal lobe, which extends off either the right or left lobe, is a remnant of the embryonic tract of the gland from the pharynx to its position in the neck. Because of this tract, ectopic thyroid tissue can be located behind the tongue or anywhere in the neck region. Histologically the gland is composed of thyroid follicular cells, which organize themselves into follicular units that surround a colloid center. C cells, which derive through a separate process from pharyngeal ectoderm, are interspersed in between the thyroid follicular units and have a distinct histological appearance.

Thyroid Hormone Synthesis and Secretion

Thyroid hormones are the only iodinated proteins in humans, and their synthesis is dependent on the appropriate dietary intake of iodine (approximately 150 ug/day). In many regions of the world, iodine intake is below the threshold, thereby leading to thyroid growth, or goiter, as the gland is stimulated by the pituitary gland to try to compensate for the deficiency of thyroid hormone production. Circulating iodine is actively concentrated in the thyroid follicular cell by the sodium-iodide symporter, which is a 13-member transmembrane protein located at the junction between the circulation and the thyroid follicular cell. After iodine enters the cell, it moves to the apical membrane where it is effluxed into the colloid space by specific transporters. When it is out of the thyroid follicular cell, iodide is oxidized by the enzyme thyroid peroxidase, which requires the production of hydrogen peroxide in the colloid space. The oxidized iodide is then coupled to tyrosyl residues present on the 660-KD protein thyroglobulin. Specific residues on thyroglobulin can either be monodeiodinated or diiodinated, thereby allowing for the formation of T_4 or T_3. When it is back in the thyroid follicular cell, the thyroglobulin backbone is lysosomally digested, and mature thyroid hormones are secreted into the blood stream. The human thyroid secretes T_4 and T_3 in a ratio of 14:1. Genetic defects in any of the key enzymatic processes (e.g., mutations in thyroid peroxidase) can lead to congenital hypothyroidism (E-Fig. 207-1).

Thyroid Hormone Transport and Metabolism

Once secreted, circulating T_4 and T_3 are tightly bound to plasma proteins, especially thyroxine binding globulin. The ratio of T_4 to T_3 in the circulation is 60:1 because T_4 is more tightly bound to thyroxine binding globulin and thus has a longer half-life than T_3 (5 to 7 days compared with about 24 hours). To mediate their genomic effects, thyroid hormones first enter target cells via specific thyroid hormone transporters that are differentially expressed across cells.[2] The most well known of these transporters is the monocarboxylate 8 transporter, which is mutated in Allen-Herndon Dudley syndrome, a rare X-linked neurologic syndrome of devastating consequences caused by the inability of thyroid hormones to cross the blood-brain barrier in utero. In addition to allowing the transport of thyroid hormones into cells, the monocarboxylate 8 transporter is also responsible for allowing T_4 to be secreted by the thyroid follicular cell into the circulation.

After thyroid hormones enter target cells, local T_3 availability is regulated by a family of deiodinases that can either activate T_4 to T_3 or inactivate T_4 to the inert reverse T_3 or inactivate T_3 to T_2. The deiodinase family contains three members. Type 1 deiodinase is highly expressed in the liver, has both activating and inactivating properties, but preferentially converts T_4 to T_3. Type 2 deiodinase, which also is an activating deiodinase, is highly expressed in the pituitary, central nervous system (CNS), and skeletal muscle. In contrast, type 3 deiodinase is an inactivating enzyme that is highly expressed during development in the CNS and in sensory organs (E-Fig. 207-2).

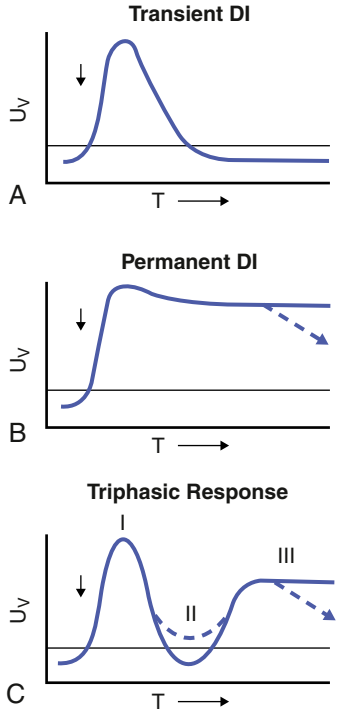

E-FIGURE 206-2. **A to C, Diagrammatic summary of the major patterns of post-operative and post-traumatic diabetes insipidus (DI).** The abscissa represents time (T) after the initial injury (*arrow*); the ordinate represents urinary volume (Uv) relative to a hypothetical "normal" urine output of 2 to 3 L/24 hours (*solid line*). See the discussion in the text. During the triphasic response (C), uncontrolled release of vasopressin from the disconnected or damaged posterior pituitary gland causes an antidiuresis that can lead to water retention and a dilutional hyponatremia. Diabetes insipidus returns as the third phase after the stored hormone in the posterior pituitary has been depleted. (From Verbalis JG, Robinson AG, Moses AM. Postoperative and post-traumatic diabetes insipidus. In: Czernichow AP, Robinson A, eds. *Diabetes Insipidus in Man: Frontiers of Hormone Research*. Basel: S Karger; 1985:247.)

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ELIZABETH N. PEARCE AND ANTHONY N. HOLLENBERG

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After thyroid hormones enter target cells, local T_3 availability is regulated by a family of deiodinases that can either activate T_4 to T_3 or inactivate T_4 to the inert reverse T_3 or inactivate T_3 to T_2. The deiodinase family contains three members. Type 1 deiodinase is highly expressed in the liver, has both activating and inactivating properties, but preferentially converts T_4 to T_3. Type 2 deiodinase, which also is an activating deiodinase, is highly expressed in the pituitary, central nervous system (CNS), and skeletal muscle. In contrast, type 3 deiodinase is an inactivating enzyme that is highly expressed during development in the CNS and in sensory organs (E-Fig. 207-2).

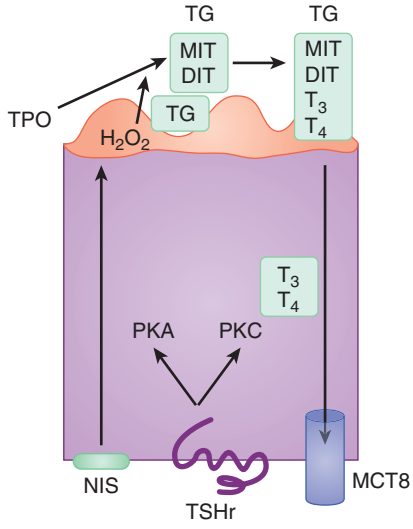

E-FIGURE 207-1. **The thyroid follicular cell: Thyroid hormone synthesis occurs in the follicular cell and requires the uptake of iodine through the sodium-iodine symporter (see text).** T_3 = triiodothyronine; T_4 = thyroxine; TG = thyroglobulin; TPO = thyroid peroxidase.

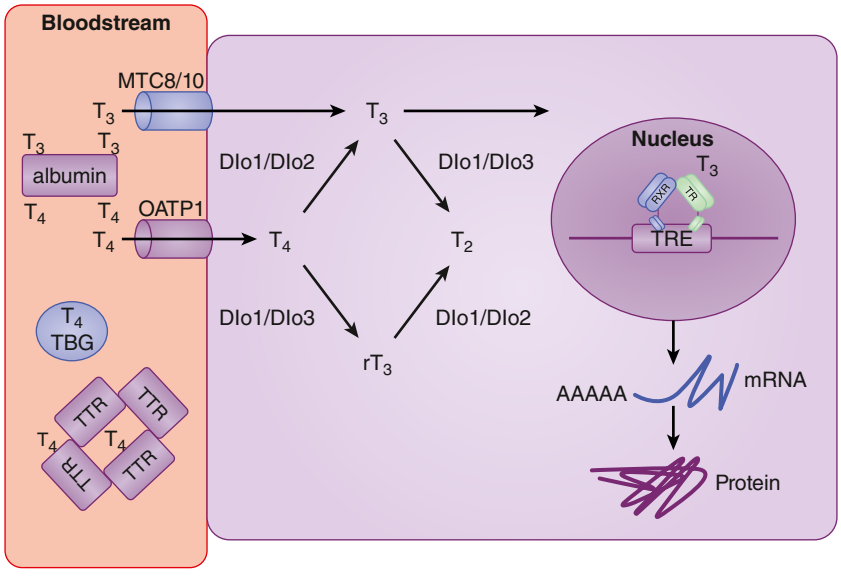

E-FIGURE 207-2. **Thyroid hormone action: Cellular thyroid hormone action depends on the uptake of T_4 (thyroxine) and T_3 (triiodothyronine) from the circulation where deiodinases control the intracellular levels of T_3.** T_3 has its principal actions in the nucleus where it regulates gene expression via thyroid hormone receptors (TR). Dio = deiodinase; RXR = retinoid X receptor; TBG = thyroid-binding globulin; TRE = thyroid hormone response elements; TTR = transthyretin. (From Mendoza A, Hollenberg AN. New insights into thyroid hormone action. *Pharmacol Ther.* 2017;173:135-145.)

ABSTRACT

The thyroid gland synthesizes both T_4 and T_3, which are essential for normal human growth and development and for normal physiologic function during adult life. Thyroid hormone levels are genetically set in each individual and are regulated by a negative feedback loop that allows for exquisite control. Disorders of thyroid hormone production, including both hypothyroidism and hyperthyroidism, have diverse causes, are exceedingly common, and present important therapeutic challenges for clinicians who are caring for these patients. Thyroid nodules, which have the potential to be malignant, are extremely common in the general population. A systematic approach is critical to discern which nodules must be evaluated further but also to avoid unnecessary therapy, including thyroid surgery.

KEYWORDS

thyroid
hormone action
hypothyroidism
hyperthyroidism
nodules
thyroid cancer

Thyroid Hormone Set Points

Circulating levels of thyroid hormones are the tip of the iceberg, because variations in both transport and deiodination can substantially alter intracellular concentrations of T_3. Nevertheless, the amount of circulating thyroid hormone is controlled tightly by the hypothalamic-pituitary thyroid axis, by which negative feedback of thyroid hormones determines the appropriate set point (E-Fig. 207-3). In the paraventricular nucleus of the hypothalamus, the tripeptide thyrotropin-releasing hormone (TRH) is synthesized and released via the median eminence to the pituitary, where it targets pituitary thyrotropes to synthesize and release thyroid-stimulating hormone (TSH). TSH is released into the circulation, where it binds to its receptor on thyroid follicular cells to stimulate the production of thyroid hormone. Critically, circulating T_4 and T_3 feed back at the level of the hypothalamus to regulate the production of TRH and at the level of the pituitary to regulate the synthesis and secretion of TSH. In this way, TSH levels rise when thyroid hormone levels are low and are suppressed when thyroid hormone levels are high, thereby making TSH the most useful screening test for disorders of thyroid function. Importantly, TSH and thyroid hormone levels remain quite constant through a person's lifetime, thereby suggesting a genetic set point for the thyroid axis.

T_3 engages its cognate nuclear receptors, which are members of the nuclear receptor family that includes receptors for vitamin D, estrogen, and androgen. All members of the family possess a modular structure that includes a DNA-binding domain and a specific ligand or hormone binding domain. The three thyroid hormone receptor isoforms have similar functions, but their actions differ based on where they are expressed. For example, TRβ2 is highly expressed in the hypothalamus and pituitary, where it controls the secretion of TSH, whereas TRβ1 is the principal isoform expressed in the liver, where it regulates the metabolism of cholesterol and fatty acids. In contrast, TRα1 is expressed in the heart, the gastrointestinal tract, and bone, where it is an important regulator of cardiac function, heart rate, intestinal motility, bone metabolism, and growth. Patients with TRβ mutations present with inappropriately high thyroid hormone levels because they cannot properly regulate the secretion of TSH. In contrast, patients with TRα mutations have a normal HPT axis but have issues with bone length and gastrointestinal motility, and they are relatively bradycardic.

CLINICAL MANIFESTATIONS AND DIAGNOSIS

Patients with thyroid disease can present with symptoms or signs of hyperthyroidism, hypothyroidism, or a goiter. Oftentimes, however, the first manifestation is an abnormal thyroid function test or a palpable goiter or one or more thyroid nodules.

Physical Examination

Physical examination of the thyroid gland starts with an inspection of the appearance of the anterior neck for visible thyroid nodules, goiter, deviation, or lymphadenopathy. The patient should be seated or standing with the neck in a neutral position. The lower anterior neck between the cricoid cartilage and the suprasternal notch is then palpated using the fingertips, with the examiner standing either in front of or posterior to the patient. When using an anterior approach, all four fingers of the right hand are used to palpate the right thyroid lobe, whereas the left thyroid lobe should be palpated with the fingers of the left hand. The size and symmetry of the gland should be noted. A normal thyroid is symmetric, nontender, weighs 10 to 20 grams, has a soft (rather than rubbery or firm) texture, and should move upward with swallowing. The size, location, texture, tenderness, and mobility of any thyroid nodules should be determined, and the presence of cervical lymphadenopathy should be assessed. To gauge the presence of a substernal goiter in the setting of thyroid enlargement or when the inferior margins of the gland cannot be palpated, the patient should be asked to raise both arms with forearms against the side of the face. Substantial substernal extension of the thyroid will cause narrowing of the thoracic inlet when the goiter shifts upward, thereby resulting in the rapid development of facial plethora and distention of the neck veins. In some patients with a diffuse goiter from Graves disease, increased thyroid vascularity causes an audible bruit over the thyroid gland on auscultation.

Laboratory Testing

Serum TSH is a sensitive screening test for primary thyroid dysfunction and should be obtained in all patients who have symptoms or signs that are concerning for thyroid disease. The reference range for the serum TSH level is typically approximately 0.5 to 4.5 mIU/L, but it is lower (about 0.1 to 4.0 mIU/L) in early pregnancy.[3] Serum TSH values also may increase somewhat with normal aging, but age-specific TSH reference ranges have not been defined. Serum TSH levels alone cannot be used to diagnose thyroid gland dysfunction in the presence of pituitary disease (Chapter 205).

Although subtle shifts in thyroid function are better detected by serum TSH values than by levels of peripheral thyroid hormones, measurement of peripheral thyroid hormones is needed to determine the degree of thyroid dysfunction when the serum TSH level is abnormal. The vast majority (>99%) of circulating T_4 and T_3 is bound to thyroxine binding globulin (TBG) and other binding proteins, and it is only the tiny unbound (free) fraction that is bioactive. Commercial assays for free T_4 are reliable in most settings. However, accurate measurement of free T_3, which is present at much lower levels, is challenging, so total T_3 levels are often used instead. Overt hypothyroidism is defined as an elevated serum TSH level with a low free T_4 level, and subclinical hypothyroidism is defined as an elevated serum TSH level with a normal free T_4 level.

Measurement of both T_3 and free T_4 is useful in the evaluation of potentially thyrotoxic patients. Overt hyperthyroidism is defined as a low serum TSH level with elevated peripheral thyroid hormone levels, whereas subclinical hyperthyroidism is defined as a low serum TSH level with normal peripheral hormone levels. In Graves disease and nodular autonomy, the thyroid gland often preferentially secretes T_3, so the ratio of circulating T_3 : T_4 is higher (above 20:1) than in thyroiditis, where the lower T_3 : T_4 ratio reflects the ratio of hormones stored in the thyroid gland. However, a number of conditions and medications can interfere with the results of thyroid function tests (Table 207-1).[4]

The presence of elevated TSH receptor stimulating antibody titers is highly sensitive and specific for the diagnosis of Graves disease. Elevated levels of serum thyroperoxidase and thyroglobulin antibody may be useful to confirm the diagnosis of autoimmune thyroiditis. Serum thyroglobulin is useful as a tumor marker for differentiated thyroid cancers, as is the serum calcitonin level for medullary thyroid cancer. The erythrocyte sedimentation rate is used in the diagnosis of subacute thyroiditis.

Imaging

Ultrasonography, which is the best imaging modality for evaluating thyroid structure,[5] can' determine the thyroid gland's size and echotexture. For example, the thyroid gland has a distinctively heterogeneous echotexture in individuals who have autoimmune thyroiditis, whereas vascularity as assessed by Doppler ultrasonography is typically increased in Graves disease and absent in inflammatory thyroiditis. Ultrasonography also can characterize the size and location of thyroid nodules, as well as whether they are solid or cystic. Although thyroid malignancy usually cannot be diagnosed based on ultrasound alone, ultrasonographic risk stratification (based on the size, shape, echogenicity, and margins of the nodule, as well as the presence of microcalcifications) can guide decision making regarding the need for fine-needle aspiration biopsy. Ultrasound is also a sensitive tool for assessing cervical lymphadenopathy. Other forms of anatomic imaging, including computed tomographic (CT) scans and magnetic resonance imaging (MRI), are less frequently used to assess the thyroid gland, but they may be helpful in establishing the presence of a substernal goiter or determining whether a goiter is causing tracheal narrowing. Positron emission tomography (^{18}FDG-PET) scanning may be used to localize metastatic thyroid cancer.

Although radioactive iodine-123 (I^{123}) uptake scanning can differentiate among various causes of thyrotoxicosis (e.g., I^{123} uptake is diffusely increased in Graves disease but is low or absent in inflammatory thyroiditis), highly sensitive and specific TSH receptor-stimulating antibody assays have largely replaced scanning for this indication. However, I^{123} scanning is still used to distinguish among hyperfunctioning ("hot"), hypofunctioning ("cold"), or isofunctioning nodules. I^{123} scans also are useful in patients with hyperthyroidism when the physical examination or ultrasound findings indicate the presence of thyroid nodularity. In addition, whole-body I^{123} scans may be used in patients with thyroid cancer to identify recurrent or metastatic disease. Radioactive iodine scanning is not effective in the setting of a recent large iodine load (e.g., from exposure to iodinated contrast media) because the gland will already be saturated with non-radioactive iodine so the uptake of the I^{123} will be low. In this setting, pertechnetate scanning is an alternative. The use of all thyroid scintigraphy is contraindicated during pregnancy.

Differential Diagnosis

The diagnosis of hypothyroidism (Table 207-2), hyperthyroidism (Table 207-3), or a thyroid nodule must prompt a search for the specific cause. Of note is that some conditions (e.g., various forms of thyroiditis) can cause transient hyperthyroidism followed by hypothyroidism. Goiters can be associated with hyperthyroidism (e.g., Graves disease, toxic multinodular goiter) or hypothyroidism (e.g., iodine deficiency) or be seen in euthyroid patients.

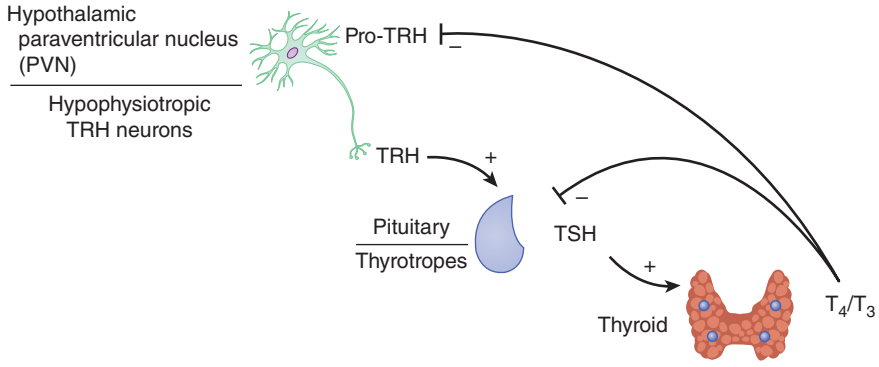

E-FIGURE 207-3. **The hypothalamic-pituitary thyroid axis controls the set point of circulating thyroid hormone levels.** T_3 = triiodothyronine; T_4 = thyroxine; TRH = thyrotropin-releasing hormone; TSH = thyroid-stimulating hormone. (Courtesy of Ricardo Sousa.)

TABLE 207-1 CAUSES OF SPURIOUS OR MISLEADING THYROID FUNCTION TESTS

CAUSE		THYROID FUNCTION TEST EFFECT
Laboratory artifacts	**Biotin** (in some assays, in patients taking biotin doses >100 mg/day)	Artifactually decreased TSH and increased free and total T_4 and T_3. Results normalize after stopping biotin. supplements for 2-3 days.
	Heterophile antibody	Artifactually increased TSH. No effect on T_4 or T_3. Most assays incorporate blocking agents to eliminate this interference.
	Thyroid hormone autoantibody	Artifactually increased total and free T_4 and/or T_3. No effect on TSH. If suspected, compare against measurements by equilibrium dialysis.
	Macro TSH (large bioinactive circulating form of TSH composed of TSH complexed with autoimmune anti-TSH antibodies)	Artifactually elevated TSH. No effect on T_4 or T_3. If suspected, polyethylene glycol can be used in the laboratory to precipitate the macro TSH.
Alterations in thyroid hormone binding	**Increased thyroxine binding globulin levels** • Hepatitis • Pregnancy • Hereditary TBG excess • Medications: *oral estrogens, selective estrogen receptor modulators, mitotane, opiates, 5-flurourcil*	Elevated total, but not free, T_4 and T_3 levels. No effect on TSH.
	Increased binding to albumin • Familial dysalbuminemic hypothyroxinemia (rare, autosomal dominant disorder)	Elevated total and sometimes free T_4. T_3 unaffected. No effect on TSH.
	Decreased thyroxine binding globulin levels • Hereditary TBG deficiency • Medications: *androgens, nicotinic acid, chronic glucocorticoid therapy, danazol, L-asparaginase*	Decreased total, but not free, T_4 and T_3 levels. No effect on TSH.
	Competition with T_4 and T_3 Binding Sites on Thyroid Hormone Binding Proteins • Medications: *Aspirin, salsalate, furosemide (high dose), heparin and low-molecular-weight heparins*	Increased free T_4 and T_3. No effect on TSH.
Inhibition of 5′-deiodination (activation from T_4 to T_3)	**Amiodarone**	Slightly high total and free T_4, slightly low total and free T_3. No effect on TSH.

T_3 = triiodothyronine; T_4 = thyroxine; TBG = thyroid-binding globulin; TSH = thyroid-stimulating hormone.

TABLE 207-2 CAUSES OF HYPOTHYROIDISM

THYROID DESTRUCTION
Autoimmune
Hashimoto disease
Postpartum thyroiditis*,†
Sporadic painless thyroiditis*,†
Post-radioactive iodine or external neck radiation
Post-thyroid surgery
Inflammatory Conditions
Subacute (de Quervain thyroiditis*,†)
Infectious thyroiditis*,†
Sclerosing (Reidel) thyroiditis†
Infiltrative thyroid disease
Amyloidosis
Scleroderma
Hemochromatosis
MEDICATIONS
Lithium
Amiodarone
Interferon
Retinoic acid
Tyrosine kinase inhibitors
Immune checkpoint inhibitors
DEFECTS IN THYROID HORMONE SYNTHESIS
Iodine deficiency†
Acute iodine load (e.g., intravenous contrast)
Congenital enzymatic deficiencies
SECONDARY OR CENTRAL HYPOTHYROIDISM
Hypopituitarism
Pituitary surgery or irradiation
Pituitary tumors
Pituitary hemorrhage (Sheehan syndrome)
Infiltrative diseases (hemochromatosis, tuberculosis, fungal infection)
Lymphocytic hypophysitis
Hypothalamic disorders
Tumor irradiation
Infiltrative disease (e.g., sarcoid, histiocytosis, vasculitis)

*Can also cause transient hyperthyroidism before later causing hypothyroidism.
†Can also cause a palpable goiter.

TABLE 207-3 CAUSES OF TRANSIENT OR SUSTAINED HYPERTHYROIDISM

SUSTAINED HYPERTHYROIDISM
Primary Thyroid Disease
Graves disease†
Toxic multinodular goiter†
Thyroid adenoma†
Functioning thyroid carcinoma†
Struma ovarii
McCune Albright syndrome
Secondary Thyroid Disease
TSH-secreting pituitary adenoma
Tumors secreting human chorionic gonadotropin
Ingestion of excess thyroid hormone, sometimes in dietary supplements
TRANSIENT HYPERTHYROIDISM
Gestational thyrotoxicosis
Postpartum thyroiditis*,†
Sporadic painless thyroiditis*,†
Subacute (de Quervain thyroiditis)*,†
Iodine administration (Jod-Basedow phenomenon in the setting of a previously euthyroid multinodular goiter)†

*Can also cause hypothyroidism.
†Can also cause a goiter.
TSH = thyroid-stimulating hormone.

HYPOTHYROIDISM

DEFINITION

Hypothyroidism refers to conditions in which levels of circulating thyroid hormones are lower than their genetic set point. Hypothyroidism can be classified as primary, when the function of the thyroid gland itself is impaired, or secondary (central), when an abnormality in the pituitary gland's secretion of TSH prevents normal synthesis and secretion of thyroid hormones by the thyroid gland. Primary hypothyroidism is further classified into overt or subclinical hypothyroidism. In overt hypothyroidism, circulating levels of T_4 and T_3 are below normal laboratory cutoffs, the

TSH level is usually above 20 mIU/L, and patients typically manifest some of the symptoms of hypothyroidism. In subclinical hypothyroidism, circulating T_4 and T_3 levels are within the normal range of the general population but, because they are lower than the individual's targeted set point, lead to an elevation of the TSH level (usually less than 10 mIU/L but occasionally as high as 20 mIU/L). Importantly, patients with subclinical hypothyroidism are often identified by routine laboratory testing, not because of clinical symptoms.

EPIDEMIOLOGY

In the United States and Europe, the prevalence of hypothyroidism is about 5% in the general population, with the majority of cases being subclinical hypothyroidism. Additionally, most of the hypothyroidism is primary, with secondary hypothyroidism likely only comprising 1% of all cases. The incidence of hypothyroidism is much higher in women than in men, and the risk increases with age, with women over age 70 years at highest risk. The incidence of hypothyroidism is, not surprisingly, doubled in persons who have another autoimmune disease, given that the most common cause of hypothyroidism is autoimmunity.[6] In the United States, the prevalence of hypothyroidism is highest in Whites and lowest in Blacks.

PATHOBIOLOGY

In 1 per 3500 births, defects in the transcription factors needed for the development of thyroid follicular cells or in the transporters or enzymes needed for the synthesis of thyroid hormone cause congenital hypothyroidism and devastating neurological consequences. Iodine deficiency also can lead to profound hypothyroidism and severe developmental abnormalities, but iodine fortification of food, particularly salt, in most countries has dramatically reduced the prevalence of iodine deficiency.

The most frequent cause of failure of the thyroid gland is an autoimmune disease, Hashimoto thyroiditis, which can occur in isolation or in conjunction with other autoimmune conditions and as a component of polyglandular autoimmune syndromes (Chapter 212). The use of immune checkpoint inhibitors and tyrosine kinase inhibitors also increases the incidence of autoimmune thyroid disease.

Hashimoto thyroiditis is characterized by a lymphocytic infiltration that is mediated by aberrantly activated T cells and by inflammation and fibrosis, which lead to failure of follicular units. Autoimmune thyroid disease is highly heritable, and gene variants in a variety of immunomodulatory genes lead to increased susceptibility.[7] The T-cell immune attack on the thyroid also leads to the measurable production of antibodies directed against both thyroid-peroxidase and thyroglobulin. However, although the titer of these antibodies can be helpful in predicting the progression from mild to severe thyroid failure, these autoantibodies themselves do not appear to be the cause of Hashimoto thyroiditis because they can also be found in patients without thyroid dysfunction.

Another common cause of primary hypothyroidism (see Table 207-2) is thyroid surgery for thyroid nodular disease, cancer, or Graves disease. Even removal of only one lobe of the thyroid can lead to hypothyroidism in a small proportion of patients, especially in the presence of antithyroid-peroxidase or antithyroglobulin antibodies. The thyroid also can be damaged by parathyroid surgery or in other significant head and neck surgery procedures. Radioactive iodine therapy for Graves disease is a frequent cause of hypothyroidism, and external beam radiotherapy for head and neck cancer can also destroy the thyroid unless it is specifically protected.

Both painless and subacute thyroiditis can lead to permanent hypothyroidism. Rarer causes of primary hypothyroidism include infiltrative diseases such as Reidel thyroiditis, which is characterized by a fibrous infiltration of the thyroid gland, sometimes with extension to the recurrent laryngeal nerve or the parathyroid glands. Hemochromatosis (Chapter 196) and amyloidosis (Chapter 174) can cause primary hypothyroidism by infiltrating the thyroid gland.

Drugs can lead to hypothyroidism by affecting the synthesis of thyroid hormone. Amiodarone, which is likely the most common agent to affect the thyroid, can cause both hypothyroidism and thyrotoxicosis. Its induction of hypothyroidism is because the large amounts of iodine contained in the drug stimulate the gland reflexively to decrease the synthesis of thyroid hormone. Amiodarone-induced hypothyroidism can be permanent, especially in patients who have autoimmune thyroid disease. Additionally, amiodarone is an inhibitor of the type 1 deiodinase, so it decreases the conversion of T_4 to T_3.[8] Lithium therapy can also lead to hypothyroidism by affecting the synthesis and release of thyroid hormone.

Acquired secondary or central hypothyroidism (see Table 207-2) is most commonly due to a pituitary tumor, either a primary adenoma or metastatic tumor, that impairs the function of the pituitary cells that synthesize TSH. In these conditions, other pituitary hormones are also affected, so hypothyroidism is essentially always accompanied by hypogonadism and adrenal insufficiency (Chapter 205). Tumors that invade the hypothalamus (Chapter 204) can impair the release of TRH, impair the production of TSH, and thereby reduce the production of thyroid hormone. Infiltrative diseases such as sarcoidosis (Chapter 83) can impair the hypothalamic-pituitary TSH-producing axis. Radiation therapy to the area can also lead to pituitary failure. The anticancer agent bexarotene is a retinoid that directly inhibits the synthesis of TSH and causes central hypothyroidism.

CLINICAL MANIFESTATIONS

Overt hypothyroidism with frankly low thyroid hormone levels and subclinical hypothyroidism may be associated with few symptoms, and the diagnosis is often made by the appearance of a mildly elevated TSH on routine blood work. The clinical manifestations of hypothyroidism are nonspecific, highly variable, and most dependent upon the degree of decrease in the levels of circulating thyroid hormones. Overt hypothyroidism is characterized by symptoms of fatigue, lethargy, weight gain, a decrease in mental acuity, cold intolerance, hair loss, and dry skin in both men and women. Women can have menstrual irregularities, most commonly prolonged heavy menses. The disease can be present for a long period before diagnosis, and the appearance or recognition of new symptoms can be difficult.

The physical findings in hypothyroidism can be myriad and relate to the cause and degree of hypothyroidism. An elevated TSH level leads to an enlarged thyroid gland, except in some individuals with Hashimoto and Riedel thyroiditis, in which the gland may be small because of fibrosis. Bradycardia may be detected, and diastolic hypertension can be seen. Hypothermia usually is present only in severe hypothyroidism. Other classic signs of hypothyroidism include loss of the outer eyebrows and general hair loss or thinning. The skin may be dry and cool, and nonpitting edema may be present peripherally. Delayed return of deep tendon reflexes is considered the most sensitive clinical finding in hypothyroidism and is probably best assessed using the ankle jerk reflex. The nails may be brittle. In severe hypothyroidism, a pericardial effusion (Chapter 62) can be present, so muffled heart sounds may be noted on the physical examination. Because of the chronic nature of the effusion, signs or symptoms of pericardial tamponade (Chapter 62) are distinctly unusual.

If thyroid hormone levels are profoundly reduced for a long period of time or if patients experience a secondary systemic insult, significant hypothermia, hypotension, bradycardia, and profound neurologic manifestations, including coma, can be seen. This syndrome, which is termed myxedema coma, is a medical emergency.

In addition to abnormalities on thyroid function testing, hypothyroidism can be associated with other suggestive laboratory findings. Probably most sensitive is an unexplained elevation in the serum cholesterol level (Chapter 190), and in particular the low-density lipoprotein (LDL) fraction, given the major role of thyroid hormone signaling in regulating cholesterol metabolism. Significant hypothyroidism can be associated with a macrocytic anemia (Chapter 145), and hypothyroidism should be in the differential diagnosis whenever a patient has an elevated mean corpuscular volume. Hyponatremia (Chapter 102) can also be seen because thyroid hormones are needed for free water clearance. The muscle dysfunction of hypothyroidism may be associated with otherwise unexplained elevations in serum levels of creatine kinase and aspartate aminotransferase.

DIAGNOSIS

The biochemical diagnosis of primary hypothyroidism is heralded by a TSH level that is above the laboratory's normal range, which is usually greater than 4.5 mU/L. An elevated TSH level always warrants measurement of circulating thyroid hormone levels, especially a free T_4 level (Fig. 207-1). Rarely, both the TSH and the free T_4 are elevated, thereby suggesting either peripheral resistance to thyroid hormone or a TSH-secreting pituitary tumor. If the TSH is only mildly elevated (between 4.5 and 20 mU/L), the free T_4 can be within the normal limits, and the diagnosis is subclinical hypothyroidism. If the TSH level is elevated and the free T_4 level is low, the diagnosis is almost always overt primary hypothyroidism.

Once the biochemical diagnosis of primary subclinical hypothyroidism or overt hypothyroidism is made, the physical examination often can establish a presumptive diagnosis. Primary hypothyroidism should be considered in

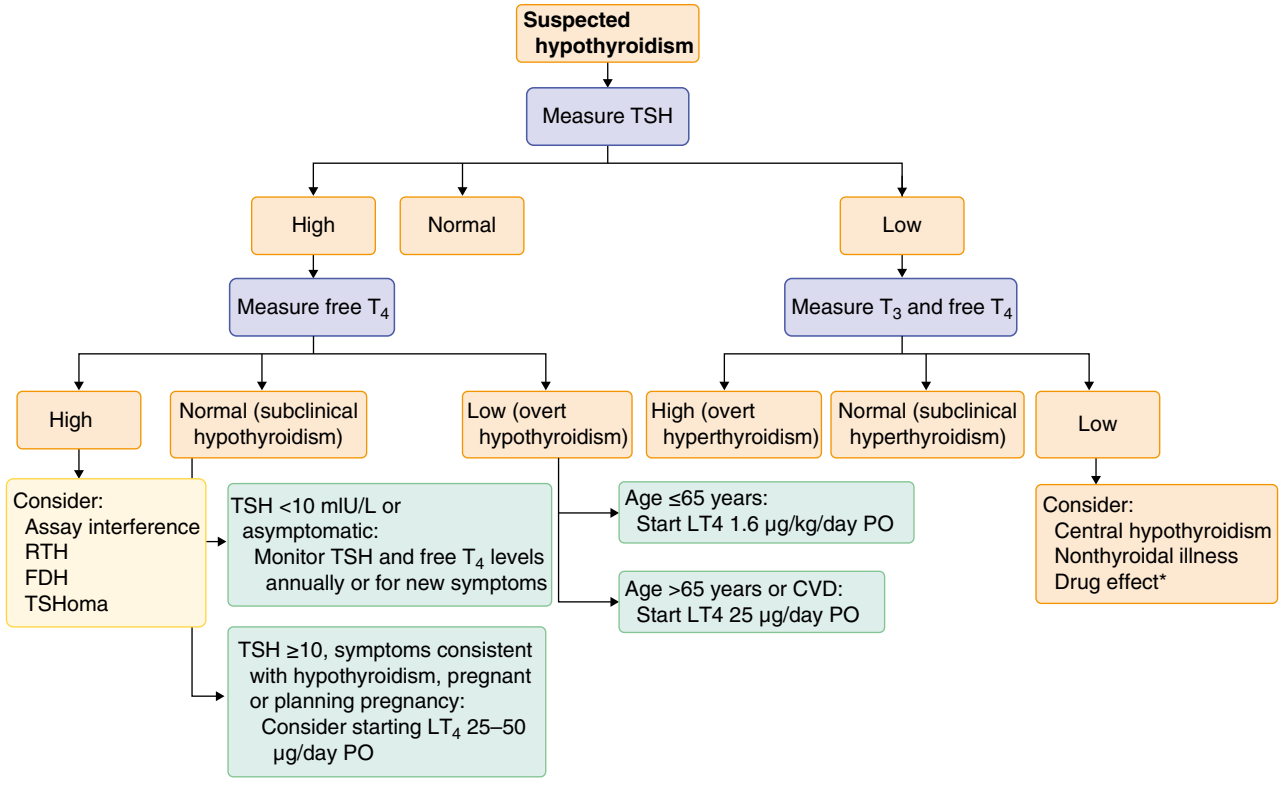

FIGURE 207-1. Evaluation of suspected hypothyroidism. *For example, suppression of TSH by dopamine, lowering free T_4 due to increased metabolism by antiseizure medications. CVD = cardiovascular disease; FDH = familial dysalbuminemic; LT_4 = L-thyroxine; PO = orally; RTH = resistance to thyroid hormone; T_3 = triiodothyronine; T_4 = thyroxine; TSH = thyroid stimulating hormone; TSHoma = TSH-secreting pituitary adenoma.

patients who have another autoimmune disease. The thyroid gland may be either enlarged or nonpalpable in Hashimoto thyroiditis, which is the most common cause. Antithyroid peroxidase or antithyroglobulin antibodies can often confirm the diagnosis of Hashimoto thyroiditis, but they are not positive in all cases.[9] Higher titers of antithyroid peroxidase or antithyroglobulin antibodies often may be helpful in predicting which cases of subclinical hypothyroidism will progress to overt hypothyroidism. By comparison, iodine deficiency is associated with a palpable goiter.

The classic finding in secondary hypothyroidism is a low, normal, or just mildly elevated TSH level despite low circulating levels of free T_4. If such patients have no history of a mass, surgery, or radiation therapy to the area of the hypothalamus or pituitary gland, it is reasonable to obtain a pituitary MRI and to measure other hormone levels.

TREATMENT

Overt Hypothyroidism

L-Thyroxine (which is available in tablets of 25 µg, 50 µg, 75 µg, 88 µg, 100 µg, 112 µg, 125 µg, 137 µg, 150 µg, 175 µg, 200 µg, and 300 µg) is typically prescribed because its long half-life allows for stable dosing and a constant supply of T_4, which can then be converted to T_3 within the circulation and in target cells. Combination T_4/T_3 therapy more closely simulates normal physiology, but current guidelines recommend against its use.

The goal of therapy in primary hypothyroidism is to return the TSH level to the normal range, unless TSH should be suppressed, as in aggressive thyroid cancers. The average required dose of L-thyroxine is 1.6 ug/kg. A major concern is that the bioavailability of L-thyroxine varies among formulations, so patients should try to remain on the same formulation if possible. If the formulation is switched, a TSH level should be evaluated 6 weeks after the change. L-Thyroxine should be taken on an empty stomach, because it is absorbed in the small intestine, where food may impair absorption. A number of other medications (Table 207-4), including iron tablets and calcium carbonate, can impair the absorption of L-thyroxine, so a spacing of a few hours is recommended between L-thyroxine and any of these medications. Very rarely, L-thyroxine can be malabsorbed, but the usual explanation for a poor response is nonadherence.

L-Thyroxine dosing can usually be begun at the predicted weight-based dose, with its effectiveness assessed by changes in clinical signs and symptoms, and by measuring the TSH level no earlier than the interval required for it to reach its new steady state (5 weeks after beginning the medication or after a change in dose). Aging is associated with a decreased L-thyroxine requirement, probably due to decreased tissue demand both centrally and peripherally. In patients in whom an increase in energy expenditure or demand could cause issues, in particular in older patients or in patients who have significant coronary artery disease, a smaller starting dose (i.e., 25 µg) should be chosen, and careful uptitration can be undertaken with changes to the dose every 6 weeks.

The most common problem with L-thyroxine is over-replacement that leads to mild hyperthyroidism with a suppressed TSH level. In patients who have secondary hypothyroidism and in whom the TSH level cannot be used as a measure of efficacy, a reasonable practice is to titrate the dose based on the free T_4 and aim for it to be in the upper half of the normal range.

TABLE 207-4 INTERFERENCE WITH THYROXINE REPLACEMENT THERAPY

FACTORS CONTRIBUTING TO UNDERREPLACEMENT
Inadequate prescribed dose
Limited compliance
Decreased absorption due to ingestion of agents that bind thyroxine
Ferrous sulfate
Calcium carbonate
Aluminum hydroxide
Sucralfate
Cholestyramine
Soy protein
Increased metabolism of thyroxine
Pregnancy
Drugs
Phenytoin
Phenobarbital
Carbamazepine
Rifampin
Diminishing residual thyroid function
Changing formulations
FACTORS CONTRIBUTING TO OVERREPLACEMENT
Excessive prescribed dose
Factitious ingestion of additional doses
Decreased metabolism of thyroxine due to aging
Increasing residual thyroid function
Changing formulations

Combination T_4/T_3 Therapy

Although the vast majority of patients treated with L-thyroxine do well, up to 15% of patients experience persistent symptoms of hypothyroidism despite normal TSH levels. Because the thyroid gland secretes both T_4 and T_3 and because L-thyroxine monotherapy results in low T_3 levels, some patients may have cellular hypothyroidism despite a normal TSH level. Although more than a dozen randomized trials have failed to show a benefit of combination therapy compared with L-thyroxine monotherapy, uncertainty persists regarding the potential benefit of combination therapy specifically in patients who are dissatisfied with monotherapy, especially if T_3 and T_4 are administered in their ideal physiologic ratios. If combination therapy is used, the dose of L-thyroxine should be decreased and replaced by 2.5 to 10 μg of T_3 daily, ideally given as a divided dose twice daily.[10]

Subclinical Hypothyroidism

Although the treatment of overt hypothyroidism with L-thyroxine is clearly beneficial, the benefit of treatment is uncertain in patients who have mildly elevated TSH levels but a normal free T_4 level.[A1–A3] For example, the treatment of subclinical hypothyroidism does not improve symptoms or quality of life in persons over age 65 years. In large population-based studies, however, L-thyroxine appears to be beneficial if the TSH level is above 10 mU/L, perhaps in part because it lowers LDL cholesterol levels.[A4] One approach is to defer treatment and recheck the TSH and free T_4 levels annually. Another is to treat individuals who have TSH levels greater than 10 mU/L or have elevated serum LDL cholesterol levels. A third approach is to treat individuals whose TSH level is in the 5 to 10 mIU/L range if they have symptoms potentially attributable to hypothyroidism or elevated titers of thyroid peroxidase antibodies.

Myxedema Coma

Because of the high mortality associated with myxedema coma, treatment with parental L-thyroxine is imperative. The usual approach is an intravenous loading dose of 200 to 300 μg followed by 1.6 μg/kg intravenously every 24 hours. Since the conversion of T_4 to T_3 may be impaired, parenteral T_3 (5 to 10 μg T_3 every 8 to 12 hours) may be added until clinical improvement is seen. High-dose glucocorticoids (100 mg of hydrocortisone every 6 hours until adrenal insufficiency is excluded) are usually added prior to starting L-thyroxine because of the concern of associated adrenal insufficiency. Hypothermia should be treated with passive rather than active rewarming to prevent further hypotension.

Pregnancy

The required dose of L-thyroxine increases during pregnancy (Chapter 221) because of an increase in thyroxine binding globulin, fetal demand (especially during the first trimester), and placental metabolism of thyroid hormones.[11] In euthyroid pregnant patients, human chorionic gonadotropin acts as a TSH receptor stimulator and allows the endogenous thyroid to increase production of thyroid hormones. If the pregnant patient has no thyroid reserve (i.e., a surgically removed thyroid gland), then a dose adjustment of up to 33 to 50% of the baseline dose may be required. If partial thyroid reserve is present (i.e., some patients with Hashimoto thyroiditis), a dose increase of 25% may be necessary. Because undetected hypothyroidism in early pregnancy has been linked to poorer fetal neurologic outcomes, it is important to increase the L-thyroxine dose as soon as pregnancy is confirmed. A simple approach is to increase the thyroxine dose from 7 tablets to 9 tablets weekly (i.e., add a second tablet on two of the days of the week). The TSH level can be evaluated 3 weeks later to ensure that it is in the target range (<2.5 mIU/L during gestation) and should be monitored every 4 weeks until mid-gestation.

PROGNOSIS

Treatment of hypothyroidism with L-thyroxine is highly effective. Once an ideal dose is found and the TSH level is normalized, patients can be followed annually with a TSH level to ensure stability. Patients should be counseled continually regarding taking their L-thyroxine on an empty stomach and being aware of other medications that can impair its absorption. Additionally, women who are considering pregnancy must know to contact their physician to increase their L-thyroxine dose and be monitored closely as soon as they know they are pregnant.

HYPERTHYROIDISM

DEFINITION

Hyperthyroidism is a clinical syndrome in which circulating thyroid hormone levels are either frankly elevated, and thereby suppress TSH levels, or are within the normal range but are too high for that person's set point, thereby at least partially suppressing TSH levels. The latter syndrome is termed subclinical hyperthyroidism. The degree of signs and symptoms depend on the cause of the hyperthyroidism as well as on the levels of circulating T_4 and T_3. Importantly, hyperthyroidism includes all syndromes related to the endogenous overproduction of thyroid hormone by the thyroid gland, whereas thyrotoxicosis includes all causes of elevated thyroid hormone levels.

EPIDEMIOLOGY

The prevalence of hyperthyroidism is 1 to 2% in women and 0.1 to 0.2% in men, including both overt and subclinical hyperthyroidism. In younger populations (ages 12 to 49 years), the prevalence of hyperthyroidism is higher in Black persons as compared with White or Hispanic persons. Graves disease, which is the most common cause of hyperthyroidism, is four-fold more common in women. Its environmental triggers may include iodine, smoking, stress, and potentially infection because epitopes on *Yersinia enterolitica* (Chapter 288) overlap with that of the TSH receptor. Additionally, drugs (e.g., interferon-α and immune checkpoint inhibitors) and the recovery from lymphopenia seen in immune reconstitution inflammatory syndrome (Chapter 357) can lead to Graves disease. Genetic predisposition is limited to autoimmune susceptibility genes. Long-standing iodine deficiency is associated with higher rates of toxic nodular goiter.

PATHOBIOLOGY

Thyrotoxicosis can result from the overproduction and release of thyroid hormones directly from the gland itself, from an ectopic source, or from exogenous ingestion of thyroid hormone (see Table 207-3). The release of thyroid hormones from the gland itself can be due to intrinsic synthesis of excess thyroid hormone independent of TSH stimulation, excess release of stored hormone from the thyroid gland because of inflammatory thyroiditis, excess TSH, or the stimulation of the thyroid gland by substances other than TSH, as occurs during pregnancy when elevated levels of human chorionic gonadotropin bind to the TSH receptor on the follicular cell.

Graves disease is caused when a circulating antibody binds to and activates the TSH receptor, thereby leading to growth of the gland and overproduction of T_4 and T_3. These antibodies can also target antigens behind the eye and in skin, thereby leading to ophthalmopathy and pretibial myxedema. In addition to thyrotropin receptor autoantibodies, many patients with Graves disease will also have antithyroid peroxidase and antithyroglobulin antibodies, thereby indicating an overlap in immune dysregulation between Graves and Hashimoto diseases.

During pregnancy, the human chorionic gonadotropin–mediated rise in thyroid hormone levels in the first trimester is necessary to meet fetal demand and to maintain stable levels of free thyroid hormones in the setting of excess thyroxine-binding globulin. A potential side effect, however, is that excess thyroid stimulation, especially coincident with hyperemesis gravidarum, can lead to significant clinical hyperthyroidism (Chapter 221).

Thyroid nodular disease can also lead to hyperthyroidism. Solitary nodules can have mutations in the TSH receptor or its downstream components, thereby leading to constitutive activation, nodular growth, and hyperthyroidism. A multinodular gland can also cause hyperthyroidism, especially in the presence of excess iodine, which often results from the use of contrast agents or amiodarone. Finally, rare TSH-producing pituitary adenomas can lead to hyperthyroidism with a TSH level that is inappropriately normal or elevated.

Exogenous causes of thyrotoxicosis include ectopic production of T_4 and T_3 in rare ovarian teratomas (termed struma ovarii) or from widely metastatic follicular thyroid carcinoma. Most commonly, however, exogenous thyrotoxicosis is secondary to over-replacement with thyroid hormone preparations or the ingestion of food (e.g., hamburger thyrotoxicosis from improperly processed meat) or supplements that contain excessive thyroid hormones.

The symptoms and signs of hyperthyroidism are directly attributable to the effects of thyroid hormones on target cells via their genomic and nongenomic actions, including activation of the sympathetic nervous system,[12] the cardiovascular system, and the systems that regulate energy expenditure. Thyroid hormones likely activate pathways that mediate activation of the adrenergic response. Thyroid hormones also have a catabolic effect on muscle.

CLINICAL MANIFESTATIONS

The clinical presentation of hyperthyroidism depends on both the level of circulating thyroid hormones and the duration of the hyperthyroidism. In mild subclinical hyperthyroidism, patients may have no clinical symptoms, whereas patients with florid Graves disease may develop hemodynamic crisis and even death, often termed thyroid storm. In general, the clinical signs and symptoms of hyperthyroidism are more apparent in younger patients, whereas elderly patients may have "apathetic" hyperthyroidism without classic hyperadrenergic symptoms.

Patients with significant hyperthyroidism often report heat intolerance, weight loss despite a vigorous appetite, palpitations, and a tremor, which may manifest as difficulty with fine motor control, including handwriting. Additional symptoms can include emotional lability, enhanced gastrointestinal motility, diarrhea, and muscle weakness. General signs on physical examination include the presence of tachycardia or atrial arrhythmias, systolic hypertension, a stare and lid lag (when the eye lags behind the upper lid on movement up or down) due to activation of sympathetic tone, tremor, and proximal muscle weakness.

Specific signs that can suggest the cause of hyperthyroidism include thyroid enlargement (goiter), which is diffuse in Graves disease but also can be due to an autonomously functioning single large nodule or multiple nodules. The diffuse enlargement in Graves disease can also be associated with a systolic bruit heard directly over the gland with the bell of the stethoscope. Although all causes of hyperthyroidism can cause lid lag, specific bulging or inflammation around the eyes is distinctive of Graves ophthalmopathy (Fig. 207-2). Similarly, peripheral nonpitting edema or redness on the extensor surfaces of the shins is consistent with pretibial myxedema that is specific to Graves disease. Rarely, clubbing of the nails (Fig. 39-9) and swelling of the distal digits of the hands, termed thyroid acropachy, can also be seen with Graves disease.

FIGURE 207-2. Graves ophthalmopathy. A, A 59-year-old woman with excess proptosis, moderate eyelid edema, and erythema with moderate eyelid retraction affecting all four eyelids. Conjunctival chemosis (edema) and erythema with bilateral edema of the caruncles, with prolapse of the right caruncle, are evident. **B**, A 40-year-old woman with excess proptosis, minimal bilateral injection, and chemosis with slight erythema of the eyelids. On slit lamp examination, she also had evidence of moderate superior limbic keratoconjunctivitis. (From Bahn RS. Graves' ophthalmopathy. *N Engl J Med*. 2010;362:726-738. Copyright 2010, Massachusetts Medical Society. All rights reserved.)

DIAGNOSIS

Thyroid function testing makes or excludes the diagnosis (Fig. 207-3). In overt hyperthyroidism, both circulating T_4 and T_3 levels will be frankly elevated, whereas the TSH level is completely suppressed. In subclinical hyperthyroidism, circulating T_4 and T_3 levels will be within the normal range, while the TSH level is either fully or partially suppressed. In women of childbearing age, a pregnancy test should be performed to exclude pregnancy-induced hyperthyroidism (Chapter 221).

The absolute levels of total T_4 and total T_3 can also be helpful. For example, Graves disease and nodular thyroid disease are likely to have a T_3 : T_4 ratio of over 20 : 1, whereas the ratio will be less in thyroiditis.

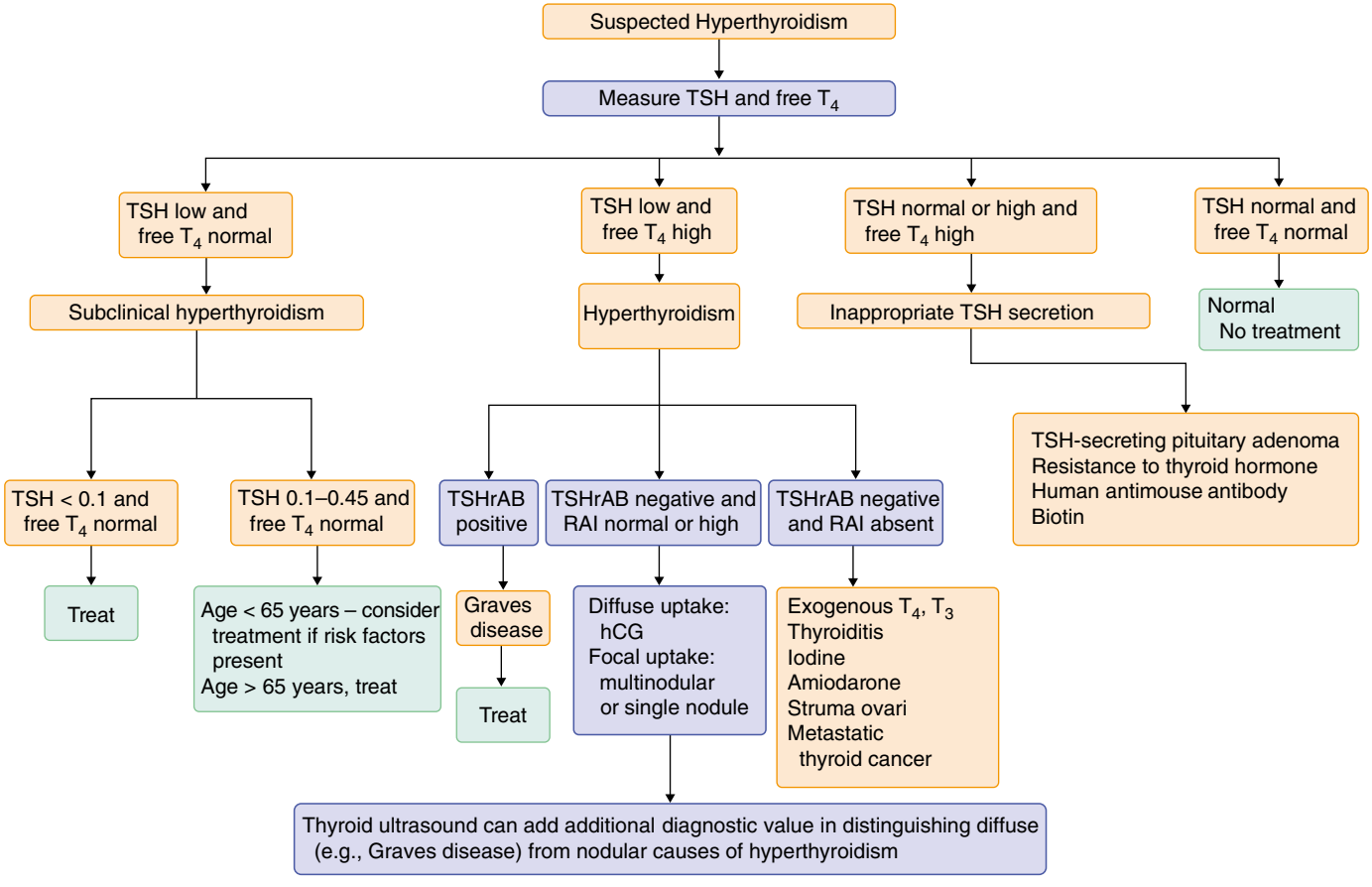

FIGURE 207-3. Algorithm for the assessment of thyrotoxicosis. hCG = human chorionic gonadotropin; RAI = radioactive iodine; T_3 = triiodothyronine; T_4 = thyroxine; TSH = thyroid-stimulating hormone; TSHrAB = TSH-receptor antibodies. (Based on De Leo S, Lee SY, Braverman LE. Hyperthyroidism. *Lancet*. 2016;388:906-918.)

TABLE 207-5 RADIOGRAPHIC EVALUATION OF SUSPECTED THYROTOXICOSIS

ETIOLOGY	FRACTIONAL 24-HOUR RADIOIODINE UPTAKE (%)	THYROID SCAN APPEARANCE
Graves disease	35-95	Diffuse increased homogeneous uptake; visible pyramidal lobe extending from isthmus
Toxic adenoma	20-60	Solitary focus of intense uptake; suppression of uptake in remainder of thyroid
Toxic multinodular goiter	20-60	Patchy heterogeneous foci of increased uptake interspersed with regions of diminished uptake
Subacute thyroiditis	0-2	Minimal to absent uptake
Autoimmune thyroiditis	0-2	Minimal to absent uptake; patchy heterogeneous uptake during recovery
Iodine-induced hyperthyroidism	0-2	Minimal to absent uptake
Exogenous thyroid hormone intoxication	0-2	Minimal to absent uptake
Metastatic differentiated thyroid cancer	0-5	Focal uptake in metastases
TSH-secreting pituitary adenoma	30-80	Diffuse increased homogeneous uptake

TSH = thyroid-stimulating hormone.

From Jonklaas J, Cooper DS. Thyroid. In: Goldman L, Schafer AI, eds. *Goldman-Cecil Medicine*, 26th ed. Philadelphia: Elsevier; 2020:1462-1476.

TABLE 207-6 TREATMENT OF GRAVES DISEASE

TREATMENT	OUTCOME
Antithyroid drugs: methimazole, propylthiouracil	About 50% remission rate; hypothyroidism unusual
Radioactive iodine (^{131}I)	About 75 to 90% cure rate (euthyroid or hypothyroid) after one dose; up to 80% risk of hypothyroidism at 1 year
Surgical total thyroidectomy	Definitive cure and universal hypothyroidism, except in very rare cases of ectopic thyroid tissue

Adapted from Jonklaas J, Cooper DS. Thyroid. In: Goldman L, Schafer AI, eds. *Goldman-Cecil Medicine*, 26th ed. Philadelphia: Elsevier; 2020:1462-1476.

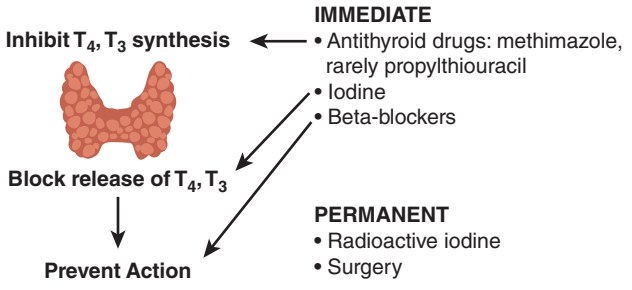

FIGURE 207-4. **Treatment of hyperthyroidism.**

The diagnosis of Graves disease can be confirmed by directly measuring TSH-receptor antibody levels. The uptake of radioactive iodine is useful when the cause of hyperthyroidism otherwise cannot be discerned (Table 207-5). Since the uptake of iodine into the thyroid gland is entirely regulated by TSH, the uptake of radioactive iodine in the thyroid should be close to zero when the TSH level is suppressed, as in thyroiditis or an exogenous or ectopic source of thyroid hormone. In contrast, the uptake of radioactive iodine will be diffusely inappropriately normal or elevated in Graves disease and focally increased in nodular causes of hyperthyroidism, including multinodular goiter and single autonomous nodules. A radioactive iodine scan is unlikely to be helpful in the presence of excess nonradioactive iodine, such as with the administration of amiodarone. Technetium scanning also can show diffuse excess uptake in Graves disease and focal uptake in nodular hyperthyroidism. Thyroid ultrasound can confirm the presence or absence of thyroid nodules and, using Doppler, identify a relative increase in blood flow, which is suggestive of Graves disease and nodular forms of hyperthyroidism.

Laboratory abnormalities associated with hyperthyroidism include elevated liver aminotransferase levels, because excess thyroid hormone signaling increases hepatocyte stress. The alkaline phosphatase level can also be elevated, likely reflecting bone resorption caused by excess thyroid hormones. The serum calcium level can be mildly elevated, sometimes associated with hypercalciuria and even nephrolithiasis (Chapter 111). Graves disease also can present with neutropenia and a lymphocytosis. Because antithyroid drugs used to treat hyperthyroidism can also cause neutropenia and abnormalities in liver enzymes, baseline values should be obtained before starting treatment.

TREATMENT

The treatment of hyperthyroidism (Table 207-6) depends on its underlying cause and severity. However, the basic approach is similar for all causes.

If thyroid hormones are being overproduced by the gland because of Graves disease or other causes, treatment must inhibit the synthesis of thyroid hormone (by removing the gland surgically, by inactivating it biologically with radioactive iodine or antithyroid drugs) potentially coupled with β-adrenergic antagonists to block the peripheral actions of the thyroid hormone if the clinical symptoms are significant. In contrast, if the problem is over-release of preformed thyroid hormone because of damage to the gland, then the only focus should be blocking the actions of thyroid hormones (Fig. 207-4).

Blocking Thyroid Hormone Action

Symptomatic control of the hyperadrenergic and cardiovascular symptoms (e.g., tremor, tachycardia, and the ventricular response rate of atrial fibrillation) of hyperthyroidism can be achieved quickly with nonselective β-blockade. The preferred β-blocker is propranolol, which inhibits type 1 deiodinase and can reduce serum T_3 by 20% at a daily dose of 80 mg. The usual starting dose of propranolol is 20 mg every 6 to 8 hours, depending on the severity of the hyperthyroidism, titrated upwards to a maximum of 240 mg over 24 hours. If propranolol is a concern or causes complications in patients with asthma or chronic obstructive lung disease, selective β-blockers (e.g., atenolol [25 to 50 mg] or metoprolol [25 to 50 mg]) can be used; these drugs do not block the activity of type 1 deiodinase but nevertheless are efficacious for treating the clinical symptoms of thyrotoxicosis.

Reducing Thyroid Hormone Levels

Antithyroid Drugs

The thionamides, methimazole and propylthiouracil, block the activity of thyroid peroxidase and, as a result, the synthesis of thyroid hormone. They may also have immunosuppressive effects, thereby blunting the autoimmune process itself. Propylthiouracil also inhibits the activation of type 1 deiodinase.

Methimazole is the recommended agent of choice for hyperthyroidism except for thyroid storm, when T_3 levels must be lowered quickly, or the first trimester of pregnancy. The usual starting dose is 20 to 30 mg given either once a day or divided into two doses. Propylthiouracil must be given two to three times per day, and 400 mg of propylthiouracil is equivalent to 30 mg of methimazole.

About 1 to 5% of patients on either medication develop a rash or urticaria, which can be treated with the use of an antihistamine (e.g., diphenhydramine 25 to 50 mg) or by switching to the other drug. More rare (about 1/1000 with either drug) is agranulocytosis, which can be idiosyncratic but is more likely in the first few months of therapy, especially in older patients and with higher doses. Monitoring of the neutrophil count is not useful because of the rapidity of onset of the process, so patients should be instructed to stop the drug and call their physician immediately if they develop fever, sore throat, or any other symptoms suggestive of infection. Recovery from the neutropenia is usual, but severe infections may require hospitalization, broad-spectrum antibiotics (Chapter 260), and the administration of growth factors (Chapter 153) to stimulate white cell growth. If this side effect does occur, neither drug can ever be given again. Another rare but serious side effect is fulminant hepatic necrosis, which is seen primarily with propylthiouracil and is a common cause of drug-related liver failure (Chapter 136). Methimazole also can cause a drug-induced hepatitis or, more commonly, cholestasis.

Treatment with methimazole or propylthiouracil will usually lower the T_4 and T_3 levels to normal within 4 to 6 weeks. As the T_4 and T_3 levels fall toward normal, their dose can be titrated down to maintain euthyroidism. The TSH level cannot be used to follow the regression of hyperthyroidism because it may remain suppressed for weeks even after T_4 and T_3 levels fall into the normal range.

In Graves disease, medical antithyroid drug therapy can induce a remission and restore the euthyroid state. If therapy for 12 to 18 months results in normalization of thyrotropin receptor autoantibody levels, remission is likely and medical therapy can be discontinued. If thyrotropin receptor autoantibody levels remain elevated, however, more definitive therapy with radioactive iodine or surgery can be pursued, although another option is to continue medical therapy for several years to see if thyrotropin receptor autoantibody levels eventually return to normal.

Iodine and Other Agents

Supraphysiologic doses of iodine are usually used only after starting antithyroid drug therapy in patients who have severe thyrotoxicosis, but they also can be utilized alone in patients who are intolerant to antithyroid drugs. Iodine is administered as a saturated solution of potassium iodide (SSKI) or as Lugol solution. Lithium also blocks thyroid hormone release and can be utilized short term to control hyperthyroidism in patients intolerant to antithyroid drugs and iodine. Cholestyramine enhances the metabolism of T_4 by the liver and can effectively lower thyroid hormone levels in severe cases.

Radioactive Iodine Therapy

Radioactive iodine kills follicular cells, thereby reducing or eliminating the production of thyroid hormone. Radioactive iodine is highly effective in the treatment of Graves disease, autonomous hyperfunctioning thyroid nodules, and toxic multinodular goiters. The goal of radioactive iodine therapy is to ablate the thyroid gland and cause hypothyroidism. For Graves disease, radioactive iodine ameliorates hyperthyroidism in 90% of patients within 6 months but may increase the risk of cancer slightly.[13] Radioactive iodine may worsen Graves ophthalmopathy and is contraindicated in patients who have significant Graves ophthalmopathy unless patients receive concomitant high doses of corticosteroid therapy for 4 to 6 weeks after the administration of radioactive iodine. Radioactive iodine treatment also may cause radiation thyroiditis and induce the release of preformed thyroid hormone, thereby transiently worsening hyperthyroidism. Pretreatment with an antithyroid drug, to deplete the gland of stored thyroid hormone and prevent radiation thyroiditis, for 5 to 6 weeks prior to the administration of radioactive iodine can be helpful in patients who have significant hyperthyroidism, who are elderly, or who are at risk of decompensation with continued hyperthyroidism (e.g., patients with cardiovascular disease). If given, antithyroid drugs should be discontinued 5 days prior to giving radioiodine so that its uptake will not be impacted.

Surgery

Thyroid surgery is very effective for the treatment of hyperthyroidism, including Graves disease and nodular hyperthyroidism. Complications include damage to the parathyroid glands or the recurrent laryngeal nerve, but these risks are extremely low when the procedure is performed by an experienced surgeon. In preparation for surgery, the patient should first be rendered euthyroid with antithyroid drugs. Patients with Graves disease should also receive potassium iodide or Lugol solution under expert guidance to decrease the vascularity of the gland.

Treatment of Select Hyperthyroid Disorders

Graves Disease

For Graves disease, the most common initial treatment is antithyroid drugs, followed by radioactive iodine, with surgery as the least chosen option.[14] In patients who have Graves ophthalmopathy or very large thyroid glands, antithyroid drugs or surgery is preferred and radioactive iodine is not recommended. The choice among therapies should be patient-centered, but data suggest that long-term quality of life will be equivalent for most patients.

Other Causes of Hyperthyroidism

For toxic multinodular goiters, which often present in elderly patients, a small dose of an antithyroid drug may be effective. For autonomously functioning single nodules, radioactive iodine or thyroid lobectomy is usually preferred.

Subclinical Hyperthyroidism

In subclinical hyperthyroidism, patients have a confirmed suppressed TSH level but normal thyroid hormone levels. The most common cause of this disorder is a toxic multinodular goiter, with autonomous nodules that do not remit; as a result, hyperthyroidism typically will worsen gradually over time if treatment is not instituted. These patients have an increased risk of atrial arrhythmias, heart failure, and bone loss, especially if they are over age 65 years. Patients over age 65 years should be treated chronically with a low dose of methimazole (2.5 to 10 mg), which typically will allow the TSH level to rise into the normal range. If the TSH level is <0.1 mIU/L, patients who are less than age 65 years should be treated if they have a comorbid condition, such as heart disease or osteoporosis, and treatment should be considered even without comorbid conditions or symptoms. If the TSH level is partially suppressed (>0.1 and <0.45), treatment should be considered in all patients who have comorbid conditions.

Hyperthyroidism and Pregnancy

Graves disease affects 1 per 500 pregnancies, usually because it was not adequately treated prior to conception. The differential diagnosis must include gestational thyrotoxicosis secondary to elevated production of human chorionic gonadotropin, generally in the first trimester and especially women with a twin pregnancy or hyperemesis gravidarum. Significant hyperthyroidism during pregnancy can be devastating for fetal survival and maternal health, although both Graves disease and gestational thyrotoxicosis tend to remit or improve starting at the end of the first trimester. Thyrotropin receptor autoantibody levels above the reference range can be the most useful test to establish the diagnosis. For symptomatic control, β-blockers (labetalol is preferred during pregnancy) can be used but only for very short periods of time and at low doses (e.g., 100 mg twice daily). If antithyroid drugs are required, propylthiouracil should be used in the first trimester rather than methimazole, but at the lowest dose needed to control symptoms. Although both antithyroid drugs are associated with a risk of fetal anomalies, propylthiouracil is considered safer than methimazole during the period of organogenesis in the first trimester.[15] The free T_4 level should be maintained at or above the upper level of normal so that the antithyroid drug does not impact the fetal thyroid gland, which is more sensitive to it than is the maternal thyroid gland.

Thyroid Storm or Crescendo Thyrotoxicosis

Thyroid storm refers to systemic destabilization and hemodynamic compromise in the setting of severe thyrotoxicosis. Mortality may approach 30%. Clinical manifestations include hyperthermia, neurologic toxicity with coma or seizures, and cardiac toxicity with arrhythmias, myocardial ischemia, and heart failure. A comorbid condition such as sepsis, an underlying cardiac problem, or unrelated surgery often triggers the decompensation. The most common cause of thyroid storm is Graves disease, but a severely toxic multinodular goiter can precipitate the syndrome. All thyroid hormone levels will be elevated, but the diagnosis is clinical because similarly high values can be seen in patients without thyroid storm. Treatment is focused on decreasing thyroid hormone levels, particularly the T_3 level, as quickly as possible and on identifying and correcting any potential precipitating cause. If high-dose β-blockade can be tolerated hemodynamically, it should be instituted with propranolol (started at 60 to 80 mg orally every 4 to 6 hours and titrated to optimize heart rate and blood pressure); if tolerance is uncertain, intravenous short-acting esmolol (started at 50 to 100 μg/kg/minute) can be used. To lower thyroid hormone levels acutely, propylthiouracil (starting at 200 to 400 mg every 4 to 6 hours) is preferred because, like propranolol and unlike methimazole, it blocks the type 1 deiodinase and prevents conversion of T_4 to T_3. Once propylthiouracil has been started, iodine (e.g., up to 5 drops every 6 hours) can then be added to block the release of thyroid hormone. High-dose glucocorticoids (e.g., 100 mg of hydrocortisone every 8 hours or 4 mg of dexamethasone every 8 to 12 hours) also inhibit the conversion of T_4 to T_3 and should be utilized until severe hyperthyroidism is controlled. In extreme crises, plasmapheresis or emergency thyroidectomy can be performed.

Non-Thyroid Complications of Graves Disease

Unlike other causes of hyperthyroidism, Graves disease presents with immune-related extrathyroidal manifestations unrelated to excess levels of thyroid hormones,[16] including Graves ophthalmopathy and dermopathy. Graves ophthalmopathy is caused when activation of the TSH receptor on orbital fibroblasts leads to the production of glycosaminoglycan and the enlargement of extraocular muscles and retroorbital tissue.

Also known as pretibial myxedema because of the location, Graves dermopathy is associated with very high levels of thyrotropin receptor autoantibodies. Activated dermal fibroblasts that express the TSH receptor are the likely mediators.

CLINICAL MANIFESTATIONS AND DIAGNOSIS

At the time when the diagnosis of Graves disease is first made, about 25% of patients have some form of Graves ophthalmopathy, and another 9% develop it subsequently. Furthermore, about 10% of patients with Graves ophthalmopathy are not biochemically hyperthyroid when diagnosed. Most patients with Graves ophthalmopathy notice initial redness in the eyes or swelling in the eye region, grittiness, and photosensitivity

(see Fig. 207-2). As the disease progresses, the eyelid retracts further and frank exophthalmos develops, with bulging of the corneal edge beyond the epicanthal edge. As severity progresses, involvement of the ocular muscles can cause diplopia and, more rarely, compression of the optic nerve. Clinically, Graves ophthalmopathy is relatively easy to diagnose and can be quantified using a variety of classification scores that measure inflammation and exophthalmos.[17]

All patients with Graves dermopathy have concomitant hyperthyroidism and Graves ophthalmopathy. Graves dermopathy is characterized by nonpitting edema with orange to violet discoloration. In severe cases, overgrowth of plaques and nodules cause a disfiguring lesions.

TREATMENT

Mild Graves ophthalmopathy is usually just observed or potentially treated with selenium (200 μg daily) for at least 6 months. For moderate to severe disease, standard first-line treatment has been intravenous pulse methylprednisolone under expert guidance over a 12-week period.[18] However, teprotumumab (10 mg/kg as an initial single dose, followed by 20 mg/kg every 3 weeks for 7 additional doses), which is a monoclonal antibody that inhibits IGF-1 receptors, can significantly improve exophthalmos and diplopia and is becoming a first-line option.[A5,A6] In patients who do not respond, second-line therapy includes orbital radiation or further immunosuppression with agents such as rituximab under expert supervision. Orbital surgery for ophthalmic nerve decompression is usually reserved for inactive Graves ophthalmopathy to improve function and cosmetic appearance.

For Graves dermopathy, no treatment is usually required. If required, treatment is usually local, with steroid creams (Table 403-10).

THYROIDITIS

Postpartum and Sporadic Painless Thyroiditis

EPIDEMIOLOGY AND PATHOBIOLOGY

Postpartum thyroiditis, which occurs after up to 10% of pregnancies, is more frequent in women with a personal or family history of autoimmunity and in women who have thyroid peroxidase antibodies during the first trimester of pregnancy. In the postpartum setting, the incidence of postpartum thyroiditis is about 20 times higher than that of Graves hyperthyroidism. The incidence of painless thyroiditis outside of the postpartum setting is unknown, but it is less frequent than postpartum thyroiditis. It typically occurs in individuals between ages 30 and 60 years and is 1.5 times more likely to occur in women than in men.

Sporadic painless thyroiditis and postpartum thyroiditis are variants of the same autoimmune disorder, essentially indistinguishable except that postpartum thyroiditis occurs in the first 12 months following delivery. Both are forms of destruction-induced thyroiditis.

CLINICAL MANIFESTATIONS

The classic sequence is a transient thyrotoxicosis due to leakage of preformed hormone from a damaged gland, followed by transient hypothyroidism owing to depleted thyroid hormone stores. However, not all patients experience both phases. About 25% of women with postpartum thyroiditis experience only transient thyrotoxicosis, and about half experience only the hypothyroid phase.

In the initial thyrotoxic phase, symptoms such as tachycardia, palpitations, and heat intolerance may occur, and a nontender goiter is usually present. However, thyroid hormone levels are lower in sporadic painless thyroiditis and postpartum thyroiditis than in Graves disease, so patients tend to be less symptomatic. Features that develop only with longstanding thyrotoxicosis, such as substantial weight loss, are rare. The toxic phase usually persists for 1 to 3 months and may be followed by a brief period of euthyroidism for 1 to 2 months. The final, hypothyroid, phase may persist for up to 1 year. Symptoms in the hypothyroid phase may include fatigue, impaired concentration, constipation, and cold intolerance. Hypothyroidism in patients who initially presented with thyrotoxicosis is often briefer and less severe than when hypothyroidism is the presenting disorder.

DIAGNOSIS

During the toxic phase of painless thyroiditis, release of hormone from the inflamed thyroid results in increases in levels of serum free T_4 and T_3 and a decrease in the serum TSH level. The serum T_3 : T_4 ratio, which is usually <20, reflects the ratio of stored hormone in the thyroid gland and differs from Graves disease, in which T_3 is often preferentially elevated. The thyroid peroxidase antibody is positive in most patients, but thyrotropin receptor autoantibody assays are negative, thereby helping to differentiate this disorder from Graves hyperthyroidism. Stigmata of Graves disease, such as exophthalmos or a thyroid bruit, are absent.

FIGURE 207-5. Goiter.

Although not routinely needed for diagnosis, a low to undetectable radioactive iodine uptake will be seen during the thyrotoxic phase (Fig. 207-5). Thyroid ultrasonography shows a heterogeneous and hypoechoic echotexture; during the toxic phase, color Doppler flow is markedly decreased, compared with the marked increase seen in Graves disease. During recovery from the acute toxic phase, the TSH level increases and the serum TSH level rises, so radioactive iodine uptake and color Doppler flow may be normal or elevated.

In patients in whom the toxic phase either was missed or never occurred, the presentation of hypothyroidism is the same as in other forms of hypothyroidism. The serum TSH level will be elevated, and, depending on the severity of the hypothyroidism, free T_4 levels may be low.

TREATMENT

The clinical course of sporadic painless thyroiditis is self-limited. If signs and symptoms of thyrotoxicosis are moderate or severe, they should be treated symptomatically with β-adrenergic blocking drugs (e.g., atenolol 25 to 50 mg daily) in the ambulatory setting until thyroid hormone levels fall and symptoms resolve. Since the synthesis of thyroid hormone is not increased, antithyroid drugs are not useful. In sporadic painless or postpartum thyroiditis, hypothyroidism requires treatment if symptoms are severe or prolonged. If levothyroxine therapy (weight based if overtly hypothyroid or low dose if subclinically hypothyroid) is initiated, it can be tapered after 6 to 12 months to determine whether the underlying thyroid function has recovered. However, levothyroxine should be continued for the duration of the pregnancy if the patient is pregnant or attempting conception.

PROGNOSIS

Although many patients return to a euthyroid state, up to 50% remain chronically hypothyroid. Permanent hypothyroidism is more frequent in the setting of high titers of thyroid peroxidase antibodies, when a thyrotoxic phase was not detected, and when hypothyroidism is more severe. Postpartum thyroiditis recurs after 70% of subsequent pregnancies.

Subacute (de Quervain) Thyroiditis

DEFINITION

Subacute thyroiditis, which is the most common cause of a painful thyroid gland, is an inflammatory disorder of unknown cause.

EPIDEMIOLOGY AND PATHOBIOLOGY

Subacute thyroiditis, which accounts for up to 5% of clinical thyroid disorders, is five times more frequent in women than in men, with a peak incidence in the fourth and fifth decades. Subacute thyroiditis often follows a viral

prodrome and occurs seasonally, coinciding with the peak in enterovirus infections. It also has been reported to follow infection with severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2).[19] The initial thyrotoxic phase is caused by leakage of preformed thyroid hormone from the damaged thyroid gland into the circulation, typically persisting for 2 to 4 months. In about one-third of patients, the initial phase is followed by a subsequent hypothyroid phase during which stored intrathyroidal hormone is depleted, but the gland has not recovered sufficiently to resume normal synthesis of thyroid hormone.

CLINICAL MANIFESTATIONS

Subacute thyroiditis often develops 2 to 3 weeks after an upper respiratory tract or other viral infection. The onset of thyroid pain or swelling may be accompanied by fever and other systemic symptoms, such as myalgias and fatigue. About 50% of patients will have thyrotoxic symptoms. Pain and tenderness are moderate to severe and may radiate to the angle of the jaw, to the ear, or to the anterior chest. Both thyroid lobes may be simultaneously involved, or pain may start on one side and migrate to the other. The thyroid is generally firm and exquisitely tender to palpation over one or both lobes. Cervical lymphadenopathy is absent.

DIAGNOSIS

Subacute thyroiditis must be differentiated from other causes of anterior neck pain, including acute hemorrhage into a nodule or cyst, infectious thyroiditis, and (rarely) rapidly enlarging thyroid carcinoma. During the painful phase, the hallmark of subacute thyroiditis is an elevated erythrocyte sedimentation rate (ESR). The white blood cell count is normal or mildly increased. The serum TSH level will be low or undetectable during the thyrotoxic phase, with a serum T_4 to serum T_3 ratio >20:1 reflecting the intrathyroidal stores of each hormone. Serum levels of thyroid peroxidase and thyroglobulin antibody are usually normal. Although the diagnosis can usually be made without imaging, radioactive iodine uptake during the thyrotoxic phase is low to undetectable and can be used diagnostically. If utilized, ultrasound examination may show generalized, multiple, or single regions of hypoechogenicity.

TREATMENT AND PROGNOSIS

Thyrotoxic symptoms are usually mild and can be managed with β-adrenergic blocking drugs (e.g., atenolol 25 to 50 mg daily) until thyroid hormone levels fall and symptoms resolve. Antithyroid drugs are not indicated. Nonsteroidal anti-inflammatory drugs can be used to manage mild to moderate thyroid pain. In more severe cases, oral glucocorticoids (e.g., prednisone 40 to 60 mg a day) may be helpful, with a slow taper over at least 4 to 6 weeks to reduce the likelihood that symptoms will recur.

The acute phase may be followed by a period of transient (1 to 2 months) asymptomatic euthyroidism. Hypothyroidism, persisting for up to 6 to 9 months, may be the final phase before recovery and may require levothyroxine therapy (weight based if overtly hypothyroid or low dose if subclinically hypothyroid) if symptomatic.

Infectious Thyroiditis

DEFINITION

Infectious thyroiditis, which is also known as acute or suppurative thyroiditis,[20] is usually caused by bacteria, but fungal and parasitic thyroiditis have also been reported.

EPIDEMIOLOGY AND PATHOBIOLOGY

Infectious thyroiditis, which is rare, represents <1% of all thyroid disease. The thyroid gland's high iodine content, vascularity, lymphatic drainage, and protective capsule make it resistant to infection. *Staphylococcus aureus* and *Streptococcus pyogenes* are the pathogens in about 40% of adults, whereas α- and β-hemolytic streptococcus and a variety of anaerobic organisms account for most cases in children. The presence of anatomic variations such as pyriform sinus fistulae may predispose to the development of thyroid infection. Immunosuppressed patients, particularly from HIV infection, are also at increased risk.

CLINICAL MANIFESTATIONS

Patients typically present with thyroid pain, tenderness, and local compression that result in dysphagia and dysphonia. Systemic symptoms such as fever, chills, tachycardia, and malaise may also be noted. The presentation may be more insidious in fungal than in bacterial infections.

DIAGNOSIS

Infectious thyroiditis may be difficult to differentiate from subacute thyroiditis in the early phases, although patients with bacterial thyroiditis tend to have a higher fever and are much less likely to have clinically overt thyroid dysfunction. The white blood cell count can be elevated in both conditions. Once abscess formation has occurred, local erythema, lymphadenopathy, hyperpyrexia, and leukocytosis should lead to the correct diagnosis. Thyroid function tests are most frequently normal, but hypothyroidism and thyrotoxicosis have been reported. Affected thyroid regions are hypoechoic on ultrasound and cold on scintigraphy. Diagnosis can be made by fine-needle aspiration with Gram stain and culture.

TREATMENT AND PROGNOSIS

The infectious microorganism should be identified from needle aspirate, from incision and drainage, or from blood culture. If no organisms are seen on the Gram stain, empiric treatment with nafcillin and gentamicin or with a third-generation cephalosporin under expert supervision is appropriate initial therapy in adults. If the patient does not respond promptly or if an abscess develops, incision and drainage is necessary. In some cases, especially if the disease is recurrent, partial lobectomy is required. Mortality is rare with appropriate treatment, and recurrence is unlikely.

Drug-Induced Thyroiditis

Amiodarone, lithium, interferon-α, multikinase inhibitors, and immune checkpoint inhibitors may cause painless thyroiditis.[21] Cytokine therapy, specifically interferon-α, also can cause a painless destructive thyroiditis in addition to other forms of thyroid dysfunction.

Amiodarone

Amiodarone, because of its high iodine content, is a frequent mediator of thyroid dysfunction. Most commonly it causes hypothyroidism especially in patients who have an underlying autoimmune thyroid disease. Unfortunately, amiodarone can also lead to hyperthyroidism in a small percentage of patients treated. Amiodarone causes hyperthyroidism through two pathways; type 1 is called iodine-induced thyrotoxicosis and is more common in patients who have underlying nodular thyroid disease; type 2 is a painless thyroiditis due to the drug. Often it is difficult to distinguish between the two clinically.

Lithium

Treatment with lithium can lead to endocrine complications including primary hyperparathyroidism, nephrogenic diabetes insipidus, and hypothyroidism. The mechanism by which lithium leads to hypothyroidism is not clear, but it can be easily treated with L-thyroxine.

Kinase Inhibitors, Interferon Therapy, and Immune Checkpoint Inhibitors

Each of these therapies can lead to a painless thyroiditis that most commonly presents with hypothyroidism but can also present with a hyperthyroid phase. Even a single dose of an immune checkpoint inhibitor can cause hypothyroidism or hyperthyroidism due to autoimmune thyroid disease. Additionally, but more rarely, immune checkpoint inhibitors can lead to pituitary dysfunction with central hypothyroidism that presents with low TSH and low thyroid hormone levels.

CLINICAL MANIFESTATIONS AND DIAGNOSIS

The key in all cases is to suspect drug-induced thyroid dysfunction. The diagnosis is usually heralded by symptoms of hypothyroidism or hyperthyroidism and can be confirmed by thyroid function testing. In amiodarone-induced thyrotoxicosis, a thyroid ultrasound with Doppler showing blood flow to the gland suggests type 1 rather than type 2 amiodarone-induced thyrotoxicosis.

TREATMENT

In the painless thyroiditis caused by immune checkpoint inhibitors and other immune modifiers, treatment depends upon the phase in which the patient presents. If the patient is hyperthyroid, treatment generally focuses on blocking the hyperadrenergic symptoms with atenolol (25 to 50 mg daily) until thyroid function tests and symptoms improve, usually over 4 to 6 weeks. If the hyperthyroidism does not remit, Graves disease can be considered. The hypothyroid phase of drug-induced thyroid dysfunction tends to be permanent and generally requires L-thyroxine therapy using a weight-based approach (1.6 ug/kg/day).

Of all the drug-induced thyroid disorders, amiodarone-induced hyperthyroidism is the most difficult to treat. If type 1 disease cannot be distinguished from type 2 disease, both should be treated simultaneously using methimazole for type 1 disease and prednisone for type 2 disease. If the hyperthyroidism is moderate, a reasonable starting dose is 10 mg twice a day of each, with close follow-up of thyroid hormone levels. If the hyperthyroidism is significant or severe, higher doses of both drugs may be necessary. Most commonly the amiodarone is also stopped, but its tissue half-life is so long that its discontinuation does not effectively treat the thyrotoxicosis. If a patient has significant cardiac complications from hyperthyroidism and the disease is resistant to medical therapy, a thyroidectomy can emergently treat the hyperthyroidism.

PROGNOSIS

The prognosis of most drug-induced thyroiditis is usually good, but they can progress to permanent hypothyroidism. However, amiodarone-induced thyrotoxicosis can be difficult to treat because of the underlying cardiovascular disease and rarely may require removal of the thyroid gland.

Sclerosing (Reidel) Thyroiditis

Sclerosing thyroiditis, which is a rare disorder of unknown cause, is characterized by dense fibrous tissue that replaces the normal thyroid parenchyma and may extend into adjacent muscle, parathyroid glands, blood vessels, and nerves.[22] It is sometimes associated with IgG4-related systemic disease, which can include fibrosis of the salivary or lachrymal glands or of the peritoneum, and it can also be associated with sclerosing cholangitis, orbital pseudotumor, or fibrosing mediastinitis.

The peak age of onset is in the fourth to sixth decades, and sclerosing thyroiditis is about four times more frequent in women than in men. This condition accounts for about 1 in 100,000 thyroid surgeries.

CLINICAL MANIFESTATIONS

Patients present with rapidly enlarging, painless goiter and often report a sensation of pressure in the anterior neck, difficulty swallowing, or progressive dyspnea. Hoarseness may occur if the recurrent laryngeal nerve is involved. If the fibrotic process affects the entire gland, patients may have symptoms of hypothyroidism. On examination, the thyroid gland is rock hard, usually nontender, and moves poorly on swallowing.

DIAGNOSIS

Most patients with Riedel thyroiditis are initially euthyroid, but some patients develop hypothyroidism. Most patients have detectable thyroid peroxidase antibodies, and some have concurrent hypoparathyroidism. On ultrasound, affected areas are hypoechoic and have absent vascularity. The local extent of the fibrosis can be determined by CT or MRI scanning. An ^{18}FDG-PET scan will show intense uptake in areas of fibrotic inflammation and can assess the possible presence of extrathyroidal disease. The definitive diagnosis is made by biopsy, and open biopsy is often required because the texture of the gland makes fine needle aspiration biopsy difficult.

TREATMENT

Surgery, with total or subtotal thyroidectomy depending on extent of disease, is usually required to relieve compressive symptoms. Thyroid hormone treatment is indicated if hypothyroidism is present. Limited evidence suggests possible benefit from glucocorticoid therapy, tamoxifen, or rituximab to improve symptoms or prevent extrathyroidal disease.

GOITER

Goiter is defined as thyroid enlargement. Goiters are usually diffuse in Graves disease or congenital defects in thyroid hormone synthesis. By comparison, goiters are nodular in the setting of a single nodule or a multinodular goiter. Rarely, thyroid enlargement can appear rapidly, usually in the setting of a poorly differentiated or anaplastic thyroid carcinoma or thyroid lymphoma. Large goiters may not come to medical attention earlier because they do not substantially alter thyroid hormone production and instead may become problematic because of their size. With significant enlargement, goiters can cause tracheal obstruction or a superior vena cava syndrome (see Fig. 86-8). Large nodular goiters can involve the mediastinum and are a cause of an anterior mediastinal mass (Chapter 86).

DIAGNOSIS

A goiter must be carefully evaluated by physical examination and diagnostic testing of thyroid function (see Figs. 207-1 and 207-3). The clinical effects of large goiters can be assessed on a careful physical examination. The Pemberton sign is noted when raising both arms above the head obstructs venous return and leads to facial plethora and redness. Tracheal compromise can be discerned by an airway flow-volume loop looking for external compression (Chapter 73), but the most sensitive technique is a noncontrast CT scan (to prevent an iodine load, which can precipitate acute hyperthyroidism) in the setting of Graves disease or toxic nodular goiter. Diffuse goiters are almost always benign, whereas asymmetric goiters can represent multinodular disease or malignancy.

TREATMENT

Treatment should focus on the underlying cause of the goiter. Large goiters can be treated with total or subtotal thyroidectomy.

THYROID NODULES

Thyroid nodules are noted in up to 60% of adults when the thyroid gland is assessed ultrasonographically, but most such nodules are not clinically significant.[23] Thyroid nodules are more frequent in individuals from iodine-deficient regions, are more common in women than in men, and their frequency increases with age. The vast majority, about 95%, are benign. The likelihood of malignancy is increased in individuals who have a history of radiation treatment to the head or neck during childhood, exposure to ionizing radiation in childhood (e.g., from close proximity to a nuclear accident), or a family history of thyroid cancer. Familial syndromes associated with increased risk for thyroid cancer include Cowden disease, familial adenomatous polyposis (Chapter 179), Carney complex (Table 212-1), and multiple endocrine neoplasia type 2 (Chapter 212).

CLINICAL MANIFESTATIONS

Patients may present with a visible or palpable mass, or nodules may be found incidentally on imaging studies such as carotid ultrasound, CT, MRI, or ^{18}FDG-PET scans. Most nodules are asymptomatic, but large nodules may cause compressive symptoms including cough, dyspnea, hoarseness (due to vocal cord paralysis), dysphagia, or a pressure sensation in the anterior neck. A history of very rapid growth suggests hemorrhage into a benign nodule, anaplastic carcinoma, or thyroid lymphoma. Patients who have autonomously functioning nodules may present with symptoms of hyperthyroidism.

DIAGNOSIS

Clinical assessment of nodules aims to determine whether treatment is needed for symptoms or malignancy and to avoid the overdiagnosis of low-risk thyroid cancers. A physical examination should include palpation to assess the size and location of the nodule(s) as well as to determine whether the nodules are fixed to other structures (suggestive of malignancy) or mobile. Enlarged and firm ipsilateral cervical lymph nodes can be a sign of local tumor metastases.

The serum TSH should be assessed in all patients who have a thyroid nodule measuring at least 1 cm to help determine whether the nodule(s) may be hyperfunctioning (Fig. 207-6). When nodularity is present in the setting of a low serum TSH level, a radioactive iodine scan is needed to establish the diagnosis of nodular autonomy. The serum calcitonin level should be measured if there is clinical suspicion for medullary thyroid cancer, such as in patients with a family history of medullary cancer or multiple endocrine neoplasia type 2.[24]

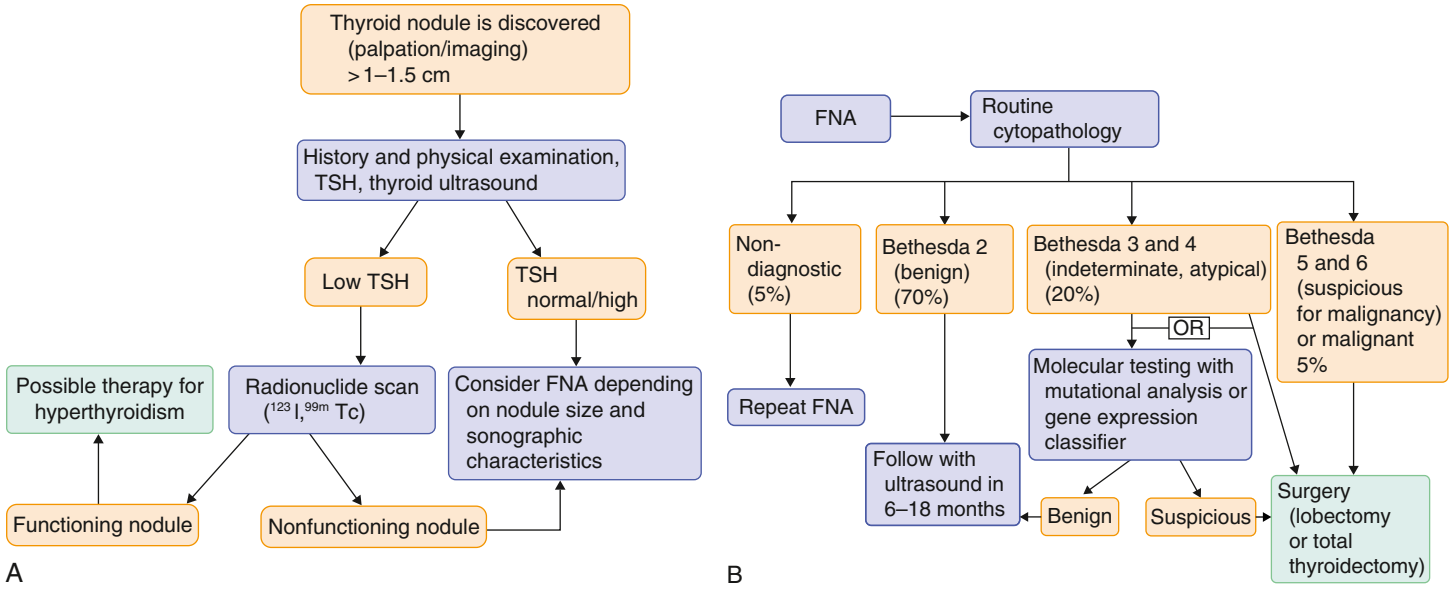

FIGURE 207-6. **A, Initial evaluation of a thyroid nodule. ^{123}I = radioactive iodine 123; ^{99m}Tc = technetium 99m; TSH = thyroid-stimulating hormone. B, Algorithm for evaluation of a thyroid nodule with fine-needle aspiration (FNA). With indeterminate nodules (Bethesda class 3 and 4), surgery, typically a diagnostic lobectomy, or molecular testing are both potential strategies. (From Jonklaas J, Cooper DS. Thyroid. In: Goldman L, Schafer AI, eds. *Goldman-Cecil Medicine*, 26th ed. Philadelphia: Elsevier; 2020:1462-1476.)**

TABLE 207-7 AMERICAN THYROID ASSOCIATION SIZE THRESHOLDS FOR THYROID NODULE FINE-NEEDLE ASPIRATION (FNA) BIOPSY BASED ON SONOGRAPHIC RISK STRATIFICATION

NODULE SONOGRAPHIC FEATURES	LIKELIHOOD OF MALIGNANCY	RECOMMENDED NODULE THRESHOLD FOR FNA
AMERICAN THYROID ASSOCIATION		
High suspicion (hypoechoic AND macrocalcifications, taller than wide configuration, irregular borders)	70-90%	≥1 cm
Intermediate suspicion (hypoechoic without suspicious features)	10-20%	≥1 cm
Low suspicion (iso- or hyperechoic without suspicious features)	5-10%	≥1.5 cm
Very low suspicion (spongiform or partially cystic without suspicious features)	<3%	>2 cm or consider not performing biopsy
Benign (simple cyst)	0	No biopsy

The American Thyroid Association system is based on ultrasonographic patterns, unlike the American College of Radiology Thyroid Imaging, Reporting, and Data System (E-Fig. 207-4), which is based on a point system.

Data from Haugen BR, Alexander EK, Bible KC, et al. 2015 American Thyroid Association management guidelines for adult patients with thyroid nodules and differentiated thyroid cancer: The American Thyroid Association Guidelines Task Force on Thyroid Nodules and Differentiated Thyroid Cancer. *Thyroid*. 2016;26:1-133.

Imaging

Ultrasonography is the best modality for assessing a thyroid nodule's size, location, echogenicity (cystic, solid, or mixed), shape, margins, calcifications, or other hyperechoic foci, as well as the presence of cervical lymph nodes that might be suspicious for metastatic disease. In patients who have thyroid nodularity and low serum TSH values, thyroid scintigraphy can determine whether nodules are nonfunctioning ("cold"), isofunctioning, or hyperfunctioning (autonomous, or "hot").[25] Autonomously functioning nodules do not require biopsy because the risk of malignancy is very low. However, hypo- and isofunctional nodules warrant biopsy if they otherwise meet criteria.

Fine-Needle Aspiration Biopsy

Based on sonographic features, the size of the nodule, and the clinical history, the probability of an underlying malignancy can guide the decision as to whether to perform a fine-needle aspiration biopsy (Table 207-7). In general, nodules <1 cm, cystic nodules, and partially cystic nodules with a spongiform appearance are likely to be benign. Concerning features include hypoechogenicity, irregular margins, being taller than wide when comparing the anteroposterior to the horizontal diameter in the transverse view, extrathyroidal extension, and the presence of microcalcifications or interrupted peripheral macrocalcifications. Additional considerations that may influence the decision about biopsy include the presence of high-risk features such as a family history of thyroid cancer, a history of childhood exposure to head or neck radiation, or comorbid conditions that might preclude thyroid surgery. ^{18}FDG-PET scanning is not recommended as part of the routine evaluation of thyroid nodules, but nodules that are known to be hypermetabolic on ^{18}FDG-PET scanning have about a 35% likelihood of malignancy and should be biopsied if ≥1 cm.

The risk of malignancy is the same when multiple nodules are present as for single nodules, and the risk of each individual nodule must be separately assessed. When multiple nodules with similar features are present, it is reasonable to biopsy the largest and observe the others.

Thyroid nodule cytopathology can usually establish the diagnosis.[26] For the approximately 2 to 16% of nodules that are reported as nondiagnostic, the fine-needle aspiration biopsy should be repeated; if it is again nondiagnostic, thyroid lobectomy can be considered. Nodules that are classified as malignant (Bethesda class VI) have a 98% probability of being papillary thyroid carcinoma. For the 20% or so of nodules that are classified as atypia of undetermined significance or as follicular neoplasm, the likelihood of malignancy ranges from about 10 to 40%; for these indeterminate nodules, options under expert supervision include repeat fine-needle aspiration biopsy, which may yield diagnostic results, diagnostic lobectomy, or molecular markers to refine the estimates of malignancy.[27]

AMERICAN COLLEGE OF RADIOLOGY THYROID IMAGING, REPORTING, AND DATA SYSTEM

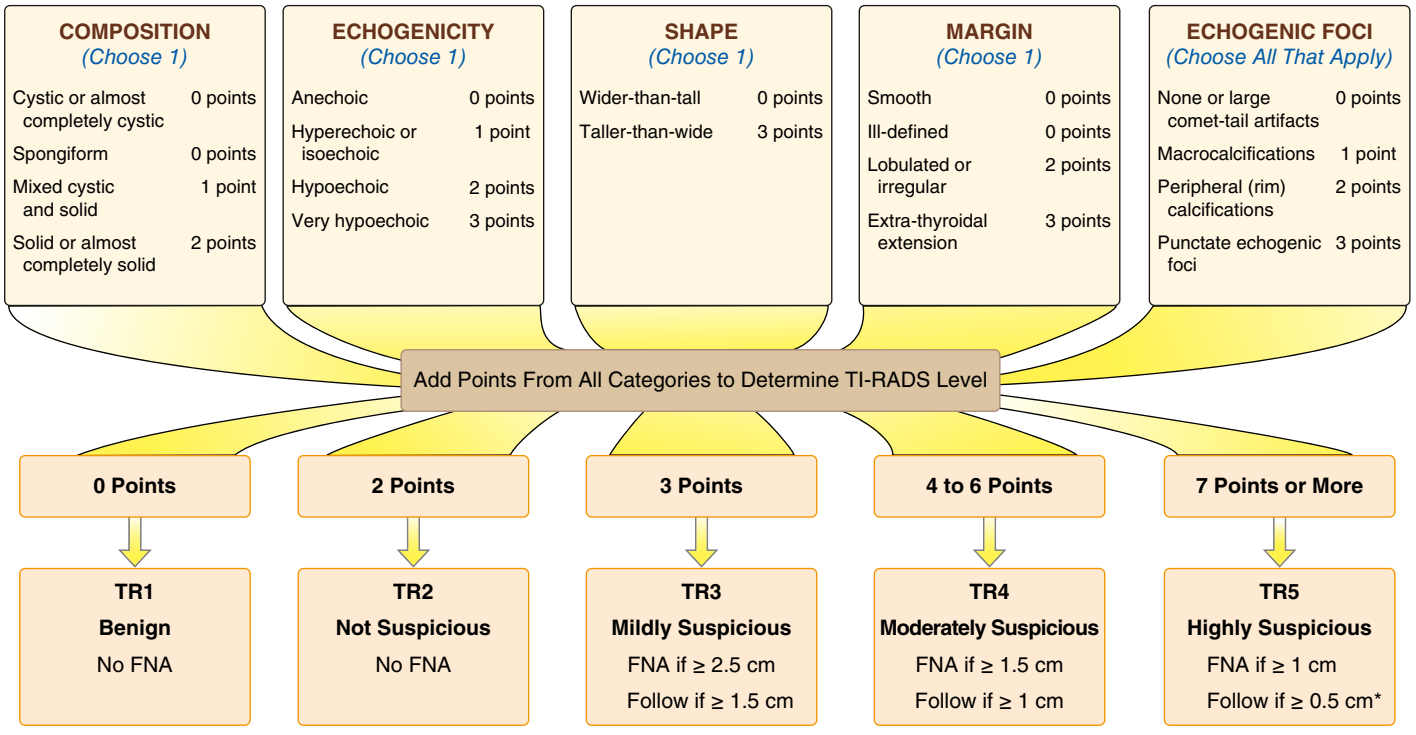

COMPOSITION	ECHOGENICITY	SHAPE	MARGIN	ECHOGENIC FOCI
Spongiform: Composed predominantly (>50%) of small cystic spaces. Do not add further points for other categories. *Mixed cystic and solid:* Assign points for predominant solid component. Assign 2 points if composition cannot be determined because of calcification.	*Anechoic:* Applies to cystic or almost completely cystic nodules. *Hyperechoic/isoechoic/hypoechoic:* Compared with adjacent parenchyma. *Very hypoechoic:* More hypoechoic than strap muscles. Assign 1 point if echogenicity cannot be determined.	*Taller-than-wide:* Should be assessed on a transverse image with measurements parallel to sound beam for height and perpendicular to sound beam for width. This can usually be assessed by visual inspection.	*Lobulated:* Protrusions into adjacent tissue. *Irregular:* Jagged, spiculated, or sharp angles. *Extrathyroidal extension:* Obvious invasion = malignancy. Assign 0 points if margin cannot be determined.	*Large comet-tail artifacts:* V-shaped, >1 mm, in cystic components. *Macrocalcifications:* Cause acoustic shadowing. *Peripheral:* Complete or incomplete along margin. *Punctate echogenic foci:* May have small comet-tail artifacts.

E-FIGURE 207-4. American College of Radiology Thyroid Imaging, Reporting and Data System point-based system for determination of need for thyroid nodule fine-needle aspiration biopsy based on sonographic risk stratification. FNA = fine needle aspiration. (From Tessler FN, Middleton WD, Grant EG, et al. ACR Thyroid Imaging, Reporting and Data System [TI-RADS]: white paper of the ACR TI-RADS Committee. *J Am Coll Radiol*. 2017;14:587-595.)

TABLE 207-8 RISK FOR PERSISTENCE/RECURRENCE IN DIFFERENTIATED THYROID CANCER

CANCER TYPE	RECURRENCE RISK	CHARACTERISTICS
Papillary	**Low**	All of the following: • No local or distant metastases • All macroscopic tumor has been resected • No tumor invasion of loco-regional tissues or structures • The tumor does not have aggressive histology (e.g., tall cell, hobnail variant, columnar cell carcinoma) • No vascular invasion • ≤5 pathologic cervical nodal micrometastases (<0.2 cm in largest dimension) Intrathyroidal microcarcinoma (<1 cm), unifocal or multifocal
	Intermediate	Microscopic invasion into perithyroidal soft tissues Radioactive iodine-avid metastatic foci in the neck on the first posttreatment whole-body ^{131}I scan Aggressive histology (e.g., tall cell, hobnail variant, columnar cell carcinoma) Vascular invasion >5 pathologic cervical nodal metastases with all involved lymph nodes <3 cm in largest dimension Multifocal microcarcinoma (<1 cm), with extrathyroidal extension
	High	Macroscopic invasion of tumor into perithyroidal soft tissues Incomplete tumor resection Distant metastases or postoperative serum thyroglobulin suggestive of distant metastases Cervical node metastases with any metastatic lymph node ≥3 cm in largest dimension
Follicular	**Low**	Intrathyroidal, well differentiated thyroid cancer with capsular invasion and no or minimal (<4 foci) vascular invasion
	High	>4 foci of vascular invasion

Adapted from Haugen BR, Alexander EK, Bible KC, et al. 2015 American Thyroid Association management guidelines for adult patients with thyroid nodules and differentiated thyroid cancer: the American Thyroid Association Guidelines Task Force on Thyroid Nodules and Differentiated Thyroid Cancer. *Thyroid*. 2016;26:1-133.

TREATMENT

Nodules that are cytologically benign or are too low risk to require biopsy can be followed with periodic ultrasonography. For nodules with high-risk features but benign cytology, repeat fine-needle aspiration may be considered within 12 months. Repeat fine-needle aspiration is also recommended for cytologically benign nodules that grow >20% in diameter or >50% in volume over the course of follow-up. Premalignant lesions, known as noninvasive follicular thyroid neoplasm with papillary-like nuclear features, require surgical resection for diagnosis. Radiofrequency ablation is now becoming an alternative option for reducing the size of benign nodules at many centers.[28] Surgery may be indicated for relief of compressive symptoms or for definitive diagnosis of nodules with suspicious cytopathology. Decisions about the extent of surgery (thyroid lobectomy or total thyroidectomy) depend on whether nodularity is bilateral and on the likelihood of malignancy. Lobectomy is generally preferred when surgery is elected for nodules with indeterminate cytopathology.

Aspiration may reduce the size of simple cysts that cause compressive symptoms or discomfort. Percutaneous ethanol injection can reduce the volume of thyroid cysts that recur following aspiration. Minimally invasive microwave, laser, or radiofrequency ablation are promising alternatives to reduce the size of solid or complex benign nodules.

THYROID CANCER

Thyroid cancers can be of multiple cell types. By far the most common are papillary carcinomas followed by follicular tumors. Medullary thyroid cancer, anaplastic thyroid cancer, and lymphomas of the thyroid are much less common.

Papillary and Follicular (Differentiated) Thyroid Cancer

EPIDEMIOLOGY

Papillary and follicular thyroid cancers occur in all age groups, with a mean age at diagnosis of 48 years. Thyroid cancer is three times more frequent in women than in men. The incidence of thyroid cancer increased about threefold in the United States starting in the 1970s, to a peak of about 14 cases per 100,000 by 2011 to 2016, but rates have started to decline in the past 5 years.[29] Despite the increased incidence, thyroid cancer–specific mortality has remained stable to modestly increased, with 5-year survival rates of >98%. These data suggest that the changes in incidence may have been more related to temporal trends in diagnostic vigor than to a true change in incidence.

PATHOBIOLOGY

Papillary and follicular tumors, which are derived from thyroid follicular epithelial cells, comprise the vast majority of thyroid malignancies (70 to 80% papillary, 10 to 15% follicular). Most papillary cancers are caused by either *BRAF* V600E or *RAS* mutations, and most follicular cancers are caused by mutations either of *RAS* or of the *PAX8-PPARγ* fusion oncogene. Although papillary and follicular carcinomas have differing underlying biology, their diagnosis and treatment are similar. Hürthle-cell carcinoma, which is a variant of follicular thyroid carcinoma, tends to be refractory to radioactive iodine.

CLINICAL MANIFESTATIONS AND DIAGNOSIS

Papillary and follicular thyroid cancers most frequently present as a thyroid nodule, either on palpation or as an incidental finding on imaging. Rarely, patients may present with symptoms of metastatic disease. Routine population screening for thyroid cancer using palpation or ultrasound is not recommended and may lead to the overdiagnosis of low-risk tumors. However, screening may be appropriate in high-risk asymptomatic individuals with a history of childhood exposure to ionizing radiation or with familial disorders linked to an increased risk of thyroid cancer (Chapter 212).

Diagnosis is as for a thyroid nodule (see above).

TREATMENT

Patients with small, low-risk tumors (solitary papillary tumors <1 cm in size and without high-risk ultrasonographic features) may elect a strategy of active surveillance rather than immediate surgery.[30] Such patients are followed with serial ultrasound examinations, and surgery is performed if the nodule grows or local lymph node metastases develop.

Primary Surgical Treatment

Otherwise, the primary treatment for thyroid cancers is surgical, preferably guided by preoperative ultrasound and performed by a high-volume thyroid surgeon to reduce the likelihood of damage to the parathyroid glands or recurrent laryngeal nerve.[31] In experienced centers, ambulatory thyroidectomy is a safe and efficacious outpatient surgery.[A7] Total thyroidectomy, which is required prior to treatment with radioactive iodine, is preferred if the primary tumor is ≥4 cm, if the tumor extends beyond the thyroid gland, or in the presence of clinically apparent involved lymph node or distant metastases. For tumors 1 to 4 cm in size without extrathyroidal extension, either lobectomy or total thyroidectomy can be elected.[32]

Postoperative Radioactive Iodine

Radioactive iodine treatment after thyroidectomy confers a survival benefit for high-risk tumors, may be considered for intermediate-risk tumors, but is of no prognostic benefit for low-risk tumors (Table 207-8).[A8] However, radioactive iodine (I-131) may be used to ablate residual normal thyroid tissue (to facilitate surveillance with serum Tg or radioactive iodine whole-body scanning) or to provide adjuvant therapy for subclinical micrometastases or clinically apparent residual or metastatic tumor. Prior to treatment, patients are given TSH or should have their thyroid hormone replacement withheld for 2 to 4 weeks to maximize uptake of the iodine.

Postoperative Thyroid Hormone Treatment

All patients who undergo total thyroidectomy and up to 66% of patients who undergo thyroid lobectomy will require thyroid hormone replacement. In patients at high risk for recurrent tumor, TSH-suppressive levothyroxine to maintain a serum TSH level of <0.1 mIU/L decreases tumor-specific mortality. In intermediate-risk tumors, the initial goal is more modest TSH suppression, with

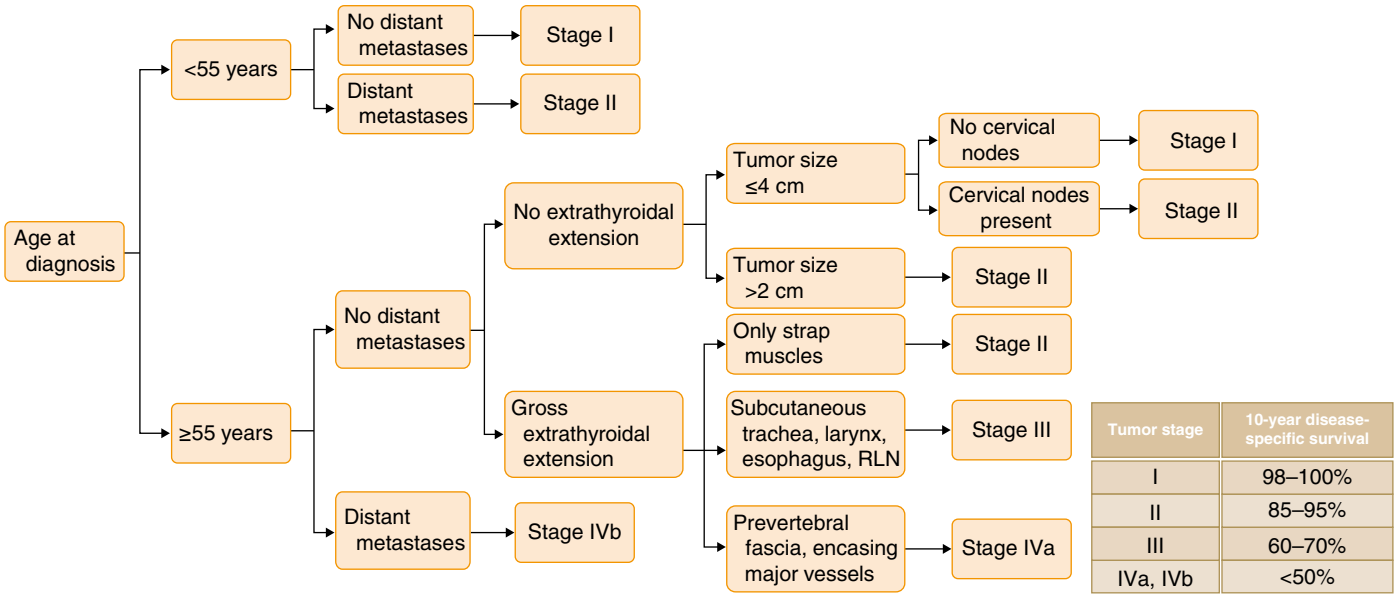

FIGURE 207-7. Prognosis of differentiated thyroid cancer. RNL = recurrent laryngeal nerve. (Data from *American Joint Committee on Cancer. AJCC Cancer Staging Manual*, 8th ed. New York: Springer International Publishing; 2017.)

a target TSH level of 0.1 to 0.5 mIU/L. Patients who are at low risk for recurrence do not benefit from TSH-suppressive levothyroxine dosing; the target in this group is in the low-normal range, or 0.5-2.0 mIU/L. TSH goals may need to be modified in patients who have an increased risk of adverse consequences from iatrogenic thyrotoxicosis, including patients who are older, have cardiovascular risk factors, or who have osteoporosis.

Recurrent or Persistent Disease

For patients with persistent or recurrent disease, central and/or lateral neck dissection may be used for locoregional extension. Repeated radioactive iodine treatment can be helpful for nonresectable locoregional recurrences or distant metastases that are radioactive iodine avid on scanning. External beam radiation therapy is occasionally used for skeletal or brain metastases.

Differentiated thyroid cancers are poorly responsive to conventional chemotherapy. The multikinase inhibitors sorafenib (400 mg twice daily) and lenvatinib (24 mg daily) are FDA-approved for the treatment of advanced differentiated thyroid cancers.[A9] Multikinase inhibitors have multiple adverse effects, including hypertension, renal toxicity, arthralgia, headache, hand-foot skin reaction, diarrhea, and muscle wasting. Larotrectinib (100 mg twice daily) and entrectinib (600 mg daily) are selective inhibitors that are FDA-approved for solid tumors with an *NTRK* fusion.[A10] Pralsetinib (400 mg daily) and selpercatinib (120 to 160 mg twice daily) are selective inhibitors that are FDA approved for *RET*-altered thyroid cancer. When possible, systemic agents should be administered in the setting of a clinical trial. The tumor's specific mutations or signaling pathway abnormalities should inform the selection of the systemic therapy drug.

Follow-Up

The serum thyroglobulin level is a sensitive tumor marker in patients who have undergone total thyroidectomy for differentiated thyroid cancer. During the initial period of follow-up, the serum thyroglobulin level should be measured at least every 6 to 12 months. Approximately 15% of the adult population has autoantibodies directed against thyroglobulin; in these individuals, serum thyroglobulin levels are unreliable, but changes in the thyroglobulin antibody titers can be used as a surrogate tumor marker.

Because the majority of persistent or recurrent papillary thyroid cancer will present in the thyroid bed or as cervical nodal metastases, neck ultrasonography is a mainstay of tumor surveillance. Neck ultrasound is initially recommended at 6 to 12 months postoperatively, with the subsequent frequency and duration of ultrasonographic surveillance dictated by the patient's risk and response to therapy.

In patients who have elevated serum thyroglobulin levels or in whom persistent or recurrent disease is suspected, whole-body radioactive iodine scanning may be helpful after thyroidectomy or radioactive iodine treatment to determine the presence of nodal or distant metastases. Scanning may be repeated at 6 to 12 months to ensure that areas of prior uptake have been ablated. Chest CT scans may be helpful to detect disease in the retropharyngeal nodes and in the mediastinum, hilum, and lungs in patients who have thyroglobulin levels >10 ng/mL but normal neck ultrasound findings ^{18}FDG-PET scanning should be considered in high-risk patients with elevated serum Tg (>10 ng/mL) when radioactive iodine imaging is negative.

PROGNOSIS

Following surgery, prognosis is based on the patient's age, the size of the tumor, the presence and extent of extrathyroidal extension, and the presence of metastases (Fig. 207-7). For the vast majority of patients with differentiated thyroid cancers, however, the risk of dying from the thyroid cancer still is low. Follicular cancers that are intrathyroidal, well differentiated, and with no or minimal (<4 foci) vascular invasion are considered low risk for recurrence, whereas tumors with more foci of vascular invasion are considered high risk. Intrathyroidal papillary carcinomas are at low risk for recurrence if there is no evidence of extrathyroidal extension, vascular invasion, or distant metastases, with or without up to five local lymph node micrometastases (<0.2 cm in largest dimension). Intermediate-risk papillary carcinomas may have microscopic extrathyroidal extension, more than five cervical lymph node metastases if all are less than 3 cm in size, vascular invasion, or aggressive tumor histology. High-risk papillary carcinomas are tumors that were incompletely resected or associated with gross extrathyroidal extension, any metastatic lymph node ≥3 cm in the largest dimension, distant metastases, or high postoperative serum thyroglobulin values suggesting the presence of distant metastases.

The initial postoperative risk stratification should be modified over time to incorporate the patient's response to therapy (Table 207-8). In patients who have had an excellent response to therapy (defined as the absence of clinical, biochemical, or structural evidence of disease: a serum Tg on levothyroxine of <0.2 mg/mL with negative neck ultrasound), the likelihood of recurrent tumor in these patients is very low, and both the degree of TSH suppression and the intensity of tumor surveillance can be relaxed. A structural incomplete response to therapy, which confers high risk, is defined as the presence of loco-regional or distant metastases on imaging. Most of these patients will have persistent disease, and patients with distant metastases have a tumor-specific mortality of up to 50%.

Medullary Thyroid Cancer

Medullary thyroid cancer is a neuroendocrine tumor of the thyroid parafollicular C cells.[33] The primary oncogene is *RET*, which encodes a tyrosine kinase receptor. Medullary thyroid cancer is rare, comprising just 1 to 2% of thyroid cancers in the United States. About 75% of medullary cancer cases are sporadic, with the remainder occurring as a manifestation of the autosomal dominant multiple endocrine adenomatosis type 2A or multiple endocrine adenomatosis type 2B syndromes (Chapter 212). All patients with multiple endocrine adenomatosis type 2A will eventually develop medullary thyroid cancer, most frequently in the third decade of life, and some also develop pheochromocytomas (Chapter 209), Hirschsprung disease (Chapter 122), and/or primary hyperparathyroidism (Chapter 227). In patients with multiple endocrine adenomatosis type 2B, medullary

thyroid cancer is highly aggressive and often presents in infancy; about 50% of affected patients will develop pheochromocytomas, and other manifestations include a marfanoid habitus, mucosal neuromas, and intestinal ganglioneuromas.

CLINICAL MANIFESTATIONS AND DIAGNOSIS

Most sporadic medullary thyroid cancers are diagnosed in patients ages 40 to 70 years. The typical presentation is with a solitary thyroid nodule. Most patients have cervical node metastases at the time of diagnosis, and distant metastases are present in 10%. Diarrhea and facial flushing may occur owing to the tumor's secretion of calcitonin, and medullary cancer can also cause ectopic Cushing syndrome (Chapter 208).

Serum calcitonin levels are elevated. On ultrasound, most medullary cancers appear as hypoechoic nodules. Immunohistochemical staining of fine-needle aspiration biopsy material can detect calcitonin, chromogranin, and carcinoembryonic antigen (CEA).

Germline *RET* testing is recommended in newly diagnosed patients with apparently sporadic disease. When a germline mutation is discovered, genetic counseling and screening should be provided for first-degree relatives. Screening for metastases (using CT of the neck and chest, CT or MRI of the liver, and axial MRI or bone scintigraphy) is recommended in patients who have baseline serum calcitonin levels >500 pg/mL, an elevated CEA level, or a large burden of disease in the neck.

TREATMENT

Treatment is total thyroidectomy, but patients should be screened for pheochromocytoma (Chapter 209) and primary hyperparathyroidism (Chapter 227) preoperatively if they have a known germline *RET* mutation or if their *RET* mutation status is unknown. Central neck dissection should be performed in all cases. More extensive surgery is guided by the results of preoperative ultrasonography and scanning.

Thyroid hormone replacement is required following thyroidectomy; TSH-suppressive dosing is not indicated. Low or undetectable postoperative levels of serum calcitonin and a normal CEA are associated with a favorable prognosis, and patients can be followed with laboratory monitoring every 6 months. If the postoperative calcitonin levels are elevated but <150 mg/mL, neck ultrasonography should be performed. In patients with higher postoperative serum calcitonin levels (≥150 pg/mL), additional periodic imaging of the chest, liver, and skeleton is also recommended.

Treatment options for patients with recurrent or persistent disease include further surgical resection or directed therapies, including external beam radiation, radiofrequency ablation, and embolization. In addition, the multikinase inhibitors vandetanib (300 mg once daily) and cabozantinib (140 mg once daily) and the *RET*-selective kinase inhibitors selpercatinib (120 to 160 mg twice daily) and pralsetinib (400 mg once daily) are FDA-approved for patients who have advanced and progressive disease.[A11]

PROGNOSIS

The 10-year survival rates are 100% for stage I disease, 93% for stage II disease, 71% for stage II disease, and only 21% for stage IV disease. Survival rates are lower in individuals over age 40 years. A calcitonin doubling time of less than 6 to 12 months predicts poor survival.

Anaplastic Thyroid Cancer

Anaplastic thyroid cancer, which is a highly aggressive undifferentiated tumor derived from thyroid follicular cells, accounts for 1 to 2% of all thyroid cancers in the United States and up to 10% globally. It is more frequent in women, and the mean age at diagnosis is 65 years.

CLINICAL MANIFESTATIONS AND DIAGNOSIS

Most patients present with a rapidly enlarging anterior neck mass, which may be painful and usually causes compressive symptoms. The trachea may be partially obstructed. Systemic symptoms may include weight loss, fatigue, and fever of unknown origin. Examination shows a large, firm, fixed, nodular goiter. Ultrasound generally shows a hypoechoic mass, but findings are nonspecific.

Rapid diagnosis is essential. Fine-needle aspiration biopsy is diagnostic in only about 60% of cases, so core biopsy is often required to establish the diagnosis.

Once the diagnosis is established, molecular profiling, particularly testing for *BRAF V600E* mutations, is recommended to inform therapeutic decisions. Radiologic staging should be performed with CT, MRI, or ^{18}FDG-PET scanning.

TREATMENT

Prompt treatment may be therapeutic or palliative, depending on the stage of disease and the patient's preferences.[34] Surgery, followed by chemotherapy, should be performed for tumors thought to be potentially resectable, although spread is usually extensive by the time of diagnosis.[35] In tumors with *BRAF V600E* mutations, neoadjuvant therapy with dabrafenib (150 mg twice daily) plus trametinib (2 mg once daily) may sufficiently decrease the tumor's size to make resection feasible. In tumors without *BRAF V600E* mutations, therapies targeted to specific tumor mutations (*ALK*, *NTRK*, or *RET* fusion mutations) may be effective. In the absence of a therapeutic response, palliative cytotoxic chemotherapy, radiation, or supportive hospice care may be elected.

PROGNOSIS

Metastatic anaplastic cancer is invariably fatal. The median survival in patients with anaplastic cancer is 5 to 6 months, and the 1-year overall survival is only 20%.

Primary Thyroid Lymphoma

Primary thyroid lymphoma is rare, with an annual incidence of 1 to 2 per million. Most primary thyroid lymphomas are B-cell lymphomas. The risk is increased 40- to 80-fold in the setting of Hashimoto thyroiditis. Most affected individuals are ages 60 to 69 years.

The clinical hallmark is rapid, painless, thyroid enlargement, often with associated compressive symptoms. Rapid enlargement from thyroid lymphoma must be differentiated from anaplastic carcinoma. Systemic symptoms of lymphoma (e.g., fever, night sweats, and weight loss) may be present.

Ultrasound may show either nodularity or diffuse thyroidal enlargement with heterogeneity. Fine-needle aspiration biopsy shows diffuse lymphocytic infiltration. Flow cytometry and immunohistochemical staining may establish the diagnosis, but open biopsy is occasionally required.

TREATMENT AND PROGNOSIS

Treatment with chemotherapy and radiotherapy under expert supervision yields 90% 5-year survival rates. Compressive symptoms typically improve with chemotherapy, and surgical resection is rarely required.

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For the General References and other additional features, please visit Elsevier eBooks+ at https://ebooks.health.elsevier.com.

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208 ADRENAL CORTEX

LYNNETTE K. NIEMAN

NORMAL ANATOMY AND FUNCTION

The adrenal glands weigh 6 to 8 g in adults (Fig. 208-1). Each contains a cortex, which makes steroid hormones, and a medulla, which produces catecholamines. Diseases of the adrenal medulla are discussed in Chapter 209. In the adrenal cortex, production of the three major classes of steroids occurs in specific zones: (1) the outermost layer, which is the glomerulosa, produces mineralocorticoids, primarily aldosterone; (2) the middle layer, which is the fasciculata, produces glucocorticoids, primarily cortisol; and (3) which is the innermost layer, the reticularis, produces adrenal androgens, primarily dehydroepiandrosterone (DHEA) and its sulfated conjugate (DHEA-S) (Fig. 208-2). This division reflects the fact that certain critical enzymes are restricted to specific zones, thereby resulting in the ability or inability to synthesize specific end products.

The actions and regulation of these steroid classes differ. Mineralocorticoids act through the renal mineralocorticoid receptor to promote the reabsorption of sodium and the secretion of potassium. In addition to this classic action, mineralocorticoids have important action on the vasculature and may exacerbate the metabolic syndrome. The secretion of aldosterone is stimulated primarily by hyperkalemia and angiotensin II (which itself is stimulated by hypovolemia and excess renin). These agents increase the production of aldosterone synthase to restore homeostasis through this feedback loop. Aldosterone production is stimulated to a much smaller degree by adrenocorticotropic hormone (ACTH).

Cortisol and other glucocorticoids act through the glucocorticoid receptor type 2 and its isoforms. The actions of this class of steroids are much broader, including effects on carbohydrate handling, lipid and calcium metabolism, and the immune and nervous systems. Cortisol production is regulated primarily by pituitary ACTH (Chapter 205), which is secreted in a circadian rhythm in response to hypothalamic corticotropin-releasing hormone (CRH; Chapter 204) so that cortisol levels are highest in the morning and fall to a nadir around midnight. Cortisol coordinates the production of ACTH through negative feedback at the pituitary (ACTH) and hypothalamus (CRH). Vasopressin secretion also plays a role in stimulating ACTH release.

DHEA and DHEA-S, which are the most abundant products of the adrenal gland, exert their estrogenic and androgenic effects as prohormones after being converted to estrogens and testosterone in the peripheral tissues, where they activate the androgen and estrogen receptors. There is no known regulator of DHEA synthesis, but its production declines with age.

DISORDERS OF ADRENAL FUNCTION

GLUCOCORTICOID EXCESS: CUSHING SYNDROME

EPIDEMIOLOGY

The annual incidence of Cushing syndrome is estimated to be between 1.8 and 3.2 cases/million.[1] It is more common in women than in men (6 : 1 ratio), with a mean age at onset in the fourth decade.

PATHOBIOLOGY

Most disorders of the adrenal cortex reflect overproduction or underproduction of the products of a single synthetic zone—cortisol, aldosterone, or testosterone or estrogen (Fig. 208-3). The congenital adrenal hyperplasias, which are an exception, manifest with both overproduction and underproduction. Abnormal secretion is suggested by clinical features of each disorder and is reflected in plasma or urine levels of the relevant hormones or by the consequent increases or decreases in feedback systems, which form the basis of the biochemical diagnostic tests.

In Cushing syndrome, higher brain pathways stimulate the release of CRH and activation of the entire hypothalamic-pituitary-adrenal axis (see Fig. 208-3E). Cortisol negative feedback inhibition on CRH and pituitary ACTH release restrains the resulting hypercortisoluria to less than four-fold greater than normal.

In Carney syndrome, in which hyperfunctioning adrenal nodules cause Cushing syndrome, myxomas, and spotty skin pigmentation, patients have mutations that lead to a truncated form of protein kinase A regulatory 1α subunit. The resultant increase in protein kinase A activation by cyclic adenosine monophosphate presumably allows tumor formation. In bilateral macronodular adrenal hyperplasia, aberrant expression of "illicit" receptors for various ligands (gastric inhibitory polypeptide, β-adrenergic, vasopressin) presumably mediates autonomous cortisol production.

CLINICAL MANIFESTATIONS

Cushing syndrome is a symptom complex that reflects excessive exposure of tissues to cortisol. Classic features of Cushing syndrome include weight gain, plethora, hypertension, and striae (Table 208-1). Not all patients have all features; the number and severity of features correlate roughly with the duration and severity of hypercortisolism. Changes in mood and cognition include irritability, crying, and restlessness; depressed mood; decreased libido; insomnia; anxiety; and decreased concentration and impaired memory.

Because many of the signs and symptoms are nonspecific, the diagnosis may be confused with psychiatric disorders (Chapter 362), polycystic ovary syndrome (Chapter 218), the metabolic syndrome (Chapter 210), simple obesity (Chapter 201), fibromyalgia, or acute illness. However, because worsening hypercortisolism may precipitate hypertension, glucose intolerance, infections, psychiatric disturbances, impaired cognition, and hypercoagulability,

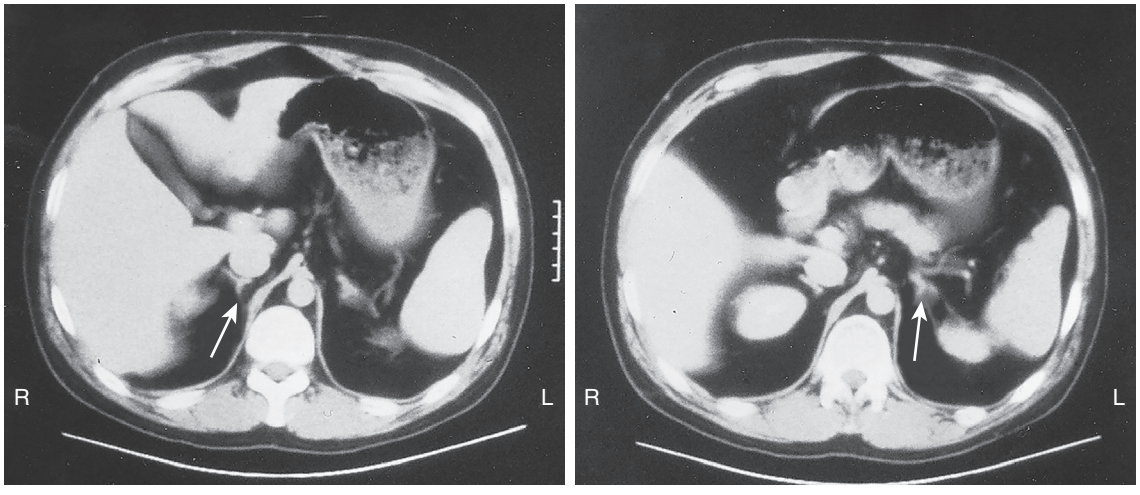

FIGURE 208-1. Magnetic resonance images of the abdomen showing the position and relative size of the normal adrenal glands.

ABSTRACT

The adrenal glands contain the cortex, which makes steroid hormones, and the medulla, which produces catecholamines. In the adult human adrenal cortex, production of the three major classes of steroids occurs in specific zones: the outermost layer, the glomerulosa, produces mineralocorticoids, primarily aldosterone; the middle layer, the fasciculata, produces glucocorticoids, primarily cortisol; the innermost layer, the reticularis, produces adrenal "androgens," primarily dehydroepiandrosterone (DHEA) and its sulfated conjugate (DHEA-S). Most disorders of the adrenal cortex reflect overproduction or underproduction of the products of a single synthetic zone—cortisol, aldosterone, or testosterone or estrogen. The congenital adrenal hyperplasias are an exception and manifest with both overproduction and underproduction. Abnormal secretion is suggested by clinical features of each disorder and is reflected in plasma or urine levels of the relevant hormones or by the consequent increases or decreases in feedback systems, which form the basis of the biochemical diagnostic tests. Current diagnostic and treatment recommendations are presented for hypercortisolism and hypocortisolism (Cushing syndrome and adrenal insufficiency), mineralocorticoid and adrenal androgen excess, and combined excess and deficiencies seen in congenital adrenal hyperplasias.

KEYWORDS

cortisol
aldosterone
DHEA
adrenal insufficiency
Cushing syndrome
congenital adrenal hyperplasia

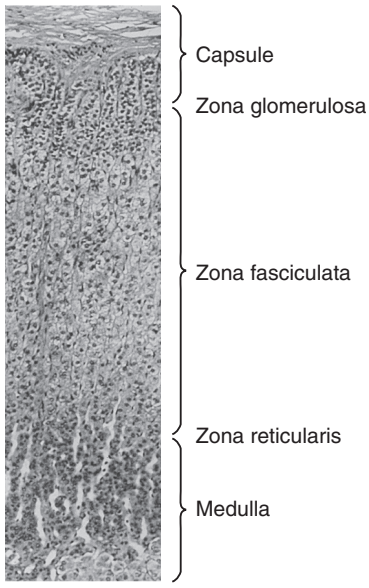

FIGURE 208-2. **Histologic section through a normal adult adrenal gland showing the progression (from outside to inside) of the zona glomerulosa, zona fasciculata, zona reticularis, and medulla.**

TABLE 208-1 THE FREQUENCY OF CLINICAL SIGNS AND SYMPTOMS OF CUSHING SYNDROME

SIGN OR SYMPTOM	PERCENTAGE
Decreased libido in men and women	100
Obesity or weight gain	97
Plethora	94
Round face	88
Menstrual changes	84
Hirsutism	81
Hypertension	74
Ecchymoses	62
Lethargy, depression	62
Striae	56
Weakness	56
Electrocardiographic changes or atherosclerosis	55
Dorsal fat pad	54
Edema	50
Abnormal glucose tolerance	50
Osteopenia or fracture	50
Headache	47
Backache	43
Recurrent infections	25
Abdominal pain	21
Acne	21
Female balding	13

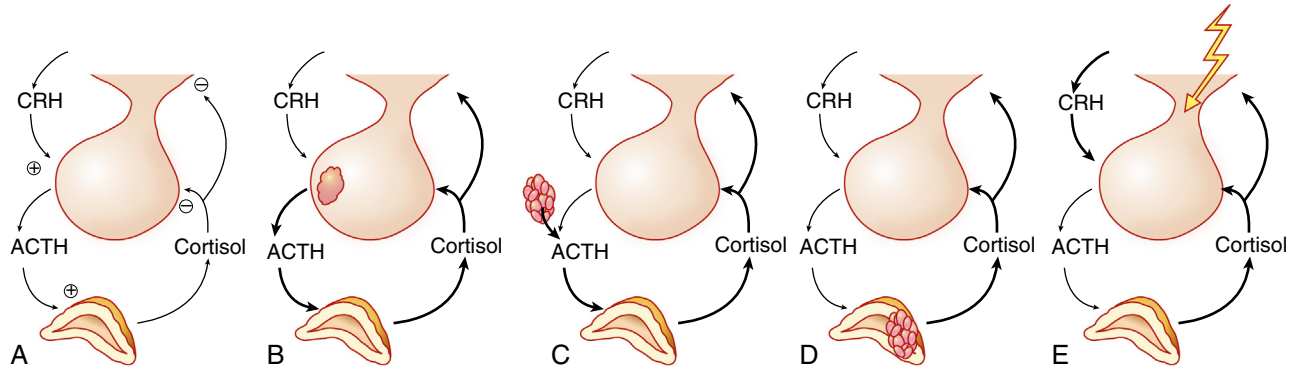

FIGURE 208-3. **Physiology of the adrenal axis in health, Cushing syndrome, and pseudo-Cushing states. A,** In healthy individuals, cortisol production is stimulated by the increased hypothalamic release of corticotropin-releasing hormone (CRH), which then travels down the pituitary stalk to stimulate adrenocorticotropic hormone (ACTH) secretion and release by corticotropes. Circulating ACTH stimulates adrenal gland production and secretion of cortisol. Cortisol then functions in a negative feedback mechanism to inhibit both CRH and ACTH. **B,** In Cushing disease, a pituitary tumor releases excessive amounts of ACTH, which results in increased cortisol secretion by the adrenal glands. **C,** In ectopic ACTH secretion, a nonpituitary ACTH-secreting tumor releases excessive amounts of ACTH, which results in increased cortisol secretion by the adrenal glands. **D,** In ACTH-independent adrenal forms of Cushing syndrome, the adrenal tumor autonomously releases excess amounts of cortisol. In all forms of Cushing syndrome, the negative feedback effects of excessive cortisol inhibit endogenous CRH and ACTH secretion, so that circulating ACTH levels reflect the underlying tumor (levels are normal or increased) or independent cortisol production (levels are suppressed). **E,** In pseudo-Cushing states, central stimulation increases CRH secretion, which in turn increases ACTH and hence cortisol production. In this setting, the negative feedback effects of excessive cortisol inhibit endogenous CRH and ACTH secretion, so that cortisol levels are ultimately constrained, albeit at an increased level.

it is important to identify this treatable disorder to prevent its associated morbidity and mortality.[2]

DIAGNOSIS

Clinical Examination

Screening for Cushing syndrome is most likely to be positive in the presence of signs that are typical of glucocorticoid excess, such as abnormal fat distribution in the supraclavicular and temporal fossae, proximal muscle weakness, wide (>1 cm) purple striae, and new irritability, decreased cognition, and decreased short-term memory. Testing is indicated when clinical features have progressed over time and in patients with adrenal masses that are incidentally detected on imaging obtained for unrelated reasons (so-called adrenal incidentalomas).[3,4] For example, oligomenorrhea is more suggestive of Cushing syndrome if a woman previously had regular menses. Serial seven subtractions and recall of three cities (or objects) are useful bedside strategies to identify deficits in cognition and memory.

Laboratory Findings

Exogenous glucocorticoid exposure should be excluded before screening for endogenous Cushing syndrome. Pseudo-Cushing states include psychiatric disorders (depression, anxiety disorder, obsessive-compulsive disorder), chronic pain, severe exercise, alcoholism, uncontrolled diabetes, and morbid obesity. In the absence of these conditions, at least two different screening tests, all of which have similar diagnostic accuracy (Fig. 208-4),[5] should be abnormal to establish the diagnosis of Cushing syndrome. Importantly, tests that are

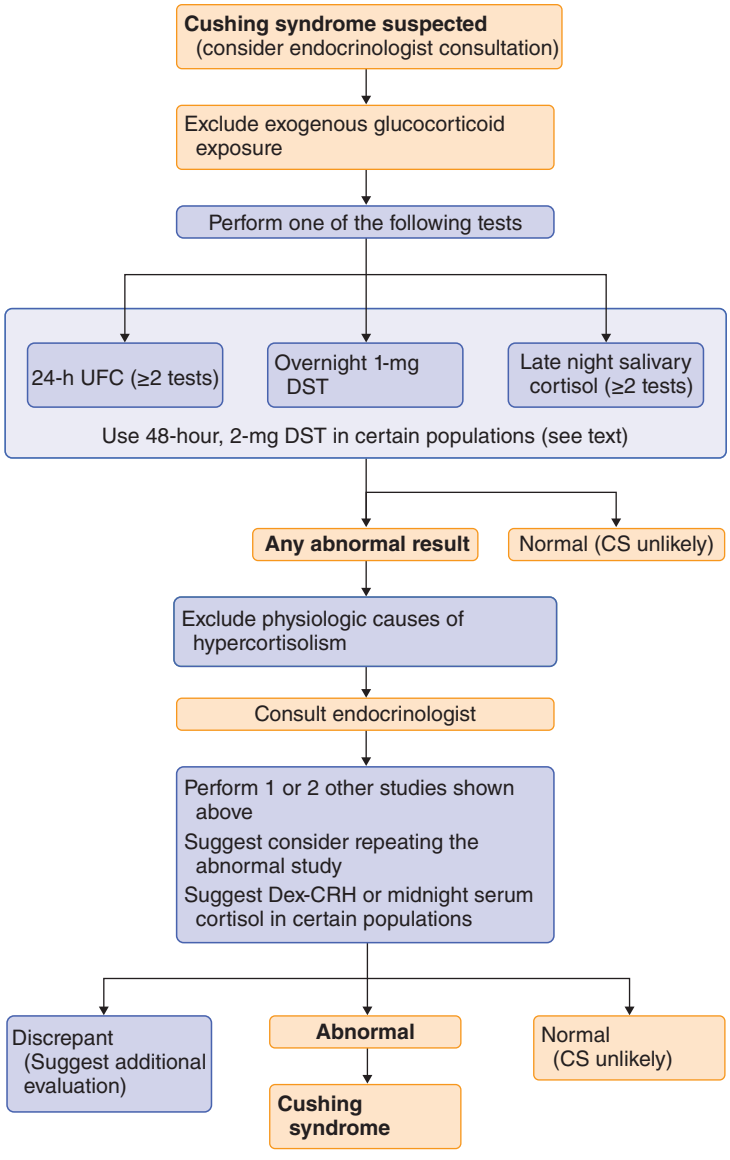

FIGURE 208-4. Algorithm for testing of patients suspected of having Cushing syndrome (CS). All statements are recommendations except for those prefaced by "suggest." Diagnostic criteria that suggest Cushing syndrome are urine free cortisol (UFC) greater than the normal range for the assay, serum cortisol greater than 1.8 μg/dL (50 nmol/liter) after 1 mg dexamethasone (1-mg DST), and late-night salivary cortisol greater than 145 ng/dL (4 nmol/liter). Dex-CRH = dexamethasone–corticotropin-releasing hormone test; DST = dexamethasone suppression test. (Reprinted with permission from Nieman LK, Biller BM, Findling JW, et al. The diagnosis of Cushing syndrome: an Endocrine Society clinical practice guideline. *J Clin Endocrinol Metab*. 2008;93:1526-1540.)

useful for diagnosing the specific cause of Cushing syndrome should not be used to make the syndromic diagnosis.

Urine and Saliva Cortisol Measurements

Urine free cortisol excretion during 24 hours is elevated in about 20% of adrenal incidentalomas (see later) and also may be increased in the so-called pseudo-Cushing states. Cushing syndrome cannot be diagnosed with certainty unless values reach the threshold of exceeding four times the normal values. Conversely, patients with Cushing syndrome may have normal urine free cortisol excretion because of mild or intermittent hypercortisolism or altered renal metabolism of cortisol. If urine free cortisol levels are only mildly elevated and clinical features are minimal, it is best to treat any pseudo-Cushing state and to remeasure the levels, with the expectation that they will normalize. Alternatively, if urine free cortisol values are normal but clinical suspicion is high, repeated measurement might disclose intermittent hypercortisolism.

Measurement of bedtime salivary cortisol is a convenient outpatient test.[6] Because the assay is technique influences the results, criteria for its interpretation differ, and each assay must be validated before it is used for this purpose.

TABLE 208-2 ETIOLOGY OF CUSHING SYNDROME

EXOGENOUS	ENDOGENOUS
Most common cause of Cushing syndrome: Glucocorticoid or ACTH driven May be factitious or iatrogenic	ACTH independent—autonomous adrenal activation (20% of all cases) • Adrenal adenoma (40-50%) • Adrenal carcinoma (40-50%) • Primary pigmented nodular adrenal disease • McCune-Albright syndrome • Primary Bilateral macronodular adrenal hyperplasia ACTH dependent—adrenal activation by excessive ACTH (80% of all cases) • Corticotrope adenoma (80%) • Ectopic ACTH secretion (20%) • Ectopic CRH secretion (rare)

ACTH = adrenocorticotropic hormone; CRH = corticotropin-releasing hormone.

Dexamethasone Suppression Tests

The dexamethasone suppression test is a simple screening test that takes advantage of the negative feedback effect of glucocorticoids to reduce ACTH (and hence serum cortisol). Dexamethasone 1 mg is given orally between 11:00 PM and midnight, and then plasma cortisol is measured between 8:00 and 9:00 AM the next morning. Using a cutoff value of 1.8 μg/dL, the test has a false-negative rate of up to about 10% in patients with Cushing syndrome and a false-positive rate of up to about 30 to 50% in patients without the condition.[7]

Any dexamethasone test may give false results in patients who have abnormal metabolic clearance of the drug. Agents that induce the cytochrome P-450 CYP3A4 enzymes (alcohol, rifampin, phenytoin, phenobarbital) increase dexamethasone clearance, whereas renal or hepatic failure decreases it. Measurement of a dexamethasone level can determine whether its clearance has been altered.

Differential Diagnosis

The causes of endogenous Cushing syndrome can be divided broadly into ACTH-dependent (80%) and ACTH-independent (20%) forms (Table 208-2 and Fig. 208-5). Hypercortisolism from autonomously functioning benign or malignant adrenal tumors suppresses ACTH, whereas ACTH levels are elevated when the adrenal glands respond to ACTH from a pituitary adenoma or extra-adrenal tumor. A normal or elevated plasma ACTH level (>15 pg/mL; 3.3 pmol/L) is consistent with an ACTH-producing tumor. Intermediate ACTH concentrations between 5 and 15 pg/mL (1.1 to 3.3 pmol/L) are not diagnostic; in such patients, suboptimal cortisol responses to CRH stimulation may identify the minority of cases of ACTH-independent Cushing syndrome with borderline basal ACTH values. In addition, a suppressed plasma DHEA-S value supports the diagnosis of an ACTH-independent disorder.

Primary Adrenal Disorders

ACTH is usually less than 10 pg/mL in primary adrenal disorders but is also suppressed by exogenous steroids, whether they are prescribed intentionally (iatrogenic Cushing syndrome) or taken factitiously. Patients must be queried closely about exogenous steroid administration, recognizing that oral, parenteral, inhaled, and topical steroids can all cause glucocorticoid excess. Patients with endogenous Cushing syndrome and low ACTH concentrations should undergo adrenal imaging to identify the site of adrenal abnormality. Nonautonomous adrenal tissue atrophies when ACTH support is subnormal, so the common ACTH-independent forms of Cushing syndrome (adrenal adenoma and carcinoma) manifest as a unilateral adrenal mass, with atrophy of the adjacent and contralateral tissue on magnetic resonance imaging (MRI) or computed tomography (CT).

Adrenal Adenoma

Adrenal adenomas, which secrete only cortisol and its precursors, present with features that range from clinically obvious Cushing syndrome with unequivocal diagnostic results, to a more subtle clinical picture with fewer biochemical abnormalities. This latter presentation may come to attention only when imaging for another reason uncovers an adrenal "incidentaloma" and diagnostic testing returns only an abnormal 1 mg dexamethasone suppression test. Although previously termed subclinical Cushing syndrome, this condition has been re-named mild autonomous cortisol excess because these patients often have features compatible with Cushing syndrome, and have increased cardiovascular mortality.[8]

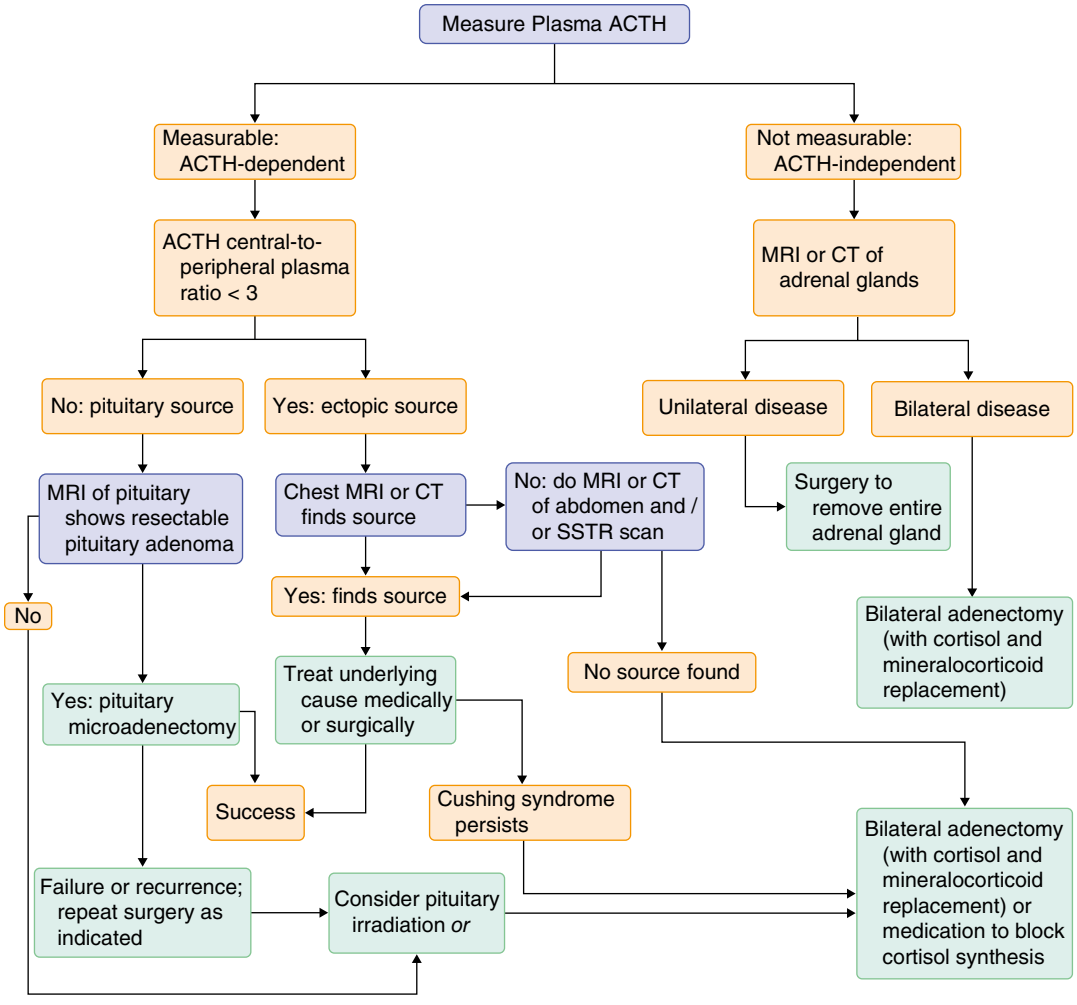

FIGURE 208-5. Approach to the differential diagnosis and treatment of Cushing syndrome. ACTH = adrenocorticotropin hormone; CT = computed tomography; MRI = magnetic resonance imaging; SSTR = somatostatin receptor scan.

Adrenal Cortical Cancer

Adrenal cortical cancer can present with hormonal excess of one or more layers of the adrenal cortex, with pure glucocorticoid excess (Cushing syndrome) being most common, followed by glucocorticoid and androgen excess (Cushing syndrome with virilization), and rarely as a pure excess of estrogen, androgen, or mineralocorticoids. Alternatively, adrenal cortical cancer may be hormonally silent and present with mass effects. In addition to measurement of adrenal cortex hormones and their precursors, imaging provides important clues to malignancy, including pre-contrast CT Hounsfield units more than 25, irregular margins, size greater than 4 cm, necrosis, or calcifications.

Bilateral Primary Adrenal Disease

Bilateral forms of primary adrenal disease are rare and may be manifested with small or large adrenal nodules. Primary pigmented nodular adrenal disease, which occurs primarily in children and young adults, is characterized by small- to normal-sized adrenal glands containing small (<5 mm) black-brown cortical nodules. About half of these patients have additional features, termed *Carney complex*, which are often inherited in an autosomal dominant fashion.[9] The clinical features of Carney complex include myxomas of the skin, breast, and heart; spotty pigmentation, such as lentigines and blue nevi; and other endocrine overactivity, such as acromegaly and testicular tumors. Bilateral nodular hyperplasia with Cushing syndrome can occur in the setting of McCune-Albright syndrome, mostly in infants or children. Bilateral macronodular adrenal hyperplasia generally is manifested after the age of 40 years with huge adrenal glands.

Excess ACTH

Cushing disease, which is almost always caused by an ACTH-secreting pituitary adenoma (Chapter 205), is the most common cause of Cushing syndrome. ACTH also may be secreted ectopically by a variety of neuroendocrine tumors (Table 208-3). Rarely, CRH from nonpituitary (ectopic) tumors may stimulate excess ACTH secretion from the pituitary or may be secreted along with ACTH from these tumors.

TABLE 208-3 THE INCIDENCE AND TYPES OF TUMORS CAUSING THE SYNDROME OF ECTOPIC ACTH SECRETION

TUMOR TYPE	PERCENTAGE
Carcinoma of lung (small cell or oat cell)	19-50
Pulmonary neuroendocrine tumor	2-37
Thymic neuroendocrine tumor	8-12
Pancreatic neuroendocrine tumor	4-12
Pheochromocytoma, neuroblastoma, ganglioma, paraganglioma	5-12
Medullary carcinoma of the thyroid	0-5
Miscellaneous*	<1

*Miscellaneous tumors reported to secrete ACTH in 1-10 cases include carcinoma or neuroendocrine tumor of the ovary, prostate, breast, thyroid, kidney, salivary glands, testes, gallbladder, esophagus, stomach, kidney and appendix; acute myeloblastic leukemia; melanoma; and cloacogenic carcinoma of the anal canal.
ACTH = adrenocorticotropic hormone.

Pituitary MRI shows a tumor in only about 40 to 50% of patients with Cushing disease, but it should be obtained routinely in patients with ACTH-dependent disease to exclude a macroadenoma or abnormal anatomy before petrosal sinus sampling or surgery. A pituitary lesion less than 6 mm is seen in up to 10% of healthy individuals and so does not always indicate Cushing disease.

Inferior petrosal sinus sampling, which has a sensitivity and specificity of about 94%, is the best test to distinguish between a pituitary and an ectopic source of excess ACTH. The test involves catheterization of a peripheral vein and also the petrosal sinuses draining the pituitary gland; simultaneous measurement of ACTH levels at each site before and 3, 5, and 10 minutes after administration of CRH; and calculation of the central-to-peripheral ACTH

ratio at each time point. Ratios of more than 2 before CRH administration or more than 3 after CRH administration are consistent with Cushing disease. When CRH is not available, desmopressin is used as a substitute, either in the peripheral test or with inferior petrosal sinus sampling, despite its lower sensitivity for Cushing disease.

Unfortunately, inferior petrosal sinus sampling carries a small risk of stroke, is expensive, and is not widely available. Other tests, such as the CRH test, the desmopressin test, and the 8-mg dexamethasone suppression test (Chapter 205), may be useful if both responses indicate Cushing disease. In this setting, the likelihood of ectopic ACTH secretion is low. However, the diagnosis is not clear if both responses are negative or if they are mixed.

If endocrine tests suggest ectopic ACTH secretion, potential tumor sources include small cell lung cancer (Chapter 177), pulmonary neuroendocrine tumors (Chapter 204), medullary thyroid cancer (Chapter 207), islet cell tumors (Chapter 211), and pheochromocytomas (Chapter 209) or paragangliomas (Chapter 213). Thin-cut CT or MRI of the chest is the best initial screens because in aggregate these tumors are most often in the thoracic cavity (see Table 164-5). Imaging that detects expression of somatostatin receptors 2 and 5 on these tumors (octreotide scintigraphy or DOTATATE/DOTANOC-PET) is a useful adjunctive test. Measurement of serum calcitonin and gastrin, as well as of plasma or urine catecholamines, may identify medullary carcinoma of the thyroid, gastrinoma, and pheochromocytoma. The process can be repeated every 6 to 12 months; tumors that make ACTH ectopically have a spectrum of malignant potential, and annual screening should continue, regardless of treatment for hypercortisolism.

TREATMENT

Surgical Therapy

The optimal treatment of Cushing syndrome is surgical resection of the lesion(s) that is producing excessive ACTH or cortisol. If such surgery is unsuccessful or cannot be done, bilateral adrenalectomy is an option.

Pituitary Adenoma

Transsphenoidal resection of a microadenoma is the optimal therapy for a patient with Cushing disease, with up to a 90% chance of cure by an experienced neurosurgeon (Chapter 205). A successful outcome is less likely if the initial surgery is not curative, in cases of recurrence, and for macroadenomas. Controversy exists about the criteria for remission; although a low postoperative cortisol level is encouraging, it does not preclude later recurrence. If recurrence develops, additional resection or alternative therapy should be considered.

Adrenal Adenoma or Tumor

Nonmalignant primary adrenal causes of overt Cushing syndrome are cured by resection of the abnormal tissue. Laparoscopy is the preferred approach. The role of surgery to reduce morbidity and mortality of patients with mild autonomous adrenal excess is controversial, because no prospective studies have been reported. Surgery is the mainstay in the treatment of adrenal cancer[10]; multiple operations may be needed to resect primary lesions, local recurrences, and hepatic, thoracic, and intracranial metastases. Adjuvant adrenolytic therapy with mitotane, with doses to achieve serum levels of 14 to 20 mg/L, may provide a chemotherapeutic benefit.

Ectopic ACTH

Patients with ectopic ACTH secretion can be cured if the tumor is not metastatic and can be removed. Otherwise, adrenalectomy or medical therapy is required. Adrenalectomy is appropriate when the patient cannot tolerate the medical toxicity, cost, or adverse psychological effects of long-term medical therapy and monitoring; when rapid correction of hypercortisolism is needed; or if maximal daily doses of ketoconazole (1600 mg) and metyrapone (6 g) given in combination do not render the patient eucortisolemic.

Role of Bilateral Adrenalectomy

Adrenalectomy is an option when the source of excess ACTH cannot be removed surgically. It provides rapid normalization of hypercortisolism, so it may be chosen by patients who have concerns about radiation-induced hypopituitarism or adherence to medications or by women who desire fertility in the near future.

Radiation Therapy

Radiation therapy to the pituitary gland, with adjunctive medical therapy to normalize cortisol levels, is an option for Cushing disease in patients who cannot undergo surgery, in patients in whom the risk of Nelson syndrome (Chapter 205) is deemed great (especially if they have local tumor invasion), and patients who have recurrent disease. Radiation can be delivered in 200-rad daily increments to a total dose of 45 Gy, or by high-energy gamma or proton radiosurgery in only one or two treatments to achieve a similar total dose. The disadvantage of radiation therapy is the length of time needed for a full response—up to 10 years—and the likelihood of panhypopituitarism.

Medical Therapy

Medical therapy is used for patients who have occult or unresectable ectopic ACTH-secreting tumors. It can also be used in combination with pituitary irradiation to treat unresectable or persistent pituitary tumors or ACTH-independent Cushing syndrome.[11]

For an ACTH-producing pituitary tumor, cabergoline (1 to 7 mg 2 to 7 times weekly) or pasireotide[A1] (600 or 900 μg subcutaneously daily or 10 or 30 mg once monthly) can normalize urine free cortisol in about 40% of patients. For all causes of Cushing syndrome, metyrapone (500 mg to 6 g per day), osilodrostat[A2] (4 to 60 mg per day), ketoconazole (600 to 1600 mg per day), and levoketoconazole (starting at 150 mg twice daily and increasing in 150-mg increments to a maximum of 600 mg twice daily until the urine free cortisol level normalizes) act at the adrenal gland to reduce cortisol production. Mifepristone (300 to 1200 mg per day), which is a glucocorticoid antagonist, may be used for either ACTH-dependent or ACTH-independent disease. Any type of medical therapy requires close monitoring and adjustment of the dose to maintain urine free cortisol in the normal range. There are limited data on the long-term efficacy of any medical therapy in Cushing syndrome.

Adrenocortical Carcinoma

Although surgery is the mainstay of treatment, mitotane (titrated to the maximal tolerated dose to maintain serum levels of 14 to 20 mg/L) treatment and radiation therapy may be recommended, depending on the stage of the disease and other prognostic factors. After complete resection, the recurrence of adrenocortical carcinoma is more common in patients who had a larger tumor size, venous tumor thrombus, and the proliferation tumor marker Ki67. For advanced adrenocortical carcinoma, rates of response and progression-free survival but not overall survival are significantly better with first-line therapy using a combination of etoposide (100 mg/m^2 on days 2 to 4), doxorubicin (40 mg/m^2 on day 1), and cisplatin (40 mg/m^2 on days 3 and 4) plus oral mitotane (to achieve a blood level of 14 to 20 mg/L) than with streptozocin plus mitotane, with similar rates of toxic events.

PROGNOSIS

Patients with Cushing disease usually can be cured by transsphenoidal surgery (Chapter 205), but have about a 2.5-fold increased risk of mortality. The major cause is cardiovascular disease, but the risks of infections and suicide are also increased.[12] For ectopic ACTH syndromes, the prognosis depends on the underlying disease. Benign unilateral adrenal adenomas and bilateral benign adrenal disease do not recur. For adrenal carcinoma, the mortality rate varies according to the grade of the tumor and the stage of disease at initial resection.

After pituitary surgery or unilateral adrenalectomy, patients require replacement glucocorticoids (generally hydrocortisone) until the hypothalamic-pituitary-adrenal axis recovers, which usually occurs within 6 to 24 months after of surgery. Some but not all patients may require glucocorticoid replacement after radiation therapy if decreased ACTH secretion from the tumor and normal corticotropes results in adrenal insufficiency. After bilateral adrenalectomy, patients require lifelong glucocorticoid and mineralocorticoid replacement. For patients who are receiving replacement glucocorticoids, additional doses of are needed during physical stress (e.g., trauma or surgery; see Treatment of Adrenal Insufficiency).

ADRENAL INCIDENTALOMA

Adrenal incidentalomas[13] are defined as abnormalities seen on imaging, typically ordered for an unrelated indication, in the absence of meeting criteria for Cushing syndrome. The evaluation should determine its hormonal activity (see Fig. 208-4). Mild autonomous hypercortisolism may be diagnosed in 30 to 50% of cases, and about 5 to 8% of incidentalomas may be malignant.[14] A consistent level above 83 nmol/L after 1 mg of dexamethasone suppression (mild autonomous cortisol excess) is associated with a two-fold or more increase in mortality.[15] Adrenal incidentalomas without a mild excess in cortisol secretion have a benign prognosis. Average growth over 4 or so years is only 2 mm, and clinical progression is rare.[16]

MINERALOCORTICOID EXCESS

EPIDEMIOLOGY

The prevalence of primary aldosteronism increases as hypertension becomes more severe, especially in patients ages 30 to 39 years, in whom up to 30% may have the condition; prevalence varies depending on the population studied: in one cross-sectional study, rates in were as high as about 13% in the primary care setting and 30% in hypertension referral practices.[17–19]

PATHOBIOLOGY

Mineralocorticoid excess can result from primary adrenal disease, in which aldosterone (or another mineralocorticoid) is produced autonomously (and renin levels are low), or it may be due to nonadrenal causes as a result of elevated renin values, which stimulate aldosterone secretion. The latter situations include states of contracted arterial intravascular volume, such as heart failure or cirrhosis with ascites, decreased renal arterial blood flow, and tumor production of renin (Table 208-4).

Familial hyperaldosteronism type 1 is caused by a genetic swap of the promoter for *CYP11B1* (11β-hydroxylase) with that of *CYP11B2* (aldosterone synthase), thereby forming a chimeric gene in which ACTH stimulates aldosterone synthase. Mutations in the *CLCN2* gene that encodes a voltage-gated chloride channel that is expressed in adrenal glomerulosa cells are found in rare early-onset familial hyperaldosteronism type 2. Somatic mutations in six genes account for nearly 90% of aldosterone-producing adenomas, with varying frequency according to sex and race.[20]

TABLE 208-4 CAUSES OF MINERALOCORTICOID EXCESS

PRIMARY HYPERALDOSTERONISM: HIGH ALDOSTERONE, LOW RENIN
Aldosterone-producing adenomas (30-50%)
Bilateral zona glomerulosa hyperplasia
Familial hyperaldosteronism
Type 1: glucocorticoid-remediable hyperaldosteronism—this results from formation of a chimeric gene containing the regulator portion of 11β-hydroxylase (normally regulated by ACTH) and the synthetic region of aldosterone synthase; as a result, ACTH stimulates aldosterone synthase and hence aldosterone production
Type 2: adrenal adenomas or hyperplasia expressed in a familial pattern
Type 3: caused by mutant *KCNJ5*, often younger and more severe than type 2
Aldosterone-producing adrenal carcinoma
Ectopic aldosterone secretion (rare): kidney, ovary
SECONDARY HYPERALDOSTERONISM: HIGH ALDOSTERONE, HIGH RENIN
Renovascular hypertension and aortic stenosis
Diuretic use
Renin-secreting tumors
Severe cardiac failure
APPARENT MINERALOCORTICOID EXCESS: LOW ALDOSTERONE, LOW RENIN
Licorice ingestion: licorice (candy or flavored tobacco) containing glycyrrhetinic acid (or similar compounds such as carbenoxolone) inhibits renal 11β-hydroxysteroid dehydrogenase type 2, reducing cortisol conversion to cortisone and enabling cortisol to act as an endogenous mineralocorticoid
Severe hypercortisolism: similar in mechanism to licorice ingestion; very high cortisol levels are thought to overwhelm the ability of 11β-hydroxysteroid dehydrogenase type 2 to convert cortisol to cortisone in the kidney; cortisol itself then acts as a potent mineralocorticoid
Liddle syndrome: mutation of the gene for the β or γ subunit of the collecting tubule sodium channel leads to a constitutive increase in sodium reabsorption and potassium excretion
11β-Hydroxylase deficiency form of congenital adrenal hyperplasia: 11-deoxycortisol accumulates because of an inability to convert it to cortisol
17-Hydroxylase deficiency form of congenital adrenal hyperplasia: deoxycorticosterone and corticosterone are increased

CLINICAL MANIFESTATIONS

Patients with mineralocorticoid excess often have few clinical symptoms apart from fatigue and muscle weakness or cramps related to hypokalemia. Most often the condition is suspected because of hypertension (Chapter 64), especially if it occurs at an early age in association with spontaneous hypokalemia or is difficult to control. Biochemically overt renin-independent aldosterone production spans a clinical spectrum from normal blood pressure and potassium level to hypokalemia and hypertension.[21]

DIAGNOSIS

Although excessive aldosterone production by one or both adrenal glands causes most of these conditions, excessive production of other mineralocorticoids or constitutive activation of the renal sodium channel must be excluded. In these latter conditions, both aldosterone and renin values are low, resulting in the so-called syndrome of apparent mineralocorticoid excess. In this setting, diagnostic information is obtained by history (licorice ingestion) or measurement of other mineralocorticoids (see Table 208-4).

Primary hyperaldosteronism is diagnosed when there is an increased ratio (>20) of morning aldosterone to plasma renin activity (Fig. 208-6). Except as noted in the figure, one of four tests (usually salt loading) is used to confirm primary hyperaldosteronism by demonstrating a lack of aldosterone suppression.

Differential Diagnosis

After making the diagnosis of aldosterone-dependent mineralocorticoid excess, the next step is to differentiate between the two most common adrenal causes, which are hyperplasia and adenoma. In the presence of a strong family history, however, the possibility of rare familial causes of hyperaldosteronism can be confirmed by genetic testing (see http://www.brighamandwomens.org/Departments_and_Services/medicine/services/endocrine/Services/gra/default.aspx). For the more common causes, adrenal CT scans may show nonfunctioning nodules and falsely suggest an adenoma. However, further testing is not recommended if the patient is less than age 35 years and has

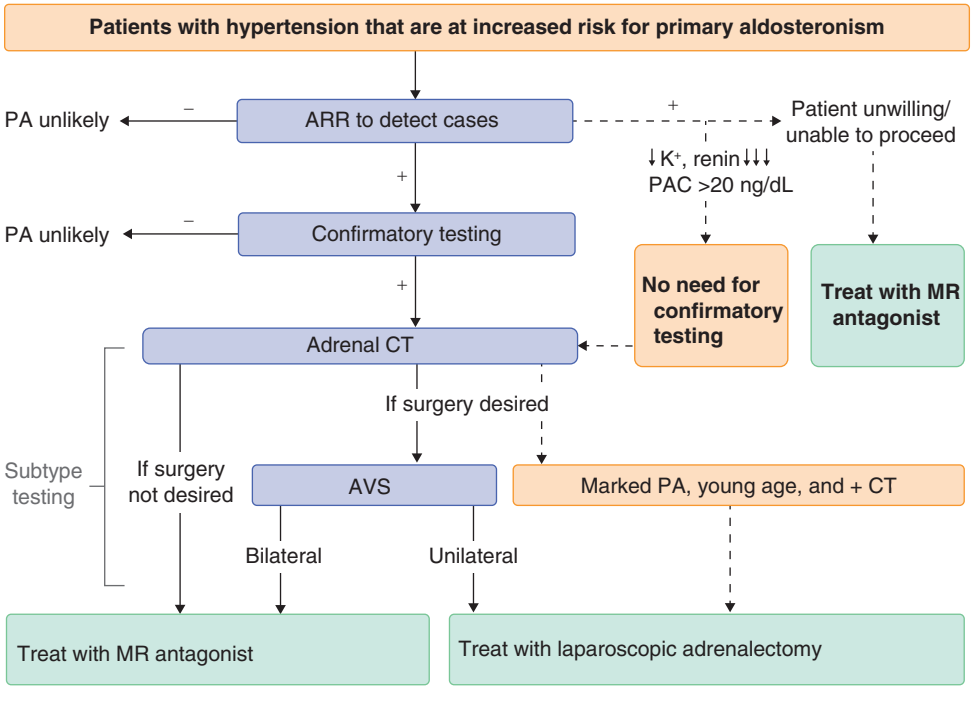

FIGURE 208-6. Algorithm for the diagnosis and treatment of primary aldosteronism (hyperaldosteronism). ARR = aldosterone-to-renin ratio; AVS = adrenal venous sampling; CT = computed tomography; MR = mineralocorticoid receptor; PA = primary aldosteronism; PAC = plasma aldosterone concentration. (Reprinted, with slight modification of text, from Funder JW, Carey RM, Mantero F, et al. The management of primary aldosteronism: case detection, diagnosis, and treatment: an Endocrine Society clinical practice guideline. *J Clin Endocrinol Metab*. 2016;101:1889-916.)

marked aldosteronism with an adrenal mass. The responses to physiologic maneuvers such as upright posture, and salt loading with oral or intravenous sodium, tend to be preserved in patients with hyperplasia, but there is significant overlap among groups of patients. The best diagnostic test involves the measurement of cortisol and aldosterone in bilateral adrenal venous effluent and a peripheral vein before and during an ACTH infusion.[22] Cortisol is used to evaluate catheter placement in the adrenal veins, as levels from the two sides should be similar. When an adenoma is present, the aldosterone-to-cortisol ratio on one side is usually at least five-fold greater than the other, which may be similar to the periphery, indicating suppression. Bilateral hyperplasia tends to produce similar values on each side.

TREATMENT

Treatment of primary hyperaldosteronism includes laparoscopic or robotic resection for adenomas. Afterward, hypokalemia generally resolves, but hypertension persists in up to 65% of patients. A mineralocorticoid antagonist (e.g., spironolactone [12.5 to 25 mg daily and titrated every 2 weeks upward to achieve normal blood pressure] or eplerenone [50 mg daily and titrated upward]) is used to treat patients who are unable to undergo surgery or who have bilateral hyperplasia. Eplerenone is a more selective mineralocorticoid antagonist (with fewer side effects of sexual dysfunction and gynecomastia compared with spironolactone). A sodium channel blocker (e.g., amiloride, 5 to 10 mg daily) may be helpful, and antihypertensive agents are continued as needed (Chapter 64).

ANDROGEN EXCESS

PATHOBIOLOGY

The adrenal causes of hyperandrogenism—congenital adrenal hyperplasia, Cushing disease, adrenal cancer, and androgen-producing adrenal adenoma—are uncommon. Most women have no clear-cut cause (idiopathic hirsutism) or polycystic ovary syndrome (Chapter 218). Rarely, androgen-secreting ovarian tumors, hyperprolactinemia, glucocorticoid resistance, or exogenous drugs cause hyperandrogenism. DHEA and DHEA-S are weak androgens that can be converted locally to testosterone in the hair follicles.

CLINICAL MANIFESTATIONS

Women with excess circulating androgens or increased sensitivity to androgens present with complaints of hirsutism, acne, and anovulation or infertility. When testosterone is secreted in great excess, women may virilize and exhibit a deepened voice, clitoromegaly, masculinized body habitus, and alopecia.

DIAGNOSIS

Patients with an adrenal source of hyperandrogenism usually have increased serum levels of DHEA, DHEA-S, or androstenedione, in contrast to the testosterone excess that is more typical of an ovarian source. Because DHEA and DHEA-S levels decline throughout adult life, these values must be interpreted within age-specific normal ranges. A tumor is more likely if DHEA-S is greater than 500 μg/dL or testosterone is greater than 200 ng/mL, but it is not excluded at lower levels.

Imaging identifies nearly all adrenal tumors but may miss a small intraovarian tumor. Urine free cortisol may be elevated in patients with virilizing adrenal carcinoma or Cushing disease (see earlier) and in patients with glucocorticoid resistance. By contrast, androgen-secreting adrenal adenomas do not have glucocorticoid excess. In women suspected of having nonclassic forms of congenital adrenal hyperplasia (see later), precursor and product hormones should be measured before and after ACTH to confirm the diagnosis.

TREATMENT

Treatment of adrenal causes of hyperandrogenism varies according to the disorder. Classic congenital adrenal hyperplasia is treated by glucocorticoids to normalize ACTH (typically dexamethasone 0.125 to 0.375 mg at bedtime) and hence androgen levels. The nonclassic forms respond well to an oral contraceptive (e.g., 20 μg or less of ethinyl estradiol) or to antiandrogen treatment (e.g., spironolactone 50 to 100 mg twice daily in the United States; cyproterone acetate 50 to 100 mg daily elsewhere) with clomiphene citrate or gonadotropins reserved for the induction of ovulation. Surgery with adjunctive medical treatment may be used in adrenal carcinoma (see earlier).

ADRENAL INSUFFICIENCY

EPIDEMIOLOGY

The prevalence of noniatrogenic adrenal insufficiency is about 100 per million in the population. In adults in industrialized countries, autoimmunity is by far the most common form, followed by infection, which is relatively more common in low income countries.

PATHOBIOLOGY

Primary Adrenal Insufficiency

Autoimmune Destruction

Autoimmune destruction of the adrenal gland usually occurs in isolation. Rarely, it occurs in association with autoimmune polyglandular syndromes (Chapter 212), either in childhood (type 1), in association with hypoparathyroidism and mucocutaneous candidiasis, or in adulthood (type 2), in association with insulin-dependent diabetes mellitus, autoimmune thyroid disease, alopecia areata, or vitiligo.

Adrenoleukodystrophy

Adrenoleukodystrophy, a rare (1 in 25,000) X-linked condition, is characterized by a deficiency of peroxisomal membrane adrenoleukodystrophy protein, which transports activated acyl-coenzyme A derivates into the peroxisomes, where they are shortened by β-oxidation. This deficiency results in the accumulation of very long chain fatty acids in the central nervous system and other tissues and increased plasma $C_{26:0}$ fatty acids. In the adrenal cortex, these very long chain fatty acids alter membrane function and inhibit signal transduction by ACTH. Incomplete penetrance of the genetic defect and variable accumulation of very long chain fatty acids in the adrenal gland, brain, testis, and liver account for the clinical phenotypes, which differ by age and presentation.[23]

Replacement of Adrenal Tissue

Infections cause about 15% of primary adrenal insufficiency. Typical infections include tuberculosis (Chapter 299) and systemic fungal diseases (e.g., histoplasmosis, coccidioidomycosis, blastomycosis [Chapter 308]), in which the adrenal tissue is replaced by caseating granulomas. End-stage AIDS-associated opportunistic infections, such as cytomegalovirus (Chapter 347) or *Mycobacterium avium-intracellulare* (Chapter 300), may reduce adrenal function. Adrenal tissue may be replaced by bilateral metastases (most commonly primary carcinoma of the lung, breast, kidney, or gut) or primary lymphoma, although adrenal insufficiency is uncommon. Intra-adrenal hemorrhage may also lead to insufficient steroidogenesis. Hemorrhage typically occurs in a stressed, hospitalized patient receiving long-term prophylactic anticoagulation and is often accompanied by back pain.

Congenital Adrenal Hyperplasias

The congenital adrenal hyperplasias[24] are a disparate group of diseases caused by a genetic deficiency of one of the enzymes needed for adrenal steroidogenesis. Patients with nearly complete deficiency of an enzyme required for cortisol synthesis present in infancy with adrenal insufficiency and salt-wasting crisis. This is most problematic in patients with mutation of the 21-hydroxylase (*CYP21A2*) or 11β-hydroxylase (*CYP11B1*) gene. The increase in ACTH levels caused by cortisol deficiency drives the intact steroidogenic pathways so that there is excessive production of the steroids just proximal to the enzymatic block—17-hydroxyprogesterone and 11-deoxycortisol, respectively, in 21-hydroxylase and 11β-hydroxylase deficiency. The increased levels of precursor steroids enable increased adrenal androgen synthesis, so that severely affected girls may be virilized in utero. Girls and women with nonclassic congenital adrenal hyperplasia present later; they have greater enzyme activity, so that cortisol production is adequate, but increased ACTH levels cause hyperandrogenism.

Rare Causes

Other rare causes of primary adrenal insufficiency (Table 208-5) include ACTH resistance, congenital adrenal hypoplasia, Smith-Lemli-Opitz syndrome (congenital cognitive impairment and multiple abnormalities owing to a deficiency in 7-dehydrocholesterol reductase), and amyloidosis (Chapter 174).

Secondary Adrenal Insufficiency

Suppression of the Pituitary Axis

Suppression of the hypothalamic-pituitary-adrenal axis by exogenous or endogenous glucocorticoids is the most common cause of secondary adrenal insufficiency. This phenomenon, which depends on the dose, duration, and schedule of glucocorticoid administration, becomes clinically manifest when glucocorticoid

TABLE 208-5 CAUSES OF ADRENAL INSUFFICIENCY AND ANCILLARY TESTS

SPECIFIC CAUSES	SUGGESTIVE CLINICAL FEATURES	USEFUL ANCILLARY TESTS
Primary adrenal insufficiency	Hyperpigmentation, orthostatic hypotension	Hyperkalemia, elevated ACTH
Idiopathic autoimmune destruction	Most common cause (80%) in developed countries; with or without other endocrinopathies, as below	Antibodies to 21-hydroxylase are present; on imaging, adrenal glands are small
Polyglandular failure type 1	Hypoparathyroidism, mucocutaneous candidiasis, vitiligo; age <20 years	
Polyglandular failure type 2	Insulin-dependent diabetes, autoimmune thyroid disease, alopecia areata, vitiligo; age >40 years	On imaging, adrenal glands are small
Infections: tuberculosis, systemic fungal diseases, AIDS-associated opportunistic infections (e.g., cytomegalovirus)	15% of patients in U.S. series	Adrenal glands tend to be large on CT and may be calcified
Space-occupying adrenal lesions	Metastases from carcinoma of lung, breast, kidney, gut; lymphoma or hemorrhage (heparin use)	Abnormal shape of adrenal glands on CT; evidence of hemorrhage
Bilateral adrenalectomy or treatment with steroidogenesis inhibitors		Ketoconazole, mitotane, aminoglutethimide, trilostane, and metyrapone reduce cortisol levels
Adrenoleukodystrophy	X-linked—screen males; in childhood, cognitive and gait disturbances; in adults, spastic paraparesis	Deficiency of peroxisomal very long chain acyl-coenzyme A synthetase leads to elevated plasma $C_{26:0}$ fatty acid levels
Secondary adrenal insufficiency		
Suppression of the adrenal axis by exogenous or endogenous glucocorticoids	Medication history; history of Cushing syndrome	Adrenal glands are small on imaging
Structural lesions of the hypothalamus or pituitary gland (tumors, destruction by infiltrating disorders, x-irradiation, and lymphocytic hypophysitis)	Other pituitary deficiencies	Adrenal glands are normal or small on imaging; MRI or CT may show pituitary or hypothalamic lesion
Isolated ACTH deficiency		
Head trauma		

ACTH = adrenocorticotropic hormone; AIDS = acquired immunodeficiency syndrome; CT = computed tomography; MRI = magnetic resonance imaging.

treatment is stopped or when the patient is successfully treated with surgery. Adrenal suppression is unusual with "replacement" doses of glucocorticoid that are roughly equivalent to daily production (e.g., total daily doses of 15 to 20 mg hydrocortisone, 5 mg prednisone, or 0.3 to 0.5 mg dexamethasone). At higher doses, adrenal suppression is usually not seen until after 3 weeks of administration, and a single morning administration is less suppressive than are divided doses given during the day. This syndrome can be minimized by gradually tapering the glucocorticoid dose, so that the adrenal-pituitary axis can recover. Chronic opiate use may suppress pituitary ACTH secretion, but the frequency of frank adrenal insufficiency appears uncommon.[25]

Lesions of the Hypothalamus or Pituitary

Secondary adrenal insufficiency also may result from structural lesions of the hypothalamus or pituitary gland that interfere with CRH production or transport or with corticotrope function. These causes include tumors, trauma, destruction by infiltrating disorders, x-irradiation, and lymphocytic hypophysitis (Chapters 204 and 205).

CLINICAL MANIFESTATIONS

The clinical presentation of adrenal insufficiency reflects the cause and duration of this uncommon condition. Primary adrenal insufficiency eventually destroys the entire adrenal cortex, with loss of both glucocorticoid and mineralocorticoid activity.

By contrast, secondary adrenal insufficiency reflects an inability of the hypothalamic-pituitary unit to deliver CRH or ACTH, thus reducing trophic support to otherwise normal glands. As a result, only cortisol production decreases because mineralocorticoid production is not very ACTH dependent (Fig. 208-7). Secondary adrenal insufficiency after the cessation of exogenous corticosteroids usually presents with fatigue, joint pain, and gastrointestinal symptoms (e.g., anorexia, nausea) within 48 hours, and the entire axis may not recover for up to 18 months.

The characteristic clinical presentation of acute primary adrenal insufficiency includes orthostatic hypotension, agitation, confusion, circulatory collapse, abdominal pain, and fever.[26,27] These features are most likely to be caused by hemorrhage, metastasis, or acute infection and can lead to death if not treated.

In chronic primary adrenal insufficiency, by contrast, the typical symptoms and signs include a longer history of malaise, fatigue, anorexia, weight loss, joint and back pain, and darkening of the skin (especially in the creases of the hands, extensor surfaces, recent scars, buccal and vaginal mucosa, and nipples). Patients may crave salt and may develop unusual food preferences, such as drinking the brine from pickles. Associated biochemical features for both acute and chronic presentations include hyponatremia, hypoglycemia, hyperkalemia, unexplained eosinophilia, and mild prerenal azotemia.

Chronic secondary adrenal insufficiency is manifested in a similar way, but without hyperpigmentation or mineralocorticoid abnormalities.

DIAGNOSIS

A morning serum cortisol measurement is an inexpensive but relatively insensitive screening test for adrenal insufficiency in patients who are not acutely ill. The diagnosis is virtually excluded by values greater than 18 μg/dL (about 500 nmol/L) when measured in immunoassays that have cross-reactivity with cortisol precursors. The diagnosis is likely if the value is less than 3 μg/dL (83 nmol/L), regardless of the assay.

However, both healthy individuals and patients with adrenal insufficiency may have indeterminate results (3 to 18 μg/dL) that require additional evaluation. In acute adrenal insufficiency, the serum cortisol value within a few hours of waking is generally inappropriately normal or subnormal in the setting of hypotension, in which cortisol values are usually well above 18 μg/dL.

Patients with acute adrenal insufficiency should be evaluated for sepsis, adrenal metastases, and hemorrhage. On MRI or CT imaging, the adrenal glands are small in autoimmune disease and large in cases of infection, metastatic disease, and adrenal hemorrhage. Imaging of the glands and other testing also may reveal an infectious or malignant cause.

For chronic adrenal insufficiency, the cortisol response to exogenous ACTH is a gold standard test. At any time of day, 250 μg of ACTH (1-24, cosyntropin) is given intravenously to provide a maximal stimulus to the adrenal gland; a serum cortisol level measured 30 and 60 minutes later should be greater than 18 μg/dL if measured by immunoassays that cross-react with cortisol precursors. When measured using more specific techniques (e.g., tandem mass spectrometry or monoclonal antibody-based immunoassay), the upper limit of normal is around 14 ug/dL.[28]

Values lower than these cutoffs indicate adrenal insufficiency. A 1-μg dose is equally good for establishing the diagnosis, if performed in the morning, but the difficulty in formulating a 1-ug dose increases the risk of a falsely normal result. A metyrapone stimulation test (a weight-based dose of metyrapone is given at midnight, cortisol and 11-deoxycortisol are measured the following morning) is useful in patients who have mild or recent secondary adrenal insufficiency and who may respond to pharmacologic doses of ACTH. Values of 11-deoxycortisol less than 7 ug/dL indicate adrenal insufficiency.

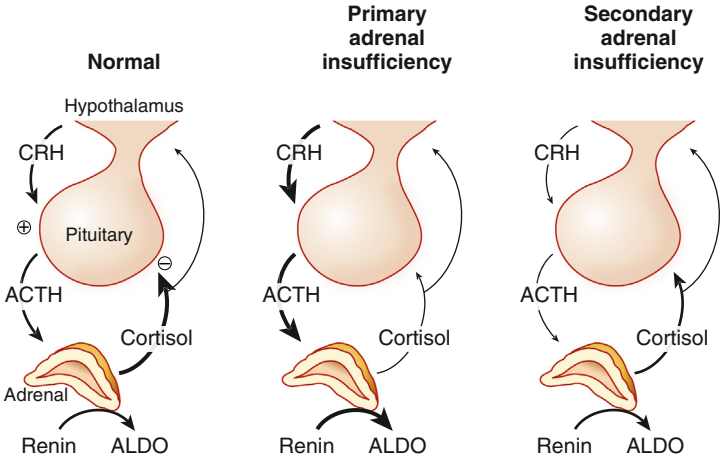

FIGURE 208-7. Physiology of the adrenal axis in health, primary adrenal insufficiency, and secondary adrenal insufficiency. ***In healthy individuals*** **(Normal), cortisol production is stimulated by the increased hypothalamic release of corticotropin-releasing hormone (CRH), which then travels down the pituitary stalk to stimulate adrenocorticotropic hormone (ACTH) secretion and release by corticotropes. Circulating ACTH stimulates adrenal gland production and secretion of cortisol. Cortisol then functions in a negative feedback mechanism to inhibit both CRH and ACTH.** ***In patients with primary adrenal insufficiency*****, destruction or replacement of the entire adrenal cortex results in decreased cortisol, aldosterone, and dehydroepiandrosterone (DHEA, not shown) secretion by the adrenal glands. As a result of decreased cortisol negative feedback, the normal hypothalamus and pituitary gland increase CRH and ACTH secretion. The decreased aldosterone levels lead to an increase in renin levels.** ***In patients with secondary adrenal insufficiency*** **(ALDO), ACTH or CRH secretion is reduced because of destruction or replacement of the hypothalamus or pituitary gland or because of disruption of the pituitary stalk. The decreased ACTH stimulation results in decreased cortisol (and, not shown, DHEA) secretion by the adrenal glands. Aldosterone production is only slightly affected by ACTH stimulation, and levels remain normal. The abnormal hypothalamus and pituitary gland do not increase CRH and ACTH secretion in response to the decreased cortisol negative feedback.**

Cerebral adrenoleukodystrophy, which presents in childhood, is characterized by cognitive and gait disturbances; the adult form, adrenomyeloneuropathy, is characterized by spinal cord and peripheral nerve demyelination. Because a substantial minority of patients in both groups present first with adrenal insufficiency, boys and young men with adrenal insufficiency should be screened for adrenoleukodystrophy.

Differential Diagnosis

Primary and secondary adrenal insufficiency can be distinguished by measurement of plasma ACTH. In primary adrenal insufficiency, ACTH levels are generally above the normal range and may exceed the normal range before the cortisol response to exogenous ACTH stimulation is subnormal. In addition, hyperkalemia and elevated renin values are characteristic of primary but not of secondary adrenal insufficiency, which is identified by a suppressed or inappropriately normal ACTH level.

Patients with primary adrenal insufficiency should undergo further evaluation to determine its cause. Detection of antibodies to 21-hydroxylase identifies nearly all patients with idiopathic disease. In a male with negative results, measurement of plasma $C_{26:0}$ fatty acids will detect adrenoleukodystrophy. Taken together, this strategy identifies the cause in nearly all adult patients with idiopathic adrenal insufficiency. Patients with autoimmune disease should be tested for other endocrine deficiencies, and those with adrenoleukodystrophy require neurologic evaluation.

Patients with secondary adrenal insufficiency not ascribed to glucocorticoid or opiate use should undergo imaging of the pituitary and hypothalamus to exclude a structural or infiltrating lesion as well as tests of other pituitary function to exclude additional deficiencies. In general, these are not reversible conditions.

TREATMENT

Acute Adrenal Insufficiency

In suspected acute adrenal insufficiency, hydrocortisone is the treatment of choice because it has both glucocorticoid and mineralocorticoid activity.[29] Treatment with intravenous saline for volume expansion, glucose for hypoglycemia, and intravenous hydrocortisone (100 mg) should be started immediately after placement of an intravenous line and withdrawal of blood for documentation of the cortisol value.[30]

Chronic Adrenal Insufficiency

Therapy for chronic adrenal insufficiency aims to provide the physiologic replacement of steroids. Glucocorticoid replacement is achieved by administration of 10 to 12 mg/m^2 of hydrocortisone daily in one to three oral doses, attempting to mimic the physiologic diurnal variation of cortisol concentrations. Hydrocortisone offers the advantage of multiple-dose tablets, which allow fine adjustment and splitting of the daily dose. Ideally, the morning dose is given as soon after waking as possible; for individuals who feel extremely fatigued in the morning before the agent is absorbed, a strategy of taking the medication 30 minutes before arising may be helpful. Some data suggest that once-daily dosing is preferable in terms of immune function, weight gain, and quality of life.[A3] Although many patients do well with a single dose, others complain of pronounced fatigue in the afternoon and evening. For these patients, a split-dose regimen, in which about one third of the daily dose is given around 4:00 PM or two afternoon doses are given, may be useful.

Other glucocorticoids may be used for daily replacement therapy. Prednisone, 4 to 7 mg daily, has the advantage of a long half-life and may be particularly helpful in patients with afternoon or evening fatigue. Dexamethasone is infrequently used because it is difficult to recommend a specific replacement dose and because few options are available for fixed doses.

Nearly all patients with primary adrenal insufficiency also require the mineralocorticoid fludrocortisone 50 to 300 μg/day. The dose is adjusted until plasma renin activity is normal. Patients should be encouraged to salt their food and not to limit salt intake. Some patients with primary adrenal insufficiency also have decreased serum DHEA levels, but evidence is insufficient to support its routine replacement.

Ensuring Proper Dosing

Education of the Patient

All patients receiving chronic glucocorticoid replacement therapy should be instructed that they must take the glucocorticoids as prescribed and that failure to take or to absorb the medication will lead to adrenal crisis and possibly death. Patients should wear a medical information bracelet or necklace. It is important to educate patients and their families about glucocorticoid adjustment during physiologic stress conditions, including the emergency administration of intramuscular glucocorticoid.

Dosing for Stress

Patients who are recovering from adrenal suppression caused by exogenous glucocorticoids should receive daily replacement glucocorticoid treatment and supplemental steroids at times of physiologic stress, depending on the degree of impairment, until the pituitary adrenal axis recovers, which may be weeks or months.[31,32] The daily oral glucocorticoid dose is usually doubled for "stressful" physiologic conditions, such as fever, nausea, and diarrhea, although this practice may lead to chronic overmedication by the patient because of a liberal interpretation of what constitutes physical stress. Thus education about when and how to change the dose of steroid should be reinforced periodically, preferably with written material, and the dangers of excessive steroid use should be emphasized. If the patient is vomiting, has severe diarrhea, or has collapsed, intramuscular glucocorticoids (e.g., 50 to 100 mg of hydrocortisone) should be given before transport to a medical facility.

The glucocorticoid dose is increased in proportion to the amount of stress. During maximally stressful situations (e.g., adrenal crisis, major surgery, trauma, labor and delivery), pharmacologic studies suggest that an initial intravenous hydrocortisone bolus of 50 to 100 mg followed by a continuous infusion of 200 mg over 24 hours is the best coverage.[33] The dose may be tapered by 50% per day if the patient is clinically stable. For more moderate stress, such as that of cholecystectomy, 75 to 100 mg of hydrocortisone is given on the day of surgery, and the dose is tapered more rapidly. Patients undergoing minimal stress, such as tooth extraction or short operative orthopedic procedures, may not require any additional supplementation.

Assessment to Ensure Proper Dosing

Clinical assessment is the best way to judge whether the glucocorticoid dose is correct. Symptoms of adrenal insufficiency improve with adequate therapy. The development of cushingoid features or osteopenia suggests frank or subtle overreplacement, respectively, and the presence of adrenal insufficiency symptoms (fatigue, anorexia, weight loss) suggests underreplacement. In women, DHEA replacement increases testosterone levels, so that hirsutism, acne, or other signs of androgen excess may suggest overreplacement.

In primary adrenal insufficiency, adequate hormone replacement results in plasma ACTH levels that decrease but remain elevated, in the range of 100 to 200 pg/mL. Renin values, however, normalize completely and may be used to judge the adequacy of mineralocorticoid replacement. Although hydrocortisone is cortisol, plasma cortisol values should not be used to monitor therapy because clearance from the bloodstream is rapid, and circulating values are low for most of the day.

PROGNOSIS

Even in educated patients with chronic adrenal insufficiency, adrenal crisis develops at a rate of 8.3 crises per 100 patient-years. Common precipitating causes include gastrointestinal infection, fever, and emotional stress (about 20% of cases each), but major pain, surgery, strenuous physical activity, heat, and pregnancy are other precipitants. About 6% of crises are fatal.

MINERALOCORTICOID DEFICIENCY

Hypoaldosteronism may be classified as a low-normal or a high renin state on the basis of plasma renin activity after 4 hours of upright posture. Renin deficiency, which is the most common cause of hypoaldosteronism, occurs most often in older patients with mild, nonoliguric renal disease who often have insulin-dependent diabetes and potentially diabetic nephropathy. Nonsteroidal anti-inflammatory drugs, calcineurin inhibitors, other prostaglandin synthesis inhibitors, as well as autonomic dysfunction associated with prolonged bed rest can also result in hyporeninemic hypoaldosteronism.

CLINICAL MANIFESTATIONS

Few clinical features are associated with mineralocorticoid deficiency, so it is usually suspected when laboratory results reveal hyperkalemia, hyponatremia, and a mild metabolic alkalosis. If glucocorticoid deficiency is excluded, isolated hypoaldosteronism is established if the circulating level of aldosterone is inappropriately low.

High renin states of hypoaldosteronism include congenital adrenal hyperplasias with mineralocorticoid deficiency and primary adrenal insufficiency when it is treated with pure glucocorticoid replacement.

Treatment of these conditions involves sodium replacement with at least 10 mEq/kg/day, roughly equivalent to the 4 g of sodium chloride found in a typical diet in the United States. For individuals who do not maintain such a diet (often the elderly or the young), fludrocortisone can be given at the same doses used in primary adrenal insufficiency.

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209 ADRENAL MEDULLA, CATECHOLAMINES, AND PHEOCHROMOCYTOMA

WILLIAM F. YOUNG, JR.

ADRENAL MEDULLA AND CATECHOLAMINES

The adrenal medulla occupies the central portion of the adrenal gland. Adrenomedullary cells are called chromaffin cells because they stain brown with chromium salts. Chromaffin cells differentiate in the center of the adrenal gland in response to cortisol; some chromaffin cells also migrate to form paraganglia.[1] The largest cluster of chromaffin cells outside the adrenal medulla is near the level of the inferior mesenteric artery and is referred to as the organ of Zuckerkandl.

Catecholamines are substances that contain catechol (*o*-dihydroxybenzene) and a side chain with an amino group—the catechol nucleus (E-Fig. 209-1). Epinephrine, which is synthesized and stored in the adrenal medulla, is released into the systemic circulation. Norepinephrine is synthesized and stored not only in the adrenal medulla but also in the peripheral sympathetic nerves. Dopamine, the precursor of norepinephrine, is found in the adrenal medulla and peripheral sympathetic nerves.

Catecholamines have many cardiovascular and metabolic actions, including increasing the heart rate, blood pressure, myocardial contractility, and velocity of cardiac conduction. Three types of specific adrenergic receptors mediate their biologic actions: α, β, and DA. Their receptor subtypes are α_1, α_2, β_1, β_2, β_3, DA_1, and DA_2. The α_1 subtype is a postsynaptic receptor that mediates vascular and smooth muscle contraction; stimulation causes vasoconstriction and increased blood pressure. The α_2-receptors are located on presynaptic sympathetic nerve endings and, when activated, inhibit the release of norepinephrine; stimulation causes suppression in central sympathetic outflow and decreased blood pressure. Stimulation of the β_1-receptor causes positive inotropic and chronotropic effects on the heart, increased renin secretion in the kidney, and lipolysis in adipocytes, as well as bronchodilation, vasodilation in skeletal muscle, glycogenolysis, and increased release of norepinephrine from sympathetic nerve terminals. The β_3-receptor regulates energy expenditure and lipolysis. DA_1 receptors are localized to the cerebral, renal, mesenteric, and coronary vasculature; stimulation causes vasodilation in these vascular beds. DA_2 receptors are presynaptic and localized to sympathetic nerve endings, sympathetic ganglia, and brain; their stimulation inhibits the release of norepinephrine, inhibits ganglionic transmission, and inhibits the release of prolactin.

Catecholamines are synthesized from tyrosine by a process of hydroxylation and decarboxylation (see E-Fig. 209-1). Tyrosine, which is derived from the diet or synthesized from phenylalanine in the liver, enters neurons and chromaffin cells by active transport. The conversion of tyrosine to 3,4-dihydroxyphenylalanine (dopa) by tyrosine hydroxylase is the rate-limiting step in the synthesis of catecholamines. α-Methyl-*p*-tyrosine (metyrosine) is a tyrosine hydroxylase inhibitor that may be used therapeutically in patients with catecholamine-secreting tumors. Aromatic L-amino acid decarboxylase catalyzes the decarboxylation of dopa to dopamine. Dopamine is actively transported into granulated vesicles where it is hydroxylated to norepinephrine by the dopamine β-hydroxylase. These reactions occur in the synaptic vesicle of adrenergic neurons and the chromaffin cells of the adrenal medulla. In the adrenal medulla, norepinephrine is released from the granule into the cytoplasm, where phenylethanolamine *N*-methyltransferase converts it to epinephrine. Expression of phenylethanolamine *N*-methyltransferase is positively regulated by glucocorticoids. Catecholamine-secreting tumors that secrete primarily epinephrine are localized to the adrenal medulla. In normal adrenal medullary tissue, approximately 80% of the catecholamine released is epinephrine.

The biologic half-life of circulating catecholamines is between 10 and 100 seconds, so plasma concentrations of catecholamines can fluctuate widely. Catecholamines are removed from the circulation by either reuptake by sympathetic nerve terminals or metabolism through two enzyme pathways (see E-Fig. 209-1), followed by sulfate conjugation and renal excretion. Almost 90% of catecholamines released at sympathetic synapses are taken up locally by the nerve endings (i.e., uptake 1). Uptake 1 can be blocked by cocaine, tricyclic antidepressants, and phenothiazine. Extraneuronal tissues also take up catecholamines (i.e., uptake 2). Most of these catecholamines are metabolized by catechol-*O*-methyltransferase. Metanephrine and normetanephrine are oxidized by monoamine oxidase to vanillylmandelic acid by oxidative deamination. Monoamine oxidase may also oxidize epinephrine and norepinephrine to 3,4-dihydroxymandelic acid, which is then converted by catechol-*O*-methyltransferase to vanillylmandelic acid. In the storage vesicle, norepinephrine is protected from metabolism by monoamine oxidase. Monoamine oxidase and catechol-*O*-methyltransferase metabolize dopamine to homovanillic acid (see E-Fig. 209-1).

PHEOCHROMOCYTOMA AND PARAGANGLIOMA

DEFINITION

Catecholamine-secreting tumors that arise from the chromaffin cells of the adrenal medulla and the sympathetic ganglia are referred to as pheochromocytomas and extra-adrenal catecholamine-secreting paragangliomas, respectively. Because the tumors have similar clinical presentations and are treated with similar approaches, many clinicians use the term *pheochromocytoma* to refer to both entities. However, the distinction between pheochromocytoma and paraganglioma is important because of differing risks for malignant transformation and different approaches to genetic testing for associated neoplasms.[2]

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The biologic half-life of circulating catecholamines is between 10 and 100 seconds, so plasma concentrations of catecholamines can fluctuate widely. Catecholamines are removed from the circulation by either reuptake by sympathetic nerve terminals or metabolism through two enzyme pathways (see E-Fig. 209-1), followed by sulfate conjugation and renal excretion. Almost 90% of catecholamines released at sympathetic synapses are taken up locally by the nerve endings (i.e., uptake 1). Uptake 1 can be blocked by cocaine, tricyclic antidepressants, and phenothiazine. Extraneuronal tissues also take up catecholamines (i.e., uptake 2). Most of these catecholamines are metabolized by catechol-*O*-methyltransferase. Metanephrine and normetanephrine are oxidized by monoamine oxidase to vanillylmandelic acid by oxidative deamination. Monoamine oxidase may also oxidize epinephrine and norepinephrine to 3,4-dihydroxymandelic acid, which is then converted by catechol-*O*-methyltransferase to vanillylmandelic acid. In the storage vesicle, norepinephrine is protected from metabolism by monoamine oxidase. Monoamine oxidase and catechol-*O*-methyltransferase metabolize dopamine to homovanillic acid (see E-Fig. 209-1).

PHEOCHROMOCYTOMA AND PARAGANGLIOMA

DEFINITION

Catecholamine-secreting tumors that arise from the chromaffin cells of the adrenal medulla and the sympathetic ganglia are referred to as pheochromocytomas and extra-adrenal catecholamine-secreting paragangliomas, respectively. Because the tumors have similar clinical presentations and are treated with similar approaches, many clinicians use the term *pheochromocytoma* to refer to both entities. However, the distinction between pheochromocytoma and paraganglioma is important because of differing risks for malignant transformation and different approaches to genetic testing for associated neoplasms.[2]

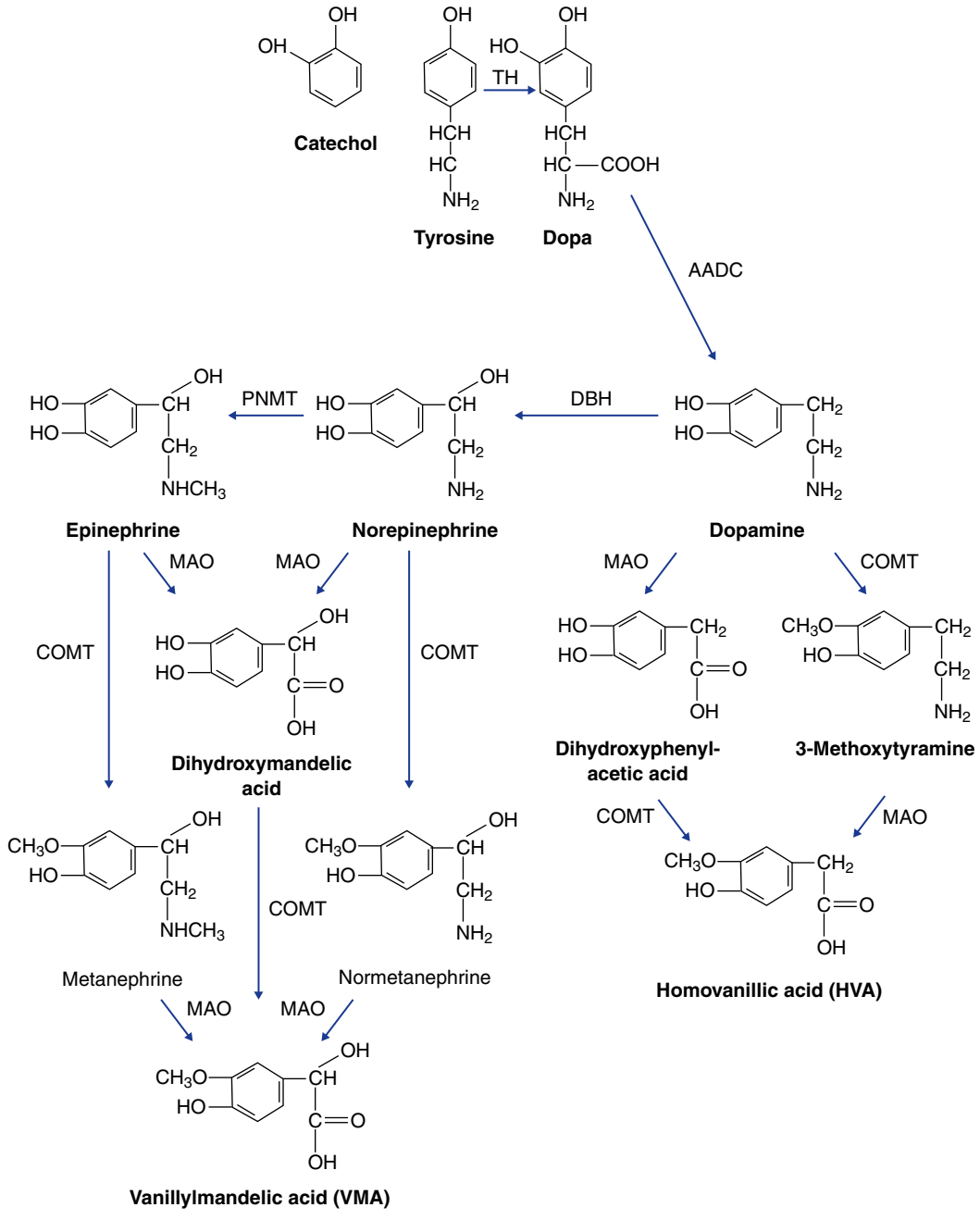

E-FIGURE 209-1. Biosynthetic and metabolic pathways for catecholamines. The term *catecholamine* comes from the catechol (*o*-dihydroxybenzene) structure and a side chain with an amino group—the catechol nucleus (*top left*). Tyrosine is converted to 3,4-dihydroxyphenylalanine (dopa) in the rate-limiting step by tyrosine hydroxylase (TH). Aromatic L-amino acid decarboxylase (AADC) converts dopa to dopamine. Dopamine is hydroxylated to norepinephrine by dopamine β-hydroxylase (DBH). Norepinephrine is converted to epinephrine by phenylethanolamine *N*-methyltransferase (PNMT); cortisol serves as a cofactor for PNMT, and this is why epinephrine-secreting pheochromocytomas are almost exclusively localized to the adrenal medulla. Metabolism of catecholamines occurs through two enzymatic pathways. Catechol-*O*-methyltransferase (COMT) converts epinephrine to metanephrine and norepinephrine to normetanephrine by meta-*O*-methylation. Metanephrine and normetanephrine are oxidized by monoamine oxidase (MAO) to vanillylmandelic acid by oxidative deamination. Monoamine oxidase also may oxidize epinephrine and norepinephrine to dihydroxymandelic acid, which is then converted by catechol-*O*-methyltransferase to vanillylmandelic acid. Dopamine is also metabolized by monoamine oxidase and catechol-*O*-methyltransferase, with the final metabolite homovanillic acid.

ABSTRACT

Catecholamines, which affect many cardiovascular and metabolic processes, form the basis for many cardiovascular, pulmonary, and neuroendocrine pharmacotherapeutics. Catecholamine-secreting tumors that arise from chromaffin cells of the adrenal medulla and the sympathetic ganglia are referred to as pheochromocytomas and extra-adrenal catecholamine-secreting paragangliomas, respectively. Although catecholamine-secreting tumors are rare, they are important to suspect, confirm, localize, and resect because of the risk of a lethal paroxysm, the likely cure of associated hypertension with surgical removal, and the ability to detect the 10% of tumors that are malignant. In addition, the detection of the 40% or so that are familial can accelerate diagnosis in other family members.

KEYWORDS

catecholamines
pheochromocytoma
paraganglioma

EPIDEMIOLOGY

Catecholamine-secreting tumors are rare, with an annual incidence of two to eight cases per million people. Over the past 3 decades, the diagnosed incidence of these tumors increased about five-fold because of smaller incidental tumors (adrenal incidentalomas; Chapter 208) detected on radiographic scans in patients with few or no symptoms.[3] Catecholamine-secreting tumors occur with equal frequency in men and women, primarily in the third, fourth, and fifth decades of life. These tumors are rare in children; when discovered, they may be multifocal, extra-adrenal, metastatic, and associated with a hereditary syndrome.[4]

PATHOBIOLOGY

Genetics

Approximately 40% of patients with catecholamine-secreting tumors have germline pathogenic variants (inherited mutations present in all cells of the body) in genes associated with the genetic disease.[5] Hereditary catecholamine-secreting tumors typically are manifested at a younger age than sporadic neoplasms. Sporadic pheochromocytoma is typically diagnosed on the basis of symptoms or incidental discovery on computed imaging,[6] whereas syndromic pheochromocytoma and paraganglioma are frequently diagnosed earlier in the course of disease because of biochemical surveillance or genetic testing.

Multiple Endocrine Neoplasia

Multiple endocrine neoplasia (MEN) type 2A is an autosomal dominant disorder (Chapter 212). The phenotype includes adrenal pheochromocytoma in 50% (usually bilateral and sometimes asynchronous), medullary carcinoma of the thyroid in 100%, hyperparathyroidism in 20 to 30%, and cutaneous lichen amyloidosis in 5%. Medullary carcinoma of the thyroid is usually detected before the pheochromocytoma. Numerous activating pathogenic variants in the *RET* proto-oncogene have been documented in persons with MEN type 2A.

MEN type 2B, which is also an autosomal dominant disorder, represents approximately 5% of all MEN type 2 cases. The phenotype includes pheochromocytoma in 50% (usually bilateral), aggressive medullary carcinoma of the thyroid in 100%, mucosal neuromas (typically involving the tongue, lips, and eyelids) in most patients, thickened corneal nerves, intestinal ganglioneuromatosis, and marfanoid body habitus. MEN 2B–associated tumors are caused by pathogenic variants in the RET protein's intracellular domain, (see Chapter 212).

Von Hippel-Lindau Disease

Von Hippel-Lindau (VHL) disease (Chapter 385) is an autosomal dominant disorder in which nearly 100% of patients have an identifiable pathogenic variant in the VHL tumor suppressor gene.[7] Certain missense mutations appear to be associated with a "pheochromocytoma only" presentation. The disease is characterized by pheochromocytoma (frequently bilateral), paraganglioma (skull base, mediastinal, abdominal, pelvic), hemangioblastoma (involving the cerebellum, spinal cord, or brain stem), retinal angioma, clear cell renal cell carcinoma, pancreatic neuroendocrine tumor, endolymphatic sac tumor of the middle ear, serous cystadenoma of the pancreas, and papillary cystadenoma of the epididymis and broad ligament. Pheochromocytoma occurs in about 10 to 20% of patients with the disease.

Neurofibromatosis

Neurofibromatosis type 1 (Chapter 385) is an autosomal dominant disorder caused by inactivating pathogenic variants in the *NF1* tumor suppressor gene. It is characterized by neurofibromas, multiple café au lait spots, axillary and inguinal freckling, iris hamartomas (i.e., Lisch nodules), bone abnormalities, central nervous system gliomas, pheochromocytoma and paraganglioma, macrocephaly, and cognitive deficits. The expression of these features is variable. Approximately 3% of patients develop catecholamine-secreting tumors; in these patients, the tumor is usually a solitary benign adrenal pheochromocytoma, occasionally bilateral adrenal pheochromocytomas, and rarely an abdominal paraganglioma.

Familial Paraganglioma

Familial paraganglioma is an autosomal dominant disorder characterized by paragangliomas that are located in the skull base and neck, thorax, abdomen, and pelvis. Most cases of familial paraganglioma are caused by pathogenic variants in succinate dehydrogenase (succinate:ubiquinone oxidoreductase) subunit genes (*SDHB, SDHC, SDHD, SDHAF2, SDHA*), which compose portions of mitochondrial complex II. In patients with *SDHD* pathogenic variants, penetrance depends on the mutation's parent of origin: the disease does not manifest when the pathogenic variant is inherited from the mother but is highly penetrant when it is inherited from the father, a phenomenon known as maternal imprinting. Multiple cofactors are required for normal activity of the succinate dehydrogenase complex, including flavin adenine dinucleotide in the SDH1 subunit. Flavin adenine dinucleotide is covalently attached to the SDH1 subunit, and deletion of *SDHAF2* causes a complete loss of flavin adenine dinucleotide cofactor attachment (flavination) of the SDH1 subunit. As in families with pathogenic variants in *SDHD*, families with mutations in *SDHAF2* also exhibit maternal imprinting and parasympathetic paragangliomas that typically occur in the skull base and neck. Patients with *SDHB* pathogenic variants have an increased risk for malignant paraganglioma.

CLINICAL MANIFESTATIONS

Symptoms, when present, are due to the pharmacologic effects of excess concentrations of circulating catecholamines (Table 209-1). The typical hypertension may be sustained (in approximately half of patients) or paroxysmal (in approximately a third of patients), but about 15% of patients have normal blood pressure. Episodic symptoms may occur in spells, or paroxysms, that can be extremely variable in presentation but usually include forceful heartbeat, pallor, tremor, headache, and diaphoresis. The spell may start with the sensation of a "rush" in the chest and a sense of shortness of breath, followed by a "pounding" heartbeat in the chest that typically progresses to a throbbing headache. Peripheral vasoconstriction with a spell results in cool or cold hands and feet as well as facial pallor. Increased sense of body heat and sweating are common toward the end of the spell. Spells may be spontaneous or be precipitated by postural change, anxiety, medications (e.g., metoclopramide, β-adrenergic inhibitors, anesthetic agents, corticosteroids), exercise, or maneuvers that increase intra-abdominal pressure (e.g., change in position, lifting, defecation, exercise, colonoscopy, pregnancy, trauma). Although the types of spells experienced by patients are highly variable, spells tend to be stereotypical for each patient. Spells may occur multiple times a day or as infrequently as once a month. The typical duration of a pheochromocytoma spell is 15 to 20 minutes, but it may

TABLE 209-1 SIGNS AND SYMPTOMS ASSOCIATED WITH CATECHOLAMINE-SECRETING TUMORS

SPELL RELATED
Anxiety and fear of impending death
Diaphoresis
Dyspnea
Epigastric and chest pain
Headache
Hypertension
Nausea and vomiting
Pallor
Palpitation (forceful heartbeat)
Tremor
CHRONIC
Cold hands and feet
Constipation (megacolon)
Diaphoresis
Dyspnea
Ectopic hormone secretion–dependent symptoms (e.g., CRH/ACTH, GHRH, PTH-RP, VIP)
Epigastric and chest pain
Erythrocytosis
Fatigue
Fever
Headache
Heart failure—dilated or hypertrophic cardiomyopathy
Hyperglycemia
Hypertension
Livedo reticularis
Orthostatic hypotension
Painless hematuria (associated with urinary bladder paraganglioma)
Palpitation (forceful heartbeat)
Raynaud phenomenon
Retinopathy (grade II to IV)
Tremor
Weight loss
NOT TYPICAL OF PHEOCHROMOCYTOMA
Flushing

ACTH = adrenocorticotropic hormone; CRH = corticotropin-releasing hormone; GHRH = growth hormone–releasing hormone; PTH-RP = parathyroid hormone–related peptide; VIP = vasoactive intestinal polypeptide.

Modified from Young WF Jr. Pheochromocytoma: 1926-1993. *Trends Endocrinol Metab*. 1993;4:122-127.

be much shorter or persist for several hours. The clinician must recognize that most patients with such spells do not have a pheochromocytoma.

Fasting hyperglycemia and diabetes mellitus are caused in part by the α-adrenergic inhibition of insulin release.[8] Some of the cosecreted hormones that may dominate the clinical presentation include corticotropin (Cushing syndrome; Chapter 208), parathyroid hormone–related peptide (hypercalcemia; Chapter 227), vasopressin (syndrome of inappropriate antidiuretic hormone secretion; Chapter 101), vasoactive intestinal peptide (watery diarrhea; Chapter 126), and growth hormone–releasing hormone (acromegaly; Chapter 205) (see Table 209-1). Cardiomyopathy (Chapter 47) and heart failure are the symptomatic presentations of pheochromocytoma that are most frequently unrecognized by clinicians. Cardiomyopathy, whether dilated or hypertrophic, may be totally reversible with tumor resection. Some patients with pheochromocytoma may be asymptomatic despite high circulating levels of catecholamines, probably as a reflection or desensitization of adrenergic receptors owing to chronic stimulation.

DIAGNOSIS

Prompt diagnosis of these tumors is critical because of the risk of a lethal paroxysm, the ability to cure associated hypertension with surgical removal, the 10% chance that the tumor is malignant, and the 40% probability that the tumor is familial and may affect family members. Pheochromocytoma should be suspected in patients who have one or more of the following: hyperadrenergic spells (e.g., self-limited episodes of nonexertional palpitations, diaphoresis, headache, tremor, or pallor); resistant hypertension; a familial syndrome that predisposes to catecholamine-secreting tumors (e.g., multiple endocrine neoplasia type 2, neurofibromatosis type 1, Von Hippel-Lindau disease); a family history of pheochromocytoma or a history of a resected pheochromocytoma; a history of recurrent hypertension or spells; hypertension and diabetes; a pressor response during anesthesia, surgery, or angiography; onset of hypertension before age 20 years; and idiopathic dilated cardiomyopathy.

On a computed tomography (CT) scan, an incidentally discovered adrenal mass (Fig. 209-1) is more likely to be a pheochromocytoma if it shows precontrast attenuation greater than 10 Hounsfield units (HU), marked enhancement with intravenous contrast medium with slow contrast washout. By comparison, if the unenhanced CT attenuation value is 10 HU or less, the likelihood of pheochromocytoma is so low that further testing for pheochromocytoma is not necessary.[9] On magnetic resonance imaging (MRI), pheochromocytomas are characterized by low signal intensity on T1-weighted imaging and high signal intensity on T2-weighted imaging. Cystic and hemorrhagic changes, bilaterality, and large size (>4 cm) are typical findings.

FIGURE 209-1. Contrast-enhanced computed tomography of the abdomen in a 32-year-old second-year medical student with the peripartum discovery of a pheochromocytoma. The plasma fractionated metanephrines were abnormal: metanephrine, 0.19 nmol/L (normal, <0.5 nmol/L); normetanephrine, 28.6 nmol/L (normal, <0.9 nmol/L). The 24-hour urine values were abnormal: norepinephrine, 781 μg (normal, <170 μg); epinephrine, 2.4 μg (normal, <35 μg); dopamine, 197 μg (normal, <700 μg); metanephrine, 117 μg (normal, <400 μg); normetanephrine, 8760 μg (normal, <900 μg). The axial image shows a typical 5-cm heterogeneously enhancing right adrenal mass, consistent with pheochromocytoma (*arrow*). After α- and β-adrenergic blockade, a 5.3 × 5.0 × 2.0 cm, 40-g pheochromocytoma was removed laparoscopically.

Differential Diagnosis

Numerous disorders can cause signs and symptoms that may lead the clinician to test for pheochromocytoma. These disorders span much of medicine and include endocrine disorders (e.g., primary hypogonadism; Chapter 216), cardiovascular disorders (e.g., idiopathic orthostatic hypotension; Chapter 386), psychological disorders (e.g., panic disorder; Chapter 362), pharmacologic causes (e.g., withdrawal from an adrenergic inhibitor), neurologic disorders (e.g., postural orthostatic tachycardia syndrome; Chapter 388), and miscellaneous disorders (e.g., mast cell disease; Chapter 235). Indeed, most patients tested for pheochromocytoma do not have it. In addition, fractionated catecholamines and metanephrines may be elevated in several clinical scenarios: withdrawal from medications or drugs (e.g., clonidine, alcohol), any acute illness (e.g., subarachnoid hemorrhage, migraine headache, preeclampsia), and administration of many drugs and medications (e.g., tricyclic antidepressants, levodopa, cocaine, phencyclidine, lysergic acid diethylamide, amphetamines, ephedrine, pseudoephedrine, phenylpropanolamine, isoproterenol) (Table 209-1).

Laboratory Findings

The diagnosis must be confirmed biochemically by increased concentrations of fractionated metanephrines in the plasma or fractionated catecholamines and metanephrines in a 24-hour urine collection (Fig. 209-2).[10] Measurement of plasma fractionated metanephrines is attractive because of its simplicity and high sensitivity (96 to 100%), but its specificity is only 85 to 89% and falls to 77% in patients older than age 60 years. Based on the low prevalence of pheochromocytoma, an estimated 97% of patients who have hypertension seen in a tertiary care practice and who have abnormal plasma fractionated metanephrine measurements do not have pheochromocytoma. As a result, if plasma levels are abnormal, the next step should be a reliable method of confirming a catecholamine-secreting tumor before embarking on expensive and time-consuming localization studies. The recommended approach is measurement of fractionated metanephrines and catecholamines in a 24-hour urine collection (sensitivity, 98%; specificity, 98%). Most laboratories now measure fractionated catecholamines (dopamine, norepinephrine, and epinephrine) and metanephrines (metanephrine and normetanephrine) by high-performance liquid chromatography with electrochemical detection or tandem mass spectroscopy.[11] These techniques have overcome the problems with fluorometric analysis (e.g., false-positive results caused by α-methyldopa, labetalol, sotalol, and imaging contrast agents).

Although it is preferable for patients not to receive any medications during the diagnostic evaluation, treatment with most medications can be continued. Tricyclic antidepressants interfere most frequently with the interpretation of fractionated catecholamines and metanephrines. For the effective detection of catecholamine-secreting tumors, treatment with tricyclic antidepressants and other psychoactive agents listed in Table 209-2 should be tapered and discontinued at least 2 weeks before any hormonal assessments. Furthermore, secretion of catecholamines may be appropriately increased in situations of physical stress or illness (e.g., stroke, myocardial infarction, congestive heart failure, obstructive sleep apnea).[12] Therefore, the clinical circumstances under which catecholamines and metanephrines are measured must be assessed in each case.

Localization of the Tumor(s)

Symptomatic pheochromocytomas are localized to the adrenal glands, with an average diameter of 4.5 cm (see Fig. 209-1). Paragangliomas are found where there is chromaffin tissue: along the para-aortic sympathetic chain, within the organs of Zuckerkandl (at the origin of the inferior mesenteric artery), in the wall of the urinary bladder, and along the sympathetic chain in the neck or mediastinum. Paragangliomas in the skull base and neck region (e.g., carotid body tumors, glomus tumors, chemodectomas) usually arise from parasympathetic tissue and typically do not hypersecrete catecholamines and metanephrines, whereas paragangliomas in the mediastinum, abdomen, and pelvis usually arise from sympathetic chromaffin tissue and usually do hypersecrete catecholamines and metanephrines.

Localization studies should not be initiated until biochemical studies have confirmed the diagnosis of a catecholamine-secreting tumor (see Fig. 209-2). Computer-assisted imaging of the adrenal glands and abdomen with CT or MRI should be the first localization test (sensitivity, >95%; specificity, >65%). Approximately 85% of these tumors are found in the adrenal glands, and 95% are found in the abdomen and pelvis. If the results of abdominal imaging are normal, localization with gallium 68 1,4,7,10-tetraazacyclododecane-1,4,7,10-tetraacetic acid (DOTA)-octreotate positron emission tomography (68-Ga DOTATATE PET) is indicated (see Fig. 209-2). Ga-68 DOTATATE PET CT has a lesion-based detection rate of 96-98% and is superior to ^{123}I

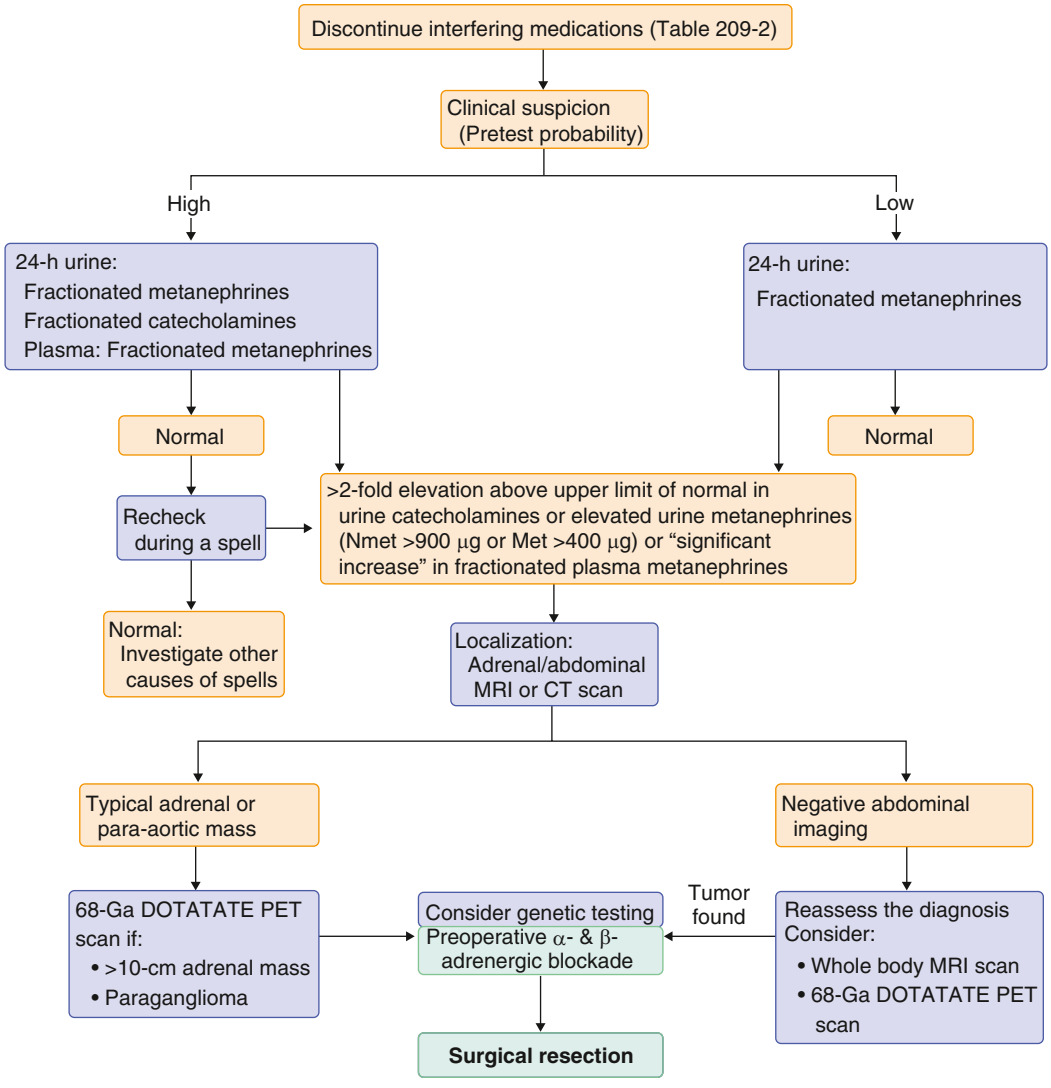

FIGURE 209-2. Evaluation and treatment of catecholamine-secreting tumors. Clinical suspicion is triggered by the following: paroxysmal symptoms (especially hypertension); hypertension that is intermittent, unusually labile, or resistant to treatment; family history of pheochromocytoma or associated conditions; or incidentally discovered adrenal mass. The details are discussed in the text. CT = computed tomography; Ga-68 DOTATATE = gallium 68 1,4,7,10-tetraazacyclododecane-1,4,7,10-tetraacetic acid (DOTA)-octreotate; Met = metanephrine; MRI = magnetic resonance imaging; Nmet = normetanephrine; PET = positron emission tomography. (Modified from Young WF Jr. Pheochromocytoma: 1926-1993. *Trends Endocrinol Metab*. 1993;4:122-127.)

TABLE 209-2 MEDICATIONS THAT MAY INCREASE MEASURED LEVELS OF CATECHOLAMINES AND METANEPHRINES

Tricyclic antidepressants (including cyclobenzaprine)
Levodopa
Drugs containing adrenergic receptor agonists (e.g., decongestants)
Amphetamines
Buspirone and antipsychotic agents
Monoamine oxidase inhibitors (MAO inhibitors)
Prochlorperazine
Reserpine
Serotonin and norepinephrine reuptake inhibitors (SNRIs)
Withdrawal from clonidine and other drugs
Ethanol

metaiodobenzyl guanidine (^{123}I-MIBG) scintigraphy.[13] If a typical (<10 cm) unilateral adrenal pheochromocytoma is found on CT or MRI, Ga-68 DOTATATE PET CT or MIBG is superfluous. If the adrenal pheochromocytoma is larger than 10 cm in diameter or if a paraganglioma is identified on CT or MRI, Ga-68 DOTATATE PET CT or ^{123}I-MIBG scintigraphy is indicated because the patient has an increased risk of malignant disease and additional paragangliomas. Ga-68 DOTATATE and ^{18}F-fluorodeoxyglucose positron emission tomography are excellent imaging modalities to detect metastatic disease.

Other localizing procedures that can be used but are rarely required include computer-assisted imaging of the chest, skull base, and neck (see Fig. 209-2). Because of marked gradients between the adrenal glands in nonpheochromocytoma patients, adrenal venous sampling for catecholamines is not helpful in the investigation of adrenal pheochromocytoma.

Genetic Testing

Genetic testing in clinically approved molecular genetic diagnostic laboratories (see https://www.ncbi.nlm.nih.gov/gtr/) should be considered in all patients with paraganglioma or pheochromocytoma. Genetic counseling is recommended prior to testing to help families understand the implications of genetic test results, to coordinate the testing of at-risk individuals, and to help families work through the psychosocial issues that may arise before, during, or after the testing process.[14]

More than 15 different pheochromocytoma and paraganglioma susceptibility genes have been reported: *NF1, RET, VHL, SDHD, SDHC, SDHB, EGLN1/PHD2, KIF1B, SDHAF2, IDH1, TMEM127, SDHA, MAX, HIF2A*, and *FH* gene encoding fumarate hydratase. The risk of familial disease is highest if a patient has one or more of the following: paraganglioma, bilateral adrenal pheochromocytomas, unilateral adrenal pheochromocytoma with a family history of pheochromocytoma or paraganglioma, onset of unilateral adrenal pheochromocytoma before age 45 years, or clinical findings suggestive of one of the previously discussed syndromic disorders.[15,16]

TREATMENT

Medical Therapy

Some form of preoperative pharmacologic preparation is indicated for all patients who have catecholamine-secreting neoplasms.[17] Combined α- and β-adrenergic blockade is one approach to control blood pressure and to prevent intraoperative hypertensive crises.[18] α-Adrenergic blockade should be started 7 to 10 days preoperatively to normalize blood pressure and to expand the contracted blood volume. A longer duration of preoperative α-adrenergic blockade is indicated in patients with recent myocardial infarction, catecholamine cardiomyopathy, or catecholamine-induced vasculitis. Blood pressure should be monitored with the patient in the seated and standing positions twice daily. Target blood pressure is less than 120/80 mm Hg (seated), with systolic blood pressure greater than 90 mm Hg (standing); both targets should be modified on the basis of the patient's age and comorbid disease. On the second or third day of α-adrenergic blockade, patients are encouraged to start a diet high in sodium (≥5000 mg daily) because of the catecholamine-induced volume contraction and the orthostasis associated with α-adrenergic blockade. This degree of volume expansion may be contraindicated in patients with heart failure or renal insufficiency. After adequate α-adrenergic blockade has been achieved, β-adrenergic blockade is initiated if the average heart rate is greater than 80 beats per minute.

Phenoxybenzamine, which is the preferred drug to control blood pressure and arrhythmia preoperatively, is an irreversible, long-acting, nonspecific α-adrenergic blocking agent. The initial dosage is 10 mg once or twice daily, and the dose is increased by 10 to 20 mg in divided doses every 2 or 3 days as needed to control blood pressure and spells. The final dosage of phenoxybenzamine is typically between 20 and 100 mg daily. The more selective α-adrenergic blocking agent doxazosin (with a starting dose of 1 mg at bedtime) appears to be about equally effective in terms of surgical safety[A1] and is increasingly being used instead of phenoxybenzamine.[19]

A β-adrenergic antagonist should be administered only after α-adrenergic blockade is effective, because β-adrenergic blockade alone may make hypertension more severe owing to unopposed α-adrenergic stimulation. Preoperative β-adrenergic blockade is indicated to control the tachycardia associated with both the high concentrations of circulating catecholamines and the α-adrenergic blockade. The clinician should exercise caution if the patient has asthma or heart failure. Chronic catecholamine excess can produce a cardiomyopathy that may become evident with the initiation of β-adrenergic blockade, thereby resulting in acute pulmonary edema. Therefore, the β-adrenergic blocker (e.g., extended-release metoprolol, 25 mg once daily) should be administered cautiously and at a low dose. Other agents that may be used to prepare the patient with pheochromocytoma for surgery include α-methyl-*p*-tyrosine (metyrosine)[20] (starting at 250 mg every 6 hours) and amlodipine (titrated as high as 20 mg daily).[A2] Despite treatment, patients with pheochromocytomas have more perioperative hemodynamic instability than nonpheochromocytoma patients undergoing adrenal surgery. Acute hypertensive crises may occur before or during an operation, and they should be treated with intravenous sodium nitroprusside, phentolamine, or nicardipine (Chapter 64). Unlike other causes of hypertensive crisis, however, β-adrenergic blockers should be avoided.

Surgical Therapy

The treatment of choice for pheochromocytoma is complete surgical resection. Surgical survival rates are 98 to 100% and are highly dependent on the skill of the endocrinologist–endocrine surgeon–anesthesiologist team. Careful preoperative pharmacologic preparation with either phenoxybenzamine or doxazosin is crucial for successful treatment. Most catecholamine-secreting tumors are benign and can be totally excised. Tumor excision usually cures hypertension.

The laparoscopic approach to the adrenal gland is the procedure of choice for a solitary intra-adrenal pheochromocytoma smaller than 8 cm in diameter. Surgical expertise is key to avoid intraoperative tumor capsule rupture. Laparoscopic adrenalectomy for pheochromocytoma should be converted to open adrenalectomy in cases of difficult dissection, invasion, adhesions, or an inexperienced surgeon. An anterior midline abdominal surgical approach is indicated for abdominal paragangliomas. Paragangliomas of the neck, chest, and urinary bladder require specialized approaches.

Management of Complications

Hypotension may occur during and after surgical resection of the pheochromocytoma, and it should be treated with fluids and colloids and then intravenous pressor agents if necessary. Postoperative hypotension is less frequent in patients who have had adequate preoperative α-adrenergic blockade and volume expansion. If both adrenal glands were manipulated during surgery, adrenocortical insufficiency should be considered as a potential cause of postoperative hypotension. Because hypoglycemia can occur in the immediate postoperative period, blood glucose levels should be monitored, and intravenous fluids should contain 5% dextrose.

PROGNOSIS

Approximately 1 to 2 weeks after surgery, fractionated catecholamines and metanephrines should be measured by collection of a 24-hour urine specimen. If the levels are normal, resection of the pheochromocytoma should be considered complete. Increased levels of fractionated catecholamines and metanephrines detected postoperatively are consistent with residual tumor owing to either a second primary lesion or occult metastases.

About 3% of pheochromocytomas recur within 6 years after what is thought to be curative surgery.[21] The 24-hour urinary excretion of fractionated catecholamines and metanephrines or plasma fractionated metanephrines should be checked annually, perhaps for life. Annual biochemical testing assesses for metastatic disease, tumor recurrence in the adrenal bed, or delayed appearance of multiple primary tumors. Follow-up CT or MRI is not needed unless the metanephrine or catecholamine levels become elevated or the original tumor was associated with minimal or no catecholamine or metanephrine excess.

METASTATIC PHEOCHROMOCYTOMA AND PARAGANGLIOMA

Distinguishing between benign and malignant catecholamine-secreting tumors is difficult on the basis of clinical, biochemical, or histopathologic characteristics. As a result, the diagnosis of malignancy is based on documentation of metastatic disease (e.g., lymph nodes, bone, lung, liver). Metastases develop at a median of 5.5 years (range, 0.3 to 53.4 years) after the initial diagnosis. There is no cure for metastatic pheochromocytoma and paraganglioma.

The clinician should assess the pace of the malignant disease and base the level of therapy on the aggressiveness of the tumor's behavior. A multimodality, multidisciplinary, individualized approach is indicated to control catecholamine-dependent symptoms, local mass effects, and overall tumor burden.[22] Metastatic lesions should be resected, if possible, to decrease the burden of tumor. Skeletal metastatic lesions that are painful or threaten structural function can be treated with external radiotherapy or thermal ablation, or they can be approached surgically. Thermal ablation may also be used to treat small (e.g., ≤3 cm in diameter) liver metastases. External radiotherapy can also be used to treat unresectable soft tissue lesions. In selected cases, long-acting octreotide has been beneficial under expert care. If the metastatic disease is considered aggressive and the tumor burden has exceeded that which can be managed with targeted treatment options (such as sunitinib under expert oversight),[23] cytotoxic chemotherapy with cyclophosphamide, vincristine, and dacarbazine under expert care can stabilize the disease. If cytotoxic chemotherapy proves ineffective, treatment can be guided by molecular imaging, with 177Lu-DOTATATE or 131I-MIBG, depending on which method showed the best expression on imaging.[24]

Median overall and disease-specific survivals are 24.6 and 33.7 years, respectively. However, 13% of patients die within 5 years of diagnosis, and shorter survival correlates with male sex, older age at the time of primary tumor detection, synchronous metastases, larger primary tumor size, elevated dopamine, and not undergoing primary tumor resection.

PHEOCHROMOCYTOMA IN PREGNANCY

Pheochromocytoma in pregnancy can cause the death of both the fetus and the mother. In one series, the diagnosis was made before pregnancy in 15% of pregnancies, during pregnancy in 55%, and after delivery in 30%.[25] The approach to the biochemical diagnosis is the same as for nonpregnant patients. MRI without gadolinium enhancement is the preferred imaging modality. ^{123}I-MIBG scintigraphy and Ga-68 DOTATATE PET-CT are contraindicated.

The treatment of hypertensive crises is the same as for nonpregnant patients, except that nitroprusside should be avoided. The preoperative preparation is the same as for nonpregnant patients.

Adverse outcomes are associated with unrecognized pheochromocytoma during pregnancy, tumors in the abdominal or pelvic areas, and catecholamine excess at least 10 times the upper limit of the normal range. For patients who are diagnosed during pregnancy, α-adrenergic blockade therapy has been associated with fewer adverse outcomes, whereas surgery during pregnancy has not been associated with better outcomes.

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210 DIABETES MELLITUS

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OVERVIEW

Diabetes mellitus is a chronic metabolic disorder characterized by raised glucose concentrations and associated alterations in the metabolism of fat, protein, and carbohydrates. Chronically elevated blood glucose levels increase the risk of developing macrovascular and microvascular complications. Diabetes comprises a cluster of heterogeneous disorders with elevated blood glucose concentrations, but the cluster includes many subcategories, each of which requires tailored prevention, diagnosis, and treatment approaches. Genetic factors may predispose or protect individuals from the deleterious effects of chronic hyperglycemia.

Depending on the context in which the patient presents, diabetes can be an acute life-threatening condition, a pregnancy-associated disorder, or a gradually evolving chronic disorder that, over many years, carries the potential for causing life-limiting complications. Diabetes-related microvascular and macrovascular complications stem from chronic suboptimal control of the metabolic disturbances—defined principally by the hyperglycemia. The risk of developing these complications can be significantly reduced by early and aggressive maintenance of near-physiologic blood glucose concentrations.

The management of diabetes can be challenging because of its varying presentations across the age spectrum, the requirement that the person with diabetes must actively participate in their own treatment, and the evolving clinical manifestations in the same patient. Because the severity of the underlying metabolic defects does not remain static, management almost always requires changes as the disease progresses. The management of diabetes can be especially challenging in vulnerable populations with limited resources or access to appropriate medical care (Chapter 4).

DEFINITION

The definition of the different types of diabetes is based on their etiology and pathogenesis (Table 210-1). Type 1 diabetes, which is caused by an autoimmune destruction of the β cells of the pancreatic islets of Langerhans, accounts for between 5% and 10% of all forms of diabetes. Type 1 diabetes should not be called "juvenile-onset diabetes," because its onset can be at any age, and is no longer termed "insulin-dependent diabetes," even though insulin is usually required from the time of diagnosis, because type 2 diabetes also may require insulin therapy.

Type 2 diabetes, which accounts for over 90% of all forms of diabetes, is characterized by impaired insulin secretion and insulin action. It should not be called "adult-onset diabetes," because it is increasingly being diagnosed in the growing number of obese children and teenagers. It also should not be called "non–insulin-dependent diabetes" because some patients require insulin therapy when a combination of lifestyle change (i.e., diet and exercise) and oral or noninsulin injectable medications are insufficient.

Gestational diabetes (Chapter 221) can develop during pregnancy in women who do not have a previous diagnosis of diabetes. About 2 to 10% of pregnant women are affected, but its incidence has been rising with the increased prevalence of obesity. Gestational diabetes usually is the result of impaired glucose tolerance owing to dysfunction of pancreatic β cells as well as impaired insulin action (insulin resistance). Gestational diabetes usually resolves at delivery, but affected women have up to a 60% lifetime risk of progressing to type 2 diabetes.

Diabetes also can be caused by diseases of the exocrine pancreas, including (but not limited to) pancreatitis (Chapter 130), trauma, cystic fibrosis (Chapter 77), neoplastic disease (Chapter 180), new-onset diabetes after transplantation, and iron deposition in hemochromatosis (Chapter 196). The presence of excessive counter-regulatory hormones, for example, Cushing syndrome (Chapter 208), acromegaly (Chapter 205), glucagonoma (Chapter 213), and pheochromocytoma (Chapter 209), can induce insulin resistance and cause type 2 diabetes. Hyperglycemia also may be associated with the use of certain drugs, including drugs that worsen insulin resistance (e.g., glucocorticoids, nicotinic acid, thiazide diuretics) and those that impair β-cell function (e.g., pentamidine, diazoxide, interferon gamma). Chemotherapeutic agents, in particular the immune checkpoint inhibitors, can also induce type 1 or type 2 diabetes.[1] Monogenic defects include neonatal diabetes and maturity-onset diabetes of the young (see Pathobiology).

In the United States, about 34 million adults over age 18 years have diabetes, thereby resulting in a prevalence of about 13 to 14%, about 95% of which is type 2. About 0.7% of U.S. adults are newly diagnosed with diabetes each year. Before the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) pandemic, diabetes was the seventh leading cause of death, accounting for nearly 90,000 deaths each year. Worldwide, the numbers are staggering. Over 500 million adults have diabetes, representing a prevalence of about 10%, and about 75% of affected individuals are in low- and middle-income countries.

TABLE 210-1 THE DIFFERENCES BETWEEN TYPE 1 AND TYPE 2 DIABETES

	TYPE 1	TYPE 2
Age at onset	Childhood or early adulthood, but can be manifested at any age	Middle age or older adults, but can be present in obese children and adolescents
Family history/genetic factors	Genetic risk defined, but most cases are sporadic	Strong genetic component, polygenic in most cases
Environmental triggers	Largely unknown	Obesity, sedentary lifestyle
Requirement for insulin therapy	Universal	Variable
Frequency among people with diabetes	5-10%	≈90%
Associated disorders	Autoimmunity and endocrine disorders (especially thyroid)	Obesity, hypertension, dyslipidemia, polycystic ovary syndrome

PATHOBIOLOGY

Maintenance of a constant blood glucose concentration is essential for normal physiology and particularly for the central nervous system, because the brain can neither synthesize nor store the amount of glucose required for its normal function. A normal blood glucose concentration requires a balance between the endogenous glucose production by the liver and kidneys and the utilization of glucose by peripheral tissues. Insulin, which is the main glucoregulatory hormone, inhibits the hepatic production of glucose and stimulates the uptake of peripheral glucose.

Insulin is initially synthesized as preproinsulin in the ribosomes of the rough endoplasmic reticulum of pancreatic islet β cells. It is then modified post-translationally to proinsulin, which in turn is transported to the Golgi apparatus, where it is packaged into secretory granules. Proinsulin is post-translationally modified by cleavage into equimolar concentrations of insulin and a connecting segment (C-peptide) in the secretory granules. A rise in the plasma glucose level results in the stimulation of insulin secretion and the release of equimolar quantities of insulin and C-peptide (as well as a small amount of proinsulin) into the hepatic portal vein. A large proportion of insulin is bound to its hepatic receptor and metabolized during its "first pass" through the liver. C-peptide, by comparison, is much less prone to hepatic metabolism, is a better reflection of insulin secretion, and therefore is useful as a biomarker to quantify insulin secretion. However, C-peptide itself is of limited usefulness in the clinical diagnosis or treatment of diabetes (Fig. 210-1).

The principal regulator of insulin secretion is glucose (E-Fig. 210-1). Glucose is taken up by the β cells through the GLUT2 glucose transporter system and then phosphorylated to glucose 6-phosphate by an islet-specific glucokinase. Glucokinase can be considered the "glucose sensor" of the β cell, and mutations in this enzyme lead to type 2 maturity-onset diabetes of the young. The conversion of glucose to glucose 6-phosphate results in a sequential increase in intracellular adenosine triphosphate (ATP) and closing of the ATP-dependent potassium (K_{ATP}) channels in the β-cell membrane. The K_{ATP} channel is usually open in the fasting state and is made up of the sulfonylurea 1 receptor (SUR1) and an inward potassium channel subunit, Kir6.2. Rising ATP concentrations lead to the closure of the K_{ATP} channel, thereby resulting in membrane depolarization and the influx of calcium. The calcium binds to calmodulin, which activates myosin light-chain kinase, which

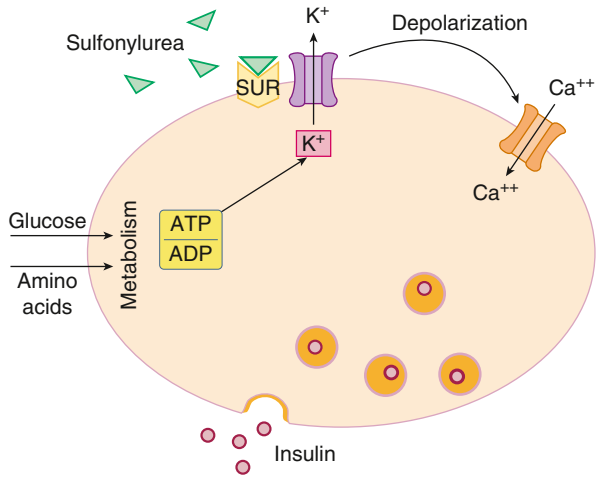

E-FIGURE 210-1. Nutrient regulation of insulin secretion. Glucose is taken up by the β cell by the GLUT2 glucose transporter and is metabolized initially by phosphorylation by glucokinase to glucose 6-phosphate. The rise in glucose 6-phosphate leads to an increase in intracellular ATP and an increase in the cytoplasmic ATP/ADP ratio, which causes closure of the ATP-dependent potassium channel (K_{ATP}), followed by membrane depolarization and the subsequent opening of voltage-gated calcium channels. The influx of calcium mobilizes the insulin secretory granules to fuse with the cell membrane and to release insulin into the extracellular fluid. The sulfonylurea 1 receptor (SUR1) is a component of the ATP-dependent potassium channel. ADP = adenosine diphosphate; ATP = adenosine triphosphate.

ABSTRACT

Diabetes mellitus is a common chronic metabolic disorder that is characterized by elevated blood glucose concentrations. The two main types are type 1 diabetes, in which autoimmune destruction of the pancreatic β cells results in a deficiency of insulin, and type 2 diabetes, which is caused by the impaired secretion and action of insulin. Other causes of diabetes include but are not limited to pancreatic disease, pregnancy, drug-induced diabetes, or genetic defects. Chronic hyperglycemia is associated with microvascular complications, including retinopathy, nephropathy, and neuropathy, as well as macrovascular complications, including coronary artery disease, peripheral vascular disease, and stroke. The treatment of type 1 diabetes requires that insulin be replaced and is helped by dietary modification. For type 2 diabetes, treatments include dietary modification, exercise, weight management, and medication. The pharmacologic options for type 2 diabetes include an array of oral and injectable medications, often used in combination. Aggressive control of hyperglycemia and optimization of other modifiable risk factors for microvascular and macrovascular disease can substantially reduce the risk of developing the complications of chronic diabetes. Acute, life-threatening diabetic complications include iatrogenic hypoglycemia, diabetic ketoacidosis, and the hyperglycemic hyperosmolar state. Newer pharmacologic agents and therapeutic options (e.g., continuous glucose monitoring and insulin infusion) have improved the control of glycemic levels and quality of life for many people who are living with diabetes.

KEYWORDS

diabetes mellitus
type 1 diabetes
type 2 diabetes
diabetic retinopathy
diabetic nephropathy
diabetic neuropathy
ketoacidosis
hyperglycemic hyperosmolar state
hypoglycemia

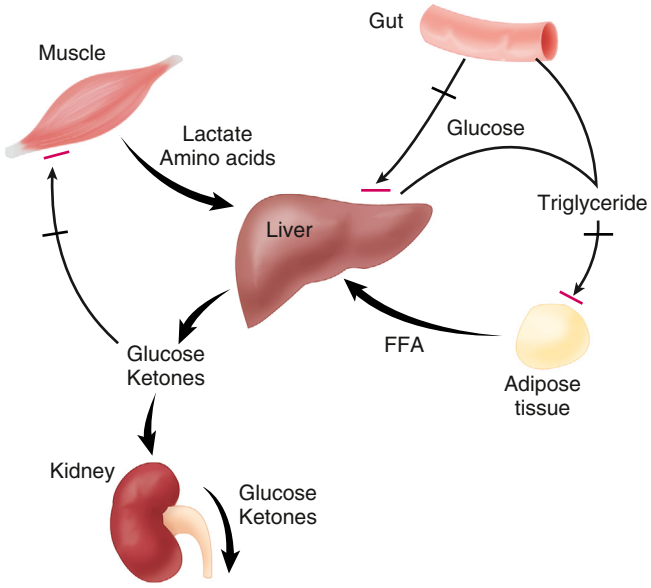

FIGURE 210-1. Effects of insulin deficiency on the metabolism of body fuel. A lack of insulin leads to a lack of cellular uptake of glucose, thereby necessitating mobilization of alternative substrates for gluconeogenesis and ketogenesis. These substrates come from amino acids in muscle and free fatty acids released from adipose tissue. These precursors are metabolized in the liver to form glucose and ketones. The impaired removal of endogenous and exogenous metabolic fuels by insulin-responsive tissues leads to worsening hyperglycemia and hyperketonemia that overwhelm renal removal mechanisms. The result is symptomatic hyperglycemia, with polyuria (and subsequent polydipsia) owing to the osmotic diuresis of glycosuria and ketonuria, as well as weight loss owing to the breakdown of muscle and adipose tissue and the loss of glucose and ketones in the urine. Genital mycotic infections can be precipitated by the presence of glucose in the urine. FFA = free fatty acids.

leads to the migration of the insulin secretory granules to the cell membrane, which fuse together to allow exocytosis of insulin into the extracellular fluid. Mutations in either the SUR1 gene or the Kir6.2 gene can lead to loss of K_{ATP} activity; as a result, the cell is continuously depolarized, thereby resulting in the chronic release of insulin and a syndrome termed "persistent hyperinsulinemic hypoglycemia of infancy." Mutations in Kir6.2 and SUR1 have also been identified in infants with permanent neonatal diabetes mellitus. Because sulfonylureas bind to the SUR1 receptor and cause insulin release, treatment with these agents can normalize insulin secretion and glucose concentrations in people with this condition.

The magnitude of the insulin secretory response is determined by the blood glucose concentration as well as by the rate and mode of glucose entry. Compared with the intravenous administration of glucose, greater amounts of insulin are produced when glucose is taken orally because of the simultaneous release of the gut-derived hormones known as incretins. These incretins include glucagon-like peptide 1 (GLP-1) and glucose-dependent insulinotropic peptide (GIP), both of which augment insulin secretion. Rapid increases in the blood glucose concentration (e.g., after intravenous administration of glucose) cause a spike of insulin secretion that peaks within a few minutes and declines quickly (so-called first-phase insulin secretion). With more persistent elevations of the plasma glucose concentration, insulin secretion is sustained (so-called second-phase insulin secretion). The earliest pathophysiologic indicator of defective β-cell function may be the loss of first-phase secretion of insulin, which precedes by years the decline in insulin secretory reserve sufficient to lead to overt glucose intolerance or diabetes.

Another abnormality in type 2 diabetes is the blunted secretion of these incretin hormones after the oral administration of carbohydrate. Drugs are now available to mimic or enhance this incretin effect (see Treatment of type 2 diabetes).

The actions of insulin on its principal target organs (i.e., muscle, fat, liver) are mediated by its interaction with the insulin receptor and have complex and coordinated effects on the metabolism of carbohydrates, proteins, and lipids (see Fig. 210-1). Insulin receptor signaling through insulin receptor substrate 1 and phosphatidylinositol 3-kinase is a major pathway in the mediation of insulin-stimulated glucose transport, notably by stimulating the translocation of the glucose transporter GLUT4 to the cell membrane. This pathway is also responsible for the vasodilator effects of insulin on large vessels and the capillary microcirculation (by an increased expression of endothelial nitric oxide synthase), an effect that may contribute to the utilization of glucose by increasing the delivery of nutrients to tissues. Defects in these intracellular signaling pathways are an important cause of impaired insulin action, or "insulin resistance" (see Pathobiology of type 2 diabetes).

TABLE 210-2 THE METABOLIC EFFECTS OF INSULIN

METABOLIC EFFECT	STIMULATED BY INSULIN	INHIBITED BY INSULIN
Carbohydrate metabolism	Glucose uptake Glycolysis Glycogen synthesis	Glycogen breakdown Gluconeogenesis
Protein metabolism	Amino acid uptake Protein synthesis	Protein breakdown
Lipid metabolism	Triglyceride uptake Lipogenesis	Lipolysis Fatty acid oxidation

The overall actions of insulin tend to promote the uptake and storage of nutrients in the fed state and the release of nutrients from body stores in the fasting state (Table 210-2). The actions of insulin are dependent on its circulating concentration. In the fasting state, declining glucose concentrations inhibit the release of insulin, thereby increasing glycogenolysis and gluconeogenesis, as well as allowing the release of glucose into the circulation. In states of absolute or relative insulin deficiency, inadequate basal insulin concentrations allow unrestrained hepatic glucose production, which results in fasting hyperglycemia. In the absence of insulin resistance, however, any carbohydrate that is ingested (e.g., in the postprandial period) stimulates insulin secretion. At the very lowest concentrations, insulin inhibits lipolysis and the production of ketones. As its concentrations rise, insulin lowers hepatic glucose production by inhibiting the release of glucagon. This rise in the insulin-to-glucagon ratio prevents glycogenolysis and the breakdown of skeletal muscle protein, so glucose levels stop rising. Further insulin then increases the peripheral uptake of glucose into skeletal muscle and adipose tissue, thereby promoting the synthesis of protein and triglycerides and lowering plasma concentrations of glucose. Eventually, higher insulin concentrations stimulate the synthesis of glycogen and the uptake of amino acids in the liver and muscle.

Inadequate insulin concentrations in the fed state—either due to β-cell failure or to an impairment of insulin secretion or action—impedes peripheral (predominantly skeletal muscle) uptake of glucose, thereby contributing to postprandial hyperglycemia. Impaired suppression of hepatic glucose production also contributes to postprandial hyperglycemia in patients with diabetes.

DIAGNOSIS

Diabetes is diagnosed using one of several criteria, including the fasting plasma glucose concentration, the plasma glucose concentration after a standard 75-g oral glucose challenge (also known as the oral glucose tolerance test), and the percentage or concentration of glycated hemoglobin (HbA_{1c}) (Table 210-3). The diagnosis of diabetes can be confirmed by the presence of two abnormal tests (fasting, 2-hour oral glucose tolerance test or HbA_{1c}) or by finding both unequivocal hyperglycemia (random plasma glucose concentration >200 mg/dL [>11.1 mmol/L]) plus typical symptoms of polyuria, polydipsia, and weight loss. In the presence of a single abnormal test, a confirmatory test is needed on a different blood sample. In individuals in whom HbA_{1c} and glucose values are discordant, fasting and 2-hour plasma glucose levels are more accurate.

Because plasma glucose concentrations range on a continuum, the selection of a specific diagnostic threshold is in some respects arbitrary. Current criteria are based on the plasma glucose or HbA_{1c} concentration above which the risk of diabetes-specific microvascular complications (e.g., retinopathy) is perceptibly increased. In situations of altered red blood cell turnover or certain hemoglobinopathies, caution should be exercised, because HbA_{1c} may not accurately reflect the mean plasma glucose concentration (see later section on glycated hemoglobin). In those circumstances, direct glucose measurement should be used. HbA_{1c} values may vary with race and ethnicity independently of glycemia, with higher HbA_{1c} in Blacks and non-Hispanic Whites. Despite these racial differences, diagnostic values are the same because the risk of complications appears to be the same across ethnicities. Separate glucose criteria exist for the diagnosis of gestational diabetes (see Gestational Diabetes).

TABLE 210-3 DIAGNOSTIC CRITERIA FOR DIABETES

	NORMAL	IMPAIRED (PREDIABETES)	DIABETES
Fasting glucose concentration mg/dL (mmol/L)	<100 (5.6)	100-125 (5.6-6.9)	≥126 (7.0)
OGTT 2-hour glucose concentration mg/dL (mmol/L)	<140 (7.8)	140-199 (7.8-11.0)	≥200 (11.1)
HbA_{1c} (%)	<5.7	5.7-6.4	≥6.5
HbA_{1c} (mmol/mol)	<39	39-47	≥48

HbA_{1c} = glycated hemoglobin; OGTT = oral glucose tolerance test.
Data from American Diabetes Association Standards of Medical Care in Diabetes—2022. *Diabetes Care.* 2022;45(Suppl 1):S17-S38.

Impaired glucose regulation that does not meet the criteria for diabetes, termed "prediabetes" or "nondiabetic hyperglycemia," is defined by a fasting glucose concentration of 100 to 125 mg/dL [5.6 to 6.9 mmol/L], a 2-hour glucose concentration of 140 to 199 mg/dL [7.8 to 11.0 mmol/L], or an HbA_{1c} concentration of 5.7 to 6.4% [39 to 47 mmol/mol]. Each of these three approaches is equally appropriate to diagnose prediabetes. Individuals with prediabetes are at increased risk (a 25 to 50% higher relative risk in the next 5 years compared with individuals with normal glucose and HbA_{1c} values) for progressing to diabetes, but some will spontaneously revert to normal glucose regulation without any specific intervention, particularly individuals who are closest to the normal range.[2] Prediabetes is also associated with an increased risk of atherosclerotic cardiovascular disease, at least partially independent of the future development of diabetes.

HbA_{1c} results may be influenced by conditions that alter red cell survival. For example, the HbA_{1c} level is lower in patients with hemolytic anemia, hemoglobinopathies, renal impairment, and after splenectomy. Assay interference may also lead to misleadingly high HbA_{1c} levels with chronic use of opioids, salicylates, or alcohol. In situations in which capillary or interstitial glucose concentrations are incongruous with HbA_{1c} values, measurement of fructosamine (glycated serum protein) or glycated albumin, both of which reflect mean glucose concentrations during the preceding 2 to 3 weeks, may provide a more accurate assessment. However, these assays have not been as well standardized, and their relationship with mean plasma glucose is less well established.

TYPE 1 DIABETES

EPIDEMIOLOGY

New cases of type 1 diabetes may occur at any time of life, but the incidence peaks around the time of puberty. No sex differences are noted during childhood, but males are affected more commonly in early adult life. Early-onset diabetes carries a higher familial risk, and affected fathers are more likely to have offspring with type 1 diabetes (6 to 9%) than are affected mothers (1 to 3%).

The incidence varies greatly across the world, with rates as high as 60 per 100,000 per year in Scandinavia, up to 20 per 100,000 per year in Southern Europe and the United States, and as low as 3 per 100,000 per year in China.[3] In the United States approximately 30% of people with diabetes are diagnosed after young adulthood.[4] The worldwide annual incidence appears to have increased by 3 to 4% per year over the past 50 to 60 years, with the highest rates of increase in lower-incidence countries and the lowest rates of increase in countries with the highest incidence. This increasing incidence of type 1 diabetes also suggests that environmental factors may be pathogenic, but such factors remain largely undetermined.

PATHOBIOLOGY

In type 1 diabetes, a complex interplay of genetic, environmental, and autoimmune factors selectively targets insulin-producing pancreatic islet β cells and ultimately destroys them.[5] Type 1 diabetes is characterized by an absolute deficiency of insulin, and over 90% of newly diagnosed individuals have one or more autoantibodies to glutamic acid decarboxylase (GAD65), pancreatic islet β cells (tyrosine phosphatase IA-2), the IA-2b zinc transporter (ZnT8), or insulin. In normoglycemic relatives of people with diabetes, the presence of two or more antibodies is highly predictive of developing type 1 diabetes within 5 years. However, some people with type 1 have no evidence of autoimmunity and have what is termed idiopathic type 1 diabetes.

β-cell destruction is largely mediated by a variety of T-cell–mediated immune responses that cause apoptosis or cellular destruction, although evidence suggests that islet-directed antibodies may also play a role. Islet-targeted inflammatory cell infiltrates (termed insulitis), which are composed of $CD8^+$ and $CD4^+$ T cells, macrophages, and pancreatic β-cells, are linked to the onset of diabetes. Over time, the islets become completely devoid of β cells and inflammatory infiltrates. Other pancreatic cells remain intact, thereby illustrating the specificity of the autoimmune attack on β cells.

The role of genetic factors in type 1 diabetes is exemplified by familial clustering with other autoimmune endocrine disorders and a 30 to 40% concordance rate in identical twins, with a significant proportion of the remainder having autoantibodies. Nonidentical siblings who are human leukocyte antigen (HLA) identical to the proband have a 12 to 15% risk for development of diabetes by the age of 20 years. The presence of an environmental trigger for type 1 diabetes is highly likely, however, because even identical twins do not express identical T-cell receptor and immunoglobulin genes.

About 60 type 1 diabetes genes are known.[6] HLA genes are located on the short arm of chromosome 6 and contribute about 50% of genetic susceptibility. Two HLA class II haplotypes, DR4-DQ8 and DR3-DQ2, are present in about 90% of children with type 1 diabetes. The genotype containing both haplotypes carries the highest risk of diabetes (about 5%) and is most commonly seen in early-onset disease. In contrast, the DR15-DQ6 haplotype is highly protective, being found in only 1% of children with type 1 diabetes in contrast to 20% of the general population. Other genes that likely contribute to the genetic susceptibility to type 1 diabetes include the insulin gene (on chromosome 11) and several other loci that are associated with other autoimmune conditions, thereby suggesting the existence of common pathways that predispose to the loss of immune self-tolerance. Another gene, *IFIH1*, located on chromosome 2, encodes a protein involved in innate immunity and plays a role in recognition of the RNA genomes of certain viruses; high IFIH1 levels might provoke exaggerated antiviral immune responses that predispose to autoimmunity. Many other genes have also been implicated, thereby underscoring the polygenic nature of this disease.

Epidemics of mumps (Chapter 340), rubella (Chapter 339), and coxsackie virus (Chapter 349) infection have been associated with an increased frequency of type 1 diabetes, apparently because they may contain molecules that resemble a β-cell protein, nullify self-tolerance, and trigger an autoimmune response in genetically predisposed individuals. This process may also explain the increase in new-onset type 1 diabetes, often presenting as an acute hyperglycemic emergency, during the SARS-CoV-2 pandemic.[7]

A critical role for T cells is suggested by studies involving pancreatic transplantation in identical twins. When a monozygotic twin with diabetes receives kidney and pancreatic grafts from a genetically identical sibling who does not have diabetes, little or no therapeutic immunosuppression is required. However, these recipients eventually experience a resumption of insulitis, with the subsequent recurrence of diabetes. Evidence implicating T cells in diabetes autoimmunity also derives from clinical trials using immunosuppressive drugs. Drugs such as rituximab, cyclosporine, methotrexate, or antibodies directed against a component of the T-cell receptor (anti-CD3) or that alter antigen presentation by β cells (anti-CD20) slow the progression of recent-onset diabetes, but this effect is not sustained if immunosuppression is withdrawn.

In the less than 10% of individuals who require insulin from the time of diagnosis and who do not have autoantibodies, pancreatic β cells are destroyed by insults that primarily involve the exocrine pancreas but also damage the adjacent endocrine pancreas. This condition is occasionally known as type 3c diabetes. Typical examples include pancreatitis (Chapter 130), cystic fibrosis (Chapter 77), and hemochromatosis (Chapter 196). Drugs such as interferon gamma, diazoxide, pentamidine, and checkpoint inhibitors can also sufficiently damage β cells to cause insulin-dependent diabetes.

CLINICAL MANIFESTATIONS AND DIAGNOSIS

The diagnosis of diabetes is usually made on clinical grounds based on symptoms or glucose criteria (see Table 210-2).[8] After what is commonly a long preclinical phase (Fig. 210-2), symptomatic hyperglycemia, manifested by polyuria, polydipsia, weight loss, and fatigue, occurs abruptly, usually in an otherwise healthy child or young adult.

At the time of clinical diagnosis, about 10 to 20% of the original β-cell mass may still be functional, and overt hyperglycemia with or without ketosis may

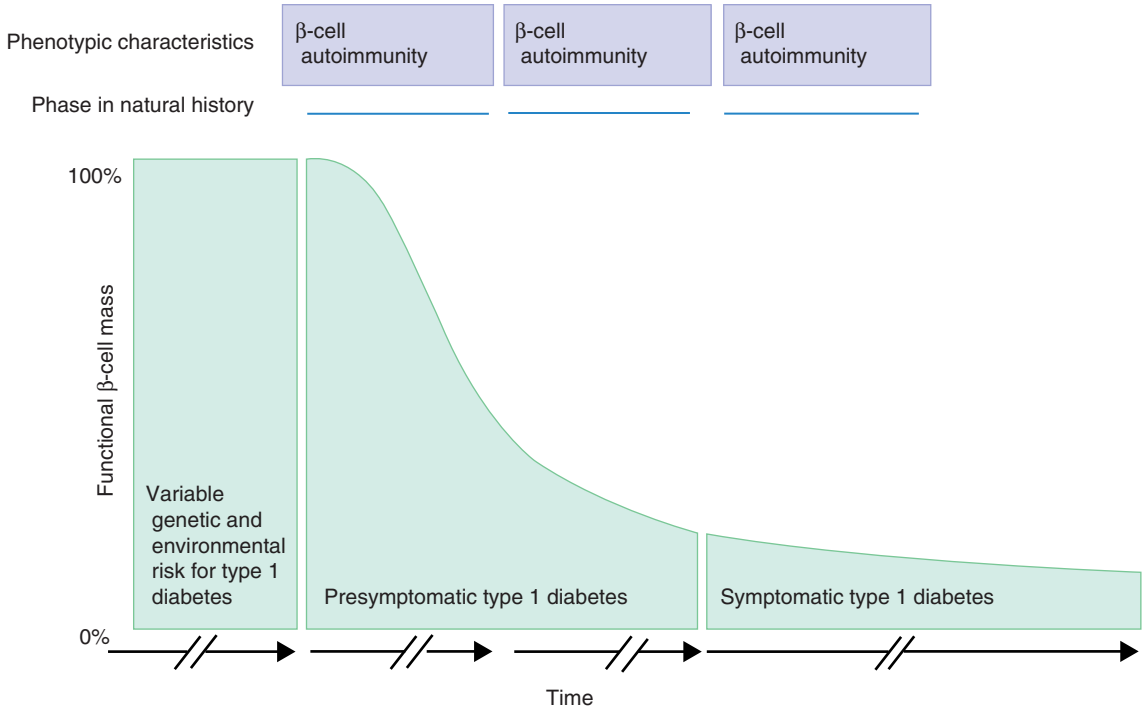

FIGURE 210-2. Summary of the sequence of events that lead to pancreatic β-cell loss and ultimately to the clinical evolution of type 1 diabetes. (From Insel RA, Dunne JL, Atkinson MA, et al. Staging presymptomatic type 1 diabetes: a scientific statement of JDRF, the Endocrine Society, and the American Diabetes Association. *Diabetes Care*. 2015;38:1964-1974.)

be precipitated when an unrelated medical illness or stress to an already-limited islet reserve triggers these clinical manifestations. The coincidence of type 1 diabetes with puberty is likely attributable to insulin resistance associated with increases in the secretion of sex and growth hormones.

In a minority of U.S. cases, but much more commonly in low- and middle-income countries, the initial presentation may be diabetic ketoacidosis if these milder symptoms were not recognized.[9] Worldwide, between 13% and 80% of individuals with type 1 diabetes present with diabetic ketoacidosis. Diabetic ketoacidosis at diagnosis is more common in children younger than age 5 years and in children whose families, often for social or economic reasons, do not have access to medical care.

The presence or absence of anti–glutamic acid decarboxylase (GAD65) or other antibodies (e.g., tyrosine phosphatase IA-2, the IA-2b zinc transporter, or insulin) is sometimes helpful to distinguish between type 1 and type 2 diabetes and to guide appropriate treatment if the diagnosis is in doubt. For example, when an individual presents in diabetic ketoacidosis but has features more typical of type 2 diabetes, such as obesity, a strong family history of type 2 diabetes, a prior history of gestational diabetes, or is over age 40 years, antibody levels may be the only way to confirm type 1 diabetes.

After initiation of insulin therapy and stabilization of plasma glucose concentrations, many patients may experience a period of weeks to months of relatively easily controlled hyperglycemia. This so-called "honeymoon phase" of type 1 diabetes results from amelioration of the underlying stress in an individual whose pancreatic function reflects severe, but not total, destruction of β cells with ongoing, albeit markedly reduced, insulin secretion. However, the underlying, ongoing, progressive autoimmune destruction continues, thereby leading to a decline in insulin production, which usually is undetectable after a few years, at which time they rather suddenly (i.e., over a few weeks or months) have a marked increase in their exogenous insulin requirements to maintain normal plasma glucose concentrations. With highly sensitive C-peptide assays, low levels of insulin production are detected in some people who have long-standing type 1 diabetes and who demonstrate more stable glycemic control and lower rates of hypoglycemia. In some individuals with type 1 diabetes in adulthood, the clinical presentation may follow a more indolent course (termed latent autoimmune diabetes in adults), perhaps because the β-cell mass declines at a slower pace. Indeed, for some of these individuals, their diabetes may be initially misdiagnosed as type 2 diabetes until the progression of insulin deficiency reveal-s the phenotype of permanent and complete insulin dependence.

TREATMENT

The key to successful treatment of type 1 diabetes is to maintain glucose concentrations within the physiologic target range using insulin replacement therapy to prevent the short- and long-term harmful consequences of hyperglycemia. All individuals with type 1 diabetes should be primarily managed by an endocrinologist or, in locales where primary endocrinology is not available, in close concert with a consulting endocrinologist. Automated or semi-automated insulin delivery systems, which require expert supervision, permit a much better approximation of normal physiology and an increase in the amount of time that glucose values are in the physiologic range.[10] However, successful achievement and maintenance of aggressive glucose management require significant commitment by the person with diabetes and by their multidisciplinary team of health care clinicians.

Insulin Therapy

Everyone with type 1 diabetes requires exogenous insulin treatment to maintain life. The approach to insulin replacement in type 1 diabetes (Table 210-4) requires consideration of basal insulin requirements (i.e., the amount of insulin required to maintain homeostasis in the fasting state) and prandial insulin (i.e., the amount required for the influx of carbohydrates that occurs with meals). Insulin can be classified into rapid-acting insulin analogues, regular (short-acting) insulin, intermediate-acting insulin, long-acting insulin analogues, premixed insulin, and premixed insulin analogues (Table 210-4). In comparison with human insulin, the rapid and long-acting insulin analogues have the advantage of producing less hypoglycemia and weight gain, but they are more expensive.

Insulins can be administered by prefixed syringes or in vials. Insulin pen devices can be disposable (i.e., discarded when the insulin is used up) or contain cartridges that can be changed. From a safety perspective, insulin should be prescribed by the full brand name, including the number in the brand name, if applicable. If prescribed by hand, the term "units" rather than "u" should be used to avoid misinterpretation.

Intermittent Subcutaneous Insulin

Subcutaneous insulin replacement regimens vary from one to five or more injections per day depending on the individual's lifestyle, whether they count carbohydrates, and their preferences. People with type 1 diabetes are often treated with a combination of long-acting "basal" insulin and short-acting mealtime "prandial" insulin, using a multiple daily insulin injection ("basal-bolus") regimen.

The total daily insulin requirement for adults with type 1 diabetes is between 0.3 and 1.0 unit/kg/day, with half of the total daily dose typically given as basal insulin and the remainder divided into premeal boluses. Prandial insulin doses are determined by the meal's carbohydrate content plus a "correction factor" if the glucose level is elevated before the meal. For example, a common approach is to use 1 unit for every 10 to 15 g of a meal's carbohydrate content plus a correction factor of 1 unit to lower the plasma glucose concentration by 20 to

TABLE 210-4 INSULIN PREPARATIONS

TYPE OF INSULIN	ONSET OF ACTION	PEAK EFFECT	DURATION OF ACTION
PRANDIAL INSULIN (RAPID-ACTING ANALOGUES)			
Lispro (U100 or U200), aspart, glulisine	15-30 minutes	30-90 minutes	3-4 hours
SHORT-ACTING INSULIN ("REGULAR")			
Human (U100 or U500)	Approximately 30 minutes	2-4 hours	5-8 hours
INTERMEDIATE-ACTING INSULIN ("NPH")			
Human	2-4 hours	6-10 hours	16-20 hours
LONG-ACTING INSULIN			
Glargine U100	1.5-2 hours	Peakless	16-20 hours
Detemir	1.5-2 hours	Peakless	16-20 hours
Degludec U100 or U200	1.5-2 hours	Peakless	36-40 hours
Glargine U300	1.5-2 hours	Peakless	30-36 hours

NPH = neutral protamine Hagedorn. Not all preparations are available everywhere.

50 mg/dL (about 1 to 3 mmol/L). However, insulin requirements are influenced by several factors that may or may not be under the control of the person living with diabetes (e.g., age, body size, insulin sensitivity, exercise, menstrual cycle, comorbid conditions, medication use) and often vary substantially among individuals, so these algorithms must be individualized. Critical to the success of physiologic insulin replacement is the need for the individual to monitor blood or interstitial glucose concentrations, generally several times a day. Monitoring, which typically relies on small portable meters with disposable strips before meals and at bedtime, allows for appropriate dosing, correction of unexpected hyperglycemia, and detection or confirmation of hypoglycemia. Several mobile phone applications and computer programs are available to assist with this calculation.

In addition to glucose testing, people who are taking insulin should be instructed to test their urine or capillary ketones (with a reagent strip) in situations in which the blood glucose concentration is unexpectedly and persistently elevated. Moderate or large amounts (≥2+ ketone readings or >1.5 mmol/L) may indicate the onset of diabetic ketoacidosis (see later) and should prompt the individual to seek urgent medical attention.

Continuous Insulin Infusion

Many people with type 1 diabetes are now administered insulin using a continuous subcutaneous infusion system, commonly termed an insulin pump. These systems consist of a control unit and an insulin reservoir, which can be attached by thin flexible tubing to a very small catheter that is inserted subcutaneously by the patient and changed every 2 or 3 days. These frequent changes of the infusion site help to avoid local inflammation and fibrosis, which can interfere with insulin absorption. Insulin pumps are also available as tubeless systems, inserted into the abdomen, flank, upper leg, or arms. Compared with intermittent subcutaneous insulin, insulin pump therapy reduces HbA_{1c} concentrations by 0.3 to 0.6% (3 to 7 mmol/mL) and also reduces the risk of severe hypoglycemia.[A1] When used appropriately, these systems can maximize the control of blood glucose levels and allow a more flexible lifestyle.

Insulin pumps, which require expert supervision, can deliver a rapid-acting insulin analogue at a variable rate. Pumps can be programmed to deliver one or multiple basal infusion rates as well as preprandial bolus doses. The basal insulin delivery rate, which is often programmed to vary throughout the day, may be especially useful to prevent hyperglycemia associated with the "dawn phenomenon" (a rising blood glucose concentration in the few hours before waking, thought largely to be due to increased secretion of counter-regulatory hormones). In addition, on-demand changes to basal rates (temporary basal rates) can increase or decrease insulin delivery when requirements change, such as at the time of physical activity. Periprandial bolus doses and correction doses are calculated by the pump based on preprogrammed settings for insulin to carbohydrate ratios, insulin sensitivity factors, the premeal glucose level, and even the carbohydrate content of the meal. The person with diabetes or their caregiver must be well-versed regarding how to use the pump and how to revert quickly to multiple daily subcutaneous insulin injections in the event of a pump malfunction, because metabolic decompensation, including diabetic ketoacidosis, can develop within a few hours since the half-life of insulin is just 5 to 10 minutes and since patients do not have a reservoir of long-acting insulin.

Insulin pump systems can include continuous glucose monitoring devices that measure glucose levels in the interstitial fluid and provide data regarding glucose trends after meals, during physical activity, and at night. Pump features can include automated glucose-responsive adjustments to the insulin dose, including suspending the delivery of insulin when a low glucose level is predicted to occur. Many systems can be programmed to sound an alarm when the glucose concentration goes outside of a preset range or rate of change. These sensor augmented pumps result in improvements in HbA_{1c} of −0.4 to −0.6% (4 to 7 mmol/mol) compared with traditional multidose insulin injections in patients with type 1 diabetes and also reduce the risk of hypoglycemia.[A2,A3]

Closed-loop insulin delivery systems or automated insulin delivery (consisting of real-time glucose monitoring and an integrated insulin control algorithm) automatically change the delivery rate of insulin by increasing, decreasing, or suspending the insulin infusion every 5 to 10 minutes to a preset glucose concentration, with the added feature of an automatic corrective bolus of insulin to mitigate hyperglycemia when a specific predetermined glucose value is reached. These "artificial pancreas systems" can improve glucose control and reduce hypoglycemia compared with conventional insulin pumps.[A4–A6] In addition to commercially available products, open-source software has been used to help people with diabetes to develop their own widely shared, closed-loop systems.

Inhaled insulin is also available but rarely recommended, except in a few specialized centers. Oral insulins, topical gels, and microneedles are in development but not ready for routine clinical use.

Adjunctive Therapies

Pramlintide (15 μg as a starting dose and increased every few days to the maintenance dose of 120 μg) is a subcutaneous injectable amylin analogue that can mitigate postprandial hyperglycemia, modestly lower the HbA_{1c} level (0.3 to 0.5% [3 to 6 mmol/mol]), and facilitate weight loss. However, it is rarely used because of associated nausea and the need for additional injections.

Low-dose dapagliflozin, which is a sodium glucose cotransporter 2 (SGLT2) inhibitor, and sotagliflozin, which is a SGLT1/2 inhibitor, cause glycosuria, reduce HbA_{1c} levels by 0.28 to 0.48% [3 to 6 mmol/mol], and facilitate weight loss. However, these agents can precipitate diabetic ketoacidosis in 3 to 6% of individuals with type 1 diabetes and also increase the risk of developing urinary and genital yeast infections. Based on these pros and cons,[11] these agents are approved for type 1 diabetes in many parts of the world but not in the United States or United Kingdom.

Diet and Lifestyle Treatment

In type 1 diabetes, the goal of dietary planning is an accurate estimation of the carbohydrate content of a meal to allow appropriate prandial insulin dosing. This goal can be approached by encouraging meal-to-meal carbohydrate consistency, which allows for a relatively fixed premeal insulin dose. A more flexible approach, however, is for individuals to learn "carbohydrate counting," which specifies an insulin dose per amount of carbohydrate in the meal. The ratio of insulin to carbohydrate can vary according to time of day. This approach requires substantial education, including how to read and understand nutritional information on food packaging, experience, and health literacy.

Dietary management should be individualized based on food preferences, religious or cultural needs, finances, schedules, physical activity, and glycemic targets. In general, rapidly absorbed carbohydrate foods ideally should be avoided, but caloric restriction is neither required nor helpful except in overweight or obese individuals. A "heart healthy" Mediterranean diet (see Fig. 13-1) is recommended as for the general population.

Whole Pancreas and Islet Cell Transplantation

Whole pancreas transplantation can achieve 5-year graft survival rates of about 70%, but the surgery is complicated, and lifelong immunosuppression is required. Pancreatic transplantation is generally reserved for persons who already have had or are concurrently receiving a kidney transplant. Otherwise, a pancreas-only transplant may be considered for individuals who have a history of frequent, acute, and severe metabolic complications (especially severe hypoglycemia) or severe and incapacitating psychosocial problems related to insulin therapy.[12]

Pancreatic islet cell transplantation is generally an experimental procedure, also requires systemic immunosuppression, and is performed in only a few centers, usually in the setting of a research study. Stem cell therapy is an active area of investigation.

PREVENTION

Proposed preventive options include primary prevention, aimed at inhibiting the development of autoimmunity against islet autoantigens; secondary prevention, aimed at halting the autoimmune processes and possibly avoiding the clinical onset of diabetes in individuals with multiple islet autoantibodies; and tertiary prevention, to slow the β-cell destructive process and to avoid or delay the onset of diabetes-related complications in individuals with newly diagnosed diabetes. A single 14-day course of the monoclonal antibody teplizumab may delay progression to clinical type 1 diabetes in high-risk relatives of people with type 1 diabetes,[A7] but no preventive intervention has shown more than limited short-term success.

PROGNOSIS

Substantial progress has been achieved in reducing the microvascular complications of type 1 diabetes (see later), largely due to more intensive glucose control as well as more effective treatment of early stages of renal disease (Chapter 109) and retinopathy (Chapter 391). Morbidity and mortality from macrovascular complications also have declined, largely due to adjunctive treatments such as lipid lowering using statins (Chapter 190) and aggressive blood pressure control using inhibitors of the renin-angiotensin-aldosterone pathway (Chapter 64).

For example, less than 1% of individuals with diabetes now become blind, require renal replacement, or have amputation due to diabetes. In the absence of renal disease, life expectancy for people with type 1 diabetes in the United States is comparable to that of the general population, but the overall mortality rate of individuals with type 1 diabetes from age 35 years onward is about twice as high as in the general population because of the presence of microvascular and macrovascular disease. As a result, affected individuals with diabetes remain at significantly higher risk (five- to six-fold higher) of all-cause and cardiovascular mortality compared with individuals who do not have diabetes.[13] Glycated hemoglobin concentrations 7.5% (58 mmol/mol) or higher or less than 5.6% (38 mmol/mol) in persons with diabetes are associated with an increased risk of all-cause mortality,[14] and the risk becomes progressively higher for HbA_{1c} concentrations above 7.9% (63 mmol/mol). Unfortunately, large variations in risk are associated with health care disparities, including by race, ethnicity, and socioeconomic status.

TABLE 210-5 RISK FACTORS FOR TYPE 2 DIABETES

Age ≥45 years
First-degree relative with diabetes
Personal history of cardiovascular disease
Overweight or obese
Sedentary lifestyle
Member of an at-risk racial or ethnic group: Asian, African American, Hispanic, Native American, or Pacific Islander
HDL-C <35 mg/dL (0.90 mmol/L) and/or a triglyceride level >250 mg/dL (2.82 mmol/L)
Impaired glucose tolerance, impaired fasting glucose
Polycystic ovarian syndrome
Acanthosis nigricans
Nonalcoholic fatty liver disease
Hypertension or on therapy for hypertension
History of gestational diabetes or delivery of a baby weighing more than 4 kg (9 lb)
Antipsychotic therapy for schizophrenia and/or severe bipolar disease
Sleep disorders, including obstructive sleep apnea, chronic sleep deprivation, and night-shift occupation
Long-term use of glucocorticoid therapy

HDL-C = high-density lipoprotein cholesterol.
Testing should be considered in all adults who are obese (BMI ≥30 kg/m^2) as well as in adults who are overweight (BMI 25 to <30 kg/m^2 or >23 kg/m^2 in Asians/Asian Americans) and also have any additional risk factors.

TYPE 2 DIABETES

EPIDEMIOLOGY

Type 2 diabetes affects more than 34 million people in the United States, where its prevalence increased from approximately 0.93% of the population in 1958, to 3% in 1995, 9% in 2015, and 10.5% in 2020.[15] Among adults, type 2 diabetes affects 13% of adults older than age 18 years and 27% of adults age 65 years or older. This increase is in part due to the aging of the population, but incidence rates are also increasing parallel to the rise of overweight and obesity (Chapter 201) as well as increasingly sedentary lifestyles. The rates of diabetes are highest among Native Americans/Alaska Natives, Hispanic Americans, and non-Hispanic Blacks, followed by non-Hispanic Asians and non-Hispanic Whites (7.5%). The prevalence of type 2 diabetes also varies significantly by education level, affecting 13.3% of adults with less than a high school education compared with 9.7% of adults with a high school education and 7.5% of adults with more than a high school education.

A similar pattern is observed globally. In 2021, an estimated 537 million people worldwide (10.5% of all adults age 20 to 79 years) had diabetes,[16] including an estimated 24% of adults over age 75 years. By 2045, about 783 million adults worldwide are projected to have diabetes. The prevalence of diabetes is higher in urban than in rural areas, but men and women have about an equal prevalence. Countries with the largest numbers of adults with diabetes are China (140 million), India (74 million), and Pakistan (33 million).

PATHOBIOLOGY

The development of type 2 diabetes is the result of interaction between environmental factors and a strong hereditary component (Table 210-5). Type 2 diabetes is caused by a combination of two primary metabolic factors: defective secretion of insulin by pancreatic β cells and the inability of insulin-sensitive tissues to respond appropriately to insulin. The relative contribution of these factors varies among individuals and even within the same individual over time because the secretion of insulin progressively declines with a longer duration of disease.

Impaired Insulin Secretion

The failure of β cells to provide enough insulin is a combination of insufficient β-cell mass and altered β-cell function. By the time of diagnosis of type 2 diabetes, up to 50% of β cells may have failed, but a 50% surgical pancreatectomy does not lead to hyperglycemia in otherwise healthy individuals. Physiologic studies show β-cell dysfunction in the early stages of type 2 diabetes, with diminished pulsatile and oscillatory release of insulin and downregulation of the pancreatic insulin receptor. An increased accumulation of amyloid in the islet cells may contribute to impaired secretory function.

Impaired Insulin Action (Insulin Resistance)

Most individuals with type 2 diabetes are overweight or obese, conditions that are associated with insulin resistance (a state of reduced insulin-mediated uptake of glucose). Resistance to insulin's action, primarily in muscle and fat but also in the liver, is typically the first abnormality. Insulin resistance stimulates compensatory hyperinsulinemia in an attempt to maintain normal glucose concentrations. Over time, hyperglycemia occurs as the consequence of the inability of β cells to produce enough insulin; subsequent pancreatic exhaustion results in insulinopenia.

Genetics

The lifetime risk of developing type 2 diabetes is 40% for individuals who have one parent with type 2 diabetes and 70% if both parents are affected. First-degree relatives of individuals with type 2 diabetes are about three times more likely to develop the disease than are individuals without a positive family history of the disease. The concordance rate among monozygotic twins is as high as 70%, whereas the concordance rate in dizygotic twins is only 20 to 30%.

Single-Gene Mutations

Monogenic defects include maturity-onset diabetes of the young (MODY), which is an autosomal dominant disorder in which mutations of at least 11 different genes can impair insulin secretion. Maturity-onset diabetes of the young accounts for 1 to 3% of diabetes diagnosed under age 30 years (about 0.4% of all diabetes). Maturity-onset diabetes of the young type 2 is associated with a mutation of glucokinase, which acts as a glucose sensor within the β cell. Higher levels of glucose are required to stimulate the release of insulin from the β cell. Maturity-onset diabetes of the young type 3 is due to a mutation of the gene for hepatic nuclear factor 1α, which is involved in early pancreatic development and in the regulation of insulin gene expression. Other forms of maturity-onset diabetes of the young have been described in only a few families.

Polygenic Risk

Common forms of type 2 diabetes are likely polygenic and represent a complex interaction between genes and the environment. More than 100 genetic risk loci collectively explain less than 15% of the heritability of the disorder. Other than rare variants that are unique to specific ethnic groups, the gene with the strongest effect size to date (odds ratio for diabetes, 1.4) is *TCF7L2*, which, like most other recognized gene variants, is associated with reduced insulin secretion. Other risk loci include a β-cell zinc transporter (ZnT-8; odds ratio, 1.15), the sulfonylurea receptor (*KCNJ11*; odds ratio, 1.1), and melatonin receptor 1B (*MTNR1B*; odds ratio, 1.1). A smaller number of gene variants associated with insulin resistance include genes encoding peroxisome proliferator-activated receptor γ (odds ratio, 1.2) and insulin receptor substrate 1 (odds ratio, 1.1). Sequence variants in *SLC16A11*, a gene that is involved in intracellular lipid metabolism, is a relatively common risk allele (odds ratio, 1.29) in Mexican populations.

Epigenetic Risk

Epigenetic changes may play an important role in the development of type 2 diabetes via DNA methylation, histone acetylation, and noncoding RNAs

that regulate gene expression in response to environmental cues. Epigenetic changes can persist for an individual's lifetime and can be passed on over two to three generations. Epidemiologic studies suggest that both fetal starvation and fetal overnutrition predispose to type 2 diabetes in adult life. Some or most of this risk is thought to be due to epigenetic changes in yet-unspecified genes.

Obesity

Nearly 90% of individuals with type 2 diabetes are overweight or obese (Chapter 201), and overweight or obesity is the single most important clinical predictor of type 2 diabetes, particularly for young or middle-aged individuals. For example, women with a body mass index (BMI) 35 kg/m^2 or greater have over a 90-fold higher odds of developing diabetes than do women with a BMI of less than 22 kg/m^2. The relationship between BMI and type 2 diabetes is linear, and an increased risk can be observed even within the BMI range defined as normal (18.5 to 25 kg/m^2).

The distribution of body fat also plays an important role, with abdominal obesity being more predictive. Compared with fat at other sites, abdominal obesity is associated with a higher secretion of proinflammatory cytokines, lower secretion of adiponectin (which is an anti-inflammatory adipokine), and the production of free fatty acids, which contribute to insulin resistance and β-cell failure. Ectopic accumulation of adipose tissue in the liver, often manifested as nonalcoholic fatty liver disease (Chapter 138), is also strongly associated with an increased risk of diabetes. Increased lipid accumulation in pancreatic islets may impair the secretion of insulin.

Other Risk Factors

Sleep deprivation (Chapter 374) is associated with important adverse cardiometabolic outcomes, including weight gain, obesity, diabetes, cardiovascular disease, hypertension, and stress. Cigarette smoking increases the risk of developing type 2 diabetes. For example, men who smoke 25 or more cigarettes per day have a 1.94 increased relative risk of incident diabetes compared with nonsmokers, and risk of developing diabetes increases with the number of cigarettes smoked per day.

CLINICAL MANIFESTATIONS

The clinical presentation of type 2 diabetes is quite variable. Classic symptoms of polyuria, polydipsia, and weight loss occur only in the presence of substantive hyperglycemia, so most patients with mild hyperglycemia (<180 mg/dL [10.0 mmol/L]) may remain asymptomatic for many years.

When the plasma glucose level exceeds the renal threshold for glucose reabsorption (about 180 to 200 mg/dL [10.0 to 11.1 mmol/L]), glycosuria leads to an osmotic diuresis, which is manifested by polyuria. Persistent glycosuria leads to hypovolemia that causes polydipsia, but increased thirst and polyuria may not be noticed because they develop slowly in most individuals. Significant glycosuria can lead to weight loss. Nonspecific symptoms such as fatigue are common.

Due to the insidious onset and delayed recognition, many individuals present with long-term microvascular complications (see later), including retinopathy (Chapter 391), neuropathy (Chapters 384 and 388), and nephropathy (Chapter 109). Among U.S. adults with type 2 diabetes, the prevalence of retinopathy or blindness is almost 12%, the prevalence of chronic kidney disease, defined as albuminuria or reduced renal function, is more than 40%, and the prevalence of diabetic neuropathy is as high as 50%.

Macrovascular complications, including ischemic cardiovascular disease (Chapter 40), heart failure (Chapter 45), peripheral vascular disease (Chapter 65), and cerebrovascular disease (Chapter 376), are the leading causes of morbidity and mortality in people with type 2 diabetes, who have approximately a 2- to 2.5-fold higher risk of developing cardiovascular disease and heart failure. Every 18 mg/dL (1.0 mmol/L) increase in the fasting glucose levels increases the estimated risk of cardiovascular events or death by 17%. Common medical conditions coexisting with type 2 diabetes (e.g., obesity [Chapter 201], hypertension [Chapter 64], and dyslipidemia [Chapter 190]) are important risk factors for cardiovascular disease, but diabetes itself confers independent risk.

DIAGNOSIS

Since most people with type 2 diabetes are asymptomatic for many years, screening of asymptomatic individuals is recommended by age 35 years in persons who have multiple risk factors (Table 210-5) to minimize the development of subsequent microvascular and macrovascular complications. The diagnosis is based on the fasting blood glucose level or the hemoglobin A_{1c} level, occasionally supplemented by an oral glucose tolerance test (see Table 210-2).

TREATMENT

Effective treatment of type 2 diabetes encompasses management of lifestyle interventions (including diet, exercise, and weight control), use of multiple oral or injectable medications, self-management and self-monitoring of blood glucose concentrations, and surveillance and treatment for acute and chronic diabetic complications.

The primary goals of treating type 2 diabetes are to prevent symptomatic hyperglycemia and to prevent the microvascular and macrovascular complications of diabetes by lowering glucose concentrations. The glucose targets should be individualized, based on the patient's life expectancy, prior vascular complications, cardiovascular risk factors, comorbid conditions, risk for hypoglycemia, and cognitive and psychological status. HbA_{1c}, which is considered the gold standard for monitoring chronic glycemia, reflects an average of blood glucose levels over the past 3 months and is associated with the long-term risk for developing long-term diabetes-related complications. In general, lowering the HbA_{1c} level to 7% (53 mmol/mol) or below is an appropriate goal for most individuals, but more stringent glycemic control (HbA_{1c} <6.5% [48 mmol/mol]) may be appropriate for some young people with a short duration of disease if it can be achieved without precipitating excessive hypoglycemia. Less stringent glycemic goals (HbA_{1c} 7 to 8% [53 to 64 mmol/mol]) are appropriate for individuals with a history of severe hypoglycemia, hypoglycemia unawareness, limited life expectancy, advanced renal disease, or extensive comorbid conditions. The HbA_{1c} level should be measured at least semiannually in anyone with diabetes and at least quarterly in those who are not meeting their glycemic target. Generally accepted targets for fasting and postprandial glucose levels are 80 to 130 mg/dL (4.4 to 7.2 mmol/L) and less than 180 mg/dL (10.0 mmol/L), respectively. In persons not on insulin, HbA_{1c} monitoring is generally preferred over home blood glucose monitoring.

Although HbA_{1c} is the cornerstone of monitoring most patients with type 2 diabetes, the HbA_{1c} level does not inform patients about blood glucose values on a daily basis, so measurements of blood glucose levels are often necessary for the day-to-day management, especially in patients who require insulin therapy. Blood glucose levels can be self-monitored using capillary (finger stick) testing, but continuous glucose monitoring, which measures interstitial glucose every 5 to 15 minutes, provides a comprehensive 24-hour glycemic assessment, detects nocturnal hyperglycemia, and may be an option when type 2 diabetes requires insulin therapy. However, this technology is not available for most people with type 2 diabetes, mainly due to cost.

Self-Management Education and Support

The active participation of the affected individual, which is critical for successful management of type 2 diabetes and can improve glycemic control by as much as a 1% (11 mmol/mol) reduction in the HbA_{1c} concentration, reduces the onset and/or progression of diabetic complications and improves quality of life.[17] Initial education and support are typically provided by an expert health professional who addresses the individual's health beliefs, cultural needs, current knowledge, physical limitations, emotional concerns, family support, financial status, health literacy, and other factors that influence the ability to meet the challenges of self-management. The seven major behaviors related to diabetes self-care management include diet, physical activity, monitoring blood glucose concentrations, adherence to proper medication, good problem solving, coping skills, and risk reduction behavior.

Lifestyle intervention provides ongoing counseling, coaching, or individualized guidance to help people with type 2 diabetes to change their diet (Chapter 13), level of physical activity (Chapter 14), or both.[A8] Dietary guidance, preferably by a registered dietician with quarterly follow-up, improves glycemic control, reduces reliance on medication, and helps reduce cardiovascular risk factors by achieving and maintaining modest (approximately 5 to 10% of body weight) weight loss, moderating carbohydrate intake, and avoiding concentrated sweets and foods high in saturated fats and cholesterol (Chapters 13 and 190). A Mediterranean diet (Fig. 13-1), the Dietary Approaches to Stop Hypertension (DASH) diets (Table 13-4), or a vegetarian or vegan diet are safe and effective ways to lose weight, but the Mediterranean diet is best studied for reducing cardiovascular disease events and mortality. However, very low carbohydrate diets must be avoided in patients who are treated with SGLT2 inhibitors or insulin because of the risk of developing diabetic ketoacidosis.

Physical activity (Chapter 14) improves glycemic control and reduces the risk of developing cardiovascular disease in people with type 2 diabetes. The American Diabetes Association recommends at least 150 minutes per week of moderate (50 to 70% of an individual's maximum heart rate) to vigorous (>70% of an individual's maximum heart rate) physical activity for people with type 2 diabetes. For example, walking 1 hour per day improves physical fitness, body composition, and glycemic control in people with type 2 diabetes. Brisk walking for at least 30 min/day (e.g., ≥15 MET-hours per week) improves insulin sensitivity, glycemic control, and the incidence of obesity. Screening stress testing is not recommended in asymptomatic individuals, but some diabetes-related complications may restrict certain activities. For example, vigorous aerobic or resistance exercise can precipitate retinal hemorrhage or detachment in people who have proliferative retinopathy (Chapter 391). Significant sensory loss due to peripheral neuropathy (Chapter 388) can increase the risk of foot injury or falling. People who have poorly controlled diabetes may develop hyperglycemia during

TABLE 210-6 NONINSULIN MEDICATIONS FOR TYPE 2 DIABETES

DRUG	DRUG FORMULATIONS	DOSING	ADVERSE EFFECTS
1. Biguanides (oral): decrease glucose release from liver; decrease intestinal absorption of glucose; improve insulin sensitivity (increase glucose uptake and utilization)			
a. Metformin	500 mg, 850 mg, 1000 mg tablets	Initial: 500 mg twice daily or 850 mg once daily Range: 500-2550 mg	Gastrointestinal symptoms (diarrhea, nausea, upset stomach), metallic taste, lactic acidosis (0.03 cases/1000 people)
	XR: 500 mg, 750 mg tablets	Initial: 500 mg once daily Range: 500-2000 mg once daily	
2. Sodium-glucose cotransporter-2 inhibitors (oral): increase glucose excretion in the urine			
a. Canagliflozin	100 mg, 300 mg tablets	Initial: 100 mg once daily Range: 100-300 mg daily	Urination or urgency, lower blood pressure, dizziness, genital yeast infections, urinary tract infections, increase in blood potassium; rare severe allergic reactions (swelling of tongue, throat, face or body; severe rash); very rare – diabetic ketoacidosis
b. Dapagliflozin	5 mg, 10 mg	Initial: 5 mg once daily Range: up to 10 mg	
c. Empagliflozin	10 mg, 25 mg tablets	Initial: 10 mg once daily Range: up to 25 mg	
3. Glucagon-like peptide-1 agonists: increase insulin secretion, reduce glucose release from liver after meals, delay food emptying from stomach, and promote satiety. Do not use in patients with medullary thyroid cancer.			
a. Liraglutide	3 mL pen that delivers doses of 0.6 mg, 1.2 mg, or 1.8 mg once daily, inject subcutaneously; available as a pen device.	Initial: 0.6 mg SQ Range: up to 1.8 mg SQ	Nausea, headache, hypoglycemia (when used with insulin secretagogue), may cause weight loss, rare reports sudden pancreatitis
b. Exenatide	5 μg or 10 μg by subcutaneous pen device 2 mg sustained release given subcutaneously weekly	Initial: 5 μg twice daily Range: up to 10 μg SQ SQ weekly	
c. Lixisenatide	10 μg or 20 μg by subcutaneous pen device	Initial: 10 μg SQ daily Range: up to 20 μg SQ	
d. Dulaglutide	0.5 mL pen that delivers doses of 0.75 mg, 1.5 mg, 3 mg, or 4.5 mg once weekly; inject subcutaneously	Initial: 1.5 mg weekly SQ (0.75 mg in vulnerable populations) Range: up to 4.5 mg SQ weekly	
e. Semaglutide (SQ injection)	1.5 mL pen that delivers 0.25 mg, 0.5 mg, or 1 mg once weekly, inject subcutaneously	Initial: 0.25 mg weekly SQ Range: up to 1 mg SQ weekly (for obesity this may be up to 2.4 mg weekly)	
f. Semaglutide (oral)	3 mg, 7 mg, or 14 mg tablets	Initial:3 mg orally daily (empty stomach, half a glass of water, then nothing to eat or drink for 30 minutes) Range: up to 14 mg daily	
g. Tirzepatide (GLP/GIP dual receptor agonist)	2.5 mg, 5 mg, 7.5 mg, 12.5 mg, and 15 mg once weekly, inject subcutaneously; available as a pen device	Initial: 2.5 mg SQ weekly Range: up to 15 mg SQ weekly	
4. Dipeptidyl peptidase 4 inhibitors (oral): increase insulin secretion, reduce glucose release from liver after meals			
a. Alogliptin	6.25 mg, 12.5 mg, 25 mg tablets	Initial dose: 25 mg once daily Range: 6.25–25 mg once daily	Stuffy or runny nose, sore throat, headache, upper respiratory infection, rare severe allergic reaction (swelling of tongue, throat, face, or body; severe rash), rare reports of pancreatitis, no weight gain
b. Sitagliptin	25 mg, 50 mg, 100 mg tablets	Initial dose: 100 mg once daily Range: 25-100 mg	
c. Saxagliptin	2.5 mg, 5 mg tablets	Initial dose: 2.5 or 5 mg once daily Range: 2.5-5 mg	
d. Vildagliptin	50 mg tablets	Initial dose: 50 mg once daily Range: up to 50 mg twice daily	
e. Linagliptin	5 mg tablets	5 mg once daily	
5. Selected single-pill combinations			
a. Sitagliptin/metformin	50 mg/500 mg, 50 mg/1000 mg	Initial: 50 mg/500 mg or 50 mg/1000 mg twice daily Range: up to 100 mg/2000 mg	Stuffy or runny nose, sore throat, headache, upper respiratory infection, rare severe allergic reaction (swelling of tongue, throat, face, or body; severe rash), rare reports of pancreatitis, no weight gain
b. Sitagliptin/metformin XR	50 mg/500 mg, 50 mg/1000 mg tablets	Initial: 100 mg/1000 mg daily Range: up to 100 mg/200 mg	
c. Saxagliptin/metformin XR	5 mg/500 mg, 5 mg/1000 mg, 2.5 mg/1000 mg	Initial: 5 mg/500 mg or 5 mg/1000 mg once daily Range: up to 5 mg/2000 mg	
6. Insulin secretagogues (oral): sulfonylureas			
a. Tolbutamide	500 mg tablets two to three times daily	Initial: 1000-2000 mg daily Range: 250-2000 mg	Hypoglycemia and weight gain
b. Glimepiride	1 mg, 2 mg, 4 mg tablets once daily	Initial: 1-2 mg Range: 1-8 mg	
c. Gliclazide	40 mg or 80 mg tablets up to twice a day	Initial: 40 mg once daily Range: up to 160 mg twice daily	
d. Glipizide	5 mg, 10 mg tablets once or twice daily	Initial: 5 mg Range: 2.5-40 mg[2]	
e. Glyburide/glibenclamide	1.25 mg, 2.5 mg, 5 mg tablets once or twice daily	Initial: 2.5-5 mg daily Range: 1.25-20 mg[2]	

TABLE 210-6 NONINSULIN MEDICATIONS FOR TYPE 2 DIABETES—cont'd

DRUG	DRUG FORMULATIONS	DOSING	ADVERSE EFFECTS
7. Insulin secretagogues (oral): glinides			
a. Repaglinide	0.5 mg tablets taken two, three, or four times daily	Initial: 1-2 mg daily (0.5 mg if A_{1c} <8%) Range: 0.5-16 mg Maximum dose per meal is 4 mg	Hypoglycemia
b. Nateglinide	60 mg or 120 mg three times daily	Initial: 120 mg three times daily (if A_{1c} close to goal, use 60 mg)	
8. Alpha-glucosidase inhibitors (oral): starch blockers—delay digestion and absorption of carbohydrates			
a. Acarbose	25 mg, 50 mg, 100 mg tablets three times daily	Initial: 25 mg three times daily Range: 75-300 mg (max 150 mg if <60 kg)	Flatulence
9. Thiazolidinediones (oral): decrease insulin resistance in the body (muscle and fat tissues)			
a. Pioglitazone (preferred over rosiglitazone)	15 mg, 30 mg, 45 mg	Initial: 15-30 mg daily Range: 15-45 mg, once daily	Anemia, edema from fluid retention, weight gain, macular edema, bone loss and fractures in women; may cause or worsen heart failure; cannot use if have liver problems or severe heart failure; requires liver monitoring. Possible risk of excess cardiovascular death with rosiglitazone
b. Rosiglitazone	2 mg, 4 mg, 8 mg once or twice daily	Initial: 4 mg daily Range: 4-8 mg	

SQ = subcutaneous; XL = extended release.

Adapted from Diabetes Education Online, Type 2 Non-Insulin Therapies: Table of Medications. Diabetes Teaching Center at the University of California, San Francisco. https://dtc.ucsf.edu/types-of-diabetes/type2/treatment-of-type-2-diabetes/medications-and-therapies/type-2-non-insulin-therapies/table-of-medications/. Accessed April 20, 2022. These illustrations are made available by written permission of The Regents of the University of California. All rights reserved.

exercise due to the production of counter-regulatory hormones, such as growth hormone, epinephrine, or cortisol, whereas individuals who are treated with insulin and insulin secretagogues could develop hypoglycemia. Adjustment in the dosage of medications and monitoring of blood glucose levels during exercise is a prudent precautionary measure.

Moderate alcohol consumption is not prohibited, with the proper consideration of calorie intake (7 kcal/g) and hypoglycemic risk if alcohol is consumed without food, particularly in persons who are insulin-treated. However, excess alcohol intake can contribute to weight gain, hypertension, cardiomyopathy, and atrial fibrillation, as well as peripheral neuropathy, fatty liver, and dementia. Individuals should consume no more than 1 to 2 drinks per day (women, ≤1 drink per day; men, ≤2 drinks per day or 12 ounces of beer, 5 ounces of wine, or 1.5 ounces of distilled spirits). Cigarette smoking (Chapter 363) substantially increases the risk of microvascular and macrovascular complications in patients with type 2 diabetes, and smoking cessation substantially reduces this risk.

Pharmacologic Therapy

Although weight control, physical activity, and nutrition form the foundation of effective management, most people with type 2 diabetes will require pharmacologic treatments, often multiple, to maintain recommended levels of glycemic control. Antidiabetic drugs can be categorized as agents that reduce excessive endogenous glucose production (gluconeogenesis) in the liver; stimulate the pancreas to secrete insulin; improve the sensitivity of peripheral tissues to insulin; enhance the effect of incretin; increase glycosuria; address other targets; or directly provide insulin or its analogues (Table 210-6). Monotherapy with most noninsulin antidiabetic agents can reduce HbA_{1c} concentrations by 0.5 to 2.0% (5 to 22 mmol/mol), so it is unlikely that any single agent will achieve the glycemic target in people who have an HbA_{1c} concentration greater than 8.5% (69 mmol/mol).[18]

Guidelines recommend a hierarchical, individualized approach to pharmacological therapy based on treatment goals; the patient's comorbid conditions; and the drug's potency, side effect profile, ease of administration, cost, and convenience (Fig. 210-3). General agreement suggests that metformin should be the initial therapy for most patients and that subsequent drugs (when needed) should be added to, but not replace, metformin, unless it is contraindicated or not tolerated. Lowering of glucose levels per se has not been shown to reduce future cardiovascular events in type 2 diabetes,[A9] but specific drugs have documented cardiovascular or renal benefits (e.g., SGLT2 inhibitors and sometimes glucagon-like peptide-1 receptor agonists) and therefore are preferred for patients with or at risk for these conditions, independent of their HbA_{1c} concentration.[19,20]

First-Line Drugs

Metformin

The biguanide drug metformin is the most widely used antidiabetic medication and is considered the preferred initial therapy for people with type 2 diabetes. Metformin lowers blood glucose by reducing the hepatic glucose gluconeogenesis, but it also may enhance insulin sensitivity and limit intestinal absorption of glucose. Metformin can reduce HbA_{1c} by 1.0 to 1.5% (11 to 16 mmol/mol) and reduce body weight; it also decreases the likelihood of cardiovascular events and death in obese individuals with type 2 diabetes. Since metformin does not increase insulin secretion, it does not increase the risk of hypoglycemia unless it is combined with insulin or insulin secretagogues.

The main adverse effects of metformin are gastrointestinal (bloating, nausea, diarrhea), but starting with a small dose (500 mg once or twice daily with meals) and gradually increasing the dose are effective ways to reduce adverse reactions. Metformin is cleared by renal filtration, so its dose should be limited to no more of 2550 mg/day, and it should not be used if the estimated glomerular filtration rate (eGFR) is less than 30 mL/minute. Metformin also should be temporarily discontinued when individuals undergo angiography with iodinated contrast agents. Metformin may increase the risk of lactic acidosis, and long-term use of metformin has been associated with vitamin B_{12} deficiency and worsening of symptoms of neuropathy, thereby suggesting that periodic testing of the vitamin B_{12} level should be performed in patients on long-term metformin therapy.

Sodium-Glucose Cotransporter 2 Inhibitors

Sodium-glucose cotransporter-2 (SGLT2) inhibitors lower blood glucose by reducing renal reabsorption of glucose at the S1 segment of proximal tubules in the kidney.

This increased urinary loss aids in controlling blood glucose concentrations, lowering body weight by 1 to 3 kg, and reducing blood pressure. SGLT2 inhibitors reduce HbA_{1c} concentrations by approximately 0.5 to 1.0% (5 to 11 mmol/mol) and reduce the risk of major adverse cardiovascular events (including cardiovascular death, acute myocardial infarction, and stroke),[A10,A11] renal events,[A12–A14] and hospitalization rates for heart failure (Chapter 46).[A15,A16] Based on their cardio-renal protective effects, SGLT2 inhibitors are now considered the second drug for type 2 diabetes after metformin in patients who have atherosclerotic cardiovascular disease, heart failure, or chronic kidney disease.

Since SGLT2 inhibitors require glomerular filtration for their glucose-lowering effect, their action diminishes if the eGFR is less than 45 mL/min. Similarly, glycosuria with SGLT2 inhibition is attenuated in patients without hyperglycemia. This primary renal effect of SGLT2 inhibitors is independent of insulin, so the risk of hypoglycemia is small. The weight reduction, which results from the glycosuria, is largely explained by loss of fat mass.

SGLT2 inhibitor-mediated natriuresis and glucosuria lower cardiac preload and reduce pulmonary congestion and systemic edema. SGLT2 inhibitors reduce albuminuria, slow the decline in eGFR, and lower rates of clinically relevant renal events, including progression toward end-stage renal disease (Chapter 109).

SGLT2 inhibitors are associated with an increased risk for genital mycotic infections and urinary tract infections, largely because of the increased urinary excretion of glucose. SGLT2 inhibitors are also associated with increased risk of diabetic ketoacidosis, especially when used in patients with type 1 diabetes but also in type 2 diabetes,[21] because the glucose-lowering effect leads to lower insulin secretion and a subsequent increased intrinsic ketogenesis related to the increased secretion of glucagon and the promotion of lipolysis.

Glucagon-Like Peptide-1 Receptor Agonists

Glucagon-like peptide-1 receptor agonists, which are peptide derivatives of either exendin-4 or human glucagon–like peptide-1, are designed to resist degradation by the enzyme dipeptidyl peptidase 4. These agents bind with specificity to the glucagon-like peptide-1 receptor to stimulate glucose-dependent

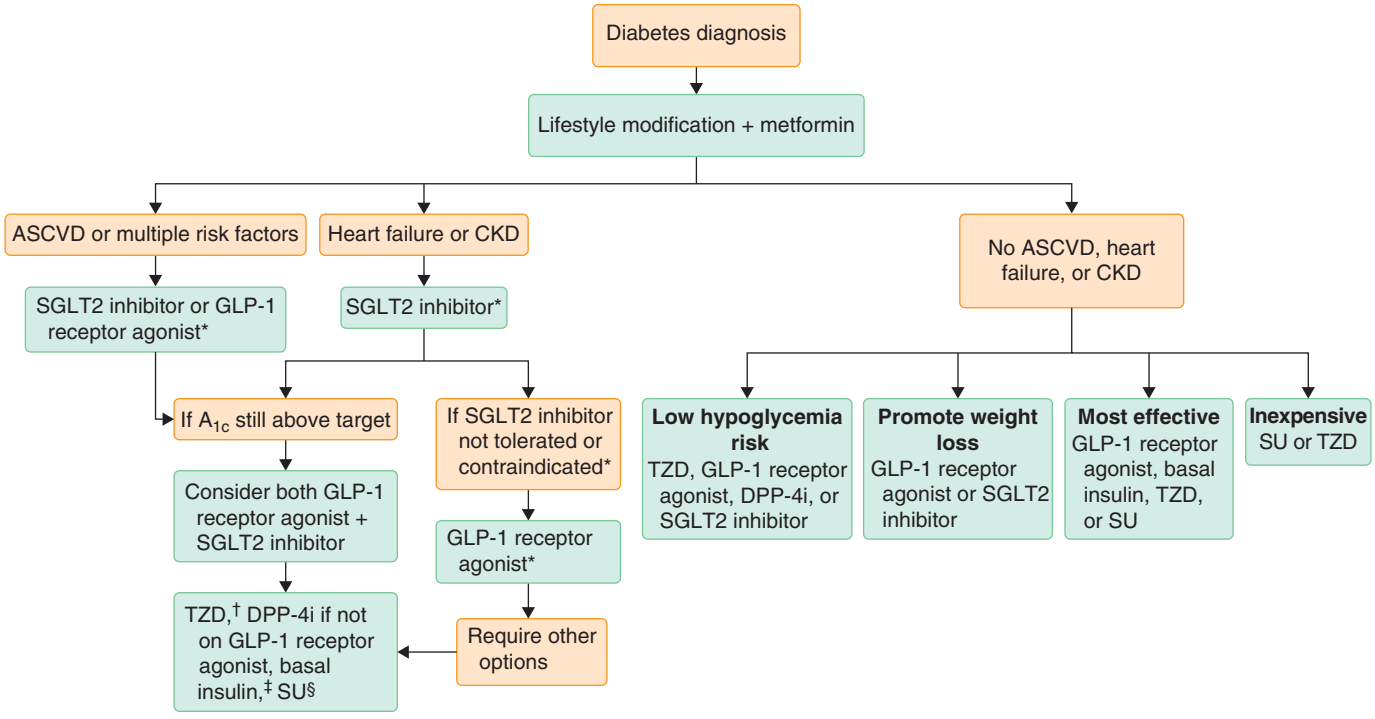

FIGURE 210-3. Algorithm for pharmacologic treatment of type 2 diabetes. *Choose drug with proven benefit for this indication (see text). †Low dose may be better tolerated though less well studied for CVD effects. ‡Degludec and U-100 glargine have demonstrated CVD safety. §Choose later-generation SU to lower risk of hypoglycemia; glimepiride has shown similar cardiovascular safety to DPP-4i. ASCVD = atherosclerotic cardiovascular disease; CKD = chronic kidney disease; CVD = cardiovascular disease; DPP-4 = dipeptidyl peptidase 4; DPP-4-i = DPP-4 inhibitor; GLP-1 = glucagon-like peptide 1; SGLT-2 = sodium-glucose cotransporter-2; SU = sulfonylurea; TZD = thiazolidinedione.

insulin release from the pancreatic β cells. These agents enhance the secretion of insulin and inhibit the secretion of glucagon in a glucose-dependent manner, delay gastric emptying, and reduce food intake via central suppression of appetite. The longer half-life of the newer glucagon-like peptide-1 receptor agonists allows for once-weekly administration.

Compared with placebo, these agents reduce HbA_{1c} by about 1 to 1.2% (11 to 13 mmol/mol). Glucagon-like peptide-1 receptor agonists also reduce body weight by about 6 percentage points in obese individuals with type 2 diabetes,[A17] triglyceride levels, and blood pressure. In people with type 2 diabetes and established cardiovascular disease or multiple cardiovascular risk factors, liraglutide, dulaglutide, and semaglutide significantly reduce the incidence of major adverse cardiovascular events, including acute myocardial infarction, cardiovascular death, and stroke compared with placebo,[A18] and guidelines recommend them in individuals who have a history of cardiovascular disease or major risk factors for it. The risk of hypoglycemia is low with monotherapy but higher when these agents are used in combination with sulfonylureas or insulin. Once-daily oral semaglutide, which is approved in many parts of the world, reduces the HbA_{1c} level (a mean reduction of 0.8 to 1.3% [9 to 14 mmol/mol]) and significantly reduces body weight by 2 to 4 kg compared with placebo[A19] and also reduces cardiovascular events.[A20] As with injectable forms, the oral formulation is associated with significant gastrointestinal adverse events, including nausea, emesis, and diarrhea, which occur mostly in the initial stage of treatment and gradually diminish over time.

Tirzepatide, which is a dual glucose-dependent insulinotropic polypeptide and glucagon-like peptide-1 receptor agonist, is a once-weekly subcutaneous agent that is more effective than pure glucagon-like peptide-1 receptor agonists for weight loss and reducing HbA_{1c} levels.[A21] It is useful as an adjunct to insulin[A22] or instead of insulin in difficult-to-control patients.[A23,A24]

Dipeptidyl Peptidase 4 Inhibitors

Endogenous glucagon-like peptide-1, which is secreted by L cells in the small intestine in response to the presence of food in the gastrointestinal tract, exerts a variety of glucoregulatory effects, including secretion of insulin, inhibition of the release of glucagon, and promotion of satiety. In people with type 2 diabetes, however, the effects of glucagon-like peptide-1 are significantly impaired, thereby greatly reducing the capacity to release insulin in response to the intake of food. Glucagon-like peptide-1 is rapidly degraded by the dipeptidyl peptidase 4 enzyme, thereby resulting in a half-life of less than 2 minutes. By inhibiting the dipeptidyl peptidase 4 enzyme, these inhibitors increase circulating concentrations of endogenous glucagon-like peptide-1, increase the secretion of insulin, and reduce the secretion of glucagon. These agents lower HbA_{1c} by 0.5 to 1.0% (5 to 11 mmol/mol), and their safety profile is generally favorable.

Dipeptidyl peptidase 4 inhibitors can be used as monotherapy when metformin is contraindicated or not tolerated or, more commonly, as add-on therapy (including as fixed-dose combinations; see Table 210-6) either initially or when metformin is insufficient. Dipeptidyl peptidase 4 inhibitors are body weight neutral and can be used in patients with liver failure. They are safe from a cardiovascular perspective; but, unlike SGLT-2 inhibitors and glucagon-like peptide receptor agonists, they do not reduce cardiovascular events.[A25] As a result, they are less preferred than these other two agents. Most agents can be used in persons with impaired renal function, but, except for linagliptin, dose adjustment is needed when used in patients with renal dysfunction (i.e., an eGFR <50 mL/minute/1.73 m^2). Dipeptidyl peptidase 4 inhibitors should be discontinued if a glucagon-like peptide-1 receptor agonist is used.

Second-Line Drugs

Insulin Secretagogues

The main pharmacologic effect of the insulin secretagogues, including the sulfonylureas and the glinides, is to increase insulin concentrations by stimulating the secretion of insulin from pancreatic β cells. These agents bind to the ATP-sensitive potassium channel in the β-cell membrane (see E-Fig. 210-1), thereby resulting in membrane depolarization and, ultimately, release of insulin from preformed secretory granules. Oral sulfonylureas are inexpensive, once- or twice-daily medications that, when used in monotherapy, reduce HbA_{1c} concentrations by 1.0 to 1.5% (11 to 16 mmol/mol). However, they are less effective when they are added to other medications. The main side effect of the sulfonylureas is hypoglycemia, which can be more severe and prolonged than that produced by insulin, particularly when longer-acting formulations such as glyburide/glibenclamide are used in the elderly. They are also associated with weight gain. Sulfonylureas have a primary failure rate of 20% and a secondary failure rate of 5 to 10% per year of treatment, probably due to apoptosis of β cells.[A26]

Thiazolidinediones

Thiazolidinediones decrease blood glucose levels primarily by improving insulin-mediated glucose uptake in peripheral tissues and by reducing the hepatic production of glucose. They bind to a nuclear receptor, peroxisome proliferator-activated receptor γ, and thus regulate the transcription of a variety of genes involved in carbohydrate and lipid metabolism. Thiazolidinediones do not cause hypoglycemia when used alone, but they may increase the risk of low blood glucose when used in combination with insulin or insulin secretagogues.

Thiazolidinediones as monotherapy can decrease HbA_{1c} by about an absolute 1% (11 mmol/mol). They reduce the risk of all-cause mortality, nonfatal myocardial infarction, and stroke in diabetic patients with cardiovascular disease. However, thiazolidinediones are associated with significant weight gain and edema, especially when used in combination with insulin, as well as an increased risk of macular edema and heart failure. Thiazolidinediones are contraindicated in patients who have active liver disease, except they can be useful in patients with nonalcoholic steatohepatitis. Thiazolidinediones also have been linked to osteoporosis and an increased risk of fracture of distal long bones, so they must be used cautiously or not at all in patients who have risk factors for osteoporosis. They also should be avoided in patients who have uninvestigated hematuria.

α-Glucosidase Inhibitors

The α-glucosidase inhibitors (e.g., acarbose and voglibose) reduce postprandial blood glucose by inhibiting the absorption of carbohydrates in the upper small intestine and can be helpful for patients who consume carbohydrates as their main food ingredient and experience postprandial hyperglycemia. In patients who are newly diagnosed with diabetes, acarbose 300 mg/day has a similar hypoglycemic effect to that of metformin 1500 mg/day. Reduction of the absorption of carbohydrates increases the disaccharide load in the colon and may lead to gaseous distention and flatulence that some individuals may tolerate poorly. Starting with a small dose and gradually increasing the dose may reduce this adverse effect. These agents are administered at the beginning of each meal and are contraindicated in patients who have inflammatory bowel disease, partial bowel obstruction, or severe renal or hepatic disease. The risk of hypoglycemia is very low when these agents are used alone, but patients must be instructed to use glucose or honey to correct hypoglycemia because dietary sucrose, complex sugars, and starchy foods will be poorly absorbed.

Insulin

Insulin treatment can be considered for people with type 2 diabetes at any stage but is usually reserved for when other therapies fail. Since progressive pancreatic β-cell failure progressively reduces the secretion of insulin, many, if not most, people who have type 2 diabetes ultimately may require insulin therapy to achieve and maintain adequate glycemic control. In addition, short-term (2 weeks to 3 months) intensive insulin treatment may be helpful when newly diagnosed individuals with type 2 diabetes have a HbA_{1c} 9.0% (75 mmol/mol) or higher with symptomatic hyperglycemia (polyuria, polydipsia, and weight loss). Insulin also is often indicated in critically ill or hospitalized hyperglycemic patients to maintain adequate glycemic control. As with type 1 diabetes, insulin treatment is ideally managed by an endocrinologist or in close collaboration with an endocrinologist in locales where an endocrinologist may not be readily accessible.

In people with uncontrolled type 2 diabetes treated with noninsulin antidiabetic agents, supplemental insulin glargine results in similar improvement in glycemic control but less hypoglycemia compared with NPH insulin. Premixed human insulin also is equally efficacious and is associated with less weight gain and hypoglycemia compared with NPH insulin.

Daily insulin requirements tend to be higher for people with type 2 diabetes compared with type 1 diabetes as a reflection of insulin resistance. Use of concentrated insulin preparations (e.g., U-200 lispro, U-200 degludec, U-300 glargine, U-500 regular) may be helpful in persons who are insulin resistant and require insulin doses exceeding 100 units per day. Once-weekly insulin is currently in development but is not yet licensed. Among patients who have type 2 diabetes and are at high risk for cardiovascular events, degludec reduces hypoglycemic events compared with glargine but is no better for reducing the incidence of major cardiovascular events.[A27]

Bariatric Surgery

Bariatric surgery (Chapter 201) is more successful than medical therapy for people living with severe obesity. In such individuals, it reduces hepatic steatosis and improves glycemic control, blood pressure, lipids, and almost all other cardiovascular risk factors, thereby allowing for medications to be reduced or sometimes even discontinued.[A28] Bariatric surgery also is associated with a reduction in all-cause mortality in patients who have severe obesity.[22] As a result, it should be recommended for such patients.

Metabolic Monitoring

Ongoing assessment of glycemic control is necessary to ensure optimal outcomes in people with type 2 diabetes. Measurement of HbA_{1c}, which reflects mean glucose levels during the preceding 2- to 3-month period, should be performed twice yearly in stable patients but quarterly in persons whose therapy has been recently changed or who are not meeting glycemic goals. Self-monitoring of blood glucose levels, and preferably continuous glucose monitoring,[A29] is recommended for anyone using insulin and may be useful for individuals who are trying to achieve target glucose control.[23]

PREVENTION

Individuals with risk factors for type 2 diabetes, especially individuals who are overweight or obese,[24] should be considered for screening with an HbA_{1c} level or a fasting glucose concentration even though screening has not been proven to reduce subsequent mortality.[A30] Screening will also allow identification of people with prediabetes, who may benefit from preventive interventions (Table 210-7).

Lifestyle intervention stressing modest weight reduction (minimum 7% of body weight) with a reduced fat, hypocaloric diet and moderate-intensity physical activity for 150 minutes/week (http://www.bsc.gwu.edu/dpp/lifestyle/dpp_part.html) can reduce incident diabetes by about 60% over 3 years and about one-third longer term. Successful weight loss is the major predictor of benefit, with every kilogram of weight loss reducing the risk of diabetes by about 15%. Primary care–led weight management programs[A31] and the use of locaserin[A32] can reduce hyperglycemia and lead to remission of type 2 diabetes. Even among individuals who do not lose weight, achieving the physical activity goal can reduce the risk of diabetes. Data also suggest that lowering blood pressure may reduce the onset of type 2 diabetes, with each 5 mm Hg reduction in systolic blood pressure from angiotensin-converting enzyme (ACE) inhibitors or angiotensin receptor blockers reducing the risk by about 15% and other medications not helpful.[A33]

Metformin (up to 1 g twice daily) and the α-glucosidase inhibitor acarbose (up to 100 mg three times daily) can reduce the short-term risk of diabetes by about 25%. Liraglutide used at the dose approved for weight loss (3 mg/day) can reduce incident diabetes by about 20% in overweight patients with prediabetes. The thiazolidinediones can prevent or delay the onset of diabetes but are not used for this purpose because of concerns about their long-term safety. Whether these interventions to prevent or delay the onset of diabetes will result in lower rates of microvascular or macrovascular complications remains to be determined. For this reason, none of these drugs is approved by the U.S. Food and Drug Administration to prevent diabetes.

TABLE 210-7 CRITERIA FOR DIABETES SCREENING IN ASYMPTOMATIC ADULTS

1. Overweight or obese (BMI >25 kg/m^2) with one or more of the following:
   - First-degree relative with type 2 diabetes
   - High-risk race/ethnicity (e.g., African American, Latino, Native American, Asian American, Pacific Islander)
   - History of cardiovascular disease
   - Hypertension
   - HDL cholesterol level <35 mg/dL or triglyceride level >250 mg/dL
   - Women with polycystic ovary syndrome
   - Physical inactivity
   - Other clinical conditions associated with insulin resistance

   Screening should begin at age 45 and be repeated at least every 3 years
2. Patients with prediabetes (HbA_{1c} ≥5.7%, IGT, or IFG) should be tested annually
3. Women with a history of gestational diabetes should be tested at least every 3 years

BMI = body mass index; HDL = high-density lipoprotein; IFG = impaired fasting glucose; IGT = impaired glucose tolerance.

Modified from American Diabetes Association. Standards of care in diabetes—2023. *Diabetes Care.* 2023;46(Suppl 1):S97-S110.

PROGNOSIS

Type 2 diabetes is a chronic and, in most cases, progressive condition with potentially serious health consequences similar to those that affect patients with type 1 diabetes (see later). However, substantial evidence indicates that early intervention with a multifactorial approach to achieve and to maintain metabolic control, combined with aggressive control of cardiovascular risk factors, can substantially reduce the burden of diabetes and improve quality of life. In people who have type 2 diabetes, life expectancy at age 50 years is 6 years lower, on average, than in people without diabetes.

GESTATIONAL DIABETES

Diabetes that appears for the first time during pregnancy and typically regresses after delivery is termed gestational diabetes (Chapter 221). Hyperglycemia is usually detected in the late second trimester (13 to 26 completed weeks of gestation) or in the third trimester (27 to 40 weeks) and resolves following delivery. Gestational diabetes affects approximately 6% of pregnant women in the United States, with a prevalence ranging from 1 to 25% depending on the ethnicity of the mother and the criteria used for the diagnosis. Women who develop gestational diabetes usually have risk factors including overweight or obesity, older age (>30 years), and a family history of type 2 diabetes (see Table 210-5).

Physiologic insulin resistance occurs during pregnancy because the placenta secretes diabetogenic hormones, such as growth hormone, corticotropin-releasing hormone, human placental lactogen, and progesterone. In a normal pregnancy, women have a 60% reduction in insulin sensitivity. In women with normal pancreatic function, the pancreas can compensate by secreting enough insulin to offset this physiologic insulin resistance of pregnancy. The inability to overcome the insulin resistance of pregnancy despite β-cell hyperplasia leads to gestational diabetes. Women who have gestational diabetes are at increased risk of serious perinatal complications, including gestational hypertension, preeclampsia, polyhydramnios, and need for cesarean section.

Offspring born to mothers with gestational diabetes are at increased risk for having fetuses that have large-for-gestational-age birth weights, which increase birth complications, including the risk of congenital malformations, need for cesarean delivery, shoulder dystocia, and birth injury. The risks of spontaneous abortion, fetal demise, neonatal hypoglycemia, and neonatal hyperbilirubinemia are also increased. Intrauterine exposure to diabetes increases the fetus's future risk of developing obesity and type 2 diabetes.[25]

DIAGNOSIS

All pregnant women should be screened for gestational diabetes at 24 to 28 weeks' gestation. Gestational diabetes can be diagnosed with either the one-step or the two-step approach using the oral glucose tolerance test (see Chapter 221).

TREATMENT

Aggressive glycemic control reduces adverse pregnancy outcomes, including macrosomia and traumatic delivery. Women should self-monitor their fasting and postprandial glucose concentrations to achieve glycemic control. Current guidelines recommended targets that women with gestational diabetes target a fasting glucose less than 95 mg/dL (5.3 mmol/L), a 1-hour postprandial glucose level less than 140 mg/dL (7.8 mmol/L), or a 2-hour postprandial glucose less than 120 mg/dL (6.7 mmol/L). Lifestyle intervention, comprising dietary modification, physical activity, and weight management, is essential and is sufficient to achieve blood glucose targets in as many as 70 to 85% of women. If blood glucose targets are not achieved with lifestyle intervention, the addition of glucose-lowering therapy as for type 2 diabetes (see Chapter 221 and earlier in the text) is warranted. Most hypoglycemic medications are contraindicated in pregnancy. Although metformin appears to be preferable to insulin therapy, escalation to insulin is often required.[A34]

PROGNOSIS

For a woman with gestational diabetes, the lifetime odds of developing type 2 diabetes are up to 20 times higher, and nearly 50% of these women will develop impaired glucose metabolism within 10 years of having gestational diabetes.[26] In addition to the higher risk of diabetes, women with a history of gestational diabetes also have a cluster of cardiovascular disease risk factors such as obesity, hypertension, and dyslipidemia.

ACUTE ISSUES FOR INDIVIDUALS WITH DIABETES

INPATIENT MANAGEMENT OF DIABETES

During hospitalization, both hyperglycemia and hypoglycemia are associated with adverse outcomes. Most people who have type 1 diabetes and who are well enough to do so can be managed with their usual insulin injection regimen during hospitalization, but extra attention should be paid to the risk of hypoglycemia because of missed or delayed meals.[27] Insulin pump therapy can be continued during hospitalization if the individual is able to direct its use and hospital personnel are sufficiently familiar with this form of treatment.

For non–critically ill hospitalized patients with type 2 diabetes, chronic diabetes medications may need to be altered. Subcutaneous insulin is preferred to maintain a fasting glucose concentration target below 140 mg/dL (7.8 mmol/L) and a random or postprandial glucose concentration to below 180 mg/dL (10 mmol/L), if these goals can be achieved with a minimal risk of hypoglycemia. Basal insulin (see Table 210-4) is sufficient for many people with type 2 diabetes, but some may require additional prandial or corrective doses of short-acting insulin.

For critically ill people with type 1 and type 2 diabetes, intensive glucose control can be harmful, particularly when it is accompanied by hypoglycemia. For critically ill patients in intensive care settings, a variable-rate intravenous insulin infusion should be titrated to maintain the plasma glucose concentration between 140 and 180 mg/dL (7.8 to 10.0 mmol/L).

Prolonged dependence on subcutaneous or variable rate intravenous insulin infusions ("sliding scales") should be avoided because of the increased risk of hypoglycemia. Persons with type 1 diabetes should return to their usual outpatient doses of insulin as soon as they are eating and drinking normally. For individuals who have with stable type 2 diabetes and who are eating consistent meals and for patients who are nearing hospital discharge, resumption of their usual oral or noninsulin injectable medications can also be considered, assuming that their preadmission glycemic control was adequate. However, the safety of SGLT2 inhibitors in inpatients remains unknown.

HYPOGLYCEMIA

EPIDEMIOLOGY

Hypoglycemia (Chapter 211), which in diabetes is always iatrogenic or due to accidental or intentional overdose, is the most frequent and serious adverse effect of insulin therapy,[28] especially in type 1 diabetes in which it accounts for about 2 to 6% of all deaths. On average, people with type 1 diabetes experience two episodes of symptomatic hypoglycemia per week and one episode of temporarily severe (i.e., requiring third-party assistance) hypoglycemia per year. Risk factors for hypoglycemia (Table 210-8) include strict glycemic control, exercise, and a mismatch between carbohydrate intake and the insulin dose.

Episodes of severe hypoglycemia also become progressively more common in people with a longer duration of type 2 diabetes, due in part to progressive β-cell failure and increased dependence on pharmacologic treatments. These risks are especially pronounced when sulphonylureas or insulin are being used aggressively in an attempt to achieve inappropriately tight glycemic control. Antidiabetic agents such as metformin, the thiazolidinediones, and incretin-based drugs (dipeptidyl peptidase-4 inhibitors, glucagon-like peptide-1 and glucagon-like peptide/gastric inhibitory polypeptide receptor agonists) are associated with measurable, albeit low, risks of hypoglycemia, but symptomatic hypoglycemia is rare unless these drugs are used in combination with insulin or sulfonylureas. The elderly are at particularly high risk for iatrogenic hypoglycemia because the intensity of reactive adrenergic symptoms may be reduced, so the degree of hypoglycemia-induced cognitive impairment may be greater.

PATHOBIOLOGY

Iatrogenic hypoglycemia usually occurs when a mismatch between insulin concentrations and carbohydrate intake develops, usually in the presence of a compromised counter-regulatory physiologic defense against a falling plasma glucose concentration. The dose of the insulin secretagogue or insulin itself may not be excessive, but factors such as missed meals, exercise, recent weight loss, or alcohol may lead to a fall in the plasma glucose concentration. Conventional risk factors for hypoglycemia include inadequate caloric consumption (skipped or delayed meals, malnutrition), increased insulin sensitivity (weight loss, exercise, medications), impaired glucose production (alcohol intake, liver, or renal disease), or decreased insulin clearance (renal failure).

In people with type 1 diabetes, the release of counter-regulatory hormones (catecholamines and glucagon) to stimulate hepatic glycogenolysis and gluconeogenesis in the liver and kidney in response to low glucose levels becomes sluggish and even defective over time. People who have recurrent hypoglycemic episodes, especially patients with liver disease or alcohol use disorder, may have insufficient liver glycogen to mount a gluconeogenic response in the face of rising concentrations of counter-regulatory hormones. Furthermore, in people with type 1 diabetes, the release of glucagon during hypoglycemia may become impaired shortly after the onset of diabetes. The release of epinephrine during hypoglycemia also becomes progressively defective. This

TABLE 210-8 RISK FACTORS FOR HYPOGLYCEMIA

Medical issues
- Strict glycemic control
- Previous history of severe hypoglycemia
- Long duration of type 1 diabetes
- Duration of insulin therapy in type 2 diabetes
- Lipohypertrophy at injection sites
- Impaired awareness of hypoglycemia
- Severe hepatic dysfunction
- Impaired renal function (including patients on dialysis)
- Sepsis
- Inadequate treatment of previous hypoglycemia
- Terminal illness
- Cognitive dysfunction/dementia
- C-peptide negativity

Lifestyle issues
- Increased exercise (relative to usual)
- Increasing age
- Alcohol
- Early pregnancy
- Breast-feeding
- No or inadequate blood glucose monitoring

Reduced carbohydrate intake/absorption
- Food malabsorption (e.g., gastroenteritis, celiac disease, gastroparesis)
- Bariatric surgery involving bowel resection

Endocrine disorders
- Hypoadrenalism
- Growth hormone deficiency
- Hypothyroidism
- Hypopituitarism

TABLE 210-9 THE EDINBURGH HYPOGLYCEMIA SCALE

AUTONOMIC	NEUROGLYCOPENIC	GENERAL MALAISE
• Sweating • Palpitations • Shaking • Hunger	• Confusion • Drowsiness • Odd behavior • Speech difficulty • Incoordination	• Headache • Nausea

decrease in the epinephrine response during hypoglycemia is accompanied by an attenuated autonomic neural response, which results in the clinical syndrome of impaired awareness of hypoglycemia. In the absence of autonomic symptoms, mild hypoglycemia may proceed unnoticed, without the usual warning signs that would alert an individual to a falling glucose level. In this vicious cycle, hypoglycemia begets hypoglycemia and an increased risk for severe hypoglycemia.

CLINICAL MANIFESTATIONS

The normal counter-regulatory response to hypoglycemia results in typical adrenergic and neuroglycopenic hypoglycemia symptoms (Table 210-9). Should the glucose level continue to drop, then the individual may become progressively more confused, eventually lose consciousness, have seizures, and may die. Cardiovascular consequences may include cardiac arrhythmias, prolongation of the QTc interval, repolarization abnormalities, and abnormalities in coagulation and inflammation, with an increased risk of atherosclerotic and vascular events, including acute myocardial infarction and stroke.

Hypoglycemia (Chapter 211) affects the daily lives of persons with diabetes and can have a dramatic effect on quality of life. It can induce great fear, preclude comfortable engagement in routine activities (e.g., driving, uninterrupted sleep), and lead the person with diabetes and their clinician to set higher glycemic targets, limit treatment, particularly with insulin, and hence accept poorer metabolic control. If prolonged, this undertreatment can increase the risk of other diabetes complications.

Nocturnal hypoglycemia (or hypoglycemia during sleep at any time) may be asymptomatic and unsuspected because the plasma glucose concentration is rarely measured during the night unless using a continuous glucose monitor. Some people with nocturnal hypoglycemia present with sleep disturbances, morning headache, chronic fatigue, or depression. Risk factors for nocturnal hypoglycemia include increased physical activity in the previous 24 hours, certain insulin regimens (e.g., use of NPH or regular insulin leads to a higher risk compared with the short- or long-acting insulin analogues), meal content (e.g., higher fat content leads to slower gut transit time, thereby increasing the risk of hypoglycemia), and alcohol consumption (alcohol prevents glycogenolysis, thereby increasing the risk of hypoglycemia). In addition, sleep is associated with a decrease in the autonomic response to hypoglycemia.

DIAGNOSIS

The threshold plasma glucose value that results in hypoglycemic symptoms is not constant; it is lower after recent antecedent hypoglycemia and higher in persons with poor glycemic control. Furthermore, the same individual may experience symptoms at different glucose concentrations depending on what they are doing. However, a self-monitored glucose of 70 mg/dL (3.9 mmol/L) or less should alert the person with diabetes or their caregiver, regardless of the presence of symptoms.

Iatrogenic hypoglycemia can be severe, documented but not severe, asymptomatic, or pseudo-hypoglycemia (Table 210-10). However, these distinctions are not always clear in clinical practice, where the severity of symptoms is often discordant with the severity of hypoglycemia. An individual may feel intense symptoms of hypoglycemia at a glucose concentration of 50 to 60 mg/dL (2.8 to 3.3 mmol/L), for which there is no evidence of cognitive impairment or imminent danger, whereas potentially dangerous plasma glucose concentrations in the range of 20 to 40 mg/dL (1.1 to 2.2 mmol/L) might go unappreciated owing to lack of classical symptoms. The only practical approach to detecting nocturnal hypoglycemia is regular nocturnal (3 AM) self-monitoring or the use of continuous glucose monitors with alarm features.

TREATMENT

At the time of their initial diagnosis, people with diabetes must be educated about the symptoms of hypoglycemia, its predisposing factors, and how to treat it. As the disease progresses, people with diabetes must be informed that the typical sympathoadrenal symptoms may diminish over time. Recurrent symptoms of potential hypoglycemia should be carefully evaluated, and possibly unrecognized events (e.g., unexplained night sweats or a clouded mental state in the morning that could be caused by nocturnal hypoglycemia) must be evaluated. If adults are conscious and able to swallow, the best approach is 15 to 20 g of rapid-acting carbohydrate in the form of dextrose tablets, 150 to 200 mL of fresh fruit juice, or 3 to 4 heaped teaspoons of sugar dissolved in water. Foods with a high fat content (e.g., chocolate) should be avoided because they delay gastric emptying, thereby slowing the absorption of carbohydrate. If the capillary glucose remains less than 72 mg/dL (4.0 mmol/L), oral treatment can be repeated up to three times, 15 minutes apart. If the glucose remains low, the individual requires formal medical attention for intramuscular glucagon or intravenous glucose. Once the glucose level has risen and the person has recovered, a longer-acting carbohydrate should be given (e.g., a slice of bread, 200 to 300 mL of cow's milk, or their next meal if it is due). The next insulin dose should not be omitted but may need to be adjusted.

For patients who can swallow but who are confused, disorientated, or poorly cooperative, the same oral measures can be tried, but an alternative is to squeeze 2 tubes of 40% dextrose gel between the mouth and the gums for rapid absorption.[29] However, intramuscular glucagon or intravenous dextrose may be necessary, especially if the patient is unconscious, having seizures, or aggressively refusing treatment. Basic life support (Chapter 50) may be emergently required.

TABLE 210-10 CLASSIFICATION OF IATROGENIC HYPOGLYCEMIA IN PEOPLE WITH TREATED DIABETES

	CLINICAL FEATURES
Severe hypoglycemia	Any episode, regardless of glucose concentration, with neurocognitive impairment that *requires* third-party assistance to treat.
Documented symptomatic hypoglycemia	Measured glucose concentration ≤70 mg/dL (3.9 mmol/L) that coincides with sympathoadrenal or neurologic symptoms. The episode is self-managed by the person with diabetes.
Asymptomatic hypoglycemia	Measured glucose concentration ≤70 mg/dL (3.9 mmol/L) but without concomitant symptoms. Absence of symptoms may be due to hypoglycemia unawareness or hypoglycemia-associated autonomic failure.
Pseudo-hypoglycemia	Typical hypoglycemia symptoms, but with measured glucose concentrations >70 mg/dL (3.9 mmol/L). Symptoms may be caused by resetting of counter-regulatory system in the setting of chronic suboptimal glucose control.

PREVENTION

In addition to educating the individual with diabetes about the risks, signs, and symptoms of hypoglycemia and potentially adjusting their medication doses, strategies to prevent nocturnal hypoglycemia include eating "long-acting" bedtime snacks (slowly absorbed carbohydrate, such as uncooked cornstarch) and regular monitoring of blood glucose concentration at bedtime so that corrective action (carbohydrate ingestion) can be taken. The use of newer, ultra-long-acting insulin formulations may also help mitigate the risk.

PROGNOSIS

An episode of severe hypoglycemia can be the immediate cause of death in people with type 1 diabetes, with reported mortality rates ranging from 4 to 10%. Mortality rates increase with increasing frequency of severe events. Prolonged episodes of very low circulating glucose (<15 mg/dL [0.8 mmol/L]) can themselves cause significant brain damage, but death due to fatal hypoglycemia may be the result of other mechanisms, such as ventricular arrhythmias precipitated by large catecholamine surges and concurrent electrolyte disturbances. Many motor vehicle licensing authorities will rescind an individual's driving license if they have hypoglycemic unawareness or have two or more episodes of severe daytime hypoglycemia in any 12-month period.

ACUTE HYPERGLYCEMIC STATES

EPIDEMIOLOGY

Diabetic ketoacidosis (DKA) and the hyperosmolar hyperglycemic state, which are the most serious acute hyperglycemic complications of diabetes, are part of the same pathophysiologic spectrum. The global incidence of diabetic ketoacidosis varies between 8.0 and 50 cases per 1000 people with type 1 diabetes per year, although it has been reported to be as high as 260 per 1000 people in China. The incidence of hyperosmolar hyperglycemic state is very difficult to estimate because of the absence of a universal definition of the condition and because it often occurs together with diabetic ketoacidosis.

Diabetic ketoacidosis is most frequently associated with type 1 diabetes, but it may also occur in type 2 diabetes under conditions of extreme stress, such as a major infection or trauma. Ketosis-prone type 2 diabetes most frequently occurs in people of African or Hispanic origin.

The condition formerly known as the hyperglycemic hyperosmolar nonketotic state or coma has been renamed the hyperosmolar hyperglycemic syndrome to highlight two important points: ketosis (and acidosis) may be present to varying degrees in hyperosmolar hyperglycemic syndrome, and alterations in sensorium most commonly occur in the absence of coma. Hyperosmolar hyperglycemic syndrome typically occurs in people with type 2 diabetes, but some affected individuals may present with ketosis and acidosis.[30] Major risk factors for hyperosmolar hyperglycemic syndrome include (but are not limited to) older age (most cases occur in people ages 65 years and older), use of medications that alter carbohydrate metabolism (e.g., glucocorticoids), intercurrent illness, and impaired cognition (i.e., impaired ability to recognize thirst or to obtain access to water).

PATHOBIOLOGY

Diabetic ketoacidosis and hyperosmolar hyperglycemic state are commonly precipitated by an acute event, which may be as simple as nonadherence with insulin therapy or a major systemic infection (Table 210-11).

Diabetic Ketoacidosis

The three fundamental biochemical features of diabetic ketoacidosis are hyperglycemia or a history of diabetes (the "D"), urinary ketone levels of 2+ or more or 3.0 mmol/L or more (the "K"), and an arterial or venous pH of less than 7.3 (the "A"). These biochemical abnormalities result from the combined effects of deficient circulating insulin and an excess of counterregulatory hormones. This hormonal milieu promotes the delivery of substrates from muscle (amino acids, lactate, and pyruvate) and adipose tissue (free fatty acids, glycerol) to the liver, where they are converted to glucose or to ketone bodies (β-hydroxybutyrate, acetoacetate, acetone). Glucose and ketones are released into the circulation at greater rates than their utilization. The hyperglycemia leads to an osmotic diuresis that promotes dehydration and loss of electrolytes. Fluid depletion leads to hemoconcentration, which further exacerbates hyperglycemia and hyperosmolality.

TABLE 210-11 THE MOST COMMON PRECIPITANTS OF DIABETIC KETOACIDOSIS AND HYPEROSMOLAR HYPERGLYCEMIC STATE

MOST COMMON
Infections
Inadequate insulin treatment or nonadherence
New-onset diabetes
Acute coronary syndrome
Unknown
OTHER PRECIPITATING FACTORS
Intercurrent illness, including (but not limited to):
Cerebrovascular accident
Acute pulmonary embolism
Acute pancreatitis
Intestinal or mesenteric thrombosis
Alcohol intoxication
Endocrinopathies:
Cushing syndrome
Thyrotoxicosis
Acromegaly
Severe burns
Hyperthermia or hypothermia
Drugs:
Corticosteroids
Clozapine
Olanzapine
Cocaine
Lithium
Sympathomimetics
Thiazide diuretics
Sodium-glucose cotransporter-2 inhibitors

Hyperosmolar Hyperglycemic State

Severe hyperglycemia can cause a hyperosmolar state because people with diabetes, particularly the elderly or physically infirm, cannot consume enough liquid to keep pace with a significant glucose-induced osmotic diuresis. The resulting hemoconcentration and prerenal renal impairment eventually further reduce glucose excretion by the kidney. In contrast to diabetic ketoacidosis, severe acidosis and ketosis are usually absent even though glucose concentrations are generally higher, probably because enough residual insulin is available to suppress lipolysis and to avoid significant production of ketones. Some people who have type 2 diabetes and who have depressed endogenous insulin secretion may be unable to suppress ketone production fully in the face of elevated counter-regulatory hormones produced by physical illness and, as a result, present with a mixed picture of hyperosmolar hyperglycemic state and diabetic ketoacidosis. However, because people with hyperosmolar hyperglycemic state have higher portal vein insulin concentrations than do patients with diabetic ketoacidosis, the production of ketones by the liver is quantitatively less, thereby causing only mild acidosis. In the hyperosmolar hyperglycemic state in the absence of concurrent acid-base disturbances, the arterial pH rarely drops below 7.30, and serum bicarbonate levels typically do not fall below 18 mmol/L.

CLINICAL MANIFESTATIONS

The most notable findings in both diabetic ketoacidosis and the hyperglycemic hyperosmolar state are usually a variety of often reversible neurologic abnormalities. Common manifestations include a reduced Glasgow Coma Score (see Table 368-1), extensor plantar reflexes, aphasia, hemisensory or motor deficits, and worsening of a preexisting organic mental syndrome.

Diabetic Ketoacidosis

Diabetic ketoacidosis may signal the onset of type 1 diabetes, especially in the developing world and in infants and very young children. Otherwise, however, diabetic ketoacidosis is more frequently seen when people with established diabetes are poorly adherent to therapy or develop an intercurrent illness. For example, the person with diabetes may be unable to maintain adequate hydration during an illness, such as a viral gastroenteritis, and may mistakenly omit insulin because of an inability to eat. Behavioral factors may also be involved; some younger people may omit insulin deliberately to promote weight loss or to call attention to a dysfunctional home situation.

The clinical history of diabetic ketoacidosis typically involves deterioration during several hours to days, with progressive polyuria, polydipsia, and other symptoms of hyperglycemia. Other common clinical features are weakness, lethargy, nausea, and anorexia. Nonspecific upper abdominal pain can mimic an acute abdomen. Reduced motility of the gastrointestinal tract or, in severe cases, paralytic ileus may further contribute to diagnostic confusion. Physical findings, which are mainly secondary to dehydration, hyperosmolality, and acidosis, include dry skin and mucous membranes, reduced jugular venous pressure, tachycardia, orthostatic hypotension, depressed mental function sometimes with frank coma, and deep, rapid respirations (Kussmaul breathing).

Hyperosmolar Hyperglycemic State

In the hyperosmolar hyperglycemic state, the clinical severity and levels of consciousness generally correlate with the severity and duration of hyperosmolarity. Up to 10% of patients with the hyperosmolar hyperglycemic state present with frank coma, and an equal percentage show no signs whatsoever of mental status change. Gastrointestinal symptoms are seen less frequently than in diabetic ketoacidosis, although a diarrhea-causing illness may be the precipitating event.

DIAGNOSIS

Diabetic Ketoacidosis

The diagnosis of diabetic ketoacidosis is based on the presence of hyperglycemia, ketosis, and acidosis (Table 210-12). Glucose concentrations may vary from normal to more than 1000 mg/dL (55.5 mmol/L), the serum bicarbonate concentration drops below 18 mmol/L, and an excess anion gap is generally proportional to the decrease in the serum bicarbonate level. Hyperchloremia may be superimposed if the individual maintains an adequate GFR and is

able to exchange ketoacids for chloride in the kidney or if the person is given large volumes of 0.9% sodium chloride solution as part of their treatment. The degree of depression of arterial pH depends largely on the degree of respiratory compensation. In mild cases, the pH may range from 7.20 to 7.30; in severe cases, it can fall below 7.00. On occasion, a degree of superimposed metabolic alkalosis (e.g., caused by vomiting or diuretic use) may obscure the true severity of the ketoacidosis; an anion gap out of proportion to the fall of bicarbonate should suggest this possibility. Other common laboratory abnormalities include a reduced measured serum sodium concentration (due to hyperosmolarity and the resulting osmotic shift of intracellular water into the intravascular space) and prerenal kidney impairment. The hemoglobin concentration and hematocrit are typically elevated as a reflection of hemoconcentration. The blood concentrations of potassium, phosphate, and magnesium may be normal, elevated, or reduced when diabetic ketoacidosis is diagnosed, but large total-body deficits of these electrolytes invariably accompany the osmotic diuresis and become readily apparent during treatment. The white blood cell count is typically elevated, sometimes as a result of the metabolic acidosis itself and not necessarily of the presence of infection. An elevated serum amylase level is usually of non-pancreatic origin and can lead to an erroneous diagnosis of pancreatitis.

Special care should be taken in interpreting the results of testing for serum or urine ketones. The rapid diagnosis of diabetic ketoacidosis usually requires qualitative assessment of serum ketones using serum dilutions and reagent strips, which depend on a nitroprusside reaction with acetoacetate. However, acetone reacts weakly with nitroprusside, and β-hydroxybutyrate does not react at all; as a result, the results of qualitative testing for ketones can be misleadingly low. Furthermore, because of the presence of intracellular acidosis, β-hydroxybutyrate levels are often much higher than acetoacetate levels, which may further conceal the true degree of ketoacidosis. Conversely, after insulin therapy is begun, the nitroprusside reaction may give the false impression of sustained ketoacidosis for hours or even days because the nonacidic acetone is slowly cleared from the circulation and because, as acidosis improves, β-hydroxybutyrate is converted to acetoacetate, thereby giving the false impression that ketosis is worsening. As technology has improved, however, bedside capillary ketone monitors are increasingly being used in many parts of the world to help guide the management of diabetic ketoacidosis.

Hyperosmolar Hypoglycemic State

The hyperosmolar hyperglycemic state has no formal definition, but is generally diagnosed when the blood glucose level is greater than 600 mg/dL (33.3 mmol/L), the pH is greater than 7.3 (and/or the serum bicarbonate is >18 mmol/L), and the serum osmolality is greater than 320 mOsmol/L.[31] Significant elevations in blood glucose, which sometimes exceed 1000 mg/dL (55.6 mmol/L), are typical. The laboratory picture is dominated by the effects of uncontrolled hyperglycemia and dehydration; renal function is usually impaired, the hemoglobin concentration and hematocrit are elevated, and liver function tests may be abnormal because of baseline hepatic steatosis. Although severe hyperglycemia would be expected to lower measured serum sodium concentration, a normal or even elevated sodium level may be noted because of the severity of dehydration.

TREATMENT

For the initial management of both diabetic ketoacidosis and hyperosmolar hyperglycemic state, the restoration of circulating volume with adequate tissue perfusion is paramount. Fluid losses of 5 to 10 liters, sodium losses of 5 to 10 mmol/kg, and potassium losses up to 7 mmol/kg are common, and fluid losses may be greater in hyperosmolar hyperglycemic state. Given the volumes of fluid and electrolytes required, patients typically require admission to an intermediate care or intensive care unit where continuous cardiac monitoring is available. In addition to correction of fluid and electrolyte imbalances and administration of insulin, treatment must also include prompt recognition and treatment for any precipitating illness or event (see Table 210-11).

Initial treatment is fluid replacement with 0.9% sodium chloride solution, even if the serum osmolality is high because 0.9% sodium chloride is still relatively hypotonic. The rate of fluid replacement should be 2 to 4 liters in the first 2 to 4 hours in diabetic ketoacidosis but somewhat slower in hyperosmolar hyperglycemic state depending on associated (sometimes precipitating) comorbid conditions, such as ischemic heart disease, heart failure, or renal impairment. In hyperosmolar hyperglycemic state, the serum sodium level may rise as the serum glucose level declines, but overall osmolality will nevertheless be declining, so the infusion should not be changed to 0.45% sodium chloride solution.

A low initial potassium suggests profound total body potassium losses and requires prompt intravenous replacement. Even when the serum potassium is elevated on the initial presentation of diabetic ketoacidosis owing to the metabolic acidosis, it quickly declines after insulin treatment is begun. Potassium replacement should not be prescribed if the serum potassium level remains above 5.5 mEq/L (mmol/L). However, 0.9% sodium chloride solution with potassium 40 mEq/L (ready-mixed) should be administered if the serum potassium level is below 5.5 mEq/L and the person is passing urine. If the serum potassium level falls below 3.5 mEq/L, the potassium regimen needs review. Where the fluid balance permits, an increase in the rate of the infusion of 0.9% sodium chloride solution with potassium 40 mEq/L is possible.

In diabetic ketoacidosis, a fixed-rate intravenous insulin infusion should start at 0.1 units/kg/hour as soon as the diagnosis is made. Once the blood glucose level falls to 250 mg/dL (13.9 mmol/L) and the ketones have fallen to less than 1.0 mmol/L, the insulin infusion rate may be reduced to 0.05 units/kg/hour to prevent hypoglycemia and hypokalemia. In hyperosmolar hyperglycemic state, intravenous fluid alone is the treatment of choice and will result in an initial decline in the glucose level because of increased absolute glycosuria. When the glucose level stops dropping, a fixed-rate intravenous insulin infusion should start at 0.05 units/kg/hour. If the individual was already on a background subcutaneous long-acting insulin, the dose should be continued along with the intravenous insulin. The intravenous insulin infusion should be titrated until the patient can eat, at which time they can resume their usual diabetes regimen, with a 1- to 2-hour overlap between the administration of the subcutaneous insulin dose and the discontinuation of intravenous insulin so as to avoid rebound ketosis. Once glucose concentrations have fallen to less than 250 mg/dL (13.9 mmol/L), 10% dextrose should be added to the fluid replacement regimen. The 0.9% sodium chloride solution acts as the resuscitation fluid, and the 10% dextrose provides a substrate for the insulin infusion.

Bicarbonate replacement is not usually advocated because of the risk of paradoxically worsening the pH in the central nervous system and because restoration of circulating volume and peripheral tissue perfusion is often sufficient to allow pH to rise. Bicarbonate administration should be considered only if the patient is not responding to intravenous insulin and fluids and remains profoundly acidotic (e.g., pH <7.0). Phosphate and magnesium levels should be measured and monitored, but intravenous replacement is not usually recommended unless the phosphate level falls below 1.0 mg/dL and the patient develops profound muscle weakness or other complications.

TABLE 210-12 DIAGNOSTIC CRITERIA FOR DIABETIC KETOACIDOSIS

SEVERITY	GLUCOSE IN MG/DL (MMOL/L)	ARTERIAL OR VENOUS PH	BICARBONATE (MMOL/L)	URINE OR SERUM KETONES	B-HYDROXY BUTYRATE (MMOL/L)	ANION GAP (MMOL/L)	MENTAL STATUS
AMERICAN DIABETES ASSOCIATION CRITERIA FOR ADULTS							
Mild	>250 (13.8)	7.25-7.30	15–18	Positive	>3.0	>10	Alert
Moderate	>250 (13.8)	7.24-7.0	10–15	Positive	>3.0	>12	Alert/drowsy
Severe	>250 (13.8)	<7.0	<10	Positive	>3.0	>12	Stupor/coma
JOINT BRITISH DIABETES SOCIETIES FOR INPATIENT CARE							
NA	>200 (11.1)	<7.30*	<15	Positive	>3.0	NA	NA
INTERNATIONAL SOCIETY OF PEDIATRIC AND ADOLESCENT DIABETES							
Mild	>200 (11.1)	<7.30*	<15	Positive	>3.0	NA	NA
Moderate	>200 (11.1)	<7.2*	<10	Positive	>3.0	NA	NA
Severe	>200 (11.1)	<7.1*	<5	Positive	>3.0	NA	NA

*Venous pH can be used to diagnose diabetic ketoacidosis.
NA = not applicable.
Adapted from Dhatariya KK, Glaser NS, Codner E, et al. Diabetic ketoacidosis. *Nat Rev Dis Primers*. 2020;6:40.

PREVENTION

Education as to why the episode occurred and what the individual can do to prevent a recurrence is critical. Patients who have been admitted with diabetic ketoacidosis or the hyperosmolar hyperglycemic state should see a diabetes educator, specialist nurse, or diabetes doctor during their hospital admission or very soon afterwards. A key component of a diabetes treatment program is education in "sick-day rules" focused on home-based prevention of diabetic ketoacidosis (e.g., frequent blood glucose monitoring, serum or urine ketone testing, intake of small but frequent carbohydrate-containing fluids, and an increased insulin requirement with small doses taken often).

PROGNOSIS

Despite aggressive treatment, mortality rates remain about 4% for diabetic ketoacidosis and up to 20% for the hyperosmolar hyperglycemic state.[32,33] Mortality is associated not only with the extremes of age (i.e., the very young and the elderly) and comorbid conditions but also with the severity of the precipitating illness or event.

CHRONIC MICROVASCULAR COMPLICATIONS OF DIABETES

EPIDEMIOLOGY

The major clinical burden associated with long-standing diabetes is the development of vascular disease, which includes characteristic microvascular complications (retinopathy, nephropathy, neuropathy) and accelerated medium- and large-vessel atherosclerosis. Complications typically develop at a younger age in people with type 1 diabetes, but the same complications also can occur in people with type 2 diabetes. Diabetes, which is the seventh leading cause of death in the United States excluding coronavirus disease 2019, is the leading cause of kidney failure (Chapter 117), nontraumatic lower limb amputations (Chapter 65), and new cases of blindness (Chapter 391) among adults in the United States. Diabetes is also a major cause of coronary heart disease (Chapter 39), heart failure (Chapter 45), and stroke (Chapter 375). The microvascular complications are directly linked, and both the duration and degree of hyperglycemia and better control of diabetes as soon as it is diagnosed reduce the risks. Other factors, including genetic susceptibility, smoking, and concomitant conditions such as hypertension, also contribute to the risk of complications.

PATHOBIOLOGY

The complex cellular and molecular mechanisms that mediate hyperglycemic tissue damage are largely related to oxidative stress and vascular damage. Levels of advanced glycation end products, which are a heterogeneous group of compounds that form from the nonenzymatic interaction of glucose with amino groups on proteins, correlate with diabetes-related vascular complications and mean glucose levels over time. Advanced glycation end products can alter the properties and function of long-lived proteins, such as collagen and elastin, thereby leading to vascular stiffness and increases in the thickness of basement membranes. Advanced glycation end products also bind to specific cell surface receptors, particularly on macrophages and endothelial cells, thereby stimulating activation of signaling cascades that promote inflammation and oxidative stress.

Intracellular hyperglycemia leads to increased de novo synthesis of diacylglycerol, which is a major activator of the protein kinase C family of enzymes, which alter gene expression and result in enhanced angiogenesis, vasoconstriction, vascular permeability (by increases in vascular endothelial growth factor), activation of cytokines, and expansion of the extracellular matrix. In the setting of hyperglycemia and excess fatty acid oxidation, increased flux of glucose through the hexosamine pathway leads to increases in glucosamine 6-phosphate and ultimately post-translational modification of cytoplasmic and nuclear proteins associated with transforming growth factor (α and β1), plasminogen activator inhibitor–1, and endothelial nitric oxide synthase.

MICROVASCULAR COMPLICATIONS

DIABETES-RELATED EYE CONDITIONS

Diabetic retinopathy (Chapter 391) is a highly prevalent, pathognomonic, microvascular complication that eventually affects more than 50% of people with long-term diabetes, although it impairs vision less frequently, especially as the control of glucose levels and blood pressure has improved. Changes include the loss of retinal supporting cells (pericytes), thickening of the basement membrane, and changes in retinal blood flow. Damaged retinal capillaries leak protein, red blood cells, and lipids, thereby leading to retinal edema. Chronic retinal hypoxia (due to capillary occlusion) promotes neovascularization; these new vessels are abnormal and prone to rupture.

TABLE 210-13 CLASSIFICATION OF DIABETIC RETINOPATHY

	CLINICAL FEATURES
Mild NPDR	At least one microaneurysm
Moderate NPDR	Microaneurysms, intraretinal (blot) hemorrhage, soft exudates, venous beading, intraretinal microvascular abnormalities
Severe NPDR	More extensive intraretinal hemorrhages (>20 in each of four quadrants) *or* venous beading in at least two quadrants *or* prominent intraretinal microvascular abnormalities
PDR	Neovascularization and/or vitreous or pre-retinal hemorrhage; traction retinal detachment
Clinically significant macular edema	Retinal thickening or hard exudates approaching or involving the center of the macula

NPDR = nonproliferative diabetic retinopathy; PDR = proliferative diabetic retinopathy.

CLINICAL MANIFESTATIONS

Transient osmotically induced refractive error is common, especially when diabetes is first diagnosed or when glucose levels are high, but it resolves with improving glucose control. Diabetic retinopathy is largely asymptomatic even with severe proliferative retinopathy. However, retinal hemorrhage, inflammation, and scarring can cause diminished visual acuity and can ultimately lead to traction retinal detachment and permanent loss of vision (Table 210-13). Age-related eye conditions, such as cataracts and glaucoma, tend to occur at younger ages among people with diabetes. Diplopia and other gaze disorders due to acute mononeuropathy involving the cranial nerves (typically III or VI) are also more common in diabetes.

Regular screening by an eye care specialist (an ophthalmologist or optometrist) is recommended for all people with diabetes because significant and potentially vision-threatening retinopathy can be present in the absence of any symptoms. Screening should begin when type 2 diabetes is diagnosed (because hyperglycemia has typically been present for years before it is recognized clinically) and at 5 years after type 1 diabetes is diagnosed.

DIAGNOSIS

Early signs of diabetic retinopathy include the presence of microaneurysms, exudates, and intraretinal hemorrhages on funduscopic evaluation (see Figs. 391-22 and 391-23). Additional tests, including fluorescein angiography and ocular coherence tomography, are helpful to detect abnormal vessel permeability and macular edema, which can threaten vision.

TREATMENT AND PREVENTION

Treatment of diabetic retinopathy (Chapter 391) includes laser photocoagulation, which can ablate abnormal vessels (thereby reducing the risk of hemorrhage) and treat macular edema,[34] or the equivalently successful use of anti-VEGF monoclonal antibodies (e.g., ranibizumab).[A35] Vitrectomy can remove hemorrhage and scar tissue that is obscuring vision.

Intensive glycemic control can prevent diabetic retinopathy, delay its progression, and reduce the long-term need for ocular surgery.[A36] However, glycemic control has limited effects on advanced retinal disease. Blood pressure (Chapter 64) control is also important to prevent worsening of retinopathy, and evidence suggests that renin-angiotensin system blockers may be especially beneficial.

PROGNOSIS

The prognosis for diabetic retinopathy is highly dependent on early detection. With early detection, glycemic control, and optimization of other risk factors, retinopathy is less likely to progress. With modern therapy, diabetic retinopathy is no longer the leading cause of sight loss in many parts of the developed world.

DIABETIC NEPHROPATHY

Diabetic nephropathy, which is the most common single cause of end-stage renal failure in Western societies, is discussed in Chapter 109.

DIABETIC NEUROPATHY

Diabetic neuropathy, which has an estimated lifetime prevalence of about 50% in individuals with diabetes, can cause a distal symmetrical polyneuropathy, autonomic neuropathy, and radiculoplexopathy. Diabetic neuropathy is discussed in Chapter 388.

DIABETIC FOOT

The combination of sensory impairment, due to peripheral sensory and autonomic neuropathy, and reduced tissue perfusion, due to large-vessel atherosclerosis (peripheral arterial disease) or microvascular dysfunction, can result in ulceration, infection, and ultimately lower extremity amputation (Chapter 65). Ulceration, often surrounded by callus formation, typically develops on the plantar surface of the foot, often underneath the metatarsal heads. Ulceration can be slow to heal because of repetitive trauma, impaired blood flow, and hyperglycemia. In the absence of protective sensation, an infection may fester for weeks and eventually invade the bone, thereby leading to osteomyelitis (Chapter 251). Altered foot mechanics can also lead to repeated (and usually undetected) fractures that destroy normal foot architecture and result in the classic Charcot foot deformity.

TREATMENT

Ulcers are treated with aggressive débridement of necrotic tissue and systemic antibiotics (guided by culture of infected tissue) if infection is present.[35] Pressure "off-loading" by use of special shoes, orthotics, or application of total-contact casts may be necessary to allow healing. Revascularization is required in patients who have significant peripheral arterial disease. Additional treatments such as specific dressings with healing accelerators and the use of autologous leukocytes and platelets may benefit patients who have nonhealing ulcers. Other treatments, including bioengineered skin substitutes, hyperbaric oxygen, and negative-pressure wound therapy have been tried but have not been proven to promote wound healing.

PREVENTION

Routine foot examination, especially for those who have evidence of sensory loss, should be performed at every medical visit, and individuals should be instructed to inspect their feet daily for cracks, fissures, ulcers, or inflammation. People with diabetes should avoid walking barefoot (even at home) and should wear protective covering (avoid sandals) outside. Thermal injuries can be prevented by avoiding use of heating pads or hot-water bottles on the feet. Referral to a foot care specialist should be considered for patients with sensory loss, foot deformity, extensive callus formation, and nonhealing ulcers.

DIABETIC CARDIOVASCULAR DISEASE

Macrovascular diabetic complications, specifically atherosclerotic cardiovascular disease, is the major cause of morbidity and mortality in patients with diabetes.

PATHOBIOLOGY

Metabolic factors, including hyperglycemia, insulin resistance, dyslipidemia, and increases in circulating free fatty acids, contribute to the formation of atherosclerotic plaques (Chapter 41). Increases in oxidation and glycoxidation of lipoproteins increase their atherogenicity and enhance the formation of foam cells. Endothelial dysfunction and inflammation also promote atherosclerosis and a prothrombotic state.

CLINICAL MANIFESTATION AND DIAGNOSIS

The clinical and pathologic features of cardiovascular disease in diabetes are generally not distinguishable from those occurring in nondiabetic individuals, but they are manifested at an earlier age, are more aggressive, and are associated with mortality rates that are two to four times higher in patients with diabetes (Chapter 40). Manifestations include coronary (Chapters 56-58), cerebral (Chapters 376 and 377), and peripheral arterial disease (Chapter 66), as well as an increased risk for diseases of the aorta (Chapter 63). Diabetes can also cause a cardiomyopathy (Chapter 47) with alterations in cardiac structure and function that are not directly attributable to coronary artery disease or hypertension. Characteristic features include cardiac hypertrophy, left ventricular dysfunction (diastolic may precede systolic), and altered myocardial metabolism.

The cardiovascular evaluation of an individual with diabetes is the same as for nondiabetic individuals. However, the threshold for diagnostic testing should be lower because of the increased prevalence of cardiovascular disease.

TREATMENT

Treatment of the acute atherosclerotic complications of diabetes is generally identical to the treatment in nondiabetic patients. However, people with diabetes and multivessel coronary disease have a better outcome (reduced rates of death from any cause or nonfatal myocardial infarction) with coronary artery bypass surgery compared with percutaneous intervention with drug-eluting stents (Chapter 59).[A37,A38]

PREVENTION

Aggressive control of cardiovascular disease risk factors, and especially of glucose levels, lipid levels, and blood pressure, is key.[36]

Glucose

Every 1% rise in the HbA_{1c} level is associated with a 40% increase in cardiovascular mortality, and intensive glucose control reduces cardiovascular events by about 60% in patients with type 1 diabetes. In type 2 diabetes, large trials have failed to show that aggressive control of hyperglycemia reduces atherosclerotic cardiovascular events, but SGLT-2 inhibitors and some glucagon-like peptide agonists can substantially reduce future cardiovascular events and all-cause mortality independently of their specific glycemic effects (see Treatment of type 2 diabetes).[A39]

Hypertension

Hypertension (Chapter 64), which is a common comorbid condition in diabetes, increases the risk of microvascular and macrovascular complications. The blood pressure goal should be less than 130/80 mm Hg for most people with diabetes. ACE inhibitors and angiotensin receptor blockers are generally considered first-line therapy for patients with diabetes (Chapter 64), but β-blockers, calcium-channel blockers, and low-dose diuretics are also recommended as add-on therapy if needed to achieve blood pressure targets. However, β-blockers should be used with caution in patients at high risk for hypoglycemia because they may blunt the autonomic warning symptoms associated with low glucose concentration.

Dyslipidemia

The characteristic atherogenic dyslipidemia of type 2 diabetes and insulin-resistant states includes low levels of high-density lipoprotein (HDL) cholesterol, elevated triglyceride levels, and elevated levels of small dense low-density lipoprotein (LDL) particles (Chapter 190). Lowering LDL cholesterol levels with statin drugs is recommended to a target of less than 100 mg/dL (2.6 mmol/L) for most adults with diabetes and less than 70 mg/dL (1.8 mmol/L) for people with diabetes with established cardiovascular disease or multiple risk factors, regardless of the baseline LDL cholesterol levels. People with diabetes with established atherosclerotic cardiovascular disease or an estimated 10-year cardiovascular risk of more than 7.5% should receive high-intensity statin treatment (regimens sufficient to lower LDL cholesterol >50% from untreated baseline), whereas all others would be considered for moderate-intensity treatment (lowering of LDL cholesterol 30 to <50%) (Table 190-2). Statin therapy slightly increases hyperglycemia, but the risk is small in magnitude (hazard ratio, about 1.2-fold increased risk of diabetes) and is far outweighed by the substantial benefits of cardiovascular protection. Specific therapy to lower triglyceride levels usually is not warranted (Chapter 190).

Antiplatelet Therapy

In people with diabetes, aspirin is not effective for the primary prevention of cardiovascular disease and increases bleeding events.[A40] Current guidelines recommend aspirin therapy 75 to 81 mg daily as secondary prevention for people who have diabetes and who have had a prior cardiovascular event. For high-risk individuals who are unable to tolerate aspirin, clopidogrel (75 mg orally once daily) is an effective alternative.

PROGNOSIS

The prognosis of cardiovascular disease in individuals with diabetes is qualitatively similar to nondiabetic individuals but tends to be worse for all clinical manifestations.

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For the General References and other additional features, please visit Elsevier eBooks+ at https://ebooks.health.elsevier.com.

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211 HYPOGLYCEMIA

KHALID HUSSAIN

DEFINITION

Hypoglycemia is a common biochemical abnormality observed in clinical practice. Hypoglycemic disorders are more frequent in neonates, infants, and children than adults. Delay in diagnosis and inappropriately treated hypoglycemia can have severe consequences, including seizures, permanent brain injury, or death.[1]

In adults, no single plasma glucose concentration categorically defines hypoglycemia. Rather, clinical hypoglycemia is defined as a plasma (or serum) glucose concentration low enough to cause symptoms or signs, which can be nonspecific but include impairment of brain function. The measured plasma or serum glucose concentration may be low owing to an artifact (e.g., when the blood sample is collected in a tube that does not contain an inhibitor of glycolysis and when separation of the plasma or serum from the formed elements is delayed).

For these reasons, guidelines in adults emphasize the value of the Whipple triad for confirming hypoglycemia: (1) symptoms and/or signs compatible with hypoglycemia, (2) a low measured plasma glucose concentration, and (3) resolution of symptoms and signs when glucose concentrations are raised. Because circulating fuels such as ketone bodies can be used by the brain, lower plasma glucose concentrations can occur in healthy individuals, particularly in women and children, without symptoms or signs during extended fasting.

EPIDEMIOLOGY

Hypoglycemic disorders in neonates, infants, and children are most often due to congenital or genetic disorders, such as disorders of insulin secretion, as well as a range of metabolic and endocrine diseases.[2] Early recognition and treatment of such persistent hypoglycemia disorders are critical to avoid developmental abnormalities, including permanent brain damage, which occurs in about 50% of cases with congenital hyperinsulinism.[3]

In adults, the overwhelming cause of hypoglycemia is as an adverse effect of anti-diabetes medicines, especially insulin. Other causes include hormone deficiencies, critical illness, and tumors that secrete insulin or insulin-like peptides (Table 211-1).

PATHOBIOLOGY

Plasma glucose concentration is regulated by a balance between glucose production and utilization. Glucose is derived from three sources: intestinal absorption after digestion of dietary carbohydrates; glycogenolysis (i.e., the breakdown of glycogen), which is the polymerized storage form of glucose; and gluconeogenesis, which is the formation of glucose from precursors (lactate, pyruvate, alanine, glutamine, and glycerol). Glucose is an obligate metabolic fuel for the brain, which cannot oxidize fatty acids or synthesize or store glucose for later use. To meet these needs, the rate of endogenous glucose influx into the circulation and glucose efflux out of the circulation (Fig. 211-1) into insulin-dependent tissues (skeletal muscle, adipose tissue, and liver) is regulated so that the plasma glucose concentration is maintained in a relatively narrow range between 70 and 110 mg/dL (3.8 to 6 mmol/L) despite periods of feeding and fasting.

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211 HYPOGLYCEMIA

KHALID HUSSAIN

DEFINITION

Hypoglycemia is a common biochemical abnormality observed in clinical practice. Hypoglycemic disorders are more frequent in neonates, infants, and children than adults. Delay in diagnosis and inappropriately treated hypoglycemia can have severe consequences, including seizures, permanent brain injury, or death.[1]

In adults, no single plasma glucose concentration categorically defines hypoglycemia. Rather, clinical hypoglycemia is defined as a plasma (or serum) glucose concentration low enough to cause symptoms or signs, which can be nonspecific but include impairment of brain function. The measured plasma or serum glucose concentration may be low owing to an artifact (e.g., when the blood sample is collected in a tube that does not contain an inhibitor of glycolysis and when separation of the plasma or serum from the formed elements is delayed).

For these reasons, guidelines in adults emphasize the value of the Whipple triad for confirming hypoglycemia: (1) symptoms and/or signs compatible with hypoglycemia, (2) a low measured plasma glucose concentration, and (3) resolution of symptoms and signs when glucose concentrations are raised. Because circulating fuels such as ketone bodies can be used by the brain, lower plasma glucose concentrations can occur in healthy individuals, particularly in women and children, without symptoms or signs during extended fasting.

EPIDEMIOLOGY

Hypoglycemic disorders in neonates, infants, and children are most often due to congenital or genetic disorders, such as disorders of insulin secretion, as well as a range of metabolic and endocrine diseases.[2] Early recognition and treatment of such persistent hypoglycemia disorders are critical to avoid developmental abnormalities, including permanent brain damage, which occurs in about 50% of cases with congenital hyperinsulinism.[3]

In adults, the overwhelming cause of hypoglycemia is as an adverse effect of anti-diabetes medicines, especially insulin. Other causes include hormone deficiencies, critical illness, and tumors that secrete insulin or insulin-like peptides (Table 211-1).

PATHOBIOLOGY

Plasma glucose concentration is regulated by a balance between glucose production and utilization. Glucose is derived from three sources: intestinal absorption after digestion of dietary carbohydrates; glycogenolysis (i.e., the breakdown of glycogen), which is the polymerized storage form of glucose; and gluconeogenesis, which is the formation of glucose from precursors (lactate, pyruvate, alanine, glutamine, and glycerol). Glucose is an obligate metabolic fuel for the brain, which cannot oxidize fatty acids or synthesize or store glucose for later use. To meet these needs, the rate of endogenous glucose influx into the circulation and glucose efflux out of the circulation (Fig. 211-1) into insulin-dependent tissues (skeletal muscle, adipose tissue, and liver) is regulated so that the plasma glucose concentration is maintained in a relatively narrow range between 70 and 110 mg/dL (3.8 to 6 mmol/L) despite periods of feeding and fasting.

ABSTRACT

Hypoglycemia is one of the most common biochemical abnormalities observed in clinical practice. Hypoglycemic disorders are more common in neonates, infants, and children than in adults. Delay in diagnosis and inappropriate management of hypoglycemia can have severe consequences, including seizures, permanent brain injury, or death. In adults, an insulinoma is the most common cause of endogenous hyperinsulinemic hypoglycemia, and other causes of hypoglycemia are relatively rare. This chapter outlines the physiologic and biochemical changes associated with maintenance of a normal blood glucose level, describes the role of the counter-regulatory hormones, reviews the clinical manifestations and diagnosis of hypoglycemic disorders, and discusses management strategies.

KEYWORDS

hypoglycemia
glucose
insulin
insulinoma
Whipple triad
hyperinsulinism

TABLE 211-1 DIFFERENTIAL DIAGNOSIS OF HYPOGLYCEMIA*

HYPERINSULINEMIC HYPOGLYCEMIA (INCLUDING POSTPRANDIAL)
Transient: infant of diabetic mother, perinatal asphyxia, Rhesus disease, intrauterine growth restriction, Beckwith-Wiedemann syndrome
Congenital: *ABCC8, KCNJ11, GCK, GDH, HADH, HNF4A, HNF1A, SLC16A1, UCP2, HK-1, PGM-1, PMM2, FOXA2, CACNA1D*
Dumping syndrome
Insulin receptor mutations and antibodies
Hypoketotic hypoinsulinemic hypoglycemia with overgrowth
Activating mutations in *AKT2, AKT3, CCND2, PIK3R2,* and *PIK3CA*
Insulinoma
Non-insulinoma pancreatogenous hypoglycemia (adults)
Gastric bypass surgery for morbid obesity
Non–islet cell tumor hypoglycemia or IGF-2-oma
Insulin autoimmune syndrome
Insulin factitious hypoglycemia
HORMONAL DEFICIENCY/RESISTANCE
Adrenocorticotropic hormone
Cortisol
Growth hormone
Glucagon†
Adrenaline†
DRUG-INDUCED
Oral hypoglycemic agents
Insulin
β-Blockers
Salicylates
Alcohol
Quinine
Haloperidol
Pentamidine
Levofloxacin
Methadone
Disopyramide
Indomethacin
Cibenzoline
Gatifloxacin
DEFECTS IN HEPATIC GLYCOGEN RELEASE/STORAGE
Glycogen storage diseases: **glucose-6-phosphatase deficiency**, **amylo-1,6-glucosidase deficiency**, liver phosphorylase deficiency, glycogen storage disease type 0
DEFECTS IN GLUCONEOGENESIS
Fructose-1,6-bisphosphatase deficiency, phosphoenolpyruvate carboxykinase deficiency, pyruvate carboxylase deficiency
CARNITINE METABOLISM
Carnitine deficiency (primary and secondary)
Carnitine palmitoyltransferase deficiency (CPT 1 and 2)
Carnitine transporter defects
FATTY ACID OXIDATION
Medium-chain acyl-CoA dehydrogenase (MCAD) deficiency
Very long-chain acyl-CoA dehydrogenase (VLCAD) deficiency
Short-chain acyl-CoA dehydrogenase (SCAD) deficiency
Long/short-chain L-3-hydroxyacyl-CoA (L/SCHAD) deficiency
DEFECTS IN KETONE BODY SYNTHESIS/UTILIZATION
HMG-CoA synthase deficiency, HMG-CoA lyase deficiency
Succinyl-CoA: 3-oxoacid-CoA transferase (SCOT) deficiency
METABOLIC CONDITIONS (COMMON ONES)
Organic acidemias (propionic, methylmalonic)
Maple syrup urine disease, galactosemia, fructosemia, tyrosinemia
Hereditary fructose intolerance
Mitochondrial respiratory chain complex deficiencies
Congenital disorders of glycosylation (CDG)
Citrin deficiency
TOXIN-INDUCED
Lychee fruit
MISCELLANEOUS CAUSES (MECHANISM[S] NOT CLEAR)
Idiopathic ketotic hypoglycemia (diagnosis of exclusion)
Infections (sepsis, malaria), congenital heart disease

*Boldface indicates more common in adults.
†No human case yet reported with glucagon or adrenaline deficiency.
HMG = 3-hydroxy-3-methylglutaryl; IGF = insulin-like growth factor.

Changes During Fasting

During fasting, the basal rate of glucose output by the liver (2.2 mg/kg/minute in healthy adults after an overnight fast) is precisely matched to glucose uptake by various body tissues. The brain is responsible for nearly two thirds of basal glucose utilization, with the remaining one third used by red blood cells, the renal medulla, and, to some extent, muscle and fat.

Glucose production results largely from a combination of glycogenolysis and gluconeogenesis in the liver, with some contribution from renal gluconeogenesis. Breakdown of stored hepatic glycogen is a readily available source of free glucose. In an average adult, however, glycogenolysis can provide less than an 8-hour supply of free glucose, so gluconeogenesis is important to augment hepatic glycogen stores during an overnight fast.

The key enzymes involved in gluconeogenesis are pyruvate carboxylase, phosphoenolpyruvate carboxykinase, and fructose-1,6-bisphosphatase. Muscle and adipose tissue, which utilize glucose in the fed state, respond to prolonged fasting by reducing their glucose uptake and satisfying their energy requirements by the β-oxidation of fatty acids. Additionally, through the process of proteolysis, muscle tissue provides amino acids to the liver to serve as gluconeogenic precursors for net glucose formation. Changes in the hormonal milieu during fasting (suppressed insulin and elevated counter-regulatory hormones) stimulate the formation of ketones, which serve as a substitute fuel and diminish the need to catabolize protein as a source of gluconeogenesis.

Changes During Feeding

After a meal, plasma glucose concentrations increase, stimulate the secretion of insulin from the pancreatic β-cells, and suppress secretion of glucagon from the pancreatic α-cells. This change in the hormonal milieu switches off endogenous hepatic glucose production and accelerates glucose utilization by liver, muscle, and adipose tissue. The glucose concentration then returns gradually to the post-absorptive level, at which the endogenous production of glucose is equal to the uptake of glucose by peripheral tissues.

Counter-Regulatory Hormonal Responses to Hypoglycemia

Counter-regulatory hormones play a key role in the maintenance of a normal plasma glucose concentration (Fig. 211-2).[4] Neurons in the portal and mesenteric veins detect changes in blood glucose prior to entry into the liver from the gut. This information is then relayed through the vagus nerve and spinal cord to the hindbrain and then to the hypothalamus. In addition, the hypothalamus, because of its location adjacent to the third ventricle and median eminence, may sample factors from peripheral circulation, including glucose, as well as hormones such as insulin and leptin. Ventromedial neurons in the hypothalamus contain the same glucose-sensing mechanisms (e.g., glucokinase, adenosine triphosphate [ATP]-sensitive K^+ channels) as found in pancreatic β-cells. In healthy individuals, this counter-regulatory system ensures that hypoglycemia is rarely experienced and would occur only during starvation or ultra-endurance sports. During the counter-regulatory hormonal response, a reduction in the plasma glucose concentration will result in a decrease in the secretion of insulin and an increase in the secretion of glucagon, epinephrine, norepinephrine, cortisol, and growth hormone secretion. Any drug or disease that inhibits the counter-regulatory system can predispose the patient to hypoglycemia.

The secretion of glucagon increases rapidly in response to decreasing plasma glucose levels, and this glucagon response is the primary essential defense mechanism against acute hypoglycemia. Insulin secretion from pancreatic β-cells is reduced in healthy individuals when the plasma glucose concentration falls below 72 mg/dL (4.0 mmol/L). As insulin secretion is reduced, the repressive effect of insulin on pancreatic α-cell function is removed, thereby rapidly increasing glucagon secretion. Glucagon acts on the liver to increase hepatic glycogenolysis and gluconeogenesis. When the plasma glucose concentration falls below about (68 mg/dL [3.8 mmol/L]), epinephrine and norepinephrine are released from the adrenal glands and nerve terminals, thereby further suppressing insulin secretion, increasing glucagon secretion, and decreasing peripheral glucose utilization in the muscle and increasing lipolysis in the adipose tissues.

Growth hormone and cortisol increase the rate of gluconeogenesis and antagonize the effects of insulin. In adults, the secretion of cortisol and growth hormone increases in response to plasma glucose concentrations within the normoglycemic range. Additional secretion of growth hormone and cortisol occurs below a plasma glucose concentration of about 66 mg/dL (3.7 mmol/L), and these hormones initiate the adaptive response to hypoglycemia (e.g., during prolonged starvation); glucose-raising actions are much slower in onset (several

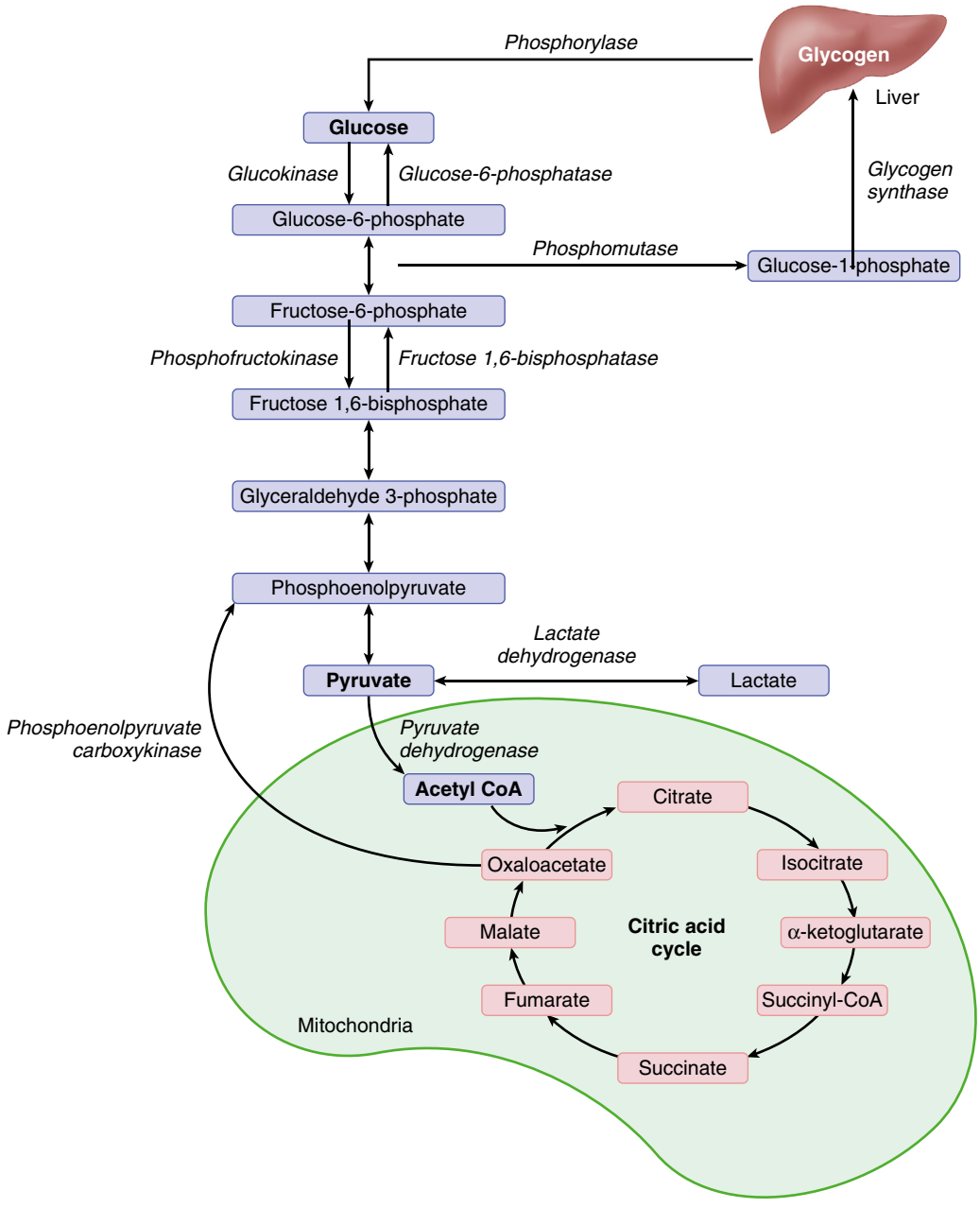

FIGURE 211-1. Outline of the biochemical pathways involved in the physiology of glucose.

hours). These hormone responses stimulate lipolysis, ketogenesis, and gluconeogenesis. Permissive amounts of cortisol and growth hormone are required for a normal hepatic response to glucagon and epinephrine.

CLINICAL MANIFESTATIONS

Symptoms of Hypoglycemia

The symptoms of hypoglycemia, which reflect the responses of the brain to a decrease in the blood glucose level, can be nonspecific and vague. Some symptoms arise as a result of the central nervous system being deprived of glucose (neuroglycopenic), whereas others arise from physiologic changes caused by the central nervous system–mediated, sympatho-adrenal discharge that is triggered by the hypoglycemia (neurogenic or autonomic). The neurogenic symptoms of hypoglycemia are largely the result of sympathetic neural, rather than adrenomedullary, activation.

Neuroglycopenic symptoms (e.g., dizziness, confusion, tiredness, difficulty with speaking, headache, inability to concentrate, coma, and seizures) arise from the failure of brain function itself and are caused by deficient supply of glucose. Neurogenic symptoms include both adrenergic responses (catecholamine-mediated symptoms, such as palpitations, tremor, and anxiety) and cholinergic responses (acetylcholine-mediated symptoms, such as sweating, hunger, paresthesias). Awareness of hypoglycemia chiefly depends on perception of the central and peripheral effects of neurogenic (as opposed to neuroglycopenic) responses.

In nondiabetic adults during acute insulin-induced hypoglycemia, autonomic symptoms become apparent at a threshold of approximately 60 mg/dL (3.3 mmol/L), whereas impairment of brain function manifested by neuroglycopenic symptoms occurs at a threshold of approximately 50 mg/dL (2.8 mmol/L) in arterialized venous blood (venous levels would be ≈3 mg/dL [0.16 mmol/L] less). However, the glycemic thresholds for responses to hypoglycemia are reset at a lower plasma glucose concentration in patients with recurrent hypoglycemia. In nondiabetic individuals, the symptoms and signs of hypoglycemia are not influenced by the rate of the decline in blood glucose levels.

SPECIFIC CAUSES OF HYPOGLYCEMIA

Hypoglycemia is more common in childhood than in adulthood, and the cause can also vary by age (see Table 211-1).

Critical Illness

Hypoglycemia frequently occurs in patients in the critical care setting and is associated with factors such as sepsis, multiorgan failure, and the inappropriate use of intensive insulin therapy. The successful management of blood glucose levels during critical illness is associated with improved outcomes.

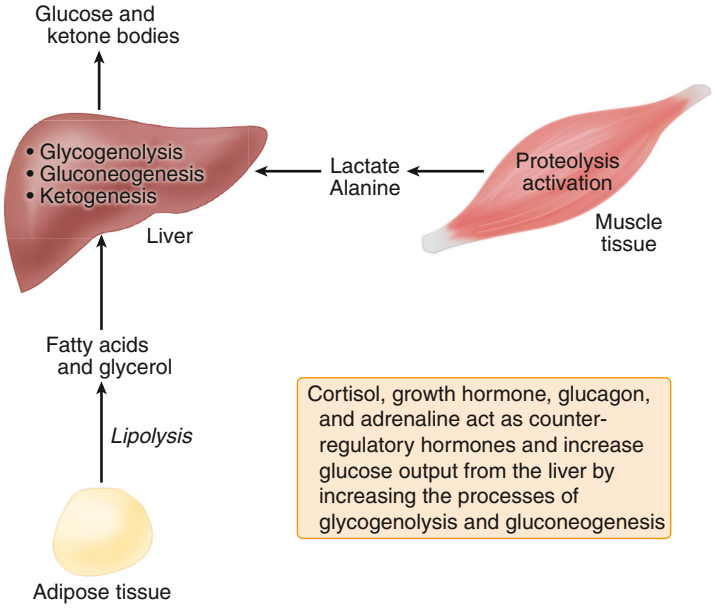

FIGURE 211-2. **The role of the counter-regulatory hormones, glycogenolysis, gluconeogenesis, and lipolysis in glucose physiology.**

Excess Production of Hormones

The two most common conditions associated with excess production are hyperinsulinemic hypoglycemia and non–islet cell tumors that secrete insulin-like growth factor (IGF).[5] The inappropriate production of insulin can lead to either fasting or postprandial hypoglycemia.

Hyperinsulinemic hypoglycemia is caused by a heterogeneous group of disorders characterized by unregulated insulin secretion from pancreatic β cells. When hypoglycemic patients have inappropriately detectable serum insulin (or C-peptide) levels, low ketone bodies, and low fatty acids, they have a glycemic response to glucagon.

Congenital Hyperinsulinemia

Congenital hyperinsulinemic hypoglycemia is related to mutations in the key genes (*ABCC8, KCNJ11, GLUD1, GCK, HADH, SLC16A1, HNF4A, HNF1A, HK-1, PGM-1, UCP2, PMM2, FOXA2,* and *CACNA1D*) that regulate insulin secretion.[6] Hyperinsulinism–hyperammonemia syndrome owing to activating mutations in the *GLUD1* gene or activating mutations in the *GCK* gene have also been described in adults, as has exercise-induced hyperinsulinemic hypoglycemia owing to activating mutations in the *SLC16A1* gene. Activating mutations in the *AKT2, AKT3, PIK3CA, PIK3R2,* and *CCND2* genes lead to autonomous activation of the insulin signaling pathway but no detectable insulin in the blood.[7]

Insulin-Receptor Mutations

Postprandial hyperinsulinemic hypoglycemia can be caused by a heterozygous mutation (Arg1174Gln) in the insulin-receptor gene. Hyperinsulinism is associated with decreased degradation rather than increased secretion of insulin, despite normal levels of serum C-peptide and reduced clearance of exogenous insulin during clamp studies.

Insulinoma

The most common cause of endogenous hyperinsulinemic hypoglycemia in adults is an insulinoma,[8] which is an insulin-secreting tumor of pancreatic origin, with an incidence of 1 to 4 cases per million, peaking in the fifth and sixth decades. The majority (90%) are benign, solitary, intrapancreatic, and less than 2 cm in diameter, but 5 to 10% are malignant.[9] Symptoms classically become evident in the fasting state or following exercise, but insulinomas also can present with postprandial symptoms. An insulinoma can occur either in isolation or in association with multiple endocrine neoplasia type 1 (MEN 1), with a lifetime prevalence of 10% among adults carrying mutations in *MEN1* (Chapter 212). About 6% of insulinomas occur in patients with MEN 1. Recurrent somatic mutations in the *YY1* gene occur in some sporadic insulinomas, and some insulinomas show increased expression of hexokinase-1.

Postprandial Hyperinsulinemic Hypoglycemia

Postprandial hyperinsulinemic hypoglycemia refers to hypoglycemia within a few hours after a meal because of inappropriate secretion of insulin in response to it. When postprandial hyperinsulinemic hypoglycemia is clinically suspected, an oral glucose tolerance test or a mixed-meal provocation test is recommended. A physiologic dip in the blood glucose level seen in the oral glucose tolerance test might lead to misdiagnosis. However, corresponding biochemical evidence of endogenous hyperinsulinemic hypoglycemia and symptoms of neuroglycopenia during a hypoglycemic episode help distinguish between pathologic postprandial hyperinsulinemic hypoglycemia and reactive hypoglycemia.

Dumping Syndrome

In adults, dumping syndrome can be seen after esophageal (distal esophagectomy, myotomy for achalasia), gastric (Nissan wrap, hiatal hernia repair, gastrojejunostomy), and bariatric (Roux-en-Y and duodenal switch gastric bypass) surgeries (Chapter 201). The rapid delivery of food, including sugars, into the duodenum and jejunum alters the regulation of insulin and can lead to postprandial hyperinsulinemic hypoglycemia.[10]

The hypoglycemia may be due to an effect on the enteroinsular axis induced by the diversion of nutrients into the small intestine. The enhanced postprandial insulin secretion involves increased secretion of glucagon-like peptide 1 (GLP-1), and glucose-dependent insulinotropic polypeptide (GIP) GLP-1 levels are increased two- to five-fold after gastric bypass. IGF-2 and IGF-1 receptor alpha (IGF1Rα) also are overexpressed. A decrease of more than 108 mg/dL (6 mmol/L) between peak and nadir blood glucose levels during an oral glucose tolerance test has been used as a diagnostic criterion for dumping syndrome in adults.

Insulin Autoimmune Syndrome

Insulin autoimmune syndrome (Hirata disease) is a rare condition characterized by hyperinsulinemic hypoglycemia caused by physiologically inappropriate levels of bioavailable insulin associated with high titers of antibodies to endogenous insulin in the absence of prior exposure to exogenous insulin.[11] It affects men and women equally and is seen more frequently in patients older than age 40 years.

After a meal or glucose load, these patients often demonstrate initial hyperglycemia, followed by hypoglycemia a few hours later. The hyperglycemia is caused by the anti-insulin antibodies that bind the insulin secreted in response to rising blood glucose levels after a meal. This binding reduces the bioavailability of the secreted insulin to the receptors in the liver and peripheral tissues, thereby resulting in hyperglycemia and further insulin secretion. Insulin levels are markedly elevated, usually above 100 mU/L. As blood glucose concentrations begin to decrease and insulin secretion declines, the insulin bound to the antibodies is released, thereby resulting in inappropriately high free insulin concentrations for the blood glucose, causing hypoglycemia.

Non-Insulinoma Pancreatogenous Hypoglycemia Syndrome

Non-insulinoma pancreatogenous hypoglycemia syndrome is characterized by postprandial neuroglycopenia despite negative prolonged fasting tests and negative perioperative localization studies for insulinoma. Immunohistologic studies of resected pancreatic tissue do not show an increased rate of proliferation of β-cells or abnormal synthesis or processing of either proinsulin or amylin, and the cause is unknown. In some patients, however, the selective arterial calcium stimulation test is positive, with the histology of the resected pancreas showing nesidioblastosis. Otherwise, the cause of this syndrome is unknown.

Insulin Factitious Hypoglycemia

Hypoglycemia also can be induced pharmacologically, either intentionally as a diagnostic tool, accidentally as a complication of the treatment of diabetes mellitus (Chapter 210), or as a consequence of poisoning either with insulin itself or with oral or subcutaneous hypoglycemia drugs that stimulate insulin release. Whenever severe hypoglycemia occurs with documented hyperinsulinism, the possibility of Munchausen syndrome or Munchausen syndrome by proxy should be considered. The possibility of malicious administration of insulin or other hypoglycemia drugs should always be suspected in cases of sudden onset of hypoglycemia in a previously healthy individual. In cases of insulin administration, laboratory testing will show a raised insulin level accompanied by a normal C-peptide level.

Tumor-Associated Hypoglycemia

Non–islet cell tumor hypoglycemia denotes the syndrome of hypoglycemia produced by or associated with any neoplasm other than an insulinoma (Chapter 164).[12] These tumors are usually of mesenchymal or epithelial origin (including hepatomas, fibromas, and fibrosarcomas). The underlying mechanism of hypoglycemia in nearly all patients with this syndrome is overproduction by the tumor of insulin growth factor-2, which includes mature insulin growth factor-2 and incompletely processed forms of insulin growth factor-2, referred to collectively as "big" insulin growth factor-2. The elevated insulin growth factor-2–related peptides mimic the fasting hypoglycemia that is characteristic of patients with insulin-producing islet cell tumors. Rarely, markedly elevated insulin growth factor-2 levels produce somatic changes suggestive of acromegaly. Typically, the elevated insulin growth factor-2 levels are associated with suppressed plasma levels of insulin, insulin growth factor-1, and growth hormone. Hypoglycemia can also occur due to paraneoplastic secretion of insulin-like growth factor-1.

Drug- and Toxin-Induced Hypoglycemia

A number of drugs have been linked to hypoglycemia (see Table 211-1). Mechanisms vary, and, except for insulin and oral hypoglycemic agents, the risks in any individual are very low.

The white-fleshed lychee berry has been implicated as the cause of large-scale, severe hypoglycemia in the Bihar state of India. In some cases, however, the clinical history and physical examination may not provide any clues, and these patients will need more extensive investigation.

In an ideal situation, the blood glucose level should be measured at the time of a spontaneous episode of hypoglycemia. In addition, levels of insulin, C-peptide, proinsulin, and β-hydroxybutyrate should be measured and a toxicology screen for oral hypoglycemic agents should be performed. If the diagnosis is not obvious, additional laboratory testing (Table 211-2) may be helpful. However, provocative testing is often required.

Hypoglycemia Due to Hormone Deficiency

Deficiencies in growth hormone, adrenocorticotropic hormone (ACTH), or cortisol, alone or in combination with other hormones, can lead to hypoglycemia by reducing the mobilization of fats and proteins, as well as by increasing the utilization of glucose owing to increased insulin sensitivity of tissues in the absence of these two hormones. Acquired hypopituitarism (Chapter 205) may result from tumors (most commonly craniopharyngioma), radiation, infection, hydrocephalus, vascular anomalies, and trauma. Addison disease (Chapter 208) results from adrenal cortical hypofunction/dysfunction, with deficient production of glucocorticoids, mineralocorticoids, and androgens, associated with high levels of both ACTH and plasma renin activity (Chapter 208). Autoimmune Addison disease accounts for about 80% of cases in adults, with 10 to 15% of cases caused by tuberculosis infection (Chapter 299) and the remaining 5% by vascular, neoplastic, or rare genetic forms.

Hypoglycemia Due to Defects in Hepatic Glycogen Release/Storage

Homozygous glucose-6-phosphatase deficiency (glycogen storage disease type I, Von Gierke disease) is the most common glycogen storage disease that causes hypoglycemia (Chapter 191). Deficiency of this enzyme results in the inability to release free glucose from glucose-6-phosphate, with resultant hepatomegaly due to stored glycogen. These children and adults present with recurrent hypoglycemia associated with lactic acidosis, hyperuricemia, and hyperlipidemia. The two other glycogen storage diseases causing hypoglycemia are due to deficiencies of the enzymes amylo-1,6-glucosidase (glycogen storage disease type III) and liver phosphorylase (glycogen storage disease type VI). (See Chapter 191.)

Hypoglycemia Due to Defects in Gluconeogenesis

Gluconeogenesis, or the formation of glucose from mainly lactate/pyruvate, glycerol, glutamine, and alanine, plays an essential role in the maintenance of normoglycemia during fasting. Inborn deficiencies are known in each of the four enzymes of the glycolytic-gluconeogenic pathway: pyruvate carboxylase, phosphoenolpyruvate carboxykinase, fructose-1,6-bisphosphatase, and glucose-6-phosphatase. Patients with defects in gluconeogenesis present with fasting hypoglycemia and lactic acidosis.

Disorders of Carnitine Metabolism and Fatty Acid Oxidation

Disorders of fatty acid oxidation are individually rare but are collectively more common because of the number of different enzymes affected. Fatty acids are taken up by hepatocytes and muscle, where they are subsequently activated to their coenzyme A (CoA) esters. When fatty acid oxidation is impaired, clinical manifestations include hypoglycemic seizures, muscle damage, cardiomyopathy, metabolic acidosis, and liver dysfunction. When defects occur in fatty acid degradation, excess acylcarnitine intermediates accumulate in the heart, liver, and skeletal muscle, where it can lead to organ dysfunction. Acyl-carnitines that spill into the blood provide a marker for diagnosis.

Primary carnitine deficiency, which is an autosomal recessive disorder of fatty acid oxidation, can present at different ages with hypoketotic hypoglycemia, cardiomyopathy, or skeletal myopathy (Chapter 189). Patients with the hepatic isoform of carnitine palmitoyltransferase (CPT)-1 deficiency present with hypoketotic hypoglycemia in the neonatal period. This disease is suspected based on reduced levels of carnitine in plasma and confirmed by measurement of carnitine transport in the patient's fibroblasts.

The most common disorder of fatty acid β-oxidation is medium-chain acyl-CoA dehydrogenase deficiency,[13] which is an autosomal recessive disease that presents in children who are typically asymptomatic except during times of fasting or metabolic stress, when they present with fasting nonketotic hypoglycemia; if undiagnosed, 20 to 25% of affected patients will die during the first episode.

TABLE 211-2 ROUTINE BASELINE INVESTIGATIONS IN PATIENTS WITH SUSPECTED HYPOGLYCEMIA

BLOOD	URINE
Glucose	Ketones
Insulin	Reducing substances such as lactose and galactose
Cortisol	Propionic, methylmalonic, and isovaleric acids
Lactate	
Growth hormone	
Non-esterified fatty acids	
3β-Hydroxybutyrate	
Carnitine (free and total)	
Blood spot acylcarnitine	
Ammonia	

Metabolic Diseases

Hypoglycemia also can be due to a number of inherited metabolic conditions (Chapter 189), including galactosemia, fructosemia, tyrosinemia, organic acidemias, maple syrup urine disease, glutaric aciduria type II, defects in the mitochondrial respiratory chain, and citrin deficiency (see Chapter 189).

DIAGNOSIS

A careful clinical history, description of symptoms, physical examination, and a systematic approach is the cornerstone of establishing a diagnosis.[14] The symptoms of hypoglycemia may be very nonspecific, so a symptomatic patient must have the blood glucose level measured and documented.

Reagent strips in combination with a reflectance meter are the most common method of measuring bedside blood glucose levels. However, these tests can be inaccurate, so the blood glucose concentration should always be checked in the laboratory. Whole-blood glucose is approximately 15% lower than serum glucose levels because of the lower glucose content and intracellular water content of the red cells. Glucose concentrations in venous blood are 10% lower than arterial blood. The blood sample for glucose measurement should be collected in a fluoride container to inhibit glycolysis, and it also should be analyzed immediately because, even in the presence of fluoride, the blood glucose concentration will decrease over time.

The clinical history, description of symptoms, and physical examination may provide important clues to the underlying cause of hypoglycemia and guide the investigations. For example, hypoglycemia occurring after a short fast (2 to 3 hours) may be suggestive of hyperinsulinism or glycogen storage disease. Hypoglycemia occurring after a long fast (12 to 14 hours) may suggest a disorder of gluconeogenesis. Postprandial hypoglycemia may indicate dumping syndrome (including after gastric bypass surgery), insulinoma, insulin autoimmune syndrome, non-insulinoma pancreatogenous hypoglycemia syndrome, hereditary fructose intolerance, or galactosemia.

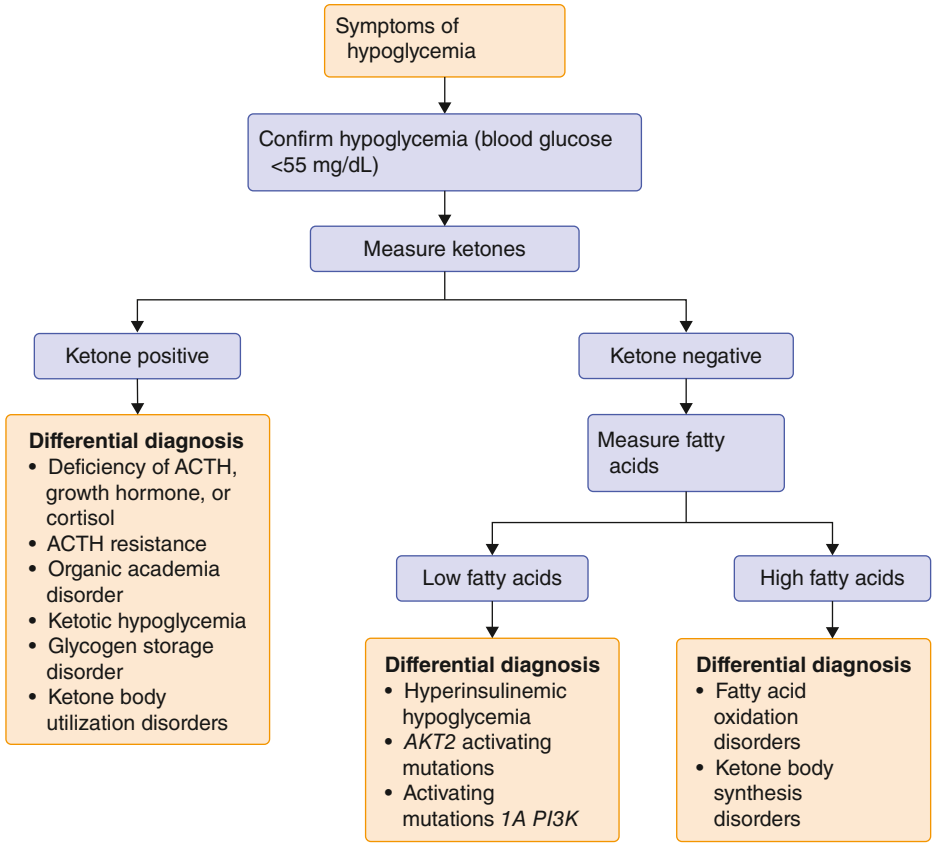

FIGURE 211-3. Diagnostic approach to hypoglycemia. ACTH = adrenocorticotropic hormone.

After the clinical history has been taken and the examination completed, a hypoglycemia diagnosis (see Table 211-1) should be a diagnostic cascade of appropriate tests that can evaluate the most common causes (Fig. 211-3). Because the signs and symptoms of hypoglycemia are nonspecific, this detailed evaluation should be undertaken only in patients who have the Whipple triad of symptoms, signs, or both consistent with hypoglycemia; a low plasma glucose concentration; and documented resolution of the symptoms or signs after the plasma glucose concentration is raised.

Fasting Tests

Controlled fasting tests are important procedures for eliciting the cause of hypoglycemia. In adults, the recommended approach is a prolonged (72-hour) supervised fast that is conducted in a standardized fashion (Table 211-3). The fast should be terminated if patients have any signs or symptoms of hypoglycemia accompanied by a documented plasma glucose concentration of 55 mg/dL (3 mmol/L) or less. The fast should not be prolonged beyond 72 hours if patients do not have any symptoms or signs of hypoglycemia or a documented low blood glucose level. Monitoring for symptoms or signs of hypoglycemia during the fast is essential because patients may experience symptoms but have serum glucose levels higher than the hypoglycemic range. In some healthy women (thin and lean) and men, blood glucose levels may drop to 40 mg/dL (2.2 mmol/L) during prolonged fasting. Some patients have lower glycemic thresholds without symptoms or signs of hypoglycemia.

The interpretation of serum insulin, C-peptide, and proinsulin during the 72-hour fast will depend on the concurrent plasma glucose concentration. Pancreatic β-cell insulin secretion becomes undetectable in healthy persons when the plasma glucose concentration falls to 55 mg/dL (3 mmol/L). Most patients with an insulinoma become hypoglycemic before 72 hours. However, continuation of the fast to 72 hours is necessary to exclude the likelihood of true hypoglycemia.

Hyperinsulinemic hypoglycemia in adults is characterized by plasma insulin concentrations of 3 μU/mL or greater (C-peptide of 200 pmol/L or more and proinsulin 5 pmol/L or more). Patients with insulinomas have plasma insulin concentrations that rarely exceed 100 μU/mL, and plasma insulin levels greater than 1000 μU/mL suggest exogenous insulin administration or the presence of insulin antibodies. In children, any detectable plasma insulin in the presence of hypoglycemia is inappropriate and is highly suggestive of hyperinsulinemic hypoglycemia.

Measurement of the plasma β-hydroxybutyrate concentration is used as a surrogate marker of insulin action at the end of the 72-hour fast in healthy adult individuals and when the Whipple triad is fulfilled during a diagnostic fast. In patients with hyperinsulinemic hypoglycemia, plasma concentrations of β-hydroxybutyrate are typically less than 2.7 mmol/L because of the suppressive action of insulin on ketogenesis. Healthy individuals will have a progressive rise in the concentration of β-hydroxybutyrate during the 72-hour test. If a value above 2.7 mmol/L is documented at any time point in the fast, the test can be terminated.

During the 72-hour prolonged fast, blood also should be collected for measurement of plasma sulfonylureas and meglitinides if the patient develops hypoglycemia. Sulfonylureas stimulate pancreatic secretion of β-cell insulin and C-peptide, and the biochemical pattern is similar to that of an insulinoma.

TABLE 211-3 PROTOCOL FOR 72-HOUR FAST IN ADULTS

1. Start the fast from the last ingestion of a meal. Stop all medications that might interfere with test.
2. The patient can drink water during the test.
3. The patient must be active during waking hours.
4. Measure plasma glucose, insulin, C-peptide, and β-hydroxybutyrate (on the same venipuncture specimen) every 6 hours until plasma glucose reaches 60 mg/dL (3.3 mM). Then measure every 1 to 2 hours.
5. End the fast when the plasma glucose is 45 mg/dL (2.5 mM) and the patient has symptoms or signs of hypoglycemia, or plasma glucose is 55 mg/dL if Whipple triad had been demonstrated previously.
6. At the end of the fast, measure plasma glucose, insulin, C-peptide, β-hydroxybutyrate, and sulfonylurea (on the same venipuncture specimen). Then inject glucagon, 1 mg intravenously, and measure plasma glucose every 10 minutes three times. Once the fast is completed, allow the patient to eat normally.

Adapted from Cryer PE, Axelrod L, Grossman AB, et al. Evaluation and management of adult hypoglycemic disorders: an Endocrine Society clinical practice guideline. *J Clin Endocrinol Metab*. 2009;94:709-728.

TABLE 211-4 SUGGESTED PROTOCOL FOR A MIXED-MEAL DIAGNOSTIC TEST IN ADULTS

1. Fast patient overnight. Stop all medications that might interfere with test.
2. Use a mixed meal similar to one that causes patient to experience symptoms.
3. Collect samples for plasma glucose, insulin, C-peptide, and proinsulin before ingestion and every 30 minutes through 300 minutes after meal ingestion.
4. Observe the patient for symptoms and/or signs of hypoglycemia and ask the patient to keep a written log of all symptoms, timed from the start of meal ingestion.
5. The mixed-meal test should be interpreted on the basis of laboratory measured plasma glucose concentrations, not those estimated with a point-of-care glucose monitor. If it is judged necessary to treat before 300 minutes because of severe symptoms, obtain samples for all the following *before* administering carbohydrates: plasma insulin, C-peptide, and proinsulin (sent for analysis only in those samples in which plasma glucose is <60 mg/dL [3.3 mmol/L]), and a measurement of oral hypoglycemic agents. If Whipple's triad is demonstrated, antibodies to insulin should also be measured.

Adapted from Cryer PE, Axelrod L, Grossman AB, et al. Evaluation and management of adult hypoglycemic disorders: an Endocrine Society clinical practice guideline. *J Clin Endocrinol Metab*. 2009;94:709-728.

Mixed-Meal Test

A mixed-meal test is performed in patients who have a history suggestive of neuroglycopenic symptoms for up to 5 hours after the ingestion of food (Table 211-4). A positive test is defined as the onset of neuroglycopenic symptoms in association with a documented low blood glucose level (e.g., ≤50 mg/dL). In postprandial hyperinsulinemic hypoglycemia, plasma insulin and C-peptide levels might be inappropriately elevated. Neuroglycopenic symptoms after a meal are reported in patients who have an insulinoma, patients who have the non-insulinoma pancreatogenous hypoglycemia syndrome, and patients who have undergone surgery for obesity.

The combination of a positive mixed-meal test and a negative 72-hour fast may occur in a patient with insulinoma or with non-insulinoma pancreatogenous hypoglycemia syndrome. The 5-hour oral glucose tolerance test should not be used as a sole diagnostic test for hypoglycemia, because a substantial percentage of healthy persons may have a serum glucose concentration of 50 mg/dL (2.7 mmol/L) or less.

Glucagon Stimulation

Another useful marker of insulin action is the glycemic increment in response to an intravenous/intramuscular injection of glucagon (1-mg dose in adults). Patients with hyperinsulinemic hypoglycemia will have increased glycogen stores, and glucagon will result in glycogenolysis. A positive response is defined as a maximal increment at least 25 mg/dL (1.3 mmol/L) greater than the terminal fasting serum glucose.

Insulin Antibodies

In patients with insulin autoimmune hypoglycemia, insulin antibodies, which may be monoclonal or polyclonal, are present in very high titers, in contrast to the much lower titers in insulin-treated diabetes. It is important to test for the presence of insulin antibodies, because even low titers—which may have no diagnostic significance—may cause spurious results of the assay for insulin. Hypoglycemia due to insulin autoimmune syndrome typically occurs in the fasting period but can occur postprandially as well.

Radiologic Investigations

When a diagnosis of insulinoma has been made, noninvasive imaging can often localize the source of pathologic insulin secretion. The sensitivity of transabdominal ultrasonography for the localization of insulinomas is poor (ranging from 9% to 64%). However, insulinomas demonstrate characteristic features when imaged with both computed tomographic (CT) scanning and magnetic resonance imaging (MRI), and the sensitivity of these techniques is 33 to 64% and 40 to 90%, respectively, with MRI generally superior to CT, especially for the detection of extra pancreatic extensions. Insulinomas generally demonstrate low signal intensity on T1-weighted images and high signal intensity on T2-weighted images.

Invasive modalities such as endoscopic ultrasound and arterial stimulation with venous sampling are highly accurate for the preoperative localization of insulinomas and are superior to noninvasive localization techniques. Endoscopic ultrasound is currently the test of choice in most Western centers, with reported detection rates of 86.6 to 92.3%. Arterial stimulation and venous sampling have greatly facilitated the precise regionalization of insulinomas smaller than 2 cm, which noninvasive techniques such as ultrasonography, CT, and MRI often fail to localize. A two- to three-fold increase in insulin concentration in the right hepatic vein in response to calcium injection into one or more of the arteries supplying the pancreas suggests that the region served by that artery may harbor abnormally functioning β-cells, whether from insulinoma or islet hypertrophy or nesidioblastosis. Calcium injection will stimulate a brisk response of insulin, C-peptide, and proinsulin simultaneously, and the magnitude of increase of both insulin and C-peptide appears to be correlated well with the degree of differentiation of the tumor cells. The positive responses to selective arterial calcium stimulation in some patients with non-insulinoma pancreatogenous hypoglycemia syndrome, despite negative radiologic localizing studies, establishes that this technique should be performed in all adults with hyperinsulinemic hypoglycemia of unknown etiology.

Insulinomas have been shown to express GLP-1R in high density, and GLP-1R imaging has been used in some patients for localization of an insulinoma.[15] Fluorine-18-L-dihydroxyphenylalanine (18F-DOPA) positron emission tomography (PET) also has been used in localizing neuroendocrine tumors. 18F-DOPA PET has been found to be useful in some patients with insulinoma who had negative CT, MRI, and ultrasound results. Intraoperative manual palpation of the pancreas by an experienced surgeon and intraoperative ultrasonography are both sensitive methods with which to finalize the location of insulinomas.

Protein/Leucine Sensitivity Testing

Protein sensitivity is observed in some patients with congenital hyperinsulinemic hypoglycemia owing to mutations in the genes *ABCC8/KCNJ11*, *GDH*, and *HADH* that lead to protein-induced hypoglycemia. These patients will demonstrate severe hypoglycemia in response to a protein or leucine load.

Exercise Test

In some patients, exercise can trigger unregulated insulin secretion—a reaction referred to as exercise-induced hyperinsulinism. Promoter-activating mutations induce expression of the *SLC16A1* gene in β-cells, in which this gene is not usually transcribed, thereby permitting pyruvate uptake and pyruvate-stimulated insulin release despite ensuing hypoglycemia. An exercise test will identify this group of patients.

Genetic Studies

Genetic testing should be undertaken in children who have been diagnosed with congenital hyperinsulinemic hypoglycemia and other causes of hypoglycemia that might have a genetic basis. Mutation in the genes *ABCC8/KCNJ11* is the most common cause of medically unresponsive congenital hyperinsulinemic hypoglycemia. All patients with insulinoma and non-insulinoma islet cell tumors should be tested for mutations in the *MEN1/YY1* genes.

TREATMENT

Emergency Management

Acute management of hypoglycemia involves administration of oral glucose (dextrose gel)[A1,A2] if the patient is able to swallow. If patients cannot swallow, a bolus of intravenous glucose (in adults a bolus of 50% dextrose) should be given to correct the blood glucose level. Glucagon (1mg intramuscularly) can be used in the emergency management of hypoglycemia if the blood glucose level does not rise after giving intravenous glucose or if an intravenous cannula cannot be inserted. New nasal forms of glucagon are now available for the treatment of hypoglycemia,[16] but the intramuscular formulation is still recommended in this setting. Glucagon can cause rebound hypoglycemia, so the patient will need blood glucose monitoring after the administration of glucagon.

Management of Specific Causes of Hypoglycemia

The long-term management of hypoglycemia depends on the underlying cause, so establishing the correct diagnosis is fundamentally important.

Critical Illness–Associated Hypoglycemia

For critical illness–associated hypoglycemia, therapy focuses on treating sepsis, addressing any organ failure (especially liver failure), and making sure that no medications are contributing to the hypoglycemia.

Congenital Hyperinsulinemic Hypoglycemia

Diazoxide (5 to 20 mg/kg/day given orally three times daily) is the first-line medical therapy in children and adults with hyperinsulinemic hypoglycemia caused by congenital mutation. Fluid retention is a major side effect. Diazoxide may be combined with a diuretic (e.g., hydrochlorothiazide 25 to 50 mg daily in adults) to reduce the side effect of fluid retention. Second-line therapies include short-acting octreotide (5 to 35 μg/kg/day as an infusion or subcutaneous injections three or four times daily) or long-acting octreotide and glucagon (1 to 10 μg/kg/hour given as a subcutaneous or intravenous infusion). mTOR inhibitors (such as sirolimus, 0.5 mg/m^2/day given in one or two divided doses) have been tried as a last resort for patients who have diffuse forms of hyperinsulinemic hypoglycemia and who do not want to undergo a near total pancreatectomy.[17]

Insulinomas and Other Pancreatic Tumors

For adult patients with insulinoma, pancreatectomy is the treatment of choice (Chapter 213). However, insulinomas in adults may respond to therapy with diazoxide and octreotide (including long-acting octreotide). The mTOR inhibitor everolimus has been reported to be effective in controlling hypoglycemia in patients with malignant insulinomas or patients who cannot undergo surgical resection. Patients who have non–islet cell tumor hypoglycemia or IGF-2-omas also require resection of the primary tumor.

Postprandial Hypoglycemia and Dumping Syndrome

Conventional treatment approaches include acarbose, diazoxide, and octreotide. However, most of these options are either ineffective or limited by poor tolerance. Recently the use of calcium channel blockers and sodium glucose cotransporter-1 inhibitors (such as canagliflozin) has been described with some success. In some severe cases a pancreatectomy may be indicated.

Other Hypoglycemic Syndromes

The insulin autoimmune syndrome will respond to therapy with glucocorticoids (e.g., prednisolone starting at 0.5 mg/kg), but some patients have responded to diazoxide and octreotide. For tumor-associated hypoglycemia (Chapter 164), the localization and resection of the tumor is the treatment of choice. For drug- or toxin-induced hypoglycemia, the removal or avoidance of the responsible toxin is the treatment of choice.

Patients who have deficiencies of growth hormone or cortisol will require replacement therapy with recombinant growth hormone (e.g., between 0.02 to 0.03 μg/kg/day) and hydrocortisone (10 to 12 mg/m^2/day). Replacement therapy with glucocorticoids and mineralocorticoids can be life-saving in patients with adrenal insufficiency (Chapter 208).

Patients with hypoglycemia due to disorders of hepatic glycogen storage and release must avoid prolonged periods of fasting (Chapter 191). Raw, uncooked cornstarch is commonly used as a slow-release source of glucose and helps with prolonging the period of fasting.

For patients who have hypoglycemia due to defects in fatty acid oxidation, disorders of gluconeogenesis, and disorders of ketone body metabolism, the principles of treatment are similar to those already discussed. However, patients with fatty acid oxidation disorders should have carnitine supplementation (2 g by mouth daily in adults).

PROGNOSIS

For adults with insulinomas, pancreatectomy provides excellent long-term results, especially when the tumor can be completely removed.[18] The prognosis for other forms of hypoglycemia varies widely and depends on whether the underlying cause can be successfully addressed.

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212 POLYGLANDULAR DISORDERS

LYNNETTE K. NIEMAN AND ALLEN M. SPIEGEL

DEFINITION

Polyglandular syndromes are disorders of dysfunction and pathology of more than one endocrine gland. These disorders can be classified into *neoplastic syndromes* with abnormal endocrine cell proliferation and often, but not invariably, hormone hypersecretion, and *autoimmune syndromes*, in which immune destruction of endocrine cells often results in hypofunction and reduced hormone secretion. Both the neoplastic and autoimmune polyglandular syndromes often have nonendocrine manifestations that are relatively syndrome specific. With the recent recognition of the many nonendocrine components of some autoimmune polyglandular syndromes, especially type 3, the term multiple autoimmune syndromes is increasingly being used.[1]

With few exceptions, the polyglandular syndromes are due to germline mutations of key growth regulatory genes (neoplastic syndromes)[2] or immune regulatory genes (autoimmune syndromes). These disorders must be differentiated from sporadic single–endocrine gland diseases for several reasons. First, recognition of a specific polyglandular syndrome should alert the clinician to look for other endocrine and extra-endocrine manifestations of the syndrome. Although some patients will present with multiple endocrine gland manifestations, some will initially present with only a single affected endocrine gland. Careful family history and screening for other endocrine and characteristic extra-endocrine manifestations are needed in such cases. Second, treatment of polyglandular disease may differ from treatment of individual gland disease. Third, because of the genetic basis of most of these syndromes, a careful family history and, in some cases, screening other family members to allow disease prevention in affected individuals are indicated.

This chapter discusses the best-characterized polyglandular disorders. Other chapters on the anterior pituitary (Chapter 205), thyroid (Chapter 207), adrenal cortex (Chapter 208), adrenal medulla (Chapter 209), pancreatic islets (Chapters 211 and 213), and parathyroids (Chapter 227) should be consulted for more detailed discussion of the diseases of individual glands.

EPIDEMIOLOGY

In the United States, the prevalence of multiple endocrine neoplasia type 1 (MEN 1) is estimated to be between 1 per 10,000 and 1 per 30,000. The total prevalence of MEN2A and B is estimated to be about 1 per 35,000.

NEOPLASTIC SYNDROMES

Seven distinct neoplastic syndromes involve more than one endocrine gland: MEN 1,[3] multiple endocrine neoplasia types 2A (MEN 2) and 2B (sometimes referred to as MEN 3),[4] multiple endocrine neoplasia type 4 (MEN 4),[5] multiple endocrine neoplasia type 5 (MEN 5),[6] Carney complex,[7] von Hippel-Lindau disease (VHL),[8] and McCune-Albright syndrome[9] (Table 212-1). Patients with polyglandular neoplastic syndromes typically present with their respective endocrine tumors at a younger age than patients with single-gland sporadic endocrine tumors.

All but McCune-Albright syndrome are caused by heterozygous germline mutations and are inherited in autosomal dominant fashion. The genes responsible for multiple endocrine neoplasia 1, 4, 5, Carney complex, and von Hippel-Lindau disease act as tumor suppressor genes. Germline loss-of-function mutations in one allele are followed by somatic mutations that inactivate the second normal allele, thereby leading to tumorigenesis. The basis for the tissue-specific expression of both the endocrine and extra-endocrine manifestations of these syndromes is not well understood, but the germline nature of the mutation and the expression of the affected gene in more than one endocrine gland explain the polyglandular aspect of the disorder. Multiple endocrine neoplasia 2A and 2B, in contrast, are caused by germline activating mutations of an oncogene, *RET*. The pattern of expression of this gene,

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ABSTRACT

Polyglandular syndromes are disorders in which there is dysfunction and pathology of more than one endocrine gland. These may be either neoplastic syndromes, involving proliferation of various tissues and often a component of hyperfunction of endocrine glands, or they may be autoimmune syndromes in which immune destruction of tissues may result in loss of function. In general, these are genetic syndromes in which key growth regulatory genes (neoplastic disorders) or immune regulatory genes (autoimmune disorders) are mutated. Patients presenting with only one feature of these syndromes should be screened for the other features to ensure that all manifestations are treated and to enable screening of other family members or genetic counseling of the patient.

KEYWORDS

autoimmune polyglandular syndrome
MEN 1
MEN 2A
MEN2B
MEN 4
MEN5
Carney complex
von Hippel-Lindau disease
McCune-Albright syndrome
multiple autoimmune syndrome

TABLE 212-1 POLYGLANDULAR NEOPLASIA SYNDROMES

SYNDROME	GENETIC BASIS*	ENDOCRINE TUMORS	NONENDOCRINE FEATURES
MEN 1	*MEN1*	Parathyroid Anterior pituitary Pancreatic islet	Subcutaneous lipomas Skin collagenomas
MEN 2 (A and B)	*RET*	Medullary thyroid cancer Pheochromocytoma Parathyroid (2A)	Mucosal neuromas (2B) Megacolon (2B)
MEN 4	*CDNK1B*	Anterior pituitary Parathyroid	Renal tumors
MEN5	*MAX*	Pheochromocytoma Paraganglioma Anterior pituitary	Chondrosarcoma Lung adenocarcinoma
Carney complex	*PKAR1A*	Adrenal cortex Anterior pituitary Thyroid	Atrial myxomas Skin lentigines Blue nevi
von Hippel-Lindau disease	*VHL*	Pheochromocytoma Pancreatic islet	Renal cell cancer CNS hemangioblastoma
McCune-Albright syndrome	*GNAS* (mosaic)	Thyroid Anterior pituitary Adrenal cortex Gonads	Fibrous dysplasia Café au lait skin lesions

*With the exception of McCune-Albright, all syndromes are caused by heterozygous germline mutations of the gene listed and show autosomal dominant inheritance.
CNS = central nervous system; MEN = multiple endocrine neoplasia.

involving chromaffin cells, helps explain the specific clinical manifestations. McCune-Albright syndrome is caused by a somatic rather than germline mutation that constitutively activates the ubiquitously expressed *GNAS* gene. This mutation, which may occur early in embryogenesis, leads to unregulated cyclic adenosine monophosphate (cAMP) formation in affected cells. The resultant mosaic distribution of the mutant gene helps explain the pleiotropic manifestations of the disease.

TREATMENT

Treatment of the polyglandular neoplastic syndromes, both in terms of the neoplastic component and the hormone hypersecretion, poses greater challenges than treatment of individual endocrine tumors.[10] For disorders with high risk of fatal cancer, such as medullary thyroid cancer in multiple endocrine neoplasia 2, early genetic diagnosis and prophylactic surgical removal of the thyroid is indicated. In other disorders such as multiple endocrine neoplasia 1 and Carney complex, less aggressive approaches such as selective tumor resection and pharmacologic treatment to reduce hormone hypersecretion may be more appropriate. More detailed discussion of the clinical features, diagnosis, and treatment of these neoplastic syndromes may be found in other chapters (multiple endocrine neoplasia 1 in Chapter 227; multiple endocrine neoplasia 2 and 3 in Chapter 213; McCune-Albright syndrome in Chapters 214 and 217).

AUTOIMMUNE SYNDROMES

Organ-specific autoimmune disease, characterized by lymphocytic infiltration and organ-specific autoantibodies, commonly results in endocrine hypofunction. Not uncommonly, however, disorders of more than one endocrine gland appear in families or individual patients. Characteristic patterns of disease presentation and genetic inheritance allow the definition of two syndromes with overlapping manifestations (Table 212-2).[11]

AUTOIMMUNE POLYGLANDULAR SYNDROME TYPE 1

DEFINITION

Autoimmune polyglandular syndrome type 1 is a rare disease that is also known as autoimmune polyendocrinopathy, candidiasis, and ectodermal dystrophy syndrome. It typically manifests in early childhood.

TABLE 212-2 CLINICAL FEATURES OF AUTOIMMUNE POLYGLANDULAR SYNDROMES

FEATURE	TYPE 1	TYPE 2
Mucocutaneous candidiasis	Very common	Not seen
Hypoparathyroidism	Common	Rare
Addison disease	Common	Common
Primary hypogonadism	Common	Occurs
Autoimmune thyroid disease	Rare	Common
Autoimmune diabetes	Occurs	Common
Alopecia	Common	Occurs
Keratopathy	Common	Not seen
Tympanic membrane calcification	Common	Not seen
Hypophysitis	Occurs	Occurs
Pernicious anemia	Occurs	Occurs
Vitiligo	Occurs	Occurs
Malabsorption syndrome	Occurs	Occurs as celiac disease
Autoimmune hepatitis	Occurs	Not seen
Autoimmune pneumonitis	Occurs	Not seen
Myasthenia gravis	Not seen	Occurs
Inheritance	Autosomal recessive	HLA association
Age at onset	Usually childhood	Usually adulthood

HLA = human leukocyte antigen.

PATHOBIOLOGY

Autoimmune polyglandular syndrome type 1 is an autosomal recessive disorder caused by a variety of inactivating mutations in the gene encoding autoimmune regulator-1 (AIRE-1),[12] which controls the expression of autoantigens by medullary epithelial cells of the thymus. These antigens are also expressed in peripheral tissues. Their expression in the thymus is important for negative selection (elimination) of autoreactive T cells, which underlies the development of (self-) tolerance. These autoreactive

T cells escape to the periphery in the absence of AIRE and, if activated, induce autoimmune destruction of the specific tissue. The appearance of organ-specific autoantibodies precedes disease presentation and predicts the development of specific end-organ damage. The role of these antibodies is unknown, however.

CLINICAL MANIFESTATIONS AND DIAGNOSIS

Mucocutaneous candidiasis (Chapter 310) occurs in virtually all patients and is usually the first manifestation of disease.[13] Each of the disease components should be sought when any patient presents with hypoparathyroidism, primary adrenal insufficiency, or mucocutaneous candidiasis.

Hypoparathyroidism (Chapter 227) and Addison disease[14] (Chapter 208) are the most common endocrine manifestations; each of these diseases occurs in 70 to 80% of patients. Hypoparathyroidism usually precedes Addison disease; both diseases typically manifest before age 15 years. Premature ovarian failure (in 60% of affected women) usually presents as secondary amenorrhea; testicular failure occurs less frequently. Insulin-dependent diabetes mellitus occurs in 12% of patients, usually in adulthood; hypothyroidism is uncommon.

Nonendocrine components of this syndrome, in addition to the mucocutaneous candidiasis, include alopecia, vitiligo, ocular complications (e.g., keratitis, blepharitis, retinitis, corneal opacities, and ptosis), cerebellar ataxia, autoimmune hepatitis, enamel hypoplasia of teeth, tympanic membrane calcification, obstructive respiratory disease, nail dystrophy, parietal cell atrophy, vitamin B_{12} malabsorption, and more general intestinal malabsorption with steatorrhea. Asplenism, with Howell-Jolly bodies on peripheral blood smears (Fig. 154-3), has been noted in several patients. Pneumonitis, present in up to 40% of patients, may be underrecognized.

TREATMENT

The hypoparathyroidism is treated like the sporadic disease, with oral elemental calcium (500 to 1000 mg every 6 to 12 hours) and 1,25-dihydroxyvitamin D (e.g., calcitriol 0.25 to 2 mg daily), although variable intestinal malabsorption can present a particular therapeutic challenge. The goal is to maintain the serum calcium level in the low normal range, 8.0 to 8.5 mg/dL (2.0 to 2.1 nmol/L), to reduce the risk of iatrogenic kidney stones. Synthetic 1-84 parathyroid hormone (50 to 100 μg subcutaneously daily) can reduce the needed doses of calcium and vitamin D. The candidiasis usually can be satisfactorily controlled with topical ketoconazole for 1 to 2 weeks, with itraconazole oral solution if needed (Chapter 310). Primary adrenal insufficiency is treated with replacement of glucocorticoids and mineralocorticoids (see Chapter 208).

PROGNOSIS

The prognosis of the variably expressed hormonal disorders is similar to that of their sporadic counterparts. When the diagnosis of autoimmune polyglandular syndrome type 1 is made, surveys for other components of the syndrome can allow earlier treatment than would otherwise occur.

AUTOIMMUNE POLYGLANDULAR SYNDROME TYPES 2, 3, AND 4

PATHOBIOLOGY

Autoimmune polyglandular syndrome types 2 and 3 are usually inherited in families with characteristic (normal) variants of genes that regulate the presentation of antigens to T cells and subsequent T-cell function. The most common genetic locus associated with this syndrome is the human leukocyte antigen (HLA) locus, particularly the B8, DR3, and DR4 alleles. The HLA associations do not predict disease absolutely, even in identical twins, so environmental or other genetic factors must influence disease presentation. Variants of the genes encoding cytotoxic T-lymphocyte antigen-4 (CTLA-4), the major histocompatibility complex class I chain-related gene A (MICA) allele 5.1, signal transducer and activator of transcription 4 (STAT4), and GATA binding protein 3 (GATA) can also predispose to Addison disease (autoimmune polyglandular syndrome type 2). The protein tyrosine phosphatase nonreceptor type 22 gene that encodes the lymphoid tyrosine phosphatase opposes signaling from the activated T-cell receptor. A variant of this gene is enriched in families with both type 1 diabetes mellitus and autoimmune thyroid disease. Genome-wide association studies have identified a large number of genes that are associated with type 1 diabetes and that influence immune responsiveness.

CLINICAL MANIFESTATIONS

Autoimmune polyglandular syndrome types 2 and 3 are considerably more common than type 1 and typically manifest in the fourth decade of life.[15] Insulin-dependent diabetes mellitus and thyroid dysfunction, either autoimmune hypothyroidism or Graves disease (Chapter 207), are the most frequent manifestations.[16] Addison disease (Chapter 208) is the third major endocrine component of this disorder, which is present only in autoimmune polyglandular syndrome type 2. Although most patients who present with autoimmune diabetes or thyroid disease have clinical involvement of only one gland, many patients with autoimmune Addison disease develop clinically evident disease in other endocrine glands. Less common components of type 2 or 3 autoimmune polyglandular syndrome include primary hypogonadism and hypophysitis. Pernicious anemia, vitiligo, celiac disease, alopecia, and myasthenia gravis (Chapter 390) are also associated with this syndrome. Additional autoimmune nonendocrine disorders in autoimmune polyglandular syndrome type 3 affect the gastrointestinal tract, pancreas, skin, and heart, as well as the hepatobiliary, nervous, and hematologic systems, and have led to the alternative term multiple autoimmune syndromes type 3.

Autoimmune polyglandular syndrome type 4 is a combination of endocrine and autoimmune diseases, including insulin-dependent diabetes, pernicious anemia, alopecia, vitiligo, or neuromuscular junction disorder but without Addison disease, thyroid disease, or hypoparathyroidism. A substantial proportion of these patients also may have positive autoantibodies against glutamic acid decarboxylase.

Organ-specific antibodies appear before clinical disease and predict subsequent disease. The role of these antibodies in organ hypofunction has not been established, however.

DIAGNOSIS

Thyroid hormone therapy can precipitate symptoms of adrenal insufficiency in patients with both disorders. Consequently, a careful history (including family history), physical examination, and a low threshold for specific laboratory testing for adrenal insufficiency should be part of the evaluation of every patient with autoimmune hypothyroidism. Further, combinations of hypothyroidism, adrenal insufficiency, and hypogonadism can mimic hypopituitarism, although specific hormonal testing (Chapter 205) can easily distinguish these disorders. Because multiple components of the syndrome can appear asynchronously, periodic evaluation for the early appearance of additional disease components is indicated.

TREATMENT

The treatment of each component of this syndrome is identical to the treatment of each disorder in isolation.

PROGNOSIS

The prognosis of the individual components of autoimmune polyglandular syndrome types 2 and 3 is the same as for the sporadic versions of each component.

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213 NEUROENDOCRINE NEOPLASMS

EDWARD M. WOLIN AND ROBERT T. JENSEN

DEFINITION

Neuroendocrine neoplasms,[1,2] formerly called neuroendocrine tumors, are now subclassified as well-differentiated neuroendocrine tumors and poorly differentiated neuroendocrine carcinomas. This new division has important implication for both prognosis and treatment. Neuroendocrine neoplasms occur in almost all tissues but have historically been divided into two large groups, pancreatic neuroendocrine neoplasms/tumors compared with neuroendocrine neoplasms in other locations, often called carcinoid tumors in older classifications.

EPIDEMIOLOGY

The annual incidence of neuroendocrine neoplasms in the United States is estimated to be about 12,000, a with prevalence of about 175,000. About 50% occur in the gastrointestinal tract, 20% in the lung, and 12% with an unknown primary.[3] Pancreatic neuroendocrine tumors account for 1 to 10% of all diagnosed pancreatic neoplasms, with a prevalence of 1 per 100,000 and an annual incidence of 1 to 4 per million. However, pancreatic neuroendocrine neoplasms are seen in 0.5 to 1.5% of autopsies, thereby indicating that the vast majority are not clinically evident. About 60 to 80% of all pancreatic neuroendocrine neoplasms are nonfunctioning (Table 213-1). Among functional pancreatic neuroendocrine neoplasms, insulinomas and gastrinomas are the most common, with annual incidences of 0.5 to 3 per million. In general, insulinomas and gastrinomas are 8-fold more frequent than VIPomas,17-fold more frequent than glucagonomas, and greater than 20-fold more frequent than the others.

PATHOBIOLOGY

Pathology/Classification

Neuroendocrine neoplasms originate from the diffuse neuroendocrine system, which is present throughout the body. All neuroendocrine neoplasms share cytologic features of an endodermal origin. Ultrastructurally, these neoplasms have electron-dense granules that contain multiple peptides/amines, neuron-specific enolase, synaptophysin, and chromogranins. Histologically, they characteristically show small cells with uniform nuclei

TABLE 213-1 PANCREATIC NEUROENDOCRINE NEOPLASMS (pNENs)

NAME OF TUMOR	NAME OF SYNDROME	MAIN SIGNS OR SYMPTOMS	LOCATION (%)	MALIGNANCY (%)	HORMONE CAUSING SYNDROME
I. FUNCTIONAL pNEN					
Gastrinoma	Zollinger-Ellison syndrome	Abdominal pain, diarrhea, esophageal symptoms	Pancreas—10-30 Duodenum—70-90 Other—0-10	60-90	Gastrin
Insulinoma	Insulinoma	Hypoglycemic symptoms	Pancreas—100	5-15	Insulin (Chapter 211)
Glucagonoma	Glucagonoma	Dermatitis, diabetes/ glucose intolerance, weight loss	Pancreas—100	60	Glucagon
VIPoma	Verner-Morrison, Pancreatic cholera, WDHA	Severe watery diarrhea, hypokalemia	Pancreas—90 Other—10 (neural, adrenal, periganglionic tissue)	80	Vasoactive intestinal peptide (VIP)
Somatostatinoma	Somatostatinoma	Diabetes mellitus, cholelithiasis, diarrhea	Pancreas—56 Duodenum/jejunum—44	60	Somatostatin
GRFoma	GRFoma	Acromegaly	Pancreas—30 Lung—54 Jejunum—7 Other—13 (adrenal, foregut, retroperitoneum)	30	Growth hormone–releasing factor (GRF)
ACTHoma	ACTHoma	Cushing syndrome	Pancreas—4-16 of all ectopic Cushing syndrome cases	>95	Adrenocorticotropic hormone (ACTH)
pNEN causing carcinoid syndrome	pNEN causing carcinoid syndrome	Diarrhea, flushing	Pancreas—<1 of all carcinoids	60-90	Serotonin, tachykinins
pNEN causing hypercalcemia	pNEN causing hypercalcemia	Signs/symptoms of hypercalcemia	Pancreas (rare cause of hypercalcemia)	>85	PTHrP, other unknown
pNEN secreting erythropoietin	pNEN secreting erythropoietin	Polycythemia	Pancreas	Unknown	Erythropoietin
pNEN secreting renin	pNEN secreting renin	Hypertension	Pancreas	Unknown	Renin
pNEN secreting luteinizing hormone syndrome	pNEN secreting luteinizing hormone	Masculinization, loss of libido	Pancreas	Unknown	Luteinizing hormone
CCKoma	CCKoma	Diarrhea, peptic ulcer, gallstone	Pancreas	Unknown	Cholecystokinin
pNEN secreting enteroglucagon	pNEN secreting enteroglucagon	Small intestinal hypertrophy	Pancreas, renal, duodenal	Unknown	Enteroglucagon
pNEN secreting IGF-2 or GLP-1	pNEN secreting IGF-2 or GLP-1	Hypoglycemic symptoms	Pancreas	Unknown	IGF-2/GLP-1
pNEN secreting secretin	Secretinoma	Diarrhea	Pancreas	Unknown	Secretin
II. NF-pNEN					
NONFUNCTIONAL/ PPoma	NONFUNCTIONAL/ PPoma	Weight loss, abdominal mass, hepatomegaly	Pancreas—100	60-90	None: pancreatic polypeptide, chromogranin released but no known symptoms due to hypersecretion

CCKoma = cholecystokinin-secreting NEN; Duod = duodenum; GLP-1 = glucagon-like peptide 1; IGF-2 = insulin-like growth factor-II; pNEN = pancreatic neuroendocrine neoplasm; PP = pancreatic polypeptide; PPoma = pancreatic polypeptide secreting NEN; PTHrP = parathormone-related peptide; WDHA = watery diarrhea, hypokalemia, and achlorhydria.

ABSTRACT

This chapter summarizes all important aspects of neuroendocrine neoplasms, including their epidemiology; pathogenesis; localization methods, including molecular imaging; and latest treatments. It also includes brief summaries and updates on the most important functional pancreatic endocrine tumor syndromes, carcinoid syndrome, and carcinoid tumors in the most frequent locations.

KEYWORDS

neuroendocrine neoplasm
neuroendocrine tumor
neuroendocrine carcinoma
carcinoid
insulinoma
Zollinger-Ellison syndrome
glucagonoma
carcinoid syndrome

and low rates of mitotic figures. Chromogranin immunoreactivity in the tumor is now widely used to identify them as neuroendocrine neoplasms. Malignancy can be determined reliably only by demonstrating the presence of metastatic disease.

Classification systems for staging and grading neuroendocrine neoplasms consider the neoplasm's differentiation[4] (good vs. poor), tumor size, invasion, and extent. The neuroendocrine neoplasms are also divided into three grades depending on proliferative indices, including mitotic rate and the expression of Ki-67. An important differentiation is between the well-differentiated neuroendocrine neoplasms as compared with the poorly differentiated neuroendocrine carcinomas.[5]

Molecular Pathogenesis

Unlike nonendocrine tumors, neuroendocrine neoplasms rarely have mutations of common oncogenes (*ras, fos, myc,* etc.) or common tumor suppressor genes *(p53, rb)*. Pancreatic neuroendocrine neoplasms, gastrointestinal neuroendocrine neoplasms, and lung neuroendocrine neoplasms all have a different molecular pathogenesis. Furthermore, the pathogenesis is different for well-differentiated neuroendocrine tumors as compared with poorly differentiated neuroendocrine carcinomas.

Pancreatic neuroendocrine neoplasms most commonly have allelic losses at chromosomal loci 1p, 1q, 3p, 11p, and 22p. Somatic mutations in pancreatic neuroendocrine neoplasms are commonly found in four main pathways, including genes involved in chromatin remodeling, DNA repair, mammalian target of rapamycin (mTOR) signaling, and telomere maintenance. Sequencing studies of pancreatic neuroendocrine neoplasms show that 44% have inactivating mutations of the multiple endocrine neoplasia type 1 gene *(MEN1),* 43% have mutations in genes encoding either of two subunits of a transcription/chromatin remodeling complex composed of DAXX (death domain–associated protein) and ATRX (α-thalassemia/intellectual disability syndrome X-linked chromatin remodeler), and 14% have mutations in the mTOR pathway.

Gastrointestinal neuroendocrine neoplasms usually have losses at chromosomal loci 18q, 18p, 9p, and 16q. For small intestinal carcinoids, sequencing studies demonstrate a low mutation rate, with recurrent somatic mutations and deletions in *CDKN1B*, which is the cyclin-dependent kinase inhibitor gene that encodes p27, in 8% of tumors.

In contrast, neuroendocrine carcinomas have distinctive activations in tumor protein 53 (TP53) and retinoblastoma gene *(RB1)*. Recent studies suggest that epigenetic dysregulation may play an important role in the pathogenesis of neuroendocrine neoplasms.[6]

Four autosomal dominant inherited disorders are associated with pancreatic neuroendocrine neoplasms: MEN1 (in 80 to 100% of patients); von Hippel-Lindau disease (VHL; in 10 to 17% of patients); tuberous sclerosis (in 0.5% of patients); and von Recklinghausen disease (neurofibromatosis-1; 12% develop duodenal somatostatinomas).[7] Familial syndromes associated with carcinoids are uncommon.

CLINICAL MANIFESTATIONS AND DIAGNOSIS

Clinical manifestations of neuroendocrine neoplasms depend on whether the tumor is functional and secretes a biologically active peptide or whether it is nonfunctional and causes symptoms via a mass effect from the tumor. Diagnosis relies on biochemical testing to detect the hormonal excess as well as imaging, endoscopic, and pathologic studies to localize the tumors and identify its neuroendocrine nature.[8]

To assess the primary location and extent of a neuroendocrine neoplasm, the initial tumor localization study is generally a cross-sectional imaging examination, such as triphasic computed tomography (CT) or magnetic resonance imaging (MRI) with contrast.[9] More than 90% of well-differentiated neuroendocrine neoplasms overexpress one of the five subtypes of somatostatin receptors (sst1-5), with sst2 the most frequently overexpressed (>80%). Somatostatin receptor imaging using radiolabeled somatostatin analogues with high affinity for sst2 is now the most sensitive imaging modality. The most frequently used modality is ^{68}Ga-DOTA (1,4,7,10-tetraazacyclododecane-1,4,7,10-tetraacetic acid)–labeled somatostatin analogues with positron emission tomography combined with CT (PET/CT) or MRI (PET/MRI).

Endoscopic studies are particularly important for localizing duodenal, gastric, and rectal neuroendocrine neoplasms. Endoscopic ultrasound is widely used to localize pancreatic neuroendocrine neoplasms and to assess the depth of penetration of gastric and rectal neuroendocrine neoplasms.

TREATMENT

Treatment should be initiated urgently in patients who have to address a heavy tumor burden with mass-related symptoms, symptoms related to an uncontrolled functional tumor,[10] compromised liver function, poorly differentiated or high-grade tumor, or rapid growth on imaging. Conversely, treatment has little urgency if tumors have small volume, are low grade, and are asymptomatic.

For patients with neuroendocrine neoplasms, two treatment issues must be addressed. First, any excess hormone state must be controlled; and second, treatment must be directed against the tumor itself because of its frequently malignant nature. Surgical resection can solve both problems, but unfortunately many patients present with disease that is advanced and unresectable.

SPECIFIC NEUROENDOCRINE NEOPLASMS

PANCREATIC NEUROENDOCRINE NEOPLASMS

Pancreatic neuroendocrine neoplasms are also called islet-cell tumors, but this latter term is also a misnomer because 7 different neoplasms (see Table 213-1) can occur outside the pancreas.[11] Several of the functional neuroendocrine syndromes are very uncommon (<5 cases reported), including neuroendocrine neoplasms that secrete renin, erythropoietin, enteroglucagon, luteinizing hormone, secretin, cholecystokinin, glucagon-like peptide-1 (GLP-1), and insulin-like growth factor-II. In addition, pancreatic neuroendocrine neoplasms can also synthesize neurotensin, calcitonin, and ghrelin, but no related syndromes have been established. Except for insulinomas, pancreatic neuroendocrine neoplasms are frequently malignant (>50%).

FUNCTIONAL PANCREATIC NEUROENDOCRINE NEOPLASMS

ZOLLINGER-ELLISON SYNDROME (GASTRINOMAS)

Zollinger-Ellison syndrome is a clinical syndrome caused by a gastrin-secreting neuroendocrine neoplasm that is usually located in the pancreas or duodenum. The syndrome is characterized by clinical symptoms and signs that result from hypersecretion of gastric acid: peptic ulcer disease, diarrhea, and esophageal reflux disease.

Zollinger-Ellison syndrome has an annual incidence of 0.5 to 2 per million. It is diagnosed most frequently between ages 35 and 65 years, but has been reported in both children and the elderly.

PATHOBIOLOGY

Gastrinomas are found in the duodenum (80 to 100%) more frequently than in the pancreas (0 to 20%). Duodenal gastrinomas are generally small (<1 cm), whereas pancreatic gastrinomas are generally larger. Occasionally Zollinger-Ellison syndrome results from a gastrinoma in the splenic hilum, mesentery, stomach, or only in a lymph node or an ovary. Extra-gastrointestinal gastrinomas producing Zollinger-Ellison syndrome have been reported in the heart and with small cell lung cancer (Chapter 177).

Gastrin stimulates parietal cells to secrete acid and has a growth effect on the gastric mucosa. Chronic hypergastrinemia leads to increased gastric mucosal thickness, prominent gastric folds, and increased numbers of parietal cells and gastric enterochromaffin-like cells. Patients with gastrinomas have increased basal and maximal acid outputs from the stomach. *Helicobacter pylori* appears not to be important in the pathogenesis of the ulcer disease in Zollinger-Ellison syndrome, in contrast to common peptic ulcers (Chapter 125). Diarrhea is common because the large-volume gastric acid output leads to structural damage to the small intestine (inflammation, blunted villi, edema), interference with fat transport, inactivation of pancreatic lipase, and precipitation of bile acids. These same mechanisms, if prolonged, can lead to steatorrhea. If acid hypersecretion is controlled, the diarrhea will stop.

From 20 to 25% of Zollinger-Ellison syndrome patients have MEN1 (MEN1/Zollinger-Ellison syndrome) (Chapter 125). These patients have hyperplasia or tumors of multiple endocrine glands (parathyroid hyperplasia [>90%], pituitary tumors [60%]). In MEN1/Zollinger-Ellison syndrome patients, 80 to 95% of the gastrinomas are in the duodenum, where they are frequently small (<0.5 cm), almost always multiple, and associated with lymph node metastases in 40 to 60% of cases.

CLINICAL MANIFESTATIONS

Abdominal pain resulting from a peptic ulcer is the most common symptom (>80%). Most ulcers occur in the duodenum (>85%), but they occasionally

occur in the postbulbar area, jejunum, or stomach, or in multiple locations. Initially, the pain is usually like that of patients with typical peptic ulcer disease (Chapter 125). With time, however, the symptoms become persistent and generally respond poorly to treatments aimed at eliminating *H. pylori* and to conventional doses of histamine-2 receptor antagonists. By comparison, conventional doses of proton pump inhibitors (e.g., omeprazole, lansoprazole, pantoprazole, esomeprazole, rabeprazole; Table 124-1) frequently control the symptoms of most patients with Zollinger-Ellison syndrome.

Heartburn is also common (20%). Diarrhea (60 to 70%) occurs frequently and may be the first symptom (10 to 20%). In MEN1, Zollinger-Ellison syndrome is the most common functional syndrome (55%), although patients typically first develop renal stones (Chapter 111) related to hypercalcemia from the associated hyperparathyroidism (Chapter 227) or have elevated prolactin levels resulting from pituitary tumors that only develop later.

Almost all the initial symptoms of Zollinger-Ellison syndrome result from the effects of acid hypersecretion, but patients can have tumor-related symptoms late in the disease. Approximately one third of patients have metastatic liver disease at presentation, but less than 20% of other patients develop metastatic disease to the liver during a 10-year follow-up period.

Up to 5% of patients with Zollinger-Ellison syndrome develop ectopic Cushing syndrome (Chapter 208) because the gastrinoma secretes adrenocorticotropic hormone (ACTH). These patients usually have a metastatic gastrinoma in the liver, have Zollinger-Ellison syndrome without MEN1, and have a poor prognosis.

DIAGNOSIS

Zollinger-Ellison syndrome should be suspected in any patient whose peptic ulcer disease is accompanied by diarrhea, is recurrent, does not heal with treatment, is not associated with *H. pylori* infection, is associated with a complication (bleeding, obstruction, esophageal stricture), is multiple, occurs in unusual locations, or is associated with a pancreatic tumor. Zollinger-Ellison syndrome also should be suspected in patients who have chronic secretory diarrhea (Chapter 126), as well as when peptic ulcer disease is associated with large gastric folds, a family/personal history of nephrolithiases/endocrinopathies, or the finding of hypercalcemia, hypergastrinemia, or acid hypersecretion.

When suspected, the initial test is a fasting serum gastrin level, which is elevated in 99 to 100% of patients with Zollinger-Ellison syndrome. Besides Zollinger-Ellison syndrome, other causes of fasting hypergastrinemia include conditions that also are associated with hyperchlorhydria (e.g., retained antrum, antral hyperfunction/hyperplasia, renal failure, *H. pylori* infections) and conditions that are associated with hypochlorhydria or achlorhydria (e.g., physiologic hypergastrinemia in pernicious anemia, atrophic gastritis, or the use of proton pump inhibitors or histamine-2 antagonists). If the serum gastrin level is elevated, a fasting gastric pH should be determined. If the serum gastrin is greater than 1000 pg/mL (normal <100) and the gastric pH is less than 2.0, the patient almost certainly has the Zollinger-Ellison syndrome. If the gastrin level is increased less than 10-fold above normal and the gastric pH is less than 2.0, basal acid output should be measured and a secretin test (see Table 126-6) should be performed. More than 95% of patients with Zollinger-Ellison syndrome have a basal acid output greater than 15 mEq/hour if no previous gastric acid–reducing surgery has been performed, and 94% have a positive secretin test (a >120 pg/mL stimulated increase in serum gastrin). If possible, proton pump inhibitors should be discontinued for up to 1 week to ensure that the cause of the hypergastrinemia is not the drug itself. Since discontinuing a proton pump inhibitor in a patient with undiagnosed Zollinger-Ellison syndrome can lead to complications of peptic ulcer disease, this approach should be undertaken with care and preferably by expert physicians who are well versed in making this diagnosis.

Differential Diagnosis

A positive secretin test in a patient who is not taking proton pump inhibitors or histamine-2 antagonists excludes other causes of hypergastrinemia and hyperchlorhydria that may mimic the Zollinger-Ellison syndrome. In all patients with Zollinger-Ellison syndrome, evaluation must exclude MEN1 syndrome by searching for other endocrinopathies and assessing the family history.

TREATMENT

Medical Therapy

Patients require medical therapy directed at controlling the gastric acid hypersecretion and, if possible, surgical therapy to remove the gastrinoma.[12] Proton pump inhibitors (Table 124-1), which are the drugs of choice, can control hypersecretion in almost every patient. The recommended starting dose is omeprazole 60 mg once a day. In 30% of patients, higher doses or more frequent doses are needed, particularly in patients with complicated disease (e.g., MEN1, previous gastric surgery, or a history of severe esophageal reflux). With time, the omeprazole dose can be reduced in most patients with uncomplicated disease to 20 to 40 mg/day. Patients must be treated indefinitely unless surgically cured. Long-term therapy is generally safe, and patients have been treated for up to 20 years with omeprazole without loss of efficacy, although reduced vitamin B_{12} levels may be a side effect that requires treatment (Chapter 150). Histamine-2 receptor antagonists (Table 124-1) are also effective, but frequent (every 4 to 6 hours), and high doses are needed. Long-acting somatostatin analogs can also control the acid hypersecretion but are uncommonly used because parental administration is needed, whereas proton pump inhibitors are effective with oral dosing.

Surgical Therapy

Surgical exploration for cure is recommended in all patients who do not have unresectable liver metastases, MEN1, or complicating medical conditions that limit life expectancy.[13] Tumors are found by experienced endocrine surgeons in 95% of patients at surgery. At exploration, a duodenotomy to locate small duodenal gastrinomas is essential, as is the use of operative ultrasound to find and stage small pancreatic tumors. Surgical treatment of MEN1/Zollinger-Ellison syndrome patients is controversial, because 80 to 90% have multiple small duodenal tumors; 50 to 60% of patients have metastatic lymph nodes and cannot be cured without extensive resections (usually a Whipple procedure).

Total gastrectomy is now performed only in patients who cannot or will not take oral antisecretory medications. Parathyroidectomy should be performed in MEN1 patients with hyperparathyroidism and Zollinger-Ellison syndrome because the procedure reduces acid secretion and increases the sensitivity to antisecretory drugs.

Metastatic Disease

If the metastatic disease can be resected, surgery should be considered (5 to 15% of cases). Otherwise, however, treatment of advanced disease is as for other advanced pancreatic neuroendocrine neoplasms (see later).

PROGNOSIS

MEN1/Zollinger-Ellison syndrome patients with an imaged tumor that is less than 2 to 2.5 cm have an excellent prognosis without surgery.[14] Approximately 25% of gastrinomas, however, show aggressive growth. Surgical resection decreases the metastatic rate, increases survival, and results in a 5-year cure rate of 30 to 40%. Patients with metastatic gastrinoma in the liver have a poor prognosis, with a 5-year survival rate of 30%. The presence of advanced gastrinoma grade or stage, large primary tumor, a pancreatic tumor, bone metastases, development of ectopic Cushing syndrome, or a high fasting gastrin level is associated with aggressive growth.

GLUCAGONOMAS

Glucagonomas are pancreatic neuroendocrine neoplasms that ectopically secrete glucagon, thereby causing a specific syndrome that includes glucose intolerance and unique dermal manifestations.

Glucagonomas have an annual population incidence of about 1 per 10 to 100 million. Patients typically present in their fifth decade. In many series, patients present late with large primary tumors, and more than 50 to 80% are metastatic at presentation.

PATHOBIOLOGY

The hypersecretion of glucagon causes glucose intolerance. The exact origin of the rash (necrolytic migratory erythema) is unclear. Some data suggest that prolonged glucagon infusions can cause the characteristic skin lesions. Zinc deficiency may play a role because the rash is similar to what can be seen with zinc deficiency (acrodermatitis enteropathica) and because the rash improves in some patients who are given zinc. The hypo-aminoacidemia is thought to be secondary to the effect of glucagon on amino acid metabolism by altering gluconeogenesis. Wasting and weight loss, which are intrinsic components of the glucagonoma syndrome, may be caused by an anorectic substance distinct from glucagon.

CLINICAL MANIFESTATIONS

The cardinal clinical features are a distinct dermatitis (necrolytic migratory erythema, seen in 70 to 90% of patients; Fig. 213-1), glucose intolerance or diabetes mellitus (40 to 90% of patients), weight loss (70 to 96% of patients), anemia (30 to 85% of patients), hypoaminoacidemia (80 to 90% of patients) with deficiencies of essential fatty acids, thromboembolism (10 to 25%), diarrhea (15 to 30%), and psychiatric disturbances (0 to 20%).[15] Necrolytic migratory erythema is usually found at intertriginous and periorificial sites, especially in the groin and buttocks. It is initially erythematous, becomes raised, and develops central bullae whose tops detach, with the eroded areas becoming crusty. Healing occurs with hyperpigmentation.

DIAGNOSIS

The diagnosis is established by demonstrating elevated plasma glucagon levels with accompanying symptoms and signs. Normal glucagon levels are 150 to 200 pg/mL, but patients with glucagonomas usually (60 to 90%) have levels greater than 1000 pg/mL. Increased plasma glucagon levels also occur in renal insufficiency, acute pancreatitis, hypercorticolism, hepatic diseases, celiac disease, severe stress, and prolonged fasting; in patients treated with danazol; and in familial hyperglucagonemia. In these conditions the level is usually less than 500 pg/mL except in patients with hepatic diseases or in those with familial hyperglucagonemia. Necrolytic migratory erythema is not specific for glucagonomas and is also seen in short bowel syndrome, myelodysplastic syndromes, malnutrition, hepatitis B infections, cirrhosis, celiac disease, other malignancies, inflammatory bowel disease, and nutritional deficiencies.

Mahvash disease is characterized by mutations in the glucagon receptor gene, glucagon cell hyperplasia, and hyperglucagonemia, but without the symptoms of the glucagonoma syndrome. Glucagon cell adenomatosis is characterized by glucagon cell hyperplasia and occasional symptoms that mimic the glucagonoma syndrome.

FIGURE 213-1. A patient with a glucagonoma with the characteristic rash (necrolytic migratory erythema). The rash is usually at intertriginous areas or periorificial sites and shows various stages of erythema and crusting (From Forbes CD, Jackson WF. *Color Atlas and Text of Clinical Medicine*. 3rd ed. London. Mosby; 2003.)

Glucagonomas are generally large when discovered (mean, 5 to 10 cm), and they most frequently occur in the pancreatic tail (>50%). Liver metastases are commonly present at the time of diagnosis (45 to 80%).

TREATMENT

Subcutaneous monthly administration of a synthetic long-acting somatostatin analogues, octreotide (octreotide [LAR], 10 to 30 mg intramuscularly every 4 weeks or lanreotide, 90 to 120 mg deep subcutaneous injection monthly controls the rash in 80% of patients and improves weight loss, diarrhea, and hypoaminoacidemia. However, it usually does not improve the diabetes mellitus. Zinc supplementation (440 mg daily) and infusions of amino acids, fatty acids, or both under expert care can diminish the severity of the rash. After tumor localization, surgical resection is preferred; even debulking of metastatic tumor may be of benefit. For advanced, nonresectable disease, treatment is as for other pancreatic neuroendocrine neoplasms (see later).

PROGNOSIS

The prognosis is largely determined by the growth of the tumor per se because the symptoms of glucagon excess can be largely controlled by somatostatin analogues. The mean 5-year survival rate is 50%, but extended survivals (>15 years) are reported in some patients who are treated with somatostatin analogs and other tumor-directed therapies.

VIPOMAS

The VIPoma syndrome, also called the Verner-Morrison syndrome, pancreatic cholera, and the WDHA syndrome (for watery diarrhea, hypokalemia, and achlorhydria), results from a neuroendocrine neoplasm, usually in the pancreas, that ectopically secretes vasoactive intestinal polypeptide (VIP).[16] The annual incidence is about 1 per million population.

PATHOBIOLOGY

VIPomas in adults are found in the pancreas in 80 to 90% of cases; rare cases result from intestinal carcinoids, ganglioneuromas, ganglioneuroblastomas, and pheochromocytomas. In children younger than 10 years and rarely in adults, the VIPoma syndrome is caused by ganglioneuromas or ganglioneuroblastomas at extrapancreatic sites. VIPomas are usually large and solitary; 50 to 75% occur in the pancreatic tail, and 40 to 70% have metastasized at the time of diagnosis. VIPomas frequently secrete both VIP and peptide histidine methionine, but VIP is responsible for the symptoms. VIP is a potent stimulant of secretion in the small and large intestine. VIP also causes relaxation of gastrointestinal smooth muscle, thereby contributing to the dilated loops of bowel and atonic gallbladder that are common in this syndrome. Hypochlorhydria is thought to result from the inhibitory effect of VIP on gastric acid secretion, the flushing is related to the vasodilatory effects of VIP, and the hyperglycemia is caused by the glycogenolytic effect of VIP. The mechanism of the hypercalcemia remains unclear.

CLINICAL MANIFESTATIONS

The cardinal clinical feature is severe, large-volume, watery diarrhea (>1 L/day) that is secretory and occurs during fasting. Hypokalemia (67 to 100%) and dehydration (83%) commonly occur because of the volume of the diarrhea. Achlorhydria is only occasionally noted, but hypochlorhydria is usually found (34 to 72% of cases). Flushing occurs in 20% of patients, hyperglycemia in 40 to 50%, and hypercalcemia in 41 to 50%. Steatorrhea is uncommon (16%) despite the volume of diarrhea.

DIAGNOSIS

The diarrhea of VIPomas characteristically persists during fasting and is large in volume (>3 L/day in 70 to 80%); the diagnosis is excluded when fasting stool volume is less than 700 mL/day. To differentiate VIPomas from other causes of large-volume fasting diarrhea, fasting plasma VIP levels should be determined. The normal value in most laboratories is less than 190 pg/mL, and elevated levels are detected in 90 to 100% of patients. The differential diagnosis of large-volume fasting diarrhea (>700 mL/day) includes Zollinger-Ellison syndrome, diffuse islet cell hyperplasia, surreptitious use of laxatives, the pseudopancreatic cholera syndrome, and, rarely, human immunodeficiency virus (HIV) infection (Chapter 359). Serum gastrin levels identify patients with Zollinger-Ellison syndrome, and plasma VIP levels are normal in most patients who abuse laxatives, in 82% of patients with pancreatic islet cell hyperplasia, and in patients with HIV-induced secretory diarrhea.

TREATMENT

The symptoms caused by the VIP are controlled initially in more than 85% of patients by daily doses of octreotide (50 to 400 μg 1 to 3 times daily) or by monthly injections of a depot form (octreotide [LAR] 10 to 30 mg intramuscularly every 4 weeks or lanreotide 90 to 120 mg deep subcutaneous injection monthly), but increased doses guided by experts may be needed over time. After tumor localization studies, surgical resection should be attempted if it is possible to remove all visible tumor; however, more than 50% of patients have generalized liver metastases at diagnosis, so complete resection may not be possible. For patients with unresectable advanced disease, treatment is similar to that for other advanced nonresectable pancreatic neuroendocrine neoplasms. In most refractory cases with advanced VIPomas, the diarrhea can be controlled with peptide receptor radionuclide therapy (see later).

PROGNOSIS

The prognosis is largely determined by the growth of the tumor per se, because the symptoms of VIP excess usually can be controlled by somatostatin analogues, antitumor treatments, or peptide receptor radionuclide therapy. The mean 5-year survival rate is 50 to 70%.

SOMATOSTATINOMAS

Somatostatinomas are neuroendocrine neoplasms that have an annual incidence of about 1 per 40 million individuals. They occur primarily in the pancreas or upper small intestine and ectopically secrete somatostatin.[17] In the gastrointestinal tract, somatostatin inhibits basal and stimulated gastric acid secretion, pancreatic secretion, intestinal absorption of amino acids, gallbladder contractility, and release of numerous hormones, including cholecystokinin and gastrin.

CLINICAL MANIFESTATIONS

The somatostatinoma syndrome includes diabetes mellitus, gallbladder disease, diarrhea, steatorrhea, and weight loss. However, most somatostatinomas do not cause these symptoms and are diagnosed incidentally.

Pancreatic somatostatinomas occur in the pancreatic head in 60 to 80% of cases. They are usually large (mean 5 cm) and solitary, but about 70 to 90% have metastasized at the time of diagnosis. In contrast, duodenal somatostatinomas (20 to 40% of cases) are smaller (mean, 2.4 cm), frequently associated with psammoma bodies on histologic examination (11%), and less frequently have metastases at diagnosis (30 to 40%).

The distinct somatostatinoma syndrome, which occurs much more commonly in patients with pancreatic than duodenal or intestinal somatostatinomas, includes diabetes, gallbladder disease, diarrhea, steatorrhea, and weight loss. Duodenal somatostatinomas occur in up to 10% of patients with von Recklinghausen disease and are usually asymptomatic.

DIAGNOSIS

Somatostatinomas are usually found incidentally, particularly during exploratory laparotomy, cholecystectomy, endoscopy, or on imaging studies. The presence of psammoma bodies on histologic examination of a duodenal neuroendocrine tumor or any duodenal lesions in patients with von Recklinghausen disease should raise the suspicion of a duodenal somatostatinoma. Somatostatinomas (primarily duodenal) are also associated with the rare, inherited syndrome polycythemia–paraganglioma/pheochromocytoma–somatostatinoma.

The diagnosis of the somatostatinoma syndrome requires the demonstration of increased concentrations of somatostatin-like immunoreactivity in the plasma and the resected tumor. However, other neoplasms outside the pancreas or intestine, such as small cell lung cancer, medullary thyroid carcinoma, pheochromocytomas, and paragangliomas, also may have elevated concentrations of somatostatin-like immunoreactivity. Somatostatinomas can be imaged using somatostatin receptor scintigraphy or, if needed, other conventional imaging studies to assess the tumor's location.

TREATMENT

Treatment with octreotide (10 to 30 mg intramuscularly every 4 weeks) or lanreotide (90 to 120 mg deep subcutaneous injection monthly) can improve symptoms. Surgery should be performed if possible. For patients with unresectable advanced disease, treatment is similar to treatment for other advanced nonresectable pancreatic neuroendocrine neoplasms (see later).

PROGNOSIS

Patients who have intestinal somatostatinomas, which uncommonly cause the somatostatinoma syndrome and are less malignant, have an excellent prognosis (5-year survival rate >80%). By comparison, patients who have pancreatic somatostatinomas, which frequently cause the somatostatinoma syndrome and present with metastatic disease (>70%), have a much reduced 5-year survival rate (<50%).

GROWTH HORMONE–RELEASING FACTOR NEOPLASMS

Growth hormone–releasing factor secreting neuroendocrine neoplasms (GRFomas) are rare tumors that can originate in the pancreas, but they also can occur in other extrapancreatic locations. The growth hormone-releasing factor may cause acromegaly that is clinically indistinguishable from that caused by a pituitary adenoma (Chapter 205).

GRFomas most commonly occur in the lung (about 55%). Most of the remainder occur in the gastrointestinal tract, including 30% in the pancreas. Pancreatic GRFomas are usually large (mean, 6 cm), 40% are metastatic at diagnosis, 40% occur in combination with Zollinger-Ellison syndrome, and 33% are in patients with MEN1.

CLINICAL MANIFESTATIONS AND DIAGNOSIS

GRFomas are a very uncommon cause of acromegaly but should be suspected in a patient who has acromegaly and abdominal complaints but no pituitary tumor. In addition, it should be considered if a patient has hyperprolactinemia, which occurs in 70% of GRFomas. The intra-abdominal features of GRFomas result from its metastases. The diagnosis is confirmed by performing a plasma assay for GRF and growth hormone.

TREATMENT

The effects of the ectopic growth hormone can be controlled with octreotide (10 to 30 mg intramuscularly every 4 weeks) or lanreotide (90 to 120 mg deep subcutaneous injection monthly) in more than 90% of patients. Treatment also should be directed at the GRFoma per se, as described for the other more common pancreatic neuroendocrine neoplasms. For patients with unresectable advanced disease, treatment is similar to that for other advanced nonresectable pancreatic neuroendocrine neoplasms (outlined later).

NONFUNCTIONAL PANCREATIC NEUROENDOCRINE TUMORS

Nonfunctional pancreatic neuroendocrine neoplasms originate in the pancreas and either secrete no peptides or secrete products that do not cause clinical symptoms. About 50% of all pancreatic neuroendocrine neoplasms are nonfunctional.

Nonfunctional pancreatic neuroendocrine neoplasms frequently secrete nonfunctional peptides, including chromogranin A (100%), pancreatic polypeptide (60%), and the α-subunit (40%) and β-subunit of human chorionic gonadotropin. Immunocytochemically, even higher percentages contain these peptides, as well as insulin (50%), glucagon (30%), and somatostatin (13%).

CLINICAL MANIFESTATIONS

Nonfunctional pancreatic neuroendocrine neoplasms are often found incidentally during investigation of unrelated symptoms or on screening. Symptoms or signs, which result from the neoplasm per se, include abdominal pain (35 to 55%), abdominal mass or hepatosplenomegaly (10 to 40%), weight loss or cachexia (10 to 45%), and jaundice (25 to 40%).

In asymptomatic patients, the incidentally detected nonfunctional pancreatic neuroendocrine neoplasms are usually less than 2 cm, without metastases. In symptomatic patients, primary neoplasms are large (70% were >5 cm) and liver metastases are frequent (38 to 62%).

DIAGNOSIS

Any patients with a long survival (>5 years) after a diagnosis of metastatic pancreatic adenocarcinoma (Chapter 180) should be suspected of having a nonfunctional pancreatic neuroendocrine neoplasm instead. An elevated plasma chromogranin A or pancreatic polypeptide level or a positive somatostatin receptor scintigraphic scan is strong evidence that a pancreatic mass is a pancreatic neuroendocrine neoplasm. Malignancy correlates with vascular/perineural invasion, increased tumor grade, a size of at least 4 cm, capsular penetration, nuclear atypia, lack of progesterone receptors, and the presence of calcitonin immunoreactivity in the neoplasm.[18]

TREATMENT

Surgical resection should be performed, whenever possible, if the nonfunctional pancreatic neuroendocrine neoplasm is greater than 2 to 3 cm, if ductal compression is found, or if a higher grade tumor is present. The role of surgery in nonfunctional pancreatic neuroendocrine neoplasms that are less than 2 to 2.5 cm is controversial, with some experts recommending observation with re-evaluation, whereas others recommended surgery.[19,20] For patients with unresectable advanced disease, treatment is similar to that for other advanced nonresectable nonfunctional pancreatic neuroendocrine neoplasms (see later).

PROGNOSIS

Survival is better in patients with smaller tumors, patients who are asymptomatic at presentation, patients with no metastases, and patients in whom surgical resection can be performed. The overall 5-year survival rate varies in different series from 30% to greater than 90%, but it is heavily dependent on the extent of the disease at diagnosis, with survival rates of 96% in patients without metastases at presentation, but only 30 to 50% with metastatic disease.

ACTHOMAS AND OTHER UNCOMMON TUMORS

Pancreatic neuroendocrine neoplasms that ectopically secrete ACTH cause 4 to 15% of the cases of ectopic Cushing syndrome (Chapter 208).[21] Cushing syndrome occurs in 5% of all cases of Zollinger-Ellison syndrome, but it is a late feature in patients with sporadic Zollinger-Ellison syndrome, in whom it occurs with metastatic liver disease. Its development is associated with a poor prognosis, and the response to chemotherapy is generally poor. However, some patients benefit from the use of long-acting somatostatin analogues (octreotide 10 to 30 mg intramuscularly every 4 weeks) or lanreotide (90 to 120 mg deep subcutaneous injection monthly).

Paraneoplastic hypercalcemia (Chapters 164 and 227) can result from a pancreatic neuroendocrine neoplasm that releases parathormone-related peptide (PTHrP), 1,25 dihydroxy vitamin D, calcitriol, or an unknown hypercalcemic substance.[22] These neoplasms are generally large, with metastatic liver disease at diagnosis. Somatostatin analogues may help control the hypercalcemia, but surgery, chemotherapy, peptide receptor radionuclide therapy, hepatic embolization, and chemoembolization are the mainstays of treatment.

Pancreatic neuroendocrine neoplasms that cause the carcinoid syndrome (see later) are usually large, and 70 to 90% are malignant.[23] Long-acting somatostatin analogues (e.g., octreotide [10 to 30 mg intramuscularly every 4 weeks] or lanreotide [90 to 120 mg deep subcutaneous injection monthly]) may control the symptoms, and the tryptophan hydrolase 1 inhibitor, telotristat (250 mg orally three times daily), may be helpful to control the diarrhea. Surgery, chemotherapy, hepatic embolization, chemoembolization, or molecular targeted therapy (everolimus, sunitinib) may be helpful.

A single case of a pancreatic neuroendocrine neoplasm that secreted renin manifested with severe hypertension; the tumor was localized with somatostatin receptor scintigraphy, and the patient's symptoms improved significantly after resection. A single case of an erythropoietin-secreting pancreatic neuroendocrine neoplasm resulting in polycythemia and a single case of a pancreatic neuroendocrine neoplasm secreting insulin-like growth factor-II or glucagon-like peptide-1 causing hypoglycemia have been described. Two symptomatic cases of pancreatic neuroendocrine neoplasms that secreted luteinizing hormone have been reported; virilization occurred in the female patient, whereas the male patient had increased acne and a rash. In both cases, the tumors were resectable and symptoms improved postoperatively. In a single case of a pancreatic neuroendocrine neoplasm secreting cholecystokinin (CCKoma), the patient demonstrated peptic ulcer disease, gallbladder disease, diarrhea, and weight loss. In one reported case, a pancreatic neuroendocrine neoplasm secreting enteroglucagon caused small intestinal hypertrophy. In one proven case of ectopic secretion of secretin, the patient had achlorhydria and diarrhea with an intestinal fluid high in bicarbonate and chloride.

NEUROENDOCRINE TUMORS OF THE GASTROINTESTINAL TRACT AND THORAX

These well-differentiated neuroendocrine neoplasms, sometimes called carcinoid, occur most often in the gastrointestinal tract (about 25% in the small intestine, 15% in the rectum, 10% in the appendix, and 5% in the stomach) and the lung (30%), but they also can occur in many other organs.

STOMACH NEUROENDOCRINE TUMORS

Gastric neuroendocrine neoplasms occur in several subtypes with differing pathophysiology, natural history, and treatment. Type 1 gastric neuroendocrine neoplasm (carcinoid), which arises in the body and fundus of the stomach in the setting of autoimmune atrophic gastritis, is the most common type, comprising 80% of cases.

In type 1 lesions, gastrin is markedly elevated due to the absence of negative feedback from gastric acid, not because the neoplasms themselves are secreting gastrin. The high gastrin stimulates proliferation of gastric enterochromaffin-like neuroendocrine cells in the body and fundus of the stomach, thereby resulting in hyperplasia of neuroendocrine cells and small multifocal neuroendocrine lesions, which occasionally progress to type 1 gastric carcinoids. These neoplasms are generally of low grade and have a low metastatic potential when less than 2 cm in size and are usually removed endoscopically. Multifocal neoplasms with multiple recurrences can be treated with a somatostatin analogue (e.g., octreotide [10 to 30 mg intramuscularly every 4 weeks] or lanreotide [90 to 120 mg deep subcutaneous injection monthly]) or, very rarely, laparoscopic antrectomy to lower the gastrin level.

Type 2 neuroendocrine neoplasms, which are associated with Zollinger-Ellison syndrome with MEN1, comprise only about 5% of gastric neuroendocrine neoplasms, thereby making them the least common type. These neoplasms are almost invariably multifocal. Unlike type 1 neoplasms, the gastric mucosa is hypertrophic rather than atrophic. The type 2 lesions, which are usually small and of low to intermediate aggressiveness, are best treated with endoscopic excision.

Type 3 neuroendocrine neoplasm is sporadic gastric neoplasm. In comparison to types 1 and 2, type 3 neoplasms are not associated with hypergastrinemia and are usually of higher stage/grade, thereby portending a worse prognosis. These neoplasms can produce an atypical carcinoid syndrome. In most cases, patients require a partial gastrectomy, as for adenocarcinoma of the stomach (Chapter 178).

SMALL BOWEL AND CECAL NEUROENDOCRINE NEOPLASMS

Patients with small bowel and cecal neuroendocrine neoplasms may present with symptoms that are related to the tumor mass or with symptoms caused by biologically active peptides that are released into the circulatory system (e.g., carcinoid syndrome).[24]

Duodenal gastrinomas can be sporadic or can occur in a background of MEN-1, in which they are often associated with Zollinger-Ellison syndrome. In MEN-1–associated cases, hyperplasia of background G cells can be observed. Duodenal somatostatinomas may be associated with psammoma bodies and type 1 neurofibromatosis (Chapter 385). A nonfunctional duodenal neuroendocrine neoplasm can produce calcitonin and serotonin. Ampullary neuroendocrine neoplasms have metastatic potential, even when small, and are also associated with neurofibromatosis.

Most small bowel neuroendocrine neoplasms arise within 60 cm of the ileocecal valve. Approximately 25% of these tumors have multiple primary small bowel foci. Abdominal primary neoplasms or metastases can cause abdominal pain and even intestinal or bowel obstruction owing to growing tumor and associated desmoplasia. A primary tumor may infrequently cause gastrointestinal bleeding. Massive liver metastases can cause palpable hepatomegaly. 5-HIAA, serotonin, chromogranin A, pancreastatin, and neurokinin A are frequently measured biomarkers.

TREATMENT

Localized neoplasms should be treated by resection of the involved segment of small bowel or with right hemicolectomy depending on location. Ampullary tumors are treated with endoscopic resection when possible, although larger, more aggressive tumors, particularly those of the ampulla, may require a modified Whipple resection

PROGNOSIS

The potential for metastasis increases with size, from less than 5% in tumors less than 1 cm to approximately 50% in tumors greater than 2 cm. When metastatic, 5-year overall survival ranges from 40 to 85% and 10-year survival ranges from 40 to 60%.

APPENDICEAL NEUROENDOCRINE NEOPLASMS

Appendiceal neuroendocrine neoplasms are frequently found incidentally at the time of simple appendectomy. If they are less than 2 cm in diameter and have no unfavorable pathologic features, prognosis is outstanding and no additional surgery is needed. However, if these tumors are greater than 2 cm, a right hemicolectomy should be performed.

Mixed neuroendocrine–non-neuroendocrine neoplasms contain both carcinoid elements and elements of adenocarcinoma. These tumors can present as solid masses, as mucinous tumors that can lead to pseudomyxoma peritoneii, or as an adenocarcinoma that overgrows the goblet cell carcinoid. These tumors arise most commonly in the appendix and, because of their aggressive nature, should be treated with a right hemicolectomy, even when less than 2 cm in diameter. These neoplasms must be distinguished from tubular carcinoids, which often have focal mucin present but have an excellent prognosis and are treated as usual appendiceal neuroendocrine neoplasms.

RECTAL NEUROENDOCRINE TUMORS

Hindgut neuroendocrine neoplasms, which arise in the distal colon and rectum, are almost never associated with functional syndromes. Mixed neuroendocrine–non-neuroendocrine neoplasms should be differentiated from high-grade adenocarcinoma of the rectum.[25] Rectal neuroendocrine neoplasms are typically detected on a screening colonoscopy and, if less than 2 cm, can be treated with endoscopic mucosal resection or transrectal excision with low risk of recurrence. However, if the neoplasm is larger than 2 cm or of higher histologic grade, the metastatic risk is greater than 50%, so a low anterior resection of the rectum or anterior posterior resection of the rectum is necessary.

LUNG NEUROENDOCRINE TUMORS

Lung neuroendocrine neoplasms (bronchial carcinoids) comprise 1 to 2% of lung malignancies (Chapter 177) in adults and 20 to 30% of cases of neuroendocrine neoplasms. The annual incidence is 1.35 per 100,000 population per year. About 90% are sporadic, 5% are associated with MEN-1, and occasional cases arise from diffuse idiopathic pulmonary neuroendocrine cell hyperplasia. There is a 5:1 female preponderance without a definite relationship to cigarette smoking

Typical carcinoid has a mitotic count less than 2 per 10 high-power fields and no necrosis. Atypical carcinoid (intermediate grade) has a mitotic count of 2 to 20 per 10 high-power fields and/or focal necrosis. Staging is exactly the same as lung cancer (Chapter 177).

CLINICAL MANIFESTATIONS AND DIAGNOSIS

Carcinoid syndrome (see later) with the production of serotonin occurs in less than 10% of cases but can be severe even in the absence of metastatic disease. Histamine-mediated atypical flushing, which persists for more than 30 minutes, is bright red and can involve limbs and upper trunk; it is associated with sweating, tearing, wheezing, burning, and sometimes rosacea. Cushing syndrome from the secretion of ACTH or corticotrophin-releasing hormone (CRH) occurs in less than 5% of patients with lung carcinoid tumors. Acromegaly can occur from ectopic production of growth hormone–releasing factor.

Diffuse idiopathic pulmonary neuroendocrine cell hyperplasia, which is characterized by infiltration of lung parenchyma with neuroendocrine cells and tumorlets (<0.5 mm), can lead to the development of multifocal bilateral lung disease. Over many years, it can lead to bronchiectasis, interstitial fibrosis, and bronchiolitis obliterans. CT of the chest, which typically shows numerous subcentimeter pulmonary nodules, should be repeated every 6 months along with pulmonary function tests, including diffusing capacity.

TREATMENT

Surgery is the treatment of choice for localized disease. Endoscopic laser debulking may be helpful to allow for recovery from distal obstructive pneumonia and to allow for a more conservative resection. In the absence of locally advanced disease, sleeve resection often can be performed with minimal loss of functional lung tissue. Video-assisted thoracoscopic surgery (Chapter 87) is recommended to perform lobectomy and lymphadenectomy for accurate staging and to maximize the chance of cure.

The temptation for radical surgery for diffuse idiopathic pulmonary neuroendocrine cell hyperplasia should be avoided to preserve as much lung parenchyma as possible. If the patient becomes symptomatic from progressive disease, somatostatin analogue therapy (e.g., octreotide, 10 to 30 mg intramuscularly every 4 weeks or lanreotide, 90 to 120 mg deep subcutaneous injection monthly) might be considered.

Cushing syndrome can be cured by resection of a localized tumor, but laparoscopic bilateral adrenalectomy is the treatment of choice if it caused by an unresectable or metastatic neuroendocrine neoplasm because medical management is usually inadequate. Acromegaly often responds to somatostatin analogs (e.g., octreotide, 10 to 30 mg intramuscularly every 4 weeks or lanreotide, 90 to 120 mg deep subcutaneous injection monthly) or surgical debulking.

THYMUS NEUROENDOCRINE TUMORS

Thymus neuroendocrine neoplasm is rare, with an annual incidence of 0.02 per 100,000 per year. It accounts for 2% of all mediastinal tumors and 5% of thymic lesions. Most cases are sporadic, but 25% are associated with MEN-1. Functional syndromes, including Cushing syndrome and acromegaly, may occur, as in lung neuroendocrine neoplasms. Criteria for pathologic grade are the same as in lung neuroendocrine neoplasm. There is no accepted staging system, but thymus neuroendocrine neoplasms are usually divided into three groups: encapsulated, invasive, and metastatic. Late presentation with invasion of vital structures is common, but complete resection is the only possible curative procedure. Careful preoperative staging is important. Definitive surgery, which typically requires median sternotomy and mediastinal node dissection and may require cardiopulmonary bypass with cardioplegic arrest, should not be done if significant extrathoracic metastases are present or if the patient is not a good surgical candidate.

CARCINOID SYNDROME

The carcinoid syndrome develops when mediators released by neuroendocrine neoplasms, most commonly metastatic and arising from the small intestine, cause systemic symptoms and signs. The incidence is about 1 to 2 per 100,000 adults. Symptoms include episodic flushing, diarrhea, wheezing, tachycardia, and fluctuations in blood pressure. Patients may eventually develop intraperitoneal and retroperitoneal fibrosis, as well as endomyocardial fibrosis that leads to valvular heart disease. Approximately 8 to 35% of all patients who have neuroendocrine neoplasm develop carcinoid syndrome, most commonly with neoplasms that originate in the small bowel and have metastases to the liver. Foregut (e.g., bronchus, stomach, pancreas, and thymus) and hindgut neuroendocrine neoplasms rarely cause carcinoid syndrome.

Carcinoid syndrome results from the production of biologically active substances, including serotonin, tachykinins, histamine, and prostaglandins that increase blood flow to the skin. Foregut carcinoids frequently produce an atypical carcinoid syndrome due to the release of 5-hydroxytryptophan rather than serotonin.

CLINICAL MANIFESTATIONS

Diarrhea of secretory type is a major feature of the carcinoid syndrome. Stool volume is typically greater than 1 L/day and persists with fasting (when on intravenous fluids). No osmotic gap is present when stool osmolality is measured. Flushing from carcinoid syndrome involves attacks of skin redness, which may be associated with burning and warmth without sweating. Redness is typically noted on the face and neck, sometimes extending to the trunk and abdomen. Psychiatric manifestations of tryptophan deficiency occur when a large percentage of dietary tryptophan is shunted to produce serotonin, thereby leaving less tryptophan to form nicotinic acid and protein. Pellagra (nicotinic acid deficiency; Chapter 199) can be seen when the urinary excretion of 5-HIAA is greater than 100 mg/day as a result of this shunting.

Carcinoid heart disease (Chapter 47) is endomyocardial fibrosis caused by serotonin.[26] The serotonin level is typically greater than 1000 pg/mL, and the urinary 5-HIAA is typically greater than 57 mg/24 hours. Cardiac fibrotic manifestations commonly include tricuspid valve regurgitation (65%), pulmonary valve regurgitation (20%), and right ventricular myocardial restrictive disease, but about 10% of patients may develop left-sided cardiac involvement. Symptoms of right-sided heart failure include swelling in legs and abdomen, shortness of breath, and fatigue. Diagnosis often is easily made by echocardiography.

Intraperitoneal and retroperitoneal fibrosis, which also results from the high level of serotonin, causes intense peritoneal fibrosis that leads to bowel obstruction in about 50% of patients, as well as mesenteric vessel occlusion and bowel ischemia. Retroperitoneal fibrosis can cause ureteral obstruction.

Carcinoid crisis, which is an attack of severe and sustained flushing with life-threatening hemodynamic compromise and bronchoconstriction, is precipitated by anesthesia, surgery, tumor necrosis, or catecholamine infusion. Other manifestations include generalized fatigue, bronchoconstriction, tachycardia, rosacea, and proximal myopathy.

DIAGNOSIS

Carcinoid syndrome should be considered if at least one clinical manifestation is present in patients with a biopsy-proven neuroendocrine neoplasm. The diagnostic hallmark is increased excretion of urinary 5-HIAA. Normally,

urinary excretion of 5-HIAA does not exceed 6 to 10 mg/day when patients have been placed on a low-serotonin diet and have avoided medications that are known to elevate 5-HIAA (e.g., acetaminophen, nicotine, caffeine) falsely before urine collection. Under these circumstances, urinary excretion of 25 mg/day or more of 5-HIAA usually establishes the diagnosis of the carcinoid syndrome. Levels of 9 to 25 mg/day also can be found in patients with vomiting, acute intestinal obstruction, or nontropical sprue. An elevated fasting plasma 5-HIAA level or a platelet 5-HIAA level is an alternative approach.[27] Plasma levels of chromogranin A are frequently elevated in carcinoid syndrome but are not diagnostic.

TREATMENT

Octreotide (subcutaneously every 8 hours, with the dose increased as rapidly as can be tolerated by the patient from 50 to 300 μg three times per day) reduces 5-HIAA excretion by 50% and can dramatically reduce the frequency and intensity of diarrhea and flushing.[A1,28] Once symptoms are improved, the patient can be switched to octreotide LAR, 20 to 30 mg intramuscularly every 4 weeks (or lanreotide 120 mg subcutaneously every month). The addition of telotristat ethyl (250 mg orally twice daily[A2]), which is a potent inhibitor of tryptophan hydroxylase, reduces 5-HIAA by 40%, thereby resulting in marked reduction of diarrhea if it is inadequately controlled by somatostatin analogue therapy alone.

Reducing the bulk of hormone-producing tumor cells by surgery, embolization, or ablation of liver metastasis is also an important component of long-term control of carcinoid syndrome. Systemic therapy with biologic agents such as everolimus, peptide receptor radiotherapy, or interferon may also improve the symptoms of carcinoid syndrome.

For carcinoid heart disease (Chapter 47), diuretics help, but more than 80% of patients die in 4 to 5 years without valve replacement. With replacement of the damaged tricuspid and pulmonic valves, 4-year survival is 50%. Bioprosthetic valves can develop carcinoid fibrosis, but mechanical valves require lifetime anticoagulation, so the choice of therapy must be individualized. Best results for valve replacement occur when the serotonin level is not massively elevated, the patient is younger than 60 years, and heart muscle function is still good (Chapter 60).

PRINCIPLES FOR CONTROLLING GROWTH OF METASTATIC NEUROENDOCRINE TUMORS

Surgery is always an option when either locoregional or metastatic neuroendocrine neoplasm is potentially resectable. Liver-dominant metastasis can potentially be treated with hepatic artery embolization, ablation, or metastasectomy. Metastatic neuroendocrine neoplasms that progress despite a somatostatin analog and that can be detected by somatostatin receptor imaging can be treated with peptide receptor radionuclide therapy. Systemic biologic agents and chemotherapy have a role in managing metastatic disease.

TREATMENT

Primary Debulking Surgery/Regional Therapy/Liver Transplantation

If it is possible to remove at least 90% of metastases surgically,[29] survival as well as symptoms of hormone secretion appear to be improved. Cholecystectomy at the time of abdominal surgery prevents cholelithiasis from somatostatin analogue therapy and makes subsequent liver embolization safer. The primary neoplasm should be removed when carcinoid syndrome is caused by ileal-jejunal neuroendocrine neoplasms to prevent or treat bowel obstruction, bleeding, and other local complications. Liver metastases can be treated with radiofrequency or microwave ablation of lesions less than 4 cm diameter, using a probe inserted into metastasis at surgery or under CT guidance. Irreversible electroporation (NanoKnife), stereotactic radiosurgery, alcohol injection, and other locally destructive techniques can also help to reduce the volume of liver metastases. When liver metastases are too extensive for these techniques, transcatheter hepatic artery embolization can be used. Hepatic artery embolization should be bland embolization or chemoembolization rather than radioembolization, which appears to increase the risk of radiation-induced liver disease when peptide receptor radiotherapy is subsequently used. Liver transplantation is occasionally used for patients who have refractory symptoms with metastatic disease restricted to the liver.

Somatostatin Analogue Therapy

Somatostatin is a peptide hormone that mediates its inhibitory effects on hormone secretion and tumor growth by binding to specific cell-surface G protein–coupled somatostatin receptors. The somatostatin analogs, octreotide and lanreotide, have a longer half-life than somatostatin and bind preferentially to receptor subtype 2, which is the receptor that is most responsible for controlling cell proliferation and secretion, and are effective treatments for controlling symptoms and prolonging survival in pancreatic and gastrointestinal neuroendocrine tumors.[A3]

Peptide Receptor Radionuclide Therapy

Peptide receptor radionuclide therapy uses the binding of a radiolabeled somatostatin analogue to the somatostatin receptor to irradiate selective sites of metastasis with minimal injury to the surrounding normal tissues.[30,31] In patients who become resistant to treatment with maximum approved doses of a somatostatin analogue, such treatment can substantially improve symptoms and progression-free survival.[A4]

Other Therapies

Inhibition of mTOR with everolimus (10 mg orally daily) can increase progression-free survival in patients who have neuroendocrine neoplasms arising from the pancreas, gastrointestinal tract, and lung.[A5] Neuroendocrine tumors are highly vascular and can be controlled with antiangiogenic agents. Sunitinib (an oral tyrosine kinase inhibitor that inhibits VEGFR, PDGFR, KIT, FLT3, and RET at 37.5 mg/day) can prolong progression-free survival in pancreatic neuroendocrine neoplasms. Significant toxicities (seen in <10% of cases) include neutropenia, hypertension, abdominal pain, diarrhea, hypoglycemia, and hand-foot syndrome. Surufatinib (another oral tyrosine kinase inhibitor) also prolongs median survival by about 7.3 months in pancreatic neuroendocrine cancers[A6] and by about 5.5 months in extrapancreatic neuroendocrine cancers.[A7] Cabozantinib and pazopanib are other antiangiogenic agents that have shown promise in neuroendocrine neoplasms and in carcinoid tumors, respectively. Bevacizumab added to everolimus in pancreatic neuroendocrine neoplasms and to octreotide in carcinoid tumors[A8] has improved the response rate but not the progression-free survival, and it currently is not recommended therapy.

For neuroendocrine neoplasms arising outside the pancreas, cytotoxic chemotherapy has a low response rate. For pancreatic neuroendocrine neoplasms, however, treatment under expert guidance can be efficacious. For example, streptozotocin (combined with doxorubicin, cyclophosphamide, or 5-fluorouracil [5-FU]) has response rates reported as high as 70%. The combination of two oral cytotoxic drugs, temozolomide plus capecitabine, appears to have similar activity in pancreatic neuroendocrine neoplasms. For advanced grade neuroendocrine neoplasms, chemotherapy with etoposide and cisplatin, irinotecan plus cisplatin,[A9] or carboplatin has a response rate of 30 to 70%, but it is usually short lasting.[32,33]

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214 SEXUAL DEVELOPMENT

PERRIN C. WHITE

DEFINITION

Individuals with differences of sexual development lack concordance of various aspects of gender. These aspects include chromosomal sex (46,XX, 46,XY, or other), gonadal or reproductive sex (ovaries, fallopian tubes, and uterus vs. testes, seminal vesicles, prostate gland, and ejaculatory ducts), genital sex (vagina and clitoris vs. scrotum and penis), and gender-specific behavior.[1-3] Depending on chromosomal sex, most patients can be classified as incompletely masculinized 46,XY males, virilized 46,XX females, and patients with abnormalities of sex chromosomes, such as individuals with mixed gonadal dysgenesis. Many conditions can cause differences of sexual development[4] (Table 214-1).

Normal Sexual Differentiation

Gonadal Differentiation

At 4 to 5 weeks' gestation, the gonadal primordia (gonadal ridges) develop from the coelomic epithelium overlying the medial surface of the mesonephros (primitive kidneys; Fig. 214-1). These primitive gonads are identical in both sexes. Germ cells form at 3 to 4 weeks' gestation and migrate through the gut mesentery into the gonads at this early bipotential stage. This first stage of gonadal development is controlled by homeobox genes.

During the seventh week, XY male gonads begin to differentiate under the influence of testis-determining genes. The first to be expressed is *SRY*, which is the key gene on the Y chromosome that controls male differentiation. Sertoli cells surround germ cells to form testis cords, which nourish primordial germ cells and direct them into the pathway for male gametogenesis. Recruitment of endothelial cells leads to development of a testis-specific vasculature that is required for normal organization of the testis.

Steroidogenic cells develop from the mesonephros and migrate into the developing adrenal cortex and testis at 8 weeks. In the testis, they become Leydig cells, which secrete the testosterone required for subsequent male reproductive development. In the first trimester, testosterone secretion is mainly under the control of human chorionic gonadotropin (HCG), but it subsequently requires luteinizing hormone (LH) secreted by the fetal anterior pituitary.

Ovaries are recognizable at approximately 10 weeks. Ovarian development requires the active participation of several signaling pathways that repress expression of testis-specific genes and promote ovarian development.

Development of Male and Female Internal Reproductive Tracts

The reproductive tracts are derived from intermediate mesoderm. The male reproductive tract develops from the mesonephric (wolffian) ducts, and the female reproductive tract develops from the paramesonephric (müllerian) ducts (Fig. 214-2). Both sets of ducts are present in normal embryos.

Development of wolffian or müllerian structures depends on the presence or absence of normally functioning testes, respectively. The Sertoli cells secrete antimüllerian hormone starting when the testes differentiate.[5] Antimüllerian hormone induces regression of müllerian structures between 8 and 12 weeks' gestation. In its absence, development of the müllerian ducts proceeds, and the female internal structures (fallopian tubes, uterus, cervix, and upper vagina) are formed.

Development of the structures derived from the wolffian ducts, including the epididymis, ductus deferens, ejaculatory ducts, and seminiferous tubules, requires high local concentrations of testosterone secreted from Leydig cells of the testis beginning at approximately 7 weeks' gestation. In the absence of testosterone, wolffian ducts regress. Levels of testosterone in the circulation are insufficient to develop wolffian structures. In conditions in which the gonads develop asymmetrically (e.g., ovotesticular disorders of sexual development or mixed gonadal dysgenesis; see later), wolffian structures develop asymmetrically as well. Development of wolffian structures requires an intact androgen receptor.

Development of the External Genitalia

External genital structures are also bipotential in early gestation and consist of the genital tubercle, genital folds (later, urethral-labial folds), and genital swelling (later, labioscrotal folds) (see Fig. 214-2). Differentiation to male genitalia occurs from approximately 8 to 14 weeks' gestation under the influence of dihydrotestosterone, which must interact with an intact androgen receptor. The genital tubercle becomes the glans penis; the genital folds fuse to become the shaft of the penis and penile urethra, and the labioscrotal folds (derived from the genital swelling) fuse to become the scrotum. Without androgens, these structures become the clitoris, labia minora, and labia majora, respectively.

Normal Gonadal and Adrenal Steroidogenesis

Many forms of genital ambiguity result from defects in steroid biosynthesis in the testes or adrenal cortex or from defective steroid metabolism in the placenta or in target tissues (E-Fig. 214-1). Steroid biosynthesis in the testes and adrenals begins with the importation of cholesterol into mitochondria, a highly regulated process controlled largely by the steroidogenic acute regulatory (StAR) protein. Levels of StAR are controlled within the adrenals by adrenocorticotropic hormone (ACTH) and within the testis by HCG during the first trimester and by LH later in pregnancy.

Within mitochondria, the side chain of cholesterol is cleaved between carbons 20 and 22 by the cholesterol side-chain cleavage enzyme (CYP11A1), which is a cytochrome P-450 enzyme. The product is pregnenolone, which is transported to the endoplasmic reticulum. Some pregnenolone is converted by 17α-hydroxylase (CYP17A1) to 17-hydroxypregnenolone. Both 17-hydroxypregnenolone and the remaining pregnenolone are converted by 3β-hydroxysteroid dehydrogenase (HSD3B2) to 17-hydroxyprogesterone and progesterone, respectively. The side chain of 17-hydroxypregnenolone is cleaved by the 17,20-lyase activity of CYP17A1 to dehydroepiandrosterone (DHEA). DHEA may also be converted to androstenedione by HSD3B2.

All the preceding steps can occur in the adrenal cortex, in Leydig cells of the testis, and (after puberty) in theca cells of ovarian follicles. Subsequent biosynthetic steps are specific to different glands. In the adrenal cortex, 17-hydroxyprogesterone is converted by 21-hydroxylase (CYP21A2) to 11-deoxycortisol, which is then converted in mitochondria to cortisol by 11β-hydroxylase (CYP11B1). Additionally, progesterone is converted to deoxycorticosterone by CYP21A2, which is then converted to aldosterone by aldosterone synthase (CYP11B2).

In Leydig cells of the testis, androstenedione is converted to testosterone by 17-ketosteroid reductase (17β-hydroxysteroid dehydrogenase type 3 [HSD17B3]); the same reaction occurs in theca cells of the ovary, catalyzed by 17β-hydroxysteroid dehydrogenase type 1 (HSD17B1). In granulosa cells of the ovary (after puberty), androstenedione and testosterone are converted by aromatase (CYP19A1) to estrone and estradiol, respectively. In the skin of the developing male external genitalia, steroid 5α-reductase (SRD5A2) converts testosterone to a more potent androgen, 5-dihydrotestosterone.

The placenta is a steroid-synthesizing and steroid-metabolizing tissue as well; it has high steroid sulfatase activity that converts DHEA sulfate from the fetal adrenal gland back to DHEA. DHEA is then successively converted by 3β-hydroxysteroid dehydrogenase type 1 (HSD3B1) and aromatase (CYP19A1) to androstenedione and estrone, respectively, which are then converted to estradiol by HSD17B1.

DIFFERENCES OF SEXUAL DEVELOPMENT

DEFECTS OF STEROIDOGENESIS

Genital ambiguity in genetic females is usually the result of exposure to excessive levels of androgens. Virilizing congenital adrenal hyperplasia, which is the most common cause of genital ambiguity in female infants, occurs in 1 in 16,000 births.

Conversely, severe deficiencies of androgens, if present early in gestation, cause ambiguous or female-appearing external genitalia in male infants. Usually, müllerian structures such as the uterus, cervix, and upper vagina are not present because the testes are able to secrete antimüllerian hormone. Thus individuals with these conditions have a short vagina ending in a blind pouch.

CONGENITAL ADRENAL HYPERPLASIA

The fundamental defect among patients with any form of congenital adrenal hyperplasia is inadequate synthesis of cortisol (see E-Fig. 214-1).[6] Inefficient cortisol synthesis signals the hypothalamus and pituitary to increase corticotropin-releasing hormone and ACTH, respectively (Chapter 204). Consequently, the adrenal glands become hyperplastic, and steroid precursors accumulate proximal to the block in biosynthesis. In some conditions, these precursors can be converted to androgens.

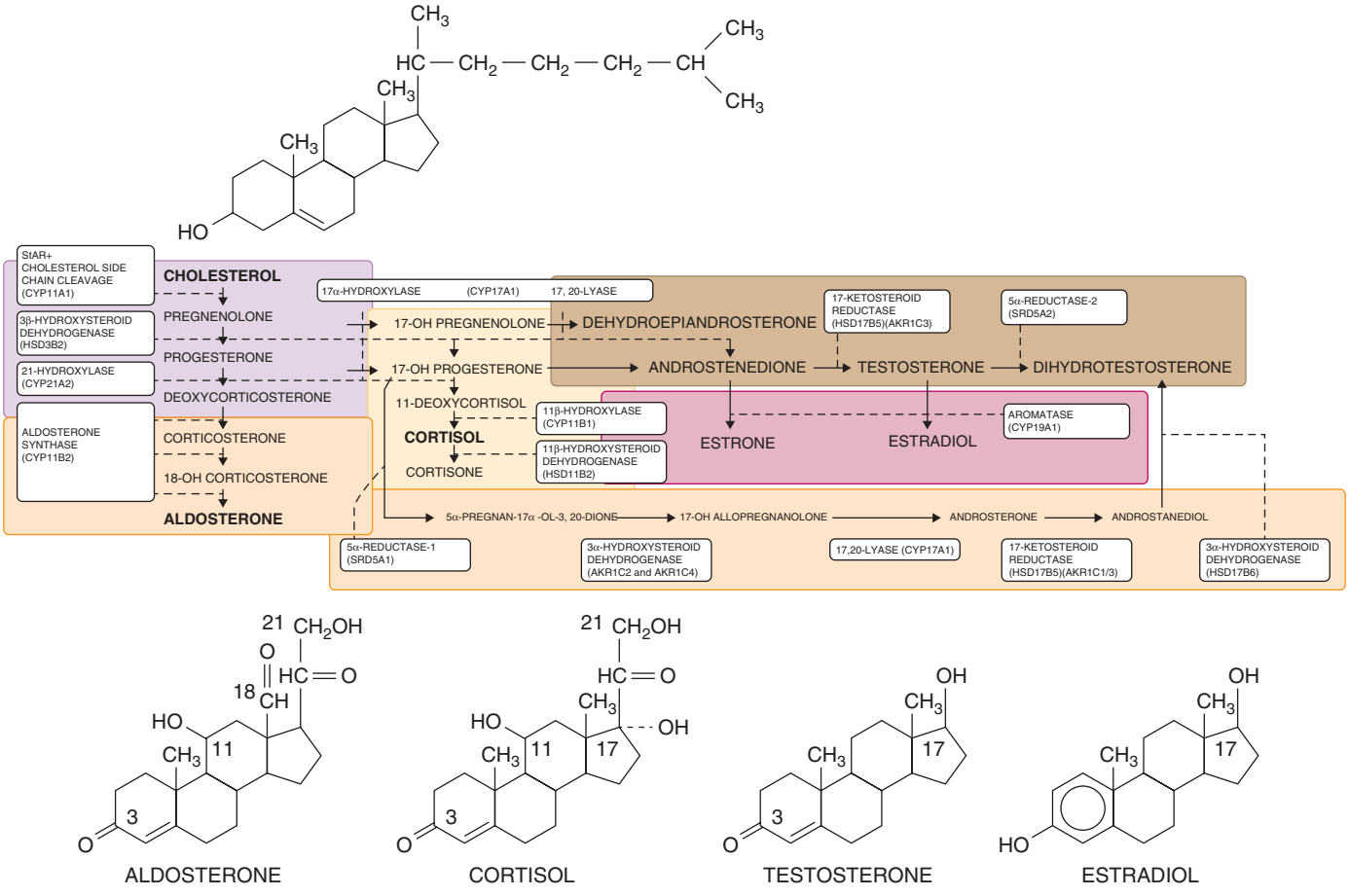

E-FIGURE 214-1. **Adrenal and gonadal steroidogenesis.** Enzymes are boxed with dotted lines extending to arrows denoting each enzymatic conversion; two enzymes, CYP11B2 and CYP17A1, catalyze several successive enzymatic conversions. There are two 11β-hydroxysteroid dehydrogenase isozymes: HSD11B1, which is expressed mainly in the liver, catalyzes reduction (e.g., cortisone to cortisol); and HSD11B2, which is expressed mainly in the kidney, catalyzes oxidation (e.g., cortisol to cortisone). Steps taking place only in the adrenal glands are in unshaded boxes; steps taking place partly or predominantly outside the adrenal cortex are denoted by shaded boxes. Planar structures of cholesterol, aldosterone, cortisol, testosterone, and estradiol are illustrated. Colored rectangles indicate the following: purple, early steps of steroidogenesis common to all zones of the cortex; orange, steps in the zona glomerulosa leading to aldosterone; yellow, steps in the zona fasciculata leading to cortisol; tan; steps in the zona reticularis and testes leading to androgens; orange, the "backdoor" or alternative pathway from 17-OH progesterone to dihydrotestosterone (for clarity, the alternative pathway from progesterone is not shown); magenta, conversions leading to estrogens in the ovary and extragonadal tissues. (Figure adapted from Claahsen-van der Grinten HL, Speiser PW, Ahmed SF, et al. Congenital adrenal hyperplasia—current insights in pathophysiology, diagnostics and management. *Endocr Rev*. 2022;43:91-159.)

ABSTRACT

Individuals with differences of sexual development lack concordance of various aspects of gender, including chromosomal sex (46,XX, 46,XY, or other), gonadal or reproductive sex (ovaries, fallopian tubes, and uterus vs. testes, seminal vesicles, and prostate gland), genital sex (vagina and clitoris vs. scrotum and penis), and gender-specific behavior. Most patients can be classified as incompletely masculinized 46,XY males, virilized 46,XX females, and patients with abnormalities of sex chromosomes, including those with mixed gonadal dysgenesis. Genital ambiguity in genetic females is usually the result of exposure to excessive levels of androgens; congenital adrenal hyperplasia is the most common cause. Conversely, severe androgen deficiencies during early gestation and androgen insensitivity cause ambiguous or female-appearing external genitalia in male infants. Many genetic syndromes interfere with normal gonadal development. Hypogonadotropic hypogonadism of any etiology may result in a micropenis. However, transgender individuals rarely have identifiable hormonal or genetic abnormalities. Children with differences of sexual development should be evaluated with a physical examination, karyotype, and, depending on context, profiles of adrenocortical hormones or sex steroids after stimulation with cosyntropin or human chorionic gonadotropin. Some patients will require gonadal biopsies. A multidisciplinary team should review diagnostic data and make recommendations as to the sex of rearing and any medical or surgical treatments. Depending on the underlying condition, patients may require replacement of pituitary or adrenal hormones and treatment with sex steroids.

KEYWORDS

androgens
estrogens
testis
ovary
adrenal
pituitary

TABLE 214-1 DIFFERENCES OF SEXUAL DEVELOPMENT*

VIRILIZATION OR SEX REVERSAL IN XX FEMALES

Virilizing forms of congenital adrenal hyperplasia
- 21-Hydroxylase deficiency (1:16,000 births) [*CYP21A2*]: salt-wasting or simple virilizing forms
- 11β-Hydroxylase deficiency [*CYP11B1*]
- 3β-Hydroxysteroid dehydrogenase deficiency [*HSD3B2*]
- Cytochrome P-450 oxidoreductase deficiency (also has a maternal effect) [*POR*]

Maternal or exogenous androgens
- Drugs (danazol, progestins)
- Luteoma
- Aromatase deficiency [*CYP19A1*]
- Transcription factor mutations
- *AKR1C* genes

Mutations in genes affecting gonadal differentiation
- *SRY* (translocation to X)
- *SOX9* (duplication)
- *SOX3* (duplication)
- *SOX10* (duplication)
- *WT1* (Denys-Drash syndrome)
- *NR5A1*(the Arg92Trp mutation causes ovotesticular difference of sexual development)
- *FOXL2* (ovarian failure associated with blepharophimosis, ptosis, and epicanthus inversus; BPES)
- *RSPO1*
- *WNT4*
- *CBX2*
- *RCA2*
- *ESR2*
- *FSHR*
- *LHX1*
- *NR2F2*
- *NUP107*
- *PSMC3IP*
- *WWOX*

Structural/idiopathic

MICROPENIS

Panhypopituitarism (combined pituitary hormone deficiency) [*PROP1, FGF8, PROKR2, WDR1*]
Septo-optic dysplasia [*HESX1, FGFR1*]
Isolated hypogonadotropic hypogonadism [*GNRH1, GNRHR, KISS1, KISS1R, TAC3, TACR3*]
Other syndromes, including hypogonadotropic hypogonadism
- Kallmann syndrome [*KAL1, AXL, FEZF1, HS6TS1, NSMF, OL14RD, PROK2, SEMA3A, SEMA7A*]
- Prader-Willi syndrome [paternal chromosome 15q11deletion]
- Adrenal hypoplasia congenita [*NR0B1*(*DAX1*)]
- CHARGE complex (colobomata, heart defects, choanal atresia, growth retardation, genital anomalies, ear defects or deafness) [*CHD7*]
- Dandy-Walker syndrome (hypoplasia of the cerebellar vermis and cystic dilation of the fourth ventricle) [*FGF17*]
- Leptin and leptin receptor deficiency (severe obesity) [*LEP, LEPR*]
- Proprotein convertase 1/3 deficiency (obesity and endocrinopathy due to impaired processing of prohormones) [*PCSK1*]
- Polyendocrine deficiencies and polyneuropathy [*DMXL2*]
- Gordon-Holmes syndrome (cerebellar ataxia and adult-onset neurodegeneration) [*RNF216, OTUD4, PNPLA6*]
- Waardenburg syndrome (pigmentary abnormalities of the hair, skin, and eyes; congenital sensorineural hearing loss) [*SOX10*]

Vanishing testes (may also cause ambiguous genitalia)

UNDERVIRILIZATION OR SEX REVERSAL IN XY MALES

Biosynthetic defects
- Lipoid adrenal hyperplasia [*STAR*]
- 17α-Hydroxylase/17,20 lyase [*CYP17A1*]
- 3β-Hydroxysteroid dehydrogenase [*HSD3B2*]
- 17-Ketosteroid reductase [*HSD17B3*]
- 5α-Reductase [*SRD5A2*]
- Cytochrome P-450 oxidoreductase deficiency [*POR*]
- Smith-Lemli-Opitz syndrome (1:20,000) [*DHCR7*]

Androgen insensitivity (1:20,000) [*AR*]: complete or partial
Luteinizing hormone insensitivity [*LHR*]
Mutations in genes affecting gonadal differentiation
- *SRY*
- *SOX9* (campomelic dysplasia)
- *NR5A1* (steroidogenic factor-1; sometimes associated with adrenal hypoplasia)
- *WT1* (WAGR, Denys-Drash, and Frasier syndromes)
- *NR0B1* (*DAX1*) or *WNT4* duplications
- *DHH* (associated with peripheral neuropathy)
- *ATRX* (X-linked α-thalassemia and mental retardation)
- *GATA4*
- *ZFPM2*(*FOG2*)
- *MAP3K1*
- *HHAT*
- *DMRT1*
- *MAMLD1*
- *ARX*
- *CBX2*
- *FGFR2*
- *RXFP2*
- *INSL3*
- *?HOXA13*
- *?TSPYL1*
- *SOX8*
- *WWOX*
- *ZNRF3*

Exposure to 5α-reductase inhibitors, other endocrine disruptors

OTHER SYNDROMES AFFECTING REPRODUCTIVE SYSTEMS

Chromosomal aneuploidy
- Turner syndrome (1:2500): 45,X; 45,X/46,XX mosaics; 46,XXr; 46,XXq−
- Klinefelter syndrome (1:1000): 47,XXY
- Mixed gonadal dysgenesis (1:20,000): 45,X/46,XY; 45,X/47,XXY
- Other: trisomy 13, trisomy 18, triploidy, 4p−, 13q−

Persistent müllerian duct syndrome in XY males
- Type 1 [*AMH*]
- Type 2 [*AMHR2*]

Mayer-Rokitansky-Küster-Hauser syndrome (vaginal atresia) (1:6000)

*Frequencies of relatively common (at least 1:20,000) diseases are noted in parentheses. When causative genetic mutations have been identified, the affected locus is noted in square brackets.
WAGR = Wilms tumor, aniridia, genitourinary abnormalities or gonadoblastoma, and mental retardation.

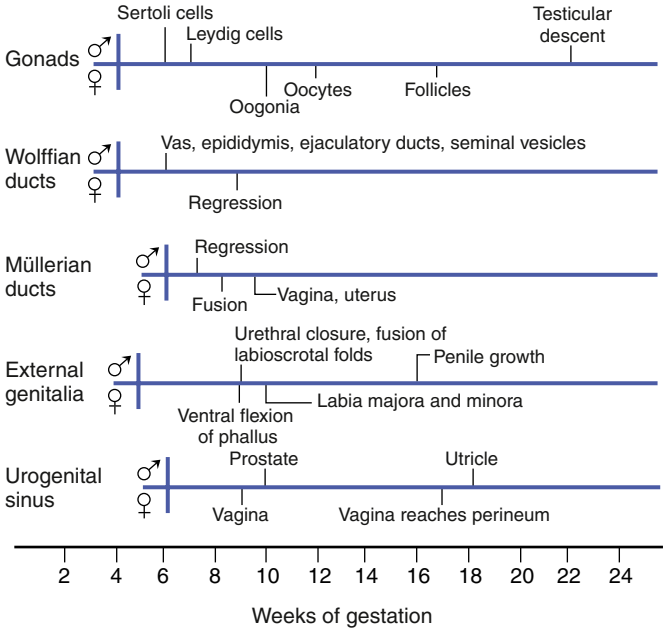

FIGURE 214-1. **Time course of prenatal sexual differentiation in male and female fetuses.** (Modified from Barthold JS, Gonzalez R. Intersex states. In: Gonzales ET, Bauer SB, eds. *Pediatric Urology Practice*. Philadelphia: Lippincott Williams & Wilkins; 1999.)

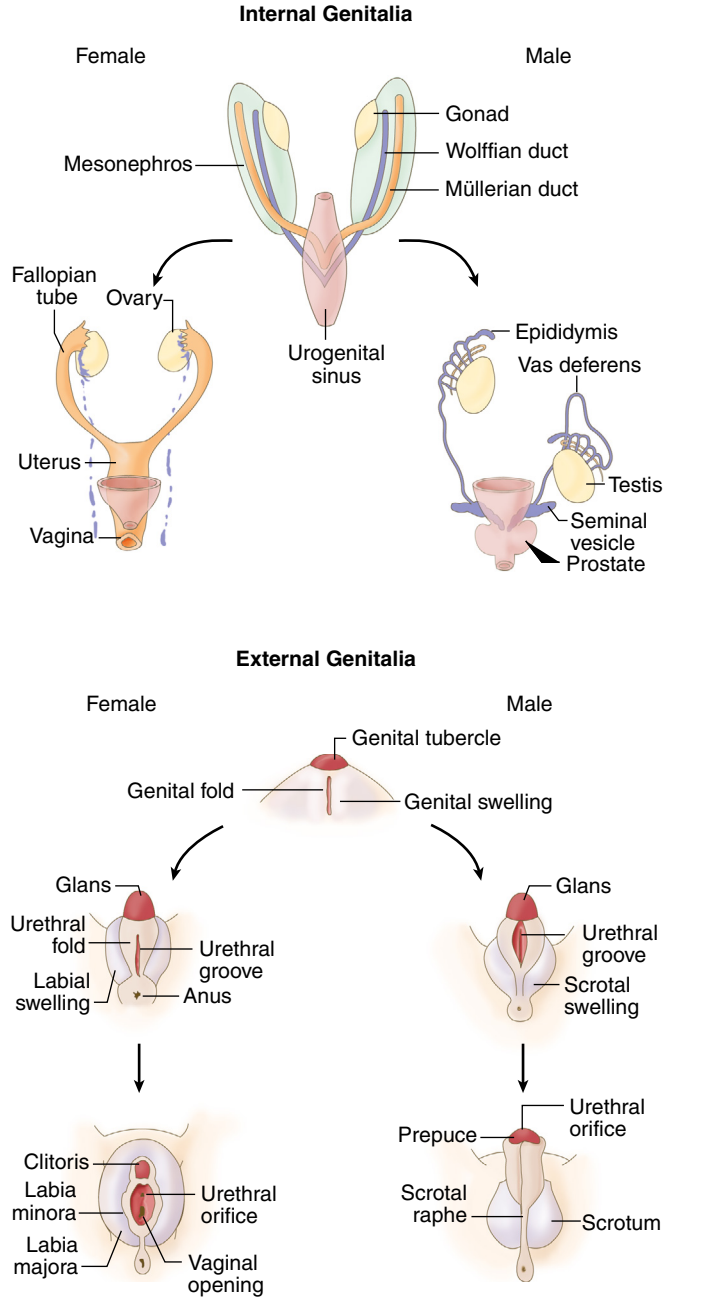

FIGURE 214-2. **Differentiation of the internal and external genitalia of the human fetus.** (Modified from Griffen JE, Ojeda SR, eds. *Textbook of Endocrine Physiology*. New York: Oxford University Press; 1996.)

Lipoid Hyperplasia

Lipoid hyperplasia results from mutations in the *STAR* gene. Cholesterol is not imported efficiently into mitochondria and thus accumulates in cells. Steroid biosynthesis is drastically reduced because of the lack of substrate, and the lipid accumulation quickly kills steroid-synthesizing cells in both the adrenals and the testes. Thus affected male patients are born as phenotypically female because they cannot synthesize testosterone. Affected female patients may undergo transient spontaneous puberty because human ovarian granulosa cells do not synthesize steroid hormones (and thus do not accumulate cholesterol) until puberty. Both sexes have adrenal insufficiency and are unable to synthesize either cortisol or aldosterone. A nearly identical but rare phenotype results from mutations in the *CYP11A1* gene that encodes the cholesterol side-chain cleavage enzyme itself.

17α-Hydroxylase/17,20 Lyase Deficiency

Severe mutations in the *CYP17A1* gene prevent the synthesis of any sex hormones. Affected male patients have female-appearing external genitalia but have no müllerian structures because the testes synthesize antimüllerian hormone. Affected female patients remain sexually infantile without hormone replacement. Milder mutations result in ambiguous genitalia in male patients. Although cortisol synthesis is also abolished, even severely affected individuals are able to synthesize corticosterone, which is an active glucocorticoid, as well as aldosterone, so they do not develop adrenal insufficiency. On the contrary, they secrete excessive amounts of deoxycorticosterone, which has mineralocorticoid activity, and are therefore prone to developing hypertension.

Whereas most *CYP17A1* mutations affect both the hydroxylase and lyase activities, rare mutations can affect the lyase activity alone. Additionally, mutations in an accessory electron transfer protein, cytochrome b_5, or the genes for two aldoketo reductases (*AKR1C2* and *AKR1C4*) can result in the same phenotype as 17,20-lyase deficiency (i.e., deficient androgen synthesis with normal cortisol synthesis).

3β-Hydroxysteroid Dehydrogenase Deficiency

Severe mutations in the *HSD3B2* gene prevent the synthesis of aldosterone, cortisol, testosterone, and estrogens. Because DHEA, a weak androgen, is synthesized and secreted at high levels, some degree of phallic growth is present. Thus affected male patients have severely ambiguous genitalia, but affected female patients may have clitorimegaly. Both sexes develop adrenal insufficiency if they are untreated.

Many children with premature adrenarche (early development of axillary and pubic hair), as well as many women with polycystic ovary syndrome, have elevated levels of DHEA. However, mutations in *HSD3B2* are rarely, if ever, found in such individuals, who instead have an imbalance in the relative levels of HSD3B2 and CYP17 activity within the adrenal cortex.

21-Hydroxylase Deficiency

More than 90% of cases of congenital adrenal hyperplasia are caused by 21-hydroxylase deficiency that results from mutations in the *CYP21A2* gene.[7] *CYP21A2* and a highly homologous pseudogene, *CYP21A1P*, are located within the major histocompatibility complex on chromosome 6p21.3, a genomic region noteworthy for a high rate of recombination. More than 90% of all mutations are the result of intergenic recombination between *CYP21A2* and *CYP21A1P*. Most are transfers of deleterious mutations from *CYP21A1P* to *CYP21A2*, whereas 20% are net deletions of *CYP21A2* resulting from unequal meiotic crossover.

In patients with 21-hydroxylase deficiency, the adrenals produce excess 17-hydroxyprogesterone, 17-hydroxypregnenolone, and progesterone, which are further metabolized to DHEA and androstenedione. Once secreted, these substances are further metabolized to active androgens (testosterone and dihydrotestosterone) and, to a lesser extent, to estrogens (estrone and estradiol). Progesterone and 17-hydroxyprogesterone can also be metabolized to dihydrotestosterone by the alternative "backdoor" pathway (E-Fig 214-1). Additionally, the adrenal gland can synthesize physiologically relevant quantities of 11-hydroxylated and 11-keto-androgens.

Adrenal secretion of excess androgen precursors does not significantly affect male sexual differentiation. In affected female patients, the urogenital sinus is in the process of septation when the fetal adrenal begins to produce excess androgens, which function to prevent the formation of separate vaginal and urethral canals. Further adrenal-derived androgens interact with androgen receptors in genital skin and induce clitoral enlargement, promote fusion of the labial folds, and cause rostral migration of the urethral/vaginal perineal orifice. However, internal wolffian structures such as the prostate gland and spermatic ducts are usually not virilized, presumably because development of the wolffian ducts requires markedly higher local concentrations of testosterone than the external genitalia. Nevertheless, severely affected female patients occasionally have some development of typically male internal genital structures.

Thus the typical result in severely affected girls is ambiguous or male-appearing external genitalia with perineal hypospadias and chordee, but without palpable testes (Fig. 214-3). The severity of virilization is often quantitated using a five-point scale developed by Prader (Fig. 214-4). The degree of genital ambiguity in female patients with classic congenital adrenal hyperplasia is correlated with the severity of enzymatic compromise conferred by each patient's mutations.

FIGURE 214-3. Virilized external genitalia in a female infant with congenital adrenal hyperplasia caused by 21-hydroxylase deficiency. No gonads are present in the scrotum.

Most patients (75%) cannot synthesize sufficient aldosterone to maintain sodium balance and are termed *salt wasters*. These patients are predisposed to episodic and potentially life-threatening hyponatremic dehydration. Patients with sufficient aldosterone production to prevent salt wasting and who have signs of prenatal virilization and/or markedly increased production of hormonal substrates of 21-hydroxylase (e.g., 17-hydroxyprogesterone) are termed *simple virilizers*. A mild nonclassic form occurs in 1/200 to 1/500 individuals and may cause postnatal androgen excess but not prenatal virilization.

11β-Hydroxylase Deficiency

Patients with 11β-hydroxylase deficiency have mutations in the *CYP11B1* gene, with elevated levels of deoxycorticosterone and 11-deoxycortisol, as well as earlier cortisol precursors such as 17-hydroxyprogesterone. These patients secrete excess adrenal androgens, with consequences similar to those seen in 21-hydroxylase deficiency. However, patients with 11β-hydroxylase deficiency synthesize aldosterone normally and do not have problems with salt wasting. Instead, they are likely to become hypertensive as a result of elevated levels of deoxycorticosterone and its metabolites.

DEFECTS OF ANDROGEN BIOSYNTHESIS

Lipoid hyperplasia, 17-hydroxylase/17,20 lyase deficiency, and HSD3B2 deficiency affect the biosynthesis of both corticosteroids and sex hormones. In contrast, two enzymatic defects affect only androgen biosynthesis. They have similar phenotypes. Affected male patients are born with ambiguous genitalia, but they virilize at puberty and often reassign themselves to a male gender if they were raised as females. They have absent müllerian structures as a result of the secretion of antimüllerian hormone by the testes.

17-Ketosteroid Reductase (17-Hydroxysteroid Dehydrogenase 3) Deficiency

This disorder is caused by mutations in the *HSD17B3* gene. Although testosterone is not synthesized well, secretion of androstenedione, an active androgen, is unimpaired. Because several other isozymes have 17-ketosteroid reductase activity in other tissues, some testosterone is invariably synthesized, especially at puberty, when circulating levels of androstenedione increase.

5α-Reductase Deficiency

Patients with 5α-reductase deficiency resulting from mutations in the *SRD5A2* gene synthesize entirely normal amounts of testosterone, but they cannot synthesize adequate amounts of dihydrotestosterone, which is the most potent naturally occurring androgen.[8] This enzyme is not expressed at high levels in the testes (circulating levels of dihydrotestosterone are relatively low); instead, it is expressed in genital skin. Internal wolffian structures do not require this enzyme and are intact; high testosterone levels at puberty induce significant phallic growth without 5α-reductase activity.

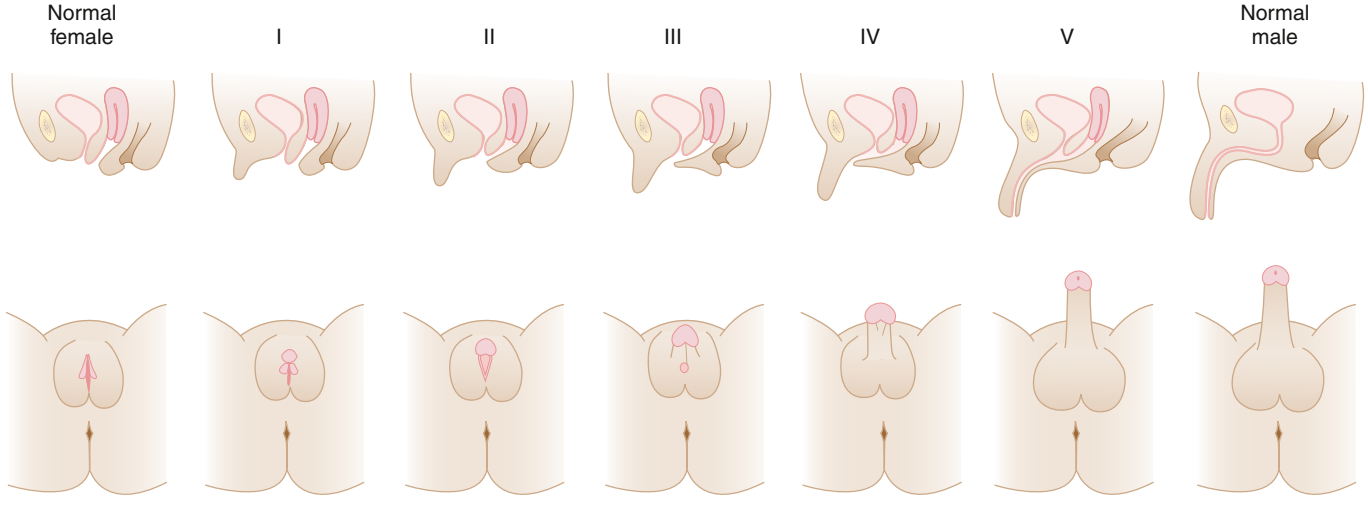

FIGURE 214-4. Abnormal differentiation of the urogenital sinus and external genitalia. Schematic representations of normal female and male anatomy flank a series of schematics illustrating different degrees of virilization of females, graded using the scale developed by Prader. The uterus (*shaded*) persists in virilized females even when the external genitalia have a completely masculine appearance (Prader grade V). (Modified from Prader A. Der Genitalbefund beim Pseudohermaphroditismus femininus der kengenitalen adrenogenitalen Syndroms. *Helv Paediatr Acta*. 1954;9:231-248.)

OTHER DEFECTS OF STEROIDOGENESIS

Aromatase Deficiency

Mutations in *CYP19A1* cause aromatase deficiency in both the fetus and the placenta. The placenta can convert DHEA sulfate to androstenedione and testosterone normally, but it cannot convert these androgens to estrone and estradiol. These androgens accumulate in both the fetal and maternal circulations and virilize both the mother and the affected fetus if it is female. Affected male infants are phenotypically normal. Affected female patients virilize further at puberty if they are untreated. The lack of aromatase activity within bone leads to tall stature in both sexes (because estrogens are required to close the growth plates) and later to osteoporosis.

Cytochrome P-450 Oxidoreductase Deficiency

This deficiency is one form of Antley-Bixler syndrome, which is characterized by skeletal anomalies and craniosynostosis; most patients also have ambiguous genitalia associated with mutations in the *POR* gene.[9] Antley-Bixler syndrome without genital abnormalities is caused by mutations in the FGF receptor (*FGFR2*) gene.

Because this disorder affects the activity of all microsomal cytochrome P-450 subsets, complete deficiency of cytochrome P-450 oxidoreductase (POR) is lethal, and identified mutations in humans yield POR with partial activity. *POR* mutations may cause skeletal anomalies (Antley-Bixler syndrome) by interfering with activity of CYP26B1, an enzyme that degrades retinoic acid. Genital ambiguity is caused by several mechanisms. Decreased activity of 17α-hydroxylase/17,20 lyase (CYP17A1) affects androgen synthesis and leads to undervirilization in males. Conversely, decreased activity of 21-hydroxylase (CYP21A2) can virilize affected females. These two deficiencies also can cause adrenal insufficiency. POR deficiency also diverts steroids into the "back-door pathway" of dihydrotestosterone biosynthesis, thereby contributing to prenatal female virilization. Finally, decreased activity of placental aromatase (CYP19A1) virilizes both the mother and the affected fetus (if female). The extent to which different CYP enzymatic activities are affected depends to some degree on the POR mutations involved.

Smith-Lemli-Opitz Syndrome

This relatively frequent (1 in 20,000 Northern Europeans) disorder of the final step of cholesterol biosynthesis (conversion from 7-dehydrocholesterol) is caused by mutations in the *DHCR7* gene that encodes 7-dehydrocholesterol reductase. The syndrome is characterized by multiple congenital anomalies, including being small for gestational age, short stature, microcephaly, mental retardation, aggressive behavior, seizures, hypotonia, polydactyly, cleft palate, cardiac defects, lung hypoplasia, and renal anomalies. Male patients have ambiguous genitalia. The range of clinical severity is wide and depends on the nature of the mutations.

MATERNAL CONDITIONS AFFECTING THE FETUS

LUTEOMA OF PREGNANCY

Luteomas, which are the most common causes of maternal virilization during pregnancy, often occur bilaterally. Although many luteomas are discovered incidentally during cesarean sections or postpartum tubal ligations, one fourth of mothers virilize during the latter half of pregnancy, and half of female infants born to these mothers also exhibit signs of virilization, most typically clitoromegaly and labial fusion. Spontaneous regression of the luteoma generally begins within days after delivery.

DRUG EXPOSURE

Depending on the agent, maternal drug exposure may affect either male or female fetuses. Females may be virilized by androgens such as 19-nor-testosterone or progestins administered to prevent spontaneous abortion. Undervirilized males can be born to women exposed to 5α-reductase inhibitors such as finasteride. The antifungal agent fluconazole can inhibit many cytochrome P-450 enzymes and can lead to a condition closely resembling Antley-Bixler syndrome.

HORMONE INSENSITIVITY SYNDROMES AND OTHER HORMONE DEFICIENCIES

ANDROGEN INSENSITIVITY

Males normally carry a single copy of the X-linked androgen receptor (*AR*) gene. Thus a single mutation can completely inactivate the receptor in males and lead to complete androgen insensitivity (formerly termed *testicular feminization syndrome*).[10] These mutations, which are among the most frequent forms of 46,XY differences of sex development, occur in approximately 1 in 20,000 male births.

Patients with the complete form of androgen insensitivity have normal female external genitalia. Unless suspicion is raised by prior knowledge of the infant's karyotype, the condition is rarely discovered before puberty unless the testes are palpated in the groin or labia on routine examination. Because the testes secrete antimüllerian hormone, müllerian structures are absent, including the uterus, fallopian tubes, and cervix. Thus the vagina is usually shallow and ends blindly. Wolffian structures are also absent. The testes may be located in the abdomen or in the labia majora and do not undergo spermatogenesis. Levels of antimüllerian hormone are elevated during the first year and (if the testes have not been removed) after puberty. Testosterone and LH levels in infancy and at puberty are elevated as a result of defective feedback regulation caused by androgen resistance at the level of the hypothalamus.

At puberty, pubic and axillary hair is scant or absent. Testosterone can be aromatized to estradiol by CYP19A1 in breast fat, and estrogen receptors are unaffected in this condition. Thus breast development is that of a normal female.

Partial androgen insensitivity (Reifenstein syndrome) is characterized by a variable degree of genital ambiguity, and both virilization and breast development occur at puberty. Mild androgen insensitivity also can occur with a male phenotype, with gynecomastia and infertility as the sole manifestations. Mutations in the androgen receptor are not detected in many mild cases, which may result from defects in other transcription factors affecting actions of the receptor.

LEYDIG CELL AGENESIS

Leydig cell agenesis or hypoplasia is a rare autosomal recessive syndrome caused by mutations in the *LHGCR* gene that encodes the LH receptor. Without stimulation by LH (or by HCG early in gestation), Leydig cells do not differentiate normally and do not secrete testosterone. Thus affected male infants are born with female-appearing or ambiguous external genitalia. Müllerian structures are absent because of unaffected secretion of antimüllerian hormone by Sertoli cells. LH levels are high in infancy and at puberty, and they respond normally to gonadotropin-releasing hormone, whereas testosterone levels are low and do not respond to stimulation by HCG. Affected females are phenotypically normal but may have oligomenorrhea resulting from primary ovarian dysfunction.

PERSISTENT MÜLLERIAN DUCT SYNDROME

Persistent müllerian duct syndrome (PMDS) is a rare autosomal recessive condition that results from mutations in the genes for either antimüllerian hormone (*AMH*, PMDS type I) or the antimüllerian hormone receptor (*AMHR2*, PMDS type II). The two are distinguished clinically by low or absent antimüllerian hormone levels in patients with antimüllerian hormone mutations and by antimüllerian hormone levels in the high-normal range in those with antimüllerian hormone receptor mutations.

Affected male patients have unimpaired testosterone secretion and thus have normal external genitalia and wolffian structures. However, the lack of antimüllerian hormone action prevents regression of müllerian structures, so these patients also retain a uterus and fallopian tubes. These structures are often closely approximated to the vas deferens. The müllerian structures are usually dragged into the inguinal canal by the descending testes. However, these structures typically prevent the testes from descending into the scrotum and thus cause bilateral inguinal hernias (with the uterus on one side) and bilateral or occasionally unilateral cryptorchidism. The condition is usually discovered only at surgery. Fertility in affected patients may be normal or impaired, with an increased risk for malignant disease in undescended testes left in the abdomen.

HYPOGONADOTROPIC HYPOGONADISM

Milder or later-appearing deficiencies of androgen biosynthesis (after 13 to 14 weeks) may allow complete fusion of the labioscrotal folds and normal positioning of the urethral meatus, but subsequent growth of the phallus is suboptimal. Such individuals have a micropenis. The most common cause is lack of gonadotropin (specifically, LH) secretion; even when LH is lacking, early male development is normal because testosterone secretion is controlled mostly by HCG during the first trimester.

Causes of hypogonadotropic hypogonadism are discussed in Chapter 216.

OTHER GENETIC CONDITIONS

ANEUPLOIDY OF SEX CHROMOSOMES

Turner Syndrome

Patients with Turner syndrome have normal female external genitalia and a normal uterus and fallopian tubes, but they have dysgenetic streak ovaries.[11] Most fetuses with Turner syndrome spontaneously abort, but the incidence in live births is approximately 1 in 2500. Classically, the karyotype is 45,X, but many patients retain an abnormal second X chromosome or even a fragment of a Y chromosome lacking *SRY*. Other patients are mosaic for 46,XX and 45,X cells and may have relatively mild phenotypes.

Untreated patients are short. Many have typical dysmorphic features, including lymphedema of the neck at birth, webbed neck, low posterior hairline, increased carrying angle of the arms, shield chest with widely spaced nipples, low-set ears, and micrognathia. Patients typically have primary amenorrhea and are infertile, but they occasionally have menarche followed by premature ovarian failure. Estrogen therapy can significantly improve bone density,[A1] but it is unclear whether it reduces fractures or improves long-term outcome.[12]

Klinefelter Syndrome

In this condition, male patients have normal development of the penis and scrotum, but the testes are small and firm. Patients tend to be tall. At adolescence, gynecomastia is frequent.[13] Signs of testosterone deficiency occur in most affected adults, and most have azoospermia. The usual karyotype is 47,XXY. Hormonal findings include elevated gonadotropin levels and a decreased serum testosterone concentration. Klinefelter syndrome is a common disorder that occurs in 1 in 500 to 1000 men.[14]

Mixed Gonadal Dysgenesis

Mixed gonadal dysgenesis, which is a frequent cause of sexual ambiguity, occurs in approximately 1 in 20,000 births. The karyotype is usually mosaic 45,X/46,XY. Gonadal pathologic features can vary from fibrous streaks indistinguishable from those in Turner syndrome to normally developed testes and a normal male phenotype. Typically, patients have a testis on one side and a fibrous streak on the other. Some patients may have a Turner-like phenotype. A fallopian tube is usually present on the side of the streak gonad. Leydig cell function, evaluated by testosterone response to HCG, and Sertoli cell function, evaluated by serum antimüllerian hormone levels, vary from poor to normal.

XX MALE SYNDROME

Males with a 46,XX karyotype have normal external and internal male genitalia, but they resemble patients with Klinefelter syndrome in that they have small testes, azoospermia, and infertility. Translocation of the *SRY* gene to the X chromosome is detected in 75 to 90% of sporadic cases. This translocation can occur because the gene is located very near the pseudoautosomal region, where the short arms of the X and Y chromosomes are homologous and meiotic recombination is possible. Duplication of the *SOX9* transcription factor gene may be responsible for some familial cases of XX sex reversal.

XY FEMALE SYNDROMES

Patients with pure XY gonadal dysgenesis (Swyer syndrome) have a normal female phenotype, including a uterus and fallopian tubes, but they have streak gonads. These patients are free of Turner-like malformations and attain normal height. Mutations of the *SRY* gene have been identified in 15% of cases. Unlike 45,X patients with Turner syndrome, these patients have an increased risk for gonadoblastoma.

Similar phenotypes result from duplication of the region of the X chromosome containing the *NR0B1* (*DAX1*) gene, from duplication of the *WNT4* gene, or from haploinsufficiency of the *NR5A1* (SF1) transcription factor.[15] XY sex reversal also can result from mutations in the *SOX9* transcription factor gene associated with campomelic dysplasia, which is a form of dwarfism. Mutations of *DHH* cause XY gonadal dysgenesis associated with peripheral neuropathy.

Frasier and Denys-Drash syndromes are rare, phenotypically overlapping diseases caused by inherited or de novo mutations in *WT1*. They are both characterized by XY gonadal dysgenesis and an increased risk for gonadal tumors. Progressive glomerulopathy developing in early childhood is associated with both syndromes, but Denys-Drash patients demonstrate diffuse mesangial sclerosis, whereas Frasier patients develop focal and segmental glomerulosclerosis (FSGS).[16]

Some 46,XY patients with absent gonads have various degrees of sexual ambiguity and no müllerian derivatives. The implication that some testicular tissue was functional at least up to 10 weeks' gestation and subsequently regressed led to the name *fetal testicular regression syndrome*.[17] Testicular regression may occur in late pregnancy or even postnatally. These fully virilized male patients have isolated anorchia.

VAGINAL ATRESIA

Mayer-Rokitansky-Küster-Hauser (MRKH) syndrome, which refers to aplasia of the uterus and upper vagina, occurs in approximately 1 in 5000 women.[18] In approximately one third of cases, it occurs along with other abnormalities, including unilateral renal aplasia and cervicothoracic somite dysplasia (type II MRKH; MURCS association). The genetic basis is unknown in most cases. Rare affected individuals have heterozygous mutations of *WNT4;* such patients usually have clinical and biochemical signs of androgen excess.

OVOTESTICULAR DISORDER OF SEXUAL DEVELOPMENT (TRUE HERMAPHRODITISM)

Ovotesticular disorder of sexual development (true hermaphroditism), which is a rare and usually sporadic disorder, is defined as the coexistence of seminiferous tubules and ovarian follicles. Most patients have an ovotestis with either an ovary or a testis on the opposite side; a gonad in the scrotum is usually a testis but may be an ovotestis.

The genitalia are usually ambiguous, but they may appear completely masculine or feminine. The anatomy of the internal reproductive tract depends on the nature of the gonads, particularly whether they secrete antimüllerian hormone. A uterus or uterine horn is present in 90% of cases. Testosterone response to HCG is variable, and antimüllerian hormone levels are usually low. Most patients experience breast development, ovulation, and even menstruation at puberty; pregnancy and successful childbirth are possible if selective removal of testicular tissue is feasible. Unless sex of rearing has already been chosen, male gender assignment should be restricted to patients with no uterus and descended testicular tissue because the latter is usually dysgenetic and prone to malignant degeneration. Most patients with ovotesticular disorder of sexual development have a 46,XX karyotype. Despite the presence of testicular tissue, they usually lack *SRY*. Some patients in different ethnic groups and locales carry a specific mutation in *NR5A1*, Arg92Trp.

MANAGEMENT OF INDIVIDUALS WITH DIFFERENCES OF SEXUAL DEVELOPMENT: GENDER ROLE AND IDENTITY

The influence of prenatal sex steroid exposure on personality is controversial.[19] In considering this question, it is important to distinguish among gender role, sexual orientation, and gender identity.

GENDER ROLE

Gender role refers to gender-stereotyped behaviors, such as the choice of toys by young children. For example, parents of young girls with congenital adrenal hyperplasia often report that their daughters prefer to play with trucks rather than dolls and tend to be tomboyish later in childhood. Decreased interest in maternal behavior, beginning with infrequent doll play in early childhood and extending to lack of interest in child rearing in older girls and women, occurs frequently.

SEXUAL ORIENTATION

Sexual orientation refers to homosexual versus heterosexual preferences. In many studies, a significant minority of women with congenital adrenal hyperplasia have been actively homosexual or bisexual or have had an increased tendency toward homoerotic fantasies. These characteristics occur more frequently in women with the salt-wasting form of 21-hydroxylase deficiency, thereby suggesting that they are a consequence of prenatal exposure of the brain to androgens. However, the vast majority of both male and female homosexuals have no identifiable endocrinologic abnormality.

GENDER IDENTITY

Gender identity refers to self-identification as male or female. Gender self-reassignment back to male has been reported in cases of male patients with penile trauma or exstrophy of the bladder who were raised as girls.

Gender self-reassignment also occurs in some 46,XY patients who have differences of sexual development and who were raised as girls, especially in cases of 5α-reductase or 17-ketosteroid reductase deficiencies, in which the fetal brain may be exposed to high circulating levels of androgens. The rate of gender change from female to male in persons with 5α-reductase deficiency ranges from about 15 to 70% in different countries, and the rate of gender changes in persons with 17-ketosteroid reductase deficiency is about 50%.

Self-reassignment to the male gender is unusual in women with congenital adrenal hyperplasia, with 4% reporting gender dysphoria, usually related to delays in gender assignment or genital surgery or to inadequate suppression of adrenal androgens with glucocorticoid therapy. Conversely, a significantly higher proportion (15%) of female patients who have congenital adrenal hyperplasia and who are raised as males experience gender dysphoria. The prevalence of gender identity disorder in patients with complete androgen insensitivity raised as females is extremely low (less than 2%), but it is much higher (12 to 25%) in patients with partial androgen insensitivity, whether they are raised as males or females.[20]

Transgender individuals (see Chapter 215) rarely have identifiable hormonal abnormalities, and the nonhormonal mechanisms governing gender identity are poorly understood. Gender identity disorders are much more likely to occur in both identical twins than in fraternal twins, thereby suggesting a high degree of heritability. Neuroanatomic studies suggest that the bed nucleus of the stria terminalis is larger in males and trans males (female-to-male transsexuals) and smaller in females and trans females (male-to-female transsexuals). Similar findings involving other sexually dimorphic brain regions have been identified by magnetic resonance imaging.[21] Thus gender identity disorder may be considered a brain-limited difference of sexual development.

DIAGNOSIS

Management of a child born with ambiguous genitalia presents a difficult challenge to medical personnel. It is important to refrain from assigning sex until diagnostic information can be gathered. Usually, test results can be obtained within 24 to 48 hours, and parents can be advised about the child's chromosomal and gonadal sex and the anatomy of internal sexual structures.

In addition, the physician must keep in mind that differences of sexual development may be associated with life-threatening biochemical or anatomic abnormalities. In particular, the most common cause of severely masculinized external genitalia in females, the salt-wasting form of congenital adrenal hyperplasia resulting from steroid 21-hydroxylase deficiency, may cause hyponatremia, hyperkalemia, hypovolemia, and shock. In contrast, male patients with ambiguous genitalia may have lipoid adrenal hyperplasia or a salt-wasting form of 3β-hydroxysteroid dehydrogenase (HSD3B2) deficiency. Males with micropenis may have panhypopituitarism; in this case they are at risk for significant hypoglycemia and hyponatremia resulting from low cortisol (because of low ACTH) and low growth hormone levels, or they may have adrenal hypoplasia congenita, in which case they could have adrenal insufficiency. Finally, patients with ambiguous genitalia are at increased risk for renal anomalies, or they may have chromosomal syndromes with other associated anomalies.

History

The gestational history should concentrate on potential exposure to agents that could interfere with normal sexual differentiation (e.g., exposure of a female infant with virilized genitalia to progestational agents or the mother of a male with incompletely masculinized genitalia to 5α-reductase inhibitors). A family history should elicit similar cases of genital ambiguity or cases of sudden infant death, which could raise suspicion of undiagnosed salt-wasting congenital adrenal hyperplasia or adrenal hypoplasia congenita.

Physical Examination

The physical examination should document the size of the phallus (clitoris or penis), the degree of chordee (ventral bowing of the phallus), and the extent of fusion of the labioscrotal folds. The urethral meatus should be identified, and careful palpation should search for gonads in the inguinal canals, labia, or scrotum. Bilateral cryptorchidism, even if an isolated finding in a phenotypic male patient, should always lead to evaluation for a possible difference of sex development.

Biochemical Evaluation of the Virilized Female

The minimal diagnostic tests should include measurement of basal serum levels of 17-hydroxyprogesterone, androstenedione, and testosterone. Preferably, a complete profile of adrenocortical hormones is obtained before and 1 hour after stimulation of the adrenal cortex with 125 to 250 μg of cosyntropin ($ACTH_{1-24}$). These assays, which should be deferred until after the first 24 hours of life, will identify potential defects in adrenal steroidogenesis (i.e., congenital adrenal hyperplasia): 21-hydroxylase deficiency is identified by elevations in 17-hydroxyprogesterone, whereas 11-deoxycortisol and 11-deoxycorticosterone are high in 11β-hydroxylase deficiency.

Biochemical Evaluation of the Undervirilized Male

In 46,XY patients with differences of sexual development, adrenal and gonadal function, as well as extragonadal androgen metabolism, must be tested. With regard to adrenal defects, 11-deoxycorticosterone and the ratio of pregnenolone to 17-hydroxypregnenolone are high in 17α-hydroxylase deficiency, 17-hydroxypregnenolone and DHEA are high in HSD3B2 deficiency, and all steroids are low in lipoid hyperplasia.

Defects in gonadal steroidogenesis are best evaluated after stimulation with HCG (1500 IU intramuscularly on days 1, 3, and 5, with blood drawn on day 6). However, 17-hydroxylase and HSD3B2 deficiencies affect both the gonads and the adrenal cortex and thus are often diagnosed by cosyntropin stimulation testing. Low levels of all androgen precursors suggest lipoid hyperplasia, 17α-hydroxylase/17,20-lyase deficiency, or a generalized defect in testicular function, such as the vanishing testes syndrome (testicular regression syndrome) or gonadotropin insensitivity. A high ratio of androstenedione to testosterone is indicative of 17-ketosteroid reductase (HSD17B3) deficiency, and a high ratio of testosterone to dihydrotestosterone is diagnostic of 5α-reductase deficiency. The diagnosis of androgen insensitivity syndrome is suspected when a 46,XY patient has ambiguous or female-appearing external genitalia despite normal or high circulating levels of testosterone and dihydrotestosterone.

Genetic Evaluation

Genetic evaluation of a patient with a possible difference of sex development almost always begins with a karyotype to count sex chromosomes, assess the degree of mosaicism, and determine chromosomal abnormalities such as translocations. If time is pressing, fluorescent in situ hybridization on metaphase nuclei may provide a count of sex chromosomes within less than a day. Next-generation sequencing may be useful in patients in whom the etiology is uncertain.

Gonadal Biopsies

Patients with mixed gonadal dysgenesis, ovotesticular disorders of sexual development, or unclear diagnoses should undergo bilateral gonadal biopsies (histology of the two gonads is often not identical). Dysgenetic gonads have a high potential for malignant transformation and usually need to be removed in childhood.

TREATMENT

Initial Medical Management

Patients with congenital adrenal hyperplasia resulting from 21-hydroxylase or HSD3B2 deficiencies and patients with lipoid hyperplasia or adrenal hypoplasia congenita require replacement of both glucocorticoids and mineralocorticoids, usually with hydrocortisone (10 to 15 mg/m^2/day in divided doses) and fludrocortisone (usually 0.1 mg/day, but as much as 0.4 mg/day in neonates with salt-wasting crises). Neonates with severe salt losses may require sodium chloride supplementation (≤8 mEq/kg/day). Patients with 11β-hydroxylase or 17α-hydroxylase deficiencies have normal aldosterone biosynthesis and usually require only glucocorticoids. Patients with panhypopituitarism usually require treatment with hydrocortisone, thyroxine, and growth hormone.

All male infants with ambiguous genitalia or micropenis in whom rearing as a boy is contemplated should have a 3- or 4-month therapeutic trial of monthly depot testosterone injections (25 mg) to attempt to increase the size of the phallus during infancy. This treatment may improve social acceptability of the genitalia later in childhood and adolescence and may make reconstructive surgery easier. In cases of suspected partial androgen insensitivity, this treatment also documents the degree to which the patient is androgen responsive and thus may provide useful information about whether rearing as a boy is feasible. Higher doses of testosterone (75 mg every 4 weeks) may be used under these circumstances.

Considerations Related to Sex Assignment

In large medical centers, a multidisciplinary team consisting of a neonatologist, a pediatric endocrinologist, a urologist, and preferably an experienced social worker and/or child psychiatrist or psychologist should promptly review the early diagnostic data and make a recommendation to the family as to the sex of rearing and any medical or surgical treatments. These recommendations should be based on both current knowledge of psychosexual development in individuals with differences of sex development and the feasibility of surgical treatment (see later).

In general, the recommended sex assignment should be that of the genetic/gonadal sex, if for no other reason than to retain the possibility of reproductive function. This approach is especially recommended for female infants with congenital adrenal hyperplasia who have normal internal genital structures and the potential for childbearing. An exception may be considered in a genetically female infant with completely male-appearing genitalia, especially if the child has been raised as a boy for more than a few months. Such children need to be castrated at puberty to avoid feminization.

Conversely, genetic male infants with completely female-appearing external genitalia (usually resulting from complete androgen insensitivity syndrome, but also seen with severe testosterone biosynthetic defects) should be raised as female because the potential for reconstruction of male genitalia is poor. However, male infants with 17-ketosteroid reductase or 5α-reductase deficiency should usually be reared as boys because they have normal levels of androstenedione or testosterone, respectively, and they often virilize significantly at puberty. Indeed, as noted previously, many of these patients reassign themselves to the male gender when they are made aware of the diagnosis. The same considerations pertain to male patients who have normal testosterone biosynthesis but who have penile trauma or anatomic abnormalities such as bladder exstrophy.

Surgical Management

Surgery for Ambiguous Genitalia

Whether, how, and when to intervene surgically in the treatment of genital anomalies are the subject of continuing debate.[22] Some adult patients with differences of sexual development are unhappy with their gender assignments or surgical outcomes. Some physicians advocate postponing cosmetic genital surgery until the affected individual is able to provide informed consent, thereby keeping all the options open if the adult patient wishes to function sexually with abnormal genitalia that nevertheless have sensation undiminished by surgery or if the patient chooses to reassign their gender. The option of deferring surgery should always be presented as part of the informed consent process.

The greatest change in practice over the past few decades probably pertains to male infants with ambiguous (but not completely female) external genitalia. Physicians are far less likely to recommend that such patients be reared as female because it is now recognized that many of these patients reassign themselves as male at puberty. Thus the ambiguous genitalia in such patients should rarely be "corrected" to female. On the contrary, surgical techniques to repair hypospadias have advanced significantly, and reconstruction of male genitalia is attempted more often, particularly if the infant responds to a course of testosterone with significant phallic growth.

Surgery for female infants with ambiguous genitalia may need to address an enlarged clitoris, the lack of a vaginal introitus, and the presence of a urogenital sinus. The clitoris is normally prominent in many infant girls. Even when enlarged in a girl with virilizing congenital adrenal hyperplasia, the clitoris can be prevented from growing larger with adequate suppression of adrenal androgens by glucocorticoids, and it will become less prominent as the patient grows. Thus mild-to-moderate clitorimegaly is often best managed without surgery. When clitoroplasty is attempted, one must keep in mind the important role of clitoral sensation in the female sexual response. Such surgery must be performed only by experienced operators with scrupulous attention to the preservation of clitoral innervation.

Consensus is lacking regarding the best age for vaginoplasty.[23] Although many surgeons advocate a first procedure in infancy, it is difficult to maintain a functionally adequate introitus in the absence of estrogen exposure and mechanical dilation (with dilators or through sexual intercourse), and many patients require reoperation as young adults. Conversely, many women with atresia of the upper vagina (owing to complete androgen insensitivity or the Mayer-Rokitansky-Küster-Hauser syndrome) can use dilators to lengthen the vagina without the need for surgery.[24] According to self-assessment surveys among sexually active women with congenital adrenal hyperplasia who have had genital surgery, most are able to have satisfactory sexual intercourse. As surgical and medical treatment regimens have improved in recent years, more women with congenital adrenal hyperplasia have successfully conceived spontaneously, completed pregnancies, and given birth.

Repair of hypospadias is usually begun in the first year of life, after testosterone treatment (if necessary to increase phallic size). Depending on the degree of hypospadias, more than one surgical procedure may be required.

Removal of Intra-abdominal Testes in 46,XY Patients with Differences of Sexual Development

Intra-abdominal testes are at increasing risk for malignant transformation over time. In a boy who has cryptorchidism and who is being reared as male, orchiopexy should be performed as quickly as possible to maximize the possibility of fertility if the underlying condition does not preclude it. Dysgenetic gonads that cannot be brought into the scrotum should be removed soon after diagnosis because the risk for malignant transformation in childhood is relatively high.

There is a lack of consensus regarding nondysgenetic testes in severely undervirilized genetic male infants in whom rearing as female is planned. In patients with complete androgen insensitivity or complete defects in testosterone biosynthesis, no possibility of fertility exists, and so there seems to be no reason to retain the testes. Conversely, the risk for malignant transformation in such gonads is low before puberty, and patients with complete androgen insensitivity can undergo spontaneous breast development at puberty. At that time, patients themselves can assent or consent to gonadectomy, which can usually be accomplished laparoscopically. This approach is of particular importance in genetic male patients with partial androgen insensitivity or incomplete defects of testosterone biosynthesis, because such patients may eventually desire a male gender role.

Patients with persistent müllerian duct syndrome have a reduced but still appreciable potential for fertility, and virilization is unaffected. Thus the testes should be removed only if they cannot be brought into the scrotum. Because the müllerian and wolffian structures are closely approximated in these patients, surgical excision of the uterus and fallopian tubes may result in ischemic and/or traumatic damage to the vas deferens and testes; thus salpingectomy and hysterectomy are indicated only in patients whose müllerian structures limit intrascrotal placement of the testes.

Treatment of vaginal agenesis in adolescent or adult women with the Mayer-Rokitansky-Küster-Hauser syndrome may include noninvasive vaginal dilations as first-line therapy or surgery. Until recently, the only option for the patients to achieve biological motherhood was through gestational surrogacy, but successful uterine transplantation has been reported.

Management of transgender adults is discussed in Chapter 215.

Psychosocial Support

Families of patients with differences of sex development should be assessed for emotional health, initially by the pediatrician and/or pediatric endocrinologist. Parents should be offered psychological counseling soon after the diagnosis is made. Intermittent assessment of family functioning may be a useful tool in predicting future problems. As children mature, they should repeatedly be informed about their condition by parents and physicians in a sensitive and age-appropriate manner. When psychotherapy is undertaken, medical and psychiatric caregivers should communicate with each other and with experts in sexual development so all are working together.

Although the psychosexual development of individuals with differences of sex development cannot be predicted with confidence, patients' families should receive anticipatory counseling. For example, counseling of parents of girls affected with congenital adrenal hyperplasia should address the high likelihood that such girls will exhibit tomboyish behavior and masculine play preferences. The endocrinologist and/or mental health professional (depending on inclination and experience) caring for adolescents with differences of sexual development should address sexual orientation, both fantasized and actual. For example, some women with congenital adrenal hyperplasia are homosexuals; such individuals should receive appropriate psychosocial support. Adult patients also should be made aware of relevant patient advocacy groups.

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215 TRANSGENDER MEDICINE

JOSHUA D. SAFER

DEFINITION AND EPIDEMIOLOGY

Gender identity is the internal sense of one's own sex, whether male, female, neither, both, or something else. Transgender is a broad term to reference individuals with gender identity that differs from sex recorded at birth, typically based on external genitalia (Table 215-1). In the United States, an estimated 0.6% of adults, or approximately 1.4 million individuals, are transgender.[1] Cisgender describes individuals with gender identity that aligns with recorded sex at birth. Other terms with similar meaning to transgender include trans, gender incongruent, gender nonbinary, gender diverse, and genderqueer—all terms being adjectives for people with gender identity that is not aligned with visible anatomy at birth. The latter three terms reference people who are less binary in their sense of their sex identity. The term transsexual is an older word that previously referenced transgender individuals who had "completed" planned treatment to change their bodies to better align with their gender identities.[2]

PATHOBIOLOGY

Historically, being transgender was considered a mental health problem with a mental health solution. Indeed, the term gender dysphoria has been used for a transgender person whose gender identity is associated with clinically significant distress or impairment in social, occupational, or other important areas of functioning.[3] However, not every transgender or gender-diverse individual experiences dysphoria, including transgender people seeking medical treatment. Further, some transgender people will suffer clinical dysphoria independent of their being transgender. In the former case, a transgender person might be treated with gender-affirming hormones or surgeries. In the latter case, a person may need mental health approaches to the clinical dysphoria independent of any need for gender-affirming medical intervention. Thus, the *International Classification of Diseases*, 11th edition removes the term *gender dysphoria* entirely and adds the term *gender incongruence* to a new sexual health section.[4]

The current model is that gender identity is a biologic phenomenon that cannot be influenced externally. Data for the biologic underpinnings to gender identity include evidence from studies of people who are intersex or have differences of sexual differentiation, evidence from twin studies, evidence from studies of the impact of prenatal androgen exposure, and evidence from studies of certain neurologic structures. For example, among XY children with cloacal exstrophy (Chapter 214), with or without penile agenesis and penile ablation, who are assigned female at birth, a substantial proportion are not comfortable with that designation.

When one identical twin is transgender, the other will also be transgender 40% of the time. By comparison the concordance rate among fraternal twins is zero or close to zero.

For XX chromosome individuals with virilizing congenital adrenal hyperplasia (Chapter 214), male gender identity may be present in 5%, nearly 10-fold the rate of male gender identity among XX chromosome people in general. Among XY individuals with complete androgen insensitivity syndrome, nearly all have female gender identity. The implication is that some androgen action on the brain may be necessary for male gender identity and that increased in utero androgen exposure may confer male gender identity in some individuals. Even if some minimal androgen action on the brain proves necessary for male gender identity, it is not sufficient. There is no evidence that most transgender people have either excess or deficient exposure to androgens.

Studies of the brains of transgender individuals suggest a physical manifestation associated with gender identity. A postmortem study of six transgender women (male-to-female) found that the size of the bed nucleus of the stria terminalis in the hypothalamus was within the female range independent of historical hormone treatment. Brain imaging studies suggest that hormonally untreated transgender men exhibit white matter microstructure more typically male than female and that untreated transgender women exhibit white matter microstructure intermediate between cisgender male and cisgender female individuals.

TABLE 215-1 DEFINITION OF GENDER TERMS

Sex/Gender: Umbrella terms to reference biologic characteristics, identification, and stereotypical behaviors that are considered male, female, or some variation. The word gender is sometimes used as a synonym for the word sex in colloquial use and is also sometimes used as shorthand for either gender identity or gender expression.
Gender Identity: Internal sense of one's own sex as male, female, both, or neither.
Gender Expression: How an individual communicates gender identity to themselves and others.
Transgender, Transsexual, Trans, Gender Diverse, Gender Nonbinary, Gender Incongruent,* Genderqueer: Adjectives for individuals with a gender identity that is not aligned with sex recorded at birth.
Cisgender, Nontransgender: Adjectives for individuals with a gender identity that is aligned with sex recorded at birth.
Gender-Affirming/Gender-Confirming Hormone Treatment and Surgeries: Medical interventions for transgender and gender-diverse individuals to align gender identity better with other physical characteristics.
Intersex: A term for people with sexual and/or reproductive anatomy that is not typical (may also be labeled people with differences of sexual differentiation).

*This term is replacing the term gender dysphoria to label the lack of alignment for some individuals between their gender identity and their sex as recorded at birth.

Adapted from Safer JD, Tangpricha V. Care of transgender persons. *N Engl J Med.* 2019;381:2451-2460.

CLINICAL MANIFESTATIONS AND DIAGNOSIS

Children may articulate gender identity as early as age 2 years and proceed to demonstrate facility with gender labeling, including their use of pronouns, by school age. About 0.6% to 2.7% of children may report some degree of gender diversity.[5] By adolescence, many children clearly articulate gender identity, such that adolescents who present as transgender people seeking gender-affirming treatment are overwhelmingly stable in their reported gender identity into adulthood. Puberty can be distressing for transgender children, with the "wrong puberty" serving as the trigger for some adolescents to report their gender identity to their parents and health care providers.

Most transgender persons present for gender-affirming medical intervention as older adolescents or adults, perhaps because of factors such as late recognition of gender identity, failure to articulate gender identity, or outside pressure to conform. Despite the older presentation, most transgender people report that, in retrospect, they were aware of their gender incongruence before puberty.

Transgender people present in heterogenous fashion.[6] Some transgender people are confident in their sense of their gender identity and their treatment goals. Others may benefit from greater support from mental health providers, either to help articulate gender identity or to help with goals.

Clinically, being transgender is ascertained on the basis of history alone. The patient should have both persistent gender incongruence and the capacity to make treatment decisions. The requirement for persistence does not have a specific time frame, but typical presentations include clarity regarding gender identity that extend back years—indeed commonly as far back as childhood. Reports of recognition of gender incongruence over shorter periods should prompt further exploration of underlying factors and goals.

Transgender persons also have higher rates of mental health morbidity, including anxiety, depression, and suicidality, often as a result of social stigma rather than gender incongruence per se. Patients should be screened for both confounding mental health issues and the ability to engage safely in treatment. Some mental health conditions may interfere with the ability to provide a reliable history. For example, patients who present as transgender might instead have an obsessive compulsive disorder or well-masked psychosis rather than true gender incongruence. Since transgender persons also can experience mental health morbidity, including obsessive-compulsive disorder and psychoses, a multidisciplinary assessment must include a careful evaluation of mental health.

Any sufficiently knowledgeable clinician should be able to ascertain that an adult is transgender. The criteria for determining whether someone is transgender are the same for children and adolescents as for adults. However, due to challenges in how children articulate gender identity, guidelines recommend including mental health professionals for assessment of minors. Clinicians also should be able to identify mental health conditions that might confound the assessment or that should include input from mental health providers who can.

ABSTRACT

Gender identity is the internal sense of one's own sex, whether male, female, neither, both, or something else. Transgender is a broad term to reference individuals with a gender identity that differs from sex recorded at birth, the latter typically based on external genitalia. Gender identity is a biologic phenomenon that cannot be influenced externally. For transgender people seeking medical intervention, treatment focuses on aligning the body with the gender identity by using hormones, surgeries, or both. Strategies for gender-affirming hormone therapy for adult transgender patients primarily involve moving circulating testosterone levels up for masculinizing therapy and down for feminizing therapy. Transgender people may consider a number of gender-affirming surgical interventions. Not all transgender people seek gender-affirming hormone therapy, and not all seek gender-affirming surgery either.

KEYWORDS

transgender
gender diverse
gender-affirming hormone therapy
testosterone
estrogens

TREATMENT

Not all transgender persons seek medical treatment. Even among those who desire intervention, treatment may be deferred due to barriers that include family circumstance, work environment, or insurance coverage.

Persons who seek medical treatment for gender incongruence benefit from providers who can help set expectations about medical interventions. Primary care clinicians can initiate and manage transgender medical interventions, including both hormone therapy and other agents that affect hormone levels, with support from endocrinologists, if needed.[7]

No convincing literature indicates any success or benefit from attempts to change a person's gender identity. In fact, such effects to conform to sex norms result in demonstrably poorer psychosocial outcomes.

Mental health support is a key element of gender-affirming care. Clinicians must address mental health conditions that may confound assessment of gender identity and treatment goals.

The current strategies for gender-affirming hormone therapy for adult transgender patients primarily involve moving circulating testosterone levels up for masculinizing therapy and down for feminizing therapy.[8] Typical agents are androgens to virilize transgender men and estrogens, in addition to other antiandrogens given as adjuncts, to reduce testosterone levels to the conventional female range for transgender women while maintaining estradiol levels in what is considered the typical female physiologic range.

Prior to beginning gender-affirming hormone therapy, clinicians should review the patient's gender identity, treatment goals, and timing for therapy, with discussion of both social and health issues. Typical informed consent for shared medical decision making includes the potential risks and benefits of hormone therapy along with the time frame for expected changes. Clinicians should be knowledgeable about routine monitoring of hormone levels, monitoring of other relevant laboratory testing (e.g., serum potassium measurement for spironolactone treatment or hematocrit for testosterone treatment), and potential adverse outcomes. In the absence of specific data for transgender people, cancer screening is typically done on the basis of the tissues and organs present and informed by guidelines for the general population.

Hormone Therapy for Transgender Men (Female to Male)

Gender-affirming hormone treatment for transgender men (female to male) is very similar to hormone replacement therapy for hypogonadal cisgender men (Chapter 216), with testosterone, usually starting at a dose that is about half the dose used for a hypogonadotropic cisgender man (see Table 216-6) and aiming for a goal testosterone level in the typical physiologic cisgender male range (300 to 1000 ng/dL).[9] Testosterone can be administered orally, transdermally, or parenterally (Table 215-2). The most popular products are testosterone enanthate or cypionate 50 to 200 mg weekly administered intramuscularly or subcutaneously. Higher doses (100 to 200 mg) can be administered every 2 weeks, but patients may not prefer the resulting greater periodicity in testosterone levels. Transdermal preparations such as testosterone gel (2.5 to 10 g/day) or a testosterone patch (2.5 to 7.5 mg/day) will achieve the same virilizing effects as intramuscular testosterone, but poor absorption may prove frustrating when trying to achieve goal testosterone levels. Also, testosterone patches may cause skin irritation. Although not widely used, oral testosterone undecanoate (160 to 240 mg/day) is also available.[10] There is no indication for antiestrogens. Some patients, including some who identify as nonbinary, may ask to be treated with smaller doses of testosterone.

Although the exact effects and time course of testosterone will vary from patient to patient, responses to treatment include increased facial/body hair, male-pattern balding, increased acne, increased libido, increased muscle mass, clitoromegaly, deepening of the voice, and redistribution of fat within the first 3 to 12 months of testosterone therapy. Menses cease in the majority of individuals within 6 months of initiating treatment.[11] Although circulating sex hormone is needed for optimal bone health, there is no known health reason to prefer a typically male hormone profile versus a typically female hormone profile, or something in between. Even low-dose hormone treatment can have dramatic physical consequences for some people. Patients should be counseled and asked to state their desired outcome before beginning treatment.

Monitoring of Masculinizing Gender-Affirming Hormone Therapy

Patients taking testosterone are typically monitored both by laboratory testing and by clinical evaluation for virilizing and adverse effects approximately every 3 months for the first year, which corresponds to the recommended interval for dose titration, and then every 6 to 12 months once stability is achieved within the intended laboratory range. Patients taking testosterone enanthate or cypionate intramuscularly or subcutaneously can have testosterone peak levels measured 24 to 48 hours after injections and occasional trough levels measured immediately prior to injections. Alternatively, levels can be checked at the midpoint between doses. Patients taking transdermal testosterone can have levels sampled any time after 1 week of treatment.

Because androgens are known to stimulate erythropoiesis, the hematocrit (or hemoglobin) level should be monitored with dose titration and on occasion afterward. Dose adjustment and/or other intervention (e.g., phlebotomy) may be required if erythrocytosis is unmasked and a reversible explanation is not identified.

Because adequate levels of sex hormones are required to maintain bone density, patients should avoid hypogonadism.[12] Bone mineral density screening can be initiated at age 60 years or if testosterone levels are consistently low.

Contraindications to initiating testosterone therapy include pregnancy, unstable coronary artery disease, and untreated polycythemia (hematocrit ≥55%). Testosterone therapy may unmask polycythemia (Chapter 152) and hyperlipidemia (Chapter 190),[13,14] but both can then be treated appropriately.

Transgender men with cervixes or breast tissue should undergo age-appropriate cancer screening. Whether testosterone therapy puts transgender men at an increased risk for uterine or ovarian cancer is unknown. However, evidence is insufficient to recommend routine hysterectomy or oophorectomy in transgender men for the purpose of preventing malignancy.

Hormone Therapy for Transgender Women (Male to Female)

The goal in hormone therapy for transgender women is to decrease circulating total testosterone levels to the typical female range (<50 ng/dL)

TABLE 215-2 TESTOSTERONE THERAPY FOR TRANSGENDER MEN (FEMALE TO MALE)

MEDICATION	DOSE	CONCERNS	COMMENTS
TESTOSTERONE		Erythrocytosis, which may unmask polycythemia that may require further evaluation	Screen for tobacco use, sleep apnea
		Acne can develop and/or be exacerbated	Acne, typically transient
Parenteral			
Testosterone enanthate or cypionate	Start at 25 to 50 mg IM/SQ weekly or 50 to 100 every 2 weeks and titrate up to 50 to 100 mg IM/SQ weekly or 100 to 200 mg IM/SQ every 2 weeks		SQ or IM injections have been demonstrated to be equally effective Target levels are more easily achieved than with transdermal products Weekly administration diminishes periodicity Monitor levels either with peaks (at 24-48 hours) and troughs (immediately prior to next dose) or with mid-dose measurement
Testosterone undecanoate	1000 mg IM every 12 weeks	Oil embolism is a rare adverse event	
Transdermal or Transbuccal			
Testosterone gel	Start at 25 mg/day and titrate up to 50 to 100 mg/day	Risk of transfer to others	Uniform levels Target levels may be harder to achieve than with parenteral products
Testosterone patch	Start at 2 mg/day and titrate up to 8 mg/day	Skin reactions are common	Uniform levels Target levels may be harder to achieve than with parenteral products
Testosterone buccal patch	30 mg to gums every 12 hours		Inconvenience of preparation may limit use

IM = intramuscular; SQ = subcutaneous.

Adapted from Safer JD, Tangpricha V. Care of transgender persons. *N Engl J Med*. 2019;381:2451-2460.

while maintaining typically physiologic female levels of circulating estradiol. Exogenous estradiol can potently suppress testosterone levels via central feedback, but incorporating an adjunctive antiandrogen allows for lower doses of estrogen,[15] thereby limiting the dose-related risk of venous thromboembolism. Standard goals are typically achieved with a treatment that includes estrogen in combination with an adjunctive antiandrogen (Table 215-3).

Estrogen Therapy

Estrogens can be administered orally, transdermally, or parenterally. Oral conjugated estrogens (2.5 to 7.5 mg) and oral 17-beta estradiol (2 to 10 mg) daily are popular because they are easy to use and readily available, but estradiol is more commonly prescribed. Data suggest fewer thrombotic events in patients using transdermal patches.[16] Estradiol also can be administered parenterally as estradiol valerate or cypionate 5 to 20 mg intramuscularly every 2 weeks or 2 to 10 mg intramuscularly every week, but levels are more difficult to monitor. Each formulation may result in metabolites that can confound the measurement of hormone levels. Ethinyl estradiol should be avoided because of its increased risk of venous thromboembolism.

Patients should be counseled to expect decreased facial/body hair, decreased libido, decreased spontaneous erections, decreased skin oiliness, decreased muscle mass, redistribution of fat, and breast development within the first 3 to 12 months. Breast growth peaks after about 2 years of hormone therapy.[17]

As for transgender men, some patients, including some who identify as nonbinary, may choose to be treated with lower doses of medication. Some circulating sex steroid is needed for bone health, but there are no other known health reasons to prefer a typically male hormone profile versus a typically female hormone profile or something in between. Even low-dose hormone regimens can have dramatic physical consequences for some people, and patients should be counseled appropriately before embarking on treatment.

Adjunctive Antiandrogen Therapy

Spironolactone, which is the most commonly prescribed adjunctive antiandrogen agent because it is the least costly, is an aldosterone receptor antagonist that also inhibits the secretion of testosterone in some people. Spironolactone is most commonly administered in doses of 100 to 200 mg daily. Doses are not typically divided because the weak diuretic properties of spironolactone may cause nocturia.

Gonadotropin-releasing hormone (GnRH) agonists, such as leuprolide (3.75 mg subcutaneously monthly), inhibit the production of luteinizing hormone and follicle-stimulating hormone and therefore testosterone. GnRH agonists are the preferred adjunct to estrogens in the United Kingdom, but they are more expensive than spironolactone and must be given by injection.

Cyproterone acetate, which is a progestin, is the most popular adjunct gender-affirming hormone treatment in Continental Europe. However, among transgender women, cyproterone acetate has been associated with elevated prolactin levels, worsening lipid profiles, and rare meningiomas.[18]

Monitoring of Feminizing Gender-Affirming Hormone Therapy

Transgender women on hormone therapy can be monitored about every 3 months for the first year, corresponding to the interval for dose titration, and then every 6 to 12 months. Hormone therapy should be titrated to goal hormone levels in the typical physiologic female range (testosterone <50 ng/dL; estradiol <200 pg/mL) rather than a physical end point or subjective sense of feminization.

Because spironolactone is a potassium-sparing diuretic and can cause hyperkalemia in rare individuals, the serum potassium level should be checked when initiating spironolactone therapy and with changes in dose. Although guidelines often suggest monitoring serum prolactin levels, elevated prolactin levels have been noted only in patients using adjunct cyproterone acetate, not in patients using other adjunct treatments or patients using estrogens alone.[19]

Clinicians should be aware of the small but apparently slightly elevated potential for venous thromboembolism (Chapter 68) with exogenous estrogens.[20] In transgender women who have a history of venous thromboembolism, the preferred approach is to maintain the hormone treatment regimen and to follow prophylaxis protocols (Chapter 68).

Bone mineral density screening should be initiated by age 60 years but earlier if sex hormone levels are consistently low. Absent specific data for transgender individuals, transgender women should be screened for breast (Chapter 183) and prostate cancer (Chapter 186) according to current guidelines for cisgender individuals. Data suggest that the incidence of breast cancer is lower among transgender women than among cisgender women.[21] Prostate tissue remains even after vaginoplasty.[22]

Surgical Treatment for Transgender Individuals

As part of the approach to align bodies with gender identities, transgender people may consider a number of gender-affirming surgical interventions, which can help address the incongruence between sexual anatomy and gender identity.[23] Just as not all transgender people seek gender-affirming hormone therapy, not all seek gender-affirming surgery. Gender affirmation surgical options may be limited due to the small number of qualified medical facilities. Furthermore, patients may opt for one or more of the available surgical options in a customized fashion.

Surgeries for Transgender Men (Female to Male)

The most common surgery is chest reconstruction surgery to create a more masculine chest. The volume of parenchyma, position of the nipple-areola complex, and degree of skin elasticity all may influence the preferred surgical approach.[24]

Due to a high degree of morbidity along with a small pool of expert surgeons and resulting limited access, only a minority of transgender men will opt for genital reconstruction surgeries, which can combine removal of the vagina, uterus, and ovaries with either metoidioplasty or phalloplasty.[25] A metoidioplasty, which lengthens the hormonally hypertrophied clitoris, can be performed with or without lengthening the urethra. With urethral lengthening, the procedure may allow for voiding while standing. The ability to engage in penetrative intercourse following the procedure is limited.

A more complete genital reconstruction surgery is called phalloplasty. The typical approach uses a radial forearm free flap, thereby allowing for a

TABLE 215-3 HORMONE TREATMENT REGIMENS FOR TRANSGENDER WOMEN (MALE TO FEMALE)

MEDICATION	DOSE	CONCERNS	COMMENTS
ESTROGENS		Exogenous estrogens are associated with increased risk of thromboembolism	Ethinyl estradiol carries the greatest risk of venous thromboembolism (VTE) among estrogen products
Oral			
Estradiol (17β-estradiol)	Titrate to 2 to 10 mg/day		Most commonly used due to inexpensive cost and wide availability
Conjugated estrogens	Titrate to 2.5 to 10 mg/day		Levels of estrogen cannot be measured in blood by conventional assays
Transdermal			
Estradiol patch	Titrate to 0.1 mg/day to 0.2 mg/day		Associated with fewer VTE events than oral estrogens, but thrombosis data do not control for dose delivered
Parenteral			
Estradiol valerate	Titrate to 5 to 10 mg IM every week or 10 to 20 mg IM every 2 weeks		Can result in wide fluctuations in estradiol levels An alternative preparation is estradiol cypionate, which is less concentrated
ADJUNCTIVE ANDROGEN LOWERING OR INHIBITING AGENTS			
Spironolactone	Titrate to 100 to 300 mg/day orally	Hyperkalemia, dehydration	Potassium levels should be monitored when initiating therapy, when doses are changed, and annually thereafter
GnRH agonists (e.g., leuprolide)	3.75 to 7.5 mg IM or SQ monthly or 11.25 to 22.5 mg IM or SQ depot every 3 months		Use may be limited by cost and convenience
Cyproterone acetate	Titrate to 50 mg/day orally	May be associated with hyperprolactinemia and meningiomas	

IM = intramuscular; SQ = subcutaneous.

Adapted from Safer JD, Tangpricha V. Care of transgender persons. *N Engl J Med*. 2019;381:2451-2460.

single-stage construction of a phallus and neourethra should lengthening of the urethra be desired. In an alternative approach, an anterior wall vaginal flap is used during phalloplasty, either without a lengthened urethra or with a lengthened urethra deferred to a future surgery. Both metoidioplasty and phalloplasty procedures may involve a scrotoplasty with testicular implants.

Surgical complications for genital reconstruction procedures occur in 40% or more of cases, often related to urethral strictures or fistulas in people who have had a urethral lengthening. Many of these patients will require subsequent urethroplasties.

Surgeries for Transgender Women (Male to Female)

Breast augmentation surgical approaches, which are similar to breast augmentation in cisgender women, are typically performed following 12 to 24 months of estrogen-induced breast growth. Laryngeal surgery or vocal feminization surgery shortens the vocal cords and better aligns the voice with gender identity.[26] Reduction thyroid chondroplasty removes excess cartilage found in the "Adam's apple," thereby causing it to be less prominent. Facial feminization procedures that might be considered cosmetic for cisgender women can be medically necessary for transgender women as key to being recognized safely as female. The typical genital reconstruction surgery is vaginoplasty, which is construction of a vagina, clitoris, and labia.[27] Penile inversion is the gold-standard technique. Following surgery, transgender women are required to dilate the neovagina indefinitely to maintain vaginal length. Dilation requirements may be less rigorous if intestinal tissue is used for vaginoplasty; however, intestinal vaginoplasty is less preferred because of increased secretion from the tissue. Perioperative pelvic floor muscle physical therapy can be useful. Orchiectomy is available to remove the source of endogenous testosterone when less surgery is desired.

Perioperative Hormone Management

Gender-affirming hormone therapy should be maintained throughout the perioperative period for most people. Transgender women can discontinue adjunct antiandrogens following vaginoplasty and/or orchiectomy.

Other Risk Considerations Connected to Gender-Affirming Hormone Treatment

Insulin resistance and changes in body fat may occur in both transgender men and women after initiating gender-affirming hormone therapy. The fact that both transgender men and transgender women are reported to share the same risk despite opposite treatment regimens may mean that the observation is not mediated by hormone treatment but rather simply reflects a secular trend.

There is no evidence of an overall increased risk of cancer related to hormonal therapy.[28] Periodic health evaluations for transgender individuals should include age-appropriate cancer screening for any tissue present. Prostate cancer has been documented in transgender women.[29] Both uterine and cervical cancer have been documented in transgender men. Breast cancer has been documented in transgender women and transgender men.[30]

PROGNOSIS

Preservation of Fertility

Gender-affirming hormone therapy and surgery may eliminate fertility. Postpubertal transgender women can consider sperm cryopreservation prior to engaging in gender-affirming medical treatment. For younger transgender girls, introducing GnRH analogue therapy later in puberty can facilitate sperm cryopreservation. Transgender boys may consider oocyte cryopreservation. Oocytes have been retrieved from transgender boys who had already started GnRH analogue therapy, and a live birth has been reported from a stimulated oocyte retrieved from a transgender man while he remained on testosterone with the embryo implanted in the uterus of his cisgender partner.

Although infrequent, some transgender people may discontinue gender-affirming hormone therapy or request reversal of gender-affirming surgical treatment to the degree such reversal is possible. Surveys suggest that the biggest reasons for such treatment change are pressures from work, family, and society. Rarely, people with mental health morbidity may receive gender-affirming treatment that was not indicated.

GENERAL REFERENCES

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216

THE TESTIS AND MALE HYPOGONADISM, INFERTILITY, AND SEXUAL DYSFUNCTION

RONALD S. SWERDLOFF AND CHRISTINA WANG

MALE REPRODUCTIVE PHYSIOLOGY

The testis is a bifunctional organ that serves as the site for synthesis of sex steroids (mainly testosterone) and the production of sperm. Androgens and their metabolites (including estrogens) also act on nonreproductive organs and serve essential roles in muscle, adipose tissue, bone, hematopoietic cells, liver, and brain.

The male reproductive axis consists of three main components: (1) hypothalamus, where the kisspeptin-neurokinin B-dynorphin neurons are located and gonadotropin-releasing hormone (GnRH) is produced; (2) pituitary, where gonadotrophs secrete luteinizing hormone (LH) and follicle-stimulating hormone (FSH); and (3) testes, which produce sex hormones and spermatozoa (sperm) (Fig. 216-1). The components of this system function in an integrated fashion to control the concentrations of circulating gonadal steroids required for normal male sexual development and function, as well as for androgen- and estrogen-mediated effects on critical sex-steroid sensitive

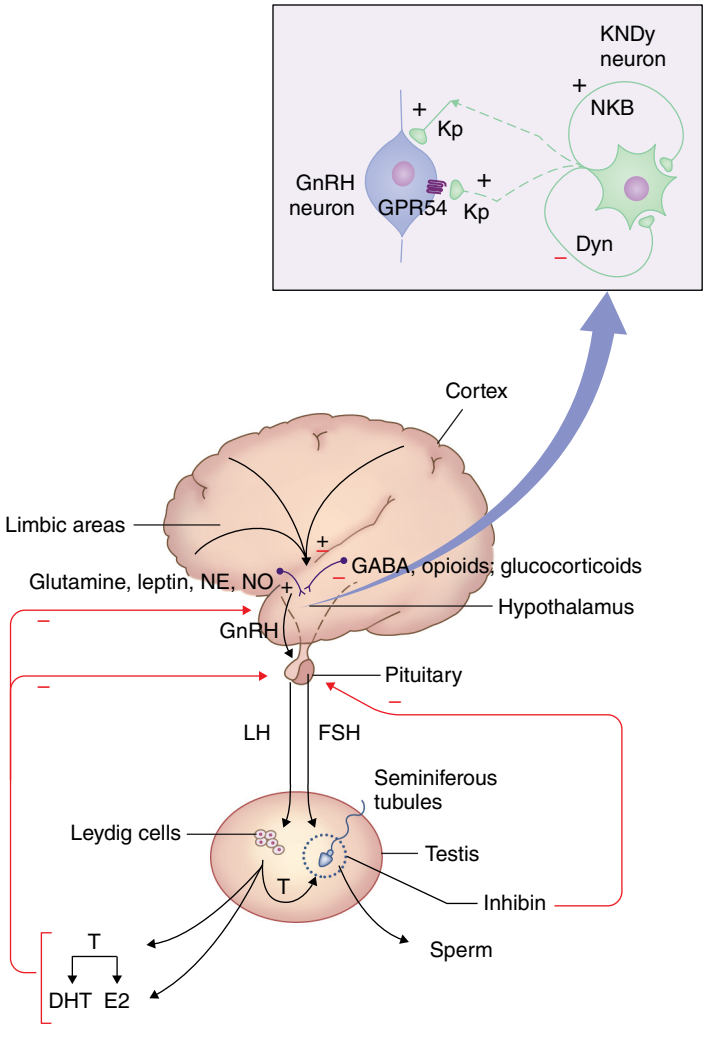

FIGURE 216-1. The hypothalamic-pituitary-gonadal axis in the male. *Inset*: The kisspeptin, neurokinin B, and dynorphin (KNDy) neurons in the hypothalamus. DHT = dihydrotestosterone; Dyn = dynorphin; E_2 = estradiol; FSH = follicle-stimulating hormone; GABA = gamma-amino butyric acid; GnRH = gonadotropin-releasing hormone; GPR54 = G-protein–coupled receptor 54; Kp = kisspeptin; LH = luteinizing hormone; NE = norepinephrine; NKB = neurokinin B; NO = nitric oxide; T = testosterone.

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single-stage construction of a phallus and neourethra should lengthening of the urethra be desired. In an alternative approach, an anterior wall vaginal flap is used during phalloplasty, either without a lengthened urethra or with a lengthened urethra deferred to a future surgery. Both metoidioplasty and phalloplasty procedures may involve a scrotoplasty with testicular implants.

Surgical complications for genital reconstruction procedures occur in 40% or more of cases, often related to urethral strictures or fistulas in people who have had a urethral lengthening. Many of these patients will require subsequent urethroplasties.

Surgeries for Transgender Women (Male to Female)

Breast augmentation surgical approaches, which are similar to breast augmentation in cisgender women, are typically performed following 12 to 24 months of estrogen-induced breast growth. Laryngeal surgery or vocal feminization surgery shortens the vocal cords and better aligns the voice with gender identity.[26] Reduction thyroid chondroplasty removes excess cartilage found in the "Adam's apple," thereby causing it to be less prominent. Facial feminization procedures that might be considered cosmetic for cisgender women can be medically necessary for transgender women as key to being recognized safely as female. The typical genital reconstruction surgery is vaginoplasty, which is construction of a vagina, clitoris, and labia.[27] Penile inversion is the gold-standard technique. Following surgery, transgender women are required to dilate the neovagina indefinitely to maintain vaginal length. Dilation requirements may be less rigorous if intestinal tissue is used for vaginoplasty; however, intestinal vaginoplasty is less preferred because of increased secretion from the tissue. Perioperative pelvic floor muscle physical therapy can be useful. Orchiectomy is available to remove the source of endogenous testosterone when less surgery is desired.

Perioperative Hormone Management

Gender-affirming hormone therapy should be maintained throughout the perioperative period for most people. Transgender women can discontinue adjunct antiandrogens following vaginoplasty and/or orchiectomy.

Other Risk Considerations Connected to Gender-Affirming Hormone Treatment

Insulin resistance and changes in body fat may occur in both transgender men and women after initiating gender-affirming hormone therapy. The fact that both transgender men and transgender women are reported to share the same risk despite opposite treatment regimens may mean that the observation is not mediated by hormone treatment but rather simply reflects a secular trend.

There is no evidence of an overall increased risk of cancer related to hormonal therapy.[28] Periodic health evaluations for transgender individuals should include age-appropriate cancer screening for any tissue present. Prostate cancer has been documented in transgender women.[29] Both uterine and cervical cancer have been documented in transgender men. Breast cancer has been documented in transgender women and transgender men.[30]

PROGNOSIS

Preservation of Fertility

Gender-affirming hormone therapy and surgery may eliminate fertility. Postpubertal transgender women can consider sperm cryopreservation prior to engaging in gender-affirming medical treatment. For younger transgender girls, introducing GnRH analogue therapy later in puberty can facilitate sperm cryopreservation. Transgender boys may consider oocyte cryopreservation. Oocytes have been retrieved from transgender boys who had already started GnRH analogue therapy, and a live birth has been reported from a stimulated oocyte retrieved from a transgender man while he remained on testosterone with the embryo implanted in the uterus of his cisgender partner.

Although infrequent, some transgender people may discontinue gender-affirming hormone therapy or request reversal of gender-affirming surgical treatment to the degree such reversal is possible. Surveys suggest that the biggest reasons for such treatment change are pressures from work, family, and society. Rarely, people with mental health morbidity may receive gender-affirming treatment that was not indicated.

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216

THE TESTIS AND MALE HYPOGONADISM, INFERTILITY, AND SEXUAL DYSFUNCTION

RONALD S. SWERDLOFF AND CHRISTINA WANG

MALE REPRODUCTIVE PHYSIOLOGY

The testis is a bifunctional organ that serves as the site for synthesis of sex steroids (mainly testosterone) and the production of sperm. Androgens and their metabolites (including estrogens) also act on nonreproductive organs and serve essential roles in muscle, adipose tissue, bone, hematopoietic cells, liver, and brain.

The male reproductive axis consists of three main components: (1) hypothalamus, where the kisspeptin-neurokinin B-dynorphin neurons are located and gonadotropin-releasing hormone (GnRH) is produced; (2) pituitary, where gonadotrophs secrete luteinizing hormone (LH) and follicle-stimulating hormone (FSH); and (3) testes, which produce sex hormones and spermatozoa (sperm) (Fig. 216-1). The components of this system function in an integrated fashion to control the concentrations of circulating gonadal steroids required for normal male sexual development and function, as well as for androgen- and estrogen-mediated effects on critical sex-steroid sensitive

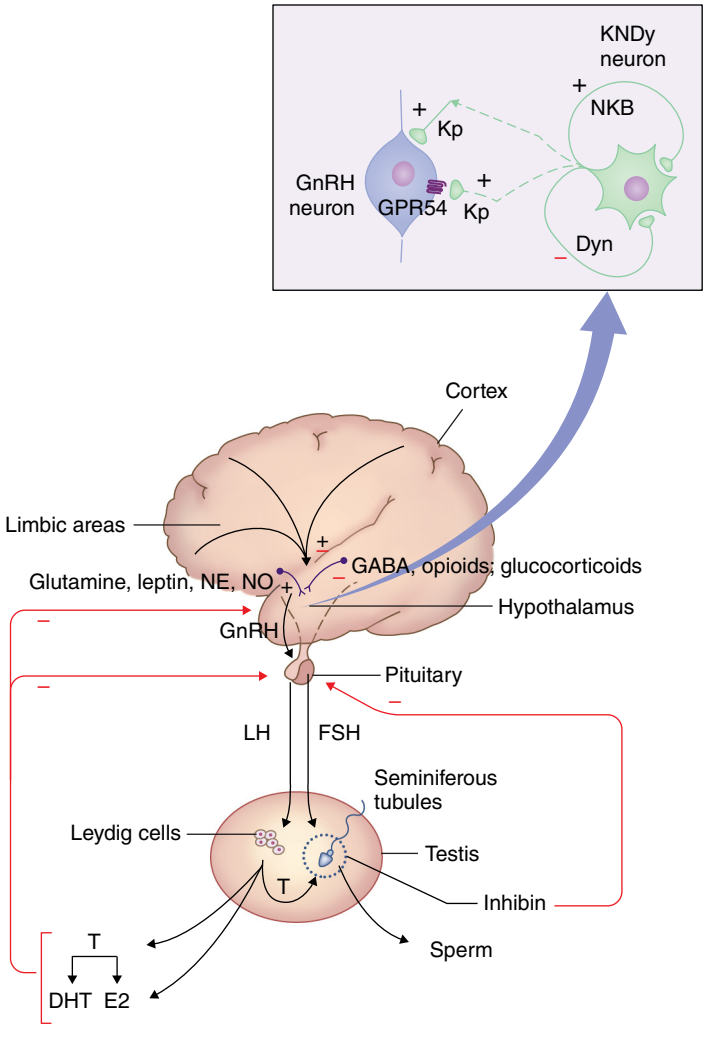

FIGURE 216-1. The hypothalamic-pituitary-gonadal axis in the male. *Inset*: The kisspeptin, neurokinin B, and dynorphin (KNDy) neurons in the hypothalamus. DHT = dihydrotestosterone; Dyn = dynorphin; E_2 = estradiol; FSH = follicle-stimulating hormone; GABA = gamma-amino butyric acid; GnRH = gonadotropin-releasing hormone; GPR54 = G-protein–coupled receptor 54; Kp = kisspeptin; LH = luteinizing hormone; NE = norepinephrine; NKB = neurokinin B; NO = nitric oxide; T = testosterone.

ABSTRACT

The hypothalamic-pituitary axis regulates testicular function, including spermatogenesis and the production of testosterone. The diagnosis of male hypogonadism is based on symptoms, the most common of which is sexual dysfunction. The diagnosis is confirmed by consistently low serum testosterone levels measured in the morning. Testosterone therapy can benefit men with low testosterone levels, but the potential risks should be discussed with the patient. The choice among available formulations of testosterone therapy should be made by the patient with advice from the physician depending on cost, availability, ease of use, and adverse effect profile. Many infertile men do not have a known cause for their infertility, but gene sequencing techniques can detect genetic deletions or mutations in up to 50% of such patients. Specific treatment with gonadotropins is available for infertility due to hypogonadotropic hypogonadism, whereas most other causes are not amenable to medical treatment. Use of assisted reproductive technology, including intracytoplasmic sperm injection with or without testicular sperm extraction, have allowed many men previously considered sterile to have a progeny. The most common sexual problem is erectile dysfunction, which is often a biomarker of cardiovascular disease. Treatment with a phosphodiesterase-5 inhibitor is effective therapy for most men with erectile dysfunction.

KEYWORDS

hypothalamus-pituitary-testis axis
spermatogenesis
puberty in boys
male hypogonadism
male infertility
male sexual dysfunction
erectile dysfunction

end organs. The reproductive axis is also responsible for normal male germ cell development and maturation. Accessory sexual organs, including the epididymides, seminal vesicles, and prostate gland, are important for sperm maturation (epididymis) and seminal fluid production (seminal vesicles and prostate). An anatomically functional sperm transport and ejaculatory system are necessary to ensure male fertility.

HYPOTHALAMIC-PITUITARY FUNCTION

The hypothalamus is responsible for the normal pulsatile secretion of GnRH (Chapter 205) that signals the anterior pituitary to release LH and FSH every 60 to 90 minutes in men. The secretion of GnRH is regulated mainly by kisspeptin, neurokinin B, and dynorphin neurons in the infundibular nucleus in the hypothalamus. Kisspeptin stimulates GnRH secretion directly, whereas neurokinin B stimulates kisspeptin neurons that in turn lead to GnRH secretion. In contrast, dynorphin has inhibitory effects on kisspeptin signaling.[1] Negative feedback from circulating levels of testosterone or its metabolic products (i.e., estradiol and dihydrotestosterone) inhibit the secretion and release of GnRH. Norepinephrine, nitric oxide, and glutamate stimulate this process, whereas gamma-amino butyric acid, prolactin, and glucocorticoid are inhibitory. Caloric restriction is associated with suppressed kisspeptin and leptin, which also are stimulants for GnRH secretion.

Both LH and FSH consist of two subunits (α and β), each of which is required for biologic activity. LH has a shorter half-life than FSH. Feedback regulation of LH and FSH secretion also occurs at the pituitary, with testosterone, dihydrotestosterone, and estradiol inhibiting the synthesis or release of both gonadotropins. The circulating testicular peptide inhibin, produced by Sertoli cells, also selectively inhibits FSH. LH and FSH act through specific cell surface receptors on the Leydig and Sertoli cells, respectively.

TESTOSTERONE

The testis is a complex organ consisting of (1) seminiferous tubules containing Sertoli cells and germ cells and (2) the interstitial space, which contains the steroid-secreting (Leydig) cells. Leydig cells synthesize steroid hormones under the regulation of LH. The LH receptors on the cell surface of the Leydig cells signal through G protein–, adenyl cyclase–, and cyclic adenosine monophosphate–mediated activation of steroid biosynthesis.

Testosterone is the principal male hormone secreted by the testes; approximately 5 to 10 mg/day is produced in adult men. Testosterone synthesis occurs in the human testes through either the Δ^4 or the predominant Δ^5 pathway The enzymatic rate-limiting steps in the process are the LH-inducible steroid acute regulatory protein and translocator protein that converts cholesterol to pregnenolone by the cholesterol side-chain cleavage enzyme (P450SCC) (E-Fig. 216-1).

Testosterone circulates mainly bound to two plasma proteins: sex hormone–binding globulin and albumin. In young adult men, approximately 54% of testosterone is bound to albumin, 44% is bound to sex hormone–binding globulin, and 2 to 3% is unbound (free). Bioavailable testosterone refers to the sum of albumin-bound and free testosterone and is measured by separating sex hormone–binding globulin–bound testosterone from total testosterone. Serum sex hormone–binding globulin levels are increased in hyperestrogenic states, hyperthyroidism, aging, phenytoin treatment, anorexia nervosa, and prolonged stress. In contrast, the levels are lowered in hyperandrogenic states (endogenous and exogenous as in androgen treatment), obesity, acromegaly, and hypothyroidism. In most instances, measurement of serum total testosterone provides biochemical support for the diagnosis of testosterone deficiency. In conditions with abnormal sex hormone–binding globulin levels, however, the total testosterone measurement may be misleading, and measurement of non–sex hormone–binding globulin–bound testosterone may allow better interpretation of the bioactive testosterone levels.

Testosterone exerts its effects either through direct action or after conversion to dihydrotestosterone by two separate 5α-reductase isozymes or to estradiol by the aromatase enzyme. Both testosterone and dihydrotestosterone bind efficiently to the androgen receptor. Testosterone also can serve as a precursor for estradiol, notably in bone and adipose tissues. After conversion, estradiol binds to the estrogen receptors (α or β) to induce its effects. Various end organs differ in their 5α-reductase isoenzyme and aromatase concentrations or activity. Congenital and acquired defects in these two enzymes, as well as in the estrogen and androgen receptors, result in distinct syndromes with characteristic phenotypes (Chapter 214).

SPERMATOGENESIS

The spermatogenic compartment of the testis consists of the Sertoli and germ cells that are intimately interactive with the interstitial compartment. The Sertoli cells bridge the entire space between the basement membrane and the lumen of the tubules. They are the target of androgen and FSH action to regulate spermatogenesis. Sertoli cells secrete a multitude of paracrine regulators of spermatogenesis (e.g., inhibin, activin, growth factors, and cytokines).

The development and maturation of germ cells depend on the proper hormonal (FSH) and paracrine (testosterone) milieu. Both testosterone and FSH stimulate progression of spermatogonia to mature spermatozoa, limit the amount of germ cell death (apoptosis), and regulate sperm release from the germinal epithelium.

After spermatogenesis is completed, mature spermatozoa are released into the lumen of the seminiferous tubule and travel through the rete testes and epididymis, where they become functionally mature, before traversing the vas deferens. The seminal fluid from the testes gains constituents from the seminal vesicles, prostate, and bulbourethral glands before ejaculation.

SEXUAL FUNCTION AND ERECTILE PHYSIOLOGY

Sexual function in men requires normal sexual desire (libido) as well as erectile, ejaculatory, and orgasmic capacity. This complex process involves cognitive, sensory, hormonal, autonomic neuronal, and penile vascular integrative actions for normal function. Defects can occur at multiple levels.

The brain is the integrative center of the sexual response system. It processes sensory input and hormonal signals to create the hypothalamic neuronal message that traverses the spinal cord to the T9-12 sympathetic and sacral parasympathetic outflow tracts. The nonadrenergic, noncholinergic autonomic plexus nerves initiate vasodilation of the cavernosal arterial and corpora cavernosal sinusoids of the penis by the release of local vasodilators (e.g., nitric oxide and vasoactive intestinal peptide) from the vascular endothelium and the sinusoidal smooth muscle cells of the sinusoids (E-Fig. 216-2). Nitric oxide produces smooth muscle dilation by the generation of cyclic guanosine monophosphate (cGMP) and the modification of calcium flux. The neurogenic mechanisms leading to vasodilation of the cavernosal arterioles and sinusoids result in a rapid increase in penile blood flow and expansion of the vascular channels; these effects inhibit venous return by compressing the venous channels against the tunica albuginea to limit venous drainage.

Testosterone's primary effect on erectile function is to enhance libido. Testosterone also increases penile nitric oxide synthase activity and enhances smooth muscle cell growth. Sexual desire and fantasy are highly sensitive to testosterone, thereby explaining the preservation of erectile capacity in many men with partial androgen deficiency.

PUBERTAL DEVELOPMENT AND AGING

Reproductive Axis Development during Childhood and Puberty

Adrenarche and Puberty

Adrenarche occurs at approximately 7 or 8 years of age when the zona reticularis of the adrenal gland undergoes maturation and secretes adrenal androgens, including androstenedione, dehydroepiandrosterone, and dehydroepiandrosterone sulfate. The process is under the control of adrenocorticotropic hormone, not LH or FSH. Androstenedione and dehydroepiandrosterone are androgenic pre-hormones, and the prepubertal growth spurt and development of pubic and axillary hair are mediated by the conversion of these precursors to testosterone and dihydrotestosterone in peripheral tissues.

Initiation of puberty is determined by an increase in the pulsatile pattern of hypothalamic GnRH secretion. The secretory pulses of GnRH are synchronized by increased kisspeptin secretion from the hypothalamic neurons and nocturnal bursts of LH secretion.[2] As puberty progresses, feedback sensitivity of the hypothalamus and pituitary to circulating steroids lessens, thereby increasing the secretion of gonadotropins. The increasing concentrations of intratesticular testosterone and circulating FSH stimulate the Sertoli cell to produce factors leading to the initiation and maturation of spermatogenesis. As spermatogenesis advances, the first sign of puberty is marked by testes increasing in size from 3 to 5 mL at the outset of puberty to 15 to 35 mL in adulthood. The majority of the extratesticular end-organ events of puberty are secondary to the increased testosterone

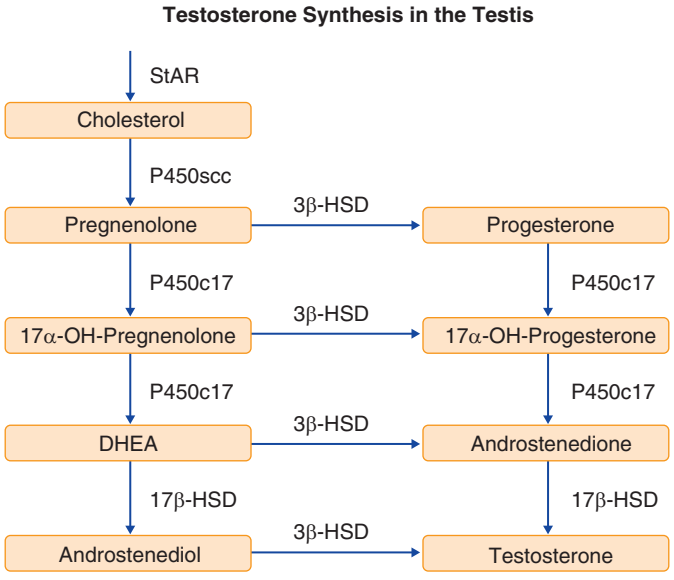

E-FIGURE 216-1. The steroid acute regulatory *(StAR)* and translocator proteins mobilize cholesterol from cellular stores to the mitochondria. Intratesticular steroidogenic pathways for the synthesis of testosterone. Although both the Δ^5 *(left)* and Δ^4 *(right)* pathways exist, the Δ^5 pathway predominates in the human testis. DHEA = dehydroepiandrosterone; HSD = hydroxysteroid dehydrogenase.

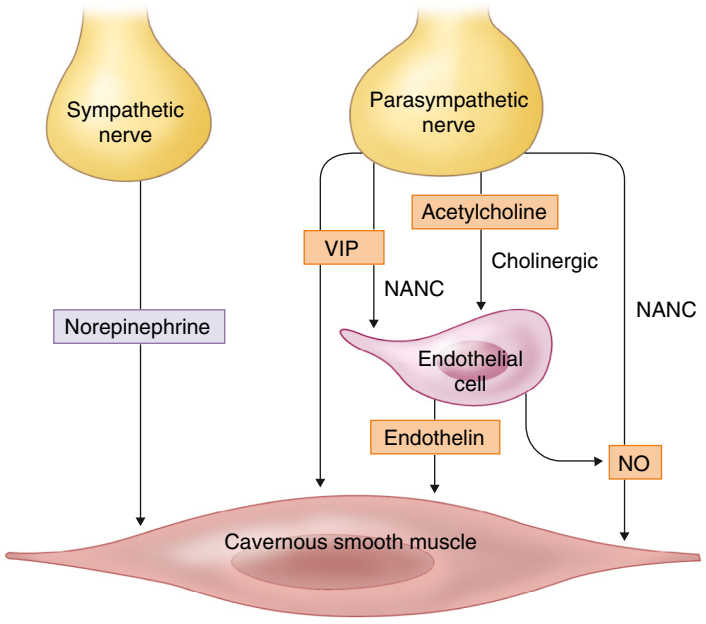

E-FIGURE 216-2. The interaction among cholinergic, adrenergic, and nonadrenergic, noncholinergic *(NANC)* neuronal pathways and their contribution to penile smooth muscle contraction and dilation *(arrows)*. NO = nitric oxide; VIP = vasoactive intestinal polypeptide. (From Lue TF. Physiology of penile erection and pathophysiology of erectile dysfunction and priapism. In: Walsh P, Retick A, Vaughn E, Wein A, eds. *Campbell's Urology*, 7th ed. Philadelphia: WB Saunders; 1998:1164.)

TABLE 216-1 PUBERTAL STAGES IN BOYS

STAGE/AGE (YEARS)	PUBIC HAIR	GENITAL
I	Absence of pubic hair	Childlike penis, testes, and scrotum (testis 5.0 ± 3.6 cm^3)
II 11.7 ± 1.3	Sparse, lightly pigmented hair mainly at base of penis	Scrotum enlarged with early rugation and pigmentation; testes begin to enlarge (6.7 ± 3.5 cm^3)
III 13.2 ± 0.8	Hair becomes coarse, darker, more curled, and more extensive	Penis has grown in length and diameter; testes now 14.7 ± 6.3 cm^3; scrotum more rugated
IV 14.7 ± 1.1	Hair adult in quality, but distribution does not include medial aspect of thighs	Penis further enlarged, with development of glans; scrotum and testes (20.1 ± 6.2 cm^3) further enlarged
V 15.5 ± 0.7	Hair is adult and extends to thighs	Penis and scrotum fully adult; testes 29.3 ± 9.1 cm^3

Modified from Marshall WA, Tanner JM. Variation in pattern of pubertal changes in boys. *Arch Dis Child.* 1970;45:13-23; Daniel WA Jr, Feinstein RA, Howard-Peebles P, et al. Testicular volumes of adolescents. *J Pediatrics.* 1982:101:1010-1012.

and its metabolic products (dihydrotestosterone and estradiol) (Table 216-1). The penis and scrotum grow and become pigmented. A progressive increase is seen in facial, axillary, chest, abdominal, thigh, and pubic hair; frontal scalp hair regresses, and the voice deepens. Genital and sexual hair development and temporal scalp hair regression require dihydrotestosterone (DHT). The increased levels of sex steroids result in closure of the epiphysis and achievement of adult height.

Aberrations of Timing of Puberty

Delayed Puberty

Delayed puberty, more common in boys than in girls, is usually diagnosed when male sexual development has not begun by age 14 years. The majority of boys with delayed development have a functional hypothalamic–pituitary disorder and a family history of delayed puberty. Most eventually attain full sexual maturation when puberty is completed within 4.5 years.[3] Other causes of delayed puberty include genetic factors (congenital hypogonadotropic hypogonadism), prior chemotherapy or radiation therapy, malnutrition, excessive exercise, chronic illnesses, and diseases of the hypothalamus and pituitary.[4]

DIAGNOSIS

Careful documentation of changing physical findings and measurement of serum LH, FSH, and testosterone concentrations may provide valuable clues to the beginning of puberty. An increase in testicular size to more than 3 mL usually heralds the onset of puberty. Inquiring and testing for hyposmia or anosmia and other midline defects may indicate a common variant of congenital hypogonadotropic hypogonadism (e.g., Kallmann syndrome; Chapter 214).

TREATMENT

The decision to institute early treatment with testosterone (e.g., testosterone enanthate 10 mg subcutaneous injections every week or 20 mg intramuscular injections every 2 weeks, with the dose increased very slowly every 3 months) depends on the perceived degree of psychological stress associated with the maturational delay. The major concern is early fusion of the epiphyses induced by treatment with testosterone, which compromises optimal height; however, with judicious dosing and monitoring of bone age, this adverse effect is unusual. In adolescent boys with delayed puberty and low levels of gonadotropins, periodic withdrawal of treatment can determine whether spontaneous puberty has occurred. Many adult men diagnosed with and treated as adolescents for a presumed diagnosis of hypogonadotropic hypogonadism achieve normal reproductive function when they discontinue therapy.

Precocious Puberty

Precocious puberty in boys is defined as the onset of pubertal (secondary sexual characteristics) development before 9 years of age. Sexual precocity can be subcategorized as either true (central) isosexual precocious puberty or pseudo–precocious (peripheral) puberty.

Central or true precocious puberty is associated with increases in GnRH-stimulated LH and FSH secretion (hypothalamic–pituitary origin), whereas pseudo–precocious puberty (peripheral precocious puberty) is independent of GnRH stimulation of LH and FSH secretion. Central precocious puberty in boys is often associated with central nervous system (CNS) disease (two thirds of boys), including hypothalamic tumors, cysts, inflammatory conditions, and seizure disorders.

DIAGNOSIS

Diagnostic findings include sexual precocity, inappropriately elevated serum LH levels, and associated elevations of testosterone. Magnetic resonance imaging can localize most lesions. Another cause of central precocious puberty is human chorionic gonadotropin secretory germinomas (hypothalamic or pineal tumors). Pseudo–precocious puberty is characterized by increased testosterone with suppressed LH.

Causes of pseudo–precocious puberty include congenital virilizing adrenal hyperplasia, and testicular testosterone-secreting neoplasms. Constitutively active LH receptor mutations result in uncontrolled testosterone secretion (testotoxicosis).

TREATMENT

Treatment of true precocious puberty is removal or correction (with surgery or radiation therapy) of the CNS lesion, if possible, and treatment with GnRH analogues (e.g., leuprolide acetate 3-month depot 11.25 or 30 mg; or triptorelin, 6 month depot 22.5 mg every 6 months)[5] to suppress LH and FSH secretion temporarily. There is no consensus on optimal age to withdraw treatment, but between 11 and 11.5 years of chronologic age has been recommended. Treatment of peripheral precocious puberty depends on the cause but includes glucocorticoids (e.g., hydrocortisone 15 mg/m^2) for congenital virilizing adrenal hyperplasia and ketoconazole (10 to 20 mg/kg/day) to suppress steroidogenesis, with or without an antiandrogen (e.g., spironolactone 5 to 7 mg/kg/day or bicalutamide 2 mg/kg/day).

Male Senescence: Decreased Testosterone and Other Anabolic Hormones

Testosterone Deficiency in the Elderly

Blood concentrations of androgen pre-hormones (e.g., dehydroepiandrosterone, dehydroepiandrosterone sulfate) peak at approximately the third decade of life and then decline at about 2% per year, thereby resulting in levels that are 10 to 20% of baseline by 80 years of age.[6] As a result, both total and free serum testosterone levels also progressively decrease (E-Fig. 216-3) by as much as 1 to 2% per year. Serum sex hormone–binding globulin levels also rise with age in men, thereby resulting in a higher percentage of circulating testosterone that is tightly bound and causing a greater decline of free testosterone with aging. Older men have increased body fat, particularly visceral fat, and low testosterone levels are associated with comorbid conditions such as obesity and the metabolic syndrome.

In men between ages 40 and 70 years, the crude prevalence rate of symptomatic testosterone deficiency is estimated to be approximately 2 to 6%. Many of the effects of low testosterone levels in aging men are similar to those observed in younger hypogonadal men: decreases in libido, erectile function, muscle mass, muscle strength, bone mass, as well as impaired mood and sense of well-being.

TREATMENT

The decision of whether to treat low testosterone levels in older men is controversial. Testosterone treatment currently is not recommended to improve energy, vitality, physical function, metabolic syndrome, diabetes, or cognition (see Testosterone treatment).

MALE HYPOGONADISM

DEFINITION AND EPIDEMIOLOGY

Hypogonadism (androgen deficiency) is diagnosed in men with consistent symptoms and signs and unequivocally low circulating levels of testosterone. Most men with more severe androgen deficiency have very low intratesticular testosterone concentrations and are infertile.

The true prevalence male hypogonadism is not known[7] except for Klinefelter syndrome, which has a prevalence of about 5 per 10,000 men. Moderate to severe brain injury may also cause low testosterone with a prevalence probably about 5 per 10,000. Classic causes of male hypogonadism (e.g., pituitary

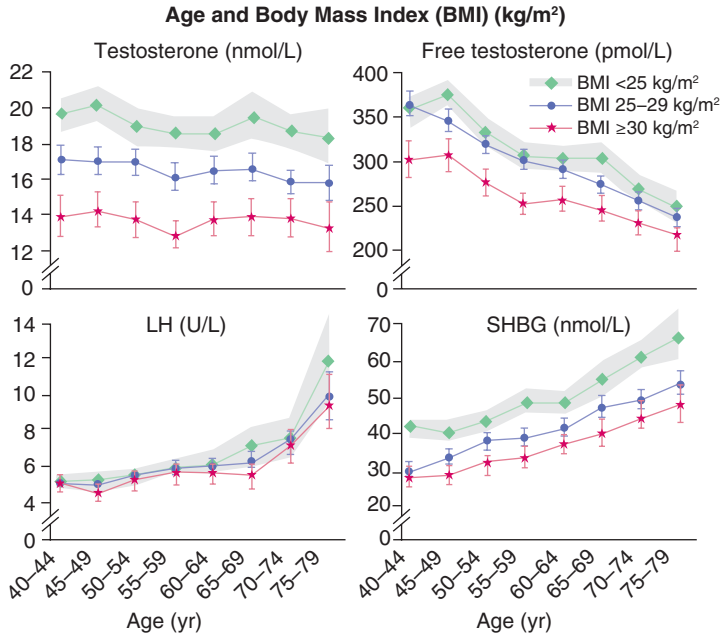

E-FIGURE 216-3. **Relationships among age, body mass index (BMI), and hormones.** The cohort was stratified according to BMI into three groups: nonobese (BMI < 25 kg/m^2), overweight (BMI 25 to 30 kg/m^2), and obese (BMI > 30 kg/m^2). Mean (95% CI in *shaded area* and *vertical lines*) total and free T and *SHBG* were significantly lower in the overweight and obese at all ages, compared with nonobese. The total T and SHBG age trends in the three BMI categories were similar (indicating no interaction between BMI and age); the free T age trend in the obese group was less steep than in the other two groups (indicating an interaction between BMI and age). Mean *LH* was not significantly different among the three groups at the median age of 60 years. LH was higher in the older than 70 years nonobese, compared with the overweight and obese groups, due to a negative BMI-age interaction. LH = luteinizing hormone; SHBG = sex hormone–binding globulin. (Wu FC, Tajar A, Pye SR, et al. Hypothalamic-pituitary-testicular axis disruptions in older men are differentially linked to age and modifiable risk factors: the European Male Aging Study. *J Clin Endocrinol Metab*. 2008;93:2737-2745.)

TABLE 216-2 CAUSES OF PRIMARY TESTICULAR FAILURE AND END-ORGAN RESISTANCE

Congenital disorders
Chromosome disorders, including Klinefelter and related syndromes (e.g., XXY, XXY/XY, XYY, XX males)
Testosterone biosynthetic enzyme defects
5α-Reductase deficiency
Androgen resistance syndrome
Myotonic dystrophy
Developmental disorders
Cryptorchidism
Acquired defects
Orchitis
Mumps and other viruses (including human immunodeficiency virus)
Granulomatous disease (e.g., tuberculosis, leprosy)
Infiltrative disease (e.g., hemochromatosis, amyloidosis)
Surgical, traumatic injuries, torsion of testis
Irradiation
Toxins (e.g., alcohol, fungicides, insecticides, heavy metals, cottonseed oil, DDT, other environmental "endocrine disruptors")
Drugs
Cytotoxic agents (alkylating agents)
Inhibitors of testosterone synthesis and antiandrogens (e.g., ketoconazole, abiraterone, cimetidine, flutamide, cyproterone, spironolactone)
Ethanol, opioids, other recreational drugs
Autoimmune testicular failure
Isolated
Associated with other organ-specific disorders (e.g., Addison disease, Hashimoto thyroiditis, insulin-dependent diabetes)
Systemic diseases* (e.g., cirrhosis, chronic renal failure, sickle cell disease,)
Aging*

*Systemic diseases and aging produce a mixed pattern of testicular and hypothalamic-pituitary dysfunction.
DDT = dichlorodiphenyltrichloroethane.

TABLE 216-3 CAUSES OF HYPOGONADOTROPIC HYPOGONADISM

IDIOPATHIC OR CONGENITAL
Isolated deficiency of gonadotropin-releasing hormone
With anosmia (Kallmann syndrome) or without anosmia
With other abnormalities (Prader-Willi syndrome, Laurence-Moon-Biedl syndrome, basal encephalocele)
Partial deficiency of gonadotropin-releasing hormone (fertile eunuch syndrome)
Multiple hypothalamic and pituitary hormone deficiency
Pituitary hypoplasia or aplasia
ACQUIRED
Traumatic brain injury, after surgery or irradiation
Neoplastic
Pituitary adenoma (prolactinoma, other functional and nonfunctional tumors)
Craniopharyngioma, germinoma, glioma, leukemia, lymphoma
Pituitary infarction, carotid aneurysm
Infiltrative and infectious diseases of hypothalamus and pituitary (sarcoidosis, tuberculosis, coccidioidomycosis, histoplasmosis, syphilis, abscess, histiocytosis X)
Hemochromatosis
Autoimmune hypophysitis and cancer immunotherapy–induced hypogonadism
Aging and systemic diseases*
Obesity
Malnutrition
Anorexia nervosa, starvation, renal failure, liver failure
Exogenous hormones and drugs including opiates
Antiandrogens, estrogens and antiestrogens, progestogens, glucocorticoids, cimetidine, spironolactone, digoxin, drug-induced hyperprolactinemia (metoclopramide, tranquilizers, antihypertensives)

*Aging and systemic diseases produce a mixed pattern of central and testicular dysfunction.

tumors, iron overload) are probably rare, seen in less than 1 per 10,000 men. Iatrogenic causes, including systemic chemotherapy and testicular and pituitary radiotherapy, are the most common etiologies of male hypogonadism other than age and obesity.

PATHOBIOLOGY

Primary hypogonadism, which is characterized by increased serum LH and FSH levels, indicates that the abnormality originates in the testis.[8] Secondary hypogonadism indicates a defect of the hypothalamus (Chapter 204) or anterior pituitary (Chapter 205), thereby resulting in decreased gonadotropins (LH, FSH, or both).

Many conditions can cause primary (Table 216-2) and secondary (Table 216-3) hypogonadism (see also Chapter 214). Combined primary and secondary hypogonadism occurs in aging and in a number of systemic diseases, such as alcohol abuse disorder (Chapter 364), liver disease (Chapter 132), type 2 diabetes mellitus (Chapter 210), human immunodeficiency virus (HIV) infection (Chapter 359), hemochromatosis (Chapter 196), and sickle cell disease (Chapter 149). Obesity (Chapter 201) leads to low total and free testosterone levels, with greater decreases in the total testosterone level because obesity not only decreases testosterone secretion but also lowers sex hormone–binding globulin levels. Decreased androgen action with normal or elevated testosterone and LH levels, mimicking androgen deficiency, may occur in patients with androgen receptor defects (androgen resistance), post-receptor signaling abnormalities, and an inability to convert testosterone to the active metabolite dihydrotestosterone (5α-reductase abnormalities).

Primary Testicular Hypogonadism

Primary hypogonadism is androgen deficiency, with or without infertility, in which the pathologic process lies at the testis level. (See Table 216-2.)

Congenital Defects

The most common congenital defect is due to chromosomal abnormalities (Klinefelter syndrome) and chromosomal translocations that are the leading causes of congenital male infertility (Table 216-2 and Chapter 214). Androgen-resistant states mimic testosterone deficiency clinically, but testosterone levels are normal or elevated. Causes of androgen resistance include genetic defects in the androgen receptor, congenital post–androgen receptor signaling defects, or 5α-reductase deficiency (Chapter 214).

Cryptorchidism[9] affects 2 to 9% of full-term newborn boys. Though testosterone deficiency is unusual, men with undescended testis have defects in spermatogenesis and an increased incidence of testicular cancer. Early surgical correction may improve fertility but does not reduce the risk of testicular cancer.

Acquired Defects

Infections

After puberty, mumps (Chapter 340) is associated with clinical orchitis in about 25% of cases, about 80% of which are unilateral. In the 20% of cases that are bilateral, a reported 30 to 90% of patients become infertile. The testes are inflamed, painful, and swollen during acute orchitis, and then gradually decrease in size. The testes may return to normal size and function, or they may atrophy. Spermatogenic defects occur more often and earlier than Leydig cell dysfunction, so patients with post-orchitic infertility may have normal testosterone and LH levels with increased serum FSH levels. Over time, elevations in LH and lower serum testosterone levels may appear. Leprosy (Chapter 301) also may cause orchitis and gonadal insufficiency. HIV infection is often associated with hypogonadism, which can be either hypogonadotropic or hypergonadotropic.

Trauma and Irradiation

The exposed position of the testes in the scrotum makes them particularly susceptible to injury, which may require emergency surgical intervention to prevent permanent testicular atrophy. Bilateral testicular torsion can result in ischemic testes that require surgery and result in androgen deficiency and infertility. Surgical injury during scrotal surgery for hernia, varicocele, and vasectomy can result in permanent testicular damage. Exposure of the testes to irradiation in the treatment of malignant diseases (e.g., testicular cancers) produces testicular germ cell, and less commonly, Leydig cell damage.

Drugs and Toxins

Chemotherapy, in particular alkylating agents, such as cyclophosphamide and busulfan, frequently leads to irreversible damage to germ cells. Heavy metals (lead, cadmium; Chapter 20) cause damage to the germ cells. Leydig cells are relatively less susceptible to most chemotherapeutic drugs than are Sertoli and germ cells. Some medications may interfere with testosterone biosynthesis (e.g., ketoconazole, abiraterone, spironolactone) or action (e.g., cyproterone, flutamide). Ethanol (Chapter 364), independent of its role in causing liver disease, inhibits the biosynthesis of testosterone. Marijuana, heroin, methadone (Chapter 365), medroxyprogesterone acetate, other progestins, and estrogens lower testosterone, mainly by decreasing LH. Medical treatment with androgens such as testosterone, dihydrotestosterone, and

synthetic anabolic steroids or their illicit use (e.g., in athletes, bodybuilders) lowers serum LH and FSH as well as sperm counts. Serum testosterone levels are low after the use of dihydrotestosterone and synthetic anabolic agents. Environmental toxins such as fungicides and insecticides (e.g., DBCP, metabolites of DDT, vinclozolin) and byproducts of the plastics industry (e.g., phthalates, bisphenol A) are called "endocrine disruptors" because these chemicals may have either weak estrogenic or antiandrogenic effects and can cause testicular dysgenesis in male offspring when administered in large doses to pregnant female rodents. Data linking "endocrine disruptors" to male reproductive dysfunction in humans are principally association studies and do not prove causality.

Autoimmune Testicular Failure

Antibodies against the microsomal fraction of the Leydig cells may occur either as an isolated disorder or as part of a multiglandular disorder (Chapter 212) involving, to variable degrees, the thyroid, pituitary, adrenals, pancreas, and other organs.

Secondary Gonadal Insufficiency (Hypogonadotropic Hypogonadism)

Congenital Hypogonadotropic Hypogonadism

Hypogonadotropic hypogonadism represents a deficiency in the secretion of gonadotropins (LH and FSH) because of an intrinsic or functional abnormality in the hypothalamus or pituitary glands (see earlier and Chapter 214). Congenital hypogonadotropic hypogonadism is caused by mutations of genes that regulate the GnRH neurons or secretion of GnRH. For example, hypogonadism, Kallmann syndrome, is associated with anosmia or hyposmia and other anomalies.[10] Genetic abnormalities of the regulation kisspeptin/neurokinin B/dynorphin release by hypothalamic neurons result in secondary Leydig cell dysfunction (see Table 216-3). The clinical manifestations depend on the age of the patient at the onset of the disorder and manifestations due to the genetic defects.

Acquired Hypogonadotropic Disorders

Anorexia Nervosa and Weight Loss

Starvation, anorexia nervosa (Chapter 200), and weight loss are examples of functional defects that result in hypogonadotropic hypogonadism with low serum testosterone levels. Strenuous exercise usually has minimal effects on testicular function, but functional hypogonadotropic hypogonadism can be caused by chronic excessive exercise.[11]

SYSTEMIC DISEASES

Severe stress (e.g., surgery, trauma) and systemic illness also lower gonadotropin and testosterone levels. Abnormalities of the hypothalamic-pituitary-testicular axis occur in a number of systemic diseases, including liver failure, renal failure, sickle cell anemia, advanced malignant disease, severe obesity, metabolic syndrome, type 2 diabetes, cystic fibrosis, amyloidosis, granulomatous and infiltrative diseases, and post-traumatic lesions in the region of the hypothalamus and pituitary (Chapter 205).

The effects of cirrhosis of the liver on testicular function are complex and may be either independent of or associated with the direct toxic effects of the continued use of alcohol. Gynecomastia, testicular atrophy, and impotence are concomitant signs of cirrhosis. Decreased spermatogenesis with peritubular fibrosis occurs in 50% of cases. Estradiol levels are usually elevated, thereby resulting in an increased ratio of serum estradiol to testosterone, often associated with gynecomastia. In sickle cell anemia and thalassemia major, boys may have impaired sexual maturation, and men are often infertile. Hemochromatosis (Chapter 196) may affect the hypothalamus-pituitary, as well as act directly on the testis. Diabetes and obesity are two major factors in hypogonadism. Emerging data show that type 2 diabetes is associated with low blood testosterone levels mainly as a result of hypothalamic-pituitary dysfunction; the decrease in serum testosterone correlates with the degree of hyperglycemia.

Pituitary Tumors

In men, prolactinomas (Chapter 205) are usually large (>1 cm in diameter; macroadenomas) by the time they are detected. Male patients with prolactin-secreting macroadenomas usually present with hypogonadism, erectile dysfunction, and visual field defects from suprasellar extension. In small tumors, hypogonadotropic hypogonadism may be due to suppressed GnRH levels, but the mass effect of large tumors can directly damage the non-neoplastic gonadotrophs. Large non–prolactin-secreting pituitary tumors (growth hormone, adrenocorticotropic hormone, glycopeptide, and null cell; Chapter 205) also may produce gonadotropin insufficiency when damage to the adjacent normal pituitary gland results in decreased serum LH and testosterone levels.

Autoimmune Hypophysitis

Autoimmune hypophysitis (Chapter 204) affects the pituitary and/or the infundibulum, thereby resulting in enlargement of the pituitary gland that may spontaneously involute or require pharmacologic treatment of the inflammation to prevent hypogonadotropic hypogonadism.[12] Cancer immunotherapy with checkpoint inhibitors (Chapter 164) may induce hypophysitis, thereby resulting in secondary adrenal, thyroid, and gonadal insufficiency. Recovery from central hypogonadism is more common than recovery from secondary adrenal or thyroid insufficiency.

CLINICAL MANIFESTATIONS

In children and adolescents, the most specific symptom of low testosterone is incomplete or delayed puberty. The most common symptoms of testosterone deficiency in adult men are sexual dysfunction, but decreased sexual drive and interest may precede erectile dysfunction. Other symptoms are loss of body hair, breast discomfort and enlargement, subfertility, hot flashes, sweat, and loss of height. Other nonspecific symptoms include decreased energy and mood, poor concentration, increased abdominal fat, and decreased muscle mass.

DIAGNOSIS

The diagnosis of hypogonadism is based on clinical symptoms and signs and a reduced serum testosterone level, compared with a normal reference range in healthy, young adult non-obese population (reported range for European and American men age 19 to 39 years, is 264 to 916 ng/dL).

History

The medical history should focus on testicular descent, pubertal development, shaving frequency, changes in body hair, and present and past systemic illnesses. A complete sexual history includes changes in libido, erectile and ejaculatory functions, frequency of masturbation, coital activity, and fertility (including that of present and previous partners). Information should be obtained on previous orchitis, sinopulmonary complaints, sexually transmitted diseases, human immunodeficiency virus (HIV) status, genitourinary infections, and previous surgical procedures that might affect the reproductive tract (e.g., orchiectomy, vasectomy, hernia repair, prostatectomy, varicocele ligation). Social history includes tobacco and alcohol intake. Medication and self-prescribed drug history includes recreational drugs; opioids; anabolic steroids; glucocorticoids; 5α-reductase inhibitors; psychiatric, antihypertensive, anti-androgenic, cytotoxic, and alternative medicine therapies; environmental toxins; and exposure to heat (including saunas and Jacuzzis), pesticides, and irradiation.

Physical Examination

The general physical examination includes height and span measurements; characterization of facial, pubic, and body hair distribution; presence of acne and facial wrinkling; breast examination for gynecomastia; assessment of muscle mass and adiposity; measurement of penile length and urethral meatus localization; digital rectal prostate examination; and visual field assessment if secondary hypogonadism is suspected. The scrotal examination should include an assessment of midline fusion (e.g., bifid scrotum, hypospadias); testicular size and consistency; presence of intratesticular masses; abnormalities of the epididymis; bilateral presence of vas deferens; and varicoceles, hydroceles, or hernias. Normal testicular volume is generally above 15 mL. Asian men have a slightly smaller mean testicular size. A decrease in testicular volume usually implies decreased spermatogenic cells because the seminiferous tubules account for more than 80% of testicular volume.

Laboratory Studies

Because of the strong diurnal rhythm in testosterone secretion in young men (highest in the morning), testosterone, LH, and FSH should be determined from morning blood samples (before 10 AM). Total testosterone measurements may be misleading indicators of Leydig cell secretory status in conditions in which sex hormone–binding globulin levels are abnormal (see earlier section). In these circumstances, measurement of free testosterone (using an equilibrium dialysis method), bioavailable testosterone (free plus albumin-bound), or calculated free testosterone (by total testosterone and sex hormone–binding globulin measurements) may be useful.

Elevated LH and FSH levels distinguish primary from secondary hypogonadism (both have low serum testosterone levels), but many older men with low serum testosterone levels may have a normal LH concentration. Serum

prolactin levels should be measured in all patients with low testosterone and low LH (hypogonadotropic hypogonadism) levels, as well as in men with known pituitary mass lesions, or galactorrhea. Dihydrotestosterone is measured in cases of abnormal differentiation of the genitalia and when 5α-reductase deficiency is suspected. Serum estradiol should be measured in cases of gynecomastia. Assessment of other testosterone precursors and products may be required in special circumstances, including suspected congenital adrenal enzyme defects.

If a young to middle-aged man has a morning serum total testosterone level that is repeatedly below 230 ng/dL (8 nmol/L), and he has symptoms or signs compatible with low testosterone state, the patient is probably hypogonadal, and testosterone replacement is indicated. If the serum testosterone level is between 230 and 320 ng/dL with normal serum LH levels, the patient may or may not be clinically hypogonadal, and androgen replacement may not improve the symptoms (e.g., sexual dysfunction). Thus, when serum total testosterone is borderline and LH is not increased, one of the measurements of bioactive testosterone is indicated (e.g., free testosterone). Because sex hormone–binding globulin levels are often increased, total testosterone levels may overestimate the biologically active forms. A serum total testosterone level above 350 to 400 ng/dL indicates that hypogonadism is very unlikely to be the cause of the symptoms, and the clinician should look for other explanations for the symptoms.[13]

TREATMENT

Indications

The main medical indication for androgen replacement therapy is male hypogonadism (Table 216-4).[14] In approximately 10% of men whose congenital or idiopathic hypogonadotropic hypogonadism reverses after testosterone therapy, the reversal is sustained after therapy is stopped. As a result, testosterone replacement should be periodically withdrawn, with serum testosterone and gonadotropins levels reassessed off therapy to be sure testosterone is still required. This phenomenon suggests that some patients with low serum testosterone due to hypogonadotropic hypogonadism may have a transient cause of the deficiency.

In younger men with symptomatic testosterone deficiency, testosterone replacement is indicated and has proven benefits.[15] At present, testosterone treatment usually is not recommended to improve energy, vitality, physical function, or cognition or for treatment of obesity or type 2 diabetes.[16–19]

Benefits and Risks of Testosterone Replacements

In hypogonadal men, androgen replacement leads to the development and maintenance of secondary sexual characteristics. In older men with relatively low serum testosterone levels, testosterone replacement therapy (up to 3 years) decreases fat mass, increases lean body mass, improves strength, and increases bone mineral density.[A1] When treatment with testosterone is sufficient to raise serum testosterone levels to the mid-normal young male range, patients report improved sexual activity libido, erectile function, and mood[A2–A4] with correction of unexplained anemia,[A5] and increases in bone mineral density and strength (Table 216-5).[A6] The effect on physical activity is modest at best, and no improvement is seen in cognition.[A7]

In hypogonadal men, testosterone treatment increases systolic blood pressure by up to 5 mm Hg. Testosterone-treated men also have significantly increased noncalcified plaque volume by coronary computed tomographic angiography,[A8] but cardiovascular adverse events have not increased over about a 3-year duration of the various randomized trials.[A9] In cohort studies with longer-duration follow-up, however, the data on cardiovascular risk are less clear.[20] Testosterone replacement therapy does not appear to affect lower urinary tract symptoms.[A10] It has no major short-term effects on the prostate gland but increases prostatic volume by an average of about 4.5 mL after 12 months in hypogonadal men. Whether testosterone treatment increases the risk of prostate cancer or of its invasiveness is uncertain. However, prostate cancer is androgen dependent, so testosterone treatment should be discontinued once prostate cancer is diagnosed.

Absolute contraindications to androgen replacement therapy include carcinoma of the prostate and the male breast. Androgens should be used with caution in older men with an enlarged prostate and urinary symptoms, elevated hematocrit, and sleep-related breathing disorders. A digital rectal examination should be performed, prostate-specific antigen level determined, and symptoms of severe urinary tract obstruction evaluated following urology standard practice before testosterone treatment is instituted in middle-aged and older men.

In older men with dehydroepiandrosterone deficiency, oral replacement with dehydroepiandrosterone raises serum dehydroepiandrosterone and dehydroepiandrosterone sulfate concentrations to the levels found in young men. However, serum testosterone levels do not change, and patients have not reported beneficial effects on quality of life, sexual function, mood, body composition, or exercise capacity.

TABLE 216-4 INDICATIONS FOR ANDROGEN THERAPY

Androgen deficiency (hypogonadism) with symptoms, signs, and a low testosterone level
Microphallus (neonatal)
Delayed puberty in boys
Angioneurotic edema
Other possible uses or under investigation
Hormonal male contraception
Sarcopenia associated with cancer, human immunodeficiency virus infection, chronic infection, frailty in older men and women

TABLE 216-5 ANDROGEN THERAPY: RISKS VERSUS BENEFITS

BENEFITS	RISKS
Development or maintenance of secondary sex characteristics	Fluid retention
Improved libido and sexual function	Gynecomastia
Increased muscle mass and strength	Acne, oily skin
Increased bone mineral density	Increased hematocrit, erythrocytosis
Improves anemia	Decreased high-density lipoprotein cholesterol (oral agents produce more effect)
Decreased body and visceral fat	Sleep apnea
Improved mood	Aggressive behavior (?)
Effect on cognition (?)	Prostate disease
Effect on vitality and quality of life (?)	Benign prostatic hyperplasia (?)
	Carcinoma of prostate (aggravate existing cancer)
	Increased cardiovascular adverse events (?)

Testosterone Delivery Systems

Testosterone treatment can be provided via different routes of administration (Table 216-6). Hydroalcoholic and nonalcoholic testosterone gels and lotions are the most widely used testosterone formulations in the United States. The usual[21] dosage is 50 to 100 mg of 1, 1.62, and 2% testosterone gel applied daily to the skin to deliver 5 to 10 mg of testosterone to the body. Transdermal delivery as gels or creams results in a more consistent serum concentration and causes little skin irritation. Transfer from the user to other people is possible during routine use and may be a concern if there is close skin contact with women and children. Protective clothing or a shower is necessary to avoid transferring testosterone through skin-to-skin contact. Testosterone gel also can be administered into the nose three times a day to provide sufficient concentrations of testosterone without a similar risk of transfer to other people. Transdermal testosterone patches deliver levels of testosterone within the normal range but have a high incidence of skin irritation (redness, swelling, and blisters). Testosterone esters, such as testosterone enanthate (or cypionate), are administered as intramuscular (150 to 200 mg once every 2 to 3 weeks, with resulting peaks and troughs of serum testosterone), whereas weekly subcutaneous injections (50 to 100 mg) result in more stable testosterone levels and are easier to use compared with intramuscular injections. Testosterone undecanoate injections (750 mg every 10 weeks or 1000 mg every 12 weeks after a second injection 4 or 6 weeks after the first injection) are the preferred replacement therapy in many parts of the world but not in the United States because of the regulatory requirement for 30 minutes of observation period after injection for cough episodes.

Oral options include testosterone undecanoate capsules (containing from 158 to 396 mg testosterone undecanoate in a self-emulsifying drug delivery system or 225 mg in a predigested triglyceride solution) twice daily with food.[22] Transbuccal testosterone (30-mg mucoadhesive tablets applied twice daily) results in physiologic-range testosterone levels by direct absorption into the systemic circulation, thereby avoiding first-pass effects on the liver. Modified 17α-alkylated androgens (methyl testosterone and many anabolic steroids), which are available in oral preparations, are not recommended as androgen replacement because they may lead to abnormalities in liver function, marked decreases in high-density lipoprotein cholesterol, and increases in total cholesterol levels compared with the testosterone esters.

Implants (pellets) of crystalline testosterone (75 mg/pellet) can maintain physiologic testosterone for 4 to 6 months depending on the number of pellets that are inserted subcutaneously. Implants are gaining popularity with U.S. urologists and are widely used in Australia and the United Kingdom.

TABLE 216-6 ANDROGEN PREPARATIONS

ROUTE	PREPARATION	DOSE AND FREQUENCY OF ADMINISTRATION
Transdermal gels	(AndroGel or Testogel; Testim; Axiron; Fortesta; Vogelxo)	1-2% gel (in packets or pumps) applied once daily delivering 50-100 mg testosterone on skin and 5-10 mg to body
Transdermal patch	Nonscrotal patch (Androderm)	Two patches, each delivering 2 mg/day; testosterone or one patch delivering testosterone 4 mg/day
Buccal/Nasal	Transbuccal testosterone, mucoadhesive tables (Striant)	30 mg two times daily
	Nasal gel (Natesto)	5.5 mg into each nostril three times/day
Injection	Testosterone enanthate (Delatestryl)	100 mg/wk IM or 150-200 mg IM every 2 wk
	Testosterone cypionate (Depo-Testosterone)	50-100 mg/wk SQ
	Testosterone undecanoate (Aveed)	750-1000 mg IM every 10-12 wk
Oral*	Testosterone undecanoate (Jatenzo, Tlando)	Jatenzo 158-396 mg or Tlando 225 mg PO two times daily with food
Implant	Testosterone implants (Testopel)	75-mg pellets (in United States), 6-10 pellets inserted once every 4-6 months

*Oral modified 17α-alkylated androgens such as methyltestosterone, fluoxymesterone, oxymetholone, stanozolol, and oxandrolone are not recommended for the treatment of androgen-deficient states because of potential hepatotoxicity and adverse effects on serum lipids.
IM = intramuscular; PO = oral; SQ = subcutaneous. Parenthesis (Registered Name).

MALE INFERTILITY

DEFINITION AND EPIDEMIOLOGY

Infertility is defined as the failure of a couple to achieve pregnancy after at least 1 year of frequent unprotected intercourse. If a pregnancy has not occurred after 3 years, infertility will most likely persist without medical treatment.

In the United States and Europe, the 1-year prevalence of infertility is 15% of couples. The prevalence in developing countries is likely to be higher because of the higher prevalence of genital tract infection. Of subfertility cases, 30 to 35% can be attributed to predominantly female factors, 25 to 30% to male factors, and 25 to 30% to problems in both partners.

PATHOBIOLOGY

Testicular disorders are the most frequent identifiable cause of male infertility (see Table 216-2), whereas hypothalamic-pituitary disorders are infrequent causes. The epididymis is the main location for sperm maturation, and lumicrine factors produced by germ cells appear to be critical to this process. Perturbations in these pathways may explain many cases of male infertility, and agents to interrupt it could become future male contraceptives.

With the advent of exome and whole-genome sequencing up to 50% of male infertility patients can now be diagnosed with genetic causes. Chromosomal disorders and translocations and Y chromosome microdeletions are increasingly recognized as a genetic cause of azoospermia and severe oligozoospermia. Up to 25% of infertile men have microdeletions in the long arm of the Y chromosome, many of which map to the Yq11 region of the chromosome, which is called the azoospermic factor (AZF). Mutations in the *AZFa* and *AZFb* regions are associated with azoospermia, whereas mutations of *AFZc* region may be associated with oligozoospermia. The gr/gr deletion removes a large segment of the *AFZc* gene and represents a significant risk factor for oligozoospermia in some but not all populations. Mutations in the testis-expressed 11 gene *(TEX11)* and many other newly discovered genes, such as *STAG3* and *DMRT1,* have been described as common causes of meiotic arrest and azoospermia in infertile men. Other genetic alterations cause ciliary dyskinesia, multiple flagellar abnormality, and sperm head defects. Y chromosome and other genetic defects may be transmissible to male offspring if patients are successfully treated with assisted reproductive technologies. Thus, genetic testing and counseling is important before technologies such as intracytoplasmic sperm injection are considered.

CLINICAL MANIFESTATIONS

The infertile man has no clinical manifestations, unless he has hypogonadism and seeks treatment for the symptoms of low testosterone. Usually, the female partner seeks medical advice when she fails to conceive after stable relationships with a male partner for 1 or 2 years (Chapter 218). A semen analysis ordered by the gynecologist identifies possible male factor infertility.

DIAGNOSIS

The approach to the diagnosis of an infertile couple includes management of both the male and the female partner (Figs. 216-2 and 216-3), often concurrently.[23,24] The history and physical examination should follow the recommendations for hypogonadism. Careful testicular examination should be performed by a skilled examiner to exclude a varicocele and for the presence of the vas deferens.

Examination of the ejaculate is the cornerstone for the investigation of an infertile man (Table 216-7). Semen samples are collected, preferably at the physician's office, after 2 to 7 days of abstinence from ejaculatory activity. The generally accepted reference values for a semen analysis (Table 216-8) represent the lower 5th percentile for semen parameters from data obtained population studies of fertile men and includes sperm concentration of 16 million/mL or higher; total sperm number of 39 million per ejaculate or higher; sperm motility of 42% or higher; and progressive motility of 30% or higher. Using strict criteria to assess sperm morphology, the percentage of morphologically normal forms is 4% or greater. Nevertheless, men with semen parameters below the 5th percentile of fertile men can be fertile, and the sperm quality of fertile and subfertile men overlaps considerably.[25] Low sperm concentration or poor sperm morphology is associated with lower chances of natural conception in the female partner. In patients with abnormal semen analyses, measurements of serum FSH, LH, and testosterone are indicated (see Fig. 216-2). Elevated FSH levels usually indicate severe germinal epithelial damage. A decreased serum inhibin B level or low antimüllerian hormone concentration reflects poor Sertoli cell function and may indicate spermatogenic dysfunction (commonly called non-obstructive azoo-spermia or oligozoo-spermia). Elevated serum LH and FSH concentrations together with a low serum testosterone level indicate pan-testicular failure with hypogonadism and infertility. Low serum FSH, LH, and testosterone concentrations indicate hypothalamic-pituitary dysfunction; serum prolactin should be measured, and additional investigations may be required. A low sperm concentration and suppressed LH level with an increased, normal, or low serum testosterone level (without clinical manifestations of androgen deficiency) may suggest exogenous androgen use. The hormonal pattern in androgen insensitivity (an uncommon cause of male infertility) is elevated LH, normal FSH, and high-normal to increased serum testosterone levels. Normal hormonal parameters (see Table 216-7) in azoospermic (no sperm in the ejaculate) men with normal-sized testes may suggest congenital or acquired obstruction in the epididymis or vas deferens (obstructive azoospermia).

TREATMENT

Correction of a varicocele appears to increase fertility and is worthwhile, even though it may not result in fertility.[26] The approach to the treatment of male infertility (see Figs. 216-2 and 216-3)[27] can be summarized in four categories. First, men with mild-to-moderate oligozoospermia, with or without decreased sperm motility and some impairment of motility, are subfertile rather than infertile. Spontaneous pregnancies can occur, but assisted reproductive technologies, including in vitro fertilization and intracytoplasmic sperm injection, have dramatically improved pregnancy rates. Second, reliable pharmaceutical treatment is limited to the 1 to 2% of infertile men with gonadotropin insufficiency. Third, in male factor infertility, azoospermia (absence of sperm in the ejaculate) may occur with obstruction of the ejaculatory system. In azoospermic patients who have had a prior vasectomy and who may for various reasons desire pregnancy of their partner, epididymovasostomy achieves patency in 90% of men, but pregnancy occurs in only about 50% of their female partners. In these patients, in vitro fertilization, and intracytoplasmic sperm injection after either percutaneous epididymal sperm extraction or microsurgical epididymal sperm extraction are highly

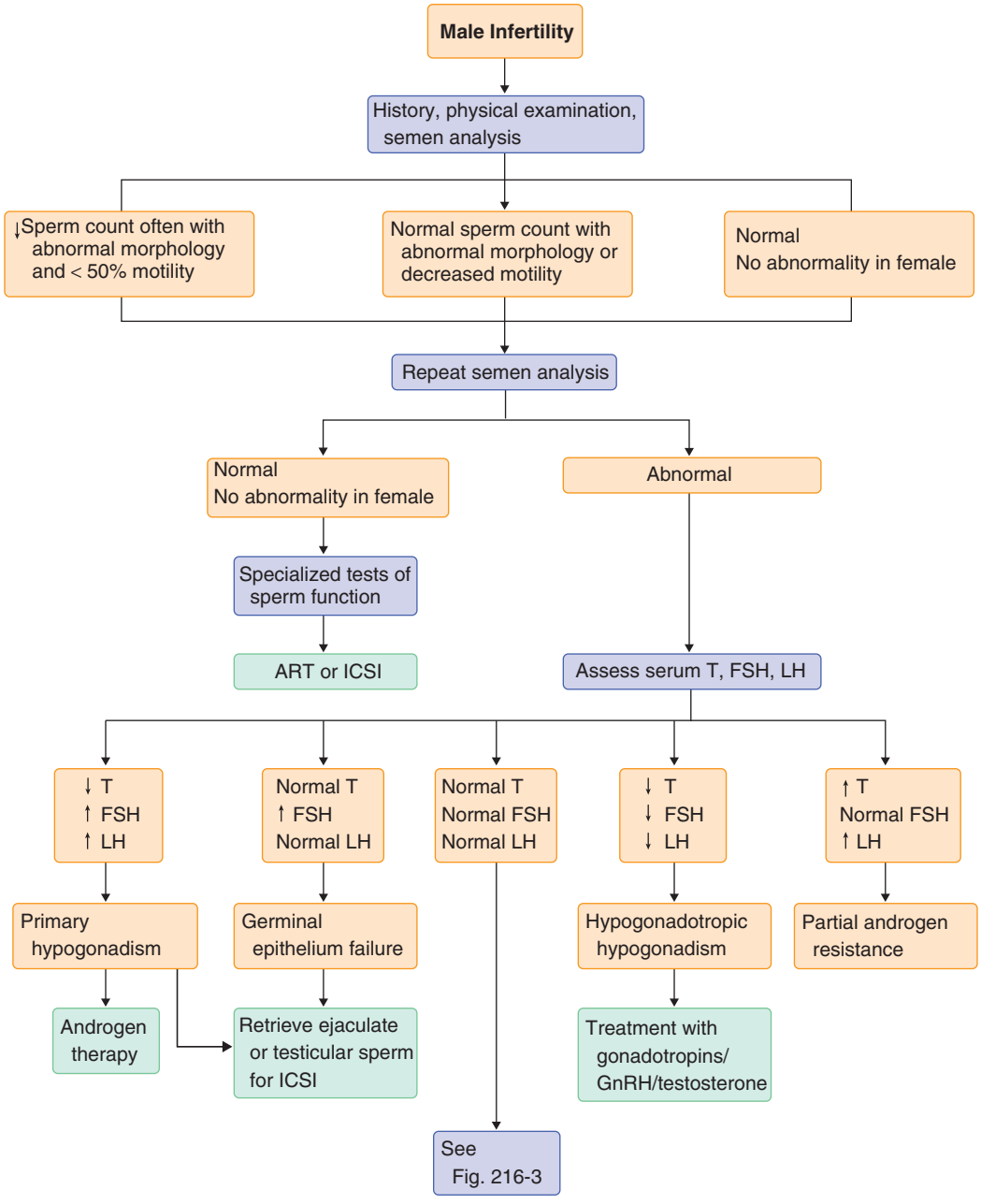

FIGURE 216-2. Algorithmic approach to the diagnosis and treatment of male infertility. ART = assisted reproductive technology; FSH = follicle-stimulating hormone; GnRH = gonadotropin-releasing hormone; ICSI = intracytoplasmic sperm injection; LH = luteinizing hormone; T = testosterone.

successful (Chapter 218).[28] Fourth, non-obstructive azoospermia resulting from impaired spermatogenesis may not be a sterile state, because sperm may be present within the testes. Microsurgical testicular sperm extraction from the testis followed by intracytoplasmic sperm injection has good success, even in patients with Klinefelter syndrome. Empirical medical treatments, such as clomiphene citrate, aromatase inhibitors, and recombinant FSH, are not generally recommended because of the paucity of reliable data, although high doses of FSH (700 to 1050 IU per week) can increase sperm concentration and motility.[A11]

SEXUAL DYSFUNCTION

Sexual dysfunction can be divided into four main categories: (1) loss of desire (libido), (2) erectile dysfunction, (3) ejaculatory insufficiency, and (4) anorgasmia. In younger men, the serum testosterone level is associated with sexual desire more than erectile function, but testosterone treatment improves sexual dysfunction in testosterone-deficient men. Total and free testosterone levels have small but statistical associations with sexual desire, erectile function, and sexual activity in symptomatic older men, and treatment with testosterone improves all aspects of sexual function in symptomatic older men with testosterone deficiency (see Table 216-5).

DECREASED LIBIDO

Loss of libido refers to a reduction in sexual interest, initiative, and frequency as well as a diminished response to internal or external erotic stimuli. Causal factors include psychogenic factors, CNS disease, androgen deficiency and resistance, and side effects from medications (e.g., antihypertensive agents, psychotropic agents, alcohol, opiates, dopamine blockers, antiandrogens, and possibly 5α-reductase inhibitors).

A low testosterone level may be the cause of low libido, and a morning level should be obtained. Treatment is directed toward the causal mechanism.

ERECTILE DYSFUNCTION

DEFINITION

Erectile dysfunction can be defined as a man's inability to obtain rigidity sufficient to permit coitus of adequate duration to satisfy himself and his partner.

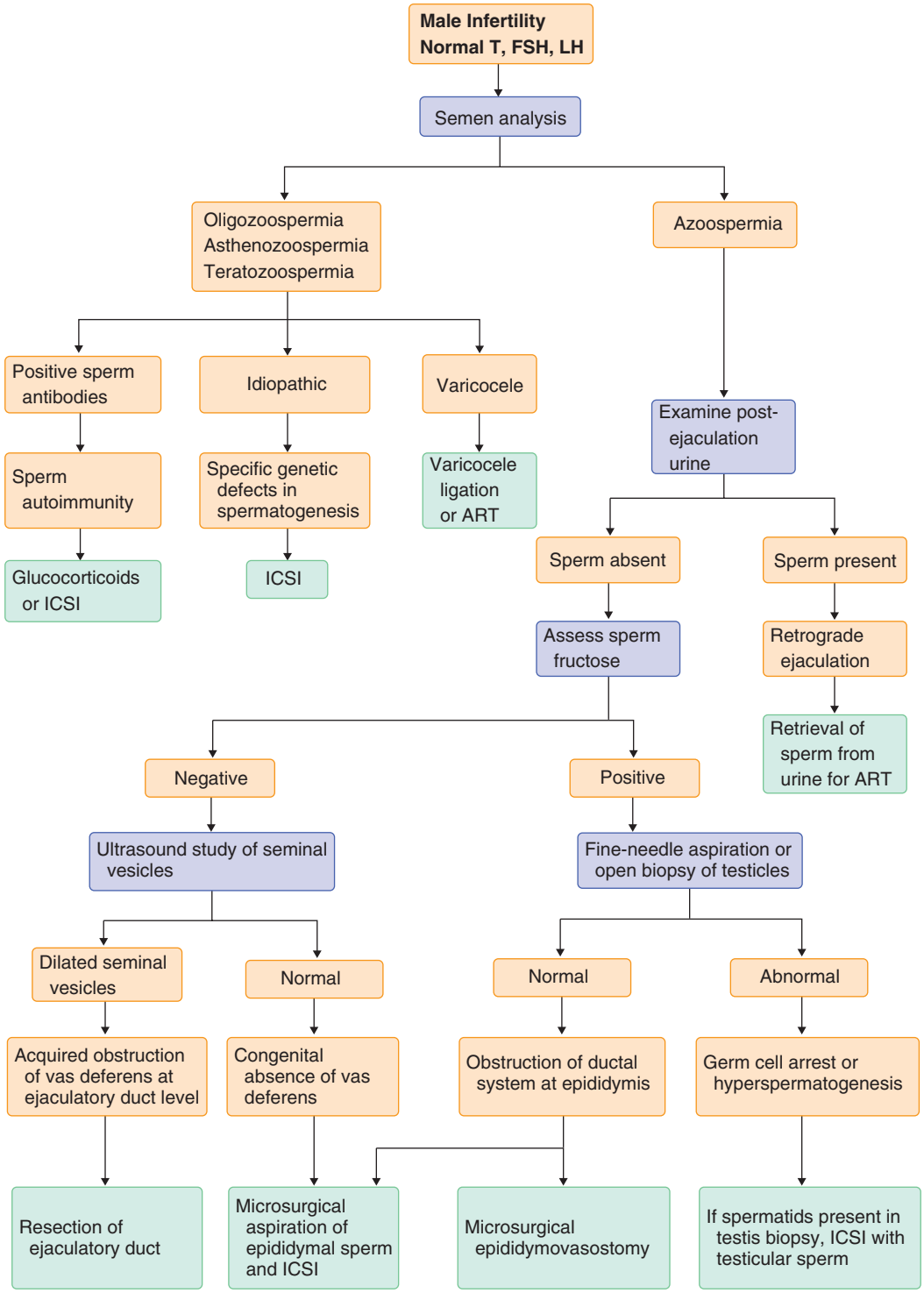

FIGURE 216-3. Algorithmic approach to the diagnosis and treatment of male infertility in patients with normal serum hormone concentrations. ART = assisted reproductive technology; FSH = follicle-stimulating hormone; ICSI = intracytoplasmic sperm injection; LH = luteinizing hormone; T = testosterone.

EPIDEMIOLOGY

Current estimates suggest that 10 to 15% of all adult American men suffer from erectile dysfunction, with the incidence progressively increasing as men become older. In one study, 52% of men ages 40 to 70 years experienced some degree of perceived erectile dysfunction. The prevalence of erectile dysfunction is even higher in men with type 2 diabetes mellitus and after radical prostatectomy for prostate cancer. Epidemiologic studies in the United States and Europe in men between 50 to 80 years indicate that erectile dysfunction is associated with lower urinary tract obstructive symptoms and benign prostatic hyperplasia (Chapter 114).[29] Erectile dysfunction is also associated with increased risks of cardiovascular disease.

PATHOBIOLOGY

The causes of erectile dysfunction are categorized as vasculogenic, psychological, endocrine, neurologic, iatrogenic (post–radical prostatectomy), drug related, systemic illness, and aging. Erectile dysfunction is common in older men, despite normal serum testosterone levels; this effect appears to be the result of impaired penile vasodilatory capacity as a result of endothelial dysfunction. Decreased nonadrenergic, noncholinergic nerve activity, and reduced production of nitric oxide by endothelial cells result in decreased relaxation of cavernous smooth muscle, decreased filling of the cavernous sinusoids, and reduced compression of the venous plexus against the tunica, leading to failure of erection. Men with erectile dysfunction share common risk factors with cardiovascular disease (smoking,

TABLE 216-7 MALE INFERTILITY: BASIC LABORATORY TESTS

SEMEN ANALYSES	HORMONE ANALYSES (IN PATIENTS WITH ABNORMAL SEMEN ANALYSES)
BASIC: Volume, pH Microscopy: Agglutination, debris Sperm: Concentration, motility, morphology, vitality Leukocytes Immature germ cells EXTENDED: Sperm DNA fragmentation Multiple sperm defects Immunologic and genetic tests Sperm antibodies Semen biochemistry	Serum luteinizing hormone and follicle-stimulating hormone Serum testosterone If luteinizing hormone and testosterone levels are low, serum prolactin

TABLE 216-8 SEMEN ANALYSIS: REFERENCE RANGE FOR FERTILE MEN*

PARAMETER	LOWER 5TH PERCENTILE
Semen volume	1.4 mL
Sperm quality	
Sperm concentration	16 million/mL
Total count	39 million/ejaculate
Motility	42% motile; 30% progressively motile
Morphology	4% normal†
Vitality (live)	54%
Leukocytes	<1 million/mL

*Men whose partners had a time-to-pregnancy of ≤12 months were chosen to provide reference distributions for semen parameters.
†This value is based on the strict criteria for assessing sperm morphology in studies using in vitro fertilization as an end point.

TABLE 216-9 DRUGS COMMONLY ASSOCIATED WITH ERECTILE DYSFUNCTION

ANTIDEPRESSANTS
Selective serotonin reuptake inhibitors Tricyclic antidepressants Monoamine oxidase inhibitors
ANTIHYPERTENSIVES
β-Blockers Verapamil Clonidine
CARDIAC DRUGS
Amiodarone Digoxin
DIURETICS
Thiazides Spironolactone
HISTAMINE RECEPTOR 2 ANTAGONISTS
Cimetidine Ranitidine
HORMONAL AGENTS
Corticosteroids Antiandrogens (flutamide, cyproterone acetate) Luteinizing hormone releasing hormone agonists (leuprolide, goserelin, triptorelin) or antagonists (degarelix, abarelix) 5α-reductase inhibitors (finasteride, dutasteride)

obesity, metabolic syndrome, hyperlipidemia, and type 2 diabetes mellitus), and men with mild erectile dysfunction should be assessed for cardiovascular disease, particularly when other risk factors are present.

CLINICAL MANIFESTATIONS AND DIAGNOSIS

The diagnosis of erectile dysfunction is based mainly on a detailed medical and sexual history of the patient and his partner when available. The history may reveal the underlying cause, such as medication use (Table 216-9), or other common disorders associated with erectile dysfunction. Physical examination should focus on genitourinary, cardiovascular, endocrine, and neurologic systems. Prostate examination is important because erectile dysfunction is commonly associated with symptomatic benign prostatic hyperplasia. Laboratory tests should include a morning serum testosterone level, and, if indicated, prostate-specific antigen, fasting glucose (or hemoglobin A_{1c}), and cholesterol levels. Specific diagnostic tests are rarely required.

TREATMENT

The first goal of treatment is to find any cause and to treat it.[30] Lifestyle interventions to reduce obesity and control glucose levels in patients with type 2 diabetes can improve erectile function.[31]

Medications

Symptoms usually can be effectively treated by the oral administration of a penile-selective phosphodiesterase-5 inhibitor (sildenafil, vardenafil, tadalafil), each of which is effective in about 60% of men.[A12] Patients with diabetes mellitus, spinal cord injuries, prostatic surgery, and pelvic irradiation also benefit, but with a somewhat lower response rate.

The usual starting dose of sildenafil is 50 mg, increasing in 25-mg increments up to 100 mg. Because of its mechanism of action, sildenafil is used on demand with recommended administration 20 to 60 minutes before intercourse. Two other potent phosphodiesterase-5 inhibitors (vardenafil and tadalafil) are widely used for the treatment of erectile dysfunction and appear to be equally effective. Vardenafil (5, 10, and 20 mg) has a relatively longer duration of action (4 to 6 hours), and tadalafil (10 or 20 mg) has an even longer duration of action (up to 36 hours). Randomized controlled trials showed that daily administration of tadalafil (5 mg) improves erectile function compared with on-demand treatment. Daily dosing of tadalafil is well tolerated and effective, so daily dosing, starting with 2.5 mg of tadalafil, may be an alternative to on-demand administration if intercourse is expected to be more frequent—for example, more than twice per week (Fig. 216-4). For patients after radical prostatectomy, early penile rehabilitation with phosphodiesterase type 5 inhibitors contributes to the recovery of erectile dysfunction.[A13]

In patients with a decreased libido and androgen deficiency (a serum testosterone concentration of less than 275 ng/dL and symptoms suggesting testosterone deficiency), sexual function responds moderately well to testosterone gel (see Table 216-5) if no contraindications to testosterone therapy are present. However, the addition of testosterone to sildenafil in partial responders does not further improve erectile dysfunction.

Phosphodiesterase type 5 inhibitors should not be administered with nitrates because the accumulation of cGMP may result in lowering of blood pressure and hypotension. Phosphodiesterase type 5 inhibitors also may interact with antihypertensive agents, including α-blockers, resulting in orthostatic hypotension.

The intraurethral prostaglandin E_1 suppository alprostadil (starting with 125 to 250 μg and increasing to a final dose of 500 to 1000 μg) is thought to work locally on the corpora cavernosa as a vasodilatory agent and is apparently successful in improving erectile function in 30 to 66% of cases. Other medications are under evaluation. For example, in patients with type 2 diabetes, cardiovascular disease, and erectile dysfunction, treatment with dulaglutide (a GLP-1 agonist) has been associated with a reduced incidence of moderate or severe erectile dysfunction.[32] Treatment with L-arginine and low-intensity shock wave therapy in combination with phosphodiesterase type 5 inhibitors also has shown potential efficacy.[33]

Intracavernosal Injection

Second-line treatment of erectile dysfunction involves intracavernosal injection with vasodilators such as prostaglandin E_1 (Alprostadil), either alone or in combination with other vasodilators (papaverine, phentolamine). These medications are injected into the cavernosal space with a 27- to 30-gauge needle in men who are refractory to oral agents. The main side effects of penile injections are pain and cavernosal fibrosis, which usually resolves after discontinuation of injections. Presence of tunica fibrosis may suggest early Peyronie disease, and local injections with vasodilators should be stopped. In such patients, a single intracavernosal injection of botulinum neurotoxin can improve erectile function in about 40 to 50% of patients.[A14]

Penile Prostheses

Surgical implantation of penile prostheses that include semi-rigid (malleable) and inflatable devices are the third line of treatment for men who prefer a permanent solution of their problem or for those who do not respond to other therapies.[34] The protheses and the surgical costs are high, and careful selection

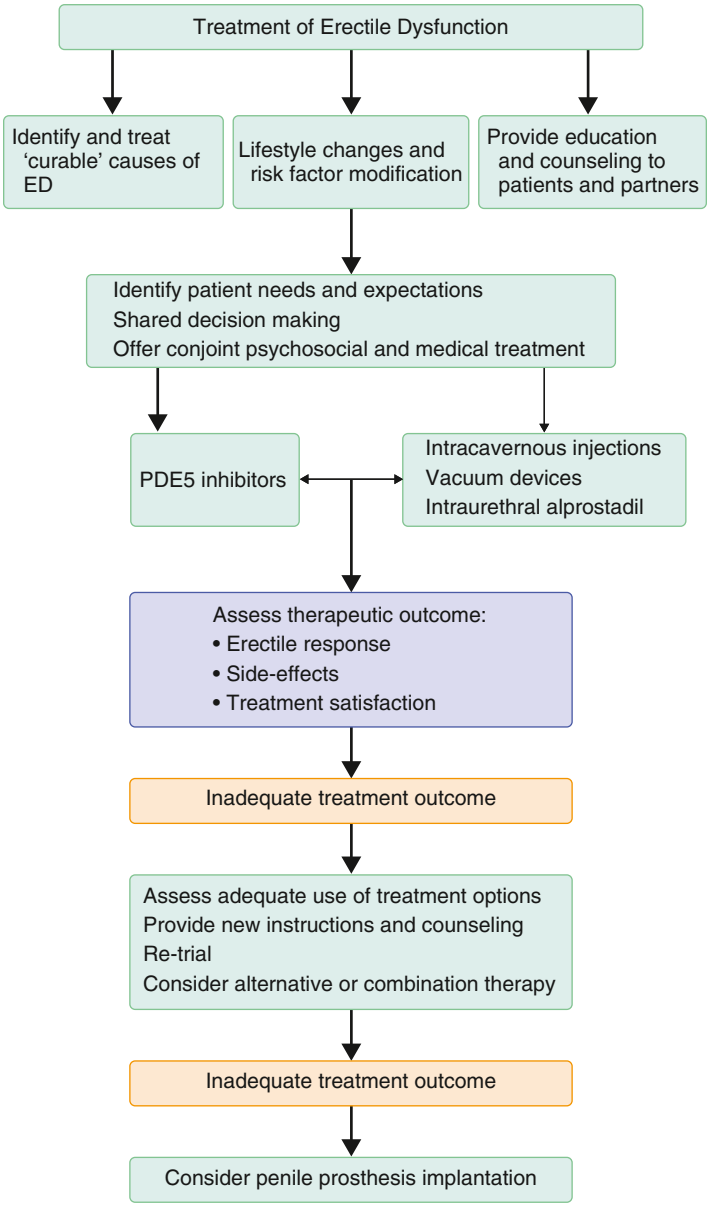

FIGURE 216-4. Treatment algorithm for erectile dysfunction (ED). PDE_5 = cyclic GMP phosphodiesterase 5. (Reprinted with permission from Hatzimouratidis K, Amar E, Eardley I, et al. Guidelines on male sexual dysfunction: erectile dysfunction and premature ejaculation. *Eur Urol*. 2010;57:804-814. 2015 update: http://uroweb.org/guideline/male-sexual-dysfunction/. Accessed March 26, 2015.)

of devices and patients is important for the best outcome. The intraoperative complications include corporal perforations as well as injury to the urethra, bladder, and bowel. Postoperative complications include pain, implant infection, and hematoma. The most common problem with the inflatable implants is mechanical failure in up to 10 to 20% of patients by 10 years. With the proper selection and preoperative preparation of the patient and his partner, long-term data show excellent patient and partner satisfaction.

EJACULATORY FAILURE AND IMPAIRED ORGASM

Ejaculatory insufficiency, which refers to absent or reduced seminal emission or impaired ejaculatory contraction, is usually associated with neurologic conditions and medication therapy. An anorgasmic state, which is a distressing but relatively uncommon condition in men, is characterized by a normal process of erection and ejaculation in the absence of the subjective sensation of pleasure initiated at the time of emission and ejaculation.

Premature ejaculation, which is the most common form of male sexual dysfunction, has a prevalence of 25 to 30%. It is defined as ejaculation occurring within approximately 1 minute of vaginal penetration before the person wishes it to occur on 75% of occasions for at least 6 months, and it associated with personal distress. The pathobiology of premature ejaculation is unknown. It may be associated with marked distress or interpersonal difficulty and is not a direct effect of substance abuse such as opiate withdrawal. The diagnosis is based mainly on sexual history and includes assessment of intravaginal ejaculatory latency time, perceived control, distress, and interpersonal difficulty.

TREATMENT

The first-line treatment for premature ejaculation is selective serotonin reuptake inhibitors (SSRIs; see Table 362-5) or a serotonin transporter inhibitor (e.g., dapoxetine 60 mg or clomipramine 15 mg as on-demand therapy)[A15] together with behavioral therapy and relationship counseling. SSRIs substantially improve symptoms, satisfaction with intercourse, and perceived control over ejaculations. The addition of a phosphodiesterase type 5 inhibitor to a SSRI has better effect than an SSRI alone in prolonging the latency time before ejaculation.[A16] Topical anesthetic creams can be used as alternatives.[A17] Oxytocin antagonists are also being studied for premature ejaculation.

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217 OVARIES AND PUBERTAL DEVELOPMENT

WILLIAM H. CATHERINO

DEFINITION

The ovaries or female gonads episodically release female gametes (oocytes or eggs) and secrete sex steroid hormones, principally estradiol and progesterone but also various androgens. Oocytes are released only during the adult reproductive years, when the secretion of sex steroids is also greatest, but the ovaries are physiologically active throughout life.

Sex steroids affect the growth, differentiation, and function of a variety of tissues and organs throughout the body, so abnormalities of the ovaries and of sex steroid secretion should be recognized by all physicians. A rational approach to the diagnosis and treatment of reproductive disorders in women requires an understanding of the functions of the ovaries and of their most important unit, the follicle, throughout life.

PATHOBIOLOGY

Ovarian Function in Childhood and Puberty

Physical Changes at Puberty

Puberty extends from the earliest signs of sexual maturation until the attainment of physical, mental, and emotional maturity. Pubertal changes in girls result directly or indirectly from maturation of the hypothalamic-pituitary-ovarian unit (Chapter 204).[1] Human puberty is characterized hormonally by a resetting of the negative gonadal steroid feedback loop, the establishment of new circadian and ultradian (frequent) gonadotropin rhythms, and the acquisition in the female of a positive estrogen feedback loop that controls the menstrual cycle as interdependent expressions of the gonadotropins and ovarian steroids. In girls, pubertal development generally occurs between 7 and 14 years of age. The age at onset and the rate of progress through puberty are variable and depend on genetic, socioeconomic, nutritional, physical, and psychological factors. Racial differences also appear to be relevant for the onset of pubertal development. For example, in the United States, pubertal development begins earlier in Black girls than in White girls.

Physical changes occur in an orderly sequence during a definite time frame in puberty (Fig. 217-1). Breast budding in girls is usually the first pubertal change, followed shortly by the appearance of pubic hair, with menarche occurring late in pubertal development. The time from breast budding (mean age of 10.0 years in White girls and 8.9 years in Black girls) to menarche is 2 years. Breast development results from increasing ovarian production of estrogen, and pubic and axillary hair results from increasing androgen production. Estrogens are required for the growth of pubic hair as well.

The ovarian sex steroids join with growth hormone and adrenal androgens to produce the adolescent growth spurt.[2] Peak growth velocity is achieved relatively early, with little growth observed after menarche. Estrogens are necessary for the normal formation, mineralization, and maturation of bones. Estrogen, not testosterone, is the primary hormone that mediates pubertal bone growth in both males and females, and more than 50 genes play roles in determining final adult height. Well-established standards exist for determining whether bone age is appropriate for chronologic age, typically by examining radiographs of the bones of the wrist. Estrogen deficiencies retard, and excesses advance, bone age in relation to chronologic age.

Lean body mass, skeletal mass, and body fat are equal in prepubertal boys and girls, but by maturity, women have twice as much body fat as men but have less lean body mass and skeletal mass as a result of differences in sex steroids.

Hormonal Changes

The ovaries function even in early childhood. Levels of luteinizing hormone (LH) and follicle-stimulating hormone (FSH) are normally low, and these levels increase if the ovaries are removed before puberty, just as they do later in life, thereby indicating the exquisite sensitivity of the hypothalamic-pituitary unit to extremely low circulating sex steroid levels. As puberty nears, a progressive decrease in the sensitivity of the hypothalamic-pituitary unit to sex steroids leads to the increased secretion of pituitary gonadotropins, stimulation of sex steroid output, and development of secondary sex characteristics. Increased secretion of both LH and FSH initially occurs at night with sleep and is associated with increased estradiol secretion the next morning (Fig. 217-2). As is true for most hormones, LH and FSH are secreted in an episodic or pulsatile rather than a continuous fashion (Chapter 205). Later in puberty, secretion of LH and FSH is increased throughout the 24-hour period, except during the early follicular phase, when nighttime increases still occur. Basal levels of estradiol, the major estrogen secreted by the ovaries, increase throughout puberty. A "critical body mass" may be required for positive estrogen feedback and ovulation. During the first 2 years after menarche, up to 90% of menstrual cycles may be anovulatory because of a delay in synchronization of the hypothalamic-pituitary-ovarian axis.

Ovarian Cysts and Adnexal Masses

Follicular growth, resulting in an ovarian cyst, is an expected finding during the reproductive years. However, palpable masses before or after the reproductive years require thorough investigation to exclude various cancers (Chapter 184). A pelvic mass during the reproductive years could represent an ovarian cyst, but could also represent an endometrioma, ovarian fibroma, intrauterine pregnancy, ectopic pregnancy (Chapter 218), uterine fibroid (Chapter 184), tubo-ovarian abscess (Chapter 264), peritubal cyst, or less likely, ovarian or tubal cancer.[3] History, physical examination, pregnancy test, and pelvic ultrasound would assist in focusing the differential diagnosis. CA-125 during the reproductive years is nonspecific and should not be used to exclude ovarian cancer (Chapter 184). Incidentally detected adnexal lesions are found in approximately 4 to 5% of women undergoing computed tomography (CT) scan and in 9 to 10% undergoing ultrasound. The overwhelming majority of

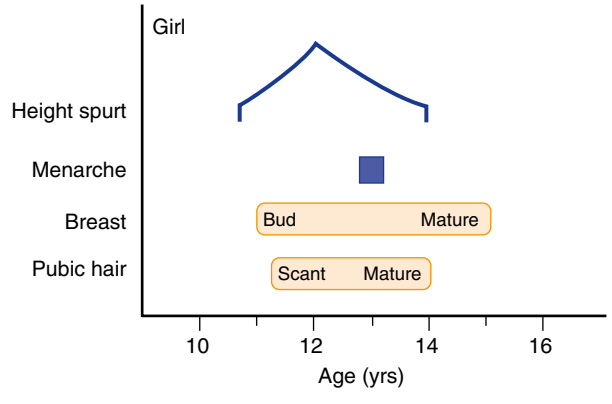

FIGURE 217-1. Temporal sequence of events for the "average" girl during puberty. (From Rebar RW. Practical evaluation of hormonal status. In: Yen SSC, Jaffe RB, Barbieri RL, eds. *Reproductive Endocrinology: Physiology, Pathophysiology, and Clinical Management*, 4th ed. Philadelphia: WB Saunders; 1999:710.)

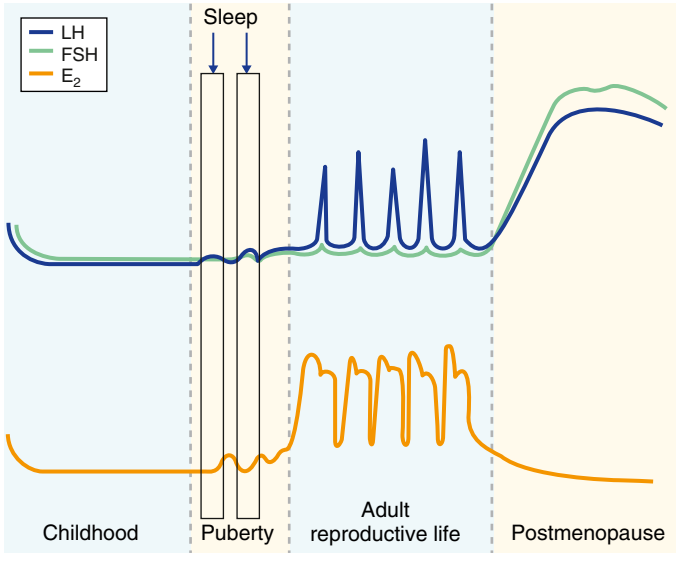

FIGURE 217-2. The changing patterns of luteinizing hormone (LH), follicle-stimulating hormone (FSH), and estradiol (E_2) concentrations in peripheral blood throughout the life of a woman. Not shown is the fact that both LH and FSH are secreted in a pulsatile fashion. The pubertal period has been expanded to illustrate the sleep-associated increases in LH and FSH followed by morning increases in E_2 that are observed during puberty. (Reprinted with permission from Endocrine and Metabolism Continuing Education Quality Control Program, 1982. Copyright American Association for Clinical Chemistry Inc.)

ABSTRACT

Pubertal changes in girls result directly or indirectly from maturation of the hypothalamic-pituitary-ovarian axis. Physical changes occur in an orderly sequence during a definite time frame in puberty. Abnormalities of pubertal development fall into four major categories: (1) precocious puberty; (2) delayed (or interrupted) puberty; (3) asynchronous pubertal development; and (4) heterosexual pubertal development (the most common of which is polycystic ovary syndrome). Diagnostic testing and treatment are discussed.

KEYWORDS

pubertal changes
precocious puberty
delayed puberty
asynchronous pubertal development
polycystic ovary syndrome

these masses are benign, and magnetic resonance imaging (MRI) can decrease the rates of resection or oophorectomy for benign lesions.

ABERRATIONS IN PUBERTAL DEVELOPMENT

Abnormalities of pubertal development[4,5] can be divided into four major categories: precocious puberty, delayed (or interrupted puberty), asynchronous pubertal development, and heterosexual pubertal development (Table 217-1).

PRECOCIOUS PUBERTY

DEFINITION

Precocious puberty represents any pubertal changes before age 9 years in Black girls and before 9 years in White, Asian, and Hispanic girls. Precocious development is isosexual when it is common to the phenotypic sex of the individual and heterosexual when the development is characteristic of the opposite sex. True or central precocious puberty is due to premature maturation of the hypothalamic-pituitary axis. In the absence of increased hypothalamic-pituitary activity, precocious pseudopuberty exists.

EPIDEMIOLOGY

The overall incidence of precocious puberty is estimated to be 1 in 5000 to 10,000 children. About 10 times as many girls as boys are affected.

PATHOBIOLOGY

As many as 20% of individuals with true precocious puberty have tumors of the ovaries (Chapter 184) or adrenal glands (Chapter 208) or one of several organic brain diseases, including tuberous sclerosis (Chapter 385), neurofibromatosis (Chapter 385), encephalitis (Chapter 383), meningitis (Chapter 381), vascular malformations (Chapter 377), and hydrocephalus. When precocious development is isosexual, the cause can be central (true precocious puberty) or peripheral, in which case it is considered gonadotropin-releasing hormone (GnRH)–independent precocious puberty or precocious pseudopuberty. Heterosexual precocity in an apparent prepubertal female is almost always due to congenital adrenal hyperplasia or to an androgen-secreting adrenal or ovarian neoplasm. Only rarely must another disorder of sexual differentiation be considered (Chapter 214).

Various clones of cells in the endocrine glands of girls with McCune-Albright syndrome function autonomously with respect to the production of cyclic adenosine monophosphate as a consequence of a mutation within exon 8 of the G protein α–subunit. This same mutation probably accounts for the bone lesions and café au lait hyperpigmentation. Other endocrine cells may be similarly affected and lead to pituitary adenomas (usually secreting growth hormone), hyperthyroidism, and, rarely, adrenal hyperplasia.

Studies on the etiologic causes for precocious puberty are ongoing,[6] but the most consistent genetic correlates are mutations in the Makorin ring finger protein 3 (MKRN3, function unknown), kisspeptin, the kisspeptin receptor, and the Delta-like homolog 1 (DLK1, a kisspeptin regulator). Kisspeptin and its receptor GPR54 are essential regulators of GnRH-induced gonadotropin secretion and pubertal onset. Activation results in stimulation of the HPO axis, and elevated kisspeptin levels are associated with precocious puberty. Additionally, kisspeptin loss-of-function mutations result in normosmic idiopathic hypogonadotropic hypogonadism.

Excessive androgens produced endogenously by abnormal fetal adrenal glands in utero or diffusing across the placenta to the fetus from the mother can virilize the external genitalia and result in female pseudohermaphroditism.

TABLE 217-1 ABERRATIONS OF PUBERTAL DEVELOPMENT

PRECOCIOUS DEVELOPMENT

- Isosexual precocity
  - Incomplete sexual precocity
    - Premature thelarche
    - Premature pubarche
    - Premature adrenarche
  - True (central) precocious puberty
    - Idiopathic (constitutional)
    - Due to central nervous system lesions
    - Primary hypothyroidism
    - Silver-Russell syndrome
  - Precocious pseudopuberty (of peripheral origin)
    - Ovarian neoplasms
    - Adrenal neoplasms
    - Iatrogenic (estrogen-containing preparations)
    - Human chorionic gonadotropin–secreting neoplasms distinct from central nervous system and ovarian tumors
    - McCune-Albright syndrome
- Heterosexual precocity
  - Ovarian neoplasms
  - Adrenal neoplasms
  - Congenital adrenal hyperplasia
  - Other rare disorders of sexual differentiation

DELAYED PUBERTAL DEVELOPMENT*

- Anatomic abnormalities
  - Müllerian agenesis or dysgenesis (Rokitansky-Küster-Hauser syndrome)
  - Distal genital tract obstruction
    - Transverse vaginal septum
    - Imperforate hymen
    - Vaginal agenesis
- Hypergonadotropic hypogonadism (FSH >30-40 mIU/mL)
  - Gonadal dysgenesis
    - With stigmata of Turner syndrome
    - Pure (46,XX or 46,XY)
    - Mixed
  - Ovarian failure with normal ovarian development
    - Genetic disorders
    - Autoimmune disorders
    - Gonadotropin receptor or postreceptor defects (resistant ovary or Savage syndrome)
    - Enzymatic defects (17α-hydroxylase deficiency, galactosemia)
    - Physical causes: irradiation, chemotherapeutic agents, viral agents
    - Idiopathic
- Hypogonadotropic or normogonadotropic hypogonadism (LH and FSH <10 mIU/mL, or LH and FSH 6-25 mIU/mL with at least one being >10 mIU/mL)
  - Isolated gonadotropin deficiency
    - In association with midline defects (Kallmann syndrome)
    - Independent of associated disorders
  - Neoplasms of the hypothalamic-pituitary axis
    - Craniopharyngiomas
    - Pituitary tumors
    - Others
  - Infiltrative processes (Langerhans-type histiocytosis)
  - Idiopathic hypopituitarism
  - "Hypothalamic" forms of amenorrhea
    - Psychogenic
    - Exercise associated
    - Associated with malnutrition
    - Anorexia nervosa
  - Miscellaneous disorders
    - Prader-Labhart-Willi syndrome
    - Laurence-Moon-Bardet-Biedl syndrome
    - Primary hypothyroidism
  - Constitutional delayed puberty

ASYNCHRONOUS PUBERTAL DEVELOPMENT

- Incomplete forms of androgen insensitivity
- Complete forms of androgen insensitivity

HETEROSEXUAL PUBERTAL DEVELOPMENT

- Polycystic ovary syndrome
- Congenital adrenal hyperplasia (female pseudohermaphroditism)
  - 21-Hydroxylase deficiency
  - 11β-Hydroxylase deficiency
  - 3β-ol-Hydroxysteroid dehydrogenase deficiency
- Male pseudohermaphroditism due to 5α-reductase deficiency
- Male pseudohermaphroditism due to partial androgen insensitivity
- Mixed gonadal dysgenesis
- Androgen-producing neoplasms
  - Ovarian
  - Adrenal
- Cushing syndrome

*No development by age 13 yr, absence of menarche by age 15 yr, or passage of ≥5 yr from breast budding without menarche.
FSH = follicle-stimulating hormone; LH = luteinizing hormone.

CLINICAL MANIFESTATIONS

The temporal sequence in which the signs and symptoms of sex steroid hormone excess appear is most important.[7] Incomplete isosexual precocious puberty indicates premature development of only a single pubertal feature. If breast budding occurs before age 8 years in the absence of any other development, the diagnosis may be premature thelarche. Premature thelarche is believed to be due to transient increases in the secretion of estrogen or increased breast sensitivity to the small quantities of circulating estrogens present before puberty. Simple ovarian cysts may be present in some girls with this disorder and may be due in some cases to the same genetic abnormality found in girls with McCune-Albright syndrome (Chapters 205 and 229). If pubic or axillary hair develops alone and persists, premature pubarche and adrenarche must be considered. These abnormalities are associated with slight increases in adrenal androgen secretion but not with clitorimegaly or other signs of virilization.

DIAGNOSIS

The nearer pubertal development begins to the mean age of the onset of puberty, the less likely it is to have a pathologic basis. Some clinicians believe evaluation is warranted only if pubertal development begins before age 7 years in White girls and 6 years in Black girls. A compromise may involve careful screening by history and physical examination of girls with early-onset puberty, looking for central nervous system (CNS) symptoms, behavioral concerns, and any other abnormal findings that might warrant further evaluation. Careful questioning of the patient and her parents may indicate the inadvertent ingestion or absorption of sex steroids (iatrogenic or factitious). The physical examination may also provide critical information about the cause of the precocious development. Cutaneous café au lait spots, facial asymmetry, polyostotic fibrous dysplasia and other skeletal abnormalities, cranial nerve deficits, and multiple ovarian follicular cysts suggest McCune-Albright syndrome (Chapters 205 and 229) in a girl with precocious development.

Abdominal and rectal examination may reveal a mass, thereby suggesting an adrenal or ovarian tumor. Because palpable ovarian cysts may rarely develop before ovulation in true precocious puberty, the presence of a mass does not confirm the diagnosis of precocious pseudopuberty.

When vaginal bleeding is the only sign of development, the diagnosis of sexual precocity should be suspect. Common causes of bleeding in this age group include irritation from a vaginal infection or foreign body, sexual assault, prolapse of the urethral meatus, and ingestion of estrogen-containing medications (most commonly, oral contraceptive preparations). A vaginal or cervical neoplasm is also a rare possibility. Thus vaginal bleeding requires a vaginal examination, which is often best performed with the patient under anesthesia, before further evaluation is undertaken.

It is important to examine the external genitalia carefully, because congenital adrenal hyperplasia is usually associated with some degree of sexual ambiguity. In female pseudohermaphroditism, the extent of virilization varies from only an enlarged clitoris to sexual ambiguity sufficient to make gender assignment difficult.

Excessive maternal androgen secretion, typically from an ovarian or adrenal neoplasm, can lead to virilization of a female fetus. This abnormality occurs very rarely because of the great capacity of the placenta to aromatize naturally occurring androgens to estrogens. Virilization of a female fetus is much more likely to occur if a pregnant woman has ingested a synthetic steroid preparation with androgenic properties, because synthetic compounds generally cannot be aromatized.

Excessive androgen secretion beginning in utero is usually associated with defective cortisol synthesis. As a consequence, pituitary corticotropin secretion is increased, thereby resulting in congenital adrenal hyperplasia and excessive androgen secretion. The three different enzyme defects in the steroidogenic pathway that can lead to virilization of the female fetus are described in Chapter 214. The most common form of congenital adrenal hyperplasia is 21-hydroxylase deficiency, which accounts for the disorder in more than 90% of affected individuals. The defect may vary from partial to complete deficiency of the enzyme.

Diagnostic Tests

The evaluation begins by obtaining blood levels of FSH, LH, estradiol, human chorionic gonadotropin, and thyroid-stimulating hormone.[8] Additional testing may involve a bone age, brain MRI, ultrasound of the abdomen and pelvis, and a 17-hydroxyprogesterone level.

Measurement of Peptide and Steroid Hormones

Levels and ratios of FSH and LH typical of pubertal as opposed to prepubertal girls help in the diagnosis of true precocious puberty. Excessively high circulating levels of estrogen (>100 pg/mL estradiol) suggest an estrogen-producing neoplasm or a functioning ovarian cyst. High levels of serum testosterone suggest an ovarian source of excess androgen in girls with heterosexual development, whereas increased levels of dehydroepiandrosterone or its sulfate (the principal precursors of 17-ketosteroids) suggest an adrenal source. High levels of serum 17-hydroxyprogesterone imply congenital adrenal hyperplasia secondary to 21-hydroxylase deficiency, whereas high levels of serum 11-deoxycortisol imply an 11β-hydroxylase deficiency (Chapter 214). In congenital adrenal hyperplasia, these hormone levels should decrease promptly after the oral administration of suppressive doses of dexamethasone. Suppression in response to exogenous corticoids occurs much less consistently in individuals with adrenal cortical adenomas and carcinomas (Chapter 208) and rarely in those with ovarian androgen-secreting neoplasms. Increased levels of immunoreactive human chorionic gonadotropin (HCG) may suggest an HCG-secreting neoplasm, most commonly an ovarian teratoma or dysgerminoma. In such cases, the HCG, which is antigenically and biologically similar to LH, stimulates ovarian steroid secretion and pseudopubertal development. Because even specific LH immunoassays show some cross-reactivity with HCG, values for serum LH may be elevated in individuals with HCG-secreting tumors. Immunoreactive HCG is always elevated in the presence of such tumors.

Administration of an exogenous GnRH agonist to stimulate endogenous LH secretion is useful, with an LH level >5 mIU/mL as confirmation of gonadotropin-dependent disease rather than gonadotropin-independent disease. Furthermore, an LH/FSH ratio >0.66 can be used to distinguish progressive from nonprogressive precocious puberty. This test is regarded as the "gold standard" for the diagnosis of central precocious puberty related to the hypothalamic-pituitary-ovarian axis.[9]

Additional Studies

Imaging of the CNS is the most important test if true central precocious puberty is present or if there are any neurologic deficits. Because of the seriousness of intracranial lesions, girls with precocious puberty must have radiographic evaluation of the CNS, most effectively by MRI. At least 75% of girls with true precocious puberty, however, have precocious puberty with no specific idiopathic or constitutional cause identified.

Ultrasonography of the adrenals and ovaries or computed tomography (CT) of the adrenals may be indicated to confirm clinically suspected abnormalities based on endocrine testing. In girls with ovarian or adrenal neoplasms, the tumor can almost always be localized radiographically. Catheterization of the ovarian and adrenal veins and measurements of the effluent steroids from each gland should be pursued only when CT, ultrasonography, or MRI fails to identify a suspected neoplasm.

Radiographic estimation of bone age is also routinely indicated. The results serve as a useful baseline to assess the results of treatment.

TREATMENT

Premature pubarche and adrenarche without puberty require no treatment, and affected girls typically begin true puberty at the usual age. Careful follow-up is required to distinguish these disorders from true precocious puberty.

Treatment of precocious puberty (Table 217-2) should be initiated promptly so that the patient's ultimate height is not compromised as a result of sex steroid–induced premature epiphyseal closure. Prompt treatment also can prevent or attenuate emotional consequences in the patient and her parents.[10,11]

In girls who present before age 6 years with central precocious puberty, GnRH analogues (see Table 217-2), which are now the preferred therapy for suppressing gonadotropin secretion, may prevent early bone maturation and increase ultimate adult height. The preferred duration of treatment is uncertain and should be tailored to patient goals.

In girls who are between 6 and 8 years of age, the indications for treatment are less clear. Some data suggest that antiandrogens (e.g., spironolactone 50 to 200 mg every other day) or oral contraceptive pills (Table 220-2) in combination with metformin (500 to 2000 mg daily) may improve hirsutism and oligomenorrhea in the teenage years.[12] These analogues are not effective in children with McCune-Albright syndrome, in whom aromatase inhibitors (e.g., letrozole 2.5 mg daily) show promise. Aqueous depot medroxyprogesterone acetate (100 to 200 mg intramuscularly every 2 to 4 weeks) also may be used to suppress gonadotropin secretion. It does not always prevent premature epiphyseal closure and the resultant short stature, but it may be helpful in regulating disrupted menses.

Individuals with CNS or steroid-secreting neoplasms must undergo therapy appropriate for the particular lesion. Girls with congenital adrenal hyperplasia are appropriately managed with glucocorticoids (plus mineralocorticoids when indicated), as outlined in Chapter 214.

DELAYED PUBERTY

Delayed (or interrupted) puberty is defined as the absence of any secondary sex characteristics by age 13 years, the absence of menarche by age 16 years, or the passage of 5 years or more from breast budding to menarche.[13] More than 50% of cases represent constitutional delay and resolve spontaneously.

TABLE 217-2 TREATMENT OF PRECOCIOUS PUBERTY

CENTRAL PRECOCIOUS PUBERTY
Treatment Time 1 month: 0.2-0.3 mg/kg leuprolide acetate IM 3 months: 11.25-30 mg leuprolide acetate IM 6 months: 45 mg leuprolide acetate SQ 6 months: 22.5 mg triptorelin acetate IM 12 months: 50 mg histrelin implant SQ
PERIPHERAL PRECOCIOUS PUBERTY
Letrozole 2.5 mg/day as first line, follow-up with endocrinologist

IM = intramuscularly; SQ = subcutaneously.

PATHOBIOLOGY

Ovarian failure, congenital absence of the uterus and vagina, and constitutional delay, or delayed but otherwise normal progression through puberty, constitute about two thirds of cases in large series. Congenital malformations of the müllerian ducts occur in 0.02% of all women. Most do not cause amenorrhea, and many do not impair reproduction. The anomalies associated with amenorrhea vary in severity from an imperforate hymen to complete aplasia of all müllerian duct derivatives, with vaginal atresia. Although aplasia generally involves all the müllerian duct derivatives, defects may involve only a single part of the distal genital tract. Family aggregates of the most common disorders of müllerian differentiation in females—müllerian aplasia and incomplete müllerian fusion—do occur and are best explained by polygenic or multifactorial inheritance. The *HOX* genes, a family of regulatory genes that encode transcription factors, are essential for proper development of the müllerian tract.

CLINICAL MANIFESTATIONS AND DIAGNOSIS

Because of the anxiety generated by delayed puberty, some evaluation is always indicated regardless of the age of the patient.

To evaluate delayed puberty, initial studies include FSH, LH, and estradiol levels. Primary ovarian failure is diagnosed if the FSH level is >20 mIU/mL.

When pubertal development progresses normally but menstruation does not begin, an abnormality in the genital tract should be considered. A müllerian duct anomaly is suggested by (1) normal levels of serum gonadotropins and steroids, (2) an abnormal outflow tract, (3) a history of cyclic abdominal pain with or without a palpable mass, and (4) normal development of secondary sex characteristics. Normal ovarian function still induces endometrial growth and shedding after menarche if the uterus is normal. In the absence of a normal outflow tract, however, the menstrual effluent is retained and may or may not escape into the abdominal cavity. Free in the abdominal cavity, the effluent may cause endometriosis. Constrained to the uterine cavity, the effluent causes hematometra and a large abdominal mass.

In the absence of a mass or cyclic pain, karyotyping is indicated in girls with evidence of an abnormal genital tract to exclude disorders of sexual differentiation (Chapter 214).[14] Such disorders, however, almost never occur together with completely normal pubertal development. In girls with a normal karyotype and a genital tract anomaly, examination under anesthesia and diagnostic laparoscopy should be undertaken to delineate the extent of the defect.

Other causes of delayed puberty and primary amenorrhea are the same as those that cause amenorrhea in older women (Chapter 218).[15] When no apparent cause of delayed development is found, constitutional delayed puberty must be entertained as a diagnosis of exclusion. A strong family history of delayed maturation supports this presumption.

TREATMENT

For constitutional delayed puberty, small doses of estrogen (starting with 5 µg of ethinyl estradiol or 0.3 mg of conjugated estrogen) can be administered to induce some pubertal development based upon the patient's wishes. However, this treatment may obscure a pathologic cause of the delay and may compromise linear growth and ultimate height.

In patients with an imperforate hymen or transverse vaginal septum only, surgical restoration can be accomplished relatively simply. Attempts to provide an outflow tract for the uterus should not be undertaken if there is no cervix because of the high risk of recurrent pelvic infection. Even with a functional cervix, the construction of an outflow tract that permits successful pregnancy is unlikely. A functional vagina can be constructed surgically or by the daily use of ever-larger dilators. To prevent shrinkage and scarring, surgery should be deferred until the patient is willing to use dilators on a daily basis or she is about to become sexually active.

ASYNCHRONOUS PUBERTAL DEVELOPMENT

Asynchronous pubertal development occurs when there is deviation from the normal pattern of pubertal development. Asynchronous pubertal development is characteristic of male pseudohermaphroditism due to androgen insensitivity, especially complete testicular feminization. This syndrome of androgen insensitivity is inherited as either an X-linked recessive trait or a sex-limited autosomal dominant trait. Despite the presence of intra-abdominal or inguinal testes, there is complete failure of virilization. Affected individuals develop breasts (but only to Tanner stage 3) and a typical female habitus with unambiguous female external genitalia, but with the absence of internal female structures and generally only a foreshortened, blind-ending vagina. Little or no pubic and axillary hair develops. The karyotype is 46,XY in these individuals. Circulating testosterone levels are equivalent to or higher than those found in normal men, LH levels are elevated, and FSH levels are normal compared with those in menstruating women. For a more detailed description, see Chapter 214.

HETEROSEXUAL PUBERTAL DEVELOPMENT

Heterosexual pubertal development occurs at the appropriate time but has some features characteristic of the opposite sex.

POLYCYSTIC OVARY SYNDROME

Polycystic ovary syndrome (PCOS), which is by far the most common cause of heterosexual pubertal development, is associated with the development of some secondary sex features characteristic of males at the normal age of puberty.[16] Many girls who develop PCOS have alterations in insulin signaling.

Feminization occurs in affected girls, who develop normal breasts and a typical female habitus but also have features of masculinization (in contrast, girls with congenital adrenal hyperplasia generally show little, if any, female development at puberty). A heterogeneous syndrome, PCOS typically begins at or near puberty with hirsutism and irregular menses from the time of menarche. Many girls who develop PCOS are overweight in childhood, and obesity worsens the phenotype. Menarche may be delayed in a few cases, so young women may present with primary amenorrhea. Basal LH levels tend to be somewhat elevated in perhaps two thirds of cases, and circulating levels of all androgens are moderately elevated.[17] Some degree of insulin resistance is commonly present as well, and hypercholesterolemia may predispose to cardiovascular disease later in life. PCOS is discussed more completely in Chapter 218.

CONGENITAL ADRENAL HYPERPLASIA

Congenital adrenal hyperplasia is generally diagnosed before puberty. Heterosexual precocious pseudopuberty or phenotypical androgenization due to adrenal tumors in females is common.[18] However, if the defect is mild and changes to the external genitalia are minimal, masculinization may occur at the expected age of puberty. This attenuated or nonclassic form of 21-hydroxylase deficiency seems to occur in families with a strong history of hirsutism. Affected girls generally have some defeminization, with flattening of the breasts, severe hirsutism, relatively short stature, and obesity. For a more detailed description, see Chapter 214.

MIXED GONADAL DYSGENESIS

Mixed gonadal dysgenesis is a rare disorder of asymmetrical gonadal development, with a germ cell tumor or a testis on one side and an undifferentiated streak, rudimentary gonad, or no gonad on the other. Affected individuals generally have a mosaic karyotype, with 45,X/46,XY being the most common.

The clinical presentation varies based upon chromosomal alterations.[19] Most individuals are reared as girls, in whom virilization occurs at puberty; some may note breast development as well. Short stature and other stigmata associated with a 45,X karyotype in Turner syndrome are less common in patients with tumors than in patients with testes. Gonadectomy is indicated in all individuals with a Y chromosome to eliminate the increased neoplastic potential of such dysgenetic gonads and in all patients in whom virilization occurs at puberty to remove the source of androgen. Estrogen replacement therapy (ethinyl estradiol 5 µg daily or conjugated estrogen 0.3 mg daily to start) is warranted after gonadectomy. Other causes of male pseudohermaphroditism associated with heterosexual pubertal development are described in Chapter 214.

OTHER CAUSES

An androgen-producing adrenal neoplasm or Cushing syndrome (Chapter 208) may occur rarely during the pubertal years and lead to heterosexual development.

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218 REPRODUCTIVE ENDOCRINOLOGY AND INFERTILITY

WILLIAM H. CATHERINO

THE NORMAL MENSTRUAL CYCLE

Endometrium

The endometrium undergoes histologic and cytologic changes that culminate with menstrual bleeding when the corpus luteum ceases to secrete progesterone (Fig. 218-1). The basal layer of the endometrium then regenerates the superficial layer of compact epithelial cells that line the uterine cavity and an intermediate layer of spongiosa. Endometrial glands proliferate under the influence of estrogen, and the mucosa thickens. In the luteal phase, the glands become coiled and secretory, with increased vascularity and edema of the stroma. When estradiol and progesterone decline, the stroma becomes edematous, endometrial and blood vessel necrosis occurs, both the superficial epithelial cells and the spongiosa are shed, and bleeding ensues. Local release of prostaglandins may initiate vasospasm, which results in ischemic necrosis, as well as the uterine contractions that accompany menstrual flow. Prostaglandin synthetase inhibitors can relieve menstrual cramping. The histologic changes are characteristic, so endometrial biopsies can identify the stage of the cycle and assess the endometrium's response to gonadal steroids.

Cervix and Cervical Mucus

During the follicular phase, cervical vascularity, congestion, and edema increase as a result of estrogen. Cervical mucus increases in quantity (10- to 30-fold) and in elasticity. So-called ferning becomes prominent. Progesterone stimulates the thickening of cervical mucus, the loss of elasticity, and loss of the ability to fern.

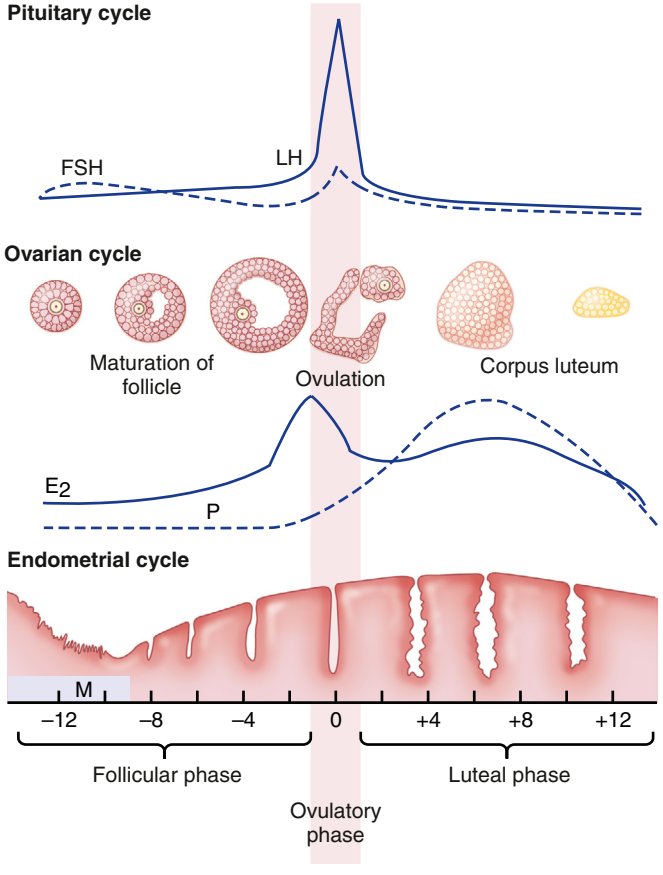

FIGURE 218-1. **The idealized cyclic changes observed in gonadotropins, estradiol (E_2), progesterone (P), and uterine endometrium during the normal menstrual cycle. The data are centered on the day of the luteinizing hormone (LH) surge (day 0). Days of menstrual bleeding are indicated by M. FSH = follicle-stimulating hormone; LH = luteinizing hormone. (From Endocrine and Metabolism Continuing Education Quality Control Program, 1982. Copyright American Association for Clinical Chemistry, Inc.)**

Vagina

Low estrogen is associated with pale, thin vaginal epithelium. As estrogens rise, the number of cornified epithelial cells increases. Subsequently, progesterone decreases the percentage of cornified cells and increases the number of precornified intermediate cells, thereby resulting in increased cellular debris and clumping of shed desquamated cells. Histologic changes in the vaginal epithelium are sensitive indicators of estrogen status.

Ovary

The ovaries produce a single dominant graafian follicle that grows and develops to the preovulatory stage during the follicular phase. This process is brought about by combined action of follicle-stimulating hormone (FSH) and luteinizing hormone (LH) on the granulosa cells that comprise the follicle wall to increase estradiol biosynthesis. The LH surge acts on the preovulatory follicle to cause the secretion of the mature fertilizable oocyte. After ovulation, the follicle wall transforms into the corpus luteum, which produces progesterone and estradiol. If implantation does not occur, the corpus luteum undergoes luteolysis and stops hormone production. In the late luteal phase, another dominant follicle develops, and a new menstrual cycle begins.

Chronology of Folliculogenesis

The preovulatory follicle begins its development when a primordial follicle is recruited into the pool of growing follicles. The two major phases of folliculogenesis are the preantral (gonadotropin-independent) and the antral (gonadotropin-dependent) phases (see Fig. 218-1). The first phase is characterized by growth of the oocyte and proliferation of the granulosa cells. Preantral folliculogenesis, which proceeds slowly, requires at least 300 days. During the second phase, granulosa and theca cells proliferate, and the antrum enlarges. The graafian follicle increases relatively rapidly as it develops. The mature graafian follicle that will ovulate requires 40 to 50 days to complete the antral phase.

Selection

The dominant follicle is selected from a cohort at the end of the luteal phase of the previous menstrual cycle. The selected follicle requires 20 days to develop to the ovulatory stage.

Shortly after the midluteal phase of the cycle, the granulosa cells show a sharp increase in the rate of mitosis. The first indication of selection is that the granulosa cells continue dividing at a high rate. As a consequence of the high sustained mitotic rate and the progressive accumulation of follicular fluid, the dominant follicle undergoes remarkable growth. The increase in plasma FSH levels that begins at the end of luteal phase and continues through the early follicular phase evokes follicle selection. The concentration of FSH in the follicular fluid of the healthy (dominant) follicle increases but does not increase in the nondominant atretic follicles. More than 99.9% of all follicles are not selected and undergo atresia.

Ovulation

At midpoint in the menstrual cycle, the preovulatory surges of LH and FSH act on the preovulatory follicle to initiate the events leading to ovulation (see Fig. 218-1). The LH surge induces meiotic maturation, a process that converts the oocyte into a fertilizable egg arrested at the second meiotic metaphase. During meiotic maturation, the granulosa cells next to the oocyte are stimulated by FSH to undergo cumulus expansion (Fig. 218-2). This step is a prerequisite for the oocyte's pickup and transport by the oviduct. The LH surge also stimulates production of proteolytic enzymes in the vicinity of the presumptive stigma. This process requires the LH stimulation of progesterone and prostaglandins, which are obligatory for stigma formation. After 36 hours, the fertilizable egg and surrounding cumulus cells are secreted through the stigma (see Fig. 218-1). A serum progesterone level higher than 3 ng/mL at 1 week before menses is probably diagnostic of ovulation.

Luteogenesis

Ovulation changes the granulosa and theca cells of the ovulated follicle to increase their production of progesterone and estradiol during the first week of the luteal phase. This event, termed *luteinization*, is important for the formation and development of a secretory endometrium. Three major

ABSTRACT

With an understanding of the biologic basis of the normal menstrual cycle, the diagnosis and management of abnormalities during the reproductive years can be addressed. Dysmenorrhea, endometriosis, premenstrual syndrome, abnormal uterine bleeding, and sexual dysfunction are common clinical syndromes that must be approached systematically. Amenorrhea can be due to anatomic factors (disorders of sexual differentiation, intrauterine adhesions, gestational trophoblastic disease), chronic anovulation (CNS-hypothalamic-pituitary dysfunction, inappropriate steroid feedback as in polycystic ovary syndrome, thyroid or adrenal disorders), or ovarian "failure" (menopause, genetic abnormalities, physical and environmental factors, autoimmune disease). Multiple male factors and female factors can cause infertility.

KEYWORDS

infertility
endometrium
gonadotropin
embryo
ovulation
menstrual cycle
dysmenorrhea
endometriosis
premenstrual syndrome
amenorrhea
polycystic ovary syndrome
sexual dysfunction

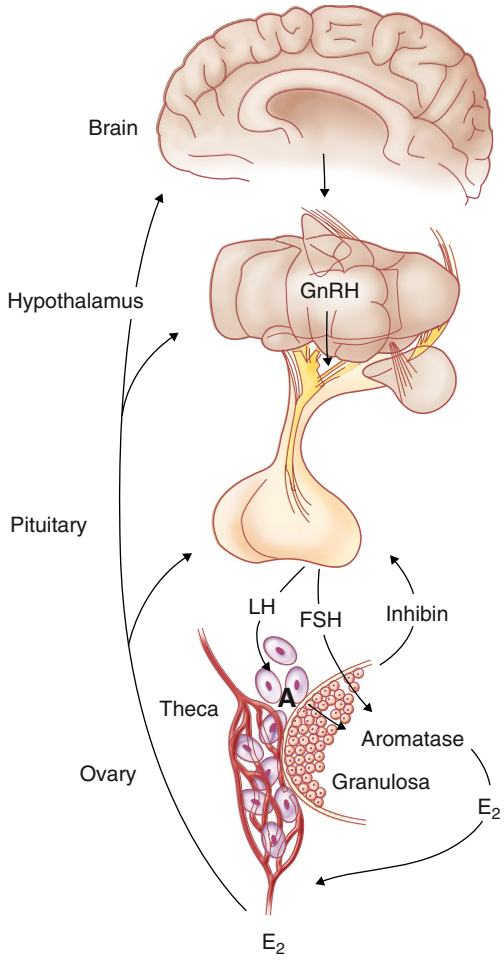

FIGURE 218-2. The hypothalamic-pituitary-ovarian axis in the regulation of follicular maturation and steroidogenesis. A = androgens; E_2 = estradiol; FSH = follicle-stimulating hormone; GnRH = gonadotropin-releasing hormone; LH = luteinizing hormone. (Modified from Endocrine and Metabolism Continuing Education Quality Control Program, 1982. Copyright American Association for Clinical Chemistry, Inc.)

physiologic mechanisms are responsible for luteinization: removal of luteinization inhibitors, secretion of LH by the pituitary, and delivery of high levels of cholesterol. The induction of steroidogenic acute regulatory protein StAR, P450c22, and 3β-hydroxysteroid dehydrogenase in the granulosa lutein cells leads to the production of progesterone by the corpus luteum. The two-cell, two-gonadotropin mechanism is responsible for the production of estradiol. If implantation does not occur, the corpus luteum initiates luteolysis, thereby decreasing progesterone and estradiol and resulting in apoptosis. When luteolysis occurs, another dominant follicle is selected, and a new menstrual cycle begins.

MENSTRUAL SYMPTOMS

DYSMENORRHEA AND ENDOMETRIOSIS

Dysmenorrhea, defined as painful menstruation, affects about 50% of postpubertal women and can be classified as primary or secondary. Endometriosis, which affects about 10% of women of reproductive age, is the ectopic presence of endometrial tissue (glands and stroma), most commonly within the abdominal cavity but sometimes in surgical scars, on the vulva, in the umbilicus, and elsewhere.[1] Endometriosis may result in dysmenorrhea, infertility, and dyspareunia (i.e., painful intercourse).

Primary dysmenorrhea usually, but not always, occurs in ovulatory cycles.[2] Prostaglandins produce dysmenorrhea by initiating painful, exaggerated uterine contractions and myometrial ischemia. Associated systemic symptoms include nausea, diarrhea, headache, and emotional changes. By comparison, secondary dysmenorrhea has a pathologic cause, with endometriosis being the most common.[3] Other causes include pelvic inflammatory disease (Chapter 264); congenital abnormalities, such as atresia of a portion of the distal genital tract and cystic duplication of the paramesonephric ducts; and cervical stenosis.

TREATMENT AND PROGNOSIS

To treat primary dysmenorrhea, over-the-counter nonsteroidal anti-inflammatory drugs (NSAIDs), which inhibit prostaglandin synthase (e.g., naproxen, ibuprofen, or prescription NSAIDs such as mefenamic acid, piroxicam, diclofenac, and meclofenamate), should be started as soon as bleeding or cramping begins and continued for up to 3 days (Table 218-1).[4] NSAIDs should not be used in women who cannot maintain adequate hydration; have underlying renal disease; are receiving anticoagulants, systemic glucocorticoids, lithium, or loop diuretics; or have a history of gastrointestinal bleeding, coagulopathy, ischemic heart disease, stroke, heart failure, liver disease, or aspirin-sensitive asthma. If the dysmenorrhea persists, addition of an oral contraceptive to inhibit ovulation and limit the release of prostaglandin is generally effective. If the pelvic pain remains intractable, additional evaluation is warranted. If thorough evaluation of the gastrointestinal and urinary tracts fails to reveal a definitive cause, examination under anesthesia and diagnostic laparoscopy may be indicated.

If endometriosis is diagnosed at laparoscopy, treatment varies according to the severity of the disease and the patient's goals regarding fertility.[5,6] Initial options include fulguration or excision of implants with lysis of adhesions. Persistent endometriosis can be treated medically, with additional surgery deferred should medical therapy fail. Medical therapy can consist of continuous suppression with oral contraceptives,[A1] progestins (e.g., norethindrone 5 mg daily),[A2] gonadotropin-releasing hormone (GnRH) analogues (e.g., leuprorelin 3.75 or 11.25 mg subcutaneously monthly), a GnRH receptor antagonist (elagolix 150 mg orally daily for up to 24 months[A3] or relugolix 40 mg orally daily),[A4] or danazol for 3 to 6 months.[A3] After a course of treatment, use of oral contraceptive agents should probably be continued until fertility is desired. Conservative surgical resection of endometriotic tissue should almost always be deferred until it is established as the cause of infertility. Surgery may be required, however, for continuing severe pain, severe endometriosis, or large ovarian cysts containing endometriosis (endometriomas).

Some patients have chronic pelvic pain that persists for more than 6 months, often related to menses or intercourse.[6,7] The cause is unknown, but patients often have coexisting fibromyalgia (Chapter 253) or migraine headaches (Chapter 367). If symptoms continue, medical causes have been excluded, or psychological overlay is suspected, multimodality psychosocial intervention or psychiatric evaluation may be indicated.

TABLE 218-1 SUGGESTED ORAL NONSTEROIDAL ANTI-INFLAMMATORY DRUGS TO INHIBIT PROSTAGLANDIN SYNTHASE IN PRIMARY DYSMENORRHEA

DRUG	INITIAL DOSE	SUBSEQUENT DOSING OVER 3 DAYS IF NEEDED
Naproxen sodium	550 mg	275 mg every 6 to 8 hours up to 1375 mg total
Ibuprofen	400 to 800 mg	400 to 800 mg every 4 to 6 hours up to 2400 mg total
Mefenamic acid	500 mg	250 mg every 6 hours up to 1000 mg
Piroxicam	20 mg	10 mg to a total dose of 20 mg once daily
Diclofenac	75 to 100 mg	50 mg every 8 hours to a total dose of 150 mg
Meclofenamate	100 mg	50 mg every 4 to 6 hours up to 400 mg total

PROGNOSIS

With effective treatment, quality of life improves significantly. Should initial therapy fail, however, referral to a reproductive endocrinologist is warranted.

PREMENSTRUAL SYNDROME

Premenstrual syndrome (PMS), also known as premenstrual tension, is a complex of physical and emotional symptoms that occur repetitively in a cyclic fashion before menstruation and that diminish or disappear with menstruation. About 50% of menstruating women have symptoms of varying severity.

The cyclic symptoms typically are sufficiently severe to interfere with some aspects of life. More than 150 different symptoms are now thought to vary with the menstrual cycle (Table 218-2). Estimates of the prevalence of premenstrual syndrome range from 25 to 100%. For most women, premenstrual syndrome is merely annoying, but severe premenstrual syndrome causes serious difficulties for 3 to 5% of women of reproductive age.

Most women seek help for premenstrual syndrome in their 30s after 10 or more years of symptoms. Many report that their symptoms began at menarche; approximately half state that symptoms followed childbirth. Severity and duration of symptoms are often reported to increase after each successive pregnancy and to become more severe with advancing age. Women with severe

TABLE 218-2 COMMON SYMPTOMS OF CYCLIC PREMENSTRUAL SYNDROME

SOMATIC SYMPTOMS	
Abdominal bloating	Constipation or diarrhea
Acne	Headache
Alcohol intolerance	Peripheral edema
Breast engorgement and tenderness	Weight gain
Clumsiness	
EMOTIONAL AND MENTAL SYMPTOMS	
Anxiety	Insomnia
Change in libido	Irritability
Depression	Lethargy
Fatigue	Mood swings
Food cravings (especially salt and sugar)	Panic attacks
Hostility	Paranoia
Inability to concentrate	Violence toward self and others
Increased appetite	Withdrawal from others

long-standing premenstrual syndrome almost always describe associated psychological reactions, including social difficulties such as marital discord, difficulty relating to their children, difficulty maintaining friendships, and withdrawal from social activities.

The diagnosis is best established by requiring affected individuals to keep prospective daily records of symptoms during a 2- to 3-month period. Less than 50% of women who complain of premenstrual syndrome are found to have the syndrome when such records are examined.

TREATMENT

General Measures

The cause of premenstrual syndrome is unknown, and patients should be informed that no one therapy has been effective in all women. Women with mild premenstrual symptoms often benefit from simple changes in lifestyle, including daily mild aerobic exercise; reduction in intake of caffeine-containing beverages, salt, and refined sugar, particularly in the luteal phase; stress reduction; and adequate rest.

Medical Therapy

Women with more severe premenstrual syndrome may benefit from symptomatic treatment.[8] Continuous oral contraceptives (see Table 220-3) have inconsistent but generally positive therapeutic benefit, although intermittent drospirenone/ethinyl estradiol (3 mg/20 µg) dosed on a 21-7 schedule (21 active pills followed by 7 placebo pills) has comparable efficacy to the continuous combined oral contraceptives.[A5] Off-label bromocriptine (generally 2.5 mg twice a day) or danazol (100 to 400 mg/day in two divided doses) may be given continuously for relief of mastalgia (breast pain), although its efficacy has not been documented by rigorous randomized trials. NSAIDs (see Table 218-1) may help reduce pain and alleviate headaches. Mild sedatives and anti-anxiety drugs (Table 362-9) may help reduce insomnia and anxiety. For example, low doses of fluoxetine (10 to 20 mg) and other selective serotonin re-uptake inhibitors (Table 362-5), administered either daily or for the last 2 weeks of each menstrual cycle, are highly effective in reducing the emotional symptoms associated with PMS.[9] Mild diuretics (especially spironolactone at doses up to 100 mg each morning) may benefit cyclic edema.

GnRH agonist therapy plus exogenous estrogen and progestin (e.g., 0.625 mg oral conjugated equine estrogen, 5 mg norethindrone acetate) have been tried with variable success. Neither natural progesterone, given in the form of vaginal suppositories,[10] nor large quantities of multiple vitamins or oil of evening primrose are of documented benefit.

Surgical Therapy

Because premenstrual syndrome requires the occurrence of cyclic ovulation, oophorectomy is occasionally considered for patients who have particularly intractable symptoms. However, oophorectomy may create new problems related to estrogen deficiency.

PROGNOSIS

Premenstrual syndrome can cause debilitating symptoms, but intervention can frequently result in substantial improvement. In the absence of oophorectomy or menopause, however, discontinuing treatment can result in recurrence of symptoms.

ABNORMAL UTERINE BLEEDING

EPIDEMIOLOGY AND PATHOBIOLOGY

Abnormal uterine bleeding may occur in 10 to 30% of women of reproductive age but is a warning sign for endometrial cancer if it develops in postmenopausal women. Prompt and accurate diagnosis is essential.

About 20% of abnormal uterine bleeding[11] is postmenarchal bleeding in adolescents, in whom immaturity of the hypothalamic-pituitary-ovarian axis results in anovulation. Another 50% of abnormal uterine bleeding is perimenopausal bleeding related to incipient ovarian failure and menopause (Chapter 222).

Abnormal uterine bleeding with no demonstrable organic genital or extragenital cause (75% of cases) is most frequently associated with anovulation and is appropriately termed *anovulatory* (sometimes termed *dysfunctional*) *bleeding*. Most anovulatory bleeding is due to either estrogen withdrawal or estrogen breakthrough bleeding. In anovulatory women, estrogen stimulates the endometrium unopposed by progesterone. The endometrium proliferates, becomes thicker, and may shed irregularly. Compared with cyclic menses, anovulatory bleeding tends to occur at less frequent intervals, whereas organic lesions tend to cause more frequent bleeding.

During the reproductive years, the causes of uterine bleeding include complications from the use of oral contraceptives; complications of pregnancy, especially threatened, incomplete, or missed miscarriages and ectopic pregnancy; coagulation disorders, most commonly idiopathic thrombocytopenic purpura (Chapter 158) and von Willebrand disease (Chapter 159); and pelvic disease, such as intrauterine polyps, leiomyomas (fibroids), and tumors of the vagina and cervix (Chapter 184). Clear cell adenocarcinoma of the vagina or cervix may occur in women exposed to diethylstilbestrol during fetal life. Affected women may also have congenital abnormalities of the upper vagina, cervix, and uterus. Women with a history of diethylstilbestrol exposure should be reassured that the incidence of malignant change is extremely low. Trauma (coital or otherwise), foreign bodies, systemic illnesses including various endocrinopathies (such as diabetes mellitus, hypothyroidism and hyperthyroidism, Cushing syndrome, and Addison disease), leukemia, and renal disease may also be associated with abnormal bleeding as the presenting manifestation.

CLINICAL MANIFESTATIONS

Heavy menstrual bleeding is now recognized as excessive menses that interfere with physical, social, emotional, and/or material quality of life. Abnormal bleeding may also occur independently of the menstrual cycle.

DIAGNOSIS

All cases of abnormal bleeding should be evaluated, beginning with a thorough history emphasizing the amount and duration of blood loss. Prospective charting of the days on which bleeding occurs may be required to evaluate the bleeding pattern. Complications of pregnancy or a bleeding diathesis must always be excluded.

The findings on physical examination (including the Papanicolaou smear) are normal in anovulatory bleeding except for signs of anemia in the more severe cases. Laboratory tests should include a complete blood count, platelet count, coagulation studies (including screening for von Willebrand disease [Chapter 159]), thyroid function tests (Chapter 207), and fasting blood glucose concentration. Anovulatory bleeding must be a diagnosis of exclusion, with management depending on the age of the patient and the extent of the bleeding.

For all women older than age 35 years and for all patients who are at increased risk for endometrial carcinoma (Chapter 184) because of prolonged anovulatory bleeding, a sample of the endometrium should be obtained by biopsy or by dilation and curettage.

TREATMENT

Even profuse bleeding in hemodynamically stable anovulatory women can almost always be successfully treated by the off-label administration of one combination oral contraceptive pill (Table 220-3) every 6 hours for 5 to 7 days. Bleeding should cease within 24 hours, but patients should be warned to expect heavy bleeding 2 to 4 days after therapy is stopped. If anemia is profound, blood transfusion may be necessary. If the bleeding continues despite therapy, curettage can be performed. Recurrence can be prevented by giving the patient combination oral contraceptive agents cyclically if pregnancy is not desired. If pregnancy is desired, ovulation can be induced.

Acute episodes of anovulatory bleeding can also be treated with conjugated estrogens administered intravenously (25 mg every 4 hours for up to three doses) until bleeding ceases. Progestin therapy (medroxyprogesterone acetate 5 to 10 mg orally for 10 days) should be started simultaneously. Withdrawal

bleeding occurs after cessation of therapy, and the patient can then be treated with oral contraceptive agents (Table 220-3) for at least three cycles.

For individuals with anovulatory bleeding without an episode of profuse bleeding, treatment with cyclic oral contraceptive agents (Table 220-3) or progestin (a standard oral contraceptive pill per day [see Table 220-3] or norethindrone 5 mg daily) can be provided unless pregnancy is desired, in which case ovulation must be induced.

Endometrial ablation by any of several methods is being used increasingly to treat persistent bleeding. However, ablation is not 100% effective, and medical management remains the first line of therapy for most women. Women suffering with uterine fibroids can be treated with oral medication (e.g., elagolix 300 mg twice daily or relugolix 40 mg daily), uterine artery embolization, or surgery (Chapter 184).

Hysterectomy may be an appropriate choice for a small number of women with refractory symptoms. It is also indicated if endometrial sampling suggests malignancy.

PROGNOSIS

The prognosis of abnormal uterine bleeding depends on its cause and treatment. Most cases resolve with effective intervention.

AMENORRHEA

Amenorrhea is the absence of menstruation for 3 months or more in women with past menses (secondary amenorrhea) or the absence of menarche by the age of 15 years regardless of the absence or presence of secondary sex characteristics (primary amenorrhea). Amenorrhea in the absence of pregnancy, lactation, or menopause occurs in about 3 to 4% of women of reproductive age, and it usually is secondary rather than primary.

If an intact genital outflow tract exists and there is no primary disease of the uterus, amenorrhea is a sign of failure of the hypothalamic-pituitary-ovarian axis to produce cyclically the hormones necessary for menses. Amenorrhea is physiologic in the prepubertal girl, during pregnancy, early in lactation, for up to 3 months after the discontinuation of oral contraceptive agents, and after menopause. At any other time, it is pathologic and demands evaluation. Similarly, individuals with menses occurring at infrequent intervals of more than 40 days or having fewer than nine menses per year, termed *oligomenorrhea*, should be evaluated identically to women with amenorrhea.

DIAGNOSIS

Clinical Evaluation

In patients with amenorrhea, even subtle hormonal abnormalities may lead to signs and symptoms. Breast development indicates exposure to estrogens, and the presence of pubic and axillary hair indicates androgenic stimulation.

Patients should be questioned especially closely for evidence of psychological disturbances, dietary and exercise habits,[12] lifestyle, environmental stresses, family history of genetic anomalies, abnormal growth and development, signs of hyperandrogenism (including hirsutism, temporal balding, deepening of the voice, increased muscle mass, clitoromegaly, and increased libido), and signs of defeminization (including decreasing breast size and vaginal atrophy). Any history of galactorrhea should be determined. A history of symptoms related to thyroid and adrenal dysfunction should also be sought (Chapters 207, 208, and 209).

The physical examination should focus on the evaluation of body dimensions and habitus, extent and distribution of body hair, breast development and secretions, and genitalia. In normal adult women, the arm span is similar to the height; in hypogonadal women, the span is generally more than 5 cm greater than the height. The distribution and quantity of body hair should be considered in view of the family history. The extent of any hirsutism should be recorded, preferably by photographs. Other signs of virilization should be sought carefully. Breast development should be graded according to the method of Tanner (Table 218-3). Breast secretion should be sought by applying pressure to the breasts while the patient is seated. Any secretion should be examined microscopically for the presence of perfectly round but variable size fat globules, which indicate galactorrhea. Finally, the female genitalia should be examined carefully because they are such sensitive indicators of the hormonal milieu. The Tanner stage of pubic hair development should be noted (see Table 218-3).

Because sensitivity of the genitalia to androgens decreases fairly early in fetal development, the extent of any virilization is important. Fusion of the labia and enlargement of the clitoris, with or without formation of a penile urethra, are observed in women exposed to androgens during the first 3 months of fetal development (Chapter 214). Significant clitoromegaly in the absence of other signs of sexual ambiguity and in the presence of other signs of virilization requires marked androgenic stimulation and strongly implicates an androgen-secreting neoplasm. The development of the labia minora in postpubertal women indicates the influence of estrogens. Overt anomalies of the distal genital tract and any evidence of obstruction to the escape of menstrual blood should be sought. Under the influence of estrogen, the vaginal mucosa changes during sexual maturation from a tissue with a shiny, bright red appearance with sparse, thin secretions to a dull, gray-pink rugated surface with copious, thick secretions.

The history and physical examination quickly differentiate among several causes of amenorrhea (Table 218-4). The various disorders of sexual differentiation and other anatomic causes are often apparent on inspection. Distal genital tract obstruction should be identified at the time of pelvic examination even if the specific abnormality is not obvious. The physical stigmata of Turner syndrome (Chapter 214) generally make the diagnosis simple. Any sexual ambiguity indicates the need for chromosomal analysis and the measurement of 17α-hydroxyprogesterone to exclude congenital adrenal hyperplasia. Pregnancy and gestational trophoblastic disease may be diagnosed by measurement of human chorionic gonadotropin (hCG). The possibility of intrauterine synechiae or adhesions (Asherman syndrome) must be considered in individuals in whom amenorrhea develops after curettage or endometritis. Tuberculous endometritis, especially in younger women, may also lead to this disorder.

Provocative Testing

Administration of a progestin (typically medroxyprogesterone acetate 5 to 10 mg given orally for 5 to 10 days, or progesterone in oil 100 mg given intramuscularly) can precipitate withdrawal bleeding, which may indicate that sufficient endogenous estrogen was present to allow for endometrial proliferation. This test is of limited value, however, because almost 50% of young women with premature ovarian failure experience withdrawal bleeding in response to progestin.

To ascertain whether the outflow tract is intact, an orally active estrogen, such as 2.5 mg of conjugated estrogen daily for 21 days, with 5 to 10 mg of oral medroxyprogesterone acetate for the last 5 to 10 days, should be administered. Withdrawal bleeding should occur if the endometrium is normal. However,

TABLE 218-3 CRITERIA FOR DISTINGUISHING TANNER STAGES 1–5 DURING FEMALE PUBERTAL MATURATION

TANNER STAGE	BREAST	PUBIC HAIR
1 (Prepubertal)	No palpable glandular tissue or pigmentation of areola; elevation of areola only	No pubic hair; short, fine vellus hair only
2	Glandular tissue palpable with elevation of breast and areola together as a small mound; areolar diameter increased	Sparse, long, pigmented terminal hair chiefly along the labia majora
3	Further enlargement without separation of breast and areola; although more darkly pigmented, areola still pale and immature; nipple generally at or above midplane of breast tissue when individual is seated upright	Dark, coarse, curly hair, extending sparsely over mons
4	Secondary mound of areola and papilla above breast	Adult-type hair, abundant but limited to mons and labia
5 (Adult)	Recession of areola to contour of breast; development of the Montgomery glands and ducts on areola; further pigmentation of areola; nipple generally below midplane of breast tissue when individual is seated upright; maturation independent of breast size	Adult-type hair in quantity and distribution; spread to inner aspects of the thighs in most racial groups

Data from Ross GT. Disorders of the ovary and female reproductive tract. In: Wilson JD, Foster DW, eds. *Textbook of Endocrinology*, 7th ed. Philadelphia: WB Saunders; 1985:206; Speroff L, Glass RH, Kase N. *Clinical Gynecologic Endocrinology and Infertility*, 3rd ed. Baltimore: Williams & Wilkins; 1983:377; and Kustin J, Rebar RW. Menstrual disorders in the adolescent age group. *Primary Care*. 1987;14:139-166.

TABLE 218-4 CAUSES OF AMENORRHEA

ANATOMIC CAUSES
Pregnancy
Various disorders of sexual differentiation
Distal genital tract obstruction (müllerian agenesis or dysgenesis)
Gonadal dysgenesis*
Ambiguity of external genitalia (male and female pseudohermaphroditism)
Intrauterine adhesions (Asherman syndrome)
Gestational trophoblastic disease
CHRONIC ANOVULATION
Due to CNS-hypothalamic-pituitary dysfunction
With inappropriate steroid feedback (e.g., polycystic ovary syndrome)
Due to thyroid or adrenal disorders
OVARIAN "FAILURE"
Menopause
Genetic abnormalities
Physical and environmental causes (e.g., chemotherapeutic agents, irradiation)
Autoimmune disorders
Idiopathic

*Gonadal dysgenesis may be viewed as both a disorder of sexual differentiation and a form of gonadal "failure."
CNS = central nervous system.

hysterosalpingography and hysteroscopy may be required for the diagnosis of Asherman syndrome because some patients with a normal endometrium may not have a withdrawal bleed due to obstruction of the cervical os by scar tissue.

Laboratory Findings

Basal levels of FSH, prolactin, and thyroid-stimulating hormone (TSH) should be measured in all amenorrheic and oligomenorrheic women to confirm the clinical impression (Fig. 218-3).[13]

Increased TSH levels with or without increased levels of prolactin imply primary hypothyroidism, and further evaluation for this disorder is indicated (Chapter 207). Although hypothyroidism commonly results in anovulation, amenorrhea occurs in only some hypothyroid women. Menorrhagia and oligomenorrhea may occur as well. The sensitive immunoassays for TSH permit identification of women with hyperthyroidism as well because TSH levels are suppressed in those individuals.

If the prolactin concentration is minimally increased and the TSH level is normal, measurement of the prolactin concentration should be repeated before more extensive evaluation is undertaken because prolactin levels are increased by nonspecific stressful stimuli, sleep, and food ingestion. Prolactin levels may be elevated in as many as one third of women with amenorrhea.

Increased FSH levels (generally above 30 mIU/mL) imply ovarian failure and require further evaluation. Incipient ovarian failure should be considered in any woman with basal FSH levels of 15 mIU/mL or higher other than during the midcycle LH surge. Chromosomal evaluation is indicated if hypergonadotropic amenorrhea begins before age 30 years, and it is often performed in all individuals with elevated FSH levels before age 40 years.

If FSH levels are low or normal, measurement of the free testosterone level may be helpful regardless of any evidence of hirsutism or virilization. Hyperandrogenic women need not be hirsute because some have relative insensitivity of the hair follicles to androgens. Mildly increased levels of free testosterone (and perhaps dehydroepiandrosterone sulfate as well) suggest polycystic ovary syndrome.

Circulating levels of LH and FSH may aid in differentiation of polycystic ovary syndrome from hypothalamic-pituitary dysfunction. LH levels are often elevated in polycystic ovary syndrome so that the ratio of LH to FSH is increased; however, LH levels may be identical to those observed in normal women in the follicular phase. In contrast, levels of LH and FSH are normal or slightly reduced in hypothalamic-pituitary dysfunction. There is some overlap between women with "polycystic ovarian-like" disorders and those with hypothalamic-pituitary dysfunction. Radiographic assessment of the sella turcica is indicated in all amenorrheic women in whom both LH and FSH levels are consistently low (both below 10 mIU/mL) to exclude a pituitary or parapituitary neoplasm (Chapter 205). Other pituitary functions should be evaluated in any individual with significantly impaired LH and FSH secretion. Both total testosterone and dehydroepiandrosterone sulfate levels should be measured in hirsute or virilized women. Testosterone levels greater than 200 ng/dL should lead to investigation for an androgen-producing neoplasm, most likely of ovarian origin. Dehydroepiandrosterone sulfate levels greater

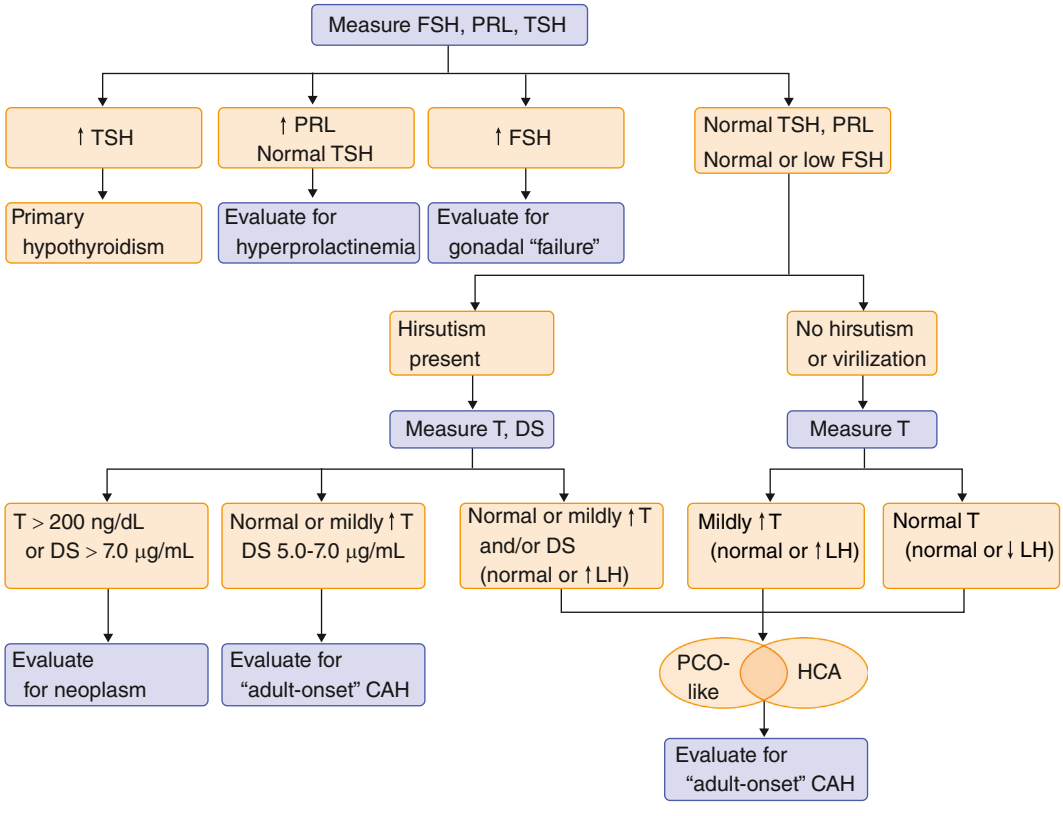

FIGURE 218-3. Biochemical evaluation of amenorrhea. This schema must be considered an adjunct to the clinical evaluation of the patient. See text for details. CAH = congenital adrenal hyperplasia; DS = dehydroepiandrosterone sulfate; FSH = follicle-stimulating hormone; HCA = hypothalamic chronic anovulation; LH = luteinizing hormone; PCO-like = polycystic ovarian syndrome–like; PRL = prolactin; T = testosterone; TSH = thyroid-stimulating hormone.

than 7.0 μg/mL should lead to evaluation for an adrenal neoplasm, and levels between 5.0 and 7.0 μg/mL should lead to evaluation for adult-onset congenital adrenal hyperplasia (Chapter 214).

HYPERGONADOTROPIC AMENORRHEA (HYPOGONADISM, PRIMARY OVARIAN INSUFFICIENCY)

Gonadal failure may begin at any time during embryonic or postnatal development and may result from many causes. Normally, the ovaries fail at menopause, when virtually no functioning follicles remain. However, premature loss of oocytes before the age of 40 years may occur and lead to premature ovarian failure. Circulating gonadotropin levels increase whenever ovarian failure occurs because of decreased negative estrogen feedback to the hypothalamic-pituitary unit.

PATHOBIOLOGY

Causes of premature ovarian failure include genetic causes (e.g., karyotypic abnormalities, single gene mutations, and complex multifactorial polygenic inheritance), physical and environmental causes, and autoimmune disturbances.[14] In addition, menopause may begin earlier than the expected age in some families without any evident pathologic cause.

Genetic Abnormalities

Several pathologic conditions with dysgenetic gonads involve elevated gonadotropin levels and amenorrhea as well as abnormalities of the X chromosome. Gonadal dysgenesis refers to individuals who have undifferentiated streak gonads in the absence of either extragonadal stigmata or abnormalities of sex chromosomes; because individuals with gonadal dysgenesis have the normal complement of oocytes at 20 weeks of fetal age but virtually none by birth, this disorder is a form of premature ovarian failure.

In Turner syndrome (see Chapter 214), phenotypic females have streak gonads composed of fibrous stroma. Most commonly, the second sex chromosome is absent (45,X), but chromosome breakage and mosaicism occur as well.

In pure gonadal dysgenesis, phenotypically female individuals with streak gonads are of normal stature without the physical stigmata of Turner syndrome. Such individuals have either a 46,XX or 46,XY karyotype.

Several regions of the X chromosome can contain mutations that may result in premature ovarian failure. More than 5% of women with 46,XX spontaneous premature ovarian failure have mutations of the *FMR1* gene. For *FMR1*, a CGG repeat sequence occurs, with up to 60 repeats being normal. Expansion to more than 200 repeats leads to fragile X syndrome, with the high level of repeats causing hypermethylation of the gene promoter and silencing of the gene. Female carriers of the premutation have an unstable intermediate number of repeats (i.e., 60 to 199) and the predisposition for premature ovarian failure. This risk is increased if there is a family history of premature ovarian failure and fragile X intellectual disability. Women with mutations in the *FMR1* gene are at risk of having a child with intellectual disability, should they be one of the 6 to 8% of women with premature ovarian failure who conceive spontaneously. A family history of fragile X syndrome, unexplained intellectual disability, dementia, developmental delay of a child, or tremor-ataxia syndrome is reason for genetic counseling.

Trisomy X (46,XXX karyotype) is also associated with premature menopause, although many such individuals have normal reproductive lives. Premature menopause can also occur in mosaic individuals with cell lines with excess X chromosomes. When gonadal abnormalities occur in women with excess X chromosomes, they seem to occur after ovarian differentiation so that some ovarian function is possible. Only later in life do such women develop secondary amenorrhea and premature ovarian failure.

In girls with the rare syndrome of 17α-hydroxylase deficiency involving *p450c17* who survive until the expected age of puberty, sexual infantilism and primary amenorrhea occur together with elevated levels of gonadotropins (also see Chapter 214). Defects in the 20,22-lyase (*p450scc*) or aromatase (*p450arom*) enzymes may also lead to ovarian failure. Women with galactosemia also experience ovarian failure early in life, even when a galactose-restricted diet is introduced early in infancy.

Mutations of several autosomal genes result in premature ovarian failure. Included in this growing list are mutations involving *FSHR* (the FSH receptor gene), *FOXL2* (a forkhead transcription factor associated with the blepharophimosis-ptosis-epicanthus inversus syndrome), *INHA* (the inhibin-α gene), *E1F2B* (a family of genes associated with central nervous system leukodystrophy and ovarian failure), *PMM2* (the gene for phosphomannomutase), *GALT* (the gene for galactose-1-phosphate uridyltransferase), and *AIRE* (leading to autoimmune polyendocrinopathy-candidiasis-ectodermal dystrophy syndrome). Myotonic dystrophy (Chapter 389), which like fragile X syndrome is caused by an autosomal triple repeat mutation, is similarly associated with premature loss of germ cells from the ovary.

Savage syndrome occurs in young amenorrheic women who have elevated peripheral gonadotropin concentrations, normal (although immature) follicles present on ovarian biopsy, 46,XX karyotype with no evidence of mosaicism, fully developed secondary sex characteristics, and ovarian resistance to stimulation with human menopausal or pituitary gonadotropins. At least some of these women have mutations in the FSH receptor.

Other Causes

Physical and Environmental

Irradiation and chemotherapeutic agents used to treat various malignant diseases may also cause premature ovarian failure. Ovulation and cyclic menses return in some of these patients even after prolonged intervals of hypergonadotropic amenorrhea associated with signs and symptoms of profound hypoestrogenism. In general, the younger the individual at the time of treatment, the less likely she is to have permanent ovarian failure after the completion of therapy. Rarely, mumps (Chapter 340) affects the ovaries and causes ovarian failure.

Autoimmune Disorders

Premature ovarian failure may occur in conjunction with a variety of autoimmune disorders. The most well-known syndrome (autoimmune polyglandular syndrome type 1) involves hypoadrenalism, hypoparathyroidism, and mucocutaneous candidiasis together with ovarian failure (Chapter 212). Testing for adrenal antibodies by indirect immunofluorescence will identify the 4% of women with spontaneous premature ovarian failure who have steroidogenic cell autoimmunity and are at risk for adrenal insufficiency. Thyroiditis is the most commonly associated abnormality. Antibodies to the FSH receptor have been identified in a few cases.

CLINICAL MANIFESTATION AND DIAGNOSES

In patients who have amenorrhea before age 40 years and who manifest symptoms similar to menopause (e.g., infertility, hot flashes, dyspareunia, vaginal dryness), the diagnosis can be confirmed by an elevated FSH level (e.g., >25 mIU/mL) on two occasions, measured at least 4 months apart. Psychological support is important, because depression is common after the diagnosis of premature ovarian insufficiency.

TREATMENT

Women with hypergonadotropic amenorrhea and ovarian failure should be treated identically, regardless of whether they have signs of hypoestrogenism or desire pregnancy. Counseling and psychological support are indicated for women in whom the diagnosis of premature ovarian failure is made. Estrogen replacement is warranted to prevent the accelerated bone loss known to occur in affected women. The estrogen should be given sequentially with a progestin to prevent endometrial hyperplasia (e.g., using 2 mg estradiol daily with 1 mg norethindrone acetate for the final 10 days). Young women with ovarian failure may require twice as much estrogen as postmenopausal women for relief of signs and symptoms of hypoestrogenism. Standard oral contraceptives (see Table 220-3) may be considered for hormone replacement, although other hormone replacement regimens may be cardioprotective (Chapter 222). Surprisingly, women with premature ovarian failure may conceive while taking exogenous estrogen, even in the form of oral contraceptive agents, at the same rate as women not taking estrogen, so barrier contraception should be discussed if pregnancy is not desired.

Women with hypergonadotropic amenorrhea may have a pregnancy and delivery rate of about 6 to 8%. Infertility treatment of young women with hypergonadotropic amenorrhea involves specialist-guided hormone replacement to mimic the normal menstrual cycle and embryo transfer by use of donor oocytes. Whether women with gonadal dysgenesis should be offered pregnancy by use of donor oocytes is now the subject of debate because of a markedly increased incidence of aortic rupture secondary to medial necrosis during pregnancy. Women with Turner syndrome contemplating pregnancy should be counseled regarding the risks.

CHRONIC ANOVULATION

Anovulation can result in either amenorrhea or irregular (generally less frequent) menses. Chronic anovulation, which is the most frequent form of amenorrhea encountered in women of reproductive age, implies that functional

TABLE 218-5 CAUSES OF CHRONIC ANOVULATION

- Chronic anovulation of hypothalamic-pituitary origin
  - Hypothalamic chronic anovulation
    - Psychogenic
      - Exercise associated
      - Associated with diet, weight loss, or malnutrition
      - Anorexia nervosa and bulimia
      - Pseudocyesis
  - Forms of isolated (idiopathic) hypogonadotropic hypogonadism (including Kallmann syndrome)
  - Due to hypothalamic-pituitary damage
    - Pituitary and parapituitary tumors
    - Empty sella syndrome
    - Following surgery
    - Following irradiation
    - Following trauma
    - Following infection
    - Following infarction
  - Idiopathic hypopituitarism
  - Hypothalamic-pituitary dysfunction or failure with hyperprolactinemia (multiple causes)
  - Due to systemic diseases
- Chronic anovulation due to inappropriate feedback (i.e., polycystic ovary syndrome)
  - Excessive extraglandular estrogen production (i.e., obesity)
  - Abnormal buffering involving sex hormone–binding globulin (including liver disease)
  - Functional androgen excess (adrenal or ovarian)
  - Neoplasms producing androgens or estrogens
  - Neoplasms producing chorionic gonadotropin
- Chronic anovulation due to other endocrine and metabolic disorders
  - Adrenal hyperfunction
    - Cushing syndrome
    - Congenital adrenal hyperplasia (female pseudohermaphroditism)
  - Thyroid dysfunction
    - Hyperthyroidism
    - Hypothyroidism
  - Prolactin or growth hormone excess
    - Hypothalamic dysfunction
    - Pituitary dysfunction (microadenomas and macroadenomas)
    - Drug induced
  - Malnutrition

ovarian follicles remain and that cyclic ovulation can be induced with appropriate therapy (Table 218-5).

HYPOTHALAMIC CHRONIC ANOVULATION

DEFINITION

Hypothalamic chronic anovulation represents a heterogeneous group of disorders with similar manifestations. Emotional and physical stress, excessive exercise, nutritional deficiencies, weight loss, reduced body fat, and other unrecognized factors may contribute in varying proportions to the anovulation. Women with hypothalamic chronic anovulation have normal neuroanatomic findings.

Anorexia Nervosa

Individuals with amenorrhea and significant weight loss should be examined for the possibility of anorexia nervosa (Chapter 200).

Isolated Hypogonadotropic Hypogonadism

Affected individuals have an absence of spontaneous pubertal development. Most have functional GnRH deficiency, but some have abnormalities of gonadotropin deficiency localized to the pituitary gland.

Kallmann syndrome is a familial disorder consisting of gonadotropin deficiency, anosmia or hyposmia, and color blindness in men or, more rarely, in women (Chapter 204). Partial or complete agenesis of the olfactory bulb is present on autopsy, accounting for use of the term *olfactogenital dysplasia*. Isolated gonadotropin deficiency in the absence of anosmia occurs as well. Sexual infantilism with a eunuchoid habitus is the clinical hallmark of this disorder, but moderate breast development may occur. Circulating LH and FSH levels are low but almost always detectable. The induction of ovulation requires exogenous gonadotropins and hCG or pulsatile GnRH by a specialist. Estrogen replacement therapy, assuming that pubertal development is complete, with a standard oral contraceptive pill (see Table 220-3), is indicated in these women until pregnancy is desired. If puberty is not initiated or completed, the regimen is complex and is best managed by a reproductive endocrinologist.

Hypopituitarism

Hypopituitarism may be obvious on cursory inspection or sufficiently subtle to require endocrine testing (Chapter 205). Failure to develop secondary sex characteristics (Chapter 217) must always raise the question of hypopituitarism. Ovulation can be induced successfully by a specialist with exogenous gonadotropins when pregnancy is desired and after the hypopituitarism is treated appropriately. Replacement therapy with standard oral contraceptives (see Table 220-3) is indicated if pregnancy is not desired and the pubertal transition has been completed.

HYPERPROLACTINEMIA

Galactorrhea associated with hyperprolactinemia, whatever the cause, almost always occurs together with amenorrhea caused by hypothalamic-pituitary dysfunction or failure. Many conditions can cause excess secretion of prolactin (Chapter 205), but a prolactinoma must be excluded. Hirsutism may be observed occasionally in association with amenorrhea-galactorrhea and hyperprolactinemia. Elevated levels of the adrenal androgens dehydroepiandrosterone and dehydroepiandrosterone sulfate may be observed and may account for the polycystic-type ovaries present in some hyperprolactinemic women.

Failure of the Hypothalamic-Pituitary Unit

The hypothalamic-pituitary unit may fail to function normally in a number of stressful, debilitating, systemic illnesses that interfere with somatic growth and development. Chronic renal failure, liver disease, and diabetes mellitus are the most prominent examples, whereas anorexia nervosa (Chapter 200) represents a potentially reversible cause.

DIAGNOSIS

Abrupt cessation of menses in women younger than age 30 years who have no anatomic abnormalities of the hypothalamic-pituitary-ovarian axis and no other endocrine disturbances suggests a diagnosis of hypothalamic chronic anovulation. Affected individuals tend to be bright, educated, and engaged in intellectual occupations and may well give a history of psychosexual problems and socioenvironmental trauma. Hypothalamic chronic anovulation is characterized by low to normal levels of gonadotropins and relative hypoestrogenism. However, affected women rarely present with signs and symptoms of estrogen deficiency. In women who appear to have hypothalamic chronic anovulation, a CT or MRI should be obtained to exclude a pituitary lesion as the cause of the hypogonadotropic hypogonadism.

TREATMENT

Psychological counseling, cognitive-behavioral therapy, or a change in lifestyle, especially for women engaged in strenuous exercise programs, may be effective in inducing cyclic ovulation and menses in women with functional hypothalamic chronic anovulation. For women who desire pregnancy, ovulation can also be induced with clomiphene citrate (50 to 100 mg/day for 5 days beginning on the third to fifth day of withdrawal bleeding). Treatment by a fertility expert with exogenous gonadotropins to induce follicular maturation followed by hCG to induce follicular rupture may be effective in women who do not ovulate in response to clomiphene. Some women with hypothalamic chronic anovulation have low circulating levels of leptin and may ovulate after therapy with recombinant leptin.

If chronic anovulation persists, osteoporosis should be prevented with daily oral conjugated or esterified estrogens (0.625 to 1.25 mg), ethinyl estradiol (20 μg), or micronized estradiol-17β (1 to 2 mg) or transdermal estradiol-17β (0.05 to 0.10 mg) daily, with oral medroxyprogesterone acetate (5 to 10 mg) added for the first 12 to 14 days of each month. Sexually active women can be given oral contraceptive agents (Table 220-3) as an alternative. Adequate ingestion of calcium should be ensured regardless of therapy. Contraception is needed for sexually active women with hypothalamic chronic anovulation because the functional defect is mild and may resolve spontaneously at any time, with ovulation occurring before any episode of menstruation.

CHRONIC ANOVULATION RELATED TO INAPPROPRIATE FEEDBACK

Polycystic Ovary Syndrome

DEFINITION

Polycystic ovary syndrome (PCOS) is a heterogeneous disorder with considerable clinical and biochemical variability among affected individuals.[14] Polycystic ovary syndrome is defined by any two of the following: (1) oligo-ovulation or anovulation, (2) hyperandrogenism, or (3) polycystic ovaries on ultrasound in women in whom other etiologies have been eliminated.

EPIDEMIOLOGY AND PATHOBIOLOGY

Polycystic ovary syndrome affects about 6 to 12% of women of reproductive age, without any obvious geographic or ethnic differences, and it is the most common endocrine abnormality of women in this age group. More than 50% of affected women develop type 2 diabetes by age 40 years. Obesity contributes to the polycystic ovarian syndrome, and the increase in the prevalence of obesity is contributing to an increased prevalence of this syndrome.

In polycystic ovary syndrome, the amenorrhea or oligomenorrhea results from inappropriate feedback of gonadal steroids from the ovaries. The hypothalamic-pituitary unit is intact, but the functional derangement, perhaps involving insulin-like growth factors within the ovary, results in abnormal secretion of gonadotropins. Polycystic ovary syndrome is characterized by insulin resistance and compensatory hyperinsulinemia in affected women across racial and ethnic groups, thereby implying that a common defect may be present. Increasing evidence points to specific genetic abnormalities, such as alterations in *CYP17* and *CYP19*.

CLINICAL MANIFESTATIONS

Although patients usually present with amenorrhea, hirsutism, and obesity, affected women may instead complain of irregular and profuse uterine bleeding, may not have hirsutism, and may be of normal weight. In the primary syndrome, the irregular menses, mild obesity, and hirsutism begin during puberty and typically become more severe with time, but they may improve in the years just before menopause.

DIAGNOSIS

Excess androgen from any source or increased extraglandular conversion of androgens to estrogens can lead to the typical findings of polycystic ovary syndrome.[15] Included are such diverse disorders as Cushing syndrome (Chapter 208), mild congenital adrenal hyperplasia (Chapter 214), virilizing tumors of adrenal or ovarian origin (Chapters 184 and 208), hyperthyroidism and hypothyroidism (Chapter 207), and obesity (Chapter 201). After exclusion of these causes, two of the following three are required for a diagnosis of polycystic ovary syndrome: (1) hyperandrogenism (clinical or biochemical), (2) oligo-ovulation or anovulation, and (3) polycystic ovaries on ultrasound examination or at surgery. Based on this definition, the diagnosis of polycystic ovary syndrome can be made in women who ovulate normally,

Patients are well estrogenized regardless of whether they present with primary or secondary amenorrhea or dysfunctional bleeding. LH concentrations tend to be elevated, with relatively low and constant FSH levels, but both may be in the normal range for the follicular phase of the menstrual cycle. Levels of most circulating androgens, especially testosterone, tend to be mildly elevated. Hirsutism should be evaluated as detailed in Chapter 409.

A particularly severely affected subset of women present with marked obesity, anovulation, mild glucose intolerance with high levels of circulating insulin, acanthosis nigricans, hyperuricemia, severe hirsutism, and elevated circulating androgen levels. These women have hyperthecosis of the ovaries, in which the androgen-producing cells in the stromal, hilar, and thecal regions are increased greatly in number.

TREATMENT

Patients generally require therapy for hirsutism (Chapter 409), for induction of ovulation if pregnancy is desired, and for prevention of estrogen-induced endometrial hyperplasia and cancer. No ideal therapy exists,[16,17] so the therapeutic approach must be individualized. The risks for metabolic syndrome, cardiovascular disease (Chapter 40), and diabetes mellitus (Chapter 210) are increased, because of the increased androgens, insulin resistance, and commonly associated hyperlipidemia (Chapter 190).

Medical Therapy

In the anovulatory woman not desiring pregnancy who is not hirsute, therapy with intermittent progestin administration (such as medroxyprogesterone acetate, 5 to 10 mg orally for 10 to 14 days each month) or oral contraceptives (Table 220-3) can reduce the increased risk for endometrial carcinoma that is present in such a woman with unopposed estrogen. All women using intermittent progestin administration should be cautioned about the need for effective contraception if they are sexually active because these agents do not inhibit ovulation when they are administered intermittently.

Improvements in insulin sensitivity through lifestyle changes (e.g., exercise [Chapter 14] and diet [Chapter 13]) or pharmacologic intervention consistently improve the reproductive and metabolic abnormalities. Metformin (1500 to 2000 mg daily in divided doses) can suppress hepatic gluconeogenesis, improve insulin sensitivity, reduce levels of insulin and androgen, and increase the likelihood of ovulation. Resumption of ovulation may occur in up to 60 to 70% of affected women.

Treatment Considering Pregnancy

Oral contraceptive agents (Table 220-3) are the first line of therapy to protect against endometrial hyperplasia in hirsute anovulatory women who do not desire pregnancy. In women who desire pregnancy, letrozole (e.g., 5 mg on days 3 to 7 after the start of the last menstrual period) is the preferred therapy, and both it and clomiphene citrate (50 mg on days 3 to 7 after the start of the last menstrual period) are preferred over metformin (500 mg to 2000 mg daily) to induce ovulation,[A6] and about 75 to 80% of women conceive with such therapy. Other methods to induce ovulation under the direction of a specialist include exogenous gonadotropins plus hCG, or laparoscopic ovarian surgery with multiple punctures of the ovary by diathermy or laser.

Laparoscopic ovarian surgery can achieve unifollicular ovulation or make it easier for the medical induction of ovulation, but it increases the risk of ovarian adhesions, which themselves lead to infertility. Surgery is often limited to the small subset of women who do not respond to medical therapy.

OTHER ENDOCRINE CAUSES

Adrenal hyperfunction (Chapter 208) causes chronic anovulation by inducing a polycystic ovarian-like syndrome secondary to increased secretion of adrenal androgens. Both hyperthyroidism and hypothyroidism (Chapter 207) are associated with a variety of menstrual disturbances, including dysfunctional uterine bleeding and amenorrhea as a result of alterations in the metabolism of androgens and estrogens. These metabolic changes in turn result in inappropriate steroid feedback and chronic anovulation.

INFERTILITY

DEFINITION

According to the World Health Organization (WHO), infertility is "a disease of the reproductive system defined by the failure to achieve a clinical pregnancy after 12 months or more of regular unprotected sexual intercourse." Sterility is total inability to reproduce. More than 10% of couples in the United States seek medical assistance for infertility.

The requirements for pregnancy to occur are several:

- The male must produce adequate numbers of normal, motile spermatozoa.
- The male must be capable of ejaculating the sperm through a patent ductal system.
- The sperm must be able to traverse an unobstructed female reproductive tract.
- The female must ovulate and release an ovum.
- The sperm must be able to fertilize the ovum.
- The fertilized ovum must be capable of developing and implanting in appropriately prepared endometrium.

In approximately 40% of cases, infertility is caused by the male (Table 218-6). In one third of couples, more than one cause contributes to the infertility.

Peak age for fertility in the female is age 25 years. For nulliparous women of this age, unprotected intercourse produces conception after an average of 5.3 months. For parous women, the average duration of intercourse until conception is 2.7 months. The reproductive performance of couples is influenced by the ages of the female and male partners, the frequency of intercourse, and the length of time the couple has been attempting to conceive. Reproductive performance declines in both females and males after age 25 years.

DIAGNOSIS

Couples who complain of infertility merit evaluation regardless of the length of infertility. Clinician-directed evaluation is warranted in all women who wish to become pregnant if conception has not occurred within 12 months of regular unprotected intercourse, and it is warranted in women ages 35 years or older after 6 months.

The evaluation begins with a detailed history and physical examination of both partners. The couple should be questioned together and separately, because separate interviews may uncover information that would not be imparted in the presence of the partner.

Initial evaluation for infertility includes assessment of semen; documentation of ovulation by basal body temperature, serum progesterone determination 6 to 8 days before menses, serum thyroid hormone, or (rarely) endometrial biopsy less than 3 days before onset of menses; and evaluation of the female genital tract by hysterosalpingography or sonohysterography.

Diagnostic laparoscopy with tubal dye instillation may infrequently be performed if results of all previous tests are normal, because 30 to 50% of

TABLE 218-6 CAUSES OF INFERTILITY AND THEIR APPROXIMATE INCIDENCE

Male factors (40%)
Decreased production of spermatozoa
Varicocele
Testicular failure
Endocrine disorders
Cryptorchidism
Stress, smoking, caffeine, nicotine, recreational drugs
Ductal obstruction
Epididymal (after infection)
Congenital absence of vas deferens
Ejaculatory duct (after infection)
After vasectomy
Inability to deliver sperm into vagina
Ejaculatory disturbances
Hypospadias
Sexual problems (i.e., impotence), medical or psychological
Abnormal semen
Infection
Abnormal volume
Abnormal viscosity
Immunologic factors
Sperm-immobilizing antibodies
Sperm-agglutinating antibodies
Female factors
Fallopian tube disease (20-30%)
Pelvic inflammatory disease or puerperal infection
Congenital anomalies
Endometriosis
Secondary to past peritonitis of nongenital origin
Amenorrhea and anovulation (15%)
Minor ovulatory disturbances (<5%)
Cervical and uterine factors (10%)
Leiomyomas and polyps
Uterine anomalies
Intrauterine synechiae (Asherman syndrome)
Destroyed endocervical glands (after surgery or after infection)
Vaginal factors (<5%)
Congenital absence of vagina
Imperforate hymen
Vaginismus
Vaginitis
Immunologic factors (<5%)
Sperm-immobilizing antibodies
Sperm-agglutinating antibodies
Nutritional and metabolic factors (5%)
Thyroid disorders
Diabetes mellitus
Severe nutritional disturbances
Idiopathic or unexplained (<10%)

women have endometriosis or tubal disease diagnosed by surgical evaluation. Alternatively, patients with initial normal findings may be merely treated as having idiopathic infertility.

TREATMENT

Treatment must be predicated on the findings of the infertility evaluation.[18] Low sperm count or poor motility is best treated either by donor insemination or in vitro fertilization with intracytoplasmic injection of a single viable sperm into each oocyte. Obstruction of the fallopian tubes may be amenable to surgical intervention, but success rates are often greater with in vitro fertilization. Endometriosis causing infertility may be treated by surgery or various suppressive drugs as indicated, but in vitro fertilization may be indicated.

Induction of ovulation in anovulatory women should never be attempted until serious disorders precluding pregnancy are excluded or treated. Furthermore, ovulation induction should not be used in women with ovarian failure because they are unresponsive to any form of induction of ovulation.

Clomiphene citrate (50 mg daily for 5 days, begun on the third to fifth days after spontaneous or induced uterine bleeding) is the first-line agent to induce ovulation in women who do not have hyperprolactinemia and who have the ability to release LH and FSH. Clomiphene, which appears to act as an antiestrogen, stimulates gonadotropin secretion by the pituitary gland to initiate follicular development. If ovulation is not achieved in the first cycle of treatment, subsequent cycles increase the daily dose in a stepwise fashion in 50-mg increments to a maximum of 200 to 250 mg daily for 5 days. The highest dose should be continued for 3 to 6 months before the patient is regarded as unresponsive to clomiphene. Off-label oral letrozole by a specialist is equivalent to clomiphene for inducing ovulation with a slightly lower frequency of multiple gestation.[A7] The ovulatory surge of LH may occur 5 to 12 days (average, 7 days) after the completion of the last day of clomiphene treatment, so couples are advised to have intercourse every other day during this interval. Ovulation can be documented by monitoring changes in basal body temperature or preferably by measuring the serum progesterone level 14 days after the last clomiphene dose. Intrauterine insemination, rather than timed intercourse, optimizes success. If pregnancy does not result, menses should occur after 3 weeks. Withdrawal bleeding with progestin can be induced if the patient fails to bleed within 4 weeks of therapy and if a serum hCG level documents that the patient is not pregnant. Testing the urine for an LH surge may also be useful in timing ovulation.

Of appropriately selected patients, 75 to 80% ovulate, and 40 to 50% can be expected to become pregnant. About 15% of pregnancies can be expected with each ovulatory cycle. The multiple pregnancy rate is about 8%, with almost all being twins. The incidence of congenital anomalies is not increased.

Side effects of clomiphene are uncommon and rarely serious. The most serious ones include vasomotor flushes (10%), abdominal discomfort (5%), breast tenderness (2%), nausea and vomiting (2%), visual symptoms (1.5%), and headache (1%). Ovarian enlargement may occur but is rare (5%), and clomiphene does not appear to increase the risk for epithelial ovarian cancer.

The administration of hCG at 7 days after the last day of clomiphene induces ovulation about 36 hours later and may be helpful in selected couples. Low-quality evidence suggests that the addition of dexamethasone 0.5 mg orally at bedtime to blunt the nighttime secretion of adrenocorticotropic hormone may be useful in hyperandrogenic women who fail to ovulate in response to clomiphene.

Women who do not respond to clomiphene typically require exogenous gonadotropins and hCG or perhaps pulsatile GnRH to induce ovulation. Exogenous gonadotropins are typically administered (intramuscularly or subcutaneously, depending on the preparation) at doses of two to four vials, each containing 75 IU, for 5 to 12 days to achieve follicular development as monitored by ultrasonography and serum or urinary estradiol concentrations. Then hCG (5000 to 10,000 IU) is administered as a single intramuscular dose when follicular maturation is apparent. The hCG should be withheld if more than three follicles mature together. GnRH analogs (ganirelix acetate or cetrorelix 0.25 mg daily) are used to suppress endogenous follicular activity before the initiation of exogenous gonadotropin therapy and continued until hCG is given. Ovulation can be induced in almost 100% of patients, but pregnancy occurs in only 50 to 70%. There is no increased risk for congenital anomalies with exogenous gonadotropins and hCG. The rate of multiple pregnancies with exogenous gonadotropins and hCG may approach 30%, with 5% being triplets or more. Because of the expense and the complication rate, thorough evaluation should be performed to exclude other causes of infertility before exogenous gonadotropins and hCG are used.

Ovarian hyperstimulation syndrome, which is the major side effect of exogenous gonadotropin therapy, may be life-threatening. The ovaries enlarge remarkably, with multiple follicle cysts, stromal edema, and multiple corpora lutea. Fluid shifts from the intravascular space into the abdominal cavity, with resultant hypovolemia and hemoconcentration. The most serious complications may include thromboembolism, renal failure, adult respiratory distress syndrome, and hemorrhage from ovarian rupture. Treatment is conservative, with monitoring of fluid and electrolyte status. Pelvic examinations should not be performed for fear of rupturing the ovaries. The hyperstimulation generally resolves slowly over about 7 days but persists longer if the cycle results in pregnancy.

In cases of unexplained infertility, clomiphene citrate or exogenous gonadotropins can be combined with intrauterine insemination of spermatozoa.[19] The intent is to increase conception rates by assuring access of sperm to several oocytes. This procedure is safe and effective,[A8] but multiple (sometimes high-order) gestations are a significant risk. The risk for multiple gestation and the costs are reduced if women who have not conceived with ovarian stimulation and natural insemination proceed immediately to treatment by in vitro fertilization.

Hyperprolactinemic Women

Both bromocriptine (2.5 mg daily) and cabergoline (0.25 mg twice weekly) are effective in inducing ovulation and pregnancy in about 80% of hyperprolactinemic women. The drug should be stopped when pregnancy is confirmed. Most women with prolactin-secreting pituitary tumors remain asymptomatic during pregnancy. It is rare for a patient with either a microadenoma or a macroadenoma to develop a problem related to the tumor that affects either the mother or the fetus during pregnancy. However, formal assessment of visual fields and computed tomography or magnetic resonance imaging should be performed in any patient experiencing suggestive symptoms. Symptoms generally abate with institution of therapy with a dopamine agonist. No adverse effects of dopamine agonists on fetuses or pregnancies have been reported.

Assisted Reproductive Technologies

The assisted reproductive technologies, in which by definition both eggs and sperm are handled outside of the body, are commonly used to treat infertile couples with tubal disease, endometriosis, oligospermia and azoospermia,

sperm antibodies, and unexplained infertility, or women whose eggs were preserved prior to cancer therapy.[20] In vitro fertilization involves ovarian hyperstimulation, retrieval of oocytes, fertilization, embryo culture, and embryo transfer. Ovarian hyperstimulation with clomiphene citrate and exogenous gonadotropins, gonadotropins alone, or a GnRH agonist or antagonist plus gonadotropins typically causes 1 to 20 oocytes to mature, depending on the patient's age and ovarian reserve. After follicular growth is judged sufficient by ultrasound examination, hCG is given to induce final follicular maturation. About 34 hours after the administration of hCG, the oocytes are retrieved by direct needle puncture of each follicle, usually transvaginally under ultrasound guidance. The oocytes are then inseminated in vitro with washed sperm, or a single sperm is injected directly into a single egg (so-called intracytoplasmic sperm injection). The embryos are cultured for about 40 to 120 hours, after which one or more embryos are transferred to the uterine cavity. Embryos may be cultured to the blastocyst stage (at 120 hours) before transfer. Additional embryos can be frozen in liquid nitrogen for transfer in a subsequent natural cycle. The success rate is most dependent on the age of the woman. In the United States the percentage of cycles resulting in live births ranges from 40% in women younger than age 35 years to 12% in women age 41 to 42 years. Approximately 4 to 9% of pregnancies are twins, and 0.1% are triplets or higher-order multiples. The early embryo can be tested preimplantation for genetic abnormalities that are known or identified by preconception screening, thereby allowing only unaffected embryos to be transferred in families with recognized and testable genetic abnormalities. Uterus transplantation is an emerging option for infertile women who have a nonfunctioning or absent uterus.[21]

SEXUAL FUNCTION AND DYSFUNCTION

Sexual Function

DEFINITION

Sexual responses historically have been divided into four phases: excitement, plateau, orgasm, and resolution. With sexual arousal and excitement, vasocongestion and muscle tension increase progressively, primarily in the genital region, manifested by vaginal lubrication in the female. The lubrication is due to formation of a transudate in the vagina. Sexual excitement is initiated by any of a variety of psychogenic or somatogenic sexual stimuli and must be reinforced to result in orgasm. With continued stimulation, the excitement phase increases in intensity into a plateau phase, during which a high state of sexual interest is maintained. The plateau phase may be short or long, and it is from this phase that an individual can shift to orgasm. The orgasmic phase, which tends to be brief, is characterized by rapid release from the developed vasocongestion and muscle tension. The orgasmic release is also known as the climax because peak psychological and physical intensity is achieved, with an attendant feeling of satisfaction. Copious secretions and transudate may flow during orgasm in women. Characteristic genital and extragenital responses occur during these phases. Estrogens magnify the sexual responses, but responses may occur in estrogen-deficient women. For women, these changes occur in the breasts and in the pudendal region and are variable from one response cycle to another. For some women, excitement proceeds quickly through plateau to orgasm, and orgasm is explosive and accompanied by vocalization and involuntary contractions of the pelvic skeletal muscles. For other women, the responses are slow in building, controlled in amplitude, and long lasting. For a few women, orgasm never occurs; for many, it is intermittently absent.

The somatic sensate focus enabling orgasmic release is variable and may include stimulation of the breasts, vagina, or clitoris. The psychological aspect of coitus may involve concentration on the current partner or act or on fantasies about other times and persons. Although orgasms may vary in physiologic intensity, what is important is psychological satisfaction. Satisfaction for both men and women may be had without orgasm. Women seek sexual experiences for intimacy as well as for sexual gratification. Women may be receptive to or seek out sexual stimuli to enhance intimacy. Biologic and psychological factors contribute to the processing of these stimuli and can enhance arousal and desire simultaneously.

Sexual Dysfunction

Women may seek consultation because of disturbances in normal sexual arousal or orgasm[22] or because of pain with intercourse (dyspareunia).[23] Such sexual dysfunction may be due to either organic or functional disturbances.

A variety of diseases affecting neurologic function, including but not limited to diabetes mellitus (Chapter 210) and multiple sclerosis (Chapter 380), may prevent sexual arousal. Debilitating systemic diseases, such as malignant disease, may also affect sexual function indirectly. Local pelvic disorders, such as endometriosis and vaginitis, cause dyspareunia and may lead to sexual avoidance. Estrogen deficiency causing vaginal atrophy and dyspareunia is a relatively common cause of sexual dysfunction.

Vaginismus, which involves involuntary contractions of the muscles surrounding the introitus, also leads to dyspareunia. It is a conditioned response engendered by a previous real or imagined traumatic sexual experience.

Feelings of guilt (caused by incest or rape, as examples), of inadequacy (caused by hysterectomy or mastectomy), or of depression or anxiety may lead to failure to be aroused. Failure to achieve orgasm may be viewed as a dysfunction if the woman is frustrated or dissatisfied.

TREATMENT

Treatment of sexual dysfunction should eliminate functional causes and provide the patient, often together with her partner, with appropriate psychological counseling. Behavioral modification is effective in treating many women with psychological sexual dysfunction.[A9,24] Sexual satisfaction also can be increased by treating women with testosterone, but dosing guidelines are not clear. Such therapy cannot be considered standard care based on current evidence.

INTERRUPTED PREGNANCY

About 10% of known pregnancies in women under age 30 years end in miscarriage, and this percentage increases to over 50% by age 45 years. About half of these miscarriages occur within the first 6 weeks, but the rate is likely much higher given the number of early miscarriages before pregnancy is confirmed. Expert evaluation is required to be sure that no placental or fetal tissue (incomplete miscarriage) remains unexpelled. For delayed or silent miscarriage, nonviable tissue that has not yet been expelled can be expelled by treatment with oral mifepristone (200 mg) combined with vaginal, oral, or sublingual misoprostol (800 mg) 2 days later.[A10] If medical therapy is unsuccessful, dilation and curettage may be performed. Persistent pregnancy of unknown location can be treated actively with methotrexate (50 mg/m^2 intramuscularly).[A11]

Tubal pregnancy, which manifests as pelvic pain and is often accompanied by light vaginal bleeding, is an emergency that requires operative intervention before tubal rupture and life-threatening hemorrhage occur. It must be suspected whenever a woman of childbearing age develops acute pelvic pain or marked lower abdominal pain or cramping, especially if a menstrual history reveals a missed period.[25] The choice between methotrexate or surgical intervention should be considered based upon the clinical scenario.

Voluntary termination of pregnancy is usually accomplished medically (as for silent miscarriage) but can also be performed interventionally (Chapter 220).

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For the General References and other additional features, please visit Elsevier eBooks+ at https://ebooks.health.elsevier.com.

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219 APPROACH TO WOMEN'S HEALTH

KAREN M. FREUND

An approach to the care of women must go beyond an understanding of differences in the incidence of disease between men and women. Providers need to consider the impact of sex differences (differences based on genetic and hormonal differences) and gender differences (differences attributable to the roles men and women are ascribed in society).[1] Therapeutic decisions should take into account both genetic and environmental differences in the presentation of disease and the effectiveness of therapeutic options, the patient's reproductive life stage, comorbid conditions, and the social and cultural contexts of care. The increased number of women participating in clinical research improved knowledge about women's health, but gaps remain regarding the gender-specific impact of new therapies and interventions owing to a lack of data on the heterogeneity of impact by sex and gender.[2]

LIFESPAN GROUPS

Many important women's health issues are linked to the social, psychological, and biologic context at certain ages and stages of life. When considering both preventive care and common causes of mortality and morbidity, these lifespan stages provide a context for organizing care (Table 219-1).

For most women, young adulthood (15 to 44 years) is marked by social transitions in family structure, such as forming one's own family, parenting, and entering the work force. Competing demands of career development and of child and eldercare needs affect both a woman's health and her own health care. During this age range, mortality rates are low, so health visits can focus on behavioral decisions that will influence the risk for future disease, such as sexual behavior, smoking (Chapter 363), alcohol (Chapter 364) and drug use (Chapter 365), diet (Chapter 13), and exercise (Chapter 14). Major sources of morbidity include intentional and unintentional injury, including interpersonal violence (Chapter 223) and motor vehicle injuries. Human immunodeficiency virus (HIV; Chapter 360) is a leading cause of morbidity and mortality in this age group. Depression and anxiety (Chapter 362) are common in this and all life stages. Reproductive issues (Chapter 218) are considered in most therapeutic decisions.

TABLE 219-1 IMPORTANT HEALTH ISSUES FOR WOMEN THROUGH THE LIFESPAN

	AGES		
ISSUE	***15-44 yr.***	***45-65 yr.***	***65+ yr.***
Behavioral issues	Risk behaviors Sexual behavior Smoking Alcohol and drug use Exercise Diet	Risk behaviors Smoking Alcohol and drug use Exercise Diet	Risk behaviors Smoking Exercise
Social roles and needs	Entering work force Relationship transitions Parenting Caregiving to several generations	Caregiving to several generations Transitions in family and work environments	Losses and social isolation Poverty due to lower lifetime earnings
Reproductive issues	Reproductive health issues	Menopause transition	
Injury	Intentional and unintentional interpersonal violence Motor vehicle injuries		Falls
Common causes of mortality and morbidity	Depression Anxiety HIV/AIDS	Cancer Obesity Diabetes Depression Anxiety	Cardiovascular disease Cancer Cognitive decline Osteoporosis Osteoarthritis Incontinence Depression Anxiety

AIDS = acquired immunodeficiency syndrome; HIV = human immunodeficiency virus.

The middle years (ages 45 to 65 years) continue to be influenced by behavioral decisions, especially diet, exercise, and alcohol and substance use. The social context includes role changes as children reach adulthood; caregiving responsibilities are now for dependent children and possibly grandchildren, as well as aging parents. The menopausal transition (Chapter 222) may be accompanied by new symptomatic concerns. Common causes of morbidity, including diabetes (Chapter 210) and obesity (Chapter 201), now reflect earlier behavioral decisions. Cancer is the leading cause of mortality.

Health issues in older women (65+ years) may occur in the context of loss of function and independence. Because women commonly survive their male partners, they are more likely at this stage of life to be unpartnered. Compared with older men, older women have a greater number of social needs, including social isolation, depression, and poverty from accumulated lower lifetime earnings. Cardiovascular disease is the major cause of mortality, followed by cancer, cerebrovascular disease, chronic obstructive lung disease, and pneumonia. Loss of independence is related to cognitive decline (Chapter 371), osteoarthritis (Chapter 241), osteoporotic fractures (Chapter 225), and incontinence (Chapter 115).

HEALTH DISPARITIES AMONG WOMEN

The health status of women is heavily influenced by racial and ethnic differences in outcomes for most common causes of mortality and morbidity. Black Americans, women from many Asian and Pacific Island nations, Native Americans, and women of Latino background share poorer outcomes for a wide variety of conditions (Chapter 4). This broad finding of poorer outcomes across many diverse ethnic and racial groups[3] emphasizes the social determinants of health (e.g., income, education, violence, housing, and food insecurity, among others; see Chapter 4). Common recommendations for health promotion, including a diet low in animal fats and processed sugars but high in whole grains, fruits, nuts, and vegetables, along with regular exercise, such as walking, may be difficult to follow in high-crime neighborhoods or in locales where a variety of affordable, nutritious food options are not available. Barriers to health care access and poor adherence to medical therapy are more common in low-income women, who may have difficulty scheduling appointments that do not interfere with their work schedules or unpaid time off from clerical or service jobs. Low health literacy and cultural barriers can add to challenges in accessing health care. The need to care for dependent children or elders may interfere with women's ability to address their own health care needs (Chapter 4).

COMMON CAUSES OF MORTALITY IN WOMEN

CARDIOVASCULAR DISEASE

Cardiovascular disease (Chapter 40) is the overall leading cause of death in women. However, because cardiovascular-related death occurs most often in women older than age 65 years, its impact is often under-recognized or underestimated. Race and ethnicity play a large role in the risk for cardiovascular disease; Black women have much higher incidence and mortality rates than any other racial or ethnic group, and Latinas and Asian women also have higher rates than White populations.

The incidence rate of cardiovascular disease in women lags 10 years behind that of men from ages 40 through 70 years; that is, a 65-year-old woman has a similar risk to a 55-year-old man. There is no abrupt increase in the risk of cardiovascular disease at menopause in women, thereby suggesting that menopausal changes in estrogen or progesterone do not account for this sex difference. Randomized clinical trials have confirmed that combined estrogen/progestin hormone therapy in women does not prevent cardiovascular disease and is not indicated for cardiovascular disease prevention, but conjugated estrogen alone may reduce the risk of heart disease over the following 18 years when begun in women ages 50 to 59 years.[A1] Estrogen monotherapy or combined estrogen/progestin therapy has complex systemic effects, and the net rates of adverse outcomes when used for chronic disease prevention may vary according to an individual woman's risk factor profile. For example, data suggest an overall benefit when estrogen therapy is started between the ages of 50 to 59 years but not if started later.[4] Therefore, an individualized risk stratification approach is advocated in menopausal women who are otherwise potential

ABSTRACT

The approach to the care of women should consider both the impact of sex differences (i.e., differences based on genetic, hormonal, and other biologic differences), as well as gender differences (i.e., differences related to the roles men and women play in society, including occupation and environmental exposures). A lifespan perspective guides an understanding of the common causes of morbidity and mortality by age and can inform preventive strategies. Providers caring for women of reproductive potential should consider the reproductive impact of every medication prescription. The prevalence, presentation, and management of many common conditions differ between women and men, including cardiovascular disease, cancer, obesity, osteoporosis, and behavioral health issues. However, the precise contribution of sex as compared with gender roles remains uncertain. Racial and ethnic disparities in outcomes on a wide variety of health conditions almost always reflect social determinants of health rather than genetic determinants.

KEYWORDS

lifespan
morbidity
mortality
teratogenicity
reproductive

candidates for hormone therapy because of other indications (see Chapter 222). Supplementation of calcium and vitamin D, which can improve bone health in women (Chapter 225), is not indicated to prevent cardiovascular disease.[A2] Other risk factors for cardiovascular disease in women are the same as those in men: elevated lipid levels (Chapter 190), lack of physical activity, obesity (Chapter 201), smoking (Chapter 363), hypertension (Chapter 64), and diabetes (Chapter 210). Women with diabetes have the same risk for cardiovascular disease as men of the same age with diabetes.

However, there are notable disparities in the burden of coronary heart disease among some groups of women, especially women who are disadvantaged because of race, ethnicity, income level, and educational attainment. Cigarette smoking continues to be an important behavioral risk factor for cardiovascular disease, especially in younger women, Native American women, and women with low incomes and low educational attainment. The incidence of many known risk factors, including obesity, hypertension, and hypercholesterolemia, is greater in Black women than in White women. Furthermore, data suggest that women are less likely to receive risk factor reduction therapy, a reflection of an inertia caused by clinicians' misperceptions of their risk for heart disease.

The presentation of coronary artery disease in women differs from that in men. Although chest pain is the most common presentation in women, atypical and noncardiac pain is a more frequent presentation in women than in men, and fewer women have typical chest tightness or pressure as their presenting complaint.[5] For this and other reasons, women often face delays in seeking and receiving emergency care for an acute coronary syndrome (Chapter 57) or acute myocardial infarction (Chapter 58), thereby increasing their risk for death and recurrent myocardial infarction.[6]

Medical management is similar for men and women with acute coronary syndromes (Chapter 57) and acute myocardial infarction (Chapter 58). Women with ST-segment-elevation myocardial infarction or any high-risk women with non–ST-segment-elevation myocardial infarction obtain the same benefits from either percutaneous cardiac interventions of coronary bypass graft surgery (Chapter 59) as do men, after controlling for other comorbid conditions, but women commonly have lower rates of revascularization. Recent randomized clinical trials indicate similar benefits of new therapies for heart failure for women and men, including sodium-glucose cotransporter-2 inhibitors,[A3] defibrillator use,[A4] and transitions of care support.[A5]

U.S. guidelines for the management of lipid disorders (Chapter 190) are based on 10-year risk of cardiovascular disease as well as absolute lipid levels.[7] Although these guidelines are not gender specific, they attempt to avoid overtreatment of younger women at very low risk while avoiding undertreatment of women with the lower low-density lipoprotein (LDL) cholesterol level but much higher overall risks of cardiovascular disease. High-intensity statin therapy is recommended as secondary prevention for women who have clinical atherosclerotic disease, as well as for primary prevention for women who have a 20% or greater risk of atherosclerotic cardiovascular disease, an LDL cholesterol level higher than 190 mg/dL, or diabetes and a 7.5% or greater 10-year risk of atherosclerotic cardiovascular disease (Chapter 190). A moderate-intensity statin is recommended for lower risk women with diabetes or with a 5 to 20% 10-year risk of atherosclerotic cardiovascular disease. Women lag behind men in use of medical therapy for lipid disorders, perhaps in part because of higher reported rates of adverse effects, especially from statins; however, most patients who report such symptoms can successfully use statins after a blinded trial (see Chapter 190).

TYPE 2 DIABETES

The rates of type 2 diabetes (Chapter 210) continue to rise, with a greater risk in women who are overweight, obese, or physically inactive. Rates are higher in many racial and ethnic groups including Black, Asian, Native American, and Latina women than among White women. Lifestyle changes (primarily diet and exercise) can reduce the incidence of type 2 diabetes.[A6] No randomized clinical trials have shown that screening for diabetes is beneficial, but current U.S. guidelines recommend screening overweight or obese adults with a high A_{1C} level as part of their cardiovascular risk assessment beginning at age 35 and continuing to age 70 years.[8] For women who develop gestational diabetes (Chapter 221), the risk of developing type 2 diabetes later in life increases five-fold,[9] so screening with hemoglobin A_{1C} levels at 6 to 12 weeks postpartum and every 3 years thereafter is recommended.[10]

The incidence of diabetes is rising in women at younger ages, with significant perinatal and maternal health implications. Ongoing discussion of fertility control and family planning is critical in diabetic women with childbearing potential. Tight glycemic control before conception and through the first trimester is critical to reduce the risk for birth anomalies, and it is important later in pregnancy to reduce the risk for adverse fetal events, including macrosomia (large for gestational age) and preterm birth (Chapter 221). Ideally, women planning a pregnancy should switch from oral agents to insulin, with home glucose monitoring for tight control (Table 219-2). Risks of maternal complications from diabetes including vascular disease, retinopathy, hypertension, preeclampsia, renal disease, and neuropathy are general related to glycemic control before and during pregnancy and usually not specifically due to pregnancy itself.

CANCER

Cancer is the leading cause of death in women ages 40 through 65 years, and it is the leading cause of years of life lost in women younger than age 65 years. Breast cancer (Chapter 183) is the most common type of cancer and the second leading cause of cancer death in women. Studies indicate that many women significantly overestimate their personal risk for the disease. The lack of understanding of the cause of most breast cancers and the limitations of the imaging modalities used as screening tests have hampered efforts at breast cancer control. Data suggesting overdiagnosis of breast cancer, especially in women ages 40 to 50 years, has prompted an appreciation for the implications of screening mammography[11] and the virtue of shared decision making, especially in this age group. After decades of an increasing incidence of breast cancer in the United States, incidence rates have fallen in the past decade. The cause of this decline is not understood; reduced use of postmenopausal hormone therapy and recent declines in screening rates have been implicated. In women who are known carriers of the *BRCA1* and *BRCA2* mutations, estimates now can be made for age-specific risks of breast, ovarian, and contralateral breast cancer (see Chapter 183).

Lung cancer (Chapter 177) is now the leading cause of cancer death in women, and rates continue to rise, commensurate with the timeline for increasing rates of smoking in women. Most lung cancers are smoking related, although women are more likely than men to have lung cancers that are not tobacco related. Based on the results of randomized trials,[A7] guidelines recommend low-dose chest tomographic screening of women as well as men who have a greater than a 20 pack-year smoking history, who are current smokers, or who quit within the previous 15 years.[12] Nevertheless, smoking cessation (Chapter 363) continues to be the most effective strategy to prevent lung cancer and should be the focus of primary prevention.

Colorectal cancer (Chapter 179) has a similar incidence in both women and men. Screening is recommended beginning at age 45 years and continuing to age 75 years for both women and men[13] using colonoscopy every 10 years, sigmoidoscopy every 5 years, annual stool testing with a fecal immunochemical test or every 1 to 3 years with a DNA fecal immunochemical test. Rates of screening in women are similar to men, but neither reach Healthy People 2030 goals for this effective preventive screening.

Ovarian cancer (Chapter 184) is relatively rare, with about 21,000 cases in the United States, and its annual and incidence has declined in recent decades. However, mortality is high owing to its presentation at late stages in most cases. Lower abdominal or pelvic pain, urinary symptoms, and changes in bowel habits are nonspecific and common in many women, thereby limiting the ability to detect this cancer at an early stage. A screening pelvic examination is not useful in asymptomatic women, and no effective screening test has been shown to reduce mortality from ovarian cancer. As a result, screening of the general population is not recommended.[A8]

The greatest advance in cancer prevention is the development of vaccines against the most carcinogenic subtypes of human papillomavirus (HPV) associated with cervical cancer (Chapters 184 and 344)[A9] and anal cancer. Although concern of tacit approval of sexual activity among young adolescents has been cited by parents as a reason to delaying vaccination, evidence does not demonstrate this concern to be founded, and vaccination is recommended for girls at ages 11 to 12 years (Chapter 15). Pap test screening can be delayed until age 21 years. Cervical cancer screening is generally recommended with cervical cytology about every 3 years in women age 21 to 29 years and then either every 3 years with cytology alone or every 5 years with HPV testing in women ages 30 to 65 years.[14] Pap tests are not recommended for women after hysterectomy for nonmalignant indications or for women older than 65 years with adequate recent screening and no high-risk factors.

OSTEOPOROSIS

Osteoporotic fractures, especially of the wrist, hip, and vertebrae (Chapter 225), are major causes of disability, loss of independence, and mortality in older women. The prevention of osteoporosis begins at puberty and extends throughout adulthood by emphasizing the intake of calcium and vitamin D,

TABLE 219-2 PREFERRED MEDICATIONS FOR WOMEN OF REPRODUCTIVE POTENTIAL

COMMON CONDITIONS IN WOMEN OF REPRODUCTIVE POTENTIAL	ISSUES TO BE AWARE OF	PREFERRED MEDICATIONS OR GROUPS OF MEDICATIONS
Depression	Must consider effects of untreated depression on mother and infant	Avoid newer medications when older drugs with more information are available SSRIs are generally considered safe; fluoxetine has most safety data
Anxiety	Commonly associated with depression in women	Benzodiazepines generally considered safe
GERD	No data on harmful effects of either H_2-blockers or PPIs Misoprostol is contraindicated (can cause miscarriage, fetal death, congenital anomalies)	Calcium-containing antacids are first-line therapy H_2-blockers preferred over PPIs
Acne	Oral isotretinoin and topical tazarotene are contraindicated owing to congenital defects	Most other topical agents are considered classes B and C
Asthma	Extensive data on safety of common drug categories: benefit ratios far exceed risk in treating women	Glucocorticoid inhalers Systemic prednisone for flares Short- and long-acting bronchodilators
Seizure disorders	Difficult to separate effects of medication from effects of seizure on fetal development All agents associated with some increased risk for fetal abnormality (4-8%, compared with 1-2% in general population); valproate and phenobarbital have highest risks	Monotherapy at lowest doses recommended Avoid medication changes in first trimester Folate supplementation in preconception period
Hypertension (not preeclampsia)	ACE inhibitors and ARBs are contraindicated in pregnancy; possibly associated with cardiovascular and neurologic anomalies in first trimester; may cause abnormalities in renal hemodynamics in third trimester Most data suggest thiazide diuretics are safe if stable use before pregnancy	β-Blockers, especially labetalol, and methyldopa are first-line choices Calcium-channel blockers are also considered safe
Lipid disorders	Circulating lipid levels are elevated with pregnancy and breast-feeding	Except in very high risk women, no medications during pregnancy; ideally, stop statins before conception
Analgesics for fever and pain management	Controversy about whether NSAIDs slightly increase risk for miscarriage in first trimester	Acetaminophen preferred; aspirin also considered safe
Headache	Controversy about whether NSAIDs slightly increase risk for miscarriage in first trimester	Acetaminophen preferred; aspirin also considered safe
Diabetes	First-generation sulfonylureas contraindicated in pregnancy; may cause fetal hyperinsulinemia and birth defects	Conversion to insulin during planned preconception period Insulin, metformin, and glyburide preferred in women of childbearing potential
Autoimmune conditions	Must weigh benefits of immunosuppressive use against potential risks to both mother and infant Methotrexate is contraindicated in pregnancy because it induces miscarriage Limited data on TNF-alpha and IL-17 inhibitors; available data indicate minimal transfer of IgG across placenta and no known birth defects or premature birth	Prednisone generally considered safe in pregnancy Azathioprine, sulfasalazine, cyclosporine, and hydroxychloroquine generally preferred if required
Tobacco control	Cigarette smoking has known harmful effects on fetus In several randomized controlled trials, nicotine replacement was associated with reduced levels of nicotine and improved birth outcomes Bupropion has not shown adverse outcomes in several small randomized controlled trials	Try nonpharmacologic approaches to cessation first Short course of nicotine replacement likely better for fetus than smoking
Polycystic ovarian disease	Metformin can restore ovulatory cycles; use with contraception	
Bacterial infections	Tetracyclines accumulate in fetal bone and teeth Sulfa drugs may increase risk for neural tube defects with use in first trimester and kernicterus with use in third trimester Trimethoprim interferes with folic acid metabolism Streptomycin and kanamycin associated with bilateral deafness	Penicillins, cephalosporins, erythromycin, azithromycin considered safe

ACE = angiotensin-converting enzyme; ARB = angiotensin receptor blocker; GERD = gastroesophageal reflux disease; IL-17 = interleukin-17; NSAID = nonsteroidal anti-inflammatory drug; PPI = proton pump inhibitor; SSRI = selective serotonin re-uptake inhibitor; TNF = tumor necrosis factor.

weight-bearing exercise, the avoidance of smoking, and moderate alcohol consumption. To maintain the structural strength of bone, women require a calcium intake of 1000 mg/day, increasing to 1300 mg in puberty and when breast-feeding and to 1200 mg after menopause. Vitamin D, which is a necessary element for the absorption of calcium (Chapter 199), is available through direct sun exposure, supplementation of milk (not most other dairy products), and supplementation of some juices. Epidemiologic data suggest widespread vitamin D deficiency in women in the United States, and screening for a single baseline serum 25-hydroxyvitamin D level can provide women with useful information about the adequacy of their diets and lifestyle. If the level is below 20 ng/mL, daily supplementation of vitamin D (600 IU, increased to 800 IU after age 70 years) is recommended for women.

Although no long-term outcome data exist on the benefits of dual-energy x-ray absorptiometry bone densitometry screening, most guidelines recommend such screening at age 65 years in women[15] but earlier at ages 50 to 65 years in women who have one or more risk factors (smoking, family history, body mass index < 22, or alcohol use). Long-term estrogen therapy is not recommended to prevent osteoporosis. Bisphosphonates are first-line therapy despite their associated risks of gastroesophageal erosions (with oral but not intravenous therapy) and rare but debilitating jaw osteonecrosis (Chapter 229). Raloxifene, a selective estrogen receptor modulator, can prevent osteoporosis while reducing the risk of breast cancer. Anabolic agents, including parathyroid hormone analogues, are recommended as secondary therapy for women who do not tolerate bisphosphonates, have

ongoing bone loss or fragility fractures despite bisphosphonates, or have severe osteoporosis.

COMMON CAUSES OF MORBIDITY IN WOMEN

OBESITY

Obesity rates continue to rise, and the prevalence of obesity is higher in women than men, especially among minority and low-income women (Chapter 201). In the United States, the rates of obesity in women have increased nearly 2.5-fold from 17% in 1976-1980 to almost 45% now. Reductions in caloric intake (Chapter 13) and increased exercise (Chapter 14) are key treatment strategies. Studies suggest that no single diet is superior to others, and many common diet strategies can reduce weight. Increasing activity during the course of one's daily routine is as effective as shorter intervals of more strenuous activity. The most effective programs include a combination of behavioral therapy, either individually or in groups, to address behavioral patterns of food intake, diet, and exercise. Weight loss targets of 1 to 2 lb/week and a total loss of up to 5 to 10% of body weight are realistic goals. Even modest changes in weight and modest increases in physical activity reduce morbidity and mortality on a population basis.

Exercise and diet changes are difficult for many people to achieve for a wide variety of reasons. The physical environment may not be conducive to physical activity owing to the sedentary nature of most workplaces, the lack of safe areas to exercise, and architectural design features, such as the lack of easy access to stairs instead of elevators. The use of prepared foods and the consumption of fast foods, which are high in calories and low in nutritional content, increase the risk for obesity.

There are currently no evidence-based interventions to support weight reduction in the setting of a brief office visit. Most guidelines focus on assessing BMI in all women and recommending weight reduction with diet restriction and exercise, including behavioral therapy to support these behavioral changes. Excessive postpartum weight retention (≥4.5 kg over prepregnancy weight at 6 to 12 months after delivery) also occurs disproportionately in minority and low-income women and is associated with similarly increased risk of complications, such as diabetes and cardiovascular disease. In contrast to current general obesity treatment guidelines that emphasize intensive, in-person interventions to affect lifestyle modification, management of postpartum weight retention is more effective using remote internet-based methods.[A10]

When behavioral interventions are inadequate, medical treatments include a pancreatic lipase inhibitor (orlistat), glucagon-like peptide 1 agonists (e.g., liraglutide and semaglutide), and combination therapy with bupropion-naltrexone or phentermine-topiramate (Chapter 201). However, pharmacotherapy should be used in conjunction with an exercise and diet program and not as sole therapy. For obese women with a BMI greater than 40 or with a BMI greater than 35 and major comorbid conditions (such as diabetes, sleep apnea, or osteoarthritis) despite behavioral and pharmacologic therapies, bariatric surgery (Chapter 201) is highly effective.

DEPRESSION

Major depression and other related disorders, including dysthymia, are more common in women (Chapter 402). Depression is a significant comorbidity in many chronic medical conditions and is also a disabling but treatable complication of the postpartum period. Somatic complaints are a common presentation of depressive disorders, so it is critical to consider depression as either a primary or a secondary diagnosis and to treat depression as part of the overall management plan.

Multiple short screening tools (see Table 361-6) have been developed to identify depression and are recommended for use in primary care settings, especially for women who are pregnant or postpartum. The treatment of dysthymia and depression includes psychotherapy (Table 362-4) and medications (Table 362-5).

ANXIETY DISORDERS

Anxiety disorders (Chapter 362) also are more common in women. They commonly coexist with depressive disorders. Anxiety disorders, including posttraumatic stress disorder, may be a consequence of violence against women, which often remains unidentified (Chapter 223). Benzodiazepines (Table 362-9) are safe and effective in trials for short-term use. Selective serotonin re-uptake inhibitors (Table 362-5) and cognitive behavioral therapies are effective for the long-term management of anxiety disorders.

OSTEOARTHRITIS

Osteoarthritis (Chapter 241) is one of the most common causes of morbidity and functional status limitation, especially as women age. Assessment of pain and functional status is at the core of management. Physical and occupational therapy to restore functional status is a critical component of care. Joint replacement (Chapter 255) should be considered and recommended when functional status interferes with activities of daily living and when supportive care and other symptom management strategies are ineffective.

SMOKING

Tobacco use, most commonly cigarette smoking, continues to be one of the major preventable causes of morbidity and mortality in women (Chapter 363). Despite progress in smoking cessation efforts, lower-income women and younger women continue to start smoking and fail to quit smoking at high rates. In the United States, girls currently initiate cigarette smoking at similar rates as boys in high school, thereby indicating that the challenges of smoking-related illness will continue in women.

Health care providers can achieve 1 to 2% reduction in smoking rates simply by asking all patients about their smoking status and making a brief statement encouraging smokers to quit. Further gains in smoking cessation are possible with targeted counseling, which involves assessing the patient's stage of readiness to change and providing counseling relevant to that stage.

Nicotine replacement therapy, bupropion, and varenicline are pharmacologic agents for smoking cessation (Chapter 363).[16] Limited data are available to assess the effectiveness of these therapies specifically in women, but nicotine replacement therapy is preferred during pregnancy, bupropion is recommended after the first trimester, and varenicline is not recommended for pregnant or breast-feeding women.

The use of electronic smoking devices has dramatically risen at similar rates in girls and boys of middle school and high school age. Although these devices may be helpful for smoking cessation, more commonly they serve as a gateway to cigarette smoking (Chapter 362) and expose users to the potential side effects of inhaled substances other than nicotine (Chapter 82).

ALCOHOL USE AND SUBSTANCE USE

Approximately 5% of women are dependent on alcohol (Chapter 364), but this dependence is under-recognized in clinical practice. It is well established that lower amounts of alcohol cause alcohol-related liver and other disease in women compared with men, and alcohol also increases the risk for breast cancer. Binge drinking (defined as four drinks or more at a sitting) by up to one in eight women who drink alcohol can lead to poor judgment and risks to personal safety. The approach to alcohol abuse is detailed in Chapter 364.

Women have lower rates of using substance abuse (Chapter 365) compared with men, and women account for only about half as many opioid-related deaths as men.[17] However, rates of opioid deaths continue to rise for women, especially for White women and especially deaths from overdoses involving synthetic opioids. All prescribing physicians must be aware of the risks of drug abuse. Approaches to preventing and treating drug abuse and dependence are described in detail in Chapters 365.

INCONTINENCE

Urinary incontinence (Chapter 115) is a frequently overlooked cause of major functional status limitations in middle-aged and older women. As many as half of affected women underreport this problem to their physicians and alter their lifestyles to adapt to the problem, including reducing fluid intake, avoiding activities that exacerbate the problem, and restricting travel where access to facilities is uncertain. Two broad categories of incontinence are stress incontinence and urge incontinence, but women commonly have aspects of both types. The distinction often can be made by a careful history, but urodynamic evaluation (Chapter 115) should be considered if the history does not clearly identify a cause. Stress incontinence is defined as leaking with increases in intra-abdominal pressure, such as occurs with sneezing or coughing as well as with running or even walking. The most common cause is laxity of the pelvic floor, often from childbirth. Kegel exercises are frequently recommended but are of limited value, so interventional procedures are often required (see Chapter 115).[18] Urge incontinence, described as detrusor muscle instability, results in the urge to void with low volumes. Both anticholinergic medications and bladder training (see Chapter 115) are effective.

HIV INFECTION

The major risk factors for HIV infection in women in the United States are heterosexual contact in about 90% of new cases and injection drug use in about 10%. Incidence rates remain lower in women than in men, with only about 20% of incident cases affecting women, in large part because male-to-male sexual contact continues to account for about two-thirds of cases in men (Chapter 353).

However, the absolute number of new infections from heterosexual contact is twice as high in women as it is in men. HIV continues to affect minority women disproportionately, with about 60% of prevalent U.S. cases affecting Black women.

Women with HIV/AIDS have poorer survival than men despite equivalent effectiveness of antiretroviral therapy (Chapter 357), perhaps because of poorer adherence, in part associated with caring for dependent children. Cervical (Chapter 184) and anal (Chapter 131) dysplasia and cancer are more common among women with HIV than women without it, so annual Pap tests are recommended for all women with HIV infection, even in the absence of positive HPV test results. Data currently are inadequate to support or refute anal screening. Prophylaxis (Chapter 356), treatment (Chapter 357), and management of complications (Chapters 358 and 359) of HIV/AIDS are discussed in detail in other chapters.

SEVERE ACUTE RESPIRATORY SYNDROME CORONAVIRUS 2

The severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) pandemic provided an example of the intersection of lifespan stages and gender differences with environmental and behavioral exposures. Initial epidemiologic data were conflicted as to whether women were more or less likely to contract and die of SARS-CoV-2 infection. Some data linked severity of infection to androgen-responsive influences on the angiotensin converting enzyme receptor by which the virus binds to cells. Conversely, elderly women constitute a disproportionate share of the elderly population and of residents of skilled nursing facilities—groups that have higher SARS-CoV-2 mortality rates. In the United States, greater numbers of women work in health care settings, where initially inadequate personal protective equipment, not gender, drove differences in rates of disease and illness. Overall, based on the best-available data, the pandemic now appears to be sex-neutral.

REPRODUCTIVE HEALTH ISSUES

All providers caring for women with reproductive potential should consider the reproductive implications of preventive and therapeutic decisions. With half of all pregnancies in the United States unplanned, providers should routinely inquire about contraceptive practices and consider these in their care plans.

All primary care providers should be comfortable counseling patients about contraceptive choices and prescribing oral contraceptives (Chapter 220). The absolute contraindications to oral contraceptives are a personal history of cardiovascular disease, thromboembolic disease, migraine headache with aura, and gynecologic or breast cancer. A family history of cancer is not considered a contraindication; in fact, data suggest that the use of oral contraceptives decreases the risk for both endometrial and ovarian cancer. Smoking while using oral contraceptives increases the risk for thromboembolic events in all women but especially in those older than 30 years. Oral contraceptive use is considered safe in nonsmoking women until menopause. Preexisting hypertension is a relative contraindication to oral contraceptive use. Some women develop elevated blood pressures on oral contraceptives, so blood pressure should be monitored at 3 months after starting the drug and then at least annually.

Unsafe and self-managed abortion must be avoided.[19] Fortunately, medical abortion is safe for primary care providers to implement with appropriate backup. The evidence-based regimen is approved for use up to 63 days of gestation, using mifepristone 200 mg orally for a single dose, followed by 800 µg of misoprostol buccally 24 to 72 hours later. Recent studies have demonstrated its safety even as telemedicine with counseling but without observed administration. Success rates range from 94 to 98%. Rates of complications, which are similar to surgical abortion, include bleeding requiring blood transfusion in 0.05% of cases and rare infections, usually with non–evidence-based methods. Women should be counseled on side effects, including nausea and abdominal pain, with bleeding and expulsion of conception products usually following misoprostol. Providers should review local regulations: providers must register with the company to prescribe mifepristone. Some locales require that the original protocol be used and have additional regulations regarding counseling.

Providers should consider the reproductive implications of all chronic medications in women of reproductive potential (Table 219-2). Given that the teratogenic effects of medications may occur during the first trimester and before an initial obstetric assessment, the principle when choosing chronic medications for women during their reproductive years is to select those with the greatest safety profile during the first trimester of pregnancy.

The risk for untreated depression during pregnancy as well as the risks of postpartum depression to the woman and her infant are substantial,[20] so screening for depression is worthwhile. Antidepressant medications generally appear to be safe during pregnancy (Chapter 221), although selective serotonin reuptake inhibitors may increase the risk of postpartum hemorrhage. For women who wish to take no medication during pregnancy, the recommendation is gradually to reduce the dosage over the course of several weeks. In the postpartum period, close surveillance is important for early detection and treatment with adequate and even increased doses of antidepressant medication to prevent the worsening of depression.

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220 CONTRACEPTION

BEVERLY WINIKOFF AND DANIEL GROSSMAN

CONTRACEPTIVE USE

Contraception enables people to avoid unwanted fertility by preventing pregnancy.[1] Methods can be classified in many ways. Some classification schemes distinguish among mechanisms (e.g., barriers to the encounter of sperm and ovum versus methods that prevent ovulation); other categories emphasize the timing of use (at the time of intercourse vs. ongoing); still other classifications focus on the permanence of the method (sterilization, which is intended as a permanent method; long-acting methods that persist for years; and short-term methods that depend on the periodic behavior of the user, such as every day or at every exposure to pregnancy). Each contraceptive method has advantages and disadvantages,[2] which should be thoroughly explained so that the individual or couple will choose the most acceptable method to suit their lifestyles and will use it most effectively.[3] Because medical contraindications to individual methods are uncommon among young women, the choice among contraceptive methods usually depends mostly on the user's preferences.

In a recent United States survey, about 65% of women of reproductive age (15 to 44 years old) were using a contraceptive method.[4] Among women not using contraception, some women were not currently sexually active (17%) or were currently pregnant, postpartum, or trying to conceive (8%). Only about 7% of women were sexually active in the prior 3 months but were not using a method of contraception, and about 3% were not using contraception for other reasons (e.g., women with nonsurgical sterility). In the United States, approximately 45% of pregnancies are unintended, that is, mistimed or unwanted.

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In a recent United States survey, about 65% of women of reproductive age (15 to 44 years old) were using a contraceptive method.[4] Among women not using contraception, some women were not currently sexually active (17%) or were currently pregnant, postpartum, or trying to conceive (8%). Only about 7% of women were sexually active in the prior 3 months but were not using a method of contraception, and about 3% were not using contraception for other reasons (e.g., women with nonsurgical sterility). In the United States, approximately 45% of pregnancies are unintended, that is, mistimed or unwanted.

ABSTRACT

Contraception enables people to avoid unwanted fertility by preventing pregnancy. In the United States, about 65% of women of reproductive age are using a method of contraception. However, nearly half of U.S. pregnancies are unintended, and more than half of such pregnancies occur to women not practicing contraception. The most common methods of pregnancy prevention are oral contraceptives and female sterilization. Use of long-acting reversible contraception has increased rapidly in recent years. Other contraceptive methods include male condoms, male sterilization, injectable progestin, and contraceptive rings or patches. Approximately 3% of women of reproductive age report using withdrawal. "Perfect use" and "typical use" are different metrics to describe the protection afforded by different contraceptives under varied circumstances. Perfect use refers to use of the method as intended/instructed and covering all acts of exposure to pregnancy. Typical use, on the other hand, is a measure of a method's effectiveness when used as people actually use them. The U.S. Centers for Disease Control and Prevention has developed evidence-based Medical Eligibility Criteria (MEC) for contraceptive use. This chapter reviews each contraceptive method and its mechanism of action, efficacy, contraindications, advantages, disadvantages, and instructions for use.

KEYWORDS

contraception
fertility
hormonal
intrauterine device
implant
sterilization

In the United States in 2017 to 2019, the most common methods of pregnancy prevention were female sterilization (18%) and oral contraceptives (OCs or "the pill;" 14%). Use of long-acting reversible contraception (e.g., intrauterine device [IUD] and implants) has increased rapidly in recent years, with about 10% of women reporting use of such methods. Other reported methods include male condoms (8%), male sterilization (6%), injectable progestin, and contraceptive ring or patch (total: 3%). All other methods accounted for 6% of contraceptive use. In the United States, the likelihood of using contraception varies rather little by educational status. However, the choice of method is related to educational attainment, with sterilization chosen more frequently by less-educated women and oral contraceptives more frequently chosen by more educated women. Unsurprisingly, female sterilization is mostly chosen by older women.

UNINTENDED PREGNANCY AND CONTRACEPTIVE USE

In the United States, approximately 45% of pregnancies are estimated to be unintended. Data indicate that 95% of unintended pregnancies occur among women who do not use contraception (54%) or use it inconsistently (41%). The highest unintended pregnancy rates are in women ages 18 to 24 years, women living on low incomes, and women who are unmarried but living with a partner. Factors associated with nonuse of contraception or gaps in its use include side effects (both experienced and feared), not liking a method, personal or religious reasons, and barriers to access, including high cost and difficulty obtaining the method.

Although there is certainly a need to develop new contraceptive methods with fewer side effects, as well as methods for men,[5] much more could be done to improve access to the full range of existing methods at low or no cost. People have different preferences regarding contraceptive methods, and matching those preferences with the most appropriate method is a critical role of the practicing physician. Physicians should address the contraceptive needs and preferences of all of their patients, including those who are transgender and gender nonconforming (Chapter 215).[6]

PERFECT USE VERSUS TYPICAL USE

"Perfect use" and "typical use" characterize different aspects of the effectiveness of the various contraceptive methods. *Perfect use* refers to use of the method as intended and covering all acts of exposure to pregnancy. For user-dependent methods such as oral pills or condoms, for example, this measure can be applied only to situations in which the user reliably uses the method every day or at every act of intercourse. Perfect use is a measure of the maximum possible efficacy of the method. *Typical use,* by comparison, is a measure of the effectiveness of a method as used by the people who actually use it. Typical use rates may be considerably lower than perfect use rates, especially if the method must be used at every act of intercourse or can be used in ways other than as intended. Different contraceptive methods have varying failure rates under conditions of perfect use and typical use (Table 220-1). The actual use (typical) failure rates of most contraceptive methods can be divided into three main classes of effectiveness (Fig. 220-1). Pregnancies conceived while using contraceptive methods do not have an increased risk of birth defects.

Methods used at the time of coitus have higher failure rates than oral contraceptives, implants, injections, IUDs, and sterilization. IUDs, implants, and sterilization have lower failure rates than oral contraceptives, patches, and injections, because they act over a longer period of time, and a user need not do anything else during their duration of effectiveness.

Cumulative failure rates for long-acting methods are low. The effectiveness of long-acting reversible contraception is superior to that of contraceptive pills, patch, or ring, and it is not altered in adolescents and young women. The cumulative failure rates of all types of tubal sterilization are 1.31% during the first 5 years after the procedure and 1.85% after 10 years; rates are higher for tubal fulguration and lower for segmental resection. The cumulative pregnancy rate for 5 years' use of the levonorgestrel-releasing IUD is 0.5%, and for 10 years' use of the copper T380 IUD, it is 1.7%.

CONTRAINDICATIONS, RISKS, AND BENEFITS

Most contraceptives can be used safely by most people, but some conditions or concomitant medications are considered contraindications to certain methods. The U.S. Centers for Disease Control and Prevention has developed evidence-based Medical Eligibility Criteria (MEC) for contraceptive use, based on a similar document developed by the WHO (https://www.cdc.gov/reproductivehealth/contraception/mmwr/mec/summary.html). For conditions that represent relative contraindications, it is important to recognize that pregnancy also may be risky, and if the method is the best choice to avoid an unintended pregnancy, it may be worth the risk.

Many contraceptive methods have additional benefits aside from prevention of unintended pregnancy. One of the most significant noncontraceptive benefits is the reduced risk of sexually transmitted infections, including human immunodeficiency virus (HIV; Chapter 356), associated with the use of male and female condoms. Another important contraceptive benefit is the reduction in dysmenorrhea and menorrhagia (Chapter 218) associated with the use of combined hormonal contraception; these methods are also associated with a reduced risk of ovarian and endometrial cancer (Chapter 184).

TYPES OF CONTRACEPTIVES

BEHAVIORAL METHODS

Methods that rely on the cyclic infertility of certain times in the menstrual cycle (Chapter 218) or life cycle are often called "natural" methods. These methods are not really more natural than other methods; rather, they rely more on a couple's behavior rather than on any specific external technology to create a state of low fertility potential. Because male sperm can live for only 5 days in the female genital tract and because female ova have a lifespan of only about 24 hours, the window for fertilization is only 5 to 6 days each month. If couples avoid unprotected intercourse on those 5 to 6 days, the potential for pregnancy is markedly reduced. The calendar method counts the days of the cycle to predict fertile and infertile days, and the symptothermal method relies on the calendar plus the biologic signals of impending ovulation (changes in vaginal mucus) and of ovulation itself (rise in basal body temperature) to enhance prediction of "safe" days for intercourse. The U.S. Food and Drug Administration (FDA) recently approved a mobile application called Natural Cycles (https://www.naturalcycles.com/) to assist users of the fertility-awareness contraceptive method.

In the postpartum period, breast-feeding also suppresses ovulation, lowers fertility, and is considered another natural method of contraception. Exclusive breast-feeding during the first 6 months after a birth provides a good level of protection against pregnancy. However, once a baby is older than 6 months or if foods other than breast milk become part of the infant's diet, then a woman is at much higher risk for ovulation and possible pregnancy.

Withdrawal, or coitus interruptus, occurs when the penis is removed from the vagina before ejaculation. This commonly used method is reported as having been used at least once by up to 60% of women. Although this method can be effective with perfect use, with a pregnancy rate of only 4% in the first year of use, failure is much more common with typical use. In one U.S. study among women ages 15 to 24 years who used withdrawal as their primary method, 21% experienced an unintended pregnancy over a 4-year period, a pregnancy rate that was significantly higher than the rate among users of other contraceptive methods.

BARRIERS

Barrier methods impose a chemical or physical barrier between ovum and sperm so that fertilization is not possible. Barrier methods include spermicides, diaphragm, and male and female condoms, among others.

Spermicides

Most spermicidal agents contain a surfactant (in U.S. products this chemical is nonoxynol-9) that immobilizes or kills sperm on contact. The spermicidal products are available in foams, creams, and vaginal suppositories that must be placed into the vagina before each coital act—and reapplied even if coital acts follow immediately after each other. The typical-use effectiveness of surfactant-based spermicides as a sole contraceptive is among the lowest of modern methods (about 28% of women using the method report an unintended pregnancy during 1 year of use). Another contraceptive vaginal gel (Phexxi) contains L-lactic acid, citric acid, and potassium bitartrate to maintain a low, spermicidal vaginal pH; its use is associated with a seven-cycle pregnancy rate of 14%, and almost 50% of users have an adverse event, including vulvovaginal burning or itching.[7]

Diaphragm

A diaphragm is a dome-shaped latex or silicone device with a flexible rim that seals off the upper genital tract from contact with deposited semen. Diaphragms are usually used with a spermicide that is applied inside and around the rim. Traditional diaphragms must be fitted by a health care provider using the largest size that does not cause discomfort or undue pressure on the vagina. A silicone diaphragm (Caya) is available in a single size that fits women who are

TABLE 220-1 PERCENTAGE OF WOMEN EXPERIENCING AN UNINTENDED PREGNANCY DURING THE FIRST YEAR OF TYPICAL USE AND THE FIRST YEAR OF PERFECT USE OF CONTRACEPTION AND THE PERCENTAGE CONTINUING USE AT THE END OF THE FIRST YEAR—UNITED STATES

	WOMEN EXPERIENCING AN UNINTENDED PREGNANCY WITHIN THE FIRST YEAR OF USE (%)		
METHOD	**TYPICAL USE***	**PERFECT USE†**	**WOMEN CONTINUING USE AT 1 YEAR (%)‡**
No method§	85	85	—
Spermicides¤	28	18	42
Fertility awareness–based methods¶	24	—	47
Standard-days method	—	5	—
2-day method	—	4	—
Ovulation method	—	3	—
Symptothermal method	—	0.4	—
Withdrawal	22	4	46
Sponge			
Parous women	24	20	36
Nulliparous women	12	9	—
Condom**			
Female	21	5	41
Male	18	2	43
Diaphragm††	12	6	57
Combined pill and progestin-only pill	9	0.3	67
Combined hormonal patch	9	0.3	67
Combined hormonal vaginal ring	9	0.3	67
Depot medroxyprogesterone acetate	6	0.2	56
Intrauterine devices			
Copper-containing	0.8	0.6	78
Levonorgestrel-releasing	0.2	0.2	80
Implant (Nexplanon)	0.05	0.05	84
Female sterilization	0.5	0.5	100
Male sterilization	0.15	0.10	100

*Among typical couples who initiate use of a method (not necessarily for the first time), the percentage who experience an accidental pregnancy during the first year if they do not stop use for any other reason. Estimates of the probability of pregnancy during the first year of typical use for spermicides and the diaphragm are taken from the 1995 National Survey Growth (NSFG) and corrected for underreporting of abortion; estimates for fertility awareness-based methods, withdrawal, the male condom, the pill, and Depo-Provera are taken from the 1995-2002 NSFG corrected for underreporting of abortion.

†Among couples who initiate use of a method (not necessarily for the first time) and who use it perfectly (both consistently and correctly), the percentage who experience an accidental pregnancy during the first year if they do not stop use for any other reason.

‡Among couples attempting to avoid pregnancy, the percentage who continue to use a method for 1 year.

§The percentages who become pregnant in the second and third columns are based on data from populations in which contraception is not used and from women who cease using contraception to become pregnant. Among such populations, approximately 89% become pregnant within 1 year. This estimate was lowered slightly (to 85%) to represent the percentage who would become pregnant within 1 year among women not relying on reversible methods of contraception if they abandoned contraception altogether.

¤Foams, creams, gels, vaginal suppositories, and vaginal film.

¶The ovulation and 2-day methods are based on evaluation of cervical mucus. The standard-days method avoids intercourse on cycle days 8 to 19. The symptothermal method is a double-check method based on evaluation of cervical mucus to determine the first fertile day and evaluation of cervical mucus and temperature to determine the last fertile day.

**Without spermicides.

††With spermicidal cream or jelly.

Adapted from Trussell J. Contraceptive failure in the United States. *Contraception*. 2011;83:397-404.

sized between 65 and 80 mm, which is the majority of women. All diaphragms must be inserted before every act of intercourse and should be left in place for 6 hours after intercourse (but not longer than 24 hours, because it may cause ulceration of the vaginal epithelium). In actual use, all diaphragms are equally effective,[A1] more effective than other barrier methods (12% unintended pregnancy rate in first year of use), and provide contraceptive protection that is almost as effective as oral contraceptives in actual use. The ideal diaphragm size for any one woman may change after a birth, miscarriage or abortion after 14 weeks, abdominal or pelvic surgery, or a substantial change in weight. The diaphragm may provide some protection against gonorrhea and chlamydia infection, but not against HIV or herpes simplex. A condom is recommended if infection is a concern. Diaphragm users have an increased risk for urinary tract infection.

Male Condom

The male condom, also called an external condom, is one of the oldest contraceptives known. It is safe, easy to use, and widely available. The modern version is a stretchy latex or plastic sheath that fits over the erect penis and captures the man's ejaculate during intercourse. It is the most effective way to prevent transmission of infections (including HIV) during sex and can be used during vaginal, oral, or anal intercourse. However, natural membrane condoms (made from sheep intestine) do not prevent sexually transmitted infections. Condoms can be used for protection against infection even if another method is used for protection against pregnancy. If the condom is used alone for contraception, in typical use about 18% of women will experience an unintended pregnancy in 1 year. For optimum protection, a new condom must be used at every sex act, and the man must actively participate in the process. Lubricants containing oil-based products may weaken latex condoms and should not be used with them; water-based lubricants are safe to use. The male condom causes no side effects except possible irritation or allergy.

Female Condom

The female condom, also called an internal condom, is a soft, loose-fitting prelubricated pouch with two flexible polyurethane rings, one at each end. The smaller ring at the closed end is inserted well into the vagina, thereby creating a barrier to sperm. The larger ring remains outside the vagina, thereby

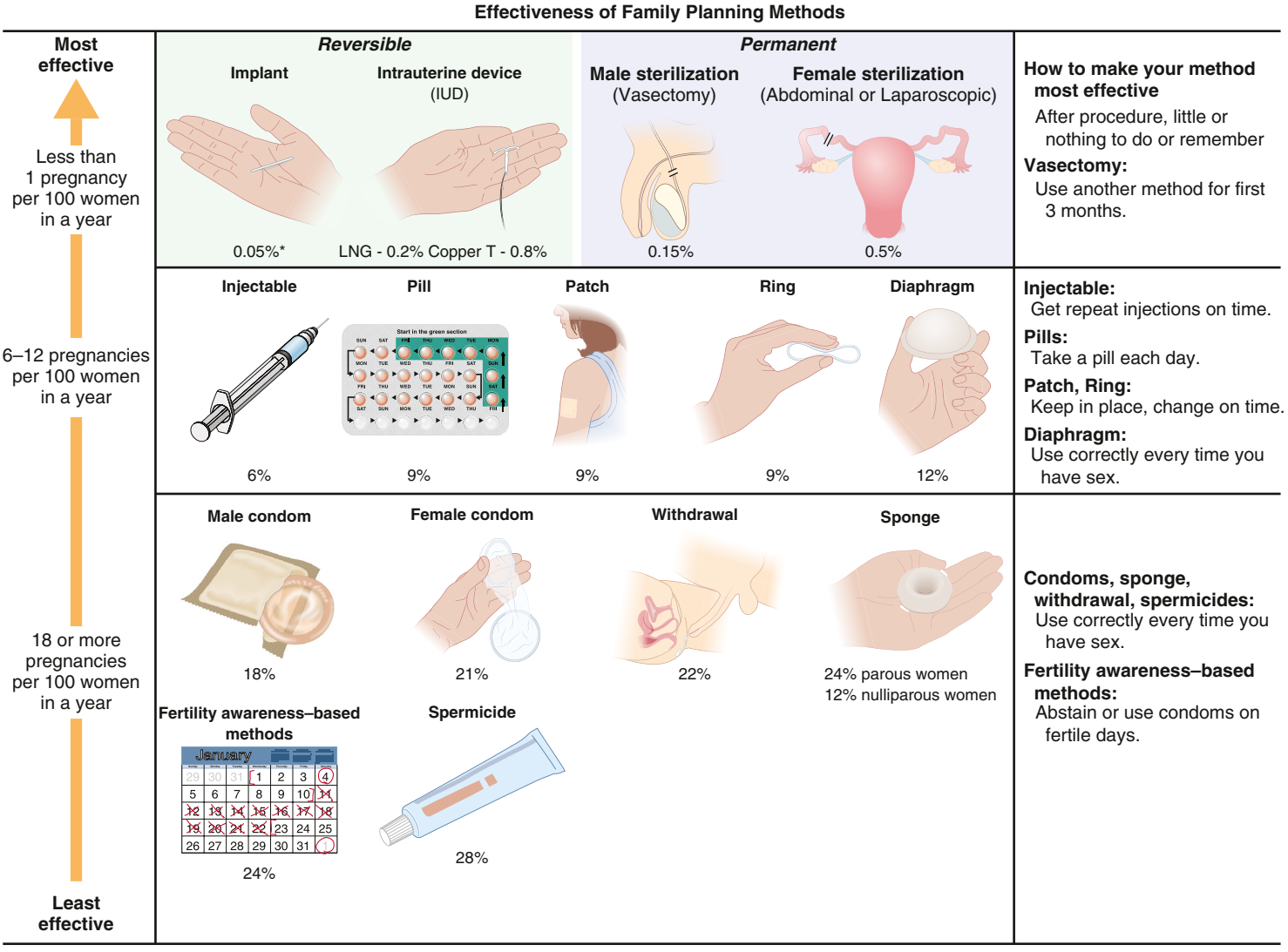

Condoms should always be used to reduce the risk for sexually transmitted infections.

Other Methods of Contraceptions

Lactational Amenorrhea Method: LAM is a highly effective, temporary method of contraception.

Emergency contraception: Emergency contraceptive pills or a copper IUD after unprotected intercourse substantially reduces risk for pregnancy.

FIGURE 220-1. Detailed chart of the effectiveness of family planning methods with instructions for subjects. *The percentages indicate the number out of every 100 women who experienced an unintended pregnancy within the first year of typical use of each contraceptive method. LNG = levonorgestrel. (Adapted from World Health Organization [WHO] Department of Reproductive Health and Research, Johns Hopkins Bloomberg School of Public Health/Center for Communication Programs [CCP], Knowledge for Health Project. *Family Planning: A Global Handbook for Providers*. 2011 updates. Baltimore, Geneva: CCP and WHO; 2011, and Trussell J. Contraceptive failure in the United States. *Contraception*. 2011;83:397-404.)

covering the vulva and providing additional protection. The female condom can be inserted before beginning sexual activity and left in place for a longer time than the male condom after ejaculation occurs. Because polyurethane is stronger than the latex used in most male condoms, the female condom is less likely to rupture. Both polyurethane and latex prevent viral transmission and should reduce the risk for acquiring HIV infection.

HORMONAL (STEROIDAL) CONTRACEPTION

Hormones (or derivatives/analogues of hormones) that occur naturally in the female reproductive cycle can alter the reproductive system so that ovulation does not occur and/or so that physical factors (e.g., mucus production, tubal motility, and endometrial thickness) that enhance the probability of fertilization or implantation are altered. All modern hormonal formulations are made from synthetic steroids. The hormones are either a combination of an estrogen and a progestin or a progestin alone. Oral contraceptives are the most commonly used of these methods.

Oral contraceptives do not cause permanent infertility. After discontinuation, the rate of return of fertility is slightly lower, however, for users of oral contraceptives than for users of barrier methods but faster than for users of Depo-Provera. Obesity and a higher body mass index may attenuate the efficacy of combined hormonal contraceptives, but the absolute reduction in efficacy, if any, is small.

From the user's point of view, the main differences among these contraceptives are route of administration, length of action, how much attention the user needs to pay to the administration of the drug, and side effects. All these methods are very effective, and, if used consistently, result in very low pregnancy rates. Even with typical use, they are among the more effective methods, although, with the exception of the implants, they are less effective than sterilization or the IUD.

Currently, the search for male hormonal contraceptives has not yielded methods with sufficient efficacy and safety. Nonhormonal medications are also being investigated but are not currently available.[8]

Because hormonal contraceptives require a prescription in the United States and many other countries, some women may experience obstacles to initiating or continuing their use. Strategies to improve access to these methods include the use of telemedicine and pharmacist-initiated provision.[9] Whether these products should be available without a prescription is currently under debate, guided by the weighing of their benefits but also their risks.

Oral Contraceptives

The three major types of oral contraceptive formulations are fixed-dose combinations, phasic combinations, and daily progestin. The combination formulations, which are the most prescribed and most widely used, consist

TABLE 220-2 COMMONLY USED ORAL CONTRACEPTIVE FORMULATIONS

ESTROGEN	PROGESTIN	NOTES
MONOPHASIC REGIMENS		
Ethinyl estradiol 20 μg	Levonorgestrel 0.09 mg Levonorgestrel 0.1 mg Norethindrone acetate 1 mg Drospirenone 3 mg	See caution regarding serum potassium level*
Ethinyl estradiol 30 μg	Levonorgestrel 0.15 mg Norgestrel 0.3 mg Norethindrone acetate 1.5 mg Desogestrel 0.15 mg Drospirenone 3 mg	See caution regarding serum potassium level*
Ethinyl estradiol 35 μg	Norethindrone 0.4 mg Norethindrone 0.5 mg Norethindrone 1 mg Norgestimate 0.25 mg Ethynodiol diacetate 1 mg	
Estetrol 14.2 mg	Drospirenone 3 mg	See caution regarding serum potassium level*
MULTIPHASIC REGIMENS (DOSAGES VARY BY WEEK)		
Estradiol valerate 1-3 mg	Dienogest 0-3 mg	
Ethinyl estradiol 10 μg	Norethindrone acetate 0-1 mg	
Ethinyl estradiol 0-20 μg	Desogestrel 0-0.15 mg	
Ethinyl estradiol 20-35 μg	Norethindrone acetate 1 mg	
Ethinyl estradiol 25 μg	Norgestimate 0.18-0.25 mg Desogestrel 0.1-0.15 mg	
Ethinyl estradiol 30-40 μg	Levonorgestrel 0.05-0.125 mg	
Ethinyl estradiol 35 μg	Norgestimate 0.18-0.25 mg Norethindrone 0.5-1 mg	
EXTENDED 91-DAY REGIMENS		
Ethinyl estradiol 20 μg	Levonorgestrel 0.1 mg	84 days of the combination and 7 days of ethinyl estradiol 10 μg only
Ethinyl estradiol 20-30 μg	Levonorgestrel 0.15 mg	84 days of the combination and 7 days of ethinyl estradiol 10 μg only
Ethinyl estradiol 30 μg	Levonorgestrel 0.15 mg	84 days of the combination and 7 days of ethinyl estradiol 10 μg only
Ethinyl estradiol 30 μg	Levonorgestrel 0.15 mg	84 days of the combination and 7 days of placebo tablets
PROGESTIN-ONLY REGIMENS		
None	Norethindrone 0.35 mg	
None	Norgestrel 0.075 mg	
None	Drospirenone 4 mg	See caution regarding serum potassium level*

*Should not be used in patients with conditions that predispose to hyperkalemia. People receiving daily, long-term treatment for chronic conditions or diseases with medications that may increase the serum potassium level should have their serum potassium level checked during the first treatment cycle or when such medications are started.

of tablets containing both an estrogen and a progestin (Table 220-2), usually given continuously for 3 weeks. Generally, no active hormonal pills are taken during the fourth week. A few formulations provide active tablets for 24 days, with 4 days of inactive tablets. Other formulations provide active tablets for 84 days followed by 7 days without active tablets or with a low dose of estrogen to allow withdrawal bleeding.

The endometrium usually begins to slough 1 to 3 days after steroid ingestion is stopped, thereby causing withdrawal bleeding that usually persists for 3 to 4 days (and which users interpret as menstrual bleeding). The uterine blood loss with oral contraceptive use averages about 25 mL per cycle, which is less than the 35 mL average for ovulatory cycles.

Three estrogens (ethinyl estradiol, estradiol valerate, and estetrol) are used in combined oral contraceptives. These estrogens are combined in the pills with a progestin, such as levonorgestrel or norethindrone. Another progestin, drospirenone, is structurally related to spironolactone and has been formulated into an oral contraceptive. In the United States, there are also daily progestin-only formulations that include norethindrone, norgestrel, or drospirenone; levonorgestrel and desogestrel progestin-only pills are approved in other countries.

Combined oral contraceptives, which contain both estrogen and progestin, consistently inhibit the midcycle gonadotropin surge and thereby prevent ovulation. The progestin-only formulations generally have a lower dose of progestin than the combined agents and do not consistently inhibit ovulation, even though they are ingested every day. Progestin-only pills containing desogestrel appear to more consistently inhibit ovulation than other progestin-only formulations. Both combined oral contraceptives and progestin-only formulations also act on the cervical mucus and tubal motility to interfere with sperm transport. Progestins also alter the endometrium so that if fertilization occurs, implantation may be prevented. For contraceptive effectiveness to be maintained with the combination formulations, the pill-free interval must be limited to no more than 7 days, a limit that is reinforced by the inclusion of placebo pills in the packet for the hormone-free days. Continuous or extended cycle combined oral contraceptives are an equally safe option for individuals who prefer them.

Side Effects

The synthetic steroids in oral contraceptives can cause a range of side effects that are directly related to the dosage and potency of the steroids in the formulation. The most frequent symptoms produced by the estrogen component include nausea, breast tenderness, and fluid retention (bloating). The progestins can produce weight gain, acne, and depression. Because estrogens decrease sebum production, women who have acne may experience improvement in their symptoms. Insufficient estrogen, too much progestin, or a combination of both may result in unscheduled (breakthrough) bleeding, a problem that is more common with formulations containing 20 μg of estrogen than with formulations containing 30 to 35 μg and that is increased in women who also smoke cigarettes. Shortening the pill-free interval to 3 or 4 days may decrease the incidence of unscheduled bleeding with low-estrogen formulations.

The synthetic estrogens used in oral contraceptives cause an increase in the hepatic production of factors V, VIII, and X and fibrinogen, thereby potentially increasing the risk of thrombosis (see later) and an increase in angiotensinogen levels, which may elevate blood pressure in some users. Blood pressure should be followed in all users of combined oral contraceptives. Patients who develop hypertension should be switched to a non–estrogen-containing method. Progestins do not affect protein synthesis except to reduce levels of sex hormone–binding globulin.

Complications and Risk Factors

Thrombosis

Women of reproductive age who are not pregnant or using oral contraceptives experience venous thrombosis (Chapter 68) at a rate of 1.9 to 3.7 per 10,000 woman-years, but the 3.5-fold increased relative risk of venous thromboembolism with combined estrogen/progesterone oral contraceptives is still less than the risk of thrombosis associated with pregnancy.[10] In the presence of an inherited hypercoagulable state (Chapter 67), the risk for venous thrombosis is increased several-fold. Screening for coagulation deficiencies before women are started on oral contraceptives is not recommended unless the individual has a personal or significant family history of thrombotic events. Women with known inherited or acquired thrombogenic conditions should not use estrogen-containing steroid contraceptives in pills, rings, or patches, because each of these agents has thrombogenic effects. Observational studies suggest there may be a small increase in the risk for venous thromboembolism in individuals who use oral contraceptives with the newer, less androgenic progestins than for agents that contain levonorgestrel with the same amount of estrogen.

Myocardial Infarction and Stroke

Myocardial infarction (Chapters 57 and 58) is rare among women of reproductive age, with a rate of about 10 per 100,000 person-years. Epidemiologic

studies indicate that use of low-dose oral contraceptives by nonsmoking women without hypertension is not associated with a significantly increased incidence of myocardial infarction or stroke. Combination oral contraceptives should not be prescribed to women ages 35 years or older who smoke cigarettes.

Cancers of the Reproductive System

Among women who use or have used oral contraceptives, the risk of breast cancer (Chapter 183) is increased by 20% compared with women who never used them.[11] The risk increases with a longer duration of use, but the absolute increases are small.[12]

For invasive cervical cancer or cervical intraepithelial neoplasia (Chapter 184), most well-controlled studies indicate no change in risk associated with the use of oral contraceptives. For endometrial cancer, data suggest that the use of oral contraceptives has a protective effect and that the decrease in risk persists for many years after oral contraceptives are discontinued. This protective effect, which also is related to duration of use, increases from a 20% reduction with 1 year of use to a 60% reduction with 4 years of use. The level of protection declines with time after use is stopped.

Oral contraceptives also reduce the risk of developing epithelial ovarian cancer, as well as cancers with low malignant potential. The magnitude of the decrease in risk, which is directly related to the duration of the use of oral contraceptives, increases from about a 40% reduction with 4 years of use to about a 60% reduction with 12 years of use. The protective effect continues for at least 20 years after the use of oral contraceptives ceases. As with endometrial cancer, the protective effect occurs only in women of low parity (fewer than four), who are at greatest risk for this type of cancer.

Data also suggest that oral contraceptives reduce the risk for development of colorectal cancer (Chapter 179) by about 20%, and the risk of hematologic malignancies may be lower as well. Oral contraceptives do not increase risk for liver cancer (Chapter 181), and current formulations also do not increase the risk of developing a benign hepatocellular adenoma. Use of oral contraceptives does not increase the risk for developing malignant melanoma or prolactin-secreting pituitary adenomas.

Contraindications

Oral contraceptives can be prescribed for most women of reproductive age, but conditions that are considered absolute contraindications to use of combined hormonal contraceptives (category 4), include smoking 15 cigarettes or more per day at age 35 or older, severe hypertension, migraine headaches with an aura, and a history of atherosclerosis or venous thrombosis (see Table 220-3), among others.[13]

Management of Oral Contraceptive Therapy

If a healthy woman has no contraindications to the use of oral contraceptives, neither a pelvic nor breast examination nor any laboratory tests are required before prescribing them, and it is reasonable to prescribe oral contraceptives during a telehealth visit. Starting pills on the day of the visit is associated with better long-term adherence. There is no reason to discontinue oral contraceptive use unless pregnancy is desired. Because of their many health benefits, including the reduction in risk for endometrial and ovarian cancer and the induction of regular cyclic uterine bleeding, oral contraceptives use can be continued until menopause.

Some drugs can interfere clinically with the action of oral contraceptives by inducing liver enzymes that convert the steroids to more polar and less biologically active metabolites and cause breakthrough bleeding. These drugs include certain anticonvulsants and rifampin, among others. Use of oral contraceptives together with fosamprenavir may result in decreased effectiveness of the antiretroviral (see Table 220-3).

A common clinical question is what to do if a pill is missed. The standard advice for combined oral contraceptives is to take the first missed pill as soon as possible and take the remaining pills at the usual time, even if it means taking two pills in one day (discarding any additional missed pills). If two or more pills are missed, the most recent missed pill should be taken as soon as possible, and the remaining pills should be taken at the usual time, even if two or more pills must be taken on the same day; reliable contraception will require an additional technique (e.g., condoms) or the avoidance of sexual intercourse until pills have been taken for at least 7 consecutive days. If pills were missed in the last week of hormonal pills (third week of cycle), the hormone-free interval should be omitted, and the new pack should be started the next day; emergency contraception should be considered. Vomiting and diarrhea for up to 48 hours should be considered as one missed pill; vomiting and diarrhea for more than 48 hours should be treated as two or more missed pills. For norethindrone-containing progestin-only pills, a pill is considered "missed" if it is more than 3 hours late.

Emergency Contraception

Emergency contraception is used to avoid pregnancy after unprotected sex acts.[14] A formulation of 1500 μg (1.5 mg) levonorgestrel in a single tablet prevents about 85% of expected pregnancies if used within 72 hours after coitus (ideally as soon as possible). Another approved agent for emergency contraception is the selective progesterone receptor modulator ulipristal acetate given as a single 30-mg dose; this agent is more effective than levonorgestrel and is effective for 5 days after intercourse.[A2] Another option is the immediate insertion of a copper intrauterine device (see later), which virtually eliminates the risk of pregnancy. A recent randomized trial found that the levonorgestrel 52-mg IUD was also an effective emergency contraceptive when inserted within 5 days after unprotected intercourse.[A3]

Transdermal and Intravaginal Steroid Contraceptives

Transdermal Patch

In the United States, two transdermal contraceptive patches contain both estrogen and progestin (Xulane and Twirla). The Xulane patch has an area of 20 cm^2 and delivers 150 μg of the progestin norelgestromin, the active metabolite of norgestimate, and 35 μg of ethinyl estradiol daily. Twirla delivers 120 μg of levonorgestrel and 30 μg of ethinyl estradiol daily. Patches may be applied to the buttocks, lower abdomen, upper arm, or upper torso (but not the breasts). The patch should be removed after 7 days, and then a new patch should be applied to a different area of skin. A woman using this method uses three patches sequentially, each for 7 days. After the third patch is removed, the woman waits 7 days before starting her next patch, thus mimicking the 28-day combined oral contraceptive cycle (21 hormone days, followed by 7 hormone-free days, during which withdrawal bleeding occurs). Because the patch does not require daily attention, continuous use is somewhat higher for the patch than for oral contraceptives, but otherwise efficacy, bleeding patterns, side effects, and the contraindications are similar. The effectiveness of the patch may be decreased among women weighing more than 90 kg. Both patches are approved only for people with a BMI <30 kg/m^2.

Intravaginal Ring

Another option for non-oral combined hormonal contraception is the vaginal ring (Nuva-Ring in the United States). This soft, flexible ring measures 58 mm in diameter and is 4 mm thick. The ring is composed of ethinyl vinyl acetate and contains the progestin etonogestrel, a major metabolite of desogestrel, and ethinyl estradiol. The ring is inserted and removed by the user. There is no "wrong" position or placement of the ring inside the vagina. Each ring is left in place for 3 weeks, after which it is removed for 1 week to allow withdrawal bleeding. Each day, 120 μg of etonogestrel and 15 μg of ethinyl estradiol are released from the ring, and bleeding is uncommon with the ring in place. Contraceptive efficacy, side effects, and contraindications are similar to those of combined oral contraceptives. Women may keep the ring in place during intercourse, or it can be safely removed for up to 3 hours and then reinserted. Tampons also may be used concurrently with the ring without affecting its efficacy. The FDA recently approved Annovera, a vaginal ring that may be used for 1 year with 4-week cycles of 3 weeks inserted and 1 week removed; this device releases approximately 13 μg of ethinyl estradiol and 150 μg of the progestin segesterone acetate daily.

Injectable Steroid Contraceptives

Constituents and Use

Although several types of injectable steroid formulations are used for contraception throughout the world, currently the only injectable available in the United States is depot medroxyprogesterone acetate. One formulation contains 150 mg of depot medroxyprogesterone acetate for intramuscular injection, whereas another formulation is a 0.65-mL solution that contains 104 mg of depot medroxyprogesterone acetate for subcutaneous administration. Both must be re-dosed every 3 months (i.e., every 13 weeks). The major contraceptive action of depot medroxyprogesterone acetate is inhibition of ovulation, but it also impedes sperm transport by thickening cervical mucus. Depot medroxyprogesterone acetate has a low failure rate of only 0.1% at 1 year and 0.4% at 2 years.

TABLE 220-3 CONTRAINDICATIONS TO COMBINED HORMONAL AND PROGESTIN-ONLY CONTRACEPTION ACCORDING TO THE U.S. MEDICAL ELIGIBILITY CRITERIA FOR CONTRACEPTIVE USE*

	COMBINED HORMONAL CONTRACEPTION		*PROGESTIN-ONLY CONTRACEPTION*	
CONDITION	**RELATIVE CONTRAINDICATION (CATEGORY 3)**	**ABSOLUTE CONTRAINDICATION (CATEGORY 4)**	**RELATIVE CONTRAINDICATION (CATEGORY 3)**	**ABSOLUTE CONTRAINDICATION (CATEGORY 4)**
Bariatric surgery (malabsorptive type)	Pills only		Pills only	
Gallbladder disease, medically treated	All			
Postpartum <42 days with or without breastfeeding†	All			
Smoker age 35 or older				
<15 cigarettes per day	All			
≥15 cigarettes per day		All		
Deep venous thrombosis (DVT)/pulmonary embolism (PE)‡		All		
Superficial venous thrombosis	All			
Peripartum cardiomyopathy		All		
Migraine headaches with aura		All		
Solid organ transplant (complicated)		All		
Known thrombogenic mutations		All		
Hypertension§		All	DMPA only	
Ischemic heart disease		All	DMPA only	
Stroke		All	DMPA only	
Diabetes complications‖				
Nephropathy, retinopathy, or neuropathy		All	DMPA only	
Vascular disease		All	DMPA only	
Diabetes of >20 years duration		All	DMPA only	
Lupus with positive antiphospholipid antibodies		All	All	
Cirrhosis (severe, decompensated)		All	All	
Liver tumors (hepatocellular adenoma or hepatoma)		All	All	
Breast cancer, current		All		All
Breast cancer, past and no evidence of disease for 5 years	All		All	
Drug interactions				
Certain anticonvulsants (phenytoin, carbamazepine, barbiturates, primidone, topiramate, and oxcarbazepine)¶	All		Pills only	
Lamotrigine**	Pills only			
Rifampin or rifabutin¶	All		Pills only	
Fosamprenavir	All			

*This is a partial list. For the full list of contraindications to each contraceptive method see https://www.cdc.gov/reproductivehealth/contraception/mmwr/mec/summary.html.
†Postpartum <21 days is a Category 4 contraindication for combined hormonal contraception.
‡Deep vein thrombosis/pulmonary embolism may be a Category 3 or 4 contraindication for combined hormonal contraception, depending on risks for recurrent DVT/PE.
§Depending on blood pressure measurement, hypertension may be a Category 3 or 4 contraindication for combined hormonal contraception.
‖Diabetes complications may be a Category 3 or 4 contraindication for combined hormonal contraception, depending on the severity of symptoms.
¶These medications may reduce the efficacy of combined hormonal contraception and progestin-only oral contraceptives.
**Combined oral contraceptives may reduce the efficacy of lamotrigine.
DMPA = depot medroxyprogesterone acetate.

Side Effects

With both formulations, mean endogenous estradiol levels remain above the postmenopausal range (40 to 60 pg/mL) and symptoms of estrogen deficiency do not occur. Bone mineral density may decline during use, but any bone loss is temporary and reverses after stopping depot medroxyprogesterone acetate.

The major side effect of depot medroxyprogesterone acetate is complete disruption of the menstrual cycle. Because this formulation contains only a progestin, endometrial integrity is not maintained, and usually light uterine bleeding occurs at irregular and unpredictable intervals. As duration of therapy increases, the incidence of frequent bleeding steadily declines and the incidence of amenorrhea steadily increases; after 2 years of use, about 70% of users are amenorrheic. After discontinuing this agent, regular ovulation cycles may not resume for as long as 12 months and may result in delay of return to fertility. Because the major reason for discontinuation of all progestin-injectable contraceptives is menstrual irregularity, several combined progestin-estrogen injectables that are given once monthly and produce regular withdrawal bleeding have been developed, but these are not available in the United States.

Most depot medroxyprogesterone acetate users gain between 1.5 and 4 kg in their first year of use and continue to gain weight thereafter. Because depot medroxyprogesterone acetate preparations contain no estrogen, their use does not cause hypertension or thromboembolism. Depot medroxyprogesterone acetate is associated with a reduction in seizures among women with epilepsy, as well as a reduction in painful crises among women with sickle cell disease.

Subdermal Implants

Constituents and Use

The only subdermal implant currently available in the United States is Nexplanon, which is a single 4-cm by 2-mm ethylene vinyl acetate rod containing 68 μg of etonogestrel, the active metabolite of desogestrel.[15] Although it has been approved for 3 years of use, evidence indicates it provides effective contraception for 5 years. The rod, which is packaged in a disposable metal

trocar inserter, does not require a skin incision for insertion but does need an incision for removal. Ovulation is inhibited by the circulating etonogestrel levels, and no pregnancies were reported in three large clinical trials. As with other progestin-only implants, irregular bleeding is the most common clinical complaint. Because efficacy is not user-dependent, the typical-use and perfect-use failure rates are identical and very low, thereby making this method essentially as effective as IUDs and sterilization. Another subdermal implant, Jadelle, consists of two 4.3-cm rods, each of which contains 75 mg of levonorgestrel and is approved for 5 years of contraception; it is not yet available in the United States.

INTRAUTERINE DEVICES

The two intrauterine contraception options that are available in the United States are the copper-containing IUD and the levonorgestrel intrauterine system. Both methods are exceedingly effective, with perfect-use and typical-use failure rates of less than 1%.

The copper T380A IUD, which is approved for use in the United States for up to 10 years, maintains its high levels of effectiveness for at least 12 years. The 52-mg levonorgestrel intrauterine system, which is approved for 5 or 6 years of use, maintains its efficacy for at least 7 years. This latter device releases a dose of approximately 20 μg of levonorgestrel into the endometrial cavity each day, thereby causing atrophy of the endometrial lining and markedly reducing the amount of uterine bleeding. Two newer levonorgestrel-containing IUDs are smaller and designed for use by nulliparous women; a 19.5-mg device is approved for 5 years of use, and a 13.5-mg device is approved for 3 years of use.

The main mechanism of action for the copper IUD is spermicidal. This effect is caused by a local leukocytic response produced by the copper as well as the plastic IUD. The levonorgestrel-releasing IUD acts mainly by preventing transport of spermatozoa through the cervical mucus, thereby preventing fertilization of the ovum. In addition, some women do not ovulate because of the systemic absorption of levonorgestrel. After removal of each type of IUD, the inflammatory reaction rapidly disappears, and resumption of fertility is prompt.

The main difference between the two IUDs is the menstrual bleeding pattern. With the copper IUD, women generally continue to have a regular menstrual period, which may be associated with more pain and heavier bleeding. With the levonorgestrel intrauterine system, irregular bleeding is common in the first 4 to 6 months of use, but then, most women develop amenorrhea, particularly with the devices containing 52 mg of levonorgestrel.

Both IUDs can be easily inserted by any clinician who has been trained. No special tests are needed routinely before insertion, and if it is reasonably certain that the woman is not pregnant, the IUD may be inserted on the same day a patient requests it. An IUD may be safely inserted immediately after a delivery or abortion, although the expulsion rate may be slightly higher.[16]

Almost all patients, including nulliparous and young women, are considered good candidates for the IUD. However, IUDs are contraindicated in women with active pelvic inflammatory disease, purulent cervicitis, unexplained uterine bleeding, or liver disease, as well as in women who have anatomic uterine abnormalities. IUDs are also relatively contraindicated in women who have a history of pelvic inflammatory disease, cervical cancer, or uterine cancer, or who cannot access follow-up care. The copper IUD is also relatively contraindicated in women who have a history of menorrhagia or severe dysmenorrhea.

Uterine perforation is a rare complication of IUD insertion, occurring in less than 0.1% of cases. Spontaneous expulsion of the IUD after insertion is also rare and happens in less than 5% of users. If there is clinical suspicion that cervicitis is present, a test for chlamydia and gonorrhea (Chapter 264) should be performed, and the insertion should be delayed until negative results are obtained. Routine antibiotics are not recommended with IUD insertion.

Development of acute salpingitis more than 1 month after insertion of the IUD is due to infection with a sexually transmitted pathogen and is unrelated to the presence of the device. All IUD-related upper genital tract infections occur only during the insertion process.

PERMANENT CONTRACEPTION

Permanent contraception, also known as sterilization (tubal ligation for women and vasectomy for men), is the most common contraceptive method used by couples in the United States. Female sterilization may be performed transabdominally, such as at the time of cesarean delivery; through a minilaparotomy incision immediately postpartum; or laparoscopically. Laparoscopic tubal ligation may be performed as an outpatient procedure. The use of salpingectomy,[A4] which is also safe and effective, is rising due to a theoretical reduction in the risk of ovarian cancer.

Vasectomy is a simple outpatient procedure that can be performed using local anesthesia. Sexual function is not affected by vasectomy. Programs are available to support contraceptive services for low-income women, but it is often more difficult for low-income men to access vasectomy.

MEDICATION (OR MEDICAL) ABORTION

Mifepristone (a selective progesterone receptor modulator) is used worldwide for the medical termination of pregnancy. The FDA-approved label for mifepristone describes a regimen in combination with misoprostol (a synthetic prostaglandin E_1 analogue) as one 200 mg tablet of mifepristone taken orally followed 24 to 48 hours later by four 200-μg tablets of misoprostol (800 μg total) placed buccally (between the gum and the cheek) for termination of early first-trimester pregnancies.[17] Other routes of misoprostol (sublingual and vaginal) also can be used. This therapy is approved for termination of the pregnancy up to 70 days after the last menstrual period; published evidence supports off-label use through the first trimester, and modified regimens can be used throughout gestation.

Treatment with this abortion regimen is highly successful, with approximately 97% efficacy in the early first trimester (defined as pregnancy terminated without intervention other than the medications). Efficacy is slightly higher if used at earlier gestational ages. The main side effects are uterine cramping and bleeding (which are, in fact, the main intended effects of the treatment), as well as less frequently reported instances of nausea, vomiting, and diarrhea. Serious adverse events, which occur in approximately 0.3% of cases, mainly fall into two categories: consequences of excessive bleeding (e.g., blood transfusion and/or surgical completion of the abortion) or infection, which is even rarer. The risk of death among users of this method is 0.00063%, 14 times lower than the risk associated with live birth. This therapy can be provided as a completely outpatient service, and hence is used by many types of providers, including family medicine and internal medicine physicians, midwives, physician assistants, and nurse practitioners. The standards of service provision have evolved with experience to allow more patient-centered treatment, with users deciding where to be when they take the medication and with whom.

In the United States, the FDA originally required that mifepristone be dispensed directly by a health care provider. During the COVID-19 public health emergency, the FDA temporarily suspended the in-person dispensing requirement and allowed providers to mail the medications to patients or to use a mail-order pharmacy. As of this writing, the FDA has made that change permanent. This policy allows the use of telemedicine to provide medication abortion without an in-person visit. Innovative services using fewer pre-abortion tests and mailing drugs directly to the user have been met with high patient acceptability and good safety and efficacy results.

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For the General References and other additional features, please visit Elsevier eBooks+ at https://ebooks.health.elsevier.com.

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221 MEDICAL ISSUES IN PREGNANCY

CATHERINE Y. SPONG AND DAVID B. NELSON

Of the over 70 million women of reproductive age in the United States, women are increasingly entering pregnancy at a later age. The mean age was 27.1 years in 2020, up from 23 years in 1994. Pregnancy, which has always served as a stress test for a woman's health, is now becoming even more of a challenge as women, especially non-White women (E-Fig. 221-1), experience it with more underlying comorbid medical conditions that can be exacerbated during pregnancy or at the time of labor and delivery.[1,2] The most common complication is bleeding, which accounts for about 75% of cases of severe maternal morbidity in the United States.[3] However, other conditions that are significantly associated with severe maternal morbidity and mortality (E-Fig. 221-2) include hypertension, diabetes, peripartum cardiomyopathy, thromboembolic disease, sepsis (most commonly from pyelonephritis), suicide, acute fatty liver of pregnancy, and thyroid storm.

GENERAL PRINCIPLES

Because of physiologic changes in pregnancy, maternal drug concentrations (and thus embryo-fetal exposure) are altered from the nonpregnant state. Physiologic changes include alterations in circulating binding proteins, volume of distribution, cardiac output, gastrointestinal transit and absorption, hepatic metabolism, and renal clearance (Fig. 221-1 and Table 221-1). Despite these differences, it is not appropriate to withhold an indicated, or necessary, intervention, simply because of pregnancy or lactation. Comprehensive counseling, including the obstetrician as well as medical surgical experts, and shared-decision making are key to understanding not only the theoretical risks but also the benefits, indications, and alternatives.

Women who enter pregnancy with medical conditions have an increased risk of complications, including preterm birth, preeclampsia, fetal growth restriction, stillbirth, and maternal morbidities. As a general rule, if the medical condition is optimized prior to conception (Table 221-2), the risk of complications to the mother and the fetus is decreased.[4] Many medical conditions affect fetal development, so enhancing access to care before conception or after delivery for intervening births must be a priority and become a central focus of health policy and advocacy. For example, hyperglycemia in the first trimester in diabetic women is associated with diabetic embryopathy, manifested by anencephaly, microcephaly, congenital heart disease, renal anomalies, and caudal regression (Fig. 221-2).[5] Because organogenesis occurs within the first 8 weeks of gestation, glycemic control (Chapter 210) should be optimized prior to conception, aiming for a hemoglobin A_{1C} level less than 6.0. Optimal control of other conditions, such as systemic lupus erythematosus (Chapter 245), can improve the outcome of pregnancy if conception occurs while the disease is in remission.

Medications

For most medical conditions, treatment of women who wish to become pregnant or are pregnant does not differ from routine care, except for the avoidance of drugs that are known to be unsafe for the fetus or situations in which drugs of proven safety are substituted for drugs of unknown safety. The care of all women of childbearing age should avoid medications known to be associated with abnormal fetal development (Table 221-3) unless adequate contraceptive methods (Chapter 220) are ensured.

Radiation Exposure

Radiographs can cause an electrochemical reaction that damages tissue (Chapter 18), thereby resulting in pregnancy loss, fetal growth restriction, congenital malformations, microcephaly, or intellectual disability. Importantly, the impact of radiation on the fetus depends on gestational age.[6] Below a threshold dose (0.05 Gy or 5 rad), radiation poses no risk, and the threshold for gross malformations is about 0.2 Gy (20 rads). Imaging should not be withheld if it is needed for diagnosis, but expert consultation should be obtained, and patients must be counseled regarding risks and benefits. Guidelines no longer require verification of pregnancy status for radiographs that do not directly expose the pelvis (Table 221-4).

TABLE 221-1 NORMAL PHYSIOLOGIC CHANGES IN PREGNANCY

CARDIAC
Cardiac output increased 40%
Blood volume increased 30-50%
Heart rate increased 10-20 beats/min
Blood pressure decreased 10-15 mm Hg
ECG changes related to widened thorax, dextrorotation of heart, elevation of diaphragm
PULMONARY
Upper airway hyperemia and glandular hyperactivity leading to increased edema and friability
Nasal congestion, gestational rhinitis, snoring
Difficult airway management and failed intubation
Minute ventilation increased (owing to an increase in tidal volume, *not* respiratory rate, which remains unchanged), which leads to relative respiratory alkalosis (pH 7.4-7.45)
Pa_{O_2} 100-105 mm Hg
Pa_{CO_2} 28-32 mm Hg
RENAL
Increased GFR to 150-180 mL/min/1.73 m^2
Serum creatinine concentration <0.8 mg/dL
Increased renal excretion of bicarbonate, limiting buffering capacity in patients who become acidotic
Decreased oncotic pressure
ALTERED PHARMACOKINETICS
Increased renal and hepatic clearance of drugs
Altered absorption
Altered protein binding
Increased volume of distribution

ECG = electrocardiogram; GFR = glomerular filtration rate.
These physiologic changes generally progress throughout gestation.
From Rosene-Montella K. Common medical problems in pregnancy. In: Goldman L, Schafer AI, eds. *Goldman-Cecil Medicine*. 26th ed. Philadelphia: Elsevier Saunders; 2020.

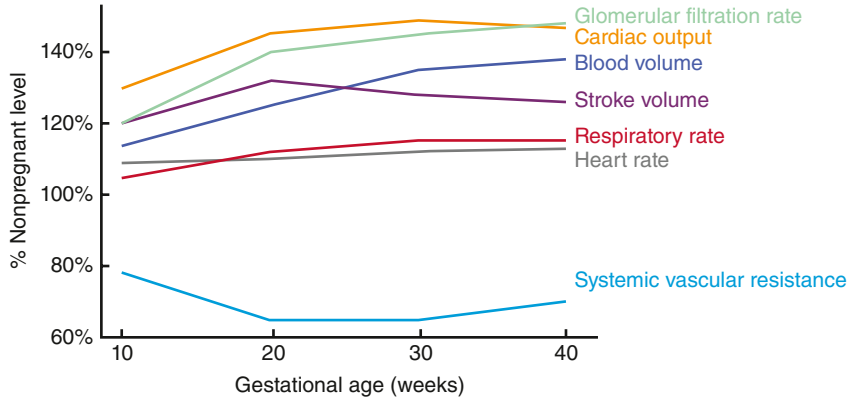

FIGURE 221-1. Physiologic changes associated with pregnancy across gestation compared to the nonpregnant individual.

ABSTRACT

Of the over 70 million women of reproductive age in the United States, women are increasingly entering pregnancy at a later age. The mean age was 27.1 years in 2020, up from 23 years in 1994. Pregnancy, which has always served as a stress test for a woman's health, is now becoming even more of a challenge as women, especially non-White women, experience it with more underlying comorbid medical conditions that can be exacerbated during pregnancy or at the time of labor and delivery. The most common complication is bleeding, which accounts for about 75% of cases of severe maternal morbidity in the United States. However, other conditions that are significantly associated with severe maternal morbidity and mortality include hypertension, diabetes, peripartum cardiomyopathy, thromboembolic disease, sepsis (most commonly from pyelonephritis), suicide, acute fatty liver of pregnancy, and thyroid storm.

KEYWORDS

pregnancy
eclampsia
preeclampsia
peripartum
peripartum cardiomyopathy

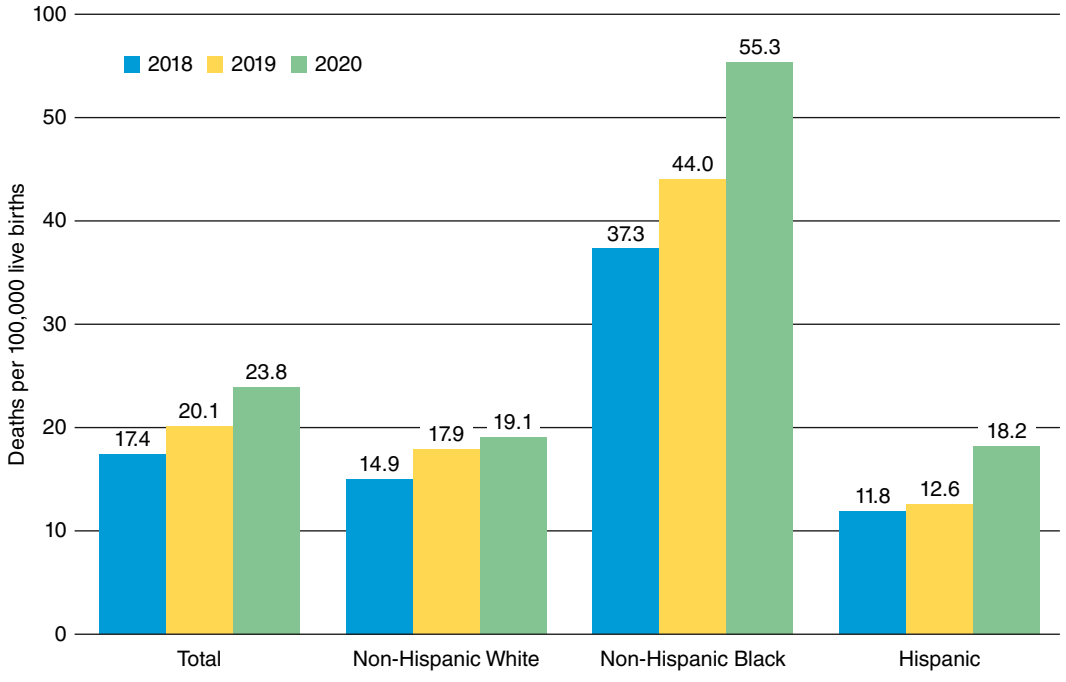

E-FIGURE 221-1. Maternal mortality rates (per 100,000 live births) by race/ethnicity in the United States, 2018-2020. (Adapted from the Hoyert DL. Maternal mortality rates in the United States, 2020. NCHS Health E-Stats. 2022. https://www.cdc.gov/nchs/data/hestat/maternal-mortality/2020/E-stat-Maternal-Mortality-Rates-2022.pdf. Accessed March 13, 2022.)

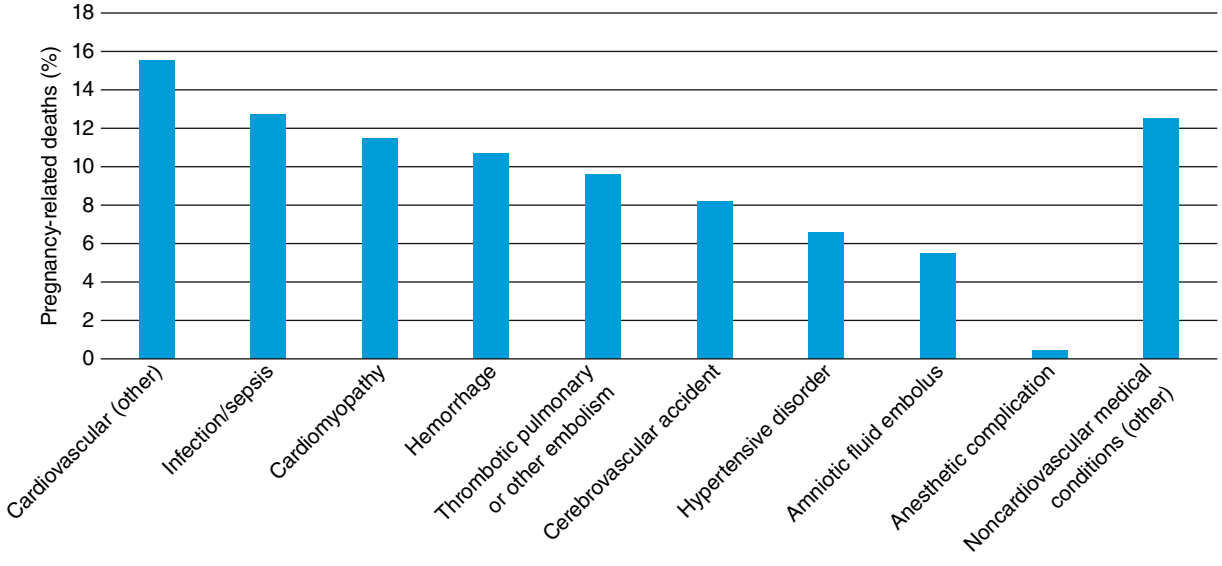

E-FIGURE 221-2. Causes of pregnancy-related death in the United States, 2014-2017. (Adapted from the Centers for Disease Control and Prevention Pregnancy Mortality Surveillance System. https://www.cdc.gov/reproductivehealth/maternal-mortality/pregnancy-mortality-surveillance-system.htm. Accessed November 18, 2021.)

TABLE 221-2 PRECONCEPTION INTERVENTIONS FOR PATIENTS WITH MEDICAL ILLNESSES

TYPE 1 AND TYPE 2 DIABETES MELLITUS
Discuss importance of hemoglobin A_{1c} before conception
Evaluate for microvascular complications
Obtain remission proliferative retinopathy
Discuss contraindication of ACE inhibitor in pregnancy
Discontinue thiazolidinediones and statins
Consider change to insulin therapy for type 2 diabetic patients on oral agents unless using metformin for ovulation induction in PCOS
Discuss probable need to reduce insulin dose in first trimester
THYROID DISEASE
Screen for hypothyroidism in women at risk
Normalize TSH and free T_4 before pregnancy
Counsel women taking levothyroxine on need to increase dose soon after conception
Diagnose cause of hyperthyroidism and consider ablative therapy for women with Graves disease requiring high doses of PTU
CHRONIC HYPERTENSION/RENAL DISEASE
Rule out secondary causes of hypertension if appropriate
Evaluate extent of end-organ disease
Quantify GFR and proteinuria
Discuss drugs of choice for hypertension and replace ACE inhibitor
Discuss risk for superimposed preeclampsia and use of low-dose aspirin for women at significant risk for preeclampsia
THROMBOEMBOLIC DISEASE
Consider evaluation for congenital or acquired thrombophilias in women with previous VTE, previous poor obstetric outcome, or family history
Discuss risks of warfarin in pregnancy, need to discontinue warfarin by 4 to 6 weeks' gestation, and conversion to unfractionated or low-molecular-weight heparin
Discuss options to combined oral contraceptives
EPILEPSY
Determine whether patient is a candidate for withdrawal of antiepileptic drugs
Consider monotherapy with most effective agent at lowest dose possible
Prescribe folate at 1 to 4 mg/day
Discuss possible ineffectiveness of low-dose contraceptives with phenobarbital, phenytoin, and carbamazepine
Consider discontinuing valproate
CARDIAC DISEASE
Obtain baseline echocardiography if congenital disease, stenotic lesion, or pulmonary hypertension suspected
Evaluate for coronary artery disease in women with multiple risk factors
ASTHMA
Verify patient's asthma action plan and peak flowmeter use
Discuss relative safety of all asthma medications except leukotriene modifiers
SYSTEMIC LUPUS ERYTHEMATOSUS AND AUTOIMMUNE DISEASE
Evaluate for renal and cardiopulmonary disease and antiphospholipid, anti-Ro, anti-La antibodies
Avoid pregnancy if disease is active
Discuss relative safety of most immunosuppressants

ACE = angiotensin-converting enzyme; GFR = glomerular filtration rate; PCOS = polycystic ovary syndrome; PTU = propylthiouracil; T_4 = thyroxine; TSH = thyroid-stimulating hormone; VTE = venous thromboembolism.

From Rosene-Montella K, Keely EJ, Lee RV, Barbour LA, eds. *Medical Care of the Pregnant Patient*. 2nd ed. Philadelphia: ACP Press/American College of Physicians; 2008.

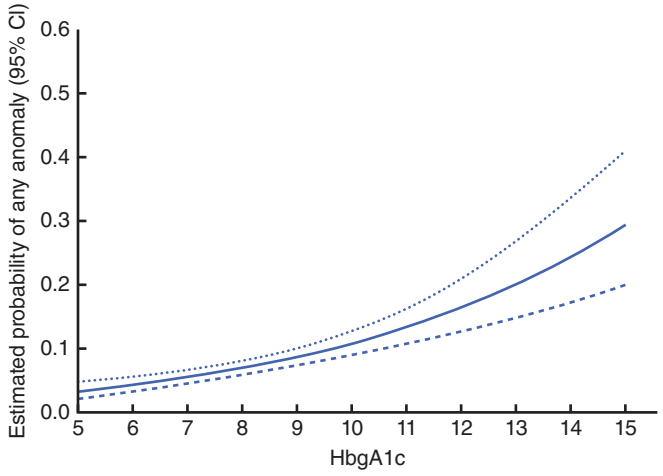

FIGURE 221-2. Probability of any fetal anomaly with increasing maternal hemoglobin A_{1c} values at time of presentation for prenatal care. CI = confidence interval. (Adapted from Martin RB, Duryea EL, Ambia A, et al. Congenital malformation risk according to hemoglobin A_{1c} values in a contemporary cohort with pregestational diabetes. *Am J Perinatol*. 2021;38:1217-1222.)

TABLE 221-3 MEDICATIONS TO AVOID IN WOMEN OF CHILDBEARING AGE CONSIDERING PREGNANCY

Angiotensin-converting enzyme inhibitors	Mycophenolate mofetil
Angiotensin-receptor blocking agents	Phenytoin
Cyclophosphamide	Radioiodine
Danazol	Retinoids—isotretinoin, acitretin, bexarotene
Doxycycline	Ribavirin
Efavirenz	Tamoxifen
Endothelin-receptor antagonists—bosentan, ambrisentan, macitentan	Trastuzumab
Leflunomide	Valproic acid
Methotrexate	Warfarin (except during the second and third trimesters in patients who have mechanical heart valves)

TABLE 221-4 IMAGING TECHNIQUES AND PREGNANCY VERIFICATION

PREGNANCY VERIFICATION NOT REQUIRED	PREGNANCY VERIFICATION REQUIRED
Chest radiography	Interventional fluoroscopic procedures of the abdomen or pelvis
Extremity radiography	Diagnostic angiography of the abdomen or pelvis
Head/Neck diagnostic examination	Hysterosalpingography
Mammography	Standard-dose CT protocols of the abdomen or pelvis
CT imaging outside of abdomen or pelvis (except hip)	Diagnostic nuclear Medicine PET/CT

CT = computed tomography; PET = positron emission tomography.

Adapted from American College of Radiology. ACR–SPR practice parameter for imaging pregnant or potentially pregnant adolescents and women with ionizing radiation. https://www.acr.org/-/media/ACR/Files/Practice-Parameters/Pregnant-Pts.pdf. Accessed November 18, 2021.

Laboratory Test Results

The physiologic changes in pregnancy alter the normal range of many laboratory values (see Appendix). For example, the increase in plasma volume relative to red blood cell volume results in a physiologic anemia and dilutional decreases in blood levels of albumin, creatinine, and platelets. By comparison, white blood cell levels, particularly neutrophils, and cholesterol, and fibrinogen levels increase across gestation (Table 221-5).[7]

Cardiopulmonary Resuscitation

When clinically indicated, cardiopulmonary resuscitation (CPR; Chapter 50) in a pregnant woman is essential for both maternal and fetal health. Because cardiac arrest is often accompanied by obstetric emergencies, such as amniotic fluid embolism (Chapter 68), understanding the impact of pregnancy on effective resuscitation is critical to optimize outcome. The pregnant woman is at higher risk of hypoxemia, and the gravid uterus causes aortocaval compression when supine. In addition, the gravid uterus elevates the diaphragm, thereby decreasing functional residual capacity by 10 to 25%. Standard high-quality CPR—meaning unchanged hand location, compression depth, and rate—should be initiated immediately along with continuous manual left uterine displacement (E- Fig. 221-3) if the uterus is palpated at or above the umbilicus. Manual left uterine displacement allows for optimal chest compressions while relieving aortocaval compression. If resuscitative efforts are not successful, a perimortem cesarean delivery should begin within 4 minutes so as to minimize fetal neurologic damage and improve maternal resuscitative efforts.

E-FIGURE 221-3. Technique for uterine displacement to limit aorto-caval compression during maternal resuscitative efforts with high-quality cardiopulmonary resuscitation. (Photo courtesy of Dr. David B. Nelson.)

TABLE 221-5 SELECTED LABORATORY VALUES IN PREGNANCY ACCORDING TO TRIMESTER COMPARED WITH NONPREGNANT INDIVIDUALS

	1st TRIMESTER	2nd TRIMESTER	3rd TRIMESTER	NONPREGNANT
Hematocrit (%)	31.0-41.0	30.0-39.0	28.0-40.0	35.4-44.4
Platelets ($\times 10^9$/L)	174-391	155-409	146-429	165-415
Albumin (g/dL)	3.1-5.1	2.6-4.5	2.3-4.2	4.1-5.3
Fibrinogen (mg/dL)	244-510	291-538	373-619	233-496
Alkaline Phosphatase (U/L)	17-88	25-126	38-229	33-96
Cholesterol (mg/dL)	141-210	176-299	219-349	<200
Creatinine (mg/dL)	0.4-0.7	0.4-0.8	0.4-0.9	0.5-0.9

Adapted from Abbassi-Ghanavati M, Greer LG, Cunningham FG. Pregnancy and laboratory studies: a reference table for clinicians. *Obstet Gynecol*. 2009;114:1326-1331.

The delivery should be performed at the site of maternal resuscitation, with ongoing resuscitative efforts, rather than transporting the mother to a separate delivery setting.

MEDICAL DISORDERS OF PREGNANCY

HYPERTENSIVE DISORDERS OF PREGNANCY

The hypertensive disorders of pregnancy can be divided into four distinct types: (1) chronic hypertension, (2) preeclampsia and eclampsia, (3) gestational hypertension, and (4) preeclampsia superimposed on chronic hypertension.

CHRONIC PREEXISTING HYPERTENSION

DEFINITION

Chronic hypertension in pregnancy is hypertension that was present before pregnancy, is diagnosed before 20 weeks of gestation, or is diagnosed during pregnancy and does not resolve postpartum. The threshold for defining chronic hypertension in pregnancy is evolving, but recent data suggest 140/90 mm Hg rather than the prior definition of a systolic blood pressure up to 160 mm Hg or a diastolic blood pressure up to 100 mm Hg.

EPIDEMIOLOGY

Chronic hypertension is present in 0.9 to 1.5% of pregnant women when using current definition of 140/90 mm Hg in pregnancy and may result in significant maternal, fetal, and neonatal morbidity and mortality, especially in the context of superimposed preeclampsia. Indeed, superimposed preeclampsia develops in as many as 20 to 50% of pregnant women who have chronic hypertension requiring therapy or systolic blood pressure above 140 mm Hg. The rate of maternal chronic hypertension is increasing, and the largest increase is among non-Hispanic Black women.

PATHOBIOLOGY

Chronic hypertension results in pathologic injury to multiple organ systems (Chapter 64), and adverse outcomes of pregnancy are directly related to the severity, duration, and existing end-organ effects of hypertension before pregnancy and whether superimposed preeclampsia develops. Chronic hypertension, which is a potential precipitant of cardiomyopathy and cerebrovascular events, is associated with a five-fold risk for maternal death, and hypertension is responsible for 6.6% of current pregnancy-related deaths (see Fig. 221-2). Both systolic and diastolic blood pressures normally decline gradually during the first half of pregnancy, so it can be difficult to assess the burden of hypertension in women who enter prenatal care at later gestational ages.

CLINICAL MANIFESTATIONS AND DIAGNOSIS

Assessment for possible end-organ effects of underlying chronic hypertension during pregnancy should include measurement of baseline levels of serum creatinine and electrolytes, measurement of urine protein : creatinine ratio, and a 24-hour quantification of proteinuria. Approximately 11% of women with chronic hypertension have proteinuria (>300 mg/day) at baseline. These baseline assessments are useful for comparison if superimposed preeclampsia may later be suspected.

An echocardiogram should assess for left ventricular hypertrophy, which may be present in about 25% of pregnant women who receive antepartum treatment for chronic hypertension and which portends a significantly greater risk for subsequent or superimposed preeclampsia. The diagnosis of superimposed preeclampsia can be challenging and is typically based on the development of significantly worsening hypertension or of new-onset features, such as headache or vision disturbances with scotomata.

TREATMENT

Treatment of chronic hypertension (Chapter 64)[8] may differ somewhat during antepartum care, at delivery, and postpartum. In all these settings, immediate antihypertensive therapy is mandatory for women with hypertension at or above 160/110 mm Hg. Angiotensin-converting enzyme (ACE) inhibitors and angiotensin receptor blockers are contraindicated during pregnancy due to their potential teratogenic risks (see Table 221-3), so they should not be used in women of childbearing age (Chapter 220). In general, β-blockers, calcium channel blockers,[A1] and methyldopa (see Tables 64-7 and 64-9) are routinely used during the antepartum period given their safety profiles during pregnancy.

To optimize perinatal outcomes, the goal blood pressure for pregnant women whose chronic hypertension is treated with antihypertensive medications is a blood pressure of 140/90 mm Hg.[A2] Control to a target diastolic blood pressure below 85 mm Hg is no better in terms of fetal outcomes and is only marginally better for reducing the frequency of progression to severe hypertension. Fetal growth may be compromised if blood pressure is treated more aggressively.

Stage-based protocols using checklists, referred to as "safety bundles," have recently been developed through both national and state-based programs for standardization of response.[9] Acute intrapartum antihypertensive therapy emphasizes timely treatment (Table 221-6). Superimposed preeclampsia also requires magnesium sulfate prophylaxis (either a 4- or 6-g intravenous loading dose, followed by continuous infusion of 2 g per hour) and prompt delivery. After delivery, persistent postpartum hypertension is typically managed with β-blockers and calcium channel blockers (see Table 64-7), as used during the antepartum period, for safe lactation and future childbearing considerations.

PREVENTION

In women with well-controlled blood pressure, perinatal outcomes are similar to outcomes in women without chronic hypertension, so a goal for prevention is to control blood pressure before conception. Since women who have chronic hypertension are at increased risk for developing preeclampsia, they should begin taking daily low-dose aspirin (81 mg) between 12 weeks and 28 weeks of gestation (optimally before 16 weeks)[A3] and continue until delivery.[10] Initiating treatment after 28 weeks of gestation is unlikely to be beneficial. Aspirin should not be used in women who have risk factors for gastrointestinal hemorrhage (e.g., bleeding disorders or peptic ulcer).

PROGNOSIS

In patients with chronic hypertension, preeclampsia tends to have an earlier onset and to be more severe, so the prognosis for the woman and her fetus is worse than in either condition alone.

HYPERTENSIVE DISORDERS UNIQUE TO PREGNANCY

The threshold for gestational hypertension and preeclampsia is new-onset blood pressure at or above 140/90 mm Hg. Gestational hypertension is the diagnosis in the absence of proteinuria, whereas preeclampsia is associated with new-onset proteinuria during pregnancy and affects virtually every organ system.

New-onset is arbitrarily defined as at 20 weeks' gestation or later, and proteinuria serves as an objective measure of the endothelial damage caused by preeclampsia. Preeclampsia is further sub-divided into: early-onset (<34 weeks) and late-onset (≥34 weeks).[11,12] Eclampsia is defined by new-onset tonic-clonic, focal, or multifocal seizures in the absence of other causative

TABLE 221-6 URGENT MANAGEMENT OF SEVERE HYPERTENSION (≥160/110 mm Hg) IN PREGNANCY AND THE IMMEDIATE POSTPARTUM PERIOD

DRUG	DOSE
ORAL	
Nifedipine IR	10-20 mg initially and 20 min later, followed by 10-20 mg q 2-6h to a maximum of 180 mg
INTRAVENOUS	
Labetalol (preferred)	10-20 mg then 1-2 mg/min (or 20-80 mg q 10-30 min) to a maximum of 300 mg
or	
Hydralazine	5 mg initially then 0.5-10 mg/hr (or 5-10 mg q 20-40 min) to a maximum of 20 mg

conditions such as epilepsy (Chapter 372), cerebral arterial ischemia and infarction (Chapter 58), intracranial hemorrhage (Chapter 377), or drug use (Chapter 365).[13]

EPIDEMIOLOGY

The most common hypertensive disorder of pregnancy is gestational hypertension, which occurs in 6 to 17% of nulliparous patients and 2 to 4% of parous patients. Preeclampsia is identified in 5 to 8% of all pregnancies, with higher risks in women who are young and nulliparous and in older women who have comorbid conditions such as chronic hypertension. A prior history of preeclampsia raises risks by about eight-fold. Non-Hispanic Black women, obese patients, and women with a family history are also higher risk.[14] The incidence of eclampsia in high-resource settings is now 1 in 2000 to 3000 deliveries.

PATHOBIOLOGY

The mechanisms by which pregnancy provokes hypertension remain unsolved but likely involve genetic, immunologic, and angiogenic responses to hormonal changes and increased blood volume. The first stage, which involves faulty endovascular trophoblastic remodeling, results in a second stage of endothelial dysfunction with overproduction of anti-angiogenic factors—soluble fms-like tyrosine kinase 1 (sFlt-1) and soluble endoglin (sEng)—that enter the maternal circulation. The phenotypic expression of the preeclampsia syndrome represents a spectrum of disease, with end-organ consequences. Hemoconcentration is a hallmark. Cardiac function becomes compromised owing to an increased afterload, and aggressive fluid support may result in pulmonary edema.

CLINICAL MANIFESTATIONS AND DIAGNOSIS

The diagnostic clinical manifestations of the preeclampsia syndrome (Table 221-7) are a blood pressure of 140/90 mm Hg or greater accompanied by proteinuria (≥300 mg/24 hours or a urine protein/creatinine ratio of ≥0.3). Following the initial documentation of proteinuria and the establishment of the diagnosis of preeclampsia, additional quantifications of proteinuria are no longer necessary.

Eclampsia, which is often preceded by neurologic complaints, such as new-onset headache or vision disturbances, should be considered in any pregnant or immediately postpartum patient who presents with convulsions at or near term. The diagnosis depends on the exclusion of other causes of seizures. In most cases, the convulsions are followed by a post-ictal state with an elevated respiratory rate in response to hypercarbia, transient hypoxia, and lactic acidemia. If intracranial bleeding is a concern, immediate brain imaging with CT scanning is indicated. In many cases, eclampsia can be corroborated when an MRI demonstrates signs of reversible encephalopathy, classically in the occipital and parietal cortical regions.

TREATMENT

The medical treatment of gestational hypertension is similar to the management of chronic hypertension. Treatment of preeclampsia aims to prevent eclampsia by using magnesium sulfate (either a 4- or 6-g intravenous load, followed by 2-g per hour infusion) to prevent seizures, immediately treating severe hypertension (160/110 mm Hg or greater; see Table 221-4), and effecting prompt delivery of the fetus. In the absence of contraindications, (e.g., myasthenia gravis; Chapter 390), a patient with convulsions late in pregnancy or early in the postpartum period should empirically be given magnesium sulfate to prevent recurrent seizures even while evaluation is underway. If seizures persist despite ongoing magnesium sulfate prophylaxis, an additional 2-g loading dose should be considered, and agents that significantly depress respiratory function should be avoided. Magnesium sulfate is cleared by the kidney, so women with compromised renal function merit close observation for toxicity, which is manifested by diminished reflexes and respiratory depression. Treatment with calcium gluconate (1 g intravenously over 2 to 5 minutes) and discontinuation of the magnesium sulfate reverses respiratory depression.

Delivery is the only cure for preeclampsia-eclampsia. However, emergent cesarean delivery is not recommended for an eclamptic event in the absence of clinical evidence for placental abruption. Fetal compromise often resolves with maternal supportive care in the minutes following the seizure.

Women should be evaluated for possible fluid overload and pulmonary edema because the majority of women with preeclampsia develop pulmonary edema after birth. Volume expansion with agents, such as albumin, may aggravate pulmonary function, and their use is not routinely recommended. Careful fluid management, diuretics (e.g., furosemide 20 mg intravenously), for pulmonary edema afterload reduction with acute intrapartum antihypertensive agents (e.g., labetalol 10 to 20 mg intravenously, hydralazine 5 to 10 mg intravenously, or immediate-release nifedipine 10 mg orally), airway management, and respiratory support are key.

Preeclampsia and eclampsia also can present during the 6 weeks postpartum. Early diagnosis is critical, and management is the same (e.g., seizure prophylaxis and antihypertensive therapy) as when they present prior to delivery.

TABLE 221-7 CRITERIA FOR PREECLAMPSIA WITH SEVERE FEATURES

FEATURES
SBP ≥160 mm Hg or DBP ≥110 mm Hg on two occasions 4 hours apart (unless antihypertensive therapy initiated)
Thrombocytopenia (<100,000/μL)
Elevated liver function tests (>2 times normal)
Severe persistent right upper quadrant pain
Epigastric pain unresponsive to medications
Renal insufficiency (creatinine >1.1 mg/dL or double baseline)
Pulmonary edema
New-onset headache
Visual disturbances

DBP = diastolic blood pressure; SBP = systolic blood pressure.
Data from American College of Obstetricians and Gynecologists. Gestational Hypertension and Preeclampsia: ACOG Practice Bulletin, Number 222. *Obstet Gynecol.* 2020;135:e237-e260.

PERIPARTUM CARDIOMYOPATHY

DEFINITION

Peripartum cardiomyopathy is defined by left ventricular dysfunction and the development of cardiac failure without another known cause in the final month of pregnancy or up to 5 months postpartum (Chapter 47). It is one of the reasons why cardiovascular-related conditions are now responsible for more than 33% of pregnancy-related deaths in the United States (see E-Fig. 221-2).

EPIDEMIOLOGY

The worldwide incidence of peripartum cardiomyopathy is approximately 1 per 1000 pregnancies but varies by geographic area and ethnicity. In Africa, for example, peripartum cardiomyopathy develops in as many as 1 per 100 pregnancies. In the United States, non-Hispanic Black women have a 5- to 15-fold increased risk compared with other ethnic groups.[15] The overall incidence of peripartum cardiomyopathy in the United States has increased from 1 in 4350 births in the early 1990s to 1 in 2230 births, perhaps in part owing to heightened awareness and improved access to echocardiography, but also likely owing to the obesity epidemic, increasing maternal age, fertility-assisted treatments, and multifetal pregnancies.

PATHOBIOLOGY

Physiologic cardiovascular adaptations to pregnancy include increased blood volume, stroke volume, heart rate, and cardiac output. The current theory is that peripartum cardiomyopathy affects genetically susceptible women who have one of several gene mutations, including *TTNC1*, *TTN*, and *STAT3*. In these susceptible patients, the pregnant state results in substantial secretion of prolactin by the maternal pituitary and high levels of antiangiogenic molecules by the placenta. The 16-kDa prolactin fragment (vasoinhibin) causes myocardial damage, which is compounded by secretion of high levels of the vascular endothelial growth factor inhibitory molecules, such as soluble fms-like tyrosine kinase (sFlt-1).

CLINICAL MANIFESTATIONS AND DIAGNOSIS

Patients with peripartum cardiomyopathy typically present with symptoms of heart failure (Chapter 45) in late pregnancy or within 5 months postpartum. An echocardiogram (Chapter 43) should be obtained to exclude valvular heart disease (Chapter 60), pericardial disease (Chapter 62), or segmental wall motion abnormalities that might suggest ischemic heart disease or a coronary artery dissection (Chapter 58). Peripartum cardiomyopathy is ultimately a diagnosis of exclusion after careful assessment of cardiac function by physical examination, laboratory testing, and echocardiography (Fig. 221-3). Transthoracic echocardiography is considered diagnostic when it demonstrates diffuse systolic dysfunction with a left ventricular ejection fraction less than 45%, motion-mode fractional shortening less than 30%, or a left ventricular end-diastolic dimension greater than 2.7 cm/m^2 in the absence of other causes of heart failure, such as hypertensive cardiomyopathy, superimposed preeclampsia, sepsis, or the use of tocolytic β-mimetics agents (e.g., terbutaline).[16]

TREATMENT

The diagnosis of peripartum cardiomyopathy is most frequently made postpartum. For women who are diagnosed before delivery, however, prompt delivery is typically recommended after maternal stabilization. Diuretics, fluid restriction, supplemental oxygen, and management with antihypertensive therapy are the mainstays of immediate care consistent with standard heart failure management (Chapter 46 and 47). Calcium channel and β-blocking agents (see Table 221-4) are commonly used for acute blood pressure control before delivery. After delivery, treatment emphasizes ACE inhibitors and angiotensin-receptor blocking agents to decrease afterload (Chapter 46). To inhibit prolactin, women should not breast-feed. Bromocriptine (1.25 mg to 2.5 mg once daily) may be added if traditional measures are not successful, but use is controversial. Because of the increased risk of thromboembolism, prophylactic anticoagulation with low-molecular-weight heparin (see Table 70-3) is typically instituted. For severe, unremitting heart failure, ventricular-assist devices and extracorporeal membrane oxygenation have been used. Reliable contraception is critical to allow for potential recovery and assessment before future pregnancy is attempted.

PREVENTION

No specific strategies prevent peripartum cardiomyopathy, but control of blood pressure and underlying cardiovascular disease should be optimized before pregnancy. Vigilance may allow for earlier diagnosis of women who have symptoms of heart failure near term and after delivery, thereby allowing earlier treatment before severe clinical deterioration.

PROGNOSIS

Serial echocardiography is recommended to evaluate left ventricular function at 1- to 3-month intervals, and the long-term trajectory of cardiac function is typically clear by 6 months postpartum. In the United States, approximately two-thirds of patients recover ventricular function, but about one-third have a left ventricular ejection fraction persistently below 45%. The risk of recurrence among women who recover left ventricular function during or after subsequent pregnancy is approximately 20%. Women who do not recover should avoid future pregnancies.

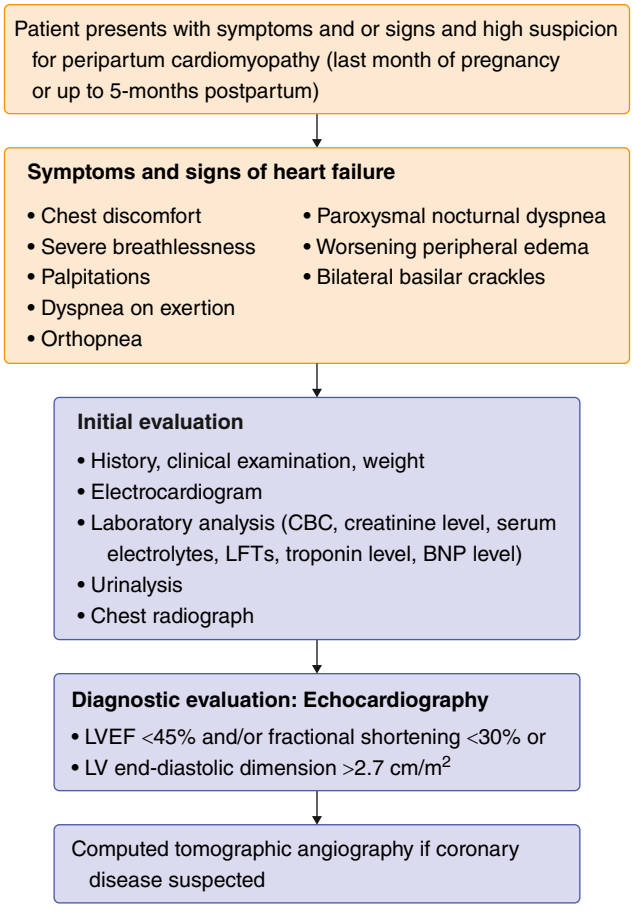

FIGURE 221-3. Evaluation of a patient with suspected peripartum cardiomyopathy. BNP = brain natriuretic peptide; CBC = complete blood count; LFTs = liver function testing; LV = left ventricular; LVEF = left ventricular ejection fraction. (Adapted from Cunningham FG, Byrne JJ, Nelson DB. Peripartum cardiomyopathy. *Obstet Gynecol*. 2019;133:167-179.)

VENOUS THROMBOEMBOLISM

EPIDEMIOLOGY

Pregnancy increases the risk of blood clots, with a sixfold higher incidence of venous thromboembolism (VTE) compared with age-matched, nonpregnant women. The risk increases across gestation, peaking in the peripartum and early postpartum period and continuing through 12 weeks postpartum.

VTE complicates 0.5 to 2 per 1000 pregnancies and represents 9% of maternal deaths (see E-Fig. 221-2). In fact, postpartum VTE is more common than antepartum (0.61 vs. 0.13 per 1000 pregnancies). Pulmonary emboli account for 20% of VTE events.

PATHOBIOLOGY

Increases in estrogen and progesterone during pregnancy result in a hypercoagulable state. Factors I, VII, VIII, and X, as well as von Willebrand factor and plasminogen activator inhibitors (PAI-1 and PAI-2), increase, whereas free protein S decreases. Since these changed levels do not reflect the nonpregnant state, thrombophilias (Chapter 67) are difficult to diagnose during pregnancy, except with DNA testing. The increase in progesterone also results in venodilation, which is further complicated by aortocaval compression of the gravid uterus, thereby increasing venous stasis and the risk that a clot will form.

CLINICAL MANIFESTATIONS AND DIAGNOSIS

Deep vein thrombosis (Chapter 68) can be difficult to distinguish from physiologic changes in pregnancy, during which leg swelling, peripheral edema, pain, and dyspnea are common. Over 90% of pregnancy-related deep vein thromboses are in the left lower extremity, in part due to compression of the left iliac vein by the right iliac artery, and classic features include pain and edema. The clinical findings of pulmonary embolism include dyspnea, chest pain, cough, tachycardia, tachypnea, apprehension, and hemoptysis. Importantly 30 to 60% of pregnant women with confirmed lower extremity acute deep vein thrombosis also have an asymptomatic pulmonary embolism.

Although negative D-dimer testing can exclude deep venous thrombosis in the nonpregnant state, it is not clinically useful during pregnancy because it is elevated even in normal pregnancy. In addition, other obstetric conditions, such as preeclampsia, are also associated with further increases in D-dimer levels. The diagnosis of deep vein thrombosis often can be established when compression ultrasonography of the proximal veins (see Fig. 68-3 in Chapter 68)

shows noncompressibility and the echoarchitecture of a thrombosed vein. However, a normal study does not exclude a pulmonary embolism, because the thrombosis may have embolized or arisen from the iliac or deep pelvic veins.[17] Magnetic resonance imaging and/or venography are useful to diagnose iliofemoral or pelvic vein thrombosis.

The diagnosis of pulmonary embolism requires exposure to ionizing radiation, but this risk is mitigated by the greater risk of missing a potentially fatal diagnosis. As in the nonpregnant state, computed tomographic pulmonary angiography is the first-line test for diagnosis (Fig. 221-4).

TREATMENT

During pregnancy, therapeutic anticoagulation with low-molecular-weight heparin (Table 221-8) is the best first-line therapy owing to better bioavailability, a reduced risk of thrombocytopenia and osteoporosis, less frequent dosing, and longer plasma half-life.[A4,18] Unfractionated heparin is an alternative if cost or availability is an issue. Warfarin should be avoided because of its known teratogenicity, especially during the first trimester. Pregnant patients with mechanical prosthetic heart valves are one of the few exceptions in which warfarin can be considered in the second and third trimester. If used in this rare circumstance, women should be converted to unfractionated heparin in the last month of pregnancy or when delivery is imminent (Table 221-8). Direct-acting oral anticoagulants against factor Xa or thrombin are not recommended because of the absence of safety data. For women who are taking low-molecular-weight heparin, anticoagulation should be changed to unfractionated heparin at approximately 36 weeks to prepare for delivery. Pneumatic compression devices are recommended for women who were anticoagulated. If labor occurs while on heparin, aPTT levels can be monitored. Reversal with protamine sulfate is rarely needed and is not indicated for prophylactic heparin.

If a pulmonary embolus occurs at time of delivery, especially a cesarean delivery, a vena caval filter should be considered. Postpartum, anticoagulation includes heparin with the initiation of oral warfarin (titrated to an international normalized ratio [INR] of 2 to 3; see Table 70-4), which is proven safe for lactation; therapeutic heparin anticoagulation is continued for 5 days until the INR is therapeutic for 2 days to avoid paradoxical thrombosis and skin necrosis from the early anti-protein C effect of warfarin. A direct-acting oral anticoagulant (Table 70-6) is an option only if the mother is not going to breast-feed.

PREVENTION

Primary prevention includes avoiding prolonged inactivity or bedrest, or using pneumatic compression devices if unavoidable. The risk of VTE is much higher after cesarean birth as compared with vaginal delivery, so pneumatic compression devices should be used. If additional risk factors, such as previous VTE, are present, both pneumatic compression devices and anticoagulation are recommended. Prophylactic, low-dose antenatal anticoagulation during and after hospitalization for both vaginal and cesarean delivery is controversial. For women who experience a pregnancy-related VTE, evaluation for a possible hypercoagulable state should be undertaken (Chapter 67) after delivery when physiologic alterations have returned to pre-pregnancy state.

PROGNOSIS

With anticoagulation, the prognosis is favorable. For subsequent pregnancies, low-molecular-weight heparin prophylaxis is generally recommended during pregnancy and for the 6 weeks after birth. Importantly, VTE may recur despite antithrombotic prophylaxis, so vigilance is paramount.

MENTAL HEALTH

Perinatal depression includes major and minor depressive episodes (Chapter 362) that occur during pregnancy or in the first 12 months after delivery.[19]

EPIDEMIOLOGY AND PATHOBIOLOGY

Although the incidence of depression varies depending on the definition and population studied, approximately 10% of women have antenatal depression, and another 10 to 20% of women develop postpartum depression. An additional 10 to 20% of women develop "postpartum blues," without meeting the criteria for depression. Maternal self-harm is a significant contributor to pregnancy-related deaths after birth,[20] and mental disorders are now tied with cardiovascular disorders for the number one cause of pregnancy-related death in some states.[21]

Major depression is multifactorial and prompted by genetic factors as well as by environmental factors, such as life events and stressors. Pregnancy itself is a life stressor that can precipitate or exacerbate depressive symptoms, but pregnancy-induced alterations in progesterone and estrogen have also been implicated. Factors associated with perinatal depression include young maternal age, prior history of depression, smoking, and serious adverse perinatal events, including injury or death to the newborn.

CLINICAL MANIFESTATIONS AND DIAGNOSIS

Peripartum depression often goes unrecognized because of changes in sleep, appetite, and libido that are inappropriately attributed to normal pregnancy and postpartum changes. Although standard depression screening tools can be used, a validated, targeted tool such as the Edinburgh Postnatal Depression Scale https://www.cope.org.au/health-professionals/health-professionals-3/calculating-score-epds/ is ideal because it consists of just 10 self-reported questions and takes less than 5 minutes to complete. This instrument also includes anxiety symptoms, which are a prominent feature of perinatal mood disorders, but excludes constitutional symptoms of depression, such as changes in sleeping patterns, which can be common in all women during pregnancy and the postpartum period.

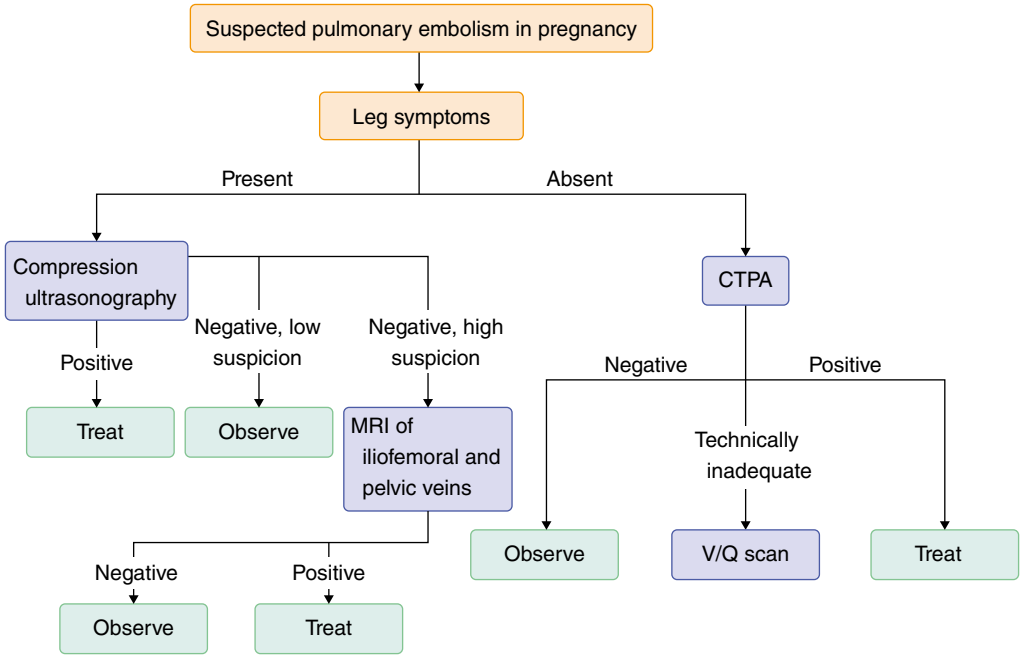

FIGURE 221-4. Diagnostic algorithm for suspected pulmonary embolism during pregnancy. CTPA = computed tomographic pulmonary angiography; MRI = magnetic resonance imaging; V/Q = ventilation/perfusion scintigraphy.

TABLE 221-8 TREATMENT OF VENOUS THROMBOEMBOLISM IN PREGNANCY: ANTEPARTUM SUBCUTANEOUS ANTICOAGULATION

	PROPHYLAXIS		*AGGRESSIVE PROPHYLAXIS*		
DRUG	***First 20 Weeks***	***20-37 Weeks***	***First 20 Weeks***	***20 Weeks To Term***	**FULL TREATMENT**
Dalteparin	5000 U/day	5000 U q12h	100 U/kg/day	100 U/kg/day	100 U/kg q12h or 200 U/kg q24h with anti-Xa monitoring
Enoxaparin	40 mg/day	30-40 mg q12h	1 mg/kg/day	1 mg/kg/day	1 mg/kg q12h with anti-Xa monitoring
Tinzaparin	3500-4500 U/day	3500-4500 U q12h	88 U/kg/day	88 U/kg/day	88 U/kg q12h or 175 IU/kg q24h with anti-Xa monitoring
Heparin	Alternative if LMWH unaffordable: 7500 U bid first 20 wk; 10,000 U bid wk 20-37		Alternative if LMWH unaffordable: 10,000 U bid to achieve anti-Xa level of 0.1-0.3 U/mL		Adjusted to mid-interval anti-Xa of 0.35-0.67 with q12h SQ injections

bid = twice daily; LMWH = low-molecular-weight heparin; SQ = subcutaneously.
Modified from Bourjeily G, Rosene-Montella K, eds. Venous thromboembolism in pregnancy. In: *Pulmonary Problems in Pregnancy, Respiratory Medicine*. New York: Humana Press; 2009.

TREATMENT AND PREVENTION

Although screening and diagnosis alone can have clinical benefits, initiation of treatment or referral to a mental health clinician offers maximum benefit. Current guidelines encourage access to psychological services through primary care clinicians or clinicians embedded within prenatal and postnatal practices,[22] because of the limited availability of other mental health resources. As with depression in general (Chapter 362), cognitive-behavioral therapy is recommended for mild symptoms. Antidepressants (see Table 362-5), predominantly selective serotonin reuptake inhibitors, are recommended in concert with psychotherapy for moderate to severe illness that is unresponsive to cognitive-behavioral therapy. For all agents, shared decision-making regarding risks and benefits is recommended. For severe, otherwise refractory postpartum depression, brexanolone is available as a continuous intravenous infusion over a period of 60 hours at a certified health care facility under the close supervision of a health care provider.[23] Regardless of the medication selected, the risk-benefit balance must be considered with the patient's input in a shared-decision making model, especially during the pregnancy.

Prevention focuses on identifying perinatal mood disorders early so that intervention can avoid more serious progressive disease. In addition, ensuring adequate access to mental health services beyond the postpartum period is important to reduce the risk of future depressive events.

PROGNOSIS

Perinatal depression is frequently recurrent, and up to 70% of women have a subsequent episode with a future pregnancy. In addition, women with history of perinatal mood disorders, including "postpartum blues," have a substantially increased risk for later-life depressive episodes.

ENDOCRINE DISORDERS

DIABETES MELLITUS

DEFINITION

Diabetes mellitus (Chapter 210), which is the most common medical complication in pregnancy, affects women who are diagnosed before pregnancy (pre-gestational diabetics) and women who are diagnosed during pregnancy (gestational diabetes). Gestational diabetes is defined by exceeding thresholds on a glucose challenge test during pregnancy.

EPIDEMIOLOGY AND PATHOBIOLOGY

About 1 to 2% of US pregnancies are complicated by diabetes. In the United States, this rate has increased over the past 20 years, paralleling the trend in obesity.

Gestational diabetes is a form of type 2 diabetes (Chapter 210) that is precipitated by the physiologic changes in glucose metabolism, such as insulin resistance. For the same reasons, pregnancy can exacerbate pre-existing (pre-gestational) type 1 or type 2 diabetes. Women who develop gestational diabetes are at increased risk of developing type 2 diabetes after pregnancy.

CLINICAL MANIFESTATIONS AND DIAGNOSIS

The diagnosis of pregestational diabetes is based on a fasting blood glucose above 125 mg/dL, a 2-hour or random blood glucose level of 200 mg/dL or more, or a hemoglobin A_{1c} level of 6.5% or higher.

Gestational diabetes is almost always asymptomatic and is diagnosed by a screening test that is typically performed between 24 and 28 weeks of pregnancy, unless earlier screening is recommended by risk factors, such as previous gestational diabetes, because treatment significantly improves fetal outcomes. The diagnosis of gestational diabetes based on the results of a blood glucose screen after a single oral challenge of 75 g of glucose is as good as a 2-step diagnosis based on a 50-g glucose challenge test followed by a 3-hour confirmatory 100-g oral glucose tolerance test in terms of predicting perinatal and maternal complications.[A5]

TREATMENT AND PREVENTION

In women who have pregestational diabetes, control should be optimized prior to conception. Insulin, with either continuation or adjustment of the current regimen, is the treatment of choice.[24] For type 2 diabetic women who have not been taking insulin, the initiation of insulin is preferable to oral hypoglycemic agents.[A6] Newer oral agents have not been extensively studied in pregnancy and are not recommended given lack of safety data.

The management of gestational diabetes is based on the fasting glucose level. The initial treatment is diet[A7] and exercise,[A8] with a carbohydrate-restricted diet. In additional to regular meals, three daily snacks are recommended. If euglycemia cannot be obtained with diet and exercise, insulin should be initiated (Chapter 210), typically with 0.7 to 1.0 units/kg/day in divided doses, aiming for a fasting glucose level of 99 mg/dL or a 2-hour postprandial level of 162 mg/dL.[A9] Two thirds of the total dose is given in the morning before breakfast, of which one third should be short-acting regular insulin, and two thirds an intermediate-acting NPH insulin. The remaining one-third of the total dose is given in the evening before dinner, with half as regular and half as NPH. The dose of insulin should then be titrated based on a capillary blood glucose level measured four times daily: fasting and 2 hours after each meal, with targets of less than 95 mg/dL fasting and less than 120 mg/dL at 2 hours after the meal. If the glucose level is measured at 1 hour after each meal, the target is less than 140 mg/dL.

Because of the impact of hyperglycemia on fetal growth and development, strict control is preferred. Insulin requirements may increase with advancing gestation as the fetus and placenta grow, so weekly values must be reviewed and insulin adjusted accordingly.

PROGNOSIS

Pregestational diabetes is associated with adverse outcomes for both the fetus and mother. Fetal complications include spontaneous abortion, preterm birth, congenital malformations, fetal growth restriction (commonly in women who have vascular disease) or fetal macrosomia, stillbirth, and polyhydramnios. The rate of congenital malformations, which is at least doubled, is related to glycemic control during organogenesis (Fig. 221-2). Maternal complications include an increased risk of preeclampsia. Diabetic ketoacidosis (Chapter 210) develops in 1% of pregnancies, commonly at blood glucose levels that are lower than in nonpregnant women.

The primary impact of gestational diabetes is macrosomia, which can be associated with birth trauma, but treatment of even mild gestational diabetes is associated with lower risk of fetal macrosomia. Gestational diabetes is a risk factor for developing diabetes after pregnancy.

THYROID

Fetal thyroid function is directly related to maternal thyroid function and medication use. Defining both hyperthyroidism and hypothyroidism (Chapter 207) follows similar principles during pregnancy as for the nonpregnant patient, with the caveat of the need to consider gestational age-dependent thresholds for levels of thyroid-stimulating hormone (TSH) and free thyroxine.

EPIDEMIOLOGY AND PATHOBIOLOGY

Depending upon the population surveyed, overt hypothyroidism complicates approximately 10 per 1000 pregnancies, whereas subclinical hypothyroidism

occurs with rates approaching 2 to 3%. By comparison, hyperthyroidism is substantially less commonly encountered.

In pregnancy, maternal serum concentrations of thyroid binding globulin are increased, thereby raising the total thyroxine level. Serum free thyroxine (free t4) levels rise only slightly, peak along with human chorionic gonadotropin (hCG) levels, and then return to normal. Although TSH does not cross the placenta, maternal thyroxine does and is important for fetal brain development, especially during the first trimester.

CLINICAL MANIFESTATIONS AND DIAGNOSIS

During pregnancy, the vast majority of cases of hyperthyroidism are caused by Graves disease, whereas Hashimoto thyroiditis is the most common cause of hypothyroidism (Chapter 207). However, the diagnosis of thyroid disease during pregnancy can be challenging, especially because pregnancy itself can mimic the oftentimes nonspecific symptoms of both hypothyroidism and hyperthyroidism. A detailed history and physical examination must be accompanied by measuring serum levels of TSH and free thyroxine and interpreting those results in the context of gestational-age-specific laboratory thresholds. In general, the recommended TSH level is about 0.6 to 3.4 mIU/L in the first trimester, 0.37 to 3.6 mIU/L in the second trimester, and 0.38 to 4.0 mIU/L in the third trimester. The excess thyroxine associated with elevations of hCG early in pregnancy may be confused with overt hyperthyroidism. Life-threatening thyroid storm can be confused with other pregnancy-related complications, such as preeclampsia. Post-ablative hypothyroidism for treatment of Graves disease is also frequently encountered in the pregnant population.

TREATMENT

To treat hyperthyroidism, propylthiouracil (PTU; 50 to 100 mg three times daily) is typically chosen in the first trimester with transition to methimazole (10 to 20 mg daily) for the second trimester and beyond; the lowest possible dose should be used to maintain thyroid indices in the upper-normal range for a given trimester. Symptoms can also be controlled with beta-blocking agents (e.g., propranolol 30 mg per day; see Chapter 207). Serial assessment of thyroid analytes, free thyroxine, free triiodothyronine, and TSH is typically conducted at 4 to 6 weeks to assess whether the dose should be adjusted. Thyroid ablation with therapeutic radioactive iodine is contraindicated during pregnancy.

Treatment of hypothyroidism with thyroxine supplementation (Chapter 207) follows similar principles, albeit with less risk associated with medication crossing the placenta. In approximately one-third of cases, pregnancy is associated with increased dosing requirements due to normal physiologic changes. For women who are already receiving thyroxine supplementation, the dose should be increased by 25% at the initiation of prenatal care because of diminished natural thyroid reserve.

PROGNOSIS

For both overt hyperthyroidism and hypothyroidism, pregnancy outcomes largely depend upon whether metabolic control was achieved. In most cases, the infant is born euthyroid. For subclinical thyroid disease during pregnancy with an elevated TSH level or a low free T_4 level, thyroid hormone–replacement therapy has no impact on the outcomes of pregnancy or the fetus, including no impact on the cognitive function of the children or on other indexes of neurodevelopment through 5 years of age. In the absence of symptoms or risk factors, routine screening for subclinical hypothyroidism is not recommended.[A10]

GASTROINTESTINAL AND LIVER DISEASE IN PREGNANCY

During pregnancy, the enlarging uterus displaces abdominal contents and alters the typical findings on physical examination for common disorders, such as appendicitis (Chapter 128). Gastroesophageal reflux (Chapter 124), manifest clinically as heartburn, is often associated with pregnancy due to the decreased tone of the lower esophageal sphincter. Measures of laboratory analytes associated with hepatic function are altered during pregnancy, and the reference ranges for nonpregnant values may not be applicable to the obstetric patient (see Table 221-8). For example, the normal total alkaline phosphatase level nearly doubles owing to placental production, the serum albumin concentration declines because of the pregnancy-associated increases in plasma volume, and pro-coagulant production is markedly increased. These laboratory changes are often dependent upon gestational age.[25]

Pregnancy can be associated with a variety of liver diseases (Table 221-9). Since the clinical presentations of these conditions can overlap, it is important to distinguish among a chronic liver disease that predates pregnancy, an acute process that occurs coincidentally during pregnancy, and an obstetric condition that is unique to pregnancy.

TABLE 221-9 LIVER DISEASES IN PREGNANCY

UNIQUE TO PREGNANCY
Acute fatty liver of pregnancy
HELLP syndrome (hemolysis, elevated liver enzymes, and low platelets)
Hyperemesis gravidarum
Intrahepatic cholestasis of pregnancy
Preeclampsia and eclampsia
INCREASED INCIDENCE DURING PREGNANCY
Budd-Chiari syndrome
Drug-induced hepatotoxicity
Gallstones
Sepsis
UNDERLYING CONDITION THAT MAY BE REVEALED
Autoimmune hepatitis
Cirrhosis
Hepatitis B and C
Primary biliary cirrhosis
Primary sclerosing cholangitis
Wilson disease

Modified from Mufti AR, Reau N. Liver disease in pregnancy. *Clin Liver Dis.* 2012;16:247-269.

HEPATITIS

Viral hepatitis during pregnancy, whether acute (Chapter 134) or chronic (Chapter 135), can affect the well-being of both the mother and infant. Cases are overwhelmingly due to the classic hepatitis viruses (A to E), most often by hepatitis B or hepatitis C, but rare cases can be caused in pregnant women by cytomegalovirus (Chapter 347), herpesvirus (Chapter 345), and Epstein-Barr virus (Chapter 348).[26] Depending on the timing and chronicity of infection, the risk of vertical transmission to the fetus or infant is an important consideration in management before, during, and after delivery.

EPIDEMIOLOGY

The incidence of viral hepatitis during pregnancy is similar to the risk in the nonpregnant population with similar demographic characteristics. Hepatitis B virus vertical transmission is responsible for approximately 50% of chronic infections worldwide, so prevention of mother-to-child transmission is an important component of maternal care. The risk of developing chronic hepatitis B infection is as high as 90% in infants who are exposed at birth without vaccination, but maternal screening programs and universal vaccination of infants have significantly reduced transmission rates. For hepatitis C virus, an increasing number of infections are occurring among women of childbearing age, so perinatal transmission is increasing. For example, 0.24% of live births in the United States in 2020 were delivered by women with hepatitis C infection reported. The recent availability of effective antiviral medications to treat hepatitis C (Chapter 135) has contributed to recommendations that all pregnant women be screened for hepatitis C.

PATHOBIOLOGY

Both hepatitis B virus and hepatitis C virus are transmitted by parenteral and sexual contact. Acute hepatitis B virus infection early in the pregnancy has been associated with a 10% perinatal transmission rate, and transmission rates significantly increase if acute infection occurs at or near the time of delivery. Approximately 10 to 20% of women who are seropositive for HBsAg alone transmit the virus to their neonates in the absence of neonatal immunoprophylaxis. In women who are seropositive for both HBsAg and HBeAg, the frequency of vertical transmission increases to approximately 90% without neonatal prophylaxis. Importantly, hepatitis B infection acquired perinatally carries an 85 to 95% risk of persistence and chronic infection, with a 25 to 30% life-time risk of serious liver disease. When acute hepatitis B infection occurs in the first trimester, up to 10% of neonates will be seropositive for HBsAg, but 80 to 90% of offspring will be infected if the mother was acutely infected in the third trimester. For hepatitis C, approximately 5 to 6% of infants born to women with infection will become infected.

CLINICAL MANIFESTATIONS AND DIAGNOSIS

Pregnant women may or may not be symptomatic, and jaundice can have multiple causes. The diagnosis depends on serologic testing (Chapter 134).

For screening, HBsAg is measured at the beginning of prenatal care, with additional testing as necessary to confirm the disease and its severity.[27] The diagnosis of hepatitis C is confirmed by the identification of the antibody to hepatitis C virus. Hepatitis C viral RNA also can be detected by polymerase chain reaction assay of serum soon after infection, as well as in chronic disease.

TREATMENT

Indications for antiviral therapy for hepatitis B in pregnant women are the same as in patients who are not pregnant (Chapters 134 and 135), with tenofovir as the preferred therapy because of its potency, safety profile in pregnancy, and low risk of resistance. At this time, treatment for hepatitis C is not recommended during pregnancy but should be initiated after delivery.

PREVENTION

For purposes of pregnancy, prevention primarily centers on diminishing risk of vertical infection to the fetus and infant. Universal active immunization against hepatitis B virus is recommended for all infants born in the United States (Chapter 15). Infants of women who are HBsAg positive or whose status is unknown at the time of delivery also should receive both hepatitis B immunoglobulin (HBIG) and hepatitis B vaccine, given intramuscularly within 12 hours of birth simultaneously at different sites. The initial vaccination should then be followed by two more injections at 1 and 6 months of life. The combination of passive and active immunization has 85 to 95% efficacy in reducing the frequency of perinatal transmission of hepatitis B virus. Currently, no preventive measures are available to lower the risk of vertical transmission of hepatitis C virus infection. Breast-feeding is not contraindicated in women who are chronically infected with hepatitis B if the infant receives HBIG passive prophylaxis and vaccine active prophylaxis, or in women with hepatitis C virus infection.

PROGNOSIS

Pregnancy per se has not been shown to influence the progression of hepatitis B or hepatitis C. The vertical transmission of infection to the infant, however, carries significant consequences later in the child's life.

GASTROINTESTINAL AND LIVER DISEASES UNIQUE TO PREGNANCY

Hyperemesis Gravidarum

EPIDEMIOLOGY AND PATHOBIOLOGY

Nausea and vomiting are common during pregnancy, with prevalence rates as high as 50 to 80%. When severe and unresponsive to antiemetic therapy, hyperemesis gravidarum is the likely cause. Hyperemesis gravidarum is the most common indication for hospital admission during early pregnancy and is second only to preterm labor as a reason for hospitalization during pregnancy.[28]

Maternal factors associated with hyperemesis gravidarum include migraine headaches, motion sickness, and a personal or family history of the disorder in prior pregnancies. Pregnancy-specific conditions that are associated with hyperemesis gravidarum include multifetal pregnancies and molar gestations.

CLINICAL MANIFESTATIONS AND DIAGNOSIS

Hyperemesis gravidarum is typically defined as persistent vomiting, beginning before 9 weeks of gestation and resulting in weight loss, dehydration, or starvation. For later-onset symptoms, the differential diagnosis includes other common gastrointestinal conditions encountered outside of pregnancy, such as genitourinary infections and metabolic disorders. New-onset nausea and vomiting in the third trimester is associated with acute fatty liver of pregnancy and should not be confused for hyperemesis gravidarum.

TREATMENT

Early outpatient treatment of nausea and vomiting with conservative measures and first-line antiemetic agents, (e.g., pyridoxine 10 mg plus doxylamine 10 mg) is encouraged to prevent progressive symptoms. When hyperemesis gravidarum develops, admission is warranted to provide intravenous crystalloids to correct dehydration as well as parenteral antiemetics (e.g., ondansetron 4 mg every 8 hours) for symptomatic relief. Correction of ketosis and vitamin deficiency should be managed with thiamine (100 mg intravenously) to prevent Wernicke encephalopathy (Chapter 384). Early enteral tube feeding is not helpful.[A11]

PREVENTION AND PROGNOSIS

No preventive measures are known to be effective. Fortunately, hyperemesis gravidarum rarely negatively affects the pregnancy, and it has no significant association with congenital anomalies.

Intrahepatic Cholestasis of Pregnancy

DEFINITION

Intrahepatic cholestasis of pregnancy, which occurs during the second and third trimester and resolves after delivery, is characterized by pruritus, typically in the absence of a rash, and elevated serum levels of bile acids. This condition poses little risk to the mother but substantial risks to the fetus.[29]

EPIDEMIOLOGY AND PATHOBIOLOGY

Intrahepatic cholestasis of pregnancy is the most common pregnancy-specific liver disorder. The incidence ranges from 0.3 to 15% depending upon the population surveyed, with most estimates being approximately 0.5%. Importantly, only approximately 50% of women with clinically suspected intrahepatic cholestasis of pregnancy are confirmed to have the condition.[30] Women with underlying liver conditions, prior intrahepatic cholestasis of pregnancy, multiple gestations, and a familial history are at highest risk.

The cause and course of intrahepatic cholestasis of pregnancy are poorly understood. Once formed, bile acids are exported out of hepatocytes by specific transport proteins, such as the ATP-binding cassette (ABC) transporters, with most transport pumps belonging to the subfamily B (ABC-B). One of the primary bile acid transport proteins is the ABCB-4 pump. The *ABCB4* gene encoding the multidrug resistance 3 (MDR3) protein is primarily involved in a subtype of progressive familial intrahepatic cholestasis. However, this defect likely represents just one example of a number of bile acid transport disruptions that lead to the disorder.

CLINICAL MANIFESTATIONS AND DIAGNOSIS

During pregnancy, pruritus is a common complaint, reported in nearly one-quarter of women. Dermatologic conditions associated with pruritus specific to pregnancy include atopic eruption of pregnancy, pruritic urticarial papules and plaques, and intrahepatic cholestasis of pregnancy. However, the pruritus associated with intrahepatic cholestasis of pregnancy is often generalized, worse at night, and not typically associated with a rash, with the exception of excoriations. If localized, pruritus is typically reported on the palms and soles.

A detailed history and physical examination is indicated. Serum levels of bile acids and aminotransferases should be measured (Table 221-10). The diagnosis of intrahepatic cholestasis of pregnancy is based upon symptoms and a total bile acid level greater than 10 μmol/L in the absence of another explanation. A bile acid level 100 μmol/L or greater is associated with an increased risk of stillbirth.

TREATMENT

The first-line treatment for symptomatic intrahepatic cholestasis of pregnancy is ursodeoxycholic acid (300 mg twice daily), which is effective for relieving pruritic symptoms and improving laboratory values but does not improve fetal outcomes.[A12] Currently, women with severe intrahepatic cholestasis of pregnancy (bile acid levels ≥ 100 μmol/L) are recommended for late preterm delivery (36 to 37 weeks) to avoid the risk of stillbirth, whereas women with bile acid levels below 100 μmol/L are offered delivery at 36 to 39 weeks gestation.

Prevention and Prognosis

To date, no strategies are proven to prevent intrahepatic cholestasis of pregnancy. Following delivery, symptoms typically resolve in several days, and aminotransferase levels gradually decline. Contraception is recommended until aminotransferase levels return to normal. During interval resolution, nonhormonal contraception options are considered. Once recovered, estrogen-containing contraceptives are acceptable although they may precipitate recurrent disease. The future risks of gallstone disease and of recurrence during future pregnancies are increased.

Acute Fatty Liver of Pregnancy

Acute fatty liver of pregnancy, which is a rare but potentially fatal condition, is characterized by hepatic failure, typically occurring in the third trimester.

EPIDEMIOLOGY AND PATHOBIOLOGY

The reported incidence varies from 1 in 7000 to 1 in 20,000. Associated risk factors include multiple gestation and fetal fatty acid oxidation disorders.

TABLE 221-10 LABORATORY AND CLINICAL FINDINGS WITH GASTROINTESTINAL COMPLICATIONS OF PREGNANCY

DISORDER	CREATININE	HEMATOCRIT	PLATELETS	FIBRINOGEN	HEMOLYSIS	AST	BILIRUBIN	CLINICAL FINDINGS
Hyperemesis gravidarum	↑	Normal	Normal	Normal	No	Normal-↑↑	Normal -↑↑	Severe nausea and vomiting
Preeclampsia	Normal-↑	↑	Normal-↓↓	Normal	Mild	Normal-↑↑	Normal	Hypertension, headache
Intrahepatic cholestasis	Normal	Normal	Normal	Normal	No	Normal-↑	Normal-↑↑	Pruritus, jaundice
Acute fatty liver of pregnancy	↑-↑↑	↓-↑	↓	↓↓	↑↑-↑↑↑	↑↑	↑↑	Nausea and vomiting, hypertension, abdominal pain, encephalopathy
Hepatitis	Normal	Normal	↓	↓	No	↑↑↑↑	↑↑↑	Nausea and vomiting, jaundice
Thrombotic microangiopathy	↑-↑↑↑	↓↓	↓↓-↓↓↓	Normal	↑↑-↑↑↑↑	Normal	Normal	Headache, hypertension

AST = aspartate aminotransferase.
Adapted from Nelson DB, Byrne JJ, Cunningham FG. Acute fatty liver of pregnancy. *Obstet Gynecol.* 2021;137:535-546.

Despite a well-known association with preeclampsia, the direct cause and effect remains unclear.

Autosomal recessive mutations in genes that encode for enzymes for the fatty acid metabolism pathway cause both the clinical features and histologic microvesicular fatty hepatocyte infiltration seen in Reye syndrome in children and in acute fatty liver in pregnant women. An example of commonly affected enzyme in acute fatty liver of pregnancy is long-chain 3-hydroxyacyl-CoA dehydrogenase (LCHAD). During normal pregnancy, the fetal-placental unit metabolizes free fatty acids for fetal growth and development. Placental enzymes catabolize triglycerides into free fatty acids, which are then transferred to the fetus. When defects exist in the fatty acid oxidation pathway of the fetal-placental unit, intermediate fatty acid metabolites accumulate and enter the maternal circulation. These intermediate metabolites and associated reactive oxygen species are taken up by the maternal liver where they cause microvesicular fatty infiltration, activate inflammatory processes, and precipitate hepatic cellular necrosis. The mechanism leading to the accumulation of fatty acids and metabolites in the maternal compartment involves two processes. First, the fetal-placental unit shares either a homozygous or compound heterozygous mutation resulting in an enzymatic defect. Second, a heterozygous mother has a decreased ability to accomplish fatty acid oxidation in late pregnancy, thereby leading to an inability to clear the accumulating fatty acid metabolites that are transferred from the deficient fetal-placental unit.

CLINICAL MANIFESTATIONS AND DIAGNOSIS

Common symptoms include nausea, vomiting, abdominal pain, often accompanied by hypertension. However, the manifestations of acute fatty liver of pregnancy range from minimal clinical findings and laboratory derangements to overt liver failure (Chapter 140) with hepatic encephalopathy.

The diagnosis of acute fatty liver of pregnancy can be challenging. The most frequent obstetric condition confused with it is the more prevalent hemolysis, elevated liver enzyme, and low platelets (HELLP) syndrome (Chapter 158).[31] Both conditions are associated with significant maternal and perinatal morbidity and mortality, but new-onset nausea and vomiting in the third trimester is often associated with acute fatty liver of pregnancy, which can be confirmed by meeting six of the diagnostic criteria (Table 221-11).

TABLE 221-11 SWANSEA DIAGNOSTIC CRITERIA FOR ACUTE FATTY LIVER OF PREGNANCY

Six or more of the following features in the absence of another explanation:

- Vomiting
- Abdominal pain
- Polydipsia/polyuria
- Encephalopathy
- Elevated bilirubin
- Hypoglycemia
- Elevated urate
- Leukocytosis
- Ascites or bright liver on ultrasound scan
- Elevated transaminases
- Elevated ammonia
- Renal impairment
- Coagulopathy
- Microvesicular steatosis on liver biopsy

From Ch'ng CL, Morgan M, Hainsworth I, et al. Prospective study of liver dysfunction in pregnancy in Southwest Wales. *Gut.* 2002;51:876-880.

TREATMENT

The clinical management of the patient with acute fatty liver of pregnancy relies on prompt recognition with in-hospital evaluation and care; supportive measures, such as reversal of coagulopathy; preparation for delivery as soon as feasible; and multidisciplinary care. Hepatic injury will continue until delivery, and maternal recovery may require days to weeks. Close maternal and fetal care should include monitoring, preparation in anticipation of the need for blood products, and a magnesium sulfate infusion if preeclampsia is being considered. Blood pressure should be controlled (see Table 221-5), with a goal of less than 160/110 mm Hg. If the patient is encephalopathic or obtunded, airway protection is critical and may require endotracheal intubation. Up to 15% of women with acute fatty liver of pregnancy will develop pancreatitis.

After delivery, serial measurements of hematologic, hepatic, and renal function should be performed every 6 to 12 hours for the first 1 to 2 days. Blood product replacement is often required because of the risk of postpartum hemorrhage, hemolysis, and diminished pro-coagulant production. Similarly, blood glucose levels should be monitored hourly, and hypoglycemia should be treated with an infusion of 10% glucose.

PROGNOSIS

Clinical recovery should usually be within a week following delivery. Hepatic dysfunction usually begins to improve 1 to 2 days after delivery. Aminotransferase levels decline linearly to levels of 100 units/L or less but may remain mildly elevated for several weeks. Hemostatic dysfunction related to liver synthetic function as well as consumptive coagulopathy improves over 4 to 6 days postpartum. In contrast, renal recovery, as measured by the serum creatinine level, may require 7 to 10 days. Rarely, expected hepatic recovery does not occur, and persistent liver failure may require transplantation.

INFECTIOUS DISEASE

PYELONEPHRITIS

Genitourinary tract infections are the most frequent bacterial infections in pregnancy. Infection that involves the renal calyces, pelvis, and parenchyma is referred to as pyelonephritis (Chapter 263).

EPIDEMIOLOGY AND PATHOBIOLOGY

Pyelonephritis, which is the leading cause of septic shock in pregnancy, is often preceded by asymptomatic bacteriuria, which develops in 2 to 7% of women. If asymptomatic bacteriuria is not treated, up to 25% of pregnant women will progress to symptomatic infection.

Female anatomy predisposes to risk of genitourinary infection, with a shorter urethra, proximity to the vagina and rectum, and common flora at the perineum. Regardless of trimester, the most common organism leading to pyelonephritis is *Escherichia coli* (Chapter 280), but other pathogens include *Klebsiella*, *Enterobacter*, and *Proteus* species (Chapters 281 and 282). Within pregnancy, urinary stasis, vesicoureteral reflux, and pregnancy-related alterations to the T-helper cell (T_H1/T_H2) ratio further enhance susceptibility to infection of the upper genitourinary tract. With urosepsis, endotoxin-induced alveolar damage can lead to respiratory insufficiency that may be further worsened by tocolytic agents, such as β-mimetics.

DIAGNOSIS

The diagnosis of pyelonephritis during pregnancy is suspected with clinical findings of fever, flank pain manifest as costovertebral tenderness on examination, and urinary complaints. Patients present most commonly during the second trimester. The differential diagnosis includes labor, chorioamnionitis, appendicitis, and adnexal torsion. Following a careful history and physical examination, a catheterized urine collection should be obtained to avoid contamination from the lower genital tract. Urinalysis reveals bacteriuria, leukocytes, and nitrites. Urine and blood cultures should be obtained.

TREATMENT

Hospital admission is advised for suspected cases of pyelonephritis during pregnancy. Intravenous fluid support to preserve adequate urinary output is paramount. Empirical antibiotics targeting anticipated pathogens should be initiated promptly (Chapter 266).[32] Typical initial empirical regimens include either ceftriaxone (1 g every 24 hours) or ampicillin (1 g every 6 hours) plus gentamicin (1.5 mg/kg every 8 hours). Intravenous antibiotics should then be tailored to culture results once available. Supportive care includes antipyretics, serial maternal assessment, and fetal monitoring for viable gestations. Notable alterations to maternal blood pressure, pulse, or respiratory function may be early indicators of urosepsis. In general, a mean arterial pressure of at least 65 mm Hg is needed to preserve maternal-fetal perfusion. If necessary despite fluid resuscitation, norepinephrine is the first-line vasopressor recommended during pregnancy (Chapter 94).[33] The clinical course is typically 3 to 4 days of recurrent spiking fevers but with gradual improvement in the temperature curve and peak fevers. For unresponsive infections after 3 to 4 days, genitourinary imaging with either sonography or magnetic resonance imaging is recommended to exclude nephrolithiasis, a perinephric abscess, or an anatomic abnormality that may be causing obstruction.

Following acute resolution of infection, intravenous antibiotics are typically transitioned to a 10- to 14-day course for outpatient management tailored to culture results. Thereafter, oral antibiotic suppression for the remainder of pregnancy is recommended because about one-third of women will have recurrent infection.

PREVENTION AND PROGNOSIS

Pregnant women should be screened for asymptomatic bacteriuria at least once during early pregnancy. Any infection should be treated (see Chapter 263), with a follow-up culture to ensure success. Beyond the immediate infection, neither mother nor fetus have any long-term sequelae treatment.

COVID-19

Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection (Chapter 336) and the disease it causes (coronavirus disease 2019; COVID-19) puts pregnant women at increased risk for hospitalization and intensive care unit admission, and it puts their fetus at increased risk of preterm birth.[34,35] Management requires a multidisciplinary team. Delivery may not improve outcomes. Vaccination during pregnancy is highly protective against infection during pregnancy and is strongly recommended.[36]

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For the General References and other additional features, please visit Elsevier eBooks+ at https://ebooks.health.elsevier.com.

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222 MENOPAUSE

NANETTE SANTORO AND GENEVIEVE NEAL-PERRY

DEFINITION

Menopause is defined as the permanent cessation of menses and is the culmination of a process of reproductive aging that typically occurs in the fifth to sixth decades of life, with a median age of 52.5 years.

EPIDEMIOLOGY

Menopause is a universal phenomenon among women, and its lived experience varies by individual. The advent of menopause and the coincident loss of gonadal steroids significantly affect multiple organ systems in affected women, thereby resulting in an increased risk for osteoporosis (Chapter 225), dementia (Chapter 371), and heart disease (Chapter 40).

Many factors influence the timing of the final menstrual period for any given woman (Table 222-1). Knowing one's mother's age at her final menstrual period is a strong predictor of when a woman is likely to have her own.[1]

TABLE 222-1 SOME KNOWN FACTORS THAT INFLUENCE THE AGE AT MENOPAUSE

FACTOR	DIRECTION	DEGREE/COMMENT
GENETIC/FAMILIAL		
CYP3A4 and *CYP1B1*	Earlier menopause	Interaction with smoking
MSH6	Earlier menopause	Detected by GWAS
MCM8	Earlier menopause	Detected by GWAS
PvuII ER polymorphism	Earlier menopause, hysterectomy	6 mo
Mosaic Turner syndrome	Earlier menopause	Variable
Fragile X	Earlier menopause	Variable
ENVIRONMENTAL		
EDCs	Earlier menopause	1.8-3.8 yrs
High altitude	Earlier menopause	1-1.5 yrs
LIFESTYLE		
Smoking	Earlier menopause	1-2 yrs
Low socioeconomic status	Earlier menopause	1-2 yrs
Oral contraceptive use	Later menopause	6 mo
RACIAL/ETHNIC		
African American race	Earlier menopause*	2 yrs
Hispanic ethnicity	Earlier menopause*	2 yrs
Asian ethnicity	Later menopause	1-2 yrs
MENSTRUAL CHARACTERISTICS		
Shorter cycles (<26 days)	Earlier menopause	1.4 yrs
Higher parity	Later menopause	Variable

*Relative to Caucasian women.

CYP1B1 = cytochrome P450 family 1 subfamily B; *CYP3A4* = cytochrome P450 3A4 enzyme; EDCs = endocrine-disrupting chemicals; ER = estrogen receptor; GWAS = genome-wide association study; *MCM8* = minichromosome maintenance 8 gene, involved in recombination factor repair; *MSH6* = mutS homolog 6 gene, involved in DNA mismatch repair.

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DIAGNOSIS

The diagnosis of pyelonephritis during pregnancy is suspected with clinical findings of fever, flank pain manifest as costovertebral tenderness on examination, and urinary complaints. Patients present most commonly during the second trimester. The differential diagnosis includes labor, chorioamnionitis, appendicitis, and adnexal torsion. Following a careful history and physical examination, a catheterized urine collection should be obtained to avoid contamination from the lower genital tract. Urinalysis reveals bacteriuria, leukocytes, and nitrites. Urine and blood cultures should be obtained.

TREATMENT

Hospital admission is advised for suspected cases of pyelonephritis during pregnancy. Intravenous fluid support to preserve adequate urinary output is paramount. Empirical antibiotics targeting anticipated pathogens should be initiated promptly (Chapter 266).[32] Typical initial empirical regimens include either ceftriaxone (1 g every 24 hours) or ampicillin (1 g every 6 hours) plus gentamicin (1.5 mg/kg every 8 hours). Intravenous antibiotics should then be tailored to culture results once available. Supportive care includes antipyretics, serial maternal assessment, and fetal monitoring for viable gestations. Notable alterations to maternal blood pressure, pulse, or respiratory function may be early indicators of urosepsis. In general, a mean arterial pressure of at least 65 mm Hg is needed to preserve maternal-fetal perfusion. If necessary despite fluid resuscitation, norepinephrine is the first-line vasopressor recommended during pregnancy (Chapter 94).[33] The clinical course is typically 3 to 4 days of recurrent spiking fevers but with gradual improvement in the temperature curve and peak fevers. For unresponsive infections after 3 to 4 days, genitourinary imaging with either sonography or magnetic resonance imaging is recommended to exclude nephrolithiasis, a perinephric abscess, or an anatomic abnormality that may be causing obstruction.

Following acute resolution of infection, intravenous antibiotics are typically transitioned to a 10- to 14-day course for outpatient management tailored to culture results. Thereafter, oral antibiotic suppression for the remainder of pregnancy is recommended because about one-third of women will have recurrent infection.

PREVENTION AND PROGNOSIS

Pregnant women should be screened for asymptomatic bacteriuria at least once during early pregnancy. Any infection should be treated (see Chapter 263), with a follow-up culture to ensure success. Beyond the immediate infection, neither mother nor fetus have any long-term sequelae treatment.

COVID-19

Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection (Chapter 336) and the disease it causes (coronavirus disease 2019; COVID-19) puts pregnant women at increased risk for hospitalization and intensive care unit admission, and it puts their fetus at increased risk of preterm birth.[34,35] Management requires a multidisciplinary team. Delivery may not improve outcomes. Vaccination during pregnancy is highly protective against infection during pregnancy and is strongly recommended.[36]

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222 MENOPAUSE

NANETTE SANTORO AND GENEVIEVE NEAL-PERRY

DEFINITION

Menopause is defined as the permanent cessation of menses and is the culmination of a process of reproductive aging that typically occurs in the fifth to sixth decades of life, with a median age of 52.5 years.

EPIDEMIOLOGY

Menopause is a universal phenomenon among women, and its lived experience varies by individual. The advent of menopause and the coincident loss of gonadal steroids significantly affect multiple organ systems in affected women, thereby resulting in an increased risk for osteoporosis (Chapter 225), dementia (Chapter 371), and heart disease (Chapter 40).

Many factors influence the timing of the final menstrual period for any given woman (Table 222-1). Knowing one's mother's age at her final menstrual period is a strong predictor of when a woman is likely to have her own.[1]

TABLE 222-1 SOME KNOWN FACTORS THAT INFLUENCE THE AGE AT MENOPAUSE

FACTOR	DIRECTION	DEGREE/COMMENT
GENETIC/FAMILIAL		
CYP3A4 and *CYP1B1*	Earlier menopause	Interaction with smoking
MSH6	Earlier menopause	Detected by GWAS
MCM8	Earlier menopause	Detected by GWAS
PvuII ER polymorphism	Earlier menopause, hysterectomy	6 mo
Mosaic Turner syndrome	Earlier menopause	Variable
Fragile X	Earlier menopause	Variable
ENVIRONMENTAL		
EDCs	Earlier menopause	1.8-3.8 yrs
High altitude	Earlier menopause	1-1.5 yrs
LIFESTYLE		
Smoking	Earlier menopause	1-2 yrs
Low socioeconomic status	Earlier menopause	1-2 yrs
Oral contraceptive use	Later menopause	6 mo
RACIAL/ETHNIC		
African American race	Earlier menopause*	2 yrs
Hispanic ethnicity	Earlier menopause*	2 yrs
Asian ethnicity	Later menopause	1-2 yrs
MENSTRUAL CHARACTERISTICS		
Shorter cycles (<26 days)	Earlier menopause	1.4 yrs
Higher parity	Later menopause	Variable

*Relative to Caucasian women.

CYP1B1 = cytochrome P450 family 1 subfamily B; *CYP3A4* = cytochrome P450 3A4 enzyme; EDCs = endocrine-disrupting chemicals; ER = estrogen receptor; GWAS = genome-wide association study; *MCM8* = minichromosome maintenance 8 gene, involved in recombination factor repair; *MSH6* = mutS homolog 6 gene, involved in DNA mismatch repair.

ABSTRACT

Menopause marks the end of a woman's reproductive life and the cessation of ovarian function. Unlike other endocrine deficiency syndromes, menopause is not a pathologic state per se, but both the transition into menopause and its aftermath of constitutively low sex steroid secretion are associated with changes in health outcomes that vary based on a number of modifiable (body mass index, socioeconomic status) and nonmodifiable (race/ethnicity) factors. The acute consequences of the menopause transition are mostly related to symptoms and their management: hot flashes, vaginal dryness, mood changes, and sleep disturbances are the predominant conditions that lead women to seek medical treatment. With progress through the menopausal transition, persistence of symptoms as well as complications of aging, such as cardiometabolic disease, bone demineralization, and cognitive decline, may lead to a need for short- or longer-term use of hormones or other agents, each with its own risks and benefits, to mitigate symptoms. Clinicians are encouraged to use shared decision making when recommending treatment of menopausal symptoms or the consequences of menopause with their patients.

KEYWORDS

menopause
menopause transition
hormone therapy
hot flashes

TABLE 222-2 STAGING REPRODUCTIVE AGING

STAGE	REPRODUCTIVE (−5 to −3)	MENOPAUSAL TRANSITION (−2 to −1)		POSTMENOPAUSE (+1 to +2)
Subdivisions	Early, peak, late	Early (−2)	Late (−1)	Early, late
Age ranges (approximate)	13-47	47-49	49-52	50+
Menses	Mostly regular	Minor irregularity	≥60-364 days amenorrhea	Amenorrhea
Hormonal hallmarks	FSH—low (rises sporadically at stage −3) AMH—high	FSH sporadically elevated AMH—normal to low	FSH more consistently elevated AMH—low	FSH consistently elevated (>25 IU/L) AMH—undetectable

The diagram distills the evidence from the STRAW paradigm (Harlow SD, Gass M, Hall JE, et al. *J Clin Endocrinol Metab*. 2012;97:1159-1168) into a brief referable item to help "place" a woman along the menopause transition. Stage 0 is the final menstrual period. Clinically helpful milestones are mostly related to menstrual regularity. FSH or AMH can be used as confirmatory tests when clinical context is unclear. AMH = antimüllerian hormone; FSH = follicle-stimulating hormone.

The menopausal transition refers to the processes of reproductive aging (Table 222-2) that involve menstrual cycle change, irregularity, and a breakdown of typical reproductive hormonal patterns and feedback mechanisms that characterize the fertile cycles of midreproductive-age women. Patterns of the production of gonadal hormones are altered, such that cycles become shorter and more sporadic and display less progesterone production. Follicle-stimulating hormone (FSH) increases sporadically as the remaining ovarian follicular pool (ovarian reserve) requires more and more stimulation to produce a preovulatory follicle. Eventually, FSH cannot sustain folliculogenesis, so menses begin to skip. Because ovarian folliculogenesis waxes and wanes over the course of the transition, cycles do not stop abruptly. Instead, ovulatory and anovulatory cycles alternate in an apparently random fashion. The resulting hormonal fluctuations trigger the onset of bothersome and sometimes debilitating symptoms for many women.

Symptoms of menopause do not simply appear with the final menstrual period; rather, they are usually present throughout the transition, although they tend to intensify as women progress through the transition. For many women, symptoms begin in the early menopausal transition and worsen by the late transition through the early postmenopausal period.

Determining a woman's proximity to her final menstrual period has implications that are important for her health. Women with an early final menstrual period will spend a greater proportion of their lifetime in a state of relative hypogonadism, which has consequences on bone health and cognition as well as on cardiovascular health. Women whose transition is later are more prone to estrogen-related diseases, such as breast cancer (Chapter 183) and endometrial cancer (Chapter 184). Additionally, women who have not yet undergone 12 months of amenorrhea may wish to know when they can safely discontinue the use of contraception. Finally, many women who are symptomatic may want to predict how long their symptoms are likely to last.

PATHOBIOLOGY

Both menopause and advancing age impose adverse effects on central nervous system (CNS) function (Chapter 371). The brain is enriched with estrogen receptors, and estrogen receptor signaling is hypothesized to mediate multiple key processes in the CNS, including but not limited to neurotrophic effects and neuroprotection.[2] Menopause and advancing age both impose adverse effects on CNS function.

Sex differences in the structure and function of the hippocampus and the temporal lobe are hypothesized to relate to differences in the activational and organizational effects of estradiol on memory performance. Estrogen-mediated structural differences in the hypothalamic cytoarchitecture translate into higher executive functioning in women. Consequently, anxiety and mood changes are more common in perimenopausal and recently menopausal women, especially in women who have a history of mood dysfunction or adverse childhood experiences. Hypogonadism of menopause may explain why perimenopausal and early postmenopausal women frequently complain of memory loss and inability to focus. However, studies of hormone therapy in menopausal women provide conflicting results regarding its benefit on attention and executive functions such as nonspatial and spatial working memory, as well as verbal memory. Moreover, many of these executive functions spontaneously recover within a few years of the final menstrual period.

Bone health is significantly affected by gonadal steroids.[3] Over the menopausal transition, serum estradiol and estrone concentrations decrease by as much as 90%. This decline closely parallels a period of accelerated and progressive bone loss (Chapter 225). Reduced estrogen signaling in menopause disrupts the balance of receptor activator nuclear factor-κβ ligand (increased) and osteoprotegerin (decreased) concentrations, with the end effect being increased osteoclast activity, accelerated bone resorption, and attenuated bone remodeling. All of these changes result in significant increases in urinary and serum markers of bone resorption, as well as accelerated changes in bone mineral density in the late menopause transition. Annual rates of bone loss approximate 1.8 to 2.3% in the spine and 1.0 to 1.4% in the hip. As much as 30% loss of trabecular and 10% loss of cortical bone occurs over the 6 to 10 years spanning the perimenopausal and early menopausal period. Menopause-driven changes in bone physiology result in an increased risk for osteoporosis (Chapter 225) and a 50 to 100% higher fracture rate.

Increased weight gain and altered fat distribution are common complaints in perimenopausal and menopausal women regardless of race, ethnicity, or socioeconomic status. Midlife women gain approximately 2 to 5 pounds on average, though with wide variation, and exhibit significant changes in their body composition. Postmenopausal weight gain and increased central adiposity may in part reflect an effect of hypogonadism on the gut microbiota. Hypogonadism may affect adipose tissue, which is an endocrine organ that expresses estrogen receptors, by disrupting adipocyte lipolysis and adipogenesis.[4] Increased central adiposity is characterized by chronic low-grade inflammation, metabolic syndrome, and more than a four-fold increased risk in cardiovascular death. Additionally, obese perimenopausal and early menopausal women experience more frequent and severe hot flashes as well as sexual dysfunction.

CLINICAL MANIFESTATIONS

Menopause is a universal phenomenon among women, and its lived experience varies from person to person. The advent of menopause and the coincident loss of gonadal steroids affect multiple organ systems and can result in increased risk for morbidity related to osteoporosis, dementia, and heart disease.

Symptoms that women report as they traverse menopause may be difficult to disentangle from those related to aging itself. Four cardinal symptoms are considered to be directly related to menopause, based on their association with the transition and their ability to be treated with hormones. These include vasomotor symptoms/hot flashes, vaginal dryness, sleep disturbances, and mood/cognition problems.[5]

Vasomotor Symptoms

Vasomotor symptoms are experienced by up to 80% of women, at an average of 4.5 years after their final menstrual period and with a median duration of 7.4 years. Vasomotor symptoms are caused by aberrant activation of the tachykinin system. Women whose symptoms begin at an earlier age and who are earlier in their transition at onset have a longer duration of symptoms, with some women experiencing vasomotor symptoms for more than a decade. About 50% of women whose vasomotor symptoms precede entry into the menopausal transition often have persistent vasomotor symptoms for 10 years or longer after their final menstrual period. Black women are also more likely to have persistent vasomotor symptoms compared with other racial/ethnic groups; approximately 40% will report post–final menstrual period persistence of 10 years or longer. Additional factors that may result in a longer duration of vasomotor symptoms include lower educational level, greater perceived stress, more depressive symptoms, and anxiety at the time of the first report of vasomotor symptoms. Whereas a higher body mass index (BMI) at the time of early menopause is associated with more vasomotor symptoms, a higher BMI at the time of late menopause is associated with fewer vasomotor symptoms.

Genitourinary Symptoms

Vaginal dryness, dyspareunia,[6] and urogenital symptoms are less common than vasomotor symptoms but still prevalent in about 25 to 50% of menopausal women.[7] Women may report dryness, chronic irritation, or burning of both the vagina and vulva. Among those who are sexually active, lack of lubrication with attempted intercourse, pain during intercourse, or bleeding after intercourse may be present. Urinary frequency, urethritis, and frequent urinary tract infections (Chapter 263) may also occur. All of these symptoms are believed to reflect hypogonadism and the absence of estrogen exposure to the vaginal and urinary tract epithelium. Unlike vasomotor symptoms, symptoms of the genitourinary syndrome of menopause do not spontaneously resolve over time.

Sleep Disturbances

Sleep disturbances (Chapter 374) are more common in women but also worsen with age, so it can be challenging to differentiate between age-related changes compared with menopause.[8] Sleep architecture in menopausal women demonstrates greater sleep disturbances in the second half of the night, in association with compromise of rapid eye movement (REM) sleep. Whereas some epidemiologic studies indicate that the menopausal transition worsens preexisting sleep problems and is associated with worse sleep, others report little independent effect of ovarian failure on sleep, except for a small, vulnerable subset of women with relatively poor sleep at baseline. Studies of premenopausal women given a gonadotropin-releasing hormone (GnRH) agonist to produce abrupt estrogen withdrawal indicate significant alterations in sleep, largely related to subjective nighttime hot flashes that prompt nighttime awakenings.

An additional complexity in attributing sleep disturbances to menopause is the possibility that concomitant independent sleep disorders (e.g., insomnia, sleep apnea, and restless legs syndrome; Chapter 374) are present. Sleep apnea is suspected based on a history of snoring, daytime sleepiness, and less perceived restfulness of sleep, and it is diagnosed by an overnight sleep assessment. Diagnostic criteria for restless legs syndrome (Chapter 374) include irresistible urges to move one's legs; symptoms present at rest; urge relieved by movement; and peak symptoms at night or in the evening. Insomnia (see Table 374-5 and Fig. 374-6) may appear at the time of the menopausal transition, but it may also be long-standing in duration. Women age 35 years or over with insomnia have the highest rates of persistence of sleep disorders in menopause.

Mood Disorders

Adverse mood is associated with traversal of menopause in a complex manner. Abrupt estrogen withdrawal using a GnRH agonist in premenopausal women results in a deterioration of mood. Depressive symptoms are associated with nighttime hot flashes and sleep disruption, thereby indicating the intimate relationship between sleep and mood. Multiple cohort studies have identified the late transition as a period of vulnerability for depression in midlife women.[9] Women are two- to four-fold more likely to experience new onset of major depression (Chapter 362) during the menopausal transition than they are before they become perimenopausal or after their final menstrual period. Concomitant anxiety and hot flashes are predictors of major depression during this time of life. Although absolute levels of hormones are not clearly associated with major depression or depressive symptoms, greater variability in FSH, luteinizing hormone, and estradiol have been linked to depressive symptoms.

DIAGNOSIS

Menopause is a clinical diagnosis typically based on amenorrhea for at least 12 months.[10] However, this definition relies on a woman having menstrual cycles with some degree of regularity. Women who are age 45 or older have a 90% probability of never having another menstrual period once they attain the milestone of 12 months' amenorrhea. In contrast, younger women have a substantially greater probability of experiencing subsequent menses. The final menstrual period is most often preceded by several years of instability in menstrual cyclicity and hormone secretion. This process, which is called the menopausal transition, usually persists for about 4 years, but with wide variation around this median. Women who enter the transition at a younger age tend to have more symptoms and a longer transition, whereas women who enter it later in life are more likely to have a rapid transition to their final menstrual period.

No diagnostic test can definitively predict when a woman will have her final menstrual period. Nonetheless, the serum level of antimüllerian hormone, which is a transforming growth factor beta family peptide synthesized by granulosa cells, is a reliable proxy of ovarian reserve (remaining follicle volume) and can be used to help approximate the timing of the final menstrual period.[11] Other measures, such as levels of FSH or the inhibins, are generally not recommended for this purpose, in part because—unlike antimüllerian hormone—they fluctuate throughout the menstrual cycle.

TREATMENT

Current guidelines for menopausal management concur that only symptomatic treatment, as needed, is indicated for this normal life transition. Clinicians should assess the patient's symptoms and offer evidence-based treatment, with periodic reevaluation of the necessity of treatment.

Whereas the need for treatment of hot flashes, sleep problems, and mood problems will very likely decrease over time, a minority of women will continue to have significant symptoms and require long-term treatment, either with extended hormonal therapy or nonhormonal alternatives. Genitourinary symptoms are long lasting, so long-term treatment may be necessary.

Symptoms most commonly associated with menopause (hot flashes, sleep dysfunction, mood, and genitourinary syndrome of menopause) are readily improved with hormone therapy. However, fear of hormones has led to widespread undertreatment of symptoms and a proliferation of nonrigorously tested but popular treatments, such as a large variety of herbal preparations.

Vasomotor Symptoms

Nonhormonal management of menopausal symptoms can include nonpharmacologic and pharmacologic methods. For mild to moderate symptoms, behavioral and nonpharmacologic approaches may be preferred. However, for more severe symptoms, pharmacologic management typically will be required.

Behavioral and Nonpharmacologic Approaches

Women may experience hot flash "triggers" from caffeine or alcohol and may modify consumption accordingly. Reducing the ambient room temperature and layering clothing to accommodate sudden changes in heat perception may also be helpful, but these recommendations are not based on medical evidence. Cognitive-behavioral therapy, which has demonstrated 50% efficacy in the treatment of hot flashes in women with breast cancer, has negligible potential for harm and can be recommended for all symptomatic menopausal women.

Weight loss has shown some efficacy in observational studies. Acupuncture has some evidence for efficacy, but not all trials have demonstrated benefit.[A1] Yoga, exercise, and consumption of black cohosh and omega-3 fatty acids have been demonstrated to be ineffective in several randomized trials.

Nonhormonal Medications

A number of nonhormonal prescription medications (Table 222-3) can be used to treat hot flashes for women who cannot or do not wish to use hormones.[12] Although many of these treatments are supported by well-conducted randomized, clinical trials, only paroxetine mesylate and fezolinetant are FDA approved as of this writing. Experimental nonhormonal agents targeting the neurokinin-3 receptor appear to have great specificity for the treatment of hot flashes and an efficacy that is comparable to estrogen.[A2]

Systemic Hormonal Therapy

Systemic hormonal therapy should be reserved for women with bothersome vasomotor symptoms.[13,14] Observational data as well as randomized clinical trials suggest that hormone therapy, when administered within the first 5 years of the final menopause, attenuates some, but not all, of the adverse effects of menopause-related hypogonadism.

Hormonal therapies include estradiol, estrogens, and, when women have a uterus, progestin (Table 222-4).[15] Risks and side effects of hormonal therapy are modulated by the route of administration, hormonal formulation, age, time since the final menstrual period, and the presence or absence of a uterus, as well as coexisting comorbid conditions, such as cardiovascular disease, dementia, and diabetes.[16] Approved prescription medications are preferred over compounded hormone products, which lack adequate data on efficacy and safety.

For women who cannot or do not wish to take estrogen, oral micronized progesterone in daily doses up to 300 mg per day has demonstrated efficacy in the treatment of hot flashes.[A3] Long-term risks and benefits are not known at this time.

Uterine neoplasia is increased under conditions of chronic unopposed estrogen exposure in a woman with an intact uterus. Thus, the primary indication of progestin therapy during menopause is to prevent estradiol-induced endometrial hyperplasia and cancer. Commonly used progestins include medroxyprogesterone acetate, norethindrone acetate, and micronized progestin (native progesterone). Progestin administered continuously or sequentially provides adequate endometrial protection. However, controversy exists as to whether micronized progestin protects the uterus as effectively as synthetic progestin.

Risks of Systemic Hormone Therapy

In the Women's Health Initiative study, the combined estrogen/progestin therapy arm was stopped prematurely after 5.2 years because of increased hazard ratios for coronary heart disease (1.29), breast cancer (1.26), stroke (1.41),

TABLE 222-3 NONHORMONAL PHARMACOLOGIC THERAPY FOR HOT FLASHES

MEDICATION	USUAL DAILY DOSES	RELATIVE EFFICACY†	SIDE EFFECTS
Citalopram	20-40 mg	50%	Nausea, somnolence or insomnia, dry mouth, dyspepsia
Clonidine	Transdermal: 0.1-0.2 mg Oral: 0.1-0.3 mg	30%	Dry mouth, orthostatic hypotension, dizziness
Desvenlafaxine	100-150 mg	60%	Nausea, dry mouth, insomnia/somnolence, constipation, high blood pressure, sexual dysfunction
Escitalopram	10-20 mg	50%	Nausea, insomnia, headache, sexual dysfunction
Fezolinetant	45 mg	?	Hepatotoxicity, abdominal pain, diarrhea
Fluoxetine	10-20 mg	50%	Nausea, insomnia, headache, sexual dysfunction
Gabapentin	100-900 mg	60%	Drowsiness, dizziness, weight gain
Paroxetine mesylate*	7.5 mg	30%	Nausea, insomnia, headache, sexual dysfunction
Venlafaxine	37.5-150 mg	60%	Nausea/vomiting, anorexia, dry mouth, sexual dysfunction, high blood pressure

*Food and Drug Administration approved.
†Relative efficacy: estimated effectiveness compared with estrogen.

TABLE 222-4 POSTMENOPAUSAL HORMONE OPTIONS FOR VASOMOTOR SYMPTOMS*

DRUG	SUGGESTED FORMULATIONS	USUAL DOSAGE
ORAL ESTROGEN/PROGESTOGEN COMBINATIONS†		
Conjugated estrogen/medroxyprogesterone (Prempro)	0.3/1.5, 0.625/2.5 mg tabs	0.3/1.5-0.625/5 mg PO once/d
Estradiol/drospirenone (Angeliq)	0.5/0.25, 1/0.5 mg tabs	0.5/0.25 or 1/0.5 mg PO once/d
Estradiol/norethindrone (Activella)	0.5/0.1, 1/0.5 mg tabs	0.5/0.1 or 1/0.5 mg PO once/d
Estradiol/progesterone (Bijuva)	1/100 mg caps	1/100 mg PO once/d
Ethinyl estradiol/norethindrone (Femhrt)	2.5 µg/0.5 mg tabs	2.5 µg/0.5 mg or 5 µg/1 mg PO once/d
ORAL ESTROGENS		
Conjugated estrogen (Premarin)	0.3, 0.625 mg tabs	0.3-0.625 mg PO once/d
Estradiol	0.5, 1 mg tabs	0.5-1 mg PO once/d
Esterified estrogen (Menest)	0.3, 0.625, 1.25 mg tabs	0.625-1.25 mg PO once/d
ORAL PROGESTOGENS		
Progesterone (micronized)	100 mg caps	100 mg PO once/d
Medroxyprogesterone	5, 10 mg tabs	5-10 mg PO once/d x 12-14 d/mo
TRANSDERMAL ESTROGENS		
Estradiol patches (Alora, Climara, or Vivelle)	0.05 mg/d patches	0.05 mg/d patch 1-2 x/wk
Estradiol gel (EstroGel, Divigel, or Elestrin)	0.75 mg/actuation (30 doses/unit) 0.25, 0.5, 0.75, 1 mg/packets 0.52 mg/actuation (100 doses/unit)	0.75 mg applied once/d 0.25-1 mg applied once/d 0.52 mg applied once/d
Estradiol transdermal spray (Evamist)	1.53 mg/spray (56 sprays/unit)	2 sprays once/d
VAGINAL ESTROGEN		
Estradiol intravaginal ring (Femring)	90-day vaginal ring	0.05 mg/d
TRANSDERMAL ESTROGEN/PROGESTIN COMBINATIONS		
Estradiol/levonorgestrel (Climara Pro)	0.045/0.015 mg/d patches	0.045/0.015 mg/d patch once/wk
Estradiol/norethindrone (CombiPatch)	0.05/0.14, 0.05/0.25 mg/d patches	0.05/0.14 or 0.05/0.25 mg/d patch 2 x/wk

*Brand names listed only when generic options are not available.
†For women with an intact uterus, estrogen plus progestogen is recommended.
d = day; mo = month; PO = orally; wk = week.
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and pulmonary embolism (2.13), as well as increased risks for cognitive dysfunction, bone disease, and gastrointestinal cancer.[A4] However, long-term follow-up showed no differences in overall mortality at 18 years.[A5] A secondary analysis of Women's Health Initiative data comparing placebo with estrogen alone, however, found a statistically significant 18% reduction in the combined incidence of coronary heart disease, invasive breast cancer, stroke, pulmonary embolism, colorectal cancer, endometrial cancer, hip fracture, and all-cause mortality[A6] in women 50 to 59 years of age who had previously undergone a hysterectomy.

Risks of Coronary Heart Disease

Premenopausal women are at reduced risk for cardiovascular events compared with age-matched men and postmenopausal women,[17] thereby suggesting that estradiol may mediate the cardioprotection observed in premenopausal women. In addition to the Women's Health Initiative, relevant data from two smaller randomized trials also suggest cardiovascular safety for postmenopausal estrogen therapy. In one trial, conjugated equine estrogen or transdermal estradiol (with added sequential micronized progesterone) begun 6 to 36 months postmenopause did not increase carotid intima-media thickness, coronary artery calcium, cardiovascular events, venous thromboembolism, or breast or endometrial cancer. In another trial of postmenopausal women, 1 mg oral estradiol plus sequential vaginal progesterone (45 mg) therapy begun within 6 years of menopause was associated with decreased progression of carotid intima-media thickness and coronary artery calcium, whereas hormone therapy begun more than 10 years after menopause was no different than placebo.[A7] Taken together, these data suggest that women who initiate hormone therapy within 5 to 6 years of their final menstrual period are unlikely to experience an increase in risk of coronary heart disease as a result of treatment.

The risk of ischemic stroke (Chapter 376) is also increased with the use of hormone therapy. The risk for stroke is greatest with oral estrogen use and in women who have thrombophilia.

Risks of Venous Thromboembolic Disease

The use of oral estrogen increases the risk for venous thromboembolism (Chapter 68). Moreover, the risk for venous thromboembolism is increased whether it is estrogen-only or combined estrogen and progestin hormone therapy. The risk for thromboembolism, which increases with advancing age and is related to the estrogen dose, is higher within the first year of hormone therapy and magnified if a preexisting risk factor, such as obesity or thrombophilia, is present. The risk of venous thromboembolism is not significantly affected by micronized progesterone, medroxyprogesterone acetate, or norethindrone, but it is increased by norpregnane derivatives.

Risks of Cognitive Dysfunction

In the Women's Health Initiative Memory Study, the incidence of dementia (Chapter 371) was increased in women over age 65 years who initiated hormone therapy, but reduced global cognitive function was not observed when women 50 to 55 initiated hormone therapy. Other clinical trials also suggest that hormone therapy taken by younger women in early menopause does not adversely affect cognitive function. Whether early intervention with hormone therapy provides long-term cognitive benefit is currently under investigation.[18]

Risk of Breast Cancer

Combined estrogen and progestin menopausal therapy increases the risk of breast cancer (Chapter 183) compared with estrogen alone. For example, in the Women's Health Initiative study, combined equine estrogen and medroxyprogesterone acetate caused a nonsignificant increased risk for invasive breast cancer after 3 years, which became significant after 5+ years and remained elevated at 13 years in the postintervention study.[A8] In a French cohort study, the risk of breast cancer was significantly increased in women who used a progestin other than progesterone or dydrogesterone and in women who reported more than 5 years of menopausal hormone use. By comparison, estrogen-only menopausal hormone therapy has had a less consistent effect on the risk for breast cancer. In the Women's Health Initiative study, for example, the risk of breast cancer was 22% lower with estrogen alone in women with a prior hysterectomy compared with the increased risk associated with combined hormone therapy in women with an intact uterus.[A9] These data suggest a link between treatment with progestin and an increased risk for breast cancer.

Extending or Discontinuing Hormone Therapy

Menopausal symptoms appear to be subjectively worst in the year before the final menstrual period and up to 2 years afterward, and many women choose to discontinue hormones after the worst of their menopausal symptoms have subsided. For the majority of women, hormone doses may be reduced, or they may attempt to discontinue either by weaning slowly off of hormones or by stopping "cold turkey." There is limited evidence to suggest that a weaning strategy is less disruptive, but it does not necessarily lead to a greater proportion of women who successfully discontinue hormone therapy.

Additionally, the risks and benefits of hormone therapy vary by organ system, the hormone therapy formulation, and the time since the final menstrual period. Observational as well as randomized clinical trials also suggest that hormone therapy, when administered within the first 5 years of final menopause, attenuates some, but not all, of the adverse effects of menopause-related hypogonadism.[19]

Women who use combined estrogen and progestin hormone therapy for more than 5.6 years have an increased risk of invasive breast cancer, and women who continue use beyond 4 to 5 years should be monitored carefully. However, hormones need not be discontinued for many healthy women, as long as they continue to serve a purpose, especially for women who are approaching 5 to 10 years on hormone therapy but continue to have severe symptoms. Such women should be tried on nonhormonal options, but extended hormone therapy may be needed to preserve quality of life if they cannot be weaned. A small proportion of women, estimated at 3 to 15%, will have lifelong persistence of severe symptoms and will require continued hormones or nonhormonal alternatives.

Uterine neoplasia (Chapter 184) is increased under conditions of chronic unopposed estrogen exposure in a woman with an intact uterus, so the primary indication for progestin therapy during menopause is to prevent estradiol-induced endometrial hyperplasia and cancer. Commonly used progestins include medroxyprogesterone acetate, norethindrone acetate, and micronized progestin (native progesterone). Progestin treatment is most often achieved with combined estrogen and progesterone formulations (Table 222-4). Alternatively, progestin administered continuously (100 mg micronized progesterone or 2.5 mg of medroxyprogesterone) or sequentially (200 mg micronized progesterone or 5 mg medroxyprogesterone) provides adequate endometrial protection, but controversy exists as to whether micronized progestin protects the uterus as effectively as synthetic progestin (Chapter 184).

Vaginal Symptoms

Unlike hot flashes, symptoms of vaginal atrophy, including urinary tract irritation, vaginal itching and burning, and dyspareunia (collectively referred to as genitourinary syndrome of menopause), do not subside over time. Therefore long-term treatment may be required to preserve quality of life.[20]

For vaginal symptoms or the genitourinary syndrome of menopause, vaginal moisturizers (which must be used regularly to achieve effectiveness) and vaginal lubricants, which are specifically helpful during intercourse, can be recommended.[21-23] A vaginal hyaluronidase-based gel is as efficacious as 10-μg estradiol tablets twice weekly for relief of the most bothersome symptom.[A10] Little attention has been paid to the exact composition of these products, which are available over the counter. Women should be advised to choose products that are pH balanced (i.e., relatively acidic) with a physiologic osmolality.

Fortunately, long-term use of local estrogen compounds appears to be safe and well tolerated (Table 222-5). Systemic absorption of estrogen through vaginal administration of pills, capsules, and rings is minimal, but vaginal creams are more likely to increase circulating estradiol levels temporarily. Dehydroepiandrosterone can be used vaginally to treat dyspareunia. Ospemifene, a selective estrogen receptor modulator that has estrogen receptor beta stimulation properties, is available as a nonestrogenic treatment; however, it is administered systemically. Laser treatment of the vagina does not improve the symptoms of the genitourinary syndrome of menopause.[A11]

Sleep and Mood Disorders

Nonhormonal treatment of adverse mood includes psychotherapy and antidepressants (Table 362-5), with or without antianxiety medication (Table 362-9) as needed. For moderate to severe mood disturbances, hormonal therapy should not be used as a first-line treatment.

Difficulty sleeping can be addressed behaviorally. Telephone-based cognitive-behavioral therapy can benefit about 85% of postmenopausal women with moderate insomnia.[A12] A self-help smartphone app (https://mobile.va.gov/app/cbt-i-coach) is available to enable patients to implement such treatment. For patients who wish to use over-the-counter treatments, diphenhydramine (25 to 50 mg) or hydroxyzine (25 to 100 mg at bedtime) may facilitate the onset of sleep. A low-dose melatonin receptor agonist (ramelteon 4 mg at bedtime) may be effective in reducing sleep-onset latency, although high-quality clinical trials are lacking in a menopausal population. Judicious, short-term use of a variety of hypnotics and melatonin receptor agonists (Table 374-7) are available for the treatment of insomnia.

Mood and sleep issues are often intertwined, and treatment that addresses one of these conditions is likely to affect the other. To make matters more complex, hot flashes or night sweats that interrupt sleep can be a contributing factor to deteriorations of both mood and sleep. For example, citalopram is better than venlafaxine for reducing hot flashes (see Table 222-3), but venlafaxine is better for improving depression.[A13] It can be difficult to disentangle these overlapping contributory factors to adverse mood in a clinical setting. When symptoms are compound or overlapping, a brief trial of hormone therapy, if possible, may be better than using multiple agents specific for mood, sleep, and hot flashes to determine which symptoms are due to the menopausal transition and which are independent of it.

PREVENTION

Cardiovascular Risk

Postmenopausal women generally have cardiovascular risks equivalent to men who are about a decade older, and cardiovascular disease is the leading cause of death in elderly women. Postmenopausal women should be screened for hypertension (Chapter 64) and hyperlipidemia (Chapter 190), with the goal of reducing their subsequent risk for atherosclerosis (Chapter 40).[24] Based on current evidence, postmenopausal hormone therapy is not recommended to reduce cardiovascular risk.

Osteoporosis

Postmenopausal women have a markedly increased risk of bone loss and osteoporosis.[25] The preventive approach is covered in detail in Chapter 225. Based on current evidence, postmenopausal hormone therapy is not recommended to prevent osteoporosis.

PROGNOSIS

The need for treatment of hot flashes, sleep problems, and mood problems decreases over time, but a minority of women will continue to have significant symptoms and require long-term treatment, either with extended hormonal therapy or nonhormonal alternatives. The symptoms of the genitourinary syndrome of menopause are long lasting, and long-term treatment may be necessary. Clinicians should continuously assess the patient's symptoms and offer evidence-based treatment, with periodic reevaluation of the necessity of treatment.

TABLE 222-5 MEDICATION OPTIONS FOR GENITOURINARY SYNDROME OF MENOPAUSE*

DRUG	FORMULATION	SUGGESTED DOSE	COMMENTS
LOCAL VAGINAL THERAPY			
Estradiol (Estring)	2 mg ring (7.5 μg/d)	7.5 μg/d	Ring remains in place continuously for 90 days
Estradiol	10 μg insert	10 μg once/d × 2 wk, then 2 ×/wk	Single-use applicator containing one tablet
Prasterone (Intrarosa)	6.5 mg insert	6.5 mg qHS	-
Estradiol	0.1 mg/g cream	2 g once/d × 1-2 wk, then 1 g once/d × 1-2 wk	1 g after vaginal mucosa restored, 1-3 ×/wk
Conjugated estrogen (Premarin)	0.625 mg/g cream	0.5-2 g once/d × 3 wk followed by 7 d off, or 0.5 g 2 ×/wk	-
Estradiol vaginal inserts (Imvexxy)	4 μg and 10 μg	4 or 10 μg twice weekly	-
SYSTEMIC ORAL THERAPY			
Ospemifene (Osphena)	60 mg tabs	60 mg once/d	-

*Low-dose vaginal estrogen preferred for women who have only genitourinary symptoms. Brand names given only when generic options are not available.
d = day; qHS = at bedtime; wk = week.
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223 INTIMATE PARTNER VIOLENCE

GENE FEDER AND HARRIET L. MACMILLAN

DEFINITION

Intimate partner violence is defined as any behavior that is within an intimate relationship or ex-relationship and that causes physical, psychological, or sexual harm.[1] Such behaviors can include physical aggression, such as hitting, kicking, and beating; psychological violence, such as intimidation or constant humiliation; various controlling behaviors, such as isolation from family and friends, monitoring movements, financial control, and restricting access to services; and sexual violence, including forced intercourse and other sexual coercion. Intimate partner violence is a gendered problem. Lifetime prevalence of isolated violent acts within relationships is comparable for men and women, but repeated coercive, sexual, or severe physical violence is perpetrated largely against women by men. Intimate partner violence is also experienced at high rates by sexual minorities,[2] and transgender individuals (Chapter 214) appear to be at higher risk compared with cisgender individuals.[3] Although intimate partner violence is present in all demographic groups, its prevalence is greater in lower socioeconomic groups globally.[4]

Historically, the stereotype was a male batterer who used severe, repeated, and unilateral violence against a nonviolent female victim, but *bilateral violence* is common, even though the overwhelming burden of morbidity and mortality related to intimate partner violence is experienced by women. Bilateral violence, sometimes referred to as *common couple violence*, is considered less severe than the pattern of abuse known as *battering* or *intimate terrorism*—a severe and escalating form of intimate partner violence characterized by threats, terrorization, multiple forms of abuse, and controlling behavior. Current data indicate that women rarely subject men to battering.

Intimate partner violence is a risk factor for a wide range of medical and psychiatric conditions that require a clinical and public health response. Intimate partner violence is a violation of human rights and a preventable public health problem that must be addressed through social and educational policies.

EPIDEMIOLOGY

The prevalence of intimate partner violence against women varies internationally,[5] but worldwide about 25% of ever-married or partnered women report having been subjected to physical and/or sexual violence at least once in their lifetime from a current or former husband or male intimate partner.[6] The likelihood of intimate partner violence is higher among women with non-White racial/ethnic identities.[7] Indigenous women also are at higher risk, in part owing to colonization, structural violence, racism, and discrimination.[8] Globally, about one in seven homicides is committed by an intimate partner, with the rate six times higher for female homicide victims compared with male homicide victims.[9]

PATHOBIOLOGY

The ecologic model attempts to integrate evidence on individual (genetic and life course), family, community, and societal factors. Most research has focused on factors associated with increased risk for women who experience violence from men (Table 223-1), but it is difficult to determine causality because data are obtained overwhelmingly from cross-sectional studies.

Social learning theory suggests that intimate partner violence is a learned behavior. Male perpetrators and female victims are more likely to report histories of exposure to violence in childhood, but most individuals exposed to violence in childhood do not go on to commit violence as adults, and not all who commit abuse have violent upbringings. Furthermore, the link between poor parenting generally, including neglect, and subsequent intimate partner violence in adulthood suggests that the effect is not simply one of modeling abusive behavior. Exposure to rejecting or neglectful parenting is associated with adverse effects on intrapersonal (e.g., poor self-worth) and interpersonal development, which are associated with intimate partner violence.

A feminist perspective understands intimate partner violence against women as a form of coercive control rooted in society's patriarchal structure and reflecting the persistent inequality in economic and social relationships between men and women. Lending support to this perspective is the finding that intimate partner violence appears to be less common in more democratic and less economically polarized societies. Although intimate partner violence occurs more often in contexts in which there is support for male authority in the family and in which women have less access to economic security, it is not clear why some individuals are more likely to be violent under such conditions than others.

Evidence is conflicting regarding an association between intimate partner violence and psychopathology. Abusive males may have deficits in one or more coping mechanisms, anger control, and communication skills, but intimate partner violence also can result from dysfunctional interactional patterns between partners.[10] Because types of intimate partner violence are not the same for all couples, there are likely multiple causes for its occurrence.

CLINICAL MANIFESTATIONS

Patients seldom present with a complaint of intimate partner violence. Injuries are the most obvious manifestation, and a clinician should have increased suspicion for intimate partner violence if a patient has multiple injuries, if the presenting history of injuries is not consistent with the physical examination, and if a delay has occurred before seeking medical care for injuries. Patients exposed to physical violence may present with injuries that vary from minor abrasions to life-threatening trauma. Although there can be overlap between injuries resulting from intimate partner violence and injuries from other causes, the former typically involve trauma to the head, face, and neck, whereas the latter are more typically injuries of the extremities. Multiple facial injuries are suggestive of intimate partner violence rather than other causes, and injuries that are more specific for intimate partner violence include zygomatic complex fractures, orbital blow-out fractures, and perforated tympanic membrane. Although facial injuries are the most common injuries associated with intimate partner violence, they have low specificity. Musculoskeletal injuries, which are the second most common type of injuries, include sprains, fractures, and dislocations. Blunt force trauma to the forearms should raise suspicion of intimate partner violence because it can occur when trying to block being struck.

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ABSTRACT

Intimate partner violence, which is a violation of human rights, is defined as any behavior within an intimate relationship or ex-relationship that causes physical, psychological, or sexual harm, including physical aggression, psychological violence (such as intimidation, constant humiliation), controlling behaviors (such as restricting access to services), and sexual violence. Intimate partner violence is present in all societies, with over a 25% global lifetime prevalence in women. Although intimate partner violence can occur in any intimate relationship, it is a gendered problem that disproportionately affects women and gender and sexual minorities. Although usually less severe than in women, intimate partner violence experienced by men also increases the risk of health problems and injuries. Although injury is the most obvious clinical manifestation of intimate partner violence, most people who experience intimate partner violence do not present to health care providers with signs of obvious trauma but rather with a constellation of overlapping physical and mental health problems. These conditions may persist even when the abuse ends—particularly chronic pain, gynecologic problems, anxiety, depression, and post-traumatic stress disorder. Universal screening for intimate partner violence is not recommended in health care settings, but clinicians should have a low threshold for asking about abuse and should know how to respond appropriately and safely, including how to facilitate referral to a specialist resource that can offer advocacy and further support. Women survivors of intimate partner violence benefit from advocacy and from trauma-informed psychological treatment.

KEYWORDS

intimate partner violence
controlling behavior
psychological violence
sexual violence
injuries
safety
advocacy

TABLE 223-1 RISK FACTORS ASSOCIATED WITH EXPERIENCING INTIMATE PARTNER VIOLENCE

INDIVIDUAL	RELATIONSHIP	COMMUNITY	SOCIETAL
Experiencing child maltreatment	Poor family functioning	Weak community sanctions against intimate partner violence	Gender-inequitable social norms
Less than high school education among parents	Relationship instability	Poverty	Lack of women's civil rights, including restrictive or inequitable divorce and marriage laws
Young age	Relationship conflict	Economic inequality	Broad social acceptance of violence as a way to resolve conflict
Unplanned pregnancy	Male dominance	Low social capital	High levels of general violence in society, including armed conflict
Harmful use of drugs and alcohol	Educational disparity where a woman has a higher level than her male partner		
Past history of abusive partners	Economic stress		
Low socioeconomic status			

Victims of intimate partner violence often experience multiple mechanisms of injury; being struck by a hand is the most common, followed by use of a household object. Injuries from weapons such as knives and guns are far less common (<1%) but are associated with higher risk of mortality. Attempted strangulation occurs frequently. Other injuries that raise suspicion of intimate partner violence include fractures of the spine or trunk, bites, hair pulling, and open wounds. Patients who are exposed to sexual abuse may show signs of trauma to the genital area, but sexual assault is associated with signs of injury in less than one third of cases.

Most victims of intimate partner violence present to health care settings with overlapping physical and mental health problems rather than signs of obvious trauma. A patient who presents with vague signs and symptoms or chronic somatic complaints, including pain, suggests the possibility of intimate partner violence. Other behaviors that suggest intimate partner violence include delay in seeking medical care, multiple cancellations of medical appointments, or a partner insisting on being present throughout the consultation.

Other physical conditions that should raise suspicion of intimate partner violence include chronic gynecologic or gastrointestinal symptoms, such as chronic pelvic pain or irritable bowel syndrome. Intimate partner violence is associated with an increased risk for sexually transmitted infections, including HIV/AIDS, as well as sexual reproductive dysfunction.

Regardless of sex or gender, victims of intimate partner violence experience an increased risk of poor health as well as chronic physical and emotional health problems and injuries. Exposure to any type of intimate partner violence, whether physical or psychological, can be associated with a wide range of emotional and behavioral symptoms; depression and post-traumatic stress disorder (PTSD) are the two most commonly associated emotional conditions, but anxiety disorders and substance use disorders are also associated with intimate partner violence (Chapter 362). Women who reported intimate partner violence at least once in their lives also reported three to four times more emotional distress, suicidal thoughts, and suicide attempts than nonabused women. The relationships appear to be bidirectional, with depressive symptoms, substance use, and depression as both risk factors and outcomes of intimate partner violence.[11,12] Women who have experienced intimate partner violence have increased rates of chronic physical conditions, particularly gynecologic, gastrointestinal, and nervous system disorders; cancer; cardiovascular disease; type 2 diabetes; and all-cause mortality,[13] but a cause-and-effect relationship between intimate partner violence and these medical conditions is not established.

Intimate partner violence may begin, increase, or decrease during pregnancy, and it is more likely if the pregnancy was unplanned or unwanted. Abuse directed to the abdomen may lead to poor pregnancy outcomes and perinatal death. Intimate partner violence is associated with negative effects on parenting, including lack of effective parenting skills, increased aggression, and diminished communication.[14] Additionally, a child's exposure to intimate partner violence is significantly associated with the child's internalizing and externalizing problems, including trauma symptoms, developmental delay, educational problems, and long-term mental health conditions. These sequelae are consistent with a cycle of abuse, with child abuse leading to increased violence against women and additional child maltreatment, which in turn increases the risk of adult violence.

DIAGNOSIS

Universal screening for intimate partner violence increases the identification of affected women[A1] but has not been shown to improve women's health outcomes or reduce the occurrence of intimate partner violence.[15] However, clinicians must be alert to the signs and symptoms associated with intimate partner violence, including the broad range of physical and mental health conditions, and have a low threshold for asking about abuse. When possible indicators are present, the clinician should begin with the presenting concern, followed by general questions about the patient's well-being, before asking about safety in the home. When asking about exposure to intimate partner violence, it is important to do so privately, with no one else present, including a child (beyond infancy) or partner. If the inquiry or response is overheard, it could put the patient at risk for further intimate partner violence.

Learning modules[16] that include scripts, "how-to videos," and interactive scenarios about how clinicians can recognize and respond safely to intimate partner violence can help guide the evaluation. Before asking specific questions, the patient should be advised about any limits of confidentiality, including the requirement for mandatory reporting in some jurisdictions, when a patient has children in the home. When the topic of intimate partner violence is raised, patients want questioning that is nonjudgmental, compassionate, and caring. Women want to be asked about intimate partner violence, but they do not want to be pressured to disclose.

Possible questions to ask if intimate partner violence is suspected include: (1) Sometimes partners or ex-partners use physical force. Has this ever happened to you? (2) Have you felt humiliated or emotionally harmed by your partner or ex-partner? (3) Are you now or have you ever been afraid of your partner or ex-partner? (4) Have you ever been physically threatened or hurt by your partner or ex-partner? (5) Have you been forced to have any kind of sexual activity by your partner or ex-partner? (6) Has your partner or ex-partner ever tried to control your behavior; for example, control where you go or whom you see?

The clinician should acknowledge the complexity of intimate partner violence and respect the patient's individual concerns and decisions. The assessment should include an evaluation of safety; the patient should be asked if it is safe for her (or him or any children) to return home. The following are examples of safety considerations: (1) Has the frequency or severity of the violence increased? (2) Is the partner or ex-partner obsessed with the patient? (3) How safe does she (he) feel? (4) Does the partner or ex-partner have a weapon or access to one? (5) Has she (he) been threatened with a weapon? Risk factors for domestic homicide include threats of deadly violence and the presence of a firearm in the home.

TREATMENT

Management of the Abused Patient

The care of patients who have suffered intimate partner violence requires compassion, understanding, and expertise[17] (Table 223-2). The initial response of clinicians to the disclosure of intimate partner violence by patients is crucial in gaining trust and is the basis of further management. Intimate partner violence is a highly stigmatized condition, with the added dimension of risk for further harm from breach of confidentiality.

Before questioning, clinicians should understand the problem, including knowing about the available community services and appropriate referral systems; ensure that the clinical environment is supportive, welcoming, and nonthreatening; place brochures and posters in the clinical setting; try to ensure continuity of care; inform abused women about matters of privacy, safety, and confidentiality; be alert to the signs of abuse and raise the matter when indicated; use verbal and nonverbal communication skills to develop trust; and be compassionate, supportive, and respectful toward abused women. When the topic of intimate partner violence is raised, they should be nonjudgmental, compassionate, and caring when questioning about abuse; be confident and comfortable asking about intimate partner violence; not pressure women to disclose abuse because simply raising the topic may be helpful to women; ask about abuse over the course of several interviews because a woman may disclose abuse at a later date; ensure that the environment is private and confidential; and provide time.

TABLE 223-2 SUMMARY OF SELECTED INTIMATE PARTNER VIOLENCE RECOMMENDATIONS FROM THE WORLD HEALTH ORGANIZATION

CATEGORY	RECOMMENDATION	QUALITY OF EVIDENCE	STRENGTH OF RECOMMENDATION
Woman-centered care	Women who disclose any form of violence by an intimate partner (or other family member) should be offered immediate support by clinicians, at a minimum. If clinicians are unable to provide this first-line support, they should ensure that someone else (within their health care setting or another that is easily accessible) is immediately available to do so.	Indirect	Strong
Identification of survivors	Universal screening is not recommended. Ask about exposure to IPV when assessing conditions that may be caused or complicated by abuse. Written information about IPV should be available in all health care settings.	Low-moderate Indirect No relevant evidence	Conditional Strong Conditional
Care for survivors	Women with preexisting diagnosed or IPV-related mental disorders should receive mental health care delivered by health care professionals with a good understanding of violence against women.	Indirect	Strong
	Cognitive-behavioral therapy or eye movement desensitization and reprocessing interventions, delivered by health care professionals with a good understanding of violence against women, should be offered to women with post-traumatic stress disorder who are no longer experiencing violence.	Low-moderate	Strong
	Women who have spent at least 1 night in a shelter, refuge, or safe house should be offered a structured program of advocacy, support, and/or empowerment.	Low	Conditional
	Pregnant women should be offered brief- to medium-duration empowerment counseling (by counselors with specific training about IPV) and IPV advocacy/support, including a safety component.	Low	Conditional
	For children exposed to IPV at home, a psychotherapeutic intervention should be offered.	Moderate	Conditional
Training of clinicians	Training at a prequalification level in first-line support for women who have experienced IPV should be given to clinicians (in particular, physicians, nurses, and midwives).	Very low	Strong
	Clinicians offering care to women should receive in-service training integrated with training on managing sexual assault.	Low-moderate	Strong
Health care policy	Care for women experiencing IPV should be integrated into existing health services rather than as a stand-alone service.	Very low	Strong
Mandatory reporting	Mandatory reporting to the police by clinicians is not recommended; clinicians should offer to report the incident to the appropriate authorities (including the police) if the woman wants this and is aware of her rights.	Very low	Strong

IPV = intimate partner violence.

Reproduced from Feder G, Wathen CN, MacMillan HL. An evidence-based response to intimate partner violence: WHO guidelines. *JAMA*. 2013;310:479-480.

The immediate response to disclosure should be nonjudgmental, with compassion, support, and conveying belief of experiences. The clinician should acknowledge the complexity of the problem and respect the woman's unique concerns and decisions, prioritize the needs identified by the woman, help ensure that social and psychological needs are met, take time to listen, validate her experiences, provide information and encouragement, respond to any concerns about safety, and offer referrals to specialist help. The response in later interactions should be patient and supportive, with emotional connection through kindness, care, recognition, understanding, and advocacy. The clinician should allow the victim to progress at her own therapeutic pace; understand the chronicity of the problem and provide follow-up and continued support; respect the woman's wishes and not pressure her into making any decisions; be nonjudgmental if a woman does not follow up with referrals immediately; and give abused women an opportunity to disclose abuse at a later date.

Beyond their initial response and managing the acute physical and mental health sequelae of abuse, most generalists have neither the expertise nor the capacity to meet the specific legal, financial, housing, and safety needs of women who experience intimate partner violence. A key step, particularly in the context of current or recent violence, is to offer referral to an advocacy program and to psychological interventions (individual or group-based). Advocacy programs, which can provide physical and psychosocial benefits,[A2] engage with individual clients who are being abused, aiming to empower them and linking them to community services. Core activities of advocacy include provision of legal, housing, and financial advice; facilitating access to and use of community resources, such as refuges (shelters, safe houses) and emergency housing; and provision of safety planning advice. Advocates can also provide ongoing support and informal counseling.[A2] If such services are not immediately available, shelters and refuges often provide these kinds of services for women both in residences and on an outreach basis. The provision of such advocacy can enable rehousing opportunities that improve mental health and safety.[18]

For women who experience intimate partner violence, psychological therapies probably reduce depression and may reduce anxiety, but they have less certain impacts on post-traumatic stress disorder, re-exposure to intimate partner violence, and safety planning; explicit trauma-informed psychological interventions may be more beneficial.[A3] If women are still in an abusive relationship, psychological therapy must be accompanied by advocacy that prioritizes the safety of the survivor.

Management of the Abusive Patient

Physicians often also interact with male patients who perpetrate intimate partner violence, thereby providing a potential to intervene.[19] If a patient discloses perpetration of intimate partner violence, physicians should assess for lethality, readiness to change, and comorbid medical conditions that could affect treatment, such as substance use disorders and mental illness. Referrals to a qualified therapist or batterer intervention program should be offered, but requirement to disclose intimate partner violence is dependent on local jurisdictions.

The detailed assessment and treatment of the abuser should be conducted by expert professionals. To date there is insufficient evidence to recommend specific treatment for those committing intimate partner violence. Behavioral interventions have been disappointing, with generally little or no benefit or potential harm (i.e., increased recidivism), but cognitive-behavioral interventions with an emphasis on gender relations may be effective in reducing violence.[A4] For perpetrators who have alcohol or substance misuse, interventions specifically for misuse are of uncertain benefit.[A5,A6]

Couples Therapy

Couples therapy is probably not appropriate or safe when intimate partner violence is present in a relationship, but it can reduce further violence in couples in which the man had not been violent in the past 6 months.[A7] If abusers are enrolled in treatment programs, women must be provided with concurrent advocacy and support.

Health Care Providers

With intimate partner violence now clearly identified as a health problem, all providers who encounter patients who may be exposed to intimate partner violence should be able to recognize the problem and initiate intervention. Training can improve knowledge and attitudes vis-à-vis intimate partner violence, as well as identification and referral rates[20] but without evidence for a sustained effect or improved patient outcomes.[A8]

PREVENTION

From a public health perspective, primary prevention of intimate partner violence is a priority. However most of the available research from economically developed countries focuses on the health care response to the survivors of intimate partner violence, both while a woman is still exposed to abuse (secondary prevention) and when she is experiencing the long-term health problems associated with intimate partner violence (tertiary prevention).

Efforts aimed at primary prevention of intimate partner violence through educational programs have generally focused on changes in attitude, knowledge, skills, or self-reports of dating (relationship) violence. Although data are limited for physical or emotional health outcomes, programs to prevent adolescent dating violence appear to have at least short-term benefits.[A9]

There is no clinical trial evidence for the effectiveness of interventions in general medical settings to prevent intimate partner violence against pregnant women. For secondary prevention, effective advocacy should include education and information on abuse, rights and resources, active referral and liaising with other services, and risk assessment and safety planning.[A10] Access to social support through the use of advocates with strong linkages with community-based structures and networks can improve mental health outcomes for survivors of intimate partner violence.[A11]

PROGNOSIS

The prognosis of intimate partner violence with and without intervention is uncertain. In a U.S. cohort study, 37% of participants were still being abused after 3.5 years. In one 3-year follow-up of participants who received an advocacy intervention after leaving a shelter, 36% had been assaulted by their original partner or a new partner in the 6 months before the interview. The difference in re-victimization at 2 years between intervention and control arms did not persist, but there was still a significant difference in quality of life and social support among women receiving advocacy.

In general, women who seek help when they have recently left or are considering leaving an abusive relationship usually have improved quality of life with less depression, post-traumatic stress, and physical symptoms, although improvement tends to plateau within 9 months.[21] The main predictor of improvement in symptoms is social support, whereas the main predictor of no improvement is continued exposure to intimate partner violence.

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224 APPROACH TO THE PATIENT WITH METABOLIC BONE DISEASE

THOMAS J. WEBER

DIAGNOSIS

History

Patients with metabolic bone disease may present to the clinician in a number of ways, ranging from no symptoms to disabling musculoskeletal pain, depending on the nature of the underlying disorder. The most common conditions, osteoporosis (Chapter 225) and primary hyperparathyroidism (Chapter 227), encompass a clinical spectrum that ranges from asymptomatic (diagnosed by low bone density and an elevated serum calcium, respectively) to severe disease (fractures and bone pain).[1,2] Less common conditions, such as osteomalacia (Chapter 226), have more predictable presentations. In osteoporosis (Chapter 225), fractures of the long bones (humerus, distal forearm, femur, and tibia) are clearly evident, whereas fractures at other sites (vertebrae, ribs, pelvis) may not be clinically apparent (see later and Chapter 225). Patients with osteomalacia may complain of deep bone pain or aches, although often it is difficult for them to distinguish such pain from muscular pain. They may also report proximal muscle weakness that impairs their ability to ascend stairs. Vitamin D deficiency (Chapter 199), the most common cause of osteomalacia, may confer similar bone and muscle complaints as well. Tumor-induced osteomalacia is a paraneoplastic disorder caused by ectopic secretion of fibroblast growth factor 23 (Chapter 226).[3] In hyperparathyroidism (Chapter 227), either self-reported or elicited fatigue may be a common complaint, along with mildly impaired cognition and memory. A history of recurrent nephrolithiasis is a hallmark of symptomatic primary hyperparathyroidism. Patients with hypophosphatasia typically present with musculoskeletal pain and history of fractures. Finally, it is important to understand many inherited metabolic bone disorders have associated dental-oral-craniofacial manifestations that help distinguish the underlying disorder.

Physical Examination

Patients may exhibit physical clues to their skeletal condition. Height loss of more than 2 inches from a self-reported maximum, measured accurately with a calibrated stadiometer, may suggest the presence of vertebral compression fractures, which are clinically silent in up to three fourths of patients. Corresponding thoracic kyphosis may be present, and tenderness to palpation or percussion over the spinous process may suggest a recent vertebral fracture. Thoracic kyphosis will also impart quantifiable physical characteristics, including decreased rib-to-pelvis (Fig. 224-1) and increased wall-to-occiput distances. The wall-to-occiput distance, which reflects the degree of kyphosis, is the space between the wall and the occiput of the head when a patient stands straight with the heel, buttocks, and back against the wall and with the epicanthal folds and superior margin of the outer ear parallel with the ground. These measurements, which may be followed clinically, predict vertebral fractures. Patients may also exhibit signs of secondary causes of osteoporosis (e.g., blue sclerae with osteogenesis imperfecta [Chapter 239], goiter and proptosis with hyperthyroidism [Chapter 207], facial plethora and purple striae with Cushing syndrome [Chapter 208]). Patients with Paget disease of bone (which is characterized by an increase in bone resorption by abnormal osteoclasts, followed by rapid formation of poorly organized, structurally weak bone; Chapter 228) may have a skeletal deformity and warmth over the affected sites.

Patients with osteomalacia often have tenderness to palpation over the tibia or other long bones owing to expansion of the subperiosteal space by undermineralized osteoid with resultant periosteal nerve irritation. These patients may also have a wide-based, "waddling" gait due to pain.

Hyperparathyroid patients may have flank tenderness if active nephrolithiasis (Chapter 111) is present and can rarely have corneal calcification if hypercalcemia is severe and long-standing. Such patients rarely have a palpable parathyroid adenoma. If present, however, a diagnosis of parathyroid carcinoma should be entertained.

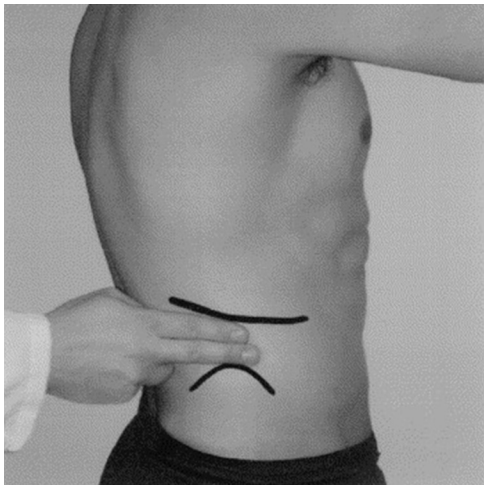

FIGURE 224-1. Method of assessing rib-pelvis distance. While standing behind the subject, the examiner holds his or her hands vertically and places them into the space between the inferior margin of the ribs and the superior surface of the pelvis in the mid-axillary line. The vertical distance is then measured in fingerbreadths.

Laboratory and Radiologic Investigations

Laboratory studies (Table 224-1) are a useful adjunct in the evaluation of metabolic bone disease, although their specificity depends on the disease in question. In some conditions, the diagnosis is reasonably more securely based on abnormal biochemical studies, such as alkaline phosphatase (elevated in Paget disease [Chapter 228] and depressed in hypophosphatasia [Chapter 226]), serum phosphorus (abnormal in disorders of fibroblast growth factor 23 metabolism), and parathyroid hormone (elevated in hyperparathyroidism). In other situations, studies for the evaluation of osteoporosis are generally not specifically diagnostic, but rather are supportive of secondary causes that may contribute to bone loss; examples include levels of thyroid-stimulating hormone, 25(OH)D, and testosterone. Additional investigations may also be required as clinically indicated, especially in individuals who have a markedly lower bone density than expected for age (see later and Chapter 225).[4] More sophisticated studies that target a specific diagnosis should be based on the history and examination (e.g., genetic testing for hypophosphatasia or osteogenesis imperfecta). Bone turnover markers, which are cellular products of bone formation and resorption that can be measured in the blood and urine of patients, may provide noninvasive information on skeletal turnover (i.e., high or low) but cannot be used for diagnosis and have not been proven to be useful for monitoring patients with metabolic bone disease.

Radiologic studies are critical to the diagnosis and management of metabolic bone disease. Most widely used and critical to management of osteoporosis is bone mineral density (BMD) testing, generally by dual energy x-ray absorptiometry (DXA; see Chapter 225). DXA, which is a low-radiation, noninvasive examination of the spine, proximal femur, and distal forearm, may be used to make serial assessments of the likelihood of future fracture and to identify and subsequently follow the treatment response to pharmacologic or conservative therapies.

Because the most common clinical event is fracture, plain radiographs of the involved skeletal sites are often indicated. However, plain radiographs are relatively insensitive in identifying stress fractures and may also lag behind a frank fracture by hours or days. As a result, additional, more sensitive modalities, including computed tomography (CT) and magnetic resonance imaging (MRI), may be preferred in these circumstances to confirm a fracture. CT and MRI can reveal characteristic patterns of skeletal involvement in certain conditions (e.g., Paget disease often involves the skull, pelvis, proximal femur, or

TABLE 224-1 LABORATORY WORKUP OF OSTEOPOROSIS

ALL OSTEOPOROTIC/OSTEOPENIC PATIENTS	AS CLINICALLY INDICATED
Serum creatinine, calcium, total protein, albumin, phosphorus, alkaline phosphatase, liver function tests	Serum and urine protein electrophoresis (SPEP and UPEP) (if total protein-to-albumin ratio is >2.0)
Complete blood count	Intact parathyroid hormone
Thyroid-stimulating hormone	24-Hour urine cortisol
24-Hour urine calcium and creatinine	Celiac panel (antigliadin/anti-endomysial antibodies)
Serum 25(OH)D	Fasting morning testosterone (men)

SPEP = serum protein electrophoresis; UPEP = urine protein electrophoresis.

ABSTRACT

Metabolic bone disease encompasses both common (e.g., osteoporosis) and more rare (e.g., X-linked hypophosphatemic rickets) conditions that may be clinically silent or present with fractures and bone pain. Diagnostic assessment of metabolic bone disease includes laboratory and radiographic studies that, although not absolutely specific, help guide evaluation and management of bone disorders. Treatments of metabolic bone disease often have common components (e.g., calcium, vitamin D, bisphosphonates) but may also include disease-specific therapy (e.g., enzyme replacement for hypophosphatasia).

KEYWORDS

metabolic bone disease
kyphosis
calcium
phosphorus
vitamin D
fractures
osteomalacia

tibia). Whole body bone scintigraphy with the radioisotope techneticum-99m is the most sensitive tool to identify an active skeletal process but is nonspecific as to the nature of the underlying process (e.g., fracture, infection, malignancy).

Finally, although rarely needed, tetracycline-labeled, transcortical bone biopsy of the iliac crest, with subsequent histomorphometric analysis, may be useful in the management of patients. Bone biopsy, which is generally performed by an orthopedic surgeon under conscious sedation, may be indicated to guide management in patients with excessive bone fragility that cannot be adequately characterized by noninvasive means (e.g., patients who have renal osteodystrophy [Chapter 116], suspected osteomalacia, or fractures with normal bone mineral density by DXA).

TREATMENT

Management of patients with metabolic bone disease is generally directed by the disease process, although there are some unifying aspects of treatment. Adequate intake of calcium and vitamin D, usually through a combination of diet and supplements, is recommended for patients with osteoporosis (Chapter 225). High-dose vitamin D is indicated for low-vitamin D–related osteomalacia (Chapter 226). Phosphorus in combination with vitamin D analogues (i.e., calcitriol) has been used traditionally to heal osteomalacia and facilitate normal longitudinal growth in children and adolescents and to promote mineralization and heal stress fractures in adults with certain osteomalacic conditions (e.g., X-linked hypophosphatemic rickets and tumor-induced osteomalacia). Weight bearing and resistive exercise are also advisable for osteoporotic patients,[5] although physical therapy consultation may be indicated in patients at high risk for fracture (previous fractures, frequent falls).

Pharmacotherapy with oral and parenteral bisphosphonates is frontline therapy for patients with both osteoporosis (Chapter 225) and Paget disease (Chapter 228)[6] because of the anticatabolic effect on excessive osteoclastic bone resorption that underlies these diseases. In addition, other antiresorptive drugs, such as raloxifene and denosumab, are approved for the treatment of osteoporosis.[7] Parenteral bisphosphonates and denosumab also are effective in combating malignancy-related bone disease (e.g., metastatic breast cancer, multiple myeloma). Finally, the anabolic bone agents teriparatide and abaloparatide, which are recombinant parathyroid hormone and parathyroid hormone–related peptide analogues, respectively, are useful in "building" bone density and reducing the risk of fracture in patients who have severe osteoporosis, defined as very low bone mineral density, high fracture risk, and/or history of multiple fractures. Medications such as the monoclonal anti-sclerostin antibody romosozumab also can target the Wnt pathway, which is critical for bone formation.[8] Burosumab, which is a skeletal-specific monoclonal antibody against the hypophosphatemia-inducing factor fibroblast growth factor 23 (FGF-23), can be useful for the treatment of X-linked hypophosphatemia (Chapter 226).

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225 OSTEOPOROSIS

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DEFINITION

Osteoporosis is defined as a skeletal disorder that is characterized by compromised bone strength and that predisposes to an increased risk for fracture. The pertinent clinical outcomes of this disease include fractures, bone pain, loss of height, and physical deformity. The concept of bone strength is central to understanding the disorder because patients who suffer an osteoporotic or fragility fracture may or may not have osteoporosis by bone mineral density criteria. The World Health Organization defines *osteoporosis* as a bone mineral density that is equal to or greater than 2.5 standard deviations below that of an average individual at peak bone mass (generally ages 20 to 30 years, depending on the measured skeletal site). Osteopenia, or low bone density, is defined as a bone mineral density between −1.1 and −2.4 standard deviations, inclusive, below young average normal.

EPIDEMIOLOGY

Approximately half of White women will develop an osteoporosis-related fracture in their lifetime, which is greater than their risk for breast cancer, heart attack, and stroke combined. In addition, one in five men will also have an osteoporosis-related fracture. Nearly three fourths of these fractures occur in women, with most occurring in White women.

The rate of osteoporotic fractures varies significantly across ethnicities and geography. Blacks have a lower lifetime risk for osteoporotic fracture, approximately half that of Whites. Differences in bone size, bone microarchitecture (thicker trabeculae in Blacks), body composition, calcium absorption in youth, and life expectancy are potential reasons for this phenomenon. Asian Americans and Hispanics have risks of fracture that are intermediate between that of Whites and Blacks, even though Asian Americans have bone mineral densities that generally approximates that of Whites. Indeed, the risk for hip fracture in U.S. Asian men and women is actually equal to or lower than that of U.S. Blacks. These U.S. data are consistent with the global experience as well, because rates of hip fracture in China are lower than those observed in the United States, despite similar bone density at the hip. Differences in hip geometry, physical activity, and diet have been proposed as possible explanations. For unknown reasons, however, rates of hip fracture have actually been increasing in the Far East, whereas they have declined somewhat in the United States. Changing patterns of nutrition and physical activity could be responsible for the former, although the latter observation remains heretofore unexplained.

The most common site of osteoporotic fracture is the spine, which accounts for more than 750,000 fractures annually. Fractures of the proximal femur, which disproportionately confer a greater cost than other osteoporotic fractures, account for approximately 300,000 fractures annually in the United States and nearly 75% of the costs. Additional sites of fracture include the distal forearm, proximal humerus, and pelvis, with the latter two more commonly occurring in elderly people.

The risk for fracture increases markedly with age,[1] although the pattern of fracture risk differs by skeletal site. The risk for Colles fractures increases until the mid-60s and then plateaus, whereas the risk for hip fractures increases exponentially in woman after the age of 65 years. The risk of vertebral fracture rises earlier than that of hip, but many spine fractures are not clinically apparent and are identified only by radiographic assessment. Although clinically silent, such fractures confer a significant independent risk for future fractures, particularly if they are recent.

Men also have an age-independent increase in the risk of fracture, although the increase in incidence generally lags at least 5 to 10 years behind that of women (Fig 225-1). This sex-based difference in the incidence of fracture is likely related to anatomic differences. Specifically, although men and woman have similar volumetric bone density at a given skeletal site, men's larger bone size confers an independent mechanical protection against fracture.

The aging of the U.S. population and the independent contribution of age to the risk of fracture predict that the morbidity and cost related to osteoporosis will increase in the United States alone to greater than 3.2 million fractures, with an associated annual cost of $95 billion by the year 2040. Despite these ominous predictions, less than one third of women who incur a low-trauma hip fracture typically undergo bone density measurement or initiate pharmacologic antifracture therapy, thereby underscoring the need for significant improvement in the delivery of osteoporosis care.

PATHOBIOLOGY

Normal Bone Biology

Bone mineral density in adults is determined by the magnitude of bone acquisition during adolescence and young adulthood compared with the rate of bone loss that ensues thereafter. These processes are generally referred to as bone modeling and remodeling, respectively. Heritable factors, including sex and ethnicity, account for 60 to 80% of the variability in skeletal development, including peak bone mass, bone size, and bone geometry, although nutrition, lifestyle, and other factors also have a significant impact. Peak bone mass is achieved in most individuals by the early to late 20s and differs in timing by skeletal site (ages 18 to 20 years for proximal femur, 25 to 30 years for spine). Modeling of the skeleton during this time represents a true increase in bone mass and bone size through endochondral ossification of the axial skeleton and periosteal apposition of the appendicular skeleton.

Skeletal remodeling is a finely orchestrated process of bone resorption and subsequent formation. It is a necessary physiologic function that results in repair of damaged bone and redistribution of the skeleton to adapt to changes in mechanical stress and to provide calcium to the systemic circulation for critical

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tibia). Whole body bone scintigraphy with the radioisotope techneticum-99m is the most sensitive tool to identify an active skeletal process but is nonspecific as to the nature of the underlying process (e.g., fracture, infection, malignancy).

Finally, although rarely needed, tetracycline-labeled, transcortical bone biopsy of the iliac crest, with subsequent histomorphometric analysis, may be useful in the management of patients. Bone biopsy, which is generally performed by an orthopedic surgeon under conscious sedation, may be indicated to guide management in patients with excessive bone fragility that cannot be adequately characterized by noninvasive means (e.g., patients who have renal osteodystrophy [Chapter 116], suspected osteomalacia, or fractures with normal bone mineral density by DXA).

TREATMENT

Management of patients with metabolic bone disease is generally directed by the disease process, although there are some unifying aspects of treatment. Adequate intake of calcium and vitamin D, usually through a combination of diet and supplements, is recommended for patients with osteoporosis (Chapter 225). High-dose vitamin D is indicated for low-vitamin D–related osteomalacia (Chapter 226). Phosphorus in combination with vitamin D analogues (i.e., calcitriol) has been used traditionally to heal osteomalacia and facilitate normal longitudinal growth in children and adolescents and to promote mineralization and heal stress fractures in adults with certain osteomalacic conditions (e.g., X-linked hypophosphatemic rickets and tumor-induced osteomalacia). Weight bearing and resistive exercise are also advisable for osteoporotic patients,[5] although physical therapy consultation may be indicated in patients at high risk for fracture (previous fractures, frequent falls).

Pharmacotherapy with oral and parenteral bisphosphonates is frontline therapy for patients with both osteoporosis (Chapter 225) and Paget disease (Chapter 228)[6] because of the anticatabolic effect on excessive osteoclastic bone resorption that underlies these diseases. In addition, other antiresorptive drugs, such as raloxifene and denosumab, are approved for the treatment of osteoporosis.[7] Parenteral bisphosphonates and denosumab also are effective in combating malignancy-related bone disease (e.g., metastatic breast cancer, multiple myeloma). Finally, the anabolic bone agents teriparatide and abaloparatide, which are recombinant parathyroid hormone and parathyroid hormone–related peptide analogues, respectively, are useful in "building" bone density and reducing the risk of fracture in patients who have severe osteoporosis, defined as very low bone mineral density, high fracture risk, and/or history of multiple fractures. Medications such as the monoclonal anti-sclerostin antibody romosozumab also can target the Wnt pathway, which is critical for bone formation.[8] Burosumab, which is a skeletal-specific monoclonal antibody against the hypophosphatemia-inducing factor fibroblast growth factor 23 (FGF-23), can be useful for the treatment of X-linked hypophosphatemia (Chapter 226).

GENERAL REFERENCES

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225 OSTEOPOROSIS

THOMAS J. WEBER

DEFINITION

Osteoporosis is defined as a skeletal disorder that is characterized by compromised bone strength and that predisposes to an increased risk for fracture. The pertinent clinical outcomes of this disease include fractures, bone pain, loss of height, and physical deformity. The concept of bone strength is central to understanding the disorder because patients who suffer an osteoporotic or fragility fracture may or may not have osteoporosis by bone mineral density criteria. The World Health Organization defines *osteoporosis* as a bone mineral density that is equal to or greater than 2.5 standard deviations below that of an average individual at peak bone mass (generally ages 20 to 30 years, depending on the measured skeletal site). Osteopenia, or low bone density, is defined as a bone mineral density between −1.1 and −2.4 standard deviations, inclusive, below young average normal.

EPIDEMIOLOGY

Approximately half of White women will develop an osteoporosis-related fracture in their lifetime, which is greater than their risk for breast cancer, heart attack, and stroke combined. In addition, one in five men will also have an osteoporosis-related fracture. Nearly three fourths of these fractures occur in women, with most occurring in White women.

The rate of osteoporotic fractures varies significantly across ethnicities and geography. Blacks have a lower lifetime risk for osteoporotic fracture, approximately half that of Whites. Differences in bone size, bone microarchitecture (thicker trabeculae in Blacks), body composition, calcium absorption in youth, and life expectancy are potential reasons for this phenomenon. Asian Americans and Hispanics have risks of fracture that are intermediate between that of Whites and Blacks, even though Asian Americans have bone mineral densities that generally approximates that of Whites. Indeed, the risk for hip fracture in U.S. Asian men and women is actually equal to or lower than that of U.S. Blacks. These U.S. data are consistent with the global experience as well, because rates of hip fracture in China are lower than those observed in the United States, despite similar bone density at the hip. Differences in hip geometry, physical activity, and diet have been proposed as possible explanations. For unknown reasons, however, rates of hip fracture have actually been increasing in the Far East, whereas they have declined somewhat in the United States. Changing patterns of nutrition and physical activity could be responsible for the former, although the latter observation remains heretofore unexplained.

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The risk for fracture increases markedly with age,[1] although the pattern of fracture risk differs by skeletal site. The risk for Colles fractures increases until the mid-60s and then plateaus, whereas the risk for hip fractures increases exponentially in woman after the age of 65 years. The risk of vertebral fracture rises earlier than that of hip, but many spine fractures are not clinically apparent and are identified only by radiographic assessment. Although clinically silent, such fractures confer a significant independent risk for future fractures, particularly if they are recent.

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The aging of the U.S. population and the independent contribution of age to the risk of fracture predict that the morbidity and cost related to osteoporosis will increase in the United States alone to greater than 3.2 million fractures, with an associated annual cost of $95 billion by the year 2040. Despite these ominous predictions, less than one third of women who incur a low-trauma hip fracture typically undergo bone density measurement or initiate pharmacologic antifracture therapy, thereby underscoring the need for significant improvement in the delivery of osteoporosis care.

PATHOBIOLOGY

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Skeletal remodeling is a finely orchestrated process of bone resorption and subsequent formation. It is a necessary physiologic function that results in repair of damaged bone and redistribution of the skeleton to adapt to changes in mechanical stress and to provide calcium to the systemic circulation for critical

ABSTRACT

Osteoporosis, which is a skeletal disorder characterized by compromised bone strength, predisposes an individual to an increased risk for fracture and accounts for almost 2 million fractures occurring annually in the United States at an estimated cost of $57 billion. Osteoporosis is most prevalent in older postmenopausal women, but it also affects men and individuals with risk factors for bone loss. It is identifiable clinically (low trauma fractures) and by testing (dual energy x-ray absorptiometry). Treatment with a number of medications approved by the U.S. Food and Drug Administration can significantly reduce the risk for low-trauma fractures.

KEYWORDS

fractures
bone mineral density
dual energy x-ray absorptiometry
calcium
vitamin D
bisphosphonates
anabolic therapy

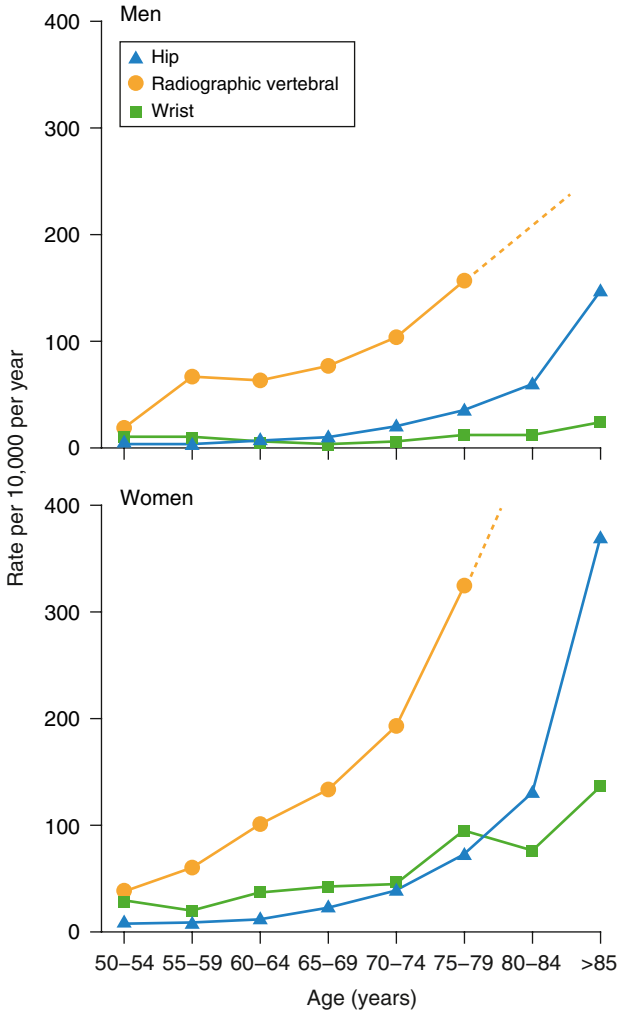

FIGURE 225-1. Age-specific and sex-specific incidence of radiographic vertebral, hip, and distal forearm fractures. (Data derived from European Prospective Osteoporosis Study and General Practice Research Database; from Sambrook P, Cooper C. Osteoporosis. *Lancet*. 2006;367:2010-2018.)

cellular processes. The osteocyte, which accounts for 90 to 95% of all bone cells, is the critical cell that regulates both resorption and formation. Osteocytes are derived from osteoblasts that are embedded within the bone matrix. During this maturation phase, this "osteoid-osteocyte" cell actively secretes and calcifies bone matrix material. In addition, mature osteocytes within bone contain dendritic processes that may directly regulate the recruitment of osteoblasts and formation of the bone. The protein sclerostin, which directly downregulates bone formation through the Wnt pathway, is an important part of this process. Mature osteocytes also may form new bone within their lacunae. In addition, osteocytes produce proteins that regulate mineralization, including positive (PHEX, DMP-1) and negative (FGF-23) factors.

Osteocytes also regulate bone resorption, both directly through apoptosis proximate to skeletal microcracks or fatigue damage in need of repair as well as indirectly through enhancement of pre-osteoblast or mesenchymal stromal cell development. These events result in the production, expression, and release of cytokines that are critical to the recruitment and development of osteoclasts, including interleukin-1 (IL-1), IL-6, osteoprotegerin (OPG), and receptor activator of nuclear factor-κB ligand (RANKL). The cognate receptor for RANKL, RANK, is expressed on the surface of the developing and mature osteoclast, which itself is a derivative of cells of the monocyte-macrophage lineage. RANKL is a critical determinant of osteoclast recruitment, development, and survival, such that disruption of RANKL signaling results in high bone density fragility disorders (e.g., osteopetrosis). OPG, which is also produced by pre-osteoblasts, is a decoy receptor for RANK and binds to RANKL, thereby preventing RANKL binding to RANK serving as an endogenous suppressor of osteoclast function. In essence, RANKL/OPG represent a "yin/yang" paradigm, in which osteoclast biology and bone resorption are intricately regulated and controlled (E-Fig. 225-1).

Factors Affecting Peak Bone Mass and Remodeling

Peak bone mass is achieved by the third decade. Longitudinal studies in children and adolescents suggest that hormonal, physical activity, nutritional, and genetic factors are important in this process. Hereditary influence is the most important determinant and least well understood. Growth hormone and sex hormones play critical roles in growth of the appendicular (long bones) and axial (vertebrae) skeleton, with the former maturing earlier than the latter (end of puberty vs. young adulthood). Males have larger bones as a result of greater periosteal (outer surface of bone) expansion of bone than occurs in females. Current evidence supports a positive effect of exercise and loading on bone size and mineral density, although a subsequent potential antifracture benefit later in adult life is not proven. Poor nutrition and concomitant disease may also affect bone accrual, primarily by delaying the onset and progression of puberty, although "catch-up" growth, which depends on the degree of insult and timing of resolution, also can occur.

Although these factors are all important, genetic factors appear to account for 60 to 80% of the variance in peak bone mineral density. Genome-wide association studies have identified 90 distinct loci that are significantly associated with bone mineral density. Additionally, the genetic determination of bone mineral density is relatively skeletal site-specific (E-Fig. 225-2). Three obligatory pathways of bone metabolism were initially identified by genome-wide association studies, (i.e., Wnt, RANK-RANKL-OPG, and endochondral ossification), and two additionally pathways (NOTCH and Indian Hedgehog) have also recently been identified, although they may interact through the Wnt pathway.[2] Wnt signaling pathway is obligatory for bone formation, owing to its role in the proliferation and differentiation of osteoblasts. Endochondral ossification, a process that involves the cartilage growth plate and subsequent ossification of the cartilaginous skeleton, is dependent on transcription factors (SOX6, RUNX2) and proteins (parathyroid hormone–related peptide, bone sialoprotein 2, and osteopontin) that are necessary for the development of the cartilage growth plate, for bone matrix mineralization, and for osteoblast differentiation. These three initially identified pathways are now the target of existing and developing therapies for osteoporosis.

In adults, bone remodeling is a physiologic process through which skeletal repair and adaption to changes in biomechanical stress occur. The bone remodeling cycle occurs in the basic multicellular unit, which itself is composed of bone-resorbing osteoclasts, bone-forming osteoblasts, bone lining cells, and embedded osteocytes and is the apparatus that facilitates remodeling (E-Fig. 225-3). After the age of 30 years, this process is reasonably matched, thereby resulting in rates of bone loss of only 0.3 to 0.5% per year from the third through fifth decades of life. As individuals age, mismatches in bone remodeling (as a result of reduced formation, increased resorption, or a combination of both) result in greater rates of bone loss. Biologic changes, such as menopause (Chapter 222) and aging, systemic disease, personal vices, and medications (most notably glucocorticoids), may contribute to this imbalance. In addition, genetic factors influence the rates of bone loss and fracture.[3]

Mechanisms of Bone Loss

"Natural" and Aging-Related Bone Loss

The rate of net bone loss accelerates during the latter decades of life because of a number of factors. Perhaps most important for women, rates of bone loss increase substantially in the perimenopausal and early postmenopausal years (Chapter 222), amounting to losses of 1 to 5% per year. Unfortunately, no biologic markers currently can determine which women a priori are "rapid losers." Bone loss is slower in obese women, likely because of higher estrogen levels afforded by production through aromatization in adipose tissue. Following both natural and surgical menopause, a decline in circulating estrogen is primarily responsible for bone loss, which is mediated primarily through upregulation of cytokines (most notably RANKL) and a resultant increase in the number, activity, and depth of osteoclast-mediated bone resorption sites. In addition, the production of osteoprotegerin is diminished, thereby further amplifying bone resorption, although estrogen replacement can restore the production of osteoprotegerin while reducing RANKL expression and thereby help mitigate bone loss during this period. Although bone resorption and formation occur sequentially during this period, resorption outpaces formation because of potentiation of the former aided by the release of soluble cytokines, thereby resulting in a significant uncoupling of bone remodeling and accelerated bone loss. Fortunately, this phase of rapid bone loss is typically limited to 2 to 3 years in most women.

Evidence also supports a key role for reduced estrogen levels in men, perhaps because reduced aromatase activity in fat tissue leads to loss of bone and an increased risk of fracture.[4] With aging, declines in circulating insulin-like growth factor-I levels also may inhibit the production of mesenchymal stromal

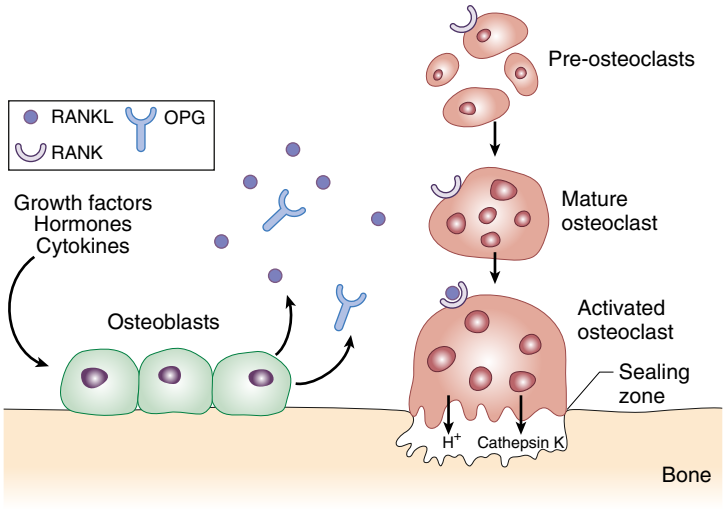

E-FIGURE 225-1. RANKL expressed by osteoblast lineage cells binds to RANK on the surface of pre-osteoclasts and mature osteoclasts, resulting in increased bone resorption through an increase in osteoclast differentiation, activity, and survival. Osteoprotegerin (OPG) is a "decoy receptor," also produced by osteoblasts, that binds to RANKL, preventing RANKL binding to RANK and thereby inhibiting osteoclastic bone resorption. It is the balance of RANKL and OPG that determines the ultimate rate of bone resorption. (Adapted from Lewiecki EM. New targets for intervention in the treatment of postmenopausal osteoporosis. *Nat Rev Rheumatol*. 2011;7:631-638.)

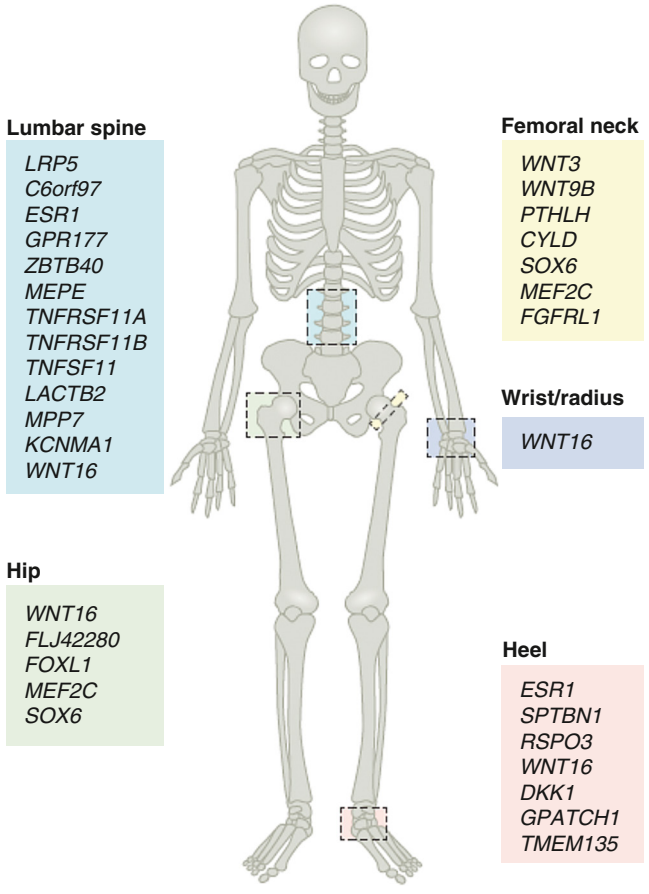

E-FIGURE 225-2. The most important genes linked to bone mineral density (BMD) variation. These are the key genes identified to date in various genome-wide association studies for BMD at various skeletal sites: the lumbar spine, hip, wrist or radius, heel, and femoral neck. (From Karasik D, Rivadeneira F, Johnson ML. The genetics of bone mass and susceptibility to bone diseases. *Nat Rev Rheumatol*. 2016;12:323-334.)

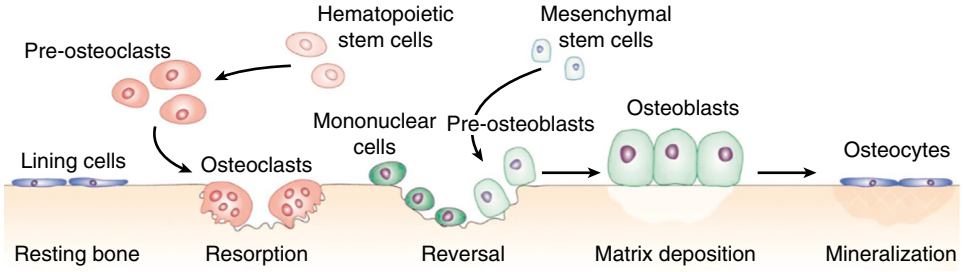

E-FIGURE 225-3. The basic multicellular unit (BMU) moving across the bone tissue. First, 10 to 20 osteoclasts resorb old or damaged tissue; then they recruit 1000 to 2000 osteoblasts, which produce new bone matrix. The BMU moves at a speed of 20 to 40 μm/day and survives for up to 6 months. (From Kapinas K, Delany AM. MicroRNA biogenesis and regulation of bone remodelling. *Arthritis Res Ther*. 2011;13:220.)

cells and pre-osteoblasts, in addition to limiting periosteal bone expansion. Bone loss in later decades also is caused by lower 25-hydroxyvitamin D (25[OH]D) levels, often related to restricted sun exposure and a reduced capacity to generate previtamin D in the skin with aging, as well as limited dietary intake of vitamin D and calcium. Low vitamin D results in secondary hyperparathyroidism (Chapter 227), which accelerates cortical bone loss, as well as likely increasing the risk for falls. Increase in bone marrow adiposity is also inversely and significantly correlated with aging-related bone loss, in part because fewer osteoblast precursors are formed. Finally, loss of weight and muscle mass (sarcopenia) is associated with bone loss, with evidence suggesting that a common factor (myostatin) may provide insights on this muscle-bone interaction.

Secondary Causes and Clinical Impact of Bone Loss

Bone loss also occurs as a result of secondary processes, such as diseases and medications (see Table 225-1), which can be identified in more than one fourth of individuals with osteoporosis. Endocrine disorders, including hypogonadism (Chapters 216 and 217) and Cushing syndrome (Chapter 208), predominate, but malabsorption (Chapter 126), chronic liver disease (Chapter 139), and certain medications (e.g., antiepileptic drugs such as phenytoin) are also implicated. Glucocorticoids, whether via exogenous administration or endogenous overproduction,[5] reduce bone formation by reducing the function and survival of osteoblasts and osteocytes. Rarely, malignancies can be the principal cause of osteoporosis, with the best example being multiple myeloma (Chapter 173), which causes bone loss through uncoupling of bone resorption and formation. Anorexia nervosa (Chapter 200) interferes with the anabolic effect of insulin-like growth factor-I on bone. Alcohol intake (Chapter 364) of only 1 or 2 drinks per day increases the risk for osteoporosis,[6] likely through suppression of osteoblast function, both directly and indirectly through associated malnutrition, as well as possibly through hypogonadism-associated bone loss from accelerated bone turnover. Tobacco use (Chapter 363) may also accelerate bone loss, owing to global effects that include reduced sex hormones, altered calcium metabolism, and weight loss and frailty, resulting in uncoupled bone remodeling. Finally, relatively rare connective tissue disorders, such as osteogenesis imperfecta (Chapter 229) and Marfan syndrome (Chapter 239), increase skeletal fragility by disturbing the skeletal matrix and mechanical integrity rather than altered bone remodeling.

The age at which bone loss occurs (e.g., young adult vs. an 80-year-old) affects the ability to recover bone mineral density with resolution or treatment of the condition (younger people have more robust recovery than elderly people) and also appears to hold for conditions of accelerated bone resorption (e.g., immobilization) or reduced bone formation (e.g., glucocorticoids). Predicated on and paralleling this observation, the response of bone mineral density to treatment is generally more pronounced in individuals with higher rates of bone turnover, likely reflecting to some extent a "filling in" of bone remodeling space. Menopausal stage in women also influences the rate of bone loss, with greater rates of decline occurring within the first 2 to 3 years of cessation of menses (Chapter 222). A faster rate of bone mineral density decline in the lumbar spine in early menopause also predicts a higher risk of fracture.[7] Concomitant vitamin D deficiency and resulting secondary hyperparathyroidism also potentiate rates of bone loss, particularly in elderly people.

TABLE 225-1 SECONDARY CAUSES OF OSTEOPOROSIS

ENDOCRINE DISORDERS
Hypogonadism: female and male
Hypercortisolism: endogenous and exogenous
Hyperthyroidism
Hyperparathyroidism
Idiopathic hypercalciuria
Diabetes mellitus: type 1 and type 2
NUTRITIONAL AND GASTROINTESTINAL DISORDERS
Malabsorption: celiac disease, gastrointestinal bypass
Vitamin D deficiency
Cirrhosis (including primary biliary cirrhosis)
Pancreatic insufficiency
Inflammatory bowel disease
Cystic fibrosis
Anorexia nervosa, bulimia
HEMATOLOGIC AND ONCOLOGIC DISORDERS
Multiple myeloma
Hemolytic anemia
Hemoglobinopathies: thalassemia, sickle cell
Myeloproliferative neoplasms
Skeletal metastases
Mastocytosis
CONNECTIVE TISSUE AND METABOLIC DISORDERS
Osteogenesis imperfecta
Ehlers-Danlos syndrome
Marfan syndrome
Homocystinuria
Gaucher disease
Pompe disease
MEDICATIONS AND EXPOSURES
Glucocorticoids
Aromatase inhibitors
Thyroxine (excessive)
Antiepileptics
Heparin
Gonadotropin-releasing hormone agonists
Depo-Provera
Immunosuppressants: tacrolimus, cyclosporine
Chemotherapy
Selective serotonin reuptake inhibitors*
Proton pump inhibitors*
Thiazolidinediones*
Sodium glucose cotransporter 2 inhibitors*
Alcohol
MISCELLANEOUS
Rheumatoid arthritis
Immobilization
Juvenile osteoporosis
Pregnancy-associated osteoporosis

*Association based.

Fragility Fractures

Most fragility fractures, which are defined as fractures occurring from the energy imparted from a fall from a standing height or less, occur in individuals who have low (osteopenia) or even normal bone mineral density. Given these observations, it is clear that other factors (e.g., falls and traumatic injuries) must also significantly influence the risk of fracture. Excluding falls and trauma, however, studies to date have also identified qualitative factors that are integral to bone strength, including skeletal microarchitecture, bone turnover, the accumulation of damage (e.g., microfractures), and the pattern or degree of mineralization. Newer technologies (including high-resolution peripheral quantitative computed tomography and high-resolution magnetic resonance imaging [MRI]) may improve the understanding of how these qualitative changes in bone compromise skeletal strength (Fig. 225-2).[8]

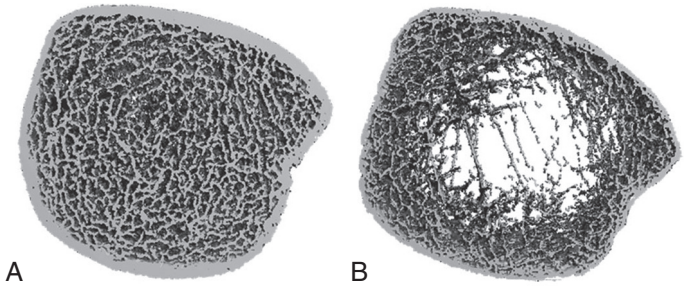

FIGURE 225-2. High-resolution peripheral computed tomography (Xtreme CT) of distal tibia in subject with normal bone mineral density (A) and severe osteoporosis (B). The deterioration in trabecular architecture with reduced trabecular number, trabecular thinning, increased trabecular spacing, generalized cortical thinning, and increased cortical porosity is readily appreciable in the osteoporotic subject. (From Griffith JF, Genant HK. New advances in imaging osteoporosis and its complications. *Endocrine*. 2012;42:39-51.)

CLINICAL MANIFESTATIONS

Low bone mass in and of itself does not cause pain, unless it is due to osteomalacia (Chapter 226). Because osteoporosis typically antedates clinical symptoms by many years, most osteoporotic individuals are asymptomatic.

Osteoporosis may be diagnosed in an individual who presents with a fragility fracture, typically of the vertebrae, proximal femur, proximal humerus, or distal forearm. Other sites that are subject to fragility fractures include the pelvis, ribs, and proximal tibia. Nevertheless, even a high-trauma fracture in a postmenopausal woman or elderly man should cause suspicion for osteoporosis.

Fractures of the spine, which are often asymptomatic, are generally from the midthoracic region through the lower lumbar region, with the greatest frequency at T11 through L2. Patients often present after a fall or a spinal flexion-loading event, in which they may hear a "pop" and complain of sharp midline back pain that may radiate to the flanks. Patients may also present with complaints of back "tiredness," which is improved with sitting or lying down; this symptom is likely related to paraspinal weakness or spasm from abnormal spinal curvature that occurs with chronic vertebral compression. Back pain may commonly be related to other pathology (Chapter 369), such as degenerative disc and spine disease that is concomitantly present.

Vertebral fractures often occur without an obvious acute precipitant. In contrast, nonvertebral fracture events are always clinically evident. Hip fractures generally occur with falls, although they may rarely occur with limited force such as twisting.

Physical Examination

Physical examination may indicate the presence of osteoporosis and associated fractures, as well as potentially identifying underlying secondary processes contributing to the disease. Measured height loss, best confirmed using a calibrated device such as a stadiometer, of greater than 4 cm since young adult maximum height is suggestive of prior vertebral fractures. Height loss also occurs with scoliosis and aging (approximately ⅓ inch of height is lost per decade after age 50 years). A kyphotic deformity (Chapter 86) of the upper thoracic spine may be present, although it is important to distinguish it from accentuated cervical lordosis with associated prominence of T1. Spinal tenderness to palpation and percussion can occur with an acute vertebral compression fracture. Palpable tenderness of the long bones may suggest underlying osteomalacia (Chapter 226) with periosteal expansion and nerve irritation. Reduced rib-pelvis and increased wall-occiput distances (<2 and >0 fingerbreadths, respectively) also are correlated with vertebral fractures as well.

DIAGNOSIS

In symptomatic patients, the diagnosis of osteoporosis is commonly made by radiographs of the involved site. Radiologic findings also may identify the presence of osteoporosis, serendipitously when obtained for other reasons in asymptomatic patients with osteoporosis.

Plain films can detect bone loss by means of accentuation of vertical striations on spine radiographs that represent loss of horizontal trabeculae, although this generally indicates bone density loss of at least 25% or more. Kyphosis and compression fractures may be present, and patients often are unaware of the deformities because nearly three fourths of such fractures occur without acute pain. Lateral chest radiographs and computed tomographic (CT) scans often identify such fractures (Fig. 225-3). The degree of compression fracture is also important because more severe fractures (>25% vertebral height loss) especially appear to predict future vertebral fractures.

When recent fractures are suspected, CT and MRI may be used, given that plain radiographs have a lower sensitivity acutely and for detecting stress fractures. MRI also can be used to define a vertebral fracture with persistent swelling and edema based on T2 characteristics, thereby potentially identifying patients who could benefit from vertebroplasty or kyphoplasty. Finally, whole-body bone scintigraphy is the most sensitive test for detecting fracture within the past 6 to 12 months but can be falsely positive because of inflammation, infection, or tumor.

Bone Mineral Density Measurement

Most patients with osteoporosis are diagnosed on the basis of a measurement of bone mineral density, generally by dual–energy x-ray absorptiometry (DXA).[9] DXA scanning is a low-radiation–based radiologic measurement of the areal bone density (g/cm) of the lumbar spine, proximal femur, and distal radius. Osteoporosis can be diagnosed if the bone mineral density of a postmenopausal woman or man older than age 50 years is more than 2.5 standard deviations below young average normal individuals (T score ≤−2.5). A T score between −1.0 and −2.5 is considered low bone density, or osteopenia, and a Z score (age-matched bone mineral density) in premenopausal women and men younger than 50 years that is more than 2 standard deviations below that of an average age-matched individual is considered low bone density for age.

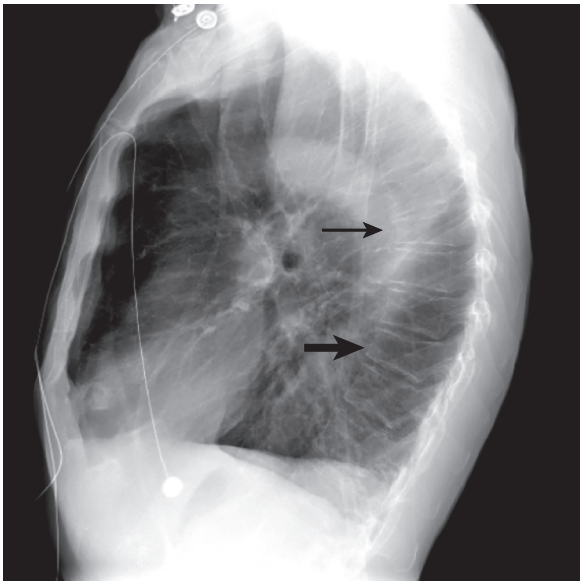

FIGURE 225-3. Incidental vertebral compression fractures on chest radiograph. Lateral radiograph of the chest of a 74-year-old man studied for cough. No relevant pulmonary abnormality was noted on the frontal radiograph (not shown). Examination of the thoracic spine shows the presence of a mild anterior wedge compression fracture of T9 *(thick arrow)* and moderate anterior wedge fracture of T6 (*thin arrow*). Neither fracture was reported on the radiographic report.

Bone mineral density is an independent predictor of future fracture, such that the relative risk for fracture increases by 1.5- to 2-fold for each 1 standard deviation decrease in T score. In addition, the risk of fracture increases exponentially below a T score of −2.5. A variety of other imaging techniques can assess bone mineral density (e.g., quantitative computed tomography [CT] or ultrasound),[10] but none are preferred over DXA scanning, which has a higher sensitivity for detecting osteoporosis and a better ability to follow bone density changes over time.

In addition to DXA, the continued development of additional imaging tools (HRpQCT and microMRI) may well further refine the risk for fragility fractures. Furthermore, the FDA recently approved biomechanical computed tomography (BCT) as an opportunistic assessment of bone mineral density and bone strength/fracture risk of the lumbar spine and proximal femur using CT imaging and finite element analysis, although it is not recommended to follow treatment response over time. At present, the use of BCT is likely most appropriate for patients who cannot undergo DXA imaging (e.g., patients with prior lumbar fusion or bilateral hip prostheses).

Although DXA is the best method to diagnose and manage osteoporosis, it cannot distinguish between low bone density and undermineralized bone matrix, the latter of which occurs in osteomalacia (Chapter 226). Bone mineral density also may be quite disparate between regions, perhaps in more than one third of individuals, especially in postmenopausal women, in patients taking corticosteroids, and in hyperparathyroidism. Degenerative changes due to aging, such as facet osteoarthritis and aortic calcification, may artifactually raise the spine bone mineral density. Given these considerations, the lowest skeletal site should be used for diagnosis. Finally, bone mineral density should be measured longitudinally on the same DXA machine, if possible, because of intermachine and intermanufacturer differences that may confound the ability to measure change over time validly.[11]

Despite its utility, bone density is limited in its ability to future predict fractures in individual patients,[12] because it does not take into account clinical factors that independently predict risk.[13] The most widely used of these prediction model is FRAX, which calculates a person's 10-year risk for hip and major osteoporotic fracture (hip, clinical spine, forearm, and proximal humerus all combined) using country-specific data on clinical risk factors as well as bone mineral density of the femoral neck (E-Fig. 225-4 and http://www.shef.ac.uk/FRAX/). FRAX does not consider a patient's history of or risk for falls. The U.S. Preventive Services Task Force recommends DXA screening for osteoporosis routinely in women over age 65 years but that screening in women younger than 65 years should consider a number of formal clinical risk

assessment tools, such as FRAX (E-Fig. 225-4 and http://www.shef.ac.uk/FRAX), which is the most robust complementary tool to bone mineral density for defining a person's risk for fracture and candidacy for pharmacologic intervention, and test only if the risk is a major osteoporotic fracture is 8.4% or greater by FRAX assessment.[14,A1] Combining FRAX with use of a trabecular bone score (E-Fig. 225-5), which is a surrogate measure of bone architecture that can be performed at the same time as DXA scanning, may better predict the risk for hip and major osteoporotic fractures, though it is not used widely in clinical practice at the present time.

Search for Causes of Bone Loss

About 20 to 25% of women and perhaps an even greater proportion of men will have identifiable additional etiologies that may contribute to bone loss (see Table 225-1). Although a recent fragility fracture with a consistent radiographic finding or a DXA scan result is a reasonable basis for diagnosis of osteoporosis, other skeletal conditions also should be entertained, including inherited and acquired osteomalacias (Chapter 226) and pathologic fracture due to malignancy, especially multiple myeloma (Chapter 173) or metastatic cancer of bone (Chapter 187). Most patients will already have had routine chemistry, hematology, and thyroid studies as part of their annual examination. The 25(OH)D level should be measured in all patients. Additional investigations may also be considered, as directed by the clinical history and physical examination. In addition, a greater degree of bone mineral density deficit (i.e., lower Z score) indicates a need for more extensive testing, given the greater likelihood of secondary causes being present. Bone turnover markers (e.g., bone-specific alkaline phosphatase, osteocalcin, type I procollagen amino-terminal propeptide, and type I procollagen carboxy-terminal propeptide as formation markers, and serum and urine C- and N-terminal peptides of type I collagen as resorption markers) should not be used in routine clinical practice but occasionally help experts manage more complicated cases of metabolic bone disease.

TABLE 225-2 TREATMENT BASED ON THE RISK OF FRACTURE

LEVEL OF FRACTURE RISK	CRITERIA	TREATMENT
Low	T score > –1.0 AND no hip or vertebral fracture, AND FRAX hip fracture < 3% and major osteoporotic fracture risk < 20%	Nonpharmacologic (calcium/vitamin D and exercise)
Moderate	T score > –2.5 AND no hip or vertebral fracture AND FRAX hip fracture < 3% and major osteoporotic fracture risk < 20%	Nonpharmacologic OR bisphosphonate
High	T score ≤ –2.5 OR prior hip or vertebral fracture OR FRAX hip fracture > 3% and major osteoporotic fracture risk > 20%	Bisphosphonate Denosumab Selective estrogen receptor modulator
Very High	T score ≤ –2.5 and fractures AND multiple vertebral fractures OR severe vertebral fracture (>40% vertebral height loss)	Anabolic agent Bisphosphonate Denosumab

Major fracture risk refers to a 10-year risk of a fracture of the hip, clinical spine, distal forearm, or proximal humerus. Severe describes the degree of vertebral body compression fracture (mild 20% to 25%, moderate 25% to 40%, and severe >40%).

Adapted from Shoback D, Rosen CJ, Black DM, et al. Pharmacological management of osteoporosis in postmenopausal women: an Endocrine Society guideline update. *J Clin Endocrinol Metab*. 2020;105:587-594.

PREVENTION AND TREATMENT

The approach to the patient with osteoporosis should be guided by the risk for fracture (Table 225-2 and http://www.shef.ac.uk/FRAX/).[15]

Calcium and Vitamin D

Adequate intake of calcium is critical to the optimal accumulation and maintenance of bone mineral density. Although calcium supplementation modestly improves bone mineral density by 1 to 2%, it does not independently reduce the risk of hip and nonvertebral fractures in patients with osteoporosis.[A2] Given the established increased risk of nephrolithiasis (Chapter 111) and a potential increase in nonfatal cardiac events with higher dose calcium supplementation,[16] adults with osteoporosis should obtain 1200 to 1500 mg of calcium primarily from dietary sources, with the adjunct use of calcium supplements as needed to achieve this goal.

Data in adults with osteopenia and osteoporosis confirm a benefit of combined vitamin D and calcium supplementation (400 to 800 IU of vitamin D combined with 1000 mg of calcium) to reduce the risk for hip fracture in postmenopausal women and men aged 65 years and older, but this benefit is small or nonexistent in community-dwelling individuals.[A3] Although some data suggest that a 25(OH)D level of at least 30 ng/mL is needed to reduce the risk for hip fracture, there is considerable controversy as to whether a vitamin D level above 30 ng/mL reduces the overall risk for fracture.[A4] Given these observations, a minimal 25 (OH)D level of 20 ng/mL is recommended for bone health.

In individuals without osteopenia or osteoporosis, routine vitamin D supplementation (with or without calcium supplementation) does not appear to prevent falls or fractures in community-dwelling adults who do not have vitamin D deficiency or prior fractures,[A5,A6] even in the presence of vitamin insufficiency (serum 25(OH) D levels less than 20 to 30 ng/mL).[A7] Although activated vitamin D analogues such as calcitriol and α-calcidiol may reduce the risk of fracture, they are generally not indicated based on unacceptable risk for hypercalcemia. The exception is to use vitamin D analogues in patients with stages 3 and 4 chronic kidney disease (Chapter 116), in which treatment of secondary hyperparathyroidism may provide skeletal benefit.

Exercise and Lifestyle

Physical activity is also critical for preventing osteoporosis and its progression.[A8] Exercise modestly improves bone mineral density in the lumbar spine (mean difference = 0.85%) and trochanter (mean difference = 1.03% in postmenopausal women), but it does not significantly improve femoral neck or total hip bone mineral density.[17] Physical activity also enhances muscle strength, improves cardiovascular status, and thereby reduces the risk of falls. Balance training and Tai Chi also reduce the risk for falling (see Chapter 24). Tobacco cessation and moderation of caffeine and alcohol intake may be helpful, but data are not available as to whether these interventions reduce overall risk of fracture.

Medications

Pharmacologic therapy, which should be based on a patient's risk for an osteoporotic fracture (see Table 225-2 and Fig. 225-4), significantly reduces the risk for osteoporotic fracture in a clinically meaningful and cost-effective manner.[18,19] A FRAX (http://www.shef.ac.uk/FRAX/) 10-year risk equal to or exceeding 3% for hip fracture and 20% for major fracture warrants consideration of pharmacologic treatment. Because medications reduce the relative risk of hip fracture by about 50%, or from about 10% to about 5% in patients with osteoporosis, about 20 patients need to be treated to prevent one hip fracture.

Medications approved for osteoporosis can be classified based on their mechanism of action: anticatabolic (i.e., antiresorptive) and anabolic (i.e., bone building).[20,21] The choice among available agents is guided by the level of risk of fractures (Table 225-2).

Anticatabolic Agents

Anticatabolic (or antiresorptive) medications inhibit the recruitment, function, and/or survival of osteoclasts, thereby resulting in reductions in skeletal turnover and bone loss. These agents improve bone mineral density, strengthen the skeletal microstructure, and reduce the risk of fracture.

Bisphosphonates

Bisphosphonates are the most widely prescribed and used medications for the treatment of osteoporosis, owing in large part to good tolerability and infrequent dosing. Bisphosphonates, which have an extremely high affinity for hydroxyapatite crystals within bone, are taken up by osteoclasts and inhibit their cellular attachment, function, and survival.

ORAL BISPHOSPHONATES. Oral agents are first-line therapy. Three oral bisphosphonates are currently available in the United States: once-weekly alendronate, once-weekly or once-monthly risedronate, and once-monthly ibandronate. Oral bisphosphonates should be taken fasting in the morning with water only, and the patient must remain fasting in a sitting or standing position for 30 to 60 minutes after the dose. The most common side effect is precipitation or aggravation of gastroesophageal reflux, although most patients tolerate the drugs without difficulty. A delayed-release formulation of risedronate may be taken immediately after breakfast, thereby likely lessening the risk for reflux-related symptoms. These drugs are contraindicated in patients with functional or anatomic disorders of esophageal transit (i.e., esophageal stricture, achalasia) or advanced renal insufficiency (i.e., a glomerular filtration rate <35 mL/min). All three drugs significantly increase bone mineral density and reduce the risk for vertebral fractures at 12 months.[A9] Data also strongly support a persistent antifracture benefit following cessation of treatment if it has been used continuously for at least 5 years (Table 225-3).

Calculation Tool

Please answer the questions below to calculate the ten year probability of fracture with BMD.

Country: US (Caucasian) Name/ID:

Questionnaire:

1. Age (between 40 and 90 years) or Date of Birth
   Age: Date of Birth: Y: M: D:
2. Sex ○ Male ○ Female
3. Weight (kg)
4. Height (cm)
5. Previous Fracture ○ No ○ Yes
6. Parent Fractured Hip ○ No ○ Yes
7. Current Smoking ○ No ○ Yes
8. Glucocorticoids ○ No ○ Yes
9. Rheumatoid arthritis ○ No ○ Yes
10. Secondary osteoporosis ○ No ○ Yes
11. Alcohol 3 or more units/day ○ No ○ Yes
12. Femoral neck BMD (g/cm^2)

Select BMD

Clear Calculate

For USA use only

Consider FDA-approved medical therapies in postmenopausal women and men aged 50 years and older, based on the following:

- A hip or vertebral (clinical or morphometric) fracture
- T-score ≤ –2.5 at the femoral neck or spine after appropriate evaluation to exclude secondary causes
- Low bone mass (T-score between –1.0 and –2.5 at the femoral neck or spine) and a 10-year probability of a hip fracture ≥ 3% or a 10-year probability of a major osteoporosis-related fracture ≥ 20% based on the US-adapted WHO algorithm
- Clinicians judgment and/or patient preferences may indicate treatment for people with 10-year fracture probabilities above or below these levels

Risk factors

For the clinical risk factors a yes or no response is asked for. If the field is left blank, then a "no" response is assumed. See also notes on risk factors.

The risk factors used are the following:

Age	The model accepts ages between 40 and 90 years. If ages below or above are entered, the programme will compute probabilities at 40 and 90 year, respectively.
Sex	Male or female. Enter as appropriate.
Weight	This should be entered in kg.
Height	This should be entered in cm.
Previous fracture	A previous fracture denotes more accurately a previous fracture in adult life occurring spontaneously, or a fracture arising from trauma which, in a healthy individual, would not have resulted in a fracture. Enter yes or no (see also notes on risk factors).
Parent fractured hip	This enquires for a history of hip fracture in the patient's mother or father. Enter yes or no.
Current smoking	Enter yes or no depending on whether the patient currently smokes tobacco (see also notes on risk factors).
Glucocorticoids	Enter yes if the patient is currently exposed to oral glucocorticoids or has been exposed to oral glucocorticoids for more than 3 months at a dose of prednisolone of 5 mg daily or more (or equivalent doses of other glucocorticoids) (see also notes on risk factors).
Rheumatoid arthritis	Enter yes where the patient has a confirmed diagnosis of rheumatoid arthritis. Otherwise enter no (see also notes on risk factors).
Secondary osteoporosis	Enter yes if the patient has a disorder strongly associated with osteoporosis. These include type I (insulin dependent) diabetes, osteogenesis imperfecta in adults, untreated long-standing hyperthyroidism, hypogonadism or premature menopause (<45 years), chronic malnutrition, or malabsorption and chronic liver disease
Alcohol 3 or more units/day	Enter yes if the patient takes 3 or more units of alcohol daily. A unit of alcohol varies slightly in different countries from 8–10g of alcohol. This is equivalent to a standard glass of beer (285ml), a single measure of spirits (30ml), a medium-sized glass of wine (120ml), or 1 measure of an aperitif (60ml) (see also notes on risk factors).
Bone mineral density (BMD)	(BMD) Please select the make of DXA scanning equipment used and then enter the actual femoral neck BMD (in g/cm^2). Alternatively, enter the T-score based on the NHANES III female reference data. In patients without a BMD test, the filed should be left blank (see also notes on risk factors) (Provided by Oregon Osteoporosis Center).

Notes on risk factors

Previous fracture

A special situation pertains to a prior history of vertebral fracture. A fracture detected as a radiographic observation alone (a morphometric vertebral fracture) counts as a previous fracture. A prior clinical vertebral fracture or a hip fracture is an especially strong risk factor. The probability of fracture computed may therefore be underestimated. Fracture probability is also underestimated with multiple fractures.

Smoking, alcohol, glucocorticoids

These risk factors appear to have a dose-dependent effect, i.e. the higher the exposure, the greater the risk. This is not taken into account and the computations assume average exposure. Clinical judgement should be used for low or high exposures.

Rheumatoid arthritis (RA)

RA is a risk factor for fracture. However, osteoarthritis is, if anything, protective. For this reason reliance should not be placed on a patient's report of 'arthritis' unless there is clinical or laboratory evidence to support the diagnosis.

Bone mineral density (BMD)

The site and reference technology is DXA at the femoral neck. T-scores are based on the NHANES reference values for women aged 20–29 years. The same absolute values are used in men.

Website Design Sheffield by Richlyn Systems

E-FIGURE 225-4. **The FRAX® tool (http://www.shef.ac.uk/FRAX) is an online fracture risk estimation application that can be used to determine an individual patient's 10-year risk for hip fracture and major osteoporotic fracture (hip, clinical spine, distal forearm, and proximal humerus).**

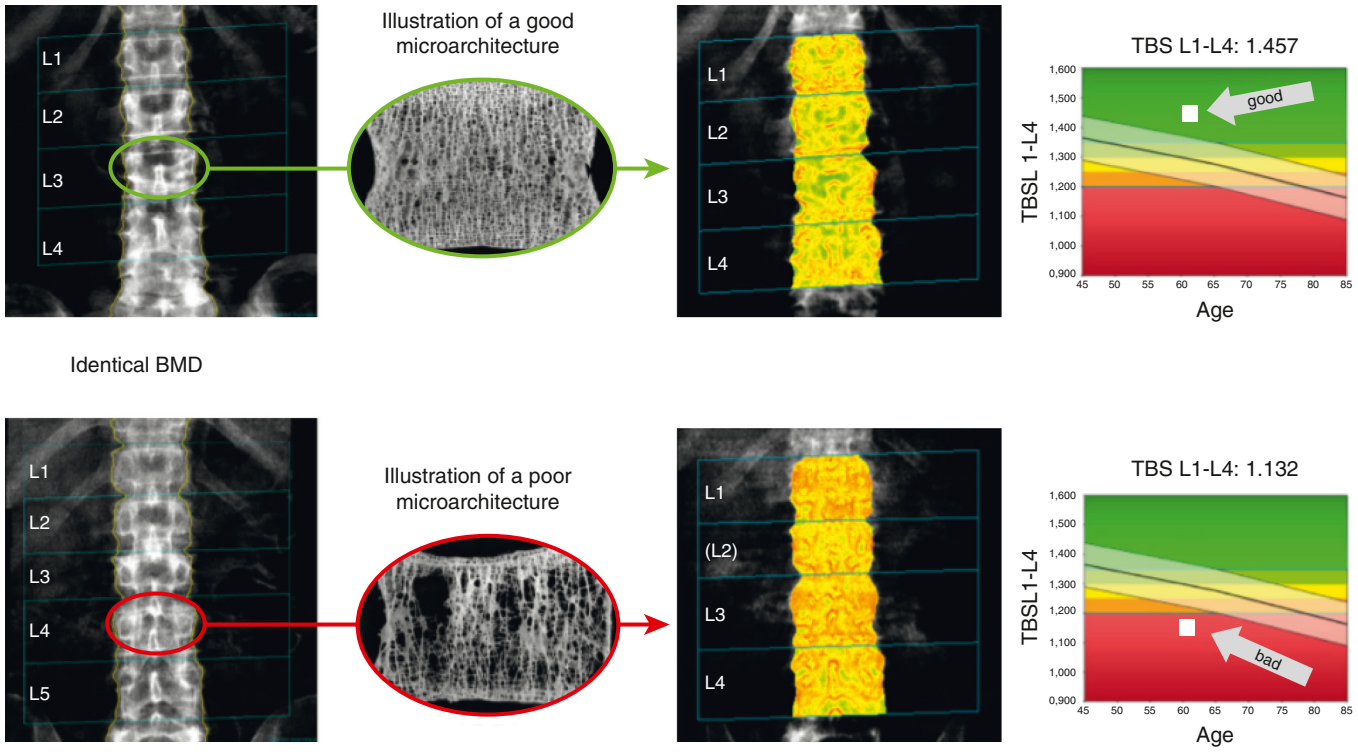

E-FIGURE 225-5. Trabecular bone score (TBS): Examples of bone mineral density images, TBS images and associated reference curves of healthy *(top)*, and osteoporotic *(bottom)* bone. Utility of the TBS in secondary osteoporosis. (Harvey NC, Glüer CC, Binkley N, et al. Trabecular bone score can analyze the quantity and quality of bone matrix and significantly add to the FRAX estimation of fracture risk. *Endocrine*. 2014;47:435-448.)

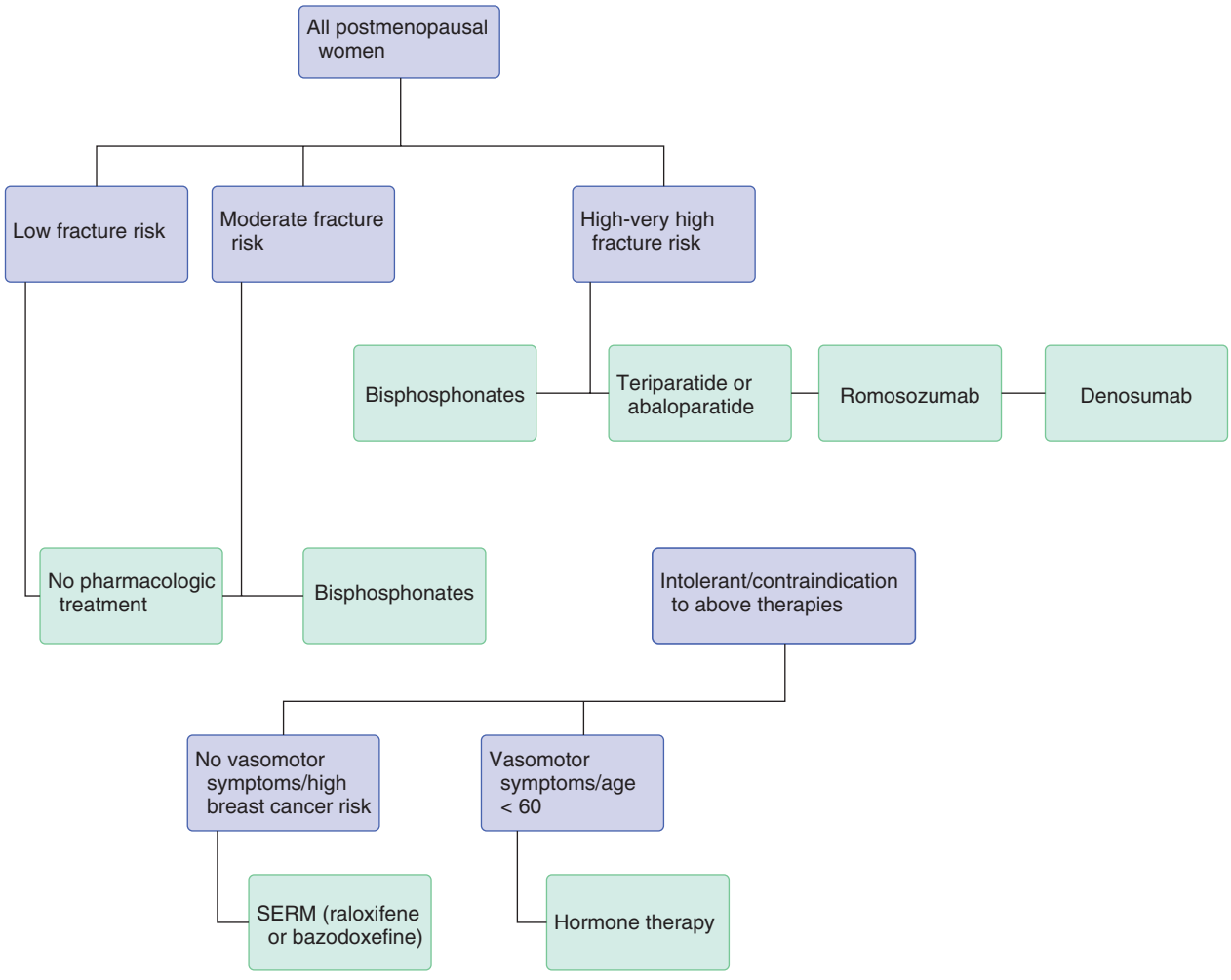

FIGURE 225-4. Approach to postmenopausal osteoporosis. SERM = selective estrogen receptor modulator. (Adapted from Shoback D, Rosen CJ, Black DM, et al. Pharmacological management of osteoporosis in postmenopausal women: an Endocrine Society guideline update. *J Clin Endocrinol Metab*. 2020;105:587-594.)

TABLE 225-3 STRENGTH OF EVIDENCE FOR THE REDUCTION OF RISK FOR FRACTURE TYPES WITH PHARMACOTHERAPY IN WOMEN WITH POSTMENOPAUSAL OSTEOPOROSIS

	FRACTURE SKELETAL SITES			
	VERTEBRAL	**NONVERTEBRAL**	**HIP**	**WRIST**
Alendronate 35 or 70 mg oral weekly	• • •	• • •	• • •	•
Risedronate 35 mg weekly or 150 mg oral monthly	• • •	• • •	• • •	•
Zoledronate 5 mg IV once yearly	• • •	• • •	• • •	1
Ibandronate 150 mg oral monthly or 3 mg IV quarterly	• • •	• •	•	1
Denosumab 60 mg SQ twice yearly	• • •	• • •	• • •	1
Raloxifene 60 mg oral daily	• • •	1	1	1
Bazedoxifene* 20 mg with 0.45 CEE oral daily	• • •	1	1	1
Teriparatide 20 mcg SQ daily	• • •	• •	•	1
Abaloparatide* 80 mcg SQ daily	• • •	• •	1	1
Romosozumab 210 mg SQ monthly	• • •	• •	• •	1

*Based on author's review of clinical trial data.

Strength of evidence symbol legend: 1 = insufficient strength of evidence; • = low strength of evidence; • • = moderate strength of evidence; • • • = high strength of evidence.

CEE = conjugated equine estrogen; IV = intravenously; SQ = subcutaneously.

Adapted with permission from Levis S, Theodore G. Summary of AHRQ's comparative effectiveness review of treatment to prevent fractures in men and women with low bone density or osteoporosis: update of the 2007 report. *J Manag Care Pharm*. 2012;18(4 Suppl B):S1-S15, discussion S13.

PARENTERAL BISPHOSPHONATES. Parenteral bisphosphonates are second-line alternative options for patients who have contraindications to oral bisphosphonates (e.g., esophageal disease, inability to sit upright and/or fast after dose), documented or expected poor adherence to oral bisphosphonates, or failure to respond to oral bisphosphonates or other therapies that are approved by the U.S. Food and Drug Administration (FDA) as evidenced by recurrent fractures and declining bone mineral density. Zoledronic acid (5 mg once yearly), reduces the risk of spine, hip, and nonvertebral fractures in women and men.[A10] Zoledronic acid also reduces mortality in women and men following a low-trauma hip fracture,[A11] although the mechanism of this mortality benefit is unknown. Bone mineral density remains stable, and the antifracture effect likely persists for 3 years after three to six annual doses of zoledronic acid.[A12] Furthermore, less frequent (5 mg every 18 months) dosing of zoledronate significantly reduces the risk for vertebral and nonvertebral fragility fractures in older women who have osteopenia but who do not meet criteria for osteoporosis.[A13] Ibandronate (3 mg every 3 months) is an intravenous alternative, but data on its benefits are not as robust as for zoledronic acid.

COMPLICATIONS OF BISPHOSPHONATES. Both intravenous bisphosphonates are associated with an approximately 15 to 20% likelihood of a flulike or acute phase reaction, typically consisting of fever, arthralgias, and myalgias, usually limited to the first infusion and generally persisting 24 to 48 hours. Higher serum levels of 25(OH)D (>30 ng/mL) and previous oral bisphosphonate treatment appear to lessen the severity of these reactions.[22]

A rare but serious adverse effect of both oral and intravenous bisphosphonates is osteonecrosis of the jaw (Chapter 229),[23] which is defined as exposed bone within the oral cavity for more than 8 weeks following an invasive dental procedure (e.g., tooth extraction, dental implant) or spontaneous tooth loss. Osteonecrosis occurs in roughly 1 in 10,000 to 100,000 patients treated with oral bisphosphonates, although it likely occurs in 1 in 1000 to 10,000 patients who are treated with intravenous bisphosphonates for osteoporosis. Patients on intravenous bisphosphonates should maintain optimal oral hygiene and consider a bisphosphonate holiday or delay in dose if invasive oral procedures are planned.

Another risk is atypical femoral fractures, which generally occur after 5 years or more of bisphosphonate therapy.[24] The estimated risk is low (about 1 in 5000 to 10,000) but increases significantly with longer use (about 1/900 risk with 8 to 10 years of continuous treatment) and is eight-fold higher in Asians than Whites for unclear reasons. Patients will typically have prodromal thigh or groin pain, which can refer to a stress fracture of a thickened lateral femoral cortex, inferior to the greater trochanter. These fractures can be bilateral and may be identified radiographically with plain films, MRI, or CT. Femoral and cortical thickening, periosteal reaction, or a medial spike on plain radiograph, or a more extensive assessment of the proximal femur on DXA scan may identify patients at risk for these fractures.

Although rare, the severe manifestations of osteonecrosis of the jaw and atypical femoral fractures make it prudent for clinicians to consider a drug holiday (i.e., cessation), particularly given strong evidence of continued benefit on discontinuation after 3 to 5 years of continuous therapy (3 years for intravenous and 5 years for oral). Although the duration of bisphosphonate drug holidays has not been defined and must be individualized, patients may subsequently restart a bisphosphonate or another osteoporosis therapy if clinically indicated based on their level of fracture risk.

Denosumab

Denosumab, which is a fully humanized monoclonal antibody to RANKL, is approved by the FDA for the treatment of osteoporosis in postmenopausal women and in men, as well as for individuals with breast and prostate cancer, to reduce bone loss associated with hormone deprivation. Administered twice yearly as a subcutaneous injection (in a medical facility), it reduces the risk for spine, hip, and nonvertebral fractures in women and vertebral fractures in men,[A14,A15] with a significantly greater improvement in bone mineral density compared with bisphosphonates.[A16] Denosumab does not undergo hepatic or renal metabolism and thus can potentially be used in patients with more advanced renal dysfunction. Unlike bisphosphonates, it is reversible, such that robust bone loss ensues after the medication is stopped, and "rebound" fractures may occur if denosumab is discontinued. As a result, an oral bisphosphonate (6 months after discontinuation) or an intravenous bisphosphonate (7 to 8 months after the last dose of denosumab) should be started after it is discontinued.[25] Although clinical trial data demonstrate effectiveness for up to 10 years of continuous use, a longer duration of denosumab use is associated with greater risk for bone loss despite subsequent use of bisphosphonates.[26] Denosumab is well tolerated but is associated with a higher incidence of skin conditions (eczema and erysipelas) and infections, including serious infections that required hospitalization.[27] Therefore, the drug is likely not suitable for patients who are immunosuppressed or at increased risk for infection.

Selective Estrogen Receptor Modulators

Selective estrogen receptor modulators bind to the estrogen receptor and thereby serve as anticatabolic agents in bone. Raloxifene, which reduces the risk for vertebral fractures by approximately 30 to 50% but does not reduce the risk for hip and nonvertebral fractures, is an alternative to bisphosphonates in postmenopausal women who have osteopenia and a relatively low risk for hip and other nonspine fractures. Raloxifene is known to be safe and effective over 8 years of continuous use, and the optimal duration of use is uncertain. The most common side effects include hot flushes and leg cramps in about 10 to 15% of patients and about 5% of patients, respectively. Selective estrogen receptor modulators also increase the risk for deep vein thrombosis, with an absolute risk of about 1 in 400, akin to that seen with oral estrogen hormone replacement therapy. Raloxifene has also been associated with an increased risk for fatal stroke in women at higher baseline risk for stroke, likely precluding its general consideration in women older than age 65 years. Another selective estrogen receptor modulator (bazedoxifene) reduces vertebral fractures by 42% and is available in a fixed combination with conjugated estrogens 0.45 mg for osteoporosis prophylaxis.

Estrogen

Estrogen replacement therapy prevents bone loss if administered to women at menopause and significantly increases bone mineral density by approximately 3 to 5% in woman who are well into their menopausal years. Although lower doses of estrogen may have skeletal benefits, more standard doses of estrogen (0.625 mg of conjugated equine estrogen and 1.0 mg of ethinyl estradiol) have been proved efficacious. Long-term estrogen therapy reduces the risk for all clinical fractures by about 27%.[A17] However, estrogen replacement therapy is associated with other risks (Chapter 222), so it is generally recommended for osteoporosis only in postmenopausal women who are at significant risk for fracture and for whom other antifracture therapies are unsuitable.[28]

Anabolic Agents

Teriparatide

Teriparatide, which is a recombinant human parathyroid hormone analogue that encompasses amino acids 1 to 34, is prescribed as a self-administered, once-daily, subcutaneous injection. Teriparatide increases bone density in the lumbar spine by about 10% over 2 years and significantly reduces the risk for vertebral fractures by approximately two thirds and nonvertebral fractures by about 50%.[A18] Teriparatide or its generic biosimilar at the same dose is generally recommended as second-line therapy for patients who have severe osteoporosis, based on bone mineral density and/or their risk of fracture, and who cannot tolerate or have contraindications to other antifracture agents.

Because bone resorption increases along with bone formation, bone loss generally ensues on cessation of therapy, thereby necessitating the initiation of an anticatabolic bone drug to preserve its increase in bone mineral density. The combination of teriparatide plus denosumab may have a synergistic effect on bone mineral density,[29] but data on the benefit of combining teriparatide with it or a bisphosphonate are inconclusive. Teriparatide should not be used after denosumab therapy, based on a proven decrease in bone mineral density when this sequence is administered.

The drug is generally well tolerated, with the most common adverse effects being dizziness and leg cramps. Hypercalcemia is a rare side effect that may be seen in patients who have undiagnosed primary hyperparathyroidism before treatment. Teriparatide may increase the risk for osteosarcoma based on animal studies, so the drug is limited to a lifetime total duration of 24 months of use and is contraindicated in patients who are at a higher baseline risk for osteosarcoma (e.g., patients with Paget disease or previous therapeutic radiotherapy, as well as younger individuals with open epiphyses).

Abaloparatide

Abaloparatide (a selective activator of the parathyroid hormone type 1 receptor; administered as 80 μg subcutaneously daily) is as effective as teriparatide for reducing fractures in postmenopausal women with osteoporosis and is associated with a lower risk of hypercalcemia.[A19] Similar to teriparatide, it is potentially linked to a higher risk for osteosarcoma based on rat toxicology data and is limited to 24 months total of lifetime use.

Romosozumab

Romosozumab (210 mg given monthly by subcutaneous injection for 1 year), which is a humanized monoclonal antibody against sclerostin, is effective for the treatment of postmenopausal osteoporosis. It significantly increases bone mineral density and reduces the risk for osteoporotic vertebral fractures by 75% at 1 year, which is the recommended duration of therapy.[A20] Unlike teriparatide, inhibition of sclerostin does not appear to stimulate bone resorption, thereby potentially affording greater and more persistent gains in bone mineral density. Romosozumab increases the risk of cardiovascular events compared with alendronate and is therefore contraindicated in women who have had a myocardial infarction or a stroke within 1 year before treatment. Given that the drug also has antiosteoclastic effects through the Wnt pathway, it may also increase the risk for rare events (osteonecrosis of the jaw and atypical femoral fractures) that are seen with antiresorptive therapies.

Other Therapies

Nasal calcitonin is FDA-approved for treating postmenopausal osteoporosis, but it is widely considered the weakest antifracture agent based on its marginal benefits. In addition, its possible link to cancer further limits its clinical utility and future availability in the United States.

Strontium ranelate, which is approved in Europe (but not available for use in the United States) for the treatment of osteoporosis, may have a dual proformation-anticatabolic effect on bone. It reduces the risk for vertebral and nonvertebral fractures as well as clinical osteoporotic fractures. Because of artifactual increases in bone mineral density related to the incorporation of the strontium salt into bone, serial DXA scanning cannot be followed in patients on strontium.

Drug Combinations and Sequencing

Current guidelines support the initial use of an anabolic therapy in patients with more severe deficits in bone mineral density and/or a high risk of fracture, followed immediately by an antiresorptive agent to prevent the bone loss that occurs with cessation of the anabolic agent. Conversely, parathyroid hormone analogues are not recommended after denosumab because of expected bone loss that occurs with this sequence.

Combination therapy with an antiresorptive agent and an anabolic agent is not currently recommended due to both cost and lack of a clear benefit. Some data, however, suggest that combination therapy may provide additional improvements in bone mineral density and possibly additional reduction in the risk of fracture compared with monotherapy,[A21] likely related to the finding that the degree of increase in bone mineral density at the lumbar spine and hip correlate with the degree to which the risk of fracture is reduced.[30] These data also suggest that future treatments may be targeted to a bone mineral density goal.

Glucocorticoid-Induced Osteoporosis

Glucocorticoids, which are potent suppressors of bone formation and at higher doses likely also increase bone resorption, are the most common cause of medication-related secondary osteoporosis. The result can be a dramatic decline in bone mineral density within the first 6 months of starting therapy. The risk of fracture is increased as well, even with prednisone doses as low as 2.5 mg per day, although the increase in risk appears to attenuate when the glucocorticoid is discontinued.

The treatment approach to glucocorticoid-induced osteoporosis is similar to that osteoporosis in general,[31] with the exception that attempts should first try to reduce the glucocorticoid dose to as low as the underlying treated disease will permit. Calcium and vitamin D at doses generally recommended for postmenopausal osteoporosis are important adjuncts but are insufficient to prevent bone loss or fractures. Although bisphosphonates are effective for glucocorticoid-induced osteoporosis in women and men,[A22] data indicate that either denosumab or teriparatide is superior to bisphosphonates in these patients.[A23] Options include 60 mg of subcutaneous denosumab every 6 months[A24] while patients are on glucocorticoid therapy or teriparatide[A25] but for no more than 24 months overall.

Vertebroplasty, Kyphoplasty, and Low-Intensity Vibration

Although often clinically silent, vertebral fractures may cause acute and severe back pain. In addition, up to one third of vertebral fractures remain chronically painful, perhaps related to incomplete healing or instability of the fracture. Vertebroplasty and kyphoplasty are invasive procedures that introduce, through the spinal pedicles, a cement-like substance (polymethylmethacrylate) into the compressed vertebral body, with (kyphoplasty) or without (vertebroplasty) use of saline-infused balloon tamps that permit a few millimeters of elevation of the vertebral end plates. Initial randomized trials in patients with acute vertebral fractures were promising, but overall data have shown little or no benefit versus conservative treatment (i.e., pain management),[A26] even if the procedure is performed soon after the acute fracture.

Low-intensity vibration is diagnosed to enhance the development of osteoblasts and hinder the development of osteoclasts, thereby "coupling" bone remodeling. Early studies suggested a modest but significant benefit on bone mineral density, but overall data show no benefit on bone mineral density or bone turnover markers.[A27]

Male Osteoporosis

Male osteoporosis historically has been underrecognized and underappreciated, but more than 2 million men in the United States have osteoporosis, 1 in 4 men older than age 50 years will suffer a fragility fracture in their remaining lifetime, and about 30% of vertebral and hip fractures occur in men.[32] In addition, men have a substantially higher mortality after hip fracture compared with women. Aging, low body weight, and prior fragility fractures are independent predictors of future fracture in men, but common secondary causes include glucocorticoid use, alcohol overuse, hypogonadism, and lower production and circulating levels of estrogen.

Despite these risks, a DXA screening strategy is not recommended to identify men at higher risk for fracture, except perhaps in men who have a high prior probability of fracture.[33] The laboratory evaluation of male osteoporosis is similar to that for women, with the exception that fasting morning testosterone level should be obtained.

TREATMENT

The primary treatment of male osteoporosis is targeted at lifestyle changes, adequate nutrition (calcium and vitamin D), and exercise. Bisphosphonates (oral and intravenous), denosumab, and teriparatide are all effective at improving bone mineral density in men, although the antifracture efficacy of non-bisphosphonates in men is less clear,[A28] except for denosumab in men who have prostate cancer and are on androgen deprivation therapy (Chapter 186). Testosterone replacement in men with significant biochemical hypogonadism (total T score <200 ng/dL) improves bone density, although data on reducing the risk of fracture are lacking. In older men (age >50 years) at a substantial risk for fracture based on history and risk factors, androgen replacement should be considered second-line or adjunctive therapy after or with specific anti-osteoporosis therapies, based on overall risk-benefit and lack of antifracture efficacy data to date.

PROGNOSIS

The osteoporotic burden incurred by individual patients and society as a whole can be significantly lessened by a combination of diagnostic, preventive, and therapeutic interventions. Although osteoporosis cannot be cured, current pharmacotherapies that increase bone mineral density are associated with about a 50% reduced risk for subsequent fractures. Moreover, available data confirm a statistically significant reduction in death with pharmacologic treatment of osteoporosis. This reduction is critical because robust evidence suggests an independent increase in mortality after an osteoporotic fracture, including fractures of the spine, proximal femur, humerus, tibia, and pelvis. These data underscore the importance of identifying and treating patients with osteoporosis.

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For the General References and other additional features, please visit Elsevier eBooks+ at https://ebooks.health.elsevier.com.

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TABLE 226-1 CAUSES OF OSTEOMALACIA

VITAMIN D DEFICIENCY
Dietary deprivation and lack of solar exposure
VITAMIN D MALABSORPTION
Postgastrectomy Gastric bypass for obesity Gluten enteropathy Inflammatory bowel disease Pancreatic insufficiency Cholestyramine therapy Laxative abuse Phytates in some cereals and flatbreads
IMPAIRED 1-HYDROXYLATION OF 25-HYDROXYVITAMIN D
Chronic kidney disease X-linked hypophosphatemia Tumor-induced osteomalacia Vitamin D–dependent rickets type I
IMPAIRED TARGET-ORGAN RESPONSE TO 1,25-DIHYDROXYVITAMIN D
Vitamin D–dependent rickets type II
HYPOPHOSPHATEMIA
X-linked hypophosphatemia Autosomal dominant hypophosphatemic rickets and iron deficiency Tumor-induced osteomalacia Antacid-induced osteomalacia Chronic metabolic acidosis Fanconi syndrome Paraproteinemia Ferric carboxymaltose Tenofovir or adefovir Cadmium
INHIBITORS OF MINERALIZATION
Etidronate Fluoride Aluminum Iron Hypophosphatasia

226 OSTEOMALACIA AND RICKETS

ROBERT S. WEINSTEIN

DEFINITION

Rickets can no longer be considered a historical disorder limited to third world countries or poor people. The COVID-19 pandemic and the loss of school dairy products in the United States has increased malnutrition and vitamin D deficiency. The primary function of vitamin D is to provide adequate levels of calcium and phosphorus by increasing their intestinal absorption, thereby making them available for normal mineralization of bone and epiphyseal cartilage. Rickets, which occurs in growing children, affects both the cartilaginous growth plate and bone, where it causes characteristic deformities. Osteomalacia, which occurs after growth has ceased, has more subtle manifestations that are frequently overlooked.

Normal mineralization requires the availability of sufficient calcium and phosphorus, the presence of normal bone collagen, the absence of inhibitors of mineralization, and an adequate amount of bone alkaline phosphatase activity. Defects in these requirements are the cause of most forms of osteomalacia. Deficiency of vitamin D in isolation has traditionally been incriminated as the cause of the osteomalacia, but today, considerable evidence indicates that the abnormal mineralization associated with vitamin D deficiency is due to inadequate calcium and phosphorus rather than the absence of a direct effect of vitamin D on bone cells. Optimal therapy requires precise identification of the etiology of the abnormal mineralization (Table 226-1), and thereby is often gratifying.

EPIDEMIOLOGY

Nutritional rickets continues to be an evolving and multifactorial problem worldwide.[1,2] About 25% of women in the United States have 25-hydroxyvitamin D levels below 20 ng/mL (adequate values are greater than 30 ng/mL), and 8% have levels below 12 ng/mL, thereby indicating that impaired bone mineralization could be a confounding factor in the treatment of their osteoporosis and that osteomalacia (defective mineralization) rather than osteoporosis (reduced amount of normally mineralized bone) is the underlying problem.

Osteomalacia and vitamin D deficiency must be excluded before administration of the antiresorptive drugs used for postmenopausal osteoporosis (Chapter 225), particularly before the use of zoledronate or denosumab, which will induce hypocalcemia and secondary hyperparathyroidism if vitamin D levels are inadequate. Vitamin D deficiency is a particular problem in the nonaffluent elderly and individuals with self-imposed diets that avoid meat, dairy products, and fish. Vitamin D deficiency is also commonly found in medical inpatients and in postmenopausal women with an acute hip fracture. The prevalence of osteomalacia due to vitamin D deficiency varies; at greatest risk are incarcerated patients, patients with cystic fibrosis (Chapter 77), gastric bypass surgery (Chapter 201), or patients who have hyperparathyroidism (Chapter 227), that is actually secondary to vitamin D deficiency. Also at risk are individuals who live in chronic care facilities or who have nonhealing fractures.

X-linked hypophosphatemia, which is the most common inherited form of hypophosphatemic osteomalacia, has a prevalence of 1:20,000.

PATHOBIOLOGY

The abnormal mineralization characteristic of osteomalacia is due to slowed or terminated mineral deposition in the organic matrix of bone (osteoid) because of one or more of the defects mentioned earlier. However, osteoblasts continue to make osteoid, which then accumulates in excessive amounts. Histologically, the osteoid width may become dramatically augmented (Fig. 226-1). Depending on the extent of the mineralization delay, overt osteomalacia may take many years to develop. After normalization of the serum calcium and phosphorus levels, bone healing may take at least 6 to 18 months.

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Vitamin D–dependent rickets type II
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INHIBITORS OF MINERALIZATION
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226 OSTEOMALACIA AND RICKETS

ROBERT S. WEINSTEIN

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The abnormal mineralization characteristic of osteomalacia is due to slowed or terminated mineral deposition in the organic matrix of bone (osteoid) because of one or more of the defects mentioned earlier. However, osteoblasts continue to make osteoid, which then accumulates in excessive amounts. Histologically, the osteoid width may become dramatically augmented (Fig. 226-1). Depending on the extent of the mineralization delay, overt osteomalacia may take many years to develop. After normalization of the serum calcium and phosphorus levels, bone healing may take at least 6 to 18 months.

ABSTRACT

Rickets can no longer be considered a historical disorder limited to third world countries or poor people. The COVID-19 pandemic and the loss of school dairy products has increased malnutrition in the United States, and vitamin D deficiency is increasingly prevalent. The primary function of vitamin D is to provide adequate levels of calcium and phosphorus by increasing their intestinal absorption, thereby making them available for normal mineralization of bone and epiphyseal cartilage. Rickets occurs in growing children, and both the cartilaginous growth plate and bone are affected, thereby causing characteristic deformities. Osteomalacia, which occurs after growth has ceased, has more subtle manifestations that are frequently overlooked. Normal mineralization requires the availability of sufficient calcium and phosphorus, the presence of normal bone collagen, the absence of inhibitors of mineralization, and an adequate amount of bone alkaline phosphatase activity. Defects in these requirements are the cause of most forms of osteomalacia. Considerable evidence indicates that the abnormal mineralization associated with vitamin D deficiency is due to inadequate calcium and phosphorus rather than the absence of a direct effect of vitamin D on bone cells. After a correct diagnosis is made, therapy is often gratifying.

KEYWORDS

osteoid
25-hydroxyvitamin D
X-linked hypophosphatemia
autosomal dominant hypophosphatemic rickets
tumor-induced osteomalacia
vitamin D-dependent rickets
hypophosphatasia

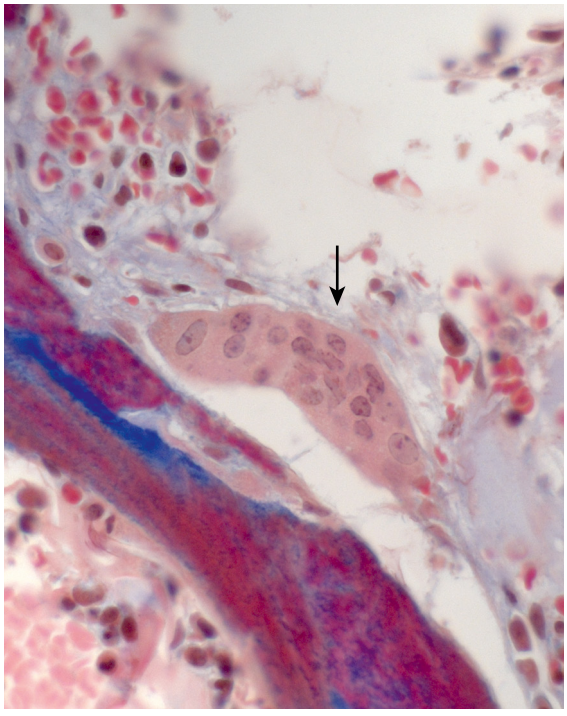

FIGURE 226-1. An undecalcified bone biopsy specimen shows the characteristic abundant osteoid and flattened osteoblasts of osteomalacia. The detached giant osteoclast (see *arrow*) containing more than 20 nuclei is a result of treating this patient with alendronate because of an incorrect diagnosis of osteoporosis. (Normally, mineralized bone appears blue and osteoid is carmine.)

X-linked hypophosphatemia, hypophosphatemic rickets, and tumor-induced osteomalacia are due to increased (or inappropriate for the low serum phosphate) serum fibroblast growth factor 23 (FGF-23) levels that cause excessive phosphaturia and inhibition of 25-hydroxyvitamin D-1α-hydroxylase. The hypophosphatemia is intensified by the inappropriately low levels of 1,25-dihydroxyvitamin D. Tumor-induced osteomalacia is a rare form of acquired, paraneoplastic, hypophosphatemic osteomalacia due to a small and often hard-to-find benign mesenchymal tumor (Chapter 187).[3]

Hypophosphatemic osteomalacia and fractures may occur after the administration of intravenous ferric carboxymaltose for refractory iron deficiency anemia. The hypophosphatemia may be detected within 1 week of the infusion, persist, and be accompanied by a two- to four-fold increase in FGF-23. This complication does not occur with administration of ferumoxytol.[4]

Osteomalacia also can be caused by inhibitors of mineralization such as etidronate (the first oral bisphosphonate, now rarely used in North America), high doses of fluoride (in bulk tea), the accumulation of a skeletal burden of aluminum from water used for dialysis (now rarely seen), iron overload as in thalassemia, and from high pyrophosphate levels in hypophosphatasia. Cholestyramine therapy for cholestasis or laxative abuse may also cause malabsorption and resistance to vitamin D supplements. Cadmium, tenofovir, or adefovir may induce Fanconi syndrome and cause osteomalacia due to the resultant hypophosphatemia.

Several presumed causes of osteomalacia (anticonvulsant drugs, metabolic acidosis without hypophosphatemia, pseudohypoparathyroidism, and chronic renal failure) have not demonstrated accumulation of osteoid due to delayed mineralization and primarily represent secondary hyperparathyroidism. Patients with the nephrotic syndrome lose albumin and vitamin D metabolites in the urine, but their serum ionized calcium and PTH levels are normal and metabolic bone disease in adults with the nephrotic syndrome is absent unless glucocorticoids have been administered.

CLINICAL MANIFESTATIONS

The clinical presentation of osteomalacia depends on three overlapping manifestations: those due to the underlying disorder such as gastrointestinal disease or surgery (especially troublesome are gastric resection, or gastric bypass for obesity [Chapter 201], celiac disease [Chapter 126], and intestinal malabsorption [Chapter 126]); those due to hypocalcemia or hypophosphatemia; and those directly due to the bone disease.

The most common symptoms and signs are pain in the pelvis and legs, muscle weakness, and bone tenderness. Bone pain is usually nonspecific and poorly localized. Because of the paucity of findings, the pains are often attributed to rheumatism or neurosis. Bone pain may be worse at night and after sudden movements, such as turning in bed or the change from sitting to standing.

The pain is worse on weight bearing, thereby resulting in a characteristic flat-footed, springless, waddling gait made worse by proximal muscle weakness. The gait has been referred to as "mother penguin's walk." Patients may complain that they can climb stairs only by pulling themselves up with the hand rail or rise from a chair or the toilet by using their hands to push off. The decrease in strength is usually far greater than the degree of muscle wasting.

Fasciculations are absent, and both reflexes and sensation remain normal. The bulbar, facial, and ocular muscles are always spared.

In X-linked hypophosphatemia, the family history is positive, and the typical presentation is short stature with lower extremity bowing. Muscle weakness is conspicuously mild or absent when the osteomalacia is due to X-linked hypophosphatemia.

Autosomal dominant hypophosphatemic rickets is characterized by a positive family history, spontaneous remissions, rather abrupt onset of profound fatigue and weakness, fractures, bone pain, and recurrent dental abscesses. This disorder may be triggered by iron deficiency from menorrhagia, nosebleeds, or pregnancy.

Hypocalcemia is usually mild to moderate but rarely can be severe enough to present with fingertip paresthesias, muscle cramps, or seizures, especially in patients with epilepsy. If the osteomalacia is mistaken for osteoporosis and treatment is started with a bisphosphonate or denosumab, the patient may experience new-onset paresthesias, muscle cramps, and palpitations. This not uncommon scenario occurs because the antiresorptive treatment interferes with the mobilization of calcium from bone by parathyroid hormone (PTH), thereby aggravating the hypocalcemia. The secondary hyperparathyroidism will also worsen the hypophosphatemia by the effect of PTH on renal excretion at the same time that intestinal absorption is impaired and mobilization from bone is blocked.

DIAGNOSIS

In osteomalacia, bone tenderness often can be elicited by rib cage compression or pressing on the tibiae, wrists, pubic rami, or iliac crests. If hypocalcemia is severe, patients may have a positive Chvostek (a facial twitch provoked by a gentle facial tap in front of the ear) or Trousseau sign (carpopedal spasm provoked by inflating a blood pressure cuff).

Biochemical changes depend on the stage of the disease and its etiology. In vitamin D deficiency, hypophosphatemia precedes and is more severe than the hypocalcemia because of the secondary hyperparathyroidism (Chapter 227) that usually accompanies the disorder by the time that osteomalacia has occurred. However, it remains unclear why some patients do not demonstrate increased PTH levels when severely vitamin D deficient. In malabsorption, hypomagnesemia may contribute to the hypocalcemia by impairing PTH secretion, and hypoalbuminemia may lead to a spurious diagnosis of hypocalcemia. Increased serum alkaline phosphatase activity is classically associated with osteomalacia due to vitamin D deficiency but usually is not an early clue. The serum 25-hydroxyvitamin D levels are often less than 10 to 15 ng/mL. In contrast, serum 1,25-dihydroxyvitamin D levels are usually elevated owing to the concomitant secondary hyperparathyroidism and usually do not contribute to the diagnosis of osteomalacia. However, in the rare autosomal recessive condition of a defective vitamin D receptor (vitamin D–dependent rickets type II), serum 1,25-dihydroxyvitamin D and PTH levels may be extraordinarily high (see Table 226-1). This condition is characterized by consanguinity, alopecia, and early-onset hypocalcemia. In another rare autosomal recessive disorder with defective 1α-hydroxylation of 25-hydroxyvitamin D (vitamin D–dependent rickets type I), serum 1,25-dihydroxyvitamin D levels may be undetectable. This disorder also is characterized by consanguinity and early-onset hypocalcemia. Quite a different pattern occurs with the inherited disease hypophosphatasia: serum 25-hydroxyvitamin D and calcium are normal, phosphorus is high-normal or slightly elevated, and alkaline phosphatase activity is below the normal age-matched range. This disease is caused by a deficiency of the tissue-nonspecific (liver, bone, and

FIGURE 226-2. Radiographic evidence of a pseudofracture of the femoral neck is suspicious for osteomalacia (*arrow*).

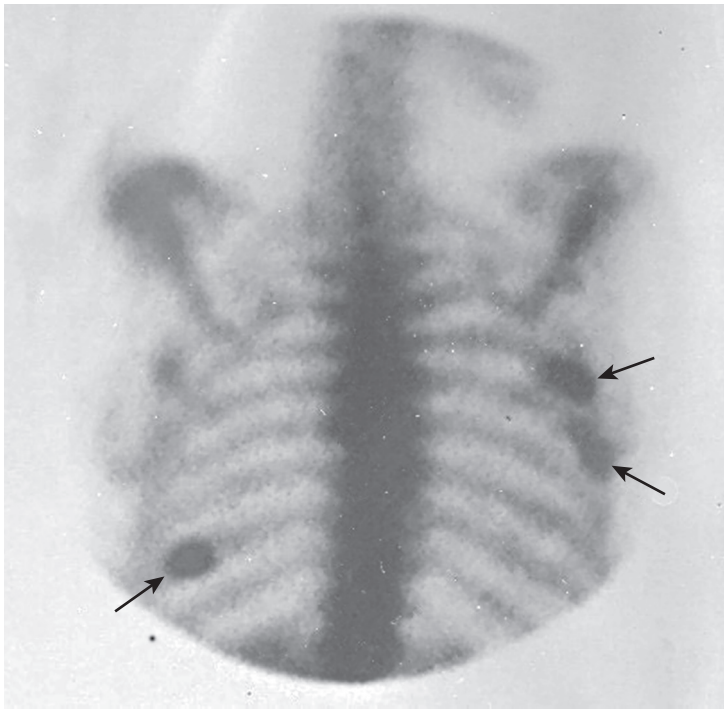

FIGURE 226-3. In osteomalacia, focal increased uptake of radionuclide on a bone scan may erroneously suggest metastatic disease (*arrows*).

kidney) isoenzyme of alkaline phosphatase, which normally prevents extracellular accumulation of inorganic pyrophosphate. If alkaline phosphatase activity is deficient and inorganic pyrophosphate collects adjacent to bone, mineralization is inhibited. The adult form hypophosphatasia may present with mild or severe osteomalacia (the prevalence is 1:100,000 to 300,000). Elevated serum vitamin B_6 is a useful marker if supplements are stopped for about 1 week before testing. Calcium pyrophosphate dihydrate crystal deposition disease (chondrocalcinosis [Chapter 252]) occurs in about 25% of affected patients.

Tumor-induced osteomalacia merits consideration in adults who present with hypophosphatemia, few or no deformities, and no family history of skeletal disease.[8] However, if the family history is vague or absent, autosomal dominant hypophosphatemic rickets can masquerade as tumor-induced osteomalacia, but serum FGF-23 levels are generally much higher in tumor-induced osteomalacia than in X-linked hypophosphatemia or autosomal dominant hypophosphatemic rickets. Included in the differential diagnosis is Fanconi syndrome, but in this disease, the hypophosphatemia is accompanied by hypokalemia, glycosuria, and hyperchloremic acidosis.

Radiology

In any form of osteomalacia, radiographic findings may be subtle or absent, and only blurred margins of the cancellous bone with thin cortices may be noted. The presence of bilaterally symmetrical, thin (2 to 3 mm) radiolucent bands known as pseudofractures (Fig. 226-2) found perpendicular to the periosteal surface in ribs, pubic and ischial rami, neck of the femur, metatarsals, and below the glenoid fossa on the outer border of the scapulae is generally considered to be pathognomonic of osteomalacia. However, this radiographic finding may be seen in disorders lacking excessive osteoid. Distinguishing features of pseudofractures in osteomalacia are the lack of callus or adjacent sclerosis and absence of an inciting event. Usually, there are at least two or three of these fractures with at least one in the rib, pubic rami, or femora, and biochemical clues (hypocalcemia and hypophosphatemia) are present. If what appears to be a pseudofracture is accompanied by normal levels of serum calcium, phosphorus, and alkaline phosphatase activity, osteomalacia is unlikely.

Pseudofractures show increased uptake on bone scans (Fig. 226-3) and may lead to an inappropriate search for a malignancy. Pseudofractures are typically located in the medial cortex of long bones and must be distinguished from atypical femoral fractures, which are located in the lateral cortex with cortical thickening and a cortical beak. Both may occur in patients receiving treatment with bisphosphonates. Subtrochanteric femoral pseudofractures also may occur in the lateral cortex in hypophosphatasia. In Paget disease (Chapter 228), cortical stress or fissure fractures may resemble pseudofractures but have a predilection for the anterior aspects of a bowed femur or tibia. In contrast to osteomalacia, the surrounding bone has a distinctly abnormal radiographic appearance. In osteomalacia, bone mineral density T-scores are often −3 or −4, with the radial diaphyseal density T-scores lower than those of the lumbar spine and total proximal femur. Bone mineral density examination of the radial diaphysis allows a unique view of non–weight bearing, appendicular, cortical bone and may be the first clue to vitamin D deficiency osteomalacia.

When the knees are involved and magnetic resonance imaging (MRI) reveals an increased T2 signal, osteomalacia can be mistaken for a stress fracture or spontaneous osteonecrosis of the knee. A check of the serum 25-hydroxyvitamin D and alkaline phosphatase levels will reveal the correct diagnosis.

The mesenchymal tumors that cause tumor-induced osteomalacia are best localized using Ga-68 DOTA-somatostatin receptor (SSTR) positron emission tomography/computed tomography (PET/CT).[6] The sensitivity of this approach for finding the offending tumor is about 85%.

Celiac Diseases

Iron deficiency anemia, hypocalcemia, weight loss, glossitis or rash, and bone discomfort in a patient with low bone mineral density point to malabsorption or celiac disease (Chapter 126), even without gastrointestinal symptoms. Patients also may have persistently low serum 25-hydroxyvitamin D levels despite high-dose vitamin D supplementation. This scenario suggests the need to test for antiendomysial immunoglobulin A and tissue transglutaminase antibodies.

Differential Diagnosis

Although characteristic clinical, radiographic, and biochemical findings may suggest osteomalacia, the absence of these findings cannot exclude the diagnosis. Bone biopsy is needed to establish the unequivocal presence of osteomalacia (see Fig. 226-1). However, bone biopsy is rarely necessary unless the patient has unusually painful disease or progressive loss of bone density and the results of the physical examination, radiographs, and biochemical findings are ambiguous. When biopsy is necessary, the best solution is to refer the patient to a bone histomorphometry center.

Unexplained elevations of the serum alkaline phosphatase activity (Chapter 133) are usually due to drugs (e.g., anticonvulsants, anabolic steroids, phenothiazines, or antibiotics) or Paget disease of bone (Chapter 228). These possibilities may be distinguished by measurement of the serum bone alkaline phosphatase by immunoassay, although there is up to 15 to 20% cross-reactivity with hepatic alkaline phosphatase. Isoenzyme determination by heat fractionation is not helpful. However, increased serum alkaline phosphatase activity is rarely the only biochemical clue to osteomalacia in a patient with skeletal discomfort. A nuclear medicine bone scan may be useful in difficult cases.

TREATMENT

The treatment of osteomalacia depends on its cause. Most osteomalacia is due to disorders of the absorption or metabolism of vitamin D or to chronic hypophosphatemia, and the remainder of cases are due to inhibitors of mineralization.

Osteomalacia Due to Vitamin D Disorders

Patients with severe disease require vitamin D and calcium supplementation.[7] A loading dose accelerates recovery and depends on the serum 25-hydroxyvitamin D level (Table 226-2). Although vitamin D_3 supplementation may be somewhat more potent than with D_2, the differences are not clinically important with the doses recommended for osteomalacia. The goal is to raise the serum 25-hydroxyvitamin D level to well above 30 ng/mL and reduce the elevated PTH concentration to normal without hypercalcemia or hypercalciuria. Pharmacologic doses of any vitamin D preparation carry the risk for vitamin D intoxication, so increases in the dose must be made carefully. However, the doses recommended in Table 226-2 will rarely result in serum 25-hydroxyvitamin D levels of 80 to 100 ng/mL, and vitamin D intoxication is unlikely even with levels of 150 ng/mL.

Approximately 1 to 1.5 g per day of oral elemental calcium is a reasonable initial dose depending on the degree of malabsorption (Table 226-3). Frequent small doses (three times a day) are more effective and tolerable than fewer larger ones, and the absorbability of calcium supplements is enhanced with meals. Urinary calcium excretion should be monitored after treatment has normalized the serum calcium level. The urinary calcium-to-creatinine ratio (mg/mg) should be kept below 0.22.

For malabsorption and celiac disease (Chapter 126), advice on nutrition and sun exposure, discontinuation of offending drugs, adherence to a gluten-free diet, and pancreatic enzyme replacement may cure the mineralization defect in some patients with mild celiac disease without the need for additional treatment. In patients with malabsorption, vitamin D requirements may rise during periods of increased diarrhea, and calcitriol may be easier for these patients to absorb. Its rapid onset of action and disappearance after cessation add to the safety of treatment, albeit at greater cost (see Table 226-2). Use of calcitriol requires great care to avoid hypercalcemia and hypercalciuria. Calcium, phosphorus, potassium, magnesium, and multivitamins also may be beneficial in patients with malabsorption (Table 226-4; see Table 226-3).

Rare patients do not tolerate any form of oral vitamin D, and the parenteral calciferol preparations available in North America are ineffective. These patients can be improved, although not restored to normal, by the use of weekly tanning bed treatments to areas of their bodies not normally exposed to the sun, with an attempt to minimize risk for solar-induced skin cancer (Chapter 188).

Calcitriol is the drug of choice in patients with vitamin D–dependent rickets type I. In patients with vitamin D–dependent rickets type II and diminished receptor sensitivity to 1,25-dihydroxyvitamin D, extraordinarily high doses of calcitriol may partially overcome the defect. If oral treatment fails, nocturnal infusions of calcium and phosphorus have been successful, thereby providing additional evidence that the osteomalacia is due to inadequate calcium and phosphorus rather than from the defect in vitamin D metabolism.

An increase in the serum alkaline phosphatase activity (the healing "flare") and a small increase in the serum and urine calcium levels are the earliest signs of effective treatment. Thereafter, the serum alkaline phosphatase activity level progressively falls as healing occurs. At the start of therapy, serum calcium levels should be measured every 2 to 3 weeks. If hypoalbuminemia is present, serum ionized calcium determinations or albumin-adjusted calcium values are useful. When therapy appears stabilized, repeat determinations at 6- to 8-week intervals are usually sufficient, but measurements should be at least three times a year even with long-term therapy. In some patients with severe osteomalacia, bone pain and paresthesias may increase and the serum calcium levels decrease during the first few weeks of therapy. This phenomenon is due to the increased skeletal avidity for mineral during healing and indicates the need for additional calcium supplementation.

Osteomalacia Due to Hypophosphatemia

Therapy of chronic hypophosphatemia is aimed at maintaining normal concentrations of serum phosphorus without inducing secondary hyperparathyroidism or hypercalciuria.[8] This considerably difficult task requires divided doses of phosphorus supplements and calcitriol to increase the absorption of phosphorus and calcium as well as to prevent the resultant increase in PTH. Regrettably, this regimen is often poorly tolerated, with side effects including diarrhea, secondary or tertiary hyperparathyroidism, nephrocalcinosis,

TABLE 226-2 VITAMIN D PREPARATIONS FOR TREATMENT OF OSTEOMALACIA

	VITAMIN D_2 (ERGOCALCIFEROL)	VITAMIN D_3 (CHOLECALCIFEROL)	CALCITRIOL† [1,25(OH)$_2$D$_3$]
Trade name	Drisdol and others*	Bio-Tech D3-50	Rocaltrol
Dosage form	Caps: 50,000 U = 1.25 mg	Caps: 50,000 U = 1.25 mg	Caps: 0.25 and 0.50 µg
Loading dosage:			
If 25(OH)D = 20-30 ng/mL	50,000 U once/wk for 10 wk‡ and once/mo thereafter (or 2000 U/day)	50,000 U once/wk for 10 wk‡ and once/mo thereafter (or 2000 U/day)	
If 25(OH)D = 10-20 ng/mL	50,000 U twice/wk for 10 wk‡ and twice/mo thereafter	50,000 U twice/wk for 10 wk‡ and twice/mo thereafter	
If 25(OH)D = <10 ng/mL	50,000 U three times/wk for 10 wk‡ and three times/mo thereafter	50,000 U three times/wk for 10 wk‡ and three times/mo thereafter	
Dosage in resistant cases	Up to 50,000 U/day	Up to 50,000 U/day	2-8 µg/day
Time to reach maximal effects	4-10 wk	4-10 wk	3-7 days
Persistence of effects after cessation	6-30 wk	6-30 wk	3-4 days
Cost	$203/100 gel caps Noncompliance may occur if the patient's insurance and pharmacy dispense only a 3-month supply and charge a large co-payment. These problems are avoided with Bio-Tech D3-50.	$28/100 capsules	$130/100 generic calcitriol capsules of 0.25 µg $200/100 generic calcitriol capsules of 0.5 µg $180/15 mL (1 µg/mL) generic calcitriol oral solution

*Gel caps are best because hard capsules may be indigestible and unreliable.

†Calcitriol is reserved for patients with persistent elevation of parathyroid hormone despite normalization of the serum 25-hydroxyvitamin D level. Hypercalcemia and hypercalciuria must be avoided.

‡If not >30 ng/mL after 10 weeks, exclude malabsorption, celiac disease, and noncompliance. Weekly tanning bed treatments may be used if oral vitamin therapy fails, or a switch to the more costly calcitriol may be necessary.

TABLE 226-3 CALCIUM PREPARATIONS FOR TREATMENT OF OSTEOMALACIA

PREPARATION	PERCENT ELEMENTAL CALCIUM	AMOUNT OF ELEMENTAL CALCIUM IN THE SUGGESTED DOSE	COST PER MONTH OF THERAPY
Calcium carbonate 600 mg tablets	40	4 tabs = 960 mg	$8
TUMS Ultra 1000 mg (chewable)	40	2 tabs = 800 mg	$8
Citracal Slow Release 1200 mg (85% calcium carbonate and 15% calcium citrate) plus 1000 units vitamin D		4 tabs = 892 mg	$9
Viactiv Chews (chocolate, caramel, or mocha) 650 mg calcium and 500 units vitamin D		2 chews = 1300 mg	$10

TABLE 226-4 PHOSPHATE PREPARATIONS FOR TREATMENT OF OSTEOMALACIA

PREPARATION	PHOSPORUS CONTENT (mg/cap or tab)	SODIUM CONTENT (mEq/cap or tab)	POTASSIUM CONTENT (mEq/cap or tab)	AMOUNT THAT CONTAINS 1 G OF ELEMENTAL PHOSPHORUS	COST
Neutra-Phos	250	7	7	4 unit dose caps*	
Phos-NaK	250	7	7	4 packets*	$39/100 packets
Neutra-Phos-K	250	0	14	4 unit dose caps*	
K-Phos Neutral	250	13	1.1	4 tabs	$72/100 tablets
K-Phos Original	114	0	3.7	9 tabs	$52/100 tablets
Phospha 250 Neutral	250	13	1.1	4 tabs	$91/100 tablets
K-Phos No 2	250	5.8	2.3	4 tabs	$99/100 tablets

*Each unit dose cap is reconstituted with at least 75 mL of water, fruit juice, or cola. The unit dose cap or packet contains the powder concentrate and is not to be swallowed undiluted. The powder preparations cost less and may be the only phosphate preparation covered by some insurance plans.

or nephrolithiasis. Therefore, a calcitriol-alone regimen should be first using about 0.25 to 0.5 µg of calcitriol once or twice daily while monitoring for hypercalciuria. Phosphate supplements (no more than 250 mg of elemental phosphorus four times daily and advanced slowly with repeat levels within 3 to 4 weeks) should be delayed until calcitriol alone has been used for several weeks without significantly increasing the serum phosphorus. If the serum phosphorus level has not changed or decreased and the PTH level has increased, the calcitriol dose rather than the phosphorus dose should be advanced to avoid secondary hyperparathyroidism (Chapter 227). Baseline and yearly renal ultrasound examinations are necessary to assess early nephrocalcinosis or nephrolithiasis. Burosumab is an FGF-23 antibody that can sustain normal levels of serum phosphorus far more effectively than treatment with phosphate and calcitriol. However, its high price generally restricts insurance coverage to patients who have genetic verification of X-linked hypophosphatemia and have failed to normalize their serum phosphorus levels with calcitriol and phosphate without developing hypercalciuria. Burosumab (1 mg/kg up to 90mg injected subcutaneously every 4 weeks with monitoring of the phosphorus and calcium levels two weeks after injection for the first few months) increases healing of fractures and improves exercise capacity, often with resultant weight loss.[A1] Treatment is lifelong. Restless leg syndrome is a possible adverse effect.

In hypophosphatasia, treatment with teriparatide (20 µg every other day) can increase bone density and repair of fractures.[9] Bone-targeted enzyme replacement therapy (asfotase alfa; 2 mg/kg three times a week) is also effective,[10] but its very high price generally restricts insurance coverage to patients with juvenile onset disease and failure to increase alkaline phosphatase activity with teriparatide.

Surveillance is required for injection site reactions and corneal calcifications. General measures remain important and include routine nutritional advice and avoidance of further bone loss due to vitamin D deficiency. High-dose vitamin D therapy in hypophosphatasia can cause nephrocalcinosis, nephrolithiasis, and renal insufficiency and should be avoided.

Tumor-induced osteomalacia can be treated with phosphorus supplementation and calcitriol, but burosumab (usually 1 mg/kg up to 90 mg subcutaneously every 4 weeks) restores phosphorus homeostasis and ambulatory status more efficiently and is recommended, despite its price, when phosphorus and calcitriol are insufficient.[11,12] Complete resection of the tumor results in cure of the osteomalacia, but offending tumors can be hard to find and difficult to remove completely.

PREVENTION

Nutritional rickets and osteomalacia are common in dark-skinned and migrant populations, and their global incidence is rising because of changing population demographics, failing prevention policies, and inadequate implementation strategies. High-risk populations require lifelong supplementation and food fortification with vitamin D or calcium. Advice about vitamin D supplementation should help to prevent osteomalacia caused by vitamin D deficiency, but routine over-the-counter supplements may be insufficient or ineffective, and compliance with nutritional supplements is poor. The optimal vitamin D supplementation dosage is not clear, but most bone and mineral problems are avoided by 50,000 U of cholecalciferol given once monthly (or, 1600 to 2000 U/day). Notable exceptions occur in patients who have celiac disease or who have had gastric surgery or bypass for obesity; these patients often require much higher doses (see Table 226-2). In patients with osteomalacia due to hypophosphatemia, the need for phosphorus supplementation may be lifelong (see Table 226-4).

PROGNOSIS

The response to appropriate treatment in most forms of osteomalacia is usually excellent. Improvements in bone pain and muscle weakness usually occur within 2 or 3 months, and skeletal lesions usually heal within 6 to 18 months. Depending on the quantity of excess osteoid, repeat bone mineral density determinations may show as much as 20% gains at the lumbar spine and total proximal femur. However, bone density at the radial diaphysis may not improve owing to the irreversible loss of cortical bone resulting from prolonged secondary hyperparathyroidism.

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Grade A **Grade A Reference**

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227 THE PARATHYROID GLANDS, HYPERCALCEMIA, AND HYPOCALCEMIA

RAJESH V. THAKKER

CALCIUM METABOLISM

A healthy adult body has a total of 1 kg of calcium, about 99% of which is within the crystal structure of bone mineral and less than 1% of which is in soluble form in the extracellular and intracellular fluid compartments. In the extracellular fluid compartment, about half of the total calcium is ionized, and the remainder is principally bound to albumin or complexed with counter-ions. Ionized calcium in the extracellular fluid plays an important role in many physiologic pathways, including muscle contraction, secretion of neurotransmitters and hormones, and coagulation pathways. The total serum calcium concentration ranges from 8.5 to 10.5 mg/dL (2.12 to 2.62 mmol/L), whereas ionized serum calcium concentrations range from 4.65 to 5.25 mg/dL (1.16 to 1.31 mmol/L).[1] However, the usual 2 : 1 ratio of total to ionized calcium may be disturbed by disorders such as metabolic acidosis (Chapter 104), which reduces calcium binding by proteins, or by changes in protein concentration, caused by cirrhosis (Chapter 139), dehydration, venous stasis (Chapter 68), or multiple myeloma (Chapter 167). As a result, the total serum calcium concentrations may need to be adjusted, or "corrected," to a reference albumin concentration by adding or subtracting 0.8 mg/dL (0.016 mmol/L) for every 1 g/dL (1 g/L) of albumin below or above the reference albumin concentration of 4 g/dL.

The control of body calcium involves a balance between the amounts that are absorbed from the gut, deposited into bone and into cells, and excreted from the kidney (Fig. 227-1). This fine balance, which involves three organs, is chiefly under the control of parathyroid hormone (PTH), which is synthesized and secreted by the parathyroid glands. Hypocalcemia leads to an increased secretion of PTH, whereas hypercalcemia results in diminished secretion of PTH. Regulation of extracellular calcium takes place through complex interactions (E-Fig. 227-1) at the target organs of the major calcium-regulating hormone, PTH, and vitamin D and its active metabolites, 1,25-dihydroxyvitamin D ($1,25[OH]_2D$), which is also referred to as calcitriol.[2]

PARATHYROID GLANDS AND PARATHYROID HORMONE

Humans usually have four parathyroid glands, which are located in close proximity to the superior and inferior poles of the lobes of the thyroid gland. The superior parathyroids are derived from the endoderm of the embryonic fourth pharyngeal pouches, and the inferior parathyroids are derived with the thymus from the endoderm of the third pharyngeal pouches. Extra parathyroid glands, which may be present in 3 to 5% of the population, are commonly found in aberrant locations along this migrating path and also within the thymus and thyroid.

Parathyroid cells express a G protein–coupled receptor (GPCR), referred to as the calcium-sensing receptor, that detects changes in extracellular calcium and leads to alterations in the secretions of PTH.[3] For example, activation of the calcium-sensing receptor, which is also expressed in renal tubular cells as a result of elevated extracellular calcium concentrations, causes G protein–dependent stimulation of phospholipase C activity, which in turn leads to accumulation of inositol 1,4,5-trisphosphate and an increase in intracellular calcium concentrations. These changes then lead to reduced circulating concentrations of PTH and increased urinary excretion of calcium. Disorders of the parathyroid glands may cause hypercalcemia or hypocalcemia, which can be classified according to whether they arise from an excess of PTH, its deficiency, or insensitivity to its effects (Table 227-1; see E-Fig. 227-1).

In chronic renal insufficiency, uremia (Chapter 116) with low serum calcium levels and elevations in serum phosphate levels, secretion of PTH increases. This physiologic secondary hyperparathyroidism in response to hypocalcemia can progress to become an independent parathyroid adenoma—defined as tertiary hyperparathyroidism (see Chronic Hyperparathyroidism).

Parathyroid Hormone and *PTH* Gene

PTH is an 84–amino acid peptide encoded by the *PTH* gene, which is located on chromosome 11p15. The mature PTH peptide is secreted from

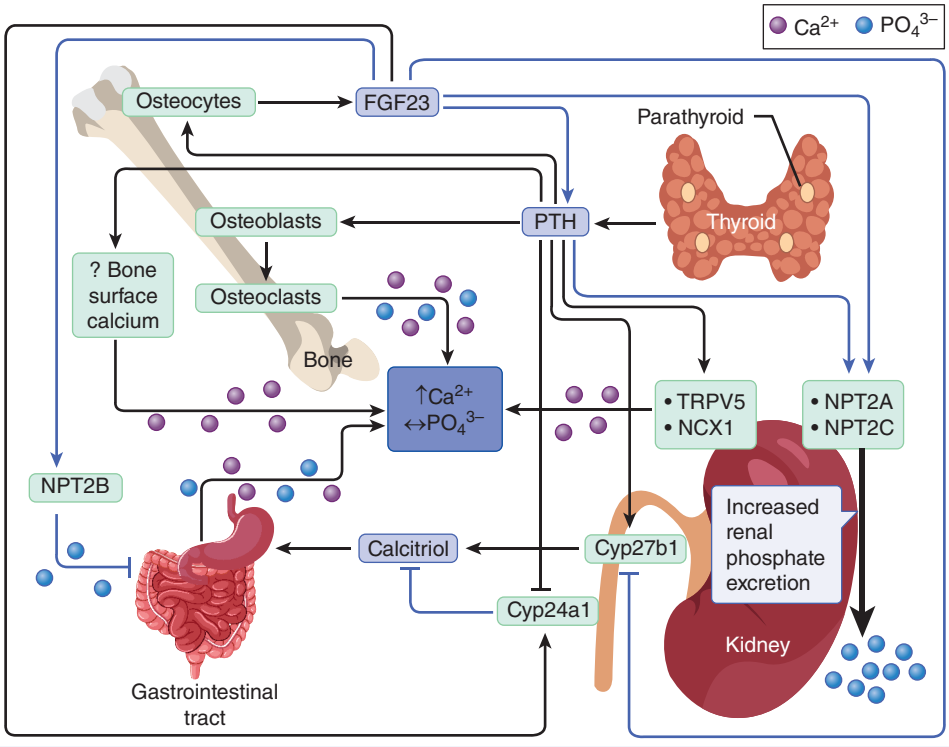

FIGURE 227-1. Regulation of calcium and phosphate economy and bone mass. The secretion of parathyroid hormone (PTH) from the parathyroid glands increases in response to low serum concentrations of calcium (Ca^{2+}). Within bone cells, PTH stimulates osteoblasts to form bone, indirectly stimulates osteoclasts to resorb bone and bring calcium and phosphate (PO_4^{3-}) into the circulation, and acts on osteocytes to stimulate the release of fibroblast growth factor 23 (FGF23). Within kidney tubules, PTH increases reabsorption of calcium and renal excretion of phosphate, and FGF23 also stimulates renal phosphate excretion. FGF23 acts indirectly on the intestines by controlling the level of calcitriol, but might also have direct actions to regulate the expression of the sodium-phosphate co-transporter 2b (NPT2B). Within intestines, calcitriol increases intestinal calcium and phosphate absorption. The integration of these regulators includes that PTH increases the release of FGF23 and increases calcitriol levels, whereas FGF23 has opposing effects to inhibit PTH and decrease calcitriol. The central, *dark-blue box* indicates the circulating or blood concentrations of calcium and phosphate. The *question mark* indicates an unclear process. *Black arrows* indicate pathways with net stimulatory actions whereas *blue arrows* are pathways with net inhibitory action. *Flat arrowheads* indicate inhibitory actions. (Reproduced with permission from Arnold A, Dennison E, Kovacs CS, et al. Hormonal regulation of biomineralization. *Nat Rev Endocrinol*. 2021;17:261-275.)

ABSTRACT

Calcium plays an important role in many physiologic pathways that include muscle contraction, the secretion of neurotransmitters and hormones, and coagulation. The control of body calcium involves a balance between the amounts that are absorbed from the gut, deposited into bone and cells, and excreted from the kidney. This fine balance, involving all these organs, is chiefly under the control of parathyroid hormone (PTH), which is synthesized and secreted by the parathyroid glands. Thus, hypocalcemia will lead to an increased secretion of PTH, whereas hypercalcemia will result in diminished secretion of PTH. Oversecretion of PTH due to parathyroid tumors is a major cause of hypercalcemia, which may be associated with kidney stones, osteoporosis, and peptic ulcers. PTH deficiency, which results in hypocalcemia, may be associated with epilepsy, tetany, cataracts, skeletal malformations, and abnormal dentition. This chapter reviews the genetic basis for disorders of calcium metabolism, the physiologic and biochemical mechanisms underlying extracellular calcium homeostasis, the clinical features of hypercalcemia and hypocalcemia, and the clinical disorders associated with abnormal calcium homeostasis, as well as the management of hypercalcemia and hypocalcemia.

KEYWORDS

parathyroid hormone
vitamin D
hypercalcemia
hypocalcemia
calcium
parathyroid tumors
congenital anomalies

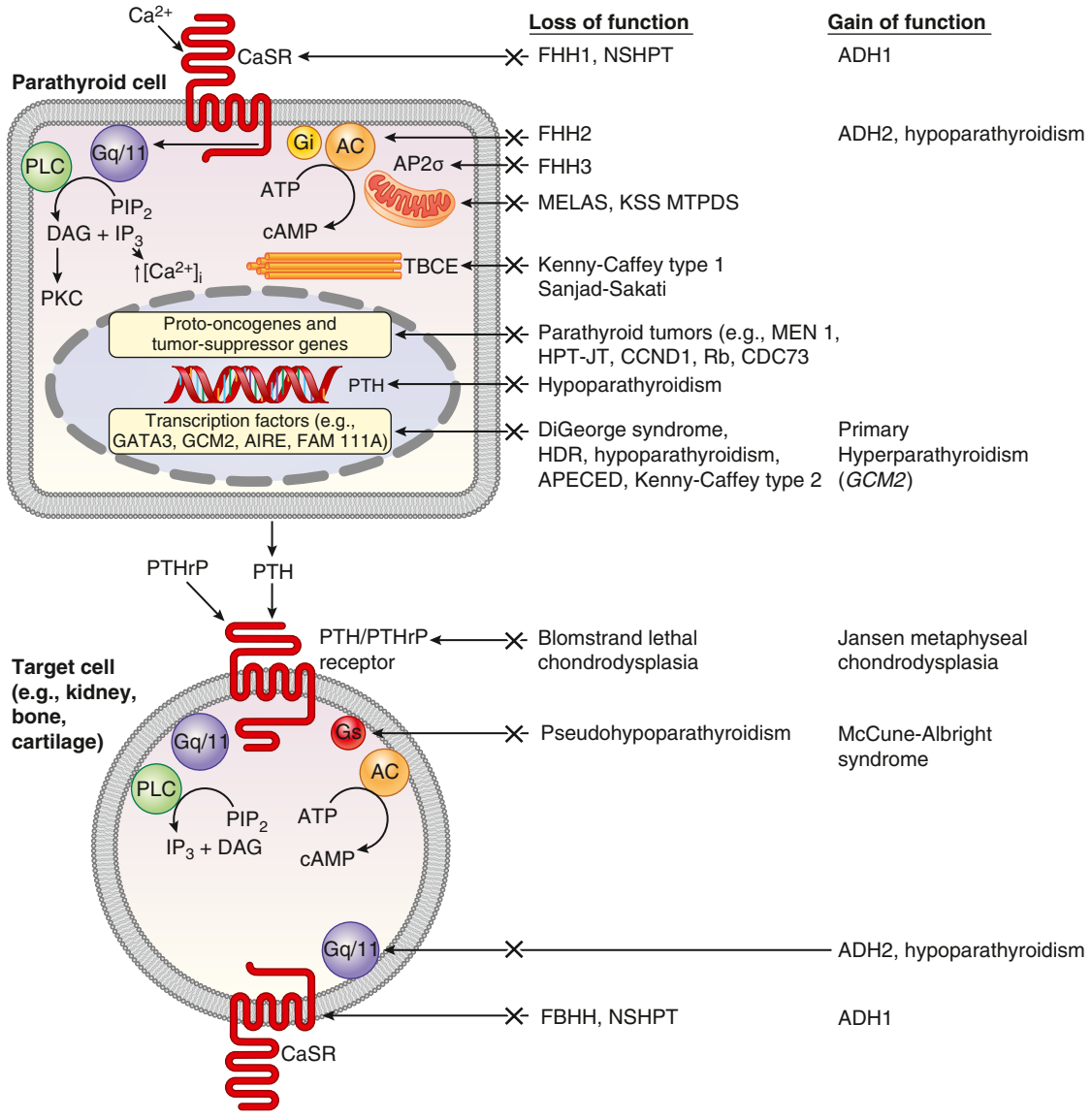

E-FIGURE 227-1. Schematic representation of some of the components involved in calcium homeostasis. Alterations in extracellular calcium are detected by the calcium-sensing receptor (CaSR), which is a 1078–amino acid G protein–coupled receptor. The PTH/PTHrP receptor, which mediates the actions of PTH and PTHrP, is also a G protein–coupled receptor. Thus, Ca^{2+}, PTH, and PTHrP involve G protein–coupled signaling pathways, and interaction with their specific receptors can lead to activation of Gs, Gi, and Gq/α11, respectively. Gs stimulates adenylcyclase (AC), which catalyzes the formation of cyclic adenosine monophosphate (cAMP) from adenosine triphosphate (ATP). Gi inhibits AC activity. cAMP stimulates protein kinase A (PKA), which phosphorylates cell-specific substrates. Activation of Gq/α11 stimulates phospholipase C (PLC), which catalyzes the hydrolysis of the phosphoinositide (PIP_2) to inositol triphosphate (IP_3), which then increases intracellular calcium, and diacylglycerol (DAG), activating protein kinase C (PKC). These proximal signals modulate downstream pathways, which result in specific physiologic effects. Loss- and gain-of-function mutations in several genes, shown with their respective sites of action on the right, have been identified in specific disorders of calcium homeostasis (also see Table 227-1). (From Thakker RV, Bringhurst FR, Jüppner H. Regulation of calcium homeostasis and genetic disorders that affect calcium metabolism. In: Jameson JL, De Groot LJ, Giudice LC, et al., eds. *Endocrinology: Adult & Pediatric*. 7th ed. Philadelphia: Saunders; 2016.)

TABLE 227-1 PARATHYROID DISEASES AND THEIR CHROMOSOMAL LOCATIONS

METABOLIC ABNORMALITY	DISEASE	INHERITANCE	GENE/GENE PRODUCT	CHROMOSOMAL LOCATION
HYPERCALCEMIA				
	Multiple endocrine neoplasia type 1	Autosomal dominant	Menin	11q13
	Multiple endocrine neoplasia types 2 and 3	Autosomal dominant	*RET*	10q11.2
	Multiple endocrine neoplasia type 4	Autosomal dominant	*CDNK1B*	12p13.1
	Hereditary hyperparathyroidism and jaw tumors (HPT-JT)	Autosomal dominant	*CDC73* Parafibromin	1q31.2
	Familial isolated hyperparathyroidism	Autosomal dominant	Menin, *CDC73, CaSR* *GCM2*	11q13, 1q31.2, 3q21.1, 6p24.2
	Sporadic hyperparathyroidism	Sporadic	*PRAD1/CCND1, PTH* Retinoblastoma Unknown	11q13, 11p15 13q14 1p32-pter
	Parathyroid carcinoma	Autosomal dominant or sporadic	Parafibromin Retinoblastoma	1q31.2 13q14
	Familial benign hypercalcemia (FBH)			
	FBH1	Autosomal dominant	*CaSR*	3q 21.1
	FBH2	Autosomal dominant	Gα11	19p13
	FBH3	Autosomal dominant	*AP2S1*	19q13
	Neonatal severe hyperparathyroidism (NSHPT)	Autosomal recessive or autosomal dominant	*CaSR*	3q21.1
	Jansen disease	Autosomal dominant	PTHR/PTHrP receptor	3p21.3
	Williams syndrome	Autosomal dominant	*Elastin, LIMK* (and other genes)	7q11.23
	Infantile hypercalcemia	Autosomal recessive	*CYP24A1, SLC34A1*	20q13.2-q13.3, *5q35*
	McCune-Albright syndrome	Mutations during early embryonic development?	Gsα	20q13.3
HYPOCALCEMIA				
	Isolated hypoparathyroidism	Autosomal dominant Autosomal recessive X-linked recessive	*PTH, GCM2* *PTH, GCM2* *SOX3*	11p15*11p15*, 6p24.2Xq26–27
	Autosomal dominant hypocalcemia type 1 (ADH1)	Autosomal dominant	*CaSR*	3q21.1
	Autosomal dominant hypocalcemia type 2 (ADH2)	Autosomal dominant	Gα11	19p13
	Hypoparathyroidism associated with polyglandular autoimmune syndrome (APECED)	Autosomal recessive	*AIRE-1*	21q22.3
	Hypoparathyroidism associated with Kearns-Sayre and MELAS	Maternal	Mitochondrial genome	
	Hypoparathyroidism associated with complex congenital syndromes			
	DiGeorge syndrome type 1	Autosomal dominant	*TBX1*	22q11.2
	DiGeorge syndrome type 2	Autosomal dominant	*NEBL*	10p14.p13
	CHARGE	Autosomal dominant	*CHD7, SEMA3E*	8q12.1-12.2, 7q21.11
	HDR syndrome	Autosomal dominant	*GATA3*	10p15
	Blomstrand lethal chondrodysplasia	Autosomal recessive	PTHR/PTHrP receptor	3p21.3
	Kenney-Caffey syndrome type 1, Sanjad-Sakati syndrome	Autosomal dominant	*TBCE*	1q42.3
	Kenney-Caffey syndrome type 2	Autosomal recessive	*FAMIIIA*	11q12.1
	Barakat syndrome	Autosomal recessive†	Unknown	?
	Lymphedema	Autosomal recessive	Unknown	?
	Nephropathy, nerve deafness	Autosomal dominant†	Unknown	?
	Nerve deafness without renal dysplasia	Autosomal dominant	Unknown?	?
	Pseudohypoparathyroidism (type 1a)	Autosomal dominant parentally imprinted	*GNAS exons 1-3*	20q13.3
	Pseudohypoparathyroidism (type 1b)	Autosomal dominant parentally imprinted	*GNAS* Upstream deletion	20q13.3
	Acrodysostosis with hormonal resistance	Autosomal dominant	*PRKAR1A*	17q23-24

*Mutations of PTH gene are identified only in some families.
†Most likely inheritance.
CHARGE = coloboma-heart anomaly atresia-retardation-genital-ear; HDR = hypoparathyroidism, deafness, and renal dysplasia; MELAS = mitochondrial encephalopathy, stroke-like episodes, and lactic acidosis; ? = location not known.

the parathyroid chief cells as an 84–amino acid peptide; however, when the *PTH* mRNA is first translated, it is as pre-proPTH peptide. The "pre" sequence consists of a 25–amino acid signal peptide (leader sequence) that is responsible for directing the nascent peptide into the endoplasmic reticulum to be packaged for secretion from the cell. The "pro" sequence is 6 amino acids in length and is also essential for correct processing and secretion of PTH. After the 84–amino acid mature PTH peptide is secreted from the parathyroid cell, it is cleared from the circulation by nonsaturable hepatic uptake and renal excretion, with a short half-life of about 2 minutes.

Actions of Parathyroid Hormone

PTH and PTH-related peptide (PTHrP) share a GPCR (see E-Fig. 227-1), which predominantly is expressed in kidney and bone, where it enhances renal calcium reabsorption, releases stored calcium from bones into the extracellular fluid, and also acts indirectly on intestinal cells (see later) to increase calcium absorption in the gut. Expression of the PTH/PTHrP receptor also occurs in the brain, heart, skin, lung, liver, and testis, where it mediates the actions of PTHrP. Mutations involving the genes that encode these proteins and receptors in this calcium-regulating pathway (see E-Fig. 227-1) are associated with hypercalcemic and hypocalcemic disorders (see Table 227-1).

Renal Actions

Calcium is absorbed by the kidneys at multiple sites along the renal tubule and by different mechanisms, including passive paracellular or active transcellular transport. The renal actions of PTH are to: stimulate activity of the proximal tubular cell 1α-hydroxylase; increase reabsorption of calcium by the cells of the distal tubule, connecting tubules, and the thick ascending loop of Henle; and inhibit phosphate reabsorption by proximal tubular cells (see Fig. 227-1). PTH increases the formation of biologically active $1,25(OH)_2D$ from its precursor 25-OH-D by stimulating the activity of the renal 1α-hydroxylase and inhibiting the 24-hydroxylase, which metabolizes $1,25(OH)_2D$ to the inactive $24,25(OH)_2D$ form (see Fig. 227-1). PTH regulates calcium reabsorption by distal tubular cells by upregulating expression of the transient receptor potential vanilloid 5 (TRPV5), thereby promoting calcium entry into the cell and increasing calbindin-D28K expression to enhance transcellular calcium reabsorption by increased buffering of subapical Ca^{2+} ions. In the thick ascending loop of Henle, PTH may increase the active transcellular transport of calcium and the paracellular transport of calcium by augmenting the transepithelial voltage gradient. Phosphate transport in proximal tubular cells is mediated by the luminal membrane sodium-phosphate cotransporters 2a and 2c (NPT2a and NPT2c), and PTH actions lead to internalization and degradation of NPT2a and NPT2c, thereby resulting in decreased reabsorption of phosphate.

Skeletal Actions

PTH acts directly on osteoblasts and indirectly on osteoclasts to increase their numbers and activity, thereby enhancing bone turnover and the release of stored calcium. PTH increases the size of the osteoblast precursor pool, increases the bone-forming activity of mature osteoblasts, and stimulates osteoblasts to release cytokines such as colony-stimulating factor 1 and receptor activator of nuclear factor-κB (NF-κB) ligand (RANKL), which stimulate the formation of new osteoclasts and activate mature osteoclasts. PTH also inhibits the production of osteoprotegerin, which is a decoy receptor that binds to RANKL and thereby inhibits the development of osteoblasts. The net result of persistent elevations of PTH is an increase in osteoclast activity more than osteoblast activity, thereby liberating the stores of calcium from bone into the extracellular fluid (see Fig. 227-1).

Intestinal Actions

Calcium is absorbed throughout the intestine by passive paracellular routes and active transcellular routes. PTH exerts indirect actions on intestinal calcium absorption by increasing the circulating $1,25(OH)_2D$ concentrations (see Fig. 227-1). The increased $1,25(OH)_2D$ concentrations facilitate enhanced calcium entry into the cell from the lumen, thereby facilitating transcellular transport of calcium.

HYPERCALCEMIA

DEFINITION

Hypercalcemia is defined as a serum calcium concentration greater than 2 standard deviations above the normal mean, which is usually a total serum calcium above 10.5 mg/dL (2.62 mmol/L) and an ionized serum calcium of above 5.25 mg/dL (1.31 mmol/L). No formal grading system defines the severity of hypercalcemia, but mild, moderate, and severe hypercalcemia are generally considered for total serum calcium concentrations less than 12 mg/dL (3 mmol/L), between 12 and 14 mg/dL (3 to 3.5 mmol/L), and greater than 14 mg/dL (3.50 mmol/L), respectively.

EPIDEMIOLOGY

The prevalence of hypercalcemia has been reported as 1% to 2% in the general population and about 2 to 5% in hospitalized patients.

PATHOBIOLOGY

Hypercalcemia may arise through one of three mechanisms: increased bone resorption, increased gastrointestinal absorption of calcium, and decreased renal calcium excretion (see Fig. 227-1). For example, lytic bone metastases cause increased bone resorption; thiazide diuretics lead to a decrease in calcium excretion; and excessive PTH will either directly or indirectly increase the production of $1,25(OH)_2D$ and stimulate bone resorption and calcium absorption from the gut and renal tubules. The causes of hypercalcemia may be classified according to whether serum PTH concentrations are elevated (i.e., primary or tertiary hyperparathyroidism due to parathyroid tumors) or reduced (i.e., not due to parathyroid tumors but instead to an excessive production of PTHrP by lytic bone metastases, multiple myeloma, drugs, or an altered set point in the calcium-sensing receptor[4]; see E-Fig. 227-1). In secondary hyperparathyroidism, by comparison, PTH levels are increased in response to a low serum calcium level (usually due to chronic renal failure or vitamin D deficiency) and, by definition, the patient cannot have hypercalcemia.

TABLE 227-2 CLINICAL FEATURES OF HYPERCALCEMIA

Renal
Stones (nephrolithiasis) and nephrocalcinosis, polyuria, polydipsia
Musculoskeletal
Bone pain, osteopenia, fractures, muscular weakness, especially proximal myopathy
Gastrointestinal
Nausea, vomiting, lack of appetite, constipation, peptic ulcers, and pancreatitis
Neurologic
Tiredness, lethargy, inability to concentrate, increased sleepiness, depression, confusion, coma
Cardiac
Bradycardia, first-degree atrioventricular block, arrhythmias, shortened QT interval

CLINICAL MANIFESTATIONS

In developed countries, the clinical presentation of hypercalcemia is most commonly as an asymptomatic, biochemical abnormality detected during routine screening. However, it also can present as a life-threatening medical emergency, especially in developing countries and in patients with cancer (Chapter 164). In general, the presence or absence of symptoms correlates with the severity of the hypercalcemia. Symptoms do not usually develop when serum calcium is below 12 mg/dL (3 mmol/L) and are nearly invariably present when the hypercalcemia exceeds 14 mg/dL (3.5 mmol/L). However, there is considerable variability, in part dependent on the rapidity of onset of mild to moderate hypercalcemia. The signs and symptoms of hypercalcemia (Table 227-2) are similar, regardless of etiology. The clinical manifestations can involve the renal, musculoskeletal, gastrointestinal, neurologic, and cardiac systems, and many of these have been referred to as "moans, groans, pains, and stones."

DIAGNOSIS

Investigations should be directed at confirming the presence of hypercalcemia and establishing the cause (Fig. 227-2). Hypercalcemia can be caused by a number of conditions (Table 227-3, and a careful initial evaluation (Table 227-4) is key. Primary hyperparathyroidism and malignancy, which are the most common causes,[5] account for more than 90% of patients with hypercalcemia. Detailed clinical history and examination will usually help to differentiate between these two diagnoses. In primary hyperparathyroidism, the hypercalcemia is often less than 12 mg/dL (3 mmol/L), asymptomatic, and may have been present for months or years. If symptoms, such as nephrolithiasis (Chapter 111), are noted, then hypercalcemia usually has been present for at least several months. In malignancy, however, patients are usually acutely ill, often with neurologic symptoms; the hypercalcemia is more than 12 mg/dL (3 mmol/L), and the cancer (e.g., lung, breast, or myeloma) is often readily apparent. If bone metastases or chronic renal failure are the cause, the serum phosphate level is typically elevated, whereas it is normal or low when the PTH level is elevated. Hypercalcemia from other causes is usually suggested by a careful history (e.g., for vitamin D ingestion, drugs, renal disease) and physical examination (e.g., for thyrotoxicosis, adrenal disease, granulomatous diseases). However, appropriate laboratory investigations (see Table 227-4 and Fig. 227-2), are essential for establishing the diagnosis.[6]

TREATMENT

The treatment of hypercalcemia depends on the severity of the hypercalcemia and the presence of symptoms. Asymptomatic patients with mild hypercalcemia do not usually need urgent treatment, patients with severe hypercalcemia require treatment regardless of symptoms, and patients with moderate hypercalcemia require urgent treatment if symptomatic.

Before instituting treatment, it is always important to consider the underlying causes (see Table 227-3) and to initiate investigations (see Table 227-4). In addition, drugs such as thiazides and vitamin D compounds, which cause hypercalcemia, should be discontinued and dietary calcium intake should be restricted.

Symptomatic Hypercalcemia

Dehydration owing to hypercalcemic symptoms (e.g., anorexia, nausea, vomiting, and polyuria because of defective urinary concentration) is very common, so the acute management of symptomatic hypercalcemia involves hydration and calcium diuresis, as well as specific measures using drugs to lower the serum calcium level. Saline, which enhances urinary calcium excretion by increasing glomerular filtration and reducing the proximal and distal renal tubular reabsorption of calcium and sodium, is given as required (5 to 10 L of 0.9% sodium

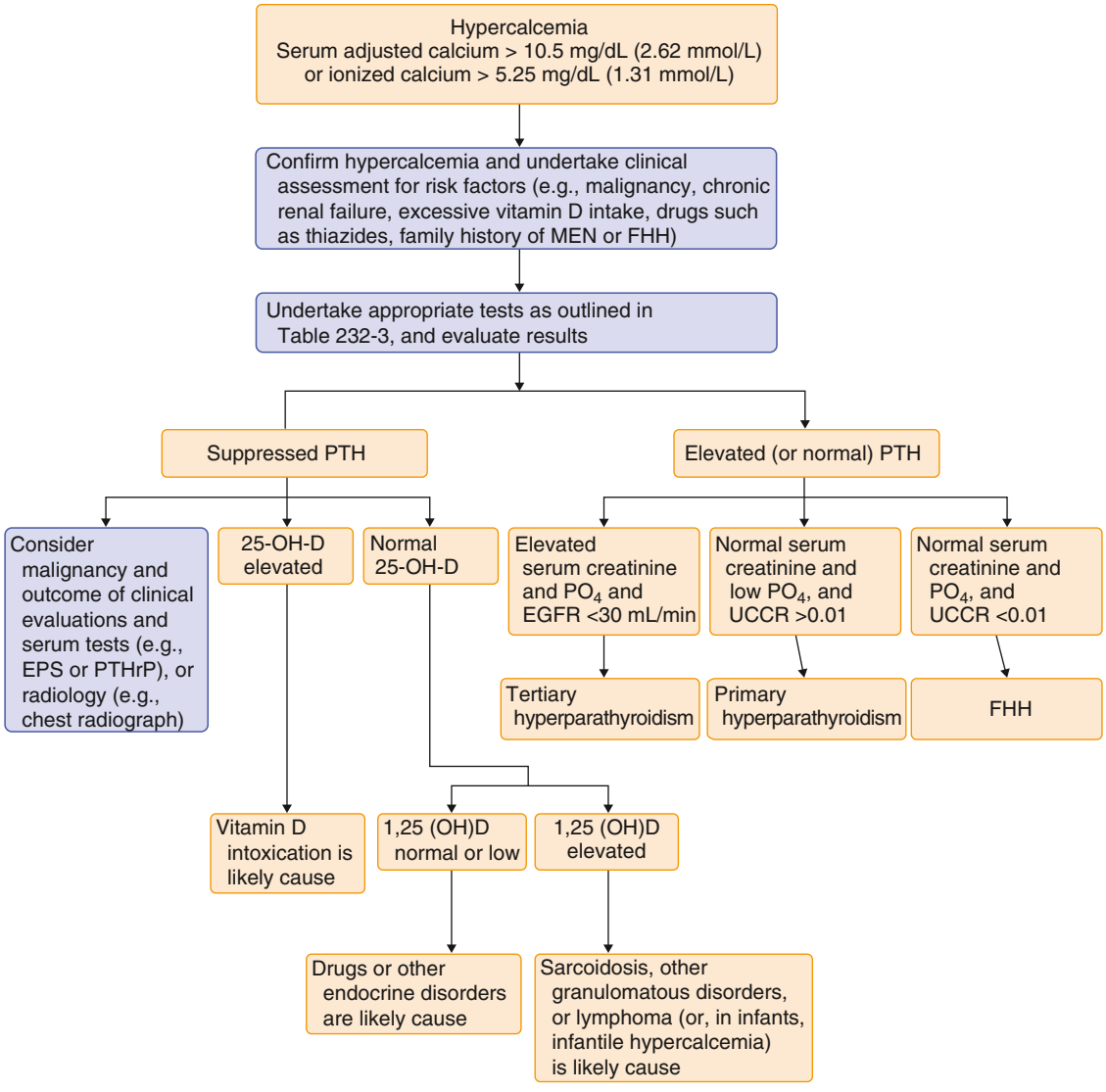

FIGURE 227-2. Clinical approach to the investigation of causes of hypercalcemia. 1,25(OH)$_2$D = 1,25-dihyroxyvitamin D; 25-OH-D = 25-hydroxyvitamin D; EGFR = estimated glomerular filtration rate; EPS = electrophoretic strip (serum protein electrophoresis); FHH = familial hypocalciuric hypercalcemia; MEN = multiple endocrine neoplasia; PTH = parathyroid hormone; PTHrP = parathyroid hormone–related peptide; UCCR = 24-hour urinary calcium clearance-to-creatinine clearance ratio.

chloride over a 24- to 48-hour period). This vigorous saline hydration, which may lower serum calcium by 1 to 3 mg/dL (0.25 to 0.75 mmol/L), may need to be combined with a loop diuretic (e.g., furosemide, 10 to 20 mg) as necessary to avoid or control complications due to volume overload, especially in elderly patients and patients who have impaired cardiovascular and renal function. The furosemide must be used carefully to avoid exacerbating volume depletion, thereby worsening the hypercalcemia. Saline diuresis may lead to hypokalemia, hypomagnesemia, and electrolyte imbalance, so these parameters must be monitored and corrected as needed.

If saline diuresis is not successful, particularly if the hypercalcemia is very severe, then more specific drugs will be required. The drugs of choice are zoledronic acid (4 mg as a single IV infusion) or pamidronate (15 to 60 mg, depending on the serum calcium concentration, in a single IV infusion or in divided doses, depending upon renal function and responses, over 2 to 4 days; maximum of 90 mg per treatment course). However, these agents should not be used if the hypercalcemia is due to primary or tertiary hyperparathyroidism; such patients ideally should be referred for surgical removal of their parathyroid tumors. Glucocorticoid therapy (e.g., hydrocortisone, 120 mg/day in three divided doses, in adults) is particularly effective when the hypercalcemia is mediated by the actions of 1,25(OH)$_2$D, for example in granulomatous disease, lymphoma, or myeloma. Dialysis using a low or zero calcium dialysate should be considered if these treatments are not effective or if the patient has renal failure. When the acute management of hypercalcemia has been completed, appropriate treatment for the underlying cause must be undertaken.

SPECIFIC CAUSES OF HYPERCALCEMIA

HYPERPARATHYROIDISM

DEFINITION

Hyperparathyroidism, which is characterized by high concentrations of serum immunoreactive PTH, can be classified as primary, secondary, or tertiary. Primary and tertiary hyperparathyroidism are essentially always associated with hypercalcemia (see Table 227-3). By comparison, secondary hyperparathyroidism, which is a physiological response to hypocalcemia, by definition is not associated with hypercalcemia; it may resolve when the hypocalcemia is corrected, or it may progress to tertiary hyperparathyroidism, which usually arises in association with chronic renal failure (see later).

A normocalcemic form of primary hyperparathyroidism is characterized by a normal serum calcium concentration in association with an elevated intact PTH level on at least two consecutive occasions over 3 to 6 months in the absence of any cause of secondary hyperparathyroidism.[7] The prevalence of normocalcemic hyperparathyroidism is reported to be less than 0.2% among persons who undergo assessment of bone mineral density. The serum calcium level may remain normal, or this condition may sometimes be a prelude to the development of primary hyperparathyroidism.

Primary hyperparathyroidism usually occurs as an isolated nonsyndromic endocrinopathy and less commonly as part of complex syndromic disorders such as multiple endocrine neoplasia (MEN; Chapter 212) and

TABLE 227-3 CAUSES OF HYPERCALCEMIA

HIGH PARATHYROID HORMONE LEVELS
Primary hyperparathyroidism* (adenoma, hyperplasia, or carcinoma): nonfamilial or familial, e.g., MEN 1, MEN 2, HPT-JT, FIHP
Tertiary hyperparathyroidism (hyperplasia or adenoma in chronic renal failure)
LOW PARATHYROID HORMONE LEVELS
Malignancy*
Primary
• Parathyroid hormone–related peptide (PTHrP): carcinoma of lung, esophagus, renal cell, ovary, and bladder
• Excess production of $1,25(OH)_2D$ (lymphoma)
Secondary
• Lytic bone metastases* (multiple myeloma* and breast carcinoma*)
• Other location, ectopic factors (e.g., cytokines)
Excess vitamin D
Exogenous vitamin D toxicity by parent D compound, 25(OH) vitamin D_3, or $1,25(OH)_2$ vitamin D_3 in vitamin preparations, cod liver oil, herbal medicines
Endogenous production of 25(OH) vitamin D_3—Williams syndrome
Endogenous production of $1,25(OH)_2$ vitamin D_3, for example, granulomatous disorders (sarcoidosis, HIV, TB, histoplasmosis, coccidioidomycosis, leprosy), lymphoma, and infantile hypercalcemia
Drugs
Thiazide diuretics
Lithium
Total parenteral nutrition
Estrogens/antiestrogens, testosterone
Milk-alkali syndrome
Vitamin A toxicity
Aluminum intoxication (in chronic renal failure)
Aminophylline
Nonparathyroid endocrine disorders
Thyrotoxicosis
Pheochromocytoma
Acute adrenal insufficiency
Vasoactive intestinal polypeptide hormone–producing tumor (VIPoma)
Immobilization
INAPPROPRIATE PARATHYROID HORMONE LEVELS DUE TO ALTERED SET POINT
Familial benign hypocalciuric hypercalcemia (FBH or FHH) types 1-3

*Most common causes.
FIHP = familial isolated hyperparathyroidism; HIV = human immunodeficiency virus; HPT-JT = hyperparathyroidism with jaw tumors; MEN = multiple endocrine neoplasia; TB = tuberculosis.

TABLE 227-4 INITIAL INVESTIGATIONS FOR HYPERCALCEMIA

BLOOD
× 2-3 estimations of serum calcium, phosphate, albumin, urea and electrolytes, creatinine, alkaline phosphatase, liver function tests
Parathyroid hormone
Complete blood count
Electrophoretic protein strip, serum protein electrophoresis, or immunofixation
25-OH-D_3 (and if indicated, $1,25[OH]_2D_3$)
Thyroid function tests
Magnesium
Parathyroid hormone–related peptide (if malignancy suspected)
URINE
× 2-3 estimations of 24-hr urinary calcium and creatinine clearance, and clearance ratios
Imaging
Chest radiograph
Radiograph of hands
Ultrasound of kidneys

hyperparathyroidism with jaw tumors. Syndromic and nonsyndromic forms of primary hyperparathyroidism may also occur as hereditary (i.e., familial) disorders, or as nonfamilial (i.e., sporadic) diseases.

Primary Hyperparathyroidism

EPIDEMIOLOGY

Primary hyperparathyroidism, which affects 3 in 1000 adults, is one of the two most common causes of hypercalcemia and is due to an excessive secretion of PTH from a parathyroid adenoma, parathyroid hyperplasia, or rarely, a parathyroid carcinoma.[8] Studies have estimated that the global prevalence of parathyroid tumors is 4 million. Primary hyperparathyroidism usually occurs as a nonsyndromic isolated endocrinopathy between the ages of 40 and 65 years, and it is three times more common in females than males.

PATHOBIOLOGY

Eighty percent of patients with primary hyperparathyroidism will have a solitary parathyroid adenoma, and 15 to 20% of patients will have hyperplasia involving all four parathyroid glands. Parathyroid carcinoma occurs in less than 0.5% of patients with primary hyperparathyroidism. The underlying causes of primary hyperparathyroidism are largely unknown. However, more than 10% of patients with clinically nonfamilial primary hyperparathyroidism occurring before 45 years of age have a germline mutation in 1 of 12 genes, including those of MEN 1 (*MEN1*), cell division cycle 73 (*CDC73*), and calcium-sensing receptor (*CaSR*). In addition, studies of nonfamilial sporadic parathyroid adenomas have shown that 35 to 50% have somatic mutation of the *MEN1* gene; 15% have overexpression of cyclin D1; and more than 85% have an abnormality of the Wnt/β-catenin pathway.

CLINICAL MANIFESTATIONS

Most patients with primary hyperparathyroidism have mild, asymptomatic hypercalcemia, detected by chance at the time of biochemical screening for other reasons. However, nearly 50% of these patients may have subtle neuromuscular symptoms, such as fatigue and weakness, that become apparent only in retrospect after a successful parathyroidectomy.

Symptomatic hypercalcemia (see Table 227-2) predominantly affects the skeletal,[9] renal, and gastrointestinal systems. Because of early diagnosis, the classic skeletal changes of osteitis fibrosa cystica due to subperiosteal resorption of the distal phalanges, tapering of the distal clavicles, a salt-and-pepper appearance of the skull, bone cysts, and brown tumors of the long bones are now identified in less than 5% of patients. However, osteopenia, as assessed by bone mineral density, occurs in 25% of patients, primarily of the cortical bone (e.g., distal third of forearm) rather than the cancellous bone (e.g., lumbar spine). The hip bones, which are an equal mixture of cortical and cancellous bone, show intermediate reductions in bone mineral density. Overall, however, the risk for bone fractures in patients with mild primary hyperparathyroidism is similar to those in matched, normal controls. Renal stone disease (nephrolithiasis [Chapter 111] and nephrocalcinosis) occurs in 20% of patients, hypercalciuria occurs in 30% of patients, and renal impairment also can occur. The gastrointestinal manifestations include peptic ulcers (Chapter 125) and pancreatitis (Chapter 130).

DIAGNOSIS

In the presence of hypercalcemia, the finding of an elevated circulating PTH concentration by an immunoradiometric or immunochemiluminometric assay establishes the diagnosis. PTH is elevated in approximately 90% of patients with primary hyperparathyroidism, who invariably have hypercalcemia (see Fig. 227-2).[10] The only other hypercalcemic disorders in which PTH may occasionally be elevated are familial benign hypocalciuric hypercalcemia, immobilization, or the use of lithium or thiazide (see Table 227-3). A careful history and cessation of drug use help to exclude these possibilities.

About one-third of patients with primary hyperparathyroidism have a low serum phosphate level (see Fig. 227-2), which otherwise is in the lower range of normal. In addition, some patients have a mild increase in the serum chloride concentration and a concomitant decrease in the bicarbonate concentration. Serum alkaline phosphatase activity may be elevated in some patients, and urinary calcium excretion is increased in 30% of patients. The circulating $1,25(OH)_2D$ concentration is elevated in some patients with primary hyperparathyroidism, although it is not of diagnostic value because it is also elevated in other hypercalcemic disorders such as sarcoidosis and lymphomas (see Fig. 227-2). The serum 25-OH-D concentration is within the normal range. Densitometric scanning can detect early skeletal changes and is useful for deciding on whether conservative as opposed to surgical management is most appropriate (Table 227-5).

Preoperative localization to define the sites of the parathyroid tumors includes ultrasonography,[11] computed tomography (CT), magnetic resonance imaging (MRI), and scintigraphy with technetium-99m sestamibi. Sestamibi scintigraphy with CT (e.g., single-photon emission computed tomography [SPECT]) is the preferred test to give a three-dimensional image with anatomic resolution,[12] but the appreciable incidence of false-positive tests with each of the noninvasive localization procedures means that a confirmation using two methods is preferable. Invasive localization tests (arteriography and selective venous sampling for PTH in the veins draining the thyroidal

TABLE 227-5 SUMMARY OF GUIDELINES FOR PARATHYROID SURGERY IN PRIMARY HYPERPARATHYROIDISM PATIENTS

Surgery* recommended if patient meets any one of the following criteria:

- Any complication of primary hyperparathyroidism (e.g., nephrolithiasis, nephrocalcinosis or bone erosions of osteitis fibrosa cystica)
- An episode of life-threatening hypercalcemia
- Serum calcium >1 mg/dL (0.25 mmol/L) above upper limit of normal
- Marked hypercalciuria (>400 mg/24 hr [>10 mmol/24 hr] in men and >300 mg/24 hr [>7.5 mmol/24 hr] in women) and an increased risk for nephrolithiasis by biochemical stone risk analysis
- Significant reduction in creatinine clearance (i.e., <60 mL/min)
- Reduction in bone mineral density (i.e., T score below –2.5, at lumbar spine, total hip, femoral neck or distal 1/3 of radius and/or previous vertebral fracture)
- Age <50 years

*Surgery is also indicated in patients for whom medical surveillance is neither desired nor possible.
Adapted from Bilezikian JP, Silverberg SJ, Bandeira F, et al. Management of primary hyperparathyroidism. *J Bone Miner Res.* 2022;37:2391-2403.

region) are time consuming, expensive, difficult, and dependent on the skill of the radiologist, so they generally should be reserved for patients who have had previous unsuccessful neck surgery.

TREATMENT

The natural history of primary hyperparathyroidism in most patients is to progress slowly or not at all. For example, among asymptomatic patients, only 25% have progressive disease, which is usually manifested as a decrease in bone mineral density during a 10-year period. For patients with asymptomatic primary hyperparathyroidism, active surveillance is as good as parathyroidectomy,[A1] and even mildly symptomatic patients who do not undergo surgery appear to do as well with medical management for a decade.[A2]

Parathyroidectomy

Parathyroidectomy is recommended for more than minimally symptomatic patients and for patients who have skeletal and renal complications (see Table 227-5). Parathyroidectomy is a safe procedure, generally performed under local anesthesia, that achieves a biochemical cure in about 98% of patients,[13] if undertaken by an experienced surgeon. Successful parathyroidectomy leads to an increase in bone mineral density over a 6- to 12-month period; this improvement continues for up to 10 years and in older adults is associated with a lower risk of fractures.[14] Complications of parathyroid surgery include damage to the recurrent laryngeal nerve and permanent hypoparathyroidism. Thermal ablation, which is an option in patients who are not good candidates for anesthesia and open surgery, is reported to have a cure rate of about 90%.[15]

Watchful Waiting

Patients who do not undergo parathyroidectomy (e.g., patients with asymptomatic primary hyperparathyroidism) should be monitored with annual measurement of the serum calcium level, PTH level, and 25-OH-D level; formal measurement of creatinine clearance (rather than an estimated glomerular filtration rate [eGFR]); 24-hour urinary calcium excretion; and bone mineral density. Patients should also have a radiograph of the spine if they have lost height or have back pain. If nephrolithiasis is suspected, abdominal imaging (e.g., ultrasonography, radiography, or computed tomographic scanning) should be obtained. In addition, patients with primary hyperparathyroidism also should avoid dehydration and remain ambulant. Any vitamin D deficiency should be corrected cautiously with oral vitamin D supplementation aimed at maintaining the serum 25-OH-D above 50 nmol/L. The dietary intake of calcium should be normal. Thiazide diuretics and herbal and tonic remedies that may contain vitamin D or vitamin A should be avoided.

Medical Therapy

The goals of medical therapy are to minimize the loss of bone mineral density and secondarily to normalize levels of serum calcium and PTH. Medications should be chosen based on the aims of the treatment. For example, bisphosphonate therapy should be chosen if the aim is to increase bone mineral density, and cinacalcet should be chosen if the aim is to reduce serum calcium concentrations. Combined use of cinacalcet and alendronate can normalize hypercalcemia and improve bone mineral density in patients with primary hyperparathyroidism.

Cinacalcet (initially 30 mg twice daily; maximum 90 mg 4 times a day, adjusted every 2 to 4 weeks according to response) can lower serum calcium concentrations to normal values with long-term treatment, with modest reductions in PTH levels and no major adverse effects in patients with primary hyperparathyroidism. However, bone mineral density in the treated patients remains unchanged despite a reduction in biochemical markers for bone resorption and formation. The use of cinacalcet is approved for adults (i.e., over age of 18 years) who have severe hypercalcemia due to primary hyperparathyroidism and are unable to undergo parathyroidectomy, have hypercalcemia due to inoperable parathyroid carcinoma, or are on dialysis with uncontrolled secondary hyperparathyroidism.

The bisphosphonates (e.g., alendronate 10 mg orally daily; see Table 225-2) inhibit bone resorption and improve bone mineral density at the lumbar spine but do not alter serum calcium or PTH concentrations. Daily high-dose (70 mg or 2800 U) cholecalciferol also can decrease PTH and improve bone density when used for 6 months before and after parathyroidectomy. However, these effects are not sustained. Denosumab (a RANKL inhibitor given as 60 mg once every 6 months by subcutaneous injections) is an alternative to improve bone mineral density in osteoporotic patients with primary hyperparathyroidism. Estrogens increase bone density in postmenopausal women with primary hyperparathyroidism, but they have only small effects on the concentrations of serum calcium and PTH and are recommended only when other drugs are contraindicated, not available, or unaffordable.

Familial Primary Hyperparathyroidism

Primary hyperparathyroidism is most frequently encountered as a nonfamilial (sporadic) disorder. However, approximately 10% of patients with primary hyperparathyroidism have a hereditary form that may either be part of the multiple endocrine neoplasia (MEN; Chapter 212) 1, MEN 2, MEN 3, and MEN 4 syndromes or part of the hyperparathyroidism-jaw tumor syndrome. In addition, hereditary primary hyperparathyroidism may develop as a solitary endocrinopathy, termed familial isolated hyperparathyroidism. Patients with these familial forms of primary hyperparathyroidism, including the MEN syndromes, have an earlier age of onset (20 to 25 years vs. 55 years) and an equal male : female ratio (1 : 1 vs. 1 : 3). Familial isolated hyperparathyroidism has been reported in several kindreds, some of which harbor mutations of the *MEN1*, *CDC73*, *GCM2* or *CaSR* genes (see Table 227-1 and E-Fig. 227-1). The familial syndromes associated with MEN 1, MEN 2, MEN 3, and MEN 4 are reviewed in detail in Chapter 212.

The hyperparathyroidism-jaw tumor syndrome is an autosomal dominant disorder characterized by the occurrence of parathyroid tumors, which may be carcinomas in approximately 15% of patients, and ossifying fibromas that usually affect the maxilla or mandible. In addition, some patients may also develop Wilms tumors, renal cysts, renal hamartomas, renal cortical adenomas, papillary renal cell carcinomas, uterine tumors that may be malignant, pancreatic adenocarcinomas, testicular mixed germ cell tumors with a major seminoma component, and Hurthle cell thyroid adenomas. Mutations of the *CDC73* gene, which is located on chromosome 1q31.2 and encodes a 531–amino acid protein, parafibromin, cause the syndrome.

MEN syndromes are associated with multiple parathyroid tumors, rather than the solitary parathyroid adenomas typically found in the sporadic form, and hyperparathyroidism-jaw tumor syndrome is associated with parathyroid carcinoma in 15% of patients. Minimally invasive parathyroidectomy is an unsuitable approach in MEN patients because of multigland disease, and patients with hyperparathyroidism-jaw tumor syndrome are likely to require early surgery because of their higher risk for parathyroid carcinoma.

Uremic Hyperparathyroidism

PATHOBIOLOGY

Serum PTH levels rise in response to hypocalcemia, regardless of the cause, but this secondary hyperparathyroidism usually resolves with treatment of the underlying cause (Table 227-6). In chronic renal failure (Chapter 116), however, the secondary hyperparathyroidism may persist for a longer time,[16] and eventually the parathyroid cells can become autonomous and secrete excessive PTH despite normocalcemic and even hypercalcemia. This state, termed tertiary hyperparathyroidism (see Table 227-2),[17] results when early, presumably polyclonal, secondary hyperplasia evolves into monoclonal tumors. Elevations in blood phosphate levels associated with chronic renal failure (Chapter 116) independently of calcitriol and calcium lead to increased production of PTH and nodular hyperplasia of the parathyroid glands, thereby promoting the parathyroid gland's resistance to calcitriol and calcium. The processes leading to tertiary hyperparathyroidism are not fully understood but appear to involve genes other than those involved in the sporadic and familial forms of primary hyperparathyroidism.

CLINICAL MANIFESTATIONS AND DIAGNOSIS

In chronic renal failure (Chapter 116), phosphate retention and decreased production of $1,25(OH)_2D$ result in hypocalcemia and secondary hyperparathyroidism. This combination of biochemical abnormalities results in renal osteodystrophy, which is a severe bone disease that shows combined features

TABLE 227-6 CAUSES OF HYPOCALCEMIA

LOW PARATHYROID HORMONE LEVELS (HYPOPARATHYROIDISM)
Parathyroid agenesis
Isolated or part of complex developmental anomaly (e.g., DiGeorge syndrome)
Parathyroid destruction
Surgery*
Radiation
Infiltration by metastases or systemic disease (e.g., hemochromatosis, amyloidosis, sarcoidosis, Wilson disease, thalassemia)
Autoimmune
Isolated
Polyglandular (type 1)
Reduced parathyroid function (i.e., parathyroid hormone secretion)
Parathyroid hormone gene defects
Hypomagnesemia*
Neonatal hypocalcemia (may be associated with maternal hypercalcemia)
Hungry bone disease (postparathyroidectomy)
Calcium-sensing receptor or Gα11 mutations
HIGH PARATHYROID HORMONE LEVELS (SECONDARY HYPERPARATHYROIDISM)
Vitamin D deficiency*
As a result of nutritional lack,* malabsorption,* liver disease, or vitamin D receptor defects
Inadequate production of active vitamin D ($1,25[OH]_2D$) as a result of chronic renal failure*
Vitamin D resistance (rickets)
As a result of renal tubular dysfunction (Fanconi syndrome) or vitamin D receptor defects
Parathyroid hormone resistance
(e.g., pseudohypoparathyroidism, hypomagnesemia)
Drugs
Calcium chelators (e.g., citrated blood transfusions, phosphate—cow's milk is rich in phosphate)
Inhibitors of bone resorption (e.g., bisphosphonates, calcitonin, plicamycin)
Altered vitamin D metabolism (e.g., phenytoin, ketoconazole)
Foscarnet
Miscellaneous
Acute pancreatitis
Acute rhabdomyolysis
Massive tumor lysis
Osteoblastic metastases (e.g., from prostate or breast carcinoma)
Toxic shock syndrome
Hyperventilation

*Most common causes.

of hyperparathyroidism and vitamin D deficiency, including bone erosions and osteomalacia. The diagnosis is established by the presence of an elevated level of PTH despite normocalcemia or hypercalcemia.

TREATMENT

Treatment is based on correcting the hypocalcemia and hyperphosphatemia (Chapter 116). Calcitriol (0.5 to 1.0 μg daily) increases the intestinal absorption of both calcium and phosphate and can suppress the development of hyperparathyroidism. However, calcitriol should not be given if the serum phosphorus level is greater than 5.5 mg/dL because increased vitamin D–mediated intestinal phosphate absorption will worsen hyperphosphatemia and increase the risk of soft tissue calcification. Careful monitoring is needed to avoid hypercalcemia or urinary calcium values above 250 mg/day, a level that increases the risk of developing kidney stones.

If dietary restriction cannot maintain serum phosphorus at or below 5.5 mg/dL, sevelamer (400- to 800-mg tablets, initially 1.2 g/day in divided doses) is generally preferred because it reduces hyperphosphatemia and is associated with a lower all-cause mortality than other options.[A3] When the serum phosphorus level is over 7 mg/dL, aluminum-based binders (600 mg of concentrated aluminum hydroxide solution with each meal) are effective but should be used for no more than 1 week to avoid aluminum neurotoxicity.

Early treatment of the metabolic disturbance will prevent or delay the onset of severe secondary hyperparathyroidism and tertiary hyperparathyroidism, which requires parathyroidectomy.[18] For patients who have end-stage renal failure and are on dialysis, cinacalcet (initially 30 mg once daily, adjusted every 2 to 4 weeks according to response to a maximum of 180 mg per day), which is the allosteric activator of the calcium sensing receptor, can be used to treat the severe secondary hyperparathyroidism. Cinacalcet will reduce the PTH concentrations and may also have an antiproliferative effect, but subtotal parathyroidectomy is better than cinacalcet for controlling hypercalcemia in kidney allograft recipients (Chapter 117).[A4]

ENDOCRINE CAUSES OF HYPERCALCEMIA OTHER THAN HYPERPARATHYROIDISM

Nonparathyroid disorders (see Table 227-3) that are associated with hypercalcemia include thyrotoxicosis (Chapter 207), pheochromocytoma (Chapter 209), Addison disease (Chapter 208), vasoactive intestinal polypeptide hormone producing tumor (VIPomas; Chapter 126), familial benign hypocalciuric hypercalcemia, Jansen disease, and Williams syndrome.

Thyrotoxicosis

The mild hypercalcemia (<12 mg/dL, or 3 mmol/L) that frequently accompanies thyrotoxicosis (Chapter 207) leads to increased bone turnover and resorption. The hypercalcemia, which may respond rapidly to treatment with β-adrenergic blockers, as well as more gradually to lowering the serum thyroxine over weeks to months, usually resolves when the hyperthyroidism resolves.

Familial Benign Hypocalciuric Hypercalcemia

Familial benign hypercalcemia, which is also referred to as familial hypocalciuric hypercalcemia, is an autosomal dominant disorder characterized by lifelong asymptomatic hypercalcemia in association with an inappropriately low urinary calcium excretion (i.e., calcium clearance-to-creatinine clearance ratio [CCR] <0.01) and normal circulating PTH concentrations in 80% of patients. Hypermagnesemia is also typically present. Although most patients with familial hypocalciuric hypercalcemia are asymptomatic, chondrocalcinosis and acute pancreatitis have occasionally been observed. Familial hypocalciuric hypercalcemia is a genetically heterogenous disorder with three subtypes (FHH1, FHH2, and FHH3 due to mutations in the calcium sensing receptor, the G-protein alpha 11 subunit, and the adaptor protein 2 sigma subunit, respectively). Patients with familial hypocalciuric hypercalcemia have been misdiagnosed as having primary hyperparathyroidism because 20% of these patients may have elevated plasma PTH concentrations. In addition, 20% of patients with familial hypocalciuric hypercalcemia may have a creatinine clearance ratio greater than 0.01 and therefore be indistinguishable from patients with primary hyperparathyroidism. Genetic analysis, which is required to distinguish patients with familial hypocalciuric hypercalcemia from patients with primary hyperparathyroidism, is important because the hypercalcemia in familial hypocalciuric hypercalcemia is generally benign and does not result in sequelae (see Table 227-2). Moreover, parathyroidectomy does not correct the hypercalcemia in familial hypocalciuric hypercalcemia. If it is symptomatic or severe, cinacalcet (30 to 60 mg daily) may be used to correct the hypercalcemia and improve symptoms.

Autoimmune Hypocalciuric Hypercalcemia

Some patients who have the clinical features of familial hypocalciuric hypercalcemia but none of the three causative mutations may have autoimmune hypocalciuric hypercalcemia. These patients have circulating antibodies to the extracellular domain of the CaSR, and the CaSR-bound autoantibodies stimulate PTH release from human parathyroid cells. Thus, autoimmune hypocalciuric hypercalcemia is a disorder of extracellular calcium sensing that should be considered in patients who have familial hypocalciuric hypercalcemia without known mutations. Manifestations include hyperthyroidism, hypothyroidism, or celiac disease, but patients can be asymptomatic if they have not yet developed any clinical features. These patients may have multiple autoimmune levels of antithyroid, antigliadin, or antiendomysial antibodies. The effects of treatment with glucocorticoids (usually prednisolone initially as high as 5 to 60 mg/day) have been variable.

Williams Syndrome

Williams syndrome is an autosomal dominant disorder characterized by supravalvular aortic stenosis, elfin-like facies, psychomotor retardation, and infantile hypercalcemia. The underlying abnormality causing hypercalcemia, which affects 5 to 50% of patients, remains unknown, but abnormal $1,25(OH)_2D_3$ metabolism and decreased calcitonin production have been implicated. Hemizygosity for a microdeletion of chromosome 7q11.23, which involes the *ELASTIN* and *LIM-KINASE* genes, may explain the respective cardiovascular and neurologic features. Treatment is as for hypercalcemia.

Malignancy

Hypercalcemia may occur in 20 to 30% of patients with a malignancy, usually due to increased bone resorption, which may be either directly due to skeletal metastases or indirectly due to tumor production of a humoral factor that stimulates osteoclastic bone resorption (Chapter 164).[19] The cancers that

typically metastasize to produce lytic bone lesions are breast cancer (Chapter 183), lymphomas (Chapters 171 and 172), or multiple myeloma (Chapter 173; see Table 227-3).[20] The associated osteolysis, mediated by recruitment and activation of osteoclasts, involves cytokines. The cancers that are typically associated with the humoral hypercalcemia of malignancy are squamous carcinomas of the lung (Chapter 177), esophagus (Chapter 178), cervix (Chapter 184), vulva (Chapter 184), skin (Chapter 188), head, or neck (Chapter 176), but other types from the kidney (Chapter 182), bladder, ovary, and breast (Chapter 183) may also occur.

CLINICAL MANIFESTATIONS AND DIAGNOSIS

Humoral hypercalcemia of malignancy accounts for up to 80% of patients with malignancy-associated hypercalcemia. The most common factor causing humoral hypercalcemia of malignancy is PTHrP, which can be measured in the serum by immunoassay. However, these assays are relatively insensitive, and the failure to detect serum PTHrP does not exclude the diagnosis. Patients with humoral hypercalcemia of malignancy generally have hypercalcemia associated with lower or undetectable serum PTH levels, marked hypercalcemia, and a reduced plasma $1,25(OH)_2D$ level. When bone metastases are the direct cause of hypercalcemia, the serum phosphate level is typically elevated.

TREATMENT

Therapy of humoral hypercalcemia of malignancy is aimed at (1) reducing the tumor load by surgery, radiotherapy, or chemotherapy; (2) reducing osteoclastic bone resorption by use of denosumab[A5] (120 mg subcutaneously on weeks 1, 2, and 3 and then every 4 weeks) plus zoledronate[A6] (4 mg typical dose, adjusted by expert consultation based on renal function, given intravenously over 15 to 30 minutes; may repeat the dose once 7 or more days later) or calcitonin (4 to 8 units/kg intramuscularly or subcutaneously every 12 hours for 2 to 3 days); and (3) increasing renal calcium clearance by a saline diuresis.[21]

For patients with bone metastases, treatment of the underlying tumor is critical.[22] Saline diuresis (see Treatment of Symptomatic Hypercalcemia) can be helpful.

Granulomatous Disorders

The granulomatous disorders that are associated with hypercalcemia (see Table 227-3) are invariably associated with elevated circulating concentrations of $1,25(OH)_2D$ owing to extrarenal synthesis. Sarcoidosis (Chapter 83) is the most frequently encountered granulomatous disorder associated with hypercalcemia; 10% of patients with sarcoidosis have hypercalcemia, and about half become hypercalciuric. The finding of raised serum angiotensin-converting enzyme (ACE) activity may help confirm the diagnosis.

TREATMENT

Glucocorticoids (e.g., 40 to 60 mg of prednisolone daily) decrease $1,25(OH)_2D$ production and restore the calcium concentration to normal by reducing intestinal absorption of calcium. Once normocalcemia is achieved, chronic dosing is highly variable depending on what may be required to maintain normocalcemia. Failure to achieve normal serum calcium concentrations within 10 days of glucocorticoid therapy suggests the coexistence of another cause for the hypercalcemia, such as primary hyperparathyroidism or malignancy.

Drugs

Several drugs (see Table 227-3) can cause hypercalcemia by different mechanisms. Compounds containing vitamins D and A are common and frequently associated with hypercalcemia. Thiazide diuretics are often associated with hypercalcemia owing to enhanced reabsorption of calcium in the distal renal tubule; hypercalcemia reverses rapidly with discontinuation of the drug.

The consumption of large quantities of milk or calcium carbonate for symptoms of acid-peptic disease (Chapter 125) may contribute to moderate to severe hypercalcemia with alkalosis and renal impairment. The amount of calcium ingested by patients with this syndrome is usually 5 to 15 g/day. Treatment consists of discontinuing the ingestion of the calcium-containing compounds and antacids, rehydration, and saline diuresis.

HYPOCALCEMIA

DEFINITION

Hypocalcemia is defined as a serum calcium concentration below the lower limit of normal range: an ionized serum calcium below 4.65 mg/dL (1.16 mmol/L) and a total serum calcium below 8.5 mg/dL (2.12 mmol/L). Mild hypocalcemia is defined as a total serum calcium of 8 to 8.5 mg/dL (2 to 2.12 mmol/L) and severe hypocalcemia as a total serum calcium below 7.6 mg/dL (1.9 mmol/L).

PATHOBIOLOGY

Hypocalcemia (see Table 227-6) can be classified by cause, according to whether serum PTH concentrations are low (i.e., hypoparathyroid disorders) or high (i.e., disorders associated with secondary hyperparathyroidism). Hypocalcemia is most commonly caused by hypoparathyroidism, a deficiency or abnormal metabolism of vitamin D, acute or chronic renal failure, or hypomagnesemia. Hypocalcemic diseases may arise because of a failure of the parathyroid glands to develop, destruction of the parathyroid glands, reduced PTH secretion, or reduced PTH-mediated actions in target tissues owing to a defect in the PTH receptor (i.e., the PTH/PTHrP receptor), or insensitivity to PTH caused by defects downstream of the PTH/PTHrP receptor (see E-Fig. 227-1).[23] The diseases also may be classified as being part of the hypoparathyroid disorders, of the CaSR abnormalities, or of the pseudohypoparathyroid disorders.

CLINICAL MANIFESTATIONS AND DIAGNOSIS

The clinical presentation of hypocalcemia ranges from an asymptomatic biochemical abnormality to a severe, life-threatening condition. In mild hypocalcemia, patients may be asymptomatic. Patients with more severe and long-term hypocalcemia may develop acute symptoms of neuromuscular irritability (Table 227-7), ectopic calcification (e.g., in the basal ganglia, which may be associated with extrapyramidal neurologic symptoms), subcapsular cataracts, papilledema, and abnormal dentition. Investigations should be directed at confirming the presence of hypocalcemia and establishing the cause (Fig. 227-3).

In hypoparathyroidism, serum calcium is low, phosphate is high, and PTH is undetectable; renal function and concentrations of the 25-hydroxy and 1,25-dihydroxy metabolites of vitamin D are usually normal (see Fig. 227-3). The features of pseudohypoparathyroidism are similar to those of hypoparathyroidism except for PTH, which is markedly increased. In chronic renal failure (Chapter 116), which is the most common cause of hypocalcemia, phosphate is high; alkaline phosphatase, creatinine, and PTH are elevated; 25-OH-D_3 is normal; and $1,25(OH)_2D_3$ is low (see Fig. 227-1). In vitamin D deficiency osteomalacia (Chapter 226), serum calcium and phosphate are low, alkaline phosphatase and PTH are elevated, renal function is normal, and 25-OH-D_3 is low (see Fig. 227-3).[24] The most frequent artifactual cause of hypocalcemia is hypoalbuminemia, such as occurs in severe cirrhosis (Chapter 139) or the nephrotic syndrome (Chapter 107).

TABLE 227-7 HYPOCALCEMIC CLINICAL FEATURES OF NEUROMUSCULAR IRRITABILITY

Paresthesia, usually of fingers, toes, and circumoral regions
Tetany, carpopedal spasm, muscle cramps
Chvostek sign*
Trousseau sign†
Seizures of all types (i.e., focal or petit mal, grand mal, or syncope)
Prolonged QT interval on electrocardiogram
Laryngospasm
Bronchospasm

*Chvostek sign is twitching of the circumoral muscles in response to gentle tapping of the facial nerve just anterior to the ear; it may be present in 10% of normal individuals.

†Trousseau sign is carpal spasm elicited by inflation of a blood pressure cuff to 20 mm Hg above the patient's systolic blood pressure for 3 minutes.

TREATMENT

Acute Hypocalcemia

The management of acute hypocalcemia depends on the severity of the hypocalcemia, the rapidity with which it developed, and the degree of neuromuscular irritability (see Table 227-7). Treatment should be given to symptomatic patients (e.g., with seizures or tetany) and asymptomatic patients with a serum calcium of less than 7.6 mg/dL (1.90 mmol/L) who are at high risk for developing complications.

The preferred treatment for acute symptomatic hypocalcemia is calcium gluconate, 10 mL 10% w/v (2.20 mmol of calcium) intravenous, diluted in 50 mL of 5% dextrose or 0.9% sodium chloride and given by slow injection (>5 minutes); this injection can be repeated as required to control symptoms. Serum calcium concentrations should be assessed regularly. Persistent hypocalcemia may be managed acutely by administration of a calcium gluconate infusion; for example, dilute 10 ampules of calcium gluconate, 10 mL 10% w/v (22 mmol of

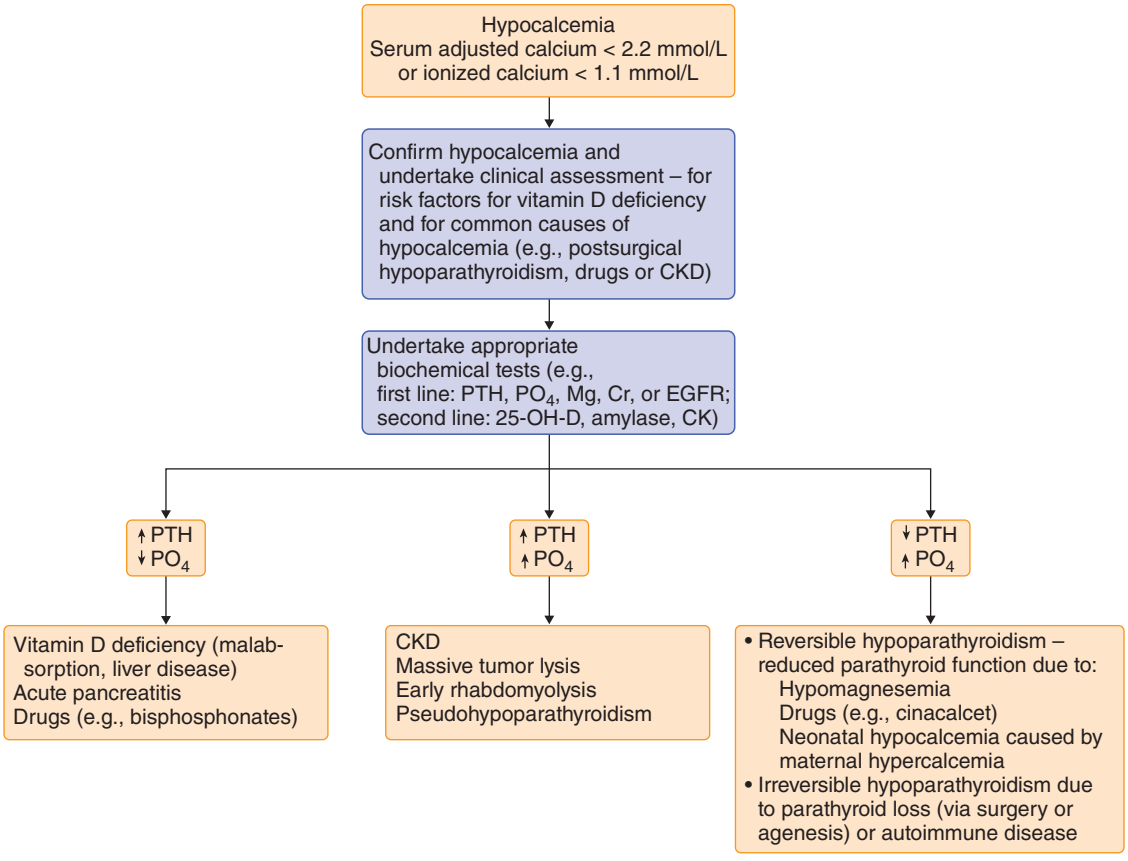

FIGURE 227-3. Clinical approach to investigation of causes of hypocalcemia. 25-OH-D = 25-hydroxyvitamin D; CK = creatinine kinase; CKD = chronic kidney disease; Cr = creatinine; EGFR = estimated glomerular filtration rate; Mg = magnesium; PO_4 = phosphate; PTH = parathyroid hormone.

calcium), in 1 L of 5% dextrose or 0.9% sodium chloride, start infusion at 50 mL/hour, and titrate to maintain serum calcium concentrations in the normal range. Generally, 1.2 to 1.6 mg/kg (0.3 to 0.4 mmol/kg) of elemental calcium infused over 4 to 6 hours increases serum calcium by 2 to 3 mg/dL (0.5 to 0.75 mmol/L).

If hypocalcemia is likely to persist, oral vitamin D therapy (see later) should also be administered. In hypocalcemic patients who are also hypomagnesemic (which may be found in the postparathyroidectomy period or in patients who have severe malabsorption, such as, for example, with celiac disease [Chapter 126]), the hypomagnesemia must be corrected before the hypocalcemia will resolve.

Chronic Hypocalcemia

The three main agents available for the treatment of chronic (long-term) hypocalcemia are vitamin D, supplemental calcium (about 10 to 20 mmol calcium every 6 to 12 hours), and PTH. Close monitoring (at about 1- to 2-week intervals) of the patient's serum and urine calcium concentrations is required initially, and follow-up at 3- to 6-month intervals is appropriate once stabilization is achieved. The aim is to avoid hypercalcemia, hypercalciuria (which may occur in the absence of hypercalcemia), nephrolithiasis, and renal failure.

For treatment of hypocalcemia due to hypoparathyroidism or chronic renal failure, calcitriol (0.25 to 2 mg/day) is the drug of choice because it is the active metabolite and, unlike alfacalcidol, does not require hepatic 25-hydroxylation. Other vitamin D preparations include vitamin D_3 (cholecalciferol), vitamin D_2 (ergocalciferol), 10,000 to 50,000 units (0.25 to 1.25 mg/day); or alfacalcidol (1α-hydroxycholecalciferol), 0.25 to 1 μg/day. Cholecalciferol and ergocalciferol are the least expensive preparations but have the longest durations of action and may result in prolonged toxicity; however, they are the preparations of choice for treating hypocalcemia associated with vitamin D deficiency (see Table 227-6). The other preparations, which do not require renal 1α-hydroxylation, have the advantage of shorter half-lives and thereby minimize the risk for prolonged toxicity.

Patients with hypoparathyroidism seldom require calcium supplements after the early stages of stabilization with vitamin D. In hypoparathyroid patients, PTH can improve the biochemical and skeletal indices, as well as mental and physical health.

CAUSES OF HYPOCALCEMIA

HYPOPARATHYROIDISM

Hypoparathyroidism is characterized by hypocalcemia and hyperphosphatemia, which are the result of a deficiency in PTH secretion or action.[25]

The incidence of hypoparathyroidism is approximately 0.8 per 100,000 person-years, with a prevalence estimated to be 22 to 37 per 100,000 person-years.

The most common cause of hypoparathyroidism is postsurgical hypoparathyroidism. Hypoparathyroidism also may result from agenesis (e.g., DiGeorge syndrome) or destruction of the parathyroid glands (e.g., autoimmune diseases), from reduced secretion of PTH (e.g., neonatal hypocalcemia or hypomagnesemia), or from resistance to PTH (which may occur as a primary disorder (e.g., pseudohypoparathyroidism or secondary to hypomagnesemia) (see Table 227-6). In addition, hypoparathyroidism may occur as an inherited syndromic disorder (see Table 227-1) that may either be part of a complex congenital defect or part of a polyglandular autoimmune disorder (Chapter 212; see Table 227-6 and E-Fig. 227-1). Hypoparathyroidism may also occur as a nonsyndromic solitary endocrinopathy, which has been referred to as isolated or idiopathic hypoparathyroidism. Familial isolated hypoparathyroidism with autosomal dominant, autosomal recessive, and X-linked recessive inheritances also occur.

Isolated Hypoparathyroidism

Isolated hypoparathyroidism may either be inherited or acquired by damage to the parathyroids at surgery, by infiltrating metastases, or by systemic disease (see Table 227-6).

Acquired Forms of Hypoparathyroidism

Hypoparathyroidism may occur after neck surgery,[26] after irradiation, or because of infiltration by metastases or systemic disease, for example, hemochromatosis (Chapter 196), amyloidosis (Chapter 174), sarcoidosis (Chapter 83), Wilson disease (Chapter 195), or thalassemia (Chapter 148) (see Table 227-6). Surgical damage to the parathyroids occurs most commonly after a radical neck dissection, such as for laryngeal or esophageal carcinoma treatment, after a total thyroid resection, or after repeated parathyroidectomies for polyglandular disease (e.g., in MEN 1 or MEN 2, discussed previously). Hypocalcemic symptoms begin 12 to 24 hours after surgery and may require treatment with oral or intravenous calcium.

Functional hypoparathyroidism, which may result from severe hypomagnesemia (<0.4 mmol/L), may be due to a severe intestinal malabsorption disorder (e.g., Crohn disease; Chapters 126 and 127) or a renal tubular disorder (Chapters 104 and 108; see Table 227-6). It is

associated with hypoparathyroidism because magnesium is required for the release of PTH from the parathyroid gland and also for PTH action through adenyl cyclase

Inherited Hypoparathyroidism

Patients with inherited autosomal dominant, autosomal recessive, and X-linked hypoparathyroidism (see Table 227-1) may develop hypocalcemic seizures in the neonatal or infantile periods. Some of the autosomal forms are due to mutations of the *PTH* gene, *CaSR*, the *Gα11* subunit (see later), and the transcriptional factor *GCMB* (glial cells missing B). The X-linked forms likely alter regulation of SOX3 (see Fig. 227-3).

AUTOSOMAL DOMINANT HYPOCALCEMIA TYPE 1 AND TYPE 2. Autosomal dominant hypocalcemia type 1 is due to gain-of-function mutations of the *CaSR* (see Table 227-1 and E-Fig. 227-1), although about 20% of patients may not have a previously reported family history because they have de novo mutations. Autosomal dominant hypocalcemia type 1 is characterized by lifelong mild or severe hypocalcemia in association with normal serum PTH concentrations in about 40% of patients or low serum PTH concentrations in about 60% of patients. Serum phosphate and magnesium concentrations may be elevated or low, respectively. Approximately 50% of these patients have asymptomatic hypocalcemia, and the remaining 50% may experience paresthesia, muscle cramps, carpopedal spasms, and seizures, which may be associated with a febrile illness. Basal ganglia or ectopic calcification may be found in more than 35% of patients. In addition, about 10% of patients may have absolute hypercalciuria, which may be associated with nephrocalcinosis and kidney stones in 35% of patients. Autosomal dominant hypocalcemia type 2 is due to gain-of-function mutations of the *Gα11* subunit, and these patients appear to have clinical features that are similar to type 1 patients.

Complex Syndromes Associated with Hypoparathyroidism

Hypoparathyroidism may occur as part of a complex syndrome that may be associated with either a congenital developmental anomaly or an autoimmune syndrome. The congenital developmental anomalies associated with hypoparathyroidism, which occurs in 1 in 4000 live births, include DiGeorge syndrome; the hypoparathyroidism, deafness, and renal anomalies syndrome; the Kenney-Caffey syndrome; and syndromes associated with either lymphedema or dysmorphic features and growth failure (see Table 227-1 and E-Fig. 227-1).

Polyglandular Autoimmune Hypoparathyroidism

Polyglandular autoimmune hypoparathyroidism (Chapter 212) comprises hypoparathyroidism, Addison disease, candidiasis, and two or three of the following: type 1 diabetes mellitus, primary hypogonadism, autoimmune thyroid disease, pernicious anemia, chronic active hepatitis, steatorrhea (malabsorption), alopecia (totalis or areata), and vitiligo (see Table 227-1). Antibodies directed against the adrenal, thyroid, and parathyroid glands are detected in the sera of some patients. The polyglandular autoimmune type 2 syndrome is characterized by adrenal insufficiency, type 1 diabetes mellitus, and thyroid disease and does not involve hypoparathyroidism.

Autoimmune Acquired Hypoparathyroidism

Twenty percent of patients who have acquired hypoparathyroidism in association with autoimmune hypothyroidism have autoantibodies to the extracellular domain of the CaSR (see Table 227-1 and E-Fig. 227-1). The CaSR autoantibodies do not persist: 72% of patients who have acquired hypoparathyroidism for less than 5 years have detectable CaSR autoantibodies, whereas only 14% of patients with acquired hypoparathyroidism for more than 5 years have such autoantibodies. The majority of the patients who have CaSR autoantibodies are female.

DiGeorge Syndrome

Patients with the DiGeorge syndrome (Chapter 231) suffer from neonatal hypoparathyroidism, T-cell immunodeficiency, congenital heart defects, and deformities of the ear, nose, and mouth (e.g., cleft lip and/or palate). Children with DiGeorge syndrome often die from infections related to the immunodeficiency.

CLINICAL MANIFESTATIONS AND DIAGNOSIS

Patients with hypoparathyroidism may present with symptoms and signs of acute or chronic hypocalcemia, as described above. The diagnosis requires accurate measurement of PTH. Serum concentrations of immunoreactive PTH are low or undetectable despite the presence of hypocalcemia. Concentrations of $1,25(OH)_2D_3$ are usually in the low-normal to low range, but alkaline phosphatase activity is normal (see Fig. 227-3). The daily urinary excretion of calcium may be reduced, although the fractional excretion of calcium is invariably increased.

TREATMENT

The main treatments for the hypocalcemia due to hypoparathyroidism are vitamin D preparations and supplemental calcium, as described previously.[27] After surgery or irradiation, parathyroid function often returns, but persistent hypocalcemia requires treatment with vitamin D preparations.

For primary hypothyroidism, calcitriol (0.25-1.0 μg per day) and alfacalcidol (0.25-1.0 μg per day) appear to provide equivalent results.[A7] Recombinant human PTH (1-84), (rhPTH, at 50 μg subcutaneously once daily) is useful to reduce the required doses of calcium and vitamin D as well as for patients whose hypocalcemia is refractory to treatment with vitamin D preparations and calcium supplements. Doses should be titrated every 4 weeks, with the goal of reducing oral calcium supplements to as low as 500 mg/day and to discontinue vitamin D supplements, while keeping serum calcium within the low-normal range. After a stable dose is achieved, serum calcium and phosphate levels should be monitored every 3 to 6 months and urinary calcium excretion at least yearly.

For autosomal dominant hypocalcemia, treatment with rhPTH (0.2-2.5 μg/kg/day) can ameliorate the hypocalcemia and even seizures.[28] By comparison, vitamin D and calcium supplementation to correct the hypocalcemia may worsen the hypercalciuria and lead to renal impairment.

For functional hypoparathyroidism caused by severe hypomagnesemia, magnesium chloride, 35 to 50 mmol intravenously in 1 L of 5% glucose given over 12 to 24 hours, may be repeatedly required to restore normomagnesemia. If required, oral magnesium glycerophosphate (24 mmol/day in 3 divided doses) can be continued if to maintain normocalcemia.

PSEUDOHYPOPARATHYROIDISM

Patients with pseudohypoparathyroidism, which may be inherited as an autosomal dominant disorder, are characterized by hypocalcemia and hyperphosphatemia due to resistance to PTH rather than PTH deficiency (see Table 227-6).[29]

PATHOBIOLOGY AND CLINICAL MANIFESTATIONS

Five variants, which form part of a group of inactivating PTH/PTHrP signalling disorders (iPPSDs), are recognized on the basis of biochemical and somatic features (Table 227-8). Patients with PHP 1a exhibit PTH resistance (hypocalcemia, hyperphosphatemia, elevated serum PTH, and an absence of an increase in serum and urinary cAMP and urinary phosphate following intravenous human PTH infusion), together with the features of Albright hereditary osteodystrophy, which includes short stature, obesity, subcutaneous calcification, intellectual disability, round facies, dental hypoplasia, and brachydactyly (i.e., shortening of the metacarpals, particularly the third, fourth, and fifth). Patients with PHP 1b exhibit PTH resistance only and do not have the somatic features of Albright hereditary osteodystrophy, whereas patients with pseudopseudohypoparathyroidism exhibit the somatic features of Albright hereditary osteodystrophy in the absence of PTH resistance.

CLINICAL MANIFESTATIONS AND DIAGNOSIS

The absence of a normal rise in urinary excretion of cAMP after an infusion of PTH in pseudohypoparathyroidism 1a indicates a defect at some site of the PTH receptor–adenyl cyclase system (see E-Fig. 227-1). Patients with pseudohypoparathyroidism 1a may also show resistance to other hormones, such as thyroid-stimulating hormone, follicle-stimulating hormone, and luteinizing hormone. Inactivating mutations of the Gsα gene (referred to as *GNAS1*), which is located on chromosome 20q13.2, have been identified in pseudohypoparathyroidism 1a and pseudopseudohypoparathyroidism patients (see Table 227-1 and E-Fig. 227-1). Pseudohypoparathyroidism 1b is due to deletions that are located upstream of the *GNAS1* gene. Moreover, in affected individuals, the deletion involves the maternal allele, whereas its occurrence on the paternal allele results in unaffected healthy carriers. This finding is consistent with parental imprinting of the *GNAS1* abnormality causing pseudohypoparathyroidism 1b.

TREATMENT

Treatment is as for other causes of hypoparathyroidism.

TABLE 227-8 CLINICAL, BIOCHEMICAL, AND GENETIC FEATURES OF HYPOPARATHYROID AND PSEUDOHYPOPARATHYROID DISORDERS

		PSEUDOHYPOPARATHYROIDISM				
	HYPOPARATHYROIDISM	**PHP 1a**	**PPHP**	**PHP 1b**	**PHP 1c**	**PHP 2**
AHO manifestations	No	Yes	Yes	No	Yes	No
Serum calcium	↓	↓	N	↓	↓	↓
Serum PO_4	↑	↑	N	↑	↑	↑
Serum PTH	↓	↑	N	↑	↑	↑
Response to PTH:						
Urinary cAMP* (Chase-Aurbach test)	↑	↓	↑	↓	↓	↑
Urinary PO_4 (Ellsworth-Howard test)	↑	↓	↑	↓	↓	↓
Gsα activity	N	↓	↓	N	N	N
Inheritance	AD, AR, X	AD	AD	AD	AD	Sporadic
Molecular defect	PTH, CaSR, GATA3, Gcm2, others	*GNAS1*	*GNAS1*	*GNAS1*†	?Adenyl cyclase	?cAMP targets
Other hormonal resistance	No	Yes	No	No	Yes	No

*Plasma cyclic adenosine monophosphate (cAMP) responses are similar to those of urinary cAMP.
†Involves deletions that are located upstream of GNAS1.
↓ = decreased; ↑ = increased; ? = presumed, but not proved; AD = autosomal dominant; AHO = Albright hereditary osteodystrophy; AR = autosomal recessive; cAMP = cyclic adenosine monophosphate; N = normal; PHP = pseudoparathyroidism; PO_4 = phosphate; PPHP = pseudopseudoparathyroidism; PTH = parathyroid hormone; X = X-linked.

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228 PAGET DISEASE OF BONE

STUART H. RALSTON

DEFINITION

Paget disease of bone is a focal disorder of the skeleton characterized by increased and disorganized bone remodeling.[1] Affected bones enlarge, become deformed, and are at increased risk for pathologic fractures.

EPIDEMIOLOGY

The prevalence of Paget disease is about 0.5% in the United Kingdom and United States.[2] It also occurs in Western Europe and in people of European descent who have migrated to other parts of the world. Paget disease is rare in Scandinavians, Africans, and Asians. These differences are thought to have a genetic basis occurring as the result of founder mutations in northwest Europe many centuries ago, with subsequent spread to the remainder of the world through emigration. The incidence of Paget disease increases with age; in the United Kingdom, the incidence in women and men respectively is 0.037 to 0.074 per 10,000 person years in individuals ages 45 to 49 years but doubles in frequency each decade thereafter to reach an incidence of about 3.7 and 6.3 per 10,000 person years in individuals ages 85 years and older. The prevalence and severity of Paget disease have diminished in the United Kingdom and many countries over the past 25 years.[3] Although the mechanisms are unclear, suggested explanations include the influx of migrants from low prevalence areas, improved nutrition, a more sedentary lifestyle with a reduction in skeletal injuries, and reduced exposure to infections.

PATHOBIOLOGY

Susceptibility to Paget disease is strongly influenced by genetic factors, but environmental factors are also important. The importance of genetics is emphasized by the facts that between 5 and 40% of patients have a positive family history and that the risk for developing Paget disease in a first-degree relative of a patient is about seven-fold higher than in the general population. In many families, the disease is transmitted in an autosomal dominant manner, although penetrance is incomplete.

The most important susceptibility gene for classical Paget disease is *SQSTM1*. Mutations of *SQSTM1* are present in up to 40% of patients with a family history and 5 to 10% of people without a family history. The *SQSTM1* gene encodes a protein called p62 that is involved in regulating signal transduction downstream of the receptor activator of nuclear factor κB (RANK), which plays a critical role in regulating osteoclastogenesis when activated by RANK ligand (RANKL) (E-Fig. 228-1). The disease-causing mutations cluster in the ubiquitin-associated domain and have the effect of upregulating nuclear factor κB (NFκB) signaling and stimulating osteoclastogenesis by complex mechanisms that are reviewed in detail elsewhere.

Genome-wide association studies have identified seven other loci that predispose to Paget disease and that individually increase the risk between 1.4- and 1.7-fold.[4] These loci have additive effects, such that individuals who carry several predisposing alleles have a substantially increased risk for developing Paget disease. Many lie close to genes that play key roles in osteoclast function, including *CSF1*, which encodes macrophage colony-stimulating factor (M-CSF); *TNFRSF11A*, which encodes RANK; *TM7SF4*, which encodes DC-STAMP; *OPTN*, which encodes optineurin; *PML*, which encodes a protein involved in regulating interferon signaling; and *RIN3*, which encodes a guanine exchange factor that is expressed in osteoclasts (see E-Fig. 228-1).

Rare inherited diseases with clinical features overlapping with those of Paget disease[5] include familial expansile osteolysis and related syndromes caused by mutations affecting the signal peptide of RANK, as well as juvenile Paget disease caused by loss of function mutations affecting osteoprotegerin. Mutations in *VCP*, *hnRNPA2B1*, *hnRNPA1*, *PFN1*, *OPTN*, and *SQSMT*, which may result in defects in the autophagy pathway, can also lead to multisystem proteinopathy where

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		PSEUDOHYPOPARATHYROIDISM				
	HYPOPARATHYROIDISM	**PHP 1a**	**PPHP**	**PHP 1b**	**PHP 1c**	**PHP 2**
AHO manifestations	No	Yes	Yes	No	Yes	No
Serum calcium	↓	↓	N	↓	↓	↓
Serum PO_4	↑	↑	N	↑	↑	↑
Serum PTH	↓	↑	N	↑	↑	↑
Response to PTH:						
Urinary cAMP* (Chase-Aurbach test)	↑	↓	↑	↓	↓	↑
Urinary PO_4 (Ellsworth-Howard test)	↑	↓	↑	↓	↓	↓
Gsα activity	N	↓	↓	N	N	N
Inheritance	AD, AR, X	AD	AD	AD	AD	Sporadic
Molecular defect	PTH, CaSR, GATA3, Gcm2, others	*GNAS1*	*GNAS1*	*GNAS1*†	?Adenyl cyclase	?cAMP targets
Other hormonal resistance	No	Yes	No	No	Yes	No

*Plasma cyclic adenosine monophosphate (cAMP) responses are similar to those of urinary cAMP.
†Involves deletions that are located upstream of GNAS1.
↓ = decreased; ↑ = increased; ? = presumed, but not proved; AD = autosomal dominant; AHO = Albright hereditary osteodystrophy; AR = autosomal recessive; cAMP = cyclic adenosine monophosphate; N = normal; PHP = pseudoparathyroidism; PO_4 = phosphate; PPHP = pseudopseudoparathyroidism; PTH = parathyroid hormone; X = X-linked.

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228 PAGET DISEASE OF BONE

STUART H. RALSTON

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EPIDEMIOLOGY

The prevalence of Paget disease is about 0.5% in the United Kingdom and United States.[2] It also occurs in Western Europe and in people of European descent who have migrated to other parts of the world. Paget disease is rare in Scandinavians, Africans, and Asians. These differences are thought to have a genetic basis occurring as the result of founder mutations in northwest Europe many centuries ago, with subsequent spread to the remainder of the world through emigration. The incidence of Paget disease increases with age; in the United Kingdom, the incidence in women and men respectively is 0.037 to 0.074 per 10,000 person years in individuals ages 45 to 49 years but doubles in frequency each decade thereafter to reach an incidence of about 3.7 and 6.3 per 10,000 person years in individuals ages 85 years and older. The prevalence and severity of Paget disease have diminished in the United Kingdom and many countries over the past 25 years.[3] Although the mechanisms are unclear, suggested explanations include the influx of migrants from low prevalence areas, improved nutrition, a more sedentary lifestyle with a reduction in skeletal injuries, and reduced exposure to infections.

PATHOBIOLOGY

Susceptibility to Paget disease is strongly influenced by genetic factors, but environmental factors are also important. The importance of genetics is emphasized by the facts that between 5 and 40% of patients have a positive family history and that the risk for developing Paget disease in a first-degree relative of a patient is about seven-fold higher than in the general population. In many families, the disease is transmitted in an autosomal dominant manner, although penetrance is incomplete.

The most important susceptibility gene for classical Paget disease is *SQSTM1*. Mutations of *SQSTM1* are present in up to 40% of patients with a family history and 5 to 10% of people without a family history. The *SQSTM1* gene encodes a protein called p62 that is involved in regulating signal transduction downstream of the receptor activator of nuclear factor κB (RANK), which plays a critical role in regulating osteoclastogenesis when activated by RANK ligand (RANKL) (E-Fig. 228-1). The disease-causing mutations cluster in the ubiquitin-associated domain and have the effect of upregulating nuclear factor κB (NFκB) signaling and stimulating osteoclastogenesis by complex mechanisms that are reviewed in detail elsewhere.

Genome-wide association studies have identified seven other loci that predispose to Paget disease and that individually increase the risk between 1.4- and 1.7-fold.[4] These loci have additive effects, such that individuals who carry several predisposing alleles have a substantially increased risk for developing Paget disease. Many lie close to genes that play key roles in osteoclast function, including *CSF1*, which encodes macrophage colony-stimulating factor (M-CSF); *TNFRSF11A*, which encodes RANK; *TM7SF4*, which encodes DC-STAMP; *OPTN*, which encodes optineurin; *PML*, which encodes a protein involved in regulating interferon signaling; and *RIN3*, which encodes a guanine exchange factor that is expressed in osteoclasts (see E-Fig. 228-1).

Rare inherited diseases with clinical features overlapping with those of Paget disease[5] include familial expansile osteolysis and related syndromes caused by mutations affecting the signal peptide of RANK, as well as juvenile Paget disease caused by loss of function mutations affecting osteoprotegerin. Mutations in *VCP*, *hnRNPA2B1*, *hnRNPA1*, *PFN1*, *OPTN*, and *SQSMT*, which may result in defects in the autophagy pathway, can also lead to multisystem proteinopathy where

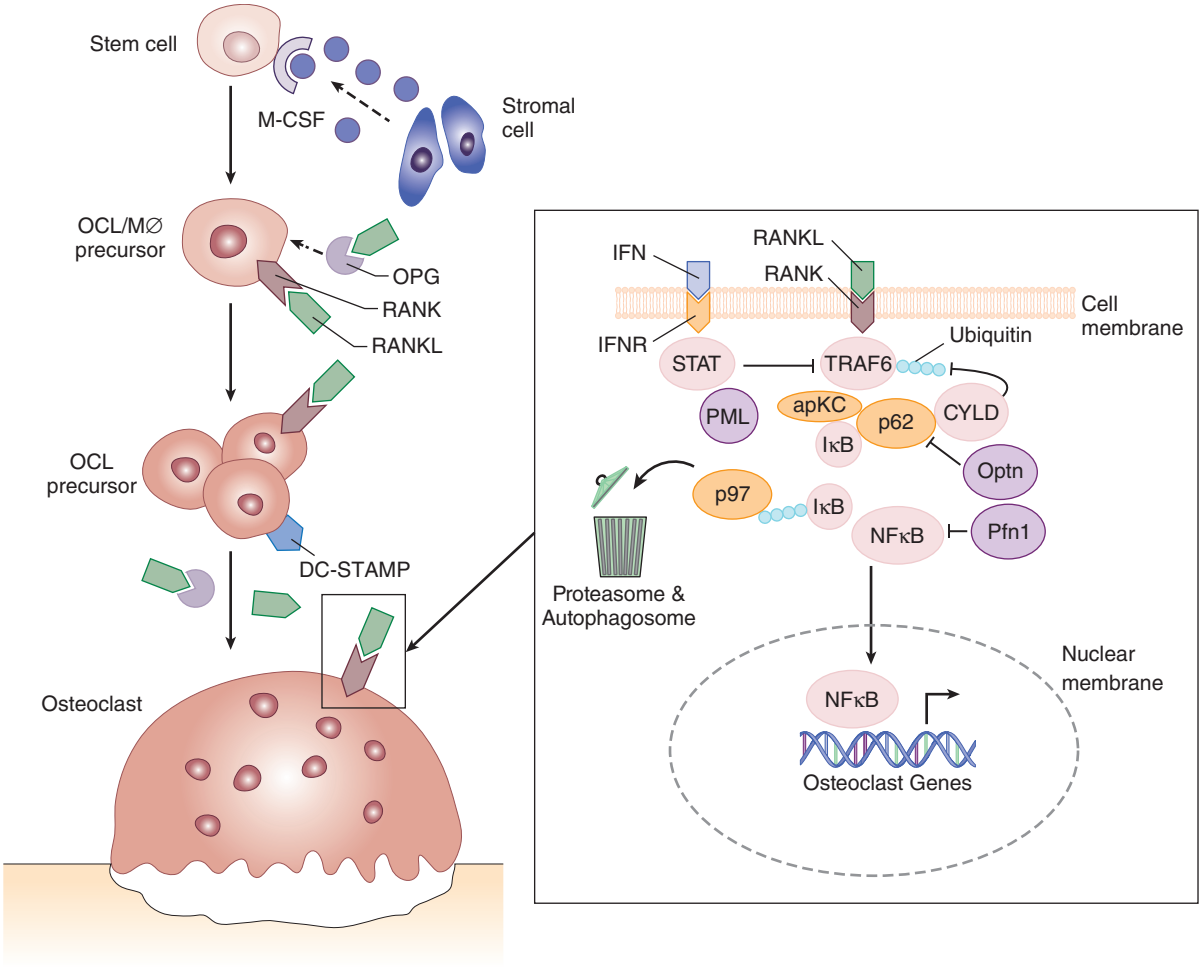

E-FIGURE 228-1. Regulators of osteoclast dysfunction in Paget disease. Some of the key molecules that have been implicated in the pathogenesis of Paget disease are illustrated. Macrophage colony-stimulating factor (M-CSF) encoded by *CSF1* is required for differentiation of stem cells to the osteoclast/macrophage (OCL/MØ) lineage. Osteoclast differentiation and activity are enhanced when RANK (encoded by *TNFRSF11A*) is activated by RANKL but inhibited by OPG (encoded by *TNFRSF11B*). Fusion of osteoclast precursors to form mature osteoclasts requires DC-STAMP (encoded by *TM7SF4*). Within the cell (*inset*), p62 (encoded by *SQSTM1*) is required for signal transduction downstream of the RANK receptor and is also involved in regulating autophagy. The p97 protein (encoded by *VCP*), Optn (encoded by *OPTN*), and Pfn1 (encoded by *PFN1*) are involved in regulating NFκB signaling and autophagy whereas *PML* acts as a mediator of interferon signaling by interacting with STAT, which negatively regulates osteoclastogenesis.

ABSTRACT

Paget disease of bone is characterized by focal abnormalities of increased and disorganized bone remodeling affecting one or more skeletal sites. It predominantly affects people of European descent and is rarely diagnosed before the age of 50 but becomes more common with increasing age. Men are affected more commonly than women. Genetic factors play an important role, and variants in the several genes have been identified that predispose to the disease by influencing osteoclast function and autophagy. Many patients are asymptomatic, but bone pain is the most common symptom in those who do come to medical attention. Other complications include deformity, pathologic fractures, deafness, osteoarthritis, nerve compression syndromes, and osteosarcoma. The diagnosis is often suspected by finding an elevated serum alkaline phosphatase or by finding typical features on a radiograph. The most sensitive imaging technique is radionuclide bone scan, which is the best way to define the extent of disease. The treatment of choice is bisphosphonates, which are indicated when bone pain is localized to an affected site. Bisphosphonates should not be prescribed with the aim of normalizing alkaline phosphatase values in asymptomatic patients. Within the bisphosphonates, zoledronic acid is most likely to give a favorable pain response and has a prolonged duration of action with effects that can persist for several years.

KEYWORDS

Paget disease of bone
osteoclast
SQSTM1
bisphosphonate

Paget disease is part of a generalized disorder in which dementia, myopathy, or amyotrophic lateral sclerosis can also occur.[6,7] Mutations in *ZNF687* cause a form of Paget disease that is accompanied by giant cell tumors. At present, the mechanisms by which *ZNF687* mutations cause this syndrome is unclear.

Bone is normally renewed and repaired in an orderly and tightly regulated fashion through the process of bone remodeling. Bone remodeling is highly abnormal in Paget disease. Osteoclasts are increased in number and size, and they are hypernucleated. Some contain nuclear inclusion bodies, which may be aggregates of undegraded proteins caused by defects in the autophagy pathway. Bone formation is markedly increased, and the amount of new bone that is formed exceeds that which is removed by osteoclastic activity, leading to enlargement and deformity of affected bones (Fig. 228-1). The newly formed bone is laid down in a disorganized fashion (woven bone) and has impaired mechanical strength. Other features include increased vascularity and marrow fibrosis.

The focal nature of Paget disease remains a puzzle. Suggested explanations include the occurrence of somatic mutations in affected bones, which locally increase osteoclast activity, or excessive mechanical loading or skeletal injuries early in life, which by causing microdamage act as a focus for localized increases in bone remodeling.

CLINICAL MANIFESTATIONS

An estimated 7 to 16% of patients with Paget disease come to medical attention, but the mode of presentation is highly variable.[8] About 20% have no symptoms; in these subjects, Paget disease is detected as the result of a raised serum alkaline phosphatase level or an abnormal radiograph in individuals who are being investigated for another reason. In the remainder, symptoms attributable to Paget disease are observed. The most common is pain, which can be due to either increased bone turnover or to a complication such as osteoarthritis (Chapter 241), spinal stenosis (Chapter 369), pseudofractures, enlarged skull, bowing of long bones, or nerve compression syndromes. Deafness, which may occur in patients with skull involvement, is usually conductive rather than due to auditory nerve compression. Osteosarcoma (Chapter 187) occurs in less than 0.5% of cases but should be suspected in patients who experience a sudden increase in bone pain or swelling of an affected site. Other, rare complications include obstructive hydrocephalus, high-output cardiac failure, and hypercalcemia in patients who are immobilized. The risk for cardiovascular disease is increased in patients with Paget disease compared with age- and gender-matched controls, probably owing to an increased prevalence of vascular calcification.

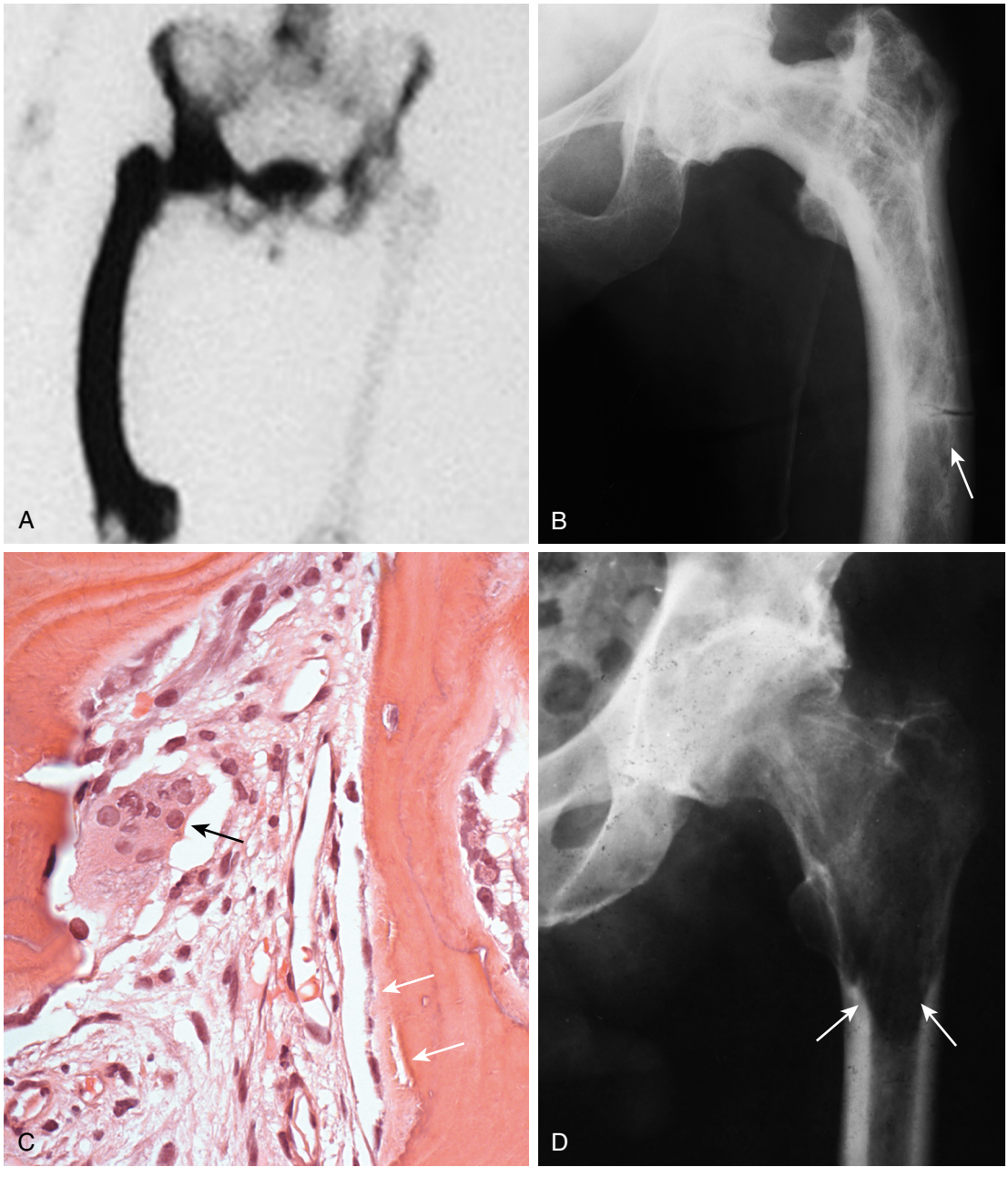

FIGURE 228-1. Radiographic and histologic features of Paget disease. A, Radionuclide bone scan image showing intense tracer uptake, typical of Paget disease of bone affecting the right femur. **B**, Radiograph of an affected left femur showing bone expansion with mixed osteolytic/osteosclerotic areas and loss of normal trabecular pattern. A pseudofracture is visible in the lateral cortex (*arrow*). **C**, Histologic features from a hematoxylin and eosin-stained section. A large osteoclast is visible (*black arrow*) close to an area of new bone formation (*white arrows*). There is extensive marrow fibrosis. Irregular cement lines typical of woven bone are apparent to the right of section. **D**, Predominantly lytic Paget disease of the left femur. The lytic area involves the intertrochanteric region and extends down the femoral shaft (*white arrows*).

Most patients have no clinical signs. However, some patients present with bone deformity (see Fig. 228-1) or warmth of the skin overlying an affected bone.

DIAGNOSIS

The diagnosis can usually be made by radiography, which shows the typical features of focal osteolysis with coarsening of the trabecular pattern, bone expansion, and cortical thickening (see Fig. 228-1).[9] Initially, the disease may be predominantly lytic in nature (see Fig. 228-1). The most sensitive way of defining the extent of Paget disease is a radionuclide bone scan in which tracer uptake is intensely increased at affected sites (see Fig. 228-1).[10] Imaging with magnetic resonance imaging and computed tomography is not usually required unless complications such as spinal stenosis or osteosarcoma are suspected.

Laboratory testing should include assessment of renal function, calcium, albumin, alkaline phosphatase, and 25(OH)D levels; liver function should be assessed to exclude the possibility that elevations in alkaline phosphatase are of hepatic origin. Typically, Paget disease presents with an elevation in alkaline phosphatase with otherwise normal biochemistries, but normal levels of alkaline phosphatase do not exclude the diagnosis. Vitamin D deficiency is a common finding but most likely reflects the fact that Paget disease predominantly affects older people in whom vitamin D deficiency is prevalent. Specialized markers such as bone-specific alkaline phosphatase or procollagen type 1 N-terminal propeptide can be useful in patients with coexisting liver disease but otherwise offer no advantage over total alkaline phosphatase for diagnosis and to assess response to the treatment. Analysis of genetic markers is being explored in the prediction of people at risk for developing Paget disease,[11] but genetic testing for susceptibility is not generally performed in routine clinical practice.

The differential diagnosis includes hyperostosis frontalis interna (a benign condition characterized by osteosclerosis of the frontal bones of the skull), fibrous dysplasia, chronic recurrent multifocal osteomyelitis (which can present with mixed osteosclerotic and osteolytic lesions), and osteosclerotic metastases, particularly from carcinoma of the prostate. Usually, Paget disease can be distinguished from these conditions clinically and through imaging, but occasionally, biopsy of an affected site may be required.

TREATMENT

The most common indication for medical treatment of Paget disease is bone pain localized to an affected site.[12] Bone pain may be caused by increased metabolic activity, but other causes may be operative, such as nerve compression syndromes, pseudofractures, secondary osteoarthritis, and other musculoskeletal conditions. Careful assessment of the patient is therefore necessary to decide on the most appropriate treatment. Bone pain caused by increased metabolic activity is localized to the affected site and is usually accompanied by a raised alkaline phosphatase level. It is common to encounter patients in whom pain occurs in the presence of coexisting osteoarthritis, bone deformity, or other musculoskeletal conditions. In such cases, it can be difficult to be sure about the origin of the pain, and many clinicians give a therapeutic trial of bisphosphonates to aid diagnosis. If the pain responds, it is assumed to be due to increased metabolic activity; if it does not, further evaluation should be undertaken to identify the cause and treat the patient appropriately. Pseudofractures, which are areas of focal osteolysis that traverse the lateral cortex of weight-bearing bones of the lower limbs, represent a distinct management problem. Some remain stable for prolonged periods without causing symptoms; others regress spontaneously; and others progress to pathologic fracture, often in association with a localized increase in pain at the affected site.

Bisphosphonates

Bisphosphonates are the drugs of first choice for the treatment of pain that is thought to be due to increased metabolic activity, and strong evidence indicates that they are more effective than placebo at improving bone pain in Paget disease (Table 228-1).[A1] Data comparing different bisphosphonates are limited, but intravenous zoledronic acid has been found to be superior to pamidronate and risedronate for lowering alkaline phosphatase level[13] and for relieving pain.

Repeated courses of bisphosphonates with the aim of normalizing alkaline phosphatase (intensive treatment) is no better in terms of pain, quality of life, or complications compared with therapy primarily aimed at controlling symptoms (symptomatic therapy).[A2] These findings demonstrate that trying to restore alkaline phosphatase to normal confers no clinical benefit over symptom-directed treatment.

After initiation of bisphosphonate therapy, levels of alkaline phosphatase start to fall within about 10 days, reach a nadir between 3 and 6 months, and can remain suppressed for many months or years thereafter, particularly with zoledronic acid.[14] Symptoms can improve while alkaline phosphatase levels are still falling, and good clinical responses are often observed in patients whose alkaline phosphatase levels are not restored to normal. Conversely, symptoms may recur before alkaline phosphatase values have become elevated again.

TABLE 228-1 BISPHOSPHONATES USED IN THE TREATMENT OF PAGET DISEASE

DRUG	DOSE	COMMON ADVERSE EFFECTS
ORAL		
Risedronate	30 mg/day orally for 2 mo	Dyspepsia, esophagitis
Alendronic acid†	40 mg/day orally for 6 mo	Dyspepsia, esophagitis
INTRAVENOUS		
Pamidronate	180 mg IV in divided doses, typically 60 mg on 3 consecutive days	Acute phase response, hypocalcemia
Zoledronic acid	5 mg IV	Acute phase response, hypocalcemia
Neridronate*	100 mg IV on 2 consecutive days	Acute phase response, hypocalcemia

*Only licensed in Italy. Can also be given intramuscularly in a dose of 25 mg daily for 8 days.
†Not licensed in the United Kingdom or Europe for Paget disease. Pamidronate and risedronate should be avoided if estimated glomerular filtration rate (eGFR) <30; zoledronic acid and alendronic acid should be avoided if eGFR <35.
IV = intravenous.

Intravenous bisphosphonates can cause transient bone pain, myalgia, headache, nausea, pyrexia, and fatigue within 1 to 3 days of the infusion in about 25% of cases (acute phase response). These symptoms can be ameliorated by acetaminophen given before and for a few days after the infusion, but they almost always subside within 7 days even without treatment. The acute phase response is much less common after second and subsequent infusions. Hypocalcemia may occur, particularly in patients with substantial elevations in bone turnover and vitamin D deficiency. The risk can be minimized by correcting vitamin D deficiency before treatment and providing calcium and vitamin D supplements for the first 1 or 2 weeks after the infusion.

Patients who take oral bisphosphonates must fast before dosing and for at least 30 minutes afterward to achieve adequate absorption. The most common adverse effect is dyspepsia. Other rare side effects of bisphosphonates include uveitis, skin rashes, atrial fibrillation, and osteonecrosis of the jaw (Chapter 229), as well as atypical subtrochanteric fractures. Bisphosphonates can cause kidney injury and are contraindicated in patients with significant renal impairment.

Other Drug Treatments

Analgesics, nonsteroidal anti-inflammatory drugs (see Table 26-4), and antineuropathic agents (e.g., amitriptyline 10 to 25 mg at bedtime or gabapentin 300 mg three times daily; see Table 26-5) may be required in patients with Paget disease, particularly when osteoarthritis or a nerve compression syndrome coexists. Calcitonin, 50 to 100 IU subcutaneously three times a week for up to 3 months can improve bone pain due to metabolic activity in Paget disease but is seldom used except in patients for whom bisphosphonates are contraindicated; adverse effects such as nausea and flushing can be problematic, and resistance may develop owing to the formation of neutralizing antibodies.

Nonpharmacologic Treatments

Nonpharmacologic approaches (e.g., acupuncture, physiotherapy, hydrotherapy, and transcutaneous electrical nerve stimulation) are often used to control pain, but their effectiveness has not been documented in controlled trials. Clinical experience suggests that specific problems such as limb shortening and deformity can be helped by aids and devices such as walking sticks and shoe raises.

Monitoring Disease Activity and the Effects of Treatment

Metabolic activity and the response to treatment are typically assessed by measuring the alkaline phosphatase level, but levels can be normal in patients with localized disease that is metabolically active. Further courses of treatment should be considered in patients who have recurrent or persistent pain and in whom alkaline phosphatase levels remain or become elevated.

Surgery

Orthopedic surgery may be required for the management of coexisting osteoarthritis, pseudofractures, fractures, bone deformity, and spinal stenosis. Osteotomy is performed infrequently, but small case series have reported good results. Surgery is much more frequently required to repair fractures and

to replace joints that are affected by osteoarthritis.[15] Although surgical treatment can be technically challenging because of deformity, osteosclerosis, and increased vascularity, the results of surgery are generally very good, and evidence from case series indicate that fractures through Pagetic bone generally heal normally. Bisphosphonates may be given before orthopedic and spinal surgery with the aim of reducing operative blood loss, but evidence to suggest that this approach actually reduces blood loss is limited. Orthopedic surgery may also be required in patients who develop osteosarcoma, but the prognosis is poor even with aggressive operative treatment. Cochlear implantation can benefit patients with deafness owing to Paget disease of the skull.

PROGNOSIS

The prognosis of Paget disease is highly variable. Some patients remain completely asymptomatic throughout life, but patients who present clinically frequently have complications and have a significant reduction in quality of life. Although modern bisphosphonates are highly effective at suppressing bone turnover in Paget disease, they have not as yet been shown to alter the natural history of the disease or prevent complications. The severity and extent of disease can be predicted by genotyping for *SQSTM1* mutations and other risk alleles, and studies are currently in progress to determine whether genetic testing can be combined with prophylactic bisphosphonate therapy to prevent or delay the onset of disease.

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TABLE 229-1 CAUSES OF OSTEONECROSIS OF CARTILAGE AND BONE

Endocrine/metabolic
Ethanol abuse
Glucocorticoid therapy
Cushing disease
Diabetes mellitus
Hyperuricemia
Osteomalacia
Hyperlipidemia
Bone antiresorptive therapy (osteonecrosis of the jaw)
Storage diseases (e.g., Gaucher disease)
Hemoglobinopathies (e.g., sickle cell disease)
Trauma (e.g., dislocation, fracture)
Human immunodeficiency virus (HIV) infection
Dysbaric conditions (e.g., caisson disease)
Collagen vascular disorders
Irradiation
Pancreatitis
Organ transplantation
Hemodialysis
Burns
Intravascular coagulation
Idiopathic, familial
Pregnancy

FIGURE 229-1. Exposed dead bone characterizes osteonecrosis of the jaw.

229 OSTEONECROSIS, OSTEOSCLEROSIS/ HYPEROSTOSIS, AND OTHER DISORDERS OF BONE

MICHAEL P. WHYTE AND KATHRYN M. DAHIR

OSTEONECROSIS

DEFINITION

Osteonecrosis (aseptic, avascular, or ischemic necrosis of bone) refers to skeletal infarction. Bone infarcts may be asymptomatic, cause self-limited discomfort, or engender painful collapse of subarticular bone and resulting joint destruction.

EPIDEMIOLOGY AND PATHOBIOLOGY

Many conditions are associated with osteonecrosis (Table 229-1). In adults, the most common causes are prior hip fracture, osteomyelitis (Chapter 251), renal dialysis (Chapter 117), ethanol abuse (Chapter 364), and long-term glucocorticoid therapy (Chapter 28).[1]

Skeletal infarction can result from blood vessel destruction (e.g., joint dislocation, fracture), obstruction (e.g., thromboemboli, sickle cell disease, fat emboli, caisson disease), or, hypothetically, compression from local expansion of fatty tissue (e.g., ethanol abuse, glucocorticoid treatment, diabetes mellitus). However, symptoms may not occur unless, weeks later, resorption of dead bone during skeletal repair leads to pathologic fracture. Certain skeletal sites (often subarticular) are predisposed to osteonecrosis, but the locations differ for traumatic compared with nontraumatic processes. Osteochondrosis refers to necrosis of ossification centers. At all ages, however, the femoral head is especially prone to infarction. Nontraumatic osteonecrosis commonly affects the humeral head, femoral condyles, distal end of the tibia, and talus. Although the pathogenesis is uncertain, administration of potent bone antiresorptive agents, especially to patients with malignant disease, and antiangiogenic agents has been associated with osteonecrosis of the jaw (Fig. 229-1).[2,3]

CLINICAL MANIFESTATIONS

Pain occurs acutely if there is skeletal collapse. Chronic arthralgia results from desquamated necrotic tissue and articular destruction.

DIAGNOSIS

Magnetic resonance imaging that demonstrates bone marrow edema is especially sensitive for detecting early osteonecrosis.[4] Bone scintigraphy discloses skeletal reconstitution with or without fracture. Relatively late in the pathologic process, radiographs first show patchy areas of osteopenia and osteosclerosis that reflect skeletal repair. A linear subchondral radiolucency (crescent sign) indicates bone collapse.

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to replace joints that are affected by osteoarthritis.[15] Although surgical treatment can be technically challenging because of deformity, osteosclerosis, and increased vascularity, the results of surgery are generally very good, and evidence from case series indicate that fractures through Pagetic bone generally heal normally. Bisphosphonates may be given before orthopedic and spinal surgery with the aim of reducing operative blood loss, but evidence to suggest that this approach actually reduces blood loss is limited. Orthopedic surgery may also be required in patients who develop osteosarcoma, but the prognosis is poor even with aggressive operative treatment. Cochlear implantation can benefit patients with deafness owing to Paget disease of the skull.

PROGNOSIS

The prognosis of Paget disease is highly variable. Some patients remain completely asymptomatic throughout life, but patients who present clinically frequently have complications and have a significant reduction in quality of life. Although modern bisphosphonates are highly effective at suppressing bone turnover in Paget disease, they have not as yet been shown to alter the natural history of the disease or prevent complications. The severity and extent of disease can be predicted by genotyping for *SQSTM1* mutations and other risk alleles, and studies are currently in progress to determine whether genetic testing can be combined with prophylactic bisphosphonate therapy to prevent or delay the onset of disease.

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Hyperlipidemia
Bone antiresorptive therapy (osteonecrosis of the jaw)
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Hemoglobinopathies (e.g., sickle cell disease)
Trauma (e.g., dislocation, fracture)
Human immunodeficiency virus (HIV) infection
Dysbaric conditions (e.g., caisson disease)
Collagen vascular disorders
Irradiation
Pancreatitis
Organ transplantation
Hemodialysis
Burns
Intravascular coagulation
Idiopathic, familial
Pregnancy

FIGURE 229-1. Exposed dead bone characterizes osteonecrosis of the jaw.

229 OSTEONECROSIS, OSTEOSCLEROSIS/ HYPEROSTOSIS, AND OTHER DISORDERS OF BONE

MICHAEL P. WHYTE AND KATHRYN M. DAHIR

OSTEONECROSIS

DEFINITION

Osteonecrosis (aseptic, avascular, or ischemic necrosis of bone) refers to skeletal infarction. Bone infarcts may be asymptomatic, cause self-limited discomfort, or engender painful collapse of subarticular bone and resulting joint destruction.

EPIDEMIOLOGY AND PATHOBIOLOGY

Many conditions are associated with osteonecrosis (Table 229-1). In adults, the most common causes are prior hip fracture, osteomyelitis (Chapter 251), renal dialysis (Chapter 117), ethanol abuse (Chapter 364), and long-term glucocorticoid therapy (Chapter 28).[1]

Skeletal infarction can result from blood vessel destruction (e.g., joint dislocation, fracture), obstruction (e.g., thromboemboli, sickle cell disease, fat emboli, caisson disease), or, hypothetically, compression from local expansion of fatty tissue (e.g., ethanol abuse, glucocorticoid treatment, diabetes mellitus). However, symptoms may not occur unless, weeks later, resorption of dead bone during skeletal repair leads to pathologic fracture. Certain skeletal sites (often subarticular) are predisposed to osteonecrosis, but the locations differ for traumatic compared with nontraumatic processes. Osteochondrosis refers to necrosis of ossification centers. At all ages, however, the femoral head is especially prone to infarction. Nontraumatic osteonecrosis commonly affects the humeral head, femoral condyles, distal end of the tibia, and talus. Although the pathogenesis is uncertain, administration of potent bone antiresorptive agents, especially to patients with malignant disease, and antiangiogenic agents has been associated with osteonecrosis of the jaw (Fig. 229-1).[2,3]

CLINICAL MANIFESTATIONS

Pain occurs acutely if there is skeletal collapse. Chronic arthralgia results from desquamated necrotic tissue and articular destruction.

DIAGNOSIS

Magnetic resonance imaging that demonstrates bone marrow edema is especially sensitive for detecting early osteonecrosis.[4] Bone scintigraphy discloses skeletal reconstitution with or without fracture. Relatively late in the pathologic process, radiographs first show patchy areas of osteopenia and osteosclerosis that reflect skeletal repair. A linear subchondral radiolucency (crescent sign) indicates bone collapse.

ABSTRACT

Osteonecrosis is ischemic bone infarction, which can range in severity from being asymptomatic to painful collapse of bone or joint destruction. Nontraumatic osteonecrosis typically affects the humeral head, femoral condyles, distal end of the tibia, or talus. Surgical procedures, such as decompression, arthrotomy, or resection, may limit disability. Osteonecrosis of the jaw can be a severe adverse event associated with the use of potent antiresorptive agents. Many conditions are associated with radiographic evidence of focal or generalized increase in bone density. Among these, osteosclerosis refers to thickening of trabecular bone, whereas hyperostosis describes widening of cortical bone. Medical therapy for most of these disorders is unsatisfactory.

KEYWORDS

osteonecrosis
osteopetrosis
fibrous dysplasia
exostosis
achondroplasia
hyperostosis
osteosclerosis
aseptic necrosis

TREATMENT

Nonweight bearing is advisable for the affected limb. Decompression by trephine insertion is used at some sites. Arthrotomy to remove debris, transpositional osteotomy, arthroplasty, or joint replacement may be necessary.[5] Medical approaches to osteonecrosis of the jaw have been disappointing,[A1,6] but teriparatide (an osteoanabolic parathyroid analogue given under expert supervision) may lead to resolution in about 60% of cases when the condition is diagnosed in its early stages.[7] Surgical resection also can be beneficial.[8]

OSTEOSCLEROSIS/HYPEROSTOSIS

Osteosclerosis refers to thickening of trabecular (spongy, cancellous) bone.[9] Hyperostosis describes widening of cortical (compact) bone. Many conditions are associated with radiographic evidence of increased bone density (Table 229-2). Skeletal dysplasias, metabolic disturbances, and various other disorders can cause generalized or focal increases in bone mass. Aberrations in skeletal growth, modeling (shaping), or remodeling (turnover) may be at fault. Increases in trabecular bone, cortical bone, or both may augment skeletal density. Most of the dysplasias can be diagnosed by gene mutation analysis.

TABLE 229-2 DISORDERS THAT CAUSE DENSE BONES

DYSPLASIAS
Central osteosclerosis with ectodermal dysplasia
Craniodiaphyseal dysplasia
Craniometaphyseal dysplasia
Dysosteosclerosis
Endosteal hyperostosis
van Buchem disease
Sclerosteosis (types 1 and 2)
Worth type (LRP5 and LRP6 activation)
Frontometaphyseal dysplasia
Infantile cortical hyperostosis (Caffey disease)
Juvenile Paget disease
Lenz-Majewski syndrome
Melorheostosis
Metaphyseal dysplasia (Pyle disease)
Mixed sclerosing bone dystrophy
Oculodento-osseous dysplasia
Osteodysplasia of Melnick and Needles
Osteopathia striata
Osteopetrosis (multiple types)
Osteopoikilosis
Progressive diaphyseal dysplasia (Engelmann disease)
Pyknodysostosis
Trichodentoosseous dysplasia
METABOLIC CONDITIONS
Carbonic anhydrase II deficiency
Heavy metal poisoning
Hepatitis C–associated osteosclerosis
Hyperparathyroidism, hypoparathyroidism, pseudohypoparathyroidism
Hypervitaminosis A, D
Hypophosphatemic rickets or osteomalacia (several types)
Milk-alkali syndrome
Renal osteodystrophy
Skeletal fluorosis (endemic and nonendemic)
OTHER DISORDERS
Axial osteomalacia
Erdheim-Chester disease
Fibrogenesis imperfecta ossium
Ionizing radiation
Lymphoma
Mastocytosis
Multiple myeloma
Myelofibrosis
Osteomyelitis
Osteonecrosis
Paget bone disease
Sarcoidosis
Skeletal metastases
Tuberous sclerosis

OSTEOSCLEROSIS

Neoplastic, hematologic, and metabolic disorders may preferentially sclerose trabecular bone because it houses marrow and remodels more rapidly than cortical bone.

FIBROGENESIS IMPERFECTA OSSIUM

This rare, usually sporadic condition features generalized osteopenia, but coarsening of the remaining trabeculae places it among the disorders that manifest osteosclerosis. The cause is unknown, but it is possibly genetic.[10] Subperiosteal bone formation and collagen synthesis in nonosseous tissues seem to be normal.

CLINICAL MANIFESTATIONS

Intractable skeletal pain typically begins gradually during middle age or later and then rapidly increases, with a debilitating course and eventual immobility. Spontaneous fractures are a prominent complication. Physical examination reveals marked bone tenderness.

DIAGNOSIS AND TREATMENT

On radiography, only the skull is spared. Initially, osteopenia and a slightly abnormal appearance of trabecular bone are noted. The skeletal lesion is a localized form of osteomalacia (Chapter 226) that varies considerably in severity from area to area.

Corticomedullary junctions become indistinct as compact bone is replaced by an abnormal cancellous pattern. Generalized osteopenia causes the remaining spongy bone to appear coarse and dense in a fishnet pattern of mixed lytic and sclerotic areas. Alkaline phosphatase activity in serum is increased. Therapy with recombinant growth hormone under expert guidance may provide short-term benefit.

HYPEROSTOSIS

PROGRESSIVE DIAPHYSEAL DYSPLASIA (CAMURATI-ENGELMANN DISEASE)

Progressive diaphyseal dysplasia, which affects all races, is inherited as an autosomal dominant trait with variable expressivity. New bone formation gradually envelops both the periosteal and endosteal surfaces of long bone diaphyses.[11] In patients with severe disease, osteosclerosis also affects the axial skeleton.

Mutations alter the gene that encodes transforming growth factor-β1. The differentiation of osteoclasts may be deranged.

CLINICAL MANIFESTATIONS

During childhood, limping or a broad-based, waddling gait is noted. Muscular dystrophy can be diagnosed erroneously. Severely affected individuals may have a characteristic body habitus featuring an enlarged head with a prominent forehead, proptosis, and thin limbs with little subcutaneous fat or muscle mass as well as tender, thickened bones. Cranial nerve palsies and raised intracranial pressure can occur. Some patients have hepatosplenomegaly and Raynaud phenomenon. Symptoms may remit after puberty.

DIAGNOSIS

Irregular hyperostosis of the diaphyses of the major long bones slowly develops as a result of periosteal and endosteal new bone formation. The femur and tibia are most commonly affected. Metaphyses may be involved. The age at onset, rate of progression, and severity are variable. Clinical, radiographic, and bone scan findings are generally concordant. Serum alkaline phosphatase activity, biochemical markers of skeletal turnover, and erythrocyte sedimentation rate may be elevated. Histopathologic study reveals newly formed woven bone that matures and becomes incorporated into cortical bone. Electron microscopy of muscle may show myopathic changes and vascular abnormalities.

TREATMENT

Glucocorticoid therapy (optimally the lowest effective dose of prednisone on alternate days) can relieve bone pain and may normalize skeletal histology. Bisphosphonates or losartan under expert guidance may sometimes be useful.

ENDOSTEAL HYPEROSTOSIS

Sclerosteosis types 1 and 2 and van Buchem disease are rare autosomal recessive disorders and the most severe forms of endosteal hyperostosis. Sclerosteosis is caused by deactivating mutations in genes *SOST* and *LRP4*. Van Buchem disease involves a deletion downstream of an *SOST* enhancer. Increased osteoblastic

activity from impaired sclerostin action, with failure of osteoclasts to compensate for the increased bone formation, leads to the skeletal changes.[12]

CLINICAL MANIFESTATIONS

Sclerosteosis (generalized hyperostosis with syndactyly) affects primarily people of Dutch ancestry. The gender distribution appears equal. Patients are tall and heavy beginning in childhood, with a prominent, square mandible. Raised intracranial pressure and headache may reflect a diminishing cranial cavity that shortens life expectancy. Van Buchem disease causes progressive asymmetrical enlargement of the jaw during puberty. Patients may be symptom free, or, beginning as early as infancy, they may have recurrent facial nerve palsy, deafness, and optic atrophy from narrowing of cranial foramina. Long bones may hurt with applied pressure but are strong.

DIAGNOSIS

In sclerosteosis, the skeleton is radiographically normal in early childhood. Congenital syndactyly involves soft tissues and bone in type 1 versus 2, respectively. Progressive bone thickening widens the skull and causes prognathism. Osteosclerosis also involves the skull base, facial bones, vertebrae, pelvis, and ribs. Periosteal and especially endosteal thickening widens diaphyseal cortices and narrows medullary canals. Computed tomography can show fusion of ossicles and narrowing of the internal auditory canals and cochlear aqueducts. Serum alkaline phosphatase activity can be increased from enhanced bone formation.

TREATMENT

Management may include surgical correction of syndactyly and mandibular overgrowth. Decompression of narrowed foramina may alleviate cranial nerve palsies. Craniectomy may become necessary.

PACHYDERMOPERIOSTOSIS

Pachydermoperiostosis (hypertrophic osteoarthropathy, primary or idiopathic) features clubbing of the digits, hyperhidrosis with thickening of the skin (especially of the face), and periosteal new bone formation, most prominently in the distal ends of the limbs. Not all patients manifest all three principal features. Loss-of-function mutations are found in the *HPGD* gene that encodes 15-hydroxyprostaglandin dehydrogenase and in the *SLCO2A1* gene in the autosomal recessive forms. Autosomal dominant inheritance is also recognized.

CLINICAL MANIFESTATIONS

Men seem more severely affected than women, and Blacks more commonly than Whites. Symptoms typically begin during adolescence, intensify during the next decade, but then become quiescent. Arthralgia and fatigue are common. Stiffness and limited mobility occur in both the appendicular and the axial skeleton. Clubbing, with slowly progressive enlargement of the hands and feet, results in a pawlike appearance. Cutaneous changes include thickening, furrowing, pitting, and oiliness, especially of the scalp and face.

DIAGNOSIS

Periostitis thickens the distal portions of the tibia, fibula, radius, and ulna. Clubbing is obvious, and acro-osteolysis can occur. Periosteal proliferation is exuberant, with an irregular texture, and it often involves the epiphyses, whereas secondary hypertrophic osteoarthropathy (pulmonary or otherwise) typically causes a smooth and undulating periosteal reaction. Ankylosis of the joints, especially in the hands and feet, may trouble older patients. Bone scanning reveals symmetrical regular uptake along the cortical margins of long bones, especially in the legs—the double stripe sign. Genetic testing can diagnose hereditary forms.

TREATMENT

Patients with painful synovial effusions may respond to nonsteroidal anti-inflammatory drugs. Contractures or neurovascular compression by osteosclerotic lesions may require surgical intervention.

OSTEOSCLEROSIS WITH HYPEROSTOSIS

OSTEOPETROSIS

DEFINITION

Osteopetrosis (marble bone disease) is a group of rare disorders featuring elevated bone mass owing to lack of osteoclast formation or action during growth.[13] The two classic clinical categories are the autosomal recessive or "malignant" type, which often results in death by early childhood if untreated, and the autosomal dominant or "benign" type (Albers-Schönberg disease), which causes lesser complications. Autosomal recessive types can also feature intermediate severity, neuronal storage disease, or renal tubular acidosis with cerebral calcification owing to deficiency of carbonic anhydrase II. Bisphosphonate-induced osteopetrosis has been reported.

PATHOBIOLOGY

The defective *CLCN7* gene causing autosomal dominant osteopetrosis encodes a chloride channel that is important for osteoclasts to release hydrochloric acid. Biallelic mutations in this gene, or ones that encode components of a vacuolar hydrogen ion (H^+) pump, result in malignant osteopetrosis. Carbonic anhydrase II deficiency is caused by deactivating mutations in the gene *CA2* that encodes this isoenzyme. Especially rare autosomal recessive cases involve deficient osteoclastogenesis from loss-of-function mutations within the genes for either receptor activator of nuclear factor κB (RANK) or its ligand (RANKL).

Histopathologic studies show that all true forms of osteopetrosis feature profound deficiency of osteoclast action. Bone-embedded primary spongiosa (calcified cartilage deposited during endochondral bone formation) persists away from growth plates and is the pathognomonic finding. Defective endosteal bone remodeling impairs the formation of marrow space. Quiescent skeletal turnover leads to bone fragility from diminished interconnection of osteons, delayed conversion of immature (woven) bone to mature (compact) bone, and failure of microcracks to heal. Neuronal storage disease (ceroid-lipofuscin) may reflect a lysosomal defect. Deficient superoxide production (necessary for bone resorption) has been considered a pathogenetic factor.

CLINICAL MANIFESTATIONS

Malignant osteopetrosis can present during infancy as nasal "stuffiness" from underdeveloped mastoid and paranasal sinuses. Small cranial foramina may cause optic, oculomotor, or facial nerve palsy. Failure to thrive, delayed dentition, and fractures are common. Hypersplenism and recurrent infection, bruising, and bleeding reflect myelophthisis. Short stature, large head, frontal bossing, nystagmus, hepatosplenomegaly, and genu valgum are characteristic physical findings. Untreated children usually die during the first decade of life of hemorrhage, pneumonia, severe anemia, or sepsis.

Benign osteopetrosis can cause fracture, facial palsy, deafness, mandibular osteomyelitis, bone marrow failure, impaired vision, psychomotor delay, carpal tunnel syndrome, or osteoarthritis. Carbonic anhydrase II deficiency can lead to failure to thrive, fracture, developmental delay, mental subnormality, short stature, and cerebral calcification, but defective skeletal modeling and osteosclerosis may resolve. Both proximal and distal renal tubular acidosis have been described.

DIAGNOSIS

A generalized increase in bone density is the radiographic hallmark of osteopetrosis. In severe disease, modeling defects in long bones produce an "Erlenmeyer flask" deformity (Fig. 229-2). The cranium is usually thickened and dense, especially at the base, and the paranasal and mastoid sinuses are underpneumatized. Skeletal scintigraphy can disclose fractures and osteomyelitis. Magnetic resonance imaging helps monitor the response to bone marrow transplantation.

Serum levels of acid phosphatase and creatine kinase (brain isoenzyme) are often increased. In malignant osteopetrosis, hypocalcemia with secondary hyperparathyroidism and elevated serum concentrations of calcitriol can accompany radiographic changes of rickets. In benign osteopetrosis, biochemical indices of mineral homeostasis are typically unremarkable, although serum parathyroid hormone and lactate dehydrogenase isoenzyme levels may be elevated. Most forms of osteopetrosis can now be diagnosed by mutation analysis.

TREATMENT

Because the molecular pathogenesis, prognosis, and treatment of the more than 10 types of osteopetrosis can differ, precise diagnosis is crucial. For malignant forms of osteopetrosis, prompt use of human leukocyte antigen–identical bone marrow transplantation to supply functional osteoclasts has remarkably benefited some children. Interferon gamma 1b under expert supervision can delay the progression of malignant osteopetrosis. Calcium-deficient diets have uncertain efficacy and may be limited by hypocalcemia and rickets. Hyperbaric oxygenation helps treat osteomyelitis. Surgical decompression of optic and facial nerves can be beneficial.

FIGURE 229-2. Osteopetrosis. Anteroposterior radiograph of the distal femur shows a widened metadiaphyseal region, with alternating dense and lucent bands that are characteristic of autosomal dominant osteopetrosis. (From Whyte MP, Murphy WA. Osteopetrosis and other sclerosing bone disorders. In: Avioli LV, Krane SM, eds. *Metabolic Bone Disease*. 2nd ed. Philadelphia: WB Saunders; 1990.)

DIFFUSE IDIOPATHIC SKELETAL HYPEROSTOSIS

This condition is discussed in Chapter 252.

PYKNODYSOSTOSIS

This autosomal recessive condition is caused by loss-of-function mutations in *CTSK*, the gene that encodes cathepsin K. Consequently, bone collagen degradation and skeletal turnover are diminished. In chondrocytes and osteoblasts, inclusions have been described.

CLINICAL MANIFESTATIONS

Characteristic features seen during infancy or early childhood include a relatively large cranium, fronto-occipital prominence, proptosis, bluish sclerae, beaked and pointed nose, small facies and chin, obtuse mandibular angle, high-arched palate, dental malocclusion with retention of primary teeth, and disproportionate short stature. Cranial sutures remain open. Fingers are short and clubbed from acro-osteolysis or aplasia of the terminal phalanges, and the hands are small and square. Repeated fractures cause a knock-knee deformity. Mental retardation occurs in approximately 10% of patients. Adult height ranges from 4 feet 3 inches to 4 feet 11 inches. Life expectancy can be shortened by sleep apnea, recurrent respiratory infections, and right-sided heart failure from chronic upper airway obstruction secondary to micrognathia.

DIAGNOSIS

Osteosclerosis is uniform, first becoming apparent in childhood and increasing with age. Skeletal modeling defects do not distort the shaping of long bones, but they appear to have thick cortices because of narrow medullary canals. Clavicles are gracile and hypoplastic at their lateral segments. The calvarium and skull base are sclerotic, orbital ridges are dense, and wormian bones are present.

TREATMENT

Administration of growth hormones (Chapter 205) may improve growth somewhat. About 50% of patients may require treatment for sleep apnea (Chapter 394).[14] Fractures of the long bones usually mend satisfactorily. Internal fixation of long bones is formidable because of their narrow medullary space and hardness. Tooth extraction is difficult. Osteomyelitis of the mandible may require antibiotic, surgical, or hyperbaric therapy.

HEPATITIS C–ASSOCIATED OSTEOSCLEROSIS

Rarely, achy and tender limbs develop in individuals infected with hepatitis C virus (Chapter 135). Radiographic studies reveal a marked generalized increase in bone mass from osteosclerosis and hyperostosis. Disturbances in the insulin-like growth factor system may explain the enhanced bone formation. Treatment focuses on effective management of the viral infection (see Chapter 135). If needed, calcitonin or bisphosphonate therapy under expert supervision can slow bone turnover.

FOCAL OSTEOSCLEROSIS/HYPEROSTOSIS

OSTEOPOIKILOSIS

Osteopoikilosis ("spotted bones") is generally a radiographic curiosity due to a highly penetrant autosomal dominant deactivating mutation of the *LEMD3* gene. The bone lesions are usually asymptomatic. However, incorrect diagnosis may lead to confusion with serious conditions, including metastatic disease.[15] Some patients have connective tissue nevi called dermatofibrosis lenticularis disseminata (or Buschke-Ollendorff syndrome). On radiologic examination, numerous small, round or oval foci of bone sclerosis appear in cancellous bone in the metaepiphyseal regions of tubular, tarsal, carpal, and pelvic bones.

OSTEOPATHIA STRIATA

Osteopathia striata is usually an autosomal dominant curiosity of asymptomatic linear striations in the metaphyseal regions of long bones and in the ilium. However, two clinically important X-linked dominant disorders with osteopathia striata affect predominantly females: osteopathia striata with cranial sclerosis due to mutation of the *WTX* gene and osteopathia striata with widespread linear areas of dermal hypoplasia and various bone defects in the limbs due to mutation of the *PORCN* gene (Goltz syndrome).

MELORHEOSTOSIS

Melorheostosis is an ultra rare and sporadic disorder that features focal, dense bone changes, typically in the limbs and often with the appearance of dripping candle wax. Postzygotic mosaicism involving *KRAS*, *MAP2K1*, or *SMAD3* mutations has been implicated.[16]

CLINICAL MANIFESTATIONS

Involvement of a single limb is usual, and bilateral disease is generally asymmetrical.[17] Cutaneous changes over affected bones are common (e.g., linear scleroderma-like areas and hypertrichosis) and often appear before the hyperostosis. Symptoms typically begin during childhood, with pain and stiffness as the major complaints. Joints may become contracted and deformed from ectopic bone. Leg-length inequality results from soft tissue contractures and premature fusion of epiphyses. Skeletal changes seem to progress most rapidly throughout childhood. During adult life, melorheostosis may or may not gradually spread, but pain is especially common.

DIAGNOSIS

Irregular, dense, eccentric periosteal and endosteal hyperostosis affects a single bone or several adjacent bones. The lower limbs are most commonly involved. Endosteal thickening predominates during infancy and childhood, and periosteal new bone formation is prominent during adulthood. Ectopic bone formation may occur, particularly near joints.

TREATMENT

Surgical correction of contractures may be helpful.

MIXED SCLEROSING BONE DYSTROPHY

Mixed sclerosing bone dystrophy is typically a sporadic disorder with enigmatic combinations of osteopoikilosis, osteopathia striata, melorheostosis, cranial sclerosis, and other skeletal aberrations in one individual. Complications derive from the specific types of osteosclerosis or hyperostosis, such as nerve palsy with cranial sclerosis and bone pain with melorheostosis.

OTHER DISORDERS OF BONE

FIBROUS DYSPLASIA

Fibrous dysplasia is a sporadic developmental disorder with one or more expansile fibrous lesions within bone. Polyostotic disease is typically seen before the age of 10 years; monostotic disease begins in adolescence or early adulthood. McCune-Albright syndrome refers to polyostotic fibrous dysplasia, café au lait spots (Fig. 229-3), and endocrine hyperfunction.

FIGURE 229-3. McCune-Albright syndrome. Typical rough-border ("coast of Maine") pigmented café au lait spots. (From Whyte MP. Metabolic and dysplastic disorders. In: Coe FL, Favus MJ, eds. *Disorders of Bone and Mineral Metabolism*. New York: Raven Press; 1992.)

FIGURE 229-4. Fibrous dysplasia. A characteristic expansile lesion with a ground-glass appearance has caused thinning of the cortex in the mid-diaphysis of the fibula. (From Whyte MP. Fibrous dysplasia. In: Favus MJ, ed. *Primer on the Metabolic Bone Diseases and Disorders of Mineral Metabolism*. 3rd ed. Philadelphia: Lippincott-Raven; 1996.)

PATHOBIOLOGY

Fibrous dysplasia and McCune-Albright syndrome (also see Chapters 205 and 212) are caused by postzygotic mosaicism of an activating mutation in the gene that encodes the α subunit of the receptor subunit/adenylate cyclase–coupling G protein, *GNAS*. Bone formation is imperfect because mesenchymal cells do not fully differentiate into osteoblasts.

CLINICAL MANIFESTATIONS

Monostotic fibrous dysplasia is more common than polyostotic disease. The skull and long bones are affected most often. The skeletal lesions can deform bones, cause fractures, and occasionally entrap nerves. Sarcomatous degeneration is rare (<1%) but typically occurs within the facial bones or femur and is more frequent with polyostotic disease. Pregnancy may reactivate quiescent lesions. McCune-Albright syndrome usually causes pseudo-precocious puberty in girls (Chapter 214) but less commonly in boys. Patients may also develop thyrotoxicosis, Cushing disease, hyperprolactinemia, or hyperparathyroidism. Excess growth hormone can be associated with more severe skeletal lesions.[18] In some patients, acquired renal phosphate wasting causes hypophosphatemic rickets or osteomalacia (see Chapters 205 and 227).

In mild disease, bone lesions may not expand. In severe cases, defects can progress and new ones may appear. Spontaneous healing does not occur, but pathologic fractures generally mend well.

DIAGNOSIS

The skeletal lesions have a characteristic radiographic appearance. In the long bones, either the metaphysis or diaphysis typically is well defined with thin cortices and a ground-glass appearance (Fig. 229-4). With aging, the defects can become lobulated, with trabeculated areas of radiolucency.

TREATMENT

Stress fractures can be difficult to detect and to treat. When the skull is involved, nerve compression may require surgical intervention. In McCune-Albright syndrome, pharmacologic control of associated endocrinopathies is important. Bisphosphonate therapy under expert supervision can sometimes be helpful, especially for bone pain.[19]

HEREDITARY MULTIPLE EXOSTOSES

This relatively common, highly penetrant, autosomal dominant disorder features irregular bone excrescences that protrude from expanded metaphyses. Mutations have been identified in the *EXT1*, *EXT2*, and *TRPS1* genes. Osteocartilaginous exostoses arise from growth plates and increase in size until linear growth ceases. Lesions, which may become detached from the parent bone, have a relatively unremarkable structure, with an outer cortex and an inner spongiosa. Disability results primarily from discrepancies in limb length when linear bone growth suffers at the expense of transverse expansion. Compression of nerves, the spinal cord, or the vascular system occurs occasionally. Sarcomatous degeneration (0.5 to 2% of patients) should be suspected when an exostosis enlarges rapidly, especially in an adult. Troublesome lesions can be resected.

ENCHONDROMATOSIS (DYSCHONDROPLASIA, OLLIER DISEASE)

This sporadic disorder features cartilaginous masses that arise from growth plates and localize within the trabecular bone. Ollier disease is caused by somatic mosaic mutations in the *IDH1* and *IDH2* genes. The disease begins with localized swelling in childhood and interferes with linear bone growth. After puberty, cartilaginous masses no longer expand, but these lesions can be replaced by mature bone. Enchondromas appear radiographically as lucent defects in flat bones or in metaphyses of tubular bones, often with central calcific stippling. When enchondromatosis occurs together with multiple hemangiomas (Maffucci syndrome), a malignancy will develop in about 50% of affected individuals.[20]

ACHONDROPLASIA

Chondrodystrophies, which are disorders of cartilage growth, result in disproportionate short stature. Achondroplasia is the most common.[21] A gain-in-function mutation occurs in the gene that encodes fibroblast growth factor receptor type 3; 80% of cases represent new autosomal dominant mutations, which are more prevalent with increasing paternal age. Short tubular bones form because of abnormal endochondral ossification in the limbs. In the chondrocranium, membranous ossification is undisturbed, so the skull vault is normal. However, the cranial base and foramen magnum are small. The head is large, with frontal bossing and midface hypoplasia. Lumbar lordosis is greatly exaggerated, and the spinal canal narrows from the upper to lower segments of the vertebral column. Radiography shows a decreasing interpediculate distance. Trunk length is relatively normal, but the limbs show rhizomelic shortening, and the hands have a trident configuration. The long bones appear massive because of their disproportionately normal width. Growth plates are not grossly disorganized, and chondrocytes appear normal. Complications can include hydrocephalus and compression of the brain stem, spinal cord, or nerve roots. Minimal impingement by a disc or osteophyte on the small spinal canal can

cause neurologic disturbances. Subcutaneous vosoritide (which is a biologic analogue of C-type natriuretic peptide given once daily under expert supervision) can increase growth in children with achondroplasia,[A2,A3] but its long-term efficacy and safety are unknown. Despite these problems, achondroplasia is compatible with good health and a normal lifespan.[22]

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230 APPROACH TO THE PATIENT WITH ALLERGIC OR IMMUNOLOGIC DISEASE

KARI C. NADEAU

Allergic diseases and disorders of the immune system affect multiple organ systems. This chapter addresses approaches to common allergic disorders and inborn errors of immunity. Specific disorders are discussed in detail in the chapters to follow.

ALLERGIC DISEASE

DEFINITION AND EPIDEMIOLOGY

Diseases characterized by hypersensitivity of the immune system and inappropriate reactions to common environmental, food, and drug substances are termed allergic diseases. In the sensitized individual, common foods (e.g., peanut, milk, eggs), airborne particles (e.g., grass pollen, cat dander), drugs (e.g., aspirin, penicillin), insect stings (e.g., bees, wasps), or other agents (e.g., latex, dyes) can trigger an allergic reaction. Reactions can range from mild to severe to life-threatening, and symptoms can occur in one or many organs after skin contact, inhalation, ingestion of allergens, stings, or injections. The prevalence of allergic diseases has increased in recent decades. Although genetics plays a role in their etiology, potential explanations for the increase include improvements in hygiene, increased exposure to environmental pollutants, and alterations in diet and lifestyle. Climate change (Chapter 17) also indirectly plays a role by increasing air pollutants (e.g., wildfires and sandstorms), altering the characteristics of pollens (concentrations, allergenic potential, and composition), and promoting the migration of species.[1]

Allergic diseases can be classified based on the organs that are affected, the type of causal allergen, the interval between the exposure to the allergen and the onset of symptoms, and underlying mechanisms of the reaction. Allergic reactions may be immediate (minutes to 1 to 2 hours) or delayed (hours or days). Traditionally, hypersensitivity reactions have been classified into Type I, II, III, and IV (Fig. 230-1). A more commonly used system classifies allergic reactions into immunoglobulin E (IgE)-mediated, mixed IgE- and cell-mediated, and non-IgE-mediated allergic diseases.[2] IgE-mediated diseases are the best characterized allergic diseases, and reactions with high IgE levels are termed atopic diseases (Table 230-1).

PATHOBIOLOGY

Patients who have IgE-mediated allergic reactions undergo an initial sensitization phase during which IgE antibodies are produced to recognize a specific allergen and are bound to high-affinity FcεRI receptors on mast cells or basophils. Further exposure to allergens can lead to cross-linkage of IgE antibodies with subsequent degranulation of mast cells or basophils. The initial sensitization phase occurs as epithelial cytokines interleukin-25 (IL-25), IL-33, and thymic stromal lymphopoietin are produced in response to the increased permeability of the allergen owing to a loss of integrity in the epithelial barrier. These cytokines enable differentiation of naïve T cells to T_h2 cells as well as upregulation of cytokines (e.g., IL-4, IL-5, and IL-13) and IgE class-switching by B cells. Degranulation of mast cells and basophils leads to the release of histamine and other inflammatory mediators (e.g., cytokines, interleukins, leukotrienes, and prostaglandins) into the surrounding tissue, thereby causing several systemic effects, including vasodilation, the secretion of mucus, eosinophilic infiltration of tissues, and contraction of smooth muscle (E-Fig. 230-1). Atopic sensitization is thought to occur via exposure to allergens through an impaired skin barrier, whereas tolerance is thought to be mediated through the gut. Loss of barrier integrity enables allergens to penetrate and to initiate an inflammatory immune cascade of events that leads to sensitization. The immune dysfunction then further exacerbates the impaired skin barrier to form a vicious cycle.[3] Non-IgE-mediated reactions are poorly defined and are generally T-cell mediated.

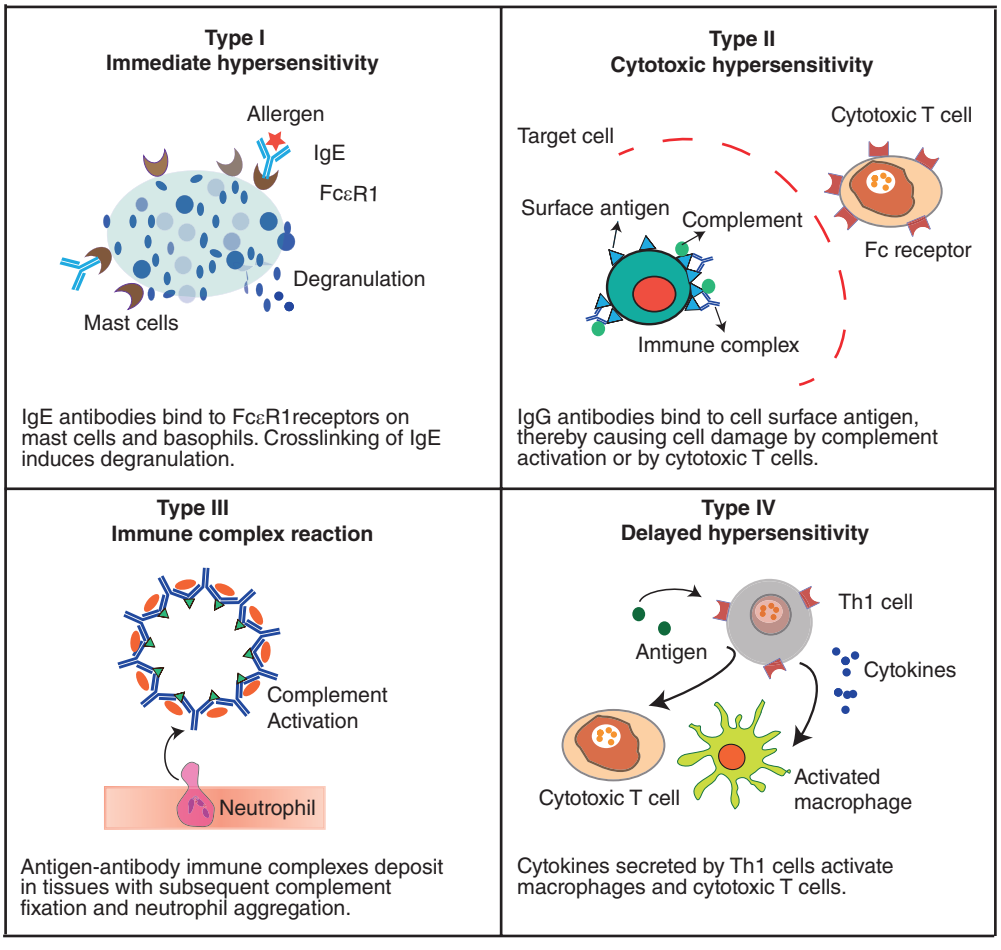

FIGURE 230-1. Types I-IV hypersensitivity reactions. Ig = immunoglobulin. (Reprinted with permission from Sampath V, et al. Vaccines and allergic reactions: the past, the current COVID-19 pandemic, and future perspectives. *Allergy*. 2021;76:1640-1660.)

ABSTRACT

Allergic diseases are hypersensitivity immune reactions that are associated with inappropriate responses to common environmental, food, and drug substances. Reactions can range from mild to severe to life-threatening, and symptoms can occur in one or many organs after skin contact, inhalation, ingestion of allergens, stings, or injections. The prevalence of allergic diseases has increased in recent decades. Although genetics play a role in the etiology of the disease, current hypotheses for the observed increases include improvements in hygiene, increased exposure to environmental pollutants, and alterations in diet and lifestyle. Allergic reactions may be immediate (within minutes to 1 to 2 hours) or delayed (hours or days).

The more than 400 primary inborn errors of immunity have variable clinical features, including immune deficiency, autoimmunity/autoinflammation, malignancy, or a combination of all three. These conditions should be suspected in patients who have recurrent, persistent, severe, or unusual infections.

KEYWORDS

allergic disease
atopy
IgE
inborn errors of immunity
mast cell
anaphylaxis
allergens
immune system

TABLE 230-1 COMMON IgE-MEDIATED, MIXED (IgE-MEDIATED AND CELL-MEDITATED), AND NON-IgE-MEDIATED ALLERGIES

DISEASE	APPROXIMATE PREVALENCE	KEY SYMPTOMS	EXAMPLES OF CAUSAL ALLERGENS
IgE-MEDIATED ALLERGIES			
Oral allergy syndrome (pollen-food syndrome)	5 to >20% (children), 10 to 60% (adults)	Rapid onset; tingling and pruritus of the lips, mouth, and oropharynx. Pharyngeal swelling in severe cases	Fresh fruits and vegetables, commonly seen in those with birch, ragweed, or grass pollen allergy
Food allergy	8% (children), 10% (adults)	Rapid onset, abdominal pain, vomiting, hives, wheezing, shortness of breath. Anaphylaxis in severe cases	Food allergens (e.g., egg, peanut, milk)
Anaphylaxis	5% in US (fatal anaphylaxis rare, 1 per million per year)	Rapid onset, progressive, multiorgan. Rapid progression to cardiovascular and/or respiratory collapse in severe cases	Foods (e.g., peanuts, shellfish), drugs, insect stings
Atopic dermatitis	10 to 20%	Pruritus, *Staphylococcus aureus* infection, lichenification, xerosis, excoriations	Foods, aeroallergens, exogenous irritants (e.g., wool, soaps)
Acute, seasonal, and perennial allergic conjunctivitis	5 to 30%	Conjunctivitis, eyelid edema, watery discharge, ocular itching, conjunctival hyperemia	Aeroallergens
Allergic asthma	7%	Chest tightness, shortness of breath, wheezing	Animal dander, mold, house dust mites
Allergic rhinitis	Up to 40% (children), 10 to 30% (adults)	Sneezing, rhinorrhea, lacrimation	House dust mites, grass pollen, tree pollen, animal dander
MIXED IgE-MEDIATED AND NON-IgE-MEDIATED ALLERGIES			
Eosinophilic GI disorders (eosinophilic esophagitis, eosinophilic colitis; eosinophilic gastritis; eosinophilic gastroenteritis)	Eosinophilic esophagitis: 10-60 per 100,000 Eosinophilic gastritis: 6 per 100,000 Eosinophilic colitis: 3 per 100,000 Eosinophilic gastroenteritis: 8 per 100,000	Symptoms dependent on region and nature of eosinophilic infiltration (mucosal, muscular, or serosal) and may include nausea, dysphagia, vomiting, failure to thrive, epigastric pain, food impaction, inflammation of some or all regions of the GI tract	Milk, egg, wheat, soy, peanuts
Urticaria (acute and chronic)	Acute urticaria: 14% Chronic urticaria: 0.1 to 1.5%	Pruritus and raised erythematous cutaneous lesions	Aeroallergens, foods, infections, insect stings, or drugs. Many cases are idiopathic
Atopic keratoconjunctivitis and vernal keratoconjunctivitis	Vernal keratoconjunctivitis: <1 per 10,000 of the population (Europe) Atopic keratoconjunctivitis: 20 to 40% of patients with atopic dermatitis; 5% (Japan)	Clinical symptoms can include photophobia and tearing in addition to commonly noted itching and grittiness as observed in ocular allergy. Ropy mucus, giant papillae, and Trantas dots are also often present. Patients who have atopic keratoconjunctivitis also have concurrent atopic dermatitis	Environmental allergens
NON-IgE-MEDIATED ALLERGIES			
Food protein–induced enterocolitis syndrome	0.35% to 0.7% (cow's milk mediated)	Vomiting, diarrhea, and failure to thrive	Milk, soy
Food protein–induced allergic proctocolitis	0.15 to 17% of infants with isolated rectal bleeding	Rectal bleeding	Cow's milk
Food protein–induced enteropathy	Prevalence unknown	Steatorrhea from malabsorption, diarrhea, and failure to thrive	Cow's milk proteins and soy proteins
Contact dermatitis	Significant variations with causal allergen	Inflammation, skin rash, and blisters	Poison oak, nickel

GI = gastrointestinal; Ig = immunoglobulin.

Specific Types of Allergies

Food Allergy

Food allergy is an immune reaction triggered by common food substances. Exposure to very small amounts of allergenic foods can trigger clinical symptoms, ranging in severity from mild to life-threatening, in one or many organs.[4] The reported prevalence of food allergies is rising.[5] Eosinophilic esophagitis (Chapter 124), food protein–induced enterocolitis syndrome, food protein–induced allergic proctocolitis, and food protein enteropathy (Chapter 126) are among the disorders in which food allergy may play a role.

Drug Allergy

Allergic reactions to drugs (Chapter 234) are a serious public health concern. Drug reactions mediated by immunologic reactions (antibodies or specific T lymphocytes) may occur immediately after exposure to the drug or may be delayed, may affect single or multiple organs, and may be mild, severe, or life-threatening.[6] Risk factors for developing a drug allergy include age (young and middle-aged adults), gender (women), genetic polymorphisms (e.g., human leukocyte antigen), and certain viral infections (e.g., HIV, Epstein-Barr virus). Other factors include increased frequency of exposure and prolonged high doses, intravenous or intramuscular route of administration, high-molecular-weight drugs, and drugs that haptenate tissue or blood proteins.[7]

Environmental Allergy and Occupational Allergy

Outdoor and indoor environmental allergens can sensitize or exacerbate allergic disease (allergic rhinitis, allergic conjunctivitis, and allergic asthma) through IgE-mediated mechanisms. Major indoor aeroallergens are derived from dust mites, cockroaches, cigarette smoking, animal dander (e.g., dog, cat, mice), and mold. Pollutants (Chapter 82) generated from diesel exhaust, gas-burning stoves, fireplaces, or heaters can also exacerbate allergies and asthma. Children who live in close proximity to major highways are more likely to be affected.[8] A number of substances used in different occupations can cause the development of allergic disease affecting the respiratory tract (Chapter 81) and skin. Examples include compounds with both low (dyes, isocyanates, metals) and high (latex, flour) molecular weight. Recurring high levels of exposure are the most important determinants in sensitizing individuals to occupational allergens.

CLINICAL MANIFESTATIONS

Allergic diseases affect different organs, such as the nose, lungs, eyes, gastrointestinal tract, or skin. Symptoms may be limited to one or more organs or, as in the case of anaphylaxis (Chapter 233), may be systemic and be life-threatening. The same allergic sensitization may manifest in different ways at

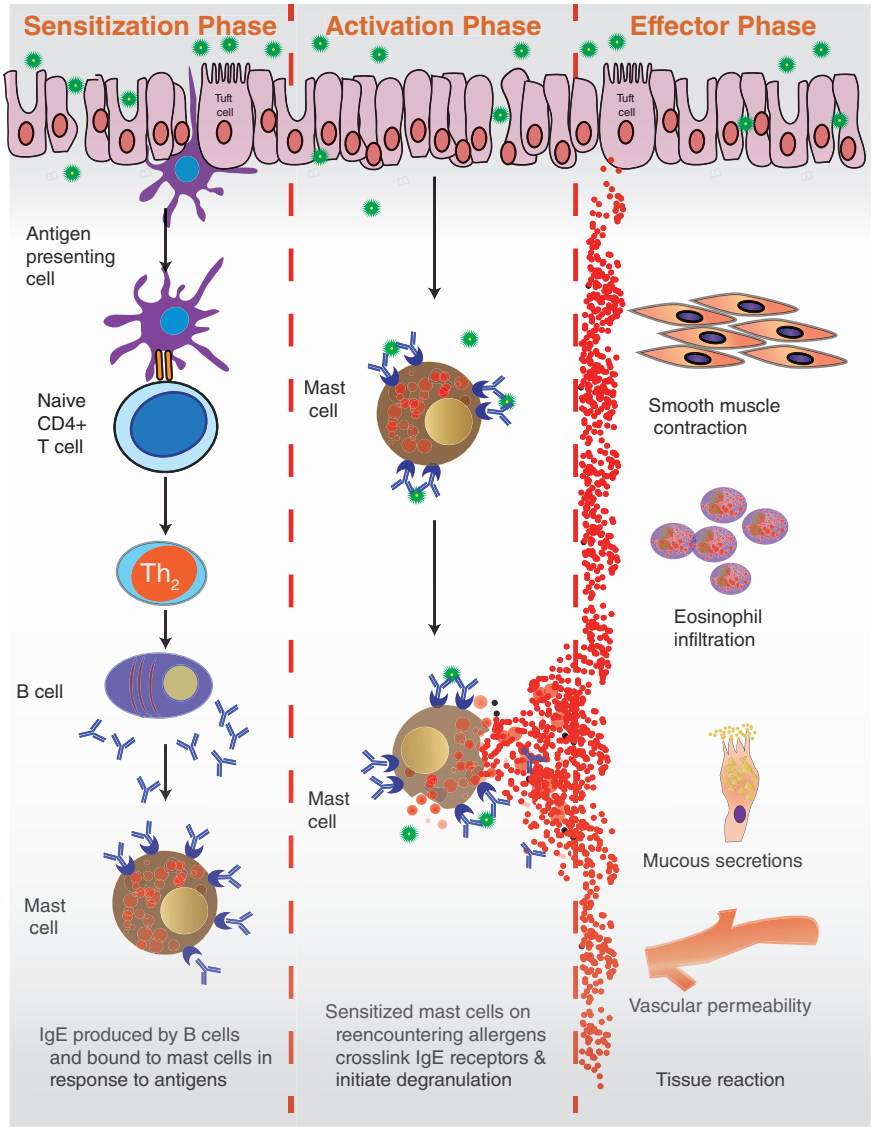

E-FIGURE 230-1. Mechanism of immunoglobulin (Ig) E–mediated allergic disease. The right column illustrates the various systemic effects of IgE-mediated allergic reactions, including smooth muscle contraction, tissue eosinophilic infiltration, mucus secretion, and vasodilation with vascular permeability.

different times in the same individual. With food allergies, allergic reactions occur within minutes to 2 hours after ingestion of the causal allergen. Oral allergy syndrome is a food allergy that requires prior sensitization to a cross-reacting inhalant allergen. Common symptoms include pruritus of the lips, tongue, and mouth.

Skin

Allergic disorders involving the skin include angioedema, acute and chronic urticaria, and atopic and contact dermatitis (Chapter 407). Symptoms of urticaria and angioedema include pruritus and transient, raised, erythematous cutaneous lesions that range in size from a few millimeters to several centimeters (Fig. 232-2).[9] Urticaria is classified based on time course and etiology. In acute urticaria, wheals and/or angioedema occur for a period of up to 6 weeks, whereas chronic spontaneous urticaria and chronic inducible urticaria are defined as recurrent or persistent lesions for 6 weeks or more.[10] Infections are considered to be the most common cause of acute urticaria, but other triggering factors may include food allergens, food additives, or drugs.

Co-occurrence of angioedema with urticaria is common and is found mainly on the face, lips, mouth, upper airways, and genitalia. Symptoms of acute urticaria or angioedema occur rapidly (often within minutes). Even without treatment, however, individual urticarial lesions typically resolve within 1 to 24 hours.

Atopic dermatitis (Chapter 405) is an IgE-mediated disease that is common in infants and children. In up to 30% of patients the disease has been linked to a loss-of-function mutation in the filaggrin gene, which is essential for skin barrier function. Increased colonization of *Staphylococcus aureus* is seen in more than 90% of patients with atopic dermatitis and may lead to secondary infections. Atopic dermatitis often precedes the development of other atopic diseases, such as food allergy, allergic rhinitis, or allergic asthma.

Allergic contact dermatitis (Chapter 405) is a common skin disease that can be caused by direct contact, airborne particles, vapors, or light.[11] The allergens that mediate allergic contact dermatitis are generally low-molecular-weight substances that combine with skin proteins to form complete allergens inducing innate and adaptive immune responses. Examples include metals (e.g., nickel), plants (e.g., poison oak), or drugs (e.g., neomycin). It is a delayed-type IV, T-cell-mediated, non-IgE reaction to common substances. Clinical manifestations of contact dermatitis vary widely, and multiple subtypes may occur simultaneously. Relapse is common, even with prolonged allergen avoidance.

Eyes

Ocular allergic conjunctivitis[12] includes simple allergic conjunctivitis (acute, seasonal, or perennial), vernal keratoconjunctivitis, atopic keratoconjunctivitis, and giant papillary conjunctivitis (Chapter 391). In simple allergic conjunctivitis, IgE-mediated reaction leads to an immediate or early response (within minutes). Further activation of chemokines leads to late-phase-mediated reactions. Vernal keratoconjunctivitis, atopic keratoconjunctivitis, and giant papillary conjunctivitis, however, appear to be mediated by both IgE and non-IgE cellular pathways.

Ocular allergies can be caused by numerous factors, such as exposure to air pollutants, insects (cockroaches and house dust mites), pet dander, or pollen. Seasonal allergic conjunctivitis and perennial allergic conjunctivitis primarily affect the conjunctiva and possibly the eyelids. In vernal keratoconjunctivitis and atopic keratoconjunctivitis, the cornea is also affected, and vision can become impaired. In seasonal allergic conjunctivitis and perennial allergic conjunctivitis, itching, redness, and swelling of the conjunctiva, along with tearing and discharge of white mucus, is common. One of the main characteristics of vernal keratoconjunctivitis is the presence of giant papillae (several millimeters in diameter) on the upper tarsal conjunctiva and seen easily on the underside of the upper eyelid. Other symptoms include ropy mucus discharge, Trantas dots (aggregation of epithelial cells and eosinophils that appear as gelatinous, mucoid nodules at the superior limbus of the conjunctiva), creasing of the lower eyelids, and pseudomembrane formation on the upper lid. A punctate keratitis may also appear in the central cornea and lead to the formation of a grayish plaque, corneal scarring, and visual impairment. In atopic keratoconjunctivitis, giant papillae and Trantas dots, similar to those found in vernal keratoconjunctivitis, may also be present. However, patients with atopic keratoconjunctivitis are generally older (ages 30 to 50 years) than patients with vernal keratoconjunctivitis (ages 10 years and younger) and often have concurrent atopic dermatitis or a positive family history of atopy. Atopic keratoconjunctivitis and vernal keratoconjunctivitis are two to three times more likely in males than females. Giant papillary conjunctivitis is most commonly seen in conjunction with the use of soft contact lenses, and it is present in approximately 5% of that population.

Upper Airway

Allergic rhinitis[13] affects the upper airways and may be classified as either seasonal (intermittent) or perennial (chronic), with approximately 20% of cases being seasonal, 40% perennial, and 40% with features of both (Chapter 394). Symptoms include sneezing, nasal pruritus, nasal airflow obstruction, and nasal discharge. In seasonal allergic rhinitis, symptoms usually occur in either spring, summer, or fall and are generally associated with pollen from trees, grass, and weeds. Pollen count and type vary with geographic regions. Even within a specific region, changes in weather patterns can cause yearly variations in pollen count and in the overall prevalence and severity of allergic rhinitis. In perennial allergic rhinitis, exposure to indoor and outdoor air pollutants such as pet dander, cockroaches, house dust mites, and molds, should be taken into consideration. In some individuals, seasonal allergies may overlap, thereby leading to perennial symptoms. Approximately 10 to 40% of individuals have concurrent asthma.

Lower Airway

The most common asthmatic phenotype is allergic asthma (Chapter 75), which is a chronic inflammatory disease of the airways. Up to 80% of childhood asthma and more than 50% of adult asthma cases may have an allergic component.[14] Examples of allergens include air pollutants, respiratory viruses, tobacco smoke, drugs, endotoxins, pollen, animal dander, cockroaches, house dust mites, and foods. IgE plays a central role in allergic asthma pathophysiology and has been implicated in both the early (wheezing, shortness of breath, chest tightness, and cough) and late (inflammatory infiltration, bronchoconstriction, and tissue remodeling) phases. Other characteristics include mucosal infiltration by eosinophils, mast cells, and $CD4^+$ T cells. It is a Th2-driven process and high-affinity IgE receptors are observed in inflammatory and resident cells. Allergic asthma is often accompanied by eczema and allergic rhinitis. Other diseases associated with allergic asthma include eosinophilic granulomatosis with polyangiitis (Chapter 249) and allergic bronchopulmonary aspergillosis (Chapter 311).[15]

Gastrointestinal Tract

Allergic inflammatory diseases that affect the gastrointestinal tract include eosinophilic gastrointestinal diseases, food protein–induced enterocolitis syndrome, food protein–induced allergic proctocolitis, and food protein enteropathy. All three are typically present in infancy and are triggered most commonly by cow's milk protein. Symptoms of food protein–induced enterocolitis syndrome include vomiting, lethargy, and dehydration. Patients with food protein–induced allergic proctocolitis present with bloody and mucous stools. Diarrhea, malabsorption, and failure to thrive are observed with food protein enteropathy. These diseases have a favorable prognosis, and most resolve by 3 to 5 years of age.

Eosinophilic esophagitis (Chapter 124) is the most common and well characterized of the eosinophilic gastrointestinal diseases. Symptoms include nausea, dysphagia, vomiting, failure to thrive, epigastric pain, food impaction,[16] and inflammation of the esophagus. Patients with eosinophilic esophagitis often have comorbid atopic diseases such as allergic rhinitis, asthma, food allergy, and atopic dermatitis.

Eosinophilic gastritis, eosinophilic colitis, and eosinophilic gastroenteritis (Chapter 126) are rare and often found in patients who have a history of atopy. Symptoms vary based on region of the gastrointestinal tract affected and extent of eosinophilic infiltration (mucosal, muscular, or serosal). In rare cases, eosinophilic ascites is observed with eosinophilic infiltration into the serosal layer.

Systemic

Anaphylaxis (Chapter 233)[17] is a serious systemic reaction to allergens, is rapid in onset (seconds to minutes), and can quickly progress to cardiovascular and/or respiratory collapse within minutes of inception. Anaphylaxis can be immunologic, nonimmunologic (previously termed anaphylactoid), or idiopathic. Nonimmunologic anaphylaxes are commonly termed complement activation-related pseudoallergy and may be due to activation of complement by nanoparticles, colloidal solutions, or liposomes without the formation of immune complexes. Regardless of the mechanism, all three types are potentially fatal. Anaphylaxis is associated with skin (flushing, urticaria, and angioedema), pulmonary (asthma, laryngeal edema), cardiac (arrhythmia), vascular (hypotension, extravascular fluid loss), gastrointestinal (abdominal

pain, nausea, vomiting, diarrhea), and nonspecific symptoms (metallic taste, sense of impending doom). Common triggers include insect stings, drugs, and food allergens.

DIAGNOSIS

Allergy is a systemic immune disease, and a patient with suspected allergies requires a comprehensive evaluation. A final diagnosis of allergy should be based on correlations among the history, physical findings, and laboratory test results. Because many of the diseases comprise distinct heterogeneous subtypes, a precision medicine approach can guide to personalized diagnosis and treatment.

Patient History

An accurate history is a crucial first step in diagnosing allergic disease. A family history of atopic disease increases risk for allergic disease. The history should include the nature of the patient's symptoms (frequency and severity) and potential exposures to allergens, such as seasonal (e.g., pollen from trees or grasses), perennial (e.g., dust mites, cockroaches), food (e.g., peanuts, tree nuts, egg, raw fruits), environmental (e.g., pets, pollutants, cockroaches, molds, fungi), drug (e.g., penicillin), and occupational (e.g., flour, latex, paints) allergen exposures (Table 230-2). A careful history of exposure, timing of reactions, and clinical symptoms can help narrow the cause of drug allergy because no definitive diagnostic test exists to confirm drug allergy. The use of angiotensin-converting enzyme inhibitors is the leading cause of acquired angioedema, and Blacks are at higher risk.

Physical Examination

Skin should be examined for possible urticaria, angioedema, or atopic dermatitis. Urticarial lesions (Fig. 407-1) typically consist of small, pink, raised, irregular wheals and may be associated with angioedema. Angioedematous lesions are most often found on the face and acral areas. Signs of atopic dermatitis (Fig. 405-5) include flexular papulae, thickening of skin due to hyperkeratinization, excoriations, and lichenification.

The eyes should be examined for signs of excessive tear production, injection and swelling of the palpebral conjunctivae, and swollen or darkened periorbital tissues. Cobblestone papillae may be present.

Internal inspection of the nasal mucosa should be focused on deviations or perforations of the nasal septum, nasal patency, presence of polyps (Figs. 394-3 and 394-4) or foreign bodies, mucosal appearance, and presence and nature of secretions. Decreases in nasal patency caused by swelling of the lower turbinates are often observed (Fig. 394-2). In allergic patients, the nasal mucosa typically appears pale, watery, edematous, and bluish, and secretions are clear and watery to mucoid in nature.

In patients with acute asthma (Chapter 75), clinical examination can help detect wheezing, prolonged expiration, tachypnea, and shortness of breath. Extremities should be checked for cyanosis. Chronic hyperinflation (increased diameter or barrel chest) can be seen in chronic asthma. Wheezing may only be present during expiration (mild or moderate asthma) or during both inspiration and expiration (severe asthma), or it may be absent (when airflow is severely limited or when it predominantly affects the small airways).

Signs of anaphylaxis (Chapter 233) generally include flushing and presence of urticaria and angioedema. Hoarseness caused by upper airway obstruction from angioedema of the tongue, oropharynx, or larynx, or wheezing secondary to asthma, may be observed. Other symptoms may include pruritus, chest tightness, cough, wheezing, rhinitis, sneezing, congestion, rhinorrhea, abdominal pain, uterine cramping, urinary and fecal urgency or incontinence, nausea, vomiting, and diarrhea. Patients may become hypoxic, and anaphylaxis with hypotension may signal shock and cardiovascular collapse.

TABLE 230-2 ALLERGIC DISEASES: SYMPTOMS AND APPROACHES TO TREATMENT

SYMPTOMS	APPROACH TO TREATMENT
Cutaneous: pruritus, rash	H_1-antihistamine
Ocular: gritty sensation, pruritus	Topical H_1-antihistamine or mast cell–stabilizing agent
Upper respiratory: palatal pruritus, clear rhinorrhea, sneeze, nasal obstruction	Topical corticosteroid, oral H_1-antihistamine, leukotriene receptor antagonist, topical nasal H_1-antihistamine
Lower respiratory: wheezing, cough, dyspnea	β_2-Agonist, inhaled corticosteroid, inhaled β_2-agonist, leukotriene receptor antagonist, oral methylxanthine, parenteral corticosteroid, parenteral anti–immunoglobulin E
Gastrointestinal: nausea, vomiting, cramping pain	Epinephrine (if caused by anaphylaxis), oral corticosteroid, oral cromolyn

Laboratory Evaluation

Allergen-specific IgE (sIgE) measurements are the most common diagnostic tool for allergy. Normal values of total IgE do not exclude the presence of allergic disease, and elevated concentrations can be found in persons who smoke and in a number of other diseases besides allergy. In some cases, however, such as allergic bronchopulmonary aspergillosis (Chapters 75 and 311), serum IgE levels may measure the severity of disease or risk for an exacerbation.

Chronic spontaneous urticaria is idiopathic in 80 to 90% of cases, so universal allergy testing for food allergens is not recommended. Fifty percent of patients with chronic spontaneous urticaria test positively for either IgE receptor, anti-FcεRIa, or anti-IgE autoantibodies in the serum. Patients with chronic spontaneous urticaria also have an increased prevalence of autoimmune disorders, such as autoimmune hypothyroidism (Chapter 207), rheumatoid arthritis (Chapter 243), or systemic lupus erythematosus (Chapter 245).

Allergen-specific IgE can be measured either by in vitro blood tests or in vivo tests (skin prick tests and intradermal testing).[18] The specific allergens tested should be based on patient history and environmental exposures. During skin prick tests, a small break in the epidermis (usually forearm or upper back) is made using a lancet or needle to allow penetration of the allergen. In intradermal skin testing, a small amount of the suspected allergen is injected under the surface of the skin. About 15 to 30 minutes after introduction of the allergen, the maximal diameter of both the wheal and the flare is obtained, and results are compared with positive (histamine) and negative (saline) controls. Contraindications include individuals at high risk for anaphylaxis, certain skin conditions such as dermographism, urticaria, cutaneous mastocytosis, and skin affected by atopic dermatitis. Medications that may affect skin prick test results when taken concurrently include antihistamines (including topical forms), tricyclic antidepressants, omalizumab, and topical steroids in the test area. Angiotensin-converting enzyme inhibitors and β-blockers do not interfere with skin prick test results but may be problematic if anaphylaxis occurs and requires treatment.

High-throughput tests for measuring allergen-specific IgE can be used in conjunction with in vivo allergen-specific IgE tests. However, positive results indicate only sensitization to an allergen, not clinically significant allergy. For some types of allergy, such as IgE-mediated food allergy, food challenges under expert supervision can provide a definitive diagnosis (Chapter 126).[19] Component-resolved diagnosis measures sIgE using purified or recombinant components of allergens, such as Ara h2 from peanuts. The basophil activation test measures levels of surface proteins (CD63 and CD203c) that are expressed on stimulation with allergenic proteins. The diagnosis of eosinophilic esophagitis is confirmed when an esophageal biopsy shows at least 15 eosinophils per high-power field.

Non-IgE tests include patch tests and inhalation tests. For allergic contact dermatitis, patch testing is the gold standard for diagnosis. Patches containing potentially allergenic substances (e.g., dyes, latex, metals) are placed on the back for about 48 hours, and a reading is obtained after 72 to 96 hours. Inhalation testing of specific allergens or chemicals may help diagnose occupational allergy or asthma.

Serum tryptase, a mast cell–specific protease, is best biologic marker of anaphylaxis. However, because it has a short serum half-life of 2 hours, tryptase levels should be measured close to the onset of anaphylaxis and again about 2 weeks after recovery. If the baseline tryptase level is elevated, patients are at increased risk for anaphylaxis, especially after an insect sting, and also should be further evaluated for an occult mast cell disorder (Chapter 235).

TREATMENT AND PREVENTION

The current standard of care consists of avoidance of the allergen and the treatment of severe systemic reactions with adrenaline (Chapter 233). Desensitization by an allergy expert is often useful for environmental allergies and is beginning to be used more often for food allergies. The early ingestion of multiple foods during infancy may prevent food allergy by training the immune system to develop tolerance,[A1] and guidelines now suggest early intervention to prevent food allergies in at-risk infants.[20] Mitigation of climate change and air pollution can help prevent further increases in the prevalence of allergic diseases.

INBORN ERRORS OF IMMUNITY

The overall incidence of inborn errors of immunity is about 1:10,000, and the majority present early in childhood. Inborn errors of immunity include more than 400 genetically defined inherited disorders of immunity that can present not only as immune deficiencies but also autoimmunity/autoinflammation, malignancy, or a combination of all three (Chapter 231).[21] Primary immune deficiency diseases include immunodeficiencies that affect cellular and humoral immunity; combined immunodeficiencies with associated or syndromic features; predominantly antibody deficiencies; diseases of immune dysregulation; congenital defects of phagocyte number, function, or both; defects in intrinsic and innate immunity; autoinflammatory disorders; complement deficiencies; bone marrow failure; and phenocopies of primary immune deficiency disease.

CLINICAL MANIFESTATIONS AND DIAGNOSIS

Inborn errors of immunity have highly variable presentations but should be suspected when patients have persistent, severe, or unusual infections. The patient history should include details of infections (age of onset of infections, number, site, and type), including any family history of frequent infections and the presence of other abnormalities, since many primary immunodeficiency diseases are hereditary.

Laboratory Evaluation

Blood counts, including enumeration of total eosinophil, neutrophil, and lymphocyte (T-cell, B-cell, natural killer [NK]-cell) counts, cytokines produced by activated lymphocytes, and determination of serum immunoglobulin levels (IgA, IgE, IgG, IgM) can assist with diagnosis of a suspected immunodeficiency disorder. A significant lymphopenia often can be the first indication of T-cell immunodeficiency. Reduced antibody levels may be indicative of B-cell and antibody immunodeficiency disorders. However, additional tests measuring specific antibody titers in response to defined stimuli (e.g., vaccinations, tetanus toxoid, or pneumococcus) may be useful in patients who have frequent infections and borderline immunoglobulin levels. When defects in neutrophils are suspected, a nitroblue tetrazolium test or dihydrorhodamine response test can assist with diagnosis. The standard screening test for deficiencies in the complement system is the total hemolytic complement assay or CH50. The AH50 can also be used for screening complement abnormalities in the alternative pathway. Targeted panel sequencing, whole-exome sequencing, and whole-genome sequencing under expert guidance have enabled identification of the causative genetic mutations for most inborn errors of immunity and are essential components of the evaluation (Chapter 231).

Chest radiographs can detect thymic shadows and cupping and flaring of the costochondral junction, which can assist with the diagnosis of certain T-cell disorders. An abdominal ultrasound can determine abnormalities of spleen size.

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231 PRIMARY IMMUNODEFICIENCY DISEASES

CHARLOTTE CUNNINGHAM-RUNDLES

Primary immune defects affect about 1 per 10,000 persons, but the prevalence rises to 1 per 400 to 1 per 5000 persons when selective immunoglobulin A (IgA) deficiency is included.[1,2] The prevalence has been increasing as the number of known defects has increased to about 450 different entities. Primary immune defects are now classified into nine categories (Table 231-1).[3] The functions of complement (Chapter 37), disorders of phagocytes (Chapter 155), autoinflammatory syndromes (Chapter 240), and bone marrow defects (Chapter 151) are described elsewhere.

TABLE 231-1 CATEGORIES OF PRIMARY IMMUNODEFICIENCY DISEASES

T- and B-cell combined deficiencies
Combined defined defects with syndromic features
Antibody deficiencies
Complement disorders
Phagocyte defects
Immune dysregulation syndromes
Defects of intrinsic and innate immunity
Autoinflammatory defects
Bone marrow failure defects

AN APPROACH TO EVALUATION OF THE IMMUNE SYSTEM

Because of the number and types of immune deficiencies, clinical recognition of the various phenotypes can be difficult, and diagnosis is often delayed. In general, the spectrum of immune defects varies with the age of the patient. Defects of both T and B cells, phagocytes (Chapter 155), immune dysregulation, and innate immunity are more commonly recognized in early childhood, whereas defects of complement (Chapter 37) and the production of antibodies as well as autoinflammatory diseases (Chapter 240) are more commonly diagnosed in adolescents and adults. However, many exceptions exist to this generalization.

For most patients, the first symptom of an immune defect is a series of relatively common infections, particularly chronic sinusitis (Chapter 394), otitis (Chapter 394), bacterial pneumonias (Chapter 85), meningitis (Chapter 381), or osteomyelitis (Chapter 251). In both children and adults with immune defects, infections are likely to persist longer, may require additional courses of antibiotics, and tend to recur. Infections may also lead to additional complications or procedures, such as empyema after bacterial pneumonia or the need for myringotomy tubes in an adult with chronic otitis. In infants and children, chronic infections lead to poor appetite and failure to thrive. For adults, some weight loss may occur, but it usually is less apparent. Because of lack of immunity, reactivated herpes zoster infection (Chapter 346) is relatively common in patients who have T-cell defects or antibody deficiencies. Other common clinical presentations include acute gastrointestinal infections with characteristic organisms such as *Giardia* (Chapter 322) or chronic intestinal inflammatory diseases that lead to malabsorption and weight loss that can mimic gluten intolerance or Crohn disease (Chapters 126 and 127). Depending on the clinical presentation (Table 231-2), a systematic approach (Fig. 231-1)[4] can efficiently guide the evaluation of patients who are suspected of having a primary immune deficiency.

Large gene panels can detect many of the known immune defects. Whole exome or whole genome sequencing can confirm a likely molecular diagnosis in unrelated probands and may influence management in nearly 25% of families.[5] With the advent of genetic testing and its use in clinical medicine, autosomal dominant genes with variable penetrance are increasingly being identified. Importantly, different mutations in the same gene can lead to either loss or gain of function and quite different clinical phenotypes.

SEVERE T- AND B-CELL COMBINED DEFECTS

DEFINITION

Combined immune defects are early-onset diseases in which both the T- and B-cell compartments are greatly impaired. In some conditions, natural killer cells and other cells of the myeloid linage are also abnormal. These disorders often include additional inflammatory features such as autoimmunity and loss of T-cell regulatory function.

EPIDEMIOLOGY

In the United States, universal newborn screening for severe combined immunodeficiency detects these defects in about 1 : 80,000 (E-Table 231-1).[6]

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231 PRIMARY IMMUNODEFICIENCY DISEASES

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Primary immune defects affect about 1 per 10,000 persons, but the prevalence rises to 1 per 400 to 1 per 5000 persons when selective immunoglobulin A (IgA) deficiency is included.[1,2] The prevalence has been increasing as the number of known defects has increased to about 450 different entities. Primary immune defects are now classified into nine categories (Table 231-1).[3] The functions of complement (Chapter 37), disorders of phagocytes (Chapter 155), autoinflammatory syndromes (Chapter 240), and bone marrow defects (Chapter 151) are described elsewhere.

TABLE 231-1 CATEGORIES OF PRIMARY IMMUNODEFICIENCY DISEASES

T- and B-cell combined deficiencies
Combined defined defects with syndromic features
Antibody deficiencies
Complement disorders
Phagocyte defects
Immune dysregulation syndromes
Defects of intrinsic and innate immunity
Autoinflammatory defects
Bone marrow failure defects

AN APPROACH TO EVALUATION OF THE IMMUNE SYSTEM

Because of the number and types of immune deficiencies, clinical recognition of the various phenotypes can be difficult, and diagnosis is often delayed. In general, the spectrum of immune defects varies with the age of the patient. Defects of both T and B cells, phagocytes (Chapter 155), immune dysregulation, and innate immunity are more commonly recognized in early childhood, whereas defects of complement (Chapter 37) and the production of antibodies as well as autoinflammatory diseases (Chapter 240) are more commonly diagnosed in adolescents and adults. However, many exceptions exist to this generalization.

For most patients, the first symptom of an immune defect is a series of relatively common infections, particularly chronic sinusitis (Chapter 394), otitis (Chapter 394), bacterial pneumonias (Chapter 85), meningitis (Chapter 381), or osteomyelitis (Chapter 251). In both children and adults with immune defects, infections are likely to persist longer, may require additional courses of antibiotics, and tend to recur. Infections may also lead to additional complications or procedures, such as empyema after bacterial pneumonia or the need for myringotomy tubes in an adult with chronic otitis. In infants and children, chronic infections lead to poor appetite and failure to thrive. For adults, some weight loss may occur, but it usually is less apparent. Because of lack of immunity, reactivated herpes zoster infection (Chapter 346) is relatively common in patients who have T-cell defects or antibody deficiencies. Other common clinical presentations include acute gastrointestinal infections with characteristic organisms such as *Giardia* (Chapter 322) or chronic intestinal inflammatory diseases that lead to malabsorption and weight loss that can mimic gluten intolerance or Crohn disease (Chapters 126 and 127). Depending on the clinical presentation (Table 231-2), a systematic approach (Fig. 231-1)[4] can efficiently guide the evaluation of patients who are suspected of having a primary immune deficiency.

Large gene panels can detect many of the known immune defects. Whole exome or whole genome sequencing can confirm a likely molecular diagnosis in unrelated probands and may influence management in nearly 25% of families.[5] With the advent of genetic testing and its use in clinical medicine, autosomal dominant genes with variable penetrance are increasingly being identified. Importantly, different mutations in the same gene can lead to either loss or gain of function and quite different clinical phenotypes.

SEVERE T- AND B-CELL COMBINED DEFECTS

DEFINITION

Combined immune defects are early-onset diseases in which both the T- and B-cell compartments are greatly impaired. In some conditions, natural killer cells and other cells of the myeloid linage are also abnormal. These disorders often include additional inflammatory features such as autoimmunity and loss of T-cell regulatory function.

EPIDEMIOLOGY

In the United States, universal newborn screening for severe combined immunodeficiency detects these defects in about 1 : 80,000 (E-Table 231-1).[6]

ABSTRACT

About 450 inborn genetic defects of the immune system are described, and others will certainly be identified in the future. The overall incidence of primary immunodeficiency diseases is estimated to be about 1 in 10,000, excluding selective IgA deficiency, but this estimate is likely low. These gene defects lead to abnormalities of structure or function of lymphocytes, monocytes, phagocytic cells, and the complement proteins, and they may result from systemic defects that impinge upon the immune system. Primary immune defects may be diagnosed in infants, children, or adults of all ages. Although the spectrum of molecular defects may vary, the clinical findings (infection, immune dysregulation leading to inflammation and/or autoimmunity) are similar, regardless of the age of the patient. For unknown reasons, more than 50% of the reported immune defects (excluding IgA deficiency) lead to defects in antibody production. Although the exact categorization of immune defects is arbitrary, primary immune deficiencies are now grouped into nine main themes, according to the predominant cell systems or mechanism(s) that are defective: T- and B-cell combined deficiencies, combined defined defects with syndromic features, antibody deficiencies, complement disorders, phagocyte defects, immune dysregulation syndromes, autoinflammatory defects, defects of intrinsic and innate immunity, and bone marrow failure syndromes.

KEYWORDS

immune globulins
antibody
cellular immunity
genetic defects
bacterial or opportunistic infections
complement
severe combined immunodeficiency (SCID)
common variable immunodeficiency (CVID)

E-TABLE 231-1 EXAMPLES OF SEVERE COMBINED IMMUNE DEFECTS

SCID TYPE	GENES	INHERITANCE	LABORATORY FEATURES	DISEASE AND COMPLICATIONS
Defects of V(D)J recombination	*RAG1, RAG2* *DCLREIC* DNA-PKcs	Autosomal recessive	Very low lymphocyte numbers with loss of T and B cells; hypogammaglobulinemia	Severe infections, failure to thrive; leaky versions may have autoreactive T cells (Omenn syndrome)
Adenosine deaminase deficiency	*ADA*	Autosomal recessive	Variably low lymphocyte numbers with loss of T and B cells; also decreased NK cells; hypogammaglobulinemia	Severe infections, failure to thrive; often with costochondral junction flaring, neurologic features, hearing impairment, lung and liver manifestations
X-linked severe combined immunodeficiency	*IL2RG*	X-linked	Low lymphocyte numbers with loss of T cells; B cells present; markedly decreased NK cells; hypogammaglobulinemia	Severe infections, failure to thrive; leaky cases may present with low T or NK cells or Omenn syndrome
JAK3 deficiency	*JAK3*	Autosomal recessive	Low lymphocyte numbers with loss of T cells; B cells present; hypogammaglobulinemia	Severe infections, failure to thrive; leaky cases may present with variable T or NK cells
IL-7 deficiency	*IL7RA*	Autosomal recessive	Low lymphocyte numbers with loss of T cells; B cells present; normal NK cells; hypogammaglobulinemia	Severe infections, failure to thrive; leaky cases may present with low T or NK cells or Omenn syndrome
T-cell receptor chain defects	γ-, ε-, and ζ-chain mutations	Autosomal recessive	Low lymphocyte numbers due to loss of T cells; normal B and NK cells; hypogammaglobulinemia	Severe infections, failure to thrive; leaky cases may present with low T or NK cells or Omenn syndrome

DNA-PKcs = DNA-dependent protein kinase catalytic subunits; IL-7 = interleukin-7; JAK3 = Janus kinase 3; NK = natural killer; SCID = severe combined immunodeficiency.

TABLE 231-2 CLINICAL PRESENTATION AND EVALUATION OF THE IMMUNE SYSTEM

CLINICAL PRESENTATION	DEFECTS	IMMUNE DEFECTS	CONDITIONS	LABORATORY TESTING
Recurrent or chronic bacterial, viral, or fungal infections Opportunistic infections	Cell-mediated immunity	Impaired killing of intracellular organisms Impaired viral immunity Hypogammaglobulinemia	Severe combined immunodeficiency and other combined syndromes	Absolute lymphocyte count Enumeration of T cells and T-cell subsets Proliferative tests for T-cell function Low immune globulins; no antibody
Bacterial infections Viral infections Autoimmunity Lymphoid hypertrophy Inflammatory diseases Enteropathy Giardiasis	B cells	Hypogammaglobulinemia Impaired bacterial killing Impaired clearance of virus Autoimmunity	Hypogammaglobulinemia Agammaglobulinemia IgA deficiency Common variable immune deficiency IgG subclass defects Antibody deficiency	Enumeration of B cells Serum IgG, IgA, and IgM Antibody testing (e.g., tetanus, diphtheria) Vaccine challenge and antibody testing (e.g., tetanus, diphtheria pneumococcal vaccine)
Bacterial infections Susceptibility to meningococcal disease Autoimmunity Angioedema	Complement	Impaired opsonization Impaired bacterial killing Lack of clearance of immune complexes	Complement C2 deficiency Other complement defects Hereditary angioedema	CH_{50} AH_{50} Measure individual complement components C1 inhibitor protein and function
Bacterial infections Poor skin healing Fungal infections Stomatitis Periodontal disease	Phagocytic cells	Impaired neutrophil mobilization Impaired opsonization Impaired bacterial killing	Chronic neutropenia Cyclic neutropenia Autoimmune neutropenia Leukocyte adhesion deficiency Chronic granulomatous disease	Absolute neutrophil counts Neutrophil oxidative burst examined by dihydrorhodamine test by flow cytometry Examination of the blood smear Antineutrophil antibodies

AH_{50} = alternative hemolytic complement; CH_{50} = total hemolytic complement; Ig = immunoglobulin.

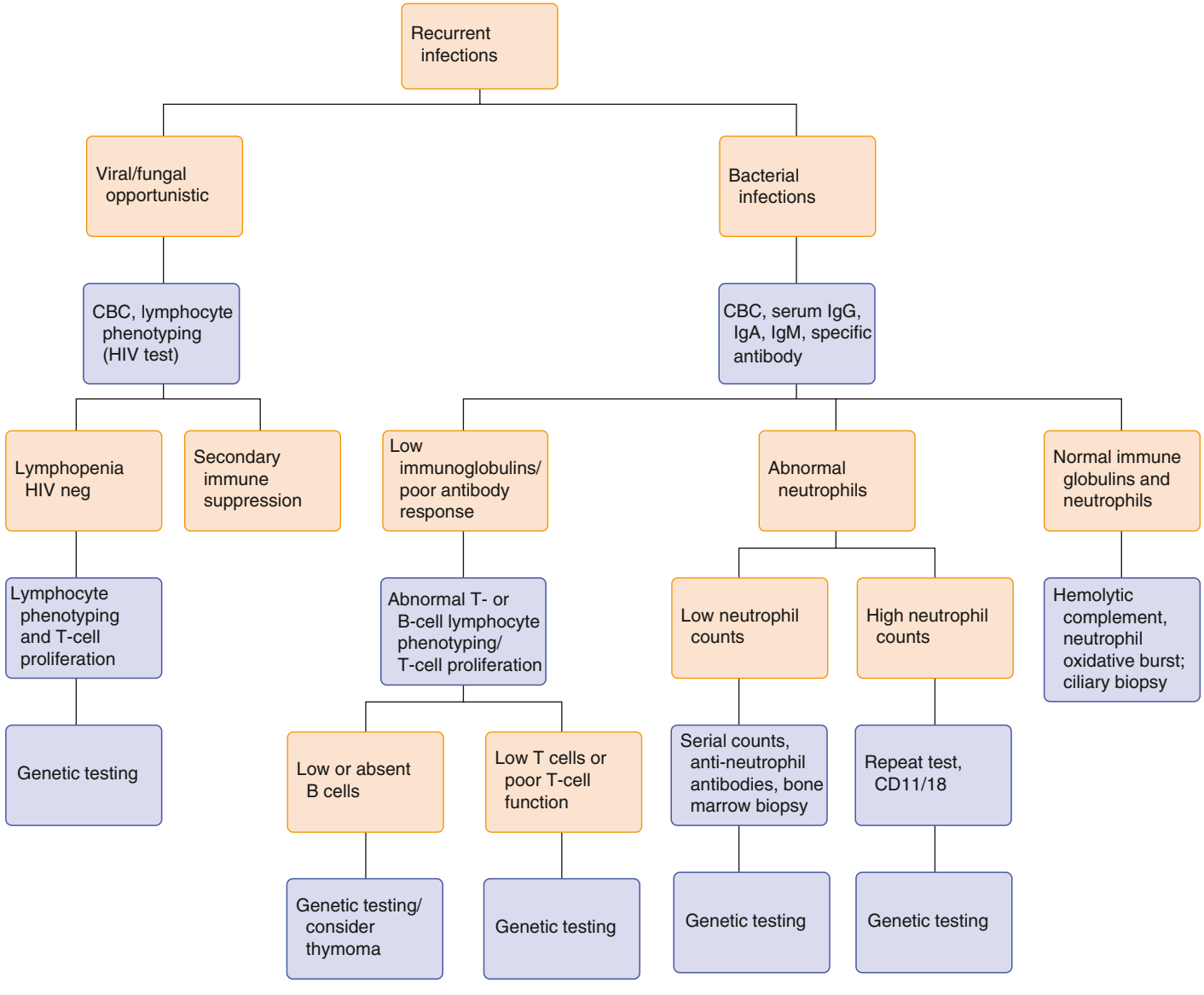

FIGURE 231-1. **Evaluation of immune defects presenting with recurrent infections.** CBC = complete blood count; HIV = human immunodeficiency virus; Ig = immunoglobulin.

PATHOBIOLOGY

The hallmark of combined defects is that they eliminate or greatly impair T-cell development, in most cases leading to profound lymphopenia. Infants with disorders that affect the formation of T- and B-cell receptors, such as when defects of the recombinase activating genes *RAG1* and *RAG2* impair VDJ recombination, have few if any T and B cells. Similarly, other defects of DNA recombination or repair genes (ARTEMIS, the product of *DCLREIC*, and DNA-PKcs) will have a similar phenotype. When T-cell immunity is absent, B cells may be present, but they will have no function, as is the case for severe combined X-linked immunodeficiency due to mutations in the cytokine γ chain, which is an essential signaling component of six cytokine receptors (interleukin [IL]–2, IL-4, IL-7, IL-9, IL-15, and IL-21). Defects of the *JAK3* gene, which is downstream from the cytokine γ chain, or of the IL-7 receptor itself lead to a similar immune profile.

CLINICAL MANIFESTATIONS

With loss of both essential limbs of the adaptive immune system, infants with combined immune defects have severe and recurrent infections that are caused by bacteria, viruses, and fungi. Other common features include diarrhea, dermatitis, and failure to thrive. Clinically, most patients present before the age of 3 months, but a significant number of infants may present later, although still usually in the first year of life. Without intervention, severe combined immunodeficiency commonly results in debilitating infections and death by age 2 years. In some cases, the immune defect is such that a few T cells can develop, but these cells are often self-reactive; such cases are often termed "leaky" severe combined immunodeficiency. When the presentation of these cases includes rashes and evidence of autoimmunity, infants are said to have Omenn syndrome.

DIAGNOSIS

All newborns in the United States are now examined by sensitive and specific DNA-based screening for severe combined immunodeficiency,[7] so the disease is now typically diagnosed before any symptoms have appeared. Newborns normally have a mean absolute lymphocyte count of 4000/μL or higher, but most infants with severe combined immunodeficiency have significant lymphopenia. A flow cytometry panel will enumerate T, B, and natural killer (NK) cells and suggest the genes that may be responsible. Further genetic testing is commonly performed. Less severe forms of combined immune deficiency (E-Table 231-2) are not identified by newborn screening because T cells are present.

TREATMENT AND PROGNOSIS

Early immune reconstitution with stem cells from human leukocyte antigen (HLA)–matched bone marrow or mobilized peripheral blood is mandatory. When the diagnosis is made early and no severe infections have occurred, hematopoietic stem cell transplantation (Chapter 163) is likely to be curative in 90% of selected cases.[8] Gene therapy also can be used for several primary immunodeficiencies, including forms of severe combined immunodeficiency (e.g., adenosine deaminase deficiency)[9] as well as Wiskott-Aldrich syndrome. For infants with severe combined immunodeficiency, lentiviral vector gene therapy combined with low-exposure, targeted busulfan conditioning can result in multilineage engraftment, reconstitution of functional T cells and B cells, and normalization of natural killer cell counts for at least 16 months with low-grade side effects.[10] Gene editing to repair the endogenous gene so it can be expressed under normal regulatory controls is an experimental procedure.

LESS SEVERE T- AND B-CELL COMBINED DEFECTS

In addition to the severe forms of severe combined immunodeficiency, a number of other genetic defects also impair both T- and B-cell limbs, but newborn screening may not identify these infants because the number of T-cells might not be sufficiently reduced. In these forms, in addition to infections, the phenotype may include not only susceptibility to bacterial infection but also atopy, severe viral infections, autoimmunity, and, in some, cancer (E-Table 231-2).

Examples of these less severe T- and B-cell combined defects include syndromes in which major histocompatibility complex (MHC) class I or class II is not expressed (sometimes called bare lymphocyte syndromes), additional defects of T-cell signaling (such as Zap-70), and syndromes that result when defects of the actin cytoskeleton prevent T-cell activation, including the dedicator of cytokinesis proteins, DOCK2 and DOCK8.

DIAGNOSIS AND CLINICAL MANIFESTATIONS

As with the more severe combined immunodeficiency states, these syndromes lead to defects of both T- and B-cell compartments, and infants present with severe and recurrent bacterial, viral, or fungal infections; diarrhea; dermatitis; and usually failure to thrive. One notable example, with atopic disease and high immunoglobulin E (IgE), is DOCK8 deficiency, which was first recognized in babies with autosomal recessive hyper-IgE syndrome (E-Table 231-2).

TREATMENT AND PROGNOSIS

Hematopoietic transplantation is the only curative measure.

COMBINED DEFECTS WITH SYNDROMIC FEATURES

Another group of combined primary immune defects has distinctive systemic characteristics, aside from the obvious abnormities in the immune system (Table 231-3). The best known of these are Wiskott-Aldrich syndrome, ataxia-telangiectasia, DiGeorge syndrome, hyperimmunoglobulin E (Buckley-Job) syndrome, cartilage-hair hypoplasia, and purine nucleoside phosphorylase (PNP) deficiency.

WISKOTT-ALDRICH SYNDROME

EPIDEMIOLOGY AND PATHOBIOLOGY

Wiskott-Aldrich syndrome is an X-linked recessive disease that is characterized by eczema, thrombocytopenia, and immune deficiency. Wiskott-Aldrich syndrome is rare, estimated at 1 to 10 cases per million males. Ethnic differences are not known.

The syndrome is caused by mutations in the *WAS* gene, which codes for the Wiskott-Aldrich syndrome protein that is an intracellular cytoplasmic scaffold protein important for the activation and mobility of all blood cells. This protein is involved in the polymerization of actin and in establishing an interface between immune cells (the immune synapse). Partly depending on the location of the mutation in the *WAS* gene, milder versions lead to X-linked thrombocytopenia in some cohorts. Another, much rarer version leads to X-linked neutropenia.

CLINICAL MANIFESTATIONS AND DIAGNOSIS

The main manifestations in early childhood include eczema, chronic thrombocytopenia sometimes leading to bloody diarrhea, and immune deficiency with recurrent infections. Autoimmunity or inflammatory diseases, including autoimmune hemolytic anemia, splenomegaly, arthritis, inflammatory bowel disease, and vasculitis can be present. The incidence of lymphoma is also increased. Family history may include male relatives with Wiskott-Aldrich syndrome or thrombocytopenia.

The diagnosis is commonly made in the first few years of life in males who have the characteristic eczema as well as thrombocytopenia that leads to petechiae. IgM levels are typically low, whereas IgA (and sometimes IgE) levels are increased. Platelet sizes are smaller than normal, and clot retraction is poor. The diagnosis can be suggested by lack of the Wiskott-Aldrich syndrome protein as detected by flow cytometry, but definitive diagnosis requires gene testing.

TREATMENT

Treatment strategies for Wiskott-Aldrich syndrome are diverse and usually determined by experts on a case-by-case basis.[11] Conservative management includes prophylactic antibiotics, immunization with conjugated polysaccharide vaccines, and intravenous or subcutaneous immune globulin for patients who have repeated infections. For eczema, standard measures are used (Chapter 405). Lifelong antibiotic prophylaxis is mandatory. Thrombopoietic agents, such as eltrombopag and romiplostim, can be helpful.[12] Platelet transfusions should be reserved for active bleeding that cannot be managed with usual methods (e.g., aminocaproic acid) and should be avoided in patients for whom hematopoietic stem cell transplantation is being considered. Splenectomy is discouraged because of the risk of post-splenectomy sepsis. Autoimmunity can be difficult to control, and immune suppression should be used with caution. Treatment of lymphomas is by standard regimens (Chapter 171).

Hematopoietic stem cell transplantation (Chapter 163) can be curative. Trials with gene therapy are also ongoing.

E-TABLE 231-2 EXAMPLES OF LESS SEVERE COMBINED IMMUNE DEFECTS

SCID TYPE	GENES	INHERITANCE	LABORATORY FEATURES	DISEASE AND COMPLICATIONS
MHC class I deficiency	*TAP1, TAP2; TAPBP; β2M*	Autosomal recessive	Low CD8, normal CD4, absent MHC I on lymphocytes	Vasculitis, pyoderma gangrenosum; granulomatous disease
MHC class II deficiency	*CIITA; RFXANK*	Autosomal recessive	Low CD4 cells Absent MHC II expression on lymphocytes	Failure to thrive, respiratory and gastrointestinal infections, liver/biliary tract disease
ZAP-70 deficiency	*ZAP-70*	Autosomal recessive	Low CD8, normal CD4 number but poor function	May have immune dysregulation, autoimmunity
DOCK8 deficiency	*DOCK8*	Autosomal recessive	Low IgM, normal to high IgG and IgA, high IgE; poorly functioning Treg	Low NK cells with poor function, eosinophilia, recurrent infections, cutaneous viral, fungal, and staphylococcal infections, eczema and food allergy, virally driven cancers
DOCK2 deficiency	*DOCK2*	Autosomal recessive	Low lymphocyte numbers; defective T, B, and NK cells	Early-onset invasive bacterial and viral infections

CIITA = class II major histocompatibility complex transactivator; DOCK = dedicator of cytokinesis gene; IG = immunoglobulin; MHC = major histocompatibility complex; NK = natural killer; Nl = normal; *RFXANK* = regulatory factor X–associated ankyrin-containing protein; SCID = severe combined immunodeficiency; TAP = antigen peptide transporter; *TAPBP* = TAP binding protein; Treg = regulatory T cell; ZAP-70 = zeta-chain–associated protein kinase 70.

TABLE 231-3 EXAMPLES OF COMBINED DEFECTS OF IMMUNITY WITH SYNDROMIC FEATURES

TYPE	GENES	INHERITANCE	LABORATORY FEATURES	ALTERED FUNCTIONS	DISEASE AND COMPLICATIONS
Wiskott-Aldrich syndrome	*WAS*	X-linked	Thrombocytopenia, small platelets, low IgM and poor antibody responses to polysaccharides	Impaired cell activation, mobility	Eczema, lymphoma, autoimmune disease, bacterial and viral infections
Ataxia-telangiectasia	*ATM*	Autosomal recessive	Some have IgA deficiency, IgG defects, lymphopenia in some, may have low T cells on newborn screening	Impaired DNA double-stranded break repair	Ataxia, telangiectasia, pulmonary infections, lymphoreticular and other malignant neoplasms, increased α-fetoprotein, x-ray sensitivity
DiGeorge/velocardiofacial syndrome/chromosome 22q11.2 deletion syndrome	22q11.2 deletion, rarely a deletion in 10p	De novo (majority) or autosomal dominant	Lymphopenia, low T-cell numbers, large deletion in chromosome 22 on fluorescence in situ hybridization	Impaired T-cell immunity	Cardiac abnormalities, hypoparathyroidism, abnormal facies
Hyper-IgE syndrome (Buckley-Job syndrome)	*STAT3*	Autosomal dominant	Eosinophilia, high IgE	Loss of normal cytokine activation, defective IL-17	Bacterial infections, eczema, distinctive facial features, osteoporosis, fractures, scoliosis, delay of shedding primary teeth, hyperextensible joints, candidiasis
Cartilage-hair hypoplasia	*RMRP*	Autosomal recessive	Lymphopenia, low T-cell numbers	Impaired processing of mitochondrial RNA	Short-limbed dwarfism, sparse hair, celiac disease, Hirschsprung disease, bone marrow failure, autoimmunity, susceptibility to lymphoma
Purine nucleoside phosphorylase (PNP) deficiency	*PNP*	Autosomal recessive	Progressive T-cell loss, immune globulins normal or low	Impaired T cell functions	Autoimmune hemolytic anemia, neurologic impairment

ATM = ataxia telangiectasia mutated; BCR = B-cell receptor; Ig = immunoglobulin; IL = interleukin; NEMO = NF-κB essential modulator; PNP = purine nucleoside phosphorylase; RMRP = RNA component of mitochondrial RNA processing endoribonuclease; STAT3 = signal transducer and activator of transcription 3; WASP= Wiskott-Aldrich protein.

PROGNOSIS

The prognosis in Wiskott-Aldrich syndrome is highly variable. Some individuals have mild thrombocytopenia and occasional nose bleeds, whereas other patients have inflammatory diseases or other complications that require additional, sometimes intensive, medical management.

ATAXIA-TELANGIECTASIA

EPIDEMIOLOGY AND PATHOBIOLOGY

Ataxia-telangiectasia is a rare neurodegenerative disease that leads to cerebellar atrophy, skin telangiectasia, and immune defects. Ataxia-telangiectasia is estimated to occur in 1 in 40,000 to 100,000 persons. Males and females are affected equally.

Ataxia-telangiectasia is due to recessive mutations in the gene that encodes the ataxia telangiectasia mutated protein (ATMp), which is important in both cell division and DNA repair. With the loss of ATMp, DNA breakage cannot be repaired, thereby leading to cell death.

CLINICAL MANIFESTATIONS

The clinical manifestations include progressive difficulty in walking, with ataxia beginning around age 5 years. Skin telangiectasias develop on the bulbar conjunctiva and behind the ears. The immune defects include IgA deficiency, IgG subclass defects, and cellular defects that can lead to recurring pulmonary infections and lung damage. Patients with ataxia-telangiectasia are radiosensitive and commonly develop lymphomas with increasing age.

DIAGNOSIS

The diagnosis of ataxia telangiectasia usually can be made by the characteristic clinical phenotype coupled with an increase in the serum α-fetoprotein blood level. Radiosensitivity can be assessed in vitro in fibroblast cell lines. Definitive diagnosis is by *ATM* gene sequencing.

TREATMENT AND PROGNOSIS

Treatment for ataxia-telangiectasia includes a medical team that can provide supportive measures and physical therapy as needed.[13] The life expectancy varies greatly, but most patients live into early adulthood.

DIGEORGE SYNDROME

EPIDEMIOLOGY AND PATHOBIOLOGY

DiGeorge syndrome is an autosomal dominant defect and one of the members of the 22q11.2 deletion syndrome that includes velocardiofacial syndrome, conotruncal anomaly face syndrome, congenital thymic aplasia, and thymic hypoplasia.[14] DiGeorge syndrome is one of the most common of the immune defects, with an estimated incidence of 1 : 4000. Both sexes are affected equally. The immune defect in DiGeorge syndrome varies widely, from complete loss of thymic development with no circulating T cells to normal T-cell numbers. In most cases, the thymus is hypoplastic.

CLINICAL MANIFESTATIONS AND DIAGNOSIS

Although it is classified as an immune defect because of thymic hypoplasia or aplasia, patients with DiGeorge syndrome are likely also to have congenital heart disease (Chapter 55), cleft palate or pharyngeal closure defects, characteristic facies, hypocalcemia due to parathyroid insufficiency, and learning disability. The more common cardiac defects include tetralogy of Fallot, interrupted aortic arch, ventricular septal defects, vascular rings, and anomalous return of brachial arteries. The mnemonic CATCH-22 has been applied: cardiac issues, abnormal facies, thymic aplasia, cleft palate, and hypocalcemia. With loss of thymic tissue, cellular immunity is mildly to moderately impaired, leading to recurrent infections. Hypogammaglobulinemia is not uncommon and may be associated with autoimmune cytopenias, especially thrombocytopenia.

Infants with DiGeorge syndrome may be first identified on a newborn screen when poor thymic function leads to low T-cell receptor excision circles (TRECs). The diagnosis of DiGeorge syndrome can be confirmed on genetic testing with fluorescence in situ hybridization, which detects the loss of the 22q11.2 gene segment or, more rarely, a loss of 10p14-p13. However, about 10% of affected individuals do not have a gene defect but have the syndrome because of maternal diabetes, fetal alcohol syndrome, or prenatal exposure to isotretinoin.

TREATMENT

Treatment of DiGeorge syndrome is based on individual needs and may require cardiac surgery, repair of the cleft palate, and supplementation of calcium and vitamin D. Some patients are hypothyroid and require thyroid supplementation (Chapter 207). Whereas the level of T cells may be subnormal for age, sufficient T-cell function remains so that no specific treatment is needed (partial DiGeorge syndrome) because infections tend to be more related to anatomic abnormalities than T-cell hypofunction. If the thymus is totally absent, thymic transplantation can supply sufficient reconstitution.[15]

PROGNOSIS

For most patients, the prognosis depends on the concomitant medical issues, such as results of cardiac surgery, surgical repair of cleft palate, management of swallowing difficulties, and resources to enhance muscle strength and to overcome speech impediments and learning disabilities. For most patients, the T-cell defect is a minor component, and a near-normal lifespan is possible. With age, however, autoimmunity may become more prominent.

HYPERIMMUNOGLOBULIN E SYNDROME

EPIDEMIOLOGY AND PATHOBIOLOGY

Hyperimmunoglobulin E syndrome, also called Buckley-Job syndrome, is an immune deficiency syndrome characterized by eczema, skin and lung abscesses, hyperextensible joints, and recurrent bone fractures, distinctive coarse facies, eosinophilia, and high levels of serum IgE. The annual incidence is about 1 per million. Males and females are equally affected.

Hyperimmunoglobulin E syndrome is an autosomal dominant defect that results from mutations in the *STAT3* gene, which encodes a transcription factor, signal transducer, and activator of transcription 3. After activation by selected cytokines and growth factors, STAT3 protein is phosphorylated and translocated to the cell nucleus.

CLINICAL MANIFESTATIONS AND DIAGNOSIS

Characteristic clinical findings include eczema, recurrent skin boils, unusual facies with tubular nose, cyst-forming pneumonias often due to *S. aureus,* and increased serum IgE. Other common manifestations include a rash in the newborn period, mucocutaneous candidiasis, delayed shedding of primary teeth, and skeletal abnormalities, such as scoliosis, osteoporosis, and fractures with minimal trauma.

The diagnosis of hyperimmunoglobulin E syndrome can be strongly suspected on clinical grounds and an elevated hyperimmunoglobulin E level. Eosinophilia is common. The definitive diagnosis is best confirmed by identifying a *STAT3* or other mutation.

Features of the hyperimmunoglobulin E syndrome also have been found in a few patients with dominant negative mutations in *IL6ST,* which is a signaling receptor subunit of IL-6, and in patients with rare autosomal recessive defects in genes that encode tyrosine kinase 2 (Tyk2) and dedicator of cytokinesis 8 (DOCK8). In both of these conditions, however, viral infections are also prominent.[16]

TREATMENT

No definitive treatment exists for hyperimmunoglobulin E syndrome. Because of the propensity for staphylococcal infections, prophylaxis with appropriate antibiotics (e.g., trimethoprim-sulfamethoxazole, 2.5 mg/kg twice daily) is commonly used, along with oral antifungals such as itraconazole (100 mg daily for patients younger than age 13 years or weighing <50 kg; 200 mg daily for patients older than age 13 years or weighing >50 kg). Surgical drainage of abscesses is also important, but wound healing may be poor. Skin care for eczema may include bleach baths to reduce bacterial burden and antihistamines to control pruritus. Optimization of calcium and vitamin D levels may be useful to strengthen bones.

PROGNOSIS

Hyperimmunoglobulin E syndrome is a lifelong disease, and infections or other complications require individual care. With increasing age, worsening respiratory dysfunction is likely. Vascular and especially arterial abnormalities can occur. Many patients survive beyond age 50 years. The most common cause of death is infection.

CARTILAGE-HAIR HYPOPLASIA

EPIDEMIOLOGY AND PATHOBIOLOGY

Cartilage-hair hypoplasia is a rare autosomal recessive form of short-limbed dwarfism associated with a variable cellular immune deficiency. In the Old Order Amish population, cartilage-hair hypoplasia affects 1 in 1300 newborns. Among individuals of Finnish descent, the incidence is about 1 in 20,000.

The genetic defect in cartilage-hair hypoplasia is in the *RMRP* gene, which encodes the RNA in a mitochondrial RNA-processing endoribonuclease that helps copy mitochondrial DNA and process ribosomal RNA. In cartilage-hair hypoplasia, the encoded RNA is unstable.

CLINICAL MANIFESTATIONS AND DIAGNOSIS

Affected individuals have skeletal dysplasia, sparse hair, and a predominantly T-cell deficiency disease. The cellular defect is variable and ranges from mildly to severely impaired immunity. Other clinical features include short stature, anemia, autoimmunity, celiac disease, Hirschsprung disease, and several cancers, including lymphoma.

The diagnosis can be suspected by inheritance patterns and clinical phenotype. However, definitive diagnosis is made by genetic sequencing of the *RMRP* gene.

TREATMENT AND PROGNOSIS

For patients with severe T-cell defects and infections similar to what are seen with a severe combined immunodeficiency, hematopoietic stem cell transplantation (Chapter 163) is required. Aside from the cellular defect, treatment is directed at the other presenting clinical issues. Life expectancy can be normal, but the prognosis is highly variable and depends on the extent of the cellular defect, the therapies required, and the associated clinical complications.

DEFECTS OF IMMUNE GLOBULIN AND ANTIBODY PRODUCTION

EPIDEMIOLOGY AND PATHOBIOLOGY

Defects of immune globulin and antibody production are due to loss of B-cell development, loss of production of one or more of the immunoglobulin (Ig) isotypes, or loss of functional antibody production. As a group, antibody defects are the most prevalent immune defects and are found in patients of all ages. Selective IgA deficiency is most common in White patients, but the incidence varies from 1 : 400 in Finland to 1: 14,000 or fewer in Black Americans or Asians. Common variable immune deficiency has an estimated incidence of 1 in 50,000; IgG subclass or selective antibody defects are also common, but the incidence is unknown.

Whereas the genetic causes have been elucidated for many of the combined forms of immune deficiency, the genes are not yet known for many of the more common B-cell defects (Table 231-4). Antibody defects can be considered in three main forms: B cells are absent, B cells are present but one or more of the immunoglobulin isotypes are not made, or B cells and immunoglobulin levels are normal but the produced immunoglobulins have no function.

CLINICAL MANIFESTATIONS

Lack of B Cells Leading to Agammaglobulinemia

Genetic Defects of the B-Cell Receptor or Signaling Pathways

In the X-linked form of agammaglobulinemia, the affected gene encodes a tyrosine kinase (BTK) that is essential for downstream signaling from the B-cell receptor. Without these signals, B cells do not survive, thereby leading to profound hypogammaglobulinemia. The incidence of this disease is approximately 1 in 100,000. Although X-linked inheritance is a central feature, the family history may or may not be positive because of de novo mutations.

The main clinical manifestations appear in the first year of life, but males may come to clinical attention later, in some cases not until the second decade. Infections are usually bacterial, generally with encapsulated organisms such as *Streptococcus pneumoniae, Haemophilus influenzae, Staphylococcus aureus,* and *Pseudomonas* species. Affected individuals also have a particular propensity for *Mycoplasma* infections, which may occur in joints or the urinary tract and can be difficult to diagnose.

Other genetic forms of agammaglobulinemia include gene defects of the B-cell receptor itself, such as the μ heavy chain, the surrogate light chain λ5, Igα, and Igβ. Similarly, mutations in signaling proteins immediately downstream from the B-cell receptor lead to the same outcome, with loss of all B cells. Since these genes are not on the X chromosome, these defects, although rare, are found in both sexes.

Good Syndrome

A special case of agammaglobulinemia with loss of B cells in adults is a poorly understood acquired immune defect associated with thymomas (Good syndrome). Although a secondary immune defect, the loss of B cells, with either agammaglobulinemia or hypogammaglobulinemia, leads to many of the same infectious manifestations as with the other profound antibody defects. Quite rare, Good syndrome occurs in adults, most often after age 40 years. Affected individuals are at increased risk of developing opportunistic infections, such as *Pneumocystis jiroveci*, *Candida* infections with nail or other cutaneous involvement, viral infections, autoimmunity, and inflammatory complications such as lichen planus. The connection between thymoma, loss of B-cell function, and the unusual infections remains unclear.

TABLE 231-4 EXAMPLES OF ANTIBODY DEFECTS

TYPE	GENES	INHERITANCE	LABORATORY FEATURES	DISEASE AND COMPLICATIONS
ABSENT B CELLS: SEVERE REDUCTIONS IN IgG, IgA, AND IgM				
X-linked agammaglobulinemia	*BTK*	X-linked	IgG, IgA, and IgM are very low or absent	Severe bacterial infections
Autosomal forms of agammaglobulinemia	Defects of the B-cell receptor or its signaling pathways; λ5, Igα, Igβ; *TCF3*	Autosomal recessive, autosomal dominant	IgG, IgA, and IgM are very low or absent	Severe bacterial infections
Good syndrome	Unknown	Unknown	Few or absent B cells; variable hypogammaglobulinemia	Associated with thymoma; may have opportunistic infections
B CELLS PRESENT: BUT LOW SERUM IgG, IgA, AND/OR IgM				
Common variable immune deficiency	Unknown in 70%	Unknown	Low IgG, IgA, and/or IgM	Bacterial infections, autoimmunity, other inflammatory complications
Defects of B-cell receptors	*CD19, CD81, CD20, CD21, TACI, BAFFr, TWEAK*	Autosomal recessive, autosomal dominant and sporadic	Low IgG, IgA, and/or IgM	Recurrent infections
Defects of signaling, activation and/or regulation (common variable immune deficiency phenotype)	*ICOS, NFKb1, NFKb2; PI3KCD; PI3KR1; CTLA4, IKAROS, LRBA, STAT3*, etc.	Autosomal recessive, autosomal dominant with variable penetrance; sporadic	Variably low IgG, IgA, and/or IgM; antibody defects. Increased IgM in *PI3KCD*	Recurrent infections and autoimmunity; variable clinical expression
B CELLS PRESENT: SEVERE REDUCTION IN SERUM IgG AND IgA BUT NORMAL OR ELEVATED IgM				
X-linked hyper-IgM syndrome	*CD40L*	X-linked	IgG and IgA decreased; IgM may be normal or increased; B-cell numbers may be normal or increased	Bacterial and opportunistic infections, neutropenia, autoimmune disease
CD40 deficiency	*CD40*	Autosomal recessive	Low IgG and IgA; normal or increased IgM	Bacterial and opportunistic infections, neutropenia, autoimmune disease
Defects of DNA recombination	*AID* and *UNG*	Autosomal recessive	IgG and IgA decreased; IgM increased	Bacterial infections; enlarged lymph nodes and germinal centers
B CELLS PRESENT: ISOTYPE DEFICIENCIES				
Selective IgA deficiency	Unknown	Unknown	IgA absent	Usually asymptomatic; allergies and autoimmunity may be more common
IgA with IgG subclass deficiency	Unknown	Unknown	Reduced IgA with decrease in one or more IgG subclass (usually IgG2/4)	Infections in some with loss of antibody
IgG subclass deficiency	Unknown	Unknown	Reduction in one or more IgG subclass	Asymptomatic in many; infections in some with loss of antibody
B CELLS PRESENT: NORMAL IgG, IgA, AND IgM				
Antibody deficiency	Unknown	Unknown	Normal serum immunoglobulins but no vaccine responses to protein and carbohydrate antigens or vaccines	May lead to recurrent infections

BAFF-R = B-cell activating factor receptor; *Btk* = Bruton tyrosine kinase; CTLA4 = cytotoxic T-lymphocyte–associated protein 4; ICOS = inducible T-cell costimulator; Ig = immunoglobulin; LRBA = LPS responsive beige-like anchor protein; *PI3KCD* = phosphatidylinositol-4,5-bisphosphate 3-kinase catalytic subunit delta; STAT3 = signal transducer and activator of transcription 3; TACI = transmembrane activator and CAML interactor; TWEAK = tumor necrosis factor ligand superfamily member 12.

Hypogammaglobulinemia with B Cells Present

Common Variable Immune Deficiency

Patients with common variable immune deficiency have varying degrees of hypogammaglobulinemia ranging from almost total loss of immunoglobulins to more modest reductions of IgG and IgA or IgM. Common variable immune deficiency is relatively common, with a prevalence of 1 : 25,000 to 1 : 50,000. An increasing number of genes leading to loss of B-cell function and the common variable immune deficiency phenotype have been identified in approximately 30% of patients, some of whom have inflammatory or autoimmune complications (see Table 231-4).[17] However, the majority of subjects with hypogammaglobulinemia do not have a known gene defect.

The clinical onset is later than for other immune defects (generally between ages 20 to 40 years), and the clinical presentation is highly heterogenous. Delays in diagnosis are common. Before diagnosis, some subjects with common variable immune deficiency will have had one or more episodes of pneumonia, sometimes leading to empyema. The bacterial species most commonly found include *S. pneumoniae, H. influenzae, S. aureus*, and *Mycoplasma* species. Over time, bronchiectasis (Chapter 78) may develop. Gastrointestinal tract issues are common and may be infectious (e.g., *Giardia, Campylobacter,* norovirus) or inflammatory, including lymphoid hyperplasia and forms of inflammatory bowel disease that lead to malabsorption. However, a biopsy will show loss of plasma cells in the gastrointestinal mucosa. About one quarter of patients with common variable immune deficiency have autoimmune conditions such as thrombocytopenia, hemolytic anemia, achlorhydria, pernicious anemia, and granulomatous disease in lymphoid organs, lungs, brain, or skin, suggesting sarcoidosis. Clinically, lymphadenopathy is common, and splenomegaly is noted in about 30% of cases. Malignant disease is also increased, usually B-cell lymphomas, but other cancers also may appear.

Hyperimmunoglobulin M Syndromes

The hyperimmunoglobulin M (hyper-IgM) syndromes are defects in which the isotype switch is lost. B cells from these patients produce IgM, but they do not secrete IgG or IgA. The prototypic form is the X-linked version in which an essential T-cell activation receptor, which is the CD40 ligand that is encoded on the X chromosome, is missing or nonfunctional. Mutations in the gene for its receptor partner, which is the CD40 ligand on B cells, lead to a similar defect. Several other genetic disorders lead

to a similar immunologic phenotype, including defects of the gene for enzyme activation–induced cytidine deaminase *(AICDA)* and uracil-DNA glycosylase, both important for DNA recombination. Three other gene defects may present with increased serum IgM: *PI3KCD, PI3KR1,* and NEMO *(IKBKG;* see Table 231-7).

The complications of the hyper-IgM syndromes include neutropenia, bacterial infections, *P. jirovecii* pneumonia, autoimmunity, enteropathy similar to common variable immune deficiency, and unusual cancers.[18] In the X-linked hyper-IgM syndrome, a predilection to infection with *Cryptosporidium* can lead to irreversible liver disease.

Selective IgA Deficiency

Selective IgA deficiency (IgA <7 mg/dL with other isotypes normal) is the most common of the primary immunodeficiency disorders, but most affected individuals are asymptomatic. Lack of infections in most subjects is generally ascribed to the overlapping and compensatory role of other immune functions. However, allergies, autoimmunity, increased serum IgE, asthma, rheumatoid arthritis, gluten intolerance, and inflammatory bowel disease are more common in individuals who have selective IgA-deficiency. Presumably owing to the loss of secretory IgA, *Giardia* infections may occur (Chapter 322). Some persons with IgA deficiency also are deficient in IgG2 and IgG4, and the loss of antibacterial antibody leads to severe infections and, in some cases, chronic lung disease.[19]

IgG Subclass Defects

The prevalence of defects in subclasses of IgG is difficult to determine, partly because normal laboratory ranges vary. Despite their structural differences, functional roles of IgG isotypes have considerable overlap, so the importance of isotype defects can be limited, especially if loss of antibody is not demonstrable. The clinical consequences depend on how much antibody function is lost. In adults, IgG3 deficiency appears to be the most common form but is likely of no clinical significance. However, low IgG2 or IgG4, most often found in individuals who have selective IgA deficiency, may lead to a profound deficiency of antibody production, especially to carbohydrate antigens such as contained in the pneumococcal vaccine.

Antibody Deficiency with Normal Immunoglobulins

The loosely described defect termed antibody deficiency with normal serum immunoglobulins, also termed specific antibody deficiency, is complex and heterogenous. All ages are affected, but the incidence is unknown. Although B cells are present, levels of IgG, IgA, and IgM are normal or near normal. Affected individuals do not form protective levels of serum antibodies after having an infectious exposure or vaccination with protein and/or carbohydrate vaccines. In milder cases, the pneumococcal vaccine does not result in sufficient antibody titers for protection. In the most severe cases, even strong immunogens such as herpes zoster or tetanus vaccines are ineffective.

DIAGNOSIS

The diagnosis of antibody defects is based on the laboratory tests of numbers of B cells, serum immunoglobulin levels (IgG, IgA, and IgM), and an evaluation of a panel of vaccine responses to determine the levels of functional antibody. If B cells are absent and the levels of immunoglobulins are very low, further antibody testing is not required. For a young male with a family history of males with immune deficiency, the diagnosis of X-linked agammaglobulinemia or hyper-IgM can be established by flow cytometry (to determine numbers of B cells for X-linked agammaglobulinemia) or by genetic tests (hyper-IgM). For older individuals (generally older than age 45 years), a thymoma may be sought by chest computed tomography, which may show a mass in the mediastinum. Most subjects with hypogammaglobulinemia will have B cells in their peripheral blood and some amount of serum IgG, IgA, or IgM. In these cases, the loss of functional antibody should be tested to determine if protective titers of antibody to common vaccine antigens (i.e., tetanus, diphtheria, *H. influenzae*, and pneumococci) can be detected. In some cases, revaccination may be needed to determine if a response occurs (tested again in 4 to 6 weeks). When high levels of B cells are found in adults, the possibility of a clonal B-cell expansion should be considered (e.g., chronic lymphocytic leukemia). For individuals who have IgG subclass defects or normal immunoglobulins levels, a panel of antibody titers should be obtained to determine immune competence or immune deficits. Genetic counseling is often important, and genetic testing can identify causative genes that may guide therapeutic decisions when autoimmune or inflammatory complications are present.

TREATMENT

The essential treatment of significant IgG antibody defects is intravenous or subcutaneous immune globulin, usually given in doses of 400 to 600 mg/kg body weight per month. Defects that require IgG replacement are conditions in which B cells are absent (X-linked agammaglobulinemia, other agammaglobulinemias, the hyper IgM syndromes, IgG subclass defects with demonstrable loss of antibody function, and some cases of loss of antibody with normal immunoglobulins; Table 231-4). Individuals who have IgA deficiency do not require immune globulin replacement unless they have a clear loss of functional antibody. The intravenous forms are usually given every 3 or 4 weeks, the subcutaneous forms weekly, biweekly, or monthly, depending on product and body weight. Indwelling ports are discouraged.

Most patients also require occasional courses of antibiotics, chosen on the basis of culture results, at intervals dictated by clinical events. Many affected individuals have recurrent pneumonias and resulting abnormal lung functions. In such patients, prophylactic antibiotics (e.g., azithromycin 250 mg three times a week) may reduce the rate of respiratory infections.[A1]

If patients develop autoimmune or inflammatory complications, treatments are as for immunocompetent persons but with a view to minimizing courses of immune suppression. Immune cytopenias may be treated with rituximab under expert supervision, but splenectomy should be avoided. For granulomatous lung infiltrations, rituximab plus azathioprine or mycophenolate mofetil can be useful.[20] Chronic interstitial lung disease, lymphoid hyperplasia, and gastrointestinal enteropathy may be difficult to treat, but treatments for Crohn disease (Chapter 127) may be successful.

PROGNOSIS

The prognosis for individuals with antibody defects is variable and depends on the degree of the defect, the response to treatment, whether organ damage has occurred, and whether other complications have developed. If patients who have a pure B-cell defect are diagnosed and treated early with sufficient immune globulin, the prognosis appears to be excellent. Individuals who have selective IgA deficiency can have a clinical course and life expectancy that are indistinguishable from age-matched healthy peers.

Patients with common variable immune deficiency have a prognosis that relates to their varying degrees of hypogammaglobulinemia, which range from almost total loss of immunoglobulins to more modest reductions of IgG and IgA or IgM. However, even patients with more modest reductions often have additional complications, in some cases because the diagnosis has been delayed until pulmonary or other damage has occurred. For individuals who have defects of IgG subclasses or antibody deficiencies and who are treated as required with immune globulin reconstitution, neither increased morbidity nor mortality is expected.

COMPLEMENT DISORDERS

The complement system (Chapter 37) is a network of proteins that both amplify and control many actions of the immune system. The three main branches of the complement system are the classical, alternative, and lectin pathways; deficiencies of individual components lead to increased susceptibility to infections, autoimmunity, and inflammatory diseases (Table 231-5).

EPIDEMIOLOGY

Complement C2 deficiency is found in 1 : 10,000 White individuals, who usually have a conserved major histocompatibility complex haplotype due to a founder defect. More than 95% of C2-deficient individuals are homozygous for the same C2 mutation. The other complement component defects are rare but found in unequal distribution in selected populations: C6 deficiency is more common in persons of African descent and C9 deficiency in Asians, with an estimated incidence of 0.036 to 0.095%.

PATHOBIOLOGY

The classical pathway is triggered by interaction of the Fc portion of an IgG1, IgG2, IgG3, or IgM antibody with C1q, which subsequently engages C1r, C1s, C2, and C3, thereby leading to activation of C4, C5, C6, C7, C8, and C9, resulting in lysis of bacteria (Chapter 37). The alternative pathway is activated in an antibody-independent manner and involves opsonization of bacteria with subsequent involvement of C3 and the alternative pathway. The lectin pathway includes other serum binding proteins that coat bacteria or fungi, thereby leading to downstream activation of complement and the assembly

TABLE 231-5 EXAMPLES OF COMPLEMENT DEFECTS

TYPE	GENES	INHERITANCE	LABORATORY FEATURES	ALTERED FUNCTIONS	DISEASE AND COMPLICATIONS
C1q, C1r, C1s deficiency	*C1qA, C1qB, C1qC; C1r, C1s*	Autosomal recessive	Absent CH_{50} hemolytic activity	Loss of early complement activation, impaired dissolution of immune complexes, impaired clearance of apoptotic cells	Bacterial infections, SLE-like syndrome, rheumatoid disease, multiple autoimmune diseases, infections
C4 deficiency	*C4A* and *C4B*	Autosomal recessive	Absent CH_{50} hemolytic activity	Loss of early complement activation	Bacterial infections
C2 deficiency	*C2*	Autosomal recessive	Absent CH_{50} hemolytic activity	Loss of early complement activation	Bacterial infections, SLE-like syndrome, vasculitis, early atherosclerosis, polymyositis, glomerulonephritis
C3 deficiency	*C3*	Autosomal recessive	Absent CH_{50} hemolytic activity	Loss of classical and alternative pathways of complement activation	Life-threatening pyogenic infections, SLE-like disease, glomerulonephritis, atypical hemolytic-uremic syndrome
C5, C6, C7, C8 deficiency	*C5*	Autosomal recessive	Absent CH_{50} hemolytic activity	Loss of complement activation	Neisserial infections, SLE
C9 deficiency	*C9*	Autosomal recessive	Reduced CH_{50} and AH_{50} hemolytic activity	Partial loss of complement activation	Some *Neisseria* infections
C1 inhibitor deficiency	*C1* inhibitor	Autosomal dominant	Activation of complement; low levels of C4 and C2	Loss of regulation of activities of complement C1	Angioedema

AH_{50} = alternative hemolytic complement; CH_{50} = total hemolytic complement; SLE = systemic lupus erythematosus.

of the membrane attack complex, which are the C7, C8, C9 components that are responsible for microbial lysis. The genes of the complement system are located on many chromosomes, and in general the defects are autosomal recessive, with the exception of defects of X-linked properdin.

More complex but equally potent is the role that the complement proteins play in immune regulation. Complement is important for clearing immune complexes and possibly apoptotic cells. In addition to the three pathways of activation, the complement system includes an even larger number of control proteins that, when genetically defective, also lead to severe infections, hemolytic-uremic syndrome, severe eclampsia, glomerulonephritis, thrombosis, and macular degeneration.

CLINICAL MANIFESTATIONS

Since opsonization of bacteria is essential for the function of antibodies, patients with these defects can have infections similar to what are seen in patients with immunoglobulin deficiencies. Loss of these classical components may lead to severe clinical consequences, but individuals who are deficient in C2 in particular but also in C4 and C5-C9 may have no history of illness. Severe bacterial infections are common, especially in individuals who have defects of C3, which lies at the convergence of the three pathways. With loss of C6,[21] C7, C8, C9, or properdin, *Neisseria gonorrhoeae* (Chapter 275) or *Neisseria meningitidis* (Chapter 274) is more common. With loss of the early components of the classical system, C1q, C1r, C1s, C2, and C4, autoimmunity, especially systemic lupus erythematosus (Chapter 245), is common[22] and occurs in more than 90% of patients who have defects of C1q and 75% of patients who have defects of C4.

DIAGNOSIS

Deficiencies of complement are diagnosed by testing total serum hemolytic complement (CH_{50}) and the alternative hemolytic complement (AP_{50}). Further testing usually includes measurement and function of individual serum complement proteins to determine the most applicable diagnosis. False-positive results can occur if the blood sample is mishandled, so abnormal tests often are repeated to confirm the diagnosis.

TREATMENT

No specific treatments are available for complement deficiencies. Prompt antibiotic therapy is indicated for acute infections, and autoimmune diseases require their usual treatments. Periodic immunizations with pneumococcal, *H. influenzae*, and meningococcal vaccines may be helpful to boost antibody titers to enhance bacterial clearance.

PROGNOSIS

The prognosis of complement defects is highly variable, and most of these defects have been found in otherwise healthy persons. The prognosis for patients who develop infections or autoimmune complications depends on the severity of the manifestations and their response to treatment. Although C2 deficiency is commonly viewed as being asymptomatic, some data suggest a higher incidence of premature arteriosclerotic cardiovascular disease.

C1 INHIBITOR DEFICIENCY

A diagnosis of C1 INH deficiency is suggested by a history of recurrent attacks of angioedema or in some cases (25%) episodes of recurrent abdominal pain due to edema (Chapter 232).

PHAGOCYTIC DEFECTS

EPIDEMIOLOGY AND PATHOBIOLOGY

Abnormalities of the phagocytic system are categorized as neutropenia, abnormal neutrophil morphology, defective cell adhesion and migration, or defective microbial killing (Chapters 153 and 155) (E-Table 231-3). Genetic defects impairing neutrophil development, adhesion, locomotion, or intracellular killing are rare. The most common genetic abnormality is chronic granulomatous disease, which has an estimated incidence of 1 : 100,000 to 1 : 200,000.

Circulating neutrophils are attracted to sites of inflammation by complement components C5a, chemokines, and bacterial byproducts, but traveling to these sites requires migration through capillaries and into tissues. The best-known diseases in which neutrophil adhesion is impaired are the leukocyte adhesion defects types 1, 2, and 3. Other defects of neutrophil motility include juvenile periodontitis, Shwachman-Diamond syndrome, and Chédiak-Higashi syndrome.

About two-thirds of patients with chronic granulomatous disease are males who have defects in an X-linked gene encoding $gp91^{phox}$. Autosomal defects in $p47^{phox}$ occur in 20% of patients and are the next most common form. Other autosomal forms due to defects in the gene encoding the $p22^{phox}$ or $p67^{phox}$ subunits each account for about 5% of cases.

CLINICAL MANIFESTATIONS

The genetic neutrophil disorders have specific clinical associations: delayed separation of the umbilical cord and poor wound healing in leukocyte adhesion defect-1; growth delay and Bombay blood group in leukocyte adhesion defect-2; peripheral nerve conduction defects, pigmentary dilution with partial oculocutaneous albinism, easy bruising, and risk of hemophagocytic disease in Chédiak-Higashi syndrome; and pancreatic insufficiency (fat malabsorption), growth failure, and skeletal abnormalities in Shwachman-Diamond syndrome (Chapter 151). For both Shwachman-Diamond syndrome and the severe congenital neutropenias (Chapter 153), patients are at risk of developing myelodysplastic disease and leukemia.

The clinical manifestations of chronic granulomatous disease[23] usually include bacterial or fungal infections. Males with the X-linked form will generally present in the first decade of life, whereas patients who have autosomal

E-TABLE 231-3 EXAMPLES OF PHAGOCYTE DEFECTS

TYPE	GENES	INHERITANCE	LABORATORY FEATURES	ALTERED FUNCTIONS	DISEASE AND COMPLICATIONS
DEFECTS OF NEUTROPHIL DIFFERENTIATION					
Severe congenital neutropenia	*ELANE, GFI1, HAX1; G6PC3; VPS45; G6PT1; WAS; LAMTOR2; TAZ; COH1 USB1; JAGN1; CLPB; CSF3R; SMARCD2*	Autosomal dominant, X-linked, or autosomal recessive	Neutropenia	Impaired myeloid differentiation	Susceptible to infections, myelodysplasia, syndromic features in some
Cyclic neutropenia	*ELANE*	Autosomal recessive	Neutropenia at 21-day intervals	Impaired and cyclic myeloid differentiation	Susceptible to infections at intervals, periodontitis
DEFECTS OF MOTILITY					
Leukocyte adhesion deficiency (types 1-3)	*ITGB2, SLC35C1; FERMT3*	Autosomal recessive	Leukocytosis	Impaired neutrophil adherence and chemotaxis	Delayed cord separation for type 1, skin ulcers, poor wound healing, periodontitis
Rac 2 deficiency	*RAC2*	Autosomal dominant	Leukocytosis	Impaired adherence, chemotaxis, O_2 production	Poor wound healing
Shwachman-Diamond syndrome	*SBDS*	Autosomal recessive	Pancytopenia	Impaired chemotaxis	Exocrine pancreatic insufficiency, chondrodysplasia, risk of leukemia
Chédiak-Higashi syndrome	*LYST*	Autosomal recessive	Neutrophils with giant inclusions; hair: pigment clumps	Impaired chemotaxis	Partial albinism, recurrent infections, late-onset primary encephalopathy, increased lymphoma risk
DEFECTS OF RESPIRATORY BURST					
Chronic granulomatous disease	*gp97phox (CYBB) p47phox (NCF1) p22phox (CYBA) p67phox (NCF2) p40phox (NCF4)*	X-linked or autosomal recessive	Normal or increased neutrophil counts but loss of respiratory burst	Impaired bacterial killing	Susceptible to bacterial and fungal infections

ACTB = actin beta; *CD18* = encodes an integrin beta chain; *CLPB* = ClpB homolog; *COH1* = Cohen syndrome; *CSF3R* = colony-stimulating factor 3 receptor; *CTSC* = cathepsin C; *CYBA* = cytochrome B-245 alpha chain; *CYBB* = cytochrome B-245 beta chain; *ELANE* = elastase; *FERMT3* = Fermitin family homolog 3; *FPR1* = formyl receptor peptide 1; *G6PC* = glucose-6-phosphatase catalytic subunit 3; *G6PT1* = glucose-6-phosphate transport; *GFI1* = growth factor independent 1 transcriptional repressor; *HAX1* = HCLS1 associated protein X-1; *ITGB2* = integrin subunit beta 2; *JAGN1* = jagunal homolog 1; *LAMTOR2* = late endosomal/lysosomal adaptor; *LYST* = lysosomal trafficking regulator; *NCF1* = neutrophil cytosolic factor 1; *NCF4* = neutrophil cytosolic factor 4; *RAC2* = Ras-related C3; *SBDS* = Schwachman-Bodian-Diamond syndrome; *SLC35C1* = solute carrier family 35; *SMARCD2* = SWI/SNF related matrix associated; *TAZ* = tafazzin; *USB1* = U6 SnRNA biogenesis phosphodiesterase 1; *VPS45* = vacuolar protein sorting 45 homolog; *WAS* = Wiskott-Aldrich syndrome; *WDR1* = WD repeat domain 1.

forms may present in their second decade of life. Regardless of the genetic cause, most patients with chronic granulomatous disease have one or more episodes of pneumonia; the most common causes of infection are *Staphylococcus, Burkholderia cepacia, Klebsiella, Aspergillus, Serratia*, and *Nocardia* species. Common clinical manifestations include acute or chronic lymphadenitis, colitis that leads to recurrent diarrhea, *Staphylococcus* liver abscess, osteomyelitis, and rectal abscess. Exposure to contaminated water or decaying plant material (compost, mulch) presents significant risk to patients who have chronic granulomatous disease because they are also prone to infections with unusual organisms, such as *Chromobacterium violaceum, Trichosporon inkin, Francisella philomiragia*, and *Granulibacter bethesdensis*.

TREATMENT

The diagnosis and management of patients with neutropenia is discussed in Chapter 153.

IMMUNE DYSREGULATION SYNDROMES

Immune dysregulation syndromes are mostly monogenic diseases and have in common lymphoid proliferation, immune activation, and inflammatory or autoimmune complications. These diseases include the hemophagocytic lymphohistiocytosis diseases (Chapter 155), the lymphoproliferative syndromes linked to Epstein-Barr virus infection, autoimmune polyendocrinopathy–candidiasis–ectodermal dystrophy, autoimmune lymphoproliferative syndrome, defects of T-regulatory cells, and immune defects that lead to severe early-onset inflammatory bowel disease (Table 231-6).

EPIDEMIOLOGY

The estimated incidence of the genetic hemophagocytic lymphohistiocytosis syndromes is 1 : 50,000, the incidence of X-linked lymphoproliferative disease is 1 to 3 in 1,000,000, and the incidence of autoimmune polyendocrinopathy–candidiasis–ectodermal dystrophy is high in Finland (1 in 25,000) and in Sardinians and Iranian Jews (1 in 9000) but otherwise much rarer. The incidence of autoimmune lymphoproliferative syndrome and defects of T-regulatory cells is unknown.

PATHOBIOLOGY

Hemophagocytic lymphohistiocytosis[24] is a genetic or secondary form of extreme and potentially life-threatening immune activation (Chapter 155). The familial form is a heterogeneous autosomal recessive disorder due to mutations in one of five genes essential for control of T-cell cytotoxicity. Immune activation leads to expansion of poorly controlled cytotoxic T cells and macrophages, thereby leading to the release of interferon-γ (IFN-γ), IL-1, IL-6, and IL-10. Patients have high fevers, cytopenias, liver dysfunction, coagulopathy, and sometimes neurologic symptoms.

Monogenic defects that lead to impaired immunity to Epstein-Barr virus produce another group of immune dysregulation syndromes.[25] The most common form is the X-linked proliferative disorder (XLP) that is caused by mutations of the X-linked *SH2D1A* gene. Other genetic causes for loss

TABLE 231-6 EXAMPLES OF DISEASES OF IMMUNE DYSREGULATION

TYPE	GENES	INHERITANCE	LABORATORY FEATURES	ALTERED FUNCTION	DISEASE AND COMPLICATIONS
Familial hemophagocytic lymphohistiocytosis syndromes	*PRF1, UNC13D, STX11, STXBP2, FAAP24 SLC7A7*	Autosomal recessive, autosomal dominant	Anemia, neutropenia, thrombocytopenia, abnormal liver functions, high ferritin and serum IL-2 receptor, hemophagocytosis in bone marrow and liver	Decreased to absent NK cells and cytotoxic activities	Fever, hepatosplenomegaly, cytopenias, hemophagocytic lymphohistiocytosis, neurologic disease in some
Chédiak-Higashi syndrome	*LYST*	Autosomal recessive	Neutrophils with giant inclusions; hair: pigment clumps	Impaired chemotaxis	Partial albinism, recurrent infections, late-onset primary encephalopathy, increased lymphoma risk
Lymphoproliferative syndromes (susceptibility to EBV)	*SH2D1A, XIAP, ITK, CD27, CTPS1, CD70, RASGRP1, MAGT1*	X-linked, autosomal recessive	Epstein-Barr virus infection; decreased NK cells and CD8+ CTL activation; deficient NK-T cells; anemia; hypogammaglobulinemia in some	Loss of function of NK-T cells leading to impaired viral control	Clinical and immunologic features triggered by Epstein-Barr virus infection; lymphoproliferation, lymphoma
Autoimmune polyendocrinopathy–candidiasis ectodermal dystrophy (APECED)	*AIRE*	Autosomal recessive	Endocrine dysfunction; hepatitis	Loss of thymic self-tolerance	Autoimmunity leading to hypoparathyroidism, hypothyroidism, diabetes, and adrenal and gonadal dysfunction; cutaneous candidiasis; hepatitis
Autoimmune lymphoproliferative syndrome (ALPS)	*FAS, FAS ligand; caspase 10; caspase 8; KRAS; NRAS*	Autosomal dominant	Increased double-negative T cells (CD4−/CD8−), increased serum B_{12}	Defects in lymphocyte apoptosis	Splenomegaly, lymphadenopathy, autoimmune cytopenias; increased risk of lymphoma
Genetic defects of T-regulatory cells	*FOXP3, CD25, CTLA4, IL2RA, IL2RB, LRBA, STAT3 (GOF), BACH2, DEF6, STAT5B* and *STAT1; STAT5b*	X-linked, autosomal recessive, autosomal dominant	Autoimmunity, diabetes, anemia, eosinophilia, high serum IgE in some	Lack of (or impaired function of) CD4+, CD25+, FOXP3+ regulatory T cells (Tregs)	Enteropathy, hepatosplenomegaly, dermatitis, eczema, early-onset diabetes, thyroiditis, hemolytic anemia, thrombocytopenia, elevated IgE and IgA; recurrent infections
Immune dysregulation leading to colitis	*IL-10, IL-10Ra, IL-10Rb, NFAT5, TGFB1, RIPK1*	Autosomal recessive, autosomal dominant	Normal lymphocyte panels	Defects of immune responses to resident microbes	Severe IBD, recurrent sinopulmonary infections

AIRE = autoimmune regulator; *BACH2* = BTB domain and CNC homolog 2; CTL = cytotoxic T lymphocyte; *CTLA4* = cytotoxic T-lymphocyte-associated protein 4; *CTPS1* = CTP synthase 1; *DEF6* = DEF6 guanine nucleotide exchange factor; EBV = Epstein-Barr virus; *FAAP24* = Fanconi anemia core complex associated protein 24; *FAS* = Fas cell surface death receptor; *FOXP3* = Forkhead box P3; IBD = inflammatory bowel disease; Ig = immunoglobulin; IL = interleukin; *IL2RA* = IL-2 receptor subunit alpha; *IL2RB* = IL-2 receptor subunit beta; *ITK* = IL-2 inducible T-cell kinase; *KRAS* = KRAS proto-oncogene; *LRBA* = LPS responsive beige-like anchor protein; *LYST* = lysosomal trafficking regulator; *MAGT1* = magnesium transporter 1; *NFAT5* = nuclear factor of activated T cells 5; NK = natural killer; *NRAS* = NRAS proto-oncogene; *PRF1* = perforin; *RASGRP1* = RAS guanyl releasing protein 1; *RIPK1* = receptor interacting serine/threonine kinase 1; *SAP* = SLAM-associated protein; *SH2D1A* = SH2 domain containing 1A; *SLC7A7* = solute carrier family 7 member 7; *STAT1* = signal transducer and activator of transcription 1; *STAT3 (gain of function)* = signal transducer and activator of transcription 3; *STAT5B* = signal transducer and activator of transcription 5B; *STX11* = syntaxin 11; *STXBP2* = syntaxin binding protein 2; *TGFB1* = transforming growth factor beta 1; *UNC13D* = Unc-13 homolog D; *XIAP* = X-linked inhibitor of apoptosis.

of control of Epstein-Barr virus are due to mutations in *XIAP* (20 to 30%) or, rarely, *ITK CD27, MAGT1,* or *CD70*. *XLP, XIAP,* and *MAGT1* are on the X chromosome; the other defects are inherited as autosomal recessive traits. In each case, infection with Epstein-Barr virus leads to an acute illness with lymphoproliferation, progressive but variable hypogammaglobulinemia, and lymphoma in *XLP, ITP,* and *CD27* defects. A unifying theme of these syndromes is loss of function of NK-T cells, a subset of T cells important in viral immunity.

A unique member of the genetic immune dysregulation diseases is autoimmune polyendocrinopathy–candidiasis–ectodermal dystrophy or autoimmune polyglandular syndrome type 1 (Chapter 212). The disease is caused by loss of thymic recognition of self-antigens due to mutations in the autoimmune regulator gene *(AIRE)*. Chronic mucocutaneous candidiasis (Chapter 310) may be related to circulating anticytokine antibodies (interferon and IL-17). The transcription factor encoded by the *AIRE* gene, which is found in thymic epithelial cells, is involved in the early negative selection of cells with autoimmune potential.

Defects in lymphocyte apoptosis lead to another form of immune dysregulation; in these subjects, because of impaired death of lymphocytes, lymph nodes and spleen enlarge, and various forms of autoimmunity, especially autoimmune thrombocytopenia and hemolytic anemia, occur. Together, these diseases are commonly referred to as autoimmune lymphoproliferative syndrome. The most common of these defects are due to autosomal dominant mutations in the *FAS* gene, which encodes the important FAS death receptor, and less commonly in the FAS ligand.[26] Both conditions are dominant but have variable penetrance. Much less common forms of autoimmune lymphoproliferation are due to mutations in caspase 8 or 10 or even more rarely the oncogenes *KRAS* and *NRAS* or protein kinase Cδ. In addition, mutations in somatic genes may mimic the clinical presentation of the congenital forms.

Defects of T-regulatory cells are another set of genetic defects that lead to loss of regulation. The defect is generally due to mutations of the X chromosome forkhead box protein 3 *(FOXP3)* gene, which is essential for the development of regulatory T cells. However, other genetic defects may lead to a similar clinical syndrome.

CLINICAL MANIFESTATIONS

Life-threatening accelerated immune activation syndromes are characteristic of hemophagocytic lymphohistiocytosis and other genetic defects that impair cytotoxicity, such as the Chédiak-Higashi syndrome. For autoimmune polyglandular syndrome type 1 (Chapter 212), the usual presentation is cutaneous candidiasis or endocrine insufficiency (i.e., hypoparathyroidism, Addison disease, hypogonadism, and secondary amenorrhea). Chronic diarrhea with malabsorption is also common. Other autoimmune complications may include hepatitis, alopecia, vitiligo, diabetes mellitus, anemia, and pernicious anemia. The immune dysregulation, polyendocrinopathy, enteropathy, X-linked syndrome, which is a generally lethal disease in males, is characterized by early-onset insulin-dependent diabetes mellitus, enteropathy with severe diarrhea, and eczema-like dermatitis.[27] Other manifestations include anemia, thrombocytopenia, and neutropenia, as well as liver or kidney autoimmune disease.

DIAGNOSIS

The diagnosis of these syndromes may be suspected from the clinical manifestations, family history, and laboratory grounds, but genetic validation is required for definitive diagnosis.

TREATMENT

For the hemophagocytic lymphohistiocytosis diseases and related syndromes, prompt immune suppression by established protocols and intense supportive care are necessary (see Chapter 155).[28] For the genetic forms, hematopoietic stem cell transplantation (Chapter 163) is often required. The lymphoproliferative syndromes associated with Epstein-Barr virus are similar in that prompt supportive care is required and transplantation is potentially curative. Rituximab has been used in these defects to reduce B-cell numbers and the burden of Epstein-Barr virus if infection occurs. Treatment of the cytopenias in the autoimmune lymphoproliferative syndrome includes corticosteroids, rapamycin, mycophenylate, and other agents. For unclear reasons, rituximab may lead to permanent hypogammaglobulinemia in autoimmune lymphoproliferative syndrome, and splenectomy is to be avoided. Patients with autoimmune polyendocrinopathy–candidiasis–ectodermal dystrophy usually require endocrine and possibly nutritional management as well as treatment for cutaneous candidiasis. For the defects of T-regulatory cells due to mutations in the immune dysregulation, polyendocrinopathy, enteropathy, X-linked syndrome, hematopoietic stem cell transplantation is the only curative measure.

PROGNOSIS

The diseases of immune dysregulation have a varied prognosis. For the genetic hemophagocytic lymphohistiocytosis syndromes, Epstein-Barr virus–related lymphoproliferative diseases, and the immune dysregulation, polyendocrinopathy, enteropathy, X-linked syndrome, immune reconstitution is required. Because of the broad spectrum of manifestations for the autoimmune lymphoproliferative syndrome and for autoimmune polyendocrinopathy–candidiasis–ectodermal dystrophy, management of the clinical issues may be sufficient.

DISEASES OF INTRINSIC AND INATE IMMUNITY

As compared with the adaptive immune system, in which a previous exposure is required to form immune memory (Chapter 35), many components of the immune system function quickly without prior exposure. These components of the innate immune system (Chapter 35) include complement, phagocytic cells, and natural killer cells. Screening of large populations for selected microbial diseases has revealed a number of defects of innate immunity (Table 231-7).

EPIDEMIOLOGY AND PATHOBIOLOGY

Innate immunity defects that cause specific infections appear to be rare, and their incidence is not known. Anhidrotic ectodermal dysplasia with immunodeficiency, which is caused by mutations in the *IKBKG* gene that encodes nuclear factor-κB (NF-κB) essential modulator (NEMO), is an X-linked disease. Genetic defects can also occur in toll-like receptors and their signaling pathways (e.g., autosomal recessive defects in *IRAK4* and *MyD88*).

Genetic disorders that lead to chronic mucocutaneous candidiasis may be autosomal dominant or recessive. Patients of any age may have defects in these pathways. The pathogenesis of some of these include genes that disrupt the dectin-1 pathway. Dectin-1 is a surface lectin receptor that recognizes the β1-3 glucan of fungi; downstream mutations in *CARD9* impair the secretion of IL-17A, IL-17F, and IL-22, cytokines that are essential in fungal clearance.

A separate and unique category of innate defects are the cytokine/receptor mutations that impair the functions of cytokines IL-12, IL-23, and IFN-γ, which are required to control mycobacterial and other intracellular infections, such as salmonella. Chronic mycobacterial infections may also occur in patients with autosomal recessive mutations in the gene for signal transducer and activator of transcription 1 *(STAT1),* a gene downstream of both IFN-γ and IFN-α receptors. Defects in toll-like receptors and their signaling pathways are autosomal recessive or X-linked disorders, whereas defects in *GATA2* are inherited in an autosomal dominant fashion.

CLINICAL MANIFESTATIONS

For anhidrotic ectodermal dysplasia with immunodeficiency, the clinical phenotype can include severe bacterial infections and mycobacterial disease as well as ectodermal dysplasia: sparse hair, abnormal tooth development, and lack of sweat glands. Defects in toll-like receptors lead to severe pneumococcal and staphylococcal infections. In contrast, defects of the TL3 pathway lead to early herpes simplex encephalitis. The genetic defects that lead to chronic mucocutaneous candidiasis are heterogenous, and clinical manifestations may range from onychomycosis to invasive fungal infections.

Patients who have cytokine or cytokine receptor defects may have severe viral or fungal infections. Dominant (activating) mutations in *STAT1* may lead to simple cutaneous candidiasis in some patients or to cutaneous candidiasis plus more complex clinical outcomes in other patients. More complex is the syndrome of GATA2 deficiency in which mycobacterial disease may also develop,[29] but other organisms (papillomaviruses, fungi) and serious complications (cytopenias, myelodysplasia, pulmonary

TABLE 231-7 EXAMPLES OF DISEASES OF INNATE IMMUNITY

DISEASE	GENES	INHERITANCE	LABORATORY FEATURES	ALTERED FUNCTION	ASSOCIATED FEATURES
Anhidrotic ectodermal dysplasia with immunodeficiency	*IKBKG*, (NEMO), *IKBA*	X-linked, autosomal dominant	Variable hypogammaglobulinemia with increased IgM in some; lack of antibody response to polysaccharides	Defective NF-κB signaling pathway	Bacterial and mycobacterial infections, ectodermal dysplasia, hair loss, heat intolerance due to loss of sweat glands, tooth abnormalities
IRAK4, MYD88	*IRAK4, MYD88, IRAK1, TIRAP*	Autosomal recessive, X-linked	cytokine responses to toll receptor activators	Defective TIR-IRAK signaling pathway	Bacterial infections, especially *Staphylococcus* and *S. pneumoniae*
Susceptibility to mycobacterial disease	*IL12, IL23R, IFNGR1, IFNGR2* *STAT1, CYBB, TYK2, ISG15, SPPL2A, JAK1, RORC*	Autosomal recessive, autosomal dominant, X-linked	Cultures positive; impaired IFN-γ/IL-23 production or responses.	IFN-γ signaling; IFNγ production defect; Impaired cellular development	Susceptibility to mycobacteria and *Salmonella*
Herpes simplex encephalitis	*TLR3* *UNC93B1* *TRAF3, TICAM1, TBK1, IRF3, DBR1*	Autosomal dominant, autosomal recessive	Impaired cytokine responses to TLR3 activators	Defective IFN-α, IFN-β, and IFN-γ induction	Herpes simplex virus 1 encephalitis
Predisposition to fungal diseases	*CARD9*	Autosomal recessive	Fungal cultures positive	Defective CARD9 signaling pathway	Invasive candidiasis and other fungal diseases
Chronic mucocutaneous candidiasis	*IL17RA, IL17C* *IL17F* *STAT1* *AIRE* *TRAF3IP2*	Autosomal recessive, autosomal dominant	Fungal cultures positive	Defective IL-17R signaling pathways	Mucocutaneous candidiasis
IL-12, IL-23 receptor deficiency	*IL12RB* *IL12* *IL23*	Autosomal recessive	Mycobacterial cultures positive	Defective cytokine receptor binding and signaling	Mycobacterial and salmonella infections
IFN-γ receptors 1 and 2 deficiency	*IFNGR1* *IFNGR2*	Autosomal recessive	Mycobacterial cultures positive	Defective IFN-γ binding and signaling	Mycobacterial and salmonella infections
GATA2 deficiency	*GATA2*	Autosomal recessive, autosomal dominant	Multilineage cytopenias; very low monocyte numbers		Infections with mycobacteria, papillomaviruses, histoplasmosis, alveolar proteinosis but also myelodysplasia and leukemias

AIRE = autoimmune regulator; *CYBB* = cytochrome B-245 beta chain; *DBR1* = debranching RNA lariats 1; *GATA2* = a member of the GATA family of zinc-finger transcription factors; IFN = interferon; *IFNGR1* = ligand-binding chain (alpha) of the gamma interferon receptor; *IFNGR2* = ligand-binding chain (beta) of the gamma interferon receptor; *IKBA* = NF-kappa-B inhibitor alpha; IL = interleukin; *IL12* = interleukin-12; *IL12RB* = interleukin-12 receptor B; *IL17* = interleukin-17; *IL17C* = interleukin-17C; IL-17R = interleukin-17 receptor; *IL17RA* = interleukin-17 receptor A; *IL23R* = interleukin-23 receptor; *IRAK1* = interleukin-1 receptor–associated kinase 1; *IRAK4* = interleukin-1 receptor–associated kinase 4; *IRF3* = interferon-regulatory factor 3; *ISG15* = ISG15 ubiquitin-like modifier; *JAK1* = Janus kinase-1; *MYD88* = myeloid differentiation primary response protein; *NEMO (IKBKG)* = NF-kappa-B essential modulator; NF-κB = nuclear-factor-κB; *RORC* = RAR-related orphan receptor C; *SPPL2A* = signal peptide peptidase-like 2A; *STAT1* = signal transducer and activator of transcription 1; *TBK1* = TANK binding kinase 1; TIR = intracytoplasmic toll and IL-1-receptor; *TIRAP* = TIR domain–containing adaptor protein; TLR = toll-like receptor; *TLR3* = toll-like receptor 3; *TRAF3* = TNF-receptor–associated factor 3; *TRAF3IP2* = TRAF3 interacting protein 2; *TRIF (TICAM1)* = TIR domain–containing adapter-inducing interferon-β; *TYK2* = tyrosine kinase 2; *UNC93B1* = Unc-93 homolog B1.

alveolar proteinosis, peripheral edema) may be foremost, and members of the same family with the same mutations may have very different clinical manifestations.

DIAGNOSIS

The diagnosis of innate defects is first based on exclusion of other causes and then confirmed by genetic testing. The family history may be helpful, but the extreme range of clinical phenotypes may obscure easy recognition of patients who have mutations in *STAT1* or *GATA2*.

TREATMENT AND PROGNOSIS

The treatment of innate defects includes antimicrobial therapy to clear active infections and often relevant prophylactic therapy under expert supervision on an ongoing basis. For the more severe defects, hematopoietic stem cell transplantation (Chapter 163) is required.

AUTOINFLAMMATORY DISORDERS

Inherited autoinflammatory syndromes are described in Chapter 240.

BONE MARROW FAILURE DEFECTS

Bone marrow failure syndromes are discussed in Chapter 151.

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For the General References and other additional features, please visit Elsevier eBooks+ at https://ebooks.health.elsevier.com.

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232 URTICARIA AND ANGIOEDEMA

SARBJIT S. SAINI

DEFINITION

Acute and chronic urticaria, which involve the dermis, are caused by the excessive release of histamine from mast cells—sometimes acute and sometimes chronic, and sometimes with and sometimes without a trigger. Angioedema, which also involves subcutaneous tissue, can accompany histamine-driven urticaria or can be caused by excessive bradykinin, either as a result of hereditary angioedema or specific provoking agents.

HISTAMINE-INDUCED ACUTE AND CHRONIC URTICARIA

Episodes of urticaria or angioedema are classified by their duration and by the presence of a known trigger. Acute urticaria persists for less than 6 weeks, whereas chronic urticaria is defined by recurrent urticaria, angioedema, or both for more than 6 weeks.[1] Chronic urticaria is further divided into the 20% or so of patients who have a specific physical stimulus or trigger (e.g., heat, cold temperature, elevation in body temperature, vibration, or sunlight) for their hives (chronic inducible urticaria)[2] as compared with the 80% or so who experience skin lesions of chronic spontaneous urticaria without a clear trigger. The most common presentation of chronic spontaneous urticaria is urticaria alone (50%), followed by both urticaria and angioedema (40%) and recurrent angioedema only (10%). The term chronic spontaneous urticaria encompasses clinical phenotypes that include both urticaria and angioedema.

EPIDEMIOLOGY

About 25% of both females and males will have an episode of acute urticaria in their lifetime.[3] For chronic urticaria, the estimated prevalence is 0.1 to 1%, with an average onset in third to fifth decade of life,[4] and adult females are more often affected than males (2:1). In the majority of patients, the duration of chronic urticaria is self-limited and ranges from 2 to 5 years.[5] In individuals with chronic inducible urticarias, however, the duration can be much longer.

PATHOBIOLOGY

A central feature of skin lesions of urticaria is the activation of mast cells, which are found throughout the skin of the body in varying numbers. Within minutes, activated mast cells can release mediators such as stored histamine, leukotriene C4, and prostaglandin D2, thereby leading to vasodilation, leakage of plasma into the dermis, and creation of the sensation of pruritus via activation of sensory nerves.[6] A few hours later, mast cells release cytokines that can lead to the recruitment of lymphocytes, eosinophils, and basophils into the skin tissue. Angioedema, which results from a similar extravasation of fluid in deeper dermal and subcutaneous tissues, takes 24 to 72 hours to resolve.

Acute Urticaria

In acute urticaria, the activating triggers for mast cells include immediate hypersensitivity reactions to drugs or foods, as well as to the inflammatory process of a viral illness. However, no clear trigger is found in over 50% of cases.[7] Among the implicated foods in children are milk, egg, and peanuts, whereas peanuts, tree nuts, fish, and shellfish predominate in adults. These food allergens and some drugs (e.g., penicillins) crosslink specific IgE that is bound to the surface of mast cells via high-affinity receptors (FcεRI) and activate the release of mediators. Commonly implicated drugs are antibiotics (penicillins, sulfonamides), nonsteroidal anti-inflammatory drugs, and muscle relaxants. Mast cells can be activated by non–IgE-based pathways via a receptor called MRGPRX2. Drugs that can activate this receptor include opioids, muscle relaxants, and antibiotics such as ciprofloxacin.[8] Hives also can be precipitated by scombroid food poisoning (Chapter 98), in which fish that are contaminated with bacteria produce histamine, which then leads to hives.[9]

Chronic Urticaria

In chronic spontaneous urticaria, the mechanisms by which mast cells are activated are less clear. Serum autoantibodies are detected in up to 40% of cases, thereby suggesting an autoimmune mechanism. Such autoantibodies include IgG that targets either the high-affinity IgE receptor (FcεRI) or IgE and thereby activates skin mast cells. Some patients with chronic spontaneous urticaria express thyroid IgG autoantibodies.[10]

FIGURE 232-1. Dermographism.

In chronic inducible urticaria, the trigger for the activation of mast cells is more specific. In the case of dermographism (writing on the skin), mild pressure or stroking of the skin will activate the local tissue mast cells (Fig. 232-1). This type of chronic inducible urticaria is often also seen in patients with chronic spontaneous urticaria. In cholinergic urticaria, patients experience short-lived hives when their body temperature is elevated, such as with exercise. Cold-induced urticaria activates mast cells beneath a well-defined temperature threshold.

Other Subtypes

In rare cases of chronic urticaria and angioedema, a food or drug allergen is identified. In addition, contact allergens such as soaps, detergents, cosmetics, or latex may be involved. Urticaria may also occur secondary to an unrecognized autoimmune condition such as rheumatoid arthritis (Chapter 243), systemic lupus erythematosus (Chapter 245), a systemic vasculitis (Chapter 249), or thyroid disease (Chapter 207) or, extremely rarely, as a paraneoplastic skin phenomenon (Chapter 164). In endemic areas, parasitic infections with strongyloides (Chapter 327) or filariasis (Chapter 327) can be associated with urticaria.

CLINICAL MANIFESTATIONS

Urticaria (hives) is a pruritic, erythematous, papular skin lesion that can be raised, can have a pale center, and can extend from several millimeters to centimeters in size (Fig. 232-2). Each individual lesion may persist for up to 24 hours. Lesions of longer duration should raise concern for other diagnoses (Chapter 407). Angioedema is defined by the rapid onset of nonpitting edema in the subdermal or mucosal tissues without erythema or well-defined borders. Areas of angioedema can be associated with a sensation of tingling, pressure, pain, or burning. Commonly involved areas include the face, cheek, lips, tongue, hands, feet, and genitalia (Fig. 232-3). Angioedema typically does not resolve as rapidly as urticaria and can persist for up to 72 hours.

Pruritus commonly precedes and then accompanies the eruption of papular hives or wheals. Hives or wheals may be round, annular, or serpiginous; they can appear in groups, can coalesce, and also appear several times a day. The typical time course of individual hives can be 30 minutes to 24 hours before full resolution of the skin without ecchymoses.

Chronic spontaneous urticaria frequently involves areas of constant pressure (e.g., the waistband), thereby supporting overlap of chronic spontaneous urticaria with chronic inducible urticarias such as dermographism. If a patient is taking antihistamines, the lesions appear flattened. The severity of pruritus can disrupt both daytime activities and sleep. In more severe cases of chronic urticaria, extracutaneous symptoms can include headache, fatigue, wheezing, gastrointestinal complaints, or a joint pain.

Some chronic inducible urticarias present with unique clinical features.[11] In cold-induced urticaria,[12] local lesions appear when the skin is exposed to a sudden drop in air temperature or cold water. In cholinergic urticaria, the wheals appear during physical exertion and resemble smaller papules with large surrounding erythematous bases. With delayed pressure urticaria, the onset of urticaria or angioedema (e.g., hand swelling hours after carrying groceries) occurs 4 hours or longer after the pressure triggers.

ABSTRACT

Episodes of urticaria or angioedema are classified by their duration and by the presence or absence of a known trigger. Acute urticaria persists for less than 6 weeks, whereas chronic urticaria is defined by recurrent urticaria, angioedema, or both for more than 6 weeks. Chronic urticaria is further subdivided based on whether patients have chronic inducible urticaria with a specific physical stimulus for their hives (about 20% of patients) or have chronic spontaneous urticaria without a clear trigger (about 80% of patients). Chronic spontaneous urticaria can be manifested as urticaria or angioedema. Angioedema is driven by mast cells, and the histaminergic angioedema of chronic urticaria must be distinguished from the bradykinin-mediated angioedema that is observed in rare types of hereditary angioedema and related diseases. The treatments for these two disorders are distinct, as are the implications for morbidity and mortality.

KEYWORDS

angioedema
urticaria
hereditary angioedema
acquired angioedema
chronic inducible urticaria

FIGURE 232-2. Extensive urticaria. Many presentations are more subtle. (From Roitt I, Brostoff J, Male D, eds. *Immunology*. 6th ed. London: Mosby; 2001.)

FIGURE 232-3. Angioedema.

DIAGNOSIS

Urticaria is usually a clinical diagnosis based on seeing the skin lesions either in person or by a photograph (Fig. 232-4). By definition, urticaria is first subdivided into acute (<6 weeks duration) and chronic forms.

Acute Urticaria

The diagnosis of acute urticaria or angioedema requires a comprehensive history and physical examination with attention to ingestions, the pattern of the eruptions, contactants, recent infections, and review of photographs of past lesions. A history of recent infections or vaccinations and any new exposures to foods and to prescribed or over-the-counter drugs should be elicited, and any close temporal relationship to potential precipitants should be explored. To prove a link to urticaria, the suspected drug or food must be withdrawn; if the reaction is mild enough to be well-tolerated, re-challenge can then confirm the cause. In the majority of cases, however, no trigger is identified.

Chronic Urticaria

For chronic urticaria, with symptoms of 6 weeks or more, subtypes include chronic spontaneous (absence of identifiable trigger) urticaria, inducible (well-defined eliciting factor) urticaria, ingestion-related urticaria, or urticaria associated with an underlying systemic process. Other diseases to consider are generalized pruritus, flushing disorders such as carcinoid (Chapter 213), urticarial vasculitis (Chapter 407), systemic mastocytosis (Chapter 235), exercise-related anaphylaxis (Chapter 233), food-associated anaphylaxis (Chapter 233), idiopathic anaphylaxis, hereditary angioedema, acquired angioedema, angiotensin-converting enzyme (ACE) inhibitor–induced angioedema, systemic lupus erythematosus (Chapter 245), autoinflammatory disease (Chapter 240), and polymorphous eruptions of pregnancy (Table 232-1).[13] Local cold-related skin eruptions must be differentiated from cryoglobulinemia (Chapter 173) and from cryopyrin-based familial fever disorders (Chapter 240).

When angioedema involves the lip, throat, or tongue, or when patients develop abdominal pain due to intestinal mucosal swelling without urticaria, drug-induced angioedema or hereditary angioedema should be considered. In 20 to 30% of patients, ingestions such as nonsteroidal anti-inflammatory drugs (NSAIDs) can exacerbate underlying chronic spontaneous urticaria.[14]

Diagnostic Testing

The evaluation of chronic urticaria should include a complete blood count with differential, a metabolic panel, liver enzymes, a C-reactive protein (CRP) level, and an erythrocyte sedimentation rate (ESR). Additional studies, including a thyroid-stimulating hormone (TSH) level, thyroid antibodies, and an autoimmune profile, generally should be reserved for patients in whom the history, physical examination, or basic laboratory studies raise a suspicion. Skin testing for foods is not recommended given lack of evidence to support food allergy as a cause in chronic spontaneous urticaria, the high rate of false-positive tests owing to the presence of dermographism in many patients who have chronic spontaneous urticaria, and the need to withdraw antihistamines to conduct such testing. Testing for autoantibodies for IgE and the high-affinity IgE receptor is controversial because of a lack of universal standards and because such autoantibodies can be elevated in healthy patients as well as in patients who have other autoimmune diseases.

For inducible urticarias, provocative testing by a specialist can assist in confirming the diagnosis and spare exhaustive investigations. Examples include an ice cube challenge for cold urticaria or scratching the skin to check for dermographism. Some subtypes of chronic inducible urticaria, such as dermographism, are also observed in patients who have chronic spontaneous urticaria.

A skin biopsy is reserved for cases in which the diagnosis is in doubt or when urticarial vasculitis is suspected because of bruising at the site of wheals or pain rather than itch as the main symptom. For example, if lesions persist for longer than 24 hours and bruise, a skin biopsy is required to confirm or refute urticarial vasculitis. The persistence of skin discoloration on resolving lesional skin should also prompt a skin biopsy. Microscopic evidence of fibrinoid necrosis, endothelial damage, and immune deposits should lead to further search for a secondary immune disorder such as systemic lupus erythematosus (Chapter 245). In individuals who present with recurrent episodes of swelling without hives or pruritus, hereditary angioedema, acquired angioedema, and angioedema due to ACE inhibitors must be considered.

Searching for Underlying Causes

About 95% of patients with chronic spontaneous urticaria will not have an identifiable trigger or systemic illness. Foods and drugs are often suspected by the patient with chronic urticaria but are unlikely to be the cause. Persistence of skin symptoms despite eliminating the suspected trigger confirms that the urticaria has a different cause.

A secondary systemic or infectious disorder is the cause of fewer than 2% of the cases of chronic spontaneous urticaria. Such conditions can include thyroid disorders (Chapter 207) and autoimmune diseases (Chapter 236), food allergy (Chapter 233), chronic rhinosinusitis (Chapter 394), atopic dermatitis (Chapter 405),[15] and, very rarely, an underlying malignancy (Chapter 164). Infectious diseases that are associated with chronic urticaria include sinus infections, dental abscesses, *Helicobacter pylori,* and tinea pedis; however, an extensive search for an unrecognized chronic infection is not recommended.

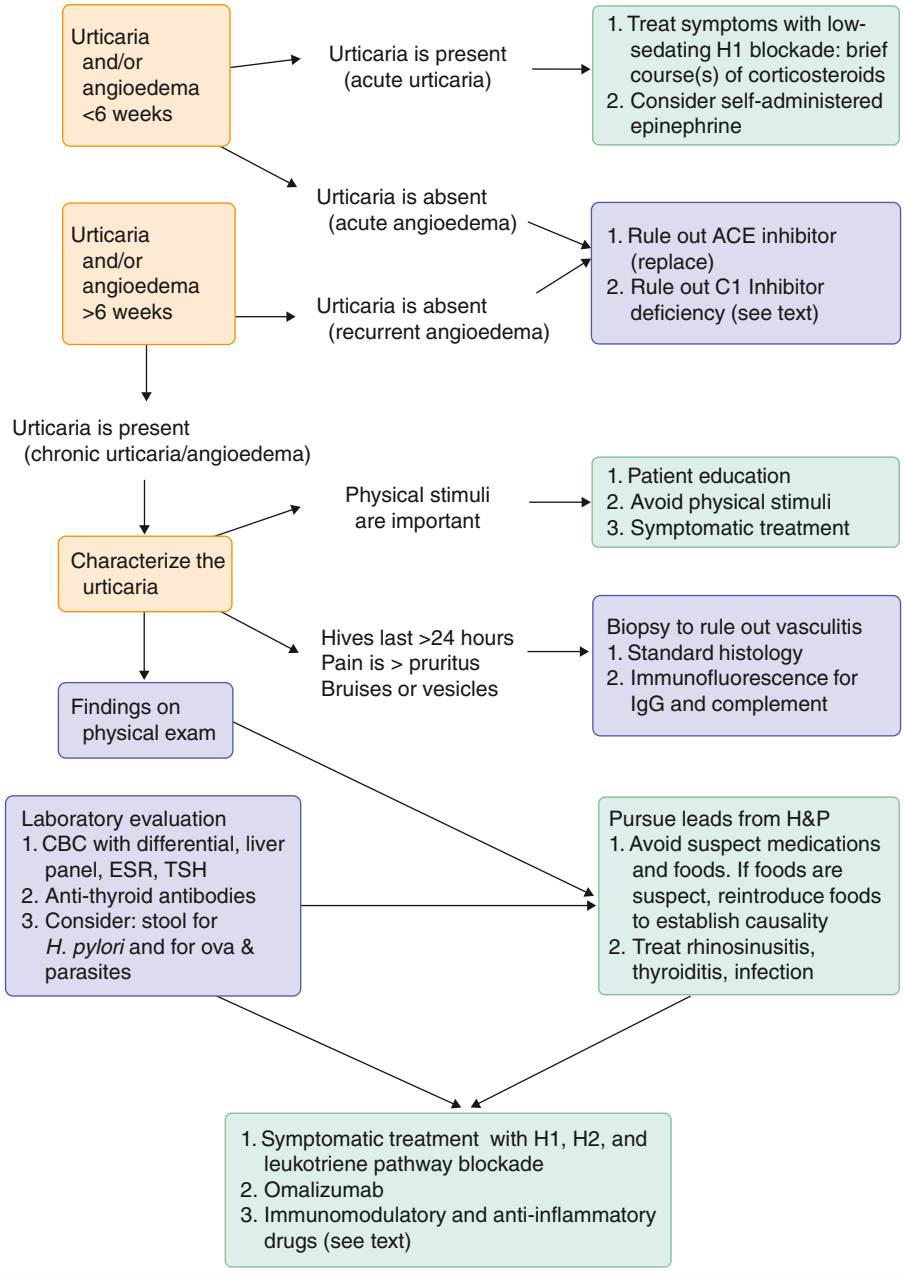

FIGURE 232-4. Evaluation and treatment of urticaria and angioedema. Treatment of urticaria with or without angioedema can be similar. However, the treatment of angioedema without urticaria depends on the cause. If the angioedema is caused by an angiotensin-converting enzyme (ACE) inhibitor, discontinuation of the medication is required. Treatment of angioedema due to deficiency or dysfunction of C1 esterase inhibitor, also called bradykinin-mediated angioedema, is discussed in the text. Recurrent angioedema is most often histaminergic but is treated as for urticaria/angioedema. CBC = complete blood count; ESR = erythrocyte sedimentation rate; H&P = history and physical examination; H1 = histamine receptor antagonist; TSH = thyroid-stimulating hormone.

TREATMENT

Acute Urticaria

Acute urticaria is self-limited and usually is responsive to antihistamines[A1] (e.g., a second-generation antihistamine such as cetirizine 10 mg, levocetirizine 5 mg, fexofenadine 180 mg, loratadine 10 mg, or desloratadine 5 mg daily). In severe cases, adding oral corticosteroids (e.g., prednisone 20 to 40 mg daily for 5 days) can provide better symptomatic relief, but intravenous corticosteroids are not beneficial.[A2] Endotracheal intubation is rarely required but is sometimes indicated in patients who have shortness of breath, drooling, and swelling of the interior tongue or pharynx.[16]

Chronic Urticaria

Treatment should begin with a second-generation antihistamine once daily, with the dose advanced, if needed, to up to four times daily at 2- to 4-week intervals.[A3,A4] NSAIDs, which can trigger episodes in up to 30% of patients, and opioids should be avoided. When these higher doses of antihistamines are unsuccessful (approximately 50% of patients), omalizumab (a monoclonal anti-IgE antibody at a dose of 300 mg every 4 weeks) should be initiated.[A5,A6] In rare severe cases of chronic spontaneous urticaria, oral corticosteroids may be tried under expert oversight. For refractory chronic urticaria, options include cyclosporine, hydroxychlorquine, sulfasalazine, dapsone, tacrolimus, and mycophenolate. Bruton tyrosine kinase inhibitors (e.g., remibrutinib) and agents that target mast cells (e.g., benralizumab, tezepelumab, and dupilumab) are under study.

PREVENTION

Patients who have chronic spontaneous urticaria are encouraged to accept that their disease is spontaneous in origin and not linked to external triggers. The therapeutic approach involves managing symptoms but does not hasten resolution of the disease. Patients who have chronic inducible urticaria are advised to avoid any identifiable triggers such as exposure to cold, hot showers, exercise, or sweating. For patients who have an identified underlying disorder, such as thyroid dysfunction or autoimmune disease, treatment of the disorder can reduce or eliminate skin symptoms.

PROGNOSIS

The prognosis for most patients with chronic spontaneous urticaria is excellent. About 50% of cases of simple urticaria resolve in 1 year, and nearly 80% resolve within 3 to 5 years. However, symptoms of chronic urticaria can recur in approximately 15% of patients even after more than 6 months without symptoms. Longer durations of disease tend to occur in patients who suffer inducible urticarias.

BRADYKININ-MEDIATED HEREDITARY ANGIOEDEMA AND RELATED DISEASES

Bradykinin-mediated angioedema, which is seen in rare types of hereditary angioedema and related diseases, must be distinguished from the mast cell–driven, histaminergic angioedema of chronic urticaria.

EPIDEMIOLOGY

Hereditary angioedema is a rare autosomal dominant disorder that affects approximately 1 in 50,000 individuals. Mutations in the *SERPING1* gene result in a deficiency of the functional C1 esterase inhibitor. Family history confirms the autosomal dominant inheritance in about 75% of cases, whereas de novo mutations likely are responsible for the other 25% of patients who lack a family history. Hereditary angioedema with normal C1 esterase inhibitor levels has a similar clinical phenotype but is more common in females.

Acquired angioedema affects older adults who often have an associated monoclonal gammopathy or underlying lymphoma. ACE inhibitor–induced angioedema occurs in approximately 0.7% of treated patients.[17] ACE inhibitor–induced angioedema is more common in Blacks and in persons who smoke tobacco. Aliskrein, which is a direct renin inhibitor, is also associated with increased risk of angioedema, as is the combination of sacubitril-valsartan.

PATHOBIOLOGY

Hereditary angioedema and acquired angioedema are related to low levels or abnormal function of the C1 esterase inhibitor, which regulates the complement (Chapter 37), fibrinolytic, and contact system (kinin-generating) pathways.[18] C1 esterase inhibitor levels and function generally must be at least 40% of normal to control the generation of kinins, but the presence of one normal gene typically results in levels that are only 5 to 30% of normal. In type I hereditary angioedema (85% of patients), the abnormal gene does not produce C1 esterase inhibitor protein. In type II hereditary angioedema (15% of patients), the C1 esterase inhibitor protein is detectable at normal levels but lacks appropriate function.

The C1 esterase inhibitor enzyme regulates cleavage of two complement products, C2 and C4. In the absence of this regulatory activity, patients with both hereditary angioedema I and II have chronic low levels of C2 and C4. However, central to the mechanism of swelling in hereditary angioedema is the inadequate regulation of the kinin pathway, thereby leading to excess production of the vasoactive mediator bradykinin. Excess bradykinin leads to vascular leak that is responsible for the episodes of swelling. A third category of hereditary angioedema, formerly called type III, is now termed hereditary angioedema with normal C1 esterase inhibitor levels. In these conditions, the levels and function of C1 esterase inhibitor protein are normal, but mutations occur in other pathways related to bradykinin.[19]

In acquired angioedema, unknown factors activate C1 esterase inhibitor protein and lead to its depletion, or autoantibodies target C1 esterase inhibitor protein and inhibit its function. ACE inhibitor–associated angioedema, which is the leading cause of the drug-induced form of acquired angioedema, is linked to the inhibition of an enzyme that is related to the breakdown of bradykinin and does not involve proteins of the complement pathway.

CLINICAL MANIFESTATIONS

The onset of hereditary angioedema types I and II is typically in the first and second decades of life. Attacks are classified as cutaneous, upper airway (laryngeal), or gastrointestinal. The skin lesions are typically nonpruritic, nonpitting, and asymmetric (Fig. 407-1). The severity of attacks worsens after puberty, with episodes that can affect all areas of the body including face and genitalia. One-third of patients report a prodromal serpiginous rash that is nonpruritic (erythema marginatum; Fig. 407-2). Swelling of the uvula and posterior pharynx can lead to life-threatening asphyxiation. More than 50% of patients can experience a laryngeal attack in their lifetime. Involvement of mucosal surfaces of the gastrointestinal tract can present as an acute abdomen and lead to unnecessary surgical interventions. Episodes of swelling typically persist for 24 to 72 hours. About 50% of patients report that local pressure or trauma can precipitate an attack. Stress can be another important trigger.

In acquired angioedema, the clinical manifestations are generally similar but are more likely to involve the facial area (see Fig. 232-3). In ACE inhibitor–induced angioedema, for example, severe swelling of the face and neck predominates. Episodes can begin during the first weeks of use but may not occur for years after therapy is initiated.

TABLE 232-1 CLASSIFICATION OF URTICARIA AND ANGIOEDEMA

ACUTE HISTAMINERGIC URTICARIA AND ANGIOEDEMA
Hypersensitivity reactions
Food allergy
Drug allergy
Insect allergy
Associated with infections (e.g., respiratory)
Non–IgE-related
Drugs: opioids, nonsteroidal anti-inflammatory drugs
Radiocontrast dye
Toxic reactions
Immune complex
Serum sickness
Transfusion related
Postviral illness
CHRONIC HISTAMINERGIC URTICARIA AND ANGIODEMA
Spontaneous
Autoantibody associated
IgG anti-IgE
IgG anti-IgE receptor (FceRI)
IgG anti-thyroid antigens
Other
Non-autoantibody associated
Inducible
Dermographism
Cholinergic
Cold-induced
Delayed pressure
Solar
Vibratory
Aquagenic
Immune complex
Urticarial vasculitis
Autoimmune disease associated
URTICARIA PIGMENTOSA AND SYSTEMIC MASTOCYTOSIS (see Chapter 235)
KININ-MEDIATED ANGIOEDEMA
Hereditary angioedema
Acquired angioedema
Angiotensin-converting enzyme–induced angioedema
Renin inhibitor induced angioedema

IgE = immunoglobulin E; IgG = immunoglobulin G.

DIAGNOSIS

The key to the diagnosis is the direct measurement, especially during an attack, of C1 esterase inhibitor protein (antigen test) and function, as well as levels of C4.[20] Features that distinguish acquired angioedema from hereditary angioedema are onset of symptoms later in life (age >40 years) or presence of an underlying malignancy, such as B-cell lymphoma (Chapter 171) or plasma cell dyscrasia (Chapter 173). Depressed levels of C1q are seen only in acquired hereditary angioedema.

In ACE inhibitor–induced angioedema, all of these test results are typically normal. Patients with normal C1 hereditary angioedema also have normal test results and an absence of hives. Patients who have histaminergic rather than bradykinin-mediated angioedema also have normal test results but respond to antihistamines and corticosteroids. The lack of response to antihistamines and corticosteroids distinguishes the bradykinin-mediated disorders that are associated with normal C1 esterase inhibitor levels and function from patients who have histaminergic angioedema. In such patients, measurement of serum immunoglobulin can exclude a plasma cell dyscrasia, but a detailed search for an occult lymphoma is not routinely indicated.

TREATMENT AND PREVENTION

The therapies for hereditary angioedema include on-demand treatment of attacks as well as prophylactic therapies, preferably as part of a personalized care plan developed with a specialist.[21]

Hereditary Angioedema

Acute Attacks

First-line treatment for an acute attack of hereditary angioedema is self-injection of a bradykinin 2 receptor antagonist (icatibant, 30 mg subcutaneously) or a kallikrein inhibitor that blocks the production of bradykinin (ecallantide, 30 mg subcutaneously). Another option is to replace the C1 esterase inhibitor protein by the infusion of

a C1 esterase inhibitor concentrate (20 units/kg) or human recombinant C1 esterase inhibitor (50 units/kg), but early self-treatment at home leads to better control of the episode. By comparison, the clinical response to epinephrine, antihistamines, or corticosteroids is poor. If neither C1 esterase inhibitor replacement therapy nor bradykinin antagonists are available, 2 units of fresh frozen plasma can replace the depleted C1 esterase inhibitor levels but at the potential risk of supplying substrates that could increase kinin levels.[22] Treating physicians must be prepared to perform intubation or tracheostomy if patients do not respond promptly to medical therapies.

Chronic Therapy

If a patient has mild disease or infrequent attacks, patients may be treated with only on-demand therapies as outlined above. For more severe or frequent symptoms, subcutaneous replacement with plasma-derived C1 esterase inhibitor (60 IU/kg twice weekly) is an option.[A7] An oral kallikrein inhibitor (berotralstat, 150 mg daily)[A8] or subcutaneous lanadelumab (an antibody that inhibits kallikrein at 300 mg every 2 to 4 weeks)[A9] can reduce the frequency and severity of attacks. Another option is replacement C1 esterase inhibitor concentrate (1000 units intravenously every 3 to 4 days). ACE inhibitors and estrogens should be avoided because of their potential to exacerbate episodes of angioedema.

Danazol (50 mg to 200 mg up to twice daily), which can increase the production of C1 esterase inhibitor and reduce symptoms, is a second-line option in settings in which more specific therapies are unavailable. Androgen therapy can cause virilizing effects and liver complications, and it is contraindicated during pregnancy.

Short-term Prophylaxis

Because trauma is a known trigger for attacks, patients should be treated prophylactically before certain medical procedures. For dental surgery, which is associated with oral swelling that can progress to airway obstruction, short-term prophylaxis with a single dose of C1 esterase inhibitor replacement 1 to 12 hours before the procedure is effective. An alternative is to use danazol for 5 to 7 days before the procedure and continue it for 2 to 5 days afterward.

Acquired Angioedema

Acquired angioedema is approached in a fashion similar to that for hereditary angioedema, but definitive treatment is linked to therapy of the underlying disease.

ACE Inhibitor–Induced Angioedema

Treatment of ACE inhibitor–induced angioedema involves acute airway management and discontinuation of the ACE inhibitor. Icatibant is of uncertain value.[23] Shifting to an angiotensin receptor blocker is typically well tolerated.

PROGNOSIS

The long-term prognosis for patients with hereditary angioedema depends on the phenotype, frequency of episodes, and access to advanced agents both for acute episodes and prophylaxis. Repeated use of therapeutic and preventive medicines appears to be safe, but long-term danazol treatment should be avoided if possible. Life expectancy should be normal given access to advanced treatments. The outlook for acquired angioedema is affected by the prognosis of the underlying disease. ACE inhibitor–induced angioedema is normally self-limited and responds to its discontinuation.

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233 ANAPHYLAXIS

LAWRENCE B. SCHWARTZ AND MARIANA CASTELLS

DEFINITION

Anaphylaxis arises when mast cells and possibly basophils secrete potent mediators that have effects on vasculature, smooth muscle, mucous glands, and nerves, thereby eliciting a systemic response.[1] Although mast cells in any organ system may be involved, dictated in part by the distribution of the instigating stimulus, the principal targets are the cardiovascular, cutaneous, respiratory, and gastrointestinal systems, where mast cells are most abundant. Anaphylaxis occurs when mast cells are activated by multivalent allergens that bind to and aggregate immunoglobulin E (IgE) and high-affinity IgE receptors (FcεRI) on their surfaces. These activated mast cells then secrete mediators, such as histamine, tryptase, prostaglandin d4, and leukotriene c4, that cause the systemic symptoms of immediate hypersensitivity.

EPIDEMIOLOGY

Approximately 1500 to 2000 deaths are attributed to anaphylaxis annually in the United States.[2] Anaphylaxis to foods and insect stings each account for about 100 deaths per year.

The lifetime incidence of anaphylaxis in adults is estimated at 2 to 8%. In children, in whom food allergy is more common, the incidence of anaphylaxis is likely higher. More than 80% of physicians practicing allergy/immunology, emergency medicine, general medicine, or pediatrics report having witnessed anaphylaxis. Medications, insect stings, and foods are the most common triggers, followed by environmental allergens and latex (Table 233-1). In some cases, the cause of anaphylaxis is unknown. About 50% of the reactions occur at home, 15% at a medical facility, and 6 to 7% at another person's home, at work, or at a restaurant. Antibiotics and radiocontrast media are the most commonly identified triggers in hospitals, and COX-1 inhibitor nonsteroidal anti-inflammatory drugs (NSAIDs) are a leading cause of anaphylaxis seen in emergency departments.[3] Chemotherapy agents (Chapter 234) and monoclonal antibodies also are common causes of anaphylaxis.[4] In the perioperative setting, anaphylactic reactions occur with a frequency of about 1 in 2000 to 10,000 cases.[5] Muscle relaxants or antibiotics are the most common triggers, but latex, induction drugs, chlorhexidine, and other agents also can be the culprit. Advanced age, use of a β-blocker or angiotensin pathway inhibitor, hereditary α-tryptasemia, and concomitant mastocytosis (Chapter 235) increase the risk for severe anaphylaxis. Hereditary α-tryptasemia, which is caused by an increased copy number of the gene that encodes α-tryptase, may be present in up to 5% of the population.[6]

Some type of food allergy is self-reported in 19% of adults and likely is present in as many as 11%, but only about half of these allergies are classified as serious. About 20% of children lose peanut sensitivity by school age, but a small portion will regain peanut sensitivity later in life, particularly if they continue to avoid this food. Most children lose their allergic sensitivities to cow's milk, egg, wheat, or soy by 5 years of age, whereas sensitivities to tree nuts and seafoods are typically persistent.

Latex provokes anaphylaxis in a small but significant group of individuals, particularly patients who have undergone multiple surgical procedures early in life and individuals with frequent exposures later in life, such as medical personnel. Estimates of the prevalence of latex hypersensitivity range from

TABLE 233-1 CAUSES OF SYSTEMIC ANAPHYLAXIS

IgE-MEDIATED	NON–IgE-MEDIATED
Insect stings	Aspirin
Foods (±exercise)	Radiocontrast media
Drugs	Exercise, cold, heat, vibration, pressure
Latex	Narcotics (except fentanyl)
Allergen extracts	Vancomycin
	Autoimmune
	Complement anaphylatoxins
	Neuropeptides
	Idiopathic

IgE = immunoglobulin E.

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a C1 esterase inhibitor concentrate (20 units/kg) or human recombinant C1 esterase inhibitor (50 units/kg), but early self-treatment at home leads to better control of the episode. By comparison, the clinical response to epinephrine, antihistamines, or corticosteroids is poor. If neither C1 esterase inhibitor replacement therapy nor bradykinin antagonists are available, 2 units of fresh frozen plasma can replace the depleted C1 esterase inhibitor levels but at the potential risk of supplying substrates that could increase kinin levels.[22] Treating physicians must be prepared to perform intubation or tracheostomy if patients do not respond promptly to medical therapies.

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233 ANAPHYLAXIS

LAWRENCE B. SCHWARTZ AND MARIANA CASTELLS

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EPIDEMIOLOGY

Approximately 1500 to 2000 deaths are attributed to anaphylaxis annually in the United States.[2] Anaphylaxis to foods and insect stings each account for about 100 deaths per year.

The lifetime incidence of anaphylaxis in adults is estimated at 2 to 8%. In children, in whom food allergy is more common, the incidence of anaphylaxis is likely higher. More than 80% of physicians practicing allergy/immunology, emergency medicine, general medicine, or pediatrics report having witnessed anaphylaxis. Medications, insect stings, and foods are the most common triggers, followed by environmental allergens and latex (Table 233-1). In some cases, the cause of anaphylaxis is unknown. About 50% of the reactions occur at home, 15% at a medical facility, and 6 to 7% at another person's home, at work, or at a restaurant. Antibiotics and radiocontrast media are the most commonly identified triggers in hospitals, and COX-1 inhibitor nonsteroidal anti-inflammatory drugs (NSAIDs) are a leading cause of anaphylaxis seen in emergency departments.[3] Chemotherapy agents (Chapter 234) and monoclonal antibodies also are common causes of anaphylaxis.[4] In the perioperative setting, anaphylactic reactions occur with a frequency of about 1 in 2000 to 10,000 cases.[5] Muscle relaxants or antibiotics are the most common triggers, but latex, induction drugs, chlorhexidine, and other agents also can be the culprit. Advanced age, use of a β-blocker or angiotensin pathway inhibitor, hereditary α-tryptasemia, and concomitant mastocytosis (Chapter 235) increase the risk for severe anaphylaxis. Hereditary α-tryptasemia, which is caused by an increased copy number of the gene that encodes α-tryptase, may be present in up to 5% of the population.[6]

Some type of food allergy is self-reported in 19% of adults and likely is present in as many as 11%, but only about half of these allergies are classified as serious. About 20% of children lose peanut sensitivity by school age, but a small portion will regain peanut sensitivity later in life, particularly if they continue to avoid this food. Most children lose their allergic sensitivities to cow's milk, egg, wheat, or soy by 5 years of age, whereas sensitivities to tree nuts and seafoods are typically persistent.

Latex provokes anaphylaxis in a small but significant group of individuals, particularly patients who have undergone multiple surgical procedures early in life and individuals with frequent exposures later in life, such as medical personnel. Estimates of the prevalence of latex hypersensitivity range from

TABLE 233-1 CAUSES OF SYSTEMIC ANAPHYLAXIS

IgE-MEDIATED	NON–IgE-MEDIATED
Insect stings	Aspirin
Foods (±exercise)	Radiocontrast media
Drugs	Exercise, cold, heat, vibration, pressure
Latex	Narcotics (except fentanyl)
Allergen extracts	Vancomycin
	Autoimmune
	Complement anaphylatoxins
	Neuropeptides
	Idiopathic

IgE = immunoglobulin E.

ABSTRACT

Anaphylaxis arises when mast cells and possibly basophils secrete potent vasoactive mediators (such as tryptase, histamine, leukotriene C4, and prostaglandin D2) that dilate smooth muscle and increase the secretion of mucus, thereby eliciting a systemic response in multiple organ systems. With a lifetime incidence of 2 to 8%, this potentially fatal condition is more common than previously appreciated. Triggers may include medications, insect stings, foods, or latex. Typically, anaphylaxis occurs when these allergens bind to IgE and lead to aggregation of the high-affinity IgE receptor on the plasma membrane, but spontaneous triggering also occurs. Anaphylaxis is sometimes associated with an underlying clonal mast cell disorder, such as a somatic gain-of-function mutation of *c-KIT* or an increased copy number of the gene encoding α-tryptase. Clinical criteria, including concurrent signs and symptoms in at least two organ systems (cutaneous, gastrointestinal, pulmonary, and cardiovascular systems), facilitate the diagnosis of anaphylaxis in real time. Laboratory tests, including an elevated acute versus baseline serum tryptase level, can support the clinical diagnosis. Appropriate acute interventions (supine positioning and timely administration of epinephrine) and preventive therapies (insect venom immunotherapy and anti-IgE medications) can be lifesaving.

KEYWORDS

mast cell
basophil
histamine
tryptase
prostaglandin D2
leukotriene C4
platelet-activating factor
anaphylaxis
mastocytosis
hereditary α-tryptasemia
c-kit
IgE
FcεRI

1 to 6% in the general population and about 10% among regularly exposed health care workers. Each year, latex-induced anaphylaxis occurs in about 200 individuals and causes an average of 3 deaths. The majority of children labeled as penicillin allergic lose their sensitivity as adults.

PATHOBIOLOGY

The mediators produced by activated mast cells and basophils initiate many of the signs and symptoms of anaphylaxis. These cells constitutively express the high affinity receptor for IgE, FcεRI, on their surface, thereby enabling these cells to be armed by antigen-specific IgE and triggered by antigens that aggregate IgE:FcεRI complexes. In addition to mast cells and basophils, other cells that likely participate in anaphylaxis include eosinophils, monocytes, antigen-presenting cells, platelets, and epithelial cells.

Most IgE-dependent mast cell activation events occur at local sites and result in local disease, such as allergic conjunctivitis, rhinitis, or asthma when allergens land on the corresponding mucosal surface of a sensitive individual and diffuse into the tissue where mast cells reside. Anaphylaxis presumably requires the allergen (or nonallergen agonist) to distribute systemically to activate mast cells at remote sites. However, activation of the contact system by mast cell products (e.g., heparin or tryptase) results in the production of bradykinin, which may also enhance the severity of anaphylaxis. Impaired metabolism of the mast cell mediator platelet-activating factor also may enhance severity.

Allergens

Most allergens are proteins or glycoproteins that serve as complete antigens, have at least two epitopes that are recognized by different IgE antibodies, and thereby are capable of aggregating IgE in a sensitized subject. The protease activity of some allergens (e.g., house dust mite Der p1) may facilitate their penetration and allergenicity at mucosal sites. Other allergens (e.g., Der p2) have lipid-binding domains that increase their antigenic potency. IgE anti–α-gal sensitization is elicited by Lone Star tick bites, most commonly found in the southeastern, mid-Atlantic, and midwestern states, but also throughout the world.

In contrast to complete antigens, most drugs act as haptens. The drugs become covalently linked to self-proteins in the circulation, in tissues, or on cells and become multivalent allergens that are able to bind and aggregate IgE:FcεRI to activate mast cells. Injected chemotherapy drugs such as platins are common drug allergens that act as haptens. Monoclonal antibodies, in particular chimeric antibodies carrying nonhuman sequences such as rituximab, can bind IgE as complete antigens and trigger anaphylaxis.[7]

Exposure to an allergen must first lead to sensitization before an immediate hypersensitivity reaction can occur. This process, which requires at least 1 week, involves antigen processing by antigen-presenting cells, which then present peptide antigens to T_H2 cells (T helper lymphocytes), which in turn instruct allergen-specific B cells to switch from production of allergen-specific IgM or IgG to IgE. Production of IL-4 or IL-13 by T_H2 cells and binding of T_H2 CD40 ligand to B cell CD40 are essential for this antibody class switch. Consequently, anaphylaxis does not occur on first exposure to an allergen (sensitization phase), because the antigen is likely gone by the time antigen-specific IgE is made, but can occur with subsequent exposures. Cross-sensitization can occur with foods or medications that contain the same or similar allergenic components, and patients can react at first exposure when previously exposed and sensitized to a related substance.

Food

Most cases of food-induced anaphylaxis in children occur in response to eggs, peanuts, cow's milk, wheat, or soy, whereas peanuts, tree nuts, sesame seeds, and seafood account for most reactions in adults.[8] An oral allergy syndrome typically occurs when individuals who are sensitive to pollen allergens eat a food that cross-reacts with it, such as when ragweed pollen IgE cross-reacts with melon or when birch pollen IgE cross-reacts with a peach or apple. Such food allergen epitopes are typically conformational (rather than linear) and more easily destroyed by heat when cooked, by acid in the stomach, or by proteases in the intestines, so they rarely progress to systemic reactions.

Food allergy–associated exercise-induced anaphylaxis occurs when sensitive subjects exercise within several hours after eating the food allergen but does not occur when the food is eaten without exercise. Shrimp and wheat are most commonly implicated.[9] Exercise appears to increase intestinal permeability to food antigens, which then enter into the systemic circulation. Aspirin, other nonsteroidal anti-inflammatory drugs, and alcohol also act to increase intestinal permeability and may help trigger food-induced anaphylaxis.

Insect Sting Venom

Hymenoptera families primarily responsible for sting venom-triggered anaphylactic reactions include the Apidae (honey bees and bumble bees), Vespidae (hornets, yellow jackets, and paper wasps), and Formicidae (fire ants).[10] Major allergens of honey bees include phospholipase A_2 (Api m 1), hyaluronidase (Api m 2), and melittin (Api m 4). Bumble bee venom proteins exhibit immunologic cross-reactivity with those of the honey bee but lack melittin. Vespid venoms cross-react among themselves and include phospholipase and hyaluronidase, the latter allergen cross-reacting with bee hyaluronidase. Fire ant venom contains various alkaloids that are not allergenic but produce sterile pustules and various allergenic proteins that cross-react with vespid allergens, such as phospholipase and scorpion venom allergens. If previously sensitized to cross-reactive venom from a different insect, a person may exhibit an anaphylactic reaction on first exposure to one insect sting. Allergens from biting insects of the Diptera order (mosquitoes, gnats, midges, true flies) are salivary in origin and do not cross-react with Hymenoptera venom allergens. Anaphylaxis to these salivary proteins appears to be uncommon, but precise epidemiologic data are problematic because people are often unaware of a mosquito bite, and commercial diagnostic reagents of high quality are not yet available.

Medications

Anaphylaxis to antibiotics including penicillin is rare, and most patients tend to lose their IgE sensitivity by 10 or more years after the initial reaction.[11] Drug allergies are described in Chapter 234.

Latex

Latex allergenic proteins are derived from the rubber tree, *Hevea brasiliensis*. Irritant dermatitis is the most frequent contact reaction and does not involve acquired immunity. Contact hypersensitivity, which results from cell-mediated immunity to haptenic chemicals used to process latex, produces a poison ivy–like local reaction that may begin the day after a sensitive subject is exposed. In contrast, IgE-dependent immediate hypersensitivity occurs against latex proteins that are present in elastic materials, catheters, balloons, and powdered latex gloves.[12] IgE-mediated cross-reactions occur between IgE anti–latex allergens and allergens in fresh foods such as bananas, chestnuts, avocados, kiwi, peaches, bell peppers, and tomato, and affected individuals may need to avoid these foods.

Vaccines

Anaphylaxis to vaccines is rare, occurring in about 1.3 per million recipients.[13] Anaphylaxis to influenza vaccine, which occurs in about 1.3 to 1.9 per million recipients, seems unrelated to a history of egg allergy. Instead, vaccine-triggered anaphylaxis may relate to sensitivities to a variety of vaccine components. Anaphylaxis to COVID-19 RNA vaccines reportedly occurs in about 1 in 100,000 recipients, typically upon first exposure, mostly in persons who have a history of anaphylaxis to other agents or foods, and more often in females than males.[14]

Non–IgE-Dependent Agonists

Many non–IgE-dependent activators of mast cells do not require processing and can elicit a response on first exposure. Examples include radiocontrast dyes, vancomycin, and most narcotics except for fentanyl. Radiocontrast dyes of low ionic strength and iso-osmolarity are less likely to elicit a systemic reaction. Vancomycin produces a non–IgE-dependent mast cell activation event known as "red man syndrome," typically involving pruritic flushing, but without cardiovascular compromise unless infused too rapidly. These reactions are usually avoided by reducing the rate of administration of the antibiotic, thereby reducing peak levels.

Endogenous mast cell activators include neuropeptides such as substance P, neurokinin A, calcitonin gene-related peptide, defensins, and the complement anaphylatoxins C3a and C5a. Although C3a and C5a each have their own receptor on mast cells, neurokinins, vancomycin, and narcotics activate a G protein–coupled receptor that is selectively expressed on mast cells, called Mas-related G protein–coupled receptor X2 (MRG-X2), thereby causing histamine secretion.

Aspirin and Nonsteroidal Anti-inflammatory Drugs

Aspirin hypersensitivity typically manifests as either a respiratory reaction with bronchospasm, nasal congestion, and rhinorrhea or a cardiovascular reaction with hypotension and urticaria. Sometimes overlap occurs with gastrointestinal signs and symptoms. In most cases, such reactions appear to be pharmacologically (not IgE) mediated, and in sensitive subjects, reactions can occur in response to any of the cyclooxygenase 1 (COX1) inhibitors. COX2-selective inhibitors appear to be safe in aspirin-intolerant asthmatic patients but not

always in patients who have cardiovascular reactions. Less commonly, sensitivity occurs to only one of the drugs within this class and is a clue that IgE against a unique chemical moiety on that particular drug is involved.

Physical Stimuli

In some individuals, urticaria or anaphylaxis can occur in response to exercise, heat, solar radiation, vibration, pressure, or cold. In some cases of familial cold- or vibration-triggered urticaria (Chapter 232), genetic defects are found.[15]

Autoimmunity, Activating Kit Mutations, and Hereditary α-Tryptasemia

Some patients experience spontaneous bouts of anaphylaxis without an obvious exogenous stimulus. Individuals with mastocytosis (Chapter 235) and hereditary α-tryptasemia are particularly prone to anaphylaxis, likely due to an excess of mast cells, the presence of mast cells that are more readily activated, enhanced tissue response to mast cell mediators, and/or the overexpression of α-tryptase. A corollary of this is that anaphylaxis to a Hymenoptera insect sting may be a presenting manifestation of these conditions.[16] A related disorder, mast cell activation syndrome, includes patients who have clonal mast cell disease, reflected by these same Kit mutations (but do not meet diagnostic criteria for systemic mastocytosis). Hereditary α-tryptasemia is an autosomal dominant disorder due to extra copies of the *TPSAB1* gene, which leads to an elevated baseline serum tryptase level (8-100 ng/mL).

Some cases of chronic urticaria are associated with IgG and IgM autoantibodies against FcεRI or IgE. Human mast cells also express FcγRIIa, which is a low-affinity IgG receptor, and FcγRI, which is the high affinity IgG-receptor. When aggregated by IgG immune complexes, either of these receptors is capable of activating mast cells and may contribute to some episodes of anaphylaxis.

CLINICAL MANIFESTATIONS

Anaphylaxis is manifested by a feeling of pruritus, lightheadedness, sweating, anxiety, confusion, nausea, and/or vomiting, accompanied by tachycardia, hypotension, and ultimately cardiovascular collapse. These symptoms and signs appear within seconds or minutes after exposure to the precipitating allergen. Respiratory or cutaneous symptoms occur in more than 50% of cases, whereas cardiovascular, neurologic, or gastrointestinal symptoms are recognized in less than 50% of cases. Most fatal anaphylactic reactions to injected venom proteins begin within 30 minutes after the sting. Most fatal food and insect sting reactions and many drug reactions are preceded by a mild immediate hypersensitivity reaction to the same allergen.

Sensitized individuals can present with delayed anaphylactic reactions 2 to 8 hours after ingestion of α-gal–containing red meats, perhaps due to transformation during digestion of monovalent to polyvalent α-gal allergens. Autoimmune progesterone-mediated anaphylaxis (progestogen hypersensitivity or catamenial anaphylaxis) tends to occur at the time of a premenstrual progesterone surge.

DIAGNOSIS

Anaphylaxis can be diagnosed clinically in real time by consensus criteria (Fig. 233-1) and by an elevated serum tryptase level. Acute concurrent onset of cutaneous signs of immediate hypersensitivity along with either hypotension or respiratory compromise in the apparent absence of allergen exposure; rapid onset of hypersensitivity signs involving at least two organs from among cutaneous, gastrointestinal, respiratory, and cardiovascular systems after exposure to a likely allergen; or rapid onset of hypotension after exposure to a known allergen.[17] Although exposure to a potential allergen should always be investigated, 30 to 60% of cases that first appear in adulthood are idiopathic and occur without a known allergen.[18]

Antigen-specific IgE, indicating sensitization, is precisely measured by either blood or skin tests. These tests should be delayed for at least 2 weeks after an anaphylactic event to prevent false-negative results. IgE sensitization is necessary but not sufficient to diagnose allergic disease, because many subjects who are sensitized to an aeroallergen, particularly at a low antigen-specific IgE level, do not have symptoms when exposed. When food allergy is suspected but not confirmed by IgE testing, oral food challenges can be performed under expert oversight,[19] using protocols to minimize the risk for severe anaphylaxis. Food-allergic reactions involving IgE should be distinguished from a variety of other types of adverse reactions, including lactose intolerance, food-induced enterocolitis (T-cell responses to cow's milk, soy, or grains), and celiac disease (Chapter 126).

An elevated serum tryptase level (normal 1 to 11 ng/mL), which peaks 30 to 120 minutes after the onset of signs or symptoms of anaphylaxis and then declines with a half-life of about 2 hours, indicates that mast cell activation has occurred. For confirmation, a level of at least $2 + 1.2 \times$ a baseline serum tryptase level measured at least 24 hours after all clinical signs and symptoms have resolved or prior to their onset is considered clinically significant. Although an increased serum total tryptase level is quite specific for anaphylaxis, its sensitivity is low for detecting anaphylaxis triggered by food ingestion and for detecting modest (no hypotension) or local (laryngeal edema) anaphylaxis. Baseline levels are above 20 ng/mL in most patients with systemic mastocytosis (Chapter 235) and above 7 ng/mL in all patients with hereditary α-tryptasemia. Elevated baseline tryptase levels correlate with an increased risk for severe insect sting–triggered anaphylaxis, likely due to the higher prevalence of a clonal mast cell disorder with an activating c-kit mutation or to increased copies of the gene encoding α-tryptase.

A patient who presents with severe life-threatening reactions to Hymenoptera venom may have an underlying clonal mast cell activation disorder such as

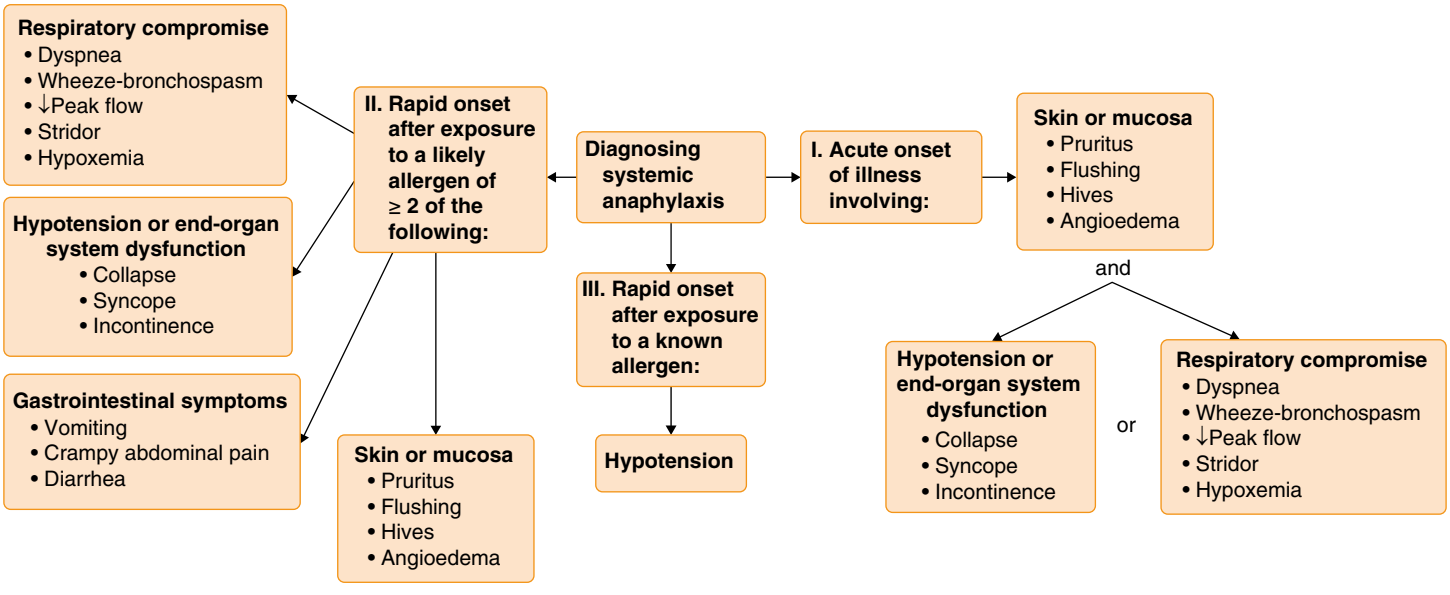

FIGURE 233-1. Diagnosing systemic anaphylaxis in a clinical setting. Acute onset of systemic anaphylaxis in the apparent absence of allergen exposure means that the signs and symptoms, once they begin, develop over minutes to an hour, while rapid onset after exposure to a likely or known allergen means that these signs and symptoms begin to occur within minutes to several hours after that exposure. (From Sampson HA, Muñoz-Furlong A, Campbell RL, et al. Second symposium on the definition and management of anaphylaxis: summary report—second National Institute of Allergy and Infectious Disease/Food Allergy and Anaphylaxis Network symposium. *J Allergy Clin Immunol*. 2006;117:391-397.)

mastocytosis (Chapter 235) or a genetic trait such as hereditary α-tryptasemia. Plasma and urinary histamine levels are less helpful as diagnostic biomarkers because of histamine's short half-life, its presence in histamine-containing foods, its production by histamine-producing mucosal bacteria, and the variability in histamine metabolism.

Use of an angiotensin-converting enzyme (ACE) inhibitor or of a nonselective β-blocker have been associated with more severe anaphylaxis. Low serum levels of platelet-activating factor acetyl hydrolase also have been associated with more severe cases of anaphylaxis.

Differential Diagnosis

Anaphylaxis should be distinguished from a variety of disorders with overlapping presentations. Vasovagal syncope (Chapter 49) causes diaphoresis, nausea, hypotension, and bradycardia, but without urticaria and tachycardia. Flushing disorders may be benign and unrelated to anaphylaxis, or they could be a manifestation of pathologic conditions such as the carcinoid syndrome (Chapter 213), with which urticaria and profound hypotension are not typically associated; pheochromocytoma (Chapter 209), which causes episodic hypertension; or VIPomas (Chapter 213), which cause facial flushing and voluminous diarrhea with hypokalemia but not episodic hypotension or urticaria. Panic attacks (Chapter 362) and vocal cord dysfunction may be difficult to distinguish from anaphylaxis, especially by history alone. Acute attacks of angioedema caused by C1 esterase inhibitor deficiency (Chapter 232) are not associated with pruritus or urticaria, and they evolve slower and persist longer than attacks of anaphylaxis. Shock due to the activation of complement or of the contact system, thereby leading to the production of bradykinin, can occur without activation of mast cells. Scombroidosis (Chapter 98) occurs 5 to 60 minutes after ingestion of histamine, typically in poorly stored fish, and manifests with flushing, palpitations, headache, and gastrointestinal symptoms. Acute serum sickness (Chapter 36), various cell activation syndromes, endotoxin-mediated septic shock (Chapter 94), and superantigen-mediated toxic shock syndromes (Chapters 267 and 269) manifest with fever, which is not characteristic of anaphylaxis by itself. Also, hypoglycemia (Chapter 211), seizures (Chapter 372), and pulmonary embolism (Chapter 68) or other acute cardiac events (Chapter 57) should be considered. In some cases, anaphylaxis may provoke another disorder (e.g., myocardial infarction [Chapter 58], with acute elevation of serum levels of both tryptase and troponin).

Systemic mastocytosis (Chapter 235) and hereditary α-tryptasemia are important conditions to consider in the setting of anaphylaxis. Hereditary α-tryptasemia is an autosomal dominant disorder associated with increased copy numbers of the *TPSAB1* gene, but only when it encodes α-tryptase. Hereditary α-tryptasemia can present with multiple-organ signs and symptoms including cutaneous flushing, pruritus, vibratory urticaria, dysautonomia with irritable bowel syndrome, hyperextensible joints, severe anaphylaxis, and/or retained primary dentition, often with a positive family history. Both disorders can present with anaphylaxis, particularly when spontaneous or when elicited by an insect sting, and each can be precisely diagnosed by specific genetic tests.

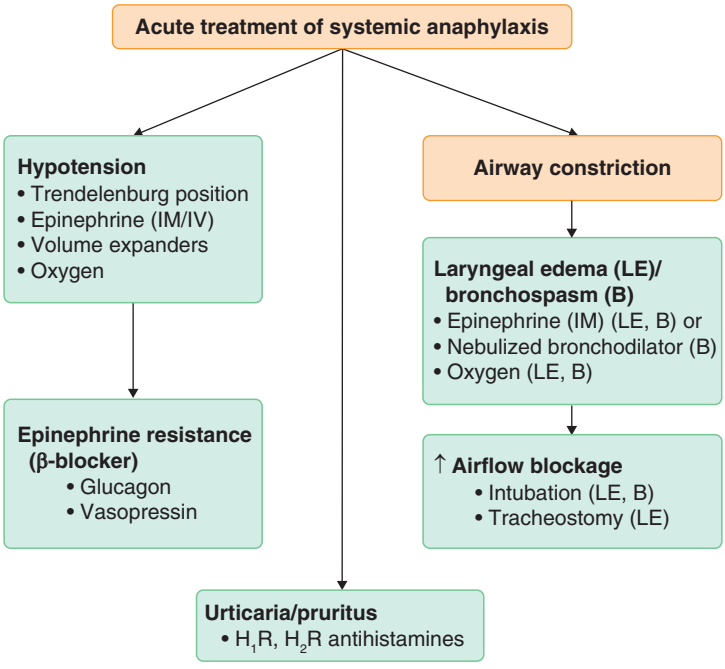

FIGURE 233-2. Acute treatment of systemic anaphylaxis. B = bronchospasm; H_1R = H_1 histamine receptor; H_2R = H_2 histamine receptor; IM = intramuscular; IV = intravenous; LE = laryngeal edema.

TREATMENT

Fatal outcomes in anaphylaxis are principally the result of either airway constriction or hypotension. Accordingly, the acute treatment of anaphylaxis requires that airway patency, blood pressure, and cardiac status be addressed (Fig. 233-2). Intubation, tracheostomy, volume expanders, and vasopressors may be needed (Chapter 92). Patients who exhibit any signs or symptoms of hypotension should immediately assume a supine position with their lower extremities slightly elevated, because almost all hypotensive anaphylactic deaths are preceded by syncope that occurs in a sitting or upright posture. Epinephrine injected intramuscularly into the thigh (0.2 to 0.5 mg for adults, 0.01 mg/kg up to 0.3 mg for children, repeated every 5 to 30 minutes as indicated) is the most effective drug, the earlier during the course of an anaphylactic event the better.[20,21] Calibrated intravenous administration of a solution of epinephrine (1 mg/100 mL solution starting at 30 to 100 mL/hour) and titrated to the lowest effective rate of infusion) can be considered in exceptional cases that do not respond to intramuscular epinephrine. Epinephrine relaxes bronchial smooth muscle and improves vascular tone and permeability, thereby counteracting bronchospasm, hypotension, and tissue edema. Although no absolute contraindication exists for the use of epinephrine to treat anaphylaxis, its benefits should be weighed against its disadvantages in elderly patients and in patients who have cerebrovascular or coronary artery disease, hypertension, diabetes, hyperthyroidism, cardiomyopathy, or narrow-angle glaucoma, in whom adverse events such as myocardial infarction, stroke, or pulmonary edema can be precipitated. Patients who are taking a β-blocker, particularly a nonselective β-blocker, may be resistant to epinephrine; in such cases, glucagon (1 mg intravenously [IV], or 1 to 5 mg/hour IV) or vasopressin (5 to 40 IU IV) may be used. Oxygen should be administered by nasal cannula. Inhaled bronchodilators can relieve bronchospasm.

Parenteral administration of H_1-receptor (diphenhydramine, 1 to 2 mg/kg up to 50 mg) and H_2-receptor (ranitidine, 300 mg IV over 5 minutes) antihistamines may prevent progression of urticaria and pruritus but is not likely to reverse hypotension or tissue edema. Evidence to support use of glucocorticosteroids to treat anaphylaxis is lacking, and their use in an emergency department setting does not appear to affect the relapse rate.

Individuals who survive an episode of anaphylaxis can have severe anxiety, including post-traumatic stress disorder, due to the life-threatening nature of the event and its unpredictability. In such cases, appropriate counseling and sometimes even medication may be required (Chapter 362).

PREVENTION

Patients who have experienced an anaphylactic reaction are at greatest risk for another episode. Such individuals should wear a Medic-Alert bracelet; carry an epinephrine autoinjector (e.g., EpiPen or AuviQ) and be instructed in its use; and understand the value of supine positioning when an attack begins.[22] Avoidance of nonspecific β-blockers and ACE inhibitors is recommended, because either may worsen the severity of an anaphylactic episode, and non-specific β-blockers might interfere with epinephrine treatment. In patients who have had recurrent attacks of anaphylaxis, prophylactic use of H_1- and H_2-receptor antihistamines, a leukotriene antagonist, a cyclooxygenase inhibitor, or cyclosporine may be considered under expert guidance. In patients with idiopathic anaphylaxis or mastocytosis (Chapter 235), omalizumab may be useful under expert supervision, but it is currently approved by the FDA only for poorly controlled cases of asthma or chronic urticaria. Glucocorticosteroids do not inhibit mast cell activation in vitro or immediate skin test wheal/flare responses to allergens in vivo, and chronic glucocorticoids

are not recommended except perhaps in selected patients with recurrent anaphylaxis under expert oversight.

Specific anaphylactic syndromes have unique considerations. Insect venom allergy can be treated by venom immunotherapy, which decreases the risk of anaphylaxis after future stings by about 97%.[23] Reactions to radiocontrast media can be prevented or attenuated by administration of intravenous hydrocortisone (200 mg) plus 50 mg of diphenhydramine 1 hour before the procedure, sometimes accompanied by oral cimetidine (300 mg) and ephedrine (25 mg). Patients who are hypersensitive to penicillin should avoid β-lactam antibiotics in general but can be desensitized if an antibiotic in this class is critically needed. Desensitization protocols also have been applied to chemotherapeutics, biologics, and other medications, thereby enabling patients to tolerate needed medications. However, desensitization is temporary; once the drug has cleared, sensitivity is likely to return.[24] Most individuals who have a history of a penicillin or amoxicillin allergy lose their sensitivity, which can be determined by allergy skin testing and oral challenge. For persons diagnosed as penicillin allergic during childhood, the promotion of universal delabeling procedures, such as skin testing and challenges, is recommended.

Autoimmune progesterone-mediated anaphylaxis may respond to medical or surgical interventions that prevent menses and to progesterone desensitization. Perimenstrual anaphylaxis may respond to the luteinizing hormone–releasing hormone analog leuprolide, oophorectomy, or conjugated estrogens.

Patients who have systemic mastocytosis (Chapter 235) should avoid using direct mast cell agonists such as vancomycin and most narcotic agents with the exception of fentanyl. Aspirin-intolerant asthmatic patients who have sinus polyps (Chapter 394) can be desensitized to aspirin and placed on a daily dose to maintain desensitization status, thereby resulting in better control of asthma, shrinkage of polyps, and reduction of hyposmia. Anti-IL-5, anti-IL-5R, or anti-IL-4Rα monoclonal antibody therapy can also control polyps and asthma (Chapter 75).

Legislation requires that foods or ingredients containing a major food allergen be specifically labeled as such. These products, which account for at least 90% of allergic food reactions, include milk, eggs, fish, shellfish, tree nuts, peanuts, wheat, soybean, and sesame. Individuals who have food allergies must practice avoidance of the provocative agent. However, anti-IgE neutralization therapy or oral immunotherapy can sometimes protect against inadvertent exposure to food allergens. Feeding peanuts to children at risk for developing peanut allergic disease prevents the majority of them from becoming allergic. Anti-IgE therapy (i.e., omalizumab) in peanut-allergic individuals can increase the threshold of peanut ingestion needed to cause an allergic reaction and reduce the risk of reactions during oral peanut immunotherapy, but it has not been FDA approved for these indications.[A1] Palforzia is an oral peanut immunotherapy that can increase tolerance to peanuts in children with peanut allergy when used under expert oversight.[A2] Exercise-dependent anaphylaxis sometimes occur within several hours of ingesting any food, regardless of whether sensitivity to the food can be documented, and might be avoided by delaying exercise until several hours after eating.

The only preventive strategy for latex allergy is avoidance. Elimination of latex-powdered gloves and the availability of nonlatex nitrile or polyvinyl gloves are diminishing the prevalence of latex allergy among medical personnel.

PROGNOSIS

Among patients with anaphylaxis seen in emergency departments, mortality is about 0.1%, but it rises to about 1% in patients who require hospitalization. Recurrences are uncommon in the first several days after the original event but are likely to occur with any subsequent exposure to the precipitating agent. Even if no cause is found, prognosis is generally excellent if patients adhere to preventive measures and always carry injectable epinephrine.

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234

DRUG ALLERGY

MARIANA CASTELLS

DEFINITION

About 80% of adverse drug reactions are predictable and dose dependent, whereas about 20% are unpredictable and dose independent (E-Fig. 234-1). These latter reactions include immediate and delayed drug allergies and hypersensitivities (Fig. 234-1).

EPIDEMIOLOGY

Drug allergy has a spectrum of presentations and can be fatal. Any drug can induce allergic and hypersensitivity symptoms in the appropriate context and host. The incidence and prevalence of drug allergy vary between inpatient and outpatient settings. Drug reactions that lead to visits to emergency departments occur in 4 per 1000 individuals and are more frequent in women.

The most common presentation of drug reaction is skin rash, which is observed in 2 to 4% of hospitalized patients. Antibiotics, chemotherapy drugs, monoclonal antibodies, small molecules, antihypertensive agents, contrast media, and antiepileptic agents are among the most frequently implicated (Table 234-1). The incidence of drug reaction among hospitalized patients is about 6%, of which about 40% are severe drug allergy reactions and 1% result in death.

The prevalence of self-reported drug allergy is about 35%, with an average of nearly two drug allergies reported per patient. Penicillin, sulfonamides, opiates, and nonsteroidal anti-inflammatory drugs (NSAIDs) are the most frequently reported drug allergies.[1,2] For example, 20% of the general population worldwide claims to be allergic to penicillin, but further evaluation confirms the allergy in less than 1%.

Risk Factors

The risk for sensitization to a drug depends on its chemical structure, dose, route of administration, and duration of treatment. Women are at greater risk for drug allergies than men, likely related to their immune and genetic background, cyclical exposure to endogenous and exogenous hormones, pregnancy, and exposures to cosmetics and household products. In one study for example, 70% of patients seen in an emergency department for drug-induced anaphylaxis were women. Progestogen hypersensitivity, which is a rare condition associated with allergic symptoms such as dermatitis and anaphylaxis, is observed in women who are exposed to birth control medications, in vitro fertilization, or interrupted menstrual cycles. White patients are more likely to report drug allergies, but allergies to thiazide diuretics, NSAIDs, and angiotensin-converting enzyme inhibitors are more frequent in Black patients, and angiotensin receptor blockers are more frequent in Blacks compared with Whites.

Recurrent exposure to drugs and other chemicals is associated with a higher risk of drug allergy. For example, patients who have cystic fibrosis (Chapter 77) or spina bifida (Chapter 385) and who undergo multiple surgical procedures are susceptible to increased sensitization to IgE and reactions to latex and antibiotics. Patients who have acquired immunodeficiency syndrome (AIDS, Chapter 355) also have a higher rate of drug allergy, especially dermatologic reactions to sulfa medications. The chemical structure of quaternary ammoniums that are present in cosmetics and other products is shared by general anesthetic agents, thereby potentially sensitizing individuals for perioperative anaphylaxis.[3]

Genetics also contribute to the risk of drug allergy. Hereditary α-tryptasemia, which is an autosomal dominant inherited trait due to the duplication of the *TPSAB1* tryptase gene, predisposes to anaphylaxis, including drug-induced anaphylaxis. This condition is present in 4 to 6% of the general population and is associated with blood tryptase levels greater than 9 ng/mL.[4]

The non-IgE mast cell receptor MRGPRX2 is the target of reactions to general anesthetics, quinolones, vancomycin, and positively charged compounds. Reactions mediated by this receptor can occur upon first exposure due to direct activation of mast cells.[5]

Multidrug hypersensitivity refers to patients who react to multiple unrelated medications. Multidrug hypersensitivity is typically associated with delayed skin symptoms, including drug reaction with eosinophilia and systemic symptoms (DRESS) and is thought to be the result of excessive T-cell

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are not recommended except perhaps in selected patients with recurrent anaphylaxis under expert oversight.

Specific anaphylactic syndromes have unique considerations. Insect venom allergy can be treated by venom immunotherapy, which decreases the risk of anaphylaxis after future stings by about 97%.[23] Reactions to radiocontrast media can be prevented or attenuated by administration of intravenous hydrocortisone (200 mg) plus 50 mg of diphenhydramine 1 hour before the procedure, sometimes accompanied by oral cimetidine (300 mg) and ephedrine (25 mg). Patients who are hypersensitive to penicillin should avoid β-lactam antibiotics in general but can be desensitized if an antibiotic in this class is critically needed. Desensitization protocols also have been applied to chemotherapeutics, biologics, and other medications, thereby enabling patients to tolerate needed medications. However, desensitization is temporary; once the drug has cleared, sensitivity is likely to return.[24] Most individuals who have a history of a penicillin or amoxicillin allergy lose their sensitivity, which can be determined by allergy skin testing and oral challenge. For persons diagnosed as penicillin allergic during childhood, the promotion of universal delabeling procedures, such as skin testing and challenges, is recommended.

Autoimmune progesterone-mediated anaphylaxis may respond to medical or surgical interventions that prevent menses and to progesterone desensitization. Perimenstrual anaphylaxis may respond to the luteinizing hormone–releasing hormone analog leuprolide, oophorectomy, or conjugated estrogens.

Patients who have systemic mastocytosis (Chapter 235) should avoid using direct mast cell agonists such as vancomycin and most narcotic agents with the exception of fentanyl. Aspirin-intolerant asthmatic patients who have sinus polyps (Chapter 394) can be desensitized to aspirin and placed on a daily dose to maintain desensitization status, thereby resulting in better control of asthma, shrinkage of polyps, and reduction of hyposmia. Anti-IL-5, anti-IL-5R, or anti-IL-4Rα monoclonal antibody therapy can also control polyps and asthma (Chapter 75).

Legislation requires that foods or ingredients containing a major food allergen be specifically labeled as such. These products, which account for at least 90% of allergic food reactions, include milk, eggs, fish, shellfish, tree nuts, peanuts, wheat, soybean, and sesame. Individuals who have food allergies must practice avoidance of the provocative agent. However, anti-IgE neutralization therapy or oral immunotherapy can sometimes protect against inadvertent exposure to food allergens. Feeding peanuts to children at risk for developing peanut allergic disease prevents the majority of them from becoming allergic. Anti-IgE therapy (i.e., omalizumab) in peanut-allergic individuals can increase the threshold of peanut ingestion needed to cause an allergic reaction and reduce the risk of reactions during oral peanut immunotherapy, but it has not been FDA approved for these indications.[A1] Palforzia is an oral peanut immunotherapy that can increase tolerance to peanuts in children with peanut allergy when used under expert oversight.[A2] Exercise-dependent anaphylaxis sometimes occur within several hours of ingesting any food, regardless of whether sensitivity to the food can be documented, and might be avoided by delaying exercise until several hours after eating.

The only preventive strategy for latex allergy is avoidance. Elimination of latex-powdered gloves and the availability of nonlatex nitrile or polyvinyl gloves are diminishing the prevalence of latex allergy among medical personnel.

PROGNOSIS

Among patients with anaphylaxis seen in emergency departments, mortality is about 0.1%, but it rises to about 1% in patients who require hospitalization. Recurrences are uncommon in the first several days after the original event but are likely to occur with any subsequent exposure to the precipitating agent. Even if no cause is found, prognosis is generally excellent if patients adhere to preventive measures and always carry injectable epinephrine.

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234

DRUG ALLERGY

MARIANA CASTELLS

DEFINITION

About 80% of adverse drug reactions are predictable and dose dependent, whereas about 20% are unpredictable and dose independent (E-Fig. 234-1). These latter reactions include immediate and delayed drug allergies and hypersensitivities (Fig. 234-1).

EPIDEMIOLOGY

Drug allergy has a spectrum of presentations and can be fatal. Any drug can induce allergic and hypersensitivity symptoms in the appropriate context and host. The incidence and prevalence of drug allergy vary between inpatient and outpatient settings. Drug reactions that lead to visits to emergency departments occur in 4 per 1000 individuals and are more frequent in women.

The most common presentation of drug reaction is skin rash, which is observed in 2 to 4% of hospitalized patients. Antibiotics, chemotherapy drugs, monoclonal antibodies, small molecules, antihypertensive agents, contrast media, and antiepileptic agents are among the most frequently implicated (Table 234-1). The incidence of drug reaction among hospitalized patients is about 6%, of which about 40% are severe drug allergy reactions and 1% result in death.

The prevalence of self-reported drug allergy is about 35%, with an average of nearly two drug allergies reported per patient. Penicillin, sulfonamides, opiates, and nonsteroidal anti-inflammatory drugs (NSAIDs) are the most frequently reported drug allergies.[1,2] For example, 20% of the general population worldwide claims to be allergic to penicillin, but further evaluation confirms the allergy in less than 1%.

Risk Factors

The risk for sensitization to a drug depends on its chemical structure, dose, route of administration, and duration of treatment. Women are at greater risk for drug allergies than men, likely related to their immune and genetic background, cyclical exposure to endogenous and exogenous hormones, pregnancy, and exposures to cosmetics and household products. In one study for example, 70% of patients seen in an emergency department for drug-induced anaphylaxis were women. Progestogen hypersensitivity, which is a rare condition associated with allergic symptoms such as dermatitis and anaphylaxis, is observed in women who are exposed to birth control medications, in vitro fertilization, or interrupted menstrual cycles. White patients are more likely to report drug allergies, but allergies to thiazide diuretics, NSAIDs, and angiotensin-converting enzyme inhibitors are more frequent in Black patients, and angiotensin receptor blockers are more frequent in Blacks compared with Whites.

Recurrent exposure to drugs and other chemicals is associated with a higher risk of drug allergy. For example, patients who have cystic fibrosis (Chapter 77) or spina bifida (Chapter 385) and who undergo multiple surgical procedures are susceptible to increased sensitization to IgE and reactions to latex and antibiotics. Patients who have acquired immunodeficiency syndrome (AIDS, Chapter 355) also have a higher rate of drug allergy, especially dermatologic reactions to sulfa medications. The chemical structure of quaternary ammoniums that are present in cosmetics and other products is shared by general anesthetic agents, thereby potentially sensitizing individuals for perioperative anaphylaxis.[3]

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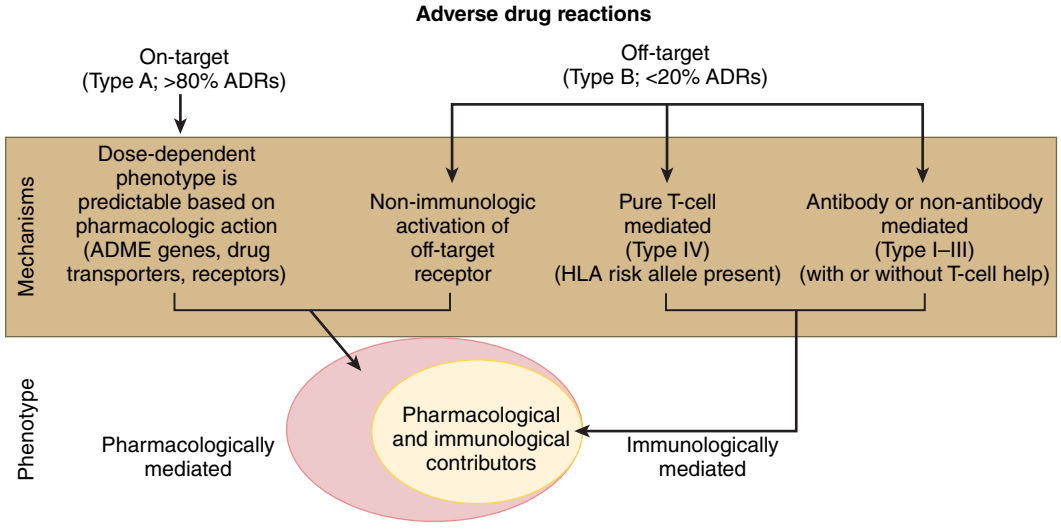

E-FIGURE 234-1. Classification of adverse drug reactions. Hypersensitivity drug reactions include Type A reactions, which are dose dependent and based on the pharmacologic action of the drugs, and Type B reactions, with non-immunologic activation of off-target receptors and immune-mediated reactions (T-cell mediated with HLA alleles risk) and antibody mediated (Type I-III). ADR = adverse drug reactions; ADME = genes involved in absorption, distribution, metabolism, and excretion; HLA = human leukocyte antigen. (White KD, Chung WH, Hung SI, et al. Evolving models of the immunopathogenesis of T cell-mediated drug allergy: the role of host, pathogens, and drug response. *J Allergy Clin Immunol*. 2015;136:219-235.)

ABSTRACT

Drug allergy and hypersensitivity are growing health care concerns that encompass a new discipline led by allergists and clinical immunologists. In the past 25 years, an explosion of new targeted drugs, such as monoclonal antibodies and small molecules, have led to an increased risk for allergic drug reactions. Desensitization has become a safe, first-line therapy for patients with drug-induced immediate and delayed allergic reactions.

KEYWORDS

drug allergy
drug hypersensitivity
phenotypes
endotypes
biomarkers
tryptase
immediate reaction
delayed reaction
HLA
desensitization
delabeling

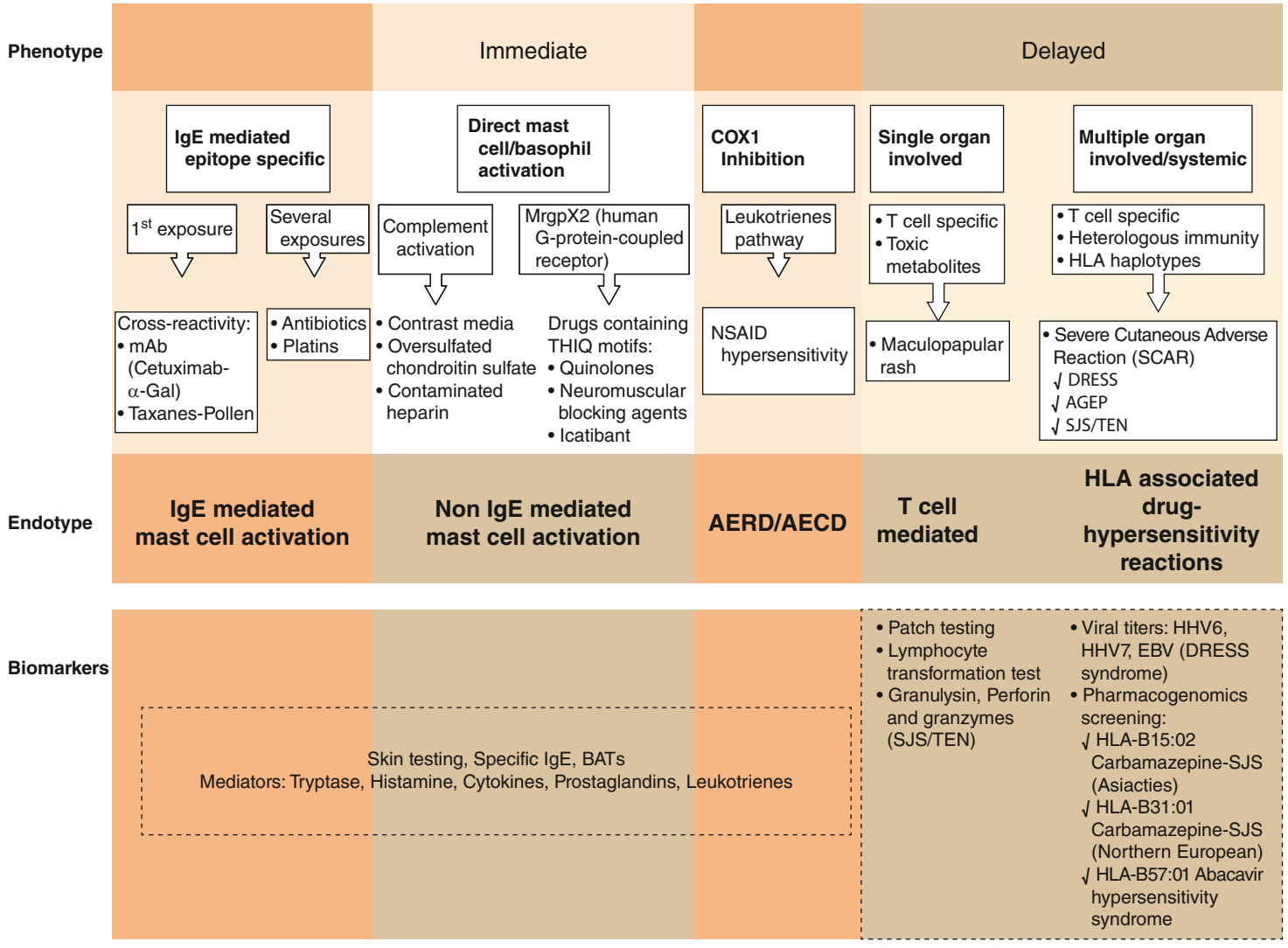

FIGURE 234-1. Type B drug reaction phenotypes. Drug reaction phenotypes include immediate and delayed reaction. Immediate reactions endotypes include IgE and non-IgE mechanisms and biomarkers such as tryptase. Delayed reaction endotypes include T-cell mediated with single organ and multisystemic involvement and biomarkers such as HLA alleles risk susceptibility. α-Gal = galactose-alpha-1,3-galactose; AECD = aspirin exacerbated cutaneous disease; AERD = aspirin exacerbated respiratory disease; AGEP = acute generalized exanthematous pustulosis; BAT = basophil activation test; DRESS = drug reaction with eosinophilia and systemic symptoms; EBV = Epstein-Barr virus; HHV6 = human herpesvirus 6; HHV7 = human herpesvirus 7; HLA = human leukocyte antigen; Ig = immunoglobulin; mAb = monoclonal antibody; NSAID = nonsteroidal anti-inflammatory; SJS/TEN = Stevens-Johnson syndrome and toxic epidermal necrolysis; THIQ = tetrahydroisoquinoline. (de Las Vecillas Sánchez L, Alenazy LA, Garcia-Neuer M, et al. Drug hypersensitivity and desensitizations: mechanisms and new approaches. *Int J Mol Sci*. 2017;18:1316.)

stimulation with a persistent increase in activated CD4+ T cells that express PD1 and CD28.[6]

PATHOBIOLOGY

Drug allergy can be divided into acute, antibody-mediated, immune complex-mediated, and delayed (T-cell-mediated) reactions. As illustrated by penicillin allergy (E-Fig. 234-2), antibody-mediated reactions include types I, II, and III; T-cell-mediated type IV reactions are divided into IVa to IVd. Drug antigens such as insulin and haptens such as penicillin and carboplatin are bound to carrier proteins and are presented to T-cells by antigen-presenting cells during sensitization, thereby leading to the generation of cytotoxic T-cells and to the production of IgG and IgE antibodies by B-cells. The severity of immediate reactions involving two or more organs is considered anaphylaxis (Table 234-1; Chapter 233). Additional phenotypes of immediate reactions include cytokine release reactions, mixed reactions, and complement-mediated reactions (Fig. 234-2). Interleukin (IL)-6 levels at the time of a reaction are predictive of fever, chills, and oxygen desaturation in cytokine-release reactions and mixed reactions.[7]

Reactions occurring 6 hours or more following drug administration can be due to immunologic and nonimmunologic off-target receptor activation and can affect a single organ or be multisystemic. Specific HLA haplotypes are associated with severe cutaneous reactions and systemic symptoms to drugs such as abacavir, carbamazepine, allopurinol, sulfonamide, and vancomycin.

TABLE 234-1 THE BROWN CLASSIFICATION OF THE SEVERITY OF DRUG REACTIONS

GRADE	SEVERITY	# OF ORGAN SYSTEMS INVOLVED	ABNORMAL VITAL SIGNS
1	Mild	1	No
2	Moderate	≥2	No
3	Severe	≥2	Yes*

*One or more of hypotension (systolic blood pressure <90 mm Hg), hypoxia (oxygen saturation <92%), or neurologic compromise (i.e., collapse, altered level of consciousness, or seizures).
Castells M, Khan D, Phillips, E. Penicillin allergy. *N Engl J Med*. 2019;381:2338-2351.

CLINICAL MANIFESTATIONS

The most common manifestation of a drug allergy is a rash, which ranges from mild to potentially life-threatening.[8] The range of dermatologic conditions (Fig. 234-3) include contact dermatitis, fixed drug eruptions, erythema multiforme (Fig. 406-16), and angioedema (Table 234-2).[9] Patients with a drug-specific IgE (Type 1 reaction) will have symptoms that may include pruritus, erythema, angioedema, wheezing, and throat tightness.

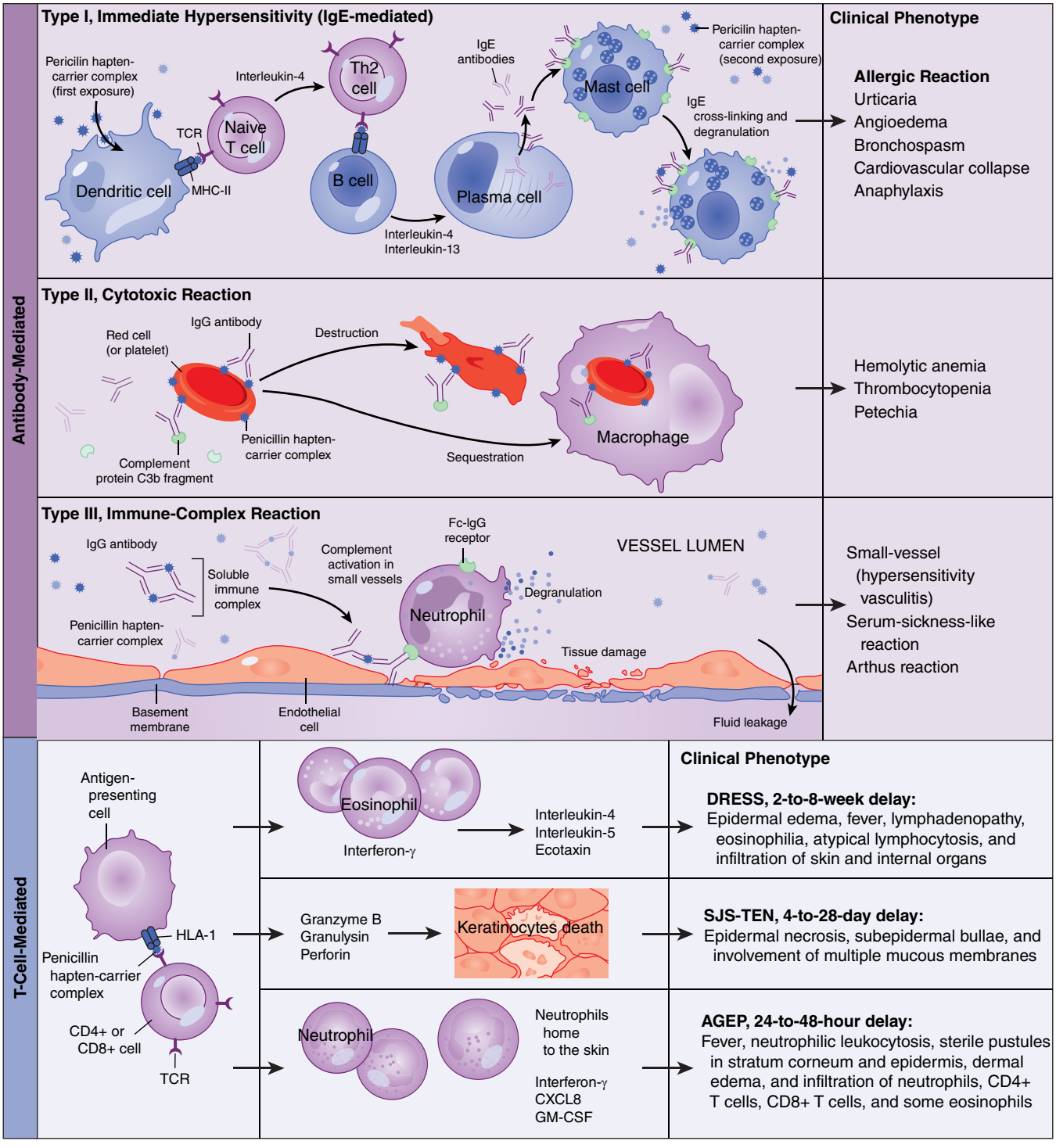

E-FIGURE 234-2. Clinical manifestations and mechanisms of adverse reactions to penicillins. Antibody-mediated reactions are Type I reactions involving the activation of mast cells and basophils through IgE and non-IgE mechanisms and the release of inflammatory mediators leading to urticaria and anaphylaxis. Type II cytotoxic reactions are mediated by IgG and complement leading to cell destruction as in hemolytic anemia. Type III reactions result from IgG immune complexes generation, complement activation, and tissue damage as in serum sickness-like reactions. Type IV reactions result from T-cell activation, which can be limited to single organ or present systemic involvement. AGEP = acute generalized exanthematous pustulosis; DRESS = drug reaction with eosinophilia and systemic symptoms; Ig = immunoglobulin; SJS = Stevens-Johnson syndrome; TCR = T-cell receptor; TEN = toxic epidermal necrolysis. (From Castells M, Khan DA, Phillips EJ. Penicillin allergy. *N Engl J Med*. 2019;381:2338-2351.)

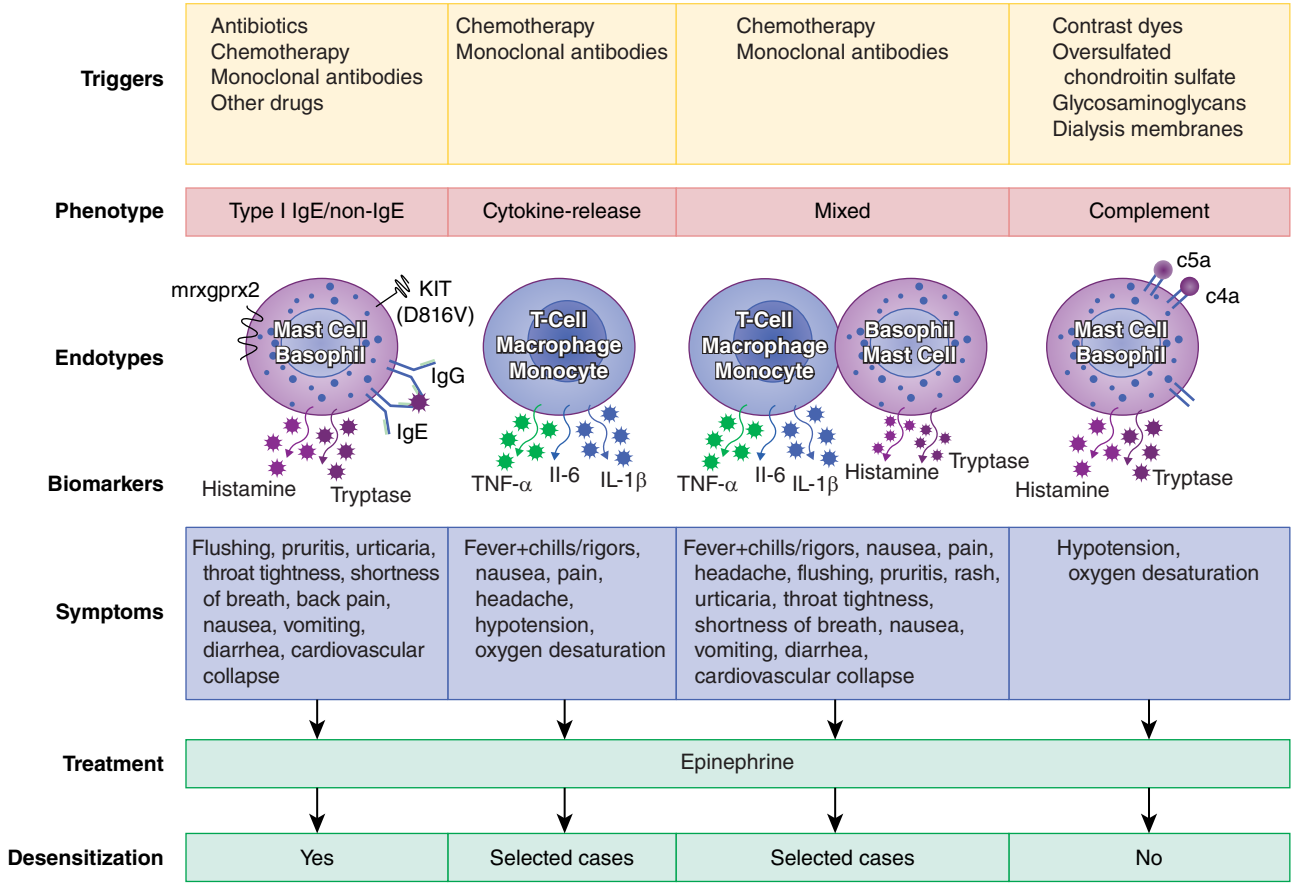

FIGURE 234-2. **Phenotypes of immediate reactions include Type I IgE and non-IgE, cytokine-release CRR, mixed reactions, and complement reactions.** Underlying endotypes and underlying mediators available clinically, such as tryptase and IL-6. Ig = immunoglobulin; IL = interleukin; TNF = tumor necrosis factor. (Adapted from Labella M, Garcia-Neuer M, Castells M. Application of precision medicine to the treatment of anaphylaxis. *Curr Opin Allergy Clin Immunol*. 2018;18:190-197.)

Hepatic Manifestations	Renal Manifestations	Lymphoid Manifestations	Cardiac Manifestations	Neurologic Manifestations	Pulmonary Manifestations	Autoimmune Manifestations	Drug-Induced Immune Cytopenias Manifestations
Cholestasis: aminosalicylic acid, dapsone **Hepatocellular damage:** phenothiazines, erythromycin **Mixed pattern:** halothane, isoniazid, diclofenac, phenytoin, sulfonamides	**Nephrotic syndrome:** gold salts, captopril, NSAIDs, penicillamine **Acute interstitial nephritis:** β-lactams, NSAIDs, sulfonamides	**Pseudolymphoma:** phenytoin, lamotrigine **Infectious mononucleosis-like syndrome:** aminosalicylic acid, dapsone	Sulfonamides β-lactams	**Peripheral neuritis:** colchicine, nitrofurantoin, sulfonamides NSAIDs	**Pulmonary infiltrates with eosinophilia:** minocycline, nitrofurantoin, taxenes **Pneumonitis & fibrosis:** bleomycin, amiodarone **Noncardiogenic pulmonary edema:** hydrochlorothiazide, cocaine, heroin, methadone	**Drug-induced lupus:** hydralazine, procainamide	**Thrombocytopenia:** quinidine, gold salts, sulfonamides, heparin, oxaliplatin **Hemolytic anemia:** penicillin, methyldopa **Agranulocytosis:** sulfonamides, propylthiouracil, quinidine, procainamide, phenytoin

FIGURE 234-3. **Organ and system specific reactions and implicated drugs.** β-lactams = beta-lactams; NSAIDs = nonsteroidal anti-inflammatory drugs. (Adapted from Grammer LC. Drug allergy. In: Goldman L, Schafer AI, eds. *Goldman-Cecil Medicine*. 26th ed. Philadelphia: Elsevier; 2020.)

Several clinical entities with extreme clinical presentations must be recognized. Type I reactions (Table 234-3) can result in anaphylaxis (Chapter 233), which can lead to death if not diagnosed and treated promptly. Drug reaction with eosinophilia and systemic symptoms (DRESS; Fig. 407-4)[10] is manifest by extensive skin rash, fever, organ involvement, and lymphocytosis/lymphadenopathy. Both Stevens-Johnson syndrome and toxic epidermal necrolysis (Fig. 407-5) are characterized by extensive skin necrosis and detachment of the epidermis. Drugs can also cause a variety of reactions that are manifested in other organs, including liver reactions (Chapter 136), acute interstitial nephritis (Chapter 108), and pulmonary infiltrates with eosinophilia (Chapter 82).

Reactions to Specific Drugs

Antibiotics

Reactions to antibiotics are reported worldwide, and children are often labeled as having antibiotic allergies when treated with them for viral infections. About 5 to 10% of hospitalized patients demonstrate an allergy to antibiotics, the most common being penicillin, sulfonamides, quinolones, and macrolides.[11]

TABLE 234-2 DRUGS FREQUENTLY IMPLICATED IN ALLERGIC DRUG REACTIONS

Allopurinol
Antibiotics (β-lactams, sulfas, nitrofurans)
Anticonvulsants (hydantoin, phenobarbital, carbamazepine)
Antihypertensive agents (angiotensin-converting enzyme inhibitors)
Antipsychotic tranquilizers
Antisera (antitoxins, antivirals)
Antituberculosis drugs (isoniazid, rifampicin)
Aspirin and nonsteroidal anti-inflammatory drugs
Biologics (monoclonal antibodies such as anti–tumor necrosis factor and other recombinant DNA protein products)
Chemotherapy agents (platins, doxorubicin, taxanes)
Enzymes (L-asparaginase, streptokinase, chymopapain)
Muscle relaxants (rocuronium, succinylcholine)
Opioids
Radiocontrast media
Vaccines (egg protein, gelatin)

From Grammer LC. Drug allergy. In: Goldman L, Schafer AI, eds. *Goldman-Cecil Medicine*. 26th ed. Philadelphia: Elsevier; 2020.

TABLE 234-3 DRUGS ASSOCIATED WITH ANAPHYLAXIS

DRUG	FREQUENCY	COMMENTS
Aspirin and NSAIDs	About 50%	Mechanism thought to be specific to NSAID; patients can tolerate other COX-1 inhibitors
β-lactam antibiotics	About 15%	Amoxicillin with clavulanic acid is common culprit
Fluoroquinolones	About 9%	
Vancomycin	Rare	Associated with "red man" syndrome and anaphylaxis
Radiocontrast media	0.045% for nonionic contrast agents	Gadolinium is reported to induce anaphylactic events only one-tenth as often as radiocontrast
Proton-pump inhibitors		High cross-reactivity; skin testing can be used to select alternate choices
Neuromuscular blocking agents	Associated with about 50% of perioperative anaphylaxis events	Mortality = 1.4%, suxamethonium, atracurium, and rocuronium are most commonly associated with anaphylaxis
Sugammadex		IgE mechanism
Barbiturates		Direct mast cell histamine release
Opioids		Can induce direct histamine release from mast cells, rarely IgE sensitization. Low potency opioids are the most common triggers; rarely seen with fentanyl
Chlorhexidine		Patients can have IgE sensitization from toothpaste, mouthwash, etc. and develop anaphylaxis during operative procedures
Dyes		For example, methylene blue and isosulfan blue used in cancer-mapping procedures
Colloids	0.05-0.1%	Gelatin and dextran more commonly associated with anaphylaxis compared to albumin and starch
Vaccines	1/1,000,000	COVID-19 vaccines have a higher frequency of anaphylaxis (1/100,000)
Local anesthetics	Rare	

COVID-19 = coronavirus-19 disease; Ig = immunoglobulin; NSAID = nonsteroidal anti-inflammatory drug.

Delayed benign rashes are the most common presentation, and type I reactions and anaphylaxis preclude further use of the medications, unless desensitization provides safe reintroduction. Antigenic determinants of penicillin include the major β-lactam ring that is common to all beta lactams and the side chain R1, which is implicated in cross reactivity with cephalosporins. Use of third-, fourth-, and fifth-generation cephalosporins, aztreonam, and carbapenems are safe in patients who have a history of penicillin allergy.

Sulfonamides are the second-most-common cause of antibiotic allergy, but such allergies do not preclude the use of nonantibiotic sulfonamides. The risk of an allergic reaction to sulfonamide nonantibiotic is lower among patients who have a history of hypersensitivity to sulfonamide antibiotics than among patients who have hypersensitivity to penicillins.

Aspirin and NSAIDS

Aspirin and NSAIDs can induce urticaria and angioedema, and they can exacerbate symptoms in patients with chronic urticaria and angioedema. Delayed reactions to NSAIDs and aspirin include fixed drug eruptions and maculopapular eruptions,[12] and both drugs can also cause anaphylaxis.[13]

Aspirin-exacerbated respiratory disease occurs in 20% of patients who have severe asthma (Chapter 75), especially among women, and is associated with recurrent nasal polyposis (Chapter 394), prior sinus surgery, and lack of sense of smell. COX-1 blockade by aspirin is associated with a decrease in prostaglandin E2 and an increase in leukotriene E4. The ingestion of aspirin and NSAIDs induces severe asthmatic episodes, which are modulated by leukotriene blockers such as montelukast, zafirlukast, and zileuton. Aspirin and NSAIDs have universal cross-reactivity, and aspirin desensitization blocks asthmatic reactions to aspirin and NSAIDs. Patients with aspirin-exacerbated respiratory disease tolerate COX-2 inhibitors.

Cancer Chemotherapy

Most chemotherapy drugs can induce allergic reactions.[14] Such reactions are commonly related to platins and taxanes, with fewer reactions seen with doxorubicin, methotrexate, cyclophosphamide, and gemcitabine. Reactions to carboplatin, cisplatin, and oxaliplatin are classical type I IgE-mediated reactions that require multiple exposures for sensitization. Desensitization is safe and effective for the continuation of first-line therapies, with limited costs and extension of life span. Oxaliplatin can induce mixed and cytokine release reactions and, in rare cases, generate oxaliplatin IgG antibodies that bind to platelets, thereby inducing thrombocytopenia and bleeding and precluding further treatment or desensitization.[15]

Reactions to taxanes can occur with or without IgE sensitization, at first exposure, or after multiple exposures; cross reactivity to environmental allergens and diluents have been implicated. Up to 10% of patients treated with taxanes can present with reactions that range from flushing to severe back and chest pain, with oxygen desaturation and cardiovascular collapse. Diluents such as cremophor and polysorbate can activate complement. IgE sensitization to paclitaxel and docetaxel is less common.

Monoclonal Antibodies

Reactions to monoclonal antibodies, which are more frequent with chimeric and humanized antibodies than with fully human monoclonal antibodies, can occur at first exposure or after repeated exposures.[16] Rituximab, infliximab, tocilizumab, brentuximab, trastuzumab, obinutuzumab, omalizumab, cetuximab, and adalimumab are among the most frequently implicated drugs. Infusion reactions are frequent and can occur with up to 10% of infusions. Type I reactions are responsible for about 65% of cases, mixed reactions for about 20%, cytokine-release reactions in about 10%, and delayed type IV reaction in about 5%.

Perioperative Anaphylaxis

Many commonly used drugs and agents in hospitalized patients are associated with anaphylaxis, especially in the perioperative environment (Table 234-3).[17] Perioperative anaphylaxis[18] is a rare, life-threatening medical emergency that occurs in about 1 per 10,000 anesthetics procedures and is associated with a mortality rate of 4%. Antibiotics such as β-lactams, latex, chlorhexidine, and neuromuscular blocking agents are the most common culprits. Paired blood levels of tryptase, obtained during the event and about 2 weeks later, provide evidence of mast cell activation and help establish the diagnosis.

Vaccines

Vaccines can rarely cause anaphylaxis (Chapter 233), with an estimated overall incidence of 1.3 per million, but the incidence is about 10-fold higher for COVID-19 vaccines.[19] Vaccines also can cause delayed hypersensitivity[20] reactions.

DIAGNOSIS

Diagnosis of drug allergy is largely based on obtaining an accurate clinical history of all drugs taken by the patient, including over-the-counter medications and alternative therapies (Chapter 30). The patient should be questioned

about prior use and past reactions to medications. Drug classes most commonly associated with drug allergies include β-lactam antibiotics, sulfa-containing medications, NSAIDs, and anticonvulsants (see Table 234-2). Unless patients have been previously exposed to the drug, allergic or hypersensitivity drug reactions rarely occur in the first week of continuous therapy. Conversely, a drug that has been used consistently for several months or longer rarely causes an allergic reaction.

For patients with presumed anaphylaxis, an elevated serum tryptase level may be useful to confirm the diagnosis (Chapter 233), although the test must be performed within 30 minutes to 6 hours from initiation of symptoms. Plasma histamine levels are not generally useful owing to their short half-life. Skin testing may be useful in the setting of immediate IgE-mediated drug reactions but should not be performed in the setting of severe reactions or in patients who are at high risk for anaphylaxis.

TREATMENT AND PREVENTION

Recognition of the symptoms of drug allergy in the appropriate clinical setting should lead to prompt discontinuation of the potential offending agents.[21] Patients with presumptive anaphylaxis should be managed with airway and blood pressure support and epinephrine (Chapter 233). Oxygen and inhaled bronchodilators may be required for patients with bronchospasm (Chapter 75). In general, the symptoms of drug allergy will resolve over time with discontinuation of the inciting agent. The mechanisms of drug-induced single organ and multi-system reactions are not well understood and require permanent discontinuation of the medication, since re-exposure can induce faster and more severe reactions.

For patients who develop reactions to monoclonal antibodies, management of anaphylactic reactions requires epinephrine (Chapter 233) and desensitization protocols, which are indicated for first-line treatment. After uneventful desensitization, patients may return to regular infusions. Type I reactions can convert into cytokine release reactions and mixed reaction during desensitization.[22]

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Delabeling Penicillin Allergy

Penicillin allergy is the most common self-reported drug allergy, and 10 to 20% of the world's population engaged in health care claims to be penicillin allergic. After careful evaluation, less than 5% of these allergies are confirmed. Penicillin allergy decays every 10 years, and patients claiming to be allergic 40 years ago are now unlikely to be allergic. Many symptoms listed as an allergy are in fact side effects, such as nausea or headache. Low-risk patients can be directly challenged with penicillin or use other β-lactams without need for testing, while high-risk patients must avoid the drug or be desensitized (E-Fig. 234-3). Formally delabeling penicillin allergy decreases the need for more expensive or less well-tolerated antibiotics, decreases the length of hospitalization, and provides patients with first-line treatments.[24,25] However, resensitization can occur after subsequent exposure, so retesting is often appropriate, especially if the original reaction was severe.[26]

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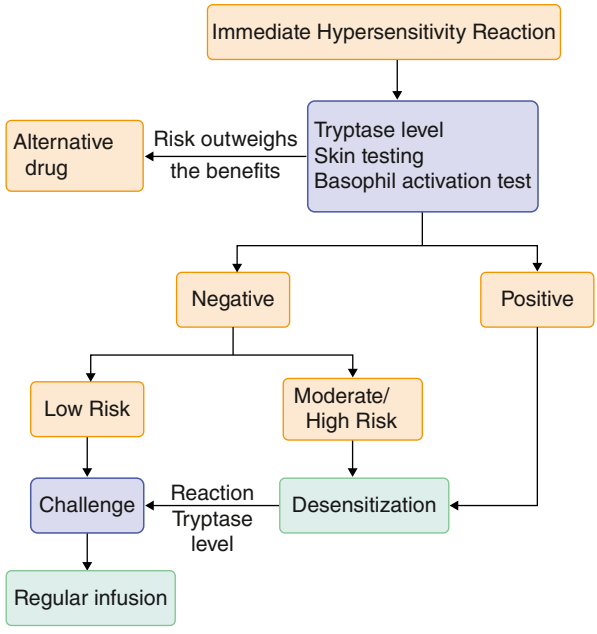

FIGURE 234-4. Approach to patients with drug allergy in need of re-exposure to first-line therapy.

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235 MASTOCYTOSIS

CEM AKIN

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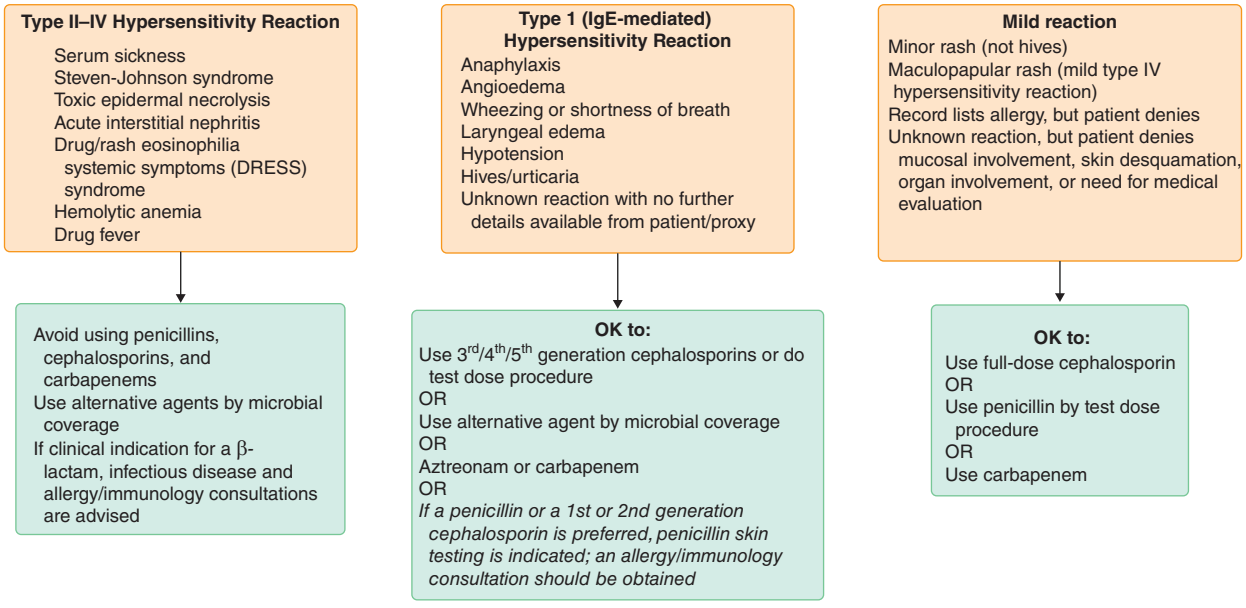

E-FIGURE 234-3. Penicillin allergy pathway to safely treat patients using risk stratification. Ig = immunoglobulin. (Data from Blumenthal KG, Huebner EM, Fu X, et al. Risk-based pathway for outpatient penicillin allergy evaluations. *J Allergy Clin Immunol Pract*. 2019;7:2411-2414.)

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about prior use and past reactions to medications. Drug classes most commonly associated with drug allergies include β-lactam antibiotics, sulfa-containing medications, NSAIDs, and anticonvulsants (see Table 234-2). Unless patients have been previously exposed to the drug, allergic or hypersensitivity drug reactions rarely occur in the first week of continuous therapy. Conversely, a drug that has been used consistently for several months or longer rarely causes an allergic reaction.

For patients with presumed anaphylaxis, an elevated serum tryptase level may be useful to confirm the diagnosis (Chapter 233), although the test must be performed within 30 minutes to 6 hours from initiation of symptoms. Plasma histamine levels are not generally useful owing to their short half-life. Skin testing may be useful in the setting of immediate IgE-mediated drug reactions but should not be performed in the setting of severe reactions or in patients who are at high risk for anaphylaxis.

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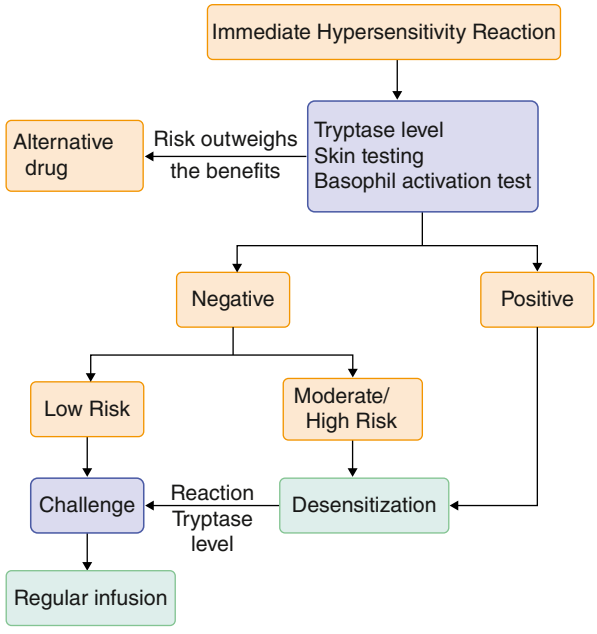

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ABSTRACT

Mastocytosis is a heterogeneous group of disorders that are characterized by pathologic mast cell accumulation in tissues, including skin and bone marrow. The current World Health Organization (WHO) classification of mastocytosis divides the disorders into two broad categories: cutaneous mastocytosis (in which abnormal mast cell infiltration is limited to skin) and systemic mastocytosis (in which other organs are involved, with or without cutaneous mastocytosis). The systemic mastocytoses range from good to very poor prognosis disorders, including indolent systemic mastocytosis, bone marrow mastocytosis, smoldering systemic mastocytosis, systemic mastocytosis with associated hematologic non–mast cell lineage neoplasm, aggressive systemic mastocytosis, and mast cell leukemia. Clinical manifestations may be caused by mediators that are released by activated mast cells as well as by tissue infiltration. These mediators include vasoactive substances (e.g., histamine, prostaglandin D2, and cysteinyl leukotrienes), proteases, and cytokines. Treatment for the less aggressive forms of systemic mastocytosis is largely symptomatic, whereas the more aggressive forms now can be treated with targeted therapies that block the primary driver *KIT* D816V mutation.

KEYWORDS

mastocytosis
KIT
anaphylaxis
mast cells
urticaria pigmentosa
mast cell activation

systemic mastocytosis describes the disorder when it involves internal organs (most commonly the bone marrow) with or without skin disease. In addition, mast cell sarcoma is a rare invasive tumor.

EPIDEMIOLOGY

Mastocytosis can be diagnosed at any age,[2] and the disease has been diagnosed in all ethnic populations. The disease is sporadic, although rare cases of familial occurrence have been described.

Estimates of the prevalence of cutaneous mastocytosis range from 1 in 500 to 1 in 8000 among patients who present to dermatology practices. The prevalence of systemic mastocytosis is estimated to be around 1 in 10,000. However, systemic mastocytosis is likely to be underdiagnosed, since neither findings on physical examination nor routine hematologic or chemistry laboratory abnormalities are specifically associated with the disease.

PATHOBIOLOGY

The pathogenesis of mastocytosis involves the accumulation of clonally expanded mast cells in tissues, where activated mast cells release mediators. The primary reason for the increased numbers of mast cells in tissues appears to be defective apoptosis rather than increased mitotic activity, and the microenvironment and altered chemotaxis may also contribute to the accumulation of mast cells.

Genetics

Mast cells are derived from hematopoietic progenitors (Chapter 137). Systemic mastocytosis is associated with somatic gain-of-function point mutations in the *KIT* (formerly *c-kit*) gene of the mast cell progenitor, thereby leading to a clonal neoplastic expansion of mast cells. *KIT* encodes a transmembrane receptor (Kit) whose intracellular portion functions as a tyrosine kinase enzyme. The extracellular portion of Kit binds the cytokine stem cell factor. The interaction between the stem cell factor and Kit provides the single most important growth and differentiation stimulus for mast cells from their progenitors. Under physiologic conditions, homodimeric stem cell factor binds and cross-links two Kit receptor molecules, thereby leading to autophosphorylation of the tyrosine amino acids of the intracellular portion of the Kit molecule. Phosphorylated tyrosine residues in turn act as docking sites for downstream adaptor and signal transduction molecules that regulate the differentiation, proliferation, chemotaxis, and functional activation of mast cells.

The most common mutation in mastocytosis involves codon 816 in *KIT* (located in exon 17), where replacement of an aspartic acid by a valine residue (D816V) in the Kit protein leads to ligand-independent autophosphorylation.[3] This D816V mutation is present in the skin or bone marrow tissue of more than 90% of adults and approximately 40% of pediatric patients with mastocytosis. Another 40% of pediatric patients carry *KIT* mutations in other exons, most commonly in exons 8 and 9. *KIT* mutations can be demonstrated in non–mast cell hematopoietic lineages in advanced variants of systemic mastocytosis, similar to the multilineage involvement observed in myeloproliferative neoplasms (Chapter 152). The sensitivity of detecting the mutation is much higher when a lesional tissue such as bone marrow or skin is analyzed compared with peripheral blood and when a sensitive technique such as allele specific polymerase chain reaction (PCR) testing is used.

Other pathogenetic factors also appear to be responsible for the final disease phenotype because the presence of the D816V *KIT* mutation alone does not explain the remarkable heterogeneity in the clinical presentation and prognosis of the disease. Molecular aberrations in *TET2*, *SRSF2*, *ASXL1*, *CBL*, *RUNX1*, and *DNMT3A* are the most frequently identified other mutations in advanced forms of systemic mastocytosis. In advanced systemic mastocytosis, most patients carry three or more mutations.

Mast cells are rich sources of cytokines. Activation of mast cells[4] results in the release of various preformed mediators that are stored in mast cell granules, *de novo* synthesis of sulfidopeptide leukotrienes such as leukotriene C_4 and prostaglandins (mostly prostaglandin D_2) from membrane lipids, and synthesis of cytokines. Preformed mediators stored in mast cell granules include histamine; proteases such as tryptase, chymase, and carboxypeptidase A; and proteoglycans such as heparin and chondroitin sulfate.

Mature tryptase enzyme is a serine protease that is stored in mast cell granules and is transiently elevated in serum or plasma after mast cell degranulation episodes, such as anaphylaxis. In contrast, tryptase precursor proenzymes (α and ß protryptases) are constitutively secreted outside the cell, and their serum levels at baseline correlate with mast cell burden.

CLINICAL MANIFESTATIONS

Symptoms

Mastocytosis is a disease with protean clinical manifestations. In general, patients with mastocytosis belong to one of two broad categories: patients who have cutaneous disease alone, and patients who have systemic disease with or without skin involvement. Although some patients may complain only about the cosmetic appearance of urticaria pigmentosa lesions (Fig. 235-1), other patients suffer from frequent episodes of vascular instability or have life-threatening hematologic disease.

The symptoms of mastocytosis are primarily related to the release of vasoactive mast cell mediators (e.g., histamine, leukotriene C_4, and prostaglandin D_2), which cause vasodilation that may lead to flushing, tachycardia, hypotension, presyncope, and syncope. Histamine also causes pruritus and stimulates gastric acid hypersecretion from parietal cells. Elevated serum levels of tumor necrosis factor-α and interleukin-6 may contribute to the fatigue and accelerated osteoporosis that are observed in some patients. In rare aggressive forms of mastocytosis, mast cells may extensively infiltrate into tissues such as the gastrointestinal tract, where they may result in malabsorption, and the liver, where they may cause portal fibrosis with associated portal hypertension.

Activation of mast cells and their release of mediators may occur after triggers, such as temperature changes (e.g., hot showers), exercise, ingestion of alcohol or spicy foods, emotional stress, insect stings, and exposure to certain drugs (e.g., opioid analgesics, nonsteroidal anti-inflammatory drugs, or muscle relaxants). Sometimes, however, activation occurs spontaneously without an obvious trigger. The prevalence of atopic disease in patients with mastocytosis is similar to that in the general population, but patients with anaphylactic sensitivity to Hymenoptera venoms appear to have a disproportionately high prevalence of mastocytosis.

Cutaneous Manifestations

Maculopapular skin lesions of urticaria pigmentosa (known as maculopapular cutaneous mastocytosis) are the most common presentation of cutaneous mastocytosis (Fig. 235-1). These lesions are also present in 50 to 90% of patients with systemic mastocytosis. Remarkably different in appearance from urticaria or hives (Chapter 232), lesions of urticaria pigmentosa are fixed, tan- to salmon-colored lesions that vary in size from a few millimeters to a few centimeters. Lesions are most prominently observed on the trunk and extremities and tend to spare the face and sun-exposed areas of the skin, although facial and scalp involvement may be seen in children. Blistering of the lesions may occur in children, mostly in the first 3 years of life. The lesions are generally not initially pruritic but may urticate after exposure to a number of triggers. Many patients note that the skin lesions become more prominent after exposure to heat or after physical irritation such as rubbing. A localized wheal-and-flare reaction limited to the lesional skin within a few minutes after rubbing or scratching it is known as the Darier sign. The lesions may be concentrated in skin areas that are prone to irritation, such as the axillae and groin. Patients with cutaneous mastocytosis may also manifest other symptoms such as abdominal pain, diarrhea, and flushing.

Uncommon presentations of cutaneous mastocytosis include mastocytomas and diffuse cutaneous mastocytosis. Mastocytomas are benign and generally solitary mast cell tumors, but they can sometimes precede urticaria pigmentosa. Mastocytomas occur almost exclusively in children, and physical irritation of the lesion may result in generalized flushing and other symptoms caused by the release of mediators from their mast cells. Diffuse cutaneous mastocytosis

FIGURE 235-1. Urticaria pigmentosa.

is also seen exclusively in children and is characterized by diffuse thickening of the skin and appendages with a peau d'orange appearance without individual urticaria pigmentosa lesions.

Telangiectasia macularis eruptiva perstans is a rare form of cutaneous mastocytosis that is characterized by diffuse telangiectatic macules. Because the lesions of telangiectasia macularis eruptiva perstans are generally seen in the presence of urticaria pigmentosa, it is uncertain whether telangiectasia macularis eruptiva perstans represents a distinct form of cutaneous mastocytosis.

Systemic Manifestations

Degranulation of mast cells can cause brief, recurrent, and self-limited multiorgan manifestations or recurrent complaints with a prolonged time course. A typical mast cell degranulation episode may variably involve flushing, conjunctival hyperemia, nausea, vomiting, abdominal cramping, diarrhea, tachycardia, and lightheadedness. These symptoms of mast cell activation may occur when mast cells are activated as a reaction to stimuli generated by another pathologic process, but a consistent trigger can be identified in only a small number of patients. Angioedema, hives, and wheezing are uncommon in mastocytosis. Flushing usually involves the face and upper chest area. The episodes usually persist for 30 minutes to a few hours. Hypotension may develop, and the episode can progress to full loss of consciousness. Hypotensive episodes can be life-threatening, particularly in the presence of comorbid conditions, such as cardiac or pulmonary disease.

Gastrointestinal Symptoms

Gastrointestinal symptoms are observed in more than 50% of patients with mastocytosis. Epigastric pain, lower abdominal cramping, nausea, vomiting, or diarrhea can occur episodically in the context of an acute mast cell degranulation episode or on a chronic basis. Gastric acid hypersecretion induced by mast cell–derived histamine may lead to esophagitis, gastritis, and peptic ulcer disease. Diarrhea alternating with constipation may be seen. Severe persistent diarrhea may be complicated by clinically significant malabsorption in patients with aggressive systemic mastocytosis. Hematochezia, hematemesis, and melena are uncommon symptoms that should prompt endoscopic evaluation to exclude coexisting disease. Mild to moderate hepatomegaly with or without elevated aminotransferase levels may be observed, but portal hypertension and ascites are rare and indicate the presence of advanced mastocytosis. Jaundice and cholangiographic findings that resemble primary sclerosing cholangitis (Chapter 141) can occur.

Musculoskeletal Symptoms

Musculoskeletal pain is common and usually resembles fibromyalgia (Chapter 253). Accelerated osteoporosis (Chapter 225) may be seen in a subgroup of patients, particularly patients who have other risk factors, such as postmenopausal women and patients who are receiving glucocorticoid therapy. Pathologic compression fractures and other fragility fractures due to bone involvement may be the initial finding in some patients.[5]

Hematologic Manifestations

Peripheral blood abnormalities are noted in up to 50% of patients with systemic mastocytosis. Mild normochromic normocytic anemia is the most common abnormality, followed by thrombocytopenia, eosinophilia, monocytosis, and leukopenia. Eosinophilia in mastocytosis rarely causes the organ damage that is observed in chronic eosinophilic leukemia or idiopathic hypereosinophilic syndrome (Chapter 156).

Approximately 20% of patients with systemic mastocytosis have evidence of another clonal non–mast cell hematologic disease. These conditions are commonly myeloid (e.g., myeloproliferative neoplasms, myelodysplastic syndromes, or myeloid leukemias) but may also include lymphoproliferative disorders such as lymphomas, myelomas, and lymphocytic leukemias.

DIAGNOSIS

Cutaneous mastocytosis (i.e., disease limited to the skin in the absence of internal organ involvement) is commonly diagnosed in children within the first year of life, whereas systemic mastocytosis is mostly diagnosed in adults by a bone marrow aspiration and biopsy. Many patients have symptoms for several years before mastocytosis is diagnosed. Mastocytosis should be considered in all patients with recurrent anaphylaxis (Chapter 233), especially patients who present with hypotension. The finding of urticaria pigmentosa in adults should always prompt consideration of possible systemic mastocytosis.

The approach to the diagnosis of mastocytosis and its classification can be facilitated by using a systematic approach (Fig. 235-2).

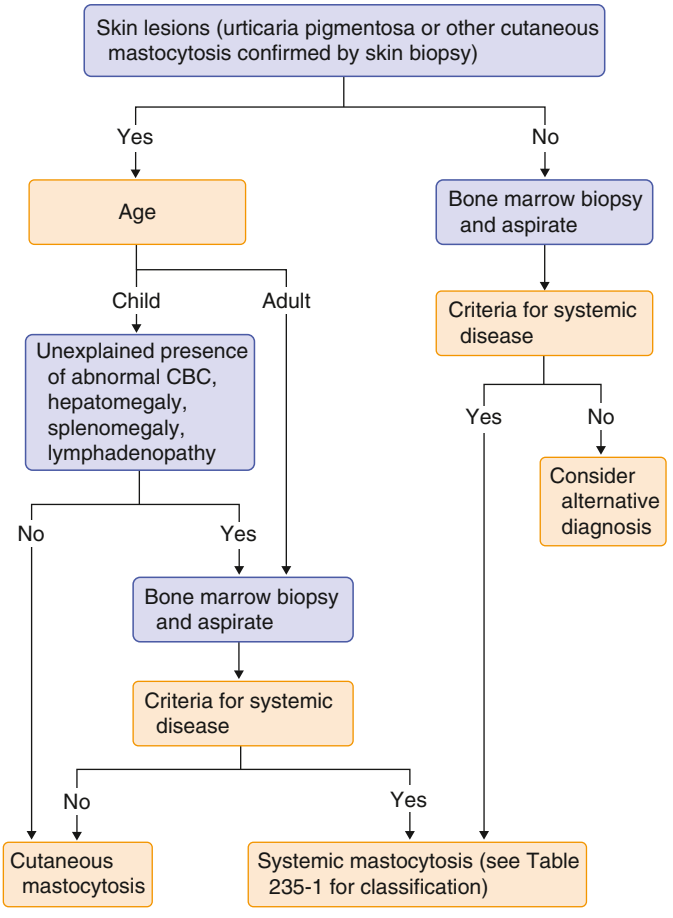

FIGURE 235-2. Suggested diagnostic algorithm for mastocytosis. CBC = complete blood count.

Cutaneous Mastocytosis

The diagnosis of cutaneous mastocytosis is established by observing the typical hyperpigmented maculopapular lesions of urticaria pigmentosa, which should always prompt consideration of mastocytosis, associated with a skin biopsy that shows infiltration of mast cells in the upper dermis, particularly in perivascular locations. Mild increases in the numbers of mast cells can be observed in other inflammatory and neoplastic skin diseases and do not establish a diagnosis of cutaneous mastocytosis without the characteristic skin lesions.

Systemic Mastocytosis

Systemic mastocytosis should be suspected in all patients who have systemic reactions to Hymenoptera stings, especially patients who develop hypotensive near-syncope or syncope. Serum levels of tryptase also may be elevated above the patient's baseline level (to be checked about 2 weeks later) if measured within 4 hours after the onset of the episode, but similar elevations can be seen in patients with mast cell degranulation or anaphylaxis, regardless of the cause.

The median baseline serum tryptase level in a healthy population is approximately 5 ng/mL, and a serum tryptase level higher than 20 ng/mL raises suspicion for systemic mastocytosis in the appropriate clinical setting. A normal tryptase level does not exclude a diagnosis of mastocytosis, and increased tryptase levels can be seen in other conditions, such as hereditary α-tryptasemia (which is seen in up to 7% of the general population), myelodysplastic syndromes, acute myeloid leukemias, chronic eosinophilic leukemia, and chronic renal insufficiency. Metabolites of histamine, such as *N*-methylhistamine, and prostaglandin D_2 can be elevated in a 24-hour urine specimen but are neither more sensitive nor more specific than the baseline serum tryptase measurement in mastocytosis.

Biopsy

The recommended diagnostic procedure to diagnose systemic disease is a bone marrow aspiration and biopsy.[6] This procedure is recommended for all patients with adult-onset urticaria pigmentosa, patients with recurrent symptoms suggestive of mast cell degranulation (such as flushing and hypotension accompanied by abdominal complaints), patients with unexplained

osteoporosis, and patients with suspected hematologic disease. Children who have late-onset skin lesions (especially uniform morphology as opposed to polymorphic lesions of various sizes) and who have persistent maculopapular cutaneous mastocytosis into adulthood should also be considered for diagnostic bone marrow evaluation.

Bone marrow mast cells in systemic mastocytosis often display atypical morphology, such as an elongated (i.e., spindle) shape, hypogranularity, and an eccentric or lobulated nucleus (Fig. 235-3B). These atypical mast cells are usually observed in close association with bone marrow spicules in the aspirate smear. Mast cells in mast cell leukemia may be very sparsely granulated. On flow cytometry, the characteristic finding of systemic mastocytosis is the aberrant expression of CD25, CD2, and/or CD30 on CD117-positive mast cells. Aberrant marker expression can also be demonstrated by immunohistochemical staining of bone marrow biopsy specimens. Bone marrow biopsy and aspirate specimens should be carefully evaluated for the presence of other hematologic disease in every patient with newly diagnosed systemic mastocytosis.

Diagnostic Criteria

The major diagnostic criterion is the presence of multifocal, dense aggregates of 15 or more mast cells in bone marrow or other extracutaneous tissue biopsy sections (see Table 235-2).[7] The mean percentage of mast cells in a healthy bone marrow aspirate is approximately 0.02%, and the percentage does not exceed 1% in most patients with mastocytosis. This major criterion plus at least one minor criterion or the presence of three or more minor criteria in the absence of the major criterion establishes the diagnosis of systemic mastocytosis and distinguishes it from reactive mast cell hyperplasia (Table 235-2). Such clusters are frequently observed around blood vessels and next to bone trabeculae in bone marrow biopsy sections by immunohistochemical staining for tryptase and CD117.

Demonstration of a codon 816 *KIT* mutation (D816V) (or another rarer gain of function mutation in KIT) may be necessary to fulfill the diagnostic criteria in patients who lack the major criterion.[8,9] Examination of lesional tissues, such as skin and bone marrow, affords the highest sensitivity. Codon 816 *KIT* mutations can also be detected in a variety of other neoplastic diseases, such as core binding factor acute myeloid leukemias, sinonasal lymphomas, and seminomas, in addition to mastocytosis. Chronic eosinophilic leukemia is commonly associated with the *FIP1L1-PDGFRA* fusion gene, whereas systemic mastocytosis is associated with codon 816 point mutations of the *KIT* gene.

A rare histologic variant with clustering of mature round mast cells without CD25 expression termed well-differentiated systemic mastocytosis has been described. These patients generally have a history of childhood-onset mastocytosis without the D816V *KIT* mutation and therefore may respond to imatinib as opposed to those with typical systemic mastocytosis carrying the D816V mutation (see Treatment).

A bone densitometry measurement should be recommended as part of the standard evaluation in all patients with systemic mastocytosis. Radiographic abnormalities are seen in up to 75% of patients with mastocytosis; in addition to generalized osteoporosis, bone surveys may show a mixture of sclerotic or lytic lesions, and skeletal scintigraphy may reveal focal or diffuse radiotracer uptake.

Mast cells also may be increased in inflammatory states that affect the gastrointestinal tract. However, quantitation of mast cell numbers in gastrointestinal biopsy specimens is generally not helpful, and the diagnosis of mast cell disease by a gastrointestinal biopsy based solely on increased mast cell numbers without evidence for other criteria should be avoided.

Disease Categories

Each patient diagnosed with mastocytosis should be assigned a disease category (see Table 235-1).[10] *Cutaneous mastocytosis* in the absence of bone marrow and internal organ involvement is the most common category in patients with pediatric-onset disease.

Systemic mastocytosis is divided into the categories of indolent systemic mastocytosis (which is the most common category in adults), bone marrow mastocytosis, smoldering systemic mastocytosis, systemic mastocytosis with an associated hematologic neoplasm, aggressive systemic mastocytosis, and mast cell leukemia (Fig. 235-4). Systemic mastocytosis with an associated hematologic neoplasm, aggressive systemic mastocytosis, and mast cell leukemia are sometimes referred to as advanced systemic mastocytosis, whereas indolent systemic mastocytosis, bone marrow mastocytosis, and smoldering systemic mastocytosis are considered nonadvanced systemic mastocytosis. In adults, indolent systemic mastocytosis is the most common category, and systemic mastocytosis with an associated hematologic neoplasm is the second most common category.

Smoldering systemic mastocytosis denotes patients who have a high burden of mast cells, as evidenced by two or more of the following so called B-findings: more than 30% infiltration by mast cells in bone marrow biopsy and tryptase greater than 200 ng/mL; signs of dysplasia or myeloproliferation without meeting the criteria for an associated hematologic neoplasm; hepatomegaly or splenomegaly without liver dysfunction or hypersplenism; D816V variant allele fraction of 10% or more without C findings or mast cell leukemia. Bone marrow mastocytosis is

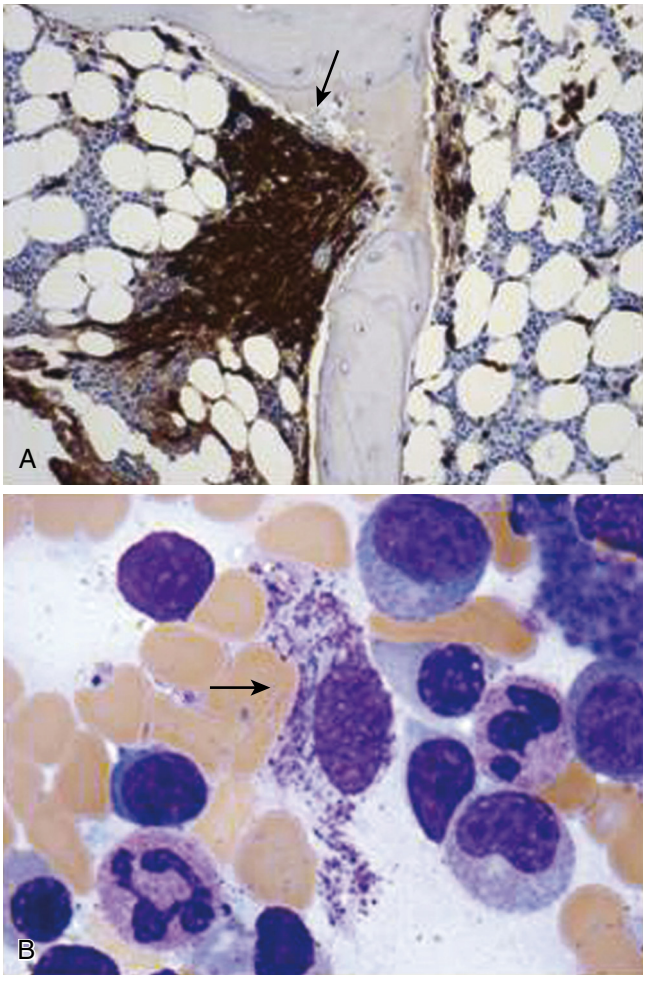

FIGURE 235-3. Diagnostic findings in the bone marrow biopsy specimen and aspirate smear. A, Characteristic mast cell aggregates on tryptase staining (major criterion) in biopsy section (*arrow*). **B,** Mast cells with atypical spindle shapes in aspirate smear (*arrow*).

TABLE 235-2 WORLD HEALTH ORGANIZATION DIAGNOSTIC CRITERIA FOR SYSTEMIC MASTOCYTOSIS

MAJOR
Multifocal, dense infiltrates of mast cells consisting of 15 or more mast cells in aggregates detected in sections of bone marrow and/or other extracutaneous organs, confirmed by tryptase immunohistochemistry or other special stains
MINOR
a. More than 25% of mast cells in the infiltrate in biopsy sections or bone marrow aspirate smears showing spindle shape or atypical morphology
b. Detection of a *KIT*-activating mutation in codon 816 or another critical region of KIT in bone marrow, blood, or other extracutaneous organs
c. Expression of one or more of the aberrant surface markers, CD25, CD2, and/or CD30, by mast cells in bone marrow, blood, or extracutaneous organs
d. Persistent elevation of serum total tryptase >20 ng/mL*

*Criterion not valid if the patient has an associated clonal myeloid disorder. In patients who have known hereditary α tryptasemia, the tryptase level should be adjusted; one method is to divide the total tryptase level by 1+ number of extra α tryptase encoding *TPSAB1* alleles.

Diagnosis requires at least one major plus one minor *or* three minor criteria.

Based on Valent P, Akin C, Metcalfe DD. Mastocytosis: 2016 updated WHO classification and novel emerging treatment concepts. *Blood.* 2017;129:1420-1427; Valent P, Akin C, Hartmann K, et al. Updated diagnostic criteria and classification of mast cell disorders: a consensus proposal. *Hemasphere.* 2021;5:e646; and Khoury JD, Solary E, Abla O, et al. The 5th edition of the World Health Organization classification of haematolymphoid tumours: myeloid and histiocytic/dendritic neoplasms. *Leukemia.* 2022;36:1703-1719.

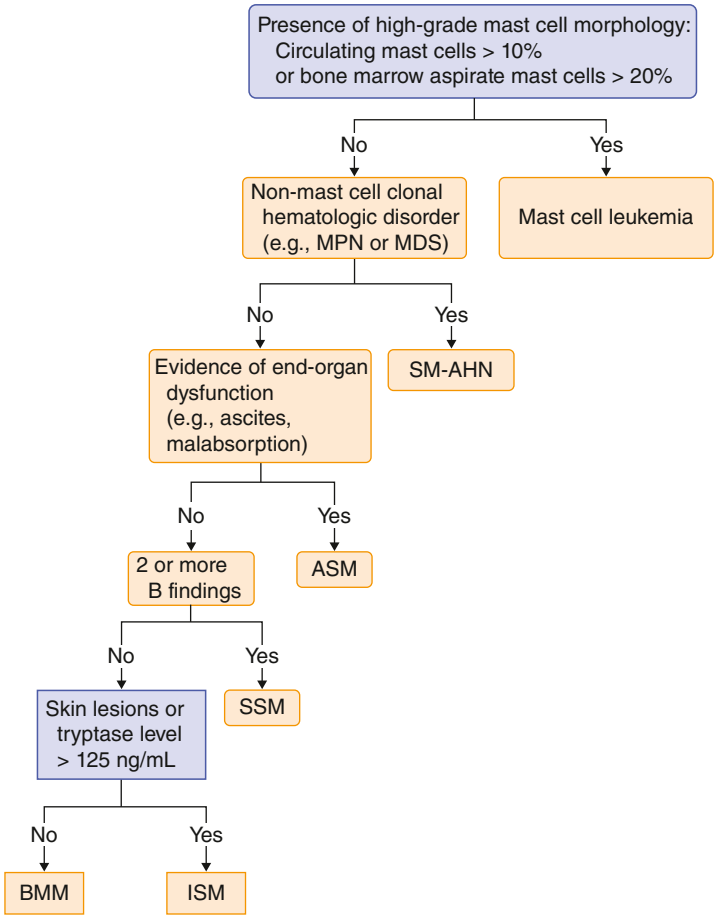

FIGURE 235-4. An algorithm for classification of systemic mastocytosis. ASM = aggressive systemic mastocytosis; BMM = bone marrow mastocytosis; ISM = indolent systemic mastocytosis; MDS = myelodysplastic syndromes; MPN = myeloproliferative neoplasms; SM-AHN = systemic mastocytosis with associated clonal hematologic non–mast cell lineage disease; SSM = systemic smoldering mastocytosis.

defined by a tryptase level less than 125 ng/mL and the absence of skin lesions, of B- and C-findings, and of features of advanced disease.

Aggressive systemic mastocytosis is a rare category characterized by the presence of organ dysfunction resulting from destructive mast cell infiltration. Aggressive systemic mastocytosis includes systemic findings (so-called C findings) that may involve the hematopoietic, gastrointestinal, and skeletal systems in the form of cytopenias (neutrophils <1000/μL, hemoglobin <10 g/dL or platelets <100,000/μL), palpable splenomegaly with hypersplenism, malabsorption with hypoalbuminemia with or without weight loss, hepatomegaly with portal hypertension and ascites, and large osteolytic lesions (≥2 cm in diameter) with pathologic fractures.

Mast cell leukemia is characterized by 10% or more mast cells in the peripheral circulation or 20% or more mast cells in bone marrow aspirate smears, or both. To diagnose mast cell leukemia, the percentage of mast cells in bone marrow aspirate smears should be assessed in an area of the slide that is sufficiently distant from the spicules. *Mast cell sarcoma* is a rare diagnosis characterized by malignant and invasive solid mast cell tumor.

A subset of patients who have recurrent idiopathic or Hymenoptera venom–induced anaphylaxis also have evidence of clonal mast cells carrying the D816V *KIT* mutation or aberrantly expressing surface CD25, without fully meeting the diagnostic criteria and without displaying urticaria pigmentosa skin lesions. Such patients are provisionally referred to as having a monoclonal mast cell activation syndrome.

TREATMENT

The major goal of treatment for all categories of mastocytosis is to control symptoms, although symptomatic treatment does not change the natural course of the disease. For disease categories with a poor prognosis (i.e., systemic mastocytosis with associated clonal hematologic non–mast cell lineage disease, aggressive systemic mastocytosis, mast cell leukemia, and mast cell sarcoma) or disabling symptoms not controllable by symptomatic management,[11] therapy may be targeted at reducing the number of mast cells.[12]

Medical Therapy

Symptomatic Treatment

Adults with cutaneous and indolent systemic mastocytosis are treated symptomatically. Pruritus in adults usually responds to scheduled doses of histamine$_1$-receptor blocker antihistamines, such as loratadine (10 mg daily), fexofenadine (180 mg with water daily), or cetirizine (5 to 10 mg daily). These doses may be doubled to twice daily if needed. Sedating antihistamines, such as hydroxyzine (25 mg three times daily) or diphenhydramine, may be used before bedtime.

Photochemotherapy (oral psoralen plus ultraviolet A) or phototherapy results in symptomatic improvement and temporary fading of the pigmented skin lesions in up to 50% of patients who have refractory pruritis. The side effects of phototherapy, including increased risk of skin cancer, should be considered.

Histamine$_2$-receptor blocker antihistamines, such as famotidine (20 mg once or twice daily), are usually prescribed as a first-line treatment for patients with gastrointestinal complaints, such as heartburn, nausea, and abdominal pain. Proton pump inhibitors (see Table 124-1) may be added in patients whose abdominal symptoms are refractory to histamine$_2$-receptor blockers. The dual H$_1$- and serotonin-receptor antagonist cyproheptadine (4 mg three times daily) may be used for diarrhea, flushing, or headaches. Oral cromolyn sodium (adult dose, 200 mg four times daily) can reduce abdominal pain, diarrhea, nausea, vomiting, and pruritus, but its benefits vary among patients. Low to moderate doses of systemic glucocorticoids can be beneficial in unusual cases of aggressive mastocytosis that present with recalcitrant diarrhea associated with malabsorption or with hepatomegaly and ascites. Montelukast (10 mg daily) or zileuton may be useful for pruritis or abdominal pain when used in conjunction with H$_1$- and H$_2$-receptor antagonists, but patients should be warned about psychiatric side effects. Masitinib, which is a KIT and LYN kinase inhibitor, has been used to treat severely symptomatic indolent or smoldering systemic mastocytosis under expert oversight.[A1] However, it is not FDA-approved, and fewer than 20% of patients have a 75% or greater improvement from baseline.

Self-administered epinephrine should be considered for all patients even if they do not have any history of anaphylactic episodes, hypotensive episodes, presyncope, or syncope. These episodes should be treated as systemic anaphylaxis (Chapter 233). Omalizumab (a humanized anti-IgE monoclonal antibody) has reduced recurrent anaphylactic or mast cell activation symptoms in case reports, but it is not FDA-approved for this indication.

Cytoreductive Therapies

Cytoreductive therapy is generally considered for advanced disease variants associated with a poor prognosis. Some patients with recurrent life-threatening episodes of mast cell mediator release unresponsive to conventional therapy may also be candidates for cytoreductive therapy after careful consideration of risks and benefits.

Tyrosine kinase inhibitors are considered first-line therapy owing to their efficacy, tolerability, and low rate of adverse effects.[13] Avapritinib is a selective D816V KIT inhibitor that can provide clinical and molecular remission in up to 75% of patients who have advanced mastocytosis with the *KIT* D816V mutation.[14] Avapritinib is approved by the U.S. Food and Drug Administration for advanced disease and is investigational for indolent systemic mastocytosis at the time of this writing. Avapritinib is contraindicated in patients whose platelet counts are less than 50,000/μL because of an increased risk of intracranial bleeding.

Midostaurin (100 mg twice daily), which is a multikinase inhibitor whose targets include the common *KIT* D816V driver mutation, provides a 17% overall response rate in patients with advanced systemic mastocytosis, including mast cell leukemia.[15] Nausea and vomiting are its common adverse effects. Bezuclastinib and elenestinib are other tyrosine kinase inhibitors that are in clinical trials for systemic mastocytosis.

Interferon alfa-2b (0.5 to 5 million units, three to five times per week), alone or with prednisone, can partially improve clinical and laboratory abnormalities in approximately 50% of patients with aggressive systemic mastocytosis, patients with osteoporosis and pathologic fractures, and patients with recalcitrant recurrent anaphylaxis, although complete histopathologic and molecular remissions are rare. Interferon alfa is difficult to tolerate because of its many side effects, including influenza-like symptoms, bone pain, and depression.

Cladribine (a synthetic purine analog given as 0.14 mg/kg in an infusion or subcutaneously on days 1 to 5 and repeated at 4 to 12 weeks until one to nine courses) provides a 22% response rate for indolent and aggressive mastocytosis. However, it is associated with a high risk for lymphopenia, neutropenia, and opportunistic infections.

Ancillary and Other Therapies

Avoidance of the triggers of mast cell degranulation is an important adjunct to the pharmacologic treatment of symptoms. General anesthesia and surgery impose an additional risk because several agents that are used perioperatively (e.g., muscle relaxants, opioid analgesics, and nonsteroidal anti-inflammatory drugs) can induce acute mast cell degranulation. Prior surgical and anesthesia records should be obtained if available, and an appropriate strategy for the anesthetic management of the patient should be determined, with close communication involving the patient, anesthesiologist, surgeon, and an allergist.

Acute mast cell leukemia usually is treated with polychemotherapy as for acute myeloid leukemia (Chapter 168). Hematopoietic stem cell transplantation (Chapter 163) has yielded variable results for the treatment of mast cell disease, but occasional complete remissions have been reported. Non–mast cell clonal hematologic disorders associated with mastocytosis should be treated according to the standard-of-care guidelines for those disorders, regardless of the presence of mastocytosis.

Venom immunotherapy is recommended for patients who have a history of systemic reactions to Hymenoptera and who have evidence of IgE-mediated sensitization (by blood or skin allergy testing). Most experts recommend that such immunotherapy be continued indefinitely because fatalities have been reported after its discontinuation. If osteoporosis is detected by bone densitometry, it should be treated per standard recommendations (Chapter 225).

PROGNOSIS

The prognosis for mastocytosis varies by the category of disease. Most patients have an indolent course. At least 50% of patients with pediatric-onset cutaneous mastocytosis have complete resolution of the disease by adolescence, and the great majority of the other 50% of patients experience improvement or fading of the skin lesions.

Patients with indolent systemic mastocytosis and bone marrow mastocytosis usually have a normal life expectancy despite persistent symptoms, and progression to a more advanced category is unusual (less than 5% of cases). Factors associated with poorer prognosis includes the absence of urticaria pigmentosa, older age at onset of symptoms, an elevated level of serum lactate dehydrogenase or alkaline phosphatase, thrombocytopenia, anemia, peripheral blood smear abnormalities, and detectability of the D816V *KIT* mutation in peripheral blood.

The prognosis for systemic mastocytosis with associated hematologic neoplasm is determined by the prognosis for the associated hematologic disorder. Aggressive systemic mastocytosis and mast cell leukemia have poor prognoses, with median survival times of less than 3 years and less than 1 year, respectively. Prognostic factors associated with advancement into secondary mast cell leukemia or acute myeloid leukemia include age over 60 years, a hemoglobin concentration less than 10 g/dL, a platelet count less than 100,000/μL, or the presence of one or more mutations in *SRSF2*, *ASXL1*, and/or *RUNX1*.[16]

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236 APPROACH TO THE PATIENT WITH RHEUMATIC DISEASE

VIVIAN P. BYKERK AND MARY K. CROW

DEFINITION

Rheumatic diseases are disorders of connective tissue in which general or localized inflammation is associated with pain, weakness, or loss of function attributable to joints, the spine, muscles, and/or related soft tissues. Systemic features and extramusculoskeletal features include stiffness, fever, weight loss, skin rashes, cardiopulmonary abnormalities, ocular inflammation, and renal dysfunction, often in distinct patterns, and are used to classify each disease.

Many of these diseases affect females more than males, with ankylosing spondylitis being a notable exception. This pattern is most striking in systemic lupus erythematosus (Chapter 245), which affects 8 to 10 women for every 1 man and typically has its onset in the childbearing years. Rheumatoid arthritis (Chapter 243) has a female-to-male ratio of approximately 3 : 1 and typically has its onset in the later adult decades.

Classification of Rheumatic Diseases

More than 100 types of rheumatic diseases have been described. Although the pathogenesis is usually dichotomized as degenerative or inflammatory, these diseases (Table 236-1) are usually subdivided as (1) diseases that are associated with degeneration of connective tissues attributable to trauma, structural/mechanical imbalances, or inherent early demise of cellular components; (2) diseases that are associated with systemic autoimmunity, often linked with measurable autoantibodies that can manifest primarily with synovitis, widespread organ involvement, inflamed blood vessels, or inflammation of muscle; (3) other inflammatory connective tissue diseases involving more dense tissues, not associated with the formation of autoantibodies, and hence termed *seronegative rheumatic diseases* or *spondyloarthropathies*; (4) diseases in which inflammation of the vasculature, particularly small, medium, or large arteries, is the predominant feature; (5) autoinflammatory diseases that can be associated with crystal deposition or genetic mutations involving cytokine pathways; and (6) pain syndromes that often must be considered in the context of these diseases, in which some syndromes appear to be comorbid and closely linked to the underlying rheumatic disease, such as diffuse pain associated with Sjögren syndrome, hypermobility of connective tissue, or regional pain syndromes that are anatomically linked to mechanical disruption. Patients who present with generalized pain syndromes require investigation to exclude a connective tissue disease. Increasingly, genomic phenotypes[1,2] are being associated with diseases as they have been categorized, and in some cases specific immunologic pathways and mediators have allowed grouping of a set of rheumatic diseases previously considered more distinct.

Mimics of rheumatic diseases exist, and clinicians must be mindful of considering these when evaluating a patient for a rheumatic disease. For instance, arthropathies and syndromes resembling a rheumatic disease can occur in the settings of both infection and malignancy. Autoimmune phenomena are increasingly being recognized in the setting of malignancy or as a consequence of treatment of malignancy with immune checkpoint inhibitors.[3] Red flags for each need to be considered in the assessment of a patient for possible rheumatic disease.

EPIDEMIOLOGY

In adults, the six prototypical rheumatic diseases most often assessed and managed by rheumatologists are rheumatoid arthritis (Chapter 243),[4] systemic lupus erythematosus (Chapter 245),[5] systemic sclerosis (Chapter 246), spondyloarthropathies (primarily ankylosing spondylitis and psoriatic arthritis; Chapter 244), Sjögren syndrome (Chapter 247), and vasculitis (Chapter 249). These diseases are ubiquitous throughout the world (Table 236-2), and for the most part they have a similar incidence globally. Autoimmune rheumatic diseases are also among the leading causes of death and morbidity in the industrial world, in part related to associated comorbid diseases, particularly cardiovascular disease, and they contribute to a significant socioeconomic burden. Increasing evidence points to risks for their genesis relating to environmental factors, socioeconomic factors, and exposure to infectious agents, ultraviolet radiation, and pollutants. Smoking, in particular, has been associated with an increased risk for systemic lupus erythematosus and rheumatoid arthritis in genetically susceptible individuals in Western cultures. Effects of migration elucidate some of these risks. For instance, Africans who migrate far away from their native environmental and cultural origins appear to have an increased susceptibility to systemic lupus erythematosus. Also, reports have linked occupational exposures, such as silica dust, mercury, pesticides, solvents, and metals, to an increased risk for systemic lupus erythematosus and rheumatoid arthritis.

In some cases, geographic clusters of a rare autoimmune disease indicate specific genetic determinants. For example, with systemic sclerosis, higher incidence, prevalence, and mortality rates have been reported in African American populations compared with White populations, and the prevalence has been reported as higher in southern Europe, particularly in Italy (prevalence of 7 to 33 per 100,000). Additionally, social and demographic factors may contribute to the epidemiology of rheumatic diseases. For example, the prevalence of systemic lupus erythematosus is reported as very high in Georgia, United States, whereas the prevalence of ankylosing spondylitis is rare in malaria endemic regions where HLA-B27 genotypes are rare. Inflammatory arthropathies, including

TABLE 236-1 COMMON RHEUMATIC DISEASES BROADLY CLASSIFIED ACCORDING TO PATHOGENESIS

DEGENERATIVE DISEASES OF JOINTS, BONE, AND SOFT TISSUES	SYSTEMIC AUTOIMMUNE DISEASES	SERONEGATIVE SPONDYLOARTHROPATHIES	VASCULAR RHEUMATIC DISEASES	AUTOINFLAMMATORY DISEASES	PAIN SYNDROMES
Osteoarthritis	Rheumatoid arthritis	Ankylosing spondylitis	ANCA- associated vasculitis	Adult-onset Still disease	Regional myofascial pain syndromes
Diffuse idiopathic skeletal hyperostosis (DISH)	Systemic lupus erythematosus	Psoriatic arthritis	Temporal artery vasculitis	Crystal diseases	Specific soft tissue syndromes (e.g., tendinopathies, enthesopathies, bursitis)
Degenerative disc disease	Sjögren syndrome	Reactive arthritis	Polymyalgia rheumatica	Pediatric periodic fever syndromes	Adhesive capsulitis
Spinal stenosis	Inflammatory myopathies (polymyositis, dermatomyositis)	Enteropathic arthritis	Behçet disease		Complex regional pain syndrome type 1 (reflex sympathetic dystrophy)
Osteoporosis	Systemic sclerosis				Hypermobility syndromes
					Fibromyalgia*

*The only pain disorder that has not been associated primarily with inflammation.
ANCA = antineutrophil cytoplasmic antibody; DISH = diffuse idiopathic sclerosing hyperostosis (also linked to metabolic factors, including elevated growth hormone).

ABSTRACT

Rheumatic diseases are common and an important cause of reduced quality of life, increased comorbidity, and reduced life expectancy. These diseases also result in a significant socioeconomic burden. A clinical-pathologic framework helps categorize patients who present with signs and symptoms suggestive of a rheumatic disease. A systematic approach to diagnosis and treatment can reduce the adverse clinical and economic consequences of these diseases.

KEYWORDS

rheumatic diseases
diagnosis
inflammatory arthritis
systemic autoimmune disease
osteoarthritis
vascular disease
pain

TABLE 236-2 WORLDWIDE PREVALENCE* AND INCIDENCE OF RHEUMATIC DISEASES ASSOCIATED WITH AUTOIMMUNITY

DISEASE	NORTH AMERICA	CENTRAL AMERICA	SOUTH AMERICA	EUROPE	MIDDLE EAST	ASIA	SUB-SAHARAN AFRICA	AUSTRALIA
Rheumatoid arthritis	600-1000 (40)	400-2000	100-500	200-900 (2-7)	200-1500	100-800 (40-90)	Rare - 900	2000
Systemic lupus erythematosus	20-60 (2-7)	50-60 (5)	N/A	20-70 (2-7)	N/A	20-70 (3)	Rare	20-80 (11)
Systemic sclerosis	13-28	N/A	N/A	<10-15 (<2)	N/A	<10	N/A	23 (2)
Spondyloarthropathy (primarily ankylosing spondylitis)	50-130 (7)	N/A	N/A	100-850 (2-9)	500	10-240	Rare	N/A
Sjögren syndrome	320 (4)	N/A	N/A	200-600 (4-5)	N/A	330-700 (China)	N/A	N/A

*Prevalence (annual incidence) per 100,000 by world regions.
N/A = not available.
Data from Shapira Y, Agmon-Levin N, Shoenfeld Y. Geoepidemiology of autoimmune rheumatic diseases. *Nat Rev Rheumatol*. 2010;6:468-476; and Chaaya M, Slim ZN, Habib RR, et al. High burden of rheumatic diseases in Lebanon: a COPCORD study. *Int J Rheum Dis*. 2012;15:136-143.

rheumatoid arthritis and ankylosing spondylitis, have a higher prevalence in North American Native populations.

PATHOBIOLOGY

Rheumatic diseases are often referred to as *connective tissue diseases,* because connective tissue is most often the target of inflammatory and/or autoimmune processes. Connective tissue, which is the most abundant tissue in the body, supports and connects other tissues and organs and hosts immune cells and their mediators. Loose and dense connective tissues include cellular components and extracellular matrix. Loose connective tissue fills space between muscle sheaths and encases blood and lymphatic vessels. Reticular fibers provide the skeleton of muscle cells, nerves, and capillaries. Dense connective tissue supports the body's soft tissues and includes more collagen fibers and fewer cells. Connective tissue is found in the dermis, joint capsules, cartilage, bone, and fascia of muscles, and it forms tendons, ligaments, and points of connection where these insert into bone (aponeurosis). Some cells in connective tissue, such as mast cells or macrophages, are migratory, whereas some, such as fibroblasts, fibrocytes, and reticular cells, are resident cells. Fibroblasts are responsible for synthesizing collagen, elastic reticular fibers, and ground substance of extracellular matrix, including tissue fluids and collagen fibers. In health, connective tissue is integrated with cells associated with the body's defense system (e.g., lymphocytes, plasma cells, macrophages, dendritic cells, and eosinophils) and provides structure and support for the vasculature. However, the close proximity of connective tissue to blood vessels, the presence of innate immune cells, and the capacity for influx of immune cells under certain pathologic conditions make connective tissue the ideal setting for immune- and vascular-mediated diseases.

CLINICAL MANIFESTATIONS

Primary care and hospital-based health care providers are often the first to evaluate a patient with an evolving rheumatic disease, and they need to be attuned to the presenting features to make a timely diagnosis. The clinical manifestations of rheumatic diseases range from mild joint-related symptoms to life- or organ-threatening conditions. The presence of constitutional, systemic, and joint symptoms should always include rheumatic disease in the differential diagnosis.

Joint Symptoms as a Common Presenting Feature

Almost all rheumatic diseases can manifest with joint-related symptoms and signs. Typically, pain, stiffness, swelling, and difficulty with joint function are the main symptoms. In some forms of joint inflammation, erythema can be prominent, as in the case of autoinflammatory diseases such as gout or pseudogout (Chapter 252) and in infectious arthritis (Chapter 251).

The pattern of joint involvement, its particular distribution, the number of inflamed joints, the speed of onset, duration, and timing of maximal symptoms all provide clues to diagnosis. Regardless of pathogenetic subclassification, certain patterns can point to inflammatory immune-mediated arthritis, and others to a degenerative process. For instance, joint pain that is worse in the morning, associated with prolonged stiffness, and improves as the day goes on and with activity is a classic presentation of inflammatory joint disease such as rheumatoid arthritis (Chapter 243) or spondyloarthritis (Chapter 244). Conversely, pain that is worse with activity, better with rest, and associated with a short period of stiffness after resting, is typical of osteoarthritis (Chapter 241), which is a predominantly degenerative arthritis.

Location provides a clue to broad classification. Patients describing "pain all over" may have a primary pain syndrome. However, pain with an inflammatory pattern localized to the spine or an enthesis (site of ligament insertion) is more likely to indicate a seronegative spondyloarthropathy.

A patient presenting with an inflammatory pattern of symptoms predominantly involving the small joints of the hands and feet is more likely to have one of the autoimmune rheumatic diseases associated with either a positive antinuclear antibody (ANA), rheumatoid factor (RF) or anti–citrullinated peptide antibody (ACPA). Asymmetric large and small joint pain, swelling, and erythema are more characteristic of psoriatic arthritis. Joint symptoms do not always indicate joint disease. Although a third of people might report having a form of debilitating arthritis, these symptoms can include periarticular and soft tissue syndromes common to many rheumatic diseases. The various locations of articular and nonarticular patterns of pain (Chapter 26; Fig. 236-1), including involvement of tendons, ligamentous insertions, and fascia, as well as the organ involvement that is typical of specific rheumatic diseases,[6] highlight the need to assess physical manifestations when making a diagnosis of any rheumatic disease.

Nonspecific Clinical Presentations

When present in the context of fever or cutaneous manifestations, including rashes, vasculitis and systemic lupus erythematosus (Chapter 245) must be considered. Sicca symptoms, though pathognomonic of Sjögren syndrome (Chapter 247), can occur concurrently in patients with systemic lupus erythematosus. Systemic features such as myalgias or fatigue are common to almost all rheumatic diseases regardless of their classification, but true muscle weakness may be the only presenting complaint of an inflammatory myopathy (Chapter 248). Renal involvement is common in seropositive systemic autoimmune diseases and vasculitis.

Cutaneous Manifestations

Although cutaneous manifestations are frequent in patients with seropositive autoimmune diseases, particularly systemic lupus erythematosus (Chapter 245), they are important manifestations of all autoimmune diseases. A nonblanching purpuric rash can indicate a vasculitis, and rashes involving specific extensor regions are common to dermatomyositis (Chapter 248). In cases of systemic lupus erythematosus or dermatomyositis, rashes are triggered or worsened by exposure to ultraviolet light and occur in a light-exposed distribution. Rashes of vasculitic origin can indicate either the presence of an autoimmune disease such as systemic lupus erythematosus or an inflammatory vascular disease such as antineutrophil cytoplasmic antibody (ANCA)-associated vasculitis. These rashes tend to be present for days and are often palpable, and a tissue biopsy of the lesions will be very helpful in diagnosis. Rashes can be transient. In adult-onset Still disease (an adult form of systemic inflammatory arthritis classified as an autoinflammatory disease; Chapter 240), patients present with daily spiking fevers, peaking late in the day, associated with a salmon-colored evanescent blanching rash lasting only 1 to 2 hours. The specific location of a rash aids in diagnosis. A facial rash that spares the nasolabial folds is classic for lupus. A rash that does not spare the nasolabial folds suggests rosacea. Psoriasis is almost always present in psoriatic arthritis (a spondyloarthropathy variant). Although psoriasis is often widespread, involving extensor surfaces, it can be missed if there are very few lesions or if it is located in areas that are not easily seen (intertriginous regions, such as in the ear, umbilicus, buttock creases,

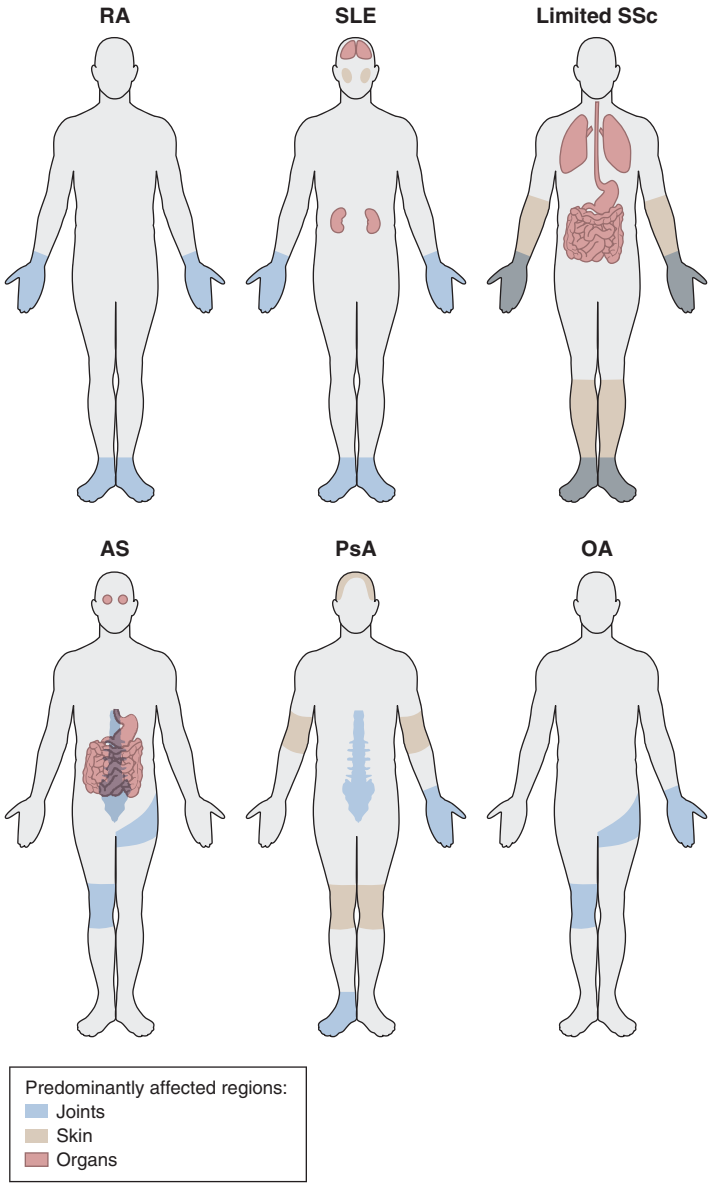

FIGURE 236-1. Patterns of joint and organ involvement in rheumatic disease. Characteristic patterns of joint and organ distribution and involvement distinguish among rheumatic diseases and aid in diagnosis. AS = ankylosing spondylitis; OA = osteoarthritis; PsA = psoriatic arthritis; RA = rheumatoid arthritis; SLE = systemic lupus erythematosus; SSc = systemic sclerosis. (From Ospelt C, Frank-Bertoncelj M. Why location matters: site-specific factors in rheumatic diseases. *Nature Rev Rheumatol*. 2017;13:433-442.)

or scalp) or if it involves only the nails. The rash of psoriasis can be seen in any of the variants of the spondyloarthropathies. Occasionally rheumatoid arthritis (Chapter 243) will manifest with nodules over the extensor surfaces; however, nodules over extensor surfaces may also indicate gouty tophi (Chapter 252).

Skin tightness is the hallmark of systemic sclerosis (Chapter 246), often referred to as scleroderma, which most often involves the extremities. Patients typically present initially with swelling of the digits, followed by tightness of the hands and ultimately tightness of the skin. Raynaud phenomenon, though not specific to systemic sclerosis, frequently precedes its onset, often by many years. Skin tightness can progress to involve the face, arms, and, in the case of diffuse systemic sclerosis, trunk, back, and legs. Distal tightening of the skin, presence of telangiectasias, and digital ulcers can be seen.

Systemic Manifestations

Rheumatologic diseases eventually can involve every organ system but particularly can cause glomerulonephritis (Chapter 113, especially systemic lupus erythematosus), interstitial lung disease (Chapter 80, especially in systemic sclerosis and rheumatoid arthritis), renovascular disease (Chapter 110, especially systemic sclerosis), pericardial and pleural disease (Chapters 62 and 86, especially systemic lupus erythematosus),[7] and neurologic manifestations (especially systemic lupus erythematosus).

Specific Clinical Scenarios

Degenerative Rheumatic Diseases

Degenerative joint diseases, which are associated with advancing age, mainly include osteoarthritis (Chapter 241) and degenerative disc disease (Chapter 369). In general, these disorders are not associated with rashes or nonspecific constitutional symptoms.

Autoimmune Rheumatic Diseases

Autoimmune rheumatic diseases include systemic lupus erythematosus, rheumatoid arthritis, systemic sclerosis, primary Sjögren syndrome, idiopathic inflammatory myositis, and the systemic vasculitides. These diseases involve multiple organ systems and are heterogeneous in their clinical manifestations. Each symptom is associated with specific signs. Cutaneous manifestations, sicca symptoms (of dry eyes or mouth), mucosal ulceration, fevers, alopecia, and Raynaud syndrome are common and often described by patients. These symptoms can occur alone or in addition to symptoms affecting the joints and muscles.

Spondyloarthropathies

Ankylosing spondylitis (Chapter 244), which manifests with lower spine disease and earlier spinal fusion, is more common in males than females. Sacroiliitis is the hallmark of this disease. Disease in females may present more atypically with cervical or thoraco-lumber symptoms. Localization of symptoms to the neck and thoraco-lumbar spine, sacroiliac joints, large upper and lower extremity joints, and nerve roots can be used to differentiate ankylosing spondylitis from rheumatoid arthritis. The typical presence of psoriatic skin lesions in patients with psoriatic arthritis can be a distinguishing feature from rheumatoid arthritis. Spinal inflammation also can be associated with inflammatory bowel disease (Chapter 127), not infrequently in the mid or upper spine as opposed to the sacroiliac joints.

Vasculitis

The vasculitic syndromes are generally grouped based on the size of the involved vessel (Chapter 249). Polymyalgia rheumatica (Chapter 250) is a common inflammatory rheumatic disease of the elderly and shares many pathogenetic and epidemiologic features with giant cell arteritis, a form of older-onset vasculitis. Patients complain of aching around the neck and bilateral involvement of the shoulder and hip girdles, along with significant stiffness that is most problematic in the morning. The onset of symptoms can be abrupt or insidious over weeks to months.

Autoinflammatory Diseases

Gout (Chapter 252), which is the most common and prototypical autoinflammatory disease, occurs more often in middle-aged and older men and is increasing in prevalence. An exquisitely painful joint with periarticular erythema and swelling are presenting features. Tophi that might be confused with rheumatoid nodules can be seen. Calcium pyrophosphate deposition disease (pseudogout) can have a similar presentation. Rare autoinflammatory diseases (Chapter 240) based on mutations in genes involved in inflammatory pathways are more typically diagnosed in children.[8]

Pain and Pain Syndromes

Pain (also see Chapter 26) is a common and nonspecific, but very important, symptom central to nearly all rheumatic diseases. The location, distribution, and patterns of pain should be elicited, along with temporal features, triggers, migratory or alleviating features, and prior history of physical or psychological trauma. In regional pain syndromes (Chapter 26), the distribution of pain is the key clue to the diagnosis. Diffuse pain without evidence of underlying pathology associated with inordinate levels of fatigue, difficulty coping, and intricately detailed descriptions of pain using colorful analogies herald fibromyalgia (Chapter 253).

Most pain syndromes are regional nociceptive pain syndromes. For instance, a regional pain syndrome relating to a mechanical neck and shoulder structural problem will result in the patient having pain not only in the neck and involved shoulder but also the trapezius, upper chest, axilla, and upper and/or lower arm and hand. A large proportion of patients who present with musculoskeletal pain will have regional pain relating to muscular imbalances or postural factors with or without a degenerative arthritis. Regional pain can be associated with a combination of muscular spasm, atrophy, and secondary impingement of tendons. Pain in a distal extremity after trauma

or surgery associated with a cold shiny extremity is suggestive of complex regional pain syndrome.

DIAGNOSIS

A comprehensive history is key to an evaluation of a patient with a rheumatic disease. In addition to considering age and gender, a patient's personal history, including marital status, occupation, and psychosocial factors, helps to elucidate a patient's diagnosis, prognosis, and treatment options. Specific clues can be helpful in making a diagnosis of one of the rheumatic diseases (Table 236-3).

Assessing clinical signs and symptoms is the cornerstone of diagnosis. Most rheumatic disorders will present with symptoms that involve, or seem to involve, joints. Pain can be limited to a specific joint or group of joints or periarticular structures. Querying the patient to determine the pattern of symptoms—whether pain, swelling, or stiffness associated with joints—is key to narrowing the differential diagnosis of a rheumatic disease. Joint symptoms should be assessed for inflammatory features such as prolonged stiffness, pain at rest, or noninflammatory and mechanical features, such as instability or giving way, locking, or increased symptoms with use. Patterns of joint involvement (see Fig. 236-1)—whether primarily small joints of the hands, wrist, and feet; large joints of the elbows, knees, ankles, or "root" (shoulders or hips); or spinal involvement—will further point to a specific diagnosis. Moreover, questions regarding recent illnesses, travel, exposure to possible infectious pathogens, and presence or absence of systemic features such as fever, fatigue, or weight loss will provide important clues. Appreciation of signs and symptoms indicating extra-articular features, particularly cutaneous, pulmonary, renal, neurologic, or vascular manifestations, will guide the differential diagnosis, and further investigations will help to determine the definitive diagnosis as well as the prognosis and required intensity of therapy.

The presence of one rheumatic disease can be associated with comorbid manifestations unrelated to connective tissue. For example, myocardial infarction is more common in many patients with rheumatic diseases. Immobility or treatment-related factors leading to obesity can increase risks for diabetes and lower joint degeneration.

The Medical History

Age and Gender

Rheumatic diseases that typically manifest in childhood include genetically based disorders, such as hemophilia associated with arthritis and a number of autoinflammatory conditions. Juvenile idiopathic arthritis refers to forms of arthritis in which the onset occurs before the age of 16 years. Autoimmune rheumatic diseases and inflammatory rheumatic diseases (e.g., spondyloarthropathies, rheumatoid arthritis,[9] and systemic lupus erythematosus) can begin in the teenage years or in young adulthood, whereas degenerative conditions such as osteoarthritis rarely begin to manifest until later in life. The peak onset of rheumatoid arthritis occurs in the late middle years, although onset can occur at almost any time in life. Elderly people are more prone to polymyalgia rheumatica, but it should be considered at all ages. Autoimmune diseases are more common in women, whereas spondyloarthropathies can be equally common in men and women. Gouty arthritis is more common in men and rarely attacks women before menopause.

Occupation and Recreation

Occupation and recreational activities may give rise to physical and psychological stresses. The demands of a patient's occupation need to be understood, particularly when repetitive activities may contribute to the development of degenerative joint disease or to regional pain syndromes. Similarly, trauma and repetitive actions from sports, including prior injuries, can be a significant contributor to degenerative joint disease.

Family History

It is important to obtain a complete family history because autoimmune diseases, spondyloarthropathies, and gout occur with an increased incidence in families. It is common to see family pedigrees in which different forms of autoimmunity occur throughout a family. Also, generalized osteoarthritis that involves the hands and other joints commonly runs in families.

Concomitant Medication Use

A careful medication history is essential because concomitant medications may contribute to the genesis of a rheumatic disease. For example, diuretics can increase hyperuricemia and the risk for gouty arthritis. Minocycline, hydralazine, and rarely isoniazid can be associated with lupus-like presentations. Antibiotics in the fluoroquinolone class have been associated with enthesopathies.

Habits and Social Circumstances

Smoking has increasingly been associated with rheumatoid arthritis and systemic lupus erythematosus. Poor socioeconomic circumstances and psychosocial or physical stress may contribute to the severity of symptoms or access to care and should be considered in planning management strategies.

TABLE 236-3 CLINICAL FEATURES AND CLUES TO FACILITATE DIAGNOSIS FOR EACH CATEGORY OF RHEUMATIC DISEASE

DEGENERATIVE DISEASES OF JOINTS, BONE, AND SOFT TISSUES	SYSTEMIC AUTOIMMUNE DISEASES	SERONEGATIVE SPONDYLO-ARTHROPATHIES	VASCULAR RHEUMATIC DISEASES	AUTOINFLAMMATORY DISEASES	PAIN DISORDERS
Investigate if persistent symptoms of pain >6 wk or failure of conservative measures (physical therapy, NSAIDs) If at risk for bone loss and fragility fracture, consider osteoporosis	Often manifest with inflammatory joint pain and/or swelling, constitutional symptoms, skin manifestations, multiorgan involvement Perform ANA, RF, ESR, CRP	Consider if these features are present: psoriasis, inflammatory back pain, known associated nonarticular features (e.g., uveitis, inflammatory bowel disease, urethritis, enthesitis, dactylitis)	Consider if the following are present: infarcted tissue, vasculitic rashes, pulmonary hemorrhage, acute or subacute renal syndromes	All can present with fever Genetically determined. Mediated by cytokines— e.g., interleukin-1 or TNF-α In adults, consider crystal diseases	Consider if pain is in excess of findings, if history of resolved trauma or repetitive strain, referred pain symptoms, diffuse pain, if high pain levels
INITIAL INVESTIGATIVE APPROACH TO CONFIRM SUSPECTED RHEUMATIC DISEASE IN EACH CATEGORY					
Image specific region associated with persistent pain (consider additional imaging in areas that may be referring pain) If osteoporosis is a concern, perform BMD and investigate using laboratory tests, including calcium, 25-OH D, and/or PTH to begin evaluation for metabolic bone diseases	Investigations should specifically target suspected diseases Specific testing should include CK if weakness or myalgia; anti-CCP (ACPA) and RF if synovitis is present; ANA in screening rheumatic disease, and dsDNA, C3, C4, ENA if SLE or sicca symptoms present	Imaging of sacroiliac (SI) joints (radiographs if long-standing symptoms, MRI if more recent onset) HLA-B27 testing if inflammatory back pain or SI pain most predominant, clinical suspicion high for inflammatory back pain, but imaging is negative	Laboratory testing should include ANCA Anti-PR3 Anti-MPO Acute phase reactants (ESR, CRP) Tissue sampling of involved organs to facilitate pathophysiologic classification	For suspected crystal disease, perform aspiration of synovial fluid or tophus and examine under polarized light microscopy	Usually a diagnosis of exclusion, based on physical examination In complex regional pain syndrome, tendonitis or enthesitis, specific physical findings and imaging can facilitate diagnosis

25-OH D = calcitriol; ACPA = anti–citrullinated peptide antibodies; ANA = antinuclear antibodies; ANCA = antinuclear cytoplasmic antibodies; anti-CCP = anti–cyclic citrullinated peptide; anti-MPO = anti-myeloperoxidase; anti-PR3 = anti-proteinase-3; BMD = bone mineral density scan; CK = creatinine phosphokinase; CRP = C-reactive protein; dsDNA = anti–double-stranded DNA; ENA = antibodies to extractable nuclear antigens (e.g., Ro, La, Sm, RNP, Scl70, Jo-1); ESR = erythrocyte sedimentation rate; MPO = myeloperoxidase; MRI = magnetic resonance imaging; NSAIDs = nonsteroidal anti-inflammatory drugs; PR3 = proteinase 3; PTH = parathyroid hormone; RF = rheumatoid factor; SLE = systemic lupus erythematosus; TNF-α = tumor necrosis factor-α.

Onset and Evolution of Symptoms

Knowledge of the pattern of onset, location, and evolution of symptoms is essential to make an accurate diagnosis of a rheumatic disease. Symptoms that develop over hours to days typically suggest an inflammatory, infectious, or traumatic process. When symptoms persist for more than 6 weeks, the onset is considered subacute, and the disease is considered chronic. Early in the presentation of some rheumatic diseases, the symptoms can be intermittent or palindromic before becoming constant. In patients who have the sudden onset of joint pain and swelling, particularly involving one or a few joints, an infectious or crystalline etiology should be considered.

Pain and Stiffness

The assessment of pain should include a description of its onset, constancy/chronicity, severity, quality, factors that trigger or improve it, and location and radiation of the pain. Stiffness, often described as tightness or linked to difficulty with movement or function, should be determined in terms of location (e.g., is it in a particular joint or more diffuse) and timing and duration (e.g., occurring after a period of rest). Stiffness that resolves in 10 to 15 minutes is more characteristic of osteoarthritis. In inflammatory disease, stiffness typically lasts longer, often at least 1 hour and even all day.

Specific Joint Symptoms

The distribution of joint involvement is key to making a diagnosis of a rheumatic disease (see Fig. 236-1). Monoarthritis describes symptoms in a single joint; oligoarthritis (or pauciarthritis) refers to symptoms in two to four joints; and polyarthritis indicates involvement of at least five joints. Peripheral arthritis involves an extremity, whereas spinal involvement is termed axial disease. Symmetrical as opposed to asymmetrical peripheral joint disease is more commonly associated with autoimmune rheumatic disorders, whereas asymmetrical arthritis can be associated with spondyloarthropathies or osteoarthritis. Similarly, predominant small joint involvement is more typical in rheumatoid arthritis or systemic lupus erythematosus, whereas large joint involvement is classic for spondyloarthropathies. In addition, the presence of associated enthesitis and axial symptoms herald spondyloarthropathy. Joint or spine symptoms associated with inflammatory causes often include predominance of symptoms in the morning, associated with stiffness for more than 60 minutes, worsening with rest, and improvement over the day and with activity. Joint or spine symptoms associated with degenerative joint disease typically worsen with activity, are often worse later in the day, are associated with stiffness, and typically resolve quickly over 15 to 30 minutes. Joint pain is usually felt at the joints (exceptions include shoulder pain, felt over the deltoid, and hip pain, felt in the groin). Joint pain from degenerative or inflammatory causes can vary in severity. Most patients will describe joint pain as aching and rarely rate the pain higher than 8/10 on an ascending severity scale unless they experience acute synovitis. Pain relating to localized myofascial pain syndromes, including tendinopathies and enthesopathies, may be described as arthritis, but it extends from joints and worsens with specific movements. In people suffering from centralized generalized pain syndromes, pain is often rated very highly (10/10), often with pain descriptions including qualifiers to impress the severity of the pain: "like a truck ran over me," is poorly localized, and is diffusely present (involving upper and lower body regions).

Effect on Activities

It is important to ask patients how their condition has affected their activities and even their mental health. Rheumatic diseases result in work disability, job loss, disruption of social relationships, and financial instability. Reduced social participation without a strong personal support system is associated with worsening of mental health (isolation, depression, anxiety), worse prognosis, and even early mortality. Function should be assessed in terms of a patient's ability to perform activities of daily living, work, and participation. Validated questionnaires of function are available to identify functional limitations.

Physical Examination

A complete examination by a physician is required to identify and classify a rheumatic disease. The examination should include an assessment of constitutional symptoms such as temperature, body mass index, affect, pain behaviors, gait, and posture, as well as organ-specific examination of the scalp, skin, eyes, lymphatic system, cardiovascular system, lungs, abdomen, joints, spine, and skeletal muscles. A systematic joint examination is key to the rheumatic disease examination and should include all regions, with comparisons of right and left sides. The pattern of joint involvement, including symmetry and axial versus peripheral involvement should be recorded. Use of a joint diagram (homunculus) helps to track joint involvement. The joint examination should include documentation of the presence or absence of tenderness, periarticular wasting, erythema, swelling, limitation in range of motion (ROM), sites of prior surgery and trauma, and joint deformity, allowing for comparison over time and between different examiners. A four-step systematic approach to joint examination should include (1) inspection (looking for asymmetry, erythema, swelling, and deformity), (2) palpation (feeling for tenderness, specifically joint line tenderness, warmth, synovial thickening and effusion, bony hypertrophy, and crepitus), (3) ROM (both active and passive for each joint), and (4) special tests specific to each joint or region. A complete examination should also consider relevant extra-articular manifestations.

The physical examination can distinguish between arthralgia (a complaint of joint pain and tenderness without heat, or swelling) and arthritis, in which pain and tenderness are associated with signs of joint swelling and warmth (synovitis), deformity, or limitation of movement. A finding of redness (erythema) can indicate more acute and/or severe inflammation. The presence of erythema is more typically seen in the case of infection or crystalline (autoinflammatory) arthritis. Joint warmth also signifies underlying inflammation. Joint swelling, a definitive sign of joint inflammation or arthritis, may indicate the presence of a joint effusion (excess synovial fluid) or synovial thickening indicating an active inflammatory process involving increased vascularization, cellular recruitment, transudate, and edema in the synovial membrane (synovitis). All rheumatic diseases except neurologically mediated pain syndromes can present with synovitis.

Palpable bony thickening around a joint, particularly distal or proximal phalangeal joints or first metacarpal joints, is due to bone reaction and proliferation or osteophytes, characteristic of osteoarthritis. Examiners should palpate for crepitus, which feels like a grinding sensation under the examiner's hand during active or passive joint motion. Fine or velvety crepitus may indicate chronic proliferative synovitis, whereas coarse crepitus may indicate either roughening of the cartilage surface or complete loss of hyaline cartilage with bone moving on bone. In some diseases such as rheumatoid arthritis, psoriatic arthritis, or Jaccoud arthropathy (a form of systemic lupus erythematosus–related deforming arthropathy), deformity occurs as a result of joint subluxation or contracture related to nature's forces on weakened, lax, distended joint capsules and lax ligaments and tendons as a consequence of chronic swelling from synovitis. Muscle atrophy can occur around arthritic joints and contribute to perceived weakness or instability.

Assessing Range of Motion

Both active and passive range of motion should be assessed to appreciate joint function. Generally, active range of motion is assessed first by asking patients to demonstrate full movement of a joint; active range of motion requires intact strength, innervation, muscle and tendon function, and joint mobility. Passive range of motion is assessed by determining joint mobility or, in some cases, ligament or tendon impingement. First, assessing active range of motion enables the examiner to appreciate potential areas of pain and where to examine carefully. If mobility is full-on passive range of motion, other causes can be considered for loss of mobility.

Establishing a Specific Diagnosis

The findings from a thorough history and physical examination, along with an appropriate set of investigations, can be used to guide diagnosis (see Table 236-3 and Fig. 236-2). Most rheumatic diseases appear spontaneously and often insidiously or with a subacute onset. Not all will manifest with all typical features at the time of presentation, and a diagnosis can take time to make as defining features present themselves. Furthermore, features may evolve sequentially over time, so rheumatic diseases from more than one category must often be considered in a patient whose disease has not yet fully manifested. When a specific diagnosis is uncertain, features should be considered in the context of the broad classifications, and terms such as *undifferentiated inflammatory polyarthritis* or *undifferentiated spondyloarthropathy* may be used in the interim to aid in diagnosis and management. When a patient's disease is not yet diagnosed, investigations and monitoring over time can help to identify a rheumatic disease as it evolves in a patient. Autoimmune and vascular rheumatic diseases are associated with high morbidity and mortality when left untreated, so timely diagnosis and initiation of therapy have significant impact on patient outcome.

The evaluation of regional pain syndromes requires a careful history of pain features, as well as a medical history, physical examination, and consideration of "red flags" or factors that indicate a more sinister pathology specific to a related organ from which pain can be referred. Pain in the setting of a history of malignancy should suggest the possibility of metastases. A tick bite may

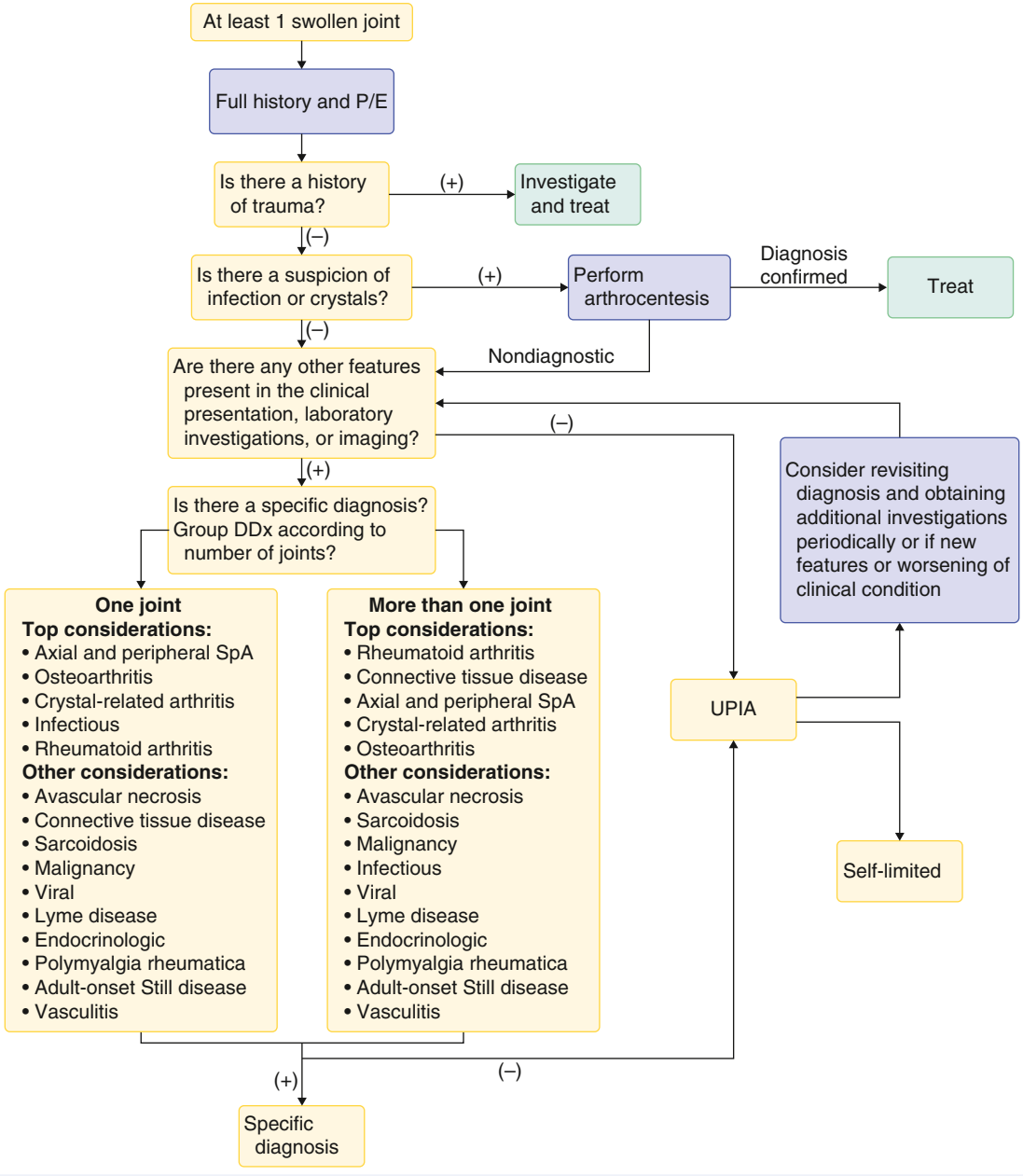

FIGURE 236-2. Algorithm for identification of undifferentiated peripheral inflammatory arthritis. Recommended minimum investigations in all patients: rheumatoid factor and/or anti–citrullinated peptide antibodies, erythrocyte sedimentation rate and/or C-reactive protein, complete blood count, and radiographs of affected joints. DDx = differential diagnosis; P/E = physical examination; SpA = spondyloarthritis; UPIA = undifferentiated peripheral inflammatory arthritis. (From: Hazlewood G, Aletaha D, Carmona L, et al. Algorithm for identification of undifferentiated peripheral inflammatory arthritis: a multinational collaboration through the 3e initiative. *J Rheumatol Suppl*. 2011;87:54-58.)

indicate prior Lyme disease (Chapter 296). Dermatomal distributions are seen with disc herniations or shingles. Most pain syndromes warrant a full medical evaluation before making a definitive diagnosis.

Autoimmune rheumatologic diseases should be further characterized by additional investigations (see Table 236-3), including measurement of characteristic autoantibodies in serum. Defined autoantibody specificities can discern subtypes of rheumatic diseases (Chapter 237, Table 237-1).

The diagnosis of polymyalgia rheumatica (Chapter 250) is primarily clinical, but includes laboratory evidence of acute-phase reactants. Mimics of polymyalgia rheumatica can include elderly-onset rheumatoid arthritis, so tests to exclude rheumatoid arthritis (Chapter 243) may be indicated. When considering polymyalgia rheumatica, giant cell arteritis should be in the differential diagnosis, particularly when acute-phase reactants are very high or musculoskeletal symptoms or manifestations are absent. A high index of suspicion for temporal artery inflammation or large vessel disease involving the aorta is needed so tissue diagnosis can be made in giant cell arteritis before it progresses to blindness, stroke, or severe vascular destruction with organ ischemia.

Diagnosis of the specific autoimmune disease is more challenging when presenting features overlap among diseases. One or more of certain features, including constitutional disturbances such as fatigue, fever, weight loss, arthralgia, arthritis, and myalgias are commonly seen in almost all rheumatic diseases. Sicca symptoms, which are the prototype of primary Sjögren syndrome (Chapter 247) and associated with Sjögren syndrome's specific autoantibody patterns, can occur concurrently in systemic lupus erythematosus and rheumatoid arthritis. Autoimmune vasculitides and systemic lupus erythematosus can share similar organ system manifestations, including involvement of the lungs, kidneys, skin, and nervous system. In some cases, tissue biopsy may help to provide a definitive answer.

Consensus

Diagnostic criteria have been established for most rheumatologic diseases (see specific chapters), but a diagnosis can be made without meeting all classification criteria because some features of a rheumatic disease are highly specific and are not associated with other diseases. By using this algorithm, patterns, and clinical findings (see Table 236-2), clinicians can hone in on a differential diagnosis and then use investigations to confirm the suspected diagnosis.

Laboratory and Imaging in Rheumatic Diseases

Identifying the presence of specific laboratory or imaging features can support a diagnosis and aid in specific classification of a rheumatic disease. For example,

a high serum uric acid level is associated with gout, though levels may lower during acute attacks. A positive antinuclear antibody test (Chapter 237) is nonspecific,[10] but testing ANCAs or imaging the vascular tree of an involved area can be key to establishing a diagnosis in patients with vasculitis.[11,12] Similarly, radiographic imaging of the sacroiliac joints of patients who have seronegative spondyloarthropathies when symptoms are sustained or MRI if the disease is of more recent onset is key. Radiographs and MRIs (Chapter 238) of specific joint areas not only help establish the diagnosis but also aid in staging the disease. In the case of rheumatoid arthritis, testing of rheumatoid factor and ACPA is critical. For other seropositive systemic rheumatic diseases, disease-specific autoantibodies can be very informative. However, some autoimmune diseases are seronegative,[13] and it can be hazardous to diagnose a rheumatic disease based on a single laboratory finding, because a constellation of findings is typically always required.

TREATMENT

The treatment approaches to each rheumatic disease differ (see Chapters 240 to 254). Therapeutic approaches to degenerative rheumatic diseases focus on control of symptoms of pain with either nonsteroidal anti-inflammatory drugs or analgesics. Physical modalities, strengthening, and encouraging activity are a key part of managing degenerative arthritis; at times, injections of glucocorticoids or other agents can manage symptoms. When conservative approaches fail, orthopedic surgery is warranted.

By comparison, the approach to systemic and inflammatory rheumatic diseases usually requires more intense or immunomodulatory therapies. Glucocorticoids are a major component of treatment regimens, particularly when organs are at risk, when other agents take time to become fully effective, and in situations in which no alternative therapeutic options are available. However, glucocorticoids carry their own risks and must be used with discretion. When glucocorticoids are used, they should be tapered as soon as possible and then used again only for disease exacerbations. Depending on the disease, glucocorticoid-sparing therapies are usually initiated early, with potency tailored to the severity and risk for the illness itself, while considering patients' other comorbid conditions and other medications being used. For example, systemic lupus erythematosus patients (Chapter 245) presenting with only a rash or synovitis may require a relatively weak agent, such as hydroxychloroquine,[14] whereas patients with renal disease may need mycophenolate mofetil, cyclophosphamide, or other parenteral immunomodulatory therapies to treat that disease manifestation effectively. Similarly, in rheumatoid arthritis (Chapter 243), patients who present with high-titer ACPA levels, a high swollen joint count, and erosions on radiographs of the hands and feet are candidates for rapidly escalating doses of methotrexate with or without other disease-modifying antirheumatic drugs and early use of biologic or targeted synthetic drugs (see Chapter 29).

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237

LABORATORY TESTING IN THE RHEUMATIC DISEASES

KEVIN D. DEANE AND DAVID S. PISETSKY

The rheumatic diseases are a diverse group of conditions that affect the musculoskeletal system as well as other organs, where they cause inflammation, damage, and functional impairment. These conditions range from mild joint pain to severe life-threatening manifestations such as systemic vasculitis and rapidly progressive renal failure.

The first steps in the diagnostic process include a detailed history, physical examination (especially focused on the joints), and basic laboratory tests to determine findings suggestive of inflammation as well as the extent of involvement of organ systems (e.g., kidneys). These basic tests can then be followed by evaluation of biomarkers that are indicative of specific diseases. In addition to their value in establishing a diagnosis, laboratory tests can help assess the activity or severity of a rheumatic disease, its prognosis, and the effects of therapy, including drug toxicity.

MARKERS OF INFLAMMATION

For many patients, the initial goal of laboratory testing is to determine the presence of inflammation (Chapter 36). The immediate response to inflammatory stimuli is termed the *acute phase response* and includes a set of proteins produced primarily in the liver in response to cytokines such as interleukin-6 (IL-6), tumor necrosis factor-α (TNF-α), and IL-1.

Although cytokines and chemokines can be measured in some commercial assays,[1] the most common clinical measures of the acute phase response are the C-reactive protein (CRP) level and the erythrocyte sedimentation rate (ESR). CRP levels provide a nonspecific but useful measure of inflammation of any cause, so they must be interpreted carefully in the evaluation of rheumatic diseases, especially when using high-sensitivity assays that can measure very low concentrations of CRP. Since CRP levels can rise and fall quickly, with a half-life of 5 to 7 hours, the level of this protein can provide a useful measure of disease activity and response to treatment.

The ESR is an indirect measure of acute phase reactants such as fibrinogen, whose production is increased in inflammatory states. The ESR has been traditionally determined using manual approaches such as the Westergren method, which measures the rate of fall of red blood cells (RBCs) in anticoagulated blood in a capillary tube over 60 minutes; in this assay, increased levels of proteins in plasma lead to a faster fall of RBCs. Automated methods to calculate the ESR have good correlation with the Westergren method.[2] The ESR is nonspecific and also depends on the age and sex of the person. In addition, a low CRP but high ESR may indicate a paraproteinemia. Since ESR levels can be slower to change than CRP levels, CRP determinations may be superior to assess the effects of treatment in some settings.

Other molecules, such as serum amyloid protein, fibrinogen, and complement, also are markedly increased during the acute phase response. Patients with inflammation frequently exhibit a leukocytosis or thrombocytosis, most likely reflecting the action of cytokines and other mediators such as glucocorticoids. With chronic inflammation, low albumin levels and anemia of chronic disease can also occur. In systemic lupus erythematosus, lymphopenia, thrombocytopenia, and low CRP values often characterize active disease, with the discordance between laboratory and clinical findings a clue to diagnosis.

LABORATORY EVALUATION OF ARTHRITIS AND RELATED DISEASES

One of the most common presentations of rheumatic diseases is pain in and around the joints, collectively called arthralgia or arthritis. The extent of inflammation varies markedly, however, with some forms such as osteoarthritis (Chapter 241) showing only limited evidence of inflammation either locally or systemically.

If inflammatory arthritis is suspected, further testing depends on the type and distribution of joint involvement. If arthritis is present in only one or two joints, joint aspiration to evaluate for infection or crystal-induced disease is typically indicated, especially for acute disease with evidence of severe inflammation such as fever or joint swelling and redness. Measuring the serum uric acid level is usually not helpful in diagnosing acute gout. Blood cultures can provide important information in assessing the presence of joint infection if joint aspiration cannot be performed.

If polyarticular inflammatory arthritis is suspected, laboratory tests often lead to a correct diagnosis. Since rheumatoid arthritis is the most common form of inflammatory polyarthritis in adults, autoantibody tests for it are typically indicated (e.g., rheumatoid factor and antibodies to citrullinated protein antigens).

RHEUMATOID FACTOR

Rheumatoid factor comprises a family of antibody specificities that bind to the immunoglobulin G (IgG) molecule and react with antigenic determinants that are most likely conformational in origin in the Fc portion.[3] IgM rheumatoid factors are the most abundant of these antibodies. Rheumatoid factors occur in approximately 60 to 80% of patients with rheumatoid arthritis (Chapter 243) and represent one criterion for the classification or diagnosis of this disease. Furthermore, high levels of rheumatoid factors are often associated with the presence of joint erosion, joint deformity, and a worse prognosis.

Rheumatoid factors also can occur in individuals with a wide range of autoimmune, inflammatory, and infectious diseases (e.g., bacterial endocarditis [Chapter 61]), as well as in normal individuals, especially as they age. The

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a high serum uric acid level is associated with gout, though levels may lower during acute attacks. A positive antinuclear antibody test (Chapter 237) is nonspecific,[10] but testing ANCAs or imaging the vascular tree of an involved area can be key to establishing a diagnosis in patients with vasculitis.[11,12] Similarly, radiographic imaging of the sacroiliac joints of patients who have seronegative spondyloarthropathies when symptoms are sustained or MRI if the disease is of more recent onset is key. Radiographs and MRIs (Chapter 238) of specific joint areas not only help establish the diagnosis but also aid in staging the disease. In the case of rheumatoid arthritis, testing of rheumatoid factor and ACPA is critical. For other seropositive systemic rheumatic diseases, disease-specific autoantibodies can be very informative. However, some autoimmune diseases are seronegative,[13] and it can be hazardous to diagnose a rheumatic disease based on a single laboratory finding, because a constellation of findings is typically always required.

TREATMENT

The treatment approaches to each rheumatic disease differ (see Chapters 240 to 254). Therapeutic approaches to degenerative rheumatic diseases focus on control of symptoms of pain with either nonsteroidal anti-inflammatory drugs or analgesics. Physical modalities, strengthening, and encouraging activity are a key part of managing degenerative arthritis; at times, injections of glucocorticoids or other agents can manage symptoms. When conservative approaches fail, orthopedic surgery is warranted.

By comparison, the approach to systemic and inflammatory rheumatic diseases usually requires more intense or immunomodulatory therapies. Glucocorticoids are a major component of treatment regimens, particularly when organs are at risk, when other agents take time to become fully effective, and in situations in which no alternative therapeutic options are available. However, glucocorticoids carry their own risks and must be used with discretion. When glucocorticoids are used, they should be tapered as soon as possible and then used again only for disease exacerbations. Depending on the disease, glucocorticoid-sparing therapies are usually initiated early, with potency tailored to the severity and risk for the illness itself, while considering patients' other comorbid conditions and other medications being used. For example, systemic lupus erythematosus patients (Chapter 245) presenting with only a rash or synovitis may require a relatively weak agent, such as hydroxychloroquine,[14] whereas patients with renal disease may need mycophenolate mofetil, cyclophosphamide, or other parenteral immunomodulatory therapies to treat that disease manifestation effectively. Similarly, in rheumatoid arthritis (Chapter 243), patients who present with high-titer ACPA levels, a high swollen joint count, and erosions on radiographs of the hands and feet are candidates for rapidly escalating doses of methotrexate with or without other disease-modifying antirheumatic drugs and early use of biologic or targeted synthetic drugs (see Chapter 29).

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237

LABORATORY TESTING IN THE RHEUMATIC DISEASES

KEVIN D. DEANE AND DAVID S. PISETSKY

The rheumatic diseases are a diverse group of conditions that affect the musculoskeletal system as well as other organs, where they cause inflammation, damage, and functional impairment. These conditions range from mild joint pain to severe life-threatening manifestations such as systemic vasculitis and rapidly progressive renal failure.

The first steps in the diagnostic process include a detailed history, physical examination (especially focused on the joints), and basic laboratory tests to determine findings suggestive of inflammation as well as the extent of involvement of organ systems (e.g., kidneys). These basic tests can then be followed by evaluation of biomarkers that are indicative of specific diseases. In addition to their value in establishing a diagnosis, laboratory tests can help assess the activity or severity of a rheumatic disease, its prognosis, and the effects of therapy, including drug toxicity.

MARKERS OF INFLAMMATION

For many patients, the initial goal of laboratory testing is to determine the presence of inflammation (Chapter 36). The immediate response to inflammatory stimuli is termed the *acute phase response* and includes a set of proteins produced primarily in the liver in response to cytokines such as interleukin-6 (IL-6), tumor necrosis factor-α (TNF-α), and IL-1.

Although cytokines and chemokines can be measured in some commercial assays,[1] the most common clinical measures of the acute phase response are the C-reactive protein (CRP) level and the erythrocyte sedimentation rate (ESR). CRP levels provide a nonspecific but useful measure of inflammation of any cause, so they must be interpreted carefully in the evaluation of rheumatic diseases, especially when using high-sensitivity assays that can measure very low concentrations of CRP. Since CRP levels can rise and fall quickly, with a half-life of 5 to 7 hours, the level of this protein can provide a useful measure of disease activity and response to treatment.

The ESR is an indirect measure of acute phase reactants such as fibrinogen, whose production is increased in inflammatory states. The ESR has been traditionally determined using manual approaches such as the Westergren method, which measures the rate of fall of red blood cells (RBCs) in anticoagulated blood in a capillary tube over 60 minutes; in this assay, increased levels of proteins in plasma lead to a faster fall of RBCs. Automated methods to calculate the ESR have good correlation with the Westergren method.[2] The ESR is nonspecific and also depends on the age and sex of the person. In addition, a low CRP but high ESR may indicate a paraproteinemia. Since ESR levels can be slower to change than CRP levels, CRP determinations may be superior to assess the effects of treatment in some settings.

Other molecules, such as serum amyloid protein, fibrinogen, and complement, also are markedly increased during the acute phase response. Patients with inflammation frequently exhibit a leukocytosis or thrombocytosis, most likely reflecting the action of cytokines and other mediators such as glucocorticoids. With chronic inflammation, low albumin levels and anemia of chronic disease can also occur. In systemic lupus erythematosus, lymphopenia, thrombocytopenia, and low CRP values often characterize active disease, with the discordance between laboratory and clinical findings a clue to diagnosis.

LABORATORY EVALUATION OF ARTHRITIS AND RELATED DISEASES

One of the most common presentations of rheumatic diseases is pain in and around the joints, collectively called arthralgia or arthritis. The extent of inflammation varies markedly, however, with some forms such as osteoarthritis (Chapter 241) showing only limited evidence of inflammation either locally or systemically.

If inflammatory arthritis is suspected, further testing depends on the type and distribution of joint involvement. If arthritis is present in only one or two joints, joint aspiration to evaluate for infection or crystal-induced disease is typically indicated, especially for acute disease with evidence of severe inflammation such as fever or joint swelling and redness. Measuring the serum uric acid level is usually not helpful in diagnosing acute gout. Blood cultures can provide important information in assessing the presence of joint infection if joint aspiration cannot be performed.

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Rheumatoid factors also can occur in individuals with a wide range of autoimmune, inflammatory, and infectious diseases (e.g., bacterial endocarditis [Chapter 61]), as well as in normal individuals, especially as they age. The

ABSTRACT

The laboratory evaluation for the rheumatic diseases involves both nonspecific and specific biomarkers to determine the extent of tissue injury, the presence of inflammation and autoimmunity, and serologic evidence for the diagnosis. Nonspecific markers of inflammation include C-reactive protein and the erythrocyte sedimentation rate. Specific markers differ by disease and include disease-related and disease-specific autoantibodies. Although common in rheumatoid arthritis, a positive rheumatoid factor can occur in other rheumatic and nonrheumatic diseases. More specific markers of rheumatoid arthritis are antibodies to citrullinated protein antigens (ACPAs). Antibodies to nuclear antigens (ANAs), which are a feature of many rheumatic diseases, target nucleic acids, nuclear proteins, and complexes of nucleic acids and proteins. The target antigens of ANAs vary by disease and include cytoplasmic as well as nuclear molecules. The pattern of ANA expression provides information for classification, diagnosis, and activity of systemic lupus erythematosus. ANAs are also present in diseases such as Sjögren syndrome, systemic sclerosis, and the idiopathic inflammatory myopathies. In the antiphospholipid antibody syndrome, antibodies to phospholipids and a protein called β2-glycoprotein1 can promote thrombosis in vivo, although they can inhibit blood clotting in vitro. For immune complex–mediated diseases, including systemic lupus erythematosus, measurement of complement proteins is useful for assessing disease activity. A group of antibodies, known as antineutrophil cytoplasmic antibodies (ANCAs), react with neutrophil proteins such as proteinase-3 and myeloperoxidase and are important markers of vasculitis. Depending on the clinical scenario, laboratory tests can diagnose and stage disease, help assess the risk for progressive disease, monitor the effects of treatment, and potentially identify appropriate therapy.

KEYWORDS

anti-citrullinated protein antibody
antinuclear antibody
antineutrophil cytoplasmic antibody
autoantibodies
complement
C-reactive protein
erythrocyte sedimentation rate
rheumatic diseases
rheumatoid factor
inflammation

frequent occurrence of rheumatoid factors in many conditions likely reflects their functional role in innate immune responses and their ability to promote the binding of IgG to antigen by Fc cross-linking. As a result, the finding of a rheumatoid factor alone may be insufficient to establish the diagnosis of rheumatoid arthritis.

ANTIBODIES TO CITRULLINATED PROTEINS

Antibodies to citrullinated proteins (ACPAs) are important biomarkers for the classification and diagnosis of rheumatoid arthritis (Chapter 243). Citrulline is a post-translational modification of the amino acid arginine that results from deimidation. This chemical reaction is catalyzed by the enzyme peptidylarginine deiminase and may occur in the setting of inflammation. Citrullination can affect many different proteins, thereby creating antigenic sites on proteins that include vimentin, enolase, and filaggrin.

Although most ACPA assays detect IgG antibodies, some assays also detect IgA. Results can vary among commercially available assays, thereby making it important to know the performance characteristics of the assay being used.

ACPAs are highly associated with rheumatoid arthritis and represent a criterion in the classification of patients with this disease.[4] Depending on the assay, these antibodies occur in 60 to 70% of patients with rheumatoid arthritis and uncommonly in patients with other forms of inflammatory arthritis. If rheumatoid arthritis is being considered, testing for both rheumatoid factor and ACPA increases the sensitivity for diagnosing rheumatoid arthritis while also providing good specificity.

Tests for antibodies to carbamylated proteins also may provide useful serologic information. Similar to citrullination, carbamylation is a post-translational protein modification.[5] Patients with rheumatoid arthritis may have neither rheumatoid factors nor ACPAs, thereby denoting their condition as seronegative rheumatoid arthritis in distinction to seropositive rheumatoid arthritis, in which both are present. Seronegativity often prompts the search for another diagnosis that can produce similar signs and symptoms as rheumatoid arthritis.

ACPAs can be expressed before the onset of other signs and symptoms of rheumatoid arthritis. In patients who have arthralgias without evidence of synovitis by examination, the presence of ACPAs may predict the development of arthritis. In the future, ACPA testing may also help identify at-risk individuals who are likely to develop rheumatoid arthritis.[6] Indeed, several randomized controlled clinical trials have been designed to prevent future rheumatoid arthritis in ACPA-positive individuals, but an effective preventive therapy has not yet been identified.[A1–A3]

LABORATORY TESTING FOR OTHER CAUSES OF INFLAMMATORY ARTHRITIS

Although rheumatoid arthritis is a common form of inflammatory arthritis, other conditions, such as Sjögren syndrome (Chapter 247), systemic lupus erythematosus (Chapter 245), and vasculitis (Chapter 249), can produce similar joint findings, and are associated with different autoantibody profiles. Other forms of inflammatory arthritis include the spondyloarthropathies (Chapter 244), such as are seen in psoriatic arthritis, ankylosing spondylitis, and arthritis associated with inflammatory bowel disease. For spondyloarthritis, genetic testing for the human leukocyte antigen (HLA) B27 allele is part of classification criteria and can be part of a diagnostic evaluation, although the frequency of HLA B27 varies markedly depending on the racial and ethnic group. Genetic testing may be helpful in evaluating systemic inflammatory diseases such as familial Mediterranean fever (Chapter 240) that can present with arthritis.[7]

Depending on the clinical findings and initial laboratory testing, other studies may help investigate less common diagnostic possibilities. For example, the serum ferritin level can be markedly elevated in adult-onset Still disease, which can present with arthritis. The laboratory evaluation of inflammatory arthritis may also include serologic tests for infections such as Lyme disease (Chapter 296), human immunodeficiency virus (HIV) infection (Chapter 355), hepatitis (Chapters 134 and 135), or other viral infections such as parvovirus (Chapter 342). Because hepatitis C can cause an inflammatory arthritis in association with an elevated rheumatoid factor, testing for this viral infection is often recommended. Older individuals may report pain, stiffness, and arthralgias as manifestations of polymyalgia rheumatica (Chapter 250), a seronegative inflammatory condition whose most notable laboratory finding is an elevated ESR and/or CRP.

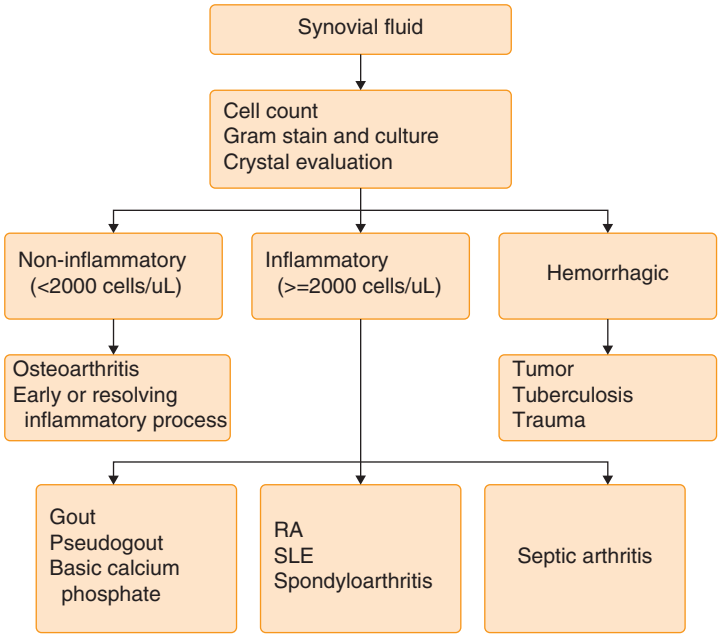

FIGURE 237-1. Algorithm for analysis of joint fluid. Examples of inflammatory arthritis are listed, although many conditions may lead to these results. RA = rheumatoid arthritis; SLE = systemic lupus erythematosus.

JOINT FLUID ANALYSIS

In the evaluation of inflammatory arthritis, analysis of joint fluid (Fig. 237-1) is essential in the setting of acute monoarthritis to investigate the possibility of infection (Chapter 251). In addition, for chronic forms of arthritis, joint fluid should be analyzed if there is uncertainty about the diagnosis or involvement of one joint out of proportion to others. The most informative measures are cell count and differential, crystals, and stains and cultures to evaluate infection.

On the basis of cell counts, joint fluid can be categorized into four main types: noninflammatory, inflammatory, septic, and hemorrhagic. A noninflammatory fluid has fewer than 2000 cells/μL with mononuclear cell predominance. An inflammatory fluid has more than 2000 cells/μL, with 50,000 cells/μL frequently used as the upper limit for this type of fluid. In an inflammatory fluid, polymorphonuclear cells predominate. A septic fluid is an inflammatory fluid in which culture or staining for microorganisms demonstrates infection. Suspicion of infection is especially high for fluids with cell counts greater than 50,000/μL. However, diseases such as rheumatoid arthritis and crystal-induced arthritis can produce cell counts of this magnitude, and an infected fluid can have counts below this level. Hemorrhagic fluids have red cell predominance that can approximate that of blood.

The evaluation for crystals is typically performed by polarization microscopy. With this technique, monosodium urate crystals in gout appear needle shaped and are negatively birefringent. In contrast, calcium pyrophosphate dihydrate crystals in pseudogout are rhomboidal in shape and are weakly positively birefringent. However, some crystals such as basic calcium phosphate, which can cause tendonitis and inflammatory arthritis, can require special microscopy for detection. Infection can coexist with crystal-induced disease, thereby necessitating microbiologic evaluation even when crystals are found. Hemorrhagic fluids can result from infection, although their presence can also indicate malignancy or trauma. In the case of intra-articular fracture, lipids may be found in synovial fluid as a result of release of fats from the bone marrow.

LABORATORY EVALUATION OF SYSTEMIC INFLAMMATORY DISEASE

In addition to arthritis, some rheumatic diseases may cause organ-threatening and life-threatening extra-articular manifestations of the skin, kidney, lung, heart, skeletal muscles, and hematologic and neurologic systems, alone or together, as the predominant issues. Examples include rheumatoid arthritis, systemic lupus erythematosus, Sjögren syndrome, idiopathic inflammatory myopathies (e.g., polymyositis, dermatomyositis), and systemic sclerosis, as well as some forms of vasculitis such as polymyalgia rheumatica/giant cell arteritis, microscopic polyangiitis, and granulomatous polyangiitis. Some rheumatic

diseases are also termed connective tissue diseases because of their pattern of tissue involvement.

ANTINUCLEAR ANTIBODIES

The expression of antibodies to components of the cell nucleus (antinuclear antibodies, or ANAs) is characteristic of connective tissue diseases and is essentially invariable in patients with systemic lupus erythematosus (Chapter 245).[8] ANA positivity is also seen in a high proportion of patients who have other rheumatic diseases such as Sjögren syndrome and systemic sclerosis (Chapter 246). These antibodies target a host of nuclear macromolecules, including DNA, RNA, and proteins as well as complexes of proteins with nucleic acid. ANAs can be either disease-related or disease-specific, depending on their pattern of expression among various conditions.

Results of ANA testing are reported in terms of the pattern of fluorescence as well as the end-point titer of sera at which fluorescence can be observed. The pattern of binding differs depending on the location of the macromolecular target, although the predominant patterns include homogeneous, rim, nucleolar, and speckled. For some sera, more than one pattern of binding may be observed at different dilutions.

Depending on the laboratory and its practices, if an ANA is positive by an immunofluorescence assay, the results can be confirmed and expanded by subsequent assays to identify antibodies to specific nuclear antigens (e.g., Ro/SSA, La/SSB). The immunofluorescence assay allows detection of antibodies directed to antigens in the cytoplasm as well as the nucleus. As for antibodies to nuclear antigens, antibodies to cytoplasmic antigens are important biomarkers. In systemic lupus erythematosus, antibodies can bind antigens in both locales, and antibodies to ribosomal P proteins in the cytoplasm are a specific marker for systemic lupus erythematosus, even though they are not a classification criterion. For several diseases, including systemic sclerosis and inflammatory muscle disease, target antigens are located in the cytoplasm.

Because the molecular targets of many ANAs to antigens within the nucleus or cytoplasm are now known, testing of individual antibodies by an enzyme-linked immunoassay (ELISA) or multiplex-based approaches allows direct identification of autoantibodies to panels of antigens in either the nucleus or cytoplasm. This approach, however, may fail to detect certain ANAs if the antigens are not included in the panel. As a result, multiplex assays are operationally easier than conventional ANA testing by immunofluorescent staining, but the immunofluorescence assay remains an important laboratory test and can be used adjunctively with a multiplex assay (Fig. 237-2).

A major limitation of ANA assays, and especially ANA testing by immunofluorescence assay, is the frequency of positive reactivity in sera of otherwise healthy individuals or individuals who lack clear-cut evidence of a connective tissue disease. Depending on the methodology as well as the cut-off level or titer used to determine positivity, the sera of as many as 20% of otherwise healthy individuals express reactivity in the immunofluorescence assay ANA test. This reactivity, which occurs more commonly in women than in men, may reflect a predisposition to autoimmunity in the absence of other immunopathologic disturbances. This frequency of ANA positivity in the population also appears to be increasing. Because ANA testing is often performed to evaluate nonspecific complaints such as arthralgias, fatigue, and fever, a positive test must be interpreted with caution and not used as evidence of a connective tissue disease in the absence of other clinical or laboratory findings. In the setting of ANA positivity, the presence of antibodies that produce a dense, fine speckled pattern may indicate that the ANA positivity is not associated with an autoimmune disease. These antibodies bind to a protein called lens epithelium-derived growth factor and are denoted as anti-DFS70 antibodies.[9]

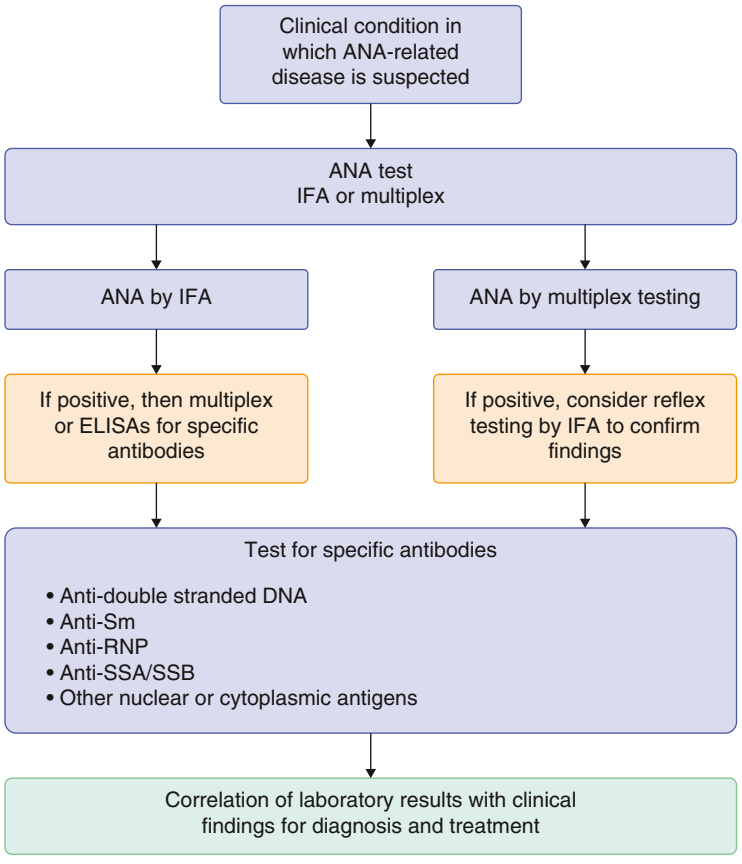

FIGURE 237-2. Approach for antinuclear antibodies (ANAs) testing. The approach to ANA testing may depend on the practices of the local laboratory. ANA testing by immunofluorescence assay or multiplex may be falsely negative owing to methodologic issues, cut-off levels, and/or the antigens included in the assay. If negative, testing using another platform or assay format may be indicated depending on the clinical scenario. Other autoimmune diseases, including idiopathic inflammatory myopathies, systemic sclerosis, and autoimmune hepatitis, may be ANA-positive; for these conditions, further evaluation may include additional testing (e.g., myositis panels). ANA = antinuclear antibody; anti-Sm = anti-Smith antibody; ELISA = enzyme-linked immunoassay; IFA = immunofluorescent assays; RNP = ribonuclear protein; SSA/SSB = anti-Sjögren type A and B.

Antibodies to DNA

Among ANAs associated with rheumatic diseases, antibodies to DNA (anti-DNA) are a highly specific marker for systemic lupus erythematosus and represent a criterion in the classification of patients with this condition. Anti-DNA antibodies also provide a measure of disease activity and response to treatment (Chapter 245).[10] These antibodies bind sites on both single-stranded (ss) and double-stranded (ds) DNA; anti-dsDNA antibodies, however, are more specific for systemic lupus erythematosus and therefore are routinely measured. Although these antibodies can bind free DNA, DNA in the cell occurs in association with histones to form a structure called the *nucleosome*, with DNA wrapped around a histone core. Anti-DNA may therefore be considered a subset of antibodies to nucleosomes or chromatin, with nucleosomes probably serving as the driving antigen for this response

The association of anti-DNA antibodies with disease activity appears strongest with glomerulonephritis, most likely because of the role of DNA–anti-DNA immune complexes in lupus renal disease (Chapter 245). The association of anti-DNA antibodies with other disease manifestations is less certain, thereby limiting the use of this marker as a measure of overall disease activity. The presence of anti-DNA also may be important in assessing the likelihood of response to therapies such as belimumab, which is indicated for the treatment of patients with active autoantibody-positive disease, as evidenced by the presence of either anti-DNA antibodies or a positive ANA.

Anti-DNA antibody assays vary with regard to the spectrum of anti-DNA antibodies detected, and results between assays may not correlate. Nevertheless, for each assay, the dynamic range for testing is large. With treatment and disease quiescence, anti-DNA antibodies may essentially disappear; with flare, levels may increase dramatically. In systemic lupus erythematosus, this property distinguishes anti-DNA antibodies from other ANAs, whose levels tend to be more consistent over time.

Other Antinuclear Antibodies

A number of autoantibodies are associated with a spectrum of rheumatic diseases (Table 237-1). Anti-Sm and anti-RNP antibodies are related antibodies that commonly occur together in the sera of patients with systemic lupus erythematosus, a phenomenon called *linkage*. These antibodies bind proteins on subcellular particles called *snRNPs* (small nuclear ribonucleoproteins) that are composed of a set of proteins and uridine-rich RNAs. Anti-Sm and anti-RNP antibodies differ in protein specificity and in the ability to cause immunoprecipitation of the bound RNA molecules. Anti-Sm antibodies are highly specific for SLE and represent a serologic marker for disease classification.

TABLE 237-1 SELECTED AUTOANTIBODIES IN RHEUMATIC DISEASES

RHEUMATIC DISEASE	AUTOANTIBODIES*
Rheumatoid arthritis (Chapter 243)	*ACPA (including anti-CCP) and rheumatoid factor*; ANA can be positive
SLE (Chapter 245)	*ANA, anti-dsDNA, anti-Sm*, antihistone, anti-Ro (SSA), anti-La (SSB), anti–ribosomal P and anti-RNP. *Antiphospholipid antibodies*
Drug-induced SLE (Chapter 245)	ANA and antihistone; in addition, anti-dsDNA, anti-Ro (SSA) may be present in some drug-induced autoimmune syndromes†
Antiphospholipid antibody syndrome (Chapter 160)	*Anticardiolipin antibody (IgG, IgM, and IgA), anti-beta-2-glycoprotein I antibody (IgG, IgM, and IgA)*‡
Sjögren syndrome (Chapter 247)	ANA, *anti-Ro (SSA), anti-La (SSB)* and rheumatoid factor
Idiopathic inflammatory myopathies (polymyositis, dermatomyositis; Chapter 248)	Myositis-specific autoantibodies include *anti–Jo-1*, anti-SRP, anti–Mi-2, anti-MDA5, anti-TIF1 gamma and alpha and anti-HBGCR. Myositis-associated antibodies include anti-Ro (SSA), anti-La (SSB) and anti-RNP
ANCA-associated vasculitis (Chapter 249)	*ANCA by immunofluorescence; PR3-ANCA, MPO-ANCA*
Mixed connective tissue disease (Chapter 246)	ANA and *anti-RNP*
Systemic sclerosis (Chapter 246)	ANA, *anticentromere, anti–SCL-70* and *anti-RNA polymerase III*

*Autoantibodies listed in italics indicate that these autoantibodies are included in established diagnostic and/or classification criteria.

†These tests may also be abnormal in idiopathic systemic lupus erythematosus. In addition, in some drug-induced autoimmune syndromes there can be broader autoantibody positivity (e.g., ANA and ANCA positivity in antithyroid drug-related autoimmune syndromes).

‡Functional tests include activated partial thromboplastin time and dilute Russell viper venom time.

ACPA = antibody to citrullinated protein/peptide antigen; ANA = antinuclear antibody; ANCA = antineutrophil cytoplasmic antibody; anti-CCP = anti–cyclic citrullinated peptide; anti-dsDNA = anti–double-stranded DNA; anti-Sm = anti-Smith antibody; HMGCR = 3-hydroxy-3-methylglutaryl coenzyme A reductase; Jo-1 = histidyl tRNA synthase; MDA5 = melanoma differentiation-associated gene 5; MPO = myeloperoxidase; PR3 = proteinase 3; RNP = ribonucleoprotein; ScL-70 = topoisomerase I; SLE = systemic lupus erythematosus; SRP = signal recognition particle; SSA/B = Sjögren-associated antigen A or B; TIF = transcriptional intermediary factor.

In contrast, anti-RNP antibodies are considered disease-related autoantibodies because they can appear in the sera of patients with other clinical diseases.[11] In the absence of anti-Sm, anti-RNP antibodies may characterize patients with overlap syndromes, including a specific entity termed mixed connective tissue disease (Chapter 246). Antibodies to Sm and RNP are also denoted as antibodies to RNA-binding proteins (RBPs). Along with other anti-RBPs, anti-Sm and anti-RNP are present in a material known as extractable nuclear antigen (ENA). ENA is a saline extract of tissue and contains antigens such as Sm, RNP, Ro, La, and Jo1. Some laboratories offer a test called an ENA panel to allow assay of this group of antibodies by various formats.

Antibodies to DNA as well as RNA-binding proteins such as Sm and RNP may contribute to overall immune dysregulation in patients with autoimmune disease because of their formation of immune complexes containing DNA or RNA. These complexes can stimulate the production of type 1 interferon by triggering both TLR and non-TLR nucleic acid sensors as well as other cellular receptors (e.g., Fc receptors). Because immunoassays of interferon are limited, the presence of interferon is demonstrated most clearly in a pattern of gene transcript expression known as the interferon signature in peripheral blood cells. Although not yet widely used clinically, transcriptomic assays are commonly performed in studies on mechanisms of disease and of responses to treatment.[12]

Anti-Ro and anti-La antibodies (or anti–SSA and anti–SSB), another set of linked ANAs, are directed to protein-RNA complexes that are involved in cellular metabolism of RNA.[13] Two forms of Ro exist. Ro60 is an RNA-protein complex, whereas Ro52 is a protein known as TRIM22. Anti-Ro and anti-La are expressed more widely in patients with connective tissue disease and appear in the sera of patients with systemic lupus erythematosus, rheumatoid arthritis, and Sjögren syndrome. Assessment of these antibodies is important because of their association with neonatal lupus syndrome, which results from the transplacental passage of antibodies and causes congenital heart block as well as rash in the neonate.

Although both Sm/RNP and Ro/La are complexes of proteins and RNA, these antibodies appear to be expressed by different patient subsets, thereby suggesting distinct mechanisms of induction and clinical associations. In systemic lupus erythematosus, anti-RBPs are expressed independently of anti-DNA.

ANAs are directed to ubiquitous antigens but nevertheless can be associated with specific clinical manifestations. These associations include anti–ribosomal P antibodies with central nervous systemic involvement in systemic lupus erythematosus. In addition, antibodies associated with manifestations of systemic sclerosis include anti-DNA topoisomerase 1 (anti–SCL-70) with diffuse disease; antibodies to centromeres with limited systemic sclerosis (calcinosis, Raynaud phenomenon, esophageal dysmotility, sclerodactyly, and telangiectasia); and antibodies to histidyl transfer RNA synthetase (anti–Jo-1) with interstitial lung disease (Chapter 246).[14] In addition, in systemic sclerosis, anti-RNA polymerase III can be associated with an increased risk for underlying malignancy.[15]

In idiopathic inflammatory myopathies (Chapter 248), the presence of certain autoantibodies may be associated with particular patterns of disease.[16] As a group, antibodies to tRNA synthetases are associated with characteristic clinical findings that have been termed anti-synthetase syndrome. Antibodies to melanoma differentiation-associated gene-5 (MDA5) are associated with a more severe course of myositis with interstitial lung disease, whereas antibodies to the enzyme 3-hydroxy-3-methylglutaryl-coenzyme A (HMG-CoA) reductase and signal recognition particle (SRP) are associated with necrotizing myositis. In addition, antibody to transcriptional intermediary factor 1 gamma (TIF1gamma) is associated with hyperkeratotic papules on the skin, as well as increased risk for underlying malignancy.

Antibodies to Phospholipids

Originally defined by their effects on in vitro clotting tests, antibodies to phospholipids are associated with in vivo thrombosis and have been termed *lupus anticoagulants*.[17] Patients with these antibodies display a clinical condition termed antiphospholipid antibody syndrome characterized by arterial or venous thrombosis, thrombocytopenia, and first-trimester spontaneous abortions (Chapter 67). This syndrome may occur by itself or in the context of systemic lupus erythematosus. Although venous and arterial clots are a hallmark of antiphospholipid syndrome, accelerated atherosclerosis, valve disease, and alveolar hemorrhage are also associated with this condition.

The laboratory evaluation of antiphospholipid syndrome involves specific assays of antibodies to phospholipids and certain proteins, as well as functional assays of clotting. Because expression of these antibodies may vary over time, testing must be performed on more than one occasion at least 6 weeks apart. Furthermore, the results of immunochemical and functional assays may not be congruent, likely related to the heterogeneity of antibodies.[18]

The serology of antibodies to phospholipids is complicated because it is related to the nature of the antigenic targets as well as heterogeneity among patients. These antigens include phospholipids such as cardiolipin. Cardiolipin, however, can bind to the protein β_2-glycoprotein 1, which is also a target for antibodies in this condition. Serologic evaluation thus involves assays with a complex of cardiolipin and β_2-glycoprotein 1 as well as β_2-glycoprotein 1 in an ELISA format using reagents to measure IgG, IgA, and IgM, although the association of antibodies with thrombosis appears strongest with IgG antibodies. In interpreting these assays, it is important to know the cut-off values used to define positivity.

Functional assays for lupus anticoagulants involve tests directed at inhibition of in vitro clotting (e.g., activated partial thromboplastin time, dilute Russell viper venom time), recognizing the discordance between in vivo thrombosis and in vitro anticoagulation. Functional assays to detect lupus anticoagulants involve a mixing step in which patient plasma is mixed with normal plasma to determine the presence of an inhibitor (i.e., an antibody) as opposed to a deficiency state. Importantly, the use and interpretations of these assays may need to be modified in individuals who are taking anticoagulants.

Complement

Assessment of the complement system can provide valuable information on the activity of diseases in which immune complex deposition can promote

inflammation and tissue injury (Chapter 37).[19] In the setting of systemic lupus erythematosus, certain forms of vasculitis, glomerulonephritis, and atypical hemolytic uremic syndrome, complement is activated by immune complexes. Activation of the complement system can be measured in terms of the total complement level, levels of C3 and C4, and levels of complement fragments bound to RBCs.

Low levels of complement proteins may reflect their consumption but also can be caused by inherited complement deficiencies or copy number variations. Genetic deficiency of C1q, for example, is highly associated with systemic lupus erythematosus. In addition, proteins of the complement system are also acute phase reactants and can increase with inflammation. With the advent of complement-directed therapies for diseases (e.g., atypical hemolytic-uremic syndrome), as well as commercial assays that can use patterns of complement activation products to identify specific disease, complement testing may become more common in clinical care.

Antineutrophil Cytoplasmic Antibodies

Antineutrophil cytoplasmic antibodies (ANCAs) are autoantibodies that react to antigens in the neutrophil and occur prominently in patients with certain forms of necrotizing vasculitis and/or rapidly progressive glomerulonephritis (Chapter 107). Reflecting the serology, conditions have been called ANCA-associated vasculitis (AAV; Chapter 249).

Two main forms of ANCAs have been distinguished on the basis of the target antigens and pattern of immunofluorescence staining of fixed neutrophils: PR3-ANCA (C-ANCA), which reacts with proteinase-3 (PR3), and MPO-ANCA (P-ANCA), which reacts with myeloperoxidase (MPO). By immunofluorescence, PR3-ANCA shows staining in the cytoplasm; staining by MPO-ANCA localizes in the perinuclear area. ANCAs can occur in conditions other than vasculitis, including an immune syndrome resulting from the drug levamisole, which is used as an adulterant in cocaine. In addition, ANCAs can be present in conditions such as inflammatory bowel disease (Chapter 127), autoimmune liver disease (Chapter 135), and systemic lupus erythematosus (Chapter 245); however, the specific antigens targeted by ANCAs in these diseases are not well characterized.

In the evaluation of severe, multisystem inflammatory disease that often involves the renal and pulmonary systems, ANCA testing is important to evaluate diagnostic possibilities.[20] ANCAs occur in association with varying clinical manifestations in patients with ANCA-associated vasculitis and help define patterns of histopathology as well as organ system involvement. PR3-ANCA occurs commonly in patients with granulomatosis with polyangiitis (GPA), as well as eosinophilic granulomatosis with polyangiitis (EGPA, formerly called Churg-Strauss disease). MPO-ANCA marks the course of vasculitis caused by microscopic polyangiitis. Despite overlap between serology and clinical features, PR3-ANCA occurs commonly in patients with upper airway disease, whereas MPO-ANCA occurs commonly in patients with rapidly progressive renal disease (Chapter 249).

As with ANA testing, ANCA testing can be done in a reflex approach in which immunofluorescence assay testing is performed first. If an ANCA is identified, then additional testing (e.g., ELISA) is done to determine whether anti-PR3 or anti-MPO is present. One approach to optimize sensitivity and specificity of ANCA testing is to test ANCA by IFA as well as ELISA for PR3-ANCA and MPO-ANCA. This allows for identification of possible non-PR3/MPO reactivities associated with an ANCA.

In patients with ANCA-associated glomerulonephritis (Chapters 107 and 249), the kidney lacks evidence of immune deposits, as indicated by the lack of staining for immunoglobulins or complement. Kidney disease of this kind is termed *pauci-immune glomerulonephritis*. Although ANCA testing is useful in initial diagnosis, its role for assessing disease activity is less certain. Occasionally, in patients who are critically ill and cannot tolerate a lung or kidney biopsy, the presence of an ANCA can provide preliminary evidence for diagnosis and allow the initiation of immunosuppressive therapy. ANCA testing is also useful for assessing the likelihood for relapse because patients who express PR3-ANCA appear at risk for recurrent disease.

ANCA-associated conditions can present as a pulmonary-renal syndrome because of the prominent involvement of these organs. Goodpasture syndrome is another example of a pulmonary-renal syndrome whose presence can be assessed by testing for antibodies to the glomerular basement membrane by an immunofluorescent method using tissue slices.

CRYOGLOBULINS

Cryoglobulins are serum immunoglobulins that precipitate in the cold and can mediate disease through tissue deposition.[21] A finding suggesting cryoglobulinemia is an elevation of rheumatoid factor with a concomitant low C4 and normal C3 level. The presence of a cryoglobulin can be detected by allowing blood, collected warm, to remain cool at 2° to 4° C for 1 or more days. After centrifugation, the amount of cryoprecipitate is measured and expressed as a cryocrit. Prior to the actual incubation in the cold, it is important that the blood remain at a temperature of 37° C.

Subsequent analysis of the cryoprecipitate by immunochemical assays allows determination of its components. Cryoglobulins can be classified into three main types on the basis of their composition: (1) single, or type I, which typically are seen in lymphoproliferative disorders such as multiple myeloma (Chapter 173); (2) mixed, type II, which can be seen in lymphoproliferative disorders as well as rheumatic diseases and in infections such as hepatitis C (Chapters 134 and 135); and (3) mixed, type III, which is associated with rheumatic diseases as well as infection, including hepatitis C. A type I cryoglobulin consists of only a monoclonal immunoglobulin that precipitates in the cold. A mixed-type cryoglobulin contains rheumatoid factors bound to polyclonal IgG to form an immune complex. In type II cryoglobulins, the IgM rheumatoid factor is monoclonal, whereas the IgM rheumatoid factor is polyclonal in type III.

The clinical findings associated with cryoglobulinemia often mimic those of primary rheumatic diseases; in addition, rheumatic diseases, especially systemic lupus erythematosus and Sjögren syndrome, may lead to cryoglobulinemia. Individuals with mixed cryoglobulins can present with a wide range of signs and symptoms resulting from cryoglobulin-mediated vasculitis, including purpura (a sign of leukocytoclastic vasculitis), weakness, arthritis, neuropathy, and nephropathy. As in the case of other connective tissue diseases and systemic inflammatory diseases, the evaluation of patients with essential mixed cryoglobulinemia demands attention to the entire patient and the impact of disease on multiple organs.

LABORATORY TESTING TO MANAGE THERAPY

Laboratory testing is increasing by being used to guide therapy. Standard tests such as complete blood counts and hepatic function panels can monitor the potential toxicity of medications. Testing can also evaluate an individual's ability to metabolize a drug (e.g., thiopurine methyltransferase levels for use of azathioprine) or predict toxicity (e.g., the HLA-B*58:01 gene is associated with increased risk for adverse reactions from allopurinol, and p-450 gene polymorphisms are associated with toxicity from nonsteroidal anti-inflammatory agents).[22] Drug levels of many agents (e.g., hydroxychloroquine and methotrexate) are now available, and some biologic agents have assays to detect antidrug antibodies that can help determine if immune responses to a drug are reducing its efficacy. An emerging area is the use of laboratory testing, which may include blood or tissue-based tests such as synovial or renal biopsy, to identify the optimal therapy for a specific patient.[23,24]

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238 IMAGING STUDIES IN THE RHEUMATIC DISEASES

RONALD S. ADLER

Advanced rheumatic disorders usually can be well characterized by conventional imaging. However, the development of new therapeutic alternatives for the inflammatory arthritides, so-called disease-modifying antirheumatic drugs (DMARDs), and chondroprotective strategies for osteoarthrosis require methods to diagnose these diseases at an earlier stage, characterize the degree of inflammation, and provide a useful metric to assess therapeutic response (Chapters 28 and 29). Indeed, it has become necessary to assess for possible joint and soft tissue abnormalities before irreversible tissue damage and when the radiographic findings are not yet abnormal. Fortunately, the requirement to achieve earlier diagnosis has paralleled advances in imaging. Ultrasonography and magnetic resonance imaging (MRI) have largely supplanted conventional radiographic evaluation in the imaging evaluation of patients with suspected rheumatologic disorders and negative radiographs. The term *molecular imaging* has been applied, particularly in the case of MRI and positron emission tomography (PET), inasmuch as these modalities reflect local tissue environment or metabolic activity.[1]

RADIOGRAPHIC EVALUATION

Radiographs are projection images. To detect an abnormality, it may be necessary to view a joint or other structure at a specific angle. For instance, subtle erosions in rheumatoid arthritis (Chapter 243) may be apparent only when viewed tangentially, as opposed to *en face*. Most radiographic evaluations contain at least two orthogonal projections. The addition of an oblique view or other specialized projection may be necessary to address a specific clinical question.

The nature and distribution of joint space narrowing, presence of osteopenia, new bone formation, soft tissue swelling, soft tissue calcification, chondrocalcinosis, presence and nature of erosions, and assessment for joint malalignment may allow a specific diagnosis (Table 238-1), as well as help determine the severity of disease (Fig. 238-1). For instance, the presence of a juxta-articular erosion extending over an adjacent area of slightly hyperdense soft tissue swelling in the setting of normal bone mineralization with maintenance of the adjacent joint space is diagnostic of gout (Chapter 252), in contrast to rheumatoid arthritis. The seronegative arthritides, such as psoriatic arthritis (Chapter 244) and reactive arthritis (Chapter 254), have a characteristic appearance in the small joints of the hand and feet, with a predilection for distal joints, asymmetry, and appositional new bone formation.

Radiographs also provide a direct means for needle localization during percutaneous procedures, predominantly joint injections, aspirations, and some biopsies. These procedures are generally performed guided by imaging in real time (fluoroscopy) using short bursts of low-intensity x-rays enhanced through an image intensifier. Injection of joints under fluoroscopic guidance provides a convenient means to ensure intra-articular deposition of the therapeutic agent or for diagnostic aspiration. Intra-articular location is verified by injection of a small amount of a standard iodinated contrast material. Arthrography using fluoroscopic guidance can be used as a primary diagnostic tool, but this application has largely been replaced by intra-articular injection of contrast followed by computed tomography (CT) or MRI.

For some procedures, CT may be preferable, depending on the location of the abnormality. The principal disadvantages of fluoroscopy relate to the use of ionizing radiation and poor soft tissue contrast. The latter becomes important with needle placement near neurovascular structures that may be potentially compromised by poor needle position. CT allows greater control over needle placement at the cost of greater levels of radiation exposure. Ultrasonography has replaced fluoroscopy and CT for a large number of percutaneous procedures. MRI provides another method to guide a variety of procedures without the necessity of ionizing radiation. These options will be discussed in greater detail later.

COMPUTED TOMOGRAPHY

CT provides a two-dimensional map of tissue attenuation obtained from external x-ray source(s) located on a rotating gantry, whose radiation is detected by

TABLE 238-1 DISTINGUISHING RADIOGRAPHIC FEATURES OF SEVERAL COMMON RHEUMATIC DISEASES

CONDITION	COMMON SITES	DISTRIBUTION	RADIOGRAPHIC FEATURES
Rheumatoid arthritis	Hands: MCP, PIP; wrists: intercarpal, DRUJ, ulnar styloid; feet: fifth MTP; cervical spine (atlantoaxial, apophyseal)	Bilateral, symmetric, polyarticular	Juxta-articular osteopenia, periarticular swelling, subluxations (e.g., ulnar, volar), uniform joint space loss, erosions (bare areas)
Osteoarthritis (primary)	Hands (DIP), wrists (basal joint, STT), feet (first MTP), hips (superolateral), knees (medial), spine (discs, facet, or apophyseal, uncovertebral)	Symmetric, weight-bearing joints	Normal or increased density, nonuniform joint space loss, subchondral sclerosis, cysts, bone formation (osteophytes) Spine: disc space narrowing, end plate sclerosis, and bone formation
Psoriatic arthritis	Hands (DIP, terminal tufts), feet (IP joints), entheses (calcaneus-plantar, posterior), spine, SI joints	Asymmetric (single ray), polyarticular, segmental (intervertebral, apophyseal)	Normal or increased density, periosteal bone formation, soft tissue swelling, ankylosis (SI joints), thick hyperostosis spine (nonmarginal syndesmophytes), juxta-articular and periarticular erosions
Ankylosing spondylitis	Spine, SI joints, fibrous joints (pubic symphysis), entheses (adductor origin), rhizomelic joints (hips, shoulders)	Symmetric, continuous (may affect entire spine: bamboo spine)	Normal or increased density, erosions (spine: squaring, shining corner) with superimposed bone formation (ankylosis: SI, thin [marginal] syndesmophytes)
Gout	Feet (first MTP), other damaged joints, elbow, knee, hindfoot	Asymmetric, extensor surfaces (elbow), abnormal joints (e.g., osteoarthritic joints)	Normal joint space, normal or increased density, dense soft tissue nodules (tophi), para-articular and subchondral erosions with bone formation along tophi (overhanging edge)
CPPD	Hands (second, third MCP), wrists (radiocarpal, TFC), knees (lateral compartment and patella-femoral, menisci)	Symmetric, fibrocartilaginous joints	Normal or increased density, hypertrophic bone formation, subchondral or periarticular cysts, chondrocalcinosis (hyaline, fibrocartilage), periarticular, peritendinous, periligamentous calcification
Infection	Any joint (pyogenic, TB)	Monoarticular (mostly), any joint	Pyogenic: osteopenia (days), joint space widened (early), joint space loss (rapid development), soft tissue swelling, erosions—both sides of joint, sequestra, periostitis TB: joint space and mineralization may be preserved, juxta-articular erosions Spine: disc space loss and end plate erosion

CPPD = calcium pyrophosphate deposition disease; DIP = distal interphalangeal; DRUJ = distal radial ulnar joint; IP = interphalangeal; MCP = metacarpophalangeal; MTP = metatarsophalangeal; PIP = proximal interphalangeal; SI = sacroiliac; STT = scaphotrapeziotrapezoid; TB = tuberculosis; TFC = triangular fibrocartilage.

ABSTRACT

Historically, rheumatic disorders have been well characterized by conventional imaging. Radiographic evaluation has been sufficient both to characterize these conditions and to provide a relatively small number of differential diagnostic possibilities regarding the specific disease. The development of new therapeutic alternatives for the inflammatory arthritides, the so-called disease-modifying antirheumatic drugs, and chondroprotective strategies in the case of osteoarthrosis require methods to diagnose these diseases at an earlier stage, characterize the degree of inflammation, and provide a useful metric to assess therapeutic response. Fortunately, the requirement to achieve earlier diagnosis has paralleled advances in imaging. Ultrasound and magnetic resonance imaging have largely supplanted conventional radiographic evaluation in much of the imaging work-up of patients with suspected rheumatologic disorders. Radiographic evaluation, computed tomography, magnetic resonance imaging, ultrasound, and nuclear medicine collectively provide important information in evaluating patients with these disorders and are briefly reviewed.

KEYWORDS

imaging
MRI
ultrasound
computed tomography
nuclear medicine
arthritis
scintigraphy

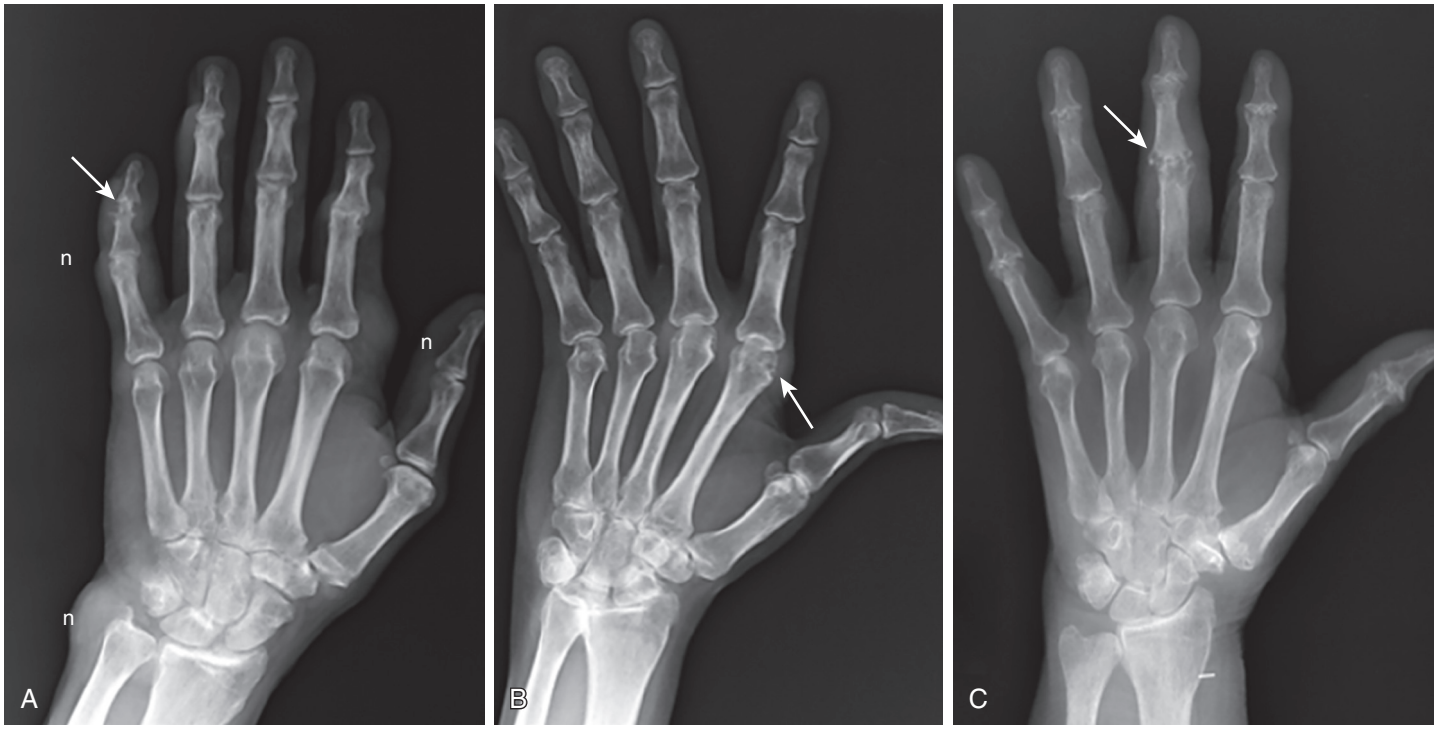

FIGURE 238-1. Three hands with different diagnoses. A, Gout. Radiograph of the left hand showing multiple dense soft tissue nodules (n) with multiple small erosions affecting the ulnar styloid, triquetrum, and fifth ray. A large erosion (*arrow*) at the fifth distal interphalangeal (DIP) joint demonstrates bone formation extending circumferentially about the adjacent tophaceous deposit typical of an overhanging edge. Bone mineralization and joint spaces are preserved. **B,** Rheumatoid arthritis (RA). There is ulnar deviation of the second through fifth metacarpophalangeal (MCP) joints with uniform joint space loss involving the MCP joints and the carpus. There is mild ulnar translation of the carpus. The DIP joints are spared. Periarticular demineralization is present with small erosions along the radiovolar aspect of the second MCP joint (*arrow*). **C,** Osteoarthrosis. Soft tissue swelling affecting the third digit with joint space narrowing and bone production affecting the DIP joints, third and fifth proximal interphalangeal (PIP) joints, basal joint of the thumb, and scaphotrapeziotrapezoid joint. There are subchondral cystic changes at the third PIP joint having an erosive character (*arrow*). Mineralization is preserved, and radiocarpal as well as MCP joint spaces are preserved.

a series of detectors opposite the source. The current generation of CT scanners employs multiple detectors (16, 32, 64, and so on), allowing rapid image acquisition that can be displayed in a single plane in real time (CT-fluoroscopy) or as extremely thin-section contiguous or overlapping acquisitions in the axial plane. The acquired images can be reconstructed in multiple planes with equivalent (isotropic) resolution elements (voxels) or as a three-dimensional rendering. Some scanners use dual energy sources to take advantage of differences in the attenuation characteristics of various tissues at different energies (Fig. 238-2), thereby enabling a definitive diagnosis with greater sensitivity in depicting tophaceous deposits even in anatomic locations not conducive to radiographs or ultrasound.

CT allows the best assessment of trabecular and cortical bone, providing an excellent means to assess fractures and erosions, the presence of new bone formation (e.g., fracture callus), and degenerative or inflammatory arthritis.[2] Soft tissue mineralization can likewise be well characterized, providing important information as to its etiology. Joints that are difficult to assess on radiographs, including the sacroiliac, temporomandibular, wrist, and sternoclavicular joints, are well seen on CT (Fig. 238-3).

CT generally has poor soft tissue contrast. Nevertheless, it is still very useful in performing a number of guided procedures because of its tomographic nature and rapid image acquisition capability. Improved soft tissue contrast can be obtained with use of iodinated contrast material. A number of soft tissue tumors, inflammatory synovitis, and infectious processes display pathologic enhancement after contrast administration. CT can likewise be used to produce angiographic displays (CTA) when used in combination with contrast, thereby providing exquisite detail of central and peripheral vascular disease, including in patients with suspected vasculitis. These agents are typically administered intravenously following well-defined enhancement characteristics. Likewise, contrast agents may be used to improve intra-articular imaging (CT arthrography) for the assessment of internal derangement in the postoperative shoulder, knee, and so on and in patients who are unable to undergo MRI (e.g., patients who have claustrophobia, aneurysm clips, or some cardiac pacemakers). Imaging of cartilage and soft tissue abnormalities usually depends on pathologic inhibition of contrast material, indicative of degeneration or tearing. A limitation of this approach resides in the fact that some abnormalities may remain occult. An example is the inability to detect a bursal-sided rotator cuff tear after shoulder CT arthrography.

The radiation dose from CT can be high, especially when using the newer scanners. Iterative image reconstruction techniques as well as sparse sampling (compressed sensing) may allow for compensatory dose reduction. Intravenous (IV) use of iodinated contrast agents is contraindicated in patients with impaired renal function or a history of allergic reaction. Nonionic agents can diminish the associated risks but still should be used with caution.

ULTRASONOGRAPHY

Ultrasound imaging takes advantage of the near-uniform speed of sound and predictable attenuation characteristics of sound propagation in soft tissue. Rapid acquisition and processing enable ultrasound to be performed in real time (approximately 30 frames per second). Ultrasonography also can evaluate blood flow, from which estimates of flow velocity can be obtained through the Doppler equation (Chapter 43).

Ultrasonography's appeal in patients with rheumatic disorders includes the absence of ionizing radiation, as well as the fact that it is real-time, inexpensive, relatively portable, and well tolerated. The traditional uses of ultrasound to detect a Baker cyst in the knee[3] or a joint effusion have expanded with the development of a new class of compact and portable ultrasound units that have excellent image quality.

The current generation of ultrasound scanners enables examination of the small joints of the hands and feet, allowing early detection of synovitis (Fig. 238-4).[4] The displacement of the joint capsule by hypoechoic (dark) soft tissue that displays vascularity on Doppler imaging or is incompressible with direct pressure by the transducer is characteristic, thereby allowing differentiation of synovitis from an effusion. In addition to the detection of synovitis, ultrasonography is more sensitive than conventional radiographs for the detection of erosions. Erosions appear as discrete irregular discontinuities in the normally smooth hyperechoic (bright), reflecting cortical surfaces, often seen in continuity with adjacent inflammatory soft tissue.

The level of vascularity on color flow imaging correlates with clinical and biochemical parameters and can reflect active inflammation.[5] When standard ultrasonography is combined with color flow imaging, the activity of the synovitis can be estimated. Ultrasound contrast agents can depict capillary flow, thereby resulting in significantly improved sensitivity for detecting synovial inflammation. These microbubble agents are encased in a lipid or polysaccharide shell that can be instilled as either bolus or constant infusion, with the

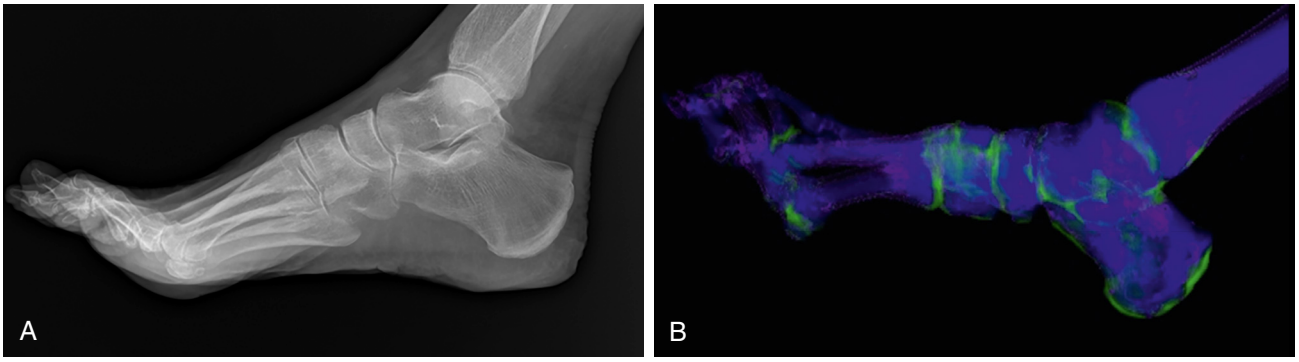

FIGURE 238-2. **Male age 62 years with right foot pain and clinically suspected gout. A,** Lateral radiograph of the right shows mild osteopenia without other evident abnormalities. **B,** Three-dimensional rendered image obtained from a dual energy acquisition, with blue representing normal cancellous and/or cortical bone and green designating tophaceous deposits scattered throughout the foot.

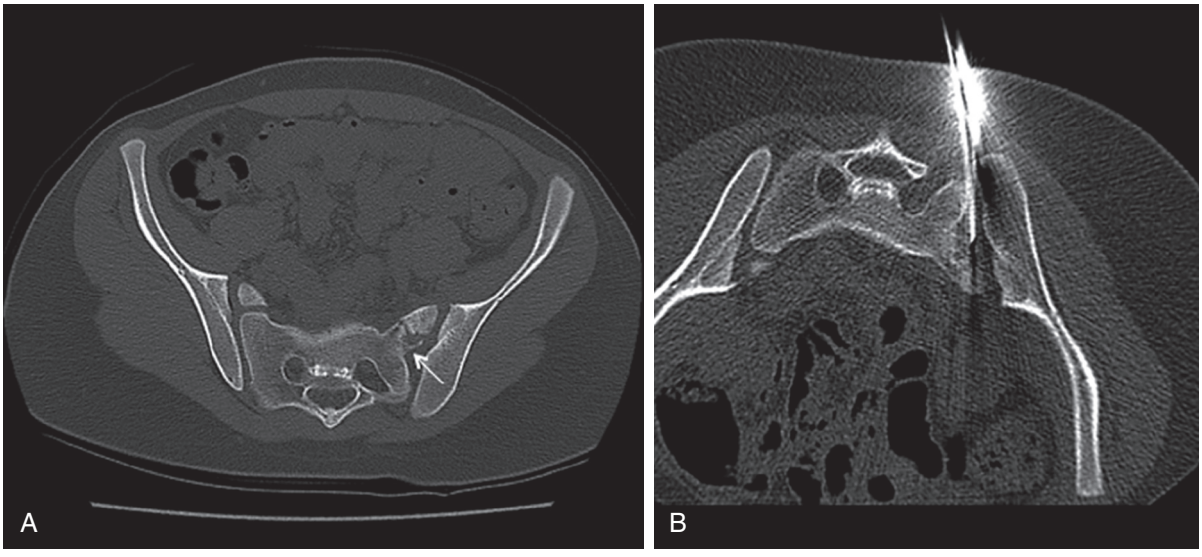

FIGURE 238-3. **Infectious sacroiliitis in a 12-year-old boy with a 2-week history of back and left hip pain. A,** Axial computed tomography (CT) image of the pelvis at the level of the sacroiliac (SI) joints photographed using window settings optimized for bone detail. There is clear asymmetry in the two SI joints, with the left appearing more irregular. The cortical margins of the left sacral ala are less distinct, and there is an isolated bone fragment (*arrow*) surrounded by soft tissue suspicious for a sequestrum. **B,** CT-guided aspiration of the left SI joint confirmed an infectious origin.

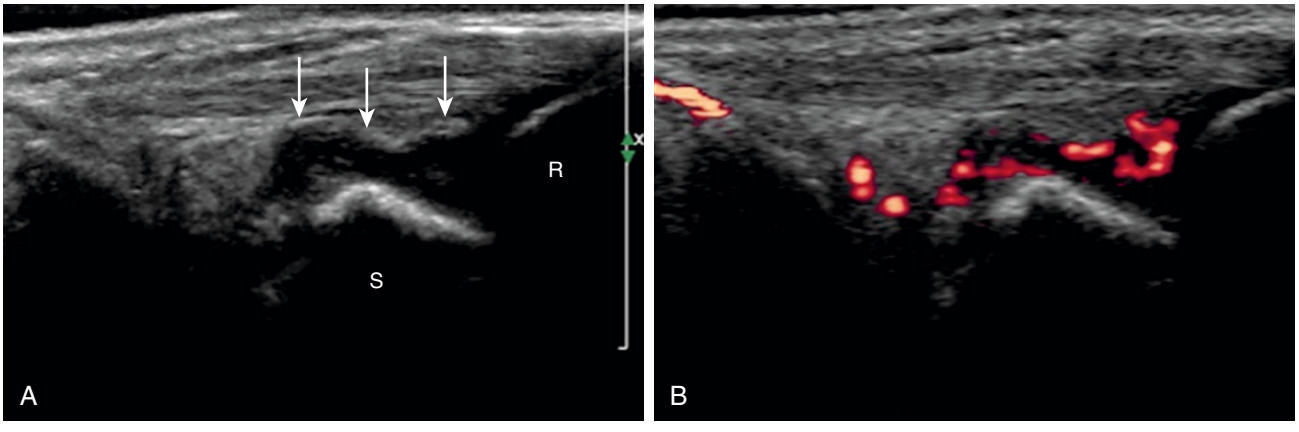

FIGURE 238-4. **Synovitis on ultrasound in a female patient with normal hand radiographs. A,** Gray-scale ultrasound image obtained along the dorsal aspect of the radioscaphoid joint shows hypoechoic soft tissue (*arrows*) distending the dorsal recess. The cortical margins of the scaphoid (S) and radius (R) appear as bright reflectors on ultrasound. **B,** Power Doppler image depicts the marked vascularity (red hues) of the soft tissue illustrating the level of disease activity.

shell being metabolized in the liver and the gas exhaled in the lungs. Although such agents have received U.S. Food and Drug Administration approval for cardiovascular and abdominal applications at this time, they can be used only off-label for the assessment of synovitis.

Articular cartilage and fibrocartilage have characteristic appearances on ultrasonography. Whereas the former appears as a thin hypoechoic band paralleling the articular surface, fibrocartilage appears hyperechoic. Chondrocalcinosis appears as discrete hyperechoic foci within the substance of the cartilage, in which case its presence is suggestive of calcium pyrophosphate deposition disease. Calcification along the margin of the articular cartilage gives rise to the double-contour sign seen in gout.

Tendons and muscles have characteristic appearances on ultrasonography. The presence of tendinosis, tendon tears, muscle edema or inflammation, atrophy, and tears can be diagnosed.[6] Ultrasonography is very sensitive,

although not specific, for the detection of small amounts of calcification or ossification. It is an excellent method to assess for calcific peritendinitis or periarthritis and to provide guidance for treatment. Abnormal fluid distention of synovial-lined structures can be assessed and treated under ultrasound guidance. Ultrasonography is an excellent modality to provide image guidance for therapeutic aspiration and injection of small and large joints, tendon sheaths, and cysts (e.g., bursae, ganglion, paralabral cysts, hematomas, abscesses) (Fig. 238-5). The real-time capability of ultrasonography is useful to demonstrate the presence of subluxations, to evaluate painful snapping, to document the distribution of injected material, and to assess adhesions. Ultrasonography is considered the method of choice to detect foreign bodies.

Newer ultrasound techniques provide a map of soft tissue mechanical properties, also known as ultrasound elastography (USE). These techniques fall into two categories, compression-based or shear-wave elastography. The former employs speckle tracking to estimate local tissue strain following minimal external compression of the tissue being examined, thereby producing a color-encoded strain map or map of tissue hardness. The latter method employs a shear wave produced either by an external source or by the transducer itself, the speed of the shear wave being an indirect measure of local Young modulus; a color-encoded map or quantitative estimate of local shear-wave speed or elastic modulus can be derived. Both techniques provide information regarding alterations of mechanical properties of tendons and muscles in a variety of degenerative, traumatic, and reparative states. For example, fatty infiltration resulting from chronic myopathic disorders produces measurable alterations in local muscle elastic modulus.

Nerves also have a characteristic appearance on ultrasonography. In cross section, a nerve often has a "cluster of grapes" or "honeycomb" appearance, with nerve fascicles appearing hypoechoic and surrounded by hyperechoic internal and external epineural fat. In the long axis, nerves display a characteristic "tram-track" appearance. Ultrasonography is useful in the diagnosis and treatment of carpal tunnel syndrome (Chapter 388)[7] and cubital tunnel syndrome. It is an excellent modality to assess for the presence of post-traumatic or post-surgical and interdigital neuromas and to provide image guidance for treatment, including therapeutic injections, nerve blocks, and ablative therapy.

Although ultrasonography is well suited to the evaluation of superficial structures, it is less well suited to assess deep structures. In some instances, soft tissue contrast can be poor. An inexperienced scanner may find ligaments and tendinous insertions difficult to differentiate from adjacent fibrofatty structures or mistake tendon anisotropy for tendinosis or complex fluid.

MAGNETIC RESONANCE IMAGING

Two tissue-dependent relaxation times, T1 and T2, vary with field strength. T1 (also known as the spin-lattice relaxation) and T2 (or the transverse relaxation time) along with proton density are the principal determinants of signal intensity. An image can emphasize either the T1 or T2 characteristics of the tissue. Different tissues have varying appearances, often based on levels of fat and water content, as reflected by their inherent T1 and T2 relaxation times. On T1-weighted or proton density images, tendon, muscle, fat, marrow, cortical bone, articular, and fibrocartilage have characteristic appearances. Many pathologic states are characterized by increased mobile water or effective T2 lengthening. Examples include soft tissue or marrow edema, inflammatory infiltrates, and neoplasm (Figs. 238-6 and 238-7). Images that emphasize T2 contrast are therefore helpful to display most pathologic states. Selective maps of T2 have been used to characterize the state of articular cartilage in early degenerative disease. Other cartilage-specific properties that relate to water content, glycosaminoglycan (GAG) content, and integrity of collagen architecture can be assessed using T2 and other parametric maps that can be derived from the MR data (Fig. 238-8).

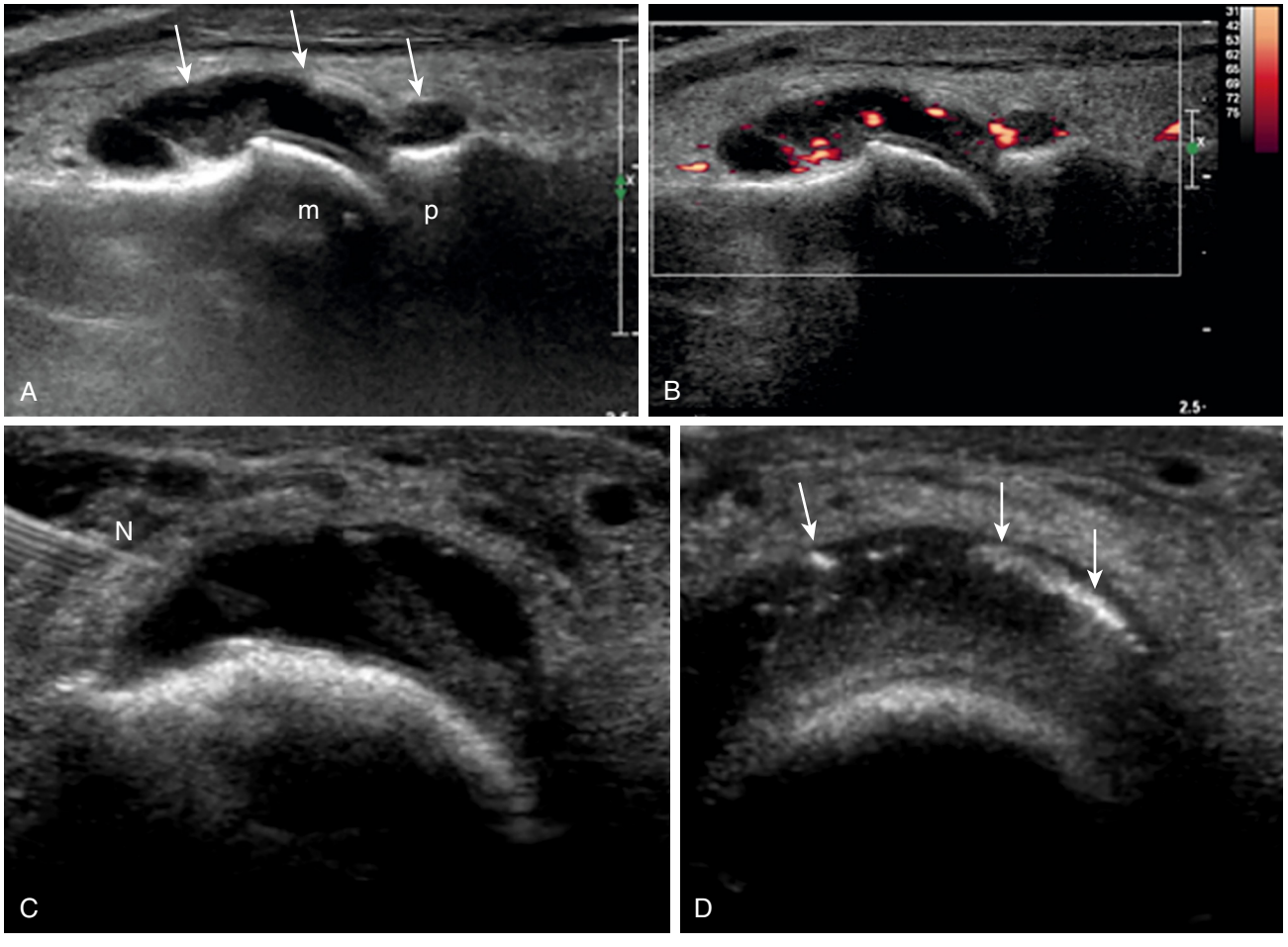

FIGURE 238-5. Ultrasound-guided therapy in the first metatarsophalangeal (MTP) joint of a female patient with pain and swelling. A, Longitudinal gray-scale image of the dorsal recess of the first MTP joint. Fluid and soft tissue distend the joint capsule (*arrows*). The metatarsal (m) and proximal phalanx (p) are labeled. Note that a thin hypoechoic (dark) band parallels the surface of the metatarsal head, corresponding to the overlying articular cartilage. **B,** Increased vascularity (red hues) demonstrated on power Doppler imaging within the dorsal recess reflects the level of disease activity. **C,** Transverse gray-scale ultrasound image shows a needle (N) within the distended dorsal recess from which several drops of synovial fluid were aspirated, followed by therapeutic injection. **D,** Postinjection transverse sonogram depicts low-level echoes (small echogenic foci within dorsal recess) and microbubbles (*arrows*) within the distended joint capsule from injected material. Microbubbles will aggregate along the nondependent portion of the distended joint capsule, whereas injected material tends to settle to the deep portion of the joint.

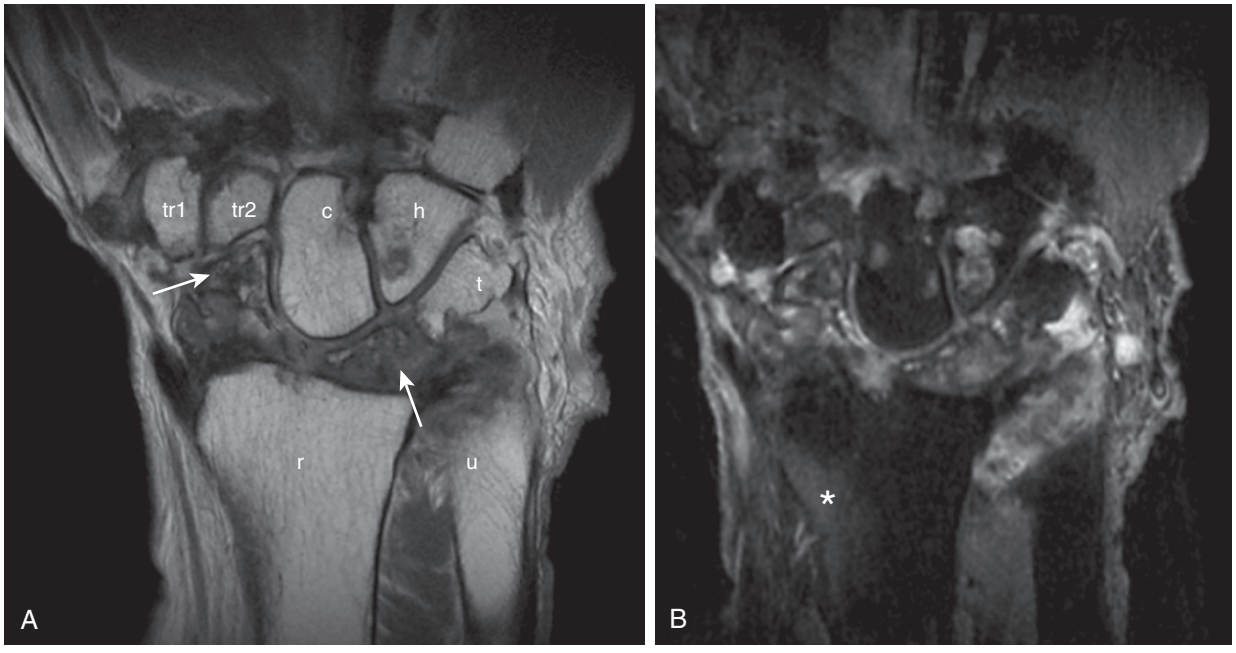

FIGURE 238-6. **Magnetic resonance imaging of the right wrist in a female patient with advanced rheumatoid arthritis. A,** Proton density coronal image shows loss of normally bright marrow signal within the scaphoid and lunate bones (*arrows*). The proximal scaphoid is eroded, and the lunate appears deformed and translocated and volarly tilted (not shown), giving rise to its triangular appearance. The distal ulna (u) is poorly visualized due to a large erosion. Intermediate-intensity material (appears dark gray) within the carpus and distal radioulnar joint is difficult to separate from the distal ulna, lunate, and scaphoid. The triquetrum (t), hamate (h), trapezium (tr1) and trapezoid (tr2), capitate (c), and radius (r) are labeled. **B,** Fluid-sensitive coronal image emphasizing T2 relaxation demonstrates increased signal intensity (bright) within the inflammatory pannus, compatible with an increase in mobile water associated with inflammation. Increased signal intensity is evident within the lunate, scaphoid, and distal ulna, including focal areas within the distal row of carpal bones, corresponding to small erosions. Diffuse increased signal within the distal radius likely reflects reactive marrow edema (*asterisk*).

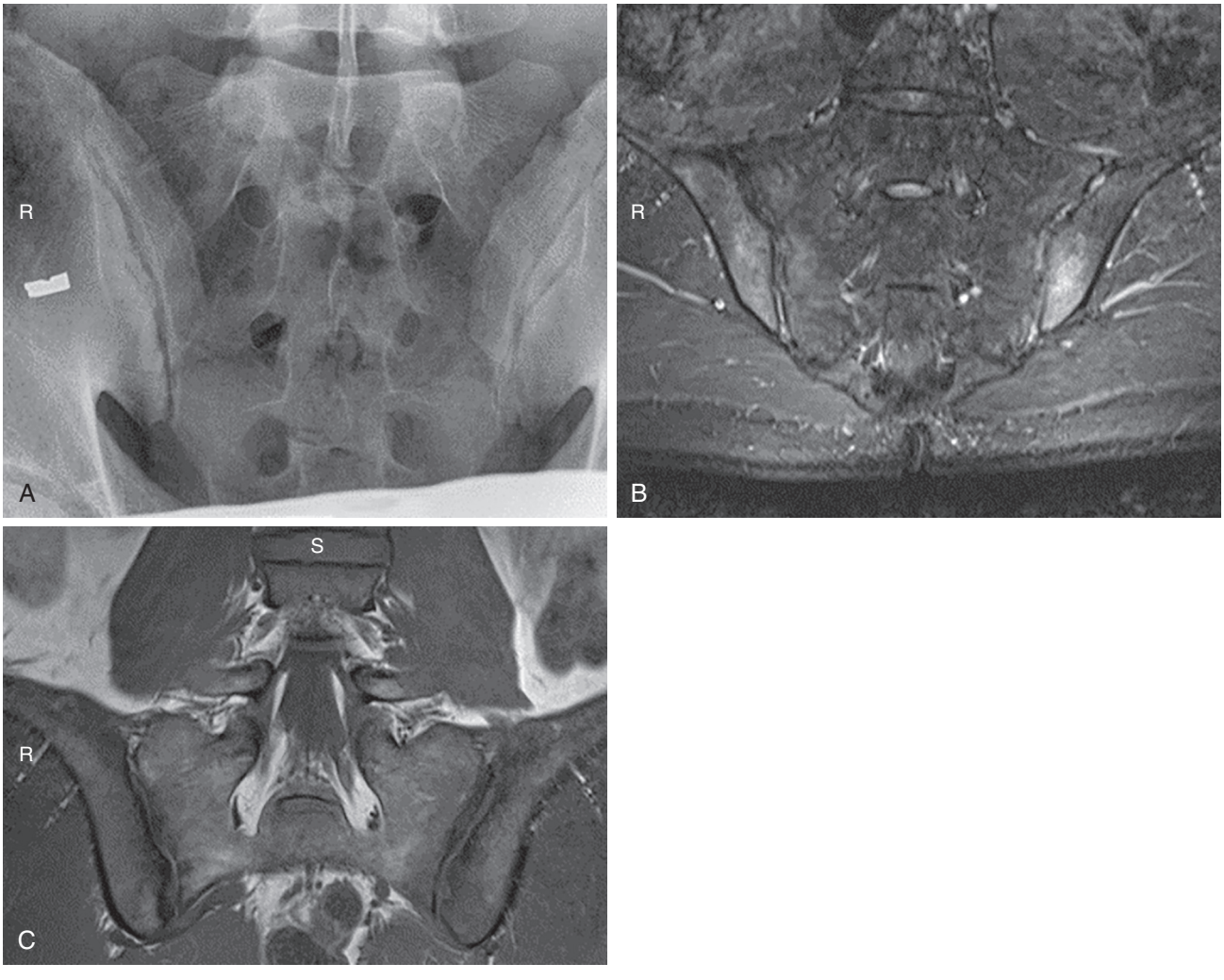

FIGURE 238-7. **Male age 42 years with low back pain and suspected seronegative arthritis. A,** Anteroposterior radiograph of the sacroiliac joints showing sclerosis involving the iliac portions of the joints bilaterally, with widening and probable erosion of the right sacroiliac joint. **B,** Oblique coronal fluid-sensitive, fat-suppressed T2-weighted. **C,** Oblique coronal T1-weighted images of the sacroiliac joints display symmetric combinations of low signal on T1 (dark areas), in part reflecting sclerosis, and high signal on T2 (bright areas), reflecting superimposed marrow edema. These features can be used to assess disease chronicity and activity.

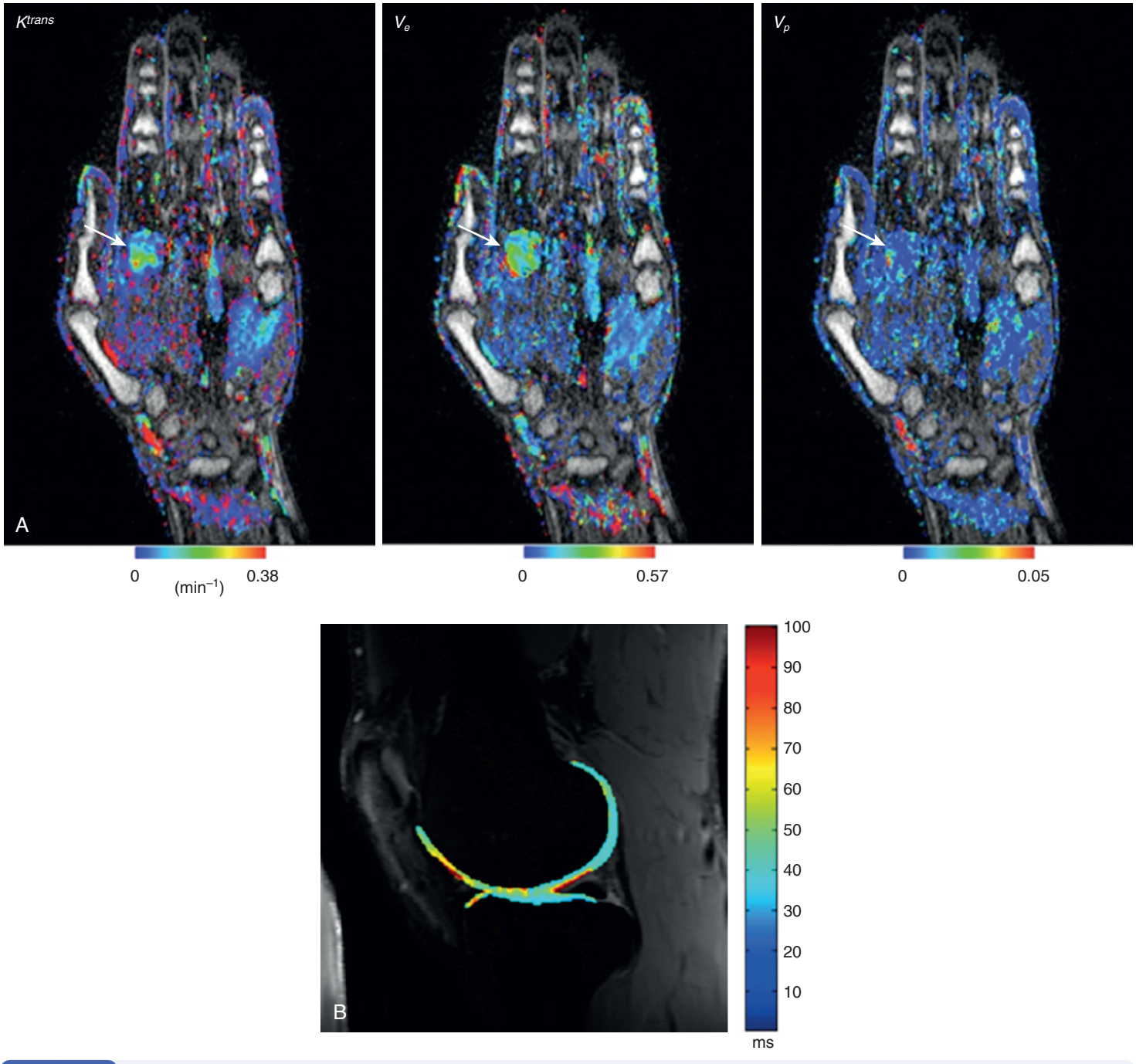

FIGURE 238-8. Functional magnetic resonance imaging. A, Parametric image derived from fitting a two-compartment model of soft tissue and synovial enhancement following intravenous administration of contrast material. Three parameters extracted from the time-intensity curves are displayed as parametric images: K^{trans} (*left*) provides a measure of contrast exchange into the extravascular soft tissues; V_e (*center*) and V_p (*right*) reflect the relative distribution volumes for the extravascular space and plasma, respectively. The *arrows* depict a region of increased synovial volume and enhancement at the second metacarpophalangeal joint. Increased values of K^{trans} and V_e illustrate increased vascular permeability at the site of inflammation. (Courtesy of Dr. Luis Beltran.) **B**, Sagittal T2 map of the knee in which relative T2 relaxation is color encoded, showing regions of higher cartilage T2 values at the femoral condyle and tibial plateau. This pattern reflects alterations in cartilage collagen architecture and water content and possibly early osteoarthritis. (Courtesy of Dr. Gregory Chang.)

Measurements and parametric images of apparent diffusion coefficient (ADC) provide a method to quantify soft tissue edema present in inflammatory states and may help to differentiate tissue inflammation from other potential sources of increased T2 contrast.[8] The loss of restrictive diffusion has likewise been employed as a quantitative metric and imaging tool to assess collagen breakdown in articular cartilage that occurs in early osteoarthritis.

The widely used contrast for MRI studies is a neutral hydrophilic salt of the gadolinium chelate, gadolinium diethylenetriamine-penta-acetic acid (Gd-DTPA). Gadolinium can be injected intravenously or directly into the joint. Intravenous injection (indirect magnetic resonance arthrography) carries the contrast in the vascular system to areas of hyperemia and inflammation (see Fig. 238-8). It can be used for assessment of synovial activity in inflammatory joint diseases. Gadolinium is taken up in inflamed synovium and is able to demonstrate thickened pannus. The slope of the early time–signal intensity curve provides a measure of tissue perfusion and can quantify inflammatory activity. Contrast material excreted into the synovial fluid provides excellent depiction of intra-articular structures and can be used in lieu of arthrographic direct techniques. In glycosaminoglycan-depleted cartilage, there can be delayed uptake of contrast into the cartilage, which would normally be inhibited by the negatively charged molecules.

Patients with renal disease who receive IV injection of gadolinium can develop nephrogenic systemic fibrosis (Chapter 246). When the kidney cannot sufficiently clear out the gadolinium, it produces fibrosis of many tissues, including the skin, muscle, heart, nerves, and pleura. The changes in the skin with nephrogenic systemic fibrosis are usually bilateral and

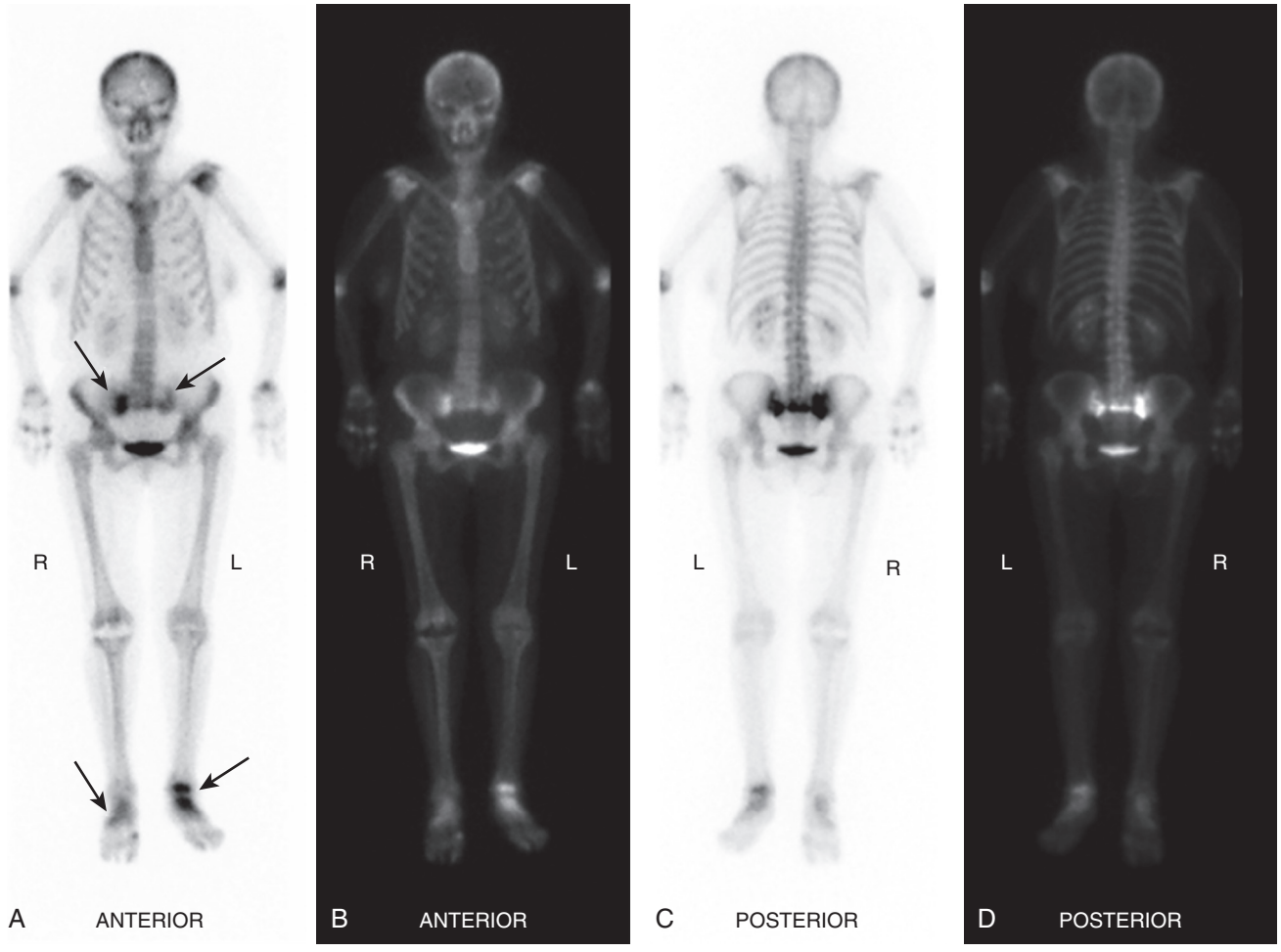

FIGURE 238-9. **Rectilinear bone scan in a patient with back pain. A, B,** Anterior and **(C, D)** posterior delayed images of the axial and appendicular skeleton demonstrate increased tracer uptake in the region of the sacral ala, left ankle, and right midfoot (*arrows*). Follow-up radiographs confirmed the presence of bilateral sacral ala fractures. Note that the central pooling of tracer in the expected location of the urinary bladder is normal. Bone scans provide a sensitive but nonspecific method to evaluate the appendicular and axial skeletons. Increased uptake in the feet in this patient was attributed to degenerative change. L = left; R = right.

symmetric, primarily involving the extremities and the trunk. These changes can mimic systemic sclerosis, but, unlike that disease, the face is usually spared. If renal function improves, the skin lesions may stabilize or improve, although the process progresses in some patients to affect mobility and cause severe pain.

Injection of dilute gadolinium into the joint (direct MR arthrography) is helpful for outlining structures and to detect morphologic damage. Injection is usually performed either under fluoroscopic or ultrasound guidance. This technique is particularly effective for the visualization of small structures such as the labrum of the hip or shoulder in the absence of a joint effusion. It is also helpful for demonstrating breakdown of soft tissue structures that normally prevent communication between joint compartments, such as the rotator cuff, triangular fibrocartilage of the wrist, and ligaments in the various joints. Techniques that enable image acquisition in near real time, as well as the development of MR-compatible needles now permit a variety of percutaneous procedures to be performed directly under MR guidance.

SCINTIGRAPHY

Scintigraphy can provide a global assessment of abnormal tracer uptake or can be performed using a targeted approach (Fig. 238-9). Images often provide high tissue contrast but are of relatively poor spatial resolution. Commonly used agents include tagged red blood cells to assess blood flow, agents that reflect bone metabolism (technetium-99m methylene diphosphate [Tc-MDP]), agents that reflect glucose metabolism (18-fluorine deoxyglucose [18-FDG]), and agents that concentrate at sites of inflammation, such as autologous white blood cells labeled with ^{111}In (indium) and ^{67}Ga-citrate (gallium). Clinical applications include detection of a variety of malignancies, osteomyelitis, vascular graft infection, multifocal infectious disease, inflammatory diseases (e.g., rheumatoid arthritis, vasculitis, inflammatory bowel disease, and sarcoidosis), fever of unknown origin, and infection of joint prostheses.

Bone scintigraphy uses Tc-MDP as the radioactive tracer. The isotope goes to areas of high bone turnover and vascular flow, as well as areas where calcium or bone is deposited. Three-phase bone scans, obtained at different intervals after injection, reflect the early vascular phase, the intermediate blood pool phase, and the late phase. Each phase allows for further characterization of the disease process. Abnormal tracer uptake is seen in areas of inflammation, infection, neoplasm, osteonecrosis, and fracture. The scan is most useful to identify the location of lesions within the skeleton but is nonspecific.

PET scans are often used in combination with either CT or MRI to achieve improved spatial registration, allow accurate estimates of soft tissue attenuation, provide high-quality anatomic images, and quantify metabolic activity.[9] Combined PET-CT or PET-MRI provides high-resolution images of abnormal metabolic activity and may ultimately provide the most definitive maps of inflammatory activity in patients with rheumatic disease.

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239 INHERITED DISEASES OF CONNECTIVE TISSUE

REED E. PYERITZ

MUCOPOLYSACCHARIDOSES

DEFINITION

Proteoglycans are ubiquitous components of the extracellular matrix and the surfaces of cells, and they are among the largest and most complex of human molecules. Proteoglycans consist of a protein core to which are covalently bound glycosaminoglycans (GAGs; formerly called mucopolysaccharides) of several types: dermatan sulfate, heparan sulfate, keratan sulfate, and chondroitin sulfate. During normal degradation, these four polymeric molecules are cleaved from their protein core in lysosomes; then they, plus hyaluronan (a GAG lacking a protein core), are catabolized further in lysosomes in a stepwise fashion by more than a dozen enzymes. Genetic defects in any one of these enzymes lead to the accumulation of GAG metabolites in lysosomes, with profound disruption of cellular physiology. The phenotypes resulting from deficiencies of these catabolic enzymes are termed *mucopolysaccharidoses* and are classified into seven types (Table 239-1). Several additional storage disorders, termed *mucolipidoses*, are caused by a genetic defect in post-translational modification of lysosomal enzymes and share features with the mucopolysaccharidoses.

EPIDEMIOLOGY

All mucopolysaccharidosis disorders are rare, each with an incidence of one or fewer cases per 100,000 births, and are without ethnic predilection.

PATHOBIOLOGY

With the exception of mucopolysaccharidosis II (Hunter syndrome), which is X-linked, each of these disorders is autosomal recessive. All mucopolysaccharidoses are caused by deficiency of a single lysosomal enzyme responsible for a specific step in GAG metabolism (see Chapter 192). Catabolism of GAG proceeds normally until the step requiring the defective enzyme, when further normal metabolism halts. Although a minor degree of nonspecific breakdown occurs, resulting in urinary excretion of cleaved GAG that can be useful diagnostically, the accumulation of GAG within lysosomes of cells of mesenchymal origin, endothelium, and, in most cases, neurons causes widespread, progressive cellular dysfunction and clinical effects. Lysosomal enzymes are targeted to lysosomes by post-translational addition of mannose 6-phosphate. Deficiency of the phosphotransferase that catalyzes the first step in this reaction results in an inability to catabolize any GAG molecules. The catabolic enzymes, which normally would be transported into lysosomes, instead are secreted from the cell and are found in unusually high concentrations in plasma, providing one diagnostic test for mucolipidoses.

Pathology

All pathologic manifestations of mucopolysaccharidosis and mucolipidosis disorders worsen with age, and some are present from early developmental stages. Gross anatomic hallmarks are hepatosplenomegaly, marked skeletal alterations (termed *dysostosis multiplex*) that result in short stature and thoracic cage deformity, thickening and narrowing of airways and arteries, and coarsening of facial features. Although mental retardation is a prominent feature of some of these conditions, the brain may show only ventriculomegaly secondary to communicating hydrocephalus. On microscopy, mesenchymal cells show a cytoplasm full of apparently empty vacuoles; these are lysosomes from which GAG has been removed by fixation. Cells cultured from patients show greatly enlarged lysosomes filled with granular material. In the severe form of mucolipidosis, dense inclusions are present, which gave rise to the common name, *I-cell disease*.

CLINICAL MANIFESTATIONS

Each of the disorders in Table 239-1 shows a wide spectrum of clinical severity. This wide spectrum has led to a classification that gives the impression of separate disorders within some of the mucopolysaccharidosis and mucolipidosis types, but these represent the apparent ends of the continuum. Some

TABLE 239-1 MUCOPOLYSACCHARIDOSES AND MUCOLIPIDOSES

TYPE	EPONYM OR COMMON NAME	CLINICAL FEATURES	INHERITANCE	OMIM*	ENZYMATIC DEFECT
MPS IH	Hurler syndrome	DM and short stature; MR; corneal clouding; HS; heart disease; death in childhood	AR	252800	α-L-iduronidase
MPS IS	Scheie syndrome	Coarse facies; stiff joints; corneal clouding; aortic valve disease; normal intelligence and lifespan	AR	252800	α-L-iduronidase
MPS II	Hunter syndrome	Severe form: coarse facies, DM and short stature, HS; MR; no corneal clouding; death by late adolescence. Mild form: coarse facies, short stature; normal intelligence; survival to adulthood	XL	309900	Iduronate sulfatase
MPS IIIA	Sanfilippo A	Severe MR and hyperactivity; mild somatic changes	AR	252900	Heparan *N*-sulfatase
MPS IIIB	Sanfilippo B	Same as MPS IIIA	AR	252920	α-*N*-acetylglucosaminidase
MPS IIIC	Sanfilippo C	Same as MPS IIIA	AR	252930	Acetyl-coenzyme A: α-glucosaminide acetyltransferase
MPS IIID	Sanfilippo D	Same as MPS IIIA	AR	252940	*N*-acetylglucosamine 6-sulfatase
MPS IVA	Morquio A	Short stature and distinct skeletal dysplasia with odontoid hypoplasia and myelopathy; corneal clouding; normal intelligence; valvular heart disease	AR	253000	Galactose 6-sulfatase
MPS IVB	Morquio B	Same as MPS IVA	AR	253010	β-Galactosidase
MPS VI	Maroteaux-Lamy	DM and short stature; corneal clouding; normal intelligence; aortic stenosis; leukocyte inclusions; hydrocephalus in severe form	AR	253200	*N*-acetylgalactosamine
MPS VII	Sly syndrome	DM; HS; widely variable, including MR	AR	253220	β-Glucuronidase
MPS IX	—	Short stature; periarticular soft tissue masses	AR	601492	Hyaluronidase
ML II	I-cell disease	Similar to but more severe than MPS IH but with cellular inclusions; no mucopolysacchariduria	AR	252500	UDP-*N*-acetylglucosamine: lysosomal enzyme *N*-acetylglucosaminyl-1-phosphotransferase
ML III	Pseudo-Hurler polydystrophy	Short stature and mild DM; stiff joints; mild MR; survival to adulthood	AR	252500	Same as ML II arthropathy, coarse facies; variable but milder

*Entries in Online Mendelian Inheritance in Man, OMIM. McKusick-Nathans Institute of Genetic Medicine. Baltimore: Johns Hopkins University. http://omim.org.
AR = autosomal recessive; DM = dysostosis multiplex; HS = hepatosplenomegaly; MR = mental retardation; UDP = uridine diphosphate; XL = X-linked.

ABSTRACT

The inherited diseases of connective tissue are diverse in phenotypic characteristics, genetic and molecular causes, and effects on health. Among more than 200 conditions, some of the more common are the mucopolysaccharidoses, Marfan syndrome, the Ehlers-Danlos syndromes, the osteogenesis imperfecta syndromes, and pseudoxanthoma elasticum. In their severe forms, all can shorten life expectancy. Fortunately, therapies such as medication, enzyme replacement, and gene therapy are becoming more frequent and effective.

KEYWORDS

mucopolysaccharidoses
Marfan syndrome
Ehlers-Danlos syndromes
osteogenesis imperfecta

of the disorders without treatment result in death by adolescence (Hurler syndrome,[1] severe Hunter syndrome,[2] mucolipidosis II), but others are commonly compatible with survival to adulthood.

The milder end of the mucopolysaccharidosis I spectrum, Scheie syndrome, may not be diagnosed until adulthood; patients present with stiffened joints, corneal clouding and glaucoma, carpal tunnel syndrome, and aortic valvular disease. Stature and intelligence are not affected. The main health risks are cardiac valvular involvement, thickening of meninges that can produce a myelopathy, and thickening of the upper airways that can produce obstructive symptoms and sleep apnea.

Mucopolysaccharidosis II, Hunter syndrome, is distinctive because it is X-linked (affecting males almost exclusively), and the cornea shows little overt clouding. Cervical myelopathy, obstructive airway disease, and cor pulmonale are important concerns. A combined conductive and neurosensory hearing loss is common.

Neither mucopolysaccharidosis IV (Morquio syndrome)[3] nor mucopolysaccharidosis VI (Maroteaux-Lamy syndrome)[4] affects intelligence. Both syndromes often are associated with severe skeletal changes, which are distinct radiographically but produce similar problems of kyphoscoliosis, pectus carinatum, restrictive lung disease, severe short stature, and joint degeneration. Cervical myelopathy resulting from a thickened dura is common to both disorders and is accentuated by odontoid hypoplasia in mucopolysaccharidosis IV. Thickening of the aortic and mitral valves may produce severe dysfunction necessitating their replacement. General anesthesia is especially hazardous because of the narrow upper and middle airways and cervical instability.

Patients with mucolipidosis III[5] (pseudo-Hurler polydystrophy) resemble patients with mucopolysaccharidosis VI but often have mild to moderate mental retardation. Aortic regurgitation is common.

DIAGNOSIS

Differential Diagnosis

Because clinical diagnosis of these conditions is difficult in young children, before most of the clinical features have progressed, many countries have instituted newborn screening.[6] The diagnosis should be considered in any person with hepatosplenomegaly and coarsening of the facial features. Evaluation requires a pedigree analysis, ophthalmologic examination, skeletal radiographic survey, echocardiography, and analysis of the urine for excretion of GAGs. Often the specific mucopolysaccharidosis is evident from radiographs, the presence or absence of corneal clouding, and the pattern of mucopolysaccharidosis. Enzymatic analysis of leukocytes confirms the diagnosis. Patients with mucolipidoses do not show mucopolysaccharidosis but have marked elevation of all the GAG catabolic lysosomal enzymes in plasma.

TREATMENT

Ventriculoperitoneal shunting is necessary if intracranial pressure is elevated. Close attention to hearing and visual problems is essential throughout life. Many adults with mucopolysaccharidosis or mucolipidosis require surgery for carpal tunnel syndrome. Cardiovascular surgery for valvular or coronary disease may be necessary. All use of anesthesia is high risk because of the narrow airways and, in the case of mucopolysaccharidosis IV, atlantoaxial instability. For patients who remain ambulatory, selective joint replacement can be beneficial. Because of the morbidity associated with thoracic cage deformity, consideration should be given to stabilizing the spinal deformity before it becomes severe.

Replacement of the deficient enzyme by intravenous infusion is available or being evaluated for most of the mucopolysaccharidosis disorders. Laronidase (Aldurazyme) has been approved in the United States for treatment of mucopolysaccharidosis I. An infusion every 2 weeks for 1 year in adolescent and adult patients resulted in substantial reduction in hepatosplenomegaly and modest improvement in pulmonary function, sleep apnea, and joint mobility. Whether early institution of therapy in young children modulates mental retardation in the Hurler variant of mucopolysaccharidosis I is uncertain. Galsulfase (Naglazyme) has been approved for the treatment of mucopolysaccharidosis VI, in which somatic rather than neurologic problems predominate. Enzyme replacement should be started in all patients when diagnosed.[7]

Bone marrow transplantation has been attempted in many of the mucopolysaccharidosis disorders, with mixed success. The earlier transplantation occurs, the better the outcome in terms of somatic problems, but prevention of mental retardation has not occurred. Current recommendations based on consensus in Europe calls for hematopoietic stem cell transplantation for patients with Hurler syndrome before the age of 2.5 years.

MARFAN SYNDROME

DEFINITION

Marfan syndrome is an autosomal dominant, pleiotropic disorder caused by defects in the principal component of the extracellular microfibril, the large glycoprotein fibrillin-1.[8] The disease manifestations occur in multiple systems, especially the eye, skeleton, heart, aorta, lung, and integument. Notable features include dislocation of the ocular lens, tall stature with particularly long limbs and digits, deformity of the thoracic cage by pectus carinatum or excavatum with abnormal curvature of the spine, mitral and tricuspid valve prolapse, dilation of the sinuses of Valsalva and predisposition to aortic dissection, spontaneous pneumothorax, abnormal skin stretch marks, hernias, and dural ectasia. If untreated, patients often die before 30 or 40 years of age from aortic dissection or congestive heart failure.

EPIDEMIOLOGY

Marfan syndrome is a common mendelian disorder, with an estimated incidence of about 1 per 5000 births. Marfan syndrome is found throughout the world, without ethnic or geographic predilection.

PATHOBIOLOGY

Pathogenesis

Mutations in *FBN1*, which maps to human chromosome 15q21.1 and encodes fibrillin-1, cause Marfan syndrome and related connective tissue disorders. Several thousand distinct mutations have been found, and few occur in more than one family. Patients are heterozygous for mutations in *FBN1*, leading to autosomal dominant inheritance. Extracellular microfibrils are polymers of many fibrillin-1 molecules and are ubiquitous in the extracellular matrix of most tissues. Latent transforming growth factor-β (TGF-β) binding protein, which keeps the cytokine inactive, bears striking homology to regions of fibrillin. Abnormalities of either the quality or the quantity of microfibrils disrupt normal signaling by TGF-β, especially during embryonic development and postnatal growth. Studies in mice engineered to harbor human mutations in *FBN1* showed that excessive TGF-β signaling causes abnormal lung septation (the precursor to pneumothorax), bone overgrowth, mitral valve prolapse, muscular hypoplasia, and aortic dilation. This fundamental shift in understanding of the pathogenesis of Marfan syndrome has suggested novel therapies, such as with small molecules that affect the activity of TGF-β or its downstream signaling.

The features of Marfan syndrome are highly variable, even among relatives who share the same mutation in *FBN1*. This variability persists after accounting for the effects of age. Men tend to be affected more severely, for unclear reasons.

Pathology

The features of Marfan syndrome are age dependent. Some severely affected infants have flagrant features and often die of mitral regurgitation and heart failure despite aggressive management. At the other end of the clinical spectrum, Marfan syndrome merges with several related disorders and patients may not come to medical attention, let alone receive a definitive diagnosis, until adulthood.

None of the gross or microscopic pathologic changes is specific for Marfan syndrome. The medial degeneration of the aortic wall, characterized by disarray and fragmentation of the elastic fibers and increased proteoglycan (often inappropriately termed *cystic medial necrosis*), also can be seen in hereditary aortopathy syndromes and in older people with hypertension. Aortic dissection (Chapter 63) usually begins just superior to the aortic valve (type A) and often progresses to the bifurcation. Death usually results from retrograde dissection and hemopericardium. About 10% of dissections begin in the descending thoracic aorta (type B).

CLINICAL MANIFESTATIONS

The lens tends to be displaced superiorly, and usually the zonules remain intact. The retina is at increased risk for detachment, especially in patients who are highly myopic. Tubular bones overgrow, accounting for the disproportionate tall stature (dolichostenomelia), long digits (arachnodactyly), and sternal deformity. Ligaments may be lax, causing scoliosis and joint hypermobility. Alternatively, congenital contractures are common, especially of the elbows.[9] The palate typically is highly arched, and the dentition can be crowded and malocclused. Mitral valve prolapse occurs in about 80% of cases, and the valve leaflets become progressively thickened (myxomatous on histopathology). The mitral annulus may dilate and calcify. Aortic root dilation begins in the sinuses of Valsalva and progresses with age, albeit at highly variable rates (Chapters 55 and 63).[10] Most males with Marfan syndrome have an aortic root dimension above the upper limit of normal for their body surface area by adolescence. Some females show a slower progression and may have a root diameter near the upper limit of normal well into adulthood. The dilation usually does not

involve the distal ascending aorta. Spontaneous pneumothorax, resulting from rupture of apical blebs, occurs in about 5% of patients.[11] Stretch marks (striae atrophicae) occur over areas of flexural stress, such as the shoulders, breasts, and lower back. Some clinical features continue to progress as lifespan has been lengthened owing to successful cardiovascular surgery.[12] The neural canal in the lumbosacral region is enlarged in most people with Marfan syndrome; this may be visible on plain radiographs, especially if the neuroforamina are widened. Imaging by computed tomography or magnetic resonance imaging is diagnostic and should be used in patients with back pain and radicular symptoms. Dural ectasia progresses with age; large anterior meningoceles in the pelvis are a severe manifestation. In addition, sleep apnea and simple cysts in the liver and kidneys are common.

DIAGNOSIS

Differential Diagnosis

The conditions that overlap clinically and genetically with Marfan syndrome include familial aortic aneurysm, familial ectopia lentis, *m*itral valve prolapse, mild *a*ortic dilation, *s*triae, *s*keleton (MASS) phenotype (which includes many families with mitral valve prolapse syndrome), and Loeys-Dietz syndrome. Most of these conditions are diagnosed clinically, so differentiating among them is arbitrary. A careful family history is essential to this process. Molecular genetic testing is important. If the causative variant in *FBN1* is known in a family, analysis of DNA can be used effectively for presymptomatic or prenatal diagnosis. Loeys-Dietz syndrome, which is associated with generalized arterial tortuosity and susceptibility to dissection, is caused by pathogenic variants in either of two receptors for TGF-β, *TGFBR1* and *TGFBR2*, and molecular analysis is clinically available. Most mutations in *TGFBR1* and *TGFBR2* do not cause Loeys-Dietz syndrome but do predispose to familial thoracic aneurysm and dissection.

A question of Marfan syndrome arises most commonly in tall, lanky adolescents who have several minor skeletal features, nearsightedness, and athletic desires. A detailed ophthalmologic examination with full pupillary dilation and a transthoracic echocardiogram are essential components in the evaluation. If these test results are negative and no one in the family has a history of Marfan syndrome or aortic dissection, the patient probably can be reassured.

TREATMENT

All patients should be seen at least annually by a physician who manages the overall care. Most patients require annual ophthalmologic and cardiologic consultation and orthopedic consultation as required by specific problems. Lens subluxation often requires surgical correction.[13]

A number of studies, but only one randomized clinical trial, support the prophylactic use of β-adrenergic blockade from an early age to slow the rate of aortic root dilation and protect against aortic dissection. Although several trials found no benefit with the angiotensin receptor blocker losartan compared with atenolol,[A1] one large European trial showed a benefit of losartan on aortic root dilation rate[A2] and a reduction in the risk of aortic dissection and death, even when adjusted for the use of β-adrenergic blockers.[A3] Furthermore, irbesartan (150 mg increased to 300 mg daily as tolerated) can significantly reduce the rate of aortic dilation, especially in younger patients, with benefit also likely in patients who are also on a β-adrenergic blocker.[A4] Based on a meta-analysis of all trials, angiotensin receptor blockers appear to provide incremental benefit for reducing the progression of aortic dilation when added to β-adrenergic blockers.[A5,A6]

Prophylactic surgical repair of the aortic root has had the greatest beneficial impact. The composite graft, involving a prosthetic valve in a Dacron tube and implantation of the coronary ostia into the graft, was the first approach to produce markedly improved survival in these patients. More recently, replacement of the aneurysm and preservation of the native aortic valve should be considered first.[13] For adults, aortic root surgery should be strongly considered when the maximal aortic diameter reaches 45 mm, and a family history of aortic dissection should prompt earlier repair (Chapter 55).[14]

PROGNOSIS

Life expectancy for people with Marfan syndrome has improved markedly, to the point that many patients can expect survival to advanced years. Increased lifespan results in the appearance of new clinical problems, such as obstructive sleep apnea, peripheral arterial aneurysms, lumbosacral meningoceles, and truncal obesity. Some data suggest that aortic dissection and cardiovascular death are more likely in patients with *FBN1* haploinsufficiency with expression of the nonmutated allele than in patients with dominant-negative mutations in which abnormal fibrillin 1 coded by the mutated allele interacts with normal fibrillin 1 coded by the normal allele. Experimental data suggest that a fluoroquinolone antibiotic should be avoided in patients with Marfan syndrome because these may increase the risk of aortic dissection and rupture.[15]

EHLERS-DANLOS SYNDROMES

DEFINITION

The Ehlers-Danlos syndromes are clinically variable and genetically heterogeneous. Diagnoses are still based largely on the bedside examination. The unifying themes among these disorders are fragility of tissues, joint hypermobility, and skin hyperextensibility.

EPIDEMIOLOGY

No accurate data exist, but an incidence of about 1 in 5000 births is a reasonable estimate of how many individuals qualify for one of the Ehlers-Danlos syndrome diagnoses. Each type represents something of a clinical spectrum, with the mild end merging with what might be considered normal variation. The extent to which normal variation in joint hypermobility, skin elasticity, and tissue fragility represents genetic variation at loci that encode collagen or other extracellular matrix genes requires considerable research.

PATHOBIOLOGY

Pathogenesis

Defects in collagen and other proteins in the extracellular matrix of various tissues underlie all forms of Ehlers-Danlos syndrome that have been elucidated so far. The specific mutations occur in a variety of genes, with the effect of altering the structure, synthesis, post-translational modifications, or stability of the collagens involved. The known molecular defects are listed in Table 239-2.[16]

Pathology

Few findings in the routine pathologic evaluation distinguish among the various types of Ehlers-Danlos syndrome or even distinguish individual types from normal.[17] Thickness of the dermis is decreased in some forms, especially the vascular type, and the walls of arteries are reduced in thickness in this type. By electron microscopy, the classic, hypermobile, and kyphoscoliotic types have abnormal collagen fibers, especially when viewed in cross section (variable and often increased fiber diameter with an irregular outline). In the vascular type, some patients have dilated endoplasmic reticulum consistent with aberrant secretion of type III collagen molecules.

CLINICAL MANIFESTATIONS

The major and minor features of each Ehlers-Danlos syndrome are detailed in Table 239-2. Infants with classic Ehlers-Danlos syndrome often are born prematurely by 4 to 8 weeks because of rupture of fetal membranes. Diagnosis of the vascular and kyphoscoliotic types is important because of their cardiovascular features. The vascular type, previously termed *Ehlers-Danlos syndrome IV*, is characterized by spontaneous rupture of large arteries and hollow organs, especially the colon and uterus, and pneumothorax. Because these events carry considerable morbidity, life expectancy is reduced, on average, by more than half. During pregnancy, women with this form of Ehlers-Danlos syndrome are especially vulnerable to rupture of major arteries and the uterus. In the kyphoscoliotic type, aortic root dilation and aortic regurgitation can develop. Patients with most forms of Ehlers-Danlos syndrome are prone to develop mitral valve prolapse, and progression to mitral regurgitation (Chapter 60) occurs more often than in the common form of mitral valve prolapse.

DIAGNOSIS

Differential Diagnosis

By careful adherence to the clinical features shown in Table 239-2 and judicious use of laboratory tests, the various defined types of Ehlers-Danlos syndrome can be differentiated. Many other specific syndromes need to be excluded. The kyphoscoliotic type of Ehlers-Danlos syndrome in infants shares some features with severe Marfan syndrome. Patients with Larsen syndrome may resemble patients with the arthrochalasis type of Ehlers-Danlos syndrome. The skin redundancy and loss of elasticity of the dermatosparaxis type of Ehlers-Danlos syndrome is reminiscent of autosomal dominant cutis laxa, which is not associated with easy bruising or tissue fragility.

TABLE 239-2 EHLERS-DANLOS SYNDROMES

TYPE	FORMER NAME	CLINICAL FEATURES*	INHERITANCE	OMIM†	MOLECULAR DEFECT
Classic	EDS I and II	Joint hypermobility; skin hyperextensibility; atrophic scars; smooth, velvety skin; subcutaneous spheroids	AD	130000 130010	Structure of type V collagen caused by mutations in *COL5A1* or *COL5A2*
Hypermobility	EDS III	Joint hypermobility; some skin hyperextensibility, with or without a smooth, velvety texture	AD AR	130020 225320	? Tenascin-X (*TNX*)
Vascular	EDS IV	Thin skin; easy bruising; pinched nose; acrogeria; rupture of large- and medium-caliber arteries, uterus, and large bowel	AD	130050 (225350) (225360)	Deficient type III collagen (*COL3A1*)
Kyphoscoliotic	EDS VI	Joint hypermobility; congenital, progressive rupture; scoliosis; scleral fragility with globe rupture; tissue fragility, aortic dilation, MVP	AR	225400	Deficiency of lysyl hydroxylase
Arthrochalasis	EDS VII A	Joint hypermobility, severe, with subluxations, congenital hip dislocation; skin hyperextensibility; tissue fragility	AD	130060	No cleavage of amino terminus of type I procollagen caused by mutations in *COL1A1* or *COL1A2*
Dermatosparaxis	EDS VII C	Severe skin fragility; decreased skin elasticity; easy bruising; hernias; premature rupture of fetal membranes	AR	225410	No cleavage of amino terminus of type I procollagen caused by deficiency of peptidase
Unclassified types	EDS V EDS VIII EDS X EDS XI EDS IX EDS, progeroid form	Classic features Classic features and periodontal disease Mild classic features, MVP Joint instability Classic features; occipital horns Classic features and premature aging	XL AD ? AD XL AR	305200 130080 225310 147900 309400 130700	? ? ? ? Allelic to Menkes syndrome Deficiency of galactosyltransferase I

*Listed in order of diagnostic importance.
†Entries in Online Mendelian Inheritance in Man, OMIM. McKusick-Nathans Institute of Genetic Medicine. Baltimore: Johns Hopkins University. http://omim.org.
AD = autosomal dominant; AR = autosomal recessive; EDS = Ehlers-Danlos syndrome; MVP = mitral valve prolapse; XL = X-linked.

The most difficult decision is whether any diagnosis of Ehlers-Danlos syndrome is warranted.[18] Patients who have only joint hypermobility without skin changes should not be labeled with Ehlers-Danlos syndrome; a diagnosis of familial joint hypermobility might be more appropriate. Familial joint instability involves a predisposition to dislocations of major joints that is rare in most types of Ehlers-Danlos syndrome except for arthrochalasis.

TREATMENT

Management of most skin and joint problems should be conservative and preventive. Sutures need to be placed with careful attention to approximating the margins and avoiding tension; removable sutures should be left in place for twice the usual time. Most instances of joint hypermobility and pain in Ehlers-Danlos syndrome do not require surgical treatment. Benefit often is derived from physical therapy designed to strengthen the muscles that provide support for the loose ligaments. All patients should receive genetic counseling about the mode of inheritance and their risk for having children affected with Ehlers-Danlos syndrome. The possibility of prenatal diagnosis exists for all of the Ehlers-Danlos syndrome types with defined molecular or biochemical defects.

The vascular type of Ehlers-Danlos syndrome requires particular surgical care; the ruptured arteries are difficult to repair because of the pronounced vascular fragility. Experienced vascular surgeons are having some success with prophylactic repair of vessels deemed to be at risk for dissection or rupture. One clinical trial suggested improved outcomes with prophylactic β-adrenergic blockade. Rupture of the bowel is a surgical emergency. Because the risk for uterine and vascular rupture is especially high during pregnancy in women with the vascular form, affected women should be advised that there is a substantial risk for death related to pregnancy and delivery. Patients should be advised to avoid contact sports and to treat blood pressure elevations aggressively. Arteriography and arterial lines should be avoided if possible. Biochemical and genetic screening holds the potential for reassuring relatives at risk that they do not have a defect in type III collagen.

The kyphoscoliotic type of Ehlers-Danlos syndrome may improve with large doses of vitamin C (1 to 4 g/day) because ascorbate is a cofactor for the enzyme that is deficient. No other metabolic or genetic therapy is effective in other forms of Ehlers-Danlos syndrome.

OSTEOGENESIS IMPERFECTA SYNDROMES

DEFINITION

The heterogeneous group of disorders called *osteogenesis imperfecta* includes, at one end of the severity spectrum, a type that is lethal prenatally or in the neonatal period and, at the other, such mild features that make distinguishing affected individuals from the general population is difficult. The unifying feature is hereditary osteopenia (insufficient bone), with primary defects in the protein matrix in bone and other tissues. The clinical syndromes all involve osteoporosis with liability to fracture (Chapter 225).

EPIDEMIOLOGY

No careful epidemiologic study has been performed, and the milder forms of type I osteogenesis imperfecta merge with the phenotypes of familial osteoporosis, fracture susceptibility, and joint hypermobility found in the general population. A crude estimate of the overall prevalence of osteogenesis imperfecta is 1 to 2 per 20,000 births. The neonatal lethal form (type II), which is almost always caused by a new mutation in a parental gamete, has an incidence of about 1 in 50,000 births.

PATHOBIOLOGY

Pathogenesis

Most patients in whom mutations have been found usually have defects in the two genes that encode the procollagen chains of type I collagen, *COL1A1* and *COL1A2*. Type I collagen is composed of two α1(I) and one α2(I) procollagen chains; the mature fiber requires considerable post-translational modification, which occurs appropriately only if the three procollagen chains have intertwined to form a triple helix that is perfect and completed at the right speed. A mutation that affects formation of the triple helix, such as substitution of one of the mandatory glycine residues that occurs at every third position, also has adverse effects on the modifications that render the molecule capable of forming effective mature fibers. As a result, a single nucleotide change resulting in a missense mutation can have profound effects on the extracellular matrix and produce a severe condition. Alternatively, and at first glance paradoxically, a mutation that eliminates an entire allele, or at least production of any product capable of intertwining with normal procollagen chains, has a much milder effect on the extracellular matrix and on the severity of osteogenesis imperfecta. Examples of the most common classes of mutations are shown in Table 239-3. Hundreds of pathogenic variants occur. Patients with mutations in *COL1A1* or *COL1A2* are heterozygous, and thus the most common forms of osteogenesis imperfecta are inherited as autosomal dominant traits. Several autosomal recessive forms of osteogenesis imperfecta occur because of mutations in genes that encode enzymes that process type I collagen into mature fibrils.

TABLE 239-3 OSTEOGENESIS IMPERFECTA

TYPE	CLINICAL FEATURES	INHERITANCE	OMIM*	BASIC DEFECTS
I	Fractures variable in number; little deformity; stature normal or nearly so; blue sclerae; hearing loss common but not always present; DI uncommon	AD	166200	Typically, one nonfunctional *COL1A1* allele
II	Lethal in utero or shortly after birth; many fractures at birth typically involving ribs (may appear "beaded") and other long bones; little calvaria; pulmonary hypertension	AD	166210	COL1A1 or *COL1A2:* substitution of glycyl residues; occasionally deletions of a portion of the triple-helical domain
		AR	259400	Deletion in *COL1A2* plus a nonfunctional allele
III	Fractures common, but long bones progressively deform starting in utero; stature markedly reduced; sclerae often blue but become lighter with age; DI and hearing loss common	AD	259420	One single amino acid substitution
		AR (rare)	259440	Two mutations in *COL1A1* and/or *COL1A2* (rarely)
IV	Fractures common; stature usually reduced; bone deformity common but rarely severe; scleral hue normal to grayish; hearing loss variable; DI common	AD	166220	Point mutations in *COL1A1* or *COL1A2*
			166240	Exon skipping mutations in *COL1A2*
V	Similar to type IV without DI or blue sclerae; fractures develop hyperplastic callus; calcification of the interosseous membrane between the radius and ulna	AD	610967	?
VI	Similar to type IV without DI, blue sclerae or wormian bones; excess osteoid present in bone	?	610968	?
VII	Similar to types II or III with fractures at birth, blue sclerae, no DI; presence of rhizomelic limb shortening and coxa vara	AR	610682	Mutations in *CRTAP*
VIII	Similar to types II or III with fractures at birth	AR	610915	Mutations in *LEPRE1*
IX	Similar to types II or III with fractures at birth	AR	259440	Mutations in *PPIB*

*Entries in Online Mendelian Inheritance in Man, OMIM. McKusick-Nathans Institute of Genetic Medicine. Baltimore: Johns Hopkins University. http://omim.org.
AD = autosomal dominant; AR = autosomal recessive; DI = dentinogenesis imperfecta.

Pathology

Other than the gross pathology associated with the clinical manifestations, the most characteristic pathology is a primary reduction in bone matrix with secondary undermineralization.

CLINICAL MANIFESTATIONS

The major phenotypic features of osteogenesis imperfecta are shown in Table 239-3. Among the most common forms, the most severe type is type II, followed in decreasing order by types III, IV, and I. In type II, infants either are stillborn or die soon after birth of pulmonary failure secondary to the small thorax, which usually is compromised further by myriad rib fractures. A few infants have survived for at least a few years but require enormous attention to their medical needs.

Type III osteogenesis imperfecta may be confused with type II at birth, but survival alone helps make the distinction. Bony deformity is pronounced and not necessarily caused by fractures. Mobility is impaired, and most patients require a wheelchair at an early age. Stature may be severely compromised. Because of progressive vertebral column deformity and rib fractures, restrictive lung disease is a common problem as patients age; many die of pulmonary complications. Basilar impression causing compression of the brain stem and the craniocervical junction can produce central sleep apnea, headache, and upper motor neuron signs.

Patients with type IV osteogenesis imperfecta generally have reduced stature, some bony deformity, and abnormal teeth that are opalescent and wear easily (dentinogenesis imperfecta). As in type I osteogenesis imperfecta, the tendency to fracture is highest in childhood and lessens with adolescence. A distinguishing characteristic of type IV osteogenesis imperfecta is a normal scleral hue.

Type I osteogenesis imperfecta is probably the most common form and is associated with a bluish or blue-gray scleral hue. People with type I osteogenesis imperfecta who also have dentinogenesis imperfecta tend to have more severe skeletal problems. The risk for fracture diminishes during adulthood but reemerges as a major concern for women after menopause. Hearing impairment in all forms of osteogenesis imperfecta is common and age related, being rare before adolescence. The deficits are of either a mixed or a predominantly conductive form.

The recessive forms of osteogenesis imperfecta (types VI to IX) range in severity from type IV to type II and may have distinctive radiologic or histopathologic findings.

DIAGNOSIS

Differential Diagnosis

The range of diagnostic possibilities in a person with multiple fractures largely depends on age. In infancy, the genetic conditions hypophosphatasia, severe osteochondrodysplasias (e.g., achondrogenesis and forms of spondyloepiphyseal dysplasia), and Menkes syndrome need to be excluded when a diagnosis of type II or type III osteogenesis imperfecta is considered. The radiographic features eventually become entirely diagnostic, but often the neonatologist has to arrive at a definitive answer in short order. Analysis of serum alkaline phosphatase and copper can be helpful. In childhood, the most common situation leading to consideration of a mild form of osteogenesis imperfecta is child abuse. In this situation, the pattern of fracture is usually distinct, and bone mineralization should be normal if the child is the object of nonaccidental or repeated accidental trauma. Abnormal scleral hue, dentinogenesis imperfecta, and wormian bones (microfractures along the cranial sutures) all support the diagnosis of osteogenesis imperfecta. The legal and child-protective systems often request exclusion of osteogenesis imperfecta by analysis of collagen production from cultured skin fibroblasts or analysis of DNA for a mutation.

TREATMENT

Management of the skeletal complications largely depends on orthopedic, physical, and occupational therapy approaches.[19] Risedronate (2.5 or 5 mg daily) increases bone mineral density and reduces both first and recurrent fractures in children with osteogenesis imperfecta.[A7] The long-term goals are for the patient to maintain function and independence as an individual. These goals can be advanced in some patients by judicious use of intramedullary rods in the long bones of the legs; if mobility and especially ambulation can be maintained, the demineralization associated with inactivity can be avoided.

Unaffected parents of a child with osteogenesis imperfecta and all affected individuals should have genetic counseling. For the parents of a child with type II osteogenesis imperfecta, the possibility of germinal mosaicism (which has been well documented in this condition) should not be overlooked. If one parent has a "new" mutation in one of the type I procollagen genes and multiple gonadal cells carry this mutation, the risk for recurrence in future children is not negligible. If the mutation in the affected child can be defined, the risk for recurrence can be quantified (through molecular analysis of sperm) if the mutation arose in the father.

In older children, the disorder idiopathic juvenile osteoporosis should be considered in any patient seen initially with repeated fractures. Many osteochondrodysplasias are associated with short stature, skeletal deformity, and a tendency to fracture. Pyknodysostosis and osteopetrosis are associated with sclerotic bones rather than osteoporotic ones. In adulthood, early-onset osteoporosis may be confused with osteogenesis imperfecta (Chapter 225). Mutations in type I collagen also cause familial osteoporosis, and the skeletal phenotypes merge; patients with true osteogenesis imperfecta may have scleral, hearing, or dental abnormalities and a positive family history.

Analysis of the specific enzymes defective in the recessive forms of osteogenesis imperfecta is useful for establishing the diagnosis and enabling reproductive counseling and prenatal diagnosis if desired.

PSEUDOXANTHOMA ELASTICUM

DEFINITION

Pseudoxanthoma elasticum is a heritable disorder of connective tissue with pleiotropic manifestations wherever elastic fibers are found but primarily in the skin, eye, and vasculature. Life expectancy is reduced, on average, because of a predisposition to myocardial infarction and gastrointestinal hemorrhage.

EPIDEMIOLOGY

The exact frequency of pseudoxanthoma elasticum is unknown, but it is probably underdiagnosed. Rough approximations suggest a prevalence of 1 in 25,000 to 100,000 births. Males and females are equally affected, although women are more likely to seek medical attention out of concern for the skin changes.

PATHOBIOLOGY

Pathogenesis

In most families, pseudoxanthoma elasticum occurs as an autosomal recessive trait, which means, given relatively small sibships, that many patients will have no affected relatives. Apparent autosomal dominant inheritance may reflect expression in occasional heterozygotes. The gene for pseudoxanthoma elasticum maps to human chromosome 16 and encodes one of the adenosine triphosphate (ATP)-binding cassette transporters (*ABCC6*). Because of the prominent histopathologic feature of calcification of elastic tissue, this gene may be important in calcium homeostasis. It is unclear, however, whether calcification is a primary or a secondary phenomenon in pseudoxanthoma elasticum.

Pathology

The hallmark of pseudoxanthoma elasticum, and an important diagnostic clue, is the histopathologic finding of hyperproliferated elastic fibers in the mid-dermis; these fibers become fragmented, clumped, and calcified. An arteriolar sclerosis develops in the media of muscular arteries and arterioles; the lumen may become progressively and concentrically narrowed. Alternatively, microaneurysms can form. Thickening of the endocardium, especially in the atria, develops in some patients. In the eye, the Bruch membrane becomes calcified and fragmented.

CLINICAL MANIFESTATIONS

Because of the pleiotropic nature of pseudoxanthoma elasticum, the diagnosis initially may be suspected by any of a variety of clinicians, especially dermatologists, ophthalmologists, cardiologists, and gastroenterologists. The condition gains its name from the dermatologic feature of yellowish papules that appear at areas of flexural stress, especially the neck, groin, and popliteal and cubital fossae; in periumbilical regions; and on the buccal mucosa. The appearance of affected skin has been likened to that of a "plucked chicken." Over time, affected areas coalesce and become thickened.[20]

Changes in the eye begin as a generalized, subtle, mottled pattern in the retina (peau d'orange) and progress to the characteristic angioid streaks. The latter changes are not specific for pseudoxanthoma elasticum and can be seen in diabetes mellitus, sickle cell disease, and a variety of other conditions. Streaks represent breaks in the Bruch membrane, an elastic lamina that lies between the retinal vasculature and the choroid. Spontaneous hemorrhages, especially those involving the macula, lead to progressive visual loss.

Involvement of arteries of various calibers produces problems because of occlusion and hemorrhage.[21] The lifetime risk for serious gastrointestinal hemorrhage from any site, but especially the stomach, is about 10%. Hypertension is relatively common, in part because of involvement of the renal vasculature. Progressive occlusion of peripheral arteries leads to absence of pulses; acral ischemia is rare because of the development of collaterals. The risk for stroke, myocardial infarction, abdominal angina, and intermittent claudication is increased independent of other risk factors. Impaired left ventricular function is common in adults.

DIAGNOSIS

Differential Diagnosis

Whole exome sequencing is an efficient and sensitive way to make the diagnosis. An acquired form of pseudoxanthoma elasticum has been reported and is also of unclear etiology. This form is difficult to differentiate from a sporadic case in a family because of heterozygosity in the parents, but it tends to affect only the skin. As suggested by the name, the cutaneous features of pseudoxanthoma elasticum need to be differentiated from those of true xanthoma, which results from a disorder of lipid metabolism (Chapter 190). The dermatologic manifestations need to be differentiated from those of Miescher elastoma, elastic tissue nevi (Buschke-Ollendorff syndrome), and solar elastosis.

TREATMENT

No cure for or means of preventing pseudoxanthoma elasticum is known.[22] In many instances, careful attention to the ocular features by a retinal specialist experienced in pseudoxanthoma elasticum can delay but not prevent loss of vision. The risk for gastrointestinal hemorrhage suggests that patients should avoid gastric irritants such as aspirin, nonsteroidal anti-inflammatory drugs, and excessive alcohol. Stool should be checked regularly for occult blood, and angiography may be necessary to detect the source of bleeding. All standard risk factors for atherosclerosis should be managed aggressively. Complaints of chest pain should prompt a rigorous investigation for coronary artery disease. Angioplasty has not been reported to be effective, and the coronary lesions tend to be diffuse. Coronary artery bypass graft surgery has been performed, but long-term results have not been reported. It may be theoretically advantageous to use vein grafts rather than the internal mammary artery for bypass. The excessive wrinkling and pseudoxanthoma in exposed areas can be ameliorated by plastic surgery.

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For the General References and other additional features, please visit Elsevier eBooks+ at https://ebooks.health.elsevier.com.

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240 THE SYSTEMIC AUTOINFLAMMATORY DISEASES

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DEFINITION

The systemic autoinflammatory diseases (Table 240-1) are a group of disorders that are characterized by seemingly unprovoked inflammation, without evidence of high-titer pathogenic autoantibodies or antigen-specific T cells, thereby distinguishing them from the more classic autoimmune diseases.[1] The first conditions recognized as autoinflammatory were the hereditary recurrent fevers, which are a group of mendelian disorders characterized by episodic or fluctuating degrees of fever and localized inflammation. The scope of autoinflammatory disease has broadened to include other heritable illnesses, including disorders in which purulent or granulomatous inflammation predominates, as well as inherited disorders of the complement system (Chapter 37).[2] In numerous autoinflammatory conditions, some of which manifest in childhood and others that occur later in life, a complex interaction of germline genetic susceptibilities, somatic mutations, and environmental factors contributes to the manifestation of the disease. Autoinflammatory illnesses include systemic-onset juvenile idiopathic arthritis (Still disease), Behçet disease, and even the crystalline arthritides. Many of the monogenic inherited autoinflammatory diseases are now considered inborn errors of innate immunity (Chapter 35), the phylogenetically more primitive part of the immune system that uses germline membrane and intracellular receptors expressed in granulocytes and macrophages to mount the body's first line of defense against pathogens.

Autoinflammatory syndromes can be grouped by key pathogenic cytokines and inflammatory pathways that are dysregulated and may be targets for effective therapies.[3] These molecular targets include interleukin-1 (IL-1), type I interferons, and the NF-κB inflammatory signaling pathway.

INTERLEUKIN-1–RELATED PERIODIC FEVER SYNDROMES

The IL-1–associated autoinflammatory diseases are linked by markedly increased expression of or cellular responsiveness to this cytokine, and resolution of symptoms with IL-1 blockade. Interleukin-1α and interleukin-1β (IL-1α and IL-1β) are structurally related cytokines released from cells in response to a number of inflammatory stimuli, such as lipopolysaccharide. These cytokines mediate inflammatory responses by binding to a common receptor that is present on the surface of a wide variety of cell types and that signals to activate inflammatory genes through the nuclear factor-kappa B (NF-κB) transcription factor complex. IL-1 is part of a larger family of cytokines (including IL-18, IL-33, and IL-36) that bind to related receptors and share the property of not having a characteristic signal peptide that normally targets cytokines to secretory vesicles. As a result, the IL-1 family cytokines may be secreted only by dead or dying cells, which function as molecular markers of cellular stress, and can trigger beneficial inflammatory responses to infection and injury. IL-1β and IL-18 are unique in that they are not biologically active until cleaved by the protease caspase-1, which also cleaves intracellular gasdermin D to induce an inflammatory form of cell death known as pyroptosis. Caspase-1 is itself activated in cytoplasmic protein complexes that contain various sensor proteins, such as NLRP3 and the adapter protein ASC. These complexes are referred to as inflammasomes because of their ability to trigger IL-1–mediated inflammation. IL-1–related autoinflammatory diseases (described later) are caused by mutations in genes encoding proteins that are directly or indirectly involved in the activation of IL-1 and the resulting inflammatory cascade.

FAMILIAL MEDITERRANEAN FEVER

DEFINITION

Familial Mediterranean fever (FMF) is a recessively inherited disease that typically manifests with 12- to 72-hour episodes of fever and localized serosal, synovial, or cutaneous inflammation. Between attacks, patients usually feel completely well, although biochemical evidence of inflammation may remain, and some patients eventually develop systemic amyloidosis (Chapter 174).

EPIDEMIOLOGY

Familial Mediterranean fever is most common in individuals of Jewish, Arab, Armenian, Turkish, and Italian ancestry. The frequency of asymptomatic carriers of a single *MEFV* mutation in these populations is as high as 1 in 10, likely because heterozygosity is associated with protection against *Yersinia pestis* infection (Chapter 288).[4] With genetic testing, familial Mediterranean fever is now frequently recognized in both Ashkenazi (eastern European) and non-Ashkenazi Jewish populations, as well as in Mediterranean populations previously thought not to be at risk. Mutation-positive individuals with typical symptoms have been documented worldwide.

PATHOBIOLOGY

MEFV, which is the gene mutated in familial Mediterranean fever, encodes a 781–amino acid protein denoted pyrin (or marenostrin) that is expressed in granulocytes, monocytes, and dendritic cells, as well as in peritoneal, synovial, and dermal fibroblasts. The N-terminal 92 amino acids of pyrin are the prototype for a motif, the PYRIN domain, that is involved in cognate interactions between proteins; this domain defines a family of more than 20 human proteins, including pyrin itself, that are involved in the regulation of cytokine production (particularly the IL-1 family), NF-κB activation, and cell death. Most of the pathogenic familial Mediterranean fever–associated mutations in pyrin reside in the C-terminal domain encoded by exon 10 of *MEFV*. An even larger number of variants of unknown significance have been described in individual patients with a spectrum of inflammatory phenotypes, and some patients with clinical presentations similar to that of familial Mediterranean fever have been found to have pyrin mutations on only one allele. The assembly of pyrin-containing inflammasomes is activated by bacterial toxins that inactivate the GTPase RhoA, including toxins derived from *Clostridia, Yersinia,* and *Vibrio* species. RhoA inactivates pyrin by inducing phosphorylation of pyrin on N-terminal serine residues, which leads to sequestration of pyrin by 14-3-3 proteins and inhibition of pyrin's ability to promote processing of the cytokine IL-1β. Familial Mediterranean fever–associated mutations in *MEFV* render pyrin resistant to RhoA-mediated inactivation, thereby providing a mechanism for the heightened secretion of IL-1β by cells harboring familial Mediterranean fever–associated pyrin mutations. These mutations also confer resistance to an important virulence factor produced by *Yersinia pestis* (the agent of plague in humans). Additional evidence for the importance of pyrin phosphorylation in the regulation of IL-1β production is that mutations in one of the phosphorylation sites of pyrin are associated with a severe early-onset syndrome of autoinflammation and neutrophilic dermatosis (PAAND).

As a consequence of its ability to depolymerize microtubules, colchicine activates RhoA, probably through the release of the RhoA guanine-nucleotide-exchange factor GEF-H1 from microtubules. Activated RhoA leads to increased phosphorylation of pyrin, thereby inactivating its pro-inflammatory function, even in cells harboring familial Mediterranean fever–associated pyrin mutations. Microtubule inhibitors also block pyrin inflammasome assembly in a phosphorylation-independent fashion.

CLINICAL MANIFESTATIONS

Familial Mediterranean fever usually manifests in childhood, sometimes even in infancy, although approximately 10% of patients experience their first attack as adults. Infrequently, symptoms first appear in persons older than age 40 years.

Episodes of familial Mediterranean fever are more properly termed recurrent rather than periodic, and some patients associate attacks with psychological stress or physical exertion. Women of childbearing age sometimes experience their attacks with menses, with remissions during pregnancy. Some patients are unaware of fever during the attacks, but fever is almost always observed when sought. Serosal involvement is usually peritoneal or pleural. Abdominal attacks are the most frequent, and they may vary from mild discomfort to frank peritonitis, with boardlike rigidity, direct and rebound tenderness, and air-fluid levels on upright films of the abdomen. Regardless of the severity of the abdominal attack, constipation is much more common than diarrhea. If a laparotomy or laparoscopy is performed during an attack, a small amount of sterile exudate rich in polymorphonuclear leukocytes may be found. Except for serosal inflammation, the appendix is normal. Repeated abdominal attacks

ABSTRACT

The systemic autoinflammatory diseases are a group of disorders characterized by seemingly unprovoked inflammation, without evidence of high-titer pathogenic autoantibodies or antigen-specific T cells, thereby distinguishing them from the more classic autoimmune diseases. The first conditions recognized as autoinflammatory were the hereditary recurrent fevers, which are a group of mendelian disorders characterized by episodic or fluctuating degrees of fever and localized inflammation. The scope of autoinflammatory disease has been broadened to include other heritable illnesses, including disorders in which purulent or granulomatous inflammation predominates, as well as inherited disorders of the complement system. Many of the inherited autoinflammatory diseases are now considered inborn errors of innate immunity, although acquired somatic mutations that affect the innate immune system are also increasingly recognized. These diseases can be subdivided based on the cytokine or inflammatory pathway that is primarily affected, such as disorders affecting interleukin-1, type I interferon, or the NF-κB signaling pathway. These categories are also helpful in guiding therapeutic approaches.

KEYWORDS

autoinflammatory disease
familial Mediterranean fever
inflammasome
interleukin-1
pyrin
tumor necrosis factor
periodic fever syndromes
interferonopathy
NF-κB
somatic mutation

TABLE 240-1 SYSTEMIC AUTOINFLAMMATORY DISEASES: A PARTIAL LISTING

INHERITED AUTOINFLAMMATORY DISEASES	INHERITANCE	GENES OR RISK FACTORS	OMIM*
INTERLEUKIN-1-BETA–RELATED DISORDERS			
Familial Mediterranean fever (FMF)	Autosomal recessive	*MEFV*†	249100
Pyrin-associated autoinflammation with neutrophilic dermatosis	Autosomal dominant	*MEFV*†	608068
Tumor necrosis factor receptor–associated periodic syndrome (TRAPS)	Autosomal dominant	*TNFRSF1A*†	142680
Hyperimmunoglobulinemia D with periodic fever syndrome (HIDS)/ Mevalonate kinase deficiency (MKD)	Autosomal recessive	*MVK*†	260920
Neonatal-onset multisystem inflammatory disease (NOMID)/Muckle-Wells syndrome (MWS)/familial cold autoinflammatory syndrome (FCAS)	Autosomal dominant/de novo	*NLRP3* (formerly *CIAS1*)†	607115 191900 120100
Schnitzler syndrome	Sporadic	*NLRP3* mosaic mutations (some)	
Multiple self-healing palmoplantar carcinoma	Autosomal dominant	*NLRP1*†	606636
Familial keratosis lichenoides chronica			615225
Autoinflammation with arthritis and dyskeratosis			617388
Deficiency of interleukin-1 receptor antagonist (DIRA)	Autosomal recessive	*IL1RN*†	147679
Deficiency of the IL-36R antagonist (DITRA)	Autosomal recessive	*IL36RN*†	605507
INTERFERON-RELATED AUTOINFLAMMATORY SYNDROMES (INTERFERONOPATHIES)			
Aicardi-Goutières syndrome	Autosomal recessive or autosomal dominant	*TREX1, RNASEH2A, 2B, 2C SAMHD1, ADAR (DRADA) IFIH1 (MDA5), LSM11, RNU7-1*	225750
STING-associated vasculopathy with onset in infancy (SAVI)	De novo	*TMEM173*†	612374 615934
COPA (coatamer subunit α) syndrome	Autosomal dominant	*COPA*†	601924
Proteasome-associated autoinflammatory diseases (PRAAS)/Chronic atypical neutrophilic dermatosis with lipodystrophy and elevated temperature (CANDLE)	Autosomal recessive, autosomal dominant, or digenic	*PSMA3,*† *PSMB4,*† *PSMB8,*† *PSMB9,*† *PSMB10,*† *POMP,*† *PSMG2*†	256040
NF-KAPPA-B–RELATED AUTOINFLAMMATORY SYNDROMES			
RELA haploinsufficiency	Autosomal dominant	*RELA*†	618287 164014
Haploinsufficiency of A20 (HA20) syndrome	Autosomal dominant	*TNFAIP3*†	191163 616744
OTULIN deficiency (otulipenia)	Autosomal recessive	*FAM105B (OTULIN)*†	615712 617099
NEMO deleted exon 5 autoinflammatory syndrome (NDAS)	X-linked (de novo)	*IKBKG*†	300248 301081
Immunodeficiency, autoinflammation, and amylopectinosis	Autosomal recessive	*HOIL1/RBCK1,*† *HOIP/RNF31*	610924 612487
Early-onset sarcoidosis/Blau syndrome	Sporadic, autosomal dominant	*NOD2/CARD15*†	186580, 605956
COMPLEMENT DISORDERS			
Hereditary angioedema	Autosomal dominant	*C1NH*	106100
Early-onset protein-losing enteropathy, and thrombosis, intestinal lymphangiectasia, and intestinal inflammation	Autosomal recessive	*CD55*	125240 226300
Hemolytic-uremic syndrome	Autosomal dominant, sporadic	*CFH* (complement factor H)	235400
Age-related macular degeneration	Complex inheritance	*CFH* (complement factor H)	603075
OTHER AUTOINFLAMMATORY SYNDROMES			
Deficiency of ADA2 (DADA2)	Autosomal recessive	*ADA2*†	607575 615688
Syndrome of periodic fever with aphthous stomatitis, pharyngitis, and cervical adenopathy (PFAPA)	Complex inheritance	*IL12A, IL10, STAT4, CCR1-CCR3, HLA-B*15:01 HLA-DQB1*06:03, HLA-DRB1*13:01, HLA-DQA-01:03*	—
Autoinflammatory disease associated with *NLRC4* mutations	Autosomal dominant	*NLRC4*†	606831 616050
Systemic-onset juvenile idiopathic arthritis (SOJIA)/adult-onset Still disease	Complex inheritance	*HLA-DRB1*11, LACC1, IL6, MIF* polymorphisms	604302
Behçet disease	Complex inheritance	*HLA-B*51*, polymorphisms in *IL10, IL23R, CCR1-CCR3, STAT4, KLRC4, ERAP1, MEFV, TLR4, IL1A-IL1B, IRF8, CEPB-PTPN1, ADO-EGR2, RIPK2, LACC1, FUT2, IL12A, NOD2*	109650
Syndrome of pyogenic arthritis with pyoderma gangrenosum and acne (PAPA)	Autosomal dominant	*PSTPIP1*†	604416
Chronic recurrent multifocal osteomyelitis (CRMO)	Sporadic, autosomal recessive	*LPIN2,*† when associated with congenital dyserythropoietic anemia (Majeed syndrome)	259680
Syndrome of periodic fever with immunodeficiency and thrombocytopenia (PFIT)	Autosomal recessive	*WDR1*†	150550 604734
Neonatal onset pancytopenia, autoinflammation, rash, and hemophagocytic lymphohistiocytosis (NOCARH syndrome)	*De novo*	*CDC42*†	
Cleavage resistant RIPK1 induced autoinflammatory syndrome (CRIA)	Autosomal dominant	*RIPK1*†	618852 603453
TBK1 deficiency	Autosomal recessive	*TBK1*	
Retinal dystrophy, optic nerve edema, splenomegaly, anhidrosis, migraine headache (ROSAH) syndrome	Autosomal dominant	*ALPK1*†	614979 607347

TABLE 240-1 SYSTEMIC AUTOINFLAMMATORY DISEASES: A PARTIAL LISTING—cont'd

INHERITED AUTOINFLAMMATORY DISEASES	INHERITANCE	GENES OR RISK FACTORS	OMIM*
Autoinflammation and PLCγ2-associated antibody deficiency and immune dysregulation (APLAID)	Autosomal dominant	*PLCG2*†	614878 600220
Vacuoles, E1 ligase, X-linked, autoinflammatory, somatic (VEXAS) syndrome	Myeloid-restricted somatic	*UBA1*†	301054 314370
Synovitis acne pustulosis hyperostosis osteitis syndrome (SAPHO)	Idiopathic	—	—
Crystalline arthropathies	Complex inheritance	*SLC2A9/GLUT9, ABCG2*	—

*Online Mendelian Inheritance in Man, an online catalogue of genetic disorders, available at http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?db=OMIM. Accessed June 6, 2022.
†An updated list of disease-associated mutations is available online at https://infevers.umai-montpellier.fr/web/. Accessed November 27, 2022.

may cause peritoneal adhesions, but ascites is rare. Pleurisy, usually unilateral, may accompany abdominal pain, or it may occur independently. Physical findings, if present, may include diminished breath sounds and a pleural friction rub, whereas chest radiograms may show a small effusion or atelectasis. With multiple attacks, pleural thickening may develop. Symptomatic nonuremic pericardial involvement has been reported but is unusual.

In adults, the arthritis of familial Mediterranean fever typically manifests as monoarticular involvement of the knee, hip, or ankle, and attacks of arthritis may persist for up to 1 week at a time. In children, oligoarticular or polyarticular joint involvement may occur. Large joint effusions are sometimes present, and the synovial fluid may have as many as 100,000 leukocytes/μL. In approximately 5% of patients who are not treated with prophylactic colchicine, chronic arthritis (usually of the hip or knee) may develop, often necessitating joint replacement surgery. Regardless of colchicine treatment or a particular human leukocyte antigen (HLA-B27) status, some patients with familial Mediterranean fever develop sacroiliitis. Arthralgia without frank arthritis is common in familial Mediterranean fever. The *MEFV* M694V mutation is a risk factor for both ankylosing spondylitis (Chapter 244) and Behçet disease (Chapter 249).[5]

Cutaneous manifestations of familial Mediterranean fever tend to be less common than serosal or synovial involvement. The characteristic skin lesion is erysipeloid erythema, which is a painful, demarcated erythematous area most often seen on the lower leg, ankle, or dorsum of the foot. This rash may occur independently, or it may accompany an episode of arthritis. Histologically, a mixed perivascular cellular infiltrate is seen. Other acute manifestations of familial Mediterranean fever include unilateral scrotal inflammation (the tunica vaginalis is an embryologic remnant of the peritoneal membrane) and myalgia, either with fever or, especially in children, without fever and induced by vigorous exercise. Henoch-Schönlein purpura may occur in children with familial Mediterranean fever, and polyarteritis nodosa is less frequently seen (Chapter 249).

DIAGNOSIS

Based on a simple recessive model of inheritance, two mutations in *MEFV,* in *trans,* should be identified to establish the genetic diagnosis of familial Mediterranean fever. Nevertheless, the interpretation of genetic testing is complicated by complex alleles that consist of various combinations of mutations in *cis,* as well as by the observations that as many as one third of patients with clinically typical familial Mediterranean fever have only one demonstrable mutation in *MEFV,* and a few patients with typical disease have no identifiable *MEFV* mutations. These latter two findings suggest that, under some circumstances, one *MEFV* mutation may be sufficient for symptoms or that additional disease-causing genes exist.

For these reasons, clinical data remain an essential part of the diagnosis of familial Mediterranean fever, and genetic testing plays an adjunctive role in settings in which clinical experience is limited.[6] Clinical criteria emphasize the duration of the attack (12 to 72 hours); recurrence of symptoms (three or more episodes); documented fever (rectal temperature >38° C); painful manifestations in the abdomen, chest, joints, or skin; and the absence of other causative factors. The differential diagnosis includes the other hereditary recurrent fever syndromes (Table 240-2), as well as other conditions specific to the clinical setting. For patients with recurrent abdominal pain, considerations include gynecologic disorders, porphyria (Chapter 194; which can be distinguished by hypertension during attacks, dominant inheritance, and urine porphyrins), and hereditary angioedema (Chapter 232; which usually does not cause fever). The syndrome of periodic fever with aphthous stomatitis, pharyngitis, and cervical adenopathy is probably the most common cause of unexplained recurrent fever in children and is also included in the differential diagnosis. In patients who present primarily with recurrent monoarthritis, joint aspiration for cultures and crystals may aid in excluding bacterial and crystalline arthritis.

Still disease in children (systemic-onset juvenile idiopathic arthritis) and adults (adult-onset Still disease) is also considered in the differential diagnosis. Adult-onset Still disease[7] (see Table 240-1) is an uncommon autoinflammatory condition of unknown cause that is not considered to be hereditary. It is characterized by spiking fever, an evanescent salmon-pink maculopapular rash, arthritis, and neutrophilic leukocytosis. It can be clinically distinguished from familial Mediterranean fever by the pattern of fever (intermittent quotidian in Still disease as compared with discrete episodes in familial Mediterranean fever), the pattern of arthritis (chronic polyarthritis vs. intermittent monoarthritis), the characteristic skin involvement (evanescent rash vs. erysipeloid erythema), and the presence of lymphadenopathy (more common in Still disease).

TREATMENT

The mainstay of therapy is daily oral colchicine, which can prevent both acute attacks and the development of systemic amyloidosis.[A1] In adults, the therapeutic dose is 1.2 to 1.8 mg/day, and nearly 90% of patients note significant improvement at this dose. The major side effects are gastrointestinal, and they usually can be minimized by gradually increasing the dosage and avoiding milk products in patients who develop lactose intolerance. Most experts continue to prescribe colchicine to patients during pregnancy, with the recommendation that amniocentesis be performed to exclude trisomy 21, for which the risk may be slightly increased. Use of colchicine in lactating women is considered safe. Intravenous colchicine should be used with extreme caution, if at all, because fatal toxicity has been reported in patients who are already receiving oral colchicine.

In adult patients who are poorly responsive to colchicine or who cannot tolerate therapeutic doses, canakinumab, a recombinant human anti–human-IL-1β antibody (starting at 150 mg subcutaneously and increasing to 300 mg if needed), is usually safe and effective in preventing flares.[A2,A3]

PROGNOSIS

Effective control of flares with colchicine and/or IL-1 inhibition prevents the development of secondary amyloidosis and appears to result in a normal life expectancy. Before the widespread use of colchicine prophylaxis, however, systemic AA amyloidosis (Chapter 174) was a frequent complication of familial Mediterranean fever, because of the ectopic deposition of a misfolded fragment of serum amyloid A, which is an acute phase reactant, in the gastrointestinal tract, kidneys, spleen, lung, testes, and adrenals. Malabsorption and nephrotic proteinuria leading to renal failure are the most common manifestations of AA amyloidosis. Cardiomyopathy is less common, and neuropathy and arthropathy are rare. Risk factors for amyloidosis include late diagnosis of familial Mediterranean fever, noncompliance with colchicine, male sex, and specific genotypes of the *MEFV* and *SAA* genes. Amyloidosis is less common with familial Mediterranean fever in the United States than in the Middle East. The diagnosis of amyloidosis in familial Mediterranean fever is best made by rectal or renal biopsy. With early diagnosis, aggressive suppression of the acute phase response with colchicine or IL-1 inhibitors may lead to improvement. For patients with renal failure, however, early renal transplantation is preferred.

TABLE 240-2 CLINICAL CHARACTERISTICS OF SELECTED AUTOINFLAMMATORY DISEASES

CLINICAL FEATURE	FAMILIAL MEDITERRANEAN FEVER (FMF)	TUMOR NECROSIS FACTOR RECEPTOR–ASSOCIATED PERIODIC SYNDROME (TRAPS)	HYPERIMMUNOGLOBULINEMIA D WITH PERIODIC FEVER SYNDROME (HIDS)	FAMILIAL COLD AUTOINFLAMMATORY SYNDROME/MUCKLE-WELLS SYNDROME/NEONATAL-ONSET MULTISYSTEM INFLAMMATORY DISEASE (FCAS/MWS/NOMID)	DEFICIENCY OF ADENOSINE DEAMINASE-2 (DADA2)
Typical ethnicity	Arab, Armenian, Italian, Jewish, Turkish	Any ethnicity	Dutch, other North European	European	Georgian Jewish origin for PAN-like disease
Age of onset	Childhood or adult	Childhood or adult	Early childhood, especially tied to immunizations	Childhood or adult (FCAS) Childhood (MWS) Infancy (NOMID)	Usually childhood
Attack duration	12-72 hr	Days to weeks	3-7 days	12-24 hr (FCAS) 1-2 days (MWS) Continuous, with flares (NOMID)	Occasional fevers Can have long asymptomatic periods
Abdominal involvement	Sterile peritonitis, constipation > diarrhea	Severe pain, vomiting, peritonitis	Sterile peritonitis, diarrhea, rarely constipation	Nausea (FCAS) Abdominal pain (MWS) Uncommon (NOMID)	Can be seen associated with abdominal vasculitis and infarctions, portal hypertension
Pleural attacks	Common	Common	Rare	Rare (MWS, NOMID)	Rare
Joint/bone involvement	Monoarthritis, rarely protracted arthritis in knee or hip	Arthritis in large joints, arthralgia	Arthralgia, symmetrical polyarthritis	Polyarthralgia (FCAS, MWS) Oligoarthritis (MWS) Clubbing (MWS, NOMID) Epiphyseal overgrowth, contractures, intermittent or chronic arthritis (NOMID)	Uncommon
Skin rash	Erysipeloid erythema on lower leg, ankle, foot	Migratory rash, underlying myalgia	Diffuse maculopapular rash, urticaria	Urticaria-like rash (cold-induced in FCAS)	Livedo reticularis, cutaneous vasculitis, scarring lesions, and necrosis can occur
Hematologic	Splenomegaly, occasional lymphadenopathy	Splenomegaly, occasional lymphadenopathy	Cervical adenopathy in children	Hepatosplenomegaly, adenopathy (NOMID, rare in MWS)	Cytopenias including pure red-cell aplasia, hypo-Ig, hepatosplenomegaly
Neurologic involvement	Aseptic meningitis?	Controversial	Headache	Headache (FCAS) Sensorineural deafness (MWS, NOMID) Chronic aseptic meningitis, intellectual disability (NOMID)	Recurrent ischemic strokes
Ophthalmologic involvement	Rare	Conjunctivitis, periorbital edema, rarely uveitis	Uncommon	Conjunctivitis (all) Uveitis (MWS, NOMID) Progressive vision loss (NOMID)	Retinal artery occlusion
Vasculitis	Henoch-Schönlein purpura (HSP), polyarteritis nodosa	HSP, lymphocytic vasculitis	Cutaneous vasculitis common, rarely HSP	Not seen (FCAS, MWS) Occasional in NOMID	Small and medium vessels, can present as polyarteritis nodosa
Systemic amyloidosis	Risk depends on *MEFV* and *SAA* genotypes; more common in Middle East	Occurs in ≈10%; risk increased with cysteine mutations	Uncommon, associated with V377I/I268T genotype	Rare (FCAS) 25% (MWS) May develop in adulthood (NOMID)	Can occasionally develop
Autoantibodies	Not usually seen	Not usually seen	Not usually seen	Not usually seen	ANCA usually negative
Effective treatments	Colchicine, IL-1 blockade	IL-1 blockade	IL-1 blockade	IL-1 blockade	TNF blockade, hematopoietic stem cell transplant for severe cytopenias

ANCA = antineutrophil cytoplasmic antibody; IL = interleukin; TNF = tumor necrosis factor.

HYPERIMMUNOGLOBULINEMIA D WITH PERIODIC FEVER SYNDROME (MEVALONATE KINASE DEFICIENCY)

Hyperimmunoglobulinemia D with periodic fever syndrome (HIDS) was first described in six patients of Dutch ancestry who had extremely high levels of immunoglobulin D (IgD) in their serum. Hyperimmunoglobulinemia D, though quite rare, is now recognized in a broader ethnic distribution, although northern Europeans still predominate. The elevated IgD levels appear to be an epiphenomenon and do not correlate with the severity of disease, either among patients or in a given patient over time. Because modestly increased IgD levels can be seen in other inflammatory conditions and up to 20% of patients (particularly young children) with typical recurrent fevers and *MVK* mutations can have normal serum IgD levels, IgD levels alone are an unreliable diagnostic tool. Consequently, some experts prefer the term *mevalonate kinase deficiency* (MKD) to denote this illness.

This autosomal recessive disease is caused by mutations in *MVK,* which encodes the mevalonate kinase enzyme involved in the biosynthesis of cholesterol and nonsterol isoprenes.[8] Enzymatic activity in patients is markedly reduced but not absent. The isoprenoid deficiency resulting from *MVK* mutations is thought to be the basis for the clinical manifestations. Reduced

prenylation inactivates the GTPase RhoA, thereby abrogating its negative regulation of the pyrin inflammasome and resulting in increased production of IL-1β. IL-1β and increased body temperature can further decrease mevalonate kinase enzymatic activity, thereby creating a vicious circle in which infection or immunization can precipitate clinical attacks.

CLINICAL MANIFESTATIONS

One of the well-recognized clinical characteristics of hyperimmunoglobulinemia D is the provocation of attacks by immunizations. Other distinguishing clinical features include a very early age of onset (average age, 6 months), a 3- to 7-day duration of attacks (intermediate between familial Mediterranean fever and tumor necrosis factor [TNF] receptor-associated periodic syndrome), prominent cervical lymphadenopathy during attacks, polyarticular joint involvement, a diffuse maculopapular rash, the predominance of diarrhea over constipation with abdominal attacks, and the infrequency of pleuritic attacks or systemic amyloidosis.

The diagnosis can be established in a patient with recurrent episodes of fever and typical associated findings by documenting either two mutations in *MVK* or elevated levels of mevalonic acid, the substrate for mevalonate kinase, in the urine during attacks. Approximately 10% of patients with otherwise typical disease have only a single identifiable *MVK* mutation.

TREATMENT AND PROGNOSIS

Nonsteroidal anti-inflammatory drugs (NSAIDs; see Table 26-4) or glucocorticoids are sometimes useful in the treatment of the arthritic manifestations, but colchicine is generally not effective. Canakinumab (starting at 150 mg monthly subcutaneously in adults and increasing to 300 mg monthly if needed) is approved for the treatment of this disorder. Patients with hyperimmunoglobulinemia D have a normal lifespan, and attacks may become somewhat less frequent in adulthood.

TUMOR NECROSIS FACTOR RECEPTOR–ASSOCIATED PERIODIC SYNDROME

EPIDEMIOLOGY

Worldwide, the tumor necrosis factor (TNF) receptor–associated periodic syndrome (TRAPS) is the second most frequently diagnosed hereditary recurrent fever syndrome, behind familial Mediterranean fever. One of the first well-characterized families with what was later defined as TRAPS was of Irish ancestry, and the condition was termed familial Hibernian fever to emphasize the ethnic background and clinical differences from familial Mediterranean fever. However, with the discovery of TNF receptor mutations in families of other ancestries, the ethnically neutral TRAPS nomenclature is now used.

PATHOBIOLOGY

TRAPS is caused by mutations in *TNFRSF1A*, encoding the 55-kD receptor for TNF (TNFR1, p55, CD120a). The p55 TNF receptor comprises four cysteine-rich extracellular domains, a transmembrane region, and an intracellular death domain. To date, nearly all of the coding mutations described have been in the extracellular domains, and approximately one third are missense substitutions of cysteine residues that abolish highly conserved disulfide bonds. Studies indicate a complex pathogenetic picture, with the extracellular mutations causing diminished receptor shedding at the cell membrane, as well as defective trafficking and intracellular accumulation of mutant TNFR1 protein. Spontaneous signaling and possibly activation of the unfolded protein response leads to production of mitochondrial reactive oxygen species, constitutive activation of mitogen-activated protein kinases, and increased production of pro-inflammatory cytokines by myeloid cells harboring the mutant receptor.[9]

DIAGNOSIS

Although genetic testing is necessary for the diagnosis of TRAPS, clinical clues that can help distinguish TRAPS from familial Mediterranean fever include ethnicity (familial Mediterranean fever is seen predominantly in Mediterranean and Middle Eastern populations, whereas TRAPS has a more widespread distribution), mode of inheritance (autosomal recessive in familial Mediterranean fever, dominant in TRAPS), and duration of attacks, which tends to be longer in TRAPS and sometimes approaches continuous symptoms. The rash of familial Mediterranean fever is typically erysipeloid erythema on the lower extremity, whereas patients with TRAPS often have a distinctive erythematous rash, often with underlying myalgia, which may migrate on the trunk or centrifugally on the extremities. Ocular involvement, with periorbital edema, conjunctivitis, and occasionally even uveitis, is observed in TRAPS. Nevertheless, the abdominal, pleural, synovial, and even scrotal manifestations of the two diseases are rather similar. The usual age of onset for TRAPS is also in childhood.

Whereas a positive genetic test is not necessary to diagnose familial Mediterranean fever, the diagnosis of TRAPS requires the identification of a TNF receptor mutation. The diagnosis of TRAPS is established by the identification of *TNFRSF1A* mutations in the appropriate clinical setting. One variant, the substitution of glutamine for arginine at residue 92 (R92Q), is present in more than 1% of individuals with European ancestry and may be associated with a broader spectrum of symptoms than is typically seen in TRAPS, including early inflammatory arthritis or, in some cases, no symptoms at all. The substitution of leucine for proline at residue 46 (P46L) has been described in African American patients with TRAPS and is associated with a receptor shedding defect, but it is also seen among healthy West African controls. These findings establish a "gray zone" for the diagnosis of TRAPS and emphasize the potential role of polymorphisms in the recurrent fever genes in other more common inflammatory phenotypes.

TREATMENT

Treatment depends on the frequency and severity of attacks. Patients with relatively infrequent, mild episodes may respond to NSAIDs (Table 26-4). Patients with more severe attacks that occur infrequently may be treated with glucocorticoids under expert oversight, although increasing doses may be required as the episodes become more frequent and toxicities may become limiting. Canakinumab (starting at 150 mg subcutaneously monthly in adults and increasing to 300 mg monthly if needed)[10] is used in patients with frequent disease flares.

PROGNOSIS

Before the availability of IL-1 inhibition, the prolonged episodes of TRAPS were associated with substantial morbidity, and systemic AA amyloidosis was seen in approximately 10% of untreated patients. The extent to which current therapies will improve this prognosis awaits longer follow-up.

CRYOPYRIN-ASSOCIATED PERIODIC SYNDROMES: THE CRYOPYRINOPATHIES

Three rare, recurrent febrile disorders usually beginning early in life have been associated with mutations in *NLRP3* (formerly *CIAS1*), the gene that encodes a protein, usually denoted as cryopyrin or NLRP3, which is a key component of the NLRP3 inflammasome that activates caspase-1. These disorders are referred to as cryopyrinopathies or cryopyrin-associated periodic syndromes (CAPS). The least severe clinical phenotype is familial cold autoinflammatory syndrome (FCAS; formerly called familial cold urticaria), which is dominantly inherited and is notable for day-long attacks of chills, fever, headache, diffuse urticarial skin rash, arthralgia, and conjunctivitis, precipitated by generalized cold exposure. Amyloidosis is rare in FCAS. Of intermediate severity is Muckle-Wells syndrome (MWS), also dominantly inherited, in which 1- to 2-day episodes of chills, fever, urticarial rash, limb pain, and arthritis occur independently of cold exposure. Sensorineural hearing loss is a common feature of Muckle-Wells syndrome, and about 25% of patients develop AA amyloidosis, often in early adulthood. The most severe *NLRP3*-associated phenotype is neonatal-onset multisystem inflammatory disease (NOMID), known in Europe as chronic infantile neurologic cutaneous and articular (CINCA) syndrome. It is usually sporadic owing to the reduced reproductive fitness of most affected individuals. Fever and constitutional symptoms occur almost daily, often from birth, with generalized urticarial skin rash, a peculiar arthropathy characterized by epiphyseal overgrowth of the long bones, and central nervous system (CNS) involvement that includes chronic aseptic meningitis, uveitis, and cochlear inflammation, which may lead to intellectual disability, blindness, and deafness. In all three cryopyrinopathies, the rash is not true urticaria because

it has a neutrophilic rather than a mast cell infiltrate, and serum histamine levels are normal.

The protein mutated in all three disorders is NLRP3, a critical component of the eponymous NLRP3 inflammasome, which serves as an intracellular scaffold for the processing of IL-1β. The alternative name of this protein, cryopyrin, refers to its amino terminal PYRIN domain, the basis for a structural and functional relationship to the protein mutated in familial Mediterranean fever. Disease-associated cryopyrin mutations are thought to decrease the threshold for inflammasome activation, thereby increasing IL-1β production. The discovery that the NLRP3 inflammasome is also necessary for IL-1β production in response to crystalline forms of monosodium urate and calcium pyrophosphate connected the pathophysiology of these rare autoinflammatory diseases to crystal-induced arthritis (Chapter 252), which shares some clinical features, such as episodic, self-limited attacks, with autoinflammatory diseases.

DIAGNOSIS

Because there are patients with FCAS, MWS, and NOMID/CINCA without demonstrable germline *NLRP3* mutations, these diagnoses remain clinical, although genetic testing serves as a valuable adjunct and has greatly increased the recognition of all three conditions. Deep sequencing has identified somatic *NLRP3* mutations in many patients with symptoms consistent with CAPS who are negative for mutations by standard genetic testing. In addition, overlap syndromes that are intermediate between FCAS and MWS and NOMID/CINCA have been reported. NLRP3 is only one of a number of inflammasomes nucleated by other members of the NLR gene family, and gain-of-function mutations in *NLRP1*, encoding an NLR family member prominently expressed in the skin, underlie a spectrum of diseases characterized by keratotic skin lesions, arthritis, systemic inflammation, and self-healing palmoplantar carcinomas. Gain-of-function mutations in *NLRC4*, another intracellular NLR family member, have been reported in patients with a spectrum of symptoms ranging from FCAS-like disease to severe inflammatory disease with infantile-onset enterocolitis and macrophage activation syndrome. IL-18, a cytokine related to IL-1 which is also intracellularly processed by NLR and pyrin inflammasomes, is particularly elevated in patients with *NLRC4* mutations.

TREATMENT

In all three cryopyrinopathies, blockade with anakinra (a recombinant IL-1 receptor antagonist at 1 to 8 mg/kg subcutaneously per day in adults) is effective in controlling fever and acute phase reactants, and it also decreases CNS inflammation and end-organ damage in NOMID/CINCA. Rilonacept (another soluble IL-1 blocker given subcutaneously as a 320-mg loading dose followed by a 160-mg weekly dose in adults) and canakinumab (150 mg subcutaneously every 8 weeks in adults) can also be used in FCAS and Muckle-Wells syndrome, but they may be less effective than anakinra against NOMID/CINCA because of reduced penetration into the CNS.

PROGNOSIS

Although the febrile episodes of familial cold autoinflammatory syndrome interfere with daily life, especially in cold climates, life expectancy is normal. In untreated Muckle-Wells syndrome, deafness by early adulthood and AA amyloidosis are both common. Before anakinra treatment, the prognosis of NOMID was grim, with many patients either institutionalized or in renal failure owing to amyloidosis by early adulthood.

DEFICIENCIES OF IL-1 AND IL-36 RECEPTOR ANTAGONISTS

Deficiency of the IL-1 receptor antagonist (DIRA) is characterized by the neonatal onset of a pustular skin rash, multifocal osteomyelitis, periostitis, and, rarely, vasculitis. Fever is not a prominent finding, although acute phase reactants are markedly elevated. DIRA is caused by recessively inherited loss-of-function mutations in *IL1RN*, which encodes the IL-1 receptor antagonist (IL-1Ra). In DIRA, the lack of IL-1Ra leads to unopposed IL-1β and IL-1α signaling, whereas in the cryopyrinopathies, *NLRP3* mutations lead to inflammasome activation and increased IL-1β production.

Patients usually present within the first 2 weeks of life with skin lesions ranging from discrete crops of pustules to generalized severe pustulosis or ichthyosiform lesions. Histologic examination demonstrates extensive neutrophilic infiltrates in the dermis and epidermis. Typical radiographic findings include multifocal osteolytic lesions, periosteal elevation of the long bones, heterotopic ossification of the proximal femurs, and widening of the anterior rib ends. Bone biopsies demonstrate sterile purulent osteomyelitis, fibrosis, and sclerosis. DIRA patients respond dramatically to anakinra (1 to 8 mg/kg subcutaneously daily), which is a recombinant form of the protein they lack. In untreated patients, childhood mortality is high.

Loss-of-function mutations in *IL36RN*, which codes for a protein that serves a similar function as IL1RA in blocking the activity of the IL-1 family member IL-36, are associated with autosomal recessive inheritance of a syndrome termed *DITRA* (for deficiency of the IL-36 receptor antagonist), which is characterized by generalized pustular psoriasis, periodic fevers, and elevation of systemic inflammatory markers. IL-1 inhibition is generally not effective in the treatment of DITRA. Case reports suggest successful treatment of DITRA with inhibitors of IL-17 or IL12/23. Given the more limited tissue distribution of expression of the IL-36 receptor relative to the IL-1 receptor, the prognosis of DITRA may be better than DIRA, but the long-term outcome currently is not known.

THE INTERFERONOPATHIES: TYPE I INTERFERON–ASSOCIATED AUTOINFLAMMATORY DISEASES

A group of hereditary syndromes marked by systemic inflammation share induced gene expression of type I interferon target genes and cytokines and have been termed *interferonopathies*.[11] These diseases mimic some aspects of the antiviral state and congenital infection syndromes without a role for a known pathogen. Unlike most other autoinflammatory syndromes, autoantibodies can be found in some type I interferonopathies, thereby placing them on the spectrum between autoinflammatory and autoimmune disease.[12]

AICARDI-GOUTIÈRES SYNDROME AND ASSOCIATED DISEASES

A neonatal syndrome characterized by severe neurologic dysfunction and pleocytosis in the cerebrospinal fluid (CSF), Aicardi-Goutières syndrome (AGS) was first associated with mutations in the *TREX1* gene encoding a 3′–5′ DNA exonuclease. The definition of this syndrome has expanded to encompass mutations in a number of other genes associated with DNA or RNA modification or sensing; delayed onset past 1 year of age in some patients, particularly in patients with *IFIH1* or *ADAR* mutations; and extracerebral features such as glaucoma, hypothyroidism, and inflammatory bowel disease. Depending on the function of the encoded protein, both loss-of-function and gain-of-function mutations have been reported, but all lead to an increase in type I interferon signaling. Certain features, such as chilblains (Chapter 66), with cold-induced vascular-based inflammatory lesions in the hands and feet, overlap with those seen in pediatric lupus, and a small number of AGS patients meet clinical criteria for systemic lupus erythematosus. The diagnosis of AGS is established by genetic testing (see Table 240-1). Untreated, the various forms of AGS progress to severe neurologic dysfunction. Trials of Janus kinase (JAK) inhibitors are aimed at limiting the progression of the disease.

PROTEASOME-ASSOCIATED AUTOINFLAMMATORY SYNDROMES

The proteasome-associated autoinflammatory syndromes (PRAAS; also known as chronic atypical neutrophilic dermatosis with lipodystrophy and elevated temperature, CANDLE) are a group of disorders caused by genetic mutations that lead to dysfunction of the proteasome, which is a macromolecular complex required for the normal degradation of proteins in both immune and nonimmune cells. To date, PRAAS/CANDLE mutations have been identified in the genes encoding the constitutive proteasome subunits (*PSMB4, PSMA3*), immunoproteasome components (*PSMB8, PSMB9, PSMB10*), and chaperone proteins (*POMP, PSMG2*).[13] Autosomal dominant, autosomal recessive, and digenic patterns of inheritance have been observed, depending on the specific gene(s) involved.

Proteasomal dysfunction leads to a type I interferonopathy that, depending on the specific genetic lesion(s), may cause recurrent fevers, neutrophilic panniculitis, lipodystrophy, metabolic syndrome, myositis, arthritis, joint contractures, developmental delay, cytopenias, and/or keratitis/episcleritis. Oral JAK inhibitors, particularly baricitinib, which block type I interferon signaling, have shown benefit for the treatment of PRAAS/CANDLE when given under expert supervision, but patients should be closely monitored for viral reactivation.[14]

STING-ASSOCIATED AUTOINFLAMMATORY SYNDROMES

The stimulator of interferon genes (STING) is an endoplasmic reticulum localized innate immune sensor of cytosolic double-stranded DNA, which may be present with double-stranded DNA viral infection. STING is activated by cyclic guanosine monophosphate-adenosine monophosphate (cGAMP), a second messenger that is synthesized by cyclic GMP-AMP synthase upon binding of double-stranded DNA. cGAMP normally induces STING to dimerize, thereby leading to the transcription of type I interferon–induced genes through the activation of interferon regulatory factor 3 (IRF-3) and TANK-binding kinase 1 (TBK1).

Gain-of-function mutations (most commonly de novo) in *TMEM173*, which encodes the STING protein, cause a severe neonatal-onset autoinflammatory disease denoted STING-associated vasculopathy with onset in infancy. These STING mutations cause STING to exit the endoplasmic reticulum, traffic to the Golgi, and become activated.

Owing to the expression of STING in endothelial cells, patients present with acral ischemia, which can cause a range of findings from Raynaud phenomenon to gangrene and loss of digits. Other manifestations include fever, interstitial lung disease with or without secondary pulmonary hypertension, polyarthritis, myositis, retinopathy, and developmental delay. Laboratory evaluation demonstrates increased acute phase reactants, cytopenias, and low titer autoantibodies. Patients experience significant morbidity and mortality owing to pulmonary involvement. Oral ruxolitinib, baricitinib, and tofacitinib under expert supervision have shown benefit, but patients should be closely monitored.

COPA syndrome is a relatively newly described disorder caused by heterozygous, dominantly inherited mutations in the coatomer subunit α, a component of a macromolecular complex that mediates retrograde Golgi-to–endoplasmic reticulum transport. Recent data indicate that COPA mutations cause cytoplasmic missorting of STING and ligand-independent STING activation.[15] The level of autoantibodies in COPA syndrome and the expansion of T_H17 cells indicate that this disorder is on the spectrum between autoinflammatory and autoimmune disorders. Patients with COPA syndrome bear phenotypic similarity to STING-associated vasculopathy with onset in infancy, including an early age of onset, capillaritis, interstitial lung disease, and increased type I interferon signaling. Arthritis and immune-mediated renal disease are also observed in COPA syndrome. Promising case reports suggest benefit with the use of JAK inhibitors in COPA syndrome, but longer term follow-up is required.

AUTOINFLAMMATORY DISEASES ASSOCIATED WITH ACTIVATION OF NF-κB

Loss-of-function mutations in NF-κB signaling are well-recognized causes of immunodeficiency disease, including disorders caused by mutations in *IKBKG* and *TNFRSF13B*. More recently, autoinflammatory disorders have been described in which NF-κB signaling is directly or indirectly activated. These disorders can be caused by mutations in NF-κB subunits, such as RelA; mutations in molecules that induce post-translational modifications of the NF-κB signaling complex, such as A20 and OTULIN (ubiquitylation) and NF-κB essential modulator (NEMO; phosphorylation); and molecules that activate innate immunity through the NF-κB pathway, such as NOD2/CARD15.

RELA HAPLOINSUFFICIENCY

RELA encodes the p65 NF-κB subunit. Heterozygous truncating mutations in *RELA* cause a dominantly inherited condition termed haploinsufficiency of RelA, in which impaired NF-κB signaling and accentuated TNF-dependent cell death causes autoinflammation. Patients present with recurrent fevers and abdominal pain, with ulcerations in the mouth and throughout the gastrointestinal tract. Flares are accompanied by leukocytosis and elevated acute phase reactants, but autoantibodies are generally not present. Patients generally respond well to TNF inhibitors under expert supervision.

HAPLOINSUFFICIENCY OF A20 AND DISORDERS OF NF-κB REGULATION

TNFAIP3 encodes a protein, sometimes denoted A20, that plays a dual role in regulating NF-κB ubiquitylation. A20 removes K63-linked ubiquitin chains that ordinarily stabilize TNF-induced proinflammatory signaling complexes and adds K48-linked ubiquitin chains to the dissociated proteins, thereby targeting them for destruction by the proteasome. Dominantly inherited, heterozygous loss-of-function mutations in A20 lead to the persistence of proinflammatory signaling complexes and a syndrome termed haploinsufficiency of A20, which presents with early-onset systemic inflammation, arthralgia/arthritis, oral, genital, and/or gastrointestinal ulcerations, ocular inflammation, venous thrombosis, and, in some patients, autoantibodies and glomerulonephritis.

OTULIN (FAM105B) encodes a deubiquitylase that removes linear (Met1-linked) ubiquitin chains that may also stabilize TNF-induced proinflammatory NF-κB signaling. Biallelic loss-of-function mutations in *OTULIN* cause neonatal-onset fever, neutrophilic dermatitis/panniculitis, lipodystrophy, arthritis, vasculitis, diarrhea, and failure to thrive.

IKBKG encodes NEMO, a component of the IκB kinase complex that phosphorylates IκBα to activate NF-κB signaling. *De novo* X-linked *IKBKG* mutations that lead to the in-frame deletion of the domain encoded by exon 5 cause a syndrome characterized by increased activation of NF-κB and neonatal-onset fevers, sterile panniculitis, optic neuritis, chorioretinitis, organomegaly, and hemorrhagic stroke, denoted the *N*EMO *d*eleted exon 5 *a*utoinflammatory *s*yndrome (NDAS).[16]

Case reports suggest successful use of IL-1, TNF, and JAK inhibitors in the treatment of patients with HA20. Both IL-1 and TNF inhibitors have shown benefit in individual patients with biallelic mutations of *OTULIN*. Glucocorticoids have been used under expert supervision to control the autoinflammatory manifestations of NDAS.

GRANULOMATOUS ARTHRITIS, DERMATITIS, AND UVEITIS (BLAU SYNDROME)

NOD2/CARD15 encodes an intracellular sensor of bacterial muramyl dipeptides. Relatively low-penetrance, common variants of this gene affect the leucine-rich repeat domain of the encoded protein and are associated with Crohn disease (Chapter 127), whereas rare heterozygous high-penetrance mutations in the nucleotide-binding domain cause Blau syndrome and some cases of early-onset sarcoidosis (Chapter 83).

In Blau syndrome, the *NOD2* mutations are associated with increased NF-κB signaling.[17] Blau syndrome is a dominantly inherited illness presenting with early-onset granulomatous synovitis often complicated by cyst formation and camptodactyly (flexion contractures of the fingers and toes); granulomatous anterior and posterior uveitis, sometimes causing retinal detachment, glaucoma, cataracts, and blindness; and an intermittent papular rash with noncaseating granulomas. Lung or other visceral involvement is generally not present. However, visceral involvement of the liver and spleen is observed in early-onset sarcoidosis, which is phenotypically quite similar to Blau syndrome. Treatment with TNF inhibitors under expert supervision has markedly improved the prognosis of Blau syndrome.

OTHER INHERITED SYSTEMIC AUTOINFLAMMATORY DISEASES

SYNDROME OF PYOGENIC ARTHRITIS WITH PYODERMA GANGRENOSUM AND ACNE

The syndrome of pyogenic arthritis with pyoderma gangrenosum and acne (PAPA) is a rare, dominantly inherited autoinflammatory disease characterized by intermittent episodes of sterile pyogenic arthritis, pyoderma gangrenosum, and severe cystic acne. It is caused by mutations in the gene encoding proline-serine-threonine phosphatase–interacting protein 1 (PSTPIP1), also known as

CD2BP1. PSTPIP1 is a cytoskeletal protein that interacts with certain other proteins involved in the immune response, including CD2; the Wiskott-Aldrich syndrome protein (WASP); a phosphatase denoted PTP-PEST; and pyrin, the familial Mediterranean fever (FMF) protein. PAPA mutations abrogate the binding of PSTPIP1 to PTP-PEST, leading to hyperphosphorylation of PSTPIP1 and increased binding to pyrin. This finding is associated with markedly increased production of IL-1β and extremely high levels of total and free IL-18 in the blood.[18]

Early in life, PAPA tends to present with monoarticular or pauciarticular pyogenic arthritis, sometimes induced by trauma. As patients reach puberty, skin manifestations begin to predominate, including disfiguring cystic acne. Pathergy also may develop, and extensive pyoderma gangrenosum may require opiates for pain control. The diagnosis of PAPA syndrome is made by documenting *PSTPIP1* mutations in the appropriate clinical setting.

High doses of glucocorticoids have been used under expert supervision with varying success in PAPA, and patients with arthritis sometimes require aspiration, intra-articular glucocorticoids, or open drainage. Small case series support the use of anakinra or canakinumab for the arthritis and monoclonal anti-TNF antibodies for the pyoderma gangrenosum of PAPA. In the absence of treatment, arthritis may progress to severe joint damage and ankylosis.

ADENOSINE DEAMINASE-2 DEFICIENCY

A syndrome characterized by fevers, early-onset strokes, and vasculopathy or frank vasculitis mimicking polyarteritis nodosa has been found to be caused by autosomal recessive mutations in *ADA2* (formerly *CECR1*), which encodes adenosine deaminase-2 (ADA2). Although ADA2 shares enzymatic activity with intracellular adenosine deaminase that is encoded by the *ADA* gene, ADA2 is not necessary for the development of lymphocytes, and patients with deficiency of adenosine deaminase-2 (DADA2) do not initially present with severe combined immunodeficiency (SCID), as is the case for ADA deficiency. ADA2 is a secreted extracellular protein, and functional studies have found that ADA2 plays a role in vascular development and regulation of macrophage differentiation. Although this disease is generally diagnosed in childhood, it should be considered in the differential diagnosis of young adults with unexplained lacunar strokes, vasculitic skin lesions, and/or polyarteritis nodosa. Transfusion-dependent anemia and severe neutropenia are uncommon manifestations.

TNF inhibition under expert supervision is highly effective in preventing stroke.[19] Hematopoietic stem cell transplantation may be curative, both for cytopenias and vascular manifestations.

GENOME SEQUENCING AND THE DISCOVERY OF NEW AUTOINFLAMMATORY SYNDROMES AND INNATE IMMUNE PATHWAYS

A major attraction of the concept of the autoinflammatory diseases has been the molecular explication of numerous inborn errors of inflammation, an enterprise that has converged with the delineation of the innate immune system (Chapter 35). With advances in genome sequencing, the number of defined autoinflammatory diseases that are associated with dramatically elevated levels of total and free IL-18 in the blood has increased rapidly. Recently defined conditions include autoinflammatory periodic fever, immunodeficiency, and thrombocytopenia (PFIT), which is caused by mutations in the actin-regulatory gene *WDR1;* neonatal-onset pancytopenia, autoinflammation, rash, and hemophagocytic lymphohistiocytosis (NOCARH syndrome),[20] which is caused by mutations in *CDC42* that activate the pyrin inflammasome; and mutations in *MEFV,* which encodes pyrin. Taken together, these findings point to a poorly understood aspect of inflammasome activation that may be amenable to therapies targeting IL-18.

Other recent genomic discoveries implicate the cell death pathways of apoptosis and necroptosis in two different autoinflammatory disorders caused by mutations in *RIPK1* and *TBK1*.[21] Gain-of-function mutations in *ALPK1,* encoding a novel innate immune sensor for seven carbon sugars (which are made by gram-negative bacteria but not by mammals), cause an autoinflammatory syndrome characterized by retinal dystrophy, optic nerve edema, splenomegaly, anhidrosis, and migraine headache (ROSAH).[22] Genomic sequencing of children carrying the diagnosis of systemic-onset juvenile idiopathic arthritis has identified *LACC1* as an important regulator of immunometabolic function in macrophages, and genomic sequencing of patients with a form of chronic recurrent multifocal osteomyelitis has identified *LPIN2* as an important regulator of osteoclast differentiation in M2 macrophages.[23] Gain-of-function mutations in *PLCG2,* which encodes the phospholipase Cγ2 enzyme that has essential functions in B-cell receptor and Fc receptor signaling, cause a dominantly inherited autoinflammatory syndrome characterized by blistering skin lesions, bronchiolitis, arthralgia, ocular inflammation, and enterocolitis in the absence of autoantibodies.

SOMATIC MUTATION AND LATE-ONSET AUTOINFLAMMATORY DISEASE

An autoinflammatory disorder caused by myeloid-restricted somatic mutations in *UBA1*, which is one of the critical regulators of ubiquitylation in all cells,[24] is manifested by fever, relapsing polychondritis (usually affecting the nasal and/or auricular cartilage but sparing the trachea), neutrophilic dermatosis, medium-vessel vasculitis, pulmonary infiltrates, neutrophilic alveolitis, venous thromboembolism, macrocytic anemia, vacuoles in myeloid precursor cells in the marrow, and hypercytokinemia. Based on the demonstration of somatic *UBA1* mutations, this condition is termed VEXAS (vacuoles, E1 enzyme, X-linked, autoinflammatory, somatic) syndrome. Because *UBA1* is encoded on the X-chromosome, VEXAS syndrome is observed almost exclusively in men, usually over age 40 years. Given the high mortality rate, early allogeneic stem cell transplantation may be advisable.

Adult-onset syndromes resembling the inherited versions of both the cryopyrinopathies and TRAPS are caused by somatic mutations in *NLRP3* and *TNFRSF1A,* respectively. The discovery of these syndromes raises the possibility of somatic mutations in other adult-onset rheumatic diseases and emphasizes the likelihood of other genetic diagnoses that cut across the boundaries of current clinical syndromes.

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For the General References and other additional features, please visit Elsevier eBooks+ at https://ebooks.health.elsevier.com.

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241 OSTEOARTHRITIS

DAVID J. HUNTER

DEFINITION

Osteoarthritis is characterized by failed repair of synovial joint tissues after intra-articular stress. The resulting breakdown of cartilage and bone can lead to symptoms of pain, stiffness, and functional disability. However, synovial joint pathology and structural changes on imaging studies may correlate poorly with patient-reported symptoms.

EPIDEMIOLOGY

Osteoarthritis is a highly prevalent, disabling disease that affects more than 500 million people worldwide, with women disproportionately affected.[1] The

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CD2BP1. PSTPIP1 is a cytoskeletal protein that interacts with certain other proteins involved in the immune response, including CD2; the Wiskott-Aldrich syndrome protein (WASP); a phosphatase denoted PTP-PEST; and pyrin, the familial Mediterranean fever (FMF) protein. PAPA mutations abrogate the binding of PSTPIP1 to PTP-PEST, leading to hyperphosphorylation of PSTPIP1 and increased binding to pyrin. This finding is associated with markedly increased production of IL-1β and extremely high levels of total and free IL-18 in the blood.[18]

Early in life, PAPA tends to present with monoarticular or pauciarticular pyogenic arthritis, sometimes induced by trauma. As patients reach puberty, skin manifestations begin to predominate, including disfiguring cystic acne. Pathergy also may develop, and extensive pyoderma gangrenosum may require opiates for pain control. The diagnosis of PAPA syndrome is made by documenting *PSTPIP1* mutations in the appropriate clinical setting.

High doses of glucocorticoids have been used under expert supervision with varying success in PAPA, and patients with arthritis sometimes require aspiration, intra-articular glucocorticoids, or open drainage. Small case series support the use of anakinra or canakinumab for the arthritis and monoclonal anti-TNF antibodies for the pyoderma gangrenosum of PAPA. In the absence of treatment, arthritis may progress to severe joint damage and ankylosis.

ADENOSINE DEAMINASE-2 DEFICIENCY

A syndrome characterized by fevers, early-onset strokes, and vasculopathy or frank vasculitis mimicking polyarteritis nodosa has been found to be caused by autosomal recessive mutations in *ADA2* (formerly *CECR1*), which encodes adenosine deaminase-2 (ADA2). Although ADA2 shares enzymatic activity with intracellular adenosine deaminase that is encoded by the *ADA* gene, ADA2 is not necessary for the development of lymphocytes, and patients with deficiency of adenosine deaminase-2 (DADA2) do not initially present with severe combined immunodeficiency (SCID), as is the case for ADA deficiency. ADA2 is a secreted extracellular protein, and functional studies have found that ADA2 plays a role in vascular development and regulation of macrophage differentiation. Although this disease is generally diagnosed in childhood, it should be considered in the differential diagnosis of young adults with unexplained lacunar strokes, vasculitic skin lesions, and/or polyarteritis nodosa. Transfusion-dependent anemia and severe neutropenia are uncommon manifestations.

TNF inhibition under expert supervision is highly effective in preventing stroke.[19] Hematopoietic stem cell transplantation may be curative, both for cytopenias and vascular manifestations.

GENOME SEQUENCING AND THE DISCOVERY OF NEW AUTOINFLAMMATORY SYNDROMES AND INNATE IMMUNE PATHWAYS

A major attraction of the concept of the autoinflammatory diseases has been the molecular explication of numerous inborn errors of inflammation, an enterprise that has converged with the delineation of the innate immune system (Chapter 35). With advances in genome sequencing, the number of defined autoinflammatory diseases that are associated with dramatically elevated levels of total and free IL-18 in the blood has increased rapidly. Recently defined conditions include autoinflammatory periodic fever, immunodeficiency, and thrombocytopenia (PFIT), which is caused by mutations in the actin-regulatory gene *WDR1;* neonatal-onset pancytopenia, autoinflammation, rash, and hemophagocytic lymphohistiocytosis (NOCARH syndrome),[20] which is caused by mutations in *CDC42* that activate the pyrin inflammasome; and mutations in *MEFV,* which encodes pyrin. Taken together, these findings point to a poorly understood aspect of inflammasome activation that may be amenable to therapies targeting IL-18.

Other recent genomic discoveries implicate the cell death pathways of apoptosis and necroptosis in two different autoinflammatory disorders caused by mutations in *RIPK1* and *TBK1*.[21] Gain-of-function mutations in *ALPK1,* encoding a novel innate immune sensor for seven carbon sugars (which are made by gram-negative bacteria but not by mammals), cause an autoinflammatory syndrome characterized by retinal dystrophy, optic nerve edema, splenomegaly, anhidrosis, and migraine headache (ROSAH).[22] Genomic sequencing of children carrying the diagnosis of systemic-onset juvenile idiopathic arthritis has identified *LACC1* as an important regulator of immunometabolic function in macrophages, and genomic sequencing of patients with a form of chronic recurrent multifocal osteomyelitis has identified *LPIN2* as an important regulator of osteoclast differentiation in M2 macrophages.[23] Gain-of-function mutations in *PLCG2,* which encodes the phospholipase Cγ2 enzyme that has essential functions in B-cell receptor and Fc receptor signaling, cause a dominantly inherited autoinflammatory syndrome characterized by blistering skin lesions, bronchiolitis, arthralgia, ocular inflammation, and enterocolitis in the absence of autoantibodies.

SOMATIC MUTATION AND LATE-ONSET AUTOINFLAMMATORY DISEASE

An autoinflammatory disorder caused by myeloid-restricted somatic mutations in *UBA1*, which is one of the critical regulators of ubiquitylation in all cells,[24] is manifested by fever, relapsing polychondritis (usually affecting the nasal and/or auricular cartilage but sparing the trachea), neutrophilic dermatosis, medium-vessel vasculitis, pulmonary infiltrates, neutrophilic alveolitis, venous thromboembolism, macrocytic anemia, vacuoles in myeloid precursor cells in the marrow, and hypercytokinemia. Based on the demonstration of somatic *UBA1* mutations, this condition is termed VEXAS (vacuoles, E1 enzyme, X-linked, autoinflammatory, somatic) syndrome. Because *UBA1* is encoded on the X-chromosome, VEXAS syndrome is observed almost exclusively in men, usually over age 40 years. Given the high mortality rate, early allogeneic stem cell transplantation may be advisable.

Adult-onset syndromes resembling the inherited versions of both the cryopyrinopathies and TRAPS are caused by somatic mutations in *NLRP3* and *TNFRSF1A,* respectively. The discovery of these syndromes raises the possibility of somatic mutations in other adult-onset rheumatic diseases and emphasizes the likelihood of other genetic diagnoses that cut across the boundaries of current clinical syndromes.

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For the General References and other additional features, please visit Elsevier eBooks+ at https://ebooks.health.elsevier.com.

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241 OSTEOARTHRITIS

DAVID J. HUNTER

DEFINITION

Osteoarthritis is characterized by failed repair of synovial joint tissues after intra-articular stress. The resulting breakdown of cartilage and bone can lead to symptoms of pain, stiffness, and functional disability. However, synovial joint pathology and structural changes on imaging studies may correlate poorly with patient-reported symptoms.

EPIDEMIOLOGY

Osteoarthritis is a highly prevalent, disabling disease that affects more than 500 million people worldwide, with women disproportionately affected.[1] The

ABSTRACT

Osteoarthritis is a heterogeneous syndrome and an increasingly prevalent source of disability. The combined impacts of aging, obesity, and increasing rates of joint injury are increasing the numbers of people with this disease. Important insights are clarifying the pathogenesis, etiology, and sources of pain. Diagnosis is based on clinical presentation with little need for imaging or laboratory investigation. Management should be individually tailored and focus on core treatments, including self-management, exercise, and maintaining a healthy weight.

KEYWORDS

osteoarthritis
phenotype
pain
assessment
management

incidence of osteoarthritis increases rapidly between ages 50 and 75 years (Fig. 241-1).[2] The age-standardized incidence and prevalence are also increasing, and an estimated 25% of the total U.S. adult population will have physician-diagnosed osteoarthritis by the year 2040.

In part as a consequence of aging, obesity, and joint injury, the number of people affected by osteoarthritis globally rose by 48% from 1990 to 2019, and osteoarthritis is now the 15th highest cause of years lived with disability worldwide.[3] Of people affected by osteoarthritis, 80% suffer from limitations in movement and 25% have difficulty in performing their major activities of daily living.[4] Osteoarthritis of the knee accounts for approximately 85% of the burden attributable to osteoarthritis. The lifetime risk of having symptomatic knee osteoarthritis is about 40% in men and 47% in women, and the risk increases to 60% among persons above a healthy weight.[5]

PATHOBIOLOGY

Osteoarthritis results in structural alterations in the hyaline articular cartilage, subchondral bone, synovium, ligaments, capsule, and periarticular muscles. This dynamic process involves a range of factors, including mechanical, inflammatory, and metabolic pathways, which create an imbalance between repair and destruction of joint tissues and ultimately lead to failure of the synovial joint.

The pathologic changes of osteoarthritis include alterations in most of the structures of synovial joint tissue.[6] Compositional changes in cartilage (initially proteoglycan attracts water, thereby leading to swelling of articular cartilage and then disruption of the type 2 collagen matrix) alter its material properties and increase its susceptibility to disruption by physical forces. Erosions occur at the cartilage surface, and then deep cartilage fissures are accompanied by the expansion of the calcified cartilage zone. Hypertrophic chondrocytes appear and exhibit increased synthetic activity, thereby reflecting an attempt at repair, and they generate matrix degradation products and proinflammatory mediators that further deregulate chondrocytic function and act on the adjacent synovium to stimulate proliferative and proinflammatory responses.[7] Breakdown products of cartilage and bone evoke a synovial inflammatory response, which becomes both hyperplastic (increased numbers of synovial lining cells) and hypertrophic (small villi or folds developing in the membrane, with infiltration of macrophages, lymphocytes, and plasma cells) and is accompanied by an increase in the vascularity in the subintimal layer.

In the subchondral bone, increased bone turnover and vascular invasion from the subchondral bone damage cartilage. The bone remodeling and repair is also associated with the development of subchondral bone marrow lesions, which are associated with both pain and progressive disease. The evolution of these lesions can lead to the formation of focal necrosis and subchondral cysts. Reactivation of endochondral ossification leads to osteophytes, which develop at the joint margins and are strongly affected by inflammatory biologic factors, overload, and abnormal joint kinematics.[8] Meniscal (myxoid degeneration, tears, and maceration) and ligamentous abnormalities are common, as are periarticular muscle atrophy and weakness.

Mechanics versus Inflammation

Mechanical load is the primary risk factor responsible for the development of osteoarthritis when excessive mechanical strain is transmitted through a normal joint (obesity, joint malalignment, occupational risk) or when a normal load traverses a joint that has lost its mechanical protection because of disruption of ligaments, meniscal damage, or muscle weakness).[9] This altered mechanical load induces activation of inflammatory signaling pathways to drive the process of joint breakdown (E-Fig. 241-1). This inflammation occurs locally within the tissues, including cartilage and subchondral bone, with synovitis and osteophytes. The process is frequently driven systemically by obesity-related inflammation.

Risk Factors

For most persons affected by osteoarthritis, its development can be linked to multiple risk factors that can be grouped either into local/systemic risk factors, which may be modifiable or nonmodifiable (Fig. 241-2). Potentially modifiable risk factors include increased body weight, joint malalignment, muscle weakness, a sedentary lifestyle, occupational exposure, and athletic injuries. In contrast, nonmodifiable risk factors include age, ethnicity, genetics, prior injury, and sex.

The genetic contribution to osteoarthritis varies by joint and is stronger for the hand than for the knee. Except for monogenetic disorders such as

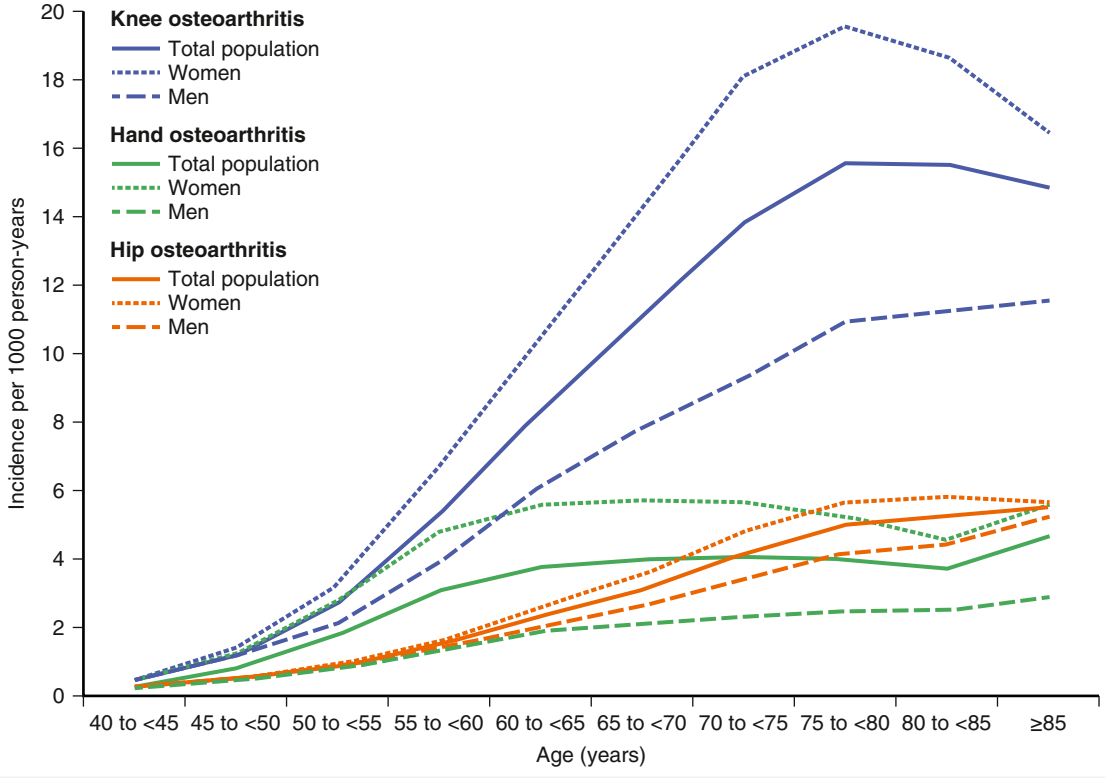

FIGURE 241-1. Incidence of osteoarthritis. Age and sex-specific incidence rates (per 1000 person-years) of knee osteoarthritis *(blue)*, hip osteoarthritis *(orange)*, and hand osteoarthritis *(green)*. Long dashed line = men; short dashed line = women; solid line = all population. (From Prieto-Alhambra D, Judge A, Javaid MK, et al. Incidence and risk factors for clinically diagnosed knee, hip and hand osteoarthritis: influences of age, gender and osteoarthritis affecting other joints. *Ann Rheum Dis*. 2014;73:1659-1664.)

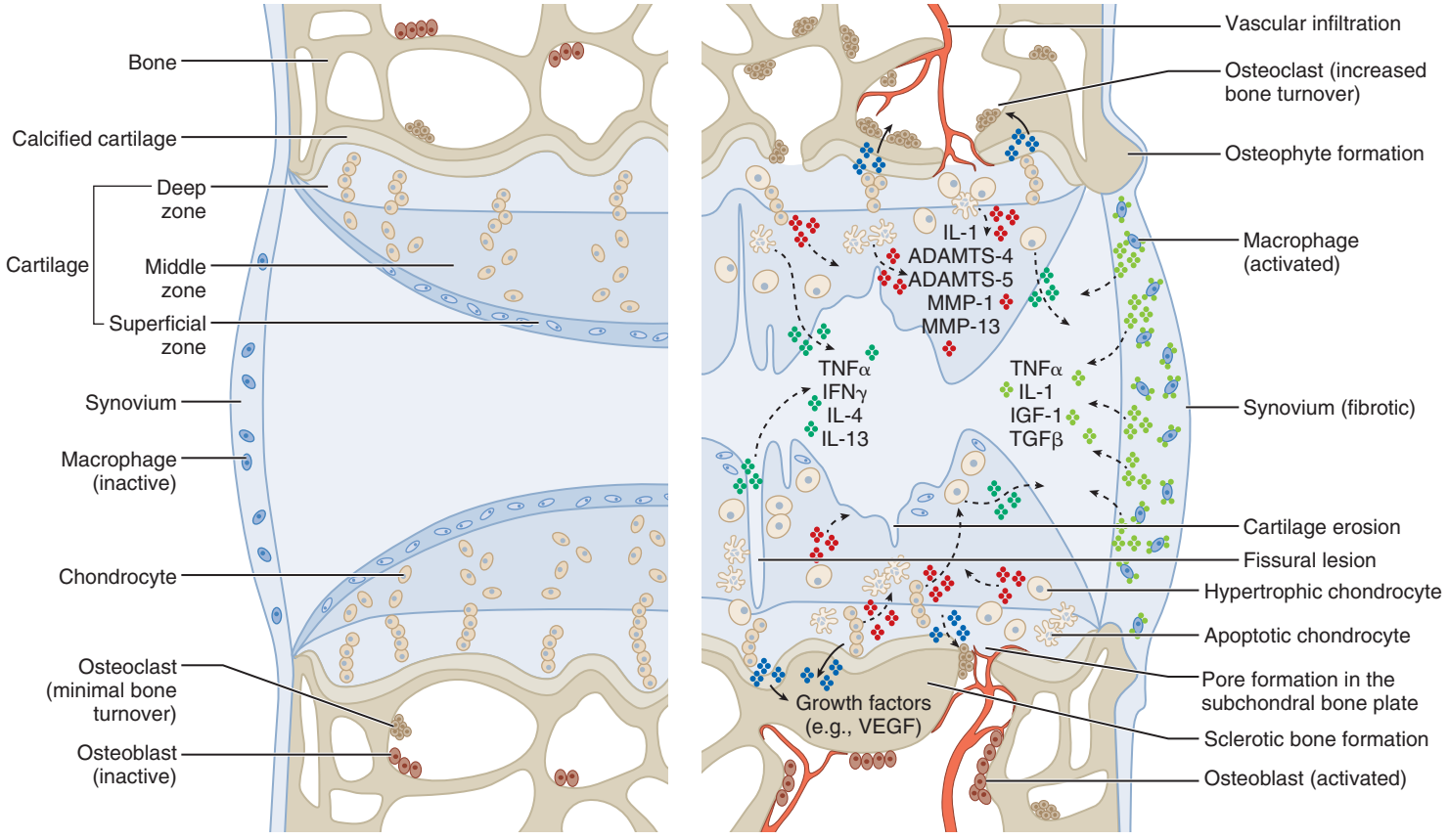

E-FIGURE 241-1. Signaling pathways and structural changes in the development of osteoarthritis. ADAMTS = a disintegrin and metalloproteinase with thrombospondin-like motifs; IFN = interferon; IGF = insulin-like growth factor; IL = interleukin; MMP = matrix metalloproteinase; TGF = transforming growth factor; TNF = tumor necrosis factor; VEGF = vascular endothelial growth factor. (From Hunter DJ, Bierma-Zeinstra S. Osteoarthritis. *Lancet*. 2019;393:1745-1759.)

chondrodysplasia, the genetic contribution to osteoarthritis is polygenic, and over 100 polymorphic DNA variants with small effects have been identified to date. These genetic variants account for over 20% of the heritability of osteoarthritis and largely map to non-protein coding regions of the genome that might regulate expression of target genes.[10] These targets include extracellular signaling molecules, intracellular enzymes, transcription factors, and cytoskeletal proteins. A number of these risk variants relate to epigenetic factors, in particular DNA methylation, whereas other variants appear to have been selected as humans adapted to bipedalism.

Phenotypes and Endotypes

Osteoarthritis is an umbrella diagnosis referring to a multifaceted and heterogeneous syndrome rather than one single disease. The commonly described identifiable predisposing factors for most forms of osteoarthritis include hormonal changes (e.g., estrogen deficiency), metabolic syndrome, post-traumatic injury, mechanical overload, inflammatory responses, genetic predisposition, and aging (E-Fig. 241-2).

Etiology of Pain

Pain is the dominant presenting symptom and typically the main driver for clinical decision-making in patients with osteoarthritis. The most useful framework for understanding pain is the biopsychosocial model (E-Fig. 241-3; Chapter 26), including psychological factors and socioeconomic factors, in contrast to the traditional biomedical approach, in which the major focus usually is on joint pathology. The degree of structural osteoarthritis bears at best a moderate association with the severity of pain.

Pain in osteoarthritis is classically considered nociceptive pain, described as mechanical in nature and arising from the loading of a damaged joint. In addition to peripheral nociceptive pain mechanisms, pain sensitization by means of neuropathic pain mechanisms and/or central pain mechanisms seem to be present in a substantial proportion of people with osteoarthritis.[11] This sensitization of central pathways influences the perception of pain, which shows marked heterogeneity among patients. People who have osteoarthritis and who demonstrate alterations in neurophysiologic nociceptive signal processing often respond poorly to standard treatments. Nevertheless, removing the stimulus through nerve block or joint replacement can relieve pain, thereby suggesting that pain signaling is dependent on peripheral triggers, presumably through joint nociceptors that remain responsive to ongoing tissue injury or inflammation.

CLINICAL MANIFESTATIONS

Symptoms

Osteoarthritis typically has a very gradual onset over a number of years, with pain as the key feature. The typically slow, insidious structural progression of osteoarthritis may be punctuated with intermittent periods of increased disease activity.[12] The natural history of osteoarthritis is highly variable and usually evolves over decades (E-Fig. 241-4).

Pain is usually mechanical in nature, occurs with activity, and is often worse towards the end of the day. In more advanced disease, pain may be present at rest. Osteoarthritis can affect any synovial joint in the body but most commonly affects the hands, knees, spine, hips, and feet.

Other symptoms include joint stiffness that is usually localized to the involved joint, rarely persists for more than 15 to 30 minutes, and is most noticeable when first mobilizing after a period of inactivity. Patients may also complain of crepitus or grating that they can feel and hear as their joints move. As the disease progresses, patients may notice limitation of joint range of motion and associated difficulty performing activities such as opening jars for hand osteoarthritis, going up and down stairs or rising from a chair for knee osteoarthritis, or getting in and out of the car or putting shoes and socks on for hip osteoarthritis. Other local symptoms include catching or locking, especially around the knee, that can be associated with falls.

Signs

In the early stages of the disease, patients may have very few visible signs. As the disease progresses, joints may be tender to palpation along the respective joint line. With time, range of motion is lost and crepitus might be palpable on movement of the joint, most prominently under the patella on flexion and extension of the knee. Joint swelling may be palpable, both bony swelling as a result of osteophytes and soft tissue swelling due to joint effusion. Ongoing damage to the joint can lead to alterations in alignment, along with muscle weakness and atrophy. Additional joint-specific features that may be present on examination of the knee include deformity (varus, fixed flexion, or less commonly valgus for the knee), instability on ligament testing, periarticular tenderness, and pain on patellofemoral compression. Early physical signs of osteoarthritis in the hip include restriction of internal rotation, with pain occurring at the end of the range of motion.

DIAGNOSIS

The diagnosis of osteoarthritis is clinical based upon symptoms (pain, brief morning stiffness, and functional limitation) and physical examination (crepitus, restricted or painful movement, joint tenderness, and bony enlargement).[13] Plain radiographs are not necessary but can be considered for atypical presentations or for diagnostic clarity.

Presenting features that might lead towards consideration of an alternative or additional diagnosis include prolonged morning joint-related stiffness (rheumatoid arthritis; Chapter 242), a recent history of trauma, the presence of a swollen hot joint (crystal deposition disease [Chapter 252] or infection

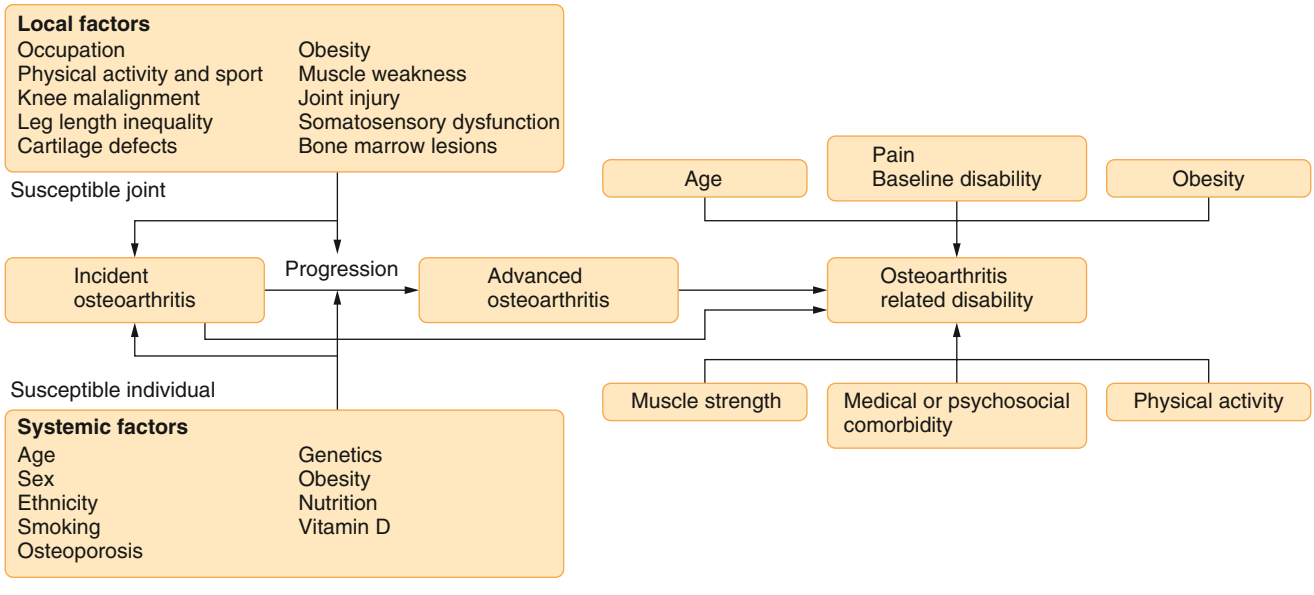

FIGURE 241-2. Risk factors for osteoarthritis of the knee and related disability. (Modified from Bennell KL, Hunter DJ, Hinman RS. Management of osteoarthritis of the knee. *BMJ.* 2012;345:e4934.)

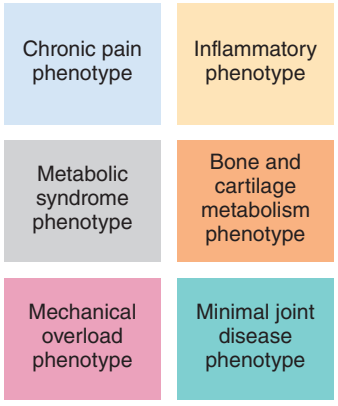

E-FIGURE 241-2. Clinical phenotypes of knee osteoarthritis. (From https://f1000research.com/articles/8-2091.)

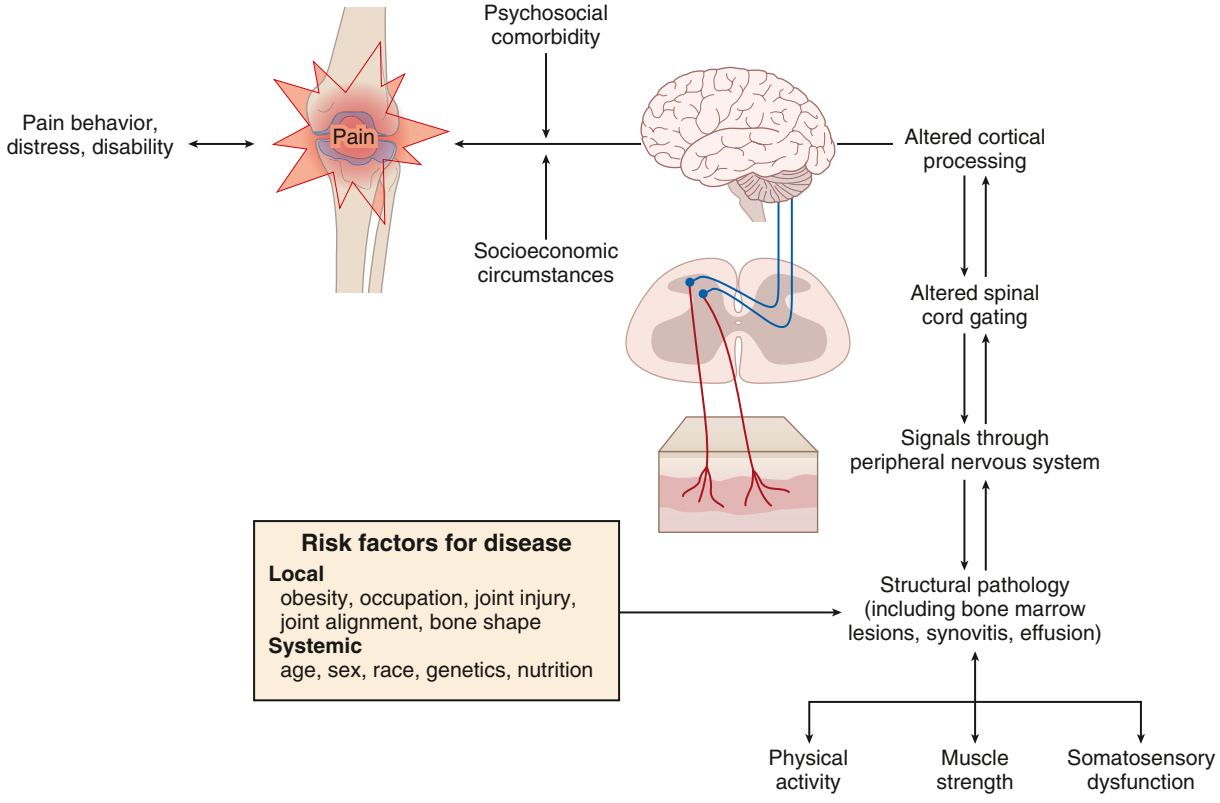

E-FIGURE 241-3. The cause of pain in osteoarthritis fits within a biopsychosocial model. (From Hunter DJ, Bierma-Zeinstra S. Osteoarthritis. *Lancet*. 2019;393:1745-1759.)

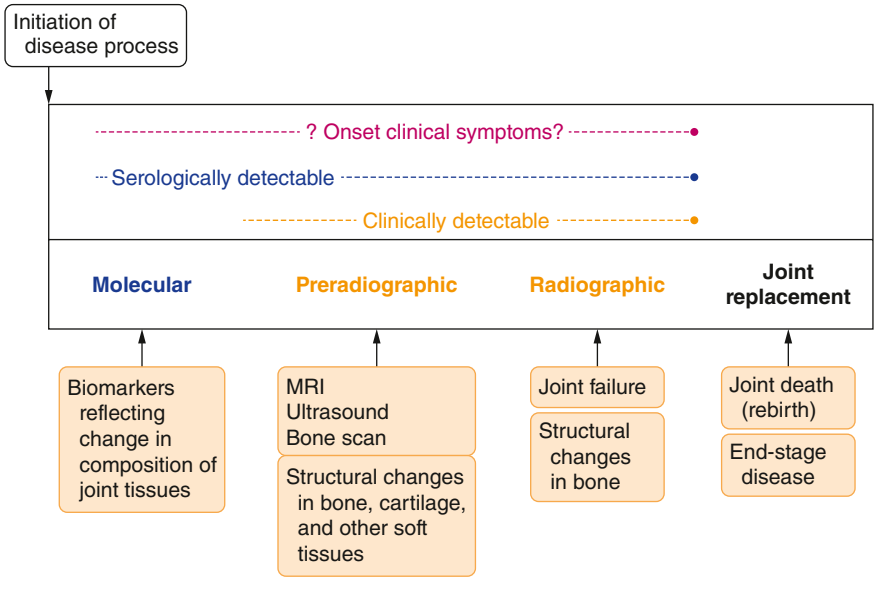

E-FIGURE 241-4. The natural history of osteoarthritis. MRI = magnetic resonance imaging. (From Hunter DJ, Guermazi A, Roemer F, et al. Structural correlates of pain in joints with osteoarthritis. *Osteoarthr Cartil*. 2013;21:1170-1178.)

TABLE 241-1 HOLISTIC ASSESSMENT OF PATIENTS WITH OSTEOARTHRITIS

Social factors: impact of the condition on activities of daily living, relationships, quality of life, and recreational and occupational activities
Health beliefs and concerns: previous knowledge of osteoarthritis; expectations of treatment; understanding of treatment options including benefits and harms
Psychological factors: screen for depression; stresses in life; mood
Attitudes to physical activity and exercise: concerns; restrictions; access to appropriate facilities
Pain assessment: nature of pain, other sites of pain, self-help strategies; use of analgesics, doses, frequency and side effects; current understanding about persistent pain
Functional capacity: such as walking ability, stair climbing, sit-to-stand, balance
Presence of support: concerns and expectations of carers (including family and friends); isolation issues
Influence of comorbidities: interaction of two or more morbidities; risk of falls
Modifiable risk factors: overweight/obesity; joint alignment; and injury/buckling

Reproduced with permission from The Royal Australian College of General Practitioners from: Guideline for the management of knee and hip osteoarthritis. Chapter 1.6: Assessment of people with hip and/or knee OA. Section 1.6.1: Holistic assessment. 2nd edn. East Melbourne, Vic: RACGP, 2018; p. 15. Available at www.racgp.org.au/getattachment/71ab5b77-afdf-4b01-90c3-04f61a910be6/Guideline-for-the-management-of-knee-and-hip-osteoarthritis.aspx.

[Chapter 251]), or rapid worsening of symptoms. Laboratory tests (e.g., rheumatoid factor, synovial fluid aspirate for crystal confirmation, erythrocyte sedimentation rate or C-reactive protein) may be helpful to confirm or exclude coexistent inflammatory disease (e.g., rheumatoid arthritis, calcium pyrophosphate crystal deposition, gout) in patients with suggestive symptoms or signs. However, routine laboratory tests on blood, urine, or synovial fluid are not required to diagnose osteoarthritis.

If a palpable moderate to large effusion is present, synovial fluid should be aspirated and analyzed to exclude inflammatory disease and to identify urate and calcium pyrophosphate crystals. In osteoarthritis, synovial fluid is typically noninflammatory with fewer than 2000 leucocytes/μL. Basic calcium phosphate crystals are often present.

Holistic Evaluation

Because osteoarthritis is so common and is a chronic disease, patients benefit from a holistic assessment. (Table 241-1).

Imaging

Imaging is limited to atypical presentations, when the clinical diagnosis is uncertain, when other diagnoses are suspected, or when interventional therapy is being planned. Many of the structural abnormalities seen on imaging are very common in older populations, for example, meniscal tears are an almost universal finding in people with osteoarthritis and are typically just age-related abnormalities and not related to symptoms. Radiographic changes and symptoms are poorly correlated with each other in osteoarthritis, and the common occurrence of structural abnormalities in older adults must be considered when evaluating radiographic computed tomographic scan or magnetic resonance images.[14] Imaging also can lead to increased use of unnecessary or harmful interventions.

TREATMENT

The management of osteoarthritis is complex and challenging, but a careful evaluation can help guide an individual treatment plan (Table 241-2).[15] Clinicians should prioritize interventions that are safe, accessible, and cost-effective.

Active, nonpharmacologic interventions are the mainstay of management and should be tried first, followed by or in concert with medications to relieve pain when necessary.[16] These core treatments include education, weight management,[A1] promotion of physical activity,[A2,A3] therapeutic exercises, and help in changing behavior.[A4] These treatments may be facilitated by providing a referral to appropriate health care professionals, including physiotherapists and dieticians.

Physical activity usually refers to everyday exercise (e.g., walking, cycling, swimming), whereas therapeutic exercise (Table 241-3) refers to planned, structured, repetitive activities undertaken to improve osteoarthritis management. Guidelines strongly recommend weight loss for anyone with a BMI of 25 kg/m^2 or higher. The recommended starting point is to lose 5 to 10% of body weight, but greater weight loss leads to greater benefits for both pain and function.

Analgesic medications can be used following or in concert with core treatments for patients with persistent or severe symptoms. Nonsteroidal anti-inflammatory drugs (NSAIDS) are usually advocated as the first-line therapy,[A5] and topical over-the-counter NSAIDs are preferred over systemic treatments (Table 26-4) owing to safety concerns. For patients who require oral analgesia, the central tenant is usually the lowest dose for the shortest duration possible. Low-dose (10 mg daily) oral prednisolone is safe and efficacious for short term (6 weeks) treatment, but symptoms return rapidly when it is discontinued,[A6] and physical therapy appears to be better than standard glucocorticoid injections for relieving pain and preserving function in patients with osteoarthritis of the knee.[A7] Physicians should avoid reliance on glucosamine, chondroitin

TABLE 241-2 COMPREHENSIVE ASSESSMENT OF PATIENTS WITH OSTEOARTHRITIS OF THE KNEE AND PRACTICAL IMPLICATIONS FOR MANAGEMENT

ASSESSMENT ELEMENTS	PRACTICAL IMPLICATIONS
Joint symptoms and signs such as joint pain, giving way, stiffness, locking or catching, effusion, diminished range of motion, tenderness on palpation, joint laxity, abnormal knee alignment in standing	Helps with differential diagnosis and establishes whether radiography and magnetic resonance imaging are needed. Neuropathic symptoms (shooting, burning pain, and pins and needles) may indicate need for a centrally active agent. Changes in pain allow assessment of response to treatment. If the patient has disabling locking or catching, consider orthopaedic referral. If the patient has giving way and laxity, consider a gait aid, physiotherapy for muscle strengthening, and referral to an orthotist for bracing. If knee malalignment is present, bracing may be beneficial
Comorbid conditions such as cardiovascular disease, diabetes, peptic ulcer, renal, liver disease, depression	Influence contraindications and precautions for treatment, in particular prescription of drugs
Functional ability, impaired activities of daily living (such as walking, stair climbing, sit to stand, balance) and history of falls	If difficulty with walking, function, balance, or if more than 1 fall in past 12 months, consider gait aid, attention to footwear, and referral to a physiotherapist for treatment including exercise prescription and manual therapy. If a varus thrust is seen during walking (visible dynamic worsening or varus alignment during stance phase), consider referral to a physiotherapist for exercise program and possibly to an orthotist for bracing
Muscle mass and strength, particularly of the quadriceps	If weak, prescribe muscle strengthening exercises; consider referral to a physiotherapist or exercise specialist
Foot posture	If abnormal, consider referral to a podiatrist for orthotics and footwear advice
Psychosocial factors, such as mood disorders (depression and anxiety), abnormal sleep, poor social support, inability to cope, reduced participation in leisure activities, relationships, and difficulties at work	If mood disorder present, consider referral to a psychologist or psychiatrist or prescription of antidepressants (Table 362-5). If difficulty coping or participating, consider referral to appropriate allied health practitioner (such as a psychologist, occupational therapist, or social worker) or relevant self-help groups for peer support
Patient's knowledge, expectations, and goals	Careful assessment can guide a patient-centered approach to management and communication, tailored to patient's needs and goals. Ensure that the patient understands the disease process, has realistic expectations, and participates in treatment decision-making by providing education, information, and resources. Consider referral to a self management program
Overweight or obesity (weight, body mass index, and waist girth)	If body mass index >25 or waist >80 cm in women or >94 cm in men, counsel about weight loss (Chapter 201) through both diet (Chapter 13) and exercise (Chapter 14: aerobic and strengthening). If possible, refer to a dietitian for nutritional assessment and weight loss support (Chapter 201). Weight loss program should aim for a 5 to 10% reduction

From Bennell KL, Hunter DJ, Hinman RS. Management of osteoarthritis of the knee. *BMJ*. 2012;345:e4934.

TABLE 241-3 EXAMPLES OF EXERCISES AND PHYSICAL ACTIVITIES FOR IMPROVING OSTEOARTHRITIS-RELATED PAIN AND FUNCTION

TYPE OF ACTIVITY	HAND	KNEE	HIP	DESCRIPTION
General physical activity	+	+	+	Many sports and everyday activities can provide aerobic exercise and improve general physical activity levels. Examples include walking or cycling for recreation or to work, gardening, dancing, walking a dog, or playing with children
Aerobic exercise	NA	+	+	Any type of exercise that raises heart rate is recommended. Land-based examples of aerobic exercises include running or jogging, cycling (stationary or moving), and power walking
Strengthening	+	+	+	Exercises to strengthen specific muscles around the affected joint(s) is recommended. Strengthening can be undertaken using body weight exercises or seated exercises (e.g., squats or seated knee extension), or using free weights, resistance machines, or resistance bands
Neuromuscular and balance exercises	NA	+	+	Neuromuscular and balance exercises specifically targeted to the ability to control and stabilize body position and to improve balance and coordination. Examples include walking on soft surfaces, wobble boards, and single leg balancing
Tai chi and yoga	NA	+	+	Tai chi and yoga are examples of mind-body exercises (Chapter 30) because they have a whole-body focus (e.g., a focus on breathing and coordinated or postured movements) and an emphasis on mindfulness (e.g., meditation and focus)
Joint mobility and stability	+	+	+	Exercises to improve joint mobility and stability are recommended. Exercises for the hand should be aimed at improving joint mobility, muscle strength, and thumb base stability, and they should be tailored for the specific joint(s)
Water-based exercises	NA	+	+	Water-based therapies can include aerobic fitness exercises (e.g., aqua aerobics, swimming, deep water running, and water-based sports) and/or exercises for enhancing the strength and range of motion of a joint in a low-impact environment (e.g., hydrotherapy)

Adapted from Bowden JL, Hunter DJ, Deveza LA, et al. Core and adjunctive interventions for osteoarthritis: efficacy and models for implementation. *Nat Rev Rheumatol*. 2020;16:434-447.

supplements, opioids, viscosupplements,[A8] or repeated injections of corticosteroids, which have at most very modest benefit in some patients.[A9,A10] Injections of platelet-rich plasma are not of documented benefit.[A11,A12]

Referral of patients with end-stage osteoarthritis to an orthopedic surgeon should be considered when all appropriate conservative options, delivered for a reasonable period, have failed (Chapter 255). Symptoms that warrant surgical evaluation include joint pain that disrupts normal sleep patterns, severely reduces walking distance, markedly restricts activities of daily living, or significantly reduces quality of life.

Newer Treatment Options

An area of active research focuses on developing disease-modifying drugs[17] that might alter the natural history of osteoarthritis by arresting structural damage. A potential promising option may be the intraarticular injection of sprifermin, which is a recombinant human fibroblast growth factor, that can increase the thickness of femorotibial cartilage but so far without obvious clinical benefits.[A13,A14]

PREVENTION

Since no cure exists for osteoarthritis, public health measures to prevent disease are of great interest.[18] Two major approaches are to prevent joint injury and to reduce weight in overweight or obese individuals. For example, a reduction in body weight from obese (body mass index [BMI] ≥30 kg/m^2) to overweight (BMI ≥26 and <30 kg/m^2) or from overweight to normal (BMI <26 kg/m^2) reduces the incidence of symptomatic knee osteoarthritis by about 20% in men and one third in women. A 5-kg or 5% weight loss can reduce incident clinical knee osteoarthritis from 21 to 7% over a 6 to 7 year follow-up.

An anterior cruciate ligament injury strongly correlates with the later development of knee osteoarthritis. Prevention programs that focus on sports-specific movements and tasks can decrease injury rates, including anterior cruciate ligament injuries, by 50 to 80%.[19]

PROGNOSIS

Osteoarthritis is characterized by marked short fluctuations, which vary in frequency, intensity, and duration and are the prime drivers of disability and health care utilization. However, the vast majority (about 85%) of individuals have a relatively flat symptomatic trajectory over years to decades.[20] Only 7% of people with knee osteoarthritis have a trajectory characterized by worsening, 85% are stable, and 8% experience a reduction in pain.

Surgical rates continue to increase, with a projected increase in total knee replacement volume of about 50% from 2021 to 2050 in the United States. The presence of comorbid conditions, including depression and lower educational level, are predictors of worsening pain trajectory. The obesity and physical limitations associated with osteoarthritis likely explain why premature mortality is increased by 20 to 25% in patients with osteoarthritis of the knee and by 20% in patients with osteoarthritis of the hip.[21]

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242

BURSITIS, TENDINOPATHY, OTHER PERIARTICULAR DISORDERS, AND SPORTS MEDICINE

JOSEPH J. BIUNDO AND JUAN J. CANOSO

DEFINITION

An array of painful and sometimes disabling musculoskeletal syndromes exist that are not articular in origin but arise from tendons, ligaments, enthesis, and bursae. These conditions are referred to by various names, in addition to *tendinosis, enthesopathy,* and *bursitis,* including the terms *nonarticular rheumatism, soft tissue diseases, regional rheumatic pain syndromes,* and *repetitive use syndromes* (Table 242-1). These entities are often ignored, misdiagnosed as arthritis, or attributed to the aging process. Awareness of the existence of these conditions and knowledge of basic musculoskeletal anatomy (Figs. 242-1 and 242-2) are the fundamental requirements for diagnosis. This knowledge is coupled with brief but specific physical diagnosis techniques. The accurate diagnosis and successful treatment of these conditions is gratifying to the clinician because many people can be relieved of their chronic painful syndromes.

Various terms regarding tendon injuries are used and may be confusing. The main term used is *tendinitis,* but *tendinosis* is the correct terminology because there are degenerative changes in the tendon but very few inflammatory cells. In addition, fatty mucoid degeneration and hyaline features occur in these tendon syndromes. Also, tendons may *rupture* or *tear,* partially or completely.

TABLE 242-1 NONARTICULAR PAIN SYNDROMES, BY REGION

SHOULDER
Rotator cuff tendinosis; rotator cuff tear
Bicipital tendinosis; biceps tendon tear
Subacromial bursitis
Adhesive capsulitis (frozen shoulder)
ELBOW
Olecranon bursitis
Medial epicondylalgia
Lateral epicondylalgia
WRIST AND HAND
De Quervain tenosinovitis
Trigger finger
Digital flexor tenosynovitis
Ganglia (dorsal and volar wrist, finger, etc.)
HIP
Greater trochanter pain syndrome (gluteus medius and minimus tendinosis and tear; trochanteric bursitis)
Iliopsoas bursitis
Ischial bursitis
Coccydynia
KNEE
Prepatellar bursitis
Infrapatellar bursitis
Pes anserine syndrome
Iliotibial band syndrome
Popliteal (Baker) cyst
Quadriceps tendon tear
Patellar tendinosis and tear
Hoffa syndrome
ANKLE AND FOOT
Achilles tendinosis, insertional and mid-tendon
Achilles tendon tear
Retrocalcaneal bursitis
Posterior tibial tendinosis and tenosynovitis
Posterior tibial tendon tear
Plantar fasciopathy (fasciitis)
Morton neuroma

The terms *tenosynovitis* and *peritendinitis* refer to an inflammatory response of the tenosynovium, such as in rheumatoid arthritis. However, tenovaginosis and peritendinosis are more appropriate terms in oversuse conditions. Tendinosis may occur when the tendon repeatedly bears more load than it can withstand. This may result from excessively high loads across normal tendons or from normal loads across degenerated tendons. In addition to load and repetitiveness, tendon changes resulting from immobility and from aging may play a role, as may the use of certain medications such as fluoroquinolones and corticosteroids.

Bursae are closed sacs lined by a synovial membrane, often discontinuous, and serve to promote smooth tissue gliding between tendon and bone, tendon and tendon, or bone and skin. A bursa can become inflamed from trauma or overuse or become infected, thereby producing a bursitis. Bursitis is typically associated with pain and swelling of the bursa.

EPIDEMIOLOGY

The incidence and prevalence of the nonarticular syndromes are high. They are more common than rheumatoid arthritis and systemic lupus erythematosus combined. For example, the incidence of shoulder pain, largely a result of rotator cuff tendinosis and rotator cuff tear, is approximately 20% in a population older than 70 years of age.

DIAGNOSIS

A precise history is needed to identify the conditions present, and more than one syndrome can occur concomitantly. A working knowledge of regional anatomy and an approach that uses a regional differential diagnosis will help in obtaining a specific diagnosis. A complete neuromusculoskeletal examination should be performed, emphasizing careful palpation, passive range of motion (ROM), and active ROM alone or sometimes with resistance. Systemic and infectious causes must be considered. Diagnostic ultrasonography is very useful in confirming a musculoskeletal diagnosis.[I] Magnetic resonance imaging (MRI) is also sometimes useful in confirming a diagnosis.

TREATMENT

The causative aspects of symptoms should be evaluated, and activity should be modified as needed. Provided that the excessive load that caused the condition is reduced, most tendinopathies tend to improve with conservative therapy such as nonsteroidal anti-inflammatory drugs (NSAIDs; Table 26-4), relative rest of the injured site, stretching and strengthening exercises, friction massage, and use of modalities such as heat, ice, and ultrasound. The goals of therapeutic exercise are to increase flexibility by stretching, increase muscle strength by resistive exercises, and improve muscle endurance by some repetitive regimen.

Splinting, corticosteroid injections (given as the equivalent of 40 mg/mL of methylprednisolone acetate), and even surgery are options for more severe or recalcitrant symptoms.[A1,A2] Caution should be exerted in performing corticosteroid injections; the injections should not be placed into the tendon proper, but rather into the peritendinous sheath. The injected solution should be placed beneath the subcutaneous tissue, to avoid skin and subcutaneous fat atrophy and skin depigmentation, and injections should not be given too frequently, to avoid the possibility of weakening and rupture of the tendon. The accuracy of injections may be improved with concomitant use of diagnostic ultrasonography to assist with determining the correct needle site.

SPORTS MEDICINE INJURIES

An overlap exists between commonly occurring conditions (e.g., tendinosis, enthesopathy, bursitis) and conditions attributed to specific sports injuries (Table 242-2). For example, lateral epicondylalgia, frequently referred to as *tennis elbow,* occurs more commonly secondary to non–sports-related causes. In contradistinction, iliotibial band syndrome is usually related to sports. Other entities that occur more often in relation to sports include ligamentous knee injuries, patellar tendinosis, ankle sprains, turf toe, and acromioclavicular separations. It is important in both categories to know the anatomy and biomechanics of the condition so the problem can be diagnosed and treated appropriately. Sports-related injuries are helped with the classic RICE treatment, consisting of *r*est, *i*ce, *c*ompression, and *e*levation. Often, anti-inflammatory and analgesic drugs are used. However, corticosteroid injections are less often used for athletic injuries than in routine cases of tendinosis and bursitis because of fear of weakening the involved structures.

DISORDERS OF THE SHOULDER REGION

Shoulder pain is one of the most common musculoskeletal complaints in people older than 40 years of age. In younger people, athletic injuries are a frequent source of such pain.

ABSTRACT

Musculoskeletal pain syndromes involving the shoulder, elbow, wrist, hand, hip, knee, ankle, and foot are common but unfortunately are often overlooked by primary care physicians. These disorders are often ignored or misdiagnosed as arthritis by nonspecialty physicians. The accurate diagnosis, based on functional musculoskeletal anatomy, and successful treatment of these painful and sometimes disabling conditions are gratifying to the patient and clinician alike.

KEYWORDS

tendinosis
tenosynovitis
enthesopathy
enthesitis
bursitis
musculoskeletal pain
regional rheumatic pain syndromes
nonarticular pain syndromes

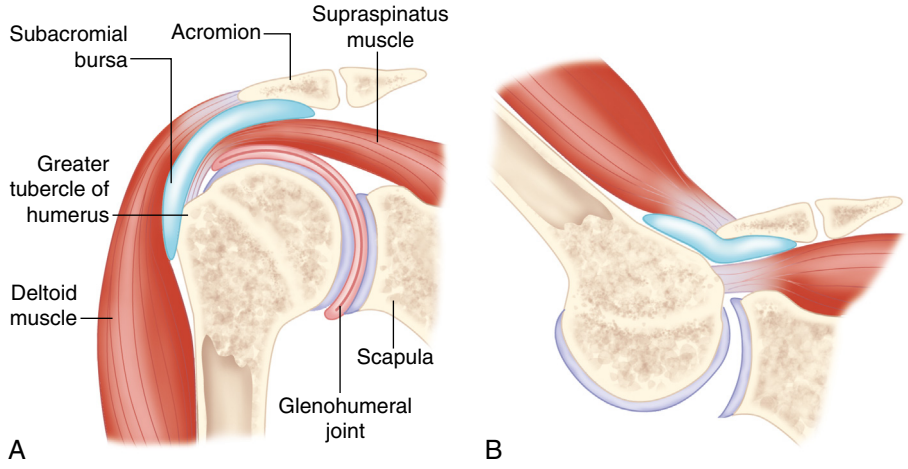

FIGURE 242-1. **Relationship of subacromial bursa (shown in *blue*) to supraspinatus muscle and acromion process. A,** In the position of adduction of the humerus, to show this bursa more clearly, it is in *blue*. The synovial membrane of the glenohumeral joint is not shown. **B,** In the position of abduction of the humerus, the acromion impinges on the subacromial bursa and the insertion of the supraspinatus tendon. (From Polley HF, Hunder GG, eds. *Rheumatologic Interviewing and Physical Examination of the Joints*, 2nd ed. Philadelphia: WB Saunders; 1978:65.)

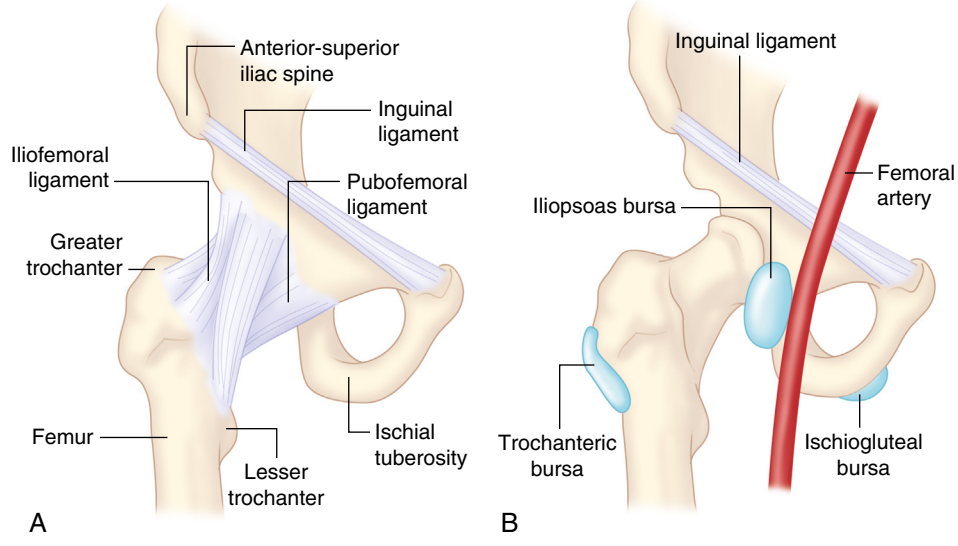

FIGURE 242-2. **Musculoskeletal anatomy of the hip. A,** Anterior aspect of the hip joint and bony structures. **B,** Relationship of the distended iliopsoas, trochanteric, and ischiogluteal bursae (shown in *blue*) to the hip joint and adjacent structures. (From Polley HF, Hunder GG, eds. *Rheumatologic Interviewing and Physical Examination of the Joints*, 2nd ed. Philadelphia: WB Saunders; 1978:183.)

Rotator Cuff Impingement

Rotator cuff tendinosis, or impingement syndrome, is the most common cause of shoulder pain. Tendinosis (and not bursitis) is the primary cause of pain, but secondary involvement of the subacromial bursa occurs in some cases. The condition may be acute or chronic and may or may not be associated with calcific deposits within the tendon. The key finding is pain in the rotator cuff on active abduction, especially between 60 and 120 degrees, and sometimes when lowering the arm. In more severe cases, pain may begin on initial abduction and continue throughout the ROM. Typically, chronic rotator cuff tendinosis manifests as an ache in the shoulder, usually over the lateral deltoid, and occurs with various movements, especially abduction, internal rotation, and the resisted action of the involved muscle(s). Other symptoms include difficulty in dressing oneself and night pain because of difficulty in positioning the shoulders. The physical findings include pain and loss of active abduction and internal rotation, less pain on passive motion, tenderness of the area of supraspinatus insertion, and a positive impingement (Neer) sign (Fig. 242-3), which is pain occurring in forced flexion. The causes of rotator cuff tendinosis are multifactorial, but normal wear and relative overuse, especially from overhead activity that causes impingement of the rotator cuff, are commonly implicated.

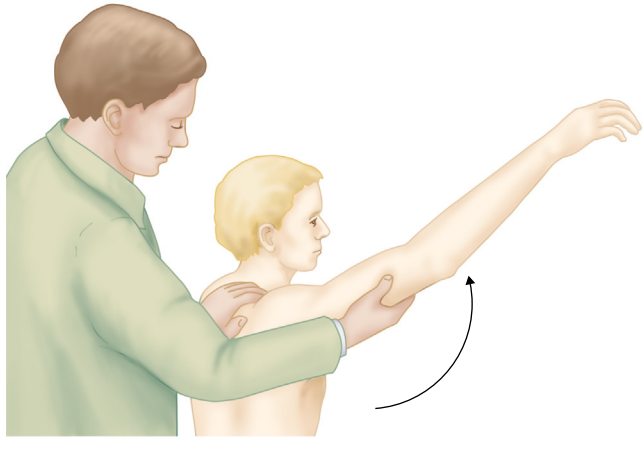

FIGURE 242-3. **The impingement sign is elicited by forced forward elevation of the arm.** Pain results as the greater tuberosity impinges on the acromion. The examiner's hand prevents scapular rotation. This maneuver may be positive in other periarticular disorders. (From Neer CS II. Impingement lesions. *Clin Orthop*. 1983;173:70-77.)

TABLE 242-2 ADDITIONAL SPORTS-RELATED CONDITIONS

SHOULDER
Acromioclavicular separation
Glenoid labial tear (SLAP lesion)
Glenohumeral instability with dislocation
ELBOW
Triceps tendinopathy
Little League elbow (apophysitis)
Distal biceps tendinosis
WRIST AND HAND
Gamekeeper's thumb (skier's thumb)
Mallet finger (baseball finger)
Extensor carpi ulnaris tendinitis
Rupture of flexor digitorum profundus tendon
Injury to triangular fibrocartilage
HIP
Adductor strain (groin pull)
Hip pointer
Hamstring strain
KNEE
Anterior cruciate tear
Posterior cruciate tear
Medial collateral ligament tear/strain
Lateral collateral ligament tear/strain
Popliteal tendinitis
Medial and lateral meniscal tears
Patellar tendinitis
Iliotibial band syndrome
ANKLE AND FOOT
Ankle sprain
Turf toe
Stress fracture

SLAP lesion = superior labrum anterior and posterior lesion.

TREATMENT

Treatment consists of rest and modalities such as hot packs, ultrasound, or cold applications, with specific range of motion exercises as soon as tolerated.[2] NSAIDs (Table 26-4) are often beneficial. Injection of a depot corticosteroid, such as 1 mL of a 40 mg/mL concentration of methylprednisolone acetate into the subacromial bursa, the floor of which is contiguous with the rotator cuff, can provide improvement for up to 8 weeks but probably not long-term benefit.[A3–A5] Extracorporeal shock wave therapy can be beneficial for chronic calcific tendinitis, but surgery is of limited benefit.[A6]

Rotator Cuff Tear

In a rotator cuff tear, an acute tear after trauma is usually easily recognized. The trauma may be superimposed on an already degenerative and possibly even partially torn cuff. In cases of trauma resulting in a ruptured cuff, fracture of the humeral head and dislocation of the joint also should be considered. However, most patients with a tear recall no trauma. In these cases, degeneration of the rotator cuff occurs gradually, resulting ultimately in a complete tear.

MR is the preferred imaging test.[3] Rotator cuff tears are classified as small (≤1 cm), medium (1 to 3 cm), large (3 to 5 cm), or massive (>5 cm). Shoulder pain, weakness on abduction, and loss of motion occur in varying degrees, ranging from severe pain and mild weakness to no pain and marked weakness. A positive drop-arm sign with inability to maintain actively 90 degrees of passive shoulder abduction may be present in patients with large or massive tears.

TREATMENT

Small complete tears and incomplete tears of the rotator cuff are treated conservatively with rest, physical therapy, and NSAIDs.[4] Although its role has not yet been established by careful studies, a subacromial injection of a corticosteroid, such as 1 mL of a 40 mg/mL concentration of methylprednisolone acetate, may relieve pain. Surgical repair may be indicated in younger patients.[A7]

Bicipital Tendinosis

Bicipital tendinosis is manifested by pain, most often in the anterior region of the shoulder and occasionally more diffusely.[5] The pain may be acute but is usually chronic and is related to impingement of the biceps tendon by the acromion. Tenosynovitis of the long head of the biceps is present, and the tendon may be frayed and fibrotic. Palpation over the bicipital groove reveals localized tenderness. The patient's response should be compared with the response to palpation of the opposite side (i.e., tendon with normal tenderness). Pain may be reproduced over the bicipital tendon in some cases by supination of the forearm against resistance (Yergason sign), shoulder flexion against resistance (Speeds test), or extension of the shoulder. Rupture of the biceps tendon can occur at the superior edge of the bicipital groove, thereby producing a characteristic bulbous enlargement of the lateral half of the muscle.

TREATMENT

Treatment of bicipital tendinitis consists of rest, hot packs, ultrasound, and, as pain subsides, passive and then active ROM exercises. NSAIDs (Table 26-4) may be helpful, and occasionally a small amount of corticosteroid, such as 0.5 mL of a 40 mg/mL concentration of methylprednisolone acetate, carefully injected into the tendon sheath or 1 mL of a 40 mg/mL concentration of methylprednisolone acetate intra-articularly in the shoulder may be of benefit.

Frozen Shoulder

Adhesive capsulitis (frozen shoulder) is associated with generalized pain and tenderness and severe loss of active and passive motion in all planes.[6] It is rare before 40 years of age but may occur secondary to any type of shoulder problem. However, not every stiff and painful shoulder is necessarily adhesive capsulitis. Inflammatory arthritis and diabetes can cause adhesive capsulitis. Additional factors such as immobility and neglect or improper initial treatment also favor the development of a frozen shoulder. Symptoms and function are adversely affected by depression and anxiety (Chapter 362).[7] Many cases, however, are idiopathic. The joint capsule adheres to the anatomic neck, and the axillary fold binds to itself, causing restricted motion. The capsule becomes thickened and contracted. Arthrography may help confirm this diagnosis by showing a decrease in volume of the shoulder joint capsule but is usually not needed.

TREATMENT AND PROGNOSIS

Oral steroids improve pain and range of motion in the short term, but a frozen shoulder is probably best treated with a comprehensive program involving NSAIDs and corticosteroid injections of 1 mL of a 40 mg/mL concentration of methylprednisolone acetate into the glenohumeral joint and the subacromial bursa. Physical therapy consists of ice packs, ultrasound, transcutaneous electrical nerve stimulation, and gentle range of motion exercises, beginning with pendulum exercises and wall climbing with the fingers and progressing to active range of motion and strengthening exercises.[A8] Depression and anxiety may require attention (Chapter 362). In a randomized trial, manipulation under general anaesthesia supplemented by a steroid injection,[A9] arthroscopic capsular release, and structured physiotherapy were equivalently effective, but arthroscopic capsular release carried the highest risks.[A10] The duration of a frozen shoulder may last up to 9 to 12 months. In prolonged duration, manipulation of the shoulder under anesthesia can be considered.

DISORDERS OF THE ELBOW REGION

Olecranon Bursitis

Olecranon bursitis occurs frequently and involves the subcutaneous olecranon bursa, either secondary to trauma or as an idiopathic condition.[8] The bursa is characteristically swollen and tender on pressure (Fig 242-4), but pain may be minimal, and usually no motion is lost. Aspiration may yield clear or blood-tinged fluid with low viscosity or grossly hemorrhagic fluid. Inflammatory olecranon bursitis may be caused by bacterial infection, gout, rheumatoid arthritis, or calcium pyrophosphate deposition disease. Localized erythema, a scab, fissure, or previous puncture at the tip of the elbow, surrounding edema, and local tenderness all suggest septic bursitis (Chapter 251). Unlike septic arthritis, in which the elbow must be kept in semiflexion, the elbow may be brought into full passive extension in septic bursitis.

FIGURE 242-4. Olecranon bursitis in an older man. There is swelling at the elbow tip and "inverted U" furrows in the skin proximal to the bursa. For aspiration, the needle should be entered through normal lateral skin, aiming to the geometric center of the bursa to prevent leakage. The aspirated fluid was noninflammatory, sterile on culture, and contained no crystals. In septic bursitis, there may be marked swelling, even suggesting a septic elbow. However, careful passive extension is complete and painless, ruling out septic arthritis.

TREATMENT

In aseptic bursitis, aspiration alone and protection from trauma are usually sufficient to resolve the condition.[9] A small dose of a corticosteroid, such as 0.5 mL of a 40 mg/mL concentration of methylprednisolone acetate, may be injected into the bursa. Septic olecranon bursitis is treated with the appropriate antibiotics (Chapter 251) and usually one or two additional needle aspirations.

Lateral and medial epicondylalgia

Lateral epicondylalgia, or tennis elbow, is a common condition in those who overuse their arms. Localized tenderness directly over or slightly anterior to the lateral epicondyle is the hallmark of this disorder. Pain may occur during handshakes, while lifting a briefcase, or with other similar activities. Probably less than 10% of patients actually acquire lateral epicondylitis through playing tennis. Job and recreational activities, including gardening and athletics, are the usual causes. Pathologically, the condition consists of degeneration of the common extensor tendon, particularly of the extensor carpi radialis brevis tendon.

Medial epicondylitis, or golfer's elbow, which mainly involves the flexor carpi radialis, is less common and less disabling than lateral epicondylitis. Local pain and tenderness over the medial epicondyle are present, and resistance to wrist flexion exacerbates the pain.

TREATMENT

Treatment is aimed at altering activities and preventing overuse of the forearm musculature. Ice packs, heat, and NSAIDs are of some benefit.[10] A forearm brace also can be used. A local corticosteroid injection, such as 1mL of a 40 mg/mL concentration of methylprednisolone acetate with a 25-gauge needle over the epicondyle, often produces satisfactory initial relief. Isometric strengthening is important as an initial part of a rehabilitation program.[A11] Occasionally, surgery may be required for sports-related medial epicondylitis.[11]

DISORDERS OF THE WRIST AND HAND

Ganglion

A ganglion is a cystic swelling that arises from a joint or tendon sheath and occurs most commonly over the dorsum or volar aspect of the wrist. A ganglion has a focal lining, does not have a synovial derivation, and contains thick, jelly-like fluid. Ganglia apparently develop secondary to trauma or prolonged wrist extension. Usually, the only symptom is swelling, but occasionally a large ganglion produces discomfort on wrist extension or compresses a neighboring nerve. Ultrasonography is useful for making the diagnosis.

TREATMENT

Temporary immobilization with a splint or brace may be helpful. Percutaneous drainage is commonly successful, but surgery is sometimes required.[12]

De Quervain Tenosynovitis

De Quervain tenosynovitis may result from repetitive activity that involves pinching with the thumb while moving the wrist. The symptoms are pain, tenderness, and occasionally swelling over and distal to the radial styloid. Pathologic findings include inflammation and narrowing of the tendon sheath around the abductor pollicis longus and extensor pollicis brevis. A positive Finkelstein test result is usually seen; pain increases when the thumb is folded across the palm and the fingers are flexed over the thumb as the examiner passively deviates the wrist toward the ulnar side. However, this test also may be positive in patients with osteoarthritis of the first carpometacarpal joint and must be differentiated from this common condition.

TREATMENT

Treatment involves splinting, local corticosteroid injection, such as 0.5 mL of a 40 mg/mL concentration of methylprednisolone acetate (Fig. 242-5), and NSAIDs (Table 26-4) as indicated.[13] Rarely, surgical removal of the obstructive tenosynovium is needed.

Trigger Finger

Trigger finger consists of chondroid metaplasia of the digital flexor pulleys[14,15] and underlying flexor digitorum superficialis and flexor digitorum profundus tendons in the palm. It is extremely common but often unrecognized. Pain in the palm is felt on finger flexion, but in some cases the pain radiates to the proximal interphalangeal (PIP) and metacarpophalangeal (MCP) joints on the dorsal side, misleading the examiner. The middle and index fingers are most commonly involved, but the ring and little fingers also can be affected. Often a nodule composed of fibrocartilaginous tissue can be palpated in the palm just proximal to the MCP joint on the volar side. The nodule interferes with the normal tendon gliding and can cause a triggering or locking, which may be intermittent and may produce an uncomfortable sensation. Similar involvement can occur at the flexor tendon of the thumb. The most common cause is overuse trauma of the hands from gripping with increased pull on the flexor tendons. Diabetes, the use of aromatase inhibitors,[16] and hypothyroidism predispose to the trigger finger. Trigger finger may be part of inflammatory conditions, such as rheumatoid arthritis, psoriatic arthritis, or apatite crystal deposition disease. It is seen frequently in conjunction with osteoarthritis of the hands.

TREATMENT

Injection of a long-acting steroid, such as 1 mL of a 40 mg/mL concentration of methylprednisolone acetate, into the tendon sheath usually relieves the problem (Fig. 242-6), although surgery on the tendon sheath may be needed in unremitting cases.[17]

Other Finger Abnormalities

Gamekeeper's thumb (skier's thumb) is caused by trauma to the thumb resulting in instability of the first MCP joint. This instability is due to laxity or rupture of the ulnar collateral ligament. It is treated by immobilization, but surgical repair may be necessary.

Avulsion of flexor digitorum profundus (jersey finger) may result from trauma, usually in football, when a player grabs onto a jersey. The distal phalanx,

FIGURE 242-5. Injection of de Quervain tenosynovitis.

FIGURE 242-7. Injection of trochanteric bursitis.

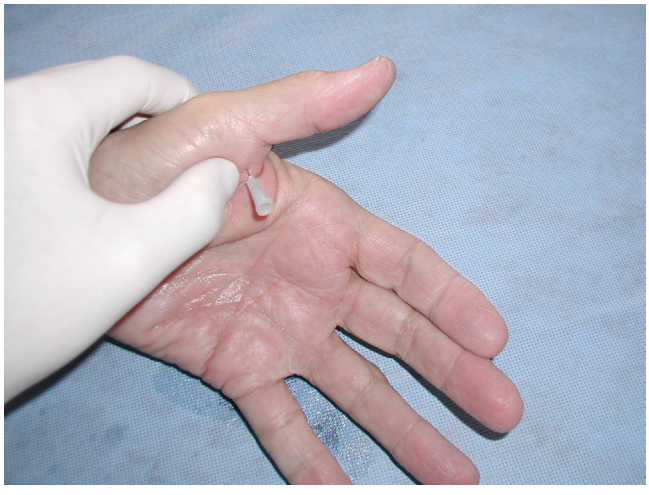

FIGURE 242-6. A trigger thumb occurs commonly. If the patient chooses a steroid injection, the clinician first identifies the two sesamoid bones at the base of the thumb. Then a thin needle is inserted between the two bones that guide the flexor tendon and injects the steroid under low pressure superficial to the tendon.

usually the fourth, is hyperextended while the digitorum profundus is contracting maximally. The avulsion of the tendon results in an inability to flex the distal phalanx of that digit. Surgery is required to correct the problem.

DISORDERS OF THE HIP REGION

Greater Trochanter Pain Syndrome

Although greater trochanter pain syndrome (formerly trochanteric bursitis) is common, it frequently goes undiagnosed. It occurs predominantly in middle-aged to elderly people and somewhat more often in women. The main symptom is aching over the trochanteric area and lateral thigh. Walking, various hip movements, and lying on the involved hip may intensify the pain. Onset may be acute, but more often it is gradual, with symptoms lasting for months. In chronic cases, the patient may fail to locate or describe the pain adequately or the physician may fail to interpret them correctly. Occasionally, the pain has a pseudoradiculopathic quality, radiating down the lateral aspect of the thigh.[18] In a few cases, the pain is so severe that the patient cannot walk and complains of diffuse pain of the entire thigh. The best way to diagnose a greater trochanter pain syndrome is to palpate over the trochanteric area and elicit point tenderness. In addition to specific pain on deep pressure over the back corner of the trochanter, other tender points may be noted throughout the lateral aspect of the thigh muscle. Pain may be worse with external rotation and abduction against resistance. The condition actually arises at the insertions of the gluteus medius and, to a lesser extent, gluteus minimus tendons. Local trauma and degeneration play a role in the pathogenesis, leading to tendinosis and/or tendon tears. Conditions that may contribute to trochanteric bursitis, apparently by adding stress to the area, include osteoarthritis of the lumbar spine or of the hip, leg-length discrepancy, and scoliosis.

TREATMENT

Treatment consists of local injection of depot corticosteroid, such as 1 mL of a 40 mg/mL concentration of methylprednisolone acetate, using a 22-gauge, 3.5-inch needle to ensure that the tender area is reached (Fig. 242-7). NSAIDs (Table 26-4), weight loss, and strengthening and stretching of the gluteus medius muscle and iliotibial band help in management.[19]

Coccydynia

Coccydynia is manifested by pain in the coccyx area when pressure is applied to the area. This most notably occurs on sitting. The patient squirms from buttock to buttock to relieve the pressure and consequent pain and often chooses to sit on a cushion. The symptoms may be chronic and severe. The condition may relate to a fall on the coccyx, dropping to a hard chair when sitting, or some related trauma to the coccyx. However, at times no obvious cause can be detected. Women are much more frequently affected, perhaps because the lordosis that often occurs in women exposes the coccyx to more trauma. The diagnosis is confirmed by finding localized tenderness over the coccyx on palpation. A plain x-ray film can be obtained to exclude a fracture or dislocation of the coccyx.

TREATMENT

Treatment with a local injection of 1 mL of a long-acting corticosteroid, such as a 40 mg/mL concentration of methylprednisolone acetate, and 2 mL of a 2% lidocaine solution is usually very effective. The exact nature of the pathology of coccydynia has not been studied, but it is presumed to be a bone bruise.

Iliopsoas Bursitis

In iliopsoas bursitis, groin and anterior thigh pain are present and worsen on passive hip hyperextension and sometimes on flexion, especially with resistance. Tenderness is palpable over an involved bursa. The patient may hold the hip in flexion and external rotation to eliminate pain and may limp to prevent hyperextension of the hip. The iliopsoas bursa lies behind the iliopsoas muscle, anterior to the hip joint and lateral to the femoral vessels. Independent from the joint at a younger age, the iliopsoas bursa communicates with the hip in approximately 30% of persons by middle age. The diagnosis is more apparent if a cystic mass is seen (approximately 30% of cases); however, other causes of cystic swelling in the femoral area must first be excluded. A bursal mass can cause femoral venous obstruction or femoral nerve compression, and it can progress into the pelvis alongside the iliopsoas muscle. As with most cases of bursitis, acute or recurrent trauma, inflammatory conditions such as rheumatoid arthritis, and a wearing hip prosthesis may lead to iliopsoas bursitis (also called *iliopectineal bursitis*). Iliopsoas tendinosis may overlap with the bursitis or occur independently in a similar clinical picture. The diagnosis is confirmed by ultrasonography, computed tomography, or MRI.

TREATMENT

Iliopsoas bursitis/tendinosis usually responds to conservative treatment, including physical therapy and corticosteroid injections, such as 1 mL of a 40 mg/mL concentration of methylprednisolone acetate. With recurrent involvement, excision of the bursa may be necessary.

Ischial or Ischiogluteal Bursitis

Ischial or ischiogluteal bursitis is caused by trauma or by prolonged sitting on hard surfaces, as evidenced by the name *weaver's bottom*. Pain is often exquisite when sitting or lying down. The hamstring muscles originate from the lateral side of the ischial tuberosity, and the ischiogluteal bursa is superficial to the tuberosity. Because the bursa separates the gluteus maximus from the tuberosity, the pain may radiate down the back of the thigh. Point tenderness over the ischial tuberosity is present.

TREATMENT

Use of cushions, hamstring stretching, and local injection of a corticosteroid, such as 1 mL of a 40 mg/mL concentration of methylprednisolone acetate, are helpful.

DISORDERS OF THE KNEE REGION

Stress Syndromes

Pes anserinus syndrome, formerly called "anserine bursitis" is seen predominantly in overweight, middle-aged to elderly women with large legs and osteoarthritis of the knees. The symptoms are pain and tenderness over the medial aspect of the knee approximately 2 inches below the joint margin, with the pain worsened by climbing stairs. The pes anserinus (Latin for "goose foot") is composed of the conjoined tendons of the sartorius, gracilis, and semitendinosus muscles. The anserine bursa extends between the above tendons and the tibial collateral ligament. Tendinopathy of these tendons or pressure on the tibial collateral ligament by a displaced meniscus may be the predominant causes of the syndrome. The diagnosis is made by eliciting exquisite tenderness over the pes area. Pes anserinus syndrome is often overlooked because it frequently occurs concomitantly with osteoarthritis of the knee, which, when present, is the assumed cause of pain; however, in some cases of dual involvement, pes anserinus syndrome may be the principal source of the pain.

Iliotibial band syndrome manifests by lateral knee pain caused by repetitive stress between the iliotibial band and the lateral femoral condyle. It is an overuse injury and is seen in runners, cyclists, and other athletes performing repetitive knee flexion activities.

TREATMENT

For pes anserinus syndrome, the treatment is rest, stretching of the adductor and quadriceps muscles, and a corticosteroid injection into the tender point, keeping the knee semiflexed. For iliotibial band syndrome, treatment focuses on limiting activities that exacerbate pain, icing, and NSAIDs (Table 26-4), followed by physical therapy. Corticosteroid injections can be used if needed.

Bursitis and Tendinitis

Prepatellar bursitis manifests as a swelling superficial to the kneecap and results from trauma such as frequent kneeling. The prepatellar bursa lies anterior to the lower half of the patella and the upper half of the patellar tendon. The pain is generally slight unless pressure is applied directly over the bursa. Skin erosion, fissures, redness, a puncture wound, or peribursal edema suggest a septic etiology of bursitis. The bursal sac should be aspirated and treated accordingly.

The infrapatellar bursa, which lies between the patellar tendon and the tibia and is homologous to the retrocalcaneal bursa,[20] is also subject to trauma. Rarely, the tibial enthesis of the patellar tendon and the infrapatellar bursa are involved in spondyloarthritis.

Patellar tendinitis (jumper's knee) is seen predominantly in athletes who engage in activities such as repetitive running, jumping, or kicking. Pain and tenderness are present over the patellar tendon.

TREATMENT

Treatment focuses on protecting the knees from irritating trauma. NSAIDs (Table 26-4) are often helpful.

Popliteal Cysts

Popliteal cysts, also known as Baker cysts, are not uncommon, and the clinician should be well aware of the possibility of their dissection or rupture. Popliteal cysts occur by fluid distention of a contiguous bursa behind the medial femoral condyle. Given a connecting bursa, any knee effusion may create a popliteal cyst via a functional unidirectional mechanism. Typically, popliteal cysts become hard in knee extension and soft in flexion.

A cystic swelling behind the knee with mild or no discomfort can be the only initial finding. With further distention of the cyst, however, a greater awareness and discomfort are experienced, particularly on full flexion or extension. The cyst is best seen when the patient is standing and examined from behind. Popliteal cysts reflect the knee conditions that cause effusion and are therefore most commonly seen in rheumatoid arthritis, osteoarthritis, or internal derangements of the knee.

A syndrome of pseudothrombophlebitis may occur as a result of cyst dissection into the calf or actual rupture of the cyst. Findings include diffuse swelling of the calf, pain, and sometimes erythema and edema of the ankle. An incorrect diagnosis of thrombophlebitis (Chapter 68) may lead to anticoagulation and result in compartment syndrome. An ultrasound of the knee confirms both the cyst and the possible dissection or rupture and serves to exclude thrombophlebitis.

TREATMENT

For a cyst related to an inflammatory arthritis, drainage[21] and injection of a depot corticosteroid into the knee joint (and possibly into the cyst itself), such as 1 or 2 mL of a 40 mg/mL concentration of methylprednisolone acetate, resolves the problem. If the cyst results from osteoarthritis or an internal derangement of the knee, an endoscopic enlargement of the connection may become necessary to promote backflow of the excess synovial fluid and prevent a recurrence of the cyst.[22]

Tendon Ruptures

In the knee area, tendon ruptures may occur, and quadriceps tendon rupture is involved approximately 50% of the time; otherwise, patellar tendon rupture occurs. Quadriceps tendon rupture is generally caused by sudden violent contractions of the quadriceps muscle when the knee is flexed. A hemarthrosis of the knee joint may follow. Patients with chronic renal failure, rheumatoid arthritis, hyperparathyroidism, or gout and patients with systemic lupus erythematosus taking steroids have been reported to have spontaneous ruptures of the quadriceps tendon. The patient experiences a sudden sharp pain and cannot extend the leg. The tendon is usually found to be degenerated. Rupture of the patellar tendon has been associated with a specific episode of trauma, repetitive trauma from sporting activities, and systemic diseases. Radiographic studies may show a high-riding patella.

TREATMENT

Surgical repair is often indicated.

Meniscal Tears

Meniscal tears are common causes of knee "locking" and pain. Physical examination may show pain, with or without clicking, when the hip and knee are bent to 90 degrees. MRI is the diagnostic test of choice.

TREATMENT

Physical therapy is often as effective as surgery,[A12,A13] even for patients who complain of knee catching or occasional locking. Isolated tears of the medial and lateral collateral knee ligaments often can be managed without surgery, but tears of the cruciate ligaments typically require surgery.[23]

DISORDERS OF THE ANKLE AND FOOT REGION

Achilles Tendinosis

The distal 2 cm of the Achilles tendon is known as the insertional tendon. The bone attachment or calcaneal enthesis is a complex structure that comprises fibrocartilage laid on the anterior tendon and the opposite calcaneal surface, the space between these cartilaginous layers (known as the retrocalcaneal bursa), and a synovial-lined fat wedge that slides in and out of the bursa with the plantar and dorsal movement of the ankle. This array of structures plus

the underlying trabecular bone is known as the Achilles entheseal organ and is a prime site of involvement in spondyloarthritis (Chapter 244). Calcium pyrophosphate dihydrate crystals and homogentisic acid in ochronosis may also involve the distal tendon. Rheumatoid arthritis and gout may also affect the bursa.

To identify retrocalcaneal bursitis, the clinician places the thumb and index fingers of one hand at either side of the insertional tendon. Then, the other index presses repeatedly over the tendon, perceiving fluid fluctuation with the exploring fingers. Superficial to the tendon insertion, improperly fitting shoes with a stiff heel may irritate the subcutaneous retro Achilles bursa and cause severe local pain. The noninsertional Achilles tendon extends from 2 to 6 cm proximal to the calcaneal insertion. Tendinopathy, tendon ruptures, gout tophi, and rheumatoid nodules tend to appear in this segment. In tendinopathy, the involved tendon feels irregularly thickened and is tender to compression. Crepitus on motion and pain on dorsiflexion may be present.

TREATMENT

Management includes NSAIDs (Table 26-4), rest, shoe corrections, heel lift, gentle stretching, and sometimes a splint with slight plantar flexion. Corticosteroid injections by an expert are also beneficial.[A14] The treatment should be followed by calf-muscle exercise therapy.[A15] Platelet-rich plasma injection is of no benefit.[A16]

Achilles Tendon Rupture

The Achilles tendon is vulnerable to rupture, which occurs with a sudden onset of pain during forced dorsiflexion. An audible snap may be heard, followed by difficulty in walking and standing on toes. Swelling and edema over the area usually develop. Diagnosis can be made with the Thompson test, in which the patient kneels on a chair with the feet extending over the edge and the examiner squeezes the calf and pushes toward the knee. Normally this produces plantar flexion, but in a ruptured tendon, no plantar flexion occurs. An intact plantaris muscle may result in a false-negative Thompson test. Achilles tendon rupture usually occurs during athletic events or with trauma from jumps or falls. The tendon is more prone to tear in older people, people with preexisting Achilles tendon disease, and in persons taking corticosteroids or fluoroquinolone antibiotics.[24]

TREATMENT

Orthopedic consultation should be obtained, and immobilization or surgery may be selected, depending on the situation,[25] with either providing equivalent results.[A17] If immobilization is chosen, early weight bearing with a functional brace is equivalent to a plaster cast.[A18]

Ankle Sprain

For acute, severe ankle sprain, a below-knee cast or Aircast produces a faster recovery than a tubular compression bandage, but there is no difference in outcomes at 9 months.

Plantar Fasciitis

Plantar fasciitis, which is seen primarily in persons between 40 and 60 years of age, is characterized by pain in the plantar area of the heel. The onset may be gradual, or it may occur with trauma or overuse from some activity, such as athletics, prolonged walking, using improper shoes, or striking the heel with some force. Plantar fasciitis may be idiopathic; it also is likely to be present in younger patients with spondyloarthritis (Chapter 244). The pain characteristically occurs in the morning on arising and is most severe for the first few steps. After an initial improvement, the pain may worsen later in the day, especially after prolonged standing or walking. The pain is burning, aching, and occasionally lancinating. Palpation typically reveals tenderness anteromedially on the medial calcaneal tubercle at the origin of the plantar fascia.

TREATMENT

Treatment includes relative rest with a reduction in stressful activities, NSAIDs (Table 26-4), use of a contoured full-length insole,[26] and stretching of the heel cord and plantar fascia. A local corticosteroid injection, such as 0.5 to 1 mL of a 40 mg/mL concentration of methylprednisolone acetate using a 25-gauge needle, is often of help. Avoid repeating these injections, which carry the risk of fat atrophy and chronic pressure pain.

Posterior Tibial Tendinitis

In posterior tibial tendinitis, pain and tenderness occur just posterior to the medial malleolus; it can be caused by trauma, excessive pronation, rheumatoid arthritis, or spondyloarthropathy. Extension and flexion may be normal, but pain is present on resisted inversion or passive eversion. The discomfort is usually worse after athletic activity, and swelling and localized tenderness may be present.

TREATMENT

Treatment usually includes rest, NSAIDs (Table 26-4), and possibly a local injection of corticosteroid with 0.5 mL of a 40 mg/mL concentration of methylprednisolone acetate. Immobilization with a splint is sometimes needed.

Posterior Tibialis Tendon Rupture

Posterior tibialis tendon rupture, which is not commonly recognized, is a cause of progressive flat foot. It can result from trauma, chronic tendon degeneration, or rheumatoid arthritis. An insidious onset of pain and tenderness may be noted along the course of the tendon just distal to the medial malleolus, along with swelling medial to the hind foot. The unilateral deformity of hind foot valgus and forefoot abduction is an important finding. The forefoot abduction can be best seen from behind; more toes are seen from this position than would be seen normally. The result of the single heel rise test is positive when the patient is unable to rise onto the ball of the affected foot while the contralateral foot is off the floor.

TREATMENT

Treatment usually includes rest, NSAIDs (Table 26-4), and possibly an orthosis. Surgical repair of the tendon is sometimes indicated.

Turf Toe

Turf toe is an injury of the big toe originally described during play on artificial turf. It results from hyperextension of the first metatarsophalangeal (MTP) joint when a fixed, dorsiflexed foot is forced into the ground. The plantar capsular ligament may be sprained or torn.

TREATMENT

Treatment is conservative, with rest, ice, elevation, and NSAIDs (see Table 26-4) as needed.

Morton Neuroma

Morton neuroma (Fig. 242-8) is a prominent cause of forefoot pain and paresthesia in individuals who wear shoes that are too narrow for the width of their metatarsal arches and high heels that drive the forefeet into those limited spaces. The compressed nerve, surrounded by reactive fibrous tissue, supplies the opposing halves of two contiguous toes, generally the third and the fourth. Multiple nerves may be involved.[27] Typically, symptoms do not appear wearing sandals.

TREATMENT

Treatment requires a change in footwear. Symptoms may be temporarily relieved by steroid injection, such as 1 mL of a 40 mg/mL concentration of methylprednisolone acetate. Neurectomy permanently relieves the local symptoms.[A19]

Stress Fracture

Stress fracture is also known as march fracture or fatigue fracture because it was first associated with spontaneous fracture after long marches in army recruits. Pain, swelling, tenderness, and occasionally erythema develop over the metatarsal area, usually without any clear history of trauma. On questioning, however, the episode of spontaneous pain related to onset of the fracture can be identified in some cases. The neck of the second metatarsal bone is most frequently involved, but the third metatarsal is also a site of fracture and less commonly seen in the fourth and fifth metatarsals. Aside from prolonged

FIGURE 242-8. Patient with Morton neuromas in both feet.

marching, other athletic events with overactivity, including jogging, are common causes. Stress fractures may be seen in patients with rheumatoid arthritis, in postmenopausal women, and in older people. The difficulty in diagnosing stress fractures is that the initial x-ray films usually show no abnormalities or, at most, only a faint fracture line. A repeat radiographic examination several weeks later shows healing with callus formation. Bone scans aid the early diagnosis of stress fractures by showing an increase in uptake over the fracture site.

TREATMENT

Usually these fractures heal spontaneously, and rest and strapping of the foot are helpful. Occasionally, a cast is needed.

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243 RHEUMATOID ARTHRITIS

IAIN B. MCINNES

DEFINITION

Rheumatoid arthritis is a chronic systemic inflammatory disease of unknown etiology that primarily targets synovial tissues. The primary target of rheumatoid arthritis is the joint, but systemic inflammation is thought to be responsible for a variety of coexistent comorbid conditions, including cardiovascular disease, osteoporosis, cognitive dysfunction, psychiatric disease, and cancer.

EPIDEMIOLOGY

Rheumatoid arthritis is a global disease with a variable geographic prevalence of 0.5 to 1% of adults. The prevalence is about three times greater in women before menopause than in men. Rheumatoid arthritis can occur at any age. Overall, the annualized incidence of rheumatoid arthritis is approximately 40 per 100,000 for women and about half that for men. Because rheumatoid arthritis is a lifelong disease and its incidence increases or is stable with age, the prevalence of rheumatoid arthritis increases with each decade. The incidence of rheumatoid arthritis may be decreasing, perhaps reflecting reductions in smoking. Geographic variations in prevalence and phenotype can be remarkable. Most notably, in rural Nigeria, cohorts in which no individuals are affected with rheumatoid arthritis have been described, though case ascertainment bias needs to be excluded. In contrast, a prevalence of 5% has been found in some studies of Chippewa, Yakima, and Inuit Native Americans. Such extreme phenotypes are poorly understood but likely reflect the impact of genetics, the gastrointestinal or respiratory microbiome, or other environmental influences.

PATHOBIOLOGY

Genetics

A combination of candidate association, twin, and genome-wide association studies (GWAS) has established a strong genetic component to the risk for developing rheumatoid arthritis and the severity of the disease.[1] Twin studies reveal a concordance rate of approximately 12 to 15% for monozygotic twins and 2 to 5% for dizygotic twins. Heritability is reported to be around 60%, with lower values for patients who are seronegative for autoantibodies.[2]

GWAS in European, North American, and recently Asian populations, combined with subsequent meta-genome analyses, demonstrate that rheumatoid arthritis is a polygenic disorder. The majority of more than 100 thus far identified informative single nucleotide polymorphisms (SNPs) implicate immune genes, indicative of a primary immunologic etiology. Around 40% of genetic risk accrues in the HLA region. Certain HLA-DR alleles (e.g., DRB*0401, DRB*0404, DRB*0101, DRB*1402) associate with an increased risk for

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FIGURE 242-8. Patient with Morton neuromas in both feet.

marching, other athletic events with overactivity, including jogging, are common causes. Stress fractures may be seen in patients with rheumatoid arthritis, in postmenopausal women, and in older people. The difficulty in diagnosing stress fractures is that the initial x-ray films usually show no abnormalities or, at most, only a faint fracture line. A repeat radiographic examination several weeks later shows healing with callus formation. Bone scans aid the early diagnosis of stress fractures by showing an increase in uptake over the fracture site.

TREATMENT

Usually these fractures heal spontaneously, and rest and strapping of the foot are helpful. Occasionally, a cast is needed.

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243 RHEUMATOID ARTHRITIS

IAIN B. MCINNES

DEFINITION

Rheumatoid arthritis is a chronic systemic inflammatory disease of unknown etiology that primarily targets synovial tissues. The primary target of rheumatoid arthritis is the joint, but systemic inflammation is thought to be responsible for a variety of coexistent comorbid conditions, including cardiovascular disease, osteoporosis, cognitive dysfunction, psychiatric disease, and cancer.

EPIDEMIOLOGY

Rheumatoid arthritis is a global disease with a variable geographic prevalence of 0.5 to 1% of adults. The prevalence is about three times greater in women before menopause than in men. Rheumatoid arthritis can occur at any age. Overall, the annualized incidence of rheumatoid arthritis is approximately 40 per 100,000 for women and about half that for men. Because rheumatoid arthritis is a lifelong disease and its incidence increases or is stable with age, the prevalence of rheumatoid arthritis increases with each decade. The incidence of rheumatoid arthritis may be decreasing, perhaps reflecting reductions in smoking. Geographic variations in prevalence and phenotype can be remarkable. Most notably, in rural Nigeria, cohorts in which no individuals are affected with rheumatoid arthritis have been described, though case ascertainment bias needs to be excluded. In contrast, a prevalence of 5% has been found in some studies of Chippewa, Yakima, and Inuit Native Americans. Such extreme phenotypes are poorly understood but likely reflect the impact of genetics, the gastrointestinal or respiratory microbiome, or other environmental influences.

PATHOBIOLOGY

Genetics

A combination of candidate association, twin, and genome-wide association studies (GWAS) has established a strong genetic component to the risk for developing rheumatoid arthritis and the severity of the disease.[1] Twin studies reveal a concordance rate of approximately 12 to 15% for monozygotic twins and 2 to 5% for dizygotic twins. Heritability is reported to be around 60%, with lower values for patients who are seronegative for autoantibodies.[2]

GWAS in European, North American, and recently Asian populations, combined with subsequent meta-genome analyses, demonstrate that rheumatoid arthritis is a polygenic disorder. The majority of more than 100 thus far identified informative single nucleotide polymorphisms (SNPs) implicate immune genes, indicative of a primary immunologic etiology. Around 40% of genetic risk accrues in the HLA region. Certain HLA-DR alleles (e.g., DRB*0401, DRB*0404, DRB*0101, DRB*1402) associate with an increased risk for

ABSTRACT

Rheumatoid arthritis is a chronic inflammatory disease affecting primarily the joints but is associated with substantial comorbidities that include cardiovascular, psychologic, oncologic, and systemic bone disease. The underlying pathogenesis of rheumatoid arthritis is incompletely understood but comprises an early breach of tolerance to a range of post-translational modifications, typically citrullination or acetylation of "self'-proteins," thereby leading to the elaboration of autoantibodies, cytokines, and chemokines, as well as dysregulated metabolism up to 10 years before clinically detectable disease. The primary target tissue is the synovium, which contains a range of activated leukocytes and stromal cells that, under the influence of inflammatory cytokines, drive local cartilage and bone destruction. Therapeutics include the sequential administration of disease modifying antirheumatic drugs (DMARDs), initially including methotrexate and escalating thereafter to the use of other DMARDS, biologic agents (including TNF and IL-6 receptor inhibitors), rituximab, abatacept, and Janus kinase inhibitors. Parallel use of NSAIDs and judicious use of corticosteroids are also common practice, though use of both should be minimized. Therapeutics should be adjusted based on formally assessed, intercurrent levels of disease activity, to seek the lowest level of disease activity or remission, whichever is more appropriate for a given patient. Long-term outcomes have improved remarkably, but a small group of patients has difficult to treat disease.

KEYWORDS

rheumatoid arthritis
immune therapeutics
synovitis
comorbidity
disease modifying anti-rheumatic drug
biologic
kinase inhibitor
autoimmunity

developing rheumatoid arthritis and thereafter progressing to more severe disease. Hypervariable regions on DR molecules are particularly important for antigen recognition by binding to antigenic peptides and presenting them to the T-cell receptor (TCR). The amino acid sequence of disease associated DRβ1 chains share a common structural motif, called the *shared epitope* (E-Table 243-1).

Peptides derived from post-translationally modified proteins (e.g., via citrullination, acetylation, carbamylation) may bind with altered avidity to the shared epitope, thereby providing a potential mechanism whereby this genetic factor can mediate the risk of disease at the molecular level. Thus, altered binding of such peptides to the HLA molecule (expressed on dendritic cells or B cells) may alter the dynamics of HLA-TCR interactions and thereby confer loss of self-tolerance upon (self-reactive) T cells inappropriately activated by this abnormal receptor engagement.

Many other immune related genes have been implicated and add considerable depth to the understanding of pathogenetic pathways. Although individual SNPs usually exhibit modest risk contribution (odds ratios ≈1.05 to 1.2-fold), they nevertheless could confer significant functional impact. Risk genes can be usefully defined on the basis of their contribution to functional immune system compartments. Adaptive immunity-associated SNPs include a functional polymorphism in protein tyrosine phosphatase nonreceptor 22 (*PTPN22*), a polymorphism that has been reproducibly associated with rheumatoid arthritis and a number of other autoimmune diseases, including type 1 diabetes, systemic lupus erythematosus, Graves disease, and Hashimoto thyroiditis. The costimulation receptors, CTLA, CD28, CD40, and signal protein kinase TYK2 have similar disease associations. An association with peptidyl arginase deiminase also has been recognized. Because this enzyme converts arginine to citrulline, it may confer a genetically predisposed risk via increased generation of a major rheumatoid arthritis autoantigen. Pathways that regulate innate immune pathways are also identified (e.g., *TRAF1-C5, STAT4*, TNF-AIP3, IRAK1) together with pathways concerned with cell migration *(ELMO1)* and fetal development *(LBH)*. Several SNPs identify cytokine or cytokine receptor coding loci, including TNF and IL-6R.

Finally, there is increased interest in the role of epigenetics in disease risk and especially propagation. Altered DNA methylation, histone modification (e.g., via acetylation), and microRNA expression patterns associate with increased or perpetuation of inflammation. These patterns have been best defined in fibroblast-like synoviocytes (e.g., differential methylation and thus gene expression has been found particularly for pathways related to cell growth and differentiation). The presence of differentially expressed microRNAs has also attracted attention in myeloid lineage cells, T cells, and fibroblast-like synoviocytes. For example, dysregulation of miR146 and miR155 promotes cytokine and inflammatory pathways in macrophages.

Etiology

Increasing evidence supports a substantial role for environmental factors including smoking, other pulmonary exposures (e.g., silica), obesity, vitamin D deficiency, and lower educational attainment as risk factors for rheumatoid arthritis. Low levels of alcohol intake may be protective (E-Fig. 243-1). Smoking in particular has long been associated with a significantly increased risk for developing rheumatoid arthritis, but only for anti-citrullinated peptide antibody (ACPA)-positive disease, especially in patients who have the shared epitope. Induction of epigenetic changes by smoking provides the most likely explanation for this etiologic link. Infectious triggers are also implicated, such as *Mycobacteria, Streptococcus, Mycoplasma, Escherichia coli, Helicobacter pylori*, and viruses (rubella, Epstein-Barr, parvovirus). The mechanisms whereby infections drive disease are poorly understood, but rheumatic fever (Chapter 269), reactive arthritis (Chapter 244), and Lyme arthritis (Chapter 296) are prime examples. Reactive arthritis in particular may occur following one of a myriad of different but specific infectious triggers presented to a specific location in the body (e.g., the gastrointestinal or genitourinary tract) on a predisposed genetic background, in most cases human leukocyte antigen (HLA)-B27. In this syndrome, age and gender and hence the maturity of the immune system may be critical in the development of clinical disease, which occurs primarily between the ages of 15 and 40 years in males. Many other examples exist in animal models of arthritis, including arthritis induced by mycobacteria and streptococci. Studies of the gastrointestinal and oral microbiome (the latter particularly in periodontal disease) have identified dysbiosis associated with early rheumatoid arthritis. Specific microbes (e.g., *Porphyromonas gingivalis*, *Prevotella copri, Aggregatibacter actinomycetemcomitans*) have been implicated. Whether these associations represent molecular mimicry, altered immune homeostasis (the gastrointestinal tract is a vital area for maintenance of peripheral immunologic tolerance), or direct stimulation of immune function (e.g., via enhanced citrullination) remains under investigation.

The use of oral contraceptives has been associated with a decrease in the incidence of rheumatoid arthritis. Because the effect appears to be strongest for oral contraceptives that have high estrogen content, it is postulated that estrogen is responsible for this protective effect.

Pathogenesis and Tissue Pathology

The overarching pathogenesis of rheumatoid arthritis remains unknown. The earliest signs of inflammation often occur in the lung: abnormal high-resolution CT scans of pre-rheumatoid arthritis patients have been reported. Pulmonary mucosal citrullination is increased, perhaps reflecting smoking or other pulmonary irritants. Increased local inflammation supports initial B-cell and then T-cell activation, with consequent "breach of tolerance" to post-translationally modified self proteins. Similar events in the oral mucosa, in periodontal disease, or conceivably in the gastrointestinal tract may also contribute in some patient subgroups. The physico-chemical properties of these self-protein derived peptides that confer increased immune activation presumably arise within the genetic architecture described above and especially the structure of the shared epitope. A prearticular clinical phase (pre-rheumatoid arthritis) ensues and may persist for up to several years, during which rheumatoid factor and autoantibodies against post-translationally modified proteins (AMPA), particularly anti-citrullinated peptide antibodies (ACPA), rise in titer and with increasingly broad specificity (epitope spreading). ACPAs, for example, can recognize citrullinated residues on a variety of self-proteins (e.g., type II collagen, vimentin, α-enolase, fibronectin, fibrinogen, and histones). The abnormalities thus appear to represent a broad failure to regulate immune homeostasis, rather than one individual (auto)antigen driving disease overall. One autoantigen may, however, serve as a trigger. In parallel, elevated levels of serum cytokines and chemokines are detected, indicative of generalized increased levels of systemic inflammation, along with lipid dysmetabolism. Biopsies of synovial tissue during this pre-rheumatoid arthritis phase are essentially normal, consistent with the systemic nature of this disease phase.

Thereafter, a transitional event heralds the onset of clinically detectable arthritis. Systemic disease becomes localized to the joint.[3] ACPA specificities are broadest (they expand before the onset of rheumatoid arthritis), and cytokine concentrations are highest immediately before the onset of disease (imminent rheumatoid arthritis). Altered ACPA glycosylation also precedes clinical disease. Early changes in synovial vascularization, deposition of immune complexes, altered neurologic supply, local infection, and microtrauma have all been postulated as articular localizing mechanisms.

Established rheumatoid arthritis is associated with the development of a dense synovial cellular infiltrate that has some degree of organization (E-Fig. 243-2). A lining layer of 4 to 8 cells in depth includes macrophages and fibroblast-like synoviocytes. The interstitial area contains large numbers of T cells, B cells, plasma cells, mast cells, and fibroblast-like synoviocytes. In some patients, lymphocytic aggregates form (ectopic germinal centers), likely serve as a source of autoantibody production, and confer a poorer clinical prognosis. Biopsy studies have identified discrete synovial appearances across patient subgroups; myeloid, lymphocytic, and fibroblastic pathotypes have been described at the transcriptional and histologic level. These pathotypes may represent clinically discrete endotypes that, in the future, could define useful biomarkers to determine optimal choices of immune targeted therapies.[4]

The synovial T-cell response is primarily of T_H1 and T_H17 type. T cells are activated via antigen presented in a CD28/CD80/86 dependent manner by macrophages, B cells, fibroblast-like synoviocytes, the local cytokine milieu (e.g., IL-7, IL-15, TNF, IL-6), or cognate cellular activation through cell contact with macrophages. The T cells secrete cytokines (e.g., IL-17 and GM-CSF) that drive further synovial proliferation. The predominant source of synovial cytokines is, however, macrophages, mast cells, and fibroblast-like synoviocytes. Macrophage-derived cytokines, particularly interleukin-1 (IL-1), IL-6, and tumor necrosis factor-α (TNF-α), play central roles in this ongoing inflammatory process. TNF and IL-6 in particular appear to have hierarchical

E-TABLE 243-1 HUMAN LEUKOCYTE ANTIGEN ASSOCIATIONS WITH RHEUMATOID ARTHRITIS (RA)

HLA TYPES (ALLELES) AND METHODS OF DETECTION			*THIRD HYPERVARIABLE REGION AMINO ACID SEQUENCES*					
ALLOANTISERA (DR)	**MLC (DW)**	**DNA (DRβ1)**	**70**	**71**	**72**	**73**	**74**	**MOST COMMON ETHNIC GROUPS**
ASSOCIATED WITH RA								
DR4	Dw4	*0401	Q	K	R	A	A	Whites (Western Europe)
DR4	Dw14	*0404		R				Whites (Western Europe)
DR4	Dw15	*0405		R				Japanese, Chinese
DR1	Dw1	*0101		R				Asian Indians, Israelis
DR6 (14)	Dw16	*1402		R				Yakima Native Americans
DR10	—	*1001	R	R				Spanish, Greeks, Israelis
NOT ASSOCIATED WITH RA								
DR4	Dw10	*0402	D	E				Whites (Eastern Europe)
DR4	Dw13	*0403		R			E	Polynesians
DR2	Dw2	*1501	D	A				Whites
DR3	Dw3	*0301				G	R	Whites

A = alanine; D = aspartic acid; E = glutamic acid; G = glycine; HLA = human leukocyte antigen; K = lysine; MLC = mixed leukocyte cultures; Q = glutamine; R = arginine; *= the same amino acid in that position as for DRB1*0401.

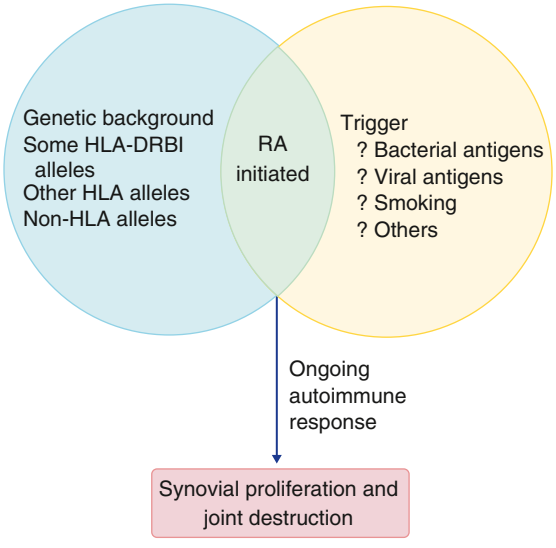

E-FIGURE 243-1. Initiation of rheumatoid arthritis (RA). HLA = human leukocyte antigen.

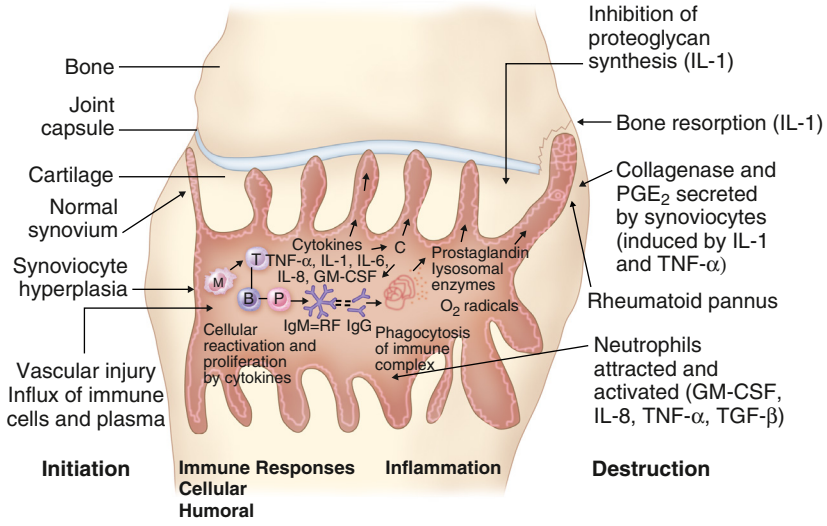

E-FIGURE 243-2. **Events involved in the pathogenesis of rheumatoid synovitis (progressing from *left* to *right*). B = B lymphocyte; C = complement; GM-CSF = granulocyte-macrophage colony-stimulating factor; IgG, IgM = immunoglobulin G, M; IL = interleukin; M = macrophage; P = plasma cell; PGE_2 = prostaglandin E_2; RF = rheumatoid factor; T = T lymphocyte; TGF-β = transforming growth factor-β; TNF-α = tumor necrosis factor-α.**

functional dominance, as reflected in successful therapeutic targeting (e.g., TNF inhibitors, tocilizumab, and JAK inhibitors).

The humoral immune system also plays a role, as reflected in the success of rituximab therapy. Rheumatoid factor and the presence of ACPAs correlate with more severe disease, including erosions of bone, and with the presence of extra-articular features. Rheumatoid factor, which is an antibody that recognizes the Fc portion of immunoglobulin G as its antigen, and ACPAs likely have a pathologic role. Via immune complex formation or perhaps functioning in isolation, these factors increase complement activation, promote macrophage activation to release lysosomal enzymes, kinins, prostanoids, and oxygen/nitrogen free radicals via Fc receptor (FcR) binding and may activate osteoclasts. ACPAs also activate macrophages via TLR/FcR cross-talk mediated via citrullinated fibronectin.

Articular damage is driven primarily by fibroblast-like synoviocytes and osteoclasts. Fibroblast-like synoviocytes are partially transformed cells that have a distinct epigenetic profile and that exhibit anchorage independence, loss of contact inhibition, low-grade proliferation, and TLR expression, thereby rendering them immunologically competent to sense tissue damage. Single cell sequencing studies have shown functionally distinct subsets of fibroblast-like synoviocytes, some with bone erosive propensity and others with a more inflammatory phenotype.[5] Fibroblast-like synoviocyte subsets release prostanoids, cytokines, chemokines, and matrix metalloproteinases (MMPs) such as MMP1, MMP3, and MMP13, in disproportion to the release of tissue inhibitors of MMPs (TIMPs). In consequence, fibroblast-like synoviocytes promote cartilage damage; this local tissue damage area is known as the *cartilage-pannus junction*. Macrophages and mast cells are also likely to contribute to this local process. Subsets of macrophages can be defined by single cell sequencing that clearly differentiates synovitis in active disease as compared with remission.[6] Bone damage requires cells with capacity to acidify the local milieu—osteoclast maturation and activation is a localized feature of rheumatoid arthritis synovium, arising as a consequence of RANKL, IL-1, TNF, and IL-17 activity. Thus activated osteoclasts localize in periarticular bone and in the adjacent bone marrow, thereby leading to the characteristic erosions detected on plain radiography. The inflammatory process underlying erosion is detected as "bone edema" on MRI. Synovitis thus results in the destruction of cartilage in marginal bone and in the stretching or rupture of the joint capsule or tendons and ligaments. Damage is directly related to disability.

Finally, generalized inflammation promotes systemic comorbidities. Circulating cytokines and immune complexes are proposed to activate endothelium and accelerate atherosclerosis, may provoke systemic osteoporosis, and can drive cognitive impairment, fatigue, and frank psychiatric presentations (e.g., depression). Inhibition of such processes should reduce comorbidities in the clinic.

CLINICAL MANIFESTATIONS

Although the presentation is variable, most patients with rheumatoid arthritis exhibit insidious onset of pain, stiffness, or swelling in multiple small joints over the course of weeks to months. Systemic features such as fatigue, low-grade fevers, and weight loss also may be present. Less commonly, the onset can be fulminant, occurring almost overnight, or patients may exhibit persistent monoarthritis or oligoarthritis for prolonged periods before manifesting the more typical pattern of joint involvement. Rarely, particularly men develop extra-articular features of rheumatoid arthritis, especially lung disease, before the joint problems appear. Periodic flares of disease are common and may be associated with an increase in circulating pre-inflammatory mesenchymal cells.[7,8]

Morning stiffness is a hallmark of inflammatory arthritis and is a prominent feature of rheumatoid arthritis. Patients are characteristically at their worst in the morning or after prolonged periods of rest. This stiffness in and around joints often persists for hours, and quantifying it is one way to measure impact of an intervention.

Articular Manifestations

Rheumatoid arthritis can affect any of the synovial (diarthrodial) joints (Fig. 243-1). Most commonly, clinically apparent disease starts in the metacarpophalangeal (MCP), proximal interphalangeal (PIP), and metatarsophalangeal (MTP) joints, followed by the wrists, knees, elbows, ankles, hips, and shoulders, in roughly that order. Early treatment limits the extent of joints involved. Less commonly, and usually later, rheumatoid arthritis may involve the temporomandibular, cricoarytenoid, and sternoclavicular joints. Rheumatoid arthritis may involve the upper part of the cervical spine, particularly the C1-C2 articulation (Fig. 243-2), but, unlike the spondyloarthropathies (Chapter 244), it rarely involves the remainder of the spine. Patients are also at an increased risk for osteoporosis (Chapter 225), and this risk should be considered and dealt with early in both women and men.

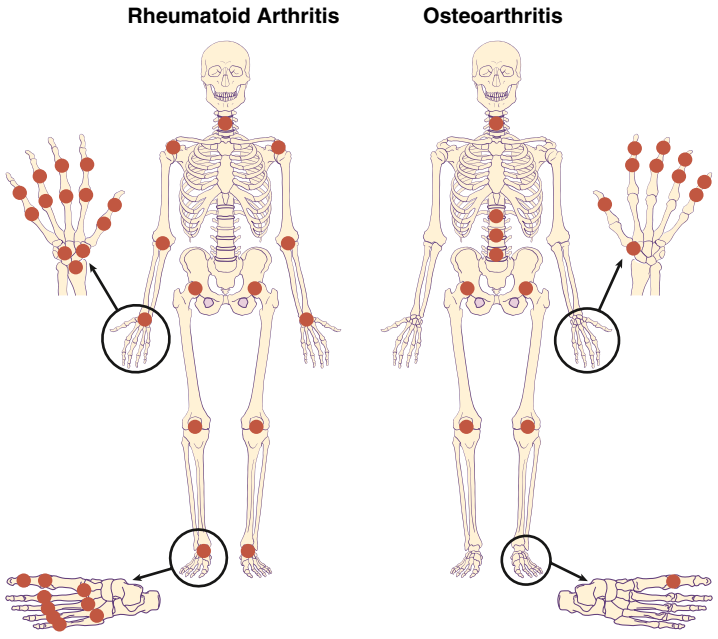

FIGURE 243-1. Distribution of involved joints in the two most common forms of arthritis: rheumatoid arthritis and osteoarthritis. ***Black circles*** **are shown over the involved joint areas.**

Hands

A significant proportion of the disability caused by rheumatoid arthritis is due to damage and dysfunction of the hands. Typically disease starts with swelling of the PIPs and MCPs. The distal interphalangeal (DIP) joints are almost never involved; significant involvement of the DIP joints should suggest the possibility of a different diagnosis (e.g., osteoarthritis or psoriatic arthritis). Manifestations that can be seen late in the disease but are rarely seen in treated patients include the classic ulnar deviation of the MCP joints (Fig. 243-3), and swan-neck deformities (hyperextension of the PIP joints). Boutonnière (or buttonhole) deformities also occur as a result of hyperflexion of the PIP joints. If the clinical disease remains active, hand function deteriorates. Sudden loss of function of individual fingers may occur as a result of tendon rupture.

Feet

Feet, particularly the MTP joints, are involved early in most patients and are often an initial site of radiographic erosion. Subluxation of the toes is common and leads to the dual problem of breakdown of the skin and ulcers on the top of the toes and malalignment of the MTP heads. Painful ambulation is caused by dislocation of the cushioning pads that usually protect the heads of the MTP joints.

Wrists

The wrist joints are involved in most patients with rheumatoid arthritis. Radial deviation is the rule, and patients with severe involvement may progress to volar subluxation. Even early in the course of the disease, synovial proliferation in and around the wrists may compress the median nerve, thereby causing carpal tunnel syndrome (Fig. 243-4). Later, this synovial proliferation may invade tendons and lead to rupture, most commonly of extensor tendons.

Large Joints

Involvement of knees, ankles, elbows, hips, and shoulders is common. Characteristically, the whole joint surface is involved in a symmetrical fashion. Rheumatoid arthritis is symmetrical, not only from one side of the body to the other but also within the individual joint. In the knee (Fig. 243-5A), both the medial and lateral compartments may be narrowed. In contrast, in

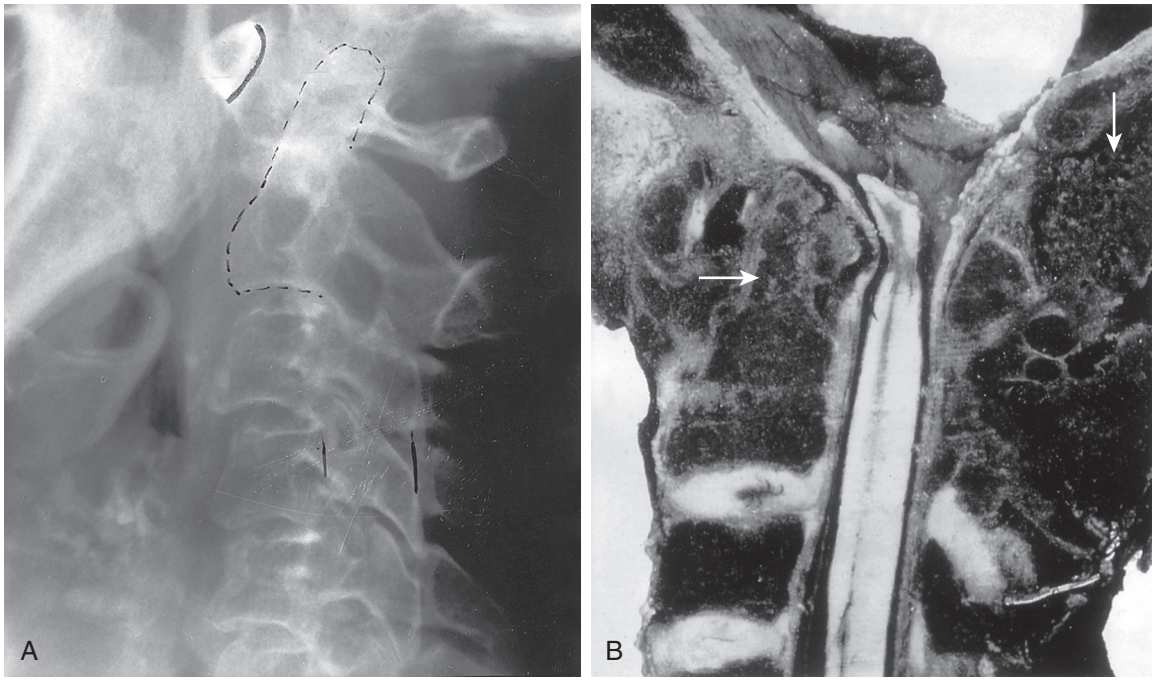

FIGURE 243-2. Subluxation of the cervical spine in patients with rheumatoid arthritis. A, In a lateral radiograph of the cervical spine, the body of C2 and its odontoid process are outlined by the *broken lines* and the posterior aspect of the anterior segment of C1 is indicated by a *solid line*. Normally, a space of only 2 to 3 mm separates C1 from C2. The space between C1 and the odontoid of C2 is markedly increased, indicative of subluxation of C1 and C2. **B,** Lateral view of a pathologic specimen from a patient who died of C1-C2 subluxation. The *horizontal arrow* shows the odontoid process that subluxed posteriorly, severely compressing and almost severing the cord. The *vertical arrow* shows a bone graft that had been put in place posteriorly in an attempt to prevent subluxation. Below the *arrow*, a nonhealing area is present through the bone graft, and inferior to that a wire fixation suture is still in place.

patients with osteoarthritis (Fig. 243-5B), only one compartment of the knee may be involved.

Synovial cysts, which may occur around any of the joints (large or small), occasionally manifest as soft, fluctuant masses that present diagnostic challenges. When the knee produces excess synovial fluid, it may accumulate in the popliteal fossa (popliteal or Baker cyst) (E-Fig. 243-3). These cysts can compress the popliteal nerve, artery, or veins. Baker cysts may dissect into the tissues of the calf (usually posteriorly), or they may rupture. Dissection may produce only minor symptoms, such as a feeling of fullness; rupture of the cyst with extravasation of its inflammatory content produces significant pain and swelling and may be confused with thrombophlebitis, the so-called pseudothrombophlebitis syndrome (Chapter 68).

Neck

Although most of the axial skeleton is spared in rheumatoid arthritis, the cervical spine is commonly involved, particularly the C1-C2 articulation. Bony erosions and ligament damage can occur in this area and may lead to subluxation (see Fig. 243-2). Most often, subluxation at C1-C2 is minor and without accompanying symptoms; patients and caregivers need only be cautious and avoid actively forcing the neck into positions of flexion. Occasionally, subluxation at C1-C2 is severe and leads to compromise of the cervical cord with neurologic symptoms and even death.

Other Joints

Other joints that may be involved include the temporomandibular, cricoarytenoid, and sternoclavicular joints. The cricoarytenoid joint is responsible for abduction and adduction of the vocal cords, and involvement of this joint may lead to a feeling of fullness in the throat, to hoarseness, and, rarely when the cords are essentially fused in a closed position, acute respiratory distress with or without stridor.

Extra-Articular Manifestations

Systemic features of rheumatoid arthritis such as fatigue, weight loss, and low-grade fevers occur frequently. All the other extra-articular features are more common in patients who are positive for rheumatoid factor, ACPA antibodies, or both (Table 243-1).

FIGURE 243-3. Severe advanced rheumatoid arthritis of the hands. There is massive tendon swelling over the dorsal surface of both wrists, severe muscle wasting, ulnar deviation of the metacarpophalangeal joints, and swan-neck deformity of the fingers. (From Forbes CD, Jackson WF. *Color Atlas and Text of Clinical Medicine*, 3rd ed. London: Mosby; 2003.)

Skin

Subcutaneous nodules are seen in approximately 20% of patients with rheumatoid arthritis, almost exclusively in patients who are rheumatoid factor- or ACPA-positive. Seronegative patients with nodules should be carefully scrutinized for a different diagnosis, such as chronic tophaceous gout (Chapter 252). Nodules may occur almost anywhere (e.g., lungs, heart, eye) but most commonly develop subcutaneously on extensor surfaces (particularly the forearms) (Fig. 243-6), over joints, or over pressure points. Rheumatoid nodules are firm on examination, usually are not tender, have a characteristic histologic picture, and are thought to be initiated by small vessel vasculitis. A syndrome

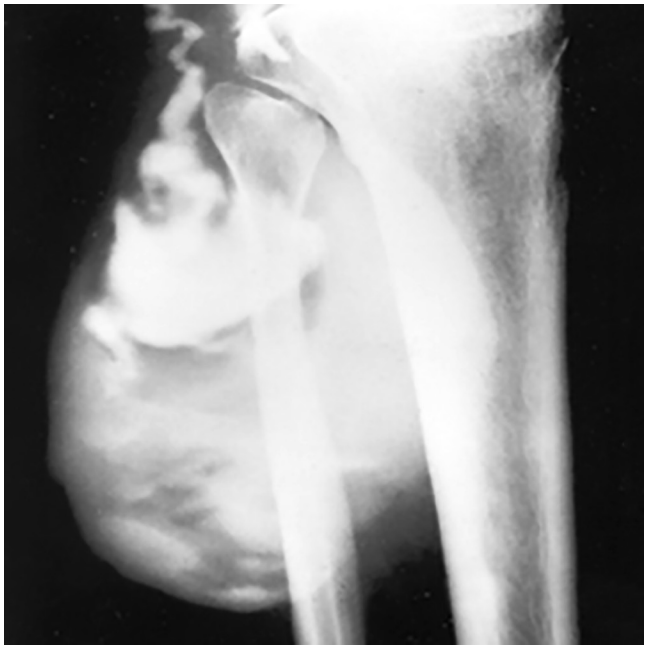

E-FIGURE 243-3. Arthrogram with a radiocontrast agent injected into the knee. The dye flows into the popliteal space and through a narrow channel into a large synovial cyst (Baker cyst) that has dissected into the soft tissue of the calf. Arthrograms are no longer used in routine diagnostics, but this dramatic image beautifully illustrates the phenomenon.

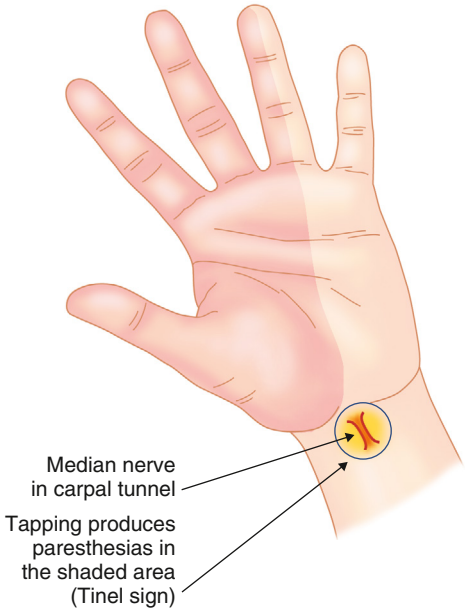

FIGURE 243-4. Carpal tunnel syndrome. Distribution of pain and/or paresthesias *(shaded area)* when the median nerve is compressed by swelling in the wrist (carpal tunnel).

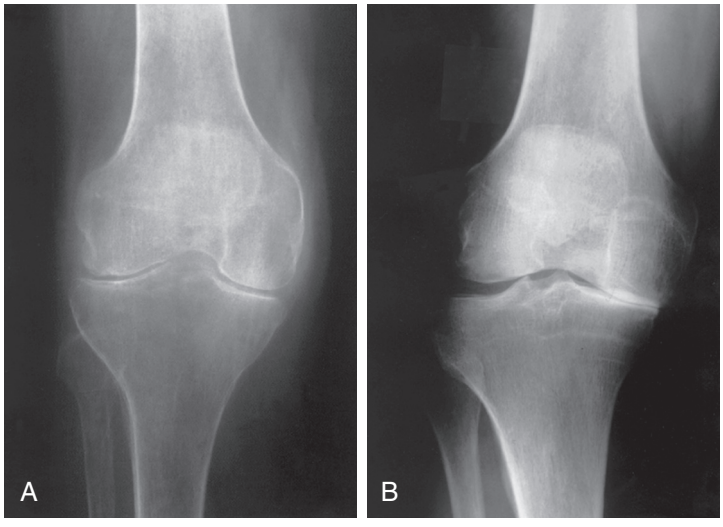

FIGURE 243-5. Radiographs of the knees in the two most common forms of arthritis: rheumatoid arthritis and osteoarthritis. A, Severe involvement in rheumatoid arthritis, with almost complete symmetrical loss of joint space in both the medial and the lateral compartments, but with little subchondral sclerosis or osteophyte formation. **B,** Typical osteoarthritis, with severe, near-total loss of joint space of one compartment and a normal or actually increased joint space of the other compartment. Note also the significant subchondral sclerosis in the involved area, typical of osteoarthritis.

of increased nodulosis, despite good control of the joint disease, has been described with methotrexate therapy (Fig. 243-7).

Small vessel vasculitis, manifested as digital infarcts or leukocytoclastic vasculitis, may occur in rheumatoid arthritis (Fig. 243-8) Vasculitis of small and medium arteries may be indistinguishable from polyarteritis nodosa. Pyoderma gangrenosum also occurs with increased frequency in association with rheumatoid arthritis.

Cardiovascular Involvement

Cardiac involvement directly related to rheumatoid arthritis is uncommon, but patients with rheumatoid arthritis have significantly increased morbidity and mortality from coronary artery disease and heart failure. Chronic inflammation superimposed on conventional risk factors (e.g., smoking, obesity) appears to be the major cause. Some of the medications used to treat rheumatoid arthritis such as glucocorticoids and a sedentary lifestyle may be additional risk factors for the development of coronary artery disease.

TABLE 243-1 EXTRA-ARTICULAR MANIFESTATIONS OF RHEUMATOID ARTHRITIS

Skin	Nodules, fragility, vasculitis, pyoderma gangrenosum
Heart	Pericarditis, premature atherosclerosis, vasculitis, valve disease, and valve ring nodules
Lung	Pleural effusions, interstitial lung disease, bronchiolitis obliterans, rheumatoid nodules, vasculitis
Eye	Keratoconjunctivitis sicca, episcleritis, scleritis, scleromalacia perforans, peripheral ulcerative keratopathy
Neurologic	Entrapment neuropathy, cervical myelopathy, mononeuritis multiplex (vasculitis), peripheral neuropathy
Hematopoietic	Anemia, thrombocytosis, lymphadenopathy, Felty syndrome, large granular lymphocyte syndrome
Kidney	Amyloidosis, vasculitis
Bone	Osteopenia

FIGURE 243-6. Rheumatoid nodules. Large rheumatoid nodules are seen in a classic location along the extensor surface of the forearm and in the olecranon bursa.

Pericardial effusions (Chapter 62) are common (50% by echocardiography) but usually are asymptomatic. Rarely, long-standing pericardial disease may result in a fibrinous pericarditis, and patients may develop constrictive pericarditis (Chapter 62). The incidence of venous thromboembolism is also increased.

Pulmonary Manifestations

Pulmonary manifestations include pleural effusions (Chapter 86), rheumatoid nodules, and parenchymal lung disease. Pleural effusions occur more commonly in men and are usually small and asymptomatic. Rheumatoid nodules may occur in the lung, especially in men (Fig. 243-9) and are usually solid but may calcify, cavitate, or become infected. Rarely, pulmonary nodules rupture and produce a pneumothorax. If patients with rheumatoid arthritis are exposed to coal or silica dust, diffuse nodular densities may occur (Caplan syndrome).

Interstitial lung disease (Chapter 80), usually clinically silent, may affect up to 45% of patients with rheumatoid arthritis.[9] Interstitial lung disease, which rarely may precede joint manifestations, may progress to increasing dyspnea and a honeycomb appearance on radiography. Rarely, bronchiolitis obliterans can be seen, with or without organizing pneumonia.

Ophthalmologic Manifestations

The most common eye manifestation of rheumatoid arthritis is keratoconjunctivitis sicca (dry eyes) from secondary Sjögren syndrome (Chapter 247). Patients may have associated xerostomia (dry mouth), parotid gland swelling, or, occasionally, lymphadenopathy. Scleritis also can occur and may be painful, with progression to thinning of the sclera (manifesting as deep pigment showing through on physical examination) and perforation (scleromalacia perforans). Rarely, tendinitis of the superior oblique muscles can result in double vision (Brown syndrome).

FIGURE 243-7. Rheumatoid nodulosis. In this patient, multiple rheumatoid nodules are present over joints. In some cases, nodules may dominate the clinical picture. Rarely, this may be seen as a side effect of methotrexate therapy.

FIGURE 243-9. Rheumatoid nodules in the lung. Chest radiograph demonstrates discrete rheumatoid nodules in both right and left lower lobes. (Courtesy Dr. Martin Lidsky, Houston, TX.)

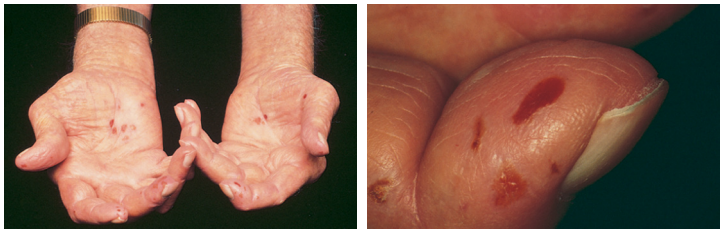

FIGURE 243-8. Small vessel vasculitis. A and B, Rheumatoid vasculitis with small brown infarcts of palms and fingers in chronic rheumatoid arthritis. (Courtesy Dr. Martin Lidsky, Houston, TX.)

Neurologic Manifestations

Peripheral nerve entrapment syndromes, including carpal tunnel syndrome (median nerve at the wrist; Chapter 388) and tarsal tunnel syndrome (anterior tibial nerve at the ankle), are common in rheumatoid arthritis. Vasculitis can lead to a stocking and glove neuropathy or mononeuritis multiplex (Chapter 388). Subluxations at C1-C2 may produce myelopathy (see Fig. 243-2). Rheumatoid nodules in the central nervous system have been described, but they are rare and usually asymptomatic.

Felty Syndrome

Felty syndrome is the triad of rheumatoid arthritis, splenomegaly, and neutropenia. This complication, which is seen in patients with severe rheumatoid factor/ACPA-positive disease but is now rare, may be accompanied by hepatomegaly, thrombocytopenia, lymphadenopathy, and fever.

Some patients who were previously thought to have Felty syndrome have peripheral white blood cell counts dominated by large granular lymphocytes with almost complete absence of neutrophils. This condition is known as the large granular lymphocyte syndrome and is thought to be a low-grade lymphoproliferative disorder characterized by the clonal proliferation of large granular lymphocytes.

DIAGNOSIS

All current treatment paradigms for rheumatoid arthritis stress the early and aggressive use of disease-modifying antirheumatic drugs (DMARDs). Therefore, the importance of accurate early diagnosis cannot be overemphasized.[10]

The distribution of involved joints is a critical clue to the underlying diagnosis. The joints that are involved at presentation are variable; typically, the symptoms start in the small joints of the hands (PIP and MCP joints) and in the toes (MTP joints). Importantly, rheumatoid arthritis usually spares the DIP joints and the small joints of the toes. Later, involvement is more common in larger joints: wrists, knees, elbows, ankles, hips, and shoulders. Although the patient's history of joint symptoms (arthralgia) is important, the diagnosis of rheumatoid arthritis requires the presence of inflammation (swelling, warmth, or both) on examination and/or imaging of the joints.

Rheumatoid arthritis has no single pathognomonic finding on physical examination or laboratory testing. Instead, the diagnosis of rheumatoid arthritis requires a collection of historical and physical features, as well as an alert and informed clinician. Inflammatory changes in the joints may be confirmed using ultrasound or magnetic resonance imaging (MRI) in early disease (Chapter 238).

Classification and Diagnostic Criteria

Classification criteria (Fig. 243-10) now serve as the gold standard for clinical trials and are widely used as diagnostic aids. However, clinicians must consider the duration of symptoms and signs in making a diagnosis and be as confident as possible that another explanation, including many virus-related syndromes, is not the cause of a self-limited polyarthritis that looks identical to rheumatoid arthritis,[11] even including the presence of rheumatoid factor. Such conditions usually persist for only 2 to 3 weeks. Classification criteria for rheumatoid arthritis do not require 6 weeks of disease and give significant weight to the presence of high-titer rheumatoid factor or ACPA positivity.[12] The presence of ACPA antibodies, even in the first few weeks of an inflammatory arthritis, is suggestive of more aggressive rheumatoid arthritis.

Laboratory Findings

The most characteristic laboratory abnormality (Chapter 237) is the presence of rheumatoid factor, which is found in approximately 75% of patients. The presence of rheumatoid factor is strongly associated with more severe articular disease, as well as with essentially all the extra-articular features. However, rheumatoid factor is seen in association with many diseases other than rheumatoid arthritis, particularly in disease processes that induce chronic stimulation of the immune system (Table 243-2).

Anti-citrullinated protein antibodies (the most commonly detected of the anti-modified protein antibodies [AMPAs]) are found in approximately 70% of patients with rheumatoid arthritis, have a high specificity (93 to 98%), may be present years before clinical disease is diagnosed, and are associated with aggressive erosive disease.

Approximately 15% of rheumatoid arthritis patients are negative for both rheumatoid factor and anti-citrullinated protein antibodies (seronegative). Rheumatoid arthritis is also associated with many other autoantibodies, including antinuclear antibodies (≈30%) and antineutrophil cytoplasmic antibodies, particularly of the perinuclear type (≈30%) (Chapter 237).

Many patients with rheumatoid arthritis have an anemia of chronic disease (or anemia of chronic inflammation), and the degree of anemia is proportional to the activity of the disease (Chapter 144). Therapy that controls the disease will normalize the hemoglobin levels. Other causes of anemia

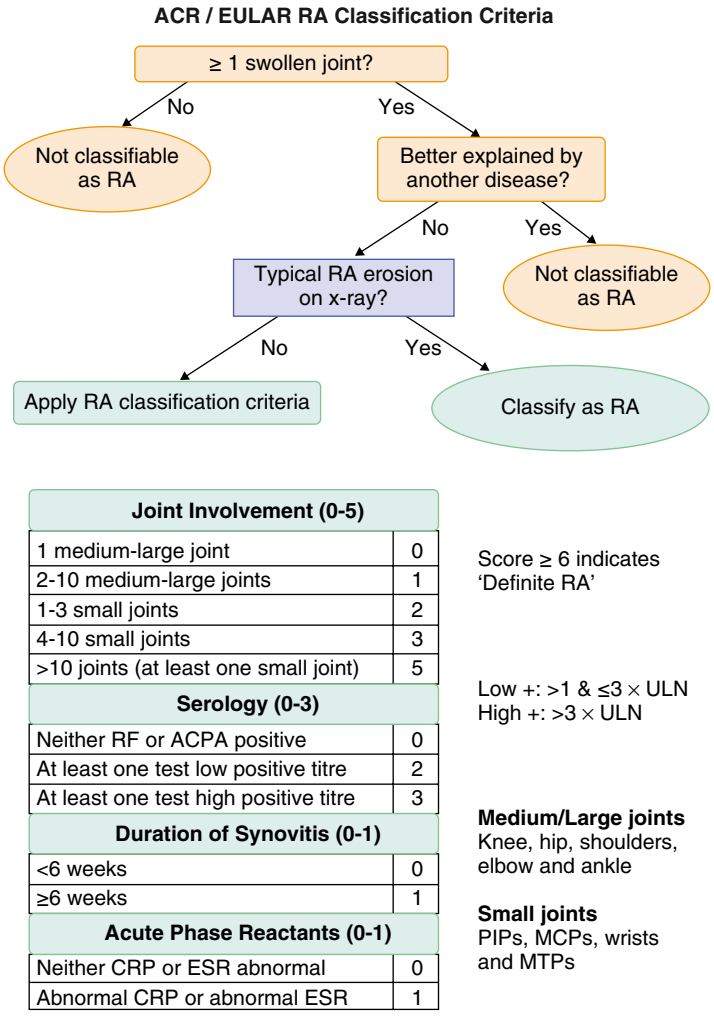

FIGURE 243-10. **American College of Rheumatology/European League Against Rheumatism (ACR/EULAR) classification criteria for rheumatoid arthritis (RA).** The classification criteria are shown as a flow diagram for initial decision making and also in tabular form to calculate American College of Rheumatology/European League Against Rheumatism (ACR/EULAR) classification criteria for rheumatoid arthritis (RA). ACPA = anti-citrullinated protein antibody; CRP = C-reactive protein; ESR = erythrocyte sedimentation rate; MCP = metacarpal phalangeal joint; MTP = metatarsal phalangeal joint; PIP = proximal interphalangeal joint; RA = rheumatoid arthritis; RF = rheumatoid factor; ULN = upper limit of normal. (Data from Aletaha D, Neogi T, Silman AJ, et al. 2010 Rheumatoid arthritis classification criteria. An American College of Rheumatology/European League Against Rheumatism collaborative initiative. *Arthritis Rheum*. 2010;62:2569-2581.)

in rheumatoid arthritis include iron deficiency anemia from gastrointestinal blood loss (especially with concomitant use of NSAIDs). Thrombocytosis is common, with platelet counts returning to normal as the inflammation is controlled. Acute phase reactants such as the erythrocyte sedimentation rate and C-reactive protein levels parallel the activity of the disease, and their persistent elevation portends a poor prognosis in terms of both joint destruction and mortality. White blood cell counts may be elevated, normal, or, in the case of Felty syndrome, depressed. Eosinophilia is present in some patients with rheumatoid arthritis.

Synovial fluid in rheumatoid arthritis is characterized by white blood cell counts in the range of 5000 to 100,000/μL, with approximately two thirds of the cells being polymorphonuclear leukocytes. There are no synovial fluid findings that are pathognomonic of rheumatoid arthritis. Pleural fluid in rheumatoid arthritis is characterized by low levels of glucose and low pH and can be confused with empyema.

Differential Diagnosis

The accurate diagnosis of rheumatoid arthritis early in its course, although challenging, is critical if patients are to benefit maximally from therapeutic intervention. Once disease has been present and active for years and the characteristic deformities and radiographic changes have occurred, the diagnosis is all too obvious. Once rheumatoid arthritis has progressed to that point, deformities may no longer be amenable to medical therapy.

TABLE 243-2 DIFFERENTIAL DIAGNOSIS OF RHEUMATOID ARTHRITIS

DISORDER	SUBCUTANEOUS NODULES	RHEUMATOID FACTOR
Viral arthritis (hepatitis B and C, parvovirus, rubella, others)	–	±
Bacterial endocarditis	±	+
Rheumatic fever	+	–
Sarcoidosis	+	+
Reactive arthritis	–	–
Psoriatic arthritis	–	–
Systemic lupus erythematosus	±	+
Primary Sjögren syndrome	–	+
Chronic tophus gout	+	–
Calcium pyrophosphate disease	–	–
Polymyalgia rheumatica	–	–
Osteoarthritis (erosive)	–	–

– = not present; + = frequently present; ± = occasionally present.

Many diseases can mimic rheumatoid arthritis (see Table 243-2). Early in the course of disease, self-limited viral syndromes must be considered, especially hepatitis B and C (Chapter 135), parvovirus (Chapter 342), rubella (infection or vaccination; Chapter 339), and Epstein-Barr virus (Chapter 348). At any time, systemic lupus erythematosus (Chapter 245), psoriatic arthritis (Chapter 244), and reactive arthritis may present differential diagnostic challenges. In the case of these three mimics, a targeted history and examination to elucidate their associated clinical features (e.g., rashes, oral ulcers, nail changes, dactylitis, urethritis, or renal, pulmonary, gastrointestinal, or ophthalmologic involvement) is critical. Especially in elderly patients with fulminant-onset rheumatoid arthritis, remitting rheumatoid factor–negative symmetrical synovitis with pitting edema (the so-called RS3PE syndrome) and paraneoplastic syndromes should be considered. Chronic tophaceous gout (Chapter 252) also may mimic severe nodular rheumatoid arthritis.

Differentiating rheumatoid lung nodules from lung cancer can be problematic, particularly if the lesion is solitary. Therefore, the presence of pulmonary nodules in a patient with rheumatoid arthritis should precipitate an aggressive diagnostic evaluation (Fig. 177-1). Hypothyroidism (Chapter 207) not only causes many rheumatic manifestations but also occurs commonly in conjunction with rheumatoid arthritis and, therefore, should be considered.

TREATMENT

General Measures

Despite many different options, rheumatoid arthritis is a lifelong disease process that has no known cure. Patients with rheumatoid arthritis should be educated about their disease and its treatment. Optimal patient care requires effective ongoing interactions among primary care clinicians and rheumatologists, as well as a multidisciplinary team that can include rheumatology specialist nurses, physical therapists, occupational therapists, and orthopedic surgeons.[A1] Because of the serious nature of the disease, the necessity for rapid introduction and revision of treatments, and the need for expertise in monitoring these therapies, all patients with rheumatoid arthritis should be evaluated early and followed closely by a rheumatologist.

Patients should have an opportunity to spend time with physical therapists and occupation therapists to learn about range-of-motion exercises, joint protection, and assistive devices. Stiffness is relieved by warmth and activity, and reducing or eliminating joint stiffness is a clear goal of therapy.

TABLE 243-3 KEYS TO OPTIMIZE OUTCOME OF TREATMENT OF RHEUMATOID ARTHRITIS

Early, accurate diagnosis
Early DMARD therapy
Strive for remission in all patients
Monitor carefully for treatment toxicities
Consider and treat comorbid conditions*

*Important comorbid conditions include cardiovascular disease, increased susceptibility to infections, and osteoporosis.
DMARD = disease-modifying antirheumatic drug.

The goal of therapy, which is disease remission (Table 243-3) or very low disease activity, should always be kept in mind.[13] When rheumatoid arthritis is treated early, remission is possible in over 50% of patients and low disease activity in at least another 35%. However, continued response requires the ongoing use of disease-modifying anti-rheumatic drugs (DMARDs), which essentially all rheumatoid arthritis patients should receive. In many patients, combinations of different DMARDs (conventional and biologic) are necessary for optimal control. Therapy should be escalated rapidly to ensure maximal suppression of disease while minimizing toxicity and expense.

Medical Therapy

Three types of medical therapies (Table 243-4) are used for rheumatoid arthritis: NSAIDs, glucocorticoids, and DMARDs (conventional, biologic and targeted synthetic). Initial therapy should always include a DMARD.[14]

Nonsteroidal Anti-inflammatory Drugs

NSAIDs (Table 26-4) are important for the symptomatic relief they provide, but they play only a minor role, if any, in altering the underlying disease process. Therefore, NSAIDs should rarely, if ever, be used to treat rheumatoid arthritis without the concomitant use of DMARDs.

Cyclooxygenase-2 (COX2)-selective agents, which are less likely to cause gastrointestinal bleeding, have been a popular choice for patients with rheumatoid arthritis, but evidence linking these agents to increased cardiovascular toxicity is particularly troubling for patients with rheumatoid arthritis, who are already at high risk for myocardial infarction and stroke. In a randomized clinical trial, however, the cyclooxygenase-2 (COX-2) selective NSAID, celecoxib, was non-inferior compared with naproxen or ibuprofen in terms of cardiovascular outcomes.[A2] If COX2-selective agents are used, they should be kept at a low dose. Consideration should be given to low-dose aspirin prophylaxis, but this therapy may increase the gastrointestinal toxicity of NSAIDs. The concomitant use of a proton pump inhibitor (Table 124-1) should be considered in all patients with rheumatoid arthritis who are taking NSAIDs. Additionally, the potential for NSAIDs to decrease renal blood flow and to increase blood pressure should be kept in mind.

Glucocorticoids

Glucocorticoids (Chapter 28) provide dramatic and rapid symptomatic improvement in patients with rheumatoid arthritis, and they also significantly decrease its radiographic progression. However, the toxicities of long-term therapy are extensive and potentially devastating, including a 25% increased risk of serious infection with doses as low as 5 mg daily and a doubling of risk at 5 to 10 mg daily[15] (Chapter 28), so these drugs must be used carefully (Table 243-5).

Because of their rapid onset of action, glucocorticosteroids are ideally suited to help control the inflammation in rheumatoid arthritis while the much slower-acting DMARDs start to work. Glucocorticoids should rarely, if ever, be used without concomitant DMARD therapy.

Prednisone, which is the most commonly used glucocorticoid, should rarely be used in doses higher than 10 mg/day to treat the articular manifestations of rheumatoid arthritis. At this dose at the start of methotrexate-based treatment, the addition of prednisone reduces erosive joint damage, disease activity, physical disability, and the use of biologic treatment at 2 years. The dose should be slowly tapered to the lowest effective dose, and concomitant DMARD therapy should be adjusted to make this possible. For example, 5 mg of prednisolone daily is effective add-on therapy in patients over age 65 years.[A3]

Some rheumatologists use intramuscular depot injection of glucocorticoids to ensure delivery and manage initial DMARD escalation or transient flare. Intra-articular glucocorticoid injection is also useful, and ultrasound guidance is helpful for difficult-to-access joints.

The goal is to have all patients off or on very low doses of glucocorticoids with their disease controlled by DMARDs. However, higher doses of glucocorticoids may be necessary to treat extra-articular manifestations, especially vasculitis and scleritis.

TABLE 243-4 TREATMENT OPTIONS FOR RHEUMATOID ARTHRITIS

MEDICATION	DOSE
NONSTEROIDAL ANTI-INFLAMMATORY DRUGS*	
Celecoxib	100 mg PO twice daily or 200 mg PO daily
Diclofenac/misoprostol	50 mg/200 mg PO 2-4 times daily
Etodolac	300 mg PO 2 or 3 times daily; or 400 or 500 mg PO twice daily
Ibuprofen	400 mg PO four times daily
Ketoprofen	75 mg PO three times daily; or 50 mg PO four times daily
Naproxen	500 mg PO twice daily
Naproxen/esomeprazole	375 mg/20 mg or 500 mg/20 mg PO twice daily
Tolmetin	400 mg PO three times daily
GLUCOCORTICOIDS*	
Prednisone	5-10 mg PO once daily
DISEASE-MODIFYING ANTIRHEUMATIC DRUGS (DMARDs)	
Conventional DMARDs	
Hydroxychloroquine	200-400 mg PO daily (5 mg/kg)
Leflunomide	10-20 mg PO once daily
Methotrexate	7.5-25 mg PO† once weekly (PO or SQ)
Sulfasalazine	500 mg PO once or twice daily for first 2 weeks; then 2 g daily in two evenly divided doses
Azathioprine	1 mg/kg (50-100 mg) PO as a single dose or twice daily; may be increased up to 2.5 mg/kg
Minocycline	100 mg PO twice daily
Biologic DMARDs	
Abatacept	500-1000‡ mg IV at 0, 2, and 4 weeks, then every 4 weeks§
Adalimumab	40 mg SQ every other week
Certolizumab	400 mg SQ at weeks 2 and 4, followed by 200 mg every other week
Etanercept	50 mg SQ once weekly
Golimumab	50 mg SQ once a month¶
Infliximab	In conjunction with methotrexate, 3-5 mg/kg IV at 0, 2, and 6 weeks, then every 4-8 weeks
Rituximab	In combination with methotrexate, two 1000-mg IV infusions separated by 2 weeks (one course) every 16-24 weeks
Tocilizumab	4 mg/kg IV every 4 weeks followed by 8 mg/kg every 4 weeks**
Targeted Synthetic DMARDs	
Tofacitinib	5 mg PO twice daily
Baricitinib	2 or 4 mg PO once daily
Upadacitinib	15 mg PO once daily

*Initial treatment should always include a DMARD; see text.
†May be administered SQ to reduce side effects and when higher doses are needed.
‡500 mg if <60 kg; 750 mg if 600-100 kg; 1000 mg if >100 kg.
§May be administered SQ once weekly with or without an IV loading dose.
¶May be administered IV at a dose of 2 mg/kg at weeks 0 and 4, then every 8 weeks.
**May be administered SQ at a starting dose of 162 mg every other week if <100 kg, or 162 mg every week if >100 kg.
DMARD = disease-modifying antirheumatic drug; PO = orally; IV = intravenously; SQ = subcutaneously.

TABLE 243-5 GUIDELINES FOR USE OF GLUCOCORTICOIDS

Avoid use of glucocorticoids without DMARDs
Prednisone, >10 mg/day, is rarely indicated for articular disease
Taper to the lowest effective dose and stop if possible.
Toxic risk is associated with average dose >8 mg daily
Use as "bridge therapy" until DMARD therapy is effective
Remember prophylaxis against osteoporosis
Can be used parenterally as well as orally

DMARD = disease-modifying antirheumatic drug.

In all patients receiving glucocorticoids, meticulous measures should be taken to prevent osteoporosis. Bisphosphonates (Chapter 225) are particularly effective but are contraindicated in women of childbearing age.

Disease-Modifying Antirheumatic Drugs

DMARDs are a group of medications that have the ability to halt the disease process in the synovium and to modify or change the disabling potential of rheumatoid arthritis.[16,17] These drugs also can halt or slow radiographic progression of the disease.

Conventional Disease-Modifying Antirheumatic Drugs

Included in this group of medications are methotrexate, sulfasalazine (Azulfidine), gold, antimalarials (hydroxychloroquine and others), leflunomide, azathioprine, and minocycline. Of these agents, methotrexate and hydroxychloroquine are still widely used, whereas sulfasalazine is also used in Europe and Asia. These conventional DMARDs require 2 to 6 months to exert their maximal effect, and all require monitoring to detect early adverse events (Table 243-6). Monitoring of the serum drug levels of biologic agents may be useful in patients in remission, because higher blood levels may predict a longer relapse-free period.[18]

These DMARDs are effective in treating both early and more advanced rheumatoid arthritis. Methotrexate is generally recommended as the initial anchor conventional DMARD. However, the selection of the best initial therapy for each patient depends on the concerns of the patient and physician about toxicity and monitoring issues, as well as the activity of disease and the presence of comorbid conditions. The critical issue is not which DMARD to start first but rather starting the DMARD early in the disease process.

Methotrexate

Methotrexate should be the initial DMARD for most patients; it is economical, serious toxicities are rare, and when used in combination it makes essentially all other DMARDs work better. Methotrexate is contraindicated in pregnancy and in patients with significant renal impairment. Relative care should be taken in patients who have diabetes. Methotrexate is effective in slowing radiographic progression and is given orally as a single weekly dose ranging from 5 to 25 mg. Oral absorption of methotrexate is variable, and subcutaneous injections, which are the norm in some clinical practices, are often effective when oral treatment is not. Side effects of methotrexate (Chapter 28) include oral ulcers, nausea, hepatotoxicity, bone marrow suppression, and pneumonitis. With the exception of pneumonitis, these toxicities respond to dose adjustments. Monitoring of blood counts and liver blood tests (albumin and aspartate aminotransaminase [AST] or alanine aminotransferase [ALT]) should be done every 3 mo, with adjustments in the dose of methotrexate as needed. Renal function is critical for clearance of methotrexate, and previously stable patients may experience severe toxicities if renal function deteriorates. Pneumonitis, although rare, is less predictable and can be fatal, particularly if the methotrexate is not stopped or is restarted. Folic acid, 1 to 4 mg/day, or 5 mg per week, can significantly decrease most methotrexate toxicities without interfering with efficacy.

If methotrexate alone does not sufficiently control disease, it may be combined with other DMARDs. Methotrexate in combination with virtually any of the other DMARDs (conventional biologic or targeted synthetic) is more effective than either drug alone.

TABLE 243-6 CAVEATS FOR MONITORING DISEASE-MODIFYING ANTIRHEUMATIC DRUG THERAPIES*

MEDICATION	CAVEATS
Prednisone	Use as bridge to effective DMARD therapy, consider prophylaxis for osteoporosis (see Table 243-5)
Hydroxychloroquine	Keep dosage lower than 5.0 mg/kg/day. Yearly eye checkup by ophthalmologist after 5 yr of therapy
Sulfasalazine	CBC for neutropenia, initially every month, then every 6 mo
Methotrexate	CBC and AST/ALT every 8-12 wk when dose is stable. Many toxicities respond to folic acid or small dose reduction. If pneumonitis, stop and do not restart. Decreasing renal function may precipitate toxicities. Absolute contraindication in pregnancy
Leflunomide	CBC and AST/ALT every 4-8 wk; long half-life may require cholestyramine washout; absolute contraindication in pregnancy
TNF inhibitors	If fevers or infectious symptoms of any kind, stop until symptoms resolve; aggressively evaluate and treat possible infections. May precipitate congestive heart failure, demyelinating syndromes, or lupus-like syndromes
IL-6 receptor inhibitors	If fevers or infectious symptoms of any kind, stop until symptoms resolve; aggressively evaluate and treat possible infections. Avoid if history of perforation or diverticulitis. Note lipids will rise within 3 mo of therapy commencement
JAK inhibitors	Watch for elevation of LFTs, creatinine kinase, creatinine levels and adhere to regional monitoring requirements. Care if at risk of or history of thrombosis. Risk of herpes zoster is considered higher than with other DMARD classes

*Patients receiving DMARDs, both conventional and biologic, should be monitored by a rheumatologist.

ALT = alanine aminotransferase; AST = aspartate aminotransferase; CBC = compete blood count; DMARD = disease-modifying antirheumatic drug; GI = gastrointestinal; IL = interleukin; JAK = Janus kinase; LFTs = liver function tests; TNF = tumor necrosis factor.

Leflunomide

Leflunomide, a pyrimidine antagonist, has a very long half-life and is most commonly started at 10 to 20 mg/day orally. Diarrhea is the most common toxicity and responds to dose reduction. Doses of leflunomide of 10 to 20 mg three to five times per week are frequently used. Also, because of the long half-life and teratogenic potential of leflunomide, women wishing to become pregnant who have previously received leflunomide, even if therapy was stopped years ago, should have blood levels drawn. If toxicity occurs or if pregnancy is being considered, leflunomide can be rapidly eliminated from the body by treatment with cholestyramine. Laboratory monitoring for hematologic and hepatic toxicity should be done during treatment with leflunomide, as recommended for methotrexate.

Antimalarial Drugs

The antimalarial drugs hydroxychloroquine and chloroquine are frequently used to treat rheumatoid arthritis. They have the least toxicity of any of the DMARDs and do not require monitoring of blood tests. Yearly monitoring by an ophthalmologist after 5 years of therapy is recommended to detect any signs of retinal toxicity (rare). Hydroxychloroquine is the most commonly used preparation and is given orally at 200 to 400 mg/day (5 mg/kg). These drugs are frequently used in combination with other DMARDs, particularly methotrexate. Hydroxychloroquine decreases cholesterol levels and decreases the incidence of diabetes in patients with rheumatoid arthritis.

Sulfasalazine

Sulfasalazine is an effective treatment when given in doses of 1 to 3 g/day. Monitoring of blood counts, particularly white blood cell counts, in the first 6 mo is recommended. Sulfasalazine and hydroxychloroquine are often combined with methotrexate, a regimen referred to as triple therapy, which has efficacy similar to the combination of a TNF inhibitor and methotrexate and is more economical.

Minocycline

Minocycline 100 mg twice daily is an effective treatment for rheumatoid arthritis, particularly when used in early rheumatoid factor–positive disease. Chronic therapy (>2 years) with minocycline may lead to cutaneous hyperpigmentation, which reverses when the drug is stopped. Minocycline has also been associated with drug-induced systemic lupus erythematosus (Chapter 245).

Biologic Disease-Modifying Antirheumatic Drugs

Biologic agents can be directed against TNF (etanercept, infliximab, adalimumab, golimumab, and certolizumab), the IL-6 receptor (tocilizumab and sarilumab), and IL-1 (anakinra). In practice IL-1 inhibitors are rarely used in the treatment of rheumatoid arthritis. Additionally, monoclonal antibodies that deplete B cells (anti-CD20, rituximab)[A4] and that block the second signal for T-cell activation (abatacept) are effective treatments for rheumatoid arthritis, but tocilizumab appears to be superior to rituximab.[A5]

All patients with rheumatoid arthritis receiving biologic therapies should be monitored by a rheumatologist, and all their physicians should be aware of the risk for infections that are often atypical.[19] In patients who have active disease despite methotrexate, all the biologics decrease disease activity and then slow radiographic progression when combined with methotrexate. Early treatment with tocilizumab plus methotrexate results in greater sustainable clinical, functional, and radiographic benefits than methotrexate alone, with acceptable safety and tolerability, in early erosive rheumatoid arthritis.

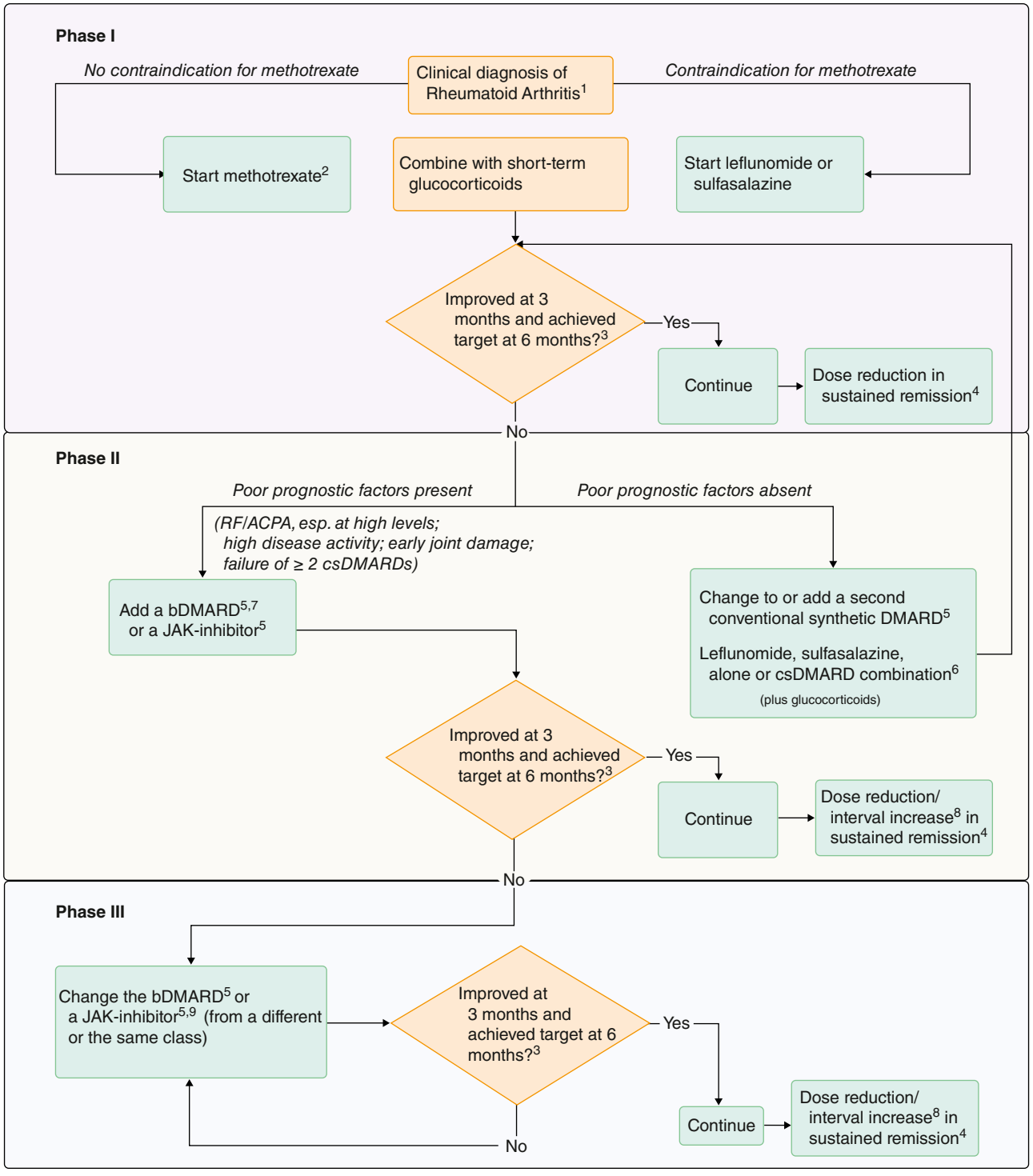

1. *2010/ACR-EULAR classification criteria can support early diagnosis.*
2. *"Methotrexate should be part of the first treatment strategy;" combination therapy with csDMARDs is not preferred by the Task Force; starting with methotrexate does not exclude its use in combination with other csDMARDs, although more adverse events without added benefit are to be expected, especially if methotrexate is combined with glucocorticoids.*
3. *The treatment target is clinical remission according to ACR-EULAR definitions or, if remission is unlikely to be achievable, at least low disease activity; the target should be reached after 6 months, but therapy should be adapted or changed if insufficient improvement (less than 50% of disease activity) is seen after 3 months.*
4. *Sustained remission: ≥ 6 months based on ACR/EULAR index or Boolean remission.*
5. *Consider contraindications and risks.*
6. *The most frequently used combination comprises methotrexate, sulfasalazine, and hydroxychloroquine.*
7. *TNF-inhibitors (adalimumab, certolizumab, etanercept, golimumab, infliximab, including EMA/FDA approved bsDMARDs), abatacept, IL-6R inhibitors, or rituximab (under certain conditions); in patients who cannot use csDMARDs as comedication, IL6-inhibitors and tsDMARDs have some advantages.*
8. *Dose reduction or interval increase can be safely done with all bDMARDs and tsDMARDs with little risk of flares; stopping is associated with high flare rates; most but not all patients can recapture their good state upon re-institution of the same bDMARD/tsDMARD.*
9. *Efficacy and safety of bDMARDs after JAK-inhibitor failure is not fully known; also, efficacy and safety of an IL-6 pathway inhibitor after another one has failed is currently unknown. Efficacy and safety of a JAK-inhibitor after insufficient response to a previous JAK-inhibitor is unknown.*

FIGURE 243-11. Recommendations for the management of rheumatoid arthritis. ACPA = anti-citrullinated peptide antibody; DMARD = disease-modifying antirheumatic drug; JAK = Janus kinase; RF = rheumatoid factor. (From Smolen JS, Landewé RBM, Bijlsma JWJ, et al. EULAR recommendations for the management of rheumatoid arthritis with synthetic and biological disease-modifying antirheumatic drugs: 2019 update. *Ann Rheum Dis*. 2020;79:685-699.)

However, standard-dose and high-dose biologic drugs (with or without traditional DMARDs) are associated with an increase in serious infections,[A6] especially tuberculosis (Chapter 299); pre-treatment screening for latent tuberculosis is mandatory. Biologic agents also should not be used in combination with each other because they significantly increase the risk of infections (see Chapter 29).

Targeted Synthetic Disease-Modifying Antirheumatic Drugs

Tofacitinib, given orally at a dose of 5 mg twice daily, is effective as initial DMARD therapy when combined with methotrexate in patients who have had incomplete responses to methotrexate or who have failed to improve with TNF inhibitors. The complete blood count and liver function tests should be monitored. Additional toxicity concerns include infections, including tuberculosis, malignancies, cardiovascular events, and reactivation of herpes zoster.

Baricitinib is effective in patients whose rheumatoid arthritis has not responded to a DMARD.[A7] Furthermore, baricitinib is better than placebo or adalimumab for patients who had inadequate response to methotrexate.[A8]

Emerging drugs that target distinct members of the JAK family include upadacitinib (15 mg daily), which is a relatively selective agent that is effective either as monotherapy or when added to other DMARDs,[A9] filgotinib (100 to 200 mg daily), which is similarly effective in patients who have an inadequate response to other DMARDs or are intolerant of them,[A10] and olokizumab, which is effective when added to methotrexate therapy.[A11]

The Order of Therapy in Rheumatoid Arthritis

The order of therapeutic choices for the treatment of rheumatoid arthritis continues to evolve (Fig. 243-11). DMARDs generally must be continued at their full dose to maintain their efficacy.[A12] Treatment is best individualized within these general guidelines by an experienced specialist.

Treatment of Underlying Conditions and Complications

Optimal care of patients with rheumatoid arthritis requires recognition of the associated comorbid conditions, including an increased risk for cardiovascular death, osteoporosis, infections (especially pneumonia), and certain cancers such as lymphomas and lung cancers.

Neck Complications

In patients with neck symptoms, neck flexion and extension films of the cervical spine should be obtained to look for significant subluxation.[20] Subluxation is often an indication for corrective surgery. When patients develop stridor as a result of severe involvement of the cricoarytenoid joint, emergent tracheotomy may be life-saving.

Felty Syndrome

Most patients with Felty syndrome do not require special therapy; instead, treatment directed toward their severe rheumatoid arthritis usually improves the white blood cell counts. If severe (<500 cells/μL) neutropenia (Chapter 153) is accompanied by recurrent bacterial infections or chronic, nonhealing leg ulcers, splenectomy may very rarely be indicated. In the presence of rheumatoid arthritis or Sjögren syndrome, large granular lymphocyte syndrome has a good prognosis, with the neutropenia often responding dramatically to therapies, particularly methotrexate.

Cardiovascular Disease

Cardiovascular disease accounts for much of the excess mortality in rheumatoid arthritis, probably because of an association between chronic inflammation and cardiovascular disease.[21] Methotrexate, tofacitinib, and TNF inhibitors can significantly decrease cardiovascular mortality, whereas tocilizumab and JAK inhibitors cause a rise in serum cholesterol levels. Patients with rheumatoid arthritis also should be aggressively treated for their cardiovascular risk factors (Chapters 39, 64, and 190).

Other Associated Diseases

Osteoporosis (Chapter 225) is common in patients with rheumatoid arthritis, and its early treatment results in long-term dividends. Patients with rheumatoid arthritis are at an increased risk for infections, and some forms of treatment further increase this risk.[22] Patients should be cautioned to seek early medical attention for even minor symptoms suggestive of infection, especially if receiving biologic therapy. All patients with rheumatoid arthritis should receive a pneumococcal vaccine, yearly influenza vaccinations (Chapter 15), and one of the zoster vaccinations.

Patients with rheumatoid arthritis have an increased risk for lymphoma. Occasionally, B-cell lymphomas (Chapter 171) are associated with immunosuppression and regress after immunosuppression is discontinued. Patients with rheumatoid arthritis have significantly decreased risk of developing colon cancer, probably because of chronic inhibition of COX by NSAIDs.

PROGNOSIS

Rheumatoid arthritis is not a benign disease and is not limited to the joints. Once established, it is a lifelong progressive disease that produces significant morbidity in most patients and premature mortality in many. With modern effective treatment, however, all-cause mortality in patients with rheumatoid arthritis is now similar to the general population. The aggressive use of disease-modifying agents and biologic agents, if needed, also is associated with substantial reductions in disability.

Patients who are rheumatoid factor– or anti-citrullinated protein antibody–positive and patients who are positive for the shared epitope have a worse prognosis, with more erosions and more extra-articular disease (see E-Table 243-1). The HLA-DRB1 locus, which is associated with disease susceptibility, may also be associated with radiologic severity, mortality, and treatment response. Once deformities are found on examination or erosions on radiography, the damage is largely irreversible. Erosions usually occur in the first 1 to 2 years, and the rate of radiographic damage can be reduced by early therapy.

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For the General References and other additional features, please visit Elsevier eBooks+ at https://ebooks.health.elsevier.com.

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244 SPONDYLOARTHRITIS

ROBERT D. INMAN AND PROTON RAHMAN

COMMON FEATURES OF SPONDYLOARTHRITIS

DEFINITION

Spondyloarthritis encompasses a group of clinical syndromes that are linked in terms of disease manifestations and genetic susceptibility. The clinical subsets most commonly recognized are ankylosing spondylitis, psoriatic arthritis, reactive arthritis, and enteropathic arthritis (Fig. 244-1). Broadly, spondyloarthritis is grouped into two subsets based on the location of predominantly affected joints: axial spondyloarthritis (dominated by back symptoms) and peripheral spondyloarthritis (dominated by peripheral joint symptoms). The Assessment of SpondyloArthritis international Society further classified axial spondyloarthritis into radiographic axial spondyloarthritis (commonly referred to as ankylosing spondylitis), in which structural damage is visible on plain radiographs of the sacroiliac joint, and nonradiographic axial spondyloarthritis, in which no structural damage to the sacroiliac joints is seen on plain radiographs.

EPIDEMIOLOGY AND PATHOBIOLOGY

Family studies note excessive clustering of the same disease entity among family members as well as common features among the distinct subsets. The impression from such studies is a shared common path of immunogenetic susceptibility, with further genetic and environmental influences that lead to characteristic clinical subsets. For example, enteropathic arthritis may occur in one family, whereas psoriatic arthritis may occur in another family.

Genetic Susceptibility

In genomic studies of families with spondyloarthritis, particularly ankylosing spondylitis and psoriatic arthritis, the strongest association is with HLA-B27.[1] About 90% of patients with ankylosing spondylitis are B27-positive, so to a certain extent it may be necessary but not sufficient for the disease. Magnetic resonance imaging (MRI) studies in asymptomatic B27-positive individuals indicate a much higher prevalence of sacroiliitis than previously recognized. Spondyloarthritis may be as common as rheumatoid arthritis.

The major histocompatibility complex (MHC), on the short arm of chromosome 6 in humans, is one of the most polymorphic regions of the human genome. This is particularly so for the B locus, which constitutes part of the class 1 MHC genes in this complex. More than 200 different alleles have been detected at this locus, of which B27 is just one. As with all HLA alleles, there is codominant expression of B locus genes, such that most individuals who are B27-positive are heterozygous for the B locus. There appears to be little clinical or prognostic significance associated with the less common homozygous B27 state.

It is clear that HLA is strongly associated with spondyloarthritis, yet the prevalence of HLA-B27 varies widely in different racial and ethnic clusters around the world. It is virtually absent in aboriginal populations in Australia, occurs in 1% of the population in Japan, in 7% in northern European countries and in North American White populations, and in 50% of some of the native tribes in western Canada.

Of the more than 30 subtypes of B27, HLA-B2705 is regarded as the primordial subtype, with variability developing over time on the basis of alterations in genomic DNA. Some subtypes, notably B2706 and B2709, do not seem to confer increased susceptibility to the development of ankylosing spondylitis. This observation has led to a search for arthritogenic peptides that are presented by the disease-associated subtypes such as B2705 and B2704, but not by the non–disease-associated subtypes. To date, no simple peptide-susceptibility relationship has been demonstrated.

Polymorphisms in the endoplasmic reticulum aminopeptidase-1 (*ERAP1*) gene on chromosome 5 are the second strongest genetic risk factor for ankylosing spondylitis after HLA-B27, and the association with ankylosing spondylitis and *ERAP1* is restricted to patients with HLA-B27+ ankylosing spondylitis, thereby suggesting a gene–gene interaction. ERAP plays a key role in trimming peptides in the endoplasmic reticulum before loading these peptide complexes onto a nascent class I MHC molecule. This finding continues to attribute a central role to MHC class I peptide presentation in the pathogenesis of ankylosing spondylitis.

Additional genetic markers outside the MHC region include the *IL-23R* gene on chromosome 1, which is associated with ankylosing spondylitis, inflammatory bowel disease, and psoriasis. Overall, more than 100 genes confer susceptibility to ankylosing spondylitis, but with the notable exception of HLA-B27, the odds ratio for each is modest.

At the level of joint histopathology, sites of chronic inflammation in rheumatoid arthritis are associated with erosions, but in spondyloarthritis, such sites are associated with new bone formation. This distinction suggests a fundamental difference in the cytokine profile in the microenvironment of the joint. Synovial histopathology in spondyloarthritis is characterized by abundant neutrophils, macrophages, and hypervascularity, whereas in rheumatoid arthritis, the prominent features are lymphoid aggregates, dendritic cells, lining cell hyperplasia, and citrullinated proteins. These differences suggest that spondyloarthritis reflects a fundamental alteration in innate immunity, whereas rheumatoid arthritis reflects dysregulation of adaptive immunity (Chapter 35).

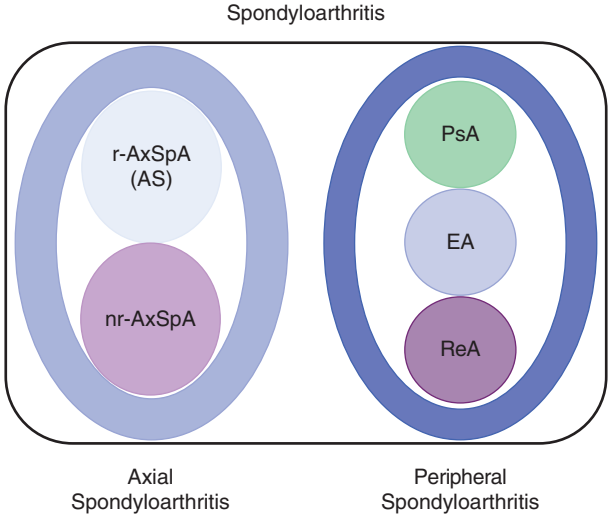

FIGURE 244-1. Schematic relationships among the different spondyloarthritis (SpA) subsets. Ankylosing spondylitis (AS), now referred to radiographic axial SpA, is considered the classic SpA, and nonradiographic axial SpA is the other subset that encompasses the essential features of axial SpA. Psoriatic arthritis (PsA), enteropathic arthritis (EA), and reactive arthritis (ReA) are a distinct subset of peripheral spondyloarthritis and share overlapping features with axial SpA. Many patients have clinical features of SpA but do not meet the diagnostic criteria for any of the five defined subsets and are termed peripheral spondyloarthritis.

CLINICAL MANIFESTATIONS

Common features among the clinical subsets of spondyloarthritis both link them with and distinguish them from rheumatoid arthritis (Chapter 243), which is the other major cause of chronic polyarthritis. Spondyloarthritis has a strong predilection for the spine, in particular the sacroiliac joints, with a tendency for new bone formation at sites of chronic inflammation to cause joint ankylosis. When peripheral arthritis occurs, it is commonly in the lower extremity and asymmetrical. There is a predilection for involvement at sites where tendon inserts into bone (entheses), so enthesitis is one of the most specific clinical manifestations of spondyloarthritis.

A predilection for ocular inflammation, particularly acute anterior uveitis, is a common feature of spondyloarthritis. Uveitis may occur in the same susceptible population of patients even in the absence of joint involvement. Finally, all spondyloarthritis subsets have an association with the class I HLA allele B27, with the strength of the association varying somewhat among them.

DIAGNOSIS

Classification criteria (Table 244-1) emphasize the common clinical features—namely, inflammatory spinal pain or asymmetrical lower extremity synovitis. To fulfill the criteria for axial spondyloarthritis, patients must have chronic back pain for at least 3 months and starting prior to age 45 years. Sacroiliitis confirmed by imaging is an important criterion, and it is referred to as radiographic axial spondyloarthritis when structural damage can be detected by plain radiographs. When active inflammation is detected only by MRI, it is referred to as non-radiographic axial spondyloarthritis. Nonradiographic axial spondyloarthritis can also be defined by the presence of the HLA-B27 allele and two additional features of spondyloarthritis.

ABSTRACT

Spondyloarthritis encompasses a group of clinical syndromes that are linked in terms of disease manifestations and genetic susceptibility. The common clinical subsets are ankylosing spondylitis, reactive arthritis, psoriatic arthritis, and enteropathic arthritis. Immune profiling has highlighted common pathways in cellular immunity in these conditions. Biologic therapies have improved the outlook for these patients, but curative therapies are still being sought.

KEYWORDS

spondyloarthritis
ankylosing spondylitis
psoriatic arthritis
reactive arthritis
enteropathic arthritis

Several distinct features differentiate spondyloarthritis from rheumatoid arthritis, the other main contributor to the differential diagnosis of chronic polyarthritis (Table 244-2). Imaging is often critical for making a diagnosis of axial spondyloarthritis or peripheral spondyloarthritis.[2,3] Useful clinical features include sex predilection, HLA association, pattern of joint involvement, and presence of rheumatoid factor, which becomes the serologic distinction between seropositive rheumatoid arthritis and seronegative spondyloarthritis.[4]

CLINICAL SUBSETS OF THE SPONDYLOARTHROPATHIES

Ankylosing Spondylitis

EPIDEMIOLOGY

Ankylosing spondylitis, now referred to as radiographic axial spondyloarthritis, is the most common inflammatory disorder of the axial skeleton. Ankylosing spondylitis occurs in about 0.2% of the general population, in about 2% of the B27-positive population, and in about 20% of B27-positive individuals with an affected family member.[5] The male-to-female ratio historically has ranged from 2.5 : 1 to 5 : 1, but recent epidemiologic studies suggest a lower ratio.

PATHOBIOLOGY

Molecular mimicry has been hypothesized in the pathogenesis of ankylosing spondylitis because of the degree of sequence homology between B27 and several candidate gram-negative enteric bacteria, but the significance of such homology remains unresolved. B27 is distinctive in its propensity to misfold in the endoplasmic reticulum, where it may induce a pro-inflammatory cascade called the unfolded protein response. Furthermore, B27 may have a distinct tendency to form heavy-chain homodimers at the cell surface.

TABLE 244-1 SPONDYLOARTHRITIS INTERNATIONAL SOCIETY CLASSIFICATION CRITERIA FOR AXIAL SPONDYLOARTHRITIS

A. Chronic back pain starting before age 45 years and persisting for >3 months
AND EITHER
B. Sacroiliitis on a plain radiograph (definite radiographic sacroiliitis according to modified New York criteria [see Table 244-3]) or on magnetic resonance imaging (active [acute] inflammation highly suggestive of sacroiliitis associated with spondyloarthritis) PLUS 1 other criterion
OR
C. HLA-B27 positivity PLUS 2 other criteria

OTHER CRITERIA

- Arthritis
- CRP level elevated
- Crohn disease/ulcerative colitis
- Dactylitis
- Enthesitis (heel)
- Family history of spondyloarthritis
- HLA-B27 positive
- Inflammatory back pain
- NSAIDs provide a good response
- Psoriasis

CRP = C-reactive protein; HLA = human leukocyte antigen; MRI = magnetic resonance imaging; NSAIDs = nonsteroidal anti-inflammatory drugs.

For full details see Rudwaleit M, van der Heijde D, Landewé R, et al. The development of Assessment of SpondyloArthritis international Society classification criteria for axial spondyloarthritis (part II): validation and final selection. *Ann Rheum Dis*. 2009;68:777-783.

B27 transgenic rats spontaneously develop pathology that is strikingly similar to human spondyloarthritis, so B27 itself may be the critical genetic factor in disease pathogenesis. These animals demonstrate pathology similar to that of Crohn disease in the gastrointestinal tract. Of interest, if such animals are raised in a germ-free environment, there is a marked reduction in joint disease, thereby implying a dynamic interrelationship between microbial triggers and background host genes.[6]

CLINICAL MANIFESTATIONS

Ankylosing spondylitis typically begins in young adulthood, but symptoms may arise in adolescence or earlier. Up to 15% of children with juvenile idiopathic arthritis are classified as having juvenile ankylosing spondylitis. During the adolescent years there is an increasing prevalence of radiographic sacroiliitis, with a significant proportion of patients manifesting this feature by the end of the teenage years. At the other end of the age spectrum, a small number of patients with late-onset ankylosing spondylitis may have sacroiliitis and oligoarthritis. The axial involvement and asymmetrical lower extremity involvement may serve to differentiate such patients from patients with late-onset rheumatoid arthritis, although there may be overlapping clinical features.

The classic manifestation of ankylosing spondylitis is the onset of low back pain that persists for more than 3 months, is accompanied by early-morning stiffness, and is typically improved by exercise but not by rest (Table 244-3). Some experts include a response to NSAID therapy as an additional feature that differentiates ankylosing spondylitis from mechanical low back pain. Back pain that awakens the patient from sleep is often a clue to inflammatory back pain that may have been misdiagnosed as the pain of degenerative disc disease (Chapter 369), which is a much more common cause of low back pain in the population at large.

The pain typically occurs in the region of the sacroiliac joints, with or without slight radiation to the buttock area. Midthoracic pain and cervical pain, particularly at night, are less common but strongly suggest inflammatory back pain when they occur. Fatigue is also a suggestive symptom and is often a major concern for the typical young male patient who has a high functional target in terms of sports and recreation. If the inflammation is inadequately controlled, stiffness may persist most of the day and progress to loss of mobility and flexibility.

TABLE 244-3 MODIFIED NEW YORK CRITERIA FOR ANKYLOSING SPONDYLITIS

CLINICAL CRITERIA
Low back pain and stiffness for >3 mo that improve with exercise but are not relieved by rest
Limitation of motion of the lumbar spine in both sagittal and frontal planes
Limitation of chest expansion
RADIOLOGIC CRITERIA
Sacroiliitis: grade ≥2 bilateral or grade 3 or 4 unilateral
GRADING
Definite AS if the radiologic criterion is associated with at least one clinical variable
Probable AS if:
The three clinical criteria are present
The radiologic criterion is present without the clinical criteria

AS = ankylosing spondylitis.

TABLE 244-2 DIFFERENTIAL DIAGNOSIS OF CHRONIC POLYARTHRITIS

FEATURE	RHEUMATOID ARTHRITIS	ANKYLOSING SPONDYLITIS	ENTEROPATHIC ARTHRITIS	PSORIATIC ARTHRITIS	REACTIVE ARTHRITIS
Male-female ratio	1 : 3	3 : 1	1 : 1	1 : 1	10 : 1
HLA association	DR4	B27	B27 (axial)	B27 (axial)	B27
Joint pattern	Symmetrical, peripheral	Axial	Axial and peripheral	Axial and asymmetrical, peripheral	Axial and asymmetrical, peripheral
Sacroiliac	Absent	Symmetrical	Symmetrical	Asymmetrical	Asymmetrical
Syndesmophyte	Absent	Smooth, marginal	Smooth, marginal	Coarse, nonmarginal	Coarse, nonmarginal
Eye	Scleritis	Iritis	+/−	+/-	Iritis and conjunctivitis
Skin	Vasculitis	Rare	Erythema nodosum	Psoriasis	Keratoderma
Rheumatoid factor	>80%	Rare	Rare	Rare	Rare

HLA = human leukocyte antigen.

Peripheral oligoarthritis is seen in up to 30% of patients with ankylosing spondylitis. Typically, it is an asymmetrical oligoarthritis with a predilection for the lower extremities. It is important to ask about concurrent or previous tendinitis (e.g., Achilles tendinitis) or heel pain (e.g., plantar fasciitis), because either may reflect an enthesitis (Chapter 242) that is part of the clinical picture. Involvement of the hip can occur at any point in the course of ankylosing spondylitis and can progress to joint destruction. On standing and walking, a hip flexion contracture may contribute to an increasing stoop that might otherwise be attributed to spinal involvement in the disease.

Ocular involvement may occur in up to 40% of ankylosing spondylitis patients, most typically acute anterior uveitis (iritis). The uveitis often manifests as a slight impairment in visual acuity, with accompanying photophobia and eye pain. Typically, it is unilateral and recurrent. Inflammatory bowel disease (Chapter 127) and psoriasis (Chapter 405) occur in approximately 10% of patients with ankylosing spondylitis. Less common manifestations include aortic insufficiency (Chapter 60), cardiac conduction defects (Chapter 51), and apical pulmonary fibrosis (Chapter 80).

DIAGNOSIS

Physical Examination

Physical examination of the spine characteristically indicates restricted movement, which in the early stages may partly reflect paraspinal muscle spasm but later in the course reflects ankylosis of the zygapophyseal joints and syndesmophyte bridging of the vertebral bodies.[7] Changes in cervical mobility can be measured as the occiput-to-wall distance, with the patient's heels against the wall as the patient attempts to touch the back of the head to the wall. Thoracic involvement is measured in chest expansion, with the chest circumference at maximal inspiration being more than 5 cm greater than the circumference at maximal expiration. In the lumbar spine, forward flexion is restricted and can be monitored by the Schober test. This test is used to measure mobility in the lower part of the back: with the patient standing upright, a 10-cm span is marked from the fifth lumbar vertebra upward. On maximal forward flexion, the distance between the marks is remeasured. With normal spinal mobility, the flexed distance should register as 15 cm or an increment of 5 cm. Restricted spinal mobility early in the course of the disease may best be detected by lateral spinal flexion, measured as the difference in the finger-to-floor distance when standing erect compared with maximal bending to the side. Inflammation in the sacroiliac joint may be reflected by joint line tenderness to direct pressure or by the FABERE test (for Flexion, ABduction, External Rotation, and Extension) or Gaenslen maneuver. In the former, the patient lies supine while the examiner flexes and externally rotates the hip. In the latter, the examiner extends the hip by letting the leg dangle off the side of the examining table. In both cases, stress is placed on the sacroiliac joint and may reproduce the back pain if it derives from this site.

Laboratory Findings

Laboratory tests in the evaluation of inflammatory back pain are relatively nonspecific. The ESR and CRP are typically elevated, but normal levels do not exclude inflammatory back pain, and the degree of elevation is typically less than would be seen in active rheumatoid arthritis. Anemia of chronic disease may be observed if the condition is long-standing. HLA-B27 is rarely the definitive factor for diagnosis, but the test has reasonably high sensitivity and specificity in the setting of characteristic back symptoms.

Imaging

Radiographic assessment is important to confirm the diagnosis, but no radiographic changes may be seen in the sacroiliac joints early in the course of disease. If the clinician has a high index of suspicion, MRI may improve the sensitivity of the plain radiograph because inflammatory changes on MRI predate radiographic changes. A routine anteroposterior pelvic radiograph is generally the standard diagnostic radiograph, and the classic findings are bilateral changes in the sacroiliac joints (Fig. 244-2). Abnormalities include erosions in the joint line, pseudowidening, subchondral sclerosis, and, finally, ankylosis that reflects complete bony replacement of the sacroiliac joints.

Radiographs of the spine may reveal squaring of the vertebral bodies (loss of the normal anterior concavity of the lumbar vertebra) and "shiny corners" (subchondral sclerosis at the upper edge of the vertebral body), both of which are manifestations of enthesitis. Syndesmophytes, which represent marginal bridging of the vertebrae (Figs. 244-3 and 244-4), eventually develop and make the diagnosis clear. Because ankylosis of the apophyseal joints may occur without syndesmophyte formation, it is important to assess the posterior joints on lateral views of the lumbosacral spine, as well as the anterior margin of the vertebrae. Eventually, the changes may result in a "bamboo spine," so called because the bridging syndesmophytes can mimic the appearance of bamboo.

Differential Diagnosis

The differential diagnosis of ankylosing spondylitis includes osteitis condensans ilii; diffuse idiopathic skeletal hyperostosis (DISH; Chapter 238); the syndrome of synovitis, acne, pustulosis, hyperostosis, and osteomyelitis (SAPHO); and some induced hyperostotic states (e.g., vitamin A intoxication, fluorosis). New bone formation occurs in degenerative disc disease, but the bulky horizontal appearance of osteophytes is usually easily distinguished from that of syndesmophytes, and narrowing of the disc space is not a feature of ankylosing spondylitis. Osteoarthritis of the sacroiliac joint is more common than previously appreciated.

REACTIVE ARTHRITIS

DEFINITION AND EPIDEMIOLOGY

Reactive arthritis is an aseptic arthritis that occurs subsequent to an extra-articular infection, most typically of the gastrointestinal or genitourinary tract.[8] Typically, the onset of arthritis occurs 1 to 3 weeks after the gastrointestinal

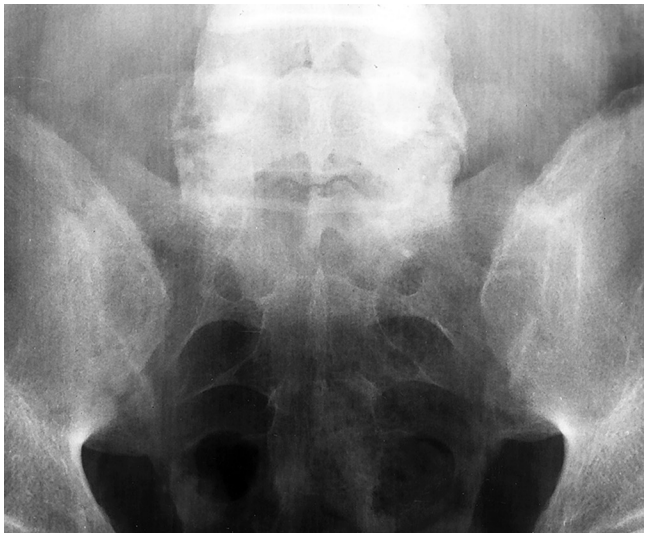

FIGURE 244-2. Bilaterally symmetrical sacroiliitis in ankylosing spondylitis.

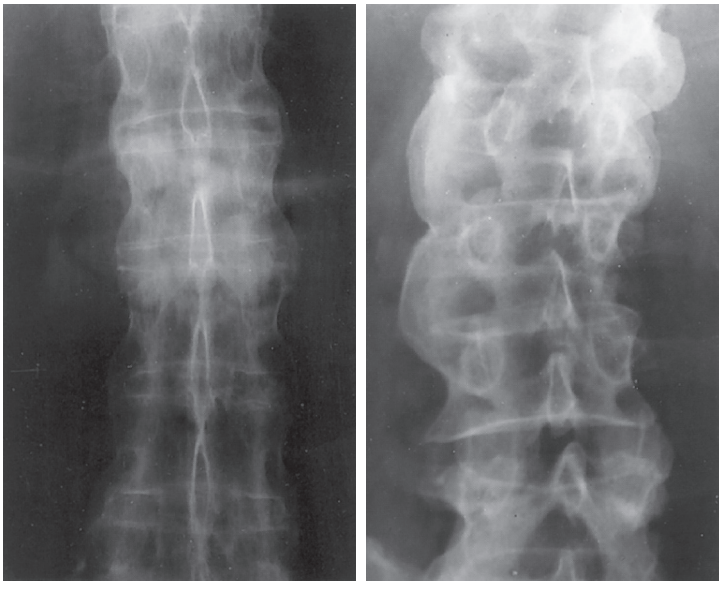

FIGURE 244-3. Lumbar spondylitis. *Left*, Lumbar spondylitis in ankylosing spondylitis, with symmetrical marginal bridging syndesmophytes and calcification of the spinal ligament. *Right*, The bulky, nonmarginal, asymmetrical syndesmophytes of reactive arthritis with lumbar spondylitis.

FIGURE 244-4. A 34-year-old man who has had ankylosing spondylitis for 9 years and neck pain. Radiographs demonstrate narrowing of the C2-C3 apophyseal joints posteriorly and anterior bridging marginal syndesmophytes extending from C2-C5.

FIGURE 244-5. Keratoderma blennorrhagicum of the feet in reactive arthritis.

or genitourinary infection, but the temporal details are often difficult to define precisely.

In the gastrointestinal tract, the key pathogens are *Salmonella typhimurium*, *Yersinia enterocolitica*, *Shigella flexneri*, and *Campylobacter jejuni*. In the genitourinary tract, *Chlamydia trachomatis* is the most common offender.

The true incidence and prevalence of reactive arthritis are not well defined. In epidemics involving *Salmonella* (Chapter 284) or *Yersinia* (Chapter 288), reactive arthritis develops in 2 to 7% of infected individuals but in as many as 20% of B27-positive infected individuals. In such epidemic studies, B27 confers risk not only for the onset of arthritis but also for axial involvement and chronicity. Genetic variants in toll-like receptor 2 (TLR-2) implicate host innate immunity as central in reactive arthritis.

PATHOBIOLOGY

Although immunofluorescence studies have identified bacterial antigens in the joints of patients with reactive arthritis after both gastrointestinal and genitourinary infections, results of polymerase chain reaction studies on synovial tissues have most consistently been positive in post-*Chlamydia* reactive arthritis, thereby suggesting that viable *Chlamydia* may persist in the joints of such patients, albeit in a metabolically altered state. Dactylitis is the net result of inflammatory changes affecting the joint capsule, entheses, periarticular structures, and periosteal bone.

Although the definition of aseptic arthritis after an extra-articular infection may include a broader range of pathogens (e.g., *Chlamydia pneumoniae*), sites of infection (e.g., streptococcal pharyngitis), and types of infections (e.g., *Giardia* infections of the GI tract), these clinical scenarios have not generally been included in the category of reactive arthritis. These postinfectious syndromes lack the other associated clinical features of spondyloarthritis and they lack an association with B27.

CLINICAL MANIFESTATIONS

The pattern of joint involvement in reactive arthritis is one of asymmetrical oligoarthritis with a predilection for the lower extremity, a pattern shared by most spondyloarthritis syndromes. Enthesitis may present as Achilles tendinitis or plantar fasciitis. Dactylitis, appearing as a sausage digit, may also be seen. Sacroiliitis may be seen in the acute phase, but radiographic changes are seen largely in patients with a more chronic course.

Reactive arthritis can be accompanied by extra-articular features such as urethritis, conjunctivitis, or mucocutaneous lesions. The urethritis may manifest as dysuria or discharge, and the rash as circinate balanitis, which appears as vesicles or shallow ulcerations on the glans penis. Painless lingual or oral ulcerations may also be seen. The fact that the cervicitis may be less symptomatic could partially account for the underdiagnosis in women. The classic skin manifestation of reactive arthritis is keratoderma blennorrhagicum, a painless papulosquamous eruption on the palms or soles (Fig. 244-5). Occasionally, nail dystrophy with pitting and onycholysis or subungual keratosis can be seen. The conjunctivitis can be bilateral and painful; in contrast, the acute anterior uveitis that can also be seen in this setting tends to be less painful and unilateral.

DIAGNOSIS

Radiographic changes of reactive arthritis can be seen in the involved peripheral joints, with early findings consisting of soft tissue swelling and juxta-articular osteopenia. Areas of periostitis and new bone formation may develop in peripheral joints. When changes in the sacroiliac joints are seen, they are typically asymmetrical (Fig. 244-6), in contrast to the symmetrical pattern seen in ankylosing spondylitis. In the chronic phase, syndesmophytes may develop, but they are bulky, nonmarginal, and often asymmetrical formations that differ from the classic syndesmophytes of ankylosing spondylitis. The frequency with which reactive arthritis evolves into bona fide ankylosing spondylitis has not been determined definitively.

The most important differential diagnosis for reactive arthropathies is septic arthritis (Chapter 251). Both *Yersinia* (Chapter 288) and *Salmonella* (Chapter 284) can cause septic arthritis, so an appropriate culture of synovial fluid should precede the diagnosis of reactive arthritis whenever possible.

REACTIVE ARTHRITIS AND HUMAN IMMUNODEFICIENCY VIRUS

An aggressive form of spondyloarthritis may be seen in patients who are concomitantly infected with HIV (Chapter 359). The frequency of reactive arthritis is not increased in patients with HIV, but HIV may alter the course of these arthropathies, with a tendency for a more aggressive and more refractory joint disease. Aggressive skin and joint disease may be seen in patients in whom psoriatic arthritis develops in the setting of HIV infection. Most North American patients with the HIV-reactive arthritis constellation are B27 positive, but studies of comparable patients in Africa have found a sizable B27-negative component in such patients. The arthritis in these patients falls into two clinical patterns: (1) an additive, asymmetrical polyarthritis or (2) an intermittent oligoarthritis that most commonly affects the lower extremities. Enthesitis, fasciitis, conjunctivitis, and urethritis can all be seen in such patients. Sacroiliitis can occur, although extensive spinal syndesmophyte formation is not common.

ENTEROPATHIC ARTHRITIS

EPIDEMIOLOGY

Enteropathic arthritis refers to the arthritis associated with Crohn disease or ulcerative colitis (Chapter 127; Table 244-4).[9] All extra-enteric manifestations, including arthritis, occur more commonly in Crohn disease than in ulcerative colitis. Peripheral arthritis occurs in 10 to 20% of patients with Crohn disease and in 2 to 7% of patients with ulcerative colitis. Axial disease occurs in 2 to

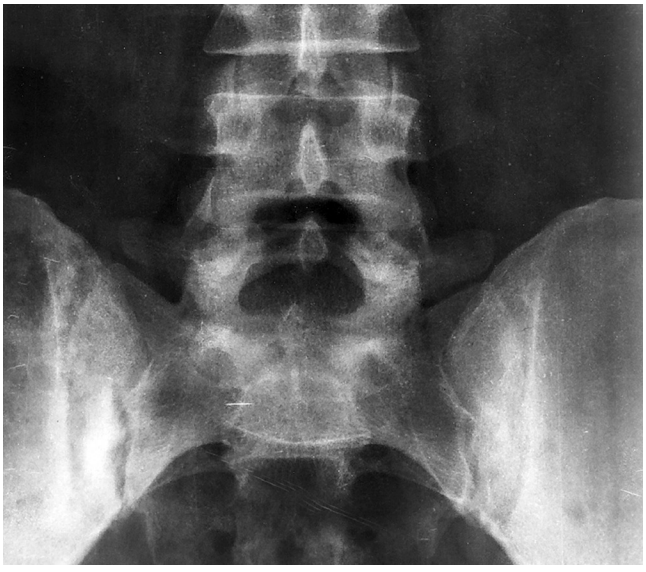

FIGURE 244-6. Bilaterally asymmetrical sacroiliitis in reactive arthritis. Erosions, pseudowidening, and ileal sclerosis are present.

TABLE 244-4 ENTEROPATHIC ARTHRITIS

FEATURE	PERIPHERAL ARTHRITIS	SACROILIITIS, SPONDYLITIS
CROHN DISEASE		
Frequency in Crohn disease	10-20%	2-7%
HLA-B27 associated	No	Yes
Pattern	Transient, symmetrical	Chronic
Course	Related to activity of Crohn disease	Unrelated to activity of Crohn disease
Effect of surgery	Remission of arthritis uncommon	No effect
Effect of anti-TNF therapy	Effective	Effective
ULCERATIVE COLITIS		
Frequency in ulcerative colitis	5-10%	2-7%
HLA-B27 associated	No	Yes
Pattern	Transient	Chronic
Course	More common in pancolitis than proctitis; related to activity of ulcerative colitis	Unrelated
Effect of surgery	Remission of arthritis	No effect

HLA = human leukocyte antigen; TNF = tumor necrosis factor.

7% of patients with either Crohn disease or ulcerative colitis. HLA-B27 is found in 50% of patients with axial arthritis.

PATHOBIOLOGY

The association of bowel inflammation and arthritis is supported by ileocolonoscopic studies in which subclinical inflammation of the bowel has been demonstrated in diseases covering the entire spectrum of spondyloarthritis. Histologic evaluation demonstrates that changes of acute ileitis are seen in postdysenteric reactive arthritis, whereas chronic inflammatory changes are more likely to be seen in patients with ankylosing spondylitis. Altered bowel permeability, with enhanced bacteremia or antigenemia, may provide the link in both cases.[10]

CLINICAL MANIFESTATIONS

Peripheral arthritis occurs more commonly in patients who have other extra-enteric features (e.g., erythema nodosum, iritis).[11] It is typically an inflammatory nonerosive polyarthritis, predominantly of large joints. In general, the clinical activity of the peripheral arthritis parallels the activity of the gut inflammation. The peripheral arthritis of enteropathic arthritis is not associated with B27. In contrast, the sacroiliitis or spondylitis of enteropathic arthritis follows a pattern in which the joint inflammation waxes and wanes independently of the bowel inflammation.

DIAGNOSIS

The musculoskeletal features of enteropathic arthritis may precede any gastrointestinal symptoms or signs. Conversely, the diarrhea preceding the onset of peripheral or axial arthritis in a young patient is just as likely to represent a food-borne pathogen (e.g., *Salmonella*, *Yersinia*) with secondary reactive arthritis as it is to represent inflammatory bowel disease with accompanying enteropathic arthritis. In the initial assessment of such a patient, it is important to perform careful and complete stool cultures. If the gastrointestinal symptoms persist, diagnostic colonoscopy is often required to resolve the diagnosis.

PSORIATIC ARTHRITIS

EPIDEMIOLOGY

One in four patients with psoriasis (Chapter 405) also has psoriatic arthritis.[12] Although most cases arise in patients with established cutaneous disease, some patients (particularly children) have arthritis that antedates the appearance of the skin lesions. Although the extent of psoriatic skin disease correlates poorly with the development of arthritis, the risk for psoriatic arthritis increases with a family history of psoriasis. The age at onset can range from 30 to 55 years, with an equal predilection for psoriatic arthritis in women and men. Psoriatic spondylitis has a slight male preponderance. Large prospective studies also suggest that obesity is a significant risk factor for psoriatic arthritis.

PATHOBIOLOGY

The genetic associations with psoriatic arthritis are complex. Psoriasis itself is associated with several HLA loci; some B alleles have been reported, but the dominant element is HLA-Cw6. HLA-B39 and HLA-B27 have been associated with sacroiliitis and axial involvement. No etiologic agent has been documented in psoriatic arthritis. The histopathology of the synovitis of psoriatic arthritis is comparable to that of the other forms of spondyloarthritis, with the absence of the local production of immunoglobulin and rheumatoid factor differentiating this disease from rheumatoid arthritis.[13]

CLINICAL MANIFESTATIONS AND DIAGNOSIS

The two most common forms of psoriatic arthritis are asymmetrical oligoarthritis that usually involves both large and small joints and a symmetrical polyarthritis that mimics rheumatoid arthritis, except for the absence of rheumatoid factor.[14] A third subset of psoriatic arthritis has selective targeting of the distal interphalangeal joints. Arthritis is often associated with nail onycholysis, subungual keratosis, pitting, and oil drop–like staining (Fig. 244-7). The fourth clinical subset is psoriatic spondylitis, which usually occurs in conjunction with peripheral arthritis but can be the sole manifestation in 2 to 4% of patients with psoriatic arthritis.[15] Approximately 30 to 50% of patients with psoriatic arthritis are B27 positive. Finally, arthritis mutilans (less than 5% of patients) is a destructive, erosive arthritis that affects large and small joints and is usually associated with marked deformities and significant disability. Dactylitis, with sausage-like digits, can be seen in up to 40% to 50% of patients and is associated with more severe radiographic joint damage (Fig. 244-8).[16] Enthesitis occurs in 30 to 50% of patients with psoriatic arthritis, with the most common sites being the Achilles tendon and plantar fascia.

Radiology

Radiographic changes in psoriatic arthritis involve soft tissue swelling (particularly in the case of dactylitis), erosions, and periostitis. Axial involvement may lead to the appearance of asymmetrical sacroiliitis with syndesmophytes that are bulky, asymmetrical, and nonmarginal. The classic "pencil-in-cup" deformity may be seen in patients with distal interphalangeal joint disease or arthritis mutilans. Acro-osteolysis is noted in a minority of patients and reflects an aggressive erosive process.

Differential Diagnosis

The diagnosis of psoriatic arthritis depends on finding the typical skin or nail changes (Chapter 405) in association with one of the articular variants described previously. The differential diagnosis for the skin lesions can include seborrheic dermatitis, dyshidrotic eczema, fungal infection, keratoderma blennorrhagicum, and palmoplantar pustulosis.

FIGURE 244-7. Nail pitting in psoriasis. The pits are more discrete and regular compared with pits affecting the nail plate in dermatitis.

FIGURE 244-8. Dactylitis in psoriatic arthritis. Dactylitis in the first and second digits as seen in this patient with psoriatic arthritis is generally associated with more severe disease.

PERIPHERAL SPONDYLOARTHRITIS

Despite careful clinical and radiographic assessment, a substantial number of patients do not fall into one of the classic diagnostic subsets of spondyloarthritis. These patients are often defined as having peripheral spondyloarthritis with peripheral enthesitis, asymmetrical arthritis or sacroiliitis, or iritis in the absence of identifiable antecedent infection or concurrent inflammatory bowel disease or psoriasis.

TREATMENT

General Measures

Spondyloarthritis necessitates a global approach to management in which education of patients is the cornerstone. Because the typical onset is during young adulthood, patients may experience significant frustration or depression if their acute arthritis evolves into a chronic disease that significantly impairs their functional capabilities and quality of life. A clinician managing patients with spondyloarthritis should be aware that these psychosocial aspects are an important part of the burden of illness. Similarly, there may be important implications for the workplace, particularly if a job demands significant bending or twisting.

Exercise is an important part of the treatment plan for patients with ankylosing spondylitis. Generally, high-impact sports should be avoided, whereas water therapy and swimming are ideal. Stretching to maintain mobility and maintenance of posture should be emphasized, and an experienced physiotherapist can greatly assist in instructing patients in daily exercises. Long car trips and air travel should include periodic stretching. Sleep position should emphasize a straight back position rather than one curled on the side. Deep breathing exercises and avoidance of smoking should be stressed.

Medications

Nonsteroidal Anti-Inflammatory Drugs

In general, joint inflammation in spondyloarthritis improves significantly with the use of nonsteroidal anti-inflammatory drugs (NSAIDs; Table 26-4). Indomethacin and diclofenac (up to 150 mg/day in divided doses) or naproxen (up to 1000 mg/day in divided doses) are generally well tolerated in this population.[A1] These agents must be used with caution in enteropathic arthritis because of concern about exacerbating possible underlying inflammatory bowel disease. For patients with axial spondyloarthritis, the goal with anti-inflammatory treatment is to achieve sufficient relief of pain and stiffness to allow an active, sustained program of exercise and physical activity that maintains posture and improves quality of life.

Biologic Therapies

Biologic agents such as monoclonal antibodies to TNF-α (infliximab, 5 mg/kg IV at 0, 2, and 6 weeks, then every 8 weeks; adalimumab, 40 mg subcutaneously every 2 weeks; golimumab, 50 mg subcutaneously every 4 weeks; and certolizumab, 400 mg subcutaneously at 0, 2, and 4 weeks, then 200 mg every 2 weeks or 400 mg every 4 weeks) or the soluble TNF receptor (etanercept, 50 mg subcutaneously weekly) are effective for the treatment of spondyloarthritis.[A2] Other FDA-approved alternatives include the interleukin[IL]-17A inhibitors secukinumab (150 mg subcutaneously weekly for 5 weeks, then 150 mg subcutaneously every 4 weeks) and ixekizumab (80 mg subcutaneously every 2 or 4 weeks), each of which significantly reduces the signs of ankylosing spondylitis.[A3–A6] The oral Janus kinase inhibitors (upadacitinib, 15 mg daily, and tofacitinib, 5 mg orally twice weekly) are another promising potential option for axial spondyloarthritis.[A7,A8] These therapies result in a prompt improvement in clinical measures, in laboratory indicators of inflammation, and in MRI evaluations of the sacroiliac joints and spine.

These biologic agents have been well tolerated, with an acceptable side effect profile,[17,18] but patients appear to relapse when treatment is discontinued.[A9] For instance, in patients whose active nonradiographic axial spondyloarthritis goes into sustained remission with adalimumab, continued therapy reduces subsequent flares compared with withdrawing treatment.[A10] Experience with longer-term treatment with TNF and IL-17A inhibitors have been encouraging with regard to the persistence of the clinical therapeutic effect, the ability to retard radiographic progression, and the infrequency of late adverse events.

Corticosteroids

The response to the intra-articular injection of steroids in the peripheral joints of patients with spondyloarthritis is often neither as dramatic nor as sustained as in those with rheumatoid arthritis. Corticosteroid injection into the sacroiliac joints, usually performed under imaging guidance (fluoroscopy or computed tomography [CT]), can result in a good response in 80% of patients, with improvement persisting for many months. Topical steroids are usually effective for the treatment of the mucous membrane and skin manifestations of reactive arthritis and psoriasis. For uveitis (Chapter 391), topical corticosteroid eye drops are an integral component of management, and treatment should be monitored jointly with an ophthalmologist.[19] Systemic corticosteroids (either orally or via an intravenous bolus protocol) are not generally recommended but have been used for severe symptomatic flares, despite few controlled trials to validate their effectiveness. The goal should be prompt tapering of the dose when symptomatic control is achieved. The recognition that osteoporosis (Chapter 225) is a significant problem in axial spondyloarthritis provides further impetus to use corticosteroids sparingly.

Other Drugs

Sulfasalazine

In patients with ankylosing spondylitis, psoriatic arthritis, and reactive arthritis, sulfasalazine (2 g/day) improves peripheral arthritis but not axial diseases compared with placebo, mostly in patients with psoriatic arthritis. For ankylosing spondylitis, etanercept is superior to sulfasalazine with respect to symptomatic improvement as well as MRI evidence of inflammation.

Methotrexate

In patients with spondyloarthritis, methotrexate has shown benefit for peripheral joint disease but not for the spinal inflammation characteristic of ankylosing spondylitis. Methotrexate does not change the course of axial involvement in ankylosing spondylitis and has not provided robust long-term benefit.

Antibiotic Therapy

It is sound clinical practice to treat any culture-proven chlamydial urethritis (Chapter 294) in conjunction with treatment of the sexual partner. For this indication, a single 1-g dose of azithromycin is as effective as doxycycline 100 mg twice a day for 7 days. The role of antibiotics in the management of reactive arthritis has been controversial, but either rifampin (300 mg orally daily) plus azithromycin (500 mg orally daily for 5 days, then 500 mg weekly) or rifampin (300 mg orally daily) plus doxycycline (100 mg orally twice daily) therapy for 6 months may be useful for *Chlamydia*-induced reactive arthritis.

Approach to Specific Spondyloarthropathies

For each form of spondyloarthritis, consensus guidelines from the American College of Rheumatology/Spondylitis Association of America/Spondyloarthritis Research and Treatment Network can help guide medical therapy (Fig. 244-9).[20–22]

Psoriatic Arthritis

As a general approach, nonsteroidal anti-inflammatory drugs are recommended to relieve musculoskeletal signs and symptoms in psoriatic arthritis.[23] The presence of concomitant extra-articular features should be considered when selecting a therapeutic agent. Patients who have failed an advanced therapeutic agent can be switched to another agent in the same class or can switch to an agent with a different mechanism of action.

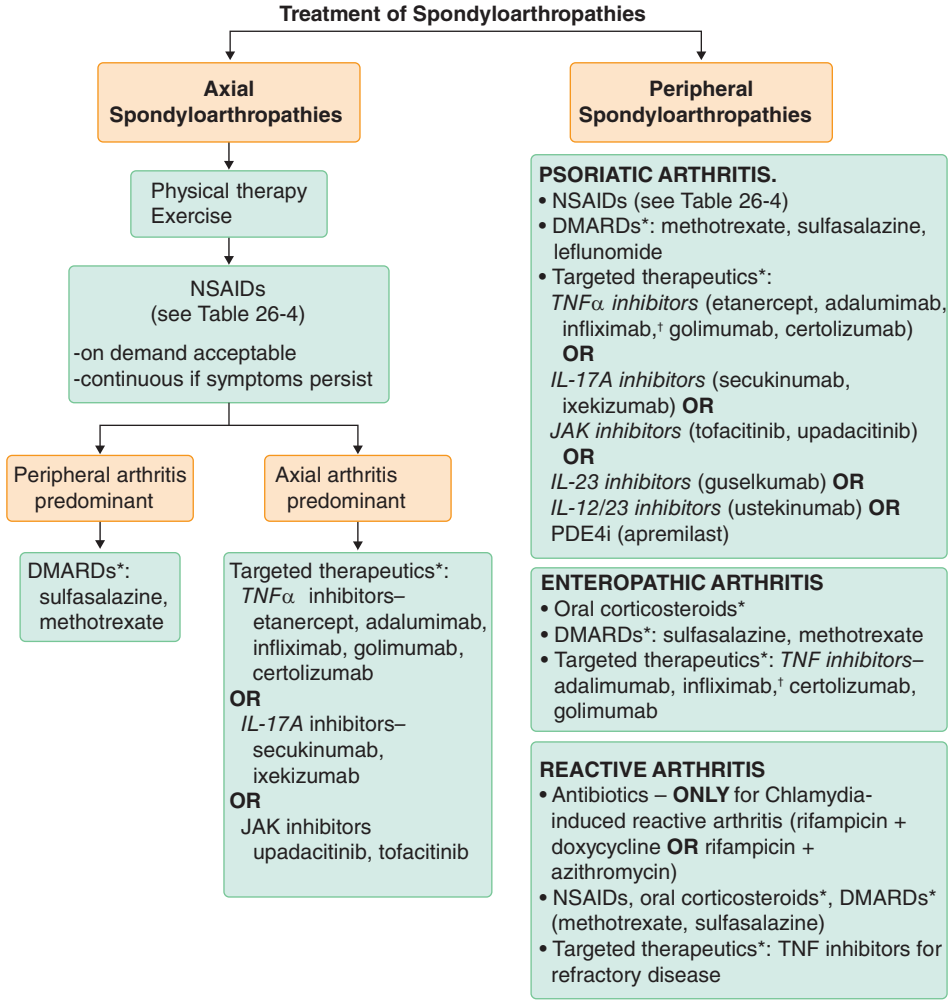

FIGURE 244-9. Treatment recommendations for the spondyloarthropathies. *See text for drug doses. †6 weeks for ankylosing spondylitis; 8 weeks for psoriatic arthritis. DMARDs = disease-modifying antirheumatic drugs; IL = interleukin; JAK = Janus kinase; NSAIDs = nonsteroidal anti-inflammatory drugs; TNF = tumor necrosis factor. (Adapted from Ward MM, Deodhar A, Gensler LS, et al. 2019 update of the American College of Rheumatology/Spondylitis Association of America/Spondyloarthritis Research and Treatment Network: recommendations for the treatment of ankylosing spondylitis and nonradiographic axial spondyloarthritis. *Arthritis Rheumatol*. 2019;71:1599-1613.)

Treatment with disease-modifying drugs (e.g., methotrexate, sulfasalazine, or leflunomide) is recommended in patients with swollen joints, structural damage in the presence of inflammation, or clinically relevant extra-articular manifestations. Tight control of inflammation using a treat-to-target approach significantly improves outcomes.[A11] Patients with mild psoriasis typically receive topical corticosteroids, whereas patients with moderate to severe psoriasis are treated with systemic therapies (Chapter 405). The anti-TNF agents, infliximab, etanercept, adalimumab, and golimumab are efficacious.[A12] Interleukin-17A monoclonal antibodies (secukinumab and ixekizumab) are also highly effective treatments for psoriatic arthritis.[A13,A14] The doses and frequency of administration for these biologics are generally similar to those used for axial spondyloarthritis. Other FDA-approved therapies include a monoclonal antibody against interleukin-12/23 (ustekinumab, 45 mg subcutaneously at 0 and 4 weeks, then every 3 months), oral Janus kinase inhibitors (tofacitinib, 5 mg twice daily, and upadacitinib, 15 mg once daily),[A15,A16] and a monoclonal antibody against the P19 subunit of interleukin-23 (guselkumab, 100 mg subcutaneously at 0 and 4 weeks, and then every 8 weeks).[A17,A18] These therapies inhibit the progression of structural damage, with continued clinical efficacy and acceptable safety. Apremilast is an oral phosphodiesterase-4 inhibitor (30 mg orally twice daily) that improves only signs and symptoms of psoriatic arthritis and with less benefit than with the biologic agents.

Reactive Arthritis

The treatment of reactive arthritis begins with therapy of the triggering infection. For example, in patients who are PCR-positive either in blood or joint fluid for *C. trachomatis* or *C. pneumonia*, a 6-month course of combination therapy with rifampicin (300 mg/day) plus either doxycycline (100 mg twice daily) or azithromycin (500 mg twice daily for 5 days followed by 500 mg once a week) yields a response in 65% of patients (compared with about 20% with placebo), and complete remission is observed in 20% (compared with 0% with placebo). For reactive arthritis, NSAIDs and glucocorticoid injections are effective. In more severe cases, sulfasalazine is often effective if started in the first 3 months.

Biologic therapies are often used in chronic HLA-B27 positive spondyloarthritis, although their efficacy is unproven, especially since about 50% of patients recover within about 6 months.

Enteropathic Arthritis

For enteropathic arthritis, sulfasalazine is more helpful in ulcerative colitis than in Crohn disease (Chapter 127), whereas the opposite is generally true for methotrexate. TNF-α inhibitors (see Fig. 244-9) are effective in spondyloarthritis related to both ulcerative colitis and Crohn disease. A multidisciplinary approach can improve the management of rheumatic disease in patients with inflammatory bowel disease, thereby allowing more comprehensive care.

PROGNOSIS

Patients are typically concerned about their prognosis, because spondyloarthritis often occurs in young, active individuals for whom physical activity is a priority.

Ankylosing Spondylitis

The clinical course and severity of ankylosing spondylitis are highly variable. Inflammatory back pain and stiffness dominate the picture in the early stages, whereas chronic pain and deformity may develop over time. In both its early and late phases, the disease may have a significant impact on work disability and quality of life. The strongest predictor of new syndesmophyte formation is the presence of syndesmophytes at baseline. In ankylosing spondylitis patients in whom new, refractory spinal pain develops, an intervertebral fracture can occur after only minimal trauma.

Osteoporosis (Chapter 225) is a significant consequence of ankylosing spondylitis, probably reflecting both the local chronic inflammation and the

abnormal biomechanical loading of the vertebrae as the disease progresses. Additional late complications may include cauda equina syndrome, osteoporotic compression fractures, spondylodiscitis, and restrictive lung disease.

Reactive Arthritis

The course of reactive arthritis is variable, and few prognostic markers are available for the clinician to predict the course in an individual case. However, the majority of patients have an initial episode lasting 2 to 3 months, but synovitis may persist for a year or longer. In one follow-up of a point source cohort of post-*Salmonella* reactive arthritis, 20% of patients had ongoing inflammatory joint disease, and some degree of functional disability was observed in 30% of patients 5 years after the onset of disease.

Enteropathic Arthritis

For peripheral arthritis, measures that control the gastrointestinal disease usually control the joint disease as well. In contrast, the course of enteropathic spondylitis or sacroiliitis tends to be chronic.

Psoriatic Arthritis

Aggressive osteolysis, fibrous ankylosis, and heterotopic new bone formation can occur in psoriatic arthritis. The coexistence of HIV and psoriatic arthritis seems to set the stage for an aggressive course of joint destruction in some patients. Patients with psoriatic arthritis can experience substantial physical impairment.[24]

Peripheral Spondyloarthritis

The natural history of peripheral spondyloarthritis has not been well defined. A number of patients may eventually meet the diagnostic criteria for axial spondyloarthritis, but many retain a distinct undifferentiated spondyloarthritis pattern for prolonged periods. The variability in prognosis for the large group of patients falling into the peripheral spondyloarthritis group is perplexing. No characteristics are reliable predictors of progression in patients with this heterogeneous cluster of articular and extra-articular features.

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For the General References and other additional features, please visit Elsevier eBooks+ at https://ebooks.health.elsevier.com.

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245 SYSTEMIC LUPUS ERYTHEMATOSUS

MARY K. CROW

DEFINITION

Systemic lupus erythematosus (SLE) is a multisystem autoimmune disease that results from immune system–mediated tissue damage. The molecular triggers of the disease are not known, but the pathogenesis involves the production of autoantibodies specific for nucleic acids and nucleic acid–binding proteins. Immune complexes, along with immune system cells and soluble mediators, generate inflammation and tissue damage. Manifestations of SLE can involve the skin, joints, kidney, central nervous system (CNS), cardiovascular system, serosal membranes, and hematologic and immune systems. The disease is highly heterogeneous, with individual patients manifesting variable combinations of clinical features. In most patients with SLE, the disease is characterized by a waxing and waning clinical course, although some patients demonstrate a pattern of chronic activity. Therapeutic approaches generally involve immunosuppression, although promising biologic agents targeting specific molecular mechanisms are in development.

EPIDEMIOLOGY

A notable feature of SLE is that it occurs much more frequently in females than in males. As in Hashimoto thyroiditis and Sjögren syndrome, the female-to-male ratio is approximately 9 : 1 in adults, and most cases are diagnosed between the ages of 15 and 44 years. In children and patients older than age 55 years, the ratio is closer to 2 : 1. The prevalence of SLE in the United States is estimated to be approximately 72.8 per 100,000, and the incidence of new cases is about 5.1 per 100,000 per year.[1,2] The prevalence, severity, and characteristics of disease differ in different ethnic groups, with SLE being three- to four-fold more prevalent in Black, American Indian, and Native Alaskan women than in White women. Asians also have a higher incidence of disease than Whites. The severity of disease, based on standardized mortality ratios, is greatest among Asians and Hispanics, although the highest percent mortality is among Blacks.[3] Studies of lupus in minority populations indicate that socioeconomic factors are major contributors to the increased prevalence and severity of disease in Blacks and Hispanic Americans.

PATHOBIOLOGY

Current understanding of lupus pathogenesis incorporates roles for genetic susceptibility based on a cumulative hit model involving multiple genes, environmental triggers (e.g., the endogenous microbiome or virome, microbial infection, sunlight), certain drugs,[4] and altered immune system function.[5] Studies of immunology, genetics, and epigenetics have focused attention on the mechanisms of nucleic acid sensing and the type I interferon pathway.[6] Impaired inactivation of the X-chromosome may partially explain the striking female sex predominance.[7] Induction of cellular stress responses, including oxidative modification of cell proteins, may link environmental triggers to altered immune function. Together, these mechanisms result in the generation

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abnormal biomechanical loading of the vertebrae as the disease progresses. Additional late complications may include cauda equina syndrome, osteoporotic compression fractures, spondylodiscitis, and restrictive lung disease.

Reactive Arthritis

The course of reactive arthritis is variable, and few prognostic markers are available for the clinician to predict the course in an individual case. However, the majority of patients have an initial episode lasting 2 to 3 months, but synovitis may persist for a year or longer. In one follow-up of a point source cohort of post-*Salmonella* reactive arthritis, 20% of patients had ongoing inflammatory joint disease, and some degree of functional disability was observed in 30% of patients 5 years after the onset of disease.

Enteropathic Arthritis

For peripheral arthritis, measures that control the gastrointestinal disease usually control the joint disease as well. In contrast, the course of enteropathic spondylitis or sacroiliitis tends to be chronic.

Psoriatic Arthritis

Aggressive osteolysis, fibrous ankylosis, and heterotopic new bone formation can occur in psoriatic arthritis. The coexistence of HIV and psoriatic arthritis seems to set the stage for an aggressive course of joint destruction in some patients. Patients with psoriatic arthritis can experience substantial physical impairment.[24]

Peripheral Spondyloarthritis

The natural history of peripheral spondyloarthritis has not been well defined. A number of patients may eventually meet the diagnostic criteria for axial spondyloarthritis, but many retain a distinct undifferentiated spondyloarthritis pattern for prolonged periods. The variability in prognosis for the large group of patients falling into the peripheral spondyloarthritis group is perplexing. No characteristics are reliable predictors of progression in patients with this heterogeneous cluster of articular and extra-articular features.

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245 SYSTEMIC LUPUS ERYTHEMATOSUS

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ABSTRACT

Systemic lupus erythematosus (SLE) is a highly complex systemic autoimmune disease that involves nearly all components of the immune system and is associated with damage to multiple organs. SLE is notable for its female predominance, with about 8 to 10 females for every 1 male affected. The disease is characterized by autoimmunity specific for nucleic acids and nucleic acid–binding proteins. Current concepts in disease pathogenesis involve nucleic acid–mediated activation of the innate immune system, production of cytokines such as type I interferon, extensive immune system dysregulation, and production of autoantibodies that form immune complexes. Therapy typically depends on immunosuppression with corticosteroids, biologics, and other agents. Current studies are investigating the potential for novel agents to provide improved efficacy over current treatment options.

KEYWORDS

autoimmunity
autoantibodies
type I interferon
lupus nephritis
malar rash
premature atherosclerosis

and deposition of immune complexes in tissue, the recruitment of lymphocytes, macrophages, and neutrophils, the activation of the complement system, and tissue damage.

Genetics

An important role for a genetic contribution to lupus susceptibility is suggested by the high concordance of disease in monozygotic twins (24%), with an estimated 44% of risk for SLE attributable to heritable factors. Rare mutations in genes encoding components of the complement pathway, including C1q, C2, and C4A, contribute to increased lupus susceptibility or severity. Impaired production of these early complement components may decrease the clearance of apoptotic or necrotic debris, thereby augmenting the pool of available autoantigens, or decrease the solubility of immune complexes. Rare mutations in genes encoding DNase enzymes can contribute to impaired degradation of endogenous DNA and induction of type I interferon. The association of SLE with the major histocompatibility complex (MHC) class II alleles human leukocyte antigen (HLA)-DR3 (DRB1*03:01-DQA1*05:01-DQB1*02:01) and HLA-DR15 (DRB1*15:01/03-DQA1*01:02-DQB1*06:01) shows the strongest risk, and these class II alleles are associated with the production of particular autoantibodies.[8] A large transancestral genome-wide association study (GWAS) of subjects of European, African, and Hispanic Amerindian ancestry identified 80 non-HLA single-nucleotide polymorphisms associated with SLE. Some associations at a high level of significance were related to ancestry (E-Table 245-1). Polymorphic variants in components of the toll-like receptor (TLR) pathways that regulate type I interferon production, including interferon regulatory factor 5 (*IRF5*) and *IRF7*, are associated with a diagnosis of SLE and increased plasma interferon activity in some populations. Polymorphisms in the Fc receptor genes *FCGR2A* and *FCGR3A* have been associated with SLE nephritis, possibly based on altered clearance of immune complexes. Variants of the *PTPN22* gene, which encodes a phosphatase that regulates T-cell activation, are also associated with SLE. GWASs have identified variations in regulators of innate immune system activation (e.g., *TNFAIP3, ITGAM, IFIH1*) and signaling molecules important in lymphocyte activation (e.g., *STAT4, BANK1*, and *BLK*). Rare mutations in genes encoding proteins that regulate nucleic acid integrity and degradation, including *TREX1*, encoding a DNase; *SAMHD1*, a triphosphohydrolase; *RNASEH2A, B*, and *C*; and *ADAR*, an RNA-specific adenosine deaminase, have been documented in some patients with a lupus-like disorder called Aicardi-Goutières syndrome, characterized by skin lesions, CNS disease, autoantibodies, and high levels of interferon. Mutations in these genes have also been documented in rare patients with SLE and highlight the likely contribution of endogenous nucleic acids to activation of the innate immune system and the pathogenesis of lupus. Composite genetic risk scores are associated with early onset of disease, tissue damage, and decreased survival.[9] These genetic loci that are associated with lupus confer either increased activation or impaired regulation of innate or adaptive immune responses (Chapter 35), with increased type I interferon often observed in association with the risk genotype.

Environmental Triggers

Epidemiologic studies have identified several classes of potential environmental triggers for lupus, including exposure to silica, smoking, and use of oral contraceptive agents or postmenopausal hormones. A role for microbial triggers—particularly virus infection—has been postulated, consistent with the constitutional symptoms that often characterize the earliest stage of the disease. Prior infection with Epstein-Barr virus (Chapter 348) is significantly higher in SLE patients than in the general population (99 vs. 94%). Orthologs of human Ro60, a common target of lupus autoantibodies, are seen in commensal bacteria.[10] Ultraviolet light exposure is a well-described trigger of lupus flares. Possible mechanisms include DNA damage, induction of cellular stress responses, and induction of apoptosis of skin cells, which result in concentration of nucleic acids and associated proteins in cell membrane blebs that can be processed by antigen-presenting cells. Certain drugs, including procainamide and hydralazine, can induce a lupus-like syndrome, but the symptoms usually abate after discontinuing use of the drug. These agents may promote demethylation of DNA, thereby altering gene expression and potentially increasing the availability of immunostimulatory DNA. Sulfa antibiotics have induced lupus flares in some patients. Administration of recombinant interferon-α to patients with hematologic malignancies or hepatitis C infection has been associated with induction of a lupus-like syndrome. In addition, anti–tumor necrosis factor agents have induced lupus autoantibodies and occasionally clinical lupus in patients with rheumatoid arthritis.

Immunologic Triggers

Genetic and environmental factors that increase the probability of development of SLE act on the immune system to induce autoimmunity and consequent tissue inflammation and damage. In addition to mechanisms that increase the availability of self-antigens (such as ultraviolet light), altered expression of gene products that mediate or regulate apoptosis or impaired clearance of apoptotic debris results in generalized activation of the immune system and contributes to autoimmunity in lupus. In parallel with the events that account for effective immune responses directed at exogenous microbes, the autoimmunity that occurs in SLE patients requires activation of both innate and adaptive immune responses (Chapter 35). Characterization of the TLR family of pattern recognition receptors has provided new understanding of the mechanisms through which the innate immune system is activated by exogenous and endogenous stimuli, including nucleic acid–containing immune complexes, and promotes induction of a self-directed adaptive immune response (Chapter 35). Impaired inactivation of the X-chromosome may augment the differentiation of B cells and the production of autoantibodies by increasing the expression of TLR7 or other X-chromosome–encoded immune response genes.

Type I Interferon

Studies of gene expression in peripheral blood mononuclear cells of SLE patients using microarray and RNA sequencing technology have demonstrated a sustained and broad "signature" of type I interferon–induced gene transcripts that reflect activation of the innate immune system. Interferon-α (IFN-α), along with other type I IFNs (e.g., IFN-β, IFN-ω, and IFN-κ in skin) may be responsible for many of the immunologic alterations observed in SLE. Immune complexes containing DNA or RNA, nuclear debris from neutrophils in the form of neutrophil extracellular traps (NETs), or extracellular mitochondrial DNA are among the stimuli postulated to induce the production of type I interferon in SLE. Demethylated CpG-rich DNA or RNA associated with nucleic acid–binding proteins can activate plasmacytoid dendritic cells and other immune system cells through TLRs and thereby result in the production of type I interferon and other proinflammatory cytokines (E-Fig. 245-1).[11] Induction of an immunostimulatory microenvironment by IFN-α may support the development of a humoral immune response directed at self-antigens, particularly intracellular particles that contain nucleic acids and nucleic acid–binding proteins. In addition to its effects on immune system function, type I interferon has been associated with altered endothelial cell function and microglial function in the brain and may contribute to the development of atherosclerotic vascular pathology and CNS disease in patients with lupus.[12]

Autoantibodies

The most characteristic lupus autoantibodies target intracellular particles that contain both nucleic acid and nucleic acid–binding proteins. Analysis of the spectrum of autoantibodies present in the sera of individuals in whom SLE is later diagnosed suggests that autoantibodies reactive with certain RNA-binding proteins, including the Ro protein, occur early in the preclinical stage of the disease, along with a positive antinuclear antibody (ANA) test. These abnormal test results are often followed by anti-double-stranded DNA antibodies and, finally, by the development of antibodies specific for the spliceosomal proteins Smith (Sm) and ribonucleoprotein (RNP) at approximately the time of diagnosis (E-Fig. 245-2). These observations suggest that individuals who demonstrate progression from antibodies targeting RNA to antibodies targeting DNA and spliceosomal proteins are those in whom sufficient autoimmunity develops to manifest clinical symptoms. Approximately one third of SLE patients have autoantibodies that are reactive with phospholipids or the proteins associated with them, particularly β_2-glycoprotein I. These autoantibody specificities can also be present independently of SLE in primary antiphospholipid antibody syndrome (Chapter 157).

Immune Complexes and Complement

Tissue and organ damage in SLE is mediated by the deposition or in situ formation of immune complexes, the activation of complement, and inflammation. The complement system (Chapter 37), which is composed of more than 30 proteins that act in concert to protect the host against invading organisms, initiates inflammation and tissue injury. Activation of complement promotes chemotaxis of inflammatory cells and generates proteolytic fragments that enhance phagocytosis by neutrophils and monocytes. The classical complement pathway is activated when antibodies bind to antigen and generate potent effectors. Activation of the alternative complement pathway is initiated by the binding of spontaneously activated complement components to the surfaces

E-TABLE 245-1 NON-HLA GENOMIC REGIONS ASSOCIATED WITH SYSTEMIC LUPUS ERYTHEMATOSUS BY ANCESTRY

GENE*	PROTEIN
EUROPEAN	
ATG5	Autophagy related 5
BANK1	B-cell scaffold protein with ankyrin repeats 1
BLK	B-lymphocyte–specific tyrosine kinase
CLEC16A	C-type lectin domain containing 16A
DEF6	DEF6, guanine nucleotide exchange factor
DGKQ	Diacylglycerol kinase theta
ETS1	ETS proto-oncogene 1
FCGR2A	Fc fragment of IgG receptor IIa
GRB2	Growth factor receptor bound protein 2
GTF2I	General transcription factor IIi
IFIH1	Interferon induced with helicase C domain 1
IKZF1	IKAROS family zinc finger 1
IKZF3	IKAROS family zinc finger 3
IL10	Interleukin 10
IL12A	Interleukin 12A
IRF5	Interferon regulatory factor 5
IRF7	Interferon regulatory factor 7
IRF8	Interferon regulatory factor 8
ITGAM	Integrin subunit alpha M
JAZF1	JAZF zinc finger 1
MSRA	Methionine sulfoxide reductase A
NMNAT2	Nicotinamide nucleotide adenylyltransferase 2
OLIG3	Oligodendrocyte transcription factor 3
PKIA	cAMP-dependent protein kinase inhibitor α
PTPN22	Protein tyrosine phosphatase nonreceptor type 22
PTTG1-MIR146A	Pituitary tumor–transforming 1
PXK	PX domain containing serine/threonine kinase–like
SLC15A4	Solute carrier family 15 member 4
SLC17A4	Solute carrier family 17 member 4
STAT4	Signal transducer and activator of transcription 4
TMEM39A	Transmembrane protein 39A-translocase of inner mitochondrial membrane
TIMMDC1	Mitochondrial membrane domain containing 1
TNFAIP3	TNF α-induced protein 3/A20
TNFSF4	TNF superfamily member 4/Ox40 ligand
TNIP1	TNFAIP3 interacting protein 1
TYK2	Tyrosine kinase 2
UBE2L3	Ubiquitin conjugating enzyme E2 L3
WDFY4	WDFY family member 4
AFRICAN	
BLK	B-lymphocyte–specific tyrosine kinase
IRF5	Interferon regulatory factor 5
ITGAM	Integrin subunit α M
PLAT	Plasminogen activator, tissue type
PTTG1	Pituitary tumor–transforming 1
HISPANIC	
CLEC16A	C-type lectin domain containing 16A
GALC	Galactosylceramidase
IRF5	Interferon regulatory factor 5
ITGAM	Integrin subunit alpha M
NCF2	Neutrophil cytosolic factor 2
TNIP1	TNFAIP3 interacting protein 1
STAT4	Signal transducer and activator of transcription 4

*Genes listed have *P* value $<5 \times 10^{-8}$.

cAMP = cyclic adenosine monophosphate; ETS = erythroblast transformation specific; HLA = human leukocyte antigen; IgG = immunoglobulin G; JAZF = juxtaposed with another zinc finger protein; PX = phox homology; TNF = tumor necrosis factor; TNFAIP3 = tumor necrosis factor, alpha-induced protein 3.

From Langefeld CD, Ainsworth HC, Cunninghame Graham DS, et al. Transancestral mapping and genetic load in systemic lupus erythematosus. *Nat Commun*. 2017;8:1-18.

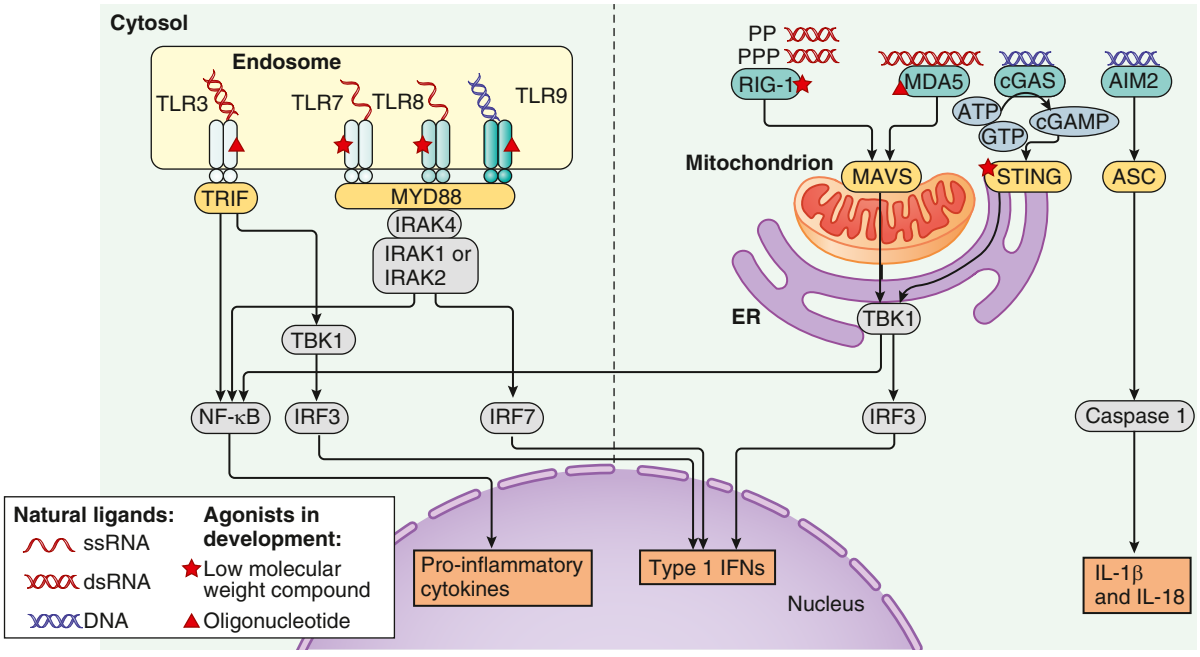

E-FIGURE 245-1. Model for induction of innate immune system activation in systemic lupus erythematosus. Both exogenous and endogenous stimuli can induce toll-like receptor (TLR) and cytosolic nucleic acid sensor activation and thereby result in new gene transcription. Among potential endogenous ligands are immune complexes containing DNA or RNA or matrix-derived components and cytosolic DNA or RNA. TLR ligands trigger the activation of intracellular adaptors, including TIR domain-containing adapter-inducing interferon-β (TRIF), TRIF-related adaptor molecule (TRAM), TIR domain-containing adapter protein (TIRAP), or myeloid differentiation primary response protein 88 (MyD88), and induce transcription of type I interferons or inflammatory cytokines. Cytosolic RNA activates RIG-I or MDA5, which signals through MAVS and TBK1. Cytosolic DNA activates cGAS, which signals through cGAMP, STING, and TBK1. Both pathways can induce type I interferon transcription. Type I interferons mediate diverse effects on immune system cells, including maturation of dendritic cells, increased immunoglobulin (Ig) class switching, and induction of cytokines that promote autoimmunity and inflammation, including B-lymphocyte stimulator (BLyS), interleukin-10 (IL-10), interferon-γ, and chemokines. AIM2 = absent in melanoma 2; ATP = adenosine triphosphate; cGAS = cyclic GMP-AMP synthase; ds = double-stranded; ER = endoplasmic reticulum; GTP = guanosine triphosphate; IFN = interferon; IRF = interferon regulatory factors; IRAK = interleukin-1 receptor-associated kinases; MDA5= melanoma differentiation-associated protein 5; NF-KB = nuclear factor-kappaB; RIG1 = retinoic acid-inducible gene 1; ss = single-stranded; STING = stimulator of interferon genes. (From Junt T, Barchet W. Translating nucleic acid-sensing pathways into therapies. *Nat Rev Immunol*. 2015;15:529-44.)

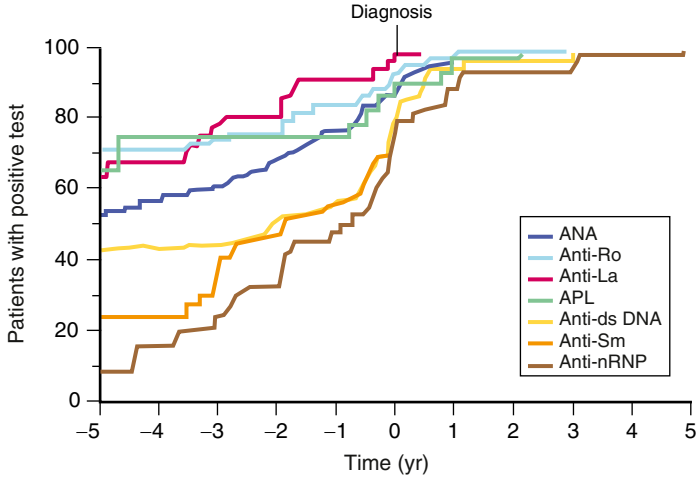

E-FIGURE 245-2. Proportion of patients with positive antibody tests relative to the time of diagnosis or appearance of the first clinical manifestation of systemic lupus erythematosus (SLE). For each autoantibody, the proportion of patients testing positive relative to the time of diagnosis or to the time of appearance of the first clinical criterion was assessed. In analyses of the time from antibody development to the diagnosis of SLE, antinuclear antibodies (ANAs) appeared significantly earlier than anti-Sm antibodies and antinuclear ribonucleoprotein (anti-nRNP) antibodies but not significantly earlier than anti-Ro, anti-La, antiphospholipid (APL), or anti-double-stranded DNA antibodies (anti-ds DNA). (From Arbuckle MR, McClain MT, Rubertone MV, et al. Development of autoantibodies before the clinical onset of systemic lupus erythematosus. *N Engl J Med*. 2003;349:16.)

of pathogens or self-tissues. C3a, which is an anaphylatoxin that binds to receptors on leukocytes and other cells, causes activation and release of inflammatory mediators. C5a is a potent soluble inflammatory, anaphylatoxic, and chemotactic molecule that promotes recruitment and activation of neutrophils and monocytes and mediates endothelial cell activation through its receptor. The release of reactive oxygen and nitrogen intermediates is an additional mechanism that contributes to tissue damage.

Tissues targeted by immune system activity in lupus include the skin (where immune complexes and complement are deposited in a linear pattern), the glomeruli, and heart valves. Antibodies reactive with hippocampal neurons in the brain can mediate excitotoxic death. Microvascular damage is observed in splenic arteries and is characterized by the typical onion-skin pattern of concentric connective tissue deposition. In addition to inflammation, thrombosis (including microthrombi) contributes to ischemia and cell necrosis in the brain and other organs.

Lupus Nephritis

In general, the pattern of renal disease reflects the site of deposition of immunoglobulins and the quality of the effector mechanisms they induce. Mesangial deposition of immunoglobulin induces mesangial cell proliferation and is associated with microscopic hematuria and mild proteinuria. Subendothelial deposition of immune complexes results in proliferative and exudative inflammation, together with hematuria, mild to moderate proteinuria, and reduced glomerular filtration rate. Subepithelial deposition of immune complexes adjacent to podocytes and along the glomerular basement membrane can result in membranous nephritis with nephrotic-range proteinuria. In addition, antiphospholipid antibodies may support the development of thrombotic or inflammatory vascular lesions within or external to glomeruli.

Neuropsychiatric Lupus

The pathophysiologic mechanisms that account for the neuropsychiatric manifestations of SLE are diverse and complex. Autoantibodies cross-reactive with neuronal cell surface glutamate receptors and DNA may mediate excitotoxic death of neurons and are proposed to contribute to cognitive dysfunction. Antibodies directed against ribosomal P protein have also been associated with neuropsychiatric lupus, and antiphospholipid antibodies can contribute to a procoagulant state, vascular thrombosis, and cerebral ischemia. Noninflammatory small vessel vasculopathy is the most common lesion and can be associated with microinfarcts. Inflammatory mediators, including the cytokines interleukin-6 (IL-6) and IFN-α, and matrix metalloproteinases may also contribute to the neuropsychiatric manifestations of SLE. IFN-α mediates microglial activation and excessive synaptic pruning.

CLINICAL MANIFESTATIONS

Symptoms and Signs

Constitutional Symptoms

SLE involves virtually all components of the immune system and can be accompanied by constitutional symptoms similar to those seen in the setting of microbial infection. Fatigue, headaches, weight loss, and fevers are common, along with generalized arthralgias, myalgias, and lymphadenopathy. The level of activity of lupus typically follows a pattern of flares and remissions, although some patients sustain active disease for prolonged periods.

Cutaneous and Mucous Membranes

The skin and mucous membranes are affected in most lupus patients (Table 245-1). The classic erythematous facial rash, with a butterfly distribution across the malar and nasal prominences and sparing of the nasolabial folds, is seen in 30 to 60% of patients (Fig. 245-1). The butterfly rash is often triggered by sun exposure, but photosensitivity can also occur diffusely in other areas of the body.

Discoid skin lesions, which are seen in about 25% of patients, are erythematous plaques with central scarring, sometimes covered with scale and involving the scalp, face, and ears. Patients may develop alopecia (Chapter 409). Discoid lesions can be present in the absence of systemic manifestations of SLE (discoid lupus). In addition to the scarring alopecia of discoid lupus, transient alopecia may be a clinical sign of increased disease activity.

Inflammation of the deep dermis and subcutaneous fat can result in lupus panniculitis, with firm, painful nodules that sometimes adhere to the epidermis, thereby causing irregularities in the superficial skin. Subacute cutaneous lupus erythematosus is seen in sun-exposed areas and can involve erythematous plaques or psoriasiform lesions. It is associated with autoantibodies to the Ro (SSA) RNA-binding protein. Mucosal ulcerations, especially of the buccal mucosa and upper palate, result from mucositis and are typical of SLE. Manifestations of vasculopathy include arteriolar spasm or infarcts in the nail folds, a diffuse lacey pattern over the skin described as livedo reticularis, and petechial-purpuric or urticarial lesions on the extremities. Vasculopathy in SLE is often associated with the presence of antiphospholipid antibodies.

Musculoskeletal System

Arthralgias and nonerosive arthritis are experienced by more than 85% of patients. The proximal interphalangeal and metacarpophalangeal joints of the hand are most commonly symptomatic, along with the knees and wrists. In about 10% of patients, deformities result from damage to periarticular tissue, a condition termed *Jaccoud arthropathy*. The heavy use of corticosteroids in many lupus patients can be accompanied by the development of osteoporosis, including osteoporotic fractures, or osteonecrosis, most commonly of the hips, although the underlying vasculopathy can also contribute to joint damage.

Inflammation of the muscles with elevated creatine kinase levels can occur rarely in SLE, and myopathy may be observed as a consequence of corticosteroid therapy. Fibromyalgia (Chapter 253), characterized by painful trigger points at characteristic locations, commonly accompanies SLE and can contribute to fatigue and depression.

Renal System

Kidney involvement with glomerulonephritis (Chapter 107) is common in SLE, with more than 50% of patients affected at some time in the course of disease.[13] Patients may initially be asymptomatic, but hypertension is common, and the nephrotic syndrome can develop. Patients often develop progressive chronic kidney disease (Chapter 116). Renal vein thrombosis (Chapter 110) also can occur.

Cardiovascular System

Pericarditis (Chapter 62) is the most common cardiac manifestation,[14] but it is sometimes recognized only on imaging studies or at autopsy. Pericarditis is usually manifested as substernal chest pain that is improved by bending forward and can be exacerbated by inspiration or coughing.

Structural valve abnormalities in SLE range from sterile nodules (Libman-Sacks endocarditis) to nonspecific valve thickening. The nodules are immobile and usually located on the atrial side of the mitral valve and sometimes on the arterial side of the aortic valve. Right-sided lesions are rare. These structural changes may in some cases result in valvular regurgitation. Although valve nodules are detected in most patients with SLE at autopsy, clinically significant valvular heart disease is much less common (1 to 18%). The verrucous valvular

TABLE 245-1 CLINICAL MANIFESTATIONS OF SYSTEMIC LUPUS ERYTHEMATOSUS

MANIFESTATION	APPROXIMATE FREQUENCY (%)
Cutaneous	88
Arthritis/arthralgias	76
Neuropsychiatric	66
Pleurisy/pericarditis	63
Anemia	57
Raynaud phenomenon	44
Vasculitis	43
Atherosclerosis	37
Nephritis	31
Thrombocytopenia	30
Sensorimotor neuropathy	28
Cardiac valvar disease	18
Pulmonary alveolar hemorrhage	12
Pancreatitis	10
Myositis	5
Myocarditis	5

FIGURE 245-1. Malar rash in a patient with systemic lupus erythematosus. Note that the rash does not cross the nasolabial fold. (From Gladman DD, Urowitz MB. Systemic lupus erythematosus: clinical features. In: Klippel JH, Dieppe PA, eds. *Rheumatology*. 2nd ed. London: Mosby; 1998.)

lesions of Libman-Sacks endocarditis are most likely inflammatory in nature and may be associated with the presence of antiphospholipid antibodies. SLE is also a significant risk factor for premature atherosclerosis independent of other cardiovascular risk factors.

Although not specific to SLE, Raynaud phenomenon (Fig. 66-9), characterized by episodic vasospasm and occlusion of the digital arteries in response to cold and emotional stress, is seen in up to 60% of SLE patients and contributes to pain and sometimes necrosis of the distal ends of extremities. The character of the digits classically changes from pallor to cyanosis and then to rubor as vascular perfusion becomes impaired and then reperfusion ensues. In addition, small arteries, arterioles, and capillaries can be affected by vasculitis and fibrinoid necrosis, with clinical manifestations that include periungual telangiectases, abdominal pain, and neuropsychiatric symptoms.

Pulmonary System

Pleuritis, which is the most frequent manifestation of pulmonary involvement in SLE, occurs in about 30% of patients at some point in their disease course. Pleuritis is characterized by pain on respiration and exudative effusions (Chapter 86). Parenchymal disease is less common but may manifest as alveolar hemorrhage (in up to 12% of patients; Chapter 79), pulmonary embolism (Chapter 68) secondary to deep vein thrombosis, or pulmonary hypertension (Chapter 69) with increased pulmonary resistance and impaired diffusing capacity.

Neuropsychiatric Involvement

Clinical features of SLE that involve the nervous system include both neurologic and psychiatric manifestations.[15] About 50% of SLE patients experience a neuropsychiatric event, with 30% of those events attributable to SLE. Both central and peripheral nervous systems can be affected by the disease. The most common manifestations that are probably attributable to SLE cerebritis include cognitive dysfunction, present in 17 to 66% of SLE patients; psychosis or mood disorder, the former reported in up to 8% of patients; cerebrovascular disease in 5 to 18% of patients; and seizures, present in 6 to 51% of patients. Headaches are also common. Although none of these CNS manifestations is found exclusively in SLE, global SLE disease activity is associated with concurrent neuropsychiatric manifestations attributable to SLE.

Cranial nerve and ocular involvement, most likely based on vasculopathy and focal ischemia, can sometimes affect vision. Ocular examination of the retina can reveal cotton-wool spots as a result of retinal ischemia or necrosis. Although rare, transverse myelopathy, frequently associated with antiphospholipid antibodies, can have devastating consequences, including paraplegia. Sensorimotor neuropathies, often asymmetrical, are more common (up to 28%) and are based on damage to small nerve fibers with vasculopathy in the small arteries that supply the nerve fibers.

Gastrointestinal System

Although uncommon, vasculitis of the gastrointestinal tract or mesentery can result in pain and bowel necrosis (Chapter 129). Less common than pleuritis and pericarditis, peritonitis can manifest as peritoneal effusion and abdominal pain. Pancreatitis (Chapter 130) occurs in less than 10% of patients but may also be due to vascular pathology.

Lymphadenopathy and Splenomegaly

About one third of SLE patients demonstrate diffuse lymphadenopathy at some time during the course of their disease (Chapter 154). The nodes are often nontender, and lymphoma is sometimes considered in the differential diagnosis. Biopsy usually reveals follicular hyperplasia, although some histopathologic findings appear similar to the histiocytic necrotizing lymphadenitis that is a feature of Kikuchi disease, a self-limited syndrome characterized by fever and lymphadenopathy. Splenomegaly (Chapter 154) is sometimes seen in SLE, and spleen pathology is characterized by a classic onion-skin histology that appears as concentric circles of collagen matrix surrounding splenic arteries and arterioles.

Hematologic System

In addition to autoantibody specificities that are fairly specific for SLE (anti-DNA, anti-Sm), antibodies that target each of the cellular blood elements are also common. Anemia is present in about 50% of patients and is multifactorial. It can be associated with a positive Coombs test or microangiopathic hemolysis (Chapter 146) or reflect chronic disease (normochromic, normocytic; Chapter 144). Leukopenia (Chapter 153), particularly lymphopenia, is observed, with the lymphocyte count decreasing in the setting of increased disease activity. Antibodies that bind to lymphocytes and neutrophils have been described, and an increased tendency for lymphocytes to undergo spontaneous apoptosis may contribute to lymphopenia. Idiopathic thrombocytopenic purpura (Chapter 158) can be an early manifestation of SLE, and thrombocytopenia induced by antiplatelet autoantibodies can sometimes lead to a life-threatening risk for hemorrhage. Autoantibodies to clotting factors can also occur and contribute to impaired clot formation and hemorrhage. Patients with SLE have a significantly increased risk of developing hematologic malignancies, particularly non-Hodgkin lymphoma (Chapter 171).[16]

Lupus During Pregnancy

Whether pregnancy increases the likelihood of lupus exacerbation has been debated, but lupus flares during pregnancy are rare or mild when disease activity at the time of conception is low and stable. However, patients with SLE have worse fetal outcomes than healthy individuals. Gestational hypertension, fetal growth restriction, and fetal distress are increased in patients with SLE and may lead to fetal loss or premature delivery. Preeclampsia (Chapter 221) can contribute to a poor outcome in both the mother and fetus and can be difficult to distinguish from a lupus flare associated with lupus nephritis.

Antiphospholipid Antibody Syndrome

Antiphospholipid antibodies represent a distinct class of autoantibodies that are seen in about one third of SLE patients but can also be present in individuals who do not carry a diagnosis of SLE (Chapter 160). Whether in primary antiphospholipid syndrome or in SLE, antiphospholipid antibodies are associated with venous and arterial thromboses (Chapter 67). Other clinical manifestations of antiphospholipid syndrome include thrombotic microangiopathic glomerular disease, cardiac valve lesions, livedo reticularis, thrombocytopenia, hemolytic anemia, and CNS disease. These autoantibodies can contribute to fetal loss and growth restriction by binding to the placenta, thereby activating the complement system and inducing inflammation. Catastrophic antiphospholipid syndrome, triggered by the acute onset of multisystemic (three or more organs) thrombosis, is resistant to anticoagulation treatment and is fatal in up to 30% of cases.

DIAGNOSIS

Classification

A careful history of present illness, detailed review of systems and triggering factors, and a family history are essential in raising suspicion for a diagnosis of SLE. Criteria for the classification of patients with SLE (Table 245-2) were designed for research studies[17] but can be helpful for establishing a diagnosis of SLE because they have a sensitivity of 96% and a specificity of 93% for expert-determined SLE. The criteria, which require a positive ANA titer and then weight 10 other features that encompass the various manifestations of

SLE, can be incorporated into an approach for evaluating patients with suspected SLE (Fig. 245-2).[18]

Because drugs can trigger a lupus-like syndrome, a careful drug history should be taken. Procainamide, hydralazine, and anti–tumor necrosis factor inhibitors present the greatest risk for development of lupus, with quinidine, isoniazid, minocycline, and recombinant IFN-α presenting a lower risk.[19]

Laboratory Findings

Laboratory tests are critical for the diagnosis of SLE (Chapter 237). All cellular elements of blood can be affected in lupus, so the complete blood count is an essential test that aids in diagnosis and management. A prolonged activated partial thromboplastin time (aPTT) can indicate the presence of pathogenic antiphospholipid antibodies (Chapter 160).

The erythrocyte sedimentation rate (ESR), although a very nonspecific indicator of systemic inflammation, is often monitored and can provide an indication of disease activity. Interestingly, the C-reactive protein is relatively uninformative in SLE because it is often low in comparison to an ESR.

Assaying and monitoring characteristic lupus serologic tests can strongly support the diagnosis of SLE (Table 245-3) and, in some cases, can assist in the assessment of disease activity. The ANA test, which is positive in virtually all patients and does not need to be repeated after it has been documented to be positive, is commonly considered a requirement for the diagnosis. Anti-double-stranded DNA antibodies are common in SLE, and their titer can be useful in assessing the activity of lupus nephritis. Autoantibodies specific for proteins that associate with nucleic acids in intracellular particles are present in many patients and can provide support for a diagnosis of SLE. Anti-Sm antibodies are highly specific for SLE and, along with anti-RNP antibodies, react with the spliceosome particle. Anti-Ro (SSA) and anti-La (SSB) antibodies are specific for proteins in an RNA-containing particle and are common in patients with Sjögren syndrome and in mothers of babies with neonatal lupus, as well as being a feature of SLE.

Decreased levels of two of the more stable complement components, C3 and C4, are often indicators of enhanced consumption and increased disease activity. Some laboratories also use a functional measure of total hemolytic complement activity (CH_{50}).

Differential Diagnosis

Even with expert guidelines, however, it is the global picture, as provided by a careful history, physical examination, and laboratory data, that supports a diagnosis of SLE.[20] There is considerable heterogeneity among patients, and any one individual may have a different combination of clinical features. At the onset of clinical symptoms, the diagnosis of SLE can be uncertain because many of the systemic manifestations of lupus can mimic other conditions, particularly viral infections or malignancy, and only some of the typical clinical symptoms may be expressed at any one point in time. Important features of SLE are its multisystemic nature and characteristic serology. The differential diagnosis of SLE includes other rheumatic disorders, such as rheumatoid arthritis (Chapter 243) and vasculitis (Chapter 249); infections, including gonococcal arthritis (Chapter 275), parvovirus B19 (Chapter 342), and mononucleosis (Chapter 348); inflammatory bowel disease (Chapter 127); thrombotic thrombocytopenic purpura (Chapter 158); drug reactions (Chapter 234); and malignancies, particularly lymphoma (Chapter 171). The clinical manifestations of lupus can demonstrate overlap with other autoimmune rheumatic diseases and can evolve over time.

Lupus Nephritis

Lupus nephritis is a glomerulonephritis characterized by an active urine sediment and progressive renal impairment. Evaluation of renal disease in

TABLE 245-2 CLASSIFICATION CRITERIA FOR SYSTEMIC LUPUS ERYTHEMATOSUS (SLE)

CONSIDER SLE

↓

ANA titer of ≥1:80 → If absent, do not classify as SLE

↓

ADDITIONAL CRITERIA* (within each domain, count only the highest weighted criterion.)

CLINICAL, HEMATOLOGIC, AND RENAL FINDINGS	POINTS
Constitutional Symptoms	
Fever	2
Neuropsychiatric Symptoms	
Delirium	2
Psychosis	3
Seizure	5
Mucocutaneous Signs	
Non-scarring alopecia	2
Oral ulcers	2
Subacute cutaneous OR discoid lupus	4
Acute cutaneous lupus	6
Musculoskeletal Signs	
Joint involvement	6
Serosal Abnormalities	
Pleural or pericardial effusion	5
Acute pericarditis	6
Hematologic Abnormalities	
Leukopenia	3
Thrombocytopenia	4
Autoimmune hemolysis	4
Renal Abnormalities	
Proteinuria >0.5 g/24 h	4
Renal biopsy: class II OR V lupus nephritis	8
Renal biopsy: class III OR IV lupus nephritis	10

IMMUNOLOGIC FINDINGS	POINTS
Antiphospholipid Antibodies	
Anticardiolipin antibodies OR anti-β_2GPI antibodies OR lupus anticoagulant	2
Complement Proteins	
Low C3 OR low C4	3
Low C3 AND low C4	4
SLE-Specific Antibodies	
Anti-dsDNA antibody† OR anti-Smith antibody	6

↓

Classify as SLE if score ≥10 points

*Additional criteria should be counted if present on ≥1 occasion and if patient does not have a more likely explanation for it than SLE.

†An assay with 90% specificity against relevant disease controls.

ANA = antinuclear antibody; anti-β_2GPI = anti-β_2 glycoprotein I; anti-dsDNA = anti–double-stranded DNA.

Adapted from Aringer M, Costenbader K, Daikh D, et al. 2019 European League Against Rheumatism/American College of Rheumatology classification criteria for systemic lupus erythematosus. *Arthritis Rheumatol.* 2019;71:1400-1412.

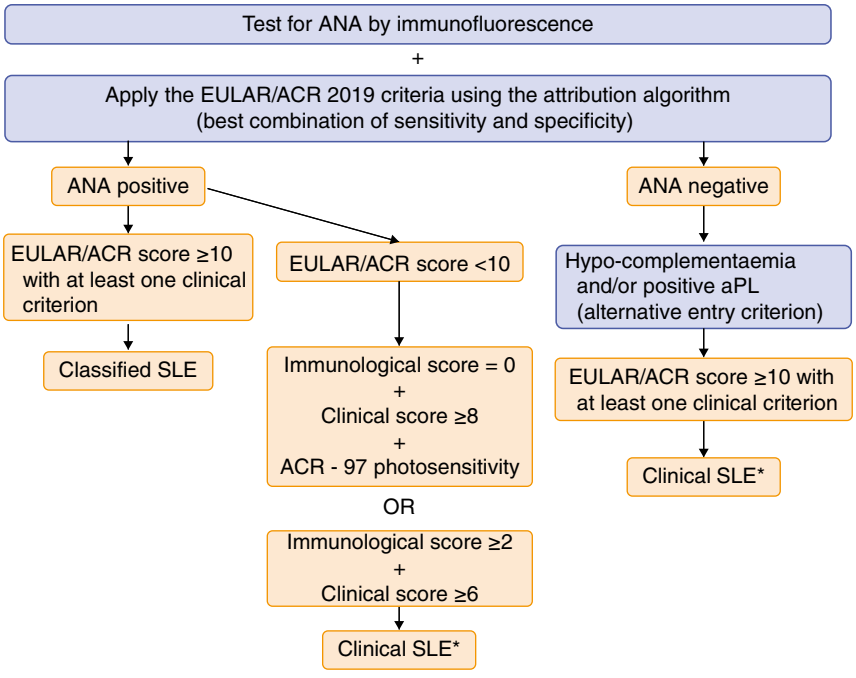

FIGURE 245-2. Diagnostic approach to the patient with suspected systemic lupus erythematosus (SLE). The diagnosis of SLE is clinical, supported by laboratory abnormalities including serologic assays. Diagnostic criteria are not available for SLE, and classification criteria are often used but with several caveats. Among classification criteria, the EULAR/ACR-2019 (Table 245-2) have the best combination of sensitivity and specificity but require positive ANA as an entry criterion. However, patients may be ANA-negative; in such cases, low complement levels and/or positive antiphospholipid antibodies could be used as an alternative entry criterion. For patients who fall short of the classification threshold (i.e., EULAR/ACR score <10), inclusion of photosensitivity or a combination of immunological and clinical features can still be used for SLE diagnosis. ACR = American College of Rheumatology; ANA = antinuclear antibody; EULAR = European League Against Rheumatism; SLE = systemic lupus erythematosus. (From Fanouriakis A, Tziolos N, Bertsias G, et al. Update on the diagnosis and management of systemic lupus erythematosus. *Ann Rheum Dis*. 2021;80:14-25.)

SLE includes urinalysis with microscopic analysis of urine sediment, serum blood urea nitrogen, and creatinine, and a spot urine protein-to-creatinine ratio to estimate protein and creatinine clearance. The glomerular filtration rate (Chapter 100) should be estimated and monitored. A low serum albumin level is consistent with persistent proteinuria and membranous glomerulonephritis, whereas red and white blood cell casts in the urinary sediment suggest a proliferative glomerulonephritis. Renal vein thrombosis can be diagnosed by ultrasonography (Chapter 110).

Renal biopsy provides important information for guiding management and informing prognosis. Renal pathology generally shows the deposition of circulating immune complexes or in situ formation of these complexes in glomeruli (Fig. 245-3). In addition to glomerular inflammation, necrosis, and scarring, renal pathology is characterized by vascular lesions, including thrombotic microangiopathy and extraglomerular vasculitis. Tubulointerstitial disease, including infiltration of the interstitium with mononuclear cells, tubular atrophy, and interstitial fibrosis, may be seen.

Lupus nephritis is classified by biopsy criteria (Table 107-9). Class I and II glomerulonephritis involves mesangial deposition of immune complexes (class I without and class II with mesangial hypercellularity), class III describes focal glomerulonephritis involving less than 50% of total glomeruli, class IV includes diffuse glomerulonephritis involving 50% or more of glomeruli, class V designates membranous lupus nephritis, and class VI is characterized by advanced sclerotic lesions. Pathologic diagnosis should include descriptions of tubulointerstitial and vascular disease as well as glomerular involvement. Several renal pathologic lesions seen in SLE patients but not encompassed in the classification scheme include lupus podocytopathy, collapsing glomerulopathy, and thrombotic microangiopathy, the latter often associated with antiphospholipid syndrome.

Neuropsychiatric Lupus

Evaluation of neuropsychiatric lupus depends on a careful clinical history and physical and laboratory examinations and, in some cases, imaging studies and analysis of cerebrospinal fluid to exclude infection. Magnetic resonance imaging is useful for detecting intracranial abnormalities, which are seen in 19 to 70% of patients and include white matter lesions, cerebral infarction, venous sinus thrombosis, and sometimes atrophy. Magnetic resonance angiography and magnetic resonance spectroscopy can be used to assess cerebral blood flow or neuronal metabolism.

TABLE 245-3 AUTOANTIBODIES ASSOCIATED WITH SYSTEMIC LUPUS ERYTHEMATOSUS

TARGET ANTIGEN	APPROXIMATE FREQUENCY
Nuclear antigens	99
Double-stranded DNA	70
Sm (Smith) nuclear antigen	38
RNP (U1-RNP)	33
Ro (SSA)	49
La (SSB)	35
Phospholipids	21
Ribosomal P	10

TREATMENT

Counseling and education are fundamental to the treatment of SLE. Patients should be advised to avoid known triggers, such as ultraviolet light, that can exacerbate the disease, and should be instructed regarding the need for adequate rest.

Conventional Medical Therapy

Clinical manifestations of lupus that do not involve major organ systems can often be managed with nonsteroidal anti-inflammatory drugs (Table 26-4), low-dose corticosteroids (Chapter 28), and antimalarials. Oral prednisone in doses ranging from 5 to 30 mg daily is effective in treating constitutional symptoms, arthralgias, pericarditis, pleuritis, and skin disease, and the disease may flare if maintenance doses as low as prednisone at 5 mg daily are discontinued.[A1] Topical corticosteroids are sometimes applied to cutaneous lesions. However, the broad immunosuppression mediated by these drugs contributes to the susceptibility to infection that is an inherent feature of SLE. Osteonecrosis, osteoporotic fractures, posterior subcapsular cataracts, diabetes, myopathy, hypertension, hypoadrenalism, and emotional disturbance are additional deleterious effects of corticosteroids (Chapter 28).[21]

Antimalarial agents, most commonly hydroxychloroquine (administered at 200 to 400 mg/day, with a daily dose ≤5 mg/kg actual body weight), can

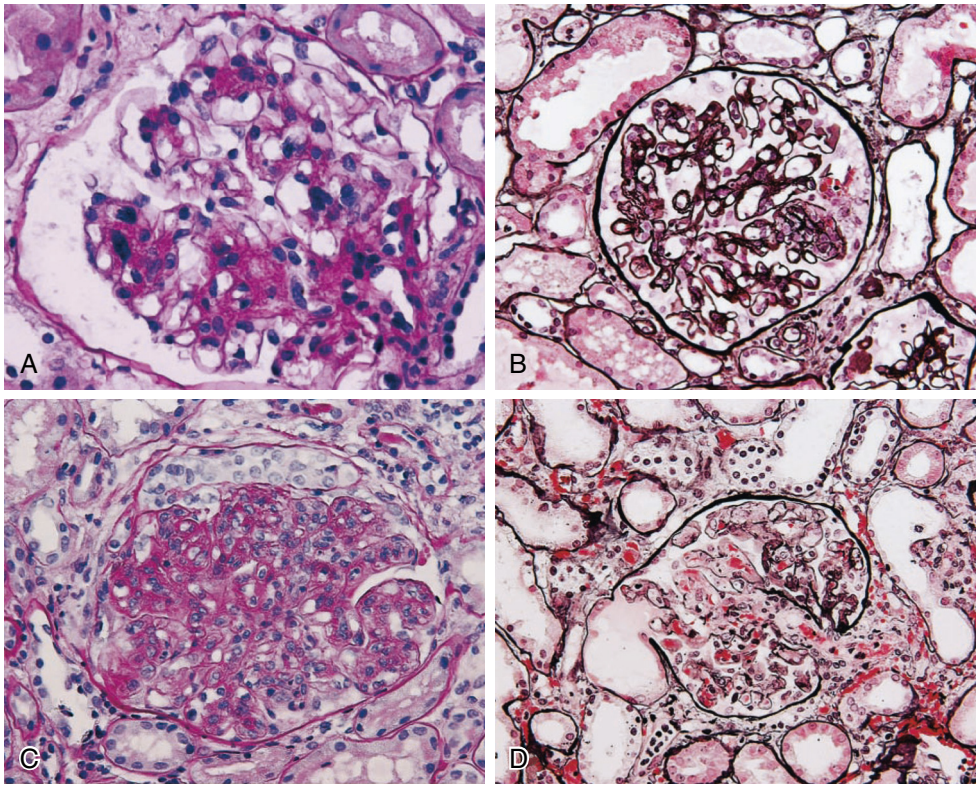

FIGURE 245-3. Histopathology of lupus nephritis. A, Lupus nephritis class II. A light micrograph of a glomerulus shows mild mesangial hypercellularity (periodic acid–Schiff). **B,** Lupus nephritis class III (A). Light micrograph showing a glomerulus with segmental endocapillary hypercellularity, mesangial hypercellularity, capillary wall thickening, and early segmental capillary necrosis (methenamine silver). **C,** Lupus nephritis class IV-G (A/C). A glomerulus manifests global endocapillary proliferation, leukocyte influx and apoptotic bodies, double contours, crescent formation with tubular transformation, early sclerosis, and disruption of Bowman capsule (periodic acid–Schiff). **D,** Thrombotic microangiopathy in a patient with systemic lupus erythematosus and circulating lupus anticoagulant. A glomerulus shows severe capillary and arteriolar thrombosis, endothelial cell swelling and necrosis, neutrophil influx, and stasis of erythrocytes. No signs of immune deposits were found (methenamine silver). (From Wenning JJ, D'Agati VD, Schwartz MM, et al. The classification of glomerulonephritis in systemic lupus erythematosus revisited. *J Am Soc Nephrol*. 2004;15:241.)

control skin involvement and arthralgias and are routinely used in most lupus patients. Hydroxychloroquine has been associated with a decreased incidence of thrombosis, a mechanism that could affect vasculopathy and end-organ damage. Antimalarials are generally well tolerated. The most serious toxicity is retinal damage, with the risk increasing at higher cumulative exposures.[22] Ophthalmologic examinations should precede initiation of therapy and be repeated every 12 months thereafter.

Management of Serious Organ-System Disease

Lupus flares involving rapid decompensation of renal function, CNS disease (including seizures, strokes, or psychosis), or widespread vasculitis or vasculopathy can be life-threatening and must be recognized and treated early and aggressively. Careful attention to monitoring for concurrent or superimposed infection is an important priority during management of a severe lupus flare, and distinguishing sepsis from active lupus or catastrophic antiphospholipid syndrome can be a particular challenge.

For more serious disease, particularly active nephritis, CNS disease, or systemic vasculitis, a traditional approach for initial therapy has been prednisone (60 mg daily) or intravenous methylprednisolone (1 g daily for 3 days), but recent recommendations suggest lower doses in combination with other medications. For new-onset proliferative lupus nephritis, the recommended initial treatment is mycophenolate mofetil (target dose of 2 to 3 g daily) or low-dose cyclophosphamide (500 mg intravenously every 2 weeks for 6 doses) plus intravenous methylprednisolone (500 to 2500 mg) over 1 to 3 days followed by oral prednisone (0.3 to 0.5 mg/kg/day)[23] (Fig. 245-4). Multitarget therapy with tacrolimus (4 mg per day), mycophenolate mofetil (1 g per day), and 3 days of pulse methylprednisolone followed by oral prednisone provides superior efficacy compared with intravenous cyclophosphamide as induction therapy for lupus nephritis.[A2] Tacrolimus is noninferior compared with mycophenolate mofetil when combined with high-dose prednisolone for induction therapy.[A3] Voclosporin (23.7 mg orally twice daily) and belimumab (10 mg/kg intravenously every 2 weeks for three doses followed by 10 mg/kg every 4 weeks or 400 mg subcutaneously weekly for four doses then 200 mg weekly) in combination with background immunosuppressive agents can increase the likelihood of a clinical response in lupus nephritis.[A4–A6] Current recommendations are to reduce the prednisone dose to 7.5 mg or less daily by 3 to 6 months after initiation of therapy.

For maintaining improvement in patients who have responded to induction therapy, current data favor mycophenolate mofetil over azathioprine.[A7] Rituximab, a B-cell–depleting monoclonal antibody targeting CD20, is sometimes used in patients who are refractory to recommended therapies. A second-generation anti-CD20 monoclonal antibody, obinutuzumab, is also a promising option.[A8] As these and other new therapies emerge, recommendations of professional societies are likely to evolve.

A similar approach to that used for proliferative lupus nephritis can be applied to other serious clinical disease flares. In general, cyclophosphamide can be added to high-dose corticosteroid therapy in the setting of severe flare, although mycophenolate mofetil has gained increased use in situations in which the physician or patient wishes to avoid the potential toxicities associated with cyclophosphamide. The symptoms and effusions associated with pericarditis are quite responsive to moderate-dose (20 to 30 mg/day of prednisone) corticosteroid treatment.

Belimumab is increasingly used in patients with moderate and sustained disease activity.[A9,A10] Anifrolumab (300 mg intravenously every 4 weeks) is a monoclonal antibody that reacts with the type I interferon receptor and is approved by the U.S. FDA to treat patients with moderate to severe SLE.[A11,A12] Janus-associated kinase inhibitors (e.g., deucravacitinib),[A13] an inhibitor of CD40 ligand (dapirolizumab pegol),[A14] low-dose IL-2 (to promote expansion of T regulatory cells),[A15,A16] and other promising agents are under investigation.[24]

Specific Immunosuppressive Therapies

Alkylating Agents

Approximately 33% of lupus patients receive cytotoxic therapy during the course of their disease. Cyclophosphamide (Chapter 28; 0.5 to 1 g/m^2 body surface area administered intravenously monthly for 6 months, followed by quarterly doses through 2 years) is usually given with oral prednisone in tapering doses or sometimes with pulse methylprednisolone. Although this regimen is often effective in controlling glomerulonephritis, overall patient survival has not been demonstrated to be increased, and high-dose cyclophosphamide is associated with significant toxicity, including cytopenia, infection, and gonadal failure. A modified therapeutic regimen for administration of cyclophosphamide, termed the "Euro-lupus regimen," involves 500 mg administered intravenously every 2 weeks for six doses, followed by

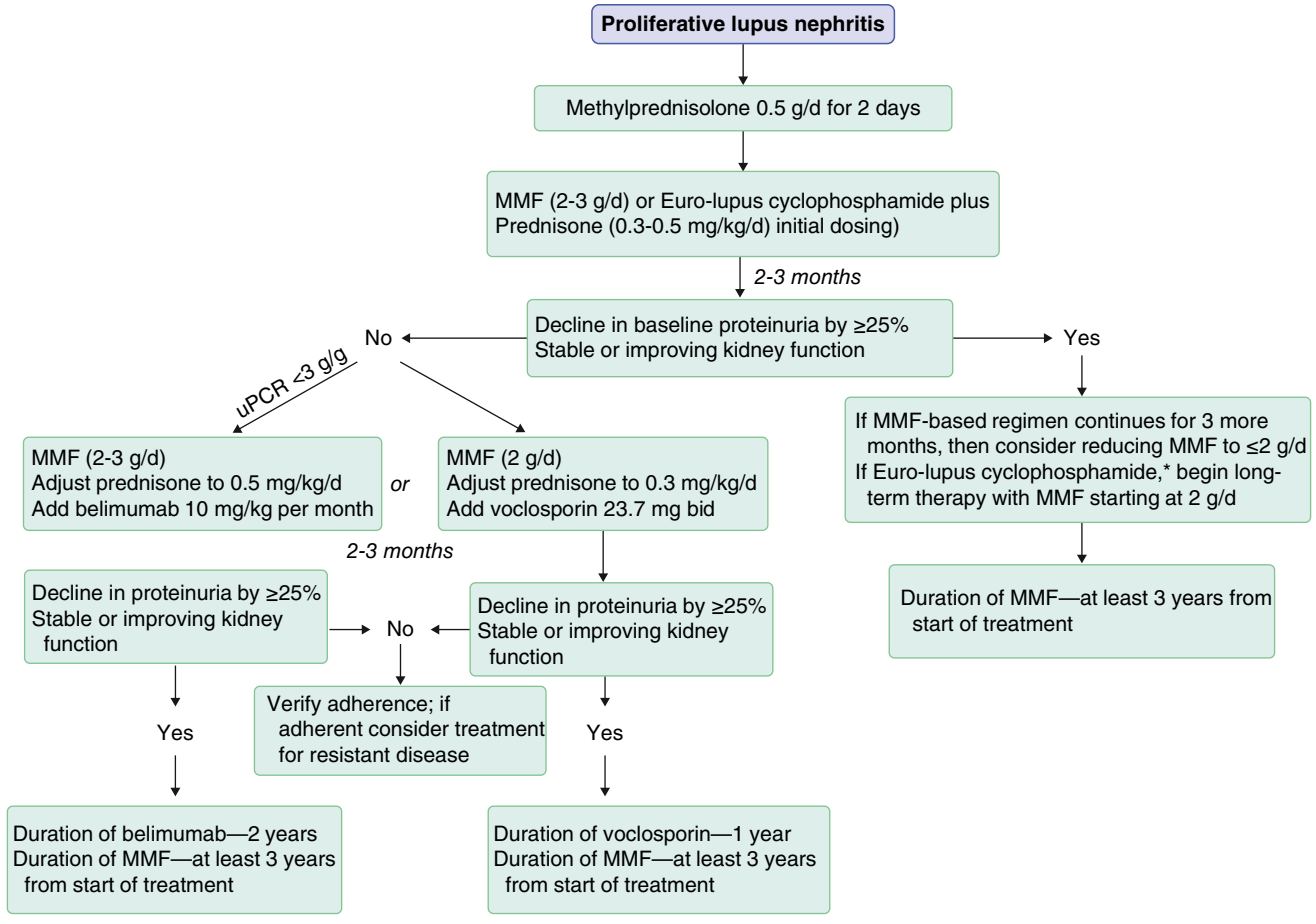

FIGURE 245-4. Algorithm for medical management of proliferative lupus nephritis. *Euro-lupus cyclophosphamide refers to the regimen described in the text and in Tamirou F, Husson SN, Gruson D, et al. Brief report: the Euro-lupus low-dose intravenous cyclophosphamide regimen does not impact the ovarian reserve as measured by serum levels of anti-Müllerian hormone. *Arthritis Rheumatol*. 2017;69:1267-1271. MMF = mycophenolate mofetil; uPCR = urine protein : creatinine ratio. (From Mejia-Vilet JM, Malvar A, Arazi A, et al. The lupus nephritis management renaissance. *Kidney Int*. 2021:S0085-2538:00874-7.)

mycophenolate mofetil or azathioprine. This approach provides long-term efficacy comparable to the high-dose cyclophosphamide regimen and is superior in maintaining ovarian reserve. Cyclophosphamide is relatively contraindicated in pregnant women and should be discontinued 3 months before conception.

Purine Synthesis Inhibitors

Azathioprine (Chapter 28; 2 to 3 mg/kg/day administered as a tablet) has been used for the treatment of lupus nephritis and as a steroid-sparing agent in SLE for many years. Toxicities target the bone marrow, where they result in cytopenias, as well as the liver. Azathioprine is rarely associated with non-Hodgkin lymphoma (Chapter 171), but it has been used safely in pregnant women.

Mycophenolate mofetil is equivalent to pulse low-dose intravenous cyclophosphamide for induction therapy in lupus nephritis.[A17] Mycophenolate mofetil (1 g twice daily) is more effective than azathioprine for the maintenance treatment of lupus nephritis, with treatment failure rates reduced from 32 to 16%. As with cyclophosphamide, mycophenolate mofetil should not be used in pregnancy and should be discontinued at least 6 weeks prior to conception.

Methotrexate

Methotrexate (Chapter 28; 15 to 25 mg/week orally for 6 months) can help control SLE and allow tapering of prednisone. The most responsive clinical manifestations are cutaneous and articular. Methotrexate should not be used in pregnancy.

Calcineurin Inhibitors

Tacrolimus (0.1 mg/kg/day in two divided doses) and cyclosporine (often started at 4 mg/kg/day with gradual lowering to 2 mg/kg/day) are oral calcineurin inhibitors used in treatment of some patients with lupus nephritis.[25,A18,A19] Voclosporin (23.7 mg twice daily) with background immunosuppressive therapy is also effective in lupus nephritis.

Biologic Therapies

Belimumab, a monoclonal antibody that blocks B-cell survival, is currently being used along with background therapy in patients with moderately active SLE and in some patients with lupus nephritis. When added to standard therapy, belimumab significantly improves response rates, reduces the activity of disease, and is generally well tolerated in SLE.

Rituximab has not been efficacious in controlled trials but nevertheless is increasingly used in patients whose lupus nephritis or cytopenias are refractory to conventional therapies.[26] Obinutuzumab (an anti-CD20 monoclonal antibody with improved capacity for B-cell depletion) is under study for treatment of lupus nephritis. Anifrolumab, a monoclonal antibody specific for the type I IFN receptor, is approved for the treatment of moderate to severe SLE in the setting of background standard of care therapy.

Intravenous Gamma Globulin

Although positive data from controlled trials of intravenous gamma globulin are not available, pooled IgG fractions can sometimes be efficacious in gaining control of lupus that is refractory to other therapies. A common regimen is 2 g/kg in divided doses over a 3- to 5-day period.

Plasmapheresis

Removal of pathogenic antibodies and immune complexes is the goal of plasmapheresis. Despite scant data, plasmapheresis has occasionally been useful in lupus patients with life-threatening complications, such as thrombotic thrombocytopenic purpura (Chapter 158), in which the clinical manifestations can be clearly attributed to pathogenic autoantibodies.

Adjunctive Therapies

In addition to controlling autoimmunity and inflammation, it is essential to control hypertension with an angiotensin inhibitor or an angiotensin receptor blocker (Tables 64-7 and 64-9). In patients with a history of thrombosis, who will usually have antiphospholipid antibodies, long-term warfarin (Chapter 67) is recommended.

Contraception and Pregnancy

Pregnancy should be undertaken with caution, careful monitoring, and the goal of minimizing activity of the disease at the time of conception. In lupus patients whose disease is stable or of low activity and who do not have antiphospholipid antibodies, data indicate that oral contraceptive agents do not contribute to disease exacerbations. Patients with moderate or severe disease activity are advised to use progestin-only oral contraceptive agents (Table 220-2) or an intrauterine device.[27] Hydroxychloroquine may reduce the risk of heart block in fetuses of pregnant mothers with SLE.[28]

PROGNOSIS

Although survival of patients with a diagnosis of SLE is good, lupus remains a potentially fatal disease. SLE demonstrates a bimodal pattern of death, with deaths within the first year attributable to active lupus and infection, whereas late deaths are mostly attributable to atherosclerotic cardiovascular disease. The incidence rate ratio of death is four times greater in patients whose disease is initially severe compared with patients whose disease is initially mild.[29]

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The prognosis of class I and class II renal disease is usually good, whereas class IV, the most common form of lupus nephritis, has the worst prognosis, particularly when the serum creatinine level is elevated at the time of diagnosis. Class V nephritis occurs in 10 to 20% of patients, and the implication for long-term outcome depends on the degree of proteinuria, with mild proteinuria having a good prognosis and nephrotic syndrome with chronic edema having a worse prognosis. About 20 to 25% of patients with lupus nephritis develop end-stage renal disease by 15 years after diagnosis, and an initially high serum creatinine (>1.5 mg/dL) is a predictor of progression to end-stage disease.[30]

Premature atherosclerotic disease represents a significant contributor to morbidity and mortality in SLE patients,[31] and mortality from atherosclerosis may be up to 10 times greater in patients with SLE than in age- and sex-matched controls. Patients with SLE have an increased risk for hematologic malignancies, particularly non-Hodgkin lymphoma (Chapter 171). Prognostic factors for an adverse fetal outcome in pregnant mothers with lupus are maternal renal disease and hypertension.

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246 SYSTEMIC SCLEROSIS (SCLERODERMA)

JOHN VARGA

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The occupational exposure most strongly linked with systemic sclerosis is crystalline silica (sandblasting, mining, ceramic, clay, and glass manufacturing). Other tentative causal exposures include polyvinyl chloride, epoxy resins, and aromatic hydrocarbons including toluene and trichloroethylene. Certain drugs, including bleomycin, pentazocine, hormone replacement therapy, cocaine, and appetite suppressants, have been anecdotally linked with systemic sclerosis or pulmonary arterial hypertension. Although early studies implied a putative association of silicone breast implants with systemic sclerosis, large-scale epidemiologic investigations failed to establish an increased risk.

PATHOBIOLOGY

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Among patients with systemic sclerosis, 1.6% have a first-degree relative with systemic sclerosis, a prevalence rate that is substantially higher than in the general population (0.026). Indeed, a family history is recognized as the strongest identified risk factor for systemic sclerosis. Additionally, patients with systemic sclerosis are more likely to have first-degree relatives with Raynaud phenomenon, interstitial lung disease, or other autoimmune diseases including multiple sclerosis, rheumatoid arthritis, and thyroiditis. Genomewide association and candidate-gene studies have identified significant genetic

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Among patients with systemic sclerosis, 1.6% have a first-degree relative with systemic sclerosis, a prevalence rate that is substantially higher than in the general population (0.026). Indeed, a family history is recognized as the strongest identified risk factor for systemic sclerosis. Additionally, patients with systemic sclerosis are more likely to have first-degree relatives with Raynaud phenomenon, interstitial lung disease, or other autoimmune diseases including multiple sclerosis, rheumatoid arthritis, and thyroiditis. Genomewide association and candidate-gene studies have identified significant genetic

ABSTRACT

Systemic sclerosis is a chronic autoimmune connective tissue disease. It is more common in women and typically has an onset in the post-reproductive years. The etiology is unknown, and familial inheritance is uncommon; however, a number of genetic variants have been associated with an increased disease risk. The disease is characterized by distinct and unique autoantibodies: fibrosis in the skin accompanied by fibrosis in the lungs, gut, heart, and most internal organs, and an obliterative noninflammatory microangiopathy. Together, these pathologic processes lead to the hallmark clinical manifestations of systemic sclerosis, including skin tightness, joint contractions, lung fibrosis, pulmonary artery hypertension, Raynaud phenomenon, digital ischemic ulcers, calcinosis cutis, and intestinal dysmotility. Renal crisis with malignant hypertension and renal failure is an uncommon but deadly complication of systemic sclerosis. The risk of certain malignancies appears to be increased. Patients with systemic sclerosis show substantial variability in the clinical manifestations, rate of disease progression, autoantibody profiles, treatment responses, and outcomes. Current therapies are primarily immunomodulatory. However, organ-specific therapies are effective in reducing symptoms, thereby mitigating complications and improving quality of life. Early accurate diagnosis, recognition of specific complications, risk stratification, and individualized management improve outcomes.

KEYWORDS

scleroderma
systemic sclerosis
autoimmunity
fibrosis
microangiopathy

association of systemic sclerosis with multiple human leukocyte antigen (HLA) loci. Non-HLA risk loci associated with systemic sclerosis include *STAT4, IRF4, PTPN22, TNFAIP3, TNIP-1, IRAK1, CD247*, and *BANK1*, each of which encodes genes involved with immune signaling or autoimmunity. Most of these genetic risk alleles are not unique for systemic sclerosis, and are also linked with other autoimmune diseases, particularly systemic lupus erythematosus.

Pathology

The protean clinical and pathologic manifestations of systemic sclerosis reflect a complex underlying biology encompassing three interrelated cardinal pathomechanistic processes: autoimmunity and inflammation, vascular injury and obliteration, and fibrosis with excessive matrix accumulation and loss of function in multiple tissues and organs (E-Fig. 246-1).

The distinguishing pathologic hallmark of systemic sclerosis is the constellation of capillary loss (rarefaction) and obliterative vasculopathy coexisting with fibrosis in most organs. In early-stage disease, perivascular inflammation can be seen even before the appearance of fibrosis. The vascular lesion is characterized by intimal proliferation in the small- and medium-sized arteries, thereby resulting in luminal narrowing and obliteration, and is commonly complicated by platelet activation and hypercoagulability. In later-stage systemic sclerosis, noninflammatory fibrosis is prominent in the skin, lungs, gastrointestinal tract, heart, tendon sheath, perifascicular tissue surrounding skeletal muscle, and some endocrine organs such as the thyroid gland. Accumulation of connective tissue rich in fibrillar collagens, fibronectin, tenascin, cartilage oligomeric matrix protein, and proteoglycans disrupts normal architecture.

In the skin, dermal collagen deposition causes obliteration of the hair follicles, sweat glands, and other adnexae. Fibrosis invades the subjacent white dermal adipose layer with entrapment of fat cells (adipocytes). The epidermis is atrophic, and the rete pegs are effaced. In late-stage disease, there is a paucity of vascular and lymphatic endothelium. In the lungs, the interstitium and alveolar spaces are infiltrated with inflammatory cells in early disease. With progression, interstitial fibrosis and vascular damage, often coexisting within the same lesions, dominate the pathologic picture. Progressive thickening of the alveolar septae results in obliteration of the air spaces, honeycombing, and loss of pulmonary blood vessels.

Intimal thickening of small pulmonary arteries (E-Fig. 246-2), best seen with elastin stain, underlies pulmonary arterial hypertension (Chapter 69). These vascular lesions resemble the changes seen in idiopathic pulmonary arterial hypertension, but the hallmark plexiform lesions are uncommon in systemic sclerosis. In the gastrointestinal tract, pathologic changes can be found at any level from the mouth to the rectum.[2,3] Fibrosis of the lamina propria and submucosa with atrophy of the muscular layers are prominent in the lower esophagus, whereas striated muscle in the upper third of the esophagus is generally spared (Chapter 124). Replacement of the normal gut architecture leads to disordered peristaltic activity with gastroesophageal reflux and dysmotility, gastroparesis, and small bowel obstruction. Chronic reflux can be complicated by esophageal inflammation, ulcerations, stricture formation, and Barrett metaplasia.

Pathologic changes in the myocardium and pericardium are common in systemic sclerosis, even in patients with no clinical evidence of cardiac involvement. Characteristic microvascular lesions include concentric intimal hypertrophy and luminal narrowing. Contraction band necrosis reflecting ischemia-reperfusion injury is prominent and may be accompanied by patchy myocardial fibrosis. In the kidneys, noninflammatory lesions occur in the interlobular arteries. Scleroderma renal crisis[4] (Chapter 110) is associated with striking changes in small renal arteries, with reduplication of elastic lamina, marked intimal proliferation, and concentric narrowing of the lumen (onion-skin), frequently accompanied by thrombotic microangiopathy with thrombosis and microangiopathic hemolysis.

Vasculopathy, Immune Dysregulation, and Fibrosis

Vasculopathy

Early vascular injury affects primarily the small- and medium-sized arteries and arterioles in multiple vascular beds. Endothelial cell injury and apoptosis result in altered balance of endothelium-derived vasodilatory (nitric oxide and prostacyclin) and vasoconstricting (endothelin-1) molecules, vascular permeability, and upregulation of adhesion molecules with transendothelial leukocyte diapedesis. Increased reactivity of platelets, activation of intravascular coagulation, defective fibrinolysis, and the resulting thrombosis further compromise vascular function. Injured capillaries lose their pericyte coverage and degenerate, thereby resulting in capillary rarefaction. Small blood vessels show intimal hyperplasia with thickening and reduplication of the basement membrane. Upon injury, endothelial cells undergo reprogramming through endothelial-mesenchymal transition. In the vascular media, myointimal cells proliferate, whereas the adventitial layers develop fibrosis. The net result is obliteration of capillaries, arterioles, and even large vessels, impaired blood flow and widespread tissue ischemia. Recurrent ischemia-reperfusion is associated with the generation of reactive oxygen species that further damage the endothelium.

Raynaud Phenomenon

The most characteristic and generally earliest vascular complication of systemic sclerosis is Raynaud phenomenon (Chapter 66),[5] which reflects abnormal thermal regulation of blood flow. Autonomic and peripheral nervous system changes in patients with Raynaud phenomenon are associated with impaired production of calcitonin gene–related peptide from sensory afferent nerves and heightened sensitivity of α_2-adrenergic receptors on vascular smooth muscle cells. In contrast to *primary* Raynaud phenomenon (also called Raynaud disease), which is a common and relatively benign condition, *secondary* Raynaud phenomenon is generally progressive and frequently complicated by vascular remodeling with irreversible structural changes that result in tissue damage.

Inflammation and Autoimmunity

Cellular Immunity

Immune dysregulation is a hallmark systemic sclerosis shares with other autoimmune diseases. In early disease, T cells, B cells, dendritic cells, and monocyte-macrophages are activated and accumulate within lesional tissues.

Tissue-infiltrating $CD4^+$ T cells display restricted TcR receptor signatures indicative of their oligoclonal expansion in response to unknown antigens. T cells show T_H2 polarization with secretion of interleukin (IL)–4, IL-13, and IL-21, and low levels of interferon (IFN)–γ. T_H2 cytokines induce TGF-β and promote the synthesis of collagen and other extracellular matrix molecules.[6] In early-stage systemic sclerosis, a predominant cytotoxic CD4 T cell accumulation may contribute to endothelial apoptosis.

Myeloid dendritic cells in systemic sclerosis show abnormally high secretion of inflammatory cytokines and chemokines such as CXCL. Macrophages are often prominent in early skin and lung lesion. Elevated expression of type I interferon-regulated genes (IFN signature) in systemic sclerosis is consistent with innate immune activation and may contribute to vascular injury.

Humoral immunity and autoantibodies

Evidence of B-cell dysregulation is prominent in systemic sclerosis,[7] and most patients have antinuclear antibodies, and a number of disease-specific autoantibodies. These autoantibodies have clinical utility as diagnostic and prognostic markers (Table 246-1). Systemic sclerosis–specific autoantibodies are commonly directed against intracellular proteins, such as topoisomerase-I, centromere, and RNA polymerases I and III. Autoantibodies directed against endothelial cells or recognizing cell surface receptors (platelet-derived growth factor receptor [PDGFR], angiotensin II receptor, and endothelin-1 receptor), and other antigens, including telomere-related proteins, have been reported in systemic sclerosis. B-cell alterations are implicated in mediating both the autoimmune and fibrotic components of systemic sclerosis.

Fibrosis

Fibrosis synchronously affecting the skin and multiple internal organs distinguishes systemic sclerosis from other rheumatic diseases. Fibrosis is characterized by the accumulation of a collagen-rich and rigid extracellular matrix elaborated by resident fibroblasts and myofibroblasts, and the replacement of tissue architecture disrupting normal function.

Myofibroblasts, which are smooth muscle cell–like mesenchymal cells with both contractile and biosynthetic properties, characterize all forms of fibrosis. Myofibroblasts normally appear transiently in damaged tissue to promote wound healing through production of extracellular matrix and of TGF-β, as well as contraction of the surrounding tissue. In systemic sclerosis, activated myofibroblasts accumulate within lesional tissue through one of three pathways: (1) in situ activation of quiescent resident fibroblasts, (2) reprogramming of injured epithelial, endothelial cells, and pericytes, or (3) differentiation of circulation-derived monocytic progenitor cells. Within the fibrotic tissue, activated myofibroblasts evade apoptosis.

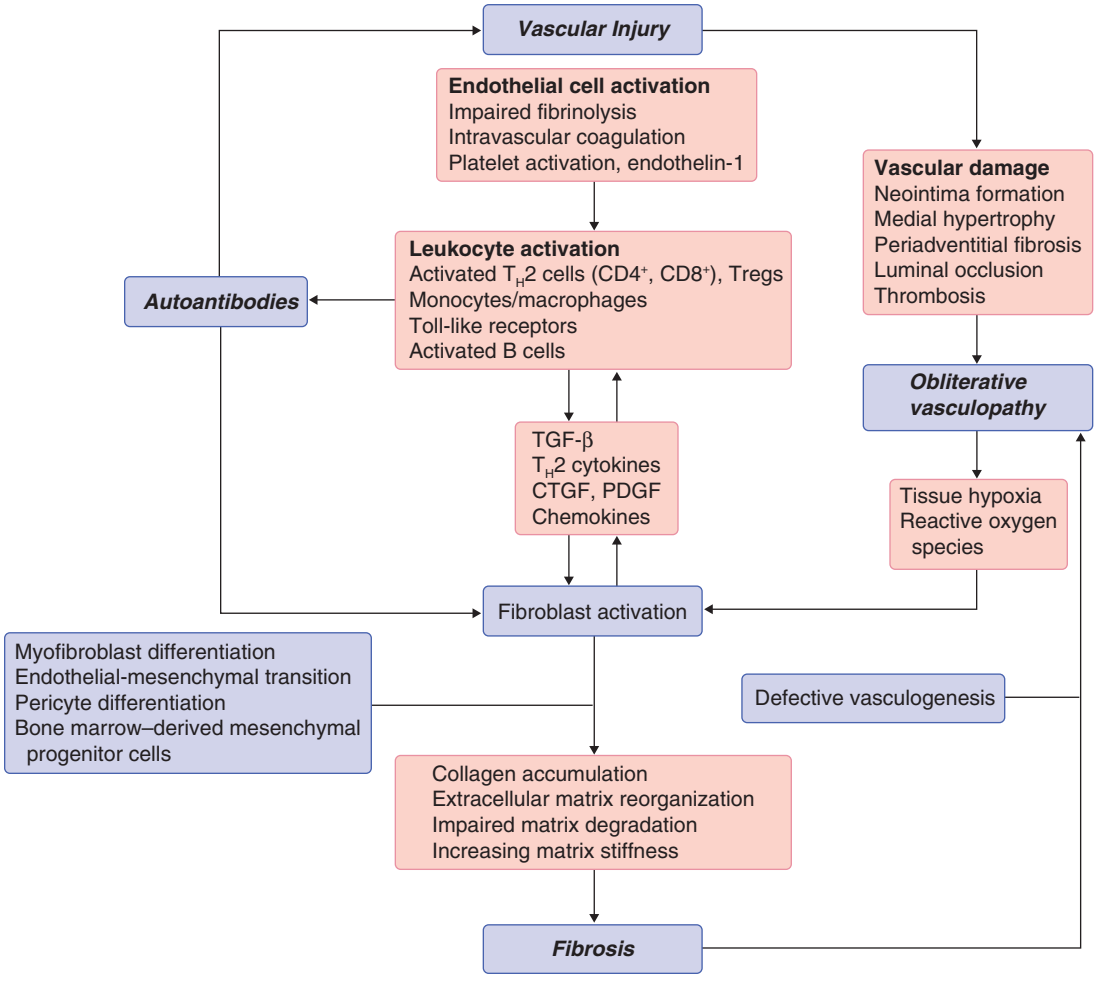

E-FIGURE 246-1. The tripartite pathogenesis of systemic sclerosis: vasculopathy, autoimmunity, fibrosis. Initial vascular injury in a genetically susceptible individual is the likely primary event of systemic sclerosis. Injury leads to vascular damage, inflammation, and autoimmunity. The inflammatory and immune responses generate cytokines and growth factors that further damage the endothelium and trigger fibroblast activation that underlies extracellular matrix remodeling and intractable fibrosis. Vasculopathy, loss of microvasculature, and reduced blood flow result in ischemia and oxidative stress that further aggravate vascular damage, tissue fibrosis, and atrophy. CTGF = connective tissue growth factor; PDGF = platelet-derived growth factor; TGF-β = transforming growth factor–β.

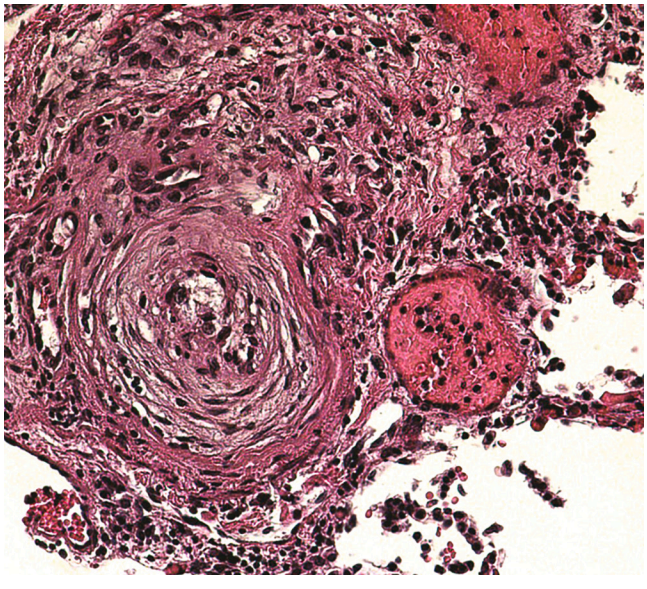

E-FIGURE 246-2. Pulmonary artery obliterative vasculopathy coexisting with fibrosis. Striking intimal hyperplasia and narrowing of the lumen of a small pulmonary artery, coexisting with interstitial pulmonary fibrosis, in a patient with systemic sclerosis.

CLINICAL MANIFESTATIONS

Virtually every organ can be affected in systemic sclerosis, but the relative frequency, tempo, and severity shows considerable patient-to-patient variability. Patients with limited cutaneous systemic sclerosis commonly present with long-standing Raynaud phenomenon, limited skin involvement, and insidious progression of internal organ disease. Patients with diffuse cutaneous systemic sclerosis characteristically develop extensive skin induration and joint stiffness associated with early-onset internal organ involvement (Table 246-2). However, many patients with systemic sclerosis defy easy classification, or show overlap with clinical and laboratory evidence of another autoimmune disease such as polymyositis (Chapter 248), Sjögren syndrome (Chapter 247), inflammatory polyarthritis (Chapter 240), or systemic lupus erythematosus (Chapter 245).

Initial Clinical Presentation

Diffuse Cutaneous Systemic Sclerosis

Patients with diffuse cutaneous systemic sclerosis typically present with puffy fingers, erythema, and pruritus, often accompanied by fatigue, stiffness, muscle weakness, and carpal tunnel syndrome. Raynaud phenomenon may not be present until later in the disease. Over weeks to months, the inflammatory edematous phase evolves into a chronic "fibrotic" phase with skin induration accompanied by dryness, hyperpigmentation, loss of body hair, and impaired sweating. Advancing skin changes commonly herald onset of internal organ involvement that is most rapidly progressive during the initial 4 years from disease onset. Thereafter, the risk for new organ involvement subsides.

Limited Cutaneous Systemic Sclerosis

In patients with limited cutaneous systemic sclerosis, the diagnosis is generally made at a later stage of the disease. Patients often have a long-standing history of Raynaud phenomenon, sometimes complicated by ischemic ulcerations at the fingertips. Disease course is indolent, with insidious progression of gastroesophageal reflux, mucocutaneous telangiectasia, or soft tissue calcinosis. Vascular manifestations tend to be more pronounced in limited cutaneous systemic sclerosis compared with diffuse cutaneous systemic sclerosis, whereas scleroderma renal crisis is uncommon.

Organ Involvement

Skin

Skin thickening typically starts in the distal fingers and is generally preceded by puffy fingers and hands. Skin involvement typically advances in a centripetal pattern from distal extremities. The skin may be hyperpigmented, but dark-skinned individuals may develop vitiligo-like "salt-and-pepper" changes which is most prominent on the scalp, upper back, and chest. Obliteration of eccrine and sebaceous glands decreases sweating and oil secretion, thereby causing dry and itchy skin. Facial changes include a beaklike nose, thinning and retraction of the lips, fine wrinkles (rhytids, radial furrowing) around the mouth, and occasionally a masklike facies due to reduced mobility of the eyelids, cheeks, and mouth (Fig. 246-1). Decreased oral aperture (microstomia) is common and can interfere with eating and oral hygiene.

In long-standing systemic sclerosis, the skin is atrophic and tethered to the underlying tissue. Telangiectasias due to dilation of postcapillary venules in the upper dermis are prominent on the face, hands, lips, and oral mucosa. Breakdown of atrophic skin can lead to painful and nonhealing ulcerations at the extensor surfaces of the interphalangeal joints, fingertips, and bony prominences such as the elbows and malleoli. Ischemic ulcerations at the fingertip heal slowly, may become secondarily infected, and give rise to pathognomonic digital tip "pitting." Ischemic soft tissue loss at the fingertips is associated with bony resorption of the terminal phalanges (acro-osteolysis) (Fig. 246-2).

Calcinosis of the skin and soft tissues is common. Concrete deposits composed of calcium hydroxyapatite crystals vary in size from tiny punctate lesions to large conglomerate masses. They can be readily visualized on plain radiographs and precisely localized and measured with dual-energy CT imaging (Fig. 246-3).

Common locations for calcinosis cutis include the hands (finger pads), extensor surfaces of the forearms, and olecranon and prepatellar bursae. Calcific deposits can ulcerate through the overlying skin, producing drainage of chalky white material, pain, and local inflammation, and may become secondarily infected.

Raynaud Phenomenon

Raynaud phenomenon (Chapter 66) is an episodic vasospastic event in virtually all patients with systemic sclerosis.[8] Typical attacks start with pallor

TABLE 246-1 CHARACTERISTIC SYSTEMIC SCLEROSIS-ASSOCIATED AUTOANTIBODIES

AUTOANTIBODY FREQUENCY	SUBSET	CHARACTERISTIC CLINICAL ASSOCIATION
Topoisomerase-I (10-40%; also called Scl-70)	Diffuse cutaneous (less commonly limited)	Tendon friction rubs, ILD, cardiac involvement, scleroderma renal crisis; isolated PAH rare
Centromere (15-40%)	Limited cutaneous	Digital ischemia, calcinosis cutis, isolated PAH, PBC; severe ILD and scleroderma renal crisis rare
RNA polymerase III (4-25%)	Diffuse cutaneous	Extensive skin involvement; tendon friction rubs, scleroderma renal crisis, increased cancer risk
U3-RNP/fibrillarin (1-5%)	Diffuse cutaneous	PAH, ILD, myositis
Th/To (1-7%)	Limited cutaneous	ILD, isolated PAH
PM/Scl (0-6%)	Limited cutaneous	Calcinosis cutis, myositis, arthritis
U1-RNP (5-35%)	MCTD	Severe PAH, myositis

ILD = interstitial lung disease; MCTD = mixed connective tissue disease; PAH = pulmonary arterial hypertension; PBC = primary biliary cirrhosis; RNP = ribonucleoprotein.

TABLE 246-2 CLASSIFICATION OF SYSTEMIC SCLEROSIS

CHARACTERISTIC FEATURES	DIFFUSE CUTANEOUS SYSTEMIC SCLEROSIS	LIMITED CUTANEOUS SYSTEMIC SCLEROSIS
Skin induration	Diffuse: fingers, extremities, face, trunk; progression rapid; tendon friction rubs	Limited to fingers, distal to elbows, face; progression slow
Raynaud phenomenon	Onset occurs coincident with or subsequent to skin involvement	Precedes skin involvement; often severe; associated with critical ischemia
Pulmonary fibrosis	Frequent, early, can be progressive and severe	Occasional, rarely severe
Pulmonary arterial hypertension	Occasional, commonly in association with pulmonary fibrosis	Frequent, late, may be isolated
Scleroderma renal crisis	Occurs in up to 15%; early	Very rare
Calcinosis cutis	Infrequent	Frequent, prominent
Characteristic autoantibodies	Anti-topoisomerase I (Scl-70), anti-RNA polymerase III	Anticentromere

(vasoconstriction) followed by cyanosis (ischemia) and erythema (reperfusion), commonly triggered by exposure to cold or emotional stress.

Distinguishing primary from secondary Raynaud can present a challenge. Compared to primary, secondary Raynaud typically develops at an older age (>30 years) and tends to be more severe. Nailfold capillaroscopy is a useful noninvasive bedside method for visualizing cutaneous capillaries using an ophthalmoscope. Patients with primary Raynaud phenomenon have capillaries that appear as regularly spaced parallel vascular loops at the nailfolds, whereas in systemic sclerosis, capillaries are distorted with widened and irregular loops, dilated lumen, areas of vascular "dropout," and microhemorrhages (Fig. 246-2A).

Gastrointestinal Involvement

Gastrointestinal tract involvement is very common in patients with both limited and diffuse cutaneous systemic sclerosis, and when severe, is a marker of poor prognosis. Smooth muscle atrophy and obliterative small vessel vasculopathy with or without fibrosis throughout the length of the gastrointestinal tract underlies altered peristaltic activity and consequent complications.

Upper Gastrointestinal Tract

Oropharyngeal manifestations of systemic sclerosis include xerostomia, microstomia, periodontal disease, and resorption of the mandibular condyles. The frenulum of the tongue may be shortened. Gastroesophageal reflux is associated with heartburn, regurgitation, and dysphagia; however, in some patients it can also be asymptomatic (Chapter 124). Reduced lower esophageal sphincter pressure frequently coexists with impaired esophageal clearance of refluxed gastric contents due to diminished motility in the distal esophagus.[9] Delayed gastric emptying further aggravates the problem.

Esophageal strictures and Barrett esophagus (Chapter 124) can complicate long-standing reflux. Hoarseness and chronic cough or throat clearing are common and may represent extraesophageal manifestations of reflux disease. Recurrent microaspiration of gastric contents may aggravate underlying interstitial lung disease. A distinct interstitial lung disease called centrilobular fibrosis, associated with esophageal dilation and chronic gastroesophageal reflux, is occasionally seen in systemic sclerosis.

Stomach

Gastroparesis and delayed gastric emptying manifest as early satiety, abdominal distention, and aggravated reflux symptoms.[10] Gastric vascular ectasia or "watermelon stomach" develops in 5% of patients and is more common in those with an anti-RNA polymerase III antibody. Patients with gastric vascular ectasia may have recurrent gastrointestinal bleeding and present with unexplained iron deficiency anemia.

Lower Gastrointestinal Tract

Impaired small bowel motility in systemic sclerosis can cause chronic diarrhea due to bacterial overgrowth. Ensuing fat and protein malabsorption, vitamin B_{12} and D deficiency, and malnutrition are associated with high mortality. Disturbed intestinal motor function can also cause recurrent intestinal pseudo-obstruction with acute abdominal pain, nausea, and vomiting. Colonic and anorectal involvement underlie constipation, rectal prolapse, and fecal incontinence. In late-stage disease, wide-mouth colonic sacculations can occur and cause perforation and bleeding. An occasional radiologic finding is pneumatosis cystoides intestinalis, which indicates air trapping in the bowel wall. Rupture of these lesions can cause pneumoperitoneum. Primary biliary cirrhosis can occur in patients with limited cutaneous systemic sclerosis.

Lung Involvement

Two major forms of lung involvement occur in systemic sclerosis: interstitial lung disease (Chapter 80) and pulmonary arterial hypertension (Chapter 69), which may coexist in many patients. Less frequent pulmonary manifestations include aspiration pneumonitis complicating gastroesophageal reflux, obliterative bronchiolitis, pleural reactions, restrictive ventilatory changes due to chest wall fibrosis, spontaneous pneumothorax, and drug-induced

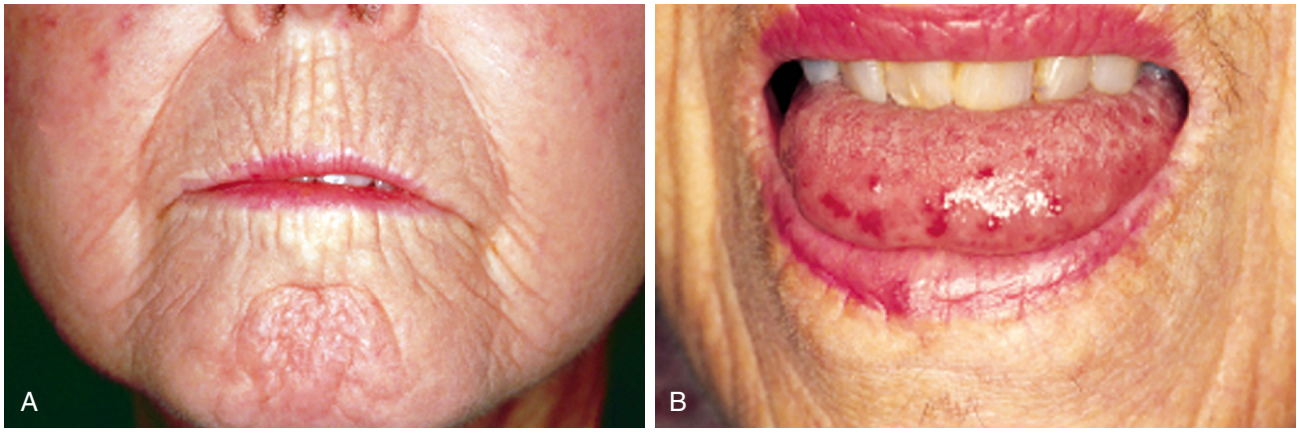

FIGURE 246-1. Facial features in systemic sclerosis. A, Perioral furrowing. Note vertical lines around the mouth in a patient with diffuse cutaneous systemic sclerosis. **B,** Telangiectasia on the lips and tongue in a patient with long-standing limited cutaneous systemic sclerosis.

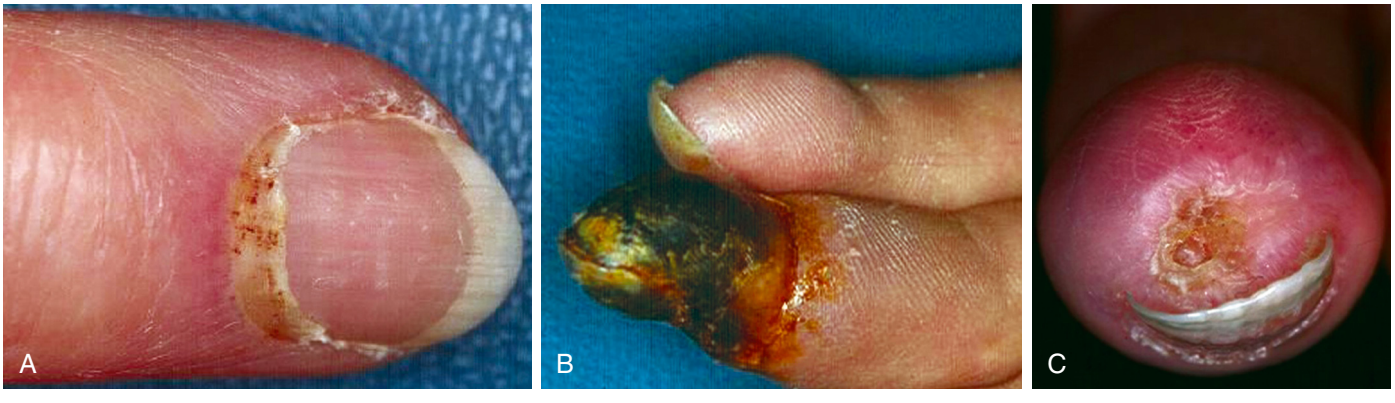

FIGURE 246-2. Vascular complications of systemic sclerosis in the fingers. A, Nailfold microvascular changes. **B,** Digital infarction. Sharply demarcated necrosis of the fingertip in a patient with limited cutaneous systemic sclerosis associated with severe Raynaud phenomenon. **C,** Ischemic digital tip ulceration and pitting.

FIGURE 246-3. Calcinosis cutis in systemic sclerosis. Dual-energy computed tomographic image of the hand of a 56-year-old woman with long-standing limited cutaneous systemic sclerosis. Note calcification along the distal pulp of the index finger extending focally to the skin. Another calcific deposit along the palmar surface of the long finger middle phalangeal head. (Courtesy of Imran Omar MD.)

lung toxicity. The risk of lung cancer, particularly bronchoalveolar carcinoma, is increased.

Interstitial Lung Disease

Interstitial lung disease (Chapter 80) in systemic sclerosis is common and can remain asymptomatic until it is quite advanced.[11] The most frequent presenting symptoms are exertional dyspnea,[12] fatigue, and reduced exercise tolerance. A chronic dry cough may be present. Physical examination may reveal "Velcro" crackles that are prominent at the lung bases.

Evidence of interstitial lung disease can be found in almost all patients with systemic sclerosis, is clinically significant in up to 50%, and may or may not progress. The most rapid progression generally occurs within the first 3 years of the onset of the disease, with patients losing greater than 100 mL/year in forced vital capacity.

Pulmonary Arterial Hypertension

Approximately 15% of systemic sclerosis patients develop pulmonary hypertension, defined as a mean resting pulmonary arterial pressure of 25 mm Hg or greater, with a pulmonary capillary wedge pressure of 15 mm Hg or less (Chapter 69). In the setting of systemic sclerosis, pulmonary hypertension can be an isolated abnormality, or it can coexist with interstitial lung disease.[13] Most patients have a progressive course, with development of right heart failure and increased mortality. Risk factors include limited cutaneous disease, older age of disease onset, severe Raynaud phenomenon, numerous cutaneous telangiectasias, and positivity for anticentromere, U1-RNP, U3-RNP (fibrillarin), Th/To, B23, or β_2-glycoprotein I autoantibodies.

The initial symptoms of pulmonary hypertension are exertional dyspnea and reduced exercise capacity, but early-stage disease is often clinically silent. With progression, angina, syncope, and symptoms and signs of right-sided heart failure manifest. Physical examination shows tachypnea, a prominent pulmonic S_2 heart sound, palpable right ventricular heave, elevated jugular venous pressure, and dependent edema.

Kidney Involvement

Scleroderma renal crisis, the most dreaded complication of systemic sclerosis, occurs in 10 to 15% of patients. It almost invariably occurs within 4 years of disease onset.[14] Vascular injury triggers obliterative vasculopathy, luminal narrowing in the renal arcuate arteries, a progressive reduction in renal blood flow, juxtaglomerular hyperplasia, and increased renin secretion, with further renal vasoconstriction resulting in a vicious cycle that culminates in accelerated hypertension and oliguric renal failure (Chapters 64 and 110). Patients characteristically present with abrupt onset of hypertension and progressive renal insufficiency, but the blood pressure remains normal or only modestly elevated in some cases. So-called normotensive renal crisis is associated with a poor outcome. Hypertensive encephalopathy and retinopathy, pericarditis, and arrhythmias may complicate scleroderma renal crisis. In many patients, oliguric renal failure develops over a period of weeks.

Risk factors for scleroderma renal crisis, beside early-stage (generally less than 4 years) disease, include rapidly progressive or extensive skin involvement with tendon friction rubs, Black race, male sex, and anti-RNA polymerases III positivity. In contrast, anticentromere positivity signals a low risk for scleroderma renal crisis. Pericardial effusion, new-onset anemia, and thrombocytopenia may be harbingers of impending scleroderma renal crisis, and recent corticosteroid use is associated with a more than 10-fold increased risk.

Abnormal renal function or proteinuria is detected in more than one third of patients with systemic sclerosis. However, such patients generally do not progress to end-stage renal disease.[15] Glomerulonephritis associated with lupus serologies or antineutrophil cytoplasmic antibody–positive renal vasculitis occurs.

Cardiac Involvement

Although frequently detected in systemic sclerosis using sensitive diagnostic tools, cardiac involvement is commonly silent.[16,17] Clinical cardiac involvement is more frequent in patients with diffuse cutaneous systemic sclerosis; it generally develops early in the course of the disease and represents a predictor of poor prognosis. The endocardium, myocardium, and pericardium may each be affected in isolation or in combination. Tachyarrhythmias, conduction abnormalities, valvular regurgitation, diastolic heart failure, and pericardial effusion can occur. Systemic and pulmonary arterial hypertension, as well as lung and renal involvement, also affect the heart. Myocarditis can develop in association with muscle inflammation. Pericardial effusion develops in more than 15% of patients but is not always clinically significant.

Musculoskeletal Complications

Carpal tunnel syndrome (Chapter 388) may be a presenting manifestation of systemic sclerosis. Joint mobility is progressively impaired, especially in the hands. Large joint contractures can be accompanied by audible or palpable tendon friction rubs that are caused by fibrosis and adhesion of the tendon sheaths and fascial planes at the affected joint. The presence of tendon friction rubs often signals aggressive disease. Frank joint inflammation is uncommon in systemic sclerosis; however, erosive polyarthritis in the hands can occur. Muscle weakness may be a sign of deconditioning, disuse atrophy, and malnutrition. Inflammatory myositis indistinguishable from idiopathic polymyositis (Chapter 248) may be seen, generally in early disease. A noninflammatory myopathy characterized by atrophy and fibrosis in the absence of elevated muscle enzyme levels is common in late disease. Bone resorption affects the distal tufts of terminal phalanges (acro-osteolysis), mandibular condyles, ribs, and distal clavicles.

Other Clinical Manifestations

In addition to microangiopathy, involvement of larger blood vessels (>100 μm) can occur in systemic sclerosis. Manifestations include occlusion of the digital and ulnar arteries, leading to ischemic ulcerations and even loss of digits or limbs. Epidemiologic studies indicate increased risk of coronary artery disease in patients with systemic sclerosis. Dry eyes and dry mouth are common in systemic sclerosis, but in contrast to primary Sjögren syndrome (Chapter 247), salivary gland biopsy in such cases may show fibrosis rather than focal lymphocytic infiltration. Hypothyroidism (Chapter 207) due to thyroid fibrosis is common and may be associated with antithyroid autoantibodies. Although the central nervous system is generally spared in systemic sclerosis, autonomic neuropathy, as well as a primarily sensory neuropathy of the trigeminal nerve due to fibrosis or vasculopathy, can occur. Pregnancy in women with active systemic sclerosis has been associated with an increased rate of adverse fetal outcomes. Furthermore, cardiopulmonary involvement might worsen during pregnancy, and scleroderma renal crisis can occur. In men, inability to attain or

maintain penile erection due to vascular insufficiency and fibrosis is frequent and may be the presenting disease manifestation.

Systemic Sclerosis and Cancer

Several studies indicate that patients with systemic sclerosis have an increased risk of cancer.[18] Lung cancer and esophageal adenocarcinoma typically occur in the setting of long-standing interstitial lung disease or gastroesophageal reflux disease, and chronic inflammation and tissue damage may be contributing factors. In contrast, systemic sclerosis-associated cancer of the breast, lung and ovaries, and lymphoma, tends to occur in close temporal association with the onset of systemic sclerosis and is often associated with anti-RNA polymerase III antibodies. In these cases, systemic sclerosis represents a paraneoplastic syndrome triggered by the antitumor immune response.

DIAGNOSIS

Induration in the fingers or proximally (associated with Raynaud phenomenon) and characteristic visceral organ manifestations are usually sufficient to establish the diagnosis of systemic sclerosis, although these features may be absent in early disease. Standardized criteria for the classification of systemic sclerosis show high degree of specificity and sensitivity (Table 246-3).

Rarely, full-thickness skin biopsy is required for excluding scleroderma mimics such as scleredema, scleromyxedema, or pansclerotic morphea (Table 246-4). Primary Raynaud (disease) is differentiated from systemic sclerosis by normal-appearing nailfold capillaries and absence of autoantibodies or other disease manifestations. Diagnosing systemic sclerosis can be difficult in the early stages of the disease because initial symptoms and findings are often nonspecific and can be mistaken for rheumatoid arthritis, systemic lupus erythematosus, inflammatory muscle disease, or undifferentiated connective tissue disease. Occasional patients whose systemic sclerosis presents with accelerated hypertension and renal failure or with gastrointestinal bleeding caused by watermelon stomach as the initial disease manifestation pose a diagnostic challenge.

Laboratory Features

Anemia is common in patients with systemic sclerosis and may reflect chronic inflammation, gastrointestinal bleeding from gastric vascular ectasia, erosive gastritis or chronic esophagitis, or folate and vitamin B_{12} deficiency due to small bowel bacterial overgrowth and malabsorption. Microangiopathic hemolytic anemia (Chapter 146) caused by mechanical trauma and red blood cell fragmentation in the damaged microvasculature is a laboratory hallmark of scleroderma renal crisis. In contrast to other rheumatic diseases, erythrocyte sedimentation rate and C-reactive protein generally show only modest elevation. Monitoring serum levels of prealbumin and vitamin K is useful in patients with small bowel bacterial overgrowth and malabsorption.

Circulating antinuclear autoantibodies are present in virtually all patients with systemic sclerosis and can be detected at, or even before, disease onset.[19] Other autoantibodies are specific for systemic sclerosis (see Table 246-1). Anticentromere antibodies are associated with pulmonary hypertension, whereas significant cardiac involvement, pulmonary fibrosis, or scleroderma renal crisis occurs only rarely in these patients. Topoisomerase-I antibody positivity is associated with pulmonary fibrosis and reduced survival. Antibodies to RNA polymerase III are associated with increased risk for scleroderma renal crisis. Uncharacterized autoantibodies showing a nucleolar pattern of immunofluorescence are generally associated with aggressive disease. Antibodies to β_2-glycoprotein I are not specific but in systemic sclerosis identify increased risk for critical ischemia.

Diagnosing Systemic Involvement

Esophageal Disease

On high-resolution computed tomography (HRCT) of the chest, the esophagus is dilated or patulous and shows intraluminal air. Endoscopy may show severe erosive esophagitis in patients with minimal reflux symptoms.

Gastric Disease

On endoscopy, parallel longitudinal mucosal folds resembling the stripes of a watermelon are seen in the gastric antrum. The histologic features of dilated thrombosed mucosal capillaries and fibromuscular dysplasia of the lamina propria represent the characteristic microangiopathy of systemic sclerosis.

Interstitial Lung Disease

Plain chest radiography is relatively insensitive for detection of early interstitial lung disease. In contrast, HRCT of the chest is highly sensitive (Chapter 72). Findings in systemic sclerosis include reticular interstitial opacities,

TABLE 246-3 THE AMERICAN COLLEGE OF RHEUMATOLOGY/EUROPEAN LEAGUE AGAINST RHEUMATISM CRITERIA FOR THE CLASSIFICATION OF SYSTEMIC SCLEROSIS

ITEM	SUB-ITEM(S)	WEIGHT/ SCORE*
Skin thickening of the fingers of both hands extending proximal to the metacarpophalangeal joints *(sufficient criterion)*	–	9
Skin thickening of the fingers *(only count the higher score)*	Puffy fingers Sclerodactyly of the fingers (distal to the metacarpophalangeal joints but proximal to the proximal interphalangeal joints)	2 4
Fingertip lesions *(only count the higher score)*	Digital tip ulcers Fingertip pitting scars	2 3
Telangiectasia	–	2
Abnormal nailfold capillaries	–	2
Pulmonary arterial hypertension and/or interstitial lung disease *(maximum score is 2)*	Pulmonary arterial hypertension Interstitial lung disease	2 2
Raynaud phenomenon	–	3
Systemic sclerosis-related autoantibodies (anticentromere, anti-topoisomerase I [anti-Scl-70], anti-RNA polymerase III) *(maximum score is 3)*	Anticentromere Anti-topoisomerase I Anti-RNA polymerase III	1 1 1

*The total score is determined by adding the maximum weight (score) in each category. Patients with a total score of 9 or higher are classified as having definite systemic sclerosis.

The criteria are not applicable to patients with skin thickening sparing the fingers or to patients who have a scleroderma-like disorder that better explains their manifestations (e.g., nephrogenic sclerosing fibrosis, generalized morphea, eosinophilic fasciitis, scleredema diabeticorum, scleromyxedema, porphyria, lichen sclerosis, graft-versus-host disease, diabetic cheiroarthropathy).

From van den Hoogen F, Khanna D, Fransen J, et al. 2013 classification criteria for systemic sclerosis: an American College of Rheumatology/European League Against Rheumatism collaborative initiative. *Arthritis Rheum*. 2013;65:2737-2747.

TABLE 246-4 CONDITIONS THAT MAY BE ASSOCIATED WITH SCLERODERMA-LIKE SKIN INDURATION

- Systemic sclerosis
  - Limited cutaneous systemic sclerosis
  - Diffuse cutaneous systemic sclerosis
- Localized scleroderma
  - Morphea (plaque, guttate, generalized)
  - Linear scleroderma, "coup de sabre"
- Pansclerotic morphea
- Paraneoplastic syndromes
- Scleredema and diabetic scleredema
- Scleromyxedema (papular mucinosis)
- Nephrogenic fibrosing syndrome (nephrogenic systemic fibrosis)
- Chronic graft-versus-host disease
- Diffuse fasciitis with eosinophilia (Shulman disease, eosinophilic fasciitis)
- Eosinophilia-myalgia syndrome
- Stiff skin syndrome
- Chemical exposure-associated scleroderma-like conditions
  - Vinyl chloride–induced disease, other solvents
  - Pentazocine-induced skin fibrosis
  - Other drug associations

predominantly in the lower lobe periphery, in isolation or in combination with ground-glass opacifications. Less common are mediastinal lymphadenopathy and honeycombing. The extent of lung disease on initial HRCT predicts progression of interstitial lung disease and may be useful when deciding the need for therapy. Bronchoalveolar lavage (Chapter 73) is occasionally needed to exclude infection, while lung biopsy is generally indicated only if lung cancer is suspected.

Pulmonary Hypertension

In patients who have pulmonary hypertension, the pulmonary artery systolic pressures as determined by screening Doppler echocardiography is greater than 40 mm Hg. Right heart catheterization is virtually always required to confirm the diagnosis of pulmonary hypertension, assess its severity, and evaluate ventricular function.

Scleroderma Renal Crisis and Nephropathy

In systemic sclerosis-associated renal disease, the urinalysis usually shows only mild proteinuria, granular casts, and microscopic hematuria. Thrombocytopenia and microangiopathic hemolysis with fragmented red blood cells can sometimes erroneously lead to the diagnosis of thrombotic thrombocytopenic purpura or hemolytic-uremic syndrome (Chapter 158). Kidney biopsy, which is occasionally required for diagnosis and prognosis, can show chronic changes including reduplication of elastic fibers, sclerosed glomeruli, tubular atrophy, and interstitial fibrosis. However, the characteristic arteriolar intimal and medial proliferation and luminal narrowing are indistinguishable from the changes of accelerated hypertension.

Cardiac Involvement

Conventional echocardiography has a low sensitivity for detecting systemic sclerosis-associated heart involvement. In contrast, tissue Doppler echocardiography, single-photon emission computed tomography, and especially cardiac magnetic resonance imaging (cMRI) commonly reveal myocardial abnormalities in systemic sclerosis. Characteristic findings include abnormal ventricular relaxation and reversible perfusion defects. An elevated serum NT-pro-BNP in systemic sclerosis is a sensitive marker for increased pulmonary artery pressure but may also indicate primary cardiac involvement.

TREATMENT AND PREVENTION

Because of the marked patient-to-patient variability in clinical presentation, a comprehensive baseline evaluation is paramount. Optimal patient management should include prompt diagnosis, accurate classification and risk stratification, early recognition and assessment of organ-based complications, and long-term monitoring of progression, disease activity, and response to therapy. Management of complications should be proactive, with regular screening and initiation of appropriate intervention at the earliest possible opportunity. Given the multisystem nature of systemic sclerosis, an integrated team approach, typically at specialized medical centers where relevant expertise is available, is optimal.

Immunosuppressive agents that are highly effective in other connective tissue diseases have shown modest or no benefit in systemic sclerosis. Corticosteroids alleviate stiffness, fatigue, and aching in early-stage disease, but do not slow disease progression and are associated with an increased risk for scleroderma renal crisis. Therefore corticosteroids should be avoided if possible; when absolutely necessary, they should be given at the lowest dose possible and for brief periods only.

Skin Care

Skin involvement in early systemic sclerosis is inflammatory, and symptoms may respond to systemic antihistamines or short-term low-dose corticosteroid treatment. Skin dryness can be managed with the use of hydrophilic ointments and emollient bath oils. Fingertip ulcerations should be protected by occlusive dressing to promote healing and prevent infection. Infected skin ulcers are treated with topical or oral antibiotics and may necessitate surgical débridement. Because of the increased risk for scleroderma renal crisis, blood pressure should be carefully monitored.

Mycophenolate (up to 3000 mg/d), cyclophosphamide (up to 2 mg/kg/d), methotrexate (15 mg/week), and rituximab (1000 mg IV on days 0 and day 15, then repeated every 6 months) have been associated with modest improvement in skin induration in early-stage systemic sclerosis. Some data support the use of abatacept, tofacitinib, intravenous immunoglobulin, and extracorporeal photopheresis for the treatment of some patients with systemic sclerosis. No medical therapy has been shown to be effective in preventing soft tissue calcification or in promoting its dissolution, and surgical therapy and lithotripsy are only occasionally effective.

Autologous hematopoietic stem cell transplantation is emerging as a therapeutic option in carefully screened patients whose severe systemic sclerosis fails to respond to other treatments (Chapter 163). This intervention can improve skin, disease, pulmonary disease, and long-term event-free survival, although it is associated with a treatment-related mortality of up to 6% at 72 months.[A1]

Interstitial Lung Disease

The optimal management of patients with subclinical interstitial lung disease is currently uncertain. Patients with symptomatic interstitial lung disease or extensive pulmonary function or radiologic abnormalities should be treated with mycophenolate (up to 3000 mg/d).[A2] Cyclophosphamide (up to 2 mg/kg/d) also can slow the progression of symptomatic interstitial lung disease in early systemic sclerosis,[A3] but these benefits are short-lived. Rituximab (given IV at 1000 mg on days 0 and 15 and then every 6 months) has shown some benefit in improving skin involvement and stabilizing lung function,[A4] but it has not been evaluated in long-term randomized trials.

If lung disease progresses despite 3 to 6 months of such treatment, the antifibrotic drug nintedanib (150 mg bid), or tocilizumab (162 mg subcutaneously weekly) should be added.[20,21] Nintedanib slows the rate of decline in the forced vital capacity of patients with systemic sclerosis-associated interstitial lung disease by about 45%, although it does not alter other disease manifestations.[A5,A6] Tocilizumab also can significantly slow the loss of lung function in patients with early disease.[A7,A8]

Gastrointestinal Complications

Because even significant gastroesophageal reflux may be asymptomatic, all patients with systemic sclerosis should be treated for this complication (Chapter 124). Proton pump inhibitors (Table 124-1) may need to be given in relatively high doses and for prolonged periods. Patients should be instructed to elevate the head of the bed and eat frequent small meals. Recurrent gastrointestinal bleeding due to gastric vascular ectasia can be treated with laser or argon plasma photocoagulation. Bacterial overgrowth (Chapter 126) is treated with antibiotics. In patients with malnutrition but intact small bowel function, enteral nutrition (Chapter 198) can be effective. Refractory hypomotility of the small bowel may respond to subcutaneous octreotide injections (Chapter 122). Anorectal complications may respond to sacral neuromodulation (Chapter 131).

Vascular Disease

The goal of vascular therapy in systemic sclerosis is to reduce the frequency and duration of vasospastic episodes, prevent ischemic complications, and enhance their healing, and slow the progression of obliterative vasculopathy.[22] Patients should dress warmly, minimize cold exposure, and avoid cigarette smoking or drugs that could precipitate or exacerbate vasospastic episodes. Calcium-channel blockers such as nifedipine and diltiazem (Chapter 66) are used commonly for Raynaud phenomenon but show only moderate benefit, and their use is often limited by side effects. Angiotensin II receptor blockers such as losartan (up to 50 mg/day) are effective and generally well tolerated. Patients with severe Raynaud phenomenon and ischemic digital ulcers may require 5-phosphodiesterase inhibitors (e.g., sildenafil 2 mg three times daily), intradigital botulinum toxin injections, bosentan (62.5 mg twice daily), local sympathetic blockade, or intravenous prostaglandins. Low-dose aspirin (81 mg daily) and dipyridamole (25 mg three times daily) prevent platelet activation and may have a role as adjunctive agents in treating Raynaud phenomenon, but they must be used with caution in light of the risk of bleeding from gastric vascular ectasia lesions.

The endothelin-1 receptor antagonist bosentan (62.5 mg twice daily) reduces development of new ischemic ulcers, and sildenafil (20 mg three times daily) may promote ulcer healing.[A9] Patients with ischemic digital ulcerations may require surgical débridement, especially if necrotic tissue is present. Empirical long-term therapy with statins and antioxidants may slow the progression of vascular damage.

Pulmonary Arterial Hypertension

All patients with systemic sclerosis should be screened for pulmonary hypertension at initial evaluation, and those high-risk patients (see Table 69-2) should be screened on a yearly basis. Rituximab (1000 mg IV on days 0 and 15, then repeated every 6 months) has shown promising results.[A10] Otherwise, treatment is as for symptomatic pulmonary hypertension (see Fig. 69-6) in general, beginning with an endothelin-1 receptor antagonist or a 5-phosphodiesterase inhibitor. If the clinical response is inadequate, 5-phosphodiesterase inhibitors may be used in combination with endothelin-1 receptor antagonists. Prostacyclin analogs can be administered intravenously, by continuous subcutaneous infusion, or by frequent inhalations (see Chapter 69). Lung transplantation remains an option for selected patients with systemic sclerosis–associated pulmonary hypertension or interstitial lung disease who fail medical therapy.

Scleroderma Renal Crisis

Early recognition of impending or early scleroderma renal crisis is essential. In patients presenting with renal crisis, hospitalization and prompt initiation of short-acting angiotensin converting enzyme (ACE) inhibitors in escalating doses

is essential. The goal is to achieve adequate blood pressure control before the onset of renal failure.

Because patients with early-stage systemic sclerosis and progressive skin involvement are at highest risk, they should be instructed to monitor their blood pressure daily and report significant alterations immediately. Corticosteroids should be used only when absolutely necessary and at the lowest possible doses. There is no evidence that prophylactic use of ACE inhibitors can prevent the development of scleroderma renal crisis or ameliorate its severity.

PROGNOSIS

Patients with diffuse cutaneous systemic sclerosis have a more rapidly progressive disease course, greater internal organ involvement, and generally worse prognosis compared with those with limited cutaneous systemic sclerosis. However, the outcome of the disease in an individual patients can be difficult to predict.

Early inflammatory symptoms such as fatigue, edema, arthralgia, and pruritus commonly subside. Skin thickening typically reaches a plateau, followed by slow regression, which characteristically occurs in an order that is the reverse of initial involvement, with softening on the trunk followed by proximal and finally the distal extremities. Sclerodactyly, finger contractures, and microstomia generally fail to resolve. Relapse or recurrence of skin thickening may occur with tapering or discontinuation of therapy. Visceral organ involvement develops and shows most rapid progression during the initial 2 to 4 years of the disease. New organ involvement rarely occurs once the skin involvement has reached a plateau. Similarly, scleroderma renal crisis almost invariably occurs within the first 4 years of disease. In patients with limited cutaneous systemic sclerosis, Raynaud phenomenon may precede other disease manifestations by years or even decades. In these patients, Raynaud, reflux, and calcinosis generally persist, and visceral organ complications such as pulmonary hypertension and primary biliary cirrhosis may develop late in the course of the disease.

Age- and gender-adjusted standardized mortality ratios (SMRs) in patients with systemic sclerosis have ranged from 1.05 to 5.40 across studies, but an overall SMR of 2.72 higher than in the general population.[23] The 10-year survival rate is 55% for patients with diffuse cutaneous systemic sclerosis and 75% for patients with limited cutaneous systemic sclerosis. Survival correlates with the extent of skin involvement, which represents a surrogate for visceral organ involvement. The leading causes of death are pulmonary fibrosis, pulmonary hypertension, renal and severe gastrointestinal involvement, and cardiac disease. Markers of poor prognosis include male sex, Black race, older age at disease onset, low body mass index, extensive skin thickening with truncal involvement, and evidence of significant or progressive visceral organ involvement. Autoantibodies to topoisomerase-I or absence of anticentromere antibodies are markers of poor prognosis. In one study, systemic sclerosis patients who had extensive skin involvement, vital capacity less than 55% of predicted, significant gastrointestinal involvement, and clinically evident cardiac involvement or scleroderma renal crisis had a less than 40% 10-year survival.

The severity of pulmonary hypertension in systemic sclerosis is correlated with mortality. Patients with a mean pulmonary artery pressure of 45 mm Hg or higher have about a 33% 3-year survival rate.

In scleroderma renal crisis, therapy with ACE inhibitors has had a dramatic effect on survival, increasing from less than 10% at 1 year in the pre-ACE inhibitor era to better than 70% 3-year survival at the present time. Despite timely intervention, however, more than 50% of patients with scleroderma renal crisis will require renal replacement therapy, although some ultimately recover sufficient renal function to be able to discontinue hemodialysis. Oliguria or a serum creatinine higher than 3 mg/dL at presentation predicts poor outcome. Kidney transplantation is appropriate for patients unable to discontinue dialysis after 2 years. Survival with renal transplantation in systemic sclerosis is comparable to that in other connective tissue diseases, and recurrence of scleroderma renal crisis in the kidney graft is rare.

OTHER SCLEROTIC DISEASES

MIXED CONNECTIVE TISSUE DISORDER

Mixed connective tissue disorder (MCTD) is an overlap syndrome that is characterized by features of systemic lupus erythematosus, systemic sclerosis, and myositis, all occurring in the same patient.[24] In the early phase, most patients have Raynaud phenomenon in association with edema of the hands and evidence of inflammatory muscle disease. Over time, these patients sequentially manifest other features of connective tissue diseases, including pericarditis, esophageal dysmotility, sclerodactyly, neuropathy, and pulmonary arterial hypertension. Erosive arthritis does not occur. However, some patients develop acute renal involvement similar to scleroderma renal crisis. In the early stage of this disorder, it can be difficult to predict whether the patient will progress to develop a distinct connective tissue disease such as systemic sclerosis or systemic lupus erythematosus.[25] A diagnostic hallmark of mixed connective tissue disorder is the presence of autoantibody specificity against U1-ribonuclear protein (U1-RNP), often at very high titer.

TREATMENT AND PROGNOSIS

The treatment of mixed connective tissue is generally symptomatic, including nonsteroidal anti-inflammatory agents (Table 26-4), with glucocorticoids (e.g., prednisone up to 1 mg/kg/day) and hydroxychloroquine (200 mg daily) for more severe disease in specific affected organs. Patients with mixed connective tissue disorder generally have a better prognosis than those with systemic sclerosis.

LOCALIZED SCLERODERMAS

Localized scleroderma refers to a family of generally benign skin conditions characterized by discreet areas of skin induration in the absence of Raynaud phenomenon or of significant systemic involvement.[26] Lesional skin is discolored and indurated and histologically may be indistinguishable from systemic sclerosis. Localized scleroderma has multiple distinct forms. When it occurs as single or multiple solitary patches of induration, it is called morphea. When these patches coalesce, the condition is called generalized morphea. The lesions are generally asymmetric in distribution and spare the digits. Induration may follow in a linear distribution, most commonly on the lower extremities (linear scleroderma). In children, linear scleroderma can be complicated by growth retardation and joint contractures.

In adults with localized scleroderma, methotrexate (15 mg per week), mycophenolate (up to 1500 mg twice daily), topical calcipotriene (0.005% applied twice daily), and ultraviolet phototherapy have shown benefit. A rare but severe variant with extensive, disabling, and treatment-resistant chronic skin induration, but lacking significant internal organ involvement, is called pansclerotic morphea.

Immunoglobulin (Ig)G4–related disease is discussed in Chapter 254.

NEPHROGENIC SYSTEMIC FIBROSIS

Nephrogenic systemic fibrosis is a complication of exposure to gadolinium-containing MRI contrast agents in patients with acute kidney injury (Chapter 106), renal insufficiency, or stage 4 or 5 chronic kidney disease (Chapter 116), with an incidence in such patients of less than 0.07%.[27] With newer contrast agents[28] and current protocols that screen for renal function before administering gadolinium, this complication has essentially disappeared. The cutaneous manifestations of nephrogenic systemic fibrosis share histopathologic and clinical features with other scleroderma-spectrum disorders. Histological hallmarks include cutaneous fibrosis with mucin deposition and accumulation of spindle-shaped CD34-positive cells. The clinical hallmark of nephrogenic systemic fibrosis is thickening and "woody" tightness of skin over the lower and, less commonly, upper extremities and contractures at large joints. Anecdotal reports describe treatment with phototherapy, imatinib mesylate, and immunosuppressive agents. However, in most patients with nephrogenic systemic fibrosis, the induration is resistant to therapy and leads to progressive induration, joint contractures, and reduced mobility. Prevention centers on avoiding the use of gadolinium in patients with renal insufficiency.

RETROPERITONEAL FIBROSIS

Retroperitoneal fibrosis, which is a rare primary or secondary fibro-inflammatory condition, involves the adventitia and periaortic tissues surrounding the infrarenal portion of the abdominal aorta, often the iliac arteries, and sometimes the thoracic aorta.[29] The process can encase the ureters and other abdominal organs. The disease has an estimated prevalence of 1.4 per 100,000 population. In the idiopathic form, the mean age at onset is 55 to 60 years, and about two-thirds of cases are in men.

About 50% of cases of primary retroperitoneal fibrosis are associated with immunoglobulin (Ig) G4-related disease (Chapter 254).[30] Most of the remainder are apparently idiopathic, but some cases may be secondary to tumors (e.g.,

carcinoid [Chapter 213], lymphomas [Chapter 171], sarcomas [Chapter 187], and retroperitoneal metastases from solid tumors), autoimmune disorders (e.g., Hashimoto thyroiditis [Chapter 207], rheumatoid arthritis [Chapter 243], systemic vasculitis [Chapter 249], systemic lupus erythematosus [Chapter 245], and Erdheim-Chester disease [Chapter 155]), infections (e.g., tuberculosis [Chapter 299]), drugs (e.g., ergot alkaloids, dopamine agonists, etanercept, and infliximab), radiotherapy (e.g., for testicular, colon, or pancreatic cancer), other fibrotic conditions (e.g., sclerosing cholangitis [Chapter 141], autoimmune pancreatitis [Chapter 130], fibrosing mediastinitis [Chapter 86]), or retroperitoneal hemorrhage. Risk factors for the idiopathic form include asbestos exposure and cigarette smoking, with the combination of the two further increasing the risk.

The pathogenesis of retroperitoneal fibrosis is not well understood, but an association with HLA-DRB1*03 suggests an autoimmune genetic component. The pathobiology is characterized by the local production of IL-6 and Th2 cytokines as well as the accumulation of CD4+ T cells, B cells, myofibroblasts, and a fibrotic extracellular matrix composed of type 1 collagen fibers. Fibrosis and inflammation often encircle small retroperitoneal blood vessels as well as the aorta, iliac arteries, and inferior vena cava.

CLINICAL MANIFESTATIONS AND DIAGNOSIS

The most common clinical symptoms are low back, flank, or testicular pain and vague constitutional symptoms. Other common clinical presentations include anorexia, nausea, and lower extremity edema. Laboratory evaluation typically shows anemia, elevated levels of acute phase reactants, and impaired renal function. A positive antinuclear antibody (ANA) is seen in a majority of idiopathic cases. Levels of IgG4 are commonly elevated in both IgG4-related disease and other forms of retroperitoneal fibrosis, as well as in mimics such as Castleman disease (Chapter 171) and Erdheim-Chester disease (Chapter 155). Patients also should have studies of renal, thyroid, and liver function, as well as a serum amylase level.

Medial deviation of the ureters often leads to obstruction. Obstructive uropathy is associated with hydronephrosis and acute kidney injury. Vascular involvement can include inflammatory abdominal aortic aneurysms. The diagnosis is often made by a contrast-enhanced computed tomographic (CT) scan or magnetic resonance imaging (MRI) showing homogeneous plaque surrounding the anterolateral abdominal aortic wall, typically encircling the common iliac arteries and inferior vena cava.[31] Retroperitoneal biopsy sometimes may be indicated to exclude secondary causes, including tumors, tuberculosis, and conditions such as pelvic actinomycosis (Chapter 304) that can mimic retroperitoneal fibrosis, especially in women who have used an intrauterine device.

TREATMENT AND PROGNOSIS

For primary or idiopathic retroperitoneal fibrosis, first-line treatment is prednisone (0.75 to 1 mg/kg gradually tapered over 6 to 9 months to 5 to 7.5 mg per day). For severe ureteral obstruction or obstruction that does not respond to prednisone therapy, ureteral stenting or a nephrostomy tube is indicated, and surgical ureterolysis may be required for refractory cases.[32] Immunomodulatory therapies, including mycophenolate mofetil, cyclophosphamide, rituximab, methotrexate, and tamoxifen, have been used under expert supervision in combination with prednisone in refractory cases, or as steroid-sparing therapies. For secondary causes, cause-specific treatment may often be accompanied by local ureteral procedures.

About 75 to 95% of patients with retroperitoneal fibrosis respond to steroid therapy, but the relapse rate is about 70%. About one third of patients develop chronic renal insufficiency, but end-stage renal disease is rare. For secondary causes, prognosis is related to the underlying disease.

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For the General References and other additional features, please visit Elsevier eBooks+ at https://ebooks.health.elsevier.com.

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247 SJÖGREN SYNDROME

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DEFINITION

Sjögren syndrome is a systemic autoimmune disease with glandular and extraglandular manifestations.[1] Its cardinal glandular features are keratoconjunctivitis sicca, or dry eyes, and xerostomia, or dry mouth, otherwise known as the sicca complex.

Sjögren syndrome can be primary or secondary. It is primary when the sicca complex occurs in the absence of another rheumatologic disease. The term secondary refers to the presence of keratoconjunctivitis sicca or xerostomia in association with another rheumatologic disease, such as rheumatoid arthritis (Chapter 243), systemic lupus erythematosus (Chapter 245), or systemic sclerosis (Chapter 246).

EPIDEMIOLOGY

Primary Sjögren syndrome has a prevalence of 0.6 to 1.5%. It is predominantly a disease of women, with a female:male ratio of approximately 10:1. The peak onset is in the fifth and sixth decades of life, but the disease may begin in childhood through the eighth decade.

The secondary form occurs most commonly in the setting of rheumatoid arthritis (Chapter 243), with a prevalence of 30 to 50%. Keratoconjunctivitis sicca and xerostomia are also present in 15 to 20% of patients with systemic sclerosis (Chapter 246) and 10 to 15% of patients with systemic lupus erythematosus (Chapter 245).

PATHOBIOLOGY

Genetics

A genetic contribution to the risk for primary Sjögren syndrome is supported by familial clustering of cases and aggregation of cases in families with other autoimmune diseases. First-degree relatives of patients with Sjögren syndrome have a higher prevalence of rheumatoid arthritis, systemic lupus erythematosus, inflammatory myopathy, type 1 diabetes mellitus, and multiple sclerosis. Nevertheless, most cases of primary Sjögren syndrome occur sporadically in the absence of a family history of autoimmune disease.

Most of the genetic susceptibility is conferred by polymorphisms in the human leukocyte antigen (HLA) loci, with the strongest effects from the HLA-DR and HLA-DQ class II HLA molecules.[2] Primary Sjögren syndrome is associated with HLA class II alleles DRB1*03:01, DQA1*05:01, and DQB1*02:01. Other genetic susceptibility loci identified in genome-wide association studies include those linked to type I interferon signaling (*IRF5*, *IL12A*, and *STAT4*, *OAS1*), B-cell development and activation (*BLK*, *EBF1*), nuclear factor kappa β (NF-κB) signaling (*TNIP1*, *TNFAIP3*), and lymphocyte trafficking (*CXCR5*).

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carcinoid [Chapter 213], lymphomas [Chapter 171], sarcomas [Chapter 187], and retroperitoneal metastases from solid tumors), autoimmune disorders (e.g., Hashimoto thyroiditis [Chapter 207], rheumatoid arthritis [Chapter 243], systemic vasculitis [Chapter 249], systemic lupus erythematosus [Chapter 245], and Erdheim-Chester disease [Chapter 155]), infections (e.g., tuberculosis [Chapter 299]), drugs (e.g., ergot alkaloids, dopamine agonists, etanercept, and infliximab), radiotherapy (e.g., for testicular, colon, or pancreatic cancer), other fibrotic conditions (e.g., sclerosing cholangitis [Chapter 141], autoimmune pancreatitis [Chapter 130], fibrosing mediastinitis [Chapter 86]), or retroperitoneal hemorrhage. Risk factors for the idiopathic form include asbestos exposure and cigarette smoking, with the combination of the two further increasing the risk.

The pathogenesis of retroperitoneal fibrosis is not well understood, but an association with HLA-DRB1*03 suggests an autoimmune genetic component. The pathobiology is characterized by the local production of IL-6 and Th2 cytokines as well as the accumulation of CD4+ T cells, B cells, myofibroblasts, and a fibrotic extracellular matrix composed of type 1 collagen fibers. Fibrosis and inflammation often encircle small retroperitoneal blood vessels as well as the aorta, iliac arteries, and inferior vena cava.

CLINICAL MANIFESTATIONS AND DIAGNOSIS

The most common clinical symptoms are low back, flank, or testicular pain and vague constitutional symptoms. Other common clinical presentations include anorexia, nausea, and lower extremity edema. Laboratory evaluation typically shows anemia, elevated levels of acute phase reactants, and impaired renal function. A positive antinuclear antibody (ANA) is seen in a majority of idiopathic cases. Levels of IgG4 are commonly elevated in both IgG4-related disease and other forms of retroperitoneal fibrosis, as well as in mimics such as Castleman disease (Chapter 171) and Erdheim-Chester disease (Chapter 155). Patients also should have studies of renal, thyroid, and liver function, as well as a serum amylase level.

Medial deviation of the ureters often leads to obstruction. Obstructive uropathy is associated with hydronephrosis and acute kidney injury. Vascular involvement can include inflammatory abdominal aortic aneurysms. The diagnosis is often made by a contrast-enhanced computed tomographic (CT) scan or magnetic resonance imaging (MRI) showing homogeneous plaque surrounding the anterolateral abdominal aortic wall, typically encircling the common iliac arteries and inferior vena cava.[31] Retroperitoneal biopsy sometimes may be indicated to exclude secondary causes, including tumors, tuberculosis, and conditions such as pelvic actinomycosis (Chapter 304) that can mimic retroperitoneal fibrosis, especially in women who have used an intrauterine device.

TREATMENT AND PROGNOSIS

For primary or idiopathic retroperitoneal fibrosis, first-line treatment is prednisone (0.75 to 1 mg/kg gradually tapered over 6 to 9 months to 5 to 7.5 mg per day). For severe ureteral obstruction or obstruction that does not respond to prednisone therapy, ureteral stenting or a nephrostomy tube is indicated, and surgical ureterolysis may be required for refractory cases.[32] Immunomodulatory therapies, including mycophenolate mofetil, cyclophosphamide, rituximab, methotrexate, and tamoxifen, have been used under expert supervision in combination with prednisone in refractory cases, or as steroid-sparing therapies. For secondary causes, cause-specific treatment may often be accompanied by local ureteral procedures.

About 75 to 95% of patients with retroperitoneal fibrosis respond to steroid therapy, but the relapse rate is about 70%. About one third of patients develop chronic renal insufficiency, but end-stage renal disease is rare. For secondary causes, prognosis is related to the underlying disease.

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For the General References and other additional features, please visit Elsevier eBooks+ at https://ebooks.health.elsevier.com.

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247 SJÖGREN SYNDROME

E. WILLIAM ST. CLAIR

DEFINITION

Sjögren syndrome is a systemic autoimmune disease with glandular and extraglandular manifestations.[1] Its cardinal glandular features are keratoconjunctivitis sicca, or dry eyes, and xerostomia, or dry mouth, otherwise known as the sicca complex.

Sjögren syndrome can be primary or secondary. It is primary when the sicca complex occurs in the absence of another rheumatologic disease. The term secondary refers to the presence of keratoconjunctivitis sicca or xerostomia in association with another rheumatologic disease, such as rheumatoid arthritis (Chapter 243), systemic lupus erythematosus (Chapter 245), or systemic sclerosis (Chapter 246).

EPIDEMIOLOGY

Primary Sjögren syndrome has a prevalence of 0.6 to 1.5%. It is predominantly a disease of women, with a female:male ratio of approximately 10:1. The peak onset is in the fifth and sixth decades of life, but the disease may begin in childhood through the eighth decade.

The secondary form occurs most commonly in the setting of rheumatoid arthritis (Chapter 243), with a prevalence of 30 to 50%. Keratoconjunctivitis sicca and xerostomia are also present in 15 to 20% of patients with systemic sclerosis (Chapter 246) and 10 to 15% of patients with systemic lupus erythematosus (Chapter 245).

PATHOBIOLOGY

Genetics

A genetic contribution to the risk for primary Sjögren syndrome is supported by familial clustering of cases and aggregation of cases in families with other autoimmune diseases. First-degree relatives of patients with Sjögren syndrome have a higher prevalence of rheumatoid arthritis, systemic lupus erythematosus, inflammatory myopathy, type 1 diabetes mellitus, and multiple sclerosis. Nevertheless, most cases of primary Sjögren syndrome occur sporadically in the absence of a family history of autoimmune disease.

Most of the genetic susceptibility is conferred by polymorphisms in the human leukocyte antigen (HLA) loci, with the strongest effects from the HLA-DR and HLA-DQ class II HLA molecules.[2] Primary Sjögren syndrome is associated with HLA class II alleles DRB1*03:01, DQA1*05:01, and DQB1*02:01. Other genetic susceptibility loci identified in genome-wide association studies include those linked to type I interferon signaling (*IRF5*, *IL12A*, and *STAT4*, *OAS1*), B-cell development and activation (*BLK*, *EBF1*), nuclear factor kappa β (NF-κB) signaling (*TNIP1*, *TNFAIP3*), and lymphocyte trafficking (*CXCR5*).

Immune Mechanisms of Disease

The immunologic mechanisms of primary Sjögren syndrome involve dysregulation of both adaptive and innate immune pathways that drive a chronic inflammatory response in the target tissues. In the salivary glands, foci of mononuclear cells infiltrate areas of preserved acinar gland architecture (E-Fig. 247-1). Immunohistochemical analyses of these infiltrates show a predominance of $CD4^+$ T lymphocytes and B lymphocytes, which together represent about 90% of the immune cells.[3] The other immune cells comprising the infiltrate consist of $CD8^+$ T lymphocytes, $CD56^+$ natural killer cells, $FoxP3^+$ T regulatory lymphocytes, macrophages, and myeloid and plasmacytoid dendritic cells. T and B lymphocytes tend to coalesce around ducts and blood vessels and, in more inflammatory lesions, form germinal center-like structures.

The salivary gland tissue is flooded with pro-inflammatory chemokines and cytokines. Activated epithelial cells secrete *CXCL12*, *CXCL13*, and *CCL2*, as well as other mediators that cooperate to recruit, retain, and promote the survival of B lymphocytes.[4] Macrophages and myeloid dendritic cells secrete tumor necrosis factor (TNF), IL-6, IL-12, and IL-18 in abundance. There is overexpression of type I interferon-inducible genes in both the salivary gland tissue and the peripheral blood.

B lymphocytes are the precursors of antibody-secreting cells, which produce the autoantibodies and lead to the hypergammaglobulinemia, cryoglobulinemia, and elevated levels of circulating immune complexes.[5] Most B lymphocytes in salivary gland tissue express a memory phenotype and immunoglobulin (Ig) domains encoded by somatically hypermutated immunoglobulin V region genes, with structural characteristics typical of an antigen-driven response. The survival of B lymphocytes is enhanced by the upregulation of B-cell activating factor, which is produced mainly by plasmacytoid dendritic cells, as well as epithelial cells and macrophages, and is inducible by type I interferon.

Antibodies to SSA (Ro) and SSB (La) antigens, while diagnostic and prognostic biomarkers, are not known to be directly involved in causing the disease. In contrast, antibodies to the muscarinic receptor 3 (MR3) may suppress glandular function. Acetylcholine binds to the MR3 receptor expressed on the surface of lacrimal and salivary acinar glands, where it stimulates tear and salivary flow.

A prominent feature of primary Sjögren syndrome is the increased risk of lymphoma, usually a marginal zone lymphoma (Chapter 171). The evolution of lymphoma in this setting is initiated by a polyclonal B lymphocyte response, with expansion of oligoclonal and monoclonal B lymphocyte populations followed by clonal transformation.[6] The mechanisms underlying malignant transformation appear to depend on the activation of NF-κB. The A20 protein is a critical gatekeeper and inhibitor of the NF-κB pathway. The *TNFAIP3* gene encoding the A20 protein is somatically deleted in some cases of marginal zone B-cell lymphoma without autoimmunity, whereas the risk for lymphoma in patients with primary Sjögren syndrome is associated with a single nucleotide polymorphism in the coding region of the *TNFAIP3* gene. This polymorphism leads to a functional abnormality in the A20 protein, which in turn, promotes overactivation of the NF-κB pathway and loss of an important escape mechanism in lymphomagenesis.

Pathobiology

A dry eye may result from a deficiency in any of the three layers of the tear film: the outer lipid layer produced by the meibomian glands, the middle aqueous layer secreted by the lacrimal glands, and the inner mucous layer derived from the conjunctival goblet cells. Dry mouth and its complications are the product of reduced salivary flow, as well as changes in the concentrations of salivary electrolytes and proteins. Fatigue, which is the most prevalent extraglandular symptom, often has a multifactorial basis and may arise from disease-related mechanisms, depression, anxiety, fibromyalgia, sleep disturbance, or medication side effects.

CLINICAL MANIFESTATIONS

The severity of symptoms in Sjögren disease can be assessed in a number of domains: glandular, constitutional, cutaneous, respiratory, renal, articular, muscular, peripheral nervous system, central nervous system, hematologic, lymphadenopathic, and biologic.[7]

Glandular (Sicca) Features

Glandular hypofunction leads to dry eyes and dry mouth, as well as dryness of other epithelial surfaces, including the skin and the mucosa of the nasopharynx, larynx, airways, esophagus, and vagina. The hallmark symptoms of dry eye are the sensation of an ocular foreign body (gritty or sandy feeling), redness, burning, photophobia, and blurred vision.

Symptoms of dry mouth include difficulty with speaking, chewing, and swallowing. Examination often reveals a dry buccal mucosa, with diminished sublingual salivary pooling, sticky and thickened saliva, and a dry fissured tongue. Patients with xerostomia are prone to cavities and cracked teeth, as well as oral candidiasis (atrophic variant) that is often accompanied by angular cheilitis.

Some but not all patients experience swelling of the parotid or submandibular glands. Sudden onset of unilateral salivary gland swelling from transient duct obstruction usually resolves within a few days. Swelling of the parotid or submandibular glands may also persist or wax and wane over the disease course. Glands with palpably firm or hard nodules, especially those that are increasing in size, may signify a lymphoma.

Extraglandular Features

Extraglandular manifestations of primary Sjögren syndrome occur in approximately 50% of patients with this disease, although only about 15% develop serious organ system involvement. Fatigue is the most common extraglandular symptom. Raynaud syndrome (Chapter 66) occurs in up to one-third of patients and may precede the onset of sicca symptoms by several years.

Polyarthralgia/polyarthritis occurs commonly in Sjögren syndrome and may precede its diagnosis. The joints most frequently affected are the wrists, hands, ankles, and feet. The degree of synovial inflammation is generally much less severe than in rheumatoid arthritis and does not lead to erosive joint damage.

The types of skin rash are varied and include annular erythema, subacute cutaneous lupus erythematosus, and cutaneous vasculitis. Annular erythema appears in different forms: a donut-ring erythema with an elevated border, a polycyclic-like erythema with marginal scaling, and a papular lesion resembling an insect bite. These lesions are not photosensitive and resolve without residual hyperpigmentation. Subacute cutaneous lupus erythematosus is associated with photosensitivity, the presence of anti-Ro/SSA antibodies, and papulosquamous lesions with scaling or with annular, polycyclic lesions with marginal scale and central clearing.

Cutaneous vasculitis may present as palpable purpura, ulcers, erythematous papules and macules, and urticarial vasculitis. Urticarial vasculitis may be distinguished from allergic urticaria by the persistence of these lesions at a single location for more than 24 hours and by their tendency to leave a bruise. Nonpalpable purpura may occur in patients with high levels of serum immunoglobulins.

Lung involvement in primary Sjögren syndrome most frequently takes the form of small airways disease or interstitial lung disease (Chapter 80),[8] especially nonspecific interstitial pneumonitis and usual interstitial pneumonitis. About 5 to 10% of patients develop clinically significant type 1 distal renal tubular acidosis (Chapter 104), tubular interstitial nephritis (Chapter 108), and glomerulonephritis (Chapter 107).[9] Type 1 renal tubular acidosis increases the risk for nephrolithiasis (Chapter 111). Immune complex–mediated glomerular diseases include mesangial proliferative, membranous, membranoproliferative, and focal crescentic forms. Membranoproliferative glomerulonephritis is the form most commonly associated with cryoglobulinemic vasculitis.

A minority of patients develop nervous system deficits, mostly distal sensory and sensorimotor peripheral neuropathies (Chapter 388).[10] A sensorimotor neuropathy usually presents in the limbs with painful, length-dependent dysesthesias, and only rarely progresses to cause distal extremity weakness. Pure sensory small fiber neuropathies often cause painful neuropathic symptoms, such as burning in the feet.

A mixed small and large fiber dorsal root ganglionopathy in patients with Sjögren syndrome produces symptoms of kinesthesia and proprioception and may be associated with signs and symptoms of autonomic dysfunction (Chapter 386). Mononeuritis multiplex (involvement of two or more peripheral nerves) may develop in the setting of a systemic vasculitis and preferentially involves the longest peripheral nerves in the body. Cranial neuropathies most often target the trigeminal nerve ganglion, usually the maxillary and mandibular divisions while sparing the ophthalmic division.

Clinically significant disease of the central nervous system (CNS) is relatively uncommon in primary Sjögren syndrome, with a prevalence of 1 to 2%. CNS involvement can include optic neuropathy, focal central lesions, demyelinating lesions mimicking multiple sclerosis, cerebellar syndromes, movement disorders, neuromyelitis optica, encephalitis, aseptic meningitis, memory loss, impaired cognition, and transverse myelitis.

Rarely, patients with primary Sjögren syndrome develop an organ-threatening, systemic vasculitis, most commonly cryoglobulinemic vasculitis (Chapter 249).[11] Either type II or type III cryoglobulins may be detected in such cases. The dominant clinical features of cryoglobulinemic vasculitis are palpable purpura, peripheral neuropathy, and glomerulonephritis.

ABSTRACT

Sjögren syndrome, which is a systemic autoimmune disease, is characterized by glandular hypofunction and extraglandular manifestations. The hallmarks of the pathogenesis of Sjögren syndrome are genetic predisposition, evidence of immune dysregulation, and the production of autoantibodies. Histopathologic analysis of salivary gland tissue from patients with this disease reveals mostly infiltrating CD4+ T lymphocytes and B lymphocytes, with fewer numbers of CD8+ T lymphocytes, macrophages, and dendritic cells. Salivary gland epithelial cells display an activated phenotype and are presumed to play an important role in driving the chronic inflammatory response. The predominant glandular features are keratoconjunctivitis sicca, or dry eyes, and xerostomia, or dry mouth. It is termed *secondary* when these sicca manifestations are associated with another rheumatologic disease, such as rheumatoid arthritis or systemic lupus erythematosus, and termed *primary* otherwise. The extraglandular manifestations include polyarthralgia/polyarthritis, Raynaud syndrome, interstitial lung disease, peripheral neuropathy, interstitial nephritis, palpable purpura, hematologic abnormalities, and an increased risk for B-cell lymphoma. The classification of Sjögren syndrome is based on a scoring system, with points for meeting objective criteria for ocular dryness and salivary flow, a positive test for anti-SSA/Ro antibodies, and a positive labial salivary gland biopsy. The treatment of Sjögren syndrome is largely symptomatic and includes tear supplements, ophthalmic cyclosporine and other immunomodulators, and secretagogues such as pilocarpine and cevimeline. Severe extraglandular organ system involvement may require treatment with glucocorticoids and other immunosuppressive drugs. Although no disease-modifying drugs are approved for the treatment of Sjögren syndrome, several novel agents are under development for this indication.

KEYWORDS

Sjögren syndrome
anti-SSA/Ro antibodies
parotid gland enlargement
B-cell lymphoma
labial salivary gland biopsy

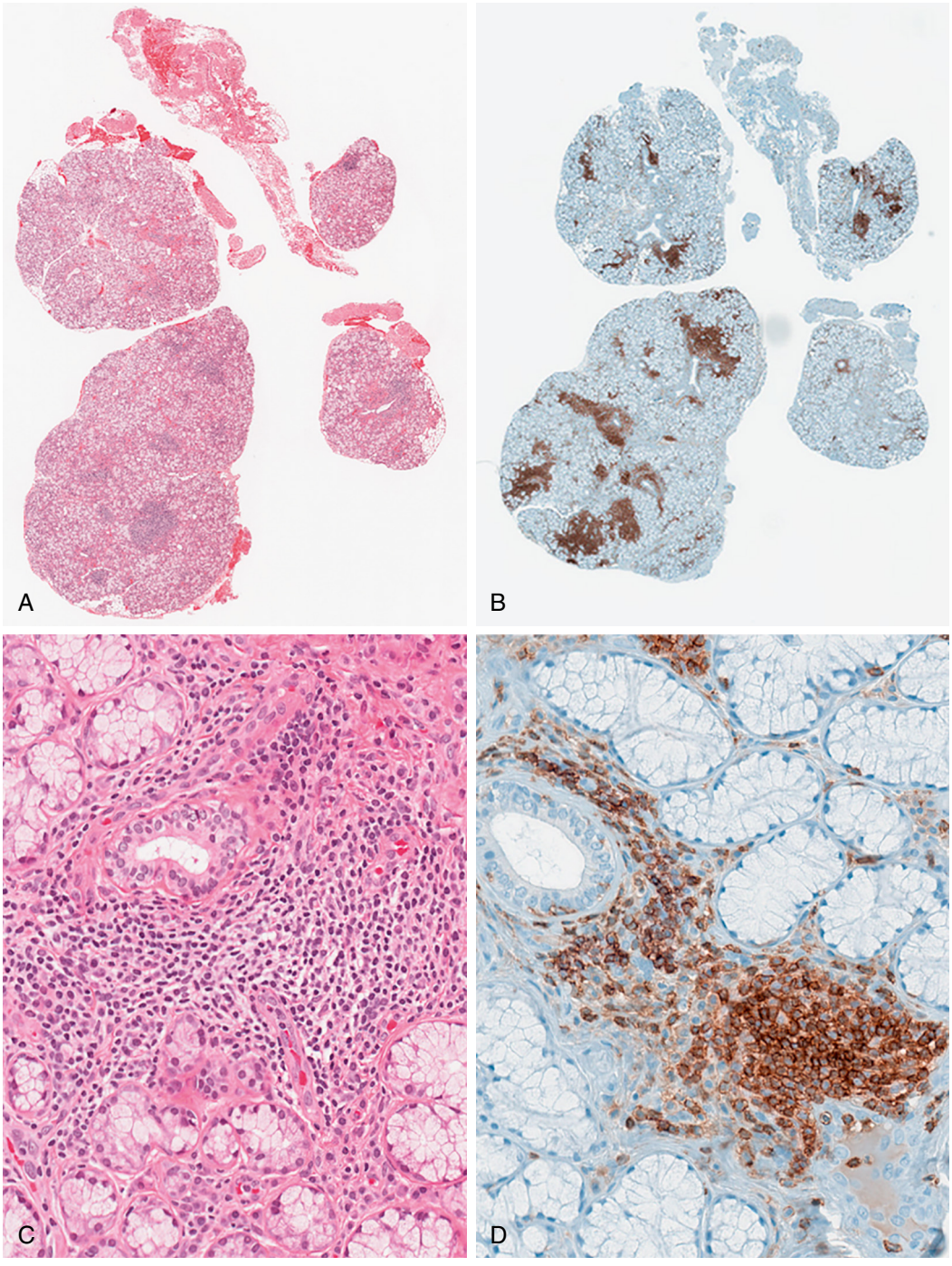

E-FIGURE 247-1. Histopathology of labial salivary glands in primary Sjögren syndrome. Hematoxylin and eosin staining (panels **A** and **C**) and anti-CD45 antibody staining (panels **B** and **D**) of labial salivary gland tissue. The low (4×) and high (20×) magnification views show the histopathologic findings of focal lymphocytic sialadenitis. Anti-CD45 antibodies stain only hematopoietic cells, including T lymphocytes, B lymphocytes, and other mononuclear cells. Multiple lymphocytic foci are evident among the different labial salivary gland lobules. The mononuclear cells can be seen to coalesce around ducts (panels **C** and **D**).

TABLE 247-1 2016 AMERICAN COLLEGE OF RHEUMATOLOGY/ EUROPEAN ALLIANCE FOR ASSOCIATIONS FOR RHEUMATOLOGY CLASSIFICATION FOR SJÖGREN SYNDROME

INCLUSION CRITERIA	
Any patient with at least 1 symptom of ocular or oral dryness or a suspicion of Sjögren syndrome	
ITEMS	**SCORE**
Histopathology showing focal lymphocytic sialadenitis with a focus score ≥1 per 4 mm^2[2*]	3
Positive test for anti-Ro/SSA antibodies	3
Ocular staining score ≥5[#,†]	1
Schirmer test ≤5 mm per 5 min in at least one eye	1
Unstimulated whole salivary flow rate <0.1 mL per minute[†]	1
RULES FOR CLASSIFICATION	
The classification of primary Sjögren syndrome is made in any individual who meets the inclusion criteria, does not have any exclusion criteria (prior diagnosis of any of the following conditions: history of head and neck radiation treatment, active hepatitis C infection, acquired immunodeficiency syndrome, sarcoidosis, amyloidosis, graft-versus-host disease, IgG4-related disease), and has a score ≥4 when the weights from the 5 criteria items are summed	

*The histopathologic examination should be performed by a pathologist with expertise in the diagnosis of focal lymphocytic sialadenitis and focus score count, using a specified protocol.
#Using lissamine green or fluorescein dye.
†Patients who are normally taking anticholinergic drugs should be evaluated for objective signs of salivary hypofunction and ocular dryness after a sufficient interval without these medications in order for these components to be a valid measure of oral and ocular dryness.
Based on Shiboski CH, Shiboski SC, Seror R, et al. 2016 American College of Rheumatology/ European League Against Rheumatism Classification Criteria for primary Sjogren's syndrome: a consensus and data-driven methodology involving three international patient cohorts. *Arthritis Rheumatol*. 2017;69:35-45.

Hematologic abnormalities are found in one-third of patients. Anemia is usually mild and has the features of anemia of chronic disease (Chapter 144). Thrombocytopenia, also usually mild, occurs in only about 2 to 3% of patients. Neutropenia, the most common hematologic abnormality, develops in 10 to 15% of patients, with neutrophil counts mostly ranging from 1000 to 2000/μL.

Lymphoma

The prevalence of non-Hodgkin lymphoma in primary Sjögren syndrome is 3 to 4%, but its risk increases about five-fold in patients who have neutropenia, low C4 levels, cryoglobulinemia, lymphadenopathy, or splenomegaly. The most common lymphoma associated with primary Sjögren syndrome is marginal zone B-cell lymphoma. Among the marginal zone B-cell lymphomas, the most common subtype is a mucosa-associated lymphoid tissue (MALT) lymphoma, which represents about 65% of all lymphomas that develop in patients with Sjögren syndrome. Other types with increased prevalence include lymphoplasmacytoid lymphoma, follicular cell lymphoma, and diffuse large B-cell lymphoma.

DIAGNOSIS

The diagnosis of primary Sjogren syndrome may be considered in any patient who has symptoms of dry eyes and dry mouth, or in a patient who has an extraglandular disorder typically associated with this disease. Consensus classification criteria (Table 247-1) have a sensitivity of 96% and a specificity of 95% for the diagnosis of primary Sjögren syndrome.

The diagnosis of dry eyes and dry mouth is aided by several objective testing methods. The aqueous component of the tear film may be quantified by a Schirmer test, which measures the distance tears elute on a strip of filter paper over 5 minutes. A distance of 5 mm or less is considered abnormal and consistent with the diagnosis of keratoconjunctivitis sicca. Vital dyes can be instilled into the eye to examine the conjunctival and corneal surface by slit lamp for any signs of damage (Chapter 391). Lissamine green dye stains the conjunctival and corneal surface and identifies degenerate cells, dead cells, and mucus (Fig. 247-1). Fluorescein dye also may be used to stain the corneal surface and to identify regions of cellular disruption.

Sialometry can measure salivary flow from individual glands (parotid, submandibular) or the mouth as a whole. In performing the test, the patient is asked to first clear their mouth of excessive saliva, then tilt their head forward and expectorate into a pre-weighed conical tube for 15 minutes. The collected samples are then weighed on an analytic balance to determine the volume (1 g = 1 mL). An unstimulated whole salivary flow rate ≤0.1 mL/minute is defined as impaired salivary flow. Ultrasonography, which can detect abnormalities in the salivary glands, has an 80% sensitivity and a 90% specificity for the diagnosis of primary Sjögren syndrome.[12]

Labial salivary gland biopsy, which is often considered the gold standard for diagnosing primary Sjögren syndrome, has a false-negative rate approaching 20%. Most patients do not require a labial salivary gland biopsy if the diagnosis is firmly established on the basis of clinical and serologic findings.

Laboratory Testing

Antinuclear antibodies (ANAs) are present in sera from most but not all patients with primary Sjögren syndrome. Two-thirds of patients test positive for anti-Ro/SSA antibodies and one-third for anti-La/SSB antibodies. About 50% of patients test positive for rheumatoid factor. A minority of patients, about 5%, test positive for anti-centromere antibodies, and their presence is associated with a higher rate of Raynaud syndrome and a higher risk of developing pulmonary hypertension. Other laboratory findings include hypergammaglobulinemia (IgG >1600 mg/dL), hypocomplementemia, and cryoglobulinemia. Serious organ system involvement is more likely in patients with serum anti-SSA/Ro antibodies, elevated serum levels of rheumatoid factor, hypergammaglobulinemia, cryoglobulinemia, and hypocomplementemia.

Extraglandular Disease

In patients with interstitial lung disease, pulmonary function studies show a restrictive pattern with reduced total lung capacity and a decrease in the diffusion capacity of lung carbon monoxide. In nonspecific interstitial pneumonitis, the chest computed tomographic (CT) findings consist of symmetrical, lower lobe, and peripherally predominant ground-glass opacities in a reticular nodular pattern, with relatively little evidence of fibrosis. Lymphocytic interstitial pneumonitis, a subset of nonspecific interstitial pneumonitis, produces a similar pattern of ground-glass opacities, as well as distinctive findings of thin-walled cysts, centrilobular nodules, interlobular septal thickening, and bronchovascular bundle thickening. In contrast, the chest CT findings of usual interstitial pneumonitis are characterized by heterogeneous, patchy, and irregularly distributed ground-glass opacities, lower lobe fibrosis, honeycombing, and traction bronchiectasis.

In the small fiber neuropathies of Sjögren syndrome, electrophysiologic studies are normal, and a skin biopsy demonstrating a reduced density of epidermal nerve fibers and sweat glands may be warranted to confirm the diagnosis. By comparison, electrophysiologic studies may show evidence of a large fiber, sensorimotor axonal peripheral neuropathy. With CNS involvement, brain magnetic resonance imaging (MRI) findings are usually nonspecific and consist of T2-weighted lesions resembling the microvascular changes associated with aging and cardiovascular disease. The cerebrospinal fluid may show abnormal findings of a lymphocytosis, an elevated IgG index, an increased protein level, and oligoclonal banding.

Differential Diagnosis

The differential diagnosis of primary Sjögren syndrome encompasses a wide range of disorders that also cause keratoconjunctivitis sicca, xerostomia, and parotid gland enlargement (Table 247-2), as well as diseases with similar extraglandular and laboratory features. The systemic disorders most frequently mimicking primary Sjögren syndrome are sarcoidosis (Chapter 83) and IgG4-related disease (Chapter 254), which may cause sicca symptoms and salivary gland enlargement, and also may affect multiple organ systems. In IgG4-related disease, the ANA is often negative, patients have high serum IgG4 levels, and their distinctive tissue histopathology is characterized by lymphoplasmacytic infiltrates, an abundance of IgG4-positive plasma cells, and storiform fibrosis. In addition, a Sjögren-like syndrome has been rarely described when patients with cancer receive checkpoint inhibitors targeting the programmed cell death (PD)-1/PD ligand-1 (PD-L1) pathway (e.g., pembrolizumab, nivolumab, and atezolizumab).

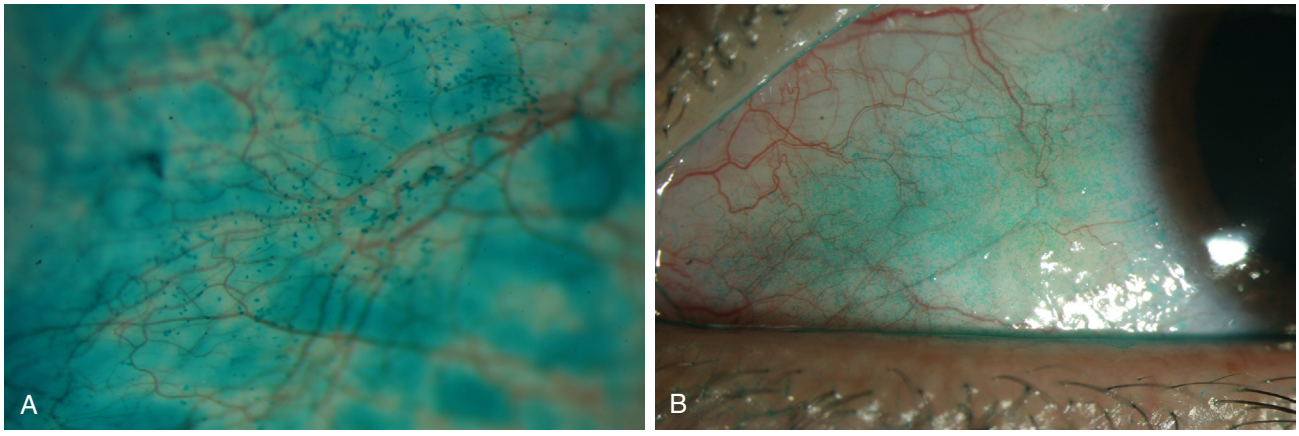

FIGURE 247-1. **Lissamine green staining of the cornea and conjunctiva in keratoconjunctivitis sicca. A,** Punctate epithelial erosions of the cornea. **B,** Bulbar staining of the conjunctiva.

TABLE 247-2 DIFFERENTIAL DIAGNOSIS OF THE GLANDULAR MANIFESTATIONS OF SJÖGREN SYNDROME

DRY EYE (KERATOCONJUNCTIVITIS SICCA)
Aqueous tear deficiency
Sarcoidosis
Chronic hepatitis C infection
Chronic graft-versus-host disease
Sensory block (from corneal surgery, contact lens wear)
Motor block from cranial nerve VII damage
Medications*
Age-related degenerative process
Evaporative tear loss
Meibomian gland dysfunction
Cicatricial pemphigoid
Vitamin A deficiency
Poor lid congruity or low blink rate
DRY MOUTH (XEROSTOMIA DUE TO HYPOSALIVATION)
Sarcoidosis
Chronic hepatitis C infection
Chronic graft-versus-host disease
Amyloidosis
Hemochromatosis
Diabetes mellitus
Radiation therapy
Medications*
Anxiety
PAROTID GLAND ENLARGEMENT
IgG4-related disease
Sarcoidosis
Diffuse infiltrative lymphocytic syndrome (from uncontrolled HIV infection)
Benign tumors (e.g., pleomorphic adenoma, Warthin tumor, oncocytoma)
Malignant carcinoma (e.g., mucoepidermoid carcinoma, actinic cell carcinoma)
MALT lymphoma (also follicular cell and mantle cell lymphoma)
Primary T-cell lymphoma (e.g., HTLV-1 associated, anaplastic large cell, diffuse pleomorphic)
Sialadenosis (from diabetes mellitus, alcohol use disorder)
Calculous duct obstruction

*Includes anticholinergics, antihistamines, tricyclic antidepressants, antipsychotics, antispasmodics, isotretinoin, benzodiazepines, β-adrenergic blockers, α-adrenergic blockers, and diuretics.
HIV = human immunodeficiency virus; HTLV1 = human T-lymphotropic virus type 1; MALT = marginal zone lymphoma.

TREATMENT

Sicca Syndrome

No disease-modifying therapy is available for the treatment of primary Sjögren syndrome,[A1] so management is largely directed towards controlling symptoms unless the patient has serious organ system involvement.[13] The treatment of dry eyes relies on the liberal use of over-the-counter tear supplements, which provide a mucoprotective film, and lipid emollients, which stabilize the tear film. Gel lubricants are often used at bedtime.[14] Patients should avoid drafty environments, cigarette smoke, and other irritants. A humidifier may reduce evaporative tear loss.

Topical ophthalmic cyclosporine (0.05% or 0.09%) and lifitegrast, which is a lymphocyte function–associated antigen-1 (LFA-1) antagonist, are effective for reducing the symptoms of keratoconjunctivitis sicca, although results have been variable across clinical trials.[A2,A3] These treatments may cause stinging and burning, which limit their tolerability.

Tears may be conserved by blocking the inferior nasolacrimal ducts (and, if indicated, the superior punctae as well) with dissolvable collagen or silicone plugs. The ducts can be closed permanently by cauterization.

Meibomian gland dysfunction, which often occurs in conjunction with a deficiency of aqueous tears, may be managed with warm compresses, eyelid massage, lid scrubs, and dietary supplements containing omega-3 fatty acids. In more refractory cases, the application of a thermal pulsation device or treatment with oral doxycycline (50 to 100 mg once or twice daily for up to 1 month) may be helpful.

Symptoms of dry mouth (Chapter 393) may be improved by chewing sugarless gum or sucking on sugarless candy. Over-the-counter preparations of artificial saliva may provide short-term symptomatic relief. Two oral secretagogues, pilocarpine (5 mg four times daily) and cevimeline (30 mg three times daily), also can reduce the symptoms of dry mouth.[A4] Common side effects include sweating and flushing, increased urination, and nausea; these drugs are contraindicated in patients who have severe asthma, narrow angle glaucoma, and iritis. Patients are advised to visit their dentist regularly and utilize measures to prevent tooth decay. Oral candidiasis may be effectively treated with a 10- to 14-day treatment course of clotrimazole troches, five times daily, although fluconazole may be required in refractory cases (Chapter 310). Angular cheilitis may be managed by prescribing a 1- to 2-week course of 1% clotrimazole cream or with combined 1% clotrimazole/0.05% betamethasone cream applied twice daily to the corners of the mouth.

Dry lips are treated by applying lip balm or the oily content of vitamin E softgel capsules. Saline nasal spray or irrigation can moisturize dry nasal passages. Vaginal dryness with dyspareunia may respond favorably to application of local moisturizers, lubricants, or topical estrogen cream. Skin moisturizers are used for the treatment of dry skin.

Sudden onset of unilateral, painful parotid gland swelling (Chapter 393) is usually managed by warm compresses, gentle parotid gland massage, and a nonsteroidal anti-inflammatory drug (Table 26-4). These episodes, which are probably due to transient duct obstruction, tend to resolve within 2 to 5 days. If the swelling is refractory to this conservative approach, a short course of prednisone therapy under expert guidance often is rapidly effective in reducing the swelling, provided that the clinical presentation does not suggest an infectious etiology.

Extraglandular and Systemic Disease

Although hydroxychloroquine has often been recommended, the largest double-blind, placebo-controlled trial failed to show any significant benefit compared with placebo.[A5] The evidence supporting the use of methotrexate, sulfasalazine, or leflunomide for the treatment of Sjögren syndrome–associated inflammatory arthritis in this setting is indirect and based on their proven efficacy for the treatment of rheumatoid arthritis (Chapter 243).

Recurrent lower limb purpura may be treated with a short course of glucocorticoids (e.g., 0.5 mg/kg/day rapidly tapered to 5 mg/day over 2 weeks under expert supervision) to bring symptomatic relief. However, subsequent tapering

and withdrawal of glucocorticoids are generally met by a recurrence of the purpura. These repeated cycles of glucocorticoid therapy can often be avoided by treating recurrent purpura with support stockings, analgesics, antihistamines, and nonsteroidal anti-inflammatory drugs.

The sensory symptoms of a peripheral neuropathy (Chapter 388) are typically managed using medications such as gabapentin, pregabalin, and duloxetine and do not routinely call for glucocorticoid or other immunosuppressive therapy. The treatment of lymphoma depends on the site and stage of the disease (Chapter 171).

Organ-threatening extraglandular pulmonary[15] and renal disease usually warrants initial treatment with moderate to high doses of glucocorticoids (e.g., 0.5 mg/kg to 1 mg/kg/day of prednisone or its equivalent), often in combination with an adjunctive immunosuppressive agent, under expert supervision. Potential indications for such a treatment approach include active and progressive interstitial lung disease, interstitial nephritis, glomerulonephritis, serious nervous system involvement, or systemic vasculitis. Subcutaneous ianalumab showed some benefit in one study[A6] but remains experimental at this time. Rituximab, abatacept, tocilizumab, infliximab, and etanercept have been investigated for the treatment of Sjögren syndrome but have not proven effective in clinical trials. Other targeted therapies are in development.[16]

PROGNOSIS

Primary Sjögren syndrome is associated with significant morbidity due in large measure to dryness, fatigue, impaired sleep, psychological dysfunction, pain/articular involvement, sexual dysfunction, and reduced physical function.[17] Severe xerostomia may also lead to extensive loss of teeth and the need for dentures or implants. However, life expectancy is not reduced except in the subset of patients who have vasculitis, hypocomplementemia, cryoglobulinemia, or lymphoma.

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248 INFLAMMATORY MYOPATHIES

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DEFINITION

The inflammatory myopathies are a heterogeneous group of acquired disorders in which the immune system is thought to play a major pathogenic role.[1] Though some genetic disorders affecting muscle also have significant involvement of the immune system and are treated with immunosuppressive therapy as the standard of care (e.g., treatment of Duchenne muscular dystrophy with corticosteroids), these genetic disorders are not classified as inflammatory myopathies. The four major subtypes of inflammatory myopathy are dermatomyositis, polymyositis, immune-mediated necrotizing myopathy, and inclusion body myositis (also called sporadic inclusion body myositis). These disorders have distinct clinical and pathologic features and pathophysiologies (Table 248-1).[2,3]

EPIDEMIOLOGY

The prevalence of dermatomyositis has been estimated at 100 to 210 per million. The estimated prevalence of polymyositis is confounded by frequent misdiagnosis of inclusion body myositis and muscular dystrophies as polymyositis. Studies show a prevalence of 35 per million for polymyositis, approximately half of the 70 per million prevalence of inclusion body myositis. Inclusion body myositis is the most common acquired muscle disease after age 50 years.[4] The prevalence of immune-mediated necrotizing myopathy is unknown.

Dermatomyositis has biphasic peaks in incidence in childhood (ages 7 to 15 years) and in midlife (ages 30 to 50 years), whereas polymyositis peaks in incidence in midlife. Inclusion body myositis is rarely diagnosed before the age of 40 years and is most common after the age of 50 years. Dermatomyositis and polymyositis have female predominance, whereas inclusion body myositis has male predominance.

PATHOBIOLOGY

The pathophysiologies of various forms of inflammatory myopathy are poorly understood. These disorders do share in common injury to muscle by the immune system.[5] Much of the theory of pathophysiology of these disorders comes from microscopic examination of muscle biopsies and the distinct pathologies of these disorders (Fig. 248-1).

The muscle pathology of dermatomyositis involves loss of blood vessels and injury to myofibers at the edges of muscle fascicles (i.e., perifascicular atrophy; see Fig. 248-1). It is likely that a common factor injures both myofibers and capillaries. Skin pathology shows features analogous to that of muscle, with an interface dermatitis consisting of injury to the basal layer of keratinocytes.

Evidence points toward dermatomyositis as mediated by the type 1 interferon cytokine family, consisting mainly of interferon (IFN)-α and IFN-β. Studies of dermatomyositis skin and muscle samples show marked upregulation of type 1 IFN-inducible transcripts and proteins uniquely in dermatomyositis among muscle diseases and similarly to systemic lupus erythematosus (Chapter 245) among skin diseases. The presence of autoantibodies in some patients with dermatomyositis, such as antibodies to the type 1 IFN-inducible protein MDA5, is of uncertain significance but seems likely due to an immune reaction to proteins that are not normally expressed at high levels or exposed to the immune system.[6] The paraneoplastic associations of dermatomyositis suggest that an immune reaction against an underlying malignancy results in bystander injury to muscle and skin in such patients.[7]

Because polymyositis is a diverse group of disorders, the mechanisms involved are likely to be varied. Pathologically, nonspecific inflammation varies among the increasingly recognized distinct subtypes, such as the antisynthetase syndrome.

Immune-mediated necrotizing myopathy is also a poorly understood disorder. It can also be paraneoplastic, thereby suggesting cross-reactions by the immune system with the underlying malignancy and with muscle antigens. More commonly, immune-mediated necrotizing myopathy occurs in association with treatment with statin drugs (Chapter 190). The identification of autoantibodies against the target of statins, 3-hydroxy-3-methylglutaryl-coenzyme A reductase (HMGCR), in the majority of patients who develop immune-mediated necrotizing myopathy in association with statin use suggests that the upregulation of HMGCR in muscle is directly toxic to muscle and triggers an immune reaction against it. Anti–signal recognition particle (SRP) autoantibodies have also been identified in some patients with immune-mediated necrotizing myopathy. Anti-SRP myopathy, anti-HMGCR myopathy, and autoantibody-negative myopathy have been considered to be three distinct subtypes of immune-mediated necrotizing myopathy.[8]

A genetic basis of inclusion body myositis has been suggested by its significant association with the class II MHC allele HLA-DRB1*03:01.[9] The pathogenesis of inclusion body myositis includes the destruction of myofibers by highly differentiated cytotoxic T cells.[10,11] Degeneration of myofibers and of myonuclei in particular, evident as formation of rimmed vacuoles, is likely a consequence of very chronic immune destruction of muscle (see Fig. 248-1A-C) and involvement of the immune system. Among all the inflammatory

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ABSTRACT

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KEYWORDS

inflammatory myopathies
myositis
inclusion body myositis
dermatomyositis
polymyositis

TABLE 248-1 CLASSIFICATION OF INFLAMMATORY MYOPATHIES

DISORDER	AGE RANGE	CLINICAL FEATURES	MUSCLE PATHOLOGY
Dermatomyositis	Juvenile and adult forms	Proximal weakness plus skin	Perimysial and perivascular inflammation, perifascicular atrophy
Polymyositis	Adult (rare in childhood)	Proximal weakness	Nonspecific inflammation
Immune-mediated necrotizing myopathy	Adult	Proximal weakness	Multifocal necrotic muscle fibers
Inclusion body myositis	Adult >40 years old	Prominent quadriceps and finger flexor weakness; treatment refractory	Endomysial inflammation with invasion of non-necrotic muscle fibers
Overlap syndromes	Adult	Myositis plus defined connective tissue disease	Nonspecific inflammation
Other (granulomatous myositis, eosinophilic myositis)	All ages	Proximal or distal weakness	Specific to type (e.g., granulomas present with granulomatous myositis)

myopathies, inclusion body myositis has the greatest evidence of a highly refined, antigen-driven, adaptive immune system response (Chapter 35). Pathology shows very chronic and often marked but variable inflammatory infiltrates of T cells, myeloid dendritic cells, and plasma cells in muscle. Studies of the T-cell receptors have strongly suggested that T-cell autoimmunity is driven by one or more specific antigens, though the identity of any of these antigens is unknown.

Studies of a B-cell pathway in inclusion body myositis have led to identification of circulating autoantibodies against a 43-kD muscle protein, identified as cytoplasmic 5′ nucleotidase 1 A (cN1A; NT5C1A). cN1A is a nucleotidase that is most abundant in skeletal muscle and is involved in the metabolism of nucleic acids. Serum anti-cN1A autoantibodies are present in 50 to 70% of patients with inclusion body myositis, depending on which assays and what cutoffs are used, and they are highly specific (>90 to 95%) for inclusion body myositis among muscle diseases.

CLINICAL MANIFESTATIONS AND DIAGNOSIS

A diagnosis of inflammatory myopathy is considered when a patient presents with proximal or distal weakness without sensory symptoms or patients develop the characteristic skin lesions of dermatomyositis. Less frequently, asymptomatic elevated levels of creatine kinase lead to a diagnosis of inflammatory myopathy. Most patients with dermatomyositis, polymyositis, or immune-mediated necrotizing myopathy present with subacute proximal weakness of the arms and legs progressing over months, though these diseases may present acutely. Patients with inclusion body myositis present later in life, usually symptomatic from slowly progressive weakness of knee extensors and finger flexors. More specific diagnostic features of these disorders are considered individually (Table 248-2). Most patients undergo muscle biopsy (or skin biopsy in the case of suspected dermatomyositis) as part of the diagnostic evaluation.

Dermatomyositis

Patients with dermatomyositis typically present with characteristic skin lesions or muscle weakness.[12,13] Virtually pathognomonic skin features are a heliotrope rash, which is a violaceous periorbital macular erythema, sometimes with edema, and Gottron papules, which are violaceous papules over dorsal metacarpophalangeal and interphalangeal joints of the hands (Fig. 248-2). Periungual telangiectasias and thrombosed capillaries, poikiloderma over photoexposed areas such as the upper back ("shawl sign"), nonscarring alopecia, and subcutaneous calcification are other suggestive signs. Prominent pruritus is also a common feature of dermatomyositis. Muscle weakness in dermatomyositis is less specific and occurs in a pattern indistinguishable from many other muscle diseases.

Useful laboratory studies for the evaluation of suspected dermatomyositis include a serum creatine kinase level (though it can be normal or even below typical laboratory lower limits of normal in patients with highly active disease) and dermatomyositis-associated autoantibody studies (e.g., anti-Jo-1, anti-Mi2, and anti-MDA5). Occasional patients have an abnormal serum aldolase level but normal creatine kinase level. Skin biopsy showing a cell-poor interface dermatitis supports the diagnosis of dermatomyositis. Muscle biopsy showing perimysial and perivascular inflammation also supports a diagnosis of dermatomyositis, whereas the presence of perifascicular atrophy in a muscle biopsy is pathognomonic for dermatomyositis.[14]

Because dermatomyositis is associated with malignancy, appropriate laboratory and radiologic studies should be performed to search for underlying malignancy in all newly diagnosed patients.[15] As for unprovoked venous thrombosis, the evaluation should include a careful history and physical examination plus a complete blood count, urinalysis, serum chemistries, liver function tests, chest radiograph, stool for occult blood, and mammogram in woman and prostate-specific antigen in men. In addition, any abnormalities on these screening tests should be pursued aggressively. The most common dermatomyositis-associated malignancies tend to reflect the overall age and gender cancer rates within the individual patient's population (i.e., breast, lung, and colorectal cancer in Western countries; nasopharyngeal cancer in Asian populations). This observation supports the notion of dermatomyositis as a paraneoplastic process that can develop in virtually any kind of cancer.

The clinical features of muscle weakness in dermatomyositis are entirely nonspecific, with no particular pattern indicative of dermatomyositis compared with other muscle diseases.[16] In practice, certain dermatologic clinical findings (heliotrope rash, Gottron papules) or muscle biopsy findings (perifascicular atrophy) are considered nearly pathognomonic for dermatomyositis (Table 248-2).

Polymyositis

The diagnosis of polymyositis is often problematic, and many patients with genetically defined limb-girdle muscular dystrophies (Chapter 389) and inclusion body myositis can be misdiagnosed as polymyositis. The core criteria for the diagnosis of polymyositis are subacute proximal weakness, elevated serum creatine kinase level, and a muscle biopsy showing endomysial inflammation without features suggestive of another diagnosis such as inclusion body myositis (see Table 248-2). Patients with defined connective tissue disorders such as Sjögren syndrome (Chapter 247) or mixed connective tissue disease (Chapter 246) have "overlap syndromes," often also classified as polymyositis. Patients who actually have immune-mediated necrotizing myopathy are increasingly recognized. Patients with inclusion body myositis may be misdiagnosed as having polymyositis because of a lack of appreciation of the characteristic inclusion body myositis finger flexor weakness and because muscle biopsies show endomysial inflammation. The presence of autoantibodies such as anti-Jo-1 argue more for polymyositis than inclusion body myositis, though these antibodies may be seen in dermatomyositis as well. As with dermatomyositis, an evaluation for occult malignancy is indicated.

Immune-Mediated Necrotizing Myopathy

Immune-mediated necrotizing myopathy is increasingly distinguished from polymyositis.[17] Acute or subacute proximal weakness indistinguishable from that of polymyositis or dermatomyositis and an elevated creatine kinase level are nonspecific, but a muscle biopsy showing scattered necrotic or regenerating myofibers without inflammation other than macrophages invading these

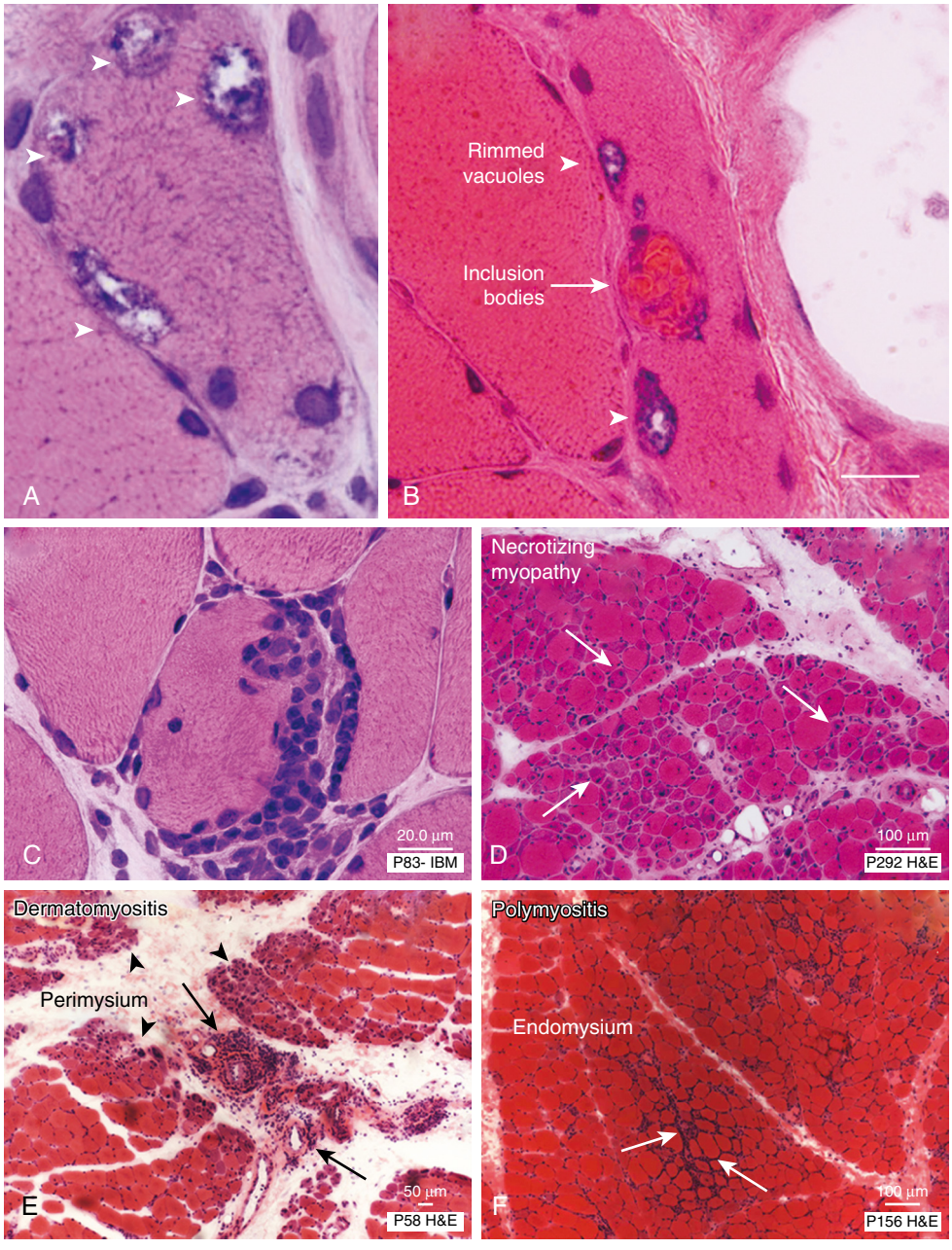

FIGURE 248-1. Pathologies of inflammatory myopathies. A and B, Rimmed vacuoles (*arrowheads*) of inclusion body myositis. **C,** Invasion of non-necrotic muscle fiber in inclusion body myositis. **D,** Scattered necrotic and regenerating myofibers in immune-mediated necrotizing myopathy. **E,** Perivascular and perimysial inflammation (*arrows*), with perifascicular atrophy (*arrowheads*), in dermatomyositis. **F,** Endomysial inflammation in polymyositis. (With permission from the Inclusion Body Myositis Foundation, Inc.)

necrotic myofibers is typical of immune-mediated necrotizing myopathy. The presence of anti-HMGCR (3-hydroxy-3-methylglutaryl-coenzyme A reductase) or anti-SRP (signal recognition particle) antibodies suggest immune-mediated necrotizing myopathy.[18] Immune-mediated necrotizing myopathy, particularly when associated with anti-SRP antibodies, may be paraneoplastic, and laboratory and radiologic evaluation for malignancy should be considered as for dermatomyositis.

Inclusion Body Myositis

Inclusion body myositis has a clinical presentation distinct from other inflammatory myopathies.[19] Weakness is always slowly progressive rather than the acute or subacute weakness more typically seen in other forms of inflammatory myopathies (see Table 248-2). Inclusion body myositis is misdiagnosed in approximately 50% of patients. Symptoms of inclusion body myositis rarely are present before age 40 years and most commonly occur after age 50 years. The distribution of weakness is usually in finger flexors or quadriceps, as compared with the proximal arm (shoulder abduction) or proximal leg (hip flexion) weakness that is more typical of polymyositis or dermatomyositis.

Inclusion body myositis is a highly atrophying muscle disease,[20] and loss of bulk in medial and lateral anterior thighs and ventral forearms is characteristic. Patients present with difficulty walking, buckling of knees, or weakness of grip. The diagnosis of inclusion body myositis can be highly suspected when patients of appropriate age have findings of quadriceps atrophy and weakness of finger flexors, especially of the flexor digitorum profundus that are responsible for flexion of distal fingertips. Examination of the strength in these distal fingertips, which must be done one finger at a time, is often the single most helpful approach to the diagnosis of inclusion body myositis.

The serum creatine kinase is either normal or modestly elevated (typically less than five times the upper limit of normal). A serum autoantibody, anti-cN1A (also called anti-NT5C1A),[21] is highly specific for inclusion body myositis among muscle diseases. Most patients undergo muscle biopsy, with the characteristic features being the presence of rimmed vacuoles on hematoxylin and eosin and Gomori trichrome staining, as well as endomysial inflammation or invasion of non-necrotic muscle fibers. Immunohistochemical stains detecting p62 or TDP-43 are of additional highly specific diagnostic value.

TABLE 248-2 CLINICAL DIAGNOSTIC CRITERIA FOR INFLAMMATORY MYOPATHIES

DISORDER	DIAGNOSIS
Dermatomyositis	1. Diagnostic skin involvement (heliotrope rash, Gottron papules) *OR* diagnostic muscle biopsy finding of perifascicular atrophy *OR* 2. All of the following: • Suggestive skin involvement • Subacute or chronic proximal or distal weakness • Muscle biopsy showing perimysial or perivascular inflammation without features suggesting another disorder (e.g., endomysial inflammation, rimmed vacuoles) *OR* skin biopsy showing interface dermatitis along with clinical exclusion of systemic lupus erythematosus
Polymyositis	All of the following: 1. Subacute or chronic proximal weakness 2. Elevated serum creatine kinase (CK) 3. Muscle biopsy showing invasion of endomysial inflammation 4. Response to immunotherapy *OR* appropriate consideration and exclusion of limb-girdle muscular dystrophies and inclusion body myositis
Immune-mediated necrotizing myopathy	Both of the following: 1. Subacute or chronic proximal weakness 2. Muscle biopsy showing necrotizing myopathy, with scattered necrotic or regenerating myofibers and a lack of inflammation other than macrophage invasion of necrotic muscle fiber
Inclusion body myositis	All of the following: 1. Adult >40 years old 2. Finger flexion or quadriceps weakness 3. Muscle biopsy showing endomysial inflammation *OR* the presence of serum anti-cN1A autoantibodies 4. Muscle biopsy showing rimmed vacuoles *OR* invasion of non-necrotic muscle fibers *OR* the presence of serum anti-cN1A autoantibodies

cNIA = cytoplasmic 5′ nucleotidase 1A.

TREATMENT

Generally, most patients with dermatomyositis, polymyositis, and immune-mediated necrotizing myopathy respond to immunomodulatory therapies, whereas patients with inclusion body myositis are almost universally refractory (Fig. 248-3).[22]

Treatment of Dermatomyositis and Polymyositis

Most patients with muscle involvement from dermatomyositis and polymyositis are treated with and respond to corticosteroids.[23,24] Dosing is typically prednisone at 1 mg/kg/day orally until significant improvement occurs (typically 1 to 3 months), followed by gradual taper of 10 mg/day/month. Apremilast also may be useful for recalcitrant cutaneous dermatomyositis.[25] Second-line agents under expert guidance include methotrexate, azathioprine, cyclosporine, and intravenous immunoglobulin.[A1] Second-line agents are used for two reasons: they may have a better side-effect profile than chronic higher doses of corticosteroids, and they may be necessary for patients whose responses are insufficient to corticosteroids alone. An important decision is whether to start second-line agents concurrently with initial corticosteroid treatment or wait and see how low a dose of corticosteroids offers satisfactory control and then add agents only if the corticosteroid dose cannot be lowered sufficiently. Thus, in the former approach, prednisone 60 mg/day and methotrexate 7.5 mg orally weekly might be started concurrently and the methotrexate dose increased to 15 to 20 mg orally weekly. Once improvement is substantial, the dose of prednisone may be tapered over 3 to 6 months. Stability on methotrexate alone would then be followed by gradual reduction in its dose. For patients with severe initial presentations, the combination of corticosteroids and periodic intravenous immunoglobulin (1 g/kg every 2 weeks) may offer a better chance for more rapid improvement.

Treatment of Inclusion Body Myositis

No therapies have demonstrated efficacy for inclusion body myositis, with negative results for prednisone, intravenous immunoglobulin, methotrexate, antithymocyte globulin, etanercept, interferon-β, and alemtuzumab. Current management of patients with inclusion body myositis is supportive, including avoidance of falls and the use of ankle supports and gait assistive devices. Tendon transfer has been used to improve hand function.

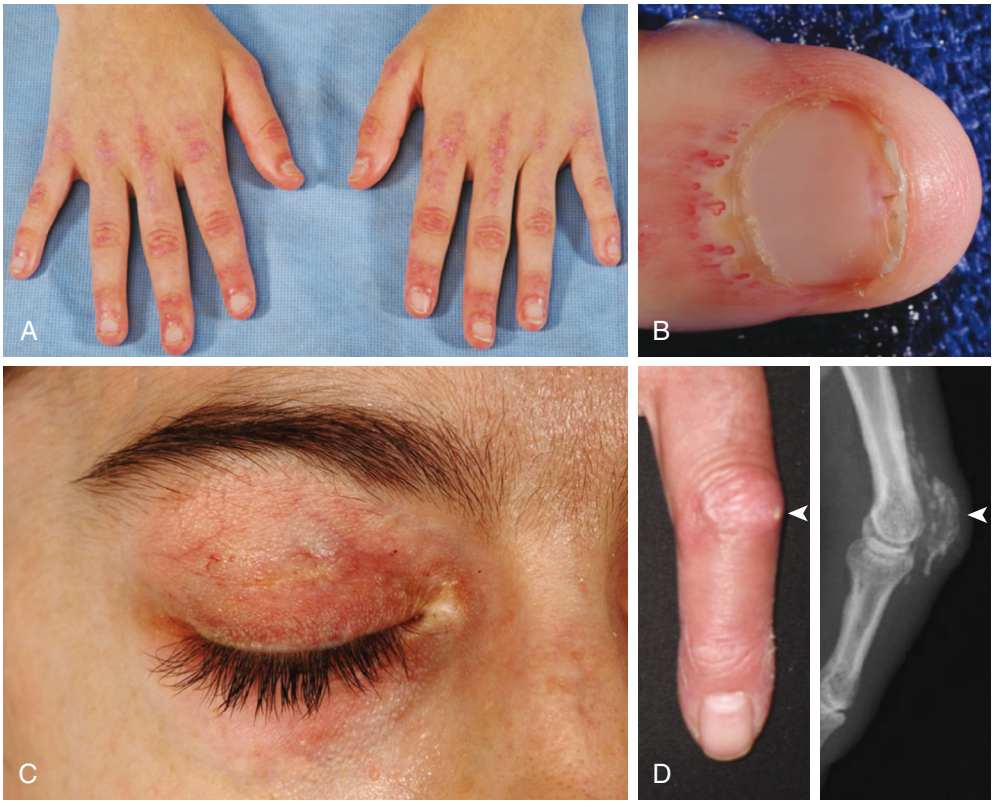

FIGURE 248-2. Clinical findings in dermatomyositis. A, Erythematous to violaceous raised papules overlying the metacarpal and interphalangeal joints, known as Gottron papules. These are considered the hallmark finding in dermatomyositis. **B**, Cuticular overgrowth and periungual capillary changes, which include dilated and tortuous blood vessels with areas of atrophy, telangiectasia, vessel dropout, and bushy loop formation along the fingernail bed. **C**, Erythema and minimal edema involving the upper eyelids, with occasional telangiectasia, known as the heliotrope rash. **D**, Subcutaneous calcification erupting through skin (*arrowhead*), seen clinically and by x-ray.

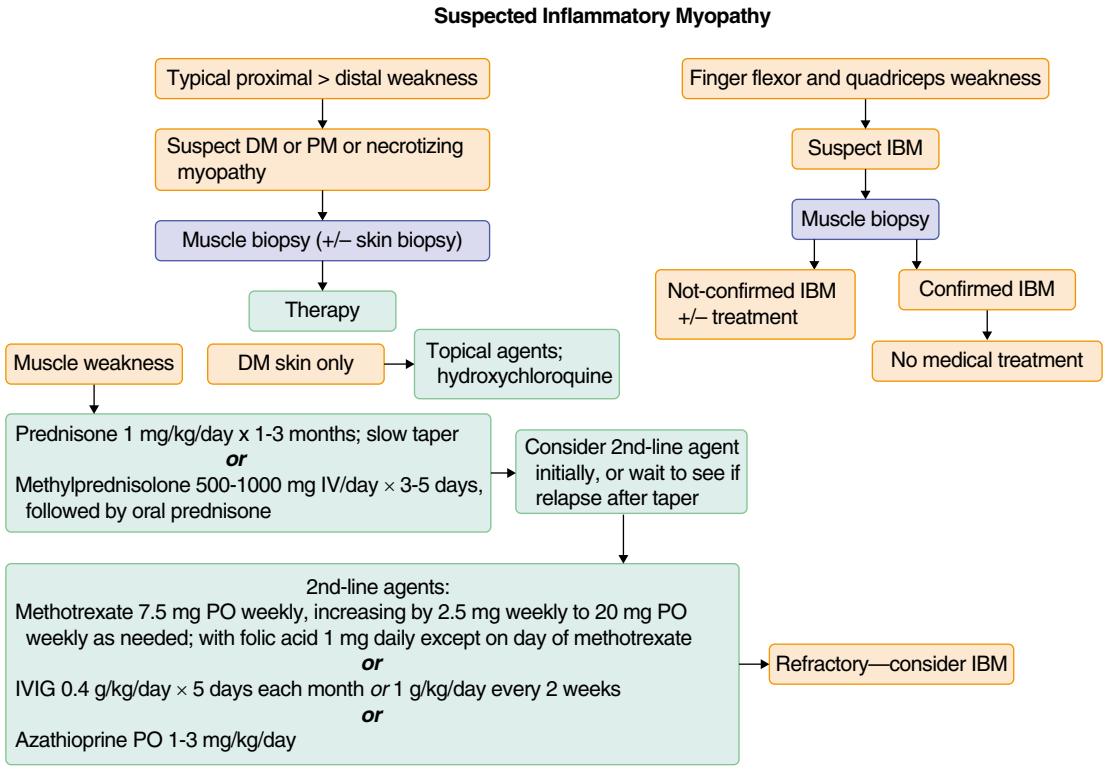

FIGURE 248-3. Approach to treatment of suspected inflammatory myopathy. DM = dermatomyositis; IBM = inclusion body myositis; IV = intravenous; IVIG = intravenous immunoglobulin; PM = polymyositis; PO = oral. (With permission from the Inclusion Body Myositis Foundation, Inc.)

PROGNOSIS

Most patients with adult dermatomyositis, polymyositis, and statin-associated immune-mediated necrotizing myopathy have a good prognosis with chronic immunomodulatory therapy. However, the annual hazard ratio for death is about five-fold higher than in the general population.[26] Patients with anti-SRP–associated immune-mediated necrotizing myopathy may have severe and difficult-to-treat disease. Patients with inclusion body myositis generally have a slowly progressive course, with one series showing a mean time to loss of ambulation of 12 years and a mean of survival of 14 years.[27]

GENERAL REFERENCES

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Grade A Reference

A1. Aggarwal R, Charles-Schoeman C, Schessl J, et al. Trial of intravenous immune globulin in dermatomyositis. *N Engl J Med.* 2022;387:1264-1278.

249 THE SYSTEMIC VASCULITIDES

JOHN H. STONE

DEFINITION

The vasculitides are a heterogeneous group of disorders linked by the common finding of destructive inflammation within blood vessel walls. The most current nomenclature scheme identifies at least 27 different forms of primary vasculitis (Table 249-1).

CLASSIFICATION

Classification by Vessel Size

The etiology of most forms of vasculitis remains unknown, and major gaps exist in our understanding of the pathophysiologic processes. The most valid basis for classification of the vasculitides is the size of the predominant blood vessels involved. The vasculitides are categorized initially by whether the vessels affected are primarily large, medium, or small (see Table 249-1). Large vessels are considered the aorta, its primary branches, and any vessel that is not located within an organ such as a muscle, kidney, nerve, or the skin. Medium-sized vessels, in contrast, consist of the main visceral arteries and their branches. Thus, the renal artery is considered a large vessel, but its intrarenal branches—the interlobar and arcuate arteries—are medium-sized vessels. Finally, small vessels include smaller intraparenchymal arteries as well as arterioles, capillaries, and venules.

Medium-vessel vasculitis and even large-vessel vasculitis can also affect small arteries. However, large-vessel vasculitis affects large arteries more often than medium- or small-vessel vasculitis, medium-vessel vasculitis affects predominantly medium arteries, and small-vessel vasculitis affects predominantly arterioles, capillaries, and venules.

Additional Considerations in Classification

Considerations other than the size of blood vessels that are relevant to the classification of vasculitis (see Table 249-2) include age, sex, and ethnic background of the patient; organ tropism; presence or absence of granulomatous inflammation; participation of immune complexes in the pathophysiologic process; and detection of characteristic autoantibodies, such as antineutrophil cytoplasmic antibodies (ANCAs), in the patient's serum.

The organ tropisms of these disorders are illustrated by the following examples. Whereas immunoglobulin (Ig)A vasculitis (also known as Henoch-Schönlein purpura) typically affects the skin, joints, kidneys, and the gastrointestinal tract, granulomatosis with polyangiitis classically involves the upper airways, lungs, and kidneys. In contrast to both IgA vasculitis and granulomatosis with polyangiitis, Cogan syndrome involves the eyes, the audiovestibular apparatus of the inner ear, and (in 10 to 15% of cases) the large arteries.

The presence or absence of granulomatous inflammation is a crucial element in the diagnosis and classification of vasculitis. The small number of vasculitides

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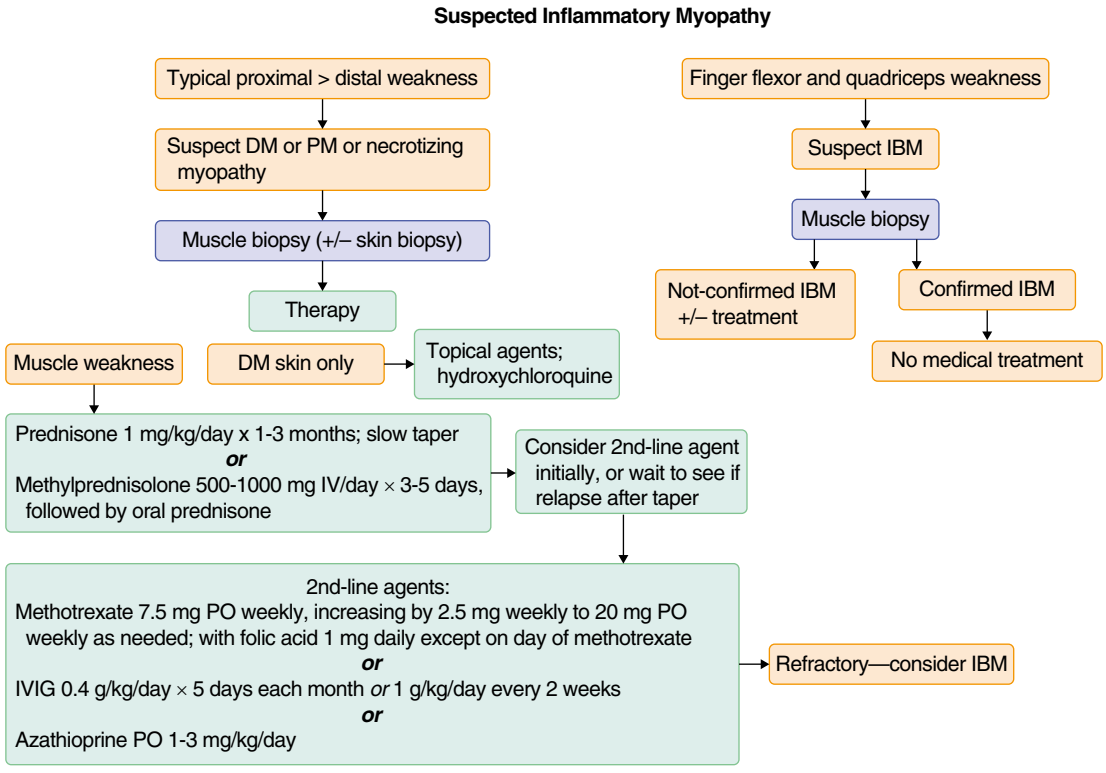

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JOHN H. STONE

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The presence or absence of granulomatous inflammation is a crucial element in the diagnosis and classification of vasculitis. The small number of vasculitides

ABSTRACT

The vasculitides are a heterogeneous group of disorders linked by the common finding of destructive inflammation within blood vessel walls. The current Chapel Hill Consensus on nomenclature identifies at least 27 different forms of primary vasculitis. The vasculitides are classified first according to the size of the blood vessel involved—small, medium, or large—but also according to whether their pathology is characterized by granulomatous inflammation, eosinophilic infiltrates, intense immune complex deposition, and other features. Patients with some forms of vasculitis (e.g., the group associated with antineutrophil cytoplasmic antibodies) typically have disease-specific autoantibodies in their blood.

KEYWORDS

systemic vasculitis
antineutrophil cytoplasmic antibody (ANCA) positive vasculitis
giant cell arteritis
Takayasu vasculitis (arteritis)
polyarteritis nodosa
Kawasaki disease
granulomatosis with polyangiitis (formerly Wegener)
eosinophilic granulomatosis with polyangiitis (EGPA formerly Churg-Strauss)
Behçet syndrome
IgA vasculitis

TABLE 249-1 NAMES FOR VASCULITIDES ADOPTED BY THE 2012 INTERNATIONAL CHAPEL HILL CONSENSUS CONFERENCE ON THE NOMENCLATURE OF VASCULITIDES

LARGE-VESSEL VASCULITIS
Takayasu arteritis
Giant cell arteritis
MEDIUM-VESSEL VASCULITIS
Polyarteritis nodosa
Kawasaki disease
Buerger disease*
SMALL-VESSEL VASCULITIS
Antineutrophil cytoplasmic antibody (ANCA)–associated vasculitis
Microscopic polyangiitis
Granulomatosis with polyangiitis (formerly Wegener granulomatosis)
Eosinophilic granulomatosis with polyangiitis (formerly Churg-Strauss syndrome)
Immune complex small-vessel vasculitis
Antiglomerular basement membrane disease
Cryoglobulinemic vasculitis
Immunoglobulin (Ig)A vasculitis (Henoch-Schönlein purpura)
Hypocomplementemic urticarial vasculitis
VARIABLE-VESSEL VASCULITIS
Behçet syndrome
Cogan syndrome
SINGLE-ORGAN VASCULITIS
Cutaneous leukocytoclastic angiitis
Cutaneous arteritis
Primary central nervous system vasculitis
Isolated aortitis
VASCULITIS ASSOCIATED WITH SYSTEMIC DISEASE
Lupus vasculitis
Rheumatoid vasculitis
Sarcoid vasculitis
IgG4-related disease
Others
VASCULITIS ASSOCIATED WITH PROBABLE ETIOLOGY
Hepatitis C virus–associated cryoglobulinemic vasculitis
Hepatitis B virus–associated vasculitis
Syphilis-associated aortitis
Drug-associated immune complex vasculitis
Drug-associated ANCA-associated vasculitis
Cancer-associated vasculitis
Others

*Buerger disease (thromboangiitis obliterans) is not always considered to be a primary form of vasculitis and was not included in this consensus statement on nomenclature.

From Jennette JC, Falk RJ, Bacon PA, et al. 2012 Revised International Chapel Hill Consensus Conference Nomenclature of Vasculitides. *Arthritis Rheum*. 2013;65:1-11.

TABLE 249-2 CONSIDERATIONS IN THE CLASSIFICATION OF SYSTEMIC VASCULITIS

Size of predominant blood vessels affected
Epidemiologic features:
Age
Sex
Ethnic background
Pattern of organ involvement
Pathologic features:
Granulomatous inflammation
Immune complex deposition vs. "pauci-immune" histopathology
Presence of ANCA in serum

ANCA = antineutrophil cytoplasmic antibody.

that demonstrate granulomatous inflammation includes granulomatosis with polyangiitis, giant cell arteritis, Takayasu arteritis, and eosinophilic granulomatosis with polyangiitis (Churg-Strauss syndrome).

Immune complexes are essential to the pathophysiologic mechanism of some forms of small- and medium-vessel vasculitis. Complexes of IgA1, for example, are found in IgA vasculitis. Immune complexes consisting of IgG, IgM, complement components, and the hepatitis C virion characterize most cases of mixed cryoglobulinemia. In contrast, "pauci-immune" types of small- and medium-vessel vasculitis, such as granulomatosis with polyangiitis and microscopic polyangiitis, have comparatively little evidence of immune complex deposition within diseased tissues. Many, but not all, patients with pauci-immune forms of vasculitis are positive for antineutrophil cytoplasmic antibodies (ANCA).

EPIDEMIOLOGY

The epidemiologic features of individual forms of systemic vasculitis vary tremendously by geography (Table 249-3)[1] as a reflection of genetic influences, variations in environmental exposures, and other unknown risk factors. For example, whereas Behçet syndrome is rare in North Americans, affecting only 1 person in approximately 300,000, this condition is several hundred times more common among inhabitants of countries bordering the ancient Silk Route. Similarly, although Takayasu arteritis (Chapter 63) is rare in the United States—on the order of 3 new cases per million people per year—this disease is reportedly the most common cause of renal artery stenosis in India, where the incidence may be as high as 200 to 300 per million per year.

Age is an important consideration in the epidemiology of vasculitis. Eighty percent of patients with Kawasaki disease are younger than age 5 years. In contrast, giant cell arteritis virtually never occurs in patients younger than age 50 years, and the mean age of patients with this disease is 72 years. Age may also have an impact on disease severity and outcome. In IgA vasculitis, the overwhelming majority of cases in children (who represent 90% of all cases) have self-limited courses, resolving within several weeks. In adults, however, IgA vasculitis has a higher likelihood of chronicity and a poor renal outcome.

The distribution of sex varies across many forms of vasculitis. The vasculitis associated with IgG4-related disease (e.g., aortitis, coronary arteritis, and even small-vessel vasculitis) is more likely to occur in males. Buerger disease (Chapter 66), which is often considered a form of vasculitis albeit not included in the Chapel Hill consensus nomenclature, has a striking male predominance that is probably explained by the higher prevalence of smoking among males in most societies. In contrast, Takayasu arteritis has an overwhelming tendency to occur in females (a 9 : 1 female-to-male ratio). The pauci-immune forms of vasculitis, such as granulomatosis with polyangiitis, eosinophilic granulomatosis with polyangiitis, and microscopic polyangiitis, occur in males and females with approximately equal frequencies, but the phenotypic expression of these conditions may be affected by both age and sex. As an example, granulomatosis with polyangiitis limited to the subglottic region is more likely to occur in female patients.

The strongest link between any single gene and vasculitis is the association of *HLA-B51* with Behçet syndrome. In Behçet syndrome, 80% of Asian patients have the *HLA-B51* gene. The prevalence of *HLA-B51* is significantly higher among patients with Behçet syndrome in Japan than among nondisease control subjects (55% versus <15%). Among the sporadic cases of Behçet syndrome involving Whites in the United States, however, *HLA-B51* occurs in less than 15% of cases.

With the exception of Buerger disease and smoking, no definitive associations have been confirmed between disease and environmental or occupational exposures. Associations have been reported but not confirmed between exposures to silica and some types of pauci-immune vasculitis. Studies of potential associations between exposures of any type and vasculitis, however, are frequently complicated by difficulties in obtaining reliable measurements of the levels of the relevant exposure, the likelihood of recall bias among patients who are diagnosed with vasculitis, and the choice of appropriate control groups.

PATHOBIOLOGY

Different forms of vasculitis have different pathologic characteristics (Table 249-4). The type of inflammatory cell infiltrate in vasculitis is independent of the size of blood vessels involved. Mixed cell infiltrates in vasculitis are the rule rather than the exception, and histopathologic patterns of vasculitis may include leukocytoclasis (degranulation and destruction of neutrophils within blood vessel walls), granulomatous findings (with or without giant cells), lymphoplasmacytic infiltrates, varying degrees of eosinophilic infiltration, necrosis, and combinations of all these findings.

Pathophysiology

Some pathophysiologic mechanisms are common to many different forms of vasculitis, regardless of the size of the predominant blood vessels involved.

TABLE 249-3 EPIDEMIOLOGY OF SELECTED VASCULITIDES

DISEASE	UNITED STATES	ELSEWHERE	AGE, SEX, AND ETHNIC PREDISPOSITIONS
Giant cell arteritis	Incidence: 240/million (Olmsted County, MN)	220-270/million (Scandinavian countries)	Age >50 yr, mean age 72 yr; females 3 : 1; Northern European ancestry
Takayasu arteritis	Incidence: 3/million	200-300/million (India)	Age <40 yr; females 9 : 1; Asian
Behçet syndrome	Prevalence: 3/million	3000/million (Turkey)	Silk Route countries
Polyarteritis nodosa	Incidence: 7/million	7/million (Spain)	Slight male predominance
Kawasaki disease	Incidence: 100/million*	900/million (Japan)	Children of Asian ancestry
Granulomatosis with polyangiitis	Incidence: 4/million	8.5/million (United Kingdom)	Whites >> Blacks

*Among children younger than 5 years.
From Watts RA, Hatemi G, Burns JC, et al. Global epidemiology of vasculitis. *Nat Rev Rheumatol* 2022;18:22-34.

TABLE 249-4 PATHOLOGIC CHARACTERISTICS OF SELECTED FORMS OF VASCULITIS

	TAKAYASU ARTERITIS	POLYARTERITIS NODOSA	GRANULOMATOSIS WITH POLYANGIITIS (WEGENER GRANULOMATOSIS)	EOSINOPHILIC GRANULOMATOSIS WITH POLYANGIITIS*	HENOCH-SCHÖNLEIN PURPURA	CUTANEOUS LEUKOCYTOCLASTIC ANGIITIS
Vessels involved	Elastic (large) or muscle (medium-sized) arteries	Medium-sized and small muscle arteries	Small arteries and veins; sometimes medium-sized vessels	Small arteries and veins; sometimes medium-sized vessels	Capillaries, venules, and arterioles	Capillaries, venules, and arterioles
Organ involvement	Aorta, aortic arch and major branches, and pulmonary arteries	Skin, peripheral nerves, gastrointestinal tract, and other viscera	Upper respiratory tract, lungs, kidneys, skin, eyes	Upper respiratory tract, lungs, heart, peripheral nerves	Skin, joints, gastrointestinal tract, kidneys	Skin, joints
Type of vasculitis and inflammatory cells	Granulomatous with some giant cells; fibrosis in chronic stages	Necrotizing, with mixed cellular infiltrate	Necrotizing or granulomatous (or both); mixed cellular infiltrate plus occasional eosinophils	Necrotizing or granulomatous (or both); prominent eosinophils and other mixed infiltrate	Leukocytoclastic, with some lymphocytes and variable eosinophils; IgA deposits in affected tissues	Leukocytoclastic, with occasional eosinophils

*Formerly named Churg-Strauss syndrome.
Ig = immunoglobulin.

Immune complex deposition, for example, is present in several types of vasculitis that involve both medium-sized and small blood vessels.

Large-Vessel Vasculitides

The pathologic process in large-vessel vasculitis appears to begin in the adventitia. In both Takayasu arteritis (Chapter 63) and giant cell arteritis (Chapter 250), abundant numbers of activated T lymphocytes are found within inflamed arterial walls, centering on the adventitia. In Takayasu arteritis, most of these T cells appear to be of the $CD8^+$ subtype. Current evidence suggests that the cytotoxic functions of these cells, mediated by perforin and granzyme B, contribute to smooth muscle cell damage in this disease. $CD4^+$ T-cell responses in Takayasu arteritis have not been well defined.

In giant cell arteritis (Chapter 250), evidence suggests an antigen-driven disease, with the site of immunologic events being the adventitia. $CD4^+$ T cells that secrete interferon (IFN)-γ appear to be recruited to the adventitia by a specific antigen(s), the identity of which remains unknown. Both the T cells that orchestrate the transmural inflammation and the inciting antigens are theorized to reach the adventitia through the vasa vasorum. Subsequently, T-cell signals from the adventitia stimulate macrophages and multinucleated giant cells to elaborate an array of downstream mediators, including metalloproteinases and platelet-derived growth factor. Interleukin (IL)-6, known to be a crucial cytokine in giant cell arteritis and probably Takayasu arteritis, is also produced by macrophages residing in the blood vessel wall. The results of this inflammatory cascade are granulomatous inflammation, destruction of the internal elastic lamina, arterial wall hyperplasia, smooth muscle cell proliferation, intimal thickening, vascular occlusion, and, in some cases, weakening of the vessel wall with subsequent dilation and aneurysm formation. Matrix metalloproteinases appear to play important roles in destruction of the internal elastic lamina, damage to other vascular tissues, and weakening of the arterial wall.

Medium- and Small-Vessel Vasculitides

Several different pathophysiologic mechanisms are operative among the medium- and small-vessel vasculitides.

Immune Complex–Mediated Vascular Injury

Immune complex–mediated tissue injury does not produce a single clinical syndrome but rather applies to many forms of vasculitis and overlaps with injuries caused by other immune mechanisms. Numerous variables influence immune complex–mediated injury, including the physical properties of the immune complexes (e.g., their size), the ability of the immune complexes to activate complement, the antigen-to-antibody ratio, and the hemodynamic features of specific vascular beds. Immune complexes participate in the pathophysiologic process of some forms of both medium- and small-vessel vasculitis, including polyarteritis nodosa, cryoglobulinemia, IgAV, cutaneous leukocytoclastic angiitis, and rheumatoid vasculitis.

Role of Antineutrophil Cytoplasmic Antibodies

Antineutrophil cytoplasmic antibodies (ANCAs) are directed against antigens that reside within the primary granules of neutrophils and monocytes. Two types of ANCA are relevant to vasculitis: (1) those directed against proteinase 3 (PR3), known as PR3-ANCA, and (2) those directed against myeloperoxidase (MPO), termed MPO-ANCA. ANCAs interact with cytokines, neutrophils, monocytes, and other elements of the immune system to amplify ongoing inflammation in certain forms of vasculitis. A striking and still unexplained feature of ANCA-associated vasculitis is that patients with primary forms of these conditions virtually never have antibodies to both PR3 and MPO.

Despite the specificity of these antibodies, however, evidence for a primary role of ANCA in the etiology of human disease is still tenuous.

In granulomatosis with polyangiitis, abnormal cytokine regulation interacts with the production of antineutrophil cytoplasmic antibodies to fuel the inflammatory response. T_H1 cytokines such as interferon (IFN)-γ, interleukin (IL)-12, and tumor necrosis factor (TNF) appear to play important roles. Under the direction of IL-12, $CD4^+$ T cells from patients with granulomatosis with polyangiitis produce elevated levels of TNF, and peripheral blood mononuclear cells secrete increased amounts of IFN-γ. Serum levels of soluble receptors for TNF are elevated in patients with active granulomatosis with polyangiitis and normalize with the induction of remission. In vitro priming of activated neutrophils with TNF markedly enhances the ability of ANCA to stimulate neutrophil degranulation. Through processes, which are promoted by a variety of cytokines, ANCA binding leads to neutrophil activation and degranulation, with the release of cytotoxic substances and activation of the alternative complement pathway.

The effectiveness of B-cell depletion for the treatment of antibody-associated vasculitis probably relates to the removal of several B-cell functions beyond their evolution into plasma cells and the production of ANCA. Such functions include the production of cytokines, the presentation of antigen, and B cell–T cell crosstalk. B-cell depletion is emerging rapidly as the treatment of choice for some forms of severe vasculitis.

Superantigen Model

The degree of immune activation in Kawasaki disease and the acute but generally self-limited nature of this illness imply a potential role for superantigens. Superantigens are proteins that are produced by microbial pathogens (e.g., *Staphylococcus aureus* or *Streptococcus* species) and that are capable of stimulating large populations of T cells in a manner unrestricted by the class II major histocompatibility complex (MHC). Superantigens bind directly to conserved amino acid residues outside the antigen-binding groove on class II MHC molecules, thereby selectively stimulating T cells that express particular β-chain variable gene segments. Through the binding of this MHC-superantigen complex to its cognate T-cell receptors, as many as 20% of circulating lymphocytes may become activated, thereby leading to a potentially enormous outpouring of cytokines. With regard to the etiology of Kawasaki disease, substantial attention has focused on toxic shock syndrome toxin 1, an exotoxin produced by *S. aureus*. Superantigens have also been postulated to play roles in the susceptibility to disease flares in granulomatosis with polyangiitis. Compelling laboratory and naturally occurring animal models of disease, combined with the known associations of hepatitis B virus and hepatitis C virus with vasculitis in humans, suggest that additional links between infection and systemic vasculitis may be established in the future.

Anti–Endothelial Cell Antibodies

Anti–endothelial cell antibodies can induce endothelial cell injury and lysis through either complement-mediated cytotoxicity or antibody-dependent cellular cytotoxicity. The ability of these antibodies to damage endothelial cells is an appealing argument for their potential role in forms of vasculitis in which the endothelium is the focus of the inflammation (as opposed to the more external vessel wall layers).

DIAGNOSIS

Vasculitis is often considered in patients who have multisystem diseases or fever of unknown origin (Chapter 259). The major categories of disease that can mimic vasculitis are also multisystem diseases (Table 249-5).

Certain features of a patient's case should raise the diagnostic suspicion for vasculitis. First, most cases of vasculitis do not begin suddenly but rather unfold subacutely during weeks or months. Second, pain is usually a prominent feature of vasculitis as a result of arthritis or arthralgias, myalgias, headaches, neuropathy, testicular infarction, digital ischemia, sinusitis, otalgia, back pain (caused by aortic inflammation), postprandial abdominal pain (caused by mesenteric vasculitis), or other disease manifestations. Third, signs of inflammation such as fever, rash, weight loss, and elevated acute phase reactants are highly characteristic. Finally, multiorgan system involvement is the rule in vasculitis.

The diagnosis of vasculitis should be established through biopsy of an involved organ whenever possible. Diagnoses based on angiography alone have many potential pitfalls, and angiographic findings that are called "consistent with vasculitis" must be interpreted in the proper context. A diverse array of other diseases, ranging from atherosclerosis to vasospasm to pheochromocytoma, may mimic the angiographic appearance of vasculitis. Systemic vasculitis can also be mimicked by two or more common medical problems or treatment complications occurring simultaneously in the same patient. Finally, high on the differential diagnosis of any individual form of vasculitis are other forms of vasculitis. For example, digital ischemia and splinter hemorrhages may be secondary to idiopathic polyarteritis nodosa. They may also be caused by polyarteritis nodosa associated with hepatitis B viral infection, granulomatosis with polyangiitis, eosinophilic granulomatosis with polyangiitis, microscopic polyangiitis, cryoglobulinemia, Buerger disease, or some other form of vasculitis. Because the appropriate interventions for these conditions vary widely, careful distinction among these potential etiologies is essential.

TABLE 249-5 MAJOR DISEASE CATEGORIES IN THE DIFFERENTIAL DIAGNOSIS OF VASCULITIDES

Other forms of vasculitis
Simultaneous occurrence of common medical problems in the same patient
Infections
Bacterial, viral, mycobacterial, fungal
Occlusive processes
Hypercoagulable states
Livedoid vasculopathy (atrophie blanche)
Atheroembolic disease
Malignant neoplasms
Lymphoma (including lymphomatoid granulomatosis)
Castleman disease
Amyloidosis
Paraproteinemias
Connective tissue disorders
Systemic lupus erythematosus, mixed connective tissue disease
Systemic sclerosis
Rheumatoid arthritis
Miscellaneous
Atrial myxoma
Calciphylaxis
Fibromuscular dysplasia
Neutrophilic dermatoses
Pyoderma gangrenosum
Sarcoidosis
Reversible cerebral vasoconstriction syndrome

TREATMENT

General Approach

The intensity of treatment in patients with vasculitis must be guided by the degree of disease activity. Specifically, the treatment of vasculitis should be predicated not only on abnormal laboratory test results but also on clear evidence of active disease. In addition, the intensity of treatment must be adapted to the type of vasculitis.

Conventional therapies such as glucocorticoids, immunomodulating agents, and cytotoxic drugs induce remissions and control most cases of vasculitis. Moreover, in some cases—a variable percentage, depending on the type of vasculitis—the disease is curable. Whereas giant cell arteritis usually responds to high doses of glucocorticoids, granulomatosis with polyangiitis nearly always requires an additional agent (e.g., rituximab, cyclophosphamide, or methotrexate) for disease control. Rituximab (500 mg or 1 g every 4 to 6 months, at least until lengthy periods of disease control are established) is replacing cyclophosphamide as the drug of choice for some forms of vasculitis, particularly in patients with antibody-associated vasculitis who demonstrate a tendency to flare. In contrast, despite the dramatic fashion in which they sometimes present, most cases of IgA vasculitis and cutaneous leukocytoclastic angiitis require no immunosuppressive treatment at all.

Unfortunately, the treatments of vasculitis have enormous potential for toxicity, especially higher doses of glucocorticoids, which remain a cornerstone for treating many forms of systemic vasculitis. When these higher doses are tapered to lower doses or discontinued, vasculitis often recrudesces. Throughout the period of their use, patients should be monitored for glucocorticoid toxicity (Chapter 28), and appropriate measures must be taken to reduce their potential adverse outcomes. For other forms of treatment, regular monitoring of patients' bone marrow, renal, and hepatic function is essential to avoid treatment-induced toxicity. Prophylaxis against opportunistic infections, particularly *Pneumocystis* pneumonia (Chapter 313), is an important part of many vasculitis treatment regimens.

A common error is treating patients for too long with high doses of immunosuppressive agents. The most appropriate use of medications such as glucocorticoids and cyclophosphamide is to induce remission as quickly as possible with early, aggressive treatment regimens and then to convert patients to safer treatments for the maintenance of remission. During the tapering of immunosuppressive medications, however, disease flares are common in many forms of vasculitis.

PROGNOSIS

Assuming that the diagnosis is made before the patient has become catastrophically ill, the prognosis in systemic vasculitis is determined largely by the answers to four questions:

1. Was the diagnosis established before the occurrence of major irreversible organ damage?
2. Was aggressive (but appropriately dosed) treatment begun in a timely fashion?
3. Was the patient carefully monitored during treatment, and were specific steps taken to avoid drug-induced toxicity (e.g., opportunistic infection)?
4. Were the potentially toxic medications that induced remission stopped at an appropriate juncture and replaced with less dangerous medications (or was treatment stopped altogether)?

For most forms of vasculitis, the factors that determine long-term drug-free remissions remain poorly understood. The likelihood of achieving sustained remissions after discontinuation of all medications (or cures) varies according to the specific type of vasculitis.

SPECIFIC VASCULITIDES

Large-Vessel Vasculitides

TAKAYASU ARTERITIS

Takayasu arteritis (Chapter 63) affects the aorta and its major branches. In contrast to atherosclerosis, which is characterized by focal irregular lesions, the lesions of Takayasu arteritis are long, smooth, tapered stenoses (Fig. 249-1). The most commonly involved arteries are the subclavian and innominate arteries.[2] Takayasu arteritis has been termed "pulseless disease" because of its ability to obliterate peripheral pulses (particularly in the upper extremities). Exuberant collateral circulation develops over time in response to the gradual narrowing of major arteries, thereby making the loss of digits or limbs from ischemia extremely rare. The extensive development of collateral circulation usually renders unnecessary any attempts to revascularize stenoses of primary aortic branches, such as the subclavian artery. The pulmonary circulation is involved in approximately 50% of cases of Takayasu arteritis.

Patients with severe narrowing of the aortic arch vessels supplying the head may develop Takayasu retinopathy, which is a hypotensive retinopathy that leads to neovascularization. This complication is particularly difficult to diagnose because vascular narrowings of large arteries to the arms and legs often lead to underestimations of the true central aortic pressure. Takayasu arteritis involvement of the ascending aorta may lead to aortic dilation, aortic regurgitation, aneurysms, and aortic rupture.

TREATMENT AND PROGNOSIS

For patients with marked symptoms and signs of an inflammatory phase, glucocorticoids (prednisone 1 mg/kg/day) are usually effective in controlling the disease.[3] The toxicity of high doses of glucocorticoids in young women, however, should stimulate the early consideration of alternative agents. IL-6 inhibition with tocilizumab (either intravenously at 8 mg/kg each month or subcutaneously at 162 mg each week) can allow the prednisone dose to be tapered to low doses (10 mg daily or less) within 3 months and ultimately be discontinued altogether,[A1,A2] if possible. The optimal duration of tocilizumab in Takayasu arteritis is uncertain. Consideration may be given to tapering (to either 4 mg/kg intravenously each month or 162 mg subcutaneously every other week) after 1 year. Large-vessel imaging may be useful in guiding decisions regarding the duration of therapy. About 50% of patients will relapse within 10 years, so some Takayasu arteritis patients may require chronic treatment with tocilizumab plus (possibly) low-dose glucocorticoids.

GIANT CELL ARTERITIS

Giant cell arteritis, which is the other primary form of vasculitis that involves arteries far larger than vasculitides of any other category, is discussed in Chapter 250.

Medium-Vessel Vasculitides

POLYARTERITIS NODOSA

Most polyarteritis nodosa is idiopathic, but about 15% of cases are linked to chronic hepatitis B viral infection (Chapter 135). Polyarteritis nodosa has a striking predilection for certain organs, particularly the skin, peripheral nerves, gastrointestinal tract, and kidneys.[4] This disease usually begins with nonspecific symptoms such as malaise, fatigue, fever, myalgias, and arthralgias. Overt signs of vasculitis may not occur until weeks or months after onset of the first symptoms. Skin lesions of polyarteritis nodosa include livedo reticularis, subcutaneous nodules, ulcers, and digital gangrene. A majority of patients with polyarteritis nodosa (>80% in some series) have vasculitic neuropathy, typically in the pattern of a mononeuritis multiplex.

The classic gastrointestinal manifestation of polyarteritis nodosa is "intestinal angina," the occurrence of postprandial abdominal pain. Polyarteritis nodosa can also affect individual gastrointestinal tract organs such as the gallbladder or appendix, presenting as cholecystitis or appendicitis, respectively. The typical renal manifestation of polyarteritis nodosa is vasculitic involvement of the medium-sized intrarenal arteries, thereby leading to renin-mediated hypertension and renal infarctions. Cardiac lesions, which usually remain subclinical, may lead to myocardial infarction or heart failure. Polyarteritis nodosa usually spares the lungs.

The diagnosis of polyarteritis nodosa requires either a tissue biopsy or an angiogram that demonstrates microaneurysms (Fig. 249-2).[5] Simultaneous nerve and muscle biopsies (e.g., sural nerve and gastrocnemius muscle) are of high yield when a vasculitic neuropathy is suspected. Symptoms suggestive of a neuropathy can be confirmed by electrodiagnostic studies that demonstrate a sensorimotor axonal neuropathy, often in a mononeuritis multiplex pattern. The pathologic changes in polyarteritis nodosa are limited to the arterial circulation, and the lesions are segmental, favoring the branch points of arteries. In gross pathologic specimens, aneurysmal bulges of the arterial wall may be visible. Histologic sections reveal infiltration and destruction of the blood vessel wall by inflammatory cells, accompanied by fibrinoid necrosis. Granulomatous inflammation is absent.

TREATMENT AND PROGNOSIS

For polyarteritis nodosa that is linked to chronic hepatitis B viral infection, antiviral therapy (see Chapters 134 and 135) combined with plasma exchange and short-term (2-week) courses of glucocorticoids are recommended. Patients with idiopathic polyarteritis nodosa and multiorgan involvement require high-dose glucocorticoid treatment initially (prednisone 1 mg/kg, up to 60 to 80 mg, daily for 4 weeks) followed by a gradual reduction to 10 mg daily or less. Approximately half of patients with idiopathic polyarteritis nodosa achieve remissions or cures with these high doses of glucocorticoids alone. Severe cases of multiorgan disease, particularly vasculitic neuropathy, should be treated with cyclophosphamide (2 mg/kg/day, adjusted for renal dysfunction) as well.[6] For patients with idiopathic polyarteritis nodosa limited to the skin or with refractory disease, tumor necrosis factor inhibitors (e.g., infliximab 5 mg/kg intravenously at 0, 2, and 6 weeks and then every 6 weeks) may be effective glucocorticoid-sparing agents. Most patients with either hepatitis B virus–associated or idiopathic polyarteritis nodosa ultimately achieve cures of their disease.

KAWASAKI DISEASE

Kawasaki disease, which is also known as mucocutaneous lymph node syndrome, occurs exclusively in young children. Cases typically follow an otherwise unremarkable infection, although cases were also reported after infection with the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) as part of a multisystem inflammatory syndrome.[7] In its acuity and severity, Kawasaki disease resembles toxic shock syndrome (Chapters 267 and 269) and scarlet fever (Chapter 269). Features of Kawasaki disease include high fevers, cervical adenopathy, conjunctival congestion, buccal erythema, prominence of the tongue papillae ("strawberry tongue"), a polymorphous truncal rash, erythema of the palms and soles, and desquamation of skin from the fingertips occurring days to weeks into the illness.[8]

In a small number of patients with Kawasaki disease, panvasculitis in the coronary vessels leads to narrowing of the vessel lumen by the migration of myointimal cells from the media through the fragmented internal elastic lamina. Direct complications include aneurysmal dilation and thrombosis of the coronary arteries, thereby leading to myocardial infarction.

TREATMENT AND PROGNOSIS

The recommended therapeutic regimen in Kawasaki disease is the combination of intravenous immune globulin (IVIG; 400 mg/kg/day on 4 consecutive days) and acetylsalicylic acid (100 mg/kg/day, lowered to 3 to 5 mg/kg/day after resolution of the fever). IVIG prevents the formation of coronary aneurysms in most cases.[9] For patients who are predicted to be unresponsive to IVIG, the combination of IVIG plus cyclosporine (5 mg/kg for 5 days) is better than IVIG alone.[A3] Glucocorticoids are reserved for salvage therapy under expert guidance in patients whose treatment with IVIG and acetylsalicylic acid has failed.[A4]

About 1 to 2% of patients with Kawasaki disease die during the acute illness. Late mortality from myocardial infarction may occur from the thrombosis of coronary artery aneurysms formed during the initial inflammatory stage. Such myocardial infarctions have been reported in middle-aged individuals who had febrile illnesses consistent with Kawasaki disease in childhood.

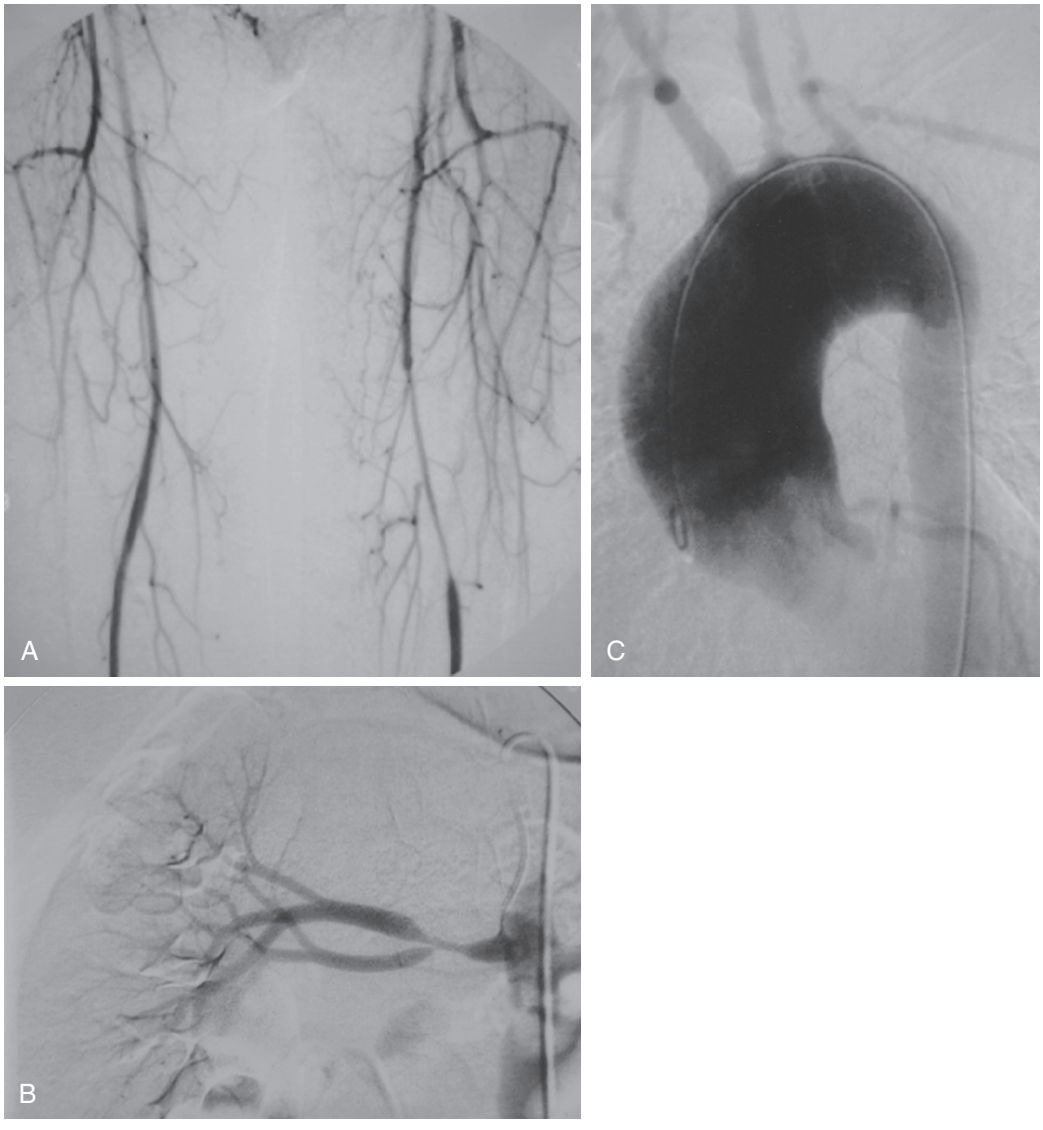

FIGURE 249-1. Large-vessel disease in Takayasu arteritis. Long, smooth tapering in the left common femoral artery (**A**) and the right renal artery (**B**). Dilation of the ascending aorta (**C**). Aortic regurgitation necessitated an aortic valve replacement and replacement of the ascending aorta with a Gore-Tex graft.

BUERGER DISEASE

Buerger disease, also known as thromboangiitis obliterans, is discussed in detail in Chapter 66.

SMALL-VESSEL VASCULITIDES

ANTINEUTROPHIL CYTOPLASMIC ANTIBODY–ASSOCIATED VASCULITIDES

Granulomatosis with Polyangiitis

Classic granulomatosis with polyangiitis involves the upper respiratory tract, lungs, and kidneys. Distinctive features may also occur in the eyes, ears, and other organs. The three pathology hallmarks of granulomatosis with polyangiitis are (1) granulomatous inflammation in the upper or lower respiratory tract, (2) necrotizing vasculitis affecting arteries or veins, and (3) segmental glomerulonephritis associated with necrosis and thrombosis of capillary loops, with or without granulomatous lesions.[10]

Approximately 90% of patients with granulomatosis with polyangiitis have nasal involvement, including crusting, bleeding, and obstruction. Cartilaginous inflammation may lead to nasal septal perforation and collapse of the nasal bridge ("saddle nose" deformity). Erosive sinus disease and subglottic stenosis (narrowing of the trachea just below the vocal cords) are highly characteristic.

Both conductive and sensorineural hearing loss can occur in granulomatosis with polyangiitis, though conductive lesions caused by middle ear disease are more common. Orbital masses ("pseudotumors" that develop behind the eye), scleritis, and peripheral ulcerative keratitis are the most dangerous ocular lesions. Episcleritis and conjunctivitis also occur. Uveitis is rare. The clinical manifestations in the lungs range from asymptomatic nodules to fulminant alveolar hemorrhage. The most common radiographic findings are pulmonary infiltrates, nodules, and cavitary lesions. Large-airway disease leading to bronchial narrowing is a challenging diagnosis to establish because patients present with few symptoms until advanced disease is present.

The clinical presentation of renal disease in granulomatosis with polyangiitis is usually rapidly progressive glomerulonephritis (Chapter 107) with hematuria, red blood cell casts, and proteinuria (usually non-nephrotic). Without appropriate therapy, end-stage renal disease may ensue within weeks.

Sixty percent of patients with granulomatosis with polyangiitis have musculoskeletal symptoms during their disease course. The presenting complaint is frequently arthralgias or an oligoarthritis that is migratory in nature. Skin lesions include the full panoply of lesions associated with cutaneous vasculitis, including purpura (Fig. 249-3). Cutaneous nodules over the extensor surfaces of joints, particularly the elbow, may mimic rheumatoid nodules. These lesions are known as cutaneous extravascular necrotizing granulomata or Churg-Strauss lesions. Meningeal inflammation, which presents with headaches, cranial neuropathies, and a clinical picture compatible with chronic meningitis, is perhaps the most common central nervous system (CNS) manifestation of granulomatosis with polyangiitis. Mononeuritis multiplex may affect the peripheral nervous system.

Granulomatosis with polyangiitis is the prototype of conditions associated with ANCA.[11] Approximately 75 to 80% of patients have antibodies directed

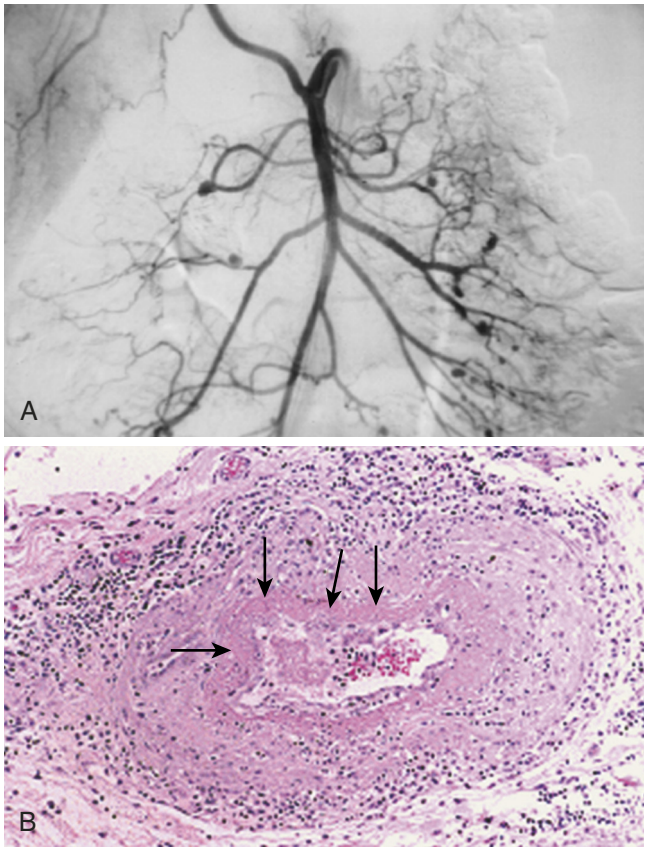

FIGURE 249-2. **Vasculitis of medium-sized arteries in polyarteritis nodosa. A,** Mesenteric angiogram showing numerous aneurysms in medium-sized arteries. **B,** Fibrinoid necrosis (*arrows*) in a jejunal artery from a patient who required surgical resection of necrotic bowel.

against proteinase 3 (PR3), which lead to positive cytoplasmic (C-ANCA) staining on immunofluorescence testing of serum against human neutrophils. In another 10 to 15% of patients, antibodies directed against myeloperoxidase (MPO) cause perinuclear staining on immunofluorescence. An ANCA-negative assay sample does not exclude granulomatosis with polyangiitis, because a substantial minority of patients are ANCA-negative. ANCA titers do not correlate precisely with disease activity and, indeed, should generally not be used as the sole guide to treatment.

TREATMENT AND PROGNOSIS

Manifestations of granulomatosis with polyangiitis can constitute immediate threats either to the function of a vital organ or to the patient's life and require urgent treatment.[12,13] For patients with polyangiitis, rituximab (375 mg/m^2 weekly times four) is at least as effective as a combination of cyclophosphamide (2 mg/kg orally daily) plus glucocorticoids and is associated with fewer adverse effects.[A5] Rituximab appears to be more effective for patients who have antibody-associated vasculitis and present with disease flares. An alternative dosing regimen of rituximab 1 g times two separated by 2 weeks may also be effective.[14] After initial therapy, extended rituximab therapy every 6 months can yield sustained remission.[A6] A reduced prednisone dose (0.5 mg/kg orally) appears to be as efficacious as higher doses, and plasma exchange is of no incremental value.[A7] Avacopan (30 mg orally twice daily), an oral complement inhibitor that blocks the C5a receptor, can be used to reduce glucocorticoid toxicity in ANCA-associated vasculitis by substantially decreasing the quantity of glucocorticoids required to induce remission induction in patients with severe disease.[A8] Limited forms of granulomatosis with polyangiitis may respond to the combination of methotrexate (up to 25 mg/week) and glucocorticoids, but rituximab is now often used in this setting as well. Rituximab (e.g., 500 mg every 6 months) is more effective than azathioprine for maintaining remission in patients who demonstrate a tendency to flare.

The prognosis of patients who achieve and maintain disease remissions, with or without ongoing remission maintenance therapy, is good. Toxicities from glucocorticoid treatment may affect quality of life and even longevity.

FIGURE 249-3. **Cutaneous small-vessel vasculitis showing palpable purpuric lesions with necrosis and crusting.**

Microscopic Polyangiitis

Microscopic polyangiitis is characterized by nongranulomatous necrotizing vasculitis with few or no immune deposits, involvement of small (and possibly medium-sized) blood vessels in the arterial or venous circulation, and tropism for the kidneys and lungs.[15] Many cases of small-vessel vasculitis once regarded as polyarteritis nodosa are now classified more properly as microscopic polyangiitis.

In contrast to polyarteritis nodosa, which is an ANCA-negative disorder, 70% of microscopic polyangiitis patients are ANCA-positive, so microscopic polyangiitis is considered to be a form of antibody-associated vasculitis. The ANCAs in microscopic polyangiitis are usually directed against myeloperoxidase, thereby leading to a perinuclear pattern of staining on immunofluorescence testing (P-ANCA). Microscopic polyangiitis is not characterized by granulomatous inflammation, and upper respiratory tract symptoms, if present at all, are much milder than in granulomatosis with polyangiitis.

TREATMENT AND PROGNOSIS

The approach to the treatment of microscopic polyangiitis is similar to the treatment of granulomatosis with polyangiitis, with the combination of rituximab and glucocorticoids as the treatment regimen of choice for most patients. Avacopan can also be administered in this setting in the interest of reducing glucocorticoid use and toxicity, though it does not supplant glucocorticoid use entirely.

The prognosis in microscopic polyangiitis is often dictated by disease-related damage present at diagnosis. For example, renal dysfunction can persist, even though remission is achieved in the great majority of patients.

Eosinophilic Granulomatosis with Polyangiitis

Eosinophilic granulomatosis with polyangiitis is an eosinophil-rich form of granulomatous inflammation that involves the respiratory tract and other organs. The disease is associated with necrotizing vasculitis of small to medium-sized vessels. Two hallmarks of eosinophilic granulomatosis with polyangiitis are asthma and eosinophilia, and several phases are described:[16,17]

- A prodromal phase characterized by the presence of allergic disease (typically asthma or allergic rhinitis), which may persist months to many years

- An eosinophilia–tissue infiltration phase, in which remarkably high peripheral eosinophilia may occur, and tissue infiltration by eosinophils is observed in the lung, gastrointestinal tract, and other tissues
- A vasculitic phase, in which systemic necrotizing vasculitis afflicts a wide range of organs, ranging from the heart and lungs to peripheral nerves and skin

Approximately 50% of cases of eosinophilic granulomatosis with polyangiitis are associated with ANCA, usually directed against myeloperoxidase, but the percentage may be higher among untreated patients.

TREATMENT AND PROGNOSIS

Patients with mild disease may be treated with prednisone. The addition of mepolizumab 300 mg subcutaneously each month has an important glucocorticoid-sparing role.[A9] Patients with evidence of neurologic, cardiac, renal, or gastrointestinal involvement should be treated with cyclophosphamide or rituximab[18] as in granulomatosis with polyangiitis, in addition to glucocorticoids and mepolizumab.

Although clinical remissions are obtained in more than 90% of patients with eosinophilic granulomatosis with polyangiitis, the majority of patients are unable to discontinue glucocorticoids entirely (primarily because of asthmatic symptoms), and disease recurrences are seen in 25%. In most cases, relapses are heralded by the return of eosinophilia.

IMMUNE COMPLEX–MEDIATED VASCULITIDES

Anti–Glomerular Basement Membrane Disease

Anti–glomerular basement membrane (anti-GBM) disease is a vasculitis that affects glomerular capillaries, pulmonary capillaries, or both, accompanied by the deposition of anti–basement membrane autoantibodies within basement membranes. Anti-glomerular basement membrane disease is discussed in detail in Chapter 107.

Immunoglobulin A Vasculitis/Henoch-Schönlein Purpura

IgA vasculitis is characterized by nonthrombocytopenic purpura, arthritis, abdominal pain, and glomerulonephritis. The histopathologic findings are those of a leukocytoclastic vasculitis with IgA deposition. IgA vasculitis can develop at any age, but 80 to 90% of the cases occur in children. Although the cause is unknown, the disease's seasonal variation and the fact that two thirds of patients experience an antecedent acute upper respiratory illness suggest an infectious trigger in the majority of cases. The diagnosis of IgA vasculitis can be confirmed only by demonstration of IgA deposition within and around blood vessel walls.

The classic patient presents with the acute onset of fever, palpable purpura on the lower extremities and buttocks, abdominal pain, arthritis, and hematuria.[19] The clinician must be alert to the possibility of IgA vasculitis even when only parts of the syndrome are present.

TREATMENT

Glucocorticoids ameliorate the gastrointestinal, joint, and skin symptoms in many cases, but some patients respond surprisingly poorly to conventional doses of glucocorticoids, even in doses on the order of 40 to 60 mg/day. Anecdotal evidence suggests that pulse glucocorticoids (e.g., methylprednisolone 500 to 1000 mg/day times three doses) may abort persistent bouts of IgA vasculitis. The efficacy of glucocorticoids in the glomerulonephritis associated with this condition is controversial. Uncontrolled studies suggest that methylprednisolone pulses (1 g/day for three doses) followed by oral prednisone combined with azathioprine or mycophenolate mofetil may be useful in severe glomerulonephritis. Most patients, especially children, have a self-limited disease that persists for an average of 4 weeks.

Hypocomplementemic Urticarial Vasculitis

At least three subtypes of urticarial vasculitis are defined: (1) normocomplementemic, a form that is generally idiopathic and benign (and may be viewed as a manifestation of cutaneous leukocytoclastic angiitis); (2) hypocomplementemic, a form that is often associated with a systemic inflammatory disease; and (3) hypocomplementemic urticarial vasculitis syndrome, a potentially severe condition usually associated with autoantibodies to the collagen-like region of C1q.[20] Most patients with the hypocomplementemic subtype have an underlying systemic disorder, such as systemic lupus erythematosus (Chapter 245) or Sjögren syndrome (Chapter 247). Many patients who have hypocomplementemic urticarial vasculitis syndrome have C1q "precipitins," which are IgG autoantibodies to the collagen-like region of C1q and which trigger the classical pathway of complement activation (Chapter 37). The role of anti-C1q antibodies in disease pathogenesis remains unclear.

The lesions of urticarial vasculitis must be distinguished from the far more common chronic idiopathic urticaria (Chapters 232 and 407). Unlike idiopathic urticaria, the lesions of urticarial vasculitis persist for more than 48 hours, often have a purpuric component (i.e., they do not blanch), and resolve with postinflammatory hyperpigmentation. In urticarial vasculitis, lesions associated with vasculitis are often accompanied by stinging or burning.

On biopsy, urticarial vasculitis affects the capillaries and postcapillary venules, with leukocytoclastic vasculitis on light microscopy. Direct immunofluorescence studies reveal both immunoglobulin and complement deposition in or around blood vessels of the upper dermis or the dermoepidermal junction.

TREATMENT

Patients with urticarial vasculitis whose serum complement levels remain normal during attacks often have self-limited disease and require little therapy. Other cases, especially hypocomplementemic urticarial vasculitis, may cause life-threatening involvement of the lungs or other organs and require periods of intensive immunosuppression. Treatment decisions, including glucocorticoids, biologic agents, and cytotoxic drugs given under expert supervision, must be individualized according to the patient's clinical status.

Cryoglobulinemia

Cryoglobulins are antibodies that precipitate from serum under conditions of cold and resolubilize on rewarming. Cryoglobulins are classified into types I, II, and III on the basis of whether monoclonality and rheumatoid factor activity (the ability to bind to the Fc portion of IgG) are present. Type I cryoglobulins, which are monoclonal but lack rheumatoid factor activity, are associated with certain hematopoietic malignant neoplasms (e.g., multiple myeloma; Chapter 173) and often lead to hyperviscosity rather than to vasculitis. In contrast, type II and type III cryoglobulins may be associated with systemic vasculitis involving small and often medium-sized blood vessels. Vasculitis results from the deposition of cryoglobulin-containing immune complexes within blood vessel walls and the activation of complement.

Cryoglobulin types II and III are termed *mixed cryoglobulins* because they consist of complexes of both IgG and IgM antibodies. The IgM components in both type II and type III cryoglobulinemia possess rheumatoid factor activity (i.e., assays for rheumatoid factor are positive, thereby indicating binding of the IgM antibody to the Fc portion of IgG). Whereas the IgM component in type II cryoglobulin is monoclonal, the IgM in type III cryoglobulin is polyclonal. Ninety percent of patients with vasculitis secondary to mixed cryoglobulins are hypocomplementemic, with C4 levels characteristically more depressed than C3. Infection with hepatitis C virus (Chapters 134 and 135) accounts for at least 80% of the vasculitis cases associated with mixed cryoglobulins.

TREATMENT

The optimal therapy for most cases of cryoglobulinemic vasculitis is successful treatment of the underlying hepatitis C viral infection (Chapters 134 and 135). For cryoglobulinemic patients with relatively mild disease (e.g., frequent purpuric lesions, shallow cutaneous ulcers), short courses of prednisone (e.g., 20 mg/day) followed by the institution of effective therapy for hepatitis C virus may be sufficient. For patients with severe cutaneous ulcers, mononeuritis multiplex, glomerulonephritis, or other manifestations of severe disease, treatment with glucocorticoids, rituximab (similar to the way that granulomatosis with polyangiitis is treated),[21] and possibly a short course of plasma exchange may be indicated.

VARIABLE-VESSEL VASCULITIDES

The variable-vessel vasculitides have no predominant type of vessel involved but rather can affect vessels of any size (small, medium, and large) and any type (arteries, veins, and capillaries).

COGAN SYNDROME

The combination of inflammatory eye disease and vestibuloauditory dysfunction is the sine qua non of Cogan syndrome.[22] In addition to inflammatory disease of the eyes and ears, up to 15% of patients with Cogan syndrome have vasculitis involving medium-sized to large blood vessels. Although the ocular manifestations vary, the classic presentation is the combination of interstitial keratitis and sensorineural hearing loss. Cogan syndrome may appear first in either the eyes or the ears. Although intervals as long as 1 to 2 years have been described between the start of disease in one organ and the appearance of disease in the other, the time between disease manifestations in these organs is usually only a matter of months. Patients usually present with photophobia and blurry vision, sometimes accompanied simultaneously by auditory or vestibular dysfunction. The vascular disease associated with Cogan syndrome remains poorly described but typically involves the primary branches of the thoracic or abdominal aorta.

TREATMENT

Rapidly progressive sensorineural hearing loss (Chapter 396) requires early and aggressive therapy with high doses of systemic glucocorticoids (e.g., prednisone 60 mg/day). Some otolaryngologists also give intratympanic injections of glucocorticoids. Cyclophosphamide, mycophenolate mofetil, and biologic agents such as tumor necrosis inhibitors or rituximab can be considered under expert guidance for patients with suboptimal responses to glucocorticoids who still have salvageable hearing. Nevertheless, attempts at treatment are begun too late in some patients, and it is important to realize when the risk of further immunosuppression outstrips the likelihood of long-term benefit. Many Cogan syndrome patients become candidates for cochlear implants (Chapter 396).

BEHÇET SYNDROME

Behçet syndrome may affect small, medium, and large vessels in either the venous or the arterial circulation.[23] The most typical lesions are mucocutaneous, thereby reflecting the involvement of small blood vessels. The triad of recurrent mouth ulcers, genital ulcers, and eye inflammation is the classic presentation. The criteria for diagnosis consist of one required manifestation—recurrent oral ulceration—plus at least two of the following: recurrent genital ulceration, characteristic eye or skin lesions, or a pathergy reaction, which is the development of pustules at the sites of sterile needle pricks. However, the spectrum of Behçet syndrome encompasses many manifestations not included in these criteria. In addition, oral ulcers are not invariably the first disease manifestation, so the diagnosis of Behçet syndrome must be considered in the occurrence of disease features otherwise highly characteristic (e.g., bilateral panuveitis).

Large-vessel complications of Behçet syndrome may include aneurysms in the pulmonary and systemic arterial systems. Venous complications include thromboses of the deep venous system, vena cava, portohepatic vein, and cerebral sinus. The pathergy reaction is seen in many patients but particularly in persons of Turkish origin. The arthritis of Behçet syndrome is a nondeforming, oligoarticular, asymmetrical arthritis of large joints. Gastrointestinal lesions in Behçet syndrome typically consist of ulcerations of the distal ileum or cecum. Crohn disease (Chapter 127), which can cause genital ulcers as well as gastrointestinal disease, may be particularly difficult to distinguish from Behçet syndrome.

TREATMENT AND PROGNOSIS

Low-dose glucocorticoids (e.g., prednisone 20 mg/day) are effective for intransigent mucocutaneous disease and may have a better side effect profile than other medications used for this purpose (e.g., thalidomide 100 mg/day). Intermittent courses of glucocorticoids during periods of particular mucocutaneous disease activity may be sufficient for patients with mild disease.[24] Apremilast, an oral phosphodiesterase 4 inhibitor (at 30 mg twice daily for 12 weeks), is effective for treating oral ulcers.[A10] Colchicine (0.6 mg daily or twice daily) is often considered for mucocutaneous disease, but its true efficacy remains uncertain, and it is not appropriate for the treatment of major organ involvement.

Severe disease in any organ system always requires initial therapy with high doses of prednisone (e.g., 1 mg/kg/day). However, TNF inhibition with infliximab (5 mg/kg IV every 4 to 6 weeks) or adalimumab (40 mg every other week) is the treatment of choice for patients with the most severe forms of uveitis or meningoencephalitis. TNF inhibition, which is highly effective and usually well tolerated, is typically continued indefinitely in patients who respond to this therapy. Patients' prognosis is determined by disease-related damage incurred before the establishment of effective therapy as well as the tolerability of treatment long-term.

SELECTED SINGLE-ORGAN VASCULITIDES

Single-organ vasculitis is defined as vasculitis within the vessels of any type or size of a single organ in the absence of any features (e.g., ANCA) to suggest one of the systemic forms of vasculitis.

CUTANEOUS LEUKOCYTOCLASTIC ANGIITIS

Cutaneous leukocytoclastic angiitis has also been termed *hypersensitivity vasculitis*. Cutaneous leukocytoclastic angiitis is the preferred name because no hypersensitivity or allergy is evident in many cases.[25] Histories of exposure to new medications or to infections may be elicited. An immune complex deposition is central to the pathophysiologic process. Although cutaneous leukocytoclastic angiitis is occasionally associated with synovitis, other signs of systemic involvement are absent.

The skin lesions in cutaneous leukocytoclastic angiitis occur in "crops" of palpable purpura (see Figs. 406-5 and 406-7) coinciding with some period of elapsed time following exposure to the inciting antigen. The usual time between the exposure and the onset of clinically evident vasculitis is 10 to 14 days. The lesions typically occur first in dependent regions, such as on the lower extremities or buttocks. The rash may be asymptomatic but is usually accompanied by burning or tingling sensations.

TREATMENT AND PROGNOSIS

Several approaches to treatment are reasonable. First is watchful waiting, since it is not clear that immunosuppression is either necessary or helpful. Moreover, attempts to treat vasospasm with calcium-channel blockers may lead to a vascular steal phenomenon, thereby potentially causing harm. Second, because it is frequently difficult to do nothing for a patient with possibly serious CNS disease, calcium-channel blockers (e.g., nifedipine 30 mg three times daily) may be tried. Third, because of the frequent diagnostic uncertainty at the time of presentation, some clinicians opt to treat empirically with glucocorticoids (prednisone 1 mg/kg/day) for 1 month, followed by a taper over several weeks. Fourth, combinations of calcium-channel blockers and glucocorticoids are also reasonable. Cytotoxic therapy is not indicated.

VASCULITIS OF THE CENTRAL NERVOUS SYSTEM

CNS vasculitis[26] includes two major categories of disease, one of which is not a true vasculitis. These conditions are primary angiitis of the CNS (PACNS) and reversible cerebral vasoconstriction syndrome (RCVS). The clinical, radiologic, and pathologic characteristics of these two conditions vary dramatically (Table 249-6).

Primary Angiitis of the Central Nervous System

Primary angiitis of the central nervous system typically develops in a subacute fashion, with the evolution of multifocal strokes, encephalopathy, headache, and other clinical features over months. Headache is often the first symptom. As the condition progresses, most patients develop lethargy, confusion, and memory loss. Some patients develop multifocal strokes, seizures, evidence of increased intracranial pressure, or myelopathy. The results of routine laboratory tests (e.g., erythrocyte sedimentation rate) are often normal in PACNS. Lumbar puncture, which should be performed in all patients in whom the diagnosis is considered seriously, demonstrates abnormalities of the cerebrospinal fluid in approximately 80% of cases, usually a modest monocytosis and elevated protein. Although the findings on lumbar puncture are nonspecific, a normal lumbar puncture argues against primary angiitis of the central nervous system, and the procedure frequently identifies important mimickers such as infection (Chapters 381, 382, and 383) or malignancy (Chapter 175).

Magnetic resonance imaging (MRI) is the critical imaging modality. Because of the subacute nature of the disorder, MRI studies reveal multifocal CNS infarctions in most cases. Strokes, hemorrhagic lesions, and mass lesions typically occur in more than one vascular territory. A normal brain MRI argues strongly against the diagnosis of primary angiitis of the central nervous system. Angiography is less helpful because the involved blood vessels are often too small to be resolved adequately, even by conventional angiography, so the false-negative rate of angiography is about 35%. Second, the "classic" angiographic string-of-beads abnormality, which is produced by segmental arterial narrowing alternating with dilations, is nonspecific and can be mimicked perfectly by a host of nonvasculitic conditions (the most common of which is reversible cerebral vasoconstriction syndrome). No angiographic pattern is pathognomonic for

TABLE 249-6 PRIMARY ANGIITIS OF THE CENTRAL NERVOUS SYSTEM VERSUS REVERSIBLE CEREBRAL VASOCONSTRICTION

	PRIMARY ANGIITIS OF THE CENTRAL NERVOUS SYSTEM (PACNS)	REVERSIBLE CEREBRAL VASOCONSTRICTION SYNDROME (RCVS)
Female-to-male ratio	1 : 1	2-3 : 1
Onset	Subacute (weeks to months)	Sudden (seconds to minutes)
Headache	Insidious, dull	Thunderclap
Typical lumbar puncture findings	Abnormal in 50-80%: lymphocytic pleocytosis; elevated protein	Normal
Typical MRI findings	Multifocal subacute infarctions	Normal Watershed infarcts in minority
Typical angiogram findings	Normal in up to 40% of cases Abnormal angiographic features when present cannot be distinguished from RCVS	Multifocal stenoses/dilatations
Utility of brain biopsy	Reasonable sensitivity in appropriately selected patients Important for excluding disease mimickers	Little to no role Helpful if confusing clinical situation confounds differentiation from PACNS or PACNS mimickers

MRI = magnetic resonance imaging.

primary angiitis of the central nervous system, and there is a significant tendency to overdiagnose "vasculitis" on angiographic grounds alone. A normal brain MRI in the setting of an abnormal angiogram suggests reversible cerebral vasoconstriction syndrome, not primary angiitis of the central nervous system. When performed in appropriately selected patients whose history and radiologic studies suggest primary angiitis of the central nervous system, brain biopsy is associated with reasonable positive and negative predictive values and frequently identifies important mimickers.

TREATMENT

Prednisone (60 mg/day, sometimes preceded by 1 to 3 days of 1000 mg/day pulse methylprednisolone) and cyclophosphamide (2 mg/kg daily, adjusted for renal dysfunction and advanced age) are appropriate for treatment of patients who have abnormal findings on brain biopsy. Treatment courses of 6 to 12 months are recommended. Patients with primary angiitis of the central nervous system respond to treatment and may achieve treatment-free remissions, but residual neurologic dysfunction and adverse effects of treatment are common and sometimes severe.

Reversible Cerebral Vasoconstriction Syndrome

Reversible cerebral vasoconstriction syndrome is probably far more common than primary angiitis of the central nervous system. Overtreatment of patients with reversible cerebral vasoconstriction syndrome who are misdiagnosed as having primary angiitis of the central nervous system leads to substantial morbidity. Eighty percent of patients with reversible cerebral vasoconstriction syndrome are women.

A careful history is the most important part of the evaluation. In contrast to the subacute course that typifies primary angiitis of the central nervous system, reversible cerebral vasoconstriction syndrome usually begins in a more dramatic fashion with a "thunderclap" headache.[27] Neurologic signs are less severe in reversible cerebral vasoconstriction syndrome (e.g., encephalopathy is less common). Reversible cerebral vasoconstriction syndrome frequently occurs in the setting of precipitants associated with vasospasm, such as in the postpartum setting or following the use of vasoactive agents such as nasal decongestants and recreational drugs.

The lumbar puncture is usually normal in reversible cerebral vasoconstriction syndrome, and brain MRI usually does not show multifocal CNS infarctions, with the exception of watershed infarctions. The typical angiographic findings in reversible cerebral vasoconstriction syndrome—vascular narrowing and beading—are generally indistinguishable from those of primary angiitis of the central nervous system and conditions that mimic them. Multifocal vascular narrowing is particularly characteristic of reversible cerebral vasoconstriction syndrome. The most distinctive angiographic feature of reversible cerebral vasoconstriction syndrome is that the abnormalities are completely reversible, usually within 4 to 8 weeks, because the abnormalities are caused by vasospasm rather than true vasculitis. In the evaluation of patients with potential reversible cerebral vasoconstriction syndrome, a diagnostic strategy that can clinch the diagnosis is a follow-up angiogram 4 to 8 weeks later, when angiographic abnormalities will have resolved.

TREATMENT AND PROGNOSIS

Keys to the management of cutaneous leukocytoclastic angiitis include exclusion of any underlying form of vasculitis that may cause subclinical involvement of other organs and removal of any agent (e.g., a medication) that may have triggered the vasculitis. For patients in whom a precipitant can be identified, elimination of the offending agent usually leads to resolution of the vasculitis within days to weeks. The type, intensity, and duration of therapy for cutaneous leukocytoclastic angiitis are based on the degree of disease severity. Mild cases may be treated simply with leg elevation, H_1 antihistamines (Table 404-3), or low-dose prednisone (starting at 20 mg/day). For persistent disease not associated with cutaneous gangrene, colchicine (0.6 mg once or twice daily), hydroxychloroquine (200 mg twice daily), or dapsone (100 mg/day) may be tried. For severe cases, high doses of prednisone (e.g., 60 mg/day) are indicated to suppress inflammation quickly and prevent skin ulceration.

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250 GIANT CELL ARTERITIS AND POLYMYALGIA RHEUMATICA

ROBERT SPIERA

DEFINITION

Polymyalgia rheumatica and giant cell arteritis, also called temporal arteritis, are companion systemic inflammatory disorders of unknown etiology that is propagated by antigen-driven, cell-mediated immune mechanisms that may be associated with specific genetic markers. These disorders represent a spectrum from severe proximal aches and pains and constitutional symptoms to an occlusive granulomatous vasculitis of medium and large vessels that can lead to permanent blindness or other organ and tissue damage. These disorders occur primarily in patients older than age 50 years, are more common in women than in men, and are highly responsive to corticosteroids.

EPIDEMIOLOGY

In the United States, the average annual incidence of polymyalgia rheumatica is 52.5 per 100,000 patients ages 50 years and older and increases with age. The prevalence is about 0.5 to 0.7%. Internationally, the frequency varies, with the highest rates occurring in the Scandinavian countries. The incidence and prevalence of giant cell arteritis are approximately one third those of polymyalgia rheumatica.

PATHOBIOLOGY

The etiology of polymyalgia rheumatica and giant cell arteritis are unknown, but both demonstrate familial aggregation and have a genetic association with human leukocyte antigen (HLA)-DR4 and a demonstrated sequence polymorphism encoded within the hypervariable region of the *HLA-DRβ1*04* gene. Infectious triggers of giant cell arteritis have been postulated. For example, some but not all studies have found varicella-zoster virus antigen in temporal artery biopsies of patients with giant cell arteritis.[1] Bacterial and viral DNA also has been demonstrated in the arterial wall of patients with giant cell arteritis using advanced DNA imaging techniques. Disease in genetically predisposed patients also may be triggered by endogenous antigens such as elastin, and the inflammatory manifestations are directed by specific patterns of cell-mediated, type 1 helper T cell (T_H1)-associated cytokines. The cytokine production by the mononuclear cells in the involved tissues appears to influence the clinical phenotype.

In the pathogenesis of giant cell arteritis, the adventitia is considered the immunologic center where toll-like receptors (TLRs) are highly expressed on dendritic cells and resident tissue macrophages. Macrophages and T lymphocytes enter the vessel wall through the vasa vasorum with the aid of adhesion molecules and come into contact with an inciting antigen. Activated CD4 cells produce interferon-γ that attracts macrophages to the arterial wall. Some of these macrophages fuse at the intima-media to form multinucleated giant cells. These cells produce vascular endothelial growth factor, which triggers neovascularization, both at the intima-media junction and at the level of the vasa vasorum. The subsequent immunologic events lead to a characteristic topography of mononuclear cells throughout the vessel wall. Products of the giant cells and macrophages at the intima-media junction include collagenase and nitric oxide, both of which probably contribute to tissue damage. The pathologic impact of cytokines leads not only to the characteristic medial damage but also to significant intimal hyperplasia that eventually, if it is not treated, may cause luminal narrowing and tissue ischemia.

In giant cell arteritis, a transmural (involving all layers of the vessel) inflammatory infiltrate, comprised of predominantly mononuclear cells and commonly with giant cells, is found in the superficial temporal arteries as well as in other large and medium-sized arteries. In elderly patients, fragmentation of the internal elastica is characteristic and helps differentiate this vascular lesion from that of atherosclerosis. Often, macrophages containing fragments of elastic tissue are found at the intima-media junction, which is the histologic center of the inflammatory process. Intimal proliferation may be prominent and lead to luminal narrowing. Damage to the elastica and loss of vascular smooth muscle cells likely contribute to the recognized increased risk of aneurysms later in the disease course.

In polymyalgia rheumatica, mononuclear cell inflammation can be found not only in the proximal joints, such as the shoulders, but also in the surrounding tendons, bursae, and soft tissues consistent with enthesitis. Although muscle pains may be present, no significant muscle inflammation is found.

CLINICAL MANIFESTATIONS

Polymyalgia rheumatica and giant cell arteritis are systemic inflammatory disorders that occur primarily in patients older than age 50 years, in women more than in men (2:1), and more commonly in Whites. Shared characteristics of the two disorders include significant cytokine-driven constitutional symptoms, such as fever, fatigue, and weight loss, as well as a markedly elevated erythrocyte sedimentation rate (ESR), anemia, and thrombocytosis.

Polymyalgia Rheumatica

The musculoskeletal hallmark of polymyalgia rheumatica is proximal, severe, and symmetrical morning and even day-long stiffness, soreness, and pain in the shoulders,[2] neck, and pelvic girdles. Fifty percent of patients with giant cell arteritis share this characteristic proximal pain syndrome. Carpal tunnel syndrome (Chapter 388) and hand and knee synovitis may be seen in patients with polymyalgia rheumatica, but the overall presentation remains predominantly proximal, as opposed to rheumatoid arthritis, in which distal synovitis dominates. Whereas patients with polymyalgia rheumatica may appear to have proximal muscle weakness, this finding is due to pain and not muscle inflammation (Table 250-1). Magnetic resonance imaging (MRI) and ultrasound studies in patients with polymyalgia rheumatica have confirmed the presence of inflammation of extra-articular synovial structures, in particular subacromial and subdeltoid bursae in the shoulders.

Giant Cell Arteritis

Specific signs and symptoms of giant cell arteritis are best appreciated in their anatomic and physiologic contexts. Giant cell arteritis preferentially affects certain blood vessels, including the branches of the external carotid artery, the ophthalmic artery and particularly its posterior ciliary branches, and the large arteries that arise from the aortic arch and abdominal aorta. Headache and scalp pain are probably the most frequent symptoms, occurring in 50 to 75% of patients. Headache is often the first manifestation of giant cell arteritis and is described as boring, severe, and constant, unresponsive to simple pain medications and persisting through the night. Classically, patients complain of persistent and prominent temporal headaches, but occipital pains can also occur. Ear, pinna, or parotid gland pain may occur secondary to involvement of the posterior auricular artery. Jaw claudication and pain due to masseter

TABLE 250-1 GIANT CELL ARTERITIS: CLINICAL FEATURES

INFLAMMATORY
Polymyalgia rheumatica: constitutional symptoms
Fever
Weight loss
Fatigue
Laboratory abnormalities
Hematologic: anemia, thrombocytosis
Elevated sedimentation rate, C-reactive protein
ISCHEMIC
Ocular
Diplopia
Amaurosis fugax
Fixed vision loss
Complete blindness
Cranial symptoms
Headache
Jaw claudication
Scalp tenderness
Scalp or lingual necrosis (rare)
Cerebrovascular accidents
Large vessel disease
Leg or arm claudication
Diminished pulses, blood pressure asymmetry
Aortic aneurysms
LATE COMPLICATIONS
Aortic aneurysms
Thoracic aorta
Abdominal aorta
Corticosteroid complications
Osteoporosis
Fractures
Cataracts

ABSTRACT

Giant cell arteritis and polymyalgia rheumatica are related inflammatory diseases affecting older individuals. Both are characterized by evidence of systemic inflammation, including elevations of acute phase reactants such as C-reactive protein and erythrocyte sedimentation rate. Polymyalgia rheumatica is a clinical syndrome characterized by symmetric pain and stiffness in the shoulder and thigh girdle, with prominent morning stiffness, and exquisite responsiveness to low-dose corticosteroid therapy. Giant cell arteritis is a large vessel vasculitis in which polymyalgic symptoms can be present in the majority of patients but characterized more specifically by large vessel inflammation that can result in ischemic complications, including headaches, jaw claudication, and most concerning, vision loss. Timely diagnosis of giant cell arteritis is essential, because vision loss, once incurred, is generally irreversible, whereas therapy with corticosteroids is protective against that dreaded complication, and typically affords prompt resolution of symptoms. The diagnosis of giant cell arteritis is generally supported by temporal artery biopsy, but large vessel imaging, including ultrasound, MRI/MRA, and PET scanning are emerging as useful diagnostic modalities. Therapy of both disorders is primarily with corticosteroids, which are effective in low doses in polymyalgia rheumatica, and in modest to high doses in giant cell arteritis. The morbidity of corticosteroids particularly with prolonged use in this vulnerable population is substantial. In patients with giant cell arteritis, the addition of tocilizumab, which is an anti-interleukin 6 receptor antibody, can improve response rates and allow for a more rapid tapering of the corticosteroid dose.

KEYWORDS

giant cell arteritis
polymyalgia rheumatica
pathophysiology
therapy
complication
temporal arteritis

muscle ischemia on chewing occur in 50% of patients. Lingual and maxillary artery involvement can lead to jaw or tongue pain on chewing or talking. A dry, nonproductive cough can be a feature of the disease and often may direct the clinician away from considering giant cell arteritis and more toward consideration of an infectious or neoplastic respiratory cause of the symptoms. Rarely, mononeuritis multiplex or sensorineural hearing loss can occur but should lead the clinician to consider other possible vasculitides such as antineutrophil cytoplasmic antibody (ANCA)-associated vasculitis or polyarteritis nodosa.

Fixed or intermittent symptoms related to vasculitic involvement of the ophthalmic arteries and its branches are the most dreaded in this illness and demand immediate therapeutic intervention.[3] These symptoms are related to vascular narrowing due to both active inflammation and endothelial injury–mediated vasospasm. Decreased vision secondary to arteritis is the most common serious consequence of giant cell arteritis, occurring in 20 to 50% of patients who present to ophthalmologists. It is the presenting symptom in 60% of patients with giant cell arteritis who develop visual loss. A careful history of most patients who present with "sudden" visual loss reveals that preceding headache, constitutional symptoms, and polymyalgia rheumatica occurred in approximately 40% of patients. Even the evolution of the visual loss is often staggered, with amaurosis fugax in 10% and a partial field defect progressing to complete blindness over days. If giant cell arteritis remains untreated, the second eye may become involved within 1 to 2 weeks.

Five percent of patients with giant cell arteritis may present with diplopia or ptosis, which may precede visual loss. The final visual abnormality can be a composite of many ischemic events occurring together in the optic nerve, the extraocular muscles, the chiasm, and the brain itself.

Large artery involvement most commonly presents as arm or leg claudication; rarer manifestations are stroke,[4] subclavian steal syndrome, intestinal infarction, and symptomatic aortic aneurysm. Some older patients classified as having giant cell arteritis can present with large vessel disease resembling Takayasu arteritis (Chapters 63) clinically, with a paucity of cranial ischemic symptoms but often the presence of polymyalgia-like symptoms. Conversely, in patients presenting with typical giant cell arteritis with cranial symptoms and a positive temporal artery biopsy, large vessel disease with aortic wall thickening is markedly more frequent even early in the disease course.

Steroid-treated polymyalgia rheumatica and giant cell arteritis are self-limited illnesses that clinically persist for 1 to 2 years in most patients. However, a subgroup of patients with both disorders can have active inflammatory disease as manifested by persistent symptoms and blood test signs of active inflammation for 7 to 10 years.

The major feared outcome in giant cell arteritis is ischemic complications of the disease, most often vision loss or, less frequently, cerebrovascular accident. Vision loss is uncommon after glucocorticoid therapy is instituted, but it can occur early in the course of treatment and is usually irreversible.

Thoracic aneurysms with giant cells in the tissue can develop as long as 15 years after the diagnosis, successful treatment, and discontinuation of steroids. Indeed, the incidence of thoracic and aortic aneurysms is markedly higher in patients with a prior history of presumably successfully treated giant cell arteritis than in age-matched control subjects. Giant cell arteritis is also associated with increased risks for myocardial infarction, stroke, and peripheral vascular disease.

DIAGNOSIS

The diagnoses of polymyalgia rheumatica and giant cell arteritis are based on clinical findings, with supporting but not diagnostic aid obtained from laboratory tests and temporal artery biopsy (Fig. 250-1).[5,6] However, both polymyalgia rheumatica and giant cell arteritis should always be considered in the setting of a fever of unknown origin (Chapter 259) because symptoms and signs can be occult or the history incomplete.

The laboratory hallmark of polymyalgia rheumatica and giant cell arteritis is an elevation in acute phase reactants such as the ESR and C-reactive protein. The ESR is usually in excess of 50 mm/hour and may exceed 100 mm/hour. An ESR in the low 20s or 30s, however, does not exclude either diagnosis if other characteristic clinical features are present and especially if the patient is already taking corticosteroids.

Normocytic, normochromic anemia and thrombocytosis occur in approximately 50% of patients with both disorders and are excellent guides to the state of inflammation. The frequencies of rheumatoid factor, antinuclear antibody, ANCA, monoclonal proteins, and cryoglobulins are not higher than in age-matched control subjects, and complement is not reduced. Alkaline phosphatase activity may be elevated in one third of patients, primarily patients

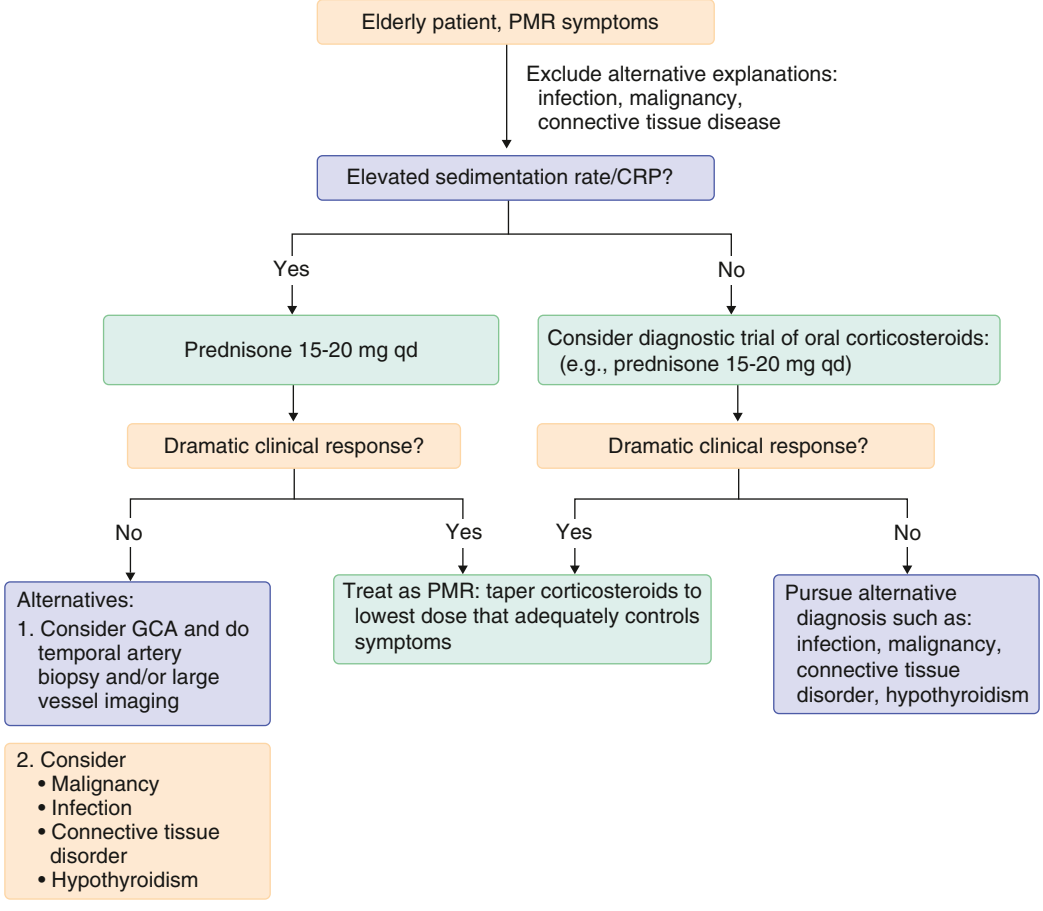

FIGURE 250-1. **Diagnostic algorithm for polymyalgia rheumatica (PMR).** CRP = C-reactive protein; GCA = giant cell arteritis; qd = once daily.

with giant cell arteritis. Creatine kinase levels are normal, and muscle biopsy is not indicated.

On ophthalmologic examination of patients with giant cell arteritis, the posterior ciliary arteries are the most frequently involved, so anterior ischemic optic neuropathy is the most common lesion and can easily be defined by an ophthalmologist. Occlusion of the central retinal artery and its branches is uncommon, so exudates, hemorrhages, and frank vasculitis are infrequent. A normal ophthalmologic examination should not dissuade the clinician from pursuing the diagnosis further.

Assessment of the Superficial Temporal Artery

Temporal artery tenderness, nodularity, and diminished pulsation are typical findings on physical examination in a patient with giant cell arteritis. On color duplex ultrasonography, a hypoechoic halo around the superficial temporal artery can be seen, but the sensitivity and specificity of this finding have varied among studies, and its incremental value above the physical examination is uncertain.[7,8] Stenosis or occlusion of temporal arteries on Doppler ultrasound is modestly sensitive and specific for the diagnosis of giant cell arteritis but is highly operator dependent. [18 F]Fluorodeoxyglucose-positron emission tomography (PET) may be helpful in identifying large vessel inflammation suggestive of giant cell arteritis, but it is not helpful in assessing the temporal arteries themselves, given their relatively small size and high background uptake in that area. Some studies suggest that MRI/magnetic resonance angiography (MRA) may be a helpful noninvasive diagnostic modality.[9] Superficial cranial arteries can be visualized, and mural inflammatory changes and luminal narrowing can be identified. Large vessel involvement also can be assessed. Conventional angiography is rarely used.

Temporal artery biopsy remains the diagnostic "gold standard" in giant cell arteritis. Given the relatively easy accessibility of the artery and potentially significant morbidity of therapy, histologic confirmation is usually recommended on the symptomatic side of the head, preferably including inflamed areas with tenderness or nodularity and incorporating 2 to 3 cm of vessel. Multiple sections should be requested because of the segmental nature of the disease process. Some rheumatologists routinely request bilateral biopsies, which may increase the likelihood of obtaining an abnormal finding by up to 5%, whereas others perform a contralateral biopsy if the first specimen is normal. Because of the skipped nature of the pathologic inflammatory lesions in the vessel wall, however as many as 20 to 30% of biopsy specimens may be normal despite an overwhelming diagnostic likelihood of giant cell arteritis. In most patients, however, diagnostic biopsy findings continue to be present for as long as 2 to 4 weeks after the clinical diagnosis is made and steroid treatment instituted, and may be seen even months into treatment.

Patients with pure polymyalgia rheumatica and no signs or symptoms of giant cell arteritis do not need a biopsy. However, because 10% of these patients may develop such clinical manifestations of giant cell arteritis within the next year, they should be told to report such symptoms immediately and have an urgent clinical assessment and possibly biopsy should those symptoms emerge.

Differential Diagnosis

The systemic nature of these disorders and the fact that they occur in elderly people demand careful diagnostic scrutiny to avoid missing a malignant neoplasm or major infection and possibly treating patients inappropriately with high-dose steroids.[10] This caveat is true in polymyalgia rheumatica because there is no definitive diagnostic test and in giant cell arteritis because biopsy findings may be normal despite active, vision-threatening vasculitis. Infections that must be considered if clinically appropriate include tuberculosis (Chapter 299), endocarditis (Chapter 61), and hepatitis B and C (Chapters 134 and 135). Malignant neoplasms such as lymphoma (Chapters 171 and 172) and multiple myeloma (Chapter 173) may mimic polymyalgia rheumatica, and an age-appropriate cancer evaluation is always indicated. Autoimmune disorders such as elderly-onset rheumatoid arthritis (Chapter 243), systemic lupus erythematosus (Chapter 245), dermatomyositis (Chapter 248), and other types of vasculitis (Chapter 249), must be considered in the differential diagnosis[11] and evaluated with serologic testing if suspected.

A form of elderly onset rheumatoid arthritis (Chapter 243) may mimic polymyalgia rheumatica because it presents with negative rheumatoid factor, a more proximal focus of joint inflammation, and a good response to low-dose prednisone. The distinction may be semantic because neither disorder tends to evolve into an erosive arthritis. A more protracted clinical course, however, is often seen in patients in whom distal synovitis is a prominent feature, and such patients are classified as having elderly onset rheumatoid arthritis.

TREATMENT

Both polymyalgia rheumatica and giant cell arteritis are highly responsive to corticosteroids, which are the treatment of choice.[12,13] Because of the high risk of visual loss, treatment should be started immediately when the clinical suspicion of giant cell arteritis is high even while awaiting temporary artery biopsy or its results. No physician should await an abnormal finding on temporal artery biopsy before making the presumptive diagnosis of giant cell arteritis in the setting of a characteristic clinical picture. If the biopsy is negative and an alternative diagnosis is likely, the corticosteroid can then be discontinued. For pure polymyalgia rheumatica, treatment is also based on the clinical diagnosis but is less urgent.

Whereas polymyalgia rheumatica usually responds to 15 mg of prednisone daily, giant cell arteritis usually requires 40 to 60 mg of prednisone per day in divided doses or higher doses if organ or tissue damage is present or threatened.[14] If visual symptoms are present as a fixed loss or amaurosis fugax in giant cell arteritis, the patient often should be treated with high-dose intravenous methylprednisolone with doses ranging from 40 mg every 8 hours to 1 g/day for up to 3 days, followed by high-dose oral steroids in divided doses. Within 2 to 3 days after the institution of steroids, most symptoms of polymyalgia rheumatica or giant cell arteritis clear rapidly, and patients describe a miraculous improvement, which supports the diagnosis. Conversely, a lack of rapid and significant improvement in signs, symptoms, and function within 5 to 7 days should lead the clinician to doubt the initial impression and consider an alternative diagnosis (e.g., tumor or infection), although some patients with giant cell arteritis might require a higher steroid dose.

The steroid dose is then maintained for 2 to 3 weeks, during which the ESR, C-reactive protein, hemoglobin, and platelet counts normalize. A steroid taper is then instituted and guided by the symptomatic response. In polymyalgia rheumatica, taper is commonly by 1 mg every 7 to 10 days; in giant cell arteritis, taper is by 5 to 10 mg every 7 to 10 days. In giant cell arteritis, alternate-day corticosteroid regimens are not recommended because of higher rates of treatment failure.

Treatment should not be based primarily in the decline in the ESR because an elderly patient would be subjected inappropriately to a dangerously high cumulative dose of steroids with their attendant side effects. An increased dose of prednisone should be based on a change in symptoms, not solely on an increase in the ESR. One possible exception is in a patient with a history of giant cell arteritis and prior abrupt vision loss in one eye, in whom any further compromise of vision would be catastrophic. The effective dose for a flare often can be as low as 5 to 10 mg/day of prednisone and uncommonly up to 60 mg/day to control symptoms (e.g., visual abnormalities).

In giant cell arteritis,[A1,A2] adding tocilizumab (a humanized monoclonal anti-IL-6 receptor antibody at 162 mg subcutaneously weekly) to corticosteroid therapy results in higher remission rates, less cumulative glucocorticoid use, and higher likelihood of sustained remission at 12 months.[A3] With the use of tocilizumab, glucocorticoids can be tapered relatively rapidly (tapered to off by month 6) without complications. Tocilizumab may provide a significant steroid-sparing benefit in polymyalgia rheumatica as well,[A4,A5] but this drug is not FDA-approved for its treatment.

Antiplatelet or anticoagulant therapy has had a marginal benefit when used together with corticosteroids in patients with established giant cell arteritis in uncontrolled studies. As a result, adjunctive therapy with low-dose aspirin (e.g., 81 to 100 mg daily) should be considered for patients who have giant cell arteritis unless there is a contraindication to its use.

The goal is to attain the best disease control with the lowest dose of steroids. In most patients, prednisone can be tapered safely in 1 to 2 years. However, some patients may need to take low doses of steroids for 2 years or more. The higher the initial dose and cumulative dose, the greater the likelihood that the patient will develop a major steroid side effect such as sepsis, osteoporosis, osteonecrosis, diabetes, emotional lability, or myopathy (Chapter 28). Appropriate immunizations, osteoporosis regimens (calcium, vitamin D, and bisphosphonates), and metabolic monitoring are mandatory in all patients prescribed chronic steroid therapy.

Alternative immunosuppressive agents have been tested in both polymyalgia rheumatica and giant cell arteritis. In giant cell arteritis, methotrexate has yielded mixed results, is of uncertain benefit, and is not routinely incorporated as first-line therapy. In polymyalgia rheumatica, methotrexate may have a steroid-sparing effect and may reduce the number of flares, but the magnitude of benefit appears to be modest at best. At present, methotrexate is not routinely used. In individual patients with refractory disease or excessive morbidity from corticosteroids, however, the addition of weekly rheumatoid arthritis–level doses of methotrexate (7.5 to 20 mg/week) or azathioprine (2 mg/kg/day) may be helpful for selected patients under expert guidance. Cyclophosphamide also may be of value in patients with refractory disease and/or unacceptable corticosteroid toxicity, but adverse events are common, and this drug is rarely used even by experts.

Treatment with abatacept, a costimulatory molecule blocker, has shown modest benefit in terms of relapse-free survival at 12 months[A6] and is presently being evaluated in a larger trial.

PROGNOSIS

In most studies, survival rates for patients with polymyalgia rheumatica and giant cell arteritis are similar to those of unaffected persons of the same age.

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251 INFECTIONS OF BURSAE, JOINTS, AND BONES

DOUGLAS R. OSMON

INFECTION OF BURSAE

Septic Bursitis

DEFINITION

Bursae are the satellite structures that form to protect tissues from bony prominences. The superficial bursae, including the olecranon, prepatellar, infrapatellar, and bursae over the first metatarsophalangeal bunions, are more likely to become infected than are the deep bursae, such as the subacromial, trochanteric, and iliopsoas bursae.

EPIDEMIOLOGY

Olecranon bursitis may occur in as many as 10 in 100,000 persons per year. The majority of cases occur in men, and antecedent trauma to the skin is frequent.

PATHOBIOLOGY

Septic bursitis of superficial bursae is most commonly due to direct inoculation through the overlying skin; less commonly, it is secondary to overlying cellulitis. Most cases of deep septic bursitis are due to contiguous spread from adjacent infected joints or hematogenous seeding.

Predisposing risk factors for septic bursitis include trauma to the skin. For example, olecranon septic bursitis may occur in plumbers, athletes, and patients with chronic obstructive pulmonary disease (COPD) who frequently lean on their elbows; prepatellar or infrapatellar septic bursitis can occur in housecleaners, gardeners, and carpet layers. At least one third of patients with septic bursitis have an underlying comorbid illness such as diabetes mellitus, rheumatoid arthritis, gout, COPD, or alcohol use disorder.

CLINICAL MANIFESTATIONS

In immunocompetent patients, septic bursitis often but not always presents with fever as well as erythema and warmth of the overlying skin; there may be swelling of the bursae. In contrast to patients with septic arthritis, patients with septic bursitis of superficial bursae have intact range of motion of the joints, which may be limited only at the extremes of flexion. Pain on motion of the joint and restriction of joint range of motion are highly suggestive of septic arthritis. Acute phase reactants such as C-reactive protein, the sedimentation rate, and the white blood cell (WBC) count may be elevated.

DIAGNOSIS

Radiography should be performed to look for a foreign body and to evaluate the surrounding bones. Aspiration of bursal fluid is helpful in the diagnosis of patients who have pain, erythema, and/or swelling of an affected area. However, given the risk for contaminating the bursa if the aspiration occurs through cellulitic skin, many clinicians choose to aspirate a bursa only if empirical antimicrobial therapy has failed. Ultrasound or computed tomography (CT) guidance greatly enhances the successful aspiration of superficial bursae. Care must be taken not to violate the joint space when aspirating a bursa to avoid inoculating it.

The leukocyte count of the bursal fluid is generally lower than what is seen in septic arthritis. A leukocyte count greater than 2000/μL has a sensitivity of 94% and a specificity of 79% for superficial (olecranon or prepatellar) bursitis. Bacterial culture and in vitro susceptibilities must be obtained; if additional fluid is available, a Gram stain may be obtained, although its sensitivity may be as low as 15%. The presence of crystals does not exclude the possibility of septic bursitis (Chapter 252). Concomitant bacteremia can occur, and blood cultures should be obtained before the initiation of therapy if possible.

Staphylococcus aureus (Chapter 267), which is the most common cause of septic bursitis, accounts for more than 70% of culture-proven cases,[1] followed by β-hemolytic streptococci. Aerobic gram-negative bacilli, including *Escherichia coli,* and pseudomonas, are less common causes of septic bursitis. Polymicrobial infection can also occur. Chronic bursitis may be associated with infections due to *Brucella* spp, atypical mycobacteria, or *Mycobacterium tuberculosis,* as well as fungi; the presence of these infections should raise the possibility of systemic infection.

Differential Diagnosis

In the immunocompetent host, nonseptic bursitis (Chapter 242) may have a somewhat more indolent presentation than septic bursitis. The differential diagnosis includes gout and pseudogout (Chapter 252), arthritis, and trauma with hemobursa. An overlying cellulitis may be confused with bursitis. Fever is usually not present in nonseptic bursitis because of mechanical or friction trauma.

TREATMENT

Treatment of septic bursitis is guided by knowledge of the putative underlying organisms, in most cases, *S. aureus* (Chapter 267). Because the Gram stain result is frequently negative and culture results are delayed, empirical therapy is guided by the clinical presentation, the host's risk factors, and knowledge of common pathogens causing infection. Most patients can be treated as outpatients,[2] but patients who are immunocompromised may require hospitalization for intravenous antibiotic therapy (Table 251-2).

Initial ambulatory treatment in patients without comorbid conditions may consist of an oral antistaphylococcal penicillin (e.g., dicloxacillin 500 mg orally four times daily) or a first-generation cephalosporin (e.g., cephalexin 500 mg orally four times daily). If community-acquired methicillin-resistant *S. aureus* (MRSA) is suspected, cotrimoxazole (e.g., one double-strength tablet orally twice daily), doxycycline (e.g., 100 mg orally twice daily), or minocycline may be added to one of these agents. In patients who are allergic to penicillin, oral clindamycin (e.g., 300 mg orally four times daily) or linezolid (e.g., 600 mg orally twice daily) may be used. In all cases, the choice among antibiotics and their doses should be guided by the patient's renal and hepatic function as well as any drug allergies or intolerances.

Patients who have severe inflammation, are septic, or are immunocompromised may require hospitalization for initiation of treatment with intravenous nafcillin, oxacillin, or cefazolin (see Table 251-2). If MRSA is suspected, intravenous vancomycin, daptomycin, or linezolid (see Table 251-2) should be used (Chapter 267). Vancomycin also can be used in patients who are allergic to penicillin.

The duration of antimicrobial therapy is guided by the clinical response and comorbid conditions. Antibiotics should be continued until bursal inflammation resolves. Resolution may require several weeks of intravenous or oral therapy and multiple aspirations. Failure of the septic bursitis to respond to initial antibiotic therapy mandates a second course of therapy. Recurrence thereafter or inability to drain the bursa adequately with needle aspiration is an indication for surgical intervention.

PREVENTION

Because superficial septic bursitis is often associated with occasional or avocational activities involving kneeling or resting on the elbows, using protective padding may be helpful.

PROGNOSIS

The optimal duration of therapy is unknown, but prognosis of superficial bursitis is generally excellent. The presence of comorbid conditions, especially conditions associated with deep bursal infections (e.g., including septic arthritis, bacteremia, and osteomyelitis), is associated with more intractable and difficult disease.

INFECTION OF JOINTS

Septic Arthritis

DEFINITION

Septic arthritis, which refers to infection of a joint by a microorganism, is associated with increased morbidity and mortality as well as loss of articular

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DOUGLAS R. OSMON

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TREATMENT

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PREVENTION

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PROGNOSIS

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INFECTION OF JOINTS

Septic Arthritis

DEFINITION

Septic arthritis, which refers to infection of a joint by a microorganism, is associated with increased morbidity and mortality as well as loss of articular

ABSTRACT

Septic bursitis, arthritis, and osteomyelitis most commonly result from direct inoculation through the skin, by hematologic spread, or following bone and joint surgery. Predisposing factors include immunosuppression, autoimmune diseases, diabetes mellitus, alcohol use disorder, and antecedent surgery, including bowel and bladder procedures and joint arthroplasty. Diagnosis is based on clinical suspicion, abnormal laboratory tests (e.g., elevated sedimentation rate, C-reactive protein, and white blood cell count), and identification of causative organisms by serology and/or in joint or bursal fluid, blood, or biopsy of bone or synovial tissue. Magnetic resonance imaging, computed tomography, radiography, and nuclear medicine techniques may aid in identification of foci of infection. Initial treatment of suspected infection is empirical, guided by the clinical presentation and informed by identification of the causative organism(s). Surgical treatment includes débridement of the affected musculoskeletal structure. Management of prosthetic joint infections requires débridement with either initial retention of the prosthesis, resection arthroplasty, or rarely amputation. Successful management is dependent on the effectiveness of the medical and surgical therapies, the maintenance of adequate vascularization for the affected tissues, and the ability to manage comorbid conditions.

KEYWORDS

septic arthritis
joints
bones
bursa
osteomyelitis
débridement
antibiotics
prosthetic joint infection

TABLE 251-1 MICROORGANISMS RESPONSIBLE FOR ACUTE SEPTIC ARTHRITIS AND ACUTE AND CHRONIC OSTEOMYELITIS

SEPTIC ARTHRITIS		*OSTEOMYELITIS: ACUTE AND CHRONIC*	
MICROORGANISM	**FREQUENCY (%)**	**MICROORGANISM**	**FREQUENCY (%)**
Gram-Positive	***60-90***	***Gram-Positive***	***80-90***
Staphylococcus aureus	50-70	*Staphylococcus aureus*	60-80
Group A, B, C streptococci	15-30	Group A, B, C streptococci	10-20
Coagulase-negative staphylococci	6-20	*Staphylococcus epidermidis*	10-15
Streptococcus pneumoniae	1-3	*Streptococcus pneumoniae*	<1
Enterococcus sp	<1	*Enterococcus* sp	1-2
Corynebacterium sp	<1	*Corynebacterium* sp	1-2
Gram-Negative	***5-25***	***Gram-Negative***	***5-20***
Salmonella sp		*Salmonella* sp	
Pseudomonas aeruginosa		*Enterobacter* sp	
Escherichia coli		*Pseudomonas aeruginosa*	
Klebsiella pneumoniae		*Brucella* sp	
Enterobacter sp		*Pasteurella multocida*	
*Kingella kingae**		*Bartonella henselae*	
Haemophilus influenzae	<1-3*	*Propionibacterium* sp	
Anaerobes	***1-2***	***Anaerobes***	
Fusobacterium sp		*Bacteroides* sp	
Bacteroides fragilis			
Miscellaneous	***<5***	***Miscellaneous***	***5-7***
Borrelia burgdorferi		*Mycobacterium* sp	
Mycoplasma		Fungi (candidiasis, coccidioidomycosis, blastomycosis, histoplasmosis)	
Ureaplasma			
Mycobacterium sp			
Fungi			
Viruses			
Algae			

*Children.
sp = species.

integrity and function. Septic arthritis is usually caused by a bacterial infection, but other microorganisms also can cause infections with clinical characteristics that differ from those of bacterial infections.

NONGONOCOCCAL SEPTIC ARTHRITIS

EPIDEMIOLOGY

The incidence of septic arthritis affecting native joints is approximately 10 per 100,000 patient years. Among patients presenting with an acutely swollen and painful joint, bacterial pathogens are the most common etiology. Nongonococcal septic arthritis is the most common form of septic arthritis and is somewhat more common in men than in women.

PATHOBIOLOGY

Staphylococci or streptococci are the most common pathogen to cause septic arthritis, but the microbiology depends on the mechanism of the infection (Table 251-1). Septic arthritis can result from direct inoculation (e.g., accidents, bites, surgery) or by extension from infected bone into an adjacent joint space. Approximately 75% of cases are due to hematogenous spread, particularly in patients who use injection drugs, have indwelling catheters, or are immunocompromised. Iatrogenic septic arthritis due to needle arthrocentesis (is estimated to be between <1/10,000 to 1/3000 procedures) or arthroscopy (estimated to be between 0.0009 to 1.1%) is very rare.

Bacteria causing septic arthritis produce an acute inflammatory reaction in the synovial membrane. Synovial hyperplasia and inflammatory cell immigration, with the release of pro-inflammatory and cartilage-destroying cytokines and proteases, result in damage to cartilage and bone. Bacterial toxins and DNA as well as superantigens, such as those seen in staphylococcal toxic shock syndrome, also damage cartilage and bone.

Risk factors for the development of septic arthritis include penetrating trauma, diabetes, alcohol use disorder, cutaneous ulcers, injection drug use, prosthetic joints, rheumatoid arthritis, osteoarthritis, and low socioeconomic status, as well as advanced age, skin infection, indwelling intravenous catheters, cancer, and immunosuppressive therapies, including biologic response modifiers used in the management of autoimmune diseases such as rheumatoid arthritis and inflammatory bowel disease.

CLINICAL MANIFESTATIONS

Most patients with bacterial arthritis feel ill and have fever. Immuno-compromised and elderly patients may not have a marked febrile response. Most cases (>80%) of septic arthritis are monoarticular; the knee is involved in more than 50% of cases. Polyarticular joint sepsis may be seen in immunocompromised patients and patients with rheumatoid arthritis (Chapter 243) or systemic lupus erythematosus (Chapter 245). Such patients frequently lack typical signs and symptoms of infection and may not appear to be particularly ill at presentation,[3] but they may have rapid cardiovascular decompensation, particularly if they are taking glucocorticosteroids, other immunosuppressive agents, or biologic response modifiers, including tumor necrosis factor-α (TNF-α) inhibitors.

Patients with septic arthritis affecting nondiarthrodial joints, such as the acromioclavicular or sacroiliac joints, may have a history of injection drug use or may have intravenous catheters in place to treat other medical conditions. Infection of the symphysis pubis is associated with previous urinary tract or gynecologic surgery, pelvic malignancy, injection drug use, or vigorous weight-bearing physical activity, such as long-distance running, in female athletes.

DIAGNOSIS

The diagnosis of septic arthritis is challenging because its signs and symptoms overlap those of other nonseptic inflammatory joint diseases (e.g., osteoarthritis [Chapter 241], gout [Chapter 252], and rheumatoid arthritis [Chapter 243]) that themselves can increase the risk for septic arthritis (Fig. 251-1).[4,5] Ultrasonography can confirm the presence of fluid. Plain radiography should be performed to evaluate the surrounding bones and joint space and to provide a baseline for comparison after therapy is completed. Imaging modalities such as plain radiography, magnetic resonance imaging (MRI), and CT are useful in cases of diagnostic uncertainty and to assess for possible associated osteomyelitis. Blood cultures are often positive.

If septic arthritis is suspected, synovial fluid arthrocentesis is indicated, and the fluid should be examined for bacterial culture and Gram stain, although the latter is positive in fewer than 50% of patients.[6] Specific cultures and stains for fungal and mycobacterial organisms should obtained in patients who have a history of exposure or if prior antibacterial therapy has failed. Polymerase chain reaction (PCR) assays and a serum Lyme serology are useful tools for diagnosing less common joint infections such as *Borrelia* in patients with risk factors for Lyme disease (Chapter 296).

Other helpful examinations include leukocyte count and differential, as well as evaluation of the synovial fluid for the presence of crystals (Chapter 252). The total WBC count and differential in synovial fluid is helpful in distinguishing infected from noninfected joints in immunocompetent patients. The higher the synovial fluid leukocyte count and percent neutrophils the more likely it is that

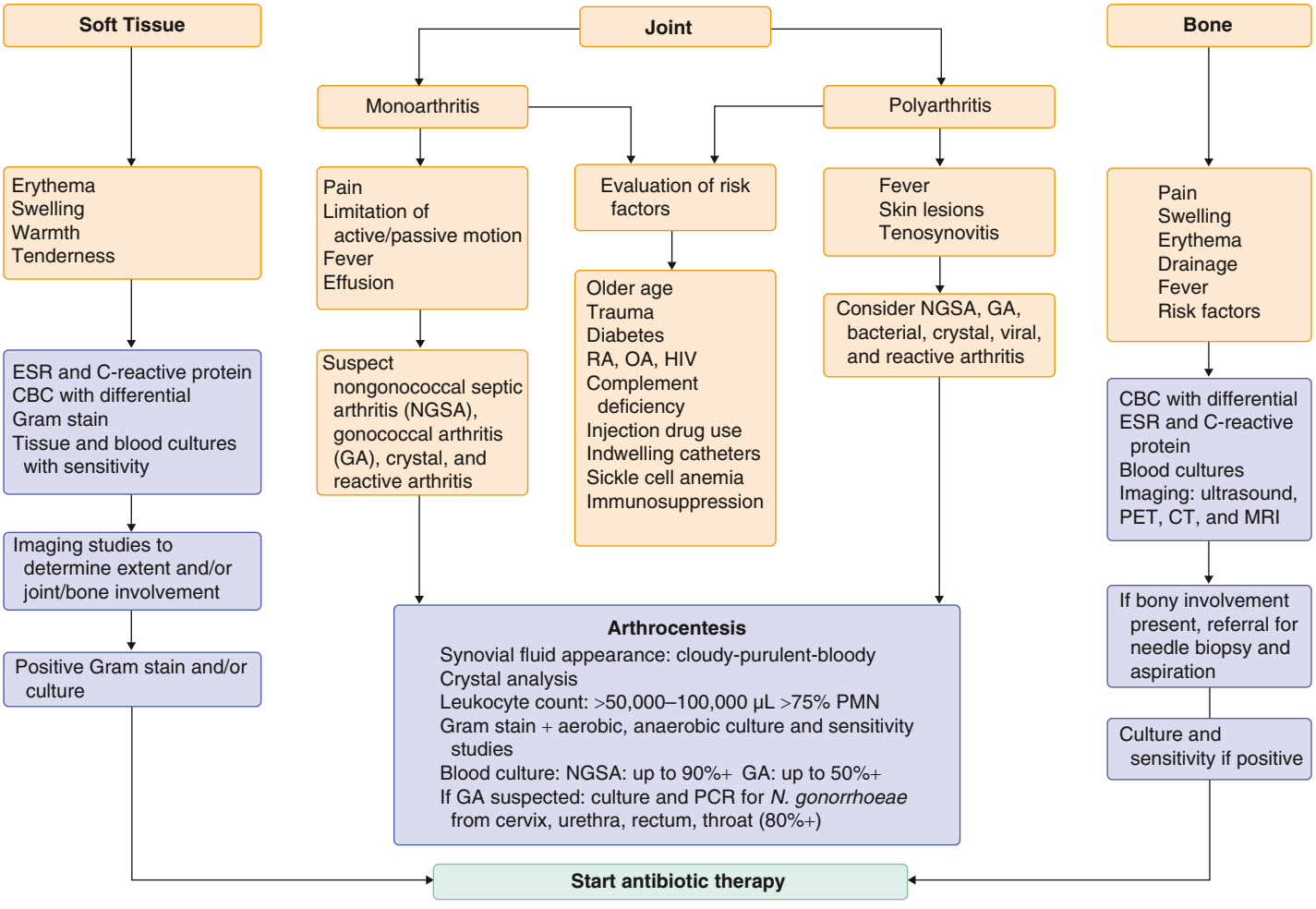

FIGURE 251-1. Clinical evaluation of infections of soft tissues, joints, and bone. CBC = complete blood count; CT = computed tomography; ESR = erythrocyte sedimentation rate; GA = gonococcal arthritis; HIV = human immunodeficiency virus; IV = intravenous; MRI = magnetic resonance imaging; NGSA = nongonococcal septic arthritis; OA = osteoarthritis; PCR = polymerase chain reaction; PET = positron emission tomography; PMN = polymorphonuclear leukocyte; RA = rheumatoid arthritis.

the septic arthritis is due to bacterial pathogens, with or without concomitant crystalline disease. It is important to realize, however, that a WBC count less than 50,000/µL, especially in immunocompromised patients, can be associated with septic arthritis, so the absolute WBC count in synovial fluid is not, by itself, a reliable way to confirm or exclude a diagnosis of septic arthritis. The presence of gout or pseudogout crystals does not exclude the possibility of septic arthritis, particularly in patients whose WBC count is above 50,000/µL. Preliminary data suggest that the level of presepsin in synovial fluid may help rapidly distinguish septic arthritis from crystal arthritis.[7]

A frequent clinical scenario is the patient who is receiving anticoagulation therapy. Because of the rapidly destructive nature of septic arthritis and the often profound systemic consequences, therapeutic anticoagulation typically is not a contraindication to arthrocentesis. The procedure may be assisted by ultrasound guidance, especially when only a small amount of joint fluid is present or when the joint is difficult to aspirate. Ultrasound or CT-guided arthrocentesis is particularly useful for aspiration of deep joints such as the hips and nondiarthrodial joints.

A finding of microorganisms in the joint should lead to an appropriate history and physical examination to identify a source of hematogenous infection, such as cellulitis, pneumonia, or urinary tract infection. Staphylococci and β-hemolytic streptococci may enter directly through open wounds, whereas gram-negative infection may be associated with bowel or bladder disease. Blood cultures are positive in up to 50% of patients with bacterial septic arthritis and should be obtained in all patients in whom this diagnosis is suspected.

Differential Diagnosis

Symptoms of septic arthritis, such as acute joint pain, swelling, and even fever, with an increase in acute phase reactants, can be caused by crystalline arthritis (Chapter 252), especially pseudogout and gout, as well as psoriatic arthritis (Chapter 244) and reactive arthritis (Chapter 244). In patients who have preexisting inflammatory joint disease, such as rheumatoid arthritis (Chapter 243), septic arthritis may be suspected if a patient has the sudden onset of acute or subacute monoarticular or pauciarticular joint swelling when the disease is otherwise well controlled. The presence or absence of fever is not a reliable indicator of an infected joint.

TREATMENT

As soon as the joint has been aspirated and ideally after blood cultures have been obtained, prompt antibiotic treatment must be instituted.[8] Removal of purulent material and, where appropriate, débridement are essential. The choice of empirical antimicrobial therapy is based on which organisms are thought to be the likely cause of the septic arthritis and on the results of Gram stain and culture (Table 251-2). No advantage of one antibiotic regimen over another has been demonstrated. If the initial Gram stain of the synovial fluid reveals gram-positive cocci, vancomycin is recommended, given the increasing frequency of infection due to MRSA and the need to initiate effective antimicrobial therapy as soon as possible. Daptomycin and linezolid are alternative agents. If the initial Gram stain reveals gram-negative bacilli, an agent with broad coverage, including activity against *Pseudomonas aeruginosa,* is recommended. Such agents include ceftazidime, cefepime, imipenem, meropenem, piperacillin-tazobactam, and ciprofloxacin. If the Gram stain result is negative, vancomycin alone in immunocompetent patients or in those unlikely to have gram-negative infection based on history and examination, or vancomycin plus one of the gram-negative antibacterials listed, is reasonable. When culture and in vitro susceptibility results are available, therapy can be modified. The duration of antibacterial therapy usually ranges from 2 to 6 weeks, with data suggesting that one aspiration and 2 weeks of therapy are usually adequate.[A1] The presence of bacteremia, osteomyelitis, or infective endocarditis will dictate a longer duration of therapy.

The role of arthroscopic versus needle versus open drainage of the joint remains unsettled.[9,10] Surgical management is appropriate for septic arthritis of the hip, for patients who fail to respond to serial needle aspiration and antibiotic therapy, and for patients who appear to be developing life-threatening complications such as necrotizing fasciitis. Patients should be mobilized as rapidly as possible to prevent joint contractures. The concomitant use of oral dexamethasone for 4 days can lead to more rapid symptomatic improvements in children,[A2] but no randomized trials have been reported in adults.

TABLE 251-2 ANTIMICROBIAL THERAPY FOR SELECTED MICROORGANISMS IN SEPTIC ARTHRITIS OR OSTEOMYELITIS IN ADULTS

MICROORGANISM	FIRST CHOICE*	ALTERNATIVE CHOICE
Methicillin/oxacillin/nafcillin–sensitive staphylococci	Nafcillin sodium or oxacillin sodium 1.5-2 g IV q4-6h for 4-6 wk *or* cefazolin 1-2 g IV q8h	Vancomycin 15 mg/kg IV q12h or daptomycin 6-10 mg/kg IV q24h for 4-6 wk; dalbavancin 1500 mg IV on days 1 and 8†
Methicillin/oxacillin/nafcillin-resistant staphylococci (MRSA)	Vancomycin‡ 15 mg/kg IV q12h *or* daptomycin 6-10 mg/kg IV q24h	Linezolid 600 mg PO/IV q12h *or* daptomycin 6-10 mg/kg IV q24h‡ *or* 500-750 mg PO/IV daily; dalbavancin 1500 mg IV on days 1 and 8†
Penicillin-sensitive streptococci	Aqueous penicillin G 20 × 10^6 U/24 hr IV either continuously or in six equally divided daily doses *or* ceftriaxone 2 g IV q24h *or* cefazolin 1-2 g IV q8h	Vancomycin 15 mg/kg IV q12h; dalbavancin 1500 mg IV on days 1 and 8
Enterococci Penicillin and vancomycin susceptible	Aqueous crystalline penicillin G 20 × 10^6 U/24 hr IV either continuously or in six equally divided daily doses *or* ampicillin sodium 12 g/24 hr IV either continuously or in six equally divided daily doses; the addition of gentamicin sulfate 1 mg/kg IV or IM q8h for 1-2 wk is *optional*	Vancomycin‡ 15 mg/kg IV q12h; the addition of gentamicin sulfate 1 mg/kg IV or IM q8h for 1-2 wk is *optional or* daptomycin 6-10 mg/kg IV q24h for 4-6 wk
Enterobacteriaceae (e.g., *Salmonella*)	Ceftriaxone 1-2 g IV q24h	Ciprofloxacin‡ 500-750 mg PO q12h
Pseudomonas aeruginosa	Cefepime 2 g IV q8-12h	Ciprofloxacin‡ 750 mg PO q12h *or* ceftazidime 2 g IV q8h or imipenem 500 mg IV q6h or meropenem

*Antimicrobial selection should be based on in vitro sensitivity data, as well as allergies, intolerances, and drug interactions in individual patients.

†See text for data for treatment of osteomyelitis.

‡Doses shown are based on normal renal and hepatic function and may need to be adjusted or serum levels monitored (vancomycin).

IV = intravenous; MRSA = methicillin-resistant *Staphylococcus aureus*; PO = oral.

Adapted from Berbari EF, Steckelberg JM, Osmon DR. Osteomyelitis. In: Mandell GL, Bennett JE, Dolin R, eds. *Mandell, Douglas, and Bennett's Principles and Practice of Infectious Diseases,* 7th ed. Philadelphia: Churchill Livingstone/Elsevier; 2010:1457-1467.

PREVENTION

In patients requiring immunosuppression or glucocorticosteroid therapy to manage their underlying diseases, every effort should be made to use the lowest possible dose of these medications.

PROGNOSIS

About 40% of patients with septic arthritis have less than a complete recovery,[11] particularly older patients and patients with preexisting diseases of the joints such as osteoarthritis or rheumatoid arthritis. The outcome may be severe enough to warrant consideration of joint replacement.

Total joint replacement after septic arthritis carries about a 12% risk of infection. Patients with diabetes and drug-resistant organisms are at higher risk.[12]

S. aureus infection (Chapter 267) is associated with poor joint outcomes in more than 50% of patients, and mortality may be as high as 10 to 15%, particularly in patients who are immunocompromised or have polyarticular sepsis. A prior history of native joint arthritis increases the risk of prosthetic joint infection following joint replacement.

GONOCOCCAL SEPTIC ARTHRITIS

EPIDEMIOLOGY

Neisseria gonorrhoeae (Chapter 275) is a common cause of polyarthralgias and arthritis as well as oligoarticular arthritis and tenosynovitis in otherwise young, healthy patients. Disseminated gonococcal infection occurs in 0.5 to 3% of patients with gonorrhea (Chapter 275), and many of these patients develop arthritis. Most patients do not have a recent history of a symptomatic genital infection. Disseminated gonococcal infection and septic arthritis due to *N. gonorrhoeae* occur two to three times more often in women than in men. Predisposing factors for disseminated gonococcal infection with arthritis include pregnancy, recent menstruation, drug-induced or congenital complement deficiencies (C5, C6, C7, or C8; Chapter 37), and systemic lupus erythematosus (Chapter 245).

CLINICAL MANIFESTATIONS

Patients with gonococcal arthritis usually present with one of two clinical syndromes. The first is a purulent arthritis without skin lesions; the second is the triad of tenosynovitis, dermatitis, and polyarthralgias without purulent arthritis.[13] The latter patients may have bacteremia and fever, as well as maculopapular, vesicular, necrotic, pustular skin lesions anywhere on the integument (see Fig. 275-4). The arthritis is usually asymmetrical and may involve large or small joints, typically the elbows and knees or more distal joints.

DIAGNOSIS

A high degree of clinical suspicion is required for diagnosis because many patients are asymptomatic for the primary infection. A thorough joint evaluation is important, as is an evaluation of soft tissues, particularly for tenosynovitis affecting the hands and feet. Cultures of blood, endocervix, and urethra are essential; cultures of the pharynx and rectum may be very helpful. *N. gonorrhoeae* is isolated in less than 30% of patients with the tenosynovitis-dermatitis syndrome and in about 50% of patients with monoarthritis. PCR testing is recommended and can detect gonococcal DNA in synovial fluid, skin lesions, urine, throat, and rectal samples, even when cultures are negative. Cultures should be submitted on Thayer-Martin media. Patients with suspected gonococcal arthritis should be screened for other possible coexisting sexually transmitted infections (Chapter 264) such as syphilis (Chapter 295), human immunodeficiency virus (Chapter 355), and chlamydia (Chapter 294), as well as hepatitis B and C (Chapters 134 and 135).

TREATMENT

Ceftriaxone (e.g., 1 g intramuscularly or intravenously every 24 hours) is administered initially in nonallergic patients and continued until clinical improvement, at which time the patient can be switched to oral therapy depending on clinical assessment, comorbid conditions, and in vitro susceptibilities. Given emerging antimicrobial resistance, the most recent U.S. Centers for Disease Control and Prevention (CDC) guidelines for treating *N. gonorrhoeae* septic arthritis (www.cdc.gov/std/gonorrhea/treatment.htm) should be consulted and followed. Gonococcal effusions should be drained as is recommended for staphylococcal arthritis. Patients also should be treated for concomitant chlamydia (with doxycycline 100 mg twice daily for 7 days).

PROGNOSIS

Most patients respond well to outpatient therapy, with complete resolution of the infection.

VIRAL ARTHRITIS

Patients with viral syndromes may have polyarthralgias or inflammatory polyarthritis, which can mimic rheumatoid arthritis (Chapter 243). The most common viral infections associated with arthritis include hepatitis A, B, and C (Chapters 134 and 135); cytomegalovirus (Chapter 347); parvovirus B19 (Chapter 342); rubella (Chapter 339); measles (Chapter 338); and HIV (Chapter 359). Other forms of viral arthritis are caused by adenovirus (Chapter 333), echovirus (Chapter 349), Epstein-Barr virus (Chapter 348), and herpes zoster (Chapter 346) in North America and Europe; chikungunya and o'nyong-nyong viruses, especially in Africa (Chapter 352); and Ross River virus in Australia (Chapter 352). Arthritis related to viral infections is likely to be principally reactive in nature,[14] rather than being caused by direct synovial infection.

Chikungunya virus infection (chikungunya fever; Chapter 352) is an arthropod-borne arbovirus infection that over recent decades has dispersed from tropical and subtropical regions of Africa and Asia to affect millions of people worldwide as an emerging threat to global public health.[15] The illness occurs in two phases: an acute viremia followed by a chronic arthritis that can be accompanied by severe, incapacitating arthralgia. Attempts to isolate chikungunya virus from synovial fluid have been unsuccessful,[16] and the chronic arthritis is now thought to be a postinfectious autoinflammatory disorder rather than persistent viral infection. It shares many clinical features with rheumatoid arthritis and responds variably to different disease-modifying antirheumatic drugs.

OTHER FORMS OF INFECTIOUS ARTHRITIS

FUNGAL ARTHRITIS

Fungal arthritis is unusual and most commonly occurs in immunocompromised patients. Treatment with high doses of immunosuppressants, anti-TNF agents, and possibly other biologic response modifiers used for rheumatoid arthritis and other autoimmune diseases may increase the risk for fungal infections. The infections are often systemic and may be indolent. An understanding of the epidemiology of the organisms as well as the patient's risk factors, including occupational and avocational risk factors, is essential to the diagnosis. The most common fungi in the United States include *Blastomyces dermatitidis, Coccidioides immitis*, and *Histoplasma capsulatum* (Chapter 308). *Sporothrix schenckii* fungal infections may be seen especially in gardeners. More unusual infections occur in immunocompromised patients, including *Aspergillus* (Chapter 311), *Candida* (Chapter 310), and *Cryptococcus* (Chapter 309). The treatment of fungal infections is detailed in their respective chapters.

LYME ARTHRITIS

Lyme disease (Chapter 296) usually causes oligoarticular arthritis, most commonly affecting the knee. Antibiotic treatment (see Chapter 296) is effective. Polyarticular disease affecting the small joints has been associated with human leukocyte antigen (HLA)-DR4, which is found in greater frequency in patients with rheumatoid arthritis.

MYCOPLASMA AND UREAPLASMA ARTHRITIS

Mycoplasma hominis (Chapter 293) causes an oligoarticular or monoarticular arthritis. Risk factors for mycoplasma and ureaplasma arthritis include immunosuppression and congenital or drug-induced hypogammaglobulinemia. Mycoplasma septic arthritis also can occur after childbirth. Nucleic acid amplification tests are more sensitive than culture for the diagnosis of these infections. The treatment of choice is tetracyclines, usually doxycycline; alternatively, clindamycin or fluoroquinolones can be used (see Chapter 293).

TUBERCULOUS ARTHRITIS

Most cases of tuberculosis (Chapter 299) in Canada, the United States, Western Europe, Australia, and New Zealand occur in immigrants. The arthritis is usually monoarticular or oligoarticular and affects larger joints. Tuberculosis should be suspected in patients who have refractory monoarticular or pauciarticular arthritis thought to be secondary to another bacterial infection or to a systemic inflammatory disease such as rheumatoid arthritis. Screening for tuberculosis is mandatory for all patients before beginning treatment with immunosuppressive drugs or biologic response modifiers.

The diagnosis of tuberculosis may be delayed by a lack of clinical suspicion because patients may not have pulmonary disease. Atypical mycobacterial infection may occur in fishermen and immunocompromised patients. Clinical suspicion and culture of synovial fluid or synovial membrane obtained at biopsy are essential to the diagnosis.

TREATMENT

Appropriate treatment for septic arthritis due to tuberculosis is based on guidelines and in vitro susceptibility testing, but it often includes isoniazid, ethambutol, or rifampin and pyrazinamide as empirical therapy (see Table 299-4). Atypical mycobacteria are often not susceptible to traditional antituberculous agents, and infectious disease consultation is recommended.

SYPHILIS

Musculoskeletal involvement by syphilis (Chapter 295) includes monoarticular or oligoarticular arthritis, polyarthralgias, tenosynovitis, sacroiliitis, spondylitis, chondritis, osteitis, and periostitis. Charcot joints, osteitis, and chronic arthritis are typical of tertiary syphilis. Arthritis may complicate congenital, secondary, and tertiary syphilis. Most patients with syphilis-related arthritis can be treated successfully (see Table 295-4).

PROSTHETIC JOINT INFECTION

More than 1 million joint replacements (Chapter 255) are performed each year in the United States, and this number continues to increase. Infection occurs in 0.3 to 1.7% of hip arthroplasties and 0.8 to 1.9% of knee arthroplasties. The risk of infection is two-fold to three-fold higher in patients with rheumatoid arthritis. Prosthetic joint infections are classified as (1) early infections, occurring within 3 months of joint replacement; (2) delayed infections, occurring 3 months to about 1 year after joint replacement; and (3) late infections, occurring more than 1 to 2 years after joint replacement. Infections occurring within the first year are usually related to the implantation surgery itself, and late infections are usually due to hematogenous spread.

Risk factors associated with the development of prosthetic joint infection include wound healing complications, prior superficial surgical site infection, prior infection of the joint, previous surgery on the joint, rheumatoid arthritis, advanced age, obesity, smoking, cancer, and diabetes mellitus. Other risk factors include simultaneous bilateral arthroplasty, prolonged operative time, requirement for blood transfusion, and infection occurring elsewhere in the body that can hematogenously seed the prosthesis.

The development of a bacterial biofilm on the prosthetic joint is characteristic of prosthetic joint infection. These biofilms are formed by bacterial glycocalyx, which increases the organisms' resistance to antimicrobial agents and likely accounts for the difficulty in obtaining viable organisms from the infected joint.

More than half of all prosthetic joint infections of hips and knees are caused by staphylococci. Other organisms, including gram-negative bacilli, anaerobes, and *Candida* species, may also cause infection. In particular, *Cutibacterium* species are commonly associated with infected shoulder arthroplasties. About 20% of cases are polymicrobial, and in 7%, cultures are negative.

CLINICAL MANIFESTATIONS AND DIAGNOSIS

Patients with early-onset infection may have classic symptoms and signs of septic arthritis, including joint pain, effusion, erythema, fever, and poor wound healing. Patients with delayed infection may have only joint pain, with or without implant loosening, requiring a high degree of clinical suspicion for the presence of infection.

An elevated sedimentation rate or C-reactive protein without another obvious cause, such as inflammatory arthritis or recent surgery, is very suggestive of infection in a patient with a painful, loose prosthesis. Plain radiographs may show loosening, new bone formation, and lucencies along the implant margin but are often nonspecific. Technetium-based scintigraphy combined with indium-labeled white blood cell scanning is suggestive of established infection but is often not performed owing to the expense. MRI and CT have low utility in diagnosing prosthetic joint infection. Aspiration of the joint for synovial fluid leukocyte count, alpha defensin, and culture can be the most frequently used presurgical diagnostic test.[17]

The definitive diagnosis of prosthetic joint infection is based on the recovery of organisms from multiple specimens of synovial fluid and periprosthetic tissue, sonication of the prosthesis itself, acute inflammation suggestive of infection on pathologic examination of periprosthetic tissue obtained at surgery, or the presence of a sinus tract communicating with the prosthesis, even in the absence of microorganisms.

TREATMENT

Surgical treatment of prosthetic joint infection typically consists of débridement with retention of the prosthesis for acute infection, resection arthroplasty with or without staged reimplantation for chronic infection, or amputation in a few limited instances.[18,19] Systemic antibiotic therapy in a patient with a prosthetic joint infection is pathogen directed and driven by the surgical therapy used to manage the infection.[20] Following an attempt at salvage of prosthesis with 2 to 6 weeks of effective intravenous antibiotic therapy, chronic suppressive therapy with oral antimicrobial agents is often used. In rifampin-susceptible staphylococcal infections, its addition to a companion intravenous or oral antimicrobial is recommended to avoid the emergence of resistance, to treat biofilm organisms, and to improve the weeks of pathogen-directed intravenous therapy before an attempt at reimplantation several weeks later. The use of depot local antimicrobial therapy with antibiotic-impregnated polymethylmethacrylate spacers following resection arthroplasty is also very common. After an appropriate surgical procedure, 12 weeks of antibiotic therapy may be superior to 6 weeks, but about 10% of patients have persistent infection despite 12 weeks of antibiotics.[A3]

PREVENTION

In addition to optimizing comorbid conditions such as diabetes mellitus and discontinuing tobacco use preoperatively, careful screening for infection, including asymptomatic urinary tract infection, is prudent when considering joint surgery. Perioperative antibiotic treatment with a cephalosporin reduces the risk for infection in patients undergoing prosthetic joint replacement by approximately three-fold. Antimicrobial therapy should be given within 60 minutes of the initial incision, ideally before tourniquet application. Cefazolin or cefuroxime based on institutional guidelines can be given to patients with normal renal function, and vancomycin can be used in patients who are allergic to penicillin.

Whether an antirheumatic agent should be stopped before joint replacement surgery is unclear. The usual practice is to hold drugs such as anti-TNF

agents, and other biologics, including abatacept and tocilizumab, for one to four half-lives before and after surgery.

OSTEOMYELITIS

DEFINITION

Osteomyelitis is a bacterial infection of bone that causes destruction and can occur through a variety of mechanisms.

EPIDEMIOLOGY

Osteomyelitis of the bones of the foot in adult patients with diabetes (Chapter 210), neuropathy (Chapter 388), and arterial insufficiency (Chapters 65 and 66) is very common, often as the result of what would otherwise be minor trauma or skin infection in patients with normal sensation and circulation. Hematogenous seeding of the spine also occurs, but less frequently. The incidence of osteomyelitis due to trauma and surgery is increasing.

PATHOBIOLOGY

Osteomyelitis can develop from hematogenous seeding from a distant infection, contiguous spread from nearby skin and joints, and penetration of microorganisms into bone at the time of trauma or surgery. Except with trauma or the presence of a foreign body, bone is typically very resistant to infection. Organisms such as *S. aureus* (Chapter 267) cause disease more frequently because they colonize the skin in up to 30 to 40% of individuals, frequently cause cellulitis and bacteremia, and have the ability to bind to bone through the expression of receptors for fibronectin and collagen.[21]

Elderly individuals and injection drug users are susceptible to hematogenous causes of osteomyelitis, usually involving two or more vertebrae and their intervening disc spaces. Bacteria gain access to these structures through the arterial and venous systems (Batson venous plexus). Bacteremia from any source can cause osteomyelitis of the spine, but injection of contaminated substances, cellulitis, urinary tract infection, and pneumonia are the most common sources. Salmonella osteomyelitis (Chapter 284) is a complication of hematogenous spread, commonly in the absence of gastrointestinal symptoms.[22]

Contiguous focus osteomyelitis is common in adults, typically occurring in the elderly. It results from the spread of infection from nearby skin, often in the feet of patients with diabetes, neuropathy, or vascular insufficiency, or in pelvic bones in patients with decubitus ulcers due to impaired sensation from spinal cord injury or disease. Alternatively, it can occur with orthopedic surgery, from contamination at the time of an open fracture, or from a human or animal bite.

Acute osteomyelitis has a duration of less than 10 days, whereas chronic infection has a duration of more than 10 days. *S. aureus* is the most common cause of hematogenous and contiguous osteomyelitis in adults. Osteomyelitis due to β-hemolytic streptococci and aerobic gram-negative bacilli is much less common, but can occur if infections caused by these organisms result in hematogenous seeding, if nosocomial contiguous osteomyelitis occurs as a result of surgical site infection, or if contamination occurs at the time of traumatic open fracture. Polymicrobial infection, including infection caused by anaerobes, is very common in osteomyelitis of the bones of the feet associated with diabetes and vascular insufficiency. Coagulase-negative staphylococci can be pathogenic in patients with orthopedic implants.

CLINICAL MANIFESTATIONS

Localized pain over the affected bones is a hallmark of osteomyelitis. A sinus tract or swelling and erythema resulting from concomitant soft tissue infection or abscess may be present in osteomyelitis secondary to contiguous infection. Constitutional symptoms, including fever, are present in the minority of cases and more often in hematogenous osteomyelitis. If neurologic structures are involved, neurologic signs and symptoms such as pain and weakness may be present. Signs and symptoms due to a coexisting infection that has caused hematogenous osteomyelitis may be present as well. The differential diagnosis of osteomyelitis includes diseases that can cause acute and chronic bone pain in adults, including osteoarthritis (Chapter 241), metastatic malignancy, fractures, and SAPHO (*s*ynovitis, *a*cne, *p*ustulosis, *h*yperostosis, and *o*steitis) syndrome, as well as postoperative pain and soft tissue infection without concomitant osteomyelitis.

DIAGNOSIS

The WBC count is often elevated in hematogenous and acute osteomyelitis. Serum inflammatory markers such as the erythrocyte sedimentation rate and C-reactive protein are often abnormal, particularly in cases of hematogenous infection, but may be normal in chronic contiguous osteomyelitis. Blood cultures are positive in 25 to 50% of cases of hematogenous infection but are almost always negative in chronic osteomyelitis unless concomitant soft tissue infection is present. In the setting of chronic contiguous osteomyelitis, plain radiographs often show specific abnormalities; they are often not helpful in confirming the diagnosis of vertebral osteomyelitis.

The ability to probe percutaneously or to palpate bone with a probe (a sterile metal probe is inserted into the ulcer, and the test is positive if a hard, gritty surface is felt) is a simple, effective diagnostic test in patients with diabetes mellitus and possible contiguous osteomyelitis of the feet. For example, the probe-to-bone test has a sensitivity of 87% and a specificity of 83% for diagnosing foot osteomyelitis.

MRI is the most sensitive and diagnostic imaging technique to identify osteomyelitis,[23] except when orthopedic implants are present. Gallium scans are more sensitive and specific than three-phase technetium-99m (^{99m}Tc) bone scans or indium-labeled leukocyte scans for the diagnosis of vertebral osteomyelitis.[24] Gallium scans may be used when spinal hardware makes MRI less useful and in cases of skull bone osteomyelitis due to malignant external otitis.

Multiple specimens of involved bone, contiguous soft tissue, and purulence should be sent for Gram stain, aerobic and anaerobic culture, and pathologic examination at the time of bone biopsy or surgical débridement. If the history, examination, or imaging is suggestive of atypical infection, culture for fungi and mycobacteria or other unusual organisms should be performed.

TREATMENT

Antimicrobials for specific pathogens are recommended (see Table 251-2) based on in vitro susceptibility testing. Oral antibiotics can achieve adequate levels in bone,[25,26] and either oral or parenteral therapies can achieve similar cure rates.[A4] Dalbavancin (1500 mg intravenously on days 1 and 8) may be an alternative for gram-positive infections[A5] but should not be used routinely.

For diabetic foot osteomyelitis, surgical consultation is recommended. Medical therapy with or without limited surgical débridement is recommended in some cases of mild to moderate infection, although surgical resection is typically required for severe infection. The role of adjunctive rifampin in the treatment of diabetic foot infections is uncertain. Arterial revascularization may be required based on evaluation of the vascular supply to the affected limb.

The duration of antimicrobial therapy is almost always dictated by surgical therapy in chronic osteomyelitis. For example, only a short course of antimicrobial therapy may be required if an amputation is performed, whereas more prolonged intravenous or highly bioavailable oral antimicrobial therapy is typically recommended[27] if an extensive débridement of chronic osteomyelitis is performed, with data suggesting that 3 weeks is as good as 6 weeks.[A6] If the surgical therapy could lead to a worse outcome than no surgery, chronic oral antimicrobial suppression may be recommended. Acute hematogenous vertebral osteomyelitis in adults typically does not require surgical intervention but can be treated with 6 weeks of intravenous antimicrobial therapy, which is as good as 12 weeks of treatment in immunocompetent patients,[A7] after identification of the pathogen through percutaneous or open biopsy. Hyperbaric oxygen therapy for chronic osteomyelitis is controversial. Medical management is the mainstay of treatment of spinal tuberculosis (Chapter 299), with surgery indicated for specific situations.[28]

PREVENTION

Improving the control of diabetes and decreasing the incidence of peripheral vascular disease will reduce the incidence of diabetic foot bone infection. Optimal strategies to prevent surgical site infection after orthopedic procedures will prevent orthopedic implant infection after surgery and open fractures.

PROGNOSIS

The success of treatment depends on the medical and surgical therapy and the ability to improve comorbid conditions such as arterial insufficiency. The ability of orthopedic surgeons to perform more extensive reconstructive surgery has allowed more extensive débridement and higher success rates, as well as restoration of function. Treatment failure can lead to relapse of infection or progression of infection to involve more of the affected bone. Long-standing osteomyelitis can be complicated by amyloidosis, squamous cell carcinoma of the skin in a chronic sinus tract, or primary bone malignancy.

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252 CRYSTAL DEPOSITION DISEASES

N. LAWRENCE EDWARDS

The three most common crystal-induced arthropathies are caused by precipitation of monosodium urate monohydrate, calcium pyrophosphate dihydrate, and basic calcium phosphate and are termed *gout, calcium pyrophosphate arthropathy*, and *basic calcium arthropathy*, respectively. Basic calcium crystals are ultramicroscopic in size and are not detected by the compensated polarized microscopy used to identify monosodium urate and calcium pyrophosphate dehydrate crystals. Like monosodium urate and calcium pyrophosphate crystals, basic calcium phosphate crystals are biologically active and can accelerate atrophic changes in bone and cartilage.

GOUT AND HYPERURICEMIA

DEFINITION

Gout is a metabolic disorder that results from the tissue deposition of monosodium urate crystals in or around joints and/or the crystallization of uric acid in the renal collecting system. Gout is the most common inflammatory joint disease in men and in older women. The metabolic derangement responsible for gout is the supersaturation of blood and body fluids with the urate ion to the point that crystal formation is possible. At physiologic pH and at normal body temperature, urate is considered to be supersaturated at concentrations of 6.8 mg/dL or greater. Therefore, from a biologic perspective, hyperuricemia is any serum urate level greater than 6.8 mg/dL in both men and women. Although hyperuricemia is a necessary prerequisite for developing gout, only 20% of all hyperuricemic subjects will ultimately develop gout.

EPIDEMIOLOGY

The incidence and prevalence of gout vary greatly throughout the world. In the United States, the United Kingdom, and much of Western Europe, the prevalence of gout ranges from 3 to 6% in men and 1 to 2% in women. In developing countries the prevalence is much lower, typically less than 1%. However, the highest prevalences have been noted in certain ethnic groups, especially in Oceanic populations, including Taiwanese Aborigines, Māori, and Pacific Islanders living in New Zealand, where prevalence estimates are more than 10%.[1,2] In Western societies, including the United States, the rate has more than doubled within the past three decades. Factors that have been proposed to explain this dramatic rise include the overall increase in longevity; the increased prevalence of hypertension, metabolic syndrome, and obesity; the increased use of thiazide diuretics and low-dose aspirin; changes in dietary trends, including the greater use of high-fructose corn syrup as a sweetener; and finally, the increase in survival of patients with end-stage renal disease and after organ transplantation.

The degree of elevation of the serum urate is directly correlated with the likelihood of developing gout. The reported annual incidence of gout in individuals with baseline serum urate levels of 9 mg/dL or higher is 4.9%, compared with only 0.5% in people with serum urate levels of 7.0 to 8.9 mg/dL.

PATHOBIOLOGY

Uric acid is the end product of purine metabolism in humans. Urate is produced by the conversion of a very soluble molecule, hypoxanthine, to the less soluble xanthine, which, in turn, is converted to the very insoluble uric acid by progressive purine ring oxidations catalyzed by the enzyme xanthine oxidase. Xanthine oxidase is present in several organs, but most activity in the body is found in the liver and intestines. In most mammals, purine catabolism is taken one step further through the enzyme uric acid oxidase or uricase, with the purine end product in these species being the very soluble allantoin. Humans and most other hominoids lost the ability to produce the enzyme uricase nearly 18 million years ago. As a result, uric acid accumulation is possible. Whether caused by overproduction of uric acid or its underexcretion by the kidneys, this accumulation leads to supersaturation of urate ion in blood and the precipitation of monosodium urate crystals in synovial fluid, soft tissues, and organs.

Because of urate's potential for causing disease, its elimination is very important. The total daily accumulation of uric acid from de novo synthesis, nucleotide degradation, and dietary consumption is normally balanced by renal excretion of approximately two thirds of the total urate turnover and by intestinal elimination of the remaining one third.

Hyperuricemia occurs when urate production is not balanced by renal excretion. In more than 90% of all patients with gout, the cause of this imbalance is renal underexcretion. Fewer than 10% of cases of gout are caused by the overproduction of purine or by a combination of overproduction and underexcretion. The nongenetic causes of hyperuricemia include other medical conditions, dietary components, and medications (Table 252-1). These factors may result in either overproduction or diminished renal clearance of uric acid. Similarly, the genetic causes of hyperuricemia (Table 252-2) may affect either production or elimination of uric acid.[3]

Renal Urate Underexcretion

Because uric acid is small and not protein bound, it is completely filtered by the glomerulus. In normal persons, approximately 8 to 10% of the filtered load is ultimately cleared in the urine. The various renal tubular transporters that are responsible for determining how much of the filtered uric acid is actually excreted are located in the proximal convoluted tubules and are referred to collectively as the *transportasome* (E-Fig. 252-1). Both reabsorption and secretion occur in this segment through the actions of several organic acid transporters, with the net effect being the reabsorption of nearly 90% of the uric acid filtered at the glomerulus. These organic acid transporters are also responsible for eliminating organic acids other than uric acid as well as many commonly used medications. The most important tubular transporter of uric acid is *URAT1*. This transporter swaps urate ions for other monocarboxylate organic ions in both directions across the luminal membrane of proximal tubular cells. This system can be driven to reabsorb more uric acid from the tubular lumen by raising tubular epithelial concentrations of lactate, pyruvate, or the ketoacids acetoacetate and β-hydroxybutyrate. Certain drugs, when present in the tubular lumen, can displace uric acid from the transporter, thereby causing more uric acid to be lost in the urine. These uricosuric agents include probenecid.

TABLE 252-1 NONGENETIC CAUSES OF HYPERURICEMIA

IMPAIRED URIC ACID EXCRETION
Clinical Conditions
Reduced glomerular filtration rate
Hypertension
Obesity
Lead nephropathy
Drugs
Thiazide diuretics
Ethanol
Low-dose salicylates (0.06-3.0 g/day)
Cyclosporine
Tacrolimus
Levodopa
Angiotensin-converting-enzyme inhibitors
β-Blockers
Nicotinic acid
Pancreatic extract
EXCESSIVE URIC ACID PRODUCTION
Clinical Conditions
Myeloproliferative and lymphoproliferative neoplasms
Obesity
Psoriasis
Diet Components
Alcoholic beverages (especially beer)
Red meat, organ meat, shellfish
High fructose corn syrup

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Obesity
Lead nephropathy
Drugs
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Low-dose salicylates (0.06-3.0 g/day)
Cyclosporine
Tacrolimus
Levodopa
Angiotensin-converting-enzyme inhibitors
β-Blockers
Nicotinic acid
Pancreatic extract
EXCESSIVE URIC ACID PRODUCTION
Clinical Conditions
Myeloproliferative and lymphoproliferative neoplasms
Obesity
Psoriasis
Diet Components
Alcoholic beverages (especially beer)
Red meat, organ meat, shellfish
High fructose corn syrup

ABSTRACT

The crystalline arthropathies are the most common causes of inflammatory arthritis in humans. Gouty arthritis is a disease of urate burden associated with the deposition of monosodium urate crystals in and around joints when the serum urate level exceeds its solubility concentration of 6.8 mg/dL. The presence of these crystals over time results in a severely painful inflammatory arthritis with destruction of bone and cartilage. Diagnostic confirmation of gout in a patient presenting with acute monoarthritis or oligoarthritis is made by synovial fluid aspiration demonstrating monosodium urate crystals on compensated, polarized microscopy or the classic ultrasound finding of the "double-contour sign." The therapeutic approach to gout requires the lowering of serum urate to below its solubility concentration so that resorption of the accumulated crystals can occur.

Calcium pyrophosphate disease is a heterogeneous condition that includes acute and chronic arthropathies and is closely associated with radiographic evidence of chondrocalcinosis. This condition can be familial or sporadic or can be a manifestation of an underlying metabolic disease. Basic calcium phosphate disease may, likewise, present as either an acute or chronic arthritis and is frequently associated with osteoarthritis. Milwaukee shoulder is the most destructive form of this basic calcium phosphate disease and occurs in the elderly. Treatment of these conditions is nonspecific and relies on nonsteroidal anti-inflammatory drugs and intra-articular glucocorticoids.

KEYWORDS

gout
calcium pyrophosphate arthritis
basic calcium arthritis
allopurinol
colchicine
chondrocalcinosis
DISH (diffuse idiopathic skeletal hyperostosis)

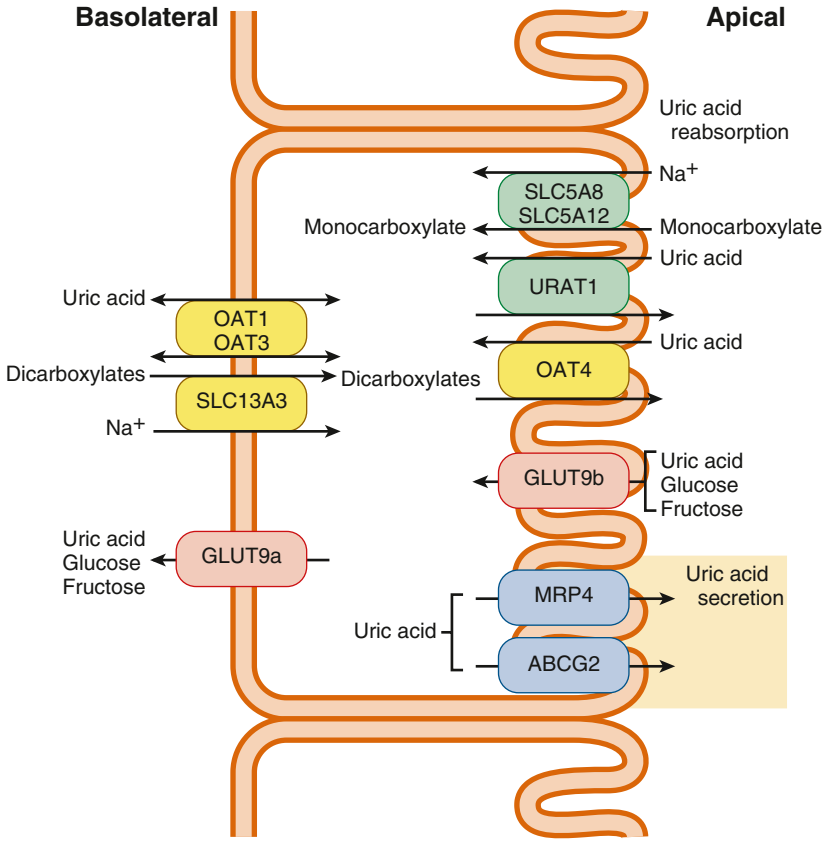

E-FIGURE 252-1. Renal transport of urate in proximal tubule of kidney. Serum urate reaches the tubule lumen by glomerular filtration and by secretion through the proximal tubular epithelium. Secretion of urate is facilitated in the luminal direction by MRP4, UAT, ABCG2, and NTP1, and at the basolateral membrane by OAT1 and OAT3. Reabsorption of urate from the tubular lumen is facilitated by URAT1, OAT4, OAT10, and the short isoform of GLUT (GLUT9b), and at the basolateral membrane by the long isoform (GLUT9a). ABCG2 = adenosine triphosphate–binding cassette transporter; GLUT = glucose transporter; MRP = multidrug-resistance-related protein; NTP = sodium phosphate transport protein; OAT = organic acid transporters; URAT = uric acid transporter.

TABLE 252-2 GENETIC CAUSES OF HYPERURICEMIA

SYNDROME	PHENOTYPE
INBORN ERRORS OF PURINE METABOLISM	
Hypoxanthine-guanine phosphoribosyl transferase deficiency	Neurologic dysfunction, renal stones, early-onset gout
Phosphoribosyl pyrophosphatase synthetase overactivity	Neurologic dysfunction, early-onset gout
EXCESSIVE CELL DEATH AND URATE GENERATION	
Glycogen storage disease I	Growth restriction, lactic acidosis, early-onset gout
Glycogen storage disease III	Early-onset gout
Glycogen storage disease V	Early-onset gout
Glycogen storage disease VII	Early-onset gout
Fructose-1-phosphate aldolase deficiency	Growth restriction, liver failure, early-onset gout
Myoadenylate deaminase deficiency	Myopathy, gout
Carnitine palmitoyltransferase II deficiency (late onset)	Rhabdomyolysis, gout
REDUCED RENAL EXCRETION OF URIC ACID	
Medullary cystic kidney disease	Renal dysfunction, early-onset gout
Familial juvenile hyperuricemic nephropathy	Renal dysfunction, early-onset gout
Uric acid transportasome mutations	
GLUT-9	Familial gout
ABCG2	Familial gout
URAT1	Familial gout

When the renal clearance of uric acid is compared between normal adult men and gouty men, the gouty subjects excrete only 70% as much uric acid as normal individuals at any given serum urate concentration. In general, gouty patients require a serum urate concentration to be 1.7 mg/dL higher to obtain the same level of excretion as seen in normal individuals.

Most genetic polymorphisms associated with gout in genome-wide association studies encode for the various components of the uric acid transportasome (see E-Fig. 252-1). Polymorphisms in the glucose transporter GLUT-9 (encoded by the *SLC2A9* gene) are statistically the most significant determinants of serum urate. ABCG2 is a multifunctional transporter that belongs to the adenosine triphosphate (ATP)-binding cassette family found primarily in the small intestine and liver.[4] Polymorphisms in the gene encoding URAT1 may lead to either hypouricemia or hyperuricemia. A loss-of-function mutation results in familial renal hypouricemia.

The serum urate variance explained by these common genetic variants is only about 6% of the total variance observed between gouty and non-gouty individuals. Similar risk-stratifying techniques demonstrate that 67% of the variance is caused by nongenetic factors such as the serum creatinine level, the consumption of ethanol, and the components of the metabolic syndrome.

Urate Overproduction

Traditionally, the causes of hyperuricemia were attributed to either the overproduction of urate or its underexcretion in the urine. The former was presumed to be the case when hyperuricemia occurred despite a 24-hour urinary uric acid collection showing more than 1000 mg while eating a standard Western diet. In many of these cases, the hyperuricemia reflects accelerated cell turnover (e.g., lymphoproliferative and myeloproliferative diseases, psoriasis, chronic hemolytic states, polycythemia vera, and certain muscle glycogenoses) or by enhanced breakdown of purine nucleotides (e.g., alcohol use disorder or ingestion of fructose). In addition to these secondary causes of urate overproduction, primary inborn errors of metabolism (e.g., phosphoribosyl pyrophosphate [PRPP] synthetase overactivity) can result in increased de novo purine synthesis, or decreased purine salvage (e.g., complete and partial hypoxanthine-guanine phosphoribosyltransferase [HPRT] deficiencies [Lesch-Nyhan syndrome and Kelley-Seegmiller syndrome, respectively]). Polymorphisms in the *ABCG2* urate transporter gene in the bowel can lead to extrarenal underexcretion of uric acid. This mechanism may account for a large percentage of cases previously considered to be due to overproduction of urate.

Pathogenesis of Monosodium Urate Monohydrate Crystals and Inflammation

Monosodium urate crystals in joints, soft tissues, and organs are the cause of pain and destruction in gout. Urate crystals will form only when physiologic conditions permit. In plasma, urate becomes insoluble at concentrations of 6.8 mg/dL (408 μmol/L) with a pH of 7.40 and normal body temperature. A reduction in pH or temperature will lower the solubility threshold even further. Not all people who are hyperuricemic will form crystals, however, and genetic factors other than those responsible for hyperuricemia affect when crystallization will occur.

Monosodium urate crystals form in joints and soft tissues of individuals long before they cause any symptoms of gout. Crystals deposit in small lattice structures called *microtophi* on the surface of cartilage and synovial lining. These microtophi slowly grow but are generally stable as long as the environment surrounding them does not change drastically with regard to pH, urate concentration, or temperature. At the time of the first and subsequent flares, these crystal lattice structures break apart and shed a massive number of crystals into the joint space. These newly released and nonopsonized crystals, which are not coated with albumin or immunoglobulins, activate receptors on synovial macrophages and are then phagocytized by monocytes and macrophages, thereby leading to the cytoplasmic assembly and activation of the NLRP3 inflammasome. The resulting rapid production of interleukin-1β is responsible for gout's cardinal features of severe inflammation.

Although monocytes and macrophages are the major cellular sources of IL-1β, neutrophils predominate at the site of inflammation (e.g., joint), where monosodium urate crystals become extremely pro-inflammatory by recruiting neutrophils that then generate reactive oxygen species. However, neutrophils also have a major role in the resolution of acute gout through the formation of neutrophil extracellular traps (NETs). Neutrophil proteases are released into the NETs and cause the formation of cell aggregates that contain cellular debris and DNA. These cellular aggregates within NETs can rapidly degrade pro-inflammatory cytokines, thereby allowing for the spontaneous resolution of joint inflammation after 3 to 6 days, even in the absence of treatment.[5]

CLINICAL MANIFESTATIONS

Classic Gout

The natural course of classic gout progresses through three stages: asymptomatic hyperuricemia, acute intermittent symptoms, and chronic persistent symptoms.[6] The rate of progression from initial symptoms to persistent symptoms varies considerably from one person to another and is dependent on numerous factors, the most important being the degree of increase in serum urate levels.

Asymptomatic hyperuricemia refers to a state in which serum urate exceeds the level of solubility (6.8 mg/dL) but symptoms of crystalline deposition have not occurred. Only 20% of all hyperuricemic people will ultimately develop monosodium urate crystals and gout. For this group, the period of asymptomatic hyperuricemia begins a stage of subclinical structural changes. In men, asymptomatic hyperuricemia frequently begins at puberty, whereas in women, it is usually delayed until menopause.

The initial clinical manifestations of gout usually follow decades of asymptomatic hyperuricemia. In men, the first flare usually occurs between the fourth and sixth decades of life. In women, the age of onset is older and varies with several factors, most importantly the age of menopause. The classic gout flare is hallmarked by the rapid development of warmth, swelling, erythema, and exquisite pain in one or occasionally two joints. The characteristically severe pain evolves from its faintest twinge to its most intense level over an 8- to 12-hour period. Initial episodes are usually monoarticular and involve lower extremity joints. The most commonly involved joint is the first metatarsal phalangeal joint (termed *podagra*), followed by the ankle, midfoot, and knee (Fig. 252-1). After years of recurrent gouty flares in the lower extremity joints, gout can involve upper extremity joints, including the wrists, elbows, and small joints of the hands.

Systemic symptoms of flares can include fever, chills, and malaise, with an intense erythema extending beyond the area of the involved joint. These symptoms and signs may lead to confusion with an infectious process.

Certain factors can provoke gouty flares by causing fluctuations in serum urate levels. Examples include trauma, surgery, starvation, bedrest, overindulgence in certain high-purine foods and beer, and the ingestion of any medication that raises or lowers serum urate.

Another characteristic of classic gout flares is their self-remitting nature. For the first several acute flares, the duration of the attack is 4 to 7 days. The resolution of symptoms is gradual but complete, even if no anti-inflammatory therapy is administered. The periods between the flares are devoid of articular pain, although synovial fluid aspirates during this stage continue to show low-grade inflammation and the presence of monosodium urate crystals.

Advanced Gout

Eventually, the untreated patient will progress to persistent gouty arthritis, also referred to as *advanced gout*. This stage usually develops after 10 or more

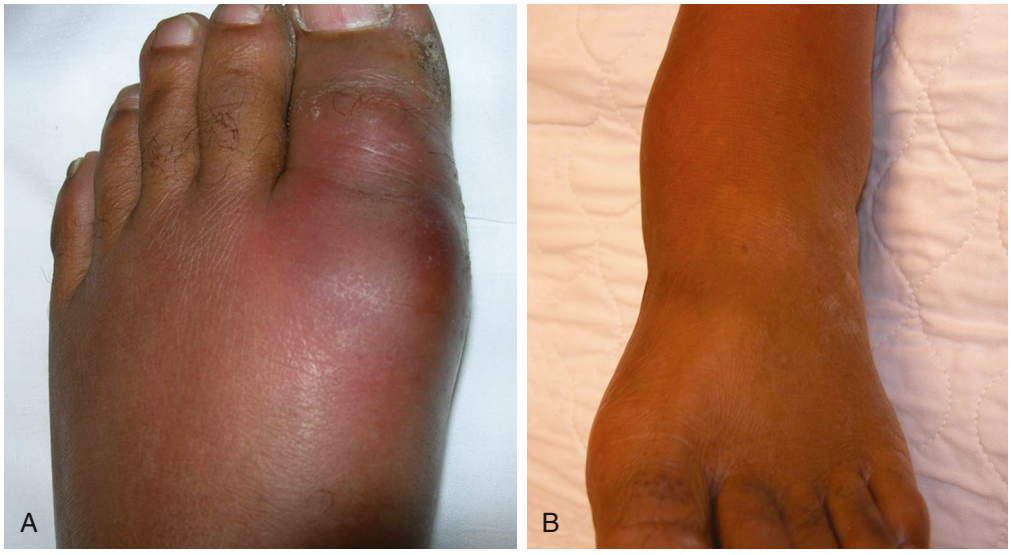

FIGURE 252-1. **The intense inflammation of acute gouty arthritis. A,** The marked swelling of the first metatarsophalangeal joint (podagra) is demonstrated. A dusky blue hue over an intense erythema is characteristic. **B,** Ankle swelling is shown with erythema extending beyond the area of the tibiotalar joint.

FIGURE 252-2. **Characteristic locations of gouty tophi. A,** At the elbow, tophi present as hard nodules along the ulnar ridge or as multiple nodules within the olecranon bursa. **B,** Ear tophi are uncommon but may be an easy source of crystal confirmation of gout when present. **C,** Small subcutaneous tophi can occur along the ventral creases of fingers. **D,** Tophi over the proximal interphalangeal or distal interphalangeal joints may be confused with Bouchard or Heberden nodes, respectively.

years of acute intermittent gout and is evident when the pain-free intercritical periods have disappeared. Gouty flares can continue to occur against this constantly painful background. The intensity of the chronic pain is not nearly as severe as that experienced with the acute flares.

The subcutaneous tophus is the most characteristic lesion of advanced gout. The development of tophaceous deposits of monosodium urate is a function of the duration and severity of hyperuricemia as well as the presence of proteinuria. Subcutaneous tophi may occur anywhere over the body but most commonly in the fingers, wrists, ears, knees, and olecranon bursa, as well as at pressure points under the ulnar aspect of the forearm and Achilles tendon (Fig. 252-2). At this stage, gout can be confused with rheumatoid arthritis (Chapter 243), especially if tophi are misdiagnosed as rheumatoid nodules.

Atypical Gout Presentations

Approximately 5% of patients with gout exhibit the onset of symptoms before age 25 years. Early-onset gout represents a special subset of patients who generally have a genetic component (see Table 252-2), with a more accelerated clinical course requiring more aggressive uric acid lowering therapy.

Women account for no more than 5% of all gout subjects, and most women with gout are postmenopausal. Premenopausal women who have gout usually have a strong genetic predilection or have renal insufficiency and hypertension and are taking thiazide diuretics. Gout in older women may differ from classic gout in its propensity to occur in joints previously damaged by osteoarthritis (Chapter 241), such as the knees or the distal interphalangeal joints with Heberden nodes.

DIAGNOSIS

Hyperuricemia is an essential risk factor for developing gout, but it is not a reliable diagnostic test because many people with elevated serum urate levels will never develop gout. Serum urate levels during an acute flare of gout are also unreliable because they may be suppressed by as much as 1.5 to 2.0 mg/dL from baseline values. The definitive diagnosis of gout is made by polarized compensated microscopy of a synovial fluid aspirate from the affected joint (Fig. 252-3).[7] The presence of intracellular needle-shaped crystals with strong negative birefringence is the diagnostic "gold standard." Similar microscopic results from a tophus aspirate or spontaneously draining fluid also confirm the diagnosis of gout.

However, synovial fluid confirmation is obtained in as few as 10% of patients said to have gout. In most cases, the presumptive diagnosis of gout is based on a pattern of acute joint symptoms coupled with the patient's own medical history or a family history. The characteristic clinical presentation is the rapid onset (over 8 to 12 hours) of severe pain in one or several lower extremity joints (especially the great toe, midfoot, and ankle). Other key features include joint erythema, difficulty walking, resolution by 2 weeks, presence of a tophus, and history of involvement of the first metatarsophalangeal joint. The presumptive diagnosis is given much greater credence if there have been similar previous attacks that spontaneously resolved to a symptom-free state. The patient's medical history also may reveal comorbid conditions frequently associated with gout or the use of medications associated with urate retention.

Radiographic evaluation is not helpful in the early phase of gout except to exclude a fracture. In advanced gout, affected joints may show punched-out periarticular erosions with classic overhanging edges. Ultrasonography can detect monosodium urate crystals layered over articular cartilage in early disease and may be diagnostic (Fig. 252-4). Magnetic resonance imaging is not part of a standard evaluation but will reveal soft tissue and intra-articular tophi long before they become clinically evident.

The differential diagnosis of acute gout includes bacterial infection (Chapter 251), trauma, sarcoidosis, and calcium pyrophosphate arthropathy (pseudogout). Diseases occasionally confused with advanced gout include rheumatoid arthritis (Chapter 243), reactive arthritis (Chapters 244 and 254), and calcium pyrophosphate arthropathy.

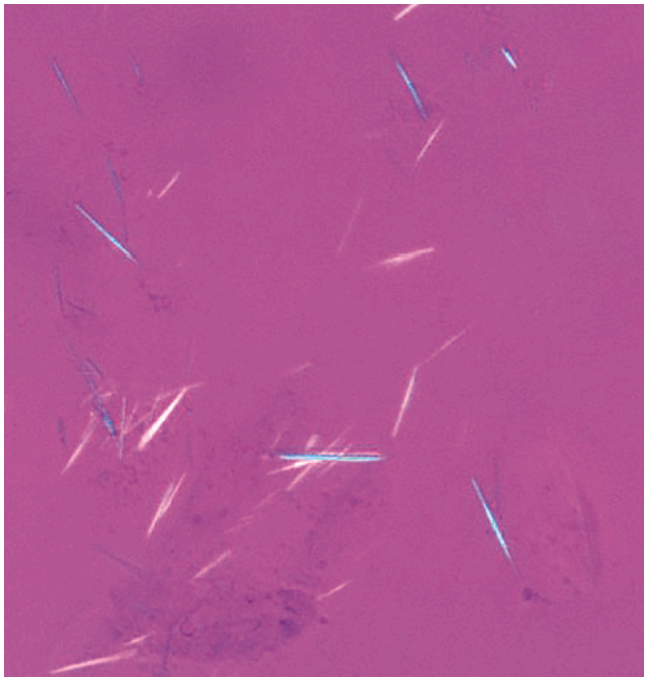

FIGURE 252-3. Urate crystals. Urate crystals seen on polarized compensated microscopy of synovial fluid in a patient with gouty arthritis.

TREATMENT AND PREVENTION

Gouty Flare

The treatment goal for gouty flare is to relieve pain and terminate the flare as quickly as possible. Resting the painful joint and applying ice are generally helpful, but pharmacologic intervention is usually necessary to alter the excruciatingly painful course that may last for several days to more than a week. The therapeutic options include nonsteroidal anti-inflammatory drugs (NSAIDs; Table 26-4),[A1] oral colchicine,[A2] and corticosteroids.[A3] NSAIDs are widely used and generally cause fewer side effects than colchicine[A4] but may be inappropriate for patients who have renal insufficiency or peptic ulcer disease or who are on chronic anticoagulation. Oral colchicine administered as 1.2 mg (two tablets) at the time of flare onset followed in 1 hour by a third 0.6-mg tablet is the recommended dosing for the first 24 hours, followed by 7 to 10 days of once-daily or twice-daily colchicine depending on renal function. This regimen for colchicine in the acute flares situation should not be used in patients chronically taking colchicine for prophylaxis. Corticosteroids can be administered orally (e.g., prednisolone, 30 mg once a day), intramuscularly, or intra-articularly for acute gout symptoms and are valuable options in patients with poor renal function or intolerance to colchicine, and are of similar efficacy and slightly safer than NSAIDs (naproxen or indomethacin) for the treatment of active, acute gout.[A5]

Issues critical to treatment success for a gouty flare are the early initiation of treatment, ensuring adequate dosing of anti-inflammatory therapy, and continuing the treatment until the flare has completely resolved (usually 6 to 10 days). During the acute flare, patients who are already taking urate-lowering therapy should continue the drug without interruption. Patients who have an acute flare can safely be started on urate-lowering therapy during the flare as long as the anti-inflammatory medication is continued for the next several months.

Chronic Urate-Lowering Therapies

The principal goal of treating gout is to lower the serum uric acid below its saturation point so that the process of crystallization will cease and the accumulated urate burden will be gradually diminished. Guidelines[8–10] recommend a "treat-to-target" approach, using a xanthine oxidase inhibitor to reduce serum uric acid levels to less than 6.0 mg/dL in patients with a history of two or more clinical flares or a single flare if the person has chronic kidney disease (Chapter 116)

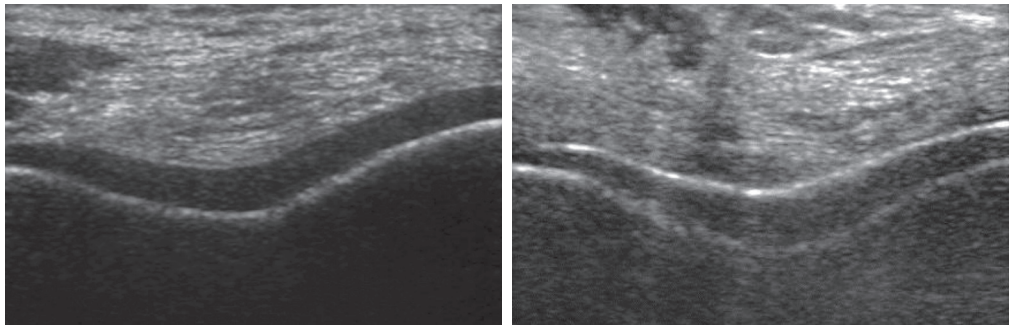

FIGURE 252-4. Double contour sign. Comparison of ultrasonographic appearance of normal (*left*) and gouty (*right*) knee with the probe in the suprapatellar, transverse orientation and the knee in flexion. The normal knee shows soft tissues overlying an anechoic *(black)* layer that represents hyaline cartilage. The single bright stripe represents the bony cortex of the anterior distal femur. The gouty knee demonstrated the "double-contour" sign composed of a layer of crystals covering the hyaline cartilage and the lower bright contour being the femoral cortex.

TABLE 252-3 SPECIFIC AMERICAN COLLEGE OF RHEUMATOLOGY RECOMMENDATIONS ON LIFESTYLE AND DIET FOR GOUTY PATIENTS

Weight loss for obese patients	Avoid: Organ meats High fructose corn syrup–sweetened drinks Alcohol overuse
Healthy overall diet	Limit: Beef, pork, lamb, shellfish Beer
Exercise to achieve fitness	Encourage: Low-fat dairy
Smoking cessation	
Stay well-hydrated	

stage 3 or greater and a serum urate of 9 mg/dL or greater.[A6,A7] An even lower target (<5.0 mg/dL) is recommended for patients with more advanced gout. Allopurinol is the first-line urate-lowering therapy, with the starting dose no greater than 100 mg/day. The dose is gradually escalated by 100 mg daily every 2 to 5 weeks, to a maximum dose of 800 mg daily, while monitoring the serum urate level until the target serum urate is achieved.[A8] In patients who have advanced chronic kidney disease, the initial dose should be 50 mg daily, with incremental dose escalations of 50 mg.

Febuxostat is an alternative urate-lowering therapy and should be used in patients who have failed allopurinol treatment or have demonstrated sensitivity or intolerance to allopurinol.[A9,11] The initial febuxostat dose of 20 to 40 mg daily can be gradually increased to 80 mg daily over the next 2 to 6 weeks of therapy if the serum urate target is not achieved. In gout patients with coexisting cardiovascular disease, overall rates of major cardiovascular events are probably similar in patients treated with febuxostat and allopurinol, although one study showed that overall mortality from any cause was more frequent with febuxostat.[A10,A11]

In patients who have gout but who have not attained the target serum urate despite maximal doses of either allopurinol or febuxostat, a uricosuric agent (e.g., probenecid, up to 2 g daily) can be added to the xanthine oxidase inhibitor. Uricosuric agents should be avoided in patients who have nephrolithiasis or have chronic kidney disease stage 4 or greater. Pegloticase (8 mg by IV infusion every 2 weeks) is an intravenously administered monomethoxypoly (ethylene glycol)-conjugated recombinant uricase that dramatically lowers serum urate levels. It is approved by the FDA for the treatment of gout in patients for whom conventional therapy has been ineffective. Pegloticase can be much more effective and less immunogenic if immunomodulatory co-therapy (methotrexate or mycophenolate mofetil) is given under expert guidance. Although not prescribed specifically for the prevention of gouty flares, empagliflozin significantly reduces uric acid and gout attacks when used in patients with heart failure.[A12]

Before the initiation of any form of urate-lowering therapy, the patient should be placed on anti-inflammatory therapy to prevent or minimize the anticipated increase in flare activity that is associated with starting urate-lowering therapy.[A13] Background anti-inflammatory prophylaxis is in the form of colchicine once or twice daily or low-dose NSAIDs. Anti-inflammatory prophylaxis should be continued for at least 3 to 6 months after initiation of urate lowering therapy and CBC and renal function should be followed during this time.

A heavy emphasis on patient education is important to obtain an optimal treatment outcome.[12] Not only should patients be informed about dietary and other lifestyle changes, such as weight loss,[A14] that will lower their serum uric acid and lessen flares (Table 252-3), but they should also know that their disease is caused by an excessive burden of monosodium urate crystals already present in their joints and soft tissues. This understanding of the disease process underlying gouty arthritis will help shift the focus from symptoms to "urate burden" as the real target of treatment.

CALCIUM PYROPHOSPHATE DIHYDRATE CRYSTAL DEPOSITION DISEASE

DEFINITIONS

The heterogeneous group of clinical conditions associated with calcium pyrophosphate dehydrate crystals are collectively called *calcium pyrophosphate crystal deposition disease*. Within this spectrum is the common radiographic finding of chondrocalcinosis that is frequently asymptomatic. The acute synovitis associated with intra-articular calcium pyrophosphate crystals can closely mimic the findings of gout and is hence referred to as *pseudogout*. The more chronic changes associated with calcium pyrophosphate-induced bone and cartilage destruction is referred to as *pyrophosphate arthropathy*. These conditions are further classified as familial (genetic), metabolic, and sporadic.

EPIDEMIOLOGY

The true prevalence of calcium pyrophosphate crystal deposition disease is unknown, but it is generally thought to be underdiagnosed because of its confusion with other forms of arthritis.[13] Radiographically appearing chondrocalcinosis is clearly an age-related phenomenon. Chondrocalcinosis of the meniscal and articular cartilage of the knee is seen in 4% of people between the ages of 55 and 59 years, in 18% of person ages 80 to 84 years, and in approximately 27% of individuals older than age 85 years.

PATHOBIOLOGY

Clinical calcium pyrophosphate disease is divided into three categories based on the etiology of altered inorganic pyrophosphate metabolism.[14] The categories are hereditary (familial), sporadic (idiopathic), and metabolic. All three types of calcium pyrophosphate disease are associated with the accumulation of extracellular inorganic pyrophosphate around chondrocytes, and extracellular inorganic pyrophosphate is necessary for the formation of calcium pyrophosphate crystals.

Hereditary forms of calcium pyrophosphate crystal deposition disease may be caused by increased transmembrane transport of chondrocytic intracellular inorganic pyrophosphate to its extracellular matrix because of diminished activity of the protective pyrophosphate hydrolases, or because of altered influences of factors that lead to increased extracellular inorganic pyrophosphate, including transforming growth factor-β, bone morphogenic protein-2 and -4, ascorbic acid, and osteopontin.

Transporter mutations are rarely observed in the sporadic form of calcium pyrophosphate disease. Aging chondrocytes in culture produce considerably more inorganic pyrophosphate than do younger chondrocytes, although the exact mechanism for this phenomenon is unclear.

The metabolic diseases that predispose to calcium pyrophosphate crystal deposition disease include hemochromatosis (Chapter 196), hyperparathyroidism (Chapter 227), hypomagnesemia (Chapter 105; as in Gitelman syndrome), and hypophosphatasia (Chapter 105). The result of these metabolic conditions is either increased extracellular inorganic pyrophosphate or alterations that are permissive for the formation of calcium pyrophosphate crystal in the cartilage matrix.

CLINICAL MANIFESTATIONS AND DIAGNOSIS

Calcium pyrophosphate crystal deposition disease presents in a variety of fashions. It is frequently asymptomatic (lanthanic) and recognized only by the appearance of chondrocalcinosis on radiographs.

The most common clinical manifestation accounting for approximately 60% of calcium pyrophosphate disease is a polyarticular arthritis affecting joints not typically involved in primary osteoarthritis (Chapter 241), including the wrists, shoulders, and metacarpophalangeal joints (particularly the second and third metacarpophalangeals). This form of calcium pyrophosphate disease is called *pseudo-osteoarthritis* and may be associated with occasional inflammatory attacks.

The acute monoarticular presentation of calcium phosphate deposition disease is known as pseudogout. The pain and swelling of pseudogout can be similar to that seen in gout. The onset is usually not as abrupt as with gout, and the attacks tend to persist for longer—frequently months. Pseudogout occurs more often in the large joints than in small joints. Calcium pyrophosphate crystal deposition disease also can occasionally present as a chronic polyarticular inflammatory disease that may mimic rheumatoid arthritis (Chapter 243) or polymyalgia rheumatica (Chapter 250).

Calcium pyrophosphate disease is diagnosed by identifying chondrocalcinosis by radiography in a patient with a clinical history suggestive of the disease (Fig. 252-5). Definitive diagnosis, when possible, is made by the finding of calcium pyrophosphate crystals by compensated polarized light microscopic examination of aspirated synovial fluid.

PREVENTION AND TREATMENT

No specific therapies are available for calcium pyrophosphate crystal deposition disease. In patients with metabolic disease–associated calcium pyrophosphate disease (e.g., hyperparathyroidism, hypomagnesemia, phosphotasia) other than hemochromatosis, treatment and control of the metabolic disease can afford some improvement in the arthritis.

For both the acute and chronic forms of calcium pyrophosphate crystal deposition disease, therapy is directed at symptoms.[15,16] Nonsteroidal anti-inflammatory drugs (NSAIDs; Table 26-4) are the mainstay of treatment. Low-dose oral colchicine (e.g., 0.6 mg twice daily) can be used in both acute and chronic settings. Intra-articular corticosteroids are also beneficial for symptomatic disease. The IL-1 inhibitor, anakinra, has been effectively used "off-label" by experts for treating calcium pyrophosphate disease flares.

FIGURE 252-5. Calcium pyrophosphate dihydrate arthropathy of the knee. Radiographic evidence of chondrocalcinosis showing fibrocartilage calcification as thick, linear deposits parallel to and separate from subchondral bone.

APATITE (BASIC CALCIUM PHOSPHATE)-ASSOCIATED ARTHROPATHY

Basic calcium phosphate crystals include several different crystal species, the most common of which is hydroxyapatite. The basic calcium phosphate crystals are unlike monosodium urate or calcium pyrophosphate crystals in that they are not identifiable by polarized microscopy. These very tiny crystals are responsible for several important clinical conditions. Although basic calcium phosphate crystals are found in 50% of osteoarthritic synovial fluids, the incidence and prevalence of the individual apatite-associated clinical manifestations have not been established, especially for the most severe and destructive apatite syndromes such as Milwaukee shoulder and tumoral calcinosis. The prevalence of the most common apatite-associated conditions, calcific periarthritis of the shoulder, is about 3%.

PATHOBIOLOGY

Basic calcium phosphate arthropathy can be idiopathic, hereditary, or related to an underlying condition such as hyperparathyroidism (Chapter 227), hypervitaminosis D (Chapter 199), sarcoidosis (Chapter 83), leukemia (Chapters 168 to 170), multiple myeloma (Chapter 173), or metastatic cancers (Chapters 164 and 227). As with monosodium urate and calcium pyrophosphate crystals, basic calcium phosphate crystals exert their pro-inflammatory effects by being phagocytized by resident synoviocytes and influxing leukocytes. Unlike monosodium urate and calcium pyrophosphate crystals, however, apatite crystals do not act through the *NLRP3* inflammasome. Rather, basic calcium phosphate crystals are dissolved in the acidic phagosome, raise intracellular calcium levels, and then activate the calcium-dependent signaling pathways. The synoviocytes are stimulated by these pathways to increase production of tumor necrosis factor-α and IL-6, and influxing neutrophils are stimulated to increase pro-inflammatory oxygen radicals. The fibroblasts in the joint lining and surrounding soft tissues are stimulated to increase production of many of the matrix metalloproteinases, such as collagenase 1, collagenase 3, and stromelysin 1.

TABLE 252-4 CLINICAL MANIFESTATIONS OF BASIC CALCIUM PHOSPHATE DEPOSITION DISEASE

Osteoarthritis and basic calcium phosphate deposition
Acute inflammatory arthritis
Acute calcific periarthritis
Chronic noninflammatory arthropathy
Diffuse idiopathic skeletal hyperostosis (DISH)
Tumoral calcinosis
Calcifications associated with hypercalcemic states
Hyperparathyroidism
Hypervitaminosis D
Sarcoidosis
Metastatic cancer
Myeloma
Leukemia

CLINICAL MANIFESTATIONS

The clinical manifestations of basic calcium phosphate deposition can be acute or chronic, and their cause can be idiopathic, hereditary, or secondary to other diseases that cause hypercalcemia (Table 252-4). Basic calcium phosphate crystals can be found in 50% of synovial fluids from osteoarthritic knees (Chapter 241). The presence of basic calcium phosphate crystals correlates with more severe radiographic changes secondary to more rapid deterioration in these osteoarthritic knees.[17] Acute inflammatory arthritis associated with basic calcium phosphate deposition is similar in many ways to that of gout and pseudogout and has been referred to as *pseudo-pseudogout*. The patients tend to be younger and usually have evidence of soft tissue basic calcium phosphate deposition elsewhere in the body. Periarticular calcifications are often asymptomatic. However, basic calcium phosphate deposition can cause an acute and severe inflammation of the ligaments, tendons, and bursae surrounding a joint, termed *acute calcific periarthritis*. Depositions frequently occur around the shoulders and hips but can also occur in fingers, toes, wrists, and ankles.

The most destructive basic calcium phosphate–associated arthropathy is Milwaukee shoulder, which is characterized by large, bloody noninflammatory effusions containing basic calcium phosphate crystals with or without calcium pyrophosphate crystals. The process results in the destruction of the rotator cuff, thereby leading to marked instability and glenohumeral cartilage dissolution. This process can also affect knees. As with the acute calcific periarthritis discussed previously, Milwaukee shoulder is observed in women four times more frequently than in men.

Diffuse idiopathic skeletal hyperostosis (DISH) is seen predominately in men and elderly individuals,[18] especially persons with obesity, diabetes, or the metabolic syndrome. The radiographic appearance of this condition is flowing ossifications along the anterolateral aspect of spinal vertebrae, especially in the thoracic spine. DISH is usually asymptomatic, but very large bridging osteophytes can cause stiffness and pain.[19] In the cervical spine, it can even result in dysphagia.[20]

Idiopathic tumoral calcinosis is rare but most prevalent in young Black patients, who develop large irregular calcifying masses in the soft tissue surrounding the shoulders, hips, and elbows. Some cases show a familial occurrence and medical conditions associated with hyperphosphatemia (Chapter 105).

TREATMENT AND PREVENTION

The treatment of most basic calcium phosphate–associated syndromes is conservative.[21] In acute inflammatory arthritis and periarthritis, low-dose oral colchicine (e.g., 0.6 mg twice daily) and NSAIDs (Table 26-4) are the mainstay of a symptomatic therapy. The persistent large effusion seen in Milwaukee shoulder should be serially aspirated to decrease intracapsular pressure. The added effectiveness of corticosteroid injections in this setting is unproved. The calcinosis associated with abnormal calcium and phosphate metabolism is best managed by treating the underlying metabolic process.

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For the General References and other additional features, please visit Elsevier eBooks+ at https://ebooks.health.elsevier.com.

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253 FIBROMYALGIA

DANIEL J. CLAUW

DEFINITION

Fibromyalgia is the term that describes chronic widespread musculoskeletal pain, for which no alternative cause can be identified. If fatigue rather than pain is the presenting complaint, individuals are often diagnosed with chronic fatigue syndrome.[1,2] Gastroenterologists often see the exact same patients and focus on their gastroenterologic complaints, and often use the terms functional gastrointestinal disorder, irritable bowel syndrome, nonulcer dyspepsia, noncardiac chest pain, or esophageal dysmotility to explain the patient's symptoms (Chapter 123). Neurologists see these patients for their headaches (Chapter 367) or unexplained facial pain, urologists for pelvic pain (Chapter 219) and urinary symptoms (and use labels such as interstitial cystitis, chronic prostatitis [Chapter 114], vulvodynia, and vulvar vestibulitis), dentists for temporomandibular disorders, and so on. Although many individuals will have only one "idiopathic" pain syndrome over the course of their lifetime, more often, individuals with one of these entities, as well as their family members, are likely to have several of these conditions. Newer terms to describe this group of conditions include chronic overlapping pain conditions or nociplastic pain.

EPIDEMIOLOGY

Chronic widespread pain is typically operationalized as pain above and below the waist, involving the left and right sides of the body, and also involving the axial skeleton. Population-based studies of chronic widespread pain suggest that roughly 4 to 12% of the population has this symptom at any given point in time.[3] Chronic regional pain is found in 20 to 25% of the population. Both chronic widespread and regional pain occur about 1.5 times more often in women than in men. These findings are very similar in different countries, ethnicities, and cultures.

Various types of environmental stressors, including but not limited to psychological factors, most likely trigger the development of fibromyalgia (Table 253-1). Fibromyalgia and related disorders are found at much higher than expected rates in individuals who have experienced specific infections (e.g., Epstein-Barr virus, Lyme disease, Q fever, viral hepatitis), and it is also likely that the long haul post-coronavirus disease (COVID) 2019 syndrome has significant nociplastic contributions.[4]

TABLE 253-1 STRESSORS CAPABLE OF TRIGGERING FIBROMYALGIA AND RELATED CONDITIONS

- Peripheral pain syndromes
- Infections (e.g., COVID, parvovirus, EBV, Lyme disease, Q fever, but not common upper respiratory infections)
- Physical trauma (automobile accidents)
- Psychological stress/distress
- Hormonal alterations (e.g., hypothyroidism)
- Drugs
- Vaccines
- Certain catastrophic events (war, but not natural disasters)

COVID = coronavirus disease 2019; EBV = Epstein-Barr virus.

Fibromyalgia is also more common after trauma (e.g., motor vehicle accidents) and wartime military service. It is also likely that part of the reason these different stressors can seemingly lead to worsening of fibromyalgia or fibromyalgia symptoms is because of how these stressors affect activity level, sleep, or overall distress, any of which then can lead to worsening of pain and other symptoms.

Secondary fibromyalgia is frequently found as a comorbid condition in other chronic pain conditions such as osteoarthritis and autoimmune rheumatic diseases. As many as 25% of patients correctly diagnosed with generalized inflammatory disorders such as systemic lupus erythematosus, rheumatoid arthritis, and ankylosing spondylitis will also fulfill diagnostic criteria for fibromyalgia. However, in clinical practice this co-expression often goes unrecognized, especially when the fibromyalgia develops after the autoimmune disorder or regional pain syndrome. In this setting when comorbid fibromyalgia goes unrecognized, patients are often unnecessarily treated more aggressively with potentially toxic biologics and immunosuppressive agents.

The "primary" form of fibromyalgia is also associated with serious comorbid conditions, with early life and ongoing stressors. Many if not most such patients have a lifetime history of a psychiatric disorder such as depression or anxiety (Chapter 362). There is typically more psychiatric and psychological comorbidity noted in individuals who are refractory to treatment. The bidirectional relationship between fibromyalgia and psychiatric conditions is likely due at least in part to common triggers to both sets of conditions, as well as shared pathophysiology. Potentially modifiable risk factors for developing fibromyalgia or worsening its course include poor sleep, obesity, physical inactivity, and job or life dissatisfaction. Cognitive factors such as catastrophizing (irrational thinking that the pain is much worse or more serious than it actually is) or fear of movement have been found to be poor prognostic factors in fibromyalgia and other chronic pain states.

PATHOBIOLOGY

Contemporary terms used to describe conditions such as fibromyalgia, irritable bowel syndrome, temporomandibular disorders, chronic fatigue syndrome, vulvodynia, and many other entities include "centralized pain" or "central sensitization" to imply that the central nervous system (CNS) is playing a prominent role in amplifying or causing the pain in most individuals with these syndromes (Table 253-2). Although peripheral nociceptive input might be involved for some such pain, CNS factors are probably amplifying it, thereby leading to other associated symptoms such as fatigue, memory problems, and disturbances of sleep and mood.[5] Many of these findings also have been noted in chronic fatigue syndrome, but the various pathophysiologic theories of chronic fatigue syndrome vary widely and are the source of considerable contention.

Genetic Factors

The strong familial predisposition to fibromyalgia and other chronic pain conditions has led many to study specific genetic polymorphisms that may be associated with a higher risk of developing fibromyalgia. First, candidate gene studies showed that genetic findings such as the serotonin 5-HT2A receptor polymorphism T/T phenotype, serotonin transporter, dopamine 4 receptor, and catecholamine *o*-methyl transferase (COMT) polymorphisms all were noted in higher frequency in fibromyalgia patients than in controls.

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253 FIBROMYALGIA

DANIEL J. CLAUW

DEFINITION

Fibromyalgia is the term that describes chronic widespread musculoskeletal pain, for which no alternative cause can be identified. If fatigue rather than pain is the presenting complaint, individuals are often diagnosed with chronic fatigue syndrome.[1,2] Gastroenterologists often see the exact same patients and focus on their gastroenterologic complaints, and often use the terms functional gastrointestinal disorder, irritable bowel syndrome, nonulcer dyspepsia, noncardiac chest pain, or esophageal dysmotility to explain the patient's symptoms (Chapter 123). Neurologists see these patients for their headaches (Chapter 367) or unexplained facial pain, urologists for pelvic pain (Chapter 219) and urinary symptoms (and use labels such as interstitial cystitis, chronic prostatitis [Chapter 114], vulvodynia, and vulvar vestibulitis), dentists for temporomandibular disorders, and so on. Although many individuals will have only one "idiopathic" pain syndrome over the course of their lifetime, more often, individuals with one of these entities, as well as their family members, are likely to have several of these conditions. Newer terms to describe this group of conditions include chronic overlapping pain conditions or nociplastic pain.

EPIDEMIOLOGY

Chronic widespread pain is typically operationalized as pain above and below the waist, involving the left and right sides of the body, and also involving the axial skeleton. Population-based studies of chronic widespread pain suggest that roughly 4 to 12% of the population has this symptom at any given point in time.[3] Chronic regional pain is found in 20 to 25% of the population. Both chronic widespread and regional pain occur about 1.5 times more often in women than in men. These findings are very similar in different countries, ethnicities, and cultures.

Various types of environmental stressors, including but not limited to psychological factors, most likely trigger the development of fibromyalgia (Table 253-1). Fibromyalgia and related disorders are found at much higher than expected rates in individuals who have experienced specific infections (e.g., Epstein-Barr virus, Lyme disease, Q fever, viral hepatitis), and it is also likely that the long haul post-coronavirus disease (COVID) 2019 syndrome has significant nociplastic contributions.[4]

TABLE 253-1 STRESSORS CAPABLE OF TRIGGERING FIBROMYALGIA AND RELATED CONDITIONS

- Peripheral pain syndromes
- Infections (e.g., COVID, parvovirus, EBV, Lyme disease, Q fever, but not common upper respiratory infections)
- Physical trauma (automobile accidents)
- Psychological stress/distress
- Hormonal alterations (e.g., hypothyroidism)
- Drugs
- Vaccines
- Certain catastrophic events (war, but not natural disasters)

COVID = coronavirus disease 2019; EBV = Epstein-Barr virus.

Fibromyalgia is also more common after trauma (e.g., motor vehicle accidents) and wartime military service. It is also likely that part of the reason these different stressors can seemingly lead to worsening of fibromyalgia or fibromyalgia symptoms is because of how these stressors affect activity level, sleep, or overall distress, any of which then can lead to worsening of pain and other symptoms.

Secondary fibromyalgia is frequently found as a comorbid condition in other chronic pain conditions such as osteoarthritis and autoimmune rheumatic diseases. As many as 25% of patients correctly diagnosed with generalized inflammatory disorders such as systemic lupus erythematosus, rheumatoid arthritis, and ankylosing spondylitis will also fulfill diagnostic criteria for fibromyalgia. However, in clinical practice this co-expression often goes unrecognized, especially when the fibromyalgia develops after the autoimmune disorder or regional pain syndrome. In this setting when comorbid fibromyalgia goes unrecognized, patients are often unnecessarily treated more aggressively with potentially toxic biologics and immunosuppressive agents.

The "primary" form of fibromyalgia is also associated with serious comorbid conditions, with early life and ongoing stressors. Many if not most such patients have a lifetime history of a psychiatric disorder such as depression or anxiety (Chapter 362). There is typically more psychiatric and psychological comorbidity noted in individuals who are refractory to treatment. The bidirectional relationship between fibromyalgia and psychiatric conditions is likely due at least in part to common triggers to both sets of conditions, as well as shared pathophysiology. Potentially modifiable risk factors for developing fibromyalgia or worsening its course include poor sleep, obesity, physical inactivity, and job or life dissatisfaction. Cognitive factors such as catastrophizing (irrational thinking that the pain is much worse or more serious than it actually is) or fear of movement have been found to be poor prognostic factors in fibromyalgia and other chronic pain states.

PATHOBIOLOGY

Contemporary terms used to describe conditions such as fibromyalgia, irritable bowel syndrome, temporomandibular disorders, chronic fatigue syndrome, vulvodynia, and many other entities include "centralized pain" or "central sensitization" to imply that the central nervous system (CNS) is playing a prominent role in amplifying or causing the pain in most individuals with these syndromes (Table 253-2). Although peripheral nociceptive input might be involved for some such pain, CNS factors are probably amplifying it, thereby leading to other associated symptoms such as fatigue, memory problems, and disturbances of sleep and mood.[5] Many of these findings also have been noted in chronic fatigue syndrome, but the various pathophysiologic theories of chronic fatigue syndrome vary widely and are the source of considerable contention.

Genetic Factors

The strong familial predisposition to fibromyalgia and other chronic pain conditions has led many to study specific genetic polymorphisms that may be associated with a higher risk of developing fibromyalgia. First, candidate gene studies showed that genetic findings such as the serotonin 5-HT2A receptor polymorphism T/T phenotype, serotonin transporter, dopamine 4 receptor, and catecholamine *o*-methyl transferase (COMT) polymorphisms all were noted in higher frequency in fibromyalgia patients than in controls.

ABSTRACT

Fibromyalgia and chronic fatigue syndrome are two of many nociplastic pain disorders characterized by widespread body pain and comorbid symptoms, such as fatigue, sleep, and memory problems. Whereas the diagnosis and label of fibromyalgia has been controversial in the medical community for some time, it is now among the best studied pain conditions, with strong evidence of prominent involvement of the central nervous system (CNS), and best treated with therapies aimed at the CNS. Treatment of these conditions should include patient education, as well as a combination of nonopioid medications, behavioral therapies, lifestyle changes, and integrative treatments, as appropriate.

KEYWORDS

fibromyalgia
nociplastic pain
centralized pain
central sensitization
chronic fatigue syndrome
myofascial pain

TABLE 253-2 MECHANISTIC CHARACTERIZATION OF PAIN

	NOCICEPTIVE	NEUROPATHIC	CENTRALIZED/NOCIPLASTIC
Cause	Inflammation or damage	Nerve damage or entrapment	CNS or systemic problem
Clinical features	Pain is well localized, consistent effect of activity on pain	Follows distribution of peripheral nerves (i.e., dermatome or stocking/glove), episodic, lancinating, numbness, tingling	Pain is widespread and accompanied by fatigue, sleep, memory and/or mood difficulties, as well as history of previous pain elsewhere in body
Screening tools		PainDETECT	Body map or fibromyalgia survey
Treatment	NSAIDs, injections, surgery, opioids	Local treatments aimed at nerve (surgery, injections, topical) or CNS-acting drugs	CNS-acting drugs, nonpharmacologic therapies
Classic examples	Osteoarthritis Autoimmune disorders Cancer pain	Diabetic painful neuropathy Post-herpetic neuralgia Sciatica, carpal tunnel syndrome	Fibromyalgia Functional GI disorders Temporomandibular disorder Tension headache Interstitial cystitis, bladder pain syndrome

Variable degrees of any mechanism can contribute in any disease.
CNS = central nervous system; GI = gastrointestinal; NSAIDs = nonsteroidal anti-inflammatory drugs.

Subsequent studies confirmed some of these associations, whereas others did not. Subsequent larger genome-wide linkage and candidate gene studies identified other putative targets. The linkage studies confirmed the strong genetic contribution to fibromyalgia and suggested linkage of fibromyalgia to the chromosome 17p11.2-q11.2 region. The large candidate gene study identified significant differences in allele frequencies between cases and controls that were observed for three genes: *GABRB3, TAAR1,* and *GBP1*. In light of the fact that classic genetic studies have not yet identified strong, reproducible polymorphisms or haplotypes associated with fibromyalgia, and because there is clear evidence of environmental factors such as stress playing a prominent role in the pathogenesis, other groups have postulated that epigenetic findings might be important in fibromyalgia.

Disturbances in Pain and Sensory Processing

The pathophysiologic hallmark of fibromyalgia is augmented central pain processing. Individuals with fibromyalgia are more tender everywhere in the body, not just in the 18 regions originally considered to be "tender points." Several potential mechanisms have been experimentally found to be potentially responsible for pain amplification in fibromyalgia, including a decrease in the activity of descending analgesic pathways, and a diffuse increase in the processing of all sensory stimuli (not just pain). Affected individuals have a CNS–mediated problem with augmented pain or sensory processing that is contributing to the pain and other somatic sensitivities the individual is experiencing, rather than simply a nociceptive focus confined to the region of the body where pain is currently being experienced.

Brain Imaging Studies

Functional, chemical, and structural brain neuroimaging studies have provided the best "objective" evidence that the pain of fibromyalgia and related pain amplification syndrome is "real." Functional MRI (fMRI) studies have demonstrated that in individuals with fibromyalgia the application of mild pressure or heat stimulus, which other individuals would sense as touch rather than pain, is experienced as pain. Individuals with or without fibromyalgia utilize similar brain activation patterns and brain areas involved in pain processing. The insula is a brain region that is consistently hyperactive and is likely to play a key pathogenic role in fibromyalgia and related conditions. This region has been noted to play a critical role in sensory integration, with the posterior insula serving a purer sensory role, and the anterior insula being associated with the emotional processing of sensations.

Patients with fibromyalgia have increased connectivity between brain regions involved in increasing pain transmission and neural networks not normally involved in pain. During a painful stimulus, connectivity is decreased between key antinociceptive regions and a region identified as a potential source of dysfunctional pain inhibition in fibromyalgia. Quantitative sensory testing studies have demonstrated that fibromyalgia patients are more sensitive to a number of sensory stimuli other than pain, and that machine learning paradigms using functional neuroimaging data can accurately distinguish fibromyalgia patients from individuals without fibromyalgia with over 90% accuracy. Some of these functional connectivity findings related to the insula and default mode network may be present early in life before children develop pain. Although conditions such as fibromyalgia have generally not been thought to have an immune basis, low-grade inflammation may exist in both the periphery and perhaps even the central nervous system.

Imaging techniques also have been used to identify the neurotransmitter abnormalities that may be "driving" the pain amplification seen in fibromyalgia and other chronic pain disorders. Decreased *mu* opioid receptor availability (possibly due to increased release of endogenous *mu* opioids) has been reported in fibromyalgia. This finding, as well as previous studies showing increases in endogenous opioids in the cerebrospinal fluid of fibromyalgia patients, has been suggested as evidence of why opioid analgesics appear not to be efficacious in fibromyalgia.

Using proton spectroscopy to probe other neurotransmitters, fibromyalgia patients have been shown to have increases in brain concentrations of the body's major excitatory neurotransmitter, glutamate, in pain processing regions such as the insula. Drugs such as pregabalin and gabapentin are likely working in part in fibromyalgia by reducing glutamatergic activity. Individuals who have fibromyalgia and who have the highest pretreatment levels of glutamate in the posterior insula are most likely to respond to pregabalin. When pregabalin leads to improvement in symptoms in these individuals, functional MRI normalizes, thereby suggesting that this neurotransmitter is playing a critical role in the pathogenesis of fibromyalgia at least in some individuals. These studies also help clarify why no single class of CNS analgesic is likely to be effective in every patient with pain of CNS origin.

The Role of Peripheral Factors

Peripheral factors also play an important role in the pathogenesis and treatment of many individuals with fibromyalgia. For example, some elements of the processes of central sensitization can be worsened or driven by ongoing nociceptive input. Many individuals who have fibromyalgia also have comorbid conditions that cause ongoing peripheral nociceptive input (e.g., myofascial pain, osteoarthritis, obesity). In fact, one of the major areas of study needed into these conditions is to try to differentiate which individuals with these phenomena are being driven from the CNS (top down) and which may be driven by ongoing peripheral nociceptive input (bottom up).

CLINICAL MANIFESTATIONS

The majority of patients with fibromyalgia develop their pain symptoms in multiple body regions early in life, frequently beginning in childhood or adolescence. Individuals who eventually progress to develop fibromyalgia are more likely to experience headaches, dysmenorrhea, temporomandibular disorders, chronic fatigue syndrome, myofascial pain, irritable bowel syndrome and other functional gastrointestinal disorders, interstitial cystitis/painful bladder syndrome, endometriosis, and other regional pain syndromes (particularly with back and neck pain). In many cases, what may appear to a health care provider to be an entirely new type of acute or subacute pain is in fact only another region of the body involved with pain. The concept is evolving among pain specialists that these "centralized" pain disorders actually represent a single lifelong disease with a spectrum of symptoms in different regions of the body over time.[6]

Other CNS-mediated symptoms that are seen commonly in fibromyalgia and related conditions include fatigue and sleep and memory issues. Subsets of individuals with any chronic pain condition (e.g., low back pain, osteoarthritis, autoimmune disorders, sickle cell disease, etc.) also have the same phenotypic features and underlying mechanisms as those seen in fibromyalgia. Many pain experts now think that much chronic pain itself is a neural disease and that many of the underlying mechanisms operative in these heretofore considered idiopathic or functional pain syndromes may be similar no matter whether that pain is present throughout the body (e.g., in fibromyalgia) or localized to the low back, the bowel, or the bladder.

DIAGNOSIS

A careful musculoskeletal history and examination remains the most important diagnostic test for individuals with chronic pain. Current diagnostic criteria for fibromyalgia (Table 253-3 and Fig. 253-1)[7] are simple to use and acknowledge the nonpain symptoms of fibromyalgia and centralized pain. Finally, in addition to these criteria being used with a cut point to diagnose someone with fibromyalgia, they also serve as a good measure of the presence and severity of fibromyalgia, or "fibromyalgianess." For example, in individuals with conditions such as rheumatoid arthritis (Chapter 243), low back pain (Chapter 26), or osteoarthritis (Chapter 241), an individual's fibromyalgia score is typically more predictive of pain and disability than are objective measures of the activity of these diseases, such as inflammation or joint damage.

TABLE 253-3 DEFINITION OF FIBROMYALGIA

Requires all of the following:
- Pain in at least 4 of 5 regions*
- Symptoms at a similar level for ≥3 months
- Widespread pain index† ≥7 and symptom severity scale score‡ ≥5 OR widespread pain index 4-6 and symptom severity scale score ≥9

*Five regions are: neck, upper back, lower back; left shoulder girdle, upper arm, lower arm; right shoulder girdle, upper arm, lower arm; left buttock/hip, upper leg, lower leg; and right buttock/hip, upper leg, lower leg.

†Number of pain locations among 19 possible locations: left shoulder girdle, right shoulder girdle, left upper arm, right upper arm, left lower arm, right lower arm, left hip (buttock), right hip (buttock), left upper leg, right upper leg, left lower leg, right lower leg, left jaw, right jaw, chest, abdomen, neck, upper back, lower back.

‡See Fig. 253-1.

Wolfe F, Clauw DJ, Fitzcharles MA, et al. 2016 Revisions to the 2010/2011 fibromyalgia diagnostic criteria. *Semin Arthritis Rheum*. 2016;46:319-329.

The pain of fibromyalgia is typically diffuse or multifocal, is difficult to localize, often waxes and wanes, and is frequently migratory in nature. These characteristics of centralized pain are quite different from nociceptive pain, in which both the location and severity of pain are typically more constant.[8] Patients may complain of discomfort when they are touched or when wearing tight clothing, and they may experience dysesthesias or paresthesias that accompany the pain, as is seen with neuropathic pain.

The physical examination is generally unremarkable in individuals with fibromyalgia, but it is helpful to assess for diffuse tenderness rather than on specific tender points. For example, individuals with fibromyalgia exhibit unusual sensitivity to the inflation of a blood pressure cuff. Assessing the pain thresholds in the hands and arms of any chronic pain patient can provide valuable diagnostic information, with diffuse tenderness over many areas being the expected finding.

Groups of individuals with conditions (e.g., fibromyalgia, chronic fatigue syndrome, irritable bowel syndrome, headache, and temporomandibular disorders) typically display disturbances in pain and sensory processing, including increased pain to normally painful stimuli or pain to normally nonpainful stimuli. This predilection can be identified in the patient's history (e.g., by asking about sensitivity to bright lights, odors, drugs) as well as by using quantitative sensory testing or functional neuroimaging. It is critical that clinicians seeing patients with chronic pain evaluate individuals for the presence of this nociplastic phenotype because it can dramatically affect which treatments will or will not work for a given individual with chronic pain.

Diagnostic Evaluation

No laboratory or imaging tests can distinguish the pain of fibromyalgia. The duration of time the patient has had symptoms should guide the intensity of the diagnostic evaluation. If the patient's symptoms have persisted for several years, minimal testing is required, whereas a more aggressive strategy should be used for acute or subacute onset of symptoms. Basic testing can be limited to complete blood count and routine serum chemistries, along with thyroid-stimulating hormone (TSH) and erythrocyte sedimentation rate (ESR). Serologic studies such as assays for antinuclear antibodies (ANAs) and rheumatoid factor are generally not needed unless clinical features are not characteristic of fibromyalgia or abnormalities are found on physical examination.

Differential Diagnosis

Aside from the many comorbid conditions associated with fibromyalgia, it may present similarly to a number of disorders or concurrently with other disorders that may confuse the diagnosis (Table 253-4). Hypothyroidism (Chapter 207) and polymyalgia rheumatica (Chapter 250) can be differentiated from fibromyalgia by laboratory testing for thyroid-stimulating hormone and the erythrocyte sedimentation rate. Sleep apnea and hepatitis C also simulate fibromyalgia and tend to present more often in men than women.

Part I. Level of symptom severity over the past week:

Fatigue score (0-3) ___ Waking unrefreshed score (0-3) ___ Cognitive symptoms score (0-3) ___

where 0 = no problem; 1 = slight or mild problems, generally mild or intermittent; 2 = moderate, considerable problems, often present and/or at a moderate level; 3 = severe: pervasive, continuous, life-disturbing problems

Total (0-9): _____

Part II. Other symptoms experienced over the past six months:

Headaches (0-1) ___

Pain or cramps in lower abdomen (0-1) ___

Depression (0-1) ___ **Total (0-3): _____**

Final symptom severity scale score is sum of Part I and Part II scores: Total (0-12): _____

FIGURE 253-1. Symptom severity scale score for fibromyalgia. (Wolfe F, Clauw DJ, Fitzcharles MA, et al. 2016 Revisions to the 2010/2011 fibromyalgia diagnostic criteria. *Semin Arthritis Rheum*. 2016;46:319-329.)

TABLE 253-4 CONDITIONS THAT SIMULATE FIBROMYALGIA

COMMON
Hypothyroidism (Chapter 207)
Polymyalgia rheumatica (Chapter 250)
Early in course of autoimmune disorders (e.g., rheumatoid arthritis [Chapter 243] or systemic lupus erythematosus [Chapter 245])
Sjögren syndrome (Chapter 247)
LESS COMMON
Hepatitis C (Chapter 135)
Sleep apnea (Chapter 374)
Chiari malformation (Chapter 385)
Celiac sprue (Chapter 126)

TABLE 253-5 THERAPIES

PHARMACOLOGIC THERAPIES
• **Strong evidence:** tricyclics (amitriptyline, cyclobenzaprine); dual-reuptake inhibitors (SNRI—venlafaxine, duloxetine, milnacipran); alpha-2-delta ligands (pregabalin, gabapentin)
• **Modest evidence:** tramadol; selective serotonin reuptake inhibitors (SSRIs); low-dose naltrexone; cannabinoids; gamma hydroxybutyrate (GHB)
• **Weak evidence:** growth hormone, 5-hydroxytryptamine, tropisetron, S-adenosyl-L-methionine (SAMe)
• **Not shown to be effective:** opioids, NSAIDs, corticosteroids, benzodiazepine and nonbenzodiazepine hypnotics, melatonin, guaifenesin, dehydroepiandrosterone
NONPHARMACOLOGIC THERAPIES
• **Strong evidence:** cardiovascular exercise, cognitive behavior therapy, patient education, multidisciplinary therapy
• **Modest evidence:** strength training, Tai Chi, yoga, mindfulness, hypnotherapy, biofeedback, balneotherapy
• **Weak evidence:** acupuncture, chiropractic, manual and massage therapy, electrotherapy, ultrasound
• **No evidence:** tender (trigger) point injections, flexibility exercise

NSAID = nonsteroidal anti-inflammatory drug; SNRI = serotonin-norepinephrine reuptake inhibitor; SSRI = selective serotonin reuptake inhibitor.

If the individual is tender only over the interphalangeal joints but not the other regions, and especially if there are additional inflammatory signs (e.g., swelling, erythema, warmth) associated with the tenderness, there should be more concern about a systemic autoimmune rheumatologic disorder. If tenderness is confined to only the bones, one might suspect a metabolic bone disease (Chapter 224) or condition causing periostitis (e.g., hyperparathyroidism; Chapter 227).

Affirming the Diagnosis

Having excluded other potential disorders in the differential diagnosis of the patient's pain, a somewhat important step in the management of fibromyalgia is asserting the diagnosis. Despite concerns that being "labeled" with fibromyalgia may in general cause more harm than good, nearly all existing studies suggest otherwise. The diagnosis of fibromyalgia is often a source of relief for the patient and leads to decreased health care utilization because of a reduction in referrals and if diagnostic testing to look for the cause of the pain.

TREATMENT

Similar types of therapies are efficacious for all nociceptive pain conditions, including both pharmacologic (e.g., tricyclic compounds, serotonin norepinephrine reuptake inhibitors, and gabapentinoids) and nonpharmacologic treatments (e.g., education, exercise, cognitive behavioral therapy). Conversely, individuals with these conditions typically do not respond to therapies that are effective when pain is caused by injury or inflammatory disorders of tissues (e.g., nonsteroidal anti-inflammatory drugs [NSAIDs], opioids, local injections, or surgical procedures).

General Approach

Individuals who are diagnosed with fibromyalgia should receive basic education regarding this disorder.[9] Clinicians can provide this education in the context of their practice (e.g., with nurse educators or other allied health professionals) or electronically using websites and videos. This education should stress the importance of the patients' active role in their own management. Patients should be informed that some of the most effective therapies are nondrug interventions such as exercise, improving sleep, and reducing stress. Although recent treatment guidelines favor the use of nonpharmacologic versus pharmacologic therapies,[A1,A2] most patients will need some coordinated combination of pharmacologic and nonpharmacologic therapies (Table 253-5) to achieve meaningful improvement in symptoms and function.[10] In addition, pragmatic factors in routine practice (lack of availability or reimbursement, patient is unwilling to try these therapies until their symptoms are somewhat better controlled) sometimes make it impractical to rely primarily on nonpharmacologic treatment.[11]

Nonpharmacologic Therapies

Patients should be strongly encouraged to engage in nonpharmacologic therapies, especially exercise and mind-body practices. The best-studied nonpharmacologic therapies in fibromyalgia are cognitive behavioral therapy and exercise, both of which are efficacious.[A3,A4] These treatments can produce sustained (e.g., longer than 1 year) improvements, especially when an individual complies with the therapy.

For exercise, it is important to "start low, go slow." Exercise of different types (aerobic, stretching, strengthening) has been particularly well studied as a treatment of both chronic fatigue syndrome and fibromyalgia and has perhaps the strongest evidence base of any therapy. Exercise typically improves fatigue, pain, and function for these conditions. In chronic fatigue syndrome, graded exercise therapy has been similarly shown to be helpful. Many fibromyalgia, chronic fatigue syndrome, and other chronic pain patients tend to be sedentary. In these individuals it might be more helpful to first focus on becoming more "active" rather than "exercising."

Among the different types of cognitive behavioral therapy, increased attention has focused on using behavioral measures to treat the sleep disorders (www.painguide.com), which play an important role in pain transmission. Self-help and adding emotional disclosure to standard cognitive behavioral therapy may be of benefit.[A5]

A number of other nonpharmacologic, complementary, and integrative therapies (e.g., mindfulness, Tai Chi, yoga, biofeedback, chiropractic manipulation, and acupuncture [Chapter 30]) may help patients assert a greater sense of control over their illness. Patients should be encouraged to choose the nonpharmacologic therapy that best resonates with their beliefs and is locally accessible.

Pharmacologic Therapy

A number of classes of drugs that can be of some benefit in fibromyalgia. However, as in other chronic pain conditions, drugs only work well in a subset of patients, and the overall effect size of any of these therapies for any type of chronic pain is small to modest at best.[12]

Tricyclic Agents

Low doses of tricyclic antidepressants—particularly amitriptyline,[A6] cyclobenzaprine, and mirtazapine[A7] (Table 362-5)—can help diminish symptoms of pain, poor sleep, and fatigue associated with fibromyalgia. Tolerability can be improved by starting with a very low dose (e.g., 10 mg of amitriptyline or 5 mg of cyclobenzaprine), giving the dose a few hours before bedtime, and then very slowly escalating the dose. Very-low-dose cyclobenzaprine is quite effective in a subset of fibromyalgia patients with the same sleep pattern.

Serotonin and Norepinephrine Reuptake Inhibitors

Selective serotonin reuptake inhibitors (SSRIs) such as fluoxetine, citalopram, and paroxetine (Table 362-5) can be useful, although the newer "highly selective" serotonin reuptake inhibitors (e.g., citalopram) appear to be less efficacious than the older SSRIs, which have some noradrenergic activity at higher doses.

Dual receptor serotonin-norepinephrine and norepinephrine-serotonin reuptake inhibitors (SNRIs and NSRIs; see Table 362-5) such as venlafaxine are often more effective than pure serotonergic drugs.[A8] Duloxetine[A9] and milnacipran are approved in the United States for the treatment of fibromyalgia, with studies generally noting modest improvement in clinical features such as pain, physical functioning, fatigue, and degree of reported physical impairment. For both compounds these effects appear to be largely unrelated to their effect on mood, thereby suggesting that the analgesic and other positive effects of this class of drugs in fibromyalgia are not simply due to their antidepressant effects. The maximum approved dose of duloxetine is 60 mg per day, but it was studied in trials at doses up to 120 mg and shown to be safe. Likewise, the initial dose of milnacipran is 100 mg, but some patients benefit from increasing the dose to as high as 200 mg. Hypertension is more likely to be a problem with milnacipran, because it appears to be more noradrenergic; for these same reasons it might

be slightly more likely to help with symptoms such as fatigue. Esreboxetine, a selective norepinephrine reuptake inhibitor, is also efficacious in fibromyalgia, but this drug is not approved for use at this time.

Anticonvulsants

Pregabalin is effective for pain, sleep disturbances, and fatigue in fibromyalgia.[A10] Gabapentin has similar efficacy and adverse effects profile in fibromyalgia.[A11] The tolerability of these drugs can be enhanced by starting at a low dose and giving either two thirds of the dose or the entire dose at bedtime. The maximally approved dose of pregabalin is 450 mg, but in trials it was studied at doses as high as 600 mg and shown to be safe and efficacious. For most patients, the gabapentin dose needed for analgesia is often 1800 to 2400 mg/day. Two other drugs that likely work similarly to the gabapentinoids by counteracting the effects of increased glutamatergic activity are memantine and ketamine, both of which have some evidence of efficacy. Another antiepileptic compound, clonazepam, has efficacy for treating temporomandibular disorder and associated jaw pain and is useful in the treatment of restless leg syndrome (Chapter 374) and thus may be of value in subsets of fibromyalgia patients with these comorbid conditions. In general, though, the risks associated with chronic benzodiazepine use likely outweigh the potential benefit.

Other CNS-Acting Drugs

Nonbenzodiazepine hypnotics, such as zopiclone and zolpidem can improve the sleep and, possibly, fatigue in fibromyalgia patients, but they have no significant effects on pain. Gamma-hydroxybutyrate (also known as sodium oxybate), a precursor of GABA with powerful sedative properties, can improve fatigue, sleep, and pain in patients with fibromyalgia. However, this drug is a scheduled substance in the United States because of its abuse potential and is not approved by the FDA because of safety concerns.

Many population-based studies show that the consumption of one drink per day of alcohol, which is a GABA agonist, may be protective against fibromyalgia. Not surprisingly, however, higher amounts of alcohol have adverse effects on pain. Cannabinoids are modestly efficacious for sleep and perhaps pain, but side effects are common.[A12]

Classic Analgesics

No adequate randomized controlled clinical trials have tested the efficacy of opioids for the pain of fibromyalgia, but they do not appear to be effective. In fact, imaging studies of patients with fibromyalgia suggest that the native state of fibromyalgia may be akin to opioid-induced hyperalgesia. Tramadol, a compound that has some opioid activity (weak μ-agonist activity), combined with serotonin/norepinephrine reuptake inhibition appears to be somewhat efficacious in the management of fibromyalgia, as both a single drug and in fixed-dose combination with acetaminophen.

A large number of fibromyalgia patients use nonsteroidal anti-inflammatory drugs (NSAIDs) and acetaminophen, but analgesics are not effective for fibromyalgia when used as single agents.[A13] However, the combination of celecoxib and acyclovir may be effective in fibromyalgia,[A14] and patients may likewise experience enhanced analgesia when treated with combinations of NSAIDs and other agents.

Combination Medical Therapy

Combining multiple classes of adjunctive pain medications has been a common practice. For example, one study demonstrated that the combination of duloxetine and pregabalin was superior to either drug alone in treating fibromyalgia.[A15]

Interventional Therapies

Transcutaneous electrical nerve stimulation (TENS) has been used to treat musculoskeletal pain and may sometimes be helpful in fibromyalgia. Newer neurostimulatory therapies include noninvasive techniques such as repetitive transcranial magnetic stimulation (rTMS) and transcranial direct current stimulation (t-DCS). Outcomes with these therapies have yielded inconsistent results.[A16] More invasive approaches such as spinal cord stimulation, deep brain stimulation, and vagal nerve stimulation show promise in refractory pain states. Trigger-point injections can be useful for the treatment of localized myofascial pain, but there is no evidence that adding corticosteroids or even local anesthetics adds anything to their beneficial effect.

PROGNOSIS

Fibromyalgia is typically a chronic, often life-long condition that waxes and wanes. Long-term complications include a higher risk of unnecessary procedures, physical injuries, and suicide. Earlier recognition and successful treatment is likely to be necessary to prevent the significant functional disability that often accompanies fibromyalgia, since at present these individuals often go decades seeking a diagnosis and treatments that are helpful.

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STERLING G. WEST AND S. LOUIS BRIDGES, JR.

Arthritis, arthralgias, and myalgias can be significant features of several systemic diseases and may be the presenting symptoms for some of these disorders (Table 254-1). Appropriate evaluation of these musculoskeletal symptoms, including selected laboratory tests and radiographs, can provide clues to the early diagnosis of these diseases. Synovial biopsies are rarely necessary but can be diagnostic. Because of the rarity of many of these diseases, evidence-based treatments with U.S. Food and Drug Administration–approved medications are lacking.

AUTOIMMUNE HEPATITIS

Patients with type I autoimmune hepatitis (Chapter 135) may present with a syndrome resembling systemic lupus erythematosus (Chapter 245).[1] Patients with the early-onset subset are frequently young and female, with complaints of polyarthralgia and occasionally various rashes and/or fever. Laboratory examination may show leukopenia, a positive antinuclear antibody (70 to 90%), elevated erythrocyte sedimentation rate, polyclonal gammopathy, and elevated liver-associated enzymes. Hypocomplementemia and antibodies against double-stranded DNA are usually not seen, whereas antibodies against the smooth muscle antigen (F1 actin) support the diagnosis.[2] Joint radiographs show soft tissue swelling without erosions or deformity. Joint pain resolves with corticosteroid therapy for the liver disease. Patients with autoimmune hepatitis have an increased risk for having a concurrent autoimmune disease, including Sjögren syndrome (Chapter 247), in about 7% of cases.

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Arthritis, arthralgias, and myalgias can be significant features of several systemic diseases and may be the presenting symptoms for some of these disorders (Table 254-1). Appropriate evaluation of these musculoskeletal symptoms, including selected laboratory tests and radiographs, can provide clues to the early diagnosis of these diseases. Synovial biopsies are rarely necessary but can be diagnostic. Because of the rarity of many of these diseases, evidence-based treatments with U.S. Food and Drug Administration–approved medications are lacking.

AUTOIMMUNE HEPATITIS

Patients with type I autoimmune hepatitis (Chapter 135) may present with a syndrome resembling systemic lupus erythematosus (Chapter 245).[1] Patients with the early-onset subset are frequently young and female, with complaints of polyarthralgia and occasionally various rashes and/or fever. Laboratory examination may show leukopenia, a positive antinuclear antibody (70 to 90%), elevated erythrocyte sedimentation rate, polyclonal gammopathy, and elevated liver-associated enzymes. Hypocomplementemia and antibodies against double-stranded DNA are usually not seen, whereas antibodies against the smooth muscle antigen (F1 actin) support the diagnosis.[2] Joint radiographs show soft tissue swelling without erosions or deformity. Joint pain resolves with corticosteroid therapy for the liver disease. Patients with autoimmune hepatitis have an increased risk for having a concurrent autoimmune disease, including Sjögren syndrome (Chapter 247), in about 7% of cases.

ABSTRACT

Arthritis, arthralgias, and myalgias can be significant features of several systemic diseases and may be the presenting symptoms for some of these disorders. Appropriate evaluation of these musculoskeletal symptoms, including selected laboratory tests, radiographs, and occasionally biopsies, can provide clues to the early diagnosis of these diseases. Owing to the rarity of many of these diseases, therapy is often empiric because most treatments are not based on evidence.

KEYWORDS

Whipple disease
amyloid arthropathy
carcinomatous polyarthritis
sarcoid arthropathy

TABLE 254-1 SYSTEMIC DISEASES ASSOCIATED WITH ARTHRITIS

DISEASE	TEST*
GASTROINTESTINAL DISEASES	
Autoimmune hepatitis (Chapter 135)	Liver-associated enzymes, *ASMA*
Primary biliary cirrhosis (Chapter 141)	Alkaline phosphatase, *antimitochondrial Ab*
Inflammatory bowel disease (Chapter 127)	Fecal occult blood testing, fecal calprotectin, *colonoscopy*
Whipple disease (Chapter 305)	*Tissue biopsy, tissue immunohistochemical stain for Tropheryma whipplei, PCR for T. whipplei DNA*
Gluten-sensitive enteropathy (Chapter 126)	*Antitransglutaminase antibody, small bowel biopsy*
Pancreatitis-arthritis syndrome (Chapter 130)	Lipase, amylase, *abdominal CT scan*
Hepatitis B/hepatitis C (Chapter 135)	Liver-associated enzymes, *hepatitis serology, cryoglobulins*
Intestinal bypass arthritis	*Cryoglobulins*
HEMATOLOGIC DISORDERS	
Hemophilia (Chapter 160)	PTT, *factor VIII and IX levels*
Hemoglobinopathies (Chapter 149)	CBC, *hemoglobin electrophoresis*
Hypogammaglobulinemia (Chapter 231)	Low total protein, *SPEP, immunoglobulins*
Plasma cell dyscrasias (Chapter 173)	High total protein, *SPEP, UPEP, IEF*
ENDOCRINE DISORDERS	
Diabetes mellitus (Chapter 210)	Glucose, *hemoglobin* A_{1c}
Thyroid disorders (Chapter 207)	TSH, *thyroxine*
Parathyroid disorders (Chapter 227)	Calcium, phosphorus, *PTH*
Acromegaly (Chapter 205)	Radiographs, *growth hormone, IGF-I*
Hyperlipoproteinemia (Chapter 190)	Lipid panel
Paget disease (Chapter 228)	Bone-specific alkaline phosphatase, radiographs, *bone scan*
MALIGNANT DISORDERS	
Hypertrophic osteoarthropathy	Radiographs (hands, wrists, chest)
Leukemia and lymphoma (Chapters 168 to 172)	CBC, LDH, *bone marrow/tissue biopsy*
Carcinomatous polyarthritis	*Cancer screen*
Palmar fasciitis and arthritis	*CA-125, pelvic CT scan, cancer screen*
OTHER DISEASES	
Hemochromatosis (Chapter 196)	Iron studies, radiographs, *HFE gene*
Multicentric reticulohistiocytosis (Chapter 155)	Radiographs, *skin/synovial biopsy*
Sarcoidosis (Chapter 83)	Chest radiograph, *ACE level, tissue biopsy*
IgG4-related disease	Serum IgG4 level, *histopathology of biopsy specimens including IgG4 immunostaining*
Alkaptonuria (Chapter 189)	Radiographs, *urine homogentisic acid level*
Fabry disease (Chapter 191)	Angiokeratomas, *a-galactosidase A level or gene mutation*
Relapsing polychondritis (Chapter 239)	*Cartilage biopsy*
Cystic fibrosis (Chapter 77)	Chest radiograph, *sweat chloride, CFTR gene mutation*
Tenosynovial giant cell tumor: diffuse type (diffuse pigmented villonodular synovitis)	Synovial fluid analysis, *MRI, synovial biopsy*
Systemic infections	Cultures, serologies (RPR, HIV, EBV, parvovirus)

*Tests listed are common laboratory tests and radiographs that are frequently ordered; this information should provide a clue that a systemic disease is a possible cause of the patient's musculoskeletal symptoms. These tests, coupled with the history and physical examination, should be followed by more specific tests and biopsies (listed in italics) to confirm the diagnosis.

Ab = antibody; ACE = angiotensin-converting enzyme; ASMA = anti–smooth muscle antibody; CBC = complete blood cell count; CFTR = cystic fibrosis transmembrane conductance regulator; CT = computed tomography; EBV = Epstein-Barr virus; HIV = human immunodeficiency virus; IEF = immunoelectrophoresis; IGF-I= insulin-like growth factor-I; IgG4 = immunoglobulin G4; LDH = lactate dehydrogenase; MRI = magnetic resonance imaging; PCR = polymerase chain reaction; PTH = parathyroid hormone; PTT = partial thromboplastin time; RPR = rapid plasmin reagin; SPEP = serum protein electrophoresis; TSH = thyroid-stimulating hormone; UPEP = urine protein electrophoresis.

PRIMARY BILIARY CHOLANGITIS (CIRRHOSIS)

Up to 50% of patients with primary biliary cholangitis (PBC) (Chapter 141) have other autoimmune disorders, including rheumatoid arthritis, Sjögren syndrome, limited systemic sclerosis, systemic lupus erythematosus, and autoimmune thyroiditis.[3] In addition to antimitochondrial antibodies, rheumatoid factor, antinuclear antibodies, and anticentromere antibodies are often present. More than 10% of patients with primary biliary cholangitis have a symmetrical or asymmetrical small joint inflammatory arthritis. Unlike rheumatoid arthritis, it can involve distal interphalangeal joints and is rarely erosive or deforming. Other musculoskeletal manifestations include osteomalacia related to vitamin D deficiency, osteoporosis related to renal tubular acidosis, and hypertrophic osteoarthropathy associated with liver disease.

INFLAMMATORY BOWEL DISEASE

Musculoskeletal symptoms are the most frequent extraintestinal manifestation occurring in patients with inflammatory bowel disease[4] (ulcerative colitis and Crohn disease; Chapter 127). The pathogenesis of these musculoskeletal manifestations is complex and includes interactions among gut microbes, mucosal immunity, and a genetic predisposition. Symptoms occur most commonly in patients who have involvement of the large bowel. Two types of inflammatory peripheral arthritis occur in about 15% of patients. Type I arthropathy is an acute, remitting (<6 months), nondestructive oligoarthritis most commonly involving the knee. This arthritis occurs early or prior to onset of bowel symptoms and is often associated with flares of inflammatory bowel disease. Type II arthropathy tends to be a nondestructive polyarthritis involving both small (e.g., metacarpophalangeal) and large joints. This arthritis persists for months, has frequent relapses, and does not parallel the activity of inflammatory bowel disease. Sacroiliitis (10%) and ankylosing spondylitis (3%) present with buttock and spinal pain and stiffness. This axial spondyloarthropathy, which can occur alone or in association with type I arthropathy, is associated with HLA-B27 (in 50 to 75% of cases), and its clinical course is not related to the activity of the inflammatory bowel disease. Other possible rheumatic manifestations include dactylitis (0 to 6%), enthesitis, septic arthritis, and hypertrophic osteoarthropathy. Treatment of the underlying inflammatory bowel disease, including conventional synthetic and/or biologic disease-modifying drugs (Chapter 123), will improve the musculoskeletal manifestations.

WHIPPLE DISEASE

An inflammatory arthritis occurs in up to 80% of patients with Whipple disease (Chapter 305) and may precede the gastrointestinal manifestations by a median of 5.5 years.[5] The joint involvement is typically an intermittent, migratory oligoarthritis, which affects large joints more than small joints or the sacroiliac joints and which persists from several hours to days. The synovial fluid is inflammatory, with a predominance of mononuclear cells. Subcutaneous nodules are occasionally seen and may lead to an erroneous diagnosis of rheumatic fever or rheumatoid arthritis. However, patients consistently test negative for rheumatoid factor and antinuclear antibodies. Synovial biopsies show rod-shaped bacilli on electron microscopy, which have been identified as *Tropheryma whipplei*. Diagnosis is suspected when duodenal, synovial, or lymph node biopsies show periodic acid–Schiff–positive macrophages. Infection is confirmed by demonstration of the organism in tissue by immunohistochemical staining with antisera specific for *T. whipplei*. Quantitative polymerase chain reaction to detect *T. whipplei* DNA is used as a confirmatory test performed on tissue and body fluids. Typically, the arthritis does not cause radiographic changes or deformities. Prolonged antibiotic therapy results in resolution of musculoskeletal as well as other symptoms of this disease. Relapses, especially neurologic, can occur in up to 35% of patients after cessation of antibiotic therapy.

GLUTEN-SENSITIVE ENTEROPATHY (CELIAC DISEASE)

An asymmetrical oligoarthritis or symmetrical polyarthritis occurs in up to 25% of adults with celiac disease (Chapter 126). The arthritis may precede the enteropathic symptoms by months to years in up to 50% of cases. Large joints such as knees and ankles, more than hips and shoulders, are most commonly involved. Axial involvement is reported. The arthritis does not cause deformities or radiographic changes and resolves with a gluten-free diet in 40 to 50% of cases. Another musculoskeletal manifestation is osteomalacia (Chapter 226) related to vitamin D malabsorption, which may mimic diffuse fibromyalgia. Arthralgias due to gluten sensitivity without celiac disease are also reported.

PANCREATITIS-ARTHRITIS SYNDROME

Pancreatic panniculitis is a systemic syndrome occurring in some patients with pancreatic acinar cell carcinoma (Chapter 180) and less commonly in patients with pancreatitis (Chapter 130) or hematologic malignancies. Prominent fat necrosis is due to the release of lipase, amylase, and trypsin

from the diseased pancreas. This syndrome is characterized by tender red nodules, usually on the extremities; these lesions are frequently misdiagnosed as erythema nodosum, but biopsy shows areas of lobular panniculitis with fat necrosis. Arthritis occurs in 60% of patients and usually involves the ankles and knees. Other manifestations include osteolytic lesions (10%) from bone marrow fat necrosis, pleuropericarditis, fever, and eosinophilia. Magnetic resonance imaging (MRI) shows multifocal intraosseous fat necrosis and arthritis of the knees and feet.[6] Synovial fluid is typically noninflammatory and creamy in color. It contains multiple lipid droplets because of necrosis of fat in the synovial membrane.

HEMOPHILIA

Hemophilia A (factor VIII deficiency) and hemophilia B (factor IX deficiency) (Chapter 160) are associated with hemarthrosis. Acute and chronic arthritis are less frequent and less severe in patients with hemophilia B compared with hemophilia A. Almost all patients with factor levels less than 1% of normal experience recurrent hemarthroses spontaneously or after minor trauma. Large joints (knees, elbows, ankles) are most commonly involved. Intramuscular hemorrhage can also occur. Recurrent hemarthrosis can lead to proliferative synovitis and cartilage degradation, thereby resulting in both erosive and degenerative changes on radiographs or ultrasonography.[7] Physical examination shows bone enlargement, crepitus, atrophic muscles, and joint contractures. Treatment of acute monoarthritis consists of factor replacement to achieve a level of 30% or greater, given at the first sign of joint swelling. Patients with fever (temperature >38° C) or who fail to respond to factor replacement need joint aspiration to exclude septic arthritis, which occurs with an increased incidence in hemophilia. Chronic arthritis is treated with COX-2 selective nonsteroidal anti-inflammatory drugs (NSAIDs; Table 26-4), which do not inhibit platelet function; arthroscopic or radiation synovectomy for chronic synovitis; and total joint arthroplasty for end-stage joint disease. Better preventative therapies have reduced the risk for developing chronic arthropathy.

HEMOGLOBINOPATHIES

Patients with sickle cell anemia (Chapter 149) or the heterozygous states of sickle β-thalassemia and sickle hemoglobin C disease frequently experience polyarthralgia.[8] Local sickling of cells leads to obstruction of the microcirculation and to bone infarctions. Patients most commonly experience painful crises causing chest, back, and joint pain, which can be caused or worsened by glucocorticoid therapy. A painful large joint arthritis (usually in the knees), which persists for days to 3 weeks, can also occur. Synovial effusions are usually noninflammatory but can be mildly inflammatory because of local phagocytosis of sickled cells. Infarcts in the metaphyses of bones are commonly found on joint radiographs. Vertebral bodies have a characteristic "Lincoln log" appearance or a central cuplike indentation ("codfish vertebrae"). Femoral and humeral head osteonecrosis can occur in up to 33% of patients with sickle cell anemia and sickle hemoglobin C disease. Because of splenic autoinfarction, septic arthritis (*Staphylococcus aureus*) and osteomyelitis (50% caused by *Salmonella*) have been associated with sickle cell disease. In adults, gout has been reported. Treatment includes intravenous hydration, oxygen, and analgesics. Hydroxyurea can reduce the frequency of painful crises. In patients with β-thalassemia major (Chapter 148), significant expansion of bone marrow, owing to increased erythroid precursors, leads to osteoporosis and microfractures that affect primarily the lower extremities. Chelation therapy with deferiprone to reduce iron overload from transfusions can cause arthralgias in 20% of patients.

HYPOGAMMAGLOBULINEMIA

Common variable immunodeficiency and selective immunoglobulin A (IgA) deficiency are the most common primary immunodeficiencies[9] (Chapter 231). Adults with common variable immunodeficiency can develop a nonerosive, noninfectious large joint oligoarthritis that responds to intravenous immunoglobulin therapy. However, septic arthritis caused by common pathogens or *Mycoplasma* can also occur and must be rigorously excluded. Autoimmune disorders, most commonly autoimmune cytopenias and pernicious anemia, occur in 30% of patients with common variable immunodeficiency and may be the presenting manifestation. Selective IgA deficiency (Chapter 231) is associated with various rheumatic manifestations, including positive autoantibodies, in the absence of clinical disease. Systemic autoimmune disorders, including systemic lupus erythematosus and organ-specific autoimmune disorders, such as type 1 diabetes mellitus and myasthenia gravis, also occur in IgA-deficient individuals.

AMYLOIDOSIS

Primary amyloidosis and myeloma-associated amyloidosis are plasma cell disorders with overproduction of monoclonal immunoglobulin light chains (Chapter 174) and their deposition in tissues. Amyloid deposits in the synovium can lead to rheumatic symptoms, which may be misdiagnosed as rheumatoid arthritis or polymyalgia rheumatica. Amyloid arthropathy occurs in up to 5% of myeloma patients and may be the initial manifestation.[10] Arthropathy affects both males and females at an average age of 60 years. Polyarthritis or oligoarthritis most commonly affects the shoulders, knees, wrists, and small joints of the hand. Subcutaneous nodules and carpal tunnel syndrome can be additional manifestations. The erythrocyte sedimentation rate is nearly always elevated, but rheumatoid factor and antinuclear antibodies are negative. Synovial fluid is usually normal or minimally inflammatory. Congo red staining of spun synovial fluid can show amyloid deposits from synovial fragments. Joint radiographs are nonerosive but may show lytic bone lesions. The arthritic symptoms do not respond to glucocorticoids or other anti-inflammatory medications.

DIABETES MELLITUS

A causal relationship between arthritis in general and diabetes mellitus is not established. However, certain specific musculoskeletal disorders are associated with diabetes.[11] Diabetic stiff hand syndrome of limited joint mobility (diabetic cheiroarthropathy) occurs in more than 30% of patients with long-standing, poorly controlled type 1 or type 2 diabetes mellitus (Chapter 210). Patients present with the insidious development of flexion contractures and thickened skin of the fingers, which may be confused with scleroderma. These changes may be due to excess glycosylation of tendinous structures and accumulation of sugar alcohols, which lead to excess water content in the tissues and increased stiffness. Additionally, intracellular hyperglycemia causes oxidative stress and the formation of advanced glycation end products, which damage vascular endothelium and form cross-links with skin and tendon collagen, thereby leading to biologic dysfunction. As a result of the inability to extend the fingers fully, the "prayer sign" is observed on physical examination. Unlike diabetic stiff hand syndrome, Dupuytren contractures are due to a chronic thickening of the palmar aponeurosis, with flexion deformities of primarily the fourth and fifth digits. Dupuytren is a frequent musculoskeletal complication, occurring in more than 20% of patients with type 2 diabetes.

A less common manifestation is neuropathic arthropathy (Charcot joints), which occur in less than 1% of all patients with long-standing diabetes annually. All patients have a diabetic peripheral neuropathy and typically present with painless swelling, usually of the foot, most commonly caused by destruction of the tarsometatarsal joints. Deformities can occur with midtarsal collapse ("rocker bottom" foot) and predispose to ulceration and infection of the skin over desensate bony prominences. Radiographs are diagnostic, and treatment should include supportive footwear and protected weight bearing.

Unlike neuropathic arthropathy (Charcot joint), diabetic osteolysis and diabetic amyotrophy are unique to diabetes. The osteolysis is characterized by resorption of the distal metatarsal bone and proximal phalanges of the feet, thereby giving radiographs a characteristic "licked candy" appearance. Pain is variable, and treatment is conservative because the process may terminate on its own.

Diabetic amyotrophy is a lumbar polyradiculopathy (L2 to L4) that arises with severe pain, dysesthesias, and rapid atrophy of the proximal muscles of one or both thighs. Carpal tunnel syndrome (20%), adhesive capsulitis of the shoulder (frozen shoulder) (20 to 30%), flexor tenosynovitis (trigger finger) of the hands (20%), diffuse idiopathic skeletal hyperostosis (type 2 diabetes), osteopenia (type 1 diabetes), diabetic muscle infarction (usually of the thigh), osteomyelitis of the foot, and septic joints are all musculoskeletal conditions that occur with increased frequency in diabetic patients. Aggressive control of blood glucose helps prevent some of these musculoskeletal complications.

THYROID DISORDERS

Musculoskeletal symptoms occur in 33% of patients with clinical hypothyroidism (thyroid-stimulating hormone levels >20 μU/mL) (Chapter 207). Patients can present with carpal tunnel syndrome, Raynaud phenomenon, or muscle aching and stiffness similar to fibromyalgia and polymyalgia rheumatica. Patients with severe hypothyroidism can experience a noninflammatory myopathy with proximal muscle weakness and an elevated creatine kinase level, which may be confused clinically with polymyositis. Similarly, myxedematous patients can develop a symmetrical arthropathy of the large joints, especially the knees, associated with noninflammatory synovial fluid with

increased viscosity. The association of hypothyroidism with chondrocalcinosis is controversial, but clearly patients beginning thyroid replacement therapy can experience an acute attack of pseudogout. Patients with hyperthyroidism can develop proximal myopathy (70%), adhesive capsulitis of the shoulder (10%), osteoporosis, or thyroid acropachy. Thyroid acropachy, which occurs in less than 1% of patients with Graves disease, consists of soft tissue swelling of the hands, digital clubbing, and periostitis, particularly involving the metacarpal and phalangeal bone shafts. Pain is usually mild, radiographs are characteristic, and there is no effective therapy. Patients with autoimmune thyroid disease have an increased prevalence of nonspecific arthralgias, positive antinuclear antibodies, and possibly an increased association with systemic autoimmune rheumatic diseases such as Sjögren syndrome.

PARATHYROID DISORDERS

Primary hyperparathyroidism (Chapter 227) can cause osteoporosis with fractures and/or chondrocalcinosis with episodes of acute pseudogout. In severe hyperparathyroidism, which is rare, vague myalgias and arthralgias resemble fibromyalgia, a reversible and painless proximal myopathy with a normal creatine kinase level can be seen, and osteitis fibrosa cystica with bone pain can develop. Osteitis fibrosa cystica occurs primarily in patients with secondary hyperparathyroidism associated with renal failure and has a characteristic radiographic appearance, with subperiosteal resorption on the radial side of the phalanges, small erosions in the hands and distal clavicles, and discrete lytic bone lesions (brown tumors). Ectopic calcifications, joint laxity, and tendon ruptures have been reported in patients with severe hyperparathyroidism. Hypoparathyroidism has also been associated with ectopic and perispinal ligament calcifications. Patients with types Ia and Ic pseudohypoparathyroidism and patients with pseudo-pseudohypoparathyroidism have a shortened fourth metacarpal bone bilaterally.[12]

ACROMEGALY

Up to 75% of patients with acromegaly (Chapter 205) develop an atypical form of osteoarthritis, which may be the presenting feature.[13] The knees, shoulders, hips, and lumbosacral and cervical spine are the most frequently symptomatic areas, although the hands reveal the most characteristic radiographic changes, with osteophytosis but, unlike primary osteoarthritis, widened joint spaces due to cartilage hypertrophy. Carpal tunnel syndrome (50%), Raynaud phenomenon (33%), diffuse idiopathic skeletal hyperostosis (20%), and proximal muscle weakness with a normal serum creatine kinase can also occur.

HYPERLIPOPROTEINEMIA

Type IIa familial hyperlipidemia (Chapter 190) is associated with tendinous and tuberous-osseous xanthomas as well as episodic Achilles tendinitis. An acute migratory, inflammatory arthritis/periarthritis persisting up to a month and resembling rheumatic fever occurs in 5 to 7% of patients. Predominantly large joints are affected. In addition, a self-limited, acute monoarticular or oligoarticular arthritis involving the knee or ankle can occur. Patients with type III familial hyperlipoproteinemia can develop tendon (Achilles, wrist, finger) and rarely bone xanthomas. Patients with human immunodeficiency virus (HIV) infection taking protease inhibitor drugs can develop dyslipidemia that leads to tendon xanthomas. In all hyperlipidemias, gout must be excluded before ascribing the symptoms to hyperlipoproteinemia.

PAGET DISEASE

Paget disease (Chapter 227) can cause bone pain and deformity.[14] An elevated bone-specific alkaline phosphatase and characteristic radiographic changes can help make the diagnosis. Joint pain caused by secondary osteoarthritis in areas of bone involvement by Paget disease most commonly occurs in the hips, knees, or vertebrae. Spinal stenosis from Paget disease of the spine has been reported. Bisphosphonate therapy (Chapter 225) is highly effective.

HYPERTROPHIC OSTEOARTHROPATHY

Hypertrophic osteoarthropathy is a syndrome that includes clubbing of the fingers and toes, periostitis of long bones (distal tibia, femur, radius), and arthritis (Fig. 254-1). Hypertrophic osteoarthropathy is classified into primary (associated with mutations in *HPGD* and *SLCO2A1*) and secondary forms.[15] Between 80 and 90% of secondary hypertrophic osteoarthropathy is associated with intrathoracic neoplasms, especially non–small cell lung cancer (Chapter 177). Other causes include other neoplasms, chronic pulmonary infections, congenital heart disease, cirrhosis, HIV infection, medications (voriconazole), and inflammatory bowel disease. Patients with secondary hypertrophic osteoarthropathy can present with acute, severe, burning bone pain and a noninflammatory arthritis caused by periarticular periostitis. Pain is accentuated by dependency of the limbs. Pitting edema, warmth, and tenderness of the legs and forearms can be seen. Radiographs show diagnostic changes of periosteal elevation, new bone formation, or both along the distal ends of long bones. Therapy is symptomatic with NSAIDs (Table 26-4). Hypertrophic osteoarthropathy improves with successful treatment of the underlying primary disease. In resistant cases, treatment with intravenous zoledronic acid (4 mg intravenously once) or octreotide (100 μg subcutaneously twice daily) has been effective in modulating symptoms.

LEUKEMIA AND LYMPHOMA

Leukemia can arise as an asymmetrical or migratory polyarthritis, monoarthritis (rare), back pain (10%), or nocturnal bone pain. Articular manifestations occur in 14 to 50% of children and 4 to 16% of adults with acute leukemia (Chapter 168) and can precede the diagnosis by months. Joint pain is attributed to leukemic synovial infiltration and usually involves the ankle or knee, but it can be polyarticular, resembling juvenile or adult rheumatoid arthritis. The joint pain is disproportionately more severe than the clinical findings. Synovial effusions are uncommon, and evidence of leukemic cells in the synovial fluid is rare. Bone pain due to subperiosteal leukemic cell infiltration occurs in up to 50% of patients, with long bone pain (lower extremities) more common in children and back pain more common in adults. Radiographs are normal in 50% of cases. The musculoskeletal symptoms are poorly responsive to NSAIDs but can resolve with successful therapy of the leukemia.

Musculoskeletal symptoms occur in 25% of patients with non-Hodgkin lymphoma (Chapter 171). Nocturnal bone pain is the most common presenting musculoskeletal complaint. A seronegative monoarthritis or polyarthritis can occur and should be suspected in patients with severe constitutional symptoms or lymphadenopathy out of proportion to the degree of arthritis.

Patients with angioimmunoblastic T-cell lymphoma may occasionally develop a chronic, nonerosive polyarthritis with erythroderma. Intravascular large B-cell lymphoma can present with arthralgias, a positive antinuclear antibody test, various skin lesions, and neurologic manifestations due to small vessel occlusion from tumor cells. Notably, lymphadenopathy is absent in these patients.

Treatment focuses on the underlying malignancy.

CARCINOMATOUS POLYARTHRITIS

Polyarthritis can rarely (<2%) be the presenting manifestation of an occult malignancy and may precede the discovery of the malignancy by several months. Breast, colon, lung, ovarian, and lymphoproliferative malignancies are the most commonly associated cancers. Clinical features suggesting carcinomatous polyarthritis include the explosive onset of a rheumatoid factor–negative, asymmetrical polyarthritis involving predominantly the lower extremities and sparing the hands and wrists in a patient older than age 50 years. Another presentation is remitting seronegative symmetrical synovitis with pitting edema of the hands and feet. Both presentations are associated with profound constitutional symptoms, elevated inflammatory markers, lack of erosions on radiographs, and poor response to glucocorticoids. Polymyalgia rheumatica and late-onset rheumatoid arthritis must be excluded. Treatment of the underlying malignancy results in improvement of the arthritis.

ARTHRITIS ASSOCIATED WITH TREATMENTS FOR MALIGNANT DISEASES

Arthralgias or bone pain is seen in most patients who receive aromatase inhibitors for breast cancer and result in discontinuation of the drug in 20% of patients. Immune checkpoint inhibitors targeting PD-1, PD-L1, or CTLA-4 can cause various immune-related adverse events in 80 to 90% of treated patients.[16] Up to 5% of patients can develop a rheumatologic event, including an inflammatory arthritis resembling rheumatoid arthritis or reactive arthritis. Other manifestations include sicca syndrome, myositis, polymyalgia rheumatica, or vasculitis. Patients may or may not respond to glucocorticoids and/or discontinuation of the cancer immunotherapy, so conventional synthetic and/or biologic disease-modifying drugs may be necessary to control symptoms.

PALMAR FASCIITIS AND ARTHRITIS SYNDROME

Ovarian carcinoma (Chapter 184) is the most common malignancy found in patients (37%) with palmar fasciitis and arthritis. This musculoskeletal manifestation can also be seen in patients with breast, gastric, or pancreatic

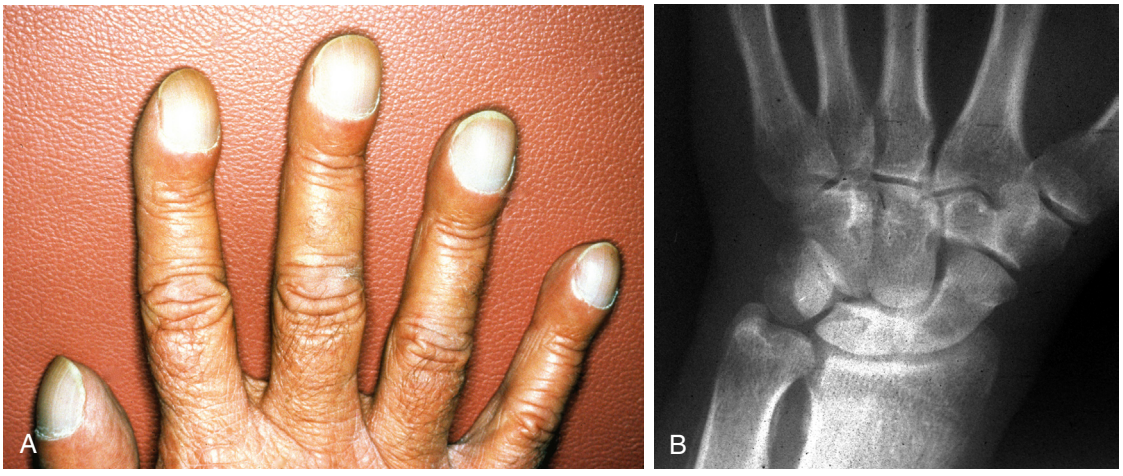

FIGURE 254-1. Hypertrophic osteoarthropathy. A, Severe clubbing of the nails. **B**, Radiograph demonstrating periosteal elevation of the distal radius and ulna.

adenocarcinoma. Patients present with a severe, painful, symmetrical inflammatory polyarthritis of the hands and wrists as well as a nodular fasciitis/tendonitis causing flexion contractures primarily of the fingers and, less commonly, the feet. Patients may have vasomotor instability, thereby causing diagnostic confusion with complex regional pain syndrome or rheumatoid arthritis. This syndrome portends a poor prognosis because it typically manifests after the tumor has metastasized. Response to treatment is poor, although clinical improvement can occur with successful eradication of the underlying tumor.

HEMOCHROMATOSIS

Joint involvement occurs in 40 to 75% of patients with hereditary hemochromatosis (Chapter 196) and may be the presenting symptom (Fig. 254-2).[17] The mechanism whereby iron causes arthritis is unclear, but it may be related to hemosiderin deposits in the synovial membrane and chondrocytes activating degradative enzymes. The metacarpophalangeal (MCP) joints (especially the second and third MCP joints), wrists, knees, hips, shoulders, and ankles are most often involved in a symmetrical pattern. The arthropathy resembles osteoarthritis, with joint swelling resulting from bone enlargement, but it is distinguished clinically by the involvement of atypical joints, such as MCP joints, wrists, and ankles. Radiographs show narrowing of the joint space, subchondral cysts, sclerosis, and hooklike osteophytes at the MCP joints. Chondrocalcinosis is present in up to 50% of patients. Joint involvement is typically asymptomatic, but in some patients it leads to attacks of acute inflammatory synovitis (pseudogout), which may result in the misdiagnosis of rheumatoid arthritis. The prevalence of overt arthritis increases with age, and it may be only minimally symptomatic when the disease arises in other organs. However, articular pain may be the initial presenting complaint (33%). Consequently, all patients (especially White males) presenting with premature osteoarthritis occurring in atypical joints, especially MCP joints and wrists, should be screened for hereditary hemochromatosis. Treatment is symptomatic with NSAIDs (Table 26-4) and, when severe, total joint arthroplasty. Phlebotomy for iron removal does not alter the course of the arthritis. Additional rheumatic manifestations in patients with hemochromatosis include osteoporosis related to hypogonadotropic hypogonadism, osteomalacia related to vitamin D deficiency when liver disease is severe, and an increased susceptibility to *Yersinia* septic arthritis.

MULTICENTRIC RETICULOHISTIOCYTOSIS

Multicentric reticulohistiocytosis (Chapter 155) is a chronic, seronegative, symmetrical, inflammatory polyarthritis most commonly affecting the hands, shoulders, and knees. It may resemble rheumatoid arthritis but can be differentiated by its prominent distal interphalangeal joint synovitis.[18] The disease may also cause a spondylitis with axial involvement (50%). Joint involvement remits and relapses initially, but in 50% of cases it worsens into a severely deforming arthritis mutilans. Firm, nonpruritic, reddish brown or yellow papulonodular lesions ("coral beads") that wax and wane occur around the nail beds and on the face, hands, ears, and other areas predominantly above the waist. Histology of skin lesions reveals characteristic histiocytes and multinucleated giant cells. In 50 to 66% of patients, these diagnostic nodules follow the onset of arthritis by months to years. Additional associations include xanthelasma (33%) and malignancies of various types (25%), which may precede or follow the onset of multicentric reticulohistiocytosis. The disease usually remits spontaneously in 8 to 10 years but often leaves permanent cutaneous and joint damage. No treatment is of proven benefit.

FIGURE 254-2. Arthropathy associated with hemochromatosis. Radiograph demonstrating degenerative changes, with hooklike osteophytes of the second and third metacarpophalangeal joints bilaterally.

SARCOIDOSIS

Joint manifestations, including arthritis, periarthritis, and arthralgias, occur in 4 to 38% of patients with sarcoidosis (Chapter 83).[19] Rheumatic involvement is divided into acute and chronic types. The acute type consists of the triad of arthritis, erythema nodosum, and hilar adenopathy on chest radiographs (Löfgren syndrome), which may be accompanied by fever.[20] Arthritis arises most often in the knees and ankles, and periarticular pain can be severe. Treatment is with NSAIDs, glucocorticoids, or both, and symptoms usually remit spontaneously over several weeks.

The less common chronic type of joint involvement (<5%) in sarcoidosis consists of synovitis that accompanies the slower onset, more chronic, systemic form of sarcoidosis. Polyarthritis, oligoarthritis, or monoarthritis can affect the small or large joints. The arthritis is typically nondestructive, but it can be aggressive. Dactylitis resulting from sarcoid bone and soft tissue involvement can occur (Fig. 254-3). In contrast to the acute type, chronic sarcoid arthropathy is characterized by mildly inflammatory synovial fluid and histologic granulomas on synovial biopsy. Treatment consists of NSAIDs (Table 26-4) and treatment for the sarcoidosis (Chapter 83).

FIGURE 254-3. Sarcoid bone involvement. Punched-out lytic lesions of the middle phalanx, with soft tissue swelling.

Other musculoskeletal manifestations of sarcoidosis include lytic or sclerotic bone lesions (3 to 13%) and symptomatic acute or chronic myopathy (3%). Notably, asymptomatic lesions involving bone and muscle are much more common on MRI and tissue biopsies.

IMMUNOGLOBULIN G4–RELATED DISEASE

Patients with IgG4-related disease are typically men (70 to 75%) older than age 50 years.[21] Patients present with a variety of local and systemic manifestations, some of which can resemble several rheumatic diseases.[22] For example, tumefactive lesions of the salivary glands can mimic Sjögren syndrome. Destructive sinus and middle ear lesions or periorbital masses can suggest granulomatous polyangiitis. Furthermore, patients with IgG4-related disease frequently (40%) have allergic manifestations, including chronic sinusitis and pulmonary symptoms, which may add to the diagnostic confusion with granulomatous polyangiitis.[23] IgG4-related disease can also cause an inflammatory aortitis with aneurysm formation that can be mistaken for giant cell arteritis. A fibrosclerotic presentation in the abdomen can mimic retroperitoneal fibrosis. Other organs that can be involved include the pancreas, biliary tree, kidneys, lymph nodes, meninges, thyroid, breast, prostate, pericardium, and skin. Although up to 70% of patients will have an elevated serum IgG4 level (>1.35 g/L), histopathologic analysis of biopsy specimens is the gold standard for diagnosis. The key pathologic features are a dense lymphoplasmacytic infiltrate organized in a storiform pattern (whorled or cartwheel), obliterative phlebitis, and a mild or moderate eosinophilic infiltrate. The plasma cell infiltrate will show more than 10 IgG4-positive cells per high-power field and a ratio of IgG4 to IgG positive cells that is higher than 40%. Glucocorticoids under expert oversight are effective in most patients. Several medications (azathioprine, mycophenolate mofetil, methotrexate) have been used as steroid-sparing agents to maintain remission. For refractory disease, B-cell depletion therapy with rituximab is effective.

ALKAPTONURIA (OCHRONOSIS)

Although it is an inherited disorder, alkaptonuria (Chapter 189) is usually not diagnosed until the patient presents with progressive premature osteoarthritis as a young adult (before age 30 to 35 years). Deposition of ochronotic pigment onto collagen fibers causes the articular cartilage to become brittle and fragmented. The spine is initially involved, followed by the knees, shoulders, and hips. Small peripheral joints are spared. Nonarticular features include bluish brown discoloration of ear pinna, sclera, and nasal cartilage. The diagnosis is often first suspected when fresh urine turns dark brown or black on standing or with alkalinization. Radiographs show multiple vacuum discs, disc space ossification, and osteoarthritic changes in the spine. The noninflammatory synovial fluid may show tiny shards of pigmented cartilage ("ground pepper"). The diagnosis is confirmed by quantitative measurement of increased homogentisic acid in urine. Testing for a mutation of the *HGD* gene that codes for homogentisate 1,2-dioxygenase can also be performed. There is no effective therapy for alkaptonuria, although the tyrosine metabolism inhibitor nitisinone is currently under investigation. The arthritis is treated symptomatically with analgesics.

FABRY DISEASE

Most patients with hereditary lysosomal storage diseases present and are diagnosed during childhood (Chapter 192). However, female heterozygotes and atypical variants of Fabry disease may have a milder and later-onset phenotype. Fabry disease is an X-linked lipid storage disease caused by a deficiency of lysosomal α-galactosidase A. Males with classical Fabry disease usually develop neuromuscular symptoms in childhood, including painful crises with burning paresthesias of the distal extremities, often accompanied by fever. Abdominal pain is common. However, in female heterozygotes and males with low residual α-galactosidase A levels, disease manifestations may occur for the first time in adulthood. Neuromuscular manifestations can range from painful acroparesthesias to fibromyalgia. Progressive or isolated cardiac, cerebrovascular, and renal disease can develop later. Fabry disease should be suspected in any patient with a paternal family history of early-onset renal failure. Patients should be examined for characteristic ocular stigmata (cornea verticillata) and dermal signs (angiokeratomas). The diagnosis is confirmed in males by determining α-galactosidase A activity in plasma or peripheral leukocytes. In contrast, female carriers must be tested for one of the specific gene mutations. Early diagnosis is important because enzyme replacement therapy can prevent irreversible organ damage.

RELAPSING POLYCHONDRITIS

Relapsing polychondritis (Chapter 239) is an uncommon multisystem disorder characterized by recurrent episodes of inflammation of cartilaginous tissues. Relapsing polychondritis may be part of the VEXAS (vacuoles, E1 enzyme, X-linked, autoinflammatory, somatic) syndrome associated with somatic mutations in *UBA1*.[24]

Patients typically present with the sudden onset of pain and erythema involving the cartilage of the external ear, larynx, trachea, or nose. A nonerosive, seronegative polyarthritis or oligoarthritis affecting small, large, or parasternal joints (23 to 47%); ocular inflammation, including episcleritis or scleritis; and audiovestibular disturbances may also be presenting symptoms. The arthritis is typically acute, migratory, and episodic, and it resolves spontaneously over days to weeks. Rarely, it can become chronic. Tenosynovitis is also common.

Treatment of relapsing polychondritis depends on the severity of the presentation and whether major organs are involved (Chapter 239). Late sequelae of relapsing polychondritis include deformity of the pinnae or nose, reduced vision or hearing, tracheal narrowing or collapse, and aortic insufficiency.

CYSTIC FIBROSIS

In up to 10% of patients with cystic fibrosis (Chapter 77), an episodic, nondestructive, inflammatory oligoarthritis develops, most commonly involving the fingers and lower extremity joints. This arthritis is thought to be due to immune complex deposition caused by chronic lung infections. Attacks persist for a few days and may be associated with fever and painful nodular skin lesions and purpura. Other musculoskeletal manifestations include osteoporosis (30 to 75%) and osteomalacia related to malabsorption and, more rarely, hypertrophic osteoarthropathy (5%) and a small vessel vasculitis.

TENOSYNOVIAL GIANT CELL TUMOR: DIFFUSE TYPE

The diffuse type of tenosynovial giant cell tumor (also called diffuse pigmented villonodular synovitis) occurs most commonly in the third and fourth decades of life.[25] Tenosynovial giant cell tumor is a nonmalignant condition commonly due to a translocation between chromosomes 1p13 and 2q35 in which the gene coding for colony-stimulating factor-1 (CSF-1) is fused to the collagen VI alpha-3 gene. Up to 15% of cells overexpress CSF-1. The remaining cells in the tumor are inflammatory cells recruited into the tumor because they contain the receptor for CSF-1.

The disease is characterized by the onset of unilateral pain and swelling of a joint, typically the knee (80%). Unusually, a tendon, bursa, or another joint can be involved. The synovial fluid is typically brown or hemorrhagic, and radiographs may show soft tissue swelling, osteolysis, subchondral cysts, and bone erosions.

Tenosynovial giant cell tumor is best diagnosed by synovial biopsy. Microscopic examination reveals a characteristic histology, including marked

synovial cell hyperplasia and subsynovial invasion by masses of polygonal cells, multinucleated giant cells, and lipid-filled macrophages. Hemosiderin deposits are between and within cells and have a characteristic appearance on MRI, with nodular foci of decreased signal on both T1- and T2-weighted images.

The treatment for pigmented villonodular synovitis is synovectomy with or without postoperative radiotherapy. Pexidartinib targeting the CSF-1/CSF-1R axis may be effective under expert oversight for patients with recurrent, resistant, and inoperable disease.[A1,A2]

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For the General References and other additional features, please visit Elsevier eBooks+ at https://ebooks.health.elsevier.com.

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255 SURGICAL TREATMENT OF JOINT DISEASES

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EPIDEMIOLOGY

Estimates of the prevalence of arthritis and other rheumatic diseases demonstrate the enormous impact that these conditions have on the U.S. populace and the health care system in general. Over 21% of U.S. adults report physician-diagnosed arthritis. Osteoarthritis (Chapter 241), which is the most prevalent form, affects upward to 31 million U.S. adults. Arthritis is already the leading cause of disability in the United States, yet the number of affected individuals with arthritis and arthritis-attributable limitations in activity is anticipated to approach 67 million by the year 2030. Despite therapeutic advances in the medical treatment of inflammatory arthritic disorders, surgical intervention is eventually required in many patients who suffer from inflammatory arthritis. Furthermore, other than exercise and rehabilitation, surgery is often the only option for degenerative arthritis. The increasing prevalence of arthritis, the desire for higher activity levels, and improvements in surgical techniques have fueled the utilization of orthopedic surgery. By the year 2030, it is predicted that over 500,000 hip replacements and 3 million knee replacements will be performed annually in the United States.

PATHOBIOLOGY

Arthritis results when damage to articular cartilage and accompanying inflammation of the synovium and joint result in the loss of the joint's mechanical properties. Without the protective layer of articular cartilage, stiffness develops. Furthermore, the nociceptive and proprioceptive receptors in the periosteum are activated, thereby leading to pain.

Osteoarthritis (Chapter 241), which is the most common cause of end-stage arthritis, is classified as primary when due to biochemical changes in the cartilage, or secondary if it results from systemic disease affecting the cartilage, joint damage from preexisting inflammatory joint disease, prior infection, previous surgery, congenital or developmental problems, or trauma. Mechanical overload and joint imbalance then lead to further degradation of cartilage. Important adaptive processes, such as subchondral sclerosis and the formation of osteophytes, occur in response to joint overload. Cysts may also form in the subarticular bone. Over time, the osteophytes or bone spurs lead to restricted range of motion (Fig. 255-1).

By contrast, inflammatory arthritis (e.g., rheumatoid arthritis [Chapter 243], psoriatic arthritis, and spondyloarthropathies [Chapter 244]) targets the synovium. The subsequent release of inflammatory mediators leads to destruction of cartilage. In contrast to osteoarthritis, mechanical overload, bone sclerosis, and osteophytes are not seen. Rather, the inflammatory synovitis leads to characteristic loss of cartilage matrix, marginal bony erosions, and osteopenia (Fig. 255-2).

In osteonecrosis (Chapter 229), blood supply to the bone is compromised, thereby leading to necrosis of the bone that supports the articular surface. The most commonly affected joints are the hip, shoulder, and knee. As the condition progresses, the necrotic bone may collapse, thereby leading to the loss of articular integrity and progressive deterioration of cartilage. Other conditions that may lead to joint damage include metabolic disorders (e.g., chondrocalcinosis, gout), tumor (e.g., synovial chondromatosis), and bleeding disorders (e.g., hemophilia).

DECIDING UPON SURGERY

Surgical treatment of joint diseases is focused primarily upon the relief of pain, and patients who are candidates for surgery have daily pain and functional limitations that hinder their quality of life despite physical therapy, pain medications, and intra-articular injections. Secondary objectives are improvement in joint motion and swelling, return to function, and prevention of continued destruction of cartilage.

FIGURE 255-1. Radiograph of an osteoarthritic left hip. Note the asymmetrical joint space narrowing and subchondral sclerosis that are characteristic of a wear-and-tear pattern of joint deterioration.

FIGURE 255-2. Radiograph of a left hip with end-stage inflammatory arthritis. Note the symmetrical pattern of cartilage loss and presence of osteopenia.

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synovial cell hyperplasia and subsynovial invasion by masses of polygonal cells, multinucleated giant cells, and lipid-filled macrophages. Hemosiderin deposits are between and within cells and have a characteristic appearance on MRI, with nodular foci of decreased signal on both T1- and T2-weighted images.

The treatment for pigmented villonodular synovitis is synovectomy with or without postoperative radiotherapy. Pexidartinib targeting the CSF-1/CSF-1R axis may be effective under expert oversight for patients with recurrent, resistant, and inoperable disease.[A1,A2]

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255 SURGICAL TREATMENT OF JOINT DISEASES

C. RONALD MACKENZIE AND EDWIN P. SU

EPIDEMIOLOGY

Estimates of the prevalence of arthritis and other rheumatic diseases demonstrate the enormous impact that these conditions have on the U.S. populace and the health care system in general. Over 21% of U.S. adults report physician-diagnosed arthritis. Osteoarthritis (Chapter 241), which is the most prevalent form, affects upward to 31 million U.S. adults. Arthritis is already the leading cause of disability in the United States, yet the number of affected individuals with arthritis and arthritis-attributable limitations in activity is anticipated to approach 67 million by the year 2030. Despite therapeutic advances in the medical treatment of inflammatory arthritic disorders, surgical intervention is eventually required in many patients who suffer from inflammatory arthritis. Furthermore, other than exercise and rehabilitation, surgery is often the only option for degenerative arthritis. The increasing prevalence of arthritis, the desire for higher activity levels, and improvements in surgical techniques have fueled the utilization of orthopedic surgery. By the year 2030, it is predicted that over 500,000 hip replacements and 3 million knee replacements will be performed annually in the United States.

PATHOBIOLOGY

Arthritis results when damage to articular cartilage and accompanying inflammation of the synovium and joint result in the loss of the joint's mechanical properties. Without the protective layer of articular cartilage, stiffness develops. Furthermore, the nociceptive and proprioceptive receptors in the periosteum are activated, thereby leading to pain.

Osteoarthritis (Chapter 241), which is the most common cause of end-stage arthritis, is classified as primary when due to biochemical changes in the cartilage, or secondary if it results from systemic disease affecting the cartilage, joint damage from preexisting inflammatory joint disease, prior infection, previous surgery, congenital or developmental problems, or trauma. Mechanical overload and joint imbalance then lead to further degradation of cartilage. Important adaptive processes, such as subchondral sclerosis and the formation of osteophytes, occur in response to joint overload. Cysts may also form in the subarticular bone. Over time, the osteophytes or bone spurs lead to restricted range of motion (Fig. 255-1).

By contrast, inflammatory arthritis (e.g., rheumatoid arthritis [Chapter 243], psoriatic arthritis, and spondyloarthropathies [Chapter 244]) targets the synovium. The subsequent release of inflammatory mediators leads to destruction of cartilage. In contrast to osteoarthritis, mechanical overload, bone sclerosis, and osteophytes are not seen. Rather, the inflammatory synovitis leads to characteristic loss of cartilage matrix, marginal bony erosions, and osteopenia (Fig. 255-2).

In osteonecrosis (Chapter 229), blood supply to the bone is compromised, thereby leading to necrosis of the bone that supports the articular surface. The most commonly affected joints are the hip, shoulder, and knee. As the condition progresses, the necrotic bone may collapse, thereby leading to the loss of articular integrity and progressive deterioration of cartilage. Other conditions that may lead to joint damage include metabolic disorders (e.g., chondrocalcinosis, gout), tumor (e.g., synovial chondromatosis), and bleeding disorders (e.g., hemophilia).

DECIDING UPON SURGERY

Surgical treatment of joint diseases is focused primarily upon the relief of pain, and patients who are candidates for surgery have daily pain and functional limitations that hinder their quality of life despite physical therapy, pain medications, and intra-articular injections. Secondary objectives are improvement in joint motion and swelling, return to function, and prevention of continued destruction of cartilage.

FIGURE 255-1. Radiograph of an osteoarthritic left hip. Note the asymmetrical joint space narrowing and subchondral sclerosis that are characteristic of a wear-and-tear pattern of joint deterioration.

FIGURE 255-2. Radiograph of a left hip with end-stage inflammatory arthritis. Note the symmetrical pattern of cartilage loss and presence of osteopenia.

ABSTRACT

Arthritis is the leading cause of disability in the adult U.S. population. Since such conditions are age-related and often require surgery, their prevalence is expected to increase markedly in the future. Hence, the need for orthopedic surgical intervention is also likely to increase in the years to come. This chapter reviews a wide range of orthopedic procedures, as well as their potential benefit and risks.

KEYWORDS

perioperative medicine
orthopedic surgery
surgical complications

The decision to proceed with surgery reflects the outcome of a partnership among the patient, their primary care physician or rheumatologist, and the orthopedic surgeon. Factors such as the severity of disease, the patient's desired activity level, and the patient's life expectancy are very relevant to decision making. Achieving the necessary decision-making balance may be complicated, especially given the increasing burden of comorbid conditions in the aging patient. Ultimately, the patient and physicians must agree that the possible benefits of surgery outweigh the risks.

Emergent circumstances include hip fracture and infected native or prosthetic joints. Because the patient's general health is at risk in these settings, the medical-surgical team must stabilize the patient as quickly as possible for surgery (Chapter 399).

In the elective setting, joint replacement and spine surgery are the most common procedures. The proportion of surgical procedures performed on an outpatient basis has increased dramatically, and an estimated 50% of total joint replacements in the United States are expected to be performed without hospital admission by 2026. Spinal disease and spine surgery are discussed in detail in Chapter 369.

ANESTHESIA IN THE ORTHOPEDIC PATIENT

General and regional anesthesia (Chapter 400) are commonly used in orthopedic patients. General anesthesia with endotracheal intubation may present a particular danger in patients with rheumatoid arthritis (Chapter 243) or ankylosing spondylitis (Chapter 244) owing to the instability of the cervical spine in the former and rigidity in the latter. Such patients may require fiberoptic intubation. Regional anesthesia with local anesthesia or peripheral nerve blocks[1] using long-acting anesthetics and infusion techniques are often preferred for minor procedures because they provide both excellent intraoperative anesthesia and postoperative pain relief. Epidural/spinal anesthesia can be used for total joint arthroplasty.

ORTHOPEDIC PROCEDURES

OSTEOTOMY

In circumstances in which a structural abnormality around a joint has led to mechanical overload, an osteotomy (bone cutting) may be an option to correct alignment problems. The most common sites for osteotomy are the hip (to treat acetabular dysplasia) and the tibia (to realign the knee). In acetabular dysplasia, the hip socket is excessively shallow, thereby leading to abnormal stresses on the articular cartilage and premature osteoarthritis. An acetabular osteotomy can be performed in patients in whom cartilage still remains. By rotating the pelvic bones, a deeper socket can be formed, thereby reducing stresses on the cartilage and slowing the arthritic process. With tibial osteotomy, the knee joint can be realigned to direct forces away from the region of cartilage damage. Usually a varus (bow-legged) deformity indicates the medial compartment of the knee is excessively worn, and a tibial osteotomy can realign the joint to direct forces to the uninvolved lateral compartment. Typically, osteotomy is considered an option for patients who are younger than age 40 years; beyond this age, the loss of cartilage generally makes total joint arthroplasty the preferred approach.

ARTHROSCOPY

Arthroscopic surgery is performed by inserting a camera and specialized instruments into a joint via small, puncture-type incisions. Arthroscopic surgery is effective in the treatment of intra-articular pathologies such as meniscal tears of the knee, labral tears of the hip, cartilage flaps, small chondral defects, and loose bodies. However, after the articular cartilage is significantly damaged, arthroscopic debridement is usually ineffective unless patients have mechanical symptoms such as locking and clicking.[A1–A4] In some instances, underlying joint arthritis may lead to tears in the meniscus or labrum; if such a tear results in new mechanical symptoms, then arthroscopic surgery may be helpful in selected cases. The benefit of arthroscopic subacromial decompression for shoulder impingement syndrome is variable but appears to be minimal overall.[A5,A6]

In patients who have femoroacetabular impingement (impingement of the femoral neck upon the acetabular rim, typically during flexion and internal rotation), the repetitive contact between the femoral neck and acetabular rim is believed to result in labral tears, cartilage damage, and eventual arthritis.[2] The bones of the femur and acetabulum can be reshaped by an osteochondroplasty, performed as an open or arthroscopic procedure, to provide good symptomatic relief in the short term.[A7] However, the long-term effects, specifically the impact on the future development of arthritis, have yet to be demonstrated for this procedure.

SYNOVECTOMY

Synovectomy is the removal of the synovial lining of the joint, either via an open or arthroscopic approach. In inflammatory conditions such as rheumatoid arthritis (Chapter 243), in which the disease process involves an actively inflamed synovium, synovectomy can relieve pain if sufficient remaining cartilage is still preserved. However, the procedure has not been predictable in terms of regaining joint motion. The most common joints that benefit from synovectomy are the knee and elbow. However, synovectomy should be considered a delaying tactic because the synovium will reappear.

ARTHRODESIS

Arthrodesis, or fusion of a joint, relieves pain by creating a nonmobile joint. The procedure removes the articular surfaces from the joint and immobilizes the bones so that they heal in a solid union. Hip fusion may be performed in young patients to treat the sequelae of slipped capital femoral epiphysis, Legg-Calvé-Perthes disease, postseptic arthritis, or osteonecrosis of the femoral head. Fusion surgery can achieve a painless supportive joint that is capable of bearing heavy loads while avoiding artificial implants. However, creating stiffness at one joint will increase stresses upon the joints above and below the fused joint. Gait mechanics are also altered, thereby requiring more energy for ambulation. Thus, the natural history of a hip fusion is the development of ipsilateral knee arthritis and low back pain after 20 to 25 years, thereby necessitating the conversion of a fused hip to a hip replacement. Although hip arthrodesis is still a viable option in the young arthritic patient, patients' desire for maintaining hip mobility in order to sit and drive have made this procedure largely a treatment of the past.

Fusion of the knee joint is generally considered a salvage procedure, mainly used in situations in which replacement is not possible (e.g., lack of muscle function or persistent infection). In addition to the lack of motion that may make it difficult to sit or climb stairs, knee fusion cannot be converted to total knee replacement.

Ankle fusion is still commonly performed as the treatment of choice of tibiotalar arthritis. Because the results of ankle replacement may not be durable, fusing the ankle is an equally good[A8] method of creating a pain-free joint. Furthermore, the ability of the knee and subtalar joints to compensate for a stiff ankle has made this procedure more tolerable.

TOTAL JOINT ARTHROPLASTY

Joint arthroplasty refers to the re-creation of congruent joint surfaces, typically with artificial parts. In certain patients and in non–load-bearing joints such as the elbow, interpositional arthroplasty can be performed by placing a tissue graft between the arthritic surfaces. For weight-bearing joints (e.g., the hip, knee) as well as the shoulder, however, metal and plastic materials produce the most durable results, so the procedures are commonly called total hip, knee, and shoulder replacements. In such procedures, the articular surfaces are replaced by shaped materials designed to recreate the joint kinematics.

In general, once the articular cartilage is completely worn or destroyed on both sides of the joint, arthroplasty becomes the most predictable option to relieve pain. Because a total joint arthroplasty involves artificial, moving components, the replaced joints are subject to the same wear and tear as native joints. Thus, they have a finite lifespan, which is dependent upon a patient's weight and activity level, as well as the implant materials. After total joint arthroplasty, it is advisable to reduce stresses upon the joint by weight loss and avoidance of impact activities. Walking, cycling, and gliding-type activities are permitted but, in general, running and jumping should not be performed. Subsequent revisions of joint replacements can be difficult and less durable, so it is wise to defer joint arthroplasty until there are no other options. Emerging data support a decreased revision rate when total hip replacements and total knee replacements are performed with computer navigation assistance. A growing trend in the United States is to perform total joint arthroplasty as an outpatient procedure in a surgical center, with selected patients able to be discharged to home on the same day of the operation.[3]

Hip

Total hip replacement, which is the treatment of choice for end-stage arthritis,[4] is the removal of the arthritic femoral head at the level of the femoral neck and removal of enough acetabular bone to place a prosthetic socket. The femoral implant is inserted into the intramedullary canal and anchored with bone-ingrowth techniques or bone cement. The surgical approach can be anterior, supercapsular,[A9] or posterior,[5] with the latter generally requiring more recovery time but associated with fewer major complications. The weight-bearing materials for the hip can be metal-on-polyethylene,

ceramic-on-polyethylene, or ceramic-on-ceramic, depending on the patient's age and activity level, as well as the surgeon's preference (Fig. 255-3). Using modern implant materials and surgical techniques, implant survival rates are 90 to 95% at 20 years, but longevity varies depending upon factors such as the patient's weight and activity.[6]

Hip resurfacing is quickly increasing as an alternative to total hip replacement in younger, more active patients.[7] The primary benefit is the preservation of proximal femoral bone in the event that future (revision) surgery is necessary. Rather than removing the femoral head and a portion of the femoral neck, as in total hip replacement, the bone is sculpted to accept a metal resurfacing cap (like a tooth), thereby preserving an additional 4 to 5 cm of bone (Fig. 255-4). The acetabulum is prepared to accept a metal socket, thereby creating a metal-on-metal joint. The preservation of the proximal femoral bone raises an additional risk of failure (i.e., femoral neck fracture below the resurfacing implant), which is estimated to occur in 1% of cases. Although hip resurfacing has no defined age limits, the best candidates have been males under the age of 55, likely because the bone quality in this demographic group is the strongest. In this age group, hip resurfacing has a 90 to 95% joint survival rate, free of revision, which is an equivalent outcome to total hip replacement at the same time point. However, concerns regarding longevity, a greater short-term failure rate than total hip replacement, poorer results in women, and metal ion release have led to questions concerning the superiority of the procedure.

FIGURE 255-3. Radiograph of a total hip replacement consisting of uncemented acetabular and femoral components. The articulating material are a metal ball and polyethylene liner.

FIGURE 255-4. Radiograph of a patient with a right total hip replacement and a left hip resurfacing. The total hip replacement consists of a longer stem placed into the medullary canal of the femur. The hip resurfacing implant preserves the proximal femoral bone.

For hip fractures, accelerated surgery within 6 hours of diagnosis is no better than standard care.[A10] In patients who are independently ambulating before suffering from displaced femoral neck fractures, total hip arthroplasty is perhaps slightly better than hemiarthroplasty in terms of future function and quality of life.[A11] If hemiarthroplasty is chosen, a cemented fixation is preferred.[8]

Knee

Total knee replacement[9] involves the removal of the arthritic surfaces of the tibia and femur, followed by their replacement with a metal femoral implant and a metal and/or polyethylene tibial component (Fig. 255-5). The recovery from total knee replacement is more difficult than after total hip replacement because of greater postoperative pain and the emphasis on regaining motion. Nonetheless, pain relief and function are usually excellent once recovery is complete.[A12] Implant survival is 90 to 95% at 15 years, depending upon patient factors.

However, only about 70 to 85% of patients may be satisfied with their pain relief following the procedure, likely because of the difficulty in reproducing the complex ligamentous interactions of the native knee joint with metal and plastic components. This problem has led to a growing use of unicompartmental or partial knee replacement in appropriate candidates, in an attempt to preserve the native ligamentous structures. In unicompartmental knee replacement, which is a bone-preserving implant for the knee, only one of the three knee compartments is replaced with a prosthetic device (see Fig. 255-6), so candidates must have arthritis limited to a single compartment. Because surgical trauma and dissection are significantly reduced compared with total knee replacement, recovery tends to be less painful and quicker. Furthermore, because the native ligaments of the knee are preserved, patients have a greater range of motion and satisfaction level compared with total knee replacement. However, the failure rate at 10 to 15 years is higher for unicompartmental knee replacement because of the possibility of developing arthritic changes elsewhere in the joint.

Shoulder

Although less commonly performed than hip and knee replacement, total shoulder replacement is an excellent pain-relieving procedure for glenohumeral arthritis.[10] Total shoulder replacement uses a stemmed humeral implant with a metal ball and metal and/or polyethylene glenoid socket. Total shoulder replacement requires an extensive rehabilitation protocol to regain range of motion and strength, but 95% of patients have pain-free use of the shoulder by 1 year after surgery.

Elbow, Ankle and Wrist

The elbow,[11] ankle, and wrist are less frequently replaced joints. With the exception of the rheumatoid wrist, these joints are less commonly afflicted by chronic arthritis. Further, the smaller bones making up these joints also translate to a diminished surface area for implant fixation, thereby reducing the durability of the surgical procedures. Although total joint arthroplasty can be successful at

FIGURE 255-5. Radiograph of a total knee replacement. The components are metal, with a polyethylene insert between the tibial and femoral components.

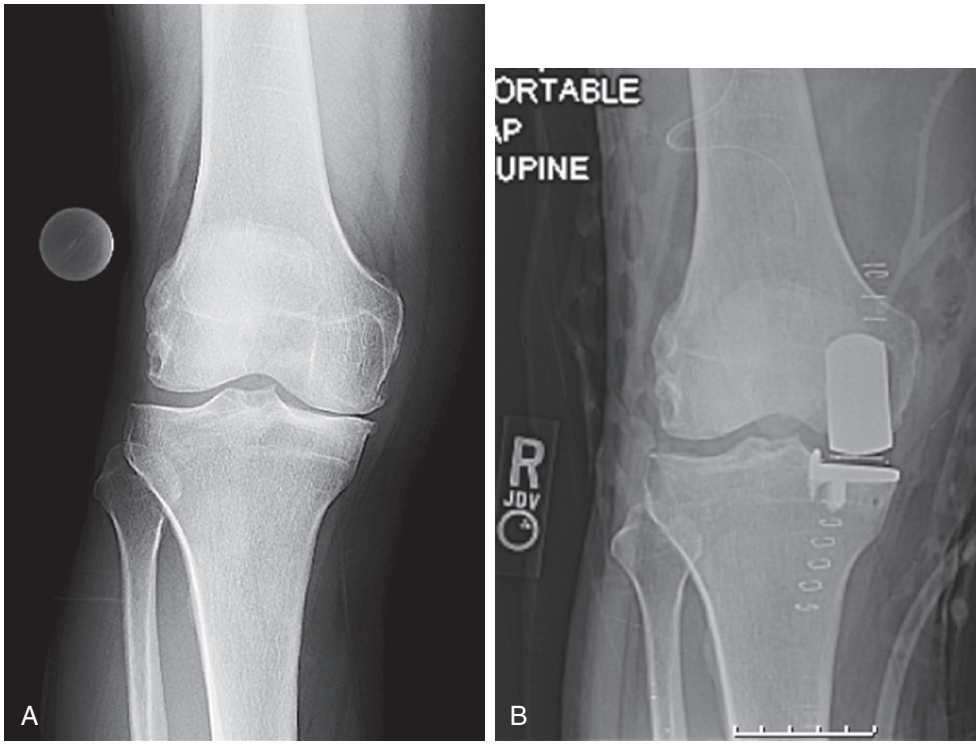

FIGURE 255-6. A, Radiograph of a knee with arthritis limited to the medial compartment. B, A medial unicompartmental knee replacement.

relieving pain in the short-term, 10-year results do not approach that of total hip or knee replacement. Synovectomy remains an effective surgical option in selected patients with inflammatory arthritis of the elbow, ankle, or wrist.

Spine

Surgery for diseases of the spine is discussed in Chapter 369.

SURGICAL COMPLICATIONS

POSTOPERATIVE PAIN

Options for the control of postoperative pain include the traditional intravenous or intramuscular routes of narcotic medications (Table 26-6), the use of spinal or epidural analgesia, and the local infiltration of anesthetics into the surgical site. In patients without contraindications (Chapter 26), parenterally administered nonsteroidal anti-inflammatory agents (NSAIDs; Table 26-4) are also useful to reduce narcotic requirements after major surgery. The direct administration of local mixtures of medications, including long-acting anesthetics and anti-inflammatory drugs, has become more popular because of the ease of use and excellent efficacy, particularly around the hip and knee joints. For both total hip replacement and total knee replacement, dexamethasone (4 to 8 mg perioperatively) can reduce postoperative nausea and vomiting, reduce pain, and facilitate earlier discharge from the hospital.[A13,A14] Nerve blocks have largely replaced patient-controlled epidural anesthesia in the outpatient setting. Pain relief facilitates postoperative physical therapy, which is important for the restoration of range of motion.

INFECTION

Periprosthetic joint infection remains a rare but devastating complication, especially after total joint arthroplasty. Because of the ability of microbiologic organisms to form biofilms on the surface of the prosthetic implant, deep joint infections involving a prosthetic joint cannot be eradicated without surgical intervention.

The gold standard in treating chronic prosthetic joint infection has been a two-stage surgical procedure that includes debridement of infected tissues and removal of the implant during the first stage, with subsequent reimplantation of a new implant constituting the second stage (Chapter 251).[12] Typically, an antibiotic-impregnated cement spacer is inserted during the first stage as a temporary implant to deliver high-dose antibiotics (see Chapter 251) locally; it also serves to facilitate some movement at the joint, thereby making eventual surgical reimplantation easier. After the first stage, intravenous antibiotics are given for 6 weeks, followed by a drug holiday to allow for reassessment of possible persistent infection. If the surgically treated joint appears to be persistently infected, the first stage is repeated. Once a treated joint is clear of infection, the goal is to proceed with the second stage, which is reimplantation of the joint without further need for antibiotics. The typical time frame between the first and second stages is 3 to 6 months.

Another option is one-stage removal and reimplantation of the prosthesis, with intravenous antibiotics for 6 weeks (see Chapter 251), followed by extended oral antibiotics. This approach is best used in an immunocompetent host without soft-tissue compromise (such as a draining sinus) and when the microbiologic organism is particularly sensitive to antibiotics. The duration of the antibiotic suppression can vary but in general is for at least 6 months after the surgical procedure.

Debridement and implant retention is another option in acute infections of less than 4 weeks' duration. In this procedure, any implant parts that can be easily removed and replaced, such as the polyethylene liner, are exchanged for new parts. Intravenous antibiotics are typically given for 6 weeks and followed by lifelong chronic oral antibiotic suppression afterward.

In view of the morbid consequences of prosthetic joint infection, efforts to prevent and detect any infectious processes preoperatively and postoperatively are of utmost importance. The skin and urinary tract are sites of specific concern. In addition, dental consultation may be appropriate in patients with poor oral hygiene and dentition. In patients with a history of infection, particularly prior methicillin-resistant *Staphylococcus aureus,* preoperative surveillance cultures with topical treatment for positive results (Chapter 267) are often performed.

Prophylactic antibiotic therapy for total joint arthroplasty patients should begin less than 2 hours before surgery and continue for 24 hours. A common protocol involves cefazolin (1 g every 8 hours for three doses) or, in penicillin-allergic patients, vancomycin (1 g every 12 hours for two doses).

PERIPHERAL NERVE INJURIES

Peripheral nerve injuries, which arise more often after upper and lower extremity surgery, generally result from excessive traction on the nerve or, alternatively, as a consequence of nerve compression as a result of prolonged positioning of the extremity during surgery or in a cast. Early detection and intervention are critical. Patients with chronic neurologic conditions, such as neuropathies in the setting of diabetes or spinal stenosis, are at increased risk of nerve injury.

VENOUS THROMBOEMBOLISM

After orthopedic surgery, a complicated balance exists between a possible life-threatening pulmonary embolus and the potential for postoperative bleeding. A shorter intraoperative time and the use of epidural or regional anesthesia may

reduce the risk of deep venous thrombosis. Other intraoperative interventions, such as hypotensive anesthesia and intraoperative heparin administration, further reduce thrombogenesis. Mechanical methods to reduce the risk of thromboembolism include compression stockings, various pneumatic devices, and foot flexion-extension exercises.

The mainstays of prevention however, are early mobilization combined with prophylactic anticoagulation. Aspirin is often used for low-risk patients after elective total hip and knee arthroplasty, and it is as safe and effective as low-molecular-weight heparin after a fracture of an extremity or of the pelvis or acetabulum.[A15] For higher risk patients,[13] regimens include direct-acting oral anticoagulants (Table 70-6)[A16] and low-molecular-weight heparin (Tables 68-7 and 70-3), with data indicating that rivaroxaban is more effective than enoxaparin to prevent venous thromboembolism in orthopedic patients undergoing lower limb surgery.[A17] Such anticoagulants are often used in combination with various mechanical compression devices. Emerging data suggest that inhibition of factor XI may be equally effective and safer for prophylaxis (Chapter 68).[A18]

FAT EMBOLISM

Fat embolization (Chapter 68), a well-described complication of skeletal trauma, may also occur after procedures involving instrumentation of the femoral medullary canal. The embolization of some amount of fat is believed to occur in almost all patients who sustain hip or femoral fractures. Among patients undergoing joint replacement surgery (particularly simultaneous bilateral procedures), 1 to 3% develop fat embolism syndrome,[14] which is discussed in detail in Chapter 68.

PERIOPERATIVE ARTHRITIS MEDICATION

The scheduling of joint surgery often must consider the ongoing use of a variety of rheumatologic medications. Guidelines are available to determine which should be continued or discontinued (E-Table 255-1).[15]

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E-TABLE 255-1 MEDICATIONS FOR THE PERIOPERATIVE MANAGEMENT OF PATIENTS UNDERGOING ELECTIVE TOTAL HIP OR TOTAL KNEE ARTHROPLASTY*

	DOSING INTERVAL	RECOMMENDED TIMING OF SURGERY SINCE LAST MEDICATION DOSE
MEDICATIONS TO CONTINUE THROUGH SURGERY		
DMARDs: continue these medications through surgery (all patients)		
Methotrexate	Weekly	Anytime
Sulfasalazine	Once or twice daily	Anytime
Hydroxychloroquine	Once or twice daily	Anytime
Leflunomide (Arava)	Daily	Anytime
Doxycycline	Daily	Anytime
Apremilast (Otezla)	Twice daily†	Anytime†
Severe SLE-specific medications: continue these medications in the perioperative period in consultation with the treating rheumatologist‡		
Mycophenolate mofetil	Twice daily	Anytime
Azathioprine	Daily or twice daily	Anytime
Cyclosporine	Twice daily	Anytime
Tacrolimus	Twice daily (IV and PO)	Anytime
Rituximab (Rituxan)	IV every 4-6 months†	Month 4-6†
Belimumab SQ (Benlysta)	Weekly†	Anytime†
Belimumab IV (Benlysta)	Monthly†	Week 4†
Anifrolumab (Saphnelo)§	IV every 4 weeks†	Week 4†
Voclosporin (Lupkynis)§	Twice daily†	Continue†
MEDICATIONS TO WITHHOLD PRIOR TO SURGERY¶		
Biologics: withhold these medications through surgery		
Infliximab (Remicade)	Every 4, 6, or 8 weeks	Week 5, 7, or 9
Adalimumab (Humira)	Every 2 weeks	Week 3
Etanercept (Enbrel)	Every week	Week 2
Abatacept (Orencia)	Monthly (IV) or weekly (SQ)	Week 5; week 2
Certolizumab (Cimzia)	Every 2 or 4 weeks	Week 3 or 5
Rituximab (Rituxan)	2 doses 2 weeks apart every 4-6 months	Month 7
Tocilizumab (Actemra)	Every week (SQ) or every 4 weeks (IV)	Week 2; week 5
Anakinra (Kineret)	Daily	Day 2
IL-17 secukinumab (Cosentyx)	Every 4 weeks	Week 5
Ustekinumab (Stelara)	Every 12 weeks	Week 13
Ixekizumab (Taltz)§	Every 4 weeks†	Week 5†
IL-23 guselkumab (Tremfya)§	Every 8 weeks†	Week 9†
JAK inhibitors: withhold this medication 3 days before surgery#		
Tofacitinib (Xeljanz)	Daily or twice daily†	Day 4†
Baricitinib (Olumiant)§	Daily†	Day 4†
Upadacitinib (Rinvoq)§	Daily†	Day 4†
Not severe SLE: withhold these medications 1 week before surgery		
Mycophenolate mofetil	Twice daily	1 week after last dose†
Azathioprine	Daily or twice daily	1 week after last dose
Cyclosporine	Twice daily	1 week after last dose†
Tacrolimus	Twice daily (IV and PO)	1 week after last dose†
Rituximab (Rituxan)	Every 4-6 months	Month 7
Belimumab IV (Benlysta)	Monthly†	Week 5†
Belimumab SQ (Benlysta)	Weekly†	Week 2†

*Dosing intervals obtained from prescribing information provided online by pharmaceutical companies. Adapted from the 2017 American College of Rheumatology/American Association of Hip and Knee Surgeons guideline.

†Recommendation that has changed since 2017.

‡Severe SLE indicates organ-threatening disease.

§Drug added for 2022 update.

¶For patients with rheumatoid arthritis, ankylosing spondylitis, psoriatic arthritis, or all SLE for whom antirheumatic therapy was withheld before undergoing total joint arthroplasty, antirheumatic therapy should be restarted once the wound shows evidence of healing; any sutures/staples are out; there is no significant swelling, erythema, or drainage; and there is no ongoing nonsurgical site infection, which is typically ~14 days.

#Recommendation pertains to infection risk and does not account for risk of cardiac events or venous thromboembolism.

DMARDs = disease-modifying antirheumatic drugs; IL-17 = interleukin-17; IV = intravenous; PO = by mouth; SLE = systemic lupus erythematosus; SQ = subcutaneous.

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256 INTRODUCTION TO MICROBIAL DISEASE: PATHOPHYSIOLOGY AND DIAGNOSTICS

ROBIN PATEL AND VICTORIA J. FRASER

Infectious diseases have profoundly influenced the human genome and the course of human history. As of early 2023, severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2; Chapters 335 to 337) infection has caused nearly 7 million deaths worldwide. Beginning in the 1980s, acquired immunodeficiency syndrome (AIDS; Chapters 353 to 359) disrupted the social fabric of many countries, especially in Africa, and distressed health care systems in the United States and other parts of the world. Approximately 38 million people worldwide are currently infected with human immunodeficiency virus (HIV), and since 1981, approximately 37 million people have died (about 700,000 in the United States alone). Deaths due to HIV/AIDS peaked at 1.9 million a year in 2005 and fell to 650,000 by 2021. Even before the SARS-CoV-2 pandemic, about 2.5 million people died annually worldwide from lower respiratory tract infections. Globally, an estimated 241 million new malaria infections occur annually, with 627,000 associated deaths. Each year, over 1.5 million people die worldwide from diarrheal diseases.

Serious infectious diseases may be associated with more morbidity over time due to rising global temperatures (Chapter 17).[1] The World Health Organization (WHO) predicts that climate change will result in 250,000 additional deaths per year between 2030 and 2050. Of this increase, about 110,000 deaths will be related to malaria (Chapter 316) and diarrheal disease owing to expansion of insect vector populations and increased coastal flooding, respectively.

Infection can be defined as the multiplication of microbes (from viruses to multicellular parasites) in blood and/or host tissues. The host may or may not experience symptoms. For example, HIV infection may not cause any overt signs or symptoms of illness for years. The definition of infection also includes multiplication of microbes on the surface or in the lumen of the host, thereby causing signs and symptoms of illness or disease. For example, toxin-producing strains of *Escherichia coli* (Chapter 280) may multiply in the gut and cause a diarrheal illness without invading tissues. Microbes can cause diseases without actually coming in contact with the host by virtue of toxin production. *Clostridium botulinum* (Chapter 271) may grow in certain improperly processed foods, producing a toxin that can be lethal on ingestion. A relatively trivial infection, caused by *Clostridium tetani* (Chapter 271) in a small puncture wound, can cause devastating illness because of a toxin released from the organism growing in tissues. It has now become apparent that multiple virulence factors of microorganisms can be carried in tandem on so-called pathogenicity islands of the genome (the "virulome").

Humans live in a virtual sea of microorganisms, with all body surfaces having indigenous bacterial microbiota (Chapter 257). An individual's native microbiota constitute as many cells as their human cells. Our normal microbiota protects us from infection. Alterations of gut microbiota increase susceptibility to infection by pathogens such as *Salmonella enterica* (Chapter 284) and *Clostridioides difficile* (Chapter 271). Bacteria that constitute normal microbiota microorganisms are thought to exert a protective effect by several mechanisms: using nutrients and occupying an ecologic niche, thus competing with pathogens; producing antibacterial substances that inhibit growth of pathogens; and inducing host immunity that is cross-reactive against pathogens. These mechanisms appear to be oversimplistic, however. For example, gut colonization with *Bacteroides fragilis* expressing an immunodominant bacterial polysaccharide causes dendritic cell activation and induction of a T_H1-mediated response, thereby leading to a splenic response characterized by normal numbers of $CD4^+$ T cells, lymphoid architecture, and systemic lymphocytic expansion. Thus, a single bacterial molecule in our gut can improve immunologic fitness, and a healthy, diverse microbiome is vital to proper immune system function.

Only a small proportion of microbial species can be considered primary pathogens, and even among these species, a relatively small number of clones cause disease. For example, epidemic meningococcal meningitis and meningococcemia (Chapter 274) are due to a small number of clones of *Neisseria meningitidis*, and the worldwide explosion of penicillin-resistant *Streptococcus pneumoniae* (Chapter 268) can be traced to a few clones originating in South Africa and Spain. This observation supports the concept that pathogenic organisms are highly adapted to the pathogenic state and have developed characteristics that enable them to be transmitted, to attach to surfaces, to invade tissue, to avoid host defenses, and thus to cause disease. In contrast, opportunistic pathogens, which may be harmless members of normal microbiota of healthy persons, can act as virulent invaders in patients who have severe defects in host defense mechanisms. However, opportunistic infection is not simply an exploitation of a weakened host by relatively avirulent pathogens. *Pseudomonas aeruginosa* (Chapter 282), for example, recognizes immunologic perturbations in the host and reacts by expressing virulence factors.

Pathogenic organisms may be acquired by several routes. For example, direct contact has been implicated in acquisition of staphylococcal disease (Chapter 267). Aerosols and droplets spread SARS-CoV-2 (Chapters 335 and 336). Contaminated water is the usual vehicle in *Giardia* infection (Chapter 322) and typhoid fever (Chapter 284). Food-borne illnesses may be caused by extracellular toxins produced by *Clostridium perfringens* (Chapter 271) and *Staphylococcus aureus* (Chapter 267). Blood and blood products may be vectors for transmitting hepatitis B and C viruses (Chapter 134) as well as HIV (Chapter 353). Sexual transmission is also important for these agents and for a variety of other pathogens, including *Treponema pallidum* (syphilis; Chapter 295), *Neisseria gonorrhoeae* (gonorrhea; Chapter 275), and *Chlamydia trachomatis* (urethritis; Chapter 294). The fetus may be infected in utero; infection may be devastating if the agent is rubella virus (Chapter 339), cytomegalovirus (Chapter 347), or parvovirus B19 (Chapter 342). Arthropod vectors are also important, as illustrated by mosquitoes for malaria (Chapter 316) and dengue (Chapter 352); ticks for Lyme disease (Chapter 296), anaplasmosis, and ehrlichiosis; and lice for typhus (Chapter 302).

Pathogens are able to cause disease because of a finely tuned array of adaptations, including the ability to attach to appropriate cells, often mediated by specialized structures, such as pili. Microbes such as *Shigella* species (Chapter 285) have the ability to invade cells and cause damage. Toxins may act at a distance or affect only infected cells. Pathogens can thwart host defenses by a variety of ingenious maneuvers. The antiphagocytic coat of the pneumococcus (Chapter 268) is an example. Organisms may change their surface antigen display at a rapid rate to outmaneuver the host immune system. Examples include influenza virus (Chapter 332) and trypanosomes (Chapters 317 and 318). Certain pathogens (e.g., *Toxoplasma gondii*; Chapter 320) can inhibit the respiratory burst of phagocytes, and others (e.g., *Streptococcus pyogenes*; Chapter 269) can destroy phagocytic cells that have engulfed them. The environment plays an important role in infection, both in transmission and in the host's ability to combat the invader. The humidity and temperature of air may affect infectivity of airborne pathogens. The sanitary state of food and water, woefully lacking in many areas of the world, is an important factor in the acquisition of enteric pathogens. It is also likely that micronutrient deficiency contributes to the invasion and multiplication of certain pathogens.

Host reaction to infection may result in illness. For example, previous infection with *Campylobacter jejuni* (Chapter 279) is responsible for about 40% of cases of Guillain-Barré syndrome (Chapter 388). The mechanism is thought to be production of antibodies against *C. jejuni* lipopolysaccharides that cross-react with gangliosides in peripheral nerves. Similarly, much of the damage resulting from meningitis is due to the host's response to invading bacterial pathogens.

With some exceptions, infectious diseases are treatable and curable, so it is important to make an accurate diagnosis and to institute appropriate therapy promptly. In acute infections such as pneumonia (Chapter 85), meningitis (Chapter 381), or sepsis (Chapter 94), rapid institution of therapy can be lifesaving. In such cases, treatment (based on history, physical examination, and epidemiology of illness in the community) should be started even if a definitive diagnosis has not been confirmed. Antimicrobial therapy for the presumptive causative agent(s) can later be re-evaluated as more definitive diagnostic information becomes available. Rapid diagnostic techniques, including Gram stains, antigen detection, or nucleic acid amplification testing, often can be helpful.

EMERGING INFECTIONS

Recent examples of emerging infections with a major impact on public health in the United States and internationally include HIV, community-associated methicillin-resistant *S. aureus* (MRSA), a hypervirulent strain of *C. difficile*, 2009 H1N1 influenza, multidrug-resistant gram-negative bacteria (e.g., carbapenem-resistant Enterobacterales), *Candida auris*, Kratom-associated salmonellosis, and SARS-CoV-2. Examples of recent localized outbreaks include but are not limited to cholera (Yemen), diphtheria (Bangladesh), H7N9 influenza

ABSTRACT

Infections are a major cause of morbidity and mortality worldwide. Only a fraction of microorganisms are recognized as primary human pathogens as a result of their having abilities to attach to and/or enter human cells, produce toxins, and/or evade the host immune system. By comparison, commensal organisms in the human microbiome are essential for human health.

Pathogenic organisms may be acquired by a variety of means, including via direct contact, aerosols, droplets, contaminated food or water, sexual contact, blood, tissue products, organ transplantation, or arthropod vectors, such as mosquitoes or ticks. Emerging infections, including most recently severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), can spread quickly in the global era.

If appropriately diagnosed, infections are often treatable, with many being curable. The diagnostic evaluation for infectious diseases requires knowledge of the appropriate test(s) to order, as well as their correct interpretation. Testing includes not only stains and cultures but also the detection of antibodies and antigens, as well as the increasing use of nucleic acid amplification tests, such as the polymerase chain reaction, and sequencing.

KEYWORDS

pathogen
microbiome
antimicrobial resistance
diagnostics
culture
PCR

(China), listeriosis (South Africa), plague (Madagascar), yellow fever (Brazil), Zika (the Americas), chikungunya (the Americas), and Ebola (West Africa).

More than 400 new, emerging, or reemerging infectious diseases have been described over the past 70 years, approximately 60% of which are zoonoses associated with geographic "hot spots." The emergence of these infections is driven largely by ecologic, socioeconomic, and environmental factors.

GENOMICS

The exact genomic sequence of thousands of microbes relevant to humans has been determined, and careful analysis will yield important information about the pathogenesis of infection.[2] For example, genome sequencing of *S. pyogenes* (Chapter 269), collected over time with relevant robust clinical information, has detected the acquisition of new determinants that are responsible for increased virulence and that result in toxic shock syndrome, necrotizing fasciitis, or both.

GENETIC SUSCEPTIBILITY AND RESPONSE TO INFECTION

Genomics can provide new and significant information relevant to an individual's response to an infectious disease. For example, an overvigorous response, with generation of tumor necrosis factor-α, may accentuate development of cerebral complications in *falciparum* malaria. Analysis of single-nucleotide polymorphisms of the human genome could lead to enhanced understanding of two fundamental issues in infectious diseases: why invasive, overt disease develops in only a small fraction of individuals challenged with a given microbe and why infections are more severe in some people than in others. Variants in genes that encode molecules that mediate attachment, pathogen recognition, inflammatory cytokine response, and innate and adaptive immunity are being identified at an astonishing rate. For example, inherited deficiencies of C3, alternative pathway components (factor D, properdin, factor H, and factor I), and terminal complement pathway components (C5 through C9) are associated with an increased incidence of invasive meningococcal and gonococcal infection.

INNATE IMMUNITY

The identification of pattern recognition receptors (e.g., toll-like receptors and nucleotide oligomerization domain–like receptors) that recognize pathogen-associated molecular patterns, as well as endogenous substances reflecting tissue injury (e.g., alarmins), has revolutionized understanding of the early host response to infection. Agonists or antagonists of toll-like receptors have already entered clinical trials as adjuvant therapies or to improve the immunogenicity of vaccines. Antimicrobial peptides (e.g., defensins, cathecidins, histatins, galectins) also have an important role in the early response to infectious disorders and can also be leveraged as diagnostics. As an example, alpha-defensin testing of synovial fluid is used to diagnose infections associated with joint prostheses.

ANTIMICROBIAL RESISTANCE

The development of new antibacterial agents has slowed despite the burgeoning problem of antimicrobial resistance. Drug-resistant bacteria can spread easily in health care facilities and through international travel. Urgent threats include carbapenem-resistant *Acinetobacter* species (Chapter 283), *N. gonorrhoeae* (Chapter 275), *C. auris* (Chapter 310), *C. difficile* (Chapter 271), and carbapenem-resistant Enterobacterales (Chapter 281), whereas serious threats include drug-resistant *Campylobacter* species (Chapter 279), *Candida* species (Chapter 310), *Salmonella* (Chapter 284) and *Shigella* species (Chapter 285), *S. pneumoniae* (Chapter 268), tuberculosis (Chapter 299), extended-spectrum beta-lactamase–producing Enterobacterales (Chapter 281), MRSA (Chapter 267), vancomycin-resistant enterococci (Chapter 270), and multidrug-resistant *P. aeruginosa* (Chapter 282).[3]

Sometimes the trade-off between antimicrobial success and antibiotic resistance is challenging. For example, mass azithromycin use can reduce childhood mortality in sub-Saharan Africa but at the expense of a seven- to eight-fold increase in macrolide resistance.[A1]

THE ROLE OF INFECTIOUS AGENTS IN CHRONIC DISEASES

Hepatitis B and C viruses (Chapter 135), human papillomavirus (Chapter 344), and *Helicobacter pylori* (Chapter 125) are among the infectious agents that can cause human cancers. Furthermore, colorectal cancers often harbor bacteria.

Many so-called idiopathic diseases also may have an infectious basis, as was discovered for Whipple disease (Chapter 305) in about 1990. Conditions for which there is some evidence (but not conclusive proof) of an infectious basis include diabetes, atherosclerosis, acute leukemia, collagen vascular diseases, and inflammatory bowel disease. Detection of uncultivatable microorganisms by newer techniques, such as 16S ribosomal RNA gene or shotgun metagenomic analysis, may uncover agents responsible for diseases hitherto considered noninfectious or suggest a role in conditions that are considered infectious but in which the pathogen or pathogens are controversial.

DIAGNOSIS

Three questions need to be answered with microbiologic testing. The first is whether a patient's illness is microbial in nature. The second is to define the organism(s) causing the illness. The third is to determine how the patient should be treated. If treatment is not directly evident from the nature of the organism detected, susceptibility testing is performed, typically on an organism recovered in culture.

Diagnostic testing for infectious diseases requires appropriate ordering and interpretation of results.[4] As clinical microbiology tests become increasingly complex, consultation with infectious diseases specialists or clinical microbiologists is recommended in challenging situations. Infections can be caused by hundreds of species of microorganisms, ranging from bacteria to viruses, fungi, protozoa, parasites, and even algae. Simply detecting an organism does not mean that it is causing the patient's illness, because of the possibility of it being contaminating or colonizing microbiota or from a prior infection. Testing methods, which include direct detection using visualization (often with specific stains), culture (which may be specialized, depending on the organism type), and molecular, proteomic, metabolomic, and immunologic methods, are ever-expanding and may vary from laboratory to laboratory. Nucleic acid amplification tests, which amplify microbial nucleic acid (DNA and/or RNA, depending on the organism targeted) are increasingly used in clinical practice. The most common nucleic acid amplification test in clinical use is the polymerase chain reaction (PCR), but many other technologies are available.[5] With PCR, a specific segment of DNA is amplified using a pair of primers (Fig. 256-1) (forward and reverse) in a reaction that includes the bases needed to synthesize DNA (deoxynucleotide triphosphates) and a heat-stable DNA polymerase. The reaction itself involves serial cycling of temperatures to anneal the primers, synthesize DNA between them (via an enzyme called DNA polymerase), and then convert DNA from double- to single-stranded DNA to allow the reaction to recur. The upshot is that at the end of temperature cycling, the targeted DNA segment, if present, is exponentially amplified; the amplified DNA is detected using one of a variety of strategies, including fluorescently labeled probes that hybridize to amplified DNA during the course of the PCR reaction—so-called real-time PCR. The cycle number at which this signal is detected, referred to as the cycle threshold value, is a general indicator of the amount of target nucleic acid present, with lower cycle threshold values correlating with the presence of higher amounts of target DNA. Measurement of host response to infection, including traditional serologic testing, interferon-γ release assays, and measurement of host transcriptional or proteomic responses, may be applied. Organisms isolated in culture are typically identified using the proteomic technology matrix-assisted laser desorption ionization time-of-flight mass spectrometry, which enables accurate identification of a myriad of bacterial and fungal isolates in minutes.

Collection of Specimens

The quality of microbiology results depends not just on testing in the laboratory but also on proper selection, collection, and transportation of specimens for testing. Specimens for microbiology testing are ideally collected, especially for culture-based tests, before administration of antimicrobial agents. It is important for those collecting specimens to ensure proper specimen collection; specimens of poor quality may be rejected by the laboratory but only if the laboratory can identify them as such (e.g., a putative sputum specimen that is really just oropharyngeal secretions). Certain types of tests are inappropriate for some specimen types (e.g., anaerobic cultures on sputum). Swabs hold minute volumes and are recommended in limited situations (e.g., throat swabs to diagnose *S. pyogenes* pharyngitis and nasal or nasopharyngeal swabs to diagnose SARS-CoV-2 infection). Flocked swabs, which efficiently release their contents, are increasingly used. If tissues or fluids can be collected, they are preferred over swabs.

Blood Cultures

Blood cultures, typically incubated for 5 days on modern continuous-monitoring blood culture instruments, allow recovery of most cultivable bacteria and most *Candida* species. Growth usually occurs within the first day of incubation; rapid tests for identification and susceptibility testing can be performed on the

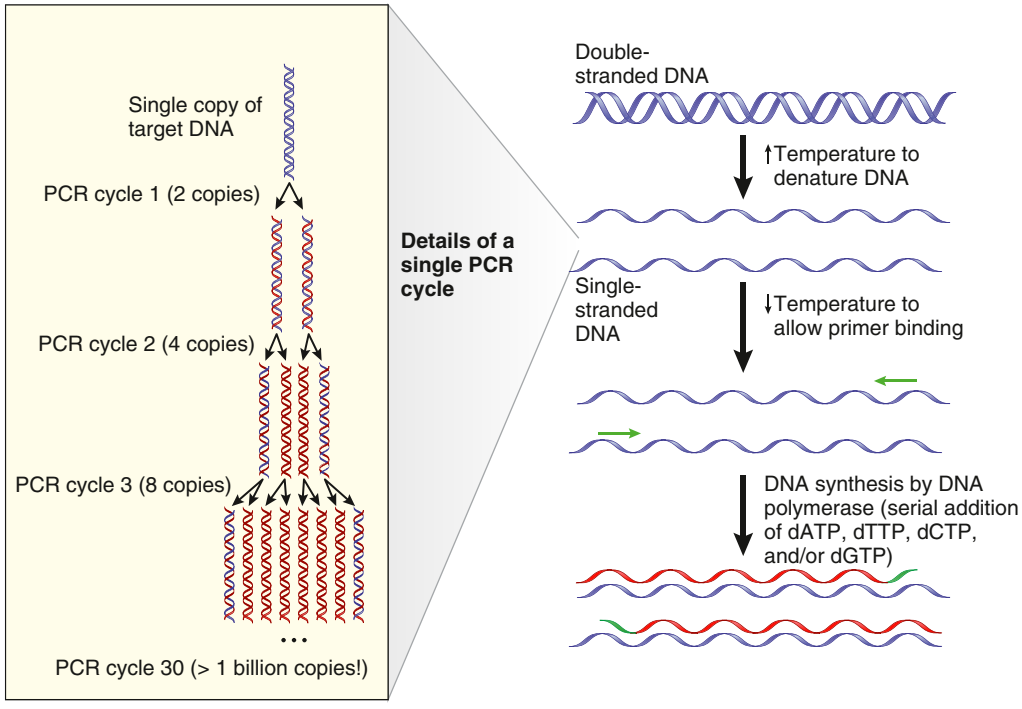

FIGURE 256-1. Polymerase chain reaction (PCR). dATP = deoxyadenosine triphosphate; dCTP = deoxycytidine triphosphate; dGTP = deoxyguanosine triphosphate; dTTP = thymidine triphosphate.

contents of positive blood cultures to provide expedited results.[6] Mycobacteria and dimorphic fungi ideally require specialized blood cultures and longer incubation times.

Collection of an optimal volume of blood and drawing blood cultures before administration of antibiotics are quality practices for conventional blood cultures. For adults, two culture sets or draws, each consisting of 20 to 30 mL of blood, should be obtained from separate venipuncture sites after each site has been disinfected (e.g., with chlorhexidine or 2% iodine tincture) and then inoculated into at least one aerobic and one anaerobic bottle per set. There is no need to space blood culture draws over time. Single-draw blood cultures are discouraged. Clinicians are notified when a blood culture becomes positive, but it may not be immediately clear whether the identified organism represents a pathogen or a contaminant. Contaminated blood cultures are common, with acceptable contamination rates as high as 3%, and can cause clinical confusion. Contamination can be recognized when blood cultures yield organisms such as coagulase-negative *Staphylococcus* species or *Corynebacterium* species from a single set. To minimize contamination, a dedicated phlebotomy team is ideal. An approach to prevent contamination is to aspirate blood initially into a separate tube or vessel and then to obtain cultures with subsequent blood aspiration.[A2]

Although catheter-drawn blood cultures are generally discouraged, a catheter-drawn blood culture set alongside a simultaneously collected peripherally drawn blood culture set may be helpful to diagnose catheter-associated bacteremia. If both grow the same organism and the blood culture collected from the intravascular catheter becomes positive more than 2 hours before the culture drawn peripherally (differential time to positivity), there is a high likelihood of catheter-related bloodstream infection. In the case of multi-lumen catheters being assessed for catheter-associated bacteremia, consideration may be given to collection of blood through each lumen, along with a peripheral draw.

To diagnose infective endocarditis (Chapter 61), routine blood cultures are suggested; if negative, *Bartonella* and Q fever serology should be considered. Histopathology, stains, and molecular diagnostics (e.g., 16S ribosomal RNA gene PCR/sequencing, *Tropheryma whipplei* nucleic acid amplification testing) may be applied to resected valves if the microbiologic diagnosis has not been established by other means.

Cerebrospinal Fluid

Cerebrospinal fluid can be useful to diagnose meningitis (Chapter 381) and some cases of encephalitis (Chapter 383) (e.g., herpes simplex virus, enterovirus). Sufficient sample should be collected for all desired tests; it is helpful to collect extra fluid to be stored in the laboratory in case add-on tests are later desired so as to avoid the need for a second lumbar puncture. Typically, three or four cerebrospinal fluid aliquots are collected in separate tubes. The first has the greatest potential for contamination and should not be used for microbiology studies. Gram stain prepared after cytocentrifugation of cerebrospinal fluid and bacterial culture should be performed (along with conventional blood cultures and measurement of opening pressure), with cell count and differential, glucose, and protein, for diagnosis of bacterial meningitis. Cryptococcal antigen testing is indicated if cryptococcal meningitis (Chapter 309) is possible. Nucleic acid amplification tests of cerebrospinal fluid are best for diagnosis of enteroviral and herpes meningitis/encephalitis. Pneumococcal antigen and nucleic acid amplification tests for varicella zoster virus should be considered in acute meningitis/encephalitis. A multiplex nucleic acid amplification test panel[7] is especially useful for detecting viruses if individual nucleic acid amplification tests are not available and in antibiotic-treated patients, but it is not a replacement for culture. For the diagnosis of tuberculous meningitis (Chapter 381),[8] acid-fast bacillus smear and culture of large volumes (≥5 mL) of cerebrospinal fluid, as well as nucleic acid amplification testing, are recommended. For more complicated cases, neurology and/or infectious diseases consultation is suggested, because the differential diagnosis is broad and the evaluation may be complex.

Respiratory Specimen Testing

S. pyogenes pharyngitis (Chapters 269 and 397) is diagnosed by collecting a swab of the throat and tonsils (avoiding the teeth, gums, and cheeks) and testing it using culture, a rapid antigen test, or a nucleic acid amplification test. Rapid antigen tests have limited sensitivity for *S. pyogenes*, especially in children, and negative results should ideally be confirmed by culture or a molecular assay. Nucleic acid amplification tests are ideally used to detect respiratory viruses[9] and *Bordetella pertussis* (Chapter 289).

For outpatient community-acquired pneumonia (Chapter 85),[10] specific testing is generally considered optional. For patients who are admitted to the hospital, however, pretreatment blood cultures, Gram stain and culture of sputum, and, if disease is severe, urine antigen tests for *Legionella pneumophila* and *S. pneumoniae* are recommended. Nucleic acid amplification tests are preferred for pneumonia caused by *Mycoplasma pneumoniae* (Chapter 293) or *Chlamydia pneumoniae* (Chapter 294) and for legionellosis (Chapter 290). For diagnosis of hospital-acquired and ventilator-associated pneumonia, induced sputum can be tested on nonintubated patients and endotracheal aspirates or bronchoalveolar lavage fluid on intubated patients, using Gram stain and culture; multiplex nucleic acid amplification test panels are available.

For diagnosis of pulmonary tuberculosis (Chapter 299), expectorated sputum (or induced sputum or bronchoscopically obtained specimens) should be submitted for acid-fast bacillus smear (three specimens), mycobacterial

culture (three specimens), and *M. tuberculosis* nucleic acid amplification testing (one specimen). In acid-fast bacillus smear–positive patients, a negative *M. tuberculosis* nucleic acid amplification test makes a diagnosis of pulmonary tuberculosis unlikely. In acid-fast bacillus smear–negative patients with an intermediate or higher level of suspicion for pulmonary tuberculosis, a negative *M. tuberculosis* nucleic acid amplification test cannot exclude pulmonary tuberculosis. Some nucleic acid amplification tests for *M. tuberculosis* both detect the organism and provide rapid molecular drug susceptibility testing (e.g., rifampin with or without isoniazid).

Stool

Community-acquired diarrhea often resolves in less than a week in the absence of treatment, so laboratory testing is not generally needed, unless the patient has fever, bloody diarrhea, dysentery, severe abdominal pain, or dehydration or is hospitalized or immunocompromised (Chapter 262). For travel-related diarrhea (Chapter 265) or community-acquired diarrhea persisting a week or longer, laboratory testing can be useful. The specimen of choice is diarrheal stool. Bacterial, parasitic, and viral gastroenteritis pathogens may be detected with commercial multiplex nucleic acid amplification tests, which can yield results in as little as 1 hour.[11] Routine stool cultures typically evaluate for *Salmonella*, *Shigella*, and *Campylobacter* species and should also include evaluation for Shiga toxin–producing *E. coli* using a nucleic acid amplification test or antigen assay. *Vibrio* and *Yersinia* culture may be separate, specific requests because they are performed using specialized media. Infection with *Giardia* species (Chapter 322), *Cryptosporidium* species (Chapter 321), or *Cyclospora cayetanensis* may present similarly to bacterial gastroenteritis, and these organisms are ideally identified using antigen detection or nucleic acid amplification tests. Likewise, norovirus (Chapter 350) and other viral etiologies of gastroenteritis are ideally detected by nucleic acid amplification tests; rotavirus (Chapter 350) can alternatively be detected using an antigen detection assay.

C. difficile–associated diarrhea is often associated with antecedent antibiotic use or hospitalization, although community-acquired cases occur; in suspected cases of *C. difficile*–associated diarrhea, specific testing is recommended by testing diarrheal stool using either a glutamate dehydrogenase antigen detection assay plus toxin A and B detection using an antigen detection assay (with or without arbitration by a nucleic acid amplification test for toxin-associated genes) or by performing a nucleic acid amplification test with toxin testing. Alternatively, a nucleic acid amplification test can be used alone, provided the patient being tested is likely to have *C. difficile*–associated diarrhea.

Urine

Differentiation of asymptomatic bacteriuria, cystitis, and pyelonephritis requires clinical evaluation because Gram stain and culture findings may be similar for the three (Chapter 263). Specimens submitted for bacterial urine culture should be collected in a way that minimizes contamination from perineal microbiota. The use of urine transport media, refrigeration after collection, and specimen collection with straight "in-and-out" catheterization decrease the growth of small numbers of contaminating organisms, which can result in false-positive results. Urine specimens from patients who have indwelling urinary catheters for even a few hours frequently have colonizing microbiota owing to biofilm formation on catheter surfaces, so positive urine cultures may not represent a true urinary tract infection.

For diagnosis of acute bacterial prostatitis (Chapter 114), the classic four-specimen approach, involving collection of the first 10-mL void, a midstream specimen, expressed prostate secretions, and a 10-mL post–prostate-massage urine may be used. The test is considered positive if there is a 10-fold higher bacterial count in the expressed prostate secretions than the midstream urine. A two-specimen version, involving only midstream urine and expressed prostate secretions, is an alternative.

Antimicrobial Susceptibility Testing

Antimicrobial susceptibility testing should be performed to guide ultimate narrow-spectrum antimicrobial agents even in situations in which broader empiric therapy must be started before culture and susceptibility results are known. The "gold standard" method for susceptibility testing is phenotypic susceptibility testing, which involves growing the organism with and without specific antimicrobial concentrations and then comparing results. The traditional measurement of susceptibility is the minimum inhibitory concentration (MIC), which is the lowest concentration of the antimicrobial agent that inhibits growth of the organism. To measure the MIC, the organism is grown in various concentrations of an antimicrobial agent. Use of the term *susceptible* implies that the MIC is at a concentration attainable in blood or other appropriate body fluid using usually recommended doses. *Resistant*, which is the converse of susceptible, implies that the MIC is not exceeded by normally attainable levels. In some situations, the MIC lies between susceptible and resistant levels, and the result may be reported as *intermediate* or *susceptible–dose dependent*, the latter to indicate that the antimicrobial agent may still be used but at increased doses. Urine levels of some antimicrobial agents (e.g., nitrofurantoin) may be so high as to enable their use to treat urinary tract infections even in the face of high MICs.

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257 THE HUMAN MICROBIOME

VINCENT B. YOUNG

The human microbiome has received considerable attention as a previously underappreciated factor in human health and disease.[1–4] Alterations in the microbiome are associated with several clinical conditions, and restoration of a normal intestinal microbiome can be beneficial in selected situations.

DEFINITIONS

The so-called normal flora of microbes that live in and on the human body are part of the normal human microbiome. Although most attention has been paid to bacteria, this term can also encompass the Archaea, yeast, and viruses. The term *microbiota* refers to the microbes themselves, whereas the term *microbiome* refers to a specific community of microbes (i.e., microbiota) and the specific environment that they inhabit. This distinction is important because the microbiome encompasses the microbiota and also the environment they inhabit. This environment is shaped not only by the microbes but also by the host and the external environment. For example, the intestinal microbiome is composed of the microbes that inhabit this organ as well as the intestinal contents, which includes compounds derived from food as well as from the human host, such as digestive enzymes, mucin, and bile acids.

STRUCTURE AND FUNCTION RELATIONSHIPS OF THE MICROBIOME

The function of microbes in a specific environment can be ascertained by examining not only the community members but also determining the complete metabolic environment that these microbes inhabit. This metabolic environment is defined not only by the microbes but also by the host.[5] A specific example is the metabolism of bile acids found in the intestinal tract. Synthesized in the liver and excreted in bile in the form of bile salts conjugated to the amino acids taurine and glycine, these primary conjugated bile salts are further metabolized by members of the intestinal microbiota, which can remove these conjugated amino acids and further alter the chemical structure through enzymatic activities such as dehydroxylation. Secondary bile acids, which result from the microbe-mediated conversion of primary bile acids, have different chemical properties and thus influence host physiology in a differential manner. Bile acid receptors are differentially stimulated by various secondary bile acids, so metabolism of bile acids by the microbiota will have a direct influence on host physiology.

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257 THE HUMAN MICROBIOME

VINCENT B. YOUNG

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The so-called normal flora of microbes that live in and on the human body are part of the normal human microbiome. Although most attention has been paid to bacteria, this term can also encompass the Archaea, yeast, and viruses. The term *microbiota* refers to the microbes themselves, whereas the term *microbiome* refers to a specific community of microbes (i.e., microbiota) and the specific environment that they inhabit. This distinction is important because the microbiome encompasses the microbiota and also the environment they inhabit. This environment is shaped not only by the microbes but also by the host and the external environment. For example, the intestinal microbiome is composed of the microbes that inhabit this organ as well as the intestinal contents, which includes compounds derived from food as well as from the human host, such as digestive enzymes, mucin, and bile acids.

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The function of microbes in a specific environment can be ascertained by examining not only the community members but also determining the complete metabolic environment that these microbes inhabit. This metabolic environment is defined not only by the microbes but also by the host.[5] A specific example is the metabolism of bile acids found in the intestinal tract. Synthesized in the liver and excreted in bile in the form of bile salts conjugated to the amino acids taurine and glycine, these primary conjugated bile salts are further metabolized by members of the intestinal microbiota, which can remove these conjugated amino acids and further alter the chemical structure through enzymatic activities such as dehydroxylation. Secondary bile acids, which result from the microbe-mediated conversion of primary bile acids, have different chemical properties and thus influence host physiology in a differential manner. Bile acid receptors are differentially stimulated by various secondary bile acids, so metabolism of bile acids by the microbiota will have a direct influence on host physiology.

ABSTRACT

The human microbiome has received considerable attention as a previously underappreciated factor in human health and disease. The microbiome plays an important role in nutrition and conditions such as inflammatory bowel diseases, intestinal and respiratory infections, and graft-versus-host disease. Restoration of a normal intestinal microbiome has beneficial effects in severe malnutrition and for the treatment of *Clostridioides difficile*.

KEYWORDS

microbiome
microbiota
microbial
ecology
precision medicine
Human Microbiome Project

STUDYING THE MICROBIOME

The microbiome is usually analyzed by nucleic acid sequencing–based techniques and mass spectrometry (E-Fig. 257-1). In some cases the information is limited to the structure (anatomy) of a microbial community in terms of the species composition and relative abundance of the microbes that are present. Functional data (physiology) can be gained by assaying metabolic potential or direct measurement of functional output in terms of gene expression and a catalog of the metabolites that are present in the microbiome. A remaining question that often lingers in these studies is whether specific changes that are associated with a specific health state is positive or merely reflects the altered environment that is created by the presence of that state. Ongoing research is endeavoring to determine whether alterations in the microbiome truly have a causal role for associated disease.

ESTABLISHMENT OF THE MICROBIOME

The birth mode can have at least a short-term effect on the composition of the microbiota of a newborn. Neonates who undergo vaginal birth have a distinct microbiome shortly after birth compared with children born by cesarean delivery. These distinctions resolve as the child grows older. What is unknown is whether these differences in early colonization have long-lasting effects on the health of the child. It is possible that these differences in initial microbiomes may underlie the known epidemiologic associations between cesarean birth and conditions such as asthma and allergies.

In addition to birth mode, a number of postnatal factors such as use of antibiotics, breast-feeding, diet, and host genetics are thought to affect the developing microbiota of the child (E-Fig. 257-2). After an "adult-like" microbiota is established, the microbiota varies by body region (Fig. 257-1) and among individuals,[6] but the sum total of the microbial genes shows much less variation (E-Fig. 257-3). The interpretation is that although the specific composition of the normal, healthy microbiota may vary from person to person, conserved functions are present in a healthy community.

ALTERATION OF THE MICROBIOME

Given the apparent conservation of microbiome function in healthy individuals, an extensive literature has evaluated alterations in the microbiota. However, a causal role by which the altered microbiota leads to disease has been demonstrated only for a few conditions.[7]

The microbiota possesses a wealth of metabolic potential for a wide range of catabolic and bioconversion activities (Fig. 257-2). Dietary substances such as carbohydrates and proteins can be metabolized by the indigenous

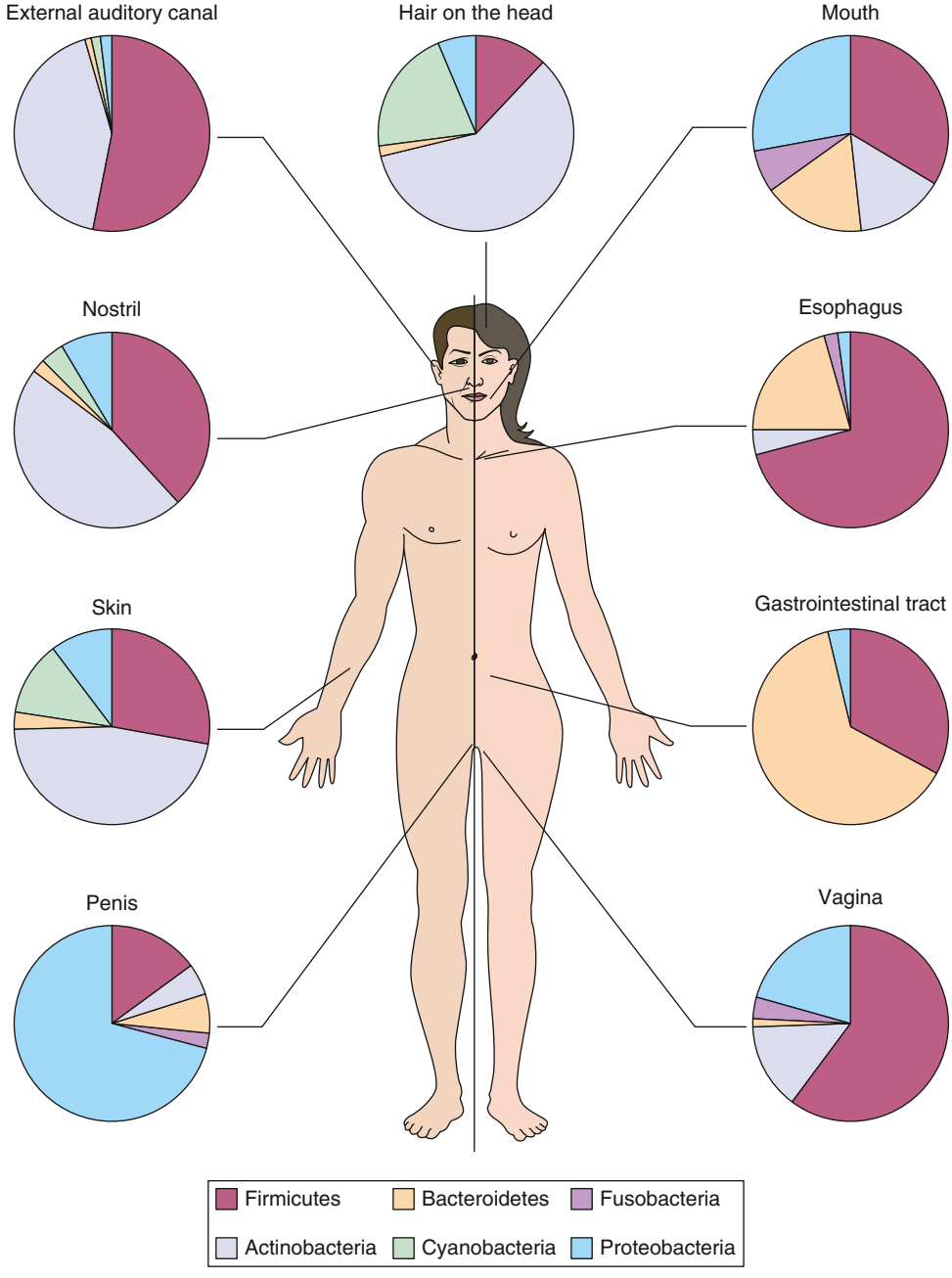

FIGURE 257-1. The relative abundances of the six dominant bacterial phyla in different body sites. Data are taken from multiple surveys of the microbiota. (From Spor A, Koren O, Ley R. Unravelling the effects of the environment and host genotype on the gut microbiome. *Nat Rev Microbiol*. 2011;9:279-290.)

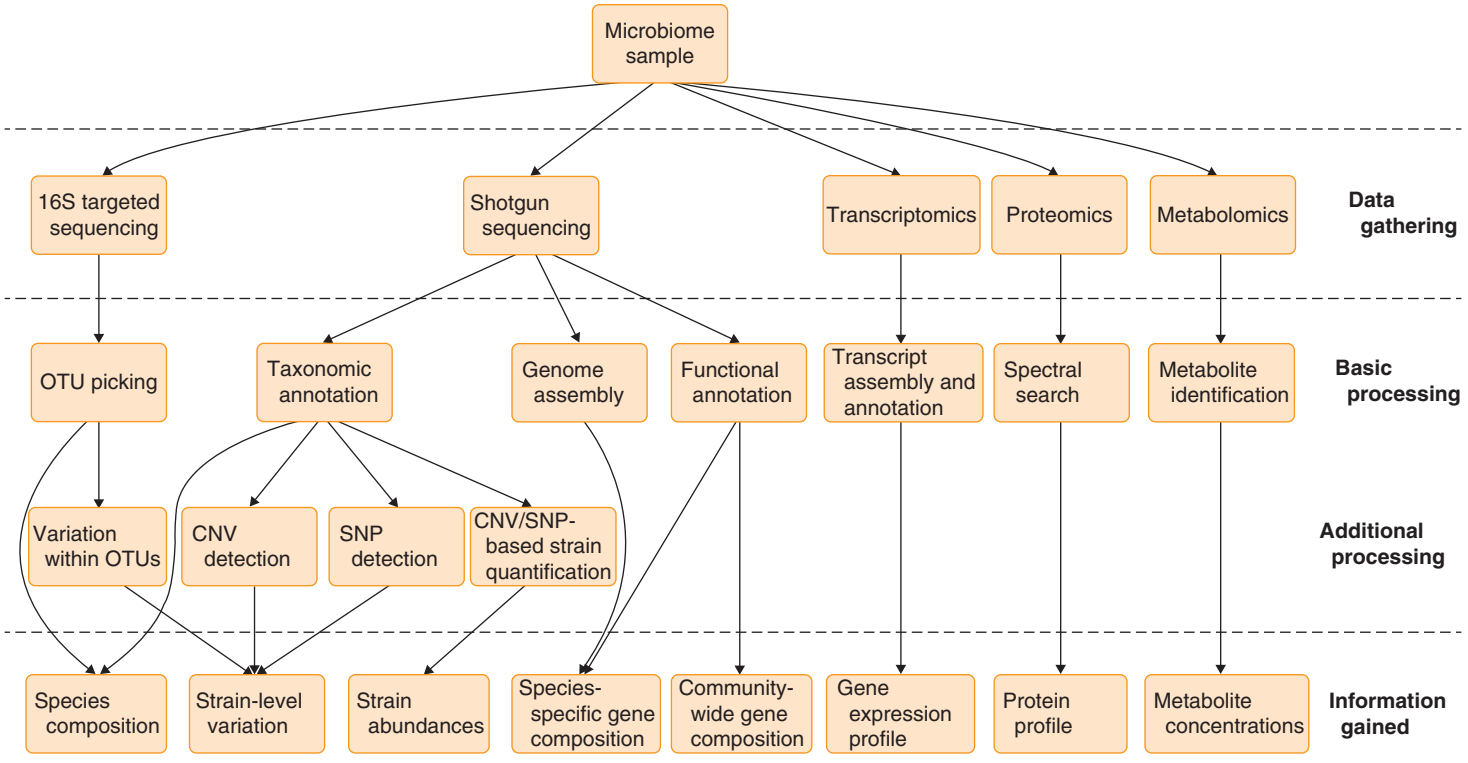

E-FIGURE 257-1. **Schemes of microbiome analysis.** Microbiome "omic" data can be processed and analyzed in various ways to address a diverse set of questions concerning the composition, capacity, and function of the microbiome. CNV = copy number variation; OTU = operational taxonomic unit; SNP = single nucleotide polymorphism. (From Noecker C, McNally CP, Eng A, Borenstein E. High-resolution characterization of the human microbiome. *Transl Res*. 2017;179:10-23.)

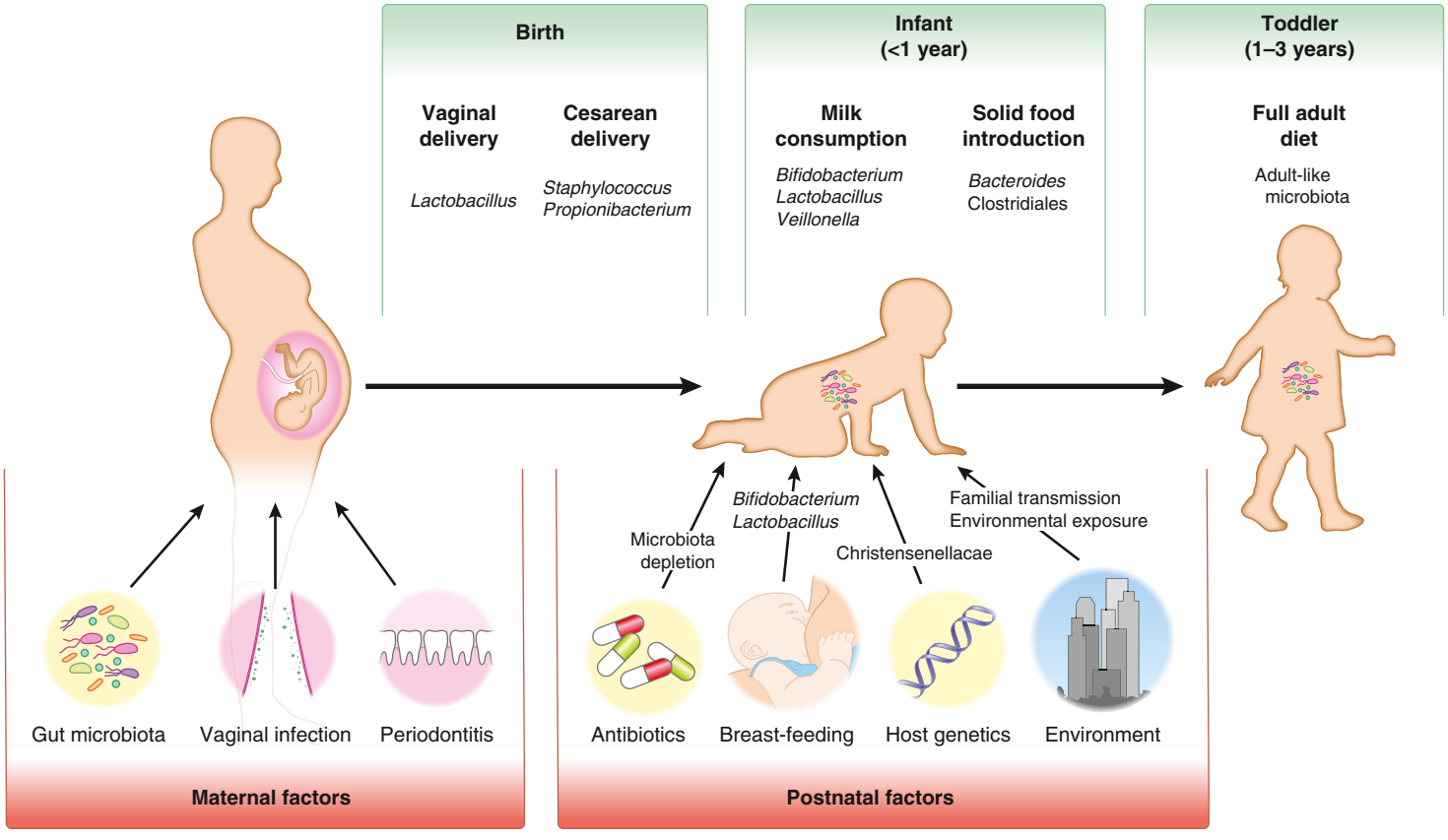

E-FIGURE 257-2. **Factors shaping the neonatal microbiome.** Maternal vaginal infections or periodontitis can result in bacteria invading the uterine environment. Delivery mode shapes the initial bacterial inoculum of the newborn. Postnatal factors such as antibiotic use, diet, genetics, and environmental exposure further configure the microbiome during early life. As diet diversifies with age, the microbiome gradually shifts toward an adult-like configuration, which is usually reached by age 3 years. (From Tamburini S, Shen N, Wu HC, Clemente JC. The microbiome in early life: implications for health outcomes. *Nat Med*. 2016;22:713-722.)

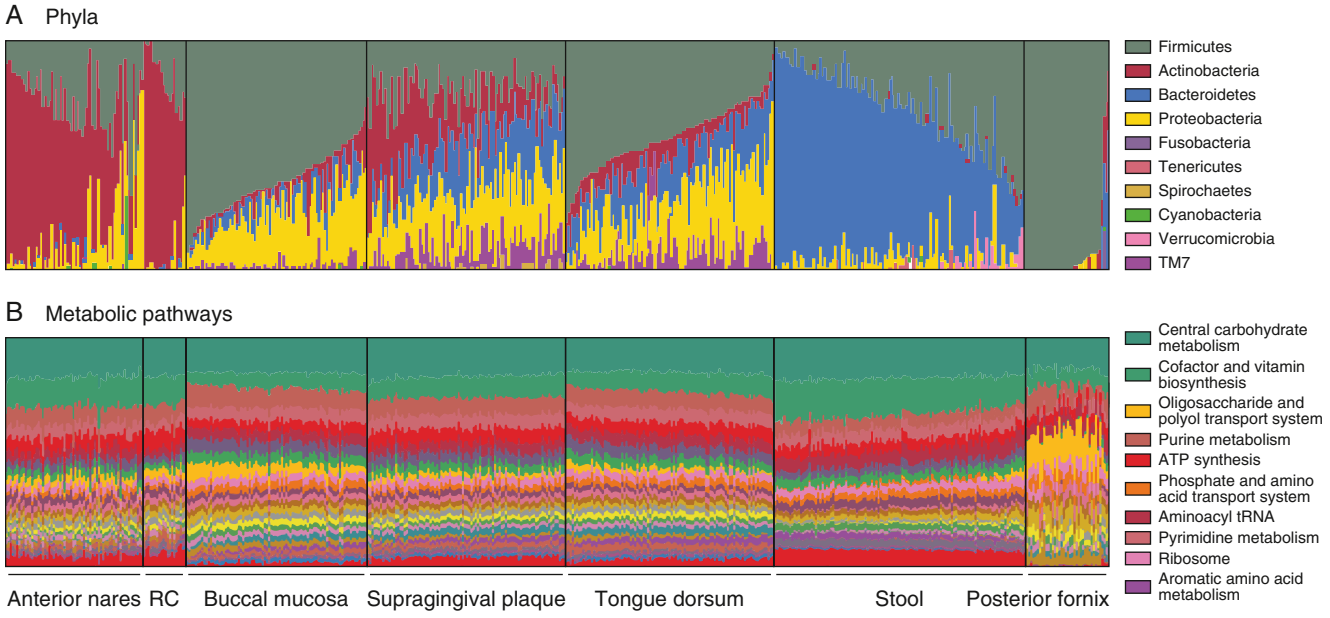

E-FIGURE 257-3. Comparison of the microbial composition (A) and predicted function (B) of the microbiota from seven different body sites of healthy individuals from the Human Microbiome Project. There is significant interindividual variation in the community composition, whereas the metabolic function is evenly distributed and prevalent across both individuals and body sites. ATP = adenosine triphosphate; RC = retroauricular crease; tRNA = transfer RNA. (From Human Microbiome Project Consortium. Structure, function and diversity of the healthy human microbiome. *Nature*. 2012;486:207-214.)

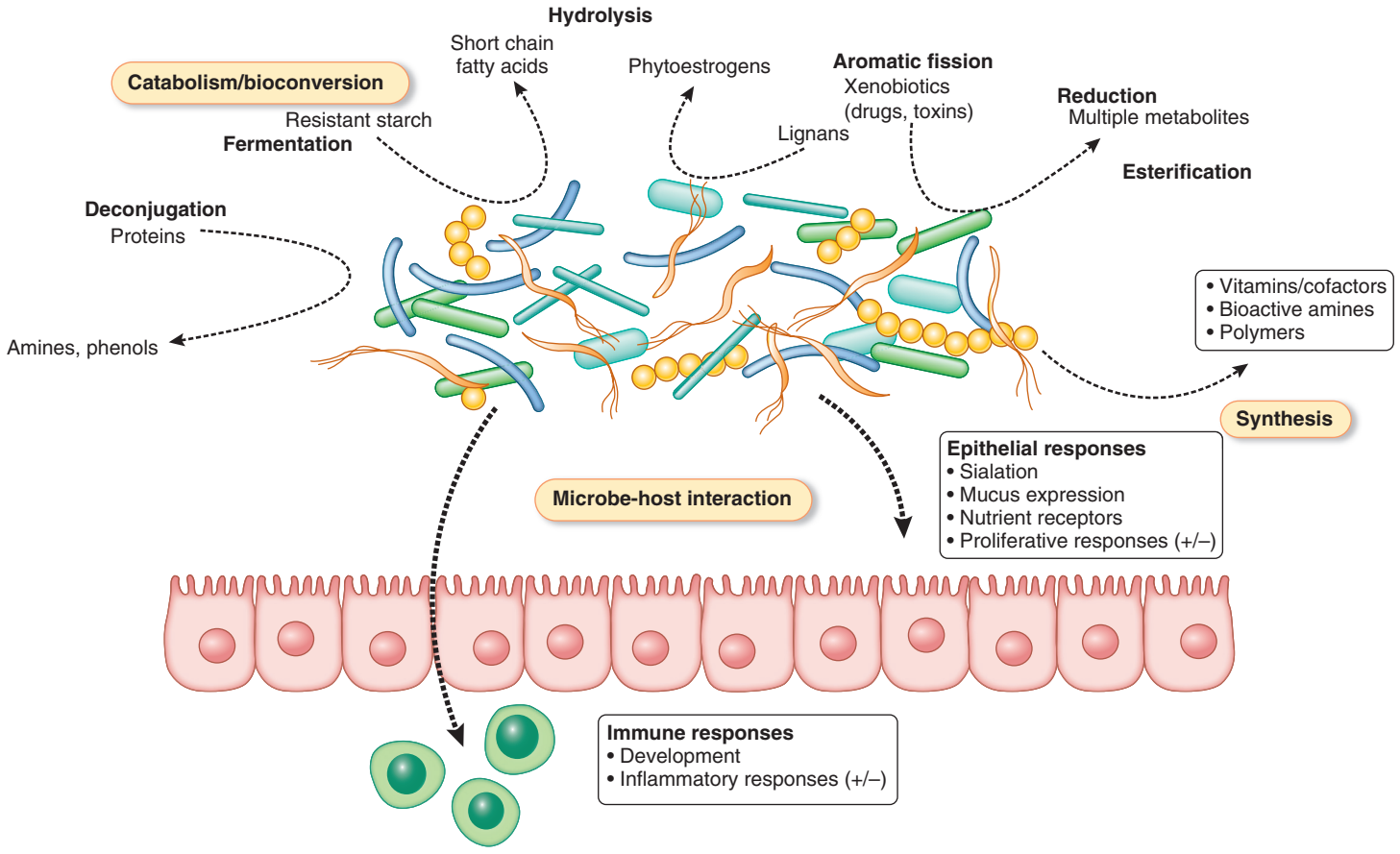

FIGURE 257-2. Potential functions of the indigenous microbiota. The microbiota can have effects through the microbes' synthetic or catabolic metabolic activity or through direct host-microbe interactions. Catabolism and bioconversion of dietary or host-derived compounds can make nutrients more available to the host or alter the bioavailability of drugs. Some members of the microbiota can synthesize important cofactors or bioactive signaling molecules such as amines. Signaling between the microbiota and the host can trigger alterations in host function, such as altered expression of mucus or alteration of the immune response. (From Young VB. The role of the microbiome in human health and disease: an introduction for clinicians. *BMJ*. 2017;356:j831.)

gut microbiota. Additionally, host-derived biomolecules, including bile acids and compounds such as mucous and mucosal secretions, can be substrates for microbial metabolism. Xenobiotics, such as drugs and environmental toxicants, also can be subject to microbe-mediated conversion. In addition to catabolism and bioconversion, microbes can synthesize vitamins and bioactive compounds, such as amines and neurotransmitters (e.g., levodopa). Finally, host-microbe contact can directly alter the function of host tissues. Microbial contact with the immune system and mucosal surfaces, during both postnatal development and maturity, can influence gene expression and thus function of the host.

Given the breadth of functions attributed to the indigenous microbiota, it is clear that alteration of microbiota can lead to disruption of homeostasis. This disruption can be due to loss of a given function, inappropriate expression of a function in time or space, or introduction of maladaptive functions (Table 257-1). These mechanisms can involve the host, microbes (both resident and invasive), and environmental factors. The latter can include factors such as medications, notably antibiotics, and surgical procedures that can alter anatomy or introduce foreign material.

DISEASE ASSOCIATIONS

The microbiome is associated with a wide range of conditions, although cause and effect are often difficult to establish.

OBESITY

The microbiota can directly influence the metabolism of its host through a variety of mechanisms (Fig. 257-3).[8] In addition to increased energy harvest, altered metabolic signaling and altered inflammatory tone combine with diet to allow the microbiota to modulate multiple pathways that can lead to obesity (Chapter 201). Obesity in people and experimental animals is associated with an altered microbiota composition. Despite these observational findings, transfer of a normal fecal microbiome into obese individuals does not appear to result in weight loss.[A1]

TABLE 257-1 FACTORS THAT CAN ALTER THE STRUCTURE AND FUNCTION OF THE MICROBIOTA

HOST FACTORS
Birth mode
Genetics
Gender
Immune status
Age
Preexisting disease
Anatomic disruption (e.g., gastrointestinal surgery, implantation of medical devices)
ENVIRONMENTAL/IATROGENIC FACTORS
Diet
Residence (urban vs. rural)
Animal exposure (including pets)
Environmental toxicants (naturally occurring or humanmade)
Antibiotics
Other drugs (e.g., chemotherapy, proton pump inhibitors, anti-inflammatory drugs)
MICROBIAL FACTORS
Infections (viral, bacterial, fungal, helminthic)
Ingestion of fermented foods (e.g., yogurt, kimchee, kefir)
Use of probiotic organisms

INFLAMMATORY BOWEL DISEASE

Evidence for a potential role for gastrointestinal microbiota in inflammatory bowel disease (Chapter 127) is based on culture data[9] and the disease's occasional response to antibiotics. Polymorphisms in genes that are involved in sensing and responding to microbes, including the nucleotide-binding oligomerization domain-containing protein 2 (*NOD2*) are associated with

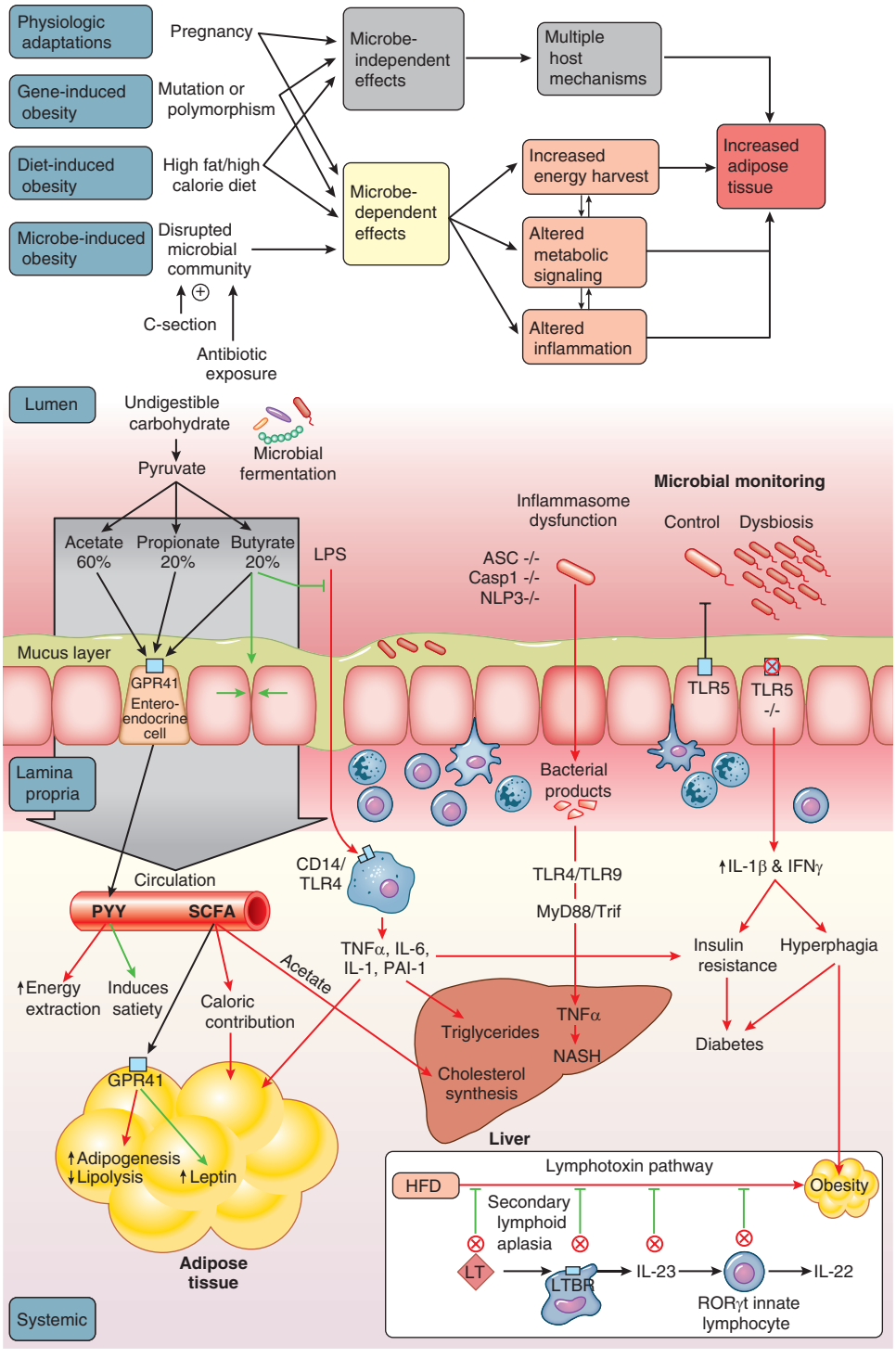

FIGURE 257-3. Mechanisms by which the microbiota can influence host metabolism. Undigested carbohydrates are fermented by the intestinal microbiota to short-chain fatty acids (SCFAs). SCFAs can signal to the host and modify metabolic activity. SCFAs are readily absorbed, contribute up to 10% of caloric intake, and can increase adipogenesis by binding GPR41 on adipocytes. Changes in inflammatory tone (e.g., via LPS stimulation) increase weight gain, total body and liver adiposity, and insulin resistance. (*Inset*) Deleting any component of the lymphotoxin pathway results in loss of control of the microbiome and blocks the ability of mice to gain weight on a high-fat diet. Cohousing lymphotoxin B receptor (LTBR)-deficient and wild-type (WT) mice restores diet-induced obesity and partially restores a WT/high-fat diet (HFD) microbiota. IFN = interferon; IL = interleukin; LPS = lipopolysaccharide; LT = lymphotoxin; NASH = nonalcoholic fatty liver disease; PAI-1 = plasminogen activator inhibitor 1; PYY = polypeptide YY; TNF = tumor necrosis factor; TLR = toll-like receptor. (From Cox LM, Blaser MJ. Pathways in microbe-induced obesity. *Cell Metab*. 2013;17:883-894.)

increased risk for inflammatory bowel disease, thereby providing further evidence for a microbial role in pathogenesis, likely by initiating and modulating mucosal immune responses.

The indigenous microbiota also is significantly different between patients with the disease and controls. Although these associations cannot prove causality, data suggest that the microbiota itself can initiate the dysregulated inflammatory response that is seen in inflammatory bowel disease in individuals with a genetic predisposition to this type of response. This observation emphasizes that the microbiota is part of a complex system of interrelated factors, including the host, the indigenous microbes, and the environment, all of which intersect to influence the homeostasis of the entire system.[10]

C. DIFFICILE INFECTION

Among the most dramatic examples of the unintended consequences of antimicrobial agents is the "collateral damage" to the indigenous microbiota. Perhaps the best example is the rise of *C. difficile* as the cause of the majority of cases of antibiotic-associated colitis.

The normal microbiota can prevent colonization and disease by *C. difficile* through a variety of mechanisms, including competition for nutrients, stimulation of host responses, and alterations of key aspects of the physiology of the organism, such as germination of spores and vegetative outgrowth with toxin production.[11] Disruption of the indigenous microbiota by antibiotics can lead to susceptibility to *C. difficile* infection (E-Fig. 257-4). *C. difficile* infection is also the best example of the potential to restore normal function by intentionally manipulating the altered microbiota.

COLON CANCER

The distal gastrointestinal tract, which harbors the largest and densest population of microbes in the human body, is where the indigenous colonic microbes are able to catalyze a large number of biotransformations that could alter susceptibility to the development of colorectal cancer.[12] For example, these intestinal microbes play a key role in the metabolism of nitrosamines and polycyclic amines, both of which can have carcinogenic activity.[13] Conversely, fermentation of nondigestible carbohydrates by the intestinal microbiota can lead to the production of short-chain fatty acids, such as butyrate, which has anti-inflammatory and antitumor activities. Furthermore, mucosal inflammation initiated by intestinal infection may play a key role in initiating the process that leads to cancer.

ASTHMA

Cesarean delivery and early exposures to antibiotics are associated with increased risk of asthma, whereas breast-feeding has a protective association. The hygiene hypothesis suggests that the microbiota may be involved in a causal pathway because these neonatal and childhood exposures have been observed to be associated with variation in the bacterial microbiota.

NEUROLOGIC DISORDERS

Changes in the gut microbiota have been associated with a variety of neurologic conditions, including autism, depression, and multiple sclerosis. As with many other associations, however, a causal relationship remains to be proven.

HEMATOPOIETIC STEM CELL TRANSPLANTATION

In patients who have undergone hematopoietic stem cell transplantation (Chapter 163), loss of fecal diversity and domination by a single taxa at the time of engraftment are associated with substantially increased mortality compared with higher diversity.[14] Growth of enterococci, which are dependent on lactose, also may exacerbate graft-versus-host disease.[15]

Although observational data suggest that repletion of a normal intestinal microbiome may be beneficial to prevent graft-versus-host disease, clinical recommendation must await randomized trials.

THERAPIES TARGETING THE MICROBIOME

Based on associations of an altered structure and function of the microbiota with various diseases, intentional modulation of the indigenous microbiota could represent a novel strategy for prevention and treatment (Table 257-2).[16] The best evidence for intentionally targeting the microbiota with therapeutic intent has been the setting of recurrent *C. difficile* infection,[17] where fecal transplantation has about an 80% efficiency for reducing recurrences[A2] and oral ingestion of live purified Firmicutes bacterial spores has about a 70% efficacy for reducing recurrent infection.[A3] The protection of the intestinal microbiota with probiotics, in the form of fermented foods and microbes isolated from fermented foods, such as lactobacilli and yeasts, also can reduce antibiotic-induced diarrhea.[A4]

Fecal transplantation also has shown benefit in the treatment of severe malnutrition.[18] For young children with moderate acute malnutrition, a microbiota-directed dietary supplement can significantly improve weight gain and markers of nutrition.[A5] By comparison, fecal transplantation has had variable and unclear impact on patients with ulcerative colitis,[A6,A7] for whom it is currently considered to be a promising but not yet standard therapy (Chapter 127).[19] For irritable bowel syndrome (Chapter 123), the benefit of probiotics is inconclusive,[20] but transplantation of the fecal microbiome may reduce symptoms in some patients with predominant abdominal bloating.[A8]

TABLE 257-2 STRATEGIES FOR TARGETING THE MICROBIOTA THERAPEUTICALLY

ADMINISTRATION OF MICROBES
Fecal microbiota transplantation
Single-agent probiotics
Designer microbial communities (multispecies probiotics)
Bacteriophage therapy
MODULATION OF EXISTING MICROBES IN A COMMUNITY
Microbial nutrients (prebiotics)
Antibiotics

CONCLUSIONS

The microbiome is an exciting component of the role that microbes play in health and disease. Assessment of the functional status of the indigenous microbiota and therapeutic manipulation of the microbiome is likely to be a key part of the developing paradigm of precision medicine (E-Fig. 257-5) that has the potential to alter the practice of medicine radically now and in the future.

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258 PRINCIPLES OF ANTI-INFECTIVE THERAPY

LOUIS B. RICE

SELECTING ANTIMICROBIAL THERAPY

EMPIRICAL ANTIMICROBIAL THERAPY

It is rare that antimicrobial therapy is instituted for a serious infection with full knowledge of the identity and antibiotic susceptibilities of the specific pathogen, so empirical antibiotic therapy typically must be initiated based on presumptions regarding the nature of the infection. The first challenge is to assess whether the patient likely has an infection and, if so, where is it located. The patient's clinical manifestations or syndromes may not be infectious. Autoimmune diseases (Chapter 236), lymphomas (Chapters 171 and 172), drug reactions (Chapter 234), hematomas, and deep vein thromboses (Chapter 68) often present with fever as a cardinal symptom, so it is important to keep in mind that empirical antibiotics may not be needed. In other situations, a careful history, thorough physical examination, and a few laboratory tests will allow identification of a clinical syndrome, such as meningitis (Chapter 381), pneumonia (Chapter 85), urinary tract infection (Chapter 263), enteric infection (Chapter 262), or sexually transmitted disease (Chapter 264). Some infectious syndromes, such as upper respiratory tract infections (Chapter 84),

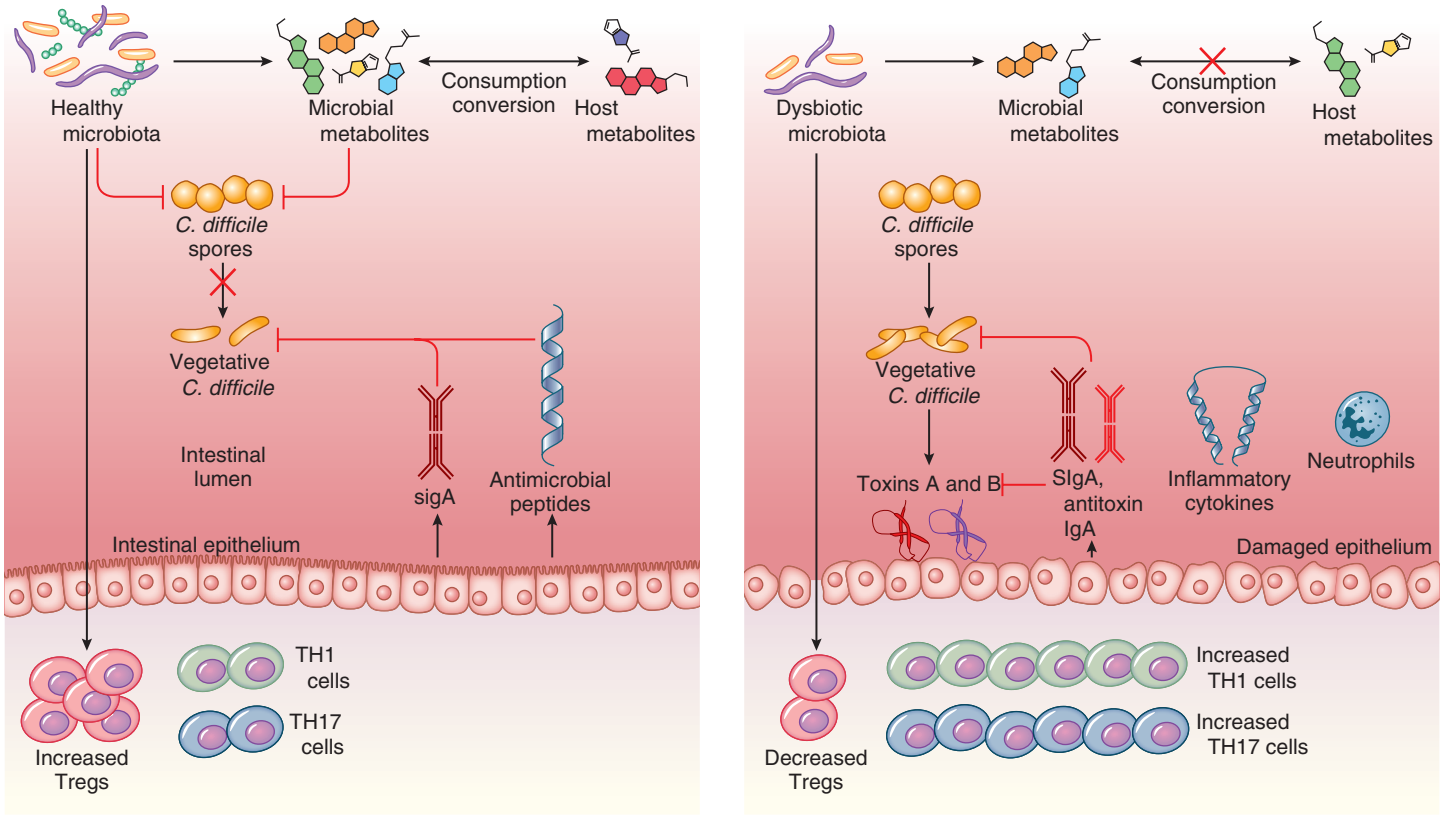

E-FIGURE 257-4. Proposed mechanisms of the microbiota on pathogen resistance and the host during *Clostridioides difficile* infection. (**A**) Both microbial and host factors can inhibit germination and growth of *C. difficile*. A healthy microbiota is capable of consuming both microbial and host-generated metabolites, limiting the growth of *C. difficile*. Cross-talk between the microbiota and the host immune system results in a regulated immune response. Furthermore, the microbiota can stimulate production of antimicrobial peptides and secretory immunoglobulin A (SIgA), which can maintain the composition of the microbiota. (**B**) Disruption of the microbiota, due to factors such as antibiotic use, drugs, diet, or inflammation, can lead to the development of *C. difficile* infection. A dysbiotic microbiota can result in the loss of colonization resistance due to changes in the structural and/or metabolic environment. The loss of specific community members potentially affects the levels of microbial and host-generated metabolites, resulting in a different functional state that promotes spore germination and vegetative outgrowth. A dysbiotic microbiota may also result in an imbalanced immune response through the loss of immune regulation and a proinflammatory state, both of which may affect disease development. Toxin production by vegetative *C. difficile* can stimulate the production of inflammatory cytokines, neutrophils, and antitoxin antibodies. Ig = immunoglobulin; SIgA = secretory IgA; Tregs = regulatory T cells. (From Seekatz AM, Young VB. *Clostridioides difficile* and the microbiota. *J Clin Invest*. 2014:124:4182-4189.)

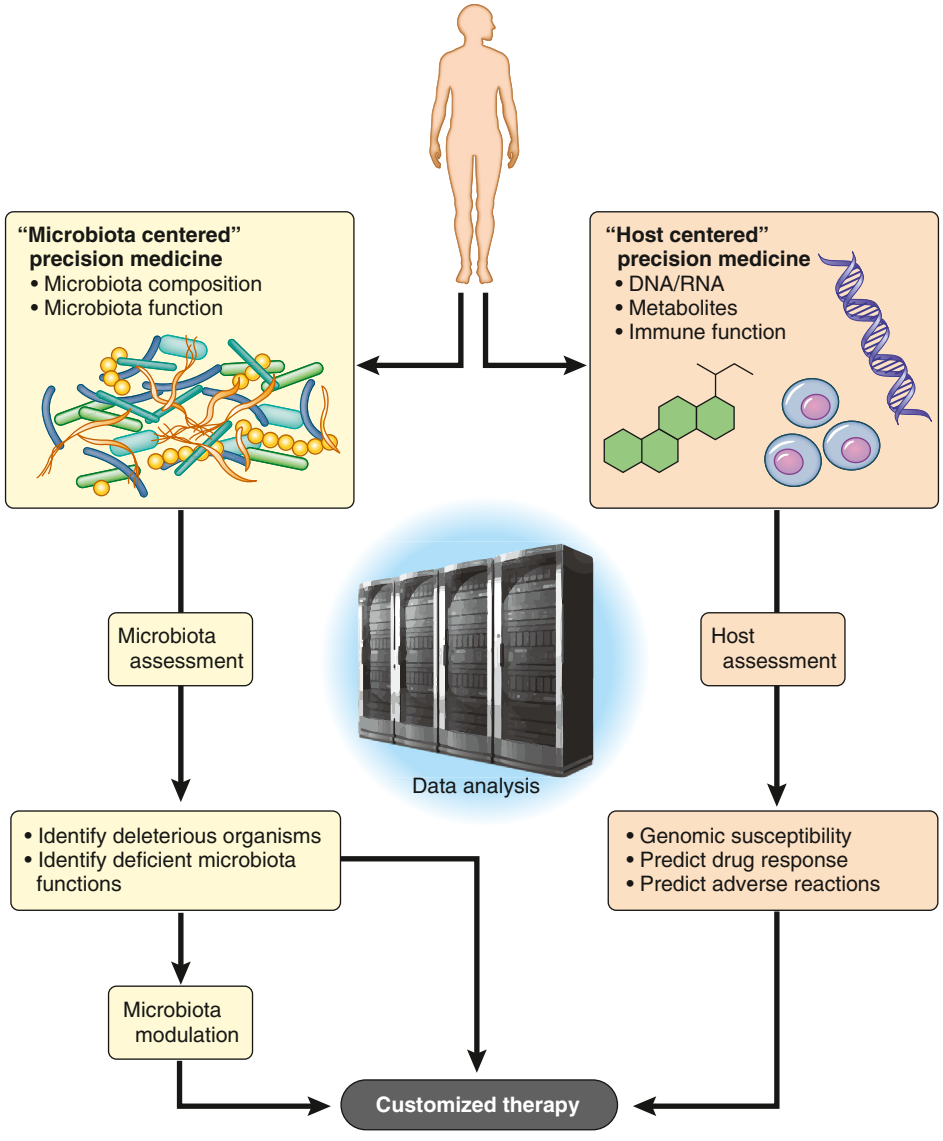

E-FIGURE 257-5. Incorporation of the microbiota into the developing precision medicine paradigm. As currently being developed, precision medicine proposes to determine responses to treatment according to the assessment of human genomics, metabolism, and immune function. On the basis of these data, susceptibility to disease, response to treatment, and potential adverse reactions can be predicted and a customized therapy designed. Because the microbiota can also influence this same susceptibility and response to treatment, we propose that assessment of the microbiota also could be incorporated into a complete precision medicine approach. (From Young VB. The role of the microbiome in human health and disease: an introduction for clinicians. *BMJ*. 2017;356:j831.)

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ABSTRACT

The introduction of antimicrobial agents into clinical use has increased life expectancy and allowed more aggressive treatment of trauma, malignancies, and organ failure. The use of antibiotics in agriculture has enhanced the productivity of both meat and vegetable producers, thereby allowing many more people around the world to be fed. Unfortunately, the general safety of most antimicrobials has made it tempting to use them indiscriminately, with the resulting emergence and spread of multidrug-resistant microorganisms.

The emergence of antimicrobial resistance in human pathogens was predictable and unavoidable, given their rapid replication (offering frequent opportunities for mutation of antimicrobial targets) and frequent genetic exchange. The rapidity of the widespread dissemination of resistance was, however, avoidable, and best practices can limit or potentially even somewhat reverse this problem.

KEYWORDS

antimicrobial agents
bacterial infections
antimicrobial therapy
antibacterial activity
pharmacokinetics and pharmacodynamics
antimicrobial combinations

may be sufficiently likely to be caused by virus such that antibiotics are likely to be of no value.

After the infectious syndrome is identified, the next step is to make a reasonable estimation of the specific pathogens that are likely to be involved. Appropriate empiric therapy is especially important when delayed effective antimicrobial coverage is associated with worse clinical outcomes,[1] such as for community-acquired pneumonia (Chapter 85), central nervous system infections (Chapters 381 to 383), and sepsis[2] (Chapter 94). In an adult patient with suspected bacterial meningitis (Chapter 381), for example, ceftriaxone covers both of the two most likely pathogens, *Streptococcus pneumoniae* (Chapter 268) and *Neisseria meningitidis* (Chapters 274). If the patient is elderly, pregnant, or otherwise at high risk if the pathogen is *Listeria monocytogenes* (Chapter 272), the regimen could be expanded to include ampicillin. If there is a reason to suspect *S. pneumoniae* with reduced susceptibility to ceftriaxone, vancomycin may be added. Finally, if the clinical picture is equivocal and includes the possibility of encephalitis, acyclovir might be added to address the possibility of herpes simplex encephalitis (Chapters 345 and 383). The difficulty of distinguishing among pathogens when treating community-acquired pneumonia (Chapter 85) leads many to prescribe both ceftriaxone (for *S. pneumoniae* [Chapter 268] and *Haemophilus influenzae* [Chapter 277]) and azithromycin (for atypical pathogens *Legionella pneumophila* [Chapter 290], *Chlamydia pneumoniae* [Chapter 294], and *Mycoplasma pneumoniae* [Chapter 293]). Conversely, if a patient presents with a community-acquired pyelonephritis (Chapter 263), *Escherichia coli* (not *S. pneumoniae*) should be at the top of the list. The likely pathogens can then guide what antimicrobial agent(s) to administer.

This syndrome to pathogen to antimicrobial agent thought process is designed to allow identification of an antibiotic regimen that is as targeted as possible, so as to have less impact on the resident flora and a lower likelihood of promoting the emergence of resistance. For example, a typical cellulitis will be most often caused by *Streptococcus pyogenes*, and less commonly, by *Staphylococcus aureus*. These two pathogens could be adequately treated by nafcillin (which has only relatively narrow gram-positive coverage) or by ampicillin-sulbactam (which has broad coverage that includes facultative and anaerobic gram-negative bacilli and a wide range of gram-positive cocci). It is obviously preferable to avoid killing the facultative gram-negative and anaerobic bacteria in the gastrointestinal tract, especially when the likelihood that they are responsible for the infection is very low. Conversely, very broad antibacterial coverage may be critical to success in other situations, such as treating an intra-abdominal infection from a perforated appendix (Chapter 128), a situation in which the polymicrobial microbiology of the likely infection will never be precisely delineated.

When considering empirical coverage, it is useful to have as much information as possible. Relevant information might include a Gram stain of material from the site of the infection. When Gram stains are not available or relevant, specific or multiplex polymerase chain reaction (PCR) amplification may give a sense of whether broader coverage is necessary.

The other major consideration in choosing an empirical regimen is the condition of the patient. If the patient is febrile but awake and fully functional, the empirical regimen can be more parsimonious, unless the situation worsens acutely. Conversely, the margin for error is much less in septic shock (Chapter 94), for which broad coverage for all conceivable pathogens is indicated until more information is obtained.

Unfortunately, real-life clinical scenarios can be challenging. For example, the severity of a patient's illness may be due to noninfectious causes, and few antibiotics are truly narrow-spectrum. As a result, the best strategy to prevent antimicrobial side effects and the emergence of resistance is to minimize exposure to antibiotics by treating only infections likely to respond to antibiotics with the right dose for the shortest effective duration possible.

DEFINITIVE ANTIMICROBIAL TREATMENT

Definitive therapy requires the identification of a pathogen (or pathogens) responsible for the infection as well as their susceptibility to specific antimicrobial agents. This task is sometimes relatively straightforward (e.g., multiple blood cultures growing *S. aureus* in a patient with clinical and imaging evidence of endocarditis) and sometimes more complicated (e.g., growing coagulase-negative staphylococci, *S. pyogenes*, *Pseudomonas aeruginosa*, and *Bacteroides fragilis* from deep cultures of a diabetic foot ulcer). Once the pathogen(s) are identified and the susceptibility to antimicrobial agents is determined, empirical broad-spectrum therapy often can be narrowed to less toxic, less complicated, or less expensive agents. In some circumstances, it may be possible to switch from a parenteral to an oral regimen, thereby reducing the risks associated with an intravenous catheter and perhaps shortening the patient's duration of hospitalization. Alternatively, culture and susceptibility testing may guide expanded regimens to include coverage for an unanticipated or resistant pathogen.

Whenever a regimen is chosen, the clinician should also consider the potential next alternative antimicrobial therapy if the first choice must be discontinued because of an allergic reaction or drug toxicity prior to completing the therapeutic course. Such contingencies should be considered in advance because they may impact the original choice of antibiotic. For example, if a patient develops a rash while being co-administered both a penicillin and a cephalosporin, both classes of drugs may need to be avoided.

Susceptibility Testing

A cornerstone of the treatment of infectious diseases is in vitro susceptibility to determine the ability of a microorganism to grow in the presence of serial dilutions of a variety of potentially useful antimicrobial agents. In standard susceptibility tests, serial dilutions of a given antibiotic are made in either broth or agar, and then a specified number of bacteria are inoculated into (broth) or onto (agar) the media and incubated at temperatures and other conditions (e.g., aerobic and anaerobic) permissive for growth. Growth is determined by visual inspection after 16 to 24 hours. The lowest antibiotic concentration at which no visible growth is seen is defined as the minimal inhibitory concentration (MIC). An alternative agar-based test is the disc diffusion assay, in which a paper disc containing a fixed concentration of an antibiotic is placed onto an agar plate previously spread with a specified number of bacteria. The antibiotic diffuses into the agar and inhibits growth of the strain at distances with sufficient concentrations of diffused antibiotic. Zone sizes are measured, and susceptibility is inferred. Another alternative is the E-test, in which a strip containing a gradient of the antibiotic is placed on an agar plate that was previously inoculated with the bacteria.

Each licensed antibiotic has a defined minimal inhibitory concentration that classifies an organism as "susceptible" or "resistant" (and sometimes as "intermediate" as well). These determinations are based on obtainable blood and tissue levels in vivo to assist the clinician in understanding the minimal inhibitory concentration number and its therapeutic implications. However, designations of "susceptible" and "resistant" are best understood as general guides, because exceptions can result in an unnecessary limitation of options in some cases and inadequate therapy in others. For example, the minimal inhibitory concentrations of a typical strain of *P. aeruginosa* (Chapter 282) fall well outside of the susceptible range for tetracycline, but tetracycline is so heavily concentrated in the urine that it achieves levels that exceed even the elevated minimal inhibitory concentrations of *P. aeruginosa* and can successfully treat *P. aeruginosa* cystitis. Conversely, pneumonia strains caused by *S. pneumoniae* with an minimal inhibitory concentration of 2 μg/mL would be readily treatable with intravenous ceftriaxone, but ceftriaxone's limited penetration into the cerebrospinal fluid (CSF) would mean that strain would be considered resistant to ceftriaxone for treating meningitis. Fine distinctions such as these are best made by expert consultants.

A final point about susceptibility is that it may be dependent on the inoculum of bacteria that are used in the assay. In most cases, a standardized quantity of bacteria is added when performing susceptibility testing. If that inoculum is increased 100-fold, the MIC may increase dramatically, as is often seen with extended-spectrum, β-lactamase–producing Enterobacteriaceae and cephalosporins. As such, it is sometimes important to estimate the inoculum of bacteria as well as the likely penetration of the antibiotic when determining whether an antibiotic that shows in vitro activity will be effective clinically. For example, a dense pneumonia, in which the bacterial inoculum is likely to be very high, may not respond to the same antibiotics that would be quite effective for treating a low-inoculum urinary tract infection caused by the same strain.

Many modern bacteriology laboratories now use automated approaches or genotypic methods, such as PCR[3] testing, to identify bacterial polymorphisms that are indicative of antibiotic resistance. These panels more rapidly provide information when they identify a resistance gene, but they are limited by the fact that they can only find the genes in the panel and not any novel resistance genes. Although use of these panels has not been shown to improve clinical outcomes,[A1] they are quite helpful when looking for specific pathogens, such as identifying nasal colonization with methicillin-resistant *S. aureus* (Chapter 267) or detecting herpes simplex (Chapter 345) as a cause of viral encephalitis (Chapter 383). Matrix-assisted laser desorption ionization–time of flight mass spectrometry is an alternative to PCR detection methods.

BACTERICIDAL ACTIVITY

Standard susceptibility assays test the ability of the antibiotic to inhibit further growth of the microorganism but do not indicate whether the strain is killed by the antibiotic. Most antibiotics are characteristically either bacteriostatic (inhibit growth) or bactericidal (inhibit and kill), but the characteristics may vary with the antibiotic-pathogen pair. Bactericidal activity is determined using time-kill assays, which assess the degree to which an inoculum of bacteria is reduced after a 24-hour period; a greater than 99.9% reduction in the inoculum is required to be designated bactericidal. Fortunately, successful treatment of most infections requires only that the pathogen be inhibited, thereby allowing the immune system time to clear the infection, so bactericidal therapy is not crucial for most infections.[A2] In some situations, however, such as in endocarditis (with poor penetration of the immune system into the vegetation), in meningitis (a desire for rapid killing to preserve brain function), and often in osteomyelitis (poor penetration and dormant state of bacteria), bactericidal therapy yields a higher degree of success than bacteriostatic therapy.

TARGETING ANTIMICROBIAL THERAPY APPROPRIATE TO THE INFECTION AND THE PATIENT

Nature of the Infection

The conditions under which antimicrobial agents are tested for activity against bacteria in the laboratory are very different from the conditions of an actual human infection, and it is remarkable that in vitro susceptibility correlates well with clinical efficacy in many clinical infections. In considering the optimal choice of agent(s), an important first determination is whether the antibiotic will reach the location of the infection in concentrations sufficient to inhibit the infecting microorganisms. For example, the fluoroquinolone antimicrobial agent norfloxacin can be used only to treat urinary tract infections because the urine is the only body fluid in which it achieves sufficient concentrations to be effective. Conversely, the fluoroquinolone moxifloxacin is effective for many infections but is not recommended for urinary tract infections because it does not achieve sufficient concentrations in the urine. These determinations are sometimes species dependent. For example, *Enterococcus faecalis* (Chapter 270) generally has MICs for the fluoroquinolone ciprofloxacin ranging from 1 to 4 μg/mL. Given the concentrations that ciprofloxacin achieves in the urine, it is a reasonable choice for treatment of a urinary tract infection (Chapter 263) caused by a susceptible strain. However, since serum concentrations of ciprofloxacin at peak are generally in the 2 μg/mL range, it is not adequate for treating tissue enterococcal infections.

The local environment can also have an impact. For example, daptomycin is not sufficiently effective in treating pneumonia because it is inactivated when it complexes with surfactant in the alveoli.

Another major consideration when treating a clinical infection is the state of the microorganisms in the infection. Bacteria reduce their rate of growth when present in a large inoculum, and some antibiotics, notably β-lactams, are more effective at killing bacteria when they are multiplying rapidly and hence may be less effective in some high-inoculum infections. Under many conditions, bacteria also form biofilms, which are carbohydrate/DNA/water matrices that impair the action of antibiotics through a variety of mechanisms, including altered metabolic activity of the microorganism and reduced access for the antibiotic. Under certain circumstances (for example, in chronic osteomyelitis; Chapter 251), *S. aureus* strains can form "small colony variants," which are also metabolically different and respond poorly to many antimicrobials. Finally, there is the phenomenon known as "persisters," a minute percentage of a large original inoculum that for some reason is not killed by the antibiotic and persists to grow again once the antimicrobial pressure has subsided. Antimicrobial therapies for these altered states are quite limited in their effectiveness, thereby emphasizing the importance of reducing the inoculum of infection by drainage or debridement whenever possible.

Infection of prosthetic material presents a major challenge. Access of antibiotics to the infection site is often limited by both physical barriers and biofilms. Prosthetic joints, prosthetic cardiac valves, intravascular stents, and fistulae can all become infected. When possible, all prosthetic material should be removed to facilitate treatment of the infection. In cases in which removal is not a viable option, prolonged therapy (often with combinations of agents that include the rapidly bactericidal agent rifampin) is required, sometimes followed by indefinite suppression with an oral agent active against the infecting strain. The goal of indefinite therapy is not to cure the infection but rather to keep it localized. Although rifampin alone is effective in some of these circumstances, resistance can be generated by just a single point mutation in the RNA polymerase gene, thereby making the emergence of resistance a high-frequency event. For this reason, rifampin should always be used in combination with other agents, although the risk of resistance remains even when used in combination.

Host Factors That Impact Choice or Amount of Antibiotic Prescribed

Allergies

Allergic reactions to antimicrobial agents (Chapter 234) can range from mild rashes to full-blown anaphylaxis (Chapters 233 and 234). A full history must be obtained from the patient before prescribing an antibiotic, and the medical record should be reviewed. Antibiotics for which even mild allergies have been experienced should be avoided if suitable alternatives are available. For β-lactam antibiotics, in the absence of anaphylaxis or a severe allergic reaction such as Steven-Johnson syndrome (Chapter 407), cross-allergy among penicillins, cephalosporins, and carbapenems are sufficiently infrequent that substitution of one class for the other is usually possible. The monobactam aztreonam is the only β-lactam that is safe to use in a patient who has suffered a severe allergic reaction to one of the other classes. In circumstances in which non–β-lactam antibiotics are not a viable option, penicillin desensitization (Chapter 234) can be attempted in controlled, monitored settings.[4] The desensitization should be repeated if subsequent infectious episodes occur that require penicillin treatment.

Pregnancy

An estimated 80% of drugs administered to pregnant women are antibiotics, and about 20 to 25% of pregnant women receive antibiotics. The use of antimicrobial agents in pregnant women requires several additional considerations.[5] The first consideration is the potential that the antimicrobial agent could cause harm to the fetus (Table 258-1). Agents that are commonly used and considered generally safe in pregnancy (most β-lactams, azithromycin, clindamycin, and vancomycin) are considered Category B (safe in animal studies but with no controlled data from humans). For Category C agents, animal studies have shown some reproductive toxicity but well-controlled human studies do not exist; the fluoroquinolones, polymyxins, and sulfamethoxazole fall into this category. Category D agents should not be used because of known human fetal

TABLE 258-1 FDA PREGNANCY CATEGORIES

CATEGORY A
Adequate and well-controlled studies have failed to demonstrate a risk to the fetus in the first trimester of pregnancy (and there is no evidence of risk in later trimesters). No antimicrobial agents are in this category.
CATEGORY B
Animal reproduction studies have failed to demonstrate a risk to the fetus, and there are no adequate and well-controlled studies in pregnant women. Antimicrobial classes in this category include most β-lactams, vancomycin, azithromycin, erythromycin, clindamycin, daptomycin, fidaxomicin, fosfomycin, metronidazole, nitrofurantoin, and the antituberculous agents ethambutol and bedaquiline.
CATEGORY C
Animal reproduction studies have shown an adverse effect on the fetus and there are no adequate and well-controlled studies in humans, but potential benefits may warrant use of the drug in pregnant women despite potential risks. Antimicrobial agents in this category include imipenem-cilastatin, fluoroquinolones, lipoglycopeptides (dalbavancin, oritavancin, telavancin), clarithromycin, telithromycin, oxazolidinones, polymyxins, sulfamethoxazole, trimethoprim, and the antituberculous agents isoniazid, pyrazinamide, and rifampin.
CATEGORY D
There is positive evidence of human fetal risk based on adverse reaction data from investigational or marketing experience or studies in humans, but potential benefits may warrant use of the drug in pregnant women despite potential risks. Antimicrobial agents in this category include aminoglycosides, tetracyclines, and tigecycline.
CATEGORY X
Studies in animals or humans have demonstrated fetal abnormalities, and/or there is positive evidence of human fetal risk based on adverse reaction data from investigational or marketing experience, and the risks involved in use of the drug in pregnant women clearly outweigh potential benefits.

FDA = U.S. Food and Drug Administration.

Source Content and Format of Labeling for Human Prescription Drug and Biological Products; Requirements for Pregnancy and Lactation Labeling (Federal Register/Vol. 73, No. 104/Thursday, May 29, 2008).

toxicity; streptomycin (eighth nerve toxicity) and tetracyclines (incorporation into teeth and bones) are in the D category.

The second consideration is the impact of changes in the metabolism of pregnant women on the pharmacokinetics of various agents. Pregnancy is associated with increases in the volume of distribution of many antibiotics, as well as their renal clearance. These factors can reduce overall antibiotic exposure, especially for agents that have substantial protein binding, such as ceftriaxone, or narrow therapeutic margins, such as the aminoglycosides. As a result, increased dosing may be required to achieve target levels of the antibiotic at the site of infection.

The final consideration when administering antibiotics to pregnant women is the potential effects on the fetal microbiota. Several studies have documented profound changes in fetal microbiota in response to antimicrobial administration to the mother. At present, the long-term impacts of these microbiota changes on the child are not known, but concerns exist regarding immune development and risk for immunologically mediated diseases such as asthma.

Age

The pharmacokinetics and pharmacodynamics of antimicrobial agents are not uniform across all age groups. In older individuals, the absorption of oral antimicrobials may be altered if their absorption depends on gastric pH, since relative or absolute achlorhydria is more common after age 60 years. Absorption of antimicrobials such as oral penicillin, which is deactivated by gastric acid, may be higher in the elderly, whereas agents that require gastric acid for absorption (e.g., ketoconazole) may be less well absorbed. Fluoroquinolones are contraindicated in elderly patients with renal insufficiency owing to the risk of torsades de pointe.

Renal and Hepatic Function

The two major routes of elimination of antibiotics are through the kidneys and the liver. An assessment of renal function, generally as calculated by the creatinine clearance, is important for the proper dosing of many antibiotics, especially when the therapeutic range is relatively narrow. For example, aminoglycosides are predominantly excreted through the kidney and have a narrow margin of safety, with nephrotoxicity and ototoxicity associated with serum concentrations that are not dramatically higher than therapeutic levels. With standard three times per day dosing, it is important to measure serum concentrations of aminoglycosides, to monitor renal function, and to adjust the dose as necessary. The bactericidal activity of aminoglycosides is most pronounced when maximum peak serum concentrations are achieved, and their toxicity is commonly associated with elevated trough levels. In some instances, it is possible to administer aminoglycosides as a once-daily dose, thereby achieving a much higher peak and a much lower trough concentration. Vancomycin also has been associated with nephrotoxicity, especially if it is administered in conjunction with an aminoglycoside. Serum concentrations of vancomycin are often measured to ensure that trough levels minimize the risks of toxicity. For most other antimicrobial agents, the margins of safety are considerably greater, so adjustments for renal insufficiency, if they are necessary, can be made empirically without measuring specific serum concentrations (see Stanford Health Care Antimicrobial Dosing Reference Guide at med.stanford.edu). Antimicrobial agents that do not require adjustment for renal insufficiency include nafcillin, ceftriaxone, doxycycline, azithromycin, and linezolid.

Antimicrobial agents that are excreted largely or partially by the liver and require dose adjustment in the presence of liver dysfunction include metronidazole, chloramphenicol, tigecycline, caspofungin, and voriconazole. Ceftriaxone, which is heavily concentrated in the bile and can even form stones in pediatric biliary trees, may need dose adjustment for patients with both renal and hepatic dysfunction.

Drug-Drug Interactions

Polypharmacy is a major problem in all hospitals and for many patients with multiple chronic diseases. Virtually all hospitalized patients who are treated with an antimicrobial agent will simultaneously be treated with a variety of other drugs, including other antimicrobials. The clinician must consider other medications that patients may be taking and the potential resulting drug-drug interactions that will amplify or inhibit the activity or toxicity of other agents or the antibiotic itself. One of the most common mechanisms is by interaction with cytochromes that are involved in the metabolism of a variety of drugs. Prominent among these agents are the triazoles that inhibit cytochrome P-450 (voriconazole, itraconazole, posaconazole). Use of these agents can result in excessive levels of other drugs, thereby resulting in toxicity (e.g., quinolones and macrolides are associated with QT prolongation, which can be amplified if they are combined with other drugs for which QT prolongation is also an adverse effect). Ciprofloxacin, which is an inhibitor of CYP1A2, can alter the metabolism of theophylline, clozapine, olanzapine, and caffeine. Linezolid, which is a reversible and nonselective inhibitor of monoamine oxidase, reduces the breakdown of serotonin and can precipitate the serotonin syndrome (Chapter 400) when used with serotonin reuptake inhibitors, opioid analgesics, or antiepileptic drugs. Rifampin, which is frequently included in antituberculosis therapy, induces the cytochrome P-450 system and can result in increased metabolism (and decreased effectiveness) of other medications, including oral contraceptive pills and warfarin.

Development of Resistance

DNA conferring resistance can be transferred between bacteria using transferable plasmids, transposons, bacteriophage, or, in some bacteria, by the uptake of naked DNA. Moreover, some resistance mechanisms (such as multidrug efflux pumps) can confer resistance to several different antimicrobial classes. As such, the best way to prevent resistance in commonly isolated human pathogens is to minimize the exposure to antimicrobials by efforts to avoid antibiotics in patients without bacterial infection, by treating with narrower-spectrum agents whenever possible, by treating patients for only as long as is required to cure the infection, and by strictly adhering to established principles of infection control.

Antimicrobial Combinations

Antimicrobial agents are commonly administered in combinations, and empiric combination therapy is often unavoidable. However, combination therapy carries potentially negative consequences of augmented toxicity (sometimes even a multiplication of the risk of toxicity), drug interactions, and increased selective pressure. Every effort should be made to tailor the regimen when data become available and to focus treatment as soon as it is safe to do so.

Treatment of Polymicrobial Infections

Polymicrobial infection is common in diabetic foot infections (Chapter 210) and intra-abdominal infections (Chapter 128). Diabetes foot infections often include staphylococci, streptococci, facultative and aerobic gram-negative bacilli, and anaerobes. Since the most responsible organism may not be clear, treatment often includes more than one agent, especially if methicillin-resistant *S. aureus* is involved. For intra-abdominal infections, the desire to cover facultative and anaerobic gram-negative rods, as well as anaerobic organisms and enterococci, frequently leads to combination treatment, but these infections can sometimes be adequately covered with a single broad-spectrum agent (such as a carbapenem) or a fixed combination (β-lactam-β-lactamase inhibitor combination).

Minimizing the Emergence of Drug Resistance

Using combinations of antimicrobial agents can prevent the emergence of resistance to either single agent,[6] a principle perhaps best exemplified by the treatment of tuberculosis and human immunodeficiency virus (Chapter 357). For tuberculosis, resistance to isoniazid occurs in about 1 in 10^8 *Mycobacterium tuberculosis* progeny through point mutations in a few different genes, and resistance to rifampin occurs in about 1 in 10^{10} through point mutations in the β-subunit of the *rpoB* RNA polymerase gene. As a result the rate of mutation needed to be resistant to both drugs would be $10^{-8} \times 10^{-10}$, or 10^{-18}. Since it is generally assumed that a tuberculosis cavity holds about 10^{12} microorganisms during disease, hundreds to thousands of resistant mutants will likely arise to each drug in any given patient, but it is extremely unlikely that a mutant will be resistant to both isoniazid and rifampin.

Combinations of antibiotics are effective in tuberculosis because of the independent and bactericidal mechanisms of action of the different antibiotics, the limited number of genetic sites that can confer resistance, and most importantly, because *M. tuberculosis* lacks the ability to share DNA with other bacteria. Efforts to prove that combinations of agents prevent the emergence of resistance in more common bacteria have generally failed in the clinical setting, mostly because of a combination of the mechanisms of resistance within a given strain and the acquisition of large segments of DNA (with multiple resistance determinants) from other bacteria.

Achieving Synergism in Antibacterial Activity

Three general types of synergism are achievable by combining more than one agent. The first is bactericidal synergism, in which either agent alone determines only bacteriostatic activity or negligible activity, but simultaneous exposure to two agents results in bacterial death. The primary example of such clinically relevant synergism is in the use of penicillins or vancomycin plus an aminoglycoside for the treatment of *E. faecalis* endocarditis (Chapters 61 and 270). In vitro, penicillins are static agents against most enterococci.

MICs for aminoglycoside exceed clinically achievable concentrations. When combined in vitro, the two agents synergize, thereby resulting in bacterial death (>99.9% kill). Unfortunately, the emergence and spread of aminoglycoside-modifying enzymes in enterococci, which yield high-level aminoglycoside resistance (MIC >2000 μg/mL), has limited the efficacy of these combinations by eliminating the synergism. More recently, combinations of ampicillin and ceftriaxone have shown efficacy against *E. faecalis* endocarditis. The mechanism for this synergism is not known, but is postulated to be inhibition of the full complement of *E. faecalis* penicillin-binding proteins. Given the prevalence of high-level aminoglycoside resistance and the more favorable toxicity profile of the double β-lactam combination, many centers have switched to ampicillin-ceftriaxone as first-line therapy for *E. faecalis* endocarditis (Chapters 61 and 270).

The second type of synergism is bacteriostatic synergism—combining two drugs to gain enhanced inhibitory activity against infecting strains. An example is the combination of trimethoprim and sulfamethoxazole, which inhibit sequential steps in the folate synthesis pathway, thereby resulting in combined activity that is greater than either antibiotic alone.

The third type of synergism uses a second agent to reverse a resistance phenotype. For example, β-lactamase inhibitors, most of which lack appreciable antibacterial activity against the target pathogens, can be combined with penicillins, cephalosporins, and carbapenems to enhance activity against many of our most resistant pathogens. In the United States, β-lactam-β-lactamase inhibitor combinations, such as ampicillin-sulbactam and piperacillin-tazobactam, are sold as fixed combinations and have become mainstays of treatment.

CONSIDERATIONS OF ANTIMICROBIAL ADMINISTRATION

ROUTE OF ADMINISTRATION

Antibiotics can be administered parenterally, orally, or locally. The chosen route depends upon the severity of the illness being treated, the characteristics of the antibiotic being administered, the ability to achieve sufficient concentrations of antibiotics at the site of infection, and, in some cases, social factors surrounding the treatment of an infection. For serious, life-threatening infections, the intravenous route is generally preferred, in part because of concerns about the reliability of gastrointestinal absorption under conditions of serious illness. Intravenous therapy facilitates achieving the peak and trough serum levels that are predicted based on body size and renal or hepatic function. The availability, safety, and durability of long peripherally inserted central catheters (PICC lines) and subcutaneous ports have facilitated long-term outpatient administration of intravenous antimicrobial agents,[7] thereby reducing hospital length of stay. Parenteral antimicrobials can also be administered by the intramuscular route, although the rapidity of absorption may be difficult to predict in patients who have a high body mass index or low blood pressure.

Oral therapy is preferred for less serious infections and for infections that require prolonged courses of treatment. Potent antimicrobial classes that have virtually 100% bioavailability when administered orally under normal circumstances include fluoroquinolones, doxycycline, metronidazole, and linezolid. Conversely, β-lactams have limited to poor oral absorption, and some antimicrobials, such as vancomycin and aminoglycosides, have very limited oral absorption. Because of this characteristic, vancomycin can be used as oral local therapy for colonic *Clostridioides difficile* infection (Chapter 271).

Antibiotics may be administered locally for a variety of reasons. Presurgical decontamination for methicillin-resistant *S. aureus* with mupirocin ointment to the nares can reduce infection after a sternotomy. Intraocular infections can be treated with direct injections into the vitreous because of the difficulty achieving appropriate concentrations with parenteral administration. Superficial eye infections are often treated with antibiotic ointments (Chapter 391). Superficial skin infections can be treated topically with combinations of agents that would be too toxic to administer by any systemic route. Treatment of peritoneal infections complicating peritoneal dialysis are often treated by incorporating sufficient concentrations of antibiotics into the peritoneal dialysis fluid.

Sometimes the route of administration is chosen based on social factors. Treatment of gonorrhea (Chapter 275), for example, often involves a single intramuscular dose of ceftriaxone, partly driven by the rates of resistance of *Neisseria gonorrhoeae* to oral agents but also by the desire to administer a single curative dose for patients who may not be reliable in completing oral tetracycline therapy, especially given the public health implications associated with continued transmission.

PHARMACODYNAMIC CONSIDERATIONS

Pharmacokinetics involves the absorption, distribution, and elimination of antibiotics in individuals of different ages, genders, and body types. The pharmacodynamics portion involves outcomes of treatment in in vitro settings to determine the extent to which inocula of bacteria are inhibited or killed, as well as the temporal parameters associated with optimal activity. These techniques can guide dosing intervals and blood level goals to maximize the efficacy and minimize the toxicity of antimicrobial therapy. For example, killing associated with ß-lactam agents best correlates with the percentage of time that the drug concentration is close to the minimum inhibitory concentration (time-dependent killing), whereas killing with fluoroquinolones and aminoglycosides is best associated with achieving a maximum concentration during the dosing interval (concentration-dependent killing); other antibiotics (e.g., vancomycin) kill best with a combination of high peak and prolonged duration (area-under-the-curve killing).

DURATION OF THERAPY

The emergence and spread of multiresistant and even pan-resistant bacterial strains have made apparent the need to reduce the selective pressure for resistance by reducing exposure to antibiotics. One component of this effort has been to examine the required duration of antimicrobial therapy for specific types of infections. More than 45 randomized controlled trials have compared the efficacy of shorter courses of antibiotics with traditional longer courses,[8] and, with very few exceptions, the shorter courses have been equally effective, whereas the longer courses have sometimes been associated with more adverse events. For example, community-acquired pneumonia can be treated for 3 to 5 days and ventilator-associated pneumonia for 7 to 8 days, compared with the traditional 14-day course (Chapter 85). Other types of infections for which shorter courses have been found to be safe and effective include streptococcal pharyngitis,[A3] exacerbation of bronchitis (Chapter 84),[A4] pneumonia,[A5] urinary tract infections (Chapter 263),[A6] skin and soft tissue infections, intra-abdominal infections, gram-negative bacteremia (Chapter 94), and neutropenic fever (Chapter 260). In the absence of surrogate markers to describe the state of the infection during treatment, such as the viral load in managing HIV infection (Chapter 357), a good general principle is that when infected patients look better and appear to have returned to baseline, they likely no longer need antibiotics.

One strategy to reduce the duration of antimicrobial exposure is the programmed variation in empirical antimicrobial usage within different areas of the hospital, most commonly in intensive care units (ICUs). This strategy has been referred to as antimicrobial cycling, or "crop rotation." The hope is that switching the most frequently used antibiotic from one agent to another after a specified period on a recurrent basis, with perhaps four different antibiotics (e.g., piperacillin-tazobactam for 3 months, cefepime for 3 months, imipenem for 3 months, ciprofloxacin for 3 months, then back to the piperacillin-tazobactam) will reduce the likelihood that local resistance will emerge to any one agent. Unfortunately, resistant bacteria from elsewhere in the hospital will often be introduced when patients are transferred into the ICU. Furthermore, different classes of antibiotics may promote resistance through the same mechanisms (e.g., selecting for overexpression of efflux pumps or β-lactamases), so resistance is unlikely to decline unless the overall usage of antibiotics declines.

ADMINISTRATIVE ASPECTS OF ANTIMICROBIAL THERAPY

ANTIMICROBIAL STEWARDSHIP

The problem of antimicrobial resistance is growing in the United States and worldwide[9,10] because of marked increase in their use,[11] and a postantibiotic world may be approaching in some geographic areas and for some medical conditions. Stewardship programs (Table 258-2) designed to improve adherence to recommended antimicrobial therapy (Chapter 261) have shown local success that offers hope for reducing or reversing some types of resistance.[A7–A10]

Stewardship programs are also important to control pharmaceutical costs, which account for the largest and fastest-growing segment of health care costs. Most hospitals control their spending on drugs by using formularies to define which drugs can be freely used by prescribing physicians, which drugs need special approval for use, and which drugs are not available because less expensive and equally effective, safe, and convenient alternatives are provided. It is critical that experts and pharmacists in infectious diseases advise these decisions so that cost is not the sole consideration when deciding among similar antibiotics.

The three components of successful strategies to address antimicrobial resistance are effective infection control measures, appropriate use of existing

TABLE 258-2 CORE ELEMENTS OF HOSPITAL ANTIMICROBIAL STEWARDSHIP PROGRAMS

Hospital Leadership Commitment: Dedicate necessary human, financial, and information technology resources
Accountability: Appoint a leader or co-leaders, such as a physician and pharmacist, responsible for program management and outcomes
Pharmacy Expertise: Appoint a pharmacist, ideally as the co-leader of the stewardship program, to lead implementation efforts to improve antibiotic use
Action: Implement interventions, such as prospective audit and feedback or preauthorization, to improve antibiotic use
Tracking: Monitor antibiotic prescribing, impact of interventions, and other important outcomes (e.g., *C. difficile* infection and resistance patterns)
Reporting: Regularly report information on antibiotic use and resistance to prescribers, pharmacists, nurses, and hospital leadership
Education: Educate prescribers, pharmacists, and nurses about adverse reactions to antibiotics, antibiotic resistance, and optimal prescribing

CDC. Core Elements of Hospital Antibiotic Stewardship Programs. Atlanta, GA: US Department of Health and Human Services, CDC; 2019. Available at https://www.cdc.gov/antibiotic-use/core-elements/hospital.html.

TABLE 258-3 RECENTLY APPROVED ANTIBACTERIAL AGENTS

ANTIBACTERIAL AGENT	YEAR APPROVED	IV/PO	INDICATION
Bezlotoxumab	2016	IV	To reduce the recurrence of *C. difficile* in patients 18 years of age or older
Secnidazole	2017	PO	Bacterial vaginosis
Meropenem/vaborbactam	2017	IV	Complicated urinary tract infection
Delafloxacin	2017	PO/IV	Acute bacterial skin and skin structure infection
Plazomicin	2018	IV	Complicated urinary tract infection
Eravacycline	2018	IV	Complicated intra-abdominal infection
Sarecycline	2018	PO	Treatment of inflammatory lesions of non-nodular moderate to severe acne vulgaris in patients ages 9 years and older
Omadacycline	2018	PO/IV	Community-acquired bacterial pneumonia/acute bacterial skin and skin structure infections
Rifamycin	2018	PO	Travelers' diarrhea caused by noninvasive strains of *E. coli*
Imipenem/relebactam	2019	IV	Hospital-acquired pneumonia and ventilator-associated pneumonia caused by resistant gram-negative bacteria
Pretomanid	2019	PO	In combination with bedaquiline and linezolid for patients who have extensively drug-resistant tuberculosis or treatment-intolerant/nonresponsive multidrug-resistant tuberculosis
Lefamulin	2019	IV	Community-acquired bacterial pneumonia
Cefiderocol	2019	IV	Complicated urinary tract infection

IV = intravenous; PO = oral.

antimicrobial agents, and the development of new antimicrobials. In recent years, the U.S. Food and Drug Administration has approved a number of new antibacterial agents (Table 258-3), some of which are effective in treating multidrug-resistant bacteria. However, because of the substantial cost of these agents, their use has been largely restricted to documented cases of resistant infections.

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259 APPROACH TO FEVER OR SUSPECTED INFECTION IN THE NORMAL HOST

MICHAEL T. MELIA

OVERVIEW OF FEVER

DEFINITION

The traditional definition of a normal temperature as 98.6° F (37.0° C) came from a study more than 150 years ago, when 98.6° F (37.0° C) was the mean temperature from over 1 million axillary temperature measurements in 25,000 patients. Multiple more recent studies show contemporary axillary temperatures to be lower, with a mean axillary temperature of 96.75° F (36° C)[1] and a mean oral temperature of about 36.5° C or 98° F.[2,3]

Human temperature also varies by time of day, with mean nadir temperatures in the early morning (i.e., 6 AM) and mean zenith temperatures in the

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TABLE 258-2 CORE ELEMENTS OF HOSPITAL ANTIMICROBIAL STEWARDSHIP PROGRAMS

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Action: Implement interventions, such as prospective audit and feedback or preauthorization, to improve antibiotic use
Tracking: Monitor antibiotic prescribing, impact of interventions, and other important outcomes (e.g., *C. difficile* infection and resistance patterns)
Reporting: Regularly report information on antibiotic use and resistance to prescribers, pharmacists, nurses, and hospital leadership
Education: Educate prescribers, pharmacists, and nurses about adverse reactions to antibiotics, antibiotic resistance, and optimal prescribing

CDC. Core Elements of Hospital Antibiotic Stewardship Programs. Atlanta, GA: US Department of Health and Human Services, CDC; 2019. Available at https://www.cdc.gov/antibiotic-use/core-elements/hospital.html.

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Bezlotoxumab	2016	IV	To reduce the recurrence of *C. difficile* in patients 18 years of age or older
Secnidazole	2017	PO	Bacterial vaginosis
Meropenem/vaborbactam	2017	IV	Complicated urinary tract infection
Delafloxacin	2017	PO/IV	Acute bacterial skin and skin structure infection
Plazomicin	2018	IV	Complicated urinary tract infection
Eravacycline	2018	IV	Complicated intra-abdominal infection
Sarecycline	2018	PO	Treatment of inflammatory lesions of non-nodular moderate to severe acne vulgaris in patients ages 9 years and older
Omadacycline	2018	PO/IV	Community-acquired bacterial pneumonia/acute bacterial skin and skin structure infections
Rifamycin	2018	PO	Travelers' diarrhea caused by noninvasive strains of *E. coli*
Imipenem/relebactam	2019	IV	Hospital-acquired pneumonia and ventilator-associated pneumonia caused by resistant gram-negative bacteria
Pretomanid	2019	PO	In combination with bedaquiline and linezolid for patients who have extensively drug-resistant tuberculosis or treatment-intolerant/nonresponsive multidrug-resistant tuberculosis
Lefamulin	2019	IV	Community-acquired bacterial pneumonia
Cefiderocol	2019	IV	Complicated urinary tract infection

IV = intravenous; PO = oral.

antimicrobial agents, and the development of new antimicrobials. In recent years, the U.S. Food and Drug Administration has approved a number of new antibacterial agents (Table 258-3), some of which are effective in treating multidrug-resistant bacteria. However, because of the substantial cost of these agents, their use has been largely restricted to documented cases of resistant infections.

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For the General References and other additional features, please visit Elsevier eBooks+ at https://ebooks.health.elsevier.com.

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259 APPROACH TO FEVER OR SUSPECTED INFECTION IN THE NORMAL HOST

MICHAEL T. MELIA

OVERVIEW OF FEVER

DEFINITION

The traditional definition of a normal temperature as 98.6° F (37.0° C) came from a study more than 150 years ago, when 98.6° F (37.0° C) was the mean temperature from over 1 million axillary temperature measurements in 25,000 patients. Multiple more recent studies show contemporary axillary temperatures to be lower, with a mean axillary temperature of 96.75° F (36° C)[1] and a mean oral temperature of about 36.5° C or 98° F.[2,3]

Human temperature also varies by time of day, with mean nadir temperatures in the early morning (i.e., 6 AM) and mean zenith temperatures in the

ABSTRACT

Fever is a sign in infectious and noninfectious illnesses that range from self-limited to life-threatening. Based upon data from young, healthy volunteers, a fever can be defined as a temperature greater than 99° F (37° C) at 6 AM or 100° F (37.8° C) any time of day. Many fevers are caused by processes that are either self-limited or readily diagnosed and treated. Some febrile syndromes, however, such as acute-onset fever and rash, fever in the returning traveler, and fever of unknown origin, have daunting and nearly limitless potential causes. For such scenarios, a thoughtful history must include information about exposures, travel, concurrent medical problems, medications, allergies, and vaccinations. A comprehensive physical examination is key. Diagnostic testing should be targeted toward conditions suggested by the history and physical examination so that diagnosis-specific therapy can be chosen.

KEYWORDS

fever
thermoregulation
fever and rash
fever of unknown origin

late afternoon and early evening (i.e., 4 to 6 PM). In one study of healthy volunteers, the maximum normal oral temperature, as defined by the 99th percentile, was 98.9° F (37.2° C) at 6 AM and 99.9° F (37.7° C) at 4 PM. By this definition, any temperature greater than 99° F (37.2° C) at 6 AM or 100° F (37.8° C) any time of day can be considered a fever.

Some studies have suggested that older individuals have lower mean temperatures than younger persons, but other studies have found that older persons' mean core temperatures are no different. Similarly, data in women as compared with men are inconsistent. Overall, any differences in normal mean temperatures by age and sex are negligible and not clinically significant.

EPIDEMIOLOGY

Most infections are transmitted from person to person to person by direct contact (e.g., hands, fomites), emanate from a common source (e.g., food, water), are spread by aerosols or respiratory droplets (e.g., viral respiratory infections), or are transmitted by vectors (e.g., mosquitos), often as zoonoses (Chapter 303). Infections also can be caused by breaches in skin integrity or self-injection. However, the source is often unknown. Risk factors therefore include contact with other sick individuals, exposure to contaminated food or water, proximity to animals, mosquito bites, and injection drug use (Chapter 365). Geographic exposures also vary, even in developed countries, where diseases such as histoplasmosis (Central and Eastern United States; Chapter 308), coccidioidomycosis (Southwestern United States; Chapter 308), Lyme disease (Chapter 296), babesiosis (Chapter 324), and ehrlichiosis (Chapter 302) are seen in certain geographic areas. Prior vaccination reduces the risk of many infections (Chapter 15), but immunity to many of those infections wanes over time.

PATHOBIOLOGY

Multiple temperature sensors throughout the body are thought to provide feedback via neural pathways to a dynamic federation of independent thermoeffector loops within the preoptic anterior hypothalamus. Each controller has its own threshold for signaling its effector to modulate the transfer of heat. These independent controllers and effectors work in a coordinated and, as appropriate, additive fashion to achieve the desired body temperature.[4]

The generation of fever involves exogenous pyrogens, of which bacterial endotoxin (lipopolysaccharide) from the outer membrane of gram-negative bacteria is a classic example, and endogenous pyrogens or pyrogenic cytokines. Exogenous pyrogens bind to pattern recognition receptors expressed by cells of the innate immune system. This binding triggers gene expression and synthesis of pyrogenic cytokines, such as interleukin (IL)-1, IL-6, tumor necrosis factor (TNF)-α, and interferon (IFN)-γ, as well as many other molecules fundamental to the febrile response. IL-6 is in turn integral to the production of many acute-phase reactants. The binding of lipopolysaccharide to pattern recognition receptors on pulmonary and hepatic macrophages also activates enzymes required for synthesis of prostaglandin E_2, which is critical to the generation of fever by its interaction with the thermoregulatory system. Medications such as nonsteroidal anti-inflammatory drugs and aspirin block the activity of enzymes involved in the synthesis of prostaglandin E_2.

When patients fail to develop a fever despite severe bacterial infection, morbidity and mortality tend to be higher. This phenomenon suggests that fever may either inhibit the multiplication of some pathogens or increase the entry of neutrophils into inflammatory sites.

CLINICAL MANIFESTATIONS

Fever is typically associated with relative or absolute tachycardia of about 2 to 5 beats per minute per 1° F increase in temperature. Temperature-pulse dissociation,[5] which is the absence of this response, is classically found in typhoid fever (Chapter 284), leptospirosis (Chapter 298), rickettsiosis (Chapter 302), dengue (Chapter 352), legionellosis (Chapter 290), and babesiosis (Chapter 324).

The peripheral vasodilation in response to fever contributes to the relative tachycardia and may blunt the increase in blood pressure that typically accompanies adrenergic activation. Relative or absolute hypotension can auger the development of septic shock (Chapter 94), which portends a poor prognosis.

The source of fever is often suggested by accompanying symptoms or signs, including headache or altered mental status in meningitis (Chapter 381) or encephalitis (Chapter 383), sore throat in pharyngitis (Chapter 397), ear pain in otitis (Chapter 394), upper respiratory symptoms in tracheitis (Chapter 84) or sinusitis (Chapter 394), cough and sputum in pneumonia (Chapter 85), abdominal pain in visceral abdominal infections (Chapters 128 and 141), diarrhea in enteric infections (Chapter 262), and pelvic pain in pelvic inflammatory disease (Chapter 264). However, localizing symptoms may be absent in infectious endocarditis (Chapter 61) and sepsis (Chapter 94). Elderly individuals and patients with diabetes mellitus are more likely to develop severe infections.

DIAGNOSIS

Just as there is no single definition of fever, there is no single approach to the evaluation of a febrile patient. An individualized approach is warranted. Most febrile patients have common, self-limited processes; some warrant further evaluation with laboratory testing and imaging, and a smaller subset have potentially serious or life-threatening conditions. A thoughtful history (including information about exposures, travel, concurrent medical problems, medications, allergies, and prior vaccinations) and a careful physical examination are always important.

Fever in Outpatients

When seeing a generally healthy febrile patient in the ambulatory setting, aggressive diagnosis may not be appropriate since the syndrome may resolve spontaneously with supportive care. For patients who appear toxic, tachypneic, or confused or have localized findings, however, blood cultures[6] and a prompt, targeted diagnostic evaluation[7] are indicated. For these sicker outpatients, molecular testing of body fluids is now a rapid way to diagnose worrisome respiratory or enteric infections. Urinalysis and urine culture are indicated for suspected urinary tract infection (Chapter 263), lumbar puncture for suspected meningitis (Chapter 381), blood culture for suspected sepsis (Chapters 61 and 94), microscopic evaluation or culture for suspected sexually transmitted diseases (Chapter 264), and aspiration or biopsy for liver infections (Chapter 137), septic arthritis, and osteomyelitis (Chapter 251).

The white blood cell count is usually elevated with a neutrophilic predominance (Chapter 153) in bacterial infections but may not be elevated in certain infections. Examples include some patients with typhoid fever or infections such as tuberculosis and histoplasmosis, which can involve the bone marrow, and patients who have overwhelming sepsis. Premature neutrophilic forms and a low serum bicarbonate level suggest severe infection. Viral infections are typically associated with a normal or only slightly elevated white blood cell count, typically with selective lymphocytosis.

Fever in Inpatients

Most hospital-associated fevers are nosocomial bacterial infections of the lower respiratory tract, urinary tract, or surgical wounds (Table 259-1). Leukocytosis is common and sometimes is the primary manifestation when fever is minimal in elderly patients or patients who are on fever-suppressing medications. Nosocomial fevers may lack obvious symptoms or signs, especially intra-abdominal processes such as acalculous cholecystitis (Chapter 141), bowel infarction (Chapter 129), viscus perforation, or abscesses (Chapter 128). Antibiotic-induced *Clostridioides difficile* (Chapter 271) can cause fever and a leukemoid reaction, even with little or no diarrhea. In hospitalized patients, drug fever (Chapter 234) is common, may be suggested by findings such as interstitial nephritis (Chapter 108) or elevated aminotransferase levels (Chapter 136), and requires withdrawal of potentially offending medications.

TABLE 259-1 MAJOR CAUSES OF HOSPITAL-ASSOCIATED FEVER

COMMON	LESS COMMON
INFECTIOUS	**INFECTIOUS**
Clostridioides difficile enterocolitis	Biliary tract disease
Pneumonia	Endometritis
Surgical wound	Intra-abdominal abscess
Urinary tract	Mediastinitis
Vascular catheter	Sinusitis
NONINFECTIOUS	**NONINFECTIOUS**
Drug-induced fever	Adrenal insufficiency
Hematoma	Gout
Immediate postoperative state	Myocardial infarction
Transfusion reaction	Organ infarction
Venous thromboembolism	Pancreatitis

From Leggett JE. Approach to fever or suspected infection in the normal host. In: Goldman L, Schafer A, eds. *Goldman-Cecil Medicine*, 26th ed. Philadelphia: Elsevier; 2020.

In severely ill patients, such as patients in intensive care units, about 80% of febrile episodes are caused by infectious processes, including pneumonia and infections related to indwelling catheters and devices. However, fever is also seen in the absence of infection after acute myocardial infarction (Chapter 58), deep vein thrombosis (Chapter 68), pulmonary embolism (Chapter 68), and ischemic or hemorrhagic stroke (Chapters 376 and 377). Fever and chills may also occur during or after transfusions of blood products (Chapter 162).

SPECIFIC FEVER SYNDROMES

FEVER AND RASH

The potential causes of fever with a rash include a long list of pathogens and processes. Diagnosis must begin with a systematic history and comprehensive physical examination (Chapter 6). The data thereby obtained can help prioritize a differential diagnosis and guide any further diagnostic testing.

History

When interviewing a patient who has fever and rash, the routine questions related to the history of present illness should be augmented by a specific set of inquiries:

- Does the patient have any known immunocompromising conditions?
- Has there been any known skin trauma or breakdown?
- Has the patient recently traveled domestically or internationally?
- Have there been any known animal contacts, including domestic as well as wild animals?
- Have there been any outdoor exposures, including to plants, gardening, spelunking, or possible arthropod bites?
- Have there been any notable ingestions, including raw seafood or undercooked meat?
- Has the patient had any water exposures, including swimming, fishing, hot tub use, or aquarium care?
- Has the patient had recent contact with anyone else known to be ill?
- Has the patient taken any new prescription or over-the-counter medications within the past 2 months?
- Does the patient have any known medication allergies?
- Has the patient had any new sex partners? Do they have any concerns regarding possible sexually transmitted infections?
- Has the patient engaged in injection drug use?
- Has the patient received all recommended childhood and adult vaccines?

Physical Examination

Understanding the nature and history of the patient's rash is also fundamental (Table 259-2). The following aspects should be ascertained by the physical examination and further focused questioning.

- What is the character of the rash?
  - Macule: flat, non-palpable lesions flush with the surface of the skin (see Fig. 406-1)
  - Papule: superficial, fleshy, palpable lesions raised above the surface of the skin (see Fig. 406-3)
  - Nodule: deeper, discrete, firm, raised lesions (see Fig. 407-22B)
  - Vesicle: fluid-filled lesion measuring ≤5 mm (see Fig. 403-10)
  - Bullae: fluid-filled lesions measuring >5 mm (see Fig. 406-11)
  - Pustule: raised lesion filled with pus (see Fig. 406-27)
  - Petechiae: pinpoint (<2 mm), non-blanching, red-brown, flat lesions (see Figs. 158-2 and 406-4)
  - Purpura: larger, non-blanching, red-brown, flat or raised lesions reflecting coalesced petechiae (see Fig. 406-5)
- What is the distribution of the lesions?
- Over what timeframe did the rash erupt and evolve as compared with the timing of onset of fever and additional signs or symptoms?
- How many lesions are there?
- In what way has the rash changed since its onset?
- Are the lesions localized to the skin (exanthem) or is there also a mucosal component (enanthem)?

In addition to the fever, a careful review of vital signs is essential because some causes of fever and rash are life-threatening. Other key aspects of the physical examination warranting attention include the presence or absence of pharyngitis or other mucosal lesions, adenopathy, hepatosplenomegaly, arthritis, and meningismus or an altered mental status.

Diagnosis

The type of skin finding and its distribution (especially to the palms or soles) can aid in the diagnosis. Syndromes of fever and rash range from self-limited skin infections to acute emergencies. Fever with a maculopapular rash in adults is seen especially in meningococcemia (Chapter 274), infectious mononucleosis (Chapter 348), West Nile virus (Chapter 352), Zika virus (Chapter 352), rubella (Chapter 339), primary human immunodeficiency virus (Chapter 355), parvovirus B19 (Chapter 342), Rocky Mountain spotted fever (Chapter 302), ehrlichiosis (Chapter 302), and exanthematous drug reactions (Chapter 234).[8]

Excluding Medical Emergencies

Neisseria meningitidis bacteremia (meningococcemia; Chapter 274) causes fulminant illness that can lead to death within days. Hemorrhagic skin lesions (Fig. 274-3) are its hallmark. In the context of sudden-onset fever and rapidly progressive septic shock with multisystem organ dysfunction, patients can initially manifest a maculopapular eruption, typically involving their extremities and trunk, before the lesions promptly evolve into petechiae and purpura fulminans. Generalized muscle tenderness is often seen, and digital gangrene is common. Although petechiae can arise in any patient with septic shock, their presence with or without purpura should prompt immediate antimicrobial therapy active against *N. meningitidis* (Chapter 274) as well as other potential pathogens, including *S. pneumoniae* (Chapter 268). Droplet precautions are warranted for *N. meningitidis*, and close contacts should receive antimicrobial prophylaxis.

Rickettsia rickettsii, the cause of Rocky Mountain spotted fever (Chapter 302), is a potentially fatal tick-transmitted infection. More than half of the cases of spotted fever rickettsioses reported in the United States occur in Arkansas, Missouri, North Carolina, Tennessee, and Virginia. Initial manifestations include fever and flulike symptoms, including headache, myalgia, and arthralgia. Rash typically is not present when the symptoms begin and is present only in about 50% of patients after 72 hours of illness, but nearly 90% of patients eventually erupt an initially maculopapular rash that evolves into petechial lesions (Fig. 302-2). The rash typically begins on the extremities and can involve the palms and soles; as it progresses, it can spread centripetally to the trunk.[9] Because of the delayed-onset rash, clinicians should maintain a high index of suspicion in appropriate epidemiologic circumstances.

Stevens-Johnson syndrome (Fig. 403-8) and toxic epidermal necrolysis (Fig. 407-5) reflect different ends of the spectrum of the same process (Chapter 407), with Stevens-Johnson syndrome involving up to 10% of total body surface, toxic epidermal necrolysis more than 30%, and 10 to 30% involvement reflecting overlap. These conditions are typically triggered by medications, including antimicrobial agents (Chapter 234). Clinical manifestations include an initial 1- to 3-day prodrome of fever, flulike symptoms, and a morbilliform rash or atypical targetoid macules followed by confluent, purpuric macules, sheets of denuded skin, and painful mucosal lesions. Untreated disease leads to widespread full-thickness epidermal necrosis and may progress to multisystem organ failure. Patients with toxic epidermal necrolysis are most appropriately managed in burn units (Chapter 97).

Although initially associated with tampon use in young menstruating women, toxic shock syndrome can follow any *Staphylococcus aureus* (Chapter 267) or *Streptococcus pyogenes* (Chapter 269) infection. Manifestations are abrupt in onset and include fever, severe myalgia, hypotension, diffuse erythema (Table 269-2), mucosal hyperemia, and multisystem organ failure. Skin desquamation follows 1 to 3 weeks after disease onset. Positive blood cultures are rare. Distinguishing Stevens-Johnson syndrome/toxic epidermal necrolysis from toxic shock syndrome, which can be accomplished by biopsy, is critically important, because the management of one commonly necessitates discontinuation of antibiotic therapy, whereas antibiotic use is essential in the other.

Necrotizing fasciitis (Chapters 97, 267, and 269) is a potentially lethal soft tissue infection triggered by antecedent cutaneous trauma. The majority of patients manifest superficial cutaneous signs, including soft tissue erythema and edema. Despite the prevalence of these findings, the hallmark of necrotizing fasciitis is pain out of proportion to findings in physical examination; a high clinical index of suspicion is warranted, because cutaneous and radiographic abnormalities can be limited or absent. Appropriate management includes immediate surgical debridement and antibiotic therapy.

Measles virus (Chapter 338) typically presents with high fever, cough, coryza, conjunctivitis, and an enanthem of small (1 to 3 mm), raised, white, grain-of-sand–like lesions on an erythematous base (Koplik spots; Fig. 338-2) within the oral (chiefly buccal) mucosa. This prodrome is followed by an erythematous maculopapular exanthem that starts over the face and spreads centrifugally to the periphery, potentially including the palms and soles (Table 259-3). The rash typically persists for 5 days, desquamates as it heals, and resolves in the sequence in which it arose. Potential complications include pneumonia and acute or chronic encephalitis.

TABLE 259-2 CAUSES OF FEVER AND RASH BY RASH MORPHOLOGY

RASH MORPHOLOGY	TREATABLE INFECTIOUS CAUSES	UNTREATABLE INFECTIOUS CAUSES	NONINFECTIOUS CAUSES
Petechial or purpuric	*C. canimorsus* Endocarditis Epidemic typhus (*R. prowazekii*) (severe) Gram-negative bacteria (purpura fulminans owing to sepsis) Hepatitis B *L. monocytogenes* *N. meningitidis* *N. gonorrhea* *P. falciparum* Rat bite fever Rocky mountain spotted fever (*R. rickettsii*) and other rickettsiae Scarlet fever (*S. pyogenes*) (Pastia lines) *S. aureus* *S. pneumoniae*	Adenovirus Cytomegalovirus Dengue virus Enteroviruses Epstein-Barr virus Rubella (soft palate) Variola Viral hemorrhagic fevers	Adverse drug reaction Amyloidosis Drug reaction with eosinophilia and systemic symptoms (DRESS) Henoch-Schoenlein purpura Cryoglobulinemic vasculitis Scurvy Small vessel vasculitis Systemic lupus erythematosus Thrombotic thrombocytopenic purpura
Maculopapular	*Bartonella* spp. *B. burgdorferi* *C. psittaci* Ehrlichiosis Epidemic typhus (*R. prowazekii*) (initial) Hepatitis B virus Human immunodeficiency virus (HIV) Leptospirosis (pretibial, rare) Murine (endemic) typhus (*R. typhi*) *M. pneumoniae* *N. meningitidis* (initial) Rat bite fever *R. conorii* and other Rickettsioses Relapsing fever (tick- > louse-borne) Rocky mountain spotted fever (*R. rickettsii*) (initial) *S. paratyphi* or *S. typhi* (rose spots) *T. pallidum*	Adenovirus Chikungunya virus Dengue virus Enteroviruses Epstein-Barr virus Human herpesvirus-6 (HHV-6) (roseola) Lymphocytic choriomeningitis virus Parvovirus B19 (fifth disease) Rubella Rubeola (measles) West Nile virus Zika virus	Adverse drug reaction Dermatomyositis Drug reaction with eosinophilia and systemic symptoms (DRESS) Erythema margninatum Erythema multiforme Serum sickness Stevens-Johnson syndrome/toxic epidermal necrolysis (initial) Still disease Sweet syndrome Systemic lupus erythematosus
Vesiculobullous	*A. hydrophila* *C. psittaci* Ecthyma gangrenosum (often *P. aeruginosa*) Herpes simplex virus HIV Necrotizing fasciitis Rickettsialpox (*R. akari*) (late) *S. aureus* Staphylococcal scalded skin syndrome *S. pyogenes* *Streptobacillus moniliformis* (rat bite fever) (hemorrhagic) Varicella-zoster virus *Vibrio vulnificus*	Enteroviruses Monkeypox Parvovirus B19 Smallpox Vaccinia Variola virus	Adverse drug reaction Contact dermatitis Eczema vaccinatum Erythema multiforme bullosum Stevens-Johnson syndrome/toxic epidermal necrolysis
Pustular	Endocarditis Herpes simplex virus (late) Hot tub folliculitis (*P. aeruginosa*) *Moraxella* spp. bacteremia *N. gonorrhea* *N. meningitidis* bacteremia (chronic) *S. aureus* Varicella-zoster virus (late)	Variola virus	Acute generalized exanthematous pustulosis (AGEP) Behçet syndrome Drug reaction with eosinophilia and systemic symptoms (DRESS) Pustular psoriasis
Erythematous	*C. hemolyticum* Scarlet fever (*S. pyogenes*) Staphylococcal scalded skin syndrome Toxic shock syndrome (rash *S. aureus* > *S. pyogenes*)	Enteroviruses	Adverse drug reaction Drug reaction with eosinophilia and systemic symptoms (DRESS) Eczema Kawasaki syndrome Lymphoma Pityriasis rubra Psoriasis Sézary syndrome Stevens-Johnson syndrome/toxic epidermal necrolysis

TABLE 259-2 CAUSES OF FEVER AND RASH BY RASH MORPHOLOGY—cont'd

RASH MORPHOLOGY	TREATABLE INFECTIOUS CAUSES	UNTREATABLE INFECTIOUS CAUSES	NONINFECTIOUS CAUSES
Nodular	*B. dermatitidis* *Candida* spp. *C. immitis* *C. neoformans* Erythema induratum (*M. tuberculosis*) *H. capsulatum* *Leishmania* spp. *N. meningitidis* (chronic) *Nocardia* spp. Nontuberculous Mycobacteria, including *M. haemophilum and M. marinum* *S. schenckii*		Erythema nodosum Rheumatic fever Sweet syndrome

spp. = multiple species.
Adapted from Schlossberg D. Fever and rash. *Infect Dis Clin North Am*. 1996;10:101-110; Juliano JJ, Cohen MS, Weber DJ. The acutely ill patient with fever and rash. In: Bennett JE, Dolin R, Blaser MJ, eds. *Mandell, Douglas, and Bennett's Principles and Practice of Infectious Diseases*. Philadelphia: Elsevier; 2020:801-818.

TABLE 259-3 INFECTIOUS ENTITIES ASSOCIATED WITH RASH INVOLVING THE PALMS AND SOLES

- Acral erythema (triggered by cytotoxic chemotherapy)
- Coxsackie virus (hand-foot-and-mouth disease)
- Endocarditis (Osler nodes, Janeway lesions)
- Erythema multiforme
- *Neisseria gonorrhea* (disseminated)
- *Rickettsia rickettsii* (Rocky Mountain spotted fever)
- Rubeola (measles)
- *Streptobacillus moniliformis* (rat bite fever)
- Toxic shock syndrome
- *Treponema pallidum* (syphilis)

Adapted from Leggett JE. Approach to fever or suspected infection in the normal host. In: Goldman L, Schafer AI, eds. *Goldman-Cecil Medicine*. Elsevier; 2019:1809-1815.

TABLE 259-4 COMMON CAUSES OF FEVER AND LYMPHADENOPATHY

REGIONAL	GENERALIZED
Cervical	Cytomegalovirus
Streptococci	Epstein-Barr virus
Tuberculosis	HIV
Viral upper respiratory tract infection	Lymphoma
Peripheral	Sarcoidosis
Bartonella henselae	Syphilis (secondary)
Herpesviruses	Toxoplasmosis
Lymphoma	Viral hepatitis
Metastatic cancer	
Sporotrichosis	
Streptococci	
Inguinal	
Chancroid	
Herpes	
Lymphogranuloma venereum	
Syphilis (primary)	

HIV = human immunodeficiency virus.
From Leggett JE. Approach to fever or suspected infection in the normal host. In: Goldman L, Schafer AI. *Goldman-Cecil Medicine*, 26th ed. Philadelphia: Elsevier; 2020:1809-1815.

FEVER AND MUSCULOSKELETAL COMPLAINTS

Fever with localized musculoskeletal tenderness, swelling, or erythema suggests a local bacterial infection such as septic arthritis (Chapter 251), osteomyelitis (Chapter 251), or a spinal epidural abscess (Chapter 382). However, polyarthritis can also accompany disseminated gonococcal infection (Chapter 275), chikungunya (Chapter 352), dengue (Chapter 352), parvovirus B19 (Chapter 342), hepatitis B and C (Chapters 134 and 135), and Lyme disease (Chapter 296). Osteomyelitis of the vertebrae is almost always initiated by discitis with symmetrical involvement of vertical adjacent vertebrae. Myositis is seen in clostridial (Chapter 271), streptococcal (Chapter 269), or mixed aerobic-anaerobic infections. Myositis of deep muscles (e.g., the psoas or gluteus) is usually due to *S. aureus* (Chapter 267) in the United States but to *M. tuberculosis* (Chapter 299) in areas where tuberculosis is endemic. Leptospirosis (Chapter 298) and toxoplasmosis (Chapter 320) can cause diffuse myositis, and rhabdomyolysis (Chapter 99) can occur with legionellosis (Chapter 290) and a variety of viral infections.

POSTOPERATIVE FEVER

Significant infections within 24 hours after surgery (Chapter 401) are usually due to *S. pyogenes* (Chapter 269) or *Clostridium* species (Chapter 271). Urinary tract infections (Chapter 263) may be seen in patients who have undergone urologic instrumentation or who have had an indwelling catheter for 3 or more days. However, the presence of abnormalities on urinalysis or even a positive urine culture does not prove that the infection is the cause of fever, so a full diagnostic evaluation is mandatory. Wound infections causing fever are uncommon but typically occur about 5 to 7 days postoperatively and are more common after gastrointestinal procedures. Toxin-producing *C. difficile* (Chapter 271) is the only significant nosocomial postoperative gastrointestinal infection. Deep venous thrombosis or pulmonary embolism (Chapter 68) is rare except in patients who have not received appropriate prophylaxis. Fever without localizing signs is often drug-related (Chapter 234) but also can be caused by conditions such as atelectasis (Chapter 78) or acalculous cholecystitis (Chapter 141).

FEVER WITH LYMPHADENOPATHY, HEPATOSPLENOMEGALY, OR JAUNDICE

Fever with lymphadenopathy can be a manifestation of infectious and noninfectious (Table 259-4) illnesses. Generalized lymphadenopathy (Chapter 154) is seen with systemic infections, whereas focal lymphadenopathy is seen with local and systemic infections.

Fever with splenomegaly (Chapter 154) suggests either a systemic infection (e.g., Epstein-Barr virus [Chapter 348], malaria [Chapter 316], babesiosis [Chapter 324], granulomatous hepatitis with hepatomegaly, *M. tuberculosis* [Chapter 299], histoplasmosis [Chapter 308], *Bartonella* species [Chapter 291], *Brucella* species [Chapter 286], *Coxiella burnetii* [Chapter 302], visceral leishmaniasis [Chapter 319], and schistosomiasis [Chapter 326]) or a malignant neoplasm, especially lymphoma (Chapters 171 and 172). Fever with hepatomegaly or jaundice (Table 259-5) is sometimes seen with systemic infections that localize to the liver (e.g., leptospirosis), but it also suggests liver-specific pathology and is likely to be associated with elevated liver enzymes. However, liver enzymes can also be elevated in severe generalized bacterial infections in the absence of detectable anatomic liver disease or jaundice.

FEVER OF UNKNOWN ORIGIN

Most patients with acute fever have either a self-limited process or a problem that is promptly diagnosed. A subset, however, has persistent fevers despite an initial diagnostic evaluation. Such patients are described as having fever of unknown origin, generally defined as an illness of more than 3 weeks' duration,

TABLE 259-5 COMMON INFECTIOUS CAUSES OF FEVER AND JAUNDICE

Bacterial sepsis
Cholangitis
Hepatic abscess
Leptospirosis
Malaria
Viral hepatitis
Yellow fever

From Leggett JE. Approach to fever or suspected infection in the normal host. In: Goldman L, Schafer AI, eds. *Goldman-Cecil Medicine*, 26th ed. Philadelphia: Elsevier; 2020:1809-1815.

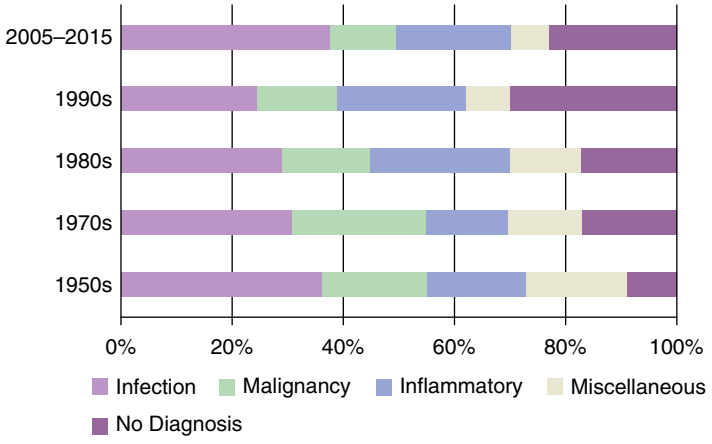

FIGURE 259-1. Proportion of fevers of unknown origin grouped by eventual diagnostic domain by decade of analysis. (Based on data from Mourad O, Palda V, Detsky AS. A comprehensive evidence-based approach to fever of unknown origin. *Arch Intern Med*. 2003;163:545-551; Figure 1. Fusco FM, Pisapia R, Nardiello S, et al. Fever of unknown origin [FUO]: which are the factors influencing the final diagnosis? A 2005-2015 systematic review. *BMC Infect Dis*. 2019;19:653; Table 4.)

TABLE 259-6 POSSIBLE CAUSES OF FEVER OF UNKNOWN ORIGIN

CATEGORY	COMMON	UNCOMMON
Infectious	Abscess, occult Cytomegalovirus infection Endocarditis, culture-negative Epstein-Barr virus infection *M. tuberculosis* infection Osteomyelitis	*Bartonella* spp. infection *Brucella* spp. infection Hepatitis A, B, or E infection HIV infection, acute Mycotic aneurysm *Salmonella* spp. infection Urinary tract infection
Malignant	Hepatocellular carcinoma Leukemia Lymphoma, Hodgkin Lymphoma, non-Hodgkin Melanoma Renal cell carcinoma	Atrial myxoma Castleman disease Colon adenocarcinoma Gastric carcinoma Mesothelioma Multiple myeloma Myelodysplastic syndrome
Inflammatory	Adult-onset Still disease Giant cell arteritis Inflammatory bowel disease Polymyalgia rheumatica Systemic lupus erythematosus Temporal arteritis	Granulomatosis with polyangiitis Kawasaki disease Polyarteritis nodosa Rheumatoid arthritis Sarcoidosis Takayasu arteritis
Miscellaneous	Drug fever Hematoma Hyperthyroidism Thromboembolism, chronic	Factitious fever Hemophagocytic lymphohistiocytosis Hypoadrenalism Necrotizing lymphadenitis Periodic fever syndrome Pheochromocytoma Thyroiditis, subacute

HIV = human immunodeficiency virus.
Adapted from Wright WF, Auwaerter PG. Fever and fever of unknown origin: review, recent advances, and lingering dogma. *Open Forum Infect Dis*. 2020;7:ofaa132; Hersch EC, Oh RC. Prolonged febrile illness and fever of unknown origin in adults. *Am Fam Physician*. 2014;90:91-96.

fever >101° F on several occasions, and continued diagnostic uncertainty despite appropriate investigations, including at least three outpatient visits or at least 3 days in the hospital.[10]

Conditions that cause persistent fevers can be grouped into five domains: infections, inflammatory (i.e., rheumatologic or connective tissue diseases), malignant, miscellaneous, and undiagnosed (Fig. 259-1).[11,12] Each of these five broad domains encompasses many individual diagnoses, thereby suggesting a role for extensive testing. Before embarking on a detailed diagnostic evaluation of a patient with a fever of unknown origin, a general principle is that atypical presentations of common infectious diseases, such as tuberculosis (Chapter 299),[13] are more likely than is a common presentation of rare entities. Clinicians should be mindful of these common diagnoses (Table 259-6) when undertaking their initial comprehensive history and physical examination. If this initial evaluation yields potential diagnostic clues, these clues should help guide initial diagnostic testing (Table 259-7).[14] The addition of molecular testing has greatly increased the ability to detect pathogens in blood and other body fluids.[15,16]

When these core tests are unrevealing, 18F-fluoro-2-deoxy-D-glucose positron emission tomography (FDG-PET)/computed tomographic (CT) imaging can detect a cause in about 30 to 60% of cases.[17,18] FDG-PET/CT can itself be diagnostic (e.g., large-vessel vasculitis) or it can identify a metabolically active focus amenable to biopsy. Tissue biopsy of a lymph node, liver, bone marrow, or temporal artery can be guided by FDG-PET/CT or other test result.

Although empiric therapy is warranted for critically ill patients, completion of the diagnostic evaluation is otherwise preferred prior to empiric treatment to avoid masking or incompletely treating the underlying disorder. If no diagnosis is reached after completion of the diagnostic evaluation, consideration should be given to screening for autoinflammatory conditions (Chapter 240)[19,20] under the guidance of expert consultation. One option is continued watchful waiting, with periodic repeat evaluations. Another option is a trial of anti-inflammatory therapy (e.g., nonsteroidal anti-inflammatory drugs or systemic corticosteroids) based upon shared decision making with the patient.

TABLE 259-7 INITIAL DIAGNOSTIC EVALUATION FOR A PATIENT WITH FEVER OF UNKNOWN ORIGIN*

- Complete blood cell counts with white blood cell differential
- Comprehensive metabolic profile
- Urinalysis with sediment
- Erythrocyte sedimentation rate
- C-reactive protein
- Blood culture (three cultures, with at least two spaced over at least 24 hours)
- HIV Ag/Ab assay (fourth-generation)
- Cytomegalovirus (CMV) IgM and IgG
- Heterophile antibody
- *M. tuberculosis* interferon gamma release assay
- Ferritin
- Lactate dehydrogenase
- Thyroid-stimulating hormone
- Rheumatoid factor
- Antinuclear antibodies
- Chest radiograph
- Hepatitis A, B, and E serologies (if liver enzymes abnormal)
- Lower extremity compression ultrasonography with Doppler (if above nondiagnostic)
- Transthoracic echocardiography (if above nondiagnostic)
- Computed tomographic scan of chest, abdomen, and pelvis (if above nondiagnostic)

*Depending upon information gathered from the history and physical examination.
Ab = antibody; Ag = antigen; HIV = human immunodeficiency virus; Ig = immunoglobulin.
Adapted from Wright WF, Auwaerter PG. Fever and fever of unknown origin: review, recent advances, and lingering dogma. *Open Forum Infect Dis*. 2020;7(5):ofaa132; Hersch EC, Oh RC. Prolonged febrile illness and fever of unknown origin in adults. *Am Fam Physician*. 2014;90(2):91-96; Mourad O, Palda V, Detsky AS. A comprehensive evidence-based approach to fever of unknown origin. *Arch Intern Med*. 2003;163:545-551.

SEVERE HYPERPYREXIA

Intrinsic thermoregulatory mechanisms almost always prevent fevers from exceeding 41° C (106° F). Temperatures above this level are usually due to central nervous system hemorrhage. Hyperthermia, whereby exogenous (e.g., prolonged exposure to high ambient temperatures) or endogenous (e.g., medications) mechanisms result in temperature elevations in the setting of unchanged thermoregulatory centers, can be difficult to distinguish from fever. In addition to medication-associated hyperthermia, other causes of hyperthermia include malignant hyperthermia (Chapter 400), heat stroke (Chapter 95), and the thermoregulatory dysfunction seen in patients with Parkinson disease (Chapter 378).

TREATMENT

Outpatient Ambulatory Setting

Most acute, undifferentiated febrile illnesses resolve spontaneously within 1 or 2 weeks without a specific diagnosis or therapy. In other cases, diagnostic clues from the history and physical examination and targeted basic tests (e.g., complete blood count, urinalysis, chest radiography) usually can guide therapy. In patients who have only nonspecific symptoms, watchful waiting with repeat evaluation by phone or in person may be sufficient. For more severe or prolonged symptoms, without localizing signs, an in-person physical examination, routine laboratory testing (e.g., a white blood cell count, metabolic profile, blood culture), and additional testing as suggested by the patient's history and epidemiologic risk factors may help guide therapy.

Empiric antibiotics should be avoided. Most pharyngitis (Chapter 397) in adults is viral, but streptococcal infection (Chapter 269) should be considered in patients who have tonsillar exudates, tender anterior cervical lymph nodes, and no cough. In such patients, a rapid streptococcal antigen test is indicated, with a positive test result prompting antibiotic treatment. Normal vital signs and a normal chest examination effectively exclude bacterial pneumonia, and antibiotics are of little, if any, value for nonspecific bronchitis (Chapter 84) or sinusitis (Chapter 394). By comparison, community-acquired pneumonia requires antibiotic therapy and often hospitalization (Chapter 85). Procalcitonin, which is an acute-phase reactant, is more likely to be elevated with bacterial than with viral infections, and procalcitonin-guided therapy can sometimes reduce unnecessary antibiotics, such as in respiratory infections,[A1] although it cannot be used in isolation to make decisions.[21] Furthermore, procalcitonin-guided therapy may not improve care in hospitals with high-quality care,[A2] in part because it poorly discriminates sepsis[A3] from nonseptic systemic inflammation. Prolonged fever and cough, which can be caused by *Bordetella pertussis* (Chapter 289), *Mycoplasma pneumoniae* (Chapter 293), and *Chlamydophila pneumoniae* (Chapter 294), should prompt a chest radiograph, molecular testing, and appropriate antibiotic treatment. For other localized infections, specific treatment is outlined in disease-specific chapters.

SUSPECTED NOSOCOMIAL INFECTION

In hospitalized patients, the history and physical examination remain the foundation of the evaluation of a patient with new-onset fever. Further diagnostic testing should be guided by these findings. Interpretation of culture data must consider the possibility of colonization, as occurs frequently in the lungs of intubated patients or in the urine of patients with indwelling urinary bladder catheters, from true infection (Chapter 261). Treatment, as outlined in disease-specific chapters, typically is guided by culture results.

FEVER IN THE RETURNING TRAVELER

Fever in the returning traveler is reviewed in Chapter 265.

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260

APPROACH TO FEVER AND SUSPECTED INFECTION IN THE IMMUNOCOMPROMISED HOST

COSTI D. SIFRI

DEFINITION

Healthy individuals possess robust antimicrobial defense systems that include physical barriers in the form of skin and mucosal membranes, innate immune defenses that are conserved through evolution, and adaptive ("acquired") immune defense systems (Chapter 35). These systems, which are highly interconnected, work in concert through an array of defensive surfaces, cells, and soluble factors to protect a host from potential microbial assailants. The normal commensal microflora of the skin and mucosa protect the host by occupying body surface niches without activating the immune system and play an important role in the maturation and homeostasis of the immune system. Nutritional status, multiorgan function, and age all contribute to normal immune function. Damage to any of these host defense components increases the risk for infection. A wide assortment of conditions, including body surface burns (Chapter 97), endocrine and metabolic disorders, and medications such as glucocorticoids, can affect components of these defense systems and place an individual at increased risk for infection. In most patients, however, a compromised immune system is due to treatment of neoplastic disease (with particular attention to hematologic disorders such as leukemia and lymphoma), recipients of solid organ or stem cell transplants, and patients who are taking immunomodulatory medications for diagnoses such as collagen vascular and rheumatologic conditions. Management of people with acquired immunodeficiency syndrome (AIDS) is discussed in Chapters 357 and 358, and a more thorough discussion of primary immunodeficiency is provided in Chapter 231.

GENERAL CONCEPTS

The innate immune system serves as the first line of host defense (Table 260-1). Components of the innate immune system (Chapter 35) include natural physical and chemical barriers, phagocytic cells, and germline-encoded signaling systems that recognize molecular components unique to microbes that are invariant because they are essential for survival of the microbe. These signaling systems rapidly (minutes to hours) distinguish "nonself" from "self," thereby leading to the activation of protective phagocytic cells, proteolytic enzyme cascades, antimicrobial peptides, and other products. The innate immune system also primes the adaptive immune system, which is distinguished by the ability to create pathogen-specific responses and immunologic memory over several days. Like the innate immune system, the adaptive immune system is composed of both cellular and soluble factors (Chapter 35).

The risk for infection depends on the specific type of defect in host defenses. For example, impaired macrophage function as a consequence of tumor necrosis factor (TNF)–directed therapy is a predisposing risk for infection due to intracellular pathogens such as *Mycobacterium tuberculosis* (Chapter 299) and *Histoplasma capsulatum* (Chapter 308), whereas splenectomy and functional asplenism (Chapter 154) predispose to sepsis due to encapsulated bacteria, including pneumococcus (Chapter 268) and meningococcus (Chapter 274). Detailed understanding of the nature of compromised host defense mechanisms and how the defect influences susceptibility to potential viral, bacterial, fungal, or parasitic pathogens can guide appropriate diagnostic evaluations, therapies, and prevention strategies (through vaccination, antimicrobial prophylaxis, pre-emptive monitoring, and lifestyle changes).

Determining whether an immunocompromised individual has a clinically significant infectious disease can be challenging. Several factors make it more difficult to identify infectious disease in individuals with compromised immune defenses. Potential causes of infection are diverse and range from typical, community-acquired pathogens to less common, opportunistic pathogens. Signs of inflammation, including fever, pain, and erythema, may be reduced. Laboratory markers of infection, such as changes in the white blood cell count and hepatic transaminase levels, may be subtle or difficult to interpret owing to the influence of baseline noninfectious processes (e.g., medications, organ dysfunction). Radiographic findings may also be blunted. Accordingly, infection

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260

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ABSTRACT

The approach to suspected infection and fever in immunocompromised hosts differs from the approach in a normal host, both in terms of the potential pathogens as well as the clinical course. Examples include treatment of fever or suspected infection in patients with neoplastic diseases (particularly hematologic disorders such as leukemia and lymphoma), organ transplantation, and collagen vascular or autoimmune diseases.

KEYWORDS

immunocompromised
immunosuppressed
fever
neutropenia
infection
transplant
autoimmune

TABLE 260-1 COMPONENTS OF THE IMMUNE SYSTEM

INNATE IMMUNE SYSTEM (IMMEDIATE, NONPATHOGEN-SPECIFIC, EVOLUTIONARILY ANCIENT, NO MEMORY)	
Physical defense mechanisms	Skin Mucous membranes (e.g., oral mucosa, olfactory mucosa, gastric mucosa, intestinal mucosa, bronchial mucosa, genitourinary mucosa) Tears Mucus Ciliated respiratory epithelium Urine flow
Innate soluble and cellular defense mechanisms	Stomach acid Complement system Phagocytes (i.e., neutrophils, macrophages, dendritic cells) C-type lectin receptors, toll-like receptors, NOD-like receptors, intracellular nucleic acid sensors Cytokines (e.g., IL-1, IL-4, IL-5, IL-6, IL-8, IL-10, IL-12, G-CSF, TNF-α, IFN-γ) Natural antimicrobial products (e.g., defensins, lactoferrin, lysozyme, reactive oxygen species) Neutrophil extracellular traps
ADAPTIVE IMMUNE SYSTEM (DELAYED, PATHOGEN-SPECIFIC, EVOLUTIONARY ORIGIN WITH JAWED VERTEBRATES [~0.5 BILLION YEARS], MEMORY)	
Cellular adaptive immune system	T lymphocytes • $CD8^+$ (cytotoxic) • $CD4^+$ (helper) • Γδ (alternative TCRs) • Treg (regulatory)
Humoral adaptive immune system	B lymphocytes • Immunoglobulins (IgM, IgG, IgA, IgE, IgD antibodies)
EFFECTORS OF IMMUNE FUNCTION	
Effector	Resident microbial flora Organ function Age Stress Nutrition Metabolic homeostasis (e.g., pH, iron, uremia)

G-CSF = granulocyte colony-stimulating factor; IFN-γ = interferon-γ; IL = interleukin; NOD = nucleotide oligomerization domain; TCR = T-cell receptor; TNF-α = tumor necrosis factor-α.

may be advanced at the time of presentation. Furthermore, multiple infections or processes may occur simultaneously. Diagnosis can be challenging because serologic testing may not be useful. However, recent advances in the development and adoption of molecular diagnostic assays have proved especially useful tools in immunocompromised patients. Finally, numerous noninfectious causes of fever, including neoplastic disease, collagen vascular disease, allograft rejection, graft-versus-host disease, and medications (e.g., antibiotic-induced fever, cytokine release syndromes following monoclonal antibody therapies) may cause febrile illnesses that are indistinguishable from infectious processes. Consequently, significant and expedited efforts should be made to establish the cause of fevers in a compromised host. Invasive procedures, such as imaging-guided biopsy, endoscopic procedures, and surgery, may be required to establish a diagnosis.

APPROACH TO THE PATIENT

Broadly speaking, the factors that predispose immunocompromised patients to infection can be divided into two categories: intrinsic host factors as a consequence of illness and factors associated with medical treatment. Intrinsic host factors include underlying immunodeficiencies, medical comorbidities, past infections, metabolic derangements, and poor nutritional status. For patients with cancer, mechanical obstruction from tumors can predispose to organ dysfunction, infection, and the formation of abscesses. Tumors of the head and neck, respiratory tract, gastrointestinal tract, and female genitourinary tract predispose to infections in and adjacent to those anatomic spaces. Patients with chronic progressive organ dysfunction and failure are predisposed to infection as a consequence of their illness. Structural lung problems, such as cavitary lung disease, increase the risk for colonization and superinfection by *Aspergillus* (Chapter 311) and nontuberculous mycobacteria (Chapter 300). Progressive respiratory failure predisposes persons to pneumonia due to community-associated, health care–associated, and opportunistic pathogens (Chapter 85). Progressive liver failure predisposes to fungal infections, including cryptococcosis (Chapter 309). Immunodeficiency as a direct consequence of acquired immune system disorders, such as hematologic malignancies or bone marrow infiltration by metastasis of solid tumors, adds another layer of risk of infection.

Medical treatment is the other major consideration that influences the risk for infection. Radiation therapy and cytotoxic chemotherapy of malignant disease directly or indirectly target cells of the immune system, thereby leading to significant risk for infection. Physical and natural barriers, such as skin, mucosal membranes, uroepithelium, and ciliated respiratory epithelium, may be injured or impaired as a consequence of disease or treatment. Surgery and medical devices, such as central venous catheters, indwelling urinary catheters, and circulatory support devices, among others, predispose to infections from a range of nosocomial pathogens, including *Staphylococcus aureus*, coagulase-negative staphylococci, enterococci, enteric gram-negative bacteria, *Pseudomonas aeruginosa*, other multidrug-resistant gram-negative bacteria, and *Candida*. Bleeding and fluid collections, such as urinomas and bilomas, may become seeded and infected after surgery. Repeated surgery is a risk for both organ transplant recipients and patients with solid tumors. Patients with primary or metastatic lung cancer are susceptible to recurrent pneumonia. Patients with head and neck cancer and brain cancer are predisposed to aspiration pneumonitis and pneumonia. The use of immunosuppressive medications following allogeneic stem cell or organ transplantation is a significant risk factor. The consequences of prior infections, empirical antibiotics, and treatment of infections lead to unbalanced changes in the composition of the gastrointestinal microbiome (termed *dysbiosis*) that may reduce barriers to colonization with drug-resistant pathogens and increase the risk of chemical infection.

The approach to the immunosuppressed patient requires detailed information about the nature of the immunodeficiency and known related risks. Specific immune defects in host responses are associated with specific underlying conditions and medical interactions (Table 260-2).

Patients with Neoplastic Disease

In patients with malignancies, the underlying condition contributes importantly to determining infectious risks. For example, absolute neutropenia or leukocyte dysfunction (Chapter 153) occurs in the setting of specific malignancies (e.g., acute or chronic leukemias). In such cases, the risk for bacterial infections is enhanced, even in the absence of chemotherapy. In other underlying conditions, such as chronic lymphocytic leukemia, patients frequently have quantitative defects in humoral host defense products, such as decreased immunoglobulins and components of the complement system, that are bactericidal. Other types of phagocytic cells include circulating monocytes and tissue macrophages, which are the fixed mononuclear cells of the reticuloendothelial system. These cells normally collaborate with helper T lymphocytes in defense against intracellular pathogens, such as mycobacteria, fungi, and some viruses and parasites. The spectrum of infectious risks is further broadened and prolonged when patients with these underlying immune defects are treated with cytotoxic drugs. Chemotherapies can also be deleterious to the function of other organs that are critical to host defenses, especially the integrity of the gastrointestinal tract's mucosal barrier and the airway's innate clearance mechanisms, thereby posing additional susceptibilities to bacterial and fungal pathogens. As a result, the underlying malignancy itself and the specific therapies that are used to treat it combine to create the profile of the types of infections to which the patient is at risk, both acutely and chronically.

Chimeric antigen receptor-modified T (CAR-T) cells and immune checkpoint inhibitors (Chapter 29), which are potent new classes of immunotherapeutics for cancer,[1] can cause severe immune-related adverse effects. CAR T-cell therapy causes cytokine-release syndrome and neurologic toxic effects, including encephalopathy. Immune checkpoint inhibitors' immune-related adverse effects can range from mild skin findings to significant inflammatory tissue injury, including colitis, hepatitis, and pneumonitis. Checkpoint blockade may also worsen pre-existing infection and even unmask subclinical infection as a consequence of enhanced immunologic function. Treatment of these immune-related adverse effects with immunomodulators such as glucocorticoids or interleukin-6 inhibitors may paradoxically increase the risk of infection.

Hematopoietic Stem Cell and Solid Organ Transplant Recipients

Hematopoietic stem cell transplantation (Chapter 163) exposes recipients to additional risks as a result of the agents used for conditioning therapy in preparation for the stem cell transplantation, variable rate and magnitude of

TABLE 260-2 CONDITIONS, INTERVENTIONS, AND IMMUNE DEFECTS TYPICALLY ENCOUNTERED IN COMPROMISED HOSTS

UNDERLYING CONDITION	INTERVENTION	TYPE OF DEFECT
Treatment of neoplastic diseases (particularly hematologic malignant neoplasms)	Underlying disease (without intervention)	Defects in production of bone marrow cells associated with defects in cellular immunity and phagocytic function (e.g., cytopenias associated with bone marrow infiltration with malignant cells)
	Cytotoxic chemotherapies	Bone marrow suppression; defects in primary and secondary humoral and cellular immunity; breach in mucosal barriers (skin, gut); impairment in mucociliary clearance; defects in other organ function (e.g., kidney, liver)
	Small molecule–targeted therapies (e.g., Bruton tyrosine kinase inhibitors, mTOR inhibitors)	Neutropenia, impaired cellular immunity
Hematopoietic stem cell transplantation	Underlying disease, without intervention (e.g., hematologic malignant neoplasms)	Defects in primary and secondary humoral and cellular immunity; defects in phagocytic cell quantity and function
	Cytotoxic conditioning therapy (± total body irradiation)	Bone marrow suppression; defects in primary and secondary humoral and cellular immunity; breach in mucosal barriers; defects in organ function
	Stem cell manipulation (e.g., T-cell depletion)	Delay in cellular engraftment
	Prophylaxis and treatment of graft-versus-host disease (e.g., glucocorticoids, calcineurin inhibitors, antimetabolites, TNF-α antagonists)	Defective function in phagocytic cells and dysfunction of primary and secondary humoral and cellular immunity
Solid organ transplantation	Underlying disease, without intervention (e.g., diabetes, end-stage liver disease)	Organ dysfunction and miscellaneous immune dysfunction
	Induction therapies (e.g., antilymphocyte globulin, anti–interleukin-2 Ab, anti-CD52 Ab)	Depletion and impairment in primary and secondary cellular and humoral immunity
	Surgical intervention and altered anatomy	Breach in mucosal barriers; defects in organ function
	Acute and chronic rejection prophylaxis and treatment (e.g., glucocorticoids, calcineurin inhibitors, antimetabolites and alkylating agents, plasmapheresis, antithymocyte globulin, monoclonal antibodies to B and T cells, anticytokine therapies, T-cell costimulation blockers)	Defective function in phagocytic cells, primary and secondary humoral and cellular immunity
Treatment of collagen vascular and autoimmune diseases	Anti-inflammatory and immunosuppressive agents (glucocorticoids, nonsteroidal anti-inflammatory drugs, calcineurin inhibitors, sirolimus, mycophenolate mofetil)	Defective function in phagocytic cells, primary and secondary humoral and cellular immunity
	Antimetabolite and alkylating agents	Bone marrow suppression, defects in primary and secondary humoral and cellular immunity
	Biologic immune response modifiers (e.g., antithymocyte globulin, monoclonal antibodies to B and T cells, anticytokine therapies, T-cell costimulation blockers)	Defective function in primary and secondary humoral and cellular immunity

Ab = antibody; mTOR = mechanistic target of rapamycin; TNF-α = tumor necrosis factor-α.

cellular engraftment, and, in recipients of allogeneic stem cell transplants, administration of additional agents to reduce risks for graft-versus-host disease (GVHD). GVHD itself and the treatments used to modulate it create additional risk for infection. Organ dysfunction, loss of natural barriers (skin and gut), and neutropenia enhance early risks for infection with bacteria and fungi that inhabit the gastrointestinal tract; impaired humoral and secondary immunity enhance late risks for infections caused by viruses, fungi, and encapsulated bacteria, especially in people who are treated aggressively for GVHD.

Immunodeficiency in solid organ transplant recipients is a consequence of the initiation and chronic maintenance of immunosuppressive therapies to suppress T- and B-lymphocyte function, so as to reduce risks for early and late graft rejection (Chapter 38). Additional factors that can exacerbate overall risks for infection include the altered anatomy preoperatively and postoperatively, the surgical intervention itself, and the potential of infection transmitted from the graft itself (i.e., donor-derived infection).

Transplant recipients have increased risks both for acute infection and for reactivation of latent infections after initiation of immunosuppression. Hence, pretransplantation evaluation should be focused on detection of latent herpesviruses (e.g., cytomegalovirus [CMV]) and other pathogens (e.g., *M. tuberculosis*) that can be transferred or reactivated with transplantation and immunosuppression.

The overall risk for infection in organ transplant recipients is determined by interactions between the patient's epidemiologic exposure and "net state of immunosuppression." Epidemiologic exposure to viral infections (both reactivation and disease) enhance risks for other infections. For example, cytomegalovirus infection (Chapter 347) is known to be a risk for additional infections by other microorganisms in recipients of both hematopoietic stem cell and solid organ transplant grafts. The "net state of immunosuppression" is a conceptual measure of all factors contributing to an individual patient's risk for infection at any given time (Table 260-3). Factors that influence the net state of immunosuppression[2] include underlying medical conditions (e.g., diabetes mellitus, advanced age, malnutrition), the use of specific immunosuppressive therapies (and their potential synergisms), technical problems during surgery, post-transplantation organ dysfunction, the administration of broad-spectrum antibiotics, and prolonged airway intubation or use of urinary and vascular access devices. This concept, which originated from an understanding of solid organ transplantation, can be applied to the care of all immunosuppressed patients.

TABLE 260-3 FACTORS CONTRIBUTING TO THE "NET STATE OF IMMUNOSUPPRESSION"

Immunosuppressive therapy: type, temporal sequence, and intensity
Prior and current therapies (chemotherapy, radiation therapy, antimicrobial agents)
Integument barrier integrity (e.g., catheters, lines, drains)
Neutropenia, lymphopenia, hypogammaglobulinemia
Underlying immune defects (e.g., autoimmune disease, genetic polymorphisms)
Metabolic conditions: uremia, malnutrition, diabetes, cirrhosis, advanced age
Viral infection (e.g., herpesviruses [CMV, EBV], HBV, HCV, HIV, RSV, influenza)

CMV = cytomegalovirus; EBV = Epstein-Barr virus; HBV = hepatitis B virus; HCV = hepatitis C virus; HIV = human immunodeficiency virus; RSV = respiratory syncytial virus.
Adapted from Fishman JA. Infection in organ transplantation. *Am J Transplant*. 2017;17:856-879.

An ever-increasing number of types of immunosuppressive therapies are frequently administered to patients with active connective tissue diseases and autoimmune conditions (Table 260-2). This population of patients is growing in importance with increasing use of biologic immune response modifiers (Chapters 28 and 29) that enhance risks for both reactivation of latent infection (e.g., *M. tuberculosis* and *H. capsulatum*) and severe manifestations of acute infection. Infectious risks should be considered in balancing need for these therapies and designing preventive regimens.

FEVER IN THE COMPROMISED HOST

The onset of fever in an immunocompromised patient can be an ominous development. Depending on the nature and magnitude of the impaired host defenses, including comorbid conditions, a febrile response can indicate the

onset of a life-threatening systemic infection. A diagnostic approach should be derived by careful consideration of the patient's signs and symptoms of infection, exact form(s) of immunocompromise, and whether the patient is at heightened risk for reactivation of latent infection. Because infection can progress rapidly, particularly in patients with absolute neutropenia (see later), empirical antimicrobial therapy is often indicated even before an infection is definitively identified.

In the setting of disease-associated or chemotherapy-induced neutropenia, fever is typically an important and often the only clinical indication of infection. Some patients with neutropenia and serious infection, especially patients who are elderly, may be afebrile or even hypothermic on presentation. The risk for bacterial infection increases proportionally with the decline in neutrophil count, especially with prolonged durations of significant neutropenia (Chapter 153). Infection rates increase with neutrophil levels below 1000 cells/μL and progressively increase as counts decline to less than 100 cells/μL. The duration of significant neutropenia is also an important determinant of the type of infection most likely to occur, with the risk for bacterial and fungal infections increasing with each successive week in which leukocyte counts are less than 500 cells/μL.

CLINICAL MANIFESTATIONS AND DIAGNOSIS

The presentation of a febrile, neutropenic patient should immediately prompt a systematic approach (Table 260-4). The differential diagnosis of fever should be influenced by local and hospital exposures as well as the type of preventive antibiotics the patient might be receiving and whether they likely altered the composition of the gastrointestinal microbiome. For example, the most common causes of fever during neutropenia are gram-negative bacteria, usually originating in the gastrointestinal tract, in the absence of the use of prophylactic and empirical antibiotics that cover them (especially quinolones and extended-spectrum β-lactams). By comparison, gram-positive bacteria are more likely in pretreated ambulatory patients, and drug-resistant gram-negative species (Chapters 282 and 283) are more common in hospitalized patients.

The type and duration of immunodeficiency (i.e., the "net state of immunosuppression") also can alter overall risk. Specific organ dysfunction, such as underlying pulmonary disease or renal impairment, can predispose to unique infectious syndromes (see later). Epidemiologic exposures should be thoroughly explored. Current and previously administered antimicrobial drugs affect risks for specific infections. For patients who are hospitalized in an acute care or chronic care facility or were recently hospitalized, it is particularly useful to have information on colonizing organisms that may display complex resistance profiles, such as vancomycin-resistant enterococci and bacteria that express extended-spectrum β-lactamases or other resistance determinants (e.g., carbapenemases). Knowledge of recent colonization with these organisms or local institutional epidemiology should be considered when tailoring initial antibiotic management.

The onset of fever in a patient who is neutropenic or otherwise immunocompromised requires a prompt and thorough bedside evaluation. Severely neutropenic patients may not be able to mobilize a sufficient number of leukocytes to develop a clinically apparent inflammatory response. For example, they may not exhibit the expected brisk peritoneal signs of an acute abdomen, meningeal signs of a central nervous system (CNS) infection, or localized tenderness, swelling, and erythema for an abscess. Beginning with examination of the head and neck, there should be a specific examination for evidence of CNS infection as well as a general evaluation of mental status. The oropharynx must be examined for evidence of pharyngitis and focal tenderness. Sinus membranes should be evaluated for the presence of erythema or necrosis. Complete examination of the heart, lung fields, and abdomen is critical, with attention to the potential presence of new murmurs, abnormal breath sounds, and intra-abdominal tenderness. The entire integument, including the perirectal area, should be examined, because severely neutropenic patients tend to get infections at either end of the gastrointestinal tract. Intravenous catheter exit sites and tunnels should be carefully inspected, and blood should be drawn through catheters for culture. Because classic signs of infection of catheter exit sites and tunnels can be absent or blunted in patients with neutropenia (with signs of infection present only after recovery of neutrophils), examination should be performed daily and with close scrutiny for evolving localized infection that may necessitate catheter removal.

Laboratory studies should emphasize tests that can yield prompt results, such as Gram stain or polymerase chain reaction (PCR) testing of body fluids, exudates, or aspirates. Blood cultures and cultures of other body fluids should be obtained promptly, preferably before initiating empirical antibiotics. Routine blood work should include a complete blood count with differential, serum creatinine concentration, and liver function studies. A chest radiograph should be part of the initial evaluation even if the chest examination is normal, as should routine urinalysis. Because routine radiographs are insensitive for detection of small nodular lesions, especially those caused by filamentous fungi, computed tomography (CT) should be performed to evaluate persistent fever, especially in the presence of airway or gastrointestinal symptoms.

Noninfectious causes of fever (e.g., drug fever) cannot be overlooked in neutropenic patients even though they might often require less urgent intervention. No biomarker has yet to be proved reliable in discriminating between severe infection and other causes of fever during neutropenia, although the utility of tests such as lipopolysaccharide-binding protein, interleukin-6 and interleukin-8, procalcitonin, presepsin, MCP-1 (monocyte chemoattractant protein-1), soluble TREM-1 (triggering receptor expressed on myeloid cells-1), C-reactive protein, and micro-RNAs is being studied. A heightened awareness of the possibility of a fungal infection is important.[3]

Multiple episodes of fever during prolonged hospitalization and neutropenia are not uncommon. Each episode requires comprehensive reassessment. After a documented infection, it should not be assumed that a subsequent episode of fever is caused by recrudescence of the same pathogen.

TABLE 260-4 APPROACH TO FEVER DURING CHEMOTHERAPY-INDUCED NEUTROPENIA

PAST AND CURRENT CLINICAL CONSIDERATIONS
What is the type and duration of immunologic deficiency?
Does the patient have any organ dysfunction that would predispose to particular infection?
Does the patient have any unique environmental or epidemiologic exposures?
What are the patient's prior infections and colonizing organisms?
What are the current and recently administered antimicrobial agents?
Are there any specific presenting signs or symptoms that suggest a particular type of infection or syndrome?

TREATMENT

Data support the liberal and prompt use of empirical antimicrobials in febrile neutropenic patients, selecting drugs that are active against the most likely pathogens based on the patients' epidemiologic exposures and colonizing organisms, especially in the gastrointestinal tract. An initial consideration in the management of fever during neutropenia is whether the patient requires hospitalization for therapy.[4] Risk assessment is an integral part of early evaluation to determine whether outpatient therapy is feasible. Risk assessment systems include the Multinational Association of Supportive Care in Cancer (MASCC) risk index score (Table 260-5), which is a validated predictor that can stratify patients for their risk of developing severe complications. However, current guidelines (Fig. 260-1) also consider other factors (such as the underlying disease, anticipated duration of neutropenia, other comorbid conditions that prompt patient access to a hospital, and the clinical judgment of the treating provider; Tables 260-6 and 260-7) when deciding whether outpatient management is appropriate for patients with febrile neutropenia.[5,6]

Progression of infection can occur rapidly in neutropenic hosts. The very high mortality rates associated with bacteremia, especially when caused by gram-negative bacteria, requires routine empirical therapies.[7] Antibiotics should be started as quickly as possible, preferably within an hour of recognition of fever during neutropenia, because delays in administering antibiotics may lead to prolonged hospital stays. The initial antibiotic choice should be tailored to patient and institutional variables (Table 260-2 and Fig. 260-2). In low-risk patients who can be potentially treated with oral antibiotics, starting combination therapy with a fluoroquinolone (e.g., ciprofloxacin, 750 mg twice daily) plus amoxicillin-clavulanate (875 mg/125 mg twice daily) is effective. In high-risk patients, admission is necessary for treatment and prompt administration of a broad-spectrum intravenous antibiotic regimen.

Monotherapy with a broad-spectrum β-lactam is generally associated with equal or better outcomes compared with the combination therapy,[A1,A2] but some evidence suggests that combination therapy may be preferred in patients who have septic shock. Current monotherapy options include third- and fourth-generation cephalosporins (e.g., cefepime 2 gm every 8 hours), antipseudomonal penicillins (e.g., piperacillin-tazobactam 4.5 gm every 6 hours), and carbapenems (e.g., meropenem 1 gm every 8 hours).[A3,A4]

The routine addition of vancomycin does not reduce all-cause or infection-related mortality and may be associated with increased adverse effects, including nephrotoxicity and rash. Nevertheless, empirical vancomycin use may be considered in specific clinical scenarios, such as documented or suspected catheter-related infection, gram-positive bacteremia pending final identification and susceptibility testing, colonization with methicillin-resistant *S. aureus*,

TABLE 260-5 THE MULTINATIONAL ASSOCIATION FOR SUPPORTIVE CARE IN CANCER (MASCC) INDEX

COMPONENTS OF THE MASCC INDEX

CLINICAL CHARACTERISTIC	SCORE*
Burden of illness (1 of the 3 options only):	
No or mild symptoms	5
Moderate symptoms	3
Severe symptoms	0
No hypotension (systolic BP >90 mm Hg)	5
No chronic obstructive pulmonary disease	4
Solid tumor or no prior fungal infection in patient with hematologic neoplasm	4
No dehydration (hydration with IV fluids not required)	3
Outpatient at onset of fever	3
Age <60 yr	2

*Maximum score: 26 (5 + 5 + 4 + 4 + 3 + 3 + 2). Low risk for complication = score ≥21; high risk for complication = score <21.

BP = blood pressure; IV = intravenous.

Data from Klastersky J, Paesmans M, Rubenstein EB, et al. The Multinational Association for Supportive Care in Cancer risk index: a multinational scoring system for identifying low-risk febrile neutropenic cancer patients. *J Clin Oncol*. 2000;18:3038-3051.

sepsis with hemodynamic instability pending culture results, pneumonia, and soft tissue infection. Use of vancomycin should be reassessed within 2 to 3 days when initiated for one of these conditions; if cultures fail to identify a resistant gram-positive pathogen, intravenous vancomycin should be discontinued.

Clinical response to the first few days of therapy is a critical determinant of the course of extended antimicrobial therapy. The median time to defervescence is shorter in low-risk than in high-risk patients (2 days vs. 5 to 7 days). If patients are stable yet still febrile during a period of prolonged and severe neutropenia, clinical judgment is required in deciding whether to maintain the initial regimen or to switch to an alternative regimen (Fig. 260-3).[8] Even if patients with neutropenia defervesce after 3 to 5 days of antibiotic therapy and cultures are negative, data are inconclusive as to the best subsequent strategy.[A5] The traditional strategy has been to continue empiric broad-spectrum antimicrobial therapy until recovery of the absolute neutrophil count, although this approach may not be possible in patients who are expected to have prolonged neutropenia. An alternative strategy is to discontinue empiric intravenous coverage or de-escalate to an oral antibiotic regimen. This latter strategy reduces total antibiotic exposure and has been shown to be safe for patients who are clinically stable and have been afebrile for at least 72 hours.[9] However, this strategy is associated with increased serious adverse outcomes in patients who are persistently febrile while receiving empiric broad-spectrum antibiotics.[A6,A7] If the neutrophil count recovers to above 500 cells/μL and fever persists, clinical judgment must be used to define the ongoing need for antimicrobial therapy while a search for the cause of the fever is continued. Clinical deterioration should trigger consideration of infections resistant to the empirical regimen.

Causes of persistent fever can be either infectious or noninfectious. Noninfectious causes include drug reactions (Chapter 234), transfusion reactions (Chapter 162), pulmonary emboli (Chapter 68), splenic infarcts, and underlying malignant disease. Persistent fever (Fig. 260-4) may indicate infection by a microorganism that is resistant or not covered by the empirical antibiotics chosen, or a loculated site of infection such as an abscess that also requires drainage for cure. In addition, nonbacterial pathogens should be considered, such as fungi (especially *Candida* and *Aspergillus* species) and should prompt evaluation and consideration of antifungal empirical therapies in the setting of fever that persists more than 4 to 7 days. Data are inconclusive as to whether early antifungal therapy guided by the depth and duration of the neutropenia is as good as routine empiric antifungal treatment.[A8,A9] Many drugs have been evaluated and shown to be effective in this setting, including azole drugs, echinocandins, and polyenes (Chapter 307).

Persistently compromised hosts may remain febrile for weeks without identification of the cause. For a patient who has persistent fever and in whom no pathogen is identified, the duration of therapy should be based on an integration of clinical data and the best estimate of the direction of the host's course. Therapy can be discontinued in stable, afebrile patients, assuming that the absolute neutrophil count exceeds 500 cells/μL. If broad-spectrum antibacterial therapy is discontinued, the patient should be monitored carefully. For patients whose neutrophil counts remain below 500 cells/μL, particularly the subset with severe profound neutropenia of less than 100 cells/μL, it is prudent to continue empirical antibacterial and antifungal therapy, with reappraisal of all diagnostic measures.

Granulocyte colony-stimulating factors can sometimes be useful for the prevention of febrile neutropenia.[A10] (see Chapter 153). For established fever in neutropenic patients, evidence-based guidelines[10] support the use of colony-stimulating factors in patients who are at high risk for infection-associated complications and poor clinical outcomes, such as patients with anticipated long and profound durations of neutropenia, advanced age, uncontrolled primary disease, hemodynamic compromise, pneumonia, and invasive fungal infections.

FEBRILE NEUTROPENIA SYNDROME

Fever in immunocompromised hosts can manifest as a variety of clinical syndromes other than just fever (Table 260-8). Common infectious and noninfectious syndromes can involve the skin, lungs, gastrointestinal tract, and CNS.

CUTANEOUS SYNDROMES

In immunocompromised patients with fever, a skin examination often can provide clues to the diagnosis.

Infectious Causes

Cutaneous manifestations can provide a clue to bacteremia, and aspiration and culture of suspicious lesions can be as valuable as a blood culture. Ascending streptococcal or staphylococcal cellulitis (Chapter 408) can occur in both immunocompromised and immunocompetent patients. Metastatic abscesses are a well-recognized complication of the *S. aureus* bacteremia syndrome. Necrotizing vasculitis is classically associated with *P. aeruginosa* infections (Chapter 282); its cutaneous lesion of ecthyma gangrenosum is an erythematous, indurated target or "bull's-eye" lesion with an area of central necrosis that can appear in crops (Fig. 260-5 and Chapter 408). However, other gram-negative endotoxin-producing bacteria have been associated with similar cutaneous lesions.

Cutaneous mycobacterial infections can occur in patients with chronic T-cell deficiency and impaired cell-mediated immunity following stem cell or solid organ transplantation or as a consequence of treatment with TNF antagonists. Nontuberculous mycobacteria (Chapter 300) typically cause tender, erythematous nodular lesions that may ulcerate. These lesions can arise either following direct inoculation (e.g., following trauma or cosmetic surgery) or, typically in immunocompromised patients, as a consequence of disseminated disease and hematogenous seeding (Chapter 300). Important species include rapidly growing nontuberculous mycobacteria (i.e., *Mycobacterium chelonae, Mycobacterium abscessus*, and *Mycobacterium fortuitum*), *Mycobacterium haemophilum* often with concurrent pulmonary disease, and *Mycobacterium marinum* following fresh or salt water exposures (Fig. 260-6). *M. tuberculosis* (Chapter 299) is a rare cause of skin disease but should be considered with suggestive epidemiology; it can arise due to contiguous spread, for example, from an infected lymph node (e.g., scrofuloderma) or with disseminated infection (e.g., lupus vulgaris).

Nocardia species are another important cause of skin and subcutaneous infections in immunocompromised and noncompromised hosts (Chapter 306). *Nocardia*, which are environmentally ubiquitous saprophytes found in the soil, can cause local infection following direct inoculation; however, cutaneous nocardiosis may also be the first sign of systemic disease in immunocompromised hosts. Identification of *Nocardia* skin or soft tissue infection in immunocompromised patients, particularly in those with no history of penetrating trauma, should prompt evaluation of disseminated infection, including imaging of the lungs and brain. Cutaneous nocardiosis can be variable in presentation, including subcutaneous nodules (often with a sporotrichoid-like lymphocutaneous distribution), ulcers, abscesses, pyoderma, and cellulitis.

In the neutropenic host, disseminated fungal infections may be initially recognized by characteristic cutaneous lesions. Disseminated candidiasis in such individuals can present with diffuse maculopapular, erythematous, and sometimes tender lesions. The appearance of cutaneous lesions typically changes in character with engraftment of neutrophils (Fig. 260-7). Disseminated infections caused by filamentous organisms such as *Aspergillus* species (Chapter 311) cause similar lesions, but usually fewer in number and more often with some component of central necrosis. Other filamentous fungi, namely those with which infection is characterized by a high fungal burden, such as *Fusarium* species, typically cause more skin lesions in multiple stages of evolution, ranging from papules to larger erythematous lesions with central necrosis. Multiple filamentous fungi such as *Aspergillus* species and Zygomycetes can also cause primary cutaneous lesions, especially with a breach in skin integrity. Infection with *Cryptococcus neoformans* (Chapter 309) can be accompanied

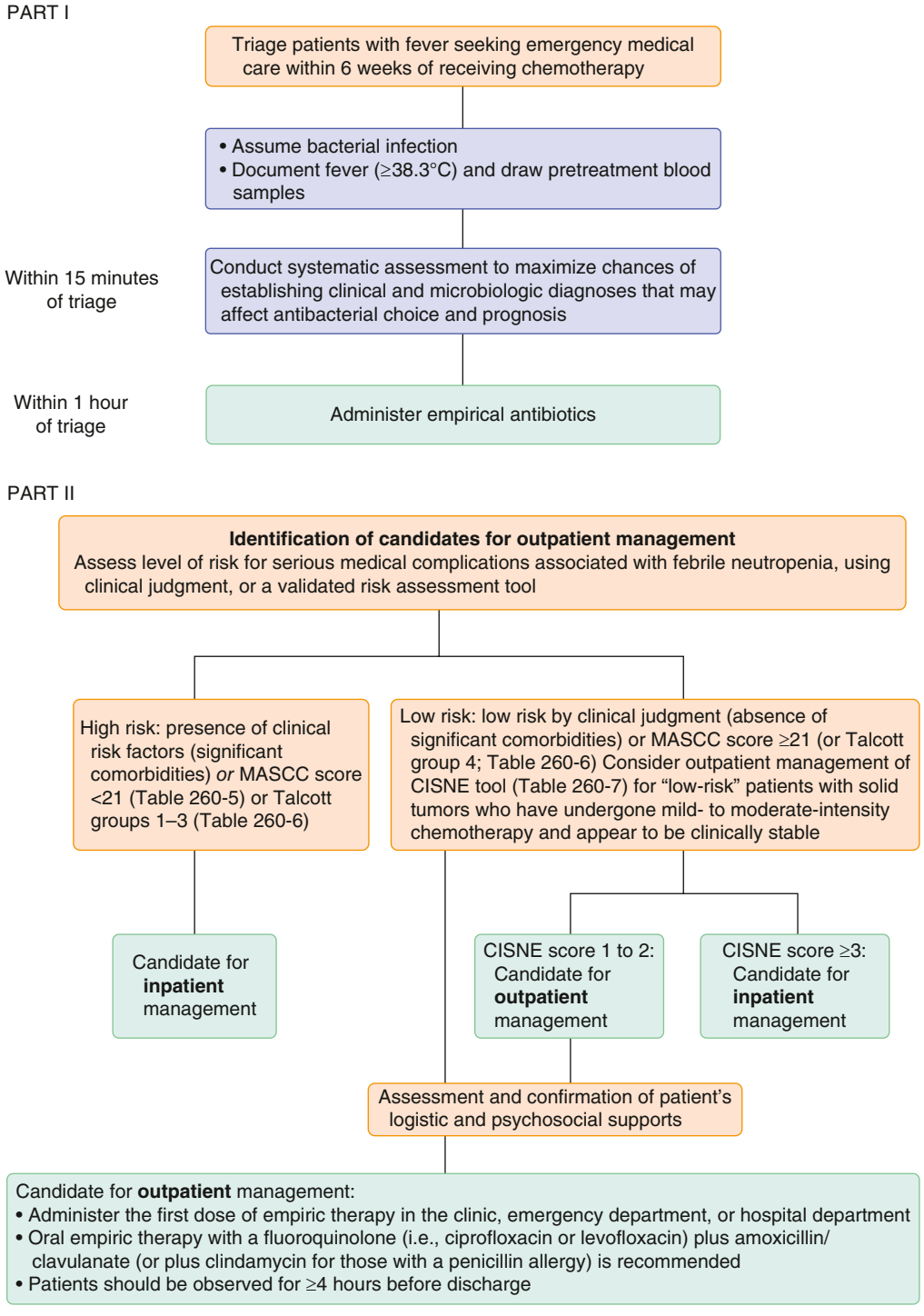

FIGURE 260-1. Summary of recommendations for outpatient management of fever and neutropenia in adults treated for malignancy. CISNE = Clinical Index of Stable Febrile Neutropenia; MASCC = Multinational Association for Supportive Care in Cancer. (Modified from Taplitz RA, Kennedy EB, Bow EJ, et al. Outpatient management of fever and neutropenia in adults treated for malignancy: American Society of Clinical Oncology and Infectious Diseases Society of America clinical practice guideline update. *J Clin Oncol*. 2018;36:1443-1453.)

TABLE 260-6 TALCOTT GROUP CLASSIFICATION

GROUP	CHARACTERISTIC
I	Inpatients (at the time of fever onset)
II	Outpatients with acute comorbidity requiring, by itself, hospitalization
III	Outpatients without comorbidity but with uncontrolled cancer
IV	Outpatients with cancer controlled and without comorbidity

Adapted from Taplitz RA, Kennedy EB, Bow EJ, et al. Outpatient management of fever and neutropenia in adults treated for malignancy: American Society of Clinical Oncology and Infectious Diseases Society of America clinical practice guideline update. *J Clin Oncol*. 2018:36:1443-1453.

TABLE 260-7 THE CLINICAL INDEX OF STABLE FEBRILE NEUTROPENIA (CISNE)

EXPLANATORY VARIABLE	NO. OF POINTS
Eastern Cooperative Oncology Group performance status ≥ 2	2
Chronic obstructive pulmonary disease	1
Chronic cardiovascular disease	1
National Cancer Institute Common Toxicity Criteria mucositis of grade ≥ 2	1
Monocytes < 200/μL	1
Stress-induced hyperglycemia	2

The six variables are integrated into a score ranging from 0 to 8, which classifies patients into three prognostic classes: low risk (0 points), intermediate risk (1 to 2 points), and high risk (≥3 points).
Adapted from Taplitz RA, Kennedy EB, Bow EJ, et al. Outpatient management of fever and neutropenia in adults treated for malignancy: American Society of Clinical Oncology and Infectious Diseases Society of America clinical practice guideline update. *J Clin Oncol*. 2018:36:1443-1453.

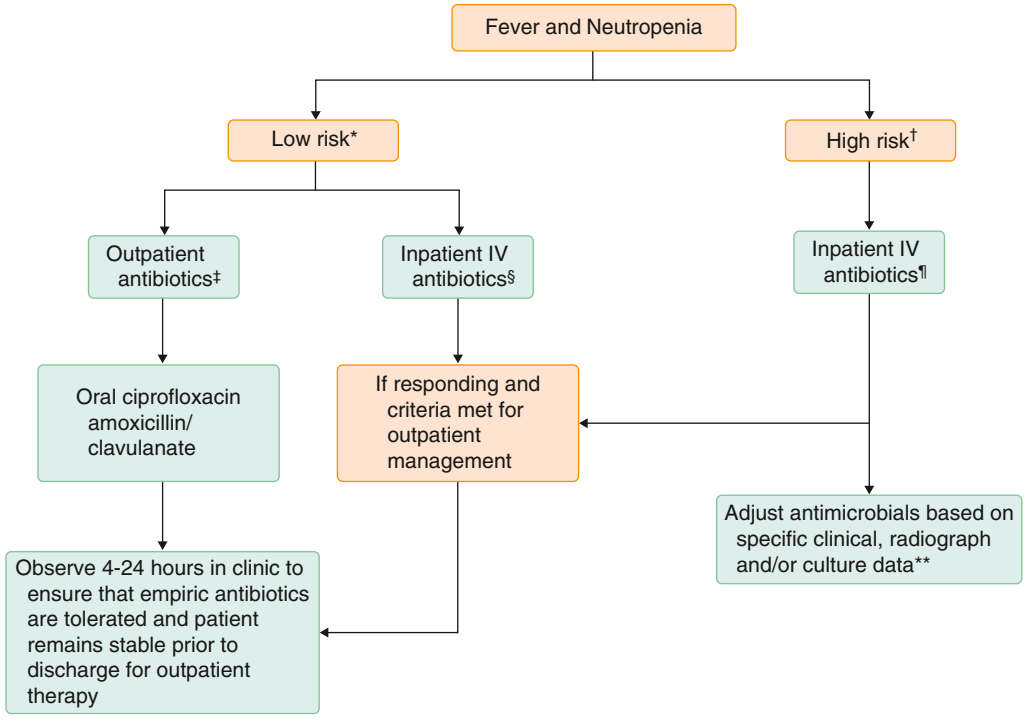

* Low Risk = anticipated neutropenia ≤7 days and clinically stable and no medical comorbidities.
† High Risk = anticipated neutropenia >7 days, *or* clinically unstable, *or* any medical comorbidities.
‡ If able to tolerate and absorb; caregiver, access, and transportation are available; patient and physician decide.
§ If there is documented infection requiring IV antibiotics; there is gastrointestinal intolerance; patient and physician decide.
¶ Empiric antibiotic monotherapy with any of the following: piperacillin/tazobactam, or carbapenem, or ceftazidime, or cefepime.
** For example: vancomycin and linezolid for cellulitis or pneumonia; add aminoglycoside and switch to carbapenem for pneumonia or gram-negative bacteremia; metronidazole for abdominal symptoms of suspected *C. difficile* infection.

FIGURE 260-2. Initial management of fever (≥38.3°C) and neutropenia (<500 cells/μL). Limited data to support recommendation. IV = intravenous. (Modified from Freifeld AG, Bow EJ, Sepkowitz KA, et al. Clinical practice guideline for the use of antimicrobial agents in neutropenic patients with cancer: 2010 update by the Infectious Diseases Society of America. *Clin Infect Dis*. 2011;52:e56-e93.)

by cutaneous involvement, with manifestations ranging from molluscum-like lesions to primary cutaneous cellulitis, which may be especially common in solid organ transplant recipients. Cutaneous lesions are an opportunity to establish diagnosis through aspiration, biopsy, and culture.

Morbilliform eruptions or maculopapular exanthems are frequent in neutropenic and transplant recipients. These rashes can be caused by drug reactions, GVHD, and numerous viral infections. Primary infection and reactivation with herpesviruses such as cytomegalovirus (Chapter 347) and Epstein-Barr virus (Chapter 348) can be accompanied by rashes. Human herpesvirus 6, the primary cause of roseola infantum in childhood, leads to latency and can cause disease in immunocompromised hosts both by reactivation and by primary infection. Disease can be accompanied by fever, rash, myelosuppression, and involvement of other organ systems (e.g., CNS). In immunocompromised patients, adenovirus (Chapter 333) can be both primarily acquired, usually through the respiratory tract, and reactivated; it causes fever, rash, and potentially disease involving multiple organ systems (lungs, gastrointestinal tract, kidneys, liver, CNS). In stem cell transplant recipients, the constellation of fever, rash, diarrhea, and hepatitis may be confused for severe GVHD. Parvovirus B19 infection (Chapter 342) can be severe in immunocompromised hosts and associated with fever, rash, and manifestations of hemophagocytosis, although there are other infectious causes of hemophagocytic syndromes as well (Chapter 155). The characteristic vesicular rash of varicella reactivation (Chapter 346) is relatively frequent in stem cell and solid organ transplant recipients with chronic T-cell deficiencies, especially in the absence of antiviral prophylaxis. Disseminated disease in immunocompromised patients is associated with high mortality rates unless prompt antiviral therapy (Chapter 328) is initiated. Antivirals administered as prophylaxis in high-risk recipients of stem cell and solid organ transplants can decrease both early morbidity and late mortality associated with herpes simplex virus, varicella-zoster virus, and cytomegalovirus disease, although drug-related toxicities must be considered in risk-benefit calculations.

Noninfectious Causes

Numerous noninfectious causes of rashes and lesions are common in immunocompromised individuals, particularly drug-induced hypersensitivity syndromes (Chapter 234) that can be both mild and severe and rarely progress to life-threatening toxic epidermal necrolysis (Fig. 403-7).

Sweet syndrome (Chapter 406), or acute febrile neutrophilic dermatosis, is characterized by skin lesions with neutrophilic infiltration in the dermis (see Fig. 406-29). It may appear during impending neutrophil recovery, treatment with granulocyte colony-stimulating factor, in association with numerous drugs, or as a paraneoplastic manifestation, particularly in hematologic malignancies (most commonly acute myelogenous leukemia). Biopsy with appropriate microbial stains and culture is essential to distinguish these lesions from infectious causes of ecthyma gangrenosum and other disseminated infections, such as those caused by mycobacteria, *Nocardia*, and fungi.

RESPIRATORY SYNDROMES

In febrile immunocompromised patients, respiratory complications can progress rapidly to respiratory failure (Chapter 90), so prompt diagnosis is critical (see Table 260-8).

Infectious Causes

Pneumonia should be suspected in a patient who has respiratory symptoms as manifested by cough, shortness of breath, chest pain, and hypoxia, even in the absence of radiographic abnormalities initially. Although opportunistic infections are always a consideration, pneumonia in immunocompromised patients is more often caused by community-acquired pathogens (Chapter 85) such as pneumococci (Chapter 268) and *Haemophilus influenzae* (Chapter 277) that can cause lobar or diffuse pneumonia.[11] Patients on ventilators are at risk for secondary gram-negative bacillary pneumonia or staphylococcal pneumonia.

Opportunistic fungi have been increasingly recognized as causes of lung infection in immunocompromised neutropenic patients and transplant recipients.

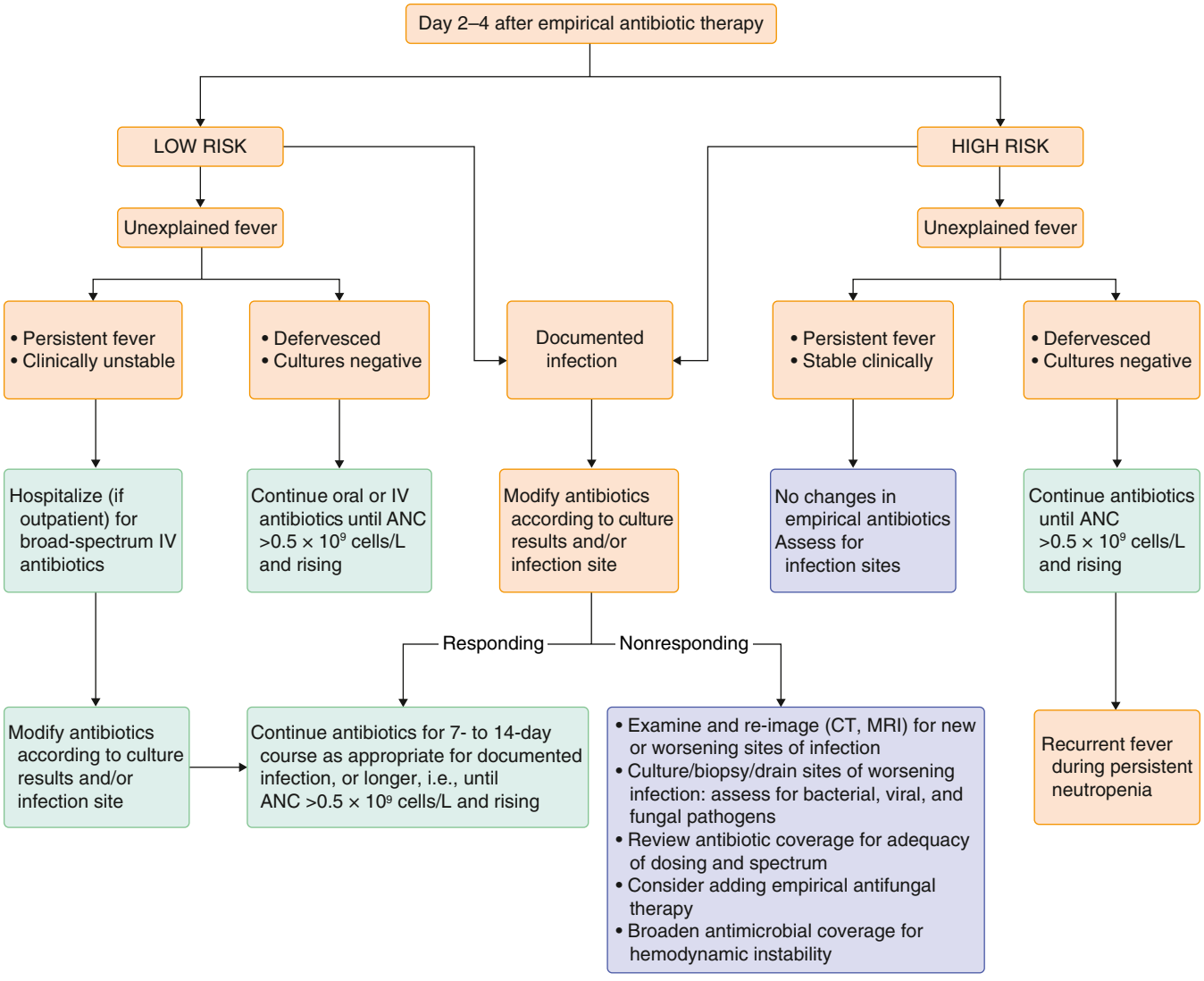

FIGURE 260-3. Reassessment after 2 to 4 days of empirical antibiotic therapy. ANC = absolute neutrophil count; CT = computed tomography; IV = intravenous; MRI = magnetic resonance imaging. (Modified from Freifeld AG, Bow EJ, Sepkowitz KA, et al. Clinical practice guideline for the use of antimicrobial agents in neutropenic patients with cancer: 2010 update by the Infectious Diseases Society of America. *Clin Infect Dis*. 2011;52:e56-e93.)

Endemic mycoses (Chapter 308) such as blastomycosis, coccidioidomycosis, and histoplasmosis may be manifested as acute pneumonia after recent exposure in immunocompromised patients, making a travel history mandatory. Although *Candida* species (Chapter 310) commonly colonize indwelling vascular and urinary catheters, candidal pneumonia is unusual in the absence of systemic candidiasis. Although classically associated with an "interstitial pattern" of lung infiltration, *Pneumocystis* species (Chapter 313) pneumonia can be manifested as local consolidation or pulmonary nodules, exhibiting granulomatous inflammation on pathologic examination. Filamentous fungi, including *Aspergillus* (Chapter 311), Zygomycetes, *Fusarium* species, and *Scedosporium* species, are challenging to treat. From an initial focus, *Aspergillus* infection can spread through the pulmonary vasculature, which sets the stage for localized hemorrhage, creating a halo sign on CT scan, and infarction and necrosis.[12] Pulmonary infection can progress to cavitary lesions. Invasive pulmonary aspergillosis is usually caused by *Aspergillus fumigatus*. These organisms can also cause primary airway disease, with features typical of tracheobronchitis, with or without findings on CT scan, this infection is particularly well described in lung transplant recipients, who may also have involvement of the bronchial anastomosis.

Patients who are treated with biologic immune response modifiers (Chapter 29) (especially TNF antagonists in the setting of autoimmune or other inflammatory diseases such as rheumatoid arthritis, psoriasis, and inflammatory bowel diseases) are at high risk for severe pulmonary infection caused by reactivation of *M. tuberculosis* (Chapter 299). The same patients are also at increased risk for invasive fungal infections, including reactivation of endemic infections (Chapter 308) such as histoplasmosis, thereby warranting enhanced screening and a high level of suspicion for disease.

A particularly common concern is reactivation pneumonitis caused by members of the herpesvirus family, especially cytomegalovirus (Chapter 347), which occurs most frequently in the setting of chronic T-cell depression associated with transplantation. Common respiratory viruses such as influenza virus (Chapter 332) and respiratory syncytial virus (Chapter 330) infect immunocompromised hosts with the same frequency as the general population but are more likely to cause lower respiratory tract disease with the potential for progression to respiratory failure and death. Hosts with suppressed cellular immunity due to organ transplantation or anticancer treatment also experience increased adverse outcomes from coronavirus 2019 disease (COVID-19; Chapter 336), although the relative contribution of immunosuppression versus underlying comorbidities remains to be determined.[13] Patients who have defects in cellular immunity typically exhibit higher viral loads and prolonged shedding, thereby causing concern for the emergence of antiviral resistance and infection control.

Noninfectious Causes

Noninfectious causes of pulmonary infiltrates in immunosuppressed hosts include early complications of chemotherapy administration (e.g., diffuse alveolar damage and hemorrhage) and late complications of GVHD and organ rejection (e.g., bronchiolitis obliterans syndromes). Certain drugs that are frequently administered in these populations of patients, like sirolimus, can cause direct lung toxicity.

GASTROINTESTINAL SYNDROMES

In febrile immunocompromised patients, diarrhea can be disabling and life-threatening. Prompt evaluation is key to determine the cause (see Table 260-8).

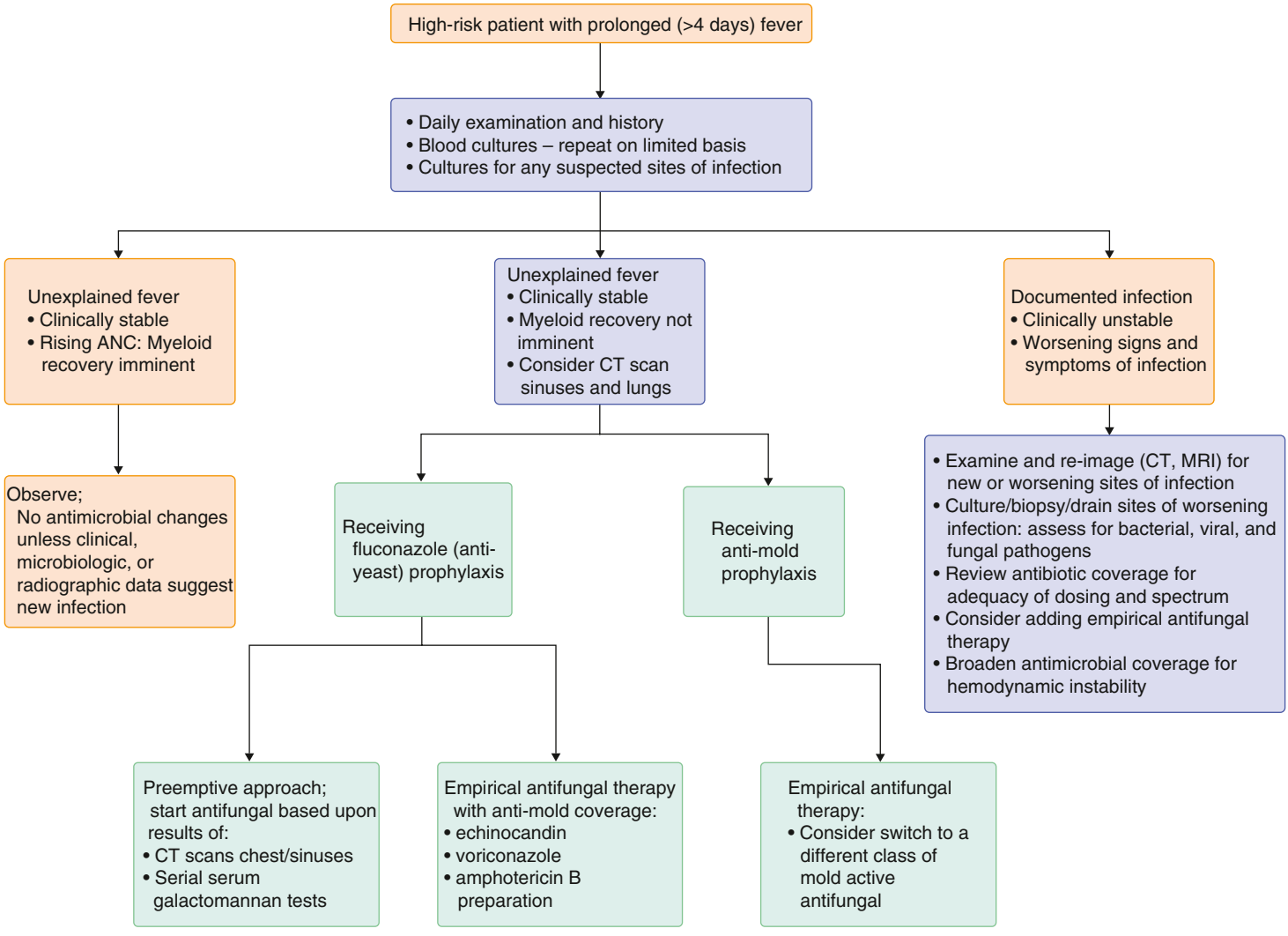

FIGURE 260-4. High-risk patient with fever after 4 days of empirical antibiotics. ANC = absolute neutrophil count; CT = computed tomography; MRI = magnetic resonance imaging. (Modified from Freifeld AG, Bow EJ, Sepkowitz KA, et al. Clinical practice guideline for the use of antimicrobial agents in neutropenic patients with cancer: 2010 update by the Infectious Diseases Society of America. *Clin Infect Dis*. 2011;52:e56-e93.)

Diarrhea in an immunocompromised host can be caused by a wide variety of infectious and noninfectious etiologies (Chapter 126),[14] including conventional enteric pathogens such as *Salmonella* (Chapter 284), *Shigella* (Chapter 285), and *Campylobacter* (Chapter 279). Currently and recently hospitalized patients who have received courses of antibiotic treatment are commonly infected with *Clostridioides difficile* (Chapter 271). *C. difficile* colitis can be both severe and persistent in immunosuppressed hosts. More recently, norovirus (Chapter 350) has emerged as an important cause of chronic gastroenteritis in immunocompromised patients, in whom diagnoses have been commonly elusive and misapplied to noninfectious syndromes (e.g., GVHD), and outcomes can be poor. Several intestinal protozoa are associated with diarrhea in compromised patients. Three acid-fast–staining protozoa (*Cryptosporidium* species, *Cystoisospora belli*, and *Cyclospora cayetanensis*) are associated with predisposing impairments in cell-mediated immunity (see Chapters 321 and 324). *Giardia lamblia* (Chapter 322) is classically associated with hypogammaglobulinemia. The Microsporidia (Chapter 324) are a family of eukaryotic obligate intracellular parasites once thought to be protozoa but more recently placed taxonomically closer to fungi. In addition to causing diarrhea in immune-suppressed patients, they are distinguished by the ability to cause extraintestinal disease in virtually any other organ.

Because acute and chronic diarrhea in immunocompromised patients can be caused by a wide array of bacterial, viral, and protozoal pathogens with broadly overlapping clinical presentations, multiplex molecular diagnostic panels are key important diagnostic tools.[15] Caution should be exercised in interpretation, however, because a positive result may reflect active infection or asymptomatic colonization. The small intestine is the primary site where calcineurin inhibitors (e.g., cyclosporine, tacrolimus) are absorbed and metabolized; toxic blood concentrations of calcineurin inhibitors may be a sign of enteritis, for example, due to rotavirus (Chapter 350) or *Cryptosporidium* (Chapter 321), perhaps as a consequence of altered drug metabolism.

Cytomegalovirus (Chapter 347) is a major cause of gastrointestinal disease in transplant recipients and increasingly recognized in patients with impaired cell-mediated immunity not due to transplantation or AIDS. Cytomegalovirus can involve the entire digestive tract from esophagus to anus, and patients typically present with signs and symptoms of disseminated disease, including fever, malaise, and bone marrow suppression (i.e., a mononucleosis-like syndrome). Symptoms of cytomegalovirus gastritis, enteritis, and colitis include anorexia, nausea, abdominal discomfort, and diarrhea. Cytomegalovirus infection also causes mild elevations in hepatic enzymes and, rarely, fulminant hepatitis or pancreatitis, typically in the context of primary infection after liver transplantation or pancreas transplantation, respectively. Quantitative cytomegalovirus nucleic acid amplification assays can establish a diagnosis of cytomegalovirus gastrointestinal disease, but testing of plasma or whole blood can occasionally be negative because tissue-invasive disease is isolated to the alimentary tract. In these cases, endoscopy is required to establish a diagnosis. Indeed, because colitis and diarrhea in immunocompromised patients can be caused by such a wide range of problems, including multiple infections, focal Epstein-Barr virus–associated post-transplantation lymphoproliferative disorder (Chapter 348), GVHD (Chapter 163), and drug-induced toxicity, uncertainty in diagnosis or failure of response to appropriate treatment requires further evaluation with endoscopy.

Individuals who have received long courses of chemotherapy, radiation, and antibiotics commonly experience *Candida* (Chapter 310) mucosal overgrowth in the mouth and esophagus. Herpes simplex virus (Chapter 345) and cytomegalovirus (Chapter 347) can cause symptoms identical to those of *Candida* esophagitis (Chapter 124). In severely neutropenic patients, anaerobic

TABLE 260-8 COMMON INFECTIOUS AND NONINFECTIOUS SYNDROMES IN IMMUNOCOMPROMISED HOSTS

PRIMARY ORGAN SYSTEM	BACTERIA	FUNGI	VIRUSES	PARASITES AND PROTISTS	NONINFECTIOUS
Cutaneous	Disseminated gram-positive and gram-negative bacteria, e.g., *Staphylococcus aureus* *Pseudomonas aeruginosa* *Mycobacterium* spp *Nocardia* spp	*Candida* spp. Filamentous fungi, e.g., *Aspergillus* spp Zygomycetes *Fusarium* spp *Scedosporium* spp *Cryptococcus* spp	Herpes simplex Varicella-zoster CMV HHV-6 Adenovirus Parvovirus B19	*Leishmania* spp Acanthamoeba *Naegleria fowleri* *Balamuthia mandrillaris*	Drug eruptions GVHD Sweet syndrome
Sinopulmonary	Gram-positive and gram-negative causes of sinusitis and pneumonia *S. aureus* *Streptococcus pneumoniae* *P. aeruginosa* *Haemophilus influenzae* Anaerobes *Legionella* *Nocardia* spp *Mycobacterium* spp	Filamentous fungi, e.g., *Aspergillus* spp Zygomycetes *Fusarium* spp *Scedosporium* spp *Cryptococcus* spp Endemic fungi, e.g., *Histoplasma capsulatum* *Coccidioides immitis* *Blastomyces dermatitidis* *Pneumocystis jiroveci*	Respiratory viruses, e.g., RSV Parainfluenza Influenza Adenovirus SARS-CoV-2 Reactivation herpes viruses, e.g., CMV, VZV	*Toxoplasma gondii* *Strongyloides stercoralis* hyperinfection syndrome	Drug-related pulmonary toxicities Pneumonitis (sirolimus) Diffuse alveolar damage Bronchiolitis obliterans syndromes
Gastrointestinal	Neutropenic enterocolitis ("typhlitis") Mixed gram-positive, gram-negative, anaerobes (*Bacteroides fragilis*, *Clostridium septicum*) *Clostridioides difficile* colitis Enteric diarrheal pathogens *Salmonella* spp *Shigella* spp *Escherichia coli* *Campylobacter* spp	*Candida* spp. Microsporidia	CMV EBV-PTLD Adenovirus Coxsackievirus Rotavirus Norovirus	*Cryptosporidium* *Giardia lamblia* *Cystoisospora belli* *Cyclospora cayetanensis* *Strongyloides stercoralis*	Drug-related toxicities, e.g., MMF
Neurologic	Gram-positive and gram-negative bacteria *Listeria monocytogenes* Pneumococcus Meningococcus *Nocardia* spp *Mycobacterium tuberculosis* Syphilis	Filamentous fungi *Cryptococcus* spp	Herpes viruses HSV HHV-6 VZV JC virus West Nile virus Miscellaneous viral encephalitides	*Toxoplasma gondii* Acanthamoeba *Naegleria fowleri* *Balamuthia mandrillaris*	Drug-related toxicities, e.g., calcineurin inhibitor toxicity PRES carbapenem-related seizures voriconazole CNS toxicity Cefepime-induced encephalopathy

CMV = cytomegalovirus; EBV-PTLD = Epstein-Barr virus–post-transplantation lymphoproliferative disorder; GVHD = graft-versus-host disease; HHV-6 = human herpes virus 6; HSV = herpes simplex virus; MMF = mycophenolate mofetil; PRES = posterior reversible encephalopathy syndrome; RSV = respiratory syncytial virus; SARS-CoV-2 = severe acute respiratory syndrome coronavirus 2; VZV = varicella-zoster virus

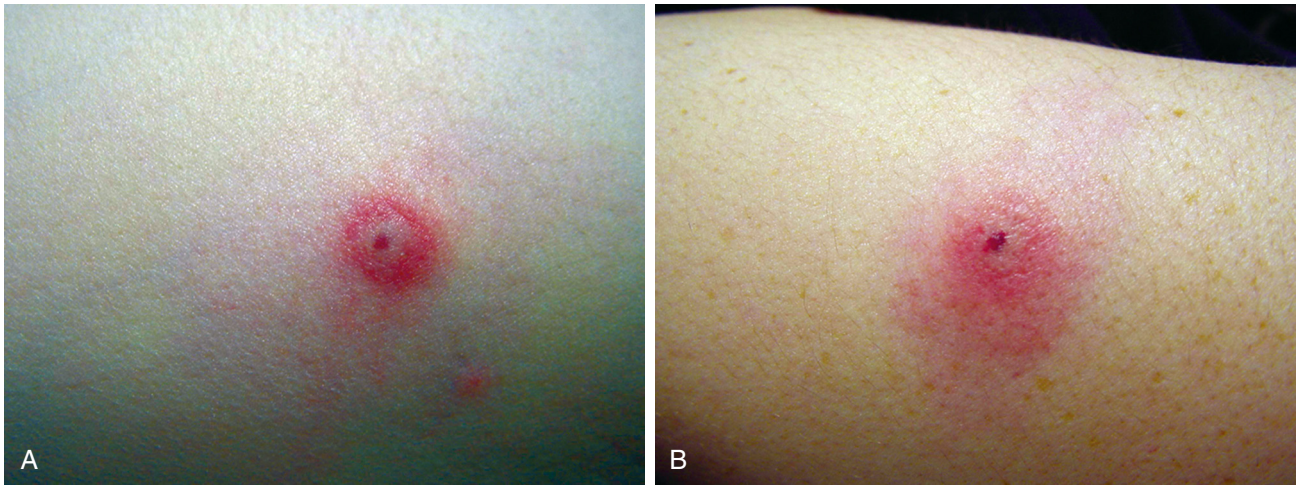

FIGURE 260-5. Ecthyma gangrenosum. A 28-year-old woman with fever and neutropenia while receiving chemotherapy for acute leukemia developed several tender edematous papules on her thighs. **A,** Central crust and surrounding erythema are shown. **B,** The papules became necrotic during 1 to 2 days, with the formation of black, well-demarcated eschar. Cultures from blood and the necrotic eschar grew *Pseudomonas aeruginosa*. (© DermAtlas; http://www.DermAtlas.org.)

streptococci and gram-negative pathogens such as *P. aeruginosa* (Chapter 282) can cause severe mucositis and pharyngitis. In cancer patients, these organisms take advantage of the cytotoxic effects of chemotherapy, which promotes sloughing of mucosal surfaces and subsequently predisposes to infection.

Neutropenic patients may also develop enterocolitis that can be of mixed anaerobic and aerobic bacterial origin. Neutropenic enterocolitis,[16] also known as typhlitis or ileocecal syndrome, results from chemotherapeutic damage to the intestinal mucosa in the setting of neutropenia. Presentation usually includes fever, abdominal pain, nausea, vomiting, and diarrhea. Because neutropenic enterocolitis can rapidly progress to intestinal perforation, sepsis, and multisystem organ failure, prompt diagnosis and aggressive medical or surgical intervention are required.

FIGURE 260-6. ***Mycobacterium marinum*. A 20-year-old man with Crohn disease receiving infliximab developed progressively worsening nonhealing foot ulcers following trauma and exposure to brackish water 2 years earlier. Biopsy cultures of the ulcer grew *Mycobacterium marinum*. A, Two necrotic ulcers with central eschars, surrounding erythema, and pedal edema at the time of diagnosis. B, After 1 month of treatment, granulation tissue is evident in the base of the ulcer, and erythema and edema are reduced. C, After 10 months of treatment, the ulcers have closed with residual scars and hyperpigmentation.**

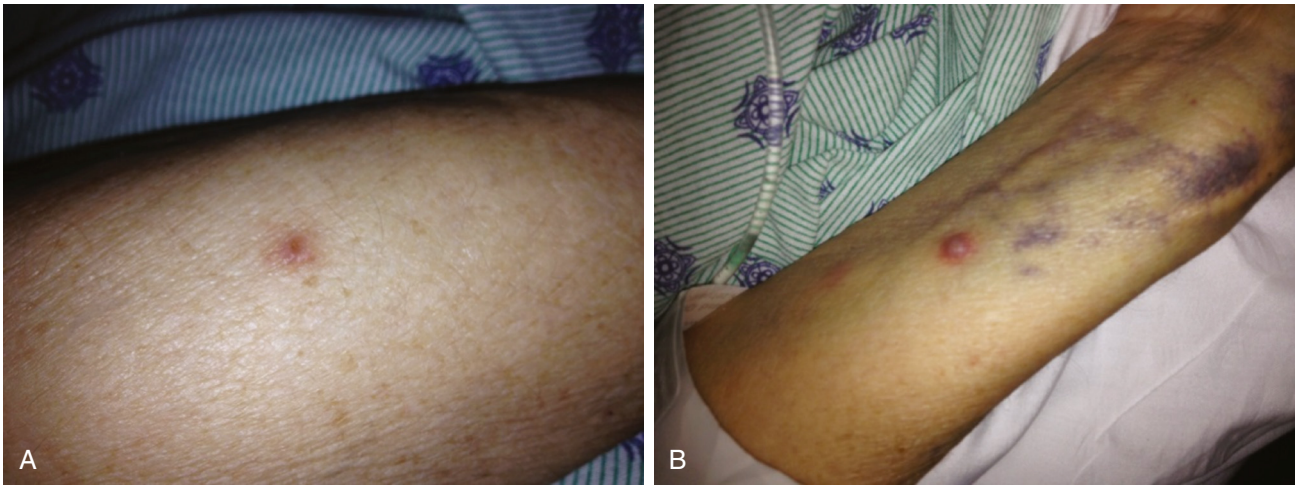

FIGURE 260-7. Disseminated candidiasis. A 60-year-old woman with fever during neutropenia that developed after receipt of therapy for acute leukemia developed tender papular lesions on her extremities, trunk, and back. A, Blood cultures returned positive for *Candida tropicalis*. B, After resolution of neutropenia, lesions developed a more pustular appearance.

NEUROLOGIC SYNDROMES

In febrile immunocompromised patients, neurologic signs or symptoms are often life-threatening, so rapid diagnosis is mandatory (see Table 260-8).

Infectious Causes

Brain abscess (Chapter 382) or meningitis (Chapter 381) can be caused in immunocompromised patients by gram-positive or gram-negative bacteria as well as by anaerobes. *Listeria monocytogenes* (Chapter 272) is a particularly common cause of meningitis in these patients. Encapsulated bacteria such as pneumococci and staphylococci can cause metastatic CNS disease and meningitis. In patients with impaired cell-mediated immunity, *C. neoformans* (Chapter 309) is a leading cause of CNS infection, usually presenting as cryptococcal meningitis or meningoencephalitis and sometimes as parenchymal mass lesions of the brain. *Aspergillus* species (Chapter 311) can infect the CNS both by direct sinus invasion and by hematogenous spread. Patients with impaired cellular immunity can develop CNS infection with *Toxoplasma gondii* (Chapter 320), *M. tuberculosis* (Chapter 299), *H. capsulatum* (Chapter 308), or *Nocardia* species (Chapter 306), either through severe infection by latent organisms or by reactivation. CNS syphilis (Chapter 295) should also be considered in patients with severe immunologic impairment.

Among the many viral etiologies of meningoencephalitis (Chapter 383) in immunocompromised individuals are enteroviruses (Chapter 349), measles, herpes simplex virus (Chapter 345), cytomegalovirus (Chapter 347), varicella zoster virus (Chapter 346), and human herpesvirus 6. Progressive multifocal leukoencephalopathy caused by JC polyomavirus (Chapter 341) may occur in those with chronic CD4 lymphocytopenia and in recipients of hematopoietic stem cell or solid organ transplants as well as individuals treated with natalizumab, rituximab, and possibly other immunomodulatory monoclonal antibodies. Transplant recipients are also at increased risk for meningoencephalitis caused by West Nile virus (Chapter 352). Patients with CNS symptoms presenting early after transplantation might be suspected of having severe infections acquired from the donor, including West Nile virus, rabies (Chapter 383), HIV, lymphocytic choriomeningitis virus (Chapter 381), Zika virus (Chapter 352), or other viruses known to be transmitted through organ donation.

Noninfectious Causes

In addition to opportunistic infection, noninfectious causes of neurologic symptoms must be considered in immunocompromised patients, including drug toxicity, immunologic disorders, paraneoplastic syndromes, and Guillain-Barré syndrome. Posterior reversible encephalopathy syndrome should be in the differential diagnosis of neurologic complications in transplant recipients, patients with autoimmune diseases, and patients who are receiving high doses of cancer chemotherapy, particularly when the clinical presentation includes the sudden onset of severe "thunderclap" headache, seizures, confusion, and visual disturbance. This syndrome can be caused by endothelial injury, vasospasm, or edema associated with certain drugs such as calcineurin inhibitors (e.g., cyclosporine, tacrolimus). The diagnosis can be confirmed by characteristic CT or magnetic resonance imaging patterns of predominantly posterior cerebral edema and angiographic evidence of reversible vasoconstriction.

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261 PREVENTION AND CONTROL OF HEALTH CARE–ASSOCIATED INFECTIONS

DAVID P. CALFEE

THE BURDEN OF HEALTH CARE–ASSOCIATED INFECTIONS

EPIDEMIOLOGY

The Centers for Disease Control and Prevention (CDC) defines health care–associated infections as infections that patients acquire during the course of receiving health care treatment for other conditions. *Nosocomial infection* is a term that refers specifically to a health care–associated infection that develops in association with hospital care. The development of infection during the course of health care is not, however, limited to the acute care hospital setting. Thus, *health care–associated infection*, which is the preferred term, refers to the broader spectrum of infections that develop during the course of health care, wherever that care may be provided, including acute care hospitals, long-term care facilities, rehabilitation facilities, dialysis facilities, infusion centers, outpatient practices, and even the patient's home during the receipt of home care services.

The most extensive data regarding the incidence of and outcomes associated with health care–associated infections come from acute care hospital settings. Each year, an estimated 700,000 or so health care-associated infections occur in U.S. hospitals (Table 261-1), a huge number but a significant reduction from 4% to 3.2% of admitted patients since 2011.[1] Approximately 1 of every 30 patients admitted to U.S. hospitals develops a health care–associated infection, thereby making health care–associated infection one of the most common complications associated with the receipt of health care. Moreover, these data indicate that health care–associated infections are one of the top 10 causes of death in the United States. Whereas many of these health care–associated infection-associated deaths occur among patients who are already severely ill and who have a high likelihood of death due to their underlying disease, a substantial proportion of health care–associated infection-related deaths occur among persons who were otherwise expected to survive their hospitalization. In one study, about 30% of unexpected in-hospital deaths were determined to be possibly or probably related to health care–associated infections. In addition to an increased risk of death, patients who develop health care–associated infections suffer a number of other adverse outcomes, including prolonged hospital stays, additional medical interventions and antibiotic treatment, discomfort, and loss of function and income. These statistics are particularly concerning when they are considered with the knowledge that many of these infections are preventable. In fact, a systematic review found that 55 to 70% of four of the most common types of health care–associated infections are preventable through the use of currently available, evidence-based preventive strategies (see Table 261-1).

Although the majority of health care–associated infection statistics come from acute care hospitals, data demonstrate that health care–associated infections are significant problems in other health care settings as well. Point prevalence surveys conducted in European and the U.S. Veterans Affairs system long-term care facilities found that the prevalence of health care–associated infection among long-term care facility residents ranged from 2.4 to 5.2%. The overall burden of health care–associated infection among long-term care facility residents has been estimated to be 1.64 to 3.83 million infections per year in the United States and at least 2.6 million infections per year in Europe. Vascular access–related infections are the most common health care–associated infections among patients requiring chronic hemodialysis for end-stage renal disease, with a reported incidence ranging from 0.16 per 100 patient-months for patients with arteriovenous fistulas to 1.83 episodes per 100 patient months for patients with central venous catheters, and they are associated with increased morbidity, hospitalization, and death. The magnitude of health care–associated infections related to care provided in other settings, such as ambulatory surgery and endoscopy centers, has not been as thoroughly studied, but such infections have been well described.

PATHOBIOLOGY

Health care–associated infections can be caused by organisms that are a part of the patient's normal microbiota (i.e., endogenous infection) or by pathogens

TABLE 261-1 ESTIMATES OF THE BURDEN, COSTS, AND PREVENTABILITY OF COMMON HEALTH CARE–ASSOCIATED INFECTIONS IN U.S. HOSPITALS

TYPE OF INFECTION	ESTIMATED NUMBER OF INFECTIONS PER YEAR[†]	AVERAGE ATTRIBUTABLE COST[*] PER INFECTION[‡]	CASE-FATALITY RATE[§]	PROPORTION PREVENTABLE[‖]
Urinary tract infection	62,700	$749-$1007	2.3%	65-70%
Catheter-associated urinary tract infection	39,188			
Surgical site infection	110,800	$11,087-$34,670	2.8%	55%
Pneumonia	176,700	$14,806-$28,508	14.4%	55%
Ventilator-associated pneumonia	63,532			
Blood stream infection	83,600	$6461-$29,156	12.3%	65-70%
Central line–associated blood stream infection	61,170			
C. difficile infection	106,759	$5682-$9124	2.9%	

[*] In 2007 U.S. dollars.
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261 PREVENTION AND CONTROL OF HEALTH CARE–ASSOCIATED INFECTIONS

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THE BURDEN OF HEALTH CARE–ASSOCIATED INFECTIONS

EPIDEMIOLOGY

The Centers for Disease Control and Prevention (CDC) defines health care–associated infections as infections that patients acquire during the course of receiving health care treatment for other conditions. *Nosocomial infection* is a term that refers specifically to a health care–associated infection that develops in association with hospital care. The development of infection during the course of health care is not, however, limited to the acute care hospital setting. Thus, *health care–associated infection*, which is the preferred term, refers to the broader spectrum of infections that develop during the course of health care, wherever that care may be provided, including acute care hospitals, long-term care facilities, rehabilitation facilities, dialysis facilities, infusion centers, outpatient practices, and even the patient's home during the receipt of home care services.

The most extensive data regarding the incidence of and outcomes associated with health care–associated infections come from acute care hospital settings. Each year, an estimated 700,000 or so health care-associated infections occur in U.S. hospitals (Table 261-1), a huge number but a significant reduction from 4% to 3.2% of admitted patients since 2011.[1] Approximately 1 of every 30 patients admitted to U.S. hospitals develops a health care–associated infection, thereby making health care–associated infection one of the most common complications associated with the receipt of health care. Moreover, these data indicate that health care–associated infections are one of the top 10 causes of death in the United States. Whereas many of these health care–associated infection-associated deaths occur among patients who are already severely ill and who have a high likelihood of death due to their underlying disease, a substantial proportion of health care–associated infection-related deaths occur among persons who were otherwise expected to survive their hospitalization. In one study, about 30% of unexpected in-hospital deaths were determined to be possibly or probably related to health care–associated infections. In addition to an increased risk of death, patients who develop health care–associated infections suffer a number of other adverse outcomes, including prolonged hospital stays, additional medical interventions and antibiotic treatment, discomfort, and loss of function and income. These statistics are particularly concerning when they are considered with the knowledge that many of these infections are preventable. In fact, a systematic review found that 55 to 70% of four of the most common types of health care–associated infections are preventable through the use of currently available, evidence-based preventive strategies (see Table 261-1).

Although the majority of health care–associated infection statistics come from acute care hospitals, data demonstrate that health care–associated infections are significant problems in other health care settings as well. Point prevalence surveys conducted in European and the U.S. Veterans Affairs system long-term care facilities found that the prevalence of health care–associated infection among long-term care facility residents ranged from 2.4 to 5.2%. The overall burden of health care–associated infection among long-term care facility residents has been estimated to be 1.64 to 3.83 million infections per year in the United States and at least 2.6 million infections per year in Europe. Vascular access–related infections are the most common health care–associated infections among patients requiring chronic hemodialysis for end-stage renal disease, with a reported incidence ranging from 0.16 per 100 patient-months for patients with arteriovenous fistulas to 1.83 episodes per 100 patient months for patients with central venous catheters, and they are associated with increased morbidity, hospitalization, and death. The magnitude of health care–associated infections related to care provided in other settings, such as ambulatory surgery and endoscopy centers, has not been as thoroughly studied, but such infections have been well described.

PATHOBIOLOGY

Health care–associated infections can be caused by organisms that are a part of the patient's normal microbiota (i.e., endogenous infection) or by pathogens

TABLE 261-1 ESTIMATES OF THE BURDEN, COSTS, AND PREVENTABILITY OF COMMON HEALTH CARE–ASSOCIATED INFECTIONS IN U.S. HOSPITALS

TYPE OF INFECTION	ESTIMATED NUMBER OF INFECTIONS PER YEAR[†]	AVERAGE ATTRIBUTABLE COST[*] PER INFECTION[‡]	CASE-FATALITY RATE[§]	PROPORTION PREVENTABLE[‖]
Urinary tract infection	62,700	$749-$1007	2.3%	65-70%
Catheter-associated urinary tract infection	39,188			
Surgical site infection	110,800	$11,087-$34,670	2.8%	55%
Pneumonia	176,700	$14,806-$28,508	14.4%	55%
Ventilator-associated pneumonia	63,532			
Blood stream infection	83,600	$6461-$29,156	12.3%	65-70%
Central line–associated blood stream infection	61,170			
C. difficile infection	106,759	$5682-$9124	2.9%	

[*] In 2007 U.S. dollars.
[†] Magill SS, O'Leary E, Janelle SJ, et al. Changes in prevalence of health care-associated infections in U.S. hospitals. *N Engl J Med*. 2018;379:1732-1744.
[‡] Scott RD. The direct medical costs of healthcare-associated infections in U.S. hospitals and the benefits of prevention. Centers for Disease Control and Prevention; 2009. Available at: http://www.cdc.gov/hai/pdfs/hai/scott_costpaper.pdf. Accessed July 25, 2021.
[§] Klevens RM, Edwards JR, Richards CL, Jr., et al. Estimating health care-associated infections and deaths in U.S. hospitals, 2002. *Public Health Rep*. 2007;122:160-166.
[‖] Umscheid CA, Mitchell MD, Doshi JA, et al. Estimating the proportion of healthcare-associated infections that are reasonably preventable and the related mortality and costs. *Infect Control Hosp Epidemiol*. 2011;32:101-114.

ABSTRACT

Health care–associated infections are a substantial cause of morbidity and mortality among persons receiving health care. These infections may be caused by organisms that are part of a patient's normal microbiota ("endogenous" organisms) or by organisms acquired during the course of health care ("exogenous" organisms). Antimicrobial resistance among many of the common bacterial causes of health care–associated infections (e.g., *Klebsiella pneumoniae*, *Pseudomonas aeruginosa*, and *Acinetobacter* species) has become a major treatment challenge and has been associated with higher rates of death and other adverse outcomes. Factors that increase the risk of health care–associated infection include disruption of normal host defenses as a result of invasive medical devices, surgical procedures, and immunosuppressive medications; alteration of the patient's normal microbiota, as can occur with receipt of antibiotics; and exposure to exogenous pathogens during the receipt of health care. Many underlying medical conditions can also predispose patients to the development of health care–associated infections. Although the epidemiology of health care–associated infections is complex, many of these infections are the result of a failure to implement basic infection prevention practices. Thus, a large proportion of health care–associated infections could be prevented by improving adherence to currently recommended, evidence-based, infection prevention strategies. These prevention strategies include, but are not limited to, hand hygiene, use of aseptic or sterile technique during invasive procedures, safe injection practices, proper cleaning and disinfection of medical equipment and high-touch surfaces within health care facilities, prompt removal of medical devices that are no longer medically indicated, and judicious use of antibiotics.

KEYWORDS

nosocomial
health care–associated infection
antimicrobial resistance
infection control
Clostridioides difficile
prevention
device-related infection

acquired during exposure to health care (i.e., exogenous infection) through the contaminated hands of health care providers, the environment, contaminated medical equipment, other patients, or visitors. A variety of factors can contribute to the development of health care–associated infections, and in many cases, these infections are multifactorial in nature. These factors can be related to the pathogen, the host, the specific health care interventions that a patient receives, the setting in which health care is received, and the methods by which these interventions are implemented. Health care–associated infection prevention strategies focus on eliminating, reducing, or modifying one or more of these risk factors.

Pathogen-Related Factors

The pathogen-related factors that contribute to the ability of an organism to cause infection include the organism's normal reservoir, mode of transmission (e.g., direct or indirect contact transmission, respiratory droplets, airborne particles), ability to survive on inanimate objects and surfaces, ability to produce biofilm, virulence factors, and resistance to antimicrobial agents or disinfectants.

Host-Related Factors

The host-specific factors that are associated with an inherent increased risk of one or more types of infection, regardless of the receipt of health care, include age (with older adults having an increased risk of infection because of senescence of the immune system), obesity, smoking, severity of illness, and certain comorbid conditions (e.g., burns [Chapter 97], end-stage liver [Chapter 140] or renal disease [Chapter 117], poorly controlled diabetes [Chapter 210], some cancers, congenital or acquired immune deficiency [Chapter 231]). These factors reflect suppression of the immune system or breaches of other normal host defense mechanisms. Whereas many of these factors are not amenable to intervention or cannot be effectively modified in the short term, interventions that address remediable risk factors (e.g., obesity, smoking, poorly controlled diabetes mellitus) have the potential to reduce the risk of health care–associated infection during future episodes of health care.

Health Care–Related Factors

Health care–related infection risk factors result from interventions that are intended to treat or otherwise provide benefit for a patient's existing medical conditions but that also introduce an increased risk of infection. These factors may disrupt normal host defenses or alter the patient's normal microbiota (Chapter 257). Health care–related risk factors include the use of invasive devices (e.g., intravascular catheters, urinary catheters, endotracheal tubes), surgical procedures, exposure to antibiotics, receipt of immunosuppressive medications, and prolonged hospitalization. Because each of these interventions poses at least some degree of increased risk of infection, the risk-to-benefit ratio of each intervention must frequently be reassessed so that patients are not exposed to unnecessary risk. For example, central venous catheters and indwelling urinary catheters are major risk factors for primary blood stream infection and urinary tract infection, respectively. In a patient who has a true medical need for one of these devices, the benefits of the catheter exceed the risk of infection. However, once the patient recovers from the condition that necessitated use of the catheter, the risks associated with the device then outweigh the benefits.

Exposure to antibiotics is a well-established risk factor for colonization and infection with multidrug-resistant organisms and development of *Clostridioides difficile* (Chapter 271) infection through a mechanism known as antibiotic selection pressure. Antimicrobial use is common in acute care hospitals and other health care settings, such as long-term care and dialysis facilities and ambulatory care practices. About one third of hospitalized European patients receive one or more antimicrobials during their hospital stay, as do about 50% of hospitalized patients in the United States.[2] The rate is even higher, over 70%, in surgical critical care units. Unfortunately, studies have shown that 25 to 75% of antimicrobial use in acute care, long-term care, and hemodialysis facilities is unnecessary or inappropriate because the regimen is broader in spectrum or longer in duration than necessary, the antibiotics do not provide activity against the causative pathogen, the patient does not actually have a bacterial infection (e.g., specimen contamination, asymptomatic colonization), or the prescribed dose is inappropriate. Misuse and overuse of antimicrobial agents in the outpatient setting are also well-recognized problems in the United States and other countries, including many countries where antimicrobials can be obtained without a prescription. This inappropriate use of antimicrobial agents introduces unnecessary risk for the development of complications of antibiotic therapy, including *C. difficile* infection, the emergence of multidrug-resistant organisms, and drug toxicity, and represents an important target for intervention.

Health Care Delivery–Related Factors

Health care delivery–related risk factors do not offer any potential benefit to patients but rather are associated only with risk. Such factors include but are not limited to failure to perform hand hygiene when indicated or to use aseptic or sterile technique during invasive procedures; unsafe injection practices (e.g., entering a multidose vial with a used needle); and failure to clean, disinfect, or sterilize the patient environment, medical equipment, and instruments. All these risks are potentially modifiable and are thus important targets for prevention initiatives. Antibiotic use, which is also a patient-specific health care–related risk factor, can also be considered a health care delivery–related risk factor because misuse of antibiotics in one patient or population can introduce risks among the larger population through changes in microbial ecology (i.e., selection and increased prevalence of antimicrobial-resistant pathogens).

Many of these health care delivery–related factors are the result of poor adherence to recommended, evidence-based infection prevention practices. Despite recognition that poor hand hygiene practice is a leading cause of pathogen transmission, the existence of major national and international guidelines, and initiatives to improve hand hygiene practices among health care providers, compliance with recommended hand hygiene practices among health care personnel remains unacceptably low.[3] In the United States, average rates of health care provider compliance with recommended hand hygiene practices have been reported to be less than 50%, with some individual studies reporting rates as low as 20% in some intensive care units (ICUs). Similarly, unsafe injection practices continue to be identified as the cause of health care–related transmission of blood-borne pathogens, such as hepatitis B and C viruses.

Environmental contamination can also contribute to the transmission of health care–associated pathogens.[4] For example, environmental contamination with *C. difficile* has been detected in up to 100% of hospital rooms occupied by patients with *C. difficile* infection, and methicillin-resistant *Staphylococcus aureus* (MRSA) has been detected on environmental surfaces in approximately 70% of hospital rooms housing patients infected and colonized with MRSA. Some, but not all, studies have identified similarly high rates of environmental contamination with multidrug-resistant gram-negative pathogens. This environmental contamination has been shown to result in patient-to-patient transmission through transient contamination of hands and equipment or by direct contact of the patient with the contaminated environment. Environmental contamination is, however, a potentially modifiable risk factor for health care–associated infection. Cleaning and disinfection of the environment and portable medical equipment that is shared among patients are often suboptimal. For example, one multicenter study conducted in 36 acute care hospitals in the United States found that at baseline, only 48% of high-risk environmental surfaces were cleaned during routine cleaning after discharge of the patient. Improvement in cleaning practices and other interventions to reduce the microbiologic burden in the health care environment can reduce the microbial burden of organisms in the environment and has been associated with a reduction in the risk of acquisition of multidrug-resistant organisms and *C. difficile* infection.[A1] Outbreaks of infection due to contaminated medical devices (e.g., duodenoscopes, heater-cooler devices used in cardiothoracic surgery procedures) highlight the critical role that cleaning, disinfection, and sterilization of medical equipment play in preventing health care–associated infections. In addition, environmental interventions are important to prevent patients from acquiring pathogens due to exposure to water (e.g., *Legionella* species; Chapter 290) and air (e.g., environmental fungi) within health care settings.

Pathogens in Health Care–Associated Infections

The organisms most commonly identified in device- and procedure-associated infections (i.e., central line–associated blood stream infection, catheter-associated urinary tract infection, ventilator-associated pneumonia, and surgical site infection) vary somewhat among the different types and sites of infection. Overall, in the United States 10 pathogen groups accounted for more than 75% of pathogens identified in device- and procedure-related infections reported to the CDC through the National Healthcare Safety Network between 2015 and 2017.[5] These pathogen groups and the proportion of reported pathogens that they represented include *Escherichia coli* (18%), *Staphylococcus aureus* (12%), *Klebsiella* species (9%), *Pseudomonas aeruginosa* (8%), *Enterococcus faecalis* (8%), coagulase-negative staphylococci (7%), *Enterobacter* species (5%), *Enterococcus faecium* (4%), *Proteus* species (3%), and *Candida albicans* (3%).

TABLE 261-2 RATES OF ANTIMICROBIAL RESISTANCE AMONG PATHOGENIC ISOLATES FROM HEALTH CARE–ASSOCIATED INFECTIONS

		PROPORTION OF ISOLATES RESISTANT TO ANTIBIOTIC		
ORGANISM	**ANTIBIOTIC CLASS**	***United States (2015-2017)****	***ICUs in 45 Asian, African, European, and Latin American Countries (2013-2018)**†*	***ICUs in 14 European Countries (2017)**‡*
Staphylococcus aureus	Anti-staphylococcal penicillins (e.g., oxacillin, methicillin)	44%	56%	24%
Klebsiella species	Extended-spectrum cephalosporins	19%	76-78%	40%
	Carbapenems	6%	49%	15%
Pseudomonas aeruginosa	Carbapenems	16%	53%	26%
Enterococcus faecium	Glycopeptides (vancomycin)	72%	29%	NR
Acinetobacter baumannii	Carbapenems	39%	92%	64%
Escherichia coli	Extended-spectrum cephalosporins	20%	66-68%	16%
	Carbapenems	0.7%	17%	0.8%
	Fluoroquinolones	36%	62%	NR

*Weiner-Lastinger LM, Abner S, Edwards JR, et al. Antimicrobial-resistant pathogens associated with adult healthcare-associated infections: summary of data reported to the National Healthcare Safety Network, 2015-2017. *Infect Control Hosp Epidemiol*. 2020;41:1-18.

†Rosenthal VD, Duszynska W, Ider BE, et al. International Nosocomial Infection Control Consortium (INICC) report, data summary of 45 countries, for 2013-2018, adult and pediatric units, device-associated module. *Am J Infect Control*. 2021;49:1267-1274.

‡European Centre for Disease Prevention and Control. Healthcare-associated infections acquired in intensive care units. In: ECDC. Annual epidemiological report for 2017. Stockholm: ECDC; 2019. Available at: https://www.ecdc.europa.eu/sites/default/files/documents/AER_for_2017-HAI.pdf. Accessed June 9, 2021.

ICUs = intensive care units; NR = not reported.

Multidrug-Resistant Bacteria

An increasingly concerning problem is the emergence of acquired antimicrobial resistance among many of the bacterial pathogens that are common causes of health care–associated infections (Table 261-2). Multidrug-resistant organisms represent a significant health threat because infections caused by many of these multidrug-resistant organisms have been associated with worse outcomes than those caused by antimicrobial-susceptible strains of the same organism, including excess length of hospital stay, increased health care costs, and higher mortality, with mortality rates approaching 50% in some studies.[6] Possible explanations for the observed increased rate of adverse outcomes associated with multidrug-resistant organism infections include the presence of more severe underlying disease, delays in initiating effective therapy, and the use of more toxic or less effective therapy for treatment of the infection. Regardless of their cause, the poor outcomes associated with multidrug-resistant organism infections highlight the critical need for effective preventive measures and development of new antibiotics with activity against them, particularly multidrug-resistant gram-negative bacilli.

Organisms can develop resistance to antimicrobial agents to which they were previously susceptible through a variety of mechanisms, including induction, genetic mutation, and acquisition of new genetic material (e.g., conjugation with cell-to-cell transfer of genetic material by plasmids or transposons). In health care settings, however, patient-to-patient transmission of multidrug-resistant organisms is more common than de novo development of resistance in a previously susceptible organism within the patient's existing microbiome. Identified risk factors for acquisition of multidrug-resistant organisms include exposure to antibiotics, frequent or prolonged exposure to health care facilities (e.g., hospitals, nursing homes), poor infection control practices among health care providers, environmental contamination with multidrug-resistant organisms, and prevalence of multidrug-resistant organisms among other patients within a health care facility.

Among the pathogens reported to the CDC between 2015 and 2017 as causes of device-associated infections and surgical site infections in adults, acquired antimicrobial resistance was relatively common (see Table 261-2). For example, 72% of *Enterococcus faecium* isolates were vancomycin resistant, and 44% of *S. aureus* isolates were resistant to methicillin (MRSA). Multidrug resistance among gram-negative pathogens also is a growing global health threat among persons receiving health care (Chapter 281). Approximately 10% of the most common gram-negative pathogens reported to the CDC in 2015-2017 demonstrated acquired resistance to at least one drug in three or more antibiotic classes. For example, 39% of *Acinetobacter baumannii* isolates, 11% of *Klebsiella* and *P. aeruginosa* isolates, and 9% of *E. coli* isolates met this definition of multidrug resistance.

Although the lack of a standardized definition of multidrug resistance limits direct comparisons of data from different populations, antimicrobial resistance is an important problem in many regions of the world. For example, International Nosocomial Infection Control Consortium data from device-associated infections in ICUs in 45 countries in Asia, Africa, Europe, and Latin America collected between 2013 and 2018 demonstrated methicillin resistance in 56% of *S. aureus* isolates, as well as carbapenem resistance in 49% of *Klebsiella* species isolates and 92% of *Acinetobacter* species isolates.

One example of the emergence and rapid dissemination of multidrug-resistant gram-negative bacilli is carbapenem-resistant Enterobacteriaceae, particularly *K. pneumoniae* (Chapter 281). In the United States, carbapenem resistance among the Enterobacterales is usually, but not always, due to the production of *K. pneumoniae* carbapenemase (KPC), a class A serine β-lactamase enzyme that hydrolyzes all β-lactam antibiotics. The *K. pneumonia* carbapenemase enzyme, which was first described in 2001, is encoded by the bla_{KPC} gene carried on a transmissible plasmid that also carries additional genes that confer resistance to several other classes of antimicrobial agents. Thus, in addition to carbapenem resistance, these organisms demonstrate resistance to other β-lactam antibiotics and to several other classes of antibiotics.

Asymptomatic carriage of multidrug-resistant organisms is relatively common among persons exposed to health care. In fact, patients with clinically apparent multidrug-resistant organism infections represent a relatively small proportion of the total burden of these pathogens. Reported rates of MRSA carriage have ranged from 4.6 to 13.6% among hospital patients, 2 to 22% among U.S. ambulatory dialysis patients, and 10 to 100% among residents of long-term care facilities. The prevalence of carriage of vancomycin-resistant enterococci among hospital patients and ambulatory dialysis patients has been reported to range from 6.3 to 67% and 0 to 16%, respectively. Studies that have included a variety of multidrug-resistant gram-negative bacilli have reported carriage rates of 19 to 32% in ICU patients and hospital patients with diarrhea, 25% among residents of long-term care facilities, and 16% among chronic hemodialysis patients. Studies that have focused specifically on carbapenem-resistant Enterobacterales have demonstrated prevalence rates ranging from 2 to 5.4% among high-risk hospital patients in the United States and 2 to 49% among post–acute care facility patients in Israel. These asymptomatic carriers play an important role in the epidemiology of multidrug-resistant organism infections. First, they represent a substantial risk of subsequent infection, with up to one third of carriers of MRSA, vancomycin-resistant enterococci, and multidrug-resistant gram-negative bacilli developing symptomatic infection within 12 months. Second, carriers of asymptomatic multidrug-resistant organisms can contribute to widespread transmission within the health care system through contamination of their surrounding environment. Several studies have demonstrated that the risk of acquiring a multidrug-resistant organism during hospitalization is related to the prevalence, or colonization pressure, of that multidrug-resistant organism among other patients. Finally, admission to a hospital room in which the prior patient was colonized or infected with MRSA, vancomycin-resistant enterococci, or multidrug-resistant gram-negative bacilli has been associated with an increased risk of acquisition of those organisms.

Over the past 15 to 20 years, encouraging data have shown a decline in the incidence of some multidrug-resistant organisms, particularly MRSA. In the United States, for example, the incidence of hospital-onset MRSA blood stream infections decreased by 74% between 2005 and 2016. These changes occurred despite the emergence of community-associated MRSA among persons without typical health care–associated risk factors and the introduction of community-associated MRSA as a health care–acquired pathogen.[7] In the United Kingdom, a 97% reduction in the number of cases of ICU-associated MRSA blood stream infection was reported through a mandatory reporting system between 2007 and 2016. In more recent years, however, the incidence of MRSA infections in hospitalized patients appears to have plateaued. The specific cause of these observed decreases in MRSA health care–associated infections is uncertain and may be the result of improvements in basic infection control practices, introduction of specific MRSA prevention practices, or other changes in the epidemiology of this pathogen.

Infection with *Clostridioides difficile*

C. difficile, the etiologic agent of pseudomembranous colitis, is the most common cause of health care–associated infectious diarrhea (Chapter 271). Although community-associated *C. difficile* infection occurs, the majority of cases are associated with receipt of health care. Clinical manifestations of *C. difficile* infection range from asymptomatic carriage to mild diarrhea to life-threatening colitis, toxic megacolon, and sepsis. The overall mortality associated with *C. difficile* infection has ranged from 2 to 6%. Compared with patients without *C. difficile* infection, hospital patients who develop *C. difficile* infection experience an extended duration of hospitalization, and approximately 15 to 30% of these patients will experience at least one recurrence of the disease, typically within 1 to 2 months of the initial episode. Between 2011 and 2017, the estimated U.S. national burden of health care–associated *C. difficile* infection decreased by 36%,[8] likely due to a reduced use of fluoroquinolones, diagnostic stewardship interventions, and increased adherence to recommended prevention practices. Despite this substantial reduction, the burden of health care-associated *C. difficile* infection remained high, with an estimated 235,000 cases occurring in 2017, and these numbers have remained relatively similar since then (Chapter 271).

The problem of *C. difficile* extends to chronic care facilities. About 20% of hospital-onset *C. difficile* infection occurs among persons with recent residence in a nursing home, and two thirds of nursing home–onset *C. difficile* infection cases occur among residents who have been recently discharged from an acute care hospital. Transmission in the health care setting can occur as the result of exposure to organisms on health care providers' hands, environmental surfaces, or medical equipment. In the absence of effective hand hygiene practices, contaminated health care providers may transmit the organism to other patients. Contamination of the environment and medical equipment with *C. difficile* is also common. Testing performed in hospital rooms has identified *C. difficile* on environmental surfaces in up to 100% of rooms housing patients with active *C. difficile* infection and in as many as 33% of non–*C. difficile* infection patient rooms. Commonly contaminated surfaces include bed rails, bedside tables, telephones, call buttons, and blood pressure cuffs. *C. difficile* spores are resistant to killing by many common hospital disinfectants and can persist in the environment for long periods of time, further contributing to the risk of exposure to a contaminated environment.

Although exposure to any antimicrobial agent may increase the risk for development of *C. difficile* infection, clindamycin, third-generation cephalosporins, penicillins, and fluoroquinolones may present the highest risk. Other factors that have been associated with an increased risk for development of *C. difficile* infection include receipt of cytotoxic chemotherapeutic agents and gastric acid suppressive medications such as proton pump inhibitors, failure to develop an antibody response to *C. difficile*, and older age (i.e., age older than 64 years).

Viruses

Respiratory Viruses

Common respiratory viruses, such as influenza (Chapter 332), can be transmitted in the health care setting by health care providers, visitors, and patients, thereby resulting in health care–acquired disease. Higher rates of morbidity and mortality have been observed among patients who acquire infection during hospitalization, probably owing to the presence of significant underlying medical illness. Several studies have associated higher influenza immunization rates among health care providers with lower rates of transmission of nosocomial influenza, thereby leading to efforts to increase influenza vaccination rates among health care providers. By the 2018-2019 influenza season, vaccination rates of 90% and 83.8% had been achieved among health care providers in acute care and long-term acute care hospitals in the United States. In addition to influenza, outbreaks of other respiratory virus infections for which vaccines are not available, such as respiratory syncytial virus (Chapter 330), continue to occur.

The health care–associated transmission of newly emerged respiratory viruses, such as the severe acute respiratory syndrome coronavirus (SARS-CoV; Chapter 334) in 2003, pandemic influenza in 2009, the Middle East respiratory syndrome coronavirus (MERS-CoV) in 2013, and especially SARS-CoV-2 (the cause of coronavirus disease 2019 [COVID-19; Chapter 336]) starting in 2019,[9] highlights the importance of surveillance to allow rapid identification of patients with potentially communicable diseases and implementation of appropriate infection control precautions.

Blood-borne Viruses

Although routine screening of the blood supply for the blood-borne pathogens hepatitis B virus, hepatitis C virus (Chapter 135), and human immunodeficiency virus (Chapter 353) has dramatically decreased the incidence of health care–associated blood-borne pathogen infections, transmission of these pathogens within health care settings continues to occur. Most health care–associated transmission of blood-borne pathogens is now due to failure to adhere to recommended basic infection control practices. Unsafe injection practices (e.g., reuse of syringes, contamination of multidose vials, improper use and disinfection of blood glucose monitoring devices that are used for multiple patients) and inadequate cleaning, disinfection, and sterilization of medical equipment and the health care environment (e.g., dialysis facilities) have been identified in several recent outbreaks of patient-to-patient transmission of blood-borne pathogens. A large proportion of documented health care–associated hepatitis B virus and hepatitis C virus transmission events has occurred in outpatient settings and long-term care facilities, thereby highlighting the importance of infection prevention programs throughout the entire health care system. Transmission of blood-borne pathogens from health care providers to patients is uncommon but can occur, typically in the setting of "exposure-prone" invasive procedures but also as a result of drug diversion by health care providers. Guidelines are available to assist health care providers and health care facilities in minimizing the risk posed to patients by blood-borne pathogen-infected health care providers while allowing most such providers to remain involved in patient care activities (E-Table 261-1).

Fungi

Candida albicans and other *Candida* species (Chapter 310) accounted for approximately 6% of all pathogens reported to the CDC between 2015 and 2017 as causes of device-associated infections and surgical site infections, thereby placing them among the most common pathogens implicated in health care–associated infections. The emergence of multidrug-resistant *C. auris* as a cause of health care facility–associated outbreaks further highlights the importance of *Candida* species in health care–associated infection epidemiology. Exposure to environmental fungi, such as *Aspergillus* species (Chapter 311), in the health care setting can result in health care–associated infection, particularly in immunocompromised hosts. Such exposure and resulting infection are most commonly associated with inadequate environmental control measures during construction, demolition, or water damage within the health care facility. A multistate outbreak of invasive fungal infections in the United States, mostly due to *Exserohilum rostratum* associated with contaminated methylprednisolone injections, demonstrated that contaminated medications and other medical products are additional potential sources of exposure to fungal pathogens during health care.

Device-Associated Infections

Central Line–Associated Blood Stream Infections

Central line–associated blood stream infections are blood stream infections that occur in patients who have a central venous catheter and in whom no other source of the infection is identified. Central line–associated blood stream infections are associated with longer hospital stays, increased risk of death, and greater hospital costs (see Table 261-1). Rates of morbidity and mortality, however, vary substantially, depending on the causative pathogen and characteristics of the patient in whom the infection occurs. Although central line–associated blood stream infections are often thought of as a complication that occurs among ICU patients, the use of central venous catheters in non-ICU hospital settings has expanded substantially, and the incidence and overall burden of central line–associated blood stream infections in some non-ICU settings now often exceeds that in ICUs. Central line–associated

E-TABLE 261-1 SELECT GUIDELINES AND EVIDENCE-BASED RECOMMENDATIONS FOR THE PREVENTION AND MANAGEMENT OF HEALTH CARE–ASSOCIATED INFECTIONS

GENERAL TOPIC	SPECIFIC TOPIC	GUIDELINES AND RECOMMENDATIONS
Device-associated infections	Vascular catheter–associated infections	Buetti N, Marschall J, Drees M, et al. Strategies to prevent central line-associated bloodstream infections in acute care hospitals: 2022 update. *Infect Control Hosp Epidemiol*. 2022;43:553-569. O'Grady NP, Alexander M, Burns LA, et al. Guidelines for the prevention of intravascular catheter–related infections. *Clin Infect Dis*. 2011;52:1087-1099. Mermel LA, Allon M, Bouza E, et al. Clinical practice guidelines for the diagnosis and management of intravascular catheter–related infection: 2009 update by the Infectious Diseases Society of America. *Clin Infect Dis*. 2009;49:1-45.
	Catheter-associated urinary tract infections	Lo E, Nicolle LE, Coffin SE, et al. Strategies to prevent catheter-associated urinary tract infections in acute care hospitals: 2014 update. *Infect Control Hosp Epidemiol*. 2014;35:464-479. Gould CV, Umscheid CA, Agarwal RK, et al. Guideline for prevention of catheter-associated urinary tract infections 2009. http://www.cdc.gov/infectioncontrol/guidelines/cauti/index.html. Hooton TM, Bradley SF, Cardenas DD, et al. Diagnosis, prevention, and treatment of catheter-associated urinary tract infection in adults: 2009 International Clinical Practice Guidelines from the Infectious Diseases Society of America. *Clin Infect Dis*. 2010;50:625-663.
	Ventilator-associated pneumonia/health care–associated pneumonia	Centers for Disease Control and Prevention. Guideline for preventing health care–associated pneumonia, 2003. *MMWR Recomm Rep*. 2004;53(RR-3):1-36. Klompas M, Branson R, Cawcutt K, et al. Strategies to prevent ventilator-associated pneumonia, ventilator-associated events, and nonventilator hospital-acquired pneumonia in acute care hospitals: 2022 update. *Infect Control Hosp Epidemiol*. 2022;43:687-713. Kalil AC, Metersky ML, Klompas M, et al. Management of adults with hospital-acquired and ventilator-associated pneumonia: 2016 clinical practice guidelines by the Infectious Diseases Society of America and the American Thoracic Society. *Clin Infect Dis*. 2016;63:e61-e111.
	Cardiovascular implantable electronic devices	Kusumoto FM, Schoenfeld MH, Wilkoff BL, et al. 2017 HRS expert consensus statement on cardiovascular implantable electronic device lead management and extraction. *Heart Rhythm*. 2017;14:e503-e551.
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blood stream infections are also important problems among nonhospitalized persons who have central venous catheters, such as patients receiving chronic total parenteral nutrition, chemotherapy, or dialysis in the outpatient or home care setting.

Blood stream infections due to central venous catheters are largely the result of contamination or colonization of the external surface or the intraluminal surface of the catheter. This contamination can occur either during or after insertion of the catheter. Effective strategies can reduce the risk of catheter contamination during insertion and throughout the time that the catheter remains in situ (see E-Table 261-1). The "central line bundle," which refers to evidence-based practices that, when used together, can reduce the risk of central line–associated blood stream infection even more than would be expected when the components are introduced individually, includes hand hygiene; maximal barrier precautions during insertion (i.e., use of sterile gown and gloves and a surgical cap and mask by the operator and covering the patient with a sterile, full-body drape); chlorhexidine skin antisepsis; optimal insertion site selection; and daily review of whether the catheter is necessary, with immediate removal if it is not. Randomized trials of cutaneous skin antisepsis prior to central venous catheter insertion show that a chlorhexidine-alcohol skin antiseptic solution provides greater protection against short-term catheter-related infections than does a povidone iodine–alcohol solution.[A2] Chlorhexidine-alcohol also leads to lower rates of infectious complications than does povidone-iodine when used for skin antisepsis for insertion of peripheral intravenous catheters.[A3] Other interventions that have been associated with reductions in central line–associated blood stream infection rates include covering of the insertion site with a sterile gauze or semipermeable transparent dressing, cleansing of the catheter insertion site with an antiseptic such as chlorhexidine, use of aseptic technique to access and to manipulate the catheter, scrubbing of the catheter hub with a disinfectant before accessing the catheter lumen for administration of medications or other products or for aspiration of blood, use of antimicrobial- or antiseptic-coated catheters, and use of chlorhexidine rather than regular soap and water for daily bathing of ICU patients. With these procedures, central venous and arterial infusion sets can be replaced every 7 days rather than every 4 days with equivalent safety.[A4] Widespread adoption of the central line bundle and other central line–associated blood stream infection prevention strategies has been associated with a 50% decrease in the incidence of central line–associated blood stream infection in U.S. hospitals between 2008 and 2016. These improvements appear to be continuing, with an additional 7% decrease observed between 2018 and 2019.

Catheter-Associated Urinary Tract Infections

A catheter-associated urinary tract infection (Chapter 263) is a urinary tract infection that develops in a patient who has or who recently had an indwelling urinary catheter. Similar to the pathogenesis of catheter-related blood stream infections, catheter-associated urinary tract infections develop by the introduction of pathogens into the bladder as a result of contamination and colonization of the internal or external surface of the catheter. Among patients with indwelling urinary catheters, the incidence of bacteriuria is 3 to 8% per day, and 10 to 25% of patients with bacteriuria will subsequently develop symptoms consistent with a urinary tract infection.

A number of basic practices, such as aseptic technique during insertion, maintenance of proper cleanliness and hygiene, securement of the catheter to avoid piston-like movement of the catheter within the urethra, and maintenance of a closed system with unobstructed flow of urine from the bladder into the collection system, are recommended to reduce the risk of catheter-associated urinary tract infection. It is estimated that by implementing such practices, 65 to 70% of catheter-associated urinary tract infections that occur in acute care hospitals can be prevented. Several studies have demonstrated that indwelling urethral catheters are often inserted for inappropriate reasons and that many catheters that were initially inserted for an appropriate indication remain in place even after the initial indication for catheterization has resolved. Additional studies found that physicians are often unaware that their patient has a urinary catheter. Thus, the greatest opportunity for catheter-associated urinary tract infection prevention is avoidance of unnecessary catheter insertion and prompt removal of catheters that are no longer necessary. Development of protocols that explicitly define appropriate indications for insertion of urinary catheters, introduction of interventions that remind clinicians to reassess the appropriateness of a patient's urinary catheter, and nurse-driven protocols that allow nurses to remove unnecessary urinary catheters have been associated with reduced use of urinary catheter and lower rates of catheter-associated urinary tract infection.

Ventilator-Associated Pneumonia

In hospitalized patients, mechanical ventilation (Chapter 91) is one of the most common risk factors for the development of pneumonia. Mechanical ventilation and the interventions required to provide mechanical ventilation (e.g., endotracheal intubation, sedation) increase the risk of pulmonary infection through a variety of mechanisms, including an increased risk of aspiration of oropharyngeal and gastrointestinal secretions and impairment of the cough reflex. From both a clinical and epidemiologic standpoint, ventilator-associated pneumonia (Chapter 85) is a difficult diagnosis to establish with certainty because of the subjective nature of many of the variables considered (e.g., chest radiographic findings, changes in the characteristics of respiratory tract secretions), alternative explanations for clinical and radiographic abnormalities (e.g., acute respiratory distress syndrome, atelectasis), and difficulty in determining whether the results of respiratory tract cultures represent true infection or colonization of the airway.

Pneumonia is the most common health care–associated infection in U.S. hospitals, and approximately 35% of cases are associated with mechanical ventilation. These infections are associated with mortality rates and health care costs that are among the highest observed among all health care–associated infections (see Table 261-1). Studies suggest that at least 55% of cases of ventilator-associated pneumonia are preventable. As with other device-associated infections, avoiding the use of the device is the most effective means to prevent infection. To prevent ventilator-associated pneumonia and other complications of mechanical ventilation, the use of noninvasive methods of ventilation, minimized use of sedation (e.g., manage patients without a sedative if possible, daily sedation interruption and assessment of readiness to be extubated), and early mobilization can eliminate or at least reduce the duration of mechanical ventilation (Chapter 91). For patients who do require mechanical ventilation, the following are routinely recommended to prevent ventilator-associated pneumonia: proper cleaning, disinfection, sterilization, use, and maintenance of respiratory equipment; minimizing pooling of secretions above the endotracheal tube cuff; and elevating the head of the bed (unless it is medically contraindicated). Chlorhexidine mouthwash or gel as part of oral hygiene care can reduce the incidence of ventilator-associated pneumonia by about 30%, but this reduction is due largely to the findings of unblinded studies, with double-blinded studies not demonstrating a clear benefit.[A5] For patients who are ventilated and treated with targeted hypothermia after out-of-hospital cardiac arrest (Chapter 50), 2 days of intravenous amoxicillin-clavulanate (at doses of 1 g and 200 mg, respectively) administered three times a day reduces the incidence of early ventilator-associated pneumonia by about 45%.[A6] In some randomized controlled trials, selective oropharyngeal or digestive decontamination has been associated with a significant reduction in ventilator-associated pneumonia, but this approach has not yet been widely adopted as a standard of care in the United States, at least in part because of concerns that it may lead to selection of antimicrobial-resistant organisms.

Other Device-Related Infections

With advances in medical technology, implantable devices are being used to treat and to manage a variety of medical conditions, particularly of the cardiovascular and nervous systems. These devices include cardiovascular implantable electronic devices such as pacemakers and implantable cardioverter-defibrillators (Chapter 54), ventricular assist devices (Chapter 46), deep brain stimulators, and intrathecal pumps. The potential benefits that these devices may offer to patients come with at least some degree of risk of device-related infection.

Surgical Site Infections

Surgical site infections are infections that develop at the site of an operative procedure. Although only a relatively small proportion of patients who undergo surgery subsequently develop a surgical site infection and the overall mortality rate is relatively low, the absolute number of surgical site infections that occur and the overall cost and burden of morbidity and mortality associated with them are large because of the volume of surgical procedures performed each year (see Table 261-1). A number of factors contribute to the risk of surgical site infection: the specific site and type of surgical procedure; duration of the procedure; tissue hypoxia at the surgical site; wound contamination with endogenous or exogenous organisms; surgical technique; perioperative infection prevention practices; environmental controls related to temperature, humidity, and air purity within the operating room; and the patient's underlying medical conditions, smoking status, and other factors that may increase the inherent risk of infection. Although some of these factors are not amenable

to corrective intervention, a number of interventions have been proven to reduce the risk of those that are.

An estimated 55% of surgical site infections could be prevented by routine application of evidence-based preventive measures. The use of sterile technique, preoperative skin preparation with an antiseptic agent,[A7] administration of antimicrobial prophylaxis within 60 minutes before the surgical incision, maintenance of normothermia, and perioperative glucose control have been demonstrated to reduce the risk of infection associated with a wide variety of surgical procedures. With such appropriate techniques, continuing antibiotic prophylaxis postoperatively does not appear to yield additional benefit for reducing surgical site infections.[A8] In some types of surgeries and some patients, the use of supplemental oxygen (e.g., 80% fraction of inspired oxygen) in the perioperative period may reduce the risk of surgical site infection. Although opportunities for improvement remain, surveillance data reported to the CDC's National Healthcare Safety Network by U.S. hospitals showed reductions in the incidence of surgical site infection occurring in association with 10 common surgical procedures from 2008 to 2017, but no further reductions since.[10]

PREVENTION

At least 55 to 70% of some of the most common health care–associated infections can be prevented. Scientific research and clinical experience have led to the publication of evidence-based guidelines for the prevention of health care–associated infections (see E-Table 261-1).[11] Strategies to prevent health care–associated infection are designed to interrupt one or more of the factors associated with pathogen transmission or the development of infection due to endogenous or exogenous organisms. Horizontal prevention strategies have the potential to prevent a wide variety of health care–associated infections or to prevent transmission of a variety of pathogens. Conversely, vertical strategies target a specific pathogen. Examples of horizontal prevention strategies include hand hygiene, education of health care providers, environmental cleaning and disinfection, antimicrobial stewardship, and use of aseptic technique for invasive procedures. Examples of vertical strategies include an influenza vaccination campaign or active surveillance testing to detect asymptomatic MRSA-infected carriers who may serve as unrecognized reservoirs for its transmission, followed by targeted decolonization therapy for persons identified as carriers.

Basic practices (e.g., most of the horizontal approaches described earlier plus a few vertical approaches, such as transmission-based precautions) should routinely be implemented in all health care facilities, whereas special or advanced interventions are added when basic practices fail to control or prevent health care–associated infections or transmission of one or more specific pathogens within the facility (see E-Table 261-1). The selection of specific strategies to be implemented within a specific health care facility should be based on an assessment of risk, local data and epidemiology, scientific evidence and guidelines, regulatory and accreditation requirements, and facility-specific cost-benefit calculations.

Antimicrobial Stewardship

Antimicrobial stewardship refers to interventions designed to improve the appropriateness of antimicrobial use by promoting the selection of an optimal antimicrobial regimen (i.e., the most appropriate drug, dose, duration, and route of administration) for a specific patient. The goals of an antimicrobial stewardship program are to optimize clinical outcomes (e.g., cure of infection related to antimicrobial use, minimize toxicity and other adverse events) but also to limit the antimicrobial selection pressure that drives the emergence of antimicrobial-resistant strains. Multidisciplinary antimicrobial stewardship programs have been associated with several desirable outcomes, including significant reductions in antimicrobial use, reduced rates of antimicrobial resistance among health care–associated pathogens, reduced incidence of adverse outcomes associated with antibiotic use (e.g., toxicity, *C. difficile* infection), improved clinical outcomes, and significant reductions in hospital antimicrobial-associated costs.

A variety of approaches have been used by successful antimicrobial stewardship programs (see E-Table 261-1).[12] One of the most commonly used and most effective strategies includes formulary restriction and requirement of preauthorization before prescribing certain antibiotics (e.g., antibiotics that are broad in their antimicrobial spectrum, are associated with significant toxicity, or are expensive). A second core strategy is a prospective audit of the appropriateness of prescribed antimicrobial therapy, with provision of feedback to the prescribing clinician if opportunities for further optimization of therapy are available (e.g., narrowing or broadening spectrum of therapy, discontinuing antimicrobial therapy, or altering drug dose or dosing interval on the basis of available clinical data). Additional approaches include education, development of guidelines and clinical pathways, computer-assisted decision support, and protocols to optimize conversion from the parenteral to the oral route of administration when appropriate. In general, using more stewardship programs reduces the overuse of antibiotics.[13] Antimicrobial stewardship programs must also address the complex and constantly changing problems and issues associated with antimicrobial resistance.

Decolonization Therapy

Decolonization refers to the administration or application of antimicrobial or antiseptic agents to a person to eliminate or to reduce the burden of carriage of one or more pathogens. Data on decolonization are promising but inconsistent, thereby suggesting that factors such as compliance and bathing technique as well as patient- and hospital-specific factors may influence the outcomes observed at the individual hospital and patient levels.

For example, selective oropharyngeal and digestive decontamination can prevent ventilator-associated pneumonia and surgical site infections after colorectal surgery. Selective digestive tract decontamination can potentially reduce in-hospital mortality among ICU patients who are receiving mechanical ventilation,[A9] but it is associated with a more pronounced increase in carriage of aminoglycoside-resistant gram-negative bacteria, thereby raising concerns about long-term risk of antimicrobial resistance.

Topical decolonization therapy, with or without systemic antibiotic therapy, can suppress or eradicate *S. aureus* among known carriers, thereby reducing the risk of infection for themselves and others. Universal decolonization with intranasal mupirocin for 5 days in addition to daily chlorhexidine bathing can significantly reduce MRSA-positive clinical cultures and blood stream infections due to any pathogen in ICU patients. In patients who are hospitalized in non–critical care units, daily bathing with chlorhexidine plus 5 days of intranasal mupirocin is not beneficial overall[A10] but does appear to be beneficial specifically for patients who have medical devices (e.g., central venous catheters, midline catheters, or lumbar drains). In patients who are colonized with MRSA, targeted treatment with chlorhexidine mouthwash, chlorhexidine baths or showers, and intranasal mupirocin for 5 days twice per month for 6 months after hospital discharge reduces MRSA infection by about 30% compared with routine hygiene education alone.[A11]

Daily bathing with chlorhexidine, rather than non-antimicrobial soap, without the use of intranasal mupirocin has had mixed results. For example, a single-site study showed no benefit for reducing the incidence of health care–associated infections in adult ICU patients,[A12] whereas a trial in eight adult ICUs and one bone marrow transplant unit found that daily bathing with chlorhexidine was associated with a 23% reduction in the combined outcome of MRSA and vancomycin-resistant enterococci acquisition. Another single-site randomized trial also showed every other day bathing with chlorhexidine was associated with a significant reduction in hospital-acquired infections.[A13] Although the precise role for decontamination therapy remains uncertain, its use has become fairly common in ICU settings and it has been incorporated into some clinical guidelines for the prevention of health care–associated infections, such as central line–associated blood stream infections.

Active Surveillance Testing

Active surveillance testing identifies asymptomatic carriers of a pathogen of interest (e.g., MRSA, vancomycin-resistant enterococci, multidrug-resistant gram-negative bacilli) with the intention to introduce additional interventions for identified carriers to prevent infection in the carrier or transmission to others. The interventions that may be applied to the identified carriers include transmission-based precautions (e.g., contact precautions), decolonization therapy (mostly applicable to *S. aureus*), and altered antimicrobial therapy (e.g., surgical antimicrobial prophylaxis). Active surveillance is commonly used in conjunction with other interventions to control outbreaks. In the nonoutbreak setting, numerous reports suggest that active surveillance as part of a comprehensive program can reduce infection with multidrug-resistant organisms in individual hospitals, large hospital systems, and health care facilities within specific geographic regions, such as a number of Northern European countries. However, a U.S. trial found no significant difference in the incidence of colonization or infection with MRSA and vancomycin-resistant enterococci in ICUs that performed active surveillance testing with introduction of contact precautions for patients found to be carriers of MRSA or vancomycin-resistant enterococci compared with ICUs that did not conduct active surveillance testing.

Routine use of gowns and gloves for all patients is another intervention that has potential for reducing the risk of transmission of pathogens among patients by reducing contamination of health care workers' hands and clothing.

A cluster-randomized study found that universal use of gowns and gloves for all patients in ICUs did not reduce the primary outcome of acquisition of either MRSA or vancomycin-resistant enterococci, but did significantly lower the acquisition of MRSA. Thus, the utility of this strategy for preventing pathogen transmission remains uncertain.

Interfacility and Regional Collaboration

Given the frequency with which patients are shared among hospitals and other health care settings within geographic regions and the evidence of interfacility patient transfer as a risk factor of introduction of multidrug-resistant organisms and *C. difficile* into a health care facility, implementation of comprehensive prevention programs in all facilities within a region may be more effective in preventing health care–associated infections and multidrug-resistant organism transmission than implementation of the same interventions in a single health care institution. The establishment of regional infection prevention initiatives offers several potential benefits, including the ability to address the complex epidemiology of health care–associated infections that involve multiple health care facilities (e.g., multidrug-resistant organism acquisition, transmission, and infection) than single-institution interventions and opportunities for collaboration and sharing of information, experiences, and resources. A number of successful regional and national initiatives for the prevention of health care–associated infection, including central line–associated blood stream infection, dialysis-related blood stream infections, MRSA, vancomycin-resistant enterococci, carbapenem-resistant Enterobacteriales, and *C. difficile*, have been described.

Incentives and Penalties

The Centers for Medicare and Medicaid Services Conditions of Participation list specific requirements for infection prevention and control processes in health care facilities that receive its funding. Hospitals found to be deficient in the implementation of the requirements are at risk of losing the funding that they receive from the agency. Similarly, hospital accreditation agencies such as The Joint Commission have established standards for infection prevention programs and periodically survey hospitals to determine if such programs are in place. In addition, public reporting of hospital-specific health care–associated infection data by the Centers for Medicare and Medicaid Services and other agencies, as well as the inclusion of health care–associated infection data in federal pay-for-performance programs, provides further incentives for hospitals to optimize their health care–associated infection prevention efforts.

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For the General References and other additional features, please visit Elsevier eBooks+ at https://ebooks.health.elsevier.com.

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262 APPROACH TO THE PATIENT WITH SUSPECTED ENTERIC INFECTION

JAMES M. FLECKENSTEIN

DEFINITION

Enteric infections are endemic in many low-income countries but may also be contracted from contaminated food or water in developed countries. Symptoms may range from minimal gastrointestinal distress to life-threatening watery diarrhea or dysentery.

EPIDEMIOLOGY

Worldwide, enteric infections are a leading cause of morbidity. In low- and middle-income countries without access to clean water and basic sanitation, young children are disproportionately affected with acute diarrheal illness and suffer sequelae ranging from malnutrition (Chapter 197) and its complications to dehydration and death. Although infrequently fatal in industrialized regions, enteric infections are ubiquitous ailments with pathogens that know no borders because of international travel to and from hyperendemic regions, as well as the globalization of food supplies. Foodborne outbreaks remain common in the United States, where pathogens are distributed widely in produce or other foods. For example, one of the largest outbreaks of *Salmonella enteritidis*, estimated to involve more than 200,000 people in the United States, resulted from national distribution of contaminated ice cream. Fortunately, many outbreaks can be mitigated when pathogens that are isolated from individual patients undergo molecular profiling by public health laboratories linked to the U.S. Centers for Disease Control and Prevention (CDC).

Etiology

Norovirus is the leading cause of infectious diarrhea in adults worldwide[1] and of enteric infection outbreaks in the United States,[2] but multiple microbial agents can cause enteric infections. Fortunately, the geographic location, exposure history, and clinical presentation often can refine the list of potential causative agents (Table 262-1).[3] For example, a patient who has recently returned from travel to a low-income country with acute watery diarrhea will likely be infected with one of several pathogens associated with traveler's diarrhea (Chapter 265),[4] particularly enterotoxigenic *E. coli*, whereas the onset of bloody diarrhea following consumption of poorly cooked ground beef is likely due to Shiga toxin–producing *E. coli* (Chapter 280). However, it is important to recognize that neither the pathogens nor their epidemiologic associations are static. The dynamic nature of the causes of outbreaks of acute enteric infections is demonstrated by the emergence and international spread of a multidrug-resistant *Shigella* strain (Chapter 285), as well as by a large European outbreak caused by a novel *E. coli* strain that had contaminated raw sprouts and acquired the ability to produce Shiga toxin (Chapter 280).

PATHOBIOLOGY

Enteric infections ultimately reflect the successful interaction of individual pathogens with their human hosts. Pathogens must overcome innate and acquired host defenses while competing with the normal human microbiota to colonize intestinal epithelia. Once established, pathogens may then elaborate toxins or produce virulence factors that promote adhesion and invasion.

Not all hosts are equally susceptible to enteric infections. The use of acid-blocking agents, such as proton pump inhibitors, impairs an important first line of host defense by decreasing gastric acidity, thereby reducing the effective

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A cluster-randomized study found that universal use of gowns and gloves for all patients in ICUs did not reduce the primary outcome of acquisition of either MRSA or vancomycin-resistant enterococci, but did significantly lower the acquisition of MRSA. Thus, the utility of this strategy for preventing pathogen transmission remains uncertain.

Interfacility and Regional Collaboration

Given the frequency with which patients are shared among hospitals and other health care settings within geographic regions and the evidence of interfacility patient transfer as a risk factor of introduction of multidrug-resistant organisms and *C. difficile* into a health care facility, implementation of comprehensive prevention programs in all facilities within a region may be more effective in preventing health care–associated infections and multidrug-resistant organism transmission than implementation of the same interventions in a single health care institution. The establishment of regional infection prevention initiatives offers several potential benefits, including the ability to address the complex epidemiology of health care–associated infections that involve multiple health care facilities (e.g., multidrug-resistant organism acquisition, transmission, and infection) than single-institution interventions and opportunities for collaboration and sharing of information, experiences, and resources. A number of successful regional and national initiatives for the prevention of health care–associated infection, including central line–associated blood stream infection, dialysis-related blood stream infections, MRSA, vancomycin-resistant enterococci, carbapenem-resistant Enterobacteriales, and *C. difficile*, have been described.

Incentives and Penalties

The Centers for Medicare and Medicaid Services Conditions of Participation list specific requirements for infection prevention and control processes in health care facilities that receive its funding. Hospitals found to be deficient in the implementation of the requirements are at risk of losing the funding that they receive from the agency. Similarly, hospital accreditation agencies such as The Joint Commission have established standards for infection prevention programs and periodically survey hospitals to determine if such programs are in place. In addition, public reporting of hospital-specific health care–associated infection data by the Centers for Medicare and Medicaid Services and other agencies, as well as the inclusion of health care–associated infection data in federal pay-for-performance programs, provides further incentives for hospitals to optimize their health care–associated infection prevention efforts.

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262 APPROACH TO THE PATIENT WITH SUSPECTED ENTERIC INFECTION

JAMES M. FLECKENSTEIN

DEFINITION

Enteric infections are endemic in many low-income countries but may also be contracted from contaminated food or water in developed countries. Symptoms may range from minimal gastrointestinal distress to life-threatening watery diarrhea or dysentery.

EPIDEMIOLOGY

Worldwide, enteric infections are a leading cause of morbidity. In low- and middle-income countries without access to clean water and basic sanitation, young children are disproportionately affected with acute diarrheal illness and suffer sequelae ranging from malnutrition (Chapter 197) and its complications to dehydration and death. Although infrequently fatal in industrialized regions, enteric infections are ubiquitous ailments with pathogens that know no borders because of international travel to and from hyperendemic regions, as well as the globalization of food supplies. Foodborne outbreaks remain common in the United States, where pathogens are distributed widely in produce or other foods. For example, one of the largest outbreaks of *Salmonella enteritidis*, estimated to involve more than 200,000 people in the United States, resulted from national distribution of contaminated ice cream. Fortunately, many outbreaks can be mitigated when pathogens that are isolated from individual patients undergo molecular profiling by public health laboratories linked to the U.S. Centers for Disease Control and Prevention (CDC).

Etiology

Norovirus is the leading cause of infectious diarrhea in adults worldwide[1] and of enteric infection outbreaks in the United States,[2] but multiple microbial agents can cause enteric infections. Fortunately, the geographic location, exposure history, and clinical presentation often can refine the list of potential causative agents (Table 262-1).[3] For example, a patient who has recently returned from travel to a low-income country with acute watery diarrhea will likely be infected with one of several pathogens associated with traveler's diarrhea (Chapter 265),[4] particularly enterotoxigenic *E. coli*, whereas the onset of bloody diarrhea following consumption of poorly cooked ground beef is likely due to Shiga toxin–producing *E. coli* (Chapter 280). However, it is important to recognize that neither the pathogens nor their epidemiologic associations are static. The dynamic nature of the causes of outbreaks of acute enteric infections is demonstrated by the emergence and international spread of a multidrug-resistant *Shigella* strain (Chapter 285), as well as by a large European outbreak caused by a novel *E. coli* strain that had contaminated raw sprouts and acquired the ability to produce Shiga toxin (Chapter 280).

PATHOBIOLOGY

Enteric infections ultimately reflect the successful interaction of individual pathogens with their human hosts. Pathogens must overcome innate and acquired host defenses while competing with the normal human microbiota to colonize intestinal epithelia. Once established, pathogens may then elaborate toxins or produce virulence factors that promote adhesion and invasion.

Not all hosts are equally susceptible to enteric infections. The use of acid-blocking agents, such as proton pump inhibitors, impairs an important first line of host defense by decreasing gastric acidity, thereby reducing the effective

ABSTRACT

Enteric infections may manifest as gastroenteritis, secretory diarrhea, bloody diarrhea, or enteric fever. The major cause of foodborne gastroenteritis worldwide is norovirus, but a variety of other viruses, enteric bacteria, and parasites can cause clinical disease. The most common cause of traveler's diarrhea is enterotoxigenic *Escherichia coli*. Bloody or mucoid stools, fever, and cramping abdominal pain should prompt cultures to identify *Shigella*, *Salmonella*, *Campylobacter*, Shiga toxin–producing *E. coli*, and *Yersinia* species. Molecular testing can frequently identify the infectious agent but not its antimicrobial susceptibility. Oral rehydration therapy and antidiarrheal agents are preferred for afebrile patients without bloody stools or severe dehydration, with antibiotic therapy recommended for more severe cases and for traveler's diarrhea when testing is not practical.

KEYWORDS

enteric infection
enteric pathogen
traveler's diarrhea
gastroenteritis
dysentery
infectious diarrhea
norovirus

TABLE 262-1 EPIDEMIOLOGY, UNDERLYING CONDITIONS, AND EXPOSURE HISTORIES RELEVANT TO POTENTIAL ETIOLOGY OF INFECTION

EXPOSURE	LIKELY PATHOGEN(S)
Travel to low- or middle-income countries	Diarrheagenic *E. coli* (ETEC, EAEC, EPEC; Chapter 280), norovirus (Chapter 350), *Campylobacter* (Chapter 279), *Shigella* (Chapter 285), nontyphoidal *Salmonella* (Chapter 284), *Giardia* (Chapter 322), *Cryptosporidia* (Chapter 321), *Entamoeba histolytica* (Chapter 323), *Cyclospora* spp. (Chapter 324), rarely *V. cholerae* (Chapter 278), *Balantidium coli* (Chapter 324).
Daycare	Low-inocula pathogens: Shiga toxin–producing *E. coli* (STEC; Chapter 280), *Shigella* (Chapter 285), *Giardia* (Chapter 322), *Cryptosporidia* (Chapter 321), norovirus (Chapter 350), rotavirus (Chapter 350)
Prior antibiotic use	*Clostridioides difficile* (Chapter 271)
Immunosuppression, including AIDS	Cytomegalovirus (Chapter 347), *Cryptosporidia* (Chapter 321), *Cytoisospora belli* (Chapter 324), *Herpes simplex* virus (Chapter 345), *Mycobacterium avium* complex (Chapter 300), *Histoplasma* (Chapter 308), microsporidia (Chapter 324)
Long-term care, prisons	*C. difficile* (Chapter 271), norovirus (Chapter 350), *Shigella* (Chapter 285), rotavirus (Chapter 350), STEC (Chapter 280), *Giardia* (Chapter 322)
Pet reptiles	*Salmonella* spp. (Chapter 284)
Petting farms, pets	STEC, *Campylobacter* (Chapter 279), *Cryptosporidia* (Chapter 321), *Yersinia* (Chapter 288)
Pigs/pig feces	*Yersinia enterocolitica* (Chapter 288), *Balantidium coli* (Chapter 324)
Hemochromatosis	*Yersinia enterocolitica* (Chapter 288)
Raw shellfish	*Vibrio* spp. (Chapter 278), norovirus (Chapter 350), *Plesiomonas shigelloides* (Chapter 126)
Cruise ship travel	Commonly norovirus (Chapter 350), occasionally ETEC (Chapter 280)
Consumption of untreated fresh water, mountain areas of the United States	*Giardia* (Chapter 322)
Imported fresh produce (particularly raspberries), travel to tropical/semitropical regions	*Cyclospora* spp. (Chapter 324)
Swimming in public pools, waterparks	*Cryptosporidia* (Chapter 321)
Anal contact	*Shigella*, including MDR spp. (Chapter 285); other pathogens such as *E. histolytica* (Chapter 323) spread via fecal-oral contact

AIDS = acquired immunodeficiency syndrome; EAEC = enteroaggregative *E. coli;* EPEC = enteropathogenic *E. coli*; ETEC = enterotoxigenic *E. coli;* MDR = multidrug resistant; STEC = Shiga toxin–producing *E. coli.*

TABLE 262-2 CLINICAL FEATURES OF ENTERIC INFECTIONS

CLINICAL SYNDROME	POTENTIAL PATHOGENIC AGENTS	NOTES
Acute watery diarrhea	Diarrheagenic *E. coli* (Chapter 280), *V. cholerae* (Chapter 278), *Shigella* (Chapter 285), *Salmonella* (Chapter 284), *Campylobacter* (Chapter 279), norovirus (Chapter 350)	Severe cholera-like diarrhea leading to rapid dehydration can be associated with ETEC as well as *V. cholerae* infection.
Bloody diarrhea or passage of multiple small-volume stools with blood/mucus (dysentery)	STEC (Chapter 280), *Shigella* (Chapter 285), *Campylobacter* (Chapter 279), *Entamoebae histolytica* (Chapter 323), *Yersinia enterocolitica* (Chapter 288), noncholera *Vibrio* spp. (Chapter 278), *Salmonella* (Chapter 284), *Plesiomonas shigelloides* (Chapter 126), *Balantidium coli* (Chapter 324)	STEC may progress from acute watery diarrhea to bloody diarrhea over several days.
Predominant vomiting (gastroenteritis)	Norovirus (Chapter 350), preformed enterotoxin syndromes (*Bacillus cereus* [Chapter 272], *Staphylococcus aureus* [Chapter 267])	Preformed toxins typically cause disease with very short incubation periods (within hours of ingestion). Noroviral infections typically resolve within 48-72 hours.
Protracted diarrhea >2 weeks	Giardia (Chapter 322) and other protozoa, occasionally persistent bacterial infections (e.g., EAEC, EPEC, ETEC; Chapter 280), norovirus (Chapter 350) in immunocompromised hosts, helminths (Chapters 326 and 327)	Post-infection syndromes, including irritable bowel syndrome and tropical sprue (Chapter 126), should be considered in the absence of evidence of sustained infection. Brainerd diarrhea, an unexplained but presumably infectious syndrome of protracted diarrhea that follows ingestion of raw milk or untreated water, can cause diarrhea that persists for weeks to months. ETEC can cause illness for >2 weeks.
Acute febrile syndrome	*Listeria monocytogenes* (Chapter 272), *Campylobacter* (Chapter 279), nontyphoidal *Salmonella* (Chapter 284), *Yersinia enterocolitica* (Chapter 288)	Older adults may exhibit fewer symptoms
Predominant febrile illness, abdominal pain	Invasive nontyphoidal *Salmonella* (Chapter 284), enteric fever (Chapter 284)	Enteric fever refers to infections with *Salmonella enterica* serotype Typhi or *S. enterica* serotypes Paratyphi A-C

EAEC = enteroaggregative *Escherichia coli*; EPEC = enteropathogenic *Escherichia coli*; ETEC = enterotoxigenic *Escherichia coli*; STEC = Shiga toxin–producing *Escherichia coli.*

inocula required for bacterial pathogens. Recent prior or concurrent use of antibiotics can alter the normal intestinal microflora, thereby reducing its ability to impair the growth of newly introduced pathogens. Host genetics can also play critical roles in determining the outcome of infection. For instance, *Vibrio cholerae* infections (Chapter 278) tend to be most severe in individuals with O blood group, likely due to more efficient intoxication of O enterocytes with cholera toxin. In contrast, enterotoxigenic *E. coli* infections (Chapter 280) appear to be more severe in individuals who express the A blood group antigen on intestinal epithelia, likely due to an A-specific lectin expressed by these bacteria.

Some pathogens, particularly norovirus (Chapter 350), *Shigella* (Chapter 285), and *Shiga* toxin–producing *E. coli* (Chapter 280), typically require very low inocula to establish infection. This characteristic has contributed to numerous outbreaks of norovirus on cruise ships and a multitude of foodborne outbreaks of Shiga toxin–producing *E. coli* (Chapter 280).

CLINICAL MANIFESTATIONS

Enteric infections can be categorized by the acute clinical presentation (Table 262-2) and/or the associated sequelae that follow the initial infection.

Significant overlap exists in the initial presentation of illness caused by individual pathogens, and essentially all enteric pathogens can initially present with watery diarrheal illness. Progression to bloody diarrhea argues against a viral cause and instead should prompt investigation for invasive bacterial pathogens (e.g., *Shigella* [Chapter 285], Salmonella [Chapter 284], *Yersinia* [Chapter 288], *Campylobacter* [Chapter 279], Shiga toxin–producing *E. coli* [Chapter 280], or amebiasis [Chapter 323]).[5–7] Most patients with Shiga toxin–producing *E. coli* infection will progress to bloody diarrhea within days of onset of diarrhea, and as many as 15% will develop the hemolytic uremic syndrome (Chapter 158).

Vomiting as a predominant symptom suggests organisms typically associated with gastroenteritis, particularly norovirus (Chapter 350) and the syndromes associated with *Staphylococcus aureus* (Chapter 267) and *Bacillus cereus* (Chapter 272) preformed enterotoxins. The latter typically occur after a short incubation period within minutes to hours on the day of ingestion.

Oftentimes, the initial diarrheal episode is self-limited and may not come to the attention of a physician, who may later evaluate the patient for the first time following development of complications related to their infection. These complications may occur while the patient still has gastrointestinal symptoms or after the symptoms have resolved and organisms have disappeared from the stool (Table 262-3).

TABLE 262-3 COMPLICATIONS AND SEQUELAE OF ENTERIC INFECTIONS

SYNDROME	PREDISPOSITION/ASSOCIATED PATHOGEN(S)
Hemolytic uremic syndrome (Chapter 158)	STEC (Chapter 280), occasionally *Shigella dysenteriae* (Chapter 285)
Guillain-Barré syndrome (Chapter 388)	*Campylobacter jejuni* (Chapter 279)
Tropical sprue (Chapter 126)	Typically, in expatriates or those with extended stays in low- to middle-income countries following repeated episodes of diarrhea; unknown/ETEC? (Chapter 280)
Irritable bowel syndrome (Chapter 123)	*Campylobacter* (Chapter 279), *Salmonella* (Chapter 284), *Shigella* (Chapter 285), STEC (Chapter 280), post-traveler's diarrhea (Chapter 265)
Environmental enteropathy (environmental enteric dysfunction)	Children in low- and middle-income countries following *Shigella* (Chapter 285) and ETEC (Chapter 280) infections
Bacteremia, metastatic extraintestinal infection	*Salmonella typhi* and nontyphoidal *Salmonella* spp. (Chapter 284), *Campylobacter* (Chapter 279), *Yersinia* (Chapter 288), *E. histolytica* (Chapter 323)
Intestinal perforation, peritonitis, toxic megacolon	Small intestine, particularly terminal ileum with enteric fever (Chapter 284); *Shigella* (particularly *dysenteriae*) (Chapter 285); *C. difficile* (Chapter 271); *E. histolytica* (Chapter 323); *Balantidium coli* (colon; Chapter 324); *Yersinia* (Chapter 288); rarely *Campylobacter* spp. (Chapter 279)
Pseudoappendicitis (Chapter 128)	*Yersinia pseudotuberculosis* (Chapter 288), *Y. enterocolitica* (Chapter 288)
Reactive arthritis (Chapter 244)/ erythema nodosum	*Campylobacter* (Chapter 279), *Shigella* (Chapter 285), *Yersinia* (Chapter 288), *Salmonella* (Chapter 284)
Meningitis (Chapter 381)	*Listeria* (Chapter 272), *Salmonella* spp. (Chapter 284) in young children

ETEC = enterotoxigenic *Escherichia coli*; STEC = Shiga toxin–producing *Escherichia coli*.

DIAGNOSIS

General Approach

In most circumstances, an acute episode of diarrhea resolves spontaneously before a patient contacts a physician. When a patient does contact a physician, the first diagnostic decision is whether further evaluation is necessary.

Patients who have more severe forms of illness, such as fever, bloody diarrhea, systemic signs of infection, or protracted symptoms, will likely benefit from a specific diagnosis that can direct treatment. For example, bloody diarrhea caused by *Shigella* or amebic dysentery may benefit from antibiotic therapy, whereas antibiotics should not be used in Shiga toxin–producing *E. coli* infections, because they can increase the risk and severity of hemolytic uremic syndrome by accelerating the production of toxin.

Nearly all acute diarrheas are caused by contaminated food or water. Other than diarrhea due to parasitic infection, diarrhea that persists for a month or more is very unlikely to be infectious.

Laboratory Evaluation

Culture-independent molecular stool testing is emerging as a useful diagnostic approach because of its rapidity and ability to diagnose bacterial, viral, and protozoal infection[8,9] and thereby to guide whether empiric antimicrobial therapy is likely to be beneficial. However, these molecular tests do not provide sensitivity data to guide the choice among antibiotics or preserve the organism for subsequent outbreak investigations. In patients who have bloody or mucoid stool, severe diarrhea, or fever, routine stool culture is indicated (Table 262-4; Fig. 262-1) to obtain sensitivity data. Although microscopic stool examination

TABLE 262-4 STUDIES APPLICABLE TO DIAGNOSIS OF ENTERIC INFECTION

DIAGNOSTIC STUDIES	INDICATIONS	COMMENTS
Culture-independent molecular diagnostic tests	Syndromic diagnosis of diarrheal illness	Pros: can potentially detect pathogens that are difficult to diagnose in some clinical microbiology laboratories (e.g., *E. coli* diarrheal pathovars, parasites, and viruses). Cons: fail to preserve isolate for resistance testing or epidemic investigation.
Stool cultures	Bloody mucoid or moderate-severe diarrhea, fever	Most laboratories routinely test only for *Shigella*, *Salmonella*, *Campylobacter*, and STEC. Special culture media are needed for O157:H7 STEC, whereas other STEC require molecular and/or toxin assays. Other *E. coli* pathovars (ETEC, EPEC, EAEC) can be identified only by molecular diagnostics. Chromogenic media are available to distinguish *V. cholerae* and *V. parahaemolyticus* spp.
Blood cultures	Signs of systemic infection, extremes of age, immunocompromised hosts, travel to areas endemic for enteric fever	Sensitivity may be impacted by prior antibiotic use and sample volume.
Ova and parasite examination: (1) Trichrome staining (2) Modified acid-fast staining (*Cyclospora*, *Cystoisospora*, *Cryptosporidia*) (3) EIA for *Giardia*, *Cryptosporidia*	Persistent diarrhea, travel, or other risk factors	As oocyst passage can be intermittent and sparse ≥ 3 specimens collected every other day may be needed. Enterotest string sampling of small intestinal fluid or upper endoscopy with biopsy can be helpful in *Giardia* and other parasitic infections when stool burden is low.
C. difficile toxin A/B testing	Prior antibiotics, chemotherapy, hospitalization	Nucleic acid amplification tests are comparable in sensitivity to "gold standard" toxin neutralization/cytotoxicity assays but also may detect asymptomatic carriage, so they should be used in conjunction with toxin A/B EIA and/or EIA for glutamate dehydrogenase.

EAEC = enteroaggregative *Escherichia coli*; EIA = enzyme immunoassay; EPEC = enteropathogenic *Escherichia coli*; ETEC = enterotoxigenic *Escherichia coli*; STEC = Shiga toxin–producing *Escherichia coli*.

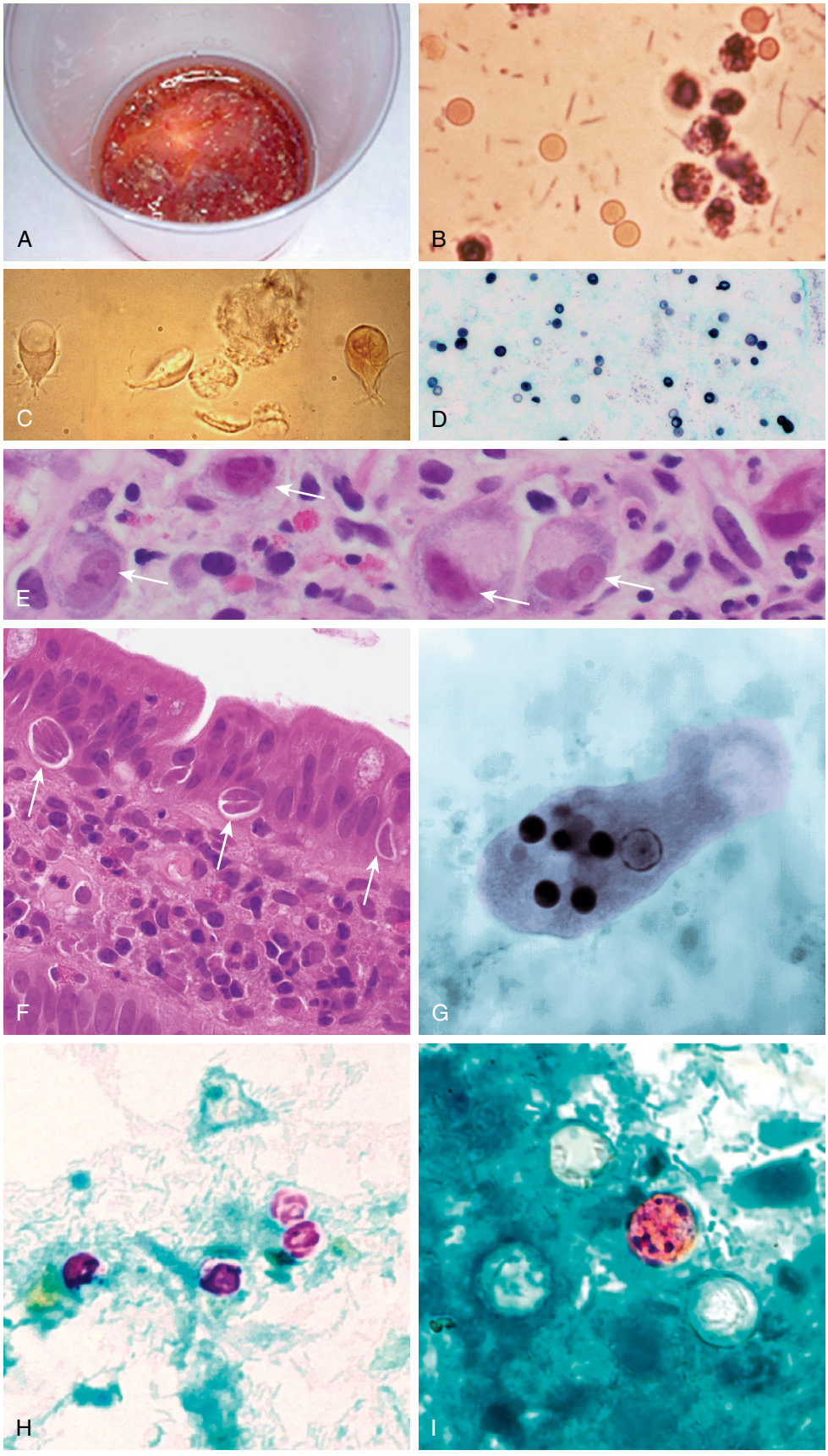

FIGURE 262-1. **Stool evaluation. A,** Dysenteric stool. **B,** Fecal leukocytes and erythrocytes in *Shigella* dysentery. **C,** *Giardia* trophozoites in small intestinal aspirate (iodine stain). **D,** Histoplasma in duodenal biopsy specimen. **E,** Cytomegalovirus-infected cells with typical "owl's eye" inclusion bodies. **F,** *Cystoisospora* oocysts in duodenal enterocytes. **G,** *Entamoeba histolytica* trophozoite with ingested erythrocytes (trichrome). **H,** *Cryptosporidium* oocyst (modified acid-fast). **I,** *Cyclospora* oocyst. (B, C, G, H, and I from the Centers for Disease Control and Prevention Public Health Image Library: https://phil.cdc.gov/default.aspx; D, E, and F courtesy of Drs. Kathleen Byrnes and Samuel Ballentine, Washington University in Saint Louis School of Medicine.)

can detect white blood cells, rapid molecular testing has diminished its utility. In patients who have persistent diarrhea especially related to travel, the stool should be examined microscopically for ova and parasites. Some infections, including cytomegalovirus (Chapter 347), histoplasmosis (Chapter 308), and protozoal infections, can be diagnosed by their appearance on intestinal biopsy specimens, which typically are obtained only in patients who have protracted cases of diarrhea or in patients who have underlying immunosuppression when neither molecular testing nor examination for ova and parasites reveals an etiology.

TABLE 262-5 TREATMENT AND PREVENTION OF INFECTIOUS DIARRHEA AND ENTERIC INFECTION

THERAPEUTIC OPTION	INDICATIONS	AGENTS
1. Rehydration		
A. Oral rehydration therapy	Moderate to severe diarrhea	Oral rehydration solution sachets of preformulated salts and sugars are available commercially (see rehydrate.org). Basic home formulation = ½ teaspoon of salt, 6 level teaspoons of sugar, and 1 liter of clean water. For children in low-income regions, additional zinc sulfate (10 mg/day [children 6 mo]) decreases severity, duration, and recurrence.
B. Intravenous hydration	Severe diarrhea and volume depletion	Ringer lactate or normal saline + oral rehydration solution as tolerated
2. Symptomatic therapies	Mild to moderate watery diarrhea	Loperamide 4 mg × 1, then 2 mg after each unformed stool up to 16 mg (use cautiously; avoid with bloody/mucoid stool or fever) Bismuth subsalicylate 524 mg every 30-60 min as needed, up to eight doses per day
3. Empiric antibiotic therapy	Acute diarrhea	Azithromycin 1-g single dose PO or 500 mg qd × 3 Ciprofloxacin 500 mg PO q12h × 3 days or levofloxacin 500 mg PO q24h × 3
	Traveler's diarrhea	Rifaximin 200 mg PO tid × 3 days (noninvasive disease) Azithromycin 1000 mg PO × 1 Ciprofloxacin 500 mg PO q12h × 3 days or levofloxacin 500 mg PO q24h × 3 (resistance in many areas)

PO = orally; qd = once daily; tid = 3 times daily.

TREATMENT

Treatment must be based on the severity of the clinical disease as well as the patient's underlying conditions.[10] Even for patients who contact a physician, the majority of acute bacterial diarrheal infections will resolve spontaneously without specific antibiotics. Based on the patient's volume status, judicious oral fluid replacement will often suffice. For young infants with moderate-severe diarrheal illness in resource-limited regions and for the frail elderly, oral rehydration solutions (see Table 262-5) are recommended. However, some pathogens, particularly *Vibrio cholerae* (Chapter 278) and enterotoxigenic *E. coli* (Chapter 280), can cause massive diarrhea and rapid volume depletion that require intravenous hydration.

For patients without fever or bloody stools, antimotility drugs such as loperamide initially (adult dose: 4 mg then 2 mg after each unformed stool up to 16 mg/day) can offer symptomatic relief. However, loperamide may prolong or exacerbate the disease, especially in the absence of specific antibiotic treatment. Bismuth subsalicylate (524 mg either in liquid or pill form as needed every 30-60 minutes, not to exceed 4200 mg/day) can reduce symptoms in mild cases of diarrhea and viral gastroenteritis.[A1] Antimotility drugs as well as antibiotics should be avoided in cases of suspected or proven Shiga toxin–producing *E. coli* because of the enhanced risk of hemolytic uremic syndrome.

Probiotics are not useful as treatment.[A2] Given the predominance of viral causes and the self-limited nature of most bacterial infections, antibiotics typically can be reserved for patients who have underlying health conditions or for cases of moderate to severe diarrhea with fever, bloody or mucosal stools, six or more stools in a 24-hour period, or dehydration.[11] Whenever possible, treatment based on the identified organism and its sensitivity is preferred over a purely empiric approach.[12]

PREVENTION

The major strategy to prevent enteric infections is judicious avoidance of potentially contaminated food and drink, careful attention to expiration labels on foods and beverages, and elimination of fecal-oral transmission. For travelers to developing countries (Chapter 265), the admonition that "if you can't boil it, peel it, or heat it, don't eat it" remains sound advice for those venturing to endemic areas where the risk of diarrheal illness is high. Genomic sequencing can identify strains linked to outbreaks, pinpoint the source, and mitigate future risk.[13]

At present, safe and effective vaccines are available for only a limited number of enteric pathogens (see Table 265-2). The oral, live-attenuated vaccine for *V. cholerae* serogroup O1 (Chapter 278) is available for travelers to endemic areas with active cholera transmission, but this vaccine is not recommended for routine travel. A live oral and a parenteral vaccine are available for prevention of typhoid fever (Chapter 284), but neither will prevent all cases. Rotavirus vaccination (Chapter 350), which is licensed for infants beginning at 2 months of age, is more than 90% effective for preventing severe diarrhea.

Passive immunoprophylaxis in the form of encapsulated bovine colostrum antibodies raised against enterotoxigenic *E. coli* is available in the United States as a dietary supplement and may provide partial protection against traveler's diarrhea, but it does not target other pathogens. Antibiotic chemoprophylaxis for traveler's diarrhea (e.g., rifaximin 200 mg twice daily for trips of 2 weeks or less; Chapter 265) is best reserved for patients whose underlying conditions place them at very high risk, such as patients with advanced HIV. Bismuth subsalicylate can be used to prevent traveler's diarrhea, but it requires multiple daily doses and can cause salicylate intoxication, particularly in young children.

TABLE 262-6 NONINFECTIOUS CAUSES OF DIARRHEA

Running	Small bowel bacterial overgrowth
Fecal impaction	Systemic mastocytosis and eosinophilic gastroenteritis
Drugs and laxatives	Tropical sprue
Enteral feeding	Celiac sprue
Irradiation	Dermatitis herpetiformis
Pancreatic insufficiency	Intestinal graft-versus-host disease
Intestinal lymphangiectasia	Thyrotoxicosis
Foods (especially dietetic)	Adrenal insufficiency
Cirrhosis and biliary obstruction	Factitious
Diabetic diarrhea	Inflammatory bowel disease
Alcoholism	Food allergy
Collagenous colitis	Carcinoid
Microscopic colitis	Villous adenoma
VIPoma	Stress with autonomic stimulation
Ischemic bowel disease	
Irritable bowel syndrome	

From Dupont HL, Okhuysen PC. Approach to the patient with suspected enteric infection. In: Goldman L, Schafer AI, eds. *Goldman-Cecil Medicine*. Philadelphia: Elsevier; 2020:1832-1835.

PROGNOSIS

The overwhelming majority of acute infectious diarrhea resolves spontaneously or with short-term treatment. When travelers to low-income countries have persistent symptoms, repeat testing is indicated, especially to exclude persistent parasitic infections (e.g., *Giardia* [Chapter 322], *Cyptosporidium* [Chapter 321]) and bacterial infections (e.g., enteroaggregative *E. coli* [Chapter 280]). For nontravelers, persistent diarrhea should raise the possibility of noninfectious causes (Table 262-6 and Chapter 126), including the onset of inflammatory bowel disease (Chapter 127), gluten-sensitive enteropathy (Chapter 126), or irritable bowel syndrome (Chapter 123).

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263 APPROACH TO THE PATIENT WITH URINARY TRACT INFECTION

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DEFINITIONS

Urinary tract infection (UTI) is bacterial or fungal infection of urine with associated signs or symptoms. The clinical presentation varies from cystitis (bladder or lower tract infection) to pyelonephritis (renal or upper tract infection) and urosepsis (systemic inflammatory response syndrome or septic shock from a urinary source). Asymptomatic bacteriuria is best considered a state of colonization that requires treatment in only specific clinical circumstances. Urethritis caused by *Chlamydia trachomatis*, *Ureaplasma urealyticum* (Chapter 264), or *Neisseria gonorrhoeae* (Chapter 275), as well as prostatitis (Chapter 114) and renal tuberculosis (Chapter 299), are addressed elsewhere in this text.

UTIs should be classified by the site of infection, tendency to recur, and presence or absence of complicating factors. Uncomplicated UTI occurs mainly in women with normal genitourinary tracts. Most uncomplicated UTIs present as cystitis; acute nonobstructive pyelonephritis also occurs in these women but at a lower frequency. Complicated UTI, which is often associated with host factors that facilitate the establishment and persistence of bacteriuria or infection (Table 263-1), typically refers to UTI occurring in patients with functional or structural abnormalities of the urinary tract. Uncomplicated UTI rarely occurs in young men, and any man who presents with a UTI should be assumed to have complicated infection until proven otherwise. Recurrent UTI is typically considered a reinfection when it is caused by a new bacterial strain and a relapse when the same strain that caused preceding infections is isolated, especially when the subsequent infection occurs within 30 days of completing therapy.

EPIDEMIOLOGY

UTI is the most common bacterial infection. It is somewhat more common in boys than in girls in the newborn period because of the higher frequency of urethral malformations in boys. Later in childhood, UTIs are more common in girls, as is asymptomatic bacteriuria. More than half of all healthy women experience at least one symptomatic UTI in their lifetime, and each year, 2 to 10% of women experience at least one episode. The estimated annual rates of outpatient clinical UTI are 5.4/100 person-years based on antibiotic prescriptions and 2.6/100 person-years based on a positive urine culture.[1]

UTI is uncommon in men with a normal genitourinary tract but increases after the age of 65 years, primarily attributable to prostatic hypertrophy and prostatitis (Chapter 114). The frequency of infection in patients with complicating factors varies by the abnormality that promotes infection. For example, patients who have a neurogenic bladder have continuing high rates of infection, but patients whose abnormalities can be corrected will no longer be at an increased risk of infection after the issue is corrected. UTI is also one of the most common hospital-acquired infections; about 80% of these are a consequence of the use of an indwelling bladder catheter. However, many of these "catheter-associated" UTIs are actually asymptomatic bacteriuria detected via unnecessary urine cultures.

Asymptomatic bacteriuria is common. Its prevalence increases from 1 to 2% of schoolgirls to 3 to 5% of sexually active premenopausal women, 10 to 20% of healthy postmenopausal women, and 40 to 50% of elderly women in nursing homes. UTIs are infrequent in men until older ages, with 5 to 10% of elderly men in the community and 35 to 40% of men in nursing homes having bacteriuria. Patients with genitourinary complications also have a very high prevalence of bacteriuria. For example, 50% of patients with a neurogenic bladder and without an indwelling catheter and virtually 100% of patients with chronic indwelling catheters have bacteriuria.

TABLE 263-1 HOST FACTORS ASSOCIATED WITH COMPLICATED URINARY TRACT INFECTION

	EXAMPLES
Obstruction	Urethral or ureteric strictures Tumor Diverticula Pelvicalyceal junction obstruction Prostate enlargement Urolithiasis Extrinsic compression
Functional	Neurogenic bladder Vesicoureteral reflux Anatomic defects Pregnancy Turbulent urethral urine flow Cystocele
Urologic interventions	Urethral or suprapubic catheters Urologic surgery Ureteric stents Nephrostomy tubes Cystoscopy Neobladders
Metabolic or congenital diseases	Urethral valves Polycystic kidneys Nephrocalcinosis Medullary sponge kidney
Immunologic abnormalities	Renal transplantation

PATHOBIOLOGY

Acute uncomplicated UTI follows ascension of normal gut flora, which have colonized the vagina and periurethral mucosa, into the bladder or kidney. The ability of these uropathogenic organisms, usually *Escherichia coli*, to colonize and to persist within the urinary tract is dependent on an array of virulence factors that include adhesins, toxins, and iron-scavenging proteins. Uromodulin, which is the most abundant protein in human urine, forms filaments that antagonize the adhesion of uropathogens and allows their clearance by micturition.[2] The organism's virulence is a major determinant of whether symptomatic infection develops and whether it is manifested as cystitis or pyelonephritis. Bacterial strains that cause uncomplicated infection typically express the FimH adhesin, but this adhesin is not specific for UTI. *E. coli* isolated from uncomplicated pyelonephritis are characterized by the presence of the P fimbria adhesin Gal(α1-4) Galβ disaccharide globoside, which initiates mucosal inflammation. Adherence of organisms in the bladder or kidney activates the innate immune response, thereby leading to release of cytokines, particularly interleukin-6 and interleukin-8, and mobilizes leukocytes. This process results in pyuria as well as local or systemic symptoms, including fever in patients with pyelonephritis.

The occurrence of acute uncomplicated UTI in healthy premenopausal women is determined by both genetic and behavioral factors. A genetic predisposition is supported by observations that a history of prior UTI is consistently one of the strongest associations with recurrent uncomplicated UTI, and women who experience these infections report a higher proportion of first-degree female relatives with recurrent UTI than do those without infection. One established genetic association is being a nonsecretor of the ABH blood group antigen (being unable to secrete blood type antigens into body fluids), with more avid binding of uropathogenic organisms to the vaginal epithelium in nonsecretors. Genetic polymorphisms affecting innate immunity are correlated with increased frequency of infection as well as with specific presentations.

Behavioral risk factors are similar for women for cystitis, pyelonephritis, and asymptomatic bacteriuria. The strongest behavioral factors are sexual intercourse and spermicide use. For sexually active premenopausal women, 75 to 90% of episodes are attributed to intercourse. This association is primarily attributed to ascension of periurethral organisms into the bladder during intercourse, but unprotected vaginal sex may also reduce endogenous anti–*E. coli* activity. The normal lactobacillus flora of the vagina maintains an acid environment that prevents colonization by potential uropathogens, and spermicides suppress this normal flora. Despite popular perceptions, use of oral contraceptives or condoms, postcoital voiding, type of underwear, personal hygiene after voiding or defecating, and taking a bath rather than a shower are not associated with recurrent UTI. Sexual intercourse is not a major contributor to UTI in postmenopausal women, in whom the most important determinants of infection are a history of UTI at a younger age and nonsecretory status (see earlier).

The risk of complicated UTI is determined by the underlying abnormality. Genitourinary abnormalities facilitate infection by increasing the entry of organisms into the bladder, such as via intermittent catheterization or urologic procedures, and the persistence of organisms within the urinary tract because

ABSTRACT

Urinary tract infection (UTI) is the most common bacterial infection, ranging in severity from cystitis to urosepsis. In younger populations UTI is more common in women, but after the age of 65 the difference between sexes narrows. The microbiology of UTI is dominated by gram-negative organisms, although staphylococci, enterococci, and *Candida* species are important exceptions. Urine testing will reveal pyuria and bacteriuria in nearly all patients with UTI; however, both pyuria and bacteriuria can be present in asymptomatic patients, and only symptoms can differentiate UTI from asymptomatic bacteriuria. Other than during pregnancy and prior to urologic procedures, treatment of asymptomatic bacteriuria is not recommended. Treatment of UTI depends on the specific syndrome. Cystitis can be treated with short courses of antimicrobials, including some that achieve high concentrations only in the bladder. More severe infections, such as pyelonephritis and urosepsis, require slightly longer durations of treatment with agents that reach the renal parenchyma and achieve therapeutic levels in the blood. Increasing antimicrobial resistance among gram-negative organisms has made the treatment of UTI more challenging, as has the use of indwelling urinary catheters.

KEYWORDS

urinary tract infection
cystitis
pyelonephritis
asymptomatic bacteriuria
catheter-associated urinary tract infection
urosepsis

of incomplete voiding or their persistence in biofilms on urologic devices. The determinants that promote symptomatic infection rather than asymptomatic colonization are not well characterized. However, obstruction and mucosal trauma with bleeding are well-recognized antecedents for bacteremia and sepsis in patients with preexisting bacteriuria. Although it is generally accepted that patients with diabetes have an increased incidence of UTI, this risk correlates more with long-term complications of diabetes, such as neurogenic bladder, than with the diabetes itself. Patients with poorly controlled diabetes, however, are at risk for more severe manifestations of infection.[3]

Acquisition of bacteriuria in individuals with indwelling urinary devices, including catheters, stents, and nephrostomy tubes, is primarily attributable to the development of biofilms along the device. Biofilms are composed of an extracellular polysaccharide material that is produced by the organisms and that incorporates urine components, including Tamm-Horsfall protein, as well as magnesium or calcium ions. After insertion of the device, a conditioning layer composed of proteins and other host components immediately coats the device. Organisms adhere to this conditioning layer and initiate the formation of biofilm. Colonization usually begins at the urethral orifice or in the drainage bag, and the biofilm then ascends the catheter. Organisms growing in the biofilm persist in an environment relatively protected from antibiotics or host defenses. For patients who have an indwelling catheter, the acquisition of bacteriuria occurs at a rate of 3 to 7% per day. Bacteriuria that follows insertion of an indwelling catheter initially is usually with a single organism, but polymicrobial flora, particularly including *Proteus mirabilis*, is typical in mature biofilms on chronic indwelling devices. *P. mirabilis* strains may produce copious biofilm, and the related production of urease creates an alkaline environment, thereby leading to precipitation of calcium and magnesium ions. The resultant "crystalline biofilm," which is similar to what causes infection-related kidney stones, may obstruct an indwelling catheter. About 80% of episodes of obstructed urinary catheters are attributable to *P. mirabilis*.

Etiology

In all types of UTI, *E. coli* (Chapter 280) is the dominant bacterial species, and it causes up to 85% of all symptomatic UTIs in women with community-acquired infections (Table 263-2).[4] The second most common species causing uncomplicated cystitis is *Staphylococcus saprophyticus*, which is isolated more frequently in later summer and early fall. In patients who have recurrent complicated UTIs, species such as *Enterococcus faecalis* (Chapter 270), *Enterococcus faecium*, *Klebsiella* species (Chapter 281), *Proteus* species (Chapter 281), *Providencia stuartii*, and *Morganella morganii* become more common. In patients with very frequent recurrences or with bladder catheters, particularly patients in hospitals and nursing homes where antimicrobials are frequently used, *E. coli* accounts for less than 50% of UTIs, and patients instead may have infections caused by *Pseudomonas aeruginosa* (Chapter 282), *Acinetobacter baumannii*, *Serratia marcescens*, and *Stenotrophomonas maltophilia* isolated. Urolithiasis attributed to infected stones is associated with urease-producing organisms; the alkaline urine created facilitates struvite formation.[5] Repeated antimicrobial treatment administered to patients with recurrent complicated UTI often leads to increased antimicrobial resistance in the organisms isolated from recurrent infections. In health care facilities, the catheterized urinary tract is the most common site for the isolation of multiple drug–resistant gram-negative organisms, including extended-spectrum β-lactamase–producing and carbapenemase-producing Enterobacteriaceae. *Candida* sp is the most common cause of fungal UTI. Patients with *Candida* UTI often have diabetes or an indwelling urinary catheter, as well as prior exposure to broad-spectrum antimicrobial agents.

TABLE 263-2 MICROBIAL ETIOLOGY OF URINARY TRACT INFECTIONS

ORGANISMS	CLINICAL CHARACTERISTICS
GRAM-NEGATIVE BACTERIA	
Escherichia coli	Typical
Klebsiella pneumoniae	Often reinfection
Enterobacter spp	Often reinfection or health care–associated infection*
Proteus spp	May indicate calculi; frequent with devices
Providencia stuartii	Often reinfection or health care–associated infection*
Morganella morganii	Often reinfection or health care–associated infection*
Serratia marcescens	Often health care–associated infection*
Acinetobacter baumannii	Often health care–associated infection*
Burkholderia spp	Often health care–associated infection*
Pseudomonas aeruginosa	Often health care–associated infection*
Stenotrophomonas maltophilia	Often health care–associated infection*
GRAM-POSITIVE BACTERIA	
Staphylococcus saprophyticus	Most common during late summer and fall
Staphylococcus aureus	May indicate focus outside the genitourinary tract
Enterococcus spp	Often reinfection
Other gram-positive bacteria	In most cases contaminants or colonizers
FUNGI	
Candida spp	May indicate focus outside the genitourinary tract

*Includes hospital and nursing home care.

TABLE 263-3 CLINICAL SYMPTOMS OF URINARY TRACT INFECTIONS

TYPE OF URINARY TRACT INFECTION	TYPICAL SIGNS OR SYMPTOMS
Cystitis	Frequency Dysuria Urgency Stranguria (difficulty in micturition) Suprapubic pain Hematuria
Pyelonephritis	Costovertebral angle pain or tenderness Fever Chills Cystitis symptoms (may be absent)
Urosepsis	Fever Chills, rigors Sepsis syndrome

CLINICAL MANIFESTATIONS

The onset of cystitis is rapid, and symptoms (Table 263-3) usually develop within 24 hours. Clinically, the lack of vaginal discharge can differentiate cystitis from urethritis (Chapter 264) caused by chlamydia, ureaplasma, or gonococci. Women who experience recurrent episodes of acute uncomplicated UTI are more than 90% reliable for self-diagnosis.

Pyelonephritis may also have a rapid onset and may or may not be associated with symptoms of cystitis. Bacteremia occurs in 10 to 30% of patients but does not have prognostic significance. The typical flank pain and tenderness, which result from inflammation and edema of the renal parenchyma, may be masked by the intake of analgesic drugs such as acetaminophen, which may also reduce the fever. An important differential diagnosis is renal calculus (Chapter 111), in which the pain may have a similar location but fever is not present unless the stone is complicated by infection.

Complicated UTI manifests across a clinical spectrum from minimal voiding abnormalities to symptoms consistent with cystitis, pyelonephritis, or severe sepsis. Urosepsis is a life-threatening condition, usually associated with bacteremia. Obstruction, which is more common in men with prostatic hypertrophy (Chapter 114), or trauma to the mucosa from an indwelling catheter or urologic surgery may precipitate bacteremia. Patients who present with urosepsis typically have complicated UTI rather than nonobstructive pyelonephritis. Urosepsis can present with or progress to septic shock (Chapter 94), which requires life-supporting treatment in addition to antibiotics.

DIAGNOSIS

Laboratory Findings

The hallmark of the diagnosis of UTI is demonstration of bacteriuria in a urine sample. A pretherapy urine culture specimen should be obtained for all patients who present with pyelonephritis, urosepsis, or complicated UTI or when the diagnosis is uncertain. Routine culture is not generally recommended for acute uncomplicated cystitis because the clinical presentation is characteristic, and empiric short-course therapy often resolves

symptoms by the time the culture is available. However, frequently recurrent cystitis raises the likelihood of bacterial resistance, so a culture should be obtained in this situation, in patients with an early recurrence post-therapy, and in patients with persistent symptoms despite appropriate empiric antimicrobial therapy.

Urine specimens for culture must be collected before institution of antimicrobial therapy because the urine is rapidly sterilized after initiation of systemic antimicrobials. The usual collection method is a midstream urine sample to limit contamination. For patients with indwelling catheters, specimens should be collected from the catheter port and not from the drainage bag. All specimens should be taken promptly to the laboratory to prevent growth of contaminants during transportation.

The interpretation of the quantitative urine culture varies with the clinical presentation and collection method (Table 263-4). Significant bacteriuria is usually 10^5 CFU/mL or more, where one colony-forming unit (CFU) is one or more bacterial cells forming a colony when growing on an agar plate. In women with symptoms of uncomplicated cystitis, 10^2 CFU/mL or more in midstream urine of *E. coli* or *S. saprophyticus* is consistent with infection. Other gram-positive organisms at any quantitative count should be interpreted as contaminants, except for *Staphylococcus aureus*, which may be identified in the urine owing to renal filtration in patients who have *S. aureus* bacteremia or endocarditis.

Pyuria is present in most patients with symptomatic UTI or asymptomatic bacteriuria. Many other abnormalities are, however, associated with pyuria, and the presence of pyuria does not diagnose infection or differentiate symptomatic from asymptomatic infection. The absence of pyuria has a high negative predictive value to exclude UTI for most patients. However, the absence of pyuria in a urine specimen from a woman with symptoms compatible with cystitis is not an indication to withhold empiric antimicrobial therapy.

For rapid screening for possible bacteriuria, identification of nitrite by dipstick urine testing may be useful, with a sensitivity of about 90%.[6] Gram-negative bacteria, with the exception of *P. aeruginosa*, will metabolize nitrate to nitrite, which can be demonstrated by a color reaction on a dipstick. Gram-positive bacteria and fungi do not metabolize nitrate. The technique is rapid (<1 minute) and inexpensive. It has a high degree of specificity but is insensitive because it does not detect infections caused by gram-positive organisms.

Conversely, some patients with evident pyuria will have negative urine cultures. Infectious causes of sterile pyuria include tuberculosis (Chapter 299), gonorrhea (Chapter 275), chlamydia (Chapter 294), mycoplasma (Chapter 293) and ureaplasma (Chapters 293 and 264), genital herpes (Chapter 345), trichomoniasis (Chapter 324), fungal infections (Chapter 314), and schistosomiasis (Chapter 326).

Blood culture specimens should be obtained in all patients with suspected urosepsis. Patients with acute pyelonephritis, but not those with acute cystitis, have increased serum levels of C-reactive protein.

Imaging

Early imaging should be performed in any patient with urosepsis to identify abnormalities that require immediate source control. The optimal imaging modality is a computed tomography scan with intravenous contrast. Magnetic resonance imaging may not identify gas in tissues or small stones. Ultrasound may provide a rapid examination to exclude significant obstruction.

TABLE 263-4 INTERPRETATION OF THE QUANTITATIVE URINE CULTURE

	QUANTITATIVE BACTERIAL COUNT
Asymptomatic bacteriuria	$\geq 10^5$ CFU/mL in two consecutive specimens for women
Acute uncomplicated cystitis	$\geq 10^2$ CFU/mL of *Escherichia coli* or *Staphylococcus saprophyticus*
Acute uncomplicated pyelonephritis	$\geq 10^4$ CFU/mL (95% have $\geq 10^5$ CFU/mL)
Complicated urinary tract infection	$\geq 10^5$ CFU/mL (lower counts may occur with diuresis)
Intermittent or in and out catheter collection	$\geq 10^2$ CFU/mL
Suprapubic or percutaneous aspiration	Any organisms isolated

CFU = colony-forming unit.

Investigations are also indicated for patients with delayed response or failure to respond to appropriate antimicrobial therapy or with early relapse of pyelonephritis after completion of therapy. Because the optimal management of a complicated urinary infection requires characterization and potential correction of any underlying anatomic abnormalities, selected patients may require imaging studies for the diagnosis of vesicoureteral reflux (Chapter 113) or to characterize differential renal function.

Differential Diagnosis

Clinical manifestations will usually differentiate acute cystitis and acute pyelonephritis (Table 263-5). New-onset frequency, dysuria, and urgency without accompanying vaginal discharge or pain have a positive predictive value of 90% for acute cystitis. The differential diagnosis for women presenting with acute irritative lower tract symptoms includes sexually transmitted infections, vulvovaginal candidiasis, and noninfectious causes such as interstitial cystitis. Some patients who present with only lower tract symptoms may have renal infection, referred to as occult pyelonephritis. Patients with appendicitis (Chapter 128) and cholecystitis (Chapter 141) can present with flank pain similar to right-sided pyelonephritis, and pelvic inflammatory disease (Chapter 264) may be misdiagnosed as urinary infection.

TREATMENT

Treatment depends on the extent of the infection (e.g., cystitis versus pyelonephritis), the presence or absence of underlying anatomic issues, and concerns about urosepsis (Fig. 263-1). Symptomatic UTIs should be treated with antimicrobials to decrease the duration of symptoms and prevent the progression of the infection. For pyelonephritis, another goal is to limit damage to renal tissue. For urosepsis, antimicrobials selected should be excreted renally, so high antimicrobial concentrations are achieved in the renal parenchyma and urine.

Cystitis

Patients with uncomplicated recurrent cystitis usually can be effectively managed with a strategy of empiric early self-treatment (Table 263-6), which usually leads to prompt improvement of symptoms. In other patients or patients who have frequent recurrences, the initial empiric treatment should be modified, as needed, based on the results of culture and sensitivity testing.[7]

In either situation, the shortest effective duration should be prescribed. Trimethoprim, trimethoprim-sulfamethoxazole, fosfomycin, pivmecillinam, and nitrofurantoin are recommended first-line treatments because they are effective with relatively short courses,[8] and their limited effect on normal flora reduces the risk of developing antimicrobial resistance. For an uncomplicated UTI in women, nitrofurantoin (100 mg three times daily for 5 days) is associated with the fewest adverse effects[9] and results in a significantly higher likelihood of clinical and microbiologic resolution at 28 days after completion of therapy compared with a single 3-gram dose of fosfomycin.[A1] Trimethoprim or trimethoprim-sulfamethoxazole should be selected for initial empiric therapy only if the local prevalence of resistance to these agents in community-acquired *E. coli* infections is less than 20%. Fluoroquinolones are not recommended for first-line therapy because of concerns about toxicity and the promotion of resistance. β-Lactam antimicrobials are about 10% less effective than the first-line agents. Nitrofurantoin and oral cephalosporins are preferred therapy for pregnant women because these are safe for the fetus.

For acute symptomatic relief, phenazopyridine (100 mg, 1 to 2 tablets up to three times daily after meals for up to 2 days) is effective. However, it should only be used in conjunction with antibiotics and not with antipyretics, since it can mask the symptoms of the infection. It can stain soft contact lenses and should not be used in patients who are wearing them.

Pyelonephritis

For antimicrobial treatment of pyelonephritis (Table 263-7), the initial decision is whether oral treatment alone will suffice or whether parenteral treatment is needed. Initial empiric intravenous therapy with an aminoglycoside (e.g., gentamicin) is associated with better outcomes and should be considered in areas with high rates of resistance to other antimicrobials.[10] After initial treatment with a parenteral drug, transition to oral treatment that achieves adequate tissue levels (i.e., trimethoprim-sulfamethoxazole, cefixime, or ciprofloxacin but not nitrofurantoin or fosfomycin) is normally possible at 24 to 48 hours if the patient has clinically improved. The recommended treatment time is 7 to 14 days, but 5 to 7 days is adequate for ciprofloxacin or levofloxacin.[A2,A3]

Complicated Urinary Infection

The antimicrobial regimen selected for treatment of complicated UTI should be individualized based on the site of infection, severity of the manifestations, new or presumed infecting organism and susceptibility, tolerance of the patient, and nature of the underlying abnormalities.[11,12] Oral or parenteral therapy is selected on the basis of the presentation and the likelihood of resistant organisms. When

symptoms are mild and not bothersome, it is reasonable to delay the initiation of antimicrobial therapy until results of the urine culture are available to allow optimal selection.

When bothersome or severe symptoms are present, empiric antimicrobial therapy should be initiated promptly. Previous urine culture results from the patient and recent history of antimicrobial exposure are helpful to assess the likelihood of resistant organisms. Options for complicated UTI with severe symptoms include intravenous plazomicin (15 mg/kg once daily) or meropenem (1 g every 8 hours) for 4 to 5 days, followed by sensitivity-guided oral therapy for another 5 to 6 days.[A4] Piperacillin-tazobactam (4.5 g every 8 hours for 7 days) and fosfomycin (6 g every 8 hours for 7 days) are about equally effective.[A5] Other options include meropenem-vaborbactam (2 g/2 g over 3 hours) or piperacillin-tazobactam (4.5 g over 30 minutes) every 8 hours for 4 to 5 days, followed by 5 to 6 days of oral sensitivity-guided therapy.[A6] Plazomicin and meropenem-vaborbactam are particularly useful for highly resistant organisms when treatment options are limited. Nitrofurantoin, either as initial treatment or as continuation after initial intravenous therapy, may be used for episodes of complicated bladder infection but is not effective for renal infection and is contraindicated in individuals with renal failure. Fosfomycin (with dosing adjustments for patients with impaired renal function) can also be used for complicated bladder but not renal infection. The empiric therapy selected should be reassessed after 48 to 72 hours, by which time the urine culture result should be available, so the response to initial therapy can be modified to an agent to which the organism is susceptible, irrespective of the clinical response. Antibiotic prophylaxis to reduce the risk of subsequent symptomatic infection at the time of catheter removal remains controversial.

Asymptomatic Bacteriuria

Evidence supports treatment of asymptomatic bacteriuria before urologic procedures with anticipated trauma to the genitourinary mucosa. There is also evidence supporting treatment of asymptomatic bacteriuria in pregnant women (see Pregnancy).[A7] Otherwise, asymptomatic bacteriuria is increasingly recognized as a major driver of unnecessary use of antimicrobial agents.[I1] For all other populations, including elderly women and men, treatment of asymptomatic bacteriuria has not been associated with improved outcomes but is consistently followed by reinfection with organisms of increasing antimicrobial resistance.

TABLE 263-5 DECISION PROCESS FOR DIAGNOSIS AND TREATMENT OF UPPER (PYELONEPHRITIS) VERSUS LOWER (CYSTITIS) URINARY TRACT INFECTIONS

	CYSTITIS	PYELONEPHRITIS
SIGNS AND SYMPTOMS		
Fever	No	Yes
Dysuria	Yes	May be present
Frequency	Yes	May be present
Flank pain	No	Yes
DIAGNOSIS		
Pyuria	Yes	Yes
Nitrite test result	Normally positive	Normally positive
Bacteriuria	Yes	Yes
C-reactive protein	Normal	Increased
Blood cultures	Negative	Positive in ≈10-30%
TREATMENT		
First line	Short-term oral therapy (Table 263-6)	Oral: fluoroquinolone for 7 days; parenteral: cephalosporin, fluoroquinolone, or aminoglycoside for 7-14 days (Table 263-7)
Second line	Fluoroquinolone for 3 days or cephalosporin for 7 days	Injectable cephalosporin until afebrile, followed by oral step-down for total of 2 weeks
Pregnant women	Nitrofurantoin or cephalosporin for 5-7 days	Injectable cephalosporin until afebrile, followed by oral cephalosporin for 14 days

TABLE 263-6 ANTIMICROBIALS USED TO TREAT CYSTITIS

ANTIMICROBIAL	DOSE* AND DURATION
FIRST-LINE THERAPY	
Trimethoprim	100-150 mg q12h for 3 days
Trimethoprim-sulfamethoxazole	160/800 mg q12 for 3 days or 320/1600 mg single dose
Nitrofurantoin	50-100 mg q8h for 5-7 days
Nitrofurantoin macrocrystals	100 mg bid for 5 days
Fosfomycin trometamol	3-g single dose
Pivmecillinam	400 mg bid for 3-5 days
OTHER	
Amoxicillin-clavulanate	500 mg (amoxicillin dose) q8h for 7 days
Amoxicillin	500 mg tid for 7 days
Cefpodoxime proxetil	100 mg bid for 3 days
Cefuroxime axetil	500 mg bid for 7 days
Cefixime	400 mg/day for 7 days
Ceftibuten	400 mg/day for 5-7 days
Norfloxacin†	400 mg q12h for 7 days
Ciprofloxacin†	250 mg q12h for 3-7 days (500 mg qd extended release)
Levofloxacin†	250-500 mg/day for 3-7 days

*Doses given are for adults with normal renal function. The need to reduce dosages because of renal impairment related to infection in the kidneys, other renal diseases, or advanced age should always be considered.

†The FDA advises that the side effects of fluoroquinolones outweigh their benefits when patients with acute uncomplicated urinary tract infections have other options.

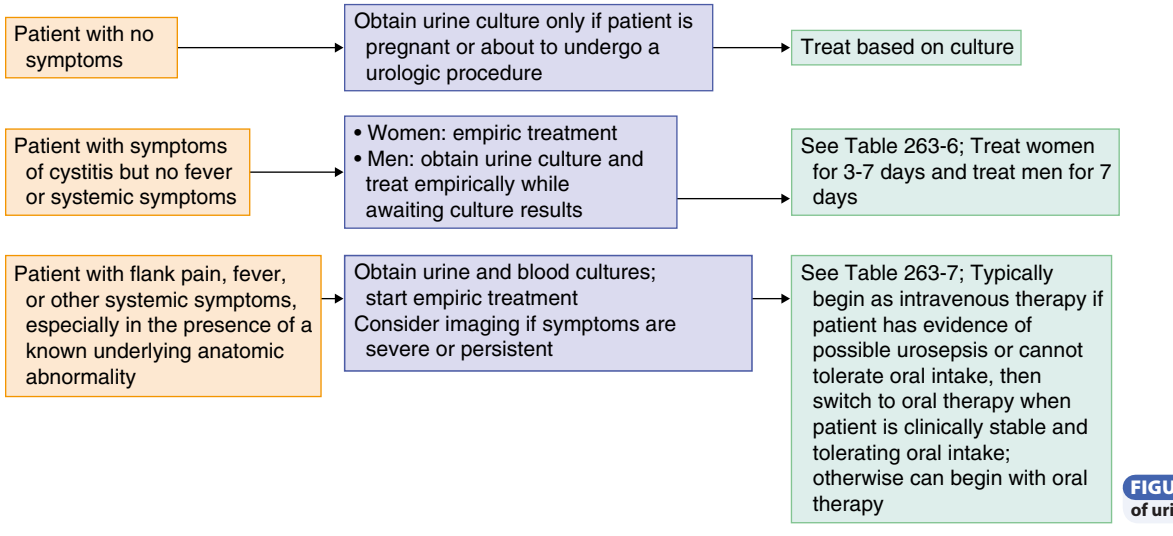

FIGURE 263-1. Approach for treatment of urinary tract infection.

TABLE 263-7 ANTIMICROBIALS USED TO TREAT PYELONEPHRITIS AND UROSEPSIS

ROUTE OF ADMINISTRATION AND ANTIMICROBIAL	DOSE*
PARENTERAL†	
First-Line Therapy	
Piperacillin-tazobactam	3.375 g q6h
Cefepime	2 g q8-12h
Cefotaxime	1 g q8h
Ceftriaxone	1-2 g qd
Ciprofloxacin	400 mg q12h
Levofloxacin	750 mg/day
Other	
Ceftazidime	1 g q8-12h
Ertapenem	1 g qd
Meropenem	500 mg q6h
Doripenem	500 mg q8h
Amikacin	15 mg/kg/day
Gentamicin	4.5 mg/kg/day
Tobramycin	4.5 mg/kg/day
Trimethoprim-sulfamethoxazole	160/800 mg q12h
ORAL	
First-Line Therapy	
Ciprofloxacin	500 mg q12h
Levofloxacin	250-500 mg/day
Other	
Amoxicillin-clavulanate	500 mg (amoxicillin dose) q8h
Cefuroxime axetil	500 mg q12h
Cefixime	400 mg/day
Ceftibuten	400 mg/day

*Doses given are for adults with normal renal function. The need to reduce dosages because of renal impairment should always be considered.

†Parenteral therapy should be converted to oral therapy once clinical stability has been achieved and susceptibility results have returned, which is typically 2-3 days after starting therapy. See text for details on duration of therapy.

In patients with indwelling catheters, bacteriuria should not be treated unless the patient has symptoms attributed to urinary infection. Administration of antimicrobials to catheterized patients with asymptomatic bacteriuria inevitably results in reinfection with more resistant organisms. The optimal treatment for patients with nonspecific symptoms (fatigue, lethargy, poor concentration) and bacteriuria is unknown. Supportive care with observation versus a trial of antimicrobial treatment are potentially valid but unstudied options.

Infections in Elderly Men

Urinary tract infection is the leading cause of bacteremia in older men, almost always in the context of underlying prostate, bladder, or kidney abnormalities, including bacterial prostatitis (Chapter 114). For lower urinary tract infections, initial empiric therapy is the same as for cystitis in women. However, culture-directed antimicrobial therapy is indicated as soon as possible, and antibiotics do not obviate the need for a urologic consultation and a full urologic evaluation, which then guides further therapy. The duration of treatment is typically longer than for women, with 14 days of trimethoprim-sulfamethoxazole or ciprofloxacin being no better than 7 days of the same agent in men without fever.[A8] In men with a febrile UTI, however, 14 days of therapy is slightly better than 7 days, mainly by somewhat reducing the likelihood of a recurrence.[A9] For men without a history of recurrence, the benefits of shorter therapy likely outweigh this small potential benefit.

Urinary Obstruction

Obstruction, whether from a urinary stone, an enlarged prostate, or a malfunctioning catheter, can lead to serious illness if urine is colonized with bacteria. In the setting of an obstructed urinary system, the combination of rising pressure from the obstruction and rapidly multiplying bacteria facilitates systemic infection (e.g., bacteremia and sepsis) unless the urinary system is drained. Drainage can be as simple as placing a temporary urinary catheter or replacing an obstructed catheter. If urologic intervention is unavailable or unable to achieve drainage, percutaneous drainage can be performed by an interventional radiologist. Regardless of the method, drainage should be achieved urgently, and antimicrobial agents for pyelonephritis or urosepsis should be initiated.

Urosepsis

The principles for managing urosepsis are similar to those for patients with severe sepsis from any site (Chapter 94). Parenteral empiric antimicrobial treatment (e.g., piperacillin/tazobactam 3.375 g IV q6h or ceftriaxone 1 to 2 g IV q24 hours) and supportive care should be initiated promptly,[13] but empiric treatment need not routinely include coverage for *Pseudomonas*.[14] The selected antimicrobials should provide broad-spectrum coverage for potential uropathogens, including resistant bacteria. Antimicrobial therapy should be reassessed when urine and blood culture results become available. Similar to pyelonephritis, therapy can be transitioned to the oral route when vital signs have normalized and oral intake is tolerated.

Perinephric Abscess

A perinephric abscess should be suspected in patients who have persistent fever and abdominal discomfort 48 to 72 hours after the initiation of active antimicrobial therapy. A contrast-enhanced CT scan is the preferred imaging modality, but nonenhanced CT, ultrasound, and MRI are alternatives in the setting of renal failure. If a perinephric abscess is identified, effective drainage is the mainstay of treatment. Most abscesses can be safely and effectively drained by an interventional radiologist, but loculated abscesses or abscesses that are difficult to access may require open surgical drainage.

Funguria

Funguria should be treated only when accompanied by symptoms of UTI.[15] Symptomatic infection is treated with fluconazole 400 mg once daily for 1 day, followed by 200 mg once daily for 7 to 14 days. If *Candida* sp resistant to fluconazole is isolated, liposomal amphotericin is the recommended alternative therapy because other antifungals have limited renal excretion. An infectious diseases expert should guide dosing, which can vary by product. The optimal duration of therapy is uncertain, but 7 to 10 days of amphotericin is usually suggested.

Follow-up

Patients do not require follow-up urine cultures unless symptomatic infection persists or recurs. If the patient develops an early (<30 days) recurrence, urine culture and sensitivity analysis is needed to ensure that appropriate antimicrobial therapy can be prescribed. If patients require empiric treatment while awaiting these results, a regimen should be selected based on the most recently available urine culture.

TABLE 263-8 PROPHYLACTIC REGIMENS TO PREVENT RECURRENT URINARY TRACT INFECTION IN WOMEN

PREFERRED	OTHER
Long-term low dose Nitrofurantoin 50 mg od or 100 mg daily Trimethoprim-sulfamethoxazole, 40/200 mg daily or every other day	Cephalexin 250-500 mg daily* Norfloxacin 200 mg daily Ciprofloxacin 125 mg daily
Postcoital (single dose) Nitrofurantoin 50 or 100 mg* Trimethoprim-sulfamethoxazole 40/200 mg Trimethoprim 100 mg	Cephalexin 250 mg* Ciprofloxacin 125 mg Norfloxacin 200 mg

*Suitable for use in pregnancy.

PREVENTION

Screening

Since asymptomatic bacteriuria should be treated only in selected circumstances (see earlier), routine screening for asymptomatic bacteriuria is not recommended.[16]

Recurrent Uncomplicated UTI

Premenopausal women with recurrent acute uncomplicated UTI should avoid the use of spermicides and may benefit from increasing their daily water intake to more than 1.5 L/day.[A10] Prophylactic D-mannose (420 mg to 2 g over the counter) can be considered, particularly if *E. coli* is the organism that is repeatedly isolated.[A11] For women with frequent recurrent acute uncomplicated UTI (more than two in 6 months or three in 12 months) presenting as cystitis or pyelonephritis, prophylactic antimicrobial therapy is effective, either as long-term low-dose prophylaxis[A12] or as postcoital prophylaxis (Table 263-8). The use of cranberry tablets or juice does not reliably decrease bacteriuria[A13]

or the frequency of recurrent infection, and probiotics are not effective. For postmenopausal women, topical vaginal estrogens can be tried to decrease the frequency of infection, but postcoital antibiotics are more effective for women with frequent recurrences.[17] Systemic estrogen therapy, however, is not associated with a decreased frequency of UTI, and it generally should be avoided in women with frequent recurrences.

Pregnancy

Current recommendations suggest pregnant women should be screened for asymptomatic bacteriuria early in the pregnancy, usually at 12 or 16 weeks.[18] If bacteriuria is present, these women should be treated and have subsequent follow-up culture specimens obtained monthly. If either asymptomatic colonization or recurrent infection occurs, prophylactic antimicrobial therapy with either cephalexin or nitrofurantoin should be considered through the duration of the pregnancy to decrease the risk of pyelonephritis in later pregnancy.[19]

Prior Complicated UTI

Prophylactic antimicrobial therapy has not been shown to be effective for patients with complicated UTI, including patients with spinal cord injury or with chronic indwelling catheters. In these patients, the abnormality leading to impaired voiding means that bacteriuria is unavoidable, and antimicrobial therapy will promote bacteriuria with increasingly resistant organisms. For patients with recurrent UTIs and a neurogenic bladder after spinal cord injury, however, limited data suggest that cyclic antibiotics (the alternate weekly use of two different antibiotics) may be efficacious without promoting antibiotic resistance.[A14]

Infection Control

Infection control programs of health care facilities (Chapter 261) should include practices to prevent catheter-associated UTI.[20] Evidence-based guidelines provide clear recommendations, including ongoing surveillance. The most important intervention is to avoid the use of an indwelling catheter wherever possible and, when there are clear indications for catheter use, to limit the duration to as short a time as possible. Meatal cleaning with chlorhexidine solution before catheter insertion can decrease the incidence of catheter-associated asymptomatic bacteriuria and UTIs.[A15] For adults who require intermittent self-catheterization, continuous antibiotic prophylaxis can reduce recurrent UTIs but at the risk of developing resistant organisms.[A16] The future development of biofilm-resistant materials may help reduce the problem of catheter-associated UTI.

PROGNOSIS

The prognosis of uncomplicated cystitis and pyelonephritis is good. Women with acute uncomplicated cystitis do not receive antimicrobial therapy, and symptoms will usually resolve by 1 to 2 weeks. Women with very frequent recurrent, acute uncomplicated UTI experience no long-term adverse outcomes, such as renal impairment or hypertension. A small proportion of women with severe presentations of acute nonobstructive pyelonephritis develop renal scars, but these are not associated with impaired renal function. Whether men also develop such scars is unknown. Patients with frequent recurrent complicated UTI may experience substantial morbidity with recurrent infections, but poor long-term medical outcomes are usually determined by the underlying abnormality rather than by infection. A perinephric abscess generally is cured by appropriate therapy and is not associated with long-term sequelae. Patients with urosepsis have a fatality rate of about 10%. Factors increasing the risk of death are advanced age and significant underlying diseases, as well as inadequate initial antimicrobial treatment.

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264 APPROACH TO THE PATIENT WITH A SEXUALLY TRANSMITTED INFECTION

HEIDI SWYGARD AND MYRON S. COHEN

SEXUALLY TRANSMITTED INFECTIONS

DEFINITION

Sexually transmitted infections (STIs) include a wide variety of organisms that are transmitted through intimate contact involving skin or mucosal surfaces of the oropharynx, vagina, penis, and rectum.[1] STIs can generally be divided into five broad categories (syndromes): urethritis, genital ulcers, epithelial cell disorders, vaginal discharge, and ectoparasites (Table 264-1). Gender inclusive models (Chapter 215) and programs of care are recommended for all persons who would benefit from such services.

EPIDEMIOLOGY

The interaction between the host and the sexually transmitted pathogen plays a critical role, and characteristic tissue changes offer clues about etiology. Several sexually transmitted pathogens cause local inflammation only (*Neisseria gonorrhoeae*, *Chlamydia trachomatis*, *Trichomonas vaginalis*), with the potential for local tissue invasion (*N. gonorrhoeae*, *C. trachomatis*) or systemic dissemination (*N. gonorrhoeae*). Some sexually transmitted pathogens cause tissue ulceration (*Treponema pallidum*, *Haemophilus ducreyi*, herpes simplex viruses 1 and 2, *Klebsiella granulomatis*). Human papillomaviruses cause epithelial cell changes and predispose to neoplasm. Several sexually transmitted pathogens (human immunodeficiency virus [HIV], hepatitis B and C viruses, cytomegalovirus) routinely enter through the genital tract without causing any local changes.

Other important systemic diseases that can be acquired through sexual transmission include Zika virus, Ebola virus, Lassa fever, and monkeypox (Chapters 343, 351, and 352). Although these infections can present with genital cutaneous lesions that can be confused with herpes simplex virus, they can cause systemic signs and symptoms that can be fatal.

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264 APPROACH TO THE PATIENT WITH A SEXUALLY TRANSMITTED INFECTION

HEIDI SWYGARD AND MYRON S. COHEN

SEXUALLY TRANSMITTED INFECTIONS

DEFINITION

Sexually transmitted infections (STIs) include a wide variety of organisms that are transmitted through intimate contact involving skin or mucosal surfaces of the oropharynx, vagina, penis, and rectum.[1] STIs can generally be divided into five broad categories (syndromes): urethritis, genital ulcers, epithelial cell disorders, vaginal discharge, and ectoparasites (Table 264-1). Gender inclusive models (Chapter 215) and programs of care are recommended for all persons who would benefit from such services.

EPIDEMIOLOGY

The interaction between the host and the sexually transmitted pathogen plays a critical role, and characteristic tissue changes offer clues about etiology. Several sexually transmitted pathogens cause local inflammation only (*Neisseria gonorrhoeae*, *Chlamydia trachomatis*, *Trichomonas vaginalis*), with the potential for local tissue invasion (*N. gonorrhoeae*, *C. trachomatis*) or systemic dissemination (*N. gonorrhoeae*). Some sexually transmitted pathogens cause tissue ulceration (*Treponema pallidum*, *Haemophilus ducreyi*, herpes simplex viruses 1 and 2, *Klebsiella granulomatis*). Human papillomaviruses cause epithelial cell changes and predispose to neoplasm. Several sexually transmitted pathogens (human immunodeficiency virus [HIV], hepatitis B and C viruses, cytomegalovirus) routinely enter through the genital tract without causing any local changes.

Other important systemic diseases that can be acquired through sexual transmission include Zika virus, Ebola virus, Lassa fever, and monkeypox (Chapters 343, 351, and 352). Although these infections can present with genital cutaneous lesions that can be confused with herpes simplex virus, they can cause systemic signs and symptoms that can be fatal.

ABSTRACT

Sexually transmitted infections (STIs) include a wide variety of organisms that are transmitted through intimate contact involving skin or mucosal surfaces of the oropharynx, vagina, penis, and rectum and are among the most common infections worldwide. Many infections are subclinical and are generally transmissible whether they are symptomatic or asymptomatic. STIs play an important role in HIV transmission and remain an important public health challenge.

KEYWORDS

STI
HIV
syphilis
gonorrhea
chlamydia

TABLE 264-1 SYNDROMES OF SEXUALLY TRANSMITTED DISEASES

SYNDROME	ORGANISM
URETHRITIS	
Gonococcal	*Neisseria gonorrhoeae* (Chapter 275)
Nongonococcal	*Chlamydia trachomatis* (Chapter 294) *Trichomonas vaginalis* (Chapter 324) *Mycoplasma genitalium* (Chapter 293) *Ureaplasma urealyticum* (Chapter 293) *Neisseria meningitidis* (Chapter 274) Herpes simplex (primary infection, Chapter 345)
GENITAL ULCERS	
Genital herpes	Herpes simplex (Chapter 345)
Syphilis	*Treponema pallidum* (Chapter 295)
Chancroid	*Haemophilus ducreyi* (Chapter 276)
Granuloma inguinale (donovanosis)	*Klebsiella granulomatis* (Chapter 292)
Lymphogranuloma venereum	*Chlamydia trachomatis* (serovars L1, L2, or L3)
EPITHELIAL CELL INFECTIONS	
Genital warts	Human papillomavirus (Chapter 344)
Cervical neoplasia	Human papillomavirus types 16 and 18 (Chapter 344)
Molluscum	*Molluscum contagiosum* (Chapter 343)
FEMALE GENITAL DISCHARGE	
Bacterial vaginosis	*Gardnerella vaginalis*, anaerobes (Chapter 273)
Vaginitis	*Trichomonas vaginalis* (Chapter 324) *Candida albicans* (Chapter 310)
Cervicitis	*Neisseria gonorrhoeae* (Chapter 275) *Chlamydia trachomatis* (Chapter 294) *Trichomonas vaginalis* (Chapter 324) Herpes simplex (Chapter 345)
Pelvic inflammatory disease	*Neisseria gonorrhoeae* (Chapter 275) *Chlamydia trachomatis* (Chapter 294)
ECTOPARASITES	
Pubic lice	*Pthirus pubis*
Scabies	*Sarcoptes scabiei*

Sexually transmitted infections are among the most common infections worldwide, but most are never reported. The World Health Organization (WHO) estimates that nearly 1 million people worldwide become infected every day with any of four curable sexually transmitted infections: chlamydia, gonorrhea, syphilis, and trichomoniasis. Each year, an estimated 2.5 million incident cases of gonorrhea, chlamydia, and syphilis are reported in the United States alone.[2] However, the total estimated number of cases of all sexually transmitted infections is likely much greater because of under-reporting and because many infections are subclinical and may escape detection. Sexually transmitted infections are generally transmissible whether they are symptomatic or asymptomatic.

Despite efforts to control the epidemic of sexually transmitted infections, the numbers of new infections continue to grow. This epidemic disproportionately impacts specific populations and geographies, sometimes leading to long-term health consequences such as infertility, poor birth outcomes, cancer, and HIV infection. In the United States, social determinants of health contribute to an unequal burden of sexually transmitted infections in Black, American Indian/Alaska Native, and Latinx communities (Chapter 4).

Chlamydia (Chapter 294), gonorrhea (Chapter 275), and syphilis (Chapter 295) are reportable to the U.S. Centers for Disease Control and Prevention (CDC). Overall, primary and secondary syphilis rates have increased every year since 2000 and increased by 6.8% from 2019 to 2020. Although rates of syphilis are lower among women compared with men, rates in women have increased nearly 150% from 2016 to 2020, and rates of congenital syphilis increased by 250% during that time period. Men who have sex with men account for almost 60% of syphilis cases among men. For gonorrhea, the overall rate is about 150 cases per 100,000 population among women and 225 cases per 100,000 in men, but rates in men and women ages 20 to 24 years are closer to 750 cases per 100,000.

Emerging pathogens also must be considered in certain groups of patients. Some of these pathogens are asymptomatic but are of public health significance (e.g., Ebola [Chapter 351], Zika [Chapter 352] viruses in genital secretions), whereas others represent relatively newly recognized pathogens (e.g., *Neisseria meningitidis* urethritis [Chapter 274] and monkeypox [Chapter 343]).[3]

Seroprevalence data and national surveys suggest a high burden of viral sexually transmitted infections. Antibodies to herpes simplex virus 2 (HSV-2) are found in the serum of about 12% of the population (ages 14 to 49 years), with seropositivity more frequent in non-Hispanic Black Americans (about 35%) compared with non-Hispanic Whites (about 8%), and in women (about 16%) compared with men (about 8%).

The severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) pandemic significantly impacted the availability of services for patients who have sexually transmitted infections, especially in urban settings. The longer-term ramifications of missed opportunities for screening and intervention remain to be seen.

The spread of sexually transmitted infections depends on the organism, the host, the length of time an infected person remains contagious, and the number of people exposed. These parameters can be summarized as:

$$R_o = B \times D \times C$$

where R_o is the basic reproductive rate of an infection, or the mean number of secondary cases a typical single infected person will cause in a population; B is the efficiency of transmission; D is the duration of infectiousness; and C is the number of sexual partners.

PATHOBIOLOGY

Sexually transmitted pathogens depend entirely on human-human transmission, although *T. vaginalis* may have some inanimate sources. The efficiency of transmission reflects the infectiousness of the index case (which depends on the concentration and phenotype of the organism in the genital tract) and the susceptibility of the sexual partner (which reflects the resistance of the host, whether it is hereditary, acquired, or innate). Because immunity to STIs is rare, reinfections are common, and vaccines have been developed only for hepatitis A, hepatitis B, and human papillomavirus.

Each sexually transmitted organism produces a characteristic syndrome because each pathogen has a proclivity for one or more tissues and, when symptomatic, can evoke a predictable inflammatory response. For example, gonococci (Chapter 275) that infect the male urethra generally produce an intense neutrophilic response that leads to a purulent discharge and pain with urination, whereas *C. trachomatis* (Chapter 294) is less likely to produce such a response in the same tissue and is more likely to produce a mild, watery discharge or no symptoms at all.

Because sexually transmitted infections are more prevalent in certain geographies and populations, coinfections are common. Detection of one sexually transmitted organism should lead to other tests. Sexually transmitted pathogens also can be synergistic: for example, sexually transmitted infections also contribute to the acquisition and transmission of HIV and hamper efforts to prevent its transmission. Genital ulcers disrupt the genital mucosal epithelium and allow the entry of HIV. Inflammation caused by ulceration recruits macrophages and lymphocytes, thereby increasing the number of target cells for HIV and the number of receptors per cell. Sexually transmitted infections also can increase the HIV viral load in genital secretions, including semen and vaginal secretions, thereby contributing to a greater risk of transmitting HIV.[4]

DIAGNOSIS

Syndromic Strategies

The syndromic approach focuses on diagnosis based on signs and symptoms, followed by empiric treatment of the index case and concomitant treatment of sexual partners. The syndromic approach is particularly critical in resource-constrained countries or wherever laboratory tests are not available or their cost is prohibitive. In the United States, microbiologic diagnosis is preferred because it confirms the choice of empiric therapy or redirects subsequent care; permits the detection and monitoring of resistance to treatment; and enables specific diagnoses to be reported to public health authorities, as is required by state law for many sexually transmitted infections.

Newer point of care nucleic acid amplification tests (NAATs) for sexually transmitted infections allow diagnosis and treatment for some syndromes (e.g., vaginitis)[5] and specific infections (e.g., gonorrhea and chlamydia) at the same outpatient visit. However, when test results are not available at the same visit, the most appropriate syndromic treatment should be provided empirically at the point of care to resolve the infection and to reduce subsequent transmission.

The diagnosis of a sexually transmitted infection suggests condomless intercourse and serves as a marker for potential HIV infection. Any person undergoing evaluation or treatment for an STI should be tested for HIV infection, because early diagnosis (Chapter 355) and treatment (Chapter 357) of HIV infection has major personal and public health benefits, including reducing secondary HIV transmission.[A1]

TREATMENT

General Approach

Although most sexually transmitted infections are self-limited and readily treated, the comprehensive and proper management of the patient with a sexually transmitted infection requires considerable skill. First, the correct syndrome must be recognized, and a decision about specific diagnostic tests must be made. Second, empiric therapy must be provided and must be sufficiently broad to promise cure or reduced duration of illness. Third, the clinician is obligated to search for other sexually transmitted infections of public health or personal significance. Fourth, the clinician must deal with the patient's sexual partners, through either referral or expedited partner therapy. Fifth, the patient needs counseling and adjunctive preventive measures, where appropriate. Such measures might include vaccination for hepatitis A, hepatitis B, or human papillomavirus or antimicrobials to prevent another sexually transmitted infection, such as incubating syphilis or HIV infection.

SEXUALLY TRANSMITTED INFECTION SYNDROMES

Urethritis

CLINICAL MANIFESTATIONS AND DIAGNOSIS

Urethritis is characterized by some combination of urethral discharge and dysuria, but prostatitis (Chapter 114) can cause similar complaints. Women with urethritis typically have some combination of dysuria and pyuria, which must be differentiated from bacterial cystitis (Chapter 263).

Urethritis is diagnosed when one or more of the following are demonstrated: (1) mucopurulent or purulent urethral discharge, (2) Gram stain of urethral secretions demonstrating two or more leukocytes per oil immersion microscopic field, (3) positive leukocyte esterase test result on first-void urine, or (4) microscopic examination of first-void urine demonstrating 10 or more leukocytes per high-power field. If no urethral discharge can be expressed from the urethral meatus, a calcium alginate swab can be inserted 5 mm into the urethra; the material collected is transferred to a slide by rolling the swab along the glass.

Urethritis is caused by a limited group of pathogens (see Table 264-1) that may be difficult to visualize microscopically or to grow in culture. Nevertheless, specific diagnosis may enhance the management of sexual partners, and the results from such tests should be reported to the health department.

A Gram stain of urethral discharge is a simple and rapid diagnostic test to document both urethritis and possible gonococcal infection (Chapter 275), which is characterized by the detection of leukocytes containing intracellular gram-negative diplococci (Fig. 275-1). Because confirmation of gonococcal urethritis does not exclude concomitant infection with *Chlamydia* or *Mycoplasma*, NAATs, which are highly sensitive and specific for the detection of these and other organisms, are routinely performed on the urethral discharge owing to the high probability of coinfection. However, clinicians should use caution in relying solely on NAATs for diagnosing gonorrhea because it does not always identify other sexually transmitted *Neisseria* species, such as *Neisseria meningitidis*.

Nucleic acid amplification tests for gonorrhea, *Chlamydia*, and *Trichomonas* also can be applied to first-void urine samples (the meatus is intentionally not cleaned so that the urine is contaminated with these organisms), urethral swab material, or vaginal swab material.[6] Extra-genital (e.g., rectal and throat swabs) NAATs are recommended for men who have sex with men or women with reported exposures, since urine-based and cervicovaginal testing alone can miss a large proportion of infected individuals.[7]

TREATMENT

In practice, patients and (in most cases) sexual partners must be treated with empiric therapy to cover the spectrum of potentially causative organisms before the results of definitive tests are available. This empiric treatment should be initiated as soon as possible after the clinical diagnosis and should be directly observed if feasible (Table 264-2).[8,9] Doxycycline appears to be more effective than azithromycin for nongonococcal urethritis and is now the preferred treatment for chlamydia because of the increasing resistance of other concomitant infections (e.g., gonorrhea and *M. genitalium*) to macrolides.

If NAAT results suggest that empiric therapy is unlikely to be successful or if the patient fails to respond to empiric therapy, the antibiotic regimen must be adjusted. For *M. genitalium*, persistent or recurrent urethritis should be treated with moxifloxacin for 7 days. *T. vaginalis*, which also should be considered in the setting of treatment failure, is susceptible to metronidazole or tinidazole. Because treatment for urinary tract pathogens (Table 263-6) may also resolve sexually transmitted urethritis, the clinician who is treating a presumed bladder infection should consider a possible sexually transmitted infection as well.

For presumed sexually transmitted proctitis, the recommended empiric treatment is ceftriaxone (500 mg IM once) plus doxycycline (100 mg orally twice daily for 7 days). For presumed sexually transmitted epididymitis, ceftriaxone (500 mg IM once) plus doxycycline (100 mg orally twice daily for 10 days) is recommended in heterosexual men, but ceftriaxone (500 mg IM once) plus levofloxacin (500 mg orally daily for 10 days) is preferred in men with suspected epididymitis due to enteric pathogens.

TABLE 264-2 SYNDROMIC TREATMENT OF URETHRITIS

GONOCOCCAL*
Recommended
Ceftriaxone 500 mg injected intramuscularly once, *and* (if chlamydia has not been excluded) doxycycline 100 mg orally twice daily for 7 days (for persons weighing >150 kg, the ceftriaxone dose should be 1 g)
NONGONOCOCCAL
Recommended
Doxycycline 100 mg orally twice daily for 7 days
Alternative
Azithromycin 1 g orally as a single dose; or 500 mg orally as a single dose followed by 250 mg orally daily for 4 days
Recurrent or Persistent
If azithromycin was used for initial episode: moxifloxacin 400 mg orally once daily for 7 days If doxycycline was used for initial episode: azithromycin 1 g orally (single dose) *PLUS* For men who have sex with women who live in areas where *T. vaginalis* is highly prevalent: Metronidazole 2 g orally (single dose) *or* Tinidazole 2 g orally (single dose)

*Uncomplicated anorectal and genital disease.

GENITAL ULCERS

In the United States, HSV-1 and HSV-2 (Chapter 345) and *T. pallidum* are responsible for virtually all genital ulcers, and HSV-1 and HSV-2 are by far the most common cause.

GENITAL HERPES

Genital herpes (Chapter 345), which usually develops after an incubation period of less than 21 days, arises as clustered vesicles on an erythematous base. The vesicles become pustular and then rupture to form shallow, painful ulcers that may coalesce. The ulcers heal by crusting over, and the process is usually completed 2 to 3 weeks after the initial lesions appear. In the recent monkeypox outbreak, the lesions were initially confused with the vesicles of herpes simplex virus. Recurrences proceed through the same stages but generally persist only about 5 to 7 days. The first (incident) episode of HSV-2 infection may be accompanied by systemic signs and symptoms including fever and headache, the latter reflecting the spread of HSV to the central nervous system. HSV-2 can cause recurrent meningitis that may occur coincident with reactivation of the genital lesions.

About 20% of infected individuals manifest the classic genital presentation, 60% have mild and atypical signs and symptoms, and the remaining 20% are completely asymptomatic. Viral shedding occurs more often in symptomatic individuals (20% of days) compared with asymptomatic individuals (10% of days), thereby posing an ongoing risk to sexual partners. Nucleic acid testing of swabs of lesions has a 97% sensitivity for detecting herpes virus.[10] However, serologic screening for genital herpes is associated with a high rate of false-positive test results and potential psychosocial harms. Treatment with antiviral medications can shorten the duration of symptoms and may be helpful for

TABLE 264-3 TREATMENT FOR GENITAL ULCERS

GENITAL HERPES
First Episode
Acyclovir 400 mg orally 3 times/day for 7-10 days *or* Famciclovir 250 mg orally 3 times/day for 7-10 days *or* Valacyclovir 1 g orally 2 times/day for 7-10 days (Treatment can be extended if healing is incomplete after 10 days of therapy.)
Recurrent Episodes of HSV-2
Acyclovir 800 mg orally 2 times/day for 5 days *or* Acyclovir 800 mg orally 3 times/day for 2 days *or* Famciclovir 1 g orally 2 times/day for 1 day *or* Famciclovir 500 mg orally once, followed by 250 mg 2 times/day for 2 days *or* Famciclovir 125 mg 2 times/day for 5 days *or* Valacyclovir 500 mg orally 2 times/day for 3 days *or* Valacyclovir 1 g orally once daily for 5 days
Chronic Suppression of HSV-2
Acyclovir 400 mg orally 2 times/day *or* Valacyclovir 500 mg orally once a day *or* Valacyclovir 1 g orally once a day *or* Famciclovir 250 mg orally 2 times/day
SYPHILIS
Primary or Secondary
Benzathine penicillin G 2.4 million units IM in a single dose
Latent
Early latent syphilis: Benzathine penicillin G 2.4 million units IM in a single dose *Late latent syphilis:* Benzathine penicillin G 7.2 million units total, administered as 3 doses of 2.4 million units IM each at 1-week intervals
LYMPHOGRANULOMA VENEREUM
Doxycycline 100 mg orally 2 times/day for 21 days
Alternative Regimens
Azithromycin 1 g orally once weekly for 3 weeks *or* Erythromycin base 500 mg orally 4 times/day for 21 days
CHANCROID
Azithromycin 1 g orally in a single dose *or* Ceftriaxone 250 mg IM in a single dose *or* Ciprofloxacin 500 mg orally 2 times/days for 3 days *or* Erythromycin base 500 mg orally 3 times/day for 7 days
GRANULOMA INGUINALE (DONOVANOSIS)
Azithromycin 1 g orally once weekly or 500 mg daily for >3 weeks and until all lesions have completely healed
Alternative Regimens
Doxycycline 100 mg orally 2 times/day for at least 3 weeks and until all lesions have completely healed *or* Erythromycin base 500 mg orally 4 times/day for >3 weeks and until all lesions have completely healed *or* Trimethoprim-sulfamethoxazole one double-strength (160 mg/800 mg) tablet orally 2 times/day for >3 weeks and until all lesions have completely healed

HSV = herpes simplex virus; IM = intramuscular.
Source: https://www.cdc.gov/std/treatment-guidelines/STI-Guidelines-2021.pdf.

preventing recurrence of HSV-2 (Table 264-3). Counseling for patients should include a discussion of the risk of shedding, disclosure, and the avoidance of sex in the viral prodrome or during outbreaks.

SYPHILIS

The ulcerative lesion of syphilis (Chapter 295 and Fig. 295-1)—the chancre—is indurated and typically painless. Some patients may have multiple ulcers rather than a single chancre. Swabs from a genital ulcer should be collected and examined by dark-field microscopy; the finding of motile spirochetes is diagnostic for syphilis. When darkfield microscopy is not available, primary syphilis can be diagnosed with serologic testing, but the nontreponemal and treponemal antibody tests may be negative in early primary infection. Secondary syphilis results when the spirochetes spread systemically, thereby leading to a characteristic maculopapular rash involving the palms and soles, alopecia, oral mucous patches, or condyloma latum.[11]

All patients who present with a sexually transmitted infection must have serologic screening (E-Fig. 264-1) for syphilis. (e.g., rapid plasma reagin test, Venereal Disease Research Laboratory [VDRL] test, toluidine red unheated serum test [TRUST]). If reactive, the diagnosis must be confirmed with a more specific treponemal antibody test (microhemagglutination assay–*T. pallidum*, fluorescent treponema antibody test). However, some large laboratories have switched to the reverse syphilis screening algorithm using newer automated treponemal tests for initial testing followed by a nontreponemal test (Chapter 295).

All patients diagnosed with syphilis should be questioned about ocular symptoms and symptoms suggestive of neurosyphilis; ocular and neurosyphilis require 14 days of intravenous aqueous penicillin G (Table 295-4). Late latent syphilis and syphilis of unknown duration are managed with three weekly injections of intramuscular penicillin.[12]

LYMPHOGRANULOMA VENEREUM

Lymphogranuloma venereum,[13] caused by a serovar of *C. trachomatis* (Chapter 294), is characterized by local lymph node suppuration, ulceration with subsequent fibrosis, the formulation of fistulas, and distal edema. Lymphogranuloma venereum can manifest as a syndrome mimicking proctocolitis with clinical findings of rectal discharge (mucoid or hemorrhagic in appearance), tenesmus, anal pain, constipation, and fever. Untreated, it can cause extensive local damage with fistulization and stricture formation. Secondary bacterial infections, some of which may be invasive, may occur. Outbreaks among men who have sex with men have been reported in the United States and Europe.

CHANCROID AND GRANULOMA INGUINALE

Chancroid (Chapter 276) infection with *H. ducreyi* produces painful, ragged ulcers and tender inguinal lymphadenopathy, which may be fluctuant. Unlike the lesions of HSV infection, these genital ulcers are likely to vary in size.

Granuloma inguinale (Chapter 292), which is caused by *Klebsiella granulomatis*, is also known as donovanosis. The disease is rare in the United States The ulcerative lesions are painless and vascular, with a beefy red appearance. The disease is slowly progressive with regional lymphadenopathy. Diagnosis is made by identification of dark staining Donovan bodies on crush biopsy or tissue preparations.

TREATMENT

Treatment is based on the specific cause (Table 264-3).

EPITHELIAL CELL INFECTIONS

HUMAN PAPILLOMAVIRUS

Sexually transmitted human papillomavirus infection (Chapter 344) is generally transient and asymptomatic, but some patients develop visible genital warts. These warts are painless, soft, moist, pink- or flesh-colored swellings that vary in shape and can be raised or flat, single or multiple, small or large, and sometimes cauliflower shaped. Warts occur in the vulva, vagina, and anus; on the cervix; and on the penis, scrotum, groin, or thigh. Genital warts are diagnosed by visual inspection.

TREATMENT AND PREVENTION

Treatment is directed at the local lesions, with topical agents (e.g., patient-applied imiquimod 3.75% or 5% cream or podofilox 0.5% solution or gel; or clinician-administered trichloroacetic acid or bichloroacetic acid 80-90% solution), cryotherapy, or surgical removal. However, such treatment generally is not curative.

Two oncogenic human papillomavirus genotypes (16 and 18) are responsible for almost all anogenital, cervical, and oropharyngeal cancers and precancerous lesions. Human papillomavirus types 6 and 11 are responsible for most cases of genital warts and recurrent respiratory papillomatosis. Papanicolaou smears are recommended for sexually active women beginning at the age of 21 years, regardless of risk factor or age at coitarche (Chapter 184). However, specific testing for human papillomavirus is not recommended for women younger than 30 years. The frequency of rescreening is influenced by age, previous screening results, and prior test results. Male gender, smoking, and HIV-positive status are significantly associated with prevalent oral human papillomavirus.

Three human papillomavirus vaccines (Chapter 15) are currently approved by the U.S. Food and Drug Administration for use in males and females: a quadrivalent vaccine (protecting against types 6, 11, 16, and 18), a bivalent vaccine (protecting against types 16 and 18), and a 9-valent vaccine (6, 11, 16, and 18, 31, 33, 45, 52, and 58). Vaccination (Table 344-2) is recommended for males and females ages 26 years and younger, including previously unvaccinated, immunocompromised persons (e.g., HIV).

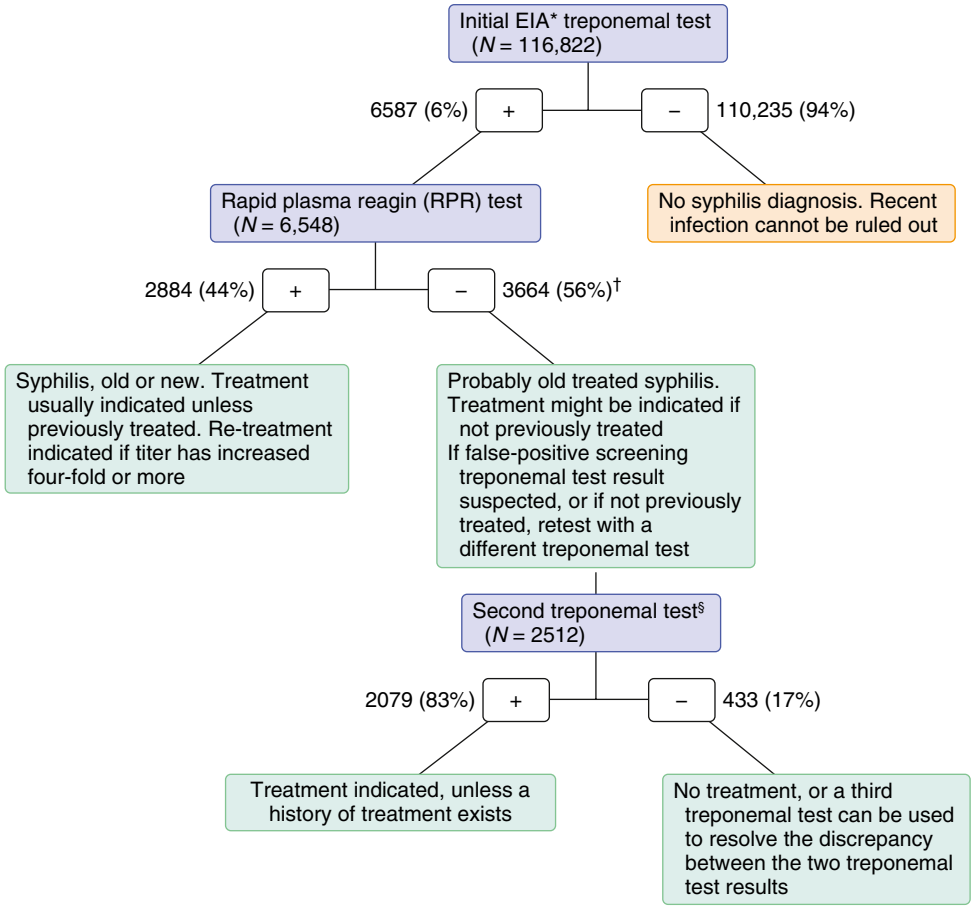

E-FIGURE 264-1. **The reverse syphilis testing algorithm using treponemal tests for initial screening.** *Enzyme immunoassay. †Reactive with EIA treponemal test but nonreactive with RPR test. §Using *Treponema pallidum* particle agglutination or fluorescent treponemal antibody tests. (Redrawn from the Centers for Disease Control and Prevention. Syphilis testing algorithms using treponemal tests for initial screening—four laboratories, New York City, 2005-2006. *MMWR Morb Mortal Wkly Rep*. 2008;57:872-875.)

MOLLUSCUM CONTAGIOSUM

Molluscum contagiosum (Chapter 343) is a generally a benign skin condition that is characterized by small raised lesions (called mollusca) that may be white, pink, or flesh-colored and may have a pearly appearance. Lesions can be distinguished from warts by the dimple or pit seen in the center. Molluscum is spread by skin-to-skin contact or contact with fomites contaminated by the virus (e.g., towels, pool toys). The lesions may occur anywhere on the body, including the genital area. Molluscum contagiosum is usually self-limited in healthy individuals, with lesions resolving in 6 to 12 months without scarring. Lesions in the genital area may require treatment (physical removal or oral or topical therapy; see Chapter 343). Immunocompromised patients may not respond to traditional treatment, and referral to a specialist may be warranted.

FEMALE GENITAL DISCHARGE

Infections of the female genitourinary tract produce several syndromes with overlapping symptoms (dysuria, vaginal discharge, vulvar irritation), the cause of which can usually be established with a careful history, examination, and laboratory tests. The initial approach depends on the primary anatomic site of infection—urinary tract, endocervix, or vagina. The columnar epithelium of the endocervix is susceptible to infection with *N. gonorrhoeae*, *C. trachomatis*, and *T. vaginalis*, and the vagina is susceptible to infection with *Candida albicans*, *T. vaginalis*, and the syndrome of bacterial vaginosis. The cervix may appear completely normal in women with cervical infection, but mucopurulence at the cervical os or mucosal friability suggests infection. Vaginitis is associated with a visible discharge, and the characteristics of the vaginal fluid offer diagnostic clues.

Female genital discharge is a condition in which syndromic management strategies generally lack sensitivity and specificity. Microscopic examination of a wet mount preparation of vaginal secretions may enhance the effectiveness of syndromic treatment, but interpretation of results is difficult and cannot exclude infection with several pathogens concurrently.

BACTERIAL VAGINOSIS

Bacterial vaginosis, which is the most common cause of vaginal discharge in the United States, is an anaerobic polybacterial dysbiosis of the vaginal microbiome (i.e., a vaginal microbiome not dominated by lactobacilli).[14] Women with bacterial vaginosis are often minimally symptomatic but may note mild vaginal discharge and vaginal odor (which is often increased after coitus).[15] The normal vaginal flora contains hydrogen peroxide–producing lactobacilli such as *Lactobacillus crispatus* and *Lactobacillus jensenii*, which probably help "defend" the vagina against a number of pathogens (an example of innate immunity). *Lactobacillus acidophilus* is rarely found in the normal vagina, so yogurt cannot serve as a remedy or a preventive agent.

Bacterial vaginosis begins with the unexplained disappearance of the normal vaginal flora and its replacement with *Gardnerella vaginalis* and many species of anaerobic bacteria. The precise mechanism causing this shift in vaginal flora (i.e., dysbiosis) is poorly understood, but *G. vaginalis, Prevotella bivia*, and other organisms may be early colonizers that lead to the subsequent development of a biofilm followed by secondary colonization.[16] Bacterial vaginosis is not necessarily a benign change in flora. It is associated with an increased rate of upper tract infection (endometritis, salpingitis) and complications of pregnancy, including premature rupture of the membranes, preterm delivery, and infertility.[17] Women with bacterial vaginosis may have increased risk for the acquisition of HIV; male partners may be at increased risk of HIV infection as well.

The discharge of bacterial vaginosis is homogeneous and may contain bubbles. Vaginal pH is elevated above the normal 4.0 to 4.5. Adding 10% potassium hydroxide to the vaginal discharge on the microscope slide or to the discharge present in the extracted speculum elicits an amine-like, fishy odor, yielding a positive "whiff" test result because of the elaboration of amines from the anaerobic flora. Examination of vaginal material as a wet mount reveals the absence of bacilli and their replacement with clumps of coccobacilli. Some vaginal epithelial cells are coated with coccobacilli, which may obscure their edges (clue cells) or the normally clear appearance of the cytoplasm, sometimes described as looking like a fried egg that has been salted and peppered. Relatively few polymorphonuclear leukocytes are observed; large numbers of leukocytes in the wet mount of a woman with bacterial vaginosis suggest a coincident infection, possibly trichomoniasis or bacterial cervicitis.

TREATMENT

Treatment of asymptomatic women who are not at high risk for preterm delivery appears to confer no benefit. For symptomatic women, treatment against the anaerobic flora consists of metronidazole (500 mg orally twice daily for 7 days or 0.75% gel at 5 g intravaginally daily for 5 days), secnidazole (2 g of oral granules in a single dose), tinidazole (2 g orally daily for 2 days or 1 gram orally once daily for 5 days), or clindamycin (2% cream as 5 g intravaginally at bedtime for 7 days, 300 mg orally twice daily for 7 days, or 100 mg ovules intravaginally at bedtime for 3 days). The relapse rate is about 30%, and treatment of male sexual partners offers no benefit. However, *Lactobacillus crispatus* CTV-05 administered vaginally can significantly reduce recurrences of bacterial vaginosis after treatment with vaginal metronidazole gel.[A2]

VAGINITIS

Candidiasis

Vulvovaginal candidiasis (Chapter 310) is common and is seen when endogenous *Candida* species outgrow normal bacterial flora, most frequently in women who are taking antibiotics or using oral contraceptives. Women usually complain of vulvar itching and discomfort and may or may not notice an accompanying discharge. The vagina generally maintains normal numbers of lactobacilli, so the vaginal pH is usually normal, which is helpful in discriminating candidiasis from other vaginal infections. The labia and vaginal walls may be erythematous. Although classically described as "curdy," the discharge of candidiasis is frequently loose and is difficult to distinguish from other discharges. Vaginal material may be treated with 10% potassium hydroxide to destroy other cellular elements and to make the fungi easier to observe. Wet mount, however, has a sensitivity of only about 50%, and a woman with a classic clinical presentation should be treated even if fungal elements are not observed.[18]

TREATMENT

A wide range of topical antifungal medications (Table 264-4) are available (many without a prescription), and all these drugs are approximately equally effective, although the cure rate with some single-dose topical treatments appears to be lower than rates with longer regimens. Fluconazole administered as a single oral dose of 150 mg is highly effective. Infection with yeasts other than *C. albicans* may require longer therapy. Recurrent vulvovaginal candidiasis is a problem for many women, and optimal management has not been defined. Oteseconazole (150 mg orally daily for 7 days, then once weekly for 11 weeks) is a newer option.[A3] Maintenance antifungal regimens with oral fluconazole may be considered. Recurrent infection should lead the clinician to consider underlying diabetes mellitus or HIV infection. Treatment of sexual partners of women with candidiasis confers no benefit.

Trichomoniasis

The estimated annual incidence of *Trichomonas vaginalis* (Chapter 324) worldwide exceeds that of chlamydia and gonorrhea combined. Women with *T. vaginalis* infection may complain of purulent discharge and vulvar irritation. The vaginal walls are red, and the vagina may contain excessive yellow or green

TABLE 264-4 SELECTED TOPICAL ANTIFUNGAL AGENTS FOR VAGINAL CANDIDIASES

CREAMS
Over-the-Counter
Clotrimazole (2% cream): 5 g intravaginally daily for 3 days Miconazole (4% cream): 5 g intravaginally daily for 3 days
Prescription
Butoconazole (2% cream): 5 g intravaginally once Terconazole (0.8% cream): 5 g intravaginally daily for 3 days
SUPPOSITORIES
Over-the-Counter
Miconazole (1,200 mg) once
Prescription
Terconazole 80 mg vaginal suppository daily for 3 days

Source: https://www.cdc.gov/std/treatment-guidelines/STI-Guidelines-2021.pdf.

discharge that is bubbly or frothy in appearance. The ectocervix may also be inflamed or have punctate microhemorrhages, thereby causing the pathognomonic "strawberry cervix" (colpitis macularis). Vaginal pH is elevated, but the whiff test result is generally negative. Wet mount reveals large numbers of polymorphonuclear leukocytes as well as motile protozoa about the same size as the leukocytes, with visible flagella; motile organisms may be recognized in about two thirds of cases. Because of poor performance of wet mount microscopy, nucleic acid testing is recommended.

TREATMENT

A 7-day course of metronidazole (500 mg twice daily) is the preferred treatment in women, but a single 2-g dose can be used in men.[19] Tinidazole (2 g orally in a single dose) is an alternative, but resistance to both regimens is increasing. Drug-resistance testing can be performed through the CDC; treatment recommendations based on resistance testing may include higher doses and a longer duration of tinidazole or metronidazole under expert guidance.

CERVICITIS

The clinical diagnosis of cervicitis is suggested by tenderness on bimanual examination, visible inspection revealing inflammation, or discharge. The specific diagnosis can be made only by detecting microorganisms from the cervix, preferably by nucleic acid testing of the discharge. *N. gonorrhoeae* and *C. trachomatis* have tropism for cervical tissue, whereas other pathogens (including HIV) can apparently infect the vaginal tissues as well.

TREATMENT

Ideally, treatment should be based on test results. Recommended treatment is doxycycline (100 mg orally twice daily for 7 days) or a single dose of azithromycin (1 g orally) for chlamydia, doxycycline (100 mg orally twice daily for 7 days) followed by moxifloxacin (400 mg once daily for 7 days) for *Mycoplasma genitalium*, and ceftriaxone (500 mg IM once) if gonococcal infection is detected or the risk for it is high. If follow-up cannot be ensured or NAAT testing is not available, empiric treatment targeted to both *C. trachomatis* and *N. gonorrhoeae* should be used for women at high risk (age < 25 years, new sexual partner, sexual partner with a sexually transmitted disease, or partners who also have other partners).

PELVIC INFLAMMATORY DISEASE

Each year, more than 800,000 women develop pelvic inflammatory disease (PID) in the United States.[20] The bacterial causes of pelvic inflammatory disease are myriad and include *N. gonorrhoeae*, *C. trachomatis* (about 35% of cases),[21] and *Mycoplasma* (especially *M. genitalium*); other anaerobic and aerobic bacteria that colonize the vagina and cytomegalovirus (Chapter 347) also have been implicated. Infection ascends from the cervix into the uterine cavity, thereby producing endometritis, occasionally with extension to the fallopian tubes, causing salpingitis. Some intrauterine devices have been associated with an increased risk of salpingitis, and some data suggest that vaginal douching is a predisposing factor.

Women with pelvic inflammatory disease often complain of pelvic pain, which may be constant or intermittent and is typically exacerbated by menses and coitus. Adnexal tenderness on bimanual examination leads to the clinical diagnosis of salpingitis. Fever, cervical tenderness, leukocytosis, and an elevated sedimentation rate are sometimes observed. Severe signs or symptoms suggest a tubal abscess or spread of the infection to the upper genital tract.

The clinical diagnosis is confirmed laparoscopically in only about 70% of cases, thereby suggesting considerable error in diagnosis. Vaginal ultrasonography or computed tomography is often helpful in defining the cause of pelvic pain syndromes. Pregnant women with evidence of salpingitis should be hospitalized. Other indications for hospitalization include nonresponse to or intolerance of an oral regimen, presence of a tubo-ovarian abscess, and inability to exclude a surgical emergency, such as appendicitis.[22]

TREATMENT

Treatment should include therapy directed at anaerobes (Chapter 273; Table 264-5),[A4] but no conclusive evidence indicates that any one recommended antibiotic regimen is safer or more effective than the other recommended options.[A5] Chlamydial salpingitis may be mild, and patients may not seek medical attention, but empirically adding initial doxycycline (100 mg orally twice daily for 7 days) treatment for chlamydia may improve the outcomes of patients with pelvic inflammatory disease.[23] Intrauterine devices, if present, should be removed if clinical improvement does not occur.

TABLE 264-5 RECOMMENDED REGIMENS FOR PELVIC INFLAMMATORY DISEASE

OUTPATIENT WITH MILD TO MODERATE DISEASE
Ceftriaxone (500 mg IM in a single dose: for persons weighing ≥150 kg, 1 g of ceftriaxone should be administered) PLUS doxycycline (100 mg orally 2 times/day for 14 days) PLUS metronidazole (500 mg orally 2 times/day for 14 days) *or*
Cefoxitin (2 g IM in a single dose) and probenecid (1 g orally administered concurrently in a single dose) PLUS doxycycline (100 mg orally 2 times/day for 14 days) PLUS metronidazole (500 mg orally 2 times/day for 14 days) *or*
Other parenteral third-generation cephalosporin (e.g., ceftizoxime or cefotaxime) PLUS doxycycline (100 mg orally 2 times/day for 14 days) PLUS metronidazole (500 mg orally 2 times/day for 14 days)
INPATIENT WITH MODERATE TO SEVERE DISEASE
Ceftriaxone (1 g IV every 24 hours) PLUS doxycycline (100 mg orally or IV every 12 hours) PLUS metronidazole (500 mg orally or IV every 12 hours) *or*
Cefotetan (2 g IV every 12 hours) PLUS doxycycline (100 mg orally or IV every 12 hours) *or*
Cefoxitin (2 g IV every 6 hours) PLUS doxycycline (100 mg orally or IV every 12 hours)

IM = intramuscular; IV = intravenous.
Source: https://www.cdc.gov/std/treatment-guidelines/STI-Guidelines-2021.pdf.

PROGNOSIS

Women should experience some clinical improvement within about 72 hours of initiation of therapy. Failure to improve is an indication for hospitalization for treatment with ceftriaxone (1 gram IV q 24 hours), doxycycline (100 mg orally or IV every 12 hours), and metronidazole (500 mg IV or orally every 12 hours). Alternative treatment regimens should include doxycycline (100 gm IV or orally every 12 hours) plus either cefotetan (2 grams IV every 12 hours) or cefoxitin (2 grams IV every 6 hours). With clinical improvement, patients may be transitioned to oral therapy with doxycycline 100 mg orally twice daily) and metronidazole (500 mg orally twice a day) to complete a total of 14 days of therapy.

Ectopic pregnancy, tubo-ovarian abscess, and infertility are complications of salpingitis. Infertility complicates approximately 15% of initial attacks of salpingitis, but the infertility rate after three or more episodes of salpingitis approaches 75%.

ECTOPARASITES

Ectoparasitic infection include pubic lice and scabies (Chapter 98). Scabies is caused by the mite *Sarcoptes scabiei* and can result in intense pruritus. Patients with pubic lice may present with symptoms of itching or note seeing nits or lice in their pubic hair.

Visualization of nits or lice confirms the diagnosis, as does identification of burrows in affected skin. Microscopic visualization of skin scrapings from affected areas can demonstrate mites, eggs, or feces, but this method is often low yield. Treatment for both conditions is local application of cidal agents or oral ivermectin (Table 264-6).

PREVENTION

Sexually transmitted infections are preventable. The U.S. CDC recommends five strategies as the foundation for an effective prevention program: (1) education and counseling of persons at risk to motivate the adoption of safer sexual behavior; (2) identification of asymptomatic infected persons and symptomatic persons unlikely to seek diagnostic and treatment services; (3) rapid and effective diagnosis and treatment of infected persons; (4) evaluation, treatment, and counseling of exposed sexual partners; and (5) preexposure vaccination of persons at risk for vaccine-preventable STIs.

Behavioral Interventions

Abstaining from sexual intercourse or being in a long-term, mutually monogamous relationship with an uninfected partner is the most reliable way to prevent sexually transmitted infections. Abstinence should be recommended during treatment for a sexually transmitted infection. Both partners should be tested for sexually transmitted infections, including HIV infection, before initiating sexual intercourse.

Counseling is essential for people with sexually transmitted infections.[24] Interactive counseling, video presentations, peer groups, and other formats that emphasize the correct use of a condom can reduce the incidence of subsequent infections by 25 to 40%.[A6] HIV testing should be offered to anyone

TABLE 264-6 TREATMENTS FOR PUBIC LICE AND SCABIES

LICE
Permethrin 1% cream rinse applied to affected areas and washed off after 10 minutes *or* Pyrethrin with piperonyl butoxide applied to the affected area and washed off after 10 minutes
Alternative Regimens
Malathion 0.5% lotion applied to affected areas and washed off after 8-12 hours *or* Ivermectin 250 μg/kg body weight orally, repeated in 7-14 days
SCABIES
Permethrin 5% cream applied to all areas of the body from the neck down and washed off after 8-14 hours *or* Ivermectin 200 μg/kg body weight orally, repeated in 14 days (oral ivermectin has limited ovicidal activity; a second dose is required for eradication) *or* Ivermectin 1% lotion applied to all areas of the body from the neck down and washed off after 8-14 hours; repeat treatment in 1 week if symptoms persist
Alternative Regimens
Lindane 1% 1 oz of lotion or 30 g of cream applied in a thin layer to all areas of the body from the neck down and thoroughly washed off after 8 hours (infants and children age <10 years should not be treated with lindane)

Source: https://www.cdc.gov/std/treatment-guidelines/STI-Guidelines-2021.pdf.

TABLE 264-7 RECOMMENDED REGIMEN FOR SURVIVORS OF A SEXUAL ASSAULT

ALL SEXUAL ASSAULT SURVIVORS
Postexposure prophylaxis recommendations for human immunodeficiency virus should be made on a case by case basis according to risk
FEMALES
Ceftriaxone (500 mg IM in a single dose; 1 g of ceftriaxone for persons weighing ≥150 kg) PLUS doxycycline (100 mg 2 times/day orally for 7 days) PLUS metronidazole (500 mg 2 times/day orally for 7 days)
MALES
Ceftriaxone (500 mg IM in a single dose; 1 g of ceftriaxone for persons weighing ≥150 kg) PLUS doxycycline (100 mg 2 times/day orally for 7 days)

IM = intramuscular.

Source: Centers for Disease Control and Prevention. Sexual assault and abuse and STIs—adolescents and adults. (https://www.cdc.gov/std/treatment-guidelines/sexual-assault-adults.htm. Accessed June 3, 2022.)

diagnosed with a sexually transmitted infection and should be offered as an opt-out; separate written consent is not required. Further, HIV preexposure prophylaxis is an important HIV risk reduction tool that may be appropriate for sexually active adolescents and adults.

Barrier Methods

When used consistently and correctly, male latex condoms are effective in preventing the sexual transmission of HIV infection and can reduce the risk of other STIs (gonorrhea, chlamydia, and trichomoniasis). However, because condoms do not cover all exposed areas, they are likely to be more effective in preventing infections transmitted by fluids from mucosal surfaces (e.g., gonorrhea, chlamydia, trichomoniasis, HIV infection) than in preventing those transmitted by skin-to-skin contact (e.g., HSV, HPV, syphilis, chancroid). Failure of male condoms usually results from inconsistent or incorrect use rather than from breakage. Nonlatex condoms (those made of polyurethane or other synthetic material) can be used by persons with latex allergy. Less information is available on the effectiveness of female condoms to reduce the incidence of STIs. Although cervical caps and diaphragms cover the cervix, there is little evidence that they can prevent STIs or HIV infection.

Male Circumcision

Male circumcision reduces the amount of mucosal tissue that is susceptible to HIV and sexually transmitted pathogens. Circumcision of adult men reduces the acquisition of HIV by more than 70% for up to 5 years after circumcision (Chapter 356).[A7] Circumcision also appears to reduce the acquisition of other viral sexually transmitted pathogens, including HSV-2 and human papillomavirus.

Partner Services

The detection of a sexually transmitted infection demands consideration of the infected person's sexual partners, who may have undetected and serious disease. In addition, if partners are not treated, reinfection of the index case can be expected. The probability that a sexual partner is also infected reflects the efficiency of transmission of the sexually transmitted pathogen. Empiric partner therapy is recommended for syphilis, *N. gonorrhoeae, C. trachomatis, T. vaginalis*. Additionally, empiric partner therapy is indicated for the clinical syndromes of urethritis, cervicitis, and ectoparasites. Exceptions to empiric partner treatment include herpes simplex virus, human papillomavirus, and candidiasis. For example, most men with gonococcal urethritis infect their partners, whereas only about 50% of patients with HIV infection have infected their partners at the time of outreach. Partners who differ in terms of their infection status are referred to as discordant.

Sexual partners can be notified directly by the infected person or by health care workers, sometimes through proactive contact tracing. In general, dependence on the infected person is a less reliable way to get partners treated. However, in many states it is legal to pursue expedited care by providing the infected patient with the appropriate treatment for his or her partners. Expedited partner care is recommended for the treatment of gonorrhea and chlamydia infections.

Preexposure Interventions

Preexposure vaccination is the most effective method for preventing the transmission of certain sexually transmitted infections. For example, because hepatitis B virus is frequently transmitted sexually, hepatitis B vaccination (Chapters 15 and 134) is recommended for all unvaccinated persons being evaluated for a sexually transmitted infection. In addition, hepatitis A vaccine (Chapters 15 and 134) is recommended for men who have sex with men and for drug users (both injection and noninjection). Vaccines for human papillomavirus (Chapters 15 and 344) demonstrate continued high rates of protection in women, and they protect men and women against precancerous lesions.

Preexposure prophylaxis with daily oral therapy can prevent HIV (Chapter 356), but only in the setting of high-level (>85%) medication adherence. Neither topical microbicides[A8] nor antibacterial mouthwash[A9] have been effective for preventing sexually transmitted herpes virus or bacterial infections. On demand preexposure prophylaxis is effective in men who have sex with men, and in transgender women,[A10] but its use is not appropriate for persons engaging in vaginal sex. Long-acting options, such as injectable cabotegravir 600 mg IM every two months (following an initial loading dose of 2 injections delivered one month apart), may be an attractive option for sexually active adults and adolescents at risk for sexually acquired HIV infection.[A11]

Postexposure Prophylaxis

After consensual or nonconsensual sexual exposure, a variety of sexually transmitted infections can be prevented with empiric antibiotics (Table 264-7). For example, for men who have sex with men, doxycycline prophylaxis (100 mg or 200 mg) can reduce transmission of syphilis and bacterial sexually transmitted infections.[A12] Prevention of HIV infection following a potential exposure requires antiretroviral agents used in combination (two nucleoside reverse transcriptase inhibitors and one integrase inhibitor) that must be initiated shortly after the exposure (<72 hours) and used for 28 days (Chapter 356).

Contraception

All methods of birth control can influence the acquisition and outcome of a sexually transmitted infection. For example, oral contraceptive pills, implants, injections, and copper intrauterine devices[A13] do not intrinsically increase the risk of HIV infection themselves, but use of any birth control option may be associated with more sexual activity and hence higher risk for HIV or any other sextually transmitted infection. In addition, pregnancy itself (in the absence of effective birth control) affects the risk of acquiring a sexually transmitted infection as well as the health of the pregnancy and the neonate. Accordingly, the management of sexually transmitted infections demands consideration of the reproductive health of both partners as well as family planning issues.

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For the General References and other additional features, please visit Elsevier eBooks+ at https://ebooks.health.elsevier.com.

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TABLE 265-1 THE PRETRAVEL CONSULTATION WITH A TRAVELER TO THE DEVELOPING WORLD—A STRUCTURED APPROACH

PERFORM RISK ASSESSMENT
The following must always be ascertained initially to determine the appropriate preventive medical recommendations. Preprinted medical record forms may be used to record these.
Exact itinerary, including regions within each country to be visited
Dates of travel to assess risk of seasonal diseases
Age
Past vaccination history
Underlying illnesses
Current medications
Pregnancy status
Allergies
Purpose of trip
Risk exposures—blood, body fluids, adventure, or extensive outdoor exposures
Urban versus rural travel
Type of accommodations
Level of aversion to risk
Review traveler-specific risk with respect to emerging infectious pathogens
Financial limitations that may necessitate prioritization of interventions
ADMINISTER IMMUNIZATIONS
Administer routine vaccinations that are not up to date.
Administer indicated travel vaccines.
Provide to patient legally mandated Vaccine Information Statements from the Centers for Disease Control and Prevention (http://www.cdc.gov/vaccines/pubs/vis/).
Provide printed checklist to patient listing vaccines administered.
Record in the clinic record vaccines administered, lot number, and date.
Document vaccines offered to but declined by patient as well as nonrecommended vaccines administered at the patient's request.
PROVIDE MALARIA PREVENTION (IF INDICATED)
Determine whether malaria risk exists for the destination country. If yes:
Does the patient's itinerary within that country put him or her at risk? If yes:
Recommend malaria chemoprophylaxis. Several equally effective drugs of choice may be indicated. Ascertain which is best suited to the individual patient and itinerary.
Educate on personal protection against arthropods.
EDUCATE ON TRAVELER'S DIARRHEA
Recommend food and water precautions.
Educate on use of oral hydration and loperamide and prescribe standby therapy for severe diarrhea with azithromycin or a quinolone.
TEACH ESSENTIAL PREVENTIVE BEHAVIORS
Most travel-related health problems, including vaccine-preventable diseases, can be avoided through simple behaviors initiated by the traveler.
Educate on appropriate strategies in the following categories (some topics are not applicable to all destinations): blood-borne and sexually transmitted diseases, safety and crime avoidance, injury prevention, swimming safety, rabies, skin/wound care, tuberculosis, packing for healthy travel, obtaining health care abroad.
DISCUSS OTHER APPLICABLE HEALTH ISSUES
Advise and prescribe for altitude illness, motion sickness, or jet lag.
Discuss prevention of specific travel-related infections that are of some risk to the traveler and have a possible preventive strategy not included in strategies above.
Discuss any minimal-risk conditions (e.g., hemorrhagic fevers) that are a frequent cause of patient anxiety.
Discuss travel restrictions and advisories; consider additional testing, quarantine, and/or vaccination requirements related to emerging infections.

265 APPROACH TO THE PATIENT BEFORE AND AFTER TRAVEL

LIN H. CHEN

Prevention strategies and medical interventions for travelers should be individualized according to a risk assessment that considers both the itinerary and factors that are dependent on the prospective traveler. A structured approach to patient interaction (Table 265-1) is the most efficient way to cover the necessary educational and preventive interventions. Providing clearly printed instructions in lay language is advised. The worldwide epidemiology of travel-related diseases is constantly changing. Special needs travelers, such as individuals who are immunocompromised, pregnant, or have significant underlying disease, should be referred to a specialized travel medicine clinic.

Globally, approximately 100 million people travel from industrialized to developing countries each year, with risks of travel-related illness determined by the route and destination. Depending on the destination, about 20 to 70% of travelers report some illness, mostly mild, self-limited conditions such as diarrhea, respiratory infections, and skin disorders. Infectious diseases account for up to 10% of the morbidity during travel but only 1% of the deaths, with malaria (Chapter 316) being the most common cause.

IMMUNIZATION

The choice of vaccines for an individual traveler is based on the risk of exposure to vaccine-preventable diseases on the planned itinerary, the severity of a disease if it is acquired, and any risks presented by the vaccine itself. Travelers differ in their tolerance of risk. For vaccine-preventable diseases, the monthly incidence for nonimmune travelers to developing countries is most significant for influenza (about 1%; Chapter 332) and for symptomatic hepatitis A (about 0.03%; Chapter 134), but the risk of symptomatic hepatitis B (Chapter 134) is most significant for long-stay travelers (e.g., missionaries) at 0.25% per month. Enteric fever (typhoid and paratyphoid) has a risk of 0.03% per month on the Indian subcontinent and is 10 times lower in Africa and parts of Southeast Asia and Latin America. The risk of contact with animals that could have rabies (Chapter 383) is also substantial, at about 1% per month. The risk of yellow fever (Chapter 351) may be as high as 0.1% per month of travel to an area with current epidemic transmission, but the risk varies greatly among destinations encompassed by the endemic area map. The risk of meningococcal meningitis (Chapter 274), cholera (Chapter 278), polio (Chapter 349), varicella (Chapter 346), and Japanese encephalitis (Chapter 352) in travelers is not known but is thought to be small (<0.0001%). Worldwide measles outbreaks and declining vaccination rates have led to a rise in travel-related

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Level of aversion to risk
Review traveler-specific risk with respect to emerging infectious pathogens
Financial limitations that may necessitate prioritization of interventions
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Administer routine vaccinations that are not up to date.
Administer indicated travel vaccines.
Provide to patient legally mandated Vaccine Information Statements from the Centers for Disease Control and Prevention (http://www.cdc.gov/vaccines/pubs/vis/).
Provide printed checklist to patient listing vaccines administered.
Record in the clinic record vaccines administered, lot number, and date.
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PROVIDE MALARIA PREVENTION (IF INDICATED)
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Advise and prescribe for altitude illness, motion sickness, or jet lag.
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Discuss any minimal-risk conditions (e.g., hemorrhagic fevers) that are a frequent cause of patient anxiety.
Discuss travel restrictions and advisories; consider additional testing, quarantine, and/or vaccination requirements related to emerging infections.

265 APPROACH TO THE PATIENT BEFORE AND AFTER TRAVEL

LIN H. CHEN

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Globally, approximately 100 million people travel from industrialized to developing countries each year, with risks of travel-related illness determined by the route and destination. Depending on the destination, about 20 to 70% of travelers report some illness, mostly mild, self-limited conditions such as diarrhea, respiratory infections, and skin disorders. Infectious diseases account for up to 10% of the morbidity during travel but only 1% of the deaths, with malaria (Chapter 316) being the most common cause.

IMMUNIZATION

The choice of vaccines for an individual traveler is based on the risk of exposure to vaccine-preventable diseases on the planned itinerary, the severity of a disease if it is acquired, and any risks presented by the vaccine itself. Travelers differ in their tolerance of risk. For vaccine-preventable diseases, the monthly incidence for nonimmune travelers to developing countries is most significant for influenza (about 1%; Chapter 332) and for symptomatic hepatitis A (about 0.03%; Chapter 134), but the risk of symptomatic hepatitis B (Chapter 134) is most significant for long-stay travelers (e.g., missionaries) at 0.25% per month. Enteric fever (typhoid and paratyphoid) has a risk of 0.03% per month on the Indian subcontinent and is 10 times lower in Africa and parts of Southeast Asia and Latin America. The risk of contact with animals that could have rabies (Chapter 383) is also substantial, at about 1% per month. The risk of yellow fever (Chapter 351) may be as high as 0.1% per month of travel to an area with current epidemic transmission, but the risk varies greatly among destinations encompassed by the endemic area map. The risk of meningococcal meningitis (Chapter 274), cholera (Chapter 278), polio (Chapter 349), varicella (Chapter 346), and Japanese encephalitis (Chapter 352) in travelers is not known but is thought to be small (<0.0001%). Worldwide measles outbreaks and declining vaccination rates have led to a rise in travel-related

ABSTRACT

The worldwide epidemiology of travel-related diseases is constantly changing, and emerging pathogens such as severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) can impose abrupt and drastic challenges in our understanding of travel-related health problems. Prevention strategies and medical interventions must be individualized according to a risk assessment that considers individual health status, the itinerary, the anticipated activities, and other factors that are dependent on the prospective traveler. A structured approach to patient interaction is the most efficient way to cover the necessary educational and preventive interventions. Because many of the measures and advice will be initiated only much later at the traveler's destination, clearly printed instructions in lay language are advisable. Special needs travelers, such as those who are immunocompromised, pregnant, or have significant underlying disease, should be referred to a specialized travel medicine clinic.

KEYWORDS

travel
immunizations
malaria
traveler's diarrhea
epidemiology
prevention
altitude illness
emerging infections

measles (Chapter 338). The severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2; Chapters 335-337) pandemic created additional risks despite associated travel restrictions.

A number of vaccines (Table 265-2; see also Chapter 15) are available for prospective travelers and can be administered in the travel medicine setting when indicated.

VERIFICATION AND UPDATE OF ROUTINE IMMUNIZATIONS

Because of the increased prevalence of many infections worldwide, routine adult immunizations (Chapter 15) must be current.[1] If no adult doses of tetanus/diphtheria/acellular pertussis (Tdap) have ever been given, a dose of Tdap should be given regardless of the time elapsed since the last tetanus/diphtheria vaccination. Persons born in the United States before 1957 or born anytime in the developing world are considered immune to measles. Other adult travelers should have received at least two doses of live measles–containing vaccine during their life unless a history of measles infection can be documented. Unvaccinated persons who meet the accepted routine indications for influenza or pneumococcal vaccines (Chapter 15) should receive these vaccines during the pretravel consultation. Two doses of varicella vaccine spaced by at least 4 weeks should be considered for adult travelers without evidence of varicella immunity, but adults born before 1980 in the United States are considered immune.

VACCINES TO CONSIDER FOR ALL DEVELOPING WORLD TRAVELERS

A number of additional vaccines should be administered depending on the travel destinations.[2]

Hepatitis A

Vaccination against hepatitis A (Chapter 134) is indicated for every nonimmune traveler to countries or areas with moderate to high risk of infection, which includes essentially any country other than the United States, Canada, Japan, Australia, New Zealand, Scandinavian countries, and developed countries in Europe. Because outbreaks also occur in developed countries, the vaccine is beneficial for all persons and has been incorporated into the routine childhood immunization schedule in the United States. A single dose of hepatitis A vaccine given any time before travel provides adequate protection. Persons with a history of hepatitis or who previously lived in an endemic country for a prolonged period may benefit from prevaccination serum antibody testing.

Hepatitis B

Pretravel hepatitis B vaccination (Chapter 134) is indicated for all nonvaccinated travelers with standard indications, such as health care providers, and all longer-stay travelers who will be visiting or residing in high- or moderate-risk areas. Transmission by routes such as sexual contact, blood transfusions, contaminated medical equipment, body piercing, tattooing, acupuncture, and sharing of bathroom facilities is difficult to control or to predict in the context of travel. Vaccination is advocated for some short-term travelers, especially younger travelers and travelers who anticipate being in close contact with local populations, even if they have no specific risk factors. Adventure travelers (accident prone), backpackers, and travelers with underlying medical conditions are more likely to require contact with the medical system. Accelerated and hyperaccelerated schedules (see Table 265-2), which are used widely in practice and are approved in many countries, are helpful in administering all

TABLE 265-2 TRAVEL-RELATED VACCINES OF ADULTS

DISEASE	VACCINE	PRIMARY COURSE (A: ACCELERATED SCHEDULE)	ROUTE	FURTHER BOOSTERS
VACCINES TO CONSIDER FOR ALL DEVELOPING WORLD TRAVELERS				
Hepatitis A	Killed virus	0, 6-18 months	IM	None
Hepatitis B	Recombinant viral antigen	0, 1, 6 months	IM	None
		A: 0, 1, 2 months and 12 months	IM	
		A: 0, 1, 3 weeks and 12 months*	IM	
	Recombinant, adjuvanted	0, 1 month	IM	None
Hepatitis A/B	Combination of monovalent preparations	0, 1, 6 months	IM	None
		A: 0, 1, 3 weeks and 12 months	IM	
Typhoid	Capsular Vi polysaccharide	Single dose	IM	2 years
	Live attenuated Ty21a bacteria	0, 2, 4, 6 days	Oral	5 years
Influenza	Inactivated viral	Single dose	IM	Annual
	Live attenuated virus	Single dose (<50 years of age only)	Nasal	Annual
Varicella	Live attenuated virus	0, 4-8 weeks	SQ	None
VACCINES FOR CERTAIN DESTINATIONS				
Yellow fever	Live attenuated 17D virus	Single dose	SQ	10 years for special-risk persons; the majority of travelers are considered to have lifelong protection from one dose
Meningococcus	Quadrivalent conjugated polysaccharide (A, C, Y, W135)	Single dose	IM	5 years
Rabies	Inactivated viral cell culture	0, 7, 21-28 days	IM†	None routinely but two doses after each exposure
		0, 7 days per WHO‡		
Japanese encephalitis (Vero cell)	Inactivated viral	0, 28 days	IM	1 year if at continued risk; no data on subsequent doses
		A: 0, 7 days	IM	
Polio§	Inactivated viral	Single dose if adequate childhood series	SQ; IM acceptable	None
Cholera	Live attenuated bacteria (CVD 103-HgR)	Single dose	Oral	3 months
	Killed bacteria + recombinant B toxin subunit	0, 1 week	Oral	2 years for cholera; 3 months for ETEC

*Regimen not approved by the U.S. Food and Drug Administration for monovalent hepatitis B vaccine but approved for combination hepatitis A/B vaccine containing the same quantity of hepatitis B antigen.
‡In the United States, the Advisory Committee on Immunization Practices considers a two-dose pre-exposure regimen to provide boostability up to 3 years, and a third dose administered from day 21 up to 3 years provides long-term boostability. An alternate option is to check the rabies antibody titer at 1 to 3 years after the 2-dose series. Long-term boostability is established if the titer is high.
†Intradermal rabies preexposure vaccine is no longer produced, and the intramuscular 1.0-mL vials are not licensed for intradermal use in a 0.1-mL dose.
§Oral polio vaccine is no longer produced or used.
A = accelerated regimen to be used for imminent departures; ETEC = enterotoxigenic *E. coli*; IM = intramuscular; SQ = subcutaneous.

three primary doses necessary for high assurance of protection in the frequent circumstance in which the traveler is leaving in a very short time and is at risk of exposure to hepatitis B. An adjuvanted two-dose hepatitis B vaccine with a 1-month interval produces excellent rapid response.

Combination Hepatitis A and Hepatitis B Vaccine

The combined hepatitis A and hepatitis B vaccine provides convenience for travelers who have indications for both vaccines. An accelerated 3-week schedule (see Table 265-2) is approved by the U.S. Food and Drug Administration.

Typhoid

Vaccination against typhoid (Chapter 284) is indicated for all travelers to the Indian subcontinent and should be considered for individuals who are traveling to other endemic areas under all but the most deluxe and protected of conditions. The risk increases with duration of the trip, lodging and eating with local residents, and extent of travel beyond the usual tourist itineraries. Current typhoid vaccines do not protect against *Salmonella paratyphi*, which is emerging in many areas.[3] Adherence to the oral vaccine regimen may be as low as 70%.

Influenza

Influenza (Chapter 332) is transmitted year-round in the tropics and is the most common vaccine-preventable illness in travelers. An increased risk of influenza also is reported among cruise ship passengers. All travelers to the tropics or to destinations where influenza virus is currently circulating should strongly consider influenza vaccination,[4] even if they are not otherwise at high risk.

VACCINES FOR CERTAIN DESTINATIONS

Yellow Fever

The primary indication for vaccination against yellow fever (Chapter 351) is to prevent infection in individuals who are traveling to high-risk areas (see www.cdc.gov/travel), but a number of African countries and one in South America (French Guiana) require proof of yellow fever vaccination from all arriving travelers. Country-specific yellow fever entry requirements can be found at www.who.int/ith/chapters/en/index.html. In general, all healthy adult travelers to areas with a risk of yellow fever transmission should be vaccinated. Neither yellow fever vaccine nor any other vaccine is currently required for readmission to the United States. The true duration of immunity from yellow fever vaccination appears to be much longer than 10 years and may exceed 30 years.

Meningococcus

Vaccination against meningococcal infection (Chapter 274)[5] is recommended for travelers to Africa's sub-Saharan "meningitis belt" during the dry season from December through June, especially if prolonged contact with the local populace is likely. Out-of-season epidemics also have occurred in Ethiopia, Somalia, and Tanzania. Muslims undertaking Hajj and Umrah pilgrimages in Saudi Arabia are at a higher risk of meningococcal disease (Chapter 274), and proof of vaccination with the quadrivalent vaccine within the past 3 years (for polysaccharide vaccine) or 5 years (for conjugate vaccine) is required to obtain pilgrimage visas. Polysaccharide vaccine is no longer produced in Western countries.

Rabies

A preexposure vaccination series against rabies (Chapter 383) is indicated for long-stay travel to endemic areas of Latin America, Asia, or Africa, where the rabies threat is constant and where access to adequate postexposure rabies immune globulin and vaccine is likely to be limited. For short-term travel, risk groups for whom immunization should be considered include adventure travelers, bikers, hikers, cave explorers, and business travelers who travel for short but frequent trips and plan to go running outdoors on these trips. The World Health Organization (WHO) endorses a two-dose schedule for preexposure prophylaxis. The Advisory Committee on Immunization Practices considers a two-dose pre-exposure regimen to provide boostability up to 3 years. To assure long-term boostability, a third dose should be administered from day 21 up to 3 years or the rabies antibody level can be checked at 1 to 3 years following the two-dose series.

Japanese Encephalitis

Japanese encephalitis (Chapter 352) is endemic to many rural farming areas of Southeast Asia and the Indian subcontinent, and sporadic cases with severe sequelae continue to occur in travelers.[6] In temperate regions, the transmission season is from May through October. In tropical or subtropical regions of Oceania and Southeast Asia, transmission may occur year-round. Vaccination is recommended for long-stay travel to an endemic rural area; expatriation to anywhere in an endemic country; short-term travel to endemic rural areas with extensive outdoor exposure, such as with adventure travel; and short-term travel in the face of a current local epidemic.

Polio

Because of eradication efforts, poliomyelitis (Chapter 349) remains in only a few countries, but complete control remains elusive. Adults who are traveling to countries where polio remains endemic or where outbreaks are occurring (updated information at www.polioeradication.org) and who have previously completed a primary vaccine series should receive a one-time, single-dose booster of inactivated polio vaccine.

Cholera

Vaccination against cholera (Chapter 278) is no longer required by any country, and the risk to typical travelers is insignificant.[7] However, medical and aid workers who are staying for short periods in disaster areas or refugee camps may consider cholera vaccine. An oral live attenuated bacterial vaccine is available in the United States, and an oral killed whole cell–B subunit vaccine is available widely outside the United States.

SEQUENCE OF TRAVEL-RELATED VACCINES

All currently indicated immunizations can and should be given at the same time and in any combination (Chapter 15), including vaccination against SARS-CoV-2. If two live viral antigens are not administered on the same day, they must be spaced by a month. Minimum intervals between vaccine doses must be respected, although 4 days or fewer before the next interval are acceptable. Regimens that involve 1-week intervals (rabies, Japanese encephalitis, accelerated hepatitis) are exceptions. There is not a maximum interval between doses of a primary vaccine series; interrupted series (except oral typhoid and rabies) need not be restarted but can be resumed beginning with the dose that is overdue.

MALARIA CHEMOPROPHYLAXIS

An average of 1500 imported cases of malaria (Chapter 316) are reported annually in the United States. Estimates of risk in travelers not taking chemoprophylaxis vary widely by destination but range from 3.4% per month in West Africa to one tenth that on the Indian subcontinent and a further 10-fold reduction in South America. The majority of cases of imported malaria in the United States and Europe occur in immigrants visiting friends and relatives abroad.

In the limited number of countries where it is still effective (e.g., mainly the Caribbean and countries west of the Panama Canal), chloroquine 500 mg salt (300 mg base) per week, beginning the week before the first exposure to malaria and continuing for 4 weeks after the last exposure, is still the drug of choice. However, atovaquone/proguanil (250/100 mg) may still be used by short-stay travelers who prefer the shorter duration of that regimen.

For all other areas of the world, four regimens are equally effective, and the choice depends on both traveler and itinerary factors. Atovaquone/proguanil (250/100 mg) is a well-tolerated, once-a-day drug that should be started 1 day before arrival in the malarious area and continued for 7 days after the last exposure. The short period of postexposure use makes it convenient for the many travelers on typical 1- to 3-week itineraries. The medications' cost and need for daily dosing make it difficult to use for extended periods. Weekly mefloquine (250 mg) is given 2 and preferably 3 weeks before the first exposure to malaria and continued for 4 weeks thereafter. Weekly dosing and a long track record of efficacy make this drug the most effective for long-stay travelers. If long-stay travelers have contraindications to mefloquine, daily doxycycline (100 mg) beginning 1 day before exposure can be used; unlike atovaquone/proguanil, it must be continued for 4 weeks after exposure. Approximately 5% of individuals who take either mefloquine or doxycycline discontinue therapy because of side effects. One advantage of doxycycline prophylaxis is that it also seems to reduce the risk of influenza-like illness.[8] Tafenoquine, licensed by the U.S. Food and Drug Administration (FDA) in 2018, can be used for chemoprophylaxis only after confirmation of an adequate G6PD enzyme level. The dosing is 200 mg daily for 3 days prior to arrival in the malarious area, continued weekly during exposure, and 1 week after the last exposure. Chemoprophylaxis may be started well before departure (3 to 4 weeks for mefloquine) in individuals who are concerned about possible intolerance

that would interfere with taking prophylaxis while abroad in locations where alternative regimens could not be obtained.

Travelers should be reminded in writing to continue antimalarial drugs for the appropriate period after the last possible exposure, that malaria can still occur despite chemoprophylaxis, and that a malaria smear or malaria rapid diagnostic test is mandatory for any febrile illness occurring within 3 months after travel. Unfortunately, up to one third of travelers may not be fully compliant with their prophylactic regimen.[9] Prevention of malaria in travelers residing in malarious areas for 6 months or more presents a more complex challenge (Chapter 316).

DENGUE, CHIKUNGUNYA, ZIKA

An estimated 100 million cases of dengue fever (Chapter 352) and 250,000 cases of dengue hemorrhagic fever occur annually (Chapter 351).[10] Dengue accounts for up to 2% of all illness in returned travelers, and dengue is the most common systemic febrile illness in returned travelers from every region except sub-Saharan Africa,[11] where malaria still predominates.

Chikungunya virus infection and Zika virus (Chapter 352) were first noted in Africa but have disseminated widely in the tropics, the Pacific Islands, and the Americas. Patients typically have self-resolving fever, mild constitutional symptoms, and sometimes arthralgias. Zika infection can cause severe abnormalities to a fetus and is also associated with a postinfection Guillain-Barré syndrome (Chapter 388) that may not manifest until after the traveler has returned home.[12]

Dengue fever, chikungunya infection,[13] and Zika virus infection are transmitted by day-biting *Aedes* mosquitoes, thereby reinforcing the need to instruct travelers to the tropics in the need for both day and night use of repellents. Several candidate vaccines are in development.

TRAVELER'S DIARRHEA

The most frequent cause of traveler's diarrhea is enterotoxigenic *Escherichia coli* (Chapter 280), and in some locations enteroaggregative *E. coli*. *Salmonella* (Chapter 284), *Shigella* (Chapter 285), and *Campylobacter* (Chapter 279) each account for about 5 to 15% (Table 265-3).[14,15] In Asia, noncholera vibrios are significant. Protozoa account for less than 5%. In adults, norovirus and rotavirus (Chapter 350) are increasingly detected. The mean duration of traveler's diarrhea, even if it is untreated, is only 4 days.

All travelers to the developing world should be thoroughly educated in self-therapy for diarrheal disease and carry the appropriate agents while traveling (Table 265-4). The majority of patients respond to loperamide. However, patients who have fever, systemic symptoms, bloody diarrhea, or diarrhea that is severe or unresponsive benefit from self-treatment with azithromycin. A single dose of 1000 mg is usually sufficient, but patients may continue 500 mg orally daily for up to 3 days if the diarrhea persists. Because of a significant prevalence of quinolone-resistant enteropathogens, particularly *Campylobacter* and *Salmonella*, ciprofloxacin (500 mg/day orally for 3 days) is a less attractive alternative. Other alternatives include oral single-dose levofloxacin (750 mg) or a 3-day course of rifaximin (200 mg 3 times daily).[A1] One of the more commonly identified nonbacterial causes of traveler's diarrhea is giardiasis, which is often refractory to standard treatment with metronidazole or tinidazole; additional therapy may be needed with antiparasitic combinations or with quinacrine (Chapter 322).[16]

For prevention of traveler's diarrhea, bismuth subsalicylate may be used. Most guidelines do not recommend antibiotic prophylaxis for the typical traveler because of potential adverse drug effects while away from medical care and because effective rapid-onset therapy is available for diarrhea should it occur. Exceptions include travelers with advanced human immunodeficiency virus (HIV) infection, individuals who have an underlying chronic medical problem that makes them more prone to adverse consequences from diarrhea, and travelers on a vital mission for a short period (less than 1 week) who cannot tolerate even a day of disability. If indicated, antibiotic prophylaxis can be carried out with rifaximin (200 mg) orally twice per day,[A2] but such prophylaxis should be used only for trips of 2 weeks or less.

SARS-COV-2

SARS-CoV-2 (Chapters 335-337) has reinforced the potential of travel to introduce and spread emerging infections worldwide. The transmission is predominantly person-to-person via droplets and aerosols, and vaccination provides robust protection against severe disease, hospitalization, and death despite breakthrough infections. All travelers should be fully vaccinated against SARS-CoV-2 but also should still take precautions during travel: avoid crowds especially indoors; avoid poorly ventilated spaces; maintain physical distance from others; wear masks in public indoor spaces, crowded outdoor spaces, and public transportation; wash hands well; and clean contaminated surfaces.

PREVENTIVE BEHAVIORS

Most travel-related health problems, including many infectious diseases, can be significantly reduced by appropriate behaviors during travel.

TABLE 265-4 TREATMENTS FOR TRAVELER'S DIARRHEA

PHARMACOLOGIC AGENT	RECOMMENDED DOSAGE	EFFECTIVENESS AND ADVERSE EVENTS
Bismuth subsalicylate	525 mg (1 oz liquid or 2 tablets chewed well) as needed up to 16 tablets in 24 hours	Moderately effective, turns stool and tongue black, may cause tinnitus from systemic salicylate absorption
Loperamide	4 mg then 2 mg orally after each unformed stool up to 8 mg/day	Rapid relief of diarrhea but must be combined with an antibiotic in patients with fever or dysentery
Azithromycin	500 mg orally daily for 3 days or single dose of 1000 mg	First choice for all severe diarrhea but nausea is frequent
Ciprofloxacin	500 mg or 750 mg orally daily for 1-3 days	Fluoroquinolones may be used for nonsevere diarrhea except for India and Southeast Asia where fluoroquinolone-resistant *Campylobacter* is common
Rifaximin	200 mg orally tid for 3 days	Ineffective against invasive pathogens (e.g., *Shigella, Salmonella, Campylobacter*)

Adapted from Steffen R, Hill DR, DuPont HL. Traveler's diarrhea: a clinical review. *JAMA*. 2015;313:71-80; and Riddle MS, Connor BA, Beeching NJ, et al. Guidelines for the prevention and treatment of travelers' diarrhea: a graded expert panel report. *J Travel Med*. 2017;24(Suppl 1):S2-S19.

TABLE 265-3 REGIONAL DIFFERENCES IN THE CAUSE OF TRAVELER'S DIARRHEA

	APPROXIMATE %			
	LATIN AMERICA AND CARIBBEAN	SOUTH ASIA	SOUTHEAST ASIA	AFRICA
BACTERIA				
Enterotoxigenic *E. coli*	≥35	15-25	5-15	25-35
Enteroaggregative *E. coli*	25-35	15-25	Unknown	<5
Campylobacter	<5	15-25	25-35	<5
Salmonella	<5	<5	5-15	5-15
Shigella	5-15	5-15	<5	5-15
VIRUSES AND OTHER				
Norovirus	15-25	5-15	<5	15-25
Rotavirus	15-25	5-15	<5	5-15
Giardia	<5	5-15	5-15	<5

Adapted from Steffen R, Hill DR, DuPont HL. Traveler's diarrhea: a clinical review. *JAMA*. 2015;313:71-80.

MOSQUITO PROTECTION

Protection against arthropods will help prevent malaria (Chapter 316), dengue (Chapter 352), leishmaniasis (Chapter 319), filariasis (Chapter 327), and a number of important arboviral diseases (Chapters 351 and 352). Travelers should be instructed to clothe themselves to reduce exposed skin as much as practicable and to apply a repellent containing active ingredients (e.g., DEET 30 to 35%, picaridin, oil of lemon eucalyptus, IR3535, or 2-undecanone) to all exposed, nonsensitive areas of the body every 4 to 6 hours. More frequent application is required for agents containing lower concentrations of DEET. Travelers should sleep under a permethrin-impregnated bed net in malarious areas[A3] unless they are in a sealed air-conditioned environment. Although anopheline mosquitoes bite at night, *Aedes* spp mosquitoes usually bite during the day, so vigilance at all times of day is necessary.

FOOD AND WATER PRECAUTIONS

Travelers to developing countries should be diligent in washing their hands frequently; avoiding food from dubious eating places, markets, and roadside vendors; avoiding buffets where there are no food covers or fly controls; avoiding high-risk foods such as shellfish, reef fish (ciguatera risk; Chapter 98), undercooked meats and poultry, dairy products, unpeeled fruits, cold sauces, and salads; avoiding both tap water and drinks or ice made from tap water; and using sealed bottled water or chemically treated, filtered, or boiled water to drink and brush their teeth.

SEX

Education on the incidence of HIV infection (Chapter 353) and sexually transmitted infections among professional sex workers abroad, on the use of condoms, and on the failure rate of condoms (3 to 5% breakage/slippage) should be given regardless of the apparent circumstances of the traveler. Unprotected sex, even with fellow travelers, is considered high risk. Travel is a disinhibiting experience in itself, and alcohol consumption tends to increase during travel. HIV pre-exposure prophylaxis (Chapter 356) has become more widely accepted, and daily prophylaxis (200 mg emtricitabine plus 300 mg tenofovir) is an option to prevent HIV infection in persons at risk of exposure through sexual contact, including travelers.

BLOOD-BORNE PATHOGENS

Blood, blood products, syringes, and contaminated medical or dental instruments are a risk after accidents or trauma. Travelers should consider carrying an infusion set, needles, and a suture kit for high-risk areas. If possible, they should defer local medical treatment and instead travel to a facility where safety can be ensured. Tattooing, acupuncture, and body piercing carry similar risks. Health care providers and others at risk in areas of high HIV prevalence without sophisticated medical infrastructure may consider carrying a 1- to 2-week supply of antiretroviral agents to begin immediate postexposure prophylaxis, with the understanding that this initial measure is designed to allow time for travel to an adequate medical facility that is able to provide sophisticated testing and counseling. Two options are (1) emtricitabine 200 mg/tenofovir alafenamide fumarate [TAF] 25 mg 1 tablet daily plus raltegravir 400 mg 1 tablet twice daily (or dolutegravir 50 mg 1 tablet daily) and (2) emtricitabine 200 mg/tenofovir 300 mg 1 tablet daily plus dolutegravir 50 mg 1 tablet daily.

PROTECTION AGAINST SKIN DISEASES

Infected mosquito bites are common. All travelers should practice good hand hygiene in dirty environments and cover open wounds. Scabies and lice infestations (Chapter 98) can be prevented by good personal hygiene. In Africa, all clothes dried outdoors should be ironed to avoid cutaneous myiasis (Chapter 98) caused by the tumbu fly. Hats and sunscreen are mandatory in the tropics. Sunscreen should always be applied to skin before, and not after, an application of DEET.

SWIMMING AND WATER EXPOSURE

Travelers should be instructed to avoid recreational (swimming, rafting, wading) or other exposure to fresh water in areas that are endemic for schistosomiasis (Chapter 326). Hikers, bikers, and adventure travelers should consider prophylaxis with 200 mg of doxycycline orally once per week because of the significant risk of leptospirosis (Chapter 298) that exists in fresh water throughout the developing world. Walking barefoot in tropical areas predisposes to hookworm (Chapter 327), *Strongyloides* infection (Chapter 327), and cutaneous larva migrans (Chapter 327).

PREVENTION OF RESPIRATORY INFECTIONS

A predeparture baseline tuberculin skin or blood test with annual retesting is indicated for long-stay travelers to developing countries. Individuals whose skin or blood tests convert to positive require appropriate treatment to prevent active tuberculosis (Chapter 299). To reduce risk of exposure to respiratory pathogens such as tuberculosis and SARS-CoV-2, travelers should avoid crowded public transportation or crowded public places, follow health authority guidance on masking, and distance themselves immediately from anyone with a chronic or heavy cough. Expatriates should screen domestic help for tuberculosis.

NONINFECTIOUS TRAVEL PROBLEMS

TRAVELER'S THROMBOSIS AND JET LAG

Travel-related immobility is associated with deep venous thrombosis and pulmonary embolism (Chapter 68) in otherwise healthy travelers, but individuals with known risk factors are at highest risk. All travelers should avoid dehydration, avoid alcohol, and exercise their legs regularly in flight. Fortunately, the risk of pulmonary embolus is very low on flights less than 6 hours. Of many recommendations for prevention, only the use of graded 15 to 30 mm Hg compression stockings for individuals at higher risk is supported by randomized trials,[A4] although prophylactic antithrombotic agents such as low-molecular-weight heparin (e.g., enoxaparin 40 mg subcutaneously 2 to 4 hours preflight) or a direct-acting oral anticoagulant (e.g., rivaroxaban 10 mg orally) are sometimes used in practice in patients with a history of thrombosis or a high risk for developing it (e.g., patients with heart failure).[17] Aspirin therapy is of no proven benefit in this setting.

Jet lag (Chapter 374) occurs after crossing three or more time zones. Melatonin (as little as 0.5 mg 30 minutes orally prior to targeted bedtime) may be helpful for reducing the severity of jet lag,[18] and zolpidem (5 mg) taken orally for a few nights at bedtime at the destination is generally effective.

ALTITUDE ILLNESS

Whether ascending by foot, car, or airplane, acute mountain sickness occurs in at least 25% of people who ascend rapidly to 2500 m or more and in most people who go quickly to 3000 m or more (Chapter 82). High altitude can also exacerbate cardiac and pulmonary conditions.[19] Gradual ascent over several days is rarely practiced by modern travelers. For prevention of altitude illness, acetazolamide 125 mg orally twice a day, beginning the morning of the day before ascent and continuing through the day after ascent, is effective.[A5] If symptoms of mountain sickness, such as nausea, vomiting, anorexia, lightheadedness, fatigue, or insomnia, persist beyond the day after ascent, travelers may continue to take one tablet orally each evening. Other medications such as dexamethasone (4 mg orally twice daily) also can be used for prophylaxis or treatment (Chapter 82).[A6] Severe complications, such as pulmonary or cerebral edema, are uncommon under 3500 m and are best treated by oxygen and immediate descent. Those traveling above 3500 m for longer than a brief transit of a few hours should consult an expert.

POST-TRAVEL CARE

The approach to the post-travel patient requires knowledge of world geography, the epidemiology of disease patterns in 230 or so countries, and the clinical presentation of a wide spectrum of disorders.[20] Most illnesses are mild and self-limited, and many are noninfectious. Based on 43,000 ill-returned travelers seen by the GeoSentinel Surveillance Network, specific travel destinations are associated with the probability of the diagnosis of certain diseases (E-Table 265-1). Diagnostic approaches and empirical therapies can be guided by these destination-specific data. Important region-specific disease occurrence data (Table 265-5) indicate that (1) febrile illness[21,22] is most important after travel to Africa and Southeast Asia; (2) malaria is one of the top three diagnoses from every region, but dengue is the most common febrile illness from every region outside of sub-Saharan Africa[23]; (3) in sub-Saharan Africa, rickettsial disease is second only to malaria as a cause of fever; (4) respiratory disease is most important in Southeast Asia and sub-Saharan Africa; and (5) acute diarrhea is disproportionately from South Central Asia. Causes of post-travel fever also depend on the incubation period for various infections (Table 265-6).

Fever alone raises the possibility of malaria (Chapter 316) and should prompt a rapid diagnostic nucleic acid test so that antimalarial or other definitive treatment can be initiated rapidly if it is indicated. Dengue virus infection (Chapter 352) usually has a 2- to 7-day incubation period, but it can be up to 14 days. High fever is usually accompanied by severe headache, myalgia, and arthralgia. Within 5 days of the onset of fever, a diffuse maculopapular rash commonly appears. Diagnosis is by PCR, antigen testing, or IgM serology testing. Chikungunya virus (Chapter 352) infection has a similar clinical presentation to dengue virus

E-TABLE 265-1 SOME KEY DISEASES REPORTED IN FIVE OR MORE TRAVELERS AMONG >43,000 REPORTED ILLNESSES

DIAGNOSES	# OF CASES	TRAVEL HISTORY
GASTROINTESTINAL		
Giardia	1426	India, Thailand, Nepal, and Ghana
Campylobacter	753	India, Thailand, Indonesia, and Tanzania
Strongyloides	483	India, Vietnam, Ghana, and Dominican Republic
Salmonella enteritis	367	Thailand, India, Indonesia, and Egypt
Shigella	271	India, Egypt, Ghana, and Indonesia
Entamoeba histolytica	340	India, Indonesia, Mexico, and Thailand
Vibrio	9	5 cases in Latin America (2 cases acquired in Mexico), 3 in Asia, 1 in sub-Saharan Africa
FEBRILE		
Plasmodium falciparum	1990	Ghana, Comoros, Nigeria, and Côte d'Ivoire
Plasmodium vivax	480	India, French Guyana, Myanmar, and Papua New Guinea
Dengue	1473	Thailand, Indonesia, India, and Brazil
Enteric fever	467	India, Nepal, Pakistan, and Bangladesh
Spotted fever rickettsia	267	South Africa (68.9%), Zimbabwe, Tanzania, and Swaziland
Chikungunya	164	India, Malaysia, Indonesia, and Thailand
Hepatitis A	120	India, Morocco, Egypt, and Mexico
Acute HIV	84	Thailand, Brazil, Guinea, and Germany
Leptospirosis	83	Thailand, Laos, and Costa Rica
Hepatitis E	45	India (40%), Pakistan, and Bangladesh
Brucellosis, acute	33	India, Sudan, and Iraq
Measles	33	India, Thailand, and France
Histoplasmosis	23	Guatemala and Costa Rica
Rickettsia typhi (flea-borne)	17	Cambodia, Malaysia, Vietnam, Indonesia, and Nepal
Visceral leishmaniasis	16	India, Greece, Portugal, and Spain
Orientia tsutsugamushi (scrub typhus)	14	Thailand and Vietnam
Rubella	11	Vietnam and Thailand
Melioidosis	9	Thailand, Singapore, and Malaysia
Mumps	8	Different country for each case (2 in Western Europe, 4 in sub-Saharan Africa, 1 in Latin America, and 1 in Asia)
African trypanosomiasis	6	Zambia (3 cases), Tanzania, Zimbabwe, and Burkina Faso
Relapsing fever	6	Senegal, South Africa, and Morocco
Ross River virus	5	Australia
DERMATOLOGIC		
Rabies prophylaxis after bite or scratch	1249	Thailand, Indonesia, China, and India
Cutaneous larva migrans	806	Thailand, Brazil, Mexico, and Malaysia
Leishmaniasis (cutaneous or mucocutaneous)	264	Bolivia, Afghanistan, and Costa Rica
Myiasis	174	Senegal, Brazil, Costa Rica, and Belize
Tungiasis	87	Brazil, Madagascar, Uganda, and Ethiopia
Gnathostomiasis	12	Cambodia and Indonesia (92% from Asia)
Leprosy	11	Pakistan and Vietnam
Cutaneous atypical mycobacteria	6	All different (Caribbean, sub-Saharan Africa, and South-Central Asia)
RESPIRATORY OR PHARYNGEAL		
Influenza	367	
H1N1	176	United States, Australia, United Kingdom, and Philippines
Influenza A or B	191	Indonesia, Thailand, India, and China
Tuberculosis	170	
MDR or XDR pulmonary tuberculosis	3	1 case each for Nigeria and India (1 case unknown)
Legionellosis	35	China, Italy, and Spain
Pulmonary atypical mycobacteria	35	China, Thailand, Kenya, South Africa, and North America
Pertussis	30	India and China
NEUROLOGIC		
Ciguatera intoxication	51	Bahamas and Dominican Republic
Neurocysticercosis	21	India
Tuberculosis meningitis or tuberculoma	13	India and Pakistan

E-TABLE 265-1 SOME KEY DISEASES REPORTED IN FIVE OR MORE TRAVELERS AMONG >43,000 REPORTED ILLNESSES—cont'd

DIAGNOSES	# OF CASES	TRAVEL HISTORY
Scombroid, neurotoxic or paralytic shellfish poisoning	7	Mauritius (2 cases) and other (2 cases in Western Europe and 2 cases in Southeast Asia)
West Nile virus	5	1 case each in Afghanistan, Costa Rica, Greece, and Israel (1 unknown)
OTHER		
Schistosomiasis	792	Malawi, Uganda, Tanzania, and Ghana
Filariasis	113	Cameroon, Gabon, Democratic Republic of Congo, and Central African Republic
Lyme disease	77	United States, Germany, and Italy
Visceral larva migrans	16	6 cases in Southeast Asia (2 cases acquired in Thailand), 5 in Latin America and the Caribbean, 3 in sub-Saharan Africa, and 2 cases unknown
Fasciola	14	Australia, Germany, France, and the Netherlands
Clonorchis	12	Thailand, Laos, and China
Trichinellosis	12	Poland and Serbia

HIV = human immunodeficiency virus; MDR = multidrug-resistant; XDR = extensively drug-resistant.
Adapted from Leder K, Torresi J, Libman MD, et al. GeoSentinel surveillance of illness in returned travelers, 2007-2011. *Ann Intern Med*. 2013;158:456-468.

TABLE 265-5 CAUSES OF FEVER ASSOCIATED WITH TRAVEL TO DIFFERENT GEOGRAPHIC AREAS

DESTINATION	COMMON CAUSES OF FEVER	OTHER POSSIBLE CAUSES OF FEVER	RARE BUT NOTABLE
Caribbean	Chikungunya virus, dengue virus, malaria, Zika virus	Histoplasmosis, leptospirosis	
Central America	Chikungunya virus, dengue virus, malaria, Zika virus, enteric fever	Leptospirosis, histoplasmosis, coccidioidomycosis, leishmaniasis, paracoccidioidomycosis, brucellosis	*T. cruzi*, hantavirus
South America	Chikungunya virus, dengue virus, malaria, Zika virus	Bartonellosis, leptospirosis, enteric fever, histoplasmosis, paracoccidioidomycosis, brucellosis	*T. cruzi*, hantavirus, yellow fever
South-Central Asia	Dengue virus, enteric fever, malaria	Chikungunya virus, *C. burnetii*, leishmaniasis (visceral), scrub typhus and other Rickettsiae	Crimean-Congo, Japanese encephalitis, Nipah virus
Southeast Asia	Dengue virus, malaria, chikungunya virus, Zika virus, enteric fever	Leptospirosis, melioidosis	Hantavirus, Japanese encephalitis, Nipah virus, paragonimiasis, scrub typhus, talaromycosis
Sub-Saharan Africa	Malaria, Rickettsiae, acute schistosomiasis (Katayama fever), dengue virus, acute HIV	African trypanosomiasis, amebic liver abscess, brucellosis, Chikungunya virus, enteric fever, *N. meningitidis* meningitis	Histoplasmosis, leishmaniasis (visceral), other arboviruses (Rift valley, West Nile, yellow fever), viral hemorrhagic fevers (Ebola, Lassa, Marburg, Crimean-Congo)

Adapted from https://wwwnc.cdc.gov/travel/yellowbook/2020/posttravel-evaluation/fever and Marks M, Johnston V, Brown M. Fever in the returned traveler. In: Ryan ET, Hill DR, Solomon T, Aronson N, Endy TP, eds. *Hunter's Tropical Medicine and Emerging Infectious Diseases*. Elsevier; 2020:1077-1086. Courtesy of Michael Melia, MD.
HIV = human immunodeficiency virus.

TABLE 265-6 DIFFERENTIAL DIAGNOSIS FOR FEVER IN THE RETURNING TRAVELER BASED UPON INCUBATION PERIOD

SHORT (<10 DAYS)	MEDIUM (10-21 DAYS)	LONG (>21 DAYS)
Malaria	Malaria	Malaria
Arboviruses (including Dengue, Chikungunya, Zika)	Enteric fever (*Salmonella typhi* and *Salmonella paratyphi*)	Schistosomiasis (acute)
Hemorrhagic fever viruses (including Ebola, Crimean-Congo, Lassa)	Acute HIV infection	*M. tuberculosis*
Enteric fever (*Salmonella typhi* and *Salmonella paratyphi*)	Hemorrhagic fever viruses (including Ebola, Crimean-Congo, Lassa)	Acute HIV infection
Spotted fever Rickettsiae, *O. tsutsugamushi*	Some Rickettsiae (e.g., epidemic typhus, endemic typhus)	Viral hepatitis
Respiratory viruses	*C. burnetii*	Filariasis
Enteritis (bacterial, viral)	Giardiasis	*C. burnetii*
Bacterial pneumonia	Cytomegalovirus	*T. pallidum*
Relapsing fever	Toxoplasmosis	Epstein-Barr virus (acute)
Amebic dysentery	Amebic dysentery	Amebic liver abscess
N. meningitidis bacteremia	Endemic fungi (including histoplasmosis, coccidioidomycosis)	Leishmaniasis
Meningitis	Brucellosis	Brucellosis
Leptospirosis	Leptospirosis	Bartonellosis (chronic)
Fascioliasis	Babesiosis	Babesiosis
Melioidosis	Rabies	Rabies
Flaviviruses (including tick-borne encephalitis and Japanese encephalitis)	East African trypanosomiasis (acute)	West African trypanosomiasis (chronic)
Brucellosis (rare)	*T. cruzi* (acute)	Cytomegalovirus
Rabies (rare)	Measles	
Trypanosomiasis (rare)	Melioidosis, flaviviruses (including tick-borne encephalitis and Japanese encephalitis) hepatitis A (rare)	

Adapted from Boggild AK, Freedman DO. Infections in returning travelers. In: Bennett JE, Dolin R, Blaser MJ, eds. *Mandell, Douglas, and Bennett's Principles and Practice of Infectious Diseases*. Philadelphia, PA: Elsevier; 2020:3828-3839; and Marks M, Johnston V, Brown M. Fever in the returned traveler. In: Ryan ET, Hill DR, Solomon T, Aronson N, Endy TP, eds. *Hunter's Tropical Medicine and Emerging Infectious Diseases*. Elsevier; 2020:1077-1086. Courtesy of Michael Melia, MD.

except that arthralgia and even arthritis are typical. Zika virus (Chapter 352) infection is usually asymptomatic in adults, but symptomatic persons may have mild nonspecific symptoms similar to chikungunya. Enteric fever (Chapter 284), which exists within the Indian subcontinent and throughout Central and South America, Africa, and other areas of Asia, can cause subacute but progressive fever; it may be diagnosed in blood or stool cultures or by serology but oftentimes requires empiric antibiotics after other causes have been excluded. Viral hemorrhagic fevers (e.g., Ebola, Lassa, and Marburg; Chapter 352), though rare, are also an important consideration because of their infectivity. Fever with dermatologic findings should suggest parasitic infection (e.g., cutaneous larva migrans, leishmaniasis, trypanosomiasis), viral infection (e.g., Zika), rickettsia (e.g., tick bite fever, scrub typhus), or bites (e.g., scabies, myiasis).[24]

Persistent gastrointestinal symptoms in a returning traveler require prompt evaluation and treatment (Table 265-7). Persistent diarrhea is a problem in up to 3% of people who return from developing countries, with parasites (especially *Giardia* [Chapter 322] and *Cryptosporidium* [Chapter 321]) and bacteria (especially enteroaggregative *E. coli* [Chapter 280] and *Shigella* [Chapter 285]) as the leading causes (see Tables 262-1 and 262-2) Diagnosis is based on molecular testing of diarrheal stool (Table 262-4),[25] with supportive care for all, and antibiotics reserved for patients with fever, bloody diarrhea, dehydration, or severe underlying disease (Table 262-5), with the exception that antibiotics should not be used in patients who have Shiga toxin–producing *E. coli*.

Travelers who become ill during or any time up to several months after a foreign trip will frequently associate that illness with a possible travel-specific

TABLE 265-7 COMMON INFECTIOUS AGENTS CAUSING CHRONIC GASTROINTESTINAL DISEASE IN THE RETURNING TRAVELER

	INCUBATION PERIOD (DAYS)	CLINICAL MANIFESTATIONS	DIAGNOSIS	TREATMENT
Giardia	7-10	Abdominal pain, nausea, persistent watery diarrhea	Stool microscopy and stool antigen	Metronidazole, 250 mg, 3 times/day for 7-10 days or 500 mg twice a day for 5-7 days; tinidazole single dose; quinacrine 100 mg 3 times/day for 5 days
Entamoeba histolytica	11-21	Abdominal pain, fever, persistent watery diarrhea	Stool antigen assay	Metronidazole, 500-750 mg, 3 times/day for 7-10 days; plus paromomycin, 500 mg, 3 times/day for 7 days
Strongyloides	11-21	Larva currens, abdominal pain, persistent diarrhea	Stool microscopy	Ivermectin, 200 μg/kg of body weight/day for 2 days
Schistosoma	14-84	Katayama syndrome, abdominal pain, persistent diarrhea, hematuria	Stool and urine microscopy	Praziquantel, 40 mg/kg divided into 2 doses for 1 day for *S. hematobium* and *S. mansoni*, and 60 mg/kg divided into 3 doses for 1 day for *S. japonicum*
Campylobacter	1-4	Acute watery diarrhea, fever	Stool culture	Azithromycin, 500 mg once a day for 3 days
Shigella	1-8	Severe diarrhea, dysentery, fever	Stool culture	Ciprofloxacin, 500 mg twice a day for 3 days
Salmonella				
Serovar Typhi	5-14	Fever, headache, malaise, abdominal pain, diarrhea	Blood and stool culture	Ciprofloxacin, 20 mg/kg/day for 7 days; or azithromycin, 20 mg/kg/day for 7 days
Nontyphoidal	8-24 hours	Fever, headache, malaise, abdominal pain, diarrhea	Blood and stool culture	Ciprofloxacin, 20 mg/kg/day for 7 days; or azithromycin, 20 mg/kg/day for 7 days

Adapted from Ross AG, Olds GR, Cripps AW, et al. Enteropathogens and chronic illness in returning travelers. *N Engl J Med*. 2013;368:1817-1825.

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266 ANTIBACTERIAL CHEMOTHERAPY

ARNOLD LOUIE

Antibiotics provide a backbone for modern interventional medicine, in which surgery, central venous catheters, urinary catheters, implantable devices, and mechanical ventilation have become commonplace. These interventions support seriously ill patients, but they also give bacteria access to normally sterile areas. Therapies for cancer and immune-mediated disease often leave patients severely immunosuppressed. Bacterial infections in such patients are serious, and antibiotics provide critical life-saving support for such patients.

Unfortunately, overuse and poor use of antibiotics have allowed many organisms to develop antibacterial resistance (Chapter 261). Multiresistant *Staphylococcus aureus* has become a plague both in the hospital and in the community. Extended-spectrum β-lactamases and *Klebsiella pneumoniae* carbapenemase enzymes have mediated resistance to many of the most potent and broad-spectrum β-lactam agents, including the carbapenems. Consequently, it is important to understand the principles of antibacterial chemotherapy to obtain the best clinical outcomes for the patient at hand, but also, in a broader sense, to lower the probability of the emergence of resistance so as to maintain the potency of the drugs currently in the therapeutic armamentarium.[1] In this context, the significant decline in the use of antibiotics in the United States in recent years is a good sign.[2]

CHOICE OF ANTIBIOTIC, DOSE, AND ADMINISTRATION SCHEDULE

As in all of clinical medicine, a thorough history and physical examination are central to proper decision making and to achieving optimal therapeutic outcomes in patients with infections. Key to choosing the correct drug, dose, and schedule of antibiotic administration is recognition that an infection exists. The next steps are to document where the infection exists, and then to identify the dominant organisms present at each site of infection. The final step is to determine whether any risk factors might predict the presence of drug-resistant pathogens.

As an example, it is known that community-associated pneumonia (Chapter 85) is caused by certain traditional bacterial pathogens. *Streptococcus pneumoniae* (Chapter 268), *Haemophilus influenzae* (Chapter 277), and *Moraxella catarrhalis* are among the classic bacterial pathogens associated with this entity (Table 266-1). "Atypical" pathogens such as *Legionella* species (Chapter 290), *Mycoplasma pneumoniae* (Chapter 293), and *Chlamydophila pneumoniae* (Chapter 294) also may be seen. In contrast, intra-abdominal infections are dominated by *Escherichia coli* (Chapter 280) and other Enterobacteriaceae (Chapter 281), and anaerobic organisms such as *Bacteroides* species. Consequently, it is important to understand the dominant pathogens present at different infection sites so that the best drug or combination of drugs can be chosen to treat the infection.

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ABSTRACT

Antibiotics have improved human health, both in the treatment of established infections and as prophylaxis against infections associated with surgical and other invasive procedures. Factors for consideration in the selection of empirical single or combination antibiotic treatment include information gained from a history and physical examination, review of available imaging studies, and understanding the likely bacterial species that are in the site of infection, as well as the epidemiologic risk factors for the probability the infection is caused by multidrug-resistant bacteria. Consultation of hospital antibiograms of bacteria encountered in intensive care and other inpatient units is an important part of this framework. Also, for infections in normally sterile sites, a Gram stain may guide the choice of empirical antibiotic therapy. Adherence to pharmacokinetic and pharmacodynamic principles can help optimize the efficacy of antibiotics. Antibiotic susceptibility testing may enable narrowing of the spectrum of activity of the antibiotic regimen.

KEYWORDS

antibiotic principles
principles of antibiotic selection
empirical antibiotic selection
antibacterial drugs
antibiotic therapy
pharmacokinetics-pharmacodynamics
antibiotic resistance

For instance, the penetration by macrolide antibiotics into skin infection sites is modest, but their penetration into the lung is good, with penetration ratios (area under the concentration-time curve [AUC] in lung epithelial lining fluid/AUC in plasma) ranging from 4 to 20. The penetration of β-lactam drugs can range from 15 to 100%, but no set of variables explains such a range of penetrations.

It is also important to understand other factors that increase the probability that a resistant organism is present at the primary infection site. An example is a patient who has recently taken antibiotics before acquiring the present infection. Other examples are the acquisition of an infection in the hospital or in an extended care facility or a patient who is immunosuppressed. In such patients, the choice of antimicrobial agents must be careful to cover more resistant pathogens.

CULTURE AND GRAM STAIN

Once the site of infection has been definitively identified or the most likely source of infection has been determined, it is critical to obtain microbial specimens from that site as well as to obtain blood culture samples. Increasingly, molecular testing is available to provide rapid diagnosis of certain bacterial infections from some sites.[A1] Nevertheless, the correct performance and interpretation of a Gram stain remains an important component for the diagnosis of many infections. Even though it is usually not possible to make a definitive diagnosis on the basis of the cellular morphology of the organism, it is possible to combine information on the morphology, the organism's gram positivity or negativity, the site of the infection, and the most likely pathogens to make an initial antimicrobial choice with the highest probability of producing effective chemotherapy.

The initial antibiotic regimen chosen to cover organisms present at the primary infection site has a significant influence on the outcome of therapy, and such initial choices should always err on the side of caution. When the specific microorganism has been identified and even before antimicrobial susceptibility testing results are available, the chemotherapy usually can be streamlined.

SUSCEPTIBILITY

Because infections occur at a specific place, it is important to have an understanding of the local antimicrobial susceptibility patterns. Oftentimes, these susceptibility patterns are different even within the same hospital. For example, patients on a general inpatient unit are generally (but not always) infected with pathogens derived from the community setting, whereas patients in an intensive care unit (ICU) are more likely to have hospital-acquired infections. In severely infected patients, particularly patients whose infections were acquired in the ICU, infections are likely to be resistant to multiple antimicrobial agents.

Antimicrobial susceptibility testing[3] can determine the minimal inhibitory concentration (MIC), or can tell whether an organism is susceptible (S), intermediate (I), or resistant (R) to an antibiotic. The MIC is often misunderstood as the concentration of drug that prevents the pathogen from growing, but it is actually the concentration of drug that allows a tube (or well) containing the pathogen to remain clear by visual examination after 16 to 24 hours. This criterion can actually allow almost a 1 $\log_{10}$ (colony forming units [CFU]/mL) increase in bacterial count over this time frame and still be read as the MIC. With all its limitations, the MIC provides critical information about drug choice. For several infections, such as meningitis, endocarditis, and perhaps bacteremia, knowing the minimal bactericidal concentration (defined as the concentration required to kill 99.9% of organisms during 16 to 24 hours) is valuable. In these cases, it is important to obtain multi-log killing of the organism to ensure a high probability of a good clinical outcome. For meningitis and endocarditis, there is also the confounding problem of penetration of the drug into the primary infection site. In other circumstances (e.g., ventilator-associated pneumonia) in which bacterial burdens are high, optimizing the probability of cure requires highly bactericidal therapy.

TABLE 266-1 PRIMARY INFECTION SITES AND THE DOMINANT BACTERIAL SPECIES PRESENT

SITE	BACTERIA
Complicated skin or skin structure infection	*Staphylococcus aureus* and *Streptococcus* spp
Diabetic foot ulcer	Organisms above plus Enterobacteriaceae
Intra-abdominal infections	*Escherichia coli* and other Enterobacteriaceae plus anaerobes
Community-acquired bacterial pneumonia	*Streptococcus pneumoniae, Haemophilus influenzae, Moraxella catarrhalis*, "atypical" pathogens
Hospital-acquired pneumonia	*S. aureus, Klebsiella pneumoniae, Enterobacter* spp, *Pseudomonas aeruginosa, Acinetobacter* spp
Meningitis	*S. pneumoniae, H. influenzae* (nontypable), meningococci; in hospital settings, *S. aureus* and gram-negatives
Urinary tract infections	Enterobacteriaceae, particularly in sexually active women; multiresistant gram-negatives in patients with complicated urinary tract infections or those instrumented; enterococci, particularly in elderly men
Prostatitis	Enterobacteriaceae, enterococci, atypical pathogens

spp = species.

DETERMINING THE "CORRECT" DRUG DOSE

The correct drug dose is the one that produces a high likelihood of achieving a good clinical response with a low probability of causing a concentration-driven adverse event. Another consideration is that the optimal dose should have a high probability of suppressing the emergence of resistant mutants. Confidence that a drug dose has a high likelihood of producing a good clinical outcome requires an understanding of the relationship between drug exposure and outcome, i.e., pharmacodynamics (Chapter 25).

When a drug is administered intravenously or orally, the drug concentration starts low, increases to a maximal value, then declines over time until another dose of the drug is given (in a multidose regimen). This drug concentration–time profile should be seen relative to a measure of drug potency against the pathogen in question: the MIC (or minimal bactericidal concentration). Protein binding is also important because, in almost all cases, it is the free or non–protein-bound drug that kills the causative pathogen. So understanding the pharmacodynamics of a drug or class of agents first requires knowledge of the drug's concentration–time profile, protein binding, and MIC (Fig. 266-1). For drugs that kill organisms much faster as their concentrations rise (e.g., fluoroquinolones, aminoglycosides), the free drug AUC/MIC ratio is most closely linked to drug effect. For other drugs (e.g., penicillins, carbapenems, cephalosporins, monobactams), the rate of kill rises with the concentration and plateaus quickly, in which case the free drug time greater than MIC (T > MIC) is most closely linked to drug effect. On occasion, the free drug peak concentration/MIC ratio is linked to drug effect, as is seen when there is a rapid and frequent emergence of resistance, and the peak concentration helps suppress the amplification of resistant mutant subpopulations.

RESISTANCE

Antimicrobial resistance is a growing problem in both the hospital and outpatient settings.[4,5] If the drug is properly chosen, the organism should have a high probability of being susceptible to it. However, during the course of therapy, the organism has many mechanisms available to make it less susceptible (the MIC increases) to the administered drug, thereby making the drug less effective than was originally envisioned and resulting in a lower probability of cure.

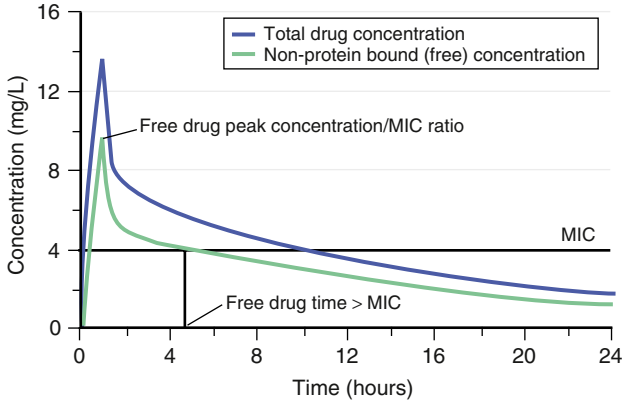

FIGURE 266-1. Three measures of drug exposure are important to the measure of potency, or the minimal inhibitory concentration (MIC). These measures are free drug peak concentration/MIC ratio, free drug time greater than MIC, and free drug area under the curve (AUC)/MIC ratio. AUC = area under the concentration-time curve.

TABLE 266-2 MECHANISMS OF ANTIMICROBIAL RESISTANCE

ANTIBACTERIAL AGENT	MECHANISM	REPRESENTATIVE ORGANISM
β-Lactams (penicillins, cephalosporins, carbapenems, aztreonam)	Altered target (penicillin-binding proteins)	Methicillin-resistant *Staphylococcus aureus* (MRSA), penicillin-resistant *Streptococcus pneumoniae, Enterococcus faecium*
	Reduced permeability	Enterobacter spp, *Pseudomonas aeruginosa, Acinetobacter* spp
	Enhanced efflux	*P. aeruginosa, Acinetobacter* spp
	β-Lactamases	*S. aureus*, Enterobacteriaceae (includes ESBLs), *Haemophilus influenzae, Moraxella catarrhalis , Neisseria gonorrhoeae, Enterococcus faecalis, P. aeruginosa, Acinetobacter* spp
Aminoglycosides	Inactivating enzymes (acetylation, adenylation, phosphorylation)	*S. aureus*, enterococci, *P. aeruginosa,* Enterobacteriaceae
	Reduced permeability	Enterobacteriaceae, *P. aeruginosa ,* enterococci
	Enhanced efflux	*P. aeruginosa*
	Decreased ribosomal binding	*S. aureus, E. faecalis,* mycobacteria (streptomycin), gram-negative pathogens (aminoglycoside ribosomal methylase)
Chloramphenicol	Enhanced efflux	*H. influenzae*
	Reduced permeability	Enterobacteriaceae
	Inactivating enzyme (acetylation)	*S. aureus, S. pneumoniae,* enterococci
Daptomycin	Altered target	*S. aureus*
Glycylcyclines	Enhanced efflux	Enterobacteriaceae, especially *Proteus*
Macrolides, clindamycin, ketolide, quinupristin	Altered target (methylation of ribosomal RNA)	*S. aureus, S. pneumoniae* (not ketolide), streptococci, *Bacteroides fragilis*
	Enhanced efflux (not clindamycin or ketolide)	*S. pneumoniae*, streptococci
	Reduced permeability	Enterobacteriaceae
	Inactivating enzymes	*Escherichia coli, Klebsiella pneumoniae, S. aureus*
Lefamulin	Altered target	*S. aureus, Mycoplasma* spp
Oxazolidinones	Altered target	Streptococci, enterococci, *S. aureus*
Quinolones	Altered target (DNA gyrase, topoisomerase IV)	Enterobacteriaceae, *P. aeruginosa*
	Reduced permeability	Enterobacteriaceae, *P. aeruginosa*
	Enhanced efflux	*E. coli, P. aeruginosa*
Tetracyclines	Altered target (ribosome)	*N. gonorrhoeae,* streptococci
	Enhanced efflux	*E. coli, S. pneumoniae*
	Reduced permeability	Enterobacteriaceae
	Drug inactivation	*B. fragilis*
Rifampin	Altered target (β-subunit of polymerase)	*E. coli, S. aureus, Mycobacterium tuberculosis*
Sulfonamides, trimethoprim	Altered target (dihydropteroate synthase or dihydrofolate reductase)	Enterobacteriaceae, *M. catarrhalis*
	Enhanced *p*-aminobenzoic acid production	*S. aureus, N. gonorrhoeae*
	Reduced permeability	*P. aeruginosa,* Enterobacteriaceae
Vancomycin and lipoglycopeptides	Altered target (peptidoglycan precursor binding site)	*E. faecium, E. faecalis, S. aureus*

ESBLs = extended-spectrum β-lactamases; spp = species.

MECHANISMS OF RESISTANCE

Five factors account for the majority of cases of resistance emerging during therapy (Table 266-2). The first is the mutational frequency to resistance of the organism being treated. Because mistakes are made by the organism during replication, mutations occur in the genome at a specific rate, which is organism-dependent. For antibiotic resistance, the mutational frequency rate is generally about 1 in 10^6 to 10^8 CFU. Some organisms, however—referred to as hypermutators—that have mutations in other parts of the genome that alter their DNA replication error–checking mechanisms. These organisms' mutational frequencies are generally 10- to 100-fold higher than those of organisms without such mutations.

The second factor is related to the bacterial burden. As the bacterial burden increases and ultimately surpasses the inverse of the mutational frequency to resistance, it becomes increasingly more likely that a preexistent antibiotic-resistant mutant already exists in the population. For example, if the mutational frequency to resistance is 1 resistant organism per 10^7 CFU and the patient has a bacterial infection in which the total bacterial burden is 10^9 organisms, it is highly likely that a resistant organism is present in the population a priori. Antibiotic pressure provides these mutants with a selective advantage; they are amplified, whereas the more susceptible bacteria are killed by the antibiotic. A calculation of the actual probability can be performed by a Poisson distribution, the bacterial burden, and the mutational frequency to resistance. Consequently, infections in which the bacterial burden is high are more likely to generate resistance during therapy. For example, in clinical trials of ventilator-associated pneumonia, single-agent β-lactam drugs or fluoroquinolones allow the emergence of antibiotic resistance during therapy 33 to 50% of the time.

The third issue is drug penetration. In some circumstances, such as an empyema, the bacterial burden is high, but the drug's penetration to the infection site is reduced. In this case the emergence of resistance is more likely. In contrast, poor penetration with relatively low bacterial burdens (e.g., meningitis) generally does not result in a high probability of the emergence of resistance.

The fourth issue has to do with error-prone replication in bacterial pathogens. When resistance develops relatively late in therapy and the bacterial burden is modest, error-prone replication is often to blame. Antibiotics differ greatly with respect to their ability to induce the bacterial isolate to perform error-prone replication. Perhaps the best example is the fluoroquinolone antimicrobials, because these drugs strike at the heart of DNA replication. The organism senses the attack of the antibiotic, and a cascade of events ensues, the most important of which is the induction of error-prone polymerases (e.g., pol V). These polymerases markedly increase the error rate in DNA replication. Most of these errors are lethal to the organism and therefore unhelpful to it. However, because this process is totally random, by chance a mutation can occur in a gene that provides protection from the onslaught of the antibiotic (e.g., a mutation in the DNA gyrase when the patient is receiving a fluoroquinolone). This selective replication advantage (emergence of resistance) results in an increase in the MIC of the mutant organism relative to the baseline organism.

The fifth factor relates to mechanisms other than antibacterial target site mutations that allow the organisms to survive in the face of appropriate antibiotic chemotherapy. One extremely common mechanism seen in the majority of both gram-positive and gram-negative organisms is the upregulation of efflux pumps. These pumps are indiscriminate in their ability to pump molecules; they can eject multiple classes of antibacterials from the organism as

well as other natural substances that can harm it, such as metal ions. These pumps keep drug concentrations at their target sites much lower than they would be in the absence of the pumps. The pumps can be induced and then downregulated once the threat has passed; or occasionally, the organism can have a mutation in the part of the genome where expression of the pump is regulated, so the pump is always expressed (constitutive expression).

A similar process is seen with the production of β-lactamases. Often, these enzymes are situated on plasmids and are produced continuously. Sometimes, as with the efflux pumps, the bacteria sense the β-lactam, and their β-lactamase production is markedly increased (the phenomenon of induction, seen with ampC-type enzymes, which generally reside on the chromosome). Sometimes, also like the pumps, the organisms have a mutation in the part of the genome that regulates production of the β-lactamase. This event is referred to as *stable de-repression,* and large quantities of the enzyme are made continuously. The enzyme hydrolyzes its substrate (the β-lactam drug), thereby preventing this antibiotic from binding to the target sites, the β-lactam–binding proteins.

Finally, in gram-negative organisms, the drug must cross the diffusional barrier of the outer membrane before binding to β-lactam–binding proteins (if the drug is a β-lactam) in the periplasm of the organism, or it must cross the inner membrane if its target site is actually inside the organism. For many agents, particularly those that are water soluble, a large percentage of their influx is due to passage through porin proteins. These proteins are water-filled channels that pass through the entirety of the outer membrane of gram-negative bacteria. Part of their function is to provide access to nutrients for the organism and allow the easy diffusion of waste products. These channels are also used to obtain passage by water-soluble antibacterial agents. The organism has the ability to downregulate these channels, either temporarily or permanently (by mutation). An example is *Pseudomonas aeruginosa* (Chapter 282), in which downregulation of the porin channel oprD markedly diminishes the penetration of carbapenem antibiotics (β-lactam agents), with a resultant two- to eight-fold rise in MIC.

These mechanisms also interact. In most cases, resistance is caused by an alteration in the target site; by an enzyme that alters the drug, thereby resulting in a lack of activity; by the drug's being pumped out of the organism; or, in the case of gram-negative pathogens, by the loss or downregulation of a transmembrane porin protein. These mechanisms, along with error-prone replication, can interact to cause large increases in the MIC. For example, a gram-negative pathogen that acquired a mutation in its gyrase enzyme would generally have only a four-fold increase in its MIC value for a fluoroquinolone antimicrobial; however, if this isolate also had an efflux pump upregulated, the MIC could change 8- to 16-fold. In the case of fluoroquinolone antimicrobials, where error-prone replication almost always occurs under pressure, the upregulation of efflux pumps relieves some of the antibiotic pressure, thereby allowing the organisms to undergo more rounds of replication per unit of time, giving the error-prone replication mechanism more time to find a mutation that is not lethal, and providing protection against the drug at the primary target site.

With all the mechanisms that can be brought to bear, it is not surprising that poor dosing and prolonged courses of therapy often lead to the emergence of resistance.

SUPPRESSING THE EMERGENCE OF RESISTANCE

Suppressing the emergence of resistance is an end point that is different from achieving a good clinical or microbiologic outcome. The antimicrobial exposure (free drug peak concentration/MIC ratio, free drug AUC/MIC ratio, or free drug time greater than MIC) necessary to suppress resistance is always at least as high as that required to attain maximal killing of bacterial cells; and in many instances, it is substantially higher.

Fortunately, it is possible to identify drug doses and administration schedules that suppress the emergence of resistance as well as provide optimal killing of bacterial cells. Unfortunately, many of the exposures necessary to achieve such an outcome are high enough to increase the probability of drug toxicity.

The other way to help suppress the emergence of resistance is to employ combination chemotherapy. Combination therapy has major advantages but significant disadvantages as well. Among the advantages are that combination therapy can improve the spectrum of coverage in the setting of empirical treatment as well as help suppress the emergence of resistance. This phenomenon is best seen in the treatment of *Mycobacterium tuberculosis* (Chapter 299), although there is growing evidence that this may also be true for difficult-to-treat pathogens such as *P. aeruginosa* (Chapter 282) and *Acinetobacter* (Chapter 283) species. Combination therapy can be effective against some pathogens in serious infections for which a single agent would not be adequate. Enterococcal endocarditis (Chapters 61 and 270) is the classic example; ampicillin or vancomycin is generally static and not up to the task of curing this disease, and the second agent (an aminoglycoside, streptomycin, or gentamicin) is somewhat resistant when it is used alone (MIC values <500 mg/L). Yet the combination produces excellent bacterial cell killing in the endocarditic vegetation, with a high probability of cure if the patient can tolerate the combination for the requisite time.

The disadvantages of combination therapy are also well known. At full doses of each, there may be added toxicity and there are certainly greater costs associated with combinations. Finally, combinations of agents may interact antagonistically instead of either additively or synergistically. For example, the combination of tetracycline plus penicillin is somewhat antagonistic and should be avoided. However, there are circumstances in which weak antagonism is tolerable. For instance, the combination of isoniazid plus rifampin, part of the standard therapy for *M. tuberculosis* (Chapter 299), is somewhat antagonistic with respect to cell killing, but the combination provides superb protection against the emergence of resistance.

MECHANISM OF ACTION

The search for new antimicrobials begins with the principle that the target that affects pathogens must not be in the human genome or must be sufficiently different that the agent in question does not cause appreciable human toxicity (Table 266-3). β-Lactam antibiotics are a good example: the inhibition of peptidoglycan synthesis has no effect on humans because this target is simply not present. An example of differing susceptibility to inhibition because of poor sequence homology between bacteria and humans can be seen in the inhibitors of the bacterial ribosome. The bacterial ribosome is much smaller than that in humans and has differing affinities for such drugs as aminoglycosides, tetracyclines, macrolides, and clindamycin. Consequently, such agents are an important part of the therapeutic armamentarium and cause only minor adverse effects related to their primary mode of action. In some cases, so-called off-target toxicity may take place. Again, an example is the β-lactams; a major toxicity is accelerated allergic reaction, even though the target for the agents is not present in humans.

Often, antimicrobials are thought of as either *bacteriostatic* or *bactericidal,* for which there are standard definitions. An agent that causes a 1000-fold decline (3 $\log_{10}$ [CFU/mL] decrease) in an in vitro test system during 18 to 24 hours is defined as being bactericidal. Any agent that causes a smaller decline is defined as bacteriostatic. Although these definitions are arbitrary, there is a clinical connection. Bacteriostatic and bactericidal antibiotics are equivalently effective for abdominal infections, skin and soft tissue infections, and pneumonia,[6] but data are not sufficient for meningitis, endocarditis, or patients who are neutropenic.[A2] Obviously, the more organisms the antimicrobial kills, the easier it is to accomplish cure. In other circumstances, such as multilobar pneumonia, it is critical to kill as many of the organisms as possible so as not to overwhelm the body's immunologic defenses. For these reasons, clinicians generally prefer bactericidal to bacteriostatic agents.

EFFECTS OF PHARMACOKINETIC CHANGES

Whereas antimicrobial pharmacodynamics is the study of the effect of a drug on an infecting organism, pharmacokinetics is the study of the effect of the body's processes on the drug concentration–time profile and the drug's ability to penetrate to the site of the infection (or the site of toxicity). A drug's pharmacokinetics are prime determinants of whether a drug will be able to kill or to inhibit the offending pathogen and, because many toxicities are concentration related, whether a serious drug-related toxicity will occur.

Each antimicrobial has an appropriate administration schedule (Table 266-4) that considers its antimicrobial activity, protein-binding ability, and whether alterations in renal or hepatic function cause major changes in its concentration-time profile. As in all chemotherapy, the aim is to achieve a concentration-time profile in the plasma and at the infection site sufficient to inhibit or to kill the pathogen without causing toxicity. In some situations, continuous infusion may be preferable to intermittent dosing to maintain therapeutic drug levels.[A3]

Although it is almost always possible to provide a reliable guide to the concentration–time profile that results in an appropriate antimicrobial effect, it is more difficult to identify a linkage between drug exposure and the occurrence of toxicity. For the aminoglycosides, the exposure-efficacy and exposure-nephrotoxicity relationships show that higher aminoglycoside AUC exposures increase the probability of treatment efficacy and drug toxicity

TABLE 266-3 MECHANISMS OF ACTION OF ANTIMICROBIAL AGENTS

AGENT	SITE OF ACTION	EFFECT	BACTERICIDAL	BACTERIOSTATIC
β-Lactams (penicillins, cephalosporins, carbapenems, aztreonam)	Cell wall: penicillin-binding proteins	Inhibit cross-linking of peptidoglycan (transpeptidation), impair cell wall synthesis	+	Occasionally (enterococci)
Vancomycin, teicoplanin, dalbavancin, telavancin, oritavancin	Cell wall: terminal D-alanyl-D-alanine of pentapeptide peptidoglycan precursor	Inhibit polymerization of disaccharide precursors to peptidoglycan (transglycosylation), impair cell wall synthesis	+	Occasionally (enterococci)
Daptomycin	Cell membrane	Rapid depolarization of membrane potential	+	Occasionally (enterococci)
Aminoglycosides	Protein synthesis: 30 S ribosome subunit	Inhibit peptide elongation, cause misreading of genetic code, inhibit protein synthesis	+	
Tetracyclines, glycylcyclines	Protein synthesis: 30 S ribosome subunit	Inhibit binding of transfer RNA, inhibit protein synthesis	Occasionally	+
Chloramphenicol	Protein synthesis: 30 S ribosome subunit	Blocks attachment of aminoacyl transfer RNA, inhibits protein synthesis	Occasionally	+
Macrolides, azalides, ketolides	Protein synthesis: 50 S ribosome subunit	Block transfer of amino acids to peptide chain, inhibit protein synthesis	Occasionally	+
Clindamycin	Protein synthesis: 50 S ribosome subunit	Blocks transfer of amino acids to peptide chain, inhibits protein synthesis	Occasionally	+
Quinupristin-dalfopristin	Protein synthesis: 50 S ribosome subunit	Block extrusion of peptide chains, inhibit protein synthesis	+	+ (with quinupristin resistance)
Linezolid and tedizolid	Protein synthesis: 50 S ribosome subunit	Blocks formation of 70 S initiation complex, inhibits protein synthesis	Occasionally	+
Rifampin	Nucleic acid synthesis: β-subunit of DNA-dependent RNA polymerase	Inhibits RNA synthesis	+	
Metronidazole	Nucleic acid synthesis	Damages nucleic acids, inhibits DNA synthesis	+	
Quinolones	Nucleic acid synthesis: DNA gyrase, topoisomerase IV	Impair supercoiling of DNA, prevent decatenation of DNA molecules after replication, inhibit DNA synthesis	+	
Sulfonamides	Folic acid synthesis: dihydropteroate synthase	Competitive inhibition of synthesis of dihydrofolate from *p*-aminobenzoic acid, pteroate, and glutamic acid	Occasionally (when used with trimethoprim)	+
Trimethoprim	Folic acid synthesis: dihydrofolate reductase	Inhibits reduction of dihydrofolate to tetrahydrofolic acid	Occasionally (when used with sulfonamide)	+
Lefamulin	Protein synthesis: 50 S ribosome subunit	Inhibits binding of transfer RNA, inhibit protein synthesis	Occasionally (microbe specific)	+ (*S. aureus*, *S. pyogenes*)

TABLE 266-4 DOSAGE REGIMENS OF ANTIBACTERIALS, PHARMACOKINETICS, AND DOSE ADJUSTMENT IN PATIENTS WITH RENAL OR HEPATIC FAILURE

CLASS/AGENT	DOSE* FOR SYSTEMIC INFECTION	ORAL FORMULATION	PEAK SERUM CONCENTRATION (μg/mL)	PROTEIN BINDING (%)	NORMAL SERUM HALF-LIFE (hr)	HEPATIC FAILURE	RENAL FAILURE	SERUM LEVELS ALTERED BY DIALYSIS
AMINOGLYCOSIDES								
Amikacin	5-6.7 mg/kg q8h or 15-20 mg/kg q24h	—	35	0	2-3	No	Major	Yes (H, P)
Gentamicin	1.7 mg/kg q8h or 5 mg/kg q24h	—	7	0	2-3	No	Major	Yes (H, P)
Netilmicin	1.7 mg/kg q8h or 5 mg/kg q24h	—	7	0	2-3	No	Major	Yes (H, P)
Plazomicin	15 mg/kg q24h	—	74	0	3-4	No	Yes	Yes (H, P)
Tobramycin	1.7 mg/kg q8h or 5 mg/kg q24h	—	7	0	2-3	No	Major	Yes (H, P)
ANTITUBERCULOUS AGENTS								
Bedaquiline	400 mg q24h (PO) for 2 wk then 200 mg 3×/wk	Yes	5.5	99.9	3,960	No	No	No
Ethambutol	15 mg/kg q24h (PO)	Yes	2	10	3.3	No	Major	Yes (H, P)
Isoniazid	5 mg/kg q24h up to 300 mg q24h (PO)	Yes	4.5	10	3	Yes	Major	Yes (H, P)
Pretomanid	200 mg q24h†	Yes	2	86	16	Unknown‡	Unknown‡	Unknown‡

TABLE 266-4 DOSAGE REGIMENS OF ANTIBACTERIALS, PHARMACOKINETICS, AND DOSE ADJUSTMENT IN PATIENTS WITH RENAL OR HEPATIC FAILURE—cont'd

CLASS/AGENT	DOSE* FOR SYSTEMIC INFECTION	ORAL FORMULATION	PEAK SERUM CONCENTRATION (μg/mL)	PROTEIN BINDING (%)	NORMAL SERUM HALF-LIFE (hr)	HEPATIC FAILURE	RENAL FAILURE	SERUM LEVELS ALTERED BY DIALYSIS
Pyrazinamide	10 mg/kg q8h (PO)	Yes	12	10	10	Yes	Yes	Yes (H)
Rifampin	10 mg/kg up to 600 mg q24h (PO)	Yes	7	81-89	3	Yes	Minor	No (H)
CARBAPENEMS								
Doripenem	0.5-1.0 g q8h	—	23	<10	1	No	Yes	Yes (H)
Ertapenem	1 g q24h	—	155	95	4-5	Unknown	Yes	Yes (H)
Imipenem	0.5-1 g q6-8h	—	40	15	1	No	Avoid in severe renal dysfunction	Yes (H)
Imipenem-relebactam	1.25 g q6h	—	104	20	1	No	Yes	Yes (H)
Meropenem	0.5-2 g q8h	—	50	<10	1	No	Yes	Yes (H)
Meropenem-vaborbactam	4 g q8h	—	50	<10	2.3	No	Yes	Yes (H)
FIRST-GENERATION CEPHALOSPORINS								
Cefadroxil	1000 mg q12h (PO)	Yes	16	20	1.5	No	Yes	Yes (H)
Cefazolin	0.5-2 g q8h	—	180	80	2	No	Major	Yes (H) No (P)
Cephalexin	250-500 mg q6h (PO)	Yes	18	15	1	No	Yes	Yes (H, P)
Cephradine	500-1000 mg q6-12h	Yes§	140	10	103	No	Yes	Yes (H, P)
SECOND-GENERATION CEPHALOSPORINS								
Cefaclor	250-500 mg q8h (PO)	Yes§	10	25	0.8	No	Yes	Yes (H)
Cefoxitin	1-2 g q6-8h	—	220	70	0.8	No	Yes	Yes (H) No (P)
Cefprozil	250-500 mg q12h (PO)	Yes	10	35	1.4	No	Yes	Yes (H)
Cefuroxime	750-1500 mg q8h	—	100	50	1.5	No	Yes	Yes (H, P)
Cefuroxime axetil	250-500 mg q12h (PO)	Yes	9	50	1.5	No	Yes	Yes (H, P)
THIRD-GENERATION CEPHALOSPORINS								
Cefdinir	300 mg q12h (PO)	Yes	2	65	1.7	Unknown	Minor	Yes (H)
Cefditoren pivoxil	400 mg q12h (PO)	Yes	4	88	1.6	No	Yes	Yes (H)
Cefixime	400 mg q24h (PO)	Yes	3-5	67	3	No	Yes	No (H, P)
Cefotaxime	1-2 g q6-8h	—	200	50	1.5	Minor	Minor	Yes (H) No (P)
Cefpodoxime proxetil	200-400 mg q12h (PO)	Yes	3	25	2.5	No	Yes	Yes (H)
Ceftazidime	1-2 g q8h	—	160	60	2	No	Major	Yes (H, P)
Ceftazidime-avibactam	2.5 g q8h	—	160	60	2	No	Major	Yes (H)
Ceftibuten	400 mg q24h (PO)	Yes	15	65	2.5	Unknown	Yes	Yes (H)
Ceftizoxime	1-2 g q6-8h	—	130	30	1.3	No	Major	Yes (H) No (P)
Ceftriaxone	1-2 g q12-24h	—	250	90-95	8	No	No	No (H)
FOURTH-GENERATION CEPHALOSPORINS								
Cefepime	1-2 g q8h	—	193	20	2	No	Major	Yes (H, P)
Cefiderocol	2 g q8h (3-h infusions)	No	138	40 - 60	2	No	Yes	Yes (H)
Ceftaroline	600 mg q8-12h	—	21.3	20	2.6	No	Major	Yes (H)
Ceftolozane-tazobactam	1.5 g q8h	—	74	16-21	3.1	No	Yes	Yes (H)
PENICILLINS								
Amoxicillin	500 mg q8h (PO)	Yes	10	20	1	No	Yes	Yes (H) No (P)
Amoxicillin–clavulanic acid‖	875/125 mg q8-12h	Yes	2.7	25	1.3	Unknown	Moderate	Yes (H, P)
Ampicillin	1 g q6h	Yes§	200	20	1	No	Yes	Yes (H) No (P)
Cloxacillin	500 mg q6h (PO)	Yes§	9	95	0.5	No	No	No (H, P)
Dicloxacillin	500 mg q6h (PO)	Yes§	18	97	0.5	No	No	No (H, P)
Nafcillin	1-2 g q4-6h	—	160	90	0.5	Yes	No	No (H, P)
Oxacillin	1-2 g q4-6h	—	200	90	0.5	Yes	No	No (H, P)
Penicillin G	3-4 million units q4-6h	Yes§	60	60	0.5	No	Yes	Yes (H) No (P)
Penicillin V	500 mg q6h (PO)	Yes	5	80	1	No	No	Yes (H) No (P)

TABLE 266-4 DOSAGE REGIMENS OF ANTIBACTERIALS, PHARMACOKINETICS, AND DOSE ADJUSTMENT IN PATIENTS WITH RENAL OR HEPATIC FAILURE—cont'd

CLASS/AGENT	DOSE* FOR SYSTEMIC INFECTION	ORAL FORMULATION	PEAK SERUM CONCENTRATION (μg/mL)	PROTEIN BINDING (%)	NORMAL SERUM HALF-LIFE (hr)	HEPATIC FAILURE	RENAL FAILURE	SERUM LEVELS ALTERED BY DIALYSIS
Piperacillin/ tazobactam	3.375-4.5 g q6-8h	—	240	50	1	Minor	Minor	Yes (H)
Ticarcillin/ clavulanate	3.1 g q4-8h		220	50	1	Minor	Major	Yes (H, P)
MONOBACTAMS								
Aztreonam	1-2 g q8h	—	250	60	2	No	Major	Yes (H, P)
QUINOLONES								
Ciprofloxacin	400 mg q8-q12h 500-750 mg q12h (PO)	Yes§	2-3	30	4	No	Minor	No (H, P)
Delafloxacin	300 mg q12h 450 mg q12h (PO)	Yes	7.4	84	3.7	No	Minor	No (H)
Levofloxacin	250-750 mg q24h (IV or PO)	Yes	6-9	30	7	No	Yes	No (H, P)
Moxifloxacin	400 mg q24h (IV or PO)	Yes	4-5	50	10	No–minor	No	No (H, P)
TETRACYCLINES, GLYCYLCYCLINES								
Doxycycline	100 mg q12-24h (PO) after 200-mg loading dose	Yes	1.5-2.1	93	15-20	Avoid	No	No (H, P)
Eravacycline	1 mg/kg q12h	—	2	79-90	20	Yes	No	No (H)
Minocycline	100 mg q12-24h (PO) after 200-mg loading dose	Yes	2.2	75	15	No	Avoid	No (H, P)
Omadacycline	300 mg q24h (PO) after a loading dose of 450 mg q24h for 2 days	Yes	5.5	20	15.5	No	No	No (H)
Tetracycline	500 mg q6h (PO)	Yes§	4	50	7	Avoid	Avoid	No (H, P)
Tigecycline	100 mg, then 50 mg q12h	—	0.6-0.9	70	37-38	Minor	No	No (H, P)
SULFONAMIDES								
Sulfadiazine	15 mg/kg q6h	Yes	30	50	3	Avoid	Avoid	Unknown
Sulfamethoxazole	0.5-1 g q6-8h (PO)	Yes	100	50	9	Avoid	Major	Yes (H) No (P)
Trimethoprim (with sulfa-methoxazole)	3-5 mg/kg q6-8h (based on trimethoprim component)	Yes	3-9	60	10	No	Avoid	Yes (H) No (P)
MACROLIDES, LINCOSAMIDES, KETOLIDES								
Azithromycin	500 mg first dose, followed by 250 mg q24h or 500 mg × 3 days (PO) Single-dose therapy of 1-2 g for STIs	Yes§	0.4	25	12-50	Unknown	No	No (H, P)
Clarithromycin	500 mg q12h (PO)	Yes	2-3	70	7	No	Minor	Yes (H) No (P)
Clindamycin	0.3-0.9 g q8h	Yes	15	90	2.5	Minor	No	No (H, P)
Erythromycin	500 mg q6h (PO)	Yes§	1.8	70	2	Minor	No	No (H, P)
Telithromycin	800 mg q24h (PO)	Yes	2	65	10	No	No	No (H)
OXAZOLIDINONES								
Linezolid	600 mg q12h	Yes	18	30	5	No–minor	No	Yes (H)
Tedizolid	200 mg q24h	Yes	2	70-90	12	No		
OTHER AGENTS								
Chloramphenicol	0.25-1 g q6h Oral administration produces higher blood concentrations than IV administration.	Yes	8-14	60	1.5	Minor	No	Yes (H) No (P)
Daptomycin	4-6 mg/kg q24h	—	58-100	90	8-9	No	Minor	No (P) Minor (H)
Metronidazole	500 mg q6h (anaerobes) 250 mg q8h (trichomoniasis) 750 mg q8h (amebiasis) (IV or PO)	Yes	25	20	8	Yes	No	Yes (H) No (P)

TABLE 266-4 DOSAGE REGIMENS OF ANTIBACTERIALS, PHARMACOKINETICS, AND DOSE ADJUSTMENT IN PATIENTS WITH RENAL OR HEPATIC FAILURE—cont'd

CLASS/AGENT	DOSE* FOR SYSTEMIC INFECTION	ORAL FORMULATION	PEAK SERUM CONCENTRATION (μg/mL)	PROTEIN BINDING (%)	NORMAL SERUM HALF-LIFE (hr)	HEPATIC FAILURE	RENAL FAILURE	SERUM LEVELS ALTERED BY DIALYSIS
Nitrofurantoin	100 mg q6h (PO)	Yes	Nil	60	0.3	No	Avoid	Yes (H)
Quinupristin-dalfopristin (30:70)	7.5 mg/kg q8-12h	—	3.2/8[¶]	90/30	3/1[¶]	Minor	No	No (P)
Spectinomycin	2 g/24 h	—	100	0	2	No	Avoid	Unknown
Vancomycin	15 mg/kg q12h	Yes[**]	35	50	6	No	Major	No (H, P)
Oritavancin	1200 mg once	—	138	85	245	No	Major	No (H)
Telavancin	10 mg/kg q24h	—	108	90	8	No	Major	No (H)
Dalbavancin	1500 mg once	—	287	93	346	No	Major	No (H)
Lefamulin	600 mg q12h (PO)	Yes	2.2	95 – 97	8	Yes	No	No (H)

*Clinical trials are examining the impact of hepatic and renal insufficiencies on pretomanid pharmacokinetics, safety, and tolerability.
[†]Administered with bedaquiline and linezolid for treatment of multidrug-resistant tuberculosis.
[‡]Dose in milligrams per kilogram body weight at hour intervals and/or oral dose in milligrams in patients with normal renal function; all doses are parenteral unless specified PO.
[§]Significant decrease or delay in absorption when administered with food.
[¶]Refers to information for clavulanic acid.
[¶]Includes parent compound and active metabolites.
**Oral vancomycin is not absorbed; it is used for intraluminal therapy only.
H = hemodialysis; P = peritoneal dialysis; PO = orally; STI = sexually transmitted infection.

(Fig. 266-2A). Importantly, increased aminoglycoside exposures may be required to optimize the treatment effect for bacteria that have increased MICs for the antibiotic. The higher drug exposures may also increase the probability of drug toxicity (Fig. 266-2A through 266-2C). The evaluation in the figure is based on twice-daily dosing; summing the milligrams of aminoglycoside in the twice-daily dosed regimen and administering that amount once daily markedly decreases the probability of nephrotoxicity by increasing the time for aminoglycoside that are enters the renal tubular cells to leave these cells between doses.

When no toxicity relationship is available, there is still a drug exposure target for good clinical effect. Achievement of this target should be paramount, and alterations for renal or hepatic impairment should strive to maintain the same high likelihood of effect that is seen in patients who have relatively normal clearance function. The options are to change the dose or to change the schedule of administration to decrease the drug's accumulation in the presence of renal or hepatic impairment (depending on the drug) and then recalculate the impact on the likelihood of attaining a good clinical outcome. For the increase in exposure relative to that in patients with normal clearance, a certain maximal amount of increased accumulation may be acceptable, provided that the dose adjustment maintains a high likelihood of a good overall outcome, considering both efficacy and toxicity. The acceptability of the increased drug exposure after dosage adjustment is usually based on a combination of preclinical and clinical toxicology data, but the overarching issue is that the proposed dose or schedule alteration must maintain a high probability of a good clinical outcome.

DRUG CLASSES AND THEIR PROPERTIES

Antimicrobial drug classes differ in their mechanisms of action, mechanisms of emergence of resistance, and whether they kill substantial numbers of organisms or only inhibit bacterial growth.

β-LACTAM AGENTS

The β-lactams include the penicillins, cephalosporins, monobactams, and carbapenems. This class of drugs is arguably the most important group of antimicrobials.[7,8] With chemical modification, they have an exceptionally broad spectrum of activity and, in general, an excellent safety profile. The major toxicity is related to allergic reactions to a degradation product of the drug.

These agents bind to their targets, bacterial β-lactam–binding proteins (also called penicillin-binding proteins). These binding proteins have an active site serine, and the drug forms a covalent bond with this site through the carbonyl of the β-lactam ring. Sometimes, the binding has direct effects on the organism's shape. For example, in gram-negative organisms, binding to penicillin-binding protein (PBP)-2 causes the organism to assume a spherical shape, whereas binding to PBP-3 causes the formation of long chains of organisms. In general, high-affinity binding to PBP-1 leads to the rapid death of the organism, sometimes accompanied by lysis. The classic response of *S. pneumoniae* (Chapter 282) to penicillin G is rapid lysis of the organism. Binding to PBP-1 (1a or 1b) leads to activation of *N*-acetylmuramic acid amidase, which destroys the bacterial cell wall, resulting in lysis.

The most common way for pathogens to protect themselves from β-lactams is by elaborating β-lactamases. The genes for these enzymes may be on plasmids or other bits of transmissible DNA, or they may reside on the bacterial chromosome. Some drugs, such as the carbapenems, are resistant to hydrolysis by many enzymes (but certainly not all of them, especially the metallo-β-lactamases and *K. pneumoniae* carbapenemase-type β-lactamases). The activity of β-lactams may be protected by administering these drugs in combination with a β-lactamase inhibitor. Examples include potassium clavulanate, sulbactam, tazobactam, and, most recently, avibactam, relebactam, and vaborbactam. These agents inhibit different types of β-lactamases, but only avibactams inhibit the ampC-type enzymes carried by *P. aeruginosa* (Chapter 282), *Enterobacter* species (Chapter 281), *Citrobacter* species (Chapter 281), *Serratia marcescens,* and indole-positive *Protea* (SPICE organisms).

All β-lactams are relatively nonconcentration-dependent in their kill rate, and free (nonprotein bound) drug time greater than MIC (T > MIC) is the pharmacodynamic index linked with increased organism killing. The classes differ somewhat, with carbapenems requiring approximately 40% free drug T > MIC for near-maximal bacterial killing. For penicillins, this percentage is approximately 50%, and for cephalosporins and monobactams, it is 60 to 70%. When these agents need to penetrate to a site of infection, such as the fluid that covers the alveolar cells or the central nervous system, the pharmacodynamic target values may change.

AMINOGLYCOSIDES

Aminoglycosides are important components of combination regimens for seriously ill patients, particularly in the empirical therapy setting for patients thought to be infected by gram-negative organisms.[9] Naturally occurring aminoglycosides include kanamycin, neomycin, gentamicin (actually a combination of three congeners), and tobramycin. Other semisynthetic agents, such as amikacin, netilmicin, and arbekacin (among others), have been synthesized.

Nephrotoxicity and middle ear toxicity (hearing loss or loss of balance) are the dose-limiting toxicities of aminoglycosides. However, most (but not all) of the nephrotoxic potential can be ameliorated by intermittent dosing of these drugs (usually once daily). Even with daily therapy, however, prolonged use can still result in nephrotoxicity or ototoxicity.

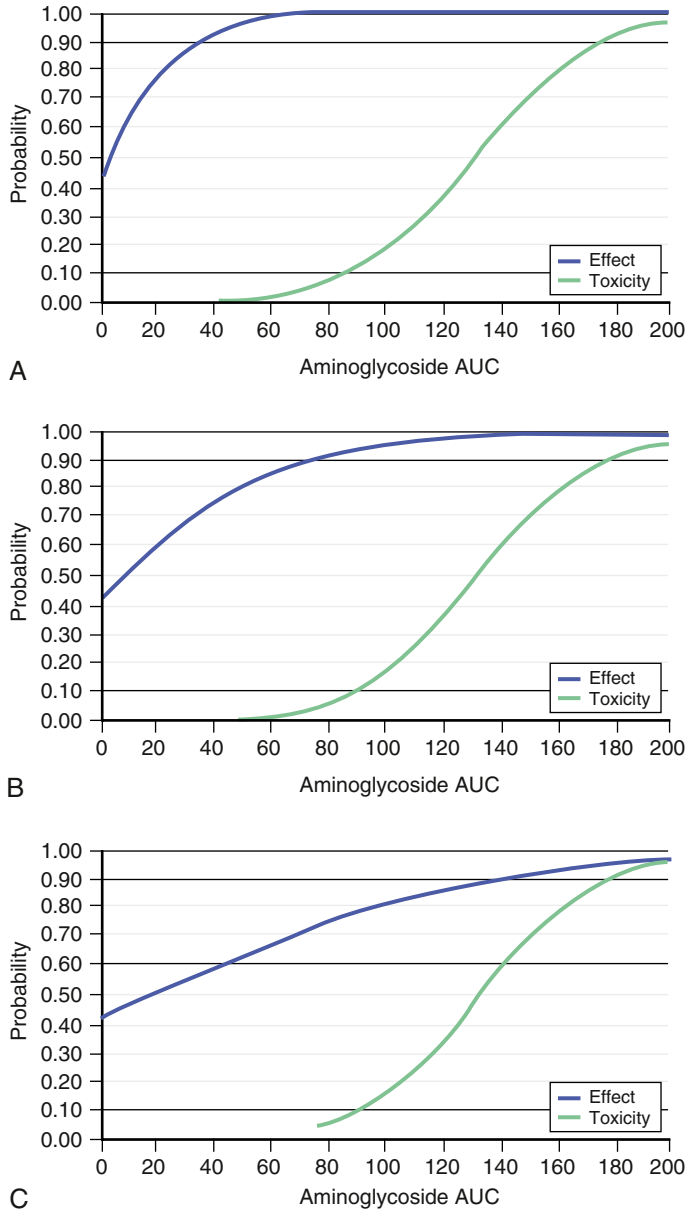

FIGURE 266-2. Probability of successful clinical effect and nephrotoxicity as a function of aminoglycoside area under the curve (AUC) for infections caused by microbes with different MICs to an aminoglycoside. A, Minimal inhibitory concentration (MIC) = 0.25 mg/L. **B,** MIC = 0.5 mg/L. **C,** MIC = 1.0 mg/L.

The recent rise in resistance, particularly among gram-negative bacteria, and new mechanisms mediating resistance even to the best β-lactam agents have resulted in renewed interest in existing aminoglycosides and a search for new ones that are more resistant to inactivation by the aminoglycoside-modifying enzymes. Plazomicin, which is a newer parenteral aminoglycoside that targets Enterobacteriaceae (Chapter 281),[10] is approved for the treatment of complicated urinary tract infections. Due to structural modifications, plazomicin remains active against many resistance mechanisms that render bacteria resistant to the other aminoglycosides.

Aminoglycosides are concentration-dependent in terms of their bacterial killing and are rapid killers. Hence, the AUC/MIC ratio (or, as sometimes reported, peak concentration/MIC ratio) is the pharmacodynamic index that is most closely associated with bacterial killing. Therefore large doses administered daily to patients with normal renal function optimize bacterial killing, as well as minimizing nephrotoxicity.

The older aminoglycosides (streptomycin and gentamicin) have the best profile for synergizing with drugs that are active against gram-positive streptococci (particularly enterococci). Tobramycin generally has the most potent activity against *P. aeruginosa* (Chapter 282) (depending on the aminoglycoside-modifying enzymes present in a specific locale), and less resistance is generally seen with amikacin (again, depending on the locale). Streptomycin and amikacin, because of the number of amino groups they carry, are usually about four-fold less potent than gentamicin or tobramycin. Consequently, their dosages are approximately three- to four-fold higher.

QUINOLONES

Quinolones are completely synthetic and do not exist in nature. They are inhibitors (depending on the drug and the organism) of topoisomerases II and IV to block DNA replication, thereby making them rapidly bactericidal. A fluorine substitution markedly enhances the microbiologic activity of these drugs, thereby making them useful for treating both community-associated infections (especially urinary tract infections and pneumonia) as well as hospital-associated gram-negative infections.

These drugs penetrate well into most body spaces and accumulate within mammalian cells, so they are active against obligate intracellular pathogens such as *Chlamydophila* (Chapter 294), *Legionella* (Chapter 290), and *Mycoplasma* (Chapter 293).[11] They also penetrate well into body spaces with tight junctions (prostate, eye, central nervous system) and into the epithelial lining fluid of the lung.

Typically, the toxicities of these drugs are "off target." Several quinolones were withdrawn from the marketplace or given black box warnings by health authorities because of the infrequent occurrence of tendon rupture, torsades de pointes (Chapter 53), or other serious and life-threatening toxicities, such as eosinophilic hepatitis. Black box warnings now include hypoglycemia that may lead to coma and mental disturbances, including memory impairment and delirium. As a result, the U.S. Food and Drug Administration advises that the side effects of fluoroquinolones outweigh their benefits when patients with uncomplicated urinary tract infections (Chapter 263) and acute sinusitis (Chapter 394) have other options.

Quinolones are concentration-dependent bacterial killers, thereby indicating that the free drug AUC/MIC ratio is best associated with a regimen's ability to kill bacteria. Of interest, particularly for a drug that is completely synthetic, are a number of resistance mechanisms that allow bacteria to escape from drug pressure. The combination of efflux pump overexpression and error-prone replication, which results in target site mutants, as well as serious underdosing, has resulted in the emergence of considerable resistance, particularly among gram-negative isolates and in the ICU setting.

MACROLIDES, TETRACYCLINES, KETOLIDES, CLINDAMYCIN, AND OXAZOLIDINONES

These agents bind to different places in the bacterial ribosome, thereby making them inhibitors of protein synthesis and, for the most part, drugs with limited bactericidal activity. An exception may be their activity against *S. pneumoniae* (Chapter 268).

Macrolides (particularly clarithromycin and azithromycin) are most useful for community-acquired respiratory tract infections, for two reasons. First, their spectrum is well suited to the classic and atypical bacteria encountered in these patients.[12] Second, they concentrate well in lung epithelial lining fluid, with an accumulation that ranges from 6-fold to almost 20-fold of that in plasma. This accumulation partially explains why these agents have fared much better in the respiratory tract setting than in the skin and skin structure setting. Telithromycin, a ketolide, retains activity against many (but not all) macrolide-resistant isolates.

The macrolides and telithromycin are free drug AUC/MIC ratio–driven drugs with respect to bacterial activity, but for different reasons. Telithromycin is somewhat concentration-dependent with regard to its microbiologic activity, whereas classic macrolides are not. Telithromycin is more like aminoglycosides or quinolones in terms of the association between exposure indices and bacterial effect. Classic macrolides, especially azithromycin, induce a long persistent or post-antibiotic effect and are *not* concentration dependent in their bacterial effect. This post-antibiotic effect suppresses bacterial regrowth after the drug concentration declines below the MIC until the next dose of drug is administered. In this way, the linkage appears to be driven by the free drug AUC/MIC ratio but with a mechanism different from that of agents whose bacterial kill rate is concentration-dependent.

Most of the toxicities seen of these drugs are off target and gastrointestinal, including antibiotic-associated diarrhea and the more serious *Clostridioides difficile* colitis. There is also some prolongation of the QT interval (Chapter 42), which presumably explains why azithromycin has been considered to carry an increased risk of ventricular arrhythmia. However, a recent systematic review and meta-analysis of the cardiovascular safety of macrolides reported no statistical association with arrhythmia or cardiovascular mortality.[13]

Tetracyclines have an exceptionally broad spectrum of activity, including both gram-positive and gram-negative pathogens, and they are active against atypical pathogens. The latest incarnation of a tetracycline-type agent (tigecycline, a glycylcycline) has good activity against methicillin-resistant *S. aureus* (MRSA) as well. Tigecycline differs from previous tetracyclines (e.g., doxycycline, minocycline) in that its structure prevents many efflux pumps from removing the drug from the bacteria and also provides a degree of ribosomal protection.

The lincosamide antibiotic clindamycin has a spectrum that covers most clinically significant anaerobic bacteria, including many in the *Bacteroides* group (Chapter 273), although some resistance is being seen. It is thus a useful agent for infections in which anaerobes play a prominent role, such as lung abscesses and intra-abdominal infections. In many areas of the country, clindamycin has retained activity against methicillin-resistant *Staphylococcus aureus* (MRSA) (Chapter 267), but this should be verified with a D-test (inducible macrolide-lincosamide-streptogramin resistance) in the microbiology laboratory. It also has good activity against many streptococci (Chapter 269). Because it is a protein synthesis inhibitor, it may provide improved results when the staphylococcal or streptococcal isolate elaborates toxins.

Linezolid and tedizolid, which are members of the oxazolidinone class of antibiotics, are inhibitors of protein synthesis. They have excellent gram-positive activity, including robust activity against MRSA (Chapter 267). Oxazolidinones penetrate well into skin as well as into the epithelial lining fluid. They are prescribed to treat skin and skin structure infections, and currently only linezolid is licensed for treating streptococcal and staphylococcal (including MRSA) community-associated and nosocomial pneumonia. Intravenous and oral formulations are available for both drugs, and both drugs have high oral bioavailabilities.

The free drug AUC/MIC ratio is the pharmacodynamic index most associated with cell killing for the oxazolidinones. Bone marrow toxicity, including thrombocytopenia, neutropenia, and anemia, is linked to the dose and duration of oxazolidinone therapy. Lactic acidosis, peripheral neuropathy, and optic neuritis have been reported. Resistance occurs rarely and is seen with enterococci more frequently than with *S. aureus*.

VANCOMYCIN, QUINUPRISTIN-DALFOPRISTIN, DAPTOMYCIN, AND LIPOGLYCOPEPTIDES

Although structured differently, these agents (along with the oxazolidinones) are distinguished by having activity against many gram-positive bacteria, including MRSA (Chapter 267). Vancomycin acts at the cell wall and alters cell membrane permeability. It is bactericidal. The free drug AUC/MIC ratio is the driver of antimicrobial effect. This glycopeptide drug has activity against many gram-positive pathogens and is active against *C. difficile* (Chapter 271) when it is administered orally. As with most drugs, wide use has caused the emergence of vancomycin resistance in both enterococci and *S. aureus*.

Although vancomycin has a reputation for being a somewhat slow killer, no new agent has significantly outperformed it, at least in trials of skin and skin structure infections. MIC creep, in which an increase in vancomycin MICs in *S. aureus* is reported in a geographic region in serial surveillance studies over time, has been documented. Although many *S. aureus* isolates were once susceptible with MIC values of 0.25 and 0.5 mg/L, these are now in the distinct minority; 1.0 mg/L represents the modal value, with a few isolates having values of 2.0 mg/L. The higher MICs make these isolates more difficult to treat reliably with standard dosing (1 g IV every 12 hours). Also, it has recently become clear that higher vancomycin doses are associated with a significantly higher risk of nephrotoxicity, even when the agent is administered alone. In addition to nephrotoxicity, vancomycin causes histamine release ("red man syndrome") when it is administered too quickly intravenously. Infusion times of approximately 1 hour are recommended for standard doses.

Oritavancin, dalbavancin, and telavancin, which are semisynthetic lipoglycopeptide derivatives of vancomycin, kill streptococci, enterococci, and staphylococci (including MRSA) in a concentration-dependent manner by the same mechanisms of action as vancomycin. They are licensed for treating skin and skin structure infections due to these microbes. Oritavancin and dalbavancin have long terminal half-lives, and a single dose is given for treating these infections. Telavancin has an 8-hour serum half-life and is dosed once daily. These drugs are not used for the treatment of *C. difficile* colitis.

Quinupristin-dalfopristin is a combination of streptogramin A and streptogramin B antibiotics. Although each individual component is bacteriostatic, the combination can produce some cell killing because the two drugs are synergistic. The synergy is lost, however, with the emergence of resistance to either drug. Further, the amount of bacterial cell killing is modest because of the drugs' rapid half-lives and the imposition of a 12-hour dosing interval. This combination product has activity against resistant enterococci (Chapter 270) as well as MRSA (Chapter 267). Its toxicity includes relatively severe muscle pain in some patients. It is also phlebitogenic and has to be administered with a central venous catheter, limiting its utility.

Daptomycin is a cyclic lipopeptide antibiotic that is effective against MRSA, as driven by its free drug AUC/MIC ratio.

This agent has been licensed for skin and skin structure infections and, of note, for complicated *S. aureus* bacteremia (Chapter 267) and right-sided endocarditis (Chapter 61). It also has activity against enterococci (Chapter 270). The drug is bound up in epithelial lining fluid by surfactant, excluding its use in the therapy for pneumonia.

Daptomycin may cause muscle toxicity, which is rare, but this may be preceded by the harbinger of an elevated creatine kinase level. The muscle damage is driven by daptomycin trough concentrations, generally above a concentration of about 25 mg/L, and can be ameliorated by once-daily dosing to minimize trough concentrations. Monitoring of creatine kinase concentration is useful in the management of patients receiving daptomycin therapy.

TOXICITIES

All antimicrobials have toxicities, which vary among and even within classes (Table 266-5).

DURATION OF THERAPY

Relatively little is known about the optimal duration of therapy for specific infections treated with specific antimicrobial agents. Shorter courses of chemotherapy are preferred, if they are effective so as to minimize side effects and costs.[14]

For trimethoprim-sulfamethoxazole and fluoroquinolones, controlled trials have shown that 3 days of therapy is adequate for uncomplicated urinary tract infections in women (Chapter 263), and 7 days is as good as 14 days in afebrile men.[A4] Gonorrhea (Chapter 275) is highly likely to be cured by a single dose of drug (ceftriaxone, cefixime, fluoroquinolones) if the organism is susceptible to the drug.

In community-acquired pneumonia (Chapter 85),[A5] controlled trials have demonstrated optimal results with 5 days of therapy. For bacterial sinusitis (Chapter 394), direct sampling from the infected sinus has demonstrated that bacterial pathogens were eradicated by day 3 of therapy or earlier, particularly for *S. pneumoniae* infections. In ventilator-associated pneumonia, a double-blind comparison of 8 versus 15 days of therapy demonstrated that, with a single exception, clinical outcomes were just as good, with less emergence of resistance, fewer antibiotics administered, and less toxicity with 8 days of therapy. The single exception was when a nonfermenting gram-negative rod was cultured (*P. aeruginosa* or *Acinetobacter* species). In this circumstance, there were significantly more relapses with 8-day versus 15-day treatment, but clinical outcomes were similar. For hospitalized patients who have gram-negative bacteremia and clinical stability before day 7, a 7-day course of antibiotics is as good as 14 days.[A6]

In some infections, the organisms are slow growing and require more time for control. For example, 2 weeks of antibiotics are as good as 4 weeks after surgical drainage of native joint nongonococcal septic arthritis,[A7] but 12 weeks of antibiotic therapy is better than 6 weeks after appropriate surgical intervention in prosthetic valve endocarditis.[A8] Even when prolonged courses of antibiotics are required, however, a shift from parenteral to oral antibiotics should be made as soon as it is safe to do so.[A9]

One of the longest durations of therapy is seen in the treatment of tuberculosis. In this case some organisms are in the "nonreplicative persister" state, thereby indicating that they are not growing or metabolically active. When recovered, they are still fully susceptible to the antimicrobials being used, but while in this state, they are not readily killed with current chemotherapy (phenotypic, not genotypic, resistance). Durations of therapy are protracted, especially for relatively resistant organisms. Even with multidrug-resistant tuberculosis, however, a combination using pretomanid, bedaquiline, and linezolid can reduce the necessary duration of treatment for multidrug-resistant tuberculosis from 18 to 24 months to 6 months.[A10]

FAILURE OF ANTIMICROBIAL THERAPY

Antimicrobial therapy occasionally fails, with failure defined as the persistence of signs and symptoms of infection or the persistence of fever. In the face of apparent failure after what was thought to be adequate antimicrobial therapy, the clinician should rapidly pursue a series of possibilities. Did resistance truly emerge, or did superinfection occur? Is there an obstructed hollow viscus (e.g.,

TABLE 266-5 DIVERSE TOXICITIES OF ANTIMICROBIAL AGENTS

AGENT	GENERAL	SKIN	GI TRACT	BLOOD CELLS	KIDNEY	NERVOUS SYSTEM	OTHER
Penicillins	Hypersensitivity, anaphylaxis, serum sickness	Rash, urticaria, erythema multiforme	Diarrhea (ampicillin, amoxicillin-clavulanate), hepatitis (oxacillin)	Coombs-positive hemolytic anemia, impaired platelet function (ticarcillin), leukopenia, thrombocytopenia	Nephritis (methicillin), hypokalemia (carboxy- and ureido-penicillins)	Seizures, twitching (high doses, renal failure)	Inactivates aminoglycosides when admixed; possible with concurrent therapy in renal failure
Cephalosporins	Serum sickness (cefaclor), hypersensitivity, anaphylaxis (rare)	Rash, urticaria	Diarrhea, hepatic dysfunction, precipitates in bile (ceftriaxone), mild increase in LFTs	Neutropenia, increased prothrombin time, bleeding (due to MTT side chain), positive Coombs test	Enhances aminoglycoside toxicity, acute renal failure (rare), interstitial nephritis		Disulfiram-like reaction with alcohol use (MTT side chain)
Carbapenems	Hypersensitivity	Rash, urticaria, erythema multiforme	Vomiting with rapid infusion (imipenem), abnormal LFTs	Bone marrow suppression, positive Coombs test	Renal dysfunction	Seizures, myoclonus	
Aminoglycosides	Fever	Rash			Reversible renal failure	Irreversible vestibular toxicity and/or auditory damage, muscle blockade (with anesthetics and myasthenia gravis)	
Vancomycin and lipoglycopeptides	Allergy, fever	Rash		Leukopenia, thrombocytopenia	Nephrotoxic	Decreased hearing, neuropathy	Histamine release with flushing and hypotension (infusion <1 hr, antihistamines can prevent)
Quinolones	Headache, allergy, anaphylaxis (rare)	Rash (gemifloxacin), urticaria, photosensitivity (lomefloxacin)	GI distress, abnormal LFTs			Dizziness, insomnia, nervousness, tremors, visual changes, seizures	Tendon rupture; arthropathy in young animals
Sulfonamides	Hypersensitivity, anaphylaxis, serum sickness, fever	Rash, Stevens-Johnson syndrome, photosensitivity	Hepatitis	Hemolysis (G6PD deficiency), agranulocytosis, marrow suppression	Crystalluria	Neuropathy	Vasculitis
Trimethoprim ± sulfamethoxazole	Fever	Rash, erythema multiforme, Stevens-Johnson syndrome, TEN	Hepatitis, pancreatitis	Marrow suppression	Hyperkalemia, acute renal failure		
Chloramphenicol	Fever			Marrow suppression (dose related), aplastic anemia	Optic neuritis, neuropathy	Circulatory collapse (gray baby syndrome in neonates)	
Tetracyclines	Hypersensitivity	Photosensitization (doxycycline)	GI discomfort, hepatotoxicity in azotemia or pregnancy		Antianabolic aggravation of azotemia (except doxycycline)	Vertigo (minocycline)	Deposition in bone (dysplasia) and teeth (staining)
Macrolides	Fever	Rash	GI discomfort			Reversible decreased hearing	Phlebitis (IV erythromycin), metallic taste (clarithromycin)
Clindamycin	Fever	Rash	Diarrhea, pseudomembranous colitis				
Metronidazole	Headache, hypersensitivity		Nausea, metallic taste, pancreatitis	Leukopenia		Peripheral neuropathy, ataxia	Mutagenic, carcinogenic in rodents, disulfiram-like reaction with alcohol
Lefamulin	Headache		Nausea, diarrhea				Possible prolonged Q-T interval with underlying cardiac condition or when used with certain drugs

GI = gastrointestinal; G6PD = glucose-6-phosphate dehydrogenase; IV = intravenous; LFT = liver function test; MTT = methylthiotetrazole; TEN = toxic epidermal necrolysis.

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267 STAPHYLOCOCCAL INFECTIONS

CATHERINE LIU, BO SHOPSIN, AND HENRY F. CHAMBERS

DEFINITION

Staphylococci are well adapted as commensals and as pathogens. Coagulase-negative species constitute a significant proportion of the normal human cutaneous microbiome. *Staphylococcus aureus*, a coagulase-positive species, is a nasopharyngeal colonizer in a third of individuals, most of whom will not become infected. As a pathogen, *S. aureus* infections range in severity from relatively trivial skin infections to lethal invasive disease. Coagulase-negative species, which are intrinsically less virulent and less invasive than *S. aureus*, nevertheless are responsible for one in four health care–associated infections, particularly those involving indwelling medical devices. The increasing prevalence of antibiotic-resistant strains of staphylococci has a profound impact on therapy.

The Pathogen

The genus *Staphylococcus* consists of more than 30 distinct species. These organisms have coevolved as normal flora of mammals and birds. These gram-positive spherical cells (i.e., cocci) are 0.5 to 1.5 μm in diameter and divide in multiple orthogonal planes to form clusters resembling grapes when viewed under the microscope. Staphylococci are nonmotile, nonsporulating, hardy organisms that are resistant to desiccation, extremes of pH, and high salt concentrations. Staphylococci can grow under both aerobic and anaerobic conditions. The ability of staphylococci to produce catalase, which is an enzyme that degrades hydrogen peroxide into water and oxygen, definitively distinguishes them biochemically from streptococci and enterococci. The coagulase test is the basis for differentiating *S. aureus* from the numerous other nonpathogenic, coagulase-negative species. Coagulase is a secreted protein that, in the presence of a prothrombin-like plasma protein, converts fibrinogen to fibrin, thereby forming a clot. *S. aureus* produces a variety of other surface proteins (e.g., protein A) that differentiate it from other species.

The staphylococcal chromosome is circular. Approximately 75% of the genes in a given strain constitute a core genome. The remaining 25% contain species-defining elements and mobile genetic elements that have been acquired by horizontal gene transfer and that shape diversity within the species. The *S. aureus* genome is abundant in genes encoding toxins, superantigens, and adhesins, whereas coagulase-negative species contain few adhesin and no toxin or superantigen genes. Genetically, *S. aureus* is sufficiently uniform to classify it as a single species; greater diversity among coagulase-negative species merits their classification as distinct species.

STAPHYLOCOCCUS AUREUS

EPIDEMIOLOGY

S. aureus is maintained in the human population primarily by asymptomatic colonization of the anterior nares, oropharynx, and other moist areas of the body, including the groin, perineum, and perianal area. Infants become colonized by strains from their mothers within weeks of birth. Carriage rates are higher in children than in adults. Higher-than-average *S. aureus* carriage rates are associated with atopic dermatitis, eczema, chronic skin ulcers, and other acute and chronic skin conditions; insulin-dependent diabetes; dialysis; human immunodeficiency virus infection; and injection drug use. Carriers have a several-fold higher risk for developing an *S. aureus* infection compared with noncarriers. The principal mode of transmission of *S. aureus* is direct contact with an infected individual or an asymptomatic carrier, probably through transient hand carriage. *S. aureus* may also contaminate environmental surfaces, where it can persist for days. The role of environmental contamination in transmission is not well defined, but it may be important if heavily contaminated surfaces or materials are contacted. Droplet and aerosol transmission of *S. aureus* plays little, if any, role.

S. aureus is responsible for millions of infections in the United States each year, most of which are community-acquired skin infections. Approximately 5 to 10% of *S. aureus* infections are invasive, three fourths of which are associated with bacteremia. *S. aureus* also causes hundreds of thousands of health care–associated[1,2] (Chapter 261) infections each year, about half of which are caused by methicillin-resistant *S. aureus* (MRSA) in the United States. MRSA strains are now prevalent in the community,[3] but the frequency of and mortality of MRSA have been declining.[4] Although MRSA is now disseminated globally, there is marked geographic variation in MRSA burden that is due mainly to differences in local infection control practices and to pathogen-specific characteristics of the indigenously circulating clones.[5] Community-associated strains circulate in both the community and the health care environments, whereas health care–associated strains are largely restricted to the health care environment. The strains are distinct from each other in several ways (E-Table 267-1). For example, Panton-Valentine leukocidin, which is frequently present in community-associated strains, causes distinct clinical syndromes, such as primary skin abscesses and necrotizing community-acquired pneumonia.

PATHOBIOLOGY

Virulence Factors

S. aureus produces well above 50 virulence factors, including adhesins, toxins, enzymes, surface-bound proteins, and capsule polysaccharides (E-Table 267-2). Genes encoding virulence factors may be located on the chromosome as part of the core genome, within mobile genetic elements (or their remnants, including bacteriophages, pathogenicity islands, and cassettes), or on plasmids. α-Toxin, Panton-Valentine leukocidin, and phenol-soluble modulins, all of which provoke potentially deleterious host inflammatory responses and cause host cells to lyse, appear to be important virulence factors that mediate the severity of disease, especially in community-associated MRSA strains. Protein A, which is a B-cell superantigen that promiscuously triggers B-cell proliferation as well as supraclonal expansion and apoptosis, interferes with the host's antibody-mediated adaptive immunity.

Virulence factors promote binding to host tissues; allow the organism to evade, circumvent, or disrupt host immune responses; and facilitate cell injury and tissue invasion.[6] Variability in both the presence of virulence determinants

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Virulence factors promote binding to host tissues; allow the organism to evade, circumvent, or disrupt host immune responses; and facilitate cell injury and tissue invasion.[6] Variability in both the presence of virulence determinants

ABSTRACT

Staphylococcal infections are among the most commonly encountered bacterial infections. *S. aureus* disease occurs by two mechanisms: tissue invasion, which may be local or systemic, and the production of toxins. The latter can occur in the absence of invasive disease in staphylococcal food poisoning and toxic shock syndrome. Skin and soft tissue infections range in severity from impetigo, furuncles, and folliculitis to necrotizing fasciitis and pyomyositis. Systemic infection can take the form of bacteremia, endocarditis, pericarditis, osteomyelitis, and septic arthritis, as well as pulmonary, orthopedic device–associated, central nervous system, and genitourinary infections. The principles of *S. aureus* treatment are source control, by drainage of abscesses and removal of infected foreign material when feasible, as well as systemic antimicrobial therapy.

KEYWORDS

Staphylococcus aureus
coagulase-negative staphylococci
methicillin resistance
bacteremia
skin and soft tissue infections
endocarditis

E-TABLE 267-1 COMPARISON OF COMMUNITY AND HOSPITAL CLONES OF METHICILLIN-RESISTANT *STAPHYLOCOCCUS AUREUS* (MRSA)

PROPERTY	COMMUNITY-MRSA	HOSPITAL-MRSA
Methicillin-resistance gene cassette	*SCCmecIV*[*]	*SCCmecI, II, III*
Common genotypes[†]	USA300 (ST8) ST59, ST80	USA100 (ST5) USA500 (ST8) USA800 (ST5)
Panton-Valentine leukocidin	Present in ≥75%	Present in <5%
Antimicrobial resistances	β-Lactams, macrolides, fluoroquinolones	β-Lactams, macrolides, clindamycin, tetracycline, fluoroquinolones, aminoglycosides
Doubling time[‡]	30 minutes	45-60 minutes
agr mutants[§]	Uncommon	Common

*Staphylococcal chromosomal cassette type; this element contains the methicillin resistance gene *mecA;* numerous other variants occur as well.
[†]Pulsed-field gel electrophoresis type with the multilocus sequence type (ST) in parentheses.
[‡]Time for the number of cells to double in broth culture.
[§]Accessory gene regulator.

E-TABLE 267-2 EXAMPLES OF VIRULENCE FACTORS PRODUCED BY *STAPHYLOCOCCUS AUREUS*

ACTIVITY	GENES	PROTEIN OR MOLECULE
Inhibition of antimicrobial peptides	*icaA, icaD, icaB, icaC, icaR*	Polysaccharide intercellular adhesin (PIA)
	isdA, isdB	Iron-regulated surface determinants of *S. aureus* (IsdA and IsdB)
	mprF	Multiple peptide resistance factor (MprF)
	Sak	Staphylokinase
Inhibition of chemotaxis	*chp*	Chemotaxis inhibitory protein of *S. aureus* (CHIPS)
	ecb	Extracellular complement-binding protein (Ecb)
	efb	Extracellular fibrinogen-binding protein (Efb; inhibitor of C5a generation)
	scn	Staphylococcal inhibitor of complement (SCIN)
Inhibition of oxygen-mediated bacterial killing	*crtM, crtN*	Carotenoid pigment, staphyloxanthin (*S. aureus* golden pigment; resistance to reactive oxygen species)
	spn	Staphylococcal peroxidase inhibitor (resistance to reactive oxygen species)
	isdA, isdB	Iron-regulated surface determinants of *S. aureus*, IsdA, and IsdB (promote resistance to neutrophil reactive oxygen species)
	sodA, sodM	Superoxide dismutase, SodA, SodM (promotes resistance to neutrophil reactive oxygen species)
Inhibition of neutrophil function	*cap5* or *cap8*	Capsular polysaccharide (inhibits phagocytosis)
	clfA	Clumping factor A (ClfA; inhibits phagocytosis)
	eap	Extracellular adherence protein (Eap; inhibits leukocyte adhesion)
	hlgA, hlgB, hlgC	Gamma hemolysin subunits A, B, and C; HlgA, HlgB, HlgC (causes cell lysis)
	lukAB, lukED lukSF-PV (Panton-Valentine)	Leukocidins (cause cell lysis)
	psm	Phenol-soluble modulin-like peptides (PSMs; causes cell lysis)
Perturbation of T-cell function	*sea, seb, sec*$_n$, sed, see, seg, seh, sei, sej, sek, sel, sep	Staphylococcal enterotoxins: SEA, SEB, SEC$_n$, SED, SEE, SEG, SEH, SEI, SEJ, SEK, SEL, SEP (superantigens)
	tst	Toxic shock syndrome toxin 1 (TSST-1; superantigen)
Perturbation of B-cell function	*spa*	Protein A (B-cell superantigen)
Adhesion	*cna*	Collagen-binding protein
	fnA, fnB	Fibronectin-binding proteins A and B
	clfA, clfB	Clumping factors A and B (binds platelets and fibrinogen)

and their expression among strains allows extreme diversity among clinical isolates, remarkable adaptability and versatility of *S. aureus* as a pathogen, and a wide spectrum of clinical syndromes. An extensive network of two component response systems, DNA-binding proteins and regulatory RNAs, controls the expression of virulence (and other) factors in response to environmental conditions. Principal among these factors is the accessory gene regulator *agr*, which is a two-component quorum sensing and global gene regulator that coordinately controls the expression of numerous surface and secreted proteins. Mutations in *agr* are associated with loss of virulence.

Biofilm formation, a feature of coagulase-negative infections in particular, occurs in the presence of foreign material, such as vascular catheters or implanted devices. Biofilms are a complex network of extracellular polysaccharides, DNA, and protein in which bacterial cells become embedded, thereby rendering them inaccessible to clearance by host defense mechanisms.[7] Organisms within biofilms tend to be metabolically inactive and show tolerance with reduced susceptibility to the lethal actions of antimicrobial agents.

Mechanisms of Disease

The pathogenesis of invasive *S. aureus* disease usually proceeds from local tissue invasion to systemic infection. This process is dependent on the local and systemic effects of many virulence factors acting in combination. The hallmark lesion in tissues is the abscess, which is a focal collection of pus (liquefied and necrotic host tissue, blood, inflammatory cells, DNA, and cellular debris) and bacterial cells surrounded by an ill-defined layer of edematous and inflamed tissue infiltrated by acute and chronic inflammatory cells.

Host defenses against *S. aureus* tissue infection primarily consist of an intact, normal skin barrier and the innate immune system. Conditions in which these defenses are breached or impaired are associated with increased risk of *S. aureus* infection. Among these conditions are injection drug use (Chapter 365), presence of vascular access devices, burns (Chapter 97), chronic skin diseases, use of systemic steroids, traumatic wounds, minor skin abrasions or trauma, surgical procedures, insulin-dependent and non–insulin-dependent diabetes (Chapter 210), peritoneal dialysis (Chapter 117), hemodialysis (Chapter 117), subcutaneous and intramuscular injections, acupuncture, prosthetic implants, congenital or acquired disorders of neutrophils (e.g., chronic granulomatous disease [Chapter 153]), and advanced age. If the cutaneous barrier is breached, the next line of defense is the innate immune system (Chapter 35). Neutrophils recruited to the site of infection ingest and kill staphylococci.

Staphylococci elaborate numerous virulence factors that specifically thwart each step of the host response. If large numbers of organisms are present, the host response is overwhelmed, infection is not contained, and dissemination occurs. Endothelial cell injury and invasion can also occur. Intracellular organisms and small colony variants within phagocytes and endothelial cells may play a role in relapse and persistent bacteremia by acting as a protected sanctuary against the innate immune host response and antimicrobial therapy. High tissue burdens of organisms and bacteremia are usually, but not always, accompanied by fever, tachycardia, and other signs of the systemic inflammatory response syndrome, including frank septic shock (Chapter 94).

Toxinoses are a separate category of disease for which a toxin is both necessary and sufficient. The three toxin-mediated syndromes, which can occur in the absence of invasive disease, are staphylococcal food poisoning, staphylococcal toxic shock syndrome, and staphylococcal scalded skin syndrome. Staphylococcal food poisoning is caused by the ingestion of a preformed heat-stable enterotoxin. The emetogenic activity of enterotoxin is mediated by the intestinal release of 5-hydroxytryptamine and the stimulation of receptors present on afferent vagal neurons. Toxic shock syndrome is caused by a specific toxin, TSST-1, or other staphylococcal enterotoxins acting as superantigens that bind to major histocompatibility complex class II molecules of antigen-presenting cells and T-cell receptors, thereby stimulating the massive release of cytokines from T cells and resulting in shock and death. Staphylococcal scalded skin syndrome and bullous impetigo are caused by either of two exfoliative toxins, A or B. These toxins are serine proteases that specifically cleave desmoglein 1, which is a desmosomal protein that anchors the overlying superficial epidermis to the stratum granulosum.

CLINICAL MANIFESTATIONS

Skin and Soft Tissue Infections

Skin and soft tissue infections are by far the most common infections caused by *S. aureus;* millions of cases occur annually in the United States (Chapter 408). This heterogeneous group of skin diseases includes impetigo (Fig. 408-1), folliculitis, furuncle (Fig. 408-2), abscess, erysipelas (Fig. 408-4), cellulitis (Fig. 408-3), mastitis (cellulitis of the breast), necrotizing fasciitis, and wound infections. Community-acquired MRSA strains encoding Panton-Valentin leukocidin have been associated with an increased rate of primary skin and soft tissue infections in the United States, and recurrent infections occur in about 20% of individuals.[8]

Impetigo, folliculitis, and furuncle (Chapter 408) are superficial infections; fever and other systemic signs of infection are not present. Impetigo, which is a focal infection of the epidermis, occurs most commonly in children (see Fig. 408-1). The typical lesion, which may be multiple or in clusters, is about 1 cm in diameter, with erythema surrounding a bulla or bullae (caused by the production of exfoliative toxin) that contains cloudy fluid or has a crusty or scabbed-over appearance. Folliculitis is a superficial infection with tender, erythematous, maculopapular or pustular lesions centered around hair follicles. A furuncle is simply a boil, a painful focal collection of pus with surrounding erythema measuring 1 to 2 cm or more in diameter that extends through the dermis into the subcutaneous tissue (see Fig. 408-2). The distinction between a furuncle and an abscess is somewhat arbitrary. Abscesses tend to be larger and deeper and may be associated with systemic signs of infection and bacteremia. Furuncles may extend to fascia or deeper tissues and coalesce into carbuncles.

Erysipelas (see Fig. 408-4) and cellulitis, which are similar in appearance, are painful, warm, indurated, erythematous, nonlocalized infections that may be accompanied by lymphangitis. Cellulitis extends into the dermis and subcutaneous fat; erysipelas is more superficial. Cellulitis due to streptococci (Chapter 269) cannot reliably be distinguished from that caused by *S. aureus* owing to their similar appearance, although associated purulence suggests staphylococcal infection.

Necrotizing fasciitis is an infection of the deep layers of skin and subcutaneous tissues, extending to muscle and along fascial planes. It is associated with systemic toxicity, leukocytosis, and severe pain often out of proportion to the physical findings. The overlying skin may appear to be uninvolved, belying the serious nature of this infection. Necrotizing fasciitis, which is more typically caused by group A streptococci (Chapter 269) or mixed aerobic and anaerobic organisms, has been associated with community MRSA infection.

Pyomyositis (also termed tropical myositis) is a deep abscess or multiple abscesses within skeletal muscle. *S. aureus* is the most common cause. The patient presents with fever, pain, swelling, and induration that can be felt on deep palpation. The overlying skin and soft tissue may appear normal. There is often a history of trauma to the infected area. Although pyomyositis can occur in otherwise normal persons, acquired immunodeficiency syndrome (Chapter 358) and other immunocompromising conditions are predisposing factors. This infection is thought to occur as a consequence of metastatic seeding from a subclinical bacteremia, although blood cultures may not be positive at the time of diagnosis. Computed tomography or magnetic resonance imaging should be obtained to identify lesions. The diagnosis is established by culture of pus collected by needle aspirate.

Secondary *S. aureus* infection due to skin injury is unlinked to Panton-Valentin leukocidin and occurs in a variety of situations such as diabetes, underlying skin diseases, and surgery. *S. aureus* causes 30% of surgical site infections overall in the United States. These infections occur at the site of incision and are associated with significant morbidity, particularly in the setting of a prosthetic device. Signs and symptoms are fever accompanied by erythema, edema, induration, drainage, pain, and tenderness at the surgical site.

Bacteremia

Bacteremia[9] is present in approximately 75% of cases of invasive infection. The most common sources of bacteremia are skin and soft tissue infections, central venous catheters and other intravascular devices, bone and joint infections, pneumonia, and endocarditis. Bacteremia can originate from any source, which may not be obvious in 25% of cases. Once organisms have invaded the bloodstream they can disseminate widely throughout the body, thereby establishing multiple metastatic sites of infection and perpetuating the bacteremia. Fever is usually, but not always, present. Patients with *S. aureus* bacteremia have high rates of organ failure and septic shock (Chapter 94).

Endocarditis

S. aureus, which is the leading cause of both native valve and prosthetic valve endocarditis (Chapter 61), accounts for approximately 30% or more of all cases. Endocarditis may be community-acquired or, increasingly, health care–associated. Risk factors include injection drug use (Chapter 365), diabetes mellitus (Chapter 210), hemodialysis (Chapter 117), presence of a prosthetic valve (Chapter 60) or other implantable intracardiac device, and recent hospitalization. Endocarditis may present as an acute febrile illness with high fever

that develops over a few days. The patient may appear toxic and septic, but some patients have surprisingly few acute symptoms and complain only of protean symptoms such as shortness of breath, malaise, and weakness. The intracardiac source of infection initially may not be evident because a pathologic murmur may not be heard when the patient first presents. A quarter or more of patients have a coincident infection of bone, joint, or skin and soft tissue. The aortic and mitral valves are most commonly involved in native valve infection, but the tricuspid valve can be involved, especially in persons who inject drugs. Systemic embolization to the brain, kidneys, spleen, gut, or other large vessels is clinically evident in about one third of cases. Peripheral manifestations, including Roth spots (Fig. 391-26), Osler nodes (Fig. 61-2), Janeway lesions, splinter hemorrhages (Fig. 39-10), and petechiae (Fig. 61-1), occur with a similar frequency.

Native valve endocarditis in persons who inject drugs involves the tricuspid valve in approximately three quarters of cases. Patients typically have fever, cough, hemoptysis, and pleuritic chest pain as a consequence of hematogenous seeding of the lung and septic emboli from the valve. The chest radiograph may show pulmonary infiltrates, signs of consolidation, or pleural effusion. Multiple, often peripheral, nodular pulmonary infiltrates with cavitation are hallmark features of septic embolization (Fig. 267-1).

Pericarditis

S. aureus is the most common cause of purulent pericarditis (Chapter 62) after cardiac surgery in adults. It may occur by contamination at the time of surgery; by bacteremic seeding from another site of infection; as a complication of endocarditis, paravalvular abscess, or myocardial abscess; or by direct extension of infection from pneumonia, lung abscess, or empyema. The presentation is that of acute pericarditis (Chapter 62), with fever and severe chest pain, tachycardia, and hemodynamic instability. The clinical course may be extremely rapid, terminating in septic shock or cardiac tamponade.

Osteomyelitis

S. aureus is the most common cause of osteomyelitis, both acute and chronic (Chapter 251). Disease arises from hematogenous dissemination or contiguous spread. Hematogenous infection is often monomicrobial. Contiguous infection is often polymicrobial and results from trauma, inoculation during surgery, or soft tissue infection. Acute osteomyelitis—defined as an initial episode with a clinical course of days to weeks, but not months—is manifested with fever and pain at the site of infection. Vertebrae (most commonly lumbar and cervical) are more commonly infected in adults,[10] but adults also can have long bone osteomyelitis, usually from a contiguous focus of infection or at a site of fracture, prior trauma, or orthopedic hardware. Vertebral osteomyelitis[11] is frequently accompanied by paravertebral or epidural abscess (Fig. 267-2; Chapter 382). Back pain accompanied by signs of cord compression, such as radicular pain, sensory loss, lower extremity weakness, urinary retention, and bowel or bladder incontinence, is an emergency.

Septic Arthritis

S. aureus is the most common cause of septic arthritis (Chapter 251), usually as a consequence of bacteremic seeding, trauma, or a surgical procedure. Risk factors include diabetes, recent joint surgery or joint prosthesis (Chapter 255), and rheumatoid arthritis (Chapter 243). Cardinal features are joint pain, history of joint swelling, and fever. Hip, knee, ankle, and wrist are most commonly affected. *S. aureus* also has a predilection for infecting the sternoclavicular, sacroiliac, and symphysis pubis joints. Multiple joints are involved in 5% of cases.

Central Nervous System Infections

S. aureus is an uncommon cause of community-acquired central nervous system infections, such as meningitis (Chapter 381), primary brain abscess (Chapter 382), or subdural empyema. These infections are often associated with endocarditis or a contiguous focus of infection, such as cavernous sinus thrombosis. *S. aureus* is an important cause of nosocomial meningitis after head trauma, craniotomy, or implantation of intraventricular or extraventricular catheters.

Pulmonary Infections

S. aureus is an uncommon cause of community-acquired pneumonia (Chapter 85), accounting for only 1 to 5% of cases but with geographic and seasonal (i.e., increased during influenza season) variability. *S. aureus* pneumonia is usually a fulminant necrotizing pneumonia accompanied by evidence of cavitation on chest radiographs.[12]

Hospital-acquired and ventilator-associated pneumonias (Chapter 91) often are caused by *S. aureus* and community-acquired or hospital-acquired MRSA strains. Patients with traumatic or medical brain injury (e.g., stroke, hemorrhage) are particularly prone to early colonization and subsequent pneumonia by this pathogen.

Lung abscess (Chapter 78) and pleural empyemas (Chapter 86) most commonly are caused by oral anaerobic bacteria but are occasionally caused by *S. aureus*. The clinical course may be subacute or even indolent. Empyema occurs as a complication of prior chest tube placement, surgery, trauma, staphylococcal pneumonia, or tricuspid valve endocarditis.

Orthopedic Device–Associated Infections

S. aureus is second only to coagulase-negative staphylococci as a cause of infections of prosthetic joints and orthopedic implants, but it is the most common cause within the first 12 weeks of surgery. The presentation may be acute, with joint pain, evidence of arthritis, fever, and systemic signs of infection. Alternatively, the infection may run a more chronic course, with pain and loosening of the prosthesis but little or no fever.

Genitourinary Infections

Genitourinary infections (Chapter 263) arise by hematogenous dissemination or as an ascending infection, usually as a result of instrumentation, urinary catheterization, or surgery. These infections include cystitis, pyelonephritis,

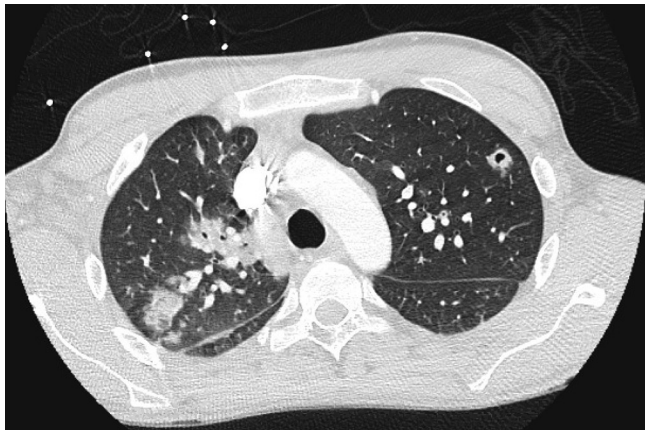

FIGURE 267-1. Computed tomography (CT) of the chest shows multiple nodular pulmonary lesions with areas of cavitation, suggestive of septic embolization, in a patient with tricuspid valve *S. aureus* endocarditis.

FIGURE 267-2. Noncontrast, non–fat-saturated, T1-weighted, sagittal sequence shows discitis, osteomyelitis, prevertebral and epidural abscess, and cord compression in a patient with S. aureus infection of the cervical spine.

microabscess, perinephric abscess, prostatitis, and prostatic abscess. *S. aureus* can also be a contaminant introduced during the collection of urine from a patient with asymptomatic vaginal or perineal colonization.

DIAGNOSIS

S. aureus infection is diagnosed by isolating the organism in culture of blood, tissue, or pus or by detecting it on a nucleic acid amplification test. Culture remains the "gold standard." Gram stain is useful for making a presumptive diagnosis of staphylococcal infection and should be performed whenever possible to look for gram-positive cocci in pus, bone or tissue samples, respiratory secretions, or body fluids such as cerebrospinal fluid, pleural or pericardial fluid, synovial fluid, or urine. Failure to isolate the organism in culture is strong evidence against *S. aureus* infection unless a patient is being actively treated with an antibiotic; even then, infected sites may remain culture positive for several days. The specificity of isolating *S. aureus* from blood or other sterile body sites is essentially 100%.

Bacteremia and Endocarditis

When blood cultures are positive, even if the primary source is known, the patient may have endocarditis and metastatic foci of infection.[13] Follow-up blood cultures should be obtained within 24 hours to document clearance. Persistent bacteremia is suggestive of endovascular infection, and failure to clear blood cultures after 2 to 3 days of appropriate therapy is associated with increased risk of mortality.[14,15] Echocardiography is generally recommended in all cases of *S. aureus* bacteremia to look for valvular vegetations or other signs of endocarditis. Transesophageal echocardiography, which is more sensitive than transthoracic echocardiography, is the preferred modality if the suspicion of endocarditis is moderate or high.[16] Factors associated with a low risk of endocarditis and in which a transesophageal echocardiogram may not be necessary include sterile follow-up blood cultures after 1 to 2 days of therapy, absence of an intracardiac device (e.g., pacemaker, prosthetic valve), acquisition in a health care setting with immediate source control (e.g., catheter removal), and absence of a secondary or metastatic focus of infection. Clinical prediction tools can stratify patients and identify those at low risk for endocarditis in whom TEE may be unnecessary.[17] Computed tomography or magnetic resonance imaging should be considered if signs and symptoms point to deep tissue abscesses or osteomyelitis.

Pericarditis

Staphylococcal pericarditis (Chapter 62) is suspected based on an enlarging cardiac silhouette in the context of an adjacent pneumonia or bacteremia. Ultrasonography can confirm the presence of an effusion, and pericardiocentesis can establish the microbiologic diagnosis.

Osteomyelitis and Septic Arthritis

MRI is the preferred imaging technique, particularly for vertebral osteomyelitis. However, the diagnosis of osteomyelitis is established via culture obtained from bone biopsy or blood. The diagnosis of septic arthritis is established by culture and by analysis of synovial fluid, in which the white blood cell count typically exceeds 25,000/μL, with 90% neutrophils. Blood cultures are positive in 30 to 50% of cases, organisms are seen on Gram stain of synovial fluid in about 50% of cases, and synovial fluid culture is almost always positive.

CNS Infections

The diagnosis of neurosurgical infections due to *S. aureus* is typically established by deep cultures obtained from an infected surgical wound or craniotomy site. For patients in whom meningitis or ventriculitis is a concern, the cerebrospinal fluid (CSF) should be sampled by lumbar puncture, a ventriculoperitoneal shunt, or an extraventricular drain if present.

Pneumonia

The diagnosis of staphylococcal pneumonia is readily established by examination of a Gram stain and culture of sputum, tracheal aspirate, or lavage fluid (obtained to avoid oropharyngeal contamination), which typically shows organisms and numerous neutrophils. The culture is less specific than the Gram stain because it can be positive in colonized patients, but it is highly sensitive.

Orthopedic Device–Related Infections

The diagnosis of a prosthetic joint infection is made by sampling the synovial fluid for cell count with differential, Gram stain, and culture. Additionally, intraoperative cultures demonstrating growth of *S. aureus* confirm the diagnosis.

Genitourinary Infections

When urinary tract infection is suspected, urine culture is required. Contamination should be suspected if the urine colony counts are low, repeated urine cultures are negative, pyuria is absent, and there are no signs or symptoms of urinary tract infection. If contamination seems unlikely and there is no well-documented history of an event that could lead to ascending infection, hematogenous dissemination should be suspected. Blood cultures should be obtained to determine whether there is ongoing bacteremia and appropriate imaging studies performed to identify a deep focus of infection and the presence of renal and perinephric abscesses.

Susceptibility Testing

The choice among curative antibiotics (see Table 267-2) is critical for successful treatment and must be guided by susceptibility testing. The critical determination is whether the isolate is methicillin resistant (i.e., resistant to β-lactam antibiotics). Clindamycin, which is usually active against community strains, is less reliable for hospital strains. Resistance to vancomycin, daptomycin, telavancin, linezolid, or ceftaroline is rare, but susceptibility testing is important for these antibiotics, particularly if the patient has had prior exposure to the drug. Strains with even intermediate susceptibility to vancomycin (4 or 8 μg/mL), which account for 1 to 3% of MRSA isolates, should be considered resistant because this finding is highly predictive of failure with vancomycin treatment. Persistent endovascular infections are particularly likely to have reduced susceptibility to vancomycin and daptomycin, in part because these drugs have poor penetration into vegetations and blunted bactericidal activity against slowly dividing organisms at high inocula.

TREATMENT

The two principles of therapy for *S. aureus* infections are (1) source control by elimination of abscesses and infected foreign material whenever feasible and (2) administration of systemic antimicrobial therapy. Infections at different sites are managed differently in terms of local source control, as well as the type, route, and duration of antibiotics (see Table 267-2). Lack of adequate source control, such as an undrained focus of infection, retention of an infected foreign body, or endovascular infection, is the most common reason for unsatisfactory clinical response, treatment failure, or relapse.

Approach to Specific Clinical Syndromes

Skin and Soft Tissue Infections

Both impetigo and folliculitis readily respond to local measures, such as application of soap and water, topical antibiotics, or antiseptics; systemic antimicrobial therapy (see Table 267-2) may be indicated for extensive or refractory infections. A furuncle may drain spontaneously with application of hot compresses or can be surgically drained with simple incision and drainage. Antimicrobial therapy improves short-term cure rates and reduces rates of recurrence. Large abscesses and carbuncles, particularly in the presence of fever and other systemic signs of infection, require surgical drainage and systemic antimicrobial therapy. Unless accompanied by bacteremia, the duration of treatment for abscesses following incision and drainage is 5 to 7 days, guided by clinical response. Cellulitis should be treated with systemic antimicrobial therapy; longer durations of up to 12 days may be required for hospitalized patients with severe cellulitis because relapse rates are higher with 6 days of therapy.[A1]

Necrotizing fasciitis requires immediate surgical intervention for débridement of involved tissue. For pyomyositis, surgical or percutaneous drainage should be performed, and systemic antimicrobial therapy is indicated.

Superficial surgical site infections respond to removal of stitches, débridement of devitalized tissue, opening of the wound to allow drainage, and a short course of antimicrobial therapy. Deeper infections may require more extensive débridement and prolonged courses of therapy, particularly if bone or a prosthetic device is involved. Removal of infected prosthetic material or a foreign body greatly increases the chance of cure.

Bacteremia and Endocarditis

Source control is the cornerstone of management and therapy. Both primary and secondary foci of infection should be identified and eliminated whenever possible because they may lead to treatment failure or relapse when antimicrobial therapy is discontinued. Antimicrobial therapy (see Table 267-2) should always be administered. A shorter duration of therapy (i.e., 14 days) is appropriate for uncomplicated bacteremia (Table 267-1). Longer courses of 4 to 6 weeks are recommended for the treatment of bacteremia complicated by slow resolution or the presence of metastatic infection; 6 weeks of therapy is recommended for endocarditis. Monotherapy with vancomycin is as good as combination therapy with fewer adverse effects.[18] For native valve endocarditis, valve replacement is indicated for heart failure (Chapter 61), myocardial abscess, severe valvular disease, or a vegetation >10 mm. Although prosthetic valve endocarditis can

TABLE 267-1 CRITERIA FOR DIAGNOSIS OF UNCOMPLICATED *STAPHYLOCOCCUS AUREUS* BACTEREMIA*

Resolution of fever and systemic signs of infection by day 3 of therapy
Sterile blood cultures within 1-2 days of initiation of antimicrobial therapy
Presence of an identifiable and easily removable focus of infection
Prompt removal of the primary focus of infection
No echocardiographic or clinical signs of endocarditis
No osteomyelitis
No hematogenous secondary foci of infection
No preexisting valve abnormalities predisposing to endocarditis (e.g., prosthetic valve, rheumatic heart disease, bicuspid aortic valve)
No implanted prosthetic device (e.g., prosthetic hip)

*Uncomplicated *S. aureus* bacteremia can be treated with a shorter course of antibiotics (see text).

be managed medically in some cases, outcomes tend to be worse, and surgery and valve reimplantation are usually required to cure the infection or to manage its complications.

Pericarditis

For staphylococcal pericarditis, immediate drainage of the infected pericardial space and administration of systemic antimicrobial therapy are indicated. Purulent pericarditis due to *S. aureus* should be managed as a complicated infection with 4 to 6 weeks of antibiotic therapy based on the adequacy of drainage and clinical response. Pericardiocentesis can provide temporary decompression of the pericardial space, but definitive therapy requires surgical or continuous tube drainage (Chapter 62).

Osteomyelitis and Septic Arthritis

For osteomyelitis, antibiotic management in conjunction with surgical débridement to remove necrotic bone and devitalized tissue is the mainstay of therapy. If source control is adequate, the recommended duration of therapy for osteomyelitis is 6 to 8 weeks, with 8 weeks preferred for MRSA infection. Longer courses may be indicated in patients who have significant residual infected bone or undrained paravertebral abscesses. The duration of therapy must be tailored under expert guidance depending on individual circumstances and whether source control has been achieved. For septic arthritis (Chapter 251), both antimicrobial therapy (see Table 267-2) and drainage of the infected joint (by repeated needle aspiration, by arthrotomy, or arthroscopically) are required to prevent destructive arthritis. Patients with *S. aureus* septic arthritis are typically treated with 3 to 4 weeks of antibiotic therapy.

CNS Infection

For patients with concern for a craniotomy site infection, subdural empyema, or spinal epidural abscess (Chapter 382), magnetic resonance imaging should be performed as soon as possible to define the location and extent of infection, and neurosurgical consultation should be obtained in anticipation of surgical decompression and drainage. The duration of treatment is typically 4 to 6 weeks but should be tailored based on clinical response and adequacy of source control under expert guidance.

For patients who have meningitis associated with a CNS shunt, shunt removal is recommended, with documentation of negative cultures prior to replacement of the shunt. A 10-day course of therapy after CSF cultures are negative is suggested.

Staphylococcal Pneumonia

When a patient with antecedent or concomitant influenza requires admission to an intenstive care unit (ICU), community-acquired staphylococcal pneumonia should be considered, and coverage for MRSA strains should be included in the empirical regimen for severe pneumonia (see Table 267-2). Coverage for *S. aureus* can be discontinued if the organism is not isolated in culture or not detected by nasal swab culture or PCR.[19] Empyemas (Chapter 86) require drainage and antimicrobial therapy. The usual duration of therapy for *S. aureus* pneumonia is 7 to 14 days, but longer durations of up to 4 weeks are indicated for patients with accompanying bacteremia or empyema.

Orthopedic Device–Related Infection

Formation of biofilm makes treatment of device infections challenging.[20] Intraoperative inspection, débridement, and hardware retention may be appropriate for infections of less than 3 weeks in duration or occurring within the first month of implantation. Otherwise, débridement and removal of the prosthesis or implant in conjunction with antimicrobial therapy offer the best chance of cure. The approach can either be a one-stage procedure, in which the infected prosthesis or implant is removed and immediately replaced, or a two-stage procedure, in which the device is removed and replaced after completion of a 6-week course of antimicrobial therapy (see Table 267-2). The duration of therapy for orthopedic device–related infections is dependent on the surgical management approach, guided by expert consultation.

Urinary Tract Infections

The management of staphylococcal urinary tract infections is dependent upon the source of infection. For patients who have a catheter-associated urinary tract infection, the catheter should be removed if no longer needed and be replaced by intermittent catheterization. If the patient requires an indwelling catheter, catheter exchange should be performed. The patient can be treated with an oral agent to which the organism is susceptible for a duration of 7 to 10 days. For patients with concern for a systemic infection, a hematogenous source of bacteriuria, or a more complicated urinary tract infection (e.g., perinephric abscess, prostatitis), a longer duration of therapy under expert guidance is indicated based on the diagnostic evaluation and response to therapy.

Antibiotic Selection

The most important consideration in selecting an antibiotic is susceptibility of the *S. aureus* isolate to β-lactams. For invasive infections, a penicillinase-resistant penicillin—for example, nafcillin (2 g every 4 hours IV), oxacillin (2 g every 4 hours IV), or a cephalosporin (e.g., cefazolin 2 g every 8 hours IV)—is the agent of choice for the treatment of methicillin-susceptible *S. aureus* (MSSA) infections; no other antibiotic, including vancomycin, is as safe or as effective as a β-lactam.[21] ß-Lactams primarily used for treatment of invasive staphylococcal infections include penicillinase-resistant pencillins, cefazolin, or penicillin (for non-penicillinase-producing, penicillin-susceptible strains). Ceftaroline, which is a β-lactam antibiotic with activity against MSSA and MRSA, has been used as salvage therapy either as monotherapy or in combination with another agent for treatment of invasive MRSA infections under expert guidance.

Methicillin-resistant strains are cross-resistant to all currently available β-lactams, except for ceftaroline (dose of 600 mg IV every 12 hours), which is indicated to treat skin and skin structure infections caused by methicillin-resistant strains. Otherwise, a β-lactam should not be used to treat infections known or suspected to be caused by a methicillin-resistant strain.

For invasive infections caused by MRSA, vancomycin is still a drug of choice. It must be administered intravenously; doses of 30 to 60 mg/kg/day, adjusted on the basis of renal function, are recommended to achieve a 24-hour area under the curve of drug concentration over time of 400 to 600 μg × h/mL for patients with bacteremia, endocarditis, or other serious infection.[22] Daptomycin is an alternative to vancomycin for the treatment of invasive MRSA infections, including bacteremia and endocarditis. Some authorities recommend higher doses of daptomycin (e.g., 8 to 12 mg/kg/day), particularly when the infection has failed to respond to vancomycin. For patients who have a serious β-lactam allergy (e.g., anaphylaxis) and invasive methicillin-susceptible *S. aureus* infection, vancomycin and daptomycin are alternative agents.

TOXIN-MEDIATED STAPHYLOCOCCAL DISEASES

Toxin-mediated staphylococcal diseases are caused by the ingestion of preformed toxin or the elaboration of toxin by *S. aureus* from a site of colonization or infection.

Staphylococcal Food Poisoning

Staphylococcal food poisoning is a gastroenteritis caused by the ingestion of enterotoxin produced in food contaminated with *S. aureus* from an infected or colonized food handler.[23] When contaminated food is kept at room temperature for several hours, organisms replicate and produce a heat-stable toxin that is not inactivated by cooking or digestive enzymes. Nausea, vomiting, abdominal pain, and diarrhea occur within 2 to 6 hours of eating the contaminated food, but fever is absent.

TREATMENT AND PROGNOSIS

Antibiotics have no role in therapy, which consists of fluid replacement to prevent dehydration. The illness is self-limited, generally persisting for no more than 1 day. Infants, small children, and the elderly are more severely affected and may require intravenous fluids.

Toxic Shock Syndrome

Staphylococcal toxic shock syndrome (Chapter 406) is caused by colonization or infection with a strain that elaborates a specific toxin, toxic shock syndrome toxin-1 (TSST-1), or another staphylococcal enterotoxin. Toxic shock syndrome toxin-1 is responsible for 100% of cases that are associated with tampon use and menstruation.[24] TSST-1 and other staphylococcal enterotoxins (SEA, SEB, and SEC) are responsible for nonmenstrual toxic shock syndrome, which is characteristically associated with an identifiable focus of infection, usually of the skin.

The diagnosis is clinical, defined by fever, erythroderma (Fig. 403-5), hypotension, involvement of three or more organ systems (renal, hematologic,

TABLE 267-2 TREATMENT OF *STAPHYLOCOCCUS AUREUS* INFECTIONS

CLINICAL SYNDROME	TREATMENTS FOR METHICILLIN-SENSITIVE *S. AUREUS*[*,†]	TREATMENTS FOR METHICILLIN-RESISTANT *S. AUREUS*[*]	COMMENTS
Skin and Soft Tissue Infection, *Oral therapy*	Cephalexin 500 mg PO qid Dicloxacillin 500 mg PO qid TMP-SMX 1-2 DS tab PO bid Doxycycline 100 mg PO bid Minocycline 100 mg PO bid Clindamycin 300-450 mg PO tid	*Preferred agents:* TMP-SMX 1-2 DS tab PO bid Doxycycline 100 mg PO bid Minocycline 100 mg PO bid Clindamycin 300-450 mg PO tid *Alternative agents:* Linezolid 600 mg PO bid Tedizolid 200 mg PO qd	Incision and drainage is a mainstay of treatment for patients with abscesses, but adjunctive antimicrobial therapy improves cure rates even for simple abscesses.[A2,A3] Oral therapy can be used in mild, localized infection without systemic symptoms. Parenteral therapy should be considered in patients with systemic toxicity, extensive soft tissue involvement, or progressive infection despite oral therapy.
Skin and Soft Tissue Infection, *Parenteral therapy*	Cefazolin 1 g IV q8h Nafcillin 1-2 g IV q4h	*Preferred agent:* Vancomycin 15-20 mg/kg IV q8-12h *Alternative agents:* Daptomycin 4 mg/kg IV qd Ceftaroline 600 mg IV q12h Dalbavancin: 1500 mg IV × 1 Linezolid 600 mg IV q12h Oritavancin 1200 mg IV × 1	Local rates of resistance should be considered when choosing empiric therapy. Cefazolin is associated with fewer treatment-related adverse events when compared with nafcillin. Use of alternative oral agents should be considered for methicillin-resistant *S. aureus* skin and soft tissue infections on an individual basis. Listed parenteral alternative agents are noninferior to vancomycin but not superior to it.[A4] Use of alternative parenteral agents for methicillin-resistant *S. aureus* should be considered on an individual basis, taking into account cost, logistics of administration, and side effect profiles.
Bacteremia and Endocarditis	Cefazolin 2 g IV q8h Nafcillin 2 g IV q4h	Vancomycin 15-20 mg/kg IV q8-12h Daptomycin 8-10 mg/kg IV qd	For patients with high inoculum infections such as endocarditis, nafcillin is recommended as initial therapy. In patients with methicillin-sensitive *S. aureus* bacteremia without endocarditis, cefazolin is at least as effective as antistaphylococcal β-lactams, with fewer treatment-related adverse events. Alternative agents may be considered in the setting of vancomycin treatment failures, which can occur even if the strain is susceptible (minimal inhibitory concentration [MIC] ≤2 μg/mL). Possible explanations include an undrained focus of infection, vancomycin's slowly bactericidal activity, or heteroresistance, in which a small fraction of the population of organisms requires a higher MIC. Combination regimens including aminoglycosides or rifampin are not recommended in *S. aureus* bacteremia and native valve endocarditis because of increased toxicity without improved outcome.[A5–A7] Adding an antistaphylococcal β-lactam to standard therapy with vancomycin or daptomycin does not significantly improve outcomes.[A8] Combination therapy may be considered as salvage therapy in patients who do not respond to standard regimens, with the guidance of expert consultation. The role of long-acting agents such as dalbavancin in treatment of bacteremia is under investigation.
Pericarditis	Cefazolin 2 g IV q8h Nafcillin 2 g IV q4h	Vancomycin 15-20 mg/kg IV q8-12h Daptomycin 8-10 mg/kg IV qd	
Bone and Joint Infections	*Parenteral therapy* Cefazolin 2 g IV q8h Nafcillin 2 g IV q4h *Oral therapy* Levofloxacin PO 500-750 mg qd plus rifampin 300-450 mg PO bid TMP-SMX 3.5-4 mg/kg q8-12 plus rifampin 300-450 mg PO bid Clindamycin 600 mg PO q8h	*Parenteral therapy* Vancomycin 15-20 mg/kg IV q8-12h Daptomycin 8-10 mg IV q24h *Oral therapy* Levofloxacin PO 500-750 mg qd plus rifampin PO 300-450 mg qd TMP-SMX 3.5-4 mg/kg q8-12 plus rifampin 300-450 mg PO qd Clindamycin 600 mg PO q8h Linezolid 600 mg PO q12h	Parenteral (initial parenteral followed by highly bioavailable oral antimicrobial therapy) or highly bioavailable oral therapy may be selected based on in vitro susceptibility and on individual circumstances, such as the presence of concurrent bacteremia, surgical débridement, and comorbid conditions. When fluoroquinolones are used as monotherapy, resistance may emerge, so the addition of rifampin is recommended. Linezolid may be considered in the initial course of therapy if other agents cannot be used. Prolonged use of linezolid is limited by bone marrow suppression, peripheral and optic neuropathy, and lactic acidosis.
CNS Infections	Nafcillin 2 g IV q4h	Vancomycin 15-20 mg/kg IV q8-12 h	For MRSA infections, vancomycin is considered the standard of care, but it penetrates the CSF poorly (approximately 1% and 5% in uninflamed and inflamed meninges, respectively). Cefazolin achieves poor CSF concentrations and should not be used for treatment of meningitis/ventriculitis. Limited data suggest benefit of adjunctive use of rifampin for CNS infections because it achieves bactericidal concentrations in the CSF. The addition of rifampin 600 mg qd or 300-450 mg bid, if the organism is susceptible, may be considered in combination with other agents for staphylococcal meningitis and ventriculitis. For patients who have intracranial hardware, such as a CSF shunt or drain that cannot be removed, rifampin is recommended in conjunction with other antistaphylococcal therapy. Data on other medications for CNS infections are limited. Linezolid has good CSF penetration (~66%) and is the preferred second-line treatment if vancomycin cannot be used.

TABLE 267-2 TREATMENT OF *STAPHYLOCOCCUS AUREUS* INFECTIONS—cont'd

CLINICAL SYNDROME	TREATMENTS FOR METHICILLIN-SENSITIVE *S. AUREUS**,†	TREATMENTS FOR METHICILLIN-RESISTANT *S. AUREUS**	COMMENTS
Pneumonia	Cefazolin 2 g IV q8h Nafcillin 2 g IV q4h Clindamycin 600 mg IV/PO q8h Linezolid 600 mg IV/PO q12h	Vancomycin 15-20 mg/ kg IV q8-12h Linezolid 600 mg IV/PO q12h	Clinical trials have found no differences in outcomes when patients with MRSA nosocomial pneumonia receive vancomycin or linezolid.[A9] Daptomycin should not be used to treat primary staphylococcal pneumonia because it is inactivated by pulmonary surfactant. It is indicated, however, for the treatment of hematogenous pneumonia, as occurs in tricuspid valve endocarditis or septic pulmonary embolization. Clindamycin and linezolid are protein synthesis inhibitors and have been shown in in vitro and animal models to inhibit toxin production. Further clinical studies are needed to define their role and that of intravenous immunoglobulin in toxin-mediated infections, such as community-acquired necrotizing staphylococcal pneumonia.
Orthopedic Device–Related Infections	*Parenteral therapy* Cefazolin 2 g IV q8h plus rifampin 300-450 mg PO bid Nafcillin 2 g IV q4h plus rifampin 300-450 mg PO bid *Oral therapy* Levofloxacin PO 500-750 mg qd plus rifampin 300-450 mg PO 450 bid TMP-SMX 3.5-4 mg/kg q8-12 plus rifampin 300-450 mg PO bid	*Parenteral therapy* Vancomycin 15-20 mg/kg IV q8-12h plus rifampin 300-450 mg PO bid Daptomycin 8-10 mg IV q24h plus rifampin 300-450 mg PO bid *Oral therapy* Levofloxacin PO 500-750 mg qd plus Rifampin PO 300-450 mg bid TMP-SMX 3.5-4 mg/kg q8-12 plus rifampin 300-450 mg PO bid	Surgical débridement with removal of hardware or two-stage exchange (in the case of prosthetic joint infections) offers the best chance of success. For orthopedic device–related infections with hardware retention or single-stage exchange, the addition of rifampin is recommended.
Genitourinary Infections	Based on susceptibility testing and clinical situation under expert guidance.	Based on susceptibility testing and clinical situation under expert guidance.	*S. aureus* is uncommonly isolated in urine culture and may represent asymptomatic bacteruria, cystitis, upper tract infection, or hematogenous seeding. No clinical trials to guide therapy. Blood cultures should be obtained if there is concern for systemic infection or upper urinary tract involvement, and treatment should be initiated with the same regimen as for bacteremia/endocarditis while awaiting blood cultures and further diagnostic results. For urinary catheter–associated infections, catheter removal (or exchange if still needed) is recommended. Cystitis can be treated with an oral agent to which the isolate is susceptible.

*Doses are for patients with normal renal function and may require adjustment for those with renal impairment.
†For patients with MSSA infections who are allergic to or intolerant of β-lactams, agents active against MRSA are effective alternatives.
bid = twice daily; CNS = central nervous system; CSF = cerebrospinal fluid; DS = double strength; IV = intravenous; MRSA = methicillin-resistant *Staphylococcus aureus*; MSSA = methicillin-sensitive *Staphylococcus aureus*; PO = oral; qd = daily; qid = four times daily; tid = three times daily; TMP-SMX = trimethoprim sulfamethoxazole.

hepatic, pulmonary, gastrointestinal, muscle, central nervous system, mucous membranes), and desquamation, especially of the palms and soles, 1 to 2 weeks after the onset of illness. Bacteremia is present in only 5% of cases.

TREATMENT AND PROGNOSIS

Treatment consists of systemic antimicrobial therapy as for bacteremia (see Table 267-2), removal of the source of toxin production, and treatment of septic shock (Chapter 94). The case fatality rate is about 5%.

Scalded Skin Syndrome

Infection or, rarely, colonization with an *S. aureus* strain that produces exfoliative toxin A or B may cause staphylococcal scalded skin syndrome,[25] which is a disease primarily of infants but occasionally seen in adults (Fig. 267-3), and bullous impetigo (Fig. 406-18), which is a pustular skin lesion. The appearance is that of a scald, burn, or blister. The diagnosis is based on history and a physical examination showing characteristic pain, erythema, blistering, and desquamation. A positive Nikolsky sign (sloughing of skin in response to slight mechanical pressure) may be observed. Cultures should be obtained from areas where purulent drainage is present or from common sites of *S. aureus* colonization (e.g., nares, nasopharynx) to confirm the diagnosis. The differential diagnosis of staphylococcal scalded skin syndrome includes drug reaction (Chapter 407), toxic epidermal necrolysis (Chapter 406), Kawasaki disease (Chapter 406), and pemphigus foliaceus (Chapter 406). Treatment is as for bacteremia (see Table 267-2).

FIGURE 267-3. Scalded skin–type lesions with multiple ruptured bullae and desquamation in a patient with aortic valve endocarditis caused by an exfoliative toxin–producing strain of S. aureus.

PREVENTION

Infection prevention strategies are critical to limiting both community-acquired and health care–associated staphylococcal infections. Because infections may

arise from the patient's resident flora or be acquired from direct contact with a contaminated source (e.g., a wound or dressing, the skin or hands of an asymptomatically colonized individual, or a contaminated health care provider), the most effective strategy is adherence to principles of basic infection control. The key intervention is hand hygiene, whether it is handwashing or use of an alcohol-based hand rub. Barrier precautions (gloves and gowns), which are important for minimizing contact with infected wounds, contaminated secretions, and dressings, should be used to interrupt transmission during uncontrolled outbreaks. The role of contact precautions outside of these scenarios is more controversial, with some studies demonstrating a benefit in reducing MRSA transmission while others do not.[26] For patients undergoing surgical procedures, surgical hand and surgical site antisepsis, aseptic surgical technique, and antimicrobial prophylaxis are important preventive measures.

Another potentially effective means of preventing infection is screening and decolonization of *S. aureus* carriers.[27] Studies to determine whether screening, decolonization, and isolation actually prevent MRSA infection have had mixed results. In the ICU setting, universal decolonization with 2% chlorhexidine baths, mouthwash, or showers plus 2% intranasal mupirocin ointment is more effective than targeted screening and decolonization or education alone in reducing rates of MRSA infection. Postdischarge decolonization of MRSA carriers with topical chlorhexidine and mupirocin twice monthly for 6 months also can reduce the risk of MRSA infection in the year after discharge compared with education alone.[A10] However, daily bathing with chlorhexidine alone does not reduce the incidence of health care–associated infections in critically ill adults in ICUs.[A11]

Decolonization may be considered in two other settings: prevention of recurrent skin and soft tissue infection and prevention of surgical site infections. The best-studied regimens are topically applied mupirocin nasal ointment and daily bathing with chlorhexidine soap for 5 to 10 days. Household decolonization may be considered in households with young children, where there are multiple family members with infections, or if there is ongoing transmission despite optimization of wound care and hygiene measures. The number of surgical site *S. aureus* infections can be reduced by the rapid screening of nasal carriers by real-time PCR assay followed by the decolonization of carriers with mupirocin nasal ointment and chlorhexidine soap.

PROGNOSIS

Prognosis of *S. aureus* infections and outcomes depend on the site of infection, adequacy of source control, presence of comorbidities (e.g., diabetes, immunosuppression, underlying cardiac, renal, or liver disease), presence and duration of bacteremia, presence of secondary foci of infection, presence of severe sepsis or septic shock, antibiotic effectiveness, and duration of therapy for complicated disease. Methicillin resistance is a risk factor for poorer outcome largely because of its health care association and occurrence in a population that is elderly and in which comorbid medical illnesses are prevalent and possibly because less effective antibiotics (non–β-lactams) are used to treat these infections.

Historically, untreated *S. aureus* bacteremia was lethal in 85% or more of cases. Antibacterial therapy, 4 to 6 weeks or longer for complicated bacteremia or infections of deep tissues, and recognition of the importance of source control have dramatically improved outcome, but mortality remains high. In *S. aureus* bacteremia, death occurs in 10 to 30% of cases.[28] Several studies have shown a strong link between elevated host interleukin-10 serum concentrations (>5 to 8 pg/mL) on clinical presentation and mortality in patients with *S. aureus* bacteremia. In patients with severe sepsis, septic shock, or endocarditis, morbidity and mortality are high, in part due to the occurrence of these infections in older patients, many of whom have comorbid medical conditions and impaired innate immunity. Mortality from endocarditis is in the 20 to 40% range. Strokes occur in approximately 20% of patients, and heart failure occurs in 40 to 50%. *S. aureus* prosthetic valve endocarditis is associated with a 40% or higher in-hospital mortality.

Staphylococcal pericarditis (Chapter 62) is associated with high morbidity due to complications such as cardiac tamponade, with mortality rates ranging from 20 to 40%. For hospital-acquired staphylococcal pneumonia, the mortality can be as high as 40 to 50%, reflecting the virulence of the organism and the comorbid conditions that contribute to poor outcomes.

For *S. aureus* osteomyelitis (Chapter 251), outcomes are highly variable and dependent on factors such as completeness of surgical débridement, the anatomic location of bony involvement, the presence of concurrent bacteremia, the underlying comorbid conditions, and vascular insufficiency.

Septic arthritis (Chapter 251) is associated with adverse joint outcomes in about one-third of patients, with in-hospital mortality rates of about 10%. Factors associated with worse outcomes include older age, pre-existing joint disease, and polyarticular joint infection.

For CNS infections due to *S. aureus*, outcomes are dependent on the nature of and extent of infection and surgical management (e.g., bone flap removal for craniotomy infections). Mortality associated with *S. aureus* meningitis ranges from about 25 to 45% and is higher in patients who have a hematogenous source compared with a postoperative source.

For orthopedic-device infections, outcomes are dependent on type of surgical procedure. For patients who have prosthetic joint infections, two-stage exchange arthroplasty is generally associated with improved outcomes when compared with débridement and retention of prosthesis.

For ascending catheter-associated urinary tract infections, outcomes are generally favorable with catheter removal and antibiotic therapy. For patients whose bacteriuria reflects hematogenous dissemination or a more complicated infection, outcomes are dependent on management of bacteremia and underlying source.

Skin infections are generally cured with appropriate antibiotic therapy accompanied by incision and drainage. Depending on the depth and severity of infection, scarring may occur.

COAGULASE-NEGATIVE STAPHYLOCOCCI

More than 30 different species of coagulase-negative staphylococci have been identified, and about half of these colonize humans. *Staphylococcus epidermidis* is the species that most commonly causes infection.[29] Coagulase-negative staphylococci infrequently cause infection unless there is a foreign body in place, and although bacteremia occurs, metastatic seeding of secondary sites of infection is distinctly uncommon. Coagulase-negative staphylococci are often resistant to methicillin and multiple other antibiotics, and they are an important reservoir of drug resistance elements that are horizontally transferrable to *S. aureus*. They are the most common cause of health care–associated infections overall in the United States (Chapter 261), they account for one third of central line–associated bloodstream infections, and they are the second most common cause of surgical site infections, particularly when a prosthetic device or other foreign material has been implanted. Coagulase-negative staphylococci, most especially *S. lugdunensis*, have been reported to cause native valve endocarditis. *S. epidermidis* and other coagulase-negative species account for about a third of cases of prosthetic valve endocarditis, particularly in cases with onset less than 2 months after valve implantation. Despite their relatively low virulence compared with *S. aureus*, mortality rates of patients with left-sided endocarditis caused by coagulase-negative staphylococci are similar to those caused by MRSA. Mortality is associated with β-lactam resistance (true for >80% *S. epidermidis*), again raising the concern of the inferiority of non–β-lactam drugs in the treatment of endovascular infections. Infections are often indolent, causing little in the way of fever or systemic signs of infection, but they may also be acute and life-threatening, as in the case of prosthetic valve endocarditis.

Coagulase-negative staphylococci are proficient biofilm producers. Consequently, débridement and removal of the infected prosthetic device or foreign body are paramount. Prosthetic joint infections occurring more than 1 month after device implantation are best managed with removal of the prosthesis and reimplantation in a one-stage or two-stage procedure. Antimicrobial therapy for these infections is similar to that for *S. aureus*, except that hematogenous seeding rarely occurs, so attention is focused primarily on source control.

Coagulase-negative staphylococci, because they are normal skin flora, are common blood culture contaminants. Approximately 75% of cases in which a blood culture is positive for coagulase-negative staphylococci reflect contamination rather than infection. Sorting out whether a positive culture represents contamination or true infection can be challenging. A single positive blood culture or blood cultures in which more than one strain is present are likely to be due to contamination. Time to blood culture positivity, quantitative blood cultures, and the presence of multiple positive cultures can be useful in determining whether a positive blood culture represents true infection. Isolation of coagulase-negative staphylococci from the blood of a patient with a prosthetic valve, intravenous pacemaker, or vascular graft can be especially problematic because these patients are at high risk for true infection. Unless the patient is hemodynamically unstable or otherwise seriously ill, it is advisable to withhold antibiotics until additional culture specimens are obtained to document the presence of true bacteremia. Isolation of coagulase-negative staphylococci from culture specimens of deep tissue, bone, prosthetic devices, or other normally sterile sites, especially if multiple cultures are positive, strongly suggests true infection.

Staphylococcus lugdunensis causes infections that clinically resemble *S. aureus* infections and can occur in the absence of a foreign body and in otherwise normal hosts. These include prosthetic valve and native valve endocarditis, bacteremia, skin and soft tissue infection, septic arthritis, prosthetic joint infection, and osteomyelitis. *S. lugdunensis* is susceptible to most antibiotics, including penicillin (approximately 75% of isolates), and methicillin resistance is rare. Management of these infections is similar to that of *S. aureus* infections.

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268

STREPTOCOCCUS PNEUMONIAE PULMONARY INFECTIONS

THOMAS MCDONALD FILE, JR.

DEFINITION

Streptococcus pneumoniae (*S. pneumoniae*) is a significant human bacterial pathogen and a major cause of community-associated bacterial infections. It is the most common bacterial cause of community acquired pneumonia (pneumococcal pneumonia; Chapter 85), sinusitis (Chapter 394), and bacterial meningitis (Chapter 381). Despite the availability of an effective vaccine, the burden of pneumococcal pneumonia remains high, particularly in older adults and in patients with underlying comorbid conditions.[1]

The Pathogen

S. pneumoniae (pneumococci) are lancet-shaped, encapsulated, gram-positive cocci. The cells are 0.5 to 1.2 µm in size and usually arranged end to end in pairs—often referred to as diplococci (Fig. 268-1). Colonies appear α-hemolytic, demonstrate fastidious growth, and require catalase (e.g., blood) to grow on agar plates. The major virulence factor is a polysaccharide capsule that covers the organism and inhibits phagocytosis. Strains of pneumococci are classified according to the type of capsule, of which there are 100 known serotypes. Most *S. pneumoniae* serotypes have been shown to cause disease, but only a minority of serotypes produce the majority of pneumococcal infections.

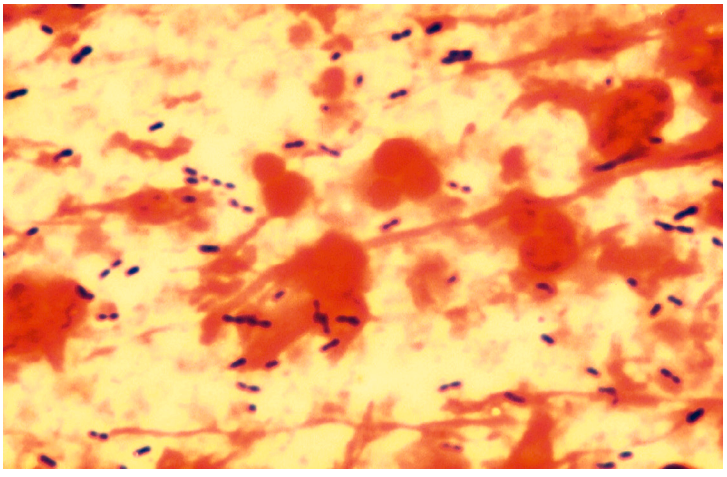

FIGURE 268-1. Gram stain of sputum from patient with pneumococcal pneumonia showing gram-positive diplococci aligned end to end.

However, serotype patterns are slowly changing, in part because of the widespread use of polyvalent vaccine. Strains of *S. pneumoniae* can occasionally change capsular type via exchanging genes between different serotypes involved in capsule synthesis. In addition, genetic mutations or deletions can result in emergence of nonencapsulated strains. Such strains are less virulent but can be associated with noninvasive infection (e.g., conjunctivitis or otitis) and less commonly pneumonia. Another significant virulence factor, pneumolysin, is a cytolysin that causes damage to host cells and interferes with host immunity.

EPIDEMIOLOGY

Each year in the United States, pneumococcal disease accounts for a substantial number of cases of invasive and noninvasive disease. Invasive pneumococcal disease includes cases with isolation of *S. pneumoniae* from normally sterile sites (e.g., blood, cerebrospinal fluid).

S. pneumoniae is the leading cause of mortality due to lower respiratory tract infections globally and causes approximately 1.2 million deaths each year.[2] In 2020, the rate of invasive pneumococcal disease (mostly due to bacterial pneumonia) in the United States was 9.6/100,000 population, with a death rate of 1.06/100,000,[3] and these rates are similar in Europe.[4] The incidence of pneumococcal pneumonia declined by about 30% in industrialized countries during the severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2) pandemic.[5]

The widespread use of pneumococcal vaccines, especially the pneumococcal conjugate vaccine (PCV13), has reduced the incidence of pneumococcal infections, but the emergence of non-PCV13 serotypes[6] has resulted in an increase back to or close to prevaccine levels.[7] Furthermore, the number of cases is expected to increase as the population of elderly individuals increases.

S. pneumoniae, which remains the most common cause of community-acquired pneumonia (Chapter 85), is isolated by culture in only 5 to 15% of cases in the United States, but quantitative molecular data indicate that the true rate is probably about 30%. Pneumococcal pneumonia is associated with bacteremia in approximately 10 to 30% of cases.

About 5 to 10% of patients with pneumococcal pneumonia will die, and the death rate is higher in patients requiring hospitalization or who are age 65 years and older. Fewer patients will develop pneumococcal meningitis (Chapter 381), but the mortality rate for this infection is much higher.

Risk factors for pneumococcal pneumonia include smoking (Chapter 363); asthma (Chapter 75); alcohol use disorder (Chapter 364); underlying chronic lung (Chapters 76, 78, and 80) or heart disease (Chapter 46); diabetes (Chapter 210); cirrhosis (Chapter 139); renal insufficiency (Chapter 116); dementia (Chapter 371); malnutrition (Chapter 198); sickle cell anemia (Chapter 149); immunocompromise, including HIV infection (Chapter 358); intravenous drug use (Chapter 365); and homelessness.[8] Prior or co-infection with a respiratory virus, especially influenza (Chapter 332), is also a risk factor for *S. pneumoniae*.[9] SARS-CoV-2 infection (Chapter 336) can similarly reduce host defenses of the respiratory tract against *S. pneumoniae*.[10,11]

PATHOBIOLOGY

S. pneumoniae is an exclusively human pathogen and is predominantly spread from direct person-to-person contact via airborne droplets. The spread of

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268

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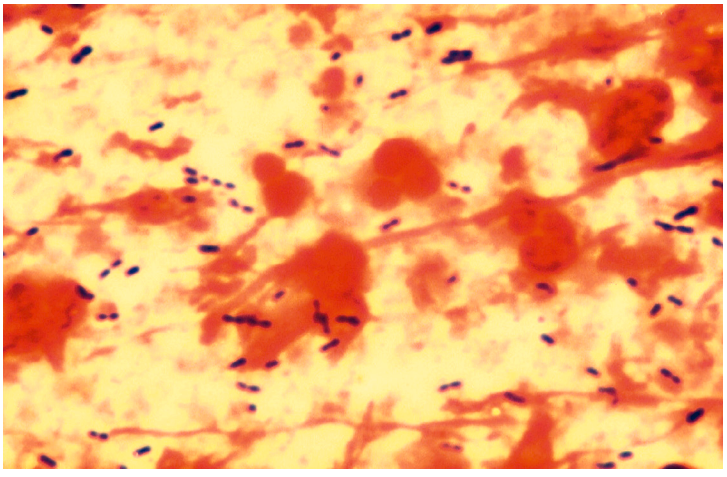

FIGURE 268-1. Gram stain of sputum from patient with pneumococcal pneumonia showing gram-positive diplococci aligned end to end.

However, serotype patterns are slowly changing, in part because of the widespread use of polyvalent vaccine. Strains of *S. pneumoniae* can occasionally change capsular type via exchanging genes between different serotypes involved in capsule synthesis. In addition, genetic mutations or deletions can result in emergence of nonencapsulated strains. Such strains are less virulent but can be associated with noninvasive infection (e.g., conjunctivitis or otitis) and less commonly pneumonia. Another significant virulence factor, pneumolysin, is a cytolysin that causes damage to host cells and interferes with host immunity.

EPIDEMIOLOGY

Each year in the United States, pneumococcal disease accounts for a substantial number of cases of invasive and noninvasive disease. Invasive pneumococcal disease includes cases with isolation of *S. pneumoniae* from normally sterile sites (e.g., blood, cerebrospinal fluid).

S. pneumoniae is the leading cause of mortality due to lower respiratory tract infections globally and causes approximately 1.2 million deaths each year.[2] In 2020, the rate of invasive pneumococcal disease (mostly due to bacterial pneumonia) in the United States was 9.6/100,000 population, with a death rate of 1.06/100,000,[3] and these rates are similar in Europe.[4] The incidence of pneumococcal pneumonia declined by about 30% in industrialized countries during the severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2) pandemic.[5]

The widespread use of pneumococcal vaccines, especially the pneumococcal conjugate vaccine (PCV13), has reduced the incidence of pneumococcal infections, but the emergence of non-PCV13 serotypes[6] has resulted in an increase back to or close to prevaccine levels.[7] Furthermore, the number of cases is expected to increase as the population of elderly individuals increases.

S. pneumoniae, which remains the most common cause of community-acquired pneumonia (Chapter 85), is isolated by culture in only 5 to 15% of cases in the United States, but quantitative molecular data indicate that the true rate is probably about 30%. Pneumococcal pneumonia is associated with bacteremia in approximately 10 to 30% of cases.

About 5 to 10% of patients with pneumococcal pneumonia will die, and the death rate is higher in patients requiring hospitalization or who are age 65 years and older. Fewer patients will develop pneumococcal meningitis (Chapter 381), but the mortality rate for this infection is much higher.

Risk factors for pneumococcal pneumonia include smoking (Chapter 363); asthma (Chapter 75); alcohol use disorder (Chapter 364); underlying chronic lung (Chapters 76, 78, and 80) or heart disease (Chapter 46); diabetes (Chapter 210); cirrhosis (Chapter 139); renal insufficiency (Chapter 116); dementia (Chapter 371); malnutrition (Chapter 198); sickle cell anemia (Chapter 149); immunocompromise, including HIV infection (Chapter 358); intravenous drug use (Chapter 365); and homelessness.[8] Prior or co-infection with a respiratory virus, especially influenza (Chapter 332), is also a risk factor for *S. pneumoniae*.[9] SARS-CoV-2 infection (Chapter 336) can similarly reduce host defenses of the respiratory tract against *S. pneumoniae*.[10,11]

PATHOBIOLOGY

S. pneumoniae is an exclusively human pathogen and is predominantly spread from direct person-to-person contact via airborne droplets. The spread of

ABSTRACT

Streptococcus pneumoniae (*S. pneumoniae*) is the most common bacterial cause of community-acquired pneumonia. Despite the availability of an effective vaccine, the burden of pneumococcal pneumonia is high, particularly in older adults and in patients who have underlying comorbid conditions. Risk factors for pneumococcal pneumonia include prior viral infections, underlying conditions, and immune deficiency. Pneumococcal pneumonia may be mild, but the wide range of severity includes overwhelming sepsis, in which the mortality rate may be greater than 50%. Potential complications include bacteremia with metastatic infection (e.g., septic arthritis, peritonitis, pericarditis, meningitis, endocarditis) and pulmonary complications (e.g., parapneumonic effusion, empyema, necrotizing pneumonia, lung abscess). Up to one third of patients hospitalized with pneumococcal pneumonia experience major cardiovascular events. Diagnostic tests for pneumonia caused by *S. pneumoniae* include sputum Gram stain and culture, blood culture, immunochromatography, and molecular methods. The majority of patients with community-acquired pneumonia are treated empirically with a regimen that is likely to have activity against *S. pneumoniae*. The choice of initial therapy is complicated by the emergence of antibiotic resistance among *S. pneumoniae*. The best way to prevent pneumococcal pneumonia is through vaccination and stabilization of underlying conditions that predispose to infection (e.g., diabetes, heart failure).

KEYWORDS

pneumococcus
pneumonia
polysaccharide capsule
pneumolysin
antimicrobial resistance
vaccination

the organism is influenced by such factors as crowding, especially during the winter and in early spring when respiratory diseases are more prevalent. After transmission, the organism commonly colonizes the nasopharynx, from which it can spread to the lungs, paranasal sinuses, or middle ear.[12] It can also be transported in the blood to distal sites such as the brain, heart, and joints. Colonization in the pharynx is mediated by the binding of the bacteria to epithelial cells by means of surface protein adhesins. Strains with a smaller capsular size have increased exposure of adhesins, which correlates with enhanced colonization. Pneumococci may be isolated from the nasopharynx of 5 to 50% of healthy persons, depending on the population and setting, and carriage is most common in winter and early spring, especially in school-aged children.

From the nasopharynx, pneumococci can migrate to the lower respiratory tract by microaspiration of oropharyngeal secretions containing the organism. Hematogenous spread from a distant infected site, direct spread from a contiguous focus, and macroaspiration are other mechanisms whereby *S. pneumoniae* may gain access to the lung.

The disease manifestations of *S. pneumoniae* are caused primarily by the host response to infection rather than the production of organism-associated toxins. The development of pneumococcal pneumonia becomes more likely when a more virulent strain or the amount of aspirated pneumococci overwhelms the host defense system in the respiratory tract (Fig. 268-2). Innate host defenses, which reduce development of pneumonia, include the physiologic removal of bacteria, which become enveloped within mucus and eliminated by the action of ciliated epithelial cells of the respiratory tract. Secretory IgA facilitates the trapping of bacteria in mucus by binding bacteria to mucin; secretory IgA protease produced by *S. pneumoniae* can overcome this host defense. In addition, the polysaccharide capsule plays a role in reducing attachment to airway mucus.

S. pneumoniae resists phagocytosis in part because of the antiphagocytic protection by its capsule. Antibodies directed against the specific type of capsular polysaccharide protect against disease caused by that specific strain by facilitating phagocytosis of the organism and killing of the bacteria. Patients with abnormalities related to antibody production (e.g., asplenia, immunoglobulin deficiencies, multiple myeloma, chronic lymphocytic leukemia) or to phagocytic function (e.g., chronic granulomatous disease, hyperimmunoglobulin E syndrome, myeloperoxidase deficiency, Chediak-Higashi syndrome) are at higher risk for pneumococcal pneumonia and for worse outcomes when infection occurs.

CLINICAL MANIFESTATIONS

The onset of clinical manifestations of pneumococcal pneumonia can be mild, but the wide range of severity includes patients with overwhelming sepsis in whom the mortality rate may be greater than 50%. Classically, the onset is abrupt with fever, chills (often shaking), cough, and pain (often pleuritic). However, this constellation of manifestations presents in only a minority of cases, and the presenting manifestations overlap with those associated with other causes of pneumonia (Chapter 85). Most patients with pneumonia have tachycardia and tachypnea. Older patients may present with delirium as an initial manifestation. Other symptoms include vomiting, diarrhea, myalgias, and arthralgias. Severe infection may be associated with multiple organ dysfunction.

Auscultatory findings of crackling rales and bronchial breath sounds are localized to the involved segment or lobe. Confusion, obtundation, and stiff neck should lead to consideration of meningitis. Hypoxia by pulse oximetry is common.

The classic description of the sputum in lobar pneumococcal pneumonia is "rusty," owing to mixed blood cells and hemoglobin in the sputum. Laboratory abnormalities include leukocytosis with left shift. Leukopenia is found in a minority of cases and is associated with a poor prognosis.

Chest radiography typically reveals a homogenous lobar or segmental alveolar infiltrate, often with a small amount of pleural fluid, but pneumococcal pneumonia also can cause a bronchopneumonia characterized by multiple opacities that tend to be patchy and/or confluent. Chest computed tomography may demonstrate additional complications including abscess, pleural effusions, or lymphadenopathy. Lung ultrasound can demonstrate subpleural consolidation, fluid-filled airspaces, irregular interfaces between consolidated and aerated areas of the lung, and hepatization, in which the lung develops a relatively fine echotexture similar to the liver.

Complications

Potential complications of pneumococcal pneumonia include bacteremia with metastatic infection (septic arthritis, peritonitis, pericarditis, meningitis,[13] endocarditis[14]) and pulmonary complications of parapneumonic effusion, empyema, necrotizing pneumonia, and lung abscess. Risk factors for a complicated course include older age, preexisting lung disease, immunodeficiency or AIDS, and, importantly, acquisition of another nosocomial infection. The risk of overwhelming pneumococcal sepsis is increased in splenectomized patients, because the spleen is a principal site for clearance of this bacterium.

Up to one third of patients hospitalized with pneumococcal pneumonia experience major cardiovascular events. In addition to the stress, hypoxemia, and inflammation associated with infection, pneumolysin may play a direct role in injury to the myocardium. Direct infection of cardiac muscle may be an additional mechanism.

Other Pneumococcal Infections

Pneumococcal species can cause meningitis (Chapter 381), endocarditis (Chapter 61), empyema (Chapter 86), sinusitis (Chapter 394), and otitis (Chapter 394). These infections are described in their respective chapters.

DIAGNOSIS

The cause of community-acquired pneumonia, based on standard diagnostic methods, is identified in a minority of cases (Table 85-1).[15] Diagnostic tests for pneumonia caused by *S. pneumoniae* include molecular methods, sputum Gram stain and culture, blood culture, and immunochromatography. Nucleic acid amplification techniques, which can detect multiple respiratory pathogens including bacteria and viruses from a single respiratory tract sample,[16] are increasingly the standard of care for community-acquired pneumonia (Chapter 85).

The etiologic role of *S. pneumoniae* can be strongly implicated by the presence of gram-positive lancet-shaped diplococci on sputum Gram stain (Fig. 268-1) and isolation by culture. Sputum culture is recommended in patients who have severe community-acquired pneumonia, especially if they are intubated, are being empirically treated for *S. aureus* (Chapter 267) or *P. aeruginosa* (Chapter 282), or have received parenteral antibiotics within the past 90 days, so that its results can potentially narrow antibiotic therapy. However, *S. pneumoniae* is recovered in a minority of sputum cultures in part because the organism has fastidious nutritional requirements and is often overgrown by contaminating oral bacteria. To be reliable, the specimen should be actual sputum and not saliva, with microscopy showing high numbers of polymorphonuclear cells and few epithelial cells.

The yield of blood cultures for patients admitted with community-acquired pneumonia is only 5 to 15%, depending on the severity of disease, with *S. pneumoniae* accounting for approximately two-thirds of the positive results. Guidelines recommend blood cultures for patients who require admission to an intensive care unit or who meet criteria for sputum culture because they may be the only documentation of pneumococcal infection.[17] Urinary antigen tests can detect pneumococcal pneumonia when cultures cannot be obtained in a timely fashion or when antibiotic therapy has already been initiated, with a sensitivity of 50 to 80% and a specificity exceeding 90%.[18]

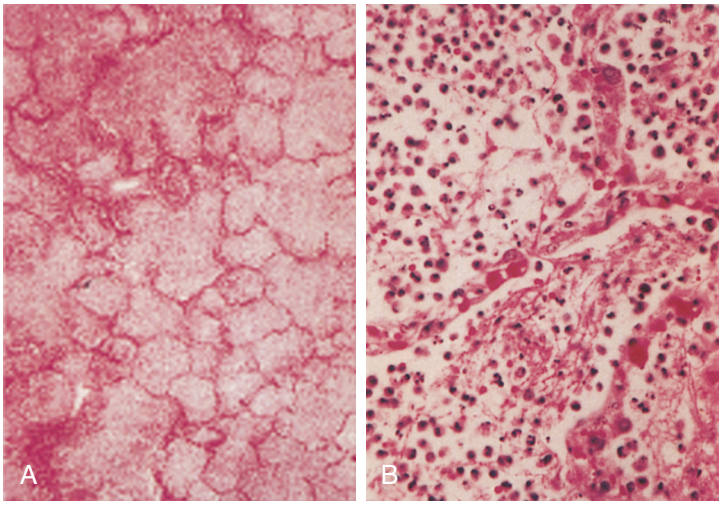

FIGURE 268-2. Pneumonia. A, Low-power magnification (×100) of hematoxylin and eosin (H&E) stain of tissue section from the left lower lobe of the lung. Note the intact alveolar walls and alveoli filled with edema and thick cellular exudates. **B,** Higher magnification (×500) H&E stain of the same section shown in A. Note the heavy infiltrate of polymorphonuclear cells and the intact alveolar walls.

TREATMENT

Choosing Antibiotic Therapy

Antibiotic therapy for community-acquired pneumonia should be begun as soon as possible on an empiric basis because the causative organism is not identified in an appreciable proportion of patients (Chapter 85).[19] Antibiotics (Table 268-1) should be started. The initial regimen should have activity against *S. pneumoniae*, then the regimen should be narrowed to just *S. pneumoniae* (E-Table 268-1) when it is documented by molecular methods, Gram stain and sputum culture, blood culture, or pneumococcal urinary antigen.

Oral agents can usually be used for outpatient therapy in many patients with community-acquired pneumonia (see Chapter 85), but many patients with confirmed pneumococcal pneumonia are sick enough to require hospital admission. Hospitalized patients are initially treated with an intravenous regimen until clinical improvement allows transition to oral therapy.

For admitted patients, combination therapy with a β-lactam plus a macrolide or monotherapy with a respiratory fluoroquinolone are generally of comparable efficacy, but the former is usually preferred. Patients who have a history of a mild penicillin reaction can receive a third- or fourth-generation cephalosporin or carbapenem safely. If there is significant concern to warrant avoidance of a cephalosporin or carbapenem, however, an alternative regimen should be given.

Risk factors for drug-resistant *S. pneumoniae* in adults include age greater than 65 years, recent antimicrobial therapy, alcohol use disorder, an immunosuppressive illness or therapy, exposure to a child in a daycare center, recent prior hospitalization, or residence in a long-term care facility. Rates of resistance are above 30% for macrolides, less than 2% to the newer fluoroquinolones (levofloxacin, moxifloxacin) in the United States but higher in some countries, and low to β-lactam drugs (e.g., amoxicillin, ceftriaxone, cefotaxime).[20]

Response to Therapy

With appropriate antibiotic therapy, some improvement in the patient's clinical course is usually seen within 72 to 96 hours. The recommended duration of therapy for patients with a good clinical response within the first 3 days of therapy is generally 5 days total, but 3 days may be adequate in patients who were not admitted to an intensive care unit and who are completely stable clinically.[A1] Before stopping therapy, the patient should be afebrile, breathing without supplemental oxygen (unless required for preexisting disease), and hemodynamically stable. A longer duration is needed for more complicated infections (e.g., empyema, extrapulmonary infection such as meningitis, endocarditis, septic arthritis).

The use of the serum biomarker procalcitonin can help guide duration of antimicrobial therapy. Procalcitonin promptly increases within 6 to 12 hours of the initial infection and decreases rapidly when the bacterial infection is controlled. Antibiotic duration guided by serial measurement of the procalcitonin level can safely reduce duration of treatment in patients with pneumococcal pneumonia.[A2]

Guidelines do not recommend routine use of corticosteroids. However, they may be beneficial for patients who have evidence of severe pneumonia with an exaggerated or dysregulated inflammatory response, defined as a severe inflammatory response, respiratory failure, or septic shock.[A3,A4,A5]

Although a clinical response to appropriate antibiotic therapy is seen relatively quickly, cough may persist for a week or longer, and auscultatory crackles may take 3 weeks to clear. Patients who do not demonstrate some clinical improvement within 72 to 96 hours are considered nonresponders. Most common causes include severe disease, resistant strains, extrapulmonary infection (e.g., empyema, metastatic infection), unstable comorbid conditions, and noninfectious causes (e.g., pulmonary embolism, lung cancer, drug reactions, or immunodeficiency).

TABLE 268-1 ANTIMICROBIAL THERAPY FOR PNEUMOCOCCAL PNEUMONIA

	PREFERRED ANTIMICROBIALS	ALTERNATIVE ANTIMICROBIALS
ORAL AGENTS		
Penicillin susceptible (MIC ≤0.06 μg/mL)*	Amoxicillin; penicillin	Oral cephalosporins (cefpodoxime; cefdinir; cefditoren; cefuroxime) Oral macrolides if susceptible in vitro† Clindamycin; doxycycline; omadacycline¶ Lefamulin¶ Respiratory fluoroquinolones (levofloxacin, moxifloxacin, gemifloxacin)
Penicillin resistant*	Fluoroquinolone; high-dose amoxicillin (3 g/day)	Clindamycin; linezolid; lefamulin¶; omadacycline¶
INTRAVENOUS AGENTS	Third-generation cephalosporin (ceftriaxone, cefotaxime); ceftaroline§; penicillin‡; ampicillin‡	Fluoroquinolones; vancomycin; clindamycin; linezolid; broad-spectrum β-lactams‖; tigecycline; lefamulin¶; omadacycline¶

*Based on nonmeningitis breakpoint for oral penicillin; parenteral penicillin nonmeningitis breakpoint is ≤2.0 μg/mL; if concern for meningitis, breakpoint for susceptible isolates is 0.06 μg/mL.

†High rate of resistance in United States and not recommended for empirical therapy without knowledge of the susceptibility results.

‡High dose (≥18 million units of penicillin or 12 g of ampicillin likely to be effective for most strains with elevated MICs).

§Ceftaroline more potent for *S. pneumoniae* than the third-generation cephalosporin (3rd-gen Ceph) and often active even if resistant to 3rd-gen Ceph.

‖Piperacillin/tazobactam, cefepime, ceftazidime, ertapenem, imipenem, and meropenem.

¶Lefamulin and omadacycline are newer agents that are active against most community-acquired pneumonia pathogens including *S. pneumoniae, H. influenza, M. catarrhalis, S. aureus*, and atypical pathogens; lefamulin lacks activity against Enterobacteriaceae so can be considered as more targeted for the community-acquired pneumonia pathogens, whereas omadacycline has activity against many Enterobacteriaceae and may be more appropriate for patients with structural lung disease.

PROGNOSIS

The mortality rate for pneumococcal pneumonia varies by severity at presentation and host factors, but overall it is as high as 11% in hospitalized patients. Patients with bacteremic pneumococcal pneumonia have higher in-hospital mortality and longer length of hospital stay. Other factors associated with increased mortality include older age, severity of disease, requirement for ventilation, shock, bilateral disease, amount and degree of underlying conditions, and renal failure.

PREVENTION

The best way to prevent pneumococcal infection is by vaccination and stabilization of underlying conditions that predispose to infection (e.g., diabetes, heart failure).

There are two types of pneumococcal vaccine recommended for adults: a pneumococcal conjugate vaccine (i.e., PCV13, PCV 15, and PCV 20) and a pneumococcal polysaccharide vaccine (i.e., PPSV23). The conjugate vaccine contains antigens for 13, 15, or 20 serotypes and is more immunogenic,[A6] whereas the polysaccharide contains antigens of 23 serotypes. Recommendations for pneumococcal vaccine are based on age and underlying conditions (Chapter 15).

Influenza vaccine also reduces pneumococcal pneumonia, because by reducing the morbidity of acute influenza, the incidence of postinfluenza bacterial pneumonia is lessened. Dental hygiene may reduce the infectious consequences of aspiration. The relatively simple act of daily teeth brushing may help prevent pneumococcal pneumonia.

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E-TABLE 268-1 ANTIMICROBIAL SUSCEPTIBILITY AMONG *STREPTOCOCCUS PNEUMONIAE* ISOLATES COLLECTED FROM 2015 TO 2016, STRATIFIED BY GEOGRAPHIC REGION

	MIC_{50} (µG/mL)	MIC_{90} (µG/mL)	% SUSCEPTIBLE ALL REGIONS*	% SUSCEPTIBLE NA*	% SUSCEPTIBLE EUR*	% SUSCEPTIBLE APAC	% SUSCEPTIBLE LATAM
Azithromycin	0.06	>4	63.1	56.2	76.6	55.0	72.8
Clindamycin	≤0.25	>1	83.1	86	83.3	65.4	84.3
Amoxicillin-clavulanate	≤1	4	93.4	94.9	94.1	87.7	93.7
Penicillin	≤0.06	2	65.8† 95.5‡	64.1 96.6	71.6 95.5	55.2 89.6	70.2 94.8
Ceftriaxone	≤0.03	1	87.1§ 96.5‖	88.2 97.7	87.6 96.4	77.7 89.5	90.6 95.8
Ceftaroline	≤0.008	0.12	99.9‖	100	>99.9	99.2	100
Linezolid	1	1	100	100	100	100	100
Levofloxacin	1	1	98.6	99.1	98.2	97	100
Tetracycline	≤0.25	>4	57.6	80.7	78.2	56.1	70.0
TMP-SMX	≤0.5	>4	77.2	73.1	72.1	63.1	64.4
Vancomycin	0.25	0.25	100	100	100	100	100

*According to Clinical and Laboratory Standards Institute breakpoints.
†Using parenteral meningitis breakpoints.
‡Using parenteral nonmeningitis (e.g., pneumonia) breakpoints.
§Using oral breakpoints.
‖Using nonmeningitis (e.g., pneumonia) breakpoints.
APAC = Asia-Pacific; EUR = Europe; LATAM = Latin America; NA = North America; TMP-SMX = trimethoprim-sulfamethoxazole.
Modified from Sader HS, Mendes RE, Le J, et al. Antimicrobial susceptibility of *Streptococcus pneumoniae* from North America, Europe, Latin America, and the Asia-Pacific region: results from 20 years of the SENTRY Antimicrobial Surveillance Program (1997-2016). *Open Forum Infect Dis.* 2019;6(Suppl 1):S14-S23.

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269 NONPNEUMOCOCCAL STREPTOCOCCAL INFECTIONS AND RHEUMATIC FEVER

DENNIS L. STEVENS, AMY E. BRYANT, AND MELISSA M. HAGMAN

CLASSIFICATION AND IDENTIFICATION OF STREPTOCOCCI

Streptococci are gram-positive facultatively anaerobic, catalase-negative coccoid bacteria that grow in chains and colonize the skin and mucous membranes. When grown on blood agar plates, they may cause complete (β), incomplete (α), or no (γ) hemolysis. Using the Lancefield classification, hemolytic streptococci can be classified into types A through G based on acid-extractable carbohydrate antigens of cell wall material. Modern classification schemes categorize hemolytic and nonhemolytic streptococci using complex biochemical and genetic techniques.

The major pathogenic β-hemolytic streptococci are group A *(Streptococcus pyogenes)* and group B *(Streptococcus agalactiae)*. Although most of this chapter is dedicated to discussing these two pathogens and the clinical diseases that they cause, the remainder of the chapter includes discussions of *Streptococcus dysgalactiae* subspecies *equisimilis* (groups C and G streptococcus), viridans group streptococcus (no Lancefield group), and zoonotic streptococci (various Lancefield groups).

STREPTOCOCCUS PYOGENES (GROUP A STREPTOCOCCUS) INFECTIONS

Acute Infections

DEFINITION

S. pyogenes contains Lancefield group A antigen on the cell surface and thus is referred to as group A streptococcus. Group A streptococci are the most significant of the streptococcal human pathogens and cause an array of clinical infections ranging from pharyngitis, superficial skin infections, deep soft tissue infections, and toxic shock syndrome. Postinfectious sequelae include rheumatic fever, post-streptococcal glomerulonephritis, and reactive arthritis.[1]

EPIDEMIOLOGY

Humans are the only known hosts for *S. pyogenes*. All group A streptococcal infections are more common in children younger than age 10 years. The asymptomatic prevalence of the group A streptococcus carrier state is also higher in children (15 to 20%) than in adults (<5%). In addition to age, group A streptococcus epidemics are also associated with crowded conditions, particularly in schools and military camps, during the winter months in temperate climates. The U.S. Centers for Disease Control and Prevention (CDC) estimates that the incidence of invasive *S. pyogenes* infections in the United States in 2019 was 7.5 cases per 100,000 population per year. Worldwide, an estimated 18 million annual infections cause about 500,000 deaths each year.[2]

Pharyngeal and cutaneous group A streptococci are transmitted from person to person by aerosolized microdroplets or direct contact. Epidemics of pharyngitis and scarlet fever occur after the consumption of contaminated food or unpasteurized milk. Group A streptococcus infections are seen in hospitalized patients during childbirth (puerperal sepsis), after surgery or burns (wound infection), and in war settings (epidemic gangrene). Thus, most clinical streptococcal infections have a clear mode of transmission and portal of entry. In contrast, among patients with streptococcal toxic shock syndrome, the portal of entry is obvious in only 50% of cases.

PATHOBIOLOGY

Mucous membranes and skin serve as the natural reservoirs for *S. pyogenes*. Group A streptococci adhere to host epithelium through complex interactions involving streptococcal factors such as M protein, lipoteichoic acid, fibronectin-binding protein, and fimbriae.[3] Although streptococci must adhere to the epithelium to cause most infections, such adherence is not always sufficient to cause disease because many individuals may have prolonged asymptomatic carriage without clinical infection.

Streptococci evade opsonophagocytosis by expression of antiphagocytic M protein, by use of immunoglobulin-binding protein, by formation of a hyaluronic acid capsule, and/or by production of a C5a peptidase that destroys or inactivates complement-derived chemoattractants and opsonins.[4] At the focus of infection, the exotoxin streptolysin O is cytotoxic and destroys approaching phagocytes. Distal to the infection, lower concentrations of streptolysin O stimulate hyperadhesion of polymorphonuclear leukocytes to endothelial cells (thereby effectively preventing a tissue inflammatory response and promoting vascular damage) and cause vascular occlusion with destruction of distal fascia and muscle. In a nonimmune host, streptolysin O, streptococcal pyrogenic exotoxins, and other streptococcal components drive the "cytokine storm" that causes hypotension and vascular leukostasis, thereby resulting in shock, microvascular injury, multiorgan failure, and even death.

M Proteins

More than 150 different M protein serotypes of group A streptococci have been described. The M protein is a coiled-coil structure that consists of four regions of repeating amino acids (A to D), a proline/glycine-rich region that intercalates the protein into the bacterial cell wall, and a hydrophobic membrane anchor. Region A, which is near the *N* terminus, is highly variable, and antibodies to this region confer type-specific protection by overcoming the antiphagocytic properties of the protein. The more conserved B to D regions bind complement regulatory proteins, sterically inhibiting antibody binding and complement-derived opsonin deposition and effectively camouflaging the organism against humoral immune surveillance. The quantity of M protein that is produced by an infecting strain progressively decreases during convalescence and during prolonged asymptomatic carriage.

Cell Wall, Lipoteichoic Acid, Fibronectin-Binding Protein (Protein F), and Fimbriae

Many different factors help group A streptococci adhere to host epithelial cells. Integral lipoteichoic acid components of the cell wall mediate hydrophobic interactions between pathogen and host cells. Fibronectin-binding protein (protein F) promotes binding to the host cell extracellular matrix. Fimbriae, flexible rods that protrude up to 3 μm from the bacterial cell surface, mediate adherence to epithelial cells and promote microcolony and biofilm formation.

Hyaluronic Acid Capsule

Some strains of *S. pyogenes* have hyaluronic acid capsules. These capsules, which bind to CD44 on epithelial cells and serve as antiphagocytic factors, are important in pharyngitis, soft tissue infection, and invasive disease.

Streptolysin O and S

Streptolysin O belongs to a family of highly homologous oxygen-labile, cholesterol-dependent cytolysins. These cytotoxins cause the broad zone of complete β-hemolysis that surrounds colonies of *S. pyogenes* grown on blood agar plates. As the name implies, cholesterol-dependent cytolysins bind to cholesterol on eukaryotic cell membranes, where they create toxin-cholesterol membrane pores that, at high doses, cause cell lysis by a colloid-osmotic mechanism. Sublytic doses stimulate cardiac cell dysfunction, leukocyte granule release, and intravascular leukostasis and blood flow occlusion. Anti-streptolysin O titers are used clinically to detect recent group A streptococcal infection and to aid in diagnosis of post-streptococcal syndromes such acute rheumatic fever and post-streptococcal glomerulonephritis. When the serum cholesterol level is high, as in the nephrotic syndrome, the anti-streptolysin O titer may be falsely elevated.

Streptolysin S is a cell-associated hemolysin that does not diffuse into the agar media. Purification and characterization of this protein have been difficult, and its only pathogenetic role may be in direct or contact cytotoxicity.

Deoxyribonucleases A, B, C, and D

The expression of deoxyribonucleases (DNases), especially the DNase B seen with group A streptococci, stimulates the production of anti-DNase antibody following both pharyngeal and skin infection. DNases may also contribute to the production of cytokines, but their importance in this setting is not essential.

Hyaluronidase and Nicotine Adenine Dinucleotidase

Hyaluronidase is an extracellular enzyme that hydrolyzes hyaluronic acid in deeper tissues, thereby facilitating the spread of infection along fascial planes. Antihyaluronidase titers rise after *S. pyogenes* infection, especially skin infections. The production of nicotine adenine dinucleotidase among group A streptococcus strains correlates with the epidemiologic emergence/reemergence of

ABSTRACT

The major pathogenic β-hemolytic streptococci are group A *(Streptococcus pyogenes)* and group B *(Streptococcus agalactiae)*. *S. pyogenes* causes an array of clinical infections ranging from pharyngitis and superficial skin infections to deep soft tissue infections and toxic shock syndrome. Postinfectious sequelae include rheumatic fever and post-streptococcal glomerulonephritis. Penicillin remains the drug of first choice for treatment of *S. pyogenes* infection. Cephalosporins are a reasonable alternative. Clindamycin should be used in addition to penicillin in serious group A streptococcal infection due to the ability of clindamycin to prevent production of exotoxins that mediate the clinical manifestations of disease. *S. agalactiae* causes infection in neonates, pregnant women, and nonpregnant adults, especially the elderly and those with diabetes and other underlying medical disease. In adults, the most common manifestations of group B streptococcal disease are soft tissue infection, osteomyelitis, and septic arthritis. Treatment is with penicillin. Although most of this chapter is dedicated to discussing group A streptococci, group B streptococci, and the clinical diseases they cause, the remainder of the chapter includes discussions of *Streptococcus dysgalactiae* subspecies *equisimilis* (group C and G streptococcus), viridans group streptococcus (no Lancefield group), and zoonotic streptococci (various Lancefield groups).

KEYWORDS

Streptococcus
pharyngitis
scarlet fever
necrotizing fasciitis
toxic shock syndrome
rheumatic fever

necrotizing fasciitis and streptococcal toxic shock syndrome. In neutrophils, nicotine adenine dinucleotidase impairs chemotaxis and changes the respiratory burst activity.

Pyrogenic Exotoxins

Streptococcal pyrogenic exotoxins types A, B, and C are also called scarlatina or erythrogenic toxins. These exotoxins act as superantigens that induce lymphocyte blastogenesis and fever, may potentiate endotoxin-induced shock, and may suppress antibody synthesis. Pyrogenic exotoxins and some M protein fragments are initially able to interact with certain V_β regions of the T-cell receptor despite the absence of classic antigen processing by antigen-presenting cells (E-Fig. 269-1). This interaction results in massive clonal proliferation of T-lymphocytes as well as stimulation of macrophages. Thus, streptococcal toxic shock syndrome causes watershed production of lymphokines (tumor necrosis factor-β [TNF-β], interferon-γ, and interleukin-2 [IL-2]) and monokines (TNF-α, IL-1, and IL-6) that results in the "cytokine storm," which in turn mediates shock and organ dysfunction. Five other group A streptococcal superantigens, including streptococcal superantigen (SSA) and mitogenic factor, may also play a role in the pathogenesis. In addition, streptococcal pyrogenic exotoxins type B, which is a cysteine protease, may contribute to the pathogenesis of necrotizing fasciitis and shock by its ability to cleave pre–IL-1β into active IL-1β.

CLINICAL MANIFESTATIONS AND DIAGNOSIS

Pharyngitis

Pharyngitis is the most common *S. pyogenes* infection, with peak incidence in children aged 5 to 15 years. Infection is characterized by an abrupt onset of fever, sore throat, and submandibular adenopathy. Chilliness is common, but frank rigors are unusual. Most patients report pain on swallowing, but cough and hoarseness are rare. On physical examination, the uvula is edematous, the tonsils are typically hypertrophied, the palate may have petechia, and the pharynx is usually erythematous with a punctate or confluent exudate (Fig. 269-1).

Acute pharyngitis induces antibodies against M protein, streptolysin O, DNase, hyaluronidase, and, if present, pyrogenic exotoxins. Even without treatment, the pain, swelling, and fever of acute pharyngitis usually resolve spontaneously in 3 to 6 days. However, depending on the virulence of the infecting strain, pharyngitis also can progress to suppurative head and neck infections, scarlet fever, bacteremia, rheumatic fever, or post-streptococcal glomerulonephritis. Streptococcal toxic shock syndrome is an uncommon sequela of symptomatic pharyngitis.

Although *S. pyogenes* is the most common cause of acute pharyngitis (20 to 40% of pediatric cases and 5 to 15% of adult cases), definitive diagnosis is difficult on purely clinical parameters. Even in older children or adolescents who have all the typical physical findings of streptococcal pharyngitis, the clinical diagnosis is correct in only about 75% of patients. The modified Centor score was designed to assist with diagnosis and to help reduce unnecessary use of antibiotics and streptococcal testing (Tables 269-1 and 397-2). If any one of the classic signs is absent, the likelihood of streptococcal pharyngitis is greatly reduced. Several societies suggest avoiding streptococcal testing and antibiotics if the modified Centor score is 0 or 1. Providers can generally avoid testing in children younger than age 3 years because of low rates of streptococcal infection complications in this age group.

Throat swabs for culture of *S. pyogenes* remain the diagnostic "gold standard." Rapid site-of-care nucleic acid testing (sensitivity 97.5% and specificity 95%) is preferred over antigen tests, which have a sensitivity of only about 85%.[5,6] A popular approach, which is supported by professional guidelines, is to obtain two throat swabs from the posterior pharynx or tonsillar surface. If a rapid streptococcal test is positive on the first swab, the patient should be treated with antibiotics, and the second swab can be discarded. If the rapid test is negative in children and adolescents, the second sample should be sent for culture and treatment should be withheld unless the result is a positive culture. In adults, the second sample usually need not be sent for culture because of the low incidence of group A streptococcal pharyngitis in adults and the low risk for subsequent acute rheumatic fever even if group A streptococcus pharyngitis is present. The delay in antibiotics for confirmed cases of group A streptococcus pharyngitis is reasonable because acute antibiotic treatment has limited effect on improving acute symptoms. Delaying treatment by several days, however, reduces unnecessary antibiotic use while still achieving the goals of preventing rheumatic fever and reducing spread of disease. Antibiotics, regardless of the timing, do not reduce the likelihood of post-streptococcal glomerulonephritis.

Scarlet Fever

Scarlet fever is the syndrome defined as streptococcal infection (most commonly pharyngitis) with fever and a characteristic rash. Ninety percent of cases of scarlet fever occur in children ages 2 to 8 years. Scarlet fever is most common during the winter months in temperate regions. The rash usually begins as small, flat, erythematous macules on the trunk 1 to 2 days after the illness begins. The rash then transforms into minute papules, giving a "sandpaper" feel to the skin as it spreads to the limbs, sparing the palms and soles. The rash can be accentuated in the skin folds and flexure creases as of the elbow (Pastia lines). Other features include flushed cheeks with circumoral pallor and enlargement of the papillae of the tongue (strawberry tongue). As the rash resolves over the course of 6 to 9 days, there is often desquamation beginning at the palms and soles. Since the advent of penicillin treatment, scarlet fever has become uncommon, but recent outbreaks have been reported in several countries.[7–9]

Impetigo and Ecthyma

Impetigo (Chapter 408) most commonly occurs in children ages 2 to 5 years. It may occur year-round in tropical areas but occurs predominantly in the summer in temperate climates. Risk factors for impetigo include poor hygiene and malnutrition. Unbroken skin is colonized, and then minor abrasions or other traumas lead to infection of the superficial keratin layer of the skin. Within 10 to 14 days,

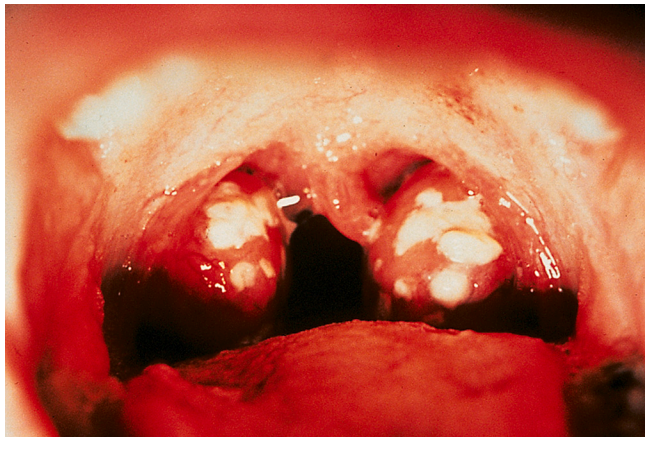

FIGURE 269-1. Acute streptococcal pharyngitis. Pus is present in the tonsillar crypts, and some palatal petechiae are seen. (From Forbes CD, Jackson WF. *Color Atlas and Text of Clinical Medicine*. 3rd ed. London: Mosby; 2003.)

TABLE 269-1 MODIFIED CENTOR CLINICAL DECISION RULE FOR DIAGNOSING GROUP A STREPTOCOCCAL PHARYNGITIS IN CHILDREN AND ADULTS

STEP 1—CALCULATE MODIFIED CENTOR SCORE	
DIAGNOSTIC CRITERIA	**POINTS**
Temperature >38° C	+1
Absence of cough	+1
Swollen, tender anterior cervical lymph nodes	+1
Tonsillar swelling or exudate	+1
Age 3-14 years	+1
Age >44 years	−1

STEP 2—DETERMINE SUGGESTED MANAGEMENT			
SCORE	**RISK FOR STREPTOCOCCAL INFECTION**	**RAPID ANTIGEN TESTING AND/OR CULTURE**	**ANTIBIOTICS**
≤0	1-2.5%	No	No
1	5-10%		
2	11-17%	Yes	If testing positive
3	28-35%		
≥4	51-53%	No	Yes, empirical

Adapted from: McIsaac WJ, Kellner JD, Aufricht P, Vanjaka A, Low DE. Empirical validation of guidelines for the management of pharyngitis in children and adults. *JAMA*. 2004;291(13):1587-1595.

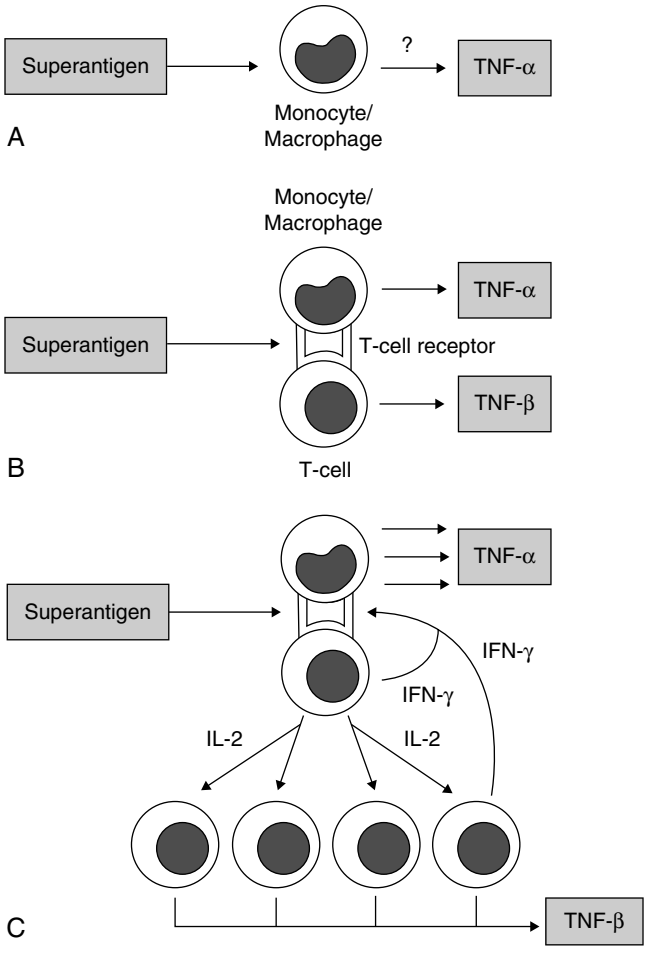

E-FIGURE 269-1. Superantigen-induced production of tumor necrosis factor-α (TNF-α) and lymphotoxin (TNF-β) by peripheral blood mononuclear cells. A, Superantigens induce human monocytes to produce TNF-α; however, it is unclear whether such production results solely from direct stimulation of the monocyte by the superantigen. **B**, In mixed mononuclear cell populations, superantigens stimulate TNF-α synthesis in monocytes and, by binding to specific V_β regions of the T-cell receptor, induce the synthesis of TNF-β from T-cells. **C**, The T-cell response to superantigen stimulation includes the production of interleukin-2 (IL-2), which results in clonal proliferation with concordant production of interferon-γ (IFN-γ) and TNF-β. IFN-γ can then amplify monocyte synthesis of TNF-α, IL-1, and IL-6. (From Stevens DL, Bryant AE, Hackett SP. Sepsis syndromes and toxic shock syndromes: concepts in pathogenesis and a perspective of future strategy. *Current Opin Infect Dis*. 1993;6[3]:374-383.)

single or multiple thick-crusted, golden-yellow lesions appear. Ecthyma is an ulcerative form of impetigo characterized by erosions into the dermis. In the past, nonbullous impetigo as described here could be confidently diagnosed as streptococcal and differentiated from bullous impetigo caused by *Staphylococcus aureus* (Chapter 268). More recently, however, *S. aureus* has been isolated with increasing frequency from nonbullous impetigo when treatment with penicillin fails to cure the infection. Gram stain and culture of exudates from the skin lesions can help determine whether group A streptococcus or *S. aureus* is the cause.

Erysipelas

Erysipelas (Chapter 408), which is caused exclusively by *S. pyogenes,* is characterized by an abrupt onset of fiery red swelling of the face or extremities. The infection is most commonly seen in infants and elderly adults. Infection is confined to the upper dermis with prominent lymphatic involvement leading to well-defined margins raised above the level of the surrounding skin, particularly along the nasolabial fold, without the crusty lesions seen in impetigo with its involvement of the superficial keratin layer of skin. Other distinctive features of erysipelas include scarlet or salmon-red rash, intense pain, and rapid progression. Flaccid bullae may develop on the second to third day, but the infection rarely extends into deeper soft tissues.

Cellulitis

Cellulitis (Chapter 408) is infection of the subcutaneous tissues resulting in a pink hue to the skin and less defined borders than with erysipelas. Group A streptococcal cellulitis is usually nonpurulent. Purulent cellulitis is most commonly caused by staphylococcal species. Risk factors for streptococcal cellulitis include impaired lymphatic drainage, venous insufficiency, edema, obesity, and disruption of the cutaneous barrier as from wounds or dermatophyte infection (e.g., tinea pedis).

Severe Group A Streptococcal Infections

Bacteremia

Group A streptococcal bacteremia is relatively uncommon in the antibiotic era, and endocarditis is even less common. In contrast to pharyngitis, scarlet fever, and impetigo, bacteremia occurs more often in the elderly and in neonates. The exceptions to these extremes of age are individuals with parenteral injection of illicit drugs and otherwise healthy middle-aged adults who develop bacteremia as part of a necrotizing soft tissue infection or streptococcal toxic shock syndrome.

Puerperal Sepsis

Patients with *S. pyogenes* puerperal sepsis typically present with fever, abdominal pain, and hypotension without tachycardia or leukocytosis. Maternal mortality is highest when infection occurs within 4 days of delivery or during the late third trimester. The incidence varies from about 6 to 80 cases per 100,000 live births, and the case-fatality rate is about 3.5%. Women who undergo cesarean section (and routinely receive prophylactic antibiotics) or are primiparous are at lower risk. Nosocomial transmission can occur, but because women are discharged home after 48 hours, acquisition may be from the home environment, particularly if young children at home have had recent streptococcal pharyngitis or are carriers of group A streptococcus.

Necrotizing Fasciitis

Necrotizing fasciitis is an infection of the deep subcutaneous tissues and fascia that is characterized by extensive and rapidly spreading necrosis (gangrene) of the skin and underlying structures.[10] Streptococcal necrotizing fasciitis can begin at a site of trivial trauma (e.g., a burn, insect bite, or varicella lesion) or in an operative incision. Half of patients with necrotizing fasciitis, however, develop infection without a defined portal of entry. In these individuals, the "cryptic" infection begins in deep tissues at a site of muscle strain, bruise, or other nonpenetrating traumatic injury. In patients who have necrotizing fasciitis with a portal of entry, warmth, erythema, swelling, and tenderness develop and then rapidly spread both proximally and distally within 24 hours. During the next 24 to 48 hours, the erythema typically turns from red to purple and then to blue, and the patient develops blisters and bullae that contain clear yellow fluid. Bacteremia is frequently present, and metastatic abscesses may occur. By the fourth to fifth day, frank gangrenous changes are evident in the affected skin, followed by extensive sloughing. The process may march inexorably over large body areas unless measures are taken to contain it. The patient with streptococcal necrotizing fasciitis appears perilously ill, with high fever and extreme prostration.

In patients with cryptic *S. pyogenes* necrotizing fasciitis/myonecrosis who lack a discernible portal of bacterial entry, classic cutaneous signs of a necrotizing process are not initially apparent. In the absence of such clinical clues, the correct diagnosis is often missed or delayed until the patient manifests systemic shock and organ failure. Pain out of proportion to the initial injury is usually an important clinical clue to the presence of the deep infection. Routine radiographs, computed tomography (CT) scanning, and magnetic resonance imaging (MRI) may show localized swelling of the deep tissues but characteristically do not show frank abscess or gas formation. Therefore, these are not definitive procedures. Unexplained tachycardia, a marked left shift, and an elevated creatine phosphokinase level can be important clues to the diagnosis of necrotizing soft tissue infections, and their presence should prompt surgical inspection of the deep tissues. Gram stains of aspirated fluid reveal chains of gram-positive cocci and few, if any, white blood cells. Similarly, a biopsy with frozen section may aid in the diagnosis of necrotizing fasciitis.

Myonecrosis

Myonecrosis is an invasive and destructive infection of the muscle and related structures. Among gram-positive organisms, *S. pyogenes* remains the most common etiologic agent. This is in contrast to myositis, which is strictly defined as a localized purulent infection of the muscle, where *S. pyogenes* is rarely involved. In myonecrosis, organisms are likely hematogenously translocated from the throat to the deep soft tissues, though antecedent or concomitant streptococcal pharyngitis is not a prerequisite for this infection.

Streptococcal Toxic Shock Syndrome

Streptococcal toxic shock syndrome (Table 269-2) is any streptococcal infection that is associated with the sudden onset of shock and organ failure.[11] Definite cases are those in which *S. pyogenes* is isolated from a normally sterile body site. Diabetes mellitus and alcohol use disorders appear to be contributing factors, but many afflicted individuals have no underlying medical conditions and are not immunocompromised. This contrasts sharply with reviews of *S. pyogenes* bacteremia from several decades ago, which found that bacteremia occurred primarily in the very young, the very old, or patients with predisposing conditions, such as cancer, renal failure, severe burns, or iatrogenic immunosuppression. Streptococcal toxic shock syndrome rarely occurs secondary to symptomatic streptococcal pharyngitis and more often follows breaches in the skin and mucous membranes. The use of nonsteroidal anti-inflammatory drugs (NSAIDs) for pain associated with muscle strain, trauma, chickenpox, or childbirth may predispose patients to increased risk and severity of infection, perhaps by masking early signs and symptoms and thereby delaying diagnosis and treatment.

The first phase of streptococcal toxic shock syndrome begins with an influenza-like prodrome characterized by fever, chills, myalgias, nausea, vomiting, and diarrhea. Hypotension follows within 24 to 48 hours. Confusion develops in more than half of patients. Phase 2 is characterized by tachycardia, tachypnea, increasing pain, and persistent fevers. In children with varicella infection, toxicity or persistence of fever longer than 4 days should prompt

TABLE 269-2 DEFINITION OF STREPTOCOCCAL TOXIC SHOCK SYNDROME

A. DEFINITION	
Definite case	Illness fulfilling criteria B1 and C (1 and 2)
Probable case	Illness fulfilling criteria B2 and C (1 and 2) if no other cause for illness is found
B. ISOLATION OF GROUP A STREPTOCOCCI	
1. From a normally sterile site (e.g., blood; cerebrospinal, pleural, or peritoneal fluid; tissue biopsy; surgical wound)	
2. From a nonsterile site (e.g., throat, sputum, vagina, superficial skin lesion)	
C. CLINICAL SIGNS OF SEVERE INFECTION	
1. Hypotension (e.g., systolic blood pressure ≤90 mm Hg in adults or below fifth percentile for age in children)	
2. Two or more of the following signs:	
Renal impairment (i.e., creatinine ≥2 mg/dL for adults, or ≥2 times the upper limit of normal for age, or ≥2 times baseline creatinine in persons with preexisting renal disease)	
Coagulopathy (i.e., platelets ≤100,000/μL or disseminated intravascular coagulation)	
Liver involvement (i.e., serum aspartate aminotransferase [AST], alanine aminotransferase [ALT], or total bilirubin levels ≥2 times the upper limit of normal for age, or ≥2 times baseline in persons with preexisting liver disease)	
Acute respiratory distress syndrome	
Generalized erythematous macular rash that may desquamate	
Soft tissue necrosis (e.g., necrotizing fasciitis, myositis, or gangrene)	

Adapted from The Working Group on Severe Streptococcal Infections. Defining the group A streptococcal toxic shock syndrome. Rationale and consensus definition. *JAMA.* 1993;269(3):390-391.

careful evaluation for streptococcal toxic shock syndrome. In phase 3, shock and organ failure develop. Laboratory tests may show evidence of renal impairment and normal to mild elevations of white blood cell count with profound left shift, low albumin, and low calcium. Metabolic acidosis develops in phase 3 of disease. Because acute respiratory distress syndrome (ARDS) develops in 55% of patients with streptococcal toxic shock syndrome, blood gas levels can be helpful to evaluate the need for mechanical ventilation.

Pneumonia

Pneumonia caused by *S. pyogenes* is frequently associated with chronic pulmonary disease or with antecedent viral infections such as influenza, measles, or varicella. In one third or fewer of the cases, patients have a history of preceding streptococcal upper respiratory infection. The onset is typically abrupt, and the disease is characterized by fever, chills, dyspnea, cough productive of blood-streaked sputum, and pleuritic chest pain. The pulmonary picture is one of bronchopneumonia, with consolidation being uncommon. Empyema (Chapter 86) develops in 30 to 40% of cases, tends to appear early in the disease, and typically consists of copious amounts of thin serosanguinous fluid. Bacteremia occurs in 10 to 15% of cases.

TREATMENT AND PROGNOSIS

Antimicrobial Susceptibility

Group A streptococci continue to be susceptible to penicillin, which remains the drug of first choice for treatment of infection. Cephalosporins are a reasonable alternative to penicillin in some cases because of ease of administration. Clindamycin should be used in addition to penicillin in serious group A streptococcal infection owing to the ability of clindamycin to prevent production of group A streptococcus exotoxins that mediate the clinical manifestations of disease. Treatment failures in patients with severe *S. pyogenes* infections have been described if clindamycin resistance is found. In the United States, clindamycin resistance is as high as 15%. In other nations, resistance may be much higher. In China, for example, 95.5% of the strains of group A streptococci causing scarlet fever are clindamycin resistant.

In penicillin-hypersensitive patients, clindamycin or macrolides are the second-line drugs of choice. As with clindamycin, macrolide resistance is increasing. Fluoroquinolones can be used as an alternative for group A streptococcal skin and soft tissue infections in penicillin-hypersensitive patients in areas where clindamycin and macrolide resistance are high. Fluoroquinolone resistance is rare. Vancomycin is an option for intravenous therapy. Linezolid and tedizolid are newer options, especially for deep tissue infection. Tetracycline resistance in group A streptococci is common, and therefore it should not be used unless sensitivities are known. Trimethoprim-sulfamethoxazole is not active against group A streptococci and therefore should not be used alone for infections in which group A streptococcus is the suspected pathogen. However, trimethoprim-sulfamethoxazole (four single-strength pills, each containing 80 mg of trimethoprim and 400 mg of sulfamethoxazole, twice daily for 7 days)[A1] is effective for uncomplicated abscesses in which *Staphylococcus aureus* is thought to be the primary pathogen and *S. pyogenes* only a potential co-pathogen.

Specific Infections

Pharyngitis

The acute symptoms of streptococcal pharyngitis usually resolve within 3 to 6 days even without treatment. The goal of treatment is to reduce the incidence of streptococcal sequelae such as suppurative head and neck infections, scarlet fever, bacteremia, and rheumatic fever.

For pharyngitis in patients over age 6 years, oral penicillin VK (1000 mg three times daily for 10 days or 800 mg four times daily for 5 days)[A2] or injectable benzathine penicillin (1.2 million units intramuscularly once) is the treatment of choice because it is cost effective, has a narrow spectrum of activity, and has long-standing proven efficacy (Chapter 397).[A3] Cephalexin (500 mg orally twice a day for 5 to 10 days) is also effective for primary treatment and for persistent infection. Patients with proven recurrent infections should receive clindamycin (300 mg orally three times a day for 10 days) or amoxicillin–clavulanic acid (875 mg orally twice a day, or 500 mg three times a day for 10 days). For patients who are allergic to penicillin, azithromycin (500 mg orally on the first day and then 250 mg daily for 4 more days) is another alternative.

Scarlet Fever

For scarlet fever, the recommended treatment is 1.2 million units of benzathine penicillin G given intramuscularly or oral penicillin VK, 500 mg four times daily for 10 days. Most patients recover after 4 to 5 days, and the rash usually resolves completely over a period of several weeks.

Skin Infections

Impetigo and Ecthyma

For impetigo and ecthyma, topical agents (e.g., mupirocin 2% ointment three times daily, retapamulin 1% ointment twice daily,[A4] or ozenoxacin 1% cream twice daily until rash resolves are usually as effective as oral antibiotics and can reduce the likelihood of transmission of the streptococci to other individuals. Penicillin VK 500 mg four times daily for 7 days or benzathine penicillin (1.2 million units once intramuscularly) is first-line treatment for ecthyma or for impetigo present at multiple skin sites caused by streptococci. If *S. aureus* is contributing to infection, treatment should be with a penicillinase-resistant semisynthetic penicillin (e.g., dicloxacillin 500 mg orally four times daily for 7 days) or a cephalosporin (e.g., cephalexin 500 mg orally four times daily for 7 days) for methicillin-susceptible strains or doxycycline (100 mg three times daily for 7 days) or clindamycin (300 mg three times daily for 7 days) for methicillin-resistant strains. Complete recovery is the rule, but none of these treatments prevents the later development of post-streptococcal glomerulonephritis (see later).

Erysipelas

For erysipelas, treatment with oral penicillin (e.g., penicillin VK 500 mg four times daily for 10 days) or, if methicillin-sensitive *S. aureus* is of concern, oral dicloxacillin (500 mg four times daily) for a 10-day course is usually effective, and surgical debridement is not indicated. Fever, pain, and the intense redness typically diminish promptly, but the swelling may progress temporarily despite treatment. About 5 to 10 days into the illness, the involved skin typically desquamates, and healing follows.

Cellulitis

For cellulitis, oral antibiotic regimens are often as effective as intravenous regimens.[A5] Penicillin VK (500 mg orally four times daily for 10 days) is usually effective in treatment of streptococcal cellulitis. In situations in which it is difficult to differentiate between streptococcal and staphylococcal skin and soft tissue infections, a penicillinase-resistant penicillin can be used. Options include oral cephalexin (500 mg four times daily for 10 days), clindamycin (300 to 450 mg four times daily for 10 days), or trimethoprim-sulfamethoxazole (160/800 mg twice daily for 10 days),[A6] depending on the suspected pathogens, the host, and the severity of systemic toxicity. Intravenous vancomycin plus intravenous imipenem (15 to 20 mg/kg twice daily and 500 mg every 6 hours, respectively, until clinical response allows transition to oral medications) can be reserved for severe cases, when the pathogen is unclear, and when organisms such as *S. aureus* and Enterobacteriaceae are possible. In penicillin-allergic patients, a first-generation cephalosporin may be used if the hypersensitivity is non–IgE-mediated. Clindamycin, linezolid, or vancomycin may be used in patients who manifest IgE-mediated anaphylactic hypersensitivity to β-lactam antibiotics. Unless cellulitis progresses to bacteremia or to deeper soft tissue infection, most cases improve in 4 to 6 days.

Penicillin (250 mg orally twice daily) is effective for preventing recurrent cellulitis in persons who have chronic lymphedema and three or more episodes of cellulitis.

Bacteremia, Necrotizing Fasciitis, Myonecrosis, and Toxic Shock

Uncomplicated bacteremia is treated with intravenous penicillin G (4 million units every 4 hours) and intravenous clindamycin (600 to 900 mg every 8 hours). After initial stabilization with both antibiotics, the 10- to 14-day course can be completed with penicillin alone. Prognosis depends on the extent of other associated diseases such as toxic shock, deep soft tissue infection, and endocarditis.

For toxic shock syndrome, myonecrosis, and necrotizing fasciitis, management involves prompt and aggressive source control, including surgical exploration and debridement of suspected deep-seated streptococcal infections. Fluid resuscitation and early antimicrobial therapy are mandatory. Initial empirical antibiotic treatment should be broad[12] to cover for possible polymicrobial infection with (1) intravenous vancomycin plus clindamycin (15 to 20 mg/kg twice daily and 600 to 900 mg every 8 hours, respectively), (2) linezolid (600 mg twice a day),[13] or (3) tedizolid (200 mg daily),[14] *plus* either (1) piperacillin-tazobactam (3.375 g every 6 hours), (2) a carbapenem (e.g., imipenem 500 mg every 6 hours), or (3) ceftriaxone (2 g daily). Once a group A streptococcal infection is confirmed, antibiotics can be changed to treatment with both high-dose intravenous penicillin G (4 million units every 4 hours) and intravenous clindamycin (600 to 900 mg every 8 hours) for 10 to 14 days, followed by oral therapy with the total duration based on the clinical course.[15]

Even with appropriate treatment (including antibiotics, aggressive fasciotomy, and surgical debridement), mortality rates are 30 to 60% for necrotizing fasciitis and myonecrosis. In cryptic *S. pyogenes* necrotizing fasciitis or myonecrosis, the delay in diagnosis results in exceedingly high morbidity and mortality (70 to 85%).

Pneumonia

Pneumonia can be treated with amoxicillin-clavulanic acid (500-125 mg every 8 hours for 5 to 7 days). For pneumonia, mortality has generally been low with penicillin therapy and adequate drainage of empyema, but it may be higher in older patients.

Puerperal Sepsis

Treatment is intravenous penicillin G (2 million units every 4 hours). Even in the antibiotic era, the case-fatality rate is about 3.5%, in part due to delay in diagnosis.

PREVENTION

Routine secondary prophylaxis against streptococcal infection is not recommended for household contacts of index patients. Chemoprophylaxis can be considered in contacts with underlying host risk factors on a case-by-case basis. Vaccines are in development,[16] but none are currently clinically available.

POST-STREPTOCOCCAL IMMUNOLOGIC PHENOMENA

ACUTE RHEUMATIC FEVER AND RHEUMATIC HEART DISEASE

Acute rheumatic fever is a result of an autoimmune response to group A streptococcal infection. Rheumatic heart disease is the long-term sequela of a single episode or repeated episodes of acute rheumatic fever (Chapter 60). The incidence of acute rheumatic fever and rheumatic heart disease is low in developed countries but continues to cause a significant burden of disease in resource-limited nations and in populations with crowded living conditions and poor access to health care. In these areas, untreated superficial *S. pyogenes* infections such as pharyngitis can lead to subsequent development of acute rheumatic fever. It is difficult to determine the incidence of acute rheumatic fever because diagnostic tools are lacking in many settings, but estimates suggest a global prevalence of about 33 million cases and about 300,000 annual deaths, with the highest rates in Oceania, South Asia, and central sub-Saharan Africa.

Acute Rheumatic Fever

EPIDEMIOLOGY

Acute rheumatic fever occurs most often in children 5 to 15 years of age.[17] Because rheumatic heart disease is often the result of recurrent infections and cumulative damage to heart valves, the peak prevalence of rheumatic heart disease is in the third and fourth decades of life. Acute rheumatic fever occurs equally in men and women, but rheumatic heart disease is more common in women.

PATHOBIOLOGY

The pathobiology of acute rheumatic fever is not entirely understood. Tissue injury is mediated through an immune mechanism that is initiated by molecular mimicry. Similarities between the infectious agent and human protein polymorphisms[18] lead to cross-activation of antibodies and T cells to human tissue. Carditis results from antibody-binding and T-cell infiltration of the heart. Transient arthritis is due to immune complexes in the joints. Chorea results from antibody binding to the basal ganglia. Skin manifestations are a result of delayed hypersensitivity reactions.

CLINICAL MANIFESTATIONS

Acute rheumatic fever develops approximately 2 weeks after the acute streptococcal pharyngitis,[19] and symptoms usually persist 2 to 4 weeks. Manifestations include fever (>90%), large-joint polyarthritis (75%), carditis (>50%), chorea (30%), subcutaneous nodules (<10%), and erythema marginatum (<10%). NSAIDs reduce arthritis pain rapidly, and the absence of symptomatic improvement with NSAIDs should prompt the clinician to think of other causes for the arthritis. The synovial fluid in acute rheumatic fever is sterile with a lymphocyte predominance. Acute rheumatic fever is typically a pancarditis that affects all parts of the heart, but the most clinically significant involvement is valvulitis of the mitral valve and, less frequently, of the aortic valve, initially with valvular regurgitation (Chapter 60). The chorea (Sydenham chorea, St. Vitus dance) of acute rheumatic fever is characterized by involuntary, nonrhythmic, and purposeless movements of the body, limbs, and face. The chorea is usually more pronounced on one side of the body. The chorea stops during sleep. Erythema marginatum is characterized by pink, nonpruritic, blanching macules or papules that spread in a serpiginous pattern on the trunk and proximal limbs. When subcutaneous nodules occur, they are usually 0.5 to 2 cm in diameter, are painless, and are seen over bony prominences or extensor tendons. Rapid sleeping pulse rate and tachycardia out of proportion to fever are occasionally observed in acute rheumatic fever.

Inflammatory markers are usually elevated, and the electrocardiogram may show a prolonged PR interval. Normochromic, normocytic anemia and leukocytosis are common.

DIAGNOSIS

There is no definitive test for acute rheumatic fever. Acute rheumatic fever is a diagnosis of exclusion, and the evaluation begins with careful assessment to exclude other causes of symptoms.

TABLE 269-3 REVISED JONES CRITERIA FOR ACUTE RHEUMATIC FEVER

A. DEFINITION	
Initial ARF	2 major or 1 major plus 2 minor criteria
Recurrent	2 major, or 1 major and 2 minor, or 3 minor
B. MAJOR CRITERIA	
LOW-RISK POPULATIONS*	**MODERATE- AND HIGH-RISK POPULATIONS**
Carditis, clinical and/or subclinical echocardiographic valvulitis	Carditis, clinical and/or subclinical echocardiographic valvulitis
Arthritis, polyarticular	Arthritis, monoarticular or polyarticular
Chorea	Chorea
Erythema marginatum	Erythema marginatum
Subcutaneous nodules	Subcutaneous nodules
C. MINOR CRITERIA	
LOW-RISK POPULATIONS	**MODERATE- AND HIGH-RISK POPULATIONS**
Polyarthralgia	Monoarthralgia
Fever ≥38.5° C	Fever ≥38.5° C
ESR ≥60 mm and/or CRP ≥3.0 mg/dL	ESR ≥30 mm and/or CRP ≥3.0 mg/dL
Prolonged PR interval (unless carditis is a major criterion)	Prolonged PR interval (unless carditis is a major criterion)

*Low-risk populations are those with an ARF incidence of <2 per 100,000 school-aged children per year or an all-age prevalence of rheumatic heart disease of ≤1 per 1000 population per year.
ARF = acute rheumatic fever; CRP = C-reactive protein; ESR = erythrocyte sedimentation rate.
Adapted from Gewitz MH, Baltimore RS, Tani LY, et al. Revision of the Jones Criteria for the diagnosis of acute rheumatic fever in the era of Doppler echocardiography: a scientific statement from the American Heart Association. *Circulation*. 2015;131(20):1806-1818.

Many patients develop characteristic heart murmurs, and an echocardiogram should be considered to confirm clinical findings. Diagnosis relies on patients fulfilling a set of criteria,[20] the most commonly used of which are the Jones criteria (Table 269-3). For the purposes of the Jones criteria, low-risk populations were defined as those with an acute rheumatic fever incidence of less than 2 per 100,000 school-aged children per year or an all-age prevalence of rheumatic heart disease of 1 or less per 1000 population per year. For low-risk populations, the criteria focus on high specificity to avoid false-positive diagnosis. In populations with higher risk for acute rheumatic fever, the Jones criteria emphasize high sensitivity to reduce false-negative diagnoses.

TREATMENT AND PROGNOSIS

Persons with acute rheumatic fever should be hospitalized. Eradication of group A streptococcus from the throat and secondary prophylaxis should be accomplished with intramuscular benzathine penicillin G 1.2 million units every 4 weeks for a minimum of 10 years (and in some cases indefinitely). Other, less favorable and less effective options include oral penicillin (250 mg twice a day) or an oral macrolide (e.g., azithromycin 250 mg daily). First-line therapy for joint symptoms has traditionally been aspirin (80 to 100 mg/kg per day in divided doses to a maximum of 4 to 8 g per day), but naproxen (10 to 20 mg/kg per day divided in twice-daily doses) has been used in small studies with success. Treatment with an NSAID should continue for 1 to 2 weeks until all symptoms of acute rheumatic fever have resolved, not just the joint symptoms.

Carditis is managed by treating the associated heart failure with goal-directed therapy (e.g., diuretics, angiotensin receptor blockers; Chapter 46), fluid restriction, and bed rest. In severe cases, some experts recommend use of systemic glucocorticoids even though high-quality evidence is lacking. Valve surgery is rarely needed for acute rheumatic fever, though it can be helpful in situations of acute rupture of a valve leaflet. Rheumatic chorea usually does not require treatment and resolves within weeks to months. Despite acute treatment, about 35 to 70% of patients progress to chronic clinical rheumatic heart disease.

Rheumatic Heart Disease

Approximately 35 to 72% of patients with acute rheumatic fever develop clinical carditis, and another 18% have carditis present on echocardiogram without clinical symptoms. Some individuals with carditis have complete resolution of cardiac abnormalities, and others progress to develop rheumatic heart disease. Resolution of carditis is most likely to occur in the first year after the acute carditis.

Rheumatic heart disease, which is almost exclusively a valvular disease (Chapter 60),[21] affects the mitral valve nearly 100% of the time and the aortic valve in 20 to 30% of cases. The pulmonic valve is rarely involved, and the tricuspid valve has histologic evidence of disease in 15 to 40% of patients, but the tricuspid valve disease is not usually clinically relevant. Mitral valve regurgitation is the most common valvular pathology in rheumatic heart disease. Mitral stenosis can occur after progressive scarring of the mitral valve leaflets, and rheumatic heart disease is the most common cause of mitral stenosis worldwide. When the aortic valve is involved, regurgitation is more common than stenosis.

Most patients have classic murmurs (see Table 39-7). Echocardiography is key to diagnosis.

Patients with rheumatic heart disease should receive secondary prophylaxis,[A7] preferably as outlined previously with intramuscular benzathine penicillin G to avoid recurrent acute rheumatic fever, which can worsen rheumatic heart disease. Rheumatic heart disease is progressive, with severe valvular disease (Chapter 60) often appearing in the third or fourth decade of life. In developing countries, rheumatic heart disease remains a leading cause of bacterial endocarditis and cardiovascular morbidity and mortality. In endemic regions, echocardiographic screening can detect latent rheumatic heart disease and guide secondary prophylaxis to reduce the prevalence of progressive disease.[A8]

PEDIATRIC AUTOIMMUNE NEUROPSYCHIATRIC DISORDERS ASSOCIATED WITH STREPTOCOCCAL INFECTIONS

Group A streptococcal infections can trigger pediatric autoimmune neuropsychiatric disorders associated with streptococcal infections (PANDAS), which is defined as acute onset of obsessive compulsive disorder, tics, and piano-playing choreiform movements of the fingers and toes in children after streptococcal infection.[22] Sometimes enuresis, separation anxiety, learning regression, and handwriting difficulties are also present. *S. pyogenes* infection appears to trigger development of anti-brain autoantibodies to dopamine receptors, thereby leading to neuropsychiatric symptoms in some individuals. Treatment for PANDAS includes antibiotics for primary management of infection and behavioral therapy for care of psychiatric symptoms.

POST-STREPTOCOCCAL GLOMERULONEPHRITIS

Post-streptococcal glomerulonephritis is a postinfectious, immune complex–mediated glomerulonephritis associated with prior skin or throat infection by group A streptococcus or occasionally groups C or G streptococcus (Chapter 107).[23] Post-streptococcal glomerulonephritis, like other postinfectious complications of streptococcal infection, is rare in developed countries. In developing countries, however, the annual incidence is approximately 9 cases per 100,000 population. Historically, the typical patient with post-streptococcal glomerulonephritis is a child between ages 2 and 18 years with a male-to-female ratio of 2 : 1. Immune complexes form in the glomeruli and invoke an inflammatory response, including activation of the complement system with reduction in circulating C3 levels.

The time between the initial streptococcal infection and nephritis is 7 to 10 days after throat infection and 2 to 4 weeks after skin infection. Post-streptococcal glomerulonephritis most commonly presents as nephritic syndrome with hematuria, edema, hypertension, and oliguria. Rarely, the presentation is of nephrotic syndrome or rapidly progressive crescentic glomerulonephritis. Asymptomatic disease, which is likely four to five times more common than clinically evident disease, manifests as microscopic hematuria and a fall in serum complement levels. In elderly individuals with post-streptococcal glomerulonephritis, azotemia, heart failure, and nephrotic-range proteinuria are more common than in children.

Serologic assays for antibodies to *S. pyogenes* antigens such as streptolysin O and DNase B are useful for retrospective diagnosis of antecedent *S. pyogenes* infections in cases of suspected post-streptococcal glomerulonephritis. The rise in antibodies occurs 7 to 14 days after disease onset and peaks 3 to 4 weeks after infection. The serum complement level, especially C3, is low. Renal biopsy is rarely necessary, but it should be considered when there is diagnostic doubt.

TREATMENT AND PROGNOSIS

If streptococcal infection is still present at the time of the diagnosis of post-streptococcal glomerulonephritis, benzathine penicillin G (1.2 million units intramuscularly) is indicated to treat the individual and to prevent the spread of the nephritogenic strain. Otherwise, treatment of post-streptococcal glomerulonephritis is supportive, with treatment of volume overload and hypertension with loop diuretics, salt restriction, and antihypertensive agents.

The short-term prognosis in children is excellent, and the symptoms resolve within 2 to 7 days. In adults, however, serious morbidity can occur, in part owing to preexisting cardiovascular and other diseases. Long-term development of end-stage renal disease is uncommon unless other contributors to renal disease (e.g., diabetes mellitus) are present.

STREPTOCOCCUS AGALACTIAE (GROUP B STREPTOCOCCUS)

S. agalactiae contains Lancefield group B antigen on the cell surface and is referred to as group B streptococci.

EPIDEMIOLOGY

Group B streptococci colonize the genital tract, gastrointestinal tract, and occasionally the upper respiratory tracts of normal humans. Group B streptococci cause infection in neonates, pregnant women, and nonpregnant adults, especially the elderly and patients with underlying medical disease.[24] About 9 cases of invasive group B streptococcus infection occur per 100,000 population in the United States, including neonates, children, and adults. In neonates, group B streptococci are the most common cause of pneumonia, sepsis, and meningitis in the United States and Western Europe.[25] Adults with group B streptococcus infections include postpartum women and patients who have risk factors such as diabetes, liver disease, peripheral vascular disease, or malignancy.

PATHOBIOLOGY

In the laboratory, these organisms grow as gray-white colonies that are slightly larger than for group A streptococci but cause a narrower zone of hemolysis. Definitive bacteriologic identification requires group-specific antiserum or commercial kits. The polysaccharide capsule, which is the prime virulence factor in group B streptococcus, is critical for the organism to evade phagocytosis. Defined capsular polysaccharide types of group B streptococcus are designated Ia, Ib, Ic, and II through IX. Immunity is based on the development of opsonic type-specific antibody.

CLINICAL MANIFESTATIONS

Early-onset group B streptococcus infection in children usually presents at or within 24 hours of birth but can occur anytime in the first 6 days of life. In adults, the most common clinical manifestations are soft tissue infection, osteomyelitis, and septic arthritis.[26]

TREATMENT

Intravenous penicillin G (400,000 units/kg/day in children or 4 million units every 4 hours in adults) for 10 to 14 days is the treatment of choice for group B streptococcus infections. Alternatives for penicillin-allergic patients include vancomycin (intravenously based on weight, with a goal trough of 15 to 20 μg/mL) or ceftriaxone (2 g daily for adults) for 10 to 14 days. Clindamycin (600 mg intravenously every 8 hours) can be used in penicillin-allergic adults when group B streptococcus susceptibility is known, but resistance is nearly 40% in some settings. Gentamicin (2.5 mg/kg every 8 to 24 hours based on weight and age in children or 1 mg/kg every 8 hours in adults) can be used in addition to penicillin in persons with meningitis, endocarditis, bacteremia, and severe soft tissue infections until the infection is under control.

PREVENTION

Vaccines are in development,[A9] but no licensed vaccine is available. The current approach is to provide intrapartum antimicrobial prophylaxis in women with prior delivery of an infant with invasive group B streptococcus infection, group B streptococcus bacteriuria during current pregnancy, culture evidence of vaginal or rectal group B streptococcus colonization, or unknown group B streptococcus status and either delivery before 37 weeks' gestation, duration of ruptured membranes of at least 18 hours, or intrapartum temperature of at least 100.4° F (≥38° C). All women at 35 to 37 weeks' gestation should be screened with rectal and vaginal swab for the presence of group B streptococcus unless some other indication for prophylaxis already exists. Prophylaxis begins at the onset of labor with intravenous penicillin G (5 million units loading dose, then 3 million units every 4 hours) or intravenous ampicillin (2-g loading dose, then 1 g every 4 hours) until delivery. In persons with penicillin allergy, group B streptococcus susceptibility testing for clindamycin (900 mg intravenously every 8 hours until delivery) is recommended. When susceptibility testing is not available or if the group B streptococcus is resistant to clindamycin, vancomycin (20 mg/kg intravenously every 8 hours until delivery) can be used.

STREPTOCOCCUS DYSGALACTIAE SUBSPECIES *EQUISIMILIS* (GROUP C AND GROUP G STREPTOCOCCUS)

The group C and group G streptococci that colonize the human genital tract, gastrointestinal tract, upper respiratory tract, and skin belong to a single subspecies, *S. dysgalactiae* subspecies *equisimilis*. They produce streptolysin O and a disease spectrum that resembles group A streptococci, including bacteremia, septic arthritis, skin and soft tissue infection, and pharyngitis.

TREATMENT

Treatment is with penicillin (4 million units intravenously every 4 hours) or vancomycin (15 to 20 mg/kg intravenously twice daily) for 5 to 14 days depending on the type and severity of infection. As with group A streptococcal infection, clindamycin (600 to 900 mg intravenously every 8 hours) for 10 to 14 days is used for *S. dysgalactiae* subspecies *equisimilis* infection for necrotizing fasciitis or for streptococcal toxic shock syndrome. Clindamycin should not be used initially as a single agent, however, because some *S. dysgalactiae* subspecies *equisimilis* are resistant to clindamycin. *S. dysgalactiae* subspecies *equisimilis* also may be resistant to macrolides (15 to 25% of cases) or fluoroquinolones, thereby limiting the utility of these antibiotics unless susceptibilities are known.

VIRIDANS GROUP STREPTOCOCCI (*STREPTOCOCCUS ANGINOSUS* GROUP/*STREPTOCOCCUS MILLERI* GROUP)

Viridans group streptococci include the *S. anginosus* group (also known as the *Streptococcus milleri* group). The *S. anginosus* group has three distinct species: *S. anginosus, Streptococcus constellatus,* and *S. intermedius*. Members of the *S. anginosus* group are nonmotile, facultative anaerobes that may be β-hemolytic but also may be α-hemolytic or nonhemolytic. *S. anginosus* group normally colonize the oropharynx, upper gastrointestinal tract, and appendix. Unlike *S. pyogenes* and *S. agalactiae, S. anginosus* group can cause abscess formation. Abscesses usually develop contiguous to the colonized mucosal surface as with dental or periappendiceal abscesses. Primary bacteremia, with or without endocarditis, can seed metastatic abscesses of the lung, joints, bone, and spleen. *S. intermedius* has tropism to form abscesses in the brain and liver. In patients with oral, head and neck, and abdominal infections, *S. anginosus* group may present as part of a polymicrobial infection and should be considered a true pathogen. Empyema with *S. anginosus* group is usually the result of a surgical procedure involving the respiratory or gastrointestinal tract and in most cases requires thoracotomy due to loculation of the empyema and difficulty treating with antibiotics and chest thoracostomy alone. In reviewing Gram stains of pus from such infections, these organisms characteristically show 20 to 30 gram-positive cocci within neutrophils. In the presence of bacteremia, the likelihood of bacterial endocarditis (Chapter 61) is over 30% with *S. gallolyticus, S. sanguinis*, *S. gordonii*, and *S. mutans* and about 20% with *S. mitis* or *S. oralis*.[27]

TREATMENT

Treatment of *S. anginosus* group is typically drainage of any abscess and therapy with penicillin G (4 million units intravenously every 4 hours) or another β-lactam antibiotic (e.g., cefazolin 500 to 2000 mg intravenously every 8 hours) because most isolates are susceptible to β-lactam agents. A parenteral third-generation cephalosporin (ceftriaxone 2 g intravenously twice daily) is recommended for brain abscesses and bacteremia. Vancomycin (15 to 20 mg/kg intravenously twice a day) is a reasonable alternative for penicillin-allergic patients. Resistance to fluoroquinolones, if not present initially, may develop rapidly. Many strains are developing macrolide resistance, most are resistant to aminoglycosides, and sulfonamides have no activity against *S. anginosus* group strains. *S. anginosus* is a reservoir for antimicrobial resistance genes and has been shown to transfer resistance traits to other pathogenic organisms such as *S. pyogenes* and *S. pneumoniae*.

OTHER VIRIDANS GROUP STREPTOCOCCI

More than 30 recognized species of viridans group streptococci (including *Streptococcus mitis, Streptococcus oralis, Streptococcus sanguinis, Streptococcus mutans,* and *Streptococcus gordonii*) are most commonly implicated in subacute bacterial endocarditis (Chapter 61),[28] catheter-related and neutropenia-related blood stream infections, and purulent abdominal, hepatobiliary, brain, and dental infections. Penicillin resistance in these organisms is 30 to 50% in some areas, so empirical treatment usually begins with vancomycin (15 to 20 mg/kg intravenously twice a day for 5 to 14 days, depending on severity of infection and host factors) and de-escalates to a β-lactam (e.g., penicillin G 4 million units intravenously every 4 hours) if the isolate is susceptible.

ZOONOTIC STREPTOCOCCUS

STREPTOCOCCUS SUIS

Streptococcus suis (Lancefield groups R, S, and T), which is a pathogen in pigs, can cause meningitis, sepsis, and arthritis in exposed humans. Most infections occur in individuals with extensive exposure to pigs, such as pig breeders, abattoir workers, and butchers. In this high-risk group of individuals, the annual risk for developing *S. suis* meningitis has been estimated at 1.2 to 3 cases per 100,000 population. *S. suis* is susceptible to penicillin G (4 million units intravenously every 4 hours), third-generation cephalosporins (e.g., ceftriaxone 2 g intravenously once to twice daily), and vancomycin (15 to 20 mg/kg intravenously twice a day). Duration of treatment varies from 5 to 14 days based on the severity and site of infection. In persons with meningitis due to *S. suis,* steroid treatment in addition to antimicrobials may help reduce death and disability, including hearing loss. Wearing gloves for the handling of raw pork, good hand hygiene, and thorough cooking of pork should prevent most cases of *S. suis* infection.

STREPTOCOCCUS CANIS

Streptococcus canis (Lancefield group G) is most commonly isolated from dogs, but it has been isolated also from cats, harbor porpoises, cows, mice, rats, and rabbits. Soft tissue infections and sepsis have occurred in humans, but infection is rare. Treatment is with a β-lactam antibiotic such as penicillin G (4 million units intravenously every 4 hours for 5 to 14 days based on the site and severity of infection).

STREPTOCOCCUS GALLOLYTICUS GROUP

Streptococcus gallolyticus complex bacteria are Lancefield group D nonenterococcal streptococci that colonize the intestines in 10% of healthy individuals. Subspecies include *gallolyticus, S. gallolyticus* subspecies *pasteurianus, S. gallolyticus* subspecies *macedonicus,* and *S. infantarius*. These bacteria are associated with hepatobiliary disease, meningitis, and subacute endocarditis in the setting of colorectal carcinoma. These bacteria are highly sensitive to penicillin G (4 million units intravenously every 4 hours for 5 to 14 days based on the site and severity of infection).

STREPTOCOCCUS INIAE

Streptococcus iniae is a β-hemolytic streptococcus without a Lancefield group antigen. It causes significant disease in fish, especially tilapia. Human infection results from the handling of live or killed fish. Skin and soft tissue infections are most common and often lead to bacteremia. Treatment is with a β-lactam antibiotic (e.g., penicillin G 4 million units intravenously every 4 hours for 5 to 14 days based on the site of infection).

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For the General References and other additional features, please visit Elsevier eBooks+ at https://ebooks.health.elsevier.com.

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270 ENTEROCOCCAL INFECTIONS

PATRICE SAVARD AND TRISH M. PERL

DEFINITION

Enterococci are endogenous human gut flora that are increasingly important health care–associated pathogens. Enterococci cause urinary tract infections, bacteremia, intra-abdominal infections, and, rarely, endocarditis and meningitis. Their emergence as major pathogens results from their inherent resistance to commonly used antimicrobial agents, persistence in the environment, association with indwelling devices, and transmission from patient to patient, mostly by way of the contaminated hands of health care personnel.

The Pathogen

Enterococci are catalase-negative gram-positive cocci that can appear singly, in pairs, or in short chains. They are facultative anaerobes that grow optimally at 35° to 37° C on sheep blood agar as α-hemolytic or nonhemolytic organisms. Unlike most streptococci, enterococci can grow in broth containing 6.5% NaCl and hydrolyze esculin in the presence of 40% bile salts (bile-esculin medium). *Enterococcus faecalis* is the causative agent for 80 to 90% of human enterococcal infections, followed by *Enterococcus faecium* (5 to 10% of the infections). *Enterococcus casseliflavus, Enterococcus gallinarum*, and *Enterococcus raffinosus* are less frequently associated with infections, but clusters have been reported. Other species isolated from humans include *Enterococcus avium, Enterococcus caccae, Enterococcus cecorum, Enterococcus dispar, Enterococcus durans, Enterococcus gilvus, Enterococcus hawaiiensis, Enterococcus hirae, Enterococcus italicus, Enterococcus malodoratus, Enterococcus massiliensis, Enterococcus mediterraneensis, Enterococcus mundtii, Enterococcus pallens, Enterococcus pseudoavium, Enterococcus thailandicus,* and *Enterococcus timonensis*.

EPIDEMIOLOGY

Enterococci are part of the normal human gut flora, and infections in both hospitalized and non-hospitalized patients can arise from either an endogenous or exogenous source. The proportion of infections caused by enterococci in hospitalized patients has increased over the past several decades. Overall, urinary tract infections (Chapter 263) are the most common clinical condition caused by enterococci. Enterococcal species also are the second most common isolates for any health care–associated infection (Chapter 261) and the single most common cause of central line–associated blood stream infections in patients who are hospitalized on regular hospital floors, intensive care units (ICUs), and inpatient oncology units.[1] Enterococci also cause about 15% of both catheter-associated urinary tract infections and surgical site infections in North America. In community settings, enterococci cause both complicated and uncomplicated urinary tract infections and are involved in approximately 5 to 15% of all cases of infective endocarditis (Chapter 61). Outside of the United States, these organisms are less common but increasingly important causes of infections.

Enterococcus species, especially *E. faecium,* in hospitalized patients increasingly may be resistant to vancomycin, ampicillin, or gentamicin. By 2017, 82% of *E. faecium* isolates and 7% of *E. faecalis* isolates from health care–associated infections were resistant to vancomycin. Vancomycin-resistant enterococci are associated with about 55,000 infections in hospitalized patients and 5400 deaths in the United States, each year. Although the proportion of vancomycin resistance among enterococcal clinical isolates in hospitalized patients has been historically lower in Europe than in the United States, about 18% of all European *E. faecium* isolates were resistant to vancomycin in 2019, with the prevalence varying from 0 to 50% in individual countries.

Most vancomycin-resistant enterococcus infections are associated with health care (Chapter 261), especially hospitalization in the prior year, and result from either an exogenous source (i.e., transmission from the environment, another patient, or the hands of health care personnel) or antimicrobial exposure.[2] Nearly all infections are preceded by a period of colonization, primarily in the gastrointestinal tract, where patients may harbor the strain for years after colonization. Although many colonized patients do not develop infections, they are still able to contaminate the environment, shed and transmit bacteria to other hospitalized patients, and precipitate an outbreak.

Apart from preexisting gastrointestinal colonization, risk factors for enterococcal infections, particularly vancomycin-resistant infections, include severe underlying conditions such as renal failure (Chapter 116), previous solid organ (especially liver; Chapter 140) or hematopoietic stem cell transplantation (Chapter 163), solid tumor and hematologic malignancies, diabetes mellitus (Chapter 210), and neutropenia (Chapter 153). Other factors associated with infection include prior surgical or gastrointestinal procedures, presence of a vascular or urinary indwelling catheter, hospital factors such as location in an ICU or an inpatient oncology service, proximity to colonized patients, prolonged length of hospitalization, and recent exposure to antimicrobial agents.[3]

Most classes of antimicrobials increase the risk of colonization with vancomycin-resistant enterococcus and subsequent clinical infections, but vancomycin, cephalosporins, and drugs that cure anaerobic organisms are especially implicated. Colonization with vancomycin-resistant enterococcus may coexist with *Clostridioides difficile* (Chapter 271) infection in high-risk patients, such as inpatients with hematologic malignancies.

PATHOBIOLOGY

Enterococci are commensal organisms that colonize the human gastrointestinal tract and female genital tract. They contaminate and also can be recovered from the environment. Although they are not as intrinsically virulent as other gram-positive pathogens, under certain conditions the commensal relationship is disrupted and serious infections occur. Several adhesion factors have been identified, including aggregation substance, which allow binding to epithelial surfaces and enhance the ability for colonization. The ability to adhere to heart valves and urinary tract epithelium enables enterococci to cause endocarditis and urinary tract infections. Enterococci are also known to secrete potential virulence factors, including cytolysin-hemolysin, which is a bacterial toxin that is produced in a higher proportion of infecting strains compared with stool-colonizing strains. Infecting strains also possess the ability to translocate across the intestinal epithelium, although the exact mechanisms of this process have yet to be determined. In addition, some encoded cell surface determinants may mediate adherence to host tissues that may be important in this organism's role in endocarditis. The exact role of capsular polysaccharides in colonization or infection is unknown. Strains have been shown to survive within phagocytic cells, yet it is unclear whether this represents successful host defense or evasion by the enterococci.

The intrinsic resistance to multiple antimicrobials (including cephalosporins, clindamycin, trimethoprim-sulfamethoxazole, and low-level aminoglycosides) that enterococci possess, along with their ability to acquire resistance to a wide range of antibiotics (including high concentrations of penicillins, fluoroquinolones, tetracycline, nitrofurantoin, and glycopeptides) through mutation or acquisition of new genes, enhances their ability to survive and multiply in the many hospitalized patients treated with broad-spectrum antimicrobials.

In the 21st century, additional antimicrobial resistance has emerged primarily in *E. faecium*. Two major genotypes, VanA and VanB, are responsible for acquired vancomycin resistance. The genes encoding the VanA phenotype, which also result in high-level resistance to teicoplanin, are carried on a plasmid or a conjugative transposon that is transferable. VanA is mostly found in *E. faecium* and, less frequently, in *E. faecalis*. VanB is associated with variable resistance to vancomycin, but isolates are usually susceptible to teicoplanin.

VanA and VanB are rarely found in other enterococci, but VanC is intrinsically recovered from *E. casseliflavus* and *E. gallinarum*. Importantly, these genetic elements have been integrated into the genome of *S. aureus* (Chapter 267) that is resistant to vancomycin. Resistance to ampicillin and high-level resistance to gentamicin have also been reported (Chapter 258).

CLINICAL MANIFESTATIONS

Enterococci cause urinary tract infections, intra-abdominal abscesses, wound infection, bacteremia (including central line–associated blood stream infections), endocarditis, and meningitis, but no specific clinical manifestations can help distinguish enterococcal infections from infections caused by other bacteria. Enterococci are not thought to cause lower respiratory tract infections and, if found in this setting, likely represent colonization and not infection. Enterococci act as opportunistic pathogens in severely ill and compromised patients, and fecal proliferation of enterococci has been implicated in graft-versus-host disease after hematopoietic stem cell transplantation (Chapter 163).[4]

Urinary Tract Infections

Urinary tract infections (Chapter 263) are the most frequent type of infection caused by enterococci. Most infections are nosocomial in origin (Chapter 261), and include uncomplicated cystitis, pyelonephritis, prostatitis (Chapter 114), and perinephric abscess. These infections are typically secondary to urinary catheterization or instrumentation.[5] In contrast to health care–associated

ABSTRACT

Enterococci, which colonize the gastrointestinal and urinary tracts, are inherently resistant to many classes of antimicrobials. They commonly cause urinary tract infections primarily after instrumentation, bloodstream infections associated with or without catheters, and intra-abdominal and postsurgical infections. They can cause endocarditis, which requires careful antimicrobial therapy. The most common species include *Enterococcus faecalis* and *E. faecium. E. faecium,* which is primarily a pathogen in immunocompromised hosts, is often resistant to vancomycin and other glycopeptides. Therapy with penicillin-based agents with or without aminoglycosides are associated with the best outcomes. For vancomycin-resistant organisms, however, antimicrobials such as linezolid and daptomycin play an important role. New combination therapies, including cephalosporins (ceftriaxone or ceftaroline or cefepime), are under study for endocarditis. As with many organisms, drainage of the source and removal of any indwelling catheters are key to improved outcomes.

KEYWORDS

Enterococcus faecalis
Enterococcus faecium
vancomycin-resistant *Enterococcus* (VRE)
urinary tract infection
bacteremia
endocarditis

urinary tract infections, enterococci cause fewer than 5% of uncomplicated cystitis or pyelonephritis cases in otherwise healthy non-hospitalized women. Patients with diabetes mellitus appear to be at increased risk for enterococcal urinary tract infections, but enterococcal bacteremia is infrequently associated with urinary tract infections.

Bacteremia

Enterococci can cause infection or contaminate cultured blood via contaminated catheter hubs and contaminated skin. Determining a true bacteremia versus a blood culture that is not clinically significant can be a challenge (Chapter 256). Specific risk factors include prolonged hospitalization, preexisting urethral catheters or intravascular lines, recent surgery, malignancy, neutropenia, and biliary tract disease.[6] Secondary bacteremia without endocarditis usually arises from the urinary tract, hepatobiliary tract, or soft tissue infection. Risk factors for bacteremia with vancomycin-resistant enterococci are similar but additionally include severe preexisting comorbid conditions, including hematologic malignancy, human immunodeficiency virus (HIV) infection, chronic renal insufficiency, and liver transplantation. Prior exposure (and especially prolonged exposure) to broad-spectrum antimicrobial drugs, particularly multiple drugs with antianaerobic activity (e.g., clindamycin, metronidazole, and piperacillin/tazobactam), is a consistent risk factor.

When enterococci are isolated alone, the course is typically indolent, and fever frequently is the only sign. Enterococcal bacteremia is frequently polymicrobial and more severe, often presenting with shock (Chapter 94) or disseminated intravascular coagulation (Chapter 161).

Endocarditis

Enterococci, particularly *E. faecalis,* are an important cause of endocarditis[7] (Chapter 61) and represent at least 10% of cases in non–intravenous drug users. About 25% of patients with *E. faecalis* bacteremia have definitive bacterial endocarditis,[8] and about 50% of patients with *E. faecalis* endocarditis have a colorectal neoplasm discovered.[9] The disease occurs most frequently in older patients, with a male predominance. Most cases appear to arise in the community. Patients with preexisting valvular heart disease (Chapter 60), including prosthetic valves, are at highest risk, but many patients do not have underlying heart disease. Enterococci more commonly cause left-sided endocarditis, primarily affecting the mitral valve. Patients typically present with subacute bacterial endocarditis symptoms for weeks or months, similar to the clinical presentation of streptococcal viridans endocarditis, before seeking medical care.

Intra-abdominal Infections

In intra-abdominal infections, enterococci are often detected as part of a polymicrobial process. These infections typically arise from a hepatobiliary source (Chapter 141), including complicated biliary stone disease and postoperative infection after liver transplantation (Chapter 140), and are complicated by hepatic abscess formation[10] and secondary bacteremia.

Skin and Soft Tissue Infections

Enterococci rarely cause cellulitis or other skin and soft tissue infections alone but are often found in mixed surgical site infections, diabetic foot infections, and decubitus ulcers along with other gram-negative bacilli, gram-positive cocci, and anaerobic bacteria. Their clinical significance in these situations is not clear. Enterococci are not thought to be primary pathogens in chronic osteomyelitis. When identified, they likely represent superinfection, so antimicrobial therapy may not require antibiotics directed at enterococcal eradication.

DIAGNOSIS

The tentative diagnosis of an *Enterococcus* infection can be made rapidly by nucleic acid testing and confirmed by isolating the organism by culture of a sterile site, such as blood or urine.

TREATMENT

Because of the complexity of enterococcal infections, an infectious diseases consultation should be considered for therapeutic guidance. For any severe enterococcal infection, empirical therapy should generally be based on the site of infection, the patient population, and local epidemiology (Table 270-1). Once susceptibility testing by an experienced microbiology laboratory is available, the results can guide effective directed therapy.

Optimal therapy for most infections includes intravenous ampicillin, penicillin, or vancomycin. Except for urinary tract infections or skin and soft tissue infections, standard therapy with penicillins and vancomycin should also include the addition of a synergistic aminoglycoside (i.e., gentamicin or streptomycin), especially for suspected endocarditis, provided that high-level resistance is not detected. Neither tobramycin nor kanamycin has synergistic activity against enterococci. Oritavancin and dalbavancin are active against vancomycin-susceptible enterococci and can be considered in skin and soft tissue infections (see Table 270-1).

E. faecium strains increasingly are resistant to penicillins, but most *E. faecalis* strains remain susceptible to ampicillin and the related piperacillin. Even when enterococcus appears susceptible to trimethoprim-sulfamethoxazole in vitro, it should not be used because clinical failures have been reported secondary to the ability of enterococci to use exogenous folate. *E. faecalis* is intrinsically resistant to quinupristin-dalfopristin, which therefore should not be used in therapy for infections caused by this species, as opposed to *E. faecium,* which remains susceptible to that drug.

For vancomycin-resistant enterococcal strains, potential agents include linezolid, tigecycline, daptomycin, and tedizolid. Linezolid, which is bacteriostatic against enterococci, is commonly the drug of choice for infections other than bacteremia,[A1] although it is associated with bone marrow suppression, including thrombocytopenia, and can cause the serotonin syndrome when used in combination with selective serotonin re-uptake inhibitors (Chapter 400). Although daptomycin is not approved by the U.S. Food and Drug Administration (FDA) to treat vancomycin-resistant enterococcus, it has been associated with good outcomes in skin and soft tissue infections and bacteremia. Tigecycline is FDA-approved to treat complicated skin and soft tissue infections and complicated intra-abdominal infections caused by vancomycin-susceptible isolates of *E. faecalis*, but an FDA-required black box warning about potentially worsened overall outcome limits its use.

Urinary Tract Infections

Single-agent therapy is usually adequate to treat enterococcal urinary tract infections. Options include ampicillin, amoxicillin, penicillin, quinolones, fosfomycin, or vancomycin (see Table 270-1). Based on pharmacodynamic data, aminopenicillins may be useful even when isolates are resistant because of their high urinary concentrations, but clinical data are very limited.[11] Vancomycin is typically reserved for penicillin-allergic patients or if the strain has high-level penicillin/ampicillin resistance. β-Lactam–β-lactamase inhibitor combinations are usually reserved for polymicrobial infections. Nitrofurantoin is also occasionally used because most strains, even if vancomycin-resistant, remain susceptible. Fosfomycin is also effective for urinary tract infections caused by susceptible *E. faecalis*.

Bacteremia without Endocarditis

Many cases of enterococcal bacteremia are transient or self-limited, but antibiotic therapy with penicillin or ampicillin (see Table 270-1) improves outcomes, especially when instituted within 48 hours.[12] Daptomycin treatment of daptomycin-susceptible, vancomycin-resistant enterococcal blood stream infections is more effective with higher daptomycin doses (≥9 mg/kg). Unlike in endocarditis, it is not known whether patients benefit from combination therapy (penicillin or ampicillin or vancomycin plus an aminoglycoside), except perhaps when an intravascular catheter is present. In the setting of an intravascular catheter, especially for VRE, removal of the catheter is indicated. If the bacteremia is secondary to another site such as an intra-abdominal abscess, drainage of the source is critical to cure.

Endocarditis

Combination therapy (intravenous penicillin, ampicillin, or vancomycin plus an aminoglycoside) with bactericidal activity to sterilize vegetations is the standard therapy for enterococcal endocarditis (Chapter 61). Another synergistic combination for patients who cannot tolerate aminoglycosides includes ampicillin plus ceftriaxone or cefotaxime to treat *E. faecalis* endocarditis but not *E. faecium*.[13,14] Adding ampicillin and ceftaroline to daptomycin may be better than daptomycin monotherapy.

If the causative enterococcal strain is highly resistant to both gentamicin and streptomycin, then alternative agents and durations must be explored, and surgery to excise infected valves should be considered. Optimal therapy of vancomycin-resistant enterococcus strains that are resistant to ampicillin is not known; options include linezolid (not FDA-approved for endocarditis treatment) and daptomycin (not FDA-approved for enterococcal infections) if the strain is found to be susceptible. However, linezolid resistance is increasingly reported even in patients without previous exposure to the antibiotic, and daptomycin resistance is also reported in both *E. faecalis* and *E. faecium* after prolonged courses of therapy.

Vancomycin-resistant enterococcal endocarditis (Chapter 61) may require early surgery because outcomes with antibiotic therapy alone can be poor. If repeated blood cultures grow for more than 7 days after the initiation of medical therapy or other signs of uncontrolled infection (persistent fever or leukocytosis) are present, valve replacement should be considered early in the treatment course if there are no absolute contraindications for surgery.

Switching from intravenous to oral medications after 10 days of therapy may be safe[A2] for *E. faecalis* endocarditis but should be carefully evaluated in consultation with an infectious diseases specialist. The overall duration of therapy is typically 4 to 6 weeks, with longer therapy in patients who had prolonged symptoms before seeking therapy, have prosthetic valve infection, or relapse after initial treatment.

TABLE 270-1 TREATMENT OPTIONS FOR DIFFERENT ENTEROCOCCAL SPP FOR VARIOUS INFECTION SITES[‖]

	ENTEROCOCCUS FAECALIS	*ENTEROCOCCUS FAECIUM*	VANCOMYCIN-RESISTANT ENTEROCOCCUS (VRE)
Urinary Tract Infection			
PCN/ampicillin susceptible*	Ampicillin (1 g IV q6h) or amoxicillin (500 mg PO TID)	Ampicillin (1 g IV q6h) or amoxicillin (500 mg PO TID)	Ampicillin (1 g IV q6h) or amoxicillin (500 mg PO TID) Fosfomycin if susceptible (3 g PO once if catheter removed)
PCN/ampicillin resistance*	If susceptible: nitrofurantoin (100 mg PO q12h†) or fosfomycin (3 g PO once if catheter removed) if uncomplicated§ Vancomycin if resistant to other agents	If susceptible: nitrofurantoin (100 mg PO q12h†) Vancomycin if resistant to other agents	If susceptible: nitrofurantoin (100 mg PO q12h†) Linezolid (600 mg PO/IV q12h) or Daptomycin (8-12 mg/kg IV q24h) or Fosfomycin if susceptible (3 g PO once if catheter removed) if uncomplicated§
Bacteremia*			
PCN/ampicillin susceptible*	PCN (4 million IV q4h) or ampicillin (2 g IV q4-6h) for 7-14 days	PCN (4 million IV q4h) or ampicillin (2 g IV q4-6h) for 7-14 days	Consider consultation with an infectious diseases specialist PCN (4 million IV q4h) or ampicillin (2 g IV q4-6h) if susceptible
With PCN allergy or PCN/ampicillin resistance	Vancomycin load with 20-25 mg/kg followed by 15-20 mg/kg q8-12h based on PK/PD dosing using actual body weight to achieve a serum level of 15-20 µg/mL (trough) Consider adding gentamicin if prolonged bacteremia and laboratory reports synergy with cell wall–active agent	Vancomycin load with 20-25 mg/kg followed by 15-20 mg/kg q8-12h based on PK/PD dosing using actual body weight to achieve a serum level of 15-20 µg/mL (trough) Consider adding gentamicin if prolonged bacteremia and laboratory reports synergy with cell wall–active agent	Linezolid (600 mg PO/IV q12h) or Daptomycin (8-12 mg/kg IV q24h) for 14 days
Endocarditis††			
PCN/ampicillin and aminoglycoside susceptible*	Consider consultation with an infectious diseases specialist Combination therapy indicated PCN (4 million IV q4h) or ampicillin (2 g IV q4h) PLUS gentamicin (3 mg/kg IV q24h) both for 4‡-6 wk Ampicillin (2 g IV q4h) PLUS ceftriaxone (2 g IV q12h) or cefotaxime (2 g IV q8h) for 6 wk	Consult an infectious diseases specialist Combination therapy indicated PCN (4 million IV q4h) or ampicillin (2 g IV q4h) PLUS gentamicin (3 mg/kg IV q24h) both for 4‡-6 wk	Consult an infectious diseases specialist Combination therapy indicated PCN (4 million IV q4h) or ampicillin (2 g IV q4h) PLUS gentamicin (3 mg/kg IV q24h) both for 6 wk
PCN/ampicillin susceptible and gentamicin resistant* or gentamicin intolerant	Consult an infectious diseases specialist Combination therapy indicated: (1) ampicillin (2 g IV q4h) PLUS ceftriaxone (2 g IV q12h) or cefotaxime (2 g IV q8h) either for 6 wk or (2) PCN (4 million IV q4h) or ampicillin (2 g IV q4h) PLUS streptomycin† (7.5 mg/kg IV or IM q12h) for 4‡-6 wk	Consult an infectious diseases specialist Combination therapy indicated PCN (4 million IV q4h) or ampicillin (2 g IV q4h) PLUS streptomycin† (7.5 mg/kg IV or IM q12h) both for 4‡-6 wk	Consult an infectious diseases specialist Combination therapy indicated PCN (4 million IV q4h) or ampicillin (2 g IV q4h) PLUS streptomycin† (7.5 mg/kg IV or IM q12h) both for 6 wk

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PCN Allergic	Consider PCN desensitization if strain susceptible Vancomycin load with 20-25 mg/kg followed by 15-20 mg/kg q8-12h based on PK/PD dosing using actual body weight to achieve a serum level of 15-20 µg/mL (trough) PLUS gentamicin (3 mg/kg IV q24h) both for 6 wk	Consider PCN desensitization if strain susceptible Vancomycin load with 20-25 mg/kg followed by 15-20 mg/kg q8-12h based on PK/PD dosing using actual body weight to achieve a serum level of 15-20 µg/mL (trough) PLUS gentamicin (3 mg/kg IV q24h) both for 6 wk	Consider PCN desensitization if strain susceptible Linezolid (600 mg PO/IV q12h) PLUS another active agent or Daptomycin (8-12 mg/kg IV q24h) PLUS gentamicin (3 mg/kg IV q24h)
PCN/ampicillin resistant and gentamicin susceptible*	Consult an infectious diseases specialist Vancomycin load with 20-25 mg/kg followed by 15-20 mg/kg q8-12h based on PK/PD dosing using actual body weight to achieve a serum level of 15-20 µg/mL (trough) PLUS gentamicin (1 mg/kg IV q8h) both for 6 wk	Consult an infectious diseases specialist Vancomycin load with 20-25 mg/kg followed by 15-20 mg/kg q8-12h based on PK/PD dosing using actual body weight to achieve a serum level of 15-20 µg/mL (trough) PLUS gentamicin (1 mg/kg IV q8h) both for 6 wk	Consult an infectious diseases specialist Linezolid (600 mg PO/IV q12h) PLUS another active agent or Daptomycin 8-12 mg/kg IV q24h PLUS gentamicin (1 mg/kg IV q8h) both for 6 wk Consider other combinations including daptomycin + ampicillin or ceftaroline**
PCN/ampicillin resistant and gentamicin resistant*	Consult an infectious diseases specialist Linezolid (600 mg PO/IV q12h) or Daptomycin (8-12 mg/kg IV q24h) for a minimum of 6 wk Consider combination of daptomycin with either ampicillin or ceftaroline** 600 mg IV q 8–12 h Failures reported; consider surgery	Consult an infectious diseases specialist Linezolid (600 mg PO/IV q12h) or Daptomycin (8-12 mg/kg IV q24h) for a minimum of 6 wk Consider combination of daptomycin with either ampicillin or ceftaroline** 600 mg IV q 8–12 h Failures reported; consider surgery	Consult an infectious diseases specialist Linezolid (600 mg PO/IV q12h) PLUS another active agent or Daptomycin (8-12 mg/kg IV q24h) for 6 wk Consider combination with either ampicillin or ceftaroline** 600 mg IV q 8–12 h Failures reported; consider surgery
Intra-abdominal/Skin and Soft Tissue Polymicrobial Infections			
PCN/ampicillin susceptible*	Ampicillin-sulbactam 1.5-3 g IV q 6 h OR Piperacillin-tazobactam 3.375 g IV q6h Other combinations can be used based on a consultation with infectious diseases specialist	Ampicillin-sulbactam 1.5-3 g IV q 6 h OR Piperacillin-tazobactam 3.375 g IV q 6 h Other combinations can be used based on a consultation with infectious diseases specialist	Ampicillin-sulbactam 1.5-3 g IV q 6 h OR Piperacillin-tazobactam 3.375 g IV q 6 h Other combinations can be used based on a consultation with infectious diseases specialist
PCN/ampicillin resistance*	Combine vancomycin PLUS other antimicrobials covering the primary pathogens	Combine vancomycin PLUS other antimicrobials covering the primary pathogens	Consult an infectious diseases specialist Linezolid (600 mg PO/IV q12h) PLUS another active agent or Daptomycin (8-12 mg/kg IV q24h) PLUS other antimicrobials covering the primary pathogens

IM = intramuscular; IV = intravenous; PCN = penicillin; PO = oral; q = every; TID = three times a day; UTI = urinary tract infection. Dose adjustment of most antibiotics is required in case of renal dysfunction. PK/PD = pharmacokinetic and pharmacodynamic dosing.

*Refer to the most recent guidelines for susceptibility cutoff values.

†Do not use with creatinine clearance less than 50 mL/min.

‡Treat for 4 weeks only when symptoms have been present for less than 3 months and there is a prompt response to therapy.

§For complicated UTI use 3 g (1 sachet) PO every 2-3 days (up to 21 days).

‖Doses are for normal renal function.

**Not FDA-approved for enterococcal infections.

††For prosthetic valve endocarditis, consult infectious diseases specialist.

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Intra-abdominal and Skin and Soft Tissue Infections
Because intra-abdominal and skin and soft tissue infections involving *Enterococcus* spp are commonly polymicrobial, specific anti-enterococcal therapy is usually not required.[15] If enterococci are thought to be a significant pathogen, a broad-spectrum β-lactam antibiotic (if susceptible) is preferred to cover a polymicrobial infection.

PRIMARY PREVENTION

Optimal infection prevention for vancomycin-resistant enterococcus, similar to many multidrug-resistant bacteria, includes proper use and compliance with hand hygiene, use of contact precautions, cohorting of colonized patients, proper management and timely removal of urinary and vascular catheters, reduction of antibiotic selective pressure through antimicrobial stewardship, and environmental cleaning of equipment and patient rooms (Chapter 261). Because vancomycin-resistant enterococci contaminate and persist in the environment for long periods of time, environmental cleaning is particularly important for preventing infections.

Since the number of patients already colonized with vancomycin-resistant enterococci in a defined geographic area ("colonization pressure") may be the most significant predictor of new acquisition of vancomycin-resistant enterococci, decontamination of patients' skin, called source control, may broadly control transmission of resistant pathogens and reduce device-related infections. Source control using daily bathing of ICU patients with chlorhexidine gluconate–saturated cloths has shown benefit in most studies, and sustained and appropriate application of chlorhexidine may also be beneficial in non–critical care inpatients in settings with high rates of vancomycin-resistant enterococcus or methicillin-resistant *Staphylococcus aureus*.[A3]

Because nearly all enterococcal infections are preceded by gastrointestinal colonization, because only 1 in 10 colonized patients is symptomatic, and because colonized patients can shed and transmit bacteria to other hospitalized patients, unrecognized colonized patients represent the target population for infection prevention and control. Active surveillance programs use rectal surveillance swabs to detect previously unrecognized colonized patients and isolate them to prevent further transmission. Surveillance cultures or PCR may be recommended at the time of hospital admission for patients at high risk for carriage of vancomycin-resistant enterococcus, and colonized patients or infected patients should be placed in isolation using contact precautions. Contact precautions typically entail private rooms and dedicated equipment such as stethoscopes. By comparison, the use of gloves and gowns does not appear to reduce the acquisition of vancomycin-resistant enterococcus (or methicillin-resistant *S. aureus*)[A4] compared with standard precautions, which include cleaning and disinfection of equipment that is used in patient rooms.

PROGNOSIS

Focal enterococcal infections other than intra-abdominal infections are curable with antibiotics. Enterococcal bacteremia, however, is associated with prolonged hospitalization and added costs compared with similar patients without enterococcal bacteremia. Bacteremia secondary to an intra-abdominal source carries an especially high mortality rate. Vancomycin-resistant enterococcal bacteremia has about a 20%[16] or higher in-hospital mortality rate, which is about twice the mortality rate of bacteremia caused by susceptible organisms. Appropriate antibiotic treatment of bacteremia within 48 hours is associated with better outcomes, and the higher mortality may be related to a delay in the administration of adequate empirical antibiotic therapy.

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For the General References and other additional features, please visit Elsevier eBooks+ at https://ebooks.health.elsevier.com.

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271 CLOSTRIDIAL AND *CLOSTRIDIOIDES* INFECTIONS

MARK H. WILCOX AND ERIK R. DUBBERKE

DIARRHEAL SYNDROMES
CLOSTRIDIOIDES DIFFICILE INFECTION

DEFINITION

The hallmark of *C. difficile* infection is diarrhea, most commonly during or after (up to 3 months) a course of antibiotics. Most cases are defined by the presence of clinically significant diarrhea (three or more loose or unformed bowel movements per day) plus evidence of toxigenic *C. difficile* or its toxins A and/or B in stool. *C. difficile* infection can also be diagnosed by direct visualization of colonic pseudomembranes on endoscopy.

The Pathogen

C. difficile is a spore-forming, anaerobic, gram-positive bacilli that is ubiquitous in nature around the world. Production of toxin B is required for *C. difficile* to cause *C. difficile* infection (toxigenic strains), but not all strains of *C. difficile* have the gene for toxin B (nontoxigenic strains).

EPIDEMIOLOGY

C. difficile has a worldwide distribution. It has been isolated from soil, water, homes of otherwise healthy people, retail establishments, meat and vegetables purchased at grocery stores, and the feces of pets, livestock, and wild animals. Upwards of 50% of asymptomatic infants are colonized with *C. difficile* at any one point in time, as are 10 to 25% of toddlers. Approximately 3% of healthy, asymptomatic adults are colonized with *C. difficile*, but the colonization prevalence of toxigenic *C. difficile* in hospitalized adults can be as high as 20%.[1] Although ambulatory adults are less likely than children to be colonized with *C. difficile*, clinical *C. difficile* infection is very uncommon in children, but the incidence increases with age, especially among people over age 60 years. For community-associated cases, new infections are mostly a result of the new acquisition of the organism followed by intestinal colonization. Most cases of health care–onset *C. difficile* infection are a result of a new acquisition of *C. difficile* after an antibiotic exposure, with a median of 3 to 7 days from the acquisition of *C. difficile* to the onset of infection.

The incidence and severity of *C. difficile* infection increased dramatically in the first decade of the 21st century, associated with a new predominant ribotype 027 strain, which was associated with dramatic outbreaks in North America and Europe. This strain, which is highly fluoroquinolone-resistant, produces a third toxin (binary toxin) and is readily transmissible in the health care setting. From 2011 to 2017, a 36% decline in the number of cases of health care–associated *C. difficile* infection (Chapter 261; from about 305,000 to about 195,000) have been associated with declines in the proportion of cases due to the 027 strain, from nearly 35% in 2011 to only 15% by 2017. This decline was likely due to improved antimicrobial stewardship and a focus on preventing *C. difficile* transmission in hospitals.[2,3] Similar declines have been noted in community-associated *C. difficile* infection cases due to the 027 strain over the same time period, but cases of community-associated *C. difficile* infection have remained constant at about 170,000 per year, apparently because of the ubiquity of *C. difficile* in the community and the stable or even increased prescribing of outpatient antibiotics.[4]

PATHOBIOLOGY

As a strict anaerobe, vegetative *C. difficile* cells die after exposure to oxygen. Its spores, however, can survive for months in the external environment and lead to colonization. The normal adult gut microbiota provides the first line of defense against *C. difficile* colonization and infection, and the decline in colonization from infancy to adolescence mirrors the maturation of the gut microbiome.[5] The metabolic activity of the healthy microbiome and competition for nutrients and binding sites determine whether *C. difficile* will colonize after an exposure and whether colonization will progress to clinical infection. For example, the microbiome converts primary bile salts, which are excreted into the bowel from the liver, into secondary bile salts that prevent *C. difficile*

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Intra-abdominal and Skin and Soft Tissue Infections
Because intra-abdominal and skin and soft tissue infections involving *Enterococcus* spp are commonly polymicrobial, specific anti-enterococcal therapy is usually not required.[15] If enterococci are thought to be a significant pathogen, a broad-spectrum β-lactam antibiotic (if susceptible) is preferred to cover a polymicrobial infection.

PRIMARY PREVENTION

Optimal infection prevention for vancomycin-resistant enterococcus, similar to many multidrug-resistant bacteria, includes proper use and compliance with hand hygiene, use of contact precautions, cohorting of colonized patients, proper management and timely removal of urinary and vascular catheters, reduction of antibiotic selective pressure through antimicrobial stewardship, and environmental cleaning of equipment and patient rooms (Chapter 261). Because vancomycin-resistant enterococci contaminate and persist in the environment for long periods of time, environmental cleaning is particularly important for preventing infections.

Since the number of patients already colonized with vancomycin-resistant enterococci in a defined geographic area ("colonization pressure") may be the most significant predictor of new acquisition of vancomycin-resistant enterococci, decontamination of patients' skin, called source control, may broadly control transmission of resistant pathogens and reduce device-related infections. Source control using daily bathing of ICU patients with chlorhexidine gluconate–saturated cloths has shown benefit in most studies, and sustained and appropriate application of chlorhexidine may also be beneficial in non–critical care inpatients in settings with high rates of vancomycin-resistant enterococcus or methicillin-resistant *Staphylococcus aureus*.[A3]

Because nearly all enterococcal infections are preceded by gastrointestinal colonization, because only 1 in 10 colonized patients is symptomatic, and because colonized patients can shed and transmit bacteria to other hospitalized patients, unrecognized colonized patients represent the target population for infection prevention and control. Active surveillance programs use rectal surveillance swabs to detect previously unrecognized colonized patients and isolate them to prevent further transmission. Surveillance cultures or PCR may be recommended at the time of hospital admission for patients at high risk for carriage of vancomycin-resistant enterococcus, and colonized patients or infected patients should be placed in isolation using contact precautions. Contact precautions typically entail private rooms and dedicated equipment such as stethoscopes. By comparison, the use of gloves and gowns does not appear to reduce the acquisition of vancomycin-resistant enterococcus (or methicillin-resistant *S. aureus*)[A4] compared with standard precautions, which include cleaning and disinfection of equipment that is used in patient rooms.

PROGNOSIS

Focal enterococcal infections other than intra-abdominal infections are curable with antibiotics. Enterococcal bacteremia, however, is associated with prolonged hospitalization and added costs compared with similar patients without enterococcal bacteremia. Bacteremia secondary to an intra-abdominal source carries an especially high mortality rate. Vancomycin-resistant enterococcal bacteremia has about a 20%[16] or higher in-hospital mortality rate, which is about twice the mortality rate of bacteremia caused by susceptible organisms. Appropriate antibiotic treatment of bacteremia within 48 hours is associated with better outcomes, and the higher mortality may be related to a delay in the administration of adequate empirical antibiotic therapy.

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271 CLOSTRIDIAL AND *CLOSTRIDIOIDES* INFECTIONS

MARK H. WILCOX AND ERIK R. DUBBERKE

DIARRHEAL SYNDROMES
CLOSTRIDIOIDES DIFFICILE INFECTION

DEFINITION

The hallmark of *C. difficile* infection is diarrhea, most commonly during or after (up to 3 months) a course of antibiotics. Most cases are defined by the presence of clinically significant diarrhea (three or more loose or unformed bowel movements per day) plus evidence of toxigenic *C. difficile* or its toxins A and/or B in stool. *C. difficile* infection can also be diagnosed by direct visualization of colonic pseudomembranes on endoscopy.

The Pathogen

C. difficile is a spore-forming, anaerobic, gram-positive bacilli that is ubiquitous in nature around the world. Production of toxin B is required for *C. difficile* to cause *C. difficile* infection (toxigenic strains), but not all strains of *C. difficile* have the gene for toxin B (nontoxigenic strains).

EPIDEMIOLOGY

C. difficile has a worldwide distribution. It has been isolated from soil, water, homes of otherwise healthy people, retail establishments, meat and vegetables purchased at grocery stores, and the feces of pets, livestock, and wild animals. Upwards of 50% of asymptomatic infants are colonized with *C. difficile* at any one point in time, as are 10 to 25% of toddlers. Approximately 3% of healthy, asymptomatic adults are colonized with *C. difficile*, but the colonization prevalence of toxigenic *C. difficile* in hospitalized adults can be as high as 20%.[1] Although ambulatory adults are less likely than children to be colonized with *C. difficile*, clinical *C. difficile* infection is very uncommon in children, but the incidence increases with age, especially among people over age 60 years. For community-associated cases, new infections are mostly a result of the new acquisition of the organism followed by intestinal colonization. Most cases of health care–onset *C. difficile* infection are a result of a new acquisition of *C. difficile* after an antibiotic exposure, with a median of 3 to 7 days from the acquisition of *C. difficile* to the onset of infection.

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ABSTRACT

Clostridial organisms are spore-forming, anaerobic, gram-positive bacilli that are found in a wide variety of environments, including soil, vegetation, and the gut of healthy animals. Their ability to produce spores allows them to survive for prolonged periods of time in challenging environments, including after exposure to many common household and hospital disinfectants. Another characteristic of clostridia that cause disease is their ability to produce toxins, and it is these toxins that often cause the hallmark features of clostridial infections. The clostridia with the greatest impact on human health today is *Clostridioides* (formerly *Clostridium*) *difficile*, which is the most common cause of health care–associated infections in the United States and is an associated complication in over 20,000 in-hospital deaths per year. By comparison, the incidence of other *Clostridioides* (e.g., *Clostridium tetani, C. botulinum*, and *C. perfringens*) has decreased due to improvements in hygiene and vaccinations, but diseases caused by those agents require prompt recognition and appropriate therapy to avoid preventable morbidity and mortality. Clostridia of emerging importance include *Paeniclostridium* (formerly *Clostridium) sordellii* (which is a cause of rapidly fatal infections in postpartum women, after medical abortions, in injection drug users, and after traumatic injuries), and *Clostridium novyi* (which is a cause of necrotizing infections in injection drug users).

KEYWORDS

Clostridioides difficile
C. tetani
C. botulinum
C. perfringens
botulism
tetanus
Paeniclostridum sordellii
Clostridium novyi

spores from germinating and growing. Primary bile salts, which can have the opposite effect, are more prevalent when their conversion to secondary bile salts is reduced by the effect of antibiotics on the microbiome.

For *C. difficile* to cause infection, it must produce toxins A and B, both of which cause glucosylation of GTPase proteins, which then lead to cytoskeletal disruption and cell death. The specific binding receptors for toxins A and B are primarily localized to the human adult colon, thereby explaining the lack of *C. difficile* infection in infants and the rarity of small bowel involvement. After the colonic mucosal cells die, toxins A and B induce acute neutrophilic inflammation, which can be visualized as pseudomembranes on endoscopy. An important secondary line of defense appears to be production of antibodies against toxins A and B, in particular toxin B, to protect against recurrent *C. difficile* infection.[6]

CLINICAL MANIFESTATIONS

C. difficile may colonize the colon without symptoms. In the face of toxin production, the clinical symptoms of *C. difficile* infection range from mild diarrhea to profuse but usually nonbloody diarrhea. More severe infection may be associated with fever, cramps, leukocytosis, and hypoalbuminemia. Life-threatening pseudomembranous colitis is characterized by major fluid losses, hypotension, toxic megacolon, and/or systemic complications.

Leukocytosis occurs in about 50% of cases. Severe infection is usually defined as a white blood cell count of >15,000/μL accompanied by a serum creatinine level of 1.5 times or more of the baseline level. Severe complicated infection is commonly defined as an extremely high white blood count (>50,000/μL), often with lactic acidosis, hypotension, shock, ileus, and/or toxic megacolon.[7]

DIAGNOSIS

Unexplained diarrhea (typically defined as three or more loose or unformed stools in ≤24 hours), especially when associated with recent or current antibiotic exposure, should raise a suspicion of possible *C. difficile* infection. However, the clinical suspicion of *C. difficile* infection is often incorrect given the many possible causes of diarrhea, especially in patients who have multiple comorbid illnesses.

No single laboratory test is adequate for the reliable diagnosis of *C. difficile* infection, The most specific test to establish a *C. difficile* infection is the detection of toxins A and/or B in stool. The most commonly used laboratory method to detect *C. difficile* toxins is an enzyme immunoassay, but its sensitivity ranges from only about 50 to 80%. Nucleic acid amplification tests (NAATs), most commonly polymerase chain reaction (PCR) testing, have a sensitivity of 90 to 95% (compared with the "gold standard" of culture for a toxigenic strain) but can lead to the overdiagnosis of infection because the diarrhea may be due to other causes in patients, especially in older individuals who have been frequently hospitalized, who have harmless carriage of a toxigenic strain of *C. difficile*. Stool culture for *C. difficile* also lacks specificity, given the potential for *C. difficile* colonization as opposed to infection. Testing of stools for glutamate dehydrogenase, or "common antigen," is a rapid and sensitive screening test, but its specificity is only about 50%, so it requires confirmation with a toxin test.

Because of the limitations of each individual test, the optimal approach for the laboratory diagnosis of *C. difficile* infection is to use a combination of tests: PCR or glutamate dehydrogenase for screening, plus detection of free toxin in stools for confirmation. If patients have documented diarrhea (three or more loose or unformed stools in <24 hours) in the absence of other identifiable causes of diarrhea (e.g., laxative use and recent antibiotic use), PCR testing alone is usually adequate to make the diagnosis. For other patients, *C. difficile* infection can also be diagnosed by observing pseudomembranous colitis directly on sigmoidoscopy or colonoscopy, but this approach is best reserved for patients with a strong clinical suspicion of *C. difficile* infection despite negative laboratory testing.

Infectious diarrhea that persists for longer than 48 hours after hospital admission in an adult patient is almost always due to either *C. difficile* or norovirus (Chapter 350) infection. Common noninfectious causes of persistent diarrhea (Chapter 126) include laxatives, irritable bowel disease (Chapter 123), ischemic colitis (Chapter 129), and inflammatory bowel disease (Chapter 127). Of note, ischemic colitis can also cause pseudomembranes, which can be confused with *C. difficile* infection. For antibiotic-associated diarrhea with a negative *C. difficile* toxin assay, the cause is usually not identified. Since a negative toxin test result does not exclude a diagnosis of *C. difficile* infection, empiric treatment of *C. difficile* infection may still be considered in patients who have clinical symptoms highly suggestive of *C. difficile* infection after alternative diagnoses are excluded.

TREATMENT

When diarrhea is mild, the discontinuation of antibiotics and supportive care may be sufficient to effect cure. However, it is not possible to identify prospectively with confidence who will respond to such management, and most patients will require specific treatment.[8] Nevertheless, the offending antibiotic(s) should be discontinued because continuing them results in lower cure rates and higher rates of reinfection.

For patients with mild/moderate or severe *C. difficile* infection (variously defined as a white blood cell count >15,000/μL or a creatinine increase to >1.5-fold above baseline), fidaxomicin (200 mg orally twice a day for 10 days) is preferred over vancomycin (125 mg orally four times a day for 10 days) because it is equally efficacious for the acute infection and better for reducing the risk of recurrent infection.[A1] A clinical response typically occurs over several days (mean time to resolution of diarrhea is about 3 days). A failure to resolve by day 5 or 6 often indicates either that *C. difficile* is not the cause of the symptoms or, less commonly, that the disease has progressed too far. For fulminant *C. difficile* infection with an ileus, vancomycin (500 mg four times a day orally or by nasogastric tube) plus metronidazole (500 mg IV every 8 hours) is recommended, with vancomycin also potentially administered by enema. If symptoms progress despite this therapy, life-saving colectomy or a colon-sparing loop ileostomy should be considered before the white blood cell count reaches 50,000/μL or the lactate concentration exceeds 5.0 mmol/L.

Approximately 15% of patients treated with fidaxomicin (as compared with about 25% after treatment with vancomycin) have a recurrence of *C. difficile* infection within 4 weeks after treatment is completed, either because of a relapse (about 80% of cases) if *C. difficile* spores are not completely eradicated or reinfection (about 20% of cases) with a new strain. Patients with multiple recurrences of *C. difficile* infection are extremely difficult to treat and may benefit from consultation with an infectious disease specialist or gastroenterologist. For such recurrences, guidelines recommend fidaxomicin (standard dosing or dosing twice daily for 5 days and then every other day for 20 days under expert guidance).[A2] in preference to a standard course of vancomycin.[9] In patients who are receiving antibiotic treatment for primary or recurrent *C. difficile* infection, bezlotoxumab (a human monoclonal antibody against *C. difficile* toxin B infused at a dose of 10 mg per kilogram of body weight) is associated with a substantially lower rate of recurrent infection than placebo[10] and has a safety profile similar to that of placebo.[A3] Guidelines recommend using bezlotoxumab plus antibiotics for patients who have a recurrent *C. difficile* infection within 6 months.[11]

For three or more confirmed episodes of *C. difficile* infection, fecal microbiota transplantation, using fresh or frozen donor material administered via enema, colonoscopy, or oral capsules,[A4] is safe and efficacious to prevent recurrent *C. difficile* infection, with about a 70% cure rate.[A5,A6] Some data also support fecal microbiota transplantation over vancomycin for a first or second infection.[A7] Fecal transplantation is also superior to fidaxomicin for the treatment of recurrent *C. difficile* infection,[A8] and it has been shown to be safe for at least 3 to 4 years after transplantation.[12] RBX2660, a fecal microbiota-based product administered by enema,[A9] was recently approved by the U.S. Food and Drug Administration (FDA), and SER109, a capsule formulation, appears promising as well. Therapies under investigation to prevent recurrent *C. difficile* infection include oral administration of spores of a nontoxigenic *C. difficile* strain, which in one trial reduced *C. difficile* infection by about 75%.[A10]

PREVENTION

The key to preventing *C. difficile* infection focuses on preventing the transmission of *C. difficile* and to decrease the risk of infection if transmission occurs. The former is accomplished by contact precautions and the latter by antimicrobial stewardship (Chapter 261). Contact precautions involve placing patients with *C. difficile* infection into private rooms, when available, using dedicated equipment (e.g., isolation stethoscopes), and having health care personnel wear gowns and gloves whenever entering the patient's room. Proper and consistent use of gowns and gloves is key to preventing contamination of health care workers' hands. Alcohol hand hygiene products do not kill or remove *C. difficile* spores, but handwashing with soap and water removes, at best, 1 log of spores, even under experimental conditions where proper handwashing technique is ensured. Thorough cleaning of the environment is essential to eliminate spores. Although not necessary if thorough environmental cleaning is accomplished, a sporicidal agent (e.g., sodium hypochlorite) is often used as well. Preventing unnecessary antibiotic use and avoiding high-risk antibiotics (e.g., clindamycin, fluoroquinolones, and extended-spectrum cephalosporins) decreases the risk of colonization and infection by preserving the microbiome, and it is likely the most effective means at preventing *C. difficile* infection.

A concerning trend is the increasing concomitant use of oral vancomycin (125 mg daily) to prevent *C. difficile* infection while patients are receiving other antibiotics in the absence of well-done trials with adequate follow-up.[13] Oral vancomycin is highly disruptive to the microbiome and leads to a greater alteration of the microbiome and a higher risk for *C. difficile* infection once it is stopped. Probiotics are not effective for preventing *C. difficile* infection.

Research is ongoing to assess interventions aimed at asymptomatic *C. difficile* carriers. *C. difficile* toxoid vaccine is currently in phase III trials.

PROGNOSIS

The vast majority (about 80 to 85%) of symptomatic cases resolve after the implicated antibiotic is discontinued and a 10-day course of fidaxomicin or vancomycin is completed, but patients with refractory, fulminant disease eventually require colectomy. The incremented mortality rate of *C. difficile* infection for hospitalized patients may be as high as 7%, with the majority of fatalities occurring in patients over age 65 years, but the overall 30-day mortality appears to be about 15% because of patients' ages and comorbid conditions. For patients who have recurrences, the risk of death is 33% higher than for patients with a single episode.

CLOSTRIDIUM PERFRINGENS TYPE A DIARRHEA

C. perfringens type A causes food poisoning after the ingestion of food, usually meat, that is heavily contaminated with enterotoxin-producing strains. Storage at room temperature rather than refrigeration is typically the underlying cause. The ingested vegetative bacteria sporulate and produce enterotoxin in the small intestine. After an incubation period of 7 to 15 hours, patients develop usually mild and self-limited diarrhea and abdominal pain.

In hospitalized or institutionalized patients, this bacterium can cause severe and protracted infectious diarrhea, often in the setting of prior or concomitant use of antibiotics.[14] In institutionalized mentally ill patients, use of antidiarrheal agents has been associated with necrotizing colitis. Diagnostic confirmation relies on detection of *C. perfringens* enterotoxin in the stool or a count of 10^6 or more *C. perfringens* organisms per gram of stool within 48 hours after the onset of a typical illness.

TREATMENT

Most cases are self-limited and do not need treatment. Metronidazole (e.g., 500 mg four times daily for 7 to 14 days) is recommended for patients who have protracted diarrhea. As with *C. difficile* infection, however, diarrhea may recur after successful treatment.

CLOSTRIDIUM PERFRINGENS TYPE C ENTERITIS

C. perfringens type C enteritis, also called enteritis necroticans, is a necrotizing proximal small intestinal infection caused by strains of *C. perfringens* that produce β-toxin. Enteritis necroticans can occur sporadically or in outbreaks, most often in developing countries, where it primarily affects children with severe protein malnutrition (Chapter 197). Enteritis necroticans also occurs sporadically in the developed world, particularly among patients with diabetes. Histopathologic findings include deep small intestinal necrosis with vascular necrosis and hemorrhage in the lamina propria.

Affected patients usually develop severe abdominal pain 12 hours to several days after eating contaminated food. Vomiting and bloody diarrhea are frequent, and the abdomen becomes distended with thickened bowel loops. The diagnosis is usually clinical. Culture to identify specific β-toxin–producing strains of *C. perfringens* remains a research tool.

TREATMENT AND PROGNOSIS

Treatment is primarily supportive, including nasogastric suction and rehydration. Surgical resection of the infected bowel is often required in patients who do not initially respond to supportive measures. Empirical antibiotics (e.g., penicillin, chloramphenicol, metronidazole) are typically prescribed under expert guidance, but their efficacy is unknown. Prognosis, which depends on the extent of disease and the availability of surgery, ranges from spontaneous recovery to death.

NECROTIZING CLOSTRIDIAL TISSUE INFECTION

CLOSTRIDIAL MYONECROSIS (GAS GANGRENE)

Clostridial myonecrosis, or gas gangrene, is a life-threatening infection that can be cause by several *Clostridium* species. Traumatic gas gangrene is typically caused by *Clostridium perfringens*. *Clostridium septicum* is associated with spontaneous gangrene, believed to be related to translocation of the bacterium from the gut associated with an occult neoplasm.

EPIDEMIOLOGY

Traumatic gas gangrene is typically seen after traumatic injury (e.g., motor vehicle accidents, gunshot and knife wounds, crush injuries, and subcutaneous injections), particularly if treatment is delayed. The vast majority of post-traumatic cases are due to *C. perfringens*, but cases also can be associated with *C. septicum*, *C. novyi*, *C. histolyticum*, *C. bifermentans*, *C. tertium*, and *C. fallax*. Approximately 30% of cases occur after bowel or biliary tract surgery because of translocation of bacteria across the gut wall, often in association with adenocarcinoma of the colon. Infection can also occur in the setting of neutropenic enterocolitis after intense chemotherapy for treatment of acute leukemia.

PATHOBIOLOGY

C. perfringens is found worldwide in soil and feces. Deep penetrating trauma can introduce spores and foreign bodies, thereby creating conditions conducive to an anaerobic environment with a low-oxidation-reduction potential and acidic pH, which support germination of spores and growth of clostridial organisms. *C. perfringens* is able to produce at least 12 toxins, but α-toxin and θ-toxin are believed to be the most important[15] for both the widespread tissue necrosis and the characteristic absence of an inflammatory tissue response. These toxins cause a rapid, irreversible ischemic muscle necrosis due to formation of intravascular aggregates of platelets and neutrophils. These aggregations then impede translocation of inflammatory cells from the vasculature to the site of infection. These toxins also contribute to shock by depressing myocardial contractility and reducing vascular resistance.

The mechanism that facilitates the translocation of *C. septicum* across the gut wall in the presence of a malignancy is unknown. *C. septicum* produces an α-toxin, unrelated to the *C. perfringens* α-toxin, that causes cell death and changes in microvascular profusion.

CLINICAL MANIFESTATIONS

Traumatic clostridial myonecrosis usually presents with sudden onset of severe pain at the site of injury.[16] The mean incubation period is less than 24 hours, but onset can be several weeks after the injury. The infected area initially may appear pale but rapidly progresses to a bronze appearance, followed by purple or red discoloration and then bullae formation. The skin becomes tense and exquisitely tender. The drainage is described as having a "dish water" appearance and smells "foul-sweet." Refractory hypotension unresponsive to fluid resuscitation is common. Approximately 15% of patients are bacteremic, sometimes complicated by brisk intravascular hemolysis. Renal failure and multisystem organ failure typically ensue. Postoperative gas gangrene should be suspected if a surgical site infection develops less than 24 hours after bowel or biliary surgery.

Spontaneous clostridial myonecrosis presents with abrupt onset of severe muscle pain. Infection progresses rapidly with development of edema and bullae. This syndrome is associated with colonic neoplasms (both known and occult), neutropenic enterocolitis, leukemia, and inflammatory bowel disease.

DIAGNOSIS

Patients typically present with severe pain at the site of infection with rapid progression from edema to discoloration to the formation of bullae. Patients typically have signs and symptoms of systemic toxicity. Gas in the tissue may be evident by crepitation on palpation or on imaging, but surgical intervention for suspected infection should not be delayed to obtain imaging to confirm the presence of gas. Drainage may be present or aspirated, and Gram stain characteristically reveals abundant gram-positive bacilli without inflammatory cells. Nucleic acid testing has too low a sensitivity to be depended upon.[17] Surgical exploration typically demonstrates muscle that does not bleed or contract when stimulated. Muscle tissue is grossly edematous and may have reddish-blue to black discoloration.

TREATMENT

Prompt recognition, surgical inspection, and aggressive (and often extensive) surgical debridement are necessary to improve survival. Initial treatment while awaiting antimicrobial susceptibility testing should be a combination of penicillin (or a β-lactam/β-lactamase combination or carbapenems for polymicrobial infections) and clindamycin under expert guidance. *C. perfringens* is more likely to be resistant to clindamycin, but clindamycin is preferred for susceptible isolates because it reduces the production of toxin. Other antibiotics with activity against susceptible strains include metronidazole, tetracyclines, and chloramphenicol.

PREVENTION

Prolonged application of tourniquets should be avoided, if possible, to maintain vascular integrity. Prompt surgical exploration of traumatic wounds with debridement of devitalized tissue; removal of foreign bodies, dirt, and debris; and drainage of hematomas are key to preventing traumatic gas gangrene.

PROGNOSIS

In one series, all patients who died had shock at the time of diagnosis, and 40% of patients with shock died compared with 20% overall. Other factors associated with a worse prognosis include advanced age, leukopenia, and hemolysis. Factors associated with a better prognosis include younger age, single limb involvement, and early aggressive surgical debridement.

PAENICLOSTRIDIUM SORDELLII

P. sordellii is a rare, gram-positive, anaerobic, spore-forming rod. It produces several toxins, some of which are antigenically similar to *C. difficile* toxins A and B, which can lead to overwhelming sepsis, necrotizing infections, and death, mainly in postpartum women, injection drug users, and survivors of trauma.

EPIDEMIOLOGY

P. sordellii can be found worldwide in sewage, soil, the intestinal tract of animals, the intestinal tracts of about 0.5% of humans, and the vaginal tracts of 0.5 to 10% of women. Clinical infection can occur after traumatic wounds, childbirth, medical or spontaneous abortion, and injection of drugs into the skin or muscle ("popping").

PATHOBIOLOGY

The main *P. sordellii* toxins are believed to be the lethal toxin and the hemorrhagic toxin, both of which are encoded by genes that are located on plasmids, which not all *P. sordellii* carry. These toxins, which are antigenically similar to *C. difficile* toxins A and B, impair cytoskeletal organization and can cause massive capillary leakage, thereby leading to progressive edema. They also can cause toxic shock even with minimal signs of local infection.

CLINICAL MANIFESTATIONS

After childbirth or after (spontaneous, medical, or surgical) abortion, patients typically present within a week with nausea, vomiting, diarrhea, tachycardia, and hypotension in the absence of fever. The uterus is often, but not always, tender on examination and enlarged on imaging. Capillary leak results in vascular collapse, toxic shock, diffuse edema, pleural and peritoneal effusions, and hemoconcentration with a hematocrit level as high as 80%. The white blood cell count is typically >50,000 cells/μL and can exceed 200,000 cells/μL.

P. sordellii is associated with necrotizing skin and soft tissue infections after trauma and with the injection of drugs into the skin or soft tissue, especially with the use of black tar heroin (a freebase form of heroin that is dark in color and sticky like tar or hard like coal due to crude processing methods that leave behind impurities). Patients typically present with necrotizing fasciitis at the site of injection, often with hypotension. Infections, which are typically polymicrobial, may occur in clusters of drug users because of shared use of a contaminated drug.

DIAGNOSIS

The diagnosis of *P. sordellii* infection can be challenging due to lack of specific symptoms before overwhelming infection leads to an almost universally fatal outcome. Infection should be suspected in a woman who presents within days of childbirth or an abortion with nausea, vomiting, or diarrhea with leukocytosis. PCR of material from the site of infection is the test of choice.

TREATMENT AND PROGNOSIS

Aggressive supportive care and surgical removal of infected tissue are paramount. Initial antimicrobial therapy should be broad spectrum and cover gram-positive, gram-negative, and anaerobic organisms since infections due to *P. sordellii* are frequently polymicrobial. Due to the infrequency of infections caused by *P. sordellii*, definitive treatment has not been identified, but antibiotics with in vitro activity against *P. sordellii* include β-lactams with anaerobic activity, carbapenems, clindamycin, metronidazole, and chloramphenicol given under expert supervision. Antitoxin is not currently available. Despite treatment, reported mortality is 100% with infection after childbirth and abortion and 50% with injection drug use.

CLOSTRIDIUM NOVYI INFECTION IN INJECTION DRUG USERS

C. novyi is found in soil and feces with a worldwide distribution. Some strains are infected with a phage that has the gene for α-toxin, a large clostridial toxin. As with other large clostridial toxins produced by *C. difficile* and *P. sordellii*, it glucosylates cellular GTPase proteins, thereby leading to the dysfuction of the actin cytoskeleton and cell death. Clusters resulted in 295 cases of infection among people who injected heroin into skin and muscle ("popping") in the United Kingdom from 2000 to 2009. Infections are associated with injection site edema, necrotizing fasciitis, generalized edema, and pleural effusions. Infections tended to be polymicrobial. Treatment involves surgical debridement and broad-spectrum antibiotics under expert supervision.

NEUROTOXIC CLOSTRIDIAL INFECTIONS

BOTULISM

DEFINITION

Botulism, which is caused by the action of botulinum toxin, is characterized by a descending flaccid paralysis.

The Pathogen

C. botulinum, which is a gram-positive, spore-forming obligate anaerobe, is widely distributed in agricultural products, soil, and marine environments. Each strain produces one of eight toxins designated by the letters A to H. The seven known botulinum neurotoxin–producing species of *Clostridium* include *C. baratii, C. argentinense, C. butyricum*, and subtypes of these species. All these neurotoxins produce the same syndrome; the usual causes of disease in humans are types A, B, and E, with rare cases caused by type F and the other types.

EPIDEMIOLOGY AND PATHOBIOLOGY

Botulism in humans is generally foodborne, wound-related, or infantile. Rarely, botulism may be iatrogenic when too much botulinum toxin is injected for cosmetic reasons or the injection is inadvertently systemic. Botulinum toxin is also a potential bioterrorism agent (Chapter 19) if inhaled or ingested.

Worldwide, foodborne botulism is most common, most often due to type A toxin, but with marked geographical differences. In the United States, the Centers for Disease Control and Prevention (CDC) has recorded hundreds of outbreaks of foodborne botulism, usually from home-canned vegetables or fermented foods, occasionally from commercially preserved and restaurant-prepared foods.[18] However, most cases are sporadic, with Alaska accounting for about one-third of cases, usually type E, related to fermented fish and marine mammals prepared and consumed by native Alaskans. In Europe, meat and meat products are more frequently implicated, with type B toxin predominating. In China, vegetable products contaminated with type A toxin predominate.

Infantile botulism is caused by the intestinal production of botulinum toxin, usually type A or type B, after presumed ingestion of spores and colonization of the colon. Contaminated honey is one source, but most often the origin is never identified. The symptoms usually start as constipation followed by poor feeding, weak cry, lethargy, and generalized weakness. This form of botulism rarely occurs in adults but has been reported in patients with anatomic or functional gut abnormalities, such as blind pouches secondary to a side-to-side intestinal anastomosis.

Wound botulism, which is the least common form, occurs sporadically in traumatic wounds that have been contaminated by spores in soil. Outbreaks have been described in black tar heroin users who inject the drug intramuscularly or subcutaneously. Most cases are due to type A or type B toxin.

Botulinum toxin is considered a prime potential bioterror agent (Chapter 19). Potential distribution methods include contamination of food, water, or commercial beverages, as well as aerosolization in densely populated locales. A single release of aerosolized toxin could potentially incapacitate or kill 10% of the population within a 0.5-km radius.

Iatrogenic botulism is an uncommon but growing concern because of the increasing use of botulinum toxin for cosmetic or therapeutic purposes. Cosmetic doses are far too low to cause systemic disease, but unlicensed products with high concentrations may cause systemic symptoms. Higher doses used for movement disorders (Chapter 379) have occasionally caused systemic botulism.

The flaccid paralysis of botulism is due to blockade of the transmission of acetylcholine across the neuromuscular junction of presynaptic motor neurons

that innervate muscles. For a 70-kg human, the estimated lethal dose of purified botulinum toxin A is 0.09 to 0.15 μg when given intravenously, 0.8 to 0.9 μg when inhaled, and 70 μg when given orally.

CLINICAL MANIFESTATIONS

Symptoms typically develop 10 hours to 5 days after consuming a suspect food, such as preserved or home-canned foods. The clinical presentation begins with symmetrical palsies of cranial nerves III, IV, and VI with blurred vision and diplopia.[19] If cranial nerves VII or IX are affected, patients develop expressionless facies with dysphagia, dysarthria, and, rarely, dysphonia. Patients next develop a symmetrical descending flaccid paralysis, with potential involvement of respiratory muscles. Nausea, vomiting, abdominal pain, and diarrhea are common early in the illness, and constipation may occur as paralysis develops. Progression over hours or days and the extent of disease are highly variable, with symptoms sometimes restricted to a few cranial nerves but sometimes progressing to complete paralysis of all voluntary muscles.

Neurologic examination shows ptosis, dilated pupils with a sluggish reaction, bilateral cranial nerve VI paresis, and a diminished gag reflex, followed by descending motor neuron involvement. Deep tendon reflexes are diminished or absent. Cognition is often retained, and vital signs are normal.

DIAGNOSIS

The clinical presentation of an acute flaccid paralysis involving the cranial nerves, particularly including bilateral dysfunction of cranial nerve VI, should prompt the inclusion of botulism in the differential diagnosis, especially if more than one person is affected. The generalized weakness and descending paralysis seen in botulism are in contrast to the ascending paralysis of Guillain-Barré syndrome (Chapter 388). In the absence of a suspect food, another source, such as potentially infected wounds and drug injection sites, should be sought. Bioterrorism-associated botulism could unfortunately be associated with large numbers of cases that may not have a typical food or wound source.

Botulinum toxin can be detected by specialist (public health) laboratories in food or in serum, stool, or gastric contents collected before the administration of antitoxin. Culture of stool and suspect food or wounds is also indicated. About one-third of adult patients with clinical evidence of foodborne botulism have detectable toxin in sera and/or in stool, and the bacterium can be recovered from stool in approximately two-thirds of cases. For wound botulism, recovery of *C. botulinum* from wound cultures or detection of toxin in serum is diagnostic.

The differential diagnosis includes myasthenia gravis (Chapter 390), Guillain-Barré syndrome (Chapter 388), tick paralysis (Chapter 383), cerebrovascular accident (Chapters 376 and 377), trichinosis (Chapter 327), Eaton-Lambert syndrome (Chapter 390), hypocalcemia (Chapter 227), hypermagnesemia (Chapter 105), organophosphate poisoning (Chapter 96), atropine poisoning (Chapter 96), and paralytic poisoning by shellfish or puffer fish (Chapter 96). On electromyography, findings are similar in both botulism and Eaton-Lambert syndrome. Cerebrospinal fluid analysis and cranial imaging are normal in botulism.

TREATMENT

Clinicians who suspect botulism should contact their state health department and can obtain expert advice from the CDC Emergency Operations Center (telephone: 770-488-7100). Similar public health agencies should be contacted in other countries.

Early administration of antitoxin is key and should not be delayed until microbiologic results are available.[20] Antitoxin does not reverse paralysis or neutralize toxin already bound to nerve endings, but it prevents progression by neutralizing circulating unbound toxin.

The standard treatment of adults is heptavalent botulinum antitoxin obtained through a CDC-sponsored FDA investigational new drug protocol. Heptavalent botulinum antitoxin contains equine-derived antibodies to all seven known botulinum toxin types (A to G). Since the antitoxin is derived from horses, hypersensitivity reactions can occur. BabyBIG (botulism immune globulin), which is a human-derived treatment for infantile botulism types A and B, is available through the California Infant Botulism Treatment and Prevention Program.

Gastric lavage, cathartics, or enemas can be used early during management to remove gastrointestinal tract toxin. Because of the risk of respiratory failure, which occurs in about 20% of cases in foodborne disease and about 60% of cases of infantile botulism, patients' respiratory status must be monitored carefully. Other supportive care commonly includes enteral or parenteral feeding (Chapter 198) and positioning in the reverse Trendelenburg position. Antibiotic treatment is unnecessary, except for wound botulism.

PREVENTION

Destroying spores in the original food source by appropriate heating, inhibiting germination, or denaturing preformed toxin (also by heating) is the basis of prevention of foodborne disease.

PROGNOSIS

Death is usually caused by respiratory failure, but the case-fatality rate has decreased from 60 to 70% for untreated botulism to 3 to 5% with treatment. In the United States, infantile botulism has a mortality rate of less than 1%. Patients who survive usually recover completely.

TETANUS

DEFINITION

Tetanus is characterized by generalized rigidity and convulsive spasm of skeletal muscles caused by a neurotoxin produced by *C. tetani* at the site of injury.[21]

The Pathogen

C. tetani is a gram-positive, anaerobic, slender, motile bacillus whose spores have a characteristic shape resembling a drumstick or tennis racket. The vegetative bacteria produce tetanospasmin, which is a protein neurotoxin whose heavy chain binds neuronal cells and whose light chain blocks the release of neurotransmitters.

EPIDEMIOLOGY

C. tetani can be found in up to a quarter of soil samples, particularly when animal manures have been applied. *C. tetani* can also be present in the feces of a variety of domestic and farm animals and poultry.

Clinical tetanus is most common in warm climates and in highly cultivated rural areas of developing countries, where an estimated 60,000 neonatal cases occur annually in low-income countries.[22] Diabetes, a history of immunosuppression, and intravenous drug use are risk factors for tetanus. An average of about 30 cases of tetanus are reported annually in the United States.

PATHOBIOLOGY

Tetanus neurotoxin, which is sometimes referred to as tetanospasmin, is lethal in humans at a dose of 2.5 ng/kg, thereby placing it among the most potent known microbial toxins. Clinical tetanus usually occurs following *C. tetani* contamination of a wound in which the oxygen tension is low because oxygen is toxic to *C. tetani*. *C. tetani* wound contamination is usually via trauma or surgery or at a drug injection site, burn, skin ulcer, or immature umbilical cord. In a low-oxygen setting, spores can germinate and produce tetanospasmin, which binds the peripheral nerve terminals and is then transported (approximately 75 to 250 mm/day) intra-axonally within membrane-bound vesicles to spinal neurons. The light chain passes to the presynaptic terminals, where it blocks the release of neurotransmitters by inhibitory afferent motor neurons. Loss of inhibitory action results in sustained muscle contraction. Toxin binding is irreversible, so recovery depends on the growth of new axon terminals.

CLINICAL MANIFESTATIONS

After a 3- to 21-day (mean: 8 days) incubation period, depending primarily on the distance between the site of injury and the central nervous system, generalized tetanus, which is the most common manifestation, occurs in 80 to 90% of reported cases in the United States. Shorter incubation periods are generally associated with more severe symptoms. Generalized tetanus is characterized by a persistent tonic spasm with short intermittent exacerbations, invariably involving the neck and jaw. This trismus (lockjaw), which is the initial complaint in about three-quarters of cases, often brings patients to a dentist or oral surgeon. Other early symptoms and signs include irritability, restlessness, diaphoresis, and dysphagia with hydrophobia and drooling. Persistent spasms of the paraspinous muscles may cause opisthotonos. As the disease progresses, all muscles contract, with larger muscles dominating smaller muscles. Noise or tactile stimuli may precipitate spasms and generalized convulsions. Involvement of the autonomic nervous system may result in laryngeal spasm, labile blood pressure, cardiac arrhythmias, profound diaphoresis, hyperthermia, rhabdomyolysis, and urinary retention. Complications include dehydration, bacterial infections, fractures from sustained contractions, and pulmonary emboli. However, patients typically remain lucid and afebrile, unless they have complicating infections.

Local tetanus is rare, shows considerable variation in severity, and is characterized by persistent muscle contractions or spasms in the extremity associated with a contaminated wound. In more severe cases, local painful spasms progress to generalized tetanus. Cephalic tetanus is also rare and generally follows a head injury or *C. tetani* infection of the middle ear. After a 1- or 2-day period,

clinical symptoms consist of isolated or combined dysfunction of the cranial motor nerves, most frequently cranial nerve VII. Dysfunction may remain localized or progress to generalized tetanus, and survival rates are poor.

Neonatal tetanus is an age-specific presentation of generalized tetanus, usually when *C. tetani* contaminates the umbilical stump soon after birth. It occurs primarily in underdeveloped countries, where it accounts for up to half of all neonatal deaths.

DIAGNOSIS

The diagnosis of tetanus is usually clinical, and *C. tetani* is recovered from wound or tissue culture in only about one-third of cases. Cerebrospinal fluid analysis is entirely normal. The differential diagnosis includes dystonic reactions (Chapter 379), seizure disorders (Chapter 372), hypocalcemic or alkalotic tetany (Chapter 227), alcohol withdrawal (Chapter 364), and strychnine poisoning (Chapter 96). Although dystonic reactions may resemble tetanus, they can be distinguished from tetanus by their rapid response to anticholinergic agents (Chapter 96). Strychnine poisoning can be diagnosed by detecting it in blood or urine.

TREATMENT

Patients with tetanus require intensive care with meticulous respiratory support, control of muscle spasms, control of autonomic nervous system dysfunction, passive and active immunization, antibiotics, and surgical debridement. The severity of disease may be attenuated by partial immunity, so some patients have mild disease, whereas other patients have more severe disease.

Supportive Care

Many patients require endotracheal intubation, benzodiazepine sedation, and neuromuscular blockade. A tracheostomy should be placed if the endotracheal tube causes spasms. A feeding tube is usually required for nutritional support.

Benzodiazepines, usually diazepam given intravenously in 5-mg increments, are used to control spasms and provide sedation. Very high doses may be required before symptoms resolve, at which time benzodiazepines should be tapered over at least 2 weeks to prevent withdrawal. If benzodiazepines cannot control spasms, neuromuscular blockade with vecuronium (6 to 8 mg/hour) is required.

Autonomic Nervous System Dysfunction

Autonomic nervous system dysfunction, which generally reflects the excessive release of catecholamines, is usually treated with labetalol (0.25 to 1.0 mg/minute) to control blood pressure. Hypotension may require norepinephrine (Chapter 92). Bradycardia may require a pacemaker (Chapter 51).

Specific Care

Human tetanus immunoglobulin (a single dose of 500 IU intramuscularly) should be administered as soon as possible to neutralize toxin that has not entered neurons. Pooled intravenous immunoglobulin and equine tetanus immunoglobulin are alternatives, but they should not be used if human tetanus immunoglobulin is available.

Passive immunization should be accompanied by active immunization with a standard three-dose schedule of tetanus toxoid at a site separate from where immunoglobulin is administered. Patients also should be given metronidazole (2 g/day intravenously for 7 to 10 days). Any wounds should be debrided and cleaned.

PREVENTION

Tetanus toxoid vaccination (Chapter 15) is extremely effective, and nearly all cases of tetanus occur in unimmunized or inadequately immunized individuals. Protective levels of serum tetanus antitoxin persist for at least 10 years in persons who complete the primary series. The incremental benefit of routine booster shots for preventing tetanus appears to be very small, at best,[23] but Td (tetanus and diphtheria toxoids adsorbed for adult use) is recommended every 10 years (Chapter 15). All adults aged 19 years and older who have not yet received a dose of Tdap (tetanus toxoid, reduced diphtheria toxoid, and acellular pertussis) should receive a single dose regardless of the interval since the last Td to protect against pertussis.[24]

Prevention of tetanus after injury (Table 271-1) requires optimal wound management, assurance of adequate immunity with a tetanus booster if indicated, and consideration of antibiotic prophylaxis. Debridement or surgery may be required to remove necrotic tissue, purulent collections, or foreign bodies that promote the low-oxygen conditions necessary for tentaus spores to germinate. Passive immunization with tetanus immune globulin is recommended only for patients who have not had adequate prior immunization and whose wound is at high risk of contamination with tetanus based on the interval since the injury, the presence of devitalized tissue, the depth of the injury, or the prlonged presence of a foreign body. Point-of-care testing for tetanus immunity is a potential method for reducing unnecessary re-immunization.[25]

TABLE 271-1 GUIDE TO TETANUS PROPHYLAXIS IN ROUTINE WOUND MANAGEMENT

HISTORY OF ADSORBED TETANUS TOXOID (NO. OF DOSES)	*CLEAN MINOR WOUNDS*		*ALL OTHER WOUNDS**	
	Tdap OR Td†	TIG‡	Tdap OR Td†	TIG‡
<3 or unknown	Yes	No	Yes	Yes
≥3	No§	No	No¶	No

*Such as (but not limited to) wounds contaminated with dirt, feces, soil, and saliva; puncture wounds; avulsions; and wounds resulting from missiles, crushing, burns, and frostbite.

†For children younger than 7 years, DTaP (pediatric diphtheria–tetanus toxoid plus acellular pertussis vaccine) is recommended; if pertussis vaccine is contraindicated, DT (pediatric diphtheria–tetanus toxoid) is given. For persons aged 7 to 9 years or 65 years or older, Td (adult tetanus–diphtheria toxoid) is recommended. For persons 10 to 64 years, Tdap (adult tetanus–diphtheria toxoid plus acellular pertussis vaccine) is preferred to Td if the patient has never received Tdap and has no contraindication to pertussis vaccine. For persons 7 years and older, if Tdap is not available or not indicated because of age, Td is preferred to TT (tetanus toxoid alone). Note that pediatric formulations (DT and DTaP) contain an amount of tetanus toxoid similar to that of adult Td, but they contain three to four times as much diphtheria toxoid. DTaP and Tdap vaccines do not contain thimerosal as a preservative.

‡TIG is human tetanus immune globulin. Equine tetanus antitoxin should be used when TIG is not available.

§Yes, if more than 10 years since the last dose.

¶Yes, if more than 5 years since the last dose.

From Gerding DN, Johnson S. Clostridial infections. In: Goldman L, Schafer AI, eds. *Goldman-Cecil Medicine*, 26th ed. New York: Elsevier Health Services; 2019:1890-1897.

Penicillin (500 mg every 6 hours) and metronidazole (500 mg every 6 to 8 hours) for 7 days may be given, but immunization and wound cleansing are more important to prevent tetanus.

PROGNOSIS

Even with antitoxin therapy, symptoms persist usually for 3 to 4 weeks because of the time required for intra-axonal toxin transport, so patients with moderate or severe generalized tetanus usually require hospital treatment for 3 to 6 weeks. The overall mortality rate with generalized tetanus is 20 to 25% despite optimal medical management. Mortality rates are low in partially immunized patients but about 50 to 60% in unimmunized patients despite expert care.[26] The highest mortality rates are at the extremes of age, usually from pneumonia. Patients who recover usually do so completely. Local tetanus has an excellent prognosis, with about a 1% mortality rate, but survival is poor for cephalic tetanus, with a 15 to 30% mortality rate.

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For the General References and other additional features, please visit Elsevier eBooks+ at https://ebooks.health.elsevier.com.

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272 GRAM-POSITIVE ROD INFECTIONS

ROSE KIM, HEATHER CLAUSS, AND ANNETTE C. REBOLI

INFECTIONS CAUSED BY *BACILLUS ANTHRACIS* AND OTHER *BACILLUS* SPECIES

DEFINITION

The genus *Bacillus* includes several species that are closely related phylogenetically. The *Bacillus cereus* group includes *Bacillus anthracis*, which is the causative agent of anthrax; *Bacillus cereus*, which causes food poisoning as well as localized and systemic infections; and *Bacillus thuringiensis*, an insect pathogen that causes eye infections and infections in immunocompromised persons.[1] Other *Bacillus* species that have caused infections in humans include *circulans, licheniformis, megaterium, pumilus, sphaericus*, and *subtilis* (Table 272-1).

The Pathogen

Bacillus species are large, aerobic or facultatively anaerobic, spore-forming, gram-positive bacilli (Fig. 272-1). The major pathogenic species of the *B. cereus* group have plasmids that carry genes for toxin proteins.

EPIDEMIOLOGY

Bacillus species are endemic in soil and water and are found worldwide. Their spores are extremely hardy and are resistant to heat and drying, so they can persist in a dormant state for prolonged periods of time. Spores may survive in soil for decades and may also survive for several years in the interior of buildings where they are protected from ultraviolet light. Spores have also been isolated from foodstuffs, insects, and plants. Persistence of spores in the soil is influenced by a variety of environmental conditions such as higher temperature, low soil moisture content, drought following a period of high annual rainfall, and alkaline pH.

Bacillus anthracis

Anthrax occurs most commonly in Africa, India, the Middle East, Southeast Asia, and parts of Central and South America. Anthrax is enzootic in sub-Saharan Africa, where cases occur in wildlife and domestic animals that ingest or inhale *B. anthracis* spores from the soil while grazing. Cases may be sporadic or occur as part of an outbreak. Human cases in Africa outnumber human cases in most of the rest of the world. In Europe and North America, animal cases are sporadic and human cases are rare. Even a single case in a nonendemic area should generate concern for an act of bioterrorism (Chapter 19).

Human cases of anthrax are usually associated with exposure to infected animals or their products. Cases can occur sporadically or be associated with outbreaks. Implicated products include meat, bone, wool (wool sorters disease), hair, hides, and items made from these materials. Transmission from flies has been reported to cause cutaneous infection.

Inhalational anthrax occurs from breathing in spores from contaminated animal products or after intentional release of spores during an act of bioterrorism. Gastrointestinal anthrax is acquired by ingesting spores or vegetative forms in the meat of infected animals or from contaminated water. Injectional anthrax infections have been reported in injection drug users who used heroin contaminated with anthrax spores.[2]

Several outbreaks have been reported. In a 1979 outbreak in Sverdlovsk, Russia, 70 cases of confirmed inhalational anthrax occurred after an accidental release of spores from a military facility. In the largest human outbreak, approximately 10,000 cases, almost all of which were cutaneous, and 182 deaths occurred over a 6-year period from 1979 through 1985 in Zimbabwe. In 2001, letters containing anthrax spores were sent via the U.S. Postal Service to recipients in Florida, New York City, and Washington, D.C. Ultimately, 22 people were infected, with 11 cutaneous infections, 11 inhalational infections, and 5 deaths. Approximately 10,000 U.S. citizens received postexposure antibiotic prophylaxis to contain the outbreak.

Bacillus cereus

The foods most commonly associated with *B. cereus* food poisoning include meats, vegetables, and sauces. The emetic form of *B. cereus* food poisoning is frequently associated with starchy foods such as rice, especially fried rice, and potato salad. Improper storage and handling of food is the most likely cause. Contaminated rice has often been stored at room temperature to preserve its texture and then been reheated. Reheating may eliminate the organism and the diarrheal toxin but not the emetic toxin.

B. cereus, which is the most frequent bacteria that contaminates breast milk,[3] can cause severe infection in very low-birthweight newborns. *B. cereus* can contaminate the product during collection, storage, or delivery. Cases of keratitis have been linked to contamination of contact lenses.

TABLE 272-1 NON-ANTHRAX *BACILLUS* SPECIES ASSOCIATED WITH HUMAN DISEASE

SITE OF INFECTION	PATHOGEN	CLINICAL SYNDROME
Blood stream	*B. cereus* *B. circulans* *B. licheniformis* *B. megaterium* *B. pumilus* *B. sphaericus* *B. subtilis*	Bacteremia Catheter-related sepsis
Bone/joints	*B. cereus* *B. alvei*	Osteomyelitis Septic arthritis
Brain/meninges	*B. cereus* *B. circulans* *B. megaterium* *B. subtilis* *B. licheniformis* *B. pumilus* *B. sphaericus*	Meningoencephalitis Meningitis CSF shunt infections Meningitis post-CSF leak
Eye	*B. cereus* *B. circulans* *B. thuringiensis*	Endophthalmitis Keratitis Corneal ulcers
Gastrointestinal	*B. cereus* *B. licheniformis* *B. subtilis* *B. pumilus*	Emetic food poisoning Diarrheal food poisoning
Heart	*B. cereus* *B. circulans* *B. subtilis*	Endocarditis
Ear	*B. subtilis*	Otitis Mastoiditis
Lung	*B. cereus* *B. subtilis* *B. sphaericus*	Pneumonia Empyema
Soft tissue	*B. cereus* *B. pumilus* *B. thuringiensis*	Cellulitis Necrotizing fasciitis Abscess
Wound	*B. cereus* *B. circulans* *B. subtilis* *B. thuringiensis*	Post-traumatic or post-surgical wound infections Infected burns

CNS = central nervous system; CSF = cerebrospinal fluid.

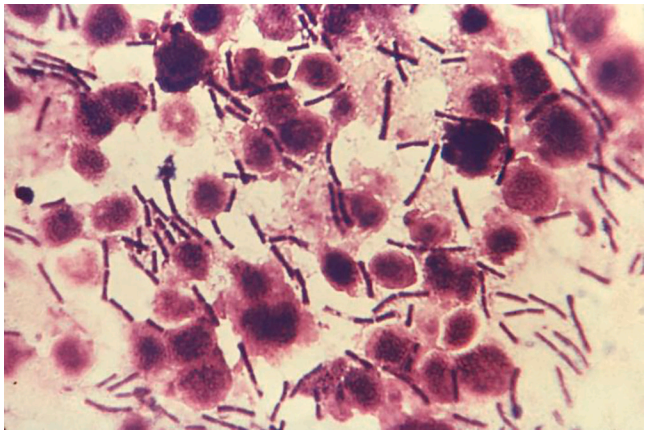

FIGURE 272-1. Gram-positive bacilli of *Bacillus anthracis*. (Source: phil.cdc.gov.)

ABSTRACT

Gram-positive bacillary organisms, including *Bacillus, Corynebacteria, Erysipelothrix*, and *Listeria*, are rod-shaped bacteria that are ubiquitous and commonly found in soil and water. Depending upon the genus, they may be spore-forming or non-sporulating. As a group, they are potentially serious but relatively rare causes of disease in humans, and sometimes they are erroneously dismissed as laboratory contaminants. Many cause zoonotic infections.

KEYWORDS

Bacillus anthracis
anthrax
Bacillus cereus
Corynebacterium diphtheriae
diphtheria
Listeria monocytogenes
listeriosis
Erysipelothrix
Erysipeloid infection

PATHOBIOLOGY

Bacillus anthracis

Cutaneous anthrax occurs when *B. anthracis* spores are introduced through microscopic or gross breaks in the skin, and injectional anthrax occurs via direct injection through intact skin. In classic cutaneous anthrax, a pustule forms at the inoculation site and ulcerates as the result of coagulation necrosis. Extensive edema surrounds the lesion. The organism multiplies locally and may spread to the blood stream or other organs via the lymphatics. The site of injectional anthrax has extensive edema but lacks the other findings of cutaneous anthrax.

Upon inhalation, *B. anthracis* spores are transported by alveolar macrophages and dendritic cells to regional lymph nodes. The spores germinate in blood and tissue. Following germination, vegetative cells produce an antiphagocytic capsule[4] and anthrax toxin proteins, which are important virulence factors. Anthrax toxin consists of three proteins: protective antigen, edema factor, and lethal factor. These toxins neutralize the innate and adaptive immune systems to cause fatal disease. The capsule not only prevents phagocytosis but also enhances cytotoxicity and induces production of cytokines. Pulmonary infiltrates, which are seen radiographically in approximately a third of cases, are areas of pulmonary edema and hyaline membrane formation, not bacterial pneumonia. Pleural effusions are caused by blockage of normal lymphatic flow in the mediastinum.

Gastrointestinal anthrax may be classified as primary or secondary. Primary gastrointestinal anthrax occurs after the ingestion of meat from an animal infected with anthrax, whereas secondary gastrointestinal anthrax results from *B. anthracis* bacteremia. Spores invade the gastrointestinal mucosa, where they cause necrosis and ulceration that may lead to hemorrhage. Spores are then transported to mesenteric lymph nodes where they replicate and cause bacteremia.

Meningitis, which may occur as a complication of any form of anthrax, results from hematogenous seeding of the meninges. The meninges are edematous and hemorrhagic. Diffuse cerebral arteritis may occur.

Bacillus cereus

The pathogenic potential of *B. cereus* is highly variable and is based on a number of virulence factors. Enterotoxins ingested with contaminated foods cause diarrhea. These toxins are heat labile and may be removed by heating food to high temperatures that kill the organism and neutralize the toxin. In addition to ingestion of preformed toxin in food, the organism can produce toxin within the gastrointestinal tract. Emesis is caused by the toxin, cereulide, which is heat stable and preformed in food. Cereulide toxin genes are found only in certain strains of *B. cereus*, whereas enterotoxin genes are found more broadly. Some highly pathogenic strains of *B. cereus*, which possess *B. anthracis* virulence plasmids that express anthrax toxins and have a capsule, have been isolated from animals in sub-Saharan Africa and from human cases. These strains produce a large amount of sphingomyelinase, which contributes to the pathogenicity.

CLINICAL MANIFESTATIONS

Bacillus anthracis

Anthrax manifests as four types of infection: cutaneous, inhalational, gastrointestinal, and injectional.[5] Most common is the cutaneous form, which accounts for approximately 95% of cases. Two to five days after inoculation of spores into the skin, a pruritic lesion appears as a painless papule that evolves into a vesicular stage and then to a painless black eschar surrounded by edema and a ring of vesicles, described as a "pearly wreath" (Fig. 272-2). Injectional anthrax is an unusual form of cutaneous anthrax that has been reported in injection drug users who injected heroin contaminated with *B. anthracis* into the skin or the blood stream. Skin lesions are not typical for cutaneous anthrax. Edema is prominent at the injection site.

For inhalational anthrax, the incubation period is usually 1 to 7 days but can be up to 60 days. The initial clinical presentation is nonspecific and consistent with an influenza-like illness with fever, malaise, dry cough, dyspnea, and chest pain. The hallmarks of inhalational anthrax are mediastinal lymphadenopathy, hemorrhagic mediastinitis, and pleural effusions. A chest radiograph or computed tomography (CT) scan reveals a widened mediastinum, as well as large, serosanguinous or hemorrhagic, usually bilateral pleural effusions (Fig. 272-3). High levels of lethal factor toxin have been found in pleural fluid. If treatment is delayed, patients develop severe respiratory distress and septic shock.

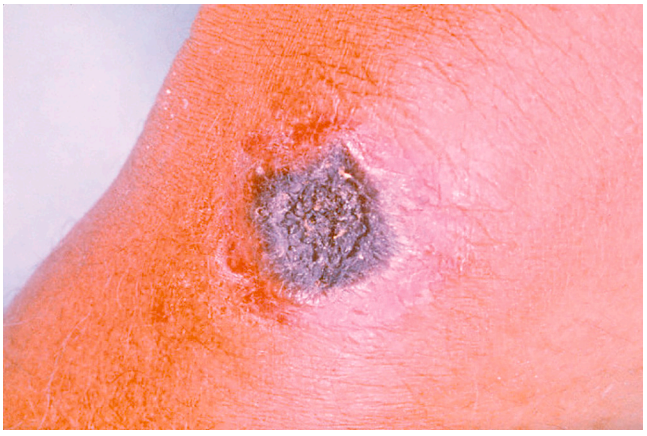

FIGURE 272-2. Cutaneous anthrax with classic black eschar. (Source: phil.cdc.gov.)

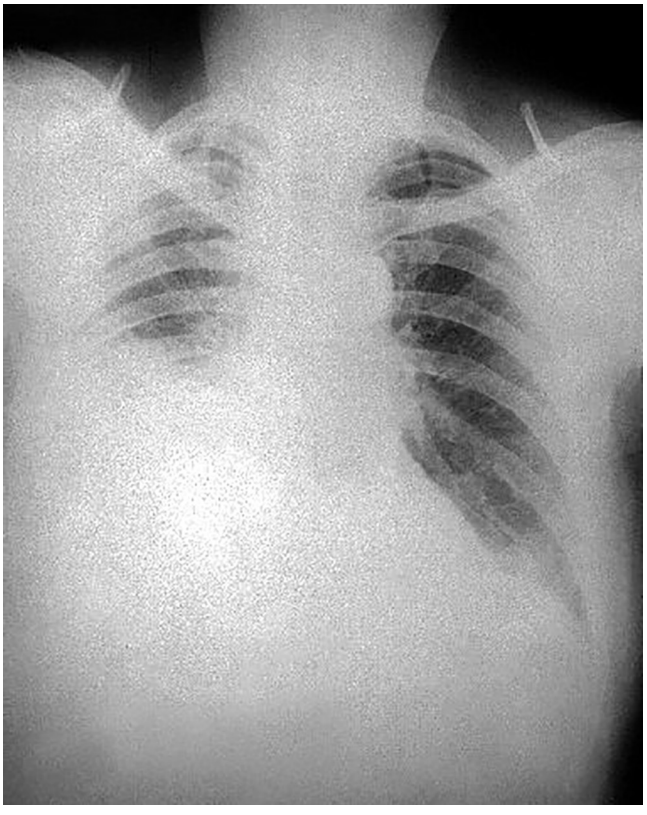

FIGURE 272-3. Chest radiograph of inhalational anthrax showing widened mediastinum and pleural effusion. (Source: phil.cdc.gov.)

Gastrointestinal anthrax, which is very uncommon and is responsible for only 1% of cases, may manifest as oropharyngeal or intestinal disease. Symptoms usually occur 1 to 5 days after ingestion of contaminated meat or drinking water. Symptoms of oropharyngeal anthrax include severe pharyngitis, dysphagia, odynophagia, and fever. Edema and lymphadenopathy may be so severe that they may cause respiratory distress. An ulcerative lesion may be seen in the mouth or pharyngeal area. Pseudomembranes may form over the lesion and may mimic diphtheria. Intestinal anthrax presents with nausea, vomiting, and fever followed by abdominal pain that may be so severe that it mimics an acute abdomen. Patients may have hematemesis, bloody diarrhea, and ascites. Secondary meningitis may occur. Gastrointestinal anthrax is likely to be associated with bacteremia/sepsis and seeding of other organs.

Anthrax meningitis occurs when bacteremia seeds the meninges during cases of inhalational or gastrointestinal anthrax. It occurs in up to 50% of inhalational cases. Symptoms and signs include severe headache, alteration of mental status, nuchal rigidity, other meningeal signs, and diffuse or focal neurologic findings. The course is frequently fulminant, with the development of delirium, seizures, and coma usually occurring within hours of initial

presentation. Cerebrospinal fluid (CSF) is hemorrhagic. Hemorrhage may also be found in the brain parenchyma and the subarachnoid space. Cerebral edema may be present.

Bacillus cereus and Other *Bacillus* Species

B. cereus causes two types of food poisoning: a diarrheal syndrome and an emetic syndrome. Similar to other toxin-mediated food poisoning (Chapter 262), the onset of symptoms with *B. cereus* occurs within 24 hours of eating the contaminated food item and usually within 8 to 16 hours. Cardinal symptoms of the diarrheal syndrome include profuse diarrhea and cramping abdominal discomfort. Fever and vomiting are rare. Onset of symptoms with the emetic form is very rapid and usually occurs within 1 to 5 hours, a time frame that is similar to food poisoning caused by *Staphylococcus aureus* (Chapter 267). Symptoms include nausea and vomiting. Diarrhea has been reported in approximately one third of cases. Both syndromes are usually self-limited and resolve within 24 hours. Rarely, the *Bacillus* toxin may lead to acute liver failure. In addition to *B. cereus*, other *Bacillus* species have been linked to food poisoning and outbreaks.

Of the systemic infections caused by *Bacillus* species, bacteremia is the most common presentation, and *B. cereus* is the most common species isolated. *B. cereus* may also cause a variety of local and systemic infections such as endocarditis; pneumonia; central nervous system (CNS) infection[6]; and infections of the urinary tract, skin, soft tissue, muscle, and wounds. Many of these infections are health care–associated (Chapter 261). Bacteremia can lead to dissemination to other body sites. Endocarditis may occur in prosthetic valves, and rare cases of native valve endocarditis are usually associated with bacteremia secondary to injection drug use. *B. cereus* can also cause eye infections, such as endophthalmitis and keratitis.[7] CNS infections, including meningitis and brain abscess, tend to occur in immunocompromised hosts, especially when they are neutropenic. When the bone marrow recovers and neutropenia resolves, immune reconstitution syndrome can be associated with a transient exacerbation of symptoms of meningitis and brain abscess.

DIAGNOSIS

Bacillus species grow readily in the laboratory on standard culture media and at temperatures of 25 to 37° C. Automated blood culture systems routinely yield growth of *B. anthracis*. Culture is the gold standard for diagnosis of anthrax infection, but polymerase chain reaction (PCR) testing can hasten the diagnosis.

Because of their ubiquitous nature in the environment and because spores can germinate rapidly on laboratory media, non-anthrax *Bacillus* species are frequent laboratory contaminants. Because *Bacillus* species rarely cause human disease and because they are such a common contaminant, identification to the species level is not commonly performed in most laboratories. However, *B. anthracis* should never be dismissed as a contaminant when it is isolated from a clinical specimen.[8]

Bacillus anthracis

For cutaneous anthrax, a Gram stain of vesicular fluid, a scraping from the base of the lesion, or a skin biopsy may show the organism. Gram stain of vesicular fluid reveals bacilli but very few leukocytes. The direct fluorescent antibody test and PCR testing can provide a rapid diagnosis. Cultures are frequently positive.

In inhalational cases, the direct fluorescent antibody test and PCR should be performed on body fluids and tissues. A Gram stain of pleural fluid may also reveal the organism. Blood and pleural fluid cultures are positive.

For suspected gastrointestinal anthrax, PCR testing as well as blood and stool cultures should be obtained. A swab of the base of an oropharyngeal lesion may reveal gram-positive bacilli; culture is frequently positive. If ascites is present, fluid should be cultured and sent for PCR testing.

Bacillus cereus and Other *Bacillus* Species

Both the diarrheal and emetic form of *B. cereus* food poisoning can be diagnosed by culturing the organism from food, stool, or vomitus. *Bacillus* species are easily cultured, but testing is not routinely performed when stool cultures are requested. PCR testing is also useful. Commercial assays for toxin testing are not widely available.

Differentiating *Bacillus* infection from contamination may be difficult. Repeated isolation from a normally sterile body fluid or site indicates infection. Most cases of true bacteremia occur in the presence of an intravascular catheter.

Serology plays a role in diagnosis and may be particularly useful when cultures and PCR are negative. Anti-protective antigen antibody is detectable approximately 1 week after the start of symptoms. Acute and convalescent samples for anti-protective antigen antibody response should be obtained in the first 7 days of illness and repeated at 14 to 28 days.

TREATMENT

Bacillus anthracis

B. anthracis is susceptible to a broad range of antibiotics, including penicillins, first-generation cephalosporins, fluoroquinolones, carbapenems, tetracyclines, macrolides, aminoglycosides, clindamycin, linezolid, rifampin, daptomycin, and dalfopristin-quinupristin.[9] For bioterrorism-associated anthrax, strains are likely to be resistant β-lactams.

The timely administration of antibiotics is essential for all forms of anthrax. For naturally occurring cutaneous anthrax with no evidence of systemic symptoms, the current treatment of choice depending on antibiotic susceptibility testing is a fluoroquinolone (e.g., ciprofloxacin 500 mg orally twice daily) or doxycycline (100 mg orally twice a day) as monotherapy for 7 to 10 days. Alternatives for adults include levofloxacin (750 mg orally once daily), moxifloxacin (400 mg orally once daily), or clindamycin (600 mg orally three times a day).[10] Penicillin VK (500 mg orally every 6 hours) or amoxicillin (1 gram orally every 8 hours) may be used once susceptibility is confirmed. For bioterrorism-related infection, the duration of therapy should be 60 days because of the risk of inhalation exposure.

All other forms of anthrax (inhalational, gastrointestinal, meningeal, injectional, and cutaneous with systemic symptoms) should be treated with two bactericidal antibiotics, a fluoroquinolone (e.g., ciprofloxacin 400 mg IV every 8 hours) plus a carbapenem (e.g., meropenem 2 g IV every 8 hours) if meningitis is suspected. If meningitis has been excluded, monotherapy with a fluoroquinolone or carbapenem should be used at the doses above. Ciprofloxacin is the preferred fluoroquinolone. For very severe or serious disease, an additional antibiotic such as linezolid (600 mg IV every 12 hours) or clindamycin (900 mg IV every 8 hours) is recommended to block protein synthesis and therefore toxin production; linezolid is preferred because of its improved CNS penetration. Penicillin G (4 million units IV every 4 hours) can be substituted for meropenem against penicillin-susceptible strains. Systemic anthrax infection should be treated with combination intravenous antibiotics for a minimum of 10 to 14 days or until clinical improvement, whichever is longer, followed by oral therapy for up to 60 days because of the long duration of viability of spores. Antitoxin therapies, such as anthrax immune globulin or one of the anti-protective antigen monoclonal antibodies (e.g., obiltoxaximab 16 mg/kg IV or raxibacumab 40 mg/kg IV [adult dosage] to 80 mg/kg IV [pediatric dose if weight is 15 kg or less])[11] may be administered along with antibiotics in severe infections, such as inhalational or systemic anthrax with signs of sepsis and in cases of serious inhalational exposures.

Serious forms of anthrax require intensive care unit management. Pleural effusions frequently require drainage. Surgical débridement may be necessary in cutaneous cases of injectional anthrax.

In the absence of controlled studies, corticosteroids (e.g., dexamethasone 10 mg intravenously then 4 mg every 6 hours until clinical improvement) may have a role in the treatment of cerebral edema and increased intracranial pressure in anthrax meningitis. Corticosteroids also have been advocated when severe edema causes airway obstruction, large pleural effusions, or massive ascites.

Bacillus cereus and Other *Bacillus* Species

Antimicrobial therapy is not indicated for the food poisoning syndromes caused by *Bacillus* species. For serious infections, the current treatments of choice are vancomycin, clindamycin, or fluoroquinolones, in consultation with an infectious disease specialist, with doses, routes, and durations varying with the type and extent of the specific infection. Dual therapy with one of these agents plus an aminoglycoside (e.g., gentamicin) may be beneficial. When *Bacillus* species bacteremia is associated with an intravascular catheter or an implanted device, removal is often necessary to effect a cure. Similarly, valve replacement is usually indicated for prosthetic valve endocarditis. Eye disease must be managed by an ophthalmologist. Keratitis can be treated with a topical fluoroquinolone, but intravitreal antibiotics and vitrectomy are indicated for endophthalmitis.

PREVENTION

Bacillus anthracis

Anthrax vaccination is recommended for adults ages 18 to 65 years who may be at risk of coming into contact with anthrax because of occupation, including U.S. military personnel, laboratory personnel who work with *B. anthracis*, and workers such as veterinarians who handle animals or animal products.[12] Vaccination is also recommended for individuals who have been exposed to anthrax in situations such as a bioterrorism attack. Anthrax vaccine adsorbed (BioThrax, licensed in the United States) may be administered as five doses intramuscularly over 18 months or as three doses over 6 months followed by an annual booster for those who continue to be at increased risk of exposure.

Anthrax vaccine precipitated (licensed in the United Kingdom) is an alternative, administered as four doses over 32 weeks followed by annual boosters. A live spore vaccine is available for veterinary use. Immunity is short-lived, so revaccination is recommended on an annual basis.

Exposed persons should receive antibiotic prophylaxis with ciprofloxacin (500 mg orally twice daily) or doxycycline (100 mg orally twice daily) for 60 days, as well as anthrax vaccine at 0, 2, and 4 weeks. Anthrax vaccine is 90% effective in protecting most people from anthrax, including the most deadly form, inhalational anthrax. Vaccination is generally well tolerated. Mild local site reactions, including myalgia at the injection site, headache, and fatigue, are the most common side effects. Persons acutely exposed to anthrax, such as during an intentional release of *B. anthracis* spores, should be decontaminated using soap and water in addition to receiving antibiotic prophylaxis.

Bacillus cereus

Prevention of *B. cereus* food poisoning is best accomplished by the safe preparation and handling of food items. Cooking food adequately kills vegetative organisms and destroys preformed diarrheal toxin but not emetic toxin. If food is not eaten in a timely fashion, it should be refrigerated as soon as possible since cold inhibits the metabolism and production of toxins.

PROGNOSIS

Mortality is approximately 20% for untreated cutaneous anthrax and approximately 30% for untreated inhalational anthrax. Skin lesions heal over a period of 1 to 3 weeks; antibiotic therapy does not affect the evolution of the localized lesion but does prevent bacteremia and serious sequelae. If untreated, inhalational anthrax has a mortality rate of 100%. With earlier recognition and timely initiation of antibiotic therapy, the case fatality rate in the 2001 bioterrorism event was 45%. Without treatment, mortality for gastrointestinal anthrax is approximately 40%. Mortality is higher (95%) if meningoencephalitis develops as a complication.

For *Bacillus* species infections, the risk of poor outcomes usually reflects the patient's underlying illness and the severity of the infection. Mortality for sepsis, meningitis, and endocarditis is higher than for catheter-related bacteremia. Endophthalmitis may lead to blindness.

DIPHTHERIA AND OTHER INFECTIONS CAUSED BY *CORYNEBACTERIA*

DEFINITION

The genus *Corynebacterium* encompasses a large group of bacteria that are typically characterized as irregularly shaped, non-spore-forming, aerobic, gram-positive rods. *Corynebacterium diphtheriae* is the causative organism for diphtheria, which is an acute illness that is mediated by toxin production and presents with a thick, adherent pseudomembrane at the site of infection. *C. diphtheriae* primarily infects the mucosa of the upper respiratory tract (e.g. nose, tonsils, pharynx, larynx), but it can also cause cutaneous disease. *Corynebacterium* species other than *C. diphtheriae* are ubiquitous in the environment (soil and water) and are commensals on skin and mucous membranes in humans. They frequently cause infection in immunocompromised hosts and in patients with indwelling devices.

The Pathogen

Corynebacteria are a heterogeneous group of pleomorphic bacteria. *Corynebacteria* are irregularly shaped, aerobic, gram-positive rods that are unencapsulated, nonmotile, not spore forming, and not acid fast. They typically form arrangements such as palisading or picket-fence configurations.

C. diphtheriae exists in toxigenic and nontoxigenic forms, with four biotypes: *gravis, mitis, intermedius, and belfanti*. Toxigenic strains carry the exotoxin (*tox*) gene that is encoded by a bacteriophage; nontoxigenic strains can be converted to toxigenic strains when the bacteriophage-encoding *tox* gene is transferred via a lysogenic cycle. *C. ulcerans* and *C. pseudotuberculosis*, which are members of the *C. diphtheriae* group, are able to produce diphtheria-like toxin, with similar clinical presentations as *C. diphtheriae*.

EPIDEMIOLOGY

C. diphtheriae

Humans serve predominantly as the natural host for *C. diphtheriae*, but the organism has been isolated from other animal hosts (including domestic animals) on rare occasions. Transmission of infection occurs with close contact, either through inhalation of infected respiratory droplets or through direct contact with infected respiratory secretions or cutaneous lesions. *C. diphtheriae* can survive in the environment for several weeks, and transmission via fomites also occurs. Asymptomatic carriers of *C. diphtheriae* serve as the reservoir for sustained transmission.

In the prevaccine era, diphtheria was a major contributor to morbidity and mortality globally. Nearly 70% of cases occurred in children under the age of 15, with case fatality rates of 5 to 10%. With the widespread use of the diphtheria toxoid vaccine, the annual number of cases of respiratory diphtheria worldwide has steadily declined since the 1980s from approximately 100,000 cases in 1980 to fewer than 9000 in 2017, and most cases in developed countries are attributable to nontoxigenic strains of *C. diphtheriae*.[13] In the United States, only 14 cases of respiratory diphtheria were reported between 1996 and 2018, and only one of the five cases that was culture positive for *C. diphtheriae* was toxigenic.[14]

Nevertheless, large outbreaks of diphtheria have occurred even in the vaccine era, typically in the setting of social or political upheaval. The largest recent resurgence occurred from 1990 to 1998 in several countries of the former Soviet Union, where over 157,000 cases and 5000 deaths were reported. More recent outbreaks have occurred in South America, including Brazil and Venezuela; Southeast Asia, including Indonesia, Thailand, and Laos; Yemen; and Haiti. In developing countries, diphtheria remains a serious disease, especially in areas where access to routine vaccinations is suboptimal. Diphtheria remains endemic in India.

Vaccine-induced immunity wanes over time; older adults who do not receive a booster dose of diphtheria toxoid vaccine are at risk for acquiring infection. A seroprevalence survey in the United States demonstrated diminished levels of protective diphtheria antitoxin antibodies for adults age 70 years and older.

Other *Corynebacteria*

To date, over 100 *Corynebacteria* species other than *C. diphtheriae* have been identified. Although recovery of *Corynebacteria* from clinical specimens was traditionally considered to represent contamination, increasing evidence indicates that *Corynebacteria* cause significant clinical disease, especially in hospitalized and immunocompromised patients.

PATHOBIOLOGY

C. diphtheriae

Respiratory diphtheria occurs when *C. diphtheriae* infects the mucosal surface of the upper airway tract, including the nasopharynx, larynx, or, less commonly, trachea or bronchus. Clinical signs and symptoms are due to exotoxin produced by replicating bacteria. Diphtheria exotoxin is a potent inhibitor of elongation factor 2, which is essential for protein synthesis. Toxin-mediated effects lead to local tissue edema, necrosis, and ulceration. The hallmark of toxin-mediated disease is the development of an adherent pseudomembrane that is composed of fibrin, nonviable epithelial cells, inflammatory cells, and organisms. Typically, pseudomembranes begin in the tonsils, the pharynx, or the nares. In severe cases, pseudomembranes can extend to the larynx or trachea and lead to airway obstruction. Toxin can disseminate hematogenously and cause disease in other organs, including the myocardium, nerves, and kidneys. Nontoxigenic strains rarely produce pseudomembranes, and respiratory disease tends to be milder.

Other *Corynebacteria*

C. ulcerans and *C. pseudotuberculosis* are primarily animal pathogens, but zoonotic disease has been reported in humans. Both *C. ulcerans* and *C. pseudotuberculosis* may produce diphtheria-like toxin and can cause toxin-meditated disease. Other *Corynebacteria* typically cause organ-specific disease that is not toxin-mediated.

CLINICAL MANIFESTATIONS

C. diphtheriae

Respiratory Diphtheria

The most common form of respiratory disease involves the pharyngeal area. After an incubation period of 2 to 5 days (range: 1 to 10 days), prodromal signs and symptoms include sore throat, cervical lymphadenopathy, malaise, and low-grade fever. Approximately 80% of untreated symptomatic cases develop membranous diphtheria two to three days after the onset of prodromal symptoms.[15] Pharyngeal erythema is followed by a whitish exudate that becomes a grayish pseudomembrane in the ensuing 1 to 2 days; the pseudomembrane is firmly adherent to the underlying mucosa and bleeds upon forceful removal.

The bull neck appearance associated with diphtheria is attributable to cervical lymphadenopathy and localized soft tissue edema. Complications from pharyngeal disease include stridor, airway obstruction, and respiratory compromise. Pseudomembranes can extend from the pharyngeal area to the nasal passages and the tracheobronchial tree.

Other areas of involvement in respiratory diphtheria include the anterior nares, laryngeal, and tracheobronchial areas. Nasal diphtheria, which typically tends to be mild, presents with serosanguinous or purulent discharge. Laryngeal diphtheria presents with hoarseness, stridor, and cough. Tracheobronchial infection is usually due to secondary spread of pseudomembranes and can lead to respiratory compromise. Severe clinical disease increases the risk of the absorption and dissemination of toxin.

Cardiac and Neurologic Toxicity

Toxin-mediated cardiac disease occurs in up to 25% of respiratory diphtheria cases. The risk of cardiac complications increases if antitoxin therapy is delayed or not administered. Myocarditis (Chapter 47), which is the most common manifestation of cardiac toxicity, typically develops during the first or second week of infection. Clinical symptoms consistent with myocarditis are nonspecific but include heart failure and diminished cardiac output. Abnormalities on electrocardiography include ST-T wave changes, heart block, and arrhythmias. In one study of 99 children in India with diphtheria, 35% developed myocarditis and 11% developed cardiogenic shock.[16]

Neurologic disease due to toxin-producing *C. diphtheriae* is less common than cardiac disease. During the acute phase, local motor neuropathy manifests with paralysis of the soft palate and pharynx. Cranial neuropathies can cause further paralysis of the larynx, facial oculomotor, and ciliary muscles. Peripheral neuritis with predominant motor deficits typically occurs 2 weeks to 3 months after the resolution of respiratory symptoms.

Cutaneous Diphtheria

Asymptomatic skin carriage serves as a reservoir for infection. Symptomatic cutaneous diphtheria,[17] which is usually caused by nontoxigenic strains, typically presents as chronic, nonhealing, deep ulcers that may have a grayish-white pseudomembrane. Infection may occur in preexisting chronic dermatoses or manifest as impetigo (Chapter 408). Co-infection with *Staphylococcus aureus* and *Streptococcus pyogenes* can occur.

Other *Corynebacteria*

Infections due to other *Corynebacteria* are broadly categorized as community acquired or health care–associated (Tables 272-2 and 272-3), but zoonotic infections also occur. Community-acquired infections include pharyngitis, skin and soft tissue infections, genitourinary tract infections, and ocular infections. Health care–associated infections include device-related infections, native and prosthetic valve endocarditis, postsurgical infections, and genitourinary tract infections.

Nonlipophilic, Fermentative *Corynebacteria*

Corynebacterium ulcerans and *C. pseudotuberculosis*, which are members of the *C. diphtheriae* group, are primarily animal pathogens. In humans, *C. ulcerans* causes exudative pharyngitis and cutaneous disease that is similar to *C. diphtheriae*[18]; it also can produce diphtheria toxin–mediated disease and complications. *C. pseudotuberculosis* infection in humans typically manifests as granulomatous lymphadenitis that mainly affects individuals who work with infected animals.

Several *Corynebacterium* species (including *C. xerosis*, *C. striatum*, *C. amycolatum*, and *C. minutissimum*) are normal skin commensals. Infections due to these organisms predominantly occur in the skin and soft tissue, often as health care–associated infections (Table 272-3).[19] *C. glucuronolyticum* and *C. riegelii* are associated with genitourinary tract infections in males and females, respectively.

Nonlipophilic, Nonfermentative *Corynebacteria*

Corynebacterium pseudodiphtheriticum is a normal commensal of the upper respiratory tract. Co-circulation with *C. diphtheriae* has been described. Infections primarily occur in immunocompromised hosts and in patients with chronic lung disease. In addition to causing respiratory disease, *C. pseudodiphtheriticum* has been implicated in infections of heart valves and the cornea. Similarly, *C. propinquum* has been associated with respiratory infections, endocarditis, and keratitis.

Lipophilic *Corynebacteria*

Corynebacterium jeikeium has been associated with severe disease in hospitalized patients, especially in immunocompromised hosts, patients with indwelling devices, and patients with prolonged hospitalization (Chapter 261) or exposure to multiple broad-spectrum antibiotics.[20] Infection due to *C. jeikeium* typically presents as septicemia due to infected indwelling devices, native and prosthetic

TABLE 272-2 COMMUNITY-ACQUIRED INFECTIONS DUE TO *CORYNEBACTERIA*

Conjunctivitis/keratitis	*Corynebacterium macginleyi* *Corynebacterium propinquum* *Corynebacterium pseudodiphtheriticum*
Pharyngitis	*C. pseudodiphtheriticum* *Corynebacterium ulcerans*
Lymphadenitis	*Corynebacterium pseudotuberculosis*
Genitourinary tract infection	*Corynebacterium glucuronolyticum* *Corynebacterium riegelii*
Chronic prostatitis	*C. glucuronolyticum*
Skin and soft tissue infections	*C. pseudotuberculosis* *Corynebacterium confusum* *Corynebacterium minutissimum* *C. ulcerans*
Breast abscess/mastitis	*Corynebacterium kroppenstedtii* *Corynebacterium tuberculostearicum*
Native valve endocarditis	*C. propinquum* *C. pseudodiphtheriticum*
Native joint infection	*Corynebacterium striatum*

Modified from Mandell GL, Douglas RG, and Bennett JE. (2019) *Mandell, Douglas, and Bennett's Principles and Practice of Infectious Diseases*, 9th edition. Chapter 205 Other Coryneform Bacteria, *Arcanobacterium haemolyticum*, and Rhodococci. Table 205.1 Community-Acquired Coryneform Infections, page 2533.

TABLE 272-3 HEALTH CARE–ASSOCIATED INFECTIONS DUE TO *CORYNEBACTERIA*

Central nervous system infections	*C. jeikeium*
Pneumonia	*C. amycolatum (C. xerosis)* *C. striatum* *C. urealyticum* *C. pseudodiphtheriticum*
Intravenous catheter–related blood stream infection	*C. jeikeium* *C. amycolatum* *C. striatum* *C. urealyticum* *Corynebacterium minutissimum* *Corynebacterium macginleyi*
Native valve endocarditis	*C. amycolatum* *C. jeikeium* *C. striatum* *C. urealyticum*
Prosthetic valve endocarditis	*C. jeikeium* *C. amycolatum* *C. striatum*
Skin and soft tissue infection	*C. amycolatum* *C. minutissimum* *C. urealyticum*
Postsurgical infections	*C. jeikeium* *C. urealyticum* *C. striatum* *C. minutissimum* *C. amycolatum*
Prosthetic joint infections	*C. jeikeium*
Urinary tract infections and encrusted cystitis	*C. urealyticum*
Continuous ambulatory peritoneal dialysis–related peritonitis	*C. jeikeium* *C. urealyticum*

Modified from Mandell GL, Douglas RG, and Bennett JE. (2019) *Mandell, Douglas, and Bennett's Principles and Practice of Infectious Diseases*, 9th edition. Chapter 205 Other Coryneform Bacteria, *Arcanobacterium haemolyticum*, and Rhodococci. Table 205.2 Nosocomial Infections Caused by Coryneform Bacteria, page 2533.

valve endocarditis, prosthetic joint infection, and CNS infection. *C. urealyticum* causes chronic and recurrent urinary tract infection, including encrusted cystitis and pyelitis, especially in patients who have abnormal urinary tract anatomy or indwelling urinary catheters, or who have had urinary tract procedures; it has also been implicated in sepsis, endocarditis, and osteomyelitis. Other notable lipophilic *Corynebacteria* include *C. macginleyi* (keratitis) as well as *C. kroppenstedtii* and *C. tuberculostearicum* (mastitis and breast abscess).

DIAGNOSIS

C. diphtheriae

Prompt diagnosis and treatment is paramount in preventing severe outcomes. Infection due to *C. diphtheriae* should be considered when a patient presents with consistent clinical signs and epidemiologic risk factors, including residence in or travel from an endemic area or a history of inadequate vaccination. Other infections in the differential diagnosis include streptococcal pharyngitis (Chapter 269), infectious mononucleosis (Chapter 348), Vincent angina (Chapter 397), acute epiglottitis (Chapter 397), oropharyngeal candidiasis (Chapter 310), and acute retroviral syndrome due to human immunodeficiency virus (HIV) infection (Chapter 355).

Clinical samples should be collected via swabbing the affected areas, including the nasopharynx, throat, and suspicious skin lesions. If a pseudomembrane is present, a sample should be obtained from underneath the membrane, or a piece of the membrane can be submitted. The microbiology laboratory should be notified about the specific concern for *C. diphtheriae*, because special media is required. Mass spectrometry[21] and PCR testing are highly accurate in identifying *Corynebacterium* species, including *C. diphtheriae*. All *C. diphtheriae* isolates should be tested for toxin production. Cultures should be obtained regardless of whether treatment has been initiated.

Other *Corynebacteria*

Because *Corynebacteria* are often cultured in polymicrobial infections or as a contaminant due to nonsterile collection technique, the microbiology laboratory should be informed when species identification is appropriate. PCR and mass spectrometry can identify *Corynebacteria* to the species level.

TREATMENT

C. diphtheriae

The mainstay of treatment for respiratory diphtheria includes administration of diphtheria antitoxin and antibiotic therapy. Treatment should be initiated promptly in cases of suspected disease to optimize favorable outcomes and mitigate potential complications. Supportive care and prevention of further transmission are additional treatment goals (Table 272-4).

Administration of diphtheria antitoxin within the first 48 hours of symptoms provides the greatest benefit in terms of halting disease progression. Diphtheria antitoxin is administered as a single dose, ranging from 20,000 units for localized tonsillar disease of 2 days duration or less, to 100,000 units for extensive disease of 3 days duration or more or for severe toxicity. Children and adults receive the same dose; routes of administration include intramuscular and intravenous, with the latter being preferred for severe cases. In the United States, diphtheria antitoxin can be obtained from the Centers for Disease Control and Prevention (CDC) under the Investigational New Drug protocol (770-488-7100; www.cdc.gov/diphtheria/downloads/protocol.pdf). To mitigate hypersensitivity reactions or serum sickness, allergy testing should be performed, followed by desensitization if necessary.

Effective antibiotic therapies to eliminate the organism and thereby its production of toxin require 14 days of treatment, usually with erythromycin (orally or intravenously at 40 to 50 mg/kg/day, up to 2 g daily in four divided doses) or intramuscular procaine penicillin G (25,000 to 50,000 units/[kg/day] for children and 1.2 million units/day for adults, in two divided doses), with transition to oral penicillin V (125 to 250 mg four times daily) when the patient is able to tolerate oral intake.[22]

Supportive care includes close monitoring of respiratory, cardiac, and neurologic status. Preemptive intubation may be needed in cases of potential respiratory failure due to airway obstruction from membranous disease. Continuous cardiac monitoring is necessary to detect and treat cases of myocarditis (Chapter 47), heart failure (Chapter 46), and arrhythmias (Chapter 49) promptly. During convalescence, diphtheria toxoid vaccine should be administered, because natural immunity may not confer protection against toxin.

For respiratory diphtheria, respiratory droplet precautions should be maintained until the patient has received 14 days of antibiotic therapy and two consecutive sputum cultures taken 24 hours apart are negative after completion of antibiotics. The local health department should be notified.

TABLE 272-4 GOALS AND INTERVENTIONS FOR SUSPECTED DIPHTHERIA

GOAL	INTERVENTION
Toxin neutralization to decrease risk of severe complications and death	Obtain and administer diphtheria antitoxin after presumptive diagnosis of diphtheria
Effective eradication of organism	Initiation of appropriate antibiotic therapy
Support acutely ill patients requiring hospitalization	Provide appropriate and intensive monitoring within the hospital setting
Confirmation of diagnosis	Collect appropriate specimens for microbiologic testing (culture, PCR, mass spectrometry)
Prevention of transmission of diphtheria	Strict respiratory isolation of index case Notification of health department Initiate postexposure prophylaxis of close contacts
Long-term protection against diphtheria in case and close contacts	Administer diphtheria toxoid vaccine as needed

PCR = polymerase chain reaction.

Other *Corynebacteria*

Isolates that are implicated in causing clinical disease should undergo susceptibility testing. *Corynebacteria* generally are susceptible to vancomycin and linezolid, with dosing and duration requiring consultation with an infectious disease expert.

PREVENTION

C. diphtheriae

Diphtheria toxoid vaccine is approximately 95% effective in adequately immunized persons and is protective for at least ten years. In the United States, diphtheria toxoid is administered as a component of diphtheria toxoid, tetanus toxoid, and acellular pertussis combination vaccines (DTaP or Tdap). A booster dose of Tdap is recommended for adolescents age 11 to 12 years, mostly to provide protection against pertussis, and then as often as every ten years in adults in the United States (see Chapter 15 and https://www.cdc.gov/vaccines/vpd/dtap-tdap-td/hcp/recommendations.html), but not by the World Health Organization because the benefit of diphtheria re-vaccination in adults is likely very small, at best.[23] Pregnant women should receive one dose of Tdap at 27 to 36 weeks of gestation.

Close contacts of cases, including household contacts, should be administered prophylactic antibiotics with either one dose of intramuscular benzathine penicillin G (600,000 units for persons <6 years of age, or 1,200,000 units for ≥6 years of age) or a 7- to 10-day course of oral erythromycin (40 mg/kg/day for children; 1 g/day for adults). Cultures should be obtained prior to and after completion of antibiotics; if cultures are positive after antibiotic therapy, an additional 10 days of treatment with erythromycin is warranted. An age-appropriate booster dose of a diphtheria toxoid–containing vaccine should be administered; all contacts who have not received a booster dose in the past 5 years should be administered diphtheria toxoid vaccine.

Other *Corynebacteria*

Prevention of infection caused by *Corynebacteria* include proper skin antisepsis prior to invasive procedures and good hand hygiene when handling animals.

PROGNOSIS

C. diphtheriae

Although diphtheria cases worldwide have diminished after introduction of the vaccine, case fatality rates remain high. For example, the case fatality rate in the Philippines is over 40%.[24] Timely administration of antibiotics and diphtheria antitoxin can reduce morbidity and mortality. Myocarditis can progress to cardiogenic shock, but neurologic disease usually resolves.

Other *Corynebacteria*

Overall outcomes for infections attributable to *Corynebacteria* are favorable, based on proper identification, antimicrobial therapy, and removal of indwelling devices, if appropriate.

ERYSIPELOID AND OTHER *ERYSIPELOTHRIX* INFECTIONS

DEFINITION

Erysipelothrix rhusiopathiae, which is a zoonotic pathogen, causes three well-defined patterns of human infection: erysipeloid, which is a cellulitis of the fingers and hands (also known as whale finger or pork finger) and is the most common manifestation of infection with *E. rhusiopathiae*; a diffuse cutaneous form; and a systemic or invasive form, with or without cutaneous involvement, usually manifesting as bacteremia that may be complicated by endocarditis.

The Pathogen

E. rhusiopathiae is a thin, pleomorphic, nonsporulating, microaerophilic, gram-positive rod. It may be confused with other gram-positive bacillary organisms, particularly *Listeria monocytogenes* and *Corynebacterium* species. It does not produce toxin. It can be differentiated from *L. monocytogenes* by its lack of motility, lack of catalase and coagulase production, and resistance to neomycin. Most strains of *E. rhusiopathiae* produce hydrogen sulfide on triple sugar iron agar slants, a feature that distinguishes *E. rhusiopathiae* from *L. monocytogenes* and from corynebacteria. Because α-hemolysis may be seen after 48 hours of incubation of *E. rhusiopathiae*, it can be confused with streptococci. The term *erysipeloid* refers to cutaneous infection by *E. rhusiopathiae* (Fig. 272-4) and should not be confused with erysipelas, which is a superficial cellulitis caused by streptococci or staphylococci.

EPIDEMIOLOGY

E. rhusiopathiae is found worldwide as a commensal or as a pathogen in a variety of wild and domestic animals, including swine, sheep, cattle, horses, dogs, cats, rodents, chickens, ducks, turkeys, penguins, and parrots, as well as in flies, ticks, mites, and lice. The greatest commercial impact of *E. rhusiopathiae* infection is due to disease in swine, but infection of sheep and poultry is also important economically. Environmental surfaces in contact with infected animals, their bodily fluids, or their products are potential sources of *E. rhusiopathiae*. It can persist for prolonged periods in contaminated soil. *E. rhusiopathiae* is killed within 15 minutes by heating to 55° C and by several commercially available home disinfectants.

The incidence of cutaneous infection in humans seems to be decreasing because of technologic advances in animal industries. Infection is usually the result of contact with infected animals or their products. Persons at greatest risk for infection include fishers, fishmongers, farmers, butchers, slaughterhouse workers, and veterinarians. The organism gains entry through cuts and abrasions on the skin and can result in infection from freshwater or seawater.[25] The seasonal incidence of erysipeloid parallels that of swine erysipeloid and is highest in the summer and early fall. The rare instances of systemic infection without an occupational link tend to occur in immunocompromised hosts, thereby suggesting that oropharyngeal or gastrointestinal colonization with the organism may occur. Chronic alcohol use disorder (Chapter 364) is a common underlying condition. Erysipeloid and erysipeloid with bacteremia have been reported rarely after cat and dog bites, thereby suggesting that *E. rhusiopathiae* may be part of the oral flora of these animals.

FIGURE 272-4. Erysipeloid with its characteristic purple, nonpurulent swelling of the finger. Also known as whale finger or pork finger, this form of cellulitis caused by *Erysipelothrix rhusiopathiae* should not be confused with streptococcal or staphylococcal erysipelas (see Fig. 408-4). (From Farrar WE, Wood MJ, Innes JUA, Tubbs H. *Infectious Diseases: Text and Color Atlas*. 2nd ed. New York: Gower Medical Publishing; 1992.)

PATHOBIOLOGY

The pathogenesis of *E. rhusiopathiae* infection is not well understood. Strains vary in virulence. Virulence is associated, at least in part, with resistance to phagocytosis by polymorphonuclear leukocytes. This antiphagocytic ability results from the organism's possession of a capsule. In the absence of specific antibodies, *E. rhusiopathiae* evades phagocytosis, but even if it is phagocytosed, it is able to replicate intracellularly in these cells. Other virulence factors include enzymes (neuraminidase and hyaluronidase) and cell wall–associated proteins, including transporter and adhesion proteins, such as SpaA, which acts as an adhesion to host endothelial cells.[26]

CLINICAL MANIFESTATIONS

Because of the mode of acquisition (contact with infected animals or their products, with organisms inoculating abrasions on the skin), lesions are usually confined to the fingers and hands (Fig. 272-4). A well-defined, slightly elevated, violaceous lesion accompanied by a very painful, throbbing, burning, or itching sensation develops within 2 to 7 days of traumatic dermal inoculation.[27] The infected area is swollen. Vesicles may be present, but suppuration is absent. The lesion spreads slowly to other fingers but rarely involves the fingertips or the skin above the wrist. As the lesion spreads peripherally, the central area clears. Systemic signs and symptoms are rare. Sterile arthritis may involve an adjacent joint. Regional lymphadenopathy or lymphadenitis occurs in about 20% of cases, and low-grade fever develops in approximately 10%. Lesions usually resolve within 3 weeks without treatment. Relapse occurs in 1% of cases.

The diffuse cutaneous form is rare. The cutaneous lesion progresses proximally from the site of inoculation or appears at remote areas. Patients often have fever and arthralgias, but blood cultures are generally negative.

Systemic infection with *Erysipelothrix* is uncommon, but bacteremia can result in endocarditis (Chapter 61), often on an apparently normal valve.[28] The presentation can be acute or subacute. One third of patients have an antecedent or concurrent skin lesion of erysipeloid. *E. rhusiopathiae* endocarditis correlates highly with occupation, exhibits a tropism for the aortic valve, affects more males than females, and is associated with high mortality, which may reflect a delay in appropriate therapy because of the empirical use of vancomycin, which is not an effective treatment of *E. rhusiopathiae*. About one-third of patients require valve replacement. *E. rhusiopathiae* bacteremia is increasingly seen in immunocompromised patients. Focal infections include brain abscess, meningitis, endophthalmitis, osteomyelitis, septic arthritis, epidural and paravertebral abscess, psoas abscess, liver abscess, necrotizing fasciitis, intra-abdominal abscess, and peritonitis. Septic arthritis can occur in native joints, in prosthetic joints, and after arthroscopic surgery. Peritonitis can complicate peritoneal dialysis.

DIAGNOSIS

Diagnosis requires a high degree of suspicion in patients who have exposures, which are usually work-related. Because *E. rhusiopathiae* is located only in deeper parts of the skin in cases of erysipeloid, biopsy of the entire thickness of the dermis from the edge of the lesion maximizes the recovery of the organism. PCR or mass spectrometry (MALDI TOF) improves the efficiency of detection and identification compared with waiting for the culture results.[29] Definitive diagnosis by skin biopsy is rarely necessary because of the classic clinical presentation and the rapid response to therapy. Routine blood culture techniques are adequate for growth and isolation of the organism in suspected cases of bacteremia or endocarditis.

TREATMENT

Penicillin G is the treatment of choice. Although erysipeloid skin lesions may resolve spontaneously, cutaneous lesions generally respond well to a 5- to 7-day course of oral penicillin VK (250 mg four times daily). Treatment hastens healing, but relapse may still occur. Bacteremia should be treated with intravenous penicillin (2 to 4 million units every 4 hours for 2 weeks). Endocarditis can be treated with intravenous penicillin G (12 million to 20 million units daily) or ceftriaxone (1 g daily) for 4 to 6 weeks, but 2 weeks of intravenous therapy followed by 2 weeks of oral therapy has been successful. Bone and joint infections require longer courses of antibiotics (at least 12 weeks). The use of quinolones or daptomycin may be considered for *Erysipelothrix* infections when the patient is allergic to β-lactams. Valve replacement may be necessary in patients with endocarditis. Infected prosthetic devices should be removed.

PREVENTION

Proper cleaning and disinfection of work surfaces and attention to hygienic work practices, including the use of gloves and hand hygiene, reduce the risk for infection. Vaccines are available for commercial use in animals only.

LISTERIOSIS

DEFINITION

Listeriosis is a food-borne infection.[30] Most infected patients have impaired cell-mediated immunity and develop life-threatening bacteremia or meningitis. However, a self-limited, febrile gastroenteritis also occurs in healthy persons.

The Pathogen

Listeria monocytogenes is a gram-positive rod that is facultatively anaerobic and does not produce endospores. The organism exists intracellularly, and it is catalase positive and beta-hemolytic when grown on blood agar.

EPIDEMIOLOGY

Widely distributed in nature, *L. monocytogenes* may be found in soil, on vegetation, and in the stool of healthy mammals, including humans. The organism causes disease in animals, especially herd animals, and in humans. *L. monocytogenes* has been isolated from many foods, including raw produce, raw milk, milk products, cheeses, ice cream, fish, poultry, and meat. Unlike most food-borne pathogens, *L. monocytogenes* can grow at refrigerator temperatures.

Non-perinatal listeriosis is almost always the result of food-borne infection. Listeriosis is a relatively rare food-borne illness (about 1% of U.S. cases). Outbreaks have been documented in association with coleslaw, milk, soft cheeses, ice cream,[31] pâté, ready-to-eat pork products, deli counter meats, hot dogs, smoked fish, butter, sprouts, taco or nacho salads, and cantaloupes.[32]

Listeriosis is a nationally reportable disease. Centers for Disease Control and Prevention's PulseNet (http://www.cdc.gov/pulsenet/) facilitates prompt detection of disease clusters that may have a common source. Each outbreak of listeriosis has a median of four cases. In 2019, the annual incidence of listeriosis in the United States was 0.3 cases per 100,000 population, and it accounted for 134 cases per year and 21 deaths. Neonates and adults older than age 60 years, and especially over age 85 years,[33] have the highest infection rates, and pregnant women represent 14% of all affected individuals. Other adults at increased risk for invasive listeriosis (bacteremia) include patients who have hematologic malignancies, advanced acquired immunodeficiency syndrome (AIDS), or a solid organ transplant, as well as any patients who are being treated with corticosteroids or an anti–tumor necrosis factor agent. Iron is a virulence factor for *L. monocytogenes*, and patients who have iron overload states (Chapter 196) are at increased risk for *Listeria* infection. Use of proton pump inhibitors also increases the risk of infection. However, as many as 25% of all cases of invasive listeriosis occur in apparently healthy persons, particularly individuals older than age 60 years.

PATHOBIOLOGY

L. monocytogenes enters the human body through the intestine, most often after the ingestion of contaminated food. The bacterium induces its own uptake by gastrointestinal cells and macrophages. Infectious or mechanical disruption of the gastrointestinal tract occasionally may promote invasion. Mother-to-child transmission occurs transplacentally or through a colonized birth canal. Within the host cell, the bacterium is enclosed in a phagolysosome, but it produces an exotoxin called listeriolysin O that destroys the phagolysosome membrane and gains access to the cytoplasm. All pathogenic strains of *L. monocytogenes* produce listeriolysin O, the major virulence factor. Phosphocholine antagonizes listeriolysin O–induced host cell responses through enzymatic activity. Listeriae actively divide in the cytoplasm, migrate to the periphery of the cell by polymerization of host cell actin, and then push out the cell membrane to form pseudopods, which are taken up by adjacent host cells. The bacteria move from cell to cell in this fashion and repeat their life cycle without exposure to antibodies or complement.

After translocation through the gastrointestinal tract, listeriae may disseminate hematogenously to any body site, but show a particular tropism for the CNS. Less commonly, they may spread intra-axonally through cranial nerves to reach the CNS; this mode of CNS invasion may result in rhombencephalitis (brain stem infection).

Immunity to infection with *Listeria* is handled chiefly through the cell-mediated arm of the immune system. Persons who have had a splenectomy or who have abnormalities solely of humoral immunity or leukocytes are not at increased risk for infection.

CLINICAL MANIFESTATIONS

Food-borne outbreaks after ingestion of *L. monocytogenes* in a sufficiently large inoculum can result in a self-limited illness consisting of fever, chills, diarrhea, abdominal cramps, and sometimes nausea and vomiting. Symptoms follow exposure by 1 to 2 days and persist for about 2 days.

The incubation period for invasive listeriosis averages about 11 days, and 90% of infections occur within 28 days. Listeriosis in an immunocompromised adult or pregnant woman is most often manifested as bacteremia without an obvious focus. In these cases, patients have nonspecific symptoms, such as fever, malaise, myalgia, and back pain. Listeriosis during pregnancy may lead to spontaneous abortion or neonatal sepsis, but early antimicrobial therapy may result in the birth of a healthy child (fetal viability 29% in second trimester; 95% in third trimester). Endocarditis with *L. monocytogenes* can occur on both native and prosthetic valves, and it carries a high rate of septic complications.[34]

L. monocytogenes bacteremia may progress to CNS infection, most commonly manifested as meningitis,[35] and *L. monocytogenes* is the most common cause of bacterial meningitis (Chapter 381) in patients with lymphomas, in organ transplant recipients, and in patients treated with corticosteroids for any reason. Affected persons may have the classic acute symptoms of meningitis, but the presentation is subacute (>24 hours) in many cases. Nuchal rigidity is present in 80%. Focal neurologic findings, including ataxia, tremors, myoclonus, and seizures, may be seen, consistent with the tropism of *Listeria* for brain parenchyma.

Meningitis can be accompanied by brain abscesses, which are often subcortical. *L. monocytogenes* is also a rare cause of encephalitis.

Listerial rhombencephalitis is an unusual form of listerial encephalitis that involves the brain stem and, unlike other listerial CNS infections, usually occurs in healthy adults.[36] The typical clinical picture is a biphasic illness with a prodrome of fever, headache, nausea, and vomiting that persists for about 4 days and is followed by the abrupt onset of asymmetrical cranial nerve deficits, cerebellar signs, and hemiparesis or hemisensory deficits or both. Respiratory failure develops in about 40% of patients. Nuchal rigidity is present in about half, and CSF findings are only mildly abnormal, with a positive CSF culture in about 40%. Almost two thirds of patients are bacteremic.

Localized infection may occur after hematogenous seeding (e.g., liver abscess, septic arthritis) or, rarely, after direct inoculation (e.g., papulopustular rash or conjunctivitis). Osteoarticular listeriosis primarily involves prosthetic joints, especially in immunocompromised patients. *L. monocytogenes*–associated pneumonia and empyema have also been reported.

DIAGNOSIS

Differential Diagnosis

Clinical situations in which a diagnosis of listeriosis should be considered include:

- Neonatal sepsis or meningitis
- Meningitis or parenchymal brain infection in patients with subacute presentations, hematologic malignancies, AIDS, organ transplantation, corticosteroid immunosuppression, treatment with anti–tumor necrosis factor agents, or age older than 50 years
- Simultaneous infection of the meninges and brain parenchyma
- Subcortical brain abscess
- Fever during pregnancy
- Blood, CSF, or other normally sterile specimen reported to have "diphtheroids" on Gram stain or culture
- Food-borne outbreak of febrile gastroenteritis when routine cultures fail to identify a pathogen

The differential diagnosis of listerial CNS infection includes the more common causes of bacterial meningitis (Chapter 381) and brain abscess (Chapter 382). Listerial meningitis or rhombencephalitis may mimic CNS tuberculosis (Chapter 299).

Laboratory

The diagnosis of listeriosis is made by routine bacterial culture of specimens from usually sterile sites, such as blood or CSF. Gram stain of CSF reveals small gram-positive rods in only about one third of cases. The glucose content in CSF is normal in more than 60% of cases; mononuclear cells predominate in 30%. *L. monocytogenes* can rarely cause recurrent meningitis. Real-time PCR analysis of CSF for the *hly* gene, which encodes listeriolysin O, has been useful in diagnosing CNS listeriosis, including cases in which

routine bacterial cultures were negative,[37] but this test is not commercially available. Magnetic resonance imaging is superior to CT for demonstrating rhombencephalitis.

Specific stool culture is recommended only when routine stool cultures are negative in the setting of an outbreak of gastroenteritis; many people have enteric colonization with *L. monocytogenes* without invasive disease. The laboratory must be advised that listerial infection is suspected because the organism is unlikely to be identified with routine stool culture media. Whole-genome sequencing enhances the real-time detection and investigation of listeriosis outbreaks. Serologic testing (antibody to listeriolysin O) is not useful for invasive disease but may be helpful in the retrospective identification of food-borne outbreaks of febrile gastroenteritis when routine cultures are negative.

Endocarditis, but not bacteremia per se, may be a clue to underlying colon cancer. Colonoscopy should be considered in all cases of listerial endocarditis.

TREATMENT

Because 20% of cases of bacterial meningitis in patients older than age 50 years are due to *L. monocytogenes*, empirical therapy for bacterial meningitis (Chapter 381) in all adults older than age 50 years should include either ampicillin or trimethoprim-sulfamethoxazole, especially in the absence of associated pneumonia, otitis, sinusitis, or endocarditis, which would suggest a cause other than *L. monocytogenes*. Cephalosporins, commonly used for the treatment of bacterial meningitis, should not be used alone when *Listeria* is a diagnostic consideration.

For confirmed cases of listeriosis, ampicillin (2 grams IV every 4 hours) is generally the drug of choice. In cases of meningitis and endocarditis and in patients with severely impaired T-cell function, gentamicin (2 mg/kg IV load and then 1.7 mg/kg every 8 hours, adjusting dose and frequency for renal function and monitoring blood levels to avoid toxicity) is usually added to ampicillin. For meningitis, therapy should be continued for at least 3 weeks; bacteremic patients without CNS involvement may be treated for 2 weeks. Endocarditis and brain abscess should be treated for at least 6 weeks. Meningitis doses should be used to treat all cases of invasive listeriosis, even in the absence of CNS or CSF abnormalities. In patients with penicillin hypersensitivity, trimethoprim-sulfamethoxazole (5 mg/kg trimethoprim component IV every 6 to 8 hours) is the preferred agent and appears to be as effective as the combination of ampicillin and gentamicin. The role of corticosteroids in the treatment of listerial CNS infection is unknown.

Infection of a prosthetic joint usually can be cured only by removing the infected implant. In patients with listeriosis and iron deficiency, it may be prudent to withhold iron replacement until antimicrobial therapy is complete.

PREVENTION

Guidelines for preventing listeriosis are similar to those for preventing other food-borne illnesses: thoroughly cooking raw food from animal sources; washing raw vegetables thoroughly before eating; keeping uncooked meats separate from vegetables and from cooked and ready-to-eat foods; avoiding raw (unpasteurized) milk or foods made from raw milk; and washing hands, knives, and cutting boards after each handling of uncooked foods.

Immunocompromised patients, pregnant women, and the elderly may choose to avoid soft cheeses such as feta, Brie, Camembert, blue-veined, and Mexican-style cheese such as queso fresco. Leftover foods or ready-to-eat foods, such as hot dogs, should be cooked until steaming hot. It is best to avoid foods from delicatessen counters, such as prepared salads, meats, and cheeses.

Listeriosis is effectively prevented by trimethoprim-sulfamethoxazole given as *Pneumocystis* prophylaxis (Chapter 313) to organ transplant recipients, patients who are receiving corticosteroid immunosuppression, or HIV-infected individuals. Except for transmission from infected mother to fetus, human-to-human transmission of listeriosis does not occur, so patients do not need to be isolated.

PROGNOSIS

Listeria meningitis carries an overall mortality rate of about 25%. Listeriosis causes approximately 20 to 30% of all food-borne disease–related deaths. The mortality rate is higher in patients with underlying malignant disease. Mortality from endocarditis and brain abscess is about 50%, and survivors of brain abscess or rhombencephalitis commonly have significant neurologic sequelae.

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273 DISEASES CAUSED BY NON–SPORE-FORMING ANAEROBIC BACTERIA

ITZHAK BROOK

DEFINITION

Anaerobic bacteria are the predominant members of the indigenous microbiota, including the skin and the oral, gastrointestinal, and vaginal mucosa (Fig. 273-1; Table 273-1). However, the types of predominant anaerobes differ by location.

The Pathogens

Advances in taxonomics have led to reclassification of many anaerobic species (E-Table 273-1) over the past several decades. *Fusobacterium nucleatum* is the predominant *Fusobacterium* species isolated from clinical specimens.

EPIDEMIOLOGY

Anaerobes are opportunistic pathogens that can cause serious infections, generally synergistic infections in combination with aerobic bacteria. Because the microbiology of these infections is often complex and because culture results may be delayed, awareness of the normal bacterial microbiota at the site of infection is an indispensable guide for the selection and institution of empirical antimicrobial therapy.

PATHOBIOLOGY

Anaerobic bacteria range from those that cannot survive even a brief exposure to oxygen to those that can survive even in the presence of atmospheric oxygen (e.g., *B. fragilis*). Most anaerobes require an environment with a low oxidation-reduction potential, which can be achieved in association with low pH, tissue destruction, byproducts from aerobic bacterial metabolism, or low oxygen content. Although they are not true anaerobes, some organisms, such as microaerophilic streptococci and other capnophilic or difficult-to-cultivate bacteria, are sometimes lumped together with anaerobes because of their fastidious nature. Some genera, such as *Lactobacillus* and *Actinomyces*, include both aerobic and anaerobic species. Anaerobic bacteria possess a variety of virulence factors that are species specific (E-Table 273-2).

CLINICAL MANIFESTATIONS

Bacteremia

Transient anaerobic bacteremia occurs in about 85% of patients immediately after dental cleaning or manipulation. An estimated 200 or more cases of endocarditis from anaerobes occur annually in the United States, usually in association with anatomic abnormalities or damaged cardiac valves (Chapter 61). However, most anaerobic bacteremias are intermittent and associated with serious intra-abdominal or female genital tract, skin, and soft tissue infections, often proximal to the gastrointestinal tract. Which organisms are involved depends on their portal of entry and the underlying disease. The most common isolates are the *B. fragilis* group (60 to 75% of isolates). About 3 to 15% of bacteremias are caused by anaerobes, and they are the sole isolates in two thirds of these cases. The most commonly implicated anaerobes in bacteremia are *Cutibacteria*, *B. fragilis*, and *Clostridioides* spp.[1,2] Bacteremia with the *B. fragilis* group generally originates from a gastrointestinal source. Pigmented *Prevotella*, *Porphyromonas*, and *Fusobacterium* spp most commonly originate from oropharyngeal and pulmonary sources, *Fusobacterium* spp usually come from the female genital tract, and *C. acnes* usually from foreign body sources. Bacteremia with peptostreptococci is associated with all sources but especially with the oropharyngeal, pulmonary, and female genital tracts.

Central Nervous System Infections

Anaerobes can cause brain abscess (Chapter 382), subdural empyema (Chapter 382), epidural abscess, and meningitis (Chapter 381). The main source of brain abscess[3] is an adjacent, generally chronic infection in the ears, mastoids, sinuses, oropharynx, teeth, or lungs. Rarely, bacteremia of another origin or endocarditis can cause such infection.

Meningitis caused by anaerobes is uncommon and can follow respiratory or dental infection or develop as a complication of a cerebrospinal fluid shunt. The isolates usually cultured from brain abscesses that complicate respiratory and

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routine bacterial cultures were negative,[37] but this test is not commercially available. Magnetic resonance imaging is superior to CT for demonstrating rhombencephalitis.

Specific stool culture is recommended only when routine stool cultures are negative in the setting of an outbreak of gastroenteritis; many people have enteric colonization with *L. monocytogenes* without invasive disease. The laboratory must be advised that listerial infection is suspected because the organism is unlikely to be identified with routine stool culture media. Whole-genome sequencing enhances the real-time detection and investigation of listeriosis outbreaks. Serologic testing (antibody to listeriolysin O) is not useful for invasive disease but may be helpful in the retrospective identification of food-borne outbreaks of febrile gastroenteritis when routine cultures are negative.

Endocarditis, but not bacteremia per se, may be a clue to underlying colon cancer. Colonoscopy should be considered in all cases of listerial endocarditis.

TREATMENT

Because 20% of cases of bacterial meningitis in patients older than age 50 years are due to *L. monocytogenes*, empirical therapy for bacterial meningitis (Chapter 381) in all adults older than age 50 years should include either ampicillin or trimethoprim-sulfamethoxazole, especially in the absence of associated pneumonia, otitis, sinusitis, or endocarditis, which would suggest a cause other than *L. monocytogenes*. Cephalosporins, commonly used for the treatment of bacterial meningitis, should not be used alone when *Listeria* is a diagnostic consideration.

For confirmed cases of listeriosis, ampicillin (2 grams IV every 4 hours) is generally the drug of choice. In cases of meningitis and endocarditis and in patients with severely impaired T-cell function, gentamicin (2 mg/kg IV load and then 1.7 mg/kg every 8 hours, adjusting dose and frequency for renal function and monitoring blood levels to avoid toxicity) is usually added to ampicillin. For meningitis, therapy should be continued for at least 3 weeks; bacteremic patients without CNS involvement may be treated for 2 weeks. Endocarditis and brain abscess should be treated for at least 6 weeks. Meningitis doses should be used to treat all cases of invasive listeriosis, even in the absence of CNS or CSF abnormalities. In patients with penicillin hypersensitivity, trimethoprim-sulfamethoxazole (5 mg/kg trimethoprim component IV every 6 to 8 hours) is the preferred agent and appears to be as effective as the combination of ampicillin and gentamicin. The role of corticosteroids in the treatment of listerial CNS infection is unknown.

Infection of a prosthetic joint usually can be cured only by removing the infected implant. In patients with listeriosis and iron deficiency, it may be prudent to withhold iron replacement until antimicrobial therapy is complete.

PREVENTION

Guidelines for preventing listeriosis are similar to those for preventing other food-borne illnesses: thoroughly cooking raw food from animal sources; washing raw vegetables thoroughly before eating; keeping uncooked meats separate from vegetables and from cooked and ready-to-eat foods; avoiding raw (unpasteurized) milk or foods made from raw milk; and washing hands, knives, and cutting boards after each handling of uncooked foods.

Immunocompromised patients, pregnant women, and the elderly may choose to avoid soft cheeses such as feta, Brie, Camembert, blue-veined, and Mexican-style cheese such as queso fresco. Leftover foods or ready-to-eat foods, such as hot dogs, should be cooked until steaming hot. It is best to avoid foods from delicatessen counters, such as prepared salads, meats, and cheeses.

Listeriosis is effectively prevented by trimethoprim-sulfamethoxazole given as *Pneumocystis* prophylaxis (Chapter 313) to organ transplant recipients, patients who are receiving corticosteroid immunosuppression, or HIV-infected individuals. Except for transmission from infected mother to fetus, human-to-human transmission of listeriosis does not occur, so patients do not need to be isolated.

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Advances in taxonomics have led to reclassification of many anaerobic species (E-Table 273-1) over the past several decades. *Fusobacterium nucleatum* is the predominant *Fusobacterium* species isolated from clinical specimens.

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CLINICAL MANIFESTATIONS

Bacteremia

Transient anaerobic bacteremia occurs in about 85% of patients immediately after dental cleaning or manipulation. An estimated 200 or more cases of endocarditis from anaerobes occur annually in the United States, usually in association with anatomic abnormalities or damaged cardiac valves (Chapter 61). However, most anaerobic bacteremias are intermittent and associated with serious intra-abdominal or female genital tract, skin, and soft tissue infections, often proximal to the gastrointestinal tract. Which organisms are involved depends on their portal of entry and the underlying disease. The most common isolates are the *B. fragilis* group (60 to 75% of isolates). About 3 to 15% of bacteremias are caused by anaerobes, and they are the sole isolates in two thirds of these cases. The most commonly implicated anaerobes in bacteremia are *Cutibacteria*, *B. fragilis*, and *Clostridioides* spp.[1,2] Bacteremia with the *B. fragilis* group generally originates from a gastrointestinal source. Pigmented *Prevotella*, *Porphyromonas*, and *Fusobacterium* spp most commonly originate from oropharyngeal and pulmonary sources, *Fusobacterium* spp usually come from the female genital tract, and *C. acnes* usually from foreign body sources. Bacteremia with peptostreptococci is associated with all sources but especially with the oropharyngeal, pulmonary, and female genital tracts.

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Meningitis caused by anaerobes is uncommon and can follow respiratory or dental infection or develop as a complication of a cerebrospinal fluid shunt. The isolates usually cultured from brain abscesses that complicate respiratory and

ABSTRACT

Anaerobes are the predominant components of normal human skin and the bacterial flora of mucous membranes. They are a frequent cause of endogenous bacterial infections. Anaerobic infections can occur in all body locations: the central nervous system, oral cavity, head and neck, chest, abdomen, pelvis, skin, and soft tissues. Treatment of anaerobic infection is complicated by their slow growth in culture, by their polymicrobial nature, and by their increasing resistance to antimicrobials. Antimicrobial therapy is frequently the only form of therapy needed, but some anaerobic infections require antibiotics, drainage, and surgery. Because anaerobes generally are mixed with aerobes, the antimicrobial chosen should provide adequate coverage of both.

KEYWORDS

anaerobes
infection
Bacteroides fragilis
Clostridioides
antimicrobial resistance
antibiotics

E-TABLE 273-1 TAXONOMY OF ANAEROBIC BACTERIA

CURRENT NAME
Alistipes finegoldii
Alistipes onderdonkii
Alistipes putredinis
Alistipes shahii
Alloprevotella tannerae
Anaerobiospirillum thomasii
Bacteroides caccae
Bacteroides dorei
Bacteroides eggerthii
Bacteroides fragilis
Bacteroides massiliensis
Bacteroides nordii
Bacteroides ovatus
Bacteroides pyogenes
Bacteroides salyersiae
Bacteroides stercoris
Bacteroides thetaiotaomicron
Bacteroides uniformis
Bacteroides vulgates
Bilophila wadsworthia
Campylobacter gracilis
Campylobacter ureolyticus
Cutibacterium acnes
Fusobacterium canifelinum
Fusobacterium necrophorum
Fusobacterium ulcerans
Odoribacter splanchnicus
Parabacteroides distasonis
Parabacteroides goldsteinii
Parabacteroides gordonii
Parabacteroides johnsonii
Parabacteroides merdae
Porphyromonas asaccharolytica
Porphyromonas gingivalis
Porphyromonas macacae
Porphyromonas somerae
Porphyromonas uenonis
Prevotella bivia
Prevotella buccae
Prevotella dentalis
Prevotella disiens
Prevotella intermedia
Prevotella melaninogenica
Prevotella nanceiensis
Prevotella nigrescens
Prevotella oralis
Prevotella oris
Prevotella timonensis
Prevotella zoogleoformans
Sutterella wadsworthensis
Tannerella forsythia

E-TABLE 273-2 POTENTIAL VIRULENCE FACTORS IN VARIOUS ANAEROBES

FACTOR	SPECIES
ADHESION	
Capsule	*Bacteroides fragilis* group, *Prevotella melaninogenica*
Pili/fimbriae	*B. fragilis* group
	Porphyromonas gingivalis
Hemagglutinin	*P. gingivalis*
Lectin	*Fusobacterium nucleatum*
INVASION/TISSUE DAMAGE	
Proteases	*Fusobacterium necrophorum*
	Bacteroides spp
	Porphyromonas spp
Hemolysins	Many species
Endotoxin	*B. fragilis*
Fibrinolysin	*B. fragilis* group
	Porphyromonas spp
Heparinase	*B. fragilis* group
	Porphyromonas spp
Neuraminidase	*B. fragilis* group
	Porphyromonas spp
ANTIPHAGOCYTIC	
Capsule	*B. fragilis* group
	P. gingivalis
Lipopolysaccharide	*B. fragilis* group
	F. necrophorum, P. gingivalis
Metabolic products	Most anaerobes
TOXINS	
Endotoxin	*B. fragilis*
	F. necrophorum
Enterotoxin	*B. fragilis*

Modified from Duerden BI. Virulence factors in anaerobes. *Clin Infect Dis.* 1994;18(Suppl 4):253.

dental infections include *Prevotella*, *Porphyromonas*, *Bacteroides*, *Fusobacterium*, and *Peptostreptococcus* spp. Microaerophilic and other streptococci are also often isolated. *C. acnes* is common in shunt infections.

Head and Neck

Dental infections (Chapter 393) associated with a variety of oral anaerobes include periodontal disease, gingivitis, pulpitis, acute necrotizing ulcerative gingivitis, localized juvenile periodontitis, adult periodontitis, pericoronitis, endodontitis, periapical and dental abscesses, and postextraction infection. Peritonsillar, retropharyngeal, and parapharyngeal abscesses (Chapter 397) are deep-seated, potentially life-threatening infections that may spread into the various potential spaces of the neck or mediastinum and cause jugular vein thrombosis. Oral anaerobes can be recovered in more than 50% of such cases, usually mixed with aerobes. Other regional infections include cervicofacial actinomycosis (Chapter 304), Ludwig angina, *Fusobacterium necrophorum* sepsis with metastatic infection (Lemierre syndrome; Chapter 397),[4] suppurative sialoadenitis (including parotitis), neck space infections, thyroiditis and chronic sinusitis (Chapter 394), otitis media (Chapter 394), and mastoiditis.

Pleuropulmonary

Anaerobes predominate in oral and upper respiratory tract normal flora, and most aspiration pneumonias[5] are due to these flora (Chapter 85). Aspiration can result from altered consciousness, dysphagia, or mechanical devices such as intubation equipment. Poor oral hygiene is associated with an increased anaerobic bacterial burden, and the presence of aerobes or necrotic tissue lowers the pH, which facilitates the growth of anaerobes. Anaerobes are involved in 90% of community-acquired aspiration pneumonia and in about a third of nosocomial aspiration pneumonia, empyema, lung abscess (Chapter 78), and pneumonia associated with tracheostomy (Chapter 85).

Intra-abdominal

Because anaerobes outnumber aerobes by 1000 to 1 in the large intestine, they play a major role in almost all intra-abdominal infections. Most visceral abscesses (e.g., hepatic; Chapter 137), chronic cholecystitis (Chapter 141), perforated and gangrenous appendicitis (Chapter 128), postoperative wound infections and abscesses, diverticulitis (Chapter 128), and any infection associated with fecal contamination of the abdominal cavity involve both aerobes and anaerobes. *B. fragilis* group members predominate because they are encapsulated, resist phagocytosis, are often resistant to many antimicrobials, and promote abscess formation. They also may be associated with concomitant bacteremia and sepsis.

Obstetric-Gynecologic

A variety of obstetric-gynecologic infections involve anaerobes. These are polymicrobial and include bacterial vaginosis; soft tissue perineal, vulvar, and Bartholin gland abscesses; endometritis; pyometra; salpingitis; tubo-ovarian abscesses; adnexal abscess; pelvic inflammatory disease (Chapter 264), which may include pelvic cellulitis and abscess; chorioamnionitis; vaginal cuff cellulitis; septic pelvic thrombophlebitis; intrauterine contraceptive device–associated infection; septic abortion; and postsurgical obstetric and gynecologic infections. Bacterial vaginosis has been associated with preterm labor or delivery, chorioamnionitis, low birthweight, postpartum endometritis, and postabortal pelvic inflammatory disease. Bacterial vaginosis can increase the risk for infection with human immunodeficiency virus (Chapter 353) and the development of other sexually transmitted diseases (Chapter 264).

Skin and Soft Tissue

Cutaneous infections include infected ulcers, cellulitis (including synergistic necrotizing cellulitis; Chapter 408), pyoderma, paronychia, hidradenitis suppurativa, and a variety of secondarily infected sites. Such sites include secondarily infected gastrostomy or tracheostomy site wounds, subcutaneous sebaceous or inclusion cysts, eczema, psoriasis, poison ivy, atopic dermatitis (Chapter 405), eczema herpeticum, scabies (Chapter 98) or kerion, and postsurgical wounds.

Subcutaneous infections include abscesses, decubitus ulcers, infected diabetic (vascular or trophic) ulcers (Chapter 210), human and animal bite wounds, anaerobic cellulitis and gas gangrene, bacterial synergistic gangrene, Fournier gangrene,[6] infected pilonidal cyst or sinus, and burn wounds (Chapter 97). Anaerobic soft tissue infections that occur deeper are necrotizing fasciitis, necrotizing synergistic cellulitis, and gas gangrene. These infections can involve the fascia and can induce myositis and myonecrosis.

TABLE 273-1 LOCATION OF VARIOUS GROUPS OF ANAEROBES AS NORMAL MICROFLORA IN HUMANS

LOCATION	NO. OF ORGANISMS PER GRAM		PREDOMINANT ANAEROBIC BACTERIA
	AEROBES	ANAEROBES	
Skin	—	—	*Cutibacterium acnes* *Peptostreptococcus* spp
Mouth/upper respiratory tract (in saliva)	10^8-10^9	10^9-10^{11}	Pigmented *Prevotella* and *Porphyromonas* spp *Fusobacterium* spp *Peptostreptococcus* spp *Actinomyces* spp
Gastrointestinal tract (in fecal material)			
Upper	10^2-10^5	10^3-10^7	*Bacteroides fragilis* group *Clostridioides* spp
Lower	10^5-10^9	10^{10}-10^{12}	*Peptostreptococcus* spp *Bifidobacterium* spp *Eubacterium* spp
Female genital tract (in vaginal secretions)	10^8	10^9	*Peptostreptococcus* spp *Prevotella bivia* *Prevotella disiens*

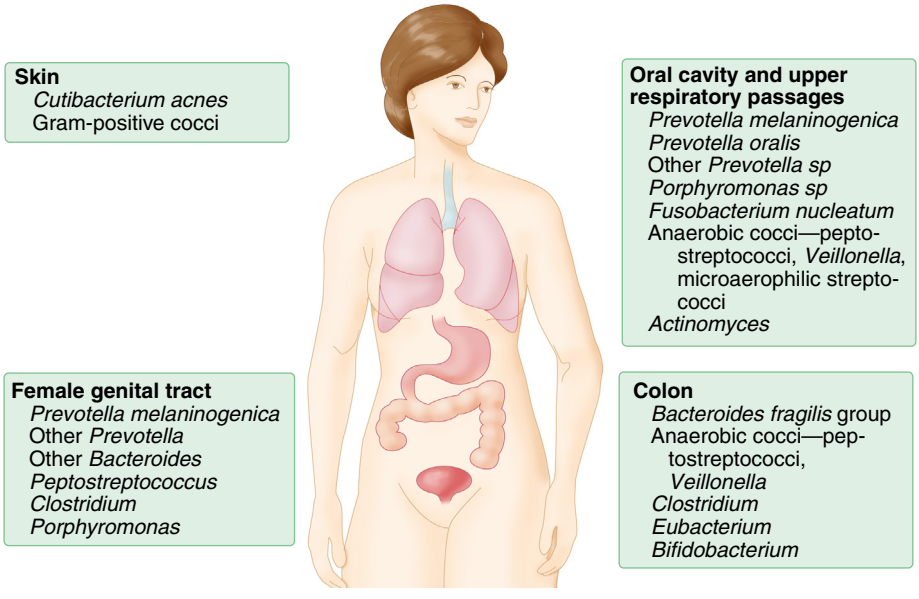

FIGURE 273-1. Anaerobes as the predominant normal microbiota of the human body by general anatomic location. (Modified from Finegold SM, Sutter VL. *Diagnosis and Management of Anaerobic Infections*. Kalamazoo, MI: Upjohn; 1976.)

Cultures of skin and soft tissue infections frequently yield isolates that are members of the normal flora of the region of the infection. In addition to oral and skin flora, human bite infections often contain *Eikenella* species, and animal bites harbor *Pasteurella multocida*. Skin infections are generally polymicrobial, and some (e.g., decubitus ulcers, diabetic foot ulcers) are often complicated by osteomyelitis or bacteremia. Deep tissue infections, such as necrotizing cellulitis, fasciitis, and myositis, often involve *Clostridioides* species (Chapter 271), *Streptococcus pyogenes* (Chapter 269), or a polymicrobic aerobic and anaerobic flora; they are often associated with gas in the tissues and putrid-like pus with a gray, thin quality and have a high rate of bacteremia and mortality.

Osteomyelitis and Septic Arthritis

Anaerobes can be involved in osteomyelitis (Chapter 251) of the long bones after trauma and fracture, osteomyelitis related to peripheral vascular disease, decubitus ulcers, and osteomyelitis of the cranial and facial bones. Most of these infections are polymicrobial.

Cranial and facial bone osteomyelitis is generally caused by spread from a contiguous soft tissue source or from sinus, ear, or dental infection. Intestinal anaerobes originating from decubitus ulcers (Chapter 407) are involved in pelvic osteomyelitis. Osteomyelitis of long bones and septic arthritis are generally caused by hematogenous spread, trauma, or the presence of a prosthetic device. The most commonly recovered anaerobes are peptostreptococci and *C. acnes* (often in prosthetic joint infection), *B. fragilis* group and fusobacteria (often of hematogenous origin), and clostridia (associated with trauma).

DIAGNOSIS

Anaerobic infections should be suspected in a number of specific clinical scenarios (Table 273-2). An appropriately collected microbiologic specimen (Table 273-3) is critical for accurate diagnosis. Anaerobic bacteremia is associated with a substantially increased risk of colorectal cancer,[7] so an appropriate evaluation is indicated unless the patient has an obvious other source.

TABLE 273-2 CLINICAL INDICATORS OF ANAEROBIC INFECTION

Infection adjacent to a mucosal surface
Foul-smelling discharge
Necrotic gangrenous tissue and abscess formation
Free gas or crepitus in tissue
Bacteremia or endocarditis with no growth on aerobic blood cultures
Infection related to the use of antibiotics effective against aerobes only (e.g., trimethoprim-sulfamethoxazole, aminoglycosides, older quinolones)
Infection related to tumors or other destructive processes
Infected thrombophlebitis
Infection after bites
Black discoloration of exudates containing *Prevotella melaninogenica*, which may fluoresce under ultraviolet light
"Sulfur granules" in discharges caused by actinomycosis
Clinical finding of gas gangrene or necrotizing fasciitis
Clinical condition predisposing to anaerobic infection (e.g., after maternal amnionitis, fistulous tracks, bites, dental infection, bowel perforation)

TABLE 273-3 SPECIMEN ACCEPTABILITY FOR ANAEROBIC CULTURE

SPECIMENS THAT SHOULD NOT BE CULTURED FOR ANAEROBES
Feces or rectal swabs
Throat or nasopharyngeal swabs
Sputum or bronchoscopic specimens
Routine or catheterized urine
Vaginal or cervical swabs
Material from superficial wounds or abscesses not collected properly to exclude surface contamination
Material from abdominal wounds obviously contaminated with feces, such as an open fistula
SPECIMENS APPROPRIATE FOR ANAEROBIC CULTURE
All normally sterile body fluids other than urine, such as blood, pleural fluid, and joint fluid
Urine obtained by suprapubic bladder aspiration
Percutaneous transtracheal aspiration, direct lung puncture, or double-lumen catheter bronchial brushing and bronchoalveolar lavage (both cultured quantitatively)
Culdocentesis fluid obtained after decontamination of the vagina
Material obtained from closed abscesses
Material obtained from sinus tracks or draining wounds

TREATMENT

General principles of treatment (Table 273-4) include appropriate antimicrobial therapy coupled with prompt drainage, decompression of closed space infections, relief of obstructions, and surgical débridement. The various clinically important anaerobes can be characterized by reasonably predictable antimicrobial susceptibility patterns (Table 273-5). However, some anaerobes have become resistant to antimicrobials,[8] and many can develop resistance during therapy. Reliable culture and sensitivity results should ultimately guide therapy. The efficacy of hyperbaric oxygen is unproven, but its use in conjunction with other therapeutic measures may be beneficial.

In choosing antimicrobials for the treatment of mixed infections, their aerobic and anaerobic antibacterial spectra and their availability in oral or parenteral form should be considered. Some antimicrobials have a limited range of activity. For example, metronidazole is active only against anaerobes and therefore cannot be administered as a single agent for the treatment of mixed infections. Others (i.e., carbapenems, a penicillin plus a β-lactamase inhibitor) have wide spectra of activity against aerobes and anaerobes.

Aside from susceptibility patterns, other factors influencing the choice of antimicrobial therapy include the pharmacologic characteristics of the various drugs, their toxicity, their effect on normal flora, and their bactericidal activity. Although identification of the infecting organisms and their antimicrobial susceptibility may be needed for selection of optimal therapy, the clinical setting and Gram stain preparation of the specimen may suggest the types of anaerobes present in the infection and the nature of the infectious process.

Even though the length of therapy for anaerobic infections is generally longer than that for aerobic and facultative infections, the length of treatment must be individualized, depending on the response. In some cases, treatment may require 6 to 8 weeks, but therapy may be shortened with proper surgical drainage. For example, management of head and neck anaerobic infection usually requires surgical drainage as well as appropriate antimicrobial therapy. An anti–gram-negative enteric agent is generally added to treat Enterobacteriaceae in managing intra-abdominal infections.

The available parenteral antimicrobials for most infections are metronidazole, chloramphenicol, clindamycin, cefoxitin, a penicillin (e.g., ticarcillin, ampicillin, piperacillin) and a β-lactamase inhibitor (e.g., clavulanic acid, sulbactam, tazobactam), a carbapenem (e.g., imipenem, meropenem, doripenem, ertapenem), and tigecycline. Resistance is emerging against clindamycin, cefoxitin, cefotetan, and moxifloxacin in the *B. fragilis* group.

An agent effective against gram-negative enteric bacilli (e.g., an aminoglycoside, fluoroquinolone) or an antipseudomonal cephalosporin (e.g., cefepime) is generally added to metronidazole and, occasionally, cefoxitin in the treatment of intra-abdominal infections. In one randomized trial of adult patients with complicated intra-abdominal infections, including infections caused by multidrug-resistant pathogens, treatment with ceftolozane/tazobactam plus metronidazole was equivalent to meropenem.[A1] By comparison, adding metronidazole to ceftriaxone and doxycycline reduces pain but does not clearly improve outcomes.[A2] Penicillin can be added to metronidazole for the treatment of intracranial, pulmonary, or dental infections to cover microaerophilic streptococci and *Actinomyces* species. Penicillin is added to clindamycin to supplement its coverage against *Peptostreptococcus* species and other gram-positive anaerobic organisms.

For *Chlamydia* and *Mycoplasma* species, doxycycline is added to most regimens in treatment of pelvic infections. Oral therapy is often substituted for parenteral therapy. The agents available for oral therapy are clindamycin, amoxicillin and clavulanate, and metronidazole.

If the anaerobic component of aspiration pneumonia is not treated, the anaerobes can cause a lung abscess (Chapter 78). Management requires good pulmonary toilet and antimicrobial therapy. Management of deep-seated soft tissue infection includes surgical débridement, drainage, and vigorous surgical management.

TABLE 273-4 GENERAL PRINCIPLES OF THERAPY FOR ANAEROBIC INFECTIONS

Decompression of closed spaces
Débridement
Drainage
Relief of obstructions
Irrigation
Provision of adequate circulation when possible
Removal of foreign bodies
Antimicrobials
Activity against most likely pathogen or pathogens: location dependent, minimal effect on normal flora
Absorption, appropriate route of administration (intravenous, oral)
Penetration into site of infection
Dosage appropriate for local tissue levels, body mass of patient, renal and liver function
Duration appropriate for condition
Susceptibility testing of isolate to guide specific therapy

TABLE 273-5 ANTIMICROBIAL SUSCEPTIBILITY PATTERNS FOR ANAEROBIC BACTERIA*

BACTERIA	PENICILLIN	A β-LACTAM PLUS β-LACTAMASE INHIBITOR†	CEFOXITIN	CEFOTETAN	CARBAPENEMS, TIGECYCLINE	MOXIFLOXACIN	CLINDAMYCIN	METRONIDAZOLE
Bacteroides fragilis	–	+	+	+	+	+	V	+
Bacteroides thetaiotaomicron	–	+	V	V	+	V	V	+
B. fragilis group, other	–	+	V	V	+	+	V	+
Prevotella spp	V	+	+	+	+	+	+	+
Fusobacterium nucleatum	V	+	+	+	+	V	+	+
Fusobacterium necrophorum	+	+	+	+	+	V	+	+
Porphyromonas spp	+	+	+	+	+	+	+	+
Peptostreptococcus spp	+	+	+	+	+	+	+	V
Cutibacterium acnes	+	+	+	+	+	+	+	–
Veillonella	+	+	+	+	+	+	+	+
Actinomyces	+	+	+	+	+	+	+	–

*Based on a variety of in vitro susceptibility studies from different laboratories and using different techniques.
†β-Lactamase inhibitor–β-lactam combination (e.g., amoxicillin-clavulanate, ticarcillin-clavulanate, ampicillin-sulbactam, piperacillin-tazobactam, ceftolozane-tazobactam, ceftazidime-avibactam).
Antimicrobials can be administered parenterally or orally in the recommended doses (see Table 266-4), with durations of treatment depending on the clinical response, typically with expert consultation.
+ = susceptible; – = resistant; V = variable.

PREVENTION

Randomized trials have shown that prophylactic antibiotics covering both anaerobic and aerobic bacteria administered intravenously before elective colorectal surgery and briefly orally thereafter reduce the risk of surgical wound infection by as much as 75%.[A3]

PROGNOSIS

Anaerobic infections usually respond to appropriate therapy. However, mortality associated with *B. fragilis* group bacteremia is 15 to 30%.

GENERAL REFERENCES

For the General References and other additional features, please visit Elsevier eBooks+ at https://ebooks.health.elsevier.com.

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A2. Wiesenfeld HC, Meyn LA, Darville T, et al. A randomized controlled trial of ceftriaxone and doxycycline, with or without metronidazole, for the treatment of acute pelvic inflammatory disease. *Clin Infect Dis.* 2021;72:1181-1189.

A3. Nelson RL, Hassan M, Grant MD. Antibiotic prophylaxis in colorectal surgery: are oral, intravenous or both best and is mechanical bowel preparation necessary. *Tech Coloproctol.* 2020;24:1233-1246.

274 *NEISSERIA MENINGITIDIS* INFECTIONS

DAVID S. STEPHENS

DEFINITION

Neisseria meningitidis (the meningococcus) is the cause of epidemic bacterial meningitis, fulminant sepsis (meningococcemia), milder bacteremia, and, less commonly, focal infections (such as pneumonia, septic arthritis, purulent pericarditis, urethritis, and conjunctivitis).

The Pathogen

N. meningitidis is an aerobic, diplococcal gram-negative β-proteobacterium and a member of the family Neisseriaceae, which also includes *Neisseria gonorrhoeae* (Chapter 275), the cause of gonorrhea. The meningococcus is a frequent commensal of the human upper respiratory tract but can also cause local and devastating invasive human disease. Human mucosal surfaces, most commonly the nasopharynx but sometimes the rectum and urogenital tract, are the important reservoirs. In addition to commensal unencapsulated meningococci, there are 12 confirmed serogroups of *N. meningitidis*, based on different capsular polysaccharide structures. However, only 6 groups (A, B, C, W, X, and Y) cause almost all invasive meningococcal disease globally (Fig. 274-1). Highly pathogenic meningococci are also distinguished by capsule expression and by genetically defined clonal complexes and genotypes that can emerge and spread worldwide.

EPIDEMIOLOGY

The meningococcus can cause sporadic disease, case clusters, epidemics, and pandemics of meningitis and septicemia and less commonly of pneumonia and other local infections. In the pre-vaccine era, an estimated 500,000 to 1 million cases occurred worldwide each year, but the incidence has been dramatically lowered, related to the widespread use of vaccines.[1] The greatest burden of disease is in sub-Saharan Africa, where endemic rates of disease have been 3 to 10 per 100,000 population, but rates were 1 per 1000 population during the historic cyclic pandemics that occurred every 8 to 10 years. The introduction in 2010 of a new meningococcal conjugate vaccine for group A (MenAfriVac) eliminated group A outbreaks in the region, but less severe outbreaks of group C, X, and W continue.[2]

Overall incidence has declined, aided by the expanded use of the meningococcal ACWY conjugate and group B directed vaccines,[3] and the decline has been accelerated by containment measures for severe acute respiratory syndrome coronavirus 2 (SARS-CoV2; Chapter 336). Nevertheless, meningococcal disease remains sporadic[4] (incidence less than 0.1 to 2 per 100,000 population), with focal outbreaks/clusters in the United States, Canada, Mexico, Europe, Japan, Australia, China, Russia, South America (Chile, Brazil, Argentina), India, Southeast Asia, and other countries. Organization-based and university outbreaks are mostly caused by group B, whereas group C is the primary cause of community-based outbreaks. Meningococcal disease has its highest incidence in children below age 4 years (often group B) and in adolescents; but in sporadic settings, half of all cases occur in adults.

Asymptomatic carriage in the oropharynx is much more common (about 7-10% among adolescents ages 15 to 19 years in developed countries) than symptomatic infection, and the prevalence of meningococcal carriage is declining in many populations.[5] Asymptomatic carriage has been linked to social

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Prevotella spp	V	+	+	+	+	+	+	+
Fusobacterium nucleatum	V	+	+	+	+	V	+	+
Fusobacterium necrophorum	+	+	+	+	+	V	+	+
Porphyromonas spp	+	+	+	+	+	+	+	+
Peptostreptococcus spp	+	+	+	+	+	+	+	V
Cutibacterium acnes	+	+	+	+	+	+	+	–
Veillonella	+	+	+	+	+	+	+	+
Actinomyces	+	+	+	+	+	+	+	–

*Based on a variety of in vitro susceptibility studies from different laboratories and using different techniques.
†β-Lactamase inhibitor–β-lactam combination (e.g., amoxicillin-clavulanate, ticarcillin-clavulanate, ampicillin-sulbactam, piperacillin-tazobactam, ceftolozane-tazobactam, ceftazidime-avibactam).
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274 *NEISSERIA MENINGITIDIS* INFECTIONS

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EPIDEMIOLOGY

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ABSTRACT

The human bacterial pathogen *Neisseria meningitidis* remains a cause of meningitis, sepsis, and focal infections (pneumonia, septic arthritis, purulent pericarditis urethritis, conjunctivitis) worldwide, but effective vaccines are improving global control. An asymptomatic carrier state is found in 8 to 25% of healthy individuals, often with unencapsulated strains or strains with low virulence. Most meningococcal disease is caused by encapsulated meningococci of groups A, B, C, W, Y, and X expressed by several hypervirulent genomic clonal complexes. Predisposing factors for systemic meningococcal disease include absence of protective bactericidal antibodies (young children), complement component deficiencies (congenital or acquired, such as individuals treated with the complement inhibitor eculizumab), and congenital or acquired antibody deficiencies. Mortality remains approximately 10% for invasive meningococcal disease, and long-term sequelae are significant in 10 to 20% of survivors. Early recognition and antibiotic therapy (e.g., ceftriaxone) are central for effective treatment of invasive meningococcal disease. Prevention of disease in close contacts is accomplished with chemoprophylaxis. Vaccines are effective to prevent disease from groups A, C, W, Y, B, and soon X in at-risk populations.

KEYWORDS

Neisseria meningitidis
meningococcus
meningococcemia
meningitis
chemoprophylaxis
vaccines

FIGURE 274-1. Epidemiology of meningococcal disease (2022 global distribution of major capsular groups causing disease by region). (Modified from Stephens DS, Greenwood B, Brandtzaeg P. Epidemic meningitis, meningococcemia, and *Neisseria meningitidis*. *Lancet*. 2007;369:2196-2210.)

behavior (e.g., attendance at pubs or clubs, intimate kissing, cigarette smoking, or exposure to passive smoke). Carriage, which can be transient or persist for days, weeks, or months, is an immunizing event leading to protective immunity (e.g., serum bactericidal activity against the meningococcus).

PATHOBIOLOGY

N. meningitidis is transmitted among humans through close contact by large respiratory droplets or saliva. Colonization of the upper respiratory or other mucosal surfaces (e.g., nasopharynx) by *N. meningitidis* is the first step in establishing a human carrier state. Acquisition of meningococci through contact with secretions can be transient, lead to prolonged nasopharyngeal carriage, or result in invasive disease. The inoculum size needed for transmission is unknown. Invasive meningococcal disease usually occurs within 1 to 14 days after acquisition. Meningococci can also spread from the nasopharynx to adjacent epithelial surfaces, where they infrequently cause local infections, including pneumonia, sinusitis, and otitis media. Meningococci also can be found in the conjunctivae, urogenital tract, and rectum, and they may be transmitted sexually.[6]

Initial contact of meningococci with mucosal epithelial cells is mediated by type IV pili. These structures provide mobility ("twitching motility") to penetrate mucus and are the initial adhesins for human epithelial cells. Meningococci proceed to proliferate and form small microcolonies on the surface of human nonciliated epithelial cells. They can disseminate from colonies by post-translational glycan modifications of pili and migrate to adjacent cells by the pili-mediated motility. Close adherence of meningococci to the host epithelial cells results in the formation of epithelial cell cortical plaques and leads to the recruitment of factors ultimately responsible for the formation and extension of host epithelial cell pseudopodia that can tightly bind the meningococcus. Intimate meningococcal association with the epithelial cell is mediated by the meningococcal surface components, including opacity proteins Opa and Opc with CD66/carcinoembryonic antigen–related cell adhesion molecules and integrins, respectively, on the surface of the human cell. Other meningococcal epithelial cell mediators include the meningococcal adhesin NadA and meningococcal lipo-oligosaccharide. The formation of epithelial cell membrane protrusions and pseudopodia stems from the organization of specific molecular complexes involving the linkers ezrin and moesin along with the clustering of several membrane-integral proteins, including CD44, intracellular adhesion molecule 1, and cortical actin polymerization. These events can lead to internalization of *N. meningitidis* in epithelial cells (E-Fig. 274-1). Intracellular meningococci reside within a membranous vacuole and are capable of translocating across the epithelial layer. Meningococci are capable of intracellular replication (in part because of the protective capsule), can survive under microaerophilic conditions, use lactate as a carbon source, and have the capacity to acquire iron through specialized transport systems.

Damage to the mucosal surface by coinfections, drying (e.g., very low humidity), or smoke exposure may increase the risk for meningococcal carriage and invasion. Meningococci may cross mucosal surfaces, enter the blood stream to cause bacteremia, and, in some individuals, produce systemic infections. Asymptomatic meningococcal carriage also has been linked to status as a secretor of glycoprotein ABO blood group antigens, which are water soluble. Similar molecular interactions noted for meningococci and epithelial cells also occur with endothelial cells, and meningococci can translocate across the blood-meninges barrier, possibly at the choroid plexus or by the opening of intercellular junctions, and proliferate in the subarachnoid space, thereby causing meningitis. In the vasculature and cerebrospinal fluid (CSF), high levels of multiplying bacteria lead to an intense inflammatory response, with pronounced increases in concentrations of tumor necrosis factor-α, interleukins (1β, 6, 8, and 10), other chemokines, and inflammatory mediators.

Meningococcal resistance to complement-mediated lysis or phagocytosis is due to the expression of the capsule, lipo-oligosaccharide, and several surface-exposed proteins (factor H–binding protein, NspA, Opc, NalP). Meningococcal endotoxin released in blebs plays a major role in the inflammatory events of meningococcemia and meningococcal meningitis. Meningococcal lipid A is responsible for much of the biologic activity and toxicity of meningococcal endotoxin. Activation of toll-like receptor 4 (TLR-4) by endotoxin requires association with the accessory protein MD-2, an *N*-glycosylated 19- to 27-kD protein expressed in both a soluble and a membrane-bound form. Binding of endotoxin to MD-2 in association with TLR-4 leads to dimerization or oligomerization of two or more TLR-4s, subsequent cellular activation, and cytokine and chemokine release.

The absence of protective bactericidal antibodies is the most important predisposing risk factor for systemic meningococcal disease, but complement deficiencies (congenital or acquired such as with the complement inhibitors eculizumab and ravulizumab [Chapter 29]), genetic polymorphisms, and other host cofactors can contribute to meningococcal disease and disease severity. Disappearance of protective maternal antibodies increases the risk in older infants and young children. Congenital and acquired antibody deficiencies also increase risk. Opsonization and phagocytic function also contribute to meningococcal host defense mechanisms, as shown by disease reduction after meningococcal vaccination in individuals with terminal complement deficiencies (Chapter 37).[7] Rapidly progressive, fatal meningococcemia can arise in patients without properdin, and there is a marked risk for recurrent meningococcal infections in individuals with defects in the terminal complement pathway (C5-C9) and C3 deficiency.

Polymorphisms in genes coding for the Fcγ-receptor II (CD32), Fcγ-receptor III (CD16), mannose-binding lectin, TLR-4, and the β_2-adrenoceptor gene have been associated with increased risk. Plasminogen activator inhibitor 1 concentrations appear to affect the severity and mortality of meningococcal sepsis, thereby suggesting that impaired fibrinolysis is an important factor in its pathophysiology. Meningococcal disease is also linked to immunosuppressive disorders, such as nephrotic syndrome (Chapter 107), congenital or acquired hypogammaglobulinemia (Chapter 231), splenectomy, and human immunodeficiency virus (HIV)/acquired immunodeficiency syndrome (AIDS; Chapter 358) (about a 10-fold increased risk for sporadic meningococcal disease). However, there has not been a documented increase in epidemic outbreaks of meningococcal disease in countries with high rates of HIV infection.

Meningococci can multiply rapidly in the vascular compartment, with an estimated doubling time of 30 to 45 minutes in some patients, or in the CSF. The release of high levels of inflammatory mediators such as meningococcal

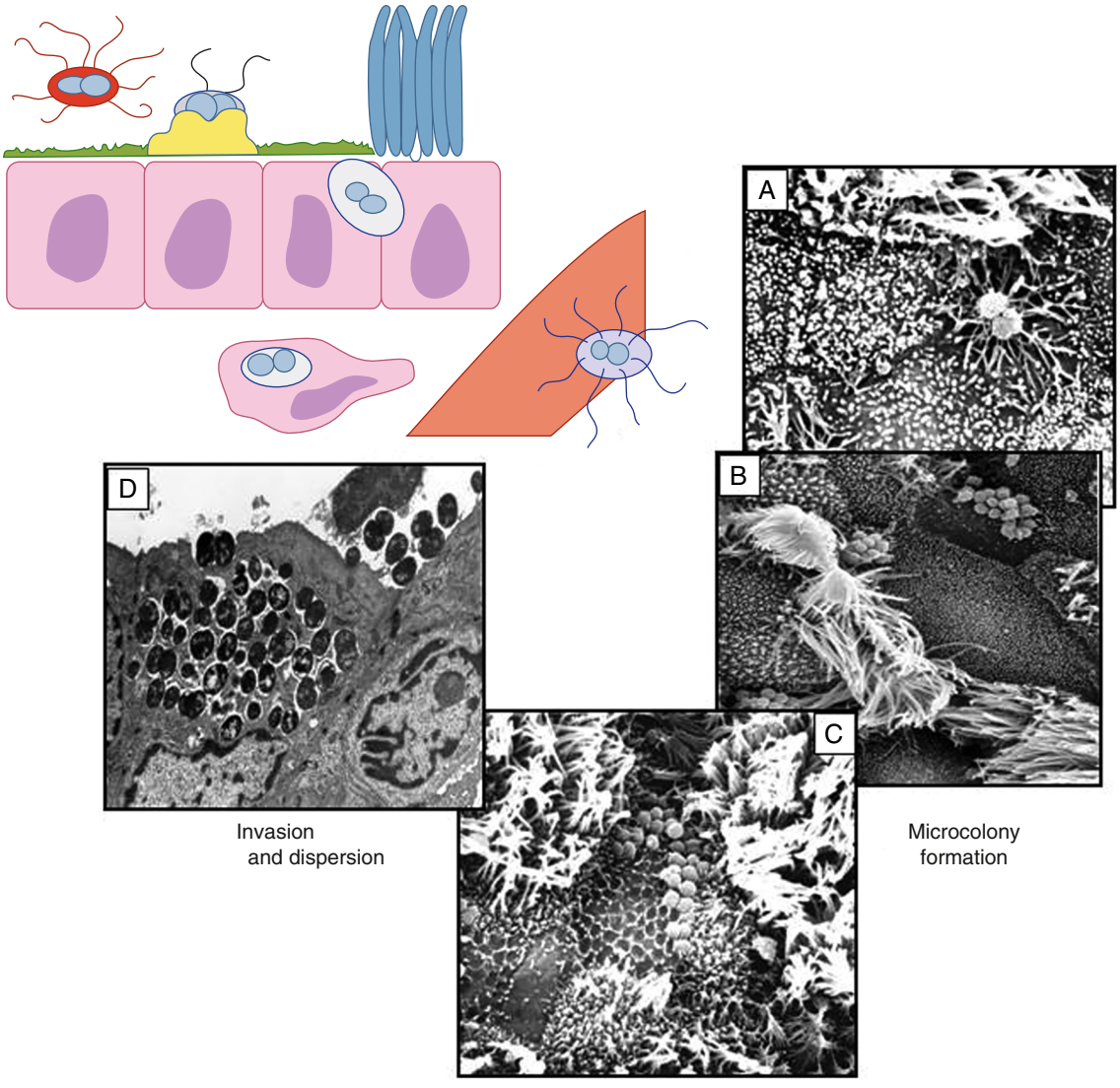

E-FIGURE 274-1. **Steps in initiation of meningococcal colonization and invasion at the human nasopharynx. A,** Adhesion and introduction of cell microvilli. **B,** Microcolony formation. **C,** Cortical plaque formation and close adherence. **D,** Human epithelial cell invasion. (Modified from Stephens DS. Biology and pathogenesis of the evolutionarily successful, obligate human bacterium *Neisseria meningitidis*. *Vaccine*. 2009;27[Suppl 2]:B71-B77.)

endotoxin in the circulation or CSF triggers an exaggerated release of chemokines, cytokines, bradykinin, and nitric oxide. Vascular dilation, hypovolemia, capillary leak, and pronounced reduction in myocardial function are the result. At a later stage, substantial complement activation contributes to the altered endothelial barrier function and relaxation of the smooth muscles in the vessel wall through the generation of high levels of anaphylatoxins (C3a and C5a). The capillary leak syndrome results in an increased flux of albumin and water across the altered capillary wall to the extravascular space. Circulatory collapse and multiorgan dysfunction are the primary causes of death due to meningococcemia. In meningitis, morbidity and death are due predominantly to cerebral edema.

CLINICAL MANIFESTATIONS

The meningococcus causes meningitis (37 to 50% of invasive cases), septicemia (meningococcemia, 10 to 18% of cases), or both (7 to 12% of cases). Less common presentations are a mild bacteremia or pneumonia (10% of cases) and, in less than 5% of cases, septic arthritis, pericarditis, chronic bacteremia, or conjunctivitis. Meningococci can cause urethritis or proctitis. In endemic and epidemic disease outbreaks, hemorrhagic skin lesions (petechiae, purpura; Fig. 274-2) are present in about 25 to 75% of patients with meningococcal disease on admission, but these lesions may be absent or difficult to see in patients with dark skin. Hemorrhagic lesions sometimes occur on mucous membranes and sclerae, but they are especially prevalent on the limbs. The petechiae of meningococcemia are usually larger and bluer than the pinpoint petechiae caused by thrombocytopenia or leukocytoclastic vasculitis induced by other infections or drugs. A nonblanching macular rash also can be a manifestation of meningococcal bacteremia. Evolving ecchymoses and purpura (diameter >10 mm) are noted mainly in patients with meningococcemia and disseminated intravascular coagulation (Chapter 161), but they may not appear until 12 hours into the illness. In addition to vasculitis, other conditions in the differential diagnosis of meningococcemia include Rocky Mountain spotted fever (Chapter 302) and enteroviral infections (Chapter 349).

Meningitis (Chapter 381) is the most common clinical presentation of invasive meningococcal disease.[8] Headache, fever, and rash with meningismus and altered mental status are the characteristic features; however, the rash may be absent, and the presentation can resemble pneumococcal or bacterial meningitis of other causes, viral meningitis, or early-stage encephalitis. Bacteremic meningococcal pneumonia has been linked more often to groups Y and W and is more common in adolescents and adults, especially older adults (approximately one third of cases occur in patients older than 65 years). Acute presentations also include isolated septic pericarditis or septic arthritis, and autoimmune- or antibody-mediated polyarthritis can be seen in the recovery phase following invasive meningococcal disease. Chronic meningococcemia can be manifested with low-grade fever and a polyarticular arthritis that can be confused with rheumatoid arthritis.

In contrast to invasive disease, an asymptomatic *N. meningitidis* carrier state is found in up to 8 to 25% of healthy individuals. Meningococcal carriage rates are affected by age, intimate personal contact, crowding (e.g., bars, dormitories), and vaccination or chemoprophylaxis interventions in the community. Variable carriage rates have been reported, even during epidemics. Meningococcal carriage is a dynamic process, is less common in young children (<3% and *Neisseria lactamica* predominates) than in older children, is highest in adolescents (7 to 37%), and increases in closed populations (e.g., military recruits, Hajj pilgrims),[9] with rates as high as 35 to 70% reported in military recruits.

DIAGNOSIS

The clinical diagnosis of meningococcal meningitis relies on the recognition of fever, rash, meningeal signs, and altered mental status. The early clinical diagnosis of meningococcemia is a challenge because a rash, meningeal signs, and high fever may not be present. General symptoms of sepsis (nausea and vomiting, drowsiness, irritability, leg pains, cold hands and feet, abnormal skin color) are present, but these symptoms and signs are not specific, and the early stages of disease can mimic viral infections such as those caused by enteroviruses (Chapter 349) or influenza (Chapter 332). Parents and relatives should be instructed to undress and inspect a febrile patient for a rash. The course can be fulminant (<24 hours), so physicians must be alert to any rapid clinical deterioration.

The definitive diagnosis of invasive meningococcal disease is based on bacteriologic isolation or identification of *N. meningitidis* DNA or antigen in a usually sterile body fluid, such as blood, CSF, synovial fluid, pleural fluid, urine, or pericardial fluid. Polymerase chain reaction (PCR) testing, which is increasingly the assay of choice for the diagnosis of meningococcal disease,

FIGURE 274-2. Clinical manifestations of meningococcal disease. A and B, Macular and petechial rashes of meningococcal bacteremia. **C,** Fulminant meningococcal sepsis with ecchymoses. **D,** Digital necrosis of meningococcemia sepsis. **E,** Hemorrhagic adrenals in fulminant meningococcal sepsis. (Modified from Stephens DS, Greenwood B, Brandtzaeg P. Epidemic meningitis, meningococcemia and *Neisseria meningitidis*. *Lancet*. 2007;369:2196-2210.)

can identify serogroups and has the potential to detect antibiotic resistance.[10] The sensitivity of PCR for the diagnosis of meningococcal meningitis is 90 to 95%; in contrast, the sensitivity of CSF or blood culture (often because of prior antibiotic administration) is less than 65%, and skin and urine are even less sensitive sites.

Blood and CSF are the most fruitful sources of positive cultures and for DNA identification by the PCR, but urine and skin lesions can also yield results in systemic meningococcal disease. The diagnosis of meningococcal meningitis is confirmed by CSF pleocytosis, Gram stain showing gram-negative diplococci (often inside neutrophils), CSF culture, PCR identifying *N. meningitidis* in CSF, or latex agglutination detecting meningococcal capsular polysaccharide in CSF. However, an increasing number of patients are now diagnosed by PCR without culture, especially if they have received empirical prehospital antibiotic treatment. Whole genome sequencing is being increasingly used as an epidemiologic and organism confirmation tool.

TREATMENT

Early recognition and administration of antibiotics (Table 274-1) are critical for successful treatment, because effective antibiotics immediately stop the growth of *N. meningitidis*.[11] Ceftriaxone and cefotaxime, which can achieve CSF concentrations 45- to 8750-fold higher than the minimal inhibitory concentrations for meningococci, are the most effective antibiotics, but meropenem is also effective in most cases.[12] Chloramphenicol is an alternative in patients who are allergic to penicillin and cephalosporins. The sensitivity of meningococci to penicillin is decreasing worldwide because of a reduced affinity for penicillin-binding protein 2 and the emergence of beta-lactamase–producing meningococci. Fluoroquinolones and aztreonam are potential alternatives, but data on meningococcal disease are limited, and fluoroquinolone-resistant meningococci have become more prevalent. First-generation cephalosporins should not be used.

Meningococci in CSF are killed within 3 to 4 hours after intravenous treatment with an adequate dose of a third-generation cephalosporin, and concentrations of endotoxin in plasma fall by 50% within 2 hours. The concentrations of key cytokines and chemokines fall in parallel. Antibiotic treatment does not induce a large release of meningococcal endotoxin or lead to an increased inflammatory response. Intravenous treatment for 3 or 4 days can provide a cure without relapse.

Prehospital antibiotic treatment is advocated if the disease is suspected. The goal is to reduce the case-fatality rate for patients with fulminant meningococcal sepsis or meningitis with rapidly increasing concentrations of meningococci and inflammatory mediators in the circulation or CSF. If antibiotic treatment is initiated before admission, ceftriaxone or another effective antibiotic can be injected intravenously or intramuscularly. During epidemics in developing countries, a single injection of ceftriaxone or long-acting chloramphenicol may be sufficient for patients with meningitis, and this simple treatment has saved many thousands of lives.

Patients with suspected bacterial meningitis of unknown cause are often given intravenous ceftriaxone or cefotaxime, often combined with vancomycin, until the causative agent has been identified. When *N. meningitidis* is identified, antibiotic treatment can be continued with an antibiotic to which it is highly sensitive.

TABLE 274-1 ANTIBIOTIC TREATMENT OF MENINGOCOCCAL MENINGITIS AND MENINGOCOCCEMIA

DRUG	AGE GROUP	DOSAGE
Ceftriaxone*	Children >3 months	50 mg/kg IV q12h
	Adults	1-2 g IV q12h
Cefotaxime	Adults	50-75 mg/kg IV q6-8h; maximum dose, 12 g/day
Meropenem	Adults	2 g IV q8h, 6 g/day
Penicillin G†	Adults	50,000 U/kg IV q4h; up to 4 million U q4h
If penicillin and cephalosporin allergic, chloramphenicol†	Adults	25 mg/kg IV q6h, up to 1 g q6h

*Because of concerns in neonates from calcium/ceftriaxone precipitates and displacement of bilirubin from albumin by ceftriaxone, babies younger than 3 months should be started on cefotaxime 50 mg/kg q6-8h.
†Use only if isolate found to be susceptible to penicillin.
‡Aztreonam or fluoroquinolones are potential alternatives.
IV = intravenous; q = once every.

Adjunctive Therapy

Meningococcemia

For meningococcal sepsis, early and aggressive management of shock can reduce case-fatality rates of meningococcal sepsis from higher than 30% to 5 to 10%. In meningococcemia with hypotension, aggressive fluid treatment starts with 1 L saline infused intravenously during 15 to 20 minutes, followed by several liters at a reduced rate. Some patients require two to three times their own blood volume during the first 24 hours. Fluid treatment may need to be combined with a vasopressor (see Chapter 94), while monitoring and correcting acidosis, hypoglycemia, hypokalemia, hypocalcemia, and hypomagnesemia.

Patients with fulminant meningococcal septicemia can develop adrenal hemorrhage (Waterhouse-Friderichsen syndrome). The corticotropin concentration is higher, the cortisol concentration is lower, and the corticotropin-to-cortisol ratio is higher in patients with fatal meningococcal shock than in survivors. Adults with septic shock and indications of inadequate adrenal function should be given low doses of steroids (e.g., hydrocortisone 50 mg intravenously over 6 hours, four times daily for 7 days).

Anticoagulant treatment of patients with meningococcemia and disseminated intravascular coagulation does not improve outcomes, nor does using hyperimmune serum, antibodies, blockade of inflammatory mediators, or recombinant bactericidal or permeability-increasing protein (designed to inactivate *N. meningitidis* endotoxin). Plasmapheresis, blood exchange, and extracorporeal membrane oxygenation have been used in patients with meningococcemia, but no controlled trials have been done. Extracorporeal membrane oxygenation has been tried in several centers.

Meningococcal Meningitis

Patients with meningitis without shock should be given the normal daily fluid requirement, supplemented with the volume lost before admission unless there is evidence of the syndrome of inappropriate antidiuretic hormone (Chapter 102). Excessive volume treatment in patients with meningitis can induce fatal brain edema and herniation. Management of raised intracranial pressure (hyperosmolar solutions, diuretics, mechanical ventilation), seizures, and hyponatremia in neurointensive care is indicated.

Pharmacologic doses of dexamethasone reduce hearing loss in pneumococcal and *Haemophilus influenzae* type b meningitis (Chapter 381).[A1] However, the benefit of dexamethasone to reduce death or to prevent other sequelae in patients with meningococcal meningitis remains unproven on the basis of large randomized controlled trials, even though trends toward reductions in hearing loss, mortality, and arthritis after meningococcal disease are reported. Many experts recommend that dexamethasone (10 mg every 6 hours; 0.15 mg/kg every 6 hours in children) be given for 4 days beginning before (for maximal efficacy) or with the first dose of antibiotics in suspected or confirmed bacterial meningitis.

Other Complications

Other major life-threatening complications requiring intervention include acute respiratory distress syndrome (Chapter 90), neurologic sequelae ranging from coma (Chapter 373) to diabetes insipidus (Chapter 206), pneumonia that is not necessarily meningococcal but may be secondary to aspiration during the obtunded state (Chapter 373), and purulent pericarditis (Chapter 62) with tamponade.

Immune complex–mediated complications, such as arthritis, cutaneous vasculitis, iritis, episcleritis, pleuritis, and pericarditis, can first appear several days to 2 to 3 weeks after onset of illness, when the patient is otherwise improving. These complications, which can be multiple, are due to the deposition of antigen-antibody complexes composed of meningococcal capsular polysaccharide or other antigens, meningococcal-specific immunoglobulins, and C3. They complicate 6 to 15% of cases of meningococcal meningitis or septicemia. Treatment is with typical doses of aspirin or nonsteroidal anti-inflammatory drugs, and resolution is complete, usually within 14 days from the onset and usually without residual sequelae.

PREVENTION

The occurrence of meningococcal disease in household contacts is approximately 100-fold higher than in the general population. Secondary cases usually occur within 1 to 14 days of the primary case. Chemoprophylaxis (Table 274-2), which is recommended for close contacts of patients to prevent further transmission and disease, eliminates meningococcal carriage and can be helpful to control localized outbreaks. Rifampin, ceftriaxone, azithromycin,[13] and quinolones (but not penicillin) have the ability to eradicate meningococci in the nasopharynx. Most meningococcal isolates are now resistant to sulfonamides; resistance to rifampin can develop rapidly, and quinolone-resistant meningococci are increasing.

Providing vaccination to at-risk individuals is the best option for the long-term control of meningococcal disease.[14] Meningococcal polysaccharide-protein conjugate vaccines for A, C, Y, and W have been used globally and can decrease nasopharyngeal carriage of meningococci as well as invasive meningococcal disease.[15] Vaccination is recommended for children ages 2

TABLE 274-2 CHEMOPROPHYLAXIS AGAINST MENINGOCOCCAL INFECTION

DRUG	AGE GROUP	DOSAGE	DURATION AND ROUTE OF ADMINISTRATION*	CONSIDERATIONS
Rifampin	Children <1 month	5 mg/kg q12h	2 days, oral	
	Children >1 month	10 mg/kg q12h (maximum, 600 mg)	2 days, oral	Rifampin can interfere with efficacy of oral contraceptives and some seizure prevention and anticoagulant medications; may stain soft contact lenses
	Adults	600 mg q12h	2 days, oral	Not recommended for pregnant women
Ceftriaxone	Children <15 years	125 mg	Single IM dose	
	Children >15 years and adults	250 mg	Single IM dose	Ceftriaxone is recommended for prophylaxis in pregnant women
Ciprofloxacin	Adults	500 mg	Single dose, oral	Not recommended routinely for persons <18 years of age, but use in infants and children (20 mg/kg) may be justified after careful assessment of the risks and benefits Not recommended for pregnant or lactating women Cases of ciprofloxacin resistance have been increasingly reported and use for prophylaxis should be based on local sensitivity of the meningococcus to the drug
Azithromycin		10 mg/kg (maximum, 500 mg)	Single dose, oral	Equivalent to rifampin for eradication of meningococci from nasopharynx, but data are limited

ANTIBIOTIC CHEMOPROPHYLAXIS FOR HOUSEHOLD OR INTIMATE CONTACTS

- Household contacts and persons sharing the same living quarters, particularly young children
- Daycare center, nursery school, or child-care contacts; frequent playmates of young children
- Close social contacts who were exposed to oral secretions in the week before onset, such as by kissing and sharing of eating and drinking utensils or toothbrushes
- For airline travel lasting more than 8 hours, passengers who are seated directly next to an infected person should receive prophylaxis.
- Routine prophylaxis is not recommended for health care professionals unless they have had intimate exposure to respiratory secretions.
- Because the risk for secondary cases is highest during the first few days after exposure, chemoprophylaxis should be initiated as soon as possible, ideally <24 hours after identification of the index patient.
- If more than 14 days have passed since the last contact with the index patient, chemoprophylaxis is not likely to be of benefit.
- Pharyngeal cultures are not helpful in determining the need for chemoprophylaxis and may unnecessarily delay the use of effective chemoprophylaxis.
- Chemoprophylaxis has also been recommended for patients given penicillin or chloramphenicol for treatment because pharyngeal carriage may not be eliminated with these antibiotics and the patient could remain colonized with a virulent strain.
- Ceftriaxone is recommended for pregnant women.
- May want to avoid ciprofloxacin or azithromycin in individuals at risk for QT-prolongation.

*Administered orally unless otherwise stated.
Recommended groups for chemoprophylaxis based on exposure to the case in the week before onset of illness.
IV = intravenous.

months to 10 years who are at increased risk for meningococcal disease and then routinely in older children and adolescents (first dose at the age of 11 or 12 years with booster at 16 years). Populations that especially benefit from new conjugate vaccines are college freshmen, military recruits, patients with immunoglobulin or complement deficiencies (inherited or chronic deficiencies such as C3, properdin, factor D, or late complement components), patients with anatomic or functional asplenia, laboratory workers who are routinely exposed to isolates of *N. meningitidis*, adults with HIV infection, and people who travel to or reside in countries where *N. meningitidis* is epidemic.

A meningococcal conjugate vaccine for Africa (MenAfriVac) costs less than $0.50 a dose and is used as a mass vaccination strategy for individuals 1 to 29 years old. By the end of 2020, more than 315 million doses were administered and over 150,000 lives saved. This program has resulted in the virtual elimination of group A meningococcal disease in the 24 meningitis belt countries vaccinated.

The development of vaccines for group B *N. meningitidis* has also shown significant progress.[A2] Two group B vaccines, MenB-4C (Bexsero) and MenB-FHbp (Trumenba), are now licensed based on their immunogenicity and safety.[16] For example, group B is the predominant cause of meningococcal disease in infants, and introduction of the group B vaccine (MenB-4C) into the publicly funded national immunization program of the United Kingdom had a 60% efficacy at 1 year.[17] These vaccines have been especially useful during localized outbreaks, such as on U.S. college campuses.[18,19] However, unlike the A, C, W, Y conjugate vaccines, group B vaccines have minimal effect on decreasing pharyngeal carriage of the organism and do not provide herd protection.[20]

Prevention of meningococcal disease in patients who are receiving C5 inhibitors (eculizumab or the long-acting derivative ravulizumab) is a special concern. Eculizumab, which is a humanized monoclonal antibody that binds C5 and inhibits the terminal complement pathway, is approved for use in complement-mediated thrombotic microangiopathies (such as paroxysmal nocturnal hemoglobinuria [Chapter 146]), atypical hemolytic uremic syndrome (Chapter 158), and myasthenia gravis (Chapter 390). The risk of meningococcal disease in individuals receiving eculizumab is increased 2000-fold. Both ACWY and Men B vaccines are recommended before individuals receive eculizumab, but vaccine-induced protection is incomplete, possibly because of eculizumab's inhibition of complement-mediated bactericidal activity and also inhibition of opsonic and phagocytic functions. Over 50% of meningococcal infections in patients who are receiving eculizumab are due to non-groupable strains. Antibiotic chemoprophylaxis is recommended, but resistant strains can develop. Education for enlightened awareness, early care, vaccination of close contacts, and administration of ceftriaxone or other effective antibiotic agents at first signs of symptoms (fever, headache, altered mental state, rash) are recommended.

PROGNOSIS

The mortality of untreated systemic meningococcal disease is 70 to 90%. Despite highly effective antibiotics and aggressive supportive care, the mortality of invasive meningococcal disease remains about 10%. The failure to recognize disease early, the very rapid development of disease (especially meningococcemia), and the delay in administering antibiotics remain the most significant challenges. The chance of surviving shock is directly correlated to plasma concentrations of endotoxin, and half of the nonsurviving patients with shock die within the first 12 hours of hospital admission.

Long-term sequelae and morbidity after invasive meningococcal disease are significant.[21] Neurologic impairment occurs in 7 to 10% with meningococcal meningitis, with palsies of the sixth, seventh, and eighth cranial nerves as well as hemiparesis and quadriparesis. Unilateral or bilateral sensorineural hearing loss occurs in 2 to 9% of cases, is profound in 2% of affected individuals, and necessitates cochlear implantation in 0.4%. Neurodevelopmental impairment, including behavioral and psychological problems, learning difficulties, memory deficits, executive function problems, decreased academic performance, spasticity, seizures, and focal neurologic signs, is seen in approximately 10%. Visual difficulties, seizures, and motor deficits are reported in 2 to 3%, with multiple

neurologic disabilities occurring in 1 to 2% of affected individuals. About 5 to 20% of survivors of meningococcal sepsis in childhood have long-term behavioral and emotional problems, decreased intellectual functioning, and illness-related physical or social consequences.

Scarring of the skin, secondary to necrotic purpura, may vary from unnoticeable to requiring skin grafting. Multiple areas may be involved; the lower limbs are most frequently affected, followed by the arms, chest, and face. Multiple amputations of the digits or limbs may be required owing to necrosis of the skin, muscle, and bone of the affected parts (see Fig. 274-2D). Bone growth disturbances, stump overgrowth, scar contractures, and soft tissue and bone infections may complicate amputations. Limb-length discrepancies, which may result from infarction of the growth plate, often necessitate further surgical intervention. Following acute renal failure at presentation, renal function recovers in most individuals; however, evidence of renal dysfunction may persist for more than 4 years in both children and adults, with the risk being higher in patients who required renal replacement therapy.

Meningococcal disease and its complications, often occurring rapidly in otherwise healthy individuals, also produce significant family, community, health care, and public health impact. The emotional toll on individuals who survive and on their families is considerable and a global phenomenon. In communities, meningococcal disease may also create fear and anxiety. In one study, post-traumatic stress disorder (Chapter 362) occurred in 15% of children, in half of the mothers, and in 20% of fathers at 3 months. Meningococcal disease and its complications also result in substantial hospital and long-term health care costs. Furthermore, delay in the diagnosis of meningococcal sepsis and meningitis and septicemia is a common reason for litigation.

If parents and health care professionals recognize the importance of fever and headache with or without a rash and seek treatment early, morbidity and mortality can be reduced with prehospital antibiotic treatment, rapid transportation to medical facilities, and stabilization in an intensive care unit. Prevention of meningococcal disease with new vaccines and vaccine strategies remains the major worldwide goal.

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275 *NEISSERIA GONORRHOEAE* INFECTIONS

JEFFREY D. KLAUSNER AND STEPHANIE N. TAYLOR

DEFINITION

Neisseria gonorrhoeae, which is predominantly a sexually transmitted infection, is a common cause of urethral discharge in men and cervical discharge in women. Because *N. gonorrhoeae* may infect mucosal epithelial cells, it also may cause pharyngeal and rectal infection in adults and conjunctival infection in the newborn. Complications of *N. gonorrhoeae* infections include epididymitis in males and pelvic inflammatory disease in females. Chronic or recurrent pelvic inflammatory disease may result in uterine tubal scarring and subsequent infertility. Additional complications may include disseminated infection with resultant skin lesions, arthritis, tenosynovitis, and rarely, endocarditis or meningitis. Gonococcal infections also may increase the risk of acquiring and transmitting the human immunodeficiency virus (HIV) infection.

The Pathogen

N. gonorrhoeae are gram-negative bacteria typically observed microscopically as diplococci. The organism is composed of an inner cytoplasmic membrane, a middle cell wall composed of peptidoglycan, and an outer membrane. The outer membrane contains various components that interact with the host, thereby enabling invasion and infection, as well as mutant surface proteins and lipo-oligosaccharides that facilitate the evasion of host immunity. *N. gonorrhoeae* have a genome of circular DNA of 2.1 million base pairs. The genome contains 2069 genes, many of which are involved in DNA repair pathways.

EPIDEMIOLOGY

N. gonorrhoeae is a sexually transmissible organism. Very rarely it can be acquired through the inadvertent inoculation of infected secretions onto a susceptible anatomic site (e.g., causing gonococcal orbital cellulitis[1] or be associated with household transmission). Mother-to-child transmission from passage of the fetus through an infected birth canal can result in neonatal gonococcal conjunctivitis, which can lead to blindness if untreated.

The infectivity of gonorrhea is about 50%, which on its own would not allow the maintenance of endemic infection without core groups of individuals who have a higher than average number of sexual contacts. The likelihood that an infected man will transmit infection to a woman during a single episode of unprotected vaginal intercourse is about 50 to 70%, and the risk that a woman will infect a man is about 20%. The risks of transmission associated with fellatio and cunnilingus are not well defined. Anal intercourse is also an efficient mode of transmission, but the absolute risk of transmission per contact is uncertain. Evidence also suggests gonococcal transmission from the use of infected saliva as a sexual lubricant.

After changes in sexual behavior due to the wide availability of oral contraceptive agents and the rise of the gay liberation movement in the 1970s, cases of gonorrhea soared in the United States. The discovery of HIV and the resultant fear of AIDS in the 1980s led to changes in sexual behaviors that reduced the incidence of gonorrhea to an all-time low by the mid-1990s. Over the past two decades, cases of gonorrhea have increased again, primarily in men who have sex with men, but also in younger minority populations and in groups with poor access to health care. Infections now are most common among females ages 15 to 24 years and males ages 20 to 29 years. Currently, gonorrhea is the second most frequently reported disease in the United States, with an estimated 1.6 million new infections per year.[2]

Globally, *N. gonorrhoeae* is the most commonly notifiable infection after *Chlamydia trachomatis*, with an estimated annual incidence of 87 million new cases and a population-level prevalence of about 0.7 to 0.9%.[3] In pregnant women in sub-Saharan Africa, *N. gonorrhoeae* has a prevalence of 2.3% overall, with higher frequencies in Southern versus Central Africa. Antimicrobial-resistant *N. gonorrhoeae* infections are widespread and increasing.[4]

PATHOBIOLOGY

N. gonorrhoeae contain a variety of virulence and growth factors. Their characteristic filamentous structures, called pili, serve to attach to membranes of human mucosal and uroepithelial cells. Variations in pili contribute to immune evasion and tissue tropism. *N. gonorrhoeae* also have porins, which are proteins on the outer membrane, that enable the transport of ions and nutrients essential for bacterial survival. Certain porins, such as porin B isoform 1A, have been associated with increased resistance to host immunity and an increased capacity for dissemination. Opacity-associated proteins are integral outer membrane proteins that determine the invasive capacity of *N. gonorrhoeae*. Gonococci may also evade host immunity by expressing enzymes such as IgA proteases, which cleave mucosal antibody and use several molecular mechanisms to vary surface antigens such as lipo-oligosaccharides.

Select complement deficiencies (Chapter 37) predispose a patient to dissemination of *N. gonorrhoeae* because of decreased complement-mediated killing of *N. gonorrhoeae*. Up to 50% of patients with C6, C7, or C8 complement deficiencies may develop bacteremia with pathogenic *Neisseria* species. Complement deficiencies also predispose patients to recurrent and perhaps subacute or even chronic infections. Eculizumab, a monoclonal antibody to C5 used in conditions such as complement-mediated hemolytic uremic syndrome (Chapter 158), also appears to increase the risk of disseminated gonococcal infection.[5]

CLINICAL MANIFESTATIONS

The clinical manifestations of gonorrhea are highly dependent on the anatomic site of infection and host factors related to inflammation. *N. gonorrhoeae* may infect the mucosal tissue of the urethra, cervix, throat, or rectum. Infections at

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neurologic disabilities occurring in 1 to 2% of affected individuals. About 5 to 20% of survivors of meningococcal sepsis in childhood have long-term behavioral and emotional problems, decreased intellectual functioning, and illness-related physical or social consequences.

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DEFINITION

Neisseria gonorrhoeae, which is predominantly a sexually transmitted infection, is a common cause of urethral discharge in men and cervical discharge in women. Because *N. gonorrhoeae* may infect mucosal epithelial cells, it also may cause pharyngeal and rectal infection in adults and conjunctival infection in the newborn. Complications of *N. gonorrhoeae* infections include epididymitis in males and pelvic inflammatory disease in females. Chronic or recurrent pelvic inflammatory disease may result in uterine tubal scarring and subsequent infertility. Additional complications may include disseminated infection with resultant skin lesions, arthritis, tenosynovitis, and rarely, endocarditis or meningitis. Gonococcal infections also may increase the risk of acquiring and transmitting the human immunodeficiency virus (HIV) infection.

The Pathogen

N. gonorrhoeae are gram-negative bacteria typically observed microscopically as diplococci. The organism is composed of an inner cytoplasmic membrane, a middle cell wall composed of peptidoglycan, and an outer membrane. The outer membrane contains various components that interact with the host, thereby enabling invasion and infection, as well as mutant surface proteins and lipo-oligosaccharides that facilitate the evasion of host immunity. *N. gonorrhoeae* have a genome of circular DNA of 2.1 million base pairs. The genome contains 2069 genes, many of which are involved in DNA repair pathways.

EPIDEMIOLOGY

N. gonorrhoeae is a sexually transmissible organism. Very rarely it can be acquired through the inadvertent inoculation of infected secretions onto a susceptible anatomic site (e.g., causing gonococcal orbital cellulitis[1] or be associated with household transmission). Mother-to-child transmission from passage of the fetus through an infected birth canal can result in neonatal gonococcal conjunctivitis, which can lead to blindness if untreated.

The infectivity of gonorrhea is about 50%, which on its own would not allow the maintenance of endemic infection without core groups of individuals who have a higher than average number of sexual contacts. The likelihood that an infected man will transmit infection to a woman during a single episode of unprotected vaginal intercourse is about 50 to 70%, and the risk that a woman will infect a man is about 20%. The risks of transmission associated with fellatio and cunnilingus are not well defined. Anal intercourse is also an efficient mode of transmission, but the absolute risk of transmission per contact is uncertain. Evidence also suggests gonococcal transmission from the use of infected saliva as a sexual lubricant.

After changes in sexual behavior due to the wide availability of oral contraceptive agents and the rise of the gay liberation movement in the 1970s, cases of gonorrhea soared in the United States. The discovery of HIV and the resultant fear of AIDS in the 1980s led to changes in sexual behaviors that reduced the incidence of gonorrhea to an all-time low by the mid-1990s. Over the past two decades, cases of gonorrhea have increased again, primarily in men who have sex with men, but also in younger minority populations and in groups with poor access to health care. Infections now are most common among females ages 15 to 24 years and males ages 20 to 29 years. Currently, gonorrhea is the second most frequently reported disease in the United States, with an estimated 1.6 million new infections per year.[2]

Globally, *N. gonorrhoeae* is the most commonly notifiable infection after *Chlamydia trachomatis*, with an estimated annual incidence of 87 million new cases and a population-level prevalence of about 0.7 to 0.9%.[3] In pregnant women in sub-Saharan Africa, *N. gonorrhoeae* has a prevalence of 2.3% overall, with higher frequencies in Southern versus Central Africa. Antimicrobial-resistant *N. gonorrhoeae* infections are widespread and increasing.[4]

PATHOBIOLOGY

N. gonorrhoeae contain a variety of virulence and growth factors. Their characteristic filamentous structures, called pili, serve to attach to membranes of human mucosal and uroepithelial cells. Variations in pili contribute to immune evasion and tissue tropism. *N. gonorrhoeae* also have porins, which are proteins on the outer membrane, that enable the transport of ions and nutrients essential for bacterial survival. Certain porins, such as porin B isoform 1A, have been associated with increased resistance to host immunity and an increased capacity for dissemination. Opacity-associated proteins are integral outer membrane proteins that determine the invasive capacity of *N. gonorrhoeae*. Gonococci may also evade host immunity by expressing enzymes such as IgA proteases, which cleave mucosal antibody and use several molecular mechanisms to vary surface antigens such as lipo-oligosaccharides.

Select complement deficiencies (Chapter 37) predispose a patient to dissemination of *N. gonorrhoeae* because of decreased complement-mediated killing of *N. gonorrhoeae*. Up to 50% of patients with C6, C7, or C8 complement deficiencies may develop bacteremia with pathogenic *Neisseria* species. Complement deficiencies also predispose patients to recurrent and perhaps subacute or even chronic infections. Eculizumab, a monoclonal antibody to C5 used in conditions such as complement-mediated hemolytic uremic syndrome (Chapter 158), also appears to increase the risk of disseminated gonococcal infection.[5]

CLINICAL MANIFESTATIONS

The clinical manifestations of gonorrhea are highly dependent on the anatomic site of infection and host factors related to inflammation. *N. gonorrhoeae* may infect the mucosal tissue of the urethra, cervix, throat, or rectum. Infections at

ABSTRACT

Neisseria gonorrhoeae, which is a predominantly sexually transmitted infection, is a common cause of urethral discharge in men and cervical discharge in women. Because *N. gonorrhoeae* may infect mucosal epithelial cells, it also may cause pharyngeal and rectal infection in adults and conjunctival infection in the newborn. Infection may or may not be symptomatic depending on the anatomic site of infection and characteristics of the host and organism.

Complications of *N. gonorrhoeae* infections include epididymitis in males and pelvic inflammatory disease in females. Chronic or recurrent pelvic inflammatory disease may result in uterine tubal scarring and subsequent infertility. Additional complications may include disseminated infection with resultant skin lesions, arthritis, tenosynovitis, and rarely, endocarditis or meningitis. Gonococcal infections may increase the risk of acquiring and transmitting the human immunodeficiency virus infection. Diagnosis is confirmed by nucleic acid testing, Gram stain, or culture.

Timely treatment with effective antibacterial therapy is highly curative, but antimicrobial-resistant infections are increasing. Gonococcal infections may be prevented with the consistent use of condoms for sexual intercourse. Routine screening of sexually active or pregnant women under the age of 25 years and of men who have sex with men is an additional strategy to prevent the complications and spread of gonococcal infections. Epidemiologic research suggests that certain meningococcal vaccines might reduce the acquisition of *N. gonorrhoeae*.

KEYWORDS

Neisseria gonorrhoeae
gonorrhea
gonococcal infections
urethritis
cervicitis
pelvic inflammatory disease
ophthalmia neonatorum
antimicrobial resistance

these sites may produce an inflammatory response with subsequent purulent discharge or pain (often burning in character) with urination or defecation, or, as is often the case in pharyngeal infection, either mild symptoms (e.g., sore throat) or no symptoms whatsoever. After a brief incubation period, typically just 1 or 2 days, acute genital infections are almost always (>90%) symptomatic in men but much less so (about 50%) in women, a difference that partly explains why asymptomatically infected women contribute to ongoing transmission.

Clinical manifestations in women may include pain with intercourse, vaginal bleeding, and lower abdominal pain and tenderness with or without fever, consistent with pelvic inflammatory disease (Chapter 264). Repeated pelvic inflammatory disease increases the risk for tubal infertility. Infection in pregnancy can lead to adverse birth outcomes including prematurity, low birthweight, and neonatal mortality.[6] In HIV-infected pregnant women, gonococcal coinfection can increase the mother-to-child transmission of HIV infection. In men, prolonged infection may lead to testicular infection and epididymitis.

Rarely, when infection does not cause acute symptoms that lead to diagnosis and effective therapy, *N. gonorrhoeae* may disseminate in the blood stream and seed normally sterile sites, including the joints, cerebrospinal fluid, and heart valves. Disseminated gonococcal infection may also be associated with a pustular skin rash and inflammation of the affected joints and tendons.

DIAGNOSIS

Diagnosis is based on recent sexual exposure, clinical signs, and symptoms. Laboratory confirmation of infection is made by the use of nucleic acid–based molecular testing (of a swab from the urethra, cervix, vagina, throat, or rectum; or of urine),[7] antigen-based immunoassays, or the observation of characteristic organisms with the distinct morphology and coloration on point-of-care Gram staining. After heat-fixing the urethral smear slide, the multistep Gram stain procedure allows visualization of the nearly pathognomonic gram-negative intracellular diplococci upon oil-immersion microscopy (Fig. 275-1A). A methylene blue/gentian violet stain (Fig. 275-1B), which does not require heat fixation and takes only 1 minute, is an equally good alternative. Because *N. gonorrhoeae* are typically restricted to specific anatomic sites of infection, testing for infection must occur with specimens from each anatomic site of sexual exposure. Urine tests detect urethral infections but not infections at other anatomic sites. Culture is rarely required except in cases of possible treatment failure or to diagnose disseminated gonococcal infection, abscesses, endocarditis, or meningitis. Rarely, other *Neisseria* species (e.g., *Neisseria meningitides*; Chapter 276) may also be present in urethral secretions and may be associated with a similar syndrome.

SPECIFIC CLINICAL SYNDROMES

Localized Infections

URETHRITIS

CLINICAL MANIFESTATIONS

Urethritis is the most common clinical manifestation of gonococcal infection in men. After an incubation period of 2 to 6 days, men develop a profuse, purulent urethral discharge that is usually white, yellow, or green in color (Fig. 275-2A). In contrast, the discharge in non-gonococcal urethritis is usually thin and clear or gray in color (Fig. 275-2B). Dysuria is common; meatal irritation, meatal erythema, and penile lymphedema can also occur. Depending on the infecting strain, 10% of men have an asymptomatic infection that is only detected by screening. Because the diplococci of *N. gonorrhoeae* adhere to mucosal columnar and cuboidal epithelial cells of the urethra and cervix, women can also have symptomatic urethritis with dysuria.

DIAGNOSIS

The diagnosis of gonococcal urethritis should be suspected based on dysuria with a urethral discharge (i.e., burning with urination). Gonococcal urethritis

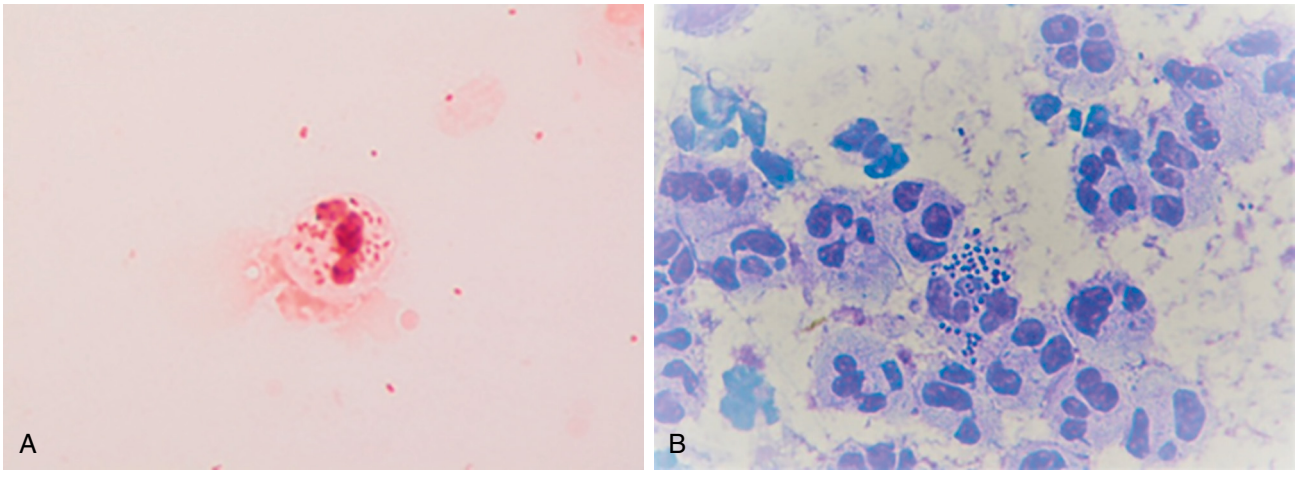

FIGURE 275-1. **Stains for gonococcus. A,** Gram stain. **B,** Methylene blue/gentian violet. (Courtesy of Stephanie N. Taylor, MD.)

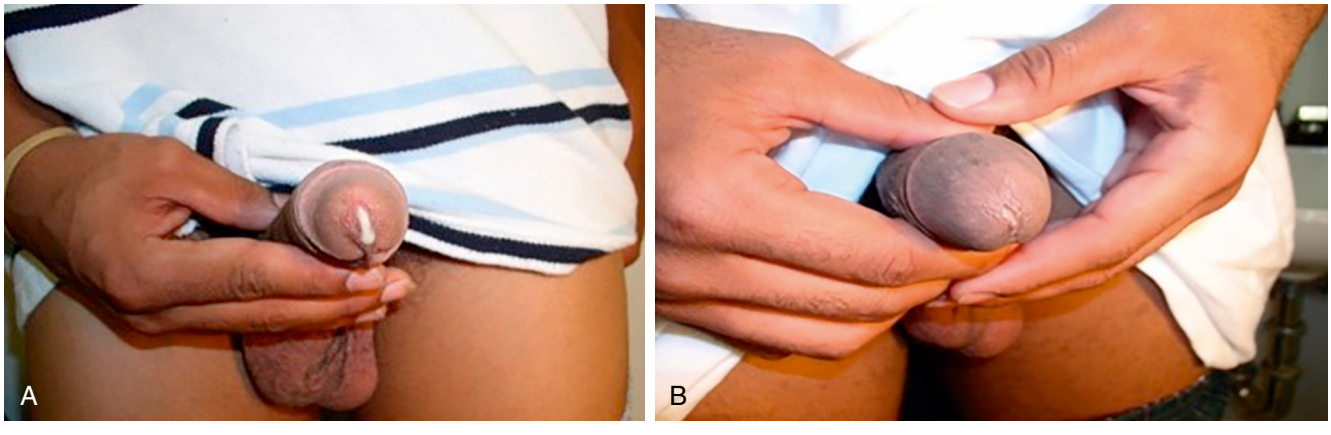

FIGURE 275-2. **Urethral discharge. A,** Gonococcal urethritis. **B,** Non-gonococcal urethritis. (Courtesy of Stephanie N. Taylor, MD.)

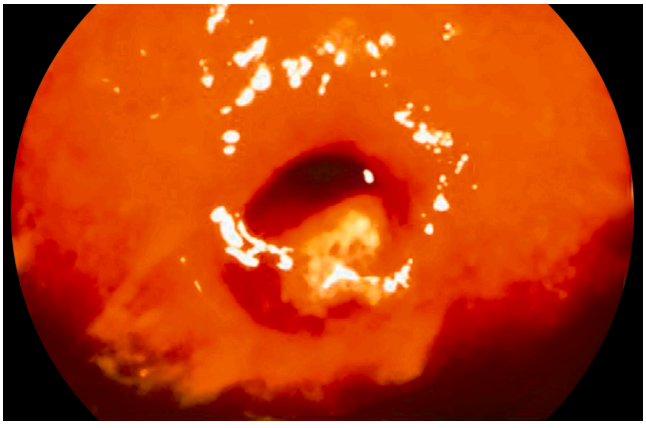

FIGURE 275-3. Cervicitis due to *Neisseria gonorrhoeae* infection.

may be confirmed with point-of-care Gram stain, methylene blue stain, or nucleic acid detection testing of the urethral discharge by a penile meatal or urethral swab. In women, nucleic acid testing of urine or self-collected vaginal swab specimens has replaced the need to collect cervical swab specimens.

CERVICITIS

CLINICAL MANIFESTATIONS

Cervicitis is the most common clinical manifestation of gonococcal infection in women, but up to 50% of infections are asymptomatic. When symptomatic, women report vaginal discharge, irritation, or itching. Postcoital bleeding, pain with vaginal sexual intercourse, and abnormal vaginal bleeding are also associated with cervicitis. The physical examination may show a purulent or mucopurulent cervical discharge (Fig. 275-3), an erythematous or edematous cervix, a friable cervix with easily induced bleeding, or, occasionally, cervical motion tenderness.

DIAGNOSIS

Nucleic acid amplification testing is the mainstay for detecting urogenital *N. gonorrhoeae* from the cervix, vagina, and urine in women because other methods are not sufficiently sensitive for detecting the organism. Other organisms that may be detected by nucleic acid testing (Chapter 264) include *Chlamydia trachomatis* (Chapter 294), *Mycoplasma genitalium* (Chapter 293), *Trichomonas vaginalis* (Chapter 324), herpes simplex viruses (Chapter 345), and *Candida* species (Chapter 310), but no etiology is found in 50% of women with cervicitis.

PROCTITIS

CLINICAL MANIFESTATIONS

Rectal gonorrhea most commonly occurs in men who have sex with men and in women. In men who have sex with men, the exposure to the organism is almost always via receptive anal intercourse. In women, the usual source of rectal *N. gonorrhoeae* is vaginal and cervical secretions that contaminate the rectum, but women who engage in receptive anal intercourse may acquire the organism by direct sexual activity as well. Heterosexual men can also acquire rectal gonorrhea from digital-anal inoculation, but rates are much lower compared with men who have sex with men and women.

Most infections are asymptomatic, but symptoms are more common in men who have sex with men due to more frequent anal intercourse and concurrent trauma, as well as the size of the inoculum. Typical symptoms are anal irritation and pruritus, rectal discharge, and mucus-coated stools. Tenesmus and pain or bleeding may occur with bowel movements.

DIAGNOSIS

Because most cases of rectal gonorrhea are asymptomatic, many cases are missed due to lack of anorectal screening. Infection is detected with nucleic acid amplification testing, often combined with testing for *Chlamydia trachomatis* (Chapter 294). A self-collected nucleic acid specimen is as accurate as specimen collection performed by a clinician.[8] In many cases, the rectum is the only site that will test positive. Rectal gonorrhea increases the risk of HIV acquisition in persons who engage in receptive anal intercourse, so such individuals should be screened for asymptomatic rectal *N. gonorrhoeae*.

Other causes of proctitis include *Chlamydia trachomatis*, herpes simplex viruses (Chapter 345), syphilis (Chapter 295), Crohn disease (Chapter 127), lymphogranuloma venereum (Chapter 294), anal fissures (Chapter 131), and other enteric microbes (Chapter 262).

PHARYNGITIS

CLINICAL MANIFESTATIONS

Over 90% of pharyngeal gonorrhea is asymptomatic. When signs and symptoms are present, they are identical to those of pharyngitis caused by other organisms (Chapter 397), especially group A streptococcus (Chapter 269). Typical clinical findings include pharyngeal erythema and edema, tonsillitis, fever, tonsillar exudates, and cervical lymphadenopathy.

DIAGNOSIS

Pharyngeal gonorrhea is confirmed with nucleic acid amplification testing. Similar to rectal gonorrhea, self-collection of a clinical specimen is an accurate alternative to a clinician-collected specimen. If positive, throat culture can aid in testing for antimicrobial susceptibility.

GONORRHEA IN PREGNANCY

Pregnancy is a risk factor for gonorrhea, and routine screening is an important preventive measure.[9] Complications of gonorrheal infection in pregnant women include miscarriage, premature delivery, premature rupture of membranes, and chorioamnionitis. A serious clinical complication is when the infection is transmitted to the newborn during delivery and causes ophthalmia neonatorum, which is a conjunctivitis that can cause corneal damage and lead to blindness. Rarely, septic arthritis or disseminated gonococcal infection may occur in the newborn.

TREATMENT

The current U.S. recommendation for the treatment of uncomplicated gonorrhea of the urethra, cervix, rectum, or throat is a single dose of ceftriaxone 500 mg by intramuscular injection.[10,11] If chlamydia is also a possibility, doxycycline (100 mg orally twice daily for 7 days) should be added (see Table 264-5); if adherence is an issue, 1 g oral azithromycin given once can substitute for doxycycline. European guidelines recommend ceftriaxone (1 g intramuscularly) plus azithromycin (2 g orally once).[12] An alternative to ceftriaxone is cefixime (800 mg one dose orally).[A1] When a molecular gyrase A test is available and predicts ciprofloxacin susceptibility, ciprofloxacin (500 mg one dose orally) may be used.[13]

If patients are allergic to cephalosporins or have a resistant organism, single-dose gentamicin (240 mg intramuscularly) plus azithromycin (2 g orally) is recommended.[A2] Gentamicin monotherapy is unreliable for pharyngeal gonorrhea, but azithromycin (2 g orally) appears to be effective.

Patients treated for pharyngeal infection should undergo a test of cure at 7 to 14 days after treatment. Pregnant women treated for gonorrhea should undergo a test of cure by repeat nucleic acid amplification testing at 3 to 4 weeks after treatment. Because of the high incidence of repeated infection, all treated patients should undergo screening at 3 months after treatment to exclude a new infection.

Treatment of Partners

Effective partner treatment, which is a mainstay of gonococcal therapy and the public health efforts to control the spread of infection, can significantly reduce the rate of repeat infection. The medical standard of care for the management of gonorrhea requires that any index patient's sex partner within the past 60 days receive treatment through a medical visit or expedited-partner therapy. Expedited-partner therapy[14,15] provides patients with either medication (e.g., a single 800-mg oral dose of cefixime) to give to their partner or partners, a prescription for the additional treatment, or an order directly with the partner's pharmacy.

PROGNOSIS

Urethritis

The overall prognosis of gonococcal urethritis is very good with appropriate treatment. Occasionally, however, urethritis can be complicated by epididymitis, penile cellulitis, periurethral abscess, penile edema, and prostatitis. Epididymitis is usually unilateral. Pain and swelling are localized to the epididymis. Treatment of epididymitis should cover both gonococci and *Chlamydia trachomatis* with a 500-mg intramuscular dose of ceftriaxone plus doxycycline (100 mg orally twice daily for 10 days). In men who have insertive anal intercourse, levofloxacin (500 mg orally daily for 10 days) should be used instead of doxycycline to cover enteric organisms and *Chlamydia trachomatis*. Acute pain in the testicle or other areas of the scrotum warrants immediate evaluation to exclude testicular torsion or abscess. Penile cellulitis, edema, and abscess usually respond to standard single-dose gonococcal treatment, and surgical intervention is not necessary.

Cervicitis

The overall prognosis of gonococcal cervicitis is very good with appropriate treatment. The most serious complication of gonococcal cervicitis is progression to upper genital tract infection or pelvic inflammatory disease (see later). Other complications include Bartholin gland abscess and infection of the Skene glands, which are located in the periurethral area. Bartholin gland abscesses may require incision and drainage. Skenitis is treated conservatively with oral antibiotics and local measures such as warm compresses. Surgical intervention is rarely needed, but may be warranted if it persists despite antibiotic therapy.

Rectal Infection

Untreated rectal gonorrhea usually resolves at a median of 2 to 3 months, but can persist for 6 to 11 months.[16] With treatment, it typically resolves within a week. Occasionally, fecal impaction and constipation may occur due to severe pain with bowel movements. Liquid stool leakage around the impaction can be confused with bowel incontinence. Complications can include anal hemorrhoids, anal tears, bleeding (Chapter 131), and rarely, tears in the colonic wall. Complications can be avoided or moderated by conservative measures, such as the use of laxatives.

Pharyngeal Infection

Even without treatment, most infections clear spontaneously within 4 months.[17] However, pharyngeal gonorrhea may place individuals at risk for disseminated infection, and gonococcal pharyngeal infection likely contributes to the community spread of infection.

PELVIC INFLAMMATORY DISEASE

CLINICAL MANIFESTATIONS

Pelvic inflammatory disease (PID; Chapter 264) is an upper genital tract syndrome that includes one or more of the following: salpingitis, endometritis, oophoritis, or peritonitis. An estimated 10 to 40% of women with untreated lower tract gonococcal infection progress to develop pelvic inflammatory disease. Women with pelvic inflammatory disease may report lower abdominal pain, nausea, vomiting, fever, chills, vaginal discharge, or abnormal vaginal bleeding. Diffuse abdominal pain or right upper quadrant pain from gonococcal peritonitis or perihepatitis (Fitz-Hugh-Curtis syndrome) can mimic cholecystitis or hepatitis. Pelvic and bimanual examination findings include cervical motion tenderness, pelvic pain, uterine fundal tenderness, diffuse abdominal pain, bilateral or unilateral adnexal pain, and cervical discharge.

DIAGNOSIS

The diagnosis is often based on clinical criteria,[18,19] which include lower abdominal pain, adnexal tenderness, cervicitis, cervical motion tenderness, and leukocytes in the vaginal discharge. Nucleic acid amplification testing can help establish an etiologic diagnosis (Chapter 264). If pelvic inflammatory disease is suspected, pelvic or transvaginal ultrasound should be the initial test. Ultrasound findings include tubal hyperemia, thickened and fluid-filled uterine tubes, free-flowing or localized fluid collections with or without complex phlegmon, or frank abscess.

Ultrasound can guide immediate drainage of an ovarian or pelvic abscess. If needed, magnetic resonance imaging (MRI) of the pelvis can better define areas of question on the ultrasound. Abdominal computerized tomographic scanning is recommended to evaluate for complications that extend beyond the pelvis, such as generalized peritonitis or perihepatitis. Laparoscopy, which is rarely used as the initial diagnostic method, typically shows edema and erythema of the tubal surface, sometimes with thick exudate on the tubal surface or exuding from the uterine tubes.

Women with *N. gonorrhoeae* may have simultaneous infection with *Chlamydia trachomatis* and with other vaginal organisms, including anaerobic bacteria as well as gram-negative and gram-positive cocci, rods, and coccobacilli. Special attention must be given to lower quadrant pain and adnexal pain to ensure that the patient does not have acute appendicitis (Chapter 128), ectopic pregnancy (Chapter 218), rupture or torsion of an ovarian cyst, a tubo-ovarian abscess, renal or ureteral stones (Chapter 111), urinary tract infection (Chapter 263), inflammatory bowel disease (Chapter 127), or another acute abdominal condition (Chapter 128).

TREATMENT

For pelvic inflammatory disease (Chapter 264), treatment may be oral or parenteral (Table 264-5), depending on how sick the patient is. Most women can be treated as outpatients, but inpatient treatment is recommended for women who are pregnant; may have other diagnoses that may require emergency surgery, such as appendicitis, or ectopic pregnancy; have significant nausea and vomiting that may preclude the use of oral medications; have disseminated gonorrhea, peritonitis, or perihepatitis; have any evidence of systemic sepsis, or have a tubo-ovarian abscess. Treatment should routinely cover gonococcal and chlamydial species (Table 264-5), as well as anaerobic organisms.[A3]

PROGNOSIS

Even with successful treatment, pelvic inflammatory disease can cause tubal scarring and tubal obstruction. After one episode of pelvic inflammatory disease, almost 10% of women may develop tubal occlusion and infertility. After two episodes, the risk is 20%, and after three or more episodes, it is 40%.[20] Even without subsequent tubal occlusion, the risk of future ectopic pregnancy is markedly increased in women with a history of pelvic inflammatory disease. Many women also have residual chronic pelvic pain.

DISSEMINATED GONOCOCCAL INFECTION

CLINICAL MANIFESTATIONS

N. gonorrhoeae bacteremia with disseminated gonococcal infection complicates less than 1% of cases. Manifestations can range from mild joint discomfort and several skin lesions to sepsis with asymmetric polyarthritis, numerous skin lesions, and prostration. Dissemination is substantially more common in women because the initial local infection is less likely to cause symptoms that lead to early treatment. In women, dissemination is often associated with menstruation or pregnancy. At the time of bacteremia, most individuals have no symptoms at mucosal sites because the strains of *N. gonorrhoeae* that are prone to disseminate are unlikely to cause local mucosal inflammation.

The two distinct presentations of disseminated gonococcal infection are tenosynovitis/dermatitis, which is seen in about 70% of cases, and metastatic infection. Tenosynovitis/dermatitis begins with tenosynovitis and migratory arthralgias of the knees, elbows, or ankles. Skin lesions are usually fewer than 30 in number, typically are seen on the extremities, are classically described as pustules on an erythematous base, and can be petechial, papular, or nodular (Fig. 275-4). Though not always a well-defined progression from tenosynovitis-dermatitis, septic arthritis of one or two joints occurs after several days in untreated patients. Tenosynovitis can progress to septic monoarticular or oligoarticular arthritis, but septic arthritis is the initial presentation in about 30% of cases. Disseminated gonococcal infection usually spares the axial skeleton—a feature that helps distinguish it from reactive arthritis.

Disseminated gonococcal infection may be complicated by endocarditis, meningitis, or osteomyelitis. Gonococcal endocarditis occurs in 1 to 2% of patients with disseminated gonococcal infection, most often involving the aortic valve. Gonococcal endocarditis (Chapter 61) can lead to rapid valvular destruction and heart failure. Gonococcal meningitis is clinically indistinguishable from meningitis secondary to *Neisseria meningitidis* or any acute bacterial meningitis.

FIGURE 275-4. Disseminated gonococcal infection. Pustules on an erythematous base.

DIAGNOSIS

Disseminated gonococcal infection should be the initial consideration in any young, sexually active person with the acute onset of arthritis. Nucleic acid amplification testing of skin lesions and cultures of synovial fluid can establish the diagnosis. Blood cultures should also be obtained. About 20% of cases of tenosynovitis/dermatitis syndrome are proven based on a compatible clinical presentation with identification of gonococci on testing of blood, synovial fluid, or skin. About 80% of cases are classified as probable based on finding gonococci in a mucosal site specimen (but not from blood or another sterile site) or documenting that a sex partner has gonococcal infection. A possible case of disseminated gonococcal infection has the compatible clinical presentation but no positive diagnostic tests from blood or any other sites tested. Disseminated gonococcal infections must be distinguished from other causes of fever and rash (Chapter 259), as well as other monoarticular or usually asymmetrical oligoarthritis (Chapter 236), including other types of septic arthritis (Chapter 251), as well as reactive arthritis, which can be triggered by sexually acquired chlamydial infection (Chapter 254) but, unlike gonococcal arthritis, frequently involves the axial skeleton.

TREATMENT

Treatment for gonococcal-related arthritis and arthritis-dermatitis syndrome is ceftriaxone (1 g IM or IV every 24 hours), with added doxycycline (100 mg orally twice daily for 7 days) if chlamydial infection cannot be excluded. The intravenous component should also be continued for a minimum of 7 days or until the patient is afebrile (whichever is longer) after which the patient may complete the 7-day course with an oral regimen (e.g., cefixime 400 mg orally twice daily).

For gonococcal meningitis and endocarditis, the recommended regimen is ceftriaxone (1 to 2 g IV every 24 hours) plus doxycycline (100 mg orally twice daily for 7 days) if chlamydial infection has not been excluded. The intravenous component should also be continued for a minimum of 7 days or until the patient is afebrile (whichever is longer). Alternatives to ceftriaxone are cefotaxime (1 g IV every 8 hours) or ceftizoxime (1 g IV every 8 hours). Intravenous treatment should be for 10 to 14 days for meningitis and 4 or more weeks for endocarditis and osteomyelitis.

Gonococcal septic arthritis infections require drainage (Chapter 251), similar to staphylococcal arthritis. About 50% of cases of gonococcal endocarditis require valve replacement.

PROGNOSIS

Many cases clear spontaneously. Most patients with the tenosynovitis/dermatitis syndrome resolve their symptoms spontaneously or quickly with antibiotics, but some cases progress to septic arthritis. For gonococcal endocarditis and meningitis, mortality can be as high as 20%.

PREVENTION

The sexual transmission of *N. gonorrhoeae* can be greatly reduced by changes in sexual practices, including the use of condoms during oral, anal, or vaginal intercourse. Complications may also be reduced by screening to detect infectious individuals. In high-income settings, the routine screening of pregnant women and the preventive application of ocular antibacterial ointment at birth has essentially eliminated ophthalmic neonatorum, but it remains a problem in some resource-limited countries.

Screening

Based on substantial evidence,[A4] the United States Preventive Services Task Force recommends annual screening for gonorrhea to prevent complications such as pelvic inflammatory disease in all sexually active females younger than age 25 years and in females with increased risk for infection ages 25 years and older.[21] The U.S. Centers for Disease Control and Prevention (CDC) recommends screening men who have sex with men at least annually (and every 3 to 6 months if at increased risk) at all anatomic sites of exposure. Routine screening is not routinely recommended for males who are exclusively heterosexual and do not live in correctional settings.

Barrier Methods

Male and female condoms are highly effective barriers that reduce the likelihood of exposure and transmission. For condoms to be effective at reducing the transmission of gonorrhea, they must be used correctly and consistently. Clinicians should assure that both male and female patients understand the different types of condoms and how to use them correctly. Persons who practice using condoms and carry condoms with them are more likely to use them. Female condoms offer a female-controlled way to prevent gonorrhea and reduce a female's dependency on a male partner. Female condoms may also be safely used for receptive anal sex by both males and females.

Behavioral Intervention

Factors that put persons at increased risk for sexually transmissible infections include alcohol and substance use disorders, poverty, stigma, and governmental and institutional policies that discriminate based on gender, race, ethnicity, sexual orientation, and gender identity. Successful interventions to reduce individual risk must occur at the individual, community, and policy level. Individual-level behavioral counseling can reduce the risk for sexually transmitted infections.[22]

Microbial Prophylaxis and Vaccination

Antimicrobial pre-exposure or post-exposure prophylaxis may be partially efficacious against *N. gonorrhoeae* in sexually active adults. Furthermore, antiseptic mouthwash is not effective for preventing oropharyngeal infection.[A5] Epidemiologic data suggest that outer-membrane-vesical–containing meningococcal type B vaccines can reduce the rate of acquisition of gonorrhea by 30 to 40%.[23]

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For the General References and other additional features, please visit Elsevier eBooks+ at https://ebooks.health.elsevier.com.

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276 CHANCROID

STANLEY M. SPINOLA

DEFINITION

Chancroid is a sexually transmitted disease that is characterized by painful genital ulcers and inguinal lymphadenitis caused by *Haemophilus ducreyi*. *H. ducreyi* also is a major cause of nonsexually transmitted cutaneous ulcers in children who live in regions of the South Pacific and Africa where yaws (Chapter 295), which is a nonsyphilitic treponematosis that causes a disfiguring and debilitating childhood infectious disease, is endemic.

H. ducreyi is a gram-negative coccobacillus that is not a true *Haemophilus* species. Within the Pasteurellaceae, *H. ducreyi* is grouped in a distinct lineage with *Mannheimia haemolytica* and *Aggregatibacter* (formerly *Actinobacillus*) *pleuropneumoniae*. *H. ducreyi* is likely to have diverged from these animal respiratory pathogens to occupy its niche in the human epithelium.

EPIDEMIOLOGY

Chancroid, which is endemic in resource-poor regions of Africa and Asia, facilitates the transmission of human immunodeficiency virus (HIV-1). In the 1990s, the World Health Organization estimated the annual global prevalence of chancroid to be 4 to 6 million cases. Because of the widespread use of syndromic management, which consists of treatment for syphilis and chancroid without diagnostic testing, the prevalence of chancroid has dramatically declined in endemic areas. Chancroid can be maintained only in networks with high rates of multiple sex partners. Infected female sex workers play an important role in its epidemiology, and targeted treatment of sex workers can eradicate the disease in endemic areas. Despite these successes, chancroid persists in many

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DIAGNOSIS

Disseminated gonococcal infection should be the initial consideration in any young, sexually active person with the acute onset of arthritis. Nucleic acid amplification testing of skin lesions and cultures of synovial fluid can establish the diagnosis. Blood cultures should also be obtained. About 20% of cases of tenosynovitis/dermatitis syndrome are proven based on a compatible clinical presentation with identification of gonococci on testing of blood, synovial fluid, or skin. About 80% of cases are classified as probable based on finding gonococci in a mucosal site specimen (but not from blood or another sterile site) or documenting that a sex partner has gonococcal infection. A possible case of disseminated gonococcal infection has the compatible clinical presentation but no positive diagnostic tests from blood or any other sites tested. Disseminated gonococcal infections must be distinguished from other causes of fever and rash (Chapter 259), as well as other monoarticular or usually asymmetrical oligoarthritis (Chapter 236), including other types of septic arthritis (Chapter 251), as well as reactive arthritis, which can be triggered by sexually acquired chlamydial infection (Chapter 254) but, unlike gonococcal arthritis, frequently involves the axial skeleton.

TREATMENT

Treatment for gonococcal-related arthritis and arthritis-dermatitis syndrome is ceftriaxone (1 g IM or IV every 24 hours), with added doxycycline (100 mg orally twice daily for 7 days) if chlamydial infection cannot be excluded. The intravenous component should also be continued for a minimum of 7 days or until the patient is afebrile (whichever is longer) after which the patient may complete the 7-day course with an oral regimen (e.g., cefixime 400 mg orally twice daily).

For gonococcal meningitis and endocarditis, the recommended regimen is ceftriaxone (1 to 2 g IV every 24 hours) plus doxycycline (100 mg orally twice daily for 7 days) if chlamydial infection has not been excluded. The intravenous component should also be continued for a minimum of 7 days or until the patient is afebrile (whichever is longer). Alternatives to ceftriaxone are cefotaxime (1 g IV every 8 hours) or ceftizoxime (1 g IV every 8 hours). Intravenous treatment should be for 10 to 14 days for meningitis and 4 or more weeks for endocarditis and osteomyelitis.

Gonococcal septic arthritis infections require drainage (Chapter 251), similar to staphylococcal arthritis. About 50% of cases of gonococcal endocarditis require valve replacement.

PROGNOSIS

Many cases clear spontaneously. Most patients with the tenosynovitis/dermatitis syndrome resolve their symptoms spontaneously or quickly with antibiotics, but some cases progress to septic arthritis. For gonococcal endocarditis and meningitis, mortality can be as high as 20%.

PREVENTION

The sexual transmission of *N. gonorrhoeae* can be greatly reduced by changes in sexual practices, including the use of condoms during oral, anal, or vaginal intercourse. Complications may also be reduced by screening to detect infectious individuals. In high-income settings, the routine screening of pregnant women and the preventive application of ocular antibacterial ointment at birth has essentially eliminated ophthalmic neonatorum, but it remains a problem in some resource-limited countries.

Screening

Based on substantial evidence,[A4] the United States Preventive Services Task Force recommends annual screening for gonorrhea to prevent complications such as pelvic inflammatory disease in all sexually active females younger than age 25 years and in females with increased risk for infection ages 25 years and older.[21] The U.S. Centers for Disease Control and Prevention (CDC) recommends screening men who have sex with men at least annually (and every 3 to 6 months if at increased risk) at all anatomic sites of exposure. Routine screening is not routinely recommended for males who are exclusively heterosexual and do not live in correctional settings.

Barrier Methods

Male and female condoms are highly effective barriers that reduce the likelihood of exposure and transmission. For condoms to be effective at reducing the transmission of gonorrhea, they must be used correctly and consistently. Clinicians should assure that both male and female patients understand the different types of condoms and how to use them correctly. Persons who practice using condoms and carry condoms with them are more likely to use them. Female condoms offer a female-controlled way to prevent gonorrhea and reduce a female's dependency on a male partner. Female condoms may also be safely used for receptive anal sex by both males and females.

Behavioral Intervention

Factors that put persons at increased risk for sexually transmissible infections include alcohol and substance use disorders, poverty, stigma, and governmental and institutional policies that discriminate based on gender, race, ethnicity, sexual orientation, and gender identity. Successful interventions to reduce individual risk must occur at the individual, community, and policy level. Individual-level behavioral counseling can reduce the risk for sexually transmitted infections.[22]

Microbial Prophylaxis and Vaccination

Antimicrobial pre-exposure or post-exposure prophylaxis may be partially efficacious against *N. gonorrhoeae* in sexually active adults. Furthermore, antiseptic mouthwash is not effective for preventing oropharyngeal infection.[A5] Epidemiologic data suggest that outer-membrane-vesical–containing meningococcal type B vaccines can reduce the rate of acquisition of gonorrhea by 30 to 40%.[23]

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276 CHANCROID

STANLEY M. SPINOLA

DEFINITION

Chancroid is a sexually transmitted disease that is characterized by painful genital ulcers and inguinal lymphadenitis caused by *Haemophilus ducreyi*. *H. ducreyi* also is a major cause of nonsexually transmitted cutaneous ulcers in children who live in regions of the South Pacific and Africa where yaws (Chapter 295), which is a nonsyphilitic treponematosis that causes a disfiguring and debilitating childhood infectious disease, is endemic.

H. ducreyi is a gram-negative coccobacillus that is not a true *Haemophilus* species. Within the Pasteurellaceae, *H. ducreyi* is grouped in a distinct lineage with *Mannheimia haemolytica* and *Aggregatibacter* (formerly *Actinobacillus*) *pleuropneumoniae*. *H. ducreyi* is likely to have diverged from these animal respiratory pathogens to occupy its niche in the human epithelium.

EPIDEMIOLOGY

Chancroid, which is endemic in resource-poor regions of Africa and Asia, facilitates the transmission of human immunodeficiency virus (HIV-1). In the 1990s, the World Health Organization estimated the annual global prevalence of chancroid to be 4 to 6 million cases. Because of the widespread use of syndromic management, which consists of treatment for syphilis and chancroid without diagnostic testing, the prevalence of chancroid has dramatically declined in endemic areas. Chancroid can be maintained only in networks with high rates of multiple sex partners. Infected female sex workers play an important role in its epidemiology, and targeted treatment of sex workers can eradicate the disease in endemic areas. Despite these successes, chancroid persists in many

ABSTRACT

Haemophilus ducreyi is a gram-negative facultative anaerobic bacterium that causes chancroid, which is a genital ulcer disease that is endemic in Africa and Asia and that facilitates transmission of HIV-1. *H. ducreyi* is sexually transmitted but is also a major cause of nonsexually transmitted cutaneous ulcers in children in yaws-endemic countries of Africa and the South Pacific islands. In chancroid, infected female sex workers serve as a reservoir for *H. ducreyi*, and transmission is thought to occur via microabrasions during intercourse. In cutaneous ulcers, asymptomatic colonization of the skin, flies, and fomites provide environmental reservoirs that allow the bacterium to cause infection following minor skin trauma. In genital ulcers, *H. ducreyi* is frequently cotransmitted with herpes simplex virus and *Treponema pallidum*, the causative agent of syphilis. In cutaneous ulcers, coinfection is common with *Treponema pallidum* subsp. pertenue, which is the causative agent of yaws. Although genital and cutaneous ulcers caused by *H. ducreyi* are typically nonindurated and very painful with ragged edges, clinical diagnosis is unreliable, so definitive diagnosis requires either a positive culture or polymerase chain reaction test. The most reliable treatment regimens are macrolides, quinolones, or third-generation cephalosporins.

KEYWORDS

Haemophilus ducreyi
chancroid
genital ulcers
cutaneous ulcers

countries, thereby implying a reservoir of untreated sex workers. Although urban outbreaks of chancroid associated with sex work occurred in the United States in the 1980s and 1990s, only 3 to 11 cases were reported annually from 2015 to 2019, most likely imported after contact with infected persons in endemic areas.

The male-to-female ratio of chancroid is 3:1, in part because of infection of multiple partners by sex workers. However, human inoculation experiments indicate that men are twice as susceptible as women to develop pustules, thereby suggesting that gender plays a role in the predominance of disease in men.

In yaws-endemic countries, *H. ducreyi* causes a chronic limb ulceration syndrome that occurs primarily in children.[1,2] Close contact of family members with ulcer cases is implicated in transmission. In yaws-endemic villages in Papua New Guinea, the prevalence of this syndrome has been 2 cases per 100 persons, and *H. ducreyi* is more common than *T. pallidum* subsp. *pertenue* in this setting. The overall prevalence of *H. ducreyi* infection in children aged 5 to 15 years can be as high as 7%. Similar data are reported from Ghana, the Solomon Islands, and Vanuatu, which together with Papua New Guinea are reported to have the highest prevalence of yaws. Travelers to endemic areas can acquire limb ulcers following minor trauma; the first case of cutaneous ulcers caused by *H. ducreyi* in the Netherlands was reported in 2018 in a person who imported it from Indonesia.[3]

PATHOBIOLOGY

In human inoculation experiments, puncture wounds are required to initiate infection, and the estimated infectious dose is as low as one bacterium. Papules develop within 24 hours and either spontaneously resolve or evolve into pustules in 2 to 5 days. Neutrophils and macrophages surround the organism and form an abscess that erodes the epidermis. Below the abscess is a collar of macrophages and regulatory T cells and a dermal infiltrate of macrophages, CD4 and CD8 T cells, natural killer cells, and dendritic cells. This histopathology, which resembles a suppurative granuloma, is associated with neutrophils and macrophages that fail to ingest the organism.

Whole-genome sequencing suggests cutaneous ulcer strains diverged from multiple lineages of genital ulcer strains during the past 180,000 years. RNA sequencing and metabolomics show that *H. ducreyi* changes its gene expression to adapt to the anaerobic, glucose-poor environment of the abscess and to scavenge alternative carbon sources, such as ascorbic acid.[4] Differential host susceptibility is associated with distinct dendritic cell responses, which may shape the responses of T cells and natural killer cells, and thereby influence the ability of phagocytes to ingest the organism.

CLINICAL MANIFESTATIONS

To cause chancroid, *H. ducreyi* is thought to enter the skin when breaks in the epithelium occur during intercourse. Papules, which form within hours to days, evolve into pustules in 2 to 3 days. After a few days to 2 weeks, the pustules ulcerate. Patients typically develop one to four painful ulcers (Fig. 276-1) but often do not seek treatment until they have had ulcerative symptoms for 1 to 3 weeks. By this time, 10 to 40% have suppurative inguinal lymphadenopathy or buboes (see Fig. 276-1).

Ulcers are classically very painful and nonindurated, with ragged edges. The ulcer, which may be covered by a yellow or gray necrotic exudate, bleeds when scraped. However, this presentation occurs in a minority of patients, and chancroid is frequently indistinguishable from syphilis (Chapter 295) and genital herpes simplex (Chapter 345).[5] Lesions in men are usually on the foreskin, coronal sulcus, or penile shaft. Lesions in women are usually on the labia, but women may have painless internal vaginal and cervical ulcers. Lesions also occur on the thighs and buttocks or at distant sites. These extragenital lesions are thought to be due to autoinoculation. Untreated, chancroid persists for months and causes giant ulcers, erosion of the infected area, or fibrosis, thereby leading to phimosis in men.

Although cutaneous ulcers occur in adults, they primarily occur in children on the lower legs (Fig. 276-2). Up to 20% of asymptomatic children in endemic areas are colonized by *H. ducreyi* on their skin, and it is likely that the organism enters and infects the skin via minor traumatic wounds. Ulcers due to *H. ducreyi* tend to be more tender, smaller, and less circular with less indurated edges than those due to yaws or dual infections, but there is a great deal of clinical overlap.

DIAGNOSIS

Clinical diagnosis is neither sensitive (about 70%) nor specific (about 55%),[6] so the definitive diagnosis of chancroid or cutaneous ulcers requires either a positive culture or a polymerase chain reaction (PCR) test. PCR has a sensitivity of 95 to 98% and a specificity of 99% for *H. ducreyi*[7,8] but is not commercially available. In comparison, the sensitivity for culture is approximately 75%.

FIGURE 276-1. Typical chancroidal ulcer and lymphadenitis in a man. (From Herpes-Coldsores.com. http://www.herpes-coldsores.com/std/chancroid_pictures.htm.)

Most sexually transmitted disease clinics do not routinely test patients for chancroid, so the diagnosis is typically made by the exclusion of genital herpes (Chapter 345) and syphilis (Chapter 295). Public health authorities should be notified so that specific diagnostic testing can be initiated in patients who have genital ulcers and lymphadenitis or who do not respond to treatment for primary syphilis.

The differential diagnosis (Chapter 264) of chancroid includes syphilis (Chapter 295), genital herpes (Chapter 345), lymphogranuloma venereum (Chapter 294), and granuloma inguinale (Chapter 292). Mixed infections with herpes simplex virus or syphilis occur in approximately 15 to 20% of cases of chancroid diagnosed by PCR. Patients with suspected chancroid should be tested for genital herpes, have serologic tests for syphilis and HIV-1, and have a dark-field examination.

For cutaneous ulcers, the differential diagnosis includes yaws (Chapter 295), *T. pallidum* subsp. *pertenue*, *Streptococcus pyogenes*, and *Fusobacteria*.[9] PCR testing, when available, is usually diagnostic.

TREATMENT

Because of syndromic management, little is known about the current prevalence of antibiotic resistance in *H. ducreyi*, but the only reliable treatment regimens are macrolides, quinolones, and third-generation cephalosporins.[A1] Current treatment recommendations for chancroid include single-dose azithromycin (1 g orally or ceftriaxone 250 mg intramuscularly), ciprofloxacin (500 mg orally twice a day for 3 days), and erythromycin base (500 mg orally three times a day for 7 days). Children with cutaneous ulcers respond to single-dose azithromycin (30 mg/kg orally).

In patients who are coinfected with HIV, chancroid ulcers may not heal as readily after antibiotic treatment with single-dose regimens. Multidose regimens are recommended if close follow-up cannot be ensured and may be considered in uncircumcised men, who are at higher risk for failure to respond to single-dose regimens. Repeated aspiration of buboes may be required to effect a cure. Incision and drainage is even more effective but is usually avoided because it can cause excessive scarring, especially keloid formation in Black patients.

PROGNOSIS

Clinical cure correlates with a reduction in pain and purulence, as well as re-epithelialization of the ulcer within 7 days. Patients who do not show improvement within 7 days should be regarded as treatment failures and given an alternative agent. Even if *H. ducreyi* is eradicated, ulcers may persist if genital

FIGURE 276-2. Cutaneous ulcer due to *Haemophilus ducreyi* in a child in Papua New Guinea. (Courtesy of Oriol Mitja.)

herpes or syphilis is present and not treated. Most ulcers heal in 2 weeks; large ulcers may take 4 weeks to heal. The same principles seem to apply to cutaneous ulcers.

PREVENTION

Circumcision reduces the risk of chancroid in men. Condoms are likely to be protective. Although several antibodies that may afford protection have been identified in animal models, no vaccine is currently available. Contacts of patients with chancroid should be treated with an approved regimen. Prevention of cutaneous ulcers is under investigation and likely will involve improved sanitation and hygiene.

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277 *HAEMOPHILUS* AND *MORAXELLA* INFECTIONS

MONICA M. FARLEY

HAEMOPHILUS INFLUENZAE

DEFINITION

Haemophilus refers to the bacteria's requirement for specific blood components for growth. In the respiratory tract, which is the primary site of colonization for most *Haemophilus* species, the most common infections include otitis media, sinusitis, bronchitis, and pneumonia. Serious invasive diseases (e.g., epiglottitis, bacteremia, endocarditis, meningitis, septic arthritis) may occur, particularly in susceptible older adults and infants (Table 277-1).

TABLE 277-1 SITES OF COLONIZATION AND INFECTIONS BY *HAEMOPHILUS INFLUENZAE*

SPECIES	NORMAL FLORA	ASSOCIATED DISEASES
H. influenzae	Nasopharynx Upper respiratory tract	Meningitis Epiglottitis Sinusitis Otitis media Pneumonia Cellulitis Septic arthritis Osteomyelitis Obstetric infections Endocarditis
H. influenzae, biogroup *aegyptius*		Purulent conjunctivitis Brazilian purpuric fever

The Pathogen

Haemophilus species are small, nonmotile, pleomorphic, gram-negative bacteria that can grow aerobically or anaerobically. *H. influenzae* are classified or typed based on the presence or absence of serologically unique capsule polysaccharides—including six capsule serotypes (a to f) as well as nonencapsulated (nontypeable) forms. Encapsulated types are relatively clonal, whereas nonencapsulated types are very heterogeneous. Isolation of *Haemophilus* species in the laboratory is best accomplished on chocolate agar medium, which supplies the hemin and nicotinamide adenine dinucleotide required for its growth, in a carbon dioxide–enriched atmosphere.

EPIDEMIOLOGY

H. influenzae can colonize the nasopharynx of both children and adults. Current vaccination rates for *H. influenzae* type b are about 70% worldwide, but the organism still causes an estimated 3 million cases of serious disease and 400,000 deaths annually.

Prior to the introduction of *H. influenzae* type b conjugate vaccines in the United States, between 3 and 5% of infants harbored *H. influenzae* type b in their nasopharynx, and about 1 in 200 children less than 5 years of age experienced invasive disease. In unvaccinated populations, *H. influenzae* type b is still the most common cause of meningitis in young children,[1] but vaccines reduce invasive *H. influenzae* type b disease by more than 99%. Furthermore, the risk of secondary invasive infections among nonimmune household contacts of a patient with invasive *H. influenzae* type b disease is increased about 600-fold.

With immunization with a protein conjugate *H. influenzae* type b vaccine, both colonization and infection with *H. influenzae* type b are greatly reduced.[2] Although nasopharyngeal colonization with nontypeable *H. influenzae* is very common in both children and adults, infection occurs in only a small proportion of colonized individuals.

In the United States, the overall annual incidence of invasive *H. influenzae* infections is now 1.70 cases per 100,000 population, with cases increasing for *H. influenzae* types a, e, and f and nontypeable species[3] even as cases of type b have remained low. From 1998 to 2007, *H. influenzae* caused 6% of meningitis cases in U.S. adults, the majority of which were nontypeable strains. Similar data are reported from other countries where conjugate *H. influenzae* vaccines are routinely used.

The risk of invasive *H. influenzae* disease is highest in infants less than 1 year of age and adults ages 65 years and older.[4] People living with human immunodeficiency virus (HIV) infection also have increased risk for *H. influenzae* infection. Other underlying conditions that increase the risk for *H. influenzae* infection include immunoglobulin deficiencies (Chapter 231), sickle cell disease (Chapter 149), anatomic or functional asplenia (Chapter 154), malignant disease, pregnancy, cerebrospinal fluid (CSF) leaks, head trauma (Chapter 368), alcohol use disorders (Chapter 364), and chronic obstructive pulmonary disease (COPD; Chapter 76).

Disproportionately high rates of invasive *H. influenzae* disease also are noted in Indigenous populations. The incidence of invasive *H. influenzae* serotype a disease is currently 17 times higher in American Indian/Alaska native children below age 5 years than among children of all other races combined.[5] In nonvaccinated

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FIGURE 276-2. Cutaneous ulcer due to *Haemophilus ducreyi* in a child in Papua New Guinea. (Courtesy of Oriol Mitja.)

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Circumcision reduces the risk of chancroid in men. Condoms are likely to be protective. Although several antibodies that may afford protection have been identified in animal models, no vaccine is currently available. Contacts of patients with chancroid should be treated with an approved regimen. Prevention of cutaneous ulcers is under investigation and likely will involve improved sanitation and hygiene.

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MONICA M. FARLEY

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DEFINITION

Haemophilus refers to the bacteria's requirement for specific blood components for growth. In the respiratory tract, which is the primary site of colonization for most *Haemophilus* species, the most common infections include otitis media, sinusitis, bronchitis, and pneumonia. Serious invasive diseases (e.g., epiglottitis, bacteremia, endocarditis, meningitis, septic arthritis) may occur, particularly in susceptible older adults and infants (Table 277-1).

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H. influenzae, biogroup *aegyptius*		Purulent conjunctivitis Brazilian purpuric fever

The Pathogen

Haemophilus species are small, nonmotile, pleomorphic, gram-negative bacteria that can grow aerobically or anaerobically. *H. influenzae* are classified or typed based on the presence or absence of serologically unique capsule polysaccharides—including six capsule serotypes (a to f) as well as nonencapsulated (nontypeable) forms. Encapsulated types are relatively clonal, whereas nonencapsulated types are very heterogeneous. Isolation of *Haemophilus* species in the laboratory is best accomplished on chocolate agar medium, which supplies the hemin and nicotinamide adenine dinucleotide required for its growth, in a carbon dioxide–enriched atmosphere.

EPIDEMIOLOGY

H. influenzae can colonize the nasopharynx of both children and adults. Current vaccination rates for *H. influenzae* type b are about 70% worldwide, but the organism still causes an estimated 3 million cases of serious disease and 400,000 deaths annually.

Prior to the introduction of *H. influenzae* type b conjugate vaccines in the United States, between 3 and 5% of infants harbored *H. influenzae* type b in their nasopharynx, and about 1 in 200 children less than 5 years of age experienced invasive disease. In unvaccinated populations, *H. influenzae* type b is still the most common cause of meningitis in young children,[1] but vaccines reduce invasive *H. influenzae* type b disease by more than 99%. Furthermore, the risk of secondary invasive infections among nonimmune household contacts of a patient with invasive *H. influenzae* type b disease is increased about 600-fold.

With immunization with a protein conjugate *H. influenzae* type b vaccine, both colonization and infection with *H. influenzae* type b are greatly reduced.[2] Although nasopharyngeal colonization with nontypeable *H. influenzae* is very common in both children and adults, infection occurs in only a small proportion of colonized individuals.

In the United States, the overall annual incidence of invasive *H. influenzae* infections is now 1.70 cases per 100,000 population, with cases increasing for *H. influenzae* types a, e, and f and nontypeable species[3] even as cases of type b have remained low. From 1998 to 2007, *H. influenzae* caused 6% of meningitis cases in U.S. adults, the majority of which were nontypeable strains. Similar data are reported from other countries where conjugate *H. influenzae* vaccines are routinely used.

The risk of invasive *H. influenzae* disease is highest in infants less than 1 year of age and adults ages 65 years and older.[4] People living with human immunodeficiency virus (HIV) infection also have increased risk for *H. influenzae* infection. Other underlying conditions that increase the risk for *H. influenzae* infection include immunoglobulin deficiencies (Chapter 231), sickle cell disease (Chapter 149), anatomic or functional asplenia (Chapter 154), malignant disease, pregnancy, cerebrospinal fluid (CSF) leaks, head trauma (Chapter 368), alcohol use disorders (Chapter 364), and chronic obstructive pulmonary disease (COPD; Chapter 76).

Disproportionately high rates of invasive *H. influenzae* disease also are noted in Indigenous populations. The incidence of invasive *H. influenzae* serotype a disease is currently 17 times higher in American Indian/Alaska native children below age 5 years than among children of all other races combined.[5] In nonvaccinated

ABSTRACT

Haemophilus influenzae is a respiratory pathogen that may also cause significant invasive disease such as bacteremia, epiglottitis, meningitis, and other serious infections. Since the introduction of *Haemophilus influenzae* capsule type b (Hib) conjugate vaccines, *Haemophilus* b disease has declined significantly, but infections due to nontypeable (nonencapsulated) and other capsular serotypes have increased. Other *Haemophilus* spp that can cause serious infections include *H. parainfluenzae* and *H. ducreyi*. *Moraxella catarrhalis* is associated with upper respiratory infections and bronchitis but less commonly with invasive disease.

KEYWORDS

Haemophilus influenzae
Haemophilus influenzae type b (Hib) bacteremia
meningitis Hib vaccines
Moraxella catarrhalis
bronchitis

populations, daycare attendance, crowding, other siblings in the household, prior hospitalizations, and prior otitis media increase the risk for *H. influenzae* type b disease in young children, whereas breast-feeding decreases the risk.

PATHOBIOLOGY

H. influenzae have six unique polysaccharide capsular serotypes (a through f) that are key factors in virulence by inhibiting opsonization, clearance, and intracellular killing of the organisms. Nontypeable strains lack this capsular polysaccharide. The *H. influenzae* type b capsule contains pentose polysaccharides, specifically polyribosyl ribitol phosphate, whereas the other serotypes contain hexose polysaccharides. *H. influenzae* type b capsule is more virulent than the other capsulated types, and the amount of polyribosyl ribitol phosphate produced is related to its resistance to complement.

Structurally and antigenically distinct encapsulated isolates (types a to f) are responsible for most of the invasive infections in unvaccinated children and of acute epiglottitis in both children and adults, whereas the nonencapsulated (nontypeable) isolates are associated with localized respiratory mucosal infections, conjunctivitis, female genital tract infections, and invasive disease in older adults and in patients who have underlying conditions such as COPD. Nontypeable *H. influenzae* is one of the most common causes of acute otitis media in children. Among non-b capsule serotypes, serotype a capsule is most similar to the type b capsule, and type a isolates can cause severe invasive disease that is similar to *H. influenzae* type b in young children. In vaccinated populations, most infections are now caused by nontypeable strains and somewhat less often by non-b serotypes (particularly *H. influenzae* serotypes a, e, and f).

Fimbriae are present in both typeable and nontypeable isolates and are important virulence factors that facilitate adherence of *H. influenzae* to mucosal surfaces. The lipooligosaccharides of *H. influenzae* also contribute to their virulence. Phase-variable modifications to the *H. influenzae* surface lipooligosaccharide alter receptor tropism and evasion of innate immune defenses. Nontypeable *H. influenzae*, with lipopolysaccharides containing more phosphorylcholine, more efficiently colonize the upper respiratory tract by binding to platelet-activating factor receptors on epithelial cells. In contrast, isolates that invade the blood stream have lipopolysaccharides that contain less phosphorylcholine to avoid complement activation and enhance their intravascular survival.[6]

A variety of outer membrane proteins also serve as virulence factors in *H. influenzae* disease by inhibiting complement killing and facilitating mucosal adhesion. Effective activation of complement is an essential component of the host defense against some *H. influenzae* diseases, and congenital complement component deficiencies (e.g., in C2, C3, and factor I; see Chapter 37) increase the risk of serious infection. Efficient scavenging of iron within the human host is crucial for *H. influenzae* to multiply. To evade the local mucosal immune response, *H. influenzae* produces immunoglobulin A1 protease, which specifically cleaves human immunoglobulin A1 (IgA1).

Serum bactericidal antibodies directed against the polysaccharide capsule are critical to protection against encapsulated *H. influenzae*, particularly type b infection. Capsule-specific antibodies facilitate opsonization and complement-mediated killing. Neonates acquire transplacental maternal antibodies that protect against invasive Hib disease for the first 3 to 6 months of life. As maternal antibodies wane, susceptibility to *H. influenzae* type b infections increases during infancy. In unvaccinated populations, most cases of *H. influenzae* type b meningitis occur in infants after they lose passively acquired maternal antibodies and before they develop active humoral immunity. Not surprisingly, patients who have functional asplenia (e.g., sickle cell disease) or who have undergone splenectomy also have an increased risk of developing severe disease with *H. influenzae* type b and, rarely, serotype a.

CLINICAL MANIFESTATIONS AND DIAGNOSIS

Meningitis

H. influenzae meningitis now more commonly occurs in unvaccinated or undervaccinated young children, immunocompromised children and adults, and patients who have a history of skull fractures or CSF leaks.[7] As with other bacterial meningitides (Chapter 381), patients typically present with fever, headache, and mental status changes, including lethargy, confusion, somnolence, and sometimes seizures.

The CSF white blood cell count is usually greater than 1000/μL, with an elevated protein level and low glucose level. The CSF Gram stain is neither sensitive for detecting nor specific for excluding *H. influenzae*, and the diagnosis is established by CSF culture or a multiplex polymerase chain reaction (PCR) panel that detects *H. influenzae* nucleic acid, even in patients who have had prior antibiotic treatment, before culture results are available.

Epiglottitis

H. influenzae type b is the most common cause of acute epiglottitis in unvaccinated children, especially before age 5 years, but is rare after vaccination.[8] Symptoms in children include the rapid onset of fever, drooling, dysphagia, respiratory distress, stridor, and life-threatening airway obstruction. In adults, symptoms may be more insidious and include fever, sore throat, dysphagia, and odynophagia. Tender cervical lymphadenopathy is common in all ages. A swollen, cherry-red epiglottis (see Fig. 331-2B) can be visualized on laryngoscopy, which should be performed only by experts who can perform emergency tracheotomy if the procedure precipitates acute airway obstruction. A lateral radiograph (see Figs. 331-2 C and D) or a computed tomographic (CT) scan of the neck may confirm the diagnosis. *H. influenzae* should be differentiated from parainfluenza virus (Chapter 331), which is the leading cause of epiglottitis in vaccinated populations. Since *H. influenzae* is often part of the normal respiratory flora, PCR and cultures of the pharynx and other mucosal surfaces may not provide a definitive diagnosis, so the diagnosis is usually established by a positive blood culture for *H. influenzae*.

Tracheobronchitis

H. influenzae tracheobronchitis (Chapter 84), which is characterized by fever, cough, and purulent sputum without radiographic evidence of pneumonia, occurs especially as an exacerbation of respiratory symptoms in patients with known COPD.[9] A sputum Gram stain that demonstrates purulence and a predominance of small, pleomorphic/coccobacillary gram-negative organisms is suggestive of the diagnosis, but definitive bacteriologic diagnosis is often difficult to achieve, and associated bacteremia is rare. A response to treatment for *H. influenzae* supports the diagnosis.

Pneumonia

In vaccinated populations, *H. influenzae* pneumonia is seen predominantly in older adults, sometimes as a nosocomial infection, including ventilator-associated pneumonia (Chapters 85 and 261). Clinical features, which are typical of bacterial pneumonia in general (Chapter 85), include fever and productive cough, as well as signs and radiographic findings of lobar consolidation.[10] Pneumonia can be complicated by pleural effusions, abscess, empyema, and respiratory failure.

A predominance of gram-negative coccobacilli in purulent sputum suggests the diagnosis, but isolation of *H. influenzae* from sputum culture may also represent respiratory colonization. Isolation of *H. influenzae* from a normally sterile site such as blood or pleural fluid may establish the diagnosis. Most *H. influenzae* isolates that cause pneumonia in vaccinated populations are nontypeable, but serotype f has been associated with bacteremic pneumonia in adults.

Cellulitis

In unvaccinated children, a distinctive *H. influenzae* type b facial cellulitis is characterized by a blue or violaceous discoloration of the skin. However, other features (e.g., fever, erythema, and tenderness) may not be different than what is seen with cellulitis from other pathogens. The diagnosis is established by blood culture, tissue aspirate from the involved area, or both.

Sinusitis and Otitis Media

H. influenzae and *Streptococcus pneumoniae* (Chapter 268) are the most common bacterial isolates obtained by needle aspiration or surgery from patients with acute sinusitis (Chapter 394).[11] The *H. influenzae* isolates are most often nontypeable.

H. influenzae, predominately nontypeable strains in vaccinated populations, is still the most common cause of otitis media (Chapter 394) in young children. Children with *H. influenzae* otitis media may experience significant ear pain or exhibit irritability. With *H. influenzae* type b, bacteremia and meningitis may complicate the otitis. Examination usually shows an inflamed, opaque, bulging, tympanic membrane. Perforation with drainage may occur. A bacteriologic diagnosis can be made by Gram stain, PCR, or culture of purulent fluid obtained by tympanocentesis.[12]

Gynecologic and Urologic Infection

Nontypeable *H. influenzae* cause tubo-ovarian abscesses and salpingitis (Chapter 264) in women. *H. influenzae* and *H. parainfluenzae* account for about 7% of cases of acute urethritis in men, possibly due to oral-genital sexual contact.

Bacteremia, Endocarditis, and Pericarditis

H. influenzae can cause primary bacteremia without an obvious source, mostly in patients with immunocompromising conditions, such as lymphoma, leukemia,

or alcohol use disorder. A careful clinical and laboratory evaluation should be pursued to avoid missing a life-threatening focal infection, especially occult meningitis or epiglottitis.

H. influenzae is an unusual cause of endocarditis (Chapter 61), which most often occurs in patients with preexisting valvular heart disease.[13] Patients are at high risk for valvular dysfunction and arterial emboli. Diagnosis is made by blood culture and echocardiography.

H. influenzae rarely causes primary pericarditis in adults, but pericarditis associated with contiguous spread from adjacent pneumonia may occur. Diagnosis is made by echocardiography, CT, and pericardiocentesis.

Septic Arthritis

Septic arthritis (Chapter 251) due to *H. influenzae* type b is common in unvaccinated children and young adults but rare in older adults. Clinical features are similar to other causes of pyogenic arthritis.[14] Cases may include polyarticular arthritis. Diagnosis is made by arthrocentesis, Gram stain, PCR, and culture of joint fluid.

Purulent Conjunctivitis and Brazilian Purpuric Fever

H. influenzae is the most common cause of bacterial conjunctivitis (Chapter 391) in children, and adults can be secondarily infected. *H. influenzae aegyptius* (Koch-Weeks bacillus) is a cause of epidemic purulent conjunctivitis, mostly in children and commonly in hot climates or in the summer season. Clinical manifestations include conjunctival erythema, edema, mucopurulent exudate, and discomfort in the eyes. A unique clone causes a severe invasive infection in infants and children, called Brazilian purpuric fever, which is characterized by petechial or purpuric skin lesions and vascular collapse occurring days to weeks after an initial episode of conjunctivitis.

TREATMENT

A third-generation cephalosporin such as ceftriaxone (adult dose, 1 to 2 g intravenously once daily or every 12 hours for meningitis) or cefotaxime (adult dose, 2 g intravenously every 6 hours) should be initiated as therapy in patients with proven or suspected *H. influenzae* meningitis, epiglottitis, pneumonia, or bacteremia and continued for 5 to 7 days (7 days for meningitis). Tracheobronchitis and otitis media are commonly treated with oral antibiotics such as amoxicillin-clavulanate (500 mg every 12 hours), levofloxacin (500 mg daily), and moxifloxacin (400 mg daily) for 5 to 7 days. For focal infections, such as pericarditis, septic arthritis, and sinusitis due to sinus obstruction, drainage of the infection is key to successful treatment.

PREVENTION

A three- or four-dose primary series and booster of a protein-conjugated *H. influenzae* type b vaccine (Chapter 15) generates an effective T-cell–dependent immune response in the most vulnerable infants and young children. These vaccines reduce or eliminate carriage of Hib in the nasopharynx, thereby reducing transmission and providing indirect protection to others who are not vaccinated.[15] Older children and adults with sickle cell disease, asplenia, HIV infection, deficiencies of antibodies or complement, or cancer undergoing chemotherapy or radiation therapy may be candidates for a single dose of vaccine if they have not completed a primary series and booster or had at least one dose after 14 months of age. For recipients of hematopoietic stem cell transplants, a three-dose series given 4 weeks apart starting 6 to 12 months after transplantation should be completed, regardless of prior vaccine history.

Antibiotic prophylaxis with rifampin (10 mg/kg once daily for 4 days to infants younger than 1 month, 20 mg/kg, up to a maximum of 600 mg once daily for 4 days, to older children and 600 mg/day for 4 days to adults) is recommended for all household members of a patient with invasive *H. influenzae* type b disease if there are any nonimmunized or underimmunized household contacts less than 4 years of age. Prophylaxis is not routinely recommended for contacts of patients who have nontypeable or non–type b *H. influenzae* disease, though some experts recommend rifampin prophylaxis for invasive *H. influenzae*–type a disease using the same dosing as for type b disease for all household contacts when at least one member of the household is less than 4 years of age or is immunocompromised.[16]

PROGNOSIS

For *H. influenzae* meningitis, mortality ranges from approximately 5 to 18% and is highest in adults with encapsulated *H. influenzae*. Permanent neurologic sequelae, including sensorineural hearing loss, may persist in as many as a third of patients who survive. In the United States, death from acute epiglottitis has essentially disappeared in the *H. influenzae* vaccination era.[17]

For tracheobronchitis and pneumonia, prognosis varies with the underlying health of the patient. The elderly, as well as patients with underlying lung disease, HIV, asplenia, immunosuppression, or multiple comorbid conditions, are at greatest risk for severe disease and worse outcomes. Invasive *H. influenzae* infection with nontypeable strains in pregnant women is associated with high rates of fetal loss and extreme prematurity. Cellulitis (Chapter 408) and sinusitis (Chapter 394) resolve with antibiotic therapy. Otitis also resolves with antibiotics and often without them (Chapter 394).

OTHER *HAEMOPHILUS* SPECIES

Haemophilus parainfluenzae, which is part of the normal microbiota of the mouth and pharynx, is associated with a variety of infections, including dental abscesses, brain abscess, epidural abscess, liver abscess, osteomyelitis, pneumonia, empyema, epiglottitis, peritonitis, septic arthritis, bacteremia, endocarditis[18] and male urethritis. Meningitis is a rare but serious manifestation of *H. parainfluenzae* infection in children and adults. *Haemophilus* species, including *H. parainfluenzae*, also are part of the HACEK (***H****aemophilus* species, ***A****ggregatibacter*, ***C****ardiobacterium hominis*, ***E****ikenella corrodens*, and ***K****ingella kingae*) group of small, fastidious organisms associated with subacute endocarditis (Chapter 61). *Haemophilus ducreyi* is the cause of chancroid (Chapter 276), which is a sexually transmitted infection that causes genital ulcer disease. Several former *Haemophilus* species also associated with endocarditis, including *H. aphrophilus*, *H. paraphrophilus*, and *H. segnis*, have been reclassified into the *Aggregatibacter* genus.

MORAXELLA INFECTIONS

DEFINITION

Moraxella catarrhalis is a respiratory pathogen associated with infections such as acute otitis media in children and exacerbations of chronic bronchitis in adults.

The Pathogen

Moraxella organisms are small, catalase- and oxidase-positive, gram-negative bacteria that may be grown in the laboratory on blood or chocolate agar. *M. catarrhalis* form diplococci that are morphologically quite similar to *Neisseria*, but other *Moraxella* species may appear as gram-negative coccobacilli on Gram stain. *M. catarrhalis* is the most important of this genus (Table 277-2).

EPIDEMIOLOGY AND PATHOBIOLOGY

M. catarrhalis is an exclusively human pathogen that is found predominantly in the respiratory tract. The frequency of colonization of the upper respiratory tract with *M. catarrhalis* may be as high as 75% in infants but decreases to <5% in adults. Infection is believed to result from contiguous spread of the organism from colonized respiratory sites, possibly due to introduction of more virulent strains to which the host lacks immunity. *M. catarrhalis* may be responsible for approximately 10% of all exacerbations of COPD (Chapter 76). Interestingly, the prevalence of clinical *M. catarrhalis* upper respiratory tract infection has declined since the introduction of the conjugated pneumococcal vaccines. *M. catarrhalis* is also the cause of about 15% of cases of acute and chronic otitis media in children.

M. catarrhalis, which is a common co-resident of respiratory secretions along with *H. influenzae*, releases biologically active outer membrane vesicles, which contain multiple virulence factors that contribute to the pathobiology of otitis media. The mechanism for coexistence of these pathogens may, in part,

TABLE 277-2 SITES OF COLONIZATION AND INFECTION BY *MORAXELLA* SPECIES

SPECIES	NORMAL FLORA	ASSOCIATED DISEASES
M. catarrhalis	Oral cavity and upper respiratory tract	Chronic bronchitis exacerbation Otitis media Pneumonia Sinusitis Bacteremia, endocarditis Arthritis, osteomyelitis, epiglottitis (all extremely rare)
M. lacunata	Upper respiratory tract	Chronic conjunctivitis, rare endocarditis, arthritis
Other *Moraxella*	Upper respiratory tract	Rare cases of bacteremia, endocarditis, arthritis, meningitis

be due to the capacity of *M. catarrhalis* outer membrane vesicles to inactivate complement, thereby enhancing survival of *H. influenzae*.

CLINICAL MANIFESTATIONS

M. catarrhalis can cause pneumonia, particularly in older adults with COPD and other underlying conditions such as diabetes mellitus. Bacteremic pneumonia is rare. Patient-to-patient spread has been demonstrated, and nosocomial pneumonia due to *M. catarrhalis* may occur.

Otitis media due to *M. catarrhalis* tends to be milder than that due to other pathogens, and complications such as spontaneous rupture of the tympanic membrane or mastoiditis are uncommon. The organism also causes sinusitis and is a rare cause of bacteremia,[19] endocarditis,[20] and other invasive infections in children and adults, typically in immunocompromised individuals.

Other *Moraxella* species rarely cause serious infections except in patients with complement deficiency, cancer, or other immune deficiencies. *M. lacunata* is associated with a chronic angular conjunctivitis.

TREATMENT

For most noninvasive *M. catarrhalis* infections, oral amoxicillin-clavulanate (usual adult dose, 500 mg every 12 hours), a second- or third-generation cephalosporin (e.g., cefuroxime 500 mg twice daily), or a non–β-lactam antibiotic such as a fluoroquinolone (e.g., levofloxacin 500 mg daily or moxifloxacin 400 mg daily) should be initiated and continued for 5 to 7 days. Susceptibility testing, other than to detect β-lactamase, usually is not performed.

PROGNOSIS

For patients who have pneumonia or exacerbations of chronic obstructive pulmonary disease (Chapter 76), the prognosis varies depending on the severity of the underlying disease. Patients who are immunocompromised or have advanced lung disease are at greatest risk of severe disease and worse outcomes. Otitis resolves with antibiotics and often without them (Chapter 394).

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278 CHOLERA AND OTHER *VIBRIO* INFECTIONS

EDUARDO GOTUZZO AND CARLOS SEAS

CHOLERA

DEFINITION

Cholera is a dreaded epidemic diarrheal disease caused by *Vibrio cholerae* serogroup O1 and, since 1992, by the new serogroup O139. The disease is characterized by acute, large-volume watery diarrhea. In its more severe form, a person may be severely dehydrated and in hypovolemic shock; the patient may die in a matter of a few hours after contracting the infection if treatment is not provided.

The Pathogen

V. cholerae is a curved gram-negative bacillus that belongs to the family Vibrionaceae and shares common characteristics with the family Enterobacteriaceae. *V. cholerae* O1 can be classified into three serotypes according to the presence of somatic antigens and into two biotypes, classic and El Tor, according to specific phenotypic characteristics. There is no evidence of different clinical spectra among the three serotypes of *V. cholerae*. The classic biotype, responsible for the first six pandemics of cholera, causes an approximately equal number of symptomatic and asymptomatic cases, whereas the El Tor biotype causes more asymptomatic infections. The classic biotype is confined to the south of Bangladesh, and the El Tor biotype is responsible for the current pandemic. Variants of El Tor biotype, which share phenotypic features of both biotypes, are responsible for the current epidemics in Asia, Africa, and Latin America and may cause more severe disease. The O139 serogroup is composed of a variety of genetically diverse strains, both toxigenic and nontoxigenic; it is genetically closer to El Tor *V. cholerae*.

EPIDEMIOLOGY

Cholera has both a predisposition to cause epidemics with pandemic potential and an ability to remain endemic in all affected areas.

Cholera is endemic today in Africa, Asia, and Latin America. Seven pandemics have been registered in history since 1817; the most recent has lasted more than five decades since its recognition in Indonesia in 1961.[1] In Africa, cholera causes an estimated million or more cases annually, far more than the 70,000 or so reported cases, and nearly 40,000 annual deaths.[2] Although cholera mostly affects developing countries, several developed countries, such as the United States, Canada, and Australia, have reported indigenous and imported cases. The most recent epidemics occurred in Haiti in 2022 to 2023[3] and Yemen in 2016 and 2017. Fig. 278-1 shows the distribution of cholera in the world from 1989 to 2019.

People of all ages are at risk to contract the infection in epidemic settings, whereas children older than 2 years are mainly affected in endemic areas. *V. cholerae* lives in riverine, brackish, and estuarine ecosystems, where both O1 and non-O1 strains coexist, with non-O1 and nontoxigenic O1 strains predominating over toxigenic O1 strains. In its natural environment, *V. cholerae* lives attached to algae or to crustacean shells and copepods, with which it coexists in a symbiotic manner. Several conditions, such as temperature, salinity, and availability of nutrients, determine the survival of *V. cholerae*; when these conditions are adverse, vibrios survive in a viable but nonculturable state. Cholera phages modulate the abundance of *V. cholerae* in the environment and determine the beginning and end of epidemics. Phages may also play a role in the emergence of new *V. cholerae* serogroups by transferring genetic material to nontoxigenic strains.

From its aquatic environment, *V. cholerae* is introduced to humans through contamination of water sources and food.[4] Once humans are infected, very high attack rates may take place, particularly in previously naïve populations. The disease can be acquired by drinking contaminated water from rivers, ponds, lakes, and even tube well sources. Drinking unboiled water, introducing hands into containers used to store drinking water, drinking beverages from street vendors, drinking beverages with contaminated ice, and drinking water outside the home are risk factors. Drinking boiled water, acidic beverages, and carbonated water and using narrow-necked vessels for storing water are protective measures. Epidemics of cholera can be associated with the ingestion of leftover rice, raw fish, cooked crabs, seafood, raw oysters, and fresh vegetables and fruits.

Person-to-person transmission is less likely to occur because a large inoculum is necessary to transmit disease. Nevertheless, high transmission rates (approximately 50%) are reported among household contacts of patients with cholera in endemic areas.

Epidemics of cholera tend to occur during the hot season. Factors affecting climate change and climate variability have an impact on the incidence of cholera. The El Niño–Southern Oscillation, which is a periodic phenomenon representative of global climate variability, causes the warming of normally cool waters in the Pacific coastline of Peru, thereby promoting phytoplankton bloom, zooplankton bloom, and the proliferation of *V. cholerae*.

Some host factors are important in the transmission of cholera. The chronic gastritis associated with *Helicobacter pylori* (Chapter 125) predisposes to cholera by inducing hypochlorhydria, which reduces the ability of the stomach to contain the infection. Use of proton pump inhibitors or histamine-2 blockers and other conditions that cause achlorhydria also increase the risk. An unexplained predisposition to severe disease due to El Tor biotype in persons with the O blood group has been observed in Asia and more recently in Latin America. Innate predisposition has also been reported in endemic areas. Thus, complex associations among climatic, seasonal, bacterial, and human factors affect the transmission of cholera.

PATHOBIOLOGY

V. cholerae O1 and O139 cause clinical disease by secreting an enterotoxin that promotes the secretion of fluids and electrolytes by the small intestine. The infectious dose of bacteria varies with the vehicle. When water is the vehicle, more bacteria are needed to cause disease (10^3 to 10^8), but when the vehicle is food, lower amounts are needed (10^2 to 10^4).

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be due to the capacity of *M. catarrhalis* outer membrane vesicles to inactivate complement, thereby enhancing survival of *H. influenzae*.

CLINICAL MANIFESTATIONS

M. catarrhalis can cause pneumonia, particularly in older adults with COPD and other underlying conditions such as diabetes mellitus. Bacteremic pneumonia is rare. Patient-to-patient spread has been demonstrated, and nosocomial pneumonia due to *M. catarrhalis* may occur.

Otitis media due to *M. catarrhalis* tends to be milder than that due to other pathogens, and complications such as spontaneous rupture of the tympanic membrane or mastoiditis are uncommon. The organism also causes sinusitis and is a rare cause of bacteremia,[19] endocarditis,[20] and other invasive infections in children and adults, typically in immunocompromised individuals.

Other *Moraxella* species rarely cause serious infections except in patients with complement deficiency, cancer, or other immune deficiencies. *M. lacunata* is associated with a chronic angular conjunctivitis.

TREATMENT

For most noninvasive *M. catarrhalis* infections, oral amoxicillin-clavulanate (usual adult dose, 500 mg every 12 hours), a second- or third-generation cephalosporin (e.g., cefuroxime 500 mg twice daily), or a non–β-lactam antibiotic such as a fluoroquinolone (e.g., levofloxacin 500 mg daily or moxifloxacin 400 mg daily) should be initiated and continued for 5 to 7 days. Susceptibility testing, other than to detect β-lactamase, usually is not performed.

PROGNOSIS

For patients who have pneumonia or exacerbations of chronic obstructive pulmonary disease (Chapter 76), the prognosis varies depending on the severity of the underlying disease. Patients who are immunocompromised or have advanced lung disease are at greatest risk of severe disease and worse outcomes. Otitis resolves with antibiotics and often without them (Chapter 394).

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278 CHOLERA AND OTHER *VIBRIO* INFECTIONS

EDUARDO GOTUZZO AND CARLOS SEAS

CHOLERA

DEFINITION

Cholera is a dreaded epidemic diarrheal disease caused by *Vibrio cholerae* serogroup O1 and, since 1992, by the new serogroup O139. The disease is characterized by acute, large-volume watery diarrhea. In its more severe form, a person may be severely dehydrated and in hypovolemic shock; the patient may die in a matter of a few hours after contracting the infection if treatment is not provided.

The Pathogen

V. cholerae is a curved gram-negative bacillus that belongs to the family Vibrionaceae and shares common characteristics with the family Enterobacteriaceae. *V. cholerae* O1 can be classified into three serotypes according to the presence of somatic antigens and into two biotypes, classic and El Tor, according to specific phenotypic characteristics. There is no evidence of different clinical spectra among the three serotypes of *V. cholerae*. The classic biotype, responsible for the first six pandemics of cholera, causes an approximately equal number of symptomatic and asymptomatic cases, whereas the El Tor biotype causes more asymptomatic infections. The classic biotype is confined to the south of Bangladesh, and the El Tor biotype is responsible for the current pandemic. Variants of El Tor biotype, which share phenotypic features of both biotypes, are responsible for the current epidemics in Asia, Africa, and Latin America and may cause more severe disease. The O139 serogroup is composed of a variety of genetically diverse strains, both toxigenic and nontoxigenic; it is genetically closer to El Tor *V. cholerae*.

EPIDEMIOLOGY

Cholera has both a predisposition to cause epidemics with pandemic potential and an ability to remain endemic in all affected areas.

Cholera is endemic today in Africa, Asia, and Latin America. Seven pandemics have been registered in history since 1817; the most recent has lasted more than five decades since its recognition in Indonesia in 1961.[1] In Africa, cholera causes an estimated million or more cases annually, far more than the 70,000 or so reported cases, and nearly 40,000 annual deaths.[2] Although cholera mostly affects developing countries, several developed countries, such as the United States, Canada, and Australia, have reported indigenous and imported cases. The most recent epidemics occurred in Haiti in 2022 to 2023[3] and Yemen in 2016 and 2017. Fig. 278-1 shows the distribution of cholera in the world from 1989 to 2019.

People of all ages are at risk to contract the infection in epidemic settings, whereas children older than 2 years are mainly affected in endemic areas. *V. cholerae* lives in riverine, brackish, and estuarine ecosystems, where both O1 and non-O1 strains coexist, with non-O1 and nontoxigenic O1 strains predominating over toxigenic O1 strains. In its natural environment, *V. cholerae* lives attached to algae or to crustacean shells and copepods, with which it coexists in a symbiotic manner. Several conditions, such as temperature, salinity, and availability of nutrients, determine the survival of *V. cholerae*; when these conditions are adverse, vibrios survive in a viable but nonculturable state. Cholera phages modulate the abundance of *V. cholerae* in the environment and determine the beginning and end of epidemics. Phages may also play a role in the emergence of new *V. cholerae* serogroups by transferring genetic material to nontoxigenic strains.

From its aquatic environment, *V. cholerae* is introduced to humans through contamination of water sources and food.[4] Once humans are infected, very high attack rates may take place, particularly in previously naïve populations. The disease can be acquired by drinking contaminated water from rivers, ponds, lakes, and even tube well sources. Drinking unboiled water, introducing hands into containers used to store drinking water, drinking beverages from street vendors, drinking beverages with contaminated ice, and drinking water outside the home are risk factors. Drinking boiled water, acidic beverages, and carbonated water and using narrow-necked vessels for storing water are protective measures. Epidemics of cholera can be associated with the ingestion of leftover rice, raw fish, cooked crabs, seafood, raw oysters, and fresh vegetables and fruits.

Person-to-person transmission is less likely to occur because a large inoculum is necessary to transmit disease. Nevertheless, high transmission rates (approximately 50%) are reported among household contacts of patients with cholera in endemic areas.

Epidemics of cholera tend to occur during the hot season. Factors affecting climate change and climate variability have an impact on the incidence of cholera. The El Niño–Southern Oscillation, which is a periodic phenomenon representative of global climate variability, causes the warming of normally cool waters in the Pacific coastline of Peru, thereby promoting phytoplankton bloom, zooplankton bloom, and the proliferation of *V. cholerae*.

Some host factors are important in the transmission of cholera. The chronic gastritis associated with *Helicobacter pylori* (Chapter 125) predisposes to cholera by inducing hypochlorhydria, which reduces the ability of the stomach to contain the infection. Use of proton pump inhibitors or histamine-2 blockers and other conditions that cause achlorhydria also increase the risk. An unexplained predisposition to severe disease due to El Tor biotype in persons with the O blood group has been observed in Asia and more recently in Latin America. Innate predisposition has also been reported in endemic areas. Thus, complex associations among climatic, seasonal, bacterial, and human factors affect the transmission of cholera.

PATHOBIOLOGY

V. cholerae O1 and O139 cause clinical disease by secreting an enterotoxin that promotes the secretion of fluids and electrolytes by the small intestine. The infectious dose of bacteria varies with the vehicle. When water is the vehicle, more bacteria are needed to cause disease (10^3 to 10^8), but when the vehicle is food, lower amounts are needed (10^2 to 10^4).

ABSTRACT

Cholera is a dreaded epidemic diarrheal disease caused by *Vibrio cholerae* serogroup O1 and, since 1992, by the new serogroup O139. The disease is characterized by acute watery diarrhea. In its more severe form, a person may be severely dehydrated and in hypovolemic shock; the patient may die in a matter of a few hours after contracting the infection if treatment is not provided. Cholera is endemic today in Africa, Asia, and Latin America. Seven pandemics have been registered in history since 1817; the most recent has lasted more than five decades since its recognition in Indonesia in 1961. Changes in the climate, the environment, and the pathogen have promoted transmission to humans. Diagnosis is suspected based on clinical presentation and confirmed by molecular methods or by isolation of *Vibrio* in culture. Treatment is based on replacing intestinal losses with rehydration solutions and, in severe cases, providing antimicrobials. Prevention includes implementing sanitation and hygiene as well as using licensed oral vaccines in endemic and epidemic settings.

KEYWORDS

cholera
Vibrio cholerae
acute diarrhea
dehydration
epidemics

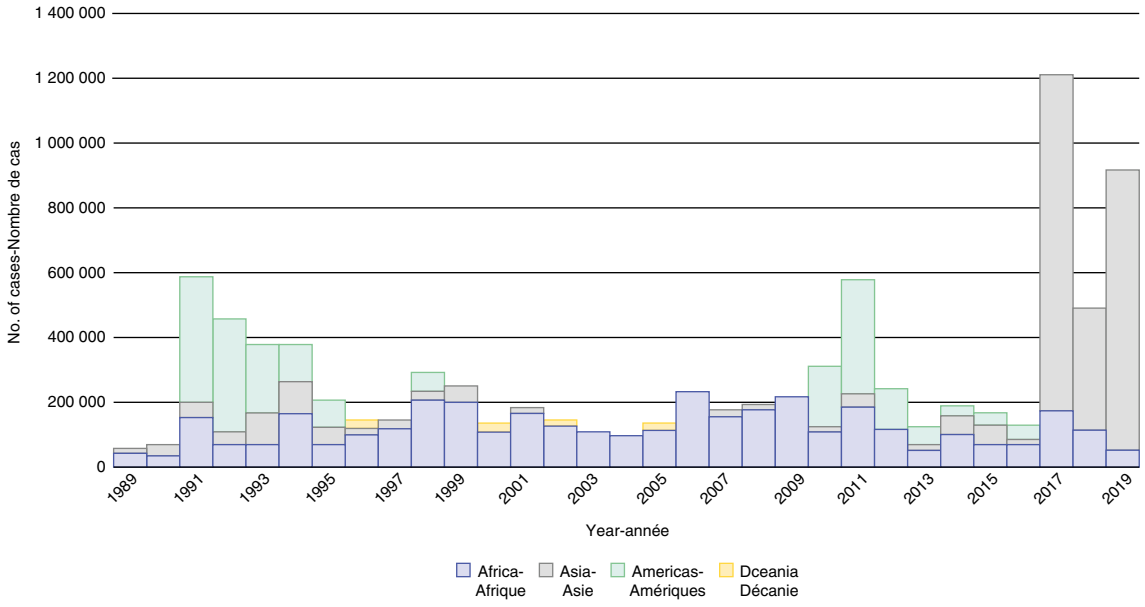

FIGURE 278-1. World distribution of cholera from 1989 to 2019 based on reports to the World Health Organization. (Reprinted with permission from the World Health Organization. Cholera, 2019. *Wkly Epidemiol Rec*. 2020;37:441-448.)

The genetic material of El Tor *V. cholerae* O1 is included in two circular chromosomes, the larger containing 3 megabases and the smaller containing 1.07 megabases. The main virulence genes are *ctxA* and *ctxB*, which encode cholera toxin subunits A and B, respectively, and *tcpA*, which codes for toxin coregulated pilus. Genes unique to El Niño–Southern Oscillation *V. cholerae* may encode specific features that allow this biotype to survive better in the environment as well as to be more infectious to humans.

Cholera toxin has two subunits, a pentamer B subunit and a monomer A subunit. The B subunit allows binding of the toxin to a specific receptor, which is a ganglioside (GM_1) located on the surface of cells lining the mucosa along the intestine of humans and certain suckling mammals. The active, or A, subunit has two components, A1 and A2, linked by a disulfide bond. Activation of adenylate cyclase by the A1 component increases cyclic adenosine monophosphate in intestinal epithelial cells, thereby blocking the absorption of sodium and chloride by microvilli and promoting the secretion of chloride and water by crypt cells. These events lead to the production of watery diarrhea with electrolyte concentrations similar to those of plasma (Table 278-1). Other toxins also have been isolated from pathogenic *V. cholerae*, but their roles in genesis of the disease are less clear.

CLINICAL MANIFESTATIONS

After an incubation period of 12 to 72 hours (median 1.4 days), symptomatic cholera is characterized by the abrupt onset of watery diarrhea, vomiting, generalized cramps, oliguria, and dehydration, which ranges from mild to severe and life-threatening.[5] Patients with mild dehydration cannot be differentiated from those infected by other enteric pathogens that cause watery diarrhea (Chapters 270, 279, 280, 284, and 285). In contrast, patients with severe dehydration secondary to cholera are easy to identify in that their stools have the appearance of rice water, and no other clinical illness produces such severe dehydration as quickly (in a matter of a few hours) as cholera.

Physical examination shows a feeble pulse, but fever is rarely present. Patients look anxious and restless. Their eyes are very sunken, their mucous membranes are dry, their skin has lost its elasticity and when pinched retracts very slowly, their voice may be almost nonaudible, and their intestinal sounds are prominent. Although watery diarrhea is the hallmark of cholera, some patients do not have diarrhea but instead have abdominal distention and ileus, a relatively rare type of cholera called cholera sicca.

Laboratory findings in patients with severe dehydration consist of an increase in hematocrit, urine specific gravity, and total serum protein; azotemia; metabolic acidosis with a high anion gap; normal or low serum potassium levels; and normal or slightly low sodium and chloride levels. The calcium and magnesium content in plasma is high as a result of hemoconcentration. Leukocytosis is observed in patients with severe cholera. Hyperglycemia, caused by high concentrations of epinephrine, glucagon, and cortisol stimulated by hypovolemia, is more commonly seen than hypoglycemia.

Acute renal failure, which is the most severe complication of cholera, has an incidence rate of about 10 cases per 1000. Patients with acute renal failure almost always have a history of improper rehydration.

Cholera carries a poor prognosis in pregnant women, who have more severe clinical illness, especially when it is acquired at the end of the pregnancy. Fetal loss occurs in as many as 50% of these pregnancies. Cholera in the elderly also carries a poor prognosis because of an increase in complications, particularly acute renal failure, severe metabolic acidosis, and pulmonary edema.

DIAGNOSIS

In the developing world, dark-field microscopy showing a high number of bacteria and chaotic bacterial movement in a stool sample from patients with diarrhea is characteristic of *V. cholerae* infection. Specific antisera against the serotype block the movement of vibrios and allow confirmation of the diagnosis. Under epidemic conditions, observing bacteria with a darting movement in a stool sample from a patient with suspected infection under dark-field microscopy is adequate to make the diagnosis.

Definitive confirmation can be achieved using DNA amplification by polymerase chain reaction (PCR) to detect vibrios in stool and environmental samples. A number of rapid tests have been developed, but few are suitable for public health purposes. The bacterium can also be identified in culture using a specific medium to isolate *V. cholerae* from stool.

TREATMENT

Rehydration

The objectives of therapy are to restore the fluid losses caused by diarrhea and vomiting, to correct the metabolic acidosis, to restore potassium deficits, and to replace continuous fluid losses.[6] Treatment of patients with milder forms of dehydration is easy, but treatment of patients with severe dehydration requires experience and proper training (Table 278-2).

Rehydration should be accomplished in two phases: the rehydration phase and the maintenance phase. The purpose of the rehydration phase is to restore normal intravascular volume, and it should last no longer than 4 hours.

The intravenous route should be restricted to patients who do not tolerate the oral route, patients who vomit more than 10 to 20 mL/kg/hour, and all patients with severe dehydration. Intravenous fluids should be infused at a total volume of 100 mL/kg during the rehydration phase in severely dehydrated patients. Lactated Ringer solution is preferred, but other solutions may be used as well (see Table 278-1).

Patients who do not have severe dehydration and who tolerate the oral route can be rehydrated with oral rehydration solutions exclusively and discharged promptly from the health center. Oral rehydration therapy uses the principle of common transportation of solutes, electrolytes, and water by the intestine not affected by cholera toxin. People with diarrhea can undergo successful rehydration with simple solutions containing glucose and electrolytes. The World Health Organization recommends an oral rehydration solution with reduced

TABLE 278-1 ELECTROLYTE COMPOSITION OF CHOLERA STOOLS AND SOLUTIONS RECOMMENDED FOR TREATMENT

	Na^+	Cl^-	K^+	HCO_3^-	GLUCOSE	OSMOLARITY
Stools of adults with severe cholera	130	100	20	44		
Intravenous lactated Ringer solution	130	109	4	28*	0	271
Intravenous normal saline	154	154	0	0	0	308
Standard oral rehydration solution promoted by the WHO	90	80	20	10†	111	311
Reduced-osmolarity oral rehydration solution promoted by the WHO	75	65	20	10†	75	245
Rice-based oral rehydration solution	90	80	20	10†		270

*Lactated Ringer solution contains citrate instead of bicarbonate.
†Bicarbonate is replaced by trisodium citrate.
Glucose concentration is in mg/dL, electrolyte concentrations are in mEq/L, and osmolarity is in mOsm/L.
Cl^- = chloride; HCO_3^- = bicarbonate; K^+ = potassium; Na^+ = sodium; WHO = Word Health Organization.
Modified with permission from Seas C, DuPont HL, Valdez LM, et al. Practical guidelines for the treatment of cholera. *Drugs.* 1996;51:966-973.

TABLE 278-2 RECOMMENDATIONS FOR TREATMENT OF CHOLERA PATIENTS

Determine the degree of dehydration on arrival.
Rehydrate the patient in two phases:
- Rehydration phase—lasts 2 to 4 hours
- Maintenance phase—lasts until the end of the diarrheal episode

Register and periodically review input and output in predesigned charts.
Use the intravenous route in the following situations:
- In all severely dehydrated patients, in whom the total volume to be infused during the rehydration phase is 100 mL/kg. For patients older than 1 year, 30 mL/kg should be infused in the first 30 minutes, the remaining 70 mL/kg should be infused in 2.5 hours. For children younger than 1 year, the first 30 mL/kg should be infused in 1 hour.
- Patients with some dehydration who are unable to tolerate the oral route
- Patients with high stool output (>10 mL/kg/hour) during the maintenance phase

Use oral rehydration solutions, glucose or rice-based, during the maintenance phase to match ongoing losses. Volumes of 800 to 1000 mL/hour are usually required. Low-osmolarity solutions are not recommended.
Start an oral antimicrobial agent in patients with severe cholera when full rehydration has been achieved and oral tolerance is confirmed. Single-dose doxycycline, 300 mg, is the preferred regimen. Erythromycin or a quinolone is a suitable alternative.
Discharge patients only if oral tolerance is adequate (≥1000 mL/hour), urine output is satisfactory (≥40 mL/hour), and stool volume is low (≤400 mL/hour).

Modified with permission from Seas C, DuPont HL, Valdez LM, et al. Practical guidelines for the treatment of cholera. *Drugs.* 1996;51:966-973.

osmolarity (245 mOsm/L) to treat all diarrheal diseases. This solution contains lower sodium than the standard oral rehydration solution (75 vs. 90 mEq/L) but does not increase the risk of symptomatic hyponatremia. The addition of L-histidine to rice-based oral rehydration solutions can reduce the volume and duration of diarrhea and the use of intravenous therapy in adults with cholera.

All signs of dehydration should have disappeared and the patient should pass urine at a rate of 0.5 mL/kg/hour or greater after the rehydration phase is finished. The maintenance phase follows immediately. During this phase, the objective is to maintain normal hydration status by replacement of ongoing losses. The oral route is preferred during this phase, and the use of oral rehydration solutions is highly recommended.

Antimicrobial Therapy

Effective antibiotics in patients with severe dehydration decrease the duration of diarrhea and the volume of stool by nearly half, but antimicrobial agents are not life-saving and always must be accompanied by fluid therapy. A single dose of oral doxycycline (300 mg) is the preferred regimen where sensitive strains predominate. Pregnant women can be treated with erythromycin (100 mg four times daily for 3 days) or furazolidone (500 mg four times daily for 3 days). Because of the emergence of resistance to tetracyclines and other antimicrobials in many endemic areas, other options are a single-dose of azithromycin (1 g or 20 mg/kg for smaller patients), a 3-day regimen with erythromycin (100 mg four times daily), a single-dose regimen of ciprofloxacin (1 g), or 3 days of norfloxacin (400 mg twice daily). The addition of oral zinc (30 mg/day) to an erythromycin regimen in children reduced the duration of diarrhea by 12%, with an additional 11% reduction in the volume of diarrhea in comparison to placebo. Antimotility agents such as loperamide or diphenoxylate, adsorbents, analgesics, antiemetics, and antisecretory drugs are not useful in patients with severe cholera.

PREVENTION

Access to potable water and ensuring proper management of excreta to avoid contamination of other water sources are important measures to reduce transmission of cholera. Alternative ways to prevent cholera transmission are necessary in developing countries. Water can be made safer to drink by boiling, adding chlorine, or filtering it with cloth made of cotton. Chemoprophylaxis of household contacts of cholera cases is not routinely recommended.

Two oral vaccines, the two-dose regimen of the inactivated vaccine WC-BS (whole cell plus B subunit) and a single dose of the live attenuated CVD 103-HgR vaccine, have been tested extensively in epidemic settings and in field trials in endemic areas. Parenteral vaccines are no longer recommended. Although the WC-BS vaccine elicits excellent immunogenicity[A1,A2] and shows good short-term protective efficacy (85% at 6 months), results at 3 and 5 years are less impressive (40% or less),[A3,A4] and children vaccinated below age 5 years have less protection after 3 years of receiving the vaccine compared with older children.[A5] Large studies have shown 80 to 90% efficacy, even during a cholera outbreak, and the potential to confer herd protection in the unvaccinated population. The live attenuated vaccine does not appear to be protective in an endemic setting. However, it is immunogenic and effective in adult travelers[7] and is licensed in the United States and Europe for this purpose.[8]

Indications for cholera vaccines include travel to endemic areas and situations in which high attack rates of cholera are expected, such as after environmental disasters, in refugee camps, and in urban slums in highly endemic areas. Complementary use of oral cholera vaccination, water sanitation, and hygienic interventions may have additive impact in endemic areas.[9] New oral vaccines, including both killed and live *Vibrio,* are being evaluated in endemic areas, with promising preliminary reports.

PROGNOSIS

Patients with severe cholera left untreated or improperly treated have a poor prognosis, with mortality rates higher than 50%. However, case-fatality rates during epidemics may be reduced to below 1% even in disaster situations, when adequate access to health care centers and proper management are provided. For example, mortality rates were extremely low during the Latin America epidemic in the 1990s, but rates of 19 to 35 deaths/1000 person-years were estimated during the epidemic in Haiti. Lack of treatment, delay in treatment, and not being managed in an established treatment center are also associated with increased mortality.

OTHER *VIBRIO* INFECTIONS

Noncholera vibrios, which have worldwide distribution and coexist in environments in which *V. cholerae* lives, cause a spectrum of clinical syndromes, including acute diarrhea, soft tissue infections, and sepsis,[10] especially in immunocompromised hosts. The CDC estimates about 80,000 cases of vibriosis annually in the United States, about two thirds of which are food-borne.[11]

Vibrio parahaemolyticus predominates (about 45% of isolates) but is associated with a case-fatality rate below 1%. In contrast, *Vibrio vulnificus* accounts for about 20% of the isolates but is associated with a case-fatality rate of about 30%. *Vibrio* illnesses in the United States are seasonal and peak during the summer. The incubation period for noncholeragenic *Vibrio* infection is usually 12 to 72 hours but can be as long as 1 week.

Nontoxigenic *Vibrio cholerae*

Nontoxigenic *V. cholerae* causes gastroenteritis, but unlike toxigenic *V. cholerae* O1 or O139, nontoxigenic *V. cholerae* does not cause epidemics. Illness ranges in severity from mild diarrhea to severe watery diarrhea. Fever and bloody diarrhea are unusual, but immunocompromised persons and those with liver disease can experience more severe illness, including fever, chills, and septic shock.

Infection with *Vibrio vulnificus*

V. vulnificus is associated with wound infections in persons in contact with contaminated water as well as with primary sepsis in immunocompromised hosts. This pathogen is responsible for 95% of seafood-related mortality in the United States. Wound infections follow trauma and are characterized by rapid progression of skin and soft tissue involvement, with necrosis and bulla formation occurring in more severe cases.[12] Fever, chills, and sepsis syndrome may ensue rapidly. Primary sepsis with bacteremia and metastatic lesions on the skin, characterized by disseminated erythematous lesions that may evolve to necrotic lesions, is a distinctive clinical manifestation in patients with chronic liver disease or alcohol dependence (Chapter 364) and in patients with blood disorders such as thalassemia (Chapter 148). Patients are acutely ill with high fever and must be managed aggressively with fluid resuscitation, surgical débridement, general supportive care, and antibiotic therapy. The recommended antibiotic therapy includes a combination of cefotaxime (2 g intravenously four times a day) plus doxycycline (100 mg orally two times a day). This combination is synergistic in vitro. Alternative antimicrobials are ceftazidime and ciprofloxacin in combination with doxycycline.

Infection with *Vibrio parahaemolyticus*

V. parahaemolyticus lives in marine environments and is a source of intestinal illness associated with the ingestion of contaminated shellfish, especially raw oysters.[13] Certain serovars have demonstrated pandemic spread (O3:K6 and O4:K68). The clinical illness may mimic cholera, but most cases are milder, with self-limited forms of acute watery diarrhea. *V. parahaemolyticus* also can cause wound infections, which are generally less severe than those caused by *V. vulnificus*. However, in persons with liver disease or those who are immunocompromised, fatal infections can occur. Oral antibiotics, as used for traveler's diarrhea (Chapter 265), are usually efficacious for diarrhea, although local resistance patterns vary. For skin infections, parenteral antibiotics are recommended as for *V. vulnificus* (see earlier).

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279 *CAMPYLOBACTER* INFECTIONS

BAN MISHU ALLOS

DEFINITION

Campylobacter jejuni is one of the most commonly recognized bacterial causes of diarrhea in developed and underresourced nations. More than 95% of campylobacter isolated in developed countries are *C. jejuni* or *C. coli*. However, other *Campylobacter* species are also associated with human disease.

The Pathogen

Campylobacter organisms are motile, curved, gram-negative rods that are found in domestic and wild animals—especially poultry—all over the world. *C. jejuni* is microaerophilic, requires 3 to 15% oxygen for growth, and is oxidase and catalase positive. It grows best at 42° C; however, other *Campylobacter* species that may also be pathogenic grow best at 37° C. The whole genome sequences for multiple *Campylobacter* species have been determined.

EPIDEMIOLOGY

C. jejuni infections are endemic in young children in underresourced nations, where it is among the three leading causes of childhood diarrhea, along with norovirus and rotavirus (Chapter 350). In industrialized nations such as the United States, *Campylobacter* infections are the most common bacterial causes of diarrhea in children and adults, and the incidence of diagnosed *Campylobacter* infections has increased recently, likely due to the more widespread use of culture-independent diagnostic tests.[1] Nonetheless, the actual burden of disease caused by *Campylobacter* is probably much higher than suggested in surveillance reports as even active surveillance systems substantially underreport the true incidence of infection. Epidemiologic studies have estimated that more than 2 million people in the United States are infected with *C. jejuni* each year. For reasons that are not clear, the incidence is highest in western states, such as California and Hawaii. Similarly high rates of infection are observed in Europe. In the United States, Europe, and Australia, *C. jejuni* infections show a substantial peak in warmer months,[2] but such seasonality is not observed in tropical underresourced countries, perhaps because of the absence of extreme temperature variations. Polymerase chain reaction (PCR) testing and other culture-independent diagnostic tests can now identify bacterial pathogens in most individuals with traveler's diarrhea (Chapter 265), which is commonly associated with *C. jejuni*, particularly in Southeast Asia.[3]

The incidence of *Campylobacter* infections is highest in early childhood, an epidemiologic feature common to many food-borne bacterial pathogens. However, in the United States and other industrialized countries, the incidence of infections peaks again in early adulthood. The incidence of infection is also higher in men, a sex difference most pronounced in young adults.

Most human *C. jejuni* infections occur sporadically, with only a tiny fraction occurring as part of outbreaks. The dominant source of sporadic infections in both developed and underresourced countries is consumption or handling of poultry,[4] although cattle and pigs also can be sources of infection.[5] Other sources of transmission in developed nations include foreign travel, contact with pets and other animals, contaminated drinking water, and consumption of unpasteurized milk. Cross-contamination within a kitchen (e.g., use of the same utensils or cutting boards to prepare uncooked chicken and to chop fruit) has led to a variety of foods being implicated as sources of human *C. jejuni* infection. In contrast to sporadic infections, the most common source of *C. jejuni* outbreaks is unpasteurized milk; large waterborne outbreaks occasionally occur. Transmission of *C. jejuni* infection from ill food handlers is uncommon. Even in households in which an individual has culture-proven *C. jejuni* gastroenteritis, secondary transmission to other family members is unusual.

PATHOBIOLOGY

Persons become infected with *C. jejuni* as a result of orally ingesting the organism, usually in contaminated food or water. Factors that affect whether *Campylobacter* infection leads to illness include the dose of bacteria ingested, the virulence of the organism, and the specific immunity of the host to the ingested organism. The minimum number of bacteria needed to cause illness varies among people, but it may be quite low. Because *C. jejuni* is susceptible to gastric acidity, ingestion of very few organisms may cause illness if gastric pH is elevated as a result of illness or medication.

In early infection, *C. jejuni* multiplies in the bile-rich upper intestines; subsequently, tissue injury is seen in the jejunum, ileum, and colon. Gross inspection of the bowel shows a diffuse, bloody, edematous enteritis. Microscopic examination shows an inflammatory infiltrate consisting of neutrophils, mononuclear cells, and eosinophils in the lamina propria. The mucosal epithelium is ulcerated, and crypt abscesses may be seen. The pathologic appearance is nonspecific and may mimic ulcerative colitis or Crohn disease (Chapter 127).

Invasion of the epithelium by *C. jejuni* appears to be central to its pathogenesis, and many factors influence how *C. jejuni* adheres to and invades intestinal tissues. A superficial conserved antigen, PEB1, appears to be a major adhesin and is a target of the immune response to *C. jejuni* infection. Other factors contributing to the invasiveness and pathogenicity of *C. jejuni* that may be encoded by a virulence plasmid include type IV secretion systems

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Nontoxigenic *Vibrio cholerae*

Nontoxigenic *V. cholerae* causes gastroenteritis, but unlike toxigenic *V. cholerae* O1 or O139, nontoxigenic *V. cholerae* does not cause epidemics. Illness ranges in severity from mild diarrhea to severe watery diarrhea. Fever and bloody diarrhea are unusual, but immunocompromised persons and those with liver disease can experience more severe illness, including fever, chills, and septic shock.

Infection with *Vibrio vulnificus*

V. vulnificus is associated with wound infections in persons in contact with contaminated water as well as with primary sepsis in immunocompromised hosts. This pathogen is responsible for 95% of seafood-related mortality in the United States. Wound infections follow trauma and are characterized by rapid progression of skin and soft tissue involvement, with necrosis and bulla formation occurring in more severe cases.[12] Fever, chills, and sepsis syndrome may ensue rapidly. Primary sepsis with bacteremia and metastatic lesions on the skin, characterized by disseminated erythematous lesions that may evolve to necrotic lesions, is a distinctive clinical manifestation in patients with chronic liver disease or alcohol dependence (Chapter 364) and in patients with blood disorders such as thalassemia (Chapter 148). Patients are acutely ill with high fever and must be managed aggressively with fluid resuscitation, surgical débridement, general supportive care, and antibiotic therapy. The recommended antibiotic therapy includes a combination of cefotaxime (2 g intravenously four times a day) plus doxycycline (100 mg orally two times a day). This combination is synergistic in vitro. Alternative antimicrobials are ceftazidime and ciprofloxacin in combination with doxycycline.

Infection with *Vibrio parahaemolyticus*

V. parahaemolyticus lives in marine environments and is a source of intestinal illness associated with the ingestion of contaminated shellfish, especially raw oysters.[13] Certain serovars have demonstrated pandemic spread (O3:K6 and O4:K68). The clinical illness may mimic cholera, but most cases are milder, with self-limited forms of acute watery diarrhea. *V. parahaemolyticus* also can cause wound infections, which are generally less severe than those caused by *V. vulnificus*. However, in persons with liver disease or those who are immunocompromised, fatal infections can occur. Oral antibiotics, as used for traveler's diarrhea (Chapter 265), are usually efficacious for diarrhea, although local resistance patterns vary. For skin infections, parenteral antibiotics are recommended as for *V. vulnificus* (see earlier).

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279 *CAMPYLOBACTER* INFECTIONS

BAN MISHU ALLOS

DEFINITION

Campylobacter jejuni is one of the most commonly recognized bacterial causes of diarrhea in developed and underresourced nations. More than 95% of campylobacter isolated in developed countries are *C. jejuni* or *C. coli*. However, other *Campylobacter* species are also associated with human disease.

The Pathogen

Campylobacter organisms are motile, curved, gram-negative rods that are found in domestic and wild animals—especially poultry—all over the world. *C. jejuni* is microaerophilic, requires 3 to 15% oxygen for growth, and is oxidase and catalase positive. It grows best at 42° C; however, other *Campylobacter* species that may also be pathogenic grow best at 37° C. The whole genome sequences for multiple *Campylobacter* species have been determined.

EPIDEMIOLOGY

C. jejuni infections are endemic in young children in underresourced nations, where it is among the three leading causes of childhood diarrhea, along with norovirus and rotavirus (Chapter 350). In industrialized nations such as the United States, *Campylobacter* infections are the most common bacterial causes of diarrhea in children and adults, and the incidence of diagnosed *Campylobacter* infections has increased recently, likely due to the more widespread use of culture-independent diagnostic tests.[1] Nonetheless, the actual burden of disease caused by *Campylobacter* is probably much higher than suggested in surveillance reports as even active surveillance systems substantially underreport the true incidence of infection. Epidemiologic studies have estimated that more than 2 million people in the United States are infected with *C. jejuni* each year. For reasons that are not clear, the incidence is highest in western states, such as California and Hawaii. Similarly high rates of infection are observed in Europe. In the United States, Europe, and Australia, *C. jejuni* infections show a substantial peak in warmer months,[2] but such seasonality is not observed in tropical underresourced countries, perhaps because of the absence of extreme temperature variations. Polymerase chain reaction (PCR) testing and other culture-independent diagnostic tests can now identify bacterial pathogens in most individuals with traveler's diarrhea (Chapter 265), which is commonly associated with *C. jejuni*, particularly in Southeast Asia.[3]

The incidence of *Campylobacter* infections is highest in early childhood, an epidemiologic feature common to many food-borne bacterial pathogens. However, in the United States and other industrialized countries, the incidence of infections peaks again in early adulthood. The incidence of infection is also higher in men, a sex difference most pronounced in young adults.

Most human *C. jejuni* infections occur sporadically, with only a tiny fraction occurring as part of outbreaks. The dominant source of sporadic infections in both developed and underresourced countries is consumption or handling of poultry,[4] although cattle and pigs also can be sources of infection.[5] Other sources of transmission in developed nations include foreign travel, contact with pets and other animals, contaminated drinking water, and consumption of unpasteurized milk. Cross-contamination within a kitchen (e.g., use of the same utensils or cutting boards to prepare uncooked chicken and to chop fruit) has led to a variety of foods being implicated as sources of human *C. jejuni* infection. In contrast to sporadic infections, the most common source of *C. jejuni* outbreaks is unpasteurized milk; large waterborne outbreaks occasionally occur. Transmission of *C. jejuni* infection from ill food handlers is uncommon. Even in households in which an individual has culture-proven *C. jejuni* gastroenteritis, secondary transmission to other family members is unusual.

PATHOBIOLOGY

Persons become infected with *C. jejuni* as a result of orally ingesting the organism, usually in contaminated food or water. Factors that affect whether *Campylobacter* infection leads to illness include the dose of bacteria ingested, the virulence of the organism, and the specific immunity of the host to the ingested organism. The minimum number of bacteria needed to cause illness varies among people, but it may be quite low. Because *C. jejuni* is susceptible to gastric acidity, ingestion of very few organisms may cause illness if gastric pH is elevated as a result of illness or medication.

In early infection, *C. jejuni* multiplies in the bile-rich upper intestines; subsequently, tissue injury is seen in the jejunum, ileum, and colon. Gross inspection of the bowel shows a diffuse, bloody, edematous enteritis. Microscopic examination shows an inflammatory infiltrate consisting of neutrophils, mononuclear cells, and eosinophils in the lamina propria. The mucosal epithelium is ulcerated, and crypt abscesses may be seen. The pathologic appearance is nonspecific and may mimic ulcerative colitis or Crohn disease (Chapter 127).

Invasion of the epithelium by *C. jejuni* appears to be central to its pathogenesis, and many factors influence how *C. jejuni* adheres to and invades intestinal tissues. A superficial conserved antigen, PEB1, appears to be a major adhesin and is a target of the immune response to *C. jejuni* infection. Other factors contributing to the invasiveness and pathogenicity of *C. jejuni* that may be encoded by a virulence plasmid include type IV secretion systems

ABSTRACT

Campylobacter organisms are small, curved, gram-negative rods that are an important cause of diarrhea in both developed and underresourced, developing nations. The most commonly encountered *Campylobacter* is *C. jejuni*, which is a leading cause of childhood diarrhea in underresourced, developing nations. In developed nations, the incidence of infection peaks again in young adulthood. Transmission to humans typically occurs from foods of animal origin, especially from poultry. An important postinfectious complication is Guillain-Barré syndrome, which complicates about 1 in 2000 *Campylobacter* infections. The gold standard for diagnosis of *Campylobacter* infection is stool culture, but culture-independent diagnostic tests are becoming more popular. The most important tenet of treatment is restoration of proper hydration and electrolyte balance. If antibiotics are needed, macrolides (azithromycin or clarithromycin) may be used.

KEYWORDS

Campylobacter
diarrhea
gastroenteritis
food-borne
Guillain-Barré syndrome

and mechanisms that disrupt microtubules in host cells. The presence of the plasmid pVir in clinical isolates is significantly associated with bloody stools. *C. jejuni* also may invade in an actin- and microtubule-independent manner. Glycolipids and glycoproteins on the surface of *C. jejuni* are important in the organism's survival in the intestinal lumen and in pathogenesis because they have an impact on cell-to-cell interactions as well as on the host's immune response to infection. The bacteria's flagella facilitate its ability to colonize the gastrointestinal tract by promoting the organism's motility and chemotaxis. *C. jejuni* may produce extracellular toxins, but their role in pathogenesis has not been confirmed, with the possible exception of the cytoskeletal distending toxin (CDT), which may facilitate intracellular activities that lead to apoptosis.

Regardless of the organism's virulence, host factors are pivotal in affecting the clinical outcome of infection. In healthy volunteers fed a fixed dose of a single *C. jejuni* strain, a spectrum of illnesses develops. Patients infected with *C. jejuni* excrete the organism in feces for 2 to 3 weeks. In underresourced nations, where the level of immunity to *C. jejuni* is higher because of recurrent exposure, the period of convalescent excretion of *C. jejuni* is shorter.

After recovery from *Campylobacter* infection, at least short-term immunity develops. The decreasing illness-to-infection ratio with age seen in underresourced nations also suggests that individuals are acquiring immunity. Specific immunoglobulin A, G, and M antibodies in serum and immunoglobulin A antibodies in intestinal secretions develop in patients infected with *C. jejuni*. Patients with congenital or acquired hypogammaglobulinemia are at risk for severe or recurrent *C. jejuni* infections. Because the incidence of *C. jejuni* infection is markedly higher in persons infected with human immunodeficiency virus (HIV; Chapter 358), cell-mediated immunity also plays a role in preventing and terminating infection.[6]

CLINICAL MANIFESTATIONS

The clinical consequences of *Campylobacter* infection range from complete absence of symptoms to fulminant sepsis and death. In most cases, however, illnesses are brief and do not require hospitalization. In developed nations, detection of *C. jejuni* in the stool of asymptomatic persons is rare. However, in underresourced nations, where infections are endemic and recurrent infections occur frequently, asymptomatic infections are more common. In both underresourced and developed nations, persons infected with *C. jejuni* typically contract a diarrheal illness that resolves within a week.

The gastroenteritis that is caused by infection with *C. jejuni* is clinically indistinguishable from that caused by other bacterial enteric pathogens, such as *Salmonella* (Chapter 284), *Shigella* (Chapter 285), or *Escherichia coli* O157:H7 (Chapter 280). The most common symptoms are diarrhea, malaise, fever, and abdominal pain (Table 279-1). Campylobacterosis incubation periods vary considerably, ranging from 2.5 to 4.3 days, depending on the subgroup. Most patients with *C. jejuni* gastroenteritis experience at least 1 day with 10 or more stools; the diarrhea may be loose, watery, or bloody. Older individuals are less likely to have bloody diarrhea but more likely to have symptoms severe enough to require hospitalization. Nausea is reported by some patients, but vomiting is less common. More than half the patients describe subjective fever. The abdominal cramping may be severe and is sometimes the predominant symptom. Severe abdominal pain that precedes the onset of diarrhea may mimic acute appendicitis (Chapter 128). Up to 5 kg of weight-loss may occasionally be observed.

TABLE 279-1 CLINICAL FEATURES OF *CAMPYLOBACTER* ENTERITIS DERIVED FROM OUTBREAKS IN WHICH MORE THAN 50 PATIENTS WERE INFECTED

SYMPTOM	MEDIAN FREQUENCY (%)	RANGE (%)
Fever	50	6-75
Diarrhea	84	52-100
Headache	41	6-69
Abdominal pain	79	56-99
Myalgia	42	28-59
Vomiting	15	1-42
Blood in feces	15	0.5-32

Modified from Blaser MJ, Engberg J. Clinical aspects of *Campylobacter jejuni* and *Campylobacter coli* infections. In: Nachamkin I, Szymanski CM, Blaser MJ, eds. *Campylobacter*. 3rd ed. Washington, DC: ASM Press; 2008:99-121.

Local complications of *C. jejuni* gastroenteritis are rare. In its most severe form, infection may lead to massive gastrointestinal hemorrhage or toxic megacolon. Infection of the biliary tract may result in obstructive hepatitis, cholecystitis (Chapter 141), or pancreatitis (Chapter 130). Other reported local complications include peritonitis (Chapter 128), splenic rupture, and exacerbations of inflammatory colitis. Bacteremia[7] is detected in 1.5 per 1000 intestinal infections, with higher rates in persons who are immunocompromised or elderly, but transient bacteremia may be more common because blood cultures are infrequently obtained in patients with diarrhea and the bacteria are killed rapidly by normal human serum. Other extraintestinal complications, such as meningitis, endocarditis, pericarditis, myocarditis, osteomyelitis, and purulent arthritis, are rare.

DIAGNOSIS

The diagnosis of *C. jejuni* infection should be considered in any patient with an acute febrile diarrheal illness. The diagnosis is established by culturing the organism from stool or tissue. Primary isolation of *Campylobacter* species from blood may take up to 14 days.

Culture-independent polymerase chain reaction (PCR) testing, which has a higher sensitivity[8] and is more rapidly available, is increasingly superceding culture for prompt diagnosis. Currently, however, such tests do not provide antibiotic-susceptibility data and also do not demonstrate if an isolate is part of a larger outbreak.

Almost regardless of the nature of the symptoms, fecal leukocytes are found in 75% of infected patients; gross or occult blood is seen in 50%. Peripheral white blood cell counts may be elevated, but liver function test results, the hematocrit, and serum electrolyte values are usually normal. Sigmoidoscopic examination reveals diffuse colonic inflammation, which is nonspecific.

The presence of curved gram-negative rods on a Gram stain of stool is specific but only 50 to 75% sensitive for detecting *C. jejuni*. Examination of fecal specimens by dark-field microscopy is useful if it is done within 2 hours of passage; the characteristic darting motility of *Campylobacter* provides a presumptive diagnosis. Serum serologic studies of stool are currently available only as research tools.

Differential Diagnosis

In patients with acute colitis and bloody diarrhea, especially patients whose symptoms last longer than 1 week, *Campylobacter* enteritis may be mistaken for ulcerative colitis or Crohn disease (Chapter 127). In such cases, it is critical to exclude infectious colitis before starting immunosuppressive therapy. In patients with severe abdominal pain, appendicitis may be suspected, and unnecessary appendectomy may result (Chapter 128).

TREATMENT

As is true for most patients with infectious or noninfectious diarrhea, the most important principle of treatment of *Campylobacter* gastroenteritis is restoration of proper hydration and electrolyte balance, typically with oral fluids. On occasion, intravenous fluids are needed, especially in elderly patients or young children. Most *C. jejuni* infections are self-limited and resolve without specific antibiotic treatment. Treatment with azithromycin (500 mg daily for 3 days) shortens the duration of illness by less than 48 hours. Prompt antimicrobial therapy is indicated for patients with high fever (>38.5° C), prolonged illness (>1 week), bloody stools, or worsening symptoms, as well as patients who have relapsed. Antimicrobial treatment is also warranted in the elderly, infants, pregnant women, and persons who are immunocompromised, including those infected with HIV.

Alternative antibiotics include fluoroquinolones (e.g., ciprofloxacin 750 mg orally every 12 hours for 3 days), carbapenems (e.g., meropenem 1 g IV every 8 hours for 7 days), aminoglycosides (e.g., gentamicin 3 to 5 mg/kg/day divided into three doses every 8 hours for 5 days), and clindamycin (300 mg orally every 6 hours for 5 days). However, resistance to quinolones is now common in many parts of the world.[9,10] In general, rates of resistance to ampicillin, amoxicillin, and cephalosporins are too high for them to be useful in the treatment of *C. jejuni* infections. A few case-reports have described success with use of fosfomycin (3 g orally, once).

Critically ill or septic persons with *Campylobacter* infection may benefit from carbapenems (e.g., meropenem 1 g IV every 8 hours for 7 days) or aminoglycosides (e.g., gentamicin 3 to 5 mg/kg/day divided into three doses every 8 hours for 5 days), to which campylobacters are exquisitely susceptible, with resistance rates consistently less than 1%. In contrast, persons with persistent or relapsing infection, especially those who are immunocompromised, may require prolonged use (sometimes months) of antibiotics such as a macrolide (e.g., azithromycin 500 mg orally daily) or quinolone (e.g., ciprofloxacin 750 mg orally every 12 hours). In the absence of continuing sepsis, oral agents may be used.

PREVENTION

Because the most common source of transmission of *C. jejuni* infection to humans in developed countries is by consumption and handling of poultry, interrupting this route of infection will probably have the greatest effect on reducing the burden of disease caused by *Campylobacter*. The nearly universal colonization of poultry flocks with *C. jejuni* makes eradication of the organism in chickens unlikely, but improvements in slaughtering plants appear to be reducing the level of contamination of products reaching humans. For the consumer, careful food preparation methods are critical; chicken must be cooked thoroughly. To avoid cross-contamination in the kitchen, cutting boards, knives, and other utensils used to prepare raw chicken should be washed with hot soapy water before being used to prepare foods eaten uncooked, such as fruits and vegetables. Person-to-person transmission of *Campylobacter* is not common; nevertheless, all persons with diarrhea, especially those who handle food, should wash their hands after using the bathroom. Travelers and campers should be cautioned against drinking untreated water. Many outbreaks of *C. jejuni* infection also might be avoided if persons abstain from drinking unpasteurized milk. Antibiotic prophylaxis for travelers is not advised. An effective anti-*Campylobacter* vaccine has not yet been developed.

OTHER *CAMPYLOBACTER* SPECIES

C. fetus may cause diarrhea and systemic illnesses, including meningitis,[11] in compromised hosts and diarrheal illnesses in normal hosts. Most *C. fetus* strains, unlike *C. jejuni,* are not susceptible to the lethal effect of normal human serum because they possess a protein capsule (S layer). In immunocompromised persons, *C. fetus* can cause extraintestinal illnesses such as bacteremia, vascular infections, and meningitis. *C. fetus* infection may also cause perinatal infection and fetal loss. Prolonged treatment with a macrolide (e.g., azithromycin 500 mg orally daily) plus either meropenem (1 g IV every 8 hours), an aminoglycoside (e.g., IV gentamicin, 5 mg/kg/day divided into three doses every 8 hours), or a third-generation cephalosporin (e.g., ceftriaxone 2 g IV every 24 hours) is indicated for serious *C. fetus* infections. The duration of antibiotic treatment depends upon the patient's clinical response but should be continued for 2 weeks in most cases.

C. upsaliensis may cause acute or chronic diarrhea in healthy or immunocompromised persons. The organism is frequently isolated from dogs with diarrhea, which could be a source for transmission to humans. Some *C. upsaliensis* strains are resistant to erythromycin, but most are susceptible to fluoroquinolones (e.g., ciprofloxacin 750 mg orally every 12 hours), doxycycline (100 mg orally every 12 hours for 3 days), third-generation cephalosporins (e.g., ceftriaxone 2 g IV every 24 hours for 3 to 5 days), and amoxicillin-clavulanate (875 mg orally every 12 hours for 3 to 15 days).

C. hyointestinalis was first recognized as a cause of proliferative enteritis in swine; *C. lari* is most often cultured from gulls and other birds. Both organisms have now been identified as rare causes of watery diarrhea and abdominal cramping in immunocompetent children and adults. Most infected patients do not require antimicrobial therapy; all isolates studied in vitro have been susceptible to erythromycin.

C. concisus, long believed to be part of the microbiota of healthy persons, is now considered a possible cause of human gastrointestinal illness. An increasing body of evidence also has linked *C. concisus* infection with childhood Crohn disease.

Helicobacter cinaedi and *H. fennelliae*, once called *Campylobacter*-like organisms, are causes of proctocolitis or enterocolitis and also have been reported to cause bacteremia in immunocompromised patients. Fluoroquinolones (e.g., ciprofloxacin 750 mg orally every 12 hours) are considered the treatment of choice in patients who require antimicrobial therapy. The organisms are also susceptible to third-generation cephalosporins (e.g., ceftriaxone 2 g IV every 24 hours), aminoglycosides (e.g., gentamicin 3 to 5 mg/kg/day divided into three doses every 8 hours for 5 days), and carbapenems (e.g., meropenem 1 g IV every 8 hours).

Other *Campylobacter* or related species that have been associated with human illness include *C. mucosalis, C. doylei, C. curvus, C. insulaenigrae, C. rectus, C. helveticus, Arcobacter butzleri,* and *A. cryaerophila*. Illnesses include diarrhea and localized infections, presumably as a result of transient bacteremia from intestinal sources. Recently identified *Campylobacter* species that may be clinically relevant include *C. ureolyticus, C. troglodytis, C. lari* subspecies *concheus*, and *C. peloridis*. New pathogenic species of *Campylobacter* are being identified with some regularity.

PROGNOSIS

Even in critically ill patients, 1 week of therapy is generally sufficient to eradicate infection. Although the symptoms resolve within 7 days in most patients, symptoms may persist in 10 to 20% of patients, and another 5 to 10% may experience a relapse. The case-fatality rate associated with *Campylobacter* infection is low, about 0.05 death per 1000 infections, but not surprisingly is highest among the elderly and persons with comorbid conditions.

Campylobacter infections in HIV-positive patients may be more severe, persist, recur, and be antibiotic resistant. More severe and extraintestinal illness is also more likely to occur in patients with acquired or congenital hypogammaglobulinemia. Most *C. jejuni* gastrointestinal infections in pregnant women are mild and self-limited, with no severe consequences for the mother or baby. However, if bacteremia develops in the mother, placental infection and fetal death may ensue. Infection during the third trimester can also cause neonatal sepsis and death if the woman is excreting *Campylobacter* in her stool at the time of delivery.

Guillain-Barré syndrome (Chapter 388), which is a postinfectious complication of *C. jejuni* infection, occurs about once in every 2000 infections; between 30 and 50% of all cases of Guillain-Barré syndrome may be triggered by a preceding *C. jejuni* infection.[12–14] Because the onset of neurologic symptoms occurs about 1 to 3 weeks after the onset of gastrointestinal symptoms, cross-reactivity between antibodies formed against the lipopolysaccharide and capsule of *C. jejuni* and proteins in peripheral nerve myelin or other glycolipids in peripheral nerves is probably the cause. Certain *C. jejuni* serotypes (O type 19, O type 41) are overrepresented in patients in whom Guillain-Barré syndrome develops after culture-documented *C. jejuni* infection. Other postinfectious complications of *C. jejuni* infection include reactive arthritis (seen mostly in persons with HLA-B27 histocompatibility antigens; Chapter 254), uveitis (Chapter 391), hemolytic-uremic syndrome (Chapter 158), erythema nodosum (Fig. 407-24 and Table 403-3), encephalitis (Chapter 383), myocarditis (Chapter 47), hemolytic anemia, and chronic gastrointestinal consequences such as irritable bowel syndrome[15] (Chapter 123), inflammatory bowel disease (Chapter 127), and celiac disease (Chapter 126).

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280 *ESCHERICHIA COLI* ENTERIC INFECTIONS

THEODORE S. STEINER

DEFINITION

Bacteria belonging to the species *Escherichia coli* are a normal component of the intestinal microbiota (Chapter 257). The majority of *E. coli* are harmless commensals, but specific isolates have acquired pathogenicity genes that enable them to cause diseases, including urinary tract infections, bacteremia, meningitis, and diarrheal illness. One particular challenge to the clinician and microbiology laboratory is how to distinguish these pathogenic *E. coli* from harmless commensal strains so as to better guide diagnosis and treatment.

Virulence traits include a variety of toxins, adherence factors, and secreted mediators that work together to perturb the host's intestinal physiology. Specific combinations of these factors produce six major pathotypes of diarrheagenic *E. coli*: enterotoxigenic, enteroinvasive, enterohemorrhagic, enteropathogenic, enteroaggregative, and diffusely adherent. In addition, these pathotypes frequently overlap, thereby leading to "hybrid" or "heteropathogenic" strains. Atypical strains also may carry partial genetic signatures of one or a combination of pathotypes. For example, *E. coli* that express Shiga-like toxins characteristic of enterohemorrhagic *E. coli* without the usual associated adherence factors are now collectively known as shigatoxigenic *E. coli*. Strains that carry more virulence genes are more strongly associated with diarrhea.

The Pathogen

E. coli is a small catalase-positive, oxidase-negative, gram-negative bacillus in the family Enterobacteriaceae. *E. coli* is the predominant member of the

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PREVENTION

Because the most common source of transmission of *C. jejuni* infection to humans in developed countries is by consumption and handling of poultry, interrupting this route of infection will probably have the greatest effect on reducing the burden of disease caused by *Campylobacter*. The nearly universal colonization of poultry flocks with *C. jejuni* makes eradication of the organism in chickens unlikely, but improvements in slaughtering plants appear to be reducing the level of contamination of products reaching humans. For the consumer, careful food preparation methods are critical; chicken must be cooked thoroughly. To avoid cross-contamination in the kitchen, cutting boards, knives, and other utensils used to prepare raw chicken should be washed with hot soapy water before being used to prepare foods eaten uncooked, such as fruits and vegetables. Person-to-person transmission of *Campylobacter* is not common; nevertheless, all persons with diarrhea, especially those who handle food, should wash their hands after using the bathroom. Travelers and campers should be cautioned against drinking untreated water. Many outbreaks of *C. jejuni* infection also might be avoided if persons abstain from drinking unpasteurized milk. Antibiotic prophylaxis for travelers is not advised. An effective anti-*Campylobacter* vaccine has not yet been developed.

OTHER *CAMPYLOBACTER* SPECIES

C. fetus may cause diarrhea and systemic illnesses, including meningitis,[11] in compromised hosts and diarrheal illnesses in normal hosts. Most *C. fetus* strains, unlike *C. jejuni,* are not susceptible to the lethal effect of normal human serum because they possess a protein capsule (S layer). In immunocompromised persons, *C. fetus* can cause extraintestinal illnesses such as bacteremia, vascular infections, and meningitis. *C. fetus* infection may also cause perinatal infection and fetal loss. Prolonged treatment with a macrolide (e.g., azithromycin 500 mg orally daily) plus either meropenem (1 g IV every 8 hours), an aminoglycoside (e.g., IV gentamicin, 5 mg/kg/day divided into three doses every 8 hours), or a third-generation cephalosporin (e.g., ceftriaxone 2 g IV every 24 hours) is indicated for serious *C. fetus* infections. The duration of antibiotic treatment depends upon the patient's clinical response but should be continued for 2 weeks in most cases.

C. upsaliensis may cause acute or chronic diarrhea in healthy or immunocompromised persons. The organism is frequently isolated from dogs with diarrhea, which could be a source for transmission to humans. Some *C. upsaliensis* strains are resistant to erythromycin, but most are susceptible to fluoroquinolones (e.g., ciprofloxacin 750 mg orally every 12 hours), doxycycline (100 mg orally every 12 hours for 3 days), third-generation cephalosporins (e.g., ceftriaxone 2 g IV every 24 hours for 3 to 5 days), and amoxicillin-clavulanate (875 mg orally every 12 hours for 3 to 15 days).

C. hyointestinalis was first recognized as a cause of proliferative enteritis in swine; *C. lari* is most often cultured from gulls and other birds. Both organisms have now been identified as rare causes of watery diarrhea and abdominal cramping in immunocompetent children and adults. Most infected patients do not require antimicrobial therapy; all isolates studied in vitro have been susceptible to erythromycin.

C. concisus, long believed to be part of the microbiota of healthy persons, is now considered a possible cause of human gastrointestinal illness. An increasing body of evidence also has linked *C. concisus* infection with childhood Crohn disease.

Helicobacter cinaedi and *H. fennelliae*, once called *Campylobacter*-like organisms, are causes of proctocolitis or enterocolitis and also have been reported to cause bacteremia in immunocompromised patients. Fluoroquinolones (e.g., ciprofloxacin 750 mg orally every 12 hours) are considered the treatment of choice in patients who require antimicrobial therapy. The organisms are also susceptible to third-generation cephalosporins (e.g., ceftriaxone 2 g IV every 24 hours), aminoglycosides (e.g., gentamicin 3 to 5 mg/kg/day divided into three doses every 8 hours for 5 days), and carbapenems (e.g., meropenem 1 g IV every 8 hours).

Other *Campylobacter* or related species that have been associated with human illness include *C. mucosalis, C. doylei, C. curvus, C. insulaenigrae, C. rectus, C. helveticus, Arcobacter butzleri,* and *A. cryaerophila*. Illnesses include diarrhea and localized infections, presumably as a result of transient bacteremia from intestinal sources. Recently identified *Campylobacter* species that may be clinically relevant include *C. ureolyticus, C. troglodytis, C. lari* subspecies *concheus*, and *C. peloridis*. New pathogenic species of *Campylobacter* are being identified with some regularity.

PROGNOSIS

Even in critically ill patients, 1 week of therapy is generally sufficient to eradicate infection. Although the symptoms resolve within 7 days in most patients, symptoms may persist in 10 to 20% of patients, and another 5 to 10% may experience a relapse. The case-fatality rate associated with *Campylobacter* infection is low, about 0.05 death per 1000 infections, but not surprisingly is highest among the elderly and persons with comorbid conditions.

Campylobacter infections in HIV-positive patients may be more severe, persist, recur, and be antibiotic resistant. More severe and extraintestinal illness is also more likely to occur in patients with acquired or congenital hypogammaglobulinemia. Most *C. jejuni* gastrointestinal infections in pregnant women are mild and self-limited, with no severe consequences for the mother or baby. However, if bacteremia develops in the mother, placental infection and fetal death may ensue. Infection during the third trimester can also cause neonatal sepsis and death if the woman is excreting *Campylobacter* in her stool at the time of delivery.

Guillain-Barré syndrome (Chapter 388), which is a postinfectious complication of *C. jejuni* infection, occurs about once in every 2000 infections; between 30 and 50% of all cases of Guillain-Barré syndrome may be triggered by a preceding *C. jejuni* infection.[12–14] Because the onset of neurologic symptoms occurs about 1 to 3 weeks after the onset of gastrointestinal symptoms, cross-reactivity between antibodies formed against the lipopolysaccharide and capsule of *C. jejuni* and proteins in peripheral nerve myelin or other glycolipids in peripheral nerves is probably the cause. Certain *C. jejuni* serotypes (O type 19, O type 41) are overrepresented in patients in whom Guillain-Barré syndrome develops after culture-documented *C. jejuni* infection. Other postinfectious complications of *C. jejuni* infection include reactive arthritis (seen mostly in persons with HLA-B27 histocompatibility antigens; Chapter 254), uveitis (Chapter 391), hemolytic-uremic syndrome (Chapter 158), erythema nodosum (Fig. 407-24 and Table 403-3), encephalitis (Chapter 383), myocarditis (Chapter 47), hemolytic anemia, and chronic gastrointestinal consequences such as irritable bowel syndrome[15] (Chapter 123), inflammatory bowel disease (Chapter 127), and celiac disease (Chapter 126).

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280 *ESCHERICHIA COLI* ENTERIC INFECTIONS

THEODORE S. STEINER

DEFINITION

Bacteria belonging to the species *Escherichia coli* are a normal component of the intestinal microbiota (Chapter 257). The majority of *E. coli* are harmless commensals, but specific isolates have acquired pathogenicity genes that enable them to cause diseases, including urinary tract infections, bacteremia, meningitis, and diarrheal illness. One particular challenge to the clinician and microbiology laboratory is how to distinguish these pathogenic *E. coli* from harmless commensal strains so as to better guide diagnosis and treatment.

Virulence traits include a variety of toxins, adherence factors, and secreted mediators that work together to perturb the host's intestinal physiology. Specific combinations of these factors produce six major pathotypes of diarrheagenic *E. coli*: enterotoxigenic, enteroinvasive, enterohemorrhagic, enteropathogenic, enteroaggregative, and diffusely adherent. In addition, these pathotypes frequently overlap, thereby leading to "hybrid" or "heteropathogenic" strains. Atypical strains also may carry partial genetic signatures of one or a combination of pathotypes. For example, *E. coli* that express Shiga-like toxins characteristic of enterohemorrhagic *E. coli* without the usual associated adherence factors are now collectively known as shigatoxigenic *E. coli*. Strains that carry more virulence genes are more strongly associated with diarrhea.

The Pathogen

E. coli is a small catalase-positive, oxidase-negative, gram-negative bacillus in the family Enterobacteriaceae. *E. coli* is the predominant member of the

ABSTRACT

Diarrheagenic *Escherichia coli* refers to a group of "pathotypes" of bacteria capable of adhering to intestinal epithelia and perturbing their function so as to cause illness. Each of six recognized pathotypes of diarrheagenic *E. coli* have distinct yet frequently overlapping epidemiologic and clinical features. Enteropathogenic *E. coli* cause infantile diarrhea in developing areas. Enterotoxigenic and enteroaggregative *E. coli* are the major causes of diarrhea in travelers to developing areas and, along with diffusely adherent *E. coli*, also cause endemic childhood diarrhea. Enterohemorrhagic *E. coli* cause sporadic and outbreak-associated hemorrhagic colitis, as well as hemolytic-uremic syndrome. Enteroinvasive *E. coli* cause a *Shigella*-like inflammatory enterocolitis. Although diarrheagenic *E. coli* infections are usually self-limited, they can lead to important complications and considerable morbidity or even mortality.

KEYWORDS

diarrhea
gastroenteritis
E. coli
traveler's diarrhea
hemorrhagic colitis
hemolytic-uremic syndrome
Shiga-like toxins

Gammaproteobacteria in the intestinal tract of humans and other mammals, although it is greatly outnumbered by members of other bacterial phyla, which largely consist of strict anaerobes.

E. coli possess a complex envelope that consists of a plasma membrane, a peptidoglycan cell wall, and an outer membrane. The microorganism's outer membrane confers mechanical properties of stiffness and strength. The lipopolysaccharide cell wall of *E. coli* contains immunostimulatory lipid A attached to a core oligosaccharide chain. Most *E. coli* have immunogenic carbohydrate chains, known as O antigens, attached to this core glycolipid to produce over 170 O serogroups. *E. coli* also have at least 56 distinct flagellar (H) antigens based on variable domains of the flagellin gene. Some 80 variably heat-labile capsular (K) antigens have also been described.

E. coli are major components of the normal gut microbiota, but diarrheagenic *E. coli* differ from these commensals in their specific abilities to cause clinically meaningful infection in the gut. These pathogens seldom spread systemically, but they share virulence traits with extraintestinal pathogenic *E. coli* and uropathogenic *E. coli*, although these latter organisms are typically hybrid strains as opposed to classic diarrheagenic strains. Numerous adherence, enterotoxic, cytotoxic, and invasiveness factors may be gained or lost by a particular serotype because they are characteristically encoded on transmissible genetic elements such as plasmids or bacteriophages. These factors convey the pathotype of disease because they allow colonization and perturbation of host intestinal physiology. Molecular analysis shows that commensal and pathogenic *E. coli* cluster into phylogenetic groups that are independent of O:H serotype.[1] Moreover, the *E. coli* taxon now also includes *Shigella*, based on genomic identity, although the latter can still be distinguished biochemically. Nevertheless, relatively few O serogroups tend to predominate in the normal human colon (O groups 1, 2, 4, 6, 7, 8, 18, 25, 45, 75, and 81), whereas others tend to be associated with specific virulence traits and thus different types of pathogenesis in the intestine.

EPIDEMIOLOGY

Enteric *E. coli* infections are acquired by the fecal-oral route, although the fecal sources and infectivity differ among the pathotypes. From the host perspective, the most important risk factors for illness due to diarrheagenic *E. coli* include young age and residence in or travel to low-income areas of the world where water purification is challenging. Nevertheless, *E. coli* is among the leading causes of hospitalization for acute gastroenteritis in the United States along with norovirus (Chapter 350) and Salmonella (Chapter 284).[2] Other host risk factors for diarrheogenic *E. coli* infection include recent use of antibiotics and loss of gastric acid. In addition, specific single-nucleotide polymorphisms in several human genes encoding inflammatory mediators are associated with traveler's diarrhea caused by enterotoxigenic *E. coli*, enteroaggregative *E. coli*, or both.[3] Interestingly, nonenteric travel-acquired *E. coli* strains rarely cause clinical disease.[4]

The advent of molecular diagnostics has expanded the understanding of diarrheagenic *E. coli* by identifying specific genes that characterize individual pathotypes. This information can be useful for an individual patient as well as for studying outbreaks of diarrhea.

Enteropathogenic and Enterotoxigenic Strains

A human reservoir is probably required for most recognized types of enteropathogenic *E. coli* and enterotoxigenic *E. coli*, but domestic dogs and cats can also harbor human pathogenic strains. The infectious dose of enterotoxigenic *E. coli* in volunteers is 10^6 to 10^{10} organisms, thereby indicating that the organism usually must multiply in contaminated food or water for its effective transmission and that spread directly from person to person is unusual, except in rare outbreaks in newborn nurseries. Heavy contamination with enterotoxigenic *E. coli* has been documented in foods prepared in homes, restaurants, and by street vendors, as well as in drinking water in many tropical areas. Contaminated water and food represent the major sources of human enterotoxigenic *E. coli* infection, primarily in warm or wet seasons.

As with most diarrheal illnesses, the highest age-specific attack rates of enterotoxigenic *E. coli* are found in young children, in whom enterotoxigenic *E. coli* account for anywhere from 3 to 39% (average, 13%) of acute diarrheal illnesses. As for immunologically inexperienced young children, a traveler visiting tropical areas has a 30 to 50% chance of acquiring traveler's diarrhea (Chapters 262 and 265) during a 2- to 3-week stay unless they avoid untreated water or ice and uncooked foods such as salads. The most commonly identified pathogen associated with diarrhea in most studies of travelers to tropical areas of the world is enterotoxigenic *E. coli*. A close second is enteroaggregative *E. coli*.

Typical enteropathogenic *E. coli* strains have been recognized primarily in poor urban areas. "Atypical" enteropathogenic *E. coli* strains, which possess the locus of enterocyte effacement but not the bundle-forming pilus gene, predominate in developed areas but can be found in developing areas as well.[5] Enteropathogenic strains remain a common pathogen, and "typical" enteropathogenic *E. coli* are still generally associated with diarrhea rather than asymptomatic colonization.

Enteroaggregative Strains

The natural reservoir of enteroaggregative *E. coli* is not known, but outbreaks have been traced to contaminated food, and live organisms can be found in drinking water, table salsa, and other consumable items in endemic tropical areas. A high infectious dose is required for acquisition, but person-to-person transmission can occur among men who have sex with men.[6] In addition to its role in traveler's diarrhea, enteroaggregative *E. coli* is an important cause of both acute and persistent diarrhea, as well as malnutrition (Chapter 197), especially in children in tropical areas and in patients with HIV/AIDS (Chapter 358). It also is a major cause of sporadic diarrhea in the United States, Europe, China, and other developed areas.

Diffusely Adherent Strains

Diffusely adherent *E. coli* remain the least well-understood pathotype and have not consistently been found more often in patients with diarrhea than in controls, except for acute diarrhea in children in developing areas. Part of the difficulty is the heterogeneity of strains, some of which express different types of adhesins and different groups of virulence traits, thereby leading to inconsistent pathogenicity.

Enterohemorrhagic Strains

Enterohemorrhagic *E. coli* frequently colonize commercial livestock but do not infect them. Enterohemorrhagic *E. coli* (O157:H7 and others) infections can be caused by undercooked hamburgers, but large outbreaks have also been associated with contamination of the domestic water supply, unpasteurized apple juice, spinach, seed sprouts, flour,[7] and other vegetable items.

Unlike enterotoxigenic strains, transmission requires only a low infectious dose of enterohemorrhagic *E. coli* O157:H7, so person-to-person spread can lead to secondary cases. Secondary cases of shigatoxigenic/enteroaggregative *E. coli* O104:H4 may have occured but appear to be very rare. Enterohemorrhagic *E. coli* and shigatoxigenic *E. coli* infections are especially alarming because of the risk of hemolytic-uremic syndrome (Chapter 158).

Enteroinvasive Strains

Limited data on enteroinvasive *E. coli* suggest that infectious doses are relatively high, but adequate numbers of organisms can readily be spread in food with high attack rates in outbreak situations. This characteristic distinguishes enteroinvasive *E. coli* epidemiologically from *Shigella* (Chapter 285), which is easily spread person-to-person as well as by contaminated food and water.

PATHOBIOLOGY

Enteric infections caused by *E. coli* may involve the small intestine, colon, or both, depending on the organism's genetic codes for virulence traits. Well-established mechanisms of pathogenesis of *E. coli* enteric diseases include secretion of enterotoxins (enterotoxigenic *E. coli*), tissue invasion leading to cell death (*Shigella* and enteroinvasive *E. coli*), and epithelial necrosis when Shiga-like toxins (Stx1/Stx2) cause food-borne hemorrhagic colitis (enterohemorrhagic *E. coli* and shigatoxigenic *E. coli*) (see Table 280-1). By comparison, the classically recognized enteropathogenic *E. coli* are neither enterotoxigenic per se nor invasive, but rather use a specialized apparatus called a type III secretion system to inject protein "effectors" directly into host cells, thereby allowing them to attach to and efface the epithelium and leading to formation of epithelial pedestals with intimately adherent bacteria. Specific gene clusters and increasing copy numbers of the locus of enterocyte effacement *eae* gene may characterize diarrheagenic strains compared with nonpathogenic colonizers.[8] Still other types of diarrheagenic *E. coli* can also exhibit aggregating (enteroaggregative *E. coli*) or diffuse adherence (diffusely adherent *E. coli*) to epithelial cells.

The pathogenesis of enteric *E. coli* infection begins with ingestion of the organism. It then faces the normal gastric acid barrier. Both enterotoxigenic *E. coli* and enteroinvasive *E. coli* appear to be sensitive to gastric acid, which increases the infectious dose by 100- to 1000-fold. Even though enterohemorrhagic *E. coli* expresses acid tolerance factors that may facilitate its survival in the stomach, hypochlorhydria is a risk factor for hemolytic-uremic syndrome. After ingestion and passage through the stomach, enteric *E. coli* colonize the

TABLE 280-1 DIFFERENT TYPES OF ENTERIC *ESCHERICHIA COLI* INFECTIONS

TYPE	MECHANISM	DETECTION	CLINICAL SYNDROMES
ENTEROPATHOGENIC *E. COLI*			
Typical enteropathogenic	Attach then efface the mucosa by injecting virulence factors via the type III secretion system	Gene probe or PCR for *eae* and *bfpA;* serotype, focal HeLa cell adhesion, pedestal formation	Infantile diarrhea in developing areas
Atypical enteropathogenic	Attach and efface but different microcolony formation	Gene probe or PCR for *eae*; cell adherence (variable)	Infantile and animal diarrhea in developed areas
ENTEROTOXIGENIC *E. COLI*			
Heat-labile toxin (LT) Heat-stable toxin (STa: STh or STp)	Activates intestinal adenylate cyclase Activates intestinal guanylate cyclase	Gene probe, PCR for LT PCR; EIA, suckling mice, 6-hour ileal loop assay, gene probes	Watery diarrhea, traveler's diarrhea Watery diarrhea, traveler's diarrhea
ENTEROAGGREGATIVE *E. COLI*			
	Colonize in aggregates by unique fimbriae; SPATE toxins, mucinase, biofilm, type VI secretion system	PCR for *aggR* and *aatA*; aggregative adherence to cells or strata; AA gene probe; biofilm formation	Endemic persistent diarrhea, acute traveler's diarrhea, sporadic acute diarrhea
DIFFUSELY ADHERENT *E. COLI*			
	Colonize (e.g., F1845 afimbriate adhesin); SPATE toxins, and type III secretion system in some isolates	Gene probe/PCR; HeLa cell adherence	Persistent diarrhea in children >18 months old
SHIGATOXIGENIC *E. COLI*			
Enterohemorrhagic	Shiga-like toxins and attaching/effacing ability via type III secretion system	PCR or EIA for Stx1/2, serotype, cell adhesion with pedestal formation; Vero cell cytotoxicity; sorbitol agar; PCR for *eae*	Hemorrhagic colitis (afebrile, bloody diarrhea); HUS in some cases
Non-enterohemorrhagic	Shiga-like toxins, only without attaching/effacing; may carry other virulence phenotypes	PCR or Stx EIA; negative for *eae*	Hemorrhagic colitis, HUS, or benign watery diarrhea
ENTEROINVASIVE *E. COLI*			
	Cell invasion and spread	PCR for *ipaH;* Sereny test, gene probe	Inflammatory dysentery

AA = aggregative adherence; EIA = enzyme immunoassay; HUS = hemolytic-uremic syndrome; LT = heat-labile; PCR = polymerase chain reaction; SPATE = serine protease autotransporter of Enterobacteriaceae.

involved part of the intestinal tract using specialized adhesins and the coordinated expression of virulence traits. The result is the production of toxins, intracellular invasion, or other disruptions of host cell physiology.

Enteropathogenic *E. coli*

Typical enteropathogenic *E. coli* strains express plasmid-encoded genes that confer localized adherence to epithelial cells (through specialized bundle-forming pili) and chromosomal genes that mediate attachment and effacement of microvilli. The latter is characterized by the formation of cellular pedestals that hold the bacteria intimately to the cell surface. These changes in the host epithelia are mediated by protein effectors injected directly into host cells by a specialized type III secretion system encoded on the chromosomal locus of enterocyte effacement. These secreted effectors cause cellular changes that lead to villous atrophy, mucosal thinning, inflammation in the lamina propria, and variable hyperplasia of crypt cells. These morphologic changes are associated with a reduction in mucosal brush border enzymes and may contribute to the impaired absorptive function and diarrhea. Atypical enteropathogenic *E. coli* strains are generally defined as strains that express the locus of enterocyte effacement but not the bundle-forming pili; they maintain the ability to attach/efface and cause epithelial injury.

Enterotoxigenic *E. coli*

Enterotoxigenic *E. coli* colonizes the upper portion of the small bowel using fimbriate or fibrillar surface proteins known as colonization factor antigens. These proteins bind the organism to cell surface receptors on enterocytes. Whereas this colonization itself can lead to mild inflammatory changes in the epithelium, the majority of enterotoxigenic *E. coli* illness is caused by its enterotoxins. Heat-labile toxin, with a molecular weight of about 86,000, consists of five binding "B" subunits and an enzymatic "A" subunit, and, like the closely related choleratoxin (Chapter 278), binds to a monosialoganglioside receptor. Also like choleratoxin, the A subunit is an enzyme that ADP-ribosylates the regulatory subunit of adenylate cyclase, thereby leading to constitutive production of cyclic adenosine monophosphate. The consequently increased chloride secretion and reduced sodium absorption combine to cause net isotonic electrolyte loss that can be as great as 1 liter/hour. Other human enterotoxigenic *E. coli* strains produce a heat-stable toxin, which is a much smaller peptide than heat-labile toxin (18 to 19 amino acids) and which activates intestinal particulate guanylate cyclase. Like cyclic adenosine monophosphate, the cyclic guanosine monophosphate thus formed also causes net secretion. Both the colonization traits and production of enterotoxin are encoded on transmissible plasmids. Besides the complications of dehydration, the only significant pathologic change with enterotoxigenic *E. coli* is depletion of mucus from intestinal goblet cells.

Enteroaggregative *E. coli*

Enteroaggregative *E. coli* is defined by a characteristic aggregative adherence pattern to cells and the substrata associated with the formation of biofilm. This adherence requires a large plasmid known as the AA plasmid, which encodes specialized aggregative adherence fimbriae and other virulence genes, including a serine protease autotransporter toxin known as Pet and an antiaggregative protein called dispersin. Chromosomal virulence traits include a mucinase (Pic) and additional enterotoxins, as well as type VI secretion systems. Data suggest that the organisms do not intimately adhere or invade but rather reside within a biofilm at the epithelial surface, where secreted factors contribute to a damaging host inflammatory response.

Diffusely Adherent *E. coli*

The fundamental pathogenesis of diffusely adherent *E. coli* appears to depend on direct interactions between specialized adhesins (Afa/Dr) and host membrane proteins such as CD55 (decay-accelerating factor) or carcinoembryonic antigen. Many diffusely adherent *E. coli* strains are closely related to uropathogenic *E. coli* with similar virulence traits. Some strains also express other virulence factors, including serine protease autotransporter toxins, such as Sat and EspP, and a type III secretion system.[9]

Enterohemorragic *E. coli*

Enterohemorrhagic *E. coli*, most notably serotype O157:H7 (but also serogroups O26, O39, and others), cause type III secretion-dependent intimate adherence and microvillous effacement like enteropathogenic *E. coli*, but they also produce Shiga-like toxins that are responsible for the characteristic colonic mucosal disruption and hemorrhage as well as the complication of hemolytic-uremic syndrome. These toxins bind to the Gb3 surface ganglioside, thereby leading to internalization and enzymatic inactivation of ribosomes and a halting of protein synthesis. The high expression of Gb3 on vascular endothelial cells in the colon, kidney, and brain may explain the predilection for hemolytic-uremic syndrome to affect these organs. Organisms that produce

Shiga-like toxins without intimate adherence and pedestal formation are known as shigatoxigenic *E. coli* or verotoxigenic *E. coli*, and they often lack the other virulence traits necessary for colonization and disease production. The terms enterohemorrhagic *E. coli*, shigatoxigenic *E. coli*, and verotoxigenic *E. coli* were often used interchangeably until the important role of the attaching/effacing ability of true enterohemorrhagic *E. coli* strains like O157:H7 was understood.[10]

Enteroinvasive *E. Coli*

Enteroinvasive *E. coli*, like the closely related *Shigella* (Chapter 285), can invade and multiply in epithelial cells, cause experimental conjunctivitis in guinea pigs (known as the Sereny test), and produce inflammatory colitis and dysenteric, or bloody, diarrhea. As with shigellosis, a striking inflammatory response occurs, with numerous polymorphonuclear leukocytes in stool. The colon shows patchy, acute mucosal and submucosal inflammation with focal denuding of the surface epithelium, usually without deeper invasion or systemic spread. The epithelial cell invasiveness of both enteroinvasive *E. coli* and *Shigella* is encoded on a large 120- to 140-Md plasmid, which some pathogenic strains have independently acquired.

CLINICAL MANIFESTATIONS

The clinical manifestations of enteric *E. coli* infections differ among the pathotypes. For example, the incubation period averages 14 hours for enteroaggregative *E. coli*, 2 days for enterotoxigenic *E. coli*, 3 to 4 days for enterohemorrhagic *E. coli* O157:H7, but 8 days for shigatoxigenic/enteroaggregative *E. coli* O104:H4.

Enteropathogenic *E. coli*

Outbreaks of enteropathogenic *E. coli* infection in newborn nurseries have ranged from mild transient diarrhea to severe and rapidly fatal diarrheal illnesses, especially in premature or otherwise compromised infants. Diarrheal illness also can affect adults but does not have any specific distinguishing features.

Enterotoxigenic *E. coli*

Enterotoxigenic *E. coli* infections generally produce watery diarrhea, particularly in young children and travelers to tropical or developing areas. Diarrhea may range from mild to very severe, and it may be life-threatening, especially in small children and elderly individuals, who are particularly prone to dehydration, undernutrition, and electrolyte imbalance (especially hypokalemia and acidosis). Other characteristic symptoms include malaise, abdominal cramping, anorexia, and occasionally nausea, vomiting, or low-grade fever. The illness is generally self-limited to 1 to 5 days and rarely extends beyond 10 to 14 days. However, the mucosal absorptive capacity may be impaired for up to 3 weeks. Infections with enterotoxigenic *E. coli* that produce both heat-stable toxin and heat-labile toxin or heat-stable toxin alone may be more severe than those caused by enterotoxigenic *E. coli* that produce only heat-labile toxin.

Enteroaggregative *E. coli*

Enteroaggregative *E. coli* has been associated with persistent diarrhea and malnutrition (Chapter 197) in children in developing areas, in patients with HIV/AIDS (Chapter 358), and in travelers (Chapter 265) who experience diarrhea (especially those genetically predisposed to greater inflammatory responses). Although infection is frequently asymptomatic, it may cause subclinical inflammation and lead to growth shortfalls. No characteristic clinical features of enteroaggregative *E. coli* have been consistently identified, although some outbreaks have been associated with bloody diarrhea and elevated inflammatory markers in stool. The median duration of illness tends to be longer than for other diarrheagenic *E. coli* pathotypes, even as long as 14 days.[11]

Diffusely Adherent *E. coli*

Diffusely adherent *E. coli* has been associated with diarrhea with no particular identifying features, largely in children older than 18 months. Strains that are associated with diarrhea also are likely to induce inflammation.[12]

Enterohemorrhagic *E. coli*

Hemorrhagic colitis associated with enterohemorrhagic *E. coli* classically begins with watery diarrhea that quickly turns grossly bloody, with a conspicuous absence of fever or inflammatory exudate in stool but with significant abdominal pain. Although this diarrheal illness is self-limited, potentially fatal hemolytic-uremic syndrome (Chapter 158) or thrombotic thrombocytopenic purpura (Chapter 158) subsequently develops in a significant number of children and older adults (Chapter 158). Outbreaks of hemorrhagic colitis secondary to enterohemorrhagic *E. coli* in nursing homes or other institutions may be common and severe. The illness is characteristically self-limited to 5 to 12 days (mean, 7.8 days). The clinical manifestations of the heat-stable toxin/enteroaggregative *E. coli* O104:H4 are similar, although rates of hemolytic-uremic syndrome (Chapter 158) are significantly higher (more than 20%), and women are disproportionately affected.

Enteroinvasive *E. coli*

Infection with enteroinvasive *E. coli* is characterized by inflammatory colitis, often with abdominal pain, high fever, tenesmus, and bloody or dysenteric diarrhea, essentially like that seen with *Shigella* (Chapter 285). The duration of diarrhea is generally self-limited to 7 to 10 days.

DIAGNOSIS

Definitive diagnosis of *E. coli* diarrhea requires documentation of the specific virulence trait or serotype, now almost always by polymerase chain reaction (PCR) or similar molecular testing of diarrheal stool.[13] PCR testing can also be used to test a suspected food or water source.[14] The identification of subtypes of *E. coli* is clinically important during outbreaks or when shigatoxigenic *E. coli* is suspected, such as in any patient who has visible blood in any stool sample.

Differential Diagnosis

Numerous other causes of diarrhea must be considered, depending on the clinical circumstances (Chapters 126 and 265). For example, self-limited, noninflammatory diarrhea in tropical, developing areas is most likely due to enterotoxigenic *E. coli*, enteroaggregative *E. coli*, rotaviruses (young children), or noroviruses (older children and adults) (Chapter 350). Noninflammatory diarrhea in older children or adults in temperate areas is more likely to be due to noroviruses (Chapter 350). *Vibrio* infections (Chapter 278) are common in areas endemic for cholera or in any coastal area where inadequately cooked seafood is frequently eaten. If diarrhea persists beyond a week, especially with weight loss, other possibilities include *Clostridioides difficile* (Chapter 271), *Giardia lamblia* (Chapter 322), *Cryptosporidium* (Chapter 320), *Cyclospora* (Chapter 324), and microsporidial infection (Chapter 324). In outbreaks of acute food poisoning, *Staphylococcus aureus* (Chapter 267), *Clostridium perfringens* (Chapter 271), and *Bacillus cereus* should be considered.

Inflammatory colitis with high fever and tenesmus as well as leukocytes, mucus, and blood in the stool may well be due to enteroinvasive *E. coli* but should prompt a stool culture for more common invasive pathogens, such as *Campylobacter jejuni* (Chapter 279), *Shigella* (Chapter 285), *Salmonella* (Chapter 284), *Yersinia enterocolitica* (Chapter 288), or noncholera *Vibrio* (Chapter 278). Inflammatory bowel disease (Chapter 127) can also present acutely as an inflammatory diarrhea and should be considered in cases where symptoms persist and no pathogen is identified. Any patient with diarrhea and a history of recent antibiotic use, gastrointestinal surgery, or parturition should be screened for toxigenic *Clostridioides difficile* (Chapter 271).

In patients with bloody diarrhea, enterohemorrhagic *E. coli* should be strongly considered, particularly in the absence of fever. It is recommended that laboratories now routinely screen for this pathogen in all stool cultures, but especially in grossly bloody samples. Ischemic colitis (Chapter 129) and cytomegalovirus colitis (Chapter 347) can mimic enterohemorrhagic *E. coli* but typically occur only in people at risk (vascular disease and immune compromise or inflammatory bowel disease, respectively).

TREATMENT

Hydration

As with all diarrheal illnesses, the primary treatment for most *E. coli* diarrhea is replacement and maintenance of water and electrolytes, usually with a simple oral rehydration solution that uses the intact, sodium-coupled glucose or amino acid absorption (or both) to replace the fluid losses. Oral rehydration solution should be given ad libitum with free water. In breast-fed infants, continued breast-feeding and early refeeding can compensate for the nutritional losses without an adverse effect on diarrhea output. Zinc supplementation is also recommended for diarrhea in children older than 6 months in developing areas where zinc deficiency is common because it significantly reduces diarrhea volume.

Symptomatic Treatment

Antimotility agents (e.g., loperamide [2 to 4 mg as a single dose, followed by 2 mg after each loose stool up at a maximum of 16 mg/day in adults]) reduce the frequency of diarrheal stools but should not be used when fever or bloody diarrhea is present because they can increase the risk of mortality due to toxic megacolon or hemolytic-uremic syndrome. Bismuth subsalicylate (262 to

524 mg up to four times a day) may reduce symptoms in traveler's diarrhea (Chapter 265) but should be used with caution to avoid toxic doses of salicylate. The enkephalinase inhibitor racecadotril, which is available in Europe but not currently in North America, also reduces diarrheal volume in children with acute gastroenteritis and is as effective as loperamide in adults but less likely to cause constipation.

Probiotics and Colostrum

Some probiotic preparations have been shown in small studies to improve symptoms when they are added to oral rehydration solution in children with infectious diarrhea but are not yet universally recommended. Powdered bovine colostrum, available as a nutritional supplement, can improve 48-hour outcomes in children under 2 with diarrhea, including rotavirus and enteric *E. coli*.[A1]

Antibiotics

Because most *E. coli* diarrhea is self-limited, the role of antimicrobial agents remains of secondary importance to rehydration except for patients with traveler's diarrhea (Chapter 265), in whom antibiotics clearly reduce the duration of symptoms.[A2] Since stool testing rarely is available in this setting, empirical options such as azithromycin (a single 1000-mg dose or 500-mg dose daily for 3 days), a fluoroquinolone (e.g., levofloxacin 500 mg single dose or daily for 3 days) or rifaximin (200 mg three times daily for 3 days) are recommended, with trimethoprim-sulfamethoxazole (1 double-strength tablet twice daily for 5 days) a somewhat less reliable alternative. Combining a single dose of fluoroquinolone (e.g., levofloxacin 500 mg) or rifaximin treatment with loperamide are very effective acute options but also are associated with acquisition of extended-spectrum β-lactamase *E. coli* at day 21, so the potential benefit of antibiotic treatment to reduce the duration of symptoms should be balanced against concerns for acquisition of drug-resistant bacteria.

Antimicrobials should not be used in enterohemorrhagic *E. coli* infection because of the possibility of increasing the production of Shiga-like toxin from bacteriophage carried within the organism, and thereby increasing the risk and severity of hemolytic-uremic syndrome (Chapter 158).[15] For persistent diarrhea due to enteroaggregative *E. coli*, ciprofloxacin (500 mg twice daily for 7 days) may be beneficial in patients with HIV/AIDS, but antibiotic treatment does not appear to be of benefit in otherwise healthy adults.

PREVENTION

Prevention of most *E. coli* enteric infections is ultimately related to basic economic development, adequate sanitary facilities, and sufficient availability of safe water. In areas where adequate water supplies and sanitary facilities are not available, exclusive breast-feeding for at least 6 to 12 months and hand hygiene reduce the likelihood of acquiring *E. coli* enteric infections. Consistent use of an alcohol-based hand sanitizer can reduce the incidence of traveler's diarrhea, although not acquisition of extended-spectrum β-lactamase–expressing organisms.[A3] Inexpensive, portable water filters can effectively reduce bacterial contamination and may reduce clinically significant diarrheal episodes in infants.[A4] Trials of hyperimmune bovine colostrum (following immunization of cows) have shown promising results in adult challenge models but are not yet clinically proven in a real-world setting.

Travelers to developing or tropical areas should avoid drinking untreated or unboiled water or ice and eating uncooked fruits or vegetables that may have been washed with highly contaminated water. Although a number of antimicrobial agents are effective during short periods when taken prophylactically, their effectiveness is ultimately limited by rapidly emerging resistance to antimicrobial drugs as well as by the potential side effects of their indiscriminate, widespread use (Chapter 265). Prophylactic probiotics may be of limited benefit for reducing the risk of traveler's diarrhea.[A5]

Sporadic enterohemorrhagic *E. coli* infections may be reduced by adequately cooking ground beef products to an internal temperature of at least 160° F (71° C) and by careful handwashing and other hygienic measures in daycare centers and nursing homes. Unfortunately, large outbreaks due to contaminated produce continue to occur and are frequently associated with items meant to be eaten raw (such as sprouts and vegetables). Irradiation of meats and some produce to reduce viable bacterial contamination is approved in the United States and Canada, but these foods are not widely sold at the present time.

Vaccine development appears to be the most promising strategy,[16] but no effective vaccine is licensed in the United States against intestinal pathogenic *E. coli*.

PROGNOSIS

Healthy adults and even adults with underlying comorbid conditions eventually always recover completely from most strains of enteric *E. coli*. Lethal infections with typical enteropathogenic *E. coli* may be associated with certain gene clusters, although it is too early to use such information for prognostic purposes. The greatest concern with enteric *E. coli* infections in developed areas is enterohemorrhagic *E. coli*/shigatoxigenic *E. coli*–associated hemolytic-uremic syndrome (Chapter 158), which develops in 3 to 7% of sporadic cases and as high as 20% of cases during outbreaks. Whereas most patients with hemolytic-uremic syndrome recover, they frequently require intensive medical care (including temporary hemodialysis), and as many as 30% of survivors have renal sequelae such as proteinuria, hypertension, reduced glomerular filtration rate, or, more rarely, dialysis dependence.[17]

On a global scale, the greatest impact of diarrheagenic *E. coli* is in children in low-income areas, where these otherwise self-limited infections can cause death from dehydration. Moreover, children who survive repeated episodes of infectious diarrhea (due to *E. coli* and other pathogens) may experience permanent deficits in growth and cognitive development, the full impact of which remains unknown.

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281 ENTEROBACTERALES: NON-ENTERIC INFECTIONS AND MULTIDRUG RESISTANCE

AMY J. MATHERS

DEFINITION

The Enterobacterales are an order of gram-negative bacilli that are responsible for a broad range of infections in humans and in animals. They may be motile or nonmotile, depending on the species. They are aerobic or facultatively anaerobic in growth and have a predilection for inhabiting the gastrointestinal tract. Only extragastrointestinal manifestations of disease are discussed in this chapter. Enteric infections caused by *Escherichia coli* are discussed in Chapter 280.

The Pathogen

These organisms are now split into seven families all under the order Enterobacterales. Members of the Enterobacterales grow on a variety of solid media and are usually readily identified by clinical microbiology laboratories. Accurate speciation remains important in a clinical setting because of inherent differences in antibiotic susceptibility among species. Medically important members of the Enterobacterales (Table 281-1) include *Salmonella* (Chapter 284), *Shigella* (Chapter 285), and *Yersinia* (Chapter 288).

EPIDEMIOLOGY

The Enterobacterales, which are among the most common pathogens to infect humans worldwide, are responsible for community-acquired, hospital-acquired,

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EPIDEMIOLOGY

The Enterobacterales, which are among the most common pathogens to infect humans worldwide, are responsible for community-acquired, hospital-acquired,

ABSTRACT

The Enterobacterales are an order of gram-negative bacteria that includes the genera *Enterobacter, Escherichia, Klebsiella, Salmonella, Shigella, Yersinia, Serratia,* and others. Having a predilection for inhabiting the gastrointestinal tract, the Enterobacterales are among the most common pathogens worldwide. They have in common the propensity for readily developing multidrug resistance at a rate that currently outstrips the rate of development of new antibiotics to combat them. Not only are multidrug-resistant strains of Enterobacterales becoming essentially endemic in some communities around the world, they have also permeated hospitals and other health care facilities. Antimicrobial multidrug resistance can be due to (1) the inherent properties of the pathogen (e.g., all *Enterobacter cloacae* are resistant to ampicillin because they carry β-lactamase in their chromosome) or (2) the pathogen's acquired antimicrobial resistance (e.g., by mutation or acquisition of genes for antimicrobial resistance through horizontal gene transfer). The properties of the pathogen and their resistance profiles have driven the spread of multidrug-resistant bacteria that challenge the control and management of patients with these infections.

KEYWORDS

Enterobacterales
multidrug resistance
extended-spectrum β-lactamases
extended-spectrum carbapenemases
health care–associated pathogens
outbreaks

TABLE 281-1 SELECTED MEDICALLY IMPORTANT MEMBERS OF THE ORDER ENTEROBACTERALES

FAMILY	GENUS	SOME IMPORTANT SPECIES
Enterobacteriaceae	*Citrobacter*	*C. freundii*
Enterobacteriaceae	*Enterobacter*	*E. cloacae*
Enterobacteriaceae	*Escherichia*	*E. coli*
Enterobacteriaceae	*Klebsiella*	*K. pneumoniae, K. aerogenes*
Enterobacteriaceae	*Salmonella*	*S. enterica, S. typhi*
Enterobacteriaceae	*Shigella*	*S. sonnei*
Morganellaceae	*Morganella*	*M. morganii*
Morganellaceae	*Proteus*	*P. mirabilis, P. vulgaris*
Morganellaceae	*Providencia*	*P. stuartii*
Yersiniaceae	*Serratia*	*S. marcescens*
Yersiniaceae	*Yersinia*	*Y. pestis, Y. enterocolitica*

and health care–associated infections. Examples of the last category include infections acquired in nursing homes and those associated with outpatient management of cancers or hematologic malignant disease. As several species are resident components of the flora of the gastrointestinal tract, isolates of Enterobacterales may represent examples of colonization rather than true infection when found in rectal swabs, urine, wounds, or respiratory secretions. In some regions, multidrug-resistant Enterobacterales have become endemic, thereby leading to substantial problems in the management of serious infections.[1] Although multidrug resistance in the United States is still largely health care–associated, resistant community-associated infections are continuing to emerge.[2]

E. coli is the most common cause of urinary tract infections, accounting for more than 80% of isolates from urine in most clinical situations (Chapter 263). *Klebsiella* spp and *Proteus mirabilis* are among other common causes of urinary tract infections. Enterobacterales infections in the urinary tract can range from uncomplicated cystitis to life-threatening acute pyelonephritis and sepsis. Complicated and recurrent urinary tract infections frequently occur in patients with urinary retention, anatomic abnormalities, or a need for frequent or chronic urinary catheterization. In some patients with complicated or recurrent urinary tract infections, multidrug-resistant Enterobacterales are seen.[3]

The spread of some strains of uropathogenic *E. coli* account for a disproportionate percentage of disease. For example, trimethoprim-sulfamethoxazole–resistant *E. coli* spread in a clonal fashion in the United States (e.g., "clonal group A" and *E. coli* O15:K52:H1). A widely spread *E. coli* clone, defined by multilocus sequence typing as sequence type 131 (ST131), is associated with resistance to ciprofloxacin and production of extended-spectrum β-lactamases.[4] This clone, which is typically associated with community-acquired urinary tract infections, has been detected in every inhabited continent.

Given that the niche of the most common Enterobacterales is in the gastrointestinal tract, it is not surprising that these bacteria are prominent as causes of abdominal infections. *E. coli* is the most common cause of both spontaneous bacterial peritonitis (occurring in cirrhotic patients [Chapter 139]) and bacterial peritonitis arising after visceral perforation (Chapter 128). Pyogenic liver abscesses (Chapter 137) and intra-abdominal abscesses may also be due to *E. coli*. *Klebsiella pneumoniae* is a leading cause of pyogenic liver abscesses (Chapter 137) and may also cause intra-abdominal infections, especially in patients who develop peritonitis after surgery for intra-abdominal disease.

The Enterobacterales may also cause pneumonia, although less commonly than urinary or abdominal infections. Enterobacterales respiratory tract infections are frequently hospital- and health care–associated pneumonias (Chapters 85 and 261) rather than community-acquired pneumonia. *K. pneumoniae*, which was prominently associated with community-acquired pneumonia (Chapter 85) in people with alcohol use disorder (Chapter 364), has declined in significance during the past few decades. Since the 1980s, a hypervirulent *K. pneumoniae* has emerged to cause serious disseminated infections, typically pyogenic liver abscess (Chapter 137), osteomyelitis (Chapter 251), and/or endophthalmitis (Chapter 391) in immunocompetent and otherwise healthy people. Although mostly antibiotic-sensitive at this time, some cases of multidrug-resistant *Klebsiella* have been identified.

Hospital-acquired pneumonia due to the Enterobacterales may be ventilator-associated (Chapters 85 and 261), and Enterobacterales rank as the third most common causes of ventilator-associated pneumonia after *Staphylococcus aureus* (Chapter 267) and *Pseudomonas aeruginosa* (Chapter 282). The Enterobacterales are not natural flora of the upper airway, but mucosal injury from ventilation and any prior infection, as well as exposure to antimicrobial agents, alters the airway microbiome to predispose patients to Enterobacterales pneumonia, including pneumonia from multidrug-resistant organisms such as *Enterobacter* sp. and *Serratia marcescens*.

Outbreaks of antibiotic-resistant *K. pneumoniae* infection in hospitals have been prominent for more than three decades. In the hospital setting, *K. pneumoniae* is usually the cause of peritonitis, pneumonia, or complicated urinary tract infection. Blood stream infection arising from another site of infection, from vascular catheters, or in association with neutropenia may also occur, but patient-to-patient transmission is otherwise rare.[5] In the past decade or so, with carbapenems considered the last line of reliable therapy for invasive infections, *K. pneumoniae* carbapenemase has become a substantial clinical and infection control issue in hospitals (Chapter 261).

PATHOBIOLOGY

Generally, Enterobacterales colonize the gastrointestinal lumen and exist in the environment, from where they are introduced into the genitourinary tract or other site to cause infection. At least 40 different virulence genes in *E. coli* can lead to extraintestinal infections. Among the virulence properties of these strains is the renowned ability of *E. coli* to adhere to uroepithelial cells. The ST131 *E. coli* clone is typically highly successful at causing extraintestinal infections. It belongs to "phylogenetic group" B2, which is known for extraintestinal pathogenic infections. In an evaluation of the ST131 clone, numerous extraintestinal virulence genes were found.

Mechanisms of Multidrug Resistance

Hard-to-treat and even untreatable infections with extended-spectrum β-lactamase and carbapenem-resistant Enterobacterales have emerged worldwide and have become a serious threat to global public health.[6] As with many infectious diseases, the emergence of highly resistant Enterobacterales is not evenly distributed, and several low- and middle-income countries have disproportionately high rates of resistance. The global spread of drug resistance is further facilitated by migration of refugees and pilgrimages.[7] In acute care hospitals in the United States, β-lactamase–resistant Enterobacterales comprise about 20% of all *Klebsiella* spp and *E. coli* isolates, and about 7% of *K. pneumoniae* isolates are carbapenem-resistant.[8] The stabilization and even decrease in infections with carbapenem-resistant Enterobacterales in acute care facilities in the United States has been attributed in part to initiatives designed to limit the use of broad-spectrum antibiotics and to prevent nosocomial transmission using detection and isolation strategies.

The molecular mechanisms of antibiotic resistance in the Enterobacterales can be either intrinsic or acquired (Table 281-2) (also see Chapter 266). Intrinsic resistance occurs when bacteria possess properties that naturally resist the action of an antimicrobial, often because of genes encoded in the chromosome of the wild-type bacterial species (e.g., all *Klebsiella* spp produce a β-lactamase that hydrolyzes ampicillin). Acquired resistance occurs by mutations in the chromosome, changes in gene expression, or acquisition of genes that confer resistance after horizontal gene transfer from other bacteria. From a molecular mechanism standpoint, bacteria resist antimicrobial agents in one of four ways: (1) alteration of antimicrobial uptake to the site of action (e.g., downregulating its expression of porins, which are nonspecific membrane channels, and thereby reducing its permeability to the antibiotic); (2) upregulating specific or multidrug-resistance pumps to increase the efflux to expel the antibiotic; (3) altering the target site so that the antimicrobial agent cannot efficiently bind (e.g., by target site mutation, acetylation, phosphorylation); or (4) destruction of the antibiotic by enzymatic activity (e.g., β-lactamases). Acquired resistance can then proliferate through (1) expansion of clonal lineages with antibiotic resistance gene mutations, including acquired β-lactamases and carbapenemases (i.e., clonal expansion) and/or (2) horizontal transfer of antibiotic-resistance genes through mobile genetic elements, such as plasmids or transposons, which can spread across strains and species.

TABLE 281-2 MECHANISMS OF ANTIBIOTIC RESISTANCE AND DRIVERS OF SPREAD OF MULTIDRUG-RESISTANT ENTEROBACTERALES

1. MECHANISMS OF ANTIBIOTIC RESISTANCE
Intrinsic Resistance
Bacterial species with inherent properties that naturally resist the action of an antibiotic often encoded in the chromosome of the wild-type population of a bacterial species (e.g., all *Klebsiella* spp produce a β-lactamase that hydrolyzes ampicillin)
Acquired Resistance
Development of resistance to an antimicrobial through mutation, altered regulation, or acquisition of genes of antimicrobial resistance through horizontal gene transfer
2. MECHANISMS OF ANTIMICROBIAL RESISTANCE
Prevent Access to the Antibiotic Target
Reduce influx of the antibiotic (e.g., downregulate porins) Increase efflux (e.g., overexpress specific or multidrug-resistance pumps)
Alter the Antibiotic Target
Change target structure through mutations to disable antibiotic binding Modify and protect the target by mutation or post-translational modification
Inactivate the Antibiotic
Enzymatically hydrolyze the antibiotic (e.g., β-lactamases, carbapenemases) Chemically alter the antibiotic to prevent antibiotic binding
3. DRIVERS OF SPREAD OF MULTIDRUG-RESISTANT BACTERIA
Clonal Expansion
Proliferation of clonal lineages with genes or mutations that can stably maintain antimicrobial resistance mechanisms
Horizontal Gene Transfer
Exchange of antimicrobial resistance genes between bacteria through mobile genetic elements, such as plasmids and transposons

Narrow-Spectrum β-Lactamases

Plasmids encoding resistance to ampicillin are widespread, and at least 40% of *E. coli* in most parts of the world now express a plasmid-mediated β-lactamase. Enterobacterales such as *Klebsiella* and *Enterobacter* spp have genes encoding β-lactamases inherent to their genome and are intrinsically resistant to ampicillin.

Extended-Spectrum β-Lactamases

Third-generation cephalosporins (such as ceftriaxone) are intrinsically active against all Enterobacterales. However, mutant genes encoding β-lactamases capable of inactivating third-generation cephalosporins have become widespread, initially because of point mutations in the plasmid-mediating β-lactamase that led to an altered amino acid sequence. In addition, many new types of extended-spectrum β-lactamase resistance have been acquired, including the cefotaximase-M type (CTX-M), which is now the most dominant extended-spectrum β-lactamase gene in *E. coli* in most regions of the globe.

Frequently, the ST131 *E. coli* clone produces a cefotaximase-M type of extended-spectrum β-lactamase (especially CTX-M-15). Although classic extended-spectrum β-lactamases are susceptible to β-lactamase inhibitors (e.g., clavulanic acid), many ST131 *E. coli* isolates produce an additional β-lactamase (OXA-1) that confers resistance to β-lactamase inhibitors. The antibiotic resistance phenotype of the ST131-positive *E. coli* is that the organisms are typically resistant to ceftriaxone, cefotaxime, fluoroquinolones, trimethoprim, trimethoprim-sulfamethoxazole, tetracyclines, and often penicillin-β-lactamase inhibitor combinations. Resistance to aminoglycosides is variable. The clone confers multidrug resistance by the presence of multiple antibiotic resistance genes, which are usually encoded on plasmids.

AmpC β-Lactamases

A number of genera within the Enterobacterales have a chromosomally encoded β-lactamase capable of producing resistance to all penicillins and all cephalosporins except for cefepime. In addition, these β-lactamases are not inhibited by β-lactamase inhibitors, such as clavulanic acid or tazobactam. These β-lactamases, which are known as AmpC β-lactamases or cephalosporinases, are not derived from narrower-spectrum parent β-lactamases. AmpC β-lactamases may be overproduced in the presence of certain antibiotics (i.e., the genes encoding the AmpC β-lactamases are "inducible"). *Enterobacter cloacae*, *Klebsiella aerogenes*, and *Citrobacter freundii* have inducible, chromosomally encoded AmpC β-lactamases. The challenge with these organisms is that they may initially test as susceptible to ceftriaxone but then begin making more AmpC and develop resistance while the patient is being treated, thereby resulting in therapeutic failure. AmpC β-lactamase genes, which have now been found on plasmids in *E. coli*, *Salmonella*, and other gram-negative bacteria, often lack regulation, thereby resulting in high-level continuous expression.

KPC, NDM, and Other Carbapenemases

With the emergence of extended-spectrum β-lactamase–producing Enterobacterales, carbapenems became widely used for the treatment of these organisms. However, a carbapenem-hydrolyzing β-lactamase capable of hydrolyzing penicillins, cephalosporins, aztreonam, and carbapenems has since been described globally in many genera of the Enterobacterales, such as *E. coli*, *K. pneumoniae*, *Enterobacter*, *Citrobacter*, and *Proteus* species. *K. pneumoniae* carbapenemase is the most frequently encountered in the United States and, despite its name, has been identified across many genera of Enterobacterales.

Another common carbapenem-hydrolyzing β-lactamase in Enterobacterales is the New Delhi metallo-β-lactamase, which is also a major cause of carbapenem resistance. The responsible enzyme is a typical metallo-β-lactamase that is not inhibited by β-lactamase inhibitors and cannot hydrolyze aztreonam. Many outbreaks of New Delhi metallo-β-lactamase–producing organisms have arisen in Southeast Asia and are often the cause of hospital outbreaks. These New Delhi metallo-β-lactamase-producing organisms also have been found in drinking water in India and in food-producing animals in China. Other carbapenem-hydrolyzing β-lactamases seen in Enterobacterales include the OXA-48-like types, which were originally found in Europe and the Middle East but have continued to spread to other parts of the world, as well as a variety of other metallo-β-lactamases. These enzymes all share the ability to render Enterobacterales resistant to carbapenems and many other β-lactam antibiotics, thereby making therapeutic decisions very challenging.

CLINICAL MANIFESTATIONS

The clinical manifestations of urinary tract infections (Chapter 263), pneumonia (Chapter 85), intra-abdominal infections (Chapter 128), and blood stream infections (Chapter 94) due to the Enterobacterales are described in other chapters.

DIAGNOSIS

Enterobacterales are readily grown in clinical microbiology laboratories after collection of appropriate specimens. Examination of the Gram stain enables a rapid identification of gram-negative bacilli from gram-positive pathogens. Molecular methods can rapidly detect many specific Enterobacterales and can also identify several of the β-lactamase genes from a positive blood culture soon after the completion of the Gram stain.[9] These results can guide empiric therapy with a carbapenem or a novel antimicrobial agent while awaiting final speciation results from culture as well as detailed susceptibility testing.

TREATMENT

Urinary Tract Infections

Treatment depends on the site of infection and the extent of antibiotic resistance. Uncomplicated cystitis due to *E. coli* and the other Enterobacterales (Chapter 263) may be treated with empiric orally administered fosfomycin, nitrofurantoin, quinolones, or trimethoprim-sulfamethoxazole if susceptible. Fosfomycin is indicated only in the setting of uncomplicated cystitis caused by *E. coli*. Empirical parenteral choices for more severe infections may include third-generation cephalosporins, fluoroquinolones, aminoglycosides, and carbapenems and should be based on local rates of resistance of the most commonly treated organisms.

Extended-Spectrum β-Lactamase–Producing Organisms

In vitro, the carbapenems (including imipenem, meropenem, doripenem, and ertapenem) have the most potent activity against extended-spectrum β-lactamase–producing organisms. To avoid overuse, carbapenem-sparing strategies should be used when feasible, even for extended-spectrum lactamase infections. Observational data suggest that quinolones or, in some instances, cefepime may be reasonable alternatives, depending on the degree and type of resistance. However, carbapenems should be regarded as the drugs of choice for serious infections with extended-spectrum β-lactamase–producing organisms.[10] For example, meropenem is generally the treatment of choice for serious infections due to extended-spectrum β-lactamase producers.[A1] The ability to

TABLE 281-3 NOVEL β-LACTAM OR β-LACTAMASE INHIBITORS APPROVED TO COMBAT MULTIDRUG-RESISTANT ENTEROBACTERALES*

MEDICATION	ACTIVITY BY ENZYME TYPE				
	Class A extended-spectrum β-lactamases	*Klebsiella pneumoniae* carbapenemases	AmpC cephalosporinases	Metallo-β-lactamases	Oxacillinases
Ceftazidime-avibactam	+	+	+	-	+/-
Imipenem-relebactam	imipenem alone is active, so relebactam is not needed	+	+	-	+/-
Cefiderocol	+	+	+	+	+
Meropenem-vaborbactam	meropenem alone is active, so vaborbactam is not needed	+	-	+/-	-
Ceftolozane-tazobactam	+	-	-	-	-

*Dosing should be supervised by experts for specific clinical scenarios.

use ertapenem once daily makes it potentially useful in serious infections with extended-spectrum β-lactamase producers in nursing home residents or patients who can continue parenteral therapy out of the hospital. There is no evidence that combination therapy involving a carbapenem is superior to use of a carbapenem alone for extended-spectrum β-lactamase producers.

Carbapenem-Resistant Organisms

Treatment of carbapenem-resistant organisms is challenging because they may lack susceptibility to all traditional β-lactam antibiotics (including penicillins, cephalosporins, aztreonam, and carbapenems), fluoroquinolones, and aminoglycosides.[11] Carbapenemase-producing organisms may sometimes appear susceptible to carbapenems such as meropenem and imipenem (although they are almost always recognized as resistant to ertapenem), but these antibiotics should not be relied upon when a carbapenemase is present. Colistin monotherapy (5 mg/kg once followed by 1.67 mg/kg every 8 hours) is a potential option.

Newer agents for multidrug-resistant Enterobacterales are designed to address the worldwide challenge. The majority of those new drugs pair unique β-lactamase inhibitors, which target the enzymes driving resistance, with an already approved broad-spectrum β-lactam antimicrobial. These agents have generally undergone an expedited approval process, so clinical trial data are not as robust as for prior antimicrobial agents. Ceftazidime/avibactam is active against *K. pneumoniae* carbapenemase, AmpC, and OXA-48–producing bacteria, although the development of resistance may be a concern in patients who have infections with a high bacterial burden[A3] (see Table 281-3). Meropenem/vaborbactam is active against *K. pneumoniae* carbapenemase-producing bacteria.[A4] Imipenem-cilastatin-relebactam also has activity against *K. pneumoniae* carbapenemase-producing Enterobacterales.[A5] None of these new agents has activity against metallo-β-carbapenemases (e.g., Verona integron-encoded metallo-β-lactamase and New Delhi metallo-β-lactamase), but cefiderocol,[12] which is a novel siderophore, should be able to avoid hydrolysis across all types of the carbapenemases, including metallo-β-lactamases.[A6]

Non-β-lactam antibiotics include eravacycline, omadacycline, plazomicin, and delafloxacin, all of which have activity against gram-negative bacteria that produce extended-spectrum β-lactamases; however, each agent should be used with caution under the oversight of an infectious disease specialist. Several additional agents are in the late stages of development.

PREVENTION

Prevention of hospital-acquired outbreaks of multidrug-resistant Enterobacterales depends on basic infection control principles (Chapter 261). First, if a focus of infection (e.g., an infected bronchoscope) exists in the hospital environment, it should be removed, and all medical devices and equipment must be appropriately sterilized. Persistent reservoirs in the hospital environment, such as wastewater plumbing systems, must be identified and mitigated.

However, transient carriage from an infected or asymptomatically colonized patient to another on the hands of health care workers appears to be the most important means of transfer of multidrug-resistant Enterobacterales. The hands of health care workers are presumably colonized by contact with the skin, stool, or bodily fluids of the infected patient or by contact with a contaminated environment around the patient. Hand carriage by health care workers is usually eliminated by good hand hygiene and use of alcohol-based agents.

In some hospital sites with ongoing issues with extended-spectrum β-lactamase, *K. pneumoniae* carbapenemase, or New Delhi metallo-β-lactamase–producing organisms, more than 30% of patients have gastrointestinal tract colonization with these organisms at any one time. These colonized patients should be placed in contact precautions. An isolation strategy of careful contact precautions in a multibed room can be as effective as contact precautions in a single-bed room.[A7] Adherence with contact isolation precautions and hand hygiene must be high to maximize the effectiveness of these interventions.

Antimicrobial exposure is known to be a risk factor for multidrug-resistant organisms because it eliminates susceptible flora, thereby selecting for resistant bacteria. A variety of interventions have tried to reduce the use of specific broad-spectrum antibiotics with variable success. Prudent use of all antibiotic classes with an emphasis on reducing duration of antibiotic use may be more useful than restrictions on individual classes of antibiotics.

PROGNOSIS

Many Enterobacterales tend to infect patients who have other comorbid conditions or who are immunosuppressed, so infected patients often have an inherently poor prognosis, which makes treatment of any infection more challenging. The prognosis of infection with the Enterobacterales depends on multiple factors, such as site of infection, presence of underlying diseases, control of the infection source, and access to needed newer antimicrobial agents. At one extreme, inadequate orally administered antibiotic therapy for uncomplicated urinary tract infections due to an extended-spectrum β-lactamase producer may have no impact on mortality, although it may have an impact on duration of symptoms and need for parenteral therapy for treatment failure. Mortality can be as high as 50% among hospitalized patients who develop blood stream infections with carbapenem-resistant Enterobacterales. At the other extreme, patients in an intensive care unit with serious infections due to KPC or NDM producers may have an in-hospital mortality rate exceeding 70%. By comparison, in-hospital mortality rates are 20 to 30% in similar patients who are not infected with *K. pneumoniae* carbapenemase or New Delhi metallo-β-lactamase producing bacteria.

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For the General References and other additional features, please visit Elsevier eBooks+ at https://ebooks.health.elsevier.com.

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282 *PSEUDOMONAS* AND *BURKHOLDERIA* INFECTIONS

MATTHEW E. FALAGAS AND PETROS I. RAFAILIDIS

PSEUDOMONAS INFECTION

DEFINITION

Infections due to *Pseudomonas* spp are caused by members of the family Pseudomonadaceae. The Pseudomonadaceae is a group of gram-negative rods, including *P. aeruginosa*, the most frequently recovered human pathogen in the family. Other *Pseudomonas* spp include *P. putida, P. alcaligenes, P. fluorescens, P. luteola, P. mendocina, P. oryzihabitans, P. pseudoalcaligenes, P. stutzeri, P. chlororaphis, P. delafieldii, P. kingii, P. pertucinogena*, and *Pseudomonas* CDC group 1.

The Pathogens

P. aeruginosa is a gram-negative, lactose nonfermenting, straight or slightly curved rod with a length ranging from 1.5 to 7 μm and a width of 0.5 to 1.0 μm. It is catalase positive, oxidase positive, and motile with one or more polar flagella. Most species oxidize glucose and reduce nitrate to nitrite or nitrogen gas. It has the ability to grow at 42° C. This pathogen contains a polysaccharide capsule along with lipopolysaccharides, pili, and flagella. The organism includes toxins such as exotoxin A, pyocyanin (blue or blue-green pigment), pyorubin (red or red-brown pigment), pyomelanin (black pigment), and pyoverdin (yellow-green pigment). *P. aeruginosa* is notorious for its ability to acquire resistance genes and to spread by horizontal transfer. The microorganism possesses a diversity of mechanisms that promote its survival, adaptation, and resistance to multiple classes of antibiotics that make it an emerging worldwide public health threat.

EPIDEMIOLOGY

P. aeruginosa is one of the most common pathogens in health care–associated infections.[1] The main types of infections associated with *P. aeruginosa* in hospital settings are ventilator-associated pneumonia, primary bacteremia associated with central venous catheters, and secondary bacteremias due to infections elsewhere in the body, urinary tract infections, and surgical site infections. Data from the National Healthcare Safety Network at the Centers for Disease Control and Prevention indicate that *P. aeruginosa* is responsible for about 8% of all health care–associated infections in the United States and is the fourth most frequent infectious agent. *P. aeruginosa* can survive in environments that have only minimal nutritional components, and it can colonize moist surfaces of the axilla, ear, and perineum. It is also isolated from other moist, inanimate environments in hospitals, including water in sinks and drains, mechanical ventilation equipment, dialysis equipment, toilets, showers, hydrotherapy pools, mops, water for flowers, and sometimes cleaning solutions.

Strains of *P. aeruginosa* resistant to multiple classes of antibiotics, including quinolones and β-lactams, are a major cause of morbidity and mortality worldwide. During a relatively short time, a multidrug-resistant *P. aeruginosa* strain can spread through neighboring countries. The use of broad-spectrum antibiotics is certainly a risk factor for the development of multidrug-resistant *P. aeruginosa*, as are deficiencies in infection control practices.

A range of hosts are particularly prone to infections by this pathogen: patients with neutropenia (Chapter 153), burns (Chapter 97), cystic fibrosis (Chapter 77), chronic obstructive pulmonary disease (COPD; Chapter 76), cancer, transplant recipients, diabetes (Chapter 210), and AIDS (Chapter 358). Patients with compromised humoral (hypogammaglobulinemia) or cellular (steroid treatment) immunity, due to a disease or its treatment, as well as patients with foreign bodies (e.g., vascular grafts, orthopedic implants) are also more vulnerable to *P. aeruginosa* infections.

Community-acquired *P. aeruginosa* infection is related to exposure to water by the use of hot tubs, whirlpools, swimming pools, spas, and other types of baths, as well as to the use of contact lenses, particularly the extended-wear variety. Puncture wounds, including through tennis shoes, can give rise to *P. aeruginosa* infection. *P. aeruginosa* endophthalmitis (Chapter 391) after eye trauma can result in visual compromise, and *P. aeruginosa* endocarditis (Chapter 61) is frequently found in intravenous injection drug users.

PATHOBIOLOGY

Pathogenesis and Pathophysiology

Innate immunity, primarily through inflammatory cytokine production and phagocytic clearance by neutrophils and macrophages, is the key to endogenous control of *P. aeruginosa* infection.[2] *P. aeruginosa* binds to the cystic fibrosis transmembrane conductance regulator (CFTR), which is a channel involved in chloride movement across the cell. Release of interleukin-1 and signaling through the interleukin-1 receptor and adaptor molecule MyD88 occur. NF-κB is translocated, followed by transcription of NF-κB–dependent genes and the production of interleukin-6, interleukin-8, and intercellular adhesion molecule 1. Polymorphonuclear neutrophils are recruited to infected tissue to resolve the infection. Patients with cystic fibrosis have a defective CFTR and thus cannot mount a normal defensive response to *P. aeruginosa*.

Bacterial Factors

P. aeruginosa survives in aquatic as well as in soil environments. Several factors, including flagella, pili, exopolysaccharides, phospholipases, proteases, endotoxins, secreted toxins (types I, II, II, IV, and VI), exotoxins, and iron-binding proteins, are involved in pathogenesis (E-Table 282-1). *Pseudomonas* produces high levels of an extracellular mucoid polysaccharide called alginate, which is the main constituent of the glycocalyx allowing growth in a biofilm. Furthermore, the expression of O side chains on the bacterium's lipopolysaccharide prevents lysis by complement. Bacterial toxins and enzymes kill immune cells and invade and degrade tissues . Exotoxin A, an adenosine diphosphate–ribosylating toxin, has activity similar to that of diphtheria. The production of this cellular toxin is affected by iron levels. *P. aeruginosa* uses pyoverdin and pyochelin, typical siderophore systems, to acquire iron.

P. aeruginosa can induce hemolysis by PlcHR, a hemolytic phospholipase C. A nonhemolytic phospholipase C, PlcN, is also made by *P. aeruginosa* strains. *P. aeruginosa* type III secretion systems allow direct injection of bacterial toxins into eukaryotic cells and disrupt cellular trafficking by inhibiting the actin cytoskeleton and by affecting protein synthesis. *Pseudomonas* communicates with other members of its microbial community through quorum sensing, thereby leading to the formation of biofilms, which limit penetration of antibiotics and make it difficult to eradicate the organism. Pili and flagella, though not considered classical components of the biofilm, are important for its maturation. Furthermore, *P. aeruginosa* and *S. aureus* coinfect the lung and chronic wounds, where they form multispecies biofilms, in which *P. aeruginosa* can outcompete *S. aureus*.[3]

Both transferable (such as β-lactamase production) and intrinsic (mutation-driven) mechanisms confer *Pseudomonas* resistance to antibiotics, including carbapenems. Transferable resistance to aminoglycosides entails modification of aminoglycosides through phosphoryltransferases, acetyltransferases, nucleotidyltransferases, or ribosomal methyltransferases (RmtA, RmtB, RmtC, RmtD, and ArmA). Chromosomally mediated resistance is related to mutations in the quinolone resistance-determining region of gyrase A and the topoisomerase IV gene *parC*, which hamper the attack of fluoroquinolones on the bacterium. Aminoglycoside-inactivating enzymes are related to the *P. aeruginosa* chromosome and involve 3-*N*-aminoglycoside acetyltransferases or nucleotidyltransferases. Impermeability resistance to aminoglycosides is also chromosomally mediated.

Pathology

The pathologic spectrum of *P. aeruginosa* infections depends on the site afflicted. Hemorrhage and necrosis may be present in severe *Pseudomonas* infections, such as in pneumonia and endocarditis. In ecthyma gangrenosum, bacteria invade the arteries and veins of the skin, with little accompanying inflammation because of the paucity of pus in these skin lesions.

CLINICAL MANIFESTATIONS

Among the constellation of manifestations in the clinical spectrum of *P. aeruginosa* infections, no symptoms or signs effectively discriminate *P. aeruginosa* infection from infections by other pathogens. Even ecthyma gangrenosum can be caused by other bacteria, such as *Staphyloccocus aureus* (Chapter 267) or *Citrobacter freundii* (Chapter 281).

Febrile Neutropenia

P. aeruginosa is a key infectious agent of concern in patients who have febrile neutropenia (Chapters 153 and 260).[4] It is the organism against which empirical coverage must always be included. The classic clinical syndromes in febrile

ABSTRACT

Pseudomonas aeruginosa is one of the most common pathogens among health care–associated infections. A wide spectrum of clinical manifestations ranges from eye, ear, urinary tract, and soft tissue infections to joint, bone, central nervous system, respiratory tract, endovascular, and intra-abdominal infections to a cause of febrile neutropenia and septic shock. Strains resistant to multiple classes of antibiotics, including quinolones and β-lactams, are a major cause of morbidity and mortality worldwide. Management of infections caused by organisms at one time classified as Pseudomonads, including melioidosis caused by what is now renamed *Stenotrophomonas maltophilia*, is also discussed in the text.

KEYWORDS

Pseudomonas
health care–associated infections
multidrug resistance
devices
febrile neutropenia
melioidosis
bacteremia

E-TABLE 282-1 VIRULENCE FACTORS FOR *PSEUDOMONAS AERUGINOSA*

LOCATION OR CLASS	EXAMPLES	ACTIVITY/EFFECTS ON HOST
Cell surface	Alginate	Antiphagocytic, resists opsonic killing
	Lipopolysaccharide	Endotoxic, antiphagocytic, avoids preformed antibody to previously encountered O antigens
	Pili (produced by type IV secretion)	Twitching motility, biofilm formation, adherence to host tissues
	Flagella	Motility, biofilm formation, adherence to host tissues and mucin components
	Injection of type III secretion factors	PcrG, PcrV, PcrH, PopB, and PopD proteins form injection bridge for type III effectors
Outer membrane	Siderophore receptors	Provides iron for microbial growth and survival
	Efflux pumps	Remove antibiotics
Secretion systems		
Type II	Elastase, lipase, phospholipases, chitin-binding protein, exotoxin A, and others	Variety of proteolytic, lipolytic, and toxic factors; degrade host immune effectors
Type III	ExoS, ExoT, ExoU, ExoY	Intoxicates cells (ExoS, ExoT); cytotoxic (ExoU); disrupts actin cytoskeleton
Type VI	Cytoplasmic and membrane-associated proteins, ATPases, lipoproteins, Hcp1 protein	Poorly characterized but found in animal studies to be needed for optimal virulence, particularly in chronic infection
Iron acquisition	Pyoverdin, pyochelin	Scavenge iron from the host for bacterial use
Secreted toxins	Hemolysins, rhamnolipid phospholipases	Kill leukocytes, hemolysis of red cells, degrade host cell surface glycolipids
Secreted oxidative factors	Pyocyanin, ferripyochelin	Produce reactive oxygen species: H_2O_2, O_2^- Inflammatory, disrupts epithelial cell function
Quorum sensing	LasR/LasI, RhlR/RhlI, PQS	Biofilm formation, regulation of virulence factor secretion

ATPases = adenosine triphosphatases; PQS = *Pseudomonas* quinolone signal.

neutropenic patients are bacteremia, pneumonia, and soft tissue infection, mainly manifested as ecthyma gangrenosum (Fig. 260-5).

Bacteremia

Bacteremia is usually caused by primary infection at a specific site, such as pneumonia, urinary tract infection, complicated intra-abdominal tract infection (peritonitis, abscess), or endocarditis. Manifestations can include those of sepsis and septic shock (i.e., fever, tachycardia, tachypnea, hypotension, and mental status changes ranging from confusion to coma; Chapter 94).[5] Multiorgan failure with adult respiratory distress syndrome (Chapter 90) and acute renal failure (Chapter 106) may occur and be accompanied by coagulation defects (e.g., disseminated intravascular coagulation; Chapter 161).

Eye Infections

Keratitis (Chapter 391) is associated with wearing contact lenses, especially extended-wear lenses, but any form of trauma, including surgery and burns, may predispose to keratitis by direct inoculation of *Pseudomonas*.[6] Pain and redness are cardinal manifestations, the entire cornea can be opacified, and perforation sometimes occurs. *P. aeruginosa* keratitis is a medical emergency because of the speed with which it can progress and lead to loss of vision.

Fulminant endophthalmitis (Chapter 391) may result from penetrating injuries, surgery, perforation of a corneal ulcer, or seeding from bacteremia. Manifestations include severe pain, chemosis, decreased visual acuity or even loss of vision, anterior uveitis, and vitreous involvement.

Other rarer eye infections include blepharoconjunctivitis, corneal ulcer, scleritis, and canaliculitis (both primary and plug-related). *P. aeruginosa* bacteremia also may lead to orbital cellulitis and gangrenous necrosis of the eyelids in neutropenic patients.

Ear Infections

Acute otitis externa (Chapter 394) with otalgia, which is commonly seen in children, results from infection of moist, macerated skin of the external ear canal. The source of the organism is likely to be hot tubs or swimming pools (swimmer's ear), particularly if they are not sufficiently chlorinated.

In patients who have diabetes or chronic HIV infection, so-called malignant otitis externa can present with fever, drainage, nerve palsies, hoarseness, dysphagia, pain on traction of the pinna, facial paralysis, and altered mental status owing to infection at the junction of bone and cartilage in the meatus.[7]

Acute Respiratory Tract Infections

P. aeruginosa is a frequent cause of ventilator-associated pneumonia and hospital-associated pneumonia (Chapters 85 and 261), accounting for about perhaps 20% of cases.[8] Clinical manifestations may include fever, productive cough, crackles, rhonchi, central cyanosis, tachypnea, use of accessory respiratory muscles, signs of septic shock, and multiorgan failure.

Community-acquired *P. aeruginosa* pneumonia also occurs, particularly in patients who have underlying structural lung disease such as COPD (Chapter 76) or bronchiectasis (Chapter 78), are immunocompromised,[9] or who have been previously treated with antibiotics.

Chronic Respiratory Tract Infections

P. aeruginosa is responsible for chronic airway infections, mainly with cystic fibrosis[10,11] and COPD. *P. aeruginosa* also can cause a diffuse panbronchiolitis, mainly in Asian populations, manifested by persistent cough and exertional dyspnea; at least 50 to 100 mL/day of sputum; chronic paranasal sinusitis; coarse crackles; bilateral, diffuse, small nodular shadows on a plain chest radiograph or centrilobular micronodules on chest computed tomography; evidence of airway obstruction, hypoxemia, and an elevated cold hemagglutinin titer.

Bone and Joint Infections

P. aeruginosa is among the main causative pathogens of bone infections (Chapter 251) in patients who have indwelling devices or prostheses[12] and in intravenous drug users (Chapter 365), in whom vertebral osteomyelitis, sacroiliac septic arthritis, and septic arthritis of the sternoclavicular joint are seen, sometimes, but not always, with pain and positive blood cultures. In vertebral *P. aeruginosa* osteomyelitis, clinical manifestations are more indolent than in staphylococcal osteomyelitis and often range from weeks to months. The affected region may be tender with a decreased range of motion. Low-grade fever is common.

Pseudomonas osteomyelitis (Chapter 251) of the foot most frequently follows puncture wounds through sneakers. The main manifestation is pain in the foot, sometimes with superficial cellulitis around the puncture wound and tenderness on deep palpation of the wound. Patients with Charcot arthropathy (neuropathic joint) and diabetes are especially at risk for *P. aeruginosa* bone infection.

Central Nervous System Infections

Involvement of the central nervous system is almost always secondary to a surgical procedure[13] or penetrating head trauma and is rare after bacteremia. The entities seen most often are postoperative or post-traumatic meningitis (Chapter 381), subdural empyema (Chapter 382), and epidural infections resulting from initial contamination of access areas. Brain abscess secondary to embolic disease from endocarditis may be seen. Extension of the infection in necrotizing malignant otitis to the brain heralds an ominous clinical course.

Urinary and Genital Tract Infections

P. aeruginosa urinary tract infections (cystitis, pyelonephritis, renal/perirenal abscess [Chapter 263]) usually occur as a complication of the presence of a foreign body, such as a catheter or stent in the urinary tract, an obstruction (mainly stone or malignant neoplasm) of the urinary system, or after instrumentation or surgery in the urinary tract. However, *P. aeruginosa* urinary tract infections can occur in any patient, often associated with bacteremia. Genital tract infections due to *P. aeruginosa* include epididymitis, orchitis, epididymo-orchitis (with or without abscess), and prostatitis (with or without abscess).

Skin and Soft Tissue Infections, Including Burns

P. aeruginosa causes a variety of skin manifestations, including ecthyma gangrenosum in neutropenic patients.[14] These small, round lesions can occur (see Fig. 260-5) either isolated or as aggregates, especially on the limbs and the perineum. The lesions evolve from vesicles to nodules that become hemorrhagic and necrotic, and eventually ulcerate. This evolution may lead to a spectacular increase in size from less than 1 to more than 10 cm in a period of less than 24 hours. However, ecthyma can also be caused by other gram-positive or gram-negative bacteria (*S. aureus, S. pyogenes, Aeromonas* spp, *Serratia* spp, *S. maltophilia*) or fungi (*Candida* spp, *Aspergillus* spp, *Mucor* spp, and *Fusarium* spp).

Maceration of normal skin, such as from soaking in a hot tub, can lead to superficial infection (Fig. 406-27) and then potentially to soft tissue infection and even hematogenous dissemination. Folliculitis and other papular or vesicular lesions have also been attributed to *P. aeruginosa*. Other types of skin and soft tissue involvement are cellulitis, abscesses, toe web infection (webspace intertrigo), paronychia usually in association with green nail syndrome, and myositis. Secondary infection of chronic skin ulcers can also occur.

Burn wound infections (Chapter 97) by *P. aeruginosa* constitute one of the most significant problems caused by this organism. A distinct clinical picture of sepsis, in which high colony counts of *P. aeruginosa* exceed 10^5 organisms per gram of tissue, is the defining feature. Patients generally exhibit the progressive formation of a black necrotic eschar, with or without bacteremia. Wound infection can also occur in pressure ulcers and at surgical sites.

Endovascular Infections

P. aeruginosa may cause endovascular infections, including infective endocarditis (Chapter 61) mainly of native valves but also of prosthetic ones. Mycotic aneurysms (Chapter 377) may occur in the setting of endocarditis. In intravenous drug users (Chapter 365), the source is generally contaminated material, needles, or other paraphernalia; in this population, *P. aeruginosa* may even lead to outbreaks of endocarditis. The manifestations of *P. aeruginosa* endocarditis resemble those of other forms of acute endocarditis, except that it appears to be more indolent than *S. aureus* endocarditis. *P. aeruginosa* may also lead to septic thrombophlebitis.

Intra-abdominal and Gastrointestinal Infections

P. aeruginosa can be involved in complicated intra-abdominal infections, usually as part of a polymicrobial infection. It is recovered in cases of secondary peritonitis, tertiary peritonitis, peritonitis associated with continuous ambulatory peritoneal dialysis (Chapter 117), spontaneous bacterial peritonitis (Chapter 139), and intra-abdominal abscesses. Gastrointestinal infections due to *P. aeruginosa* include necrotizing enterocolitis in children and typhlitis in neutropenic patients (neutropenic enterocolitis; Chapter 128).

Uncommon *P. aeruginosa* Infections

P. aeruginosa can cause toe web infections; paronychia, the "green nail syndrome" as a result of diffusion of pyocyanin into the nail bed; and *Pseudomonas* hot-foot syndrome, which is manifested with tender plantar nodules.

Infection Due to *Pseudomonas* spp Other than *P. aeruginosa*

P. fluorescens may lead to bacteremia associated with central venous catheters or transfusion-related bacteremia. Notably, a multistate outbreak occurred in the United States owing to contaminated heparinized saline flush. Reports of *P. stutzeri* infections include peritonitis, meningitis, endocarditis, pneumonia, bacteremia, and endophthalmitis. *P. putida* has been reported as a causative pathogen in bacteremia, pneumonia, cholecystitis, cholangitis, and skin and soft tissue infections.

DIAGNOSIS

Multiplex polymerase chain reaction (PCR) tests are especially valuable in intensive care unit settings, where rapid diagnosis is important.[15] PCR in this setting has a reported sensitivity of 96.5% and a specificity of 99.7%, and it can also provide information on antibiotic susceptibility.[16] However, the role of multiplex PCR is still evolving, so the definitive diagnosis of *P. aeruginosa* typically depends on the culture of the pathogen from various human biologic samples or fluids (blood, urine, sputum, bronchoalveolar lavage, pleural, cerebrospinal fluid, wound, burn, pus) pertinent to the clinical presentation. A Gram stain of the pertinent biologic sample can often provide interim clues while awaiting culture results. Computerized tomography of the brain, chest, abdomen, pelvis or magnetic resonance imaging of the brain, spine, or symptomatic bony area can document the presence of infection but cannot corroborate *P. aeruginosa* as the potential pathogen.

Three sets of blood cultures in the time span of 1 hour and expeditious use of echocardiography are recommended for the diagnosis of endocarditis. For ventilator-associated pneumonia, endotracheal aspiration with semi-quantitative cultures is preferred over invasive sampling (performing bronchoscopy for bronchoalveolar lavage or obtaining samples through a protected specimen brush or blind bronchial sampling).

In patients with *Pseudomonas* otitis, it is the only organism cultured in one third of patients but part of a polymicrobial infection in the others. In malignant otitis externa, culture specimens should be taken from the external auditory canal. Computed tomography or magnetic resonance imaging findings include temporomandibular joint destruction, infratemporal fossa or nasopharyngeal soft tissue involvement, and evidence of meningitis or empyema. In the setting of osteomyelitis, the acquisition of bone through fine-needle aspiration guided by CT or bone biopsy and culture through open biopsy may be necessary if blood cultures are sterile. The cerebrospinal fluid profile of *P. aeruginosa* meningitis is that of pyogenic meningitis. The differential diagnosis includes other bacterial and fungal pathogens that can lead to the same spectrum of diseases, especially in the hospital environment (Chapter 261). External otitis, infection after a nail injury, or infection after immersion in water can provide some important clues to suggest *P. aeruginosa*. Other clues can come from knowing that the patient has a high pretest probability of having a *P. aeruginosa* infection (e.g., neutropenic patients, patients with burns and wounds, cystic fibrosis patients, patients who have medically inserted equipment or foreign bodies).

At times, clinical acumen is needed to differentiate frank infection due to *P. aeruginosa* from colonization. Clues include local symptoms and signs (pain, erythema, necrosis, exudate, edema, loss of function, dysuria, productive cough) or systemic symptoms and signs (fever, hypotension, tachycardia, dyspnea, hypoxia, rash, organ failure, radiologic change of previous imaging) of infection.

TREATMENT

In neutropenic patients, the possibility of *P. aeruginosa* infection requires empirical therapy as would be used for *Pseudomonas* bacteremia. In other high probability settings (e.g., patients who have burns, cystic fibrosis, inserted foreign bodies, or classic eye, ear, or skin findings), antibiotic coverage for *Pseudomonas* is indicated until microbiologic data from either cultures or PCR tests exclude pseudomonas and establish an alternative cause. A de-escalation protocol can then be performed to narrow the antibiotic spectrum.

Treatment of *P. aeruginosa* Bacteremia

Antibiotic Options

For severe infections associated with respiratory failure (Chapter 90) and septic shock (Chapter 94), empiric combination therapy[17] for *P. aeruginosa* bacteremia should be started within 1 hour. Options include an antipseudomonal β-lactam plus either an aminoglycoside or a fluoroquinolone within 1 hour. Alternatives associated with less toxicity without compromising effectiveness are monotherapy with β-lactam/β-lactamase inhibitor (piperacillin-tazobactam) or an antipseudomonal carbapenem (meropenem or imipenem-cilastatin). However, combination therapy should not be routinely used for ongoing treatment of most other serious infections, including bacteremia and sepsis without shock or for neutropenic sepsis/bacteremia.[18]

Local in vitro antimicrobial susceptibility data regarding the level of resistance of local clinical isolates of *P. aeruginosa* to various antibiotics should guide the choice of this initial empiric therapy.[19] About 25% of *P. aeruginosa* strains causing bloodstream infections in hospitalized patients are resistant to fluoroquinolones, about 20% are resistant to carbapenems, and about 15% are resistant to piperacillin-tazobactam.[20] Depending on the antibiotic susceptibility of *P. aeruginosa* isolates routinely found in a specific setting, one of the following regimens would be appropriate for *P. aeruginosa* bacteremia, provided renal function as assessed by creatinine clearance is relatively normal (>50 to 60 mL/minute): intravenous (IV) piperacillin-tazobactam (3.375 to 4.5 g infused over 4 hours every 6 to 8 hours), ceftazidime (2 g every 8 hours), cefepime (2 g every 8 to 12 hours), meropenem (1 to 2 g infused over 3 hours every 8 hours), imipenem (0.5 to 1 g every 6 hours), doripenem (0.5 g [1-hour infusion] every 8 hours), or aztreonam (1.5 to 2 g every 6 to 8 hours, used mainly for patients with β-lactam allergy). The addition of an aminoglycoside to these regimens depends on the level of resistance to β-lactam antibiotics seen at any given institution. If administration of a second drug is indicated, amikacin (15 mg/kg every 24 hours) may be added to the β-lactam antibiotic therapy. Addition of ciprofloxacin (400 mg IV every 8 to 12 hours) instead of an aminoglycoside can also be considered. For bacteria that are resistant to all β-lactams (including carbapenems) and quinolones, either ceftazidime-avibactam (2.25 g every 8 hours administered over 3 hours) or imipenem-cilastatin-relebactam (1.25 g every 6 hours) is recommended.[21]

If the *Pseudomonas* is resistant to carbapenems, options include polymyxin B, fosfomycin, and several forms of colistin.[22] For polymyxin B, a loading dose of 20,000 to 25,000 IU/kg over 1 hour should be followed by 1.25 to 1.5 mg/kg (equivalent to 12,500 to 15,000 IU/kg) every 12 hours, infused over 1 hour. A parenteral formulation of fosfomycin sodium (8 g every 8 hours infused over 6 hours) also can be used, only in combination with other antibiotics with an antipseudomonal spectrum. The several forms of colistin require careful dosing under the guidance of an infectious diseases expert.

Current guidelines then advise de-escalation to the most appropriate single-agent therapy in response to the susceptibility profile or to clinical improvement or resolution of the infection after 3 to 5 days. The total duration of treatment of bacteremia is usually approximately 14 days in non-neutropenic patients. Eight to 10 days may be equally efficacious in uncomplicated bacteremia, but longer courses are appropriate for patients with undrainable foci of infection, endocarditis, osteomyelitis, abscesses of the brain or kidneys, immunologic deficiencies including neutropenia, or a slow clinical response. The duration of treatment for endocarditis should be 6 weeks, in addition to potential cardiothoracic surgery. In neutropenic patients, at least 14 days are necessary, and antibiotics should be continued until the absolute neutrophil count is equal to or greater than 500 cells/μL. Bacteremia in the neutropenic patient may necessitate prolonged treatment of 4 to 6 weeks of appropriate antibiotic treatment in the presence of endocarditis, deep-seated infection, septic thrombosis, or persistent bacteremia occurring more than 72 hours after removal of a catheter.[23]

Removal of an infected vascular catheter or another infected foreign device (urinary catheter, implant) is recommended to control device-related infection due to *P. aeruginosa*. Source control of an infection nidus (drainage of an abscess or empyema, excision of necrotic tissue) is also of paramount significance. If the source can be controlled, 7 to 10 days of antibiotic treatment is often adequate.

Treatment of Pulmonary Infection

Antibiotic Options

Patients with ventilator-associated pneumonia and health care–associated pneumonia due to *P. aeruginosa* may have isolates resistant to many antibiotics. Provided that renal and liver function is normal, empiric therapy can begin with double antipseudomonal coverage using (1) IV ceftazidime (2 g every 8 hours), cefepime (2 g every 8 to 12 hours), imipenem (500 mg every 6 hours or 1 g every 8 hours), meropenem (1 g every 8 hours), piperacillin-tazobactam (4.5 g every 6 hours) or aztreonam (2 g IV q 8 hours) plus a quinolone (levofloxacin 750 mg IV once daily or ciprofloxacin 400 mg IV every 8 hours) or an aminoglycoside (amikacin 15 to 20 mg/kg once daily, with a trough level of less than 4 to 5 μg/mL for amikacin, gentamicin 5 to 7 mg/kg IV every 24 h or tobramycin 5-7 mg/kg every 24 h) **or** a polymyxin. Dosing is based on colistin-based activity: 30 mg of colistin based activity (which corresponds to about 80 mg of the prodrug colistimethate) is 1 million international units. In the absence of other options, aztreonam is suggested as an adjunct to another β-lactam for the treatment of ventilator-associated pneumonia and for health care–associated pneumonia. Additional options include ceftazidime-avibactam (2 g of ceftazidime and 0.5 of avibactam infused over 2 hours when creatinine clearance is >50 mL/min, with modifications if it is lower); ceftolozane-tazobactam[A1] (3 g every 8 hours infused over 1 hour if the creatinine clearance is >50 mL/min, with modifications if it is lower); cefiderocol[A2] (2 g every 8 hours infused over 3 hours if the creatinine clearance is >60 mL/min, with modifications if it is lower); or imipenem-cilastatin-relebactam[A3] (500 mg + 500 mg + 250 mg every 6 hours infused over 30 minutes if clearance is 60 to 89 mL/min or higher and 0.75 g [imipenem 300 mg, cilastatin 300 mg, and relebactam 150 mg] if clearance is 30 to 59 mL/min, with modifications if it is lower). Doripenem is not recommended for pneumonia.

If patients with ventilator-associated pneumonia/health care-associated pneumonia due to *P. aeruginosa* are not in septic shock or at high risk for death and if the results of antibiotic susceptibility testing are known, current guidelines suggest switching to monotherapy. However, combination therapy should be continued for patients with shock or a high risk for death. A 7-day course of antibiotic therapy is the current recommendation for ventilator-associated and hospital-associated pneumonia, depending on the rate of improvement of clinical, radiologic, and laboratory parameters.

Cystic Fibrosis

Aminoglycosides are not optimally active in the lungs at concentrations used for intravenous administration, and oral ciprofloxacin (750 mg every 12 hours) is as good as intravenous therapy for patients with cystic fibrosis (Chapter 77).[A4] The administration of aerosolized aminoglycoside also may provide adequate drug levels in the tracheobronchial tree. Inhaled tobramycin (300 mg daily) and aztreonam lysine (75 mg three times daily for 28 days) are safe and efficacious for patients with cystic fibrosis.[A5] Inhaled colistin, which is also effective and safe in patients with cystic fibrosis, can be combined with an intravenous polymyxin (colistin or polymyxin B: see earlier) in patients without cystic fibrosis on a compassionate basis if the *P. aeruginosa* is susceptible only to polymyxins.

Endocarditis

Combination antibiotic therapy with an antipseudomonal β-lactam (antipseudomonal penicillin or cephalosporin or carbapenem [meropenem or imipenem]) and either an aminoglycoside or antipseudomonal fluoroquinolone for 6 weeks is suggested for the treatment of endocarditis. Surgery is required in a significant number of patients with *P. aeruginosa* left-sided endocarditis but hopefully can be avoided in right-sided endocarditis because the background of intravenous drug use will expose the patient to the subsequent risk of prosthetic valve endocarditis.

Meningitis/Brain Infection

Standard therapy to treat meningitis due to *P. aeruginosa* includes ceftazidime or cefepime. Alternative therapies are aztreonam, ciprofloxacin, and meropenem; the addition of aminoglycosides to these alternatives should be considered as well. The duration of treatment should be a total of 3 weeks or 2 weeks after the first sterile cerebrospinal fluid culture. Brain abscess and epidural and subdural empyema generally require surgical drainage in addition to antibiotics.

For shunt-related cerebrospinal fluid infections, removal of all components of the infected shunt plus appropriate antimicrobial therapy appears to be the most effective treatment. For patients with an infected shunt, the daily intraventricular dose is 1 to 8 mg for gentamicin, 5 to 20 mg for tobramycin, 5 to 50 mg (usually 30 mg) for amikacin, 5 mg for polymyxin B, and 10 mg for colistin. By comparison, the ventriculitis of the shunt infection appears to clear more rapidly with the drainage catheter still in place until the infection has cleared. Reshunting (placement of a new shunt) necessitates 10 to 14 days of sterile cerebrospinal fluid culture. Brain abscesses require an effort either to aspirate or drain them except if they are multiple, in difficult locations, of small size (less than 2.5 cm), or the patient has unacceptably high surgical risk. In addition, antibiotic treatment is needed for 6 weeks after adequate drainage and for 6 to 8 weeks if drainage is not performed.

Eye Infections

For keratitis, topical aminoglycosides or fluoroquinolones are recommended. If involvement is extensive, ceftazidime or gentamicin may be given by subconjunctival injection.

For endophthalmitis, therapy includes both systemic and intravitreal antibiotics. Ceftazidime has been the most frequently used antibiotic for this entity. Aminoglycosides are also injected subconjunctivally, by intraocular routes, and sometimes intravenously. Adjunctive surgery is generally performed to remove infected vitreous (vitrectomy).

Ear Infections

Acute otitis externa is treated with topical antibiotic agents (otic solutions), such as acetic acid (acetic acid 2% and acetic acid 2%/hydrocortisone 1%), aminoglycoside-containing otic solutions (neomycin plus polymyxin B and hydrocortisone), or quinolone-containing otic solutions (ciprofloxacin 0.2%/hydrocortisone 0.1%, ciprofloxacin 0.3%/dexamethasone 0.1% or ofloxacin 0.3%). Gentle removal of debris and cleaning with a mixture of acetic acid, alcohol, and distilled water may also help. The ear must be protected from scratching or mechanical injury. Chronically draining ears may require more intensive topical therapy.

Malignant external otitis requires débridement of the ear canal, including any necrotic tissue, cartilage, and adjacent bone. Antibiotic treatment with intravenous ciprofloxacin (usually 400 mg IV every 8 to 12 hours, but 750 mg orally every 12 hours if no cranial nerve involvement) or an antipseudomonal β-lactam (a cephalosporin such as ceftazidime or cefepime, carbapenem [meropenem or imipenem], or monobactam) dosed as for bacteremia is necessary for 6 to 8 weeks. Good glycemic control is very important for the resolution of the infection.

Urinary Tract Infection

The majority of *P. aeruginosa* urinary tract infections (Chapter 263) are complicated. Urinary catheters, stents, or stones should be removed if possible. In general, 7 to 10 days of antibiotic treatment will suffice, but up to 2 weeks is recommended for severe pyelonephritis. Abscesses (renal, perirenal) should be drained (especially if ≥3 cm), and a protracted course of antibiotics (4 to 6 weeks) should be administered. Quinolones (ciprofloxacin, 400 mg IV every 8 to 12 hours), levofloxacin (750 mg IV once daily), and aminoglycosides (e.g., amikacin at 15 mg/kg per 24 hours) have the pharmacodynamic advantage of excellent concentrations in the urinary tract. Antipseudomonal β-lactam/β-lactamase inhibitors (e.g., piperacillin-tazobactam 4.5 g every 8 hours) and carbapenems (e.g., doripenem at 500 mg IV [infusion over 1 hour] every 8 hours for 10 days) are equally acceptable, given their normally high levels of urinary excretion. Ceftazidime-avibactam 2 g of ceftazidime and 0.5 of avibactam, infused over 2 hours and administered every 8 hours, when creatinine clearance is >50 mL/min, with modifications if it is lower) and ceftolozane-tazobactam (1.5 g every 8 hours; half the dose suggested for pneumonia; infused over 1 hour if the creatinine clearance >50 mL/min, with modifications if it is lower) are other options. For difficult-to-treat *P. aeruginosa*, ceftazidime-avibactam,[A6] ceftolozane-tazobactam, imipenem-cilastatin-relebactam,[A7] and cefiderocol (as dosed for bacteremia) are first-line agents for cystitis, pyelonephritis, and complicated urinary tract infections. A single dose of aminoglycoside (e.g., amikacin 15 mg/kg every 24 hours) is also an option for cystitis. For pyelonephritis and complicated urinary tract infections, the alternative treatment suggested is once-daily aminoglycoside (e.g., amikacin 15 mg/kg every 24 hours).

Intra-abdominal Infections

For intra-abdominal infections, drainage of any abscess cavity is critical. Antibiotic options include the same treatments as for complicated urinary tract infections. For difficult-to-treat infections, ceftazidime-avibactam, ceftolozane-tazobactam,[A8] or imipenem-cilastatin-relebactam, in the same doses as noted earlier, are suggested as preferred treatment with cefiderocol as an alternative only if these antibiotics are not tolerated. For complicated intraabdominal infections, ceftazidime-avibactam (2.5 g every 8 hours) and ceftolozane-tazobactam (1.5 g every 8 hours) must be combined with metronidazole (loading dose 15 mg/kg infused over 1 hour, and maintenance dose 7.5 mg/kg infused over 1 hour every 6 hours) for anaerobic coverage. The duration of antibiotic treatment should be 7 to 10 days.

Skin Infections

Ecthyma gangrenosum is treated as for bacteremia. Burn wound infection requires extensive débridement of colonized eschar or necrotic tissue in addition to antibiotic treatment, which is as for bacteremia.

Hot tub folliculitis is usually self-limited; in difficult-to-resolve infections oral ciprofloxacin (500 mg twice daily for 7 days) is effective. For toe web infections, topical acetic acid (3 to 5%) compresses two to four times daily for 4 to 16 weeks is recommended. Concurrent treatment of tinea pedis (Chapter 405), if present, is necessary. If typical therapy fails, débridement of the onycholytic part of the nail and oral ciprofloxacin (500 mg twice daily for 7 days) are recommended. Topical polymyxins have also been used.

Bone Infection

Osteochondritis complicating puncture wounds of the foot requires intravenous antibiotics (cefepime, ceftazidime, or piperacillin-tazobactam) in the same doses as for bacteremia or oral ciprofloxacin (500 mg twice daily for 7 to 14 days) in addition to tissue biopsy and removal of necrotic cartilage.

Vertebral osteomyelitis requires surgical drainage in the presence of neurologic compromise, significant vertebral destruction with instability, a large epidural abscess, intractable back pain, or failure of medical treatment. Patients should receive a 6-week course of the following antibiotics: as first choice (adjusted for renal function) are cefepime (2 g IV every 8-12 hours) or meropenem (1 g IV every 8 hours) or doripenem (500 mg IV every 8 hours). Alternatives include ciprofloxacin (750 mg orally every 12 hours or 400 mg IV every 8 hours) or ceftazidime (2 g IV every 8 hours). For penicillin-allergic patients and quinolone-resistant strains, aztreonam (2 g IV every 8 hours) is suggested. Combination therapy with use of an antipseudomonal β-lactam plus ciprofloxacin or an antipseudomonal β-lactam plus an aminoglycoside can be considered when the disc space has been infected via hematogenous seeding.

For treatment of chronic osteomyelitis, oral ciprofloxacin (750 mg twice daily) for 6 to 12 weeks is acceptable as an alternative to parenteral treatment. Chronic osteomyelitis and sternoarticular osteomyelitis often require débridement of necrotic bone tissue. For prosthetic joint infection, removal of the prosthesis (two-stage exchange usually in the United States, but one-stage exchange has also been used) is usually required.

PREVENTION

Primary prevention includes preventing pollution of water by *Pseudomonas* in both the public and the hospital environments. Since outbreaks have been linked to whirlpools, swimming pools, and spas, proper antibacterial treatment of water is essential. Contamination of various equipment and devices (i.e., breast implants, ocular implants, and sinus irrigation devices) must be avoided. Handwashing is critical. Hospital point-of-use water filtration can be helpful. Barrier nursing practices may decrease horizontal transmission, especially in

the critical care environment. Isolation of patients infected with extensively drug-resistant and pandrug-resistant *P. aeruginosa* and strict infection control measures (dedicated personnel and equipment, use of gowns and gloves) may be needed to avoid intrahospital spread. Nevertheless, even antiseptic solutions may be contaminated by *P. aeruginosa*

PROGNOSIS

Even with treatment, mortality rates of 30% have been reported for *P. aeruginosa* bacteremia, pneumonia, bone infections, and CNS infections, with mortality rates twice as high when inappropriate antibiotics are used (usually for multidrug-resistant strains). Furthermore, *P. aeruginosa* infections are associated with increased length of hospitalization and medical costs. Loss of vision is the grave outcome of ophthalmic infection. Antibiotic resistance associated with *P. aeruginosa* will most likely continue to pose an enormous burden on human lives and financial resources in years to come.

Otitis externa usually resolves without sequelae, but it can cause drainage or progress to chronic suppurative otitis media, perichondritis, or acute mastoiditis.

BURKHOLDERIA INFECTIONS

Gram-negative bacillary members of the genus *Burkholderia* include *B. pseudomallei*, *B. mallei*, and *B. cepacia* complex (*B. cepacia* complex). *B. cepacia* and *B. pseudomallei* are motile, gram-negative, lactose nonfermenting bacteria, whereas *B. mallei* is nonmotile.

MELIODOSIS (*BURKHOLDERIA PSEUDOMALLEI*)

Melioidosis, which is an infection due to *Burkholderia pseudomallei*, occurs mainly in Southeast Asia and Australia,[24] (where its incidence is about 50/100,000 population), as well as in the Indian subcontinent and Sri Lanka. However, it also has been reported in Mexico, the northern part of South America, and Madagascar. More than three quarters of cases occur during the local rainy season. The portal of entry includes the respiratory system, the skin, and the gastrointestinal system, with intense inflammation with abscess formation and necrosis in the affected organs, such as the skin, liver, spleen, or lungs. Infection can also afflict immunocompetent travelers to the regions mentioned. Risk factors for acquisition of melioidosis include renal failure, diabetes mellitus, heavy alcohol consumption, chronic respiratory disease, thalassemia, glucocorticoid therapy, and cancer.

Clinical manifestations vary from asymptomatic infection to localized skin infection, pneumonia, and fulminant sepsis due to bacteremia.[25] The formation of abscesses is a usual feature of the disease. Other manifestations include septic arthritis, osteomyelitis, prostatitis, neurologic manifestations (e.g., brain stem encephalitis associated with cranial nerve palsies or myelitis with peripheral motor weakness), and kidney and spleen involvement. Suppurative parotitis, bilateral in 10% of cases, is seen in Thailand and Cambodia. The bacterium may remain dormant and then reactivate in approximately 75% of cases.

Culture remains the cornerstone of diagnosis. Serology and PCR have high specificities, but their current sensitivities are below 80%.[26]

TREATMENT

Bacteremia requires 10 to 14 days of intravenous ceftazidime (2 g every 8 hours), meropenem (1 g every 8 hours), or imipenem (1 g every 6 hours).[27] A switch from ceftazidime to meropenem is warranted if the patient develops organ failure or a new focus of infection, or if blood cultures remain positive after 1 week of treatment. In cases of ongoing septic shock, deep-seated or organ abscesses, extensive pulmonary disease, osteomyelitis, septic arthritis, or melioidosis with neurologic manifestations, parenteral treatment often must be continued for 4 or more weeks. After initial intravenous antibiotics, a 12-week course of oral eradication with trimethoprim/sulfamethoxazole (320 mg/1600 mg twice daily for patients weighing over 60 kg; 240 mg/1200 mg twice daily for patients weighing 40 to 60 kg) is required.[A9] Alternatives in the case of allergy or adverse events are amoxicillin-clavulanate (three 500/125-mg tablets three times daily for patients weighing 60 kg or more; two 500/125-mg tablets three times daily for patients weighing less than 60 kg)

B. pseudomallei is a bioterrorism factor B (Chapter 19), so appropriate infection control and notification of authorities are mandatory. Postexposure prophylaxis may be necessary for 3 weeks with trimethoprim/sulfamethoxazole or amoxicillin/clavulanate in the same doses as for oral eradication treatment.

GLANDERS (*BURKHOLDERIA MALLEI*)

Glanders is an equine infection due to *B. mallei*. Humans acquire the disease from contact with horses or, more rarely, donkeys or mules in an occupational setting. The disease has been eradicated in many countries, but cases can occur, especially in association with an occupational risk in veterinarians, veterinary students, farriers (hoof care workers), flayers (hide workers), transport workers, soldiers, slaughterhouse personnel, farmers, and horse fanciers. *B. mallei* remains a significant cause of zoonosis and is also a significant class B bioterrorism agent (Chapter 19).

The clinical manifestations are primarily tracheobronchitis, pneumonia, skin lesions, or lymphadenopathy.

DIAGNOSIS

Identification of the pathogen is based on culture of relevant biologic fluids. As an adjunct, PCR testing may be helpful.

TREATMENT

The approach to treatment is similar to melioidosis, with intravenous meropenem, imipenem, or ceftazidime initially and then oral trimethoprim-sulfamethoxazole for 3 to 12 months.

BURKHOLDERIA CEPACIA

B. cepacia is a plant and human pathogen. *B. cepacia* belongs to the *B. cepacia* complex, which includes also *B. ambifaria, B. anthina, B. arboris, B. cenocepacia, B. contaminans, B. diffusa, B. dolosa, B. latens, B. lata, B. metallica, B. multivorans, B. pseudomultivorans, B. pyrrocinia, B. seminalis, B. stabilis, B. stagnalis, B. territorii, B. ubonensis*, and *B. vietnamiensis*. *B. cenocepacia*, *B. multivorans*, and *B. cepacia* are the predominant species of the *B. cepacia* complex that infect mainly patients with cystic fibrosis (Chapter 77), chronic granulomatous disease (Chapter 153), sickle cell disease (Chapter 149), burns (Chapter 97), bronchiectasis (Chapter 78), or malignancy. However, *B. cenocepacia*, *B. multivorans*, and *B. cepacia* infections (and of other *B. cepacia* complex species) can infect hospitalized patients with central venous catheters, manipulation of the urogenital tract (catheterization, instrument insertion, and biopsy), burns, and wounds (surgical and other). In the hospital environment, outbreaks have been linked to aerosolized medications, chlorhexidine solutions, napkins, and prefabricated clothes.[28] Horizontal patient-to-patient transmission also occurs, with significant morbidity and mortality.

B. cepacia complex is implicated in infections of the lung, blood, and other sites in immunocompromised patients and even in immunocompetent patients. Patients with cystic fibrosis typically present initially with asymptomatic carriage but can develop pneumonia associated with a progressive decline of lung function. The most dramatic presentation is the cepacia syndrome, which is a fulminant necrotizing pneumonia often accompanied by bacteremia. Other manifestations include meningitis, endophthalmitis, pericarditis, endocarditis, burn wound infection, cholangitis, peritonitis, abscesses in the abdomen, perineum, or scrotum, and post-lung transplant pneumonia. Diagnosis is based on culture of relevant biologic fluids. PCR testing may also aid to expedite diagnosis.

TREATMENT

Trimethoprim-sulfamethoxazole (10 to 15 mg/kg/day based on trimethoprim component) is the first-line treatment, but some isolates are resistant to it. Other first-line options are meropenem (1 to 2 g every 8 hours) or ceftazidime (2 g every 8 hours). Minocycline (100 mg IV every 12 hours) is a second-line option. Ciprofloxacin, ticarcillin/clavulanate, and piperacillin/tazobactam can be used depending on sensitivity testing. In critically ill patients, especially with resistant species, combination antibiotic treatment may be required.

PROGNOSIS

Melioidosis is associated with a 14% mortality rate in Australia and up to 40% in Southeast Asia. Glanders is rare in humans, but mortality even with treatment is about 40 to 50%. *B. cepacia* has a predilection for patients with cystic fibrosis and often signals impaired overall prognosis in these patients. In patients who present with the cepacia syndrome, survival is unusual. Furthermore, *B. cepacia* adversely affects transplantation, and many transplant centers will not undertake transplantation when *B. cepacia* is present because of the grave prognosis associated with the infection in the post-transplantation period.

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For the General References and other additional features, please visit Elsevier eBooks+ at https://ebooks.health.elsevier.com.

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283

DISEASES CAUSED BY *ACINETOBACTER* AND *STENOTROPHOMONAS* SPECIES

KEITH S. KAYE AND ROBERT A. BONOMO

ACINETOBACTER SPP

DEFINITION

The Pathogen

Acinetobacter spp are gram-negative, aerobic, coccobacillary bacteria, which are generally non–lactose-fermenting, nonfastidious, catalase positive, oxidase negative, and nonmotile, though their description of being "nonmotile" is questioned. The Gram stain appearance of *Acinetobacter* spp is highly dependent on the life cycle. In the early growth phases, *Acinetobacter* spp appear rod shaped. In the stationary phase, they acquire a coccobacillary morphology. *A. baumannii* and other members of the *A. calcoaceticus-baumannii* (Acb) complex are the most common human pathogens[1] among the more than 70 validated *Acinetobacter* spp (see E-Table 283-1 for 30 representative species) and more than 20 species that are reported but unvalidated and unnamed.[2]

EPIDEMIOLOGY

Acinetobacter spp are present in food and water,[3] and they can colonize many body surfaces and cause infection in almost any organ system. In the United States, *Acinetobacter* species are a leading cause of ventilator-associated pneumonia. The majority of infections originally was observed only in critically ill, immunocompromised, or injured hosts in intensive care units (ICUs), but infections can occur in non-ICU patients and patients in long-term care settings.[4] *Acinetobacter* spp also can cause superinfections complicating the course of patients with severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2).[5] Since the coronavirus disease 2019 (COVID-19) pandemic, the U.S. Centers for Disease Control and Prevention (CDC) reported a 35% increase in hospital-based carbapenem-resistant *Acinetobacter* and a 78% increase in hospital-onset cases.[6]

For example, in tropical regions of China, Asia, Australia, and the South Pacific, *Acinetobacter* spp can account for more than 15% of cases of community-acquired pneumonia. The common comorbid conditions predisposing to community-acquired pneumonia due to *Acinetobacter* spp are mainly chronic obstructive pulmonary disease (Chapter 76), renal disease (Chapter 116), diabetes mellitus (Chapter 210), and alcohol use disorder. In Saudi Arabia, *Acinetobacter* is one of the most common pathogens associated with late-onset and recurrent ventilator-associated pneumonia.

Outbreaks of *A. baumannii* skin infections were common among U.S. military personnel in Iraq and Afghanistan. *Acinetobacter* infection also has become increasingly common among patients in burn units (Chapter 97), sometimes resulting in unit-wide outbreaks. The frequency of *Acinetobacter* infections is often greater in the summer than in other seasons.

PATHOBIOLOGY

Acinetobacter spp colonize the oropharynx and tracheostomy tubes in patients on ventilators, so it is not surprising that the upper respiratory tract is the most common site for infection. The main factors associated with health care–associated pneumonia due to *Acinetobacter* spp are mechanical ventilation, previous antibiotic exposure, ICU stay, surgery, and underlying pulmonary disease. In hospital environments, *Acinetobacter* spp can withstand drying (desiccation) and may even be transmitted by aerosol/respiratory droplet. Among the resistance genes found in *Acinetobacter* spp are a large collection of genes encoding β-lactamases, aminoglycoside-modifying enzymes, and many efflux pumps.[7]

CLINICAL MANIFESTATIONS

The most common infections are respiratory (pneumonia), blood stream (bacteremia), urinary tract, wound, skin and soft tissue, and burn infections; osteomyelitis secondary to trauma, and meningitis. *Acinetobacter* spp infections have few distinguishing features except, in some instances, skin manifestations.

Pneumonia

The two distinct syndromes associated with respiratory tract infection due to *Acinetobacter* are community-acquired pneumonia and health care–associated pneumonia (Chapter 85). Community-acquired pneumonia due to *Acinetobacter* species is associated with a high incidence of bacteremia, acute respiratory distress syndrome (Chapter 90), sepsis, and death, with mortality rates sometimes exceeding 50%. Rarely, community-acquired pneumonia due to *Acinetobacter* species can be manifested with consolidation and multiple lung abscesses.

More frequently, *Acinetobacter* spp are a cause of pneumonia in patients who have risk factors for antimicrobial resistant organisms, often manifested as ventilator-associated pneumonia (Chapter 85). Health care–associated pneumonia due to *Acinetobacter* largely resembles the clinical spectrum of gram-negative pneumonias (bilateral infiltrates, pleural effusion, cavitations, hypoxemia, and bacteremia). Most cases are in patients on ventilators.

Bacteremia

Blood stream infection due to *Acinetobacter* spp is often a consequence of infection of intravenous catheters (i.e., central line–associated blood stream infection) or is secondary to health care–associated pneumonia. Less commonly, wound infections can cause bacteremia. Infective endocarditis (Chapter 61) is uncommon, with about 40% of cases involving a prosthetic valve.[8]

Urinary Tract Infection

Urinary tract infections are only rarely caused by *Acinetobacter* spp. An indwelling bladder catheter is the major risk factor.

Wound, Burn, and Skin and Soft Tissue Infections

Traumatic or postoperative wounds, burns (Chapter 97), and skin and soft tissue infections are among the most common sites of *Acinetobacter* infections. Prior antibiotic use or devitalized tissues are predisposing factors. The spectrum of infection can range from cellulitis to necrotizing fasciitis.

Necrotizing skin and soft tissue infections with *A. baumannii* occur in hosts with underlying comorbidities (e.g., trauma, cirrhosis), especially associated with the use of central venous catheters and parenteral nutrition, *Acinetobacter* spp–associated skin infections can be manifested with a peau d'orange appearance, with overlying tiny vesicles (Fig. 283-1), and, when untreated, can progress to necrotizing infection with bullae (hemorrhagic and nonhemorrhagic). Concomitant bacteremia is common.

Osteomyelitis

Osteomyelitis due to *Acinetobacter* spp occurs as a complication of open fractures or exposed bone. Gross findings include purulence, necrotic tissue, or

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283

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Osteomyelitis

Osteomyelitis due to *Acinetobacter* spp occurs as a complication of open fractures or exposed bone. Gross findings include purulence, necrotic tissue, or

ABSTRACT

Acinetobacter and *Stenotrophomonas* spp are most frequently recovered from hospitalized patients, especially in intensive care units. These pathogens most commonly cause respiratory tract infections. Recovery of these pathogens from the respiratory tract does not equal infection—colonization occurs, particularly among patients who are mechanically ventilated. Antimicrobial resistance is commonly detected among both pathogens. Infections due to *Acinetobacter* spp are often treated with either sulbactam (given as ampicillin-sulbactam in the United States) or a carbapenem (meropenem or imipenem). Extremely drug-resistant (XDR) strains can be treated with minocycline, tigecycline, cefiderocol, or polymyxins. Combination therapy is often reserved to treat XDR *Acinetobacter* spp strains. For infections due to *Stenotrophomonas* spp, trimethoprim-sulfamethoxazole is considered the treatment of choice. Infection prevention is important in curtailing spread of these pathogens.

KEYWORDS

Acinetobacter
Stenotrophomonas
antibiotic resistance
nosocomial
polymyxin
ventilator-associated pneumonia (VAP)

E TABLE 283-1 REPRESENTATIVE MEMBERS OF THE *ACINETOBACTER* GENUS*

SPECIES	FORMER NAMES & SYNONYMS	TYPE STRAIN	REFERENCES
Acinetobacter albensis	Novel	CCM 8611	doi: 10.1099/ijsem.0.000511
Acinetobacter apis	Novel	JCM 18575	doi: 10.1007/s12275-014-4078-0
Acinetobacter baumannii	*Acinetobacter* genomospecies 2	ATCC 19606	doi: 10.1099/ijsem.0.000932; doi: 10.1099/00207713-36-2-228
Acinetobacter baylyi	Novel	DSM 14961	doi: 10.1099/ijs.0.02486-0
Acinetobacter beijerinckii	Novel	DSM 22901	doi: 10.1099/ijs.0.001230-0
Acinetobacter bereziniae	*Acinetobacter* genomospecies 10	ATCC 17924	doi: 10.1099/ijsem.0.000932; doi: 10.1099/ijs.0.013656-0
Acinetobacter bohemicus	Novel; synonym: *Acinetobacter pakistanensis*	DSM 102855	doi: 10.1016/j.syapm.2014.07.001; doi: 10.1099/ijsem.0.001530
Acinetobacter bouvetii	Novel	DSM 14964	doi: 10.1099/ijs.0.02486-0
Acinetobacter calcoaceticus	*Acinetobacter* genomospecies 1	ATCC 23055	doi: 10.1128/jb.95.5.1520-1541.1968; doi: 10.1099/ijsem.0.000932; doi: 10.1099/00207713-36-2-228
Acinetobacter colistiniresistens	*Acinetobacter* genomospecies 13BJ or 14TU	DSM 107593	doi: 10.1099/ijsem.0.000932; doi: 10.1016/0923-2508(89)90021-1; doi: 10.1099/ijsem.0.001903
Acinetobacter courvalinii	*Acinetobacter* genomospecies 14BJ	CIP 110480	doi: 10.1016/0923-2508(89)90021-1; doi: 10.1099/ijsem.0.000932
Acinetobacter disperses	*Acinetobacter* genomospecies 17	CIP 110500	doi: 10.1099/ijsem.0.000932
Acinetobacter genomospecies 15BJ	Novel	N/A	doi: 10.1016/0923-2508(89)90021-1
Acinetobacter genomospecies 16BJ	Novel	N/A	doi: 10.1016/0923-2508(89)90021-1
Acinetobacter genomospecies 6	Novel	N/A	doi: 10.1111/j.1699-0463.1989.tb00449.x
Acinetobacter gerneri	Novel	DSM 14967	doi: 10.1099/ijs.0.02486-0
Acinetobacter guillouiae	*Acinetobacter* genomospecies 11	ATCC 11171	doi: 10.1099/ijsem.0.000932; doi: 10.1099/ijs.0.013656-0
Acinetobacter haemolyticus	*Acinetobacter* genomospecies 4	ATCC 17906	doi: 10.1099/ijsem.0.000932; doi: 10.1099/00207713-36-2-228
Acinetobacter johnsonii	*Acinetobacter* genomospecies 7	ATCC 17909	doi: 10.1099/ijsem.0.000932; doi: 10.1099/00207713-36-2-228
Acinetobacter junii	*Acinetobacter* genomospecies 5; synonym: *Acinetobacter grimontii*	ATCC 17908	doi: 10.1099/ijsem.0.000932; doi: 10.1099/00207713-36-2-228; doi: 10.1099/ijs.0.65129-0
Acinetobacter lwoffii	*Acinetobacter* genomospecies 9	ATCC 15309	doi: 10.1099/ijsem.0.000932; doi: 10.1128/jb.95.5.1520-1541.1968; doi: 10.1099/00207713-36-2-228; doi: 10.1016/j.syapm.2018.10.004
Acinetobacter nosocomialis	*Acinetobacter* genomospecies 13TU	DSM 102856	doi: 10.1099/ijsem.0.000932; doi: 10.1016/j.resmic.2011.02.006
Acinetobacter parvus	Novel	DSM 16617	doi: 10.1099/ijs.0.02631-0
Acinetobacter pittii	*Acinetobacter* genomospecies 3	ATCC 19004	doi: 10.1099/ijsem.0.000932; doi: 10.1016/j.resmic.2011.02.006
Acinetobacter radioresistens	*Acinetobacter* genomospecies 12	ATCC 43998	doi: 10.1099/ijsem.0.000932; doi: 10.1111/j.1699-0463.1989.tb00449.x.
Acinetobacter schindleri	Novel	ATCC BAA-618	doi: 10.1099/00207713-51-5-1891
Acinetobacter seifertii	"close to 13TU"	DSM 102854	doi: 10.1099/ijs.0.000043
Acinetobacter tandoii	Novel	DSM 14970	doi: 10.1099/ijs.0.02486-0
Acinetobacter tjernbergiae	Novel	DSM 14971	doi: 10.1099/ijs.0.02486-0
Acinetobacter townerii	Novel	DSM 14962	doi: 10.1099/ijs.0.02486-0
Acinetobacter ursingii	Novel	ATCC BAA-617	doi: 10.1099/00207713-51-5-1891
Acinetobacter variabilis	*Acinetobacter* genomospecies 15TU	DSM 102977	doi: 10.1099/ijsem.0.000932; doi: 10.1099/ijs.0.000028
Acinetobacter venetianus	Novel	ATCC 31012	doi: 10.1016/S0923-2508(97)85244-8; doi: 10.1099/ijs.0.003541-0

*Genome species designations are added. Type strain accession numbers are provided for species validly published under the International Code of Nomenclature of Prokaryotes (ICNP), American Type Culture Collection (ATCC), Collection de l'Institut Pasteur (CIP), German Collection of Microorganisms and Cell Cultures (DSM), or Japan Collection of Microorganisms (JCM).
doi = digital object identifier.

FIGURE 283-1. Cellulitis caused by *Acinetobacter baumannii*. There is characteristic edematous peau d'orange erythema, with associated vesicles that may coalesce to form nonhemorrhagic bullae. (From Guerrero DM, Perez F, Conger NG, et al. *Acinetobacter baumannii*–associated skin and soft tissue infections: recognizing a broadening spectrum of disease. *Surg Infect [Larchmt]*. 2010;11:49-57.)

environmental contamination. Fever higher than 38° C and leukocyte count greater than 12,000/μL are common, and *Acinetobacter* spp can be identified from culture of deep wound tissue obtained intraoperatively.

Meningitis

Acinetobacter is a very uncommon cause of meningitis in the community. *Acinetobacter* is occasionally a cause of hospital-acquired meningitis, particularly among patients with meningitis associated with an indwelling intraventricular catheter in the postoperative neurosurgical setting.

DIAGNOSIS

The classification and identification of the more than 70 different species in the genus *Acinetobacter* remain problematic. Diagnosis is usually assigned by culture, but polymerase chain reaction (PCR) arrays are now available for rapid typing and antibiotic genotypic susceptibility of the most common species. However, automated and biochemical systems are sometimes inaccurate.

TREATMENT

The major challenge complicating nosocomial pneumonia due to *Acinetobacter* species is the frequent recovery of multidrug resistant (MDR) and sometimes extensively drug resistant (XDR) strains. For skin infections, multiple drug resistance and the presence of co-pathogens frequently complicate treatment.

Antimicrobial Therapy

An increasing number of strains of *Acinetobacter* species are multidrug-resistant (MDR) or extremely drug-resistant (XDR) strains that are resistant to three or more classes of antibiotics, and in some cases, all antibiotics,[9] are often responsible for outbreaks in large hospitals. The emergence of strains of *Acinetobacter* that are resistant to carbapenems,[10] sulbactam, colistin, and polymyxin B leaves few treatment options, many of which need to be adjusted based on the degree of renal insufficiency with the aid of expert consultation.

When it is "susceptible," *Acinetobacter* is usually treated with sulbactam (ampicillin-sulbactam 3 g IV every 4 to 6 hours) or a carbapenem such as imipenem (500 to 1000 mg IV every 6 hours) or meropenem (500 to 1000 mg IV every 8 hours). Some experts recommend higher doses of meropenem (1 g IV every 6 hours or 2 g IV every 8 hours) and ampicillin-sulbactam (3 g IV every 4 hours over 4 hours).[11] Treatment is usually for 7 to 10 days for complicated urinary tract infection, 7 to 14 days for pneumonia and skin and soft tissue infections, 7 to 14 days for bacteremia, 21 days for meningitis (and longer if cerebrospinal fluid cultures remain positive), and 4 to 6 weeks for osteomyelitis. Susceptibility to imipenem does not always translate to susceptibility to meropenem. Aminoglycosides (e.g., amikacin 15 to 20 mg/kg then dose by therapeutic drug monitoring) are an option for treatment of urinary tract infection and potentially for systemic infections. The presence of methyl transferases limits the use of aminoglycosides, including plazomicin.

Treatment of infection with XDR *Acinetobacter* requires expert consultation, and many experts recommend combination therapy.[12] Tigecycline (100 to 200 mg loading dose, then 50 to 100 mg IV every 12 hours) and minocycline (200 mg IV or PO initially, followed by 100 to 200 mg IV or PO every 12 hours for 7 to 10 days) have good in vitro activity against many strains of XDR *Acinetobacter*. These agents are appropriate for treatment of skin and soft tissue infections, but monotherapy usually should be avoided, and combination therapy with at least 2 active agents is preferred. For example, initial therapy for invasive infections such as bacteremia and pneumonia might also include combination therapy with tigecycline or minocycline until clinical improvement is noted, with therapy then switched to single agent to complete the course of treatment. Sometimes, there is no choice but to use tigecycline as it might be the only available agent with in vitro activity against infecting *Acinetobacter* strains. Eravacycline (1 mg/kg IV every 12 hours), which is a new synthetic fluorocycline, may also be useful against *Acinetobacter* spp.

Cefiderocol, (3-hour IV infusion of 2 g every 8 hours) has excellent in vitro activity against *Acinetobacter* spp.[13] It appears to be equivalent to meropenem for the treatment of gram-negative pneumonia[A1] but inferior to other regimens for the treatment of invasive *Acinetobacter* spp infections.[A2]

Invasive infections due to XDR strains, such as bacteremia, pneumonia, and deep wound infections, are often treated with a polymyxin antimicrobial, either colistin or polymyxin B for 7 to 10 days. For colistin, a loading dose of 300 mg should be administered, followed by maintenance dosing of 150 to 180 mg every 12 hours, with subsequent dose adjustments made according to renal function.[14] If polymyxin B is used, a loading dose of 2.5 mg/kg × 1 should be administered intravenously, followed by a dose of 2.5 to 3.0 mg/kg/day in divided doses every 12 hours infused over a period of 60 minutes.[15] The major adverse effect of polymyxin therapy is nephrotoxicity.

Clinicians often treat invasive infections due to XDR *Acinetobacter* with combination therapy, despite a lack of randomized trial data demonstrating its superiority. Agents often combined with sulbactam[16] or polymyxin include imipenem or meropenem, sulbactam (ampicillin-sulbactam), tigecycline or minocycline, and aminoglycosides. Cefiderocol is another agent to consider in combination therapy. In controlled trials, however, neither rifampin nor meropenem added measurable clinical benefit over colistin monotherapy for the treatment of serious infection due to MDR or XDR *Acinetobacter*.[A3,A4] The role of combination therapy in preventing the emergence of polymyxin resistance during therapy remains uncertain.

For *Acinetobacter* meningitis, treatment should be intravenous meropenem (2000 mg every 8 hours) plus the intraventricular/intrathecal administration of an aminoglycoside (gentamicin [4 mg once daily every 1 to 3 days] or amikacin [30 mg once daily], if required, depending on susceptibilities), until clinical and microbiologic improvement occurs. For cases of meningitis due to XDR *Acinetobacter,* intravenous colistin or polymyxin B should be supplemented with intraventricular or intrathecal colistin (10 mg/day), or polymyxin B (5 to 10 mg/day). Other options to consider include high dose ampicillin-sulbactam and cefiderocol.

Surgical Therapy

Necrotizing skin infections require surgical débridement. Bone infections frequently require multiple surgical débridements of necrotic bone.

PREVENTION

Infection prevention practices, including hand hygiene, use of contact precautions, maintenance of environmental cleanliness, and implementation of antimicrobial stewardship, can help prevent spread of *Acinetobacter* in the hospital (Chapter 261).[A5] Removal of indwelling devices from patients, including vascular catheters and endotracheal tubes, can help prevent colonization and infection with *Acinetobacter*. However, the benefit of universal gloves and gowns is small if at all. During outbreaks, cohorting of patients and use of dedicated staff to care for cohorted patients can be necessary to control spread.

PROGNOSIS

Invasive infection due to *Acinetobacter* has been associated with crude mortality rates in excess of 50%, increases in duration of ICU stay of 6 days, and increases in duration of total hospital stay of more than 14 days. Furthermore, data indicate that infection is a cause of, not a marker of, poorer prognosis. In most series, mortality associated with blood stream infection ranges from approximately 15% to greater than 50%. *Acinetobacter*

meningitis in the neurologic setting has a mortality exceeding 15 to 30%. Fatal *A. baumannii* infections in relatively immunocompetent patients appear to be related to clade B. With appropriate early empirical therapy, however, the mortality rate for community-acquired infection can be as low as 11%.[17]

In general, infections due to more resistant strains of *Acinetobacter* are associated with less favorable outcomes than are infections due to more susceptible strains. These worse outcomes are likely due in part to limited and suboptimal treatment options as well as delays in the time to implementation of effective antimicrobial therapy for patients with infections due to MDR and XDR *Acinetobacter* strains.[18]

STENOTROPHOMONAS MALTOPHILIA

DEFINITION

S. maltophilia has attracted significant attention because it is often multidrug resistant due to intrinsic and acquired factors. *S. maltophilia* infection contributes significantly to morbidity, but usually not mortality, in immunocompromised patients.

The Pathogen

S. maltophilia are gram-negative bacteria that need methionine for growth and, like *Pseudomonas aeruginosa* and *Acinetobacter* spp, are non–lactose fermenters. *S. maltophilia* possess flagella that are multitrichous (more than one flagellum arising from the pole) and are distinguished from *P. aeruginosa* as oxidase negative. Colonies of *S. maltophilia* may appear pale yellow or lavender-green on blood agar plates. The organism emits a mild ammonia-like odor that is used for preliminary identification.

EPIDEMIOLOGY

S. maltophilia is an opportunistic global pathogen of environmental, mainly plant-associated origin. *S. maltophilia* can colonize and form biofilms on inanimate surfaces in the hospital, including catheters, intravenous fluid, water supplies, and hospital equipment.[19] This pathogen may also survive in hospital-grade disinfectant. Other health care–associated sources of *S. maltophilia* include contaminated intravenous fluids, hospital water and ice supplies, nebulizers, dialysis machines, ventilator circuits, thermometers, blood gas analyzers, intra-abdominal balloon pumps, and central venous or arterial pressure monitors.

A number of risk factors are associated with infection by *S. maltophilia* (Table 283-1). Although *S. maltophilia* is regarded as primarily a nosocomial pathogen (it is the third most common nonfermenting gram-negative bacillus health care–associated pathogen), community-acquired infection can occur. *S. maltophilia* infection primarily affects immunocompromised patients, including patients with hematologic malignancies; patients who have undergone solid organ transplantation; patients who are mechanically ventilated; hemodialysis patients with intravascular catheters; combat trauma patients; and patients with cystic fibrosis (Chapter 77).

The respiratory tract is the most common site of isolation of *S. maltophilia* in the hospital. Surveillance programs report a rate of culture-positivity of *S. maltophilia* from hospitalized patients with pneumonia of more than 3% in the United States.

TABLE 283-1 RISK FACTORS FOR INFECTION BY *STENOTROPHOMONAS MALTOPHILIA*

Prolonged hospitalization or intensive care unit stay
Intravascular catheters
Indwelling devices
Mechanical ventilation or tracheostomy
Neutropenia or cytotoxic chemotherapy
Solid organ transplantation
Immunocompromised state
Mucositis
Malignant disease
Chronic lung disease (especially cystic fibrosis and chronic obstructive pulmonary disease)
Human immunodeficiency virus infection
Hemodialysis
Antibiotic exposure (especially to carbapenems, extended-spectrum cephalosporins, and fluoroquinolones)
Exposure to other patients with *S. maltophilia*

PATHOBIOLOGY

Isolates are generally genotypically and phenotypically diverse. However, there is phylogenetic clustering, and recent studies have demonstrated the predominance of strains belonging to the lineage Sm6 (former genomic group 6) causing human infections.[20] The association of Sm6 with antibiotic resistance and virulence genes points towards a potential adaptation of this lineage to human infection and enhanced virulence.

CLINICAL MANIFESTATIONS AND DIAGNOSIS

Respiratory Tract

S. maltophilia is frequently isolated from pulmonary aspirations in patients who are on mechanical ventilators, have tracheostomy tubes in place, or are receiving broad-spectrum antibiotics, including about 3% of patients who are hospitalized with pneumonia.[21] Nosocomial pneumonia due to *S. maltophilia* is often associated with significant underlying pulmonary disease, such as emphysema (Chapter 76), bronchiectasis (Chapter 78), cystic fibrosis (Chapter 77), lung transplantation, or endobronchial obstruction (Chapter 87). Among mechanically ventilated patients, it can be challenging to differentiate *S. maltophilia* colonization from infection.

Community-acquired pneumonia due to *S. maltophilia* has been reported but is very rare. In cystic fibrosis (Chapter 77), infection often occurs when patients develop resistance to antipseudomonal antibiotics.

Blood Stream Infection and Endocarditis

Bacteremia may be secondary to a respiratory, urinary, or gastrointestinal source but is most commonly due to infection of an indwelling intravascular device. In many cases, except for those involving intravenous catheters, the portal of entry is not apparent. Immunocompromised patients are at particularly high risk. Intravenous drug users are at especially high risk for contaminating prosthetic valves with S. *maltophilia*.

Other Sites of Infection

Although *S. maltophilia* is frequently recovered from urine specimens in patients with indwelling urinary catheters, the role of this organism as a pathogen in this setting is unclear. Central nervous system infections due to *S. maltophilia* are rare, and typically associated with central nervous system devices or antecedent neurosurgery.[22]

S. maltophilia can be isolated from postoperative wounds, but its role as a pathogen in this setting is unclear. In contrast, *S. maltophilia* can cause burn wound sepsis (Chapter 97), manifested as a syndrome very similar to ecthyma gangrenosum (Chapter 408) in immunocompromised oncology patients.

TREATMENT

S. maltophilia exhibits intrinsic resistance to many antibiotics,[23] including imipenem, piperacillin-tazobactam, ceftazidime, and aminoglycosides (Table 283-2). Various combination regimens for invasive *S. maltophilia* infections have been studied, but their efficacy in clinical settings remains unclear. Inhaled antibiotics are a therapeutic option for cystic fibrosis, but their clinical effectiveness remains unknown.

Trimethoprim-sulfamethoxazole (10 to 15 mg/kg/day IV, based on the trimethoprim component) is the drug of choice. Treatment duration is uncertain; it is usually 7 to 14 days but might be longer for deep-seated or endovascular infections. Resistance to trimethoprim-sulfamethoxazole has become more common, particularly in patients with cystic fibrosis (Chapter 77). In these cases, minocycline (200 mg followed by 100 to 200 mg every 12 hours, not to exceed 400 mg in 24 hours), some of the fluoroquinolones (particularly levofloxacin 750 mg every 24 hours and moxifloxacin 400 mg every 24 hours), and tigecycline (200 mg loading dose then 100 mg every 12 hours) may be useful agents. Cefiderocol (3-hour IV infusion of 2 g every 8 hours) has good in vitro activity and is a promising agent, but clinical experience is limited. Polymyxin-based regimens may serve as alternatives in the face of resistance to trimethoprim-sulfamethoxazole, but susceptibility should be confirmed prior to administration. Polymyxin B has greater in vitro activity than colistin (see earlier for details regarding polymyxin treatment). The addition of the β-lactam/β-lactamase inhibitor combination ceftazidime-avibactam to aztreonam can preserve aztreonam activity in the setting of β-lactamase production. For moderate to severe infections, some experts recommend combination therapy, such as trimethoprim-sulfamethoxazole plus minocycline.

For blood stream infections, removal of any infected device is an important component of management. In the case of endocarditis, favorable outcomes are reported with antimicrobial therapy, but surgery may also be required.

TABLE 283-2 MECHANISMS OF RESISTANCE IN *STENOTROPHOMONAS MALTOPHILIA*

DRUG	MECHANISM OF RESISTANCE
β-Lactams, including imipenem	L1 and L2 β-lactamases Outer membrane permeability/efflux
Aminoglycosides	Aminoglycoside-modifying enzymes, transport
Ceftazidime	Efflux pump SmeH

PROGNOSIS

Among patients with ventilator-associated pneumonia or bacteremia due to *S. maltophilia*, overall mortality rates are in the range of 60%, with an attributable mortality due to invasive *S. maltophilia* infection of 12 to 38%. Patients who receive early appropriate antibiotic therapy appear to do better. Bacteremia is associated with poor outcomes, particularly in patients with malignancy or severe immunocompromising conditions.

In patients with cystic fibrosis (Chapter 77), *S. maltophilia* infection is associated with increases in exacerbations, a decline in lung function, hospitalization, need for lung transplantation, and mortality. Whether *S. maltophilia* has a causative association with these poor outcomes or is merely a marker for severe underlying disease is less clear.[24]

PREVENTION

Standard infection control practices, including hand hygiene and thorough environmental cleaning, can help prevent spread of *Stenotrophomonas* in the hospital (Chapter 261). In outbreak settings, contact precautions and possibly cohorting of patients have been used to control spread.

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For the General References and other additional features, please visit Elsevier eBooks+ at https://ebooks.health.elsevier.com.

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284 *SALMONELLA* INFECTIONS (INCLUDING ENTERIC FEVER)

JOHN A. CRUMP

DEFINITION

Many of the more than 2500 serovars (also called serotypes) of *Salmonella enterica* subspecies *enterica* infect humans and cause a range of clinical conditions from asymptomatic intestinal carriage to intestinal infection to invasive disease with extraintestinal complications.[1] Each serovar designation follows the species name (e.g., *Salmonella enterica* subspecies *enterica* serovar Typhimurium) and is frequently abbreviated as simply *Salmonella* followed by the serovar name (e.g., *Salmonella* Typhimurium).

The Pathogen

Members of the order Enterobacterales (also see Chapter 281), salmonellae are gram-negative, non-spore-forming bacilli. They can be differentiated into more than 2500 serovars by their somatic (O) antigens, which are composed of lipopolysaccharides and are part of the cell wall, and by their flagellar (H) and capsular (Vi) antigens. *Salmonella* serogroups were traditionally designated by letters based on O antigens (e.g., A, B, C1, C2). The growing number of serogroups then made it necessary to move to a numeric designation (e.g., O:2, O:4, O:6,7, O:8). Some of the important serovars and their serogroups are Typhi (group O:9), Choleraesuis (group O:7), Typhimurium (group O:4), and Enteritidis (group O:9). *Salmonella* Enteritidis and Typhimurium are the most common nontyphoidal serovars that cause human disease. Today, serovar can be inferred by whole genome sequencing, and subdivision within serovars, useful for epidemiologic investigations, is usually achieved by molecular or genomic subtyping methods.

EPIDEMIOLOGY

Salmonella Typhi, *Salmonella* Paratyphi A, *Salmonella* Paratyphi B, *Salmonella* Paratyphi C, and *Salmonella* Sendai are either solely or almost exclusively pathogens of humans; they cause primarily enteric fever rather than diarrhea, and transmission is usually through water or food. As a result of modern sewage and water treatment facilities, as well as improved food safety practices, typhoid fever and paratyphoid fever have become rare in high-income countries, but they remain a problem in countries that lack adequate sanitation and a safe water supply. Fewer than 500 cases of typhoid fever are usually reported annually in the United States, and most of those infections were acquired abroad. In contrast, an estimated 10.9 million typhoid illnesses occurred globally in 2017 and caused more than 135,000 deaths.[2,3] Nontyphoidal *Salmonella* serovars are a leading cause of community-onset bloodstream infection in sub-Saharan Africa, where children younger than 3 years and HIV-infected adults carry most of the burden of invasive disease.

Other serovars of *Salmonella* (described here as nontyphoidal *Salmonella*) have reservoirs in warm-blooded animals and cause human illness after the consumption of contaminated meat or animal products, contamination of produce or water by animal feces or animal products, or exposure to animals and their environments. Some nontyphoidal *Salmonella* serovars appear frequently in particular animal species, and about 10% of *Salmonella* infections may be attributable to animal exposure, including small pet turtles. *Salmonella* Enteritidis has a reservoir in chickens, and infection is often linked to the consumption of undercooked eggs and poultry products or to exposure to live chicks. Such a relationship is less clear for some other nontyphoidal serovars (e.g., *Salmonella* Typhimurium). Foodborne nontyphoidal *Salmonella* is estimated to be associated with approximately 1 million domestically acquired illnesses and about 450 deaths annually in the United States, and it is the leading cause of foodborne outbreaks of enterocolitis in the European Union.[4] In the United States, a disproportionate number of infections occur in July through October, probably related to warm weather. *Salmonella* infections are most common among infants and children younger than 5 years of age. Worldwide, nontyphoidal *Salmonella* causes an estimated 150 million illnesses and 50,000 to 60,000 deaths per year, with about 50% of these estimated to be foodborne.

Salmonellae are transmitted by the ingestion of fecally contaminated food or water; contact with animals, their environments, and other fomites; and, rarely, close contact with infected persons (e.g., oral-anal intercourse). The ultimate sources of contamination are humans or animals that are acutely ill or are shedding the organism without symptoms.

Contaminated Animal Products

Nontyphoidal *Salmonella* infection in humans usually occurs from ingestion of contaminated animal food products, most often eggs, poultry, and meat. *Salmonella* Choleraesuis is associated with pig products, *Salmonella* Dublin with cattle and unpasteurized milk from cattle, and *Salmonella* Enteritidis with poultry and poultry products, including eggs. Fecal material on poultry and other animal carcasses can spread at slaughterhouses, such as when many poultry carcasses are placed in the same hot-water tank to remove feathers. *Salmonella* that is contaminating carcasses can multiply to high levels if meat or other animal products are not refrigerated. Human illness may result if such animal products are inadequately cooked or if utensils or other uncooked foods are cross-contaminated during preparation. A wide range of foods can be contaminated with animal or human feces, from production on the farm through consumption in the home. Reports of produce-associated *Salmonella* outbreaks, due to contamination by animal or human feces during production,

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TABLE 283-2 MECHANISMS OF RESISTANCE IN *STENOTROPHOMONAS MALTOPHILIA*

DRUG	MECHANISM OF RESISTANCE
β-Lactams, including imipenem	L1 and L2 β-lactamases Outer membrane permeability/efflux
Aminoglycosides	Aminoglycoside-modifying enzymes, transport
Ceftazidime	Efflux pump SmeH

PROGNOSIS

Among patients with ventilator-associated pneumonia or bacteremia due to *S. maltophilia*, overall mortality rates are in the range of 60%, with an attributable mortality due to invasive *S. maltophilia* infection of 12 to 38%. Patients who receive early appropriate antibiotic therapy appear to do better. Bacteremia is associated with poor outcomes, particularly in patients with malignancy or severe immunocompromising conditions.

In patients with cystic fibrosis (Chapter 77), *S. maltophilia* infection is associated with increases in exacerbations, a decline in lung function, hospitalization, need for lung transplantation, and mortality. Whether *S. maltophilia* has a causative association with these poor outcomes or is merely a marker for severe underlying disease is less clear.[24]

PREVENTION

Standard infection control practices, including hand hygiene and thorough environmental cleaning, can help prevent spread of *Stenotrophomonas* in the hospital (Chapter 261). In outbreak settings, contact precautions and possibly cohorting of patients have been used to control spread.

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For the General References and other additional features, please visit Elsevier eBooks+ at https://ebooks.health.elsevier.com.

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284 *SALMONELLA* INFECTIONS (INCLUDING ENTERIC FEVER)

JOHN A. CRUMP

DEFINITION

Many of the more than 2500 serovars (also called serotypes) of *Salmonella enterica* subspecies *enterica* infect humans and cause a range of clinical conditions from asymptomatic intestinal carriage to intestinal infection to invasive disease with extraintestinal complications.[1] Each serovar designation follows the species name (e.g., *Salmonella enterica* subspecies *enterica* serovar Typhimurium) and is frequently abbreviated as simply *Salmonella* followed by the serovar name (e.g., *Salmonella* Typhimurium).

The Pathogen

Members of the order Enterobacterales (also see Chapter 281), salmonellae are gram-negative, non-spore-forming bacilli. They can be differentiated into more than 2500 serovars by their somatic (O) antigens, which are composed of lipopolysaccharides and are part of the cell wall, and by their flagellar (H) and capsular (Vi) antigens. *Salmonella* serogroups were traditionally designated by letters based on O antigens (e.g., A, B, C1, C2). The growing number of serogroups then made it necessary to move to a numeric designation (e.g., O:2, O:4, O:6,7, O:8). Some of the important serovars and their serogroups are Typhi (group O:9), Choleraesuis (group O:7), Typhimurium (group O:4), and Enteritidis (group O:9). *Salmonella* Enteritidis and Typhimurium are the most common nontyphoidal serovars that cause human disease. Today, serovar can be inferred by whole genome sequencing, and subdivision within serovars, useful for epidemiologic investigations, is usually achieved by molecular or genomic subtyping methods.

EPIDEMIOLOGY

Salmonella Typhi, *Salmonella* Paratyphi A, *Salmonella* Paratyphi B, *Salmonella* Paratyphi C, and *Salmonella* Sendai are either solely or almost exclusively pathogens of humans; they cause primarily enteric fever rather than diarrhea, and transmission is usually through water or food. As a result of modern sewage and water treatment facilities, as well as improved food safety practices, typhoid fever and paratyphoid fever have become rare in high-income countries, but they remain a problem in countries that lack adequate sanitation and a safe water supply. Fewer than 500 cases of typhoid fever are usually reported annually in the United States, and most of those infections were acquired abroad. In contrast, an estimated 10.9 million typhoid illnesses occurred globally in 2017 and caused more than 135,000 deaths.[2,3] Nontyphoidal *Salmonella* serovars are a leading cause of community-onset bloodstream infection in sub-Saharan Africa, where children younger than 3 years and HIV-infected adults carry most of the burden of invasive disease.

Other serovars of *Salmonella* (described here as nontyphoidal *Salmonella*) have reservoirs in warm-blooded animals and cause human illness after the consumption of contaminated meat or animal products, contamination of produce or water by animal feces or animal products, or exposure to animals and their environments. Some nontyphoidal *Salmonella* serovars appear frequently in particular animal species, and about 10% of *Salmonella* infections may be attributable to animal exposure, including small pet turtles. *Salmonella* Enteritidis has a reservoir in chickens, and infection is often linked to the consumption of undercooked eggs and poultry products or to exposure to live chicks. Such a relationship is less clear for some other nontyphoidal serovars (e.g., *Salmonella* Typhimurium). Foodborne nontyphoidal *Salmonella* is estimated to be associated with approximately 1 million domestically acquired illnesses and about 450 deaths annually in the United States, and it is the leading cause of foodborne outbreaks of enterocolitis in the European Union.[4] In the United States, a disproportionate number of infections occur in July through October, probably related to warm weather. *Salmonella* infections are most common among infants and children younger than 5 years of age. Worldwide, nontyphoidal *Salmonella* causes an estimated 150 million illnesses and 50,000 to 60,000 deaths per year, with about 50% of these estimated to be foodborne.

Salmonellae are transmitted by the ingestion of fecally contaminated food or water; contact with animals, their environments, and other fomites; and, rarely, close contact with infected persons (e.g., oral-anal intercourse). The ultimate sources of contamination are humans or animals that are acutely ill or are shedding the organism without symptoms.

Contaminated Animal Products

Nontyphoidal *Salmonella* infection in humans usually occurs from ingestion of contaminated animal food products, most often eggs, poultry, and meat. *Salmonella* Choleraesuis is associated with pig products, *Salmonella* Dublin with cattle and unpasteurized milk from cattle, and *Salmonella* Enteritidis with poultry and poultry products, including eggs. Fecal material on poultry and other animal carcasses can spread at slaughterhouses, such as when many poultry carcasses are placed in the same hot-water tank to remove feathers. *Salmonella* that is contaminating carcasses can multiply to high levels if meat or other animal products are not refrigerated. Human illness may result if such animal products are inadequately cooked or if utensils or other uncooked foods are cross-contaminated during preparation. A wide range of foods can be contaminated with animal or human feces, from production on the farm through consumption in the home. Reports of produce-associated *Salmonella* outbreaks, due to contamination by animal or human feces during production,

ABSTRACT

Salmonella Typhi, *Salmonella* Paratyphi A, *Salmonella* Paratyphi B, *Salmonella* Paratyphi C, and *Salmonella* Sendai are either solely or almost exclusively pathogens of humans; they cause primarily enteric fever rather than diarrhea, and transmission is usually through water or food. Other serovars of *Salmonella*, described here as nontyphoidal *Salmonella*, have reservoirs in warm-blooded animals and cause human illness after the consumption of contaminated meat or animal products, contamination of produce or water by animal feces or animal products, or exposure to contaminated animals and their environments. Although diarrhea due to nontyphoidal *Salmonella* is usually managed symptomatically, enteric fever and invasive nontyphoidal *Salmonella* disease require timely and appropriate antimicrobials. However, antimicrobial resistance is a growing problem among *Salmonella*, and resistance to ampicillin, chloramphenicol, and trimethoprim-sulfamethoxazole is widespread. Resistance to azithromycin, fluroquinolones, and extended-spectrum cephalosporins is emerging. Vaccines are available to prevent typhoid fever, and prevention efforts for *Salmonella* infections focus on the provision of safe water and food.

KEYWORDS

serovar
enteric fever
bacteremia
diarrhea
paratyphoid fever
typhoid fever
Salmonella

are increasing. *Salmonella* outbreaks have occurred from contaminated cheese, ice cream, vegetables, fruit, juice, and alfalfa sprouts.

Contaminated Food and Water

Nontyphoidal *Salmonella* infections may be acquired after contamination of food or water with the feces of pet reptiles, turtles, chicks, ducks, birds, dogs, cats, and many other species. *Salmonella* infection can also be acquired by eating food or by drinking water contaminated by human fecal shedders who have not adequately washed their hands. Infection has been spread by the fecal-oral route among children, by contaminated enema and fiberoptic instruments, by diagnostic and therapeutic preparations made from animal or insect products (e.g., pancreatic extract, carmine dye), and from intentional or unintentional contamination of restaurant salad bars.

Contact with Animals and Their Environments

Both healthy and sick animals may harbor and shed *Salmonella*. Transmission of *Salmonella* from animals and their environment to humans occurs primarily by the fecal-oral route. Animal hides and saliva often harbor fecal organisms, and transmission can occur when persons pet, touch, feed, or are licked by animals. Transmission has also been associated with contaminated animal bedding, flooring, barriers, other environmental surfaces, and clothing and shoes. Contact with calves, turtles and other reptiles, rodents, and young poultry and their environments has been associated with *Salmonella* outbreaks.

Contact with Infected Persons

Close contact with persons shedding *Salmonella* is an occasional source of infection. Transmission has been documented among persons handling feces (e.g., parents changing the diapers of an infected infant) and is associated with certain sexual practices (e.g., oral-anal intercourse).

Antimicrobial Resistance

Salmonellae have become increasingly resistant to antimicrobial agents, often by acquiring resistance transfer factors (e.g., plasmid mediated). Mutations in the *waaY*, *phoP*, and *pmrB* genes also confer resistance to antimicrobial peptides. Antimicrobial resistance in the human-restricted salmonellae (e.g., *Salmonella* Typhi) is likely driven primarily by antimicrobial use in humans, whereas antimicrobial resistance among the nontyphoidal salmonellae (e.g., *Salmonella* Typhimurium) may be associated with the use of antimicrobial agents in farm animals. Among *Salmonella* Typhi recently isolated in the United States, about 80% were resistant or intermediate to ciprofloxacin, 12% were multiple drug resistant (i.e., resistant to the traditional first-line antimicrobials ampicillin, chloramphenicol, and trimethoprim-sulfamethoxazole), and 4% were extensively drug resistant (i.e., resistant to ampicillin, ceftriaxone, chloramphenicol, ciprofloxacin, and trimethoprim-sulfamethoxazole).[5] In Asia, about one-third of *Salmonella* Typhi are multidrug resistant, including about 8% resistant to azithromycin, and about 6% are resistant to third-generation cephalosporins. Resistance to third-generation spectrum cephalosporins remains rare among *Salmonella* Paratyphi A. Among human nontyphoidal *Salmonella* bloodstream isolates in the United States, resistance to three or more antimicrobial classes is common. In addition, about 5.0% of human nontyphoidal *Salmonella* bloodstream isolates are resistant to ceftriaxone and 4.5% are resistant to ciprofloxacin.

PATHOBIOLOGY

After the ingestion of organisms, the likelihood for developing infection, as well as the severity of infection, is related to the dose, the virulence of the *Salmonella* strain, and the status of host defense mechanisms. Usually at least 10^2 to 10^3 bacteria are required to produce clinical infection in a normal host. Higher inocula are associated with more severe disease, whereas smaller inocula are more likely to result in transient intestinal carriage. Gastric acid serves as a host defense mechanism by killing many of the ingested organisms, and intestinal motility is probably another host defense mechanism. In the absence of or with a decrease in gastric acidity (e.g., in infants and the elderly; after gastrectomy, vagotomy, or gastroenterostomy; or with the use of drugs that reduce gastric acidity) and with decreased intestinal motility (e.g., the use of antimotility drugs), much smaller inocula can produce infection, and the infection tends to be more severe. Administration of antimicrobial agents before the ingestion of salmonellae can markedly reduce the size of the inoculum needed to produce infection, presumably by reducing the concentration of protective bowel flora.

To produce infection, invasion must occur across the mucosa of the intestine. When the organisms reach the lamina propria, an influx of polymorphonuclear leukocytes serves as a host defense mechanism to prevent invasion of the lymphatics. Certain serovars seem to have a greater ability than others to invade the lymphatics and subsequently to produce bacteremia (e.g., *Salmonella* Choleraesuis and *Salmonella* Dublin, which commonly produce bacteremia after intestinal infection). Both the small intestine and the colon are involved in the inflammatory process.

In the case of *Salmonella* Typhi and other causes of enteric fever, salmonellae invade the mononuclear phagocytes in Peyer patches in the ileum and mesenteric lymph nodes. Some intracellular salmonellae form a nonreplicating population of "persisters" that can provide a reservoir for relapsing infection; intracellular persistence is determined by conditions in the vacuolar environment of the infected cells. Other organisms multiply intracellularly and are carried through the lymphatic system and blood stream to the liver, spleen, bone marrow, and other parts of the reticuloendothelial system. When in the reticuloendothelial system, organisms multiply intracellularly in mononuclear phagocytes and produce the systemic manifestations of enteric fever. The onset of fever is associated with bacteremia and the release of cytokines (e.g., tumor necrosis factor and interleukins) from mononuclear phagocytes. Ulcerations over Peyer patches are responsible for the intestinal manifestations of enteric fever, such as pain, perforation, and bleeding.

In *Salmonella* enterocolitis, the organisms remain localized in the intestinal mucosa, and diarrhea results from the inflammation produced by polymorphonuclear leukocytes. In addition, watery diarrhea may occur, apparently the result of the secretion of water and electrolytes by small intestinal epithelial cells in response to an enterotoxin secreted by some of the *Salmonella* strains or in response to tissue mediators of inflammation.

CLINICAL MANIFESTATIONS

Although any *Salmonella* serovar can produce any of the *Salmonella* syndromes (transient asymptomatic carrier state, enterocolitis, enteric fever, bacteremia, and chronic carrier state), each serovar tends to be associated with certain syndromes much more frequently than with others. For example, *Salmonella* Anatum usually causes asymptomatic intestinal infection, whereas *Salmonella* Typhimurium generally causes enterocolitis. *Salmonella* Choleraesuis is more likely to produce bacteremia (often with metastatic infection) than asymptomatic infection or enterocolitis, and some serovars such as *Salmonella* Typhi and *Salmonella* Paratyphi A[6] are most likely to cause enteric fever as well as the chronic carrier state. Fortunately, most *Salmonella* serovars are of relatively low pathogenicity for humans. Therefore, although food products are commonly contaminated, large outbreaks tend to involve the more virulent serovars.

Patients with diseases that impair host defense mechanisms seem to have an increased frequency of severe *Salmonella* infection. A striking association has been recognized between diseases producing hemolysis and *Salmonella* bacteremia. Specifically, *Salmonella* bacteremia is common in patients with sickle cell disorders (Chapter 149), malaria (Chapter 316), and bartonellosis (Chapter 291). In fact, because of the frequency of *Salmonella* bacteremia in sickle cell diseases and the underlying bone disease in these patients to which salmonellae localize, these organisms are the most common cause of osteomyelitis (Chapter 251) in patients with sickle cell disorders (Chapter 149). Prolonged *Salmonella* bacteremia may occur in patients with hepatosplenic schistosomiasis (Chapter 326), possibly related to localization on and in the intravascular schistosomes. Patients with lymphoma and leukemia (Chapters 168 to 172), are also more prone to the development of *Salmonella* bacteremia. A markedly increased frequency and severity of *Salmonella* infections in general have been observed in patients with human immunodeficiency virus (HIV) infection (Chapter 358), particularly those with $CD4^+$ T-lymphocyte counts less than 200 cells/μL. Prolonged and recurrent, refractory *Salmonella* bacteremia is common among these patients. Other risk factors that increase the frequency and severity of *Salmonella* infection are extremes of age, immunocompromised states (e.g., from immunosuppressive agents), malnutrition (Chapter 198), and probably diabetes (Chapter 210).

Asymptomatic Intestinal Carrier State

The asymptomatic intestinal carrier state may result from inapparent infection (which is the most common form of *Salmonella* infection), or it may follow clinical disease (in which case the patient becomes a convalescent carrier). The carrier state is usually self-limited to several weeks to months, with the prevalence of positive stool cultures rapidly decreasing over time. By 1 year, far less than 1% of carriers still have positive stools. The main exception is *Salmonella* Typhi, which about 3% of infected individuals excrete for life.

Women and older men are more likely to become chronic carriers, likely related to underlying abnormalities in their biliary tracts (Chapter 141). For example, a patient who has had salmonellae in the stool for 1 year (chronic carrier) is likely to become a lifelong carrier, with the reservoir in the biliary tree, usually in calculi in the gallbladder. Patients with *Schistosoma haematobium* (Chapter 326) infection also are predisposed to become chronic urinary carriers of salmonellae.

Enterocolitis

After an incubation period of usually 12 to 48 hours, the illness starts suddenly with crampy abdominal pain and diarrhea. Nausea and vomiting may occur but are usually not prominent or persistent. The diarrhea may be watery and of large or small volume. Stools may contain mucus and are occasionally bloody. Polymorphonuclear leukocytes are present in the stool. Diarrhea may be mild or severe, with up to 20 to 30 stools a day. Fever is present in most patients, and the temperature may reach 40° C (104° F) or higher. The abdomen is tender to palpation. Transient bacteremia may occur and is most commonly seen in infants, the elderly, and patients with impaired host defense mechanisms.

Symptoms generally improve during a period of fever persisting for no more than 2 to 3 days and diarrhea persisting for no more than 5 to 7 days. However, these symptoms occasionally persist for up to 14 days. More severe disease is seen with malnutrition (Chapter 198), inflammatory bowel disease (Chapter 127), and HIV infection (Chapter 358). Older patients are less likely to have bloody diarrhea but more likely to have severe illness requiring hospitalization.[7] Reactive arthritis (Chapter 254) may follow enterocolitis in up to 7% of cases, especially among patients who are HLA-B27 positive.

Enteric Fever

Enteric fever is produced by *Salmonella* Typhi (typhoid fever); *Salmonella* Paratyphi A, B, and C (paratyphoid fever)[8]; and occasionally other serovars. Sometimes it immediately follows classic enterocolitis caused by the same organism. In untreated disease, an incubation period of 5 to 21 days (generally 7 to 14 days) is followed by fever and malaise, often associated with cough. A small proportion of patients may have diarrhea during the incubation period. The fever tends to rise in a stepwise fashion during the first few days to a week and then becomes sustained, usually at 39.4° to 40.0° C (103° to 104° F) or higher. Relative bradycardia is seen in up to half of patients. Apathy, confusion, delirium, and even psychosis may occur. Abdominal distention, pain, and tenderness may occur in the first week and may be associated with diarrhea or constipation; these symptoms are generally more pronounced during the second week of fever. Most patients have abdominal tenderness during the course of the illness.

In about 30% of untreated light-skinned patients, but rarely in patients with darker skin, rose spots become visible on the abdomen or chest (or both) toward the end of the first week or during the second week of fever. These faint, salmon-colored maculopapular lesions are subtle and may be difficult to see, particularly in dark-skinned patients. Salmonellae can be cultured from punch biopsies of these lesions. Hepatosplenomegaly occurs in about half of patients. Leukopenia and neutropenia are seen in about 20%. Abnormal liver function test results are common.

After 2 weeks of untreated illness, the severe complications of intestinal hemorrhage and perforation related to necrosis of Peyer patches may be observed in about 5% of patients.

Rarely, patients may develop pancreatitis (Chapter 130), cholecystitis (Chapter 141), infective endocarditis (Chapter 61), meningitis (Chapter 381), pneumonia (Chapter 85), hepatic or splenic abscess (Chapter 137), orchitis, or focal infection at virtually any site. The illness usually resolves by the end of the fourth week in an untreated patient. Relapse may occur in untreated as well as in treated patients, but the illness is milder than the original episode.

Bacteremia

Patients with *Salmonella* bacteremia usually complain of fever and chills that persist for days to weeks. Gastrointestinal symptoms are unusual, but *Salmonella* bacteremia occasionally follows classic enterocolitis. Other symptoms are nonspecific, such as malaise, anorexia, and weight loss. Metastatic infection of bones, joints, aneurysms (particularly of the abdominal aorta), meninges (mainly in infants), pericardium, pleural space, lungs, heart valves, cysts, uterine myomas, malignant neoplasms, and other sites is common, and symptoms may be related to the site of metastatic infection. Stool cultures are often negative for salmonellae, but blood cultures are positive.

Although any *Salmonella* serovar can produce bacteremia, *Salmonella* Dublin, *Salmonella* Choleraesuis, *Salmonella* Heidelberg, *Salmonella* Oranienburg, *Salmonella* Panama, and *Salmonella* Sandiego are associated with increased likelihood of bacteremia.[9] *Salmonella* bacteremia occurs with increased frequency in infants, the elderly, and patients with diseases associated with hemolysis (e.g., sickle cell diseases, malaria, bartonellosis), HIV infection, lymphoma, leukemia, disseminated histoplasmosis, and perhaps systemic lupus erythematosus.[10] Localization to bone is common in patients with sickle cell diseases (Chapter 149), but osteomyelitis also can occur in immunocompetent patients without any risk factors.[11] In Africa, the common symptoms of invasive nontyphoidal *Salmonella* disease, which is seen predominantly in patients with HIV infection, malaria, and malnutrition, are fever, hepatosplenomegaly, and respiratory symptoms; features of enterocolitis are often absent.

Prolonged *Salmonella* bacteremia lasting for months may occur in patients with hepatosplenic schistosomiasis (Chapter 326). In patients with HIV infection, recurrent, relapsing *Salmonella* bacteremia may develop, which may be difficult to cure with antimicrobial agents.

DIAGNOSIS

Enterocolitis

Polymerase chain reaction (PCR) testing of stool specimens can provide accurate and rapid diagnosis.[12] When culture-independent diagnostic testing is positive for *Salmonella*, a definitive culture is still needed to yield an isolate for public health purposes. However, by the time the results of stool culture are available, most patients are recovering. A stained smear of the stool usually demonstrates polymorphonuclear leukocytes.

Although *Salmonella* enterocolitis is an invasive disease, the differential diagnosis includes all causes of acute diarrhea, including invasive bacteria such as *Campylobacter jejuni* (Chapter 279), *Shigella* species (Chapter 285), invasive *Escherichia coli* (Chapter 280), *Yersinia enterocolitica* (Chapter 288), and *Vibrio parahaemolyticus* (Chapter 278); toxigenic bacteria such as *Vibrio cholerae* (Chapter 278), enterotoxigenic *E. coli*, enterohemorrhagic *E. coli* (e.g., *E. coli* O157:H7; Chapter 280), *Staphylococcus aureus* (Chapter 267), *Bacillus cereus* (Chapter 272), *Clostridium perfringens* (Chapter 271), and *Clostridioides difficile* (Chapter 271); viruses (Chapters 349 and 350); and protozoa such as *Entamoeba histolytica* (Chapter 323), *Giardia intestinalis* (Chapter 322), and *Cryptosporidium* species (Chapter 321). The invasive bacterial causes of diarrhea, enterohemorrhagic *E. coli* and *C. difficile* infection, are also associated with polymorphonuclear leukocytes in stool, whereas bacterial toxigenic causes (other than *C. difficile* and enterohemorrhagic *E. coli*), viruses, and protozoa generally are not. The bacterial toxigenic causes of diarrhea other than *C. difficile* and enterohemorrhagic *E. coli* do not produce fever.

Bacteremia and Enteric Fever

The diagnosis of enteric fever is best proved by isolation of the microorganism from blood or bone marrow. Stool culture may be positive but cannot differentiate carriage from acute infection. During the first week of illness, blood cultures are positive in about 90% of patients, but culture positivity decreases in the next 2 weeks to less than 50% during the third week of illness. Stool cultures are usually negative during the first week but are generally positive by the third week. Bone marrow cultures give the highest yield, with up to 95% being positive; they should be considered in suspected cases with negative blood culture results. Bone marrow cultures may be positive even after several days of antimicrobial treatment, when blood cultures have become negative. Urine cultures and cultures of punch biopsies of rose spots may also be positive. The string test to obtain samples of bile from the duodenum has likewise yielded positive cultures. The peripheral leukocyte count is usually normal, but leukopenia, which occurs in about 20% of cases, may be suggestive of enteric fever. Fecal leukocytes are generally present.

PCR testing lacks sensitivity for diagnosis from blood and other specimens. Serologic tests that detect serum antibodies against *Salmonella* Typhi have poor sensitivities and specificities,[13] and they rarely provide useful information to guide management of the patient.

The differential diagnosis of enteric fever is broad and depends in part on the area of the world where the infection was acquired.[14] All causes of sustained fever are in the differential diagnosis, including infective endocarditis (Chapter 61), disseminated tuberculosis (Chapter 299), brucellosis (Chapter 286), tularemia (Chapter 287), *Mycoplasma pneumoniae* infection (Chapter 293), rickettsial infections (Chapter 302) including Q fever, and viral infections such as infectious mononucleosis (Chapter 348). Depending on the site of acquisition, diseases such as malaria (Chapter 316), amebic abscesses of the liver (Chapters 137 and 323), and visceral leishmaniasis (Chapter 319) also enter into the differential diagnosis.

TREATMENT

The emergence of widespread antimicrobial resistance has complicated the treatment of all *Salmonella* infections.[15,16] Any general guidance must be subject to local resistance profiles and the results of susceptibility testing.

Enterocolitis

The primary approach to the treatment of *Salmonella* enterocolitis is fluid and electrolyte replacement. Drugs with antiperistaltic effects, such as loperamide (4 mg orally initially followed by 2 mg after each unformed stool up to 16 mg per day), can relieve cramps and reduce diarrhea, but they should not be used in patients who are febrile or have bloody diarrhea because they can prolong the course of the disease (Chapter 262).

Salmonella enterocolitis is usually self-limited, and antimicrobial therapy has little effect on mild disease. Antimicrobial therapy typically is reserved for patients who are febrile, have bloody diarrhea, or are at high risk for invasive disease. In the presence of gross bloody diarrhea, however, antimicrobial therapy should be withheld until the possibility of infection with Shiga toxin–producing *E. coli* has been eliminated because antimicrobial therapy may increase the frequency of hemolytic-uremic syndrome 17-fold.

When antimicrobial therapy is reasonable, ciprofloxacin (500 mg every 12 hours orally or 400 mg every 12 hours intravenously for 3 to 5 days or until defervescence) is usually effective. An extended-spectrum cephalosporin such as ceftriaxone (2 g intravenously every 12 to 24 hours for 3 to 7 days) is an alternative. Other agents, such as amoxicillin and trimethoprim-sulfamethoxazole, have also been widely used in severely ill adults, but many strains of *Salmonella* are now resistant to these agents. Azithromycin (1000 mg orally once on the first day, followed by 500 mg once daily to complete a 7-day course) may be an alternative.

Enteric Fever

Fluoroquinolones (e.g., ciprofloxacin 500 mg orally twice a day for 7 to 14 days or 400 mg intravenously until oral therapy can be started) are the agents of choice to treat enteric fever in many parts of the world. Where resistance is sufficiently common, an alternative is ceftriaxone (2 g every 12 to 24 hours for adults and 75mg/kg/day for children, given intravenously or intramuscularly for 7 to 14 days), which can cure 95% of patients.[A1,A2] In treated patients, the temperature usually returns to normal after 3 to 5 days of therapy, but it may take longer in patients treated with extended-spectrum cephalosporins than in patients treated with fluoroquinolones.

Azithromycin (500 mg/day orally for 7 days) is effective in the treatment of patients with uncomplicated typhoid fever[A3] caused by multidrug-resistant and some extensively drug-resistant strains. The oral route of administration makes it a particularly attractive choice in settings where multidrug resistance is common and intravenous extended-spectrum cephalosporins are impractical, unavailable, or too expensive. Severe disease due to extensively drug-resistant *Salmonella* Typhi may respond to meropenem (1 g intravenously every 8 hours for 7 to 14 days).

Among the salmonellae causing enteric fever, resistance to ampicillin, chloramphenicol, and trimethoprim-sulfamethoxazole has emerged worldwide. Outbreaks of extensively drug-resistant, including ceftriaxone-resistant, *Salmonella* Typhi are occurring in South Asia. If the *Salmonella* isolate is shown to be susceptible by antimicrobial susceptibility testing, however, ampicillin (25 mg/kg intravenously every 6 hours), chloramphenicol (50 mg/kg/day orally or intravenously, divided into four doses), or trimethoprim-sulfamethoxazole (4/20 mg/kg intravenously or orally every 12 hours) may be given for 7 to 14 days.

Patients often require supportive care with intravenous saline, correction of electrolyte and acid-base disturbances, and, in the setting of intestinal bleeding, blood transfusion. If perforation is suspected, abdominal imaging should be performed to evaluate for free air. If perforation seems likely, laparotomy should be performed as soon as possible to repair it. In the setting of perforation, antimicrobial therapy should be broadened to cover bowel flora.

Steroid therapy is beneficial in some patients with severe enteric fever complicated by coma, delirium, or shock. Dexamethasone is administered at doses of 3 mg/kg initially, followed by 1 mg/kg every 6 hours for 48 hours. Steroids can mask the signs and symptoms of abdominal perforation and should not be continued for more than 48 hours. Salicylates should be avoided.

Bacteremia

The agents of choice to treat *Salmonella* bacteremia are the fluoroquinolones, such as ciprofloxacin (400 mg every 12 hours intravenously), and the extended-spectrum cephalosporins,[A4] such as ceftriaxone (2 g every 12 to 24 hours intravenously). When the salmonellae are known to be susceptible, ampicillin (1 to 2 g intravenously every 4 to 6 hours) or trimethoprim-sulfamethoxazole (8 mg/kg/day of the trimethoprim component intravenously) can be used. Chloramphenicol (50 mg/kg/day orally or intravenously, divided into four doses) is another option. Antimicrobial susceptibility testing is necessary because of the emergence of infections resistant to the fluoroquinolones, extended-spectrum cephalosporins, and sometimes both.

In cases of sustained bacteremia, the possibility of endovascular infection or osteomyelitis should be investigated. For transient bacteremia or bacteremia without localization, therapy is continued for 7 to 14 days. With localization to bone, aneurysms, heart valves, and various other sites, antimicrobial therapy should be given for much longer periods (e.g., 6 weeks and even longer for osteomyelitis). Surgical drainage, removal of foreign bodies, or resection of an aneurysm is often necessary to cure localized infection. The possibility of schistosomiasis (Chapter 326) should be considered and treated, when present, in patients with sustained *Salmonella* bacteremia. Patients with HIV infection (Chapter 358) tend to experience repeated relapses after treatment courses for *Salmonella* bacteremia. In these patients, initial treatment with ciprofloxacin for 2 weeks or longer is recommended.

Carriers

Chronic carriers (i.e., >1 year) of salmonellae other than *Salmonella* Typhi are uncommon. Stools of convalescent carriers spontaneously become negative during a period of weeks to months, and no therapy should be given.

For patients with persistent carriage despite adequate antimicrobial therapy and without an identifiable anatomic abnormality, chronic suppressive therapy may be considered.[17] The rare chronic carrier of typhoidal *Salmonella* serovars other than Typhi (usually infected with *Salmonella* Paratyphi A, B, or C) may also be treated. Treatment of carriers is with a ciprofloxacin (500 to 750 mg orally twice daily); amoxicillin (6 g/day orally in three or four divided doses plus probenecid 2 g/day in divided doses); or trimethoprim-sulfamethoxazole (160/800 mg twice daily) plus rifampicin (300 mg twice daily).

Patients who experience relapse usually have gallbladder disease (most often calculi) and will not be cured with antimicrobial therapy alone. Cholecystectomy plus antimicrobial therapy may cure these patients, but it is doubtful that the carrier state alone is a sufficient indication for cholecystectomy. Patients with persistent urinary carriage and *S. haematobium* infection (Chapter 326) should be treated with praziquantel before eradication of *Salmonella* Typhi is attempted.

Chronic carriers who do not prepare food and who practice adequate personal hygiene usually do not constitute a public health hazard. Therefore, after the institution of appropriate personal hygienic precautions, and in the absence of evidence of a chronic carrier infecting others, cholecystectomy is probably not indicated to eradicate the carrier state.

PREVENTION

The widespread presence of salmonellae in the animal kingdom means that reducing the risk for *Salmonella* infections requires a multifaceted approach.[18] *Salmonella* infection is best prevented by protecting the water supply, preventing fecal contamination during food production, cooking and refrigerating foods, pasteurizing milk and milk products, and handwashing before preparing foods. Travelers should judiciously avoid consuming untreated water (including ice), raw vegetables, and fruits. Food should be cooked or peeled, and drinks should be boiled, carbonated, or commercially bottled.

No licensed vaccine is available for *Salmonella* infection other than for *Salmonella* Typhi. Travelers should be vaccinated before going to areas that are endemic for typhoid fever. Two types of effective vaccines[A5] are available in the United States. One is the typhoid Vi capsular polysaccharide vaccine, which is administered as a single intramuscular injection, with booster doses given every 2 years if needed. This vaccine provides a degree of herd protection against typhoid fever when it is used at the population level. The other licensed typhoid fever vaccine type is the oral live attenuated Ty21a vaccine. Revaccination is necessary every 5 years, if indicated. Ty21a vaccine should not be used in immunocompromised persons or those receiving antimicrobials. Both types of vaccines confer greater than 75% protective efficacy. A third type of vaccine, the Vi polysaccharide protein-conjugate vaccines, are recommended as a single dose from age 6 months in typhoid-endemic countries,[A6,A7] but these vaccines are not yet licensed in the United States.

Vaccines afford only partial immunity to typhoid fever. Persons who have been vaccinated should still restrict their diets to avoid potentially contaminated food and fluids. When cases of imported typhoid are identified in the United States, the local health department should be informed and will monitor stool cultures. Typhoid fever acquired in the United States is typically investigated by the public health department to identify potential sources and chronic carriers.

PROGNOSIS

Mortality in patients with *Salmonella* enterocolitis is rare. Outbreaks in nurseries and among the elderly in nursing homes are associated with the highest case-fatality ratios (>5%), with death occurring as a result of dehydration and electrolyte imbalance. Mortality from nontyphoidal *Salmonella* bacteremia is not uncommon, can be as high as 15% in sub-Saharan Africa,[19] and is most likely to occur in the very young, the very old, the malnourished, and the immunocompromised.

Before the advent of antimicrobial therapy, the case-fatality ratio of typhoid fever was 15 to 20%, but it is now less than 1% in industrialized countries.

However, the case-fatality ratio for typhoid fever in Africa remains over 5% in patients who do not require surgery[20] and is far higher among those who do.

In the era before antimicrobial therapy, 5 to 10% of patients who recovered from typhoid fever had relapses. Relapses continued to occur in 10 to 15% of patients treated with chloramphenicol, ampicillin and trimethoprim-sulfamethoxazole, but relapse seemed to be much less frequent (<5%) among those treated with ceftriaxone and fluoroquinolones. Relapses of typhoid fever may be treated with the same antimicrobial regimen as for the initial attack or with an alternative regimen, depending on the results of antimicrobial susceptibility testing. Long-term suppressive therapy has been suggested for patients who experience frequent relapses.[21]

Intestinal perforation is the leading cause of death from enteric fever. Intestinal bleeding or perforation occurs in about 5% of patients. In patients who require surgery for gastrointestinal perforation, the 30-day mortality rate is 9%.

Up to 3% of patients recovering from *Salmonella* Typhi and nontyphoidal *Salmonella* infection become chronic carriers, persistently shedding the organism in their stool. Most persistently infected patients are immunocompetent, and about two thirds have relapsing diarrhea, indicating that they are not truly asymptomatic.

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285 SHIGELLOSIS

CALMAN A. MACLENNAN

DEFINITION

Shigellosis results from inflammation of the large intestine due to infection with bacteria of the genus *Shigella*. Clinical presentation is either with acute watery diarrhea or bloody diarrhea, known as dysentery, and is commonly accompanied by fever.[1] Shigellosis is a major global health problem compounded by increasing levels of antimicrobial resistance. It is the most common cause of diarrheal deaths for which no vaccine is currently available.

The Pathogen

Bacteria of the genus *Shigella,* family Enterobacteriaceae, are facultative anaerobic, nonmotile gram-negative bacilli. The four species are distinguished by the O-antigen component of lipopolysaccharide. *Shigella flexneri,* which has 15 serotypes, is the most common cause of shigellosis in low- and middle-income countries. *Shigella sonnei,* which is responsible for the majority of shigellosis in high-income countries, exists as just one serotype. *Shigella dysenteriae* occurs as 15 serotypes, including serotype 1, which has been responsible for outbreaks of shigellosis. *Shigella boydii,* which consists of 19 serotypes and is relatively uncommon, is found mostly in South Asia.

EPIDEMIOLOGY

Shigella is a human-restricted pathogen. Transmission most commonly occurs via the fecal-oral route, predominantly from direct person-to-person contact or via fomites. Infection is more common among populations in which overcrowding is common and without access to clean water and proper sanitation. A low number of bacilli, as little as 10 organisms for *S. dysenteriae* and 180 for *S. flexneri* and *S. sonnei,* is required for infection.

Transmission also occurs through contaminated food and water. *Shigella* was the third most common pathogen associated with food-borne gastroenteritis in the United States in 2016. Transmission by infected asymptomatic food-handlers presents a particular risk. In settings in which open defecation is common, transmission can be facilitated through house flies. Shigellosis is also increasingly recognized as a sexually transmitted disease, particularly among men who have sex with men.[2]

Shigellosis is predominantly a disease of low- and middle-income countries. Worldwide, *Shigella* is the second most common cause of diarrheal death, following rotavirus (which is also the most common cause of moderate to severe diarrhea; Chapter 350), and it is the most common bacterial cause. *Shigella* is the main pathogen associated with dysentery (attributable fraction 64%), and the second most attributable pathogen for watery diarrhea (attributable fraction 13%). The Global Burden of Disease 2019 report estimated about 150,000 worldwide deaths attributable to *Shigella*, with about 95,000 occurring among children under 5 years of age. Disability-adjusted life years lost to shigellosis are much higher and are estimated at about 10.5 million overall, about 8.5 million of which are lost in children under age 5 years.[3] By serotyping, 66% of *Shigella* isolates are *S. flexneri,* predominantly *S. flexneri* 2a, whereas 24% are *S. sonnei,* 5% are *S. dysenteriae,* and 5% are *S. boydii*.

Children under 5 years and adults who live in poor and crowded circumstances are at high risk of shigellosis.[4] Daycare centers present an environment where transmission of shigellosis is common. At the other end of the age spectrum, the elderly are also at increased risk of shigellosis, especially elderly individuals living in residential care facilities.

The incidence of shigellosis is much lower in high-income countries compared with low- to middle-income countries. Nevertheless, shigellosis is the second most common cause of acute gastroenteritis outbreaks in the United States after norovirus (Chapter 350). Shigellosis is common in the military, and *Shigella* has been estimated to be responsible for 2 to 9% of cases of travelers' diarrhea (Chapter 265).

S. dysenteriae type 1 was responsible for four pandemics with high attack rates and case fatality rates between 1968 and the 1990s. For unknown reasons, *S. dysenteriae* type 1 has largely disappeared in the 21st century, but has the potential to reemerge, particularly in settings of natural disasters with displaced peoples and poor sanitation and hygiene.

Although incidence levels have remained high, deaths due to shigellosis have decreased, likely because of improved management with antibiotics, oral rehydration solution, supplementation of zinc and vitamin A, and less preinfection baseline malnutrition. The change in profile of *Shigella* species, with the disappearance of *S. dysenteriae* type 1 and increased proportion of mild shigellosis due to *S. sonnei* in developed countries, also may be responsible.

PATHOBIOLOGY

Low-dose inocula of *Shigella* are able to resist gastric acid and transit to the intestine, where watery diarrhea is induced by the action of several factors, including *Shigella* enterotoxins 1 and 2 (ShET 1 and 2). More severe disease is induced by the secretion of Shiga toxin by *S. dysenteriae* type 1. The primary site of *Shigella* infection and multiplication is the colon, where *Shigella* bacteria outcompete commensal bacteria of the microbiota and then penetrate the mucus lining of the intestine by the secreting of mucinases that allow them to access the intestinal epithelium.

Shigella lacks fimbriae for adhesion to the colonic epithelium and instead gains entry through invasion of M cells overlying Peyer patches and subsequent phagocytosis by macrophages. The bacteria escape from the phagolysosome into the cytoplasm, where they trigger pyroptotic death of the macrophage, thereby resulting in their release into the lamina propria. Pyroptosis triggers the innate immune system to produce an inflammatory response, with production of proinflammatory cytokines, including interleukin (IL)-1, IL-8, IL-18, and interferon (IFN)-γ. The inflammatory response results in the recruitment of neutrophils to the site of infection and disruption of epithelial tight junctions,

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ABSTRACT

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KEYWORDS

shigellosis
dysentery
antibiotic resistance
hemolytic-uremic syndrome
reactive arthritis

TABLE 285-1 CLINICAL SYNDROMES AND COMPLICATIONS OF SHIGELLOSIS

STAGE	TIME OF APPEARANCE AFTER ONSET OF ILLNESS	SYMPTOMS AND SIGNS	PATHOLOGY AND PATHOGENESIS
Prodrome	Earliest findings	Fever, chills, myalgias, anorexia	None or early colitis with cytokine response
Watery diarrhea	0-3 days	Fever, abdominal cramps, loose stools	Mild colitis with fecal leukocytes and erythrocytes
Bloody diarrhea	1-3 days	Frequent stools containing blood and mucus, abdominal cramps and tenderness, fever, anorexia	Colitis with fecal leukocytes and erythrocytes
Dysentery	1-5 days	Frequent small-volume stools consisting of blood, mucus, and pus; severe abdominal cramps; tenesmus	More extensive colitis with crypt abscesses and mucosal ulcerations
Acute complications	3-7 days	Seizures, obtundation, bacteremia, colonic obstruction, mucosal perforation, peritonitis	Severe colitis, terminal ileitis
Additional acute complications due primarily to infection with *Shigella dysenteriae* type 1	3-7 days	Toxic megacolon, leukemoid reaction, hemolytic-uremic syndrome	Severe colitis, expression of Shiga toxin
Postinfectious syndromes	1-3 weeks	Reactive arthritis, with or without urethritis and conjunctivitis	Autoimmune inflammatory response, most common in individuals expressing HLA-B27 antigen

HLA = human leukocyte antigen.
From Keusch GT, Zaidi AKM. Shigellosis. In: Goldman L, Schafer AI. *Goldman-Cecil Medicine*. 26th ed. Philadelphia: Elsevier; 2020.

thereby allowing *Shigella* bacteria to have direct access to the lamina propria. The ensuing tissue damage results in mucosal abscesses and erosions, as well as the characteristic release of blood and mucus into the intestinal lumen and stool.

With access to the basolateral surface of intestinal epithelial cells, shigellae induce their own uptake through the assembly of the type III secretion system (T3SS) needle apparatus encoded on the virulence plasmid and injection of virulence effectors into epithelial cells. In contrast to macrophage pyroptosis, this process promotes the survival of epithelial cells and suppresses the production of antimicrobial peptides. Injected proteins cause rearrangement of the actin cytoskeleton and fragmentation of the epithelial cell Golgi apparatus. This effect permits phagocytosis of *Shigella* bacteria, followed by release into the cytoplasm, replication, and infection of neighboring epithelial cells by clathrin-dependent endocytosis. As shigellae invade throughout the epithelium, acquired immunity is suppressed by the action of *Shigella* effector proteins, which downregulate inflammation and disrupt B-cell and T-cell activities. Over the course of about 5 to 7 days, the *Shigella* infection is normally cleared by the influx of neutrophils.

CLINICAL MANIFESTATIONS

Asymptomatic infection is common. The onset of symptoms typically follows an incubation period of up to 4 days, but the incubation period can be twice as long when infection is with *S. dysenteriae* type 1.

Symptoms at the outset are commonly fever, chills, myalgias, and anorexia, with watery diarrhea ensuing a few hours later (Table 285-1). Although the classic presentation of shigellosis is dysentery, most symptomatic cases of shigellosis present as watery diarrhea and are difficult to distinguish from other causes of diarrhea (Chapter 126). In more severe cases, shigellosis progresses to bloody diarrhea/dysentery.

Disease is most severe with *S. dysenteriae* type 1 and with *S. flexneri,* which has a high incidence in low- to middle-income countries, and less severe with *S. sonnei,* which is common in high-income countries. *S. boydii* is mostly associated with mild disease. In otherwise healthy individuals, symptoms often resolve within a few days.

Frank dysentery may be manifested as multiple episodes (as high as 40/day) of small-volume bloody stools that are often mixed with mucus. Diarrhea is often accompanied by lower abdominal cramps and tenesmus. Intestinal complications include rectal prolapse, toxic megacolon secondary to intestinal inflammation, and obstruction. Rarely, patients may develop intestinal perforation and peritonitis.

Extraintestinal complications include seizures in 5 to 30% of children admitted to the hospital with shigellosis. Occasional patients may develop obtundation or encephalopathy. Bacteremia is a rare complication, mostly seen in individuals infected with HIV or young and malnourished children. Meningitis, osteomyelitis, and arthritis are uncommon. Shigellosis in pregnancy may result in preterm labor and transmission to the neonate. Shigellosis with *S. dysenteriae* type 1 can result in the hematologic complications of leukemoid reactions (Chapter 153) and hemolytic uremic syndrome (Chapter 158).

In high-income countries, up to 1 to 2% of individuals with shigellosis, particularly patients with the human leukocyte antigen (HLA)-B27 gene, will develop reactive arthritis (Chapter 244), which is an immune-mediated seronegative spondyloarthropathy. The arthritis can be accompanied by other extra-intestinal manifestations including uveitis, urethritis, and erythema nodosum. *Shigella* infection also increases the risk of subsequent irritable bowel syndrome (Chapter 123).

DIAGNOSIS

No clinical manifestation can reliably distinguish shigellosis from other causes of watery diarrhea. Stool microscopy, which typically shows red blood cells and leukocytes is also nonspecific. Modern diagnosis relies on quantitative polymerase chain reaction (PCR) testing of stool[5] (Chapter 262), which is more sensitive than stool culture,[6] followed by culture, either from stool directly or from a rectal swab, to determine antibiotic susceptibility.[7] Work is underway to develop low-cost molecular technologies suitable for field use in low- to middle-income countries.

TREATMENT

In many individuals, particularly in high-income countries where shigellosis presents as uncomplicated diarrhea, the disease is self-limiting and no treatment is required or recommended for uncomplicated diarrhea. When diarrhea results in dehydration, supportive treatment with oral rehydration solution is often needed[8]; intravenous fluids (glucose and saline) can be reserved for severe dehydration or the inability to tolerate oral fluids. Oral rehydration solution should be supplemented with zinc sulfate (20 mg), which reduces the duration of shigellosis. Antimotility agents should not be used because of concern about prolonged symptoms and shedding as consequences of lengthened exposure to *Shigella* bacteria in the intestinal tract.

Antibiotics reduce the duration of fever, diarrhea, and bacterial shedding when given to treat *Shigella* dysentery. Antibiotics are routinely recommended for dysentery, for severe illness in immunocompromised patients, and during epidemics, but antibiotics are not routinely recommended for non-febrile watery diarrhea.

A range of antibiotics appear to be equally effective, but rising antimicrobial resistance increasingly limits treatment options, which initially should be based on local susceptibility data, when available, and then on sensitivity profile of the individual patient's infections when such results are available. For adults, empirical oral ciprofloxacin (500 mg orally once daily for 3 days) is recommended (Fig. 285-1). Where local strains of *Shigella* are ciprofloxacin-resistant, other options include oral azithromycin (500 mg orally twice daily for 1 day), cefixime (400 mg once daily for 3 days), or trimethoprim-sulfamethoxazole (160 mg/800 mg twice daily for 5 days). Intravenous or intramuscular ceftriaxone (1 g daily for 3 days for adults and 50 to 75 mg/kg daily for 2 to 5 days for children) is the antibiotic of choice for severe shigellosis and when vomiting or unconsciousness precludes

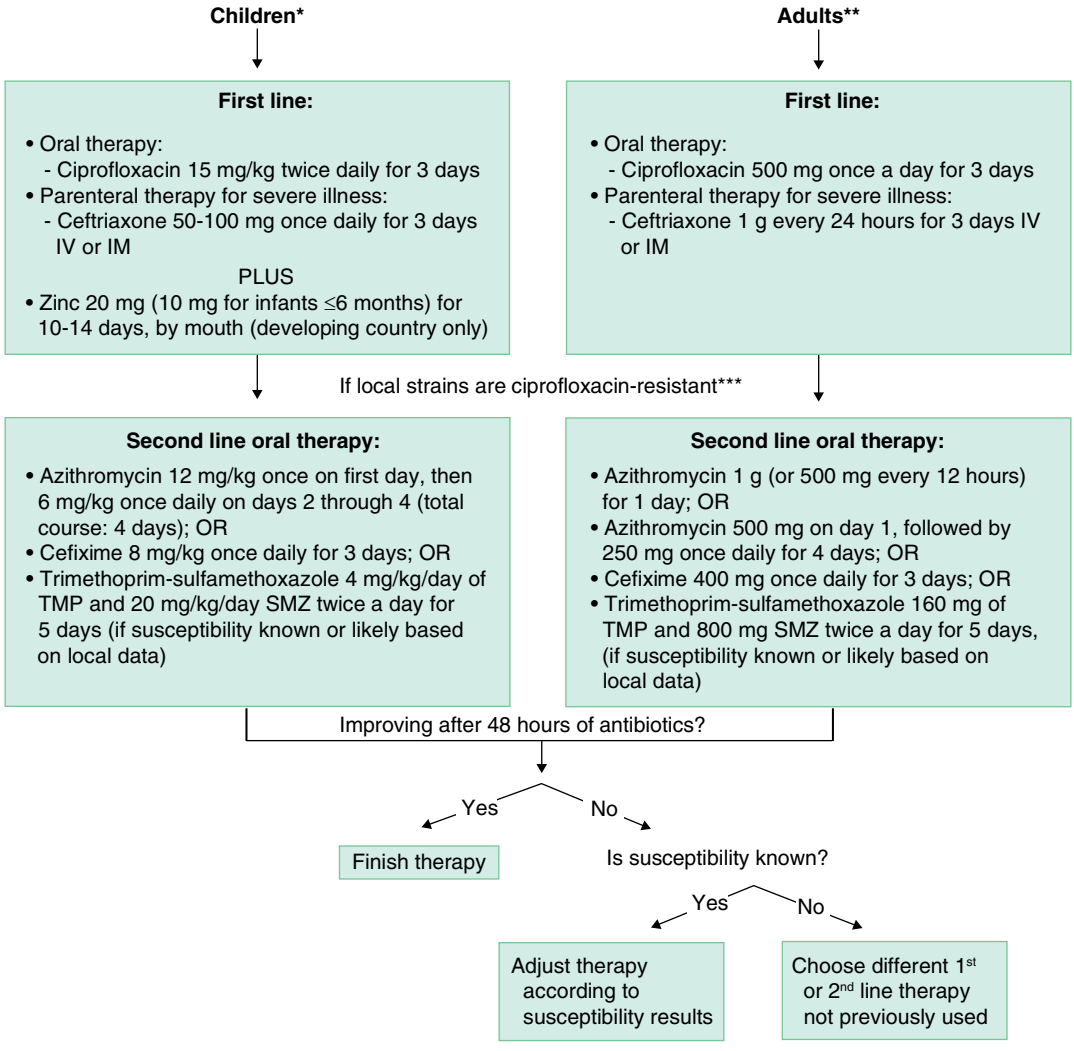

FIGURE 285-1. Treatment of shigellosis.
*The WHO Expert Committee on the use of essential medicines 2017 currently recommends no antibiotic treatment for non-bloody, non-febrile diarrheal episodes, including those caused by *Shigella*. IM = intramuscular; IV = intravenous. Source: The selection and use of essential medicines: report of the WHO Expert Committee, 2017 (including the 20th WHO Model List of Essential Medicines and the 6th WHO Model List of Essential Medicines for Children). Geneva: World Health Organization; 2017. https://apps.who.int/iris/bitstream/handle/10665/259481/9789241210157-eng.pdf?sequence=1&isAllowed=y. Accessed January 12, 2023.
**CDC recommends limiting antibiotic treatment of *Shigella* to patients who are immunocompromised or have severe illness, defined as requiring hospitalization, or suffering from invasive disease or complications. Source: Centers for Disease Control and Prevention. CDC recommendations for diagnosing and managing *Shigella* strains with possible reduced susceptibility to ciprofloxacin. CDC Health Alert Network; 2017. https://emergency.cdc.gov/han/han00401.asp. Accessed January 12, 2023.
***CDC recommends that *Shigella* strains with an MIC of 0.12 µg/mL or higher should not be treated with fluoroquinolones. Source: Centers for Disease Control and Prevention. CDC recommendations for diagnosing and managing *Shigella* strains with possible reduced susceptibility to ciprofloxacin. CDC Health Alert Network; 2017. https://emergency.cdc.gov/han/han00401.asp. Accessed January 12, 2023. (Adapted from Keusch GT, Zaidi AKM. Shigellosis. In: Goldman L, Schafer AI. *Goldman-Cecil Medicine*. 26th ed. Philadelphia: Elsevier; 2020.)

the use of oral medication. Immunosuppressed patients should be treated for 7 to 10 days.

Once sensitivity data are available by molecular methods[9] or culture, the antibiotic regimen should be adjusted. Antimicrobial resistance to shigellosis is a major global public health concern.[10] Ciprofloxacin-resistant *S. sonnei* emerged in South Asia and have spread widely.[11,12] If the *Shigella* isolate has a minimal inhibitory concentration of 0.12 µg/mL or greater for ciprofloxacin, fluoroquinolones must not be used due to concern about increasing the severity of the disease and prolonging bacterial shedding.[13] Azithromycin-resistant *Shigella* is common among men who have sex with men and people living with HIV.[14] Resistance to third-generation cephalosporins has been reported in Asia.

In patients who have severe intestinal complications such as obstruction, perforation, and peritonitis, surgery may be indicated. Rectal prolapse is usually correctable by manipulation, and the rectal mucosa must be kept moist until reduction is performed as soon as possible.

PREVENTION

Personal hygiene is important for preventing the spread of shigellosis, particularly in the context of outbreaks. Handwashing with soap and water greatly reduces the quantity of *Shigella* bacteria carried on the hands. Adequate sanitation and access to clean water are key for breaking the cycle of infection given the fecal-oral route of *Shigella* transmission.

The development of an effective vaccine is a priority, especially given the growing problem of antibiotic resistance. Currently, 4-valent O-antigen–based vaccines are in clinical trials,[15,16] but no internationally recognized vaccine is licensed for shigellosis.

PROGNOSIS

Although shigellosis is often self-limiting with no sequelae in high-income countries, it is associated with excess mortality and stunted growth in the year following infection among children in lower-middle-income countries.[17] *S. dysenteriae* type 1 has most often been associated with extra-intestinal complications, such as hemolytic-uremic syndrome (Chapter 158) that can result in long-term renal impairment or failure. Reactive arthritis (Chapter 244) and irritable bowel syndrome (Chapter 123) secondary to shigellosis usually resolve in about 12 months and do not become chronic.

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286 BRUCELLOSIS

EDSEL MAURICE T. SALVANA

DEFINITION

Brucellosis, previously known as Malta fever, Mediterranean fever, or undulant fever, is a zoonotic disease caused by bacteria of the genus *Brucella*. Human infection, which has protean manifestations, is acquired via direct contact, ingestion, or inhalation. Most disease is acquired by eating unpasteurized dairy products or undercooked meat. Occupational infection typically occurs by inhalation, inadvertent exposure to live attenuated vaccines, or through contamination of exposed wounds and mucous membranes. Human-to-human transmission occurs but is rare. Brucellosis remains a significant public health and economic burden in many countries despite advances in detection, treatment, and prevention. In regions where the disease is endemic, brucellosis has far-reaching deleterious effects on humans and animals alike.[1]

The Pathogen

Brucella is a slow-growing, small, aerobic, nonmotile, non-encapsulated, non–spore-forming, gram-negative coccobacillus. *Brucella abortus* (from cattle, bison, elk), *B. suis* (from pigs and feral swine), *B. melitensis* (from sheep, goats, and camels), and *B. canis* (from dogs) are the species that most commonly infect humans. Genetic analysis shows a high degree of homology among different species despite disparate preferred hosts. Virulence factors can also vary between and within species. Whole-genome sequencing shows that *Brucella* is closely related to saprophytic soil-dwelling bacteria, and some species within *Ochrobactrum* are genetically very similar to *Brucella*.[2]

EPIDEMIOLOGY

More than 500,000 cases of brucellosis are reported yearly to the World Health Organization (WHO) from 100 countries, but the true incidence is estimated to be 10 to 25 times higher. *B. melitensis* infection accounts for most diagnosed cases owing to difficulties in immunizing free-range sheep and goats, which harbor this species. Most cases occur in the Mediterranean region,[3] Latin America, the Arabian Gulf, China, and the Indian subcontinent. *B. abortus* infection occurs worldwide and is responsible for most outbreaks in Mexico, China, Greece, and Brazil. *B. suis* is found in the United States, South America, and Southeast Asia. *B. canis* infection occurs in North America, South America, Japan, and Central Europe. In Africa, high rates of *Brucella* seropositivity have been reported in local wildlife[4] and in communities that keep livestock and consume unpasteurized milk.

In animals, brucellosis is a chronic infection that can persist throughout life. Control programs in animals have decreased human brucellosis dramatically in the United States from more than 6000 cases in 1947 to about 80 to 120 cases annually, with most cases reported in Texas, California, Arizona, and Florida.[5]

Brucella infection in the United States occurs mostly through direct contact with animals or animal secretions in high-risk groups, including slaughterhouse workers, farmers, dairy workers, and veterinarians. Laboratory workers handling infected animals or *Brucella* cultures are also at risk. More than one half of reported cases are associated with meat processing, particularly from "kill areas." Many cases of *B. abortus* infection in veterinarians are from accidental exposure to live vaccines used to immunize livestock. Human infections in hunters of feral swine occur sporadically. Imported goat milk and cheese from Mexico (unpasteurized) is an important source of *B. melitensis* infection. Brucellosis contracted abroad may not become symptomatic until the traveler returns. Childhood brucellosis, which occurs mostly in school-aged children, accounts for 3 to 10% of all reported cases worldwide.

Human-to-human transmission is rare and has occurred through sexual transmission, breastfeeding, blood transfusion, bone marrow transplantation, nosocomial exposure, and perinatally. For example, a family cluster of brucellosis in China involved vertical transmission and sexual transmission following occupational exposure of the index case.[6]

PATHOBIOLOGY

Pathogenesis

Entry of *Brucella* organisms into humans is usually through the mucosal route, via ingestion or inhalation. The bacteria then translocate through the intestinal mucosa or the respiratory epithelium. Oral, conjunctival, and direct skin inoculation can also occur. *Brucella* in naïve individuals induces a delayed inflammatory response, with mostly macrophages and dendritic cells involved in the early response. Granulomas composed of lymphocytes, infected macrophages, and dendritic cells eventually form. Phagocytosed *Brucella* subsequently spread to regional lymph nodes. If host defenses within the lymph nodes are overwhelmed or the burden of infection is high, bacteremia follows. The usual incubation period from infection to bacteremia is 2 to 4 weeks. Bacteremia is accompanied by phagocytosis of free *Brucella* organisms by macrophages, primarily in the spleen, liver, and bone marrow, where small, noncaseating granulomas form and can serve as persistent sources of infection.[7]

Brucella organisms avoid initial detection by the host through multiple mechanisms. Its cell wall lipopolysaccharide differs significantly from most other bacteria in two important ways: *Brucella* has very little effect on toll-like receptor type 4 (TLR4) activation, and it is resistant to complement activation. In addition, *Brucella* deploys a protein that interferes with TLR signaling. Upon successful entry into the host, about 10% of *Brucella* organisms in phagosomes are able to survive acidification and lysosome fusion to form an endosomal *Brucella*-containing vacuole, thereby maintaining a persistent presence.[8] To replicate, *Brucella* organisms intercept traffic between the endoplasmic reticulum and the Golgi apparatus.

Apart from structurally helping to maintain cell envelope integrity, *Brucella* outer membrane proteins Omp25/Omp31 contribute to virulence by mediating direct interactions between the brucellae and mammalian cells.[9] Other important virulence factors that enable pathogenic *Brucella* to survive the hostile intracellular niche include catalase, superoxide dismutase, alkyl hydroperoxide reductase, cytochrome oxidase, nitric oxide reductase, *Brucella* virulence factor A, and the *Nramp1* gene.

Inflammation from the innate host immune response is likely the main driver of pathology because no secreted proteolytic enzymes or bacterial toxins have been found. *Brucella* induces the production of host proinflammatory cytokines and metalloproteinases, which cause tissue damage, particularly in osteoarticular areas of the body.

Immunity

Innate immunity to *Brucella* is mediated by activation of toll-like receptors, which produce inflammatory cytokines and recruit phagocytic cells, such as macrophages and dendritic cells, which attempt to control the initial infection and activate adaptive immunity. Platelets also release cytokines, which recruit more monocytes and macrophages in an attempt to clear infection.

Similar to other intracellular organisms, cell-mediated immunity is the predominant adaptive immunologic response to *Brucella*. Macrophages, activated with T helper 1 (T_H1)–type cytokines (most importantly interferon-γ, tumor necrosis factor-α, interleukin-1, and interleukin-12), kill *Brucella*. Antibody production seems to play a peripheral role in clearing infection and is not considered essential. Increasing evidence suggests that *Brucella*-infected neutrophils dampen adaptive immunity and may act as "Trojan horses" that aid dispersal of bacterial infection throughout the body.[10]

CLINICAL MANIFESTATIONS

Strain-Specific Illness

Brucella abortus is usually associated with mild to moderate sporadic disease. *B. suis* and *B. melitensis* infections are associated with suppurative or disabling complications and can have a prolonged course. Infection with *B. canis* has an insidious onset, relapses frequently, and has a chronic but relatively mild course. Two marine species, *B. pinnipedialis* (from seals) and *B. ceti* (from porpoises and dolphins) can cause neurobrucellosis in humans. *Brucella microti* (from the common vole and red fox) has a high potential for pathogenicity, but no instances of human infection have been reported. Three strains of *B. inopinata* (*BO1*, breast implant infection; *BO2*, chronic destructive pneumonia; *BO3*, generalized lymphadenopathy and pneumonia) are genetically similar to atypical *Brucella* from frogs. *Brucella* spp. are considered select agents for bioterrorism (Chapter 19) owing to their pathogenicity and long-term viability.[11]

Clinical Syndromes

Clinically, human brucellosis infection can be divided into subclinical illness, acute or subacute disease, and localized disease. After treatment, some patients develop relapsing infection or chronic disease (Table 286-1).

Subclinical Illness

Asymptomatic or clinically unrecognized human brucellosis often occurs in high-risk groups, including slaughterhouse workers, farmers, and veterinarians. The diagnosis is usually made through serologic means. More than 50%

ABSTRACT

Brucellosis, previously known as Malta fever, Mediterranean fever, or undulant fever, is a zoonotic disease caused by intracellular bacteria of the genus *Brucella*. Human infection, which has protean manifestations, is acquired via direct contact, ingestion, or inhalation. Most disease is acquired by eating unpasteurized dairy products or undercooked meat. Occupational infection typically occurs by inhalation, inadvertent exposure to live attenuated vaccines, or through contamination of exposed wounds and mucous membranes. Human-to-human transmission occurs but is rare. Brucellosis remains a significant public health and economic burden in many countries and is proving a resilient disease despite advances in detection, treatment, and prevention. *Brucella* is a potential agent of bioterrorism due to its pathogenicity.

KEYWORDS

Brucella
zoonosis
foodborne illness
occupational exposure
sacroiliitis
bioterrorism
abortion

TABLE 286-1 CLINICAL CLASSIFICATION OF HUMAN BRUCELLOSIS

CLASSIFICATION	DURATION OF SYMPTOMS BEFORE DIAGNOSIS	MAJOR SYMPTOMS AND SIGNS	DIAGNOSIS	COMMENTS
Subclinical		Asymptomatic	Positive (low-titer) serology, negative cultures	Occurs in abattoir workers, farmers, and veterinarians
Acute and subacute	Up to 2-3 months and 3 months to 1 year, respectively	Malaise, chills, sweats, fatigue, headache, anorexia, arthralgias, fever, splenomegaly, lymphadenopathy, hepatomegaly	Positive serology, positive blood or bone marrow cultures	Presentation can be mild, self-limited (*B. abortus*) or fulminant with severe complications (*B. melitensis*)
Localized	Occurs with acute or chronic untreated disease	Related to involved organs	Positive serology, positive cultures in specific tissues	Bone or joint, genitourinary, hepatosplenic involvement most common
Relapsing	2-3 months after initial episode	Same as acute illness but may have higher fever and more fatigue, weakness, chills, and sweats	Positive serology, positive cultures	May be extremely difficult to distinguish relapse from reinfection
Chronic	>1 year	Nonspecific presentation, but neuropsychiatric symptoms and low-grade fever most common	Low titer or negative serology, negative cultures	Most controversial classification; localized disease may be present

of abattoir workers and up to 33% of veterinarians have high anti-*Brucella* antibody titers but no history of recognized clinical infection. Children in endemic areas frequently have subclinical illness.

Acute and Subacute Disease

After an incubation period of several weeks or months, acute brucellosis may occur as a mild, transient illness (*B. abortus* or *B. canis*) or as an explosive, toxic illness with the potential for multiple complications (*B. melitensis* or *B. suis*). Approximately 50% of patients have an abrupt onset over days, but the remainder have an insidious onset over weeks and may present with fever of unknown origin (Chapter 259).[12] Symptoms in brucellosis are protean and nonspecific. More than 90% of patients experience malaise, chills, sweats, fatigue, and weakness. More than 50% of patients have myalgias, anorexia, and weight loss. Some patients complain of arthralgias, cough, testicular pain, dysuria, ocular pain, or blurring of vision.

Few localizing physical signs are apparent. Fever, with temperatures often greater than 39.4° C (103° F), occurs in 95% of patients. An undulating or intermittent fever pattern is not unusual. A pulse-temperature deficit (i.e., relative bradycardia) may occur. Splenomegaly is present in 10 to 15% of cases, and lymphadenopathy occurs in about 14% of patients. Axillary, cervical, and supraclavicular lymphadenopathy are most frequent and may be related to hand wounds or oropharyngeal routes of infection. Hepatomegaly is less frequent. Laboratory findings in acute or subacute disease may include mild anemia; lymphopenia; or neutropenia (especially with bacteremia); lymphocytosis; thrombocytopenia; or, in rare cases, pancytopenia.

Localized Disease and Complications

Brucella organisms may occur at multiple sites or can localize to almost any organ. Infection usually targets the bones, joints, central nervous system, heart, lung, spleen, testis, liver, gallbladder, kidney, prostate, pancreas, thyroid, and skin. Among osteoarticular complications, sacroiliitis is the most common acute presentation and should prompt evaluation for brucellosis in the appropriate setting. Spondylitis and spondylodiscitis, particularly in the lumbar area, are also common and can be associated with paravertebral, epidural, and psoas abscesses. Peripheral arthritis, prosthetic joint infections, osteomyelitis, tenosynovitis, and bursitis are less frequent but should prompt an evaluation in endemic areas. Brucellosis in pregnancy has been associated with spontaneous abortions, congenital abnormalities, and neonatal infections.

DIAGNOSIS

Many common illnesses mimic brucellosis, and a thorough history is essential, including occupation, travel to endemic areas, avocations, and ingestion of at-risk food and beverages. Nucleic acid amplification tests can rapidly and highly accurately diagnose brucellosis in blood, bodily fluids, or tissue samples.[13] Since nucleic acid can persist in tissues, however, nucleic acid amplification tests cannot be used to confirm cure. Such testing is especially useful when no viable material is available for culture.

Despite the accuracy of nucleic acid amplification testing, the most conclusive means of establishing the diagnosis of brucellosis is the recovery of the organism from a culture from normally sterile body fluid or tissue. Sensitivity of cultures ranges from 15 to 90%, depending on the methods used, species, timing, stage of disease, prior use of antimicrobial agents, and the specimen type. Handling of *Brucella* cultures is potentially hazardous to laboratory personnel, so the laboratory should be informed if this organism is suspected. Longer incubation times may increase yield.

Blood cultures are positive in 10 to 30% of cases of acute brucellosis, but this rate can be as high as 85% with *B. melitensis*. The sensitivity of blood cultures decreases with increasing duration of illness. In *B. melitensis* infection, bone marrow cultures are more sensitive than blood cultures. In localized brucellosis (e.g., lymph nodes, spleen, liver, skeletal system), cultures of purulent material or tissues usually yield *Brucella* organisms. Culture of cerebrospinal fluid is positive in 45% of patients with meningitis.

Immunologic Testing

In the absence of microbiologic confirmation or specimens for nucleic acid amplification testing, a presumptive diagnosis can be made by history and serology.[14] The most frequently used test, which is the standard (tube) agglutination test (SAT), measures antibody titers against *B. abortus* antigen. A four-fold or greater rise in titer over 2 weeks is considered significant. A presumptive case is one in which the agglutination titer is positive (1:160 in endemic areas; 1:80 in nonendemic areas) in single or serial specimens, with symptoms consistent with brucellosis. This test detects antibodies to *B. abortus, B. suis,* and *B. melitensis* but not to *B. canis*. Serologic confirmation of *B. canis* infection requires *B. canis* or *B. ovis* antigen. Titers are not useful in differentiating relapsing infection from other febrile illnesses in patients with a history of past *Brucella* infections.

In chronic brucellosis, antibodies which do not agglutinate at neutral pH increase and replace agglutinating antibodies, and so a complementary test that detects antibodies to smooth lipopolysaccharide, such as the *Brucella* Coombs test is recommended. The U.S. Centers for Disease Control and Prevention uses a modified SAT known as the *Brucella* microagglutination test (BMAT). False-positive SAT titers have been associated with *Brucella* skin testing, cholera vaccination, or infection with *Vibrio cholerae, Francisella tularensis*, or *Yersinia enterocolitica*.

TREATMENT

Effective treatment of *Brucella* infection requires antibiotics that can penetrate the intracellular compartment, have little or no toxicity even with the prolonged use needed to prevent relapse, and are bactericidal for adequate treatment of central nervous system infection and endocarditis (Table 286-2). There remains considerable debate over which antibiotic regimen is best. In adults, the combination of oral doxycycline at 100 mg orally twice a day for 6 weeks plus either streptomycin 1 g intramuscularly daily for 3 weeks or gentamicin 3 to 5 mg/kg/day for 1 to 2 weeks is the preferred regimen.[A1] A quinolone plus rifampicin may be better tolerated than doxycycline plus rifampicin as alternative therapy.[15] These regimens are less effective for cases of spondylitis, which may require up to 3 months of treatment with any of the previous regimens. For *Brucella* endocarditis (Chapter 61), medical treatment alone is associated with a much higher risk of death compared with a combined medical and surgical approach. About 25% of prosthetic joint infections respond to medical therapy, but the remainder need débridement or revision.[16]

TABLE 286-2 TREATMENT FOR BRUCELLOSIS

	TREATMENT	COMMENTS
Acute, with no endocarditis or CNS involvement; not pregnant; children older than 8 years old	Preferred: oral doxycycline (200 mg/day) for 6 weeks PLUS IM streptomycin (1 g/day) for 2-3 weeks OR IM gentamicin 3-5 mg/kg/day for 1-2 weeks Alternatives: oral ofloxacin (800 mg/day) PLUS rifampin (15 mg/kg/day) for 6 weeks; oral doxycycline (200 mg/day) PLUS rifampin (15-20 mg/kg/day, maximum 900 mg) for 6 weeks; oral doxycycline (200 mg/day) PLUS TMP-SMX (10/50 mg/kg, maximum 320/1600 mg in 2 doses) for 6 weeks; oral TMP-SMX (10/50 mg/kg, maximum 320/1600 mg in 2 doses) PLUS rifampin (15-20 mg/kg/day, maximum 900 mg) for 6 weeks (preferred regimen in children <8 years old); oral rifampin or doxycycline at above doses × 6 weeks PLUS gentamicin (5 mg/kg IM in 1-3 doses) for 5-10 days	Treatment of choice by WHO; widely used; low rate of relapse; IM administration of streptomycin may be difficult; gentamicin is more readily available
In children <8 years old and pregnant women	Oral TMP-SMX (10/50 mg/kg, maximum 320/1600 mg in 2 doses) PLUS rifampin (15-20 mg/kg/day, maximum 900 mg) for 6 weeks	
CNS disease	Oral doxycycline (200 mg/day) PLUS rifampin (15-20 mg/kg/day, maximum 900 mg) and TMP-SMX (10/50 mg/kg, maximum 320/1600 mg in 2 doses) for 6 weeks, but can extend longer if with residual disease	Third-generation cephalosporin such as ceftriaxone 2 g IV q12 × 6 weeks can be substituted for one of the agents if susceptible
Localized disease	Surgically drain abscesses PLUS antimicrobial therapy for ≥6 weeks	
Brucella endocarditis	Bactericidal drugs (fluoroquinolones, aminoglycosides, β-lactams if susceptible; for 6 weeks; see earlier for dosing); early valve replacement may be necessary	Possible aortic valve destruction and/or major arterial emboli

CNS = central nervous system; IM = intramuscular; IV = intravenous; TMP-SMX = trimethoprim-sulfamethoxazole; WHO = World Health Organization.

PREVENTION

The control of human brucellosis is directly related to prevention programs in domestic animals and the avoidance of unpasteurized milk and milk products. In slaughterhouses, important means of prevention include careful wound dressing, the use of protective glasses and clothing, the prohibition of raw meat ingestion, and the use of previously infected (immune) individuals in high-risk areas. Work is ongoing to find an effective vaccine for humans. Postexposure antimicrobial prophylaxis is controversial.

PROGNOSIS

The majority of infected individuals recover completely without sequelae if diagnosed early with prompt initiation of therapy. With early antimicrobial therapy, brucellosis is usually cured, and cases of relapsing brucellosis, chronic brucellosis, or localized complications are rare. With acute brucellosis, however, severe weakness and fatigue may frequently make patients unable to work for up to 2 months.

Immunity to reinfection follows initial *Brucella* infection in the majority of individuals. Of the patients who die of brucellosis, 84% have endocarditis involving a previously abnormal aortic valve, often associated with severe heart failure.

Relapsed Infection

Up to 10% of patients with brucellosis relapse after antimicrobial therapy because of intrinsic or acquired resistance to antibiotics. Antimicrobial agents may be unable to penetrate efficiently enough to kill all intracellular bacteria. Relapses usually occur 3 to 6 months after completion of therapy but may be seen up to 2 years after initial treatment. Relapsing infection is difficult to distinguish from reinfection in high-risk groups with continued exposure. Relapses are associated with inappropriate or insufficient antimicrobial therapy, growth on blood cultures during the initial presentation, and an acute onset of disease. Triple-combination doxycycline (200 mg a day in 1 to 2 doses for 6 weeks), streptomycin (1 g IV/IM once a day for 2 to 3 weeks), and rifampicin (600 to 900 mg once a day for 6 weeks) clears *Brucella* DNA better than dual therapy and may be useful for treatment in chronic brucellosis.

Chronic brucellosis, which is defined as disease that persists for more than 1 year, occurs in perhaps 5 to 20% of cases. A majority of patients classified as having chronic brucellosis really have persistent disease caused by inadequate treatment of the initial episode, or they have focal disease in bone, liver, or spleen. About 20% of patients diagnosed with chronic brucellosis complain of persistent fatigue, malaise, and depression. Treatment is as for the acute infection, typically using alternative antibiotics other than what were used acutely.

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287 TULAREMIA AND OTHER *FRANCISELLA* INFECTIONS

KAREN C. BLOCH AND FRED A. LOPEZ

DEFINITION

Tularemia is an infectious zoonosis caused by *Francisella tularensis*, which is an aerobic, pleomorphic, gram-negative bacillus. Many animal species harbor this organism, most prominently rabbits, squirrels, and muskrats. Humans acquire the infection by various means, including direct contact with infected animal tissues, ingestion of contaminated water or meat, the bite of an infected tick or deer fly, or inhalation of aerosolized bacteria.[1] *F. tularensis* is highly infectious and is a well-recognized risk to laboratory personnel who manipulate culture plates of the organism. Deer flies can transmit the infection from animals to humans, and colloquially the disease is often referred to as *rabbit fever* or *deer fly fever*.

The Pathogen

The organism occurs in two major subspecies (biovars).[2] *F. tularensis* biovar *tularensis* (type A), which is the common North American biovar, can be further divided into two subtypes. A.1, which is the most virulent strain, is endemic to the central eastern regions along the west coast of the United States. Subtype

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TABLE 286-2 TREATMENT FOR BRUCELLOSIS

	TREATMENT	COMMENTS
Acute, with no endocarditis or CNS involvement; not pregnant; children older than 8 years old	Preferred: oral doxycycline (200 mg/day) for 6 weeks PLUS IM streptomycin (1 g/day) for 2-3 weeks OR IM gentamicin 3-5 mg/kg/day for 1-2 weeks Alternatives: oral ofloxacin (800 mg/day) PLUS rifampin (15 mg/kg/day) for 6 weeks; oral doxycycline (200 mg/day) PLUS rifampin (15-20 mg/kg/day, maximum 900 mg) for 6 weeks; oral doxycycline (200 mg/day) PLUS TMP-SMX (10/50 mg/kg, maximum 320/1600 mg in 2 doses) for 6 weeks; oral TMP-SMX (10/50 mg/kg, maximum 320/1600 mg in 2 doses) PLUS rifampin (15-20 mg/kg/day, maximum 900 mg) for 6 weeks (preferred regimen in children <8 years old); oral rifampin or doxycycline at above doses × 6 weeks PLUS gentamicin (5 mg/kg IM in 1-3 doses) for 5-10 days	Treatment of choice by WHO; widely used; low rate of relapse; IM administration of streptomycin may be difficult; gentamicin is more readily available
In children <8 years old and pregnant women	Oral TMP-SMX (10/50 mg/kg, maximum 320/1600 mg in 2 doses) PLUS rifampin (15-20 mg/kg/day, maximum 900 mg) for 6 weeks	
CNS disease	Oral doxycycline (200 mg/day) PLUS rifampin (15-20 mg/kg/day, maximum 900 mg) and TMP-SMX (10/50 mg/kg, maximum 320/1600 mg in 2 doses) for 6 weeks, but can extend longer if with residual disease	Third-generation cephalosporin such as ceftriaxone 2 g IV q12 × 6 weeks can be substituted for one of the agents if susceptible
Localized disease	Surgically drain abscesses PLUS antimicrobial therapy for ≥6 weeks	
Brucella endocarditis	Bactericidal drugs (fluoroquinolones, aminoglycosides, β-lactams if susceptible; for 6 weeks; see earlier for dosing); early valve replacement may be necessary	Possible aortic valve destruction and/or major arterial emboli

CNS = central nervous system; IM = intramuscular; IV = intravenous; TMP-SMX = trimethoprim-sulfamethoxazole; WHO = World Health Organization.

PREVENTION

The control of human brucellosis is directly related to prevention programs in domestic animals and the avoidance of unpasteurized milk and milk products. In slaughterhouses, important means of prevention include careful wound dressing, the use of protective glasses and clothing, the prohibition of raw meat ingestion, and the use of previously infected (immune) individuals in high-risk areas. Work is ongoing to find an effective vaccine for humans. Postexposure antimicrobial prophylaxis is controversial.

PROGNOSIS

The majority of infected individuals recover completely without sequelae if diagnosed early with prompt initiation of therapy. With early antimicrobial therapy, brucellosis is usually cured, and cases of relapsing brucellosis, chronic brucellosis, or localized complications are rare. With acute brucellosis, however, severe weakness and fatigue may frequently make patients unable to work for up to 2 months.

Immunity to reinfection follows initial *Brucella* infection in the majority of individuals. Of the patients who die of brucellosis, 84% have endocarditis involving a previously abnormal aortic valve, often associated with severe heart failure.

Relapsed Infection

Up to 10% of patients with brucellosis relapse after antimicrobial therapy because of intrinsic or acquired resistance to antibiotics. Antimicrobial agents may be unable to penetrate efficiently enough to kill all intracellular bacteria. Relapses usually occur 3 to 6 months after completion of therapy but may be seen up to 2 years after initial treatment. Relapsing infection is difficult to distinguish from reinfection in high-risk groups with continued exposure. Relapses are associated with inappropriate or insufficient antimicrobial therapy, growth on blood cultures during the initial presentation, and an acute onset of disease. Triple-combination doxycycline (200 mg a day in 1 to 2 doses for 6 weeks), streptomycin (1 g IV/IM once a day for 2 to 3 weeks), and rifampicin (600 to 900 mg once a day for 6 weeks) clears *Brucella* DNA better than dual therapy and may be useful for treatment in chronic brucellosis.

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287 TULAREMIA AND OTHER *FRANCISELLA* INFECTIONS

KAREN C. BLOCH AND FRED A. LOPEZ

DEFINITION

Tularemia is an infectious zoonosis caused by *Francisella tularensis*, which is an aerobic, pleomorphic, gram-negative bacillus. Many animal species harbor this organism, most prominently rabbits, squirrels, and muskrats. Humans acquire the infection by various means, including direct contact with infected animal tissues, ingestion of contaminated water or meat, the bite of an infected tick or deer fly, or inhalation of aerosolized bacteria.[1] *F. tularensis* is highly infectious and is a well-recognized risk to laboratory personnel who manipulate culture plates of the organism. Deer flies can transmit the infection from animals to humans, and colloquially the disease is often referred to as *rabbit fever* or *deer fly fever*.

The Pathogen

The organism occurs in two major subspecies (biovars).[2] *F. tularensis* biovar *tularensis* (type A), which is the common North American biovar, can be further divided into two subtypes. A.1, which is the most virulent strain, is endemic to the central eastern regions along the west coast of the United States. Subtype

ABSTRACT

Tularemia is a zoonotic infection that causes human disease throughout the world. Infection is spread by direct contact with animals, ingestion of contaminated food or water, an insect bite, or inhalation of aerosolized bacteria. This latter mechanism of transmission makes tularemia a potential agent of bioterrorism. Classically, six distinct clinical syndromes have been described but with significant overlap among these presentations. Symptoms typically develop within a week of exposure, and fever is almost universally present. Clinical presentations include ulceroglandular disease characterized by skin lesions and lymphadenopathy, typhoidal disease presenting as an undifferentiated febrile illness, oculoglandular disease characterized by ocular inflammation and regional lymphadenopathy, oropharyngeal disease characterized by pharyngitis, and pneumonic disease. Regardless of the syndrome, the recommended treatment is streptomycin or gentamicin, but other agents, including doxycycline and fluoroquinolones, have activity against this organism. No vaccine is commercially available, and prevention entails reducing exposure to vectors.

KEYWORDS

tularemia
Francisella
zoonoses
vector-borne infections
bioterrorism agents
pneumonia
lymphadenopathy
skin ulcers
pulse-temperature dissociation
ulceroglandular
oculoglandular

A.II, which causes a milder disease, is localized to the Western United States.[3] In contrast, *F. tularensis* biovar *holarctica* (type B) is less virulent and occurs commonly in Europe and Asia.[4] Type B is most frequently isolated from rodent species, including muskrats, mice, beavers, voles, water voles, and prairie dogs. An additional subspecies, *F tularensis* biovar *mediasiatica*, has been identified in Central Asia but does not cause human disease.

EPIDEMIOLOGY

Tularemia has been reported in the United States, Canada, Mexico, Japan, and Europe.[5] In Iran, seroprevalence ranges from 2 to 14%, with the highest rates in farmers.[6] It has not been reported in the United Kingdom or the Southern Hemisphere. In the United States, reported cases declined from a high of 2291 cases in 1939 to fewer than 300 cases per year now (E-Fig. 287-1). In the United States, the highest annual incidence rates are in Arkansas (3.1 per 100,000), South Dakota (1.9 per 100,000), and Nebraska (0.9 per 100,000).[7]

In the United States, tularemia is usually acquired from tick bites or from contact with infected animals, especially rabbits. Tick-associated cases, which now constitute the most common route of transmission, primarily occur during the summer. The most common vectors in the United States are the wood tick (*Dermacentor andersoni*), the dog tick (*Dermacentor variabilis*), and the Lone Star tick (*Amblyomma americanum*). A smaller peak of autumn and winter cases is a consequence of rabbit hunters skinning and eviscerating their game. Public health education materials aimed at decreasing the hazards of handling wild animals have contributed to the reduction of tularemia in hunters. Mosquitoes are common vectors in Northern Europe.[8] Occasionally infections occur following the bite of an infected animal or, more likely, from the bite of an animal whose mouth was contaminated from recently eating a diseased animal. The latter likely explains most instances of cat-bite tularemia. Contaminated fresh water is another source of infection.[9]

Males experience a higher incidence of disease than females in all age groups, probably owing to greater exposure to the outdoors and animal-related activities. Persons in all age groups are affected, with children 5 to 14 years of age and older adults most prominently infected. In the United States, Native American and Alaska Natives experience the highest annual incidence (0.5 per 100,000); Whites have a lower risk (0.04 per 100,000), but Blacks and Asians/Pacific Islanders have the lowest risks (≤0.01 per 100,000).

Although tularemia is usually a sporadic infection, outbreaks of disease have been traced to laboratory exposure, contaminated groundwater, muskrat handling, dressing a dead hare, lawn mowing, and brush cutting. In the latter two cases, pneumonic tularemia occurred following creation of an environmental aerosol of organic material that had been contaminated with *F. tularensis* excreted in the urine and feces of infected rodents. An outbreak of oropharyngeal tularemia in Turkey affecting 55 patients was ultimately traced to contaminated tap water. Epidemiologic evaluation following diagnosis of oropharyngeal tularemia in six grape harvesters identified inadvertent crushing of an infected rodent in the freshly pressed grape must with subsequent ingestion as the route of transmission.[10] The organism can survive in water, mud, and straw for weeks to months. Human-to-human transmission has not been reported.

Tularemia's high infectivity (as few as 10 organisms induces pneumonic disease), its ease of dissemination, and the difficulty of rapidly diagnosing acute illness are characteristics that make tularemia a Tier 1 bioterrorism agent (Chapter 19). Infections must be reported immediately to local public health authorities to investigate both conventional and bioterrorist sources.

PATHOBIOLOGY

F. tularensis can infect humans through several portals of entry, including the skin, the mucous membranes, and the gastrointestinal and respiratory tracts. The organism persists intracellularly and can multiply within macrophages and other cells. After inoculation into the skin and subcutaneous tissue, local bacterial multiplication evokes a suppurative necrotic reaction, which is characterized by an initial polymorphonuclear response followed by an influx of macrophages and lymphocytes. These suppurative lesions evolve into granulomas. Bacteremia can occur both early and late during this process. The infection can disseminate to the lymph nodes, liver, spleen, lungs, and pleura. Viable *F. tularensis* can persist in tissues for long periods, thereby contributing to the tendency to relapse after treatment.

CLINICAL MANIFESTATIONS

Classically, the clinical manifestations of tularemia have been separated into six categories: ulceroglandular, glandular, oculoglandular, typhoidal, oropharyngeal, and pneumonic.[11] However, many patients have features of several types. The course of illness is determined by the portal of entry, the degree of systemic involvement, and the dose and virulence of the infecting strain of *F. tularensis*.

The general features of tularemia are similar regardless of the portal of entry. After exposure, the usual incubation period is 3 to 5 days (range, 1 to 21 days). The disease begins abruptly with the onset of fever (≥101° F), chills, malaise, and headache. Myalgia, vomiting, sore throat, and abdominal pain can also occur. Almost 50% of patients have a pulse rate that is substantially slower than would be anticipated based on the degree of fever (pulse-temperature dissociation). The fever may abate somewhat after 1 to 3 days, only to recur and continue, accompanied by other symptoms, for 2 to 3 weeks. Untreated, weight loss, easy fatigability, and lymphadenopathy may persist for weeks longer.

Ulceroglandular Disease

Ulceroglandular disease is the form of infection most readily recognized by physicians. In addition to fever and other constitutional symptoms, the patient calls attention to tender, swollen lymph nodes that drain an inoculation site. The nodes are usually axillary or inguinal, and a local lesion appears concurrently or 1 or 2 days before or after the lymphadenopathy. The lesions at the site of inoculation begin as small, red, tender, or painful papules that progress to pustules and then undergo necrosis to produce an ulcer with sharp, somewhat elevated edges and a flat base that becomes black (Fig. 287-1). Untreated, the ulcers heal over a period of weeks and leave scars.[12] Tick-induced infections produce lesions on the trunk, about the waist, and in the perineum, as well as local adenopathy. Children often have occipital and cervical adenopathy from tick bites on the neck and in the hair. Animal exposure often produces lesions, which may be multiple, on the hands and forearms. Because the organisms evoke a localized granulomatous response, frank lymphangitis does not occur in uncomplicated tularemia, but an occasional patient manifests a chain of nodules in sporotrichoid fashion along the lymphatic drainage.

Patients with such apparently localized disease often have symptoms and findings indicating a more widespread infection. Sore throat with or without an erythematous pharynx occurs. Chest radiography can show patchy infiltrates in the lower lobes, pleural effusions, and hilar adenopathy.

Glandular and Typhoidal Disease

Glandular disease is essentially the same clinical syndrome as ulceroglandular disease but without an obvious local lesion. The patient has fever, constitutional symptoms, and lymphadenopathy. The local lesion may have been on a part of the body where it was not seen, or it may have been small and already healed by the time the patient sought medical care. Glandular disease accounts for only 3 to 20% of cases.

In typhoidal disease, which accounted for nearly 50% of cases in a series of patients in Arkansas, the patient does not have lymphadenopathy and essentially presents with fever of unknown origin (Chapter 259). In these cases, the illness will not be diagnosed unless the physician specifically considers the possibility of tularemia.

Oculoglandular Disease

Oculoglandular disease is rare (<5% of cases) and occurs when the conjunctival sac is the portal of entry via an aerosol, splash, or contaminated fingers.[13] It is almost always unilateral and can have a dramatic presentation with inflamed, swollen eyelids, chemosis, and painful conjunctivitis. The palpebral conjunctiva often shows small yellow nodules and ulcers, counterparts to the skin lesions of ulceroglandular disease. The affected regional lymph nodes are those of the head and neck.

Oropharyngeal Disease

Oropharyngeal disease, which is also uncommon in the United States, occurs when the mucous membranes of the mouth and pharynx are the portal of entry. Contaminated water or food (inadequately cooked game meat) is the source. Painful exudative pharyngitis and tonsillitis, pharyngeal ulcers, and swollen retropharyngeal and cervical lymph nodes are seen.

Pneumonic Disease

Although pneumonia may be one aspect of the other tularemic syndromes, primary pneumonic tularemia, which is the form of the disease that would result from bioterrorism, accounts for about 10% of reported cases and occurs from inhalational exposure.[14] In addition to fever and malaise, patients may have a dry cough, substernal discomfort, pleural pain, dyspnea, and sore throat, but hemoptysis is uncommon. These pulmonary symptoms may not be very prominent in the context of the systemic illness. The physical examination reflects the extent and distribution of the pneumonic process, which may range

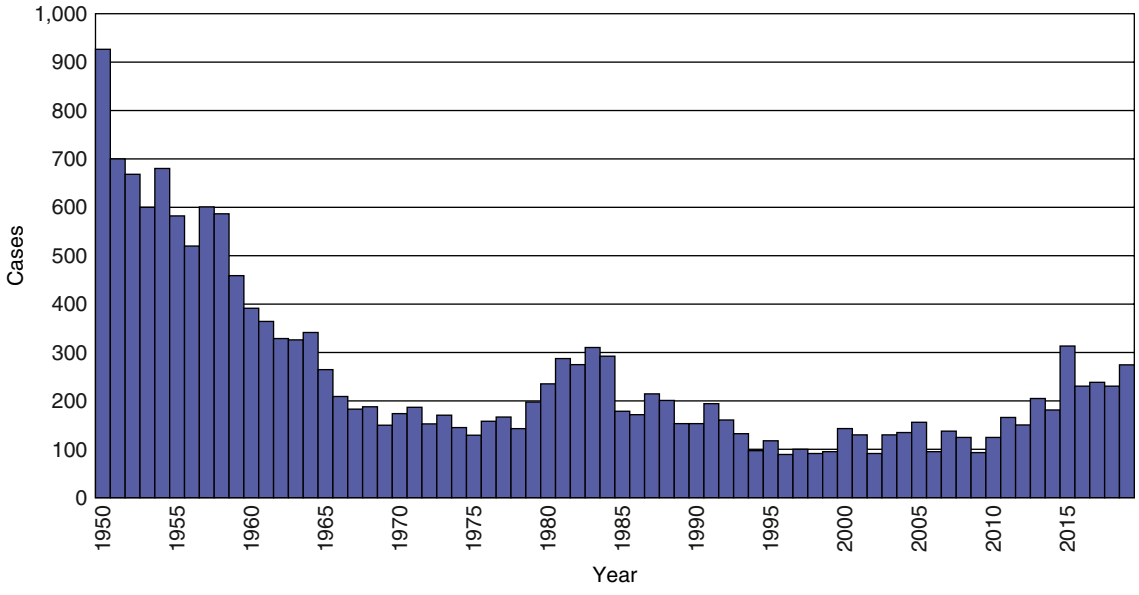

E-FIGURE 287-1. Tularemia cases reported annually in the United States, 1950-2019. (Source: https://www.cdc.gov/tularemia/statistics/index.html.)

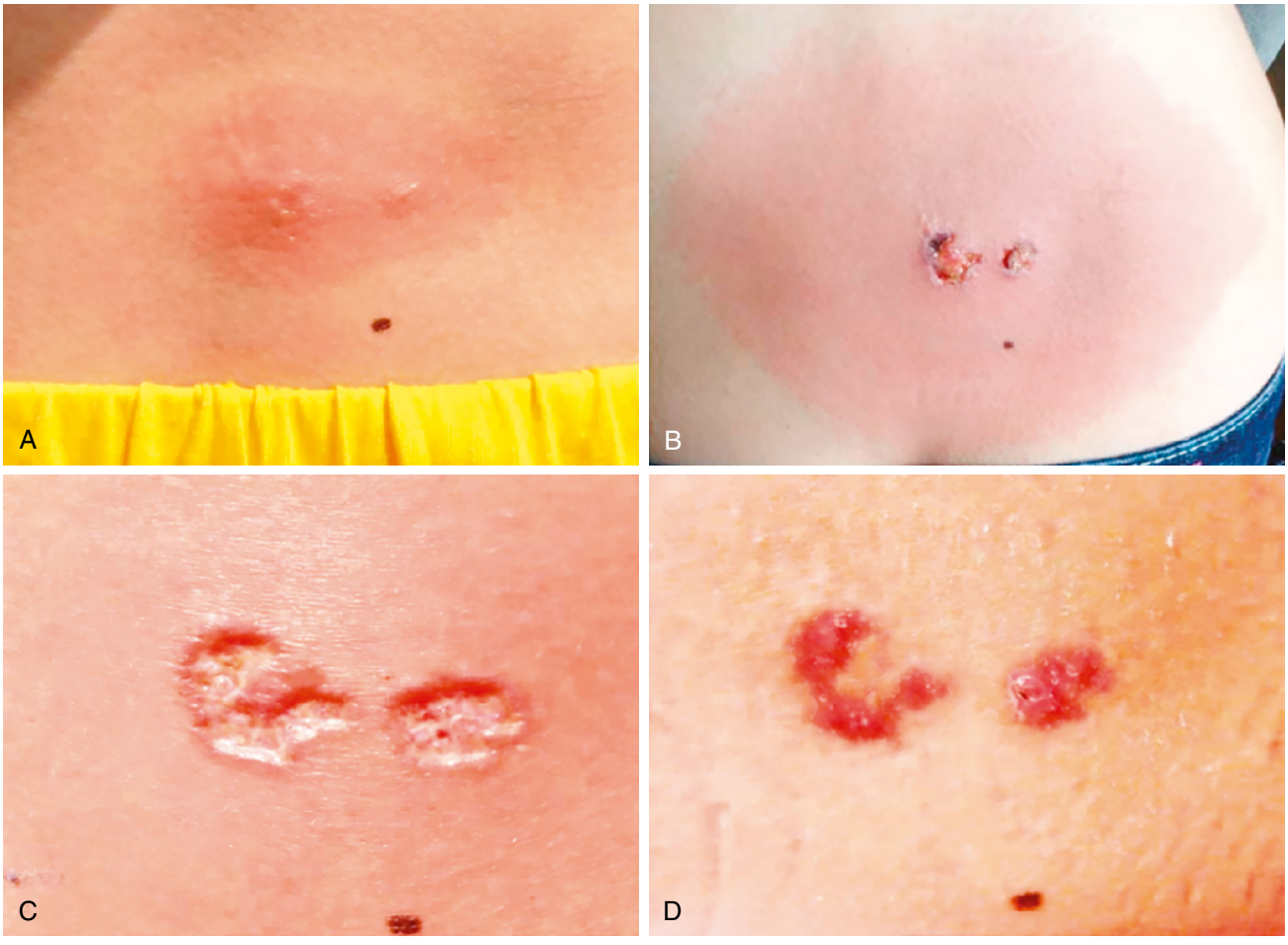

FIGURE 287-1. Ulcerative tularemia. (Source: Holland SD, Michelow IC. Tularemia masquerading as ecthyma. *J Pediatr*. 2016;178:299. doi:10.1016/j.jpeds.2016.07.023. [Epub 2016 Aug 22.])

from barely evident to frank consolidation with pleural effusion. Radiographic findings range from modest peribronchial infiltrates early in the illness to distinctive bronchopneumonia with effusion. Hilar adenopathy is present in more than one third of cases.

Other Clinical Presentations

Intestinal manifestations, including diarrhea, vomiting, or abdominal pain, may predominate. Cardiac involvement, including myocarditis and endocarditis, has been reported. Localized infections of prosthetic joints are increasingly recognized. Tularemia can also be associated with cranial neuropathies,[15] likely as an immune-mediated manifestation.

DIAGNOSIS

Routine laboratory studies are nonspecific. Leukocyte counts may be within normal limits or elevated; thrombocytopenia, elevated liver enzymes, and sterile pyuria occur with some frequency. For pneumonic disease, sputum examination is not helpful. Pleural effusions generally contain more than 1000 lymphocytes/μL. Gram stain results are typically negative, and pleural biopsies occasionally contain granuloma, thus inviting confusion with tuberculosis.

The suspected diagnosis of tularemia, initially based on exposure risk and clinical presentation, is confirmed by diagnostic testing. Identification of the organism in tissue specimens by polymerase chain reaction can provide rapid confirmation of the diagnosis.[16] Serum antibody levels do not reach diagnostic levels until after the 11th day of illness. A presumptive diagnosis can be made based on a single positive titer; a confirmed diagnosis requires seroconversion with a four-fold rise in antibody titers between acute and convalescent specimens.[17] Titers of both immunoglobulin M and immunoglobulin G antibodies may remain elevated for many years after the illness. False-positive serologic cross-reactions have been reported with *Brucella* (Chapter 286), *Legionella* (Chapter 290), *Salmonella* (Chapter 284), and *Yersinia* species (Chapter 288).

F. tularensis may be isolated from blood cultures and tissue specimens when media containing cysteine are used. Especially with typhoidal disease, the diagnosis can be made fortuitously when a positive blood culture is reported. Laboratory personnel should be notified when tularemia is suspected so that appropriate media can be used, incubation can be extended, and Biosafety Level 3 precautions are in place to protect against the production of hazardous aerosols.

Differential Diagnosis

The differential diagnosis of patients with tularemia is substantial. The local lesions can be confused with cat-scratch disease (Chapter 291), brown recluse spider bites (Chapter 98), *Mycobacterium marinum* infection (Chapter 300), herpes simplex infection (Chapter 345), and even syphilis (Chapter 295) and chancroid (Chapter 276) when the lesions are in the perineum or on the penis. Pneumonic tularemia resembles common community-acquired pneumonia (Chapter 85), as well as less common infections such as psittacosis (Chapter 294), legionellosis (Chapter 290), and Q fever (Chapter 302). The glandular and typhoidal forms can resemble typhoid fever (Chapter 284), brucellosis (Chapter 286), ehrlichiosis (Chapter 302), and other illnesses accompanied by nonspecific fevers.

TREATMENT

The preferred antimicrobials are streptomycin (1 g intramuscularly twice daily) or gentamicin (5 mg/kg intramuscularly or intravenously once daily), given for 10 to 14 days[18] (see https://www.cdc.gov/tularemia/clinicians/index.html). For patients with less severe illness, ciprofloxacin (500 to 750 mg orally twice daily for 10 to 14 days) is also effective; alternatively, doxycycline (100 mg orally twice daily for 14 to 21 days) can be used.

In patients who do not have a suggestive history of tick or animal exposure, tularemic pneumonia may be misdiagnosed as poorly responding community-acquired pneumonia (Chapter 85). Either levofloxacin (500 to 750 mg orally daily for a minimum of 5 days) or doxycycline (100 mg orally twice daily for a minimum of 5 days), as commonly used as empirical therapy for community-acquired pneumonia, has activity against tularemia; however, the duration of treatment must be 14 days for tularemia. Patients with glandular disease may require incision and drainage in addition to antibiotics for cure.

Treatment in pregnancy is complicated by the potential teratogenic effects of the first-line therapies. Limited data suggest that azithromycin may be an effective alternative for pregnant women, but the optimal dose and duration are not known and should be guided by expert consultation. Cranial neuropathy is usually treated with intravenous immunoglobulin therapy (0.4 g/kg/d for 5 days) rather than these antibiotics.

PREVENTION

Prevention of tularemia entails minimizing exposure to ticks and avoiding direct exposure to wild animals. Tick protection includes clothing that extends to the wrists and ankles, regular inspection for attached ticks, and the use of insect repellents containing diethyltoluamide (DEET). Gloves should be worn when skinning and dressing game animals, especially rabbits, and all wild rabbit and other game meats should be cooked thoroughly. A live, attenuated vaccine was used in the past to provide some protection to researchers working with *F. tularensis*, but it is no longer licensed in the United States or in Europe.

PROGNOSIS

Before treatment was available, acute tularemia often persisted for as long as 1 month, followed by several months of debility, with a mortality rate that approached 10%. When appropriately diagnosed and treated, however, the mortality rate from tularemia is now 1% or less, and most patients recover fully without long-term sequelae.[19]

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288

PLAGUE AND OTHER *YERSINIA* INFECTIONS

PAUL S. MEAD AND CHRISTINA A. NELSON

The genus *Yersinia* currently contains 26 officially recognized species, of which three are known to be important human pathogens, *Yersinia pestis, Y. enterocolitica,* and *Y. pseudotuberculosis*. The remaining species are generally considered nonpathogenic and are most frequently isolated from environmental sources. Two possible exceptions are *Y. intermedia* and *Y. frederiksenii,* which have been isolated from clinical samples, thereby suggesting a possible role as rare human pathogens.

PLAGUE

DEFINITION

Plague is a life-threatening flea-borne disease that is best known as the cause of the Black Death of the Middle Ages.[1] The illness most often presents with regional lymphadenopathy but can also take the form of a primary pneumonia. Plague can be cured if treated promptly with appropriate antimicrobials.

The Pathogen

Plague is caused by *Y. pestis*, which is a microaerophilic, gram-negative, nonmotile, and nonsporulating coccobacillus that belongs to the family Enterobacteriaceae. *Y. pestis* can exist as a facultative intracellular pathogen and exhibits bipolar staining with Wayson, Giemsa, and Wright stains (Fig. 288-1). *Y. pestis* lacks a true capsule but has a carbohydrate-protein envelope comprising the *capsular* or *fraction 1 antigen*. Although only one serotype is thought to exist, most isolates can be classified into three principal biovars (*Antiqua, Mediaevalis*, and *Orientalis*) based on their ability to ferment glycerol and reduce nitrates. All three biovars occur in Asia, which is generally accepted as the continent where plague originated. Two biovars exist in Africa (*Antiqua* and *Orientalis*), but only *Orientalis* occurs naturally in the Americas. All are highly virulent and appear to cause virtually identical signs and symptoms in humans.

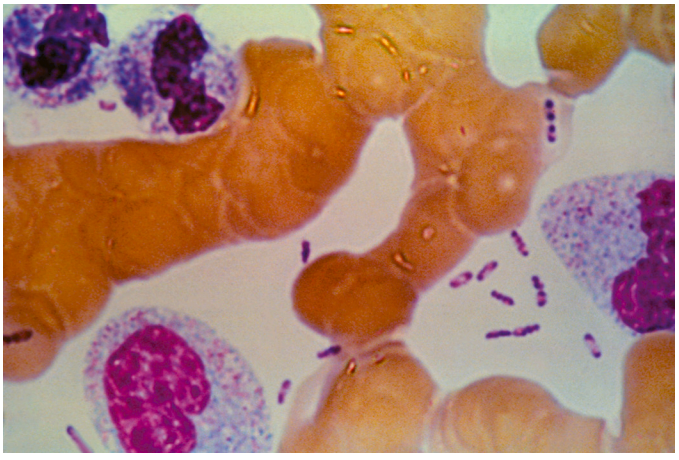

FIGURE 288-1. Wayson-stained blood smear showing bipolar staining bacilli with "safety pin" appearance from a fatal case of human plague. (Centers for Disease Control and Prevention.)

EPIDEMIOLOGY

Plague is endemic in discrete areas of Africa, Asia, and the Americas (E-Fig. 288-1), including the Western United States (Fig. 288-2).[2] In nature, *Y. pestis* is maintained by transmission cycles involving certain rodent species and their fleas, which act as vectors. Two general types of cycles have been postulated. Enzootic cycles involve low-level transmission among relatively resistant rodent species and are thought to pose little immediate risk to humans. Spread to more susceptible rodent species, however, can trigger an epizootic cycle in which the pathogen spreads rapidly through the rodent population, causing mass mortality. As rodent hosts die, infected fleas seek blood meals from nonrodent species, including humans. Although nonrodent mammals are typically dead-end hosts, some secondary transmission can occur, and rodent-consuming carnivores and raptors can potentially spread the disease to neighboring areas through the transport of infected rodent fleas. *Y. pestis* has some capacity to survive in soil, and recent work suggests a possible role for free-living ameba in maintaining *Y. pestis* in the environment.[3]

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Despite the presence of plague-endemic areas on multiple continents, human infection is relatively uncommon. Prior to the discontinuation of routine notification in 2007, only 1000 to 6000 human plague cases were reported to the World Health Organization (WHO) each year. Over the last half century, the bulk of reported human cases has shifted from southeast Asia to sub-Saharan Africa. According to the most recently released WHO statistics covering the period 2013 through 2018, Madagascar, the Democratic Republic of Congo, Uganda, and Tanzania accounted for 97% of the world's reported cases (see E-Fig. 288-1). Another 3% were reported from three countries in

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Treatment in pregnancy is complicated by the potential teratogenic effects of the first-line therapies. Limited data suggest that azithromycin may be an effective alternative for pregnant women, but the optimal dose and duration are not known and should be guided by expert consultation. Cranial neuropathy is usually treated with intravenous immunoglobulin therapy (0.4 g/kg/d for 5 days) rather than these antibiotics.

PREVENTION

Prevention of tularemia entails minimizing exposure to ticks and avoiding direct exposure to wild animals. Tick protection includes clothing that extends to the wrists and ankles, regular inspection for attached ticks, and the use of insect repellents containing diethyltoluamide (DEET). Gloves should be worn when skinning and dressing game animals, especially rabbits, and all wild rabbit and other game meats should be cooked thoroughly. A live, attenuated vaccine was used in the past to provide some protection to researchers working with *F. tularensis*, but it is no longer licensed in the United States or in Europe.

PROGNOSIS

Before treatment was available, acute tularemia often persisted for as long as 1 month, followed by several months of debility, with a mortality rate that approached 10%. When appropriately diagnosed and treated, however, the mortality rate from tularemia is now 1% or less, and most patients recover fully without long-term sequelae.[19]

GENERAL REFERENCES

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288

PLAGUE AND OTHER *YERSINIA* INFECTIONS

PAUL S. MEAD AND CHRISTINA A. NELSON

The genus *Yersinia* currently contains 26 officially recognized species, of which three are known to be important human pathogens, *Yersinia pestis, Y. enterocolitica,* and *Y. pseudotuberculosis*. The remaining species are generally considered nonpathogenic and are most frequently isolated from environmental sources. Two possible exceptions are *Y. intermedia* and *Y. frederiksenii,* which have been isolated from clinical samples, thereby suggesting a possible role as rare human pathogens.

PLAGUE

DEFINITION

Plague is a life-threatening flea-borne disease that is best known as the cause of the Black Death of the Middle Ages.[1] The illness most often presents with regional lymphadenopathy but can also take the form of a primary pneumonia. Plague can be cured if treated promptly with appropriate antimicrobials.

The Pathogen

Plague is caused by *Y. pestis*, which is a microaerophilic, gram-negative, nonmotile, and nonsporulating coccobacillus that belongs to the family Enterobacteriaceae. *Y. pestis* can exist as a facultative intracellular pathogen and exhibits bipolar staining with Wayson, Giemsa, and Wright stains (Fig. 288-1). *Y. pestis* lacks a true capsule but has a carbohydrate-protein envelope comprising the *capsular* or *fraction 1 antigen*. Although only one serotype is thought to exist, most isolates can be classified into three principal biovars (*Antiqua, Mediaevalis*, and *Orientalis*) based on their ability to ferment glycerol and reduce nitrates. All three biovars occur in Asia, which is generally accepted as the continent where plague originated. Two biovars exist in Africa (*Antiqua* and *Orientalis*), but only *Orientalis* occurs naturally in the Americas. All are highly virulent and appear to cause virtually identical signs and symptoms in humans.

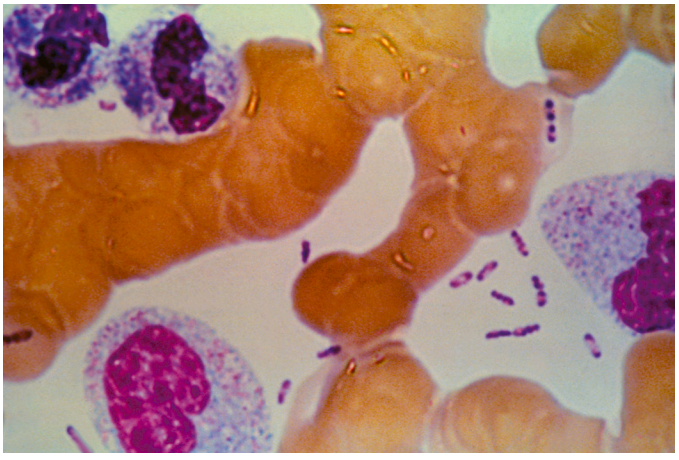

FIGURE 288-1. Wayson-stained blood smear showing bipolar staining bacilli with "safety pin" appearance from a fatal case of human plague. (Centers for Disease Control and Prevention.)

EPIDEMIOLOGY

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ABSTRACT

The genus *Yersinia* includes *Yersinia pestis*, which is the flea-transmitted cause of plague, as well as two enteric pathogens, *Y. enterocolitica* and *Y. pseudotuberculosis,* which are transmitted primarily through fecal-oral routes. The three species share a number of identified virulence factors, some of which are regulated in a temperature-dependent manner. Plague occurs in discrete, endemic areas in Asia, Africa, and North and South America. The enteric yersinioses are more cosmopolitan in distribution. Whereas human infection with *Y. pestis* is life-threatening without prompt antimicrobial treatment, the enteropathic *Yersinia* typically cause self-limited illness that does not require antimicrobial therapy.

KEYWORDS

Yersinia pestis
Yersinia enterocolitica
Yersinia pseudotuberculosis
human
plague
yersiniosis
bubo
enterocolitis
pseudoappendicitis

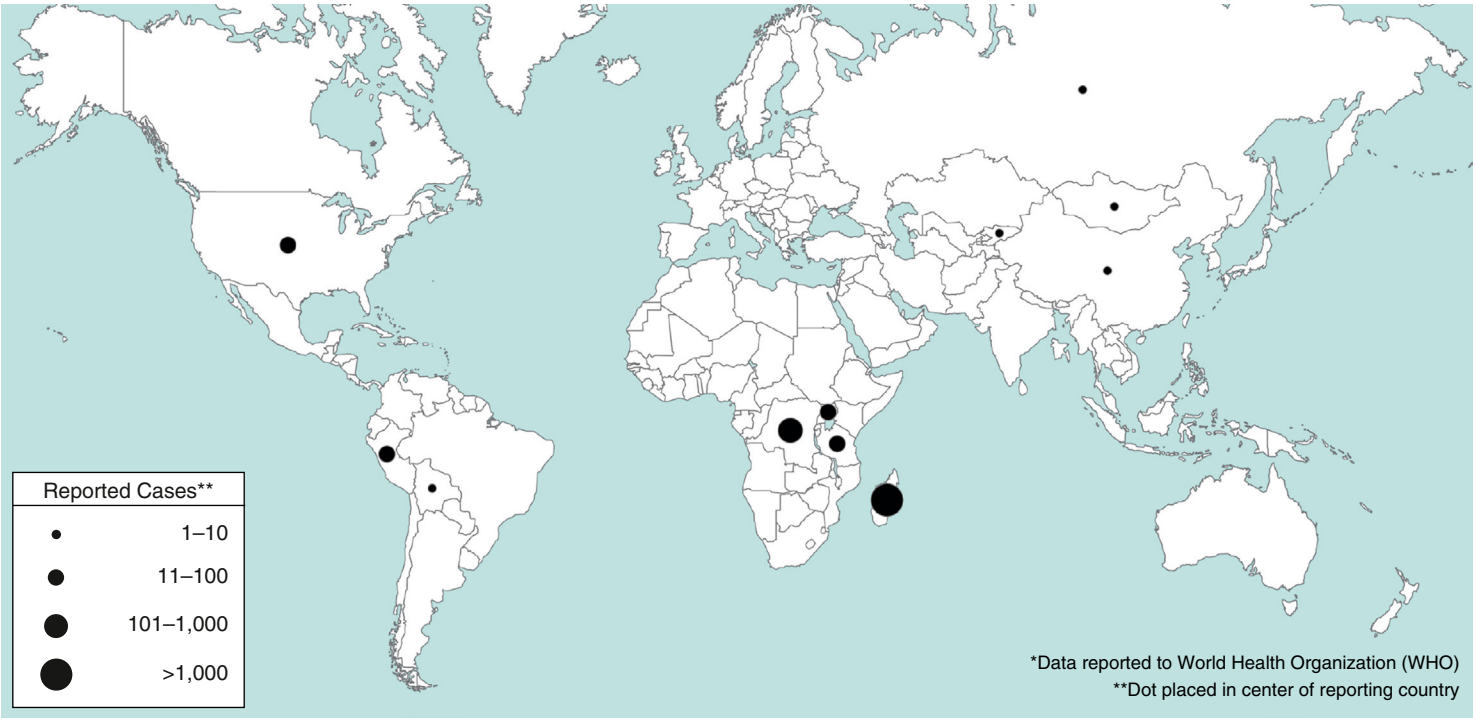

E-FIGURE 288-1. Worldwide distribution of plague in humans, 2013 to 2018. (Data compiled from the World Health Organization, Centers for Disease Control and Prevention, and other sources.)

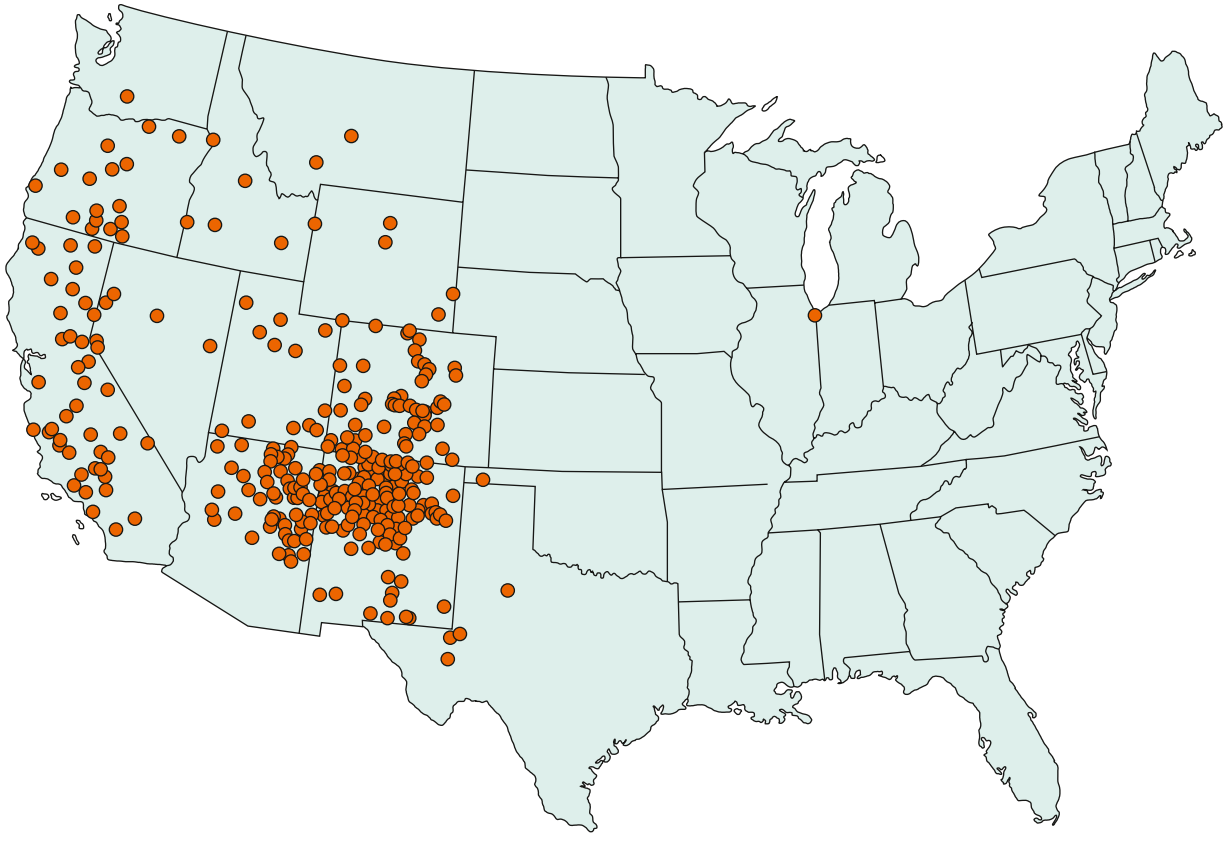

FIGURE 288-2. Distribution of human plague cases in the United States, 1970 to 2019. One dot per plague case is placed randomly within the county where exposure occurred. (Centers for Disease Control and Prevention.)

the Americas—Bolivia, Peru, and the United States; Asian countries accounted for only 0.4% of total cases.

Much of the concern regarding plague stems not from the average case counts but from the potential for sudden outbreaks. In August 2017, for example, a man in Madagascar died of pneumonic plague during a long bush taxi ride that triggered an outbreak in which over 2400 suspected cases were identified.[4] Although it is likely that many of these patients did not actually have plague, the economic and social consequences were substantial.

In the United States, plague is found in the continental states west of the 100th meridian. New Mexico accounts for the majority of human cases, followed by Arizona, California, and Colorado (see Fig. 288-2). Since 2000, the annual number of cases has ranged from 1 to 17, with most cases occurring in the spring and summer. Cases are occasionally reported in other states, either due to travel to the west or to laboratory exposure, as occurred in Illinois in 2009. Occupation-related infection has occurred among veterinary staff, biologists, and trappers, including cases of primary pneumonic plague among persons handling cats or dogs with signs of plague pneumonia, pharyngitis, or oral abscesses. Although human-to-human spread of primary pneumonic plague has not been confirmed in the United States since 1924, possible person-to-person transmission was identified in 2014 during an outbreak in Colorado.

Concern has been raised that *Y. pestis* could be used as an agent of bioterrorism (Chapter 19). In most projected scenarios, bioterrorists would spread *Y. pestis* in an aerosol form, thereby potentially resulting in numerous primary pneumonic cases, a high mortality rate, and widespread panic. The possibility of engineered resistance to antimicrobials would need to be considered during an intentional release of *Y. pestis*.

PATHOBIOLOGY

Few bacteria are more pathogenic for humans than *Y. pestis*. The organism's virulence reflects the need to achieve high levels of bacteremia in order to ensure onward transmission to uninfected fleas. The process begins when *Y. pestis* enters the body, usually through the bite of an infected flea or other percutaneous exposure. Some bacteria are killed by polymorphonuclear leukocytes. Other bacteria, however, enter into mononuclear cells and are carried via lymphatics to the regional lymph nodes, where they replicate. Infected lymph nodes, termed buboes (Fig. 288-4), can appear edematous and congested early in the course of illness but exhibit little evidence of inflammatory infiltrates or vascular injury histologically. Within a few days, however, they contain massive numbers of *Y. pestis* and heavy neutrophil infiltrates, thereby causing the substantial swelling and tenderness that are the hallmark of bubonic plague. As the illness progresses, hemorrhagic necrosis and vascular damage in the node become apparent; some nodes spontaneously rupture. Additional complications, seen in autopsy specimens, include diffuse hemorrhagic splenic necrosis, renal glomeruli containing fibrin thrombi, and multifocal necrosis in the liver.

Of particular concern is hematogenous spread to the lungs, which can result in secondary pneumonic plague. Secondary pneumonic plague initially presents with scant sputum production and diffuse pulmonary infiltrates. Without prompt treatment, *Y. pestis* spreads from the interstitial spaces of the lung to the pulmonary alveoli; sputum increases in quantity and may become pink or blood tinged. At this point, a patient with secondary pneumonic plague can transmit infection to others through coughed respiratory droplets.

Inhalation of infectious droplets from humans or animals with pneumonic plague causes primary pneumonic infection, which is a rapidly progressive lung infection that is initially lobular, then lobar, and finally multilobar, with large numbers of *Y. pestis* present in the alveoli and pulmonary secretions (Fig. 288-5).

A small percentage of patients with plague develop septicemia in the absence of recognized buboes, pneumonia, or other signs of localized infection, a condition referred to as primary septicemic plague. These patients commonly have abdominal pain without other localizing symptoms, perhaps reflecting infection through the gastrointestinal tract or by a flea bite on the trunk in a location where regional lymph nodes are mostly internal and not clinically apparent.

Successful evasion of the host's immune system by *Y. pestis* is enabled by both chromosomal and plasmid-encoded virulence factors. The ability to escape from the host's innate immune defenses and disseminate to regional lymph nodes depends in part on a protease (Pla) encoded on the 9.5-kb plasmid that helps degrade fibrin clots and promote the production of excess plasmin, which can affect inflammatory exudates, break down extracellular proteins and basement membranes, and reduce levels of chemoattractants. Another virulence factor, *Yersinia* outer protein M, is one of many *Yersinia* outer proteins encoded by genes on the midsized (70 to 75 kb) plasmid of *Y. pestis*. Although such proteins are degraded by the Pla protease, *Yersinia* outer protein M is resistant to its activity and probably aids in the dissemination of *Y. pestis* by competing with platelets for thrombin, thereby reducing clotting, inhibiting

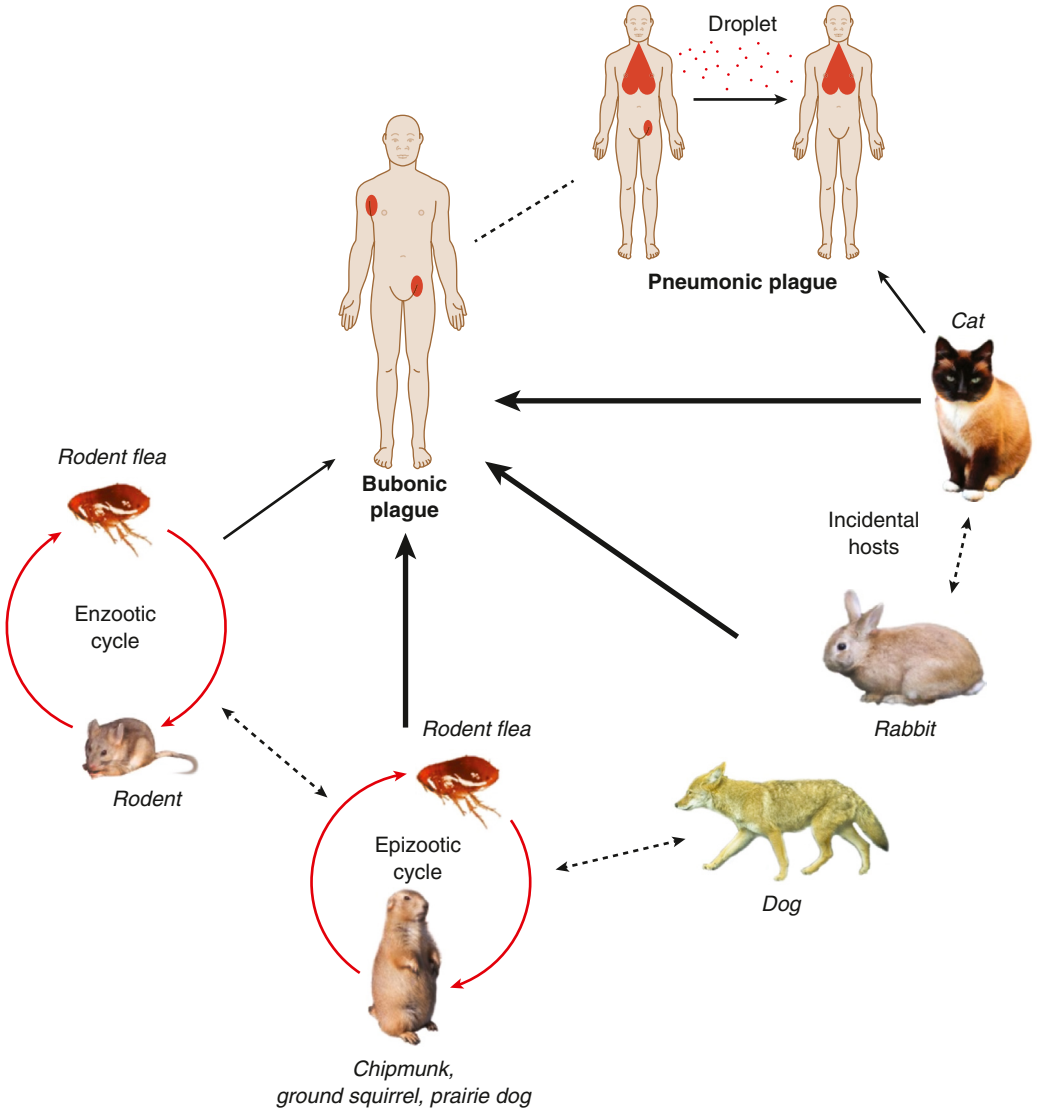

FIGURE 288-3. Ecology and transmission of plague. *Red circles* indicate zoonotic cycles. Common routes of transmission to humans indicated by *bold arrows* and uncommon routes by *thin arrows*. (Centers for Disease Control and Prevention.)

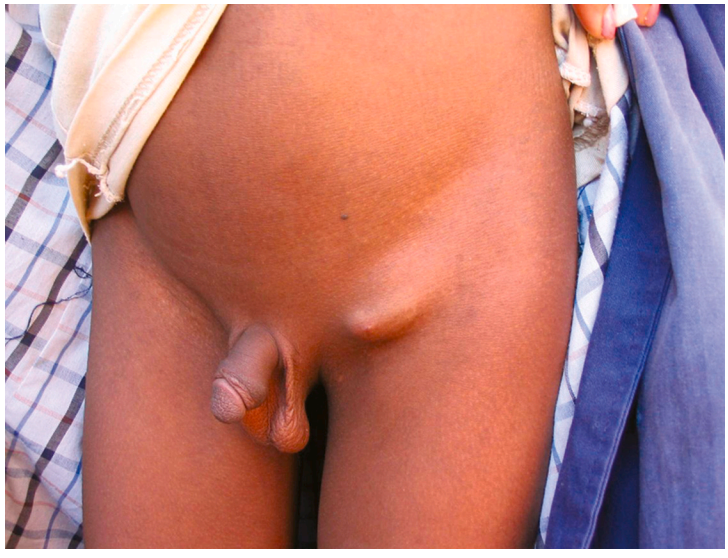

FIGURE 288-4. Young Malagasy boy with a bubo. (Courtesy Brook Yockey, Centers for Disease Control and Prevention.)

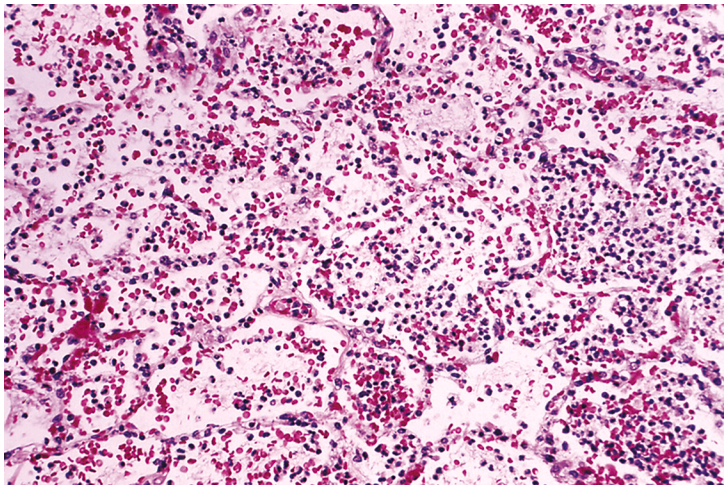

FIGURE 288-5. Photomicrograph of lung tissue from fatal case of primary pneumonic plague. Note filling of alveolar spaces with inflammatory cells and debris. (Centers for Disease Control and Prevention.)

the activation of platelets, and lowering local inflammatory responses.[5] Initial invasion and dispersal to regional lymph nodes also depends on the ability of *Y. pestis* to survive for at least brief periods inside host phagocytes. Survival in such environments is promoted by other *Yersinia* outer proteins that work in concert with a type III secretory apparatus to deliver into host phagocytes those *Yersinia* outer proteins that act as intracellular effectors. These effector proteins disturb the cytoskeletal dynamics of phagocytic cells and block their

FIGURE 288-6. Hand of a patient with plague displaying acral gangrene. (Centers for Disease Control and Prevention.)

production of proinflammatory cytokines. Affected phagocytes are rendered incapable of killing the invading *Y. pestis*, thereby allowing this bacterium to survive extracellularly in lymphoid tissues.

Survival of *Y. pestis* in mammalian hosts also depends on its ability to acquire sufficient quantities of iron for growth. The most important means of iron uptake in *Y. pestis* is a siderophore (yersiniabactin) system that can effectively compete with host iron-binding molecules for this essential nutrient. The capacity of *Y. pestis* to survive within host phagocytes is complemented during later stages of infection by the expression of a glycoprotein capsular antigen (caf1 or fraction 1 antigen) that confers resistance to phagocytosis. Expression of caf1 is temperature dependent, being repressed at the cooler temperatures found in the flea vector and upregulated at mammalian host body temperatures.

CLINICAL MANIFESTATIONS

The three most commonly observed forms of plague (in order of decreasing occurrence) are bubonic, septicemic, and pneumonic. Unusual manifestations of plague include meningitis, pharyngitis, skin ulcers, and osteomyelitis. In rare instances, *Y. pestis* has been inoculated through the conjunctiva, thereby resulting in oculoglandular plague. The incubation periods are 2 to 6 days for bubonic plague and 1 to 4 days for primary pneumonic plague.

Bubonic Plague

The characteristic swollen and tender lymph nodes (buboes) of bubonic plague usually appear in nodes located proximal to the site of initial inoculation (see Fig. 288-4). Most cases of bubonic plague in the United States are thought to be acquired from flea bites on the legs, as indicated by inguinal or femoral lymph node involvement on the side where the flea bite occurred. Axillary buboes, which are also common, result from the handling of an infected animal or carcass. Cervical buboes are uncommon in the United States but prevalent in some developing countries where people may sleep on the floor, thereby increasing their chance of being bitten about the head and neck by infectious fleas. Occasionally, a skin lesion or small papule appears at the site of an infectious flea bite or other source of inoculation.

As the architecture of the infected lymph nodes breaks down, large numbers of *Y. pestis* enter the circulation, thereby producing signs and symptoms typical of gram-negative sepsis, including fever, chills, myalgia, arthralgia, headache, malaise, and prostration. Disseminated intravascular coagulation (Chapter 161) can trigger thrombosis within capillaries, vascular necrosis, ecchymoses, acral gangrene, and cutaneous, mucosal, and serosal petechiae (Fig. 288-6).

Untreated patients with bubonic plague become increasingly toxic, remain febrile, and experience tachycardia, agitation, confusion, delirium, and convulsions. Patients also may develop secondary pneumonic plague with cough, sputum, and the ability to transmit primary pulmonary plague (see later) to others.

Septicemic Plague

Septicemic plague manifests as a rapidly progressive, overwhelming endotoxemia in the absence of clinically apparent bubos. Patients often complain of gastrointestinal symptoms, including nausea, vomiting, diarrhea, and abdominal pain. Disseminated intravascular coagulation (Chapter 161) can also occur with the appearance of petechiae, ecchymoses, bleeding, and ischemia in the tips of the extremities. Later-stage septicemic (Chapter 94) patients are likely to experience refractory hypotension, renal dysfunction, obtundation, and other signs of shock. Patients with late-stage septicemic plague can also exhibit acute respiratory distress syndrome (Chapter 90), which has occasionally been confused in the American Southwest with hantaviral pulmonary syndrome (Chapter 351).

Pneumonic Plague

Pneumonic plague, which occurs 1 to 4 days after inhalation of infected droplets, can be accompanied by fever, cough, chest discomfort that becomes increasingly painful, tachycardia, dyspnea, bacteria-laden sputum, chills, headache, myalgias, weakness, and dizziness. As the illness progresses, patients may experience increasing respiratory distress, hemoptysis, cardiopulmonary insufficiency, and circulatory collapse. In the early stages of illness, patients with primary pneumonic plague may have signs of localized pulmonary involvement, beginning in a single lung and rapidly progressing to segmental consolidation and later bronchopneumonia, with death ensuing in as little as 1 to 3 days after the onset of symptoms. Localized infection is unlikely to be observed in the lungs of patients with secondary pneumonic plague because the lung tissues are infected initially through circulatory spread, which results in a diffuse interstitial pneumonitis. The appearance of sputum also differs in primary versus secondary pneumonic plague, being watery or mucoid, frothy, and perhaps tinged with blood in primary pneumonic cases but scanter, thicker, and more tenacious in secondary pneumonic cases.

DIAGNOSIS

A presumptive diagnosis of *Y. pestis* can be obtained rapidly by detecting *Y. pestis* DNA by polymerase chain reaction (PCR) assays[6] on bubo aspirates, sputum samples, or tracheal washes. Another option is a direct fluorescent antibody assay, but this procedure is generally available only through public health laboratories. Rapid immunochromatographic tests to detect plague antigen or antibodies are available in some countries, but their reliability and clinical performance are not well established, especially when testing sputum.

Laboratory confirmation currently relies on bacterial culture accompanied by specific bacteriophage lysis tests or detection of a four-fold rise in antibody titer to the *Y. pestis* F1 capsular antigen over a period of 2 to 4 weeks. Preferred laboratory samples for culture include blood, bubo aspirates, sputum, bronchoalveolar fluid, and swabs of skin lesions or pharyngeal mucosa. Cerebrospinal fluid also can be collected from patients in whom plague meningitis is suspected. Automated identification systems frequently misidentify *Y. pestis* as a different organism (e.g., *Pseudomonas luteola*, *Y. pseudotuberculosis*) and thereby delay proper diagnosis.

Differential Diagnosis

Plague fatalities are typically related to delays in seeking treatment and to misdiagnosis. The differential diagnosis of plague in its various clinical forms includes staphylococcal (Chapter 267) or streptococcal adenitis (Chapter 269) or pneumonia (Chapter 85), cat-scratch disease (Chapter 291), tularemia (Chapter 287), chancroid (Chapter 276), acute filarial lymphadenitis (Chapter 327), mycobacterial infection (Chapter 300), strangulated inguinal hernia, septicemia caused by other bacteria, meningococcemia, mycoplasma pneumonia and other community-acquired pneumonias, legionnaires disease (Chapter 290), Q fever, influenza pneumonitis (Chapter 332), hantaviral pulmonary syndrome (Chapter 351), and viral pneumonia caused by respiratory syncytial virus (Chapter 330), cytomegalovirus (Chapter 347), or other viruses.

TREATMENT

Because cases of plague can rapidly progress to a life-threatening illness, it is essential that patients with suspected plague receive appropriate empirical antimicrobial therapy immediately after samples are taken. The most commonly recommended agent for treating plague is streptomycin (see Table 288-1), but gentamicin, ciprofloxacin, and levofloxacin are also effective for treating plague in adults and children. Moxifloxacin is another first-line option for adults. Additional options include doxycycline for treating uncomplicated cases of bubonic plague and chloramphenicol[7–9] for plague meningitis. Trimethoprim-sulfamethoxazole is also an alternative option. Antimicrobial resistance has not been identified in North America, but rare instances of in vitro resistance to tetracyclines, streptomycin, and chloramphenicol have been reported from Madagascar.

TABLE 288-1 TREATMENT OF ADULTS AND CHILDREN WITH PNEUMONIC OR SEPTICEMIC PLAGUE OR BUBONIC PLAGUE* AND FOR POSTEXPOSURE PROPHYLAXIS

PATIENT CATEGORY	RECOMMENDED THERAPY
TREATMENT	
Adults	Preferred choices: Streptomycin 1 g IM twice daily Gentamicin 5 mg/kg IM or IV once daily Ciprofloxacin 400 mg IV three times daily or 750 mg PO twice daily Levofloxacin 750 mg IV or PO once daily Moxifloxacin 400 mg IV or PO once daily Alternative choices: Doxycycline 200 mg IV loading dose, then 100 mg IV or PO twice daily Chloramphenicol 12.5-25 mg/kg IV four times daily† Trimethoprim-sulfamethoxazole 5 mg/kg (trimethoprim component) three times daily IV or PO
Children§	Preferred choices: Streptomycin 15 mg/kg IM twice daily (maximum daily dose, 2 g) Gentamicin 4.5-7.5 mg/kg IM or IV once daily‖ Ciprofloxacin 10 mg/kg IV two or three times daily, or 15 mg/kg PO two or three times daily§ Levofloxacin: body weight <50 kg, 8 mg/kg IV or PO twice daily (maximum 250 mg/dose); body weight ≥50 kg, 500-750 mg IV or PO once daily Alternative choices: Doxycycline: if ≥45 kg, give adult dosage; if <45 kg, give 4.4 mg/kg loading dose then 2.2 mg/kg IV twice daily (maximum, 200 mg/day) Chloramphenicol 12.5-25 mg/kg IV four times daily† Trimethoprim-sulfamethoxazole (infants and children aged ≥2 mo to ≤17 yr): 5 mg/kg (trimethoprim component) three times daily IV or PO
Pregnant women	Preferred choice: Gentamicin *plus* either ciprofloxacin or levofloxacin Gentamicin 5 mg/kg IM or IV once daily‖ Ciprofloxacin 400 mg IV three times daily or 500 mg PO three times daily Levofloxacin 750 mg IV or PO once daily Alternative choices: Doxycycline 200 mg IV loading dose, then 100 mg IV or PO twice daily Trimethoprim-sulfamethoxazole 5 mg/kg (trimethoprim component) three times daily IV or PO
POSTEXPOSURE PROPHYLAXIS**	
Adults	Preferred choices: Doxycycline 100 mg PO twice daily†† Ciprofloxacin 500-750 mg PO twice daily Levofloxacin 500-750 mg PO once daily Moxifloxacin 400 mg PO once daily Alternative choice: Trimethoprim-sulfamethoxazole 5 mg/kg (trimethoprim component) PO twice daily
Children§	Preferred choices: Doxycycline††: if ≥45 kg, give adult dosage; if <45 kg, give 2.2 mg/kg PO twice daily Ciprofloxacin 15 mg/kg PO twice daily Levofloxacin: body weight <50 kg, 8 mg/kg PO twice daily (maximum 250 mg/dose); body weight ≥50 kg: 500-750 mg PO once daily. Alternative choice: Trimethoprim-sulfamethoxazole (infants and children ages ≥2 mo to ≤17 yr): 5 mg/kg (trimethoprim component) PO twice daily
Pregnant women	Preferred choices: Ciprofloxacin 500 mg PO three times daily or 750 mg PO twice daily Levofloxacin 750 mg PO once daily Alternative choice: Doxycycline 100 mg PO twice daily††

*Regimens are the same for all three forms of plague, with the exception that doxycycline is considered a first-line agent for patients with bubonic plague. In general, one antimicrobial agent should be selected, and therapy should be continued for 10-14 days. Oral therapy should be substituted when the patient's condition improves. Although animal and limited human studies support its use, gentamicin is not currently approved by the U.S. Food and Drug Administration (FDA) for treatment of plague in humans, nor is trimethoprim-sulfamethoxazole. Streptomycin, levofloxacin, ciprofloxacin, and moxifloxacin are FDA approved for treatment of plague. For details and additional treatment options, see reference below.

†The concentration should be maintained between 5 and 20 μg/mL. Concentrations >25 μg/mL can cause reversible bone marrow suppression.

§In children, the ciprofloxacin dose should not exceed 1 g/day.

‖Aminoglycoside dosages must be adjusted based on renal function. Evidence suggests that gentamicin 5 mg/kg intravenously or intramuscularly once daily would be efficacious in children and may reduce adverse effects. Neonates up to 1 wk of age and premature infants should receive gentamicin 2.5 mg/kg intravenously twice daily.

**The duration of treatment of plague is 10-14 days. The duration of postexposure prophylaxis to prevent plague infection is 7 days.

††Tetracycline can be substituted for doxycycline.

IM = intramuscular; IV = intravenous; PO = oral.

Adapted from Nelson CA, Meaney-Delman D, Fleck-Derderian S, et al. Antimicrobial treatment and prophylaxis of plague: recommendations for naturally acquired infections and bioterrorism response. *MMWR Recomm Rep* 2021;70:1-27.

PREVENTION

Killed whole-cell and live attenuated vaccines have limited efficacy and frequent side effects, and none are recommended or currently available in the United States. Newer recombinant vaccines designed to stimulate immune responses to the F1 and V antigens of *Y. pestis* have yielded promising results and are effective in mice, but they are not licensed for use in humans.

The risk of human plague can be reduced by surveillance programs that rapidly identify human cases or evolving epizootics and allow implementation of intervention measures. When appropriate, affected areas can be treated with insecticides to reduce the risk for flea bite exposure. Efforts also should be made to reduce the amount of food and shelter available to rodents. In rare instances, rodenticides can be used to reduce host numbers, but their use is not recommended before the implementation of effective flea control measures. Persons living in or visiting areas where plague is endemic should avoid contact with sick and dead animals and use insect repellents to reduce the risk for infectious flea bites. Dogs and cats should be prevented from roaming freely in rodent-infested areas, and these animals should be treated with flea control agents that safely and effectively kill fleas. Although most dogs appear to be somewhat resistant to plague, they can become infected and transmit infection directly to humans. Cats are

highly susceptible, often experience severe illness, and can serve as sources of infection for their owners or veterinary staff. Cats that roam outside in endemic areas and suddenly become seriously ill should be taken to a veterinarian for evaluation.

Persons with pneumonic plague should be held in respiratory isolation for at least 48 hours after the initiation of appropriate antimicrobial therapy, and individuals caring for such patients should follow respiratory droplet precautions (masks, gloves, gowns, and eye protection). Although human-to-human transmission has not been confirmed in the United States for many decades, rare cases of primary pneumonic plague have occurred after face-to-face contact with infected cats that had oral lesions or symptoms of pneumonic plague. Veterinary staff from plague-enzootic areas should take appropriate precautions (masks, gloves, gowns, eye protection) when handling sick cats with illnesses suggestive of plague.

Prophylactic antimicrobial therapy is generally recommended for persons with possible plague exposure only in relatively high-risk situations, such as after close contact with patients with pneumonic plague, handling of *Y. pestis*–infected animals, or being bitten by rodent fleas in an area with epizootic activity. The most recently recommended prophylactic antimicrobials are doxycycline, ciprofloxacin, levofloxacin, and moxifloxacin (Table 288-1).

PROGNOSIS

Patients with uncomplicated bubonic plague respond quickly to appropriate antimicrobial therapy and typically defervesce, with relief from most other systemic manifestations within 2 to 5 days. Large buboes can remain swollen, however, for more than 1 week and may require incision and drainage if necrotic. In rare instances, ischemic necrosis in septicemic cases has resulted in the amputation of digits.

The case fatality rate for plague in the United States is typically less than 15% overall and is less than 6% among patients who are treated with an effective antimicrobial. Primary pneumonic plague is nearly always fatal in the absence of prompt antimicrobial treatment. Because septicemic plague is likely to be fulminant and fatal, favorable outcomes depend on rapid diagnosis and prompt treatment with appropriate antimicrobials.

YERSINIOSIS

DEFINITION

Yersiniosis is principally an intestinal illness caused by *Yersinia enterocolitica* or *Y. pseudotuberculosis*. These enteropathogenic species differ substantially from *Y. pestis* in that they rarely cause death and are spread through the fecal-oral route.

The Pathogens

The enteropathogenic *Yersinia* are gram-negative pleomorphic bacilli that grow slowly under aerobic and anaerobic conditions and do not ferment lactose or form spores. Genetically, *Y. enterocolitica* and *Y. pseudotuberculosis* are distant from one another despite producing similar illness in humans. Unlike *Y. pestis*, both species are urease positive and motile at temperatures lower than 30° C. Unlike many Enterobacteriaceae, both species can grow at refrigerator temperatures. *Y. enterocolitica* includes diverse strains that can be divided into six biotypes (1A, 1B, 2-5) and over 70 serotypes, many of which are not human pathogens. Human illness is associated most often with bio/serotypes 1B/O:8, 4/O:3, 2/O:9, and 2,3/O:5,27. *Y. pseudotuberculosis* includes six distinct serotypes (1-6) that are pathogenic for humans.

EPIDEMIOLOGY

Enteropathogenic yersiniae are transmitted by contaminated food and water and occasionally by contact with infected persons or animals. Rare but serious infections have resulted from transfusion of blood from an infected donor. The oral infectious dose is thought to be relatively large, between 10^5 and 10^9 bacteria. *Y. enterocolitica* infection, which accounts for 80 to 90% of cases in most countries, is strongly associated with consumption of contaminated pork products. This route reflects the organism's affinity for colonizing the tonsils of healthy swine. Other species including rabbits, hares, sheep, goats, cattle, rodents, and dogs can harbor pathogenic strains and serve as sources of human infection, either directly or by contamination of milk or produce.

Yersinia pseudotuberculosis, which is also found in a wide range of animals, causes illness and epizootics, particularly among hares and rabbits. Although sources of human infection are less well defined, outbreaks of *Y. pseudotuberculosis* infection in Northern Europe have been linked to stored produce, especially root vegetables and lettuce. Consumption of carrots and lettuce was also identified as a risk factor in an unusually large New Zealand outbreak in 2014. Milk has been implicated as a source for *Y. pseudotuberculosis* outbreaks, as has contact with kittens and puppies.

Yersiniosis occurs worldwide but is generally more common in cooler, temperate regions. Annual rates of reported illness range widely from less than 1 per 100,000 population in parts of southern Europe to more than 20 per 100,000 population in New Zealand.[10] Countries with historically higher rates include the Scandinavian countries, Germany, and Belgium. Dietary practices likely play a role in these high rates, as well as in the apparent rarity of yersinosis in predominantly Muslim countries where pork consumption is discouraged. Bio/serotype 4/O:3, which is found commonly in swine, predominates in most countries. The second most common bio/serotype, 2/O:9, is typically isolated from sheep, cows, and goats. Human infections with *Y. pseudotuberculosis* are most commonly reported in northern Europe and in Asia, including Japan.

In the United States, the reported incidence as determined by culture is approximately 0.4 cases per 100,000. However, when considering results from culture-independent testing, which has become more common in recent years, the incidence in 2021 was 1.4 cases per 100,000 population.[11] From 2015 to 2020, the incidence was highest among adults over age 65 years, at nearly 1.9 cases per 100,000 population, and the peak onset was in the summer months. In the United States, rates are now highest in Whites and lowest in Blacks. Asian and Pacific Islanders have the second highest incidence, slightly lower than that of Whites. Rates among Hispanics are approximately one third that of non-Hispanics.

Transmission by blood transfusion is thought to result from occult bacteremia in donors combined with the bacterium's ability to multiply in blood stored at cold temperatures. Dozens of such cases have been reported, many fatal.

PATHOBIOLOGY

Nearly all pathogenic *Yersinia* share an approximately 70-kb plasmid that encodes key virulence factors. Principal among these are an adhesin, YadA, and a type III secretion system that injects host cells with effector proteins that blunt the immune response and can trigger apoptosis.[12] YadA works in conjunction with chromosomally encoded proteins to promote epithelial cell attachment, host cell invasion, and complement resistance. The pathogenic potential of common *Y. enterocolitica* serotypes is blunted by their limited ability to acquire iron; which may explain their enhanced virulence in hosts with iron-overload syndromes. In contrast, the genomes of *Y. enterocolitica* 1B/O:8 and pathogenic *Y. pseudotuberculosis* include a high pathogenicity island, which encodes a siderophore that enhances the acquisition of iron from the environment and thus virulence. *Y. enterocolitica* also produces a heat-stable enterotoxin, Yst, but its role in pathogensis remains uncertain. Strains of *Y. pseudotuberculosis* from Asia are notable for their production of a superantigen, YPMa, which is implicated in Far East scarlet-like fever syndrome.

Following ingestion, enteropathogenic *Yersinia* penetrate the mucus layer and adhere to mucosal epithelial cells. Areas of the terminal ilium and proximal cecum appear particularly susceptible, though colonization of the tonsils also occurs and can cause pharyngitis. Following attachment, intestinal M cells translocate the pathogen into adjacent Peyer patches, where they can replicate. Spread to mesenteric lymph nodes produces an inflammatory response, mesenteric adenitis, and abdominal pain. Further dissemination may lead to the formation of microabscesses in the liver and spleen.

CLINICAL MANIFESTATIONS

After an incubation period of 3 to 7 days, yersiniosis typically presents as acute enteritis or mesenteric adenitis. Young children are more likely to have fever and diarrhea, which may be bloody and difficult to distinguish from gastroenteritis caused by *Salmonella* (Chapter 284) or *Campylobacter* (Chapter 279). In teenagers and young adults, symptoms of mesenteric adenitis and terminal ileitis are more common and can mimic appendicitis (Chapter 128)[13] with fever and right lower quadrant pain. Abdominal computed tomography (CT) showing mesenteric adenitis with a normal appendix suggests the diagnosis. Pharyngitis occurs in up to 20% of patients and is a diagnostic clue because other infectious enteritidies lack this feature.

Sepsis and metastatic infection are uncommon but a serious threat in patients with underlying conditions. Medical conditions associated with iron overload (e.g., hemochromatosis, thalassemia, cirrhosis) or its treatment (deferoxamine) greatly increase the risk of infection and complications.[14] Other conditions including HIV infection, diabetes, and older age also increase risk. Metastatic spread of infection can result in osteomyelitis, septic arthritis, endocarditis,[15] mycotic aneurysms, ophthalmitis, and meningitis. Although relatively rare, infection by transfusion can result in overwhelming sepsis and shock.

Yersiniosis is remarkable for several extraintestinal complications. Reactive arthritis (Chapter 254), occasionally with uveitis and urethritis, is well described, especially in patients who are positive for the human leukocyte antigen (HLA)-B27. Oligoarticular joint symptoms appear 1 to 3 weeks after infection, most often in the lower extremities. Erythema nodosum is also relatively common, especially among women. Thought to be a form of delayed hypersensitivity, symptoms of erythema nodosum usually begin 2 weeks after onset of gastroenteritis. Rare complications, presumably immunologically mediated, include glomerulonephritis and myocarditis. Rare reports also suggest an association between *Y. pseudotuberculosis* and Kawasaki disease (Chapter 249).

DIAGNOSIS

Yersiniosis should be suspected in patients who have abdominal pain and fever, with or without frank diarrhea. The diagnosis is best accomplished by identifying the bacterium from stool, blood, or other appropriate samples. Culture-independent methods are increasingly common, and PCR or other DNA-based methods are likely to result in more rapid and sensitive detection of these bacteria.[16]

Culture of *Y. enterocolitica* and *Y. pseudotuberculosis* from stool and environmental samples is complicated by the presence of other, faster-growing bacteria in the sample. Biotyping and serotyping, which are often available only in research or public health reference laboratories, can provide useful epidemiologic information.

Tube or microagglutination tests also can identify antibodies to the pathogenic *Y. enterocolitica* serogroups O:3, O:9, O:5,27, and O:8, but cross-reactivity can be a problem, particularly between *Y. enterocolitica* O:9 and *Brucella* spp. Immunologically mediated *Yersinia* illnesses, including reactive arthritis, are associated with the production of immunoglobulin (Ig) antibodies that can be detected by enzyme-linked immunosorbent assay (ELISA) or immunoblotting. IgG antibodies can persist for many years, but persistence of IgA antibodies for more than a few months could indicate a chronic *Yersinia* infection.

TREATMENT

Antimicrobial therapy has not been shown to improve the course of uncomplicated enterocolitis or mesenteric adenitis and is not generally recommended for intestinal forms of the disease. There also is no evidence that antimicrobial treatment reduces the frequency of reactive arthritis or erythema nodosum.

Antimicrobial therapy is recommended, however, for immunocompromised patients, patients with septicemia, and patients with systemic disease or extraintestinal foci of infection. Recommended agents for treatment of sepsis or other severe forms of disease are standard dosages of an aminoglycoside (e.g., gentamicin, 5 mg/kg per day in one to three divided doses) combined with either a third-generation cephalosporin (e.g., ceftriaxone, 2 g per day) or with ciprofloxacin (400 mg IV two to three times daily; all adult dosages). Duration of therapy is poorly defined, but 2 to 3 weeks has proven successful in retrospective series. Emerging resistance to the quinolones has been observed in some countries; and the choice of definitive therapy should be guided by susceptibility testing.

PREVENTION

Vaccines are not currently available. Prevention depends on basic sanitation measures. These include using proper sewage disposal methods, protecting water supplies from contamination with human or animal waste, following appropriate procedures for animal husbandry and slaughtering, thoroughly cooking meats (especially pork), avoiding long-term storage of meats at temperatures higher than 4° C, and consuming only pasteurized milk. Food handlers should thoroughly wash their hands before and after handling potentially contaminated foods, especially pork intestines. Persons with diarrhea should not work in food-handling areas, care for young children, or work with patients, and hospital staff should follow enteric precautions.

PROGNOSIS

Yersiniosis is generally self-limited after a 2- to 3-week course of illness in most healthy individuals, but patients with underlying conditions may experience life-threatening sepsis or metastatic infection. Patients often shed the organism in stool while symptomatic and potentially for up to several months following recovery.

Sequelae most commonly include erythema nodosum, which generally resolves within 1 month, and reactive arthritis, which generally resolves within 6 months. Other sequelae can include endocarditis, pericarditis, and osteomyelitis. As with many other infectious agents, enteropathogenic *Yersinia* has been implicated in the pathogenesis of autoimmune thyroid disease,[17] though a definitive role has not been established.

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289

WHOOPING COUGH AND OTHER *BORDETELLA* INFECTIONS

CHRISTOPHER J. GILL AND ERIK L. HEWLETT

DEFINITION

Whooping cough, also known as pertussis, is a toxin-mediated, highly contagious respiratory illness that affects all age groups and is characterized by distinctive, violent, paroxysmal coughing episodes, which end in the classic inspiratory whoop that gives the disease its name. Each paroxysm may last several minutes, and patients often feel entirely normal between paroxysms. Severe and fatal disease is concentrated among infants, in whom pertussis may be manifested by spells of apnea and cyanosis, alone or in conjunction with coughing. Whooping cough is primarily caused by infection with *Bordetella pertussis* or, much less frequently, *Bordetella parapertussis* or *Bordetella bronchiseptica*.

The Pathogens

Bordetellae are gram-negative coccobacilli, many of which are motile under specific conditions. Sixteen known species of *Bordetella* include the classic species of *B. pertussis*,[1] *B. parapertussis*, and *B. bronchiseptica*, which is primarily a veterinary pathogen. *B. holmesii* is a cause of pulmonary infections and mild whooping cough–like illness, as well as invasive tissue infections. Other *Bordetella* species (E-Table 289-1) are associated with bacteremia and wound infections in patients with comorbid, immune-compromising conditions, such as diabetes, cancer/chemotherapy, or chronic cholangitis. *B. avium* (primarily a pathogen for turkeys and other poultry) and *B. hinzii* can cause difficult-to-treat nosocomial infections, principally sepsis and ventilator-associated pneumonias. Additional bordetellae are present in soil, but little is known about their ability to cause disease in humans.

EPIDEMIOLOGY

Historically, pertussis was a childhood illness. Although children below 1 year of age are at the highest risk of death, more than 50% of cases in the United States now occur in individuals over 10 years of age. However, reported cases likely represent only 5 to 10% of total cases, and the population burden of disease is uncertain. The first-generation whole-cell pertussis vaccines, beginning in the 1940s, reduced total cases by 99% and also shifted the age distribution of disease to adolescents and adults. In unvaccinated populations, pertussis was contracted throughout childhood; although the resultant immunity was not lifelong, continued exposure to pertussis in the population allowed such unvaccinated individuals to reinforce their immunity with little or no subsequent clinical disease. The introduction of acellular pertussis vaccines for infants and children resulted in a marked reduction of disease, except in infants too young to have acquired immunity from vaccination, but the incidence of pertussis increased relatively and absolutely in adolescents and adults, partly due to the relatively brief duration of protection offered by the acellular vaccines, with failure rates approaching 50% after 2 to 3 years.

Beginning in the 1990s, the transition from whole-cell products to acellular pertussis vaccines in response to concerns about the safety of the former contributed to major increases in pertussis, which is now resurgent in the United States and elsewhere in the world. About 20,000 cases of pertussis are now reported annually in the United States, and approximately 60% of these cases are in adolescents and adults.[2] Some of these cases are detected by polymerase chain reaction (PCR) testing only, which explains an increase

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289

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Beginning in the 1990s, the transition from whole-cell products to acellular pertussis vaccines in response to concerns about the safety of the former contributed to major increases in pertussis, which is now resurgent in the United States and elsewhere in the world. About 20,000 cases of pertussis are now reported annually in the United States, and approximately 60% of these cases are in adolescents and adults.[2] Some of these cases are detected by polymerase chain reaction (PCR) testing only, which explains an increase

ABSTRACT

Whooping cough, also known as "pertussis," is a respiratory illness that affects all age groups and is characterized by distinctive, violent, paroxysmal coughing that is followed by gasping inhalation to produce the eponymous "whooping" sound. Pertussis is resurgent in the United States and elsewhere in the world, and vaccine practices have shifted the age-specific incidence of the disease from infants to adolescents and adults. Individuals also can be contagious asymptomatic "carriers." The paroxysmal stage can last several weeks or even months, during which adults seek medical care for chronic cough. Diagnosis by polymerase chain reaction–based tests or by culture have limitations. Antibiotics do not provide symptomatic relief or alter the course of the illness, but they are used because affected individuals can remain culture positive and potentially transmit *Bordetella pertussis* for several weeks after the onset of symptoms. Continued progress in vaccine development is likely to alter vaccination practices.

KEYWORDS

whooping cough
pertussis
paroxysmal stage
diagnosis
vaccine development

E-TABLE 289-1 CHARACTERISTIC FEATURES OF *BORDETELLA* SPECIES

BORDETELLA SPECIES	PRIMARY HOST	PRIMARY SYNDROME	OCCASIONAL SYNDROMES	ROLE OF HOST IMMUNE STATUS		FREQUENCY	TREATMENT	COMMENTS
				NORMAL HEALTHY	IMMUNOCOMPROMIED			
B. pertussis	Humans	Whooping cough	Pneumonia	X		Common	First line: Macrolides Second line: Sulfonamides quinolones Resistant to cephalosporins and penicillins	Highest mortality in young infants. Disease largely mediated by toxins rather than tissue invasion. True burden of disease is likely underestimated.
B. parapertussis	Humans (separate lineage is pathogen for sheep)	Whooping cough (milder than *B. pertussis*)		X		Common	Same as for *B. pertussis*	Similar to pertussis, though milder illness. Carries pertussis toxin gene but does not express it in vivo. Easily missed if using PCR probing for IS481 to screen for *B. pertussis*.
B. holmesii	Humans, possibly birds	Whooping cough (milder than *B. pertussis*)	Pneumonia, bacteremia, endocarditis, septic arthritis	X	X	Common	First line: Quinolones Second line: Macrolides, sulfonamides, carbapenems Resistant to cephalosporins and penicillins	Similar to pertussis but milder and with higher propensity for nonpulmonary disease. Often misclassified as pertussis due to expression of IS481. Most microbiology laboratories are unable to distinguish *B. pertussis* from *B. holmesii*. More susceptible to first-generation cephalosporins and less to macrolides than *B. pertussis*.
B. bronchiseptica	Dogs (kennel cough), pigs, cats, rabbits	Whooping cough (mild)	Pneumonia		X	Rare	First line: Quinolones, tetracyclines, aminoglycosides, and anti-pseudomonal penicillins Generally resistant to macrolides; variable resistance to sulfonamides	Mild disease
B. trematum	Unknown, probably birds	Wound infections			X	Extremely rare	Insufficient data	Identified in wound infections and patients with chronic otitis media. Genetically very similar to *B. avium*, found in birds.
B. ansorpii	Unknown	Bacteremia			X	Extremely rare	Insufficient data	Two case reports only, both in patients undergoing chemotherapy (sarcoma and leukemia)
B. avium	Turkeys, other birds	Chronic and ventilator pneumonias			X	Extremely rare	Insufficient data	Identified in patients with cystic fibrosis in one case series. Formally a subtype of *Alcaligenes faecalis*.
B. hinzii	Unknown	Bacteremia, ventilator pneumonias			X	Extremely rare	Insufficient data	Most cases identified in patients with severe chronic medical illnesses or cancers. Formally a subtype of *A. faecalis*.
B. petrii	Unknown	Bacteremia			X	Extremely rare	Insufficient data	Most recently identified species; case report in a patient with mandibular osteosarcoma

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in the detection of milder and atypical cases. Nevertheless, severe and fatal disease in infants has also increased, thereby suggesting the overall increased burden of disease is real and not an artifact of detection bias.

Pertussis remains endemic even in countries with high rates of vaccination,[3] with spikes in reported cases occurring in the United States in 3- to 5-year cycles, an interval that is postulated to reflect the accumulation of susceptible individuals in the population. The fact that whole-cell pertussis vaccines resulted in a longer interepidemic cycle time strongly suggests that they were more effective than acellular vaccines for interfering with person-to-person transmission, as well as preventing clinical disease. Animal data also indicate that both whole-cell and acellular vaccines block symptomatic disease, but whole-cell vaccines also reduce the density and duration of mucosal carriage, thereby impeding person-to-person spread. Furthermore, infant baboons who have received acellular vaccines remain contagious and easily spread their infection to unvaccinated cage mates.

Worldwide, pertussis continues to be a major problem not only in developed countries with vaccine programs, especially for individuals with chronic health conditions,[4,5] but also in developing countries.[6] For example, Zambia, Pakistan, and South Africa have had ongoing transmission of pertussis. Fortunately, most detected cases were clinically mild and did not progress to classic pertussis, thereby suggesting that the existing vaccine programs are preventing severe disease but not all transmission.

Although *B. pertussis* is a relatively fastidious organism that is not easily cultured, pertussis is a highly contagious infection, with spread believed to be primarily by aerosol droplets from both symptomatic and asymptomatic hosts. Transmission by asymptomatic hosts occurs frequently in adults and in infants, in whom asymptomatic infections are far more common than symptomatic infections.[7]

PATHOBIOLOGY

Pertussis usually is not a tissue-invasive disease; rather, its pathogenesis is mediated indirectly through its toxins acting in situ or, in the case of pertussis toxin, systemically. *B. pertussis* and related organisms produce a number of toxins, and interdiction of pertussis toxin, as, for example, by vaccines that target pertussis toxin can prevent severe disease.[8] The precise molecular mechanisms underlying the classic paroxysmal cough still have not been identified, but bradykinin-induced inflammation and pertussis toxin–mediated interference with the anti-inflammatory effects of sphingosine-1-phosphate[9] appear to be contributing factors.

Knowledge about the toxins and adhesins is important both for their potential roles in pathogenesis and for their use as antigens in acellular pertussis vaccines. Filamentous hemagglutinin,[10] pertactin, and fimbriae are adhesins that are components in most of the acellular vaccines, and all currently available vaccines include pertussis toxoid. Pertussis toxin is a soluble toxin with local and systemic effects, including direct induction of leuko-lymphocytosis and enhancement of glucose-stimulated insulin secretion, both of which may contribute to the pertussis syndrome. Pertussis toxin also has an immunomodulatory effect that promotes prolonged survival of *B. pertussis* in the respiratory tract. Early in disease, pertussis toxin downregulates immune responses and likely perpetuates infection by inhibiting alveolar macrophages on mucosal surfaces and interfering with the recruitment of neutrophils. Later in the disease, pertussis toxin upregulates inflammatory responses, perhaps as a mechanism to enhance shedding and infectivity. Adenylate cyclase toxin binds to CR3 to enter host cells and produce supraphysiologic levels of cyclic adenosine monophosphate (cAMP). The antibacterial functions of macrophages and neutrophils are inhibited by the increased cAMP, thereby leading to limited immunosuppression, which likely enhances the survival of *B. pertussis*.

Bacteria adherent to the cilia cause damage to respiratory epithelial cells, some of which are lost from the mucosa. Mucus secretion is prominent, especially during later stages of the illness. Intracellular *B. pertussis* organisms have been demonstrated, but their significance remains unknown.

CLINICAL MANIFESTATIONS

Following exposure to a patient with active pertussis, typically by aerosol from coughing or sneezing but also likely through asymptomatic chains of transmission, an infected individual will experience an onset of nonspecific upper respiratory symptoms (mainly coryza) about 1 to almost 3 weeks later. Clinical signs that indicate onset of the catarrhal phase (rhinorrhea, increased lacrimation, conjunctival injection, and sometimes low-grade fever) are nonspecific and may be self-resolving. Furthermore, clinically trivial or asymptomatic infections occur commonly,[11] particularly in adults and to a lesser degree in infants, thereby suggesting that asymptomatic adults may be responsible for a substantial fraction of overall transmissions.

Although the classic paroxysmal cough of pertussis is striking and unforgettable, not all symptomatic children or adults experience it.[12] The diagnosis of pertussis often is not even considered until a patient manifests the striking cough, which consists of a series of uncontrollable expirations, followed by gasping inhalation that is responsible for the "whooping" sound. Episodes of coughing can be associated with cyanosis and end with gagging and vomiting. Eighty percent or more of adolescents and adults with classic pertussis have paroxysmal cough, but the frequency of whoop and post-tussive vomiting is variable.[13] This paroxysmal stage can persist more than 4 weeks, and the development of fever or worsening pulmonary function during this time suggests the possibility of secondary bacterial pneumonia. During the paroxysmal stage, adults may experience atypical symptoms, such as a scratchy throat and episodes of sweating.

A reduction in the frequency and severity of coughing marks the transition to the convalescent phase, which can persist several months. It is often during this time that adults present to the health care system with a chronic cough (Chapter 71) and may be evaluated for conditions such as asthma (Chapter 75), tuberculosis (Chapter 299), other chronic lung diseases, malignancies, and gastroesophageal reflux (Chapter 124). After the cough appears to have ended, patients may experience return of paroxysmal cough in conjunction with an unrelated upper respiratory illness, which is often incorrectly interpreted as a recurrence of pertussis.

Although *B. pertussis* and *B. parapertussis* can rarely cause bacteremia, infections with these organisms are principally localized to the respiratory tract.

Complications

In infants and children younger than age 5 years with severe pertussis, hospitalization is common; 5 to 10% have pneumonia, nearly 1% of infants experience seizures, and encephalopathy is seen in 0.1%. Adolescents and adults have these same complications with lower frequency,[14] but the severe cough can sometimes cause cough syncope (Chapter 49), a herniated intervertebral disc (Chapter 369), sudden-onset hearing loss (Chapter 396), episodes of angina (Chapter 56), and even carotid artery dissection (Chapter 376). The paroxysmal cough and associated post-tussive vomiting can be severe and protracted enough to cause rib fractures, muscle injuries, conjunctival hemorrhages, and other forms of tissue trauma.

DIAGNOSIS

Although pertussis can have a classic clinical presentation, milder presentations may be indistinguishable from other common respiratory infections.[15] PCR-based diagnostic tests, which are sensitive and can remain positive for several days or weeks into antimicrobial treatment, can distinguish *B. pertussis*, *B. parapertussis*, and *B. bronchiseptica*. Culture of the nasopharynx has a sensitivity of only about 50% and is even lower if antimicrobial treatment has been initiated before the specimen was collected. Detection of serum antibodies to products of *B. pertussis* can identify patients late in infection, but care must be taken to distinguish an acute response from residual antibodies to vaccine or nonvaccine antigens.

In resource-limited settings, a clinical case definition for the diagnosis of pertussis is 21 or more days of paroxysmal coughing with laboratory confirmation or epidemiologic linkage. However, this definition misses cases of lesser severity or shorter duration, as well as asymptomatic cases. Adults with preexisting asthma or chronic obstructive pulmonary disease are about twice as likely to be diagnosed with clinical pertussis.[16] Diagnosis of the very rare environmental and nonrespiratory *Bordetellae* is difficult outside of research settings, and no standardized diagnostic tests exist.

TREATMENT

Supportive Therapy

For infants, young children, and seriously ill adults, supportive therapy is often the most important component of medical care. Close observation is essential to ensure adequate nutrition, oxygenation, and hydration. After onset of paroxysmal cough, neither antibiotics nor other pharmacologic interventions are effective for ameliorating the cough.

Antimicrobial Agents

Since pertussis is a toxin-mediated disease and since the biologic effects of the toxins can persist even after the bacteria have been eradicated, antimicrobial agents may not offer much symptomatic relief or alter the course of illness unless initiated within the first week of symptoms, well before onset of paroxysmal cough. However, treatment is important to limit transmission to other individuals.

The recommended treatments of pertussis in adults are azithromycin (500 mg on day 1, followed by 250 mg/day on days 2 to 5), clarithromycin (1 g/day in two divided doses for 7 days), erythromycin (2 g/day in four divided doses for 7 days), or trimethoprim/sulfamethoxazole (trimethoprim 320 mg/day, sulfamethoxazole 1600 mg/day in two divided doses for 14 days). For parapertussis, *B. holmesii*, and *B. bronchiseptica*, treatment is as for pertussis. Resistance to macrolide antibiotics is extremely common in some parts of China but not currently in other locales.[17]

PREVENTION

Immunization

Killed, whole-cell pertussis vaccines, which became widely used in the United States, reduced reported cases of pertussis from more than 200,000 annually to less than 2000 in 1980. However, concerns about side effects led to the switch to acellular pertussis vaccines, which cause significantly fewer adverse reactions but lose effectiveness after 2 to 3 years and have very limited ability to block person-to-person transmission of the pathogen.[A1]

In the United States, infants typically receive DTaP (diphtheria, tetanus, acellular pertussis), administered with inactivated polio vaccine and either hepatitis B vaccine or *Haemophilus influenzae* type B vaccine (Chapter 15). Booster vaccines (i.e., Tdap, where the capitalized T represents full-dose tetanus, and the lowercase "d" and "ap" refer to reduced-dose diphtheria and acellular pertussis, respectively) are recommended starting at age 11 years. Outside of the United States, whole-cell pertussis vaccines are similarly combined with other common injectable antigens in various combinations, including diphtheria, tetanus, and either *H. influenzae* type B or hepatitis B.

By 5 to 10 years after introduction of acellular pertussis vaccines, which elicit a shorter duration of immunologic protection compared with whole-cell vaccines, rates of clinical disease began to climb, reaching about 20,000 cases per year in the United States, though with significant year-to-year variation. Part of the problem may be a steady accumulation of *B. pertussis* strains that no longer express one or more of the virulence factors used as acellular vaccine antigens, presumably as an evolutionary response.

In addition, although both whole-cell and acellular pertussis vaccines are effective at preventing clinical illness, whole-cell vaccines abbreviate the duration of infection and reduce bacterial loads in the nasopharynx, whereas acellular vaccines have no impact on either the duration of colonization or the bacterial load. Consequently, recipients of acellular vaccine can infect others and perpetuate outbreaks, thereby undermining the strategy of vaccinating the household contacts of a newborn to prevent spread to the infant, a practice commonly referred to as "cocooning."

By contrast, maternal Tdap given later in pregnancy augments infants' passive IgG-mediated immunity to pertussis and is highly effective at reducing infant pertussis. Although such passive immunity is transient, it creates a bridge through the first 3 months of life, when infants are most vulnerable to severe pertussis and when pertussis deaths are concentrated. As a result, it is now recommended routinely in the United States for all pregnant women.

Candidate third-generation pertussis vaccines being tested in humans include a live-attenuated nasal vaccine designed to optimize local mucosal immune responses and a polysaccharide-protein conjugate vaccine linking *B. pertussis* capsule to pertussis toxin.[18] The emerging consensus is that the next generation of pertussis vaccines must block person-to-person spread by sterilizing mucosal immunity.

Chemoprophylaxis

Chemoprophylaxis with 5 days of azithromycin (500 mg on day 1, then 250 mg on days 2 to 5) is an important mechanism for controlling outbreaks in hospitals or the community. This approach is highly effective when initiated before the onset of symptoms but much less effective if started more than 14 days after the onset of symptoms in the index case.[19] Chemoprophylaxis is recommended for individuals exposed within the preceding 3 weeks, high-risk persons with underlying health problems, infants, other individuals who have not been immunized, and recently exposed individuals who have frequent occupational or other contact with susceptible hosts.

PROGNOSIS

Most patients will eventually clear *B. pertussis*, even without antimicrobial treatment, but 80% of adults with pertussis have an illness of at least 3 weeks' duration, and about 25% are still coughing after 90 days. Antimicrobial agents do not alter the course, and symptoms persist well beyond elimination of the causal organism. In contrast, infections with *B. bronchiseptica* are often long-lasting and require antibiotic treatment for clearance.

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290 *LEGIONELLA* INFECTIONS

JONAS MARSCHALL AND VICTORIA J. FRASER

DEFINITION

Legionellosis refers to two clinical syndromes caused by *Legionella* bacteria: pneumonia and Pontiac fever. *Legionella* pneumonia (legionnaires disease) can be episodic or occur in outbreaks, and it can be acquired in the community or in health care settings. Pontiac fever is an acute, self-limited febrile illness caused by inhalation or aspiration of *Legionella* spp. *Legionella* extrapulmonary infections include meningitis, cellulitis, and skin and soft tissue abscesses. Endocarditis and wound infections also rarely occur.

The Pathogen

Legionellae are slender, noncapsulated, non-spore forming, obligatory aerobic, nutritionally fastidious, pleomorphic gram-negative bacilli (0.3-0.9 μm wide by 2-20 μm long) that belong to the Legionellaceae family (E-Fig. 290-1A to 1D). *Legionella* are facultative intracellular pathogens. *L. pneumophila* have a single polar flagellum. *L. longbeachae* differ in that they do not have a flagellum but have a capsule. *Legionella* spp. stain poorly on Gram stain. Warthin-Starry or Dieterle stains can demonstrate organisms in tissue. *L micdadei* and some other *Legionella* spp. may stain weakly acid-fast.

Legionella spp. have genomes that range in size from 2.37 to 4.88 Mb, but the core genome is comprised of only 1008 genes (6%). Recombination plays an important role in the organism's evolution and likely accounts for the development of new virulent strains as well as strains adapted to surviving in man-made water systems.[1]

EPIDEMIOLOGY

The Legionellaceae family has more than 60 species with more than 70 serogroups. *L. pneumophila*, which accounts for up to 90% of human infections, has more than 15 serogroups. Serogroup 1 is the most common cause of human infections, followed by serogroups 3, 4, and 6, although all groups can infect humans. *L. longbeachae*, which is more virulent than *L. pneumophila*, is the second most common species causing human disease, particularly in Australia and New Zealand. More than 25 *Legionella* spp. including: *L. micdadei, L. bozemanae, L. feeleii, L. anisa,* and *L. dumoffii* have been reported to cause human disease.

Legionella spp. are present in the environment worldwide. *L. pneumophila* and most *Legionella* spp. live in streams and lakes, and they thrive in man-made indoor and outdoor water systems, including drinking water, hot water pipes, fountains, air conditioning systems, and cooling towers. Almost all cases of legionnaires disease are due to exposure from *Legionella* contamination of man-made water sources.[2] *Legionella* can live either freely or as intracellular parasites in a number of different protozoans including *Acanthamoeba* and *Hartmannella* species (E-Fig. 290-1E). Growth of *Legionella* is promoted by warm temperatures, stagnation, and the presence of sediment in water systems. *Legionella* can withstand temperatures of 32 to 154° F (0 to 68° C), and they form biofilms that help them resist chlorination. The reservoir of *L. longbeachae* is in soil, including potting soil and compost, in contrast to other *Legionella*, which are more commonly found in water.

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ABSTRACT

Legionellosis refers to both *Legionella* pneumonia (legionnaires disease) and Pontiac fever. *Legionella* pneumonia, which can be sporadic or epidemic, can be acquired in the community or health care setting. Pontiac fever is an acute, self-limited febrile illness caused by inhalation of *Legionella* spp. *Legionella* spp. are slender, noncapsulated, nonspore-forming, aerobic, nutritionally fastidious, gram-negative bacilli that belong to the Legionellaceae family. *L. pneumophila* serogroup 1 is the most commonly identified species that causes human disease. *Legionella* spp. are facultative intracellular pathogens found worldwide in water, both in the natural environment and in man-made water systems. Disease is caused by inhalation or microaspiration of water contaminated with *Legionella* spp. Waterborne outbreaks due to contaminated drinking water, air conditioning systems, water cooling towers, hot tubs, and other sources continue to occur, and reported rates of *Legionella* pneumonia are increasing. Signs and symptoms of *Legionella* pneumonia are similar to other causes of community-acquired pneumonia. A high index of suspicion is required to identify risk factors, perform specific laboratory testing, and establish the diagnosis. Early appropriate empiric antibiotic therapy improves outcomes.

KEYWORDS

Legionella
Legionella pneumophila
Legionella longbeachae
Legionella micdadei
legionellosis
legionnaires disease
Pontiac fever

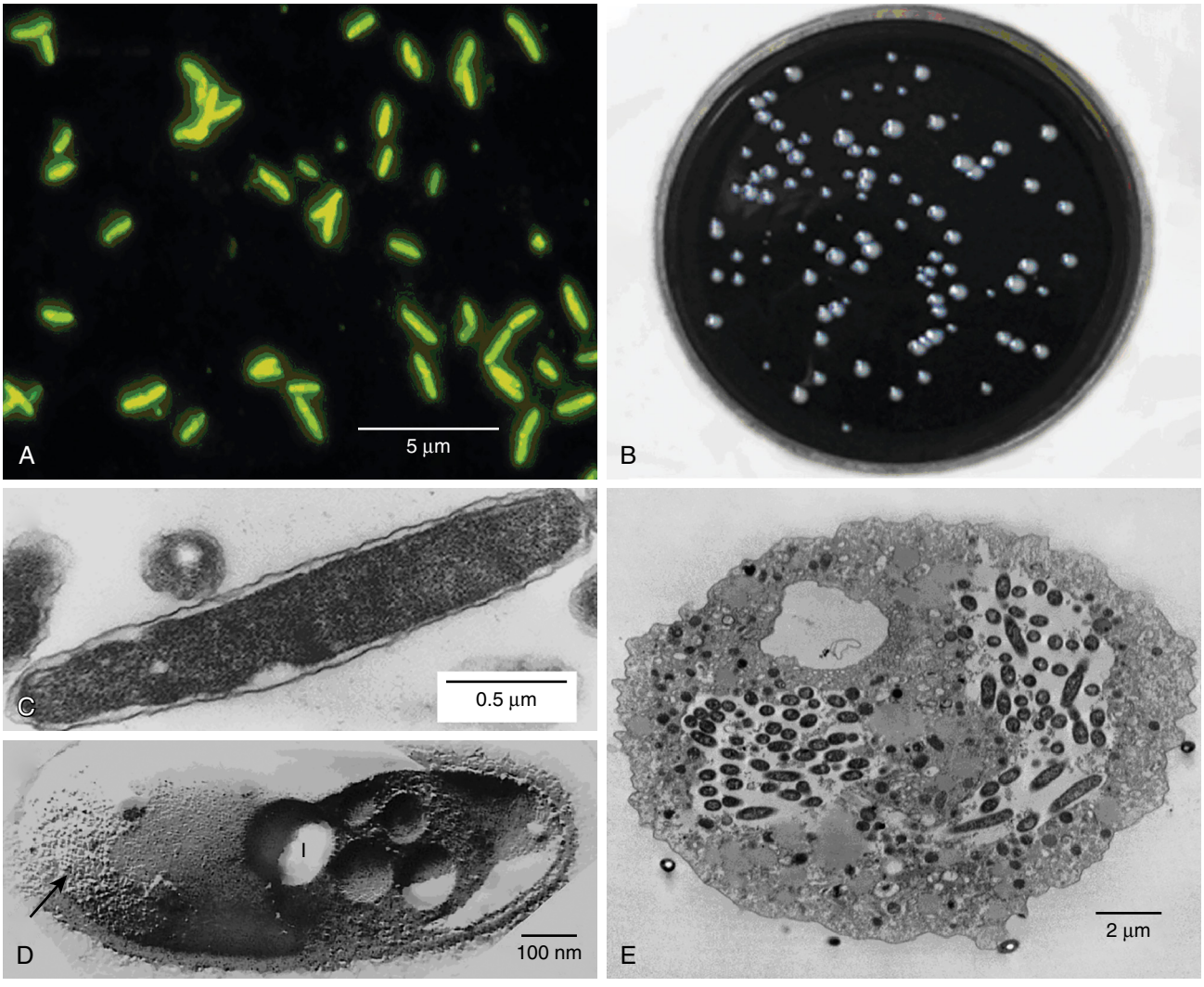

E-FIGURE 290-1. Identification of *Legionella* species. A, Direct fluorescent antibody stain of *Legionella pneumophila*. **B,** Colonies of *L. pneumophila* growing on a buffered charcoal yeast extract plate. **C,** Thin section of replicative form of *L. pneumophila*. **D,** Freeze-fracture replica of the mature infectious form obtained after growth in ameba. The latter shows prominent cytoplasmic inclusions (I) and a polar distribution of membrane proteins (*arrow*). **E,** Electron micrograph of *L. pneumophila* growing within *Acanthamoeba castellani*. (**A,** Courtesy Dr. Paul Hoffman, University of Virginia. **B,** Courtesy Dr. Sharon Berk, Tennessee Technical University. **C** to **E,** Courtesy Drs. Rafael Garduno and Gary Faulkner, Dalhousie University.)

Early *Legionella* outbreaks were difficult to solve and some persisted for months and even years. Since the eponymous outbreak at a Legionnaire's convention in Philadelphia in 1976, owing to a contaminated air conditioning system, numerous large, waterborne outbreaks around the world have involved drinking water, air conditioning systems, and water cooling towers in hospitals, in long term care facilities, in hotels, in apartment buildings, and on ships.

The incidence of *Legionella* infections varies geographically, related to the concentrations of *Legionella* in water systems as well as local heat and humidity. *L. pneumophila* infection is more common in the northeastern United States and Mediterranean regions.

Humans are accidental hosts for *Legionella*. Infection is typically acquired from inhalation or aspiration of *Legionella* contaminated water, including water used for drinking and bathing, air conditioning systems, hot tubs, birthing pools, decorative fountains, swimming pools, and water cooling towers. *Legionella* have surpassed gastrointestinal pathogens as the most common cause of waterborne outbreaks.

Legionella are commonly present in very low concentrations in cold, disinfectant-treated, potable water; however, bacterial density is amplified by growth in biofilms and replication in warm water and in older water systems with low or no flow. Significant changes in water pressure or water flow can disrupt biofilms, thereby releasing large numbers of organisms into the water. Contaminated water can be inhaled, aspirated, or ingested, thereby resulting in sporadic and epidemic infections. The exact dose required for infection is not known, but high numbers of organisms (>1000) are likely necessary.

L. pneumophila infections are more common in summer (E-Fig. 290-2), and most outbreaks occur between April and October. *L. longbeachae*, which is most commonly identified in soil and compost sources, usually causes disease in late spring and early summer in New Zealand and Australia, where it may account for 50% of *Legionella* cases.

Legionella can cause sporadic or epidemic, community-acquired pneumonia (Chapter 85) and health care–associated pneumonia (Chapters 85 and 261). Estimates of *Legionella* as a cause of community-acquired pneumonia requiring hospitalization range from 0.5 to 10% (average 2 to 5%). *Legionella* may account for up to 30% of nosocomial pneumonia. The reported incidence of legionnaires disease in the United States increased almost five- to six-fold from 1992 to 2018[3] (to approximately 2.29/100,000 persons), likely due to increased numbers of immunosuppressed individuals, the increased age of the population, increased testing, and greater awareness. Most U.S. cases are in the northeast, mid-Atlantic, and central regions. Of the 7500 annual cases, about 80% are in persons over age 50 years, about 60% of cases are in men, and the incidence rate is about 80% higher among Blacks compared with Whites.[4]

However, legionnaires disease is likely underdiagnosed and under-reported, and an estimated 18,000 to 88,000 total cases may occur per year in the United States. Most cases are sporadic and occur in outpatients, whereas outbreaks account for only 5 to 10% of legionnaires cases in the United States.

Activities that increase the risk of exposure to *L. pneumophila* spp. include overnight travel, recent plumbing work, disruptions of water supplies, older plumbing, use of whirlpools, hot springs, and proximity to cooling towers and decorative fountains. Travel–associated outbreaks are generally caused by contaminated potable water and cooling towers in hotels and contaminated hot tubs in ship–related outbreaks.[5] Risk factors for infection with *L. longbeachae* include working with compost or potting soil, smoking, chronic obstructive lung disease, and lack of handwashing after working with soil. Risk factors for developing symptomatic legionnaires disease include male gender, smoking, advanced age, dialysis-dependent renal failure, chronic lung or cardiovascular disease, diabetes mellitus, hematologic malignancies, and immunosuppression, particularly decreased cell mediated immunity, and the use of biologic immunosuppressive agents.

Nosocomial infections occur when contaminated water is inhaled, aspirated, or inoculated into the respiratory tract, most commonly from use of contaminated tap water used in nebulizers, humidifiers, and nasogastric feeding.[6] Health care–associated outbreaks typically account for more than half of the epidemics and more than 85% of the deaths due to *Legionella*.[7,8]

Pontiac fever has very high attack rates and more commonly occurs in outbreaks, in which 80 to 90% of exposed individuals become sick. Pontiac fever has been reported with *L. pneumophila*, *L. micdadei*, *L. anisa*, and other *Legionella* spp. High levels of *Legionella* contamination of potable water, showerheads, and cooling towers have been associated with outbreaks of Pontiac fever.

PATHOBIOLOGY

Free-living *Legionella* can enter low metabolic states and remain viable but not cultivable, so they are both resistant to biocides and difficult to recover from the environment. They also form biofilms, which aid in their resistance to biocides and chlorination. The ability to grow in temperatures from 68 to 107.6° F (20 to 42° C) and tolerate pH ranges from 5 to 8.5 contributes to their resilience. *Legionella* cannot be cultured on ordinary media; buffered charcoal yeast extract agar is required to cultivate *Legionella*, which grow best at 35° C in humidified air. Colonies are generally visible at 3 to 5 days, but incubation up to 14 days may be necessary to identify unusual species. Given the difficulties growing *Legionella* in the laboratory, negative culture results do not exclude the diagnosis.

After inhalation or microaspiration of *Legionella* contaminated water, droplet nuclei, which are less than 5 μm in size, reach the alveoli. In the alveoli, bacteria attach to macrophages and epithelial cells using outer membrane porins, flagella, and pili. Human complement component C3 mediates phagocytosis in conjunction with a virulence factor, macrophage infectivity potentiator protein, which is expressed on the cell surface of *L. pneumophila*.[9] Once phagocytized, *L. pneumophila* translocates hundreds of effector proteins into a specialized compartment, termed the *Legionella*-containing vacuole, through a Dot/Icm (delayed in organ trafficking/intracellular multiplication) type IV secretion system. Phagosome-lysosome fusion is inhibited by the effector proteins, which allow *L. pneumophila* to survive intracellularly in the *Legionella* containing vacuole. The vacuole is transformed into an organelle through recruitment of vesicles from the host's endoplasmic reticulum. Intracellular bacterial replication causes the vacuole to expand, ultimately filling the cell. When the host cell's nutrients are exhausted, the bacteria transition to a stationary growth phase and develop flagella. Caspase-1, which is triggered by the flagella, induces apoptosis and releases bacteria from the cell.

Legionella are able to resist complement and cationic peptides in the extracellular space, thereby avoiding free radicals. Bacteria in the extracellular space reenter more cells and trigger additional replication cycles, thereby amplifying the concentration of bacteria in the lung. *Legionella* uses a type II secretion system to secrete degradative enzymes and toxins. Infected macrophages release chemokines and cytokines that trigger a severe inflammatory response. A progressive, destructive pneumonia is caused by chemotactic substances, which attract polymorphonuclear leukocytes and monocytes, as well as the subsequent inflammatory response.

The predominant mechanism of immune control of *Legionella* is through Th1 cell mediated immunity. Infected alveolar macrophages incite the recruitment of neutrophils and stimulate natural killer cells to produce interferon gamma, which is key to eradicating *Legionella* from the lung. Innate immunity against *Legionella* involves toll-like receptors (TLR) 2, TLR 4, TLR5 and TLR89. Formation of inflammasomes leads to proteolytic activation of caspase-1. Cleavage of pro-interleukin – β (IL-Iβ) and release of IL-1β leads to an inflammatory form of cell death called pyroptosis. Pyroptosis is thought to be the main mechanism by which host cells control the growth of *L. pneumophila*. Individuals with TLR5 stop codon polymorphisms are more susceptible to legionnaires disease, whereas TLR4 polymorphisms are protective.[10]

Pontiac fever is caused by inhaling *Legionella* contaminated aerosols. The aerosols often contain *Legionella*, endotoxins, and other microorganisms, so it is not clear if the disease is due to the *Legionella* bacteria alone, a polymicrobial aerosol, or endotoxins from *Legionella* or other organisms. The short incubation period of 4 to 6 hours in some patients supports a toxin-mediated illness, whereas the longer incubation of 35 hours in some patients suggests bacterial illness.

Very little is known about the pathogenesis, virulence, and cell biology of infections caused by *Legionella* spp. other than *L. pneumophila*. However, different species have different virulence factors and effector proteins. *L. longbeachae* lacks flagella and has a larger genome than *L. pneumophila*. These additional genetic sequences may increase *L. longbeachae's* pathogenicity.

Gross pathology from post-mortem examination of patients who died from legionnaires disease demonstrates patchy or focal lesions in a third of cases, focal hemorrhage in one quarter of patients, and lobar pneumonia in 50% of patients. Microscopic examination demonstrates diffuse alveolar damage, bronchopneumonia and dense congestion with macrophages, neutrophils, and inflammatory debris (E-Fig. 290-3A to 3D). Blood vessel inflammation suggesting vasculitis may occasionally be present.

CLINICAL MANIFESTATIONS

Pneumonia

After an incubation of usually 2 to 10 days but occasionally as long as 28 days after exposure, patients with legionnaires disease often present with a nonspecific prodrome that persists for hours to days with anorexia, asthenia, headache, myalgia, and fever. Rigors, nausea, vomiting, diarrhea, and abdominal pain may precede pulmonary symptoms. Neurologic symptoms including headache and confusion are common. The prodromal phase often results in delayed diagnosis because the systemic symptoms do not relate to the lower respiratory track.

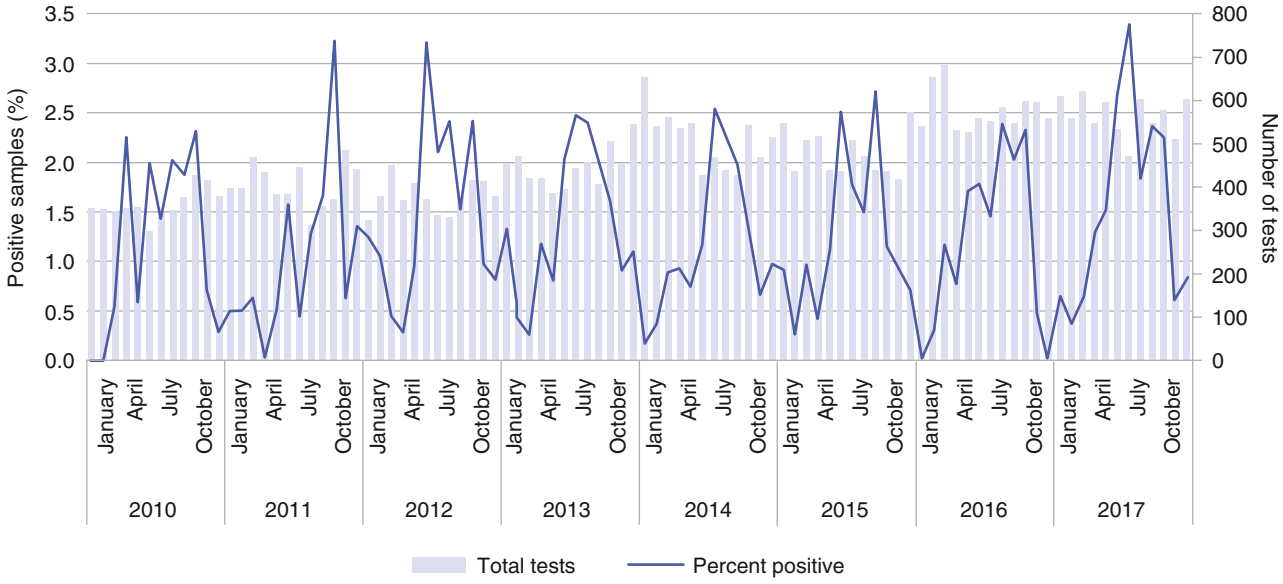

E-FIGURE 290-2. **Seasonality of *Legionella* detection by real-time polymerase chain reaction (PCR).** Data were obtained with PCR testing of more than 44,000 *Legionella* PCR tests on Mayo Clinic and Mayo Laboratories patients between January 2010 and December 2017. Average monthly *Legionella* PCR-positivity rates and test volumes over 8 years (2010–2017). The *dark-blue line* represents the mean monthly positivity, and the *light-blue bars* represent average monthly test volumes. (From Rucinski SL, Murphy MP, Kies KD, et al. Eight years of clinical *Legionella* PCR testing illustrate seasonal pattern. *J Infect Dis*. 2018;218:669-670.)

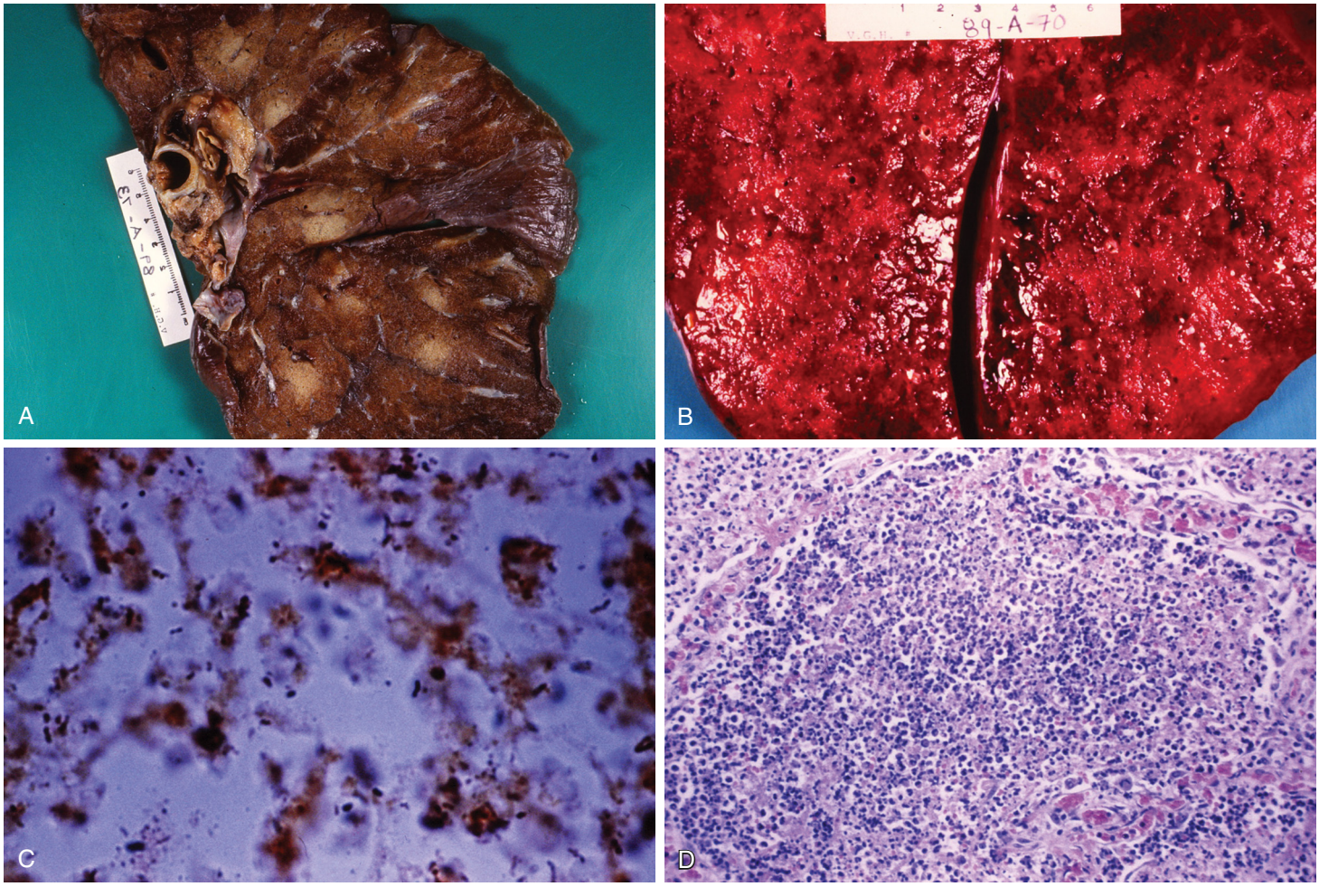

E-FIGURE 290-3. **Pathology in fatal legionnaires disease.** **A**, Gross pathology specimen of formalin-fixed lung from a patient with nosocomial legionnaires disease. Note the multiple nodular consolidated areas. **B**, Gross appearance of fresh lung tissue from a patient with legionnaires disease. Note the "hepatization of the lung" representing consolidation. **C**, Dieterle stain on lung tissue from a patient with legionnaires disease showing many microorganisms (magnification ×1000). **D**, Histologic appearance of pulmonary tissue from a patient with legionnaires disease. Note the dense inflammatory infiltrate with evolving microabscesses (magnification ×200).

Patients with pneumonia typically seek medical care at an average of 4.7 days after the onset of symptoms.[11] The clinical manifestations of *Legionella* pneumonia are similar to pneumococcal pneumonia and other causes of bacterial and atypical community acquired pneumonia (Chapter 85). Typical symptoms include high fever (of 40.5° C in up to a third of patients), rigors, cough, and shortness of breath. The cough is typically nonproductive, but some patients have thin watery sputum or purulent sputum, occasionally with blood streaking. Pleuritic or nonpleuritic chest pain may be reported. Acutely ill patients can develop rhabdomyolysis and acute kidney injury. *L. longbeachae*, which is the second most common cause of legionnaires disease, has clinical manifestations similar to that of *L. pneumophila*.

The initial lung examination may demonstrate only a few crackles before full-blown consolidation is evident. Abdominal tenderness, organomegaly, nuchal rigidity, and focal neurologic deficits have been reported.

Nonspecific laboratory abnormalities include hyponatremia (in 50% of patients, sometimes severe), hypophosphatemia, and elevated levels of serum creatinine, aminotransferases, bilirubin, and creatine kinase. Myoglobinuria and proteinuria can be associated with rhabdomyolysis. Leukopenia and thrombocytopenia may be present in severely ill patients. Cold agglutinins may be present. A serum procalcitonin level greater than 1.5 ng/mL is seen more commonly in *Legionella* patients admitted to intensive care units.

Chest radiographic findings in legionnaires disease are similar to other community-acquired pneumonias (Chapters 72 and 85). Unilobular or multilobular consolidated opacities in the middle or lower lobes are common (Fig. 290-1), and up to one third of patients have pleural effusions. Interstitial and nodular infiltrates can develop. Lung abscesses and cavitation are uncommon but can occur, particularly in immunosuppressed patients. Chest computed tomographic (CT) scanning is more sensitive than chest radiography and should be considered in patients who fail to respond to appropriate antibiotic therapy to evaluate for pulmonary complications.

Pontiac Fever

Within 4 to 6 hours after exposure, fatigue, malaise, and myalgias occur in more than 90% of patients with Pontiac fever. Fever and chills develop in 80 to 90% of patients, and headache in 80%. Cough, anorexia, arthralgia, nausea, vomiting, and abdominal pain each occur in less than 50% of patients. Mild to moderate leukocytosis may be present. Pneumonia does not occur.

Extrapulmonary Infections

Extrapulmonary *Legionella* infections are rare and generally are a result of bacteremic seeding in the setting of pneumonia or as direct complications of pneumonia. However, a wide variety of extrapulmonary infections can occur in immunosuppressed hosts, including septic arthritis, prosthetic joint infections, native and prosthetic valve endocarditis, intraabdominal abscesses, surgical wound infections, myocarditis, pericarditis, osteomyelitis, skin and soft tissue infections, and meningitis. Extrapulmonary infections are more likely to be caused by *Legionella* spp. other than *L. pneumophila*.

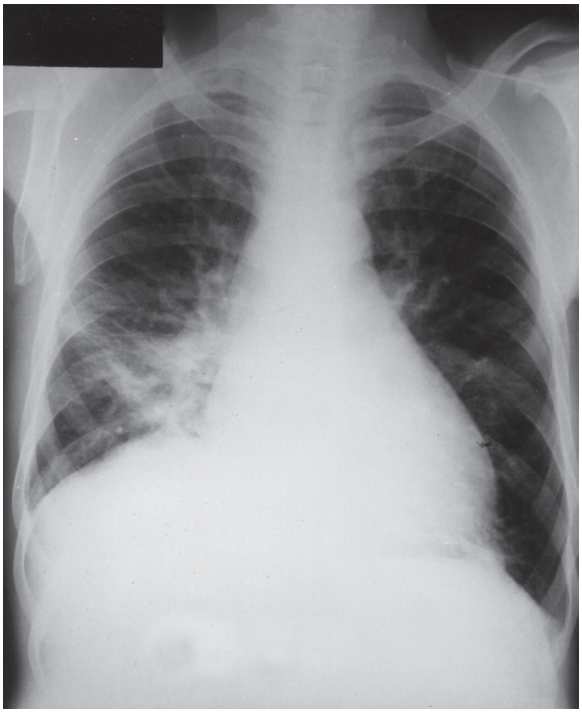

FIGURE 290-1. Posteroanterior chest radiograph of a patient with community-acquired pneumonia due to *Legionella pneumophila*. There is patchy consolidation at the right base, with subsegmental atelectasis and elevation of the right hemidiaphragm.

DIAGNOSIS

Legionnaires disease should be suspected in patients with rapidly progressive and/or moderate to severe pneumonia. No particular signs or symptoms reliably differentiate legionnaires disease from other pneumonias, but gastrointestinal symptoms (e.g., diarrhea, nausea, vomiting, elevated liver enzymes) and failure to respond to β-lactam monotherapy should raise suspicion for *Legionella* infection.[12]

In routine clinical care, symptoms and signs rarely differentiate among the various causes of community acquired pneumonia (Chapter 85), and treatment with a macrolide or fluoroquinolone antibiotic commonly obviates the need for the specific identification of *Legionella* spp. However, diagnostic testing for legionnaires disease should be performed in patients with severe community–acquired pneumonia, pneumonia that is unresponsive to outpatient therapy, immunosuppressed patients, patients with risk factors or water exposures, hospitalized patients, patients who progress on monotherapy with β-lactam antibiotics, and during outbreaks.

Polymerase chain reaction (PCR) testing can be performed on sputum, bronchial alveolar lavage specimens, tracheal aspirates, pleural fluid, or other tissues and fluids. Lower respiratory specimens are preferred for diagnosis. Real-time PCR rapidly detects all *Legionella* spp. and serogroups with high diagnostic accuracy (sensitivity 95 to 99% and specificity > 99%).[13] Genus specific PCR tests to detect all known *Legionella* spp. are helpful in immunosuppressed patients and patients who may not have *L. pneumophila*. Genetic sequencing of positive PCR samples or whole genome sequencing can be used for molecular epidemiology and species level identification.

Urinary antigen testing is readily available, inexpensive, and rapid, but it detects only *L. pneumophila* serogroup 1 with a sensitivity that ranges from 70 to 80% and specificity that approaches 100%.[14] Antigen can be detected within a day of the onset of symptoms and 1 to 2 weeks afterward.

A positive culture for *Legionella* is considered the gold standard. Culture can be performed on sputum, bronchoalveolar lavage specimens, tracheal aspirates, or pleural fluid. Sputum samples may be difficult to obtain in patients with *Legionella* pneumonia; the sensitivity of sputum culture ranges widely from less than 10% to 70 to 80%, and prior antimicrobial therapy decreases the likelihood of positive culture results. Tracheal aspirates and bronchoscopically obtained deep respiratory samples have higher yields and should be performed in patients with severe disease, immunosuppressed patients, patients who are progressing on therapy, and patients with risk factors for *Legionella*. Culture, which can detect all *Legionella* spp., provides bacterial isolates for susceptibility testing, and its isolates can be sequenced to investigate outbreaks.

The diagnosis of extrapulmonary infections is made by culture or performing PCR on tissues or fluid from the infected site. The value of blood cultures is limited. However, up to 10% of critically ill and immunocompromised patients may be bacteremic.

The most commonly used serologic tests are indirect fluorescent antibody tests or ELISA tests. A four-fold rise in antibody titers, ideally at 4, 6, and 12 weeks, is diagnostic and useful for retrospective confirmation and for the evaluation of outbreaks. Pontiac fever, which is often identified in outbreaks with high attack rates of 70 to 90%, is diagnosed by a fourfold rise in serology.

Differential Diagnosis

The differential diagnosis of *Legionella* pneumonia includes common causes of community–acquired pneumonia (Chapter 85), including *Streptococcus pneumoniae* (Chapter 268), *Haemophilus influenzae* (Chapter 277), Mycoplasma (Chapter 293), and viral pneumonias. For health care–associated pneumonias (Chapters 85 and 261), the differential diagnosis includes *Staphylococcus aureus* (Chapter 267), *Pseudomonas* (Chapter 282), and other gram-negative bacterial pneumonias (Chapters 282 and 283).

TREATMENT

Community-Acquired Pneumonia

Early empiric therapy of community-acquired pneumonia (Chapter 85) is associated with improved outcomes for patients with *Legionella* infections. The recommended treatment is levofloxacin (750 mg orally or intravenously once daily for 5 to 10 days) or azithromycin (500 mg orally or intravenously daily for a total of 3 to 7 days; Table 290-1),[A1,A2] Levofloxacin (750 mg orally or intravenously once daily for

TABLE 290-1 TREATMENT FOR LEGIONNAIRES DISEASE

SEVERITY OF *LEGIONELLA* PNEUMONIA	PREFERRED REGIMENS	ALTERNATIVE REGIMENS
Mild pneumonia (CURB-65 [see Table 85-4] score of 0 or Pneumonia Severity Index [see Fig. 85-3 and Table 85-3] class I-II) It is not necessary to change from alternate to preferred therapy if patients are responding to alternate therapy.	Azithromycin 500 mg orally once daily Levofloxacin 750 mg orally once daily	Ciprofloxacin* 500 mg orally twice daily Moxifloxacin 400 mg orally once daily Clarithromycin* 500 mg orally twice daily Doxycycline 200 mg orally once followed by 100 mg orally twice daily (should not be used for *L. longbeachae* as this organism is resistant to tetracyclines)
Moderate to severe pneumonia (hospitalized patients or patients with CURB-65 score ≥1 or Pneumonia Severity Index ≥II) IV therapy is recommended initially for hospitalized patients and those with moderate-severe pneumonia. IV therapy can be converted to oral when patients are hemodynamically stable, able to tolerate oral therapy and clinically improving.	Azithromycin 500 mg IV or orally once daily Levofloxacin 750 mg IV or orally once daily	Ciprofloxacin* 400 mg IV twice daily or 750 mg orally twice daily Moxifloxacin 400 mg IV or orally once daily Clarithromycin* 500 mg IV or orally twice daily (IV formulation not available in the United States)

*Ciprofloxacin and clarithromycin need dose adjustment for renal dysfunction.

Duration of therapy is determined based on the patient's severity of illness, presence of comorbid conditions, immunosuppression, and infectious complications. In general, short course therapy with minimum duration of 5 days of therapy is possible for patients with mild pneumonia who have been clinically stable and afebrile for 48 hours. Mild pneumonia is generally treated with 5 to 7 days of therapy. Patients with severe infection or multiple chronic comorbidities usually require 7 to 10 days of therapy. Longer duration of therapy (up to 21 days or longer) may be required for immunosuppressed patients and patients who have extrapulmonary infections, lung abscess, or empyema.

IV = intravenous.

5 to 10 days) is recommended for extrapulmonary infections. Intravenous therapy is preferred for patients with moderate-severe disease and should be transitioned to oral therapy when the patient is improving and able to tolerate oral medications. Alternatives include moxifloxacin (400 mg orally or intravenously once daily for 7 to 10 days) or doxycycline (200 mg orally as a loading dose followed by 100 mg orally twice daily for 10 to 14 days). Dual therapy is not recommended for *Legionella* unless a coinfection or superinfection is suspected. None of the β-lactam, monobactam, aminoglycoside or phenicol antibiotics are active against *Legionella*. In outbreak settings, moderate to severe pneumonia, patients with multiple comorbid conditions, immunosuppressed patients, and high prevalence areas, empiric therapy with a fluoroquinolone or macrolide antibiotic to cover *Legionella* should be started early while awaiting results of diagnostic testing.

The optimal duration of therapy is not well defined. Short course (minimum of 5 days) therapy can be used in otherwise healthy patients who have mild disease, are clinically improving, are hemodynamically stable, and are afebrile for 48 hours. Longer duration (7 to 10 days) of therapy is recommended for severe disease and in elderly patients who have multiple comorbid conditions. Immunosuppressed patients and transplant recipients should receive at least 14 days of therapy. Patients with extrapulmonary infections, lung abscess, or empyema generally require longer therapy and possibly debridement, drainage, or surgical interventions based on the nature of the infection and complication.

L. longbeachae, which is more common in Australia and New Zealand, is often resistant to doxycycline and other tetracyclines, which should not be used to treat it. In these areas, fluoroquinolone or macrolide therapy is the preferred empiric regimen.[15]

Correction of fluid and electrolyte abnormalities and of hypoxemia (Chapter 90) is important. The indications for adjunctive therapy, including minimizing immunosuppression or using glucocorticoids to control inflammation, are similar as for other community-acquired pneumonias (Chapter 85). Mechanical ventilation (Chapter 91) and extracorporeal membrane oxygenation can improve survival in patients with potentially reversible, severe respiratory failure.

Some patients, particularly elderly patients with multiple comorbid conditions, continue to worsen despite appropriate therapy. Failure to respond to specific therapy should prompt investigation of alternative diagnoses or the possibility of coinfections or superinfections, which complicate about 10% of patients with legionnaires disease.[16]

PREVENTION

Legionella is not transmitted person to person, so patients do not require isolation. No vaccine is available. Prior infection does not prevent reinfection. Antibiotic prophylaxis with the same drugs, doses, and durations used for treatment can also be used to prevent legionnaires disease in exposed immunosuppressed hosts during outbreaks.

A single case of *Legionella* should prompt communication with the microbiology laboratory and public health officials to assess for a common source and outbreak. Health care–associated legionellosis should prompt extensive investigations to identify the source of contamination. Retrospective review of microbiology results may identify additional cases that were presumed to be sporadic. Prospective laboratory testing for *Legionella* in patients with nosocomial and community-acquired pneumonia may be indicated to define the extent of an outbreak. Epidemiologic investigations, environmental cultures, and molecular analysis are necessary components in investigations of a potential outbreak and can guide interventions to eliminate the source of contamination.

Prevention of legionellosis depends upon identifying the environmental source and decreasing colonization of potable water to prevent further exposures. Water systems should be designed to reduce the risk of heavy *Legionella* colonization by avoiding dead spaces, stagnation, and materials that allow accumulation of sediment. Surveillance and monitoring for *Legionella* spp. is recommended for water systems in high-risk areas, such as hospitals and long-term care facilities.

Water disinfection is common in developed countries and includes use of point source filters, copper-silver ionization, heat shock, chlorine dioxide, and monochloramine. Use of monochloramine to treat drinking water decreases colonization with *Legionella* spp. and nosocomial legionnaires disease. Long-term control and prevention of *Legionella* overgrowth in water systems is complicated and requires expert public health and engineering input.[17-19] In areas where *L. longbeachae* is prevalent, gardeners and persons working with soil or compost should be advised to use good handwashing, avoid contaminating their face with dirt, and minimize aerosolizing compost and soil, especially if they are immunocompromised.

PROGNOSIS

Early diagnosis and appropriate treatment are associated with improved outcomes.[20] Most patients respond quickly to appropriate therapy, with improvement or resolution of myalgias, headache, abdominal pain, diarrhea, nausea, vomiting, anorexia, and confusion within 12 to 24 hours. Cough, sputum production, and shortness of breath usually respond more slowly. Patients generally become afebrile in 2 to 5 days. Radiographic changes are slower to resolve and may take up to 2 months or longer to return to baseline. Convalescence and complete recovery may take months, especially in immunosuppressed and elderly patients.

The reported mortality for legionnaires disease ranges from 1 to 80%, but the average mortality for sporadic hospitalized cases is estimated to be 10 to 15%. Mortality is higher in patients who are elderly, immunosuppressed, or have multiple comorbid conditions. The mortality is also higher when effective therapy is not begun promptly. Oliguria and acute renal failure may occur and dialysis may be required in severely ill patients.

Pontiac Fever

Pontiac fever is generally acute and self-limited and it usually resolves over 1 to 9 days without specific therapy. However, fatigue and nonspecific complaints may persist for months in some patients.

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For the General References and other additional features, please visit Elsevier eBooks+ at https://ebooks.health.elsevier.com.

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291 *BARTONELLA* INFECTIONS

JEAN-MARC ROLAIN AND DIDIER RAOULT

DEFINITION

Bartonella are vector-borne bacteria responsible for a wide spectrum of human acute and chronic diseases. More than 40 different bacterial species from this genus have been isolated from animals and humans. The human infections linked to these different bacteria include cat-scratch disease, Oroya fever, verruga peruana, trench fever, endocarditis, bacillary angiomatosis, and peliosis hepatis.

The Pathogen

Bartonella species belong to the α-2 subgroup of Proteobacteria and are closely related to the genera *Brucella*, *Agrobacterium*, and *Rhizobium*. *Bartonella* species are small, gram-negative, fastidious, pleomorphic coccobacilli or slightly curved rods (0.5 by 1 to 2 μm). The bacteria can grow on enriched blood-containing media with a 5% carbon dioxide atmosphere after 5 to 15 days to up to 45 days on primary culture. The optimal growth temperature ranges from 28° C for *B. bacilliformis* to 35° to 37° C for the other species. *Bartonella* species can also be cocultured with endothelial cells. *Bartonella* species are either flagellated or nonflagellated cells. *B. bacilliformis* uses flagella for binding and deforming into the surface of erythrocytes. Bacteria can either persist in the blood stream of the host as intraerythrocytic parasites or colonize human endothelial cells.

EPIDEMIOLOGY

More than 40 known *Bartonella* species have been isolated from both animals and humans. These bacteria are zoonotic, and the strains that are associated with human infections include *B. henselae, B. quintana, B. bacilliformis, B. elizabethae, B. clarridgeiae, B. vinsonii* subsp. *arupensis, B. vinsonii* subsp. *berkhoffii, B. alsatica, B. tamiae, B. grahamii, B. washoensis, B. rochalimae, B. koehlerae, B. mayotimonensis*, and *B. ancashensis* (Table 291-1). The other *Bartonella* species have been isolated only from the blood of animals, including rodents, felids, canids, dolphins, bats, and ruminants. The route of transmission of *Bartonella* species in mammals and humans is by fleas, ticks, mites, and lice (see Table 291-1).

TABLE 291-1 *BARTONELLA* SPECIES CAUSING HUMAN DISEASE

BARTONELLA SPECIES	RESERVOIR HOST/ VECTOR	HUMAN DISEASE
B. alsatica	Rabbit	Endocarditis, lymphadenopathy
B. ancashensis		Verruga peruana
B. bacilliformis	Human/sandfly	Carrión disease, Oroya fever, verruga peruana
B. clarridgeiae	Cat/cat flea	Cat-scratch disease
B. elizabethae	Rat	Endocarditis, neuroretinitis
B. grahamii	Rat, insectivore	Neuroretinitis
B. henselae	Cat/cat flea	Cat-scratch disease, endocarditis, bacillary angiomatosis, bacillary peliosis, Parinaud oculoglandular syndrome, neuroretinitis, osteomyelitis, arthropathy, bacteremia with fever
B. koehlerae	Cat	Endocarditis
B. mayotimonensis	Unknown	Endocarditis
B. quintana	Human/body louse	Trench fever, endocarditis, bacillary angiomatosis
B. rochalimae		Bacteremia, fever, splenomegaly
B. tamiae		Febrile illness
B. vinsonii arupensis	Dog, rodent/ticks	Bacteremia with fever
B. vinsonii berkhoffii	Dog	Endocarditis
B. washoensis	Ground squirrel	Myocarditis

Almost all *Bartonella* species are vector-borne bacteria (see Table 291-1). Some are limited geographically, such as *B. bacilliformis*, which is found only in the Andes Mountains in South America at high altitudes, where its principal vector, *Lutzomyia verrucarum*, is distributed. Others have a worldwide distribution, such as *B. henselae* and *B. quintana*. Each *Bartonella* species is highly adapted to its mammalian reservoir, in which bacteria usually cause a long-lasting intraerythrocytic bacteremia that may be asymptomatic. Humans are the hosts and reservoirs for *B. bacilliformis* and *B. quintana*. *B. quintana*, which is transmitted by the human body louse by inoculation of arthropod feces through broken skin, is more common in homeless persons[1] and in poorer countries.[2] Cats represent the main reservoir hosts for *B. henselae* infection; this pathogen is the agent of cat-scratch disease in humans, caused by cat bites or scratches. In the United States, about 12,000 outpatients and 500 inpatients are diagnosed annually.[3] *B. henselae* infection is transmitted from cat to cat by the cat flea. Cat fleas may also be infected by *B. quintana*. The role of dogs as reservoir hosts has been documented for several species, including *B. vinsonii* subsp. *arupensis*, *B. vinsonii* subsp. *berkhoffii*, and *B. henselae*. Wild rabbits are the reservoir hosts for *B. alsatica*, which is an agent of endocarditis and lymphadenopathy in humans in close contact with rabbits. For other *Bartonella* species known to cause diseases in humans, the pathogenic role and mode of transmission are not fully understood.

PATHOBIOLOGY

A single *Bartonella* species can cause either acute or chronic infections and either vasculoproliferative or suppurative manifestations but with different pathogenetic mechanisms that mainly depend on the patient's immune status. For example, *B. henselae* usually causes cat-scratch disease (a self-limited disease) in immunocompetent hosts, whereas it is responsible for bacillary angiomatosis in immunocompromised patients. *B. quintana* is responsible for trench fever as well as for endocarditis, bacteremia in the homeless population, and vasculoproliferative diseases, whereas *B. bacilliformis* is the agent of Carrión disease, which corresponds to either an acute intraerythrocytic bacteremic disease (Oroya fever) or a chronic vasculoproliferative disease (verruga peruana). *B. bacilliformis* (Oroya fever) and *B. quintana* (trench fever and bacteremia in the homeless) infect red blood cells, whereas *B. henselae* and *B. koehlerae* have been seen in erythrocytes of infected cats. *B. henselae* can cause granulomatous disease (i.e., cat-scratch disease), which affects lymph nodes, but it can also be responsible for other clinical manifestations or complications, such as endocarditis. Vasculoproliferative diseases include bacillary angiomatosis caused by *B. henselae* and *B. quintana*, peliosis hepatis caused by *B. henselae*, and verruga peruana caused by *B. bacilliformis*. In patients with a previous valvulopathy, any *Bartonella* infection may lead to endocarditis.

CLINICAL MANIFESTATIONS

Bartonella infections can lead to a wide spectrum of either acute or chronic diseases. The status of the host immune response plays an important role in the development of the different manifestations. Four different groups of clinical syndromes may occur with *Bartonella* infections: (1) infection of red blood cells and erythrophagocytosis, (2) granulomatous disease controlled by the immune response, (3) bacteremia and blood culture–negative endocarditis, and (4) vasculoproliferative diseases (bacillary angiomatosis, peliosis hepatis, and verruga peruana) (Table 291-2). In a recent French study, 89% of *Bartonella* infections were cat-scratch fever, 9% were endocarditis, and 2% were bacillary angiomatoses or peliosis hepatis.[4]

INTRAERYTHROCYTIC BACTEREMIA: OROYA FEVER AND TRENCH FEVER

EPIDEMIOLOGY AND PATHOBIOLOGY

The vector of *B. bacilliformis* is the mosquito *Lutzomyia verrucarum*, whereas *B. quintana* is transmitted via human body louse. In Oroya fever, *B. bacilliformis* invades up to 80% of erythrocytes and produces their massive lysis, which results in severe hemolytic anemia, the major symptom of the disease. Similarly, trench fever is characterized by intracellular erythrocyte parasitism by *B. quintana*, with the percentage of infected red blood cells ranging from 0.001 to 0.005% (Fig. 291-1). Bacteria can also be seen extracellularly and in erythroblasts. This intracellular erythrocyte parasitism can presumably preserve the pathogens for efficient transmission by body lice, protect *B. quintana* from the host immune response, and contribute to decreased antimicrobial efficacy. During bacteremia in the homeless, *B. quintana* can also be seen in red blood cells.

CLINICAL MANIFESTATIONS

Oroya Fever

Oroya fever is the acute or hemolytic phase of Carrión disease,[5] which is also associated with a chronic phase called verruga peruana (see later). Oroya fever

ABSTRACT

Bartonella are vector-borne bacteria responsible for a wide spectrum of human acute and chronic diseases. More than 40 different bacterial species from this genus have been isolated from animals and humans. The human infections linked to these different bacteria include cat-scratch disease, Oroya fever, verruga peruana, trench fever, endocarditis, bacillary angiomatosis, and peliosis hepatis.

KEYWORDS

Bartonella
cat-scratch disease
endocarditis
trench fever
Carrión disease
bacillary angiomatosis
peliosis hepatis

TABLE 291-2 CLINICAL MANIFESTATIONS ASSOCIATED WITH *BARTONELLA* SPECIES

CLINICAL MANIFESTATION	*B. BACILLIFORMIS*	*B. QUINTANA*	*B. HENSELAE*	*B. ALSATICA*	OTHERS
INTRAERYTHROCYTIC BACTEREMIA*	+	+	+		
Oroya fever	+				
Trench fever		+			
GRANULOMATOUS DISEASE					
Cat-scratch disease			+		
Lymphadenopathy		+	+	+	+
SENLAT with skin lesion			+		
Meningoencephalitis			+		
Uveitis-retinitis		+	+	+	+
BACTEREMIA AND ENDOCARDITIS					
Chronic bacteremia	+	+	+		+
Infective endocarditis		+	+	+	+
VASCULOPROLIFERATIVE DISEASE					
Bacillary angiomatosis		+	+		
Peliosis hepatis			+		
Verruga peruana*	+				

*The combination of intraerythrocytic bacteremia and verruga peruana is also known as Carrión disease.
CSD = cat-scratch disease; SENLAT = scalp eschar and neck lymphadenopathy.

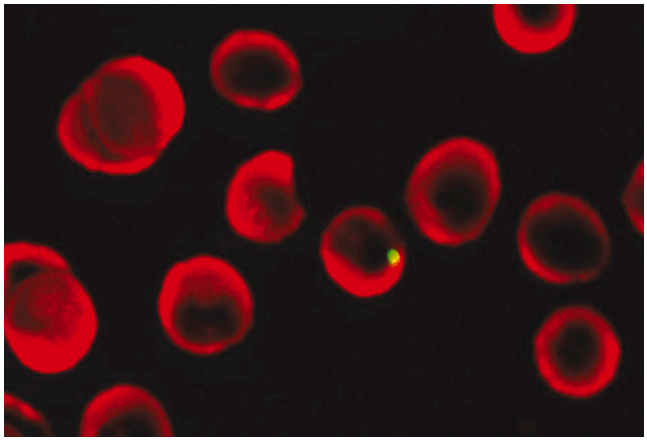

FIGURE 291-1. Section of human red blood cell infected with *Bartonella quintana* as viewed by confocal microscopy.

usually develops 3 to 12 weeks after inoculation with *B. bacilliformis* and results from the massive invasion of erythrocytes. The onset is usually abrupt, with high fever, chills, headache, and anorexia. Patients have intense myalgias and arthralgias, abdominal pain, and jaundice. Complications are frequent, including meningoencephalitis, dyspnea, delirium, and superinfection leading to death. Asymptomatic persistent bacteremia may serve as the reservoir of the organism.

Trench Fever

Trench fever, which is transmitted by lice, is the clinical manifestation of *B. quintana*. Trench fever affected more than 1 million people during World War I; more recently, *B. quintana* has been recognized in immunocompromised hosts, homeless people, and people with chronic alcohol use disorder. Clinical manifestations of trench fever may range from asymptomatic infection to severe, life-threatening illness. After an incubation period of 2 to 3 weeks, sudden onset of fever persists for 1 to 3 days and is associated with headache, shin pain, and dizziness. The disease may persist for 4 to 6 weeks and result in prolonged disability. Relapses may occur years later in some cases with bacteremia but no clinical signs.

CAT-SCRATCH DISEASE

EPIDEMIOLOGY AND PATHOBIOLOGY

Transmission from cat to human occurs directly by a cat scratch or cat bite or possibly by a cat flea or tick bite. Little is known about the pathogenesis of the long-lasting lymphadenopathy in cat-scratch disease. Immunopathogenesis is assumed to play an important role in cat-scratch disease because bacteria have only rarely been isolated from affected lymph nodes. Thus, the disease is usually controlled by the host immune response, and few or no viable bacteria are seen on lymph node biopsy specimens, which are necrotic by pathologic examination.

CLINICAL MANIFESTATIONS

Typical cat-scratch disease, which is the most common manifestation of infection with *B. henselae*, usually is manifested as a self-limited regional lymphadenitis. A typical papule or pustule may be seen 3 to 10 days after the scratch or bite at the site of inoculation and may persist for 1 to 3 weeks. The subsequent lymphadenopathy is localized mainly to the axillary, cervical, or submaxillary nodes that drain the area where the cat scratch occurred. The enlarged lymph node is often painful and tender. Tick-borne *B. henselae* infection can present as a scalp eschar and neck lymphadenopathy.

Lymphadenopathy sometimes persists for months, and in a few cases it can persist for as long as 1 to 2 years. In some cases, the lymph node may suppurate if it is not drained. Most patients are not febrile during the course of typical cat-scratch disease. Systemic or severe disease may occur in about 5 to 14% of patients, owing to disseminated infection.

After exposure to *B. henselae*, patients may develop bacteremia with or without clinical signs of typical cat-scratch disease; in patients with preexisting valvular lesions, this bacteremia may result in infective endocarditis.[6] Since the organism is rarely grown on typical blood culture media, it is often a cause of fever of unknown origin[7] (Chapter 259) or "culture-negative endocarditis" (Chapter 61).[8]

Approximately 10% of patients with cat-scratch disease have atypical clinical manifestations, including prolonged fever (>2 weeks), malaise, neuroretinitis, encephalitis, erythema nodosum, hepatitis, fatigue, weight loss, and splenomegaly. Musculoskeletal manifestations are present in more than 10% of patients, are often severe, and may evolve into chronic forms that persist for more than a year. Myalgia and arthropathy are the most common manifestations. Myalgia has a mean duration of 4 weeks. Arthropathy, which has a mean duration of 5.5 weeks, is more common in female patients over age 20 years, affects large and medium joints (half being weight-bearing joints), and is associated with symmetrical erythema nodosum. Tendinitis, neuralgia, and osteomyelitis are less common, with incidences lower than 1%.

Ocular and Neurologic Manifestations

Parinaud oculoglandular syndrome is a self-limited conjunctivitis associated with preauricular lymphadenopathy. Other atypical manifestations include neurologic syndromes (meningoencephalitis, meningitis, neuroretinitis).[9] Encephalopathy may occur in 2 to 4% of patients with cat-scratch disease,[10] mainly adolescents and adults. Patients usually have persistent headaches with or without fever and may develop seizures. Acute neurologic disorders, which

may range from self-limited nuchal rigidity to pupillary dilation or aphasia and hemiplegia, can persist for several weeks to months.

Neuroretinitis most commonly is manifested as papilledema associated with macular exudates that cause stellar retinitis. Neuroretinitis can present as a sudden unilateral loss of visual acuity.[11] *B. grahamii* and *B. quintana* also can cause nongranulomatous or granulomatous uveitis.[12]

BACTEREMIA AND ENDOCARDITIS

EPIDEMIOLOGY AND PATHOBIOLOGY

B. quintana, B. henselae, B. alsatica, B. vinsonii subsp. *Berkhoffii, B. elizabethae*, and "*Candidatus* Bartonella mayotimonensis" are common causes of blood culture–negative endocarditis (Chapter 61). Sporadic cases of endocarditis have also been associated with *B. koehlerae, B. vinsonii* subsp. *Berkhoffii, B. vinsonii* subsp. *Arupensis, B. elizabethae, B. alsatica*, and "*Candidatus* Bartonella mayotimonensis." Patients with endocarditis usually have preexisting heart valve disease that promotes the development of infective endocarditis. Endocarditis caused by *Bartonella* species exhibits slight inflammation, with a few inflammatory mononuclear cells and small vegetations; the bacteria are seen extracellularly in dense immunopositive clusters that are mainly included in vegetations and in the cytoplasm of neutrophils and macrophages.

CLINICAL MANIFESTATIONS

The most commonly identified agents of *Bartonella* endocarditis are *B. quintana*, followed by *B. henselae* and other *Bartonella* species. Patients appear to have chronic, blood culture–negative endocarditis, usually with fever (90%). Echocardiography reveals vegetations in 90%.[13] Infections with *B. henselae* are epidemiologically linked to close contact with cats or cat fleas and previous valvular heart disease, whereas *B. quintana* endocarditis is frequently described in patients who are homeless, have alcohol use disorder, and are infected with body lice but do not have previous valvular lesions. The onset is usually subacute, with some patients being afebrile at the time of admission. About 50% of patients have embolic phenomena.

VASCULOPROLIFERATIVE DISEASE: BACILLARY ANGIOMATOSIS, PELIOSIS HEPATIS, AND VERRUGA PERUANA

PATHOBIOLOGY

Bartonella species have the ability to cause vasculoproliferative lesions through a process of pathologic angiogenesis that results in the formation of new capillaries from preexisting ones. These typical vasoproliferations can be expressed as skin lesions in bacillary angiomatosis, which is caused by *B. quintana* and *B. henselae*, or as a cystic form in the liver and spleen in peliosis hepatis, which is caused only by *B. henselae*.

Bacillary angiomatosis, which is a neovascular proliferation that has been reported most commonly in patients who have acquired immunodeficiency syndrome (AIDS), involves the skin and lymph nodes; it occurs less frequently in patients with other causes of immunosuppression and only exceptionally in immunocompetent patients. In bacillary angiomatosis, lesions comprise proliferating endothelial cells, bacteria, and mixed infiltrates of macrophages/monocytes and polymorphonuclear neutrophils, thereby leading to chronic inflammation. Bacteria are clustered as aggregates both surrounding and within endothelial cells, thereby indicating that the vascular endothelium represents a target tissue for intracellular and extracellular colonization in vivo. On histologic evaluation, bacillary angiomatosis is a lobular proliferation of small blood vessels that contain endothelial cells and bacteria, usually seen in clusters when stained with Warthin-Starry.

As in bacillary angiomatosis, lesions of verruga peruana, which is the chronic form of Carrión disease, are characterized by lobular proliferations and atypical endothelial cells that form both relatively solid sheets and small, well-formed vessels with patent lumens. Lesions are typically infiltrated, thereby indicating a chronic inflammatory process.

CLINICAL MANIFESTATIONS

In bacillary angiomatosis, cutaneous lesions often arise in crops and can be subcutaneous or dermal nodules with red or purple papules millimeters to centimeters in diameter (Fig. 291-2). When cutaneous lesions are absent, the diagnosis is often difficult and delayed because signs of visceral involvement are usually nonspecific. The potentially systemic nature of bacillary angiomatosis is reflected by the involvement of brain, bone, lymph node, bone marrow, skeletal muscle, conjunctiva, and mucosal surfaces of the gastrointestinal and respiratory tracts.

Peliosis hepatis affects solid internal organs, primarily the liver, with reticuloendothelial elements. In the liver, it is defined as a vascular proliferation of sinusoidal hepatic capillaries, thereby resulting in blood-filled spaces. The spleen, abdominal lymph nodes, and bone marrow may also be involved.

FIGURE 291-2. Skin lesion of bacillary angiomatosis.

Following acute Oroya fever, patients usually develop angioproliferative cutaneous tumors called verruga peruana after a latent period ranging from weeks to months. The infection is characterized by benign cutaneous vascular lesions that typically consist of round papules, which are frequently pruritic and bleeding. The infection is accompanied by malaise and arthralgias. Skin lesions may change over time from miliary to nodular subcutaneous lesions to large mulaire lesions. These large lesions are often engorged with blood and prone to ulceration and bleeding. This eruptive phase clinically resembles Kaposi sarcoma or bacillary angiomatosis. However, it has a low morbidity, and there are no reports of mortality.

DIAGNOSIS OF *BARTONELLA* INFECTION

Molecular Detection Methods

Because of their slow growth and the lack of reproducible biochemical methods for their identification, *Bartonella* are best identified by molecular methods regardless of the species or site of infection. Direct detection and final identification of *Bartonella* species from blood, bodily fluids, and tissue specimens, including lymph node, cardiac valve, skin, and liver, can be achieved with high sensitivity by polymerase chain reaction (PCR) amplification and sequencing of various housekeeping genes.[14,15] PCR can also detect *Bartonella* at the species level from lymph nodes in cat-scratch disease, directly from cardiac valves in patients with endocarditis, and in specimens from patients with bacillary angiomatosis or peliosis hepatis.

Mass Spectrometry

Matrix-assisted laser desorption/ionization time-of-flight mass spectrometry is an alternative for species identification and is an accurate and reproducible alternative method for the rapid and inexpensive identification of *Bartonella* species. This technique is useful if the bacterium is cultivated in the laboratory.

Alternative Methods

Some patients may be suspected of having *Bartonella* infection but not have bacteremia or obvious accessible infective sites. In these patients, other methods for the diagnosis of *Bartonella* infection include serology,[16] microscopy, culture, direct immunofluorescence, and immunohistochemistry (Table 291-3).

Serology remains the most widely used method for the diagnosis of cat-scratch disease. By immunofluorescence assay, an immunoglobulin G titer of 1:64 or greater is considered positive for cat-scratch disease, whereas patients with endocarditis usually have higher antibody titers (≥1:800).

The diagnosis of Oroya fever is often based on the examination of a peripheral blood smear stained by Giemsa; the percentage of infected red blood cells is sufficiently high so that bacteria are visible. Similarly, *B. quintana* can be seen within red blood cells with the use of a specific monoclonal antibody by immunofluorescence and confocal microscopy (see Fig. 291-1). Microscopic examination after Warthin-Starry silver staining or immunohistochemistry of a cardiac valve or skin biopsy specimen is also confirmatory for the diagnosis of *Bartonella* organisms in patients with endocarditis and bacillary angiomatosis.

Despite its association with culture-negative endocarditis, *Bartonella* species can be recovered from the blood of bacteremic patients. Culture is also confirmatory for cardiac valves, as well as skin and liver biopsy specimens, but rarely for lymph nodes. Cultures are usually positive after 2 weeks of incubation, but up to 45 days may be necessary for primary isolation.

TABLE 291-3 LABORATORY METHODS FOR THE DIAGNOSIS OF *BARTONELLA* INFECTIONS

CLINICAL MANIFESTATION	SEROLOGY	CULTURE	MOLECULAR METHODS	IMMUNOHISTOCHEMISTRY (WARTHIN-STARRY STAIN)	MICROSCOPY FOR INTRAERYTHROCYTIC ORGANISM (GIEMSA OR IF)
Oroya fever	–	+	+	–	+++
Verruga peruana	–	–	+	+	–
Trench fever	+/–	+	+	–	+
Chronic bacteremia	+/–	+++	+	–	–
Infective endocarditis	+++	+++	+++	+++	–
Bacillary angiomatosis	+/–	++	+++	+++	–
Peliosis hepatis	+/–	++	+++	+++	–
Cat-scratch disease	+	–	+++	+/–	+/–
SENLAT with skin lesion	+	+	+++	+	–
Meningoencephalitis	++	–	++	–	–
Uveitis-retinitis	++	–	++	+	–

The usefulness of these techniques varies according to the disease being tested.
IF = immunofluorescence; SENLAT = scalp eschar and neck lymphadenopathy.

Differential Diagnosis

The differential diagnosis of bacillary angiomatosis is Kaposi sarcoma (Chapter 187), but PCR testing or visualization of bacteria in the tissue specimen can help distinguish between these two entities. Trench fever may be confused mainly with typhus group rickettsiosis (Chapter 302), relapsing fever (Chapter 297), and malaria (Chapter 316). Cat-scratch disease may be confused with tularemia (Chapter 287), pyogenic lymphadenitis, mycobacterial infection (Chapters 299 and 300), and neoplasia.

TREATMENT

Trench Fever

Patients with *B. quintana* bacteremia should be treated with gentamicin (3 mg/kg body weight/day IV for 14 days) in combination with doxycycline (200 mg/day PO) for 28 days. Because the intraerythrocytic presence of *B. quintana* decreases antimicrobial efficacy, the duration of treatment is critical in trench fever.

Oroya Fever and Verruga Peruana

In Oroya fever, treatment with penicillin, streptomycin, or fluoroquinolones (e.g., tetracycline or erythromycin) produces rapid defervescence and disappearance of the organisms from the blood, usually within 24 hours. Because coinfection with *Salmonella* species is common, the recommended regimen is either ciprofloxacin (500 mg orally twice daily) plus ceftriaxone (2 g every 12 to 24 hours intravenously) for 10 days or chloramphenicol (500 mg orally or intravenously four times a day) for 14 days in combination with another antibiotic (especially a β-lactam compound; e.g., ampicillin 1 to 2 g intravenously every 4 to 6 hours depending on local resistance patterns or susceptibility testing).

Streptomycin (15 to 20 mg/kg/day intramuscularly for 10 days) is effective for verruga peruana, but oral rifampin (10 mg/kg/day orally for 14 days) has become the drug of choice for the treatment of eruptive-phase bartonellosis, even though rifampin treatment failures have been reported. Ciprofloxacin (500 mg orally twice daily for 7 to 10 days) is an alternative for multiple eruptive-phase lesions in adults.

Cat-Scratch Disease

Typical cat-scratch disease is a self-limited illness that resolves within 2 to 6 months and usually does not respond to therapy because the bacteria are not alive within necrotic lymph nodes. In cases of long-lasting lymphadenopathy, patients should be reassured that the disease is benign and will probably subside spontaneously. Management consists of analgesics for pain and prudent follow-up. However, azithromycin (500 mg PO on day 1 and 250 mg PO on days 2 to 5 as single daily doses) is an alternative for patients with large, bulky lymphadenopathy. If lymphadenopathy does not resolve, lymph nodes can be removed surgically.

For cat-scratch disease with manifestations beyond lymphadenopathy, data are limited regarding the benefit of specific antimicrobial therapy for immunocompetent patients. For neuroretinitis, the combination of doxycycline (100 mg PO or IV twice daily) with rifampin (300 mg PO twice daily) seems to promote disease resolution, improve visual acuity, reduce optic disc edema, and decrease the duration of disease.

Endocarditis

Patients with suspected or PCR-proven *Bartonella* endocarditis or proven *B. quintana* endocarditis should be treated with oral doxycycline (100 mg twice a day for 6 weeks) in combination with gentamicin (3 mg/kg/day in one intravenous daily dose for 14 days).

Bacillary Angiomatosis and Peliosis Hepatis

Antibiotic treatment is warranted in all cases of *Bartonella*-associated vasculoproliferative disease. Erythromycin (500 mg four times daily) for 3 months is first-line therapy. The response of bacillary angiomatosis in immunocompromised patients can be dramatic, with resolution of palpable subcutaneous lesions within hours. Doxycycline (100 mg PO or IV twice daily) is an appropriate alternative. In patients with serious infections, erythromycin or doxycycline can be used in combination with rifampin (300 mg PO twice daily). The duration of therapy should be at least 3 months for bacillary angiomatosis and 4 months for peliosis hepatis. Peliosis hepatis responds slowly, and hepatic lesions continue to improve after several months of treatment, whereas cutaneous bacillary angiomatosis demonstrates improvement after 4 to 7 days of treatment and resolves after about 1 month of treatment. Relapses of peliosis hepatis and bacillary angiomatosis lesions after antibiotic treatment have been reported frequently, especially in immunocompromised patients who received shorter durations of therapy. Patients who relapse after the recommended treatment should be retreated for 4 to 6 months with erythromycin (500 mg PO four times daily) or doxycycline (100 mg PO twice daily), and patients who have repeated relapses should receive antibiotic therapy for as long as they are immunocompromised.

PREVENTION

Because arthropods play an important role in the transmission of feline *Bartonella* species to humans, rigorous arthropod control should be recommended by health care workers, particularly when advising immunocompromised individuals on the risks related to pet ownership. Cat fleas live on both cats and dogs and are best controlled by fumigating areas where these animals live.

PROGNOSIS

Without antibiotic treatment, Oroya fever causes death in up to 85% of untreated patients because of hemolysis or opportunistic infections, such as salmonellosis. With antibiotic treatment, however, the morality rate is rare.

Trench fever is not a fatal disease, but antibiotic treatment is required to avoid more severe disease, especially in patients who have abnormal heart valves and are at risk for endocarditis. Patients with *Bartonella* endocarditis have a higher death rate and undergo valvular surgery more frequently than patients with endocarditis caused by many other pathogens. Cat-scratch disease usually resolves spontaneously without any treatment in immunocompetent patients; however, patients who have complications or who are immunocompromised require antibiotic therapy to which they usually respond well, with a mortality rate of only about 1% even in hospitalized patients.[17] Without appropriate therapy, bacillary angiomatosis and peliosis hepatis spread systemically and can involve virtually any organ, sometimes with a fatal outcome. For these vasculoproliferative diseases, antibiotics are usually effective if they are given for a prolonged period, but cutaneous lesions in verruga peruana may benefit from surgery.

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292 GRANULOMA INGUINALE (DONOVANOSIS)

WALTER BELDA, JR.

DEFINITION

Granuloma inguinale, also known as donovanosis, is a chronic and progressive bacterial ulcerative disease that predominantly affects the skin and mucous membranes of the genital, inguinal, perirectal, and anal regions, often associated with sexual transmission.

The Pathogen

Donovanosis is caused by *Klebsiella granulomatis*, which is a gram-negative, facultatively aerobic coccobacillus that is intracytoplasmic, immobile, and can be encapsulated. In lesions, these microorganisms are found inside macrophages in the form of small oval bodies called Donovan corpuscles, which are visible on Giemsa, Leishman, or Wright stains.

EPIDEMIOLOGY

Granuloma inguinale is uncommon but occurs more often in individuals with less access to soap and water for personal hygiene. It is endemic in tropical and subtropical countries such as Papua New Guinea, Australia, Argentina, and Brazil,[1] and sporadic cases are also reported in India and the Caribbean. In South Africa, no cases have been reported for more than a decade,[2] and the disease is very uncommon in the United States.

Donovanosis is generally considered to be primarily a sexually transmitted infection because the main clinical manifestations occur in the genital region. Infectivity is low, however, and multiple sexual contacts with infected partners are necessary to transmit the disease. It typically affects adults ages 20 to 40 years without a gender predilection. Congenital infection has been reported, but the few documented cases of perinatal transmission of donovanosis show an apparent predilection for otorhinolaryngologic structures.

PATHOBIOLOGY

In infected lesions, the dermis shows an inflammatory infiltrate consisting of lymphocytes, plasma cells, and histiocytes. Histiocytes are usually voluminous and have a vacuolar appearance, inside of which the inclusion corpuscles are usually easily identified with Giemsa, Leishman, or Wright stain.

CLINICAL MANIFESTATIONS

The incubation period of donovanosis is controversial, with studies indicating periods ranging from 2 weeks to 1 month. The lesion starts as a subcutaneous nodule or papule at the inoculation site and then evolves slowly to an erythematous, shiny, friable surface ulceration. In general, the lesions are not painful. Inguinal adenopathy is usually absent, but early-stage lesions that are located in the inguinal region simulate a bulb (pseudobulb).

The ulcerous forms can be lenticular in shape, with everted edges and a mild inflammatory reaction. Lesions grow slowly and become well defined, with a granular background, centrifugal and serpiginous in character, covered with a thick and fetid exudate. Ulcerative lesions have abundant secretions and bleed easily (Fig. 292-1). The lesion's edges are variable in appearance, firm in consistency, smooth, and may be flat or hypertrophic. The edges may eventually appear raised, thereby clearly defining the lesion and sometimes simulating a carcinomatous appearance.[3] Secondary bacterial infection can occur.

Lesions can multiply by self-inoculation, favored by the draining of the exudate. In the ulcerovegetating form, the abundant granulation tissue at the bottom of the ulcerated lesion exceeds the lesional contour and is a clinical form that bleeds very easily. The vegetating forms, in turn, lack secretions and usually present with small dimensions and well-defined borders.

Elephantiasis almost always occurs with long-lasting ulcerated forms of infection, which promote lymphatic alterations and create lymphedema as well as local stasis. As the lesions progress, they heal with intense fibrosis, which destroys the lymphatic pathways. These forms, which are found mainly on the female genitalia, are the most frequent complication of donovanosis. Squamous cell carcinomas of the vulva can develop in patients with long-standing, chronic disease.

FIGURE 292-1. Ulcerated nodule lesion with a granular fundus and bleeding located in the preputial balano sulcus.

Extra-genital locations can be a consequence of unusual sexual practices or be acquired by direct inoculation into the skin, particularly by contaminated fingers. Extra-genital lesions can occur in the gums, larynx, neck, armpits, chest, abdomen, joints, and bones, particularly the tibia. Hematogenous dissemination to internal organs, especially in immunocompromised patients, mainly involves the lungs, intestines, spleen, and liver.

DIAGNOSIS

The diagnosis is made by demonstrating Donovan bodies in material obtained from the lesions, using cytologic preparations and histology for confirmation. Direct microscopy is the fastest and most reliable diagnostic method. Infected material should be collected from the active granulation areas and inspected on a glass slide with Giemsa, Leishman, or Wright stains for direct visualization. The presence of cells with the bodies of Donovan is pathognomonic of the infection.

Polymerase chain reaction (PCR) for diagnosis is generally restricted to disease eradication programs. The culture of the etiologic agent in the yolk sac of a chicken embryo is extremely difficult and is not routinely available owing to its high cost, technical challenges, and high failure rate. No serologic tests are currently available to diagnose donovanosis. Biopsies should be performed on extensive lesions that have necrosis or sclerosis, to exclude the possibility of malignancy.

Differential Diagnosis

The differential diagnosis of donovanosis lesions includes primary syphilis (Chapter 295), flat condyloma (Chapter 344), chronic herpetic ulcers (Chapter 345), giant condyloma acuminata (Chapter 344), lymphogranuloma venereum (Chapter 294), and squamous cell carcinoma.[4,5] Other causes of ulcerous granulomatous lesions include cutaneous tuberculosis (Chapter 299), paracoccidioidomycosis (Chapter 308), and pyoderma gangrenosum (Chapter 407).

TREATMENT

The duration of antimicrobial treatment, regardless of the therapeutic regimen used, should continue at least until all lesions are completely healed. The current recommended first-line therapy is azithromycin (two 1-g tablets orally) per week for 3 weeks or until complete healing of the lesions. Alternatives, also for a least 3 weeks or until healing is complete, are doxycycline (200 mg orally per day), ciprofloxacin (750 mg orally twice a day), or sulfamethoxazole-trimethoprim (400/800 two tablets twice a day).[6] If lesions do not respond within the first several days, an aminoglycoside (e.g., gentamicin 1 mg/kg/day intravenously, three times a day for at least 21 days) should be added.

For refractory lesions or patients who are immunosuppressed or infected with the human immunodeficiency virus (HIV), the same therapeutic regimens are recommended, but parenteral therapy with gentamicin or chloramphenicol 500 mg orally four times a day should be considered instead in the most severe cases. For pregnant women, 500 mg of erythromycin should be given four times a day for at least 3 weeks.

Sexual contacts should be identified and examined, but asymptomatic contacts do not require treatment. For prophylactic treatment of neonates of mothers who have genital lesions of donovanosis, azithromycin (20 mg/kg/day for 3 consecutive days) is effective to avoid infection in the newborn.

ABSTRACT

Donovanosis is a chronic and progressive bacterial disease that affects the skin and mucous membranes of the genital and perigenital regions, often associated with sexual transmission and with low infectivity.

KEYWORDS

donovanosis
granuloma inguinal
sexually transmitted infection

PROGNOSIS

With prompt therapy, patients are usually cured. However, delayed diagnosis or treatment can lead to genital lymphedema, deforming and unsightly scarring, destruction of the body of the penis, and stenosis of the urethral, vaginal, and anal orifices. Malignant transformation to squamous cell carcinoma can occur.

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293

MYCOPLASMA INFECTIONS

DAVID L. GOLDMAN

MYCOPLASMA PNEUMONIAE

DEFINITION

Mycoplasma organisms of the class Mollicutes are ubiquitous as pathogens and colonizing agents in the plant, animal, and insect kingdoms. They represent the smallest known free-living forms, but because they have fastidious growth requirements, they are difficult to culture. The presence of several species of *Mycoplasma* as commensals in animals and on human oral and genital mucosa frequently results in contamination of cell cultures. Such contamination led to the false implication of mycoplasmas as causative agents in many human diseases, both trivial and life-threatening. Of the human diseases that have proven to be due to mycoplasmas, pneumonia caused by *Mycoplasma pneumoniae* is by far the most clinically important.[1] This infection constitutes a significant proportion of cases previously classified as atypical pneumonia (Chapter 85), a nonspecific term for patchy pneumonias that generally do not respond to β-lactam antibiotics and have etiologic agents that are not easily cultured or visible on Gram stain. The term *atypical pneumonia* persists despite our increasing ability to identify specific etiologic agents, such as viruses, *Legionella* (Chapter 290), and *Chlamydophila* (Chapter 294).

The Pathogen

Mycoplasmas are short rods (10 × 200 nm) that have no cell wall and are bounded by a sterol-containing membrane. They are unaffected by cell wall–inhibiting antimicrobials such as β-lactams. In tissue culture, mycoplasmas are intracellular; but in vivo infection is primarily extracellular and affects epithelial cells and their organelles, such as cilia. Attachment to respiratory epithelium is by way of terminal adhesin proteins in specialized tip organelles.

EPIDEMIOLOGY

M. pneumoniae infection is spread person to person by respiratory droplets produced by coughing. Relatively close association with the index case appears to be required. The disease is usually introduced into families by a young child; in some studies, most of the infected adults were the parents of young children. As opposed to most viral respiratory infections, which are manifested 1 to 3 days after infection, *Mycoplasma* has an incubation period of 2 to 3 weeks. Therefore, a careful history showing several weeks between cases within a family may be an important clue to the mycoplasmal etiology. Organisms can be cultured from the sputum of infected individuals for weeks to months after effective treatment.

Most cases of *Mycoplasma* respiratory infection occur singly or as family outbreaks. However, in closed populations, such as military recruit camps and boarding schools, *Mycoplasma* can cause mini-epidemics and may be responsible for 25 to 75% of cases of pneumonia in such settings. Serologically based epidemiologic studies have documented the high incidence of *Mycoplasma* respiratory infection throughout the world. In the United States, it is estimated that each year at least one case of *Mycoplasma* pneumonia occurs for every 1000 persons, or more than 2 million cases annually. The incidence of *Mycoplasma* nonpneumonic respiratory infection may be 10 to 20 times greater. The highest attack rates are in individuals 5 to 20 years old, but *M. pneumoniae* infection can occur at any age.

As opposed to viral respiratory infections that peak in winter in temperate climates, a few studies have reported a peak incidence of *M. pneumoniae* outbreaks in the fall. Most surveys, however, show little or no seasonal predominance. Recurrent epidemic 4-year cycles have been described in several countries.

There is an age-related relationship of upper versus lower respiratory tract infection caused by *M. pneumoniae*. In children younger than 3 years, primarily upper respiratory tract infection develops, whereas bronchitis and pneumonia tend to occur in individuals ages 5 to 20 years. In older adults, pneumonia predominates.

PATHOBIOLOGY

Inoculation onto animal tracheal organ cultures is followed by ciliary damage and desquamation of surface epithelium. This latter effect is probably responsible for the hacking cough in *Mycoplasma* respiratory infection.

Several characteristics of *M. pneumoniae* probably play a direct role in the respiratory pathogenicity of this organism. The first is the affinity of *M. pneumoniae* for respiratory epithelial cells. Attachment appears to be between a terminal organelle at one end of the filamentous organism and a sialylated glycoprotein (I-FI) on the surface of both respiratory epithelium and erythrocytes that acts as a receptor. *M. pneumoniae* attaches to ciliated epithelial cells at the base of cilia and appears to produce most of its physiologic and cytolytic changes while remaining extracellular. Hydrogen peroxide produced by *M. pneumoniae* (the only human mycoplasma to do so) may be responsible for some in vivo cell damage, as it is for the hemolysis seen when the organisms are grown on blood agar plates. *Mycoplasma* infection activates T and B cells and induces many pro-inflammatory and anti-inflammatory cytokines as well as chemokines that may play a role in inflammation-related cell destruction. *M. pneumoniae* also secretes a community-acquired respiratory distress syndrome toxin, which binds surfactant protein and dysregulates host adenosine diphosphate (ADP) ribosylation. High levels of this toxin are produced during infection, and inoculation of this toxin in an animal model induces many of the pathologic features of *M. pneumoniae* infection, including vacuolization, cilostasis, and inflammatory changes.[2,3] Strain-specific elaboration of biofilms probably plays a role in protecting the organism from host immune cells and may decrease antimicrobial penetration. Functional asplenia and its attendant opsonization deficiencies may contribute to overwhelming infection with *M. pneumoniae*, as they do with *Streptococcus pneumoniae* infection.

In the course of *M. pneumoniae* infection, several classes of antibody are produced. Some of these fulfill the desired role of antibody production (i.e., neutralization of the agent), and others appear to be autoantibodies. The latter include agglutinins to lung, brain, cardiolipins, and smooth muscle. The best studied of these autoagglutinins are the cold isohemagglutinins, which are capable of clumping erythrocytes at 4° C.

These oligoclonal M-type immunoglobulins (IgM) cross-react with I antigens, one of the blood group antigens common to almost all mature human erythrocytes. High titers of the cold reactive antibody may cause hemolysis (presumably as a result of complement-activated, Coombs-positive erythrocyte destruction). As with other IgM antibodies, the *Mycoplasma*-induced cold agglutinins (Chapter 146) develop early in the disease (7 to 10 days) and are often present by the time the patient seeks medical attention. The titer of these agglutinins peaks at 2 to 3 weeks, and they persist for 2 to 3 months (Fig. 293-1).

CLINICAL MANIFESTATIONS

Although *M. pneumoniae* is predominantly an upper and lower respiratory tract infection, it can involve multiple organ systems.

Respiratory Infection

The majority of *M. pneumoniae* infections involve only the upper respiratory tract. After a 2- to 3-week incubation period, the disease has an insidious onset consisting of fever, malaise, headache, and cough (see Fig. 293-1). Cough is the clinical hallmark of *M. pneumoniae* infection. The frequency and severity of the cough increase during the next 1 to 2 days, and it may become debilitating. The gradual onset of symptoms is in contradistinction to the often fulminant manifestation of respiratory infection caused by influenza virus or adenovirus.[4]

In 5 to 10% of patients, depending somewhat on age, the infection progresses to tracheobronchitis or pneumonia. In these cases, the initial manifestations persist, and the cough becomes more severe. Although the pneumonia is generally mild and self-limited, fulminant and severe cases can occur.

The cough is usually relatively nonproductive but may yield white or occasionally blood-flecked sputum. With continued cough, parasternal chest

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PROGNOSIS

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293

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In 5 to 10% of patients, depending somewhat on age, the infection progresses to tracheobronchitis or pneumonia. In these cases, the initial manifestations persist, and the cough becomes more severe. Although the pneumonia is generally mild and self-limited, fulminant and severe cases can occur.

The cough is usually relatively nonproductive but may yield white or occasionally blood-flecked sputum. With continued cough, parasternal chest

ABSTRACT

Mycoplasma pneumoniae is a leading cause of community-acquired respiratory infections in children and young adults. It can cause disease sporadically and as outbreaks in closed communities such as boarding schools and military recruit camps. Pneumonia secondary to this organism is remarkable for a paucity of auscultatory chest findings, and radiographic findings are nonpathognomonic. A host of extrapulmonary complications have been reported, but many of these may be coincidental because the underlying disease is very common. Diagnosis is usually made on clinical grounds, but nucleic acid–based assays provide excellent sensitivity and specificity. Disease is usually self-limited and rarely fatal. Because of the absence of a cell wall, β-lactam antibiotics are ineffective. Treatment with either macrolides or doxycycline shortens the clinical course. Other mycoplasmas causing human disease are also briefly discussed.

KEYWORDS

Mycoplasma pneumoniae
pneumonia
community-acquired pneumonia
macrolides
Mycoplasma hominis
urethritis

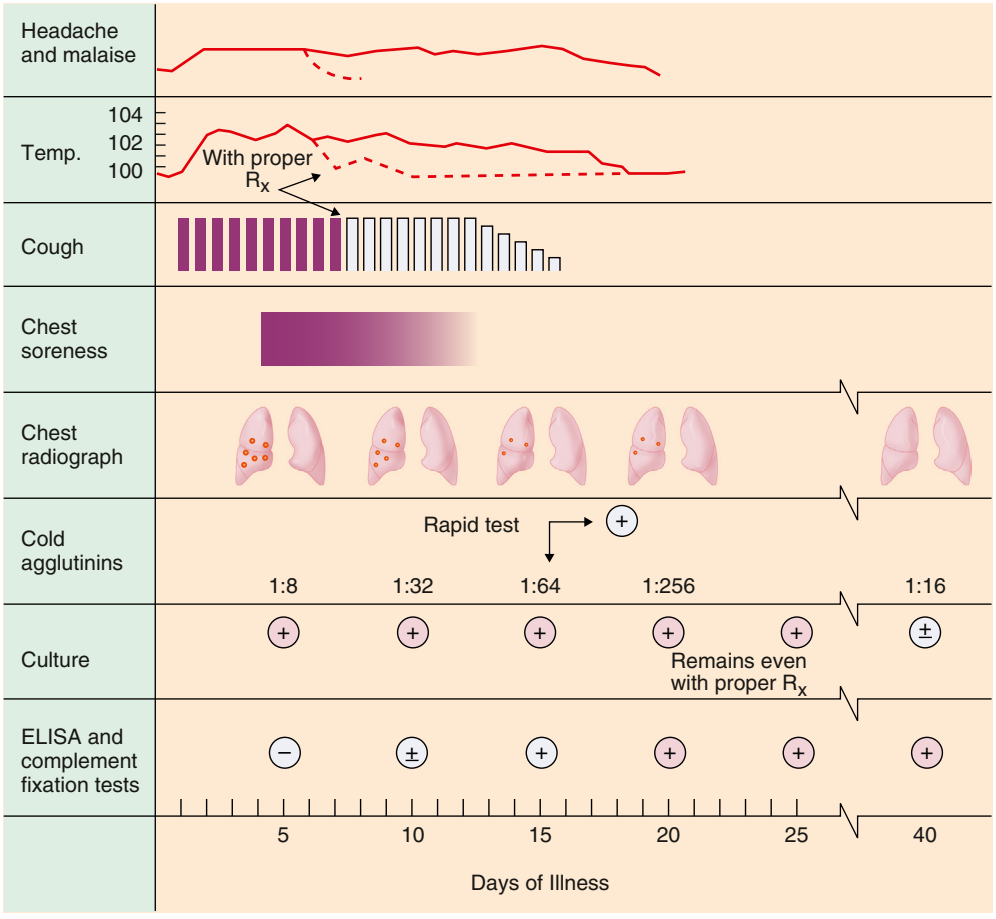

FIGURE 293-1. Major clinical and laboratory manifestations of mycoplasmal pneumonia. ELISA = enzyme-linked immunosorbent assay; R_x = treatment; Temp. = temperature. (Modified from Baum SG. Mycoplasmal infections. In: Wyngaarden JB, Smith LH Jr, eds. *Cecil Textbook of Medicine*. 17th ed. Philadelphia: Saunders; 1985:1506.)

soreness may develop as a result of muscle strain, but true pleuritic pain is unusual. Fever is usually at the level of 101° to 102° F and may be associated with chills. As opposed to pneumonia caused by *Streptococcus pneumoniae* (Chapter 268), that caused by *M. pneumoniae* rarely produces true shaking chills. In comparison to influenza (Chapter 332), which also can be manifested as an atypical pneumonia syndrome, myalgias and gastrointestinal complaints of nausea and vomiting are unusual. Diarrhea, sometimes a concomitant of adenoviral (Chapter 333) or *Legionella* (Chapter 290) pneumonia, is uncommon in *Mycoplasma* infection. Unfortunately, no clinical signs or symptoms can reliably differentiate *M. pneumoniae* infections from other community-acquired pneumonias.

On physical examination, the patient usually does not appear to be severely ill. Mycoplasma is the paradigm of the term *walking pneumonia*. The pharynx may be injected and erythematous, usually without the marked cervical adenopathy seen with group A streptococcal pharyngitis. Pharyngitis is uncommon, and myringitis and otitis are rare.

Examination of the chest in patients with *Mycoplasma* pneumonia is often unrevealing, even in patients with severe, productive cough. There may be no auscultative or percussive findings, or only minimal rales (crackles) may be present. Although wheezing can occur, the wheezing isolation is more suggestive of viral respiratory pathogens, such as respiratory syncytial virus (Chapter 330). *M. pneumoniae* is not a common pathogen in patients with preexisting chronic obstructive lung disease, and bacterial superinfection after *M. pneumoniae* respiratory infection is rare.

The radiographic finding of interstitial or patchy alveolar pneumonia does not differentiate *M. pneumoniae* from any of the other causes of atypical pneumonia, but the disparity between the physical findings and radiographic evidence of pneumonia in this condition may be the greatest of any of the atypical pneumonia syndromes (Fig. 293-2).

Pleural effusion (usually small) occurs in 5 to 25% of patients.[5] If effusion is present, thoracentesis reveals serous fluid that is exudative, with minimal inflammatory reaction. The cell differential count in the fluid is variable, and bloody effusions are rare. It is unusual to isolate *M. pneumoniae* from effusions when they do occur.

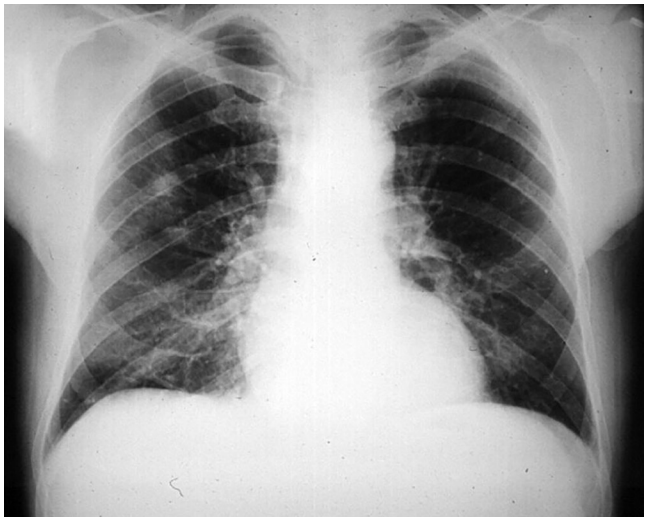

FIGURE 293-2. Chest radiograph showing moderate interstitial pneumonia due to *Mycoplasma pneumoniae* infection in a patient with a paucity of findings on chest auscultation.

Extrapulmonary Involvement

Extrapulmonary manifestations of *M. pneumoniae* infection can involve almost every organ system.

Dermatologic Involvement

Transient dermatologic conditions in conjunction with *Mycoplasma* pneumonia include macular, morbilliform, and papulovesicular eruptions, as well as erythema nodosum, urticaria, and a debilitating form of *M. pneumoniae*–associated mucositis without skin involvement.[6]

FIGURE 293-3. Stevens-Johnson syndrome in a child with *Mycoplasma* pneumonia. (From Baum SG. *Mycoplasma pneumoniae* and atypical pneumonia. In: Mandell GL, Bennett JE, Dolin R, eds. *Mandell, Douglas, and Bennett's Principles and Practice of Infectious Diseases*. 6th ed. Philadelphia: Churchill Livingstone; 2005:2274.)

Up to 7% of patients with *Mycoplasma* pneumonia develop Stevens-Johnson syndrome (Fig. 293-3 and 403-8), which consists of erythematous vesicles, plaques, and bullae involving the skin, with particular localization at mucocutaneous junctions (Chapter 407). The conjunctivae as well as organs of the gastrointestinal and genitourinary tracts and the joints may also be involved. Stevens-Johnson syndrome can occur with or without prior antibiotic therapy, tends to occur in younger patients, and has a definite male preponderance (2 : 1 to 4 : 1). Most patients clear the lesions in 1 to 2 weeks without scarring unless impetiginization supervenes.

Cardiovascular Complications

Cardiac abnormalities are among the most commonly reported extrapulmonary manifestations of *M. pneumoniae* infection. Signs and symptoms suggesting involvement of the heart are arrhythmia, heart failure, chest pain, and electrocardiographic abnormalities, particularly conduction defects. Although cardiac abnormalities have been reported in as many as 10% of cases of *M. pneumoniae* infection, other reports indicate a much lower prevalence. Cardiac complications are more common with increasing age. They prolong the illness but rarely lead to death. The mechanism of heart damage is unknown, but *M. pneumoniae* can rarely be isolated from pericardial fluid.

Raynaud phenomenon (Chapter 66; Fig. 66-9) in *M. pneumoniae* may be related to the in vivo action of cold agglutinins. Other reported vascular complications in *M. pneumoniae* infection include internal carotid artery occlusion and cerebral infarction.[7]

Neurologic Complications

Neurologic complications are rare (about 0.1% of patients). Aseptic meningitis (Chapter 381), acute disseminated encephalomyelitis (Chapter 383), transverse myelitis (Chapter 369), brain stem dysfunction, posterior reversible encephalopathy syndrome, Guillain-Barré syndrome (Chapter 388), cerebral ataxia (Chapter 379), and peripheral neuropathy (Chapter 388) have all been reported. In patients with neurologic involvement, cerebrospinal fluid (CSF) findings are variable, but the cellular response is usually minimal, with slightly elevated protein level and normal to slightly depressed glucose concentration. Most often, the diagnosis of *Mycoplasma*-related central nervous system involvement is based on the exclusion of other causes, the presence of an antecedent or intercurrent respiratory illness, and a rise in antibody titer to *M. pneumoniae* in serum. Polymerase chain reaction (PCR) testing for *M. pneumoniae* in CSF is typically negative, thereby suggesting immune mechanisms of neural damage.

Hematologic, Musculoskeletal, and Renal Complications

The cold agglutinins generated by the immune response to *M. pneumoniae* can cause hemolytic anemia, which can range from mild to severe (Chapter 146).[8] Polyarthralgias are common in *Mycoplasma* pneumonia, but monoarticular or migratory arthritis is rare. Rhabdomyolysis (Chapter 99) may be associated with very high levels of muscle enzyme, interleukin-18, and tumor necrosis factor-α levels. Renal complications associated with immune complex deposition and high-titer cold agglutinins have been reported.

Sickle-Cell Disease

In patients with sickle cell disease or sickle-related hemoglobinopathies (Chapter 149), large pleural effusions and marked respiratory distress may develop. *M. pneumoniae* is also associated with acute chest syndrome, especially in children. Some sickle cell disease patients with *M. pneumoniae* infection and extremely high cold agglutinin titers may experience digital necrosis.

DIAGNOSIS

The diagnosis of *Mycoplasma* pneumonia is suspected primarily on clinical grounds. However, the very high incidence of *Mycoplasma* respiratory infection when it is studied epidemiologically in large populations compared with the rarity of individual sporadic diagnoses suggests this entity is seldom diagnosed in routine clinical practice.

The diagnosis can be confirmed by rapidly available, highly sensitive and specific PCR assays,[9,10] of nasopharyngeal, oropharyngeal, or sputum samples, typically as part of a respiratory panel that can detect multiple respiratory pathogens. A PCR-based assay for the determination of erythromycin resistance is available through the Centers for Disease Control and Prevention (CDC). The available antibody assays do not have acceptable sensitivity and specificity compared with PCR assays.

Gram staining of sputum reveals inflammatory cells but no predominant bacterial species. Culture of the organism in cell-free media requires weeks and is not widely available.

Cold Agglutinins

Immunoassays can detect cold agglutinins, which may help explain clinical manifestations such as Raynaud phenomenon. When testing for cold agglutinin, the results will not be available for at least a day, but a rapid version can be done at the bedside. In this test, 1 mL of the patient's blood is drawn into the tube used to collect specimens for prothrombin determination. Before cooling, examination shows a smooth coating of the tube by red cells. The blood is cooled to 4° C by placing it on liquid ice or in a standard refrigerator. After several minutes, the tube is examined for the presence of macroscopic erythrocyte agglutination. The tube is then rewarmed to 37° C in an incubator or by exposure to body heat and reexamined. The agglutination should dissociate at 37° C, and the appearance should be as it was before cooling. A positive result in the bedside test correlates with a laboratory titer of 1 : 64 and is highly suggestive of *Mycoplasma*-related cold agglutination. Other conditions associated with lower titers include mononucleosis caused by Epstein-Barr virus (Chapter 348), cytomegalovirus infection (Chapter 347), some other viral diseases, and lymphoma (Chapter 171). Nevertheless, a titer of 1 : 32 or greater is highly suggestive of infection with *M. pneumoniae*.

The presence of cold agglutinins can also artifactually give rise to macrocytic red blood cell indices by the Coulter counter method because of in vitro clumping of erythrocytes. When the phenomenon occurs, the red cell distribution width is high, indicative of heterogeneity in the measured red cell size.

TREATMENT

Despite the accuracy of PCR assays, most cases of *M. pneumoniae* infection are treated empirically in the ambulatory setting based on the clinical syndrome without definite microbiologic confirmation. Although pneumonia caused by *Mycoplasma* is usually self-limited and not life-threatening, antimicrobials as used for community-acquired pneumonia (Chapter 85) may shorten the duration of illness and, by reducing cough and the number of organisms per unit volume of sputum, may reduce the spread of infection to contacts. For mycoplasmal infection limited to the upper respiratory tract, antimicrobial therapy is not necessary.

Recommended therapy includes doxycycline (100 mg every 12 hours for 7 to 14 days) or azithromycin (500 mg on day 1 and then 250 mg every 24 hours to complete a 5-day course). Resistance to macrolides is not common in North America, but it is commonly encountered in Asia.[11,12] Other alternative antimicrobial options are fluoroquinolones (e.g., moxifloxacin, 400 mg daily or levofloxacin 750 mg daily) for 7 to 10 days.

In some pediatric studies, the addition of corticosteroids (e.g., prednisolone 1 mg/kg twice daily for 3 days then tapered over 1 week) has been reported to shorten the duration of symptoms in severe or refractory infections.[A1] However, corticosteroids are not recommended in adults with *M. pneumoniae* pneumonia. The treatment of cold agglutinin-associated hemolytic anemia is described in Chapter 146 (see Fig. 146-1).

PREVENTION

Vaccines using attenuated wild-type and temperature-sensitive mutant mycoplasmas are only about 50% for precipitating an antibody response, and volunteers who receive vaccine but do not mount an antibody response have more severe disease when rechallenged with wild-type *Mycoplasma* than do nonvaccinated persons. Prophylactic antibiotics decrease clinical disease in family members exposed to patients with *Mycoplasma,* but seroconversion is not prevented. In long-term care facilities, azithromycin prophylaxis (500-mg loading dose and 250 mg/day on days 2 through 5) can significantly reduce the secondary attack rate of *M. pneumoniae* infection.

PROGNOSIS

In many patients, *M. pneumoniae* infection is mild and self-limited. For more substantial illness, appropriate antibiotic therapy significantly shortens the duration of illness, but radiographic findings may take a week or longer to resolve, and organisms may continue to be cultured from sputum for several weeks after a complete course of clinically effective treatment.

Long-term sequelae are rare. Neurologic complications are usually reversible, but mortality in patients with central nervous system involvement is higher than in those without such involvement.

OTHER *MYCOPLASMA* SPECIES

Other proven *Mycoplasma* infections include those in the urogenital tract caused by *Ureaplasma* species, *M. hominis,* and *M. genitalium;* wound infections caused by *M. hominis;* and overwhelming systemic infection in immunocompromised patients caused by *Mycoplasma fermentans* (*incognitus* strain).

EPIDEMIOLOGY

Infections due to *Ureaplasma urealyticum, Ureaplasma parvum , M. hominis,* and *M. genitalium* are spread venereally, are not well documented (Table 293-1), and are difficult to culture but can be better identified by nucleic acid amplification testing. Their true incidence and prevalence are uncertain, as is their public health impact.

PATHOBIOLOGY

The genital mycoplasmas attach to cells using an adhesion protein as well as lipid-associated membrane proteins that adhere by way of toll-like receptors. Once within the cell, *M. genitalium* triggers elaboration of numerous cytokines that cause inflammation.

CLINICAL MANIFESTATIONS

Diseases attributed to *Ureaplasma* species include urinary tract infection with and without calculus formation.[13] This organism also has been implicated as a cause of low birthweight in neonates.

TABLE 293-1 SITES AND INFECTIONS RELATED TO HUMAN MYCOPLASMAS OTHER THAN *MYCOPLASMA PNEUMONIAE*

SUBGROUP	SITES OF ISOLATION	DISEASES	OCCURRENCE
M. hominis	GU tract (F > M)	Cervicitis, vaginitis, ?prostatitis	Common
	Conjunctivae (neonate)	Conjunctivitis	
	Blood (peripartum)	Peripartum sepsis	
	Surgical wounds, joints	Sternotomy infection, arthritis	
M. orale	Oropharynx	?	Common
M. salivarium	Oropharynx, gingiva	?Periodontal disease	Common
M. fermentans	GU tract, blood, tissues	Multisystem disease in AIDS	Uncommon
M. genitalium	GU tract	Urethritis, cervicitis, PID	Uncommon
Ureaplasma spp	GU tract	Urethritis, upper GU infection	Common

AIDS = acquired immunodeficiency syndrome; F = female; GU = genitourinary; M = male; PID = pelvic inflammatory disease; spp = multiple species.

M. genitalium infection can cause nongonococcal urethritis (Chapter 264)[14] in males and cervicitis and pelvic inflammatory disease (Chapters 264, 275, and 294) in females, in whom it leads in some cases to tubal factor infertility (Chapter 218), preterm birth, and spontaneous abortion. Chronic *M. genitalium* infection may enhance the acquisition of human immunodeficiency virus (HIV; Chapter 353) through increased shedding, and the prevalence of *M. genitalium* appears to be higher in patients with HIV than in the general population. Coinfection of *M. genitalium* with *Neisseria gonorrhoeae* (Chapter 275) is also noted,[15] and untreated *M. genitalium* is implicated in patients who have recurrent symptoms after standard treatment for a sexually transmitted infection (Chapter 264).

M. hominis, which is a common genitourinary and oral commensal, can cause endometritis and postpartum fever. It can also cause sternal wound infection after cardiothoracic surgery and has been implicated in arthritis in immunocompromised patients.

M. salivarium may be involved in periodontal disease. *M. fermentans, incognitus* strain can cause overwhelming multisystem involvement in immunocompromised patients.

DIAGNOSIS

PCR testing has enhanced the ability to detect *M. genitalium,*[16] and genital mycoplasmas, including *Ureaplasma* species and chlamydial organisms in secretions in a single panel, but the sensitivity and specificity of these tests appear to vary.

TREATMENT AND PROGNOSIS

Susceptibility testing for *M. hominis, M. genitalium,* and *Ureaplasma* spp is of limited clinical utility because these organisms grow slowly. As a result, the findings usually are not available when treatment decisions must be made.

M. hominis, unlike *M. pneumoniae,* is not sensitive to macrolides but is often sensitive to tetracyclines, clindamycin, and fluoroquinolones.[17] Treatment regimens for *M. hominis* are not well standardized but should take into account the severity of disease and the underlying immune status of the host. Uncomplicated genitourinary infections can be treated with doxycycline (100 mg orally twice a day for 7 days).

Increasing antimicrobial resistance also has been noted for *M. genitalium*, so the standard therapy for pelvic inflammatory disease (Chapter 264) is insufficient to cure these infections.[18,19] For infections due to *M. genitalium* (e.g., urethritis and cervicitis), a two-stage approach is recommended depending on the availability of susceptibility testing results. In the absence of susceptibility testing or documented resistance, patients should be treated with doxycycline (100 mg orally twice a day) for 7 days followed by moxifloxacin (400 mg orally once daily) for 7 days. For macrolide-susceptible organisms, treatment consists of doxycycline (100 mg orally twice a day) for 7 days followed by azithromycin (1 g orally initial dose, followed by 500 mg orally once daily for 3 additional days). Test of cure is not indicated. Testing and treatment (as for the index case) of all infected sexual partners is paramount to prevent transmission, if it has not already occurred, and reinfection.

PROGNOSIS

Prognosis of early disease without scarring of the cervix and fallopian tubes in women and urethra in men is relatively good. Prognosis also depends on the susceptibility of the offending organisms. It is highly likely that antimicrobial resistance will increase in the future, thereby complicating the treatment of infections due to these organisms and highlighting the need for improved susceptibility testing.

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294 DISEASES CAUSED BY CHLAMYDIAE

HILARY E.L. RENO AND WILLIAM M. GEISLER

DEFINITION

Chlamydiae are obligate intracellular bacteria that cause a variety of human and animal diseases and much morbidity. Within the *Chlamydia* genus are now 11 validated species: *C. trachomatis, C. pneumoniae, C. psittaci, C. abortus, C. avium, C. caviae, C. felis, C. gallinacea, C. muridarum, C. pecorum,* and *C. suis.*[1] *C. trachomatis* is classified into a trachoma biovar and lymphogranuloma venereum (LGV) biovar.

The Pathogen

Chlamydiae have a gram-negative cell wall structure consisting of an outer membrane that contains lipopolysaccharide and an inner cytoplasmic membrane. The outer membrane contains a single 40-kD major protein (OmpA, also known as MOMP) and two cysteine-rich, minor outer membrane–associated proteins (OmcA and OmcB). Through intermolecular and intramolecular disulfide bonding, these proteins form a complex that provides structural rigidity.

Chlamydiae have small genomes (*C. trachomatis* contains 894 protein-coding genes, and *C. pneumoniae* contains 1052 genes). Most strains of *C. trachomatis* and some strains of *C. psittaci* contain a 7-kilobase cryptic plasmid.

Chlamydiae grow only within intracellular membrane-bound vacuoles, termed inclusions, which seclude the organism from extracellular and cytoplasmic environments. All chlamydiae share a distinct biphasic developmental cycle (Fig. 294-1) that includes an extracellular, metabolically inactive, infectious form (an elementary body) and an intracellular replicative form (a reticulate body). In vitro studies have shown that chlamydiae may enter a persistent state under certain conditions (e.g., penicillin treatment, challenge with certain cytokines, restriction of select nutrients) in which they have reduced metabolic activity and may be more refractory to antibiotic treatment. Chlamydiae are unable to synthesize adenosine triphosphate and therefore depend on the host cell for nutrients to meet their energy requirements.

PATHOBIOLOGY

Macrophages are the principal host cells for *C. psittaci* and *C. trachomatis* lymphogranuloma venereum biovar, whereas the principal host cells for *C. trachomatis* trachoma biovar and *C. pneumoniae* strains are columnar epithelial cells at mucosal sites. Host cell tropism correlates with the type of inflammation elicited by chlamydiae. The lymphogranuloma venereum biovar and *C. psittaci* produce granulomatous inflammation, characteristic of delayed hypersensitivity reactions. The trachoma biovar produces neutrophilic exudate during acute infection and submucosal mononuclear infiltration with lymphoid follicle formation during later stages of infection.

Chlamydiae elicit both humoral and cellular immune responses. Infection can persist or recur even after an adaptive immune response develops, thereby suggesting that the organism has evolved strategies for immune evasion. Persistent or recurrent infections can elicit inflammatory cellular immune responses that cause tissue injury.

CHLAMYDIAL DISEASES

Chlamydiae cause a wide range of human diseases (Table 294-1).

CHLAMYDIA TRACHOMATIS

C. trachomatis is a common cause of bacterial infection in humans and accounts for significant morbidity worldwide. *C. trachomatis* isolates have been differentiated into 18 major serovars (i.e., OmpA types) based on OmpA variations that can be identified on antigen cross-reactivity in the microimmunofluorescence test. The major diseases caused by *C. trachomatis* are trachoma, caused by serovars A, B, Ba, and C; sexually and perinatally transmitted diseases, caused by serovars D through K (and, rarely, serovars B and Ba); and sexually transmitted lymphogranuloma venereum, caused by serovars L1, L2, L2a, and L3. Sequencing of the *ompA* gene has led to the recognition of more OmpA variants, including L2b.

Trachoma is endemic in developing areas of the world. By comparison, sexually and perinatally transmitted *C. trachomatis*, including lymphogranuloma venereum chlamydial infections, occur worldwide.

TRACHOMA

EPIDEMIOLOGY

Trachoma is a chronic follicular conjunctivitis. The overall incidence is unknown, but the World Health Organization (WHO) estimates that 21.4 million people have active trachoma. Trachoma is endemic in more than 44 countries, and an estimated 137 million people are living in trachoma-endemic areas. Trachoma is especially common in poor areas of sub-Saharan Africa, where its prevalence in children may exceed 40%.

Trachoma is the most common preventable cause of blindness worldwide, affecting 1.9 million people by WHO estimates. Active trachoma often occurs in the first few years of life. The inflammation from recurrent or persistent trachoma can lead to conjunctival scarring, which can ultimately cause corneal

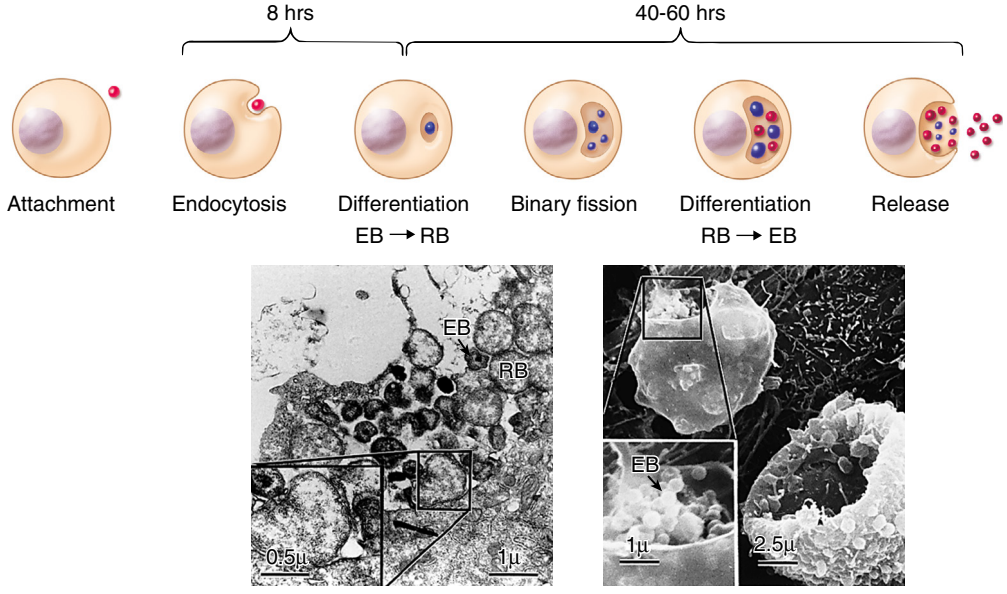

FIGURE 294-1. Developmental cycle of chlamydiae. The *top panel* shows the developmental cycle common to all chlamydiae. The *red dots* represent elementary bodies (EBs), and the *blue dots* represent reticulate bodies (RBs). Chlamydiae infect eukaryotic cells through multiple attachment mechanisms. After attachment, EBs enter the cell within a membrane-bound vacuole that remains unfused with lysosomes. EBs reorganize into RBs and asynchronously replicate 8 to 12 times, with a doubling time of 2 to 3 hours. At the conclusion of the growth cycle, RBs differentiate back to EBs, and each inclusion yields 100 to 1000 new infectious EBs. The *bottom left panel*, a transmission electron micrograph taken 40 hours after infection, shows the large RBs and the smaller EBs, which have a condensed nucleoid structure within their cytoplasm. The *bottom right panel*, a scanning electron micrograph taken 60 hours after infection, shows a membrane-bound vacuole containing many EBs exiting from an infected HeLa cell.

ABSTRACT

Chlamydiae are gram-negative obligate intracellular bacteria that grow only within intracellular vacuoles, called inclusions, which seclude the microorganism from extracellular and cytoplasmic environments. Major diseases caused by *Chlamydia trachomatis* are trachoma, the most common preventable cause of blindness worldwide; chlamydia, the most prevalent bacterial sexually transmitted infection in the United States; and lymphogranuloma venereum. Infections are difficult to diagnose clinically because most patients are asymptomatic, and even when symptoms or signs are present, they are nonspecific. Nucleic acid amplification testing is the recommended diagnostic method for clinical testing for chlamydia. *C. trachomatis* is susceptible to tetracyclines, macrolides, and select quinolones (levofloxacin and ofloxacin but not ciprofloxacin). Regimens vary depending on clinical manifestations.

KEYWORDS

chlamydia
trachomatis
pneumoniae
psittaci
lymphogranuloma venereum

TABLE 294-1 MAJOR DISEASES CAUSED BY CHLAMYDIAE IN HUMANS AND ASSOCIATED CLINICAL AND LABORATORY FEATURES

SPECIES	SEROVAR	DISEASE	TRANSMISSION ROUTE	DIAGNOSIS	PREVENTION
C. trachomatis	A–C	Trachoma	Fomites, eye-seeking flies	Clinical criteria or culture/NAAT	SAFE strategy
	D–K	Urethritis, cervicitis, proctitis, epididymitis, PID	Sexual contact	NAAT	Abstinence or monogamy, education, condoms, partner treatment
	D–K	Inclusion conjunctivitis, infant pneumonia	Perinatal contact	Culture, DFA, NAAT	Prenatal chlamydia screening: treat infected mothers
	L1–L3	Lymphogranuloma venereum	Sexual contact	NAAT with OmpA typing, culture, or serology	Abstinence or monogamy, education, condoms, partner treatment
C. pneumoniae	One	Upper respiratory infections, atypical pneumonia, asthma exacerbations	Respiratory droplet	Serology or culture/PCR	None
C. psittaci	Multiple	Psittacosis, atypical pneumonia, febrile illness	Aerosolized bird secretions, dust	Serology	Quarantine and chlortetracycline for imported birds, avoidance or precautions for at-risk subjects

DFA = direct fluorescent antibody test; NAAT = nucleic acid amplification test; OmpA = outer membrane protein A; PCR = polymerase chain reaction; PID = pelvic inflammatory disease; SAFE = World Health Organization's recommended strategy acronym for: surgery (for trichiasis), antimicrobials (periodic community-wide treatment), facial cleanliness, and environmental improvement.

damage and blindness later in life. The *C. trachomatis* serovars that produce trachoma are spread by direct contact with fingers or fomites (e.g., washcloths, handkerchiefs) that are contaminated with eye discharge from an infected person or by eye-seeking flies. Because of this mode of transmission, trachoma often clusters in households. Risk factors for trachoma include poor facial hygiene, limited access to water, poor sanitation, and proximity to other infected persons or to a heavy density of eye-seeking flies.

CLINICAL MANIFESTATIONS

The two stages of trachoma disease can overlap. Initially, trachoma begins as an inflammatory follicular conjunctivitis (i.e., active trachoma). On eversion of the upper eyelid, white to pale yellow lymphoid follicles can be visualized on the superior tarsal conjunctival surface, and papillae may be noted between follicles. Minimal watery or mucoid ocular discharge also may be seen. In more severe active trachoma, the conjunctiva can be thickened and edematous. Subsequently, conjunctival inflammation can progress to cause scarring of the upper tarsal conjunctiva (the cicatricial stage of disease). Scarring deforms the eyelid and can lead to an inward turning of the eyelashes, which can result in corneal abrasion (trichiasis). Over time, trichiasis causes corneal edema, ulceration, vascularization (pannus), scarring, and opacification. The corneal damage leads to decreased vision or blindness, mostly in young adults and middle-aged persons. Viral conjunctivitis (e.g., adenovirus; Chapter 333) presents similarly to active trachoma, but it is self-limited and usually resolves within a week. Trachoma can be complicated by superinfection with other bacterial pathogens (e.g., *Haemophilus influenzae*), which should be considered when purulent ocular discharge or significant inflammation of the bulbar conjunctiva is present.

DIAGNOSIS

Because the majority of trachoma cases occur in developing countries without access to laboratory testing or the necessary resources, trachoma is often diagnosed clinically on the basis of findings of active trachoma (follicles on the upper tarsal conjunctiva or pronounced inflammatory thickening of the tarsal conjunctiva) or cicatricial disease. When laboratories are available, detection of *C. trachomatis* by nucleic acid amplification is the most sensitive diagnostic test, provides definitive evidence of active trachoma, and may identify infection in subjects with minimal clinical evidence of active trachoma. For adults with late scarring, *C. trachomatis* usually is not detected by any of these assays.

TREATMENT

Active trachoma is best treated with a single-dose oral azithromycin (20 mg/kg; maximum of 1g),[A1] which also treats extraocular sites, such as the nasopharynx, that may be infected in young children. A less suitable alternative is tetracycline eye ointment (twice daily for 6 weeks), but its efficacy depends on adherence and can be limited by side effects, such as ocular irritation.

Surgical intervention is the only effective management for trichiasis. Eyelid rotation surgery prevents the eyelashes from abrading the cornea, thereby preventing blindness and other nonvisual symptoms. Unfortunately, trichiasis can recur after surgery in 10 to 30% of patients.

PREVENTION

The WHO is committed to eliminating blinding trachoma by 2030 and recommends that all countries with endemic trachoma adopt the SAFE strategy: surgery (for trichiasis), antimicrobials (periodic community-wide treatment), facial cleanliness, and environmental improvement. Mass treatment of a community with single-dose oral azithromycin is safe, can dramatically reduce the prevalence of infection for up to 1 year after treatment, and reduces mortality in children.[A2] Annual azithromycin treatment is recommended for trachoma-endemic areas. However, trachoma can recur after mass treatment, due in part to decreased herd immunity. Repeated mass treatment (every few months) provides herd protection to the entire community.[A3]

Mass antibiotic treatment is unlikely to be successful as the sole intervention for eliminating trachoma if other factors that facilitate transmission are not addressed. Face washing and good hygiene help reduce the risk for transmission through contact with fingers and flies. Better environmental conditions through measures that reduce the density of flies in households and the community, improved waste management, and access to clean water can also limit transmission. Improvement in socioeconomic conditions in a community correlates with a decline in the prevalence of trachoma.

SEXUALLY TRANSMITTED CHLAMYDIAL INFECTIONS

EPIDEMIOLOGY

Chlamydia is the most prevalent bacterial sexually transmitted infection in the United States. About 1.6 million infections were reported to the Centers for Disease Control and Prevention (CDC) in 2020.[2] The number of reported cases has increased since a chlamydia screening program was implemented,[3] but data also support a true increase in the number of cases. Taking into account underreporting and underscreening, the CDC estimates that more than 2.8 million new chlamydial infections occur annually in the United States.

Higher prevalence rates of chlamydia have been associated with younger age sexually active adolescents and young adults, as well as with new or multiple sexual partners. The prevalence is highest in the Southeastern United States. The prevalence of chlamydia is higher in women than in men, but it is unclear whether this higher prevalence is due to higher screening rates in women or whether women may be more susceptible to acquisition or persistence of infection. The estimated total cost attributable to chlamydial disease in the United States exceeds $691 million annually.[4] From a global perspective, WHO estimates that approximately 127 million new cases of chlamydia occur annually. In addition to the adverse effects on the reproductive health of women, chlamydia has a substantial impact on prenatal and perinatal outcomes, and it facilitates the transmission of human immunodeficiency virus (HIV).

CLINICAL MANIFESTATIONS

Urethritis

C. trachomatis is one of the most common causes of nongonococcal urethritis (Chapter 264) in men,[5] being responsible for 20 to 50% of cases. Although the majority of men with chlamydial urethritis do not have symptoms, studies in high-prevalence venues (e.g., sexually transmitted disease clinics) report

FIGURE 294-2. Clinical manifestations of genital *Chlamydia trachomatis* infection. A, Cloudy urethral discharge of urethritis. **B**, Urethral specimen Gram stain revealing nongonococcal urethritis findings: two or more polymorphonuclear cells per oil field (1000×) and the absence of intracellular gram-negative diplococci. **C**, Purulent endocervical discharge of mucopurulent cervicitis. (A, Courtesy James Sizemore, MD. B and C, From *Practitioner's Handbook for the Management of Sexually Transmitted Disease*. Retrieved from http://depts.washington.edu/handbook.)

that 40 to 60% of men with chlamydial urethritis have symptoms. The most frequent symptoms are urethral discomfort (itching or pain) with urination and urethral discharge. On examination, a mild to moderate amount of clear or cloudy/mucoid (rarely purulent) urethral discharge may be visualized (Fig. 294-2A). Urethral discharge sometimes becomes apparent only after stripping the urethra from the base of the penis to the glans; this manuever should be considered in men who report urethral symptoms without urethral discharge on initial inspection.

C. trachomatis urethritis also occurs in women, who may have no symptoms or present with an acute urethral syndrome characterized by dysuria, urinary frequency, and/or pyuria. This acute urethral syndrome mimics a urinary tract infection (Chapter 263), and chlamydia should be suspected in women with pyuria but negative urine nitrite and/or negative urine culture, especially in sexually active adolescents and young adults. Mild urethral discharge may be seen. Pelvic examination should be considered in women with suspected chlamydia urethritis to search for other clinical findings of chlamydia (e.g., cervicitis).

Epididymitis

Chlamydia can spread from the urethra to the epididymis and cause epididymitis,[6] which is found in up to 1% of chlamydia-infected men. In men younger than age 35 years, *C. trachomatis* is the principal cause of epididymitis; by comparison, complicated urinary tract infection (Chapter 263) with uropathogens is a more common cause in men older than age 35 years, especially in men with prostatic disorders (Chapter 114). Symptoms typically include unilateral testicular pain with scrotal erythema and swelling. On examination, palpable swelling and tenderness of the epididymis may be accompanied by testicular tenderness, scrotal erythema and swelling, urethral discharge, or hydrocele.

Cervicitis

C. trachomatis is responsible for up to 50% of cases of cervicitis. The majority of women with endocervical chlamydial infection are asymptomatic. When present, symptoms are often mild and nonspecific, such as vaginal discharge, intermenstrual vaginal bleeding, dysuria, and pain during intercourse (dyspareunia). On pelvic examination, up to 13% of women with asymptomatic cervical chlamydial infection have mucopurulent cervicitis (Fig. 294-2C), which is characterized by a purulent or cloudy endocervical discharge visible in the endocervical canal or on the tip of an endocervical swab. A similar proportion may have endocervical bleeding that is easily induced with passage of a swab through the cervical os. Nonspecific findings may include vaginal discharge and edematous ectopy (a darker red area of columnar epithelium visible on the face of the cervix).

Pelvic Inflammatory Disease

Chlamydia can spread from the cervix to the endometrium (causing endometritis), fallopian tubes (causing salpingitis), and peritoneum (causing peritonitis or perihepatitis).[7] These upper genital tract infections are collectively referred to as pelvic inflammatory disease (PID; Chapters 264 and 275). Estimates of the proportion of cervical chlamydial infections that progress to pelvic inflammatory disease vary greatly but are most commonly 10 to 35%. The majority of cases are subclinical or silent. Symptoms of pelvic inflammatory disease include pelvic or lower abdominal pain (especially during menses or the first 2 weeks of the menstrual cycle) and nausea. Fever is less common. Findings on physical examination include cervical motion tenderness and tenderness of the uterus or adnexa. Although most cases of chlamydial pelvic inflammatory disease are due to the natural progression of infection, they may also occur postpartum or after the termination of pregnancy.

Complications during Pregnancy

Some evidence suggests that genital chlamydial infection during pregnancy can lead to adverse outcomes, including preterm labor, low birthweight, miscarriage, and stillbirth,[8] but the data are conflicting.[9] Because the prevalence of chlamydia in pregnant adolescents and young adults in the United States can be high (>5%), the

potential morbidity associated with perinatally transmitted chlamydia is considerable. Neonates exposed to *C. trachomatis* during passage through the birth canal may develop inclusion conjunctivitis (about 20 to 40%) or pneumonia (about 10 to 20%).

Proctitis

Proctitis caused by non-lymphogranuloma venereum *C. trachomatis* OmpA types is usually asymptomatic. Subjects with acute symptomatic proctitis may report rectal pain or bleeding, tenesmus, pruritus, rectal discharge, or diarrhea. Anoscopy or sigmoidoscopy may reveal friable mucosa and a mucoid or mucopurulent discharge.

Conjunctivitis

An acute follicular conjunctivitis may rarely occur in adolescents or adults with genital chlamydial infection. The presumed mode of acquisition is autoinoculation with infected genital secretions. The typical clinical presentation is a subacute or indolent infection characterized by unilateral conjunctival redness, mucoid or mucopurulent ocular discharge, a foreign body sensation, and preauricular adenopathy.

Oropharyngeal Infection

C. trachomatis in the oropharynx of sexually active subjects is usually asymptomatic in most instances. *C. trachomatis* can be transmitted from oropharyngeal sites to the genital tract, providing rationale for treatment of oropharyngeal chlamydia. However, because oropharyngeal chlamydia prevalence is very low in most populations and the clinical significance of *C. trachomatis* detected in the oropharynx is unclear, routine oropharyngeal chlamydia screening is not recommended.

Lymphogranuloma Venereum

Lymphogranuloma venereum is a sexually transmitted infection caused by invasive *C. trachomatis* lymphogranuloma venereum OmpA serovars. In contrast to infection with other chlamydial strains, lymphogranuloma venereum is a more invasive systemic infection that involves lymphoid tissue (causing lymphadenitis) and can be ulcerative. Lymphogranuloma venereum is endemic in parts of Africa, India, Southeast Asia, South America, and the Caribbean. It also is a leading cause of proctitis and proctocolitis in men who have sex with men in Europe and North America.

In the early stage (3 to 30 days after acquisition) of genital lymphogranuloma venereum, a primary skin lesion or lesions may develop on the genital mucosa or adjacent skin in the form of a papule, ulcer, or herpetiform lesion. The lesion is usually asymptomatic and goes unnoticed, but it may be erosive; it heals quickly without scarring. Early genital lymphogranuloma venereum also may manifest as a nonspecific inflammatory syndrome (e.g., urethritis and cervicitis), similar to infection with other chlamydial strains. Two to four weeks later, genital lymphogranuloma can progress to an inguinal syndrome, characterized by painful, erythematous inguinal lymphadenopathy (buboes) and systemic manifestations, including fever, headache, arthralgias, myalgias, and leukocytosis. The buboes are commonly unilateral; about one third spontaneously rupture, drain pus, and can be complicated by fistulas or sinus tracts. Unruptured buboes usually heal.

Lymphogranuloma venereum may also manifest as an anogenital syndrome with invasive proctitis. Up to 20 to 30% of patients do not have symptoms, but common symptoms include fever, tenesmus, anal pruritus, and a rectal discharge that may be mucoid or, less commonly, mucopurulent or bloody. The rectal mucosa is friable, with multiple superficial ulcerations, and biopsy may reveal submucosal granulomas and crypt abscesses. These clinical and histopathologic findings resemble Crohn disease (Chapter 127).

DIAGNOSIS

C. trachomatis infections are difficult to diagnose clinically. A majority of infections are asymptomatic. Symptoms or signs, when present, are nonspecific. White blood cells are frequently found on a Gram stain of a urethral swab (Fig. 294-2B) or rectal swab or on a vaginal wet mount, but such findings cannot reliably distinguish chlamydia from other sexually transmitted infections (Chapter 264). A definitive diagnosis relies on detecting the organism using nucleic acid amplification tests, on a genital or rectal swab performed by a clinician, on noninvasively collected specimens (first-catch urine or a self-collected vaginal swab or rectal swab), or on infected material in patients with lymphogranuloma venereum.[10] Currently, serology is of limited clinical utility.

Nucleic acid amplification tests not only confirm the clinical diagnosis in patients with clinical manifestations, they also detect infection in symptom-free individuals. The CDC recommends annual chlamydia screening for sexually active women younger than age 25 years as well as for older women with risk factors (e.g., new or multiple sexual partners), men who have sex with men, and transgender persons.[A4,11,12] The recommended specimens for screening are first-catch urine in males and vaginal swabs in females. Chlamydia screening in women reduces the rate of pelvic inflammatory disease (Chapter 264). Universal chlamydia screening in men who have sex with women is not recommended. Selective chlamydia testing is also appropriate in venues with high prevalences (e.g., sexually transmitted infection clinics, correctional facilities), for high-risk men, or for men who have symptoms. However, although nucleic acid amplification tests can confirm the presence of *C. trachomatis*, they do not confirm the OmpA type; to confirm lymphogranuloma venereum, specific OmpA typing must be performed.

TREATMENT

C. trachomatis is susceptible to tetracyclines, macrolides, and select quinolones (ofloxacin and levofloxacin but not ciprofloxacin). The CDC's recommended treatment for uncomplicated chlamydia in nonpregnant individuals is doxycycline (100 mg orally twice daily for 7 days); azithromycin (1g orally in a single dose) is an alternative but has about a 5% lower cure rate for urogenital chlamydia compared with doxycycline.[A5] For rectal chlamydia, 1 week of doxycycline (100 mg twice daily) is also significantly more efficacious than single-dose azithromycin.[A6-A8] Another alternative treatment regimen for nonpregnant chlamydia-infected person is levofloxacin (500 mg orally once a day for 7 days).

However, adherence to the treatment is higher with single-dose azithromycin, so it may be considered for persons in whom adherence with the doxycycline regimen is a concern.[13] Because of its safety in pregnant women, azithromycin is also the recommended treatment for chlamydia-infected pregnant women.

C. trachomatis epididymitis and pelvic inflammatory disease should be treated with doxycycline (100 mg twice daily) for 10 and 14 days, respectively. Since treatment of these syndromes is usually empirical before test results are available (Chapter 264), ceftriaxone (500 mg intramuscularly in a single dose) is added to doxycycline to cover gonorrhea and metronidazole (500 mg orally twice daily for 14 days) is also added for anaerobic bacteria coverage in pelvic inflammatory disease.

Lymphogranuloma venereum should be treated with doxycycline (100 mg orally twice daily for 7 days) for 3 weeks. Some experts recommend azithromycin (1g orally weekly for 3 weeks) as an alternative.[A9] Infant chlamydial infections are treated with erythromycin base (50 mg/kg/day orally divided into four daily doses) for 14 days; data on other macrolides are limited, but a shorter treatment course with azithromycin (20 mg/kg/day orally) may be effective.

PREVENTION

Education and the provision of condoms are preventive measures that should accompany chlamydia treatment. Sexual partners (including current partners and partners in the preceding 60 days) and parents of chlamydia-infected infants should be evaluated and treated empirically. Expedited partner therapy, whereby chlamydia-infected patients are offered medication or a prescription to give to their sexual partners, or whereby clinicians provide medication to contacts without an examination, may reduce the risk for recurrent chlamydia. Patients and their partners should remain abstinent until treatment is completed.

Routine chlamydia screening may reduce the risk for pelvic inflammatory disease in sexually active young women. No chlamydia vaccine is available, but several are under investigation.

PROGNOSIS

A test of cure (4 weeks after completion of chlamydia treatment) is recommended routinely only for pregnant women but also should be considered if nonadherence with treatment is suspected or if symptoms persist. Recurrent chlamydia occurs in approximately 10 to 20% of chlamydia-infected persons within a few months of treatment, so repeated chlamydia testing is recommended approximately 3 months after treatment.

Outcomes of untreated genital chlamydia include spontaneous resolution (i.e., immune-mediated clearance in 10 to 40% of cases) and persisting infection; the latter may be subclinical or may progress to clinical manifestations (e.g., urethritis, cervicitis), which can remain uncomplicated or lead to a complication (e.g., pelvic inflammatory disease). Data in females suggest that up to 50% of genital chlamydial infections resolve after a year, but a small percentage (<10%) may persist.

Reactive arthritis, characterized by the classic triad of trigger infection (e.g., chlamydia), conjunctivitis, and arthritis, can complicate chlamydial infection (Chapter 244). Reactive arthritis cases triggered by chlamydia is more likely in males, with an estimated incidence of less than 1% of men who present with chlamydial urethritis.

Up to 15% of cases of chlamydial epididymitis are complicated by chronic pain (Chapter 26) that is usually idiopathic and often unresponsive to antibiotics. Other complications include decreased fertility and, rarely, testicular abscess. The long-term consequences of chlamydial pelvic inflammatory disease include infertility, ectopic pregnancy, and chronic pelvic pain.[14]

In the later stages of genital lymphogranuloma venereum infection, genital tract fibrosis can lead to complications such as infertility, elephantiasis, strictures, fistulas, and subcutaneous sclerosis. Late complications of rectal lymphogranuloma venereum include rectal strictures, anal fistulas, and lymphorrhoids (perianal growths of lymphatic tissue).

CHLAMYDIA PNEUMONIAE

Chlamydia pneumoniae[15] can cause community-acquired pneumonia (Chapter 85), upper respiratory tract infections (bronchitis, pharyngitis, laryngitis, and sinusitis), and exacerbations of chronic bronchitis and asthma. Possible links to atherosclerosis, Alzheimer disease, and multiple sclerosis are unproven.

EPIDEMIOLOGY

The majority of adults in the United States and other developed countries are seropositive for *C. pneumoniae*, up to 80% in some populations. Seroconversion often occurs during childhood or adolescence and may be subclinical. Studies incorporating culture or polymerase chain reaction (PCR) suggest that infection is not uncommon in children younger than 5 years. The CDC estimates there are 300,000 *C. pneumoniae* infections annually in the United States. *C. pneumoniae* causes an atypical pneumonia syndrome, with an estimated annual incidence of one case per 1000 population; epidemiologic studies suggest a 4-year cycle of increased pneumonia incidence. Up to 10% of community-acquired pneumonias are attributed to *C. pneumoniae*, and coinfection with other respiratory pathogens such as *Streptococcus pneumoniae* and *Mycoplasma pneumoniae* is not uncommon. The organism is believed to be acquired through the inhalation of infected respiratory droplets from persons with disease and possibly from symptom-free carriers. This mode of transmission can facilitate the spread of infection among household members and can cause epidemics in enclosed populations, such as persons in military barracks, nursing homes, and schools.

CLINICAL MANIFESTATIONS

Most *C. pneumoniae* infections occur in children, who often have mild clinical manifestations or do not have symptoms. Clinical manifestations are more evident in adults, especially the elderly, who have the highest incidence of *C. pneumoniae* pneumonia. *C. pneumoniae* causes an atypical pneumonia that is usually of mild to moderate severity. The incubation period may be several weeks, and the onset of disease is gradual. A nonproductive cough is usually present and is often preceded or accompanied by nasal congestion, sore throat, and hoarseness. Headache may occur in up to half of patients. Fever and dyspnea occur less commonly. *C. pneumoniae* may be manifested as isolated bronchitis, sinusitis, laryngitis, or nonexudative pharyngitis. On physical examination, localized pulmonary crackles or rhonchi are often heard.

In patients with pneumonia, chest radiography shows pneumonitis, most often evident as a single subsegmental lower lobe infiltrate. The leukocyte count is usually normal.

DIAGNOSIS

C. pneumoniae infection is usually diagnosed by polymerase chain reaction (PCR) testing of respiratory specimens as part of a diagnostic panel used in patients with community-acquired pneumonia. An alternative is serology showing a four-fold rise in IgG from paired sera or a single high IgM (>1:16) or IgG (>1:512) titer.

TREATMENT

The recommended treatment regimens for community-acquired pneumonia (Chapter 85) are effective for treating chlamydial pneumonia. Options for documented *C. pneumoniae* include azithromycin (500 mg on day 1 then 250 mg for 4 more days), doxycycline (100 mg twice daily for up to 14 days), clarithromycin (500 mg twice daily for 10 days), and levofloxacin (750 mg daily for 5 days). The clinical response to treatment may be slow, and some patients may need retreatment. Chronic *C. pneumoniae* infections may require even longer courses of treatment (e.g., 6 weeks), and azithromycin under the guidance of an expert has been suggested in this setting.

PROGNOSIS

The symptoms of *C. pneumoniae* upper respiratory tract infections may be protracted for several weeks, even with appropriate antibiotic treatment. Protective immunity may not occur after *C. pneumoniae* infection, so reinfection is common.

CHLAMYDIA PSITTACI

EPIDEMIOLOGY

C. psittaci naturally infects a variety of mammals and birds. *C. psittaci* strains appear to be host specific, and most human infections are linked to contact with an infected bird.[16] *C. psittaci* infection in humans is termed psittacosis, in part because exposure to psittacine birds (parrots, parakeets, and budgerigars) is commonly implicated in infections. However, because human cases have been linked to exposure to finches, pigeons, pheasants, ducks, turkeys, chickens, seagulls, and other birds, ornithosis may be a more appropriate term. Psittacosis disease in birds ranges from an asymptomatic carriage state to a mild symptomatic illness manifested by ruffled feathers, anorexia, shivering, dyspnea, diarrhea, or depression. Infected birds shed *C. psittaci* in urine, feces, or secretions from their beaks or eyes. Their feathers and surrounding environment become contaminated. Transmission to humans is primarily by inhalation of aerosolized bird secretions or dust. Infected birds may shed the organism for months. Person-to-person transmission rarely occurs.

Human psittacosis is a rare infection, due in part to antibiotic-laced bird feed and a mandated quarantine for imported birds. The number of cases of psittacosis in the United States has been stable for the past 10 years, with fewer than 10 confirmed cases reported annually; a larger number of cases are reported but not confirmed. Outbreaks have been attributable to occupational exposure in poultry processing plants. An outbreak of psittacosis occurred in 2014 in New South Wales from a novel source, exposure to abnormal equine fetal membranes. This outbreak suggests that horse exposure may be a potential risk factor for psittacosis and highlights the potential for humans to acquire the infection from other infected mammalian hosts.

CLINICAL MANIFESTATIONS

Psittacosis initially involves the lungs and then spreads to the reticuloendothelial system. The clinical spectrum of infection ranges from asymptomatic to fulminant, and clinical manifestations may resemble several other nonspecific febrile systemic illnesses, including Q fever (Chapter 302), typhoid fever (Chapter 284), and Legionnaires disease (Chapter 290). In contrast to *C. pneumoniae* pneumonia, psittacosis is more severe, with high fever and absent or minimal upper respiratory complaints.

After an incubation period of 5 to 14 days, some patients may present with a nonspecific virus-like illness or a mononucleosis-like syndrome. The presentation most suggestive of psittacosis is an acute febrile atypical pneumonia.[17] Patients initially have an abrupt onset of shaking chills and a temperature as high as 40.5° C. Temperature-pulse dissociation (i.e., elevated temperature with a normal pulse) may occur. Constitutional symptoms, including headache, myalgias, and arthralgias, are prominent. A cough, usually nonproductive, appears early in the illness and may accompany chest pain, which is usually nonpleuritic. Auscultation may be normal or reveal bilateral crackles. Chest radiograph findings are usually more dramatic than lung examination findings; the most common finding is single lower lobe consolidation, but multiple localized bronchopneumonic patches, diffuse ground-glass changes, and a miliary pattern have been described. Small pleural effusions may be seen.

Extrapulmonary findings frequently occur in psittacosis. Splenomegaly is common. A faint erythematous, blanching, maculopapular rash (Horder spots), resembling the rose spots of typhoid fever, can occur, as can erythema nodosum. Signs of hepatitis, endocarditis (culture negative), pericarditis, myocarditis, meningoencephalitis, hemolytic anemia, or disseminated intravascular coagulation may be noted. *C. psittaci* infection has also been associated with nongastrointestinal extranodal marginal zone lymphomas of mucosa-associated lymphoid tissue, including ocular and central nervous system sites.

DIAGNOSIS

Psittacosis should be suspected in patients who have a febrile illness (especially atypical pneumonia) and who report exposure to sick or imported birds or regular exposure to birds, including bird owners, pet shop workers, veterinarians, zookeepers, and poultry processing plant workers. The diagnosis is best made with serology. *C. psittaci* is a biocontainment level 3 agent because of its stability in the environment and aerosol transmission. Laboratory-acquired *C. psittaci* infections are well documented, so culture is discouraged. A serologic diagnosis of psittacosis is made by demonstrating (1) a four-fold or greater rise in complement-fixing or migration inhibitory factor antibodies against *C. psittaci* to a titer of at least 1:32 from acute to convalescent sera collected

at least 2 weeks apart (3 to 6 weeks is recommended) or (2) an IgM titer of 1:16 or greater against *C. psittaci* by migration inhibitory factor.

TREATMENT

Untreated psittacosis can be fatal, but mortality is rare with prompt antimicrobial treatment. Because of the delay in laboratory diagnosis, empirical therapy should be provided on the basis of clinical suspicion. The recommended treatment regimen, based on clinical experience, is either tetracycline (500 mg four times a day) or doxycycline (100 mg twice a day) for 10 to 21 days. Azithromycin (250 mg to 500 mg daily for 10 to 14 days) is a potential second-line alternative if patients cannot tolerate tetracycline drugs. Treatment of endocarditis includes prolonged antibiotic therapy and consideration of valve replacement.

PREVENTION

Epidemic psittacosis is preventable by a 30-day period of quarantine for all imported psittacine birds and their treatment with feed containing chlortetracycline. The U.S. Department of Agriculture recommends extending treatment for an additional 15 days after quarantine. Prevention of epidemic and endemic psittacosis also relies on avoidance of or protection from exposure to dust or body secretions from birds or their living areas, as well as avoidance of the handling of sick birds. Environmental sanitation is another important preventive measure because of the organism's resistance to drying.

PROGNOSIS

The response to treatment can be dramatic, with defervescence and marked clinical improvement within 24 to 48 hours. Full recovery may take several weeks, and relapse or reinfection can occur.

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295

SYPHILIS AND NONSYPHILITIC TREPONEMATOSES

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SYPHILIS

DEFINITION

Syphilis, which is a chronic infectious disease caused by the bacterium *Treponema pallidum* subspecies *pallidum*, is usually acquired by sexual contact with another infected individual. Syphilis is remarkable among infectious diseases for its large variety of clinical manifestations. If untreated, it progresses through primary, secondary, and tertiary stages. The early stages (i.e., primary and secondary), when lesions are present, are infectious. Spontaneous healing of early lesions is followed by a long latent period. In about 30% of untreated patients, late disease of the heart, central nervous system, or other organs may develop years after the initial infection. Syphilis remains a clinical challenge because of its protean manifestations.[1]

The Pathogen

The causative agent of syphilis, *T. pallidum* subspecies *pallidum*, is closely related to other pathogenic spirochetes, including those causing yaws (*T. pallidum* subspecies *pertenue*) and pinta (*Treponema carateum*). *T. pallidum* is a thin, helical bacterium approximately 0.15 µm wide and 6 to 15 µm long. The organism has 6 to 14 spirals and is tapered on either end. It is too thin to be seen by ordinary Gram stain microscopy but can be visualized in wet mounts by dark-field microscopy or in fixed specimens by silver stain or fluorescent antibody methods.

Unlike most bacteria, which have protein-rich outer membranes, the *T. pallidum* outer membrane appears to be composed of predominantly phospholipids, with few surface-exposed proteins. This structure may help syphilis progress despite the fact that non–surface-exposed internal antigens elicit a brisk antibody response that is the basis for serologic tests for the diagnosis and management of syphilis. Between the outer membrane and the peptidoglycan cell wall are six axial fibrils; three are attached at each end, and they overlap in the center of the organism. These fibrils are structurally and biochemically similar to flagella and are in part responsible for the organism's motility. All isolates studied are antigenically similar and susceptible to penicillin.

EPIDEMIOLOGY

The only known natural hosts for *T. pallidum* are humans and certain primates. With the exception of congenital syphilis, syphilis is acquired almost exclusively by intimate contact with the infectious lesions of primary or secondary syphilis (e.g., chancres, mucous patches, condylomata lata). Disease is usually acquired through sexual intercourse, including anogenital and orogenital intercourse. Occasional parenteral transmission still occurs in the setting of shared contaminated needles, although sexual transmission can be difficult to exclude in these cases. Transmission has been documented following organ transplantation. Transmission by contact with fomites is extremely uncommon. Occupational exposure among health care workers during direct examination of infectious skin lesions rarely leads to infection, and the last reported case of transfusion-transmitted syphilis in the United States occurred in 1966.

Syphilis is most common in large cities among sexually active individuals. The highest rate is found in men between the ages of 20 and 34 years. In the United States, regional prevalence is highest in the West and in the South.[2]

Syphilis spares no class, race, or group. U.S. syphilis rates are about five-fold greater in Blacks than in non-Hispanic Whites. In 2020, more than 80% of early syphilis cases occurred in men. When stratified by sexual partner information, about 50% of cases occurred among men who reported having sex with men.

The incidence of syphilis has generally declined worldwide for more than 100 years, with the exception of periods of war or social upheaval. With the introduction of penicillin treatment in 1943, primary and secondary syphilis declined rapidly to approximately 4 cases per 100,000 people in 1957. However, syphilis epidemics continue to occur, especially in men who have sex with other men, heterosexual individuals who use drugs of abuse, and adults living with HIV.

In 2020, the rate of reported primary and secondary syphilis in the United States was 11.9 cases per 100,000 population, more than five times the nadir rate of 2.1 cases per 100,000 in 2000. During that interval, primary and secondary syphilis rates increased among men of all ages, races, and ethnicities across all regions. Rates among women rose by about 1.5-fold between 2016 and 2020, mostly among women of ages 20 to 34 years who used injection drugs and methamphetamine, This increase has led to a four-fold increase in the rate of congenital syphilis, from 12.4 to 57.3 cases per 100,000 live births.[3] Patients with clinically evident late (i.e., tertiary) infection, particularly patients with cardiovascular or gummatous syphilis, are infrequently identified in high-income countries, likely because of the effectiveness of penicillin therapy for early stage syphilis.

PATHOBIOLOGY

T. pallidum may penetrate through normal mucosal membranes and minor abrasions on epithelial surfaces. The first lesions appear at the site of direct,

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at least 2 weeks apart (3 to 6 weeks is recommended) or (2) an IgM titer of 1:16 or greater against *C. psittaci* by migration inhibitory factor.

TREATMENT

Untreated psittacosis can be fatal, but mortality is rare with prompt antimicrobial treatment. Because of the delay in laboratory diagnosis, empirical therapy should be provided on the basis of clinical suspicion. The recommended treatment regimen, based on clinical experience, is either tetracycline (500 mg four times a day) or doxycycline (100 mg twice a day) for 10 to 21 days. Azithromycin (250 mg to 500 mg daily for 10 to 14 days) is a potential second-line alternative if patients cannot tolerate tetracycline drugs. Treatment of endocarditis includes prolonged antibiotic therapy and consideration of valve replacement.

PREVENTION

Epidemic psittacosis is preventable by a 30-day period of quarantine for all imported psittacine birds and their treatment with feed containing chlortetracycline. The U.S. Department of Agriculture recommends extending treatment for an additional 15 days after quarantine. Prevention of epidemic and endemic psittacosis also relies on avoidance of or protection from exposure to dust or body secretions from birds or their living areas, as well as avoidance of the handling of sick birds. Environmental sanitation is another important preventive measure because of the organism's resistance to drying.

PROGNOSIS

The response to treatment can be dramatic, with defervescence and marked clinical improvement within 24 to 48 hours. Full recovery may take several weeks, and relapse or reinfection can occur.

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295

SYPHILIS AND NONSYPHILITIC TREPONEMATOSES

JODIE A. DIONNE AND KHALIL G. GHANEM

SYPHILIS

DEFINITION

Syphilis, which is a chronic infectious disease caused by the bacterium *Treponema pallidum* subspecies *pallidum*, is usually acquired by sexual contact with another infected individual. Syphilis is remarkable among infectious diseases for its large variety of clinical manifestations. If untreated, it progresses through primary, secondary, and tertiary stages. The early stages (i.e., primary and secondary), when lesions are present, are infectious. Spontaneous healing of early lesions is followed by a long latent period. In about 30% of untreated patients, late disease of the heart, central nervous system, or other organs may develop years after the initial infection. Syphilis remains a clinical challenge because of its protean manifestations.[1]

The Pathogen

The causative agent of syphilis, *T. pallidum* subspecies *pallidum*, is closely related to other pathogenic spirochetes, including those causing yaws (*T. pallidum* subspecies *pertenue*) and pinta (*Treponema carateum*). *T. pallidum* is a thin, helical bacterium approximately 0.15 µm wide and 6 to 15 µm long. The organism has 6 to 14 spirals and is tapered on either end. It is too thin to be seen by ordinary Gram stain microscopy but can be visualized in wet mounts by dark-field microscopy or in fixed specimens by silver stain or fluorescent antibody methods.

Unlike most bacteria, which have protein-rich outer membranes, the *T. pallidum* outer membrane appears to be composed of predominantly phospholipids, with few surface-exposed proteins. This structure may help syphilis progress despite the fact that non–surface-exposed internal antigens elicit a brisk antibody response that is the basis for serologic tests for the diagnosis and management of syphilis. Between the outer membrane and the peptidoglycan cell wall are six axial fibrils; three are attached at each end, and they overlap in the center of the organism. These fibrils are structurally and biochemically similar to flagella and are in part responsible for the organism's motility. All isolates studied are antigenically similar and susceptible to penicillin.

EPIDEMIOLOGY

The only known natural hosts for *T. pallidum* are humans and certain primates. With the exception of congenital syphilis, syphilis is acquired almost exclusively by intimate contact with the infectious lesions of primary or secondary syphilis (e.g., chancres, mucous patches, condylomata lata). Disease is usually acquired through sexual intercourse, including anogenital and orogenital intercourse. Occasional parenteral transmission still occurs in the setting of shared contaminated needles, although sexual transmission can be difficult to exclude in these cases. Transmission has been documented following organ transplantation. Transmission by contact with fomites is extremely uncommon. Occupational exposure among health care workers during direct examination of infectious skin lesions rarely leads to infection, and the last reported case of transfusion-transmitted syphilis in the United States occurred in 1966.

Syphilis is most common in large cities among sexually active individuals. The highest rate is found in men between the ages of 20 and 34 years. In the United States, regional prevalence is highest in the West and in the South.[2]

Syphilis spares no class, race, or group. U.S. syphilis rates are about five-fold greater in Blacks than in non-Hispanic Whites. In 2020, more than 80% of early syphilis cases occurred in men. When stratified by sexual partner information, about 50% of cases occurred among men who reported having sex with men.

The incidence of syphilis has generally declined worldwide for more than 100 years, with the exception of periods of war or social upheaval. With the introduction of penicillin treatment in 1943, primary and secondary syphilis declined rapidly to approximately 4 cases per 100,000 people in 1957. However, syphilis epidemics continue to occur, especially in men who have sex with other men, heterosexual individuals who use drugs of abuse, and adults living with HIV.

In 2020, the rate of reported primary and secondary syphilis in the United States was 11.9 cases per 100,000 population, more than five times the nadir rate of 2.1 cases per 100,000 in 2000. During that interval, primary and secondary syphilis rates increased among men of all ages, races, and ethnicities across all regions. Rates among women rose by about 1.5-fold between 2016 and 2020, mostly among women of ages 20 to 34 years who used injection drugs and methamphetamine, This increase has led to a four-fold increase in the rate of congenital syphilis, from 12.4 to 57.3 cases per 100,000 live births.[3] Patients with clinically evident late (i.e., tertiary) infection, particularly patients with cardiovascular or gummatous syphilis, are infrequently identified in high-income countries, likely because of the effectiveness of penicillin therapy for early stage syphilis.

PATHOBIOLOGY

T. pallidum may penetrate through normal mucosal membranes and minor abrasions on epithelial surfaces. The first lesions appear at the site of direct,

ABSTRACT

Syphilis, which is a chronic infectious disease caused by the bacterium *Treponema pallidum* subspecies *pallidum*, is usually acquired by sexual contact with another infected individual. If untreated, it progresses through primary, secondary, and tertiary stages. The early stages (i.e., primary and secondary), when lesions are present, may be transmitted sexually. Spontaneous healing of early lesions is followed by a long latent period. In about 30% of untreated patients, late disease of the heart, central nervous system, or other organs may develop years after the initial infection. The nonsyphilitic treponematoses—yaws, endemic syphilis (previously known as bejel), and pinta—are the spirochetal diseases caused by *Treponema pallidum* subspecies (yaws and endemic syphilis) or by the closely related organism *Treponema carateum* (pinta). Like syphilis, the nonsyphilitic treponematoses are usually transmitted through direct contact with an infectious cutaneous or mucosal lesion.

KEYWORDS

syphilis
neurosyphilis
STD
Treponema pallidum
sexually transmitted infection
aortitis
tabes dorsalis
chancre
yaws
endemic syphilis
pinta
Treponema carateum

primary inoculation. The minimal number of treponemes needed to establish infection is not known but may be as low as one. Multiplication of organisms is slow, with a division time in rabbits of approximately 33 hours. *T. pallidum* can be cultured, but is difficult to sustain in vitro, so culture is of no use in clinical practice. The slow growth of treponemes in humans probably accounts in part for the protracted nature of the illness, the relatively long incubation period, and the need for relatively long duration of therapy.

Syphilis is a systemic disease from the onset. Treponemes are capable of specific attachment to host cells. Most treponemes are found in the intercellular spaces, but they are occasionally seen within phagocytic cells. However, there is no evidence of prolonged intracellular survival of treponemes. *T. pallidum* is not known to produce toxins.

The primary pathologic lesion of syphilis is a focal endarteritis with an increase in adventitial cells, endothelial proliferation, and the presence of an inflammatory cuff around affected vessels. Lymphocytes, plasma cells, and monocytes predominate in the inflammatory lesion, and polymorphonuclear cells can be seen. The vessel lumen is frequently obliterated. With healing, considerable fibrosis develops. Treponemes can be identified in early syphilitic lesions as well as some late lesions, such as meningoencephalitis associated with general paresis. In general paresis, a perivascular and meningeal chronic inflammatory reaction includes thickening of the meninges, granular ependymitis, degeneration of the cortical parenchyma, and abundant spirochetes in tissues.

Granulomatous reaction is common in secondary and late syphilis. The granulomas are histologically nonspecific, and cases of syphilis have been incorrectly diagnosed as sarcoidosis or other granulomatous diseases. Human inoculation studies suggest that the pathogenesis of the gumma, which is a granulomatous lesion, involves hypersensitivity to small numbers of virulent treponemes introduced into a previously sensitized host.

Intracutaneous inoculation of partially purified antigens of *T. pallidum* into patients with syphilis in various stages has shown that delayed cellular hypersensitivity develops late in secondary syphilis and is uniformly present in latent syphilis. Patients with primary and secondary syphilis sometimes exhibit temporary hyporesponsiveness of lymphocytes to treponemal antigens, and the waxing and waning of lesions in early syphilis may depend on the balance between the development of effective cellular immunity as compared with the suppression of thymus-derived lymphocyte function.

The host responds to infection by producing numerous antibodies; in some instances, circulating immune complexes may be formed as well. For example, nephrotic syndrome (Chapter 107) has occasionally been recognized in secondary syphilis. Renal biopsy specimens from these patients show membranous glomerulonephritis characterized by focal subepithelial basement membrane deposits containing immunoglobulin G, C3, and treponemal antibody.

FIGURE 295-1. Syphilis lesions. A, Chancre in primary syphilis. **B,** Palmar lesions of a coppery color in secondary syphilis. **C,** Mucous patch in secondary syphilis. **D,** Condylomata lata in secondary syphilis. (A, C, and D from Forbes CD, Jackson WF. *Color Atlas and Text of Clinical Medicine*. 3rd ed. London: Mosby; 2003. B from Habif TP, Cambell JI, Quitadamo MJ, et al. *Skin Disease: Diagnosis and Treatment*. St. Louis: Mosby; 2001.)

CLINICAL MANIFESTATIONS

Primary Syphilis

The incubation period from the time of exposure to the development of the primary lesion averages approximately 21 days (range, 10 to 90 days). Initially, a painless papule develops at the site of inoculation and soon breaks down to form a clean-based ulcer—the chancre—with raised, indurated margins (Fig. 295-1). The borders of the ulcer are raised, firm, and indurated. On occasion, secondary infections change the appearance of the ulcer and can cause the lesion to become painful. Most chancres are single, although multiple ulcers occur in up to 30% of persons. An untreated chancre persists for 2 to 6 weeks, heals spontaneously, and leaves a faint scar. The syphilitic chancre is usually associated with unilateral or bilateral regional lymphadenopathy. Regional lymph nodes are movable, discrete, and rubbery, but they may not be palpable if the chancre occurs in the cervix or rectum.

Chancres can occur at any site of inoculation by direct contact, and most occur in anogenital locations. Chancres can also be seen in the pharynx, on the tongue, around the lips, on the fingers, on the nipples, and other exposed areas. The morphology of the chancre depends in part on the location of the lesion and the host immune response. In previously infected individuals, chancres may be small and remain opular. Chancres of the finger may appear erosive and can be quite painful. Chancres located inside the female genital tract or anal canal are often missed unless clinical suspicion is high and a careful examination is performed.

Secondary Syphilis

If the initial lesion is not effectively treated, the natural history of syphilis infection (Fig. 295-2) is to progress to secondary syphilis between 4 and 8 weeks after the appearance of the primary chancre. Signs and symptoms of secondary syphilis include malaise, fever, headache, sore throat, and other systemic complaints. Most patients have generalized lymphadenopathy, including involvement of the epitrochlear nodes. Approximately 30% of patients have evidence of a healing chancre, although many patients (including a disproportionate number of women and men who have sex with men) give no history of a primary lesion.

At least 80% of patients with secondary syphilis have cutaneous or mucocutaneous lesions at some point in their illness. Usually, the diagnosis is suspected on the basis of the cutaneous eruption. The rash, which is often minimally symptomatic, tends to be faint and can be difficult to visualize, particularly on dark-skinned individuals; as a result, many patients with late syphilis do not recall having a rash. Syphilitic rashes are varied in appearance but have certain characteristic features. Typical lesions are widespread, have symmetrical distribution, and are pink, coppery, or dusky red in color. They are generally nonpruritic and are rarely vesicular or bullous in adults. Lesions usually become indurated after the early macular stage, and they frequently have a superficial scale (i.e., papulosquamous lesions). Skin lesions tend to be polymorphic and rounded and can leave long-term residual pigmentation or depigmentation.

Early macular lesions are typically seen on the trunk, followed by spread to the rest of the body. The face is often spared, except for the perioral area. Next, a papular rash appears that is usually generalized and characteristically marked on the palms and soles (Fig. 295-1B). These rashes are often associated with a superficial scale and may be hyperpigmented. Facial rashes may be pustular and can resemble acne vulgaris. On occasion, the scaling may be so prominent that it resembles psoriasis. Ulceration may occur and produce lesions resembling ecthyma. In malnourished or debilitated patients, extensive and destructive ulcerative lesions with a heaped-up crust may occur, the so-called rupial lesions. Lesions around the hair follicles may result in patchy alopecia of the beard or scalp.

Ringed or annular lesions may occur, especially around the face and particularly on dark-skinned individuals. A lesion at the angle of the mouth or the corner of the nose may have a central linear erosion, the so-called split papule.

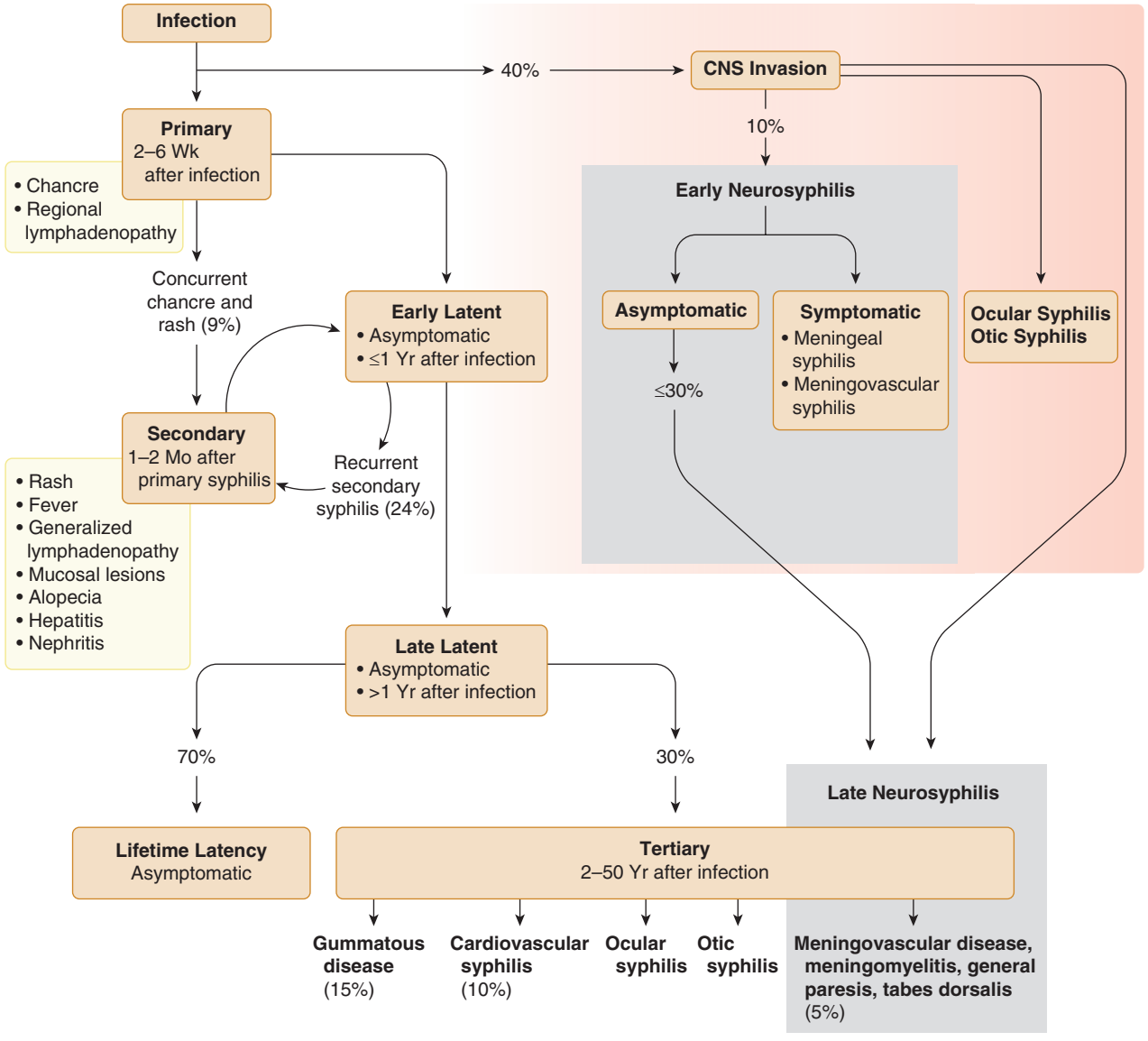

FIGURE 295-2. Natural history of syphilis infection. The time intervals between stages of syphilis are shown, along with the approximate percentages of persons progressing to the indicated stages. Invasion of the central nervous system (CNS) by treponemes may not be a necessary prerequisite for the development of certain forms of ocular syphilis. (Reproduced from Ghanem KG, Ram S, Rice PA. The modern epidemic of syphilis. *N Engl J Med*. 2020;382:845-854.)

In approximately 30% of secondary syphilis patients, so-called mucous patches (Fig. 295-1C) develop. These slightly raised, oval areas are covered by a grayish white membrane that, when raised, reveals a pink base that does not bleed. These lesions may be seen on the genitalia, mouth, tongue, palate, and pharynx.

In warm, moist areas such as the perineum, large, pale, flat-topped papules may coalesce to form condylomata lata (Fig. 295-1D). Papules may also be seen in the axilla and rarely occur in a generalized form. These papules are not to be confused with the common venereal warts (i.e., condylomata acuminata), which tend to be smaller, multiple, verrucous in appearance, and more sharply raised than condylomata lata. Like mucous patches, condylomata lata are highly infectious.

Other systemic manifestations of secondary syphilis include hepatitis, which has been reported in up to 10% of patients, and symptomatic gastritis. Jaundice is rare, but an elevated alkaline phosphatase level is common. Liver biopsy reveals small areas of focal necrosis and mononuclear infiltrate or periportal vasculitis. Spirochetes can often be visualized with silver stains. Periostitis with widespread lytic lesions of bone has been reported. An immune complex nephropathy with transient nephrotic syndrome (Chapter 107) has been documented. Between 10 and 30% of patients have cerebrospinal fluid (CSF) pleocytosis, but symptomatic meningitis is uncommon (<1%). Ocular involvement with iritis and anterior uveitis can also occur during the secondary stage (see Ocular Syphilis section). Secondary manifestations heal spontaneously within 2 to 6 weeks, and the infection then becomes latent.

Relapsing Syphilis

After resolution of the primary or secondary skin lesions, 20 to 30% of patients experience cutaneous recurrences. Rarely, the relapse takes the form of recurrence of the primary chancre. Recurrent lesions may be fewer or more firmly indurated than the initial lesions. Like the typical lesions of primary or secondary syphilis, relapsing infection can be transmitted to exposed sexual partners.

Latent Syphilis

By definition, latent syphilis is the stage at which there are no clinical signs of syphilis. Latency, which may last for a lifetime, is usually detected by reactive serologic tests for syphilis (see Diagnosis). Congenital syphilis must also be excluded before the diagnosis of latent syphilis can be made. Patients may or may not have a clinical history of earlier primary or secondary syphilis manifestations.

Latency has been divided into two stages: early and late. Most infectious relapses occur in the first year, and epidemiologic evidence shows that the most infectious period is during the first year after infection. Early latency is therefore defined as occurring within the first year after infection or as a newly reactive serologic test response for syphilis in an otherwise asymptomatic individual who has had a negative serologic test result within the preceding year. With the exception of vertical transmission (which can occur during any stage of syphilis in a pregnant woman), late latent syphilis and latent syphilis of unknown duration are considered noninfectious to sexual contacts.

TABLE 295-1 NEWLY DIAGNOSED TERTIARY SYPHILIS IN 105 PATIENTS IN DENMARK, 1961-1970

TYPE OF TERTIARY SYPHILIS	NO. OBSERVED*
Neurosyphilis	72
Asymptomatic	45
Tabes dorsalis	11
General paresis	13
Meningovascular	1
Optic atrophy	2
Cardiovascular syphilis	44
Aortic insufficiency	16
Aortic aneurysm	13
Uncomplicated aortitis†	15
Late benign syphilis (gumma)	4

*Some patients had more than one form of late syphilis.
†Autopsy diagnoses only.

Late (Tertiary) Syphilis

Without antibiotics, about one third of infected patients develop the destructive lesions of tertiary syphilis, involving the eyes, the central nervous system, the heart, and other organs, including the skin, years to decades after primary infection. In developed countries, however, tertiary syphilis is now very rare.

Late or tertiary syphilis (Table 295-1) is usually slowly progressive, although certain neurologic syndromes may have a sudden onset because of endarteritis and central nervous system thrombosis. Although any organ of the body may be involved, three main types of disease can be distinguished: late benign (gummatous), cardiovascular, and neurosyphilis.

Late Benign Syphilis

Syphilitic gummas, which are granulomas that typically develop 1 to 10 years after initial infection, can occur in any part of the body and are considered relatively benign since they respond rapidly to treatment. Gummas may be solitary or multiple and most often come to medical attention as space-occupying lesions. They are usually asymmetrical and are often grouped. Gummas may start as a superficial nodule or as a deeper lesion that breaks down to form punched-out ulcers. They are ordinarily indolent, slowly progressive, and indurated on palpation.

Gummas may involve the skin, bones, or deep visceral organs, particularly the respiratory and gastrointestinal tracts. Gummas of the stomach can masquerade as carcinoma of the stomach or lymphoma. Gummas of the liver can manifest with hepatosplenomegaly, anemia, fever, and jaundice. Skeletal gummas, which are most often found in long bones, skull, and clavicles, can present as nocturnal pain. Syphilitic gummas can resemble other chronic granulomatous diseases caused by tuberculosis (Chapter 299), sarcoidosis (Chapter 83), leprosy (Chapter 301), and deep fungal infections.

Cardiovascular Syphilis

Cardiovascular syphilis usually begins within 5 to 10 years of the initial infection but may not be manifested clinically until 20 to 30 years later. Cardiovascular syphilis does not occur after congenital infection.

The primary cardiovascular complications of syphilis are aortic aneurysm (Chapter 63), usually of the ascending aorta, and aortic insufficiency (Chapter 60), owing to aortic valve dilation (with normal valve cusps). In aortic insufficiency resulting from dilation of the aortic ring, the decrescendo murmur is often loudest along the right sternal margin. Less commonly, other large arteries may be affected, and involvement of the coronary ostia rarely results in coronary insufficiency. An aneurysm occasionally is manifested as a pulsating mass bulging through the anterior chest wall. Syphilitic aortitis may also involve the descending aorta proximal to the renal arteries.

Syphilitic aneurysms are typically saccular and do not lead to aortic dissection. Between 10 and 20% of patients with cardiovascular syphilis have coexistent neurosyphilis.

Neurosyphilis

Central nervous system involvement occurs throughout the natural history of syphilis. An estimated 1.8% of U.S. patients with early (primary, secondary, and early latent) syphilis have neurosyphilis, which may be found more often in patients who are living with HIV.[4]

Neurosyphilis[5] can be divided into five groups: asymptomatic, syphilitic meningitis, meningovascular syphilis, tabes dorsalis, and general paresis. Asymptomatic neurosyphilis can occur at any time, whereas syphilitic meningitis is most common during the secondary stage of infection. Meningovascular syphilis, tabes dorsalis, and general paresis are typically manifestations of late syphilis. The divisions are not absolute, and overlap between syndromes is typical.

Syphilitic Meningitis

Acute to subacute aseptic meningitis, which can occur at any time but usually occurs within the first year of infection, frequently involves the base of the brain and may result in unilateral or bilateral cranial nerve palsies. Mild aseptic meningitis may be relatively common, but severe disease occurs in only about 1.5% of untreated patients. Syphilitic meningitis typically resolves without treatment.

Meningovascular Syphilis

Some patients have sufficient endarteritis and perivascular inflammation to result in cerebrovascular thrombosis and infarction, on average at about 5 to 10 years after the initial infection but often earlier in patients with coexistent HIV infection. Patients frequently have associated aseptic meningitis. Most cerebrovascular accidents are not caused by syphilitic arteritis, even in patients who have a reactive serologic test result for syphilis. However, syphilis should be considered a potential cause in relatively young patients with a history of syphilis and without other risk factors for cerebrovascular disease.

General Paresis

General paresis, which is a chronic meningoencephalitis that results in the gradual and progressive loss of cortical function, typically occurs 10 to 20 years after the initial infection. In its early stages, general paresis results in nonspecific symptoms of early dementia, such as irritability, fatigue, headaches, forgetfulness, and personality changes. Later, symptoms include impaired memory, defective judgment, lack of insight, confusion, and often depression or marked elation. Patients may be delusional, and seizures sometimes occur. There may also be loss of other cortical functions, including paralysis or aphasia.

Physical signs are primarily those of the altered mental status. Cranial nerve palsies are uncommon, and optic atrophy is rare. The Argyll Robertson pupil is also uncommon (bilaterally small pupils that fail to constrict further in response to light but respond normally to accommodation; Chapter 392), but irregular or otherwise abnormal pupils can be seen. Peripheral reflexes are often increased.

Tabes Dorsalis

Tabes dorsalis is a slowly progressive, degenerative disease that involves the posterior columns and posterior roots of the spinal cord and results in progressive loss of peripheral reflexes, impairment of vibration and position sense, and progressive ataxia. The onset of tabes dorsalis is usually first noticed 20 to 30 years after the initial infection. Its cause is unclear, and spirochetes cannot be demonstrated in the posterior column or dorsal root. It is far less common now than in the prepenicillin era.

Sensory changes may lead to chronic destructive changes in the large joints of the affected limbs in advanced cases (i.e., Charcot joints). Urinary incontinence and impotence are common. Sudden and severely painful crises of uncertain origin are a characteristic part of the syndrome. Severe, sharp abdominal pain may lead to exploratory surgery. About 90% of patients have Argyll Robertson pupils (Chapter 392), and optic atrophy is seen in 20% of cases.

Ocular and Otic Syphilis

The eyes and ears may be affected during any stage of syphilis. Panuveitis and posterior uveitis are the most common ocular manifestations, but any portion of the eye may be affected.[6] Bilateral involvement is noted in 50 to 70% of involved cases. The clinical manifestations of ocular syphilis are broad and can include optic neuropathy, interstitial keratitis, and retinal vasculitis. In up to 70% of cases, concomitant CSF abnormalities consistent with neurosyphilis are detected.

Otosyphilis presents with sudden fluctuating or persistent sensorineural hearing loss or vestibular symptoms. Common complaints, in addition to hearing loss, include tinnitus and vertigo. In half the cases, both ears are affected. Unlike ocular syphilis, over 90% of persons with otosyphilis will have a normal CSF examination.

Syphilis-HIV Interactions

Syphilis, like other genital ulcer diseases, is associated with a two- to three-fold increased risk for acquisition of HIV infection (Chapter 353).[7] Presumably,

genital ulcers act as portals of entry through which HIV may more readily infect exposed individuals. As a result, HIV serologic testing 3 months after a diagnosis of syphilis is recommended for all patients. People living with HIV who acquire syphilis are somewhat more likely than people without HIV to present initially with secondary syphilis and coexistent chancres. Coinfected patients may also be at higher risk of developing neurologic complications, particularly early neurosyphilis.

Congenital Syphilis

Congenital syphilis, which results from the transplacental, hematogenous spread of syphilis from the mother to the fetus, can occur during any stage of pregnancy.[8] Less than 2000 cases of congenital syphilis are now reported annually in the United States,[9] with an estimated 660,000 annual cases worldwide.[10] The risk for fetal infection is highest in the early stages of untreated maternal syphilis and declines slowly thereafter, but the untreated mother can infect her fetus during at least the first 5 years of her infection. Untreated maternal infection may result in stillbirth, neonatal death, prematurity, or syndromes of early or late congenital syphilis in surviving infants.

Manifestations of early congenital syphilis are often seen in the perinatal period, but 60 to 90% of exposed neonates are asymptomatic. In the absence of treatment, clinical signs typically develop within the first 3 months of life. The disease resembles secondary syphilis in adults, except that the rash may be vesicular or bullous. The child often has rhinitis, hepatosplenomegaly, hemolytic anemia, jaundice, and pseudoparalysis (i.e., immobility of one or more extremities) as a result of painful osteochondritis.

Late congenital syphilis is defined as congenital syphilis diagnosed more than 2 years after birth. The disease may remain latent, with no manifestations of late damage. Cardiovascular alterations have not been observed in patients with congenital syphilis, but neurologic manifestations are common and may include eighth cranial nerve deafness and interstitial keratitis. Periostitis may result in prominent frontal bones of the skull, depression of the bridge of the nose (saddle nose), poor development of the maxilla, and anterior bowing of the tibia (saber shins). There may be late-onset arthritis of the knees (Clutton joints). The permanent dentition may show characteristic abnormalities known as Hutchinson teeth; the upper central incisors are widely spaced, centrally notched, and tapered in the manner of a screwdriver. The molars may show multiple poorly developed cusps (mulberry molars).

TABLE 295-2 SEROLOGIC TESTS FOR SYPHILIS

TYPE	USE
NONTREPONEMAL (ANTICARDIOLIPIN) ANTIBODIES	
VDRL (slide flocculation)	Screening, quantitation of response to treatment
RPR (circle card) (agglutination)	Screening, quantitation of response to treatment
SPECIFIC TREPONEMAL ANTIBODIES	
FTA-ABS (immunofluorescence with absorbed serum)	Confirmatory, diagnostic; not for routine screening
TP-PA (microhemagglutination)	Similar to FTA-ABS but can be quantified and automated
EIA and CIA	Confirmatory and increasingly used for screening; automated

CIA = chemiluminescence immunoassay; EIA = enzyme immunoassay; FTA-ABS = fluorescent treponemal antibody absorption test; RPR = rapid plasma regain test; TP-PA = *Treponema pallidum* particle agglutination; VDRL = Venereal Disease Research Laboratory.

TABLE 295-3 FREQUENCY OF POSITIVE SEROLOGIC TEST RESULTS IN UNTREATED SYPHILIS

STAGE	VDRL (%)	FTA-ABS (%)	TP-PA (%)
Primary	70	85	50-60
Secondary	99	100	100
Latent or late	70	98	98

FTA-ABS = fluorescent treponemal antibody absorption test; TP-PA = *Treponema pallidum* particle agglutination; VDRL = Venereal Disease Research Laboratory.

DIAGNOSIS

Dark-Field Examination

The most definitive means of diagnosis is finding typical spirochetes in lesions of early acquired or congenital syphilis. Dark-field examination is often positive in primary syphilis and in the moist mucosal lesions of secondary syphilis and congenital syphilis, but a single negative result is insufficient to exclude syphilis. However, few facilities have access to or skill with dark-field microscopes. Confusion may also arise because of the presence of spirochetes (e.g., *Treponema denticola*) that are morphologically indistinguishable from *T. pallidum* organisms in the mouth, particularly around the gingival margins.

Serologic Tests

Two basic types of serologic antibody tests (Table 295-2) are widely used to diagnose infection with *T. pallidum:* (1) nontreponemal tests to detect antibodies that react with diphosphatidylglycerol (cardiolipin), which is a normal component of many tissues,[11] and (2) tests that detect antibodies to specific treponemal antigens.[12]

Nontreponemal Tests

The standard tests to detect anticardiolipin antibody are the rapid plasma reagin (RPR) and Venereal Disease Research Laboratory (VDRL) tests, which are slide flocculation tests. The RPR and VDRL are readily quantified, so they are the tests of choice for monitoring patients' responses to treatment. The relative proportion of patients with a false-positive RPR or VDRL result depends on the prevalence of syphilis in the community; the lower the prevalence of syphilis, the higher the proportion of reactive RPR and VDRL test results from nonsyphilitic causes.

The RPR and VDRL test result begins to turn positive less than 1 week after onset of the chancre, so a nonreactive RPR or VDRL test result does not exclude primary syphilis, particularly if the lesion is less than 1 week old. The RPR or VDRL test result is positive in 99% of patients with secondary syphilis (Table 295-3). Patients with advanced HIV infection may have negative test results, and some patients have such high titers of antibody that they are in antibody excess; dilution of their serum paradoxically results in conversion of a negative test result to a positive one, the so-called prozone reaction. RPR and VDRL reactivity tends to diminish in later stages of syphilis, and only about 70% of patients with cardiovascular syphilis or late neurosyphilis have positive RPR or VDRL test results.

Although a single titer is diagnostic by itself, the quantitative titer of the RPR or VDRL test is somewhat useful in diagnosis and is quite useful for monitoring of the therapeutic response. RPR titers are highest during secondary syphilis, and most patients have titers of at least 1:16. Significant rises (fourfold or greater increase in titer, also referred to as a two-dilution increase) in paired sera strongly indicate acute syphilis. Most patients with false-positive RPR or VDRL test results have titers of less than 1:8.

Treponemal Tests

When the RPR or VDRL is used for screening, treponemal tests are required to confirm that the individual has antibodies to *T. pallidum*. These tests are sensitive and have a high degree of specificity, in that only approximately 1% of normal individuals have reactive treponemal test results. They are reactive in 85% of patients with primary syphilis, 99% with secondary syphilis, and at least 95% with late syphilis. They may therefore be the only test with a positive result in patients with cardiovascular or neurologic syphilis. For patients with late syphilis, treponemal test results often remain reactive for life, despite adequate therapy.

Options for treponemal testing include the fluorescent treponemal antibody absorption (FTA-ABS) test, as well as the newer treponemal enzyme immunoassays (EIAs) and chemiluminescence immunoassays (CIAs) that use cloned treponemal antigens to detect treponemal antibodies. The FTA-ABS test is reported in terms of relative brilliance of fluorescence, from borderline to 4 plus, with most laboratories reporting only test results with 2 plus or greater reactivity as positive. For patients lacking historical or clinical evidence of syphilis but with a reactive treponemal test result, the test should be repeated. Use of a different confirmatory treponemal test is recommended.

Because EIA and CIA serologic tests permit the screening of large numbers of sera and have performance characteristics (sensitivity, specificity, predictive values) similar to those of other treponemal tests, they have been increasingly used for syphilis screening, in contrast with the traditional approach that began with a nontreponemal (RPR or VDRL) screening test.[13,14] Persons with reactive treponemal antigen EIAs or CIAs should be tested with a quantitative RPR

or VDRL test to permit the use of that latter test to evaluate the subsequent response to therapy. It is not unusual for patients to have a reactive EIA or CIA test result for syphilis and a nonreactive RPR or VDRL test result. A substantial proportion of these EIA- or CIA-only positive test results are detecting long-standing, often previously treated, syphilis. Occasionally, they may detect very recent infection before RPR or VDRL test results become positive.

Point-of-care serologic tests for syphilis can detect treponemal antibodies, nontreponemal antibodies, or both. The performance characteristics of these tests vary but, in general, they are reasonably good, with a sensitivity as high as 98.5% and a specificity as high as 96%.[15]

Differential Diagnosis

The differential diagnosis of a genital ulcer (Chapter 264) includes genital herpes (Chapter 345), chancroid (Chapter 276), lymphogranuloma venereum (Chapter 294), and a number of other ulcerative processes.[16] Classically, herpetic ulcers are multiple, painful, superficial, and vesicular in their early stages. However, atypical manifestations may be indistinguishable from a syphilitic chancre. Genital herpes is much more common than syphilis and is now the most common cause of a "typical chancre" in North America. Syphilitic chancres may also be coinfected with herpes simplex virus in about 15% of cases. The ulcers of chancroid (Chapter 276) are usually painful, often multiple, and frequently exudative and nonindurated. Lymphogranuloma venereum (Chapter 294) may produce a small, papular lesion associated with regional adenopathy. Other conditions that must be distinguished include granuloma inguinale (Chapter 292), drug eruptions, carcinoma, superficial fungal infections (Chapter 405), traumatic lesions, and lichen planus (Chapter 405). In most cases, the final distinction is based on dark-field examination, which is positive only in syphilis, and on serologic test results.

The differential diagnosis of the skin lesions of secondary syphilis includes pityriasis rosea (Chapter 405), which can be differentiated by the occurrence of lesions along lines of skin cleavage and frequently by the presence of a herald patch. Drug eruptions, acute febrile exanthems (Chapter 406), psoriasis (Chapter 405), lichen planus (Chapter 405), scabies (Chapter 98), and other diseases must also be considered in some cases. A mucous patch may superficially resemble oral candidiasis (i.e., thrush). Infectious mononucleosis (Chapter 348) may appear similar to secondary syphilis, with sore throat, generalized adenopathy, hepatitis, and a generalized rash. Hepatitis (Chapter 134) and rash due to medication exposure may also simulate secondary syphilis.

False-Positive Serologic Test Results for Syphilis

The RPR or VDRL test result is reactive in patients with other treponemal diseases, such as pinta, yaws, and endemic syphilis. These nontreponemal tests may also be falsely reactive in persons who do not have treponemal infections based on a negative clinical history or negative results of serum treponemal tests.

For example, false-positive RPR or VDRL test results occur with low frequency in patients with atypical pneumonia (Chapter 85), malaria (Chapter 316), and other bacterial or viral infections, and they may occur after smallpox (Chapter 343) or other vaccinations, as well as during pregnancy. Chronic false-positive RPR test results (persisting >6 months) are relatively common in patients with autoimmune disorders such as systemic lupus erythematosus (Chapter 245), injection drug users (Chapter 365), patients with HIV (Chapter 359), patients with leprosy (Chapter 301), and the aged. Between 8 and 20% of patients with systemic lupus erythematosus have false-positive RPR or VDRL test results. Chronic false-positive RPR or VDRL test results in female patients 20 years or younger may indicate a risk for the future development of systemic lupus erythematosus, thyroiditis (Chapter 207), or other autoimmune disorders. As many as a third of injection drug users have false-positive RPR and VDRL test results. More than 1% of persons 70 years old and 10% of those older than 80 years also have low-titer, false-positive RPR or VDRL test results. In most cases of false-positive RPR or VDRL test results, the titer is less than 1:8, although a few patients with lymphoma (Chapters 171 and 172) and other diseases have very high-titer, false-positive results.

Treponemal test results can also be false-positive in chronic inflammatory diseases associated with hyperglobulinemia, including rheumatoid arthritis (Chapter 243) and biliary cirrhosis (Chapter 141), but such results are less likely than with an RPR or VDRL test. Lyme disease (Chapter 296) has been associated with false-positive treponemal tests, as has severe gingivitis. On occasion, reproducible positive treponemal test results are obtained in patients with no clinical or historical evidence of syphilis and no evidence of diseases typically associated with false-positive treponemal test results. If the diagnosis is in doubt and if the patient is not allergic to penicillin, it is often prudent to treat for possible syphilis.

Cardiac Syphilis

Asymptomatic aortitis (Chapter 63) is best diagnosed by visualizing linear calcifications in the wall of the ascending aorta by radiography, which may show an aneurysm that can be confirmed by echocardiography or computed tomographic (CT) scanning. The echocardiographic signs of syphilitic aortic insufficiency are the same as for aortic insufficiency of other causes (Chapter 60).

Neurosyphilis

Routine lumbar punctures to examine CSF are not indicated in neurologically asymptomatic, immunocompetent patients with early syphilis. Lumbar punctures are also not recommended for isolated ocular and/or otic signs and symptoms because the CSF parameters will be normal in up to 40 and 90% of patients, respectively. Although persons with HIV, particularly those with a CD4 count less than 350 cells/μL or an RPR titer ≥ 1:32, may be more likely to have CSF abnormalities consistent with neurosyphilis, there is no evidence that lumbar punctures in these asymptomatic patients lead to improved clinical outcomes.

Lumbar puncture is, however, indicated in all patients who have serologic evidence of syphilis and neurologic signs and symptoms. It is also indicated in patients who have cardiovascular syphilis or gummatous syphilis, even in the absence of neurologic signs or symptoms.[17] The VDRL and RPR tests do not perform equally for CSF, and only the VDRL, which has a sensitivity of about 50%, is recommended. Although numerous other processes can cause CSF pleocytosis or protein elevations, false-positive CSF VDRL test results are rare in the absence of a traumatic tap. A nonreactive CSF treponemal antibody test result may be useful to exclude the diagnosis, but the diagnosis of neurosyphilis should not be based solely on a reactive CSF treponemal test because of its lower specificity.

In syphilitic meningitis, the CSF shows a lymphocytic pleocytosis, with increased protein and usually normal glucose concentrations. The CSF VDRL test may be reactive. Rarely, the CSF glucose concentration is decreased.

In tabes dorsalis, the serum VDRL test is nonreactive in as many as 30 to 40% of patients, and 10 to 20% of patients have normal CSF VDRL results. Serum treponemal antibody tests are nearly always reactive. In general paresis, the CSF is nearly always abnormal, with a lymphocytic pleocytosis and an increased total protein concentration.

SCREENING AND PREVENTION

Annual syphilis screening is recommended in sexually active persons living with HIV. People who have HIV and are at high risk of syphilis infection should be screened as often as every 3 months. Screening is also recommended for persons with a previous syphilis infection, an infected sexual partner, or more than four sex partners in the preceding year.[18]

All patients with syphilis should be reported to public health authorities. In the absence of an effective vaccine, control of syphilis depends on finding and treating persons with infectious lesions of primary and secondary syphilis before they can transmit the disease, as well as finding and treating individuals with incubating syphilis before infectious lesions develop. All patients with early syphilis (primary, secondary, or early latent) should be carefully interviewed by qualified persons to determine the nature of their recent sexual contacts. Epidemiologic contact investigations for syphilis are limited when patients are not comfortable sharing sex partner details or report anonymous sex with partners identified through social media, and the numbers of sex partners identified and treated have declined in recent years. Approximately 16% of the named recent contacts of patients with early syphilis are found to have active, untreated syphilis on examination.

Treatment of the sexual contacts of patients with early syphilis with 2.4 million units of benzathine penicillin G intramuscularly is recommended even if the contacts are clinically and serologically normal on examination, because syphilis eventually develops in 30% of clinically normal untreated contacts. In general, preventive treatment is given to all sexual contacts in the past 90 days, although nearly all cases of syphilis in contacts develop within 60 days of exposure.

Doxycycline can be used as postexposure prophylaxis to decrease the incidence of syphilis (and/or other sexually transmitted infections).[A1] Pending large trials, however, doxycycline is not routinely recommended to prevent syphilis infection.

Congenital Syphilis

In pregnant women, a serologic test for syphilis should be performed universally at the first prenatal care visit, and it should be repeated at 28 weeks of gestation and at the time of delivery in women at high risk, including women

living in areas where syphilis is relatively common.[18,19] Adequate treatment of the mother before the 16th week of pregnancy usually prevents clinical illness in the neonate, but later treatment may not prevent late sequelae of the disease in the child.

TREATMENT

Treatment can be based on a positive dark-field examination or on serologic testing. *T. pallidum* is inhibited by less than 0.01 μg/mL of penicillin G. Because treponemes divide slowly and penicillin acts only on dividing cells, serum levels of penicillin must be maintained for many days (Table 295-4).[20,21]

Early Infectious Syphilis

Early syphilis (<1 year) can be treated with a single injection of 2.4 million units of benzathine penicillin G, which provides low but effective serum levels for about 2 weeks and cures approximately 95% of patients. It is not necessary to examine CSF at this stage because penicillin is highly effective at preventing the later development of neurosyphilis. The combination of oral amoxicillin 3 g plus probenecid is highly effective and tolerable for the treatment of syphilis in patients with HIV infection. For nonpregnant adult patients allergic to penicillin, 100 mg of doxycycline orally twice daily for 14 days is recommended.

Ceftriaxone (1.0 g intravenously once daily for 10 days) is noninferior to benzathine penicillin G (2.4 million units, intramuscularly, once weekly for 2 weeks) in nonpregnant, immunocompetent patients with early syphilis.[A2] Single-dose therapy with 2.0 g of azithromycin administered orally is also as effective as benzathine penicillin therapy in early syphilis,[A3] but treatment failures have been reported in persons with coexistent HIV infection. Particularly careful follow-up is necessary for patients treated with drugs other than penicillin because these regimens have been less than fully evaluated clinically and because patients may not be fully compliant with prolonged courses of oral therapy.

Syphilis of More than 1 Year in Duration

Prolonged therapy with intramuscular injections of 2.4 million units of benzathine penicillin G weekly for 3 weeks is recommended for the treatment of late latent syphilis and latent syphilis of unknown duration. Limited evidence suggests that treatment of latent syphilis with a total dose of 7.2 million units of benzathine penicillin during a 3-week period is curative, even if the patient has asymptomatic neurosyphilis. For nonpregnant adult patients allergic to penicillin, 100 mg of doxycycline orally twice daily for 28 days is recommended to treat late latent syphilis.

Cardiovascular Syphilis

Although there is no evidence that therapy with antimicrobial drugs is clinically beneficial in patients with cardiovascular syphilis, treatment is recommended to prevent further progression of disease and because approximately 15% of patients with cardiovascular syphilis have associated neurosyphilis.

Neurosyphilis, Ocular Syphilis, and Otosyphilis

Current guidelines recommend up to 24 million units of intravenous penicillin G per day for at least 10 days in all patients with neurosyphilis, ocular syphilis, or otosyphilis (see Table 295-4). General paresis responds well to penicillin therapy if it is administered early, although progressive neurologic decline may develop later in as many as a third of treated patients. Carbamazepine in doses of 400 to 800 mg/day can be used to treat the lightning pains of tabes dorsalis.

Syphilis in Pregnancy

Because of the risk to the fetus, evaluation and treatment of a pregnant RPR- or VDRL- reactive patient must be rapid, particularly for those patients first seen in the later stages of pregnancy. If a confirmatory treponemal test result is reactive and the patient has not been treated, penicillin should be administered in doses appropriate for early or late syphilis, as outlined earlier. Penicillin-allergic patients should undergo penicillin desensitization; in rare circumstances in which desensitization is not effective or tolerated, expert consultation is advised. Patients should not be treated with tetracycline or erythromycin because of potential toxicity (tetracycline) or lack of efficacy (erythromycin). For patients who are RPR or VDRL reactive but treponemal test negative and have no clinical signs of syphilis, treatment may be withheld; a quantitative RPR test and another treponemal test should be repeated in 4 weeks. If the treponemal titer has risen four-fold or more, or if clinical signs of syphilis have developed, the patient should be treated. If, after repeated examination, the diagnosis remains equivocal, the patient should be treated to prevent possible disease in the neonate. After treatment, a quantitative RPR titer should be monitored monthly; if it rises four-fold, the patient should be treated a second time.

Congenital Syphilis

Proper treatment of the mother usually prevents active congenital syphilis in the neonate. However, infected infants may be clinically normal at birth, and the infant may be seronegative if the mother's infection was acquired late in pregnancy. The infant should be treated at birth if the mother has received no treatment or inadequate treatment or has been treated with drugs other than penicillin, if the mother has not yet responded to possibly effective therapy, or if the infant cannot be carefully monitored for several months after birth. The infant's CSF should be examined before treatment. If the CSF is normal, the child can be treated with a single intramuscular injection of 50,000 units/kg (up to 2.4 million units) of benzathine penicillin G. If the CSF is abnormal, the infant should be treated with 50,000 units/kg of aqueous penicillin G given intramuscularly or intravenously twice daily for a minimum of 10 days. Alternatively, a single daily intramuscular injection of 50,000 units/kg of procaine penicillin may be given for 10 days. Antimicrobial agents other than penicillin are not recommended for treatment of congenital syphilis.

Jarisch-Herxheimer Reactions

Up to 60% of patients with early syphilis and a smaller (<10%) proportion of patients with later stages of syphilis experience a transient febrile reaction after therapy for syphilis. The pathogenesis is unclear, but it may be caused by the liberation of antigens from spirochetes, thereby resulting in a cytokine-release syndrome.

This reaction usually occurs in the first few hours after therapy, peaks at 6 to 8 hours, disappears within 12 to 24 hours of therapy, and is not related to the dose of penicillin. On occasion, Jarisch-Herxheimer reactions are mistaken for allergic reactions to syphilis therapy. Temperature elevation is usually low grade and is often associated with myalgia, headache, and malaise. The skin lesions of secondary syphilis are frequently exacerbated during the Jarisch-Herxheimer reaction, and cutaneous lesions that were not visible may become visible. The reaction is generally of no clinical significance and usually can be treated symptomatically with aspirin or a nonsteroidal anti-inflammatory drug (see Table 26-4). Premature labor may be a rare consequence in pregnant women.

TABLE 295-4 PENICILLIN TREATMENT FOR SYPHILIS AS RECOMMENDED BY THE CDC

	DOSAGE AND ADMINISTRATION[‡]	
INDICATIONS FOR SYPHILIS THERAPY*	**BENZATHINE PENICILLIN G**	**AQUEOUS BENZYLPENICILLIN G OR PROCAINE PENICILLIN G**
Primary, secondary, and early latent syphilis (<1 year); epidemiologic treatment	Total of 2.4 million units; single IM dose of two injections of 1.2 million units in one session	
Late latent (>1 year); cardiovascular syphilis, late benign (cutaneous, osseous, visceral gumma)	Total of 7.2 million units IM in doses of 2.4 million units at 7-day intervals during a 14-day period	
Symptomatic or asymptomatic neurosyphilis	2-4 million units aqueous (crystalline) penicillin G IV every 4 hours for at least 10 days	2-4 million units procaine penicillin IM daily and probenecid 500 mg orally four times daily, for 10-14 days
Congenital		
Infants	CSF normal: total of 50,000 units/kg IM in a single or divided dose at one session	CSF abnormal: total of 50,000 units/kg/day IM for 10 consecutive days[‡]
Older children	CSF normal: same as for early congenital syphilis, up to 2.4 million units	CSF abnormal: 200,000-300,000 units/kg/day aqueous crystalline penicillin IV for 10-14 days

*In pregnancy, treatment depends on the stage of syphilis.
[†]Individual doses can be divided for injection in each buttock to minimize discomfort.
[‡]For aqueous penicillin, give in two divided intravenous doses per day; for procaine penicillin, give as one daily dose intramuscularly.
CDC = U.S. Centers for Disease Control and Prevention; CSF = cerebrospinal fluid; IM = intramuscular; IV = intravenous.
Data from Workowski KA, Bachmann LH, Chan PA, et al. Sexually transmitted infections treatment guidelines, 2021. *MMWR Recomm Rep*. 2021;70:1-187.

PROGNOSIS

Follow-up Examinations

All HIV-seronegative patients with early or congenital syphilis should return for quantitative VDRL or RPR titers, and a clinical examination 6 and 12 months after treatment. For persons with HIV, serologic tests should be repeated at 3, 6, 9, and 12 months. Patients with late latent syphilis should also be examined 24 months after therapy.

In about 80 to 85% of patients with early (i.e., primary, secondary, or early latent) syphilis, quantitative RPR titers decline two or more dilutions (four-fold) by 12 months after therapy, but titers may take 24 months to decline following treatment of late-stage disease. In serofast patients (i.e., those whose titers do not decline appropriately), prolonged reactive RPR test results are associated with older age, lower initial RPR titers, prolonged infection, or more advanced stage (primary < secondary < early latent) infection. Retreatment of patients with serofast RPR results in the absence of evidence for reinfection has not been shown to impact short-term or long-term outcomes. Chronic, low-titer RPR reactivity after therapy is much more common in cases of late syphilis and should not be viewed with alarm. Treponemal test results may remain positive for years (even for a lifetime) despite adequate therapy. A four-fold or greater rise in RPR titer after therapy is sufficient evidence for repeated treatment. Patients with treated early syphilis are susceptible to reinfection, and many clinical and serologic relapses after therapy are probably reinfections.

Patients with neurosyphilis should be monitored with serologic tests for at least 3 years. Repeat CSF examinations are not recommended in immunocompetent persons and patients who are living with HIV and who are on effective antiretroviral therapy, provided that they demonstrate favorable clinical and serologic responses.

Antibiotic therapy should ultimately cure more than 95% of all patients with early or secondary syphilis, although treatment failures may occur more frequently in patients with concomitant HIV infection. In tabes dorsalis, penicillin usually arrests progression but does not reverse the symptoms. Meningovascular syphilis generally responds well, except for residual damage resulting from ischemic infarctions.

NONSYPHILITIC TREPONEMATOSES

DEFINITION

The nonsyphilitic treponematoses—yaws, endemic syphilis (previously known as bejel), and pinta—are the spirochetal diseases caused by *T. pallidum* subspecies (yaws and endemic syphilis) or by the closely related organism *Treponema carateum* (pinta). Like syphilis, the nonsyphilitic treponematoses are usually transmitted through direct contact with an infectious cutaneous or mucosal lesion. The natural history of the nonsyphilitic treponematoses also has a number of similarities to syphilis.

The Pathogen

Yaws is caused by *T. pallidum* subspecies *pertenue*, endemic syphilis is caused by *T. pallidum* subspecies *endemicum*, and pinta is caused by *T. carateum*. The *T. pallidum* subspecies causing nonsyphilitic treponematoses are closely related to *T. pallidum* subspecies *pallidum*, which causes venereal syphilis; there is a high degree (more than 99.8%) of DNA homology, and they share unique pathogen-restricted antigens. Like *T. pallidum*, these treponemes are spirochetal bacteria with helical structures and measure about 0.2 µm in diameter and 10 µm in length. They are visible by dark-field microscopy but cannot be cultivated for prolonged periods in vitro.

EPIDEMIOLOGY

Worldwide, the nonsyphilitic treponematoses are rare. The prevalence of these diseases was reduced dramatically in the 1950s by mass penicillin treatment campaigns, but the prevalence has increased subsequently, and as many as 2.5 million persons, 75% of whom are younger than age 15 years, are now infected worldwide. Yaws is prevalent in moist, humid regions, including rural areas of tropical Africa, the Americas, Southeast Asia, and the Western Pacific. Most cases are concentrated in three countries: Ghana, Papua New Guinea, and the Solomon Islands.[22] The highest incidence occurs in children between 2 and 5 years of age. Endemic syphilis occurs in more arid climates, including Africa, eastern Mediterranean countries, the Arabian Peninsula, Central Asia, and Australia. Pinta occurs in rural areas of tropical Central and South America and affects mostly older children and adolescents. Humans are the only known carriers of the nonsyphilitic treponematoses, although *T. pallidum* strains associated with genital lesions have been described in wild primates.[23]

The spirochetes enter the skin only after it is broken, such as by a scratch or an insect bite. Transmission is believed to occur by contact of the skin directly or by indirect contamination through hands or fomites; it is facilitated by conditions of poor personal hygiene and crowding.

PATHOBIOLOGY

Primary nodular or ulcerative lesions typically develop at sites of inoculation after an incubation period of several weeks. Untreated primary lesions serve as a source for local spread through scratching or for hematogenous dissemination, which gives rise to a secondary stage of infection characterized by the development of widespread manifestations involving the skin, lymph nodes, and bone or cartilage. Without therapy, the primary and secondary manifestations of infection resolve, and the infection becomes latent and detectable only with serologic testing. However, periodic recurrent secondary manifestations may occur for several years. A proportion of persons with long-standing untreated infection are at risk for late sequelae, which may include bone deformities, destruction of nasal cartilage, or chronic skin changes. Unlike syphilis, the nonsyphilitic treponematoses are primarily diseases of children, are not thought to be transmitted across the placenta, and may be less likely to invade the central nervous system to cause clinical disease.

CLINICAL MANIFESTATIONS

Yaws, the most common nonsyphilitic treponematosis, produces a skin papule at the inoculation site after an incubation period of 3 to 4 weeks. The most common sites are the legs and buttocks. The papule enlarges, ulcerates, and forms a serous crust from which treponemes can be recovered. Regional lymphadenitis may accompany the papule, which heals spontaneously within 6 months. A generalized secondary rash occurs before or after the initial lesion heals; this rash is also papular and is often covered with brown crusts. Relapsing crops of lesions can occur. Papillomas may result, and the plantar surfaces of the feet are involved with hyperkeratotic lesions. Periostitis of the long bones leads to tenderness, and fever may be present. Relapsing lesions of early yaws may occur during a period of several years and result in chronic ulcerations and destructive gummatous lesions affecting the skin and bones. *Haemophilus ducreyi*, the causative agent of chancroid (Chapter 276), also causes cutaneous ulcers, which are difficult to differentiate from those of yaws in children in yaws-endemic areas, such as Papua New Guinea.[24]

Endemic syphilis, which produces patches on the mucous membranes of the oral cavity and pharynx, can cause split papules at the mucocutaneous junction of the oral angles. Anal, genital, and other intertriginous skin areas can be affected by lesions that resemble secondary syphilis. Regional lymphadenitis is common, and generalized rashes are rare. Healing of these early lesions is followed by latency, manifested as seropositivity, or by late lesions that resemble gummatous tertiary syphilis. Lesions include nodular skin ulcers, bone deformities, and ulcerative lesions that can perforate the palate.

Pinta starts similarly as a cutaneous papule with regional lymphadenitis, followed by a generalized maculopapular eruption. One to 3 years after healing of the initial lesion, large hyperpigmented brown or blue macules develop; they subsequently lose their pigment and become white. The time required for lesions to pass through these stages varies, so the same patient may have coexisting areas of increased pigment and loss of pigment.

DIAGNOSIS

The clinical differentiation of cutaneous ulcers, which may be challenging, requires the integration of epidemiologic features, clinical findings, and supportive but not diagnostic laboratory test results. The skin lesions of the endemic treponematoses may resemble other cutaneous processes, including impetigo (Chapter 408), scabies (Chapter 98), cutaneous fungal infections (Chapter 405), chancroid (Chapter 276),[25] and other diseases. By dark-field microscopy, the causative spirochetes from early skin lesions can be observed directly, but dark-field microscopy is rarely available in settings where nonsyphilitic treponematoses are seen. No test is specific for any of the nonsyphilitic treponematoses, but serologic tests for syphilis detect cross-reacting antibodies in these diseases. The nontreponemal tests (RPR and VDRL) and the specific treponemal tests give positive results if serum is obtained at least 2 weeks after the lesions initially appear. Point-of-care tests also have adequate performance characteristics for the serologic detection of yaws.

PREVENTION

Whereas penicillin is effective for both treatment and prevention of infection, single-dose oral azithromycin, which is effective both for yaws and chancroid,

has simplified and expanded practical intervention strategies. For example, data from Papua New Guinea indicate that mass treatment with azithromycin could temporarily reduce the prevalence of active and latent yaws infection in endemic areas, and three rounds of mass drug administration are better than a single round.[A4]

TREATMENT AND PROGNOSIS

Single-dose, long-acting benzathine penicillin G, 1.2 million units intramuscularly, is effective in patients with early lesions.[26] For patients with late manifestations, this therapy should be repeated twice at approximately 7-day intervals. The early lesions heal rapidly, and most seropositive cases convert to seronegative status. Late destructive lesions take longer to show improvement.

Oral azithromycin, 30 mg/kg up to a maximal dose of 2.0 g, is as effective as penicillin for yaws,[A5] thereby providing the first readily administered, single-dose alternative to penicillin for treatment and prevention of nonsyphilitic treponematoses. Azithromycin resistance, while still rare, is concerning, however.

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For the General References and other additional features, please visit Elsevier eBooks+ at https://ebooks.health.elsevier.com.

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296 LYME DISEASE

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DEFINITION

Lyme disease (also known as Lyme borreliosis) is a zoonotic infection that is transmitted by certain *Ixodes* tick species and caused by a group of related spirochetes referred to formally as *Borrelia burgdorferi* sensu lato, or more simply as Lyme borrelia. Lyme disease was first described in 1977 after an investigation of a cluster of cases of arthritis among children living in the area of Lyme, Connecticut. With approximately 475,000 cases estimated to be diagnosed annually,[1] it is the most common vector-borne infection in the United States; Lyme disease is also an infection of public health importance in both Europe and Asia. The most common clinical manifestation is a characteristic skin lesion called erythema migrans. This lesion is a result of inflammation associated with the centrifugal spread of the spirochete within the skin from the site where the tick deposited the microorganism. The spirochete may also spread hematogenously to other skin locations, thereby resulting in secondary erythema migrans skin lesions, or to nonskin sites, such as the joints, nervous system, or heart, thereby leading to a variety of extracutaneous clinical manifestations.

The Pathogen

In the United States, the species of Lyme borrelia that causes the vast majority of human infections is *B. burgdorferi* (also referred to as *B. burgdorferi* sensu stricto). Although *B. burgdorferi* also causes Lyme disease in Europe, collectively other species of Lyme borrelia that can be distinguished genotypically account for the majority of infections there, especially *Borrelia afzelii* and *Borrelia garinii*. The fact that at least six species of Lyme borrelia may cause infection in Europe has created serodiagnostic challenges and accounts for a wider variety of possible clinical manifestations there than in the United States (see later). *B. garinii* appears to be the most neurotropic and *B. burgdorferi* the most arthritogenic among the species of Lyme borrelia.

Lyme borrelia are motile, microaerophilic, spirochetal bacteria with 3 to 10 loose coils arranged in a helical shape. The cells are 10 to 30 µm in length and 0.2 to 0.5 µm in width, and they contain at least seven periplasmic flagella that are responsible for the organism's motility. Borrelia are too thin to be seen by Gram stain, but live organisms can be visualized by dark-field or phase contrast microscopy. In tissues, they can be recognized by light microscopy after application of silver stains or by fluorescent microscopic methods. Lyme borrelia can be grown in vitro in a highly enriched culture medium.

EPIDEMIOLOGY

In the United States, more than 95% of cases of Lyme disease are concentrated in just 14 states: 12 eastern states and 2 in the North Central region.[2] The states with the largest number of cases are Pennsylvania, New York, New Jersey, and Massachusetts. *Ixodes scapularis* (also known as the deer tick or black-legged tick) is the tick vector in these states. *Ixodes pacificus* is the vector for cases that occur in the Northwest region. Lyme disease also occurs in limited areas of Canada. Although Lyme borrelia exist in enzootic cycles in the Southern United States, cases of Lyme disease arising indigenously have not been well documented in states south of North Carolina.

Cases of Lyme disease occur throughout the temperate regions of Europe and are especially common in Scandinavia and countries of Central Europe such as Slovenia, Austria, and Germany.[3] *Ixodes ricinus* transmits the infection in Europe, and *Ixodes persulcatus* is the vector in the Asian region of Russia, China, and Japan.

The principal reservoirs for Lyme borrelia (i.e., source of infection for ticks) in the United States and Eurasia are small mammals such as mice and certain species of birds. Deer play an essential role in the life cycle of the *I. scapularis* tick species but are not a competent reservoir for *B. burgdorferi*.

The likelihood of acquiring Lyme disease is directly related to exposure to environments in which infected ticks are present. Of the three feeding stages in the life cycle of *I. scapularis*, the second or nymphal stage is the most important epidemiologically for transmission of infection to humans. The first or larval stage is uninfected and cannot transmit this infection. Although the third stage (i.e., the adult stage of the tick) is more likely to be infected with *B. burgdorferi* than the nymphal stage is, it is less important in transmission to humans because this stage is present in smaller numbers in the environment and because there is less human activity outdoors during the time periods in the spring and fall when this stage is seeking a blood meal. In addition, adult ticks are larger and their bites cause more skin irritation than bites of nymphal ticks do, thereby increasing the likelihood that they will be noticed and detached by a person who has been bitten. If they are not removed, *Ixodes* ticks will usually feed for at least 3 days (Fig. 296-1). Transmission of *B. burgdorferi* by *I. scapularis* or *I. pacificus* ticks is typically delayed for more than 36 hours from the start of the blood meal, thereby providing the opportunity to prevent infection simply by finding and removing the tick. Transmission of *B. afzelii* by the European tick *I. ricinus* is considerably faster, however, often occurring within the first 24 hours of feeding.

Most cases of erythema migrans in the United States occur during June through August. The age distribution is bimodal, with the highest incidences in children 5 to 15 years old and in adults 45 to 55 years of age, but individuals of all ages are at risk. The reported incidence of Lyme disease in the United States is rising, partially as a result of expansion of the deer population and the spread of infected *I. scapularis* ticks to new geographic areas.

Extracutaneous manifestations are somewhat less likely than erythema migrans to occur during June to August because the time from the tick bite until the onset of these manifestations is longer. Because adult *I. scapularis* ticks may become active on warm days during the winter, cases of erythema migrans may occasionally occur even in the colder months.

PATHOBIOLOGY

B. burgdorferi is deposited by the tick into the skin rather than directly into the blood stream. Hematogenous dissemination seems to be an important mechanism responsible for spread of the spirochete to other sites. Alternatively,

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has simplified and expanded practical intervention strategies. For example, data from Papua New Guinea indicate that mass treatment with azithromycin could temporarily reduce the prevalence of active and latent yaws infection in endemic areas, and three rounds of mass drug administration are better than a single round.[A4]

TREATMENT AND PROGNOSIS

Single-dose, long-acting benzathine penicillin G, 1.2 million units intramuscularly, is effective in patients with early lesions.[26] For patients with late manifestations, this therapy should be repeated twice at approximately 7-day intervals. The early lesions heal rapidly, and most seropositive cases convert to seronegative status. Late destructive lesions take longer to show improvement.

Oral azithromycin, 30 mg/kg up to a maximal dose of 2.0 g, is as effective as penicillin for yaws,[A5] thereby providing the first readily administered, single-dose alternative to penicillin for treatment and prevention of nonsyphilitic treponematoses. Azithromycin resistance, while still rare, is concerning, however.

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For the General References and other additional features, please visit Elsevier eBooks+ at https://ebooks.health.elsevier.com.

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296 LYME DISEASE

GARY P. WORMSER

DEFINITION

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Lyme borrelia are motile, microaerophilic, spirochetal bacteria with 3 to 10 loose coils arranged in a helical shape. The cells are 10 to 30 µm in length and 0.2 to 0.5 µm in width, and they contain at least seven periplasmic flagella that are responsible for the organism's motility. Borrelia are too thin to be seen by Gram stain, but live organisms can be visualized by dark-field or phase contrast microscopy. In tissues, they can be recognized by light microscopy after application of silver stains or by fluorescent microscopic methods. Lyme borrelia can be grown in vitro in a highly enriched culture medium.

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PATHOBIOLOGY

B. burgdorferi is deposited by the tick into the skin rather than directly into the blood stream. Hematogenous dissemination seems to be an important mechanism responsible for spread of the spirochete to other sites. Alternatively,

ABSTRACT

Lyme disease is a spirochetal infection that occurs in North America and Eurasia. It is the most common tick-borne disease in North America. Early localized infection after tick bite is manifested by a single erythema migrans skin lesion, which is the most common and most characteristic clinical manifestation of Lyme disease. Early disseminated infection can take the form of Lyme carditis or early neurologic Lyme disease. Late disease is usually characterized by arthritis. Typical erythema migrans can be diagnosed clinically and does not require laboratory testing. For later, non–erythema migrans presentations of Lyme disease, the mainstay of laboratory diagnosis is two-tier serologic testing. The first tier test is a sensitive enzyme-linked immunoabsorbent assay (EIA). If this test is positive or equivocal, most often separate IgM and IgG immunoblots are performed on the original blood sample. With persistent symptoms for more than 4 weeks, the IgG immunoblot should be positive. Oral antibiotic therapy with doxycycline, amoxicillin, or cefuroxime axetil is the preferred treatment for the most frequent clinical manifestation (i.e., erythema migrans).

KEYWORDS

Lyme disease
Borrelia burgdorferi
spirochete
tick-borne infection
erythema migrans
Ixodes scapularis

FIGURE 296-1. From left to right is an unfed nymphal stage *Ixodes scapularis* tick, a nymphal stage *I. scapularis* tick after about 48 hours of feeding, a nymphal stage *I. scapularis* tick after about 126 hours of feeding, and a sesame seed. The distance between the ruler marks is 1 mm. (Courtesy Kam Truhn of Fordham University.)

FIGURE 296-2. Erythema migrans skin lesion on the posterior aspect of the right thigh.

FIGURE 296-3. **Acrodermatitis chronica atrophicans.** This late cutaneous manifestation of Lyme borreliosis is characterized by slowly expanding red violaceous lesions that typically involve the dorsal surfaces of acral sites and do not heal spontaneously. The lesions are initially inflammatory and later on more and more atrophic. (Courtesy Dr. Franc Strle.)

spread of the spirochete to other sites might occur through tissue planes. The likelihood of entry into the blood stream is affected by the strain of Lyme borrelia causing the infection. Unlike patients who are bacteremic with more conventional pathogens, patients with spirochetemia rarely appear "septic." In one study, only 5% of 93 spirochetemic patients were febrile when the blood culture specimen was obtained, and almost none was found to have leukocytosis. The lack of fever and other clinical signs of sepsis may be due to the absence of lipopolysaccharide within the borrelial cell wall.

B. burgdorferi resides in the midgut of the *Ixodes* tick through attachment of its outer surface protein A (OspA) to the cells lining this site. Genetic studies suggest the nearly complete absence of biosynthetic pathways, thereby making the microorganism dependent on its environment for nutritional requirements. With the onset of the blood meal, the spirochete increases in number and undergoes a sequence of phenotypic changes, including downregulation of OspA expression and upregulation of another outer surface protein, OspC. This set of events releases the spirochete from the midgut and permits migration to the salivary gland. At that site, OspC binds to a salivary protein, Salp15, that is induced during the blood meal in borrelia-infected ticks; this binding protects the spirochete from antibody-mediated killing and aids in transmission to a vertebrate host.

Infection of humans or animals elicits innate and adaptive immune responses,[4] thereby resulting in both macrophage and antibody-mediated killing of the spirochete. The inflammatory response in tissue typically shows an infiltration of lymphocytes, macrophages, and plasma cells, although granulocytes predominate in synovial fluid samples of patients with Lyme arthritis. The potential for persistence of infection despite a robust humoral and cellular immunologic response is, however, typical of infection with Lyme borrelia, as it is with *Treponema pallidum* infection (Chapter 295). The virulence factors responsible for persistence of infection include the spirochete's ability to downregulate expression of certain immunogenic surface-exposed proteins, including OspC, and to alter rapidly and continually by recombination of the antigenic properties of a surface lipoprotein known as variable major protein–like sequence expressed (VlsE). In addition, the spirochete's motility and ability to bind to various components of the extracellular matrix may also contribute to persistence.

All of the objective clinical manifestations of Lyme disease are thought to be due to an inflammatory response to live spirochetes or to their undegraded antigens. Obliterative endarteritis has been seen histologically in synovial tissue, but its importance in pathogenesis is unclear. Lyme borrelia are not known to produce toxins. In humans, the only role so far established for host genetic factors is in the development of antibiotic-refractory Lyme arthritis, also known as post-antibiotic Lyme arthritis, which is seen most often in patients with certain HLA DR alleles, some of which coincide with those associated with rheumatoid arthritis.

CLINICAL MANIFESTATIONS

The clinical manifestations are often categorized as follows:

- Early localized infection, typically manifested by a single erythema migrans (Fig. 296-2) skin lesion, with or without viral infection–like symptoms but without objective extracutaneous manifestations
- Early disseminated infection, usually manifested by multiple erythema migrans skin lesions or by an objective manifestation of early neurologic Lyme disease or Lyme carditis
- Late disease, usually manifested by arthritis but may also include certain rare neurologic manifestations or the skin condition known as acrodermatitis chronica atrophicans (Fig. 296-3).

Children and adults have similar clinical manifestations. In a large European series, erythema migrans by itself was seen in about 90% of cases, arthritis in 5%, early neurologic manifestations in about 3%, borrelial lymphocytoma (see later under "Borrelial Lymphocytoma") in 2%, acrodermatitis chronica atrophicans in 1%, and cardiac manifestations in less than 1%; none of the patients had late neurologic Lyme disease. In a recent case series in the United States, findings have been similar except for the absence of borrelial lymphocytoma and acrodermatitis chronica atrophicans. The much higher prevalence of neurologic, cardiac, or joint manifestations in older studies may have been related to ascertainment bias or to the failure to treat patients with erythema migrans before the development of extracutaneous complications.

Early Localized Infection

Single Erythema Migrans Skin Lesion

Erythema migrans is by far the most common clinical manifestation of Lyme disease. Although the appearance of the skin lesion is often distinctive (see Fig. 296-2), it is not pathognomonic for Lyme disease. Erythema migrans appears 7 to 14 days (range, 3 to 30 days) after tick detachment and is characterized by an expanding, flat to slightly raised, erythematous skin lesion (usually ≥5 cm in diameter) that is round or oval. The bite mark from the preceding tick bite

TABLE 296-1 CLINICAL SYMPTOMS AND SIGNS PRESENT IN AT LEAST 20% OF PATIENTS WITH ERYTHEMA MIGRANS

CHARACTERISTIC	UNITED STATES (95% CI)
Viral infection–like	65% (52-76%)
Fatigue	47% (37-58%)
Headache	36% (27-46%)
Myalgias	35% (26-45%)
Arthralgias	35% (25-46%)
Fever	33% (23-43%)
Stiff neck	31% (21-43%)
Lymphadenopathy	22% (13-33%)
Dysesthesia	20% (12-32%)
	EUROPE (95% CI)
Viral infection–like	37% (27-49%)
Dysesthesia	35% (25-47%)
Headache	20% (14-29%)

CI = confidence interval.
Modified from Tibbles CD, Edlow JA. Does this patient have erythema migrans? *JAMA*. 2007;297:2617-2627.

FIGURE 296-4. Borrelial lymphocytoma. A rare cutaneous manifestation of Lyme disease that is seen predominantly outside the United States; it is manifested as a solitary bluish-red swelling most commonly on the earlobe of children and the breast in adults. (Courtesy Dr. Franc Strle.)

can sometimes be identified at or near the center of the lesion and is called a punctum. Approximately 80% of patients in the United States with erythema migrans have just a single skin lesion. Nonspecific viral infection–like symptoms or signs, such as malaise, neck pain, headache, fatigue, migratory arthralgias, or chills and fever, may be present (Table 296-1) but are more common in patients infected with *B. burgdorferi* or *B. garinii* compared with *B. afzelii*. Prominent respiratory or gastrointestinal symptoms are highly atypical for Lyme disease. An acute febrile illness in the absence of a skin lesion or other objective clinical manifestation has been attributed to early Lyme disease, but the possibility of misdiagnosis is greater in this situation because of the potential for false-positive serologic test results.

Erythema migrans skin lesions can vary in appearance. Some (especially lesions of short duration) are nearly uniform in color, whereas others may show central clearing or a target-like appearance. About 5% have a vesicular-pustular center. Erythema migrans on the lower extremities may sometimes be purpuric. Lesions may be scaly when they are long-standing and fading or after topical corticosteroid creams have been applied. The most common locations include the thigh, back, shoulder, and calf. Lesions are often asymptomatic but can be mildly painful or pruritic, and tender regional lymphadenopathy may be present. The majority of U.S. patients with erythema migrans, as for all other clinical manifestations, do not recall a preceding tick bite.

Borrelial Lymphocytoma

Borrelial lymphocytoma, which is a rare cutaneous manifestation of Lyme disease, almost never occurs in the United States. It often is manifested at or near a preceding tick bite as a solitary bluish-red swelling with a diameter of up to a few centimeters. The most common locations are the earlobe in children and the breast in adults (Fig. 296-4). Histologic examination shows a dense infiltration of the cutis and subcutis by predominantly polyclonal B lymphocytes, frequently with germinal center formation. Histologic evaluation may be necessary to exclude malignant disease for patients with suspected borrelial lymphocytoma at a location other than the earlobe.

Early Disseminated Infection

Multiple Erythema Migrans Skin Lesions

In the United States, approximately 20% of patients with erythema migrans have multiple skin lesions at the time of presentation. Secondary erythema migrans skin lesions can be smaller than 5 cm, do not have a punctum, and are usually not tender or pruritic; they arise from hematogenous dissemination to the skin rather than from additional tick bites.

Early Neurologic Lyme Disease

Within weeks to several months after infection, patients may develop neurologic manifestations, the most common of which are cranial neuropathy (particularly peripheral seventh nerve palsy that may be bilateral), lymphocytic meningitis, and sensory (often painful) radiculopathy.[5,6] Less common manifestations include mononeuritis multiplex (multifocal involvement of anatomically unrelated nerves) and brachial or lumbosacral plexopathies. A pseudotumor cerebri–like picture has been reported occasionally in children. The presence of a concomitant erythema migrans lesion or the patient's recollection of a recent lesion consistent with erythema migrans may be helpful diagnostically.

Cardiac Lyme Disease

Weeks to months after infection, patients may develop cardiac manifestations of Lyme disease, most often fluctuating degrees of atrioventricular heart block or other manifestations of a myopericarditis (Chapter 47), which may cause the patient to complain of lightheadedness, palpitations, dyspnea, chest pain, or syncope.[7] Heart block is typically at or above the atrioventricular node. Erythema migrans is often, but not invariably, present concurrently. Valvular dysfunction is not known to occur, and chronic cardiomyopathy has been reported only rarely in Europe.

Late Lyme Disease

Lyme Arthritis

If patients with erythema migrans in the United States are not treated with antibiotics, approximately 60% will develop a monoarticular or oligoarticular arthritis at a mean of 6 months after disease onset (range, 4 days to as long as 2 years). In untreated patients, Lyme arthritis is characterized by intermittent attacks of synovitis that persist for a few weeks to several months. One or two joints are involved at a time. Primarily large joints are affected,[8] but the temporomandibular joint, small joints, and periarticular sites may be involved. The most commonly involved joint is the knee. Baker cysts (Chapter 242) may form and rupture. Joint swelling is often pronounced, but pain is usually relatively modest. Children in particular may have concomitant fever, but adults are often minimally symptomatic aside from the arthritis.

In about 10% of adult patients with Lyme arthritis in the United States, involvement of a large joint (almost always the knee) may persist despite appropriate antibiotic treatment.[9] Erosion of cartilage or bone may develop in such cases.

Late Neurologic Lyme Disease

After months to years of infection, the late neurologic manifestation, encephalomyelitis, may develop. In untreated patients, encephalomyelitis has been monophasic and slowly progressive, mainly involving white matter. It is the

most severe neurologic manifestation and, although infrequent, is probably more common in Europe than in the United States.

Acrodermatitis Chronica Atrophicans

Acrodermatitis chronica atrophicans (Fig. 296-3), which is a late skin manifestation of Lyme disease, is most commonly seen in women older than age 40 years. Although presumably any of the species of Lyme borrelia may cause acrodermatitis chronica atrophicans, by far the most common etiologic agent is *B. afzelii*. Therefore, this manifestation is rarely seen in the United States.

This skin lesion develops insidiously several years after initial infection, usually on the extensor surfaces of the hands and feet. Early lesions are characterized by a slight bluish-red discoloration and doughy swelling. Histologic examination shows lymphocytes and plasma cells in the skin and sometimes in the subcutis, with or without atrophy. Initially unilateral, the lesion may later become bilateral. Over time, the edema resolves, but skin atrophy may develop. Nodules may develop over bone prominences. About two thirds of patients have an associated peripheral neuropathy, primarily of the affected extremity, usually manifested as local sensory loss.

DIAGNOSIS

The diagnosis of Lyme disease requires clinical suspicion and often requires targeted laboratory testing (Table 296-2). In the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) era, diagnosis can be delayed, either because symptoms are misattributed or patients delay seeking medical care.[10,11]

Erythema migrans skin lesions may go unnoticed by the patient because of the absence of prominent local symptoms and occurrence on parts of the body that are difficult for the patient to visualize. Therefore, a complete skin examination should be performed for any patient thought to have early localized or disseminated Lyme disease. Erythema migrans, which is the only clinical manifestation sufficiently distinctive to allow a clinical diagnosis in the absence of a supporting laboratory test, is diagnosed on the basis of recognition of the characteristic appearance of the skin lesion in persons who live in or have recently traveled to areas endemic for Lyme disease.

For non–erythema migrans presentations of Lyme disease, the mainstay of laboratory diagnosis is two-tier serologic testing in which the first-tier test is usually a sensitive enzyme-linked immunosorbent assay (EIA).[12,13] If the EIA result is positive or equivocal, separate IgM and IgG immunoblots are performed on the original serum sample. If symptoms have persisted for at least 4 weeks, then specifically the IgG immunoblot should be positive for the results to be interpreted as evidence of seropositivity. An alternative two-tier testing strategy is to use a different EIA as the second-tier test. Untreated patients who remain seronegative for 6 to 8 weeks are unlikely to have Lyme disease, and other possible diagnoses should be pursued.

TABLE 296-2 DIAGNOSIS OF LYME DISEASE

DIAGNOSTIC MODALITY	APPLICATION	COMMENT
Visual inspection	Erythema migrans	Usually seronegative at time of presentation
Two-tier serology* with a positive IgM and/or IgG immunoblot	Lyme carditis	Look for concomitant erythema migrans
	Early neurologic Lyme disease	Look for concomitant erythema migrans; intrathecal antibody may be detectable before serum antibody in Europe; PCR sometimes positive in CSF
	Borrelial lymphocytoma	Biopsy may be needed to exclude a malignant neoplasm
Two-tier serology with a positive IgG immunoblot	Lyme arthritis	PCR often positive on synovial fluid
	Late neurologic Lyme disease	Intrathecal antibody positivity expected in Lyme encephalomyelitis
	Acrodermatitis chronica atrophicans	

*Two-tier serologic testing consists of a sensitive enzyme immunoassay (EIA) as the first-tier test, followed by separate IgM and IgG blot testing if the EIA is reactive. An alternative two-tier testing strategy is to use another EIA as the second-tier test (see text).
CSF = cerebrospinal fluid; Ig = immunoglobulin; PCR = polymerase chain reaction.

Omitting the first-tier EIA or interpreting the immunoblot with alternative criteria that are not evidence based will potentially decrease the specificity of testing and is not recommended. False-positive results on the IgM immunoblot may be due to cross-reactive antibodies that arise from polyclonal B-cell stimulation. Probably the most common cause of false-positive results, however, is the overreading of nonspecific weak bands. Background rates of seropositivity, which may exceed 4% in highly endemic areas of the United States and be even higher in Europe, may also confound the interpretation of seroreactivity. Therefore, a positive serologic test result does not mean that the patient necessarily has active Lyme disease. The positive predictive value is most informative when the pretest probability based on the clinical features is at least 20%.

Cerebrospinal fluid (CSF) testing may be performed in patients with suspected Lyme neuroborreliosis, including testing for intrathecal antibody production.[14] In encephalomyelitis, CSF examination typically shows a >90% lymphocytic pleocytosis, a moderately elevated protein level, and a normal glucose level, with evidence of intrathecal production of antibody to borrelia. Magnetic resonance imaging of the affected part of the brain or spinal cord can demonstrate areas of inflammation, typically with increased signal on T2 and fluid attenuation inversion recovery imaging and enhancement after administration of contrast material. Of note, positive test results for intrathecal antibody may persist for long periods despite successful antibiotic treatment. The sensitivity of polymerase chain reaction testing (PCR) in CSF is too low for it to be a useful diagnostic test.

Examination of the synovial fluid may be performed in patients with suspected Lyme arthritis. Synovial fluid in Lyme arthritis typically shows approximately 25,000 white cells/μL (range, 500 to 110,000/μL) with a polymorphonuclear predominance. PCR testing for detection of borrelial DNA is positive on synovial fluid specimens in up to approximately 80% of untreated patients with Lyme arthritis, and a positive result lends support for this diagnosis in a patient who is IgG seropositive.

General Laboratory Testing

Blood counts are usually normal in Lyme disease, unless coinfection with *Anaplasma phagocytophilum* (ehrlichiosis; Chapter 302), *Babesia microti* (Chapter 324), or a tick-borne encephalitis virus (Chapter 352) is present (see later). Lymphopenia, however, may be found in the absence of a recognized coinfection. In patients with erythema migrans, mild abnormalities of liver function tests (particularly elevations of aspartate and alanine aminotransferase levels) can be seen in approximately 35% of patients. The erythrocyte sedimentation rate may be modestly elevated in all stages of Lyme disease, but values greater than 80 mm/hour are distinctly uncommon.

Differential Diagnosis

Erythema Migrans

Tick-bite hypersensitivity reactions can be mistaken for erythema migrans, but these reactions occur within 48 hours of a tick bite, are usually pruritic, and tend to wane within a few days. In contrast, erythema migrans skin lesions in untreated patients will persist for a median of approximately 4 weeks in the United States and even longer in Europe. Bacterial cellulitis (see Fig. 408-2) rarely occurs at the most frequent skin sites for erythema migrans and would not be expected to demonstrate central clearing or a target-like appearance. Erythema migrans, unlike erythema multiforme (see Fig. 406-16), does not involve the mucous membranes, palms, or soles. Southern tick-associated rash illness (STARI) is the most likely diagnosis in patients with erythema migrans–like skin lesions who were bitten by an *Amblyomma americanum* tick or developed this lesion in the Southern United States. Other considerations in the differential diagnosis of erythema migrans that usually can be readily distinguished include tinea versicolor (often pruritic with a thin, raised, scaly border; see Fig. 405-29), nummular eczema (symmetrical pruritic lesions with a tendency to scale and crust; see Fig. 405-2), granuloma annulare (acral location, especially on the dorsum of hands and feet, relatively fixed in size and <5 cm in diameter), contact dermatitis (pruritic with streaking along the area of contact and a vesicular component; see Table 403-5), urticaria (raised, pruritic, and usually <5 cm in diameter; see Fig. 407-1), fixed drug eruption (usually on genitals, hands, feet, or face and fixed in size; see Fig. 407-3), pityriasis rosea (multiple moderately pruritic lesions with peripheral scale and relatively fixed in size; see Fig. 405-18), and a spider bite (often very painful and necrotic with a central eschar; Chapter 98).

Extracutaneous Lyme Disease

Included in the differential diagnosis of early neurologic Lyme disease is Bell palsy (Chapter 388). Even in highly endemic areas of the United States, other causes of

seventh nerve palsy outnumber Lyme disease by a margin of 3 : 1. Viral meningitis (Chapter 381) and mechanical radiculopathy (Chapter 369) can also potentially be confused with manifestations of early neurologic Lyme disease. Viral or other causes of myopericarditis (Chapter 47) may resemble cardiac Lyme disease. Many causes of synovitis (Chapters 236 and 254) might be considered in the differential diagnosis of Lyme arthritis, but the pattern of joint involvement, such as symmetrical small joint involvement in rheumatoid arthritis (Chapter 243), is often distinctly different from that found in Lyme arthritis. Lyme encephalomyelitis may occasionally be confused clinically with a first episode of relapsing-remitting multiple sclerosis or primary progressive multiple sclerosis (Chapter 380). Testing for borrelial antibody in serum (and CSF for the last condition) usually suffices to differentiate these conditions from Lyme disease.

TREATMENT

Although most manifestations of Lyme disease will resolve spontaneously without treatment, antibiotic therapy may hasten resolution and prevent progression. Lyme borrelia are highly susceptible to tetracyclines, most penicillins, and many second- and third-generation cephalosporins but are resistant to certain fluoroquinolones, rifampin, and first-generation cephalosporins.

Erythema Migrans

For erythema migrans, oral doxycycline, amoxicillin, and cefuroxime axetil are each highly effective[A1] and are the preferred agents (Table 296-3).[15] Macrolides such as azithromycin are somewhat less effective and are not recommended as first-line therapy.

Doxycycline is the only first-line agent proven to be effective against *A. phagocytophilum* coinfection. Doxycycline, however, may cause photosensitivity, which is a concern because early Lyme disease occurs most commonly during the summer months. When erythema migrans cannot be reliably distinguished from community-acquired bacterial cellulitis, cefuroxime axetil is preferred because it is generally effective against both types of infection.

Within 24 hours of initiation of antimicrobial therapy, up to 15% of patients treated for erythema migrans will experience a Jarisch-Herxheimer–like reaction characterized by an increase in the size or intensity of erythema in the skin lesion and more intense viral infection–like systemic symptoms. Fever, if present, should resolve within 48 hours and the skin lesion itself within 7 to 14 days. Other symptoms, such as fatigue or arthralgia, tend to improve but not invariably to resolve within this time frame, lasting for more than 3 months in one quarter of patients. Oral antibiotic therapy is also used as first-line treatment for the other cutaneous manifestations of Lyme disease.

Neurologic Lyme Disease

For early neurologic Lyme disease, especially uncomplicated seventh nerve palsy, meningitis, and radiculitis, oral doxycycline is recommended as a first-line therapy.[A2–A4] Amoxicillin is an alternative for patients with uncomplicated seventh nerve palsy, but seventh nerve palsy typically resolves at the same rate with or without antibiotic treatment. Therefore, the primary reason to treat such patients is to prevent the subsequent development of later complications, particularly Lyme arthritis.

Parenteral antibiotic therapy is recommended to treat patients with late neurologic Lyme disease. The preferred parenteral agent is ceftriaxone, which is highly active, crosses the blood-brain barrier, and has a long serum half-life that allows once-daily administration (see Table 296-3). Alternative parenteral options are cefotaxime and intravenous penicillin.

The presence of either papilledema or sixth cranial nerve palsy may indicate the presence of increased intracranial pressure in patients with neurologic Lyme disease. The elevated pressure will typically fall in response to antibiotic therapy, but other measures conventionally used to lower pressure may need to be considered in individual cases.

Lyme Myocarditis

Symptomatic patients with cardiac Lyme disease and those with high-grade first-degree atrioventricular heart block (PR interval of ≥300 msec) and second- or third-degree block should be hospitalized and closely monitored (Chapter 51). Temporary cardiac pacing may be required. In treated patients, complete heart block generally resolves within 1 week, and lesser conduction disturbances resolve within 6 weeks.

Lyme Arthritis

The treatment of Lyme arthritis typically begins with a 28-day course of an oral antibiotic. Patients whose arthritis is improved but not resolved after an initial course of oral therapy may be re-treated with a second course of oral antibiotics, with parenteral antibiotic therapy reserved for those without any significant clinical response.

Lyme in Pregnancy

Pregnant patients with Lyme disease are generally treated similarly to nonpregnant patients except that doxycycline is relatively contraindicated. No data convincingly support a congenital Lyme disease syndrome.

TABLE 296-3 RECOMMENDED THERAPY FOR ADULT PATIENTS WITH LYME DISEASE*

THERAPY	MANIFESTATION	DURATION
Doxycycline 100 mg PO bid *or*	Erythema migrans	10-14 days[‡]
	Borrelial lymphocytoma	14 days
Amoxicillin 500 mg PO tid *or*	Acrodermatitis chronica atrophicans	21-28 days
	Lyme arthritis	28 days
Cefuroxime axetil 500 mg PO bid	Lyme carditis—mild	14-21 days
	Cranial neuropathy	14-21 days[§]
Doxycycline 200 mg PO daily or 100 mg PO bid	Lyme meningitis or radiculopathy	14-21 days
Ceftriaxone 2 g IV daily[†]	Lyme arthritis that failed to respond to oral therapy	14-28 days
	Late neurologic Lyme disease	14-28 days
	Lyme carditis requiring hospitalization	14-21 days
	Lyme meningitis or radiculopathy requiring hospitalization	14-21 days
Azithromycin 500 mg PO daily	Erythema migrans in a patient intolerant of doxycycline and β-lactam antibiotics	7 days

*Regardless of the clinical manifestations of Lyme disease, complete response to treatment may be delayed beyond the treatment duration. Relapse may occur with any of these regimens; patients with objective signs of relapse may need another course of treatment.

[†]Cefotaxime 2 g IV q8h or IV penicillin G 18-24 million U per day IV (total daily dose is divided into an every-4-hour regimen) are alternative choices for patients with normal renal function.

[‡]10 days for doxycycline; 14 days for amoxicillin or cefuroxime axetil.

[§]Although any one of first-line oral antibiotics appears to be effective in patients with cranial neuropathy, there is only limited experience in patients with a cranial neuropathy other than seventh nerve palsy or with agents other than doxycycline.

bid = twice daily; IV = intravenous; PO = oral; tid = 3 times daily.

Modified from Lantos PM, Rumbaugh J, Bockenstedt LK, et al. Clinical practice guidelines by the Infectious Diseases Society of America, American Academy of Neurology, and American College of Rheumatology: 2020 guidelines for the prevention, diagnosis, and treatment of Lyme disease. *Clin Infect Dis*. 2021; 72:e1-e48.

Coinfections

Ixodes ticks may be coinfected with and transmit Lyme borrelia along with other pathogens, such as *A. phagocytophilum*, *B. microti* (the primary cause of babesiosis), and a tick-borne encephalitis virus. The likelihood of coinfection is dependent on the particular species of *Ixodes* tick and on the geographic area. Thus, bites from *I. scapularis* ticks in certain areas may lead to the development of Lyme disease, human granulocytic anaplasmosis (Chapter 302), or babesiosis (Chapter 324) as a single infection or, less frequently, as a coinfection. In addition, this tick species can potentially transmit the deer tick virus subtype of the Powassan virus, an *Ehrlichia* species referred to as *Ehrlichia muris eauclarensis*, and *Borrelia miyamotoi*. In Europe, the most common coinfection is Lyme disease with tick-borne encephalitis virus infection.

Coinfection should be considered in patients from geographic areas endemic for these pathogens who present with more severe initial symptoms than are commonly observed with Lyme disease alone: high-grade fever for more than 48 hours despite antibiotic therapy appropriate for Lyme disease, recurrent fever, or unexplained leukopenia, thrombocytopenia, or anemia. Coinfection might also be considered when the erythema migrans skin lesion has resolved, but the viral infection–like symptoms either did not improve or worsened.

Reinfection

Patients who are treated for early Lyme disease do not appear to develop an immunologic response that is adequate to protect against reinfection with a different strain of *B. burgdorferi*. Therefore, patients with erythema migrans may become reinfected at a different skin site if bitten by another infected tick. Reinfection has been well documented only in patients who were treated for early infection (nearly always erythema migrans) and not after late manifestations of Lyme disease, such as Lyme arthritis. Clinical manifestations of reinfection appear to be similar to those of the primary infection. Treatment is as for the initial infection.

PREVENTION

Lyme disease can be prevented by avoiding tick-infested environments, as well as by covering bare skin and using tick repellents on skin and clothing when in such environments.[16] The tick density around individual residences can be reduced by removing leaf litter, placing wood chips where lawns abut forests, and constructing fences to keep out deer. Applying acaricides to residential

property can reduce the number of ticks but not necessarily to a level that will reduce household tick exposure or human diseases.[A5] Bathing within 2 hours of tick exposure has been shown to decrease the risk of Lyme disease. For outdoor workers with high exposure to potentially infected ticks, long-lasting permethrin-impregnated clothing can reduce tick bites by about 60%.[A6]

Daily inspections of the entire skin surface (including scalp) to remove attached ticks is recommended because of the grace period between the time of tick attachment and transmission of *B. burgdorferi*. Removal is accomplished by grasping the tick as close to its mouth parts as possible with a forceps (or tweezers) and then gently pulling it out. Clinical studies have demonstrated that without any other intervention, more than 96% of patients who find and remove an attached *I. scapularis* tick will remain free of Lyme disease, even in highly endemic geographic regions. If the tick is not found or removed, the probability of infection approaches the infection rate in the regional tick population (typically >20% of nymphal stage *I. scapularis* ticks are infected in highly endemic areas of the Northeast and Midwest United States).

A single 200-mg dose of doxycycline within 72 hours of tick removal is about 70 to 90% effective in preventing erythema migrans at the tick bite site.[A7,A8] This chemoprophylaxis should be considered for persons who are in highly endemic areas and who are known to have been bitten by a nymphal or adult *I. scapularis* tick that was estimated to have been attached for at least 36 hours. Given the uncertain efficacy of a short course of amoxicillin in this situation, observation rather than chemoprophylaxis has been recommended for individuals for whom doxycycline is contraindicated. Topical azithromycin provides no prevention effect.[A9] No vaccine is currently available to prevent Lyme disease in humans.

PROGNOSIS

The outcome of treatment in most patients with erythema migrans is excellent.[17] Serologic testing is not indicated in routine follow-up of patients after treatment because either IgM or IgG borrelial antibodies may persist for many years in successfully treated patients.

Chronic Lyme Arthritis

Approximately 10% of adult patients with Lyme arthritis in the United States do not respond clinically to antibiotic therapy and are said to have antibiotic-refractory Lyme arthritis, also known as post-antibiotic Lyme arthritis, which is defined as persistent synovitis for at least 2 months after completion of a course of intravenous ceftriaxone (or 1 month after completion of two 4-week courses of an oral antibiotic). Because these patients are no longer believed to be actively infected, they are customarily treated with nonsteroidal anti-inflammatory agents, intra-articular injections of corticosteroids, or a 6- to 12-month course of disease-modifying antirheumatic drugs (see Chapter 243). Arthroscopic synovectomy has also been used successfully for patients with this condition.

Cardiac Lyme disease typically resolves completely. For neurologic disease, treatment prevents progression but does not always completely resolve neurologic dysfunction.

Post–Lyme Disease and Syndrome

When questioned at 6 months or more after treatment of erythema migrans, approximately 10% of patients will report purely subjective symptoms such as fatigue or musculoskeletal pains. These subjective symptoms are typically mild and may wax and wane in intensity. Patients who have them are referred to as having post–Lyme disease symptoms or syndrome, depending on the symptom duration and severity. The cause of these symptoms is currently unknown. Careful microbiologic evaluations have failed to find evidence of either persistent *B. burgdorferi* infection or a coinfection with a second *Ixodes*-transmitted pathogen. In patients with persistent symptoms attributed to Lyme disease, retreatment with antibiotics, irrespective of duration, has provided either no measurable benefit or a benefit so modest or ambiguous that it was outweighed by the risks associated with the antibiotic therapy.[A10] Therefore, only symptomatic treatment is recommended for such patients.[18]

The term chronic Lyme disease is poorly defined but widely used. Most often, chronic Lyme disease is used as a diagnosis for patients with persistent pain, neurocognitive complaints, or fatigue, without objective clinical or serologic evidence of past or present *B. burgdorferi* infection. In this usage, the term is a misnomer and treatment for Lyme disease is not indicated.

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For the General References and other additional features, please visit Elsevier eBooks+ at https://ebooks.health.elsevier.com.

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297

RELAPSING FEVER AND OTHER *BORRELIA* INFECTIONS

WILLIAM A. PETRI, JR.

DEFINITION

Relapsing fever is a spirochetal infection with bacteria of the genus *Borrelia*. The two modes of transmission are epidemic louse-borne and endemic tick-borne relapsing fever.[1] Disease is characterized by recurrent bouts of fever and spirochetemia separated by short fever-free periods.

The Pathogen

Members of the genus *Borrelia* are motile spirochetes that measure 0.5 µm in diameter and 5 to 40 µm in length. The spirochetes are aerophilic and require long-chain fatty acids for growth. Louse-borne relapsing fever is caused by *Borrelia recurrentis*. Tick-borne relapsing fever organisms, which are named after their tick vector, include the closely related species *Borrelia duttonii* (Old World); *Borrelia hermsii, Borrelia turicatae*, and *Borrelia parkeri* (North America); and *Borrelia miyamotoi* (Old and New World).[2]

EPIDEMIOLOGY

Louse-borne epidemic relapsing fever, which is caused by *B. recurrentis*, is carried from person to person by the human body louse (*Pediculus humanus*). There is no animal reservoir. The spirochete lives in the louse hemolymph; infection is transmitted to humans when the louse is crushed on human skin and infective spirochetes penetrate the skin or mucous membranes. Epidemics have occurred during famines and wars, when breakdown in sanitation favors the transmission of body lice. Louse-borne disease remains endemic in Central and East Africa (Ethiopia, Somalia, Chad, and the Sudan)[3] and in the South American Andes (Bolivia and Peru). It is also seen in Eastern Europe[4] and in recent refugees to Western Europe.

Tick-borne endemic relapsing fever, which occurs throughout the world, is transmitted to humans by *Ornithodoros* soft ticks. The ticks become infected by feeding on wild rodents (including mice, rats, squirrels, and chipmunks), which serve as natural reservoirs for the organisms. In the United States, relapsing fever is limited to humid mountainous areas of the West at altitudes of 1500 to 8000 feet, where the tick vector *Ornithodoros hermsii* resides in forests of ponderosa pine and Douglas fir trees. A key diagnostic clue has been a history of sleeping in rodent-infested cabins in western U.S. national parks.

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Post–Lyme Disease and Syndrome

When questioned at 6 months or more after treatment of erythema migrans, approximately 10% of patients will report purely subjective symptoms such as fatigue or musculoskeletal pains. These subjective symptoms are typically mild and may wax and wane in intensity. Patients who have them are referred to as having post–Lyme disease symptoms or syndrome, depending on the symptom duration and severity. The cause of these symptoms is currently unknown. Careful microbiologic evaluations have failed to find evidence of either persistent *B. burgdorferi* infection or a coinfection with a second *Ixodes*-transmitted pathogen. In patients with persistent symptoms attributed to Lyme disease, retreatment with antibiotics, irrespective of duration, has provided either no measurable benefit or a benefit so modest or ambiguous that it was outweighed by the risks associated with the antibiotic therapy.[A10] Therefore, only symptomatic treatment is recommended for such patients.[18]

The term chronic Lyme disease is poorly defined but widely used. Most often, chronic Lyme disease is used as a diagnosis for patients with persistent pain, neurocognitive complaints, or fatigue, without objective clinical or serologic evidence of past or present *B. burgdorferi* infection. In this usage, the term is a misnomer and treatment for Lyme disease is not indicated.

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297

RELAPSING FEVER AND OTHER *BORRELIA* INFECTIONS

WILLIAM A. PETRI, JR.

DEFINITION

Relapsing fever is a spirochetal infection with bacteria of the genus *Borrelia*. The two modes of transmission are epidemic louse-borne and endemic tick-borne relapsing fever.[1] Disease is characterized by recurrent bouts of fever and spirochetemia separated by short fever-free periods.

The Pathogen

Members of the genus *Borrelia* are motile spirochetes that measure 0.5 µm in diameter and 5 to 40 µm in length. The spirochetes are aerophilic and require long-chain fatty acids for growth. Louse-borne relapsing fever is caused by *Borrelia recurrentis*. Tick-borne relapsing fever organisms, which are named after their tick vector, include the closely related species *Borrelia duttonii* (Old World); *Borrelia hermsii, Borrelia turicatae*, and *Borrelia parkeri* (North America); and *Borrelia miyamotoi* (Old and New World).[2]

EPIDEMIOLOGY

Louse-borne epidemic relapsing fever, which is caused by *B. recurrentis*, is carried from person to person by the human body louse (*Pediculus humanus*). There is no animal reservoir. The spirochete lives in the louse hemolymph; infection is transmitted to humans when the louse is crushed on human skin and infective spirochetes penetrate the skin or mucous membranes. Epidemics have occurred during famines and wars, when breakdown in sanitation favors the transmission of body lice. Louse-borne disease remains endemic in Central and East Africa (Ethiopia, Somalia, Chad, and the Sudan)[3] and in the South American Andes (Bolivia and Peru). It is also seen in Eastern Europe[4] and in recent refugees to Western Europe.

Tick-borne endemic relapsing fever, which occurs throughout the world, is transmitted to humans by *Ornithodoros* soft ticks. The ticks become infected by feeding on wild rodents (including mice, rats, squirrels, and chipmunks), which serve as natural reservoirs for the organisms. In the United States, relapsing fever is limited to humid mountainous areas of the West at altitudes of 1500 to 8000 feet, where the tick vector *Ornithodoros hermsii* resides in forests of ponderosa pine and Douglas fir trees. A key diagnostic clue has been a history of sleeping in rodent-infested cabins in western U.S. national parks.

ABSTRACT

Relapsing fever is a spirochetal infection with bacteria of the genus *Borrelia*. There are two modes of transmission: epidemic louse-borne and endemic tick-borne relapsing fever. Disease is characterized by recurrent bouts of fever and spirochetemia separated by short fever-free periods. An abrupt onset of fever (temperature >39° C in most patients), headache, myalgia, and shaking chills characterizes the onset of illness. Signs include fever, tachycardia, lethargy, or confusion; conjunctival injection; and epistaxis. Hepatosplenomegaly, jaundice, and often a truncal petechial rash are common signs in louse-borne relapsing fever. Neurologic findings may occur, including meningitis, meningoencephalitis, and facial palsy, although these entities are more common with tick-borne relapsing fever. Elevated liver enzyme levels, neutropenia, and thrombocytopenia are common. The diagnosis should be considered in patients with fever who are in or traveled from the mountainous and high-elevation areas of the western United States. Because the number of organisms in blood is extremely high, the diagnosis is most often made by direct visualization on a blood smear, although polymerase chain reaction testing is more sensitive. Tetracycline, doxycycline, and erythromycin are all effective antibiotics.

KEYWORDS

Borrelia
relapsing fever
tick-borne
louse-borne
jaundice
thrombocytopenia
neutropenia
tetracycline

In Tanzania, where house infestation with *Ornithodoros* tick vectors can be very high, relapsing fever can be identified in about 10% of children seen at a clinic with fever. By comparison, the prevalence of antibodies to *Borrelia miyamotoi* is nearly 50%, as high as for *Borrelia burgdorferi* (Chapter 296), in the northeastern United States.

PATHOBIOLOGY

Borrelia infection begins in the skin at the site of the louse or tick bite and is followed by rapid dissemination of the spirochetes through the blood stream. The spirochete burden in blood positively correlates with the severity of symptoms. Clearance of spirochetes from blood is associated with the production of serotype-specific immune sera; anti-*Borrelia* antibodies are the major mechanism of immune clearance of infection.

Relapses are associated with cyclic antigenic variation in the variable major proteins, which are the abundant outer membrane proteins of the spirochete and which carry the serotype-specific epitopes.[5] Antigenic variation is the consequence of recombination events that occur among variable major protein genes at silent and expression sites on linear plasmids. A single *B. hermsii* bacterium may produce as many as 40 distinct serotypes. Because spirochetes undergo one or several antigenic phases during infection, no specific or standard procedure has been developed for routine serodiagnosis of relapsing fever.

CLINICAL MANIFESTATIONS

An abrupt onset of fever (temperature >39° C in most patients), headache, myalgia, and shaking chills characterizes the onset of illness in louse and tick-borne disease. Cough, nausea, vomiting, and fatigue are less frequent complaints. Additional signs include tachycardia, lethargy, confusion, conjunctival injection, and epistaxis.[6] Hepatosplenomegaly, jaundice, and often a truncal petechial rash are common signs in louse-borne relapsing fever. Neurologic findings may include meningitis, meningoencephalitis, and facial palsy, although these manifestations are more common with tick-borne relapsing fever.

Untreated louse-borne disease persists 6 days, and relapses occur once in untreated patients after an afebrile period of 9 days and then do not recur. The initial illness of tick-borne relapsing fever persists for about 4 days without antibiotic treatment, with an average of two relapses (each after an average 10-day intervening afebrile period) before the diagnosis is made; relapses eventually no longer recur even in untreated patients.[7]

B. miyamotoi presents with high fever, chills, marked headache, and myalgia or arthralgia. Elevated liver enzyme levels, neutropenia, and thrombocytopenia are common.

Relapsing fever in pregnancy can cause placental damage and intrauterine growth retardation, with miscarriage in a third of patients. Neonatal infection by both the tick- and louse-borne forms is accompanied by jaundice, hepatosplenomegaly, and often sepsis and hemorrhage. Fever and hepatosplenomegaly are also common signs in children. It has been also recognized in immunocompromised patients.

DIAGNOSIS

In the United States, the diagnosis should be considered in patients who have fever and who are returning from a stay in the mountainous and high-elevation areas of the Western United States.[8,9] Only a few patients will remember tick exposure because *O. hermsii* is a night feeder, has a painless bite, and remains attached for only 15 minutes. Internationally, relapsing fever can occur sporadically or among travelers wherever dwellings are infected with *Ornithodoros* ticks, as well as in epidemics with louse-borne disease.[10]

Polymerase chain reaction testing is highly sensitive and specific.[11] The number of organisms in blood is extremely high, and spirochetes can be demonstrated in a Wright-stained peripheral blood smear taken during febrile episodes in about 70% of patients (Fig. 297-1). Additional sensitivity may be gained by examination of a buffy coat preparation of peripheral blood. Because of their characteristic locomotion, spirochetes can be readily detected by direct visualization of thick blood films under low-power microscopy. The white blood cell count is generally normal, but platelet counts of less than 50,000/μL occur in up to 90% of cases of louse-borne disease. Prothrombin and activated partial thromboplastin times are often prolonged. In louse-borne disease, elevations in liver function test results (serum aminotransferase and bilirubin levels) and blood urea nitrogen are common. Urinalysis may reveal proteinuria and microscopic hematuria. Examination of cerebrospinal fluid may show a lymphocytic pleocytosis, and spirochetes may be directly visualized.

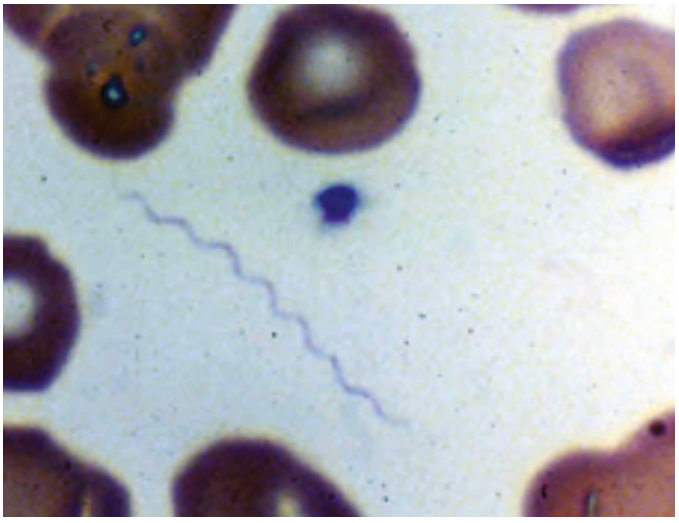

FIGURE 297-1. A single spirochete is seen in a Wright-stained thin blood smear from a patient with relapsing fever.

TREATMENT

Borrelia is generally quite sensitive to antibiotics. For louse-borne disease, options include oral doxycycline (100 mg twice daily for 7 days), tetracycline (500 mg four times daily for 7 days), erythromycin (500 mg four times daily for 10 days), or intravenous ceftriaxone (2 g twice daily for 10 to 14 days). For tick-borne relapsing infection, treatment should extend for 7 days to reduce the risk for persistent infection. Tetracycline should not be used in pregnant women and children younger than 7 years (in whom tetracyclines can stain the permanent teeth).

Antibiotic therapy can result in accelerated phagocytosis of spirochetes by neutrophils and a transient elevation in tumor necrosis factor–α (TNF-α) and interleukin (IL)-6, IL-8, and IL-10. The clinical manifestation is a Jarisch-Herxheimer reaction,[12] which is typically characterized by a 1° C rise in body temperature, rigors, a rise in blood pressure followed by a fall, and transient leukopenia about 2 to 3 hours after treatment. This reaction is more common in louse-borne disease and less common in tick-borne disease. Death as a result of shock from the Jarisch-Herxheimer reaction occurs rarely. In small numbers of patients with louse-borne relapsing fever, anti–TNF-α antibodies have been effective in prevention.

PREVENTION

Prevention of louse-borne relapsing fever hinges on improving hygienic conditions, delousing affected areas, and antibiotic treatment of patients and close contacts. Tick-borne relapsing fever can be prevented by reducing the risk of contact with rodents and ticks, including repair of structural flaws in cabins and other residences so rodents cannot nest in or around them, as well as spraying infested indoor environments. Tick-bite screening and prophylactic treatment with doxycycline (a single 200-mg dose)[11] in highly endemic areas has been reported to be practical, safe, and about 75% effective for preventing tick-borne relapsing fever.

PROGNOSIS

Epidemics of louse-borne relapsing fever have been reported to have mortality rates approaching 40%, with as much as 5% of the mortality related to Jarisch-Herxheimer reactions with treatment. Mortality from tick-borne disease is less than 5%. Autopsies of patients with louse-borne disease have documented intracranial hemorrhage, brain edema, bronchopneumonia, hepatic necrosis, and splenic infarcts.

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298 LEPTOSPIROSIS

DAVID A. HAAKE

DEFINITION

Leptospirosis is a zoonotic bacterial infection caused by pathogenic spirochetes belonging to the genus *Leptospira*. It has a global distribution and is most prevalent in tropical areas with poor urban infrastructure and heavy rainfall. Leptospirosis is transmitted to humans either by direct contact with infected animals or by contact with soil or water contaminated by rodent urine. The disease ranges in severity from a relatively mild, self-limited infection to a life-threatening, sepsis-like syndrome characterized by the triad of jaundice, acute renal insufficiency, and bleeding, sometimes complicated by severe pulmonary hemorrhage.

The Pathogen

The name *Leptospira* comes from the Greek words for thin (*leptos*) and coil (*speira*). These highly motile bacterial spirochetes measure 0.1 microns in diameter and 6 to 20 microns in length. The trailing end may be hooked when translocating through a liquid medium, thereby giving the organism the shape of a question mark and inspiring the naming of the species *Leptospira interrogans* (Fig. 298-1), which most commonly causes human infection. However, 64 different species have been described, including pathogens and commensals of host animals as well as free-living, saprophytic species.[1] Leptospiral pathogens include over 25 serogroups and 250 serovars that differ by geographic distribution and host specificity. Leptospiral genomes are characterized by extensive interspecies horizontal gene transfer, which may facilitate adaptation to a broad range of ecologic niches and reservoir host animals. Colonization of the renal tubules of infected animals leads to urinary shedding of the organism in soil and water.

EPIDEMIOLOGY

Leptospirosis, which is the most widespread zoonosis (Chapter 303) and a leading cause of morbidity and mortality worldwide, is estimated to cause about 1 million clinical infections and nearly 60,000 deaths each year. Even these numbers are likely to be underestimates, however, because leptospirosis predominantly affects medically underserved populations and is frequently misdiagnosed as dengue (Chapter 352), malaria (Chapter 316), or influenza (Chapter 332) when it presents as a nonspecific acute febrile illness.

Transmission to humans frequently involves rodent reservoir hosts, especially the urban brown rat, *Rattus norvegicus*, in which the organism is associated with high rates of renal colonization. *R. norvegicus* appears to become infected with *L. interrogans* serovar Icterohaemorrhagiae early in life and persistently sheds leptospires in its urine. Other sources include both domestic and wild animals.[2]

Leptospirosis is endemic in many developing countries with high temperatures and rainfall, such as India, Malaysia, and Brazil.[3] Leptospirosis is predominantly a disease of poverty, with high rates of exposure and infection in vulnerable populations living in settings where rodents are able to gain access to human living spaces and where urban flood control infrastructure is inadequate. In such settings, leptospirosis infections spike during heavy rainfalls when rodents are forced from their burrows and leptospires are washed into floodwaters.[4] The incidence of leptospirosis is likely to increase as extreme rainfall events become more common as a result of climate change.

Leptospirosis infections also occur among individuals taking part in adventure travel. For example, participants in the 2000 "Eco-Challenge" in Malaysian Borneo had a 42% infection rate of leptospirosis, presumably because participants floated down the Segama River, which had become swollen by heavy rainfall in the days leading up to the competition. Individuals with prolonged exposure to contaminated water are at higher risk of infection, particularly when cutaneous abrasions are present. The HLA-DQ6 haplotype is an independent risk factor for human infection.

PATHOBIOLOGY

Leptospiral morphology, motility, and invasiveness facilitate penetration of abraded skin and mucous membranes followed by dissemination via the blood stream. Leptospires have a surprisingly rich arsenal of mechanisms to evade detection and killing by the innate immune system.[5] Leptospiral proteins bind lipopolysaccharide and peptidoglycan, thereby shielding these target molecules from detection by the innate immune system.[6] Leptospiral surface proteins bind complement regulators, which renders them resistant to complement-mediated killing. Dissemination to multiple organs, including the kidney and brain, is facilitated by disruption of tissue barriers such as endothelial cell junctions. Leptospires are found in the hepatic sinusoids, and the resulting hepatocellular disruption leads to bile leakage and jaundice. Disruption of tissue barrier and impaired hemostasis mechanisms, including thrombocytopenia and coagulation disorders, leads to bleeding in various organs, most notably the lungs.

Leptospirosis is a biphasic illness consisting of an initial leptospiremic phase followed by an immune phase characterized by formation of agglutinating antibodies and clearance of organisms from the blood stream. During the leptospiremic phase, organisms disseminate to various organs and are found in the blood and urine. Shedding of organisms in the urine is the result of colonization of the renal tubules. Proximal renal tubular infection causes impaired sodium and water reabsorption due to decreased expression of transporter proteins, thereby leading to potassium wasting and fluid loss. Urinary shedding is transient in humans due to clearance by the inflammatory response, which is observed histopathologically as interstitial nephritis with cellular infiltration and edema of the renal interstitium (Fig. 298-2). During the subsequent immune phase, generalized activation of the immune system may occur, resulting in a sepsis-like syndrome and multiorgan system failure.

CLINICAL MANIFESTATIONS

The incubation period for leptospirosis is highly variable but appears to be about 6 to 29 (median 15) days. Most cases of leptospirosis are mild and self-limited and can even be asymptomatic. In symptomatic patients, initial manifestations (Fig. 298-3) typically include sudden onset of fever, chills, and headache.[7] The headache is often described as a severe, bitemporal, frontal throbbing headache accompanied by retro-orbital pain and photophobia. Muscle pain and tenderness is common and characteristically involves the

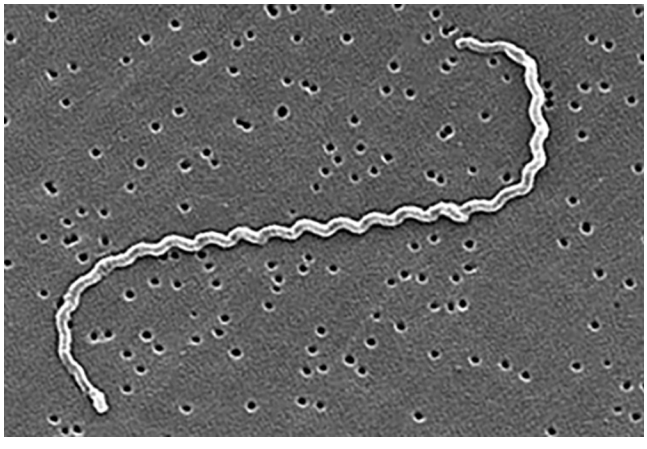

FIGURE 298-1. Leptospiral morphology. Scanning electron micrograph of *Leptospira interrogans* showing helical morphology and hooked ends.

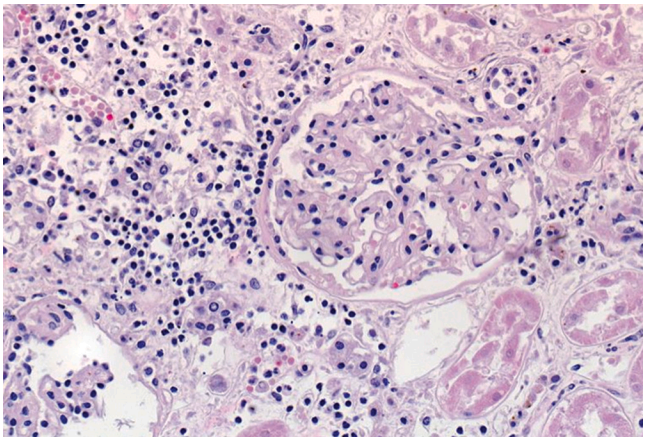

FIGURE 298-2. Interstitial nephritis. Pathologic features of interstitial nephritis due to severe leptospirosis. (From Zaki S, Shieh WJ. Leptospirosis. In: Goldman L, Schafer AI, Cecil RL, eds. *Goldman-Cecil Medicine*. 26th ed. Philadelphia: Elsevier; 2020.)

ABSTRACT

Leptospirosis is a zoonosis caused by spirochetal bacteria belonging to the genus *Leptospira*. It has a global distribution and is maintained in nature by chronic renal colonization of carrier animals, especially rodents. Infections typically occur after occupational or recreational exposure to water or soil that has been contaminated with rodent urine. In resource limited countries, outbreaks of leptospirosis occur regularly in urban settings after heavy rainfall and flooding. Early leptospirosis often presents with the abrupt onset of fever, headache, myalgias, and conjunctival suffusion, but it can be difficult to distinguish from other acute febrile illnesses. A high index of suspicion based on signs, symptoms, and epidemiologic exposure is required to identify patients who may benefit from early antimicrobial therapy. Severe leptospirosis is characterized by the triad of jaundice, acute renal insufficiency, and bleeding (Weil disease). Polymerase chain reaction assays of serum and urine have high sensitivity for detecting early infection. Serologic tests are helpful when positive but have lower sensitivity during the first week of illness. Blood cultures can helpful early in the course of the disease, and urine cultures can be helpful later in the course. For mild disease, doxycycline or azithromycin is recommended. For more severe disease, intravenous penicillin, ampicillin, or ceftriaxone is indicated. Patients who have early renal disease with high-output renal dysfunction and hypokalemia should receive aggressive volume repletion and potassium supplementation. Patients with oliguric renal failure should undergo rapid initiation of hemodialysis or peritoneal dialysis. Leptospirosis can be prevented by limiting direct contact with infected animals and indirect contact with urine-contaminated soil and water. Prophylactic antibiotics or immunization can be effective in situations in which high-risk exposure cannot be avoided.

KEYWORDS

leptospirosis
zoonosis
hepatorenal failure
pulmonary hemorrhage
conjunctival suffusion
water
rat
rodent
acute febrile illness

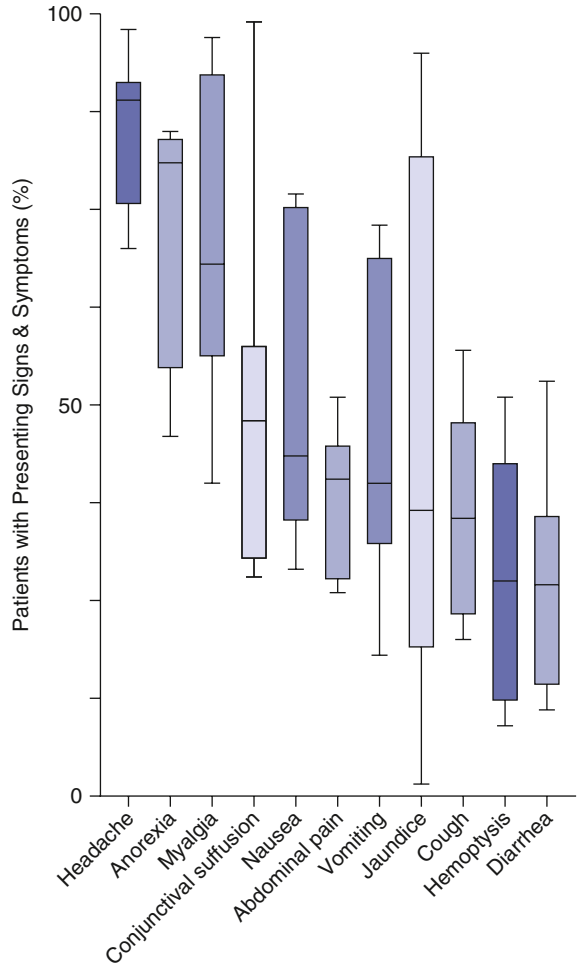

FIGURE 298-3. Signs and symptoms of leptospirosis. Box plots showing the percentage of presenting signs and symptoms of leptospirosis across nine large case series. (Data from Levett, P. N. and Haake, D. A., "Leptospira Species [Leptospirosis]," Table 239.2. In: Mandell, G. L., Bennett, J. E., and Dolin, R., eds. Principles and Practices of Infectious Diseases, Ninth Edition, Elsevier, Amsterdam, Chapter 240 [2020].)

FIGURE 298-4. Conjunctival suffusion and scleral icterus in a 37-year-old man with Weil disease. Conjunctival suffusion is a characteristic sign of leptospirosis. (Reproduced from Jansen A, Schneider T. Weil's disease in a rat owner. *Lancet Infect Dis*. 2011;11:152.)

calves and lower back. Ocular findings (Fig. 298-4) include conjunctival suffusion (a pathognomonic injection without exudate), subconjunctival hemorrhages, and icterus.[8] Nonproductive cough can occur in up to about 50% of cases. Gastrointestinal symptoms including nausea, vomiting, diarrhea, and abdominal pain are common and, together with a nonoliguric renal insufficiency, may lead to poor fluid intake and exacerbation of dehydration and precipitation of oliguric renal failure. Abdominal pain may indicate pancreatitis, although elevations of serum amylase levels may occur without pancreatitis in the setting of reduced creatinine clearance.

TABLE 298-1 LEPTOSPIROSIS CASE DEFINITIONS

Suspect Case: Acute febrile illness (≥38.5° C) and/or severe headache with:
- Myalgia
- Prostration and/or conjunctive suffusion, and
- History of exposure

Probable Case (clinical definition): Suspect case with any **two** of the following:
- Calf tenderness
- Cough with or without hemoptysis
- Shortness of breath
- Skin rash
- Jaundice
- Hemorrhagic manifestations
- Meningeal irritation
- Anuria/oliguria and/or proteinuria
- Cardiac arrhythmias

Probable Case (laboratory definition)**:** Suspect case with a positive rapid IgM test and/or any three of the following:
- Urinary findings: proteinuria, white blood cells, blood
- Relative neutrophilia (>80%) with lymphopenia
- Platelets <100,000/μL
- Elevated serum bilirubin (>2 mg); liver enzymes moderately raised

Confirmed Case: Suspect or probable case with any one of the following:
- Isolation of leptospires from clinical specimens
- Positive PCR result
- Seroconversion from negative to positive or four-fold rise in MAT titer
- MAT titer ≥400 in a single sample

Ig = immunoglobulin; MAT = microscopic agglutination test; PCR = polymerase chain reaction.

A maculopapular erythematous rash may occur after the onset of symptoms, particularly in the pretibial area of the legs. However, cutaneous manifestations occurring early in the course of an acute febrile illness are more common in dengue (Chapter 352) and chikungunya fever (Chapter 352).

Infection by pathogenic species and serovars, such as *Leptospira interrogans*, serovar Icterohaemorrhagiae, may result in more serious illness in about 10% of patients. The combination of jaundice, renal failure, and hemorrhage corresponds to the original description of leptospirosis as Weil disease. Bleeding manifestations are usually mild and limited to findings such as petechiae and ecchymoses, but some patients have severe gastrointestinal or pulmonary hemorrhage.

Multiorgan involvement of the liver, kidney, lungs,[9] and brain represents the disseminated infection. Acute hemolytic anemia, which can contribute to jaundice, is more common in patients who have glucose 6 phosphate dehydrogenase deficiency. Early infection may be associated with non-oliguric renal insufficiency, potassium wasting, and hypokalemia.

DIAGNOSIS

A high index of suspicion is needed to identify patients who may benefit from early antimicrobial therapy. A provisional diagnosis of acute leptospirosis should be based primarily on clinical and epidemiologic grounds so as to enable early treatment. Leptospirosis should be suspected in patients who have an acute febrile illness (≥38.5° C) and/or severe headache and who have relevant risk factors and/or a history of exposure, particularly if myalgia, prostration, and/or conjunctival suffusion are present (see Table 298-1). Additional clinical manifestations that support the diagnosis include calf tenderness, cough with or without hemoptysis, shortness of breath, jaundice, hemorrhage, meningeal irritation, oliguria and/or proteinuria, and cardiac arrhythmias.

The most sensitive approach to the laboratory diagnosis of acute leptospirosis, which is DNA amplification methods on blood, urine, or cerebrospinal fluid,[10] is now often feasible even in resource-poor settings.[11] Leptospires may be cultured directly from clinical specimens, especially blood or urine, using specialized media if specimens are obtained early in the course of disease and prior to administration of antibiotics. Serologic tests may initially be negative and should not be relied on to diagnose acute infection. IgM antibodies usually become detectable during the first week of illness; seroconversion from a negative to a positive serology, a four-fold rise in titer, or a single titer of 1 : 400 or more is diagnostic. Procalcitonin and C-reactive protein levels are elevated in leptospirosis and are valuable to differentiate leptospirosis from viral infections such as dengue fever (Chapter 352).[12,13]

Many patients have leukocytosis (greater than 80% neutrophilic), thrombocytopenia, and coagulopathies, including an elevated international normalized ratio, active partial thromboplastin time, and D-dimer levels. Lumbar puncture in patients with headache often shows an aseptic meningitis, with

increased cells (predominantly lymphocytes) and an elevated protein level but a normal glucose level. Patients typically have mild to moderate elevations in liver aminotransferase level elevation of direct (conjugated) bilirubin in more severe disease. Renal findings can include pyuria, hematuria, and elevated urine protein levels as well as elevations in serum blood urea nitrogen and creatinine levels. Bilirubin and liver enzymes are typically moderately elevated. Diffuse pulmonary ground-glass opacities and airspace nodules on chest computed tomography reflect diffuse alveolar hemorrhage.

Differential Diagnosis

Early leptospirosis can initially be difficult to distinguish from a variety of acute febrile illnesses. The differential diagnosis depends on other concurrent diseases in the geographic area, most frequently malaria (Chapter 316), dengue (Chapter 352),[14] typhoid fever (Chapter 284), melioidosis (Chapter 282), scrub typhus (Chapter 302), and rickettsial diseases (Chapter 302). Other diseases to consider include influenza (Chapter 332), acute viral hepatitis (Chapter 134), yellow fever (Chapter 351), bacterial and viral meningitis (Chapter 381), bacterial sepsis (Chapter 94), Zika virus (Chapter 352), Chikungunya virus (Chapter 352), and Hantavirus infection (Chapter 303). Useful diagnostic clues are conjunctival suffusion, muscle tenderness, and pulmonary hemorrhage.

TREATMENT

Many cases of leptospirosis are relatively mild and self-limited. However, if patients are sick enough to come to medical attention, early empiric antimicrobial therapy should be initiated to minimize symptoms and reduce urinary shedding. Leptospires are susceptible to a wide variety of antimicrobials.[15] Adult outpatients should be treated with doxycycline (100 mg orally twice daily for 7 days) or azithromycin (500 mg orally once daily for 3 days). Pregnant women should be treated with azithromycin (500 mg orally once daily for 3 days) or amoxicillin (500 mg orally three times daily for 7 days). Inpatients should be treated with penicillin (1.5 mU IV every 6 hours), ampicillin (0.5 to 1 g IV every 6 hours), or ceftriaxone (1 g IV every 24 hours) for 7 days.[A1] A Jarisch-Herxheimer reaction (e.g., fever, headache, chills or rigors, vomiting, tachycardia, and even hypotension; see Chapter 295) may occur, depending on the serovar that is causing infection and the time from onset of symptoms to the initiation of antimicrobial therapy.

Patients should be assessed for fluid balance and ability to hydrate orally. Supportive care with intravenous hydration may be indicated to correct dehydration and prevent acute tubular necrosis and renal failure. Potassium supplementation should be included for patients with hypokalemia. When oliguric renal failure occurs, prompt initiation of peritoneal dialysis, which is usually needed only on a short-term basis, or hemodialysis can be lifesaving.

Patients with severe pulmonary hemorrhage syndrome (Chapter 79) who have poor pulmonary compliance benefit from protective ventilation strategies based on low tidal volumes (<6 mL/kg) and high postexpiratory end pressures (Chapter 90). Extracorporeal membrane oxygenation has been used successfully to manage respiratory failure caused by leptospirosis.

PREVENTION

The most important prevention measures involve avoidance or reduction of high-risk exposures. Contact with potentially infected animals or with potentially contaminated soil and water should be reduced. Personal protective equipment should include boots, goggles, overalls, and gloves that are impermeable to liquids. Rodent control measures and immunization of domestic animals can be effective in endemic settings. Individuals who participate in adventure races or recreational water sports or who swim in natural bodies of water such as lakes and streams may be candidates for prophylaxis with doxycyline 200 mg or azithromycin 500 mg orally weekly beginning 1 to 2 days before exposure. Such antimicrobial prophylaxis and immunization have also been used in highly exposed workers in endemic settings[A2] and in the setting of flooding[A3] and large-scale epidemics.

PROGNOSIS

Many cases of leptospirosis are relatively mild and self-limited, but it can be difficult to predict which patients will benefit from more aggressive interventions. The risk of mortality for infection complicated by hepatorenal failure is 10%. In one study of 370 hospitalized patients, the overall case fatality rate was 24%; independent odds ratios were 6.0 for pulmonary involvement, 3.0 for oliguria, 2.3 for a creatinine level greater than 3.0 mg/dL, 2.2 for age older than 40 years, and 2.2 for a platelet count less than 70,000/μL. The odds ratio of death is also about 11-fold higher in patients over age 60 years compared with patients ages 19 years or less. Severe pulmonary hemorrhage syndrome is an ominous development and is associated with an increased mortality rate of up to 50%, and altered mental status is the strongest predictor of death.

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299 TUBERCULOSIS

THOMAS C. BAILEY AND JENNIFER A. PHILIPS

DEFINITION

Tuberculosis (TB) is a granulomatous disease caused by the slow-growing, acid-fast bacillus *Mycobacterium tuberculosis*. Prior to the emergence of severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2; Chapter 337), TB was the leading infectious disease cause of death worldwide. People become infected with *M. tuberculosis* by inhaling infectious organisms through aerosol transmission from a person who has active TB.

The Pathogen

The *M. tuberculosis* complex is a group of highly genetically related species that cause tuberculosis in humans, livestock, and wildlife. *M. tuberculosis* and *Mycobacterium africanum*, which cause TB in humans, are obligate human pathogens with no known environmental reservoir. Other members of the *M. tuberculosis* complex cause infection in distinct mammalian hosts, including *Mycobacterium bovis* in cattle, *Mycobacterium caprae* in goats and sheep, *Mycobacterium pinnipedii* in sea lions, and *Mycobacterium microti* in voles.[1] Although humans with active TB can infect animals, subsequent transmission of *M. tuberculosis* from animal to animal or back to humans is extremely rare. Animal-adapted members of the *M. tuberculosis* complex can also infect humans, most often when *M. bovis* (or *Mycobacterium orygis* in Africa and Southeast Asia) is retransmitted from infected cattle or unpasteurized dairy products, but subsequent human-to-human transmission is rare. Members of the *M. tuberculosis* complex likely arose from a common ancestor that resembles *Mycobacterium canettii*, which is a species that is phylogenetically positioned between mammalian pathogens and environmental mycobacteria and that has been isolated in rare cases of human tuberculosis from the Horn of Africa.

M. tuberculosis is a nonmotile, non-spore-forming, facultative anaerobe that is rod-shaped and approximately 2 to 4 μm in length. Unique features of *M. tuberculosis* include its "waxy" cell envelope, extremely slow growth, and ability to replicate intracellularly. *M. tuberculosis* doubles every 18 to 24 hours, so culturing the bacilli from clinical specimens may take weeks. The waxy coat prevents decolorization of carbol fuchsin stain after washing with strong acids, thereby leading to the characteristic "acid-fast" staining. A plasma membrane, peptidoglycan layer, arabinogalactan layer, outer membrane, and capsule comprise the cell envelope. The outer membrane contains mycolic acids and a complex array of unique lipids, such as phthiocerol dimycocerosate, phenolic glycolipids, trehalose dimycolates, and sulfolipids. This complex cell envelope, which is important for pathogenesis and transmission, also creates a formidable barrier to the entry of antibiotics.[2] The ability of *M. tuberculosis*

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ABSTRACT

Mycobacterium tuberculosis, the causative agent of tuberculosis (TB), is estimated to have infected one quarter of the world's population and is a leading cause of infectious disease death worldwide. *M. tuberculosis* is spread by aerosol transmission. Most often, infected individuals develop latent TB infection, but approximately 10% of individuals will develop active disease, either due to progressive primary infection or reactivation of latent infection. Interferon-gamma (IFN-γ), tumor necrosis factor-alpha (TNF-α), and CD4 T cells are critical in host immune control of infection. In individuals in whom these responses are impaired, such as inborn errors in the IL-12-IFN-γ signaling axis, treatment with anti–TNF-α agents, and HIV coinfection, the risk of developing active infection and disseminated disease is markedly increased. Active TB is most often pulmonary, but a wide variety of extrapulmonary disease manifestations also occur. The challenges associated with diagnosing and treating TB are compounded by HIV coinfection and drug resistance. As a result, TB remains an enormous global health threat.

KEYWORDS

Mycobacterium tuberculosis
latent tuberculosis infection
tuberculous meningitis
tuberculous lymphadenitis
tuberculous pericarditis
tuberculous peritonitis
genitourinary tuberculosis
tuberculosis-associated immune reconstitution inflammatory syndrome
multidrug-resistant TB
extensively drug-resistant TB

to withstand adverse conditions and disrupt host immunity depends upon this unique cell envelope.

M. tuberculosis is classified into distinct phylogenetic lineages that are thought to have originated in the Horn of Africa and spread to other parts of the world in association with human migration. The more ancestral strains (lineages 1 and 5 to 7) are geographically restricted. Lineages 5 and 6 are *M. africanum* lineages found almost exclusively in West Africa. The "modern" *M. tuberculosis* lineages (lineages 2 to 4) are responsible for the global epidemic of TB. Although all lineages cause the same spectrum of disease, lineage appears to impact pathogenesis and epidemiologic spread.[3] For example, certain lineage 2 strains are more likely to cause severe pulmonary infection, to develop drug resistance more rapidly, and to be more transmissible. Lineage identification is not part of routine clinical care, but more detailed strain typing is useful in investigations of outbreaks to establish whether cases are epidemiologically linked. Strain typing can be performed by restriction fragment length polymorphism of the insertional element IS6110, spoligotyping, mycobacterial interspersed repetitive unit analysis, and whole-genome sequencing. In addition, genotyping can be used to distinguish relapse from reinfection in high burden settings and in relatively rare instances of laboratory cross-contamination of diagnostic specimens.

EPIDEMIOLOGY

The World Health Organization (WHO) estimates that 1.7 billion people, a quarter of the world's population, are latently infected with *M. tuberculosis*. In 2018, an estimated 10 million new active cases of TB and 1.2 million deaths occurred worldwide, with the majority occurring in low- and middle-income countries.[4] As a result, TB was the leading infectious disease killer prior to being overtaken by SARS-CoV-2 during the coronavirus disease 2019 (COVID-19) pandemic. Worldwide, 35% of cases occur in women, and the prevalence of disease peaks in young adults. HIV has a profound impact on the epidemiology of TB: 10% of TB cases worldwide occur in people with HIV infection, and TB is the leading cause of death among persons living with HIV (Chapter 358).

The risk of TB depends upon the country of origin. The prevalence of latent TB infection is estimated to be 4% in the United States but exceeds 20% in Southeast Asia, the Western Pacific, and Africa.[5] The same geographic disparity is seen for active disease. In Southeast Asia, the incidence of TB is 220 per 100,000 persons per year, whereas most high-income countries have an incidence of less than 10 per 100,000 persons per year (Fig. 299-1). In high-burden settings with substantial ongoing transmission, active TB most often occurs because of progression during the first 2 years after initial infection. In low burden settings, however, active TB is more likely to result from reactivation of more long-standing latent infection. Although most people develop an adaptive immune response that controls infection, this response does not prevent reinfection. In high-burden settings, individuals previously treated for TB are at increased risk of being infected with a new strain of *M. tuberculosis* compared with individuals without a TB history.

For over 100 years, the incidence of TB has declined in the United States, with the notable exception of 1984 to 1992, when the rise of the HIV epidemic led to an increasing incidence. In 2019, the 8920 reported active cases (2.7 per 100,000 persons) were the lowest since reporting began in the early 1950s but still far from the goal of eliminating TB, which is generally defined as an incidence below one case per million people per year. In the United States, the majority (about 70%) of TB cases occur in immigrants from high-incidence countries. This elevated risk of TB disease persists in immigrants from high-prevalence countries long after their arrival in the United States; for example, approximately 45% of new TB cases among foreign-born residents were diagnosed 10 or more years after they first arrived in the United States. Other risk factors for TB infection and progression to active disease include having household contact with active pulmonary TB, HIV disease or other causes of immunosuppression, residence in a homeless shelter or correctional faculty, diabetes mellitus, and underlying lung disease (Table 299-1). In general, people who are at highest risk for active TB disease are individuals who were recently infected and who are immunosuppressed. These risk factors also inform the interpretation of tuberculin skin testing and treatment strategies for latent TB (see later).

The worldwide problem of TB is compounded by drug resistance. In 2019, about 3% of new TB cases and 18% of previously treated cases had drug-resistant TB. Multidrug-resistant TB (resistant to both isoniazid and rifampin) exists worldwide, with the majority of cases occurring in India (27%), China (14%), and Russia (8%). Extensively drug-resistant (XDR) TB, which is resistant to isoniazid, rifampin, fluoroquinolones, and at least one of the three second-line injectable agents, is estimated to occur in about 10% of patients with multidrug-resistant TB. The epidemic of drug resistance is driven both by transmission of drug-resistant isolates and the acquisition of drug resistance due to inappropriate treatment.[6]

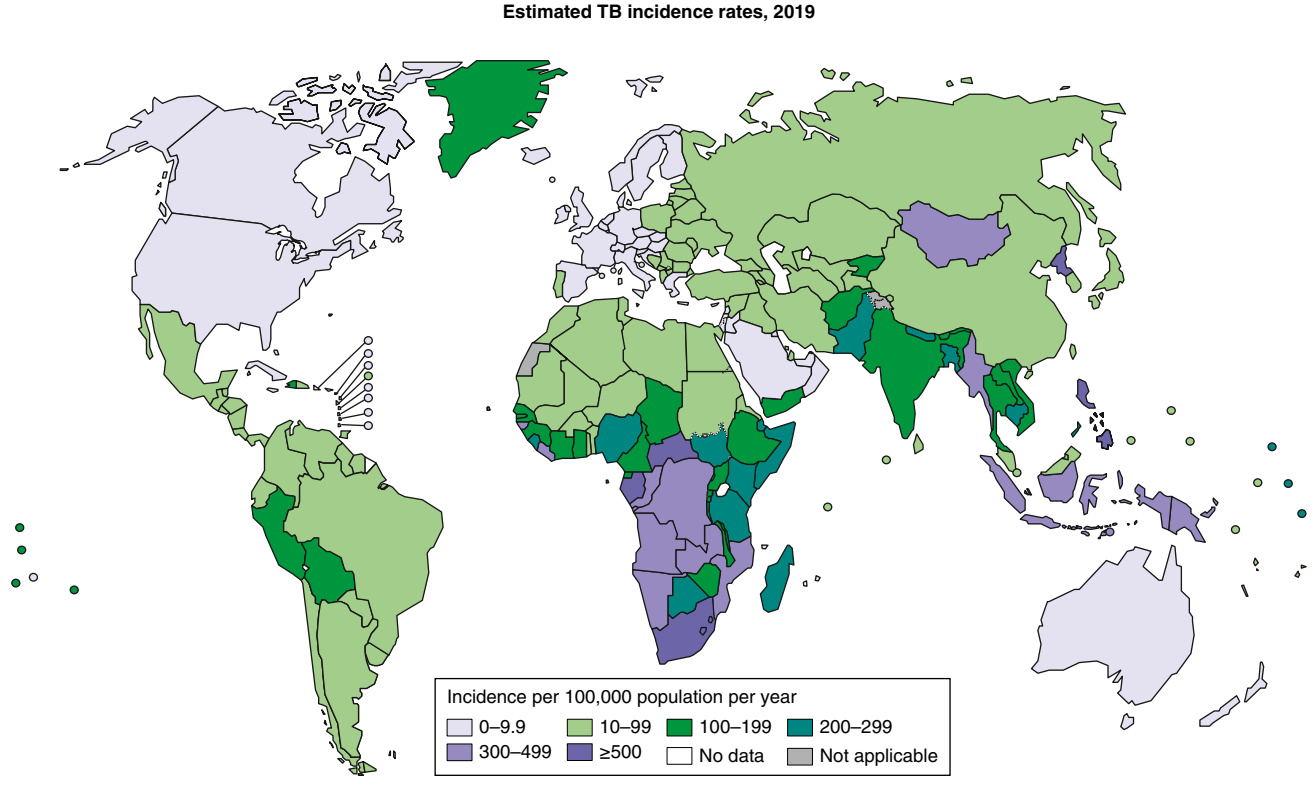

FIGURE 299-1. Estimated TB incidence rates, 2019 (from Global Report, 2020). The severity of national TB epidemics in terms of the annual number of incident TB cases relative to population size (the incidence rate) in 2019. High-income countries and low-income countries had widely divergent TB incidence rates. (Reprinted from the Global tuberculosis report 2020. Geneva: World Health Organization; 2020. Licence: CC BY-NC-SA 3.0 IGO.)

TABLE 299-1 RISK FACTORS FOR TUBERCULOSIS

RISK FACTOR	INCREASED RISK OF RECENT INFECTION*	INCREASED RISK OF PROGRESSION TO ACTIVE DISEASE	DEFINITION OF A POSITIVE TB SKIN TEST
Household contact of active pulmonary TB	X		≥5 mm
Solid organ transplant recipient, immunosuppressive treatment (TNF-α inhibitors, prednisone >15 mg/day for >1 month), fibrotic lesion on chest radiograph consistent with prior TB		X	≥5 mm
HIV infection		X	≥5 mm
Birth or extended residence in higher-prevalence countries; persons using nonprescription injectable drugs who are known to be HIV-negative; children under 5 years old; children and adolescents exposed to adults in high-risk categories	X		≥10 mm
Residents or employees in hospitals, homeless shelters, correctional facilities, nursing homes, residences for HIV-infected	X		≥10 mm
<90% IBW or BMI ≤20; cigarette smoking; silicosis; diabetes mellitus (particularly insulin-dependent or poorly controlled); end-stage renal disease; post-gastrectomy or jejuno-ileal bypass; carcinoma of the head and neck; lung cancer; lymphoma; leukemia		X	≥10 mm
None			≥15 mm

*Recent infection itself also increases the risk of progressing to active disease.
BMI = body mass index; HIV = human immunodeficiency virus; IBW = ideal body weight; TNF = tumor necrosis factor.

In response to the rise in HIV/TB coinfections and multidrug-resistant *M. tuberculosis* in 2013, the WHO declared TB a global public health emergency and developed the End TB Strategy. Unfortunately, the COVID-19 pandemic has interfered with these efforts. TB services have been disrupted by worldwide lockdowns, overwhelmed health care systems, and the reallocation of health care workers and resources to care for COVID-19 patients. In 2020, 1.4 million fewer TB cases were reported worldwide than in 2019, almost certainly owing to underreporting rather than a true reduction in incidence. The reduction in detection and, hence, in prompt treatment in 2020 is projected to result in 0.5 million excess TB deaths, with worldwide TB mortality climbing back to levels last seen in 2010.[7]

PATHOBIOLOGY

M. tuberculosis effectively disarms the innate immune response, persists in the face of adaptive immunity, and disseminates, thereby leading to a wide spectrum of infectious manifestations. The infection cycle begins when *M. tuberculosis* is transmitted from a person with active pulmonary TB through aerosolized particles that are small enough to reach the alveoli (1 to 5 μM; Fig. 299-2). The degree of infectiousness depends upon the severity of cough, which is promoted by sulfolipid in the mycobacterial cell envelope, and the extent of bacterial burden.[8] Patients with cavitary lesions, which can have 10^7 to 10^9 bacilli, are the most infectious. Patients who do not have visible acid-fast bacilli on sputum smears are much less likely to transmit, but they still can infect others. Patients with HIV are less likely to develop cavitary disease, to be smear positive, or to transmit infection. On average, infectious individuals will infect 3 to 10 people per year. In household settings, where exposure may be intense and prolonged, 25 to 50% of contacts become infected.

A central feature of the pathogenesis of *M. tuberculosis* is its ability to survive and grow in host phagocytic cells that normally clear infection.[9] When *M. tuberculosis* bacilli reach the distal alveoli, they are first taken up by alveolar macrophages, which normally kill microbes and clear debris, but they are poorly equipped to handle *M. tuberculosis* (Fig. 299-2). Over time, monocyte-derived macrophages, interstitial macrophages, and neutrophils are recruited to the site of infection, but they also fail to control *M. tuberculosis* replication. Infected dendritic cells travel to the draining lymph node, where presentation of *M. tuberculosis* antigens leads to priming and expansion of antigen-specific T cells, which return to the infected lung. Once an adaptive immune response develops, T cells, B cells, and activated macrophages form the characteristic granuloma, and bacterial control is established. The interval from the initial infection to the development of a positive tuberculin skin test and/or IFN-γ release assay (IGRA) is usually between 2 and 8 weeks. This delay in the adaptive immune response allows *M. tuberculosis* to establish infection, which is often asymptomatic, and grow relatively unhindered for weeks.

Some individuals may sterilize the initial infection by virtue of their innate immune response by clearing bacilli before an adaptive immune response has time to develop. Individuals who are highly exposed to *M. tuberculosis* and appear to resist infection, as evidenced by persistently negative tuberculin skin test and/or IGRA, appear to have increased expression of metabolic pathways that respond to free fatty acids as well as increased *M. tuberculosis*–specific antibody responses.[10]

Granulomas, which are the histopathologic hallmark of *M. tuberculosis* infection, are thought to be important in preventing progressive disease after infection is established. Granulomas are an organized collection of macrophages, neutrophils, and lymphocytes. Macrophages within the granuloma can undergo an epithelioid transformation, form multinucleated giant cells, or become lipid-laden and "foamy" in appearance. Characteristically, the granulomas become necrotic and have a caseating appearance (like cheese). Over time, these granulomas calcify. CD4 T cells and TNF-α are critical in the formation of granulomas and to host protection. CD4 T cells secrete cytokines, such as IFN-γ, which promote the microbicidal activities of macrophages. Patients with CD4 T-cell dysfunction from HIV infection or patients treated with TNF-α inhibitors fail to form well-organized granulomas, and they are at high risk for developing active TB and disseminated infection. Similarly, patients who have inborn errors of IFN-γ signaling or who acquire IFN-γ neutralizing antibodies are highly susceptible to active disease and have a greater likelihood of developing disseminated and recurrent disease. Although granulomas prevent progressive infection, they may also facilitate bacterial persistence. Granulomas may enhance bacterial spread between aggregated macrophages, create an immunosuppressive environment, and keep CD4 T cells peripherally located, away from the more central, infected macrophages, thereby obstructing key immune cell interactions.[11] Even within an infected individual, different granulomas establish different degrees of immune control.[12]

Once infected, some patients will develop active disease over the first year of infection (termed progressive primary infection). However, most often, the initial infection, while disseminated, is controlled, thereby resulting in latent tuberculosis infection. Although the distinction between latent tuberculosis infection and active disease is extremely important clinically, the classification oversimplifies what is a more complex spectrum of infectious stages that include bacterial elimination and subclinical disease (Fig. 299-3). Some patients diagnosed with latent tuberculosis infection may sterilize the infection, but it is impossible, with current diagnostics, to tell whether the tubercle bacilli have been cleared by the adaptive immune response or are still viable but controlled.

Recent infection and a variety of conditions (see Table 299-1) increase the risk of active disease. HIV infection (Chapter 358) is the strongest known risk factor, even among individuals with relatively preserved CD4 T-cell counts. The majority of patients with active TB have no identified immunologic risk factor, but neutrophil-driven inflammation and a type I IFN response seem to promote progressive disease.

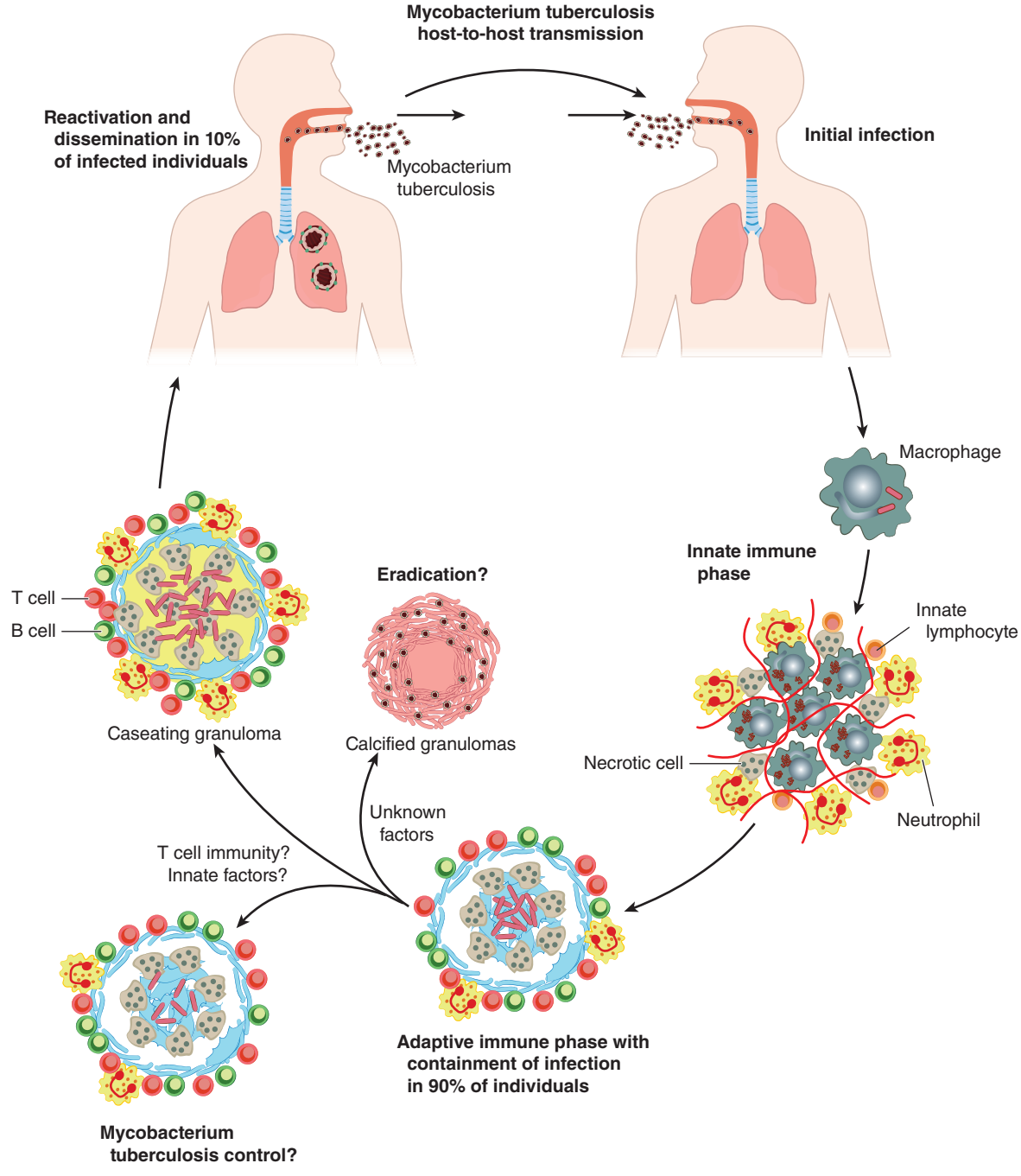

FIGURE 299-2. Pathogenesis of tuberculosis. *M. tuberculosis* is transmitted by aerosol and first infects alveolar macrophages in the distal alveoli. During the innate immune phase of the infection, inflammatory cells are recruited to the site of infection, but they fail to control bacterial replication. The adaptive immune response leads to control of infection, and well-organized granulomas are important in preventing dissemination. Approximately 10% of infected individuals will go on to develop active disease, which most often results in cavitary lung disease but can disseminate and involve any organ system. (From Claudio Nunes-Alves et al, *Nat Rev Micro*, 2014.)

CLINICAL MANIFESTATIONS

Primary Tuberculosis

Most cases of primary TB go clinically unrecognized and resolve without treatment. Individuals may develop fever, shortness of breath, nonproductive cough, and, rarely, erythema nodosum. Chest radiographs may show a small area of patchy opacity in the mid-lung fields (called a Ghon focus) with associated hilar lymphadenopathy (together called a Ghon complex) (Fig. 299-4A). Patchy, linear, or nodular parenchymal opacities may be seen. Lymphadenopathy, which is often unilateral, involves the hilum and right paratracheal nodes. Enlarged lymph nodes can cause bronchial compression, thereby leading to upper or middle lobe collapse. A transient pleural effusion may develop (Fig. 299-4B).

In most cases, the outcome of primary TB is latent tuberculosis infection. However, particularly in the absence of an effective adaptive immune response, primary infection can progress to pulmonary and extrapulmonary disease, including TB meningitis and miliary TB. Progressive primary infection is more likely to occur in children, the elderly, and the immunocompromised.

Latent Tuberculosis Infection

Most often, the immune response controls primary TB, thereby leading to clinically silent infection. Diagnosis of latent tuberculosis infection is made by demonstrating an immunologic response to *M. tuberculosis* antigens. Chest radiography may show evidence of prior infection; the Ghon complex may leave a calcified Ghon lesion in the mid-lung fields or calcified hilar nodes (when found together this is referred to as a Ranke complex). However, these radiographic findings are nonspecific and can also occur in other granulomatous infections, such as healed histoplasmosis (Chapter 308).

Pulmonary Tuberculosis

Active TB disease most often involves the lungs. When pulmonary TB occurs within the first year of infection, it is called progressive primary infection.

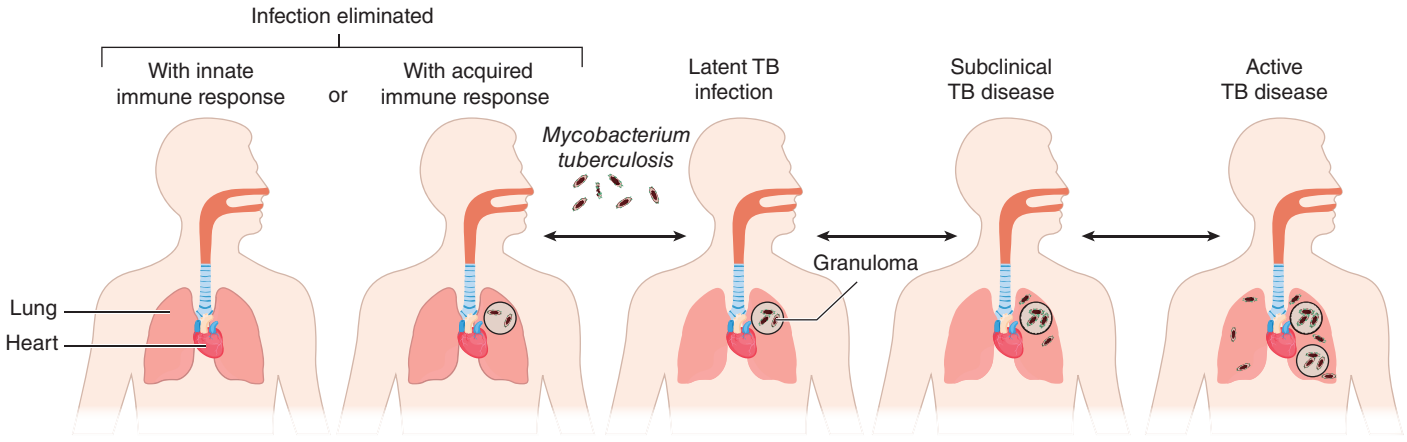

TST	Negative	Positive	Positive	Positive	Usually Positive
IGRA	Negative	Positive	Positive	Positive	Usually Positive
Culture	Negative	Negative	Negative	Intermittently positive	Positive
Sputum smear	Negative	Negative	Negative	Usually negative	Positive or negative
Infectious	No	No	No	Sporadically	Yes
Symptoms	None	None	None	Mild or none	Mild to severe
Preferred treatment	None	None	Preventive therapy	Multidrug therapy	Multidrug therapy

FIGURE 299-3. Spectrum of outcomes after TB infection. Clinically it is critical to distinguish latent TB infection from active disease in order to initiate the appropriate therapy. It is likely that other infection outcomes, including bacterial elimination and subclinical disease, also occur but are not possible to distinguish from latent TB infection with current diagnostic tools. IGRA = interferon gamma-release assay; TST = Mantoux tuberculin skin test. (From Pai, M. et al. and Raviglione M, Tuberculosis, *Nature Reviews Disease Primers*, Vol 2, 2016. This figure was also reproduced in Furin, Cox and Madhukar, *The Lancet*, DOI: https://doi.org/10.1016/S0140-6736(19)30308-3, an Elsevier journal.)

Pulmonary TB that occurs more distant to the initial infection is considered reactivation of latent tuberculosis infection (also termed "post-primary disease"). The most common symptom of pulmonary TB is a persistent cough, which can be productive or nonproductive and accompanied by fever, chills, night sweats, and weight loss; hemoptysis may occur in advanced disease. However, up to 25% of persons with culture-confirmed pulmonary TB do not report cough.

Physical examination findings are not specific. There may be abnormal breath sounds, such as post-tussive rales in the upper lung zones. Amphoric breath sounds can indicate a cavity. Lymphadenopathy is not common in immunocompetent adults with pulmonary TB.

Leukocytosis and anemia may be present. Progressive primary disease typically results in dense consolidation on chest radiography, with a predominant involvement of the middle and lower lobes (Fig. 299-4C,D), but the clinical and radiographic features of progressive primary and reactivation disease overlap. Reactivation pulmonary TB usually manifests as cavitary disease involving the apical and posterior segments of the right upper lobe and the apical-posterior segment of the left upper lobe, distant from the site of the primary infection (Fig. 299-5). Other radiographic findings can include fibrotic scars, loss of lung volume, and calcification. Endobronchial spread to lower portions of the lungs can lead to radiographic tree-in-bud opacities. Erosion into blood vessels or lymphatics can lead to dissemination and a miliary pattern.

In patients coinfected with HIV (Chapter 358), the clinical manifestations depend upon the degree of immune dysfunction. Disease in HIV-infected patients with relatively preserved immune function may be indistinguishable from disease in immunocompetent hosts, but as the degree of immunosuppression increases, the disease manifestations become more atypical. Persons living with HIV are less likely than immunocompetent individuals to be sputum-smear positive, less likely to have cavitary disease, and more likely to develop disseminated infection. Although most patients with pulmonary TB have abnormal chest radiographs, persons with HIV may have a normal chest radiograph despite smear-positive disease; a computed tomographic (CT) scan is more sensitive in these cases.

Extrapulmonary TB

Because primary infection is a disseminated process prior to immunologic control, extrapulmonary disease can affect nearly any organ system. Extrapulmonary disease can also mimic a wide array of other disorders, and it can be difficult to make a microbiologic diagnosis, since the bacterial burden may be relatively low and the site of infection may be difficult to access.

Pleural TB

Involvement of the pleural space can occur during primary infection or reactivation.[13] Most often TB pleuritis occurs when a small number of organisms gain access to the pleural space and elicit an inflammatory response. During primary infection, TB pleuritis may be clinically silent and resolve spontaneously, or it can result in cough, pleuritic chest pain, and systemic symptoms, with associated exudative pleural effusions (Fig. 299-4B). Pleural involvement most often occurs 3 to 6 months after primary infection. In some cases, effusions can be large and cause dyspnea, but most often they are small and unilateral. More rarely, TB can cause an empyema when a large number of bacilli erode into the pleural space from a cavity or parenchymal focus.

Miliary TB

Miliary TB is a multisystem form of TB in which 1- to 2-mm granulomatous nodules are found in the lungs and other organ systems. The most commonly involved organs are lungs, liver, bone marrow, kidney, adrenal glands, and spleen. Miliary TB usually presents with systemic symptoms (including fever, weight loss, and night sweats), often in the absence of localizing symptoms. The physical examination also may reveal choroidal tubercles (white-yellow plaques on fundoscopic exam), lymphadenopathy, and hepatomegaly. Chest radiographic abnormalities may initially be subtle, with the classic miliary pattern seen in about 85% of patients (Fig. 299-6). Patients also may have other chest radiographic abnormalities, such as cavities, pleural effusions, or pericardial effusions. Since HIV-infected patients and patients who are being treated with TNF-α inhibitors may not form well-circumscribed granulomas, their findings on plain chest radiography may be absent or subtle, and a CT scan is more sensitive. In 20 to 40% of patients with advanced AIDS and miliary TB, blood cultures are positive for *M. tuberculosis*.

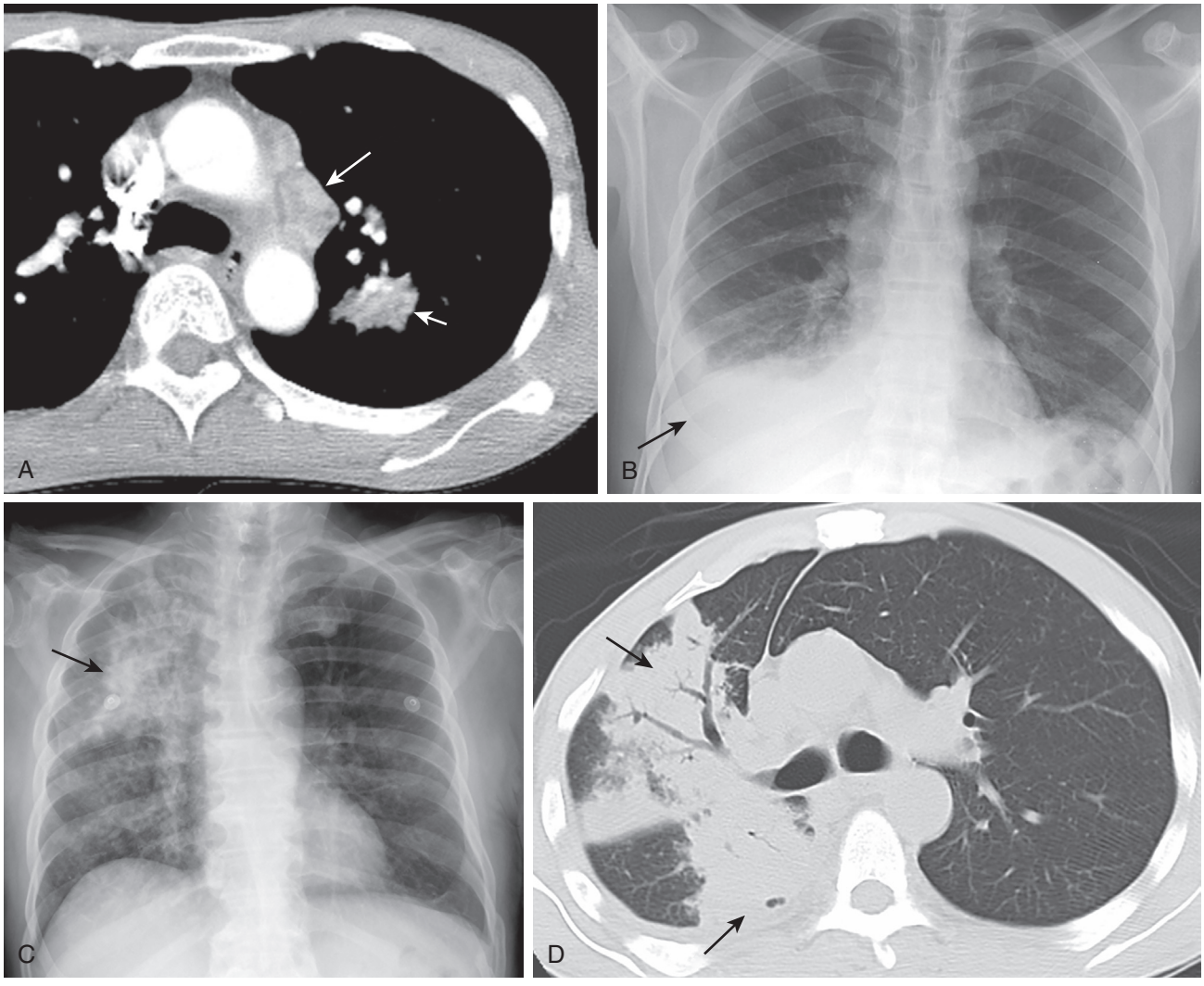

FIGURE 299-4. Radiographic images of primary and progressive primary tuberculosis (TB). A, Ghon focus in a 33-year-old woman. Chest computed tomographic image at the level of the aortopulmonary window shows the left-sided focal parenchymal opacity *(short arrow)* with ipsilateral lymphadenopathy *(long arrow)*. **B,** Chest radiograph (CXR) shows an ill-defined right lower lobe opacity with an ipsilateral pleural effusion *(arrow)* in a patient with primary TB. **C** and **D,** TB pneumonia in a 46-year-old man with progressive primary TB. **C,** Multiple opacities with dense airspace consolidation in the right upper lobe are seen on CXR. **D,** Noncontrast CT shows air bronchograms in the right upper and lower low lobes *(arrows)*. (Adapted from Restropo CS, et al. Imaging manifestations of thoracic tuberculosis, *Radiologic Clinics of North America*, 2016; 54; 453-473, an Elsevier journal.)

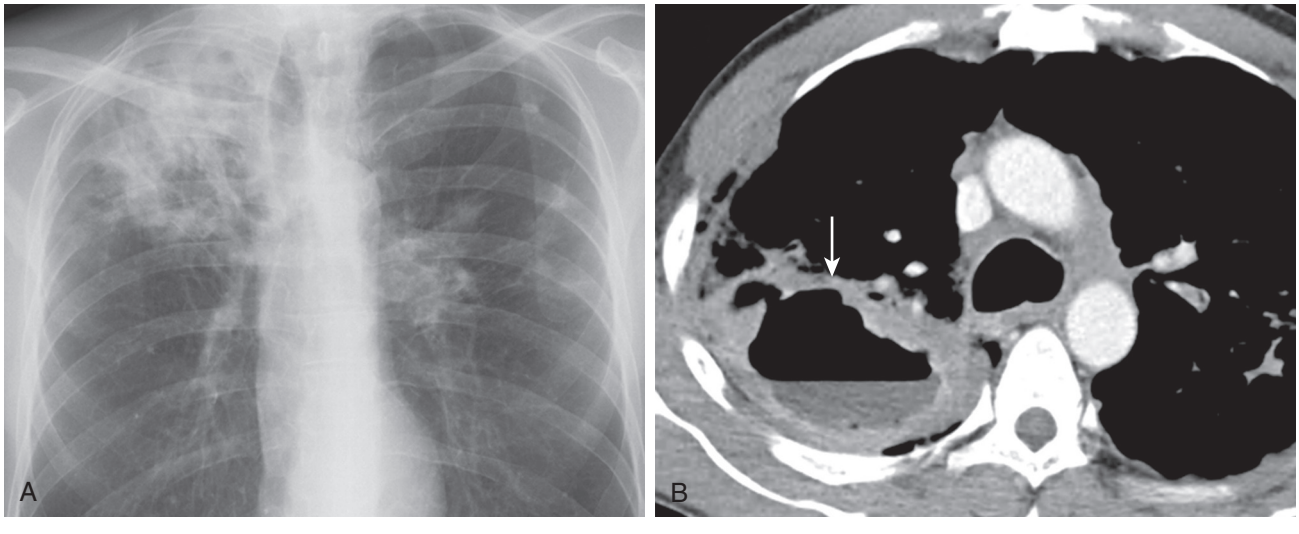

FIGURE 299-5. Cavitary tuberculosis. A, Chest radiograph shows an area of cavitation with an extensive opacity in the right upper lobe in a patient who also has left-sided nodular opacities and left hilar lymphadenopathy. **B,** Contrast-enhanced CT axial image shows the irregular cavity with an air-fluid level in the posterior right upper lobe *(arrow)*. (From Restropo CS, et al. Imaging manifestations of thoracic tuberculosis, *Radiologic Clinics of North America*, 2016; 54; 453-473.)

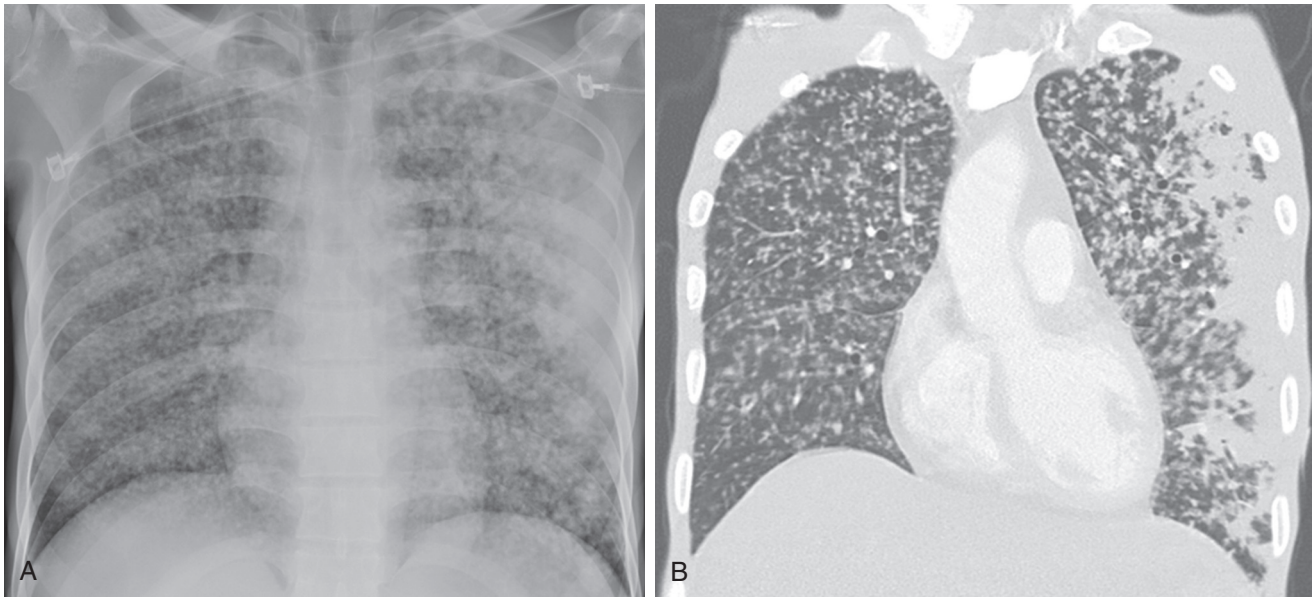

FIGURE 299-6. Miliary tuberculosis (TB). Miliary TB in a 33-year-old man. (A) Chest radiograph and (B) coronal chest computed tomographic image demonstrate very extensive micronodular disease in the bilateral lung with more confluent disease and consolidation in the periphery of the lung. (From Restropo CS, et al. Imaging manifestations of thoracic tuberculosis, *Radiologic Clinics of North America*, 2016; 54; 453-473.)

Central Nervous System TB

Central nervous system involvement with *M. tuberculosis* can manifest as a rapidly fatal meningitis or a slowly growing focal tuberculoma. TB meningitis (Chapter 381) can occur owing to meningeal seeding from a hematogenous source or rupture of a parameningeal focus into the subarachnoid space. HIV infection is the major epidemiologic risk factor for developing TB meningitis.[14] Patients with TB meningitis present with fever, headache, and neck stiffness. Cranial nerves can be involved, and the level of consciousness may be decreased. The time between the onset of symptoms and clinical presentation ranges from 5 to 30 days. More than half of patients with TB meningitis also have pulmonary disease (often miliary) and dissemination to other extrapulmonary sites.

In contrast to the 1- to 4-week course usually associated with TB meningitis, CNS tuberculomas are generally slow-growing and result in ring-enhancing lesions on imaging. They usually cause focal findings, although occasionally they cause increased intracranial pressure without focal findings.

TB Lymphadenitis

Tuberculous lymphadenitis most often causes painless involvement of posterior cervical and supraclavicular nodes (called scrofula), but it can involve any lymph node.[15] Although the lung is the likely original portal of entry, most TB lymphadenitis occurs without coexistent clinical pulmonary disease. However, lymphadenitis is more likely to accompany pulmonary TB in individuals who are coinfected with HIV.

As the disease progresses, the lymph node may suppurate and form sinus tracts. Isolated TB lymphadenitis is more common in children and adolescents than older adults, with a slight female predominance. In the United States, scrofula is more often caused by non-tuberculous mycobacteria than TB.

A variety of secondary manifestations depend upon which lymph nodes are involved. For example, intrathoracic adenopathy can cause bronchial compression, cervical node enlargement, and upper airway obstruction, whereas intrathoracic or intraabdominal nodes can disrupt lymphatics, thereby causing chylothorax or chylous ascites.

Genitourinary TB

TB involving the genitourinary system occurs in 15 to 40% of cases of patients with extrapulmonary disease.[16] Some individuals are asymptomatic and first suspected in patients who have sterile pyuria or hematuria (Chapter 100). Patients may have mild dysuria and urinary frequency, generally without systemic symptoms. TB involvement of the genital tract in women can lead to pelvic pain, menstrual irregularities, and infertility. In men, the most common presenting symptom is a scrotal mass, but prostatitis, orchitis, and epididymitis may also occur. Progressive disease can cause more severe hematuria, flank pain, and renal failure. In genitourinary TB, CT scans can show renal cortical scarring, renal masses or cavitary lesions, papillary necrosis with calyceal and ureteral dilation, or "beading" of the ureter owing to strictures. More than 50% of patients with genitourinary TB have an abnormal chest radiograph owing to prior or concurrent lung disease.

TB Pericarditis

In immunocompetent patients, TB pericarditis (Chapter 62) usually develops slowly, thereby allowing for the accumulation of large volumes of pericardial fluid without tamponade.[17] Clinical manifestations, which can be chronic or subacute, include fever, night sweats, cough, dyspnea, orthopnea, ankle edema, and chest pain. In contrast to the more chronic process in immunocompetent individuals, TB pericarditis can develop rapidly in HIV-infected individuals, in whom it is more likely to lead to tamponade and can also involve the myocardium. Over time, constrictive pericarditis occurs owing to a fibrotic reaction.

TB Peritonitis

TB peritonitis[18] (Chapter 128) occurs when *M. tuberculosis* enters the peritoneal space from adjacent lymph nodes. Patients most often present with subacute abdominal pain, anorexia, abdominal swelling, and systemic symptoms (fevers, night sweats, weight loss), although it can also mimic an acute abdomen (Chapters 118 and 128). Patients often have underlying liver disease, usually without coexistent pulmonary disease. Intra-abdominal lymphadenopathy may be seen on a CT scan.

Intestinal Tuberculosis

TB can involve any portion of the gastrointestinal tract, but it most often involves the terminal ileum or regions distal to the terminal ileum. In addition to *M. tuberculosis*, intestinal disease may also be caused by *M. bovis* from unpasteurized dairy products.

Patients most often present with abdominal pain and gastrointestinal obstruction. They also may have fever, nausea, diarrhea, weight loss, or gastrointestinal bleeding. The disease can mimic Crohn disease (Chapter 127) or be mistaken for acute appendicitis (Chapter 128) or carcinoma (Chapter 179).

Osteoarticular Tuberculosis

TB can cause subacute synovitis or osteomyelitis in any bone or joint. Usually only one bone or joint is involved, and approximately half of patients have chest radiographic abnormalities consistent with prior or concurrent pulmonary disease. TB of the spine (Pott disease) is most common, followed by disease in the hips or knees.

Spinal TB presents with back or radicular pain, most often involving the lower thoracic and upper lumbar vertebrae. The disease starts in the subchondral region of the anterior portion of the vertebral body and typically extends to involve two adjacent vertebrae and the intervertebral disc (Fig. 299-7). Paravertebral abscesses may develop along with sinus tracts. Anterior collapse of the vertebral bodies may lead to a gibbus deformity, which can cause spinal cord compression and kyphosis.

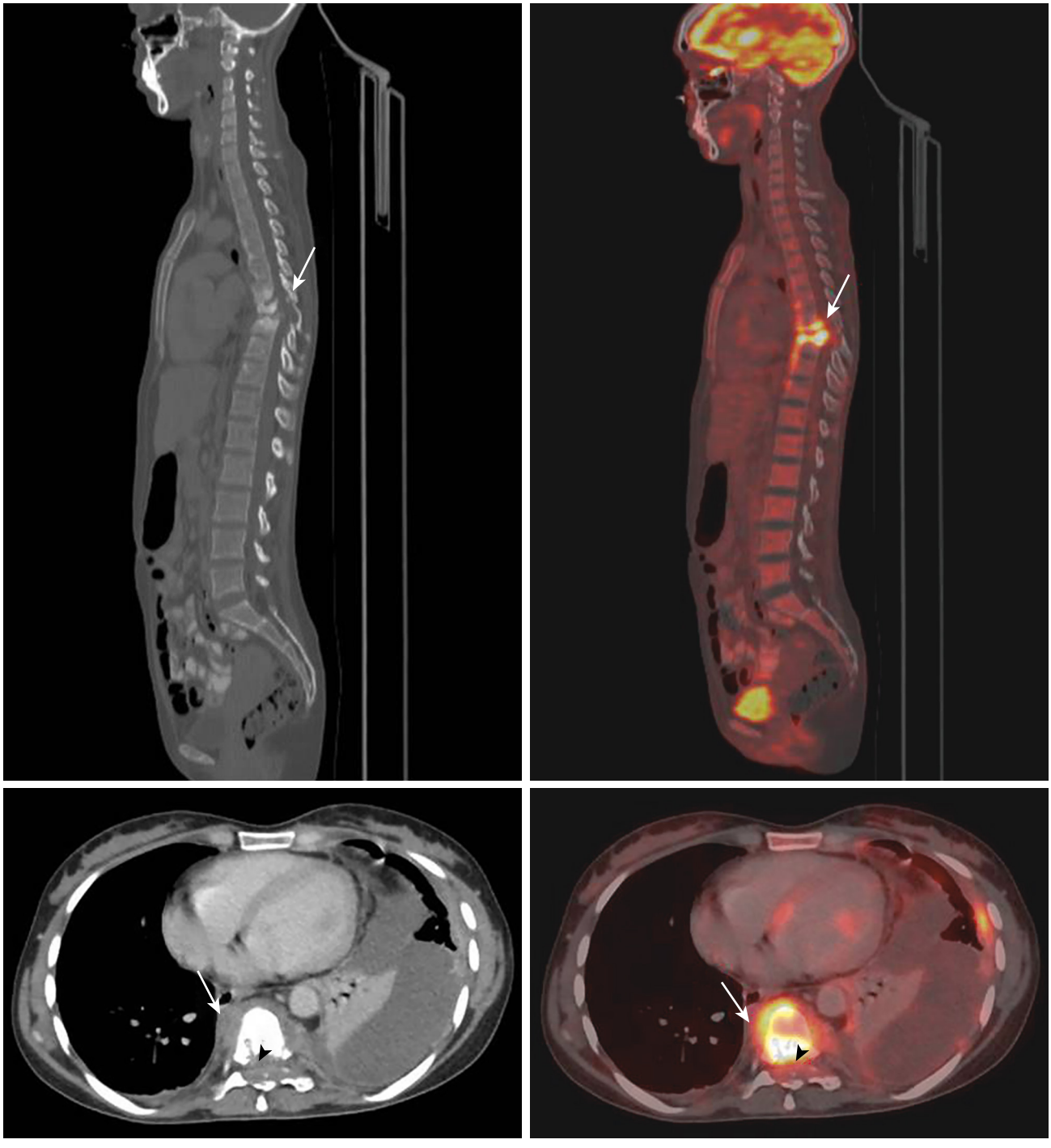

FIGURE 299-7. Pott disease. Computed tomography (CT) *(left panel)* and ^{18}F-fluorodeoxyglucose positron emission tomography (^{18}F-FDG PET)/CT-fused images *(right panel)*: transaxial and sagittal sections. Moderate to intense ^{18}F-FDG uptake is seen in a paravertebral soft tissue mass lesion extending from the level of T7–T10 vertebrae with associated lytic sclerotic changes in T7–T9 vertebrae and collapse of the T8 vertebra *(arrows)*. The lesion infiltrates into the spinal canal at the level of the T8 vertebra and involves the spinal cord *(small arrow)*. The lesion is seen to extend along the left costal margin, with faint ^{18}F-FDG uptake and foci of calcification, likely representing a cold abscess (courtesy of Prof. B.R. Mittal). (From Skoura E, Zumla A, Bomanji J. Imaging in tuberculosis. *Int J of Inf Dis*. 2015;32:87-93.)

Immunologic Manifestations of TB

Hypersensitivity reactions to mycobacterial antigens can lead to erythema nodosum and erythema induratum (see Figs. 407-24 and 407-25), both of which cause subcutaneous nodules, most often on the lower extremities. These immune-mediated cutaneous reactions (termed tuberculids) differ from cutaneous TB that is due to actual infection of the skin. When reactive arthritis occurs in conjunction with erythema nodosum, the syndrome is referred to as Poncet disease.

TB-associated immune reconstitution inflammatory syndrome (Chapter 358), which is an exuberant inflammatory response in the context of reduced immunosuppression and high burden of *M. tuberculosis* antigen, occurs in 5 to 50% of patients who are started on antiretroviral therapy for HIV (see HIV-TB coinfection, later).[19] The immune recovery can lead to a dysregulated inflammatory response against *M. tuberculosis* antigens, with either a paradoxical clinical worsening (e.g., fever, lymphadenitis) or unmasking of previously undiagnosed TB. TB-associated immune reconstitution inflammatory syndrome that involves the central nervous system is associated with a high morbidity and mortality. Paradoxical reactions after initiating appropriate TB therapy also can lead to clinical or radiologic worsening in patients without HIV.

DIAGNOSIS

Skin Testing for Latent TB Infection

Latent tuberculosis infection is defined by the absence of TB symptoms and signs, together with a positive test indicating the presence of delayed-type hypersensitivity to TB antigens. By definition, the diagnosis of latent tuberculosis infection first requires that active TB be excluded, followed by a

positive indirect test that indicates the presence of *M. tuberculosis*. In low-risk populations, most positive skin tests will be a false positive.[20] Testing for latent tuberculosis infection should be performed once to exclude latent TB and again after any potential re-exposure in persons with the following risk factors:

- Birth or residence in a country in which the incidence rate of TB is high (TB incidence >100/100,000 population/year) or medium (TB incidence 10 to 100/100,000 population/year) regardless of year of emigration. These countries include most countries in Asia, Africa, Latin America, the Pacific Islands, and Eastern Europe.
- Close contact to someone with infectious TB disease.
- Immunosuppression, current or planned, including HIV infection; organ transplantation; or treatment with a TNF-α antagonist (e.g., infliximab, etanercept, others), corticosteroids (equivalent of prednisone ≥2 mg/kg/day, or ≥15 mg/day for ≥1 month), or other immunosuppressive medication.
- Other medical conditions or social circumstances that meet criteria in state or local recommendations, such as homelessness, incarceration, or occupational risk of TB. In cases with potential ongoing exposure, annual testing may be indicated.

No gold standard determines the presence or absence of latent tuberculosis infection, so clinical judgment is required to interpret these indirect tests.

The Mantoux tuberculin skin test uses an intradermal injection of five tuberculin units of *M. tuberculosis* purified protein derivative (PPD). After 48 to 72 hours (and up to 96 hours), the width of dermal reaction reflects infiltration of host immune effector cells. Cut points define a positive test based upon the prior probability of infection and the likelihood of progression to active TB if infected (see Table 299-1).

The tuberculin skin test is highly dependent upon appropriate storage, correct administration, and accurate interpretation. The response to the test can also be nonspecific: a positive response may reflect exposure to nontuberculous mycobacteria or to prior bacille Calmette-Guérin (BCG) vaccination rather than to *M. tuberculosis* infection. Given these limitations, the interferon-gamma release assay (IGRA), described later, is the test of choice in persons with a history of BCG vaccination. A confirmatory IGRA should be performed if a patient has a positive tuberculin skin test result without any known risk for TB exposure or has a history of BCG vaccination. Response to the tuberculin skin test wanes over time, so a positive reaction may disappear by 10 years after infection but may reappear after being "boosted" by a PPD/tuberculin skin test or by exposure to environmental nontuberculous mycobacterial antigens. A boosted PPD/tuberculin skin test response is not a false-positive response, but it does not reflect recent TB infection. If individuals undergo serial PPD/tuberculin skin tests, such as employees in health care settings, a two-step approach should be used for first-time testing: if the initial test is negative, a second test administered at least a week after the first test to unmask a waned tuberculin skin test response. Because the booster phenomenon may last a year or more, failure to perform a two-step test in initial testing may give the false impression that an individual with a positive test on a subsequent annual test has acquired TB infection in the interim. When individuals are tested serially, a positive test (or tuberculin skin test "conversion") is defined by induration that increases by at least 6 mm compared with prior testing and results in 10 mm or greater induration. True skin test conversion within a 2-year period implies recent infection and is a significant risk factor for progression to TB.

IGRA blood testing is generally preferred over the tuberculin skin test for the diagnosis of latent tuberculosis infection.[21] Two assays are licensed in the United States: the QuantiFERON-TB Gold Plus (QFT-G+) and the T-SPOT.*TB* (Tspot). Both tests measure the amount of IFN-γ released by T lymphocytes in response to exposure to TB-specific antigens. These antigens are not present in BCG or most nontuberculous mycobacteria (exceptions include *Mycobacterium kansasii*, *Mycobacterium marinum*, *Mycobacterium gordonae*, and *Mycobacterium szulgai*), so these tests are much more specific than the tuberculin skin test, and they should be used in persons with a history of BCG vaccination. Other advantages of the IGRAs include objective measures of response that are not subject to inter-rater measurement variability and the lack of need for a return visit to measure the response. Disadvantages include cost and, in some instances, the reproducibility of the results. The QFT-G+ is an enzyme-linked immunosorbent assay (ELISA)–based test that is considered positive if the result is ≥0.35 IU/mL. However, a significant number of individuals with results just above this threshold will subsequently have a negative test, so current recommendations suggest repeat testing in a person with a positive result if the prior probability for a positive test is low. Repeat testing is also recommended for indeterminate QFT-G+ or invalid Tspot results, which reflect the failure of a positive or negative control in the test.

Testing with both a Mantoux tuberculin skin test and an IGRA is warranted in persons who are both at high epidemiologic risk of TB infection (e.g., household contact of recently diagnosed person with pulmonary TB) and at high risk for progression to active TB if infected (e.g., poorly controlled HIV). If either the PPD/tuberculin skin test or the IGRA is positive, treatment for latent tuberculosis infection is indicated. PPD/tuberculin skin test may be preferred in household contact investigations because it may turn positive earlier than an IGRA. In some instances, treatment for latent tuberculosis infection may be warranted despite a negative tuberculin skin test and IGRA, for example, in a person with poorly controlled HIV who resides in a household where there is evidence for household transmission or in a person with poorly controlled HIV who lives in a country with a high TB burden.

The sensitivity of these tests is reduced in immunocompromised persons, persons with sarcoidosis, after live virus vaccination, and in persons with active TB. In instances in which both a measles/mumps/rubella vaccination and a TB test are indicated, both may be administered simultaneously. However, if a live virus vaccine has already been given more than 1 day prior, at least 28 days should elapse before administering the PPD/tuberculin skin test or IGRA. These tests cannot be used to exclude or establish a diagnosis of active TB. In addition, both the tuberculin skin test and IGRA tests typically remain positive despite treatment for latent tuberculosis infection, although their degree of positivity may wane over time. Treated and untreated patients should be instructed that no further testing for latent tuberculosis infection is indicated because no change in the results is expected.

Active Tuberculosis

In countries with limited resources and a high burden of TB, the diagnosis of active TB may be based solely upon typical clinical symptoms and signs, with or without sputum microscopy. All persons with TB should be tested for HIV because of its strong epidemiologic association with TB.

An empiric treatment approach has the advantage of early treatment of persons who are at high risk of rapid progression of disease, such as individuals with advanced HIV disease, but it also leads to overdiagnosing and overtreating TB, as well as failing to detect drug resistance. In higher-resource settings, empiric TB treatment, if required, should be done in concert with procedures to confirm the diagnosis and characterize drug susceptibility. In some cases, particularly in patients with paucibacillary disease in which the number of organisms is small in clinical specimens (e.g., extrapulmonary TB), observing an appropriate response to standard TB therapy while excluding alternative diagnoses may be the only way to confirm TB.

Pulmonary TB

The diagnosis of pulmonary TB begins with a careful history and clinical suspicion. Patients with pulmonary TB typically have had symptoms for weeks to months. Although patients may minimize these symptoms, they are usually more than sufficient to warrant radiographic imaging, which usually shows pulmonary infiltrates (see Figs. 299-4 and 299-5). A misdiagnosis of community-acquired pneumonia (Chapter 85) may lead to inappropriate treatment with one of the respiratory quinolones, which have activity against TB and can provide transient clinical improvement and delay the correct diagnosis. These errors are more common in low-prevalence areas, where experience in the diagnosis of TB is limited.

When pulmonary TB is suspected, sputa should be collected for microscopic examination, culture, and PCR testing. Three sputum specimens should be collected at least 8 hours apart, with two of them collected in the morning on separate days. Sputum induction with aerosolized saline increases the yield. The gold standard for diagnosis is growth of *M. tuberculosis* in culture, typically within 1 to 3 weeks by modern testing methods. PCR testing and direct microscopic examination can yield a diagnosis more quickly, but they are less sensitive than culture. Fluorochrome stains, which are standard in clinical TB laboratories, are more sensitive for detecting *M. tuberculosis* than classical AFB stains, but approximately 50% of patients with pulmonary TB are sputum smear negative. DNA amplification testing by GenXpert MTB/RIF, which is more than 95% sensitive and specific in diagnosing TB from smear-positive sputum, can rapidly confirm the diagnosis of TB and detect the presence of *rpoB* mutations that confer rifampin resistance, which is strongly correlated with multidrug-resistant TB. When the clinical suspicion is high, it is worthwhile to perform PCR testing on three smear-negative specimens, for which its sensitivity is approximately 70%. If TB is not confirmed by direct testing of sputa using DNA amplification, *M. tuberculosis* can be confirmed by testing with DNA probes or other methods as soon as growth is detected in selective mycobacterial media.

Lipoarabinomannan, a glycolipid of the *M. tuberculosis* cell wall, can be detected in the urine of patients with pulmonary or extrapulmonary TB and advanced HIV, but this test is not available in the United States. In patients who are from high-prevalence countries and who are unable to produce sputum, a gastric aspirate for AFB smear and TB DNA testing is a potential option.

Although the majority of patients with pulmonary TB can be diagnosed by noninvasive means, bronchoscopy with bronchoalveolar lavage may be required to diagnose TB or make an alternative diagnosis, particularly in severely ill or immunocompromised patients in whom diagnostic delays may lead to poor outcomes. In many cases, the diagnosis rests on the clinical and radiographic response to therapy in the appropriate epidemiologic setting.

Extrapulmonary TB

Extrapulmonary TB often presents a diagnostic challenge. As with pulmonary TB, an index of suspicion is required to maximize the likelihood for making a diagnosis. The number of organisms in an extrapulmonary specimen is smaller than in pulmonary TB, so negative AFB stains and cultures are common. Furthermore, if a tissue is biopsied and infection is not initially considered, the sample may be placed in formalin and not submitted to the microbiology laboratory. PCR for TB can be performed by reference laboratories on fixed tissue, but the sensitivity is lower than with culture, particularly for specimens that stain negatively for AFB.

AFB stains, cultures, and TB DNA amplification should be performed on normally sterile fluids in persons with suspected TB. The yield of AFB stains and culture on these fluids is lower than in tissue, so large volumes should be submitted.

The cerebrospinal fluid (CSF) in TB meningitis may show a predominance of neutrophils but classically shows a lymphocytic CSF pleocytosis (although polymorphonuclear leukocytes may also predominate), with a low glucose level and a modestly elevated protein level. Rarely, TB meningitis may be eosinophilic (Chapter 381). A magnetic resonance imaging (MRI) scan of the head can show contrast enhancement of the basilar meninges, infarctions, hydrocephalus, and focal inflammatory lesions (tuberculomas).

For TB adenitis, lymph node biopsy or aspirations will typically show granulomas (except in patients who are on TNF inhibitors), with or without acid-fast organisms, and cultures are positive in approximately 70% of cases. Infected pleural (Chapter 86), pericardial (Chapter 62), and peritoneal (Chapter 128) fluids are exudative with a low glucose level and a lymphocytic predominance. Pleural effusions or ascites caused by TB may be chylous.

In pleural TB, the pleural fluid is often paucibacillary, so a pleural biopsy may be needed to diagnose TB pleuritis. In TB empyema, smears and cultures of the pleural fluid are usually positive, thereby making pleural biopsy unnecessary.

In TB peritonitis, ascitic fluid is most often exudative, and it is commonly negative for acid-fast bacilli on smear and culture. The highest diagnostic yield is achieved with peritoneal biopsy. For intestinal TB (due to either *M. tuberculosis* or *M. bovis*), histopathology and culture are used to establish the diagnosis. TB involving the genitourinary tract is suggested by sterile pyuria and can be diagnosed by culturing an early morning urine sample specifically for mycobacteria.

TB pericardial effusions (Chapter 62) may be massive and hemorrhagic. Malignancy, empyema, and rheumatologic disorders may also result in exudative effusions with low glucose levels. In TB pericarditis, *M. tuberculosis* can often be cultured from the fluid, although pericardial biopsy is more sensitive.

The possibility of nontuberculous mycobacteria (Chapter 300) should be considered in appropriate clinical circumstances, as should other infectious agents that may result in granulomas with negative AFB stains, including, but not limited to, endemic fungal infections (Chapter 308), cryptococcus (Chapter 309), bartonella (Chapter 291), and coxiella (Chapter 302). Noninfectious causes of granulomatous inflammation in various tissues include sarcoidosis (Chapter 83), Crohn disease (Chapter 127), lymphoma, and granulomatosis with polyangiitis (Chapter 249).

TREATMENT

Latent TB Infection

Treatment of latent TB infection reduces the lifetime risk of active TB by 75 to 90%, depending on adherence to treatment.[22] Three rifamycin-based regimens are preferred over two alternative isoniazid-based regimens (Table 299-2 and https://www.cdc.gov/tb/topic/treatment/ltbi.htm), because the former require shorter durations of therapy.

The strongly recommended regimen is 3 months of rifapentine plus isoniazid given weekly for 12 doses to adults, including patients with HIV infection, unless there are contraindicated drug interactions.[23] Directly observed therapy (DOT), whereby a health care provider or another designee watches a person with TB take each dose, assists with adherence to therapy and detection of adverse drug events. When administered by directly observed therapy, this regimen is as effective as 9 months of daily isoniazid, with superior completion rates (despite higher rates of discontinuation due to side effects) and less hepatotoxicity in HIV-negative patients.[A1] The completion rate for self-administered therapy is inferior to the completion rate with directly observed therapy, except in the United States.[A2] Disadvantages of this regimen include cost, particularly if provided by direct observation, pill burden, and a 1 per 1000 persons risk of hypotension and syncope severe enough to require hospitalization but not to cause death. The second preferred regimen is 4 months of daily rifampin, which is appropriate for HIV-negative adults but without sufficient evidence to recommend it in HIV-positive patients. It is equivalent in effectiveness, has higher rates of completion, and is less toxic than 9 months of isoniazid.[A3] The primary disadvantage of this regimen is drug-drug interaction with many medications, including but not limited to methadone, hormonal contraceptives, azole antifungals, and warfarin. Rifabutin has fewer drug interactions and may be used in some cases when rifampin is contraindicated. The third preferred regimen is 3 months of rifampin plus isoniazid for adults, including HIV-positive patients, barring contraindicated drug interactions. It appears to have similar effectiveness and risks of toxicity compared with 6 months of isoniazid.

Six months of daily isoniazid is an alternative regimen that is highly effective for HIV-negative adults and conditionally recommended for HIV-positive adults. Among HIV-positive persons living in an area with a high incidence of TB, 6 months of daily isoniazid is complementary to antiretroviral therapy in preventing TB disease regardless of IGRA results. Nine months of isoniazid is an alternative regimen for adults who are HIV-positive or HIV-negative. When isoniazid is prescribed, pyridoxine (25 to 50 mg daily) should be administered to prevent peripheral neuropathy. Baseline liver tests should be obtained in patients who are over age 35 years, are infected with HIV, or have underlying liver disease or significant alcohol use. Laboratory monitoring (see Drug Monitoring, later) for potential drug toxicity is recommended only in patients who have symptoms or signs suggestive of toxicity.

Active Pulmonary Tuberculosis

All patients who have active TB should be managed by or with the guidance of an experienced TB clinician. Within the United States, expertise is available through the National TB Centers of Excellence. Outside the United States, expertise can be obtained through groups such as the Global TB Network, a working group within the World Association for Infectious Diseases and Immunological Disorders (http://www.waidid.org/site/workinggroups).

All TB patients should have their isolates tested for drug susceptibility. Molecular methods enable rapid identification of TB in appropriate specimens and identify drug-resistant TB. Commercially available molecular technology (Xpert MTB/RIF) simultaneously detects *M. tuberculosis* DNA and the presence of rifampin-resistance mutations. Substantial data can guide the choice of drug regimens for patients with drug-susceptible TB or drug-resistant TB, as well as how to screen for potential adverse events and manage any that occur. For example, resistance to rifampin strongly correlates with multidrug-resistant TB.

Treatment of persons with TB serves the dual role of curing the disease in the individual and preventing its spread to others. In the United States, most treatment is provided in public health clinics or academic centers under the guidance of the four regionally assigned TB Centers of Excellence, which cover all 50 states and U.S. territories (https://www.cdc.gov/tb/education/tb_coe/default.htm).

Patients who have pulmonary TB are considered infectious until they have had at least 2 weeks of therapy, show a clinical response (e.g., reduced cough, weight gain, resolution of fever and night sweats), and have no detectable acid-fast bacilli by microscopy on three sputum specimens at least 8 hours apart. Patients may be discharged from the hospital prior to being noninfectious if they are tolerating TB therapy and are going to their own homes or to facilities with proper isolation rooms, provided that the clinicians have notified the appropriate health department, verified contact information, and have a follow-up plan in place.

Follow-up must include monthly visits for clinical assessment and examination of sputum until the sputum is negative on at least two consecutive cultures. By 2 months after the start of therapy, about 75 to 80% of patients with pulmonary TB will be sputum culture negative, and about 95% will be negative after 3 months. If the sputum culture is persistently positive at 3 months, causes include nonadherence, low therapeutic drug levels, an alternative or complicating diagnosis, and unrecognized or emerging drug resistance. A positive sputum culture at 4 months defines treatment failure, which is rare in properly treated drug-sensitive disease and should prompt expert guidance and more complex treatment options. A single drug should never be added to a failing TB regimen, since this approach promotes further resistance.

Treatment of active TB requires multidrug therapy to prevent the selection of resistant organisms.[24] In drug-susceptible pulmonary TB, an initial four-drug intensive phase for 8 weeks is followed by a two-drug continuation phase for 4 to 6 months (Tables 299-3, 299-4, and 299-5). Rifampin (or rifabutin in selected patients who are intolerant to rifampin or in whom it risks drug-drug interactions), isoniazid, pyrazinamide, and ethambutol comprise the intensive phase,

TABLE 299-2 ADULT ORAL DOSES FOR TREATMENT OF LATENT TUBERCULOSIS INFECTION TREATMENT REGIMENS

DRUG	DURATION	DOSE PER KG BODY WEIGHT	FREQUENCY	TOTAL DOSES
PREFERENCE ROUTINES				
1. Isoniazid* and rifapentine†	3 mo	Isoniazid: 15 mg/kg rounded up to the nearest 50 or 100 mg (maximum dose 900 mg) Rifapentine: 25.1-32.0 kg 600 mg 32.1-49.9 kg 750 mg ≥50.0 kg 900 mg (maximum dose)	Once weekly	12
2. Rifampin‡	4 mo	10 mg/kg (maximum dose 600 mg)	Daily	120
3. Isoniazid* and rifampin‡	3 mo	Isoniazid*: 5 mg/kg (maximum dose 300 mg) Rifampin‡: 10 mg/kg (maximum dose 600 mg)	Daily	90
4. Isoniazid*	6 mo	5 mg/kg (maximum dose 300 mg)	Daily	180
		15 mg/kg (maximum dose 900 mg)	Twice weekly§	52
5. Isoniazid	9 mo	5 mg/kg (maximum dose 300 mg)	Daily	270
		15 mg/kg (maximum dose 900 mg)	Twice weekly§	76

*Isoniazid is formulated as 100-mg and 300-mg tablets. Note: pyridoxine (vitamin B_6), 25 to 50 mg/day, is given with isoniazid to all persons at risk of neuropathy.
†Rifapentine is formulated as 150-mg tablets in blister packs that should be kept sealed until use.
‡Rifampin (rifampicin) is formulated as 150-mg and 300-mg capsules.
§Must be provided by directly observed therapy (i.e., a health care worker observes the ingestion of medication).

TABLE 299-3 TREATMENT OF DRUG-SUSCEPTIBLE PULMONARY TUBERCULOSIS (SEE TABLES 299-4, 299-5, AND 299-6 FOR DOSING)

	INTENSIVE PHASE		*CONTINUATION PHASE*			
REGIMEN	**DRUG***	**INTERVAL AND DOSE* (MINIMUM DURATION)**	**DRUGS**	**INTERVAL AND DOSE* (MINIMUM DURATION)†**	**COMMENTS‡**	**REGIMEN EFFECTIVENESS**
1	Isoniazid Rifampin Pyrazinamide Ethambutol	5 or 7 days/week for 8 weeks	Isoniazid Rifampin	5 or 7 days/week for 18 weeks	Preferred for newly diagnosed pulmonary tuberculosis	Greater
2	Isoniazid Rifampin Pyrazinamide Ethambutol	5 or 7 days/week for 8 weeks	Isoniazid Rifampin	3 times weekly for 18 weeks	Preferred alternative when more frequent DOT is difficult to achieve	
3	Isoniazid Rifampin Pyrazinamide Ethambutol	3 times weekly for 8 weeks	Isoniazid Rifampin	3 times weekly for 18 weeks	Missed doses can lead to treatment failure, relapse, and acquired drug resistance, especially in patients with HIV and/or cavitary disease	
4	Isoniazid Rifampin Pyrazinamide Ethambutol	7 days/week for 2 weeks, then twice weekly for 6 weeks	Isoniazid Rifampin	Twice weekly for 36 doses (18 weeks)	Do not use twice-weekly regimens in HIV-infected patients or patients with smear-positive and/or cavitary disease	Lesser

*When DOT is used, drugs may be given 5 days per week. DOT should be used when drugs are administered <7 days per week.
†Patients with cavitary disease and positive cultures at completion of 2 months of therapy should receive a 7-month continuation phase.
‡Pyridoxine (vitamin B_6), 25-50 mg/day, is given with isoniazid to all persons at risk of neuropathy (e.g., pregnant women; persons with human immunodeficiency virus; patients with diabetes, alcoholism, malnutrition, or chronic renal failure; or patients with advanced age). For patients with a pre-existing peripheral neuropathy, the pyridoxine dose should be increased to 100 mg/day.
DOT = directly observed therapy; HIV = human immunodeficiency virus.
Adapted from Nahid P, Dorman SE, Alipanah N, et al. Official American Thoracic Society/Centers for Disease Control and Prevention/Infections Diseases Society of America clinical practice guidelines: treatment of drug-susceptible tuberculosis. *Clin Infect Dis*. 2016;63:e147-e195.

TABLE 299-4 ADULT DOSES OF ANTITUBERCULOSIS DRUGS

DRUG	PREPARATION	POPULATION	DAILY	THRICE WEEKLY (SEE TABLE 299-3)
FIRST-LINE DRUGS				
Isoniazid	Tablets (50 mg, 100 mg, 300 mg)	Adults	5 mg/kg (typically 300 mg)	15 mg/kg (typically 900 mg)
Rifampin	Capsule (150 mg, 300 mg)	Adults	10 mg/kg (typically 600 mg)	10 mg/kg (typically 600 mg)
Pyrazinamide	Tablet (500 mg scored)	Adults	See Table 299-5	See Table 299-5
Ethambutol	Tablet (100 mg; 400 mg)	Adults	See Table 299-5	See Table 299-5

Modified from Nahid P, Dorman SE, Alipanah N, et al. Official American Thoracic Society/Centers for Disease Control and Prevention/Infectious Diseases Society of America Clinical Practice guidelines: treatment of drug-susceptible tuberculosis. *Clin Infect Dis*. 2016;63:e147-e195.

TABLE 299-5 PYRAZINAMIDE AND ETHAMBUTOL DOSES, USING WHOLE TABLETS, IN ADULTS WITH NORMAL RENAL FUNCTION

	WEIGHT, Kg*,†		
	40-55	56-75	76-90
PYRAZINAMIDE			
Daily (mg/kg)	1000 mg (18.2-25.0)	1500 mg (20.0-26.8)	2000 mg (22.2-26.3)
Thrice weekly (mg/kg)	1500 mg (27.3-37.5)	2500 mg (33.3-44.6)	3000 mg (33.3-39.5)
Twice weekly (mg/kg)	2000 mg (36.4-50.0)	3000 mg (40.0-53.6)	4000 mg (44.4-52.6)
ETHAMBUTOL			
Daily (mg/kg)	800 mg (14.5-20.0)	1200 mg (16.0-21.4)	1600 mg (17.8-21.1)
Thrice weekly (mg/kg)	1200 mg (21.8-30.0)	2000 mg (26.7-35.7)	2400 mg (26.7-31.6)
Twice weekly (mg/kg)	2000 mg (36.4-50.0)	2800 mg (37.3-50.0)	4000 mg (44.4-52.6)

*Based on estimated lean body weight. Optimal doses for obese patients are not established.
†Numbers in parentheses are the calculated mg/kg doses for patients at the highest and lowest body weights in the weight band.

which should be followed by rifampin and isoniazid in the continuation phase. Ethambutol can be discontinued if drug susceptibility studies demonstrate that the patient's isolate is sensitive to both isoniazid and rifampin. The precise duration of the continuation phase is determined by the presence or absence of cavitary disease and the rapidity of the microbiologic response to therapy. For nonresistant TB infection, 4 months of therapy with rifapentine, moxifloxacin, isoniazid, and pyrazinamide might be as good as 6 months of four-drug therapy with rifampin, isoniazid, pyrazinamide, and ethambutol[A4]; however, both groups in that study had high rates of unfavorable outcomes, so further studies will be required to recommend this shorter regimen. Vitamin B_6 (pyridoxine) supplementation often is used in all patients but is especially recommended in patients who are at risk for isoniazid-induced peripheral neuropathy (e.g., pregnant women, elderly patients, or patients with HIV, diabetes, alcoholism, malnutrition, or chronic renal failure). For patients with peripheral neuropathy, experts recommend the pyridoxine dose should be 100 mg/day. Some experts substitute linezolid (600 mg daily),[A5] moxifloxacin (400 mg orally daily), or levofloxacin (750 mg orally daily) for ethambutol during the intensive phase when ethambutol is contraindicated or instead of isoniazid throughout treatment in adults in whom isoniazid cannot be used because of side effects or resistance to it. Inclusion of pyrazinamide in the intensive phase of therapy allows completion of therapy after 26 weeks in persons whose sputum cultures convert to negative within 2 months of initiating treatment. For patients who are unable to tolerate pyrazinamide, similar outcomes are achieved with a 9-month regimen of isoniazid plus rifampin. Shorter courses of therapy using bedaquiline/linezolid plus isoniazid, pyrazinamide, and ethambutol have shown promising results in patients who have rifampin-susceptible TB.[A6]

Directly observed therapy, which is considered the standard of care for treatment of tuberculosis in the United States, is provided daily 5 days a week, with or without self-administered therapy on weekend days, preferably for the duration of therapy. Alternative administration schedules risk higher rates of relapse, but directly observed therapy administered three times weekly can be considered for the continuation phase in situations in which more frequent directly observed therapy is difficult to achieve; however, this schedule should be used with caution in patients who have HIV or cavitary disease. Twice-weekly regimens are generally discouraged. Daily electronic directly observed therapy using a secure connection is a suitable alternative to intermittent in-person directly observed therapy in patients who can use this technology (https://www.cdc.gov/tb/publications/pdf/tbedottoolkit.pdf). Multifaceted, patient-centered treatment strategies using enablers to remove economic barriers to treatment and incentives (food or cash) should be incorporated in case management programs to facilitate adherence and to promote patient satisfaction.

Drug Monitoring

Monitoring of therapeutic drug levels should be considered for patients who respond poorly to therapy, obese or frail patients, and patients who have HIV, severe renal insufficiency, or conditions associated with impaired drug absorption. Routine periodic laboratory monitoring is not required but is indicated for patients who report new fever, nausea, vomiting, abdominal pain, or unexplained weight loss, as well as for patients who may be unable or less likely to report these symptoms owing to language, cultural, or other barriers. Persons with TB should be carefully instructed to report these symptoms, and directly observed therapy personnel should be trained to inquire about and to document them systematically. Therapy should be interrupted if the alanine aminotransferase (ALT) level is 3 times or more the upper limit of normal in the presence of gastrointestinal symptoms or 5 times or more the upper of limit of normal in the absence of symptoms. Other causes of elevated aminotransferase levels should be sought (e.g., viral hepatitis [Chapter 134 and 135], biliary disease [Chapter 141], alcohol use [Chapter 138], and other hepatoxic prescription or over-the-counter drugs or supplements [Chapter 136]). The optimal approach to reintroduction of TB treatment is unknown and requires clinical judgment by a TB expert.

Extrapulmonary TB

Most patients with drug-sensitive extrapulmonary TB can be managed with standard 6- to 9-month therapy. Nine- to 12-month therapy is recommended for scrofula and for miliary, meningeal, bone, joint, genitourinary, gastrointestinal, or spinal TB. Surgical débridement may be required for bone or spinal TB. Adjunctive corticosteroids (e.g., dexamethasone 0.4 mg/kg/day for 7 days then 0.3 mg/kg/day for 7 days, then 0.2 mg/kg/day for 7 days, then 0.1 mg/kg/day for 7 days, then 4 mg/day for 7 days, and then tapered off by 1 mg/day each week) confer a mortality benefit in both HIV-negative and HIV-positive persons with TB meningitis (Chapter 381).[25] Clinical worsening may require that doses be increased or tapered more slowly. However, corticosteroids have no proven benefit for TB at other sites. Shunting may be required for TB-related hydrocephalus.

HIV-TB Coinfection

All persons with TB should be tested for HIV because of its strong epidemiologic association with TB. For TB-infected HIV patients who are not yet on antiretroviral therapy and have CD4 counts less than 50 cells/μL, antiretroviral therapy (Chapter 357) should be initiated within 2 weeks after TB therapy has begun, except a 2-week delay is recommended in patients with TB meningitis. For HIV-infected persons who have no overt evidence of TB, have low CD4 counts (<100/μL), and live in high-burden countries, empiric TB treatment is not superior to TB screening and targeted treatment and results in more side effects.[A7] Patients with low CD4 counts are at higher risk of TB-immune reconstitution inflammatory syndrome (Chapter 358) when antiretroviral therapy is initiated early than are patients with higher CD4 counts, but the mortality benefit from early antiretroviral therapy outweighs this risk. TB-immune reconstitution inflammatory syndrome, which is associated with apparent, paradoxical worsening of TB owing to inflammation associated with immune reconstitution, generally occurs 2 to 8 weeks after initiating antiretroviral therapy. The initiation of antiretroviral therapy also can unmask underlying TB when undiagnosed TB becomes clinically evident with immune reconstitution. For patients with CD4 counts 50/μL or higher, antiretroviral therapy should be started no later than 8 to 12 weeks after initial TB treatment.

For patients whose HIV is already being treated with antiretroviral therapy, standard daily 6-month TB therapy results in cure rates that are comparable to non–HIV-infected persons. Daily regimens reduce the risk of relapse compared with intermittent regimens, which are not recommended. For HIV-infected persons who have not been taking antiretroviral therapy, a continuation phase of 7 months is recommended (for a total of 9 months of therapy). A 7- to 10-month continuation phase is also recommended for patients who have cavitary disease and still have positive cultures at 2 months, as well as patients who have TB meningitis or TB of the bone, joint, or spine.

Because of the risk of significant drug-drug interactions (e.g., rifamycins with antiretroviral therapy owing to induction of hepatic CYP3A and the transporter P-glycoprotein), concomitant antiretroviral therapy and TB therapy are best managed by clinicians familiar with HIV, TB, and these interactions.[26] A practical, well-tolerated option to treat TB in suitable drug-susceptible patients substitutes standard-dose rifabutin for rifampin and uses an antiretroviral therapy approach composed of once-daily dolutegravir, once-daily tenofovir disoproxil fumarate, and emtricitabine. Rifampin may be used without dose adjustment with efavirenz-based regimens and adjusted to twice daily with dolutegravir-based regimens. Half-dose rifabutin may be used with ritonavir-boosted protease inhibitors, but nonadherence to this HIV treatment can result in subtherapeutic levels of rifabutin, thereby leading to rifamycin resistance. Tenofovir alafenamide–containing regimens are not recommended with either rifampin or rifabutin.

Drug-Resistant Tuberculosis

Monoresistance to isoniazid has no effect on the outcome of treatment when identified early and addressed appropriately. For patients with isoniazid-monoresistant TB, the isoniazid should be discontinued and replaced with moxifloxacin (400 mg daily orally) or levofloxacin (750 mg daily orally), if susceptible, as part of a 6-month regimen that also includes daily rifampin, ethambutol, and pyrazinamide.[A8] The duration of pyrazinamide can be shortened to 8 weeks for patients who have noncavitary pulmonary or extrapulmonary disease. If the organism is not sensitive to a fluoroquinolone, expert consultation is required. *M. tuberculosis* that is monoresistant to rifampin can also be treated successfully with oral antibiotics.[A9,A10]

Multidrug-resistant TB, which is defined by resistance to at least isoniazid and rifampin, requires the assistance of an expert in the treatment of

TABLE 299-6 DOSING RECOMMENDATIONS FOR ADULTS WITH CREATININE CLEARANCE <30 ML/MIN OR RECEIVING HEMODIALYSIS

DRUG	RECOMMENDED DOSE AND FREQUENCY
Isoniazid	300 mg once daily or 900 mg 3 times/week
Rifampin	600 mg once daily or 600 mg 3 times/week
Pyrazinamide	25-35 mg/kg 3 times/week
Ethambutol	20-25 mg/kg 3 times/week

Medications should be given after dialysis on the day of dialysis.
Monitoring of serum drug concentrations should be considered to ensure adequate drug levels and to avoid toxicity.
Based on estimated lean body weight. Optimal doses for obese patients are not established.

multidrug-resistant TB.[27,28] Failure to recognize and properly treat multidrug-resistant TB is associated with poor outcomes. An all-oral regimen is possible, as determined by drug susceptibility testing: five active drugs for a 5- to 7-month intensive phase, followed by four active drugs in the continuation phase that continues for a total treatment duration of between 15 and 21 months under expert guidance after cultures convert from positive to negative. Options for oral drugs include moxifloxacin or levofloxacin, bedaquiline, linezolid, clofazimine, and cycloserine under expert guidance.[A11,A12] Pyrazinamide and ethambutol are oral options if other, more effective drugs cannot be used to construct a five-drug regimen. If an effective all-oral regimen cannot be constructed, amikacin or a carbapenem (imipenem or meropenem) in conjunction with amoxicillin-clavulanate (as a source of clavulanate) may be used under expert guidance if the isolate is sensitive to these agents. Partial surgical resection in conjunction with medical therapy can be considered in selected patients who have localized pulmonary multidrug-resistant TB.

Extensive drug resistance (XDR-TB) is a subset of multidrug-resistant TB, with resistance to at least isoniazid, rifampin, a fluoroquinolone, and a second-line injectable agent (amikacin or streptomycin). Pre-extensively drug-resistant TB is an intermediate step between multidrug-resistant TB and extensively drug-resistant TB, with retained susceptibility to either a fluoroquinolone or to second-line injectable agents. The standard treatment approach to extensively drug-resistant TB and pre-extensively drug-resistant TB parallels multidrug-resistant TB treatment principles, with a total treatment duration of between 15 and 24 months after culture conversion. As with multiple-drug-resistant TB, treatment of extensive drug-resistant TB requires the assistance of an expert. A shorter option is a seven-drug regimen (moxifloxacin, kanamycin, ethionamide, clofazimine, high-dose isoniazid, pyrazinamide, and ethambutol) for 4 to 6 months, followed by four drugs (moxifloxacin, clofazamine, pyrazinamide, and ethambutol) for another 5 to 6 months, for a total course of 9 to 12 months.[A13,A14] A promising 6-month regimen combining bedaquiline (400 mg orally daily for 2 weeks, then 200 mg 3 times weekly for 24 weeks, for a total duration of 26 weeks), pretomanid (200 mg orally daily for 26 weeks), and linezolid (1200 mg orally daily for 26 weeks, with dose reductions to 600 mg for adverse reactions and further reduction to 300 mg for myelosuppression, peripheral neuropathy, or optic neuropathy) has shown good outcomes in patients with multidrug-resistant and extensively drug-resistant TB.

PREVENTION

Preventing future TB cases requires disrupting the infection cycle by preventing new infections and the reactivation of latent TB infection. Testing of household contacts of patients with pulmonary TB is an important aspect of preventing TB and central to infection control programs. Active case finding, prompt diagnosis, and effective treatment all limit the duration that a person is infectious. Optimizing environmental factors to minimize crowding and enhance ventilation also prevent transmission. In clinical settings, patients should be placed in negative air pressure rooms with high-efficiency particulate air (HEPA) filtration. The infected patient should wear a surgical mask, and health care personnel should wear a fit-tested N95 mask to reduce transmission of infectious respiratory particles.[29]

The global burden of individuals with latent tuberculosis infection represents a constant source of new infections. Treating patients with latent tuberculosis infection reduces their risk of developing active TB by 75 to 90%. In low-prevalence settings, recommendations focus on identifying and treating individuals by targeting the testing for latent tuberculosis infection towards persons who are at high risk of recent infection or progression to active disease (see Diagnosis and Treatment sections, earlier). Treatment of latent tuberculosis infection requires resources that are often beyond what is available in resource-limited settings, so it is not a common practice in high-burden countries. With a quarter of the world potentially infected with TB, being able to target latent tuberculosis infection treatment to persons most at risk of reactivation would strongly help focus resources of global infection control programs. For example, among people living with HIV, early initiation of antiretroviral therapy can prevent the development of active TB. Considerable interest has also focused on identifying biomarkers that might predict which individuals are at highest risk of reactivation. Transcriptomic-based risk signatures can discriminate between individuals who are likely to progress to active TB over 6 to 12 months, but a recent clinical trial failed to show benefit of signature-guided preventive therapy in reducing progression to active disease.[A15] For persons living with HIV in highly endemic areas outside of the United States where reinfection is likely, secondary prevention therapy with daily isoniazid (300 mg daily) for 6 months or with rifapentine/isoniazid (900 mg/900 mg) given once weekly for 3 months each year may reduce the likelihood of active infection.[A16]

An effective vaccine that prevents infection or disease progression would have a major impact in the TB epidemic. The bacille Calmette-Guérin (BCG) vaccine (an attenuated strain of *Mycobacterium bovis*) is effective in preventing severe forms of TB in children, but it does not provide reliable protection against active pulmonary disease in adults. In nonhuman primates, a CMV-based vaccine and BCG administered by the intravenous route provided unprecedented levels of protection. Although neither of these approaches may be clinically feasible, they provide, for the first time, the opportunity to define correlates of protection. In addition, a recent clinical trial in adolescents who received a booster of the BCG vaccine showed a potential reduction in infection,[A17] and the M72/AS01$_E$ vaccine candidate reduced disease progression in patients with latent tuberculosis infection.[A18] These recent advances provide an optimistic outlook for the development of a preventative or therapeutic TB vaccine.

PROGNOSIS

In the absence of treatment, approximately 50% of patients who develop active TB disease will succumb to it. By comparison, patients who have drug-susceptible TB and who successfully complete therapy have cure rates approaching 100%. For multiple-drug-resistant and extensive drug-resistant TB, the cure rates are 50 to 60% and 2 to 22%, respectively, but outcomes have been improving with new drug combinations. For example, a recent clinical trial using bedaquiline, pretomanid, and linezolid had a success rate of 90% in patients with extensive drug-resistant TB.[A19] Overall, treatment success is now reported in 85% of patients globally and 95% of patients in the United States.

After the first 2 weeks of effective treatment of pulmonary TB, bacterial colony counts decline by 99.9%, cough decreases, and patients quickly become noninfectious. Patients who have HIV and TB coinfection with drug-susceptible TB convert their sputum culture from positive to negative as quickly as non–HIV-infected patients and have similar outcomes compared with non–HIV-infected patients. However, patients who are successfully treated for pulmonary TB often have permanently impaired lung function.

Favorable outcomes for people living with HIV, the elderly, patients with diabetes, and other patients who have compromised immune systems depend upon early diagnosis and appropriate treatment.

If untreated, TB meningitis is rapidly fatal, with a median time to death from symptom onset of 19 days. Patients with TB meningitis have a mortality rate of about 25%, and HIV patients with TB meningitis have a mortality rate of nearly 50%, even when treated.

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For the General References and other additional features, please visit Elsevier eBooks+ at https://ebooks.health.elsevier.com.

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M. fortuitum	Line infections, lung
M. smegmatis	Almost never associated with disease
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M. marinum	Skin, tendons (fish tank granuloma)
M. xenopi	Lung
M. simiae	Lung
M. szulgai	Lung
M. malmoense	Lung
M. scrofulaceum	Lymph node
M. haemophilum	Disseminated, skin
M. genavense	Disseminated
M. ulcerans	Skin (Buruli ulcer; toxin producing)
M. neoaurum	Disseminated
M. celatum	Disseminated
M. gordonae	Almost never causes disease
M. terrae complex	Disseminated

M. = *Mycobacterium*.

300 THE NONTUBERCULOUS MYCOBACTERIA

STEVEN M. HOLLAND AND KENNETH N. OLIVIER

DEFINITION

Nontuberculous mycobacteria generally include the growing number of mycobacteria other than *Mycobacterium tuberculosis* and its close relatives (Chapter 299) and *M. leprae* (Chapter 301). Other names that have been used include *atypical mycobacteria*, *mycobacteria other than tuberculosis*, and *environmental mycobacteria*. Over 190 species of nontuberculous mycobacteria are now known, and the number continues to grow as DNA sequencing identifies additional species.

The Pathogens

Nontuberculous mycobacteria are acid-fast bacteria that differ from tuberculous mycobacteria, primarily by their reservoir or mode of acquisition. Nontuberculous mycobacteria are acquired from the environment, whereas *M. tuberculosis* is acquired primarily from person-to-person transmission. Nontuberculous mycobacteria are broadly differentiated into rapidly growing (<7 days) and slowly growing (>7 days) forms. *M. tuberculosis*, by contrast, typically requires 2 or more weeks to grow. Formation of pigment in light (photochromogens) or dark (scotochromogens) and lack of pigment (nonchromogens) can also help categorize nontuberculous mycobacteria. Current diagnostics use both mass spectrometry and molecular based methods including probes or gene sequencing for speciation (Table 300-1). For purposes of diagnosis, prognosis, and therapy, identification of nontuberculous mycobacteria should be taken to the species level.

EPIDEMIOLOGY

As a group, the nontuberculous mycobacteria are ubiquitous in soil and water. They are often found in certain animals (e.g., *M. avium* subspecies *paratuberculosis* cause Johne disease in cattle, whereas *M. avium* or *M. genavense* cause avian tuberculosis), but they rarely cause disease in humans. Human-to-human transmission of nontuberculous mycobacteria is rare, but *M. abscessus* subspecies *massiliense* has caused outbreaks of infection in cystic fibrosis centers.

Because these infections are not reported to health agencies and because their identification is sometimes problematic, reliable data on incidence and prevalence are lacking. Worldwide, documented infections with nontuberculous mycobacteria are increasing,[1] and isolates of nontuberculous mycobacteria have exceeded those for *M. tuberculosis* in the United States for many years. In patients with cystic fibrosis (Chapter 77), for example, rates of clinical nontuberculous mycobacterial infection range up to 40% in older patients, but even more patients harbor the organism. Differentiating active disease from commensal harboring of the organism remains problematic. Other patients, including patients with bronchiectasis (Chapter 78), also have elevated but undefined rates of nontuberculous mycobacterial infection. The bulk of nontuberculous mycobacterial disease in North America is due to *M. kansasii*, *M. avium* complex (MAC),[2] and *M. abscessus*.

Predisposing factors for lung infections include underlying lung disease,[3] such as bronchiectasis (Chapter 78),[4] pneumoconiosis (Chapter 81), chronic obstructive pulmonary disease (Chapter 76), primary ciliary dyskinesia (Chapter 78), and cystic fibrosis (Chapter 77).[5] Bronchiectasis and nontuberculous mycobacterial infection often coexist and progress in tandem, thereby making causality difficult to determine. Patients with pulmonary alveolar proteinosis (Chapter 79) are prone to pulmonary nontuberculous mycobacterial and *Nocardia* infections (Chapter 306), likely reflecting their association with anti–granulocyte-macrophage colony-stimulating factor (anti–GM-CSF) autoantibodies and impaired alveolar macrophage function.

M. avium complex infection most commonly occurs in women in their sixth or seventh decades. When compared with male smokers with upper lobe cavitary disease, who tend to carry the very same single strain of *M. avium* complex indefinitely, nonsmoking females with nodular bronchiectasis tend to have several strains simultaneously, which also change over the course of their disease process.

Esophageal motility disorders such as achalasia (Chapter 124) have been associated with pulmonary disease, especially that caused by rapidly growing nontuberculous mycobacteria such as *M. abscessus*. Numerous outbreaks of skin infections caused by rapidly growing mycobacteria have been due to skin contamination from instruments used for surgical procedures (especially cosmetic surgery), injections, and other procedures.

PATHOBIOLOGY

Exposure to nontuberculous mycobacteria is essentially universal, but disease is rare, so normal host defenses must be highly effective. For *M. avium* complex, the portal of entry that leads to dissemination is the bowel, with subsequent spread to bone marrow and the blood stream.

$CD4^+$ T lymphocytes are key effectors against nontuberculous mycobacteria, and patients with advanced human immunodeficiency virus (HIV) infection are especially susceptible to disseminated mycobacterial infection (Chapter 358).

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$CD4^+$ T lymphocytes are key effectors against nontuberculous mycobacteria, and patients with advanced human immunodeficiency virus (HIV) infection are especially susceptible to disseminated mycobacterial infection (Chapter 358).

ABSTRACT

Nontuberculous mycobacterial infections are increasing in frequency but remain difficult to diagnose and complicated to manage. The two broad categories of clinical disease are disseminated disease and pulmonary disease. Disseminated disease, which often occurs earlier in life, reflects immune failure to restrict nontuberculous mycobacteria to epithelial compartments and is almost always due to an underlying immune deficiency, either congenital (e.g., mutations in the IFN-γ/IL-12 pathway) or acquired (e.g., HIV). Autoantibodies to IFN-γ block the critical cytokine pathway that controls nontuberculous mycobacteria, thereby leading to disseminated disease. In contrast, pulmonary disease tends to occur in older adults and almost never disseminates. Pulmonary disease usually occurs in the setting of bronchiectasis and may be associated with either underlying congenital lung disease (e.g., cystic fibrosis or primary ciliary dyskinesia) or acquired lung disease (e.g., tobacco-related damage). Although these infections are typically acquired from the environment, person-to-person transmission can occur among patients who have cystic fibrosis. *Mycobacterium abscessus* lung disease is increasing in North America. Prolonged multidrug therapy, which is the cornerstone of treatment, may extend over years, especially for lung disease.

KEYWORDS

interferon gamma
interleukin-12
bronchiectasis
immunodeficiency
disseminated

Specific mutations in the interferon (IFN)-γ/interleukin (IL)-12 synthesis and response pathways also predispose to dissemination, but only about 70% of non-HIV patients with disseminated infection have an identifiable genetic mutation. Autoantibodies to IFN-γ mimic genetic defects in the pathway.

Mycobacteria are typically phagocytosed by macrophages, which respond with the production of IL-12, a heterodimer composed of p35 and p40 moieties that together constitute IL-12p70 (E-Fig. 300-1). IL-12 activates T lymphocytes and natural killer (NK) cells through binding to its receptor (composed of IL-12Rβ1 and IL-12Rβ2/IL-23R) and results in phosphorylation of STAT4 (signal transducer and activator of transcription 4). IL-12 stimulation leads to production and secretion of IFN-γ, which activates neutrophils and macrophages to produce reactive oxidants and increase major histocompatibility complex display and Fc receptors. IFN-γ signals through its receptor (composed of IFN-γR1 and IFN-γR2), thereby leading to phosphorylation of STAT1, which in turn regulates IFN-γ–responsive genes such as those for the production of IL-12 and tumor necrosis factor (TNF)-α. Therefore, the positive feedback loop between IFN-γ and IL-12/IL-23 is pivotal in the immune response to mycobacteria and other intracellular infections (most importantly *Salmonella* [Chapter 284], *Histoplasma* [Chapter 308], and *Coccidioides* [Chapter 308]). The advent of potent TNF-α inhibitors such as infliximab, adalimumab, certolizumab, etanercept, and golimumab (Chapter 29) has provided the ability to neutralize this critical cytokine to treat inflammatory disease but at the expense of an increased risk for developing mycobacterial and fungal infections.

Nontuberculous mycobacterial osteomyelitis is especially common in patients who have dominant negative mutations in IFN-γR1. Adult-onset disseminated disease may be associated with GATA2 deficiency (monocytopenia, NK and B cell cytopenia). Some patients with disseminated disease, especially women from southeast Asia, have high-titer autoantibodies to IFN-γ.

CLINICAL MANIFESTATIONS

Disseminated Disease

Disseminated nontuberculous mycobacterial disease secondary to *M. avium* complex can occur commonly in the setting of advanced HIV and the acquired immunodeficiency syndrome (AIDS). This infection is now uncommon in North America because of prophylaxis and improved treatment of HIV infection[6] with highly active antiretroviral therapy (Chapter 357), but it remains a problem in many parts of the developing world.

Rapidly growing mycobacteria such as *M. fortuitum* sometimes infect central venous catheters. The severe disseminated infection seen with immune defects is typically associated with malaise, fever, and weight loss. It is often accompanied by organomegaly and lymphadenopathy.

Pulmonary Disease

Lung disease caused by nontuberculous mycobacteria is by far the most common form of the infection in North America. *M. avium* complex infection is typically associated with months to years of frequent throat clearing, a chronic cough that may be nonproductive early in the clinical course, and fatigue. The manifestations of *M. kansasii* infection, which can be very similar to those of tuberculosis (Chapter 299), consist of hemoptysis, chest pain, and cavitary lung disease.

Lung disease rarely disseminates, thereby illustrating that the defects leading to isolated pulmonary involvement are specific to the respiratory epithelium, whereas those defects leading to disseminated disease affect immune cells. Therefore, evaluation of isolated lung disease should focus on respiratory tract causes.

Cervical Lymph Nodes

Isolated cervical lymphadenopathy, most frequently caused by *M. avium* complex, is the most common form of nontuberculous mycobacterial infection in young children in North America. However, other nontuberculous mycobacteria such as *M. canettii*, which is mostly seen in Africa, also cause adenitis.[7] The cervical swelling is often firm and relatively painless with a paucity of systemic signs. Because the differential diagnosis of painless adenopathy (Chapter 154) includes malignancy, many of these infections are incidentally diagnosed at biopsy. Local fistulae usually resolve completely with resection or antibiotic therapy or both.

Skin and Soft Tissue Disease

M. marinum causes skin infections, usually papules or ulcers, associated with water exposure and is known as "fish tank granuloma."[8,9] Skin infections associated with *M. abscessus*, *M. fortuitum*, and *M. chelonae* are typically accompanied by painful, erythematous, draining subcutaneous nodules, usually without associated fever or systemic symptoms. *M. ulcerans* infection, which mostly occurs in West Africa, Australia, and Central America, causes Buruli ulcer disease, in which painless swelling progresses to large ulcers, usually on the arms and legs.

DIAGNOSIS

Identifying the Organism

Nontuberculous mycobacteria are now the most common mycobacteria isolated from humans in North America.[10] *M. kansasii*, *M. szulgai*, and *M. marinum* all can cross react in the standard interferon gamma release assay (IGRA) for *M. tuberculosis*. Isolation of nontuberculous mycobacteria from blood specimens is clear evidence of disease.

Usually, however, nontuberculous mycobacteria are typically first detected on acid-fast smears of sputum or other body fluids. When levels of organisms are high, mycobacteria may be seen on Gram stain as gram-positive beaded rods, but this finding is unreliable. The first step in identification is to request the appropriate smear (acid-fast or fluorochrome) and culture. Direct nucleic acid amplification tests such as real-time polymerase chain reaction (PCR) and digital PCR can decrease the detection time and may increase sensitivity. However, they cannot distinguish between living and dead organisms or between causative pathogen and contaminants in respiratory specimens. The application of PCR and matrix-assisted laser desorption-ionization time-of-flight assays on liquid cultures grown in mycobacteria growth indicator tubes have the potential to accelerate the identification of the specific mycobacterial species.[11]

Because the slow-growing nontuberculous mycobacteria typically do not grow well in routine blood culture media, the diagnosis must be suspected to be made. Isolation of nontuberculous mycobacteria from a biopsy specimen is strong evidence of infection, but cases of laboratory contamination can occur. Identification of organisms on stained sections of biopsy material confirms the authenticity of the culture. Some unusual nontuberculous mycobacteria require lower incubation temperatures or special additives for growth (e.g., *M. haemophilum*).

Radiology

The radiographic appearance of nontuberculous mycobacterial disease in the lung is similar to that seen in tuberculosis and ranges from nodules and bronchiectasis to air space disease and extensive cavity formation (Fig. 300-1).[12] The presence of bronchiectatic changes or especially cavitation on a chest computed tomographic (CT) scan can help distinguish active infection from colonization.[13]

FIGURE 300-1. **Chest computed tomography in a patient with severe pulmonary *Mycobacterium abscessus* infection.** *Arrows* indicate bronchiectasis. Note the extensive left upper lobe destruction and diffuse pleural reaction. In addition, the left lung is smaller than the right as a result of extensive loss of lung parenchyma.

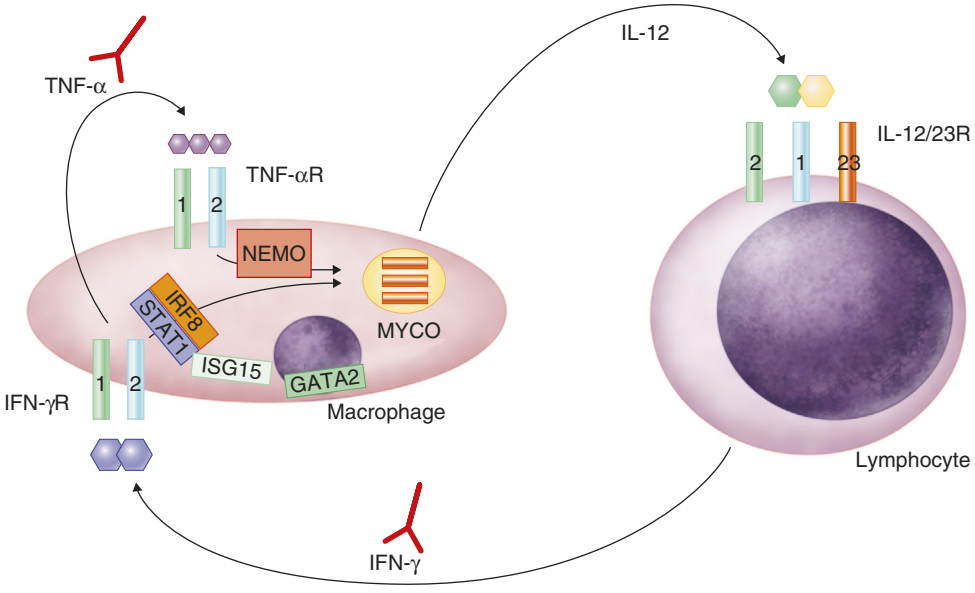

E-FIGURE 300-1. Schematization of the critical cytokine interactions between infected macrophages and T and natural killer lymphocytes. Organisms (MYCO) infect macrophages, which release heterodimeric interleukin (IL)-12. This acts on the IL-12/23 receptor complex and leads to the production of homodimeric interferon (IFN)-γ. IFN-γ acts on its receptor to stimulate the production of tumor necrosis factor (TNF)-α and kill intracellular organisms such as mycobacteria, salmonellae, and some fungi. Homotrimeric TNF-α acts on its own receptor and also contributes to killing of intracellular organisms. Both IFN-γ and TNF-α lead to upregulation of IL-12. TNF-α–inhibitors work either by blocking the ligand (infliximab, adalimumab, certolizumab) or by providing soluble receptor (etanercept). Mutations in both chains of IFN-γR, IL-12p40, and IL-12Rβ1, IL-12Rβ2, and signal elements for IFN-γR and TNF-αR have been identified through their predisposition to mycobacterial infections. IRF8 = interferon regulatory factor 8; ISG = interferon-stimulated gene; NEMO = nuclear factor kappa-B essential modulator; STAT1 = signal transducer and activator of transcription 1.

Isolation of nontuberculous mycobacteria from respiratory samples presents special problems in both sensitivity and specificity. *M. gordonae* is often recovered from respiratory samples and is almost never thought to be a real pathogen. Many patients, especially patients with bronchiectasis, will occasionally have nontuberculous mycobacteria recovered from sputum culture without such mycobacteria being seen on smear.

Diagnostic Criteria

Criteria for definitive diagnosis of nontuberculous mycobacterial lung disease with *M. avium* complex, *M. abscessus*, and *M. kansasii* require characteristic symptoms and radiographic findings plus: two of three sputum samples grow nontuberculous mycobacteria, regardless of smear findings; a positive bronchoscopic alveolar sample, regardless of smear findings; or a biopsy specimen of pulmonary parenchyma showing either granulomatous inflammation or mycobacteria and growing nontuberculous mycobacteria on culture. These guidelines are likely useful for other nontuberculous mycobacteria as well.

Additional Evaluation

Disseminated (two or more organs) involvement in a child without an underlying iatrogenic cause should always prompt an investigation of the IFN-γ/IL-12 pathway. Since the advent of effective antiretroviral therapy, disseminated mycobacterial infection has become much less common in HIV-infected persons. However, HIV infection should always be considered when a patient has disseminated mycobacterial infection and a low CD4 count (Chapter 358).

TREATMENT

General Principles

Emergency treatment is rarely indicated for nontuberculous mycobacterial infections, which are relatively slowly progressive, chronic infections that evolve over a period of weeks to years, not hours to days. Some asymptomatic or minimally symptomatic patients who have respiratory infection but have negative smears, are not underweight, and do not have lung cavities are at lower risk for progression and may require no therapy. In these cases, the decision to treat can be deferred unless and until the patient progresses on clinical follow-up as evidenced by increased symptoms, radiographic changes, or an increased burden of organisms.[14,15] In asymptomatic patients in whom a pulmonary nodule incidentally shows nontuberculous mycobacteria, surgical resection also can be adequate therapy.[16,17] Therefore, empiric medical therapy usually is not needed, and identification of the species is advisable before starting complex, often poorly tolerated, and potentially toxic regimens.

Once isolated, the nontuberculous mycobacteria should be classified to help determine the broad class of antimycobacterial therapy to be used.[18] Initial isolates of *M. avium* complex that have not been exposed to macrolides are almost always susceptible to them. Drug susceptibility testing is of limited and largely unproven value. For pulmonary disease, however, clarithromycin and amikacin susceptibility testing is recommended for *M. avium* complex and *M. abscessus* and rifampin susceptibility testing is recommended for *M. kansasii*. Any nontuberculous mycobacteria that have resisted a course of antimicrobials should probably be tested for antibiotic susceptibility as well. Similar to infection with tuberculosis, single-drug therapy is almost always associated with the emergence of antimicrobial resistance and is strongly discouraged.

Antibiotic and Surgical Treatment

M. avium complex infection frequently requires complex multidrug therapy, the foundation of which is a macrolide (clarithromycin or azithromycin), ethambutol, and a rifamycin (rifampin or rifabutin; see Table 300-2).[19] Treatment is recommended for 12 months after the sputum culture changes from positive to consistently negative. In patients who have cystic fibrosis and who are on CFTR modulator therapy (Chapter 77),[20] the use of rifamycins is contraindicated. For pulmonary *M. avium* complex disease with nodular bronchiectatic disease, three-times-weekly administration is adequate, but daily treatment with the addition of either streptomycin or amikacin is recommended for severe bronchiectatic or cavitary disease. Other drugs with activity against *M. avium* complex under the guidance of an expert include amikacin (either intravenous or inhaled), fluoroquinolones, and clofazimine (see Table 300-2). Amikacin liposome inhalation suspension is useful for treatment-refractory pulmonary *M. avium* complex infections.[A1] Adjuvant pulmonary resection can be thoracoscopically performed in selected patients who have antibiotic-refractory disease with a relatively low complication rate and a relatively high level of success.[21]

M. kansasii lung disease is similar to tuberculosis in many ways, including its susceptibility to rifampin, and it is usually effectively treated with a three-drug combination of either isoniazid or a macrolide plus rifampin and ethambutol.[22] Treatment should continue for a fixed duration of 1 year. In patients with rifampin-resistant isolates, a fluoroquinolone is indicated, and amikacin may be needed for patients who do not respond. For skin ulcers caused by *M. ulcerans*, which is sensitive to temperatures above 37° C, local thermotherapy is highly effective and safe.

Rapidly growing mycobacteria such as *M. chelonae or M. abscessus* pose special therapeutic problems. Extrapulmonary disease in an immunocompetent host is usually due to inoculation (e.g., surgery, injection, trauma) or line

TABLE 300-2 DRUG DOSING FOR MANAGEMENT OF NONTUBERCULOUS MYCOBACTERIAL DISEASE

DRUG	DAILY	THRICE WEEKLY	HEPATIC ADJUSTMENT	RENAL ADJUSTMENT
Oral				
Azithromycin	250–500 mg per day	500 mg per day	N/A	N/A
Ciprofloxacin	500–750 mg twice per day	N/A	N/A	250–500 mg dosed at intervals according to CrCl
Clarithromycin	500 mg twice per day	500 mg twice per day	N/A	Reduce dose by 50% if CrCl <30 mL/min
Clofazimine	100–200 mg per day	N/A	Caution in severe hepatic impairment	N/A
Doxycycline	100 mg once to twice a day	N/A	N/A	N/A
Ethambutol	15 mg/kg per day	25 mg/kg per day	N/A	Increase dosing interval (e.g., 15–25 mg/kg , three times per week)
Isoniazid	5 mg/kg up to 300 mg per day	N/A	Caution	N/A
Linezolid	600 mg once or twice per day	N/A	N/A	N/A
Moxifloxacin	400 mg per day	N/A	N/A	N/A
Rifabutin	150–300 mg per day (150 mg per day with clarithromycin)	300 mg per day	Caution	Reduce dose by 50% if CrCl <30 mL/min
Rifampin	10 mg/kg (450 mg or 600 mg) per day	600 mg per day	Caution	N/A
Parenteral				
Amikacin (IV)	10–15 mg/kg per day, adjusted according to drug level monitoring	15–25 mg/kg per day, adjusted according to drug level monitoring	N/A	Reduce dose or increase dosing interval (e.g., 15 mg/kg, two to three times per week)
Cefoxitin (IV)	2–4 g, two to three times daily (maximum daily dose is 12 g per day)	N/A	N/A	Reduce dose or increase dosing interval
Imipenem (IV)	500–1000 mg, two to three times per day	N/A	N/A	Reduce dose or increase dosing interval

TABLE 300-2 DRUG DOSING FOR MANAGEMENT OF NONTUBERCULOUS MYCOBACTERIAL DISEASE—cont'd

DRUG	DAILY	THRICE WEEKLY	HEPATIC ADJUSTMENT	RENAL ADJUSTMENT
Streptomycin (IV or IM)	10–15 mg/kg per day, adjusted according to drug level monitoring	15–25 mg/kg per day, adjusted according to drug level monitoring	N/A	Reduce dose or increase dosing interval (e.g., 15 mg/kg, two to three times per week)
Tigecycline (IV)	25–50 mg once or twice per day	N/A	25 mg once or twice daily per day if severe hepatic impairment	N/A
Inhalation				
Amikacin liposome inhalation suspension	590 mg per day	N/A	N/A	N/A
Amikacin, parenteral formulation	250–500 mg per day	N/A	N/A	N/A

CrCl = creatine clearance; IM = intramuscular; IV = intravenous; N/A = not applicable.
Adapted from Daley CL, Iaccarino JM, Lange C, et al. Treatment of nontuberculous mycobacterial pulmonary disease: an official ATS/ERS/ESCMID/IDSA clinical practice guideline. *Eur Respir J.* 2020;56:2000535.

infection and is often treated successfully with a macrolide, either clarithromycin or azithromycin, plus another drug, which may be guided by in vitro susceptibility, along with removal of the offending focus. By comparison, pulmonary disease, especially infection caused by *M. abscessus*, is extremely difficult to eradicate if it is macrolide resistant, although repeated courses of treatment are usually effective in reducing the infectious burden and symptoms. Therapy generally includes a macrolide, either clarithromycin or azithromycin (if susceptible), plus intravenous agents such as amikacin, a carbapenem, cefoxitin, or tigecycline. Other oral agents, guided by in vitro susceptibility testing and tolerance, include fluoroquinolones, omadacycline, clofazimine, and linezolid along with inhaled amikacin.

In patients with *Mycobacterium ulcerans*, once daily oral rifampicin (10 mg/kg) plus oral clarithromycin (15 mg/kg extended release) for 8 weeks is as effective as oral rifampicin (10 mg/kg) plus intramuscular streptomycin (15 mg/kg once daily) for 8 weeks for the treatment of early Buruli ulcer lesions, with cure rates of about 95%.[A2] Treatment of the other nontuberculous mycobacteria is less well defined, but macrolides and aminoglycosides are usually effective, with other agents added as indicated under expert consultation.[23]

Treatment in HIV-Infected Patients

The treatment of *M. avium* complex in HIV-infected patients is described in Chapter 358 (see Table 358-2).

PREVENTION

Prophylaxis of *M. avium* complex disease in patients infected with HIV is started when the $CD4^+$ T-lymphocyte count is less than 50 cells/μL. Azithromycin 1200 mg weekly, clarithromycin 1000 mg daily, and rifabutin 300 mg daily are effective.

PROGNOSIS

The effect of nontuberculous mycobacterial infection on longevity is closely tied to the underlying condition (e.g., IFN-γ/IL-12 pathway defect, HIV, cystic fibrosis). With inadequate treatment, symptoms can be intrusive, and the infections can lead to fatal complications, including overwhelming infection or severe lung destruction. When treatment is indicated, the failure to follow guideline-based treatment is associated with poorer outcomes.[24]

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301 LEPROSY (HANSEN DISEASE)

SUNIL DOGRA

DEFINITION

Leprosy (Hansen disease), which is caused by *Mycobacterium leprae,* is a chronic infection found worldwide but with about 75% of cases reported in India, Brazil, and Indonesia.[1] The primary clinical manifestation is hypopigmented, hypoesthetic or anesthetic, nonpruritic skin lesions. Peripheral nerve damage, which can be a result of the immune response to the infection, leads to loss of sensation and decreased motor function. The peripheral neuropathy (Chapter 388) can be complicated by painless injuries, secondary bacterial infections, and muscle atrophy and contractures. Leprosy is not a fatal disease, but the debility associated with leprosy increases the risk of death from malnutrition or other infections. Although the transmissibility of *M. leprae* is low and effective medications can cure it, the substantial stigma associated with it remains an ongoing challenge.

The Pathogen

M. leprae is a nonmotile, non–spore forming, microaerophilic, acid-fast staining, slow-growing, rod-shaped bacterium measuring 1 to 8 microns in length and 0.3 microns in diameter. *M. leprae* contains a mycolic acid-rich cell wall and a single membrane. *M. leprae,* which has an average generation time of 14 days, probably evolved from the same common ancestor as *M. tuberculosis,* but it has approximately 2000 fewer genes and lacks the genes that are necessary for independent growth. *M. leprae* needs an optimum temperature of about 30° C, so it mostly involves cooler parts of the body, such as the ears, nose, and the superficial course of peripheral nerves. *M. leprae* cannot be cultivated in vitro in any artificial medium, but propagation of *M. leprae* in mouse foot pads provides a tool for assessing the viability of a preparation of bacteria and testing the drug susceptibility of clinical isolates.

EPIDEMIOLOGY

Leprosy is a neglected tropical disease that has reached a crucial junction of worldwide control. The targeted goal of fewer than 10 cases per 10,000 population was achieved globally in 2000 and in India in 2005. However, leprosy still occurs in more than 120 countries, with more than 200,000 annual new cases, about 75% of which are from India, Indonesia and Brazil.[2] During the severe acute respiratory syndrome coronavirus-2019 (SARS-CoV-19) pandemic, the case detection rate declined, and only about 130,000 cases were on treatment worldwide in 2020 for a rate of 16.6 per million population. During 2021, 140,594 new cases were reported globally for a case detection rate of about 18 per million population. The rate of detection of new cases increased by 10.2% as compared with 2020. In the U.S., leprosy is extremely uncommon, with fewer than 250 cases diagnosed annually, mostly in immigrants from India, Brazil, the Philippines, the Dominican Republic, and Mexico.

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ABSTRACT

Leprosy (also known as Hansen disease) is a neglected tropical disease that results from infection with *Mycobacterium leprae*. The target level of leprosy elimination (<10 cases/10,000 population) was achieved at the global level by the year 2000 and at the national level in India in 2005. However, leprosy still occurs in more than 120 countries worldwide, and more than 200,000 new cases were noted annually (about 75% of which were reported from India, Indonesia, and Brazil) before the severe acute coronavirus syndrome-2019 (SARS-CoV-19) pandemic resulted in lower reported rates. In 2020, about 130,000 patients were being actively treated for leprosy. During 2021, 140,594 new cases were reported globally. The most common clinical manifestations are skin lesions and peripheral neuropathy. Multidrug therapy can cure leprosy but does not reverse established nerve damage.

KEYWORDS

Hansen disease
leprosy

M. leprae can survive outside the human body in humid tropical environments for 7 to 10 days and in moist soil for a few weeks. Humans are thought to be the natural host for *M. leprae*, but it also grows in nine-banded armadillos found in the Americas. Other potential sources proposed for *M. leprae* are red squirrels,[3] non-human primates (mangabey monkeys), rats, and vectors such as amoeba, ticks, mosquitoes, soil, and water. However, there is little established evidence for other potential sources of *M. leprae* infection other than from humans.

Individuals with multibacillary disease are the major source of human spread, although transmission also can occur from paucibacillary cases. The usual route of transmission is respiratory droplets, but the organisms also may enter via breached skin. *M. leprae* is not highly transmissible. Even in endemic areas, leprosy is rare except in persons who have prolonged, close contact with infected cases,[4,5] so travelers are not at substantial risk.

PATHOBIOLOGY

Because only 0.1 to 1% of the exposed population develops clinical disease and the disease spectrum varies among infected individuals, the susceptibility to infection, progression to clinical disease, and the severity of disease are mostly determined by host factors.

Immunogenetics

By genome-wide scans, susceptibility to tuberculoid leprosy has been located to chromosomal region 10p13. Susceptibility genes associated with leprosy include major histocompatibility complex (MHC) loci (HLA-A*1102-B*4006-Cw*1502 haplotype and the human leukocyte antigen [HLA]-DRB1 locus). HLA-DR2 and HLA-DR3 genes, which are class II HLA/MHC genes, have been implicated in influencing the spectrum of disease a patient develops.[6] Single nucleotide polymorphisms also have been identified in tumor necrosis factor (TNF) alpha and interleukin (IL)-10 genes. Several genes are involved in the host's response to the *M. leprae*; some may have a role in the adaptive immune response (e.g., *HLA, TAP2 , VDR , PTPN22*), whereas others may have a role in innate immunity (e.g., *NRAMP1, TLR2 , MICA , TNF-α , MRC1*).[7] Depending on the alleles that an individual possesses, the individual may get a milder or more severe form of the disease or may be able to resist the infection entirely.

Pathogenesis

Dendritic antigen-presenting cells of the host recognize the lepra bacilli via their complement receptor and upregulate both MHC class II and CD40 ligands, thereby resulting in the production of IL-12. Subsequently, cytokines and chemokines, which are produced locally, regulate the type of infiltrate and thereby the course of cell-mediated immunity via a helper T-lymphocyte dominant response.[8] The pathophysiology is not exactly known, but the features resemble type III hypersensitivity as demonstrated by the deposition of antigen, antibody, and complement (immune complexes) in the dermis. The helper T-lymphocyte response drives immunity to *M. leprae* and determines whether an individual will develop tuberculoid or lepromatous leprosy. Patients with tuberculoid leprosy have a T-helper 1 (T_H1) response that is associated with production of IL-12, TNF-α, and IFN-γ, thereby favoring a delayed-type hypersensitivity reaction. Lepromatous disease is associated with a weak T_H1-type response and a relative increase in T_H2-type cytokines. T_H1 cytokines are associated with activation of toll-like receptor-1 (TLR1) and toll-like receptor-2 (TLR2), and whereas T_H2-type cytokines are associated with inhibition. The expression of TLR1 and TLR2 is stronger on monocytes and dendritic cells in tuberculoid leprosy than in the lepromatous lesions. As a result, lesions of tuberculoid leprosy have more lymphocytes and transformed macrophages, called epithelioid cells, because of cell-mediated immunity and the paucity of bacilli. By comparison, the lymphopenic lesions in lepromatous leprosy have numerous bacilli within macrophages. During the course of chronic disease, erythema nodosum leprosum occurs mainly in patients who have lepromatous/borderline leprosy. Classic histopathologic features of active erythema nodosum leprosum lesions are increased vascularity with dilated capillaries in the upper and lower dermis, as well as intense infiltration with neutrophils and generally fragmented and granular bacilli. Reversal reaction or type 1 reactions are associated with borderline leprosy (E-Fig. 301-1).

Pathogenesis of Nerve Damage

M. leprae has the unique ability to invade peripheral nerves, and its presence within a nerve fiber is a pathognomonic sign of leprosy. Leprosy neuropathy is a slowly progressive sensorimotor infective polyneuropathy. Invasion of Schwann cells and axons by *M. leprae* leads to demyelination and axonal degeneration. *M. leprae* binds to the G domain of the laminin alpha-2 chain that is expressed on the surface of the Schwann cell–axon unit, through a 21-kDa histone-like protein. The terminal trisaccharide of phenolic glycolipid 1, which is a surface-exposed *M. leprae*–specific antigen, helps to bind to laminin-2. Subsequently, *M. leprae* alter the interior milieu of the cell, thereby producing metabolic and functional changes in nerves. *M. leprae* prefer to localize in the cooler regions, so segments of nerve trunks that are superficial and in close contact with the skin are predominantly involved. Polyneuritis is severe during acute episodes of leprosy reactions and more so during type 1 reactions. The volume of the granuloma, its inflammatory cells, and intraneural and perineural edema cause pressure effects and axonal damage. Although polyneuritis continues to occur during the course of leprosy, these effects are accentuated during acute leprosy reactions. If untreated, this process progresses to nerve destruction, fibrosis, and irreversible nerve damage.

The neuropathic pain of leprosy can be caused by disorders of the somatosensory nervous system, owing to infection itself, or by lepromatous reactions to the infection. Neuropathic pain, which usually is observed in patients who have completed multidrug therapy, can persist for months to years. The pain is generally considered to be a small fiber sensory neuropathy, with painful paresthesia as its most common effect.

CLINICAL MANIFESTATIONS

The incubation period for leprosy is estimated to range from 2 to 20 years, with an average of 5 years, and about 95% of infected people may never develop clinical disease owing to their innate immune response. In the remaining individuals, the disease may self-resolve or it may progress to a clinical stage, which will resolve only if treated.

Leprosy commonly involves the skin and peripheral nerves, and its manifestations are determined by the polarity of the disease: paucibacillary (tuberculoid) or multibacillary (lepromatous). Patients commonly present with skin lesions,[9] weakness or numbness of hands or feet caused by a peripheral-nerve involvement, deformities, resorption of fingers and toes, or a burn or ulcer in an anesthetic hand or foot. Some patients may present with acute nerve pain, sudden palsy, new skin lesions, a painful red eye, or a systemic febrile illness.

Leprosy-related neuropathic pain includes a wide spectrum of symptoms, including paresthesia, dysesthesia, hyperesthesia (increased sensitivity to normal painful stimuli), and allodynia (pain in response to a stimulus that is not normally painful) along the nerve and in its area of distribution.[10] The reported prevalence of neuropathic pain in leprosy ranges from 11 to 70% in various studies. The neuropathic pain can be severely debilitating, affect a patient's quality of life, and result in substantial psychological distress.

Classification of Disease

Leprosy also can be categorized as paucibacillary or multibacillary, based on the number of skin lesions, nerve involvement, and bacteriologic status (Table 301-1). Another categorization based on clinical, bacteriologic, histologic, and immunologic features (Table 301-2) classifies leprosy as tuberculoid, borderline tuberculoid, borderline borderline, borderline lepromatous, and lepromatous leprosy.[11] In general, paucibacillary disease is equivalent to tuberculoid and borderline tuberculoid disease, whereas multibacillary is equated with borderline, borderline lepromatous, and lepromatous disease.

Tuberculoid Leprosy

Tuberculoid leprosy is a less common, benign, and relatively stable form of disease. The number of skin lesions is usually one to three, seldom measuring more than 10 cm in diameter and infrequently positive on bacteriologic examination. The typical lesion is a well-defined erythematous plaque with raised and clear-cut edges sloping inward. The surface is dry, hairless, anesthetic, and usually scaly. A solitary peripheral nerve trunk may be thickened

TABLE 301-1 WORLD HEALTH ORGANIZATION CLASSIFICATION OF LEPROSY

	CRITERIA
Paucibacillary	1 to 5 skin lesions, without bacilli in a skin smear and without nerve involvement
Multibacillary	Any one of: • More than five skin lesions • Nerve involvement (pure neuritic) • Any number of skin lesions and nerve involvement • Demonstrated presence of bacilli in a slit-skin smear, irrespective of the number of skin lesions

From World Health Organization. *Guidelines for the Diagnosis, Treatment and Prevention of Leprosy*. Geneva: World Health Organization; 2018.

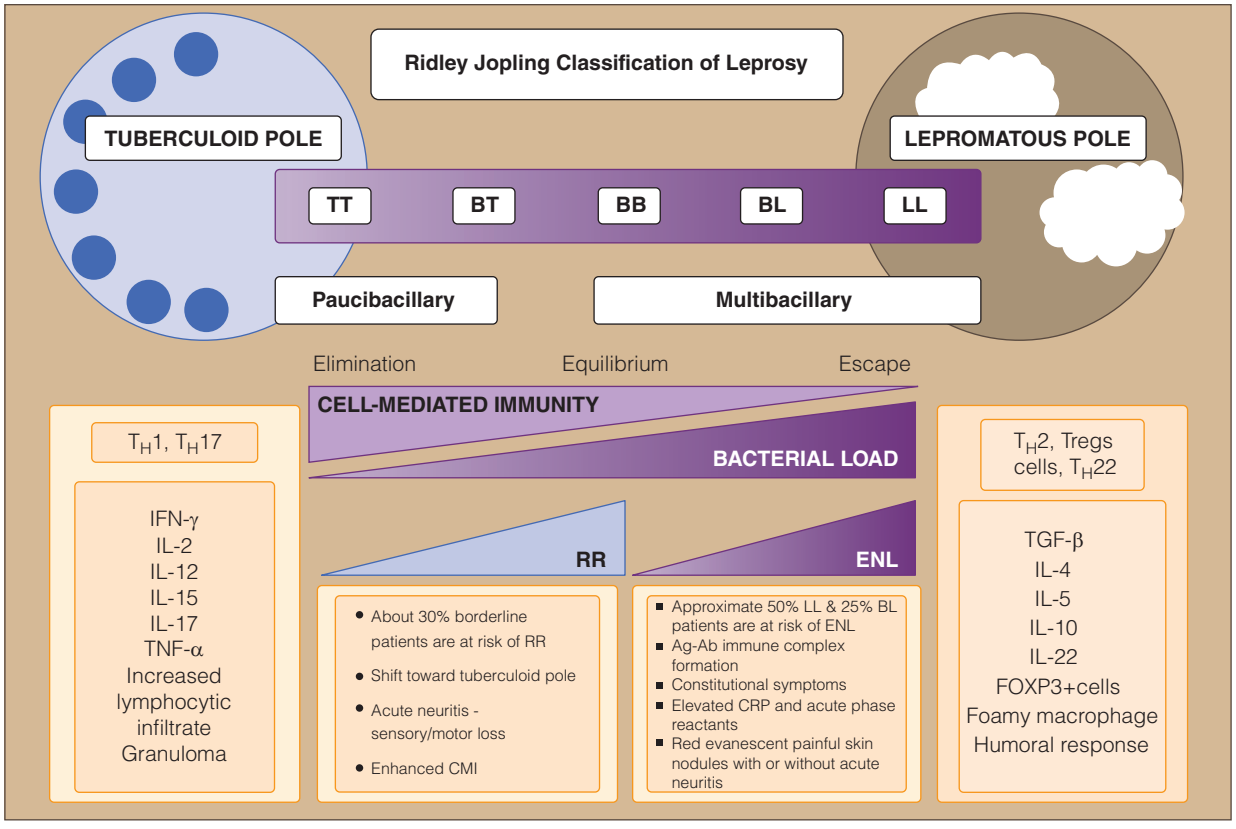

E-FIGURE 301-1. The bacteriologic, immunologic, and clinical spectrum of leprosy. Towards the tuberculoid pole, cell-mediated immunity is strong, with predominance of a T-helper (T_H) and T_H17 immune response. This response keeps the bacillary load in check (paucibacillary), and biopsy specimens of skin lesions or slit skin smears reveal few or no bacilli. Lepromatous (multibacillary) leprosy has a strong T_H2 and regulatory T cell (Treg) response, which allows the bacilli to replicate; biopsy and slit skin smears are often teeming with acid-fast bacilli. The intermediate forms can resemble either tuberculoid or lepromatous leprosy, based on the host's prevalent immune response. BB = borderline borderline; BL = borderline lepromatous; BT = borderline tuberculoid; CMI = cell-mediated immunity; CRP = C-reactive protein; ENL = erythema nodosum leprosum; FOXP3 = forkhead box P3; IFN = interferon; IL = interleukin; LL = lepromatous; RR = reversal reaction; TGF = transforming growth factor; TT = tuberculoid leprosy.

TABLE 301-2 CHARACTERISTICS OF THE FIVE CLINICAL CLASSES OF LEPROSY *

OBSERVATION	TUBERCULOID LEPROSY	BORDERLINE TUBERCULOID	BORDERLINE BORDERLINE	BORDERLINE LEPROMATOUS	LEPROMATOUS LEPROSY
Number of lesions	Usually single (up to 3)	Few (up to 10)	Several (10-30)	Many (>30), asymmetrical	Innumerable, symmetrical
Size of lesions	Variable, usually large	Variable, some are large	Variable	Usually small, but some can be large	Small
Surface	Very dry, scaly, lesions look turgid	Dry, scaly, lesions look bright and infiltrated	Dull/slightly shiny	Shiny	Shiny
Sensations in lesions	Absent	Markedly diminished	Moderately diminished	Slightly diminished	Minimally diminished, not affected
Hair growth in lesions	Absent	Markedly diminished	Moderately diminished	Slightly diminished	Not affected initially, but almost all body hair is lost in long-standing disease
AFB in lesions	Nil	Nil or scanty	Moderate in number	Many	Plenty, including globi
Lepromin reactivity	Strongly positive (+++)	Weakly positive (+ or ++)	Negative/ weakly positive –/+	Negative	Negative
Histopathology	Granuloma consisting of lymphocytes, epithelioid and giant cells, small nerves completely effaced by caseating granuloma. AFB-negative	Granuloma consists of epithelioid cells and an admixture of macrophages and lymphocytes. Giant cells are also seen. Nerves replaced by granuloma. AFB may be positive or negative.	Granuloma consisting predominantly of epithelioid cells, macrophages and scattered lymphocytes. Nerve shows cut onion appearance. AFB+	Granuloma around nerve, neurovascular bundle consists primarily of macrophages and isolated clumps of epithelioid cells. Nerves show concentric perineural cell infiltration. AFB ++ including small globi	Expansive and loose granuloma with plenty of macrophages loaded with AFB. Nerves are minimally involved.

*All features can occur in various combinations as the disease progresses.
AFB = acid fast bacilli.
From Kumar B, Dogra S. Case definition and clinical types of leprosy. In: *IAL Textbook of Leprosy*. 2nd ed., Jaypee Publishers, India; 2017.

in the vicinity of a lesion. Skin lesions may appear at any site on the skin, but with a predilection for body parts not covered by clothing.

Borderline Tuberculoid Leprosy

Borderline tuberculoid leprosy disease spans the spectrum between the tuberculoid and lepromatous poles. It is the most important part of the spectrum in terms of number of patients, frequency, severity of reactions, and nerve damage. Patients with borderline disease suffer most of the disabilities and deformities seen in leprosy. The skin lesions resemble those of tuberculoid leprosy, but the disease is not fully contained. Individual lesions do not show the well-defined margins, and their borders may start sloping outward and even fade imperceptibly into the normal skin. Lesions may have small extensions at one edge (pseudopodium), or satellite lesions may be seen. The number of lesions may vary from 3 to 10, with variation in size and contour. The lesions tend to be large and can even cover an entire limb. The lesions have sensory loss, dryness, and scaling, with erythema or hypopigmentation (Fig. 301-1). Several peripheral nerves are likely to be enlarged in an asymmetrical pattern. Nerve damage with anesthesia or a motor deficit is often found at the time of presentation and can progress to nerve damage, paralysis, and deformity. Some untreated patients with repeated reactions deteriorate to borderline borderline or lepromatous leprosy.

Borderline Borderline Leprosy

Borderline borderline leprosy is an immunologically unstable, short-lived form of the disease that, if left untreated, mostly progresses towards the lepromatous form. Characteristic skin lesions are annular, with the inner edge well-demarcated (punched out) and the outer edge ill-defined and sloping towards normal skin. Clinically normal-looking skin within such plaques gives a "Swiss cheese" appearance (Fig. 301-2 and E-Fig. 301-2). The face may be infiltrated with occasional nodules over the ears and chin.

Borderline Lepromatous Leprosy

Borderline lepromatous leprosy manifests with numerous skin lesions, classically distinct but not so well defined. Lesions occur as slightly infiltrated, round or oval macules with a copper hue. Lesions are 2 to 3 cm in diameter, often symmetrical, and with areas of apparently normal skin in between (Fig. 301-3 and see E-Fig. 301-2). As the disease progresses, papules, nodules, and plaques may develop, with sloping margins that merge imperceptibly into normal skin. Eyebrows are either not involved or are partially lost. Skin smears show a moderate number of bacilli in the majority of the lesions. Peripheral nerve trunks become thickened at the sites of predilection, with corresponding asymmetrical anesthesia and paresis.

FIGURE 301-1. Borderline tuberculoid leprosy. A large well-defined, hypopigmented, infiltrated patch with xerosis, wrinkling of skin, loss of hairs, and pseudopodia.

Lepromatous Leprosy

Early lesions of lepromatous leprosy are innumerable small macules that are widely disseminated and distributed symmetrically. Although the infiltration initially may

E-FIGURE 301-2. Type 1 reaction in borderline tuberculoid leprosy. The existing lesion on forehead has become erythematous, edematous and shiny.

FIGURE 301-2. Annular lesions of borderline borderline leprosy. The inner edge is well demarcated and "punched out," and the outer edge is ill-defined and slopes towards normal skin.

FIGURE 301-3. Borderline lepromatous leprosy. Multiple small, hypopigmented to coppery colored infiltrated macules tending to coalesce distributed symmetrically on back.

FIGURE 301-4. Lepromatous leprosy. Diffuse infiltration of the face with edematous, waxy look with partial madarosis and few papulonodular lesions on the chin.

not be very apparent clinically, these macules are found to be slightly infiltrated; their edges are indistinct, merging imperceptibly into the normal skin. The surface of the lesion is shiny and erythematous, rather than hypopigmented. Insidious onset and steady progression may allow the disease to advance for years before a shiny, waxy appearance is recognized. Lepromatous leprosy with infiltrated lesions presents as diffuse, infiltrated, or nodular forms (Figs. 301-4 to 301-6). The sensory loss is symmetrical, usually first detected over the forearms, legs, hands, and feet. Sensory loss gradually progresses in the typical stocking and glove distribution, and autonomic dysfunction (Chapter 386) can occur.[12] Weakness usually starts early in the intrinsic muscles of the hands and feet, possibly because of direct bacillary invasion as well as involvement of the peripheral nerves. Anosmia, nasal crusting or bleeding, and nasal septal perforation occur in up to 40% of patients in long-standing disease. Eye involvement[13] includes partial to complete loss of eyebrows, often associated with corneal anesthesia owing to bacillary infiltration of the corneal nerves and later from damage to the ophthalmic division of the trigeminal nerve. Other ocular manifestations in advanced disease include lagophthalmos, corneal ulceration, perforation, corneal opacity, uveitis, and even blindness.

Reactions

Leprosy reactions are immunologically mediated episodes of acute or subacute inflammation that affect predominantly the skin and nerves. Leprosy reactions are important causes of nerve damage and, unless promptly treated, can result in deformity and disability.

Type 1 Reactions

Type 1 reaction is a delayed hypersensitivity reaction associated with sudden alteration of cell-mediated immunity, sometimes associated with a shift in the patient's position in the leprosy spectrum of disease. Type 1 reactions are mostly observed in the borderline disease spectrum. Some or all of the preexisting skin patches or plaques become erythematous and swollen, and they may become tender and mimic erysipelas. Necrosis and ulceration can occur in severe cases (E-Fig. 301-3). Crops of inflamed skin lesions in the form of plaques may appear in areas where skin was previously clinically uninvolved. Edema of extremities or face is frequent. Rapid swelling, with severe pain and tenderness of one or more peripheral nerves, commonly occurs close to the inflamed skin lesion or situated below the inflamed lesion. In severe forms, nerve abscesses may form.

Type 2 Reactions

Type 2 reaction, popularly known as erythema nodosum leprosum, is a multisystem immune-mediated reaction noted in lepromatous leprosy and borderline lepromatous leprosy disease. The reaction is characterized by the eruption of tender skin lesions accompanied by constitutional signs and symptoms. Erythema nodosum leprosum lesions appear as crops of evanescent (persisting for few days), pink (rose) tender papules, nodules, or plaques, which are variable in size. Lesions tend to be warm, painful, and tender to touch, and they blanch with light finger pressure. New erythema nodosum leprosum lesions appear as old lesions subside. An individual lesion typically changes color from pink/red to bluish and brownish over 24 to 48 hours and finally becomes dark after a week or 10 days. Lesions subside with desquamation or peeling of the superficial skin. Erythema nodosum leprosum lesions also may become vesicular, pustular, bullous, and

E-FIGURE 301-3. **Type 1 reaction in borderline tuberculoid leprosy on the face.** Erythema and edema of pre-existing lesions are evident. Ulceration of plaques, as seen in this case, is a feature of severe type 1 reaction.

FIGURE 301-5. Lepromatous leprosy. Classic earlobe nodules along with diffuse infiltration of the face. The lesions are shiny and succulent in consistency. The greater auricular nerve can be seen as a thickened cord-like structure.

FIGURE 301-6. Lepromatous leprosy. Nodular lesions over the face along with madarosis. Slit-skin smears are usually highly positive in such cases.

necrotic; they also can break down to produce ulceration called erythema nodosum necroticans (E-Fig. 301-4). Neuritis, which is the most common extracutaneous manifestation of type 2 reaction, may be acute, recurrent, or chronic. Associated features may include lymphadenopathy, myositis, arthritis, dactylitis, synovitis, laryngitis, iridocyclitis, epididymo-orchitis, and nephritis.

Other Clinical Variants

Lucio Phenomenon and Lucio Leprosy

Lucio leprosy is commonly seen in Mexico and Costa Rica, not infrequently in the Gulf coast, but quite rarely in other parts of the world. The disease, which develops in the untreated diffuse form of lepromatous leprosy, is often unmasked by a specific severe reactional state, termed the Lucio phenomenon, which occurs in patients who have no previous evidence of discrete lesions. Endothelial cell injury is the main pathogenetic event. Lucio phenomenon presents as multiple, well-defined, angular, jagged purpuric lesions, which evolve into massive ulcerations that spread in a characteristic ascending fashion over the extremities and heal with atrophic scarring. The skin looks waxy and has a shiny appearance (lepra bonita, beautiful leprosy), with obvious diffuse infiltration of the ear lobes and forehead, loss of eyebrows and sometimes eyelashes, and not infrequently all body hair. The voice may be hoarse, and numbness and edema of the hands and feet may mimic what is observed in myxedema. Unlike erythema nodosum leprosum, patients have no nodules, lymphadenopathy, or arthritis.

Histoid Leprosy

Histoid leprosy is a rarely reported entity. Clinically, the histoid lesions commonly appear as smooth, shiny, hemispherical, dome-shaped, nontender soft to firm nodules, which may be superficial, subcutaneous, or fixed deeply under the skin, accompanied by plaques or pads appearing on otherwise normal-looking skin (Fig. 301-7). The number of lesions may vary from a few to a hundred. Lesions are usually located on the face, back, buttocks, extremities, and over bony prominences, especially around the elbows and knees. Histopathologically, the striking feature is predominance of spindle- shaped cells and unusually large numbers of acid-fast bacilli. Because lesions of histoid leprosy may mimic many dermatologic conditions, diagnosis requires a high index of suspicion. Histoid patients with a high bacillary load may serve as reservoirs of infection and continue to transmit infection, so early diagnosis and treatment is essential.

Pure Neuritic Leprosy

Pure neuritic leprosy is characterized by sensory loss along the distribution of an involved nerve trunk, with or without motor deficit, in the absence of any skin lesions. Neuritic leprosy is seen more frequently in India and Nepal, where it accounts for 5 to 10% of all patients with leprosy. The nerve involvement, which may range from single to multiple, is generally asymmetrical. Up to one-third of patients may later develop skin lesions, thereby implying that a neuritic phase often precedes the development of cutaneous lesions.

Systemic Involvement

Features of systemic involvement, which usually occur in long-standing disease, are seen mainly in patients near the lepromatous pole of the spectrum of disease. Systemic involvement is due to bacillary deposits and associated granulomatous infiltration affecting various organs, especially the nasal mucosa, larynx, eyes, bones, testes, kidneys, lymph nodes, liver, and spleen. Systemic manifestations also include constitutional symptoms such as fever, malaise, joint pains, and acute inflammation of eyes, joints, reticuloendothelial system as a part of an erythema nodosum leprosum (type 2 reaction). In the era of declining leprosy prevalence and expertise, some patients with systemic symptoms may go undiagnosed for many months until astute clinical assessment raises suspicion and leads to confirmatory diagnostic testing.

Leprosy in Immunocompromised Hosts

Unlike other mycobacterial diseases, the course of leprosy is not markedly modified by the HIV infection. However, the immune reconstitution inflammatory syndrome (Chapter 358) following initiation of highly active antiretroviral therapy can develop in patients with leprosy–HIV coinfection when immunity is restored. Clinically, the immune reconstitution inflammatory syndrome usually presents as a type 1 reaction with the development of erythematous, edematous skin lesions that may ulcerate, as well as neuritis with nerve paresis and paralysis.

Leprosy has been reported in recipients of kidney, heart, lung, and bone marrow transplants, and it should be considered in the differential diagnosis of skin manifestations in organ transplant patients. Post-transplantation, multibacillary forms of leprosy predominate. The consequences of coinfection with leprosy and the SARS-CoV-2 infection are uncertain.

Leprosy and Pregnancy

In contrast to the frequent involvement of the testes in lepromatous disease, the female reproductive organs are not significantly involved in leprosy. Because of suppression of cell-mediated immunity during pregnancy and its recovery postpartum, leprosy becomes more active during pregnancy and lactation. Pregnant women can experience relapse, reactivation, and transient exacerbation of the neuropathy, as well as reversal despite multidrug therapy.

E-FIGURE 301-4. Erythema nodosum leprosum. Multiple erythematous tender nodules in varying stages of evolution over the trunk in a case of lepromatous leprosy. Note gynecomastia and wrinkling of skin in long-standing disease.

FIGURE 301-7. Histoid leprosy. Skin-colored, smooth, waxy cutaneous nodules, some with umbilication with an apparently normal appearing intervening skin. In some places, nodules coalesce to form an annular pattern.

DIAGNOSIS

A thorough history and clinical examination is essential for diagnosis. Morphologic details of the skin lesions, the extent of peripheral nerve involvement, areas of sensory loss, and systemic involvement allow the clinician to assess the patient's spectrum of disease, to individualize therapeutic decisions, and to assess the risk of complications that the patient may face during the course of illness and treatment.[14] The physical examination should specifically focus on a careful cutaneous and mucosal examination to identify the type and number of skin lesions; evaluation of peripheral and cranial nerves; and testing for sensory and motor impairment. Pregnancy should be determined in women of childbearing age because some medications used to treat leprosy may be contraindicated in such settings.

Laboratory Testing

Although an expert physician can identify most patients by clinical examination alone, laboratory testing plays an important role in early diagnosis as well as in monitoring the response to treatment. Slit-skin smear examination, which is the most simple and valuable test,[15] helps to confirm the diagnosis, classify the spectrum of disease, and determine its activity. The number of acid-fast bacteria in each field is counted and graded from zero to 6+ as the bacteriologic index.

The morphology of the bacilli should be carefully examined to determine the percentage of *M. leprae* that are alive or dead, termed the morphologic index. Solid stained bacilli are live and viable, whereas the granular, broken, and fragmented bacilli are dead and nonviable.

Skin biopsy at an active, infiltrated edge of the most active lesion can confirm the diagnosis and type of leprosy, as well as identify type 1 and type 2 reactions, but leprosy is often a clinical diagnosis in endemic countries. Fine needle aspiration cytology can diagnose neuritic leprosy with increased sensitivity when it is combined with multiplex polymerase chain reaction (PCR) testing. Rapid molecular assays for detection of *M. leprae,* such as PCR-based techniques, have a specificity of 100% and a sensitivity ranging from 34 to 80% in the paucibacillary form of leprosy but a sensitivity greater than 90% in the multibacillary form. RNA analysis using 16 S rRNA and reverse-transcription PCR has the added benefit of measuring the viability of *M. leprae*.[16] Nerve biopsies can confirm the diagnosis of leprosy, especially in patients who present with pure neuritic leprosy without skin lesions[17]; a thickened sensory nerve, such as the radial cutaneous nerve at the wrist or the sural nerve at the back of the leg, is preferred for biopsy.

Diagnostic Criteria

The diagnosis of leprosy is established by finding at least one of the following cardinal signs: 1) definite loss of sensation in a pale (hypopigmented) or reddish skin patch; 2) thickened or enlarged peripheral nerve, with loss of sensation and/or weakness of the muscles supplied by that nerve; and 3) presence of acid-fast bacilli in a slit-skin smear. The sensitivity and specificity of each one of these signs is high, but the most important potential source of error is inter-observer variation in the examination of an individual patient and reading of the skin smears.

TREATMENT

Multidrug Chemotherapy

Multidrug therapy, which consists of rifampicin, dapsone, and clofazimine (Table 301-3),[18–20] is highly successful for curing all forms of leprosy.[A1] The duration of treatment is 6 months for paucibacillary leprosy and 12 months for multibacillary leprosy. In general, leprosy and lepra reactions respond equally well even in immunosuppressed patients.

Rifampicin may color bodily secretions (tears, urine, etc.) red or orange. Gastrointestinal side effects include epigastric distress, nausea, vomiting and diarrhea. The most important adverse effect is hepatitis, which is usually not serious, unless compounded by another drug that also affects the liver. Rare but significant side effects include a flu-like syndrome, renal failure, and thrombocytopenia, particularly with intermittent therapy. Rifampicin also induces liver enzymes, so some other drugs (e.g., oral contraceptives) may be rendered less effective because they are metabolized more quickly. Clofazimine causes orange-brown discoloration and darkening of the skin, mucosa, cornea, and body fluids, but the discoloration is generally reversible after the drug is stopped. At high doses, clofazimine builds up in the tissues and can precipitate to form crystals, especially in the intestinal mucosa (crystal enteropathy), lymph nodes, and in fatty tissue. The formation of crystals in the gastrointestinal tract may lead to abdominal pain, nausea, and diarrhea, which, although rare, may be fatal in severe cases. Splenic infarction, eosinophilic enteritis, and cardiac arrhythmias also have been reported. Dapsone's adverse effects include anemia and methemoglobinemia. An insignificant degree of hemolysis occurs in virtually every patient but may be of clinical concern in patients with glucose-6-phosphate deficiency (Chapter 147). Dapsone hypersensitivity syndrome, which generally manifests by 4 to 6 weeks after starting dapsone, is a rare but sometimes fatal complication characterized by fever, skin rashes (ranging from a maculopapular eruption to toxic epidermal necrolysis), generalized lymphadenopathy, hepatitis, and hepatosplenomegaly.

Leprosy Drug Resistance

Resistance to triple therapy, though unusual, has been reported in several countries. Patients whose infection is resistant to rifampicin should be treated using at least two of the following second-line drugs: clarithromycin 500 mg daily), minocycline (100 mg daily), or a quinolone (e.g., ofloxacin [400 mg daily], levofloxacin [500 mg daily], or moxifloxacin [400 mg daily]) plus clofazimine (50 mg daily) for 6 months, followed by clofazimine plus one of the second-line drugs daily for an additional 18 months. When ofloxacin resistance is also present, a fluoroquinolone should not be used as part of second-line treatment. The regimen of choice in such cases should be 6 months of clarithromycin, minocycline, and clofazimine followed by clofazimine plus either clarithromycin or minocycline for an additional 18 months.

Immunotherapy

Mycobacterium indicus pranii, which is a rapidly growing, nonpathogenic, cultivable mycobacterium that shares several antigens with *M. leprae*, is administered intradermally as a killed vaccine (0.1 mL in two equally divided doses on both the arms) and repeated every 3 to 6 months until the end of treatment). Adding this immunotherapy, particularly in highly infected patients, can result in more rapid bacterial clearance, an earlier achievement of smear negativity, and more rapid clearance of skin lesions on histopathology in a significantly higher percentage of patients.[21] Topical insulin may be helpful to promote healing of trophic skin ulcers,[A2] but other local therapies have been disappointing.[A3]

Treatment of Reactions

The goals of treating reactions are to control the skin and nerve inflammation, relieve pain, prevent further episodes of reaction, reduce morbidity, and prevent deformities. For mild type 1 reactions, standard doses of a nonsteroidal anti-inflammatory drug (e.g., aspirin, indomethacin, ibuprofen, diclofenac, or acetaminophen [see Table 26-4) should be given for several weeks. Reassurance is very important to the patient as well as to family members. For moderate to severe type 1 reactions, prednisolone (between 0.5 and 1.0 mg/kg of body weight/day, equivalent to 30 or 40 mg daily for most adults) is given orally for 20 weeks.[A4] In patients who do not respond to steroids or who experience steroid-related adverse effects, alternative treatments under expert care have included systemic methotrexate, cyclosporine, azathioprine, mycophenolate mofetil, and topical tacrolimus. In the acute phase, the inflamed nerves must be kept in a resting position; appropriate splinting and padding give relief. Surgical nerve decompression may sometimes be indicated to relieve persistent increased intraneural pressure, tenderness, and acute inflammation if they lead to ischemia in the nerve.

TABLE 301-3 RECOMMENDED ORAL MULTIDRUG THERAPY

AGE	DRUG	DOSAGE & FREQUENCY	DURATION	
			MULTIBACILLARY	*PAUCIBACILLARY*
Adult	Rifampicin Clofazimine Dapsone	600 mg once a month 300 mg once a month and 50 mg daily 100 mg daily	12 mo	6 mo
Children (10-14 yr)	Rifampicin Clofazimine Dapsone	450 mg once a month 150 mg once a month and 50 mg on alternate days 50 mg daily	12 mo	6 mo
Children (<10 yr old or <40 kg)	Rifampicin Clofazimine Dapsone	10 mg/kg once a month 100 mg once a month and 50 mg twice weekly 2 mg/kg/daily	12 mo	6 mo

Data from World Health Organization. *Guidelines for the Diagnosis, Treatment and Prevention of Leprosy*. Geneva: World Health Organization; 2018.

Mild type 2 reactions can be managed with anti-inflammatory drugs and analgesics, as for type 1 reactions, but some patients may respond to tramadol (50 to 400 mg/day) or colchicine (0.5 mg up to three times daily with a tapering course). Aspirin can be given at a dose as high as 600 mg every 6 hours with meals (up to a maximum dose of 2.8 g/day), with the dose reduced slowly as signs and symptoms are controlled. For severe type 2 reactions, oral corticosteroids (prednisolone not exceeding 1 mg/kg of body weight/day for a total duration of 12 weeks) rapidly control inflammation and relieve pain; the dose should be tapered rapidly to the lowest dose required to keep the reaction under control. For corticosteroid-dependent, nonresponsive, chronic, or recurrent cases, clofazimine should be given as 300 mg daily for 1 month, followed by 200 mg daily for 3 to 6 months, followed by 100 mg daily for as long as the erythema nodosum leprosum symptoms remain. At this high dose, the drug often worsens the reddish-brown skin pigmentation (reversible over 4 to 6 months of stopping) and increases the risk of clofazimine-induced crystal enteropathy and cardiotoxicity. Thalidomide (started at a dose of 400 mg daily; 200 mg twice or 100 mg four times daily) is also effective for men and postmenopausal women with severe type 2 reactions and difficult-to-manage erythema nodosum leprosum,[22] steroid-dependent patients, and patients in whom steroids are contraindicated; however, thalidomide is a second-line option because of its teratogenicity, cost, and limited availability. Thalidomide typically controls the reaction within 3 to 7 days, at which time the dose should then be tapered to 300 mg (100 mg in the morning and 200 mg in the evening daily) over 4 weeks, followed by a 100-mg dose reduction each month. If thalidomide is used in women of childbearing age, successful contraception is critical. Alternative therapies occasionally tried for type 2 reactions under expert care include pentoxifylline, azathioprine, cyclosporine, mycophenolate mofetil, immunotherapy, zinc, minocycline, anti–TNF-α agents (e.g., infliximab, etanercept, adalimumab), leukotriene inhibitors, and apremilast and thalidomide derivatives.

Leprosy and Pregnancy

Leprosy treatment should be continued unchanged during pregnancy and breast-feeding, except that thalidomide, methotrexate, azathioprine, cyclosporine, apremilast are contraindicated during pregnancy. Cases of dapsone-induced hemolytic anemia have been reported in mothers and their babies, with symptoms resolving after discontinuing dapsone. Oral corticosteroids (see above) are the preferred anti-reaction drugs in pregnancy.

PREVENTION

Leprosy probably cannot be eliminated by the successful treatment of infected individuals, and no vaccine is currently available. Single-dose rifampicin (Table 301-4)[23] treatment of adults and children ages 2 years and above who are contacts (defined as a person who has been living, working, or having social activities for more than 3 months and 20 hours per week with a newly detected case of leprosy in the last year) of patients who have leprosy reduces the risk of leprosy by 57% at 2 years and by 30% after 5 to 6 years. This intervention should be implemented only by programs that can ensure adequate management of contacts and consent of the index case to disclose his/her disease. Contacts who are found to have leprosy or tuberculosis (Chapter 299) require full treatment for active disease.

Bacillus Calmette-Guérin (BCG) vaccine at birth is effective in reducing the risk of leprosy,[24] so its use should be continued in all high-burden countries or settings. BCG vaccine at birth also appears to potentiate the protective effect of single dose rifampicin in contacts from 57% to 80%.[A5] Data are insufficient to recommend BCG vaccination of contacts.[A6] Moderate-quality evidence indicates the efficacy of vaccination using *Mycobacterium indicum pranii* in preventing leprosy.[25]

TABLE 301-4 SINGLE-DOSE RIFAMPICIN

AGE/WEIGHT	RIFAMPICIN SINGLE DOSE
15 yr and above	600 mg
10-14 yr	450 mg
Children 6-9 yr (weight ≥20 kg)	300 mg
Children <20 kg (≥2 yr)	10-15 mg/kg

Data from World Health Organization. *Guidelines for the Diagnosis, Treatment and Prevention of Leprosy*. Geneva: World Health Organization; 2018.

Global Strategies

The Global Partnership for Zero Leprosy aims to reduce the burden of disease by about 70% to fewer than about 63,000 cases worldwide. To achieve the goal, effective diagnostics for early detection, newer therapies, and vaccines likely will have to be combined with programs that address social and environmental factors.

PROGNOSIS

Untreated tuberculoid leprosy may sometimes remit, but multibacillary leprosy is always progressive with devastating consequences for the patients and the risk of spreading infection in community. Multidrug chemotherapy cures most patients, but sequelae such as drug reactions, neuropathic pain, and trophic ulcers may persist after treatment. Relapse rates are reported to be about 0.1% per year in paucibacillary leprosy but can be as high as 5% per year in multibacillary leprosy, particularly in patients who have a high bacteriologic index at baseline.[26]

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For the General References and other additional features, please visit Elsevier eBooks+ at https://ebooks.health.elsevier.com.

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302 RICKETTSIAL INFECTIONS

PIERRE-EDOUARD FOURNIER AND DIDIER RAOULT

DEFINITION

Rickettsial diseases are emerging infectious diseases.[1] Because of better diagnostic tools, increased awareness, and changes in tick exposure, new rickettsial diseases continue to be described in recent years. Three families of diseases are grouped under rickettsioses: ehrlichioses and anaplasmoses and Q fever (Table 302-1).

The Pathogens

The agents of rickettsial diseases are small, gram-negative, intracellular bacteria that are associated with eukaryotic cells. Except for *Coxiella burnetii*, which is the agent of Q fever, they have not yet been grown in axenic media, but rather require living hosts (e.g., cell cultures, embryonated eggs, or susceptible animals) for growth. With the exception of *Rickettsia prowazekii*, which is the agent of epidemic typhus and which is specifically associated with the human body louse, these bacteria infect humans incidentally and are mainly animal pathogens. Polymerase chain reaction (PCR) amplification of DNA from blood samples, biopsy specimens, and cutaneous eschar swabs has helped identify new species.

RICKETTSIOSES (DISEASES CAUSED BY *RICKETTSIA* SPECIES AND *ORIENTIA TSUTSUGAMUSHI*)

PATHOBIOLOGY

Rickettsia spp are small gram-negative bacteria that multiply freely in the cytoplasm of their host cells. The genome of *Rickettsia* is small, between 1.1 and 1.6 Mb; some have plasmids and potential for conjugation. These bacteria have a family of outer membrane proteins of the surface cell antigen family, including rOmpA (lacking in the typhus group) and rOmpB. These proteins are major antigens that help identify the rickettsial species by serology, and their encoding genes are used for amplification and sequencing for diagnostic or taxonomic purposes. Complete genome sequencing of *Rickettsia* species demonstrates that these bacteria are undergoing a genomic reduction process as a result of various phenomena, including progressive gene degradation and genomic rearrangements and also a paradoxical expansion of small RNAs and short palindromic elements.[2] Genome sequence–based taxonomic information can reliably classify rickettsial isolates at the genus and species levels.[3]

The target cells in humans are vascular endothelial cells or monocytes, and vasculitis is the most prominent result. These bacteria invade cells by phagocytosis and escape the phagosome vacuole.

TICK-BORNE RICKETTSIOSES

ROCKY MOUNTAIN SPOTTED FEVER

EPIDEMIOLOGY AND PATHOBIOLOGY

Rocky Mountain spotted fever (RMSF), which is the most severe of tick-borne rickettsioses, is caused by *Rickettsia rickettsii* (Table 302-2). Rocky Mountain spotted fever is the major tick-borne rickettsiosis recognized in America[4] and is prevalent in at least 44 states in the United States (Fig. 302-1)[5] as well as in Central and South America (Argentina, Brazil, Colombia, Costa Rica, Mexico, and Panama).

In ticks, *R. rickettsii* is transmitted transovarially from one generation to the next. The infecting ticks are mainly *Dermacentor andersoni* (a wood tick) in the Western United States; *Dermacentor variabilis* (the American dog tick) in the East, the Midwest, and the South; and *Rhipicephalus sanguineus* in Arizona. In Central and South America, *Amblyomma cajennense* is the major vector. Humans are infected through infected saliva after a tick bite. The duration of attachment is critical in any tick-borne rickettsiosis. Transmission is unlikely when the tick feeds for less than 20 hours.[6] Since the tick bite is painless, it is often unnoticed. An eschar at the tick bite site is rarely observed. The epidemiology of Rocky Mountain spotted fever varies annually. This temporal repartition is determined by tick activity and human encounters. More than 500 cases occur each year, and more than 90% are reported from April to September. The disease is more common in children under 10 years of age.

CLINICAL MANIFESTATIONS

Two days to two weeks after the tick bite, fever and headaches appear. The fever is high (temperature >102°F) and associated with nonspecific symptoms such as malaise, myalgias, nausea, vomiting, anorexia, and diarrhea. Due to the absence of specific symptoms, Rocky Mountain spotted fever is not frequently diagnosed at this stage, but patients with high fever who live in or have a history of travel to an endemic area during the "tick season" and, possibly, have a history of tick bite should be considered as possible cases of Rocky Mountain spotted fever.

The most characteristic feature is a rash. However, the classic triad of fever, headache, and rash is present in only 44% of confirmed cases. A rash is found in 14% of cases on the first day of disease and in less than 50% in the first 3 days. The rash is macular; spots are 1 to 5 mm in diameter and can evolve from pink to purpuric (Fig. 302-2). The rash appears first on the ankles and wrists and then generalizes, but it can appear later or even not at all. Involvement of the palms and soles theoretically differentiates the typhus diseases (in which it is absent) from spotted fever rickettsioses. "Spotless" Rocky Mountain spotted fever represents one-third of cases.

Untreated patients worsen progressively. The disease is associated in various degrees with general manifestations related to vascular inflammation and increased vascular permeability, which can lead to multiple organ dysfunction syndrome. In severe forms, patients suffer from edema, hypovolemia, hypoalbuminemia, and hypotension leading to shock. In very severe cases, necrosis and gangrene of the extremities occur. In some instances, noncardiogenic pulmonary edema develops; pulmonary involvement leading to respiratory distress can cause death. Renal failure can result either from hypovolemia and shock and be reversible or from acute tubular necrosis and require hemodialysis. The usual neurologic symptoms are confusion, lethargy, and stupor. In severe cases, delirium, coma, and seizures are observed.[7] In some series, cerebrospinal fluid (CSF) sampling exhibits meningitis in one third of cases; in general, a few mononuclear cells (10 to 100) are observed, along with increased protein but normal glucose levels. Cardiac arrhythmias may occur. Intestinal tract involvement is manifested as abdominal pain, diarrhea, vomiting, and severe bleeding. Upper gastrointestinal hemorrhage can cause death. Ocular involvement may consist of conjunctivitis and retinal abnormalities, including hemorrhages, papilledema, and arterial occlusion.

The white blood cell count is usually normal, but immature myeloid cells are frequently present. Thrombocytopenia is observed in 30 to 50% of cases and may be marked in severe cases. Anemia develops in 30% of patients. Coagulopathy with decreased clotting factors (including fibrinogen) and prolonged coagulation times may contribute to bleeding. There may be hypoalbuminemia, and proteins of the acute phase response are increased (C-reactive protein, ferritin, fibrinogen). Hyponatremia and hypocalcemia may be noted and correlate with severity, as does an increase in creatinine. Increased concentrations of serum liver and muscle enzymes such as aminotransferases (aspartate [AST] and alanine [ALT] aminotransferase), lactate dehydrogenase (LDH), and creatine kinase usually reflect the severity of organ involvement, including the lung, heart, liver, and rhabdomyolysis.

DIAGNOSIS

The diagnosis of Rocky Mountain spotted fever should rely on clinical and epidemiologic findings. The most important clue is unexplained fever in a patient with a history of tick exposure in an endemic area. When a rash is present, Rocky Mountain spotted fever should be suspected and the patient should be treated accordingly unless another cause is demonstrated.

The differential diagnoses include other rickettsioses (such as those caused by *R. parkeri* in southern states), meningococcemia (Chapter 274), enterovirus infections (Chapter 349), typhoid (Chapter 284), leptospirosis (Chapter 298), ehrlichiosis, gonococcemia (Chapter 275), toxic shock syndrome (Chapters 267 and 269), syphilis (Chapter 295), rubella (Chapter 339), measles (Chapter 338), and Kawasaki syndrome (Chapters 254 and 406). Drug hypersensitivity (Chapter 234), especially after antimicrobial use for febrile illness, is sometimes confused with Rocky Mountain spotted fever.

Direct detection of the bacterium by demonstration of specific antigens by immunodetection or genomic amplification by PCR provides a definite diagnosis of infection.[8] A biopsy specimen or a swab of a skin lesion, preferably of an inoculation eschar, is the best sample for this purpose. Direct detection in removed ticks using PCR is also very useful. In contrast, blood contains inhibitors and only a few copies of rickettsial DNA.

ABSTRACT

Rickettsioses, which include infections that are mostly arthropod-borne and zoonotic, are caused by *Rickettsia* sp, *Ehrlichia* sp, or *Coxiella burnetii*. These infections are encountered worldwide, and their distribution mimics that of their reservoirs and/or vectors. Rickettsioses represent a heavy disease burden in both farm animals and humans and are among the main causes of travel-associated infections. They may be difficult to diagnose because most patients will present with mild symptoms, but some of the rickettsioses, such as Mediterranean spotted fever, have a characteristic clinical picture. Epidemic typhus and Rocky Mountain spotted fever are associated with significant mortality.

KEYWORDS

rickettsioses
ehrlichiosis
anaplasmosis
Q fever
zoonoses
arthropods

TABLE 302-1 GENETIC CLASSIFICATION OF RICKETTSIALES

	GENUS	GROUP	SPECIES	SUBSPECIES
Rickettsiae	*Rickettsia*	Typhus	*R. prowazekii*	
			R. typhi	
		Spotted fever	*R. aeschlimannii*	
			R. africae	
			R. akari	
			R. asembonensis	
			R. australis	
			R. conorii	*Conorii*
				Israeli
				Caspia
				Indica
			R. felis	
			R. fournieri	
			R. helvetica	
			R. heilongjiangensis	
			R. honei	
			R. japonica	
			R. massiliae	
			R. monacensis	
			R. parkeri	
			"*R. philipii*"	
			R. raoultii	
			R. rickettsii	
			R. sibirica	*Sibirica*
				Mongolitimonae
			R. slovaca	
			R. tillamookensis	
			Candidatus R. xinyangensis	
	Orientia	Scrub typhus	*O. tsutsugamushi*	
Ehrlichiae	*Ehrlichia*		*E. chaffeensis*	
			E. ewingii	
			E. canis	
			E. muris–like	
			Candidatus Neoehrlichia mikurensis	
	Anaplasma		*A. phagocytophilum*	
	Neorickettsia		*N. sennetsu*	
	Wolbachia		*W. pipientis*	
Coxiellae	*Coxiella*		*C. burnetii*	

TABLE 302-2 RICKETTSIAL DISEASES IN HUMAN BEINGS

DISEASE	ORGANISM	ARTHROPOD HOST	GEOGRAPHIC AREA	RASH	ESCHAR TACHE NOIRE	REGIONAL LYMPH NODE	HIGH FEVER	FATALITY RATE
TICK-TRANSMITTED SPOTTED FEVERS								
Rocky Mountain spotted fever	*R. rickettsii*	*Dermacentor andersoni* *Dermacentor variabilis* *Rhipicephalus sanguineus* *Amblyomma cajennense*	America (North, Central, and South)	Yes, may be purpuric	Very rare	No	Yes	High
Mediterranean spotted fever, Astrakhan fever, Indian tick typhus, Israeli spotted fever	*R. conorii*	*Rhipicephalus sanguineus*	Mediterranean, India, Caspian Sea, Africa	Yes, papular; may be purpuric	Yes	No	Yes	Moderate
African tick-bite fever	*R. africae*	*Amblyomma hebraeum* *Amblyomma variegatum*	Sub-Saharan Africa, West Indies	Yes, half of cases may be vesicular	Yes (frequently multiple)	Yes	No	Low
Queensland tick typhus	*R. australis*	*Ixodes holocyclus*	Eastern Australia	Yes, may be vesicular	Yes	?	Yes	Moderate

TABLE 302-2 RICKETTSIAL DISEASES IN HUMAN BEINGS—cont'd

DISEASE	ORGANISM	ARTHROPOD HOST	GEOGRAPHIC AREA	RASH	ESCHAR TACHE NOIRE	REGIONAL LYMPH NODE	HIGH FEVER	FATALITY RATE
Siberian tick typhus	*R. sibirica*	*Dermacentor nuttallii*	Siberia, China, Mongolia	Yes	Yes	No	Yes	Low
Scalp eschar, neck lymphadenopathy after tick bite (SENLAT)	*R. slovaca* or *R. raoultii*	*Dermacentor marginatus* *Dermacentor reticulatus*	Europe, Pakistan	Very rare	Yes, may be erythematous	Yes (painful)	No	Low
Lymphangitis-associated rickettsiosis (LAR)	*R. sibirica mongolitimonae*	*Hyalomma asiaticum*	Mongolia, Africa, Europe	Yes	Yes	Yes	Yes	Low
Flinders Island spotted fever	*R. honei*	*Ixodes granulosus*	Flinders Island, eastern Australia	Yes	Yes	Yes	Yes	Low
Japanese spotted fever	*R. japonica*	*Ixodes ricinus*	Japan, Korea (China?)	Yes	Yes	No	Yes	Low
Pacific coast tick fever	"*R. philipii*"	*Dermacentor occidentalis*	Northern California	Yes	Yes	No	Yes	Unknown
Unnamed	*R. aeschlimannii*	*Hyalomma* sp	Mediterranean, Africa	Yes	Yes	Yes	Yes	Unknown
	R. helvetica	*Ixodes ricinus*	Europe, Asia	No	Yes	No	No	Unknown
	R. massiliae	*Rhipicephalus sanguineus*	Europe, United States	Yes	Yes	No	Yes	Unknown
	R. monacensis	*Ixodes Ricinus*	Europe	Yes	Yes	No	Yes	Unknown
	R. parkeri	*Amblyomma maculatum*	America	Yes	Yes	No	Yes	Unknown
	Candidatus R. xinyangensis	*Haemaphysalis longicornis*	China	No	Yes	Yes	Yes	Unknown
FLEA-TRANSMITTED DISEASES								
Murine typhus	*R. typhi*	*Xenopsylla cheopis* *Ctenocephalides felis* (mosquitoes)	Worldwide	Yes	No	No	Yes	Low
Flea-borne spotted fever	*R. felis*	*Ctenocephalides felis*, *Aedes* mosquitoes	Worldwide	Sometimes	Sometimes	Unknown	Yes	Unknown
Unnamed	*R. asembonensis*	*Ctenocephalides felis*	Peru, Zambia	Unknown	Unknown	Unknown	Yes	Unknown
LOUSE-TRANSMITTED DISEASES								
Epidemic typhus	*R. prowazekii*	*Pediculus humanus corporis* *Amblyomma* ticks (?)	Worldwide	Yes	No	No	Yes	High
American sylvatic typhus	*R. prowazekii*	Flying squirrel ectoparasites	United States	Yes	No	No	Yes	Low
Brill-Zinsser disease (relapse of epidemic typhus)	*R. prowazekii*		Worldwide	Yes, could lack	No	No	No	Low
MITE-TRANSMITTED DISEASES								
Rickettsialpox	*R. akari*	*Liponyssoides sanguineus*	Worldwide	Yes, vesicular	Yes	Yes	Yes	Low
Scrub typhus	*Orientia tsutsugamushi*	*Leptotrombidium* sp (chiggers)	Central and Eastern Asia, Australia	Yes	Yes	Yes	Yes	High, may relapse

sp = species.

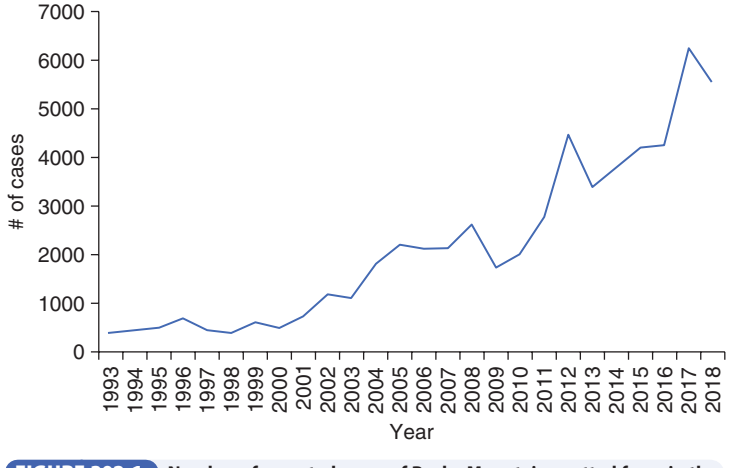

FIGURE 302-1. Number of reported cases of Rocky Mountain spotted fever in the United States, 1993 to 2018.

The diagnosis can also be confirmed by serology, but treatment should never be delayed to obtain its results. Criteria for laboratory confirmation include a four-fold or greater change in antibody titer determined by serology (measured by immunofluorescence antibody assay). Two serum samples should be tested (early and convalescent). The early serum is usually negative because patients seroconvert between the 7th and 15th days. A cutoff value of 1:64 for total immunoglobulin and 1:32 for IgM antibodies is required for diagnosis. The latex agglutination cutoff is 1:64 or 1:128.

However, serology is nonspecific. Cross-reactive antibodies have been reported, mainly with infections caused by other rickettsioses, but also infections with *Ehrlichia, Bartonella, Legionella*, and *Proteus* spp. False-positive results, including IgM, may be observed when rheumatoid factor is present in serum and in patients who have viral infections that generate nonspecific B-lymphocyte proliferation (e.g., cytomegalovirus [Chapter 347], Epstein-Barr virus [Chapter 348]).

Culture of rickettsiae takes 3 to 7 days and is restricted to specialized laboratories. Immunodetection by immunofluorescence antibody assay or immunohistochemistry is sensitive and specific but requires specific antibodies. It

FIGURE 302-2. Rocky Mountain spotted fever. Maculopapular rash observed in a patient with Rocky Mountain spotted fever. (Courtesy Gerardo Alvarez, MD, University of Sonora, Mexico.)

can be performed with frozen or fixed and paraffin-embedded material and allows retrospective diagnosis.

TREATMENT

Doxycycline is life-saving in patients with Rocky Mountain spotted fever,[9] and the prognosis depends on the timing of antimicrobial treatment. The recommended dose is 100 mg two times a day, and treatment should be continued for at least 3 days after the fever resolves. Oral treatment is effective, but the intravenous route should be used in patients with gastric intolerance or coma. Fluoroquinolones, rifampin, and some macrolides (azithromycin and clarithromycin but not erythromycin) are also effective in vitro, but lack of clinical experience precludes their use for Rocky Mountain spotted fever. β-Lactam antimicrobials, aminoglycosides, and cotrimoxazole are not effective.

Severely ill patients should be treated in intensive care units. Fluid administration must be carefully monitored. Mechanical ventilation is used in case of respiratory distress (Chapter 90), hemodialysis in patients with renal insufficiency (Chapter 117), and antiseizure drugs in patients with seizures (Chapter 372). Anemia and coagulation abnormalities may also be corrected. For patients with gangrene of the extremities, amputation may be necessary. Glucocorticoids have not proved useful.

PREVENTION

Prevention is based on the use of repellents, protective garments, or both to avoid tick bites. Repellents containing permethrin can be sprayed on boots and clothing and will persist for several days. Repellents containing DEET (*N,N*-diethyl-*m*-toluamide) can be applied to the skin but will persist only a few hours before reapplication is necessary. After being outdoors in areas of potential tick exposure, careful examination of the scalp, groin, and axillae is also recommended. The tick can be removed by forceps, and the skin should be disinfected (Fig. 302-3).

PROGNOSIS

The prognosis of Rocky Mountain spotted fever depends strongly on the timing of diagnosis and antimicrobial treatment. The overall case-fatality rate is 2.5%, but it is higher in patients older than age 70 years (9%). No significant difference in outcome has been observed between Blacks and Whites. Patients with glucose-6-phosphate dehydrogenase (G6PD) deficiency are more susceptible to severe infection. Recovery is usually complete, but neurologic sequelae can remain, and amputation of extremities may be necessary after gangrene.

OTHER TICK-BORNE RICKETTSIOSES

EPIDEMIOLOGY

Tick-borne rickettsioses have a limited geographic distribution that is determined mainly by the ecology of the tick vector (Fig. 302-4). *R. parkeri* has been identified in the United States and South America. *R. philipii* is seen in the United States. In Europe, *R. conorii* is distributed around the Mediterranean and Caspian seas (*caspia* subspecies); *R. slovaca, R. raoultii*, and possibly *R. helvetica* are seen in Western and Central Europe; and *R. sibirica mongolitimonae*

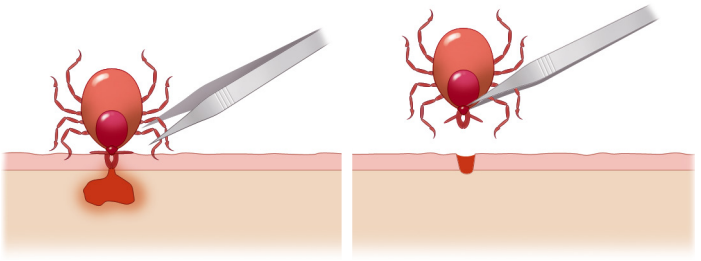

FIGURE 302-3. Tick removal technique.

is detected in France and Greece. Elsewhere, a number of specific agents of rickettsial disease have been identified (see Table 302-2).

R. africae causes African tick-bite fever, which may be the most common rickettsiosis worldwide. It is extremely common in travelers visiting safari parks in Southern Africa.[10] It is transmitted by *Amblyomma hebraeum* and *Amblyomma africanum* ticks. These ticks are often infected; as many as 60% can harbor *R. africae*. They usually feed on ungulates but also attack human beings in groups and cause a high prevalence of infection in rural Africa and in travelers. The tick attacks typically generate clusters of cases as well as multiple eschars in safari tourists.

CLINICAL MANIFESTATIONS

R. conorii comprises different but closely related subspecies. Many names are given to the infection caused by *R. conorii*: mainly Mediterranean spotted fever, but also boutonneuse fever, Marseilles fever, and Kenya tick typhus for infections caused by the subspecies *R. conorii conorii*; Astrakhan fever (caused by *R. conorii caspia*); Israeli spotted fever (caused by *R. conorii israelensis*); and Indian tick typhus (caused by *R. conorii indica*). *R. conorii* is closely related to *R. rickettsii*, with which it shares many common antigens that generate cross-reactive antibodies.

Mediterranean spotted fever resembles Rocky Mountain spotted fever but has some distinguishing features. A malignant form of the disease that includes purpuric rash, shock, and multiple organ dysfunction has been described in elderly, debilitated patients and in patients with liver disease, diabetes, human immunodeficiency virus (HIV) or G6PD deficiency. The typical clinical presentation is that of a patient with fever, a rash, and a tache noire (i.e., an inoculation eschar at the site of the tick bite). A tache noire is found in 50 to 80% of cases. Multiple eschars are rare because the dog tick vector, *R. sanguineus*, seldom bites humans. The rash is frequently maculopapular and involves the palms and soles but spares the head.

Israeli tick-bite fever and Astrakhan fever appear to be milder than typical Mediterranean spotted fever. A tache noire is usually lacking.

African tick-bite fever differs from Mediterranean spotted fever in that it is much milder. Fever is frequently absent. Rash, which is observed in only about 50% of patients, may be vesicular (which has never been reported in confirmed Mediterranean spotted fever). Moreover, several eschars are frequently observed, often on the lower limbs and associated with draining lymphadenopathy in the groin.

Japanese spotted fever (caused by *Rickettsia japonica*) and Siberian tick typhus (caused by *R. sibirica*) resemble Mediterranean spotted fever. Lymphangitis-associated rickettsiosis, caused by *R. sibirica mongolitimonae*, also resembles Mediterranean spotted fever but in some cases exhibits distinguishing clinical features, including an eschar, groin lymphadenopathy, and lymphangitis joining these two lesions. *Rickettsia australis* (Queensland tick typhus) and *Rickettsia honei* (Flinders Island spotted fever) cause diseases resembling Mediterranean spotted fever, but their rash can be vesicular.

R. slovaca and *R. raoultii* cause a common disease in Europe named scalp eschar and neck lymphadenopathy transmitted by ticks (SENLAT, reported in the Czech Republic, France, Hungary, Germany, Italy, Lithuania, Romania, Spain, Turkey). Its tick vectors, *Dermacentor marginatus* and *Dermacentor reticulatus*, preferentially bite in cold months and bite the scalp. In contrast to other tick-borne rickettsioses, the disease is more prevalent in children and women. It is rarely exanthematic; the typical clinical picture consists of an inoculation eschar at the site of the tick bite on the scalp and draining neck lymphadenopathy (which may be painful). Rarely, patients may exhibit fever and a rash. Deep postinfectious asthenia and residual alopecia at the site of the tick bite can be observed. Other *Rickettsia* species that rarely have been identified as causing SENLAT include *Rickettsia massiliae*, *Rickettsia sibirica mongolitimonae*, and *Candidatus* Rickettsia rioja.

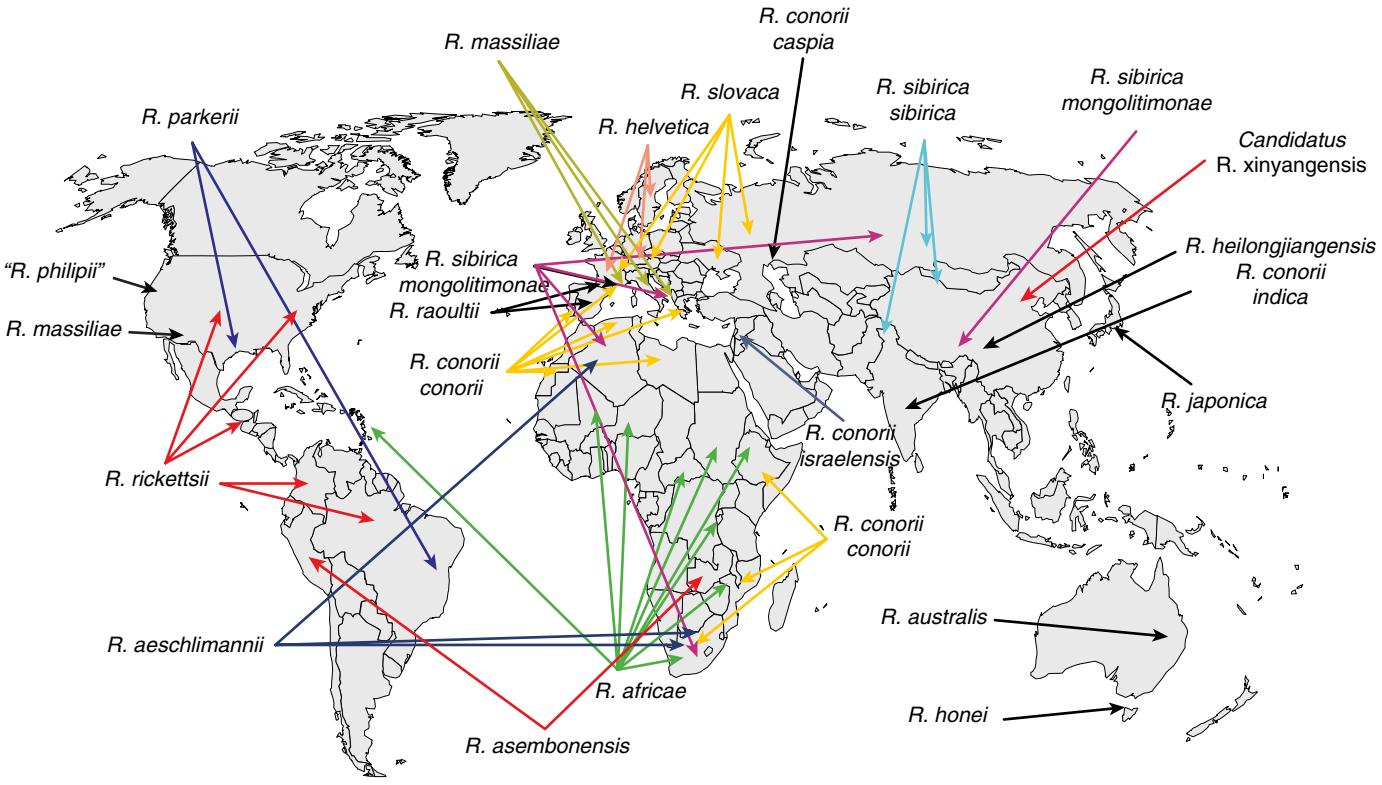

FIGURE 302-4. **Geographic distribution of tick-borne rickettsioses.**

DIAGNOSIS

The diagnosis of other tick-borne rickettsioses is similar to that of Rocky Mountain spotted fever, mainly by serology,[11] although PCR testing is becoming increasingly available.[12] An exception is *R. slovaca* infection, in which the serologic response is weak, possibly because of its lack of general infection; in this case, PCR of a skin eschar sample by a swab or a lymph node aspirate provides the highest diagnostic yield. In *R. africae* infection, the serologic response occurs later than in Rocky Mountain spotted fever and Mediterranean spotted fever; late serum samples (i.e., 4 weeks after onset of symptoms) are therefore recommended.

TREATMENT

Doxycycline (100 mg twice daily for adults or 4.4 mg/kg body weight per day in two divided doses for children under 45.4 kg [100 lb]) is the drug of choice. A single day of therapy usually suffices; in adults with more severe disease, however, it should be administered until the patient is afebrile for 24 hours. Quinolones (e.g., ciprofloxacin 1 g daily) and newer macrolides (e.g., azithromycin 500 mg daily for 5 days) provide results that are comparable to those of doxycycline but require longer treatment courses. In pregnant women, josamycin, a macrolide antimicrobial, has proved efficient at a dose of 3 g daily for 7 days for Mediterranean spotted fever.

PROGNOSIS

Most patients recover completely with treatment, but hospitalized patients have a fatality rate of 1.5 to 2.5%.

FLEA-TRANSMITTED DISEASES

Fleas (Chapter 98) can harbor three rickettsial species: *Rickettsia typhi*, which is the agent of murine typhus; *Rickettsia felis*, which is the agent of flea-borne spotted fever; and *R. asembonensis*. Both *R. typhi* and *R. felis* can be transmitted transovarially in the flea. Vectors are *Xenopsylla cheopis* and *Pulex irritans* but also *Ctenocephalides felis*, which is a cat flea. Rats, cats, opossums, and dogs can propagate infected fleas. These reservoirs and vectors are distributed worldwide, so these diseases have a global distribution. Fleas can be infected by both species at the same time. *R. asembonensis*, the agent of an unnamed rickettsiosis, has been associated with cat fleas worldwide but detected in humans only in Peru and Zambia.

MURINE TYPHUS

EPIDEMIOLOGY AND PATHOBIOLOGY

In the United States, 50 to 100 cases are reported yearly, mainly in Southern California and southern Texas.[13] In California, a transmission cycle involving opossums and cat fleas has been demonstrated. Murine typhus is extremely common in China, Southeast Asia, and North Africa, and it also is a common cause of fever in travelers to those areas.

Fleas are usually infected by *R. typhi* when feeding on apparently healthy rats that have blood-borne infection. Humans and other mammals are infected through autoinoculation by scratching a flea bite that is contaminated with feces from an infected flea. Murine typhus, because of its cycle, is more prevalent in hot and humid areas, when rats proliferate.

CLINICAL MANIFESTATIONS

The incubation period is generally 8 to 16 days. The disease begins with abrupt fever, nausea, vomiting, myalgias, arthralgias, and headache. A rash, which develops in 40 to 50% of patients about 6 days after the onset, is detected less frequently in patients with dark skin. The rash begins as pink maculae that can evolve to be maculopapular. The rash is often discrete, starting in the axilla and spreading to the trunk but not usually to the face, palms, or soles. In severe cases, it can become purpuric.

The most frequently involved organ is the lung. One third of patients have a cough, and about 25% of patients develop a nonspecific interstitial pneumonia that is sometimes associated with a pleural effusion. In severe forms, respiratory failure occurs. Digestive involvement can manifest as vomiting, abdominal pain, jaundice, and, in severe cases, hematemesis. In patients with severe disease, neurologic symptoms range from confusion and stupor to coma and seizures. Cerebral hemorrhages may occur.

The white blood cell count shows leukopenia and then leukocytosis. Thrombocytopenia can be noted as well as anemia, specifically when hemolysis is observed (frequently in patients with G6PD deficiency). A moderate increase in serum liver enzymes is common. In patients with severe disease, hyponatremia and hypoalbuminemia are observed.

DIAGNOSIS

The diagnosis of murine typhus, as with Rocky Mountain spotted fever, is based mainly on serology immunofluorescence antibody assay. *R. typhi* cross-reacts with *R. prowazekii*, but it can be differentiated by additional testing.

Skin biopsies and blood samples for culture and PCR may be valuable but cannot currently substitute for serologies.

TREATMENT

Treatment is the same as for Rocky Mountain spotted fever.

PROGNOSIS

The prognosis is usually favorable, but about 35% of patients require urgent hospital admission and 1% die.[14] Older patients and patients with G6PD deficiency (Chapter 147) or chronic debilitating conditions are at higher risk.

FLEA-BORNE SPOTTED FEVER CAUSED BY *RICKETTSIA FELIS*

In fleas, *R. felis* is mainly transmitted transovarially. Its genome comprises one or two plasmids, one being apparently conjugative. The bacterium is found in fleas in the Americas, Asia, Europe, Africa, and New Zealand. *R. felis* has been found at very high prevalence in the blood of febrile sub-Saharan Africans and is suspected to be transmitted by mosquitoes. Isolated cases have been reported from Texas, Mexico, Brazil, France, and Germany. Among reported cases, all exhibited fever, most had a rash, and an inoculation eschar was visualized in some cases. The diagnosis can be based on serologic testing using immunofluorescent assay or using PCR on blood swabs or skin biopsy samples. Treatment has not been established, but the bacterium is highly susceptible to doxycycline (as for Rocky Mountain spotted fever) and resistant to erythromycin.

LOUSE AND MITE INFECTIONS

EPIDEMIC LOUSE-BORNE TYPHUS

Epidemiology and Pathobiology

The human body louse, *Pediculus humanus humanus* (Chapter 98), lives in clothes and multiplies rapidly when cold weather and lack of hygiene permit. The body louse transmits three bacterial diseases: trench fever (caused by *Bartonella quintana* [Chapter 291]), relapsing fever (caused by *Borrelia recurrentis* [Chapter 297]), and exanthematic or epidemic typhus (caused by *R. prowazekii*). Louse-transmitted diseases killed more people than weapons did during Central and Eastern European wars in the 19th and 20th centuries. The body louse is prevalent in cold seasons during wars, in poor countries, and in the homeless population of rich countries, including the United States and Europe. Over the past 30 years, epidemic typhus has been reported in Burundi, where a 100,000-person outbreak occurred in 1997 during the civil war.

The epidemiology of *R. prowazekii* is mainly related to humans as reservoirs and lice as vectors. In the United States, the eastern flying squirrel (*Glaucomys volans volans*) is also a reservoir, and its fleas, lice, and mites can be infected and, occasionally, infect humans.

R. prowazekii has also seldom been found in *Amblyomma* ticks, but their role in the epidemiology of the bacterium is unknown. The louse is infected when feeding on blood of an infected individual, which it does five times a day. *R. prowazekii* multiplies in the gut of the louse and is released in feces. After a few days, it destroys the louse intestinal epithelium, thereby causing blood to spread from the gut. The patient is usually contaminated by infected feces (in which *R. prowazekii* survives for weeks), through aerosols, or by skin autoinoculation after scratching.

CLINICAL MANIFESTATIONS

Epidemic typhus begins abruptly with fever, headaches, and myalgias, which may lead to the crouched posture termed *sutama*, as observed in the largest recent outbreak in Burundi. Cough and neurologic signs (stupor, confusion, or coma) are common.[15] A rash, which is observed in 20 to 80% of patients, generally starts in the axilla and then spreads. The rash is usually macular but can be papular or purpuric in severe cases. In some cases, diarrhea and jaundice are reported. Splenomegaly is infrequently found. In severe cases, shock occurs. Leukopenia, thrombocytopenia, and anemia, as well as an increase in serum hepatic enzymes, may be noted.

Sylvatic typhus in the United States is caused by a *R. prowazekii* variant and is a milder disease. The most prominent clinical features are neurologic. Few cases have been described, and nearly all occurred in areas where the eastern flying squirrel is found, east of the Mississippi.

Brill-Zinsser disease, which is relapsed bacteremia typhus, is difficult to diagnose because a rash is rare and recent exposure to lice can be lacking. Interviewing the patient may reveal prior exposure to lice, associated or not with a history of epidemic typhus in previous years.

DIAGNOSIS

The diagnosis of typhus should be considered when grouped cases of high fever with confusion are observed in patients exposed to lice. The diagnosis of epidemic typhus should primarily be clinical because the fatality rate is high in untreated patients, whereas treatment is safe and efficient. Any outbreak of unexplained fever in unhygienic environments may suggest typhus, including outbreaks during civil wars, during social collapses, in jails, and in chronically poor countries, particularly in the cold season.

The diagnosis is mainly based on serology, with immunofluorescent assay being the reference method. However, cross-reaction with *R. typhi* is common (see earlier). When the investigation is performed under difficult field conditions, a drop of blood applied on filter paper and sent to a reference laboratory is valuable for serologic testing. Culture and PCR are helpful and can be performed with a skin biopsy sample or blood, but serology remains the preferred test. Lice are good diagnostic tools because they can be tested even when dry and can be sent in closed containers without specific temperature conditions.

The most common diagnostic error is to attribute the findings to typhoid (Chapter 284), which can have fatal consequences because the antimicrobials typically prescribed for that condition (β-lactams, cotrimoxazole, and quinolones) are ineffective treatment of typhus. In tropical countries, typhus is frequently confused with malaria (Chapter 316), viral hemorrhagic fever (Chapter 351), and dengue (Chapter 352). In people with lice, it can be confused with trench fever (Chapter 291) and relapsing fever (Chapter 297), but treatment for both can be prescribed.

TREATMENT

Treatment of typhus is extremely simple, cheap, and effective; 200 mg of doxycycline orally in two divided doses is life-saving. Comatose patients should be treated with intravenous doxycycline. In allergic patients, intravenous chloramphenicol is the only known alternative, prescribed at a dose of 2 g/day for 10 days. There is no current vaccination, and the fight against lice is the major prevention strategy. Because lice are fragile, changing and boiling clothes are efficient. When this is not possible, insecticides (primarily permethrin) or oral ivermectin should be used.

PROGNOSIS

The fatality rate of untreated epidemic typhus is 20 to 30%. Patients who recover from typhus may harbor the bacterium in a dormant form and suffer relapses under stressful conditions years later. In this relapsing form, named Brill-Zinsser disease, a bacteremia may allow the start of a new outbreak if lice bite the patient. Brill-Zinsser disease itself is mild, and the prognosis is good.

SCRUB TYPHUS (*ORIENTIA TSUTSUGAMUSHI*)

EPIDEMIOLOGY AND PATHOBIOLOGY

Scrub typhus is a neglected tropical disease transmitted by the bite of trombiculid mite (Chapter 98) larvae infected by *O. tsutsugamushi*. These mites, also named chiggers, are vertically infected by transovarial transmission. Although rare cases have been reported in Chile, sub-Saharan Africa, and United Arab Emirates, scrub typhus distribution is mostly limited to a triangle extending between northern Japan, eastern Australia, and eastern Russia, including the Far East, China, and the Indian subcontinent.[16] Altogether, 1 billion people may be exposed, and the number of annual cases is estimated to be 1 million. Travelers returning from endemic countries are also at risk.

Seasonality is determined by the emergence of mite larvae. Scrub typhus is one of the three most common causes of prolonged fever in rural Asia. In temperate zones, it occurs mainly in autumn and to a lesser extent in spring. *O. tsutsugamushi* exhibits a wide genetic heterogenicity that may allow the definition of several species, but a single species with many serotypes (the most frequent being Kato, Karp, Gilliam, and Kawasaki) is currently recognized.

CLINICAL MANIFESTATIONS

The disease occurs in patients exposed to rural or urban foci of scrub typhus after a delay of 10 or more days. The onset, which is usually sudden, includes fever, headache, and myalgias. Attentive examination may reveal an inoculation eschar at the site of the mite bite as well as tender draining lymph nodes. Most patients with scrub typhus present with relative bradycardia. Generalized lymphadenopathy and rash may be observed. The symptoms vary according to organ involvement. Neuromeningeal symptoms are relatively common.[17] Severe forms can present as septic shock.

Leukopenia, thrombocytopenia, and increased levels of hepatic enzymes can occur. Scrub typhus is not more severe in HIV-infected patients, and surprisingly, HIV-suppressive factors appear to be produced during infection.

DIAGNOSIS

Diagnosis may be difficult. Because the clinical features are frequently not specific, epidemiologic factors are critical. The bacterium can be detected by PCR of blood, CSF, pleural fluid, or biopsy specimens.[I8] The most reliable serologic techniques are immunofluorescence antibody assay and enzyme-linked immunosorbent assay tests using the three or four major serotypes. Point-of-care testing for scrub typhus still lacks standardized methodology and diagnostic accuracy.

TREATMENT

In severe forms, intravenous doxycycline (200 mg daily) is recommended for 7 days. Otherwise, the currently recommended regimen is doxycycline (100 mg orally twice a day, for 7 days).[A1] Single-day treatment with doxycycline is followed by relapses, and even repeated treatment for 2 days at a 7-day interval does not prevent all relapses. Cases resistant to doxycycline have been reported, and rifampin (600 mg orally daily) or chloramphenicol (2 g daily) may be used as alternative therapies.[A2] Quinolones should be avoided. Prophylaxis is based on the use of repellents.

PROGNOSIS

The mortality rate of untreated scrub typhus is 6% but can range from 0 to 30%, but the mortality is 1% or less with doxycycline treatment. Abortion commonly occurs in pregnant women. Relapses may occur in patients who initially respond to treatment.

RICKETTSIALPOX (*RICKETTSIA AKARI*)

EPIDEMIOLOGY AND PATHOBIOLOGY

Rickettsialpox was first described in New York City, where it is still prevalent. *Rickettsia akari*, the causal agent, is transmitted by the bite of the mouse mite (*Liponyssoides sanguineus*). Its prevalence is probably underestimated. Cases have also been reported in Arizona, Utah, and Ohio. High seroprevalence was reported among intravenous drug users in Baltimore. Cases have also been reported from Russia, Ukraine, Slovenia, South Africa, and Korea.

CLINICAL MANIFESTATIONS

Ten days after the mite bite, the onset of illness is marked by fever, headache, and myalgia. Careful examination reveals an inoculation eschar and draining lymphadenopathy that could be mistaken for cutaneous anthrax (Chapter 272). Two to 6 days later, a rash appears and comprises 5 to 40 macular and then papular and vesicular spots. This aspect led to the name of the disease. It is frequently mistaken for chickenpox (Chapter 346).

DIAGNOSIS

The diagnosis can be made by PCR of skin lesions or by immunofluorescent assay serologic testing. Specific antigens react with high titer, but cross reactions with other *Rickettsia* may be detected.

TREATMENT

Oral doxycycline (200 mg daily for 7 days) is highly effective in these patients. Prevention is based on the control of mice.

PROGNOSIS

The disease is usually mild and resolves even without treatment.

EHRLICHIOSES AND ANAPLASMOSES

EPIDEMIOLOGY AND PATHOBIOLOGY

Ehrlichioses can be acquired through tick bites, by ingestion of nematodes through contaminated water or animals (fish, snails), or as a consequence of filariasis. All *Ehrlichia* spp pathogenic for humans except *E. ewingii* can be cultured. The ehrlichiae have been reclassified into four genera, mainly on the basis of 16S ribosomal RNA–derived phylogenetic analysis. Two are the tick-associated genera *Ehrlichia* and *Anaplasma* (*A. phagocytophilum*). One is a helminth-associated genus, *Neorickettsia*, including *Neorickettsia sennetsu*. The fourth is *Wolbachia pipientis*, a bacterium associated with arthropods (insects, crustaceans, and acarids) and helminth worms (mainly filaria). These organisms elicit cross-reactive antibodies.

Ehrlichiae multiply exclusively in vacuoles of their eukaryotic cell host, where they form clusters known as morulae. The vacuoles are derived from phagosomes and help the organism escape bactericidal lysosomal fusion. In humans, ehrlichiae infect monocytes (*E. chaffeensis, E. canis, N. sennetsu*) or polymorphonuclear neutrophils (*A. phagocytophilum, E. ewingii*).

AMERICAN HUMAN MONOCYTIC EHRLICHIOSIS (*EHRLICHIA CHAFFEENSIS*)

EPIDEMIOLOGY

Human monocytic ehrlichiosis is caused by *E. chaffeensis*. This organism has been isolated or identified by PCR mainly in the United States, particularly in the southeastern, south central, and mid-Atlantic states and in California (Table 302-3). In the United States, *A. americanum* (Lone Star tick) is the vector (Chapter 98), and the white-tailed deer is the main mammalian reservoir. Immature ticks are infected by blood while feeding on persistently bacteremic mammals. *E. chaffeensis* is transmitted transstadially in the tick and infects its next host (deer or human) during its next blood meal.

The epidemiology of the disease reflects the tick's habitat and activity, with most cases being contracted in the Southern United States, in rural areas, and from April to September. In 2019, 2000 cases were reported to the Centers for Disease Control and Prevention (CDC). The severity is age-dependent, which may explain the lower incidence reported in children. Males are more often affected than females, with a sex ratio of 4:1.

CLINICAL MANIFESTATIONS

The incubation is about 7 to 10 days after an identified tick exposure in 80% of cases. Patients have fever, headache, malaise, nausea, and anorexia. Untreated patients worsen and may require intensive care. Digestive tract involvement consisting of nausea, vomiting, diarrhea, and abdominal pain is common. Central nervous system infection may be polymorphic, ranging from confusion to coma. A rash is observed in one third of cases and lymphadenopathy in one fourth. In severe forms, sepsis syndrome and multiple organ dysfunction may occur.

The white blood cell count typically shows both lymphopenia and neutropenia. Thrombocytopenia is also frequent, and anemia may appear later. In severe forms, coagulopathy may be observed. Increases in aminotransferase levels indicate liver involvement, and renal dysfunction can occur. CSF examination in patients with neurologic symptoms reveals pleocytosis (with monocytes or neutrophils) and increased protein levels.

DIAGNOSIS

The diagnosis of human monocytic ehrlichiosis should be considered in patients with a history of tick exposure and unexplained fever. The disease resembles Rocky Mountain spotted fever, but rash is less frequent. Later in the disease,

TABLE 302-3 EHRLICHIOSES AND ANAPLASMOSES

DISEASE	AGENT	VECTOR	GEOGRAPHIC REPARTITION
American monocytic ehrlichiosis	*Ehrlichia chaffeensis*	*Amblyomma americanum*	South central, southeastern, mid-Atlantic coastal states
Human granulocytic ehrlichiosis	*Anaplasma phagocytophilum*	*Ixodes ricinus* *Ixodes scapularis*	Europe, China Northeast, upper Midwest, northern California
Japanese monocytic ehrlichiosis	*Neorickettsia sennetsu*	Helminth of the gray mullet?	Japan
Unnamed	*Ehrlichia canis*	*Rhipicephalus sanguineus*	Venezuela
	Ehrlichia ewingii	*Amblyomma americanum*	South central, southeastern, mid-Atlantic coastal states
	Ehrlichia muris–like	*Ixodes scapularis*	Indiana, Michigan, Minnesota, North Dakota, Wisconsin
	Candidatus Neoehrlichia mikurensis	*Ixodes ricinus*	Central and Eastern Europe, northeastern China

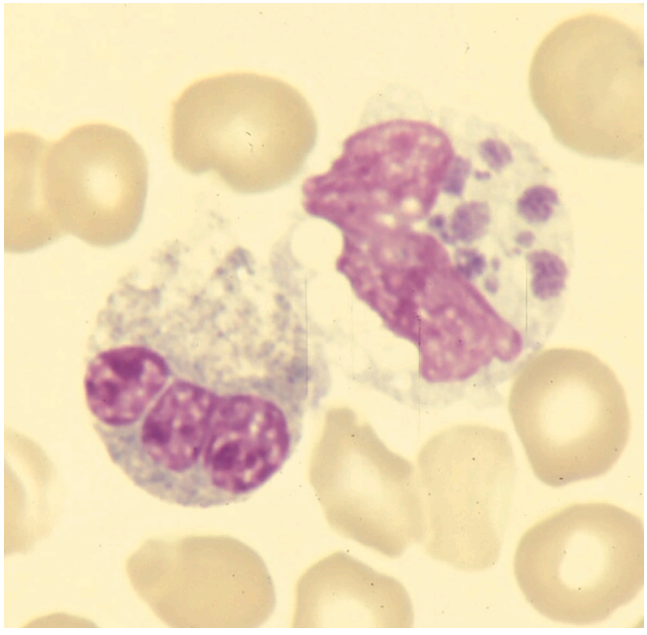

FIGURE 302-5. Blood smear in *Ehrlichia*. Note *Ehrlichia chaffeensis* morulae in a monocyte. (Courtesy Christopher D. Paddock, Centers for Disease Control and Prevention, Atlanta, GA, USA.)

human monocytic ehrlichiosis can be misdiagnosed as any other cause of severe sepsis (Chapter 94).

Leukopenia associated with thrombocytopenia and an increase in liver enzyme levels may suggest the diagnosis. Careful examination of blood and CSF smears may help identify typical morulae (Fig. 302-5).

The diagnosis can be made by PCR of blood or CSF.[19] Alternatively, seroconversion or a four-fold or greater increase in antibody titer by immunofluorescent assay is also diagnostic. Cross-reactive antibodies are common among *Ehrlichia* species and with *A. phagocytophilum*. Western blotting may be valuable to distinguish among these bacteria.

TREATMENT

Suspected cases should be treated without delay. Doxycycline (100 mg twice daily for adults) is the drug of choice for ehrlichiosis. The optimal duration of therapy has not been established, but current regimens recommend continuation of treatment for at least 3 days after the fever subsides and until evidence of clinical improvement, for a minimum total course of 5 to 7 days. Because tetracyclines are contraindicated in pregnancy, rifampin (10 mg/kg/day for 10 days) has been used successfully in a limited number of pregnant women with documented human monocytic ehrlichiosis.

PROGNOSIS

The prognosis depends on early antimicrobial treatment, but the fatality rate is still about 2.5% even with treatment.[20] In persons coinfected with HIV, it may be most severe; in one series, 6 of 13 patients died.

HUMAN GRANULOCYTIC EHRLICHIOSIS (*ANAPLASMA PHAGOCYTOPHILUM*)

EPIDEMIOLOGY AND PATHOBIOLOGY

A. phagocytophilum infection is distributed in America, Asia, and Europe (Fig. 302-6). It is transmitted by *Ixodes* ticks (*I. scapularis* [eastern North America], *I. pacificus* [western North America], *I. ricinus* [Europe], and *I. persulcatus* [Asia]), which are the vectors of Lyme disease (Chapter 296), and its epidemiology is similar.[21] Coinfection with the two diseases may occur. The temporal distribution of the disease parallels that of nymph tick activity, with two peaks in spring and autumn.

In 2017, a peak of 5762 cases was reported to the CDC. Males are more frequently infected than females, with a sex ratio of 3:1.

Ticks are born free of *A. phagocytophilum* and are infected while feeding on bacteremic small mammals. Deer play a major role as hosts of adult ticks and reservoirs.

CLINICAL MANIFESTATIONS

The incubation time is usually between 7 and 10 days, and 80% of patients report a history of tick exposure. Many infections may be asymptomatic or too mild to require a diagnostic procedure. The onset of disease is frequently abrupt, with fever, headache, malaise, and myalgias that may be particularly severe. A rash is found in less than 10% of cases. Visceral involvement can include digestive symptoms such as nausea, vomiting, and diarrhea. Neurologic symptoms may include confusion, meningitis, and meningoencephalitis.

Laboratory findings consist of the association of thrombocytopenia and leukopenia. Serum aminotransferase levels are frequently elevated.

DIAGNOSIS

PCR of blood can easily confirm the diagnosis. An alternative is serologic testing with an immunofluorescent assay, which is comparable to that in human monocytic ehrlichiosis (see earlier). The diagnosis can also be made by careful examination of blood smears for morulae within neutrophils. Culture from blood is also possible.

TREATMENT

Treatment is similar to that of human monocytic ehrlichiosis—doxycycline 100 mg twice daily for at least 5 to 7 days and at least 3 days after fever resolves and symptoms improve.

PROGNOSIS

The prognosis of the disease is favorable in most cases, even without specific therapy, but the disease may progress to septic shock in some patients.[22] Patients with underlying diseases are more at risk for death. However, the case fatality rate is less than 1%. Most deaths are the consequence of *Anaplasma*-induced immunosuppression, and patients may develop opportunistic infections such as invasive aspergillosis, candidiasis, cryptococcosis, and herpes esophagitis.

OTHER *EHRLICHIA*

Canine granulocytic ehrlichiosis is caused by *E. ewingii*. The vector of *E. ewingii* is *Amblyomma americanum*, which also transmits *E. chaffeensis*. To date, more than 260 cases of *E. ewingii* infection have been reported to the CDC. The disease has been prevalent in immunocompromised hosts coinfected with HIV or receiving immunosuppressive drugs. Patients who report tick exposure exhibit fever, thrombocytopenia, leukopenia, and various symptoms, including meningitis. Morulae may be seen in neutrophils on blood smears. The diagnosis should be considered when ehrlichiosis is suspected in immunocompromised patients exposed to *A. americanum* ticks.

Canine monocytic ehrlichiosis is caused by *E. canis* and transmitted by the dog tick *R. sanguineus*. This tick is found worldwide and is prevalent in temperate and hot areas. Recently, cases have been reported in patients in Venezuela and Costa Rica. Signs and symptoms are similar to those caused by *E. ewingii*.

More than 60 cases of ehrlichiosis have been caused by an *Ehrlichia* that is closely related to *E. muris*. The bacterium has also been cultured from *Ixodes scapularis* ticks in Wisconsin and Minnesota. Patients have fever, headache, myalgias, lymphopenia, thrombocytopenia, and elevated aminotransferase levels. *Candidatus* N. mikurensis, transmitted by *Ixodes* ticks, has been reported in febrile immunocompromised patients in Europe and China.

DIAGNOSIS, TREATMENT, AND PROGNOSIS

For these *Ehrlichia*, PCR of blood can be diagnostic. Patients respond dramatically to doxycycline as for *E. chaffeensis*. The prognosis in treated patients is good.

WOLBACHIA SPECIES

Wolbachia bacteria are endosymbionts of arthropods and nematodes. These bacteria manipulate the fertility of their host. Eradication of *Wolbachia* in filariae may lead to infertility and stop the microfilariae from spreading. This effect was demonstrated by field treatment with doxycycline in patients with onchocerciasis (Chapter 327). The patients improved when treated with this drug, which is effective on *Wolbachia* and subsequently on the worm's fertility but not on the worm itself. The adverse reactions observed after treatment of lymphatic filariasis (Chapter 327) may be caused by the release of *Wolbachia* from destroyed worms. Some experts suggested that eradicating *Wolbachia*

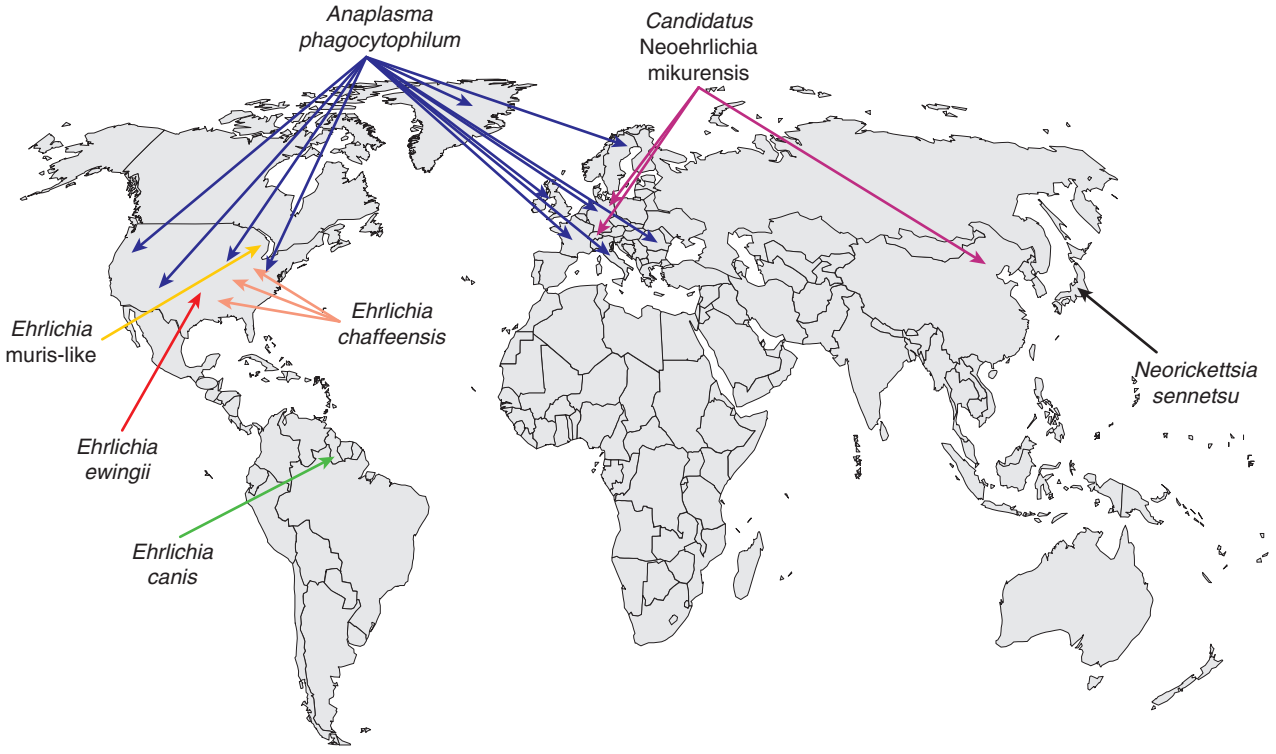

FIGURE 302-6. **Geographic distribution of ehrlichioses.**

using oral doxycycline (200 mg daily) before the anthelmintic prescription would avoid these reactions. *Loa loa* (Chapter 327) do not harbor *Wolbachia*, and the genome of *Wolbachia* integrated in the *Brugia malayi* genome makes it inaccessible to therapy.

Q FEVER

EPIDEMIOLOGY

Q fever is a worldwide zoonosis caused by *Coxiella burnetii*. Human infection varies in its severity, clinical expression, and natural course (i.e., acute or chronic). It is considered by the CDC to be a potential agent of bioterrorism.

C. burnetii infects a wide range of domestic and wild animals, including mammals, birds, and ticks. Ungulates are the most common source of the disease. Mammals are infected through aerosols and may shed *Coxiella* in feces, urine, milk, and birth products. Ruminants, in particular sheep and goats, are the major sources of human infection. Infection may occasionally be acquired following contact with pets.

Humans are usually infected by aerosols or, less frequently, by exposure to milk products. Rare cases of interhuman infections through sexual intercourse, during delivery, or by blood transfusion have been reported.

Coxiella can survive in the environment and can be spread far by the wind. The disease may cause outbreaks following exposure to infected sheep and goats. A large outbreak (>4000 cases) was reported in the Netherlands from 2007 to 2010. The disease is partly seasonal and related to lambing time. Males have more severe disease but are not more often exposed to Q fever, and middle-aged people are more frequently affected and hospitalized.[23] The number of reported cases recently increased dramatically in Europe and Asia. Many American soldiers were infected in Iraq.

PATHOBIOLOGY

C. burnetii is a gram-negative bacterium that naturally infects its host's monocytes and endothelial cells. In macrophages, the bacterium multiplies in an acidic vacuole, the phagolysosome. Strains are heterogeneous genetically and antigenically, and they cause acute infections of variable severity. In vitro, *C. burnetii* generates a deleted mutant also named phase II. This mutant exhibits diagnostic antigens that are useful because they are more reactive during acute infection.

C. burnetii may persist in the human body after acute infection. In immunocompromised hosts and patients with infected cardiac valves or arterial lesions, *C. burnetii* is able to multiply despite high levels of antibodies and to cause chronic infections. Control of the disease in acute Q fever is associated with the formation of a granuloma.

CLINICAL MANIFESTATIONS

After contamination by *C. burnetii*, 60% of patients seroconvert without apparent disease, 38% experience a self-limited disease, and only 2% require diagnostic evaluation.[24] Months to years after the primary infection, a chronic infection develops in 0.2 to 0.5% of patients, associated with an immunocompromised state, a cardiac valve lesion, or a vascular prosthesis or aneurysm.[25]

Patients with acute infection may have a variety of symptoms and signs (Table 302-4). Isolated prolonged fever was observed in 15% of patients.

TABLE 302-4 SITUATIONS THAT SHOULD PROMPT SEROLOGIC TESTING FOR Q FEVER

ACUTE Q FEVER (PHASE II ANTIGEN AND IgG ≥200 AND IgM ≥50)
Fever in a patient in contact with ungulates (hoofed mammals)
Unexplained prolonged fever (>7 days)
Granulomatous hepatitis
Fever and thrombocytopenia
Meningoencephalitis
Myocarditis
Erythema nodosum
Fever during pregnancy
Fever in a patient in contact with a parturient pet
Unexplained atypical pneumonia
Fever and an increase in transaminases (2-5 times the normal level)
Aseptic meningitis
Guillain-Barré syndrome
Pericarditis
Spontaneous abortion
CHRONIC Q FEVER (PHASE I ANTIGEN AND IgG ≥800 AND IgA ≥100)
Blood culture–negative endocarditis
Patient with a valvulopathy and unexplained:
Fever
Weight loss
Fatigue
Increased erythrocyte sedimentation rate
Increased transaminases
Thrombocytopenia
Patient with unusually rapid degradation of a prosthetic valve
Fever in a patient with a vascular aneurysm or prosthesis
Aseptic osteomyelitis
Chronic pericarditis
Multiple spontaneous abortions

Ig = immunoglobulin.

Pneumonia is found in 35 to 40% and is the only symptom in 15 to 20%. Some cases may be associated with respiratory distress. Hepatitis is found in about 60% of patients and is the sole manifestation in about 40%. The association of fever and a moderate increase in aminotransferase levels is an important clue. Other rare manifestations, which occur in only 1 to 2% of cases, include a rash, neurologic manifestations (e.g., meningitis, encephalitis, meningoencephalitis, or peripheral neuropathy), cardiovascular manifestations (e.g., pericarditis, or, more rarely, myocarditis or acute endocarditis), and prosthetic joint infection.

Patients with chronic Q fever endocarditis (Chapter 61) often suffer from low-grade fever, progressive degradation of valve function, and progressive heart failure. Fever is intermittent, and vegetations are frequently absent on echocardiography. Endocarditis is therefore not frequently considered in the initial differential diagnosis. If it is not diagnosed, the disease progressively worsens, and it can be complicated by emboli (mainly cerebral), renal insufficiency, splenomegaly, and hepatomegaly. Digital clubbing may also be seen. Chronic osteomyelitis, hepatitis, and infection of an aneurysm and vascular prosthesis have been reported.[26]

Thrombocytopenia is frequent, as are increases in hepatic enzymes; leukopenia may be observed. A lupus anticoagulant associated with antiphospholipid antibodies may be detectable (Chapter 160), as may anti–smooth muscle antibodies. With endocarditis, antinuclear antibodies, microhematuria, and a positive rheumatoid factor are frequent.

DIAGNOSIS

The main clue to the diagnosis in a patient with a valvulopathy and exposure to ungulates is unexplained sickness (fatigue, weight loss, fever), a biologic abnormality (leukopenia, increased erythrocyte sedimentation rate, thrombocytopenia, increase in hepatic enzymes), or rapid degradation of a prosthetic valve. The diagnosis is mainly based on serology (see Table 302-4). Direct detection by PCR, culture, or immunochemistry in valve, liver, or blood samples is also useful, but serologic evaluation by immunofluorescent assay is the reference method. Two antigens (phase I and phase II) can be tested. Acute Q fever is diagnosed when seroconversion or a four-fold increase is obtained with phase II antigen. A single serum test exhibiting IgG antibodies of 200 or greater and IgM of 50 or greater against phase II is also diagnostic. During chronic Q fever, antibodies are at higher titer and directed against both phase I and phase II. IgG against phase I at a titer of 800 or 1600 is diagnostic of chronic infection, as is IgA at 100 or greater. Serology also is useful for following patients with acute Q fever and with treated chronic Q fever.

Routine echocardiography may be warranted to diagnose or exclude endocarditis in all patients with acute Q fever, in whom the overall prevalence of endocarditis is about 3%.[27] In patients with vascular infection or prosthetic valve endocarditis, fluorodeoxyglucose (FDG)–positron emission tomography (PET)/computed tomography (CT) has proved useful. In patients with hepatic abnormalities, liver biopsy, when performed, exhibits granulomas that may be typified by a doughnut shape, with a lipid vacuole that is surrounded by a fibrinoid ring.

TREATMENT

For acute Q fever, oral doxycycline (200 mg daily) is the most efficient antimicrobial, and it should be prescribed for 2 weeks. Some patients with hepatitis do not respond well because of an excessive immune response; these patients rapidly improve with a short course of glucocorticoids (e.g., prednisolone 10 mg daily for 3 days). In pregnant women, doxycycline is contraindicated, but oral cotrimoxazole (320 mg of trimethoprim and 1600 mg of sulfamethoxazole daily) during the entire pregnancy may decrease the chance of an unfavorable outcome.

For endocarditis and for chronic Q fever, which occurs in 1 to 5% of patients,[28] the recommended treatment is a combination of doxycycline (200 mg daily) and hydroxychloroquine (600 mg/day, then adjusted to reach a 1-mg/mL plasma concentration). This regimen is prescribed for 18 to 36 months based on serologic results. The major adverse effect of this treatment is photosensitivity; sun exposure should be avoided. A more rapid favorable outcome can be obtained with doxycycline serum levels higher than 5 μg/mL.

An alternative treatment is a combination of doxycycline and ofloxacin for 3 years or more. Some strains may be resistant to doxycycline (200 mg daily), and macrolides may be an alternative.

PREVENTION

Prevention is based on veterinary control in animals. A human vaccine is currently available in Australia.

PROGNOSIS

Prognosis is usually favorable even without treatment. In pregnant women, symptomatic or not, Q fever may compromise the pregnancy. When infected during the first trimester, the patient usually aborts spontaneously. When the patient is infected later, the disease can result in fetal death or prematurity, although in many the outcome may be normal. Chronic uterine infection may develop in 50% of the patients infected during pregnancy, and these women may later experience multiple spontaneous abortions. Thirty to 50% of patients with heart valve or vascular lesions may experience chronic endocarditis or vascular infection within 2 years. This development is not prevented by initial treatment. The mortality of Q fever endocarditis is about 10%.

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303 ZOONOSES

MEGAN E. RELLER AND J. STEPHEN DUMLER

DEFINITION

Zoonoses, derived from the Greek words *zōio* (animal) and *nósos* (disease), are infectious diseases transmitted from animals, both wild and domestic, to humans or from humans to animals. Among emerging or reemerging infectious diseases, 60 to 75% are zoonoses. Most recently, severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2; Chapters 335, 336, and 337) has shown the devastating effects of zoonotic transmission[1–3] followed by travel-related human spread.

EPIDEMIOLOGY AND PATHOBIOLOGY

Zoonotic pathogens or their toxins can be transmitted by several different routes: direct contact with animals or their products (e.g., tissue, urine, or excreta); animal bites and scratches; arthropod vectors; and consumption of contaminated food or water. Zika virus (Chapter 352), *Borrelia burgdorferi* (Chapter 297), *Babesia microti* (Chapter 324), and *Plasmodium knowlesi* (Chapter 316) are well-recognized vector-transmitted zoonotic pathogens.[4] However, many arthropod vector–borne pathogens, such as *Plasmodium falciparum* (Chapter 316) or *Bartonella quintana* (Chapter 291), are not zoonotic because they are transmitted from human to human through the vector but lack an animal reservoir. Similarly, many infections acquired from the environment also are not zoonoses; examples include melioidosis (*Burkholderia pseudomallei*; Chapter 282) and histoplasmosis (*Histoplasma capsulatum*; Chapter 308). Understanding the epidemiology and transmission of zoonotic versus nonzoonotic infections is critical for implementing control measures at local, regional, and international levels.

Zoonotic spillover occurs when barriers that prevent a zoonotic agent from gaining access to and infecting a human are breached or fail. Such issues include factors related to the interaction between the reservoir host and the pathogen, including where the reservoir host lives; the prevalence of the pathogen within the host; the likelihood of its release from the infected reservoir host; the ability of the pathogen to survive and disseminate after release from the host; and human characteristics that affect the ability of the pathogen to enter and propagate within humans, such as structural barriers, immunity to infection,

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ABSTRACT

Zoonoses are infections and/or diseases acquired by humans from animals. They are distinct from anthroponoses that only involve humans, even if infected through an arthropod vector. Zoonoses make up a significant proportion of all emerging infections and are caused by a complete range of pathogens, including prions, viruses, bacteria, fungi, protozoa, and helminths. The emergence of zoonoses is in part determined by the concept of zoonotic "spillover," whereby barriers that prevent access of zoonotic agents to humans are breached.

Specific risks for emergence of zoonoses include origins in tropical forest regions; increases in mammal biodiversity; and changes in land use due to agricultural practices, residential encroachment, and urban development. Zoonoses can be acquired by direct animal contact, animal bites or scratches, bites or mechanical transmission from arthropod vectors, and consumption of contaminated food or water. The clinical manifestations, diagnostic methods, and treatments are specific for individual infectious agents and disease, but many can be prevented by appropriate use of vaccines, protective clothing, and other prophylactic measures.

KEYWORDS

zoonosis
vectors
climate change
human activity
zoonotic spillover

and genetic predisposition to infection. Zoonotic infections, not surprisingly, are difficult to predict because distinct barriers are not equally shared for each pathogen/reservoir combination owing to the great genomic diversity of animals, humans, and microbes.[5]

In the United States, about 60% of people own a pet. Dogs and cats are most frequent. However, other pets include fish, birds, reptiles, hamsters, guinea pigs, rabbits, and horses. Moreover, exotic animals, including large cats, primates, and bears, are legal with or without a permit in many U.S. states. Wildlife-related recreation exposes more than 90 million U.S. residents to increased risk for zoonoses, and 72 million observe, feed, or photograph birds and other wildlife.

Climate change (Chapter 16) can both increase the likelihood of spillovers (the complicated process by which pathogens defy natural barriers and infect new animal species) and affect chains of transmission.[6] Climate change is expected to increase the risk for zoonoses over the next 50 years because of extreme temperatures that cause increased rainfall and violent storms, rising sea level and floods that could augment zoonotic diarrheal disease, loss of biodiversity, collapse of ecosystems, an increase in pests, and the spread and increase in both neopteran (biting insect) and acarid (tick and mite) vectors of zoonotic pathogens.

Most emerging zoonoses are acquired from contact with wildlife.[7] Key factors that predict emergence of zoonoses are origin in tropical forest regions, increases in mammal biodiversity, changes in anthropogenic land use related to agricultural practices, and illegal wildlife trade[8] (Fig. 303-1). Residential and other land development directly related to human activity is by far the strongest predictor of risk.

Zoonoses are transmitted through one or more of several mechanisms: direct contact with animals or infected materials and/or related inhalation; animal bites and scratches; bites or mechanical transmission by arthropod vectors; and consumption of contaminated foods (Table 303-1). Direct contact with animals is a well-documented mechanism for acquiring viral, bacterial, protozoan, and fungal zoonotic pathogens. The risk is particularly high for individuals whose occupations or recreations involve contact with animals. For example, in a study of veterinarians in Oregon, contact-related ringworm was the most common zoonosis, and rabies the most dangerous; cats were the most likely source of contact-related zoonoses. Significant risks also exist for farmers, abattoir workers, and animal handlers. Leptospirosis (Chapter 298),[9] which likely is one of the most neglected of all zoonoses worldwide with an estimated 1 million cases and nearly 60,000 deaths annually, is commonly acquired through direct contact with contaminated rodent urine; however, many wild and domestic animals can become colonized and excrete the spirochete in their urine. *Coxiella burnetii* (Chapter 302) is distributed worldwide and acquired by inhalation of dust contaminated with excretions, such as milk, urine, and feces, and/or birth products, from infected animals.[10]

In addition to direct tissue injury, animal scratches and bites are a common cause of zoonotic infections. In the United States alone, an estimated 4.5 million dog bites occur annually and 900,000 result in infection; therefore, approximately 1 in every 72 people is affected. Examples of pathogens include *Capnocytophaga canimorsus* from dog bites, as well as *Pasteurella multocida* (Chapter 288) and *Bartonella henselae,* the etiologic agent of cat-scratch disease, from cat bites. In some regions of the world, endemic rabies (Chapter 383) is rampant.

Perhaps the best known zoonoses are transmitted through arthropod bites, such as mosquitoes, flies, or ticks and mites. Vector-borne zoonotic viral infections include West Nile virus (Chapter 352), Eastern equine encephalitis virus (Chapter 352), Nipah virus (Chapter 383), and Hendra virus (Chapter 331). *P. knowlesi* (Chapter 316), *Babesia microti* (Chapter 324), *Leishmania* spp (Chapter 319), and *Trypanosoma* spp (Chapters 317 and 318) are examples of vector-borne zoonotic protozoal infections. *Leishmania*, with 700,000 to 1 million new cases per year, is associated with epidemics across southern Asia, northern Africa, and South America.[11] *Trypanosoma brucei rhodesiense* and *T. brucei gambiense,* agents of African trypanosomiasis and human sleeping sickness (Chapter 317), are transmitted by biting tsetse flies in Africa; cases have been declining in recent years as a result of control efforts, with fewer than 1000 new cases reported in 2019 despite an estimated 65 million people at risk.[12]

Ticks and mites are the most important vectors of zoonotic disease in the developed world. In the United States from 2012 to 2016, 217,000 of 242,000 (90%) reported cases of vector-borne zoonosis were attributed to tick-borne infections, especially *B. burgdorferi* (Chapter 297; Fig. 303-2); recent studies provide evidence that the actual number of *B. burgdorferi* infections is more than 10 times that reported. Worldwide, ticks, lice, and mites are also significant, but underrecognized, causes of vector-borne bacterial zoonoses. Examples of neglected vector-borne bacterial zoonotic disease include tick- and louse-borne relapsing fever borreliosis (Chapter 297); spotted fever group rickettsioses (Chapter 302), transmitted principally by hard body (ixodid) ticks; and typhus group rickettsioses (Chapter 302), transmitted by fleas and lice. Scrub typhus (Chapter 302), caused by the rickettsia *Orientia tsutsugamushi* and transmitted by the larval stage (chigger) of a trombiculid mite, occurs across much of Asia and Oceania and is now emerging in Africa and South America; it is estimated to cause as many as 1,000,000 infections each year globally.[13]

Many important zoonotic infections are acquired through consumption of contaminated foods or water. The list of potential pathogenic agents is vast and includes viruses (such as hepatitis A and E virus; Chapter 134); prions (such as bovine spongiform encephalopathy; Chapter 371); bacteria (e.g., *Salmonella* [Chapter 284], *Campylobacter* [Chapter 279], *Listeria* [Chapter 272]; and *Brucella* [Chapter 286]); protozoa (such as *Cyclospora* [Chapter 324], *Cryptosporidium* [Chapter 321], *Toxoplasma* [Chapter 320],[14] and *Giardia* [Chapter 322]); and helminths (such as *Taenia* [Chapter 325], *Trichinella* [Chapter 327], *Opisthorchis* [Chapter 326], and *Clonorchis* [Chapter 326]).

CLINICAL MANIFESTATIONS

The clinical manifestations of zoonoses are as variable as those for nonzoonotic infections. Symptoms and signs may be referent to the skin, the gastrointestinal tract, the respiratory tract, the central nervous system, the musculoskeletal system, or major organs such as liver, kidneys, and heart; zoonotic infections can also present as undifferentiated fever,[15] sepsis, or toxic shock–like syndromes. For the clinical manifestations with specific zoonotic agents or syndromes, the individual chapters that address each should be consulted. Although most zoonoses are acquired locally, early identification requires taking a comprehensive history, including possible animal exposures and domestic and international travel.

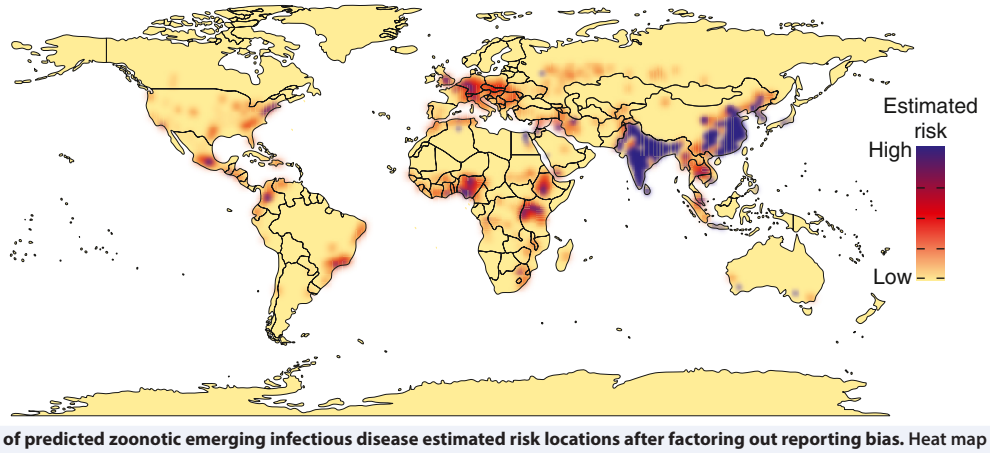

FIGURE 303-1. Heat map of predicted zoonotic emerging infectious disease estimated risk locations after factoring out reporting bias. Heat map estimated risk scale on right: highest risk is *blue*; lowest risk is *yellow*. (Adapted from Allen T, Murray KA, Zambrana-Torrelio C. Global hotspots and correlates of emerging zoonotic diseases. *Nat Commun*. 2017;8:1124.)

TABLE 303-1 EXAMPLES OF RECENTLY EMERGED AND REEMERGING ZOONOSES

DISEASE/ETIOLOGIC AGENT	TRANSMISSION	RESERVOIR HOST	CLINICAL MANIFESTATIONS
VIRUSES			
Bourbon virus	Ticks?	?	Fever, fatigue, rash, headache, myalgia, nausea, vomiting; leukopenia, thrombocytopenia
Heartland viruses	*Amblyomma americanum* tick bites	Deer?	Fever, headache, fatigue, anorexia, nausea, myalgia, arthralgia; thrombocytopenia, leukopenia
Zika virus	*Aedes aegypti* and *Aedes albopictus* mosquito bites	Nonhuman primates, sheep, bats, rodents	Rash, fever, arthralgia, conjunctivitis, myalgia, headache, retroorbital pain; congenital microcephaly, Guillain-Barré syndrome
Avian influenza (H5N1)	Inhalation	Poultry, wild and domestic waterfowl, other birds	Influenza-like illness, shortness of breath, difficulty breathing, viral pneumonia with or without acute respiratory distress syndrome, respiratory failure, multiorgan diseases
Hendra virus	Direct contact; horses	Flying fox	Fever, cough, sore throat, meningitis, encephalitis
Nipah virus	Contact, ingestion	Bats	Fever, headache, shortness of breath, difficulty breathing, encephalitis
BACTERIA AND RICKETTSIAE			
Q fever *Coxiella burnetii*	Indirect (aerosol) exposure	Goats, sheep, cattle, wildlife	Acute: fever, fatigue, photophobia, headache; cough with pneumonia; hepatitis; chronic: endocarditis, immunosuppression, chronic renal insufficiency
Spotted fever rickettsiosis Maculatum rickettsiosis *Rickettsia parkeri* Pacific Coast tick fever *Rickettsia philipii* 364D	*Amblyomma maculatum* ticks, *Dermacentor occidentalis* ticks	Small mammals, cattle? Small mammals	Fever, rash, eschar, myalgia, chills, fatigue, arthralgia, headache, lymphadenopathy Fever, headache, myalgia, arthralgia, malaise, lymphadenopathy (children), rash, eschar
Plague *Yersinia pestis*	Fleas	Small mammals	Fever, chills, headaches, carbuncles, lymphadenopathy with buboes, pneumonia, sepsis
PROTOZOA AND HELMINTHS			
Zoonotic malaria *Plasmodium knowlesi*	*Anopheles leucosphyrous* group mosquitoes	Macaques and monkeys	Fever, chills, headache, rigors, malaise, myalgia, cough, nausea, abdominal pain, vomiting, diarrhea
Babesiosis *Babesia microti*	*Ixodes scapularis* ticks	Small mammals	Fever, anemia, thrombocytopenia, elevated lactate dehydrogenase, hyperbilirubinemia, increased alanine aminotransferase and aspartate aminotransferase
Chagas disease *Trypanosoma cruzi*	Triatomine insects in *Triatoma*, *Rhodnius*, and *Panstrongylus* genera	Rodents, raccoons, skunks, coyotes	Chagoma (Romaña sign), fever, lymphadenopathy, edema, hepatosplenomegaly, myocarditis, meningoencephalitis; cardiomyopathy (arrhythmia, heart failure, atrioventricular/branch blocks, thromboembolism); gastrointestinal (dysperistalsis, megaesophagus, megacolon)
Baylisascariasis *Baylisascaris* spp	Ingestion of contaminated materials	Raccoons, skunks, badgers	Larva migrans (visceral, neural); diffuse unilateral subacute neuroretinitis
FUNGI			
Talaromycosis *Talaromyces (Penicillium) marneffei*	Direct contact, indirect contact?	Bamboo rats	Fever, cutaneous or subcutaneous lesion(s), malaise, anemia, dyspnea, weight loss, lymphadenopathy, nonproductive cough, anemia

DIAGNOSIS

The differentiation of zoonotic from nonzoonotic diseases is complex and challenging but often includes the same general diagnostic approaches. The key is to obtain sufficient historical details that might suggest a zoonotic exposure and which kind. Acquisition of information regarding potential exposure to animals must be thorough and should include occupation, travel, recreation, as well as pets (e.g., reptiles, exotic birds). The clinician should enquire about travel to suburban and rural areas, where ticks are generally more prevalent, as well as international travel. The patient should be asked about possible direct or indirect contact with animals, including bites and scratches, and exposure to vectors associated with zoonotic infection. Finally, the patient should be questioned about ingestion of specific food types associated with food-borne zoonoses, such as unpasteurized dairy products associated with *Brucella* and *Listeria*.

A careful physical examination, including a thorough skin evaluation of rashes, eschars, ulcers, or other lesions, is important. General laboratory and imaging studies as required can provide additional data. Depending on the specific suspected agent, confirmation of the etiology could require point-of-care nucleic acid testing,[16] blood culture, blood smear, paired acute and convalescent serology to document a four-fold rise in antibody titer, and/or molecular testing.[17] Mandatory reporting is required for some agents to protect the public's health. Some examples of zoonotic diseases included on the National Notifiable Infectious Diseases list for 2022 are anthrax (Chapter 272), babesiosis (Chapter 324), brucellosis (Chapter 286), campylobacteriosis (Chapter 279), Chikungunya virus disease (Chapter 352), cryptosporidiosis (Chapter 321), cyclosporiasis (Chapter 324), dengue (Chapter 352), ehrlichiosis and anaplasmosis (Chapter 302), hantavirus infection (Chapter 351), leptospirosis (Chapter 298), listeriosis (Chapter 272), malaria (Chapter 316), Q fever (Chapter 302), trichinellosis (Chapter 327), and Zika virus infection (Chapter 352).[18] Some tests are only available from large reference laboratories or at the U.S. Centers for Disease Control and Prevention.

TREATMENT

As diverse as they are, zoonoses will have specific treatments based on identification of the causative agent. This information is supplied in detail in the relevant chapters of this textbook.

PREVENTION

Prevention of zoonotic diseases requires use of personal protection (frequent handwashing, gloves, and disinfectants) to avoid direct contact with infected animals; application of insect repellent to minimize exposure to vectors and their bites; and avoidance of consumption of undercooked meats, unpasteurized dairy products, uncooked seafood, and tap water in areas of the world where sanitation is inadequate. For some diseases, vaccines are available, and individuals at risk because of occupation (e.g., farmers, veterinarians, forestry workers, microbiology laboratorians), recreation, or travel to endemic areas

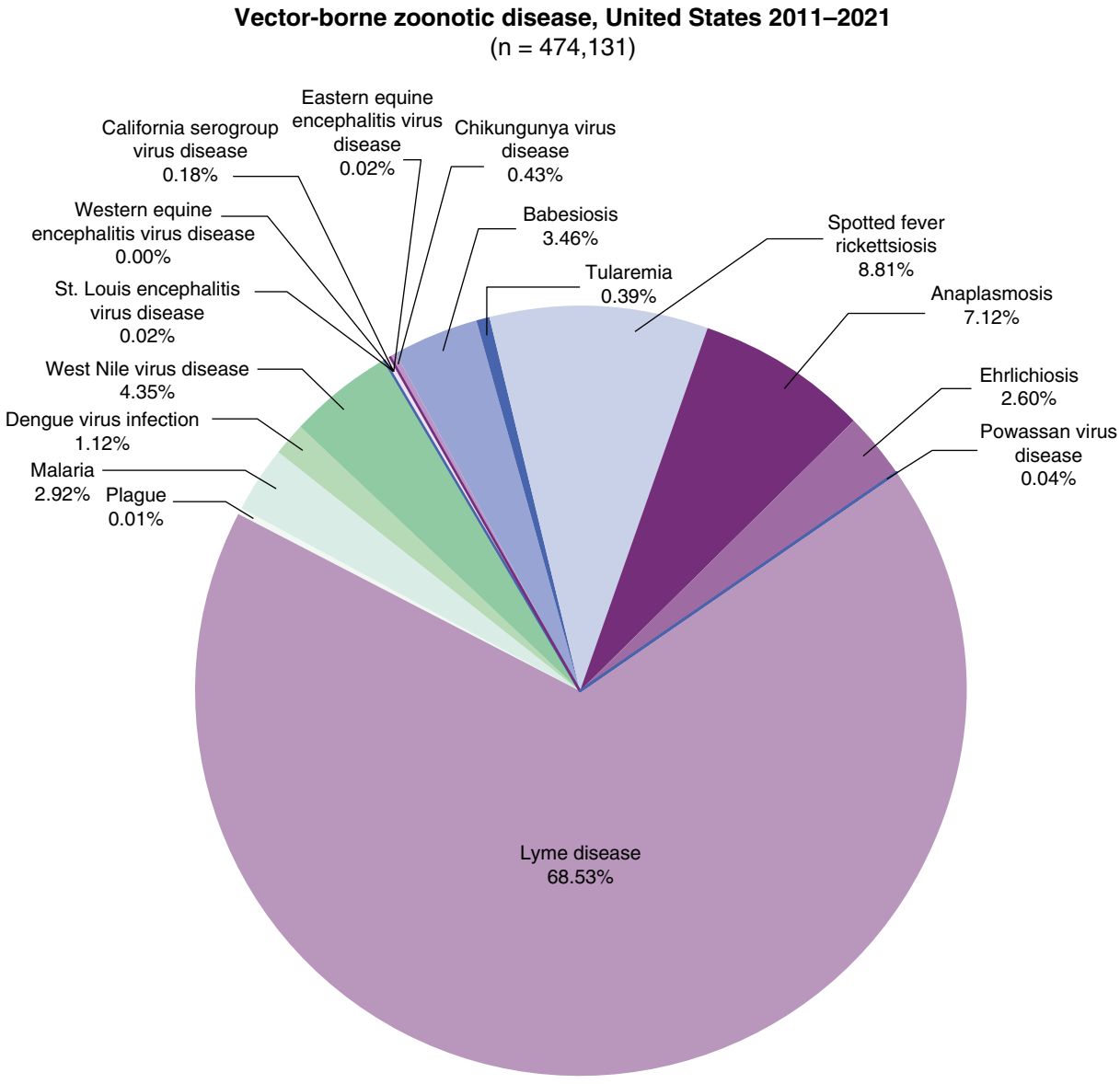

FIGURE 303-2. **Proportion of vector-borne zoonoses by pathogenic agent as reported to the U.S. Centers for Disease Control and Prevention in the United States between 2011 and 2021, except for Lyme disease and spotted fever rickettsiosis, for which data were available between 2011 and 2019; N = 474,131 cases.**

should be vaccinated. When possible, pets and domestic farm animals also should be vaccinated. Immunocompromised individuals who are potential hosts must be particularly careful.

Finally, some pathogens warrant patient isolation to prevent spread. Historically, this list has included hemorrhagic fever viruses (Chapter 351), Hantaviruses (Chapter 351), rabies (Chapter 383), severe acute respiratory syndrome (SARS) and Middle East respiratory syndrome (MERS) coronaviruses (Chapter 334), and anthrax (Chapter 272); however, the list has grown, and biocontainment units are increasingly required in tertiary care referral hospitals.

Examples of global strategies that have been proposed to have high impact on prevention of zoonotic infections include implementation of controls on wildlife trade and consumption, identification of land use conversions that most likely lead to emergence of zoonoses, and targeted global surveillance programs to identify novel pathogens of zoonotic potential before they emerge.[19]

PROGNOSIS

The prognosis of zoonoses is highly variable and dependent on the specific agent and disease. However, some zoonoses have high case fatality rates.

GENERAL REFERENCES

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304 ACTINOMYCOSIS

ITZHAK BROOK

DEFINITION

Actinomycosis is an uncommon, subacute to chronic bacterial infection that induces both suppurative and granulomatous inflammation. Localized swelling with suppuration, abscess formation, tissue fibrosis, and draining sinuses characterize this disease. The infection spreads contiguously and often forms draining sinuses that extrude characteristic, but not pathognomonic, "sulfur granules." Infections of the oral and cervicofacial regions are the most common, but any site in the body can be infected, including the thoracic region, abdominopelvic region, and central nervous system (CNS). Musculoskeletal, cutaneous, or disseminated disease is rare but does occur. Actinomycosis sometimes mimics other diseases, particularly malignancy.

The Pathogen

Actinomycetes of the genera *Actinomyces*, *Propionibacterium*, and *Bifidobacterium* act as the principal pathogens. However, 98 to 99% of actinomycoses are caused

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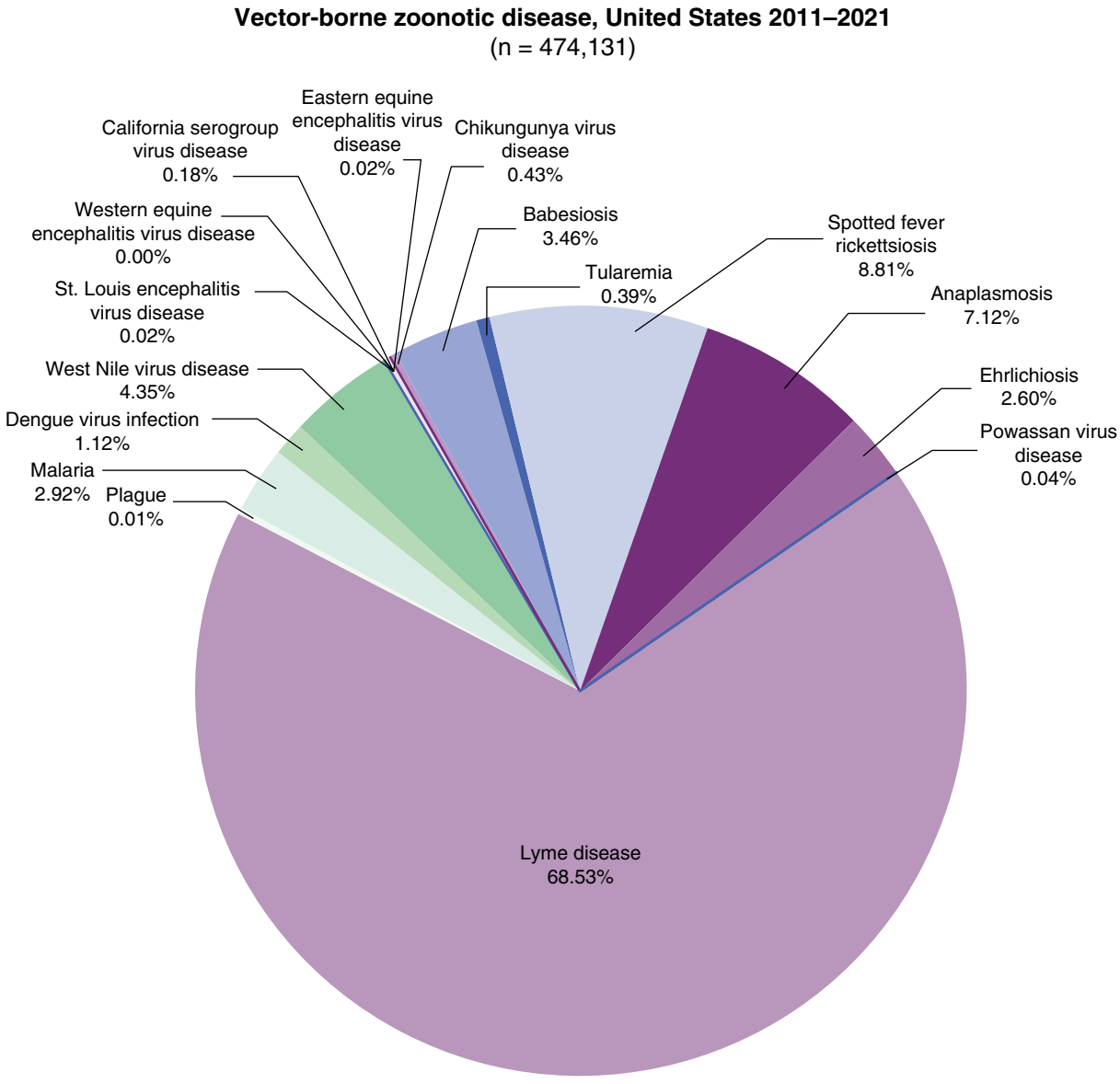

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ABSTRACT

Actinomycosis is an uncommon, subacute to chronic bacterial infection that induces both suppurative and granulomatous inflammation. Localized swelling with suppuration, abscess formation, tissue fibrosis, and draining sinuses are characteristic. The infection spreads contiguously and often forms draining sinuses that extrude characteristic, but not pathognomonic, "sulfur granules." Infections of the oral and cervicofacial regions are the most common, but any site in the body can be infected, including the thoracic region, abdominopelvic region, and central nervous system. Musculoskeletal, cutaneous, or disseminated disease is rare but does occur.

KEYWORDS

actinomycosis
"sulfur granules"
cervicofacial
thoracic
abdominopelvic
central nervous system
musculoskeletal
cutaneous
disseminated disease

by non–spore-forming anaerobic or microaerophilic bacterial species of the genus *Actinomyces*, family Actinomycetaceae, order Actinomycetales. Of the 49 *Actinomyces* spp, 26 may cause disease in humans: the strictly anaerobic *A. israelii, A. gerencseriae, A. odontolyticus, A. naeslundii, A. meyeri, A. viscosus, A. pyogenes,* and *A. georgiae. A. israelii* is the most common species causing human disease. *Pseudopropionibacterium propionicum* (formerly known as *Arachnia propionica*) and *Bifidobacterium dentium* (formerly known as *A. eriksonii*) also are associated with clinically indistinguishable infection.[1] The organisms are filamentous, branching, gram-positive, pleomorphic, non–spore-forming, non–acid-fast anaerobic, or microaerophilic bacilli. *Actinomyces* organisms are fastidious bacteria that require enriched culture media; 6 to 10% ambient CO_2 may aid in their growth, which takes up to 2 to 3 weeks in culture.

EPIDEMIOLOGY

Actinomyces spp are members of the endogenous mucous membrane flora in the oral cavity, lower gastrointestinal tract, bronchi, and female genital tract. No external environmental reservoir, such as soil or straw, has been documented, nor has person-to-person transmission of pathogenic *Actinomyces* spp been demonstrated. Although infection can occur in all age groups, it is rarely seen in children or patients older than 60 years. Most cases are encountered in individuals in the middle decades of life. A male-to-female infection ratio of 3:1 is reported in most series. The explanation for this ratio is the higher prevalence of poor oral hygiene and oral trauma in men. The annual reported incidence in the United States is fewer than 100 cases. However, because of the fastidious nature of the organism, many cases are undiagnosed, and the true incidence is probably much higher.

Oral and cervicofacial diseases are commonly associated with dental caries and extractions, gingivitis and gingival trauma, infection in erupting secondary teeth, chronic tonsillitis, otitis or mastoiditis, diabetes mellitus, immunosuppression, immunodeficiency, malnutrition, and neoplastic disease. Pulmonary infections generally arise after aspiration of oropharyngeal or gastrointestinal secretions and have been reported in patients with underlying lung disorders, such as emphysema, chronic bronchitis, and bronchiectasis. Gastrointestinal infection frequently follows loss of mucosal integrity, such as with surgery, trauma, foreign bodies, perforated appendix or diverticulitis, neoplasia, foreign bodies, and emergency colonic surgery. Extended use (>2 years) of intrauterine contraceptive devices (IUDs) increases risk for the development of actinomycosis of the female genital tract.

PATHOBIOLOGY

Actinomyces spp are agents of low pathogenicity and require mucosal barrier disruption to cause disease. Actinomycosis usually occurs in immunocompetent persons but may affect individuals with diminished host defenses. Risk factors include corticosteroids, bisphosphonates, leukemia with chemotherapy, human immunodeficiency virus (HIV), alcoholism, solid organ transplant, and local tissue damage caused by trauma, recent surgery, or irradiation.

Other bacterial species that are frequently copathogens with *Actinomyces* spp may assist in the spread of infection by inhibiting host defenses and reducing local oxygen tension. Once the organism is established locally, it may spread progressively to surrounding tissues. The infection tends to spread without regard for anatomic barriers, including fascial planes and lymphatic channels. The end result is a chronic, indurated, suppurative infection (usually with draining sinuses and fibrosis, especially in pelvic and abdominal infection). The fibrotic walls of the mass before suppuration are "wooden" in nature and may be confused with a neoplasm. Hematogenous spread can be fulminant but is rare.

Actinomyces spp grow in microscopic or macroscopic clusters of tangled filaments surrounded by neutrophils. Plasma cells and multinucleated giant cells are often observed with lesions, as are large macrophages with foamy cytoplasm around purulent centers. When visible, these clusters are pale yellow and exude through sinus tracts; they are called sulfur granules. These granules (1 to 2 mm in diameter) are made of aggregates of organisms and contain calcium phosphate. A central purulent loculation surrounds the granules. Their centers have a basophilic staining property, with eosinophilic rays terminating in pear-shaped "clubs." One to six granules can be present per loculation, and up to 50 loculations can be present in a lesion. Multicenter giant cells can be seen as well.

CLINICAL MANIFESTATIONS

Physicians must be aware of typical clinical manifestations, such as cervicofacial actinomycosis following a dental focus of infection, pelvic actinomycosis in women with an IUD, and pulmonary actinomycosis in smokers with poor dental hygiene.[2,3]

FIGURE 304-1. Actinomycosis of the jaw, observed at Letterman General Hospital, San Francisco, California, in a sergeant who had punctured the floor of his mouth while picking his teeth. (Courtesy Office of Medical History, Office of the Surgeon General, U.S. Army.)

Cervicofacial

Cervicofacial infection is the most common manifestation of actinomycosis (Fig. 304-1).[4,5] It is generally odontogenic and evolves as a chronic or subacute, painless or painful soft tissue infection that is characterized as a slowly progressive, nontender swelling or mass involving the submandibular or paramandibular region.[6] However, the submental and retromandibular spaces, temporomandibular joint, cheek, chin, and upper jaw can also be involved. The swelling may have a ligneous consistency caused by tissue fibrosis.

Depending on the composition of the concomitant synergistic flora, the onset of actinomycosis may be acute, subacute, or chronic. When *Staphylococcus aureus* (Chapter 267) or β-hemolytic streptococci (Chapter 269) are involved, an acute painful abscess or a phlegmatous cellulitis may be the initial manifestation. Pain and trismus can be disproportionate to the degree of inflammation apparent.

The chronic form of the disease is the most common presentation and is characterized by painless infiltration and bluish or reddish induration that generally progresses to form multiple abscesses and draining sinus tracts, which discharge pus that may contain sulfur granules in up to 25% of instances. Periapical infection, trismus, dyspnea, dysphagia, fever, pain, and leukocytosis may be present. The infection can extend to the carotid artery, tongue, nasal cavity,[7] sinuses, ears, mastoid, orbit, salivary glands, pharynx, masseter muscle, thyroid, larynx, trachea, or thorax. Bone (most commonly the mandible) may be invaded from the adjacent soft tissue, thereby resulting in periostitis or osteomyelitis. Cervical spine or cranial bone infection may lead to subdural empyema and invasion of the CNS. The differential diagnosis includes tuberculosis (scrofula) (Chapter 299), fungal infections (Chapter 308), nocardiosis (Chapter 306), suppurative infections by other organisms, and neoplasms.

Thoracic

Thoracic actinomycosis is an indolent, slowly progressive process involving the pulmonary parenchyma and pleural space.[8,9] This form accounts for 15 to 30% of actinomycosis cases and is caused by aspiration of infective material from the oropharynx (as well as rarely after esophageal perforation), by extension into the mediastinum from the neck, by spread from an abdominal site, or by hematogenous spread to the lung. Infection can spread from a pneumonic focus across lung fissures to involve the pleura and the chest wall, with eventual fistula formation and drainage containing sulfur granules (Fig. 304-2). The mediastinum, endocardium, and pericardium also rarely can be affected. Granules are seldom present in sputum. The incidence of this complication, as well as the destruction of thoracic vertebrae and adjacent ribs, has declined in the antimicrobial era.

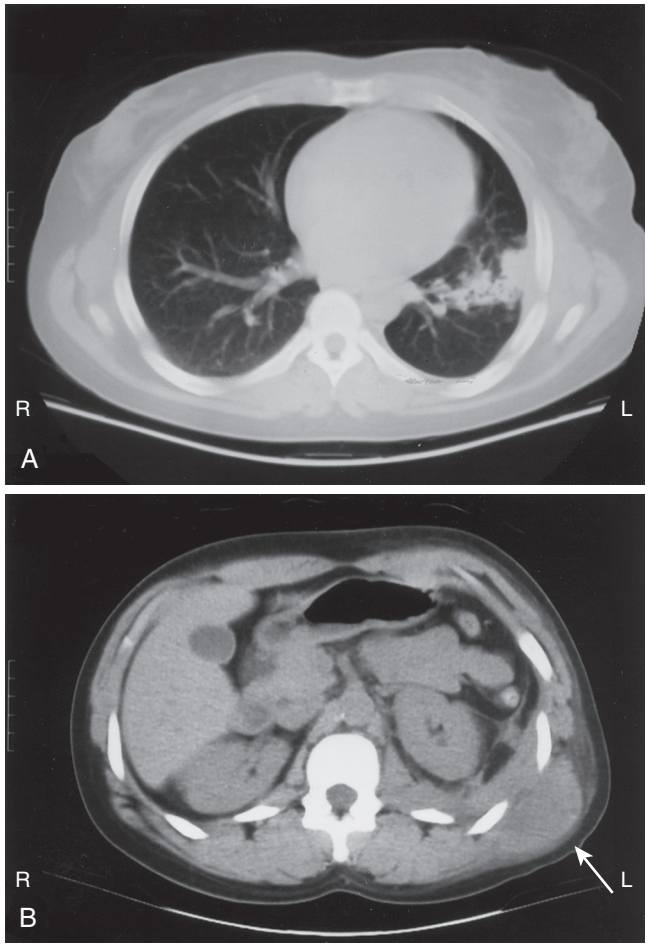

FIGURE 304-2. Thoracic computed tomography scan of a 43-year-old woman with pulmonary actinomycosis. A, There is consolidation of the lung with pleural thickening adjacent to the parenchymal disease. **B,** Abscess extended into the left breast and inferiorly to the costophrenic sulcus, to the retroperitoneum, and into the lateral abdominal wall (*arrow*).

The complaints of patients with thoracic actinomycosis are nonspecific, most commonly chest pain, productive cough, dyspnea, weight loss, and fever. Anemia, mild leukocytosis, and elevated sedimentation rate are relatively common. Patients often have a history of underlying lung disease and are rarely initially seen in an early stage of infection. The pulmonary lesion is either a mass lesion or pneumonitis and may resemble tuberculosis (Chapter 299), especially when cavity formation occurs, or blastomycosis, which may destroy ribs posteriorly but rarely forms sinuses. Nocardiosis (Chapter 306), aspergilloma (Chapter 311), bronchogenic carcinoma (Chapter 177), cryptococcosis (Chapter 309), aspiration pneumonia (Chapter 85), and lymphoma (Chapters 171 and 172) also can mimic thoracic actinomycosis. Pleural thickening, pleural effusion (Chapter 86), and emphysema are common.

Abdominal

Abdominal actinomycosis, which comprises approximately 20% of all cases of actinomycosis, is a chronic, localized inflammatory process that can occur weeks, months, or years after the integrity of the gastrointestinal mucosa is breached by surgery, cancer, or trauma. Abdominal infection also can be the result of direct extension from the thorax or pelvis or of hematogenous dissemination.[10] The ileocecal region is involved most frequently (usually after a perforated appendix), often with the formation of a mass lesion.[11] The infection extends slowly to contiguous organs, especially the liver, and may involve retroperitoneal tissues, the spine, or the abdominal wall. Hepatic, renal, or splenic dissemination is an uncommon complication. Persistent draining sinuses may form, and sinuses involving the perianal region[12] can simulate Crohn disease (Chapter 127) or tuberculosis (Chapter 299). The extensive fibrosis of actinomycotic lesions, recognized by the examiner as a mass, often suggests tumor. A frequent finding on computed tomography (CT) is an infiltrative mass with dense inhomogeneous contrast medium enhancement. Constitutional symptoms and signs are nonspecific, the most common being fever, diarrhea or constipation, weight loss, nausea, vomiting, pain, and the sensation of a mass.

Pelvic

Pelvic infection can occur in patients with prolonged use of IUDs and also may occur from extension of intestinal infection, commonly from indolent ileocecal disease.[13] Manifestations may range from a chronic vaginal discharge to pelvic inflammatory disease (Chapter 264) with tubo-ovarian abscesses or pseudomalignant masses. Patients generally have abnormal vaginal bleeding or discharge, abdominal or pelvic pain, menorrhagia, fever, and weight loss.

Endometritis is the earlier form of the infection, followed by tubo-ovarian abscesses. Extension to the uterus, bladder, rectal area, abdominal wall, peritoneum, pelvic bones, thorax, and systemic circulation also can occur.

Central Nervous System

Infections of the CNS are very rare and generally manifest as single or multiple encapsulated brain abscesses (Chapter 382)[14] that appear as ring-enhancing lesions with a thick wall that may be irregular or nodular on contrast-enhanced CT scans. No features readily distinguish actinomycosis from other causes of chronic brain abscesses. Rarely, solid nodular or mass lesions termed *actinomycetomas* or *actinomycotic granulomas* are found.[15] Headache and focal neurologic signs are the most common findings. Most actinomycotic infections of the CNS are seeded hematogenously from a distant primary site, but direct extension of cervicofacial disease also occurs. Sinus formation is not characteristic of CNS disease. Meningitis (Chapter 381) caused by *Actinomyces* may be misdiagnosed as tuberculous meningitis because it is chronic and basilar in location, and the cerebrospinal fluid pleocytosis is usually lymphocytic. The meningitis of actinomycosis is characteristically a pachymeningitis that involves thickening of the dura mater. Extension to the cranial epidural or subdural space and spinal epidural space also can occur from adjacent foci.

DIAGNOSIS

Appropriate microbiologic and pathologic studies are essential for diagnosis. A high index of suspicion should be communicated to the microbiology laboratory, along with material from draining sinuses, from deep-needle aspiration, or from biopsy specimens. CT or ultrasound needle aspiration can be used to obtain a biopsy specimen. It is important to avoid contamination of the specimen by normal flora and administration of antimicrobial therapy before specimens are obtained. Multiple biopsy sections from different tissue levels are recommended to improve the histopathologic diagnosis.

The presence, in pus or tissue specimens, of non–acid-fast, gram-positive organisms with filamentous branching is suggestive of the diagnosis. Direct testing of clinical specimens can facilitate identification by using specific polymerase chain reaction probes, staining with fluorescent-conjugated monoclonal antibodies, and matrix-assisted laser desorption ionization time-of-flight mass spectrometry.[16]

The characteristic morphologic features of sulfur granules within are also helpful. In tissue sections stained with hematoxylin-eosin, sulfur granules are round or oval basophilic masses with a radiating arrangement of eosinophilic terminal clubs. However, *Actinomyces* spp are infrequently visible in sections stained with hematoxylin-eosin; visualization is facilitated by special stains such as Gomori methenamine silver, *p*-aminosalicylic acid, McCallen-Goodpasture, and Brown-Brenn. The granules must be distinguished from similar structures that are sometimes produced in infections caused by *Nocardia, Monosporium, Cephalosporium, Staphylococcus* (botryomycosis), and other organisms.

Actinomyces and *Arachnia* can generally be differentiated from other gram-positive anaerobes by means of their slow growth rate production of catalase and by gas-liquid chromatography. Anaerobic culture is required to grow the organism, and no selective media are available to restrict overgrowth of the slow-growing *Actinomyces* by associated microflora.

Most actinomycotic infections are polymicrobial and involve other aerobic and anaerobic bacteria. The most common co-isolates depend on the infection site and are *Actinobacillus actinomycetemcomitans, Aggregatibacter aphrophilus, Eikenella corrodens, Bacteroides, Fusobacterium, Capnocytophaga*, aerobic and anaerobic streptococci, *Staphylococcus*, and Enterobacteriaceae.

Imaging methods such as conventional radiography, CT, and magnetic resonance imaging do not provide a specific diagnosis.[17] However, they are often critical for accurate definition of the dimensions and extension of the infection, as well as to monitor the efficacy of therapy.

TREATMENT

Adequate local drainage is indicated if abscesses are present. Surgical removal of infected tissue also may be necessary in some cases, especially if extensive necrotic tissue or fistulas are present, if malignant disease cannot be excluded, and if large abscesses cannot be drained by percutaneous aspiration.

Penicillin G is the drug of choice for treatment of an infection caused by any of the *Actinomyces*. Most deep-seated infections can be expected to respond to intravenous penicillin G (3 to 4 million units every 4 hours, given for 2 to 6 weeks) followed by an oral phenoxypenicillin (2 to 4 g/day). A few additional weeks of oral penicillin therapy may suffice for uncomplicated cervicofacial disease, but complicated cases and extensive pulmonary or abdominal disease may require treatment for 12 to 18 months. Little evidence exists of acquired resistance to penicillin G by *Actinomyces* during prolonged therapy. The combination of a penicillin (i.e., amoxicillin, piperacillin) and a β-lactamase inhibitor (i.e., clavulanate, tazobactam) offers the advantage of coverage against penicillin-resistant aerobic and anaerobic copathogens. For example, clinical and microbiologic cure is achieved in >85% of cases of cutaneous actinomycosis with amoxicillin/clavulanic acid 875/125 mg orally, twice daily for up to 12 weeks. Alternative first-line antibiotics include amoxicillin alone (500 mg orally four times daily) for up to 12 weeks, tetracycline (500 mg orally four times daily for up to 12 weeks), erythromycin (500 to 1000 mg intravenously or 500 mg orally four times daily for up to 12 weeks), and clindamycin (500 mg intravenously or 300 to 450 mg orally four times daily, for up to 12 weeks). Ceftriaxone, imipenem, and fluoroquinolones have also been used successfully. Metronidazole, aminoglycosides, oxacillin, and cephalexin are not effective. In vitro antimicrobial susceptibility testing of *Actinomyces* is difficult, and the results may not be predictive of antimicrobial effects in vivo.

Whether treatment of co-isolates is warranted depends on the organism and site of infection. Treatment of coexisting *S. aureus* (Chapter 267), *Proteus* (Chapter 282), and *Pseudomonas* (Chapter 282) is always warranted, and antimicrobial coverage for other known pathogens also is appropriate, especially for invasive and lower abdominal infections.

When well-defined IUD-related symptoms and Papanicolaou smears demonstrate *Actinomyces* by specific fluorescence-labeled antibody, the IUD should be removed. Antimicrobial administration for a 2-week period may be indicated. More serious infections require prolonged therapy.

PROGNOSIS

The availability of antimicrobial treatment has greatly improved the prognosis for all forms of actinomycosis. At present, cure rates are high, and neither deformity nor death is common.

GENERAL REFERENCES

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305 WHIPPLE DISEASE

THOMAS RUDOLF SCHNEIDER

DEFINITION

Whipple disease is a rare chronic systemic infection that is caused by *Tropheryma whipplei* and is characterized by a wide range of symptoms including fever, diarrhea, malabsorption, weight loss, arthralgias, arthritis, central nervous system involvement, lymphadenopathy, and serositis. *T. whipplei* can also cause asymptomatic infection, acute transient infections, and isolated endocarditis or pneumonia.

The Pathogen

T. whipplei is a gram-positive, slowly replicating, rod-shaped bacterium, 0.25 × 1.5 to 2.5 μm in length and surrounded by a trilaminar plasma membrane and a homogenous 20-nm-thick cell wall. Replication of *T. whipplei* is very slow, with a doubling time of about 17 days. The genome of *T. whipplei* is small (925 kilobases) with a single circular chromosome and considerable sequence variation. The organism's lack of key biochemical pathways contributes to dependence on the host for replication. The organism is phylogenetically in the actinomycetes subdivision and similar to actinobacteria and nocardioforms.

EPIDEMIOLOGY

Classical Whipple disease occurs rarely. The incidence is less than 1 per million, and the prevalence is approximately 3 per million in Europe and 10 per million in the United States.[1] In the United States, Whipple disease accounts for about 4 to 5 per million hospitalizations.[2] It is even more rare in Asia and rather unknown in Africa. White middle-aged males appear to be more commonly affected. In a German cohort, for example, 77% of patients were men, and the mean age at diagnosis was 57 years. Humans are the only identified host for *T. whipplei*. Environmental reservoirs include water and sewage, and humans presumably are exposed through contaminated drinking water. *T. whipplei* has been identified in human saliva and feces.

PATHOBIOLOGY

The pathobiology ranges from asymptomatic colonization of the oropharynx and gastrointestinal tracts to disseminated disease. *T. whipplei* has been identified in macrophages in the small intestine, polymorphonuclear leukocytes, mast cells, plasma cells, and endothelial and epithelial cells. It is likely that bacteria replicate in the digestive system, are phagocytized by macrophages, and then replicate in peripheral blood mononuclear cells and macrophages. Infection of the lamina propria of the small bowel leads to diarrhea, abdominal pain, bloating, malabsorption, and weight loss. Dissemination of the organism through the blood and lymphatic system leads to infection of the central nervous system, lymph nodes, heart valves, lungs, and other organs. Overall, about 2 to 4% of the population are asymptomatic carriers of *T. whipplei*, a percentage that dwarfs the low estimated prevalence of classical Whipple disease, thereby suggesting that an underlying genetic or immunologic predisposition is likely necessary for an individual to develop classical Whipple disease. Dysfunction of immune cells, including T cells, macrophages, plasma cells, and dendritic cells, is associated with the development of Whipple disease. Multifactorial predisposition towards the development of Whipple disease has been reportedly related to specific human leukocyte antigen (HLA) associations (e.g., DRB1*13 and DQB1*6, but not B27) or polymorphisms within certain cytokine genes. Patients with classic Whipple disease have reduced $CD4^+$ T-cell responses against the organism, thereby leading to multisystem disease.

In classical Whipple disease, uncontrolled bacterial replication and mucosal destruction results in translocation of the bacteria from the gastrointestinal tract into the blood stream, with subsequent development of systemic infection. Pathology demonstrates edematous, thick, flattened, and widened villi of the duodenum and jejunum. On microscopy, yellow lipid deposits are visible, and foamy granular periodic acid–Schiff (PAS)–positive inclusions are seen in the lamina propria. PAS-positive macrophages and *T. whipplei* nucleic acid (on polymerase chain reaction [PCR] testing) can be detected in many organs, body fluids, and tissues including liver, spleen, lymph nodes, synovium, bone marrow, heart, lung, central nervous system (CNS), and cerebrospinal fluid. Other pathologic manifestations include organomegaly, polyserositis, and CNS demyelination.

CLINICAL MANIFESTATIONS

The clinical spectrum of diseases is categorized as asymptomatic carriage, transient and acute infections, localized infections, classical and systemic Whipple disease, and Whipple disease associated with immunosuppression.

Asymptomatic Infection

Healthy asymptomatic persons can carry *T. whipplei* in their oropharyngeal and gastrointestinal tract and shed the organism in their saliva and stool. The highest incidence of asymptomatic carriage occurs in rural regions of sub-Saharan Africa (about 30% in stool and 3.5% in saliva).[3] In Europe, *T. whipplei* has been identified in stool samples of 1 to 11% of healthy adults. Stool carriage is more common in sewage workers (12 to 26%).

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CLINICAL MANIFESTATIONS

The clinical spectrum of diseases is categorized as asymptomatic carriage, transient and acute infections, localized infections, classical and systemic Whipple disease, and Whipple disease associated with immunosuppression.

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ABSTRACT

Whipple disease is a rare chronic systemic infection caused by *Tropheryma whipplei*. The incidence of classical Whipple disease is less than 1 per million, and the prevalence is approximately 3 per million in Europe and 10 per million in the United States. It is even more rare in Asia and rather unknown in Africa. The pathobiology ranges from asymptomatic colonization of the oropharynx and gastrointestinal tracts to disseminated disease. *T. whipplei* has been identified in macrophages in the small intestine, polymorphonuclear leukocytes, mast cells, and plasma cells, as well as in endothelial and epithelial cells. Infection of the lamina propria of the small bowel leads to diarrhea, abdominal pain, bloating, malabsorption, and weight loss. In classical Whipple disease, dissemination of the organism via the blood stream or lymphatic system leads to a wide range of symptoms, including fever, arthralgias, arthritis, central nervous system involvement, lymphadenopathy, and serositis. *T. whipplei* can also cause asymptomatic infection, acute transient infections, and isolated endocarditis or pneumonia. Classical Whipple disease is fatal without treatment, but effective antibiotic treatments significantly improve outcomes.

KEYWORDS

Whipple disease
Tropheryma whipplei

TABLE 305-1 MAJOR SYMPTOMS OF CLASSICAL WHIPPLE DISEASE

SYMPTOM	AFFECTED PATIENTS (%)
Weight loss	85-95
Anemia	80-90
Arthropathy	70-85
Diarrhea	70-80
Abdominal pain	55-60
Lymphadenopathy	45-60
Fever	40-45
Hyperpigmentation	35-45
CNS involvement	10-40
Ocular signs	5-10

CNS = central nervous system.

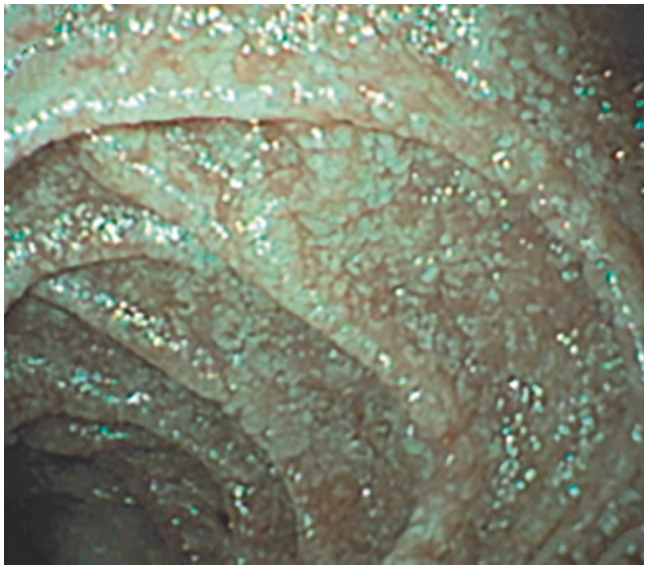

FIGURE 305-1. Characteristic appearance of the duodenal mucosa and classical diagnosis of Whipple disease from the duodenum. Macroscopic view at endoscopy of a heavily affected case with clumsy and dilated villi with ecstatic lymph vessels. (From Schneider T, Moos V, Loddenkemper C, et al. Whipple's disease: new aspects of pathogenesis and treatment. *Lancet Infect Dis*. 2008;8:179-190.)

Transient and Acute Infection

T. whipplei may cause acute gastroenteritis in children, most commonly in Africa and France, and 15% of young children with diarrhea in one study had *T. whipplei*. In addition to diarrhea, acute infection can be associated with bacteremia and cough. *T. whipplei* has been identified on bronchoalveolar lavage in 3% of HIV-positive patients with pneumonia.

Localized infection most commonly presents as culture-negative bacterial endocarditis (Chapter 61), with slowly degenerating valvular lesions.[4] In one German cohort of patients with culture-negative endocarditis without classical Whipple disease, *T. whipplei* was the most common agent identified.

Classical Whipple Disease

The clinical spectrum of classical Whipple disease (Table 305-1) may be quite variable based on the stage of disease, the organs involved, and the host's underlying characteristics. The uncontrolled bacterial replication and systemic infection of classical Whipple disease cause severe disseminated disease.

Gastrointestinal manifestations, including diarrhea, abdominal pain, bloating, malabsorption, and associated weight loss, are common. Chronic diarrhea may progress to severe cachexia, with resulting hypoproteinemia, ascites, and peripheral edema.

Common systemic manifestations include arthralgias, arthritis, neurologic manifestations, low-grade intermittent fever, night sweats, and lymphadenopathy. Chronic, nonproductive cough, polyserositis, and organomegaly may occur. Skin hyperpigmentation has been reported.

In about 70% of patients, joint symptoms may have been present for many years and misdiagnosed as seronegative rheumatoid arthritis.[5] Nondestructive, migratory, seronegative arthralgia and arthritis typically involve the peripheral joints and are often associated with myalgias.[6]

The most serious manifestations involve the CNS.[7] Rare progressive supranuclear ophthalmoplegia with oculomasticatory myorhythmia or oculofacioskeletal myorhythmia are considered pathognomonic for CNS Whipple disease. Other symptoms include cognitive dysfunction, ataxia, headache, insomnia, seizures, meningitis, and involvement of the peripheral nerves and spinal cord. Ocular involvement, such as uveitis, affects 11% of cases.

Whipple disease associated with immunosuppression can occur when patients with undiagnosed disease receive tumor necrosis factor blocker therapy, thereby accelerating the course of the disease from local symptoms to systemic disease. Immunosuppressive therapy may also exacerbate diarrhea or lead to endocarditis or CNS disease.

DIAGNOSIS

The diagnosis of Whipple disease can be difficult because of its nonspecific nature and multisystem manifestations. Diagnosis is often delayed and requires a high index of suspicion. The differential diagnosis of Whipple disease is large and includes a number of diseases such as seronegative rheumatoid arthritis (Chapter 243), sarcoidosis (Chapter 83), celiac disease (Chapter 126), tropical sprue (Chapter 126), Crohn disease (Chapter 127) with reactive arthritis, and a variety of neurologic diseases.

Classical Whipple disease usually can be diagnosed on duodenal biopsies. Multiple deep biopsies are indicated. Duodenal endoscopic features include a pale yellow mucosal surface with disordered dilated villi (Fig. 305-1). Ectatic lymph vessels may also be present (Fig. 305-2A). However, macroscopic changes are absent in the majority of cases. The hallmark of classical Whipple disease is the accumulation of foamy macrophages filled with *T. whipplei* in the duodenal mucosa detected by PAS staining (Fig. 305-2B). PAS-positive cells may persist for years within the tissues, but PAS-staining fades and the number of PAS-positive macrophages decreases during treatment.

Duodenal histology may be positive even in the absence of gastrointestinal symptoms, but a negative duodenal biopsy does not exclude the disease in suspected cases, especially in the absence of diarrhea. In such cases, biopsies from alternative tissues (e.g., the CNS, lymph nodes, muscles, joints, synovium, eyes, lung, or excised heart valves) can establish gastrointestinal infection (Fig. 305-3).

PCR testing is useful for diagnosis and follow-up.[8] PCR testing is preferred for sterile body fluids such as cerebrospinal fluid (CSF), synovial fluid, ascites, pleural effusion, or brain biopsies. PCR from CSF should be routinely performed, because asymptomatic CNS infection occurs in up to 50% of patients, and eradication of the agent from the CNS is essential to guide proper treatment. High-volume positive PCR in feces (above 32,500 copies/mL) is strongly associated with clinical disease,[9] but the normal carriage of *T. whipplei* in otherwise healthy individuals means that an isolated positive PCR from oral, gastrointestinal, stool, or bronchial specimens does not ensure the diagnosis (see Fig. 305-3).

PCR usually becomes negative shortly after appropriate antibiotic treatment, so a negative PCR in an antibiotic pretreated patient is not helpful. In patients treated with antibiotics, *T. whipplei*–specific immunohistochemistry is preferred because it remains positive and detects *T. whipplei* within the tissue after antibiotic treatment.

TREATMENT

Without appropriate treatment, Whipple disease can be fatal. Initial intravenous induction therapy is recommended with ceftriaxone (2 g intravenously [IV] daily for 2 weeks for general therapy but 2 g IV daily for 4 weeks for CNS disease or endocarditis) followed by at least 1 year of trimethoprim/sulfamethoxaxole (160/800 mg orally twice daily). Equally good alternatives are 4 weeks of meropenem (1 g IV three times per day) for CNS infection or penicillin G (10 million total units IV daily) for endocarditis.[10]

Some data also suggest that 2 weeks of 2 g of IV ceftriaxone followed by 3 months of trimethoprim-sulfamethoxazole is equally good for all types of infection. In cases of allergy or relapse, doxycycline (100 mg twice daily) plus hydroxychloroquine (200 mg orally three times daily) for 1 year followed by

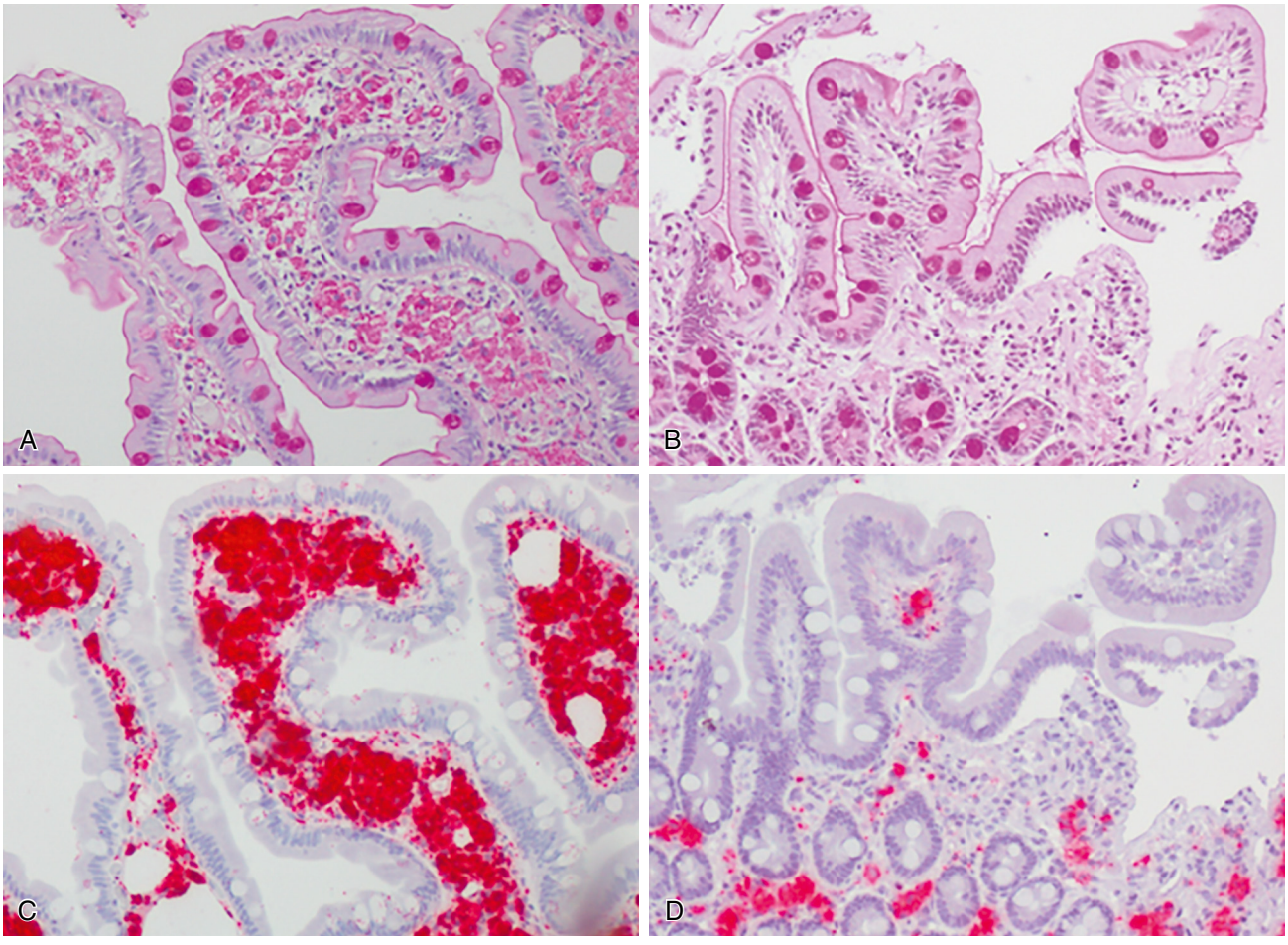

FIGURE 305-2. **Characteristic (A) and very weak (B) periodic acid–Schiff (PAS) staining and corresponding *T. whipplei*–specific immunohistochemistry (C, D) of duodenal biopsies of two untreated Whipple disease patients. A, C,** Duodenal mucosa with typical histologic appearance with flattened villi and lymphangiectasia, PAS-positive sickle particle–containing (SPC) cells, and strong immunohistochemical staining within the villi. **B, D,** Biopsies of a patient without typical PAS staining but evidence of *T. whipplei* infection by positive specific immunohistochemistry, especially in deeper regions of the mucosa around the crypts.

lifelong treatment with doxycycline (200 mg/day) is recommended. If these options are not tolerated, penicillin, minocycline, chloramphenicol, or antibiotic combinations can be used under expert supervision.

In about 10% of cases, treatment is complicated by an immune reconstitution inflammatory syndrome, with recurrence of inflammation and symptoms in the absence of other detectable causes. The risk for immune reconstitution inflammatory syndrome is increased in patients who were receiving immunosuppressive therapy prior to the diagnosis of Whipple disease.[11] For severe or life-threatening symptoms, treatment with corticosteroids can be effective (e.g., 1 mg/kg/daily until acute symptoms improve followed by reductions of 5 to 10 mg every 2 to 3 weeks, then a slow taper from 10 mg to zero). Some patients may require a slower taper or a 5-mg daily dose for several months.

PREVENTION

Currently, no prevention strategies are recommended. Lifelong antibiotic treatment is not recommended.

PROGNOSIS

Classical Whipple disease with systemic manifestations is always eventually fatal without treatment, but mortality is usually below 5% with treatment. Appropriate treatment improves symptoms rapidly, and most cases achieve clinical remission. Diarrhea and fever often resolve within a few days, whereas the recovery from arthritis and neurologic symptoms can take weeks. CNS manifestations may progress and ultimately lead to death despite ongoing antibiotic treatment.

Relapses or reinfection after adequate therapy is very rare, but lifelong clinical follow-up is recommended for all patients. Given the complexity of diagnosis, treatment, and long-term management, clinicians experienced in the management of Whipple disease should be involved in the care of these patients.

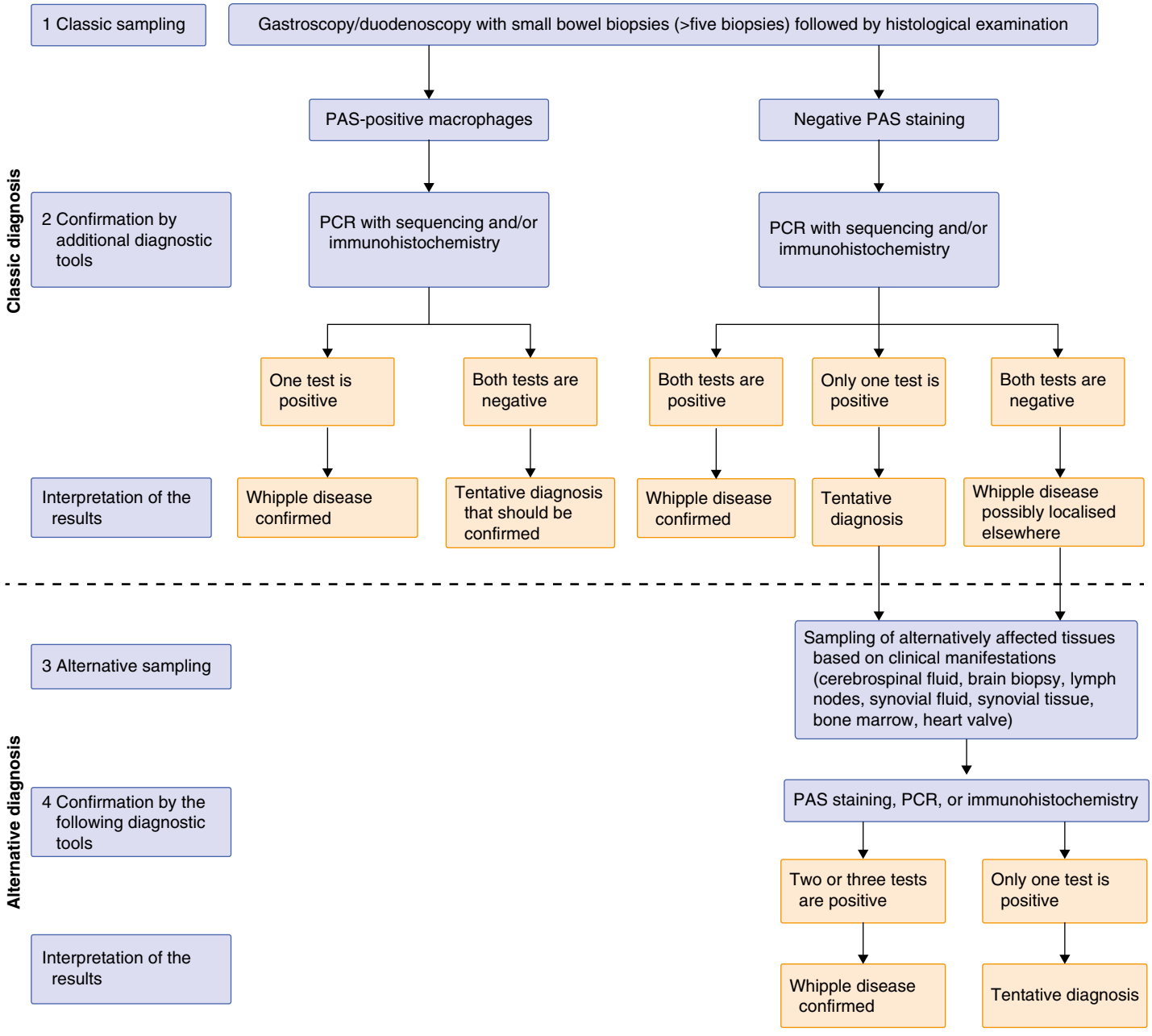

FIGURE 305-3. Hierarchic scheme for the diagnosis of Whipple disease based on clinical symptoms. PAS = periodic acid–Schiff; PCR = polymerase chain reaction. (From Schneider T, Moos V, Loddenkemper C, et al. Whipple's disease: new aspects of pathogenesis and treatment. *Lancet Infect Dis*. 2008;8:179-190.)

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306 NOCARDIOSIS

FREDERICK S. SOUTHWICK

DEFINITION

Nocardiosis refers to infections caused by *Nocardia* spp. *Nocardia* most commonly causes pneumonia but also can infect the central nervous system (CNS) and the skin. Less commonly, this organism can disseminate throughout the body. These infections usually occur in immunosuppressed patients.

The Pathogen

Nocardia spp are thin, aerobic, gram-positive bacilli that form branching filaments.[1] The bacteria stain irregularly and appear beaded on Gram stain and positive on modified acid-fast stain. The species are now identified by gene sequencing and DNA-DNA hybridization. The number of species causing human disease is large and includes *N. abscessus, N. brevicatena/paucivorans* complex, *N. nova* complex, *N. transvalensis* complex, *N. farcinica, N. cyriacigeorgica, N. otitidiscaviarum, N. veterana, N. brasiliensis*, and *N. pseudobrasiliensis*.

EPIDEMIOLOGY

Nocardia spp are ubiquitous and primarily originate in soil. Despite being found throughout the environment, they rarely cause symptomatic infection in humans. Because nocardiosis is not a reportable disease, the frequency of this disease is unknown. The annual incidence has been estimated to be 0.4 to 0.5 in 100,000.[2] The risk for symptomatic *Nocardia* infection is greatly increased (estimated to be 140 to 340 times greater) in individuals who are immunocompromised, including patients who are receiving immunosuppressive agents following a stem cell[3] or solid organ transplant,[4] and patients with acquired immunodeficiency syndrome (AIDS). Corticosteroids are the most frequent immunosuppressant associated with nocardiosis, but cases also have been reported in patients who are receiving anti–tumor necrosis factor-α antibody agents as well as other immunosuppressants. Trimethoprim-sulfamethoxazole prophylaxis, as is used to prevent infections with *Pneumocystis jiroveci*, does not always protect against *Nocardia*. Other

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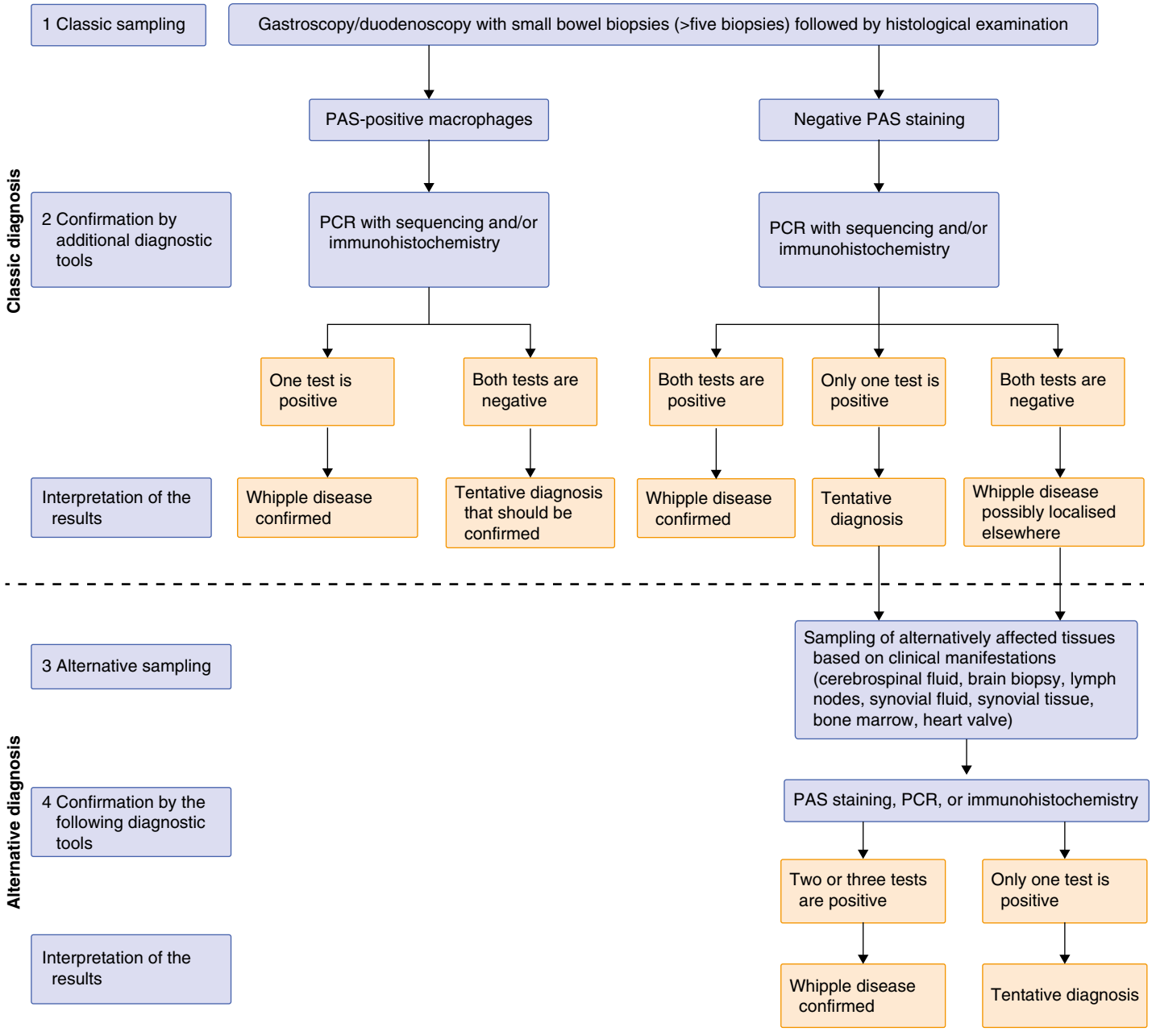

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ABSTRACT

Nocardia species is a gram-positive and acid-fast filamentous aerobic bacteria found in the soil that infects humans primarily through *inhalation* of dust and, less commonly, secondary to cutaneous inoculation following trauma. This bacterium can cause nodular lung lesions and lymphocutaneous infections. When nocardia disseminates into the blood stream, it can result in multiloculated brain abscesses that can be identified by head CT scan with contrast. These infections are more common in immunocompromised patients. The organism is slow growing and takes several days to be identified. Speciation is now performed by polymerase chain reaction (PCR) testing, and certain strains, particularly *N. farcinica*, are trimethoprim-sulfa resistant; therefore, for serious infections combination therapy is recommended with ceftriaxone, imipenem, or amikacin. Linezolid and moxifloxacin have also been shown to be effective in some cases. In patients with brain abscess, surgical drainage in addition to long-term antibiotics is required. The recommended duration of therapy is 4 to 6 months for a normal host and 6 to 12 months for immunocompromised patients.

KEYWORDS

nocardiosis
immunocompromised host
lung nodule
lymphocutaneous infection
brain abscess
mycetoma

at-risk groups include patients with cancer, Cushing syndrome (Chapter 208), chronic granulomatous disease (Chapter 231), and hypogammaglobulinemia (Chapter 231). Patients with chronic pulmonary disorders, particularly alveolar proteinosis (Chapter 79), are also more susceptible to this infection.[5] In approximately one third of patients with nocardiosis, no predisposing condition can be identified.

PATHOBIOLOGY

Most *Nocardia* spp gain entry to the host via the respiratory tract or, less commonly, by skin inoculation. Invading bacteria elicit a neutrophilic response that inhibits but does not kill the organism. The bacteria are phagocytosed by neutrophils and macrophages and then become enclosed in a membrane-bound phagolysosome. In this closed environment, neutrophils and macrophages can kill many species of bacteria by synthesizing superoxide and hydrogen peroxide. However, *Nocardia* can survive by producing superoxide dismutase, an enzyme that inactivates these toxic oxygen byproducts. In addition, *Nocardia* spp produce a mycolic acid called cord factor that inhibits the fusion of lysosomes with the phagolysomal compartment, thereby preventing toxic proteases and other antibacterial products from reaching the intracellular bacteria. Cell wall extractable lipids impair phagocytosis and inhibit bacterial killing. In addition to neutrophils and macrophages, cell-mediated and humoral immunity also play roles in protecting the host against *Nocardia* invasion, thereby explaining the wide range of immunocompromised patients that are at increased risk for contracting nocardiosis.

CLINICAL MANIFESTATIONS

Nocardiosis has no pathognomonic characteristics. Failure of a pulmonary or skin infection to respond to conventional antibiotic therapy should raise the possibility of a *Nocardia* spp infection. *Nocardia* also can rarely cause bacteremia[6] and even endocarditis.[7] The symptoms and signs of nocardiosis are comparable in immunocompromised and nonimmunocompromised patients.

Pulmonary Nocardiosis

Approximately two thirds of patients with nocardiosis present with pulmonary infection.[8] Pulmonary disease is usually subacute in onset, similar to a fungal (Chapter 308) or mycobacterial infection (Chapters 299 and 300). The most common complaints are a persistent cough with purulent sputum, fever, anorexia, and weight loss. Less commonly, patients may report pleuritic chest pain and dyspnea. Hemoptysis is rare but can develop in patients with large cavitary lesions. Acute onset of pneumonia has occasionally been reported in the immunocompromised host.[9]

Central Nervous System Infection

Approximately 5% of patients with a *Nocardia* infection have CNS involvement, with multilocular brain abscess the most common manifestation,[10] usually the consequence of transient bacterial dissemination from the lung. Lesions can occur in any region of the brain, and symptoms depend on location. Headache is the usual initial complaint and is frequently localized to the site of the abscess. Patients also may present with neurologic deficits and seizures. Meningitis is a less common CNS manifestation and is often associated with brain abscess.

Cutaneous Infection

Skin infection is usually caused by *N. brasiliensis* and typically follows a break in the skin that is contaminated by soil. Cutaneous disease has been reported in association with trauma, a postoperative wound, insect bites, thorn bush scratches, or even a cat scratch. Initially, a pustule or a moderately erythematous, nonfluctuant nodule develops at the site of inoculation. Erythema can extend along the lymphatic system and is associated with tender lymphadenopathy.[11] This form of cutaneous infection has been termed *lymphocutaneous* or *sporotrichoid* disease. In the immunocompromised host, disseminated infection may be manifest by multiple erythematous raised nodules and is an ominous finding. In tropical regions of South and Central America, *Nocardia* spp can cause ulcerations and large tumor-like lesions called *mycetomas* that are usually found on the lower legs.

DIAGNOSIS

Delays in diagnosis are common because nocardiosis has no specific clinical manifestations. Pulmonary disease is most commonly misdiagnosed as tuberculosis.[12] The combined findings of a lung nodule on a chest radiograph and a ring-enhancing CNS lesion are often mistaken for metastatic lung carcinoma.

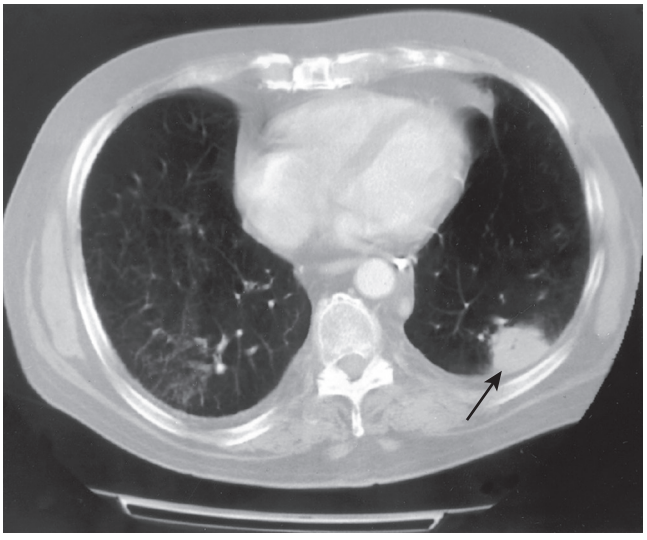

FIGURE 306-1. Chest computed tomography showing a peripheral nodular lung lesion (*arrow*) caused by *Nocardia* infection.

Other diagnoses that should be considered when an immunocompromised host presents with both a lung and CNS lesion are disseminated aspergillosis (Chapter 311) and toxoplasmosis (Chapter 320). Skin manifestations similar to *Nocardia* infection are seen with other etiologies, including cat scratch disease (Chapter 291), tularemia (Chapter 287), *Mycobacterium marinum* (Chapter 300), and sporotrichosis (Chapter 324).

Radiology

In pulmonary disease, chest radiographic findings are variable, with pulmonary nodules or mass lesions being seen most often (Fig. 306-1). Less frequently, consolidation, cavitary lesions with air-fluid levels, interstitial infiltrates, and pleural effusions are found. A chest computed tomographic (CT) scan often demonstrates areas of low attenuation within consolidations, multiple nodules, and chest wall extension of the infection. Patients with AIDS are more likely to have multiple pulmonary nodules, cavitary lesions, and upper lobe infiltrates. In some patients, the infiltrate may resolve, particularly in patients with normal immune function. However, the patient may present with brain abscess several months later because of transient bacteremia. In CNS infection CT or magnetic resonance imaging with contrast usually demonstrates one or more ring-enhancing lesions (Fig. 306-2). *Nocardia* brain abscess is more commonly multiloculated; otherwise, the radiologic findings are consistent with other bacterial brain abscesses (Chapter 382). Positron emission tomography is not helpful in differentiating *Nocardia* brain abscess from tumor because both demonstrate increased uptake.

Diagnostic Procedure

Polymerase chain reaction testing has been shown to be sensitive and specific for diagnosing *Nocardia* infections in research studies, but these tests are not usually commercially available. As a result, invasive procedures are generally required for specific diagnosis. For pulmonary infection, bronchoscopy with transbronchial biopsy or needle biopsy is recommended.

In nocardial meningitis, the cerebrospinal fluid (CSF) cell count usually reveals neutrophils, and the CSF culture may be positive, particularly if the culture is held for a prolonged period. CT-guided needle aspirate is the diagnostic procedure of choice for brain abscess. Histopathologic examination usually reveals an acute inflammatory response with a predominance of neutrophils.

Micronodular abscesses with minimal capsular formation are usually found. Gram stain or Brown-Brenn stains reveal gram-positive, beaded, branching forms. The morphology is identical to that of *Actinomyces* (Chapter 304), although the high lipid content of its cell wall often renders *Nocardia* modified acid-fast positive.

Bacteriology

Isolation of the organism on culture provides a definitive diagnosis from needle aspirate samples of brain abscess and a presumptive diagnosis when grown from respiratory and cutaneous samples. Because the organism needs 3 to 5 days to form colonies on blood agar, other organisms can overgrow. When *Nocardia* is suspected, the clinical laboratory should be notified to allow the use of selective

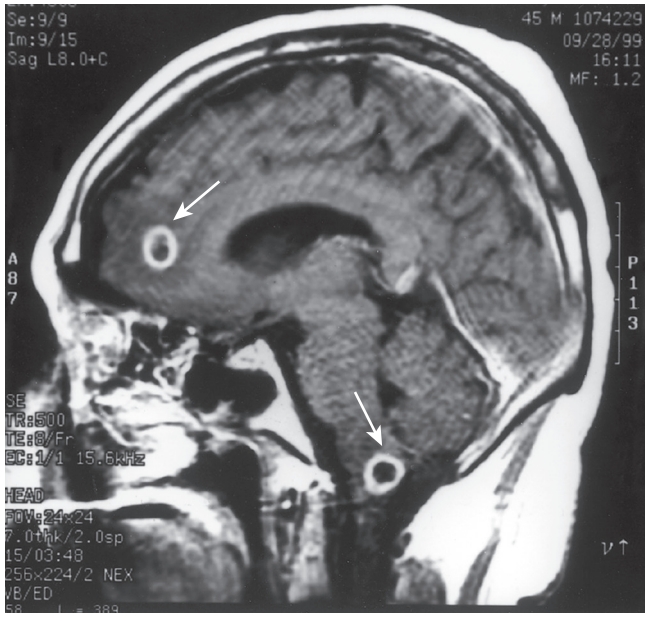

FIGURE 306-2. **Multiple gadolinium-enhanced brain lesions (*arrows*) caused by *Nocardia* infection.**

media and prolonged incubation.[13] RNA gene sequencing allows rapid speciation of isolates,[14] but its role in diagnosis is uncertain in pulmonary samples because it cannot differentiate true infection from colonization.[15] Antibiotic susceptibility testing always should be performed to guide the choice of therapy.[16]

TREATMENT

Because of the rarity of nocardiosis, no prospective treatment trials have been performed, and all recommendations are based on retrospective studies and in vitro sensitivity testing. For pulmonary and cutaneous infections, trimethoprim-sulfamethoxazole given orally at a dose of 160/800 mg (one double-strength tablet) three times daily is the most commonly used adult regimen.

For patients with disseminated and/or CNS infections, however, combination therapy is generally recommended,[17] with the exact regimen guided by antibiotic susceptibility testing. One recommended empirical regimen is trimethoprim-sulfamethoxazole (15 mg/kg/day IV of the trimethoprim component divided into two to four doses) and amikacin (7.5 mg/kg IV every 12 hours), plus either ceftriaxone (2 g IV twice daily) or imipenem (500 mg IV four times daily). Prolonged therapy with linezolid (600 mg twice daily) has been used successfully against nearly all strains of *Nocardia*,[18] and it can be used as monotherapy with CNS or disseminated disease or as a substitute for trimethoprim/sulfamethoxazole in multidrug regimens[19] with less toxicity than trimethoprim-sulfamethoxazole. However, because of its bone marrow toxicity, peripheral cell counts should be monitored weekly. Moxifloxacin (400 mg/day orally) has activity against several strains of *Nocardia*, including *N. farcinica* and *N. brasiliensis*, and can be useful in patients who cannot tolerate sulfonamides; however, relapse has been reported. Minocycline (100 mg orally twice daily) and amoxicillin-clavulanate (875/125 mg orally twice daily) are other potentially effective substitutes for trimethoprim-sulfamethoxazole as monotherapy or combined therapy for *Nocardia*. Because of the intracellular nature of *Nocardia* and its slow rate of growth, antibiotic treatment is usually required for 6 to 12 months to prevent relapse in the immunocompromised host and for 4 to 6 months in the normal host.[20] For patients with a brain abscess[21] or subcutaneous abscesses, surgical drainage as well as antibiotics are required for cure.

PROGNOSIS

The overall mortality for nocardiosis is approximately 25%. In otherwise healthy individuals, pulmonary nocardiosis has a better prognosis (15% mortality). The survival rate is worse in patients with bacteremia, patients with acute infection (symptoms for <3 weeks), patients receiving corticosteroids or cytotoxic agents, patients with disseminated disease involving two or more noncontiguous organs, and patients with meningitis.

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307

SYSTEMIC ANTIFUNGAL AGENTS

DAVID W. DENNING AND DAVID A. STEVENS

Methods for in vitro testing of antifungal susceptibility are available as standardized tools. A variety of assays also are available for therapeutic monitoring of drug levels in the serum and other bodily fluids. The increasing prevalence of drug resistance requires careful antifungal stewardship programs.[1,2] Drug-drug interactions are a particular prescribing challenge for triazole antifungal agents.

AZOLE ANTIFUNGAL AGENTS

Mechanisms of Action

The azole ring confers antifungal activity on a variety of synthetic organic compounds. *N*-substitution of imidazoles has created a family of drugs called *triazoles* that have the same mechanism of action as imidazoles, a similar or broader spectrum of activity, and less effect on human sterol synthesis. Both imidazoles and triazoles inhibit C-14α demethylation of lanosterol in fungi; this leads to reduced concentrations of ergosterol, which is essential for a normal fungal cytoplasmic membrane. The principal pharmacodynamic driver for the response of *Candida* spp to the triazole antifungal agents has been the ratio of total drug exposure (area under the curve) to the minimum inhibitory concentration. For *Aspergillus* spp, the critical driver has been the amount of time that the drug is above a critical inhibitory threshold. Because of their interaction with the cytochrome P-450 (CYP) system and, in some cases, the P-glycoprotein pumps, the azoles as a class have a large number of drug-drug interactions, about 10% of which cause important clinical events.[3] Careful attention must be paid to these potential interactions whenever azoles are prescribed (see https://www.aspergillus.org.uk/antifungal-drug-interactions/).

Newer triazoles have properties that make them preferable to ketoconazole. These properties include not only less hormonal inhibition but also better distribution into body fluids, the availability of both parenteral and oral formulations, less hepatotoxicity, and a broader spectrum. Resistance to azoles is emerging in previously susceptible species, and new resistant species, such as *Candida auris*, have spread globally. Resistance mechanisms include increased drug efflux, as well as altered or increased C-14α demethylase. Some of the common resistance mutations seen in *Aspergillus* isolates from certain geographic areas may have arisen owing to the widespread agricultural use of azole fungicides. All agents in this class have the potential for embryotoxicity and teratogenicity, so they generally should be avoided during pregnancy, particularly during the first trimester.

ITRACONAZOLE

Formulations and Pharmacology

Itraconazole is marketed as a capsule, as a new super bioavailable (SUBA)-itraconazole capsule with better bioavailability, and as an oral and intravenous suspension in cyclodextrin (an oligosaccharide ring). The ring entraps the hydrophobic, water-insoluble drug, thereby making it soluble. Oral absorption of the capsule is significantly enhanced by food, whereas absorption of the oral solution is best on an empty stomach. By comparison, absorption of SUBA-itraconazole does not vary with food. Peak levels with oral preparations are achieved 4 to 6 hours after a dose. Steady state is achieved only after 13 to 15 days, at which time the β-elimination half-life is approximately 19 to 22 hours. Absorption of the capsule is markedly depressed in patients who have graft-versus-host mucositis and in patients who have enteritis caused by acquired immunodeficiency syndrome (AIDS), but this problem can be alleviated by using the solution or SUBA-itraconazole.

Bioassays of itraconazole yield much higher concentrations than by direct measurement because of the hydroxyitraconazole metabolite. Hydroxyitraconazole, which appears in the blood in amounts roughly twice that of the parent drug, has antifungal activity and pharmacokinetics similar to those of the parent compound. Concentrations of itraconazole in tissue, pus, and bronchial secretions are generally higher than those in plasma. Ocular levels are low. Saliva concentrations persist for 8 hours after administration of the solution and may be beneficial in treating oral disease or eradicating oral colonization. The drug is metabolized in the liver (so its half-life is prolonged in patients with cirrhosis) and excreted in feces as metabolites. No useful

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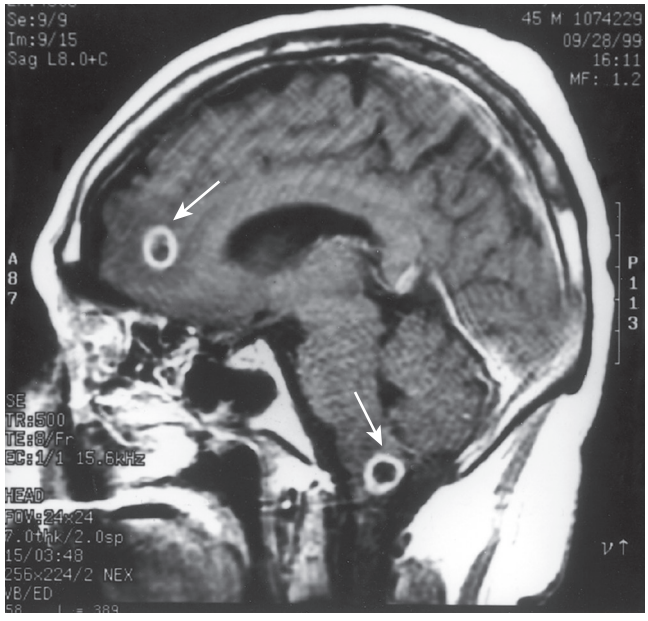

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AZOLE ANTIFUNGAL AGENTS

Mechanisms of Action

The azole ring confers antifungal activity on a variety of synthetic organic compounds. *N*-substitution of imidazoles has created a family of drugs called *triazoles* that have the same mechanism of action as imidazoles, a similar or broader spectrum of activity, and less effect on human sterol synthesis. Both imidazoles and triazoles inhibit C-14α demethylation of lanosterol in fungi; this leads to reduced concentrations of ergosterol, which is essential for a normal fungal cytoplasmic membrane. The principal pharmacodynamic driver for the response of *Candida* spp to the triazole antifungal agents has been the ratio of total drug exposure (area under the curve) to the minimum inhibitory concentration. For *Aspergillus* spp, the critical driver has been the amount of time that the drug is above a critical inhibitory threshold. Because of their interaction with the cytochrome P-450 (CYP) system and, in some cases, the P-glycoprotein pumps, the azoles as a class have a large number of drug-drug interactions, about 10% of which cause important clinical events.[3] Careful attention must be paid to these potential interactions whenever azoles are prescribed (see https://www.aspergillus.org.uk/antifungal-drug-interactions/).

Newer triazoles have properties that make them preferable to ketoconazole. These properties include not only less hormonal inhibition but also better distribution into body fluids, the availability of both parenteral and oral formulations, less hepatotoxicity, and a broader spectrum. Resistance to azoles is emerging in previously susceptible species, and new resistant species, such as *Candida auris*, have spread globally. Resistance mechanisms include increased drug efflux, as well as altered or increased C-14α demethylase. Some of the common resistance mutations seen in *Aspergillus* isolates from certain geographic areas may have arisen owing to the widespread agricultural use of azole fungicides. All agents in this class have the potential for embryotoxicity and teratogenicity, so they generally should be avoided during pregnancy, particularly during the first trimester.

ITRACONAZOLE

Formulations and Pharmacology

Itraconazole is marketed as a capsule, as a new super bioavailable (SUBA)-itraconazole capsule with better bioavailability, and as an oral and intravenous suspension in cyclodextrin (an oligosaccharide ring). The ring entraps the hydrophobic, water-insoluble drug, thereby making it soluble. Oral absorption of the capsule is significantly enhanced by food, whereas absorption of the oral solution is best on an empty stomach. By comparison, absorption of SUBA-itraconazole does not vary with food. Peak levels with oral preparations are achieved 4 to 6 hours after a dose. Steady state is achieved only after 13 to 15 days, at which time the β-elimination half-life is approximately 19 to 22 hours. Absorption of the capsule is markedly depressed in patients who have graft-versus-host mucositis and in patients who have enteritis caused by acquired immunodeficiency syndrome (AIDS), but this problem can be alleviated by using the solution or SUBA-itraconazole.

Bioassays of itraconazole yield much higher concentrations than by direct measurement because of the hydroxyitraconazole metabolite. Hydroxyitraconazole, which appears in the blood in amounts roughly twice that of the parent drug, has antifungal activity and pharmacokinetics similar to those of the parent compound. Concentrations of itraconazole in tissue, pus, and bronchial secretions are generally higher than those in plasma. Ocular levels are low. Saliva concentrations persist for 8 hours after administration of the solution and may be beneficial in treating oral disease or eradicating oral colonization. The drug is metabolized in the liver (so its half-life is prolonged in patients with cirrhosis) and excreted in feces as metabolites. No useful

ABSTRACT

Advances in medicine have increased the incidence and prevalence of mycoses but also have improved the availability of effective antifungal therapies. The clinician now has a choice among several classes of drugs, each with a different mechanism of action. Clinicians should be familiar with the indications and risks for these agents so as to choose what is best for their patients. The in vitro susceptibility of the patient's pathogen and therapeutic drug monitoring in body fluids assist the clinician in selecting therapy, monitoring its efficacy, and avoiding side effects. Nevertheless, the emergence of resistance to these available drugs and the emergence of new, resistant fungal species pose an ongoing challenge.

KEYWORDS

azoles
echinocandins
polyenes
flucytosine
pharmacology
antifungal efficacy

TABLE 307-1 DOSING OVERVIEW FOR ANTIFUNGAL AGENTS

ANTIFUNGAL	LOADING DOSE	STANDARD DAILY DOSING IN ADULTS (RANGES)	RENAL DYSFUNCTION	LIVER DYSFUNCTION	AGE >75 YEARS	OBESE	MORBIDLY OBESE
Itraconazole	Yes if very ill, 200 mg tid, for 3 days	200 mg bid*,† (300-600 mg)	No change‡	Avoid	No change†	No change	No data
Fluconazole	Yes for candidaemia, 1600 mg on day 1	200-800 mg*	Reduce	No change	No change	Use AdjBW	Use AdjBW
Voriconazole	Yes, 400 mg bid for 1 day	200 mg bid*,† (150-300 mg bid)	No change‡	Reduce or avoid	Lower dose†	Use AdjBW†	Use AdjBW†
Posaconazole	Yes if very ill, 300 mg bid	300 mg	No change‡	No change	No change	No change	No change
Isavuconazole	Yes, 200 mg bid for 1 day	200 mg	No change	No change	No change	No change	No data
Liposomal amphotericin B	No	3 mg/kg	No change§	No change	No change	300 mg	300 mg
Caspofungin	Yes (70 mg)	50 mg (70 mg)	No change	Reduce	No change	70 mg	70 mg
Micafungin	No	100-150 mg	No change	No change	No change	150 mg	150 mg
Anidulafungin	Yes, 200 mg	100 mg	No change	No change	No change	200 mg	200 mg
Flucytosine	No	25 mg/kg qid†	Reduce	No change	No change†	Use AdjBW†	Use AdjBW†
Ibrexafungerp	No	200 mg tid	No change	No change	No change	No data	No data

*Doses are for various serious fungal diseases; expert consultation is advised.
†Therapeutic drug monitoring particularly recommended, especially in complex and elderly patients, neonates, those with intestinal disease, cystic fibrosis, renal or hepatic dysfunction.
‡For IV dosing, note accumulation of carrier cyclodextrin.
§Moderate renal dysfunction may deteriorate, no known impact on anuric patients.
AdjBW = adjusted body weight; bid = twice daily; qid = four times daily; tid = three times daily.
For potential drug-drug interactions, see *https://www.aspergillus.org.uk/antifungal-drug-interactions/*.

amount of bioactive itraconazole appears in urine. Plasma concentrations do not increase in patients with renal insufficiency or decrease with hemodialysis.

Indications and Dosage

Itraconazole is useful for the treatment of invasive aspergillosis (Chapter 311), allergic bronchopulmonary aspergillosis,[A1] chronic pulmonary aspergillosis,[4] blastomycosis (Chapter 308), histoplasmosis (Chapter 308), meningeal and nonmeningeal coccidioidomycosis (Chapter 308), paracoccidioidomycosis (Chapter 308), sporotrichosis (Chapter 308), talaromycosis, phaeohyphomycosis (Chapter 314), mucosal candidiasis (Chapter 310), ringworm (including terbinafine-resistant infections),[A2] and tinea versicolor (Chapter 405). Itraconazole is also useful for the prevention of relapse of disseminated histoplasmosis in patients with AIDS. SUBA-itraconazole or oral solution can be used for antifungal prophylaxis in immunosuppressed and neutropenic patients, and intravenous itraconazole can be used as empiric therapy for episodes of febrile neutropenia (Chapter 260).

For deep mycoses, an initial oral itraconazole dose of 200 mg three times daily is recommended for the first 3 days to achieve high serum and tissue levels quickly (Table 307-1). SUBA-itraconazole requires only 100 mg twice daily. For intravenous use, a 200 mg loading dose four times daily is then followed by 200 mg twice daily.

Drug Interactions

Drugs that decrease gastric acidity reduce the absorption of capsules, except for SUBA-itraconazole. Some of the most notable drug interactions are rifampin, rifabutin, isoniazid, phenytoin, and carbamazepine, all of which decrease itraconazole blood levels. Itraconazole decreases rifampin blood levels and increases blood levels of some antihistamines and ivabradine, thereby potentially causing ventricular tachycardia. It also increases blood levels of warfarin, benzodiazepines, statins, dihydropyridine calcium-channel blockers, digoxin, quinidine, cyclosporine, tacrolimus, methylprednisolone, human immunodeficiency virus (HIV) protease inhibitors (e.g., ritonavir, indinavir, elvitegravir/cobicistat), and vinca alkaloids.

Adverse Effects

The most common adverse effect is dose-related nausea and abdominal discomfort, but symptoms rarely necessitate stopping therapy. Dividing the dose and administering the drug twice daily can improve tolerance and raise blood levels. Hypokalemia and edema may occur at doses of 400 mg/day or higher. Allergic rash is seen occasionally. Itraconazole is rarely hepatotoxic. Diarrhea, nausea, and other gastrointestinal complaints are more frequent with the oral solution. A negative inotropic effect, which is manifested as subacute onset of heart failure, is rarely seen. Longer-term use can result in peripheral neuropathy. Itraconazole during pregnancy is associated with increased fetal loss.

FLUCONAZOLE

Formulations and Pharmacology

Fluconazole is currently available in oral and vaginal tablets, as a powder for oral suspension, and as an intravenous formulation. Fluconazole is well absorbed from the gastrointestinal tract. Of the oral dose, 60 to 75% appears unchanged in the urine. Fluconazole penetrates into the brain, cerebrospinal fluid (CSF), saliva, sputum, and urine.

Fluconazole's half-life increases with diminished renal function. Although the dose may be reduced in such circumstances, the drug's toxicity is minimal even at high exposures, so the tendency to reduce the dose must be weighed against the risk of undertreatment. The dose should be doubled in patients who are receiving hemofiltration because of rapid clearance. Patients receiving hemodialysis should have one daily dose after each session.

Indications and Dosage

Candidiasis (Chapter 310)

Provided the infection is not caused by fluconazole-resistant *Candida*, fluconazole (see Table 307-1) is effective for the treatment of oropharyngeal and esophageal candidiasis. A single dose of 150 mg is as effective for vulvovaginal candidiasis. For candidemia or deep-seated candidiasis in immunosuppressed patients or for rapidly progressing or severely ill patients, especially in initial therapy before susceptibilities are known, an echinocandin or an amphotericin preparation is preferred. Fluconazole can be useful for prophylaxis (in some immunocompromised patients, with intra-abdominal surgery, and in severe pancreatitis) and as oral continuation therapy at hospital discharge. Use of this drug for prophylaxis may, however, result in shifts to less susceptible species in patient flora. In patients with *Candida* endocarditis (Chapter 61), long-term fluconazole therapy has been used to prevent relapse.

Cryptococcal Meningitis (Chapter 309)

Initial fluconazole is not as good as amphotericin B combined with flucytosine as therapy for cryptococcal meningitis.[A3] High-dose fluconazole is often given with these two agents in initial therapy, and it may be combined with flucytosine for dual therapy in patients who are not HIV-infected.[5] Continuation therapy with oral fluconazole 400 mg/day for 2 months is commonly used if the patient is clinically stable, followed by 200 mg/day at least until antiretroviral therapy results in a substantial rise in the CD4 count. Resistance to fluconazole is an increasing concern. Fluconazole is effective for the eradication

of genitourinary foci. For patients without AIDS, fluconazole is useful for patients who have completed a course of amphotericin B and are at high risk for relapse. It is effective for primary prophylaxis but is rarely used for this purpose.

Other Mycoses

Fluconazole is useful for coccidioidomycosis, especially meningitis, soft tissue infections, and pulmonary infections (Chapter 308), but itraconazole is commonly preferred for skeletal infections owing to its superior efficacy. For cutaneous sporotrichosis, ringworm, histoplasmosis, and blastomycosis, itraconazole is superior to fluconazole.

Drug Interactions

Among other drug interactions, fluconazole can cause significant increases in the blood level of phenytoin, glipizide, glyburide, tolbutamide, warfarin, rifabutin, cisapride, quinidine, bosentan, and cyclosporine. Rifampin lowers fluconazole blood levels by approximately 25%.

Adverse Effects

Adverse effects are uncommon. Even with chronic therapy, including doses exceeding 400 mg/day, headache, usually reversible alopecia, and anorexia are the most common symptoms; about 10% of patients develop elevated aspartate aminotransferase levels. Toxicity is, however, increased with doses over 1200 mg/day. Fluconazole use during pregnancy increases cardiac defects at birth by about three-fold.

VORICONAZOLE

Formulations and Pharmacology

Voriconazole is marketed as tablets, an oral solution, topical eye drops, and a solution in sulfobutyl ether β-cyclodextrin for intravenous administration. Voriconazole is cleared by hepatic metabolism, with less than 2% of the dose excreted unchanged in the urine. Voriconazole exhibits nonlinear pharmacokinetics in adults, owing to saturation of the clearance pathways at higher doses, but linear kinetics in children, who usually clear the drug rapidly. The principal enzymes involved in clearance are hepatic CYP2C19 and CYP3A4. Despite significant genetic polymorphisms that affect the drug's metabolism, achieved plasma levels overlap, and an initial dose adjustment based on genotype or racial group is not necessary. Therapeutic drug monitoring with dose adjustments as necessary is recommended because favorable outcomes correlate with serum concentrations greater than 1 to 2 μg/mL, but neurologic/psychiatric, hepatic, or cardiac side effects occur with levels greater than 5 μg/mL.

Standard loading doses followed by maintenance doses that are 50% of normal are recommended for patients who are older than 75 years or have mild-to-moderate hepatic cirrhosis. Dosage adjustments are not required for renal dysfunction, and voriconazole is not significantly cleared by hemodialysis.

Indications and Dosage

The standard dosing of voriconazole in adults is 6 mg/kg intravenously and 200 to 300 mg orally, both twice daily, preceded by loading doses for 1 day in severely ill patients (see Table 307-1). Doses should be adjusted by therapeutic drug monitoring, and lower doses such as 150 mg twice daily are preferred in older (age >75 years) and low weight (<50 kg) patients. Treatment is given for weeks or months.

Aspergillosis (Chapter 311)

Voriconazole is superior to amphotericin B for the treatment of invasive aspergillosis, in which it increases the likelihood of a successful outcome from about 30% to about 50%. Voriconazole is also recommended for chronic pulmonary aspergillosis.

Other Mycoses

Voriconazole also is effective for the treatment of invasive fusariosis and scedosporiosis.[6] Infections by *Scedosporium apiospermum* complex may respond, but *Lomentospora (Scedosporium) prolificans* infections are commonly resistant. The drug is efficacious in esophageal candidiasis (Chapter 124), invasive candidiasis (Chapter 310), refractory candidiasis, chronic pulmonary aspergillosis (Chapter 311), and allergic bronchopulmonary aspergillosis.[A4] It is useful for prophylaxis (in doses similar to what are used therapeutically) during periods of highest risk in high-risk allogeneic hematopoietic cell transplant recipients (Chapter 163) and in patients with severe aplastic anemia,[A5] but breakthrough mucormycosis can occur.

Drug Interactions

Voriconazole has many drug interactions. Rifampin, carbamazepine, long-acting barbiturates, glucocorticoids, and ritonavir induce the hepatic enzymes responsible for the clearance of voriconazole and thereby reduce voriconazole levels. Sirolimus levels are increased dramatically. Prolonged sedation is likely if voriconazole is coadministered with methadone, hydrocodone, alfentanil, fentanyl, or other short-acting opiates. Reduction in the clearance of pimozide, quinidine, ivabradine, and some antihistamines increases the risk for QT prolongation. Coadministration should be avoided with naloxegol, everolimus, St. John's wort, and venetoclax. Cyclosporine, tacrolimus, warfarin, statins, benzodiazepines, calcium-channel blockers, sulfonylureas, and vinca alkaloids can be coadministered, but the dosages of these drugs may need to be reduced, and clinical or laboratory monitoring is suggested. Coadministration of voriconazole with omeprazole or elvitegravir-cobicistat elevates the levels of both drugs. Voriconazole with rifabutin, phenytoin, or efavirenz results in lower voriconazole levels and elevated levels of the other drug. Numerous other interactions have been documented, and any cytochrome P-450 inhibitors, blockers, or inducers could have an interaction with voriconazole.

Adverse Effects

Transient, reversible visual disturbance beginning approximately 30 minutes after a dose is common. Hallucinations, unsteadiness, confusion, and liver enzyme abnormalities also have been associated with higher blood levels. Photosensitivity can be severe and has been associated with skin cancers in rare instances. Prolongation of the QT interval and tachyarrhythmias have been noted in patients with pro-arrhythmic risk factors, such as electrolyte abnormalities. Periostitis has been noted after prolonged therapy, apparently related to the fluoride atoms in the molecule. Leukoencephalopathy has been rarely reported.

POSACONAZOLE

Formulations and Pharmacology

Posaconazole is available as an oral suspension, as tablets, and as an intravenous form admixed with sulfobutyl ether β-cyclodextrin. Absorption of the tablet is superior to the suspension. The half-life is 20 to 35 hours. Clearance is primarily by fecal excretion, with only 13% excreted via renal clearance. Hepatic metabolism via uridine diphosphate glucuronidation plays only a small role in clearance, and CYP-mediated oxidation does not occur. The drug is concentrated in phagocytes.

Indications and Dosage

Posaconazole has a very broad spectrum of activity against molds, including many Mucorales,[7] and the least cross-reactivity among the azoles to resistance-causing mutations in the ergosterol synthesis pathway. It is effective in preventing opportunistic mycoses in transplant patients with graft-versus-host disease (Chapter 163) and in patients with hematologic malignancies and neutropenia.[A6] Intravenous posaconazole is equivalent to isavuconazole for invasive aspergillosis (Chapter 311),[A7] and it also is effective for chronic pulmonary aspergillosis (Chapter 311), coccidioidomycosis (Chapter 308), mucormycosis (Chapter 312),[8] and superficial candidiasis (Chapter 310).

The dose is 300 mg/day twice daily orally or intravenously on the first day, then 300 mg/day for treatment of deep-seated mycoses and for prophylaxis, whereas 100 to 200 mg oral solution has been used for mucosal candidiasis (see Table 307-1). Duration of therapy, which is dependent on the indication, can be many weeks or months for deep-seated mycoses. At steady state, 300 mg/day of tablet or intravenous preparation yields concentrations of about 1.4 μg/mL. Therapeutic drug monitoring is advisable in patients who are taking the solution and in patients who are taking tablets while also on proton pump inhibitors. Levels greater than 0.7 μg/mL correlate with efficacy in prophylaxis. Dosage adjustment is not needed for hepatic or renal failure or hemodialysis.

Drug Interactions

Although posaconazole has fewer interactions than itraconazole and voriconazole, significant interactions include increased levels of calcium-channel blockers, cyclosporine, sirolimus, tacrolimus, quinidine, ivabradine, atazanavir, amiodarone, cisapride, corticosteroids, digoxin, benzodiazepines, methylprednisolone, venetoclax, and drugs used for erectile dysfunction. Posaconazole levels may be increased by cobicistat. Posaconazole levels are reduced by cimetidine, efavirenz, metoclopramide, rifampin, and, in some studies, with diarrhea and proton pump inhibitors. Posaconazole with phenytoin, carbamazepine, or rifabutin results in lower posaconazole levels and elevated levels of the other drug.

Adverse Effects

Gastrointestinal symptoms, headache, acneiform rashes of the face, and abnormal liver function are occasionally seen. Electrolyte abnormalities should be rectified before therapy to avoid electrophysiologic effects, which manifest clinically as arrhythmias. A unique effect in up to 25% of patients is pseudohyperaldosteronism syndrome, which presents with hypokalemia and hypertension. The mechanism appears to be inhibition of the 11-β-hydroxylase enzyme, thereby resulting in an accumulation of aldosterone precursors, particularly 11-deoxycorticosterone, with effects on the mineralocorticoid receptor resulting in potassium excretion and hypertension. A second effect is inhibition of 11-β-hydroxysteroid dehydrogenase type 2, resulting in accumulation of cortisol, which also activates the mineralocorticoid receptor. This syndrome is more common in older patients, patients with a higher baseline blood pressure, and patients with higher blood drug levels. Rarely, glucocorticoid deficiency has been seen in these patients.

ISAVUCONAZOLE

Formulations and Pharmacology

Isavuconazonium is a water-soluble prodrug cleaved virtually completely by plasma esterases to form isavuconazole. Isavuconazonium is available for oral or intravenous use.[9] The pharmacokinetics are linear. The drug is highly protein bound. After oral administration, peak levels are reached in 2 to 3 hours, with a very long half-life of 60 to 130 hours. If given intravenously, the bottle should not be shaken to avoid precipitation. Switching at any time from intravenous to oral dosing is facilitated by the fact that the pharmacokinetics are unchanged. The pharmacology is unaffected by meals, renal impairment, or the patient's age, race, or gender. Hepatic insufficiency produces small pharmacologic changes, and no dose alteration is recommended.

Indications and Dosage

The enthusiasm for this drug relates directly to its activity in patients with mucormycosis (Chapter 312)[A8] and aspergillosis (Chapter 311).[A9] The antifungal activity in vitro is broad, the biggest exceptions being *Aspergillus niger*, *Fusarium*, and *Wangiella* species. Activity against species of Mucorales is broad and probably less variable than posaconazole. In small series of patients, activity appears promising against cryptococcosis, paracoccidioidomycosis, coccidioidomycosis, histoplasmosis, and blastomycosis. However, it appears to be inferior to caspofungin for the treatment of candidemia and invasive candidiasis (Chapter 310). The recommended dosing is to load with 372 mg (equivalent to 200 mg isavuconazole) three times daily for 2 days, then switch to once daily for weeks or months, depending on the clinical indication, degree of immunosuppression, response to therapy, and tolerance (see Table 307-1).

Drug Interactions

Although there are interactions with hepatic CYP 3A4 enzymes, the frequency of drug interactions is lower than with other triazoles. Undetectable isavuconazole concentrations are seen with rifampin and probably rifabutin because of induction of CYP3A4. Methotrexate, efavirenz, and lopinavir/ritonavir levels are increased. Drug dosage adjustments and monitoring may be required for cyclosporine, tacrolimus, sirolimus, mycophenolate, midazolam, bupropion, bosentan, etravine, and digoxin.

Adverse Effects

QT intervals are shortened, and the drug is contraindicated in patients with familial short QT intervals. Common side effects include nausea (26%), vomiting (25%), and diarrhea (22%), with headache, hypokalemia, dyspnea, cough, and edema noted in 10 to 20% of patients. The overall frequency of serious side effects appears to be less than for voriconazole.

AMPHOTERICIN PREPARATIONS

Mechanism of Action

Amphotericin B is a lipophilic molecule that may exert its antifungal effect by inserting itself into the fungal cytoplasmic membrane and causing an increase in membrane permeability or may act by adsorption of ergosterol at the surface of the fungal cell membrane. The resulting loss of intracellular molecules impairs fungal viability. The onset of action is rapid. The antifungal activity of amphotericin B also may be enhanced by its effects on oxidation.

Formulations and Pharmacology

Conventional amphotericin B is formulated in deoxycholate and as multiple lipid-associated formulations, including liposomal amphotericin B. Although lipid-associated preparations usually carry less toxicity, larger doses (usually about three-fold) are required for the same level of efficacy. The precise lipid formulation affects the tissue distribution,[10] the circulating pharmacokinetics, and the toxicity profile of each preparation, so they are not identical or even equivalent. When compared on a milligram-per-kilogram basis, lipid-associated formulations produce tissue concentrations that range from 90% lower to 500% higher than seen with conventional amphotericin B, with the most consistent relative reduction seen in the kidney. Liposomal amphotericin B penetrates brain tissue at a higher concentration than conventional amphotericin. Liposomal amphotericin B, which has the least toxicity, has been used more extensively than other lipid-associated preparations.

All formulations of amphotericin B must be infused in 5% dextrose with no electrolytes added. Infusion bottles need not be protected from light. Based on years of experience, the deoxycholate preparation of amphotericin B tends to be used for topical, intravitreal, intrathecal, and oral infections.

Liposomal amphotericin B is formulated as small bilayer liposomes (<100 nm) containing cholesterol, hydrogenated soy phosphatidylcholine, and distearoylphosphatidylglycerol. These components ensure that the amphotericin B remains associated with the liposome, with high concentrations in blood, reticuloendothelial tissue, and brain but lower concentrations in the kidney and lung. Liposomes bind to fungal cell walls and then pass through it to allow amphotericin B to intercalate with ergosterol in the fungal cell membrane. Once the liposomes penetrate into tissues, amphotericin may be released into the circulation, where it appears to bind to host lipids. Penetration into activated vascular endothelium at sites of infection likely contributes to its efficacy. Given the retention of amphotericin B in circulating liposomes, there is uncertainty about release into vegetations on heart valves. Penetration of amphotericin B into the eye, urine, pleural, bronchial, peritoneal fluid, synovial fluid, and cerebrospinal fluid is low and likely to be even lower with liposomal amphotericin B.

Indications and Dosage

Amphotericin B is active against most fungi, and its spectrum of activity is not influenced by the choice of formulation. Amphotericin B is infused intravenously over a 2- to 4-hour interval. More rapid infusion in patients with severely compromised renal function may lead to acute, marked hyperkalemia and ventricular fibrillation.

When resistance occurs, it is generally attributed to reductions in the biosynthesis of ergosterol and the synthesis of alternative sterols that lessen the ability of amphotericin B to interact with the fungal membrane; oxidant scavengers also may be produced. Primary resistance is common for *Aspergillus terreus* and *Aspergillus nidulans*, *Scedosporium*, *Lomentospora*, and *Trichosporon* species. Among the *Candida* species, primary resistance is noted at meaningful frequencies most often for *Candida lusitaniae* and sometimes for *Candida auris*. Development of resistance in isolates of normally susceptible species is rare. The principal pharmacodynamic driver of in vivo response is likely the ratio of the peak serum concentration to the minimum inhibitory concentration.

Intravenous liposomal amphotericin B at a dose of 3 mg/kg daily is appropriate for almost all indications, typically for 1 to 6 weeks (see Table 307-1). It is the antifungal agent of first choice for disseminated histoplasmosis, talaromycosis, cryptococcal meningitis, and mucormycosis. It is also effective for invasive candidiasis, but echinocandins are preferred. It is a second choice for invasive aspergillosis, unless azole resistance is demonstrated. Higher doses lead to greater toxicity without any clear therapeutic benefit, although a dose as high as 5 mg/kg is usually recommended for mucormycosis (Chapter 312). In visceral leishmaniasis (Chapter 319), a single dose of 40 mg/kg is effective, but 30 mg/kg combined with miltefosine is better. For cryptococcal meningitis in advanced HIV disease, a single dose of 10 mg/kg combined with flucytosine is effective.[A10] Lower daily doses have been used for prophylaxis in neutropenic hematology patients under the guidance of expert consultants.

Local instillation of amphotericin B into cerebrospinal fluid, joints, or pleura is rarely indicated. Fungal endophthalmitis (Chapter 391) is often treated with a single intravitreal dose of 5 to 10 μg conventional amphotericin. Coccidioidal meningitis (Chapter 308) may be treated with intrathecal amphotericin because it may produce superior results to systemic azole therapy, particularly in the long term, although with far greater toxicity.

Drug Interactions

The azotemia caused by amphotericin B is often worse in patients who are taking other nephrotoxic drugs but is not impacted by the use of intravenous radiographic contrast material. Renal dysfunction caused by amphotericin B can result in flucytosine toxicity. In patients with leishmaniasis (Chapter 319), the combination of amphotericin B and sodium stibogluconate should be avoided.

Adverse Effects

Amphotericin B can rarely cause anaphylaxis. In patients with a history of reaction to amphotericin B, a test dose of 1 mg (or 10 mg if liposomal amphotericin B) should be given over 15 minutes with subsequent observation.

Chills, fever, and tachypnea occur in some patients during infusion with liposomal amphotericin B but are much more common with conventional amphotericin. Slowing the infusion rate helps. Such reactions should not be mistaken for anaphylaxis or considered a contraindication to further use of amphotericin B. A patient with underlying cardiac or pulmonary disease may develop hypoxemia. These infusion-related reactions are less common in patients who are receiving corticosteroids. Milder reactions are usual with subsequent daily dosing. Premedication with acetaminophen is helpful. Patients with rapidly progressive mycoses should receive a full therapeutic dose within 24 hours.

Amphotericin B causes a dose-dependent decrease in the glomerular filtration rate because of a direct vasoconstrictive effect on afferent renal arterioles that reduces glomerular and renal tubular blood flow. Other effects on the kidney include potassium, magnesium, and bicarbonate wasting, as well as decreased erythropoietin production. Loss of renal function is due to the destruction of renal tubular cells, disruption of the tubular basement membrane, and loss of functioning nephron units. All of these toxicities are substantially reduced, but not eliminated, with liposomal amphotericin B. The serum creatinine level should be measured daily in the first few days of therapy and then at least twice weekly. Saline loading, such as the infusion of 1 L saline before infusion, may reduce nephrotoxicity. Potassium and magnesium wasting, which may be ameliorated with daily amiloride, often requires supplementation of these electrolytes. Curtailing of amphotericin B therapy is appropriate if the creatinine clearance falls by 40 to 50%, but longer courses of liposomal amphotericin B result in some permanent loss of renal function in about 15% of patients.

Administration via a peripheral cannula rather than a central line is possible with liposomal amphotericin B but not conventional amphotericin, because of phlebitis. Nausea, anorexia, and vomiting are common but much milder with liposomal amphotericin B than with conventional amphotericin. Bone pain, which is an uncommon but particular feature of liposomal amphotericin B, can be severe. Normocytic normochromic anemia occurs gradually, but the hematocrit rarely falls below 20 to 25% unless other causes of anemia are present. Rarely, thrombocytopenia, modest leukopenia, elevated transaminase levels, arrhythmias, coagulopathy, hemorrhagic enteritis, tinnitus, vertigo, encephalopathy, seizures, hemolysis, reticular rash, nephrogenic diabetes insipidus, or dysesthesia of the soles of the feet may be observed.

Amphotericin B and its lipid derivatives appear to be safe during pregnancy.

ECHINOCANDIN ANTIFUNGAL AGENTS

Mechanisms of Action

The echinocandin antifungal agents act by inhibiting the synthesis of 1,3-β-D-glucan in the fungal cell wall. The principal pharmacodynamic driver of in vivo response is the ratio of the peak concentration to the minimum inhibitory concentration. The three currently licensed echinocandins are caspofungin, micafungin, and anidulafungin; another agent with a very long half-life, thereby allowing once-weekly administration, is in late-stage clinical development. These agents are similar to one another, with very few drug interactions, an admirably low adverse event rate (except they are contraindicated during pregnancy), and essentially identical antifungal spectra. Of the three drugs, caspofungin has the broadest array of approved indications and the most clinical data. All are cyclic lipopeptides that must be given intravenously.

The echinocandins are fungicidal against all *Candida* species, including isolates resistant to other agents, although they have reduced activity against isolates of *C. parapsilosis*, *C. guilliermondii*, and *C. famata*. Resistance, though uncommon, has increasingly been noted, especially in *C. auris* and *C. glabrata*, and it sometimes develops during therapy. All the agents are active against *Aspergillus* species, but activity is limited to growing and dividing hyphal elements, so they are fungistatic, and occasional resistant isolates have been described. Their activity against other fungi is limited.

CASPOFUNGIN

Formulations and Pharmacology

The clearance of caspofungin is through a combination of spontaneous chemical degradation, hydrolysis, and *N*-acetylation. Dose adjustments are not required for impaired renal function or hemodialysis. The clearance of caspofungin is modestly reduced in patients with moderate hepatic insufficiency, in whom dose reduction is recommended. Penetration into infected tissues appears to be good.

Indications and Dosage

Caspofungin is indicated for the treatment of invasive candidiasis (Chapter 310), where it appears to be superior to isavuconazole,[A11] and esophageal candidiasis (Chapter 124). Caspofungin is also indicated for invasive aspergillosis (Chapter 310) in patients who are refractory to or intolerant of other therapies. Because of its activity against these two major opportunistic pathogens, caspofungin is useful for empiric therapy in neutropenic patients, such as patients undergoing treatment for acute leukemia.[A12] The usual dose is 50 mg once daily (see Table 307-1), but doses greater than 70 mg daily appear to be well-tolerated. Treatment is typically given for 2 to 4 weeks, occasionally longer.

Drug Interactions

Caspofungin has few meaningful drug interactions. Cyclosporine coadministration increases blood caspofungin levels, probably due to reduced hepatic uptake of caspofungin and has been associated with increased hepatic aminotransferase levels, so concomitant use requires caution. Caspofungin reduces tacrolimus levels by approximately 20%, and dosage adjustments may be required. Rifampin reduces caspofungin blood levels by approximately 30%, so the daily dosage of caspofungin should be increased from 50 to 70 mg if these drugs are coadministered. Likewise, limited data on other inducers of drug clearance (efavirenz, nevirapine, phenytoin, dexamethasone, carbamazepine) suggest that reduced caspofungin levels are possible and that increasing the daily dose to 70 mg should be considered.

Adverse Effects

Adverse reactions with caspofungin are infrequent and minor. Phlebitis and symptoms possibly related to histamine release during rapid infusion have been reported. Occasional episodes of confusion are noted.

MICAFUNGIN

Micafungin has an in vitro spectrum and properties similar to those of caspofungin.

Formulations and Pharmacology

The drug is light sensitive. After an intravenous infusion, the terminal half-life is approximately 15 hours. Metabolism appears to be mostly through fecal excretion, with less than 1% excreted in the urine. The drug penetrates particularly well into the lungs, liver, kidneys, and gastric mucosa. No adjustment for hepatic or renal insufficiency is needed.

Indications and Dosage

Efficacy for invasive candidiasis (Chapter 310) and *Candida* esophagitis (Chapter 124) is similar to that of amphotericin or caspofungin. The recommended dose is 100 to 150 mg/day for 10 to 14 days (see Table 307-1). Once-daily dosing produces steady state in 3 days. For prophylaxis in neutropenic patients being treated for acute leukemia or myelodysplastic syndrome or in patients undergoing hematopoietic cell transplantation, 50 mg/day is efficacious.[A13] Limited experience suggests activity comparable to caspofungin against invasive aspergillosis (Chapter 311) and modest efficacy in chronic pulmonary aspergillosis.

Drug Interactions

Micafungin has fewer drug interactions than caspofungin. There is no interaction with cyclosporine or rifampin, but slight increases in blood levels of sirolimus, nifedipine, itraconazole, and amphotericin B have been noted.

Adverse Effects

Micafungin has an excellent safety profile. Histamine release, manifested most prominently by total body erythema, can be avoided by slow infusion. Phlebitis has been reported.

ANIDULAFUNGIN

Formulations and Pharmacology

Anidulafungin is slowly degraded by the chemical opening of its ring structure. A 100-mg dose produces a C_{max} (peak concentration achieved) of 8.6 μg/mL at a time of peak concentration (T_{max}) of 6 to 7 hours. The half-life is 30 to 50 hours. Dose adjustments are not required for renal or hepatic insufficiency.

Indications and Dosage

A single loading dose of 200 mg (3 mg/kg) should be given on day one followed by 100 mg (1.5 mg/kg) daily thereafter for 10 to 14 days (see Table 307-1), occasionally longer. Anidulafungin is indicated for the treatment of

invasive candidiasis (Chapter 310) and esophageal candidiasis (Chapter 124), where it is at least as efficacious as fluconazole. Its efficacy against *Candida parapsilosis* is least certain.

Drug Interactions

Anidulafungin has no meaningful CYP enzyme interactions. As a result, it is the best echinocandin to use in the presence of liver failure.

Adverse Effects

Histamine-mediated symptoms (e.g., rash, urticaria, flushing, pruritus, dyspnea, hypotension) have been noted on occasion, as has anaphylaxis, but they are infrequent when the rate of infusion does not exceed 1.1 mg/minute. Other adverse reactions to anidulafungin have generally been infrequent and minor (diarrhea, hypokalemia, elevated liver function tests, neutropenia, nausea, headache, dermatitis). Patients with hereditary fructose intolerance should not be given anidulafungin.

FLUCYTOSINE

Formulation and Pharmacology

Flucytosine (5-fluorocytosine) is the fluorine analog of a normal body constituent, cytosine. Flucytosine is marketed as 250- and 500-mg capsules and, in a few countries, as an intravenous formulation. Absorption from the gastrointestinal tract is rapid and complete, with approximately 90% of the dose excreted unchanged in the urine. Cerebrospinal fluid concentrations are approximately 75% of simultaneous serum concentrations. The drug also penetrates well into aqueous humor, joints, bronchial secretions, peritoneal fluid, brain, bile, and bone, and it is readily cleared by hemodialysis and peritoneal dialysis.

The half-life of the drug in the serum of patients with normal renal function is 3 to 5 hours. Abnormal hepatic function has no influence on its half-life, but decreased renal function prolongs the half-life.

Mechanisms of Action

Isolates of *Candida* species are usually susceptible, as are most isolates of *Cryptococcus* spp, as well as the melanin-pigmented molds that cause chromoblastomycosis. Flucytosine is not active against isolates of *Aspergillus* species at pH 7.4. Flucytosine interferes with DNA synthesis by its conversion to 5-fluouridine triphosphate, which, when incorporated into RNA, causes aberrant transcription. The principal pharmacodynamic driver of response is the proportion of time the blood level exceeds the minimum inhibitory concentration. Resistance may be due to loss of the cytosine permease that permits flucytosine to cross the fungal cell membrane or loss of any of the enzymes that lead to its conversion into forms that interfere with DNA or RNA synthesis.

Indications and Dosage

For cryptococcal meningitis, where flucytosine contributes to increased survival when given with amphotericin B or fluconazole, the most studied dose is 100 mg/kg/day in four divided doses, usually for 14 days (see Table 307-1). As an approximation, the total daily dose should be reduced to 75 mg/kg with a creatinine clearance of 26 to 50 mL/minute and to 37 mg/kg when the creatinine clearance is 13 to 25 mL/minute. Ideally, the blood level should be measured in azotemic patients 2 hours after the last dose and immediately before the next dose. These values should range between 10 and 100 µg/mL. Patients requiring hemodialysis can be given a single post-dialysis dose of 37.5 mg/kg. Further doses are adjusted by blood level.

Drug Interactions

Flucytosine is used in combination with other agents for candidiasis, such as infection in sanctuary sites (eye, brain, heart valve, urine), for multiresistant organisms, and in chromoblastomycosis at the same dose as for cryptococcal meningitis. Monotherapy is rarely used because primary drug resistance is not uncommon in *Candida* infection, and secondary drug resistance is common in cryptococcosis and chromoblastomycosis.

Adverse Effects

Flucytosine may cause nausea, rash, diarrhea, and hepatic dysfunction but is generally well tolerated. In the presence of azotemia (such as that caused by concomitant administration of amphotericin B), leukopenia, thrombocytopenia, and enterocolitis may appear. These complications seem to be far more frequent among patients whose flucytosine blood levels exceed 100 to 125 µg/mL. Patients whose renal function is changing while receiving flucytosine should have their serum flucytosine concentrations determined twice weekly. Uncommonly, vomiting, bowel perforation, confusion, hallucinations, headache, sedation, and euphoria have been reported. Flucytosine is contraindicated in pregnancy.

IBREXAFUNGERP

Ibrexafungerp is the first of a new class of oral glucan synthase inhibitors.[11] Although the mode of action and spectrum of activity are similar to the echinocandins, its oral bioavailability sets it apart. Its first licensed indication is for vulvovaginal candidiasis (Chapter 310), but additional indications are likely.

Mechanisms of Action

Ibrexafungerp is a noncompetitive inhibitor of β-(1,3)-D-glucan with different binding sites than the echinocandins. Amino acid mutations in either of the glucan synthase copies in *Candida* spp lead to ibrexafungerp resistance.

Ibrexafungerp is about 50% bioavailable after oral administration, with some variability among patients. Peak concentrations occur after 6 to 9 hours, and the half-life is 16 to 24 hours. It is extensively distributed to most tissues in much greater concentrations than in plasma (4- to 50-fold) but not to the brain. Metabolism is via cytochrome P-450 CYP3A4, so that greater than 90% is excreted via the liver and bile and less than 2% in urine.

Indications and Dosage

For vulvovaginal candidiasis, the dose of ibrexafungerp is 300 mg orally twice a day for a single day (see Table 307-1).[A14] Ibrexafungerp also is fungicidal for most *Candida* spp, including azole-resistant strains and *C. auris*, and it is fungistatic for *Aspergillus* spp. It also has good activity against *Penicillium* spp, most dermatophytes, *Paecilomyces variotii*, *Scytalidium dimidiatum*, *Alternaria* spp, and *Cladosporium* spp, with some activity against the multiresistant *Lomentospora prolificans*. Activity against *C. lusitaniae* and *C. krusei* is lower than other *Candida* spp. Ibrexafungerp has potent activity against most, but not all, echinocandin-resistant *C. glabrata*.

Drug Interactions

Blood levels of ibrexafungerp may increase if given in combination with strong CYP3A4 inhibitors such as diltiazem. Lower concentrations of ibrexafungerp are likely if given concomitantly with rifampin, carbamazepine, phenytoin, St. John's wort, bosentan, efavirenz, or etravirine.

Adverse Effects

The most common adverse events during therapy are diarrhea, nausea, abdominal discomfort, vomiting and light-headedness. Unusual or rare side effects include dysmenorrhea, flatulence, back pain, elevated transaminases, vaginal bleeding, or skin rash. Ibrexafungerp is teratogenic in some experimental animals and is contraindicated in pregnancy.

OTHER AGENTS

Combinations of antifungal agents with different mechanisms of action are increasingly used to cover possible resistant pathogens, overcome the relatively high frequency of low serum concentrations of voriconazole in certain clinical situations (e.g., intensive care), and improve the very poor response rates in some diseases. Although synergy in vitro may be relatively easy to demonstrate, there are few examples of synergy in animal model studies and even fewer in patients. The clinical advantages of the amphotericin-flucytosine combination in cryptococcosis have yet to be documented definitively in other situations.

Immunomodulators, particularly cytokines, hold promise, but insufficient clinical data exist to determine where and how these drugs might be used. Granulocyte-macrophage colony-stimulating factor can improve outcomes when given prophylactically to high-risk leukemia patients during induction therapy.[A15] Gamma interferon can help preserve graft function in renal transplant patients with invasive aspergillosis and reduce hospitalization in patients who have chronic pulmonary aspergillosis and are low producers of gamma interferon.[12]

Therapy for the various forms of tinea and of onychomycosis with systemic agents is discussed in Chapter 405. Terbinafine, which is useful in these settings, is rarely effective in other mycoses unless the mycosis involves only the skin. Although *Pneumocystis jirovecii* is now classified among the fungi, the drugs used to treat it are not used to treat other mycoses (Chapter 313).

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TABLE 308-1 BLASTOMYCOSIS: CLINICAL CHARACTERISTICS AND TREATMENT

CHARACTERISTIC	DESCRIPTON
Causative fungi	*Blastomyces dermatitidis* and other *Blastomyces* spp.
Primary geographic distribution	South central and north central regions of the United States and Canadian provinces surrounding the Great Lakes, Africa, and Middle East
Primary route of acquisition	Respiratory (inhalation of conidia)
Principal site of disease	Lungs and skin are most common sites. Disseminated disease to bone, central nervous system, liver, spleen, and lymph nodes is uncommon but serious. Pulmonary disease with acute respiratory distress syndrome may occur
Opportunistic infection in compromised hosts	Diffuse pneumonia and widespread infections common in patients with T-cell defects or during high-dose corticosteroid therapy or TNF-α inhibitors
Drug of choice for most patients	All patients with blastomycosis should receive antifungal therapy; itraconazole for mild to moderate pulmonary or disseminated disease Patients with severe pulmonary or disseminated disease, CNS involvement and all immunocompromised hosts should be treated with lipid formulation amphotericin B
Alternative therapy	Voriconazole, posaconazole

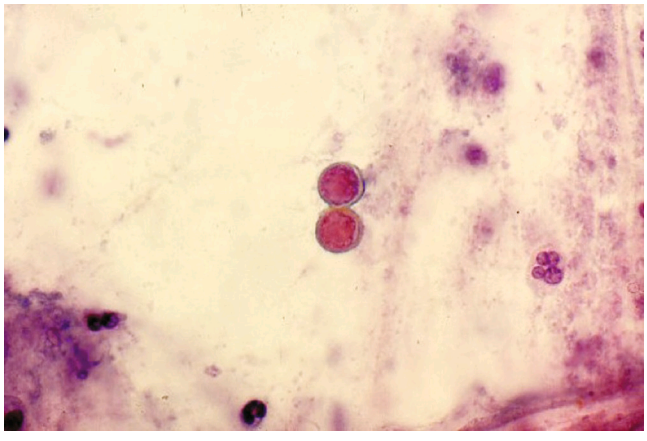

FIGURE 308-1. Papanicolaou stain of sputum showing a thick-walled yeast with broad-based budding typical of *Blastomyces dermatitidis*.

308 ENDEMIC MYCOSES

GEORGE R. THOMPSON, III, AND MARISA H. MICELI

BLASTOMYCOSIS

DEFINITION

Blastomycosis (North American blastomycosis) is an endemic mycosis that primarily causes infection of the lungs and skin and, less commonly, infection of the osteoarticular and genitourinary systems[1] (Table 308-1).

The Pathogen

Blastomyces spp. are thermally dimorphic fungi, and numerous new species have been recently identified.[2] In the mold phase in the environment, the organism produces conidia, which when aerosolized and inhaled cause infection. At 37° C on culture media and in tissues, the organism is a distinctive appearing yeast that is 5 to 20 μm in diameter with a thick refractile cell wall, and single broad-based buds (Fig. 308-1).

EPIDEMIOLOGY

Blastomyces spp. exist in diverse geographic areas worldwide, but most cases of blastomycosis are reported from the south central and north central regions of the United States[3] and the Canadian provinces surrounding the Great Lakes. Blastomycosis also occurs in Africa and the Middle East.[4] The natural niche of *B. dermatitidis* is thought to be soil and decaying vegetation, especially in areas associated with rivers and lakes. Although most cases occur sporadically, several well-described outbreaks have occurred, often in association with activities along waterways. The typical patient with blastomycosis is a middle-aged man who has an outdoor occupation or hobby. Blastomycosis develops in both hunters and their dogs in endemic areas.

PATHOBIOLOGY

After the inhalation of conidia, *B. dermatitidis* transforms into the yeast phase and causes pulmonary infection. Although most patients manifest only pulmonary symptoms, others have cutaneous lesions in the absence of other organ involvement or have disseminated infection. It is likely that most patients have asymptomatic hematogenous dissemination after the initial pulmonary infection, so cutaneous lesions should be viewed as a manifestation of hematogenous spread of the organism. Except in rare instances, blastomycosis is not acquired by inoculation. Cellular immunity involving T lymphocytes and macrophages is an important component of the host response to infection with *B. dermatitidis*, but neutrophils also play a role. Most patients with blastomycosis are healthy. Patients who are immunosuppressed are more likely to have severe disease. Infection in an immunosuppressed host can occur after new exposure to *Blastomyces* spp. or less often, from reactivation of a latent focus of infection acquired years earlier.

CLINICAL MANIFESTATIONS

Pulmonary

Most patients with acute pulmonary blastomycosis are asymptomatic or are thought to have community-acquired pneumonia. Patients with acute

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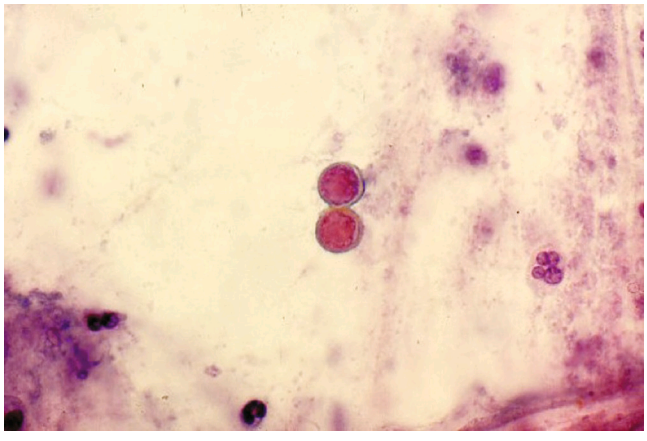

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308 ENDEMIC MYCOSES

GEORGE R. THOMPSON, III, AND MARISA H. MICELI

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CLINICAL MANIFESTATIONS

Pulmonary

Most patients with acute pulmonary blastomycosis are asymptomatic or are thought to have community-acquired pneumonia. Patients with acute

ABSTRACT

The endemic mycoses are caused by dimorphic fungi that exist as molds in the environment and convert to a yeast form or, in the case of *Coccidioides* species, a spherule, in the body and at 37° C. Endemic mycoses are geographically restricted, and infection is acquired from the environment and not transmitted person-to-person. The prominent diseases in North America are coccidioidomycosis, histoplasmosis, and blastomycosis. *Coccidioides* species are found in the desert southwest, and *Histoplasma* spp. and *Blastomyces* spp. are most often, but not exclusively, found in the Midwest. Initial infection is often asymptomatic but can progress to cause a spectrum of pulmonary findings, including respiratory distress. All these organisms can cause disseminated disease involving many organs, especially in immunocompromised patients. *Paracoccidioides* spp. are found in the soil in South America; most commonly, symptomatic disease develops in farm laborers years after the initial exposure. Sporotrichosis has a worldwide distribution; it differs from the other endemic mycoses in that it almost always follows direct inoculation of the organism through the skin, where it causes localized subcutaneous infection. Standardized diagnostic criteria can distinguish proven and probable disease from colonization. Treatment depends on the organism and the severity of the illness. The duration of treatment, except for sporotrichosis, is generally 3 to 6 months.

KEYWORDS

blastomycosis
histoplasmosis
coccidioidomycosis
sporotrichosis
paracoccidioidomycosis
environmental exposure
endemic mycosis

pneumonia have fever, malaise, a nonproductive cough, and a pulmonary infiltrate that shows lobar or multilobar patchy or nodular infiltrates on chest radiographs. Development of classic, verrucous draining skin lesions is a strong clue for blastomycosis.

Chronic pulmonary blastomycosis must be differentiated from tuberculosis (Chapter 299), other fungal infections, and lung cancer (Chapter 177). Fever, night sweats, weight loss, fatigue, cough, sputum production, hemoptysis, and dyspnea are commonly noted. On chest radiograph, the lesions are cavitary, nodular, fibrotic, or masslike in appearance. Hilar and mediastinal lymphadenopathy and pleural effusions are not commonly observed. Overwhelming pulmonary disease with acute respiratory distress syndrome (ARDS) occurs infrequently.[5]

Disseminated Infection

Cutaneous lesions are the most common manifestation of disseminated blastomycosis. The lesions, which can be single or multiple, are usually well circumscribed and painless (Fig. 308-2). Papules, nodules, plaques, and ulcers can occur; often they are verrucous and develop multiple punctate draining areas in the center. The lesions clinically mimic those associated with nontuberculous mycobacteria, other fungal infections, or pyoderma gangrenosum (Table 408-5). An uncommon manifestation, seen in immunocompromised patients, is the appearance of pustular lesions that readily reveal the organism when aspirated.

Another manifestation of disseminated blastomycosis is osteoarticular involvement. Osteomyelitis can be associated with contiguous skin lesions or can appear at sites distant from cutaneous lesions. Genitourinary involvement may be asymptomatic or be associated with signs of prostatism and the presence of a nodule on digital examination. Infrequent findings include laryngeal and oropharyngeal nodules; ocular lesions; central nervous system (CNS) involvement with either meningitis or intracerebral mass lesions; and dissemination to the liver, spleen, and lymph nodes.

DIAGNOSIS

The definitive diagnostic test for blastomycosis is growth of the organism from an aspirate, tissue biopsy specimen, sputum, or body fluid.[6] The mold phase takes several weeks to grow at room temperature. Once growth has occurred, the organism can be rapidly identified as *Blastomyces* spp. with a highly specific and sensitive DNA probe.

In this setting, the distinctive large, thick-walled yeast with a single broad-based bud (see Fig. 308-1) may be identified by: histopathologic examination of cutaneous or pulmonary lesions; cytologic examination of sputum, bronchoalveolar lavage fluid, or other tissue fluids; or calcofluor fluorescent staining of sputum or purulent material from pustular lesions. Identification of characteristic organisms on histopathology allows a tentative diagnosis of blastomycosis and initiation of antifungal therapy before culture results are known.

An enzyme immunoassay for *B. dermatitidis* cell wall antigens is available for use on serum, urine, or bronchial alveolar lavage fluid. The sensitivity of this assay varies with different reports. Because *B. dermatitidis* and *H. capsulatum* share many cell wall antigens, this assay is often positive in patients with histoplasmosis, as well as in those with blastomycosis.

It is helpful to obtain a bone scan in all patients with disseminated blastomycosis because of its propensity to infect bone.

FIGURE 308-2. Skin lesion—blastomycosis. A well-circumscribed painless ulcer in a patient with disseminated blastomycosis.

TREATMENT

With the exception of patients who have acute pulmonary blastomycosis that has totally resolved before the diagnosis is established, all patients with blastomycosis should be treated with an antifungal agent.[7] Patients who have mild-to-moderate pulmonary or disseminated blastomycosis should be treated with itraconazole (oral solution or capsules 200 mg three times a day for 3 days then once or twice daily for 6 to 12 months) to achieve mycologic cure and prevent relapse. If itraconazole is not tolerated, voriconazole or posaconazole can be used under expert guidance. The echinocandins are not active against *B. dermatitidis* and should not be used.

Patients who have severe pulmonary or disseminated blastomycosis, all patients with CNS infection, and most immunosuppressed patients should be treated initially with a lipid formulation of amphotericin B. The dosage is 3 to 5 mg/kg IV daily, except for CNS infection, for which 5 mg/kg IV daily should be used. After clinical improvement has occurred, usually within 1-2 weeks, therapy can be changed to itraconazole (oral solution or capsules, 200 mg three times a day for 3 days then twice daily) for a total of at least 12 months of therapy. For all patients who are treated with itraconazole, serum itraconazole levels should be determined when steady state has been reached after 2 weeks of therapy to ensure adequate absorption. Serum concentrations should be greater than 1 μg/mL.[8]

Corticosteroids have been helpful as adjunctive therapy for patients with blastomycosis-associated acute respiratory distress syndrome (ARDS) (Chapter 90), but this practice remains controversial. In patients who remain seriously hypoxic despite mechanical ventilation, extracorporeal membrane oxygenation may be lifesaving.

PROGNOSIS

The prognosis for patients with pulmonary or disseminated blastomycosis is excellent; more than 90% are cured. Most reported deaths occur in patients with overwhelming pneumonia and ARDS. In patients who require mechanical ventilation, the mortality rate is about 40%.[9]

HISTOPLASMOSIS

DEFINITION

Histoplasmosis is the most common endemic mycosis in the United States. Most infections are self-limited, but the organism has the ability to cause acute and chronic pulmonary infections as well as disseminated infection (Table 308-2).

TABLE 308-2 HISTOPLASMOSIS: CLINICAL CHARACTERISTICS AND TREATMENT

CHARACTERISTIC	DESCRIPTION
Causative fungi	*Histoplasma capsulatum* var *capsulatum* and other *Histoplasma* spp.
Primary geographic distribution	North and Central America. Endemic in the Mississippi and Ohio River Valleys, with extension into the St. Lawrence Basin
Primary route of acquisition	Respiratory (inhalation of microconidia)
Principal site of disease	Lungs and mediastinal lymph nodes most common; spread to skin, bone marrow, meninges, and other viscera uncommon but serious
Opportunistic infection in compromised hosts	Diffuse pneumonia and widespread infections common in patients with T-cell defects or during high-dose corticosteroid therapy or TNF-α inhibitors
Drug of choice for most patients	No antifungal is required for uncomplicated pneumonia; itraconazole for mild to moderate pulmonary histoplasmosis. Lipid formulation amphotericin B for moderate to severe/disseminated disease
Alternative therapy	Fluconazole, posaconazole

The Pathogen

Histoplasma capsulatum var *capsulatum* is a thermally dimorphic fungus. In the environment and at temperatures lower than 35° C, it exists as a mold that produces conidia. It produces both tuberculate macroconidia, which are helpful for identification purposes in the laboratory, and microconidia, which are the infectious form. In tissues and at 35 to 37° C, *H. capsulatum* converts into 2- to 4-μm oval yeasts that reproduce by budding and parasitize macrophages. African histoplasmosis is caused by a different subspecies, *H. capsulatum* var *duboisii*, and has different disease manifestations, particularly involvement of skin, subcutaneous tissues, lymph nodes, and bone but only rarely the lungs or other internal organs.

EPIDEMIOLOGY

Histoplasmosis, though found worldwide, is primarily a disease of North and Central America. *H. capsulatum* is endemic in the Mississippi and Ohio River Valleys, with extension into the St. Lawrence Basin; microfoci exist in discrete isolated areas in several eastern states and may represent novel species. Soil, caves, and abandoned buildings that contain high concentrations of bird or bat guano support growth of the organism. Every year, thousands of individuals who live in areas endemic for *H. capsulatum* are infected. Most cases are sporadic, and the exact source of exposure is unknown. Point source outbreaks occur in association with disruption of soil; cleaning attics, bridges, or barns; renovating or tearing down old structures laden with guano; and spelunking.

PATHOBIOLOGY

After inhalation of microconidia into the alveoli, a localized pulmonary infection ensues. Neutrophils and macrophages phagocytize the organism, which is now in the yeast phase. The organism is able to survive and travels within macrophages to the hilar and mediastinal lymph nodes and throughout the reticuloendothelial system by hematogenous dissemination. Such dissemination, which probably occurs in most persons who are infected, is typically asymptomatic in normal hosts. After several weeks, T-cells specifically sensitized by *Histoplasma* antigens activate macrophages, which are then able to kill the intracellular fungi.

The extent of disease is determined by both the number of conidia inhaled and the immune response of the host. A small inoculum can cause severe infection in immunosuppressed patients. Persons at greatest risk include patients who have acquired immunodeficiency syndrome (AIDS), lymphoma, or are organ transplant recipients, as well as patients who are taking corticosteroids or tumor necrosis factor inhibitors.[10] Reactivation of latent infection occurs in patients who have deficient cell-mediated immunity, as evidenced by the occurrence of histoplasmosis in immunosuppressed persons who grew up in the endemic area but have not returned to that area for years.

CLINICAL MANIFESTATIONS

Acute Pulmonary Histoplasmosis

Most individuals infected with *H. capsulatum* are asymptomatic. Patients who develop symptomatic pulmonary infection usually have a self-limited illness that begins several weeks after exposure and is characterized by fever, chills, fatigue, nonproductive cough, anterior chest discomfort, and myalgias. The chest radiograph typically shows a patchy lobar or multilobar reticulonodular infiltrate.[11]

Acute pulmonary histoplasmosis can be life-threatening. In patients who have experienced heavy exposure to *Histoplasma* spp., as might occur during the demolition of old buildings or while spelunking in a heavily infested cave, and in those who are immunosuppressed, high spiking fevers, chills, prostration, dyspnea, and cough are prominent, and ARDS can occur.

Chronic Pulmonary Histoplasmosis

Chronic cavitary pulmonary histoplasmosis is a progressive, often fatal form of histoplasmosis that develops almost exclusively in older patients who have chronic obstructive pulmonary disease (Chapter 76). Symptoms include fever, fatigue, anorexia, weight loss, cough productive of purulent sputum, and hemoptysis. On chest radiography the usual findings are unilateral or bilateral upper lobe infiltrates with multiple cavities and extensive fibrosis in the lower lobes.

Complications of Pulmonary Histoplasmosis

The mediastinal and hilar lymph nodes frequently calcify as the infection resolves; years later they can erode into bronchi and cause hemoptysis and expectoration of broncholiths. Granulomatous mediastinitis is an uncommon syndrome characterized by continuing inflammation and necrosis in the mediastinal lymph nodes. The enlarged nodes are readily apparent on chest radiographs, and computed tomography (CT) shows central necrosis and, in some cases, impingement on adjacent structures, including the esophagus, airways, and blood vessels. Although the symptoms usually resolve without treatment, obstructive syndromes can be severe, and the nodes can persist for years.

Fibrosing mediastinitis is a rare complication of histoplasmosis in which the host responds to the infection with an inappropriate excessive fibrotic response. Obstruction of the airways, superior vena cava, or pulmonary arteries and veins can occur with resultant progressive right heart failure and respiratory insufficiency. Bilateral obstruction of the pulmonary vasculature is less common than unilateral involvement and carries a worse prognosis. Mediastinal widening is seen on chest radiographs, and CT and angiography define the extent of invasion and obstruction of mediastinal structures. Pericarditis (Chapter 62) is a manifestation of a local inflammatory reaction to adjacent histoplasmosis.

Disseminated Histoplasmosis

Symptomatic acute disseminated histoplasmosis occurs mostly in immunosuppressed patients, especially patients who have AIDS with CD4+ counts lower than 150/μL as well as patients who have a hematologic malignancy, have received an organ transplant, or are taking corticosteroids or tumor necrosis factor inhibitors. Symptoms and signs include chills, fever, anorexia, weight loss, hypotension, dyspnea, hepatosplenomegaly, and skin and mucous membrane lesions. Pancytopenia, diffuse pulmonary infiltrates on chest radiography and CT, findings of disseminated intravascular coagulation (Chapter 161), and acute respiratory failure can be seen.

Chronic progressive disseminated histoplasmosis is an uncommon, fatal form of histoplasmosis that occurs mostly in middle-aged to elderly persons who have no known immunosuppressive illness. The illness is characterized by fever, night sweats, weight loss, anorexia, and fatigue. Patients appear chronically ill, hepatosplenomegaly and mucocutaneous ulcerations are common, and adrenal insufficiency (Chapter 208) can develop. An increased erythrocyte sedimentation rate, elevated alkaline phosphatase level, pancytopenia, and diffuse reticulonodular infiltrates on chest radiography and CT are typical. Patients with this form of histoplasmosis often have fever of unknown origin (Chapter 259). Miliary tuberculosis (Chapter 299), lymphoma (Chapters 171 and 172), and sarcoidosis (Chapter 83) must be excluded.

Involvement of almost every organ system has been reported with disseminated infection. Adrenal insufficiency (Chapter 208) must be excluded in any patient who has unexplained hypotension, hyponatremia, and hyperkalemia. Abdominal CT shows markedly enlarged adrenal glands. Central nervous system involvement manifests as either meningitis or focal lesions seen on magnetic resonance imaging and is more common in patients with AIDS. Skin lesions, which are also more common in patients with AIDS, can be papular, pustular, or ulcerated. *Histoplasma* endocarditis is a rare form of disseminated infection.

DIAGNOSIS

Identifying the Organism

Because the clinical manifestations of histoplasmosis are nonspecific,[12] diagnosis depends upon identifying the organism.[13] The definitive diagnostic test for histoplasmosis is growth of the organism in culture. Unfortunately, *Histoplasma* spp. may require as long as 6 weeks to grow in vitro. Tissue samples, bronchoalveolar lavage fluid, sputum, and blood are appropriate for culture. For patients who have evidence of dissemination, blood cultures are best performed with the lysis-centrifugation (Isolator tube) system; bone marrow and liver biopsy material often yield *Histoplasma* in disseminated disease. If pulmonary histoplasmosis is a diagnostic consideration, the laboratory should be informed so that a special medium that decreases the growth of commensal fungi can be used for the culture of pulmonary samples. As soon as growth of a mold has been detected, highly specific DNA probes for *Histoplasma* spp. allow rapid identification of the organism.

If the patient is acutely ill, tissue biopsy should be performed to search for the distinctive 2- to 4-μm oval yeasts with single buds (Fig. 308-3), which allows a tentative diagnosis to be made as quickly as possible. Routine tissue stains do not show yeasts; biopsy material must be stained with methenamine silver or periodic acid–Schiff stains. In patients with disseminated disease, bone marrow, liver, skin, and mucocutaneous lesions usually reveal many

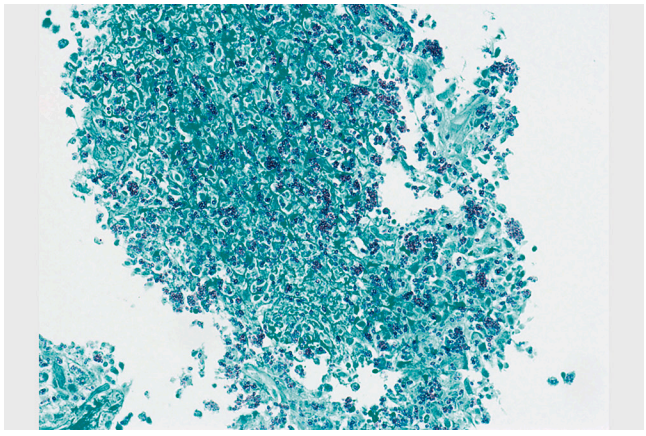

FIGURE 308-3. Tissue biopsy in a patient with histoplasmosis. Distinctive 2-4 µm oval yeast, each with a single bud.

organisms. The organisms also can be seen within neutrophils in peripheral blood smears from patients with acute disseminated infection. In patients with chronic pulmonary histoplasmosis or granulomatous mediastinitis, biopsy of the lung or lymph nodes may reveal the organism.

Serology plays an important role in the diagnosis of both acute and chronic forms of histoplasmosis.[14] A four-fold rise in complement fixation titer or the appearance of an M band by immunodiffusion assay is very suggestive of histoplasmosis. Serology is rarely helpful in immunosuppressed patients, who often cannot mount an antibody response. Because serologic tests are not definitive in patients with mediastinal lymphadenopathy, the results always should be confirmed by tissue biopsy.

An *H. capsulatum* enzyme immunoassay, which can detect polysaccharide antigen and detect the antigen in urine and serum, is extremely helpful in patients with disseminated infection and/or acute pulmonary infection. A serum immunoassay is positive in as many as 90% of patients with acute pulmonary histoplasmosis. Almost 75% of patients who have experienced heavy exposure and demonstrate diffuse pulmonary infiltrates and more than 90% of patients who have disseminated histoplasmosis have a positive urinary antigen test. The assay is less useful for patients who have chronic cavitary histoplasmosis and not useful for granulomatous or fibrosing mediastinitis. PCR testing can be helpful if culture and serology are negative.

The differential diagnosis of acute pulmonary histoplasmosis includes pneumonia from *Blastomyces* spp., *Mycoplasma pneumoniae* (Chapter 293), *Legionella* spp. (Chapter 290), and *Chlamydia pneumoniae* (Chapter 294). When enlarged hilar or mediastinal lymph nodes are present, histoplasmosis should be strongly considered. The most difficult diagnosis to differentiate is for acute pulmonary blastomycosis because the endemic areas overlap, a comparable history of outdoor activities is often obtained, and radiographs show similar findings. The clinical presentation and radiological findings of chronic pulmonary histoplasmosis may mimic tuberculosis (Chapter 299), other fungal pneumonias (especially blastomycosis), and nontuberculous mycobacterial infections (Chapter 300).

Disseminated histoplasmosis is clinically indistinguishable from sepsis of any bacterial or viral cause. In patients with AIDS, the differential diagnosis includes cytomegalovirus (Chapter 347), disseminated *Mycobacterium avium* complex infection (Chapter 300), and tuberculosis (Chapter 299).

TREATMENT

Itraconazole is the drug of choice for mild-to-moderate histoplasmosis. Lipid formulations of amphotericin B should be used as initial therapy for severe, life-threatening infections. Posaconazole has been used in fewer patients but appears to be effective. Fluconazole is less active and should be considered a second-line agent. The echinocandins are not effective for histoplasmosis.

Pulmonary Histoplasmosis

For acute pulmonary histoplasmosis, treatment is not usually given because the diagnosis often is not made until after the symptoms have resolved. However, if the patient remains symptomatic for at least 4 weeks, therapy with itraconazole (oral solution or capsules, 200 mg three times a day for 3 days and then once or twice daily) for 6 to 12 weeks should be given.

All patients who have severe pulmonary histoplasmosis and all immunosuppressed patients should be treated with an antifungal agent.[15] Lipid formulations of amphotericin B (3 to 5 mg/kg/day) are recommended for several weeks until a response is noted, at which time therapy can be changed to oral itraconazole (200 mg three times daily for 3 days and then 200 mg twice daily). A short course of methylprednisolone is recommended under expert guidance for patients in whom respiratory distress develops in association with acute pulmonary histoplasmosis.

For chronic pulmonary histoplasmosis antifungal therapy should be given to all patients. Itraconazole (200 mg three times a day for three days and then twice daily for 12 to 24 months), is recommended. Itraconazole levels should be monitored in all patients to ensure adequate absorption and therapeutic levels are achieved.

A trial of itraconazole for 6 to 12 weeks is often given to patients who have symptomatic granulomatous mediastinitis, although no data prove such therapy to be effective. Surgical resection of lymph nodes that cause obstructive symptoms may be beneficial. Antifungal therapy offers no benefit for patients who have fibrosing mediastinitis. Surgery is not indicated and carries a high operative mortality rate. Intravascular stents have been used successfully in patients who have vascular obstruction.

Disseminated Histoplasmosis

All patients with symptomatic disseminated histoplasmosis should receive antifungal therapy. Patients who have only mild-to-moderate symptoms with acute disseminated disease and many patients with chronic progressive disseminated histoplasmosis can be treated with itraconazole (200 mg twice daily after a loading dose of 200 mg three times daily for 3 days). A total of 12 months of therapy is generally adequate, but patients with chronic progressive disease may need longer treatment.

Patients who have moderately severe to severe disseminated histoplasmosis should be treated with liposomal amphotericin B (3 mg/kg/day). Therapy can be changed to itraconazole (see earlier) after the patient has responded to amphotericin to complete a total of 12 months of therapy. For patients who are immunosuppressed, therapy with itraconazole (200 mg/day) should continue until the immunosuppression resolves. For patients with AIDS (Chapter 358), suppressive therapy can be safely stopped in patients who have had a year of therapy, are receiving antiretroviral therapy, have CD4+ counts greater than 150 cells/µL, and have an undetectable HIV blood viral load for at least 6 months.[16]

Patients with pericarditis (Chapter 62) respond promptly to anti-inflammatory medications without antifungal therapy. Hemodynamic compromise, though unusual, requires drainage of pericardial fluid; only rarely has progression to constrictive pericarditis been documented.

PREVENTION

Prevention of histoplasmosis is difficult because exposure can occur without the person's knowledge in highly endemic areas. Persons who are immunosuppressed should be advised to avoid demolition areas, spelunking, and cleaning of farm buildings or attics. In patients with AIDS, itraconazole (200 mg/day) is effective for preventing infection and is indicated for patients whose CD4+ counts are lower than 150/µL and who live in a highly endemic area with a rate of histoplasmosis that is greater than 10 cases per 100 patient years. Neither primary or secondary prophylaxis is currently recommended for other immunosuppressed patients (e.g., solid organ transplant recipients).

PROGNOSIS

Acute pulmonary histoplasmosis is usually a self-limited disease. Patients who require treatment generally respond promptly to antifungal agents. However, the response of patients with chronic cavitary pulmonary histoplasmosis is often poor, primarily because of their severe underlying pulmonary disease. Mediastinal fibrosis has a poor prognosis, but intravascular stenting has led to improvement in many patients.

Patients with disseminated histoplasmosis, even those with advanced AIDS, usually respond promptly to antifungal therapy; most deaths in immunosuppressed patients occur when the diagnosis is delayed. Older patients with chronic progressive disseminated histoplasmosis have a slower but usually complete response to therapy.

COCCIDIOIDOMYCOSIS

DEFINITION

Coccidioidomycosis is a systemic fungal infection caused by *Coccidioides* spp. endemic to some arid regions of the western hemisphere (Table 308-3).

The Pathogen

Coccidioides immitis and *C. posadasii* are dimorphic fungi classified as Ascomycetes by ribosomal gene homology. In their vegetative state, mycelia

TABLE 308-3 COCCIDIOIDOMYCOSIS: CLINICAL CHARACTERISTICS AND TREATMENT

CHARACTERISTIC	DESCRIPTION
Causative fungi	*Coccidioides immitis* and *Coccidioides posadasii*
Primary geographic distribution	Arid regions of the western hemisphere, including parts of Arizona, California, New Mexico, and Washington; western Texas; parts of Central and South America
Primary route of acquisition	Respiratory (inhalation of arthroconidia)
Principal site of disease	Lungs most common; spread to skin, bones, meninges, and other viscera uncommon but serious
Opportunistic infection in compromised hosts	Diffuse pneumonia and widespread infections common in patients with T-cell defects or during high-dose corticosteroid therapy or TNF-α inhibitors
Drug of choice for most patients	No antifungal is required for uncomplicated pneumonia; fluconazole or itraconazole for progressive forms of infection
Alternative therapy	Amphotericin B (especially with diffuse pneumonia or rapidly progressive infections), voriconazole, posaconazole, isavuconazole

TNF = tumor necrosis factor.

with true septations mature to produce arthroconidia (spores), which are single cells approximately 2 to 5 μm in diameter. After infection, an arthroconidium enlarges to a spherule up to 75 μm in diameter and undergoes internal septation to produce scores of endospores. When the spherules rupture, endospores are released and produce more spherules in infected tissue or revert to mycelia if removed from the body.

EPIDEMIOLOGY

Coccidioides organisms can be recovered from the soil of the low deserts of Arizona; Los Angeles County and the Central Valley of California; parts of other states, including New Mexico, Nevada, and Texas[17,18]; and parts of Central and South America. Isolated pockets of endemicity also have been found unexpectedly elsewhere, such as in Washington State. Coccidioidomycosis is endemic in arid regions, which are characterized by modest rainfall, mild winters, and low humidity. However, even in the most highly endemic areas, fungal colonies are sparse and occupy only a tiny fraction of the total acreage. Mycelia multiply during periods of rain, and arthroconidia develop as the soil dries. Rates of infection are highest during dry months, occasionally accentuated when soil is disturbed by windstorms or construction equipment. Exposure to contaminated bales of cotton or other fomites can rarely result in infection beyond the endemic regions.

In general, the annual risk for infection within the most strongly endemic areas is 3%, thereby resulting in approximately 150,000 new infections per year. Reported clinical illness following infection is increasing. For example, from 1998 to 2016, reported infections increased more than 10-fold in California. With unusually intense exposure, such as archaeology sites or during military maneuvers within endemic regions, infections can develop in most individuals who are exposed for as little as a few days.

PATHOBIOLOGY

Inhaling even a single arthroconidium to the level of the terminal bronchiole may cause infection. Fungal proliferation engenders granulomatous inflammation, which is associated with intact spherules, and acute inflammation, which includes eosinophils and is associated with spherule rupture and proliferation. Focal pneumonia is often associated with ipsilateral hilar adenopathy; less frequently, infection enlarges the paratracheal, supraclavicular, and cervical nodes. Lesions occurring elsewhere are the result of hematogenous dissemination, and most become apparent within 2 years of the initial infection.[19] Although progressive dissemination occurs in less than 1% of infections, as many as 8% of persons with self-limited infection manifest asymptomatic chorioretinal scars, thereby suggesting that subclinical hematogenous spread may be frequent. Within weeks after infection, durable T-cell immunity normally arrests fungal proliferation, allows the inflammation to resolve, and prevents reinfection in the future. However, control of the infection occurs without sterilizing existing lesions, so reactivation of the dormant infection is possible even many years later in patients whose cell-mediated immunity becomes deficient. Arthritic and dermatologic manifestations or primary infection are mediated by circulating immune complexes or other immunologic phenomena rather than by fungal dissemination.

CLINICAL MANIFESTATIONS

About two thirds of infections are asymptomatic[20] and are detected only by finding dermal hypersensitivity to coccidioidal antigens. Patients who become ill usually experience pulmonary syndromes that eventually are self-limited. However, some patients develop complications or progressive forms of infection that display a broad variety of manifestations and pose difficult management problems.

Primary Pulmonary Infections

Symptoms develop within 5 to 21 days after exposure. For residents of, or recent visitors to, southern Arizona or the Central Valley of California, coccidioidomycosis accounts for approximately 25% of cases of community-acquired pneumonia. Fever, weight loss, fatigue, dry cough, and pleuritic chest pain are common but nonspecific complaints.[21] Arthralgia of multiple joints without significant effusion is also frequent and is referred to as "desert rheumatism." Occasional skin manifestations include a short-lived nonpruritic maculopapular rash, erythema multiforme, or erythema nodosum. Both joint and skin lesions resolve without tissue destruction.

Radiographs of the chest may not detect any abnormalities or may demonstrate pulmonary infiltrates that are either segmental or lobar. Hilar adenopathy is often a distinctive finding. Parapneumonic pleural effusions may occur and generally resolve without intervention. Eosinophilia may be a prominent finding in differential leukocyte counts of peripheral blood, and the erythrocyte sedimentation rate is generally elevated. Symptoms frequently persist for many weeks before improvement is clearly underway, and the illness, especially lassitude, may persist for months.

Extrapulmonary Dissemination

Coccidioidomycosis in patients with deficiencies in cellular immunity, such as solid organ recipients, patients receiving other immunosuppressive therapy, those with AIDS or lymphoma, and women during their third trimester of pregnancy, usually results in dissemination beyond the lungs.[22] Mutations of interferon-γ or the interleukin-12 receptor genes also predispose to dissemination. However, disseminated infection occurs in some patients who have no obvious underlying disease and do not manifest heightened susceptibility to other infections. Disseminated infection is more likely to occur in men than in women and in persons of certain ancestry such as Africans, Filipinos, or Native Americans compared to Caucasians. The most common locations for disseminated lesions are the skin (cutaneous papules or subcutaneous abscesses); joints (especially the knee); bones, including the vertebrae; and basilar meninges. Such infections may produce one or many lesions and are frequently subacute or chronic in their manifestation. In broadly immunosuppressed patients, coccidioidal infections may be more fulminant, with fungemia detectable in blood cultures and the development of diffuse reticulonodular pulmonary infiltrates. Although the kidneys and the urinary bladder are rarely involved, *Coccidioides* may be recovered from concentrated specimens of urine, usually because of focal dissemination to the prostate. In contrast to histoplasmosis, the gastrointestinal tract is rarely involved in coccidioidomycosis.

DIAGNOSIS

Since clinical manifestations are nonspecific, diagnosis depends on methods that identify the organism. Delayed-type hypersensitivity skin testing can identify past infection with *Coccidioides* species but cannot be relied upon to diagnose ongoing active infection.

The diagnosis is definitively established by recovering *Coccidioides* spp. from clinical specimens. On direct examination of respiratory specimens or tissue, spherules appear as large structures with refractile walls and internal organization; they are also seen on hematoxylin-eosin, silver, or periodic acid–Schiff stains of histologic preparations. Gram stain does not detect spherules. In culture, mycelial growth is often evident within the first week of incubation, and PCR allows rapid genus identification. Recovery of *Coccidioides* spp. from scant respiratory secretions or from the cerebrospinal fluid of patients with meningitis may be difficult. In patients who have pleural effusion, cultures of pleural biopsies usually yield *Coccidioides* spp.

A presumptive diagnosis of coccidioidal infection is often based on the detection of specific antibodies in serum, which are about 84% sensitive and about 96% specific. Within the first weeks of the initial infection, a precipitin-type antibody is detected (IgM), usually by immunodiffusion techniques. Later,

complement fixation–type antibodies (IgG) generally appear. However, these tests may be falsely negative as often as half the time during the first weeks of illness. When reported quantitatively, concentrations of complement fixation antibodies are usually highest in the most extensive infections and decrease in patients whose infections are controlled.[23] PCR testing can be highly sensitive and specific when available.[24,25]

An important means of diagnosing coccidioidal meningitis is the detection of *Coccidioides* antigen or complement fixation antibodies in cerebrospinal fluid, along with other abnormalities such as leukocytosis, an elevated protein concentration, and a low glucose concentration. Eosinophilia of the CSF can suggest coccidioidomycosis but is not always present.

TREATMENT

The role of antifungal therapy for primary uncomplicated infections is unsettled because it is not known whether treatment either shortens the course of symptoms or diminishes the rate of complications.[26] However, the value of treatment is clear for patients with progressive or disseminated infection.

Because many coccidioidal infections are chronic, initial treatment often consists of oral azole antifungal agents, such as fluconazole and itraconazole.[27] Responses to these two medications are similar, but itraconazole is preferred in patients with skeletal infections. Doses of these azoles are 400 mg/day or higher, and treatment is usually continued for a year or more. Satisfactory responses are obtained in approximately two-thirds of patients. Fluconazole is effective therapy for coccidioidal meningitis and has greatly reduced the number of patients treated with intrathecal amphotericin B. Unfortunately, cessation of azole therapy is often followed by a recurrence of symptoms, especially in patients who have coccidioidal meningitis. Therefore, many patients need protracted or even lifelong therapy to control disease activity. The limited evidence available for the newer azole antifungals (voriconazole, posaconazole, isavuconazole) indicates that they are also effective in some patients and are sometimes useful for refractory infections. Amphotericin B is generally preferred for patients with rapidly progressive disease or when treatment with azole antifungals has failed. Daily doses range from 0.4 to 1 mg/kg for the original deoxycholate formulation and up to 5 mg/kg per day for newer lipid formulations. In addition to antifungal medications, necrotic tissue may need to be removed surgically.

Diagnosis and Treatment of Complications of Primary Pulmonary Infection

The primary pulmonary process can produce a variety of sequelae. The most frequent is the development of a pulmonary nodule (Fig. 308-4), typically measuring 1 to 4 cm and lying within 5 cm of the hilum. Despite their benign nature, coccidioidal nodules may cause concern because of their similarity to a malignant mass (Chapters 72 and 177). Positron emission tomography scans are typically positive. Management usually requires percutaneous needle aspiration or resection.

Another consequence of pulmonary coccidioidomycosis is cavitation of the infiltrate, which occurs in approximately 5% of cases of pneumonia. Most cavities are solitary and thin walled and reside in an upper lobe, close to the pleura. Occasionally, they produce pain, hemoptysis, or adjacent infiltrates. Mycetoma or fungus ball formation with either *Coccidioides* spp. or other colonizing molds is a complication of a coccidioidal cavity. Infrequently, a cavity ruptures into the pleural cavity, thereby resulting in pneumothorax, pyopneumothorax, or bronchopleural fistula. In many cases, this rupture is the first symptom of coccidioidal infection, especially in otherwise healthy young men. An air-fluid level in the pleural space, detectable by radiography, often helps differentiate this problem from a spontaneous pneumothorax.

Prompt surgical resection of the cavity is the preferred treatment of this complication. The least common pulmonary complication is persistent fibrocavitary infection that progresses to involvement of both lungs and requires long courses of antifungal therapy.

Person-to-person transmission of pulmonary infection has not been reported. Isolation precautions are unnecessary, even in acute care areas.

PROGNOSIS

After resolution of the initial infection, most patients maintain lifelong immunity, and infections after re-exposure are rare. However, cessation of symptoms is frequently accomplished without eradicating *Coccidioides* completely, so recurrence of the original infection many years after the original episode is a well-recognized risk, especially during any intercurrent periods of profound immunosuppression. Antifungal retreatment of rheumatic patients whose coccidioidal infections reactivate during treatment with biologic response modifiers and/or disease-modifying antirheumatic drugs appears to be safe in some patients. For patients in whom the initial infection cannot be resolved, the disease typically follows a protracted course. Although infection is more often debilitating than fatal, fulminant respiratory failure can occur. If untreated, coccidioidal meningitis is nearly always fatal within 2 years. Treated meningitis has a more favorable prognosis, but complications and relapse are still common.

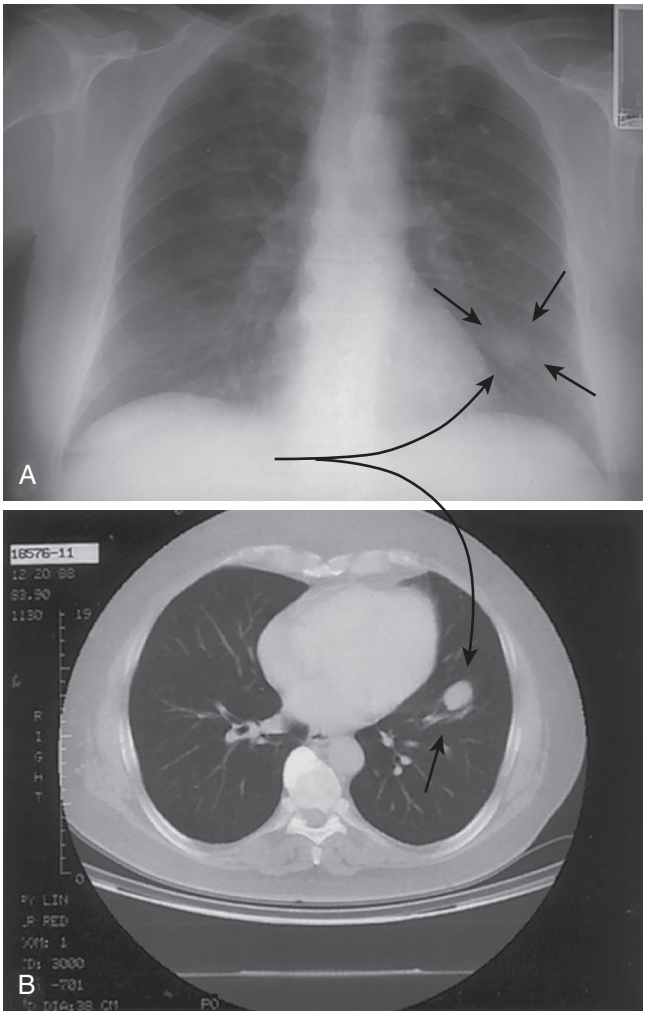

FIGURE 308-4. Coccidioidomycosis. A, Benign nodule secondary to coccidioidomycosis (*arrows*). **B,** Computed tomography scan of the nodule shown in **A** (*arrows*).

SPOROTRICHOSIS

DEFINITION

Sporotrichosis is a subacute or chronic infection that is usually localized to cutaneous and lymphocutaneous structures, but pulmonary, osteoarticular, and disseminated infection can occur in patients with varying states of immunodeficiency.

The Pathogen

Sporothrix spp. are thermally dimorphic fungi. In the environment at temperatures ranging from 25° to 35° C, the organism exists as a mold and produces conidia, which are the infectious form. In tissues and at 37° C, *Sporothrix* spp. transform into the yeast phase.

EPIDEMIOLOGY

Sporothrix spp. are found worldwide in climates ranging from temperate to tropical. The organism exists in a variety of environmental niches, including soil, sphagnum moss, hay, decaying wood, and other vegetation. Infection is seen almost exclusively in persons whose vocation, avocation, or living conditions brings them into contact with the organism in the environment. Most cases of sporotrichosis are sporadic, but outbreaks have been described. For example, an extensive outbreak extended over many years in Rio de Janeiro, Brazil, mostly in children and women who were exposed to infected domestic cats.[28]

PATHOBIOLOGY

Infection, which is almost always acquired by inoculation of conidia, remains localized to the immediate and contiguous cutaneous, subcutaneous, and

FIGURE 308-5. Lymphocutaneous sporotrichosis. The lesion at the inoculation site has ulcerated. (From Watanakunakorn C. Photoquiz. *Clin Infect Dis*. 1996;22:765.)

lymphatic structures. Inhalation of conidia, which occurs less commonly, can result in pulmonary and, rarely, disseminated sporotrichosis typically in immunocompromised patients. The typical host response to infection with *Sporothrix* is a mixed neutrophilic and granulomatous reaction. Cell-mediated immunity is important in containing the infection. In individuals who have underlying illnesses, including alcohol use disorder, diabetes mellitus, and chronic obstructive pulmonary disease, *Sporothrix* spp. are more likely to involve osteoarticular structures and the lungs. Widespread dissemination develops in persons with advanced AIDS but is unusual in normal hosts.

CLINICAL MANIFESTATIONS

Lymphocutaneous

Days to weeks after inoculation of *Sporothrix* spp. conidia, a papular lesion develops at the inoculation site; the lesion becomes nodular and often ulcerates (Fig. 308-5).[29] Drainage is not grossly purulent, and the lesion is not terribly painful. Similar lesions occur along the lymphatic distribution proximal to the primary lesion. Verrucous or ulcerative fixed cutaneous lesions do not exhibit lymphatic extension. The differential diagnosis of lymphocutaneous sporotrichosis includes *Nocardia* infections (Chapter 306), atypical mycobacterial infections (especially *Mycobacterium marinum*; Chapter 300), *Leishmania braziliensis* infections (Chapter 319), and tularemia (Chapter 287).

Visceral and Osteoarticular

Pulmonary sporotrichosis occurs most often in middle-aged men who have chronic pulmonary disease and alcohol use disorder. Fever, night sweats, weight loss, fatigue, dyspnea, cough, purulent sputum, and hemoptysis are common. Chest radiographs show unilateral or bilateral upper lobe cavities with variable amounts of fibrosis and nodular lesions. The disease mimics reactivation tuberculosis (Chapter 299).

Osteoarticular sporotrichosis occurs most often in middle-aged men and more frequently in patients with alcohol use disorder. The joints most commonly affected are the knee, elbow, wrist, and ankle. Isolated bursitis, tenosynovitis, and nerve entrapment syndromes have been reported. Osteoarticular infection can follow local inoculation or can be secondary to hematogenous spread.

Disseminated sporotrichosis, manifested as widespread ulcerative cutaneous lesions with or without visceral involvement, is uncommon. Most cases have been reported in patients with advanced HIV infection.

DIAGNOSIS

Growth of *Sporothrix* spp. from culture of material aspirated from a lesion, a tissue biopsy specimen, sputum, or body fluid is the most effective method of establishing the diagnosis of sporotrichosis. Growth of the mold phase of the organism is usually evident within a few days. Histopathologic examination of biopsy material shows a mixed granulomatous and pyogenic process; the organisms are often present in small numbers and are frequently not seen. PCR testing at a fungal reference laboratory can confirm the diagnosis. Serology is less useful.

TREATMENT

Because sporotrichosis is usually a localized subacute to chronic infection, oral antifungal agents are preferred. Amphotericin B is reserved for severe infections.[30] Itraconazole is the drug of choice for lymphocutaneous sporotrichosis. The usual dosage of itraconazole is 200 mg daily, and treatment should continue for several weeks after all lesions have disappeared, generally for a total of 3 to 6 months. Saturated solution of potassium iodide (SSKI) can be used to treat sporotrichosis in resource-poor settings but currently has a limited role. The initial dose is 5 to 10 drops three times daily in water or juice, with the dose increasing over a period of several weeks to a maximum of 40 to 50 drops three times daily. SSKI has many side effects, including salivary gland swelling, metallic taste, rash, and fever; the only advantage is that it is inexpensive. Fluconazole is less effective than itraconazole but for occasional patients can be used at a dosage of 400 to 800 mg daily. Posaconazole has been used successfully under expert guidance in a few patients with sporotrichosis. Isavuconazole appears to have limited activity and voriconazole is not active against *Sporothrix* spp.

Osteoarticular and pulmonary sporotrichosis are usually treated with itraconazole (200 mg twice daily for 12 months). Longer therapy may be necessary based on the extent of disease. Other azoles are less effective, and SSKI is ineffective for these manifestations.

In a seriously ill patient with pulmonary sporotrichosis, a lipid formulation of amphotericin B at a dosage of (3 to 5 mg/kg daily) should be used as initial therapy. After the patient has shown improvement, therapy can be changed to itraconazole. A lipid formulation of amphotericin B (3 to 5 mg/kg daily) is the drug of choice for disseminated sporotrichosis. Therapy can be changed to itraconazole (200 mg twice daily) once the patient has stabilized. Patients with HIV infection and disseminated sporotrichosis should remain on lifelong maintenance therapy with itraconazole (200 mg daily).

PROGNOSIS

The prognosis for patients with cutaneous and lymphocutaneous sporotrichosis is excellent. Almost all patients are cured. Extracutaneous forms of sporotrichosis do not respond well to therapy, partly because of delays in diagnosis and partly because of the underlying diseases that are frequently found in these patients. The outcome of disseminated sporotrichosis in patients with HIV infection is less favorable but has improved in recent years with effective antiretroviral therapy.

PARACOCCIDIOIDOMYCOSIS

DEFINITION

Paracoccidioidomycosis (South American blastomycosis) is a subacute to chronic mycosis that is endemic in Central and South America. The disease is characterized primarily by pulmonary, mucous membrane, and cutaneous lesions, but disseminated disease also occurs.[31]

The Pathogen

Paracoccidioides spp. are thermally dimorphic fungi. In the environment and at temperatures below 35° C, the organisms grow as a mold. In tissues and at 37° C in vitro, the organism assumes the yeast form with multiple narrow-based daughter cells attached to the mother cell.

EPIDEMIOLOGY

Paracoccidioides spp. exist only in humid areas of Central and South America. More than 80% of cases are from Brazil. The presumed ecologic niche is in soil. The disease is most prevalent in middle-aged to elderly men from rural areas. Although the disease classically develops later in life, it is likely that initial exposure occurs many years earlier. Cases seen in areas outside Central and South America have all been linked to previous residence in the endemic area.

PATHOBIOLOGY

Paracoccidioidomycosis develops after the inhalation of aerosolized conidia encountered in the environment. Once in the alveoli, the mycelial phase converts to the yeast phase. In most patients, manifestations of disease do not develop at the time of the initial infection. The host defense mechanism against *P. braziliensis* appears to be primarily cell-mediated immunity. The histopathologic picture includes both neutrophilic and granulomatous responses. Paracoccidioidomycosis in patients with advanced HIV and in other immunosuppressed patients manifests as widespread disseminated infection. Reactivation of latent infection acquired years earlier is the presumed pathogenesis of most cases of the chronic adult form of paracoccidioidomycosis and cases that appear years after the patient has left the endemic area.

CLINICAL MANIFESTATIONS

Acute-Subacute (Juvenile) Paracoccidioidomycosis

The acute-subacute form of paracoccidioidomycosis, which occurs in less than 10% of patients, is a disease of the reticuloendothelial system with widespread dissemination to the liver, spleen, lymph nodes, and bone marrow. Patients younger than age 30 years typically have this form of paracoccidioidomycosis, but older adults, especially patients who are immunosuppressed, also can manifest this type of rapidly progressive disease. In patients with advanced HIV infection, rapid progression occurs with multiple cutaneous lesions, lymphadenopathy, hepatosplenomegaly, and hypoxemic pulmonary involvement.

Chronic (Adult) Paracoccidioidomycosis

Chronic paracoccidioidomycosis, which is slowly progressive over many years, is the form seen in more than 90% of patients. Pulmonary involvement is prominent and clinically mimics tuberculosis (Chapter 299) and other chronic fungal pneumonias.[32] Radiographically, nodular, interstitial, or cavitary lesions are seen, usually in the middle and lower lung fields. Many patients also have ulcerative or nodular mucous membrane lesions, primarily in the anterior nares, the oral cavity, and the larynx; these lesions are slowly destructive and can lead to dysphonia and stenosis of the airway. Cutaneous lesions, particularly on the face, are also common and may be papular, nodular, ulcerative, or plaquelike. The mucocutaneous lesions must be differentiated from mucocutaneous leishmaniasis and squamous cell carcinoma. Adrenal involvement has been reported in more than 90% of fatal cases at autopsy, but adrenal insufficiency (Chapter 208) is clinically noted in only about half of cases.

DIAGNOSIS

The definitive diagnosis of paracoccidioidomycosis is established by growth of *Paracoccidioides* in culture. The organism may require as long as 4 weeks to grow. For seriously ill patients, direct examination of body fluids, sputum, or purulent material treated with potassium hydroxide or calcofluor fluorescent stain or histopathologic examination of tissue biopsy samples can provide a presumptive diagnosis. The characteristic appearance of *Paracoccidioides* consists of thick-walled yeast cells that have multiple small, circumferentially attached, narrow-based budding daughter yeast cells—a distinctive morphologic picture likened to a ship's steering wheel. Polymerase chain reaction testing may be useful in tissue samples.[33]

A variety of immunodiffusion assays, enzyme immunoassays, and complement fixation assays are available in endemic areas, but sensitivity and specificity vary greatly. The immunodiffusion assay appears to be most useful.

TREATMENT

The drug of choice for the treatment of paracoccidioidomycosis is itraconazole (200 mg/day for 6 to 9 months for mild disease and for 12 to 18 months for moderate disease).[34] Voriconazole is as effective as itraconazole when used under expert guidance, and a few studies report the successful use of posaconazole and isavuconazole. Fluconazole is less effective and should not be used. Sulfonamides can be used to treat paracoccidioidomycosis inexpensively, but relapse rates are higher than with the azoles. Amphotericin B is effective but rarely used, except under expert guidance in immunosuppressed patients who have life-threatening disseminated disease. Most patients with advanced HIV have been treated with amphotericin B as initial therapy, followed by lifelong suppressive therapy with either itraconazole or trimethoprim-sulfamethoxazole under expert guidance.

PROGNOSIS

Patients with paracoccidioidomycosis have an excellent response to antifungal therapy. Patients who have extensive pulmonary involvement at the time of diagnosis are at high risk for progressive fibrosis despite antifungal therapy.

GENERAL REFERENCES

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309

CRYPTOCOCCOSIS

SHARON C-A CHEN

DEFINITION

Cryptococcosis occurs most often in persons who are immunosuppressed, especially individuals who are infected with human immunodeficiency virus (HIV; see Chapter 358). Meningoencephalitis is the most common clinical manifestation, but the lungs and other organs can be involved as well.[1]

The Pathogen

Cryptococcus neoformans and, much less often, *Cryptococcus gattii* are the predominant *Cryptococcus* species that cause infection in humans. In the environment, *Cryptococcus* species exist as yeasts that have minimal capsules and are easily aerosolized and inhaled. In human tissue, the yeasts are enveloped by a large polysaccharide capsule that is a major virulence factor. *C. neoformans* is found in the soil and grows well in avian droppings that have high nitrogen content.

EPIDEMIOLOGY

Before the widespread availability of antiretroviral therapy, cryptococcosis occurred in 5 to 10% of patients with acquired immunodeficiency syndrome (AIDS; Chapter 357), especially in patients whose CD4 counts were less than 50 cells/μL. Cryptococcosis is less commonly seen now in developed countries but remains very common in Africa,[2] where it is estimated that the prevalence among HIV-infected patients is as high as 30%.

C. neoformans is seen worldwide. *C. gattii* is more restricted geographically,[3] but its distribution has been increasing beyond Australia and Southeast Asia, where its ecologic niche is the eucalyptus tree, to Brazil, the Pacific Northwest, and other areas of North America. Other cryptococcal species rarely cause human disease.[4]

In the non-AIDS population, cryptococcosis is a frequent opportunistic infection in patients who have received a solid organ transplant, have been treated with corticosteroids or other immunosuppressive therapies, or have underlying illnesses, such as malignancy, diabetes mellitus, renal failure, cirrhosis, or chronic pulmonary disease. Rare cases have been transmitted from infected solid organ donors to organ recipients.[5] For some patients, the only risk factor appears to be older age, and approximately 20% of non-HIV patients who are infected with *C. neoformans* have no known underlying illness. By comparison, about 40 of cases of *C. gattii* are in apparently normal hosts.[6]

PATHOBIOLOGY

The organism is inhaled from the environment and initially causes pulmonary infection. The primary host defense at this stage is complement-dependent phagocytosis and killing by macrophages and neutrophils. Natural killer cells also have the ability to kill the organism. Ultimately, however, T-cell immunity is the most important host determinant in limiting the replication of *C. neoformans*. In most normal hosts, the infection remains localized to the lungs and does not cause symptomatic infection, but a few organisms likely exist as walled-off, subpleural granulomas in many individuals who have had pulmonary infection.

If the host becomes immunosuppressed, the organism can then reactivate and disseminate to other sites. *C. neoformans* is clearly neurotropic, and the primary disease manifestation is meningoencephalitis. However, dissemination to many organs is likely, especially in patients whose T-cell immunity is deficient.

Virulence factors for *C. neoformans* include the capsule, which requires opsonization for efficient phagocytosis, and the production of melanin, which enables the organism to resist intracellular killing. Both of these factors may help explain the virulence of the organism once it has reached the central nervous system (CNS). Antibody and complement levels are low in the brain, so phagocytosis of the organism is minimal. Brain tissue provides high concentrations of substrates, such as catecholamines, for the organism's phenol oxidase enzyme systems that produce melanin, thereby aiding its survival.

CLINICAL MANIFESTATIONS

Central Nervous System Infection

The most common manifestation of cryptococcosis is CNS infection, which typically is a subacute to chronic meningoencephalitis. Patients usually have

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CLINICAL MANIFESTATIONS

Acute-Subacute (Juvenile) Paracoccidioidomycosis

The acute-subacute form of paracoccidioidomycosis, which occurs in less than 10% of patients, is a disease of the reticuloendothelial system with widespread dissemination to the liver, spleen, lymph nodes, and bone marrow. Patients younger than age 30 years typically have this form of paracoccidioidomycosis, but older adults, especially patients who are immunosuppressed, also can manifest this type of rapidly progressive disease. In patients with advanced HIV infection, rapid progression occurs with multiple cutaneous lesions, lymphadenopathy, hepatosplenomegaly, and hypoxemic pulmonary involvement.

Chronic (Adult) Paracoccidioidomycosis

Chronic paracoccidioidomycosis, which is slowly progressive over many years, is the form seen in more than 90% of patients. Pulmonary involvement is prominent and clinically mimics tuberculosis (Chapter 299) and other chronic fungal pneumonias.[32] Radiographically, nodular, interstitial, or cavitary lesions are seen, usually in the middle and lower lung fields. Many patients also have ulcerative or nodular mucous membrane lesions, primarily in the anterior nares, the oral cavity, and the larynx; these lesions are slowly destructive and can lead to dysphonia and stenosis of the airway. Cutaneous lesions, particularly on the face, are also common and may be papular, nodular, ulcerative, or plaquelike. The mucocutaneous lesions must be differentiated from mucocutaneous leishmaniasis and squamous cell carcinoma. Adrenal involvement has been reported in more than 90% of fatal cases at autopsy, but adrenal insufficiency (Chapter 208) is clinically noted in only about half of cases.

DIAGNOSIS

The definitive diagnosis of paracoccidioidomycosis is established by growth of *Paracoccidioides* in culture. The organism may require as long as 4 weeks to grow. For seriously ill patients, direct examination of body fluids, sputum, or purulent material treated with potassium hydroxide or calcofluor fluorescent stain or histopathologic examination of tissue biopsy samples can provide a presumptive diagnosis. The characteristic appearance of *Paracoccidioides* consists of thick-walled yeast cells that have multiple small, circumferentially attached, narrow-based budding daughter yeast cells—a distinctive morphologic picture likened to a ship's steering wheel. Polymerase chain reaction testing may be useful in tissue samples.[33]

A variety of immunodiffusion assays, enzyme immunoassays, and complement fixation assays are available in endemic areas, but sensitivity and specificity vary greatly. The immunodiffusion assay appears to be most useful.

TREATMENT

The drug of choice for the treatment of paracoccidioidomycosis is itraconazole (200 mg/day for 6 to 9 months for mild disease and for 12 to 18 months for moderate disease).[34] Voriconazole is as effective as itraconazole when used under expert guidance, and a few studies report the successful use of posaconazole and isavuconazole. Fluconazole is less effective and should not be used. Sulfonamides can be used to treat paracoccidioidomycosis inexpensively, but relapse rates are higher than with the azoles. Amphotericin B is effective but rarely used, except under expert guidance in immunosuppressed patients who have life-threatening disseminated disease. Most patients with advanced HIV have been treated with amphotericin B as initial therapy, followed by lifelong suppressive therapy with either itraconazole or trimethoprim-sulfamethoxazole under expert guidance.

PROGNOSIS

Patients with paracoccidioidomycosis have an excellent response to antifungal therapy. Patients who have extensive pulmonary involvement at the time of diagnosis are at high risk for progressive fibrosis despite antifungal therapy.

GENERAL REFERENCES

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309

CRYPTOCOCCOSIS

SHARON C-A CHEN

DEFINITION

Cryptococcosis occurs most often in persons who are immunosuppressed, especially individuals who are infected with human immunodeficiency virus (HIV; see Chapter 358). Meningoencephalitis is the most common clinical manifestation, but the lungs and other organs can be involved as well.[1]

The Pathogen

Cryptococcus neoformans and, much less often, *Cryptococcus gattii* are the predominant *Cryptococcus* species that cause infection in humans. In the environment, *Cryptococcus* species exist as yeasts that have minimal capsules and are easily aerosolized and inhaled. In human tissue, the yeasts are enveloped by a large polysaccharide capsule that is a major virulence factor. *C. neoformans* is found in the soil and grows well in avian droppings that have high nitrogen content.

EPIDEMIOLOGY

Before the widespread availability of antiretroviral therapy, cryptococcosis occurred in 5 to 10% of patients with acquired immunodeficiency syndrome (AIDS; Chapter 357), especially in patients whose CD4 counts were less than 50 cells/μL. Cryptococcosis is less commonly seen now in developed countries but remains very common in Africa,[2] where it is estimated that the prevalence among HIV-infected patients is as high as 30%.

C. neoformans is seen worldwide. *C. gattii* is more restricted geographically,[3] but its distribution has been increasing beyond Australia and Southeast Asia, where its ecologic niche is the eucalyptus tree, to Brazil, the Pacific Northwest, and other areas of North America. Other cryptococcal species rarely cause human disease.[4]

In the non-AIDS population, cryptococcosis is a frequent opportunistic infection in patients who have received a solid organ transplant, have been treated with corticosteroids or other immunosuppressive therapies, or have underlying illnesses, such as malignancy, diabetes mellitus, renal failure, cirrhosis, or chronic pulmonary disease. Rare cases have been transmitted from infected solid organ donors to organ recipients.[5] For some patients, the only risk factor appears to be older age, and approximately 20% of non-HIV patients who are infected with *C. neoformans* have no known underlying illness. By comparison, about 40 of cases of *C. gattii* are in apparently normal hosts.[6]

PATHOBIOLOGY

The organism is inhaled from the environment and initially causes pulmonary infection. The primary host defense at this stage is complement-dependent phagocytosis and killing by macrophages and neutrophils. Natural killer cells also have the ability to kill the organism. Ultimately, however, T-cell immunity is the most important host determinant in limiting the replication of *C. neoformans*. In most normal hosts, the infection remains localized to the lungs and does not cause symptomatic infection, but a few organisms likely exist as walled-off, subpleural granulomas in many individuals who have had pulmonary infection.

If the host becomes immunosuppressed, the organism can then reactivate and disseminate to other sites. *C. neoformans* is clearly neurotropic, and the primary disease manifestation is meningoencephalitis. However, dissemination to many organs is likely, especially in patients whose T-cell immunity is deficient.

Virulence factors for *C. neoformans* include the capsule, which requires opsonization for efficient phagocytosis, and the production of melanin, which enables the organism to resist intracellular killing. Both of these factors may help explain the virulence of the organism once it has reached the central nervous system (CNS). Antibody and complement levels are low in the brain, so phagocytosis of the organism is minimal. Brain tissue provides high concentrations of substrates, such as catecholamines, for the organism's phenol oxidase enzyme systems that produce melanin, thereby aiding its survival.

CLINICAL MANIFESTATIONS

Central Nervous System Infection

The most common manifestation of cryptococcosis is CNS infection, which typically is a subacute to chronic meningoencephalitis. Patients usually have

ABSTRACT

Cryptococcosis is an opportunistic yeast infection that occurs mostly in patients who are immunosuppressed, especially individuals who have advanced HIV infection (AIDS). The two major species are *C. neoformans* and *C. gattii*. The latter is relatively restricted geographically, is less common, and occurs more often in immunocompetent individuals. Meningoencephalitis is the major manifestation of infection with *C. neoformans*. The portal of entry is the lungs, but pulmonary infection is often asymptomatic, so the patient presents for medical attention only after the organism has spread through the blood to the central nervous system. Less often, patients have isolated pulmonary infection. In patients with severe immunosuppression, the organism can disseminate to infect almost every organ system and often results in death. The cryptococcal antigen test is a sensitive and specific point-of-care test that can quickly identify patients with the infection. Treatment of meningitis and disseminated infection is with amphotericin B and flucytosine for 2 weeks, followed by fluconazole consolidation therapy for an additional 8 weeks and then suppressive therapy with fluconazole. The length of suppressive therapy depends on the patient's immunocompetence. Isolated pulmonary cryptococcosis is treated with oral fluconazole unless the patient is severely ill, in which case the initial therapy should be amphotericin B plus flucytosine.

KEYWORDS

cryptococcosis
Cryptococcus neoformans
amphotericin B
fluconazole
cryptococcal antigen
increased intracranial pressure
HIV

increasingly severe headaches[7] over a period of several weeks, although some patients present over several days. Other symptoms and signs include nuchal rigidity, lethargy, personality changes, confusion, visual abnormalities (photophobia, diplopia, decreased visual acuity, papilledema, extraocular nerve palsies), nausea, and vomiting.[8] Less commonly, hearing loss, ataxia, and seizures occur. Fever is present in only approximately 50% of patients. Elderly persons with cryptococcal meningitis may present with cognitive impairment without other neurologic findings. AIDS patients often have subtle CNS symptoms but usually have fever and other constitutional symptoms, as well as rapidly developing signs of systemic dissemination.

Pulmonary Infection

In non–HIV-infected patients, the most common underlying risk factor for pulmonary cryptococcal infection[9] is chronic obstructive pulmonary disease (Chapter 76), followed by corticosteroid use and receipt of a solid organ transplant. *C. neoformans* may merely be an airway colonizer in some patients; in others, symptomatic infection, manifested by fever, cough, and dyspnea, requires treatment with an antifungal agent. The typical lesion noted with pulmonary cryptococcosis is a pleural-based nodule. However, patchy pneumonitis, multiple nodular lesions, cavitary lesions, mass-like lesions, and diffuse pulmonary infiltrates all have been noted with pulmonary cryptococcosis. Patients with advanced HIV infection are likely to have diffuse infiltrates that can progress rapidly to acute respiratory insufficiency (Chapter 90).

Involvement of Other Organs

C. neoformans can infect most organs during the course of disseminated infection, especially in AIDS patients (Chapter 358). Skin lesions are a prominent clue to dissemination, although isolated cutaneous cryptococcosis can occur in organ transplant recipients as well as in immunocompetent hosts. Papules that resemble molluscum contagiosum (Chapter 406) or an acneiform rash, nodules, ulcers, plaques, draining sinuses, and cellulitis all have been reported. Focal involvement can occur in the prostate and other organs of the genitourinary tract, in osteoarticular structures, in the breast, and in the eye, larynx, and other head and neck structures. The prostate, in particular, has been noted as a sanctuary from which persisting organisms can later disseminate.

DIAGNOSIS

The latex agglutination assay for cryptococcal polysaccharide antigen (CRAG) is a highly sensitive and specific diagnostic test. CRAG is positive in cerebrospinal fluid (CSF) in almost 100%[10] and in serum in about 75% of patients who have meningitis.[11] In AIDS patients, serum CRAG is almost always positive and is an excellent screening tool.[12] In these patients, titers in both CSF and serum are exceptionally high because of the enormous burden of organisms. In non-AIDS patients who have pulmonary cryptococcosis, the CRAG assay is positive in only 25 to 50% of cases. False-positive results with the CRAG assay are uncommon but have been reported in patients with *Trichosporon asahii* infections because of cross-reacting antigens shared by both fungi.

A point-of-care option is lateral flow analysis to detect cryptococcal polysaccharide antigen on a dipstick assay that can be performed in serum or CSF. This technique is as sensitive and specific as the classic CRAG test, including in isolated pulmonary infection.

The diagnosis of cryptococcosis is established when the yeast is grown in culture. Appropriate specimens for culture include CSF, blood, sputum, material from skin lesions, and other body fluids or tissues that appear to be infected. The organism grows in several days on most standard agar media. Most automated blood culture systems allow rapid growth of *C. neoformans* as well as *C. gattii*. Visualization of the capsule and performance of a few simple tests differentiate cryptococci from other yeasts. Tissue biopsy shows the 5- to 10-μm yeast surrounded by the capsule. Definitive diagnosis of cryptococcosis can be made by mucicarmine staining, which selectively stains the polysaccharide capsule a deep rose color. In CSF or other body fluids, an India ink preparation is useful in that it allows visualization of the budding yeast cells surrounded by the large capsule, but a negative test does not exclude a diagnosis of cryptococcosis (approximately 50% sensitivity in cryptococcal meningoencephalitis).

Lumbar Puncture

All immunosuppressed patients who have pulmonary cryptococcosis and all patients with any CNS symptoms should undergo lumbar puncture to be certain that meningitis is not present. Whether normal hosts with isolated pulmonary cryptococcosis and with negative serum antigen tests require lumbar puncture remains controversial.

The opening pressure on lumbar puncture may be elevated. The CSF of patients with cryptococcal meningitis typically has an increased number of white blood cells (but rarely >500/μL), a predominance of lymphocytes (although neutrophils are sometimes prominent early in the course), an elevated protein level, and a decreased glucose level. AIDS patients most often have normal or only mildly abnormal findings as a result of their markedly defective immune response. Every AIDS patient with a headache must have a CRAG or lateral flow analysis test and culture performed on their CSF, regardless of whether their CSF cell count, protein level, or glucose level is normal. Especially in AIDS patients, extremely high opening CSF pressure (>350 mm H_2O) has been associated with poor outcomes and must be aggressively lowered.

Imaging

All patients with cryptococcal meningitis should undergo computed tomography or magnetic resonance imaging of the brain to look for mass lesions and to assess ventricular size. Whether normal hosts with isolated pulmonary cryptococcosis require cerebral imaging should be considered in the context of the individual patient. Obstructive hydrocephalus is uncommon, and any increase in intracranial pressure is usually associated with normal-sized ventricles and is due to blockage at the arachnoid villi or increased brain edema (or both), perhaps related to the osmotic effect of the polysaccharide capsule.

TREATMENT

The treatment of cryptococcal infection requires appropriate antifungal therapy but also careful attention to local complications.[13]

Central Nervous System Infection

Antifungal Treatment

In the AIDS population, current recommendations are to give induction therapy with intravenous amphotericin B deoxycholate, 0.7 to 1 mg/kg daily, combined with oral flucytosine, 100 mg/kg daily given in four divided doses for at least 2 weeks, followed by consolidation therapy with oral fluconazole, 400 mg daily for a minimum of 8 weeks, and then suppressive therapy with fluconazole, 200 mg daily for 6 to 12 months. Lipid formulations of amphotericin B are increasingly used because they are less nephrotoxic, although they are often not available in developing countries. For example, single-dose liposomal amphotericin B (10 mg/kg) plus 14 days of flucytosine (100 mg/kg/day) and fluconazole (1200 mg/day) for 10 days is as good as a longer course of amphotericin.[A1] Induction therapy with amphotericin B (1 mg/kg per day for 4 weeks) plus flucytosine (100 mg/kg per day for 2 weeks) is also associated with improved survival among HIV-positive patients with cryptococcal meningitis compared with either amphotericin B alone or amphotericin B plus fluconazole (400 mg twice daily for 2 weeks).[A2] Unlike bacterial meningitis, adjunctive dexamethasone is not beneficial and appears to be detrimental in HIV-infected patients.

In non-AIDS patients, the course of treatment can be shorter. Antifungal therapy with a combination of amphotericin B and flucytosine for 6 weeks is preferred over amphotericin B alone for 10 weeks. High-dose fluconazole (800 mg/day) plus flucytosine may be another alternative.[14]

In HIV-positive patients, shorter regimens and regimens using amphotericin B with fluconazole or flucytosine with fluconazole[A3] are less effective but reasonable alternatives when the preferred regimen of amphotericin B plus flucytosine is not available. For example, 1 week of amphotericin B (1 mg per kilogram per day) plus flucytosine (100 mg per kilogram per day) and 2 weeks of fluconazole (1200 mg per day) plus flucytosine is effective as induction therapy[A4] and can be used to treat cryptococcal meningitis in resource-limited settings.

Case reports support the use of voriconazole and posaconazole (Chapter 307) for salvage treatment of cryptococcal meningitis. These are reasonable alternatives if no other azoles can be used. The echinocandins are not active against *C. neoformans* and should not be used.

Suppressive therapy with fluconazole is recommended for 6 to 12 months in transplant recipients. Suppressive therapy (e.g., fluconazole 200 mg daily) can be stopped in HIV patients who have undergone 12 months of antifungal therapy, who have $CD4^+$ counts higher than 100/μL, and whose HIV viral load is undetectable on antiretroviral therapy.

Increased Intracranial Pressure

Increased intracranial pressure, which is a cause of early death from cryptococcal meningitis, requires aggressive diagnosis and treatment in both AIDS and non-AIDS patients. Treatment to improve survival rates includes daily lumbar puncture or placement of a temporary lumbar drain or ventriculostomy until the opening pressure remains lower than 190 mm H_2O. Treatment with corticosteroids, acetazolamide, or mannitol has not proved efficacious.

Immune Reconstitution Syndrome

The development of immune reconstitution inflammatory syndrome (IRIS) can occur when patients with AIDS are receiving effective antiretroviral therapy that increases their CD4 count (Chapters 357 and 358).[15] Symptoms of meningitis reappear and are due to the inflammatory response, with an influx of CD4 lymphocytes and monocytes into the CSF and not to a relapse of disease. In HIV-positive patients who have cryptococcal meningitis and who have not previously received antiretroviral therapy, deferred antiretroviral therapy (5 weeks after diagnosis) is associated with significantly improved survival compared with earlier antiretroviral therapy (1 to 2 weeks after the diagnosis),[A5] especially among patients with a paucity of CSF white cells. IRIS can also occur in transplant recipients in whom immunosuppressive therapy is decreased rapidly. Generally, no specific therapy is needed for mild IRIS, but sometimes corticosteroids are needed under expert guidance if increased intracranial pressure occurs and/or if there is evidence of cerebral edema, even though they are otherwise unhelpful or even detrimental.

Pulmonary and Other Nonmeningeal Infections

Treatment of nonmeningeal cryptococcosis depends on the severity of the infection. Many patients with isolated pulmonary or other focal infections are not severely ill, and oral fluconazole, 400 mg daily for 6 to 12 months, is recommended. For patients who are severely ill, therapy is the same as noted earlier for CNS infection.

PREVENTION

Screening for cryptococcal antigen among HIV-positive patients with CD4 counts <200 cells/μL can detect presymptomatic diseases and guide early treatment.[16] In such patients, fluconazole, 200 mg three times per week, is safe and effective when used as primary prophylaxis, both before and during early antiretroviral treatment,[A6] but mortality may be as high as 25% even with early treatment.[17] By comparison, prophylactic treatment of asymptomatic HIV-positive individuals based on cryptococcal antigen screening has not been shown to be beneficial.[A7]

PROGNOSIS

The outcome for both AIDS and non-AIDS patients with cryptococcal meningitis has improved markedly in the developed world.[18] In one U.S. series of HIV-positive patients with cryptococcal infection (about 70% with meningitis), early mortality was only 17% but more than 50% of patients died by about 42 months.[19] In Africa, however, the mortality from cryptococcal meningitis in AIDS patients approaches 100% in some areas because of lack of access to specific therapy. Among patients with HIV, a predominant T_H1 cytokine profile in the CSF and blood at diagnosis appears to predict a better survival.

Even in non-AIDS patients in the United States, outcomes typically include substantial neurologic abnormalities.[20] Dementia, which usually occurs in older patients, hearing loss, and visual loss may not be reversed even though mycologic cure is achieved.

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310 CANDIDIASIS

PETER G. PAPPAS

DEFINITION

Candidiasis encompasses a wide variety of clinical syndromes caused by yeasts of the genus *Candida*. Of the species that cause infection in humans, *Candida albicans* is the most common; *Candida glabrata, Candida parapsilosis*, and *Candida tropicalis* are responsible for most of the remaining infections, but *Candida auris* has emerged as a major pathogen in some parts of the world.[1] Organisms such as *Candida krusei, Candida lusitaniae*, and *Candida guilliermondii* are less common causes of infection.

The Pathogen

Candida species are 2- to 6-μm yeastlike organisms that reproduce by budding. Most species, with the exception of *C. glabrata*, form pseudohyphae (elongated buds that remain attached to the mother cell) and hyphae in tissues.

Candida species cause a wide spectrum of diseases ranging in severity from localized mucous membrane infection to life-threatening disseminated disease. The major determinant of the severity of infection is the host's immune response. Local infections are often related to overgrowth of *Candida* as a result of changes in the normal microbiota. Invasive infections that remain within an organ system, such as urinary tract infections, usually occur because of local anatomic abnormalities. In an immunosuppressed host, especially a patient with neutropenia, widespread visceral dissemination is common.

EPIDEMIOLOGY

C. albicans is the species most commonly found colonizing humans; *C. glabrata* is the second most common species, and *C. tropicalis, C. parapsilosis*, and others are found less often. *C. glabrata*, a species that is increasingly resistant to fluconazole, has become a prominent pathogen in many hospitals. In many parts of the world, *C. auris*, a previously uncommon multidrug-resistant *Candida* species, has caused outbreaks and created new challenges in understanding the epidemiology, treatment, and prevention of this organism.

Though uncommon, acquisition of *Candida* from environmental sources has been noted. The *Candida* species most often associated with transmission from contaminated fluids or devices, especially central intravenous catheters, is *C. parapsilosis*.

Candidiasis is the most common opportunistic fungal infection as a result of both the organisms' ubiquity and the increasing number of patients who have risk factors for infection with these organisms.[2] The classic immunosuppressed host at risk for serious *Candida* infections is a neutropenic patient who has a hematologic malignancy and who has received cytotoxic agents and corticosteroids. Candidiasis is increasingly being seen in patients who are in intensive care units (ICUs). Risk factors for the development of serious *Candida* infections in ICU patients include diabetes,[3] the use of broad-spectrum antimicrobial agents, indwelling central venous catheters, intravenous drug use (Chapter 365),[4] previous surgical procedures, renal failure, parenteral nutrition, pancreatitis, dialysis, and a high Acute Physiology and Chronic Health Evaluation (APACHE) score. Certain ICU populations, especially burn victims (Chapter 97), are at even higher risk for *Candida* infection than is the typical ICU patient.[5]

The primary manifestation of *Candida* infection in patients with HIV/AIDS (Chapter 358) is mucocutaneous infection, primarily oropharyngeal candidiasis. The development of mucosal *Candida* infection is related to deficient T-cell immunity as reflected by a low CD4 lymphocyte count. With current antiretroviral therapy, oropharyngeal and esophageal candidiasis are much less common.

PATHOBIOLOGY

The usual mode of infection with *Candida* is egress from its normal niche into the bloodstream or other tissues; the source is usually the gastrointestinal tract, but the skin and genitourinary tract are other sources. The primary host defense in response to this event is phagocytosis and killing by neutrophils, monocytes, and macrophages. C-C chemokine receptor 2 (CCR2)-expressing inflammatory monocytes and their tissue-resident derivatives play

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EPIDEMIOLOGY

C. albicans is the species most commonly found colonizing humans; *C. glabrata* is the second most common species, and *C. tropicalis, C. parapsilosis*, and others are found less often. *C. glabrata*, a species that is increasingly resistant to fluconazole, has become a prominent pathogen in many hospitals. In many parts of the world, *C. auris*, a previously uncommon multidrug-resistant *Candida* species, has caused outbreaks and created new challenges in understanding the epidemiology, treatment, and prevention of this organism.

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The usual mode of infection with *Candida* is egress from its normal niche into the bloodstream or other tissues; the source is usually the gastrointestinal tract, but the skin and genitourinary tract are other sources. The primary host defense in response to this event is phagocytosis and killing by neutrophils, monocytes, and macrophages. C-C chemokine receptor 2 (CCR2)-expressing inflammatory monocytes and their tissue-resident derivatives play

ABSTRACT

Candida species reside in the gastrointestinal and genitourinary tracts and on the skin of humans. The species that is most commonly encountered as a cause of infection is *Candida albicans*, but in some medical centers, *C. glabrata, C tropicalis, C. parapsilosis,* and *C auris* also are major pathogens. Infections caused by *Candida* species vary from benign localized mucous membrane infections to focal invasive infections to disseminated infections with a high mortality rate. Examples of mucous membrane infections are oropharyngeal candidiasis, esophagitis, and vulvovaginitis. These infections are generally treated with oral fluconazole. Focal invasive infections include urinary tract infections, osteoarticular infections, meningitis, and endophthalmitis. Urinary tract infections can be treated with fluconazole in most patients, but endophthalmitis, meningitis, and osteoarticular infections are more complicated, must be treated with longer courses of therapy, and for some patients will require initial treatment with another agent, such as amphotericin B. Candidemia and non–central nervous system invasive candidiasis should be treated initially with an echinocandin; transition to oral fluconazole after the patient has responded to initial intravenous therapy is reasonable if the *Candida* species causing the infection is susceptible.

KEYWORDS

Candida
candidemia
invasive candidiasis
mucocutaneous candidiasis
fluconazole
echinocandin

an essential antifungal role, particularly in the first 48 hours after *Candida* infection. Phagocytosis is enhanced in the presence of specific anti-*Candida* antibody and complement. Several different mechanisms are operative within neutrophils and macrophages that allow the killing of yeasts. Thus, patients who are leukopenic (Chapter 153), especially those with chemotherapy-induced disruption of the gut mucosa, are at great risk for invasion with *Candida* species. Once *Candida* gains access to the bloodstream, widespread hematogenous dissemination is the rule. Biopsy of involved organs shows multiple microabscesses composed of neutrophils (in a host who has these cells), budding yeasts, and often pseudohyphae or hyphae. Over time, the lesions show a mixed neutrophilic and granulomatous response.

T-cell immunity is an important host defense against infection with *Candida* at mucosal surfaces. In contrast to patients with neutropenia, patients with deficient T-cell immunity are at risk for persistent and recurrent mucocutaneous candidiasis, but invasive infection rarely develops.

CLINICAL MANIFESTATIONS

Mucocutaneous Candidiasis

Oropharyngeal Candidiasis

Local mucous membrane and cutaneous lesions are the most common forms of *Candida* infection.[6] Oropharyngeal candidiasis, or *thrush* (Chapter 393), can be due to either local factors or T-cell dysfunction. Local factors include the use of broad-spectrum antimicrobial agents, inhaled corticosteroids, xerostomia (Chapter 393), and radiation treatment of the head and neck. Denture stomatitis occurs frequently in persons who wear full upper dentures, especially individuals who do not remove their dentures at night.

Thrush secondary to T-cell dysfunction is most commonly seen in patients with HIV infection (Chapter 358) and is the most frequent opportunistic infection noted in patients with AIDS. The appearance of thrush in a previously healthy individual with no known risk factors should immediately raise suspicion of HIV infection.

Thrush manifests with white plaques on the buccal mucosa, palate, oropharynx, or tongue (Fig. 310-1). Scraping the lesions with a tongue depressor reveals an erythematous, nonulcerated mucosa under the plaques. Denture stomatitis almost always manifests as a painful erythematous palate without plaques. Angular cheilitis, or perlàche, which is the presence of painful cracks at the corners of the mouth, can occur with or without thrush.

Esophagitis

Esophagitis may accompany oropharyngeal candidiasis or may occur independently of lesions in the oropharynx (Chapter 124). The development of *Candida* esophagitis is almost always related to immune dysfunction and not simply to local factors.[7] *Candida* esophagitis occurs in patients with AIDS and low CD4 counts, patients with leukemia, and patients who are taking immunosuppressive agents. *Candida* esophagitis occurs rarely in otherwise normal hosts. The classic symptom of *Candida* esophagitis is odynophagia localized to a discrete substernal area. The differential diagnosis includes ulcerations due to herpes simplex or cytomegalovirus and, in patients with AIDS, idiopathic ulcers.

Vulvovaginitis

Candida vulvovaginitis is a common infection in women of childbearing age and is the most frequent mucocutaneous manifestation of *Candida* infection.

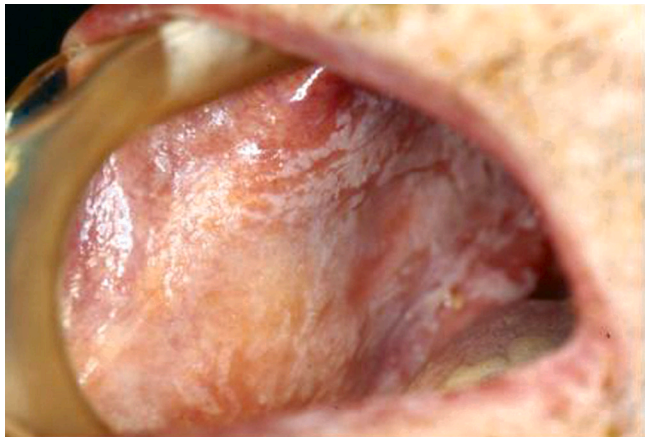

FIGURE 310-1. Thrush.

Risk factors include conditions associated with increased estrogen levels, such as the use of oral contraceptives and pregnancy, diabetes mellitus, therapy with corticosteroids or broad-spectrum antimicrobials, and HIV infection. Symptoms include vaginal discomfort, discharge, and vulvar pruritus.[8] The discharge is usually curdlike, but it can also be thin and watery. The labia are erythematous and swollen, and the vaginal walls show erythema and white plaques. Although most women have only a few episodes throughout their lives, a minority have frequent recurrences; in most of these patients, no discrete risk factor can be identified, and the cause is presumed to be local immune dysregulation.

Cutaneous Candidiasis

Candida infection of the skin (Chapter 405) occurs mostly in the intertriginous areas or under a large pannus or pendulous breasts. The lesions, which are erythematous, pruritic, and frequently pustular, have a distinct border and are almost always associated with smaller satellite lesions, which help distinguish candidiasis from tinea cruris or corporis. *Candida* onychomycosis results in thickened, opaque, and onycholytic nails (Chapter 409). *Candida* can also cause paronychia, especially in patients whose occupation involves frequent immersion of the hands in water.

Chronic Mucocutaneous Candidiasis

Chronic mucocutaneous candidiasis is an uncommon syndrome that usually begins in childhood and is characterized by recalcitrant and relapsing thrush, esophagitis, vaginitis, onychomycosis, and hyperkeratotic skin lesions on the face, scalp, and hands. Autosomal dominant chronic mucocutaneous candidiasis is associated with mutations in the CC domain of *STAT1*, thereby leading to defective T_H1 and T_H17 responses. Some patients have associated autoimmune endocrinopathies, including hypoparathyroidism, hypothyroidism, and hypoadrenalism (autoimmune polyendocrinopathy-candidiasis-ectodermal dystrophy [APECED]), which is caused by a loss-of-function mutation of the autoimmune regulator gene, *AIRE*; in these patients autoantibodies against interleukin-17 (IL-17) and IL-22 are found (Chapter 212).

Disseminated Infections

Candidemia

The most common manifestation of disseminated *Candida* infection is candidemia.[9] However, candidemia merely implies the presence of *Candida* in blood; it does not define the extent of visceral involvement. *Candida* obtained from a blood culture should never be considered a contaminant and should always prompt a search for the probable source and the extent of infection. Risk factors for candidemia include broad-spectrum antimicrobial therapy, central intravenous catheters, parenteral nutrition (Chapter 198), renal failure, pancreatitis (Chapter 130), any type of dialysis (Chapter 117), surgical procedures involving the gastrointestinal tract, neutropenia, and corticosteroid therapy (Chapter 28).[10] The attributable mortality from among all patients with candidemia approaches 40%. Mortality is higher in elderly patients and among patients with severe sepsis (Chapter 94) and poor control of the infectious source.

Although candidemia is the most obvious manifestation of serious infection with *Candida* species, septic shock (Chapter 94) can occur and be accompanied by invasion of multiple viscera even in the absence of positive blood cultures. The clinical picture of invasive candidiasis is indistinguishable from that of bacterial infection. The characteristic histologic picture consists of multiple microabscesses in many organs. The eyes, kidneys, liver, spleen, and brain are the most commonly involved sites, but virtually all organs can be involved. Clinical clues to the diagnosis of invasive candidiasis include the appearance of skin and retinal lesions. The nonpainful, nonpruritic skin lesions are papular to pustular and surrounded by a zone of erythema (Fig. 310-2). Classical eye lesions appear as distinctive white exudates in the retina (Fig. 310-3); with extension into the vitreous body, the retina becomes obscured.

Endocarditis

Candida endocarditis (Chapter 61), which is an uncommon and often fatal complication of candidemia, occurs most often on native valves among intravenous drug users and in patients who have prosthetic cardiac valves or indwelling intravascular devices.[11] Blood cultures are usually persistently positive, and echocardiography reveals large vegetations that can readily embolize to major vessels.

Chronic Disseminated (Hepatosplenic) Candidiasis

Disseminated hepatosplenic candidiasis almost always occurs in leukemic patients who have had an episode of neutropenia. After the neutrophil count

FIGURE 310-2. Skin lesions in invasive candidiasis.

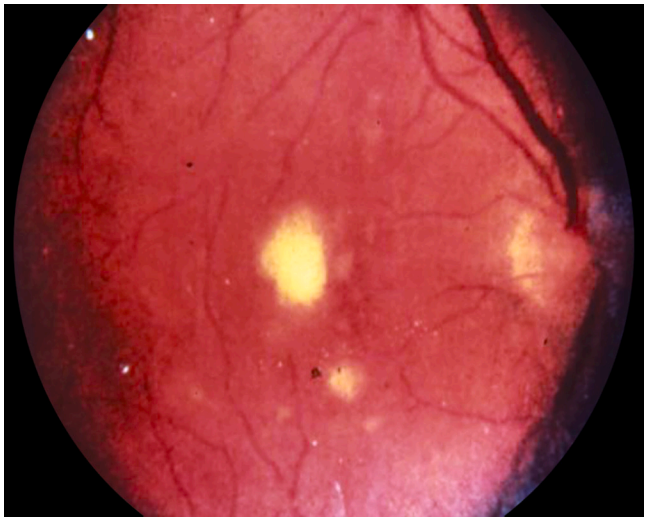

FIGURE 310-3. Retinal involvement.

returns to normal, fevers that are often quite high, right upper quadrant tenderness, and nausea develop. The alkaline phosphatase level is generally elevated, and distinctive punched-out lesions are seen in the liver, spleen, and sometimes the kidneys on computed tomography (Fig. 310-4). Biopsy of these lesions shows microabscesses that may contain budding yeasts.

Focal Invasive Infections

Focal invasive candidiasis infections result from local inoculation, contiguous spread, or hematogenous spread. Hematogenous spread, which often goes undetected, is probably the most common pathogenetic mechanism.

Urinary Tract Infections

Candiduria, which is a frequent finding in hospitalized patients, is related to factors such as diabetes mellitus, broad-spectrum antimicrobial treatment, indwelling urinary devices, and genitourinary tract structural abnormalities. Most patients with candiduria have only bladder colonization and not true infection. Urinary tract infection with *Candida* species can arise by two mechanisms. Patients with candidemia can develop multiple microabscesses secondary to hematogenous spread to the kidneys. Other patients, who have the risk factors noted earlier, can develop cystitis or ascending infection with pyelonephritis. Patients with cystitis or pyelonephritis have symptoms indistinguishable from those of bacterial infections (Chapter 263). A fungus ball composed of fungal hyphae can develop at any level of the collecting system and lead to obstruction, with subsequent infection.

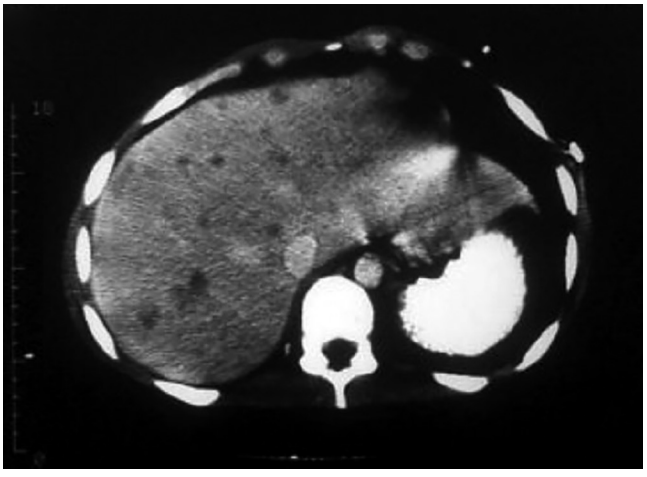

FIGURE 310-4. Computed tomography scan of a patient with chronic disseminated candidiasis (hepatosplenic candidiasis). Note the distinctive punched-out lesions in the liver.

Osteoarticular Infections

Osteoarticular infections arise secondary to hematogenous seeding or exogenous inoculation during intra-articular injection, a surgical procedure, or trauma. Vertebral osteomyelitis (Chapter 251) is the most common manifestation of osteoarticular candidiasis. The symptoms of back pain and fever may occur many weeks after an episode of fungemia.

Endophthalmitis

Exogenous endophthalmitis (Chapter 391) occurs secondary to trauma or ophthalmic surgery. Most often, the procedure involved is cataract extraction, with or without lens implantation, and the most common infecting species is *C. parapsilosis*. Primary infection occurs in the anterior chamber, but ultimately the posterior chamber is also involved. Endogenous *Candida* endophthalmitis, which results from hematogenous seeding of the choroid and retina, is one of the most serious complications of candidemia. Characteristic white lesions are visible in the retina. With progression of the infection, vitritis occurs, and the risk for loss of vision is quite high.

Peritonitis

Candida peritonitis can follow bowel surgery or perforation. Symptoms are the same as those noted in bacterial peritonitis (Chapter 128). Usually, this type of infection is polymicrobial, and abscess formation is common. In patients maintained on continuous ambulatory peritoneal dialysis (Chapter 117), *Candida* peritonitis generally develops as a late infection after previous episodes of bacterial peritonitis. A cloudy dialysate, abdominal pain, and fever are typically noted.

Meningitis

Acute *Candida* meningitis occurs as part of disseminated infection, especially in low-birthweight neonates. Chronic meningitis, an uncommon manifestation of candidiasis, resembles cryptococcal or tuberculous meningitis with regard to symptoms and cerebrospinal fluid findings. Foreign body–associated meningitis (e.g., an infected ventriculoperitoneal shunt, or Ommaya reservoir) clinically more closely resembles bacterial meningitis.

DIAGNOSIS

Mucocutaneous Candidiasis

The diagnosis of mucocutaneous candidiasis is often made clinically. Culture is rarely indicated. Confirmation can be sought by scraping the lesions and performing either a potassium hydroxide preparation or a Gram stain to look for budding yeasts (Chapter 403). If the lesions are recurrent or unresponsive to standard therapy, they should be cultured to establish whether a more resistant species, such as *C. glabrata* or *C. krusei*, is the causative agent. In the event of suspected esophagitis, endoscopy shows plaquelike lesions or

ulcerations (Fig. 124-13), and biopsy shows mucosal invasion with budding yeasts and pseudohyphae.

Invasive Candidiasis

The diagnosis of invasive candidiasis is more difficult. Blood cultures are not sensitive enough for clinicians to rely on them to establish the diagnosis of invasive candidiasis in all cases or to exclude candidiasis as a diagnostic possibility. In addition, 1 to 4 days are required for growth to occur; in a desperately ill patient, this delay is problematic. As a result, non–culture-based techniques are increasingly used to aid in the diagnosis of invasive candidiasis,[12] including β-D-glucan, which is a cell wall component of many fungi, including *Candida* species.[13] The β-D-glucan assay is not specific for *Candida* infections, but it has moderately good sensitivity in patients who are at high risk for invasive candidiasis. Polymerase chain reaction (PCR) testing is not standardized, but some studies show that it is more sensitive than β-D-glucan and blood cultures. A rapid technique testing whole blood samples to identify *Candida* species by use of magnetic biosensor technology is coming into broader use in North America and Europe.[14]

The tips of intravenous catheters that have been removed should be sent for culture. However, no studies have evaluated the number of yeasts that is indicative of infection, and many physicians accept the growth of any yeast as affirming infection that requires treatment. Many focal forms of candidiasis are indistinguishable from bacterial infection, and biopsy should be performed for histopathologic and culture studies.

In a seriously ill patient suspected of having candidiasis, the development of pustular skin lesions or typical retinal lesions can be helpful. Budding yeasts typical of *Candida* species should be sought by smearing material from a pustule on a slide and staining it with Gram stain or by performing a biopsy of a lesion and staining the tissue section with a silver stain. All patients who are candidemic or suspected of having disseminated *Candida* infection should undergo a dilated ophthalmologic examination by an experienced examiner or an ophthalmologist to look for typical retinal lesions.

Imaging studies are invaluable for certain forms of candidiasis, especially chronic disseminated candidiasis, and they can be of major help in defining the extent of infection in other types of *Candida* infection, such as osteoarticular and urinary tract infections and endocarditis.

TREATMENT

Mucocutaneous disease is treated much differently than disseminated, life-threatening infection. Because diagnostic tests are not sensitive, empirical therapy is indicated in some circumstances, and antifungal prophylaxis can decrease the risk for *Candida* infection in highest-risk patients (see later under Prevention).

Mucocutaneous Infections

Most mucocutaneous infections should initially be treated with local creams, solutions, troches, or suspensions. For thrush, clotrimazole troches (10 mg four or five times daily for 7 to 14 days) are preferred to nystatin suspension (commonly given as "swish and swallow" four times daily). Patients with AIDS may not respond to local therapy, especially when their CD4 counts are low; in this situation, oral fluconazole (100 to 200 mg daily for 7 to 14 days) is given.[A1] For vulvovaginal candidiasis, a variety of creams and vaginal tablets (miconazole, clotrimazole, and others) are effective, but many women prefer to take a single 150-mg fluconazole tablet orally.[15] Ibrexafungerp (300 mg twice daily for 1 day) is another alternative.[A2] Recurrent vaginitis, which is a more complicated therapeutic issue, often requires chronic suppressive therapy with fluconazole. Esophagitis should always be treated with a systemically absorbed agent; the usual treatment is fluconazole 200 mg/day for 14 days.[16]

In patients with advanced AIDS and low CD4 counts, who are often taking fluconazole to prevent recurrent candidiasis, fluconazole-refractory disease may develop. For these patients, increasing the dosage of fluconazole or switching to itraconazole suspension 200 mg daily, voriconazole 200 mg twice daily, or posaconazole suspension 400 mg or extended-release tablets 300 mg, each given once daily, should be effective. If oral tablets and solutions are no longer effective, intravenous amphotericin B (0.3 to 0.7 mg/kg daily), caspofungin (50 mg daily), anidulafungin (200 mg daily), or micafungin (100 mg daily) for 14 to 21 days are alternatives. Patients with the syndrome of chronic mucocutaneous candidiasis require lifelong suppressive therapy with oral azole agents (e.g., fluconazole 200 to 400 mg daily). More recent alternatives, ibrexafungerp (300 mg twice daily) and oteseconazole (600 mg day 1, 450 mg day 2, then 150 mg weekly for 2 to 12 weeks), may play a role in the treatment of drug-resistant mucosal infections (ibrexafungerp), as well as in the treatment and prevention of recurrent vulvovaginal candidiasis (oteseconazole).[17]

Candidemia and Invasive Candidiasis

Culture-Positive Patients

All patients with candidemia should be treated with an antifungal agent, including patients who have only one blood culture that yields *Candida*. The rationale for this recommendation is related to the high rate of metastatic foci in major organs associated with hematogenously disseminated candidiasis. Vascular catheters should be removed if at all feasible because removal has been shown to help clear *Candida* from blood more quickly.

Randomized controlled trials have documented the effectiveness of the following antifungal agents for the treatment of candidemia: fluconazole (400 or 800 mg/day); the three echinocandins (caspofungin 50 mg/day, anidulafungin 100 mg/day, and micafungin 100 mg/day)[A3,A4]; voriconazole (3 mg/kg twice daily); amphotericin B (0.7 mg/kg/day); and a lipid formulation of amphotericin B (3 to 5 mg/kg/day). Current guidelines recommend an echinocandin (caspofungin, micafungin, or anidulafungin; see earlier) as initial therapy in both neutropenic and non-neutropenic patients. Fluconazole is an acceptable alternative, but only for patients who are not severely ill and who are considered unlikely to have an azole-resistant *Candida* species. Isavuconazole is not as efficacious as caspofungin[A5] and is not approved for candidemia. Patients who have stabilized clinically and are found to have an isolate, such as *C. albicans*, that is likely to be susceptible to fluconazole can be transitioned to fluconazole from an echinocandin. Voriconazole can be used for step-down therapy if the organism is susceptible, but it offers little advantage over fluconazole. Amphotericin B formulations are used infrequently, except for patients who are neutropenic and for neonates.

Repeated blood cultures should be obtained to ascertain that the fungemia has resolved, and treatment should continue for at least 2 weeks after the date of the first negative blood culture.[18]

Empiric Treatment

Because diagnostic tests are not sensitive, seriously ill patients who could have invasive candidiasis may need to be treated before culture confirmation. This approach is used frequently in neutropenic patients, in whom empiric liposomal amphotericin B, caspofungin, and voriconazole have been shown in randomized clinical treatment trials to be effective. In the ICU setting, empiric antifungal treatment is often used, but empiric fluconazole therapy has failed to show a benefit, and the overall value of this approach is less certain.[19] Current guidelines recommend that empiric therapy be reserved for febrile, critically ill patients who have risk factors for invasive candidiasis. The preferred treatment is an echinocandin (caspofungin, micafungin, or anidulafungin). In non-neutropenic, nontransplanted, critically ill patients who have ICU-acquired sepsis, *Candida* colonization, and multiorgan failure while taking broad-spectrum antibiotics, empirical micafungin (100 mg daily for 14 days) can decrease the rate of new invasive fungal infection but does not increase fungal-free survival at day 28.[A6]

Endocarditis should be treated with a lipid formulation of amphotericin B (3 to 5 mg/kg/day for 6 weeks), with or without flucytosine (25 mg/kg four times daily). An echinocandin (e.g., caspofungin 70 mg, micafungin 150 mg, or anidulafungin 200 mg) given daily is an acceptable alternative. Infected valves should be replaced. In a few patients for whom valve replacement was not an option, lifelong suppression with fluconazole (400 to 800 mg daily) may be effective.

Chronic disseminated candidiasis generally requires months of therapy for cure. Most patients begin therapy with a lipid formulation of amphotericin B (3 to 5 mg/kg/day) or an echinocandin (e.g., caspofungin 50 mg, micafungin 100 mg, or caspofungin 50 mg daily) for 14 days and are then switched to fluconazole (400 to 800 mg) daily for several weeks to months and treated until the lesions disappear on computed tomographic scanning. This process of radiographic resolution may require several months.

Focal Invasive Infections

Treatment of focal infections depends on the organ system involved. Perhaps the simplest to treat are urinary tract infections. Most patients with candiduria are not infected but merely colonized; removing the selective pressure of antimicrobials and indwelling catheters eliminates candiduria in many of these patients. For those who have infection, oral fluconazole (200 mg/day orally for 2 weeks) is recommended. Bladder irrigation with amphotericin B (50 mg/L saline for 5 days) can be used for resistant *Candida* species (e.g., fluconazole-resistant *C. glabrata* or *C. krusei*), but this treatment eradicates only bladder colonization, requires that a catheter be placed in the bladder, and is associated with a high recurrence rate. None of the newer antifungal agents has a proven role in the treatment of urinary tract infections.

Osteoarticular infections require months of therapy; a lipid formulation of amphotericin B (3 to 5 mg/kg/day) or an echinocandin (e.g., caspofungin 50 mg, micafungin 100 mg, or anidulafungin 100 mg daily) can be given initially for at least 2 weeks, followed by long-term therapy with fluconazole (400 mg daily) for at least 6 months. Peritonitis associated with chronic ambulatory peritoneal dialysis can be treated with amphotericin B (3 to 5 mg/kg/day), fluconazole (400 mg daily), or a daily echinocandin (e.g., caspofungin 50 mg/day, micafungin 100 mg/day, or anidulafungin 100 mg), depending on the species of *Candida* causing infection, for 7 to 14 days. Intraperitoneal administration of amphotericin B can be extremely irritating and should generally be avoided. The dialysis catheter should be removed. Meningitis should be treated initially with a lipid formulation of amphotericin B (5 mg/kg/day) and flucytosine (25 mg/kg

four times daily) for at least 14 days; patients with more chronic disease can be switched to fluconazole (400 to 800 mg daily) for a longer duration of therapy, typically for several weeks.

Treatment of *Candida* eye infections varies with the extent of ocular involvement. Lesions discovered early at the stage of choroidal or retinal involvement can be treated effectively with intravenous amphotericin B (3 to 5 mg/kg), an echinocandin (e.g., caspofungin 50 mg daily, micafungin 100 mg daily, or anidulafungin 100 mg daily), fluconazole (400 mg daily), or voriconazole (200 mg twice daily) for at least 2 weeks after the first negative blood culture. Many experts prefer to use an agent, such as voriconazole or fluconazole, that achieves higher concentrations in the eye. Lesions extending into the vitreous require more aggressive therapy. The best results have been obtained with pars plana vitrectomy, injection of amphotericin B or voriconazole into the vitreous, and a systemic antifungal agent such as fluconazole (400 mg daily) or voriconazole (200 mg twice daily) for several weeks. Management must be individualized and performed in concert with an ophthalmologist experienced in the treatment of this infection. Treatment of endophthalmitis associated with an intraocular lens implant requires removal of the implant, vitrectomy and local amphotericin B injections, as well as therapy with fluconazole or voriconazole.

PREVENTION

For patients at the highest risk for invasive candidiasis and other fungal infections, prophylactic antifungal agents can prevent infection. The populations for whom prophylaxis is recommended include stem cell transplant recipients (Chapter 163), patients with acute leukemia who are undergoing induction chemotherapy (Chapter 168), high-risk liver transplant recipients (Chapter 140), and pancreas and small bowel transplant recipients. In these groups, a variety of different agents are effective. In the ICU population, prophylaxis with fluconazole (400 mg daily) can be effective, but it is recommended only in units that have a high rate of invasive candidiasis, and only in patients at the highest risk for infection. For example, using caspofungin (50 mg daily) as antifungal prophylaxis in adults who were in the ICU for at least 3 days, were ventilated, received antibiotics, had a central line, and had at least one additional risk factor was safe and reduced the incidence of invasive candidiasis in one randomized trial, but the benefit was not statistically significant.[A7] Restricting the use of prophylaxis to individuals at higher risk for candidiasis is essential to prevent the widespread use of azoles, with subsequent selection of resistant species. An experimental vaccine has shown promise in reducing recurrent symptomatic vulvovaginal candidiasis.[A8]

PROGNOSIS

The prognosis for patients with mucocutaneous infections is excellent. The prognosis for focal invasive infections depends on the organ involved and the patient's immune status. For example, whereas pyelonephritis may respond well to antifungal therapy, endocarditis and meningitis are more difficult to treat and have poor outcomes.

For invasive candidiasis, overall mortality is about 30 to 40%.[20] Significant predictors of mortality include increasing age, use of immunosuppressive therapy, and infection with *C. tropicalis*. Improved survival and clinical success are associated with early treatment with an effective antifungal agent, the use of an echinocandin, and the removal of central venous catheters. In candidemic patients who have septic shock, mortality rates as high as 98% are seen in patients in whom antifungal therapy and effective source control (i.e., draining abscesses and removing central venous catheters) is delayed beyond 24 hours after the onset of shock.

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For the General References and other additional features, please visit Elsevier eBooks+ at https://ebooks.health.elsevier.com.

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311 ASPERGILLOSIS

THOMAS J. WALSH AND THOMAS F. PATTERSON

DEFINITION

Aspergillosis is a disease caused by one or more of the species of the genus *Aspergillus*. Sporelike structures called *conidia* are aerosolized from the mold form of the organism growing in the environment. When conidia reach tissue, they germinate to form invasive filaments called *hyphae*.

The Pathogens

The most common species infecting humans are *Aspergillus fumigatus, Aspergillus flavus, Aspergillus terreus*, and *Aspergillus niger. Aspergillus* species are usually identified in culture by characteristic microscopic features of hyphae and the structures producing conidia. When some species are not readily identifiable, they may be reported by the clinical laboratory as "*Aspergillus* species" or "*Aspergillus* sp." *A. fumigatus* may be reported as "*A. fumigatus* species complex." *A. terreus* is resistant to amphotericin B. Aspergilli within tissue appear as dichotomously branched (Y-shaped) septate hyphae. *Scedosporium* and *Fusarium* species also may produce septate hyphae in tissue. The presence of septa and dichotomous branching differentiates *Aspergillus* species from the Mucorales, which are the causative organisms of mucormycosis (Chapter 312).

EPIDEMIOLOGY

Aspergillus species are ubiquitous organisms in the external environment, including soil, decaying matter, and air, in temperatures as high as 40 to 50° C. Aspergilli are easily isolated from houses, particularly from basements, crawl spaces, bedding, humidifiers, ventilation ducts, potted plants, dust, condiments (e.g., pepper), and marijuana samples. Aspergilli cause abortion in cattle and are important pathogens of marine organisms, insects, and domesticated and wild birds. Aflatoxin, which is one of the most potent carcinogens known, is produced by strains of *A. flavus* at ambient temperature on stored grain, spices, and nuts. Foodborne ingestion of preformed aflatoxin may cause hepatic necrosis or hepatocellular carcinoma (Chapter 181) in animals and humans.

Aspergillus species may be acquired from airborne conidia in inpatient and outpatient health care settings. Nosocomial aspergillosis is associated with building renovation, new construction, unfiltered air, contaminated ventilation systems, and fireproofing materials. Hospital water, which may become aerosolized during activities such as showering, also can be a potential source of aspergilli. As human pathogens, *Aspergillus* species may cause acute invasive disease, chronic infection, or allergic symptoms[1] (Table 311-1).

Acute invasive aspergillosis develops in immunocompromised patient populations, particularly patients with severe neutropenia (Chapter 153), hematologic malignancies,[2] hematopoietic stem cell transplantation (Chapter 163), severe aplastic anemia (Chapter 151), primary immunodeficiencies (Chapter 231), and solid organ transplantation, especially of heart, lung, and liver. Genetic deficiency of the soluble pattern-recognition receptor called PTX3 (long pentraxin 3) caused by homozygous haplotype (h2/h2) in the *PTX3* gene of donor cells leads to impaired neutrophilic antifungal capacity and an increased risk for invasive aspergillosis in recipients of stem cell transplants. Persistent neutropenia, corticosteroids, other immunosuppressive agents, graft-versus-host disease (GVHD), and cytomegalovirus disease are the most frequently observed clinical risk factors. Patients who have influenza

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four times daily) for at least 14 days; patients with more chronic disease can be switched to fluconazole (400 to 800 mg daily) for a longer duration of therapy, typically for several weeks.

Treatment of *Candida* eye infections varies with the extent of ocular involvement. Lesions discovered early at the stage of choroidal or retinal involvement can be treated effectively with intravenous amphotericin B (3 to 5 mg/kg), an echinocandin (e.g., caspofungin 50 mg daily, micafungin 100 mg daily, or anidulafungin 100 mg daily), fluconazole (400 mg daily), or voriconazole (200 mg twice daily) for at least 2 weeks after the first negative blood culture. Many experts prefer to use an agent, such as voriconazole or fluconazole, that achieves higher concentrations in the eye. Lesions extending into the vitreous require more aggressive therapy. The best results have been obtained with pars plana vitrectomy, injection of amphotericin B or voriconazole into the vitreous, and a systemic antifungal agent such as fluconazole (400 mg daily) or voriconazole (200 mg twice daily) for several weeks. Management must be individualized and performed in concert with an ophthalmologist experienced in the treatment of this infection. Treatment of endophthalmitis associated with an intraocular lens implant requires removal of the implant, vitrectomy and local amphotericin B injections, as well as therapy with fluconazole or voriconazole.

PREVENTION

For patients at the highest risk for invasive candidiasis and other fungal infections, prophylactic antifungal agents can prevent infection. The populations for whom prophylaxis is recommended include stem cell transplant recipients (Chapter 163), patients with acute leukemia who are undergoing induction chemotherapy (Chapter 168), high-risk liver transplant recipients (Chapter 140), and pancreas and small bowel transplant recipients. In these groups, a variety of different agents are effective. In the ICU population, prophylaxis with fluconazole (400 mg daily) can be effective, but it is recommended only in units that have a high rate of invasive candidiasis, and only in patients at the highest risk for infection. For example, using caspofungin (50 mg daily) as antifungal prophylaxis in adults who were in the ICU for at least 3 days, were ventilated, received antibiotics, had a central line, and had at least one additional risk factor was safe and reduced the incidence of invasive candidiasis in one randomized trial, but the benefit was not statistically significant.[A7] Restricting the use of prophylaxis to individuals at higher risk for candidiasis is essential to prevent the widespread use of azoles, with subsequent selection of resistant species. An experimental vaccine has shown promise in reducing recurrent symptomatic vulvovaginal candidiasis.[A8]

PROGNOSIS

The prognosis for patients with mucocutaneous infections is excellent. The prognosis for focal invasive infections depends on the organ involved and the patient's immune status. For example, whereas pyelonephritis may respond well to antifungal therapy, endocarditis and meningitis are more difficult to treat and have poor outcomes.

For invasive candidiasis, overall mortality is about 30 to 40%.[20] Significant predictors of mortality include increasing age, use of immunosuppressive therapy, and infection with *C. tropicalis*. Improved survival and clinical success are associated with early treatment with an effective antifungal agent, the use of an echinocandin, and the removal of central venous catheters. In candidemic patients who have septic shock, mortality rates as high as 98% are seen in patients in whom antifungal therapy and effective source control (i.e., draining abscesses and removing central venous catheters) is delayed beyond 24 hours after the onset of shock.

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311 ASPERGILLOSIS

THOMAS J. WALSH AND THOMAS F. PATTERSON

DEFINITION

Aspergillosis is a disease caused by one or more of the species of the genus *Aspergillus*. Sporelike structures called *conidia* are aerosolized from the mold form of the organism growing in the environment. When conidia reach tissue, they germinate to form invasive filaments called *hyphae*.

The Pathogens

The most common species infecting humans are *Aspergillus fumigatus, Aspergillus flavus, Aspergillus terreus*, and *Aspergillus niger. Aspergillus* species are usually identified in culture by characteristic microscopic features of hyphae and the structures producing conidia. When some species are not readily identifiable, they may be reported by the clinical laboratory as "*Aspergillus* species" or "*Aspergillus* sp." *A. fumigatus* may be reported as "*A. fumigatus* species complex." *A. terreus* is resistant to amphotericin B. Aspergilli within tissue appear as dichotomously branched (Y-shaped) septate hyphae. *Scedosporium* and *Fusarium* species also may produce septate hyphae in tissue. The presence of septa and dichotomous branching differentiates *Aspergillus* species from the Mucorales, which are the causative organisms of mucormycosis (Chapter 312).

EPIDEMIOLOGY

Aspergillus species are ubiquitous organisms in the external environment, including soil, decaying matter, and air, in temperatures as high as 40 to 50° C. Aspergilli are easily isolated from houses, particularly from basements, crawl spaces, bedding, humidifiers, ventilation ducts, potted plants, dust, condiments (e.g., pepper), and marijuana samples. Aspergilli cause abortion in cattle and are important pathogens of marine organisms, insects, and domesticated and wild birds. Aflatoxin, which is one of the most potent carcinogens known, is produced by strains of *A. flavus* at ambient temperature on stored grain, spices, and nuts. Foodborne ingestion of preformed aflatoxin may cause hepatic necrosis or hepatocellular carcinoma (Chapter 181) in animals and humans.

Aspergillus species may be acquired from airborne conidia in inpatient and outpatient health care settings. Nosocomial aspergillosis is associated with building renovation, new construction, unfiltered air, contaminated ventilation systems, and fireproofing materials. Hospital water, which may become aerosolized during activities such as showering, also can be a potential source of aspergilli. As human pathogens, *Aspergillus* species may cause acute invasive disease, chronic infection, or allergic symptoms[1] (Table 311-1).

Acute invasive aspergillosis develops in immunocompromised patient populations, particularly patients with severe neutropenia (Chapter 153), hematologic malignancies,[2] hematopoietic stem cell transplantation (Chapter 163), severe aplastic anemia (Chapter 151), primary immunodeficiencies (Chapter 231), and solid organ transplantation, especially of heart, lung, and liver. Genetic deficiency of the soluble pattern-recognition receptor called PTX3 (long pentraxin 3) caused by homozygous haplotype (h2/h2) in the *PTX3* gene of donor cells leads to impaired neutrophilic antifungal capacity and an increased risk for invasive aspergillosis in recipients of stem cell transplants. Persistent neutropenia, corticosteroids, other immunosuppressive agents, graft-versus-host disease (GVHD), and cytomegalovirus disease are the most frequently observed clinical risk factors. Patients who have influenza

ABSTRACT

Aspergillosis propagates by airborne conidia and invades tissue by hyphae. *Aspergillus fumigatus* is the most common species. *Aspergillus* species are found ubiquitously in nature and in buildings. *Aspergillus* species cause acute invasive diseases of the lungs and sinuses from which dissemination to other tissues may occur in immunocompromised patients. They also cause chronic pulmonary infections and allergic sinopulmonary diseases. Acute invasive pulmonary aspergillosis is diagnosed in immunocompromised patients by a combination of symptoms, diagnostic imaging features (nodules, halo signs, cavities), and microbiologic features, including bronchoalveolar lavage. Disseminated infection is best diagnosed by direct biopsy or needle aspirate. Chronic forms of aspergillosis include aspergilloma, chronic necrotizing aspergillosis, and chronic cavitary aspergillosis. Allergic bronchopulmonary aspergillosis may develop in patients with asthma and in those with cystic fibrosis. Treatment of invasive aspergillosis relies on a triad of antifungal therapy, reversal of immunosuppression, and, where appropriate, surgical resection of infected tissue. Voriconazole or isavuconazole is recommended as the preferred agents, but posaconazole and liposomal amphotericin B are considered acceptable alternatives of comparable efficacy.

KEYWORDS

Aspergillus
galactomannan
β-D-glucan
voriconazole
isavuconazole
posaconazole
amphotericin
invasive aspergillosis
allergic bronchopulmonary aspergillosis

TABLE 311-1 CLASSIFICATION OF ASPERGILLOSIS

CATEGORY	SPECIFIC FORMS OF ASPERGILLOSIS
Acute invasive aspergillosis	Invasive pulmonary aspergillosis Pulmonary infarction and necrosis Empyema Tracheobronchial infection Extrapulmonary aspergillosis Acute sinusitis Focal rhinitis Cerebral, cerebellar, or brain stem infarction Endophthalmitis Osteomyelitis Epidural abscess Cardiac aspergillosis Myocarditis Endocarditis Pericarditis Gastrointestinal aspergillosis Renal infection Cutaneous lesions (nodules, ulcers) Disseminated aspergillosis
Chronic aspergillosis	Aspergilloma Chronic necrotizing pulmonary aspergillosis Chronic cavitary pulmonary aspergillosis *Aspergillus* otomycosis
Allergic forms of aspergillosis	Allergic bronchopulmonary aspergillosis Extrinsic allergic alveolitis Allergic *Aspergillus* sinusitis

(Chapter 332) and immunosuppressed patients with coronavirus disease 2019 (COVID-19; Chapter 336) also are at risk for pulmonary aspergillosis.[3,4]

Invasive aspergillosis complicates the care of up to 13% of immunocompromised patients. Invasive aspergillosis is associated with increased hospital mortality and 30-day readmission rates, as well as excess duration of hospitalization and costs.

PATHOBIOLOGY

Conidia of *Aspergillus* spp. are the key infectious propagules that are acquired by humans from the inanimate environment via organisms that grow in decaying organic matter. These asexual, sporelike structures are 3-5 μ in diameter and have an outer surface covered by rodlets composed of hydrophobin proteins that confer hydrophobicity and adherence to mammalian cell surfaces. The hydrophobins and dihydroxynaphthalene melanins of conidia protect the fungus against host defenses. Inhaled conidia are mechanically cleared by the mucociliary escalator of the pseudostratified columnar respiratory epithelium. Conidia that reach the alveolar space adhere to pulmonary alveolar macrophages via lectin-like attachment sites, including dectin-1, DC-SIGN, and pentraxin 3. When (1→3)-β-D-glucans of swollen conidia are recognized by dectin-1, macrophages are activated to release cytokines and chemokines. Conidia are normally engulfed within phagosomes and destroyed via nonoxidative phagolysosomal mechanisms. Conidia that are not destroyed may germinate to form hyphae, which are then damaged by neutrophils.

These innate host defenses are abrogated in immunocompromised patients. Corticosteroids suppress phagocytosis and nonoxidative killing by macrophages. The recruitment of neutrophils is dependent on the release of chemokines by the lung epithelial cells and CARD 9 signaling. Defects in CARD9 signaling can lead to increased host susceptibility to *Aspergillus*. Defects in the genes encoding NADPH oxidase lead to chronic granulomatous disease, which strongly predisposes to invasive aspergillosis. Neutropenia and neutrophil dysfunction allow hyphae to invade the respiratory epithelium and vascular endothelium, thereby leading to thrombosis, infarction, and hemorrhage. Among the putative virulence factors of *A. fumigatus*, serine proteases, elastases, phospholipases, and gliotoxin further contribute to tissue injury, invasion, and dissemination.

This capacity to invade blood vessel walls (angioinvasion) results in hemorrhagic infarction. These processes lead to formation of a necrotic center surrounded by a ring of hemorrhage and edema, which correlates with a "halo sign" surrounding the nodular density. Galactomannan, which is a heteropolysaccharide of the *Aspergillus* cell wall, is a useful biomarker that is released into the circulation and alveolar spaces during invasive pulmonary aspergillosis. (1→3)-β-D-glucan is another *Aspergillus* cell wall polysaccharide that is detected in serum during invasive disease.

An aspergilloma consists of a fungal ball composed of matted hyphae and debris in a preformed cavity from previous pulmonary tuberculosis, histoplasmosis, or fibrocystic sarcoidosis. Chronic necrotizing pulmonary aspergillosis characteristically causes a slowly progressive inflammatory destruction of lung tissue superimposed on chronic lung disease. Chronic cavitary pulmonary aspergillosis is defined as the presence of multiple *Aspergillus*-related cavities, which may or may not contain an aspergilloma. Patients with chronic cavitary pulmonary aspergillosis may have genetically mediated deficits in innate host defenses.

Allergic bronchopulmonary aspergillosis results in a hypersensitivity response that develops in the chronic settings of asthma (Chapter 75) and cystic fibrosis (Chapter 77) with a type I hypersensitivity response that results in elevated IgE to *Aspergillus* antigens, mast cell degranulation, and bronchoconstriction. Type III hypersensitivity reactions in allergic bronchopulmonary aspergillosis result in elevated interleukin (IL)-4 and IL-5, the latter contributing to eosinophilia.

CLINICAL MANIFESTATIONS

Acute Invasive Aspergillosis

Invasive Pulmonary Aspergillosis

The classic clinical manifestations of invasive pulmonary aspergillosis in immunocompromised hosts are fever and focal pulmonary infiltrates, nodules, or wedge-shaped densities resembling infarcts.[5] Cough, pleuritic pain, and hemoptysis also may be present. Focal pulmonary infiltrates may progress to a cavity on recovery from neutropenia. Pulmonary infiltrates may also present as bronchopneumonia in an immunosuppressed patient. Concomitant pleural effusion may develop and represent *Aspergillus* empyema. Tracheobronchial aspergillosis in immunocompromised patients presents as ulcerative, pseudomembranous, or plaquelike large airway disease that may presage pulmonary parenchymal invasion. This invasive form has been seen in mechanically ventilated patients,[6,7] including patients with COVID-19 (Chapter 336).

Acute Sinusitis

Acute *Aspergillus* sinusitis may occur concomitantly or independently of invasive pulmonary aspergillosis. Although symptoms may include fever, localized pressure, and pain, they may be absent in severely immunocompromised patients. Eschar on the nasal septum and turbinates may be observed by speculum examination or endoscopy. Acute *Aspergillus* sinusitis of the ethmoid and sphenoid sinuses may progress to cavernous sinus thrombosis with symptoms referable to cranial nerves III, IV, $V_{1,2}$, and VI. *A. flavus* has a high propensity for causing acute sinus infection.

Extrapulmonary Aspergillosis

The tissue targets of extrapulmonary and disseminated aspergillosis most commonly include the CNS,[8] where abscesses and infarcts are characteristic. Patients with CNS aspergillosis present with focal paresis, cranial nerve deficits, and seizures. The glucose level in cerebrospinal fluid (CSF) is usually normal, and cultures of CSF are negative. Other extrapulmonary manifestations include endophthalmitis, myocardial infarction, gastrointestinal disease, renal infarction, cutaneous lesions, and Budd-Chiari syndrome. Esophageal ulcers and mesenteric thrombosis may produce gastrointestinal bleeding. Renal infection may present as flank pain and hematuria.

Aspergillus endocarditis usually begins as an isolated infection in intravenous drug users or after cardiac valvular surgery. *Aspergillus* endocarditis most commonly presents as major arterial emboli to brain, lung, kidney, and bone. Blood cultures, which are seldom positive, may be delayed in growth by as much as 14 to 21 days. *Aspergillus* pericarditis may arise from contiguous pulmonary lesions or through transmural infection from endocardial infection.

Locally invasive aspergillosis usually develops in immunocompromised patients as cutaneous ulcers, focal rhinitis, osteomyelitis, and septic arthritis. Cutaneous ulcers have been associated with use of contaminated adhesive tape and arm boards. Keratitis, endophthalmitis, and infection of burn wounds may develop from traumatic inoculation in otherwise immunocompetent patients.

Chronic Pulmonary Aspergillosis

Aspergilloma

An aspergilloma appears on chest radiograph as a fungus ball in a cavity (Fig. 311-1).[9] Symptomatic patients present with cough, hemoptysis, dyspnea, weight loss, fatigue, chest pain, or fever. Sputum culture is typically positive for *Aspergillus* species, particularly *A. niger*. Pleural aspergillosis may complicate surgical resection of aspergilloma or develop spontaneously as a bronchopleural fistula or concomitantly with tuberculosis.

As a stage in the repair process of infarcted lung tissue in neutropenic patients, one or more apparent "aspergillomas" may develop in consolidated lesions during recovery from neutropenia. These apparent aspergillomas do not develop in preexisting cavities and create an "air-crescent sign," or Monod sign, during their formation.

Chronic Necrotizing Pulmonary Aspergillosis

Chronic necrotizing pulmonary aspergillosis and chronic cavitary pulmonary aspergillosis occur in patients with underlying chronic lung disease and chronic immunosuppression. In chronic necrotizing disease, the clinical manifestations of worsening pulmonary function, cough, and dyspnea may be indistinguishable from concomitant primary chronic respiratory disease.

Chronic cavitary disease occurs with symptoms of cough, hemoptysis, and dyspnea. The progressive cavities of chronic cavitary pulmonary aspergillosis tend to coalesce with the loss of functional lung tissue.

Aspergillus otomycosis is a chronic infection that usually involves the external auditory canal with symptoms of pain, pruritus, hypoacusis, and otic discharge in patients who have impaired mucocutaneous immunity, such as patients with chronic eczema (Chapter 405), hypogammaglobulinemia (Chapter 231), diabetes mellitus (Chapter 210), or HIV infection (Chapter 358), as well as patients who are receiving corticosteroids. *Aspergillus* may involve the middle ear and extend into the mastoid sinus if the tympanic membrane has been perforated.

Allergic Forms of Aspergillosis

Allergic Bronchopulmonary Aspergillosis

Allergic bronchopulmonary aspergillosis[10] develops most frequently in patients with a history of chronic asthma (Chapter 75) or cystic fibrosis (Chapter 77). Occurring in genetically susceptible patients exposed to specific *Aspergillus* antigens, allergic bronchopulmonary aspergillosis is characterized by episodic airway obstruction, fever, eosinophilia, positive sputum cultures, mucous plugs containing hyphae, the presence of grossly visible brown flecks in sputum (hyphae), transient infiltrates and parallel "tramline" or ring markings on chest radiographs, proximal bronchiectasis, upper lobe contraction, and elevated levels of total immunoglobulins G and E (IgG and IgE). Eosinophilia may be present in blood, sputum, and lung tissue. Mucous plugs contribute to the development of pulmonary infiltrates, atelectasis, and peribronchial inflammation. The parallel or ring markings are caused by thickened ectatic bronchi, whereas the upper lobe changes are due to progressive apical fibrosis. Pulmonary infiltrates in allergic bronchopulmonary aspergillosis may be nonsegmental and transient in association with eosinophilia and asthma; alternatively, they may be segmental and associated with bronchial obstruction by mucous plugs, wherein asthma and eosinophilia may be absent.

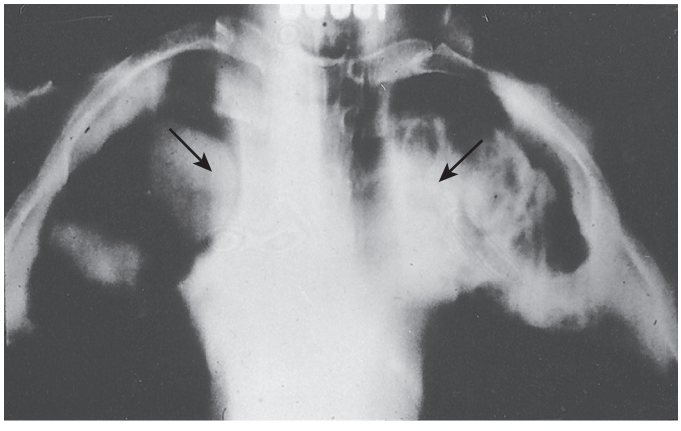

FIGURE 311-1. Tomogram of pulmonary aspergillomas (*arrows*).

Extrinsic Allergic Alveolitis

Extrinsic allergic alveolitis is an unusual allergic form of *Aspergillus* lung disease that is most frequently associated with *Aspergillus clavatus* in malt workers. A hypersensitivity pneumonitis with dyspnea and fever develops approximately 4 hours after exposure. Diffuse reticulonodular interstitial infiltrates may be present at the time of symptoms. Patients have IgG precipitins and cell-mediated immune reactions against *Aspergillus* antigens. Granulomas are present in lung tissue. In contrast to allergic bronchopulmonary aspergillosis, eosinophilia is not a feature of *Aspergillus* extrinsic allergic alveolitis.

Allergic *Aspergillus* Sinusitis

Allergic *Aspergillus* sinusitis is a noninvasive form of sinus disease that typically presents in patients with asthma, nasal polyps, sinus opacification, and eosinophilia. Sinus aspirate yields mucinous material containing eosinophils, Charcot-Leyden crystals (eosinophil-derived rhomboid crystals of galectin-10), and hyphal elements. Allergic *Aspergillus* sinusitis and allergic bronchopulmonary aspergillosis may coexist in some patients. Advanced forms of allergic *Aspergillus* sinusitis may present with proptosis and optic neuropathy that require prompt surgical intervention.

DIAGNOSIS

Invasive Aspergillosis

Diagnosis of invasive pulmonary aspergillosis and disseminated aspergillosis is difficult[11] because no clinical manifestations are pathognomonic. Nevertheless, characteristic computed tomographic (CT) scan features include nodules, halo signs, wedge-shaped infiltrates, and air-crescent signs during invasive pulmonary aspergillosis in immunocompromised patients (Fig. 311-2). For example, infarct-shaped consolidations and smooth bronchial wall thickening are more frequent in invasive pulmonary aspergillosis, whereas mass-shaped consolidations and centrilobular nodules (<10 mm, clustered) are more frequent in tuberculosis (Chapter 299). However, infections caused by *Fusarium* species, *Scedosporium* species, the Mucorales (Chapter 312), and *Pseudomonas aeruginosa* (Chapter 282) may be radiologically indistinguishable from invasive pulmonary aspergillosis.

Microbiologic confirmation is important to differentiate aspergillosis from tuberculosis and from other filamentous fungal infections. Specimens can be

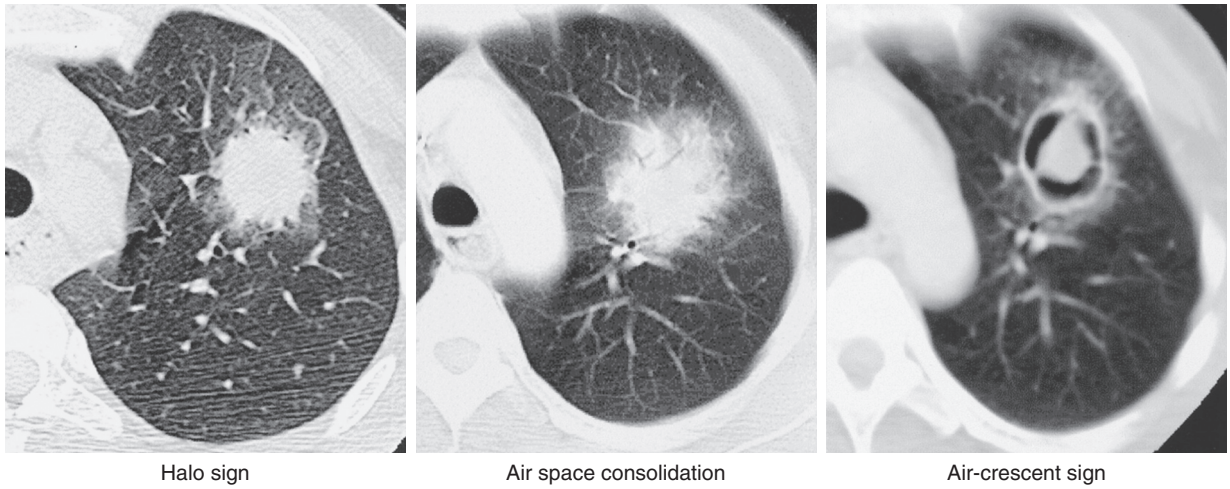

FIGURE 311-2. Evolution of radiography of invasive aspergillosis in an immunocompromised host. D = days after the lesion is first noted.

obtained from bronchoalveolar lavage, percutaneous needle aspiration, video-assisted thoracoscopic (VATS) biopsy, and, if necessary, open lung biopsy. Dichotomously branching septate hyphae may be seen by direct microscopy, or *Aspergillus* species may grow in culture. Both microscopy and culture are highly specific, so a positive finding carries a high probability for diagnosis of invasive aspergillosis, but neither is very sensitive for finding the organism.

Alternative options[12,13] include polymerase chain reaction (PCR)[14] testing, detection of galactomannan by enzyme immunoassay[15] in serum, or bronchoalveolar lavage. The combined use of diagnostic imaging, microscopy, culture, PCR, and cell wall biomarkers in patients with compatible clinical manifestations can hasten the diagnosis of invasive aspergillosis and guide the early initiation of therapy.[A1] Diagnostic criteria for invasive pulmonary aspergillosis include compatible clinical and radiologic features in a susceptible host as well as microbiologic evidence of *Aspergillus* (i.e., positive PCR, positive cultures, an elevated galactomannan level).

Diagnosis of locally invasive extrapulmonary aspergillosis causing mucocutaneous lesions, osteomyelitis, and septic arthritis is best accomplished with biopsy, direct microscopy, PCR, and culture. A diagnosis of *Aspergillus* keratitis is established by direct examination, culture, and, occasionally, PCR of corneal lesions by an ophthalmologist.

Allergic Forms of Aspergillosis

Bronchopulmonary Aspergillosis

Diagnosis of allergic bronchopulmonary aspergillosis is based on the presence of a combination of clinical, biologic, and radiologic criteria (Fig. 311-3). A biphasic skin test response may assist in the diagnosis. A scratch test with *Aspergillus* antigens produces an immediate wheal-and-flare reaction that is mediated by IgE and blocked by antihistamines but not by corticosteroids. An intracutaneous test with the antigens produces a later (6 to 8 hours) reaction that is mediated by IgG and complement and blocked by corticosteroids.

For patients who do not have cystic fibrosis, criteria for allergic bronchopulmonary aspergillosis include asthma, an immediate cutaneous reaction to *A. fumigatus* antigen, a total serum IgE concentration higher than 1000 ng/mL, elevated *A. fumigatus*–specific serum IgE levels, precipitating serum antibodies to *A. fumigatus*, central bronchiectasis, peripheral blood eosinophilia, and characteristic pulmonary infiltrates. The latter two features (eosinophilia and pulmonary infiltrates) are considered nonessential because they only may be present during an acute phase of allergic bronchopulmonary aspergillosis.

For patients with cystic fibrosis (Chapter 77), distinguishing between allergic bronchopulmonary aspergillosis and an episode of clinical deterioration with colonization by *Aspergillus* species is challenging. The current criteria are clinical deterioration (coughing, wheezing, increased sputum production, decreased exercise intolerance, and decrease in pulmonary function); immediate hypersensitivity to *A. fumigatus* (positive skin test or IgE response); total serum IgE concentration higher than 1000 ng/mL; precipitating antibodies to *A. fumigatus*; abnormal chest radiograph (central bronchiectasis); mucous plugs; or unexplained changes compared with previous chest radiographs).

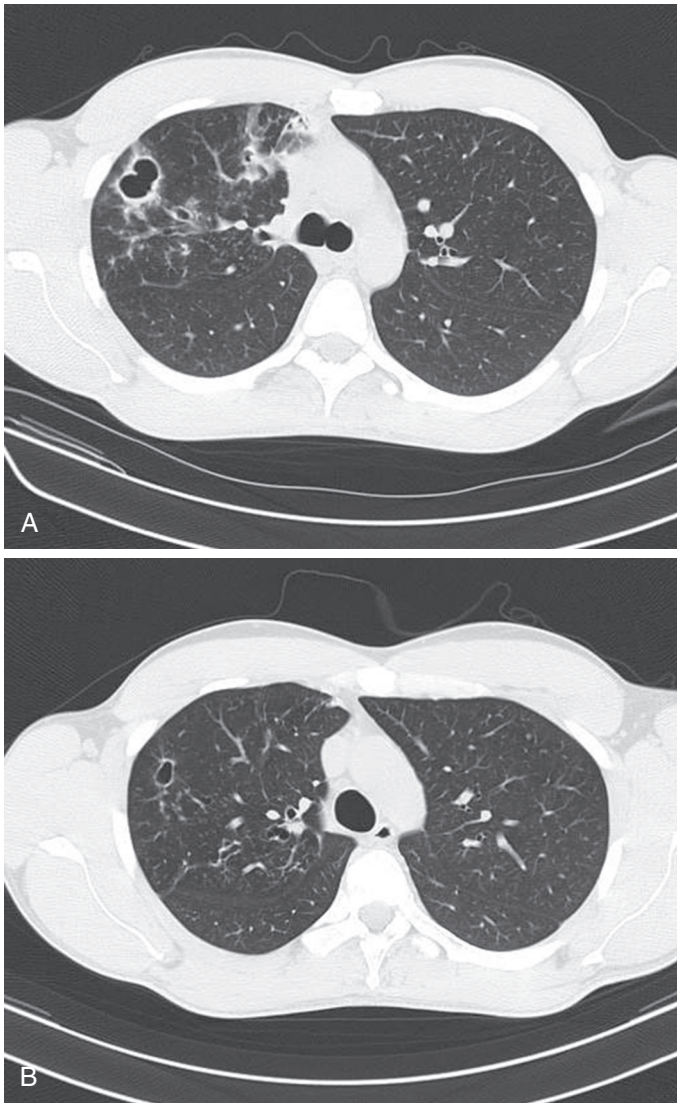

FIGURE 311-3. Allergic bronchopulmonary aspergillosis in a patient with a long history of asthma. A, A thin-slice computed tomographic image showing bronchiectasis with cystic changes in the right upper lobe. This patient had an underlying history of asthma and a markedly elevated immunoglobulin E level and other findings consistent with allergic bronchopulmonary aspergillosis. **B,** The same patient after treatment with systemic steroids; the cystic bronchiectasis has markedly improved. (Courtesy of Anne E. O'Donnell, MD.)

Other Allergic Forms

For extrinsic allergic alveolitis, an occupational history of exposure is critical to the diagnosis. A typical history of recurrent episodes developing within 24 hours after inhalation of conidial antigens in an agricultural environment, in conjunction with a negative scratch test, a positive intradermal test, and granulomas with immunoglobulins and complement in tissue, is diagnostically consistent with *Aspergillus* extrinsic allergic alveolitis. For allergic *Aspergillus* sinusitis, a sinus aspirate yielding mucinous material containing eosinophils, Charcot–Leyden crystals, and hyphal elements establishes the diagnosis.

TREATMENT

Invasive Aspergillosis

The foundation of treatment of invasive aspergillosis consists of three interventions: antifungal medical therapy (Table 311-2); reversal of immunosuppression; and, where appropriate, surgical resection of infected lesions.[16–18]

Antifungal Agents

Voriconazole or isavuconazole is recommended in most patients for the primary treatment of invasive aspergillosis, including pulmonary, disseminated, and extrapulmonary isolated infection. The recommendation for voriconazole is based on a randomized trial showing that voriconazole is superior to deoxycholate amphotericin B (D-AmB) as primary treatment for invasive aspergillosis, as well as extensive clinical experience with the drug. However, voriconazole should not be used in patients with substantially elevated hepatic aminotransferase levels, hepatic dysfunction, a prolonged QTc interval, or a history of intolerance to it. Such patients can be treated with isavuconazole, which is equally effective with fewer drug-related adverse events, more predictable pharmacokinetics, and possibly becoming the treatment of choice. For patients with invasive aspergillosis, posaconazole is an acceptable alternative that is noninferior to voriconazole for all-cause mortality and is less toxic.[A2] Unfortunately, recent emergence of resistance to triazole antifungals (voriconazole, isavuconazole, and posaconazole) may threaten the future utility of the anti-*Aspergillus* triazoles. Another option is liposomal amphotericin B (L-AmB) as primary therapy, based on a randomized trial that demonstrated comparable efficacy of approximately 70% using dosages of 3 mg/kg/day and 10 mg/kg/day of L-AmB in patients who had predominantly hematologic malignancies.

Second-line or salvage antifungal therapy is indicated in patients who are intolerant of or whose infection is unresponsive to primary therapy. Among the antifungal agents used in this setting are a lipid formulation of amphotericin B, posaconazole, or isavuconazole if not used as primary therapy, itraconazole, or an echinocandin (caspofungin is the only agent licensed for this indication). For patients who are already receiving voriconazole, a change of class to a lipid formulation and use of another azole are alternative possibilities. For invasive aspergillosis in patients who have hematologic malignancies and/or have undergone recent allogeneic stem cell transplantation, initial treatment with a combination of voriconazole and anidulafungin[A3] may be associated with reduced all-cause mortality at 6 weeks compared with voriconazole monotherapy. In patients with more extensive infection or risk factors for a poor outcome, combination therapy with voriconazole plus an echinocandin should be considered under the guidance of expert consultants.

TABLE 311-2 ANTIFUNGAL THERAPY OF INVASIVE ASPERGILLOSIS*

FIRST-LINE TREATMENT IN ADULTS†	
Drug of choice:	
Voriconazole	IV therapy: 6 mg/kg q12h for two doses, then 4 mg/kg q12h Oral therapy: 300 mg or 4 mg/kg bid
or	
Isavuconazole	IV or oral therapy: 372 mg (isavuconazonium prodrug) q8h for 6 doses, then 372 mg q24h
Alternate (see text for conditions):	
Liposomal amphotericin B	3-5 mg/kg IV daily
or	
Posaconazole	300 mg PO (delayed-release tablet) or IV q12h day 1, then 300 mg PO or IV daily
SECOND-LINE OR SALVAGE TREATMENT IN ADULTS†	
Amphotericin B lipid complex	5 mg/kg IV daily
or	
Caspofungin	70 mg IV daily for first dose, then 50 mg IV daily
or	
Micafungin	100 mg IV daily
or	
Itraconazole	400 mg PO (capsules) daily (in either one or two doses); or 2.5 mg/kg PO (solution) q12h

*Refer to package insert for dosage modification of antifungal agents in liver disease or renal impairment.

†Duration of antifungal therapy depends on therapeutic response of documented lesions, burden of disease, host immunocompetence, and type of aspergillosis (e.g., acute invasive vs. chronic vs. allergic). Guidelines of Infectious Diseases Society of America recommend at least 6 to 12 weeks for invasive pulmonary aspergillosis. Patients who are immunosuppressed continue treatment throughout the period of immunosuppression and until resolution of lesions. In patients previously diagnosed with invasive aspergillosis, antifungal therapy should be continued or reinitiated during subsequent periods of immunosuppression (e.g., chemotherapy, stem cell transplantation, graft-versus-host disease) to prevent recrudescence.

bid = twice daily; IV = intravenous; PO = orally.

See Patterson T, Thompson GR 3rd, Denning DW, et al. Executive summary: practice guidelines for the diagnosis and management of aspergillosis: 2016 update by the Infectious Diseases Society of America. *Clin Infect Dis*. 2016;63:433-442, for more details.

Antifungal therapy for invasive aspergillosis should be continued until lesions have resolved, cultures and biomarkers are negative, and reversible underlying predispositions have abated. Data also support monitoring serum galactomannan levels as a marker for therapeutic response.[19] Reinstating therapy in patients who have previously responded should be considered if immunosuppression is reinstituted or if neutropenia recurs.

Local infusion of antifungal agents, particularly intravitreal therapy of endophthalmitis, provides high concentrations to compartments that may not be reached by systemic therapy. Topical irrigation with voriconazole, amphotericin B, or if available, pimaricin (natamycin) is an important adjunct to the management of *Aspergillus* keratitis.

Reversal of Immunosuppression

Reversal of immunosuppression is a critical factor in the successful management of invasive aspergillosis. Recovery from neutropenia and decreasing the daily dosage or discontinuation of corticosteroids, where feasible, are two of the most important forms of improving host response. Depending on the protocol used, granulocyte transfusions (Chapter 162) may stabilize *Aspergillus* lesions until recovery from neutropenia. Granulocyte colony-stimulating factor (G-CSF) and granulocyte-macrophage colony-stimulating factor (GM-CSF) may accelerate recovery from neutropenia (Chapter 153). The role of GM-CSF, G-CSF, or interferon-γ in immunocompromised non-neutropenic patients with invasive aspergillosis remains to be further defined.[20]

Surgery

Surgical management is important for several manifestations of invasive pulmonary aspergillosis: recurrent hemoptysis from a single cavitary lesion, invasion of a pulmonary lesion into the chest wall, and pulmonary lesions contiguous with great vessels or the pericardium. *Aspergillus* empyema requires closed chest tube drainage and possibly débridement of the infected pleural cavity. Débridement of sinus aspergillosis, particularly when the ethmoid and frontal sinuses are infected, may prevent extension into the orbit or into the cavernous sinus. Surgical resection of selected CNS lesions, depending on their location and the clinical manifestations they cause, may be indicated for establishing a diagnosis, reducing increased intracranial pressure, and/or protecting critical neural centers. Surgical management of infected lesions also is an important adjunctive component of primary therapy for several forms of invasive nonpulmonary aspergillosis: endocarditis, pericarditis, osteomyelitis, epidural abscess, infected vascular catheters and prosthetic devices, and skin and soft tissue infection.

Chronic Aspergillosis

Antifungal Agents

Medical therapy has limited benefit in the treatment of aspergilloma, but some patients may benefit from extended use of an antifungal triazole (voriconazole, posaconazole, or isavuconazole in doses outlined for invasive pulmonary aspergillosis [see earlier]). For example, 12 months of oral itraconazole can reduce clinical relapses from about 40% to about 10% compared with 6 months of therapy, but without any difference in death rates.[A4] Lifelong commitment to an antifungal triazole should be balanced against the natural history of approximately 10% of aspergillomas resolving spontaneously. By comparison, medical therapy with itraconazole or voriconazole is the standard of treatment for chronic cavitary pulmonary aspergillosis. Patients with chronic cavitary pulmonary aspergillosis typically achieve improvement of symptoms and stabilization or improvement of radiologic changes. Patients with chronic necrotizing pulmonary aspergillosis also should receive an antifungal triazole, but assessment of response is more difficult because of the underlying chronic lung disease.

Interventional Therapy

The role of surgical resection in patients with solitary aspergilloma or chronic cavitary pulmonary aspergillosis is limited because of development of bronchopleural fistula, *Aspergillus* infection of the pleural space, and potentially further worsening of already compromised pulmonary function. However, surgical resection may have a more important role in treating patients with recurrent and severe hemoptysis, for which the benefits of removing the cavity usually outweigh the known risks. Bronchial artery embolization and transthoracic direct intracavitary instillation of antifungal agents for aspergilloma have only limited benefits[A5] but substantial risk.

Otomycosis

Topical irrigating solutions of boric acid, acetic acid, or an antifungal azole cream may be effective in treating *Aspergillus* otomycosis. Voriconazole, posaconazole, or itraconazole may be necessary for refractory cases or perforated tympanic membranes.

Allergic Forms of Aspergillosis

Allergic bronchopulmonary aspergillosis (Chapter 75) is treated with a combination of corticosteroids and itraconazole (200 mg twice daily orally for 16 weeks). The optimal doses of corticosteroids are unknown but commonly include an initial prednisone dose of 0.5 mg/kg/daily for 2 weeks followed by an every other day dose of 0.5 mg/kg, then tapering off over a 16-week period. Higher doses may be needed in patients with a concomitant asthma flare, but are associated with more side effects.[A6] Voriconazole (200 mg twice daily) is another alternative that may be better tolerated than itraconazole.[A7] Intermittent use of corticosteroids or substantially raising the dose in patients who are receiving chronic therapy can produce rapid resolution of intercurrent symptomatic episodes. At this time there is a lack of evidence for the efficacy and safety of anti-IgE (omalizumab and dupilumab) therapy in patients with allergic bronchopulmonary aspergillosis and cystic fibrosis and in other non–cystic fibrosis patients.[A8]

Extrinsic allergic alveolitis is best managed by removing patients from the allergenic environment. An accurate occupational and home environment history is critical to this intervention.

Allergic *Aspergillus* sinusitis is treated by endoscopic drainage to relieve obstruction by tenacious mucin. Itraconazole and systemic steroids in regimens as described earlier, or nasal corticosteroids, alone or in combination, may be beneficial in some patients with allergic *Aspergillus* sinusitis. Caution is warranted with chronic use of systemic or nasal corticosteroids. Itraconazole may have a corticosteroid-sparing effect.

PREVENTION

Several strategies may be used for prevention of invasive aspergillosis in immunocompromised patients: primary prophylaxis, empirical therapy, and secondary prophylaxis. In patients undergoing stem cell transplantation and in patients with acute myelogenous leukemia or myelodysplastic syndromes, posaconazole prophylaxis (200 mg by suspension three times daily) can significantly reduce invasive fungal infections more effectively than either fluconazole or itraconazole and also improves overall survival.[A9] Posaconazole suspension is poorly absorbed and not well tolerated so that its use has been replaced by posaconazole extended-release tablets at 300 mg orally per day. Empirical antifungal therapy, either routine or guided by the depth and duration of neutropenia,[A10,A11] provides early treatment for persistently febrile immunocompromised patients and systemic antifungal prophylaxis in doses as described earlier for high-risk hosts with or without pulmonary infiltrates. L-AmB, caspofungin, micafungin, posaconazole, and voriconazole (see Table 311-2) have been used for this strategy. Secondary prophylaxis of invasive aspergillosis with voriconazole at doses described earlier is used for patients who have a history of previous aspergillosis and who are scheduled for a subsequent cycle of immunosuppression that may increase the risk for recurrence.

Reduction of exposure to airborne conidia, such as by HEPA filtration of hospital air, avoiding activities that increase conidial aerosols (room maintenance,

dust exposures, and contaminated materials [e.g., potted plants]), as well as providing clean water distribution systems, may reduce acquisition of *Aspergillus* by immunosuppressed or neutropenic patients.

For patients with allergic forms of aspergillosis, use of corticosteroids and itraconazole, alone or in combination, may prevent debilitating exacerbations. The toxicity of chronic administration of prednisone warrants strategies for intermittent administration of prednisone or corticosteroid-sparing use of itraconazole. Aerosolized antifungal agents are a promising option to prevent exacerbations of allergic bronchopulmonary aspergillosis.

PROGNOSIS

Untreated invasive aspergillosis is associated with severe morbidity and high mortality in immunocompromised patients. For example, the mortality of acute invasive aspergillosis in recipients of stem cell transplants varies from close to 100% with CNS infection or endocarditis to approximately 65% with pulmonary infection. Early recognition of clinical manifestations followed by prompt initiation of empiric antifungal therapy may improve the ominous prognosis of acute invasive aspergillosis, especially if accompanied by reversal of immunosuppression and successful treatment of the underlying primary disease. For patients with chronic aspergillosis, including allergic bronchopulmonary aspergillosis, multidisciplinary specialized supportive care may improve outcome and quality of life.

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312 MUCORMYCOSIS

DIMITRIOS P. KONTOYIANNIS AND LUIS OSTROSKY-ZEICHNER

DEFINITION

Mucormycosis is the unifying term used to describe infections caused by fungi belonging to the order Mucorales. Mucorales typically cause aggressive, acute-onset, frequently fatal or disfiguring, angioinvasive infections, especially in immunosuppressed hosts.

EPIDEMIOLOGY

Mucorales fungi are distributed worldwide and found in decaying organic substrates. The true incidence of mucormycosis is not known and probably is underestimated because of difficulties in antemortem diagnosis. The most common microbiologically confirmed infecting species are *Rhizopus* (about 50% of cases); and *Mucor* (about 20% of cases), but other species include *Cunninghamella bertholletiae*, *Apophysomyces elegans*, *Absidia*, *Saksenaea*, and *Rhizomucor pusillus*. *Apophysomyces* is predominant in Asia, and *Lichtheimia* species predominate in Europe. The thermophilic Mucorales *Saksenaea vasiformis elegans* caused necrotizing soft tissue infections in victims of combat-related injuries in Afghanistan. *Apophysomyces elegans* were implicated in victims of the Joplin tornado in 2011, and a major mucormycosis outbreak in coronavirus disease 2019 (COVID-19) patients in India[1,2] was attributable to *Apophysomyces* and *Rhizomucor* species. Worldwide, COVID-19 infection has been associated with an increased incidence of mucormycosis, primarily but not exclusively in the nasopharynx.[3]

The classic risk factors for mucormycosis include hematologic malignancy, hematopoietic stem cell or solid organ transplantation, poorly controlled diabetes mellitus, chronic acidemia, prematurity, profound chronic debilitation, trauma, burns, and, very rarely, intravenous drug use.[4] Nosocomial cutaneous infections related to contaminated materials or fomites can develop at sites of surgical wounds or intravenous catheter insertion. Breakthrough mucormycosis also is observed when patients with leukemia and recipients of hematopoietic stem cell transplants receive *Aspergillus*-active drugs without anti-Mucorales activity (e.g., voriconazole).

PATHOBIOLOGY

Mucorales species are saprophytic, rapidly growing fungi. Angioinvasive growth that results in infarction and necrosis of surrounding tissue is the hallmark of mucormycosis. The major modes of transmission are inhalation, ingestion, and direct inoculation, with inhalation of spores from environmental sources being the most common. Cutaneous or percutaneous transmission with traumatic disruption of skin barriers is the most important mode of transmission in immunocompetent hosts. Gastrointestinal acquisition, although less common, has occurred in patients who repeatedly ingest spores in the setting of severe malnutrition; ingestion of non-nutritional substances (pica); and contaminated herbal, homeopathic, or medicinal products.

Host immunity in healthy hosts prevents germination of fungal spores unless the inoculum is heavy. To establish invasive infection, spores must overcome both innate and adaptive immune responses to germinate into hyphae. Defects in phagocytic activity (e.g., neutropenia) and functional defects (e.g., caused by glucocorticoids, hyperglycemia, and/or acidosis) allow unimpeded proliferation of fungi because of the absence of a coordinated, effective host response.[5] *Rhizopus* interacts with glucose-regulated protein 78 (GRP78) on nasal epithelial cells via its spore coat protein CotH3 to invade and damage the nasal epithelial cells. Both GRP78 and CotH3 are upregulated in the acidemic hyperglycemic environment. Mucorales also produce a ricin-like toxin, called mucoricin, which can inhibit protein synthesis and increase its virulence.[6] Mucormycosis is often disseminated in severely immunosuppressed patients, with high mortality rates.

Free iron is an essential component of the pathogenesis of mucormycosis, and patients with iron overload are predisposed to such infections, especially if they are being treated with deferoxamine to chelate iron. *Rhizopus oryzae* can utilize deferoxamine as a xenosiderophore to form a ferrioxamine complex and to obtain more iron for use.

Poorly controlled diabetes mellitus, which is a major predisposing factor, is reported in 36 to 88% of all cases of mucormycosis. In particular, diabetic patients with ketoacidosis are susceptible to mucormycosis. Normal human serum cannot support the growth of *R. oryzae*, whereas serum in diabetic patients can do so. Acidosis disrupts the normal inhibitory activity of serum by attenuating the ability of transferrin to bind iron from the fungus. In addition, quantitative and qualitative neutrophilic and phagocytic cell dysfunction in diabetic patients with ketoacidosis may play a role in the pathogenesis of mucormycosis.

CLINICAL MANIFESTATIONS

The clinical presentation of mucormycosis depends on the host's underlying immunologic status and medical condition.[7] Patients often have indolent clinical presentations until extensive invasion or dissemination occurs.

Infectious syndromes associated with Mucorales are grouped based on clinical presentation into one of six categories: rhinocerebral (about 76% of cases); cutaneous (about 8.5% of cases); pulmonary (about 7.5% of cases); gastrointestinal; disseminated; and unusual presentations.[8]

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ABSTRACT

Mucormycoses describe a spectrum of chronic, subacute, and rapidly progressing infections caused by the fungi Mucorales. Clinical presentations, which are pleiotropic, include sinusitis (pansinusitis, rhino-orbital, or rhinocerebral), pulmonary, cutaneous, gastrointestinal, disseminated, and other uncommon presentations. Mucormycosis is typically seen following extensive trauma, in patients with uncontrolled diabetes, and in the setting of severe and prolonged immune suppression. In heavily immunocompromised patients, Mucorales have proclivity for angioinvasion, thereby resulting in tissue infarction, necrosis, and dissemination. Diagnosis requires a high index of clinical suspicion based on risk factors, clinical and radiologic presentation, and biopsy for histopathology and culture of the affected areas. Noninvasive rapid diagnostic tests are lacking. Reversal of immunosuppression and control of underlying metabolic abnormalities are important pillars of therapy, along with surgery and appropriate early antifungal agents. Despite the recent introduction of mold-active oral triazoles (posaconazole and isavuconazole) in addition to amphotericin B products, no randomized trials are available to guide therapy. Aggressive surgical resection of necrotic tissue is critical, especially in localized infection. Delayed diagnosis and the degree of immunosuppression are key determinants for poor outcome.

KEYWORDS

mucormycosis
Mucorales fungi
rhinocerebral mucormycosis
pulmonary mucormycosis
gastrointestinal mucormycosis
posaconazole
isavuconazole
amphotericin B

Rhino-orbital or rhinocerebral mucormycosis is the characteristic presentation in patients with diabetic ketoacidosis. Cutaneous mucormycosis is seen in both immunocompetent and immunocompromised hosts, typically following local trauma or burns that compromise skin integrity or after subcutaneous tissue injuries. Pulmonary mucormycosis is most common in neutropenic or corticosteroid-treated patients (e.g., hematopoietic stem cell and solid organ transplant recipients).

Rhinocerebral Mucormycosis

Rhinocerebral mucormycosis, which is the most common infectious manifestation, originates in the paranasal sinuses after inhalation of Mucorales spores and then extends to the orbit (sino-orbital) or brain (rhinocerebral), particularly in patients who have diabetic ketoacidosis or profound neutropenia.[9] Early signs and symptoms of sinus invasion (sinus pain, congestion, headache, mouth pain, otologic symptoms, and hypo-osmia/anosmia) may be indistinguishable from common causes of sinusitis (Chapter 394). Involved tissues become red, then violaceous, and finally black due to thrombosis and tissue necrosis. Signs of extensive, rapidly progressing infection include necrotic eschar of the nasal cavity and turbinates, facial lesions, and exophytic or necrotic lesions of the hard palate. A painful black eschar on the palate or nasal mucosa is a classic diagnostic but late sign, and its absence does not exclude rhinocerebral infection because necrotic nasal or palatal lesions are seen in only 50% of patients within 3 days of onset of infection. Signs and symptoms of periorbital and orbital involvement, which may be seen when the patient first presents, include periorbital swelling, preseptal and/or orbital cellulitis, proptosis, chemosis, blurred vision or rapidly progressing external ophthalmoplegia, diplopia, eyelid gangrene, retinal detachment, and endophthalmitis. Patients with extensive rhino-orbital or rhinocerebral disease also may present with trigeminal or other cranial nerve palsy, which is consistent with perineural invasion. Infection can rapidly progress through the cavernous sinuses into the central nervous system, thereby resulting in cavernous sinus and internal carotid artery thrombosis. A bloody nasal discharge may be the only sign indicating that the infection has invaded through the nasal turbinates and into the brain. Patients with advanced infection also may have altered consciousness, bone destruction, frontal lobe necrosis, epidural and subdural abscesses, and/or basilar artery aneurysm.

Skin and Soft Tissue Mucormycosis

Cutaneous mucormycosis, which typically occurs in victims of severe skin or muscular injury or in postoperative patients,[10] usually starts as erythema and skin induration at a puncture site and progresses to necrosis with a black eschar. Cutaneous infections can quickly extend into the deep fascia and muscle. Neutropenic patients in particular are susceptible to lymphatic and blood vessel invasion, infarction, and necrosis with eventual dissemination. Skin lesions in patients with suspected mucormycosis should raise concerns about disseminated disease and prompt careful clinical evaluation.

Pulmonary Mucormycosis

The clinical manifestations of pulmonary mucormycosis are indistinguishable from those of invasive pulmonary aspergillosis (Chapter 311).[11] Fever refractory to broad-spectrum antibiotics, nonproductive cough, and progressive dyspnea are the most common presenting symptoms.[12] Less commonly, pleuritic chest pain, hemoptysis, and pleural effusion are seen. If the major pulmonary blood vessels are invaded by fungal hyphae, massive and potentially fatal hemoptysis can occur. Clues for distinguishing pulmonary mucormycosis from invasive pulmonary aspergillosis include the presence of pansinusitis, a history of prophylaxis with antifungals against *Aspergillus* but not Mucorales (e.g., voriconazole, echinocandins), and possibly continual absence of detectable *Aspergillus galactomannan* antigen in serum. In rare circumstances, pulmonary mucormycosis can present as an endobronchial or tracheal lesion with a less fulminant course, especially in diabetics. Tracheobronchial mucormycosis may cause airway obstruction or erosion of major pulmonary blood vessels and fatal hemoptysis.

In immunocompetent hosts, pulmonary mucormycosis may present with more atypical, slowly progressing manifestations. As with *Aspergillus* species, Mucorales can form mycetomas in preexisting lung cavities and cause slowly necrotizing pneumonia and hypersensitivity syndromes.

Gastrointestinal Mucormycosis

Symptoms and signs of gastrointestinal mucormycosis include fever, abdominal distention, nausea, vomiting, abdominal pain, diarrhea, melena, hematemesis, hematochezia, and masslike appendiceal and ileal lesions. Primary gastrointestinal mucormycosis, which is rare, can present as necrotizing enterocolitis and involve any part of the alimentary tract, primarily in malnourished patients but also in immunocompetent hosts.[13] The liver, spleen, and pancreas also can be involved. Liver abscesses can occur following ingestion of herbal products contaminated by *Mucor indicus*. Fungi can invade the bowel wall and blood vessels, thereby resulting in bowel perforation, peritonitis, and massive gastrointestinal hemorrhage. Secondary gastrointestinal involvement results from seeding of the gastrointestinal tract, especially in neutropenic patients.

Disseminated Mucormycosis

Disseminated mucormycosis is rarely apparent antemortem. Severely immunosuppressed patients (e.g., patients with prolonged and profound neutropenia, allogeneic stem cell transplant recipients with severe graft-versus-host disease) and patients receiving deferoxamine iron chelation therapy are at the highest risk. Symptoms vary depending on the site of dissemination and degree of vascular infarction of the affected organs. The most common source of dissemination is the lung, and the most common site of spread is the brain.

Rare Clinical Presentations of Mucormycosis

Mucormycosis has protean manifestations that can involve any organ. Isolated cases of tracheal, mediastinal, bone, heart, kidney, otitis externa, and corneal involvement occur. Cerebral mucormycosis, often presenting as brain abscess involving the basal ganglia, has been typically observed in conjunction with infective endocarditis in patients using intravenous drugs.[14] Peritonitis can rarely occur in patients undergoing continuous ambulatory peritoneal dialysis.

DIAGNOSIS

The clinical signs and symptoms of local and disseminated mucormycosis are nonspecific, so a high level of suspicion is of paramount importance in susceptible patients.[15,16] Rapid diagnosis is critical because virtually all patients with disseminated mucormycosis die without rapid diagnosis and treatment.

Radiology

For suspected rhinocerebral mucormycosis, accurate diagnosis and prompt medical and surgical intervention are critical because of the rapid progression of the infection. Computed tomography (CT) and magnetic resonance imaging (MRI) can reveal soft tissue involvement around the nerve sheaths as well as bone destruction. CT frequently shows mucosal thickening, air-fluid levels, and bony erosion. Orbital thickening may be detected earlier by using MRI. CT and MRI scans of the orbits may be unremarkable during the initial stages of mucormycosis, thereby highlighting the importance of serial imaging. Extraorbital muscle thickening, which is often the first sign of orbital involvement, should prompt empirical antifungal therapy followed by surgical exploration or biopsy.

Pulmonary mucormycosis usually has no specific radiographic findings to distinguish it from other pneumonias, especially other fungal pneumonia. However, pulmonary mucormycosis can progress and invade adjacent organs by traversing tissue planes, including the diaphragm, chest wall, and pleura (Fig. 312-1).

Clinical Specimens

Biopsy and culture from sterile sites are critical, because tissue swabs and cultures of sputum, sinus secretions, and bronchoalveolar lavage fluid are usually nondiagnostic. Clinical specimens can be contaminated, so growth in culture may not represent clinically significant invasive mucormycosis. However, a Mucorales-positive culture and especially repetitive positive cultures are an important indication of infection in immunocompromised patients. Molecular techniques for detecting Mucorales are not widely available but are reported to have a sensitivity of 85% and a specificity of 90%.[17]

For rhinocerebral disease, necrotic lesions should be biopsied and evaluated histologically. For pulmonary disease, diagnosis is usually made by transbronchial biopsy. For necrotic skin lesions, especially in neutropenic patients, biopsy specimens should be obtained from the center of the lesion down to the subcutaneous fat. For potential disseminated disease, biopsy of suspected sites is critical because of the low yield of blood cultures and suboptimal recovery of the fungus from respiratory specimens.

Histopathology

Histopathologic examination of infected tissue typically shows characteristic broad (3 to 25 μm in diameter), thin-walled, primarily aseptate

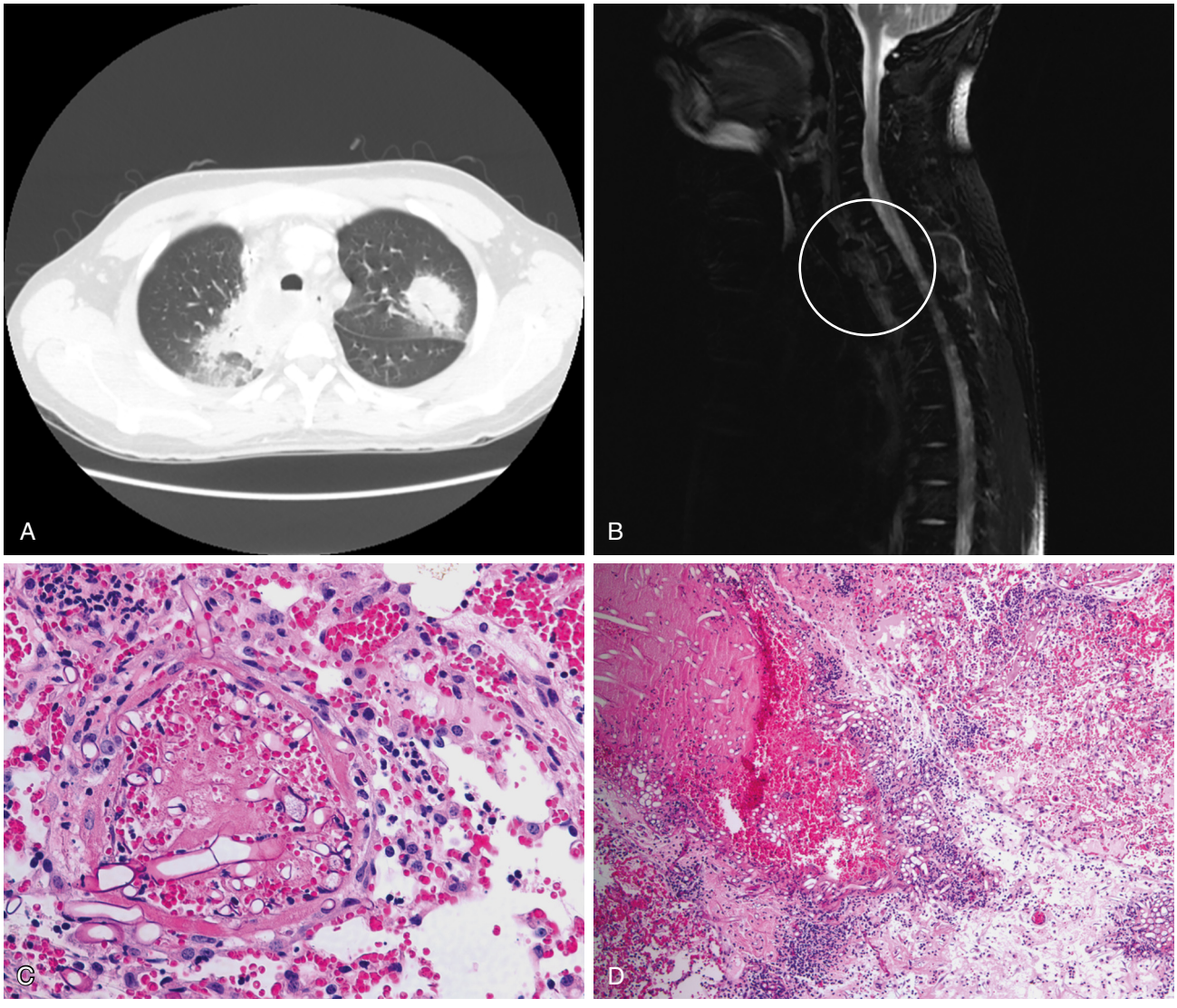

FIGURE 312-1. Extensive, progressive pulmonary mucormycosis in a patient with active leukemia and neutropenia. Characteristic extensions of the infection across tissue planes to trachea (producing a fistula) and mediastinum (**A**) and adjacent spine (**B**) are shown. The histopathologic characteristics of profound necrosis and hemorrhage and pauciseptate, broad-based, ribbon-like Mucorales are also shown (**C** and **D**). Culture of a tissue biopsy specimen remained negative. The patient died 3 weeks after diagnosis, despite aggressive use of a high-dose lipid formulation of amphotericin B (AMB) and adjunct immune therapy.

hyphae; focal bulbous dilation; and nondichotomous irregular branching at occasional right angles accompanying tissue necrosis and fungal angioinvasion (see Fig. 312-1). Perineural invasion is found in 90% of tissues containing nerves. Fungal hyphae can be examined directly using a potassium hydroxide preparation of a tissue specimen or bronchial alveolar lavage fluid. Although contamination is always possible, discovery of fungal elements in a specimen obtained from an immunocompromised host is considered significant.

Culture

Mucorales fungi characteristically produce large, ribbon-like hyphae with irregular diameters and only occasionally septa, thereby resulting in characterization of these organisms primarily as aseptate fungi. Identification can be confirmed by observing the characteristic saclike fruiting structures (sporangia), which produce internally spherical yellow or brown spores (sporangiospores). Spores range from 3 to 11 μm in diameter and are easily aerosolized. Blood cultures are rarely positive for these pathogens despite their angioinvasive nature. Paradoxically, even when fungal hyphae are seen in histopathologic analysis, fungal cultures may not be positive because the friability of nonseptated hyphae make them more susceptible to damage during tissue manipulation. Culture must be performed in a well-qualified laboratory that is knowledgeable about appropriate methods. Data on the antifungal susceptibility of Mucorales species are limited, and minimal inhibitory concentration (MIC) testing is rarely available outside research or reference laboratories.

TREATMENT

Early diagnosis is critical to the outcome, and delayed administration of systemic antifungal therapy increases the probability of death. Successful treatment of mucormycosis relies on a multifaceted strategy (Fig. 312-2) that includes (1) aggressive diagnosis and rapid initiation of effective antifungal therapy, (2) extensive surgical débridement, and (3) rapid control of underlying medical conditions.[18-20]

Antifungal Therapy

Mucorales are resistant to many antifungals, including flucytosine, ketoconazole, fluconazole, voriconazole, and the echinocandins. Also, they have variable susceptibility to itraconazole. Amphotericin B, isavuconazole, and posaconazole are the most active agents in vitro, although their activities differ among different Mucorales families.

Lipid formulations of amphotericin B (liposomal amphotericin B, amphotericin B lipid complex, amphotericin B colloidal dispersion), which are less nephrotoxic and can be given at higher doses (e.g., 5 to 10 mg/kg per day) than standard amphotericin, are the drugs of choice for mucormycosis.[21] Amphotericin B by transthoracic injection or aerosol has been successful in conjunction with concomitant systemic therapy in selected patients with pulmonary mucormycosis. Topical amphotericin B and other polyenes (natamycin) may be effective against primary cutaneous and ocular mucormycosis. Combining an echinocandin (see Chapter 307) with liposomal amphotericin B may be better than liposomal amphotericin B for diabetic patients with rhino-orbital mucormycosis compared with amphotericin B alone, especially in patients with cerebral involvement, but not in patients with underlying hematologic cancer who develop mucormycosis. Isavuconazole (loading dose 372 mg every 8 hours for six doses IV/oral; followed

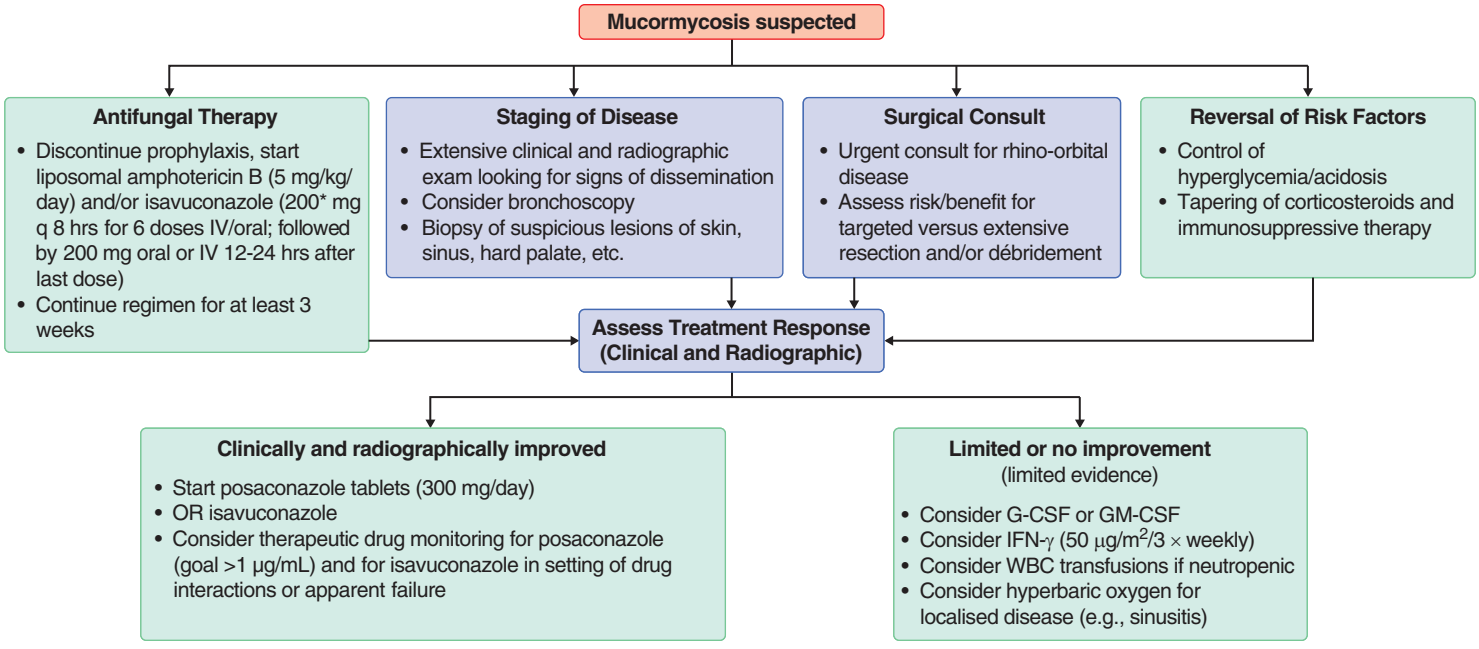

FIGURE 312-2. **Diagram of the management approach to patients with suspected mucormycosis.** *200 mg of isavuconazole = 372 mg of isavuconazonium sulfate. G-CSF = granulocyte-colony stimulating factor; GM-CSF = granulocyte-macrophage-colony stimulating factor; IFN = interferon; IV = intravenous; WBC = white blood count.

by 372 mg oral or IV 12 to 24 hours after the last dose) appears to be as efficacious as amphotericin B in a matched case-control analysis. Posaconazole (800 mg suspension or 300-mg tablet orally daily) can be useful as salvage therapy in patients with refractory mucormycosis, but it is uncertain whether posaconazole alone or combined with a lipid formulation of amphotericin B or other agent (e.g., deferasirox) is of value otherwise.

The duration of antifungal therapy should be determined on an individual basis. Near-normalization of radiographic imaging, negative follow-up biopsy specimens, negative cultures from the affected site, and recovery from immunosuppression are important indicators for stopping antifungal therapy.

Surgery

Because of the aggressively invasive nature of mucormycosis, surgical débridement of cutaneous lesions is crucial and must be done without delay to improve prognosis. Small focal lesions can be surgically resected before they progress to involve critical structures or distal organs. For device-related mucormycosis, prompt removal of the device and several weeks of systemic antifungal therapy are essential for resolution of the infection.

Repeated removal of necrotic tissue or aggressive surgical measures such as enucleation of the eye may be required to control the infection. A CT scan or MRI before surgery and intraoperative frozen section analysis can help guide the extent of the procedure.

Management of Comorbidity and Adjunct Treatments

Rapid correction of underlying conditions, such as control of hyperglycemia, reversal of ketoacidosis, rapid tapering of glucocorticoid therapy, and discontinuation of deferoxamine treatment, can improve outcomes. Hyperbaric oxygen may be a beneficial adjunctive therapy, particularly in diabetic patients with rhinocerebral disease, but it has not been studied rigorously and cannot be routinely recommended. In refractory neutropenic patients, granulocyte transfusion may be beneficial until granulocyte recovery (Chapter 153). Instituting deferasirox or substituting it for other iron chelation agents does not appear to be beneficial.

PROGNOSIS

Because the first-line antifungal typically used for aspergillosis is voriconazole, which lacks activity against Mucorales, failure to achieve a timely diagnosis of pulmonary mucormycosis and delayed antifungal therapy is associated with rapidly worsened outcome. However, the prognosis of mucormycosis appears to be improving with earlier diagnosis and better treatment. Isolated sinusitis is curable by following timely surgical intervention and systemic antifungal therapy. In one review of 929 documented cases of mucormycosis, the mortality rate was 62% in rhinocerebral mucormycosis, 24% in sino-orbital involvement, and 16% in isolated sinus disease. Mortality also remains over 50% in pulmonary mucormycosis.[22] Primary gastrointestinal mucormycosis is associated with an 85% mortality rate.

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313

PNEUMOCYSTIS PNEUMONIA

JOSEPH A. KOVACS

DEFINITION

Pneumocystis jirovecii is a fungus that causes pneumonia almost exclusively in immunodeficient patients. *Pneumocystis* pneumonia (PCP) has been the most common life-threatening opportunistic infection in persons infected with human immunodeficiency virus (HIV), especially those with acquired immunodeficiency syndrome (AIDS). Although the frequency of PCP has decreased in HIV-infected patients, first in association with the widespread use of anti-*Pneumocystis* prophylaxis and later with the introduction of effective combination antiretroviral therapy for HIV/AIDS, it continues to be seen commonly in HIV-infected and other immunodeficient patients.[1] The risk of PCP has been increasing among renal transplant recipients, especially in Europe and Australia.

The Pathogen

Pneumocystis is an ascomycete fungus of the subphylum Taphrinomycotina, most closely related to *Schizosaccharomyces*, *Taphrina*, and *Saitoella* species of fungi. Molecular studies, including whole-genome sequencing, demonstrate that the genus *Pneumocystis* includes a group of closely related organisms that are unique species, each of which can likely infect only a single host species. The organisms previously called *Pneumocystis carinii* are reserved for a species that infects rats, whereas the organism infecting humans is named *P. jirovecii*. Despite the name change, PCP (for *Pneumocystis* pneumonia) remains the preferred acronym for human disease.

Pneumocystis species show a fairly strict host specificity: attempts to transmit, for example, rat or human *Pneumocystis* to mice have been unsuccessful. Molecular evolutionary studies suggest that *Pneumocystis* species coevolved with their hosts, with host jumps rarely occurring. *Pneumocystis* does not

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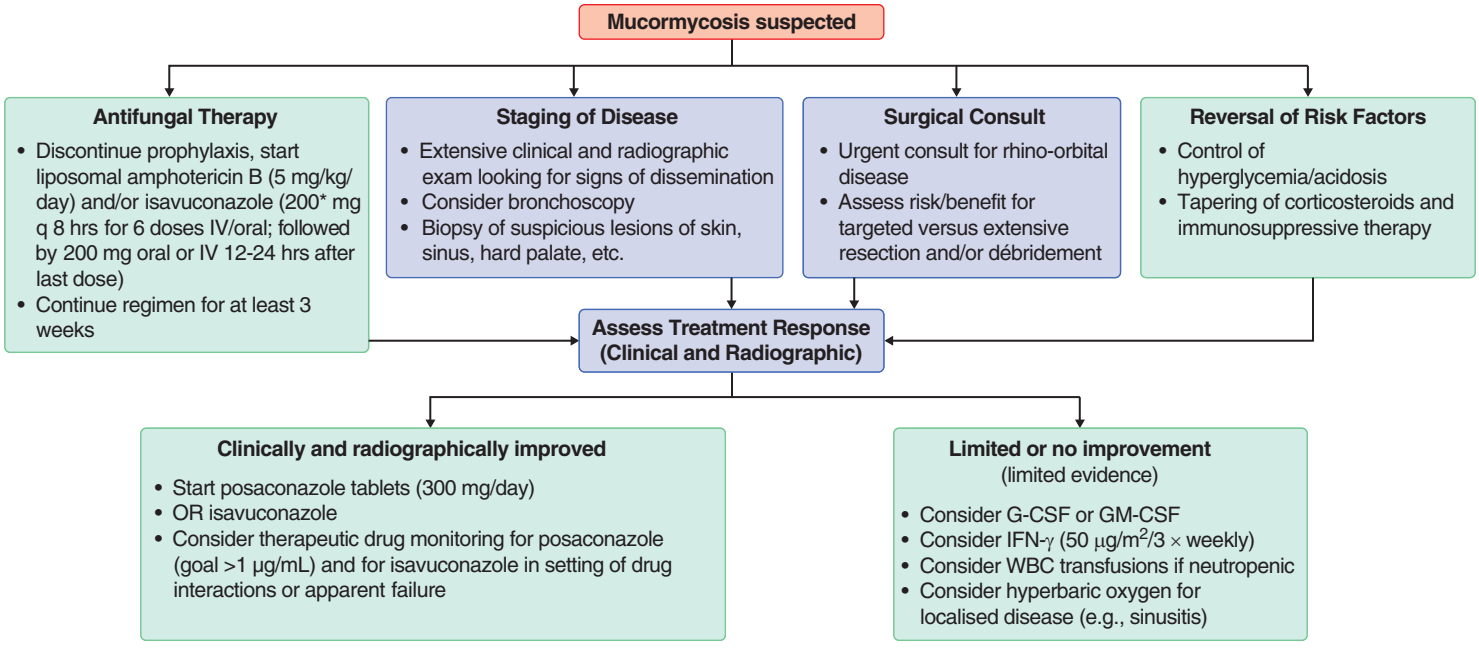

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313

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ABSTRACT

Pneumocystis jirovecii is a fungus that causes pneumonia (PCP) almost exclusively in immunodeficient patients, especially patients with HIV infection, renal transplant recipients, and patients receiving intensive immunosuppressive regimens for cancer or inflammatory diseases. Patients with PCP typically present with fever, a nonproductive cough, and progressive shortness of breath. Although chest radiographs may be normal early in the disease process, they will often show bilateral interstitial infiltrates that progress to a diffuse alveolar pattern if untreated. Because *Pneumocystis* cannot be cultured, diagnosis is based on detection of the organism by colorimetric or immunofluorescent stains or by polymerase chain reaction (PCR) testing, in respiratory samples, especially bronchoalveolar lavage fluid and induced sputum. Trimethoprim-sulfamethoxazole is the treatment of choice for PCP. Alternatives include dapsone plus trimethoprim, clindamycin plus primaquine, atovaquone, and pentamidine. Adjunctive corticosteroids improve survival in HIV-infected patients with hypoxia ($Pao_2 < 70$ mm Hg). Anti-*Pneumocystis* prophylaxis is effective in preventing PCP in patients at high risk, including HIV-infected patients with CD4 counts less than 200 cells/μL in the absence of combination antiretroviral therapy. Effective prophylactic regimens include trimethoprim-sulfamethoxazole (the first-line agent), dapsone alone or combined with pyrimethamine plus leucovorin, atovaquone, and aerosol pentamidine administered by nebulizer.

KEYWORDS

PCP
HIV
AIDS
Pneumocystis pneumonia
immunocompromised
fungus

grow in culture for a sustained period, so its life cycle is unknown. The two easily recognized forms of the organism are trophic forms (about 2 to 6 µm in diameter) and cysts (also called asci; about 5 to 8 µm in diameter), which can contain up to eight intracystic bodies (ascospores); additional intermediate forms are also seen. Trophic forms, which have an amorphous shape, are estimated to outnumber cysts, which are spherical, by approximately 10:1 in an infected lung.

The genome of *P. jirovecii*, approximately 8.2 million base pairs, is markedly contracted compared with other fungi and has lost multiple metabolic pathways, including enzymes needed to synthesize all amino acids de novo, enzymes needed for chitin synthesis and degradation, and carbonic anhydrase, an enzyme important for regulation of intracellular pH.[2] These findings suggest that *Pneumocystis* lives exclusively in the mammalian host and cannot survive in the external environment other than for the brief periods of time needed to transmit infection to another host.

EPIDEMIOLOGY

Pneumocystis has a worldwide distribution based on serologic studies that show a high prevalence of anti-*Pneumocystis* antibodies in all studied populations. In America and Europe, serologic studies show that most humans develop antibodies to *Pneumocystis* by an early age, thereby suggesting that the organism is ubiquitous.

Pneumocystis is transmitted by the respiratory route, and cysts are required for transmission. There is no evidence that water or fomites play a role in transmission. Data also suggest that transmission can occur transplacentally.

Given its strict host specificity, the source of human infection is presumably other humans, as suggested by occasional outbreaks of a single genotype, especially in recipients of renal transplants.[3] Since clinically apparent PCP is rare and nearly all healthy humans are infected at a young age, *Pneumocystis* infection is also likely acquired from apparently healthy humans, in whom subclinical infection (either asymptomatic or minimally symptomatic) must be quite common.

Molecular genotyping has shown that clinical PCP is often caused by newly acquired strains; whether reactivation of latent infection that was acquired at an early age also contributes to development of pneumonia is unknown. In patients who develop recurrent PCP, however, the recurrence can be due to relapse, especially for early recurrences, or to reinfection with a novel strain.

In immunocompetent hosts, *Pneumocystis* does not appear to cause significant disease. Clinically significant PCP occurs almost exclusively in patients with severe levels of immunodeficiency that are usually associated with a high risk for other opportunistic pathogens: individuals with congenital immunodeficiencies (Chapter 231), especially severe combined immunodeficiency (SCID), hyper–immunoglobulin M (IgM) syndrome, and, to a lesser extent, interleukin-21 (IL-21) receptor deficiency; patients with HIV infection (Chapter 354) and human T-lymphotropic virus-1–associated lymphoma (Chapter 171); patients receiving chemotherapy for the treatment of malignancies, especially lymphoma; transplant patients receiving immunosuppressive therapy; and patients being treated with prolonged courses of immunosuppressive drugs (Chapter 28), especially corticosteroids. In non-HIV patients, up to 90% of patients may be receiving corticosteroid therapy, and higher dose and longer duration increase the risk. Not all patients who receive corticosteroids are at risk, however; for instance, asthmatic patients receiving corticosteroid therapy are at low risk. Biologic agents (Chapter 29), such as alemtuzumab, rituximab, and agents targeting tumor necrosis factor-α (TNF-α), are also associated with an increased absolute risk for PCP, as are idelalisib, ibrutinib, gemcitabine, and iguratimod.[4]

Risk factors for non–HIV-infected patients include underlying disease, older age, use of immunosuppressive drugs, radiation therapy, graft-versus-host disease, graft rejection, and concomitant cytomegalovirus infection (Chapter 347). Patients with malignancies, especially hematologic malignancies but increasingly solid tumors as well, are at risk for PCP primarily owing to the therapies they receive; the incidence can range from 1 to 43% in the absence of prophylaxis and is highly dependent on the intensity and duration of immunosuppression. The incidence of PCP in patients who are receiving chemotherapy for acute myeloid leukemia may be as high as 6 to 7%.[5] In the absence of prophylaxis, the risk for developing PCP in transplant patients, whether hematopoietic stem cell transplantation (Chapter 163) or solid organ transplantation (Chapter 38), is reportedly about 5 to 15%, although lung and heart-lung transplant patients appear to have a higher incidence (up to 43%). Among patients who have a collagen vascular disease, the reported risk is less than 2% without prophylaxis, although patients who have granulomatosis with polyangiitis (Chapter 249) reportedly have a risk of up to 12%. In patients with inflammatory bowel disease (Chapter 127), the incidence is about 1% per year, with a greater risk for Crohn disease compared with ulcerative colitis. PCP also can occur together with coronavirus disease 2019 (COVID-19) infection (Chapter 336) or during the recovery phase, in part probably related to the use of corticosteroids to treat COVID-19.

Among patients with HIV infection, patients with CD4 counts less than 200 cells/µL, and especially those with CD4 counts less than 100 cells/µL, are at greatest risk. Patients with a prior history of PCP and those with unexplained fever, weight loss, or thrush are also at increased risk. Among non-HIV patients, CD4 counts less than 200 cells/µL also appear to increase risk.

PATHOBIOLOGY

Exposure for as little as 1 day to a *Pneumocystis*-infected animal results in transmission of infection. *Pneumocystis* has evolved mechanisms to avoid host initial innate and adaptive immune responses, presumably to facilitate the establishment of primary infection and reinfection in immunocompetent hosts. β-Glucans are masked by surface proteins, and enzymes needed to synthesize outer chain mannans have been lost; both can be recognized by host pattern recognition receptors. The most abundant surface protein of *Pneumocystis*, the major surface glycoprotein, is found on both cysts and trophic forms and is encoded by a multicopy gene family, only one of which is apparently expressed in a given organism; this provides *Pneumocystis* with the potential for antigenic variability. Although more than one *Pneumocystis* species can infect a single animal host species (e.g., rats, dogs), to date only a single *Pneumocystis* species has been found to infects humans; however, molecular typing techniques have demonstrated a high level of diversity among human *Pneumocystis* isolates.

In animal models, an adaptive immune response, which develops against primary infection by approximately 5 to 6 weeks, leads to control and clearance before the burden of organisms produces symptoms. CD4 cells are critical to this control, although B cells and macrophages also are important; B cells appear to have a major role in antigen presentation. CD8 cells can contribute to the associated inflammation. In immunodeficient animal models, the inability to control *Pneumocystis* replication leads to severe pneumonia by 2 to 3 months.

Host inflammatory responses, in part attributable to organism-derived β-glucans, appear to play a critical role in the development of pulmonary symptoms. This relationship may explain why symptoms of PCP develop in patients in whom corticosteroids are being tapered, as well as why the exacerbations of hypoxia can develop approximately 4 days after the initiation of anti-*Pneumocystis* therapy in the absence of concomitant corticosteroid therapy.

Lung pathology in patients with PCP demonstrates an acellular, foamy, eosinophilic, intra-alveolar exudate associated with mild interstitial inflammation (E-Fig. 313-1). This exudate is composed almost entirely of *Pneumocystis* organisms. With progressive disease, hyaline membranes form, and interstitial and intraluminal fibrosis develops. Atypical pathology, including noncaseating granulomas and intrapulmonary cystic changes, can also be seen.

In addition to the previously noted congenital immunodeficiencies and acquired immunosuppression, rare dominant negative allelic variants in the transcription factor Ikaros also appear to confer a very high risk of PCP. Among HIV-infected patients, polymorphisms in the genes for FcγRIIa, IL-4, and the chemokine receptor gene for CCRL2 also have been associated with an increased risk.

Although *Pneumocystis* cannot be cultured, molecular studies have identified mutations in genes that are the targets of anti-*Pneumocystis* therapy, and these mutations may represent the development of resistance by *Pneumocystis* to these agents. Mutations in the DHPS gene of *Pneumocystis*, which is the target of sulfamethoxazole and dapsone, occur more frequently in patients who are receiving trimethoprim-sulfamethoxazole or dapsone for prophylaxis.

CLINICAL MANIFESTATIONS

In immunocompetent humans, no well-defined clinical syndrome is associated with *Pneumocystis* infection, although clinically significant pneumonia rarely has been reported in adults. *Pneumocystis* also has been detected by polymerase chain reaction (PCR) testing in patients with chronic obstructive pulmonary disease (COPD; Chapter 76), but it has not been associated with a worsening clinical course.

In immunosuppressed patients, pneumonia is the primary clinical manifestation of *Pneumocystis* infection. PCP typically presents with a fever, nonproductive cough, and shortness of breath[6] that initially occurs only on exertion but, without therapy, inevitably progresses to dyspnea at rest. Symptoms may be insidious, developing over the course of a few weeks, as is common in patients with HIV infection,[7] or over the course of only a few days, as is more common in non-AIDS patients. Purulent sputum production is unusual, and chills and chest pain occur in a minority of patients. Patients

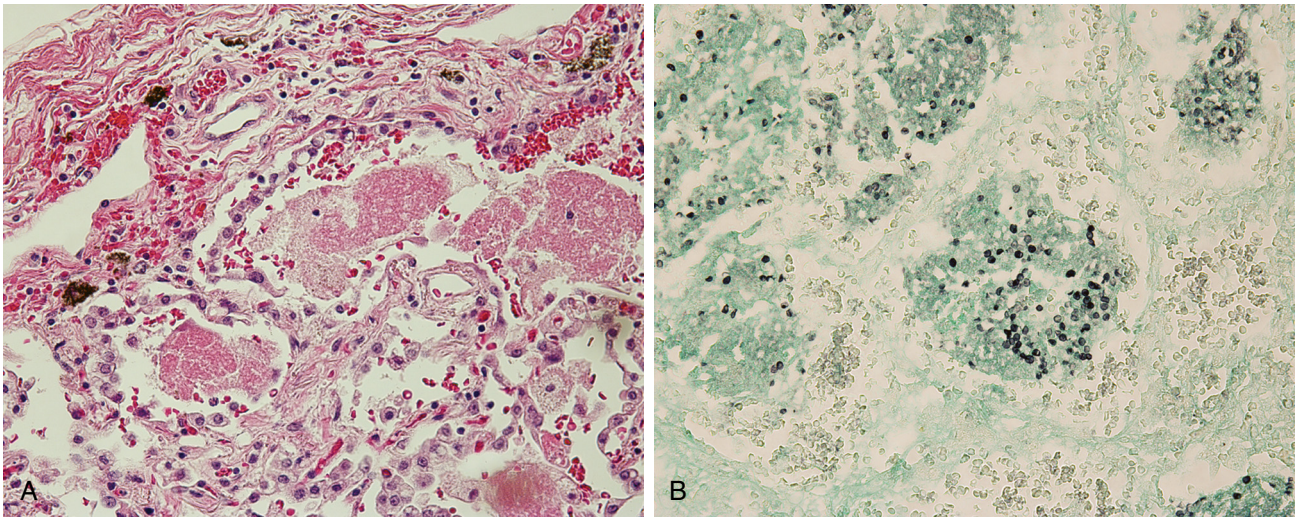

E-FIGURE 313-1. **Histopathology of the lung of a patient who died from *Pneumocystis* pneumonia (PCP). A,** The hematoxylin and eosin–stained section shows the characteristic acellular, eosinophilic, intra-alveolar exudate that is typical of PCP. **B,** Methenamine silver staining of lung tissue from the same patient demonstrates black-staining cysts scattered throughout the intra-alveolar exudates.

with HIV infection may present with other manifestations of immunodeficiency, including weight loss and thrush. In non-AIDS patients, in whom corticosteroids (Chapter 28) are a common risk factor,[8] clinical manifestations may develop as corticosteroids are being tapered, presumably representing the unmasking of an inflammatory response to the infection as immunosuppression is decreased.

Extrapulmonary disease can rarely involve the skin, eye (choroiditis), central nervous system, bone marrow, thyroid, spleen, liver, gastrointestinal tract, lymph node, or multiple organs in disseminated disease (E-Fig. 313-2), with or without concurrent pneumonia. The risk is somewhat higher but still extremely rare in HIV-infected patients who use aerosolized pentamidine for prophylaxis. Symptoms, which are related to the particular involved site, may be nonspecific, and the diagnosis is often made at autopsy.

DIAGNOSIS

PCP can be the initial presentation of HIV infection. Given the nonspecific symptoms, especially early in the disease process, clinicians must have a high index of suspicion for PCP even in patients not known to be immunosuppressed.[9] Knowledge of the most recent CD4 count is helpful in assessing HIV-infected patients because PCP is rare if the CD4 counts are above 200 cells/μL.

Physical examination and routine laboratory tests are nonspecific and usually not helpful in making the diagnosis of PCP. Even though patients may be tachypneic and appear to be in respiratory distress, they may have an entirely normal lung examination early in the disease course. Lymphopenia is common but is a manifestation of the underlying disease rather than PCP. Lactate dehydrogenase (LDH) levels are often elevated but have poor specificity. Serologic tests also are generally not helpful in diagnosing PCP.

The initial evaluation should include a chest radiograph and assessment of arterial oxygenation, either by blood gas measurement or by pulse oximetry. The chest radiograph typically shows perihilar or diffuse bilateral interstitial infiltrates that progress to a diffuse alveolar pattern (Fig. 313-1). However, PCP has been associated with unilateral disease, focal disease, consolidation, nodules, cavities, pneumothorax, and, rarely, pleural effusions. In up to 30% of patients with HIV infection, the chest radiograph appears normal; in this situation, a computed tomography (CT) scan of the chest, especially high-resolution CT, is invariably abnormal and usually shows a patchy or diffuse ground-glass pattern (see Fig. 313-1).[10]

Arterial oxygenation at rest is often abnormal, although in 30% or more of cases it is within normal limits. Exercise testing induces desaturation and an increase in the alveolar-arterial oxygen (A-a O_2) gradient in the majority of patients with PCP, even those with normal oxygenation at rest or a normal chest radiograph. An abnormal resting diffusing capacity is also common.

Because *Pneumocystis* cannot be cultured, a definitive diagnosis of PCP requires detection of the organism in a respiratory sample.[11] Although expectorated sputum has a low diagnostic yield, induced sputum, combined with immunofluorescent staining (Fig. 313-2)[12] specific for *Pneumocystis*, can be performed and interpreted rapidly and can have a sensitivity approaching 90%. In many centers, however, the diagnostic yield is much lower, likely due in part to variability in the methods used for induction and processing. Ideally, sputum induction should be the first step in diagnosis, followed by bronchoscopy with bronchoalveolar lavage (Fig. 313-3). Bronchoscopic or open lung biopsy is rarely needed to make the diagnosis.

PCR-based assays are 10- to 100-fold more sensitive than stains for detecting *Pneumocystis* and can detect the organism in expectorated sputum, nasopharyngeal aspirates, oropharyngeal wash samples, whole blood samples, and cell-free DNA from serum or plasma,[13] which have a lower organism burden than induced sputum or bronchoalveolar lavage (BAL) samples.[14] This increased sensitivity, however, is associated with decreased specificity because of detection of colonization or subclinical infection that does not require specific anti-*Pneumocystis* therapy. Quantitative PCR assays may help distinguish colonization from clinically significant infection.

The differential diagnosis of pulmonary infiltrates in immunosuppressed patients is very broad and includes infections such as COVID-19 (Chapter 336), adenovirus (Chapter 333), cytomegalovirus (Chapter 347), tuberculosis (Chapter 299), cryptococcosis (Chapter 309), histoplasmosis (Chapter 308), aspergillosis (Chapter 311), and toxoplasmosis (Chapter 320), as well as noninfectious processes such as tumor, heart failure (Chapter 45), pulmonary emboli (Chapter 68), radiation- and chemotherapy-induced pneumonitis, and, especially in HIV-infected patients (Chapter 359), nonspecific interstitial pneumonitis and Kaposi sarcoma.

TREATMENT

Specific anti-*Pneumocystis* therapy should be initiated promptly when the diagnosis is suspected in a potentially susceptible patient. The diagnosis must be definitively confirmed as soon as possible so as to avoid delaying therapy for another process, but delaying such confirmation for a few days after the initiation of therapy will not decrease the diagnostic yield because organisms can be detected in clinical samples for more than 3 weeks after the initiation of therapy.

The treatment of choice for PCP or extrapulmonary *Pneumocystis* disease is trimethoprim-sulfamethoxazole (Table 313-1). HIV-infected patients should be treated for 21 days and non-HIV patients for at least 14 days.[15] Observational data suggest the lower doses (<10 mg/kg/day of trimethoprim and <50 mg/kg/day of sulfamethoxazole) may be as efficacious as higher doses and better tolerated.[16]

Oral therapy should be reserved for patients with mild to moderate disease in whom poor absorption is not a concern. Outpatient therapy should be reserved for patients with mild to moderate disease who will reliably return for follow-up.

The major toxicities associated with trimethoprim-sulfamethoxazole include fever, rash, neutropenia, thrombocytopenia, nausea, vomiting, and transaminase elevations. Hyperkalemia and crystalluria have also been reported, and hyponatremia is seen primarily in association with intravenous administration. Toxicities, which usually appear after the first week of therapy, are much more common in HIV-infected patients, in whom they occur in about 50 to 60% of cases; 15 to 35% of these patients discontinue therapy because of the adverse events.

Alternative Antimicrobials for Mild to Moderate PCP

For patients with mild to moderate disease, alternative regimens include trimethoprim-dapsone and clindamycin-primaquine, both of which have response rates (about 90%) and dose-limiting toxicity rates (about 30%) that are similar to trimethoprim-sulfamethoxazole.[17] Adverse reactions to trimethoprim-dapsone include rash, fever, nausea and vomiting, transaminase elevations, methemoglobinemia, anemia, and mild hyperkalemia. Approximately 20 to 30% of patients with adverse reactions to trimethoprim-sulfamethoxazole experience adverse reactions to trimethoprim-dapsone. Toxicities associated with clindamycin-primaquine include fever, rash, diarrhea, anemia, neutropenia, elevations in liver aminotransferase levels, and methemoglobinemia (Chapter 144). For both dapsone and primaquine and, to a lesser extent, sulfamethoxazole, glucose-6-phosphate dehydrogenase deficiency (Chapter 147) can increase the risk for hemolytic anemia and methemoglobinemia.

Another alternative is atovaquone suspension, which should be taken with food to increase its bioavailability and should be avoided in patients with potentially decreased gastrointestinal absorption (e.g., diarrhea). Efavirenz can decrease plasma concentrations of atovaquone. Toxicities of atovaquone include rash, fever, nausea, vomiting, diarrhea, neutropenia, elevations in liver aminotransferase levels, and anemia.

Alternative Antimicrobials for Severe PCP

Therapeutic alternatives to trimethoprim-sulfamethoxazole for patients with disease requiring parenteral therapy are limited to clindamycin-primaquine (but only clindamycin is available for intravenous administration) and pentamidine. Caspofungin should not be used as monotherapy and is of uncertain benefit when added to other agents.[18]

Intravenous pentamidine, which is as efficacious as trimethoprim-sulfamethoxazole, must be given as a slow (>1 hour) infusion. However, toxicities occur in about 50 to 60% of patients treated with pentamidine and frequently result in discontinuation of the drug. These toxicities include hypoglycemia, nephrotoxicity, hyperglycemia, fever, neutropenia, thrombocytopenia, hypotension, hyperkalemia, aminotransferase elevations, and pancreatitis. Hypoglycemia may be life-threatening and may precede the development of hyperglycemia; hyperglycemia may be irreversible. Torsades de pointes (Chapter 53) has also rarely been reported.

Adjunctive Corticosteroid Therapy

In HIV-infected patients with moderate to severe disease (Pao_2 < 70 mm Hg or A-a O_2 gradient > 35 mm Hg), a tapering 21-day regimen of adjunctive corticosteroids (see Table 313-1) is indicated to reduce the likelihood of respiratory failure and mortality by 50%. Adjunctive corticosteroids are not associated with a significant increase in opportunistic complications other than localized herpes simplex infection.[A1] Corticosteroids do not benefit patients with mild disease. They also are not of proven benefit if started more than 72 hours after treatment has begun, although it is reasonable to add them if patients exhibit deterioration after this time.

In non-HIV patients, who are often receiving corticosteroids as part of the treatment regimen for their underlying disease, the optimal dosing of corticosteroids is uncertain. Treatment is usually individualized with expert consultation to balance the immunosuppressive effects that potentially contributed to the development of PCP against the anti-inflammatory effects that may ameliorate life-threatening pulmonary dysfunction.[19] A reasonable current approach is to administer corticosteroids to non-HIV patients with moderate or severe disease if they were not receiving corticosteroids, using the same regimen as for HIV-infected patients; for patients already taking corticosteroids at lower doses, the dosage could be increased (see Table 313-1).

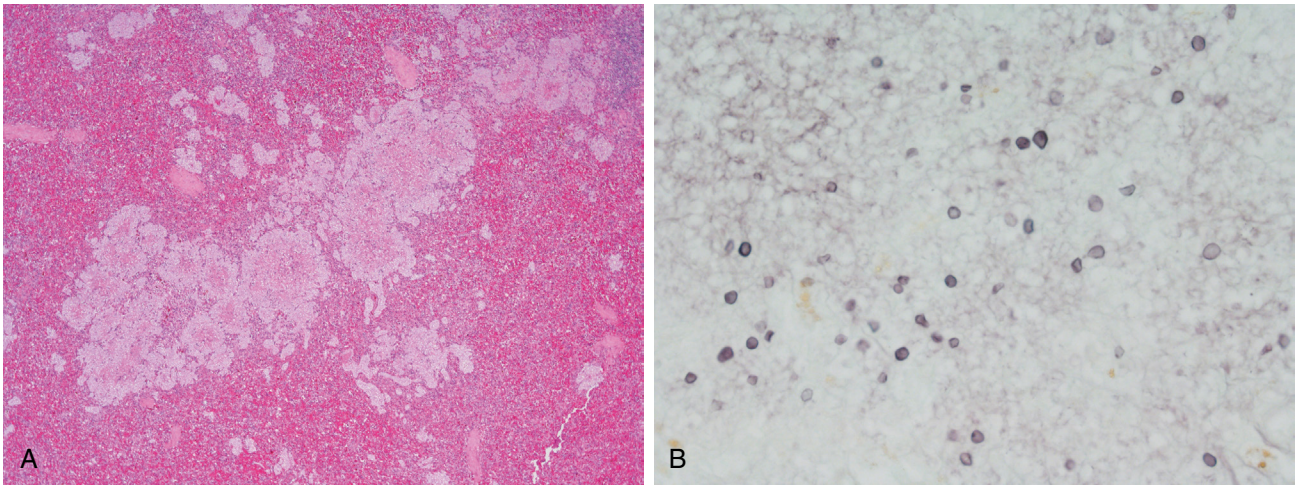

E-FIGURE 313-2. Histopathology of the spleen of a patient who died from disseminated *Pneumocystis* infection. A, The hematoxylin and eosin–stained section of the spleen shows large aggregates of *Pneumocystis* organisms. **B**, Methenamine silver stain demonstrates multiple cysts in the spleen. This patient, who was infected with the human immunodeficiency virus, had multiple prior episodes of *Pneumocystis* pneumonia and, at autopsy, had *Pneumocystis* organisms in multiple organs, including the lungs, endocardium, liver, testes, brain, and dermal capillaries. (Courtesy of David Kleiner, MD, PhD, National Cancer Institute.)

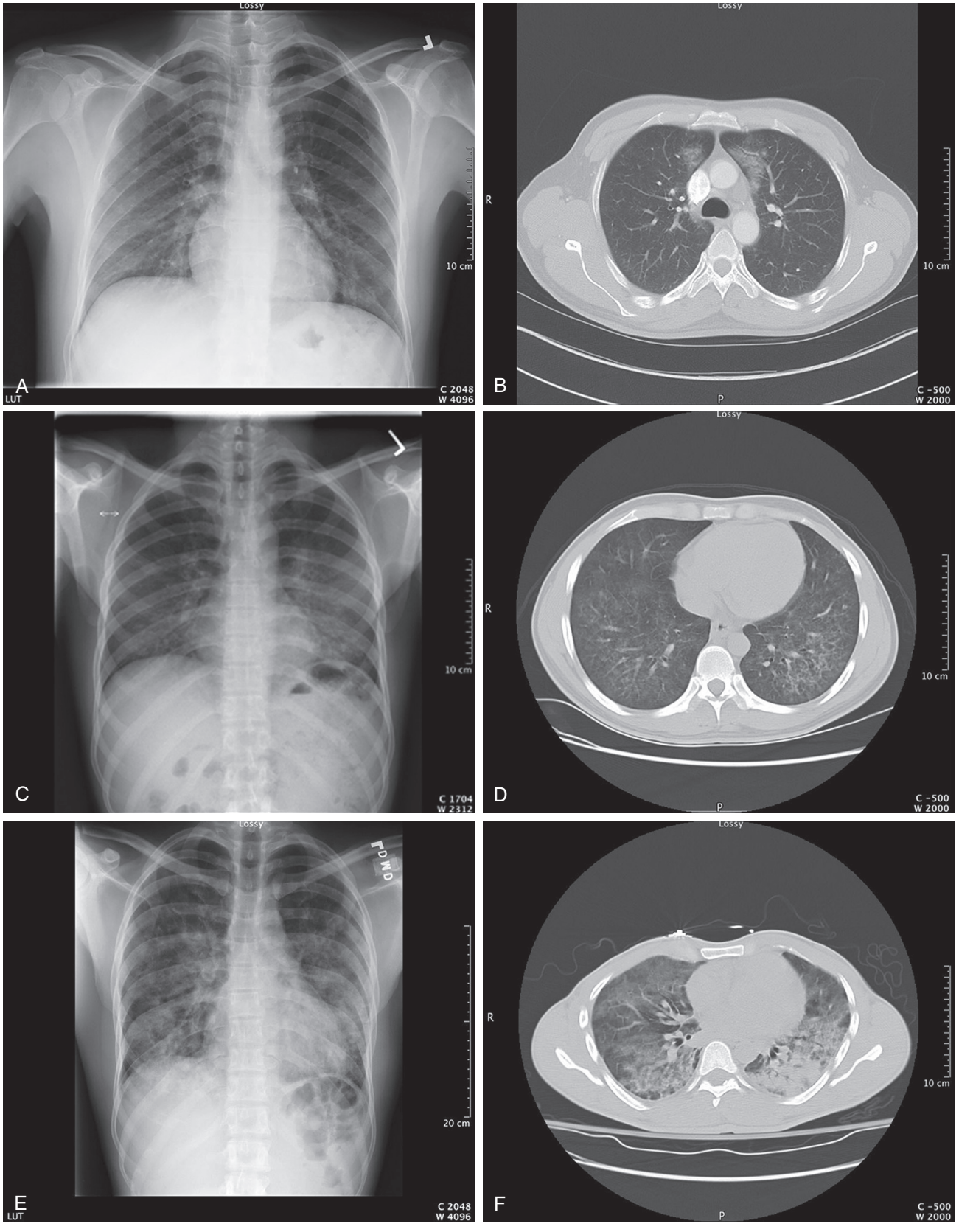

FIGURE 313-1. Chest radiographs (A, C, E) and corresponding computed tomography (CT) scans (B, D, F) from three HIV patients diagnosed with laboratory-confirmed *Pneumocystis* pneumonia. Patient 1 presented with no symptoms; had minimal abnormalities on an incidental chest radiograph (**A**), suggesting an interstitial process; and had focal infiltrates on CT (**B**). Patient 2 presented with fever and weight loss but no shortness of breath. Pulse oximetry demonstrated 99% saturation at rest, with a decrease to 89% with exercise. Chest radiograph (**C**) showed bilateral lower lobe infiltrates, and CT (**D**) showed bilateral lower lobe interstitial infiltrates with patches of ground-glass attenuation. Patient 3 presented with a 2-week history of fever, night sweats, shortness of breath, and weakness. His Pao_2 at diagnosis was 67 mm Hg, and his A-a O_2 gradient was 53 mm Hg. Chest radiograph (**E**) showed bilateral mid and lower lung field infiltrates, and CT (**F**) showed bilateral infiltrates with lower lung consolidation.

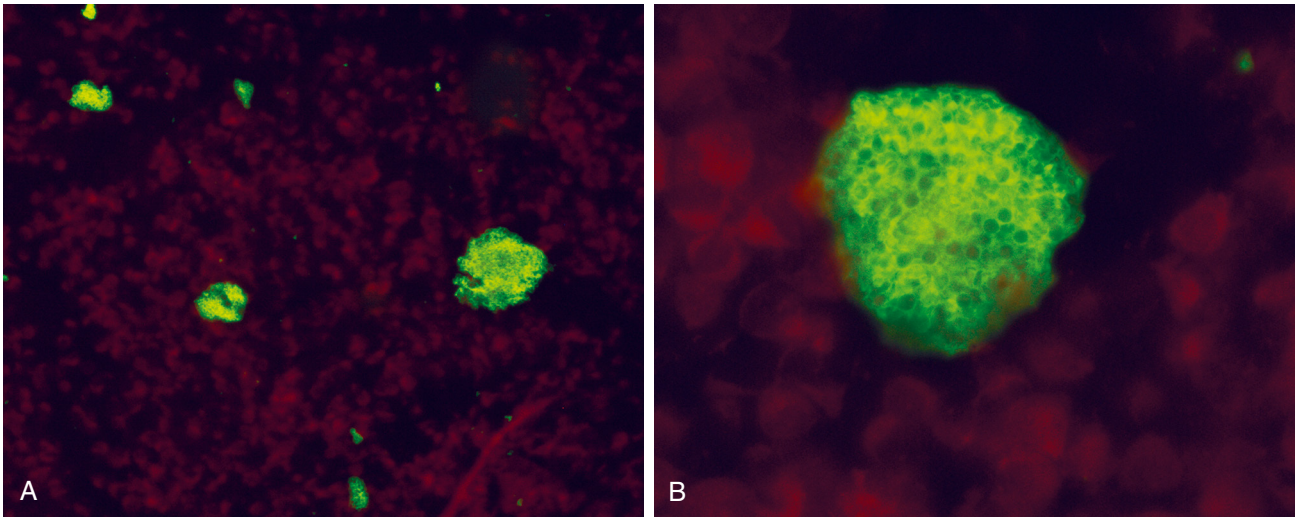

FIGURE 313-2. **Immunofluorescent detection of *Pneumocystis* using a direct fluorescent antibody test to examine an induced sputum sample. A,** Low power (100× original) allows visualization of multiple clusters of organisms staining bright green. **B,** With high power (400× original), individual organisms can be seen within a single cluster.

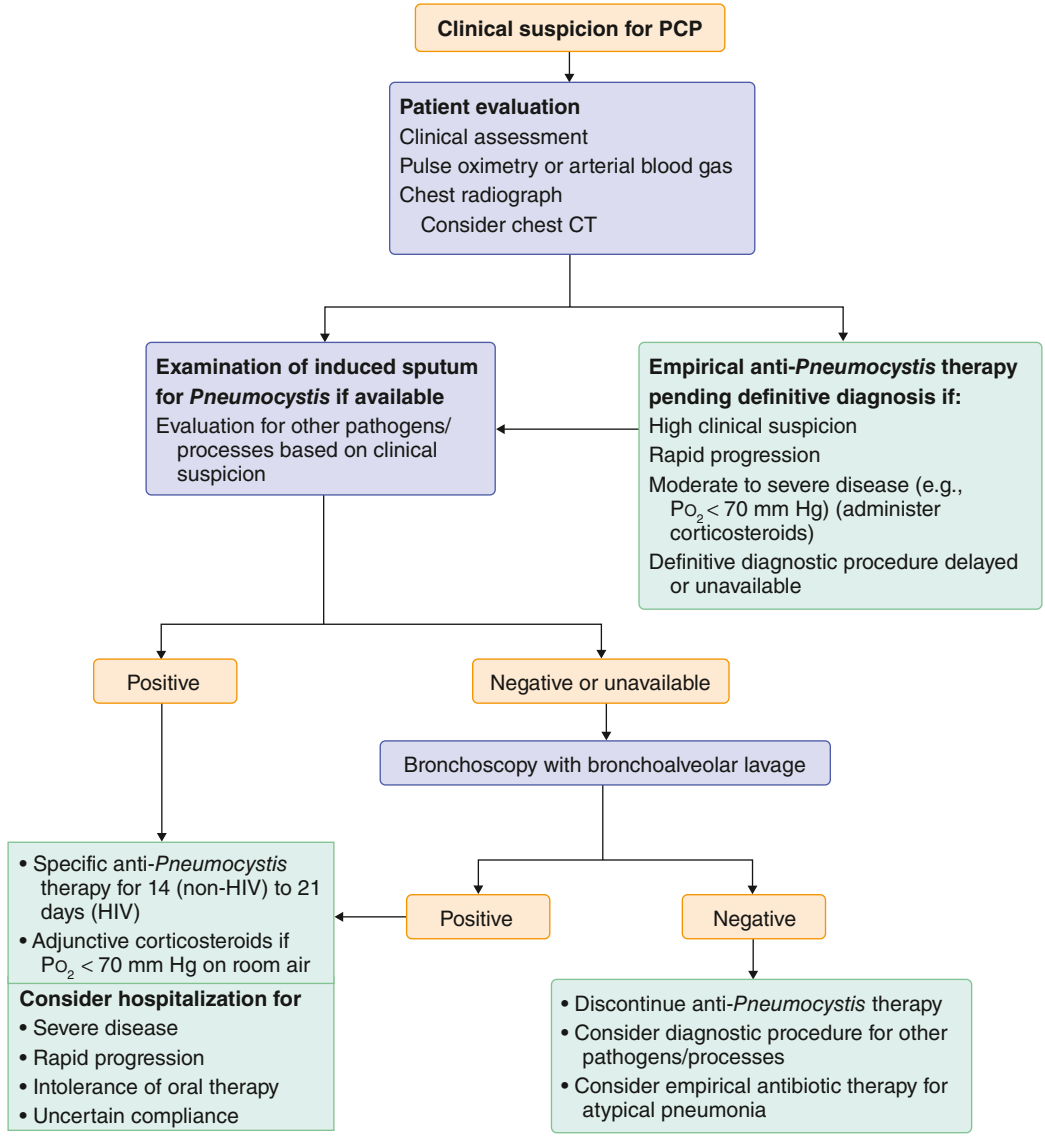

FIGURE 313-3. **Algorithm for the evaluation of patients with suspected *Pneumocystis* pneumonia (PCP).** CT = computed tomography; HIV = human immunodeficiency virus.

TABLE 313-1 DRUG REGIMENS FOR TREATMENT OF PNEUMOCYSTIS PNEUMONIA (PCP)

INDICATION	REGIMEN PREFERENCE	DRUG	ROUTE	DOSE	COMMENTS
Mild PCP: PaO_2 ≥70 mm Hg or A-a O_2 gradient <35 mm Hg	Preferred	Trimethoprim-sulfamethoxazole (TMP-SMX)	PO	2 double-strength (160 TMP + 800 SMX) tablets tid	
	Alternative	Trimethoprim plus	PO	5 mg/kg tid (15 mg/kg/d)	If possible test for G6PD deficiency before use
		Dapsone	PO	100 mg qd	
	Alternative	Clindamycin plus	PO	450 mg qid or 600 mg tid	If possible test for G6PD deficiency before use
		Primaquine	PO	30 mg (base) qd	
	Alternative	Atovaquone	PO	750 mg bid with food	
Moderate to severe PCP: PaO_2 <70 mm Hg or A-a O_2 gradient >35 mm Hg; moderate PCP (A-a O_2 gradient 35 to 45 mm Hg); can be treated with an oral regimen	Preferred	TMP-SMX	IV	5 mg/kg q8h TMP and 25 mg/kg q8h SMX (15 mg/kg/d TMP and 75 mg/kg/d SMX)	May switch to oral therapy following clinical improvement
	Alternative	Pentamidine	IV	3-4 mg/kg qd	Infuse over >60 min
	Alternative	Clindamycin plus	IV	600 mg q6h or 900 mg q8h	May switch to oral therapy following clinical improvement
		Primaquine	PO	30 mg (base) qd	No parenteral formulation is available
Adjunctive therapy for moderate to severe PCP: PaO_2 <70 mm Hg or A-a O_2 gradient ≥35 mm Hg	Preferred	Prednisone	PO	40 mg bid, days 1-5; 40 mg qd, days 6-10; 20 mg qd days 11-21	Begin as early as possible and within 72 hr; efficacy if started later has not been demonstrated
	Preferred	Methylprednisolone	IV	30 mg bid, days 1-5; 30 mg qd, days 6-10; 15 mg qd days 11-21	Use if parenteral therapy is necessary

Note: HIV-infected patients should receive 21 days of therapy; non-HIV patients should receive at least 14 days of therapy. Nonrandomized studies have found similar efficacy but better tolerability with lower doses of trimethoprim-sulfamethoxazole (e.g., ≤10 mg/kg/d TMP and 50 mg/kg/d SMX).
Bid = twice daily; G6PD = glucose-6-phosphate dehydrogenase; IV = intravenously; PO = orally; qd = daily; qid = 4 times daily; tid = 3 times daily.

Initiation of Antiretroviral Therapy

Many HIV-infected patients who are diagnosed with PCP are not yet receiving antiretroviral therapy. In general, it is preferable to initiate antiretroviral therapy while patients are being treated for PCP, because such therapy appears to be associated with an improved outcome (Chapter 358).[A2] Major concerns about initiating antiretroviral therapy include the risk for adverse drug reactions, which may be confused with adverse reactions to anti-PCP therapy; the risk for overlapping toxicities, which may complicate management; and the risk for immune reconstitution (Chapters 357 and 358), which has been rarely reported but can be life-threatening. Thus, many clinicians initiate antiretroviral therapy during or immediately after completion of anti-*Pneumocystis* therapy but after the patient has shown clinical improvement and is able to tolerate oral medications. A recurrence of symptoms after starting antiretroviral therapy may be caused by the immune reconstitution syndrome (IRIS; Chapter 358), which may require corticosteroid therapy. Although optimal treatment regimens have not been well-defined, a reasonable initial regimen for severe immune reconstitution inflammatory syndrome is 1 to 2 mg/kg of prednisone or equivalent, with a subsequent taper based on the improvement of symptoms.

Treatment Failure

In patients who have progressive respiratory deterioration despite therapy, it is critical to confirm the diagnosis of PCP, usually by bronchoscopy, to exclude other concurrent processes (e.g., other infections, heart failure, pulmonary emboli). Parenteral therapy should be used to eliminate concerns about drug absorption. Because patients who will ultimately respond can deteriorate for 3 to 4 days, especially in the absence of concomitant corticosteroid therapy, it is reasonable to wait 5 to 8 days before considering a change in drug therapy, other than to add corticosteroids if not already prescribed.

When a change in anti-PCP therapy is indicated because of nonresponse or toxicity, trimethoprim-sulfamethoxazole should be the first choice if the patient has not previously had a life-threatening adverse reaction to it. Rapid desensitization (similar to penicillin desensitization), ideally in consultation with an allergy specialist, can be considered in patients with prior adverse reactions, but patients with a history of Stevens-Johnson syndrome or toxic epidermal necrolysis should not be rechallenged. Clindamycin-primaquine likely is superior to pentamidine in patients who have failed to respond to a first-line regimen.

PREVENTION

Although *Pneumocystis* is transmitted by the airborne route, exposure to the organism appears to be ubiquitous in humans, thereby suggesting that avoidance of exposure may be difficult. Respiratory isolation of patients with active PCP is not required, although recent outbreaks in renal and liver transplant patients strongly suggest that a susceptible patient should not share a room with a PCP patient.

Trimethoprim-sulfamethoxazole is highly effective in preventing *Pneumocystis* infection in a wide range of susceptible populations.

Patients with HIV/AIDS

Primary prophylaxis is indicated in HIV/AIDS patients with CD4 counts below 200 cells/μL in the absence of antiretroviral therapy. Although 10 to 15% of patients who develop PCP have higher CD4 counts, the incidence is very low in such patients. Nevertheless, patients whose CD4 counts are greater than 200 cells/μL but who have a CD4 percentage of less than 14% or a history of an AIDS-defining illness are also candidates for primary prophylaxis. Patients who develop PCP should be placed on secondary prophylaxis after the treatment regimen is successfully completed. When the CD4 count has been above 200 cells/μL for at least 3 months (ideally in the setting of controlled HIV replication), both primary and secondary prophylaxis can be safely discontinued because the risk for developing PCP is no greater than in patients whose CD4 counts never fell below 200 cells/μL. Recent observational studies suggest that prophylaxis can also be safely discontinued in patients who have CD4 counts between 100 and 200 cells/μL and who have virologically suppressed HIV[20]; a reasonable approach is to discontinue prophylaxis in such patients if the viral load remains below detection limits for 3 to 6 months. In patients with CD4 counts less than 100 cells/μL, prophylaxis should be maintained regardless of the viral load.

Non-HIV Patients

Prophylaxis is also recommended for high-risk patients who do not have HIV infection (Table 313-2). Prophylaxis is recommended for allogeneic stem cell transplant recipients (Chapter 163) from the time of engraftment to at least 6 months after transplantation, and longer for patients who continue receiving immunosuppressive therapy or who have chronic graft-versus-host disease. For recipients of autologous stem cell transplants who have a lower risk for PCP, prophylaxis for 3 to 6 months should be considered if the degree of immunosuppression is substantial owing to underlying disease or therapy (e.g., patients with leukemia or lymphoma receiving intensive conditioning or immunosuppressive therapy). Cancer patients meeting the following conditions should receive prophylaxis: acute lymphocytic leukemia, throughout therapy; therapy with alemtuzumab, for 2 months after completion and until CD4 is greater than 200 cells/μL; therapy with idelalisib with or without rituximab, or with prolonged corticosteroids, or temozolomide combined with radiation therapy, at least through active therapy; therapy with purine analogues or other T-cell–depleting regimens, consider until CD4 is greater than 200 cells/μL.[21]

TABLE 313-2 RECOMMENDATIONS FOR ANTI-*PNEUMOCYSTIS* PROPHYLAXIS IN PATIENTS WITHOUT HIV INFECTION

CATEGORY	DISEASE OR DRUG	DURATION OF PROPHYLAXIS
Solid organ transplant recipients	All solid organ transplant recipients	At least 6-12 months post-transplant, with longer duration in certain settings as noted later
	Lung and small bowel transplant recipients	Lifelong
	Heart, liver, and renal transplant recipients	Some experts recommend prolonged, possibly lifelong, depending in part on the level of immunosuppression
	Greater immunosuppression (e.g., for GVHD, rejection)	Prolonged; maintain during periods of increased immunosuppression
	CMV disease	Prolonged
Hematologic malignancies	Acute lymphoblastic leukemia	From induction to end of maintenance
	Adult T-cell leukemia/lymphoma	From diagnosis to end of therapy
	Allogeneic stem cell transplant	For >6 months after engraftment and as long as immunosuppression continues; consider extending after cord blood transplant or when the GVHD prophylaxis involved T-cell depletion
	Autologous stem cell transplant, for recipients with substantial immunosuppression related to an underlying condition or its treatment, including brentuximab vedotin therapy	For 3 to 6 months post-transplant, longer if immunosuppression is continued
	Long-term corticosteroid treatment with >20 mg daily prednisone or the equivalent for >4 weeks	Until corticosteroid dose is reduced to below threshold levels
	Idelalisib	Per package insert, during therapy; consider continuing for 2 to 6 months after discontinuation
	Fludarabine + cyclophosphamide + rituximab therapy	>6 months after completion of treatment
	Alemtuzumab	Per package insert, >2 months after completion of therapy or until the CD4+ count is >200 cells/mL, whichever occurs later; consider continuing for >6 months after completion of therapy
	Temozolomide (in combination with radiotherapy)	Per package insert, during therapy, and until lymphopenia resolves; consider continuing for >6 months after completion of therapy
	Can consider for:	
	R-CHOP14 or escalated BEACOPP	Duration of immunosuppressive therapy
	Purine analogs (e.g., cladribine, fludarabine) or other T-cell–depleting agents	Duration of immunosuppressive therapy; consider continuing until CD4 cell count is >200 cells/μL
	Brain irradiation with high-dose corticosteroids	Duration of immunosuppressive therapy
	CD4 cell count <200 cells/μL	Until CD4 cell count is >200 cells/μL
Inflammatory bowel disease	On triple immunosuppressive therapy, including corticosteroids, methotrexate, thiopurines, and biologics	Duration of immunosuppressive therapy
	Can consider if:	
	On double immunosuppressive therapy, especially if one of these is a calcineurin inhibitor	Duration of immunosuppressive therapy
	For any combination of high-dose corticosteroids, low lymphocyte count, or JAK inhibitors	Duration of immunosuppressive therapy
Rheumatologic diseases	Long-term corticosteroids with >20 mg prednisone daily or the equivalent for >4 weeks, especially when combined with another immunosuppressive agent (e.g., cyclophosphamide)	Duration of immunosuppressive therapy
	Granulomatosis with polyangiitis and eosinophilic granulomatosis with polyangiitis receiving rituximab or cyclophosphamide	Duration of immunosuppressive therapy
Other indications	Prior *Pneumocystis* pneumonia	Until underlying risk factor resolves
	Long-term corticosteroids with >20 mg prednisone daily or the equivalent for >4 weeks in the setting of an underlying inflammatory disease or malignancy	Until corticosteroid dose is reduced to below threshold levels

Note: Criteria for anti-*Pneumocystis* prophylaxis in non-HIV patients and duration of prophylaxis are often not well-defined. Recommendations are based on product inserts, published guidelines, and expert opinion.
BEACOPP = bleomycin, etoposide, doxorubicin hydrochloride (Adriamycin), cyclophosphamide, vincristine (Oncovin), procarbazine, and prednisone; CHOP14 = cyclophosphamide, doxorubicin, vincristine, prednisolone on a 14-day interval; CMV = cytomegalovirus; GVHD = graft-versus-host disease; JAK = Janus kinase.

For solid organ transplant patients, prophylaxis has been used primarily in centers with a known incidence greater than 3%. Guidelines recommend the administration of prophylaxis for 6 to 12 months[22] in most solid organ transplant patients, with lifelong prophylaxis in recipients of lung and intestinal transplants, and consideration of extended prophylaxis in recipients of heart, liver, and renal transplants. If extended therapy is not used, prophylaxis is recommended during periods of increased risk (e.g., recent or concurrent cytomegalovirus infection, increased immunosuppression for graft rejection, higher-dose corticosteroid therapy, and treatment with rituximab or belatacept).[23]

Patients with inflammatory bowel disease (Chapter 127) appear to be at increased risk as newer immunosuppressive agents are used. Consensus-based guidelines recommend prophylaxis for patients who are receiving triple immunomodulator therapy.

Although there are no consensus guidelines on the use of prophylaxis for patients receiving corticosteroids, one reasonable approach is to provide prophylaxis to patients with an underlying immunosuppressive or inflammatory disease who receive at least 20 mg of prednisone or equivalent for longer than 1 month.[24,25] Among non–HIV-infected patients, a CD4 count below 200 cells/μL also appears to increase susceptibility. However, CD4 counts are not routinely measured, and clinical decisions generally are not based on them.

Trimethoprim-sulfamethoxazole, which is the first-line agent for prophylaxis in all populations (Table 313-3), is highly effective.[A3] Limited data from small studies suggest that one half-strength dose per day may be as efficacious and less toxic compared with higher doses.[A4,A5] Alternatives include dapsone alone or combined with pyrimethamine plus leucovorin, atovaquone, and aerosolized pentamidine. Patients who are receiving pyrimethamine, sulfadiazine, and leucovorin to treat toxoplasmosis do not require additional anti-*Pneumocystis* prophylaxis because this regimen also prevents PCP.

HIV-infected patients with a prior history of a mild sulfa allergy (e.g., mild rash, excluding those with prior Stevens-Johnson syndrome or toxic epidermal necrolysis) can often be safely rechallenged with trimethoprim-sulfamethoxazole. Dose escalation over a 6- to 13-day period is associated with better tolerance than direct rechallenge with full-dose trimethoprim-sulfamethoxazole, and up to 75% of patients can continue to receive trimethoprim-sulfamethoxazole for at least 6 months.

PROGNOSIS

Mortality for untreated PCP approaches 100%. With therapy, the survival rate for HIV-infected patients with confirmed PCP is now as high as 95%, but a poorer survival rate of about 75% has been reported in patients without HIV

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Alternative	Dapsone	PO	100 mg daily or 50 mg twice daily	Test for G6PD deficiency before use
Alternative	Dapsone plus	PO	50 mg daily	Test for G6PD deficiency before use; also active in preventing toxoplasmosis
	Pyrimethamine plus	PO	50 mg once weekly	
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Alternative	Atovaquone	PO	1500 mg daily with food	Likely active in preventing toxoplasmosis; efavirenz can decrease concentrations
Alternative	Pentamidine	Aerosol	300 mg via the Respirgard II nebulizer once monthly	Not active in preventing toxoplasmosis
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Note: Patients receiving pyrimethamine-sulfadiazine and atovaquone therapy for toxoplasmosis do not appear to need additional prophylaxis for PCP; patients receiving clindamycin-pyrimethamine therapy for toxoplasmosis will need additional prophylaxis for PCP.
G6PD = glucose-6-phosphate dehydrogenase; IV = intravenously; PO = orally.

infection. Risk factors for death in HIV-infected patients include more severe hypoxia, older age, recurrent episodes of PCP, low hemoglobin level, and the presence of comorbid conditions. Higher LDH levels may be associated with increased mortality in both HIV and non-HIV patients.[26] Although mortality for patients admitted to an intensive care unit (ICU) is high, survival for HIV-infected ICU patients now approaches 75%.

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314 MYCETOMA AND DEMATIACEOUS FUNGAL INFECTIONS

PETER G. PAPPAS AND DIMITRIOS P. KONTOYIANNIS

DEFINITION

Dematiaceous fungi represent a large group of fungal organisms characterized by the presence of abundant melanin in the cell wall. This melanin gives rise to a brown-black coloration on artificial culture media and in histopathologic specimens. A related term, *phaeohyphomycosis,* refers broadly to infection by these pigmented fungi. The two terms are often used interchangeably. Dematiaceous fungal infections generally fall into three broad categories: mycetoma (e.g., Madura foot), chromomycosis (also known as chromoblastomycosis), and phaeohyphomycosis.[1,2]

The Pathogens

More than 100 dematiaceous fungi have been identified as causes of human disease. The most common organisms and their related conditions are listed in Table 314-1. The taxonomy of the dematiaceous fungi is complicated because these agents belong to different classes, including Hyphomycetes, Ascomycetes, Basidiomycetes, Coelomycetes, and Zygomycetes. The most common agents of phaeohyphomycosis include species in the following genera: *Alternaria, Bipolaris, Curvularia, Exophiala, Cladosporium, Cladophialophora, Fonsecaea, Exserohilum, Verruconis, Phialophora, Phaeoacremonium,* and *Chaetomium*. These agents are ubiquitous saprophytes of soil and decaying matter, and some are important plant pathogens. In tissue, these organisms exist as yeastlike cells, septated hyphae, or a combination of yeast and hyphae. Most of these organisms demonstrate melanin pigmentation (brownish coloration) in the cell walls on microscopic examination.

EPIDEMIOLOGY

Dematiaceous fungi are found in the environment worldwide. Allergic fungal sinusitis associated with dematiaceous fungi appears to be more common in the southern United States. Chronic infections of the lower extremities are more commonly seen in men and in tropical areas. Chromomycoses are more prevalent in rural populations in the tropics and are hyperendemic in certain geographic areas such as Madagascar, India, Brazil, and other poorer countries in Africa and South America. Cutaneous infections usually occur as a result of minor skin trauma and direct inoculation of the organism.

Phaeohyphomycosis is an important emerging fungal infection in medically advanced regions, particularly among immunocompromised patients such as recipients of solid organ[3] and hematopoietic stem cell transplants, patients with prolonged neutropenia, and other immunocompromised individuals. Risk factors for extracutaneous infection include intravenous drug use, chronic sinusitis, freshwater immersion, and chronic immunosuppression. Phaeohyphomycosis is reported in human immunodeficiency virus (HIV)-infected patients but is far less common than other opportunistic fungi. Extracutaneous invasive disease can also occur in otherwise normal patients but is much less common. Subtle host immune abnormalities, including *CARD*-9 mutations and other disorders associated with T_H17 deficiency, have been identified in a subset of these previously "normal" individuals.

Dematiaceous fungal infections can be seen following invasive procedures in health care settings.[4] In the United States, a striking example was an epidemic of fungal meningitis, epidural abscess, sacroiliitis, vertebral osteomyelitis, discitis,

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EPIDEMIOLOGY

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ABSTRACT

Mycetoma and dematiaceous fungal infections are caused by over 100 fungal species that have the characteristic of being "melanized" or pigmented, thereby leading to a brown or darkish pigmentation in histopathologic samples and in culture. These organisms cause a range of disorders that vary from benign conditions such as onychomycosis, to extremely destructive and disfiguring mycetoma, to life-threatening, invasive infection in an immunocompromised individual. Diagnosis is based on the identity of characteristic fungi on pathologic specimens and is confirmed by culture. The triazole antifungals (e.g., itraconazole, voriconazole, and posaconazole) have the best in vitro and clinical activity versus these pathogens. A combined medical/surgical approach is preferred for patients with mycetoma and extensive tissue involvement and for patients with disseminated phaeohyphomycosis, especially if their central nervous system is involved.

KEYWORDS

phaeohyphomycoses
dematiaceous fungi
mycetoma
Madura foot
chromomycosis

and peripheral arthritis that involved over 750 persons and was caused by *Exserohilum rostratum* following injection of contaminated methylprednisolone acetate from a single compounding pharmacy. Previous reports of infection caused by *Exophiala* species following contaminated steroid injections, infected breast implants, other prosthetic materials, and, rarely, contaminated intravascular catheters and intravenous fluids underscore the importance of these organisms as potential health care–associated pathogens.

Mycetoma has a global distribution (E-Fig. 314-1), but it occurs primarily in the tropical zones. The disorder is quite prevalent in India, Latin America, the Middle East, and sub-Saharan Africa (the "mycetoma belt").[5] Sudan has a particularly high burden of mycetoma. Indigenously acquired mycetoma is sporadic in North America and Europe. The relative frequency of actinomycetoma and eumycetoma differs among geographic areas. Eumycetoma is more common in India and Africa, whereas actinomycetoma is more common in Central and South America. The causative agents of mycetoma differ in their geographic distribution. For example, *Scedosporium apiospermum* is the most common agent of mycetoma in North America, and *Actinomadura* and *Nocardia* species are predominant in Central and South America. *Leptosphaeria senegalensis* and *Madurella mycetomatis* are predominant in sub-Saharan Africa and India.

The ratio of male to female patients with mycetoma is 5 : 1. The disease is typically seen in rural areas and in persons susceptible to local trauma and contamination from soil. Hence, farmers, gardeners, woodcutters, herders, and people who work outside while barefoot are more susceptible to this infection.

PATHOBIOLOGY

Most cases of chromomycosis are caused by three species: *Fonsecaea pedrosoi, Cladosporium carrionii*, and *Phialophora verrucosa*. The distinctive histologic appearance is characterized by the presence of thick-walled, dark brown bodies known as *sclerotic cells* or *copper pennies*, which represent individual organisms and may be seen in clusters or as single cells. The etiologic fungi causing chromomycosis are indistinguishable on histologic examination of tissue.

TABLE 314-1 DEMATIACEOUS FUNGI AND ASSOCIATED DISEASES

CLINICAL CONDITION	COMMON ETIOLOGIC AGENTS
Chromomycosis	*Fonsecaea pedrosoi* *Cladophialophora carrionii* *Phialophora verrucosa*
Cutaneous or subcutaneous disease	*Exophiala jeanselmei* *Exophiala dermatitidis* *Phialophora* spp *Bipolaris* spp *Alternaria* spp
Sinusitis	*Bipolaris* spp *Curvularia* spp *Exserohilum* spp *Alternaria* spp
Central nervous system	*Cladophialophora bantiana* *Verruconis gallopava* *Rhinocladiella mackenziei* *Chaetomium atrobrunneum* *Exophiala dermatitidis*
Health care associated	*Exserohilum rostratum* *Exophiala* spp
Disseminated	*Exophiala dermatitidis* *Exophiala jeanselmei* *Bipolaris* spp *Verruconis gallopava* *Phialophora* spp *Lomentospora prolificans*
Eumycetoma	*Madurella mycetomatis* *Exophiala* spp *Curvularia* spp *Leptosphaeria senegalensis*
Non-dematiaceous fungi	*Scedosporium apiospermum* *Acremonium* spp *Fusarium* spp

spp = species.

Mycetoma is caused by two groups of organisms: (1) the filamentous aerobic actinomycetes (actinomycetoma) and (2) a wide range of saprophytic soil and woody plant fungi (eumycetoma). Eumycetoma accounts for about 50% of cases of mycetoma.[6] A variety of *Nocardia* (Chapter 306) species (e.g., *Nocardia brasiliensis, Nocardia asteroides*), *Actinomadura* species (e.g., *Actinomadura pelletieri, Actinomadura madurae*), and *Streptomyces* species (e.g., *Streptomyces somaliensis*) cause actinomycetoma. Most cases of eumycetoma are due to *Madurella* species (e.g., *Madurella mycetomatis* causes 70% of all cases of eumycetoma worldwide). Other causes of eumycetoma include some nondematiaceous fungi such as *Fusarium* species, *Acremonium* species, *Scedosporium apiospermum,* and several phaeohyphomycetes, including *Exophiala* and *Curvularia* species. Eumycetoma is further characterized on the basis of the color of the granular drainage: white- to yellow-grain mycetomas (white piedra) are typically caused by hyalohyphomycetes (e.g., *S. apiospermum, Fusarium* species, *Acremonium* species), and black-grain eumycetomas are caused by *Madurella* species and other less common fungi.

Local trauma (e.g., wood splinters), introduces a mycetoma-causative organism into the skin and subcutaneous tissues, initiates a chain of events that leads to chronic, suppurative granulomatous inflammation, tumefaction, formation of multiple fistulous tracts and sinuses, deep abscesses, fibrosis, and scar formation. Infection can extend to adjacent connective tissue across the lines of least resistance (fascia) and ultimately to bones, muscles, nerves, and tendon sheaths, thereby leading to gross anatomic distortion of the affected site.

The genetics and immunopathogenesis of mycetoma are not well defined, but it appears that there are differences in host susceptibility as some infected persons have impaired or delayed hypersensitivity reactions or polymorphisms in genes encoding for chemokines (e.g., CCL50) and cytokines (e.g., interleukin-10). Mycetoma does not appear to be more common in immunocompromised hosts.

CLINICAL MANIFESTATIONS

Chromomycosis

Chromomycosis is manifested as a cutaneous or subcutaneous lesion that may range in size from a small papule to a large confluent plaque involving a major portion of an extremity (Fig. 314-1). Single or multiple lesions are seen; ulceration may occur. Lesions may remain unchanged in size and consistency for months or years, although most tend to progress in the absence of specific therapy. Chronic lesions may become dry and crusted with a raised border, which may be smooth or irregular, and which may take on a verrucous, warty appearance. Multiple lesions can coalesce to form larger plaques in which central scarring may develop. Cutaneous lesions usually remain confined to one anatomic site, although nodular lymphangitis and multifocal cutaneous disease from autoinoculation may occur. Common complications include local disfigurement due to scarring and extensive tissue involvement. Disseminated disease involving visceral organs is rare.

Phaeohyphomycosis

Superficial phaeohyphomycosis is characterized by tinea nigra and black piedra. Tinea nigra is a darkening of the skin caused by growth of *Phaeoannellomyces*

FIGURE 314-1. A 42-year-old renal transplant recipient with lower extremity chromomycosis due to *Fonsecaea pedrosoi*.

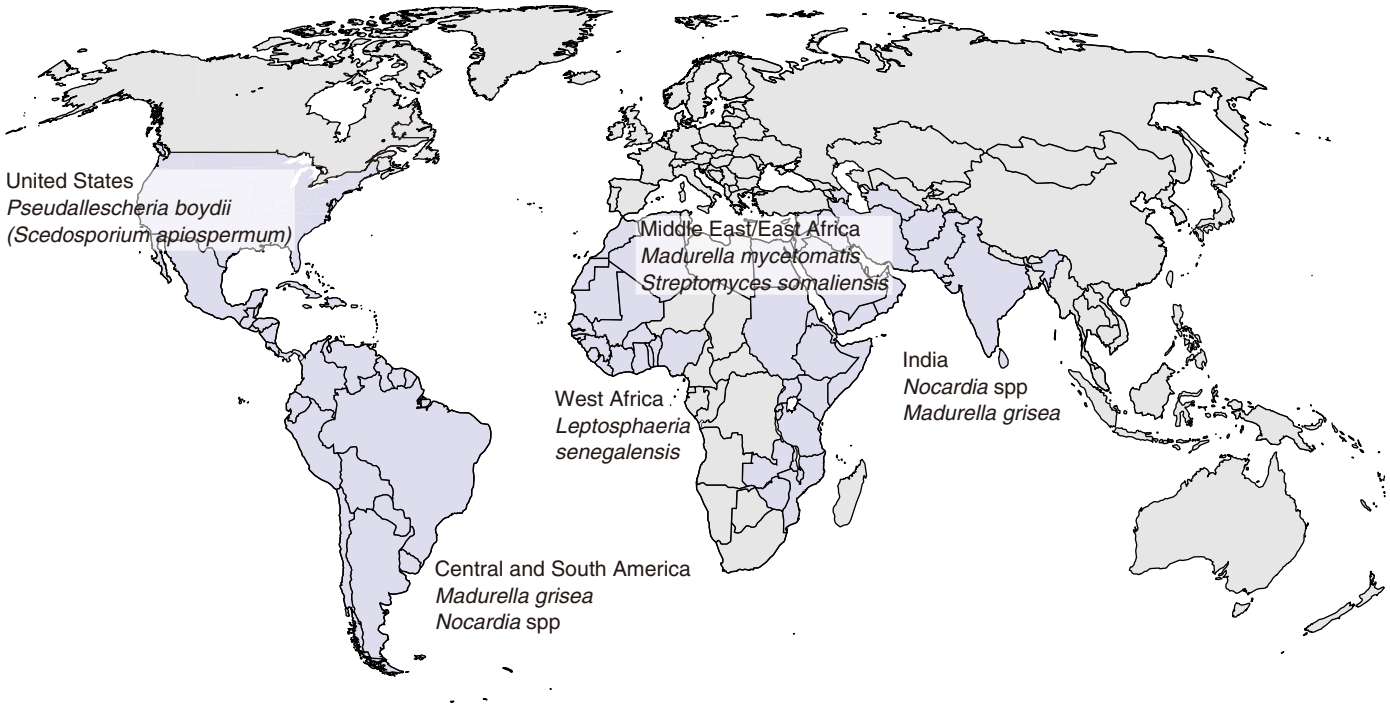

E-FIGURE 314-1. **Predominant agents of mycetoma according to region.**

werneckii in the stratum corneum. Black piedra is associated with the development of focal thickening on the hair shaft and results from colonization of the shaft by *Piedraia hortae*. Cutaneous phaeohyphomycosis involves deeper skin structures and results in dermatomycosis and onychomycosis; this lesion is frequently due to agents such as *Scytalidium* and *Phyllosticta* species.

Subcutaneous phaeohyphomycosis may be confused clinically with chromomycosis. Patients have discrete subcutaneous nodules or cysts that result from direct inoculation or penetrating trauma. The most common organisms are *Exophiala jeanselmei, Exophiala dermatitidis, Alternaria alternans, and Phialophora* species. Mycotic keratitis as a result of infection with *Curvularia, Exophiala*, and *Exserohilum* species may occur after corneal trauma or surgery.

Foreign body–related infections are seen in patients undergoing chronic ambulatory peritoneal dialysis in whom fungal peritonitis develops, in patients with indwelling intravenous catheters, and in other devices such as breast implants.

Fungal sinusitis (Chapter 394) is commonly associated with dematiaceous fungi and can be manifested as allergic fungal sinusitis, a fungus ball in a sinus cavity, and invasive fungal sinusitis associated with extension into bone, soft tissue, and the central nervous system. This destructive process is indistinguishable from that of rhinocerebral zygomycosis (Chapter 312) or invasive *Aspergillus* sinusitis (Chapter 311). *Bipolaris, Curvularia, Exserohilum*, and *Alternaria* species are the most common organisms causing invasive fungal sinusitis.

Systemic phaeohyphomycosis may result from direct extension from a colonized area or dissemination from a distant source. Most patients with systemic disease have significant underlying immunosuppression, and the organisms have a proclivity for involvement of the brain, lungs, endocardium, and other visceral organs. Among patients with primary central nervous system disease, *Cladophialophora bantiana, Rhinocladiella mackenziei,* and *Chaetomium atrobrunneum* are the most common etiologic agents, and the majority of cases are in otherwise healthy patients with little or no underlying immunodeficiency. Among immunocompromised patients, *Verruconis gallopava, Bipolaris* species, and *Exophiala dermatitidis* are seen more commonly.

In severely immunocompromised patients, especially patients who have hematologic malignancies or have received a stem cell transplant with or without prolonged and profound neutropenia, infection with *Lomentospora prolificans* can present as multiorgan dissemination. Infection with this multidrug-resistant pathogen is associated with an exceptionally high mortality rate.

Mycetoma

Mycetoma is a chronic, slowly progressive infection that starts in the subcutaneous tissue and spreads across tissue planes to contiguous structures.[7] The lesion is usually confined to one anatomic site. The clinical manifestations and natural history of mycetoma are variable and, to some degree, related to the pathogenic agent involved. For example, the progression of eumycetoma tends to be slower than that of actinomycetoma. In addition, eumycetoma lesions tend to be more confined and have less inflammation and fewer granulomas and fistulas but more fibrosis compared with actinomycetoma lesions. The foot is the most common site involved in mycetoma (Fig. 314-2), followed by the hands, but any other part of the body may become involved. Painless nodular and/or papular swelling is a common early manifestation of mycetoma, followed by a slow evolution to painless, fixed woody induration. This infection typically runs a chronic, relentless course, sometimes spanning several decades. It is characterized by recurring cycles of suppuration, draining sinuses, bacterial superinfection, and scar formation. Old sinuses close, and new ones occur. Satellite lesions are common. Constitutional symptoms are rare. The presence of fever often indicates bacterial superinfection. Substantial bone involvement mimicking chronic osteomyelitis with cavitary bone lesions, periosteal reaction or sclerosis (seen with radiography, computed tomography, or magnetic resonance imaging [MRI] studies), osteoporosis, and reactive periosteal bone formation may occur. However, pathologic fractures are rare. Because nerves are relatively spared, neuropathic manifestations are uncommon. Inexorable limb deformity and misuse because of destruction of deeper tissues may be seen in chronic, refractory, and advanced cases. Regional lymphadenitis may occur, but mycetoma does not spread hematogenously, so visceral dissemination is not seen.

DIAGNOSIS

The diagnosis of a dematiaceous fungal infection is suggested by direct examination of a clinical specimen with a 10% potassium hydroxide preparation or special stains to demonstrate pigmentation in the cell walls of these organisms. For patients with chromomycosis, the finding of sclerotic cells or copper pennies

FIGURE 314-2. Clinical presentation of mycetoma. A 40-year-old farmer from rural Venezuela with a 10-year history of foot edema and slowly progressive deformity following an injury caused by being struck by a hammer presented with chronic crusted plaques, multiple confluent tender abscesses with fistulization, and release of black grains. The range of motion of the patient's ankle and foot joints was limited, but the joints were not painful. A deep skin biopsy with hematoxylin and eosin staining, periodic acid–Schiff staining, foot radiography, sampling of black grain smears, and a mycology culture were performed. The foot radiograph showed osteofibrosis, destruction of articular surfaces, osteoporosis, and ankylosis, and *Madurella* spp grew in the culture. (Courtesy of Dr. M. Mendoza, Instituto De Biomedicina, Laboratorio de Micología, San Jose Caracas, Venezuela.)

on skin biopsy is characteristic, and special stains are usually unnecessary. For patients with other forms of phaeohyphomycosis, the Fontana-Masson stain is useful in distinguishing organisms with significant melanin content. Culture remains the means by which a specific etiologic diagnosis is established, and the identity of the organism is largely based on colony and microscopic morphology. A reliable polymerase chain reaction–based diagnostic assay was developed for *Exserohilum rostratum* in the context of the fungal meningitis outbreak, but serologic studies and molecular diagnostics are not generally available for other organisms, especially in endemic settings.

The diagnosis of mycetoma is complicated by the fact that nonfungal organisms are frequent etiologic agents. The diagnosis is suspected in the presence of granular drainage from a characteristic skin lesion. However, grains in tissue alone may be difficult to culture because they may be composed of dead organisms. Furthermore, grains may be contaminated by surface bacteria or fungi. Thus, a deep-tissue biopsy specimen is ideal for staining (hematoxylin and eosin, Gram stain, modified Ziehl-Neelsen stain, Gomori methenamine silver, periodic acid–Schiff) and appropriate selective bacterial and fungal cultures. Alternatively, aspiration of grains from unopened sinus tracts can provide suitable material for culture. The culture should be maintained for several weeks because some of the causative agents of mycetoma (e.g., *Nocardia* and *Streptomyces* species) may require 4 to 6 weeks for detection by culture methodology.

Differential Diagnosis

The specific manifestations of chromomycosis, cutaneous and subcutaneous phaeohyphomycosis, and mycetoma are often confused with other entities.[8] It is important to consider benign or malignant skin tumors, other chronic granulomatous lesions (e.g., thorn granuloma), and verrucous leishmaniasis (Chapter 319). Deep skin and subcutaneous infections due to other fungi (e.g., blastomycosis [Chapter 308], sporotrichosis [Chapter 308], cryptococcosis [Chapter 309], and coccidioidomycosis [Chapter 308]), and higher-order bacteria (e.g., nocardiosis [Chapter 306], mycobacteriosis [Chapter 299 and 300]), must be considered. Skin lesions without fistulas can occasionally resemble unusual forms of sporotrichosis (mycetomatous lymphatic sporotrichosis) and granulomatous dermatophyte infections. The latter infection, which is typically seen in Africans and sometimes called pseudomycetoma (Majocchi granuloma), is a painless granulomatous induration of the skin and subcutaneous tissues caused by dermatophytes that may be associated with grains consisting of fungi. Unlike mycetoma, pseudomycetoma is confined to the skin and subcutaneous tissue and does not spread to deeper tissues. Chronic severe botryomycosis (typically caused by *Staphylococcus aureus*; Chapter 267) with purulent exudates, grains, and draining sinus tracts may be confused with mycetoma. Actinomycosis (Chapter 304), which is caused by endogenous microaerophilic actinomycetes, also has a propensity for grains and formation of draining sinus tracts, but its location is characteristic in

the neck, chest, abdomen, and pelvis. Differentiation between mycetomas with bone involvement and chronic osteomyelitis or osseous tumors may be challenging. Ultrasonography has been used to reliably differentiate mycetoma from either tumor or osteomyelitis.[9] The dot-in-circles sign seen on MRI (tiny hypodense foci, representing grains, within high-hyperintensity spherical lesions, representing granulomas, scattered by areas of fibrosis) may provide an early and specific diagnostic clue for mycetoma.

TREATMENT

Chromomycosis

For chromomycosis, surgical excision of a cutaneous or subcutaneous lesion is often curative,[10] although antifungal therapy (Chapter 307) is usually given in conjunction with surgery. The triazoles, including itraconazole (200 mg orally twice daily), voriconazole (200 mg twice daily), and posaconazole (300 mg daily), demonstrate the best in vitro activity, although clinical studies with these agents are very limited. Terbinafine (500 mg orally twice daily) is an effective alternative for chromomycosis. Duration of therapy, with or without surgical excision, is generally 3 to 12 months, depending on clinical response.

Phaeohyphomycosis

For phaeohyphomycosis, the orally available expanded-spectrum triazoles, including itraconazole (200 mg twice daily), voriconazole (200 mg twice daily), posaconazole (300 mg daily), and isavuconazole (372 mg once daily), demonstrate excellent in vitro activity against the most common pathogenic dematiaceous fungi.[11] Regardless of which of these agents is selected, the recommended duration of treatment is at least 6 months. Amphotericin B has modest in vitro activity against most of these fungi and is usually reserved for patients with life-threatening or disseminated disease. Amphotericin B is administered as 0.6 to 1.0 mg/kg daily for up to 6 weeks to gain control of the infection before transitioning to oral therapy with an azole, usually to complete a dependent 6-month course of therapy but sometimes as longer term chronic suppressive therapy.

Most patients with epidemic *Exserohilum rostratum* infections have been treated successfully with voriconazole 4 mg/kg twice daily (intravenous, then oral) for up to 6 months, with or without a lipid formulation of amphotericin B (3 to 5 mg/kg daily), for severe central nervous system involvement. Posaconazole (300 mg orally daily for up to 6 months) has been used as salvage therapy for patients who are intolerant to voriconazole or in whom voriconazole has failed, and isavuconazole is also an option.[12]

The length of antifungal therapy for any of the systemic phaeohyphomycoses is unclear. However, therapy should probably be continued for at least 4 to 6 months or until 1 month after resolution of all signs and symptoms of disease.

Mycetoma

For mycetoma, therapy is individualized because no therapy had been proven to be preferred. Treatment is dependent upon distinguishing actinomycetoma from eumycetoma, identification of the causative pathogen, and the extent of tissue invasion.[13]

For actinomycetoma, optimal treatment consists of antimicrobial therapy (at least 5 to 6 weeks) in conjunction with limited debulking surgery in selected cases. Trimethoprim-sulfamethoxazole (2 double-strength tablets twice daily for 5 weeks) plus amikacin (7.5 mg/kg twice daily for 3 weeks) is usually successful. Alternative options include a combination of tetracycline (100 mg twice daily), dapsone (100 mg daily), and/or rifampin (600 mg daily), each administered orally, together with intramuscular streptomycin (0.5 to 1 g daily) for 4 to 6 weeks. These agents are used in different sequences and combinations depending on the organism (e.g., trimethoprim-sulfamethoxazole with or without dapsone for *Nocardia* species (Chapter 306), streptomycin or amikacin with dapsone for *A. madurae*). Parenteral streptomycin is usually reserved for refractory cases that do not respond to oral therapy. Response to therapy is slow (usually within 4 weeks), and relapse is common. Several cycles of therapy may be necessary for chronic recurrent disease.

The best treatment results for eumycetoma have been achieved with at least 9 to 12 months of agent such as ketoconazole (200 to 400 mg daily) or itraconazole (200 to 400 mg daily), combined with appropriate surgery. In vitro activity and clinical experience with the newer azoles (voriconazole, débridement, and isavuconazole) and terbinafine are promising, but data are very limited. Clinical results with amphotericin B for refractory cases have been generally disappointing, and many of the causative agents demonstrate in vitro resistance to this compound.

Surgery often plays a pivotal role in eumycetoma because most disease is refractory to antifungal therapy alone. The need and extent of surgery depend on the specific agent and the degree of tissue invasion. Wide-margin surgery for localized lesions is usually curative. Extensive débridement and disfiguring surgery are reserved for severe and refractory cases.

PREVENTION

Mycetoma is a frequently ignored infection despite the significant socioeconomic burden it causes in many impoverished regions of the world. No preventive measures are of proven efficacy, but consistent use of footwear seems advisable, because minor trauma is an important predisposition to development of foot mycetoma.

PROGNOSIS

The prognosis for mycetoma depends on the anatomic site and degree of tissue involvement.[14] Extension into bony structures is associated with the worst long-term consequences, so early diagnosis and intervention are critical in optimizing outcomes.

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315 ANTIPARASITIC THERAPY

PHILIP J. BUDGE AND RICHARD D. PEARSON

Although substantial progress has been made in reducing the impact of protozoal and helminthic infections, parasitic diseases remain a major cause of morbidity and mortality worldwide, particularly in impoverished tropical regions. In the United States, parasitic diseases are most often encountered among immigrants and international travelers to endemic areas and among a growing number of persons with compromised immunity due to human immunodeficiency virus/acquired immunodeficiency syndrome (HIV/AIDS), organ transplants, immunosuppressive medications, neoplasms, or other causes. A number of drugs (Table 315-1) are available to treat protozoal and helminthic diseases, but physicians practicing in industrialized countries may not be familiar with their use. This chapter focuses on their therapeutic indications, pharmacology, and major side effects. Generalizations emerge that help in organizing an otherwise vast array of information.

Detailed information about the diagnosis and treatment of specific parasitic diseases can be found in the chapters to follow and from the U.S. Centers for Disease Control and Prevention (CDC) (see A-Z Index; https://www.cdc.gov/parasites/az/index.html).[1] Many antiparasitic drugs are commercially available in the United States, whereas others can only be obtained directly from the manufacturer, special pharmacies, or the CDC Drug Service through investigational new drug protocols. Major challenges in recent years have arisen from a shortage of some antiparasitic drugs and, in the United States, massive increases in the cost of others. Some drugs used to treat bacterial or fungal pathogens are also effective in the treatment of parasitic diseases (see Chapters 266 and 307).

PROTOZOAL DISEASES

MALARIA (*PLASMODIUM* SPECIES): TREATMENT AND PREVENTION

Most drugs that are available for the treatment and prophylaxis of malaria act on *Plasmodium* species within erythrocytes. The antimalarial drug of choice depends on the infecting species and the likelihood of resistance (Chapter 316). Resistance to chloroquine is widespread among *Plasmodium falciparum* in most regions of the world and well documented in *Plasmodium vivax* in some areas. Artemisinin-based combination therapy (ACT), including the fixed drug combination artemether-lumefantrine, is the treatment of choice for acute malaria acquired in areas with chloroquine resistance. The fixed drug combination atovaquone-proguanil or the antibiotic doxycycline is commonly used for prophylaxis in travelers to areas with chloroquine-resistant *Plasmodium* species. Chloroquine is used for treatment and prophylaxis only in areas where *Plasmodium* species are sensitive. Only primaquine and tafenoquine kill hypnozoites of *P. vivax* and *Plasmodium ovale* in the liver. Country-specific recommendations for prophylaxis and treatment are provided by the CDC (www.cdc.gov/travel/) and in "CDC Health Information for International Travel 2020."[2]

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ABSTRACT

Parasitic infections remain a major cause of morbidity and mortality worldwide, particularly in impoverished tropical regions. It is helpful to group parasitic diseases and treatment into those caused by protozoa, single-celled organisms that multiply by cell division, and helminths, multicellular worms and flukes with complex internal structures. The most important protozoal diseases are attributable to members of the Apicomplexa that cause malaria, babesiosis, toxoplasmosis, and cryptosporidiosis and to the Kinetoplastida that are responsible for Chagas disease, human African trypanosomiasis (sleeping sickness), and leishmaniasis. Ameba and other types of protozoa also are important human pathogens. Helminths are subdivided into nematodes, or roundworms, which can be grouped into those that live in the gastrointestinal tract or elsewhere in the body, and platyhelminths, or flat worms, which are subdivided into cestodes, or tapeworms, and trematodes, or flukes. Depending on the helminth, albendazole, diethylcarbamazine, ivermectin, praziquantel, or another drug is used. Shortages of some antiparasitic drugs and substantial increases in the cost of others complicate therapy. Many antiparasitic drugs are commercially available in the United States; others can only be obtained from the Centers for Disease Control and Prevention Drug Service.

KEYWORDS

artemisinin-based combination therapy
granulomatous amebic encephalitis
leishmaniasis
malaria
miltefosine

TABLE 315-1 TREATMENT OF PARASITIC DISEASES

DRUG	INDICATIONS AND COMMENTS	USUAL ADULT DOSAGES
1. MALARIA (*PLASMODIUM* SPECIES): TREATMENT AND PREVENTION		
Artemether-lumefantrine	Uncomplicated malaria treatment (in combination with primaquine if *P. vivax* or *P. ovale*)	4 tablets (20 mg artemether/120 mg lumefantrine) PO per dose × 6 doses
Artesunate	Severe malaria: duration depends on response and ability to tolerate PO therapy	2.4 mg/kg/dose IV q12h
Atovaquone-proguanil	Malaria prophylaxis; begin 2 days prior to travel and continue through 1 week post-travel Malaria treatment (use in combination with primaquine if *P. vivax* or *P. ovale*)	1 tablet (250 mg atovaquone/100 mg proguanil) PO daily 4 tablets (250 mg atovaquone/100 mg proguanil) PO daily × 3 days
Chloroquine	Malaria prophylaxis (ONLY in areas of known susceptibility); begin 2 weeks prior to travel and continue through 4 weeks post-travel	500 mg (300 mg base) weekly
Clindamycin	Malaria treatment (in combination with quinine sulfate or primaquine)	20 mg/kg/day PO divided q8h × 7 days
Doxycycline	Malaria prophylaxis; begin 2 days prior to travel and continue through 4 weeks post-travel Malaria treatment (in combination with quinine sulfate or primaquine)	100 mg PO daily 100 mg IV or PO bid × 7 days
Hydroxychloroquine	Malaria prophylaxis (ONLY in areas of known susceptibility); begin 2 weeks prior to travel and continue through 4 weeks post-travel	400 mg PO once weekly
Mefloquine	Malaria prophylaxis; begin 2 weeks prior to travel and continue through 4 weeks post-travel Malaria treatment (use in combination with primaquine if *P. vivax* or *P. ovale*)	250 mg PO weekly 750 mg PO once followed by 500 mg PO 6-12 hours later
Primaquine	Malaria prophylaxis; begin 2 days prior to travel and continue through 1 week post-travel Malaria treatment (*P. vivax* or *P. ovale*) or presumptive anti-relapse therapy	30 mg once daily 30 mg once daily × 14 days (in combination with another appropriate agent)
Tafenoquine	Malaria prophylaxis; begin 3 days prior to travel and continue through 1 week post-travel Malaria presumptive anti-relapse treatment (*P. vivax* or *P. ovale*)	200 mg PO daily × 3 doses, then 200 mg PO weekly 300 mg PO once, taken after leaving malarious area
Quinidine gluconate	Malaria treatment (switch to oral therapy one parasitemia <1% and patient tolerating PO)	324 mg IV q8-12h
Quinine sulfate	Malaria treatment (in combination with doxycycline, tetracycline, or clindamycin)	648 mg PO q8h × 3-7 days
2. TOXOPLASMOSIS, BABESIOSIS, AND AMOEBIC ENCEPHALITIS		
Atovaquone	Babesiosis (in combination with azithromycin); longer duration may be necessary in patients at high risk of relapse Toxoplasmosis prophylaxis (either as monotherapy or in combination with pyrimethamine and leucovorin) Toxoplasmosis treatment (alternative agent, used in combination with pyrimethamine plus leucovorin, or with sulfadiazine)	750 mg PO bid × 7-10 days 1.5 g PO daily 1.5 g PO bid
Azithromycin	Babesiosis (in combination with atovaquone); longer duration may be necessary in patients at high risk of relapse	500 mg IV or PO × 1, then 250-500 mg IV or PO daily × 7-10 days
Clindamycin	Babesiosis (in combination with quinine); longer duration if high risk of relapse Toxoplasmosis encephalitis or pneumonitis (in combination with pyrimethamine and leucovorin)	600 mg IV q6h-q8h × 7-10 days 600 mg IV q6h × 6 weeks or longer
Dapsone	Toxoplasmosis prophylaxis (in combination with pyrimethamine and leucovorin)	50 mg PO daily or 200 mg PO weekly
Miltefosine	Free-living amoeba infections (*Naegleria, Balamuthia, Acanthamoeba*) including amoebic encephalitis, in combination with other medications	50 mg PO bid (<45 kg) or tid (>45 kg)
Pyrimethamine	Toxoplasmosis prophylaxis (in combination with dapsone and leucovorin) Toxoplasmosis encephalitis treatment (in combination with sulfonamide or clindamycin, and leucovorin)	50-75 mg PO weekly 25-75 mg PO daily
Spiramycin	Acute toxoplasmosis of pregnancy	1 g q8h
Sulfadiazine	Toxoplasmosis encephalitis (in combination with pyrimethamine and leucovorin, or in combination with atovaquone)	1-1.5 g PO q6h (acute) or 2-4 g daily in 2-4 divided doses
Trimethoprim/sulfamethoxazole	Toxoplasmosis prophylaxis Toxoplasmosis encephalitis treatment (alternative agent)	1 DS tablet daily or 1 DS tablet 3 times weekly or 1 SS tablet daily 10 mg/kg/day (TMP component) IV or PO in 2 divided doses × ≥6 weeks
Quinine sulfate	Babesiosis (in combination with clindamycin); longer duration if high risk of relapse	650 mg PO q6-8h × 7-10 days
3. INTESTINAL AND VAGINAL PROTOZOA		
Chloroquine	Extraintestinal amebiasis	1 g (600 mg base) daily × 2 days, then 500 mg daily × 2-3 weeks
Ciprofloxacin	Cystoisosporiasis in patients with HIV (if sulfa-intolerant)	500 mg PO bid × 7-10 days
Diloxanide furoate	Intestinal amebiasis	500 mg PO tid × 10 days
Metronidazole	Amebiasis, intestinal or liver abscess (followed by an intraluminal agent such as paromomycin) Intestinal protozoa (balantidiasis, *Dientamoeba fragilis*, giardiasis)	500-750 mg PO q8h × 7-10 days 500-750 mg PO tid × 5-10 days

TABLE 315-1 TREATMENT OF PARASITIC DISEASES—cont'd

DRUG	INDICATIONS AND COMMENTS	USUAL ADULT DOSAGES
Nitazoxanide	Giardiasis Cryptosporidiosis (immunocompetent) Cryptosporidiosis (immunosuppressed)	500 mg PO q12h × 3 days 500 mg PO q12h × 3 days 500 mg-1 g q12h × 14 days
Paromomycin	Intestinal amebiasis (luminal agent) Cryptosporidiosis-associated diarrhea in patients with HIV	25-35 mg/kg PO daily in 3 divided doses × 5-10 days 500 mg PO qid × 14-21 days
Pyrimethamine	Cystoisosporiasis in patients with HIV (in combination with leucovorin)	50-75 mg (treatment) or 25 mg (secondary prophylaxis) PO daily
Tinidazole	Giardiasis, trichomoniasis (initial infection) Intestinal amebiasis, amebic liver abscess Trichomoniasis (persistent or recurrent)	2 g PO single dose 2 g PO daily × 3-5 days 2 g PO daily × 7 days
4. TRYPANOSOMIASIS AND LEISHMANIASIS		
Benznidazole	American trypanosomiasis (Chagas disease)	5-7 mg/kg/day PO in 2 divided doses × 60 days
Eflornithine	Human African trypanosomiasis (with CNS involvement) monotherapy Human African trypanosomiasis (with CNS involvement) in combination with nifurtimox	100 mg/kg/dose q6h × 14 days 200 mg/kg/dose q12h × 7 days
Fexinidazole	Human African trypanosomiasis (reduce dose to 1.2 g followed by 600 mg if <35 kg)	1.8 g PO daily × 4 days, then 1.2 g daily × 6 days
Liposomal Amphotericin B	Leishmaniasis; schedule and duration vary by disease type (visceral, mucocutaneous, or cutaneous) and immune status	2-4 mg/kg/day IV
Melarsoprol	Human African trypanosomiasis (with CNS involvement)	2-3.6 mg/kg IV daily
Miltefosine	Leishmaniasis	50 mg PO bid (<45 kg) or tid (≥45 kg) duration varies with disease type and immune status
Nifurtimox	Human African trypanosomiasis (with CNS involvement) in combination with eflornithine American trypanosomiasis (Chagas disease)	15 mg/kg/day PO in 3 divided doses × 10 days 8-10 mg/kg/day PO in 3-4 divided doses × 90 days
Pentamidine	Human African trypanosomiasis (without CNS involvement)	4 mg/kg IV daily × 7 days
Stibogluconate sodium	Leishmaniasis; duration varies by disease type (visceral, mucocutaneous, or cutaneous) and immune status	20 mg/kg/day IV/IM
Suramin	Human African trypanosomiasis (without CNS involvement)	4-5 mg/kg IV once (test dose), then 20 mg/kg (max. 1 g/dose) IV on days 1, 3, 7, 14, and 21
5. HELMINTHIC DISEASES (ROUNDWORMS, TAPEWORMS, AND FLUKES)		
Albendazole	Many nematode infections, including ascariasis and pinworm (for pinworm, repeat in 2 weeks) Cutaneous larva migrans Trichuriasis (whipworm), often in combination with ivermectin Toxocariasis (visceral larva migrans, occular larva migrans) Some cestode infections, including gnathostomiasis, echinococcosis, and neurocysticercosis (in combination with praziquantel and corticosteroids); microsporidiosis Trichinellosis	400 mg PO single dose 400 mg PO daily × 3 days 400 mg PO daily × 3 days 400 mg PO bid × 5 days to 2 weeks 400 mg PO bid × 10 days (or longer) 200-400 mg PO tid × 3 days, then 400-500 mg tid × 10 days
Diethylcarbamazine (DEC)	Lymphatic filariasis elimination programs, in combination with albendazole and/or ivermectin; may NOT be used where onchocerciaisis or loiasis are co-endemic Lymphatic filariasis, including tropical pulmonary eosinophilia; contraindicated if concurrent onchocerciasis or loiasis Loiasis in patients with microfilarial blood counts <2500; available only through consultation with CDC	6 mg/kg PO single dose, annually 6 mg/kg PO daily in 3 divided doses × 12-21 days 9 mg/kg PO daily in 3 divided doses × 21 days; begin with 1 mg/kg daily and increase to full dose by day 4
Ivermectin	Onchocerciasis and/or lymphatic filariasis elimination, usually in combination with albendazole Ascariasis Stronglyloidiasis, gnathostomiasis (without CNS involvement) Lice, scabies, skin mites	150-200 mcg/kg PO single dose, annually 200 mcg/kg PO single dose 200 mcg/kg PO daily × 2 doses (uncomplicated infection) or until symptoms resolve and stool/sputum are negative for at least 2 weeks (hyperinfection syndrome) 200-400 mcg/kg PO weekly × 2-3 doses
Mebendazole	Pinworm (repeat in 2 weeks) Ascariasis, hookworm, trichuriasis (whipworm) Toxocariasis (visceral larval migrans) Capillariasis	100 mg PO single dose 500 mg PO single dose OR 100 mg PO bid × 3 days 100-200 mg PO bid × 5 days 200 mg PO bid × 20 days
Moxidectin	Onchocerciasis elimination	8 mg PO single dose, annually
Praziquantel	Intestinal tapeworms (hymenolepsiasis, taeniasis, diphyllobothriasis) Chlonorchis/opisthorchis Schistosomiasis Neurocysticercosis (usually in combination with albendazole and corticosteroids); expert consultation advised.	5-25 mg/kg PO single dose 25 mg/kg/dose PO tid × 1-2 days 40-60 mg/kg/day PO in 2-3 divided doses × 1 day 50 mg/kg/day PO in 3 divided doses × 10-14 days
Pyrantel pamoate	Ascariasis, trichostrongylus, pinworm (repeat in 2 weeks) Hookworm	11 mg/kg PO single dose 11 mg/kg PO daily × 3 days
Triclabendazole	Fascioliasis (liver fluke)	10 mg/kg PO q12h × 2 doses

bid = twice daily; CDC = Centers for Disease Control and Prevention; CNS = central nervous system; DS = double strength; HIV = human immunodeficiency virus; IM = intramuscularly; IV = intravenously; PO = orally; tid = 3 times daily; TMP = trimethoprim.

Dosing reference: Lexicomp. *Adult Drug Information: A Clinically Relevant Resource for All Healthcare Professionals*, 30th ed. Wolters Kluwer.

Artemisinins and Artemisinin Combination Therapy

Artemisinins are the most rapidly acting drugs available for the treatment of malaria.[A1] They are sesquiterpene lactone derivatives of the wormwood plant *Artemisia annua*, from which qinghaosu, the Chinese herbal medication for fever, is derived. Artemisinins are endoperoxide-containing compounds. In the presence of intraparasitic iron, they are converted into free radicals and other intermediates that alkylate specific malarial proteins and act rapidly to kill intraerythrocytic parasites. The artemisinins are administered with a second antimalarial drug that has a different mechanism of action and longer half-life to prevent the development of resistance. The route of administration of artemisinins varies; some are well absorbed orally, whereas others must be administered intravenously, intramuscularly, or by suppository. Their short half-lives preclude their use for prophylaxis. Side effects in humans are common but seldom result in discontinuation of treatment.

Artemether-Lumefantrine

Artemether-lumefantrine, a fixed drug combination, is used throughout the world (including the United States) to treat chloroquine-resistant malaria. It is taken with food, but grapefruit juice should be avoided. Common adverse reactions in adults are headache, anorexia, dizziness, asthenia, arthralgia, and myalgia. The most common adverse reactions in children are fever, cough, vomiting, anorexia, and headache. These side effects do not usually result in discontinuation of therapy. Of greater concern, lumefantrine can prolong the QT interval and is contraindicated in persons with an abnormal QTc. Lumefantrine also inhibits CYP206 and can thereby reduce the metabolism of other medications, including those that prolong the QTc. It can also decrease the effectiveness of birth control pills. Care must be taken to review the recipient's medication list for potential interactions.

Artesunate

Artesunate, which is the only available recommended therapy for severe malaria in the United States,[3] is commercially available and also available from the CDC under emergency conditions (contact the CDC Malaria Hotline for information at 770-488-7788 weekdays and 770-488-7100 nights/weekends and ask for the on-call malaria expert). Studies in malaria-endemic regions suggest that parenteral artesunate has a higher success rate and lower adverse event rate than quinidine. In addition to the side effects of artemether, artesunate has been associated with delayed hemolysis (unrelated to glucose-6-phosphate dehydrogenase [G6PD] deficiency) up to 4 weeks after therapy.

Quinine and Its Derivatives

Chloroquine

Widespread resistance among *P. falciparum* and, in some locations (especially Papua New Guinea and Indonesia), among *P. vivax* limits the utility of chloroquine. Its half-life, which varies among persons, averages 4 days, thereby permitting once-weekly administration for prophylaxis. Chloroquine is concentrated in the hemoglobin-containing digestive vesicles of asexual intraerythrocytic parasites. It inhibits the parasite's heme polymerase that incorporates ferriprotoporphyrin type IX complexes, which are potentially toxic to the parasite, into insoluble, nontoxic, crystalline hemozoin. Chloroquine-resistant strains of *P. falciparum* actively transport chloroquine out of the intraparasitic compartment.

Chloroquine is generally well tolerated when used at the doses recommended for the prophylaxis and treatment of malaria. Side effects include headache, nausea, vomiting, blurred vision, dizziness, and fatigue. Some patients with African ancestry experience pruritus, which responds to antihistamines. Rare side effects include depigmentation of hair, exacerbation of psoriasis, blood dyscrasias, seizures, neuropsychiatric effects, and reactions in persons with porphyria. Retinal damage has occurred in persons receiving chloroquine at high doses for the treatment of rheumatologic disorders, but it has not been documented as a problem in those taking it weekly over a period of many years for malaria prophylaxis. Cardiopulmonary collapse and death can occur after accidental overdose and in adults attempting suicide. As little as 5 g of chloroquine can be fatal unless treatment is promptly initiated with mechanical respiration, anticonvulsants, and blood pressure support.

Hydroxychloroquine

Hydroxychloroquine, which is used for rheumatologic diseases, is also effective against chloroquine-sensitive *Plasmodium* species. The side effects are similar to those of chloroquine.

Mefloquine

Mefloquine, a quinoline methanol compound derived from quinine, is occasionally used for the treatment of chloroquine-resistant *P. falciparum* malaria, but concern about neuropsychiatric and other toxicities and the availability of better alternatives now limit its use. Mefloquine is available for oral administration only. Slowly and incompletely absorbed, it is 99% protein bound. It has a variable half-life ranging from 6 to 23 days with a mean of approximately 14 days. It is metabolized and excreted slowly through bile and feces. It is associated with nausea, dizziness, vivid dreams, fatigue, and lassitude. Less common side effects, but of greater concern, are anxiety, depression, acute psychosis, and seizures. Mefloquine is contraindicated in persons with a history of epilepsy or psychiatric disorders. It also depresses atrioventricular conduction and should not be used in persons taking β-blockers for cardiac indications. Mefloquine now carries a U.S. Food and Drug Administration (FDA) black-box warning. Although not approved for use during pregnancy or in children weighing less than 15 kg, mefloquine has been used in these situations when its potential benefits are judged to outweigh its risks. It has been reported to have no adverse effects on pregnancy outcomes (such as stillbirths and abortions) and no effects on low birth rate and prematurity.[4]

Primaquine

Primaquine, an 8-aminoquinoline, kills the hypnozoite stage of *P. vivax* and *P. ovale* in the liver. Primaquine is used as a 14-day course at the end of treatment or prophylaxis to prevent late relapses in persons who are or may have been infected with these *Plasmodium* species. It is also an alternative for daily primary prophylaxis for *P. vivax*[A2] and other species. In that case, it is begun 1 or 2 days before exposure and continued during and for 7 days after a traveler leaves a malaria-endemic area.

Primaquine is absorbed orally and rapidly converted to carboxyprimaquine, which has a half-life of approximately 7 days. It is generally well tolerated, although some recipients experience abdominal cramps, epigastric distress, and nausea. The major concern with primaquine is hemolysis in persons with G6PD deficiency (Chapter 147). The G6PD status of the recipient must be determined before it is administered. Rarely, primaquine causes neutropenia, methemoglobinemia, hypertension, or arrhythmias. Primaquine is contraindicated during pregnancy and in breast-feeding mothers because life-threatening hemolysis may occur if the fetus or baby is deficient in G6PD.

Tafenoquine

Tafenoquine, which is an analogue of primaquine, is administered as a single 300-mg dose following treatment of acute malaria due to *P. vivax* and *P. ovale* to prevent relapse. It can also be used for primary prophylaxis in travelers; 200 mg daily for 3 days before travel, then once weekly while in the malarious region, then in the week following exit, a final dose 7 days after the previous dose in the malarious region.[5]

Tafenoquine is better absorbed than primaquine, has a half-life of approximately 15 days, and is less likely to cause gastrointestinal problems. Tafenoquine can cause severe psychiatric reactions and is contraindicated in persons with a history of psychiatric disorder. Tafenoquine also can cause hemolysis in patients with G6PD deficiency and is contraindicated during pregnancy and breast-feeding.

Quinine Sulfate and Quinidine Gluconate

Quinine sulfate, a cinchona alkaloid, is the oldest of the antimalarials. It is rapidly absorbed after oral administration and has a half-life of 16 to 18 hours in persons with malaria. Quinine has the poorest therapeutic to toxicity ratio of any antimalarial drug. The side effects, known collectively as cinchonism, include tinnitus, decreased hearing, headache, nausea, vomiting, dysphoria, and visual disturbances. They are dose related and reversible. Quinine has also been associated with severe hypoglycemia in persons with heavy *P. falciparum* infections as a result of the utilization of glucose by intraerythrocytic *Plasmodium* and release of insulin from the pancreas. Hypoglycemia can be treated and prevented by the intravenous administration of glucose. Rare complications with quinine include massive hemolysis in patients with heavy *P. falciparum* infection resulting in hemoglobinuria and renal failure (blackwater fever), cutaneous hypersensitivity reactions, agranulocytosis, and hepatitis. Quinine can cause respiratory paralysis in persons with myasthenia gravis. It stimulates uterine contractions during pregnancy and can result in abortion, but it has saved the lives of many pregnant women with *P. falciparum* malaria. Quinine dihydrochloride given intravenously can cause myocardial depression, peripheral vascular collapse, respiratory depression, and potentially death. Quinidine

gluconate, the stereoisomer of quinine, administered intravenously for the treatment of malaria is no longer available in the United States.

Atovaquone-Proguanil

Atovaquone-proguanil, a fixed drug preparation, is used for the treatment of uncomplicated, chloroquine-resistant and -sensitive malaria, as well as prophylaxis. Atovaquone is a highly lipophilic compound with low aqueous solubility. Administration with food enhances its absorption two-fold. Plasma concentrations do not increase proportionately with dose. Atovaquone is highly protein bound with a half-life exceeding 60 hours. It undergoes extensive enterohepatic cycling and is eventually excreted unchanged in feces. Atovaquone selectively inhibits electron transport in the mitochondria of susceptible *Plasmodium* at the level of the cytochrome bc_1 complex, thereby resulting in collapse of the mitochondrial membrane potential. It also affects pyrimidine biosynthesis, which is obligatorily coupled to electron transport in *Plasmodium*.

Atovaquone is generally well tolerated but can cause nausea, vomiting, diarrhea, rash, and pruritus. Unfortunately, resistance develops rapidly when atovaquone is used alone to treat malaria.

Proguanil is absorbed slowly after oral administration. The serum level falls to zero within 24 hours, so it must be administered daily. Its triazine metabolite, cycloguanil, inhibits dihydrofolate reductase in susceptible *Plasmodium* species. Resistance is well documented when proguanil is used alone. In addition, proguanil acts synergistically with atovaquone to collapse the mitochondrial membrane potential in susceptible *Plasmodium* species.

The combination of atovaquone-proguanil is the best tolerated of the options for prevention of chloroquine-resistant malaria. It is begun 1 to 2 days before departure and continued during the time of exposure and for 7 days thereafter. Higher doses of atovaquone-proguanil, administered over a 3-day period, are used to treat acute, uncomplicated malaria. Potential side effects include abdominal pain, nausea, vomiting, diarrhea, headache, pruritus, and rash. Asymptomatic, transient elevations in liver enzymes have been observed with treatment doses.

Doxycycline and Tetracycline

Doxycycline (100 mg daily) provides effective prophylaxis against all *Plasmodium* species. It is begun 1 to 2 days before exposure and continued during the time of exposure and for 4 weeks after departure from a malaria-endemic area. Doxycycline or tetracycline can also be administered with quinine to treat acute chloroquine-resistant malaria, but neither doxycycline nor tetracycline acts rapidly enough to be used alone for treatment. Doxycycline is generally well tolerated, although it can cause gastrointestinal symptoms and "pill" esophagitis. To avoid the latter, it should be taken with a full glass of water, and the recipient should remain upright for an hour or more after ingestion. Other important potential side effects include photosensitivity dermatitis, *Candida albicans* vaginitis, and *Clostridioides difficile* colitis. Finally, doxycycline and tetracycline should not be used in children younger than 8 years or in women who are pregnant or breast-feeding unless the potential benefits outweigh the risks.

TOXOPLASMOSIS, BABESIOSIS, AND AMOEBIC ENCEPHALITIS

Toxoplasma gondii (Chapter 320) and *Babesia* species (Chapter 324) are other important pathogens of the phylum Apicomplexa. Pyrimethamine and sulfadiazine, which are useful to treat toxoplasmosis, inhibit sequential steps in the folic acid metabolic pathway. Pyrimethamine preferentially inhibits dihydrofolate reductase. It is well absorbed orally. The major side effect is macrocytic anemia, which can be prevented by the concurrent administration of leucovorin. Sulfonamides reduce the activity of dihydropteroate synthetase and the binding of *p*-aminobenzoic acid to it. In ocular toxoplasmosis with macular involvement, corticosteroids are used along with anti-*Toxoplasma* (Chapter 320) therapy to minimize the local inflammatory response. Clindamycin plus pyrimethamine or atovaquone plus pyrimethamine are therapeutic options in sulfonamide-intolerant patients. Patients with AIDS, $CD4^+$ counts less than 100/μL, and serologic evidence of *T. gondii* infection should receive prophylaxis with one of the following regimens: daily trimethoprim-sulfamethoxazole, pyrimethamine (with leucovorin) plus dapsone, pyrimethamine (with leucovorin) plus atovaquone, or atovaquone alone. Spiramycin, a macrolide, is used for the treatment of toxoplasmosis during pregnancy. Pyrimethamine is currently in short supply. Trimethoprim-sulfamethoxazole is a potential alternative when it is not available.

Two therapeutic regimens are available for babesiosis (Chapter 324). The combination of clindamycin plus quinine is usually used in persons with severe babesiosis, but side effects are common. Long-term treatment (≥6 weeks) is often necessary for immunocompromised patients. Atovaquone plus azithromycin is better tolerated and used for less severe babesiosis (Chapter 324). Clofazimine has been used successfully to treat babesiosis in severely immunocompromised patients.[6]

The addition of miltefosine, an FDA-approved antileishmanial drug,[7] to multidrug regimens has improved the likelihood of survival in persons with granulomatous amebic encephalitis due to *Acanthamoeba* or *Balamuthia*. It is now recommended as part of multidrug regimens to treat granulomatous amebic encephalitis as well as primary amebic meningoencephalitis due to *Naegleria*.[8]

INTESTINAL AND VAGINAL PROTOZOA

Several major luminal pathogens, including *Entamoeba histolytica* (Chapter 323), *Giardia lamblia* (Chapter 322), and *Trichomonas vaginalis* (Chapter 324), live in anaerobic conditions in the intestine or vagina. The 5-nitroimidazoles, metronidazole and tinidazole, are first-line therapy for them, but refractory giardiasis and trichomoniasis are documented. Tinidazole has more favorable pharmacodynamics and is generally better tolerated. Because neither metronidazole nor tinidazole reliably eradicates cysts of *E. histolytica* in the colon, either paromomycin, a poorly absorbed aminoglycoside, or iodoquinol, both of which are active in the lumen of the bowel, should be administered as well. Either one of these drugs or diloxanide furoate is used alone to treat persons with asymptomatic cyst excretion.

Giardiasis can also be treated with nitazoxanide. Nitazoxanide, which is the only drug effective in the treatment of cryptosporidiosis (Chapter 321), can cure immunocompetent persons but not patients who are immunodeficient. The combination of antiretroviral therapy (Chapter 357) plus nitazoxanide may improve symptoms in persons who have HIV and cryptosporidium-related diarrhea, but relapses can occur if the immune status deteriorates. Trimethoprim-sulfamethoxazole, which inhibits successive steps in the folic acid pathway, is the drug of choice for *Cystoisospora* (*Isospora*) *belli* and *Cyclospora cayetanensis* (Chapter 324). Ciprofloxacin is a second-line alternative for the former. Either tetracycline, metronidazole, or nitazoxanide can be used to treat symptomatic *Balantidium coli* infection.

Metronidazole is rapidly absorbed after oral administration and has a half-life of 8 hours. More than half of each dose is metabolized in the liver. The metabolites and remaining parent drug are excreted in urine. Metronidazole is activated by reduction of its 5-nitro group through a sequence of intermediate steps involving microbial electron transport proteins of low redox potential. It is concentrated in susceptible anaerobic organisms and serves as an electron sink. Nausea, vomiting, diarrhea, and a metallic taste are often associated with the use of metronidazole. They are less common, with the lower doses recommended for the treatment of giardiasis than with the higher doses used for amebiasis. Other untoward effects include headache, dizziness, vertigo, and numbness. Potentially severe disulfiram-like reactions occur in patients who ingest alcohol while taking metronidazole.

Tinidazole has a similar mechanism of action and spectrum of activity as metronidazole, but it has more favorable pharmacodynamics and is generally better tolerated. It has been used widely around the world for the treatment of giardiasis, intestinal amebiasis, and trichomoniasis and is preferred over metronidazole for treating giardiasis. In comparison with metronidazole, it has a longer half-life, a shorter and less complicated dosing regimen, and fewer gastrointestinal side effects. It, too, can cause severe disulfiram-like reactions after alcohol ingestion.

TRYPANOSOMIASIS AND LEISHMANIASIS

The Kinetoplastida (*Trypanosoma brucei rhodesiense* and *Trypanosoma brucei gambiense*, which cause human African trypanosomiasis [sleeping sickness; Chapter 317]; *Trypanosoma cruzi*, the etiology of Chagas disease [Chapter 318]; and *Leishmania* species, which cause cutaneous, mucosal, and visceral leishmaniasis [Chapter 319]) often pose substantial therapeutic challenges.

African Trypanosomiasis (Sleeping Sickness)

Fexinidazole, suramin, pentamidine, eflornithine, and melarsoprol are used for the treatment of human African trypanosomiasis (Chapter 317). Fexinidazole is the first all-oral treatment for human African trypanosomiasis and is the WHO-recommended therapy for *T. brucei gambiense* in patients >6 years of age and in first stage (hemolymphatic) or nonsevere second stage (central nervous system [CNS] involvement but <100 leukocytes in cerebrospinal fluid [CSF]) disease. Fexinidazole must always be taken with food because its absorption is insufficient on an empty stomach and will not result in therapeutic levels,

especially in the CNS. For *T. brucei gambesiense* patients with severe stage II disease (>100 WBC in CSF), combination therapy with nifurtimox-eflornithine is preferred.[9] Where fexinidazole is not available, suramin or pentamidine is recommended for the hemolymphatic stage of *T. brucei rhodesiense* and *T. brucei gambiense*, respectively. Both drugs are associated with potentially serious side effects, and suramin can cause severe reactions in persons co-infected with *Onchocerca volvulus*.

Eflornithine, which is much better tolerated, is effective against both the hemolymphatic and CNS stages of *T. brucei gambiense* infection. It does not have activity against *T. brucei rhodesiense*. Unfortunately, eflornithine is costly and supplies are limited. It is available in the United States from the CDC. It can be used alone, but eflornithine is often co-administered with nifurtimox for CNS *T. brucei gambiense* infection.

Melarsoprol is used for persons with CNS involvement due to *T. brucei rhodesiense* and *T. brucei gambiense* when eflornithine is not available or to treat relapses. Melarsoprol can result in severe toxicity, including life-threatening encephalopathic reactions.

Chagas Disease

Benznidazole or nifurtimox orally is used to treat *T. cruzi* infections (Chapter 318). Benznidazole has been the drug of choice in endemic areas of Latin America and nifurtimox in the United States. Both drugs, which are now commercially available in the United States, lower mortality and shorten the duration of acute Chagas disease. Treatment is recommended for persons with recent infection as well as asymptomatic children and adults through middle age with indeterminate-stage *T. cruzi* infection. Neither benznidazole nor nifurtimox can reverse the cardiac or gastrointestinal manifestations of chronic Chagas disease. Side effects are common with both drugs and increase in frequency and severity with age. Benznidazole is administered daily for 1 month and is associated with allergic dermatitis, peripheral neuropathy, insomnia, and gastrointestinal symptoms, including anorexia and weight loss. Nifurtimox is administered daily for 3 months and is associated with anorexia, nausea, vomiting, weight loss, headache, dizziness or vertigo, paresthesias, weakness, and polyneuropathy.

Leishmaniasis (Cutaneous, Mucosal, and Visceral)

Treatment of cutaneous leishmaniasis (Chapter 319) depends on the size, number, complexity, and location of skin lesions; their cosmetic impact; the infecting *Leishmania* species; and its propensity to cause mucosal disease.[10] Uncomplicated lesions acquired in Europe, Africa, and Asia, where mucosal involvement is rare, can be followed without therapy if they appear to be healing spontaneously. Lesion-directed treatment options include cryotherapy; heat therapy, which requires a specialized delivery system; or intralesional injection of stibogluconate sodium, which is not available in the United States. Topical therapy with direct application of paromomycin is another option. An ointment containing 15% paromomycin and 12% methylbenzethonium chloride in white paraffin developed in Israel has been used. A U.S. Army formulation of topical paromomycin also appears promising.

Parenteral or oral antileishmanial therapy is used for persons with complicated cutaneous leishmaniasis and for those who are or may be infected with *Leishmania braziliensis* or related New World species potentially associated with mucosal leishmaniasis.[A3] Miltefosine is FDA-approved for the oral treatment of cutaneous leishmaniasis due to *Leishmania braziliensis*. The efficacy with other *Leishmania* species varies. Liposomal amphotericin B and amphotericin B deoxycholate are effective, but more toxic, parenteral alternatives. Stibogluconate sodium and meglumine antimoniate are rarely used because of their toxicity, the requirement for parenteral administration, and increasing resistance. Fluconazole and other imidazole antifungals have activity against some *Leishmania* species.

Mucosal leishmaniasis (Chapter 319) is less responsive to treatment than cutaneous leishmaniasis, and relapses are common. Therapeutic options include liposomal amphotericin B, miltefosine, amphotericin B deoxycholate, stibogluconate sodium, or meglumine antimoniate.

Visceral leishmaniasis (Chapter 319) is a potentially fatal disease. The drug of choice is liposomal amphotericin B. Miltefosine and amphotericin B deoxycholate are alternatives for visceral leishmaniais[11] and post-kala-azar dermal leishmaniasis.[A4] Sodium stibogluconate and meglumine antimoniate are used in some geographic areas where resistance has not yet emerged.

Liposomal amphotericin B was the first drug approved by the FDA for treatment of visceral leishmaniasis (Chapter 319) in the United States. Liposomes deliver amphotericin to macrophages where leishmania reside. Liposomal amphotericin B is better tolerated than amphotericin B deoxycholate, which is an alternative. Other lipid-associated amphotericin B preparations appear to be effective, but they have been less extensively studied and are not FDA-approved for this indication.

Miltefosine, an alkylphospholipid and phosphocholine analog, initially developed as an antineoplastic drug, is FDA-approved for the treatment of visceral leishmaniasis and post-kala-azar cutaneous leishmaniasis due to *L. braziliensis*. A major advantage is oral administration. The pharmacokinetics are characterized by a long elimination half-life and extensive drug accumulation. The mechanism of action is uncertain, but miltefosine induces apoptosis-like changes in the parasite. Side effects are frequent but typically mild to moderate. Dose-dependent gastrointestinal toxicity can result in nausea, vomiting, and diarrhea, which tend to decrease with continued administration of the drug. Elevations in liver enzymes and creatinine are common but usually transient. Miltefosine is embryotoxic and is thus contraindicated during pregnancy. Contraceptive coverage is mandatory in women of childbearing years during and for 4 months after therapy. Relapses have been reported after the treatment of visceral leishmaniasis. They are frequent in persons with concurrent AIDS.

Stibogluconate sodium (available from the CDC) and meglumine antimoniate (still used in some areas of Latin America) are pentavalent antimony drugs that were used to treat visceral leishmaniasis in the past, but resistance is now common among *Leishmania donovani* isolates in India, adjacent countries, and some other areas of the world. Pentavalent antimony drugs require parenteral administration. Side effects increase with age and include gastrointestinal symptoms, pancreatitis, myalgias, headache, malaise, elevated liver enzyme levels, and occasionally bone marrow suppression. Nonspecific ST-T wave changes are common. Sudden death has been reported in older persons and in those receiving more than the recommended dose.

HELMINTHIC DISEASES

The treatment of helminthic diseases is discussed based on their taxonomy and the site of infection. A number of anthelminthic drugs are available. Albendazole, mebendazole, ivermectin, and pyrantel pamoate have replaced older anthelmintics that were more toxic, such as piperazine and thiabendazole, or less effective.[A5]

ANTHELMINTIC DRUGS

Albendazole

Albendazole is poorly soluble in water, but it is well absorbed when administered with a fatty meal. It undergoes rapid first-pass metabolism in the liver to albendazole sulfoxide, which has excellent anthelmintic activity. The serum half-life of albendazole sulfoxide is 8 to 9 hours. Elimination of albendazole sulfoxide and other metabolites is primarily through the kidney. Albendazole binds to tubulin in susceptible parasites, inhibits microtubule assembly, and decreases glucose absorption. It does not affect human tubulin. It also inhibits fumarate reductase in helminths. Concurrent administration of dexamethasone, which is frequently given to prevent cerebral edema in persons with neurocysticercosis, increases serum levels by approximately 50%. The CSF concentration of albendazole is approximately 40% that in serum.

Albendazole is generally well tolerated when given as a single dose for the treatment of intestinal roundworm infections, although gastrointestinal discomfort may develop, or patients may experience migration of adult *A. lumbricoides* from the nose or mouth or see them in their stool. Albendazole at higher doses and for longer duration (e.g., 15 mg/kg/day in two divided doses for 10 to 14 days) is used for persons with neurocysticercosis.[12] Corticosteroids are administered concurrently to reduce intracranial inflammation and increased intracranial pressure. Albendazole is contraindicated in persons with cysticerci in the eye or spinal cord. High-dose, prolonged therapy with albendazole, such as that recommended for echinococcal disease, can be complicated by alopecia, hepatitis, or bone marrow suppression, which is not always reversible after discontinuation of the drug. Albendazole is embryotoxic in animals and contraindicated during pregnancy.

Albendazole is used for inoperable *E. granulosus* and *Echinococcus multilocularis* disease and in persons in whom medical treatment is preferred for other reasons. Administered at a dose of 400 mg twice daily for adults, generally for 1 to 6 months, albendazole may cure approximately one third of uncomplicated *Echinococcus granulosus* liver cysts. Potentially fatal bone marrow suppression and hepatitis are concerns in persons receiving high-dose, prolonged albendazole therapy.

Albendazole is active against *A. lumbricoides*, the hookworms, and *T. trichiura*. Administered as a single 400-mg dose, it has been widely used in mass treatment programs in areas where these soil-transmitted roundworms are prevalent.[13] However, reinfection is common, and treatment is often repeated

at 3- to 4-month intervals. The CDC recommends presumptive treatment of immigrants from endemic regions with a single dose of albendazole before arrival in the United States. Daily doses of albendazole for 3 days are recommended for persons with heavy *T. trichiura* infection. Albendazole (400 mg twice daily for 7 days) is used as an alternative to ivermectin for the treatment of *Strongyloides stercoralis* infection. Albendazole is effective against *Enterobius vermicularis*, the pinworm, in a single dose that is repeated in 2 weeks. It can be used for cutaneous larva migrans, which is caused by migrating stages of *Ancylostoma braziliense* and other intestinal roundworms of animals. It is the drug of choice for trichinosis, and it has been used for the treatment of *Trichostrongylus* species and *Capillaria philippinensis*. There has been a massive increase in the cost of albendazole in the United States.

Mebendazole

Mebendazole is only slightly soluble in water and is relatively poorly absorbed from the gastrointestinal tract. This characteristic is advantageous for the treatment of intestinal parasites but limits its effectiveness against tissue-dwelling helminths. Absorbed drug is metabolized in the liver and excreted in urine. Mebendazole selectively binds to helminthic tubulin, blocks its assembly into microtubules, and inhibits glucose uptake. This leads to depletion of glycogen stores and ultimately death of the parasite. Mebendazole is relatively well tolerated in the doses used to treat intestinal helminths. Transient abdominal pain and diarrhea occur in a small number of recipients. Mebendazole is contraindicated during pregnancy.

Mebendazole (100 mg orally twice daily for 3 days) has a similar spectrum of activity as albendazole against *A. lumbricoides*, hookworms, and *T. trichiura*. In this regimen, it is more effective than a single dose of albendazole and is considered the treatment of choice for heavy *T. trichiura* infections. A single 500-mg dose of mebendazole has been used in mass treatment programs. Mebendazole is effective in treating pinworms when given at 100 mg orally in one dose followed by a second dose after 2 weeks. It is an alternative to albendazole for the treatment of trichinosis. Mebendazole is poorly absorbed and ineffective against *S. stercoralis*.

Ivermectin and Other Avermectins

Ivermectin is a macrocyclic lactone produced by *Streptomyces avermitilis*. It has a broad spectrum of activity against helminths and arthropods, including *Sarcoptes scabiei*, the cause of scabies. It is well absorbed after oral administration. Ivermectin is highly protein bound, has a serum half-life of 12 hours, and accumulates in adipose tissue and the liver. It is subject to enterohepatic recirculation and ultimately eliminated in stool. Ivermectin activates the opening of gated chloride channels in susceptible helminths and arthropods. The result is an influx of chloride ions and paralysis of the pharyngeal pumping mechanism of helminths. Ivermectin is generally well tolerated in humans, although inflammatory reactions can develop in response to antigens released from dying parasites.

Ivermectin at an oral dose of 200 µg/kg daily for 2 days is considered the treatment of choice for uncomplicated *S. stercoralis*. In immunocompromised persons with hyperinfection, daily doses are given until stool and sputum exams are negative for larvae for 2 weeks. It is also effective against cutaneous larva migrans and *A. lumbricoides* but not hookworms. It is an alternative to mebendazole for the treatment of *T. trichiura*.

Ivermectin is the treatment of choice for onchocerciasis. It is administered as a single dose of 150 µg/kg. It does not kill adult *Onchocerca volvulus*, but it decreases ova production and reduces microfilariae in the skin and eyes. Retreatment is usually necessary at 6- to 12-month intervals until the patient is free of symptoms. For *Onchocerca volvulus*, biannual treatment leads to substantial reductions in community infection rates after four or five rounds of therapy. Ivermectin has activity against the microfilariae of *W. bancrofti* and *Brugia* species, the agents of lymphatic filariasis, but it does not kill adult worms and is not recommended for definitive treatment of these organisms. Ivermectin is used widely in mass drug administration programs for reducing the transmission of lymphatic filariasis and onchocerciasis, and it has the added benefit of reducing the transmission of scabies.[A6] Ivermectin should not be given to persons with heavy concurrent *Loa loa* infections because it kills *Loa loa* microfilaria rapidly and can result in encephalopathy.

Moxidectin, an avermectin compound similar to ivermectin, has long been used in veterinary medicine and is now approved for treatment of onchocerciasis. Single-dose moxidectin provides longer clearance of *O. volvulus* skin microfilariae than single-dose ivermectin, an effect that is likely related to the prolonged (about 23 days) half-life of moxidectin.[A7] Moxidectin is not yet approved for use in children <12 years of age, and data are insufficient regarding its safety in pregnant or breast-feeding women.

Pyrantel Pamoate and Oxantel Pamoate

Pyrantel pamoate is a relatively safe, poorly absorbed over-the-counter drug with activity against *A. lumbricoides*, hookworms, and pinworm, but it is not effective against *T. trichiura* or *S. stercoralis*. When used for pinworm infection, it is administered as an oral suspension at a dose of 11 mg/kg (to a maximum of 1 g), which is repeated after 2 weeks. A structural analogue, oxantel pamoate, has increased activity against *T. trichiura* but is not available in the United States. Three-drug therapy with pyrantel pamoate, oxantel pamoate, and albendazole is superior to two-drug combinations for hookworm and provides high cure rates for *T. trichiura* and *A. lumbricoides*.[A8]

Praziquantel

Praziquantel is well absorbed after oral administration. It undergoes extensive first-pass metabolism, and the metabolites, which are inactive, are excreted in urine. Praziquantel is approximately 80% protein bound, with a serum half-life of 4 to 6 hours. It is rapidly taken up by susceptible cestodes and trematodes. In the case of schistosomes, praziquantel damages the tegument, which results in intense vacuolation and increased permeability to calcium. Adult schistosomes are paralyzed and translocated to the liver through the portal circulation. Sequestered antigens are exposed on their surface, permitting binding of antibodies and phagocytes resulting in immune destruction.

Praziquantel has a broad spectrum of activity against tapeworms (Chapter 325) and flukes. It is the drug of choice for adult tapeworms in the human intestinal tract. It is effective against *Taenia solium* (pork tapeworm), *Taenia saginata* (beef tapeworm), *Taenia asiatica* (Asian tapeworm), *Diphyllobothrium latum* (fish), and *Hymenolepis nana* (dwarf tapeworm) when administered as a single dose. Praziquantel (50/mg/kg/day for 10 to 14 days) is used in combination with or as an alternative to albendazole for the treatment of neurocysticercosis. The concurrent administration of corticosteroids, which are necessary to decrease inflammation and edema in the brain, reduces the serum concentration of praziquantel. The concentration in CSF is approximately 15 to 20% that of serum.

Praziquantel is frequently associated with mild, transient side effects, including headaches, lassitude, dizziness, nausea, vomiting, and abdominal discomfort, but they are seldom severe enough to interrupt therapy. Untoward reactions attributed to release of parasite antigens have been reported in patients treated for schistosomiasis and pulmonary paragonimiasis. Increased intracranial pressure resulting from release of cysticercal antigens is a potentially life-threatening consequence in patients receiving praziquantel for neurocysticercosis. Corticosteroids should be administered concurrently. Praziquantel is contraindicated in persons with cysticerci in the eye or spinal cord.

Praziquantel is the drug of choice for the treatment of all forms of schistosomiasis (Chapter 326), as well as intestinal, lung, and liver flukes (Chapter 326), with the exception of *Fasciola hepatica*. For schistosomiasis, two or three doses of praziquantel are given in 1 day depending on the species. Oxamniquine is an alternative for *Schistosoma mansoni*, but it is more toxic and less effective.

Diethylcarbamazine

Diethylcarbamazine, a piperazine derivative, is well-absorbed orally and has a half-life of 8 hours. The parent drug and its metabolites are excreted through the kidney. Although the mechanism of action is uncertain, the piperazine moiety may result in paralysis of sensitive helminths. Diethylcarbamazine also alters the surface membranes of susceptible microfilariae, thereby resulting in destruction by the host's immune system. Side effects include those caused by the drug and those that result from release of the parasite antigens and lipopolysaccharide from filaria-harbored, endosymbiotic *Wolbachia*. Adverse effects include nausea, vomiting, anorexia, headache, malaise, weakness, arthralgias, and rarely, acute psychotic reactions. In patients with lymphatic filariasis, localized swelling or nodules may develop along the lymphatics during treatment, and transient lymphedema or hydrocele may develop.

Diethylcarbamazine is the drug of choice for the treatment of lymphatic filarial infections (Chapter 327) caused by *Wuchereria bancrofti*, *Brugia malayi*, and *Brugia timori*, as well as for tropical pulmonary eosinophilia. It promotes the host's killing of microfilariae of these species and also damages or kills adult worms. Inflammatory side effects are common. They are due in part to the release of lipopolysaccharide from endosymbiotic *Wolbachia* bacteria within dying filaria. *Wolbachia* are necessary for filarial development and are a potential drug target. Long-term therapy with doxycycline results in their

elimination and has been used for therapy. Diethylcarbamazine is also used for *Loa loa* infections in persons with acceptably low levels of microfilaremia (<8000/mL). Encephalopathy may result from treatment of those with more. In that case, apheresis or treatment with albendazole is used first to reduce the number of microfilariae. Diethylcarbamazine should not be used for onchocerciasis. It kills the microfilariae of *O. volvulus* rapidly, and the release of parasite and *Wolbachia* antigens can result in severe ocular and systemic inflammatory responses. The latter, known as the Mazzotti reaction, can be life-threatening and is characterized by fever, urticaria, lymphadenopathy, tachycardia, hypotension, arthralgias, peripheral edema, and abdominal pain. Diethylcarbamazine has also been used prophylactically to prevent loiasis.

Other Drugs

Niclosamide, which is not absorbed, is an effective alternative for the treatment of *T. saginata* and *D. latum*. It also kills adult *T. solium*, but disintegration of the worm and release of viable ova into the intestinal lumen raise the theoretical possibility of autoinfection. Nitazoxanide also has activity against *T. saginata* and potentially other tapeworm species. In the case of *H. nana*, a dose of nitazoxanide 500 mg twice daily for 3 days provides an alternative to praziquantel.

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316 MALARIA

PHILIP J. ROSENTHAL AND MOSES R. KAMYA

DEFINITION

Malaria is caused by infection with protozoan parasites of the genus *Plasmodium*, all of which are transmitted by bites of infected anopheline mosquitoes.[1] Malaria is typically characterized by an acute febrile illness, with parasites infecting large numbers of erythrocytes, and classically entails recurrent episodes of fever and chills. Malaria causes hundreds of millions of illnesses each year throughout most of the tropics. Severe disease can occur, primarily with *Plasmodium falciparum* infection, with the acute development of serious organ dysfunction. Chronic and repeated infection leads to severe anemia.

The Pathogen

P. falciparum, which is responsible for most episodes of severe malaria, is endemic in most malarious areas and is by far the predominant species in Africa. *Plasmodium vivax* is about as common as *P. falciparum*, except in Africa, but it causes severe disease much less commonly.[2] *Plasmodium ovale* and *Plasmodium malariae* are much less common causes of disease and generally do not cause severe illness. *Plasmodium knowlesi*, which is a parasite of macaque monkeys, is a fairly common zoonosis in parts of Southeast Asia and has been responsible for malarial illnesses, including severe disease, in individuals exposed to macaque-biting vectors in forested areas. Other zoonotic plasmodia, including *Plasmodium cynomolgi* in southeast Asia and *Plasmodium simium* and *Plasmodium brasilianum* (which may be zoonotic forms of *P. vivax* and *P. malariae*, respectively, in Brazil), occasionally cause human disease.

EPIDEMIOLOGY

Malaria in Endemic Countries

Malaria, which is the most important parasitic disease of humans, is endemic in most of the tropics, including many parts of Africa, South and Central America, the Middle East, the Indian subcontinent, Southeast Asia, and Oceania. Transmission, morbidity, and mortality are greatest in Africa, where infection with *P. falciparum* predominates. In most other endemic areas, disease caused by both *P. falciparum* and *P. vivax* is common. In highly endemic areas, the group at greatest risk is young children, who experience the most episodes of disease and the most deaths. A second high-risk group is pregnant women, with high risks of maternal and fetal morbidity from *P. falciparum* malaria, including many deaths secondary to low birthweight. In highly endemic areas, in addition to extensive mortality, malaria exerts a massive toll through its adverse effects on child development; contributions to school and work absenteeism; and, overall, billions of dollars in lost income among the poorest citizens of the poorest countries of the world. In areas of developing countries with lower levels of malaria transmission, malaria can be epidemic, with intermittent increases in transmission that cause major morbidity in relatively nonimmune populations. Increased control activities worldwide reduced malaria deaths by almost 60% from 2000 to 2015, but morbidity and mortality appear to have stabilized since 2015.[3] Currently, malaria is estimated to cause nearly 250 million clinical cases and over 600,000 deaths annually worldwide.[4]

Malaria in Travelers

Malaria is also common when travelers of any age travel from nonendemic areas to the tropics, with symptoms sometimes not manifesting until many months after travel (Chapter 265). Malaria is the most common documented cause of febrile illness in travelers returning from the tropics to developed countries. Malaria is also occasionally transmitted in areas considered nonendemic, including the United States, when imported parasites are transmitted by local anopheline mosquitoes, by blood products, or by congenital spread.

Malaria Transmission

Malaria is transmitted by multiple species of mosquitoes of the genus *Anopheles*, which vary in geographic distribution, ecologic preferences, and susceptibility to mosquito control measures. Anopheline mosquitoes bite at night, so personal mosquito control measures focus on avoidance of mosquito bites during sleep. Levels of malaria transmission in endemic areas vary greatly, from areas where residents experience only rare infectious bites to regions of Africa where individuals may receive hundreds of infectious bites each year.

PATHOBIOLOGY

Parasite Life Cycle

Malaria is transmitted by the bite of infected female anopheline mosquitoes. During feeding, mosquitoes inject sporozoites, which circulate to the liver and infect hepatocytes, thereby causing asymptomatic liver infection (Fig. 316-1). Merozoites are subsequently released from the liver, and they rapidly infect erythrocytes to begin the asexual erythrocytic stage of infection that is responsible for human disease. Multiple rounds of erythrocytic development, with production of merozoites that invade additional erythrocytes, lead to large numbers of circulating parasites and clinical illness. Each erythrocytic cycle lasts approximately 24 hours for *P. knowlesi*; 48 hours for

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ABSTRACT

Malaria, which is the most important parasitic disease of humans and one of the most important infectious disease problems in the world, causes hundreds of millions of illnesses and hundreds of thousands of deaths each year. Progress toward the elimination of malaria is evident in many areas, but the disease remains an enormous problem in much of the tropics, and in particular in Africa. Malaria commonly presents as an uncomplicated febrile illness, but it can progress to severe disease. Treatment of malaria with older agents is challenged by drug resistance, but artemisinin-based combination therapy is generally highly effective, except in areas of southeast Asia, where resistance to these therapies is a growing problem. The control of malaria relies on control of mosquito vectors, prompt treatment of infections, and use of drugs to prevent infection. Multiple approaches to malaria vaccines are under study.

KEYWORDS

malaria
Plasmodium falciparum
Plasmodium vivax
artemisinin

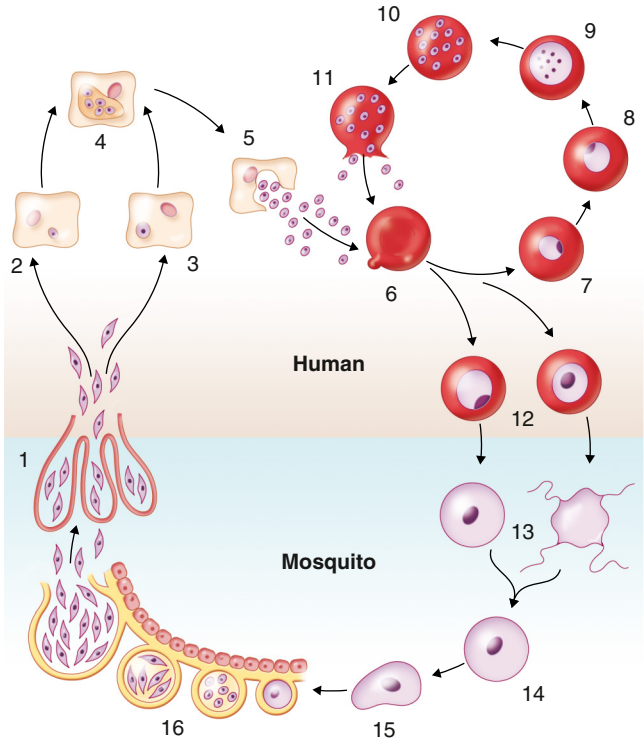

FIGURE 316-1. Life cycle of the malaria parasite. The *upper* and *lower halves* of the diagram indicate the human and anopheline mosquito parts of the cycle, respectively. Sporozoites from the salivary gland of a female *Anopheles* mosquito are injected under the skin (1). They then travel through the blood stream to the liver (2) and mature within hepatocytes to become tissue schizonts (4). Up to 30,000 parasites are then released into the blood stream as merozoites (5) and produce symptomatic infection as they invade and destroy red blood cells. However, in *Plasmodium vivax* and *Plasmodium ovale* infection, some parasites remain dormant in the liver as hypnozoites (3), which can later develop to tissue schizonts and merozoites, leading to relapse. Within the blood stream, merozoites (5) invade erythrocytes (6) and mature to the ring (7, 8), trophozoite (9), and schizont (10) asexual stages. Mature schizonts lyse their host erythrocytes and release the next generation of merozoites (11), which invade previously uninfected cells. Some erythrocytic parasites differentiate to sexual forms (male and female gametocytes) (12). When taken up by a mosquito, the gametocytes mature to male and female gametes (13), fuse to form zygotes (14), and then develop into ookinetes that invade the gut of the mosquito (15) and develop into oocysts (16). Mature oocysts produce sporozoites, which migrate to the salivary gland of the mosquito (1) to allow another human infection. (From Krogstad DJ: Blood and tissue protozoa. In: Schaechter M, Medoff G, Eisenstein BI, eds. *Mechanisms of Microbial Diseases*. 2nd ed. Baltimore: Williams & Wilkins; 1993:600.)

P. falciparum, *P. vivax*, and *P. ovale;* and 72 hours for *P. malariae*. Some erythrocytic parasites also develop into sexual gametocytes, which are taken up by mosquitoes. In the mosquito, gametocytes mature to gametes, and after fusion of male and female gametes to produce zygotes, parasites develop into ookinetes, oocysts, and then salivary gland sporozoites that are infectious for humans, thereby allowing completion of the life cycle and infection of others. *P. vivax* and *P. ovale* also cause a chronic liver infection, in which hypnozoites persist in hepatocytes in a dormant state not eradicated by most therapies for acute disease and subsequently can progress to erythrocytic infection and a relapse of clinical illness.

Pathogenic Features of Malaria Parasites

The most common clinical feature of malaria is fever. Fever coincides with rupture of large numbers of schizont-infected erythrocytes at the completion of the erythrocytic cycle and with high circulating levels of tumor necrosis factor (TNF). Severe falciparum malaria is associated with very high levels of TNF and other inflammatory cytokines, but the specific roles of cytokines in pathogenesis are not well understood. *P. falciparum* infects erythrocytes of all ages, so it is capable of routinely causing high parasitemias, with infection of more than 1% of erythrocytes and more than 10^5 infected erythrocytes per microliter of blood. Non–*P. falciparum* parasites infect smaller numbers of erythrocytes, thereby limiting the extent of infection and morbidity. Non–*P. falciparum* parasites are more likely to cause highly synchronous infections, so untreated infected patients can have regular cycles of fever every 48 (*P. vivax* and *P. ovale*) or 72 (*P. malariae*) hours, often with minimal symptoms between fever episodes.

The contribution of parasitic virulence determinants to the severity of malaria is poorly understood. A key biologic feature of *P. falciparum* infection is the ability of parasites to mediate the adherence of infected erythrocytes to a number of ligands on endothelial cells. By this mechanism, erythrocytes infected with the more mature stages of erythrocytic parasites do not circulate but rather adhere within small blood vessels in the brain and other organs. This phenomenon, termed cytoadherence, allows parasites to avoid passing through the spleen, where abnormal erythrocytes would be cleared. Cytoadherence is also likely to play a major role in mediating severe manifestations of *P. falciparum* malaria, with local inflammatory changes mediated by large numbers of adherent parasites leading to organ dysfunction. Pregnancy selects for a subset of *P. falciparum* strains that specifically bind to ligands in the placenta.

P. falciparum parasites use antigenic variation to evade the host immune response. The principal protein that mediates the cytoadherence of infected erythrocytes to endothelial cells, *P. falciparum* erythrocyte membrane protein-1 (PfEMP-1), is transported to the erythrocyte surface and is a target of host immune responses that limit infection. The PfEMP-1 family comprises about 60 proteins, but only one PfEMP-1 variant is expressed on the surface of an infected erythrocyte at a time. During the course of an infection, parasites frequently vary the expression of PfEMP-1s to stymie host responses. This factor and the high variability in sequence of many PfEMP-1 molecules present a broad repertoire of antigens and probably help explain the slow acquisition of protective antimalarial immunity. Antigenic variation and other aspects of immunologic diversity are not clearly understood for non–*P. falciparum* malaria parasites, but each species appears capable of repeated infections.

Host Immunity and Genetics

The nature of human immune responses to malaria is not well characterized, but protective responses require multiple infections and apparently humoral and cell-mediated responses.[5] Where *P. falciparum* malaria is common, disease occurs primarily in children. After some protection during the first few months of life, probably because of protective effects of maternal antiplasmodial antibodies and fetal hemoglobin, young children are infected frequently, experience repeated febrile malaria illnesses, and are at high risk of severe disease. With repeated episodes of malaria, children develop partial immunity. Immunity develops gradually, with some protection against severe malaria after only a few infections, increasing protection against symptomatic illness, and eventually strong protection against infection. However, antimalarial immunity is not complete; malaria can occur in individuals of any age. In addition, immunity requires boosting by repeated infections, so adults are at increased risk of disease if they return to a highly endemic site after an extended stay in a nonendemic area.

A number of human genetic polymorphisms offer protection against malaria. The best characterized is sickle hemoglobin (Chapter 149). Hemoglobin S heterozygotes are partially protected against severe *P. falciparum* malaria, leading to a balanced polymorphism in which the survival advantage of the polymorphism allows persistence of sickle cell disease in homozygotes. Other erythrocyte polymorphisms that also are likely to offer protection against malaria include hemoglobin C and E, thalassemias (Chapter 148), glucose-6-phosphate dehydrogenase deficiency (Chapter 147), and ovalocytosis (Chapter 147). The Duffy antigen, an erythrocyte chemokine receptor of uncertain function, is the principal receptor on human erythrocytes for attachment and subsequent invasion of *P. vivax*. Most Africans lack the erythrocyte Duffy antigen, explaining the uncommon prevalence of *P. vivax* in most of Africa.

CLINICAL MANIFESTATIONS

In highly endemic areas, young children experience frequent episodes of malaria, older children are frequently infected but less commonly symptomatic, and adults are uncommonly parasitemic or symptomatic; nevertheless, some risk of severe malaria remains at all ages. Infection can be severe in adults who are from nonendemic areas or who have lived away from endemic areas for an extended period of time.

Uncomplicated Malaria

Most malarial episodes, even with *P. falciparum* infection, are uncomplicated. The incubation period after an infectious bite is usually 10 to 14 days for *P. falciparum* and about 2 weeks for other species, but it can be much longer, especially in non–*P. falciparum* malaria and in individuals with prior immunity. The hallmark of malaria is fever, often with a nonspecific influenza-like

prodrome including headache and fatigue followed by a classic malarial paroxysm including chills, high fever, and then sweats. Patients may be remarkably well between febrile episodes. Fevers are typically irregular early in the illness, but without therapy, they may become regular, with 48-hour (*P. vivax* and *P. ovale*) or 72-hour (*P. malariae*) cycles, especially with non–*P. falciparum* disease. Headache, malaise, myalgias, arthralgias, rigors, confusion, cough, chest pain, abdominal pain, anorexia, nausea, vomiting, and diarrhea are common. Seizures are often simple febrile convulsions, especially in young children, but they also may represent evidence of severe neurologic disease.

Physical findings may be absent or include signs of anemia, jaundice, splenomegaly, and mild hepatomegaly. Rash and lymphadenopathy are not typical in malaria and thus are suggestive of another cause of fever.

Laboratory studies commonly show anemia, thrombocytopenia, and liver and renal function abnormalities. Anemia is caused by destruction of infected and uninfected erythrocytes, decreased hematopoiesis, and bleeding. In many endemic areas, most asymptomatic young children who have chronic *P. falciparum* infection have chronic anemia, sometimes exacerbated by nutritional deficits and intestinal roundworm infections.

Plasmodial parasites other than *P. falciparum* do not cause cytoadherence of infected erythrocytes, infect lower numbers of erythrocytes, and are much less commonly responsible for complicated and severe disease. However, *P. vivax* can cause severe disease, in particular respiratory compromise. *P. vivax* is also particularly prone to cause splenic rupture, although this complication can be seen with all malarial species. *P. malariae* most commonly causes a mild febrile illness, but chronic or repeated infection has been associated with an immune complex–mediated glomerulonephritis with nephrotic syndrome (Chapter 107). *P. knowlesi* can cause severe illness, including deaths. The short (24-hour) erythrocytic cycle of *P. knowlesi* may partly explain the propensity of this zoonotic parasite to cause severe illness.

Severe *P. falciparum* Malaria

Severe malaria can present with signs of severe illness or organ dysfunction (including prostration, impaired consciousness, convulsions, respiratory distress, shock, acidosis, severe anemia, excessive bleeding, hypoglycemia, jaundice, hemoglobinuria, and renal impairment) or a high parasite load (generally peripheral parasitemia >5% or >200,000 parasites/μL).[6] *P. falciparum* malaria can progress to cerebral malaria, including coma; noncardiogenic pulmonary edema, including severe respiratory compromise; and renal failure, severe anemia, acidosis, hypoglycemia, and other syndromes of organ dysfunction.

Cerebral malaria, the most common severe complication in children, is generally defined as altered consciousness in the setting of *P. falciparum* malaria. Seizures are common, and deep coma, abnormal posturing, focal neurologic findings, and abnormal respiratory patterns can be seen.

Severe anemia is a common presentation, particularly in young children. Respiratory failure is caused by noncardiogenic pulmonary edema and is more common in adults than in children. Acute renal failure is also more common in adults and generally due to hypoperfusion and acute tubular necrosis. Blackwater fever, including intravascular hemolysis and hemoglobinuria, has an uncertain etiology but can be caused by quinine; hepatic dysfunction, including jaundice, can be seen. Jaundice also may be caused by hemolysis. Splenic enlargement is common, and splenic rupture can occur. Hypoglycemia is common because of glucose consumption by parasites, increased demand, impaired gluconeogenesis, and quinine-induced insulin secretion. Metabolic acidosis, particularly lactic acidosis, is common, and electrolyte derangements can be seen. Coagulopathy, caused by consumption of clotting factors, and marked thrombocytopenia, caused by increased platelet turnover, can lead to significant bleeding. Bacterial infection and sepsis can coexist with malaria.

Pregnant women in endemic areas, in particular women in their first pregnancy who lack antibodies specific for placenta-binding parasites, are at high risk of morbidity, including anemia from high parasitic loads in the placenta. Poor fetal outcomes, including intrauterine growth restriction, spontaneous abortion, and low birthweight, are common.

Complications of Non–*P. falciparum* Malaria

The large majority of infections with non–*P. falciparum* parasites are uncomplicated both in endemic areas and in nonimmune travelers. Nonetheless, *P. vivax* infection is common in many areas, and it is responsible for about a quarter of children hospitalized with severe malaria in Asia and Oceania. Important features of severe *P. vivax* malaria include severe anemia and respiratory distress. All malarias, but in particular *P. vivax* infection, can be complicated by splenic rupture.

Chronic malaria infections can be complicated by hyperreactive malarial splenomegaly, with massive splenomegaly and findings of hypersplenism. Chronic infections can also lead to the nephrotic syndrome (Chapter 107), particularly with *P. malariae* infection.

DIAGNOSIS

Clinical Features

In individuals with febrile illness and malaria risk, it is essential to make a diagnosis promptly and important to distinguish the different species that infect humans because management differs according to the infecting species. Malaria is the most common cause of febrile illness in many areas that have limited diagnostic capabilities, so it is frequently diagnosed based only on presentation with a febrile illness. However, formal diagnosis is preferred. In travelers returning from endemic areas with fever, the travel history can aid in the diagnosis (Chapter 265). Malaria is most likely in individuals who failed to use measures to prevent infection and in travelers to the most highly endemic areas, such as rural sub-Saharan Africa. *P. falciparum* malaria generally has a fairly short incubation period in nonimmune individuals, so it presents within 1 to 2 months of return in more than 90% of infected travelers.[7] Infection with the other malarial species can present a number of months and uncommonly more than 1 year after exposure.

Blood Smears

The gold standard means of diagnosis in malaria-endemic areas is by thick blood smear.[8] In this procedure, one drop of blood is dried on a slide and parasites are stained with Giemsa. Parasites are easily identified by trained microscopists, and the density of parasites can be estimated on the basis of counts relative to those of leukocytes. However, thick blood smears do not allow identification of erythrocytic morphology, which is helpful in species diagnosis, and are difficult for individuals with limited training. Giemsa-stained thin blood smears offer an improved means of characterizing parasitic morphology, but the process is more time-consuming than for thick smears. Thus, thick smears are the standard means of diagnosis in highly endemic areas, whereas thin smears are preferred where malaria is uncommon and where laboratory personnel have ample time to examine multiple microscopic fields.

It is important to distinguish infecting species of malaria parasites. In *P. falciparum* infection, generally only ring-form asexual parasites are seen. Trophozoites of *P. vivax* and *P. ovale* are present in enlarged (and ovoid in the case of *P. ovale*) erythrocytes that contain inclusions known as Schüffner dots. Intraerythrocytic *P. malariae* and *P. knowlesi* trophozoites are often elongate in shape. Sexual stage gametocytes (which have a characteristic oblong shape in *P. falciparum*) are also seen on blood smears.

Antigen Detection

Multiple simple antigen detection tests incorporate colorimetric detection of one or two antigens in an assay that requires limited training and only a few minutes. The most used assays in Africa use histidine-rich protein-2 (HRP2), a protein that is abundant and long-lived but expressed only by *P. falciparum*. Other assays identify plasmodial lactate dehydrogenase and aldolase, which are produced by all human malarial species. Some tests use two antigens to separately identify *P. falciparum* and all-species plasmodial infection. Rapid diagnostic tests have become a standard component of many malaria control programs. One test is approved in the United States. However, there is increasing evidence of *P. falciparum* lacking HRP2 in some areas, in particular in parts of South America and the Horn of Africa, thereby leading to concern that HRP2-based diagnostic tests may miss some cases of falciparum malaria, and that diagnostic approaches may need to be changed.[9]

Other Diagnostic Tests

Serologic tests can identify prior malaria infection, but responses develop slowly and persist for an extended period, so these tests have limited value for acute diagnosis. Malaria parasites can be identified with molecular amplification assays using primers encoding genus- and species-specific sequences. These tests are highly sensitive and convenient for research purposes because they can be conducted on DNA extracted from blood spotted onto filter paper in field settings. Quantitative polymerase chain reaction assays are most sensitive, but loop-mediated isothermal amplification and related assays are highly sensitive and more practical for many field settings. Molecular assays are not practical for routine diagnosis, however, because of the time required, the uncertain significance of a positive result in endemic areas where low-level parasitemia may be clinically insignificant, cost, and logistical requirements.

Human Immunodeficiency Virus (HIV) Coinfection

HIV infection appears to disrupt the acquired immune response to malaria and thereby increases the incidence and severity of malaria. Acute malaria elevates the HIV viral load and so may increase the risk of HIV transmission. HIV infection also may be associated with reduced efficacy of antimalarial treatment, especially in the setting of severe immune suppression. Therapies for each infection may have an impact on the other, thereby leading to unanticipated effects on drug efficacy or toxicity. For example, daily prophylactic trimethoprim–sulfamethoxazole in HIV-infected patients with low CD4 counts offers partial protection against malaria.

TREATMENT

Prompt treatment is key for optimal outcomes, especially for *P. falciparum*. With severe illness, treatment should be started as soon as a presumptive diagnosis is made. Most treatments do not eradicate gametocytes, so persistence of these forms for a few weeks is not a sign of treatment failure.

Antimalarial Drug Treatment

The treatment of falciparum malaria is challenging because of evolving patterns of drug resistance. Artemisinin-based combination therapy is recommended in nearly all countries with endemic *P. falciparum* malaria (Table 316-1).[10] Non–*P. falciparum* malaria is still generally treated with chloroquine, although chloroquine resistance is increasing in *P. vivax;* resistant vivax malaria can be treated with other drugs used to treat falciparum malaria.

Artemisinins

Artemisinin, the active component of an herbal medicine from China, and a number of its analogues offer rapid elimination of circulating malaria parasites and activity against gametocytes to limit disease transmission. These drugs are short-acting, thereby leading to frequent recrudescences of infection after short-course monotherapy. For this reason and to limit selection of resistance, artemisinins are now used in combination with longer-acting drugs to treat malaria in 3-day regimens. These combinations have become the standard therapies for *P. falciparum* malaria (Table 316-2). Leading regimens are fixed-dose combinations of artemether–lumefantrine (Coartem; the only artemisinin-based combination therapy approved in the United States), artesunate–amodiaquine, artesunate–mefloquine, dihydroartemisinin–piperaquine, and artesunate-pyronaridine. All these regimens have demonstrated excellent treatment efficacy in Africa,[A1,A2] including in children[A3] and pregnant women[A4]; different regimens have had optimal efficacy in different regions. Artemisinin-based combination therapies also have shown excellent efficacy for the treatment of vivax malaria.[A5] Other artemisinin-based combination therapies that are not currently recommended by the World Health Organization (WHO) but are available for the treatment of malaria in some countries and have also shown good efficacy include artero-lane–piperaquine,[A6] artemisinin–piperaquine,[A7] and artemisinin–naphthoquine. Resistance of *P. falciparum* to artemisinins, manifesting as a prolonged time to parasite clearance after therapy, has emerged in Southeast Asia in association with mutations in the *kelch13* gene.[11] Of great concern, treatment efficacies of artemisinin-based combination therapies have waned in parts of Southeast Asia, most notably for dihydroartemisinin–piperaquine, with resistance to both components of the regimen leading to high clinical failure rates. In Africa, parasites with genetic polymorphisms suggestive of similar resistance phenotypes have recently emerged in Rwanda[12] and Uganda[13]; these polymorphisms have been accompanied by delayed clearance of malaria parasites, but it is not yet clear if they are associated with poorer efficacy for artemisinin combinations.

Artemisinins also have a key role for the treatment of severe malaria. IV artesunate is superior to quinine for the treatment of severe malaria, and it is the first-line therapy for severe malaria in the United States. For settings with limited infrastructure, intramuscular artemether and intramuscular or intrarectal artesunate[A8] have also shown excellent efficacy. Artemisinins are generally very well tolerated, with minimal toxicity, although delayed hemolysis can occur after therapy, in particular with IV artesunate.

Chloroquine and Other Aminoquinolines

Chloroquine, which remains the treatment of choice for non–*P. falciparum* malaria and *P. falciparum* malaria in the few areas without resistance (Central America and the Caribbean), is generally rapidly effective and well tolerated. For *P. vivax* and *P. ovale* infections, primaquine or tafenoquine also must be given to eradicate dormant liver forms and thereby prevent subsequent relapse. Chloroquine remains effective as weekly chemoprophylaxis to prevent malaria in areas without resistance.

Amodiaquine and piperaquine probably share mechanisms of action with chloroquine, but they are routinely active against chloroquine-resistant parasites because of increased potency compared with chloroquine and some differences in mechanisms of resistance; each is now a component of a leading artemisinin-based combination therapy (see Table 316-2). Amodiaquine is somewhat less well tolerated than other aminoquinolines. It is generally safe for short-term use but can cause rare serious hepatic and bone marrow toxicity,

TABLE 316-1 TREATMENT OF MALARIA*

CHLOROQUINE-RESISTANT PLASMODIUM FALCIPARUM, RESISTANT PLASMODIUM VIVAX, OR SPECIES UNIDENTIFIED	
ORAL TREATMENT OF UNCOMPLICATED DISEASE	
Coartem (artemether 20 mg, lumefantrine 120 mg)	4 tablets orally twice daily for 3 days
or	
Malarone (atovaquone 250 mg, proguanil 100 mg)	4 tablets daily for 3 days
or	
Quinine	650 mg quinine sulfate 3 times daily for 3-7 days
plus	
Doxycycline	100 mg twice daily for 7 days
or plus	
Clindamycin	600 mg twice daily for 7 days
or	
Mefloquine	750 mg followed by 500 mg in 6-8 hours; also can be given as a single 1250-mg dose, although this is less well tolerated than the divided dose
COMPLICATED *P. FALCIPARUM* MALARIA OR UNABLE TO TOLERATE ORAL MEDICATIONS†	
IV artesunate	2.4 mg/kg every 12 hr on day 1; then daily for 2 additional days
or	
IV quinine dihydrochloride§,‖	20 mg/kg over 4 hr; then 10 mg/kg every 8 hr
or	
IM artemether‖	3.2 mg/kg IM; then 1.6 mg/kg/day
CHLOROQUINE-SUSCEPTIBLE *P. FALCIPARUM* AND OTHER SPECIES	
Chloroquine phosphate	1 g, followed by 500 mg at 6, 24, and 48 hr *or* 1 g at 0 and 24 hr; then 0.5 g at 48 hr
plus (for *P. vivax* and *P. ovale* only)	
Primaquine¶	30-mg base (52.6 mg primaquine phosphate) daily for 14 days
or	
Tafenoquine¶	300 mg single dose

*Dosages are for adults.
†IV regimens should be given until the patient can tolerate oral agents and then followed by a course of oral therapy (doxycycline, clindamycin, or full treatment courses of other drugs, as listed) when patients can tolerate this.
§Cardiac monitoring should be in place during IV administration of quinine.
‖Not available in the United States.
¶Use primaquine or tafenoquine only after demonstrating normal levels of glucose-6-phosphate dehydrogenase.
IM = intramuscular; IV = intravenous.

TABLE 316-2 RECOMMENDATIONS FOR THE TREATMENT OF *PLASMODIUM FALCIPARUM* MALARIA IN DEVELOPING COUNTRIES*

REGIMEN	NOTES
Artemether–lumefantrine (Coartem, Riamet)	First-line therapy in many countries; FDA approved
Artesunate–amodiaquine (ASAQ)	First-line therapy in some African countries
Artesunate–mefloquine	Standard therapy in parts of Southeast Asia
Dihydroartemisinin–piperaquine	Limited by resistance in Southeast Asia, but highly effective elsewhere
Artesunate-pyronaridine	Highly efficacious newer regimen

*Recommendations modified from World Health Organization. Guidelines for malaria, 2021 (https://www.who.int/teams/global-malaria-programme/guidelines-for-malaria).
FDA = U.S. Food and Drug Administration.

especially with chronic use, and so it is not recommended for chemoprophylaxis. The artemisinin-based combination therapy dihydroartemisinin-piperaquine has shown excellent efficacy in most regions, but frequent failures, mediated by resistance to both components of the regimen, are seen in parts of Southeast Asia.

Mefloquine, Lumefantrine, and Pyronaridine

Mefloquine offers effective therapy and chemoprophylaxis for most chloroquine-resistant strains of *P. falciparum* as well as for other species. Resistance to mefloquine is uncommon but has been seen in parts of Southeast Asia, with failures of the artemisinin-based combination therapy artesunate-mefloquine. Mefloquine is one of three drugs recommended for chemoprophylaxis against *P. falciparum* by the Centers for Disease Control and Prevention (CDC). Tolerability of chemoprophylactic and especially treatment doses of mefloquine is often limited by neurologic and gastrointestinal toxicity. Lumefantrine is used only in combination and offers effective therapy with artemether as Coartem, the most widely used artemisinin-based combination therapy used to treat falciparum malaria. The artemisinin-based combination therapy artesunate-pyronaridine offers another effective treatment for falciparum malaria. Importantly, there is no clear evidence of *P. falciparum* resistance to either lumefantrine or pyronaridine.

Quinine

Quinine offers rapid action against all species with limited known resistance except in Southeast Asia, where failures against *P. falciparum* malaria are fairly common. Quinine can be used to treat uncomplicated malaria, but gastrointestinal and other nonspecific toxicities lead to difficulty in tolerating a full 7-day treatment course. This problem is circumvented by combining a 3-day course of quinine with other agents. For severe disease, intravenous (IV) quinine is a standard therapy but is not as efficacious as IV artesunate.

Primaquine and Tafenoquine

Primaquine (typically 30 mg daily for 14 days)[A9] and tafenoquine (a single 300-mg dose)[A10,A11] are related aminoquinolines that are the only available drugs to eradicate dormant liver forms of *P. vivax* and *P. ovale* and to prevent the relapses that will otherwise occur often after therapy with chloroquine and other agents. Primaquine and tafenoquine are also alternative agents for chemoprophylaxis against *P. falciparum* and other species. Both drugs can cause hemolysis or methemoglobinemia (Chapter 144) in individuals who have a deficiency in glucose-6-phosphate dehydrogenase (G6PD) (Chapter 147), and patients should be tested for this deficiency before prescribing these drugs. A single low dose of primaquine in conjunction with artemisinin-based combination therapy can lower transmission to mosquitoes.

Inhibitors of Folate Metabolism

Inhibitors of dihydrofolate reductase and dihydropteroate synthase are used in fixed-dose combination regimens for the treatment and prevention of malaria, although resistance of *P. falciparum* to sulfadoxine–pyrimethamine is common in most endemic areas. For chemoprophylaxis, sulfadoxine–pyrimethamine is no longer recommended because of drug resistance and rare life-threatening dermatologic toxicities. However, less frequent dosing in intermittent preventive therapy regimens has been well tolerated and has decreased malaria in high-risk African groups, particularly pregnant women and young children, although efficacy is limited by drug resistance. Seasonal malaria chemoprevention with monthly combined sulfadoxine–pyrimethamine and amodiaquine during the transmission season is now recommended for malaria control in areas of Africa with highly seasonal transmission and limited drug resistance, mostly in West Africa.

Atovaquone–Proguanil (Malarone)

This fixed-dose combination of a dihydrofolate reductase inhibitor pro-drug and atovaquone, which has a unique antimalarial mechanism, has excellent efficacy against most *P. falciparum* infections. It is approved for both treatment and chemoprophylaxis of *P. falciparum* malaria and other species in the United States, where it is now widely used for both indications. Malarone offers excellent efficacy with minimal toxicity. Adverse effects may include gastrointestinal symptoms, elevations in liver enzymes, headache, and rash. Widespread use in developing countries is limited by high cost and concerns about resistance.

Antibiotics

A number of antibacterials are slow-acting antimalarials. Tetracyclines and clindamycin should not be used alone to treat malaria but are combined with quinine to allow a shorter duration of therapy with that drug. In addition, doxycycline is effective in chemoprophylaxis of most *P. falciparum* malaria and is recommended for this purpose by the CDC, in particular for travelers to regions of Southeast Asia, where malarial parasites have high-level resistance to other drugs.

Multimodal Treatment of Severe Malaria

Severe malaria is a medical emergency and requires parenteral therapy. With appropriate prompt therapy and supportive care, rapid recoveries may be seen even in very ill individuals. Standard therapy for severe malaria is IV artesunate (see Table 316-1). If acquisition is delayed, short-term therapy with an oral agent is appropriate until IV artesunate is available. Appropriate care of severe malaria includes close nursing care; maintenance of fluids, electrolytes, and glucose; respiratory and hemodynamic support; and consideration of anticonvulsants for seizures (Chapter 372). Blood glucose levels should be observed closely, with glucose replacement as needed. Transfusions should be avoided when possible but play a key role in the management of patients with severe anemia. For respiratory failure, mechanical ventilation can be life-saving. Presumptive use of antibiotics is warranted when signs of sepsis are noted. Hemofiltration or hemodialysis can be life-saving for acute renal failure (Chapter 117). Aggressive fluid resuscitation, blood transfusion for moderate anemia, exchange transfusion, and specific treatment of acidosis are of uncertain value. The course of IV artesunate should be followed by oral longer-acting drugs, typically a full course of an oral artemisinin-based combination therapy, Malarone, mefloquine, or quinine plus doxycycline or clindamycin.

PREVENTION

Key malaria control interventions in malaria-endemic regions are personal protection against mosquito bites with insecticide-impregnated bed nets[A12]; control of mosquito vectors with residual spraying of insecticides; routine prompt use of artemisinin-based combination therapies, which offer rapid control of malaria infections and activity against gametocytes to limit transmission to mosquitoes; and selected use of intermittent preventive therapies to decrease malarial incidence in high-risk groups. A long-lasting piperonyl butoxide-treated insecticidal net and indoor residual spraying interventions have shown improved control of a malaria transmission compared with standard long-lasting insecticidal nets.[A13–A15] However, elimination remains challenging in many areas, in part because asymptomatic individuals infected with malaria parasites can be major drivers of transmission.[I4] Reactive focal vector control and reactive focal mass drug administration, whether implemented alone or in combination, can reduce malaria transmission compared with standard screening and treatment of individuals in close proximity to index cases.[A16] Ivermectin,[I5] which is used to treat some helminth infections, is also mosquitocidal and can reduce malaria transmission when provided in addition to standard malaria therapy.[A17] Daily prophylactic trimethoprim–sulfamethoxazole (typically 1 double-strength tablet daily), which is commonly used to prevent opportunistic infections in individuals with HIV infection, has some protection against malaria in Africa.

The RTS,S vaccine, which is based on an immunogenic sporozoite antigen, is now recommended for the prevention of falciparum malaria in children who live in regions with moderate to high transmission. This recommendation is based on multiple clinical trials that showed about 25 to 50% protection in the year after immunization (but lower levels of protection in very young children in areas of highest malaria exposure), though less protection over longer periods of time.[A18] R21, another vaccine based on the same antigen, recently demonstrated about 75% preventive efficacy.[A19] Based on these results, a new concept is seasonal malaria immunization, with provision of short-acting vaccines, potentially in conjunction with preventive drugs during the high transmission season.[A20] Another approach under study is immunization with *P. falciparum* sporozoites, with strategies including inoculation of sporozoites that are radiation-attenuated, chemoattenuated (with concurrent therapy to eliminate blood stream parasites), or genetically attenuated.[I6] Other approaches under study include preventive monoclonal antibodies[A21] and vaccines containing erythrocytic, liver-stage, and sexual-stage antigens.

Preventive Measures for Travelers to Malaria-Endemic Regions

It is important for nonimmune travelers (Chapter 265) to endemic areas to be protected against potentially lethal malaria. Travelers should decrease exposure to night-biting anopheline mosquitoes by use of insecticide repellents and sleeping in rooms that are screened or equipped with insecticide-impregnated bed nets. Standard advice for travelers to endemic areas is also to use low doses of preventive drugs chosen on the basis of the resistance profile of the particular region. Chloroquine is still recommended for malaria-endemic regions of Central America and the Caribbean. For nearly all other areas, the CDC recommends use of daily Malarone, weekly mefloquine, or daily doxycycline; details of dosing vary, but it is important to continue therapy after return from travel to eliminate parasites as they emerge from the liver (Table 316-3). Primaquine and tafenoquine (given as 200 mg/day for 3 days before departure, then 200 mg/week during travel and for 1 week post travel)[A22] offer alternative chemoprevention regimens. For areas with high risk of *P. vivax* malaria, some authorities recommend a full treatment course of primaquine after travel to

TABLE 316-3 ORAL CHEMOPROPHYLAXIS OF MALARIA*

AREAS WITH CHLOROQUINE-RESISTANT *PLASMODIUM FALCIPARUM*	
Malarone	1 tablet (250 mg artesunate/100 mg proguanil) daily
Mefloquine	250 mg weekly
Doxycycline	100 mg daily
Primaquine†	30 mg daily during exposure (chemoprophylaxis) or 30 mg daily for 14 days (terminal prophylaxis against *P. vivax* and *P. ovale*)
Tafenoquine†	200 mg daily for 3 days prior to travel, then 200 mg weekly during travel
AREAS WITHOUT CHLOROQUINE-RESISTANT *P. FALCIPARUM*	
Chloroquine phosphate	500 mg weekly

*Recommendations may change on the basis of drug resistance patterns. For additional details and pediatric dosing, see Centers for Disease Control and Prevention guidelines (http://www.cdc.gov). Begin 1 to 2 weeks before travel for mefloquine and 2 days before for doxycycline, Malarone, and primaquine; continue for 4 weeks after leaving the endemic area (1 week for Malarone and tafenoquine; 2 weeks for primaquine). All doses refer to salts unless indicated.

†Use primaquine only after demonstrating normal levels of glucose-6-phosphate dehydrogenase.

eliminate dormant liver stages. No chemoprophylaxis or mosquito avoidance methods are fully protective, so consideration of malaria as a cause of fever in returned travelers is essential (Chapter 265).

PROGNOSIS

Patients with malaria caused by *P. vivax, P. ovale,* or *P. malariae* generally respond well to chloroquine and make an uneventful recovery. Chloroquine-resistance is increasing with *P. vivax* from many areas; failures of initial treatment are usually not dangerous but should be followed by treatment with another regimen, such as an artemisinin-based combination therapy, Malarone, or mefloquine.

Patients with *P. falciparum* malaria also generally respond well to prompt therapy as long as the disease is not overly advanced at presentation. The mortality rate in patients with uncomplicated *P. falciparum* malaria is about 0.1%. For cerebral malaria, the mortality rate is 15 to 25%, with about 10% developing persistent neurologic sequelae, but many patients do remarkably well with appropriate therapy.

A common cause of death from *P. falciparum* malaria, in particular in children in endemic areas, is severe anemia. With frequent malarial infections and chronic anemia, children are ill equipped to manage acute worsening of the anemia caused by acute malarial illness. With limited access to health care, children often present for medical care late in the course of illness if at all and many deaths result. Key contributing factors to most deaths from *P. falciparum* malaria are delays between the appearance of symptoms and presentation for definitive therapy, as well as the use of suboptimal therapies. Presentation with high-level parasitemia (>200,000 parasites/μL or >5% parasitemia) or signs of severe malaria are predictive of a poor outcome. However, with aggressive support, even individuals with severe disease can often experience complete recoveries.

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317 AFRICAN SLEEPING SICKNESS

WILLIAM A. PETRI, JR.

DEFINITION

Human African trypanosomiasis, commonly known as sleeping sickness, is a vector-borne parasitic disease transmitted to humans and animals by the bite of the tsetse fly (genus *Glossina*). Infection is caused by protozoa of the genus *Trypanosoma* and species *brucei*. In humans, two forms of illness are caused by two distinct subspecies that are morphologically identical but differ in their geographic range and clinical presentations. *Trypanosoma brucei gambiense* is typically found in West and Central Africa and *Trypanosoma brucei rhodesiense* in East Africa. *T. b. gambiense* has a more chronic course, whereas *T. b. rhodesiense* causes a rapid disease course; both have late stages marked by meningoencephalitis that results in coma and death if untreated. A third subspecies, *Trypanosoma brucei*, causes chronic infection called nagana in cattle, but humans are not susceptible to this organism. Chagas disease, or American trypanosomiasis, is covered in Chapter 318.

The Pathogen

The surface of the trypanosome is covered by a dense, homogeneous coat of variant surface glycoproteins (VSGs), which are immunodominant. Each individual trypanosome expresses only one VSG at a time but possesses more than 1000 different silent copies of the VSG gene, and switching to a new VSG occurs at a frequency of about 1 per million parasites. Hence, the trypanosomes expressing a given VSG will eventually be cleared by the host's antibody response, but any individual trypanosome that has switched to a new VSG will evade immune clearance, thereby resulting in a new peak of parasitemia.[1]

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TABLE 316-3 ORAL CHEMOPROPHYLAXIS OF MALARIA*

AREAS WITH CHLOROQUINE-RESISTANT *PLASMODIUM FALCIPARUM*	
Malarone	1 tablet (250 mg artesunate/100 mg proguanil) daily
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317 AFRICAN SLEEPING SICKNESS

WILLIAM A. PETRI, JR.

DEFINITION

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The Pathogen

The surface of the trypanosome is covered by a dense, homogeneous coat of variant surface glycoproteins (VSGs), which are immunodominant. Each individual trypanosome expresses only one VSG at a time but possesses more than 1000 different silent copies of the VSG gene, and switching to a new VSG occurs at a frequency of about 1 per million parasites. Hence, the trypanosomes expressing a given VSG will eventually be cleared by the host's antibody response, but any individual trypanosome that has switched to a new VSG will evade immune clearance, thereby resulting in a new peak of parasitemia.[1]

ABSTRACT

Human African trypanosomiasis, commonly known as sleeping sickness, is a vector-borne parasitic disease transmitted to humans and animals by the bite of the tsetse fly. Infection is caused by protozoa of the genus *Trypanosoma* and species *brucei*. In humans, two forms of illness are caused by two distinct subspecies that are morphologically identical but differ in their geographic range and clinical presentations. *Trypanosoma brucei gambiense* is typically found in West and Central Africa and *Trypanosoma brucei rhodesiense* in East Africa. *T. b. gambiense* has a more chronic course, whereas *T. b. rhodesiense* causes a rapid disease course; both have late stages marked by meningoencephalitis that results in coma and death if untreated. Treatment depends on the infecting organism and the stage of disease.

KEYWORDS

African sleeping sickness
Trypanosoma brucei
tsetse fly
pentamidine
nifurtimox
eflornithine
meningoencephalitis

Recombination between VSG alleles ensures a virtually limitless repertoire of new VSGs, so antibody-mediated parasite eradication is impossible.

EPIDEMIOLOGY

Human African trypanosomiasis is diminishing in importance as a result of increased in public health control efforts. In the past, major epidemics occurred in the Congo basin and Uganda between 1896 and 1906, in numerous endemic countries in the 1920s, and then again in the early 20th century. More recently, however, access of at-risk populations to diagnosis and treatment has led to a dramatic reduction to less than 2000 cases in 2017-2018. Since 2015, more than 90% of reported cases are due to *T. b. gambiense*, the majority being from the Democratic Republic of the Congo, and less than 100 cases of *T. b. rhodesiense* have been reported annually since 2015. However, many people are thought to die of human African trypanosomiasis without an accurate diagnosis, and African trypanosomiasis remains a looming threat to an estimated 60 million people who live in tsetse fly–inhabited areas among 36 countries of sub-Saharan Africa.[2]

The geographic distribution includes areas where the vector, parasite, reservoir hosts, and human hosts cohabit (E-Fig. 317-1). In general, these locales include focal areas on the African continent within 15 degrees north and 15 degrees south latitude, with a predilection for wooded rural areas. Humans at greatest risk for infection rely on animal husbandry, agriculture, fishing, and hunting for their livelihoods. Often, disease is concentrated among foci of rural areas, having significant socioeconomic impact on affected villages. With a few exceptions, this infection is never found in urban areas. Fewer than 50 cases are reported annually outside of Africa, usually the result of travel by North Americans or Europeans to African game reserves.[3]

T. b. gambiense is transmitted by tsetse flies from the *Glossina palpalis* group. Tsetse flies are typically found along riverbanks of wooded areas in the more tropical areas of Central and West Africa. *T. b. gambiense* is not generally considered a zoonotic disease. The reservoir hosts and the focus of public health campaigns are mainly humans. The role of animal reservoirs for this organism remains undetermined, but natural infections have been reported in domestic animals such as dogs, sheep, cattle, and pigs.

T. b. rhodesiense is transmitted by tsetse flies that belong to the *Glossina morsitans* group and that are commonly found among woodland and savannah areas of East and Central Africa. *T. b. rhodesiense* is a zoonotic disease with numerous wild and domestic species of animals acting as reservoirs that sustain the parasite. Domestic species, especially cattle, can drive outbreaks and, as a result, are the focus of successful prevention campaigns.

PATHOBIOLOGY

After the bite of a tsetse fly carrying metacyclic trypomastigotes, a local reaction (chancre) may form at the inoculation site. This sign is seen with *T. b. rhodesiense* infection and is more frequently observed in travelers, but it is rarely seen with *T. b. gambiense* infection. Parasites subsequently disseminate into the blood and lymphatic systems in what is considered stage I of the disease. Spread of the parasites into the central nervous system (CNS) defines stage II of the disease, which is invariably fatal if untreated. The parasite appears to remain extracellular throughout the course of infection. As an extracellular microbe, the parasite must evade immune clearance to establish a persistent infection.

Peaks and waves of parasitemia occur during stage I disease and result in the classic symptom of intermittent fever. These bouts of fever correspond to a type 1 inflammatory response (Chapter 36), in which classically activated macrophages produce high levels of tumor necrosis factor (TNF) and nitric oxide. This response helps control the parasitemia but also contributes to tissue damage. Type 2 inflammatory responses with high levels of interleukin-10 then limit the production of TNF and nitric oxide after the initial parasitemia has been controlled. Antibody responses are directed to VSGs and other trypanosome antigens (e.g., antigens from lysed parasites), but autoantibodies are also produced. Generalized febrile episodes are observed in association with lymphadenopathy, myocardial inflammation, and pericardial inflammation. Cardiac involvement is typically more severe with *T. b. rhodesiense* infection.

In stage II of the disease, parasites cross the blood-brain barrier and invade the CNS. Acute meningoencephalitis develops, and the variety of inflammatory cells that infiltrate the brain include macrophages, lymphocytes, plasma cells, Mott cells (plasma cells with spherical cytoplasmic inclusions composed of immunoglobulin), and morular cells (plasmacytoid cells with transparent hyaline vesicles in the cytoplasm). These inflammatory cells are found in the meninges, which become thickened, as well as in the perivascular spaces and neuropil. Edema, hemorrhage, and granulomatous lesions are often present; thrombosis and neuronal degeneration may also be observed.

Genetic resistance to African sleeping sickness is due to a common (in individuals of African descent) polymorphism in the gene for $APOL_1$, which is a component of high-density lipoprotein. This gene product mediates serum resistance to the parasite. An untoward consequence of this polymorphism is that individuals with two copies of the variant allele (15% of African Americans) are at increased risk of chronic kidney disease (Chapter 107).[4]

CLINICAL MANIFESTATIONS

The clinical manifestations of human African trypanosomiasis differ on the basis of the infecting organism. *T. b. gambiense* usually is more of a chronic disease, with an estimated average duration of 3 years. By comparison, infection with *T. b. rhodesiense* progresses much more rapidly, leading to coma and death within weeks to months. However, infection with *T. b. gambiense* also can cause a rapid decline. Other similarities include an early hemolymphatic stage (stage I) and a late stage characterized by prominent CNS disease, including meningoencephalitis (stage II).[5]

West African Sleeping Sickness

Infection starts after the bite of a fly infected with *T. b. gambiense*. At the site of inoculation, a painful, indurated, and erythematous trypanosomal chancre may develop 1 to 2 weeks after the bite and resolve spontaneously after several weeks. On occasion, the chancre may ulcerate. However, these features are rarely seen at the time of clinical presentation and sometimes are not known to have occurred on history; thus many patients develop disseminated disease without awareness of a localized infection.

The hemolymphatic stage, when parasites disseminate throughout the body, may not be manifested clinically until weeks or months after the initial bite. Typical symptoms include intermittent spiking fevers, occasionally accompanied by headaches and malaise. These features may persist for weeks or months because of the cyclic nature of parasitemia and antibody production against the various antigens sequentially expressed by the parasite.

Lymphadenopathy (Chapter 154) is a common finding in West African sleeping sickness. Whereas regional lymphadenopathy may develop after the initial bite, generalized lymphadenopathy around the head and neck is often found as chronic illness develops. Enlargement of nodes in the posterior cervical triangle, commonly known as Winterbottom sign, is the classic finding, but other cervical and supraclavicular nodes may also be involved. Affected nodes are discrete, movable, rubbery nodes that are nontender to palpation; over time, they may become more indurated because of fibrosis.

Other symptoms reported include pruritus, occasionally accompanied by rash, arthralgias, and periarticular swelling, as well as by transient edema of the extremities and face. Less common symptoms include features consistent with neuroendocrine dysfunction, including loss of libido and impotence, amenorrhea and infertility, alopecia, and gynecomastia. Signs of disease include hepatomegaly and splenomegaly; cardiac dysfunction, including tachycardia; electrocardiographic abnormalities such as prolonged QTc intervals and repolarization changes; and, less commonly, pericarditis or myocarditis. Hemolytic anemia and derangements in liver function test results may occur.

Months or even years after the initial infection, stage II disease develops and is characterized by headaches, daytime somnolence, and neuropsychiatric features. Behavioral changes, including irritability, confusion, inability to concentrate, and lassitude, are among the first signs of CNS disease; psychosis has also been described. Neurologic findings are numerous and include a variety of motor and sensory disturbances, including extrapyramidal features, dysesthesias, and visual impairment. The symptoms have given the infections its common name of sleeping sickness and are manifested by daytime somnolence and nocturnal irritability. Late-stage disease is marked by cerebral edema and meningoencephalitis. Progressively, a loss of neurologic function can lead to paralysis. Patients may succumb to aspiration pneumonias or malnutrition; otherwise, coma leads to death in the absence of treatment.

East African Sleeping Sickness

Compared with Gambian sleeping sickness, East African sleeping sickness is more rapidly progressive. The infective bite is more frequently associated with the development of a chancre, although some studies report a chancre in only 20% of patients. An incubation period of days to weeks elapses before other signs or symptoms occur. Initial symptoms include severe intermittent fevers that may resemble those found with malaria. Posterior cervical lymphadenopathy is not as common as with *T. b. gambiense*. Skin changes are more prominent, and rashes in the early stage of infection are particularly common in expatriates with the infection. In addition, cardiac manifestations are more commonly and clinically relevant; tachycardia, arrhythmias, myocarditis, and heart failure

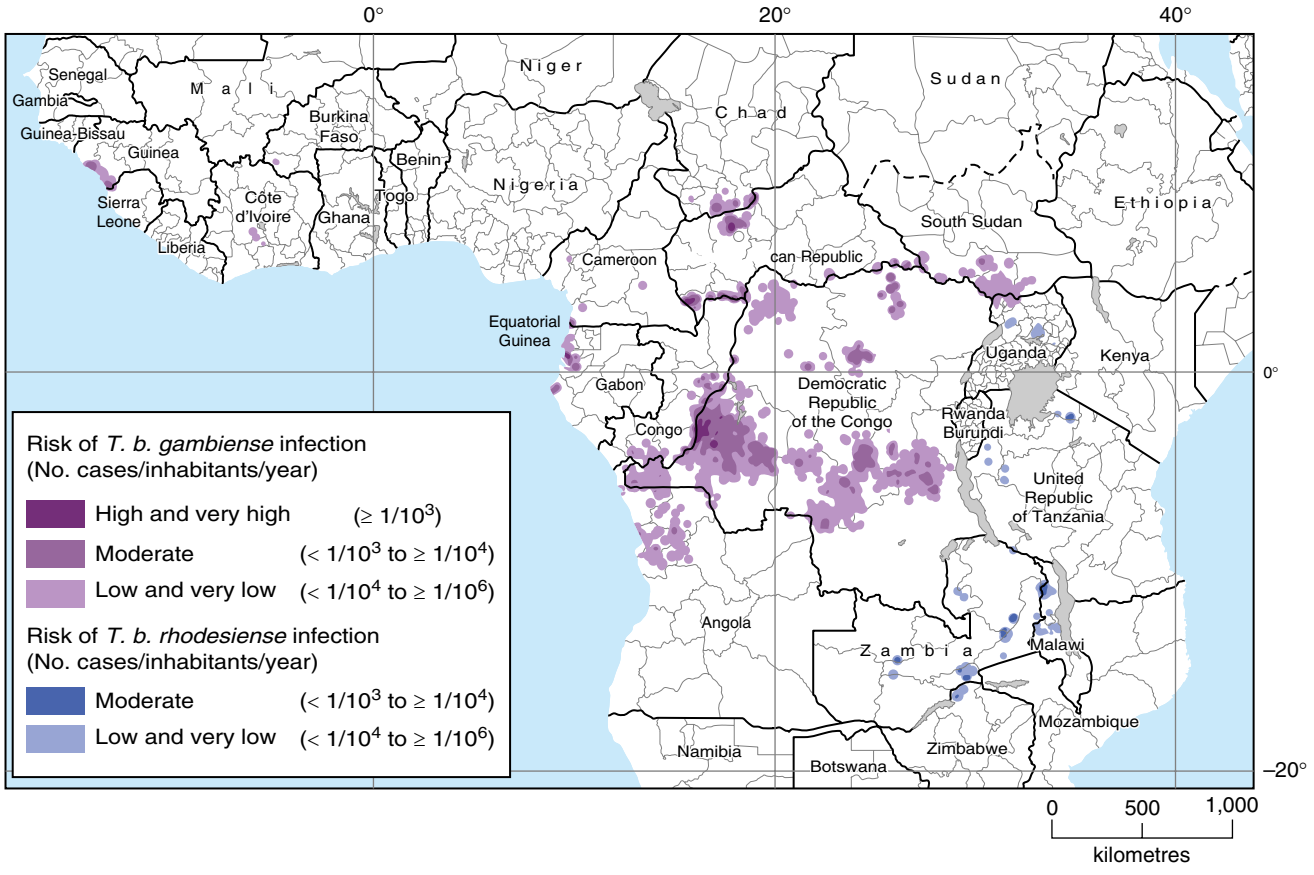

E-FIGURE 317-1. **Map of human African trypanosomiasis.**

may be severe enough to cause death before the development of severe CNS disease. CNS disease mirrors that of West African sleeping sickness, but the onset occurs earlier and the rate of deterioration is more rapid. Hematologic abnormalities include anemia,[6] thrombocytopenia, and disseminated intravascular coagulation. Death may ensue after weeks or months without treatment.

DIAGNOSIS

Epidemiologic clues and clinical findings may together suggest the diagnosis of human African trypanosomiasis, but definitive diagnosis relies on demonstration of the parasite. In the early stage of disease, light microscopy and Giemsa stain can visualize the highly motile parasites directly from fresh specimens of fluid expressed from chancres or lymph node aspirates. Peripheral blood smears (Figure 317-1), including Giemsa-stained thick and thin smears and bone marrow aspirates, also can show the parasite, especially blood during stage I disease when parasitemia is high. The threshold for visualization of parasites by thick smear is approximately 5000 parasites/mL, so direct visualization is more common with *T. b. rhodesiense* infection, given the higher parasite load. Polymerase chain reaction (PCR) analysis of blood, if available, is more sensitive than smears or culture of blood and lymph nodes.[7]

Serologic tests are also available to diagnose *T. b. gambiense* infection. The *T. b. gambiense* card agglutination test, which is commonly used in screening programs, has a sensitivity that ranges from 87% to 98%, depending on the population under study, with a specificity that may be as high as 95%. Rapid serologic tests for infection with *T. b. gambiense* include human African trypanosomiasis SeroStrop (which uses a dipstick method) and the human African trypanosomiasis Sero + K SeT test (which uses a lateral flow device) for testing blood or plasma, respectively. No serologic tests are available for *T. b. rhodesiense* infection.

Cerebrospinal fluid (CSF) must also be analyzed to determine the most appropriate treatment. Abnormalities in CSF include an elevated opening pressure, increased cell counts and total protein levels, and an increased polyclonal immunoglobulin M (IgM). Stage II disease is defined by the presence of more than 5 white blood cells/μL, the presence of trypanosomes, or an elevated total protein (>370 mg/L) in the CSF. PCR or latex-agglutination testing for CSF IgM hold promise but have not proven superior to direct visualization or culture.

FIGURE 317-1. ***Trypanosoma rhodesiense*** **in peripheral blood. It has a nucleus, posterior kinetoplast, undulating membrane, and flagellum (×1500).**

TREATMENT

Very few drugs have been available for treatment of human African trypanosomiasis, and those that have been commonly used are quite toxic (Table 317-1). Treatment depends on the infecting organism and the stage of disease. Distribution of drugs is through the World Health Organization (WHO) in Geneva.

For stage I *T. b. gambiense* infection, pentamidine is the drug of choice.[A1] The standard regimen is daily parenteral administration for 1 week.

For stage I *T. b. rhodesiense*, suramin[8] is administered in a slow intravenous infusion periodically during 3 weeks. Although anaphylaxis is rare (approximately 1 in 20,000 patients), a test dose is recommended before full treatment is initiated. A number of side effects, including nephrotoxicity, require close monitoring. Urinalysis is recommended before each dose, and the drug should be discontinued if proteinuria persists and casts are seen in the urine sediment.

For stage II *T. b. gambiense*, the treatment of choice is a combination of nifurtimox and eflornithine.[A2] Nifurtimox is administered orally, whereas eflornithine requires frequent intravenous administration. For stage II *T. b. rhodesiense* infection, melarsoprol remains the only available agent; it is a highly effective but impressively toxic drug that can be used for stage II disease with either organism. The side effects are numerous, but the most important is the life-threatening encephalopathy that may develop from the arsenic (highly fatal) or as an inflammatory reaction. Concomitant corticosteroid administration under expert guidance is helpful in reducing the risk of encephalopathy and death without compromising the efficacy of melarsoprol. The risks of encephalopathy can be reduced by a gradual increase in the first round of treatment between 2 and 3.6 mg/kg in divided doses three times daily during 3 days. Unfortunately, resistance to melarsoprol is widespread.[9]

Few therapeutic options are available to treat the late stage of African trypanosomiasis. However, oral fexinidazole,[10] given once daily orally, is effective and safe for *T. b. gambiense* infection.[A3] It is also an option for stage I and stage II disease.[11]

PREVENTION

No vaccine is available against human African trypanosomiasis. The mainstays of prevention include active case finding with early treatment and vector control.[12] Given the nature of each infection, active case surveillance is more suitable for infection with *T. b. gambiense*, but vector control is more effective for prevention of infection with *T. b. rhodesiense*. The goal of active case finding is to identify infected individuals who may still be in the asymptomatic stage or early stage. This approach, which is more suited for disease from *T. b. gambiense*, typically consists of a screening examination for lymphadenopathy

TABLE 317-1 DRUGS USED TO TREAT HUMAN AFRICAN TRYPANOSOMIASIS

DRUG	CLASS	STAGE	ROUTE	ADULT DOSE	ADVERSE EFFECTS
TRYPANOSOMA BRUCEI GAMBIENSE					
Pentamidine	Aromatic diamidine	I	IM or IV	4 mg/kg daily for 7 days	Pain, GI symptoms, hypoglycemia or hyperglycemia, electrolyte abnormalities, leukopenia, thrombocytopenia
Eflornithine	Ornithine carboxylase inhibitor	II	IV	100 mg/kg q6h for 14 days	GI symptoms, bone marrow toxicity, seizures
Eflornithine plus nifurtimox				Nifurtimox 15 mg/kg per day orally in three doses × 10 days; eflornithine 400 mg/kg per day intravenously in two 2-h infusions (each dose diluted in 250 mL of water for injection) × 7 days	
TRYPANOSOMA BRUCEI RHODESIENSE					
Suramin	Polysulfonated naphthylamine derivative of urea	I	IV	1 g IV on days 1, 3, 7, 14, and 21 (after test dose of 100-200 mg)	Anaphylaxis, nephrotoxicity, fever, rash, pruritus, arthralgias, reversible peripheral neuropathy, and bone marrow toxicity
Melarsoprol	Trivalent arsenical	II	IV	1.2 mg/kg q8h for 3 consecutive days each week for 3 weeks (maximum daily dose, 180 mg)	Encephalopathic syndromes, peripheral neuropathy, paralysis, cardiac dysrhythmias, GI symptoms, rash, pruritus, thrombophlebitis. Resistance to melarsopol also a problem.

GI = gastrointestinal; IM = intramuscular; IV = intravenous.

followed by serologic testing. If results are positive for both, the patient should undergo further evaluation with lymph node aspirate and blood testing. If PCR is positive or trypanosomes are seen, the patient should be treated.

Vector control measures include tsetse fly traps and insecticide-impregnated screens; the traps are easily maintained by locals, but the screens require regular retreatment, so they are more labor intensive and costly to maintain. Mass spraying is not routinely used, but ground or aerial spraying combined with disruption of the animal reservoir's habitat may be the most effective method of achieving rapid vector control during an epidemic.

Travelers to endemic areas should be aware of this disease and should use basic protective measures. Protective clothing of at least medium weight should be worn; neutral colors are most effective because flies are attracted to bright and dark colors. Tsetse flies are attracted to moving vehicles but rest in the shade or bushes. Although use of insect repellant is prudent for other vector-borne illnesses that may be endemic in these areas, it has not been proven to reduce the risk of tsetse fly bites. There is no recommended chemoprophylaxis for travelers.

PROGNOSIS

Stage I disease is treatable and curable. Stage II disease is uniformly fatal if untreated, but about 95% of treated patients can be cured of late-stage disease, usually with a resolution of symptoms.

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318 CHAGAS DISEASE

LOUIS V. KIRCHHOFF

DEFINITION

Chagas disease, or American trypanosomiasis, is caused by the protozoan parasite *Trypanosoma cruzi*. The terms *Chagas disease*, *American trypanosomiasis*, and *T. cruzi infection* are synonyms.

The Pathogen

Several dozen species are included in the genus *Trypanosoma*, but only the African trypanosome *Trypanosoma brucei* (subspecies *T. b. gambiense* [West African] and *T. b. rhodesiense* [East African]) (Chapter 317) and the American trypanosome *T. cruzi* cause disease in humans.

EPIDEMIOLOGY

Epizootiology of *T. cruzi*

Many species of triatomine insects, also called kissing bugs, act as vectors for *T. cruzi*, and many species of wild and domestic mammals, as well as humans, are involved in the complex lifecycle of this organism. The triatomine vectors that transmit *T. cruzi* are found in the Americas from southern Argentina through the southern half of the United States. The parasite has been isolated from more than 100 species of domestic and wild mammals, which for the most part become infected when they eat infected vectors or through congenital transmission. Armadillos, wood rats, raccoons, and opossums are typical wild mammalian reservoirs, and these and other species that harbor *T. cruzi* can be found in large numbers in the southern and southwestern parts of the United States.

Typically, humans acquire *T. cruzi* infection, which is lifelong, when they live in houses in enzootic areas where the sylvatic cycle of transmission is active. The process begins when vector species adaptable to living in human dwellings take up residence in niches in the primitive wood, mud, and stone houses that are typical in many endemic regions. These vectors become domiciliary, and they then take blood meals, mostly at night, from the humans who occupy the dwellings that they have invaded, as well as from domestic animals that sleep there, particularly dogs.[1] Thus, Chagas disease is primarily a public health problem among poor people who live in rural areas.

Endemic Chagas Disease

Chagas disease is a zoonosis that is endemic in Mexico and in all the countries of Central and South America, but it is not endemic in the Caribbean islands. In 2018, the Pan American Health Organization estimated that in the 21 endemic countries, 6 to 8 million people are chronically infected with *T. cruzi*, 28,000 new cases occur each year, and up to 12,000 deaths result from Chagas disease annually.[2] Since 1991, a major international vector control program in the southern countries of South America (Chile, Argentina, Paraguay, Brazil, Bolivia, and Uruguay) has achieved a marked reduction in vector transmission of *T. cruzi* through housing improvement, education of people at risk for acquiring the infection, and spraying insecticides.[3] Substantial reductions in prevalence rates in school-aged children and in blood donors constitute clear evidence of the success of the program. Uruguay, Chile, and Brazil were certified as being free of vector transmission in 1997, 1999, and 2006, respectively. Marked reduction in transmission has been achieved in Argentina as well. Similar programs have been initiated in Central America and the Andean countries. In parallel with the vector control programs, donor screening has been implemented throughout almost the entire endemic range.

Chagas Disease in the United States

The sylvatic cycle of *T. cruzi* exists in much of the southern and southwestern regions of the United States, but only seven cases of autochthonous (disease spread from one individual and acquired in another individual in the same place) acute Chagas disease have been reported: four in Texas and one each in Tennessee, Louisiana, and California. Moreover, in the first 4 years of U.S. blood donor screening starting in January of 2007, only 16 *T. cruzi*–infected donors, all of whom appeared to have acquired the infection autochthonously, were identified in approximately 29 million units. Only two cases of acute *T. cruzi* infection have been reported in tourists returning to the United States, but three such instances have been reported in Europe as well as one in Canada. Thus, acute Chagas disease is extremely rare in the United States, and there is no indication that its incidence is increasing.

A recent estimate puts the number of *T. cruzi*–infected persons currently living in the United States at about 240,000 to 350,000,[4] including about 40,000 women of childbearing age.[5] Since blood donor screening began in the United States in 2007, more than 100 million units have been screened, and several thousand *T. cruzi*–infected donors have been identified and permanently deferred from donation. The confirmed rate of *T. cruzi* infection in donors is about 1 in 13,300. With the goal of reducing the enormous cost of universal screening ($100 to $200 million per year), a U.S. Food and Drug Administration (FDA)-approved selective screening protocol based on previous negative test results has been implemented.

In Europe, infection is seen primarily in Latin American immigrants to Spain, Italy, France, the United Kingdom, and Switzerland. The pooled seroprevalence among such immigrants is about 4%, with an 18% seroprevalence among immigrants from Bolivia. In the United States, transplantation of organs from three persons with undiagnosed chronic *T. cruzi* infection resulted in acute Chagas disease in five recipients, one of whom died of the infection. To date, two instances of congenital transmission of *T. cruzi* here have been reported. A reasonable estimate of the number of babies born in the United States each year with congenital Chagas disease ranges from 63 to 315. Most babies with congenital Chagas disease are asymptomatic, and limited knowledge about congenital Chagas disease leads to underreporting.

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T. cruzi vectors become infected by ingesting blood from mammals that have parasites in their blood stream. The parasites then multiply in the gut of the

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PATHOBIOLOGY

T. cruzi vectors become infected by ingesting blood from mammals that have parasites in their blood stream. The parasites then multiply in the gut of the

ABSTRACT

Chagas disease, or American trypanosomiasis, is a zoonotic infection caused by the single-cell protozoan parasite, *Trypanosoma cruzi*. *T. cruzi* is spread by blood-sucking triatomine insects among its various mammalian hosts, which include domestic and wild animals as well as humans. *T. cruzi* also can be transmitted from mother to fetus, through blood products and organ transplantation, by ingestion of contaminated food and drink, and in laboratory accidents. Infection with *T. cruzi* in humans is lifelong. Chagas disease is endemic in Mexico, as well as in all the countries of Central and South America but not in any of the Caribbean islands. Approximately 6 to 8 million persons are chronically infected with *T. cruzi,* about 28,000 new infections occur each year, and roughly 12,000 persons die of the illness annually. An estimated 240,000 to 350,000 immigrants with Chagas disease from endemic countries currently live in the United States. About 10 to 30% of persons who are chronically infected with *T. cruzi* ultimately develop cardiac and/or gastrointestinal symptoms related to the persistent presence of the parasite. The diagnosis of acute and congenital Chagas disease is made by parasitologic methods, typically direct microscopic examination of blood or polymerase chain reaction (PCR) assay. Chronic *T. cruzi* infection is diagnosed serologically. Nifurtimox and benznidazole are the only two drugs available for treating *T. cruzi* infections, and the latter is preferred by most experts. Parasitologic cure rates are relatively high for acute and congenital infections but unfortunately very low in persons with long-standing infections. No convincing data from randomized controlled trials indicate that treatment of chronically infected persons with either drug significantly affects long-term outcomes.

KEYWORDS

cardiomyopathy
Chagas disease
congenital transmission
megacolon
megaesophagus
triatomine vector
Trypanosoma cruzi
chagoma
conjunctiva

insects and are ultimately discharged in the feces of the vector. Transmission to a new mammalian host occurs when parasite-laden vector feces contact the mucosae of the mouth or nose, the conjunctivae, or breaks in the skin. The contaminating parasites enter local cells and multiply intracellularly; as parasitized cells rupture, they are released into the lymphatics and blood stream. The circulating organisms enter new cells at distant sites and maintain an endless process of asynchronous multiplication. The life cycle is completed as parasites are swept up in blood meals taken by vectors.[6] In addition to vector-borne transmission, *T. cruzi* can be transmitted by blood or organs donated by infected persons, from mother to unborn child,[7] by the ingestion of contaminated food or drink,[8,9] and in laboratory accidents.

In acute Chagas disease, an inflammatory lesion, called a chagoma, may appear at the site where the parasite enters. Local histologic changes include intracellular parasitism of muscle and other subcutaneous tissues, lymphocytic infiltration, interstitial edema, and hyperplasia of lymph nodes that drain the area. As the parasites spread systemically through the lymphatics and blood stream, the most heavily parasitized tissues are muscles, including the myocardium, but the organisms can invade essentially any tissue. Myocarditis may develop in association with focal areas of infected cardiomyocytes, inflammation, and necrosis. The characteristic pseudocysts seen in sections of *T. cruzi*–infected tissues are actually host cells filled with multiplying forms of the parasite (Fig. 318-1). In some patients, parasites can be seen in cerebrospinal fluid (CSF).

In persons with chronic Chagas disease, the heart is the organ most commonly affected. Hearts obtained at autopsy from patients who died of Chagas cardiomyopathy usually have a global appearance reflecting biventricular enlargement and thinning of ventricular walls (E-Fig. 318-1). Mural thrombi are frequently present, and an apical aneurysm of the left ventricle is typical in patients with advanced disease. At the cellular level, the process that underlies these gross pathologic abnormalities is a chronic inflammation with mononuclear cell infiltration, diffuse interstitial fibrosis, and atrophy of myocardial cells. The chronic inflammation also affects the conduction system and causes a variety of rhythm disturbances, including atrial bradyarrhythmias and fibrillation; premature ventricular contractions; left anterior fascicular block; bundle branch blocks, often of the right bundle; ventricular tachycardia; and third-degree atrioventricular block. Parasites are rarely seen in diseased tissues by conventional histologic methods, but several studies using polymerase chain reaction (PCR) assays found a correlation between the intensity of inflammation and the presence of parasites. Evidence accumulated to date implicates the persistence of parasites and the resulting chronic inflammation in affected tissues—rather than autoimmune mechanisms—as the basis for the pathogenesis in patients with chronic *T. cruzi* infection.

Chagas disease of the digestive tract can cause striking dilation and hypertrophy of the esophagus or colon. Focal inflammatory lesions with lymphocytic infiltration are seen on microscopic examination of affected tissues. The number of neurons in the myenteric plexus is reduced, and periganglion and intraganglion fibrosis with Schwann cell proliferation and lymphocytosis is present. In most patients, the clinical consequences of this parasympathetic denervation are limited to the esophagus or colon (or to both), but the ureters, biliary tree, and other hollow viscera can be affected as well.

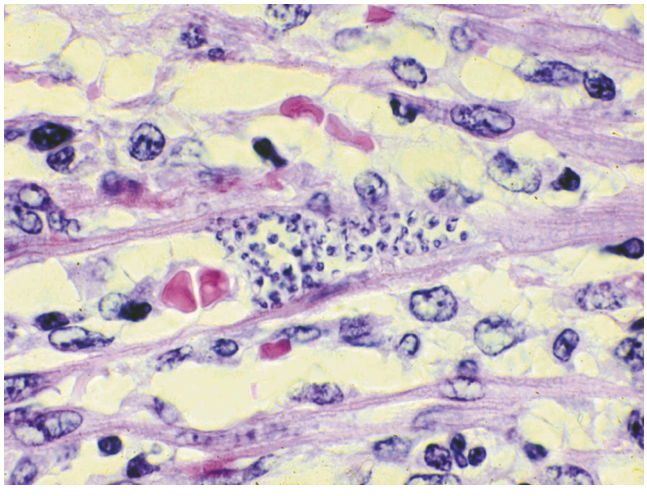

FIGURE 318-1. ***Trypanosoma cruzi*** **in cardiac muscle of a child who died of acute Chagas myocarditis. An infected myocyte containing several dozen *T. cruzi* amastigotes is in the center of the field (hematoxylin and eosin staining, ×900).**

CLINICAL MANIFESTATIONS

Acute Chagas Disease

Acute Chagas disease is usually an illness of children but can occur at any age. Symptoms are typically mild and nonspecific (Table 318-1).[10] When the parasite has entered through a break in the skin or the site of a vector's puncture, a chagoma may appear with local lymphadenopathy. The Romaña sign, which is the classic finding in acute Chagas disease, consists of painless edema of the palpebrae and periocular tissues and may appear when the conjunctiva is the portal of entry. These initial local signs can be followed by fever, malaise, anorexia, and edema of the face and lower extremities. Generalized lymphadenopathy and hepatosplenomegaly also may be present. Severe and even fatal myocarditis may develop. Meningoencephalitis is a rare complication. In untreated patients the acute illness resolves spontaneously over 6 to 8 weeks as the patient enters the indeterminate phase of Chagas disease, which is characterized by subpatent parasitemia, absence of associated signs and symptoms, and detectable specific antibodies to *T. cruzi*.

Chronic Cardiopathy

Only 10 to 30% of persons who are chronically infected with *T. cruzi* have clinical symptoms or signs, which can develop insidiously over years and often decades after the initial infection. Chagas cardiopathy often manifests as rhythm disturbances, cardiomyopathy with heart failure, and thromboembolism,[11,12] Dizziness, syncope, and even seizures can result from a wide variety of arrhythmias. The cardiomyopathy often leads to biventricular failure, and right-sided heart failure can predominate in patients with advanced disease. Chronic Chagas disease is an independent risk factor for stroke.[13]

Chronic Gastrointestinal Disease (Megadisease)

In patients with megaesophagus, symptoms are similar to those of idiopathic achalasia (Chapter 124) and may include cough, dysphagia, odynophagia, and regurgitation. Hypersalivation and consequent salivary gland hypertrophy develop in some patients with advanced esophageal dysfunction. Aspiration

TABLE 318-1 CLINICAL MANIFESTATIONS AND DIAGNOSIS OF CHAGAS DISEASE

PHASE OR FORM	CLINICAL MANIFESTATIONS	DIAGNOSIS	TREATMENT SUCCESS
Acute infection	Usually nonspecific mild symptoms	Wet prep of blood or PCR	80-100%
Congenital infection	Asymptomatic or nonspecific mild symptoms	Wet prep of blood or PCR	80-100%
Chronic infection	Asymptomatic, without ECG change	Positive serology	Benefit not established
Cardiomyopathy	Arrhythmias, syncope, left ventricular dysfunction, heart failure, ECG conduction abnormalities	Positive serology	Benefit not established
Gastrointestinal	Dilation of esophagus, colon, or both	Positive serology	Benefit not established
Reactivation in immunosuppressed hosts	Acute myocarditis, CNS abscesses, skin chagomas	Wet prep of blood or PCR	Suppression of acute symptoms and parasitemia, but long-term benefit not clear

CNS = central nervous system; ECG = electrocardiogram; PCR = polymerase chain reaction.
Adapted from Bern C. Chagas disease. *N Engl J Med*. 2015;373:456-466.

E-FIGURE 318-1. Chest radiograph of a patient from Bolivia with chronic *Trypanosoma cruzi* infection, rhythm disturbances, and cardiomyopathy. Pacemaker wires can be seen in the area of the left ventricle.

can occur, especially during sleep, and repeated episodes of aspiration pneumonitis are common in untreated patients. Weight loss and even cachexia can occur with severe megaesophagus.

Patients with chagasic megacolon have intermittent abdominal pain and chronic constipation, sometimes with several weeks between bowel movements. Rarely, acute obstruction, occasionally with volvulus, can lead to perforation and sepsis.

Immunosuppression and Transplantation

When persons with chronic carriage of *T. cruzi* become immunosuppressed, the infection can reactivate, sometimes with an intensity that is more severe than acute Chagas disease in immunocompetent persons. Reactivation can occur after renal transplantation, but Chagas disease is not a contraindication to kidney transplantation. When *T. cruzi*–infected patients undergo transplantation, they should have periodic monitoring for signs and symptoms of acute Chagas disease, including careful neurologic evaluation, and parasitologic testing.

Reactivation of *T. cruzi* infection can also occur in persons who are coinfected with human immunodeficiency virus (HIV) or are otherwise immunosuppressed. Although the risk is low, all such patients with geographic or maternal risk should be screened for *T. cruzi* infection.[14] HIV viral loads can increase in the context of reactivated acute Chagas disease.[15]

DIAGNOSIS

Acute Chagas Disease

The first step in considering the diagnosis of acute Chagas disease is establishing that a person is at risk for *T. cruzi* infection. Risk factors include recent residence or blood transfusion in an endemic area, birth to a mother with geographic- or transfusion-associated risk in the case of a newborn, or a laboratory accident involving the parasite.

Definitive diagnosis of acute Chagas disease requires the detection of parasites. PCR assays are the most sensitive method[16] but often are not readily available. Parasites often can be seen in wet preparations of anticoagulated blood, in a buffy coat, or in Giemsa-stained blood smears. In infected immunocompromised patients, parasites can sometimes be found in lymph node aspirates, biopsy specimens of skin lesions, bone marrow, endomyocardial tissue, CSF, and pericardial fluid.

Chronic Chagas Disease

Chronic *T. cruzi* infection is usually diagnosed by detecting immunoglobulin G (IgG) antibodies that specifically bind to parasitic antigens on at least two different serologic tests (enzyme-linked immunoassay, indirect immunofluorescence, and chemiluminescence),[17] and isolation of the organism is rarely necessary. In chronic Chagas disease, the sensitivity of PCR assays has ranged from 44.7 to 100% but has been higher than 90% in most shades. It is generally accepted that the level of sensitivity of these assays is not high enough to justify their use for confirmatory testing of serologically positive clinical or donor samples. In contrast, PCR assays may be useful in persons who have borderline serologic results, in patients suspected of having congenital or acute disease but in whom parasites are not detected microscopically, and in infected patients who have received specific treatment. In all such persons, however, the less than optimal sensitivity of PCR means that positive results can be taken as being truly indicative of infection, but a negative result does not exclude infection.

TREATMENT

Antiparasitic Drugs

The two drugs currently available for treating Chagas disease (benznidazole and nifurtimox) are of limited benefit (Chapter 315). Treatment is indicated in all patients with acute or congenital infections, as well as in chronically infected children up to age 18 years. By extension, it would be reasonable to treat anyone age 18 years or older known to have acquired *T. cruzi* infection within the past 17 years. Benznidazole is considered the drug of choice by most experts in endemic countries.

Benznidazole (at 5 mg/kg daily for 60 days) is effective in adults, and it can cure more than 90% of babies with congenital infection at 5 to 10 mg/kg/day for 60 days.[18] Side effects can include rash, peripheral neuropathy, and granulocytopenia.

In patients with acute Chagas disease, nifurtimox (8 to 10 mg/kg body weight per day for adults, 12.5 to 15 mg/kg/day for adolescents, and 15 to 20 mg/kg/day for children) in four divided doses for 90 to 120 days reduces symptoms and decreases mortality rates, with an approximately 70% rate of parasitologic cure.

Unfortunately, cure rates may be less than 10% in adults with long-standing chronic *T. cruzi* infection. Disadvantages of nifurtimox include its long course of treatment and frequent side effects, including anorexia, nausea, vomiting, weight loss, and abdominal pain. Patients taking the drug also may have neurologic symptoms such as insomnia, restlessness, paresthesias, twitching, polyneuritis, and even seizures. In 2020, the FDA approved nifurtimox for the treatment of Chagas disease in pediatric patients (birth to less than age 18 years).

There is broad agreement that persons with advanced symptomatic *T. cruzi* infection should not be given specific treatment. An enduring question is whether adults with long-standing indeterminate-phase infections, who by far constitute the largest group of *T. cruzi*–infected persons, should be treated. In two studies of asymptomatic PCR-positive patients, treatment with benznidazole for a year suppressed parasitemias and resulted in a negative PCR in 90% of treated patients.[A1] Similar suppression was observed in another study in which adults with indeterminate Chagas disease were treated with 300 mg daily for 4 weeks, and no further advantage was evident with 8 weeks of therapy.[A2] However, there is no clear evidence from these or other previous studies that the suppression of parasitemias delays the onset of symptoms, slows the progression of disease, or reduces mortality.[A3]

Based on available data, individuals who were born in or lived in endemic areas of Mexico, Central America, and South America should be screened serologically.[19] Women determined to be positive but not currently pregnant should be treated with a full course of benznidazole with the goal of reducing the rate of congenital transmission to babies they may have, even years later.

Management of Symptomatic Chagas Disease

Patients who have newly diagnosed *T. cruzi* infection with symptomatic cardiac or gastrointestinal disease should be referred to appropriate specialists (Fig. 318-2). Treatment of acute and chronic Chagas disease (Chapter 47) is similar to managing such symptoms in patients with cardiomyopathy (Chapter 47), heart failure (Chapter 46), and arrhythmias (Chapters 51 to 53) from other causes.[20] Some data suggest that carvedilol (up-titrated to 25 mg twice daily) may reduce mortality in Chagas cardiomyopathy.[A4] Pacemakers are useful in patients with bradyarrhythmias. Combined endocardial and epicardial catheter ablation can significantly reduce ventricular arrhythmias,[A5] but the usefulness of implantable cardioverter-defibrillators in patients with recurrent ventricular tachycardia has not been clearly established.[21]

Heart transplantation (Chapter 46) is an option in patients with end-stage Chagas cardiac disease, and several hundred such patients have undergone the procedure in Argentina, Brazil, and the United States. As is the case with other *T. cruzi*–infected patients who are immunosuppressed, reactivation is a risk but is manageable with standard treatment protocols.[22] The usefulness and side effects of prophylaxis for reactivation with benznidazole in *T. cruzi*–infected patients after heart transplantation is being evaluated. The long-term survival of Chagas patients with heart transplants appears to be longer than that of patients undergoing cardiac transplantation for other reasons, probably because the lesions of *T. cruzi*–associated pathology affect mostly the heart.

Chagas megaesophagus should be treated similarly as for idiopathic achalasia (Chapter 124), which usually responds to balloon dilation of the lower esophageal sphincter when symptoms are mild. Peroral endoscopic myotomy may be required in patients who do not respond to repeated attempts at balloon dilation.[23]

Chagas megacolon in its early stage can be treated with a high-fiber diet and occasional laxatives or enemas. Fecal impaction may require manual disimpaction, and toxic megacolon requires surgery. In patients with advanced megacolon, volvulus (Chapter 128) can develop when an enlarged and lengthened sigmoid colon twists and folds on itself; volvulus causes a constellation of symptoms and in many cases requires immediate surgery. Even if the symptoms associated with volvulus are resolved without operative intervention, however, surgical treatment is usually ultimately necessary because the volvulus tends to recur. Several surgical procedures to treat advanced Chagas megacolon require resection of the sigmoid and removal of part of the rectum.

PREVENTION

Reducing human contact with triatomine vectors through education of at-risk persons, improved housing, and spraying of residual insecticides (which kill insects that land or crawl on surfaces) in endemic countries has reduced or eliminated the vector transmission of *T. cruzi* in a major part of the endemic range, and progress in this regard is expected to continue. Serologic screening of donated blood has essentially eliminated transfusion-related transmission of the parasite in most endemic areas. Outbreaks of acute Chagas disease through oral transmission can be avoided by the implementation of better food safety standards. Drug treatment of *T. cruzi*–infected women before pregnancy reduces the likelihood of congenital transmission. No protocols have been defined and validated for preventing reactivation of *T. cruzi* infection in chronically infected persons who are immunosuppressed iatrogenically or by HIV. A treatment regimen that reliably results in parasitologic cure is needed to prevent the onset or progression of chronic symptomatic Chagas disease.

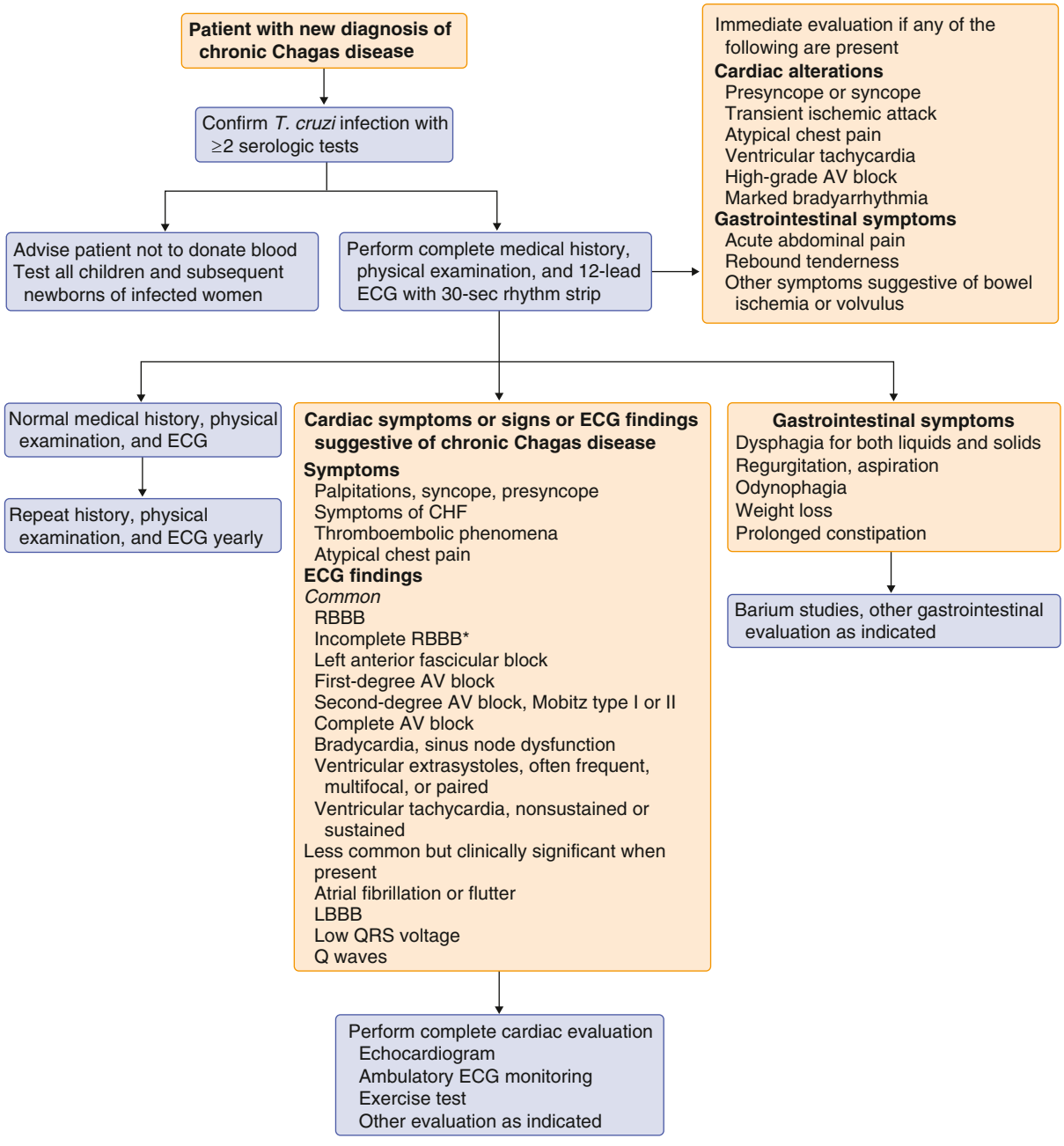

FIGURE 318-2. **Algorithm for baseline evaluation of a patient with newly diagnosed chronic *Trypanosoma cruzi* infection.** *QRS interval of 0.10 to 0.11 seconds in adults. Criteria based on the *Minnesota Code Manual of Electrocardiographic Findings* with modifications from Maguire et al. Different criteria may be required for ECGs in children. AV = atrioventricular; CHF = congestive heart failure; ECG = electrocardiogram; LBBB = left bundle branch block; RBBB = right bundle branch block. (From Bern C, Montgomery SP, Herwaldt BL, et al. Evaluation and treatment of Chagas disease in the United States: a systematic review. *JAMA*. 2007;298:2171-2181.)

TABLE 318-2 PREDICTING DEATH IN CHAGAS HEART DISEASE

CHARACTERISTIC		POINTS
Male sex		2
Functional class III or IV		5
Low QRS voltage on electrocardiography		3
Cardiomyopathy on chest radiography		5
Left ventricular systolic dysfunction on echocardiograph		3
Nonsustained ventricular tachycardia on Holter monitoring		3
10 year mortality:	0-6 points	9%
	7-11 points	37%
	12-20 points	85%

Adapted from Rassi A, Jr., Rassi A, Little WC, et al. Development and validation of a risk score for predicting death in Chagas' heart disease. *N Engl J Med*. 2006;355:799-808.

PROGNOSIS

For acute Chagas disease, the prognosis is generally excellent because most acutely infected persons have only mild symptoms that resolve spontaneously, even without specific treatment. However, the reported mortality rate for foodborne acute Chagas disease may be as high as 1%.[24] The occasional patient who has symptomatic acute Chagas myocarditis should generally do well if treated early.

For chronic *T. cruzi* infection, mortality is not increased for chronically seropositive individuals without cardiomyopathy,[25] and the lifetime risk for the development of related cardiac or gastrointestinal dysfunction is only 10 to 30%. A validated risk score assessment tool can estimate prognosis in the absence of heart transplantation (Table 318-2).

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For the General References and other additional features, please visit Elsevier eBooks+ at https://ebooks.health.elsevier.com.

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319 LEISHMANIASIS

PIERRE A. BUFFET, SIMON L. CROFT, AND MITALI CHATTERJEE

DEFINITION

Leishmaniasis, which is caused by protozoan parasites of the genus *Leishmania*, is generally transmitted between mammalian hosts by female phlebotomine sandflies. The parasite exists as an extracellular flagellated form, the promastigote, in the gut of the female sandfly, and as an intracellular form, the amastigote, in the phagolysosomal compartment of macrophages in the mammalian host. The disease in humans affects either the skin/mucosae or internal organs and ranges in severity from a single, self-curing skin lesion to widespread multilesional cutaneous involvement, or a potentially fatal visceral disease that affects the spleen, liver, and bone marrow.

The Pathogen

Leishmaniasis is caused by 20 different species of *Leishmania*, which are widely distributed in Europe, Asia, Africa, and South and Central America, with foci in South East Asia.[1] *Leishmania* are unicellular eukaryotic protozoa with a well-defined nucleus and 36 chromosomes. *Leishmania* exist in two forms. In the promastigote form in the alimentary tract of the sandfly, it is an extracellular, motile organism with a long flagellum. In its amastigote form in mammals, it is found in mononuclear phagocytes, where it is intracellular, is nonmotile, and lacks a flagellum. *Leishmania* are 1 to 3 μm in breadth in mammals compared with 15 to 30 μm in length and 5 μm in width in the sandfly. The kinetoplast and basal body lie towards the anterior end.

EPIDEMIOLOGY

An estimated 1.0 million clinical cases of leishmaniasis occur each year, but this number is probably an underestimate because leishmaniasis is not a reportable disease in many of the endemic countries and territories where it is known to occur.[2]

Infection is established in the mammalian host following a bite of the female sandfly belonging to either *Phlebotomus* spp in Europe, Asia, and Africa or *Lutzomyia* spp in the Americas. Different species of sandfly are associated with transmission of different *Leishmania* species. Most leishmaniasis is caused by 12 species (Table 319-1). Most species that cause cutaneous leishmaniasis are acquired from another mammal (zoonotic transmission cycle), with the exception of *Leishmania tropica*, which is frequently transmitted between human beings (anthroponotic cycle). Visceral leishmaniasis is usually anthroponotic (in the case of *Leishmania donovani*) or zoonotic (in the case of *Leishmania infantum*). The predominant mammalian hosts (the reservoirs) are associated with different *Leishmania* species in diverse ecosystems (Fig. 319-1).

Visceral leishmaniasis is caused by either *L. donovani* or *L. infantum* (which is identical to *Leishmania chagasi* in South America). These species have different geographic distributions, with the highest incidence found in the poorest communities in eight countries (India, Sudan, South Sudan, Ethiopia,

TABLE 319-1 CHARACTERISTICS OF THE MAIN *LEISHMANIA* SPECIES

LEISHMANIA SPP	*LEISHMANIA SUBGENUS*	DISTRIBUTION: OLD WORLD	DISTRIBUTION: NEW WORLD	PRIMARY FORM	SECONDARY FORMS	ANTHROPONOTIC: AREAS OF TRANSMISSION	ZOONOTIC: RESERVOIR	ALTERNATIVE NAME
L. donovani	*Leishmania*	South East Asia (mainly India, Bangladesh, Nepal, Sri Lanka) and East Africa		Visceral	Post–kala-azar dermal Cutaneous, mucosal OIVL	South East Asia East Africa		Kala-azar
L. infantum (L. chagasi)	*Leishmania*	Europe Asia	South and Central America	Visceral	Cutaneous, mucosal Opportunistic*		Canid	
L. major	*Leishmania*	Asia, North and East Africa, Europe		Cutaneous			Rodent	Biskra nail
L. tropica	*Leishmania*	Asia, Europe		Cutaneous	Recidivans	Syria Afghanistan	Rodent	Aleppo boil
L. aethiopica	*Leishmania*	Ethiopia		Cutaneous	Diffuse cutaneous		Hyrax	
L. mexicana	*Leishmania*		Central America	Cutaneous			Rodent	Chiclero ulcer
L. amazonensis	*Leishmania*		Central and South America	Cutaneous	Diffuse cutaneous		Rodent	
L. braziliensis	*Viannia*		South America	Cutaneous, mucosal	Disseminated cutaneous Lymph		Rodent, marsupial	ML-espundia
L. panamensis	*Viannia*		Central and South America	Cutaneous	Mucosal Nodular lymphangitis		Edentate rodent	Ulcera de bejuco
L. guyanensis	*Viannia*		South America	Cutaneous	Mucosal Nodular lymphangitis		Rodent, edentates	Pian bois
L. peruviana	*Viannia*		South America	Cutaneous			Canid	Uta
L. martiniquensis/ siamensis	*Leishmania*	South East Asia/ West Indies		Cutaneous, visceral	Diffuse cutaneous			

*Opportunistic visceral leishmaniasis in patients infected with the human immunodeficiency virus.
ML = mucosal leishmaniasis; OIVL = opportunistic infection visceral leishmaniasis; spp = species.

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EPIDEMIOLOGY

An estimated 1.0 million clinical cases of leishmaniasis occur each year, but this number is probably an underestimate because leishmaniasis is not a reportable disease in many of the endemic countries and territories where it is known to occur.[2]

Infection is established in the mammalian host following a bite of the female sandfly belonging to either *Phlebotomus* spp in Europe, Asia, and Africa or *Lutzomyia* spp in the Americas. Different species of sandfly are associated with transmission of different *Leishmania* species. Most leishmaniasis is caused by 12 species (Table 319-1). Most species that cause cutaneous leishmaniasis are acquired from another mammal (zoonotic transmission cycle), with the exception of *Leishmania tropica*, which is frequently transmitted between human beings (anthroponotic cycle). Visceral leishmaniasis is usually anthroponotic (in the case of *Leishmania donovani*) or zoonotic (in the case of *Leishmania infantum*). The predominant mammalian hosts (the reservoirs) are associated with different *Leishmania* species in diverse ecosystems (Fig. 319-1).

Visceral leishmaniasis is caused by either *L. donovani* or *L. infantum* (which is identical to *Leishmania chagasi* in South America). These species have different geographic distributions, with the highest incidence found in the poorest communities in eight countries (India, Sudan, South Sudan, Ethiopia,

TABLE 319-1 CHARACTERISTICS OF THE MAIN *LEISHMANIA* SPECIES

LEISHMANIA SPP	*LEISHMANIA SUBGENUS*	DISTRIBUTION: OLD WORLD	DISTRIBUTION: NEW WORLD	PRIMARY FORM	SECONDARY FORMS	ANTHROPONOTIC: AREAS OF TRANSMISSION	ZOONOTIC: RESERVOIR	ALTERNATIVE NAME
L. donovani	*Leishmania*	South East Asia (mainly India, Bangladesh, Nepal, Sri Lanka) and East Africa		Visceral	Post–kala-azar dermal Cutaneous, mucosal OIVL	South East Asia East Africa		Kala-azar
L. infantum (L. chagasi)	*Leishmania*	Europe Asia	South and Central America	Visceral	Cutaneous, mucosal Opportunistic*		Canid	
L. major	*Leishmania*	Asia, North and East Africa, Europe		Cutaneous			Rodent	Biskra nail
L. tropica	*Leishmania*	Asia, Europe		Cutaneous	Recidivans	Syria Afghanistan	Rodent	Aleppo boil
L. aethiopica	*Leishmania*	Ethiopia		Cutaneous	Diffuse cutaneous		Hyrax	
L. mexicana	*Leishmania*		Central America	Cutaneous			Rodent	Chiclero ulcer
L. amazonensis	*Leishmania*		Central and South America	Cutaneous	Diffuse cutaneous		Rodent	
L. braziliensis	*Viannia*		South America	Cutaneous, mucosal	Disseminated cutaneous Lymph		Rodent, marsupial	ML-espundia
L. panamensis	*Viannia*		Central and South America	Cutaneous	Mucosal Nodular lymphangitis		Edentate rodent	Ulcera de bejuco
L. guyanensis	*Viannia*		South America	Cutaneous	Mucosal Nodular lymphangitis		Rodent, edentates	Pian bois
L. peruviana	*Viannia*		South America	Cutaneous			Canid	Uta
L. martiniquensis/ siamensis	*Leishmania*	South East Asia/ West Indies		Cutaneous, visceral	Diffuse cutaneous			

*Opportunistic visceral leishmaniasis in patients infected with the human immunodeficiency virus.
ML = mucosal leishmaniasis; OIVL = opportunistic infection visceral leishmaniasis; spp = species.

ABSTRACT

Leishmaniasis, which is caused by protozoan parasites of the genus *Leishmania,* is transmitted by sandflies. The 20 species of *Leishmania* are widely distributed in Europe, Asia, Africa, and South and Central America, with limited foci in South East Asia. The predominant mammalian hosts (the reservoirs) are associated with different *Leishmania* species in diverse ecosystems. The disease in humans affects either the skin/mucosae or internal organs, and it ranges in severity from a single, self-curing, limited skin lesion to widespread multilesional cutaneous involvement, and from a single lymphadenopathy to potentially fatal visceral disease affecting the spleen, liver, and bone marrow. An estimated 1 million new cases of cutaneous and 30,000 cases of visceral leishmaniasis occur annually in 82 and 93 countries, respectively. Visceral leishmaniasis is caused by either *Leishmania donovani* or *Leishmania infantum*. The highest incidence is found in the poorest communities of India, Sudan, South Sudan, Ethiopia, Eritrea, and Brazil. Since 2005, the annual incidence has declined by more than 90% in South East Asia (India, Bangladesh, Nepal). Diagnostic confirmation of visceral leishmaniasis is generally made by the rK39 dipstick, but alternative approaches include visualization of Leishman Donovan bodies on splenic or bone marrow aspirates, polymerase chain reaction testing, or serology. Treatment of visceral leishmaniasis is based on liposomal amphotericin B at most foci but is more complex in East Africa and challenging in immunodeficient patients. Cutaneous leishmaniasis self-cures in 20 to 90% of patients within 3 to 18 months, and treatment is usually by local measures.

KEYWORDS

leishmaniasis
visceral
cutaneous
mucosal
amphotericin B
paromomycin
sodium stibogluconate

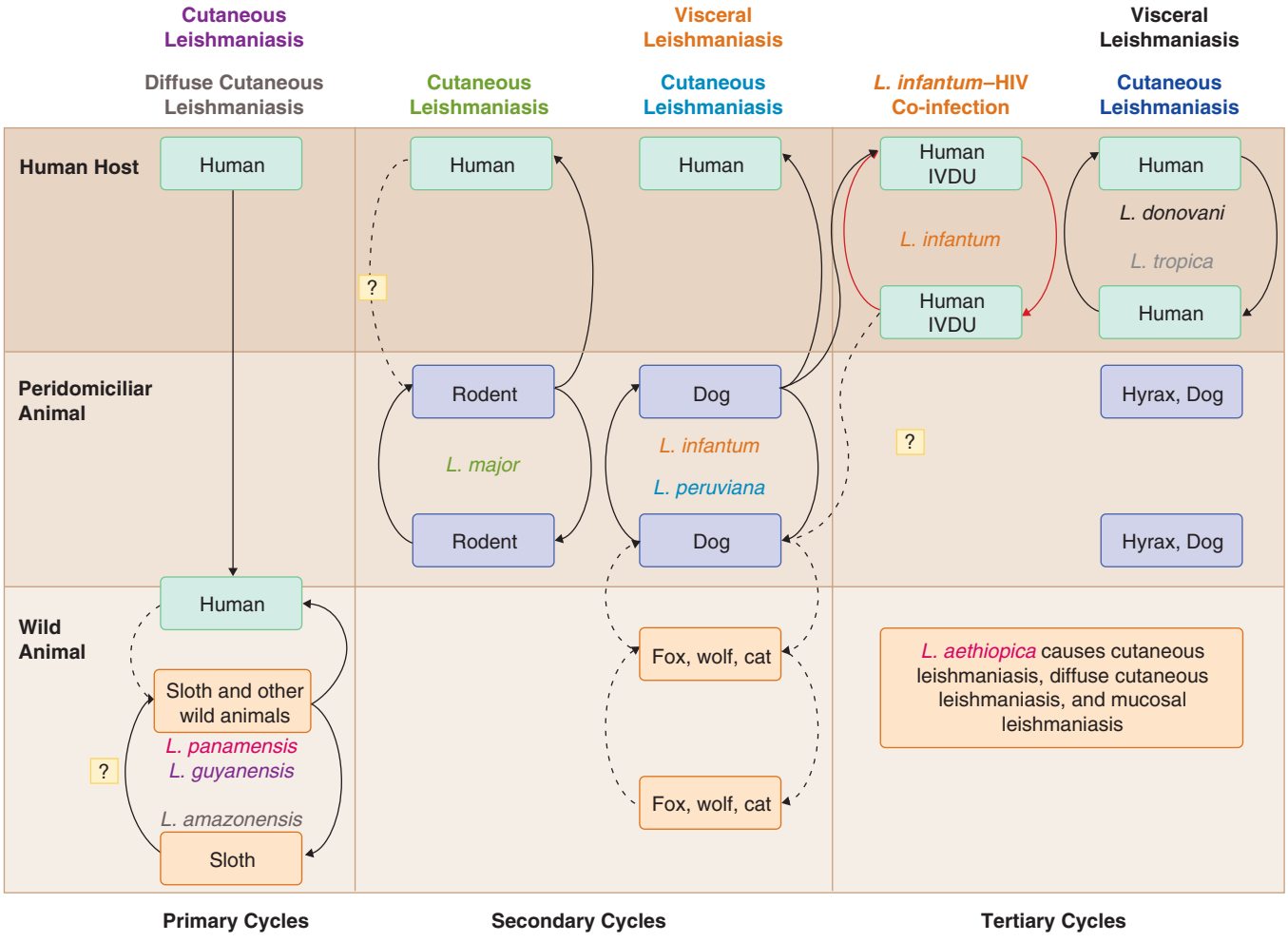

FIGURE 319-1. **Old World and New World zoonotic and anthroponotic life cycles of the main species of *Leishmania*.** Leishmaniasis is often referred to as a "disease complex" because different forms of disease can be caused by the same parasite species and similar forms of disease can be caused by different parasite species. HIV = human immunodeficiency virus; IVDU = intravenous drug use.

Eritrea, Somalia, Kenya, and Brazil). An estimated 1 in 5 to 1 in 50 infections are symptomatic, depending on the parasite species and host immunity. Since 2005, an initiative in South East Asia has reduced the annual incidence of the disease by more than 90%, but the economic burden of infection remains enormous.[3]

Cutaneous leishmaniasis is widely distributed, but its prevalence is difficult to estimate because of underreporting. Leishmaniasis is more common in children under age 16 years and in working-age men, but is uncommon in persons over age 65 years. This age prevalence may be related to the acquisition of immunity and to risk factors, including the presence of domestic animals, rodents, or other mammalian hosts. Ecologic conditions for sandflies, including shaded and humid habitats in crevices and mammal burrows, have been identified. Urbanization, deforestation, and migration have resulted in changing patterns of disease, with transmission occurring in peridomestic cycles. Other forms of transmission, such as through organ transplantation, blood transfusion, intravenous needles shared by drug users, transplacental or perinatal passage, or laboratory exposure, have been reported.

PATHOBIOLOGY

The infection is initially established in the skin after the inoculation of infective metacyclic promastigotes by the sandfly. These infective forms have a glycoprotein coat (a lipophosphoglycan) that enables them to resist complement and attach to and invade host cells. Peptides in the saliva of sandflies (e.g., maxadilan) cause vasodilatation and erythema and help establish infection in the dermal layer of the skin. Early responses to infection involve neutrophilic infiltration and invasion of resident macrophages. Progress of the disease depends on the parasitic species and the host response. For both visceral leishmaniasis and cutaneous leishmaniasis, progression of the disease depends on the maintenance of a parasite-specific immunosuppressive state. During established disease, host cell macrophages polarize from a classic (M1 phenotype) to a nonclassic, alternatively activated (M2 phenotype). Following successful treatment, macrophages become classically activated and are then able to kill the intracellular parasites, which are sensitive to nitric oxide and oxygen radicals, in the phagolysosomal compartment. After the activation of macrophages, resolution of disease is enhanced by a helper T-cell type 1 (T_H1) response following interaction between antigen-presenting cells (e.g., dendritic cells) with $CD4^+$ and $CD8^+$ T cells, as well as subsequent secretion of pro-inflammatory cytokines (e.g., interleukin-12 [IL-12], interferon-γ, tumor necrosis factor-α). In clinical forms such as active visceral leishmaniasis or diffuse cutaneous leishmaniasis, a mixed T_H1/T_H2 cell response occurs with the latter predominating, and downregulation of macrophage activity follows the production of cytokines such as IL-4, IL-10, IL-13, and transforming growth factor-β.[4]

In patients with visceral leishmaniasis, the absence of a T-cell-specific immune response to leishmanial antigens is associated with uncontrolled progression of infection. Progression is linked to elevated levels of IL-10 and decreased production of interferon-γ. Genetic susceptibility to *L. donovani* in Sudan has been associated with a solute carrier family that regulates the activation of macrophages and with a polymorphism in the IL-4 gene.

In localized simple cutaneous leishmaniasis, patients show a T_H1-type response and a delayed-type hypersensitivity response. Chronic infections show a T_H2-type response, most predominantly in patients with diffuse cutaneous leishmaniasis, in whom there is complete anergy to *leishmania* antigen and no delayed-type hypersensitivity response. Patients with mucosal leishmaniasis have a T_H1 or T_H2 cell response or both, and they also have a strong or weak delayed-type hypersensitivity response.

Post–kala-azar dermal leishmaniasis, which is a rare sequela after cure of visceral leishmaniasis, is seen in two geographically distinct zones, the Sudanese/East African form and the South East Asian form. The Sudanese and South

East Asian forms differ in that the former appears along with visceral leishmaniasis (para–kala-azar dermal leishmaniasis), whereas the latter appears 1 to 5 years later (post–kala-azar dermal leishmaniasis), The presence of alternatively activated M2 macrophages and a predominant CD8 T-cell milieu have been identified in the South East Asian form, whereas the immunopathology remains poorly defined in the Sudanese form.

VISCERAL LEISHMANIASIS

CLINICAL MANIFESTATIONS

Leishmania infection can be asymptomatic in about 11% of the population in endemic areas, and many cases are not diagnosed until several months after the onset of symptoms.[5] The onset of visceral leishmaniasis, previously referred to as kala-azar when caused by *L. donovani,* occurs weeks to months after the initial infection. Clinical signs and symptoms, such as fever and hepatosplenomegaly, do not definitively distinguish visceral leishmaniasis from other infectious or hematologic conditions. Moderate to severe anemia, mild to moderate leukopenia, thrombocytopenia, systemic inflammation, and polyclonal hypergammaglobulinemia, either isolated or combined, suggest but do not confirm the diagnosis. Parasitologic tests are therefore indispensable before making a therapeutic decision.[6]

DIAGNOSIS

Polymerase chain reaction (PCR) is more sensitive than microscopic examination and is the first-line diagnostic test when it is available.[7] Quantitative PCR with a kinetoplast DNA target and validated thresholds allows accurate diagnosis with venous blood.

Microscopic visualization of amastigotes in samples from the lymph nodes, bone marrow, liver, spleen, or other organs is an option if PCR testing is not available. Splenic aspiration should be performed only in trained facilities and only if other, lower risk methods cannot be used. Parasites also occasionally can be found in the blood or urine.

Antigen-based tests have a high specificity but only moderate sensitivity and are not widely used, except in patients who are infected with the human immunodeficiency virus (HIV). Serologic tests to detect *Leishmania* antibody have high diagnostic accuracy but require equipment that is poorly adapted to field settings. Specific antibodies remain detectable for several years after asymptomatic infection or cure.

COMPLEX MANIFESTATIONS OF VISCERAL LEISHMANIASIS

VISCERAL LEISHMANIASIS–HUMAN IMMUNODEFICIENCY VIRUS COINFECTION

In patients who have visceral leishmaniasis and who are infected with HIV but who do not have severe immunosuppression, the clinical manifestations are generally similar to those in immunocompetent patients. In patients who have low $CD4^+$ T-cell counts (<200/μL), however, classic signs (e.g., splenomegaly) may be absent. A substantial proportion of patients coinfected with *Leishmania* and HIV may have other opportunistic infections that complicate the clinical diagnosis. The parasitic load is usually higher, and parasites may be found in tissues other than spleen, liver, bone marrow, or lymph nodes (e.g., gut or lung), especially in severely immunosuppressed patients. As a result, the sensitivity of microscopic examination, culture, or PCR of blood (whole blood or buffy coat) or bone marrow aspirates is generally higher than that in immunocompetent patients with visceral leishmaniasis. Limited data have also shown high sensitivity of the latex agglutination based antigen testing in coinfected patients but not of antibody testing. Increased sensitivity can be achieved by using a sequential combination of different serologic tests.

POST–KALA-AZAR DERMAL LEISHMANIASIS

After successful treatment of visceral disease due to *L. donovani,* some patients in Sudan and South East Asia progress to widespread cutaneous disease.[8] In Sudan, the skin lesions appear concomitantly during visceral leishmaniasis in 50% of cases. In South East Asia, however, skin lesions appear in 5 to 10% cases of visceral leishmaniasis about 2 to 10 years after apparent cure. With active case surveillance,[9] these proportions of post–kala-azar dermal leishmaniasis have been increasing. In a very small proportion of patients with post–kala-azar dermal leishmaniasis, uveitis occurs with poor visual prognosis. PCR testing is more sensitive than smears in macular cases. Serologic tests are of limited value because a positive finding may be the result of persistent antibodies following a past episode of visceral leishmaniasis, but they can be helpful when a previous history of visceral leishmaniasis is uncertain.

TREATMENT

General Principles

The therapeutic management of patients with visceral leishmaniasis requires re-nutrition, broad-spectrum antibiotics if bacterial superinfection is suspected, transfusion in cases of severe anemia, and proper hydration, especially when amphotericin B is used for the specific antileishmanial treatment.

The clinical response to antileishmanial agents depends on the clinical form, the infecting species and subspecies (zymodeme), and geography. Many antileishmanial agents are toxic, expensive, or difficult to administer in field conditions, but they can be administered on an outpatient basis in developed countries.[9] No single satisfactory option for treating most of the clinical forms or species has been validated.

In nonendemic and some endemic countries, treatment of visceral leishmaniasis is based on liposomal amphotericin B,[10] but treatment is more complex in East Africa and in some endemic countries where liposomal amphotericin B is less effective.[11] Expert advice is typically required for relapsing visceral leishmaniasis in immunocompromised patients, as well as for cutaneous leishmaniasis or mucosal leishmaniasis.

Visceral Leishmaniasis in Immunocompetent Patients

Single-Agent Therapies

Liposomal amphotericin B, which is the first-line option in most nonendemic countries, cures 100% of patients at 30 days and 96% of patients at 6 months in South East Asia with a single infusion of 10 mg/kg; it is recommended in the national program to eliminate visceral leishmaniasis. In East Africa, the doses of liposomal amphotericin B required to cure visceral leishmaniasis (30 to 50 mg/kg cumulatively) are markedly higher than in India, and the drug fails in about 20% of patients, even with these higher doses. Liposomal amphotericin B is not adequately effective to treat post–kala-azar dermal leishmaniasis.[12] Amphotericin B (cumulative dose of 7 to 15 mg/kg) cures more than 98% of patients in India, whereas treatment of visceral infection with *L. infantum/chagasi* requires at least 14 mg/kg (generally 21 mg/kg cumulative dose over 10 days).

Pentavalent antimonials (sodium stibogluconate, meglumine antimoniate) are still prescribed as first-line therapy in many areas outside of Southeast Asia, where resistance is high. In other locations, failure rates of initial treatment do not exceed 10% if patients are treated with the correct dose (20 mg/kg/day of pentavalent antimony for 28 days). In an endemic country, mortality in treated patients may exceed 10%, with toxicity positively correlating with age. Pentavalent antimonials are contraindicated in patients with heart, kidney, or liver disease or advanced age and in pregnant women. Generic formulations have not consistently demonstrated activity and tolerance identical to that of sodium stibogluconate.

Miltefosine (an oral alkyl phosphocholine at 2.5 mg/kg/day for 28 days) is very effective for visceral leishmaniasis in South East Asia. In Ethiopian patients with visceral leishmaniasis (28% with HIV infection), miltefosine is more effective than generic sodium stibogluconate (98% survival vs. 90% survival). Miltefosine is contraindicated in women who are pregnant or may become pregnant. Due to the drug's terminal elimination half life of 30 days, contraceptive measures must be observed for more than 3 months after therapy. Abdominal pain, nausea, and vomiting are frequent adverse events, and rarely corneal disorders (especially in post–kala-azar dermal leishmaniasis) has been reported. For post–kala-azar dermal leishmaniasis, treatment remains to be clearly defined; presently, miltefosine (50 mg orally daily if <25 kg, 50 mg twice daily if >25 kg) administered orally for 12 weeks is preferred over liposomal amphotericin B.[A1]

Paromomycin (aminosidine sulfate) (15 mg/kg in sulfate form equivalent to 11 mg of base per kilogram intramuscularly for 21 days) is highly effective in India; however, its efficacy is significantly lower in East Africa, and it is used only in combination with other drugs. *Pentamidine* is efficient in treating visceral leishmaniasis only when high doses (more than seven injections of 4 mg/kg) are used. Such doses are sufficiently toxic[13] that pentamidine is no longer used for the initial treatment of visceral leishmaniasis. Lower doses (fewer than four injections of 4 mg/kg every 2 or 4 weeks) induce much fewer adverse events and are still used for the secondary prophylaxis of visceral leishmaniasis in HIV-infected patients.

Combinations/Coadministration

To limit extension of drug resistance, shorter courses of two drugs are potentially preferable to monotherapy. For example, combinations of amphotericin B plus oral miltefosine (sequential) or intramuscular paromomycin plus miltefosine can achieve cure rates of up to 98% with 7- to 10-day courses of therapy in East Africa. A single infusion of liposomal amphotericin B followed by oral miltefosine has been highly effective in India.

Visceral Leishmaniasis in Immunodeficient Patients

As with other major opportunistic infections during HIV infection, treatment may be subdivided into initial course and secondary prophylaxis. The potential risk for the widespread emergence of resistance to antileishmanial agents is more significant for *L. donovani,* which (unlike *L. infantum*) can be transmitted by sandflies from humans to humans.

For initial treatment, the efficacies of pentavalent antimonials and amphotericin B are similar, but the dose is higher than in immunocompetent patients

(40 mg/kg in cumulative dose). Patients benefit from effective antiretroviral treatment (Chapter 357). If HIV patients remain immunocompromised, secondary prophylaxis with amphotericin B lipid complex (1 mg/kg monthly) moderately reduces the frequency of recurrences. Miltefosine (50 mg three times per week) is another option, especially if the reduction in parasitic load is documented by quantitative PCR testing. Administration of pentamidine (monthly infusions of 4 mg/kg) once or twice a month is another potential option because drug levels persist for weeks or months after a single administration. Pancreatic tolerance should be monitored closely.

Liposomal amphotericin B 30 mg/kg plus miltefosine (usually 2 daily doses of 50 mg for 28 days) can achieve a higher initial cure rate than liposomal amphotericin B alone (40 mg/kg) for *L. donovani* in East Africa.[A2] However, the best strategy to reach sustained cure without relapse will require further research.

CUTANEOUS LEISHMANIASIS

CLINICAL MANIFESTATIONS

The clinical consequences of cutaneous leishmaniasis are dermatologic, and concomitant visceral impairment is very unusual. Although the signs and symptoms of cutaneous leishmaniasis vary considerably (Fig. 319-2)—from pure nodular lesions to developing ulceration through dry crusty lesions and squamous plaques—some features are fairly constant. First, firm infiltration is almost constant (the exception being the initial macule of post–kala-azar dermal leishmaniasis). Second, the evolution is subacute. A lesion that reaches its maximum size in less than a week is most likely not due to cutaneous leishmaniasis. Finally, except in patients with numerous satellite papulopustules, the lesion or lesions are sharply defined. Colonization of the cutaneous leishmaniasis ulcer with bacteria may give the lesion a purulent appearance, whereas true superinfection adds an erythematous ring distinctly overflowing the infiltrated edge of the ulcer, and transforms a usually cold and painless lesion into a hot and painful lesion.

The intensity of the discomfort, related to one or several oozing or unsightly lesions, and the impact of atrophic, hypopigmented, or hyperpigmented scars depend on the lesions' topography. In the New World, mucosal impairment may affect up to 1 to 15% of patients, with greater incidence in Bolivia. Tegumentary infection with *Leishmania infantum* may also spread to mucosae in up to 20% of patients.

DIAGNOSIS

Several dermatologic conditions such as staphylococcal (Chapter 267) or streptococcal (Chapter 269) infection, mycobacterial ulcer (Chapters 299 and 300), leprosy (Chapter 301), fungal infection, cancer, sarcoidosis (Chapter 83), and tropical ulcer mimic cutaneous leishmaniasis or mucosal leishmaniasis lesions (see Fig. 319-2). Diagnostic confirmation is necessary because treatment is costly and potentially toxic.

Parasitology

Scraping, fine-needle aspiration, or biopsy of lesions provides appropriate samples in which amastigotes can be identified, more easily on smears or imprints (cytology) than on tissue sections (histology) (Fig. 319-3). Scraping should be performed under local anesthesia at both the center and edges of the lesion with a curved scalpel blade. The 2- to 4-mm skin fragment obtained by punch biopsy provides abundant material, which facilitates the search for scarce parasites and for an alternative diagnosis by culture. PCR testing, which is preferred if available, enables the identification of the specific *Leishmania* species in regions where several *Leishmania* species coexist.

Microscopic examination of Giemsa-stained material is the most widely available method.[14] Serologic diagnosis is of limited use for cutaneous leishmaniasis because of low sensitivity.

COMPLEX MANIFESTATIONS OF CUTANEOUS LEISHMANIASIS

MUCOSAL LEISHMANIASIS

A proportion of cutaneous leishmaniasis infections (about 1 to 10% in South America) caused by *Leishmania braziliensis* or *Leishmania guyanensis* progress to a metastatic infection of the mucosa of the oral/nasal cavity or larynx, often 1 to 5 years after healing of the initial simple cutaneous lesion. Mucosal infection has also been reported in travelers returning from endemic countries[15] in South America or, more recently, in southern and western Europe where this complication of *Leishmania infantum* infection is often associated with underlying immunosuppression.[16] Immunopathology shows extensive destruction of local tissue. Allergic rhinitis (Chapter 394), paracoccidioidomycosis (Chapter 308) or other deep mycosis (Chapter 312), leprosy (Chapter 301), cancer and sarcoidosis (Chapter 83) may mimic the lesions of mucosal leishmaniasis. Positive serology or leishmanin skin testing indicates possible mucosal leishmaniasis. Parasites are scarce in mucosal lesions, so a search for parasites by microscopy in mucosal scrapings or biopsy has a poor sensitivity, but PCR testing of scraping or biopsy material has a high sensitivity.

DIFFUSE CUTANEOUS LEISHMANIASIS

Patients with diffuse cutaneous leishmaniasis have an anergic response to *Leishmania* antigens. This form of the disease is found in South America and East Africa, often associated with *Leishmania amazonensis* and *Leishmania aethiopica* infection. Nonulcerative nodules, loaded with parasites, disseminate from the initial site of infection to multiple skin sites. There is no self-cure, and treatment is difficult.

TREATMENT

The risk for metastasis (affecting the nose or less frequently other otorhinolaryngeal zones) has strongly influenced therapeutic decisions.[17] Although many patients with cutaneous leishmaniasis cure spontaneously within 3 to 18 months, local therapy[A3] with intralesional injections of pentavalent antimonials[18] (preferentially following a brief application of liquid nitrogen),[A4] photodynamic therapy,[A5] and thermotherapy are attractive options (Fig. 319-4). However, implementation of these methods is hampered by logistic constraints and requires skilled health care providers. Paromomycin ointment is efficacious and well tolerated for cutaneous leishmaniasis caused by several species in North Africa and Central America and in travelers.[A6]

Topical liposomal amphotericin B gel also may be tried.[A7] When local treatment cannot be administered or fails, systemic therapy is used. Oral therapy with relatively nontoxic drugs (e.g., fluconazole 200 to 600 mg/day for 42 days,[A8] or miltefosine 2 to 2.5 mg/kg/day for 28 days[A9]) is the simplest option, but no optimal drug regimen has been solidly validated. In cutaneous leishmaniasis caused by *L. guyanensis* or *Leishmania panamensis*, low doses of pentamidine (1 to 3 intramuscular injections of 7 mg/kg every 72 hours or preferably a slow intravenous infusion in dextrose) generally cure more than 75% of patients.[A10] The efficacy of systemic liposomal amphotericin B in cutaneous leishmaniasis is markedly lower than in visceral leishmaniasis, and it presently is not considered an adequate first-line option. Inadequate surgical excision or excessive doses of systemic parenteral treatments, especially without sufficient follow-up, may carry more risk than benefit for patients with cutaneous leishmaniasis.[19]

RECIDIVANS CUTANEOUS LEISHMANIASIS

Recidivans cutaneous leishmaniasis is characterized by the development of lesions containing granulomatous tissue. The lesions often require many years to heal and may arise years after healing of a simple localized lesion. New ulcers and papules may form over the edge of the old scar. Infections are normally associated with *L. tropica* infection and are difficult to treat.

DISSEMINATED CUTANEOUS LEISHMANIASIS

Disseminated cutaneous leishmaniasis is characterized by the presence of more than 10 lesions in more than two distant sites. It has been described in Brazil and is associated with a higher risk of mucosal involvement. The same term is used to describe multilesional involvement in immunosuppressed patients generally infected with *L. infantum*.

PREVENTION

No vaccines or prophylactic drug regimens are currently available.[20] Sandflies are sensitive to most insecticides, so transmission may be reduced by residual spraying in houses. Insecticide-impregnated bed nets and dog collars (to prevent transmission of zoonotic cutaneous leishmaniasis) have been investigated. Personal permethrin-impregnated clothing is protective against cutaneous leishmaniasis.

PROGNOSIS

Most untreated patients with established visceral leishmaniasis ultimately die, but the death rate is less than 2% in patients treated early with liposomal amphotericin B. Mortality increases when bleeding (mainly from the digestive tract or lung) or secondary bacterial infection occurs, usually after prolonged untreated evolution or unresponsiveness of visceral leishmaniasis to first-line agents. Post-therapeutic relapse is very frequent in HIV-coinfected patients with initially or persistently low $CD4^+$ counts. In immunosuppressed patients, visceral leishmaniasis contributes to a fatal outcome. A proportion of *L. donovani*–infected patients experience post–kala-azar dermal leishmaniasis weeks to years after the initial episode, sometimes complicated by severe ocular involvement.

FIGURE 319-2. Clinical features of cutaneous leishmaniasis. A, Typical forms of cutaneous leishmaniasis. **A1**, Papular-nodular. **A2**, Squamous. **A3**, Crusty. **A4**, Ulcerated. **A5**, Superinfected lesions. **B**, Atypical forms of cutaneous leishmaniasis and mucosal leishmaniasis. **B1**, Multiple papules on the face (*L. infantum*, Balearic islands). **B2**, Nodular lymphangitis (*L. braziliensis*, Brazil). **B3**, Multiple lesions with numerous peripheral papules (*L. major*, Tunisia). **B4**, Initial spread to the nasal mucosa (anterior septum, *L. braziliensis*, Bolivia). **B5**, Infiltration and ulceration of the tonsils (*L. infantum*, France). **C**, Clinical manifestations that are not cutaneous leishmaniasis. **C1**, Multiple papules (late secondary syphilis) (Chapter 295). **C2**, Nodular lymphangitis (sporotrichosis) (Chapter 308). **C3**, Single crusty ulceration (*Mycobacterium ulcerans* infection) (Chapter 300). **C4**, Ulcerated acute *Staphylococcus aureus* infection (Chapter 267). **C5**, Ulcerated nodule keratoacanthoma (Chapter 188).

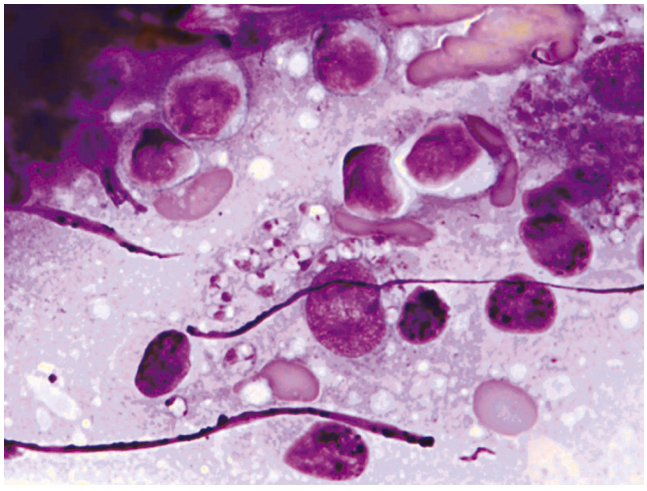

FIGURE 319-3. **Amastigotes of *Leishmania major* in scrapings from a skin ulcer.**

Cutaneous leishmaniasis undergoes self-cure in 20 to 90% of patients within 3 to 18 months, depending on the infecting species and the geographic location. Cutaneous leishmaniasis caused by *L. braziliensis, L. guyanensis,* and *L. infantum* may metastasize to the nose and other mucous membranes with variable frequency in different areas. Cutaneous leishmaniasis caused by *L. tropica* often relapses (recidivans cutaneous leishmaniasis). A small proportion of patients infected with *L. amazonensis* and *L. aethiopica* experience diffuse cutaneous leishmaniasis. Even when treated, many cutaneous leishmaniasis lesions leave disfiguring, hypotrophic, hypopigmented, or hyperpigmented scars that can be stigmatizing.

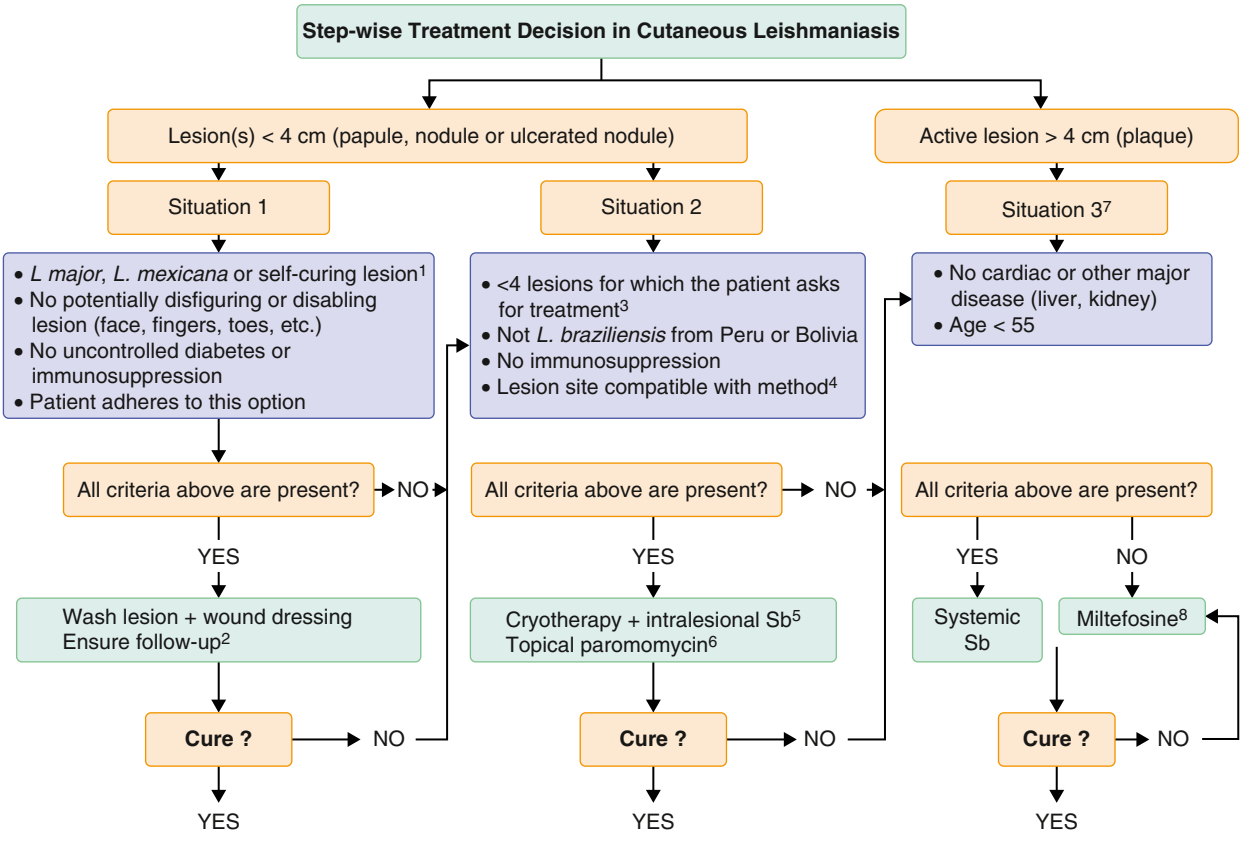

FIGURE 319-4. **Algorithm of treatment options for cutaneous leishmaniasis—an example of decision making.** (1) Self-curing lesions show flattening or reduction in the surface of the ulceration and/or induration. (2) Washing lesion, wound dressing, and follow-up performed in all situations. (3) Lymphatic dissemination in itself does not influence treatment decisions, except when it increases the number of lesions requiring therapy. (4) Most lesions of limbs, trunk, cheek, upper cheek, chin, and face can be injected, including those close to large joints. Injection in ears, fingers, and toes is very painful. (5) When/where cryotherapy is not available, simpler physical methods can be adopted. (6) In 2022, the validated formulation of topical paromomycin is available only through clinical trials or compassionate use. (7) In case of pregnancy, wait until after delivery or use liposomal amphotericin B. (8) Miltefosine should be used with caution or dose adaptation (or both) in patients with liver or kidney involvement or with gastrointestinal symptoms. Sb = pentavalent antimony.

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320 TOXOPLASMOSIS

ANITA A. KOSHY

DEFINITION

Toxoplasmosis refers to symptomatic disease, whereas *T. gondii* infection refers to latent, asymptomatic disease. *Toxoplasma gondii* is a ubiquitous protozoan parasite. Although felids are *T. gondii*'s only definitive host (i.e., where parasitic sexual reproduction occurs), the parasite's intermediate hosts include most warm blooded animals, from birds to humans. In both the definitive and intermediate hosts, *T. gondii* causes an acute infection followed by the establishment of a long-term persistent or latent infection. The initial acute infection can be symptomatic, but *T. gondii* is predominantly known for causing congenital disease in children of mothers with a primary infection during pregnancy and encephalitis in persons with severe acquired immune deficiencies.

The Pathogen

T. gondii has a sexual and asexual life cycle. During the sexual life cycle, which occurs in felid enterocytes, the parasite differentiates into male and female gametocytes, which fuse to form a diploid zygote. This diploid form is surrounded by a protective wall, which collectively forms the unsporulated oocyst that is expelled into the environment via felid feces (Fig. 320-1A). After being expelled, the oocysts sporulate to form haploid sporozoites, which are infectious if ingested.[1] These oocysts, which are extremely hardy, can potentially survive for years in the environment. Felids apparently are the only definitive host because only their enterocytes have the excess levels of linoleic acid that are required for sexual reproduction owing to their lack of the delta-6-desaturase enzyme, which helps convert linoleic acid to arachidonic acid.[2]

In the asexual life cycle, which is subdivided into lytic and latent stages, *T. gondii* replicates its haploid genome and divides into two daughter cells via a process called endodyogeny, by which the two daughter cells form within the mother, and then the mother cell dissolves. During the lytic cycle, parasites are in a fast-replicating form called a tachyzoite (see Fig. 320-1B). As tachyzoites rapidly expand in number and disseminate throughout the body, they generate a robust immune response. As the immune response clears tachyzoites, the tachyzoites convert to bradyzoites, which are a slow-replicating form of *T. gondii* that forms tissue cysts in certain organs and cell types, especially neurons and striated muscle (see Fig. 320-1C). These tissue cysts, which can contain hundreds or even thousands of bradyzoites, typify the latent stage of the life cycle. At this stage, the organism can evade the host's immune system, thereby enabling long-term infection. This long-term latent infection is essential for passage of *T. gondii* between intermediate hosts,[3] a process thought to underlie *T. gondii*'s success as a parasite (geographically ubiquitous and with a broad intermediate host range).

EPIDEMIOLOGY

Humans become infected with *T. gondii* via the ingestion of undercooked meat that contains tissue cysts (both commercial and game) or oocyst-contaminated water or food[4,5]; vertical transmission from mother to child; rarely from solid organ transplantation; and potentially from transfusions. Infection from a cat occurs when oocysts or cat feces contaminate food or water, or when caretakers use poor hand-hygiene when exposed to cat feces (i.e., cleaning kitty litter). Thus, risk of infection depends on a variety of parameters such as cultural habits (e.g. having cats as pets, drinking unpasteurized goat's milk) and access to clean water and hygiene, which often correlate with geography and socioeconomic status.

As estimated by seropositivity surveys, rates of infection with *T. gondii* vary in different countries and within a single country. For example, although the overall U.S. seropositivity rate is estimated to be about 11%,[6] the seropositivity among the Old Order Amish in Lancaster County, Pennsylvania is over 50%.[7] Similarly, people living in the former East Germany have a higher *T. gondii* seroprevalence than people who live in the former West Germany, a distinction that is postulated to arise from the East German tradition of eating raw minced beef and pork. In developed nations, *T. gondii* seroprevalence is higher in rural populations compared with urban populations; but in Brazil, urban populations have a higher seroprevalence. Although seropositivity often increases with age, presumably owing to increased exposure over a lifetime, high levels of seropositivity are seen even at a young age in urban areas in Brazil.[8]

In the era before highly active anti-retroviral therapy, approximately 30 to 50% of patients who were seropositive for human immunodeficiency virus (HIV) and had the acquired immunodeficiency syndrome (AIDS) developed toxoplasmic encephalitis, but that risk is now very low in patients who are on effective therapy. Both primary and reactivation disease has been seen in patients who are taking immunosuppressive drugs (e.g., anti-TNF therapy, rituximab, and mycophenolate mofetil), but these risks are relatively rare compared with HIV/AIDS patients with low CD4 counts.[9]

Patients who undergo hematopoietic stem cell transplants (Chapter 163) or solid organ transplantation are at risk for toxoplasmosis. The risk of toxoplasmosis is highest for allogenic hematopoietic stem cell transplants when the recipient is seropositive for toxoplasmosis and the donor is seronegative; in this situation, the recipient has a high likelihood of latent *T. gondii* infection, but the donor's immune system lacks preexisting adaptive immunity to *T. gondii*.[10] For recipients of solid organ transplants, the risk of symptomatic toxoplasmosis is just the opposite—highest when the recipient is seronegative but the donor is seropositive. The risk is highest in recipients of heart transplants, presumably because heart tissue is known to harbor persistent, encysted parasites. For other solid organ transplants,[11] infection can be seen clinically months to years after transplantation, when it is difficult to determine whether the parasite came from the transplanted organ or whether the recipient developed a symptomatic primary or reactivation infection because of long-term immunosuppression.

Congenital toxoplasmosis most commonly occurs when a seronegative pregnant woman develops a primary infection. The likelihood of transmitting the infection to the fetus increases with gestational age, with a 6% or less risk for maternal seroconversion at less than 13 weeks of gestation and above 70% risk for seroconversion at 36 weeks or more. Infections in early gestation have a higher likelihood of severe infection compared to late infections. Mother-to-child infection is unusual in HIV patients who have a CD4 count above 200 cells/μL.

The genotype of the infecting *T. gondii* strain may also influence the severity of the primary infection in an immunocompetent host as well as vertical transmission of congenital disease and ocular infection in immunocompromised patients. Limited data from congenitally infected infants and their parents also suggest that human polymorphisms in *nalp1/nlrp1* and *alox12* may play a role in susceptibility to congenital toxoplasmosis. The mechanisms by which these polymorphisms contribute to this susceptibility are unknown, but differences in NLRP1-triggered pyroptosis determine the likelihood of *T. gondii* infection in different strains of rats.

PATHOBIOLOGY

In postnatally acquired infection, most individuals become infected with *T. gondii* by ingesting either tissue cysts or oocysts. Once ingested, bradyzoites or sporozoites are released via digestive enzymes, followed by infection of epithelial cells. During this enteral stage, parasites convert to the tachyzoite stage, which disseminates throughout the body. The innate and adaptive immune response targets the tachyzoites, thereby controlling the infection in a manner that is highly dependent upon the production of interferon (IFN-γ) by immune cells, especially $CD8^+$ effector T cells, and subsequent IFN-γ responses in hematopoietic and nonhematopoietic cells.[12] Key innate immune cells include the antigen presenting dendritic cells, natural killer cells, neutrophils, tissue-infiltrating monocytes, and tissue macrophages such as microglia.[13]

In the face of this stress, tachyzoites transition to encysting bradyzoites, which are not fully cleared from specific organs (e.g., eye, brain) thereby leading to long-term persistence. In hosts who become immunocompromised and occasionally even in immunocompetent individuals, these persistent parasites reactivate to cause symptomatic disease. The conversion to the bradyzoite/encysted stage, which includes changes in the parasite's surface antigens, is thought to help parasites evade the tachyzoite-directed immune response. Although the human immune response to bradyzoites/cysts may be muted, some degree of a bradyzoite-directed immune response probably does occur.[14]

Human Pathology Findings

Biopsies of *T. gondii*–infected lymph nodes show nonsuppurative lymphadenitis with reactive follicular hyperplasia, uneven clusters of epithelioid histiocytes/cells that blur germinal center margins, and monocytoid B lymphocytes in focally distended sinuses. Toxoplasmic encephalitis typically causes multiple focal necrotizing (untreated) or organized abscesses (treated), but a more diffuse necrotizing form also can be seen. Pulmonary toxoplasmosis can cause interstitial pneumonitis, consolidation, empyema, or a combination of these pathologies. Ocular toxoplasmosis commonly presents as a focal, full-thickness,

ABSTRACT

Toxoplasmosis is the symptomatic disease caused by the ubiquitous protozoan parasite *Toxoplasma gondii*. *T. gondii* is a common parasitic infection that causes a long-term, generally asymptomatic infection that can reactivate in the immunocompromised. The major organs in which *T. gondii* persists are the skeletal and cardiac muscle and the central nervous system (especially the brain and retina). In immunocompetent individuals, acute *T. gondii* infection can cause lymphadenitis, chorioretinitis, and rarely more severe infections. Congenital infection and infection in immunocompromised patients can lead to life-threatening disease, most commonly with brain manifestations. Universal screening is recommended in all pregnant women. A positive polymerase chain reaction test or detection of toxoplasma tachyzoites in any bodily fluid is diagnostic. Common treatment regimens are trimethoprim-sulfamethoxazole, pyrimethamine (plus folinic acid) plus sulfadiazine, clindamycin, or atovaquone. With early treatment, outcomes are generally good, but congenital infection is associated with a high rate of miscarriage and severe malformations.

KEYWORDS

Toxoplasma gondii
toxoplasmic encephalitis
congenital toxoplasmosis
ocular toxoplasmosis
AIDS
transplant
parasites
brain abscess

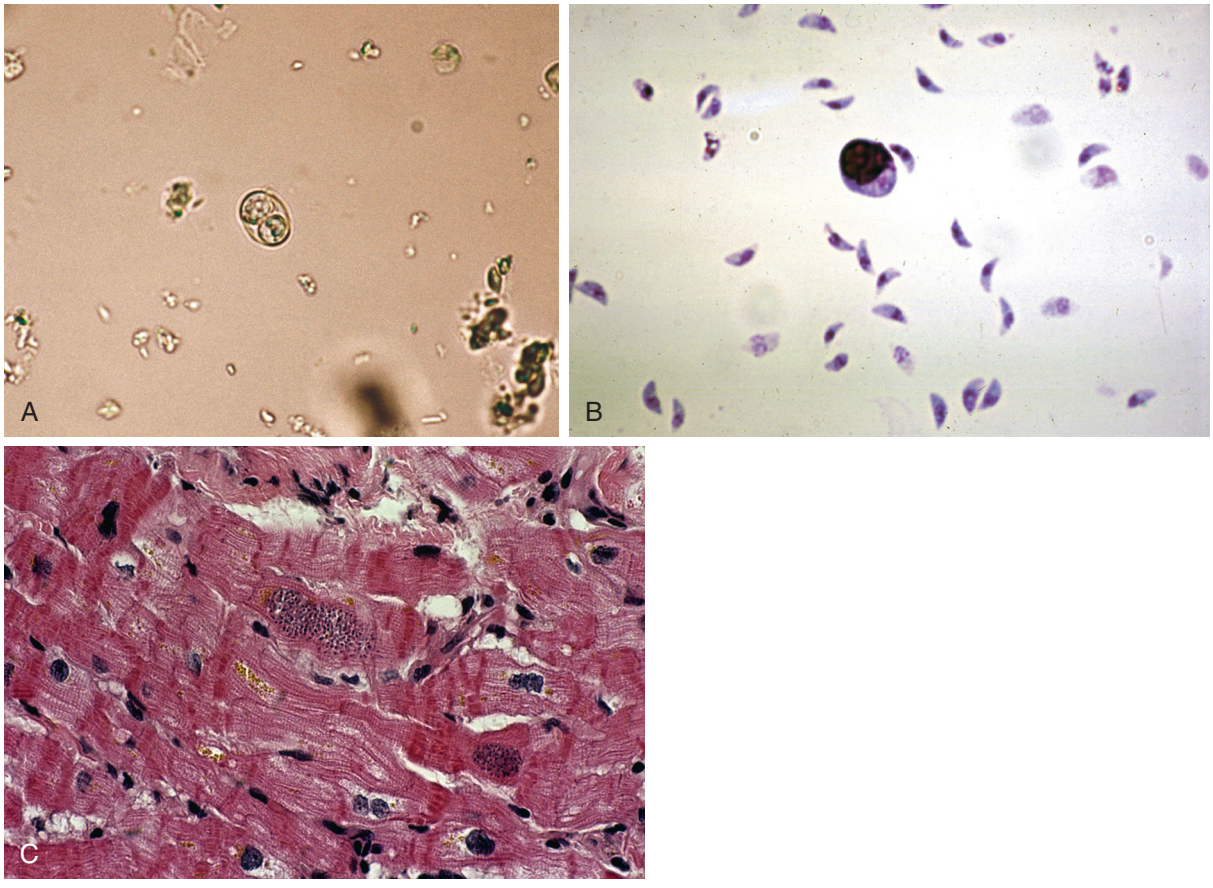

FIGURE 320-1. ***Toxoplasma gondii*** **exists in nature primarily in three forms. A, Oocysts isolated from cat's feces are subspherical to spherical and measure 10 × 12 μm in diameter. B, Tachyzoites are bow shaped, measure 2 to 3 μm wide and 5 to 7 μm long, and can be stained with Wright-Giemsa stain. C, Tissue cyst observed in human myocardial tissue stained with hematoxylin and eosin. Tissue cysts vary in shape and size and may reach more than 100 μm. (Courtesy of José Montoya, MD.)**

chorioretinitis, with or without scars, and it also can be fulminant with panophthalmitis and even orbital cellulitis in immunocompromised hosts. Rare reports of myocarditis and myositis also show focal necrosis.

CLINICAL MANIFESTATIONS

T. gondii infections cause a wide range of symptoms, which vary from acute as compared with chronic infection and are different in immunocompetent individuals as compared with immunocompromised patients or patients with congenital infection (Table 320-1).

Infection in Immunocompetent Patients (Including Pregnant Women)

Patients who are acutely infected with *T. gondii* typically experience a mild febrile illness that is similar to infectious mononucleosis (Chapter 348) and is commonly associated with lymphadenopathy (Chapter 154), fatigue, headaches, and myalgias.[15] In the non-outbreak setting, most immunocompetent individuals do not know when they became infected with *T. gondii*.

In Latin America (Brazil, French Guiana, Suriname), small numbers of immunocompetent patients have experienced atypically severe acute infections, including multiorgan failure, pneumonia, and death. Most of these patients have been males who ate raw or undercooked game or drank potentially contaminated water, and they often were infected by *T. gondii* strains that appear to be more virulent than the common strains seen in the U.S. and Europe.

The frequency of acute ocular toxoplasmosis in immunocompetent patients varies by setting (outbreak vs. non-outbreak) and country. In the United States, an estimated 21,000 patients will develop ocular disease, but only about 5000 of these cases are symptomatic. Ocular symptoms include blurred vision, loss of vision (scotoma or central vision if the macula is involved), pain, and tearing. Some patients who present with what seems to be an acute infection already have retinal scars in non–vision affecting areas, thereby suggesting they are having a reactivation event rather than a new acute infection.

Rare cases of acute encephalitis have been reported in apparently immunocompetent patients. Although retrospective reports have suggested an association between *T. gondii* seropositivity and a wide range of mental and neurologic diseases, no substantial or convincing evidence links *T. gondii* infection to these noninfectious psychiatric or neurologic conditions.

Infection in Immunocompromised Patients

Patients with HIV/AIDS or on Immunosuppressive Medications

Encephalitis is the most common manifestation of toxoplasmosis in HIV/AIDS patients whose CD4 count drops below 100 cells/μL. These patients can present with nonspecific symptoms, such as lethargy and altered mental status, as well as focal abnormalities such as hemiparesis, cerebellar signs, or seizures.[16,17] The course is usually subacute over days to weeks, but acute presentations can occur.

Patients can also present with symptoms and signs of chorioretinitis, pneumonia, and rarely gastrointestinal or musculoskeletal symptoms. Immune reconstitution syndromes and *T. gondii* encephalitis rarely have been described when HIV/AIDS patients are treated and their CD4 counts rise to above 200 cells/μL. In the limited number of cases of toxoplasmosis in patients who have been on immunosuppressive drugs, encephalitis with multiple, ring-enhancing lesions has been the most common presentation.

Organ Transplantation

Both primary and reactivation toxoplasmosis can be seen in patients after organ transplantation; distinguishing between the two can be difficult and will not change management. The range of signs and symptoms includes fever, rash, lymphadenopathy, chorioretinitis, pneumonia, myocarditis, hepatosplenomegaly, rash, toxoplasmic encephalitis, and even sepsis.[18,19] Although toxoplasmic encephalitis in organ transplant recipients can present as the typical ring-enhancing lesion (i.e., abscess-like), cases of diffuse infiltration also have been reported. In these patients, a suspicion for toxoplasmosis must be based upon discordant serologies in the donor as compared with the recipient, absence of appropriate prophylaxis for a history of *T. gondii*, and other risk factors for exposures to *T. gondii*.

Congenital Infection

The signs and symptoms of congenital infection vary widely from spontaneous abortion to mild or severe disease. Severe congenital infection can present with a range of nonspecific symptoms such as petechial rash, splenomegaly,

TABLE 320-1 CLINICAL MANIFESTATIONS OF TOXOPLASMOSIS IN HUMANS

CLINICAL CATEGORIES	CLINICAL MANIFESTATIONS AND SYNDROMES
PRIMARY INFECTION	
Immunocompetent individuals	Most patients are asymptomatic or have a nonspecific flu-like febrile illness often with lymphadenitis. Acute chorioretinitis can present with blurred vision, loss of vision, pain, and tearing. Often the fundoscopic examination will show fluffy white, necrotizing chorioretinitis close to a pigmented chorioretinal scar. Rare cases of acute multiorgan failure, pneumonia, hepatitis, myocarditis, myositis, and death have been reported, primarily in Latin America.
Immunocompromised host (e.g., solid organ transplant recipient)	Encephalitis/focal brain abscess, pneumonia/pneumonitis, chorioretinitis, multiorgan involvement, hepatitis, renal failure
CHRONIC INFECTION	
Immunocompetent individuals	Most persons with chronic toxoplasmosis are asymptomatic. Reactivation of chorioretinitis can occur in congenitally or postnatally acquired disease.
Reactivation in immunocompromised patients, including seropositive recipients of a stem cell transplantation from a seronegative host	Multiple brain abscesses, diffuse encephalitis, seizures, chorioretinitis, fever of unknown origin, pneumonia, myocarditis, hepatosplenomegaly, lymphadenopathy, rash
CONGENITAL TOXOPLASMOSIS	
Fetus	Ultrasound study can be normal or reveal hydrocephalus, brain or hepatic calcifications, splenomegaly, ascites, pericarditis. Infection can also result in spontaneous abortion.
Newborn	Newborn can be normal or have nonspecific signs, symptoms, or findings, including CNS calcifications, microphthalmia, chorioretinitis, seizures, abnormal cephalic perimeter (microcephaly or hydrocephalus), hepatomegaly, splenomegaly, petechial rash, thrombocytopenia, or anemia.
Children and adults	Children can continue to suffer from chronic sequelae such as psychomotor retardation, seizures, and vision loss. Asymptomatic infants may be become symptomatic during childhood, adolescence, or adulthood, with the most common manifestation being chorioretinitis.

CNS = central nervous system.
Modified from Montoya JG. Toxoplasmosis. In: Goldman L, Schafer A, eds. *Goldman-Cecil Medicine*. 26th ed. Philadelphia: Elsevier; 2020.

hepatomegaly, brain calcifications, chorioretinitis, microphthalmia, microcephaly, hydrocephalus, and prematurity. Given the nonspecific nature of these signs and symptoms, other common causes of congenital infection must be excluded (e.g., syphilis [Chapter 295], rubella [Chapter 339], cytomegalovirus [Chapter 347], herpes simplex [Chapter 345], Zika virus [Chapter 352]), although the constellation of chorioretinitis, hydrocephalus, and brain calcifications should raise the suspicion for toxoplasmosis. In the absence of treatment, even infants who appear asymptomatic at birth can develop symptoms such as chorioretinitis as they grow older.

DIAGNOSIS

The most common tests used to diagnose *T. gondii* include serology, polymerase chain reaction (PCR) testing, and histopathology (Table 320-2). For most scenarios, especially in immunocompetent patients, the first step is serology because negative serologic testing (both immunoglobulin [Ig]-M and IgG) makes *T. gondii* highly unlikely. PCR is very specific but its sensitivity, especially in immunocompetent patients, can be low.[20] Except for lymphadenitis, for which histopathology is very specific, most patients require a positive specific test such as *T. gondii*–specific immunohistochemical or fluorescent

TABLE 320-2 LABORATORY METHODS FOR THE DIAGNOSIS OF *TOXOPLASMA GONDII* INFECTION AND TOXOPLASMOSIS* IN HUMANS

METHOD	CLINICAL INTERPRETATION
Serologic tests	
IgG	A positive test result establishes that the patient has been infected with *T. gondii*. However, a negative test result can be seen in patients infected within 4 weeks before serum sampling or in patients unable to produce IgG (e.g., immunocompromised hosts).
IgM	A positive test result suggests but is not necessarily diagnostic of an acute infection. Sera with positive IgM test results should be sent to a reference laboratory for confirmatory testing that includes a more specific IgM assay and additional tests, including avidity, acetone (AC)-fixed versus formalin (HS)-fixed (AC/HS) differential agglutination test of tachyzoites, and IgA and IgE.† Positive IgM test results can be seen in chronically infected patients because of persistence of the IgM response or false-positive results observed in certain commercial kits.
Confirmatory testing for positive IgM test results	IgG avidity test; differential agglutination (AC/HS); IgA, IgE performed at a reference laboratory.† A high IgG avidity test result‡ or a nonacute AC/HS test result indicates that the patient has been infected for more than 4 mo (avidity) or 12 mo (AC/HS).
Polymerase chain reaction (PCR)	The B1 gene and the 529-bp repetitive element are the most common gene targets for amplification. PCR test can be performed in any body fluid, including amniotic fluid, peripheral blood, cerebrospinal fluid, bronchoalveolar lavage fluid, vitreous fluid, aqueous humor, peritoneal fluid, pleural fluid, ascitic fluid, and urine. PCR can also be performed in any tissue. A positive test result in any body fluid establishes that the patient has either acute or reactivated toxoplasmosis. However, a positive PCR test result in tissue is more difficult to interpret because it does not differentiate symptomatic toxoplasmosis from a latent infection. Although DNA extraction is more cumbersome, it can be done in paraffin-embedded tissue.
Direct visualization of the parasite	Identification of tachyzoites in any body fluid or tissue is diagnostic of toxoplasmosis due to acute infection or reactivation of a chronic infection. Tachyzoites can be identified by hematoxylin and eosin or cytologic studies but are better visualized with Wright-Giemsa and immunoperoxidase stains. Identification of cysts by hematoxylin and eosin or immunoperoxidase stains confirms the presence of *T. gondii* in the host but does not necessarily establish that the patient has toxoplasmosis.
Attempts to isolate the parasite	A positive isolation study in any body fluid establishes the diagnosis of toxoplasmosis. Isolation of *T. gondii* in cell cultures or peritoneal cavity of mice can be attempted at reference laboratories. These studies can be important in trying to establish a correlation between the genetics of the parasite and its clinical manifestations.
Histology of the lymph node	Classic histologic triad is considered diagnostic: nonsuppurative lymphadenitis with reactive follicular hyperplasia, uneven clusters of epithelioid histiocytes that blur germinal center margins, and monocytoid B lymphocytes in focally distended sinuses.
Fundoscopic examination	Unilateral, focal infection showing fluffy white, necrotizing chorioretinitis with vitritis (sometimes with a pigmented chorioretinal scar) can be associated with anterior uveitis, vasculitis, and optic neuritis (though involvement of the optic nerve is relatively rare)

**T. gondii* infection = asymptomatic presence of the parasite. Toxoplasmosis = active symptoms and signs are present.
†For example, https://www.sutterhealth.org/services/lab-pathology/toxoplasma-serology-laboratory; remingtonlab@sutterhealth.org or (650) 853-4828
‡The window of exclusion for acute infection varies for different avidity kits (usually between 3 and 5 months).
bp = base pairs; Ig = immunoglobulin; PCR = polymerase chain reaction.
Modified from Montoya JG. Toxoplasmosis. In: Goldman L, Schafer A, eds. *Goldman-Cecil Medicine*. 26th ed. Philadelphia: Elsevier; 2020.

staining. Because many healthy individuals have latent *T. gondii* infection, caution must be exercised to ensure that *T. gondii* is the causative agent rather than an incidental finding, especially in atypical clinical scenarios.[21] Evidence of an active infection includes a positive PCR test on blood, cerebrospinal fluid (CSF), or aqueous fluid; identification of tachyzoites on histopathology; or robust inflammation around a cyst.

Immunocompetent Patients

Diagnosing acute or active toxoplasmosis in the immunocompetent individual is essential but complicated for several reasons: the frequency of latent *T. gondii* infections; the fact that *T. gondii* IgM can be positive for 1 to 2 years post-infection; the tendency for non-reference laboratories to have a higher rate of false positive IgM testing; and the nonspecific symptoms of acute toxoplasmosis. Distinguishing between acute and chronic infection is extremely important in situations in which a tissue diagnosis is difficult to obtain or in pregnant women, in whom the likelihood of fetal infection and need for prenatal treatment is often determined by the acuity of the infection. In these scenarios, expert consultation and advanced testing, such as IgG avidity,[22] should be obtained from a reference laboratory.

Immunocompromised Patients

In immunocompromised patients, the diagnosis of toxoplasmosis is based on a positive PCR test on fluid (e.g., CSF, bronchial alveolar lavage, peripheral blood) or tissue or by identifying an active *T. gondii* infection via a histopathologic study. In patients undergoing stem cell or heart transplantation, who are at the highest risk, routine monitoring of peripheral blood by PCR for *T. gondii* parasitemia may permit diagnosis before patients become sick.

Ocular Toxoplasmosis

The diagnosis of ocular toxoplasmosis is commonly initially made when an ophthalmologist's fundoscopic examination shows fluffy white necrotizing chorioretinitis close to a pigmented chorioretinal scar (Fig. 320-2 and see Table 320-2).[23] Primary infection is suspected when no old scars are identified in either eye, whereas the presence of such scars would suggest reactivation disease. Serologic confirmation by IgG plus IgM in the blood of patients who have acute or chronic *T. gondii* infection is important because a negative serology essentially excludes ocular toxoplasmosis except in rare severely immunocompromised patients. If the fundoscopic examination is atypical but the concern is high, anterior chamber or vitreous fluid can be tested for parasitic DNA by PCR or IgM and IgG antibody levels in the eye fluid can be compared with serum antibody levels. Such testing should be done in consultation with physicians with expertise in diagnosing ocular toxoplasmosis.

Toxoplasmic Encephalitis in HIV/AIDS Patients

Brain imaging with contrast will often show multiple ring-enhancing lesions (Fig. 320-3), with magnetic resonance imaging (MRI) being more sensitive than computed tomography (CT). In HIV/AIDS patients who have CD4 counts below 200 cells/μL and a positive *T. gondii* IgG, the presence of multiple ring-enhancing lesions on CT or MRI establishes a presumptive diagnosis of toxoplasmic encephalitis and requires empirical treatment. Patients who improve clinically within 7 days are presumed to have toxoplasmic encephalitis, though caution must be exercised in patients who are also prescribed corticosteroids (for cerebral edema) because the reduction in edema and/or response of CNS lymphoma to corticosteroids can lead to clinical improvement in the absence of toxoplasmosis.

If, however, the patient shows clinical progression within 3 days, does not improve by 10 to 14 days, or has evidence of progression/new lesions on brain imaging, then further evaluation is required. Similarly, patients who have a single enhancing lesion on MRI or CT or whose *T. gondii* IgG is negative also require further evaluation. This evaluation can be pursued by CSF cytology and PCR (to test for *T. gondii*, Epstein-Barr virus, JC virus [Chapter 341], mycobacteria [Chapters 299 and 300], and cryptococcus [Chapter 309]). Stereotactic brain biopsy is an alternative, which is indicated if the patient deteriorates or does not appropriately improve over 10 to 14 days. For HIV/AIDS patients whose *T. gondii* is thought to be causing pneumonia or myositis, the diagnostic approach is to obtain PCR or biopsy on an appropriate fluid or tissue.

Congenital Toxoplasmosis: Prenatal and Postnatal Diagnosis

If an acute infection is documented or highly suspected in a pregnant woman, fetal ultrasound and PCR on amniotic fluid can determine if the fetus has been infected. Finding brain calcifications or hydrocephalus on a fetal ultrasound can suggest acute fetal infection but generally is not diagnostic. A positive PCR on amniotic fluid is essentially 100% specific for confirming fetal infection, but its sensitivity ranges from 60 to 90%, with the higher sensitivity when performed between 17 and 21 weeks of gestational age.

Congenital toxoplasmosis is confirmed in the setting of a persistent positive IgG, IgM taken at or after 5 days of age, and/or a positive IgA taken at or after 10 days of age. Brain imaging showing calcifications and hydrocephalus can also confirm the diagnosis. Given the complexity of diagnosing congenital toxoplasmosis and its implications for treatment, expert consultation is highly recommended in these situations.

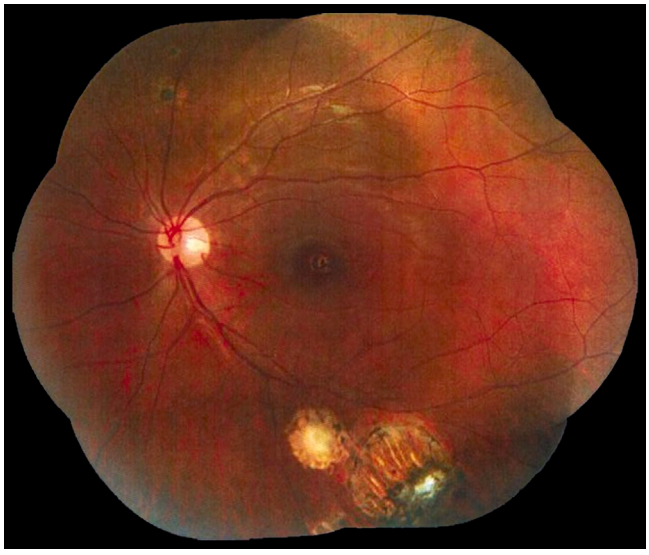

FIGURE 320-2. The morphology of the retinal lesions on funduscopic examination thought to be characteristic of toxoplasmic retinochoroiditis. An active whitish infiltrate is usually attached to the darkly pigmented border of an older scar. (Courtesy of José Montoya, MD.)

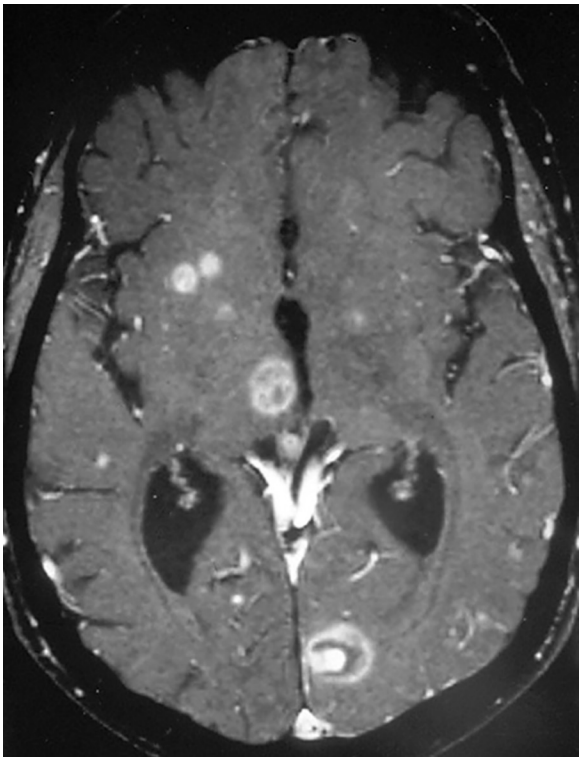

FIGURE 320-3. Radiologic manifestations of central nervous system toxoplasmosis. Magnetic resonance image of the brain of a patient with the acquired immunodeficiency syndrome reveals multiple ring-enhancing brain lesions. (Courtesy of José Montoya, MD.)

TREATMENT

Immunocompetent Patients

Most patients with acute toxoplasmosis are asymptomatic or have transient nonspecific symptoms that resolve without treatment. For patients with lymphadenopathy or lymphadenitis (Chapter 154) most cases will resolve without any intervention, though enlarged lymph nodes can persist for more than 6 months. One month of trimethoprim-sulfamethoxazole leads to a faster resolution of symptoms and serologies compared with placebo. For patients who have more concerning symptoms suggestive of visceral organ involvement, treatment (Table 320-3) for 2 to 4 weeks followed by re-assessment may be appropriate.

Immunocompromised Patients

The preferred primary regimen for immunocompromised patients is pyrimethamine, sulfadiazine, and folinic acid (see Table 320-3). Trimethoprim-sulfamethoxazole is an easier alternative, especially in resource-limited regions of the world, although aggregate data suggest it may be slightly less effective.[A1] In HIV/AIDS patients who are not yet on anti-retroviral treatment, immediate initiation of both anti-retroviral therapy and anti-toxoplasma therapy is no more likely to trigger the immune reconstitution syndrome than is delayed toxoplasmosis treatment.[A2]

Ocular Toxoplasmosis

For ocular toxoplasmosis, systemic treatment is required, as for acute infection (see Table 320-3) based on whether the patient is immunocompetent or immunosuppressed, because of the potential loss of vision.[A3,A4] However, treatment also includes subconjunctival, topical, or intravitreal treatments under the direction of an ophthalmologist. An active recurrent unilateral ocular lesion in an immunocompetent patient should be treated with double-strength trimethoprim-sulfamethoxazole (1 dose twice daily for 45 days, followed by 1 dose every other day for 1 year).[A5]

Pregnant Women with Acute Infection

To reduce the likelihood of maternal-to-child-transmission, the usually recommended approach has been to initiate treatment as soon as possible, and ideally within no more than 3 weeks after maternal infection, with spiramycin (which is not teratogenic) for maternal infections occurring before 14 weeks of gestation (Table 320-4).[24] The combination of pyrimethamine plus sulfadiazine plus folinic acid is slightly more effective and, in at least in one trial, was equivalently safe,[A6] so this combination is probably preferred. Unfortunately, spiramycin does not cross the placenta. If fetal infection is confirmed (by amniotic fluid PCR) or highly suspected by fetal ultrasound, treatment should be pyrimethamine, sulfadiazine, and folinic acid (see Table 320-4) after 14 to 18 weeks of gestational age.[25] Whether to use this regimen earlier is controversial, with recommendations varying among experts. Postnatal treatment should be provided to infants with toxoplasmosis by their pediatricians.

TABLE 320-3 TREATMENT REGIMENS FOR PATIENTS WITH ACUTE OR PRIMARY TOXOPLASMOSIS AND IMMUNOCOMPROMISED PATIENTS WITH TOXOPLASMOSIS DUE TO REACTIVATION*

	IMMUNOCOMPETENT PATIENTS WITH ACUTE INFECTION†	IMMUNOCOMPROMISED PATIENTS
A. Pyrimethamine and folinic acid‡ (PO)	100 mg daily for 1-2 days, followed by 25-50 mg daily	200 mg loading dose, followed by 50 mg/day (<60 kg) to 75 mg/day (>60 kg)
	10-20 mg daily (during and 1 wk after therapy with pyrimethamine)	10 to 25 mg daily (up to 50 mg daily or twice daily; during and 1 wk after therapy with pyrimethamine)
	Plus either sulfadiazine, clindamycin, or atovaquone as follows:	*Plus sulfadiazine (preferred), or clindamycin (preferred for sulfa allergic or poor response to pyrimethamine/sulfadiazine), or atovaquone*
PLUS		
Sulfadiazine (PO)	1000 mg every 6 hr	1000 mg (≤60 kg) to 1500 mg (>60 kg) every 6 hr
or		
Clindamycin (PO or IV)	300 mg every 6 hr	600 mg every 6 hr
or		
Atovaquone** (PO)	1500 mg orally twice daily	1500 mg orally twice daily
or		
B. Trimethoprim-sulfamethoxazole (PO or IV)	5-10 mg/kg/day (trimethoprim component) in two doses	TMP 5 mg/kg/day and SMX 25 mg/kg/day twice daily
or		
C. Pyrimethamine and folinic acid *plus* azithromycin (PO)	Same doses as above 250 to 500 mg/day (for severe systemic disease consider 1000 mg/day)	

*Preferred regimens: pyrimethamine, sulfadiazine, and folinic acid.

†Particularly in the setting of myocarditis, myositis, hepatitis, pneumonia, brain or skin lesions, and lymphadenopathy accompanied by severe or persisting symptoms. Also indicated for those with active ocular disease due to primary infection or reactivation.

‡Folinic acid = leucovorin; folic acid is not an appropriate substitute for folinic acid.

**Atovaquone 1500 twice daily also can be used on its own or with sulfadiazine.

In immunocompromised patients, the combination regimen for the acute or primary therapy phase is for 6 weeks, with the extent of primary treatment dependent on the clinical and radiologic extent of disease and response. The chronic maintenance dose regimens can be found at: https://clinicalinfo.hiv.gov/en/guidelines/adult-and-adolescent-opportunistic-infection/toxoplasma-gondii-encephalitis.

IV = intravenous; PO = oral.

Modified from Montoya JG. Toxoplasmosis. In: Goldman L, Schafer A, eds. *Goldman-Cecil Medicine*. 26th ed. Philadelphia: Elsevier; 2020. Dunay IR, Gajurel K, Dhakal R, et al. Treatment of toxoplasmosis: historical perspective, animal models, and current clinical practice. *Clin Microbiol Rev*. 2018;31:e00057-17.

PREVENTION

Primary infection

Given that most persons will be infected with *T. gondii* by ingesting food, water, or unpasteurized milk that is contaminated with oocysts or by ingesting undercooked meat that contains tissue cysts, interventions to stop *T. gondii*

TABLE 320-4 TREATMENT REGIMENS FOR PREGNANT WOMEN WHO HAVE LIKELY ACQUIRED *TOXOPLASMA GONDII* INFECTION DURING GESTATION

	DURING PREGNANCY
Spiramycin (oral)	Recommended for pregnant women suspected of having or confirmed to have acquired the infection during gestation and before 14 weeks' gestation. Spiramycin should be administered until delivery in those with negative amniotic fluid PCR test results and normal follow-up ultrasound studies or low suspicion of fetal infection. Spiramycin is not teratogenic, and it is available in the United States only through the Investigational New Drug (IND) process at the Food and Drug Administration (301-796-1400). Dosage: 1 g (3 million units) every 8 hr (for a total of 3 g or 9 million units per day)
Pyrimethamine (oral) plus sulfadiazine (oral) plus folinic acid† (oral)	Recommended for women >14 weeks' gestation in whom it is suspected or confirmed that the acute infection has been acquired at or after 14 weeks' gestation or who have a positive amniotic fluid PCR test result or an abnormal ultrasound study suggestive of congenital toxoplasmosis Pyrimethamine is teratogenic and should not be used during pregnancy before week 14 (in some centers in Europe, it is used as early as week 14). Sulfadiazine should not be used alone. Dosages: Pyrimethamine: 100 mg daily for 2 days followed by 50 mg daily Sulfadiazine: 1000 mg q8h (<80 kg) or 1000 mg q6h (≥80 kg) Folinic acid† (leucovorin): 10-20 mg daily (during and for 1 wk after pyrimethamine therapy)

†Folic acid is not an appropriate substitute for folinic acid.

CSF = cerebrospinal fluid; PCR = polymerase chain reaction.

Modified from Montoya JG. Toxoplasmosis. In: Goldman L, Schafer A, eds. *Goldman-Cecil Medicine*. 26th ed. Philadelphia: Elsevier; 2020.

infection should be targeted to these exposures. Women of child-bearing age should be careful to ensure hand hygiene and to avoid any exposure to cat feces.[26] For seronegative pregnant women, prenatal care should include focused education about preventing *T. gondii* exposure and periodic serologic screening starting at 11 weeks of gestation and continuing throughout pregnancy, with prompt (within 3 weeks) treatment of presumed new infections (see Table 320-4). Overall data suggest that these interventions have led to a decline in congenital toxoplasmosis.[27]

Prevention of Reactivation

Transplantation

All donors and recipients of stem cells and of all solid organ transplants must be screened for *T. gondii* via serology. In donor positive/recipient negative heart transplantation patients, prophylaxis with trimethoprim-sulfamethoxazole one double-strength tablet three times/per week for the remainder of their lives is highly recommended. For other solid organ transplant recipients, the evidence for prophylaxis is less clear, but most patients receive trimethoprim-sulfamethoxazole for 6 to 12 months.[28] In hematopoietic stem cell transplant donor negative/recipient positive transplantations, trimethoprim-sulfamethoxazole prophylaxis (one double-strength tablet 3 times per week) is usually started after engraftment because of the drug's bone marrow suppressive effects. For other stem cell recipients, treatment is usually based on the prevention of pneumocystis pneumonia (Table 313-2). Highly immunosuppressed patients who are at risk for acute toxoplasmosis also should be educated about how to avoid exposure to *T. gondii*.

HIV/AIDS and Other Immunosuppressed Patients

Reactivation Disease in Immunosuppressed Patients

Because of the relatively frequent development of toxoplasmic encephalitis in HIV/AIDS patients with decreased CD4 cell counts, HIV/AIDS patients with CD4 counts less than 100 cells/μL should receive daily prophylaxis with double-strength trimethoprim-sulfamethoxazole (160 mg/800 mg daily), which is also effective prophylaxis for *Pneumocystis jiroveci* (Chapter 313). Daily dapsone (50 mg) plus weekly pyrimethamine (50 mg) and leucovorin (25 mg) or weekly dapsone (200 mg), pyrimethamine (75 mg), and leucovorin (25 mg) are the preferred options for those who are intolerant to trimethoprim-sulfamethoxazole, although atovaquone (1500 mg) daily with or without daily pyrimethamine (25 mg) and folinic acid (10 mg) is also an accepted alternative. Prophylaxis should be stopped if the CD4 count rises to above 200 cells/μL for 3 or more months. For patients who are on long-term immunosuppressive therapy such as corticosteroids, the same regimen or one double-strength trimethoprim-sulfamethoxazole tablet 3 times weekly should be prescribed.

PROGNOSIS

The prognosis for *T. gondii* infection depends on many factors, but especially on the patient's immune status and potentially the genotype of the infecting *T. gondii* strain. Most immunocompetent patients who acquire *T. gondii* postnatally will be asymptomatic, and essentially all others will have their symptoms resolve, even without treatment. However, serious complications such as a permanent decrease in visual acuity or very rarely death can occur when patients develop symptomatic ocular toxoplasmosis or deep-seated organ infection (primarily seen in Latin America). In both congenital infection and immunosuppressed patients, the prognosis varies with extent of infection and rapidity of diagnosis and treatment. For all transplant patients, the development of symptomatic toxoplasmosis carries a significant risk of morbidity and mortality.[29] In severely immunocompromised patients, disseminated toxoplasmosis can frequently lead to permanent neurologic sequelae or death even with appropriate care.

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321 CRYPTOSPORIDIOSIS

CIRLE A. WARREN AND ALDO A.M. LIMA

DEFINITION

Cryptosporidiosis is the disease in humans and animals caused by protozoal parasites of the genus *Cryptosporidium* (phylum Apicomplexa). *Cryptosporidium* spp are major waterborne parasites worldwide, and more than 20 species have been documented to infect humans.[1]

The Pathogen

The family Cryptosporidiidae has a hidden sporocyst and undergoes monoxenous completion of its cycle in one host, where it can cause predominantly intestinal, cloacal, and gastric infections. The life cycle begins with ingestion of *Cryptosporidium* oocysts (2 to 5 μm) by the vertebrate host, with subsequent excystation within the lumen of the small intestine to release four sporozoites (Fig. 321-1). Polarized sporozoites cells harbor the apical secretory organelles typical for *Apicomplexa* species, including micronemes, dense granules, and a single rhoptry. The sporozoites move probably by using the canonical glideosome, which is dependent on actin and myosin, and attach to and enter the host's epithelial cells to form intracellular but extracytoplasmic parasitophorous vacuoles, where they develop into trophozoites and subsequently type 1 meronts (schizonts).[2] This interface suggests that the *Cryptosporidium* is dependent on the host's metabolism. The parasite uses glycolysis fermentation as its sole source of energy. By asexual nuclear division, schizonts multiply and release six to eight type 1 merozoites that invade neighboring host cells and develop into type 2 meronts, or trophozoites, to complete the asexual reproductive cycle. Type 2 meronts undergo two nuclear divisions and release four type 2 merozoites that can infect the host's cells and further develop into male (microgamont) or female (macrogamete) forms. Microgametes released from the microgamont can penetrate the macrogametes to form zygotes. Approximately 20% of the zygotes develop into thin-walled autoinfectious oocysts; some 80% become thick-walled oocysts, which are excreted in stool.

EPIDEMIOLOGY

Cryptosporidiosis is seasonal and related to precipitation and temperature fluctuations worldwide. Excystation of *C. parvum* increases in water temperatures up to 46° C (natural sunlight for 12 hours). *Cryptosporidium* spp can be found in wastewater, surface water, drinking water, reservoir water, groundwater, and swimming pool water.[3] In the United States from 2015 to 2019, *Cryptosporidium* spp accounted for about 85% of nearly 3000 cases in 155 outbreaks of diarrhea associated with treated recreational water.[4] In addition to exposure to treated recreational water, other significant outbreak exposures include contact with cattle and contact with infected persons in child-care settings.[5] Food-borne outbreaks also have been reported in association with contaminated apple cider, unpasteurized milk, chicken salad, vegetables, raw produce, and shellfish.

C. hominis and *C parvum* are responsible for over 90% of human infections. *C. hominis* is the dominant species in developing countries, whereas both *C. hominis* and *C. parvum* are the dominant species in industrialized nations. *C. hominis* is more commonly associated with clinical illness. Less common *Cryptosporidium* spp such as *C. meleagridis*, *C. felis*, *C. canis*, *C. viatorum*,

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321 CRYPTOSPORIDIOSIS

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The family Cryptosporidiidae has a hidden sporocyst and undergoes monoxenous completion of its cycle in one host, where it can cause predominantly intestinal, cloacal, and gastric infections. The life cycle begins with ingestion of *Cryptosporidium* oocysts (2 to 5 μm) by the vertebrate host, with subsequent excystation within the lumen of the small intestine to release four sporozoites (Fig. 321-1). Polarized sporozoites cells harbor the apical secretory organelles typical for *Apicomplexa* species, including micronemes, dense granules, and a single rhoptry. The sporozoites move probably by using the canonical glideosome, which is dependent on actin and myosin, and attach to and enter the host's epithelial cells to form intracellular but extracytoplasmic parasitophorous vacuoles, where they develop into trophozoites and subsequently type 1 meronts (schizonts).[2] This interface suggests that the *Cryptosporidium* is dependent on the host's metabolism. The parasite uses glycolysis fermentation as its sole source of energy. By asexual nuclear division, schizonts multiply and release six to eight type 1 merozoites that invade neighboring host cells and develop into type 2 meronts, or trophozoites, to complete the asexual reproductive cycle. Type 2 meronts undergo two nuclear divisions and release four type 2 merozoites that can infect the host's cells and further develop into male (microgamont) or female (macrogamete) forms. Microgametes released from the microgamont can penetrate the macrogametes to form zygotes. Approximately 20% of the zygotes develop into thin-walled autoinfectious oocysts; some 80% become thick-walled oocysts, which are excreted in stool.

EPIDEMIOLOGY

Cryptosporidiosis is seasonal and related to precipitation and temperature fluctuations worldwide. Excystation of *C. parvum* increases in water temperatures up to 46° C (natural sunlight for 12 hours). *Cryptosporidium* spp can be found in wastewater, surface water, drinking water, reservoir water, groundwater, and swimming pool water.[3] In the United States from 2015 to 2019, *Cryptosporidium* spp accounted for about 85% of nearly 3000 cases in 155 outbreaks of diarrhea associated with treated recreational water.[4] In addition to exposure to treated recreational water, other significant outbreak exposures include contact with cattle and contact with infected persons in child-care settings.[5] Food-borne outbreaks also have been reported in association with contaminated apple cider, unpasteurized milk, chicken salad, vegetables, raw produce, and shellfish.

C. hominis and *C parvum* are responsible for over 90% of human infections. *C. hominis* is the dominant species in developing countries, whereas both *C. hominis* and *C. parvum* are the dominant species in industrialized nations. *C. hominis* is more commonly associated with clinical illness. Less common *Cryptosporidium* spp such as *C. meleagridis*, *C. felis*, *C. canis*, *C. viatorum*,

ABSTRACT

Cryptosporidiosis is caused by protozoal parasites of the genus *Cryptosporidium*. Infection is acquired by ingestion of water that is contaminated with *Cryptosporidium* oocysts, followed by completion of the parasite's life cycle in the intestinal mucosa and then by excretion of infectious oocysts in the environment, often thereby contaminating the supply of drinking water and recreational water facilities. Cryptosporidiosis often leads to self-limited diarrhea in immunocompetent hosts during outbreaks or travel exposure but to persistent diarrhea in immunocompromised adults in endemic settings. *Cryptosporidium* species have emerged as an important cause of diarrhea in recipients of solid organ or hematologic transplants. Detection of the parasite is improved by immunoassays and molecular techniques. Therapeutic and preventive interventions are limited, especially for immunocompromised hosts. Transmission of disease may be controlled by treatment of water supplies to inactivate oocysts in drinking and recreational water facilities.

KEYWORDS

Cryptosporidium
cryptosporidiosis
diarrhea
parasite
protozoa
waterborne
recreational water

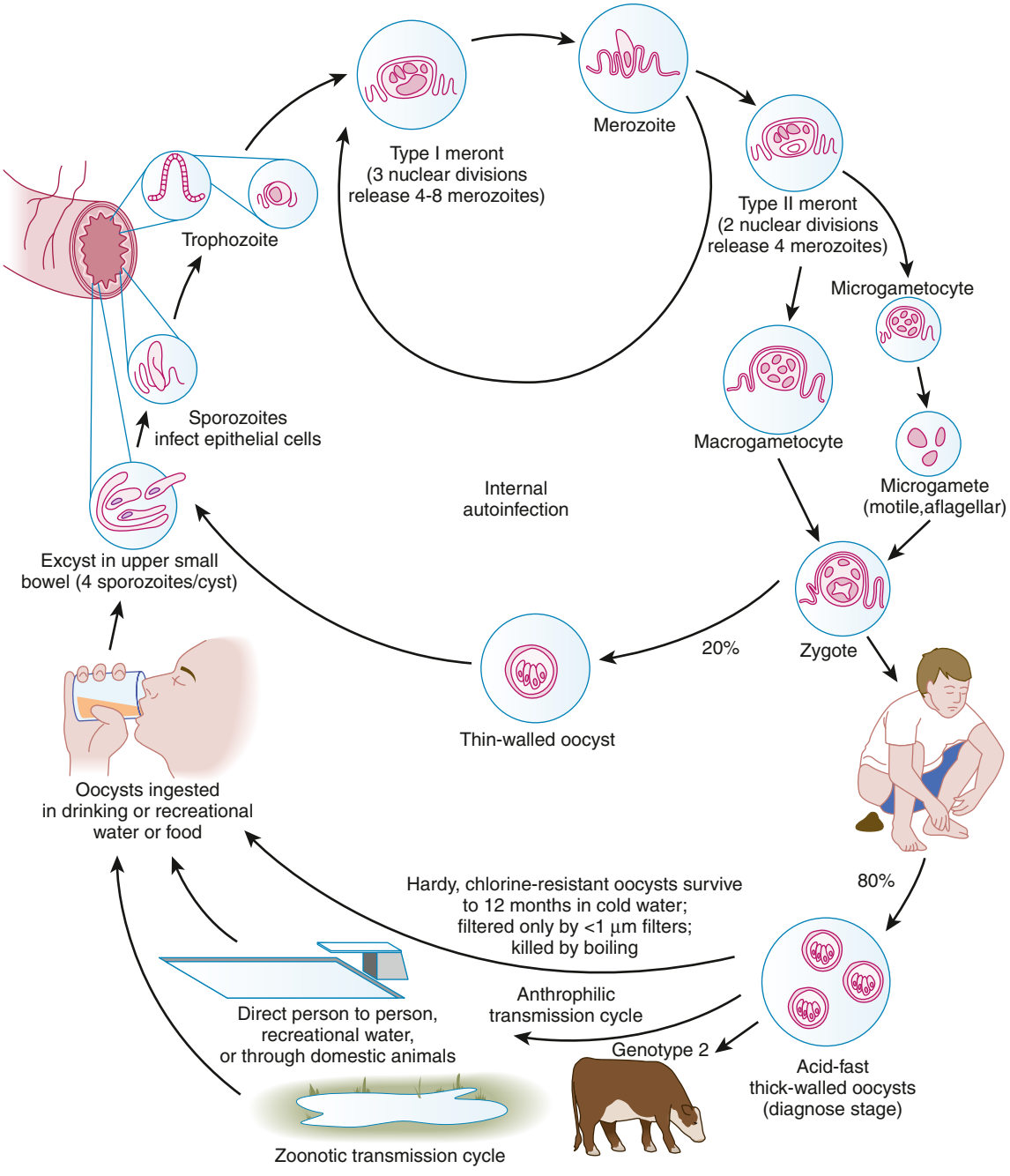

FIGURE 321-1. Life cycle of *Cryptosporidium* spp. (Redrawn with permission from Kosek M, Alcantara C, Lima AAM, et al. Cryptosporidiosis: an update. *Lancet Infect Dis*. 2001;1:262-269.)

and *C. muris* are largely seen in developing countries, and *C. ubiquitum*, *C. cuniculus*, and *C. chipmunk* genotype I are mainly seen in industrialized nations. *C. parvum* infection is associated with animal exposures, especially cattle and dogs, as well as residence in rural settings, whereas *C. hominis* infection is more common with daycare or child care and residence in urban settings.[6]

The prevalence of cryptosporidiosis varies by geographic region,[7] with the highest rates seen in children in developing countries, where it is one of the five pathogens (including norovirus, rotavirus, *Campylobacter* spp, and astrovirus) with the highest attributable burdens of diarrhea in the first year of life.[8] Cryptosporidiosis causes more than 48,000 annual deaths worldwide in children under 5 years of age.[9]

Cryptosporidiosis continues to be a significant cause of intestinal infection among individuals with human immunodeficiency virus (HIV) and acquired immunodeficiency syndrome (AIDS) who are not on effective antiretroviral therapy (Chapter 358).[10] In resource-sufficient settings, cryptosporidiosis has emerged as an important cause of diarrhea among HIV-negative individuals who are recipients of either solid organ or hematopoietic stem cell transplants. The incidence of cryptosporidiosis is also high among recent international travelers (Chapter 265) and men who have sex with men.[11]

PATHOBIOLOGY

Cryptosporidium oocysts and sporozoites interact with host cells, in the processes of excystation, gliding motility, attachment, invasion, parasitophorous vacuole formation, intracellular maintenance, and host cell damage. Oocysts of *Cryptosporidium* spp use their cysteine and serine proteases and aminopeptidase for excystation in the upper part of the small bowel and release infective sporozoites that invade the mucosal epithelium and occasionally Peyer patch M cells, often extending to the terminal ileum and colon. The sporozoites secrete proteins from the apical organelles for locomotion and attachment. In immunocompromised patients, the organisms can be found throughout the gut, biliary tract, pancreas, and respiratory tract. Sporozoites and merozoites are internalized by similar invasion machinery and actin reorganization. Two classes of proteins, mucin-like glycoproteins and thrombospondin-related adhesive proteins, mediate adhesion of the parasite. The parasite uses proteases for the proteolytic processing of surface and apical complex proteins for invasion and for egress from the host cells. Entry into the host's cell occurs within 30 seconds and is dependent on the parasite's actomyosin cytoskeleton to enter host-derived bimembrane parasitophorous vacuoles in a unique intracellular but extracytoplasmic niche. Dense polymerized actin forms at the base fusion of the host-parasite bimembranes. Invasion of cells of the host leads to

displacement of the microvillous border, villous atrophy, blunting and crypt cell hyperplasia, and marked infiltration by lymphocytes, plasma cells, and some neutrophils into the lamina propria, with apoptosis of infected cells. The intestinal epithelial barrier function is disrupted by the effects of *Cryptosporidium* on tight junction proteins.[12] Upregulation of nuclear factor κB and the proinflammatory cascade causes secretory and mildly inflammatory diarrhea. Proinflammatory cytokines, such as tumor necrosis factor-α, interleukins-1β and -8, and lactoferrin, are significantly increased and upregulate cyclooxygenase 2, which results in the synthesis of prostaglandin in the epithelial cells and production of substance P by the inflammatory cells. These processes decrease net sodium absorption and increase net chloride secretion, thereby causing the secretory diarrhea and clinical dehydration often seen with this infection.

Cryptosporidium oocysts have at least five characteristics that make this organism a common problem and that help define the potential risk for person-to-person spread and for waterborne and food-borne disease outbreaks. First, *Cryptosporidium* oocysts are resistant to many chemical disinfectants, such as chlorine. Second, the organism is highly infectious, with the median *C. parvum* infectious dose being 132 or fewer oocysts. Third, the size of the oocysts, 2 to 5 µm, allows them to pass through many conventional filters. Fourth, the monoxenous life cycle allows infectious oocysts to be excreted in large numbers in feces, from where they can easily spread. Fifth, the organism is associated with geographic, seasonal, and socioeconomic differences in its distribution.

CLINICAL MANIFESTATIONS

In immunocompetent hosts, cryptosporidiosis is a self-limited infection that affects all age groups and both sexes. In developing countries, the disease occurs most frequently in children younger than 5 years because of high rates of fecal-oral exposure and the development of partial immunity in older children and adults. In developed countries, the disease occurs at all ages, and most cases are associated with small waterborne outbreaks, frequently with contamination of recreational water.

After an incubation period of approximately 1 week (range of 1 to 30 days), diarrhea can be of sudden onset, frequently with voluminous watery stools, abdominal pain, nausea or vomiting, bloating, malaise, fatigue, dehydration, weight loss, and occasional fever. Rarely, respiratory infection and cough have been reported. In normal hosts, the disease usually persists for 1 to 3 weeks but sometimes persists for more than a month. Shedding of oocysts typically continues for 1 to 2 weeks but can occur for up to 2 months. Patients who have T-cell immune deficiency (e.g., patients with hematologic malignant neoplasms, primary T-cell deficiencies, solid organ transplants, and HIV/AIDS) are at high risk for more severe disease and death.

Immunocompetent Host

Most patients who are infected during outbreaks or travel are adults, who usually have watery diarrhea with a median duration of 14 days (range of 1 to 100 days), regardless of whether the infection is with *C. parvum* or *C. hominis*. Recurrence of diarrhea is common and occurs in about 30 to 40% of patients. Abdominal pain (about 85 to 95%), vomiting (about 50 to 65%), fever (about 55 to 60%), and bloody diarrhea (about 10%) are common accompanying symptoms. Patients may continue to shed oocysts for 7 months despite being asymptomatic.

Immunocompromised Hosts

Low $CD4^+$ lymphocyte counts in HIV-infected patients are associated with severe cryptosporidial diarrhea. For example, patients with $CD4^+$ counts higher than 180/µL usually have transient or self-limited disease, whereas patients with $CD4^+$ counts lower than 50/µL often have severe disease with more than 2 L of stool per day. Not surprisingly, the introduction of highly active antiretroviral therapy has greatly reduced rates of cryptosporidiosis in patients with HIV/AIDS (Chapter 357). In resource-limited settings, asymptomatic carriage of the parasite is common in individuals with HIV/AIDS.

Patients who have other immune disorders or hematologic malignant neoplasms are at higher risk for more severe, prolonged, or extensive disease, with infection occasionally extending to the gallbladder, the pancreatic duct, and even the bronchial tree. Complications can include pancreatitis, cholecystitis, sclerosing cholangitis, papillitis, and terminal bile duct stenosis, with subsequent biliary cirrhosis.

Cryptosporidium spp infection can also cause diarrhea in recipients of solid organ transplants, either as sporadic infection or infection associated with outbreaks related to exposure to recreational water.[13] Coinfection with other pathogens, extraintestinal involvement (biliary tract and lungs), and relapse also occur in these patients.

Childhood Cryptosporidiosis in Developing Countries

In developing countries, cryptosporidiosis is associated with prolonged (7 to 13 days) or persistent (≥14 days) diarrhea, increased overall burden of diarrhea, risk for malnutrition, stunted growth, impaired cognitive function, and mortality.[14] Immunocompetent hosts in endemic settings acquire immunity and are less susceptible to infection compared with travelers from nonendemic settings. Immunocompromised hosts are prone to symptomatic infections and prolonged asymptomatic shedding/carriage, regardless of their area of residence.

DIAGNOSIS

The clinical manifestations and physical examination findings in patients with cryptosporidiosis are not unique. The differential diagnosis should include other causes of infectious gastroenteritis, such as *Giardia* (Chapter 322), *Cyclospora* (Chapter 324), *Isospora* (Chapter 324), microsporidia (Chapter 324), *Escherichia coli* (Chapter 280), *Campylobacter* (Chapter 284), *Salmonella* (Chapter 279), *Shigella* (Chapter 285), rotavirus (Chapter 350), norovirus (Chapter 350), and others (Chapter 262).

Definitive diagnosis of *Cryptosporidium* enteric infection is made by stool examination. Commercially available enzyme-linked immunoassays have a sensitivity and specificity approaching 100% for *Cryptosporidium*.[15] Polymerase chain reaction testing can detect as few as 50 to 500 oocysts per milliliter of liquid stool and can be used to differentiate or even to quantify *Cryptosporidium* spp and genotypes.[16] Traditional microscopic methods, which require staining of oocysts, are less sensitive and now rarely used in developed countries.

TREATMENT

For severe disease, oral rehydration therapy or intravenous fluid replacement is key to preventing dehydration and risk for immediate death. In immunocompetent adults, nitazoxanide (500 mg twice daily for 3 days) can increase the rate of resolution of symptoms within 4 days, from about 30% to over 90%, and speed the clearing of oocysts.[A1]

In immunosuppressed patients, however, nitazoxanide has not been proven to be beneficial.[17] In patients with HIV/AIDS, highly active, antiretroviral therapy is the most important treatment to prevent and reduce the severity and frequency of cryptosporidiosis. In transplant recipients, prolonged courses of antiparasitic treatment (e.g., nitazoxanide 500 to 1000 mg twice daily for at least 2 weeks) and/or reduction of immunosuppression have been reported to yield anecdotal success.

PREVENTION

Prevention of person-to-person spread is dependent on personal hygiene, such as frequent handwashing after using or cleaning the toilet, changing diapers, and caring for a person with diarrhea.[18] Individuals who are infected with cryptosporidiosis should be excluded from the workplace setting until 48 hours after the last diarrheal episode. Handwashing facilities should be available and used at farms to facilitate personal hygiene.

Because most outbreaks of cryptosporidiosis are linked to oocysts in source water, routine surveys of treated water for this parasite are key for preventing major spread of this disease. Optimization of multibarrier approaches, including chemical treatment and water filtration, is highly recommended. Ultraviolet irradiation and ozone can effectively inactivate *Cryptosporidium* cysts in water and may prove useful in controlling the transmission of waterborne protozoa.

PROGNOSIS

In adults, cryptosporidiosis is usually a self-limited disease. Nevertheless, systemic (fatigue), gastrointestinal, and joint symptoms can persist for several months after the initial infection. In epidemics, the mortality rate may be as high as 3 per 10,000 in symptomatic people in the general population. For severely immunocompromised AIDS patients, cryptosporidiosis can be difficult to eradicate and is associated with a poor prognosis.

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Grade A **Grade A Reference**

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322

GIARDIASIS

DAVID R. HILL

DEFINITION

Giardia lamblia (*Giardia duodenalis, Giardia intestinalis*) is a ubiquitous, small intestinal protozoan parasite of humans and other mammals. It is the most common parasitic infection of the gastrointestinal tract in the United States as well as worldwide, and it is responsible for outbreaks of diarrhea and sporadic endemic disease.[1,2]

The Pathogen

Giardia has a simple life cycle. The trophozoite, which is 9 to 21 µm long, 5 to 15 µm wide, and 2 to 4 µm thick (Fig. 322-1), resides in the small intestine and is responsible for the manifestations of disease. It has four pairs of flagella, two nuclei, and a ventral sucking disc by which it may adhere to intestinal epithelial cells. The dorsal surface is pear shaped and bilaterally symmetrical, with the two highly characteristic nuclei best visualized after staining. In the lower small intestine, the trophozoite develops into an environmentally resistant cyst (Fig. 322-2). Detection of soluble cyst wall proteins in the feces forms the basis of many stool antigen assays.

Excreted cysts, which are mature and infectious, are oval and about 8 to 12 µm in length and 7 to 10 µm in width (see Fig. 322-2). After ingestion and exposure to acid and proteases in the stomach and intestines, they excyst in the small intestine, where each cyst forms two trophozoites, which quickly divide. In vitro, trophozoites double in number every 6 hours for the fastest growing isolates.

A number of morphologically identical but genetically distinct *Giardia* infect humans and animals and are divided into eight assemblages. Humans, as well as some animals, are typically infected with either assemblage A or B; other assemblages occasionally infect humans.[3,4] Assemblages A and B are genetically and biologically diverse and appear to be two separate species.[5]

Giardia is well adapted to its existence as a parasite. It has two equal functioning nuclei and lacks mitochondria and peroxisomes. It has a simplified metabolism and is dependent on the host for nutrients such as purines, pyrimidines, cysteine, phospholipids, cholesterol, and most amino acids except for alanine. The WB isolate, assemblage A, has a compact genome (11.7 Mb) with unusually short promoters. The parasite's rigid cytoskeleton is composed of unique families of structural proteins and carbohydrates.[6]

Giardia is the only bowel-dwelling parasite that undergoes antigenic variation. Only one of a family of about 250 variant-specific proteins (VSPs) is expressed on the surface of the trophozoite at a time. Both immune and biologic selection of trophozoites that express specific VSPs occurs in humans and animals with giardiasis. Expressed VSPs must be compatible with the host's intestinal environment; antibodies to VSPs are inhibitory or cytotoxic. Whereas all VSPs are transcribed, all but one of the transcripts are eliminated by RNA interference–based mechanisms, thereby resulting in expression of a single VSP surface protein. Exactly how selection and switching occur is unclear.

EPIDEMIOLOGY

Giardia is among the most common parasitic infections of humans. It is highly infectious, and cysts are frequently excreted in large numbers (as high as 10^7 cysts per gram of feces), especially in young children. Cysts can survive for months in cold water, are relatively resistant to chlorination, but are intolerant of desiccation and heat compared with the ova of cryptosporidia (Chapter 321) and helminths. Experimentally, between 10 and 100 cysts are sufficient to establish infection. Consequently, ingestion of water or food that contains low levels of contamination can result in infection.

The overall incidence rate is about 6 cases per 100,000 population in the United States, and approximately 20,000 cases are reported annually.[7] However actual infections may exceed 1 million per year because of underreporting.

Infections are most common in young children and are more frequent in summer and fall months, possibly due to increased travel and exposure to environmental water during the warmer months. In low-income, highly endemic regions, almost all children are infected by 2 to 3 years of age, about 20% of them persistently. In these settings simultaneous infection with other enteric pathogens is common.

Giardiasis is acquired after ingestion of contaminated water or food or through person-to-person contact. Before the advent of modern water treatment methods, large outbreaks in high-income countries such as the United States occurred after ingestion of contaminated drinking water obtained from surface sources such as reservoirs, lakes, and mountain streams. Now, however, ingestion of contaminated recreational water from pools or lakes is a more common source of outbreaks.[8] Outbreaks from contaminated food or infected food handlers are well described. Currently, only 1 to 2% of giardiasis cases are associated with identified outbreaks. Backpackers who ingest untreated surface water are at risk.

Worldwide, person-to-person transmission is the most common source of infection, especially in daycare centers, among family members with infected children, and following sexual practices that lead to fecal-oral contact.[9] Although partial immunity can develop in previously exposed adults, reinfection after treatment in children is common in highly endemic areas. Longer-term travel, particularly to South Asia, increases the risk of giardiasis. For the returned traveler (Chapter 265) with intermittent or persistent diarrhea, giardiasis should be excluded. *Giardia* infections tend to be severe in patients who have common variable immunodeficiency but are not more common in persons with selective immunoglobulin (Ig) A deficiency.

FIGURE 322-1. ***Giardia lamblia.*** This scanning electron micrograph reveals some of the external ultrastructural details displayed by a flagellated *G. lamblia* protozoan parasite.

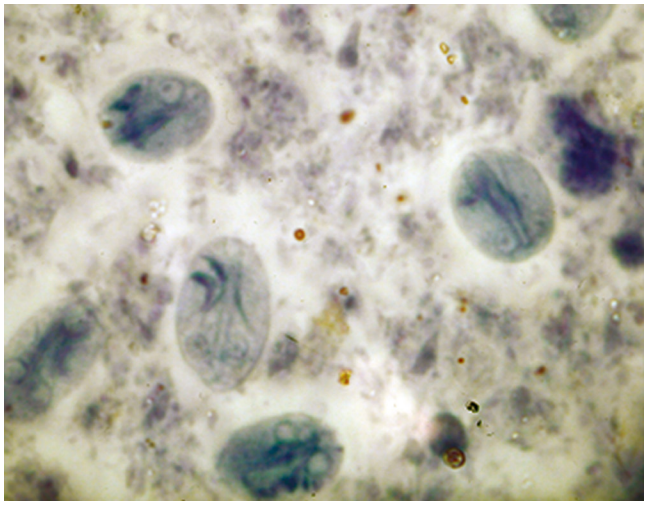

FIGURE 322-2. Iron hematoxylin stain of *Giardia lamblia* cysts from stool.

ABSTRACT

Giardia lamblia is a global enteric parasite that affects upward of 300 million people annually. *Giardia* is highly infectious; its cysts, which can survive for months in cold water, are excreted in large numbers in feces, especially in young children. The parasite is acquired after ingestion of contaminated water or food or through person-to-person contact, with the latter being the most frequent mode of infection among children and their families. Clinical manifestations, course, and duration of infection are variable. Acute disease manifests with diarrhea, nausea, anorexia, gas, distention, and abdominal cramping, but patients generally are not as sick as those with bacterial diarrhea. Acute symptoms can resolve, wax and wane, or transition into a chronic phase. Constant reinfection is common in children in highly endemic regions. Diagnosis is made by detection of cysts, trophozoites, parasitic antigens, or DNA in fecal samples. Nitroimidazole drugs, such as tinidazole, are the treatment of choice.

KEYWORDS

Giardia lamblia (Giardia intestinalis, Giardia duodenalis)
gastrointestinal parasite
protozoan
antigenic variation
malabsorption
tinidazole

PATHOBIOLOGY

Giardia infections involve complex interactions between host and parasite. The two assemblages (A and B) that typically infect humans are composed of genetically distinguishable isolates, which may vary in infectivity, antigenicity, and virulence.[10] In addition, human hosts vary in susceptibility to infection and disease and in the response or tolerance to infection. Multiple pathogenic mechanisms likely explain the varied clinical manifestations as well as the contrasting situation in which high rates of infection and disease are seen in water-borne outbreaks of giardiasis in regions where infections are sporadic, as in the United States, compared with the mostly asymptomatic infections in children in highly endemic low-income regions. In addition, infection with *Giardia* can lead to malabsorption, weight loss, and nutritional deficiencies in some settings and little effect on nutritional parameters in other settings.[11]

Giardia is strictly an intraluminal parasite that likely adheres to the epithelium by way of an adhesive or sucking disc. Invasion of the epithelium either does not occur or is rare. Large numbers of parasites can cover the intestinal epithelial surface, thereby potentially interfering with brush border disaccharidase activity. *Giardia* produce cysteine proteases, including cathepsin B–like proteases, that experimentally can disrupt epithelial cell tight junctions, lead to epithelial cell apoptosis, break down intestinal mucus, and degrade host immune factors. There is no evidence of production of a classic secretory enterotoxin. Of patients with persistent giardiasis after treatment, nearly half exhibit inflammation on small bowel biopsy specimens, thereby supporting the view that chronic inflammatory responses contribute to disease at least in this subset.

The intestinal microbiome, the nutritional status of the host, and available nutrients also can affect pathogenesis.[12,13] Experimentally, high glucose can counteract caspase-3–dependent apoptosis, and parasite arginine consumption may increase gut colonization. Sequential coinfection of mice with *Giardia* and then enteroaggregative *Escherichia coli* can increase weight loss. Alteration of the intestinal microbiome in giardiasis may contribute to both susceptibility and resistance to infection, perhaps explaining some of the clinical differences of *Giardia* infection between children in highly endemic as compared with low-incidence regions.

In experimental human challenges, in which the infecting parasite was well characterized and the inoculum known, rechallenge with the same isolate after treatment results in brief, asymptomatic infection, thereby suggesting partial immunity. Based on animal studies, intestinal antibodies (IgA), T-cells (particularly $CD4^+$ helper T-cells), and interleukin-17 appear to be important for the immune response to infection.

CLINICAL MANIFESTATIONS

The clinical manifestations, course, and duration of *Giardia* infections are variable. Infections may be self-limited or persistent, asymptomatic or symptomatic.[14] About 50% of newly infected individuals may develop symptoms.

In a well-documented foodborne outbreak of giardiasis, the incubation period was 2 to 19 days, with peak symptoms at 5 to 6 days. Symptoms in this outbreak continued for a median of 18 days.

Acute disease manifestations are characterized by diarrhea, nausea, anorexia, dehydration, flatulence, eructation, foul-smelling stools, distention, abdominal cramping, and weight loss. Malabsorption is more commonly seen in chronic infection. Fever and vomiting are uncommon. Blood, mucus, and polymorphonuclear cells in the stool, which are not usual features of small bowel infections, should suggest an alternative or additional diagnosis. Patients generally are not as sick as patients who have bacterial diarrheas, but dehydration, although uncommon, may be severe and require hospitalization. On occasion, nausea and vomiting will predominate and suggest other causes.

Acute symptoms can resolve, wax and wane, or settle into a chronic phase, which can be prolonged and persist for weeks to months. These long-lasting symptoms should prompt a search for *Giardia*. Lactose deficiency (Chapter 126), which is common and can persist for weeks after treatment, must be distinguished from relapse or reinfection. In extreme cases, malabsorption and weight loss are severe and mimic celiac disease (Chapter 126).

A typical clinical scenario is a mildly to moderately ill person who complains of an increased number of urgent loose stools, with flatus, cramping, anorexia, and weight loss. There may be periods when the person feels better only to relapse and become noticeably worse. After days to several weeks, the individual will seek medical help. Similar to other causes of infectious diarrheas, symptoms can continue after successful treatment. Some patients will develop persistent irritable bowel syndrome (Chapter 123) and/or chronic fatigue syndrome (Chapter 253).[15] Uncommonly, *Giardia* is found in biliary and pancreatic ducts and can cause cholecystitis and pancreatitis. Extraintestinal manifestations including rash, reactive arthritis,[16] eye complaints, and cognitive deficiencies, are uncommon.

In highly endemic regions *Giardia* is an uncommon cause of acute, moderately severe, or severe diarrhea compared with agents such as rotavirus (Chapter 350), enterotoxigenic *E. coli* (Chapter 280), *Shigella* (Chapter 285), *Campylobacter* (Chapter 279), and *Cryptosporidium* (Chapter 321). Nevertheless, endemic *Giardia* can be associated with long-lasting diarrhea (≥14 days), and chronic infection can lead to malnutrition and stunting. In settings of repeated infection, it is possible that *Giardia* protects against other enteric pathogens.

DIAGNOSIS

Many patients who seek care for gastrointestinal symptoms consistent with giardiasis are not diagnosed until they have had multiple visits. The clinician should consider the diagnosis by putting risk factors and symptoms together, and test for *Giardia*.

The diagnosis of giardiasis is based on detection of parasite antigens, DNA, cysts, or trophozoites in fecal samples. Stool antigen tests are more sensitive than microscopy and do not require a trained microscopist. Molecular detection methods, often as part of an array of other enteric pathogens, are the most sensitive approach.[17] Because excretion of cysts may be variable or in low concentrations, a single-stool microscopy for ova and parasites is only 50 to 80% sensitive, so three stool examinations may be necessary. Cysts appear in the stool 6 to 15 days (mean, 9 days) after infection; *Giardia* antigen may be detected before cysts are excreted.

Examination of small intestinal biopsy samples or intestinal contents for trophozoites is rarely needed to establish or to confirm the diagnosis because of the high sensitivity and specificity of stool antigen or molecular assays. Biopsy may be performed, however, when looking for other causes of an enteric syndrome.

Other laboratory findings are nonspecific. The white blood cell count and liver enzymes are usually normal. Electrolyte disturbances can be present if diarrhea and vomiting are severe. White blood cells, lactoferrin, blood, and mucus are not found in the stool. Immunoglobulin levels will be abnormally low or absent in susceptible hypogammaglobulinemic individuals.

TREATMENT

A single dose of tinidazole (Tindamax), which is a nitroimidazole drug similar to metronidazole (Flagyl), is the treatment of choice for giardiasis.[A1] In adults, the dose is 2 g orally; in children, the dose is 50 mg/kg up to a maximum of 2 g. Other nitroimidazoles (e.g., ornidazole and secnidazole) that are not approved in the United States are also effective. Metronidazole, which is less efficacious and has more side effects, has been used to treat giardiasis for decades but has never been approved by the U.S. Food and Drug Administration (FDA) for this indication; it requires multiple dosing at 250 mg orally three times a day for 5 to 7 days for adults and 15 mg/kg/day in three divided doses for 5 to 7 days for children. Alcohol should not be taken concomitantly with any of the nitroimidazoles because of the possibility of a disulfiram-like reaction with these drugs.

Albendazole (400 mg/day for 5 days), not presently approved by the FDA for treatment of giardiasis, may be an acceptable alternative to the nitroimidazoles, with fewer side effects. However, experience with this drug is limited.

Nitazoxanide has broad activity against protozoa, helminths, and bacteria and is FDA-approved for the treatment of giardiasis with an efficacy of 65 to 85%.[A2] It is given at a dose of 100 mg orally every 12 hours for 3 days for children ages 12 months to 3 years, 200 mg orally every 12 hours for 3 days for children 4 to 11 years of age, and 500 mg orally every 12 hours for 3 days for persons older than 12 years. Because it is available in a liquid suspension as well as in a 500-mg tablet, it may be easier to give to young children. It should be given with food. Most of the side effects are gastrointestinal symptoms and headache.

Paromomycin, a nonabsorbable aminoglycoside, has been used in pregnant women to avoid the theoretical fetal adverse events of nitroimidazoles, particularly during the first trimester. It is given to adults at a dose of 500 mg three times a day for 5 to 10 days and to children at 25 to 35 mg/kg/day orally in three divided doses for 5 to 10 days. Quinacrine (100 mg orally three times per day for 5 days)[18] and furazolidone (100 mg orally four times per day for 7 to 10 days under expert supervision) are also active against *Giardia* but should generally be reserved for use in particular situations, such as nitroimidazole resistance.[19]

Patients who do not respond to treatment frequently have a return of symptoms days to weeks after cessation of therapy and require either re-treatment with an alternative class of drug or combination therapy. Nitroimidazole-resistant infections are increasingly common, particularly in returned travelers from South Asia. These patients usually respond to combination treatment (e.g., metronidazole plus albendazole; metronidazole plus quinacrine) or quinacrine monotherapy.[20]

PREVENTION

Infection is prevented by personal hygiene, proper disposal of sewage, removal or killing of cysts from water supplies, and preventing contamination of food and water. Cysts are susceptible to heating and filtration with small-volume water filters of 0.2 to 1 μm. Heating water (bringing it to a boil) inactivates *Giardia* as well as other common enteric pathogens. Cysts are not reliably susceptible to chlorination because the concentrations of chlorine, and water temperatures, turbidity, and pH present when treating commercial water supplies are suboptimal. Four drops of 5.25% bleach to 1 L for 1 hour at room temperature is sufficient for killing. At lower temperatures, inactivation may not be complete.

PROGNOSIS

Most persons who are diagnosed and treated will recover without long-term consequences, but a subset develop long-term irritable bowel syndrome. Patients who have common variable immunodeficiency (Chapter 231) have more severe disease that is difficult to treat. Even though most human immunodeficiency virus–infected patients respond to usual treatment, a subset develop recurrent or repeated infections that are difficult to treat.

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323 AMEBIASIS

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The Pathogen

E. histolytica has a low infectious dose (<100 organisms), is resistant to chlorine, and is environmentally stable. Certain genotypes of *E. histolytica* appear to be associated with the propensity for colonization, whereas others are associated with invasion. Its tissue-destructive properties are the reason for the parasite's being named *histolytica*.

EPIDEMIOLOGY

Most *E. histolytica* infections occur in the developing world, including the Indian subcontinent, Southeast Asia, sub-Saharan Africa, and Central and South America, as a result of fecal-oral transmission. A national serologic survey in Mexico demonstrated antibody to *E. histolytica* in 8.4% of the population. In an urban slum of Fortaleza, Brazil, 25% of the population carried antibody to *E. histolytica*, and the prevalence in children 6 to 14 years of age was 40%. In Dhaka, Bangladesh, where diarrheal diseases are the leading cause of childhood death, the annual incidences of amebic infection, diarrhea, and dysentery are about 45%, 9%, and 3%, respectively. The annual incidences of amebic liver abscess was 21 cases per 100,000 inhabitants in Hue City, Vietnam. The best current estimate by the World Health Organization is that *E. histolytica* infection results in nearly 50 million symptomatic cases each year worldwide and as many as 100,000 deaths annually.

In the United States, amebiasis is the third most common parasitic infection after giardiasis and cryptosporidiosis (1.2 cases/100,000 U.S. population). Most cases in industrialized countries occur in travelers to and immigrants from endemic regions as well as in institutionalized individuals. In returning travelers (Chapter 265), diarrhea is the predominant reason for a patient to visit a physician, and amebiasis is the second most common cause of diarrhea in returning travelers. Previously reported high rates of *E. histolytica* infection in men who have sex with men in the United States[1] actually reflect a high prevalence of *Entamoeba dispar* infection in this population. In contrast, in Asia, amebiasis is more frequently an initial symptom of human immunodeficiency virus (HIV) infection and acquired immunodeficiency syndrome because of the common risk for acquisition of both HIV infection and amebiasis through the sexual practices of men who have sex with men. The typical patient with an amebic liver abscess in the United States is a 20- to 40-year-old Hispanic male immigrant. Several groups are at increased risk for severe amebiasis, including the very young or old, malnourished persons, pregnant women, and patients treated with corticosteroids.

PATHOBIOLOGY

Killing of host cells[2] is required for invasion of the intestine by the parasite. The process of host cell destruction includes sequential steps of adherence, a nibbling-like process termed *amebic trogocytosis*, contact-dependent cytotoxicity, and finally phagocytosis of the host cell corpse. The initial contact of parasite to host is mediated by the parasite's galactose and *N*-acetyl-D-galactosamine (Gal/GalNAc)–specific lectin, which binds to carbohydrate determinants on the host's intestinal epithelium.[3] Human cells die by apoptosis induced by *E. histolytica*, a process that requires attachment of the Gal/GalNAc lectin to a host cell's receptor, as well as the parasite's acid intracellular vesicles, which may serve as delivery vehicles for an amebic pore-forming protein.[4] *E. histolytica* initiates apoptosis in host cells by directly activating the host cell's distal apoptotic machinery; caspase 3 is activated within minutes of *E. histolytica* adherence, a caspase 3 inhibitor blocks *E. histolytica* killing, and caspase 3–deficient or bcl-2–overexpressing mice are resistant to amebic infection. Recognition and ingestion of the apoptotic host cell's corpse are required for colonic infection by the parasite, and multiple ligands and receptors are involved, including the Gal/GalNAc lectin, a phosphatidylserine receptor, serine-rich *E. histolytica* protein, and collectins. After ingestion of the corpse of the host cell, additional parasitic factors participate in invasion into the intestinal mucosa. For example, *E. histolytica* encodes at least 44 cysteine proteinase genes that have been implicated in degradation of colonic mucin glycoproteins; digestion of extracellular matrix, hemoglobin, and villin; and inactivation of interleukin-18 (IL-18).

The innate immune response to amebic infection is coordinated by lymphoid cells type 2, which produce a protective type 2 immune response in response to amebic infection. In the murine model of intestinal amebiasis, innate resistance is conferred by nonhematopoietic cells, thus suggesting the importance of epithelial production of cytokines such as tumor necrosis factor-α (TNF-α), IL-1α, IL-6, IL-8, growth-related oncogene-α (GRO-α), and granulocyte-macrophage colony-stimulating factor. Granulocytes are the earliest innate cellular immune response (within 1 to 2 days) for both intestinal and hepatic amebiasis. Depletion of neutrophils or eosinophils in a murine model results in exacerbated amebic hepatic and intestinal disease. Macrophages and T lymphocytes are also recruited by day 3 of an infection. Macrophages acquire amebicidal activity after in vitro stimulation with interferon-γ (IFN-γ), TNF-α, or colony-stimulating factor 1.

The acquired immune response reflects the opposing roles of IL-4 and IFN-γ in persistence and clearance of amebic infection, respectively. Inbred mice of the CBA strain are susceptible to intestinal amebiasis and develop a rapid T_H2 phenotypic immune response, and this response is deleterious insofar as inhibition of IL-4 can convert the response to a healing IFN-γ response. The IL-33-ILC2 pathway also appears to be an important host defense mechanism.[5] Effective acquired immunity in humans is associated with both a systemic IFN-γ and a mucosal immunoglobulin (Ig)A response directed at the Gal/GalNAc lectin. Children with mucosal IgA against the Gal/GalNAc lectin have 86% fewer new *E. histolytica* infections in the following year. Similarly, the risk for amebiasis is 50% lower in children who are in the 50th percentile and above for the production of IFN-γ by peripheral blood mononuclear cells stimulated with soluble amebic antigen. Children with an amino acid polymorphism in the receptor for leptin are protected from symptomatic infection with amebiasis, thereby reflecting the importance of leptin for gut mucosal innate immunity.

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ABSTRACT

The parasitic ameba *Entamoeba histolytica* is the cause of amebic colitis and liver abscess. Infection is mostly limited to low- and middle-income countries where poor sanitation facilitates fecal-oral spread. Diagnosis is by a combination of detecting parasitic DNA or antigen in feces and a positive blood serology. The mainstay of treatment is metronidazole. Free-living amebae including *Acanthamoeba, Balamuthia,* and *Naegleria* are causes of central nervous system infection, and *Acanthamoeba* also causes keratitis. Diagnosis is by PCR detection of amebic DNA, and treatment requires combination antimicrobials.

KEYWORDS

Entamoeba
Naegleria
Balamuthia
Acanthamoeba
Sappinia
amebiasis
colitis
liver abscess
metronidazole

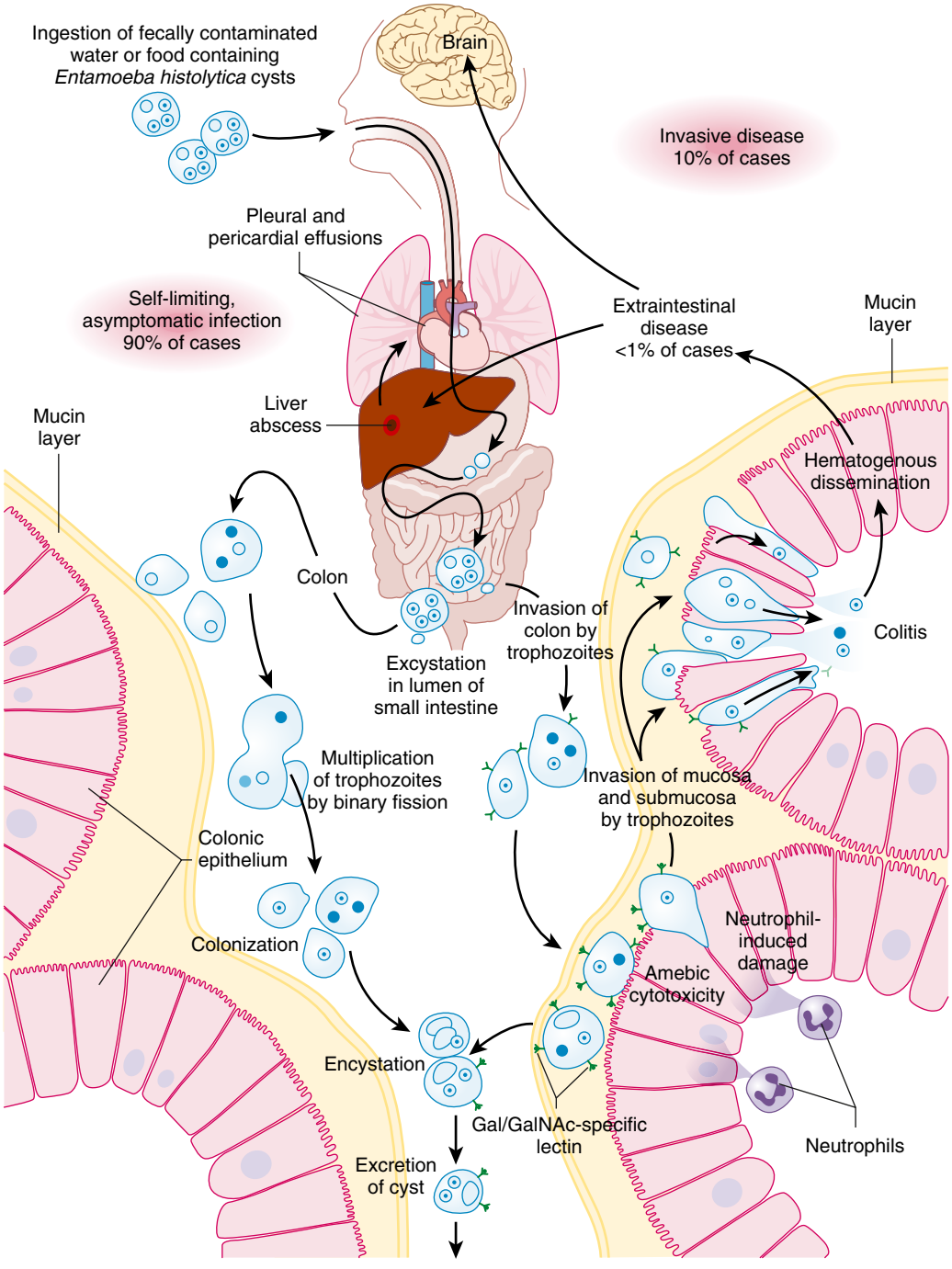

FIGURE 323-1. Life cycle of *Entamoeba histolytica*. Infection is normally initiated by the ingestion of fecally contaminated water or food containing *E. histolytica* cysts. The infective cyst form of the parasite survives passage through the stomach and small intestine. Excystation occurs in the bowel lumen, where motile and potentially invasive trophozoites are formed. In most infections, the trophozoites aggregate in the intestinal mucin layer and form new cysts, which results in a self-limited and asymptomatic infection. In some cases, however, adherence to and lysis of the colonic epithelium, mediated by the galactose and *N*-acetyl-D-galactosamine (Gal/GalNAc)–specific lectin, initiates invasion of the colon by trophozoites. Neutrophils responding to the invasion contribute to cellular protection at the site of invasion. Once the intestinal epithelium is invaded, extraintestinal spread to the peritoneum, liver, and other sites may follow. Factors controlling invasion, as opposed to encystation, probably include parasitic "quorum sensing" signaled by the Gal/GalNAc-specific lectin, interactions of amebae with the bacterial flora of the intestine, and innate and acquired immune responses of the host. (Redrawn with permission from Haque R, Huston CD, Hughes M, et al. Current concepts: amebiasis. *N Engl J Med*. 2003;348:1565-1573.)

The composition of the gut microbiome also is associated with symptomatic amebiasis, likely by induction of an inflammatory immune response.

CLINICAL MANIFESTATIONS

Asymptomatic Intraluminal Amebiasis

The asymptomatic cyst-passing carrier state is the most common type of amebic infection. All *Entamoeba moshkovskii* and *E. dispar* infections and as many as 80% of *E. histolytica* infections are asymptomatic.[6] Asymptomatically infected individuals represent a risk to the community because they are a source of new infections and a risk to themselves because 1 in 10 to 20 colonized individuals progress to symptomatic infection.

Amebic Diarrhea

Amebic diarrhea without dysentery, which is defined as diarrhea in an *E. histolytica*–infected individual, is the most common amebic disease.[7] The mean duration of amebic diarrhea is about 3 days, and approximately 2% of cases of diarrhea are severe enough to warrant hospital evaluation in developing countries.

Amebic Dysentery or Colitis

Diarrhea with mucus or visible or microscopic blood in a patient with *E. histolytica* infection is the definition of amebic dysentery or colitis.[8] Approximately 15 to 33% of patients with *E. histolytica* diarrhea also have amebic dysentery. The onset of symptoms is typically gradual during a period of 3 or 4 weeks after infection, with abdominal tenderness and increasingly severe diarrhea being the primary

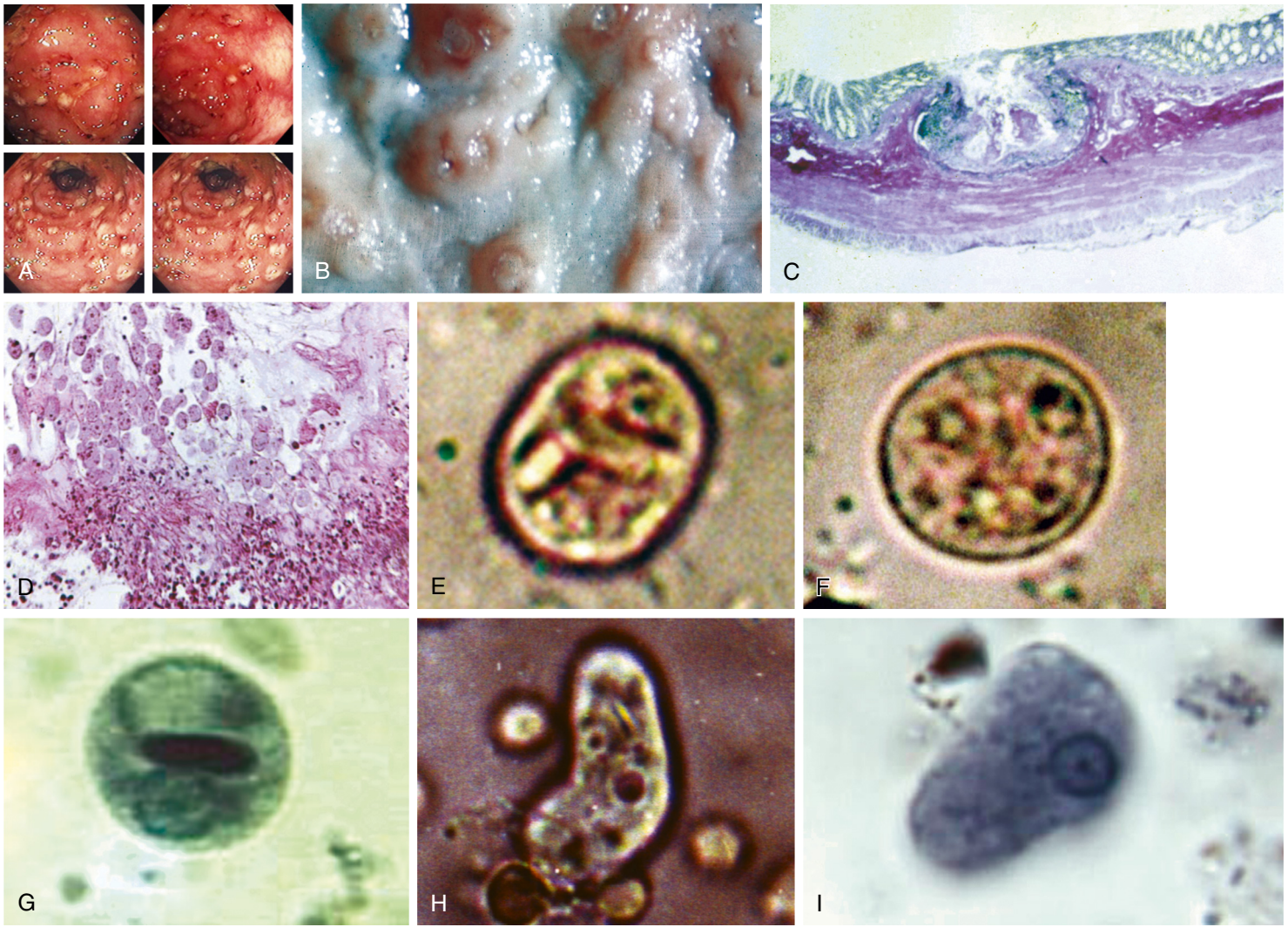

FIGURE 323-2. Endoscopic and pathologic features of intestinal amebiasis. A, Colonoscopic appearance of intestinal amebiasis. **B**, Colonic ulcers averaging 1 to 2 mm in diameter on gross pathologic examination. **C**, Cross section of a flask-shaped colonic ulcer (hematoxylin-eosin stain, magnification ×20). **D**, Inflammatory response to intestinal invasion by *Entamoeba histolytica* (hematoxylin-eosin stain, magnification ×100). **E** and **F**, *E. histolytica* cysts in a saline preparation (magnification ×1000). **G**, Iodine-stained cyst from stool (magnification ×1000). **H**, *E. histolytica* trophozoite with an ingested erythrocyte in a saline preparation from stool (magnification ×1000). **I**, Trophozoite from stool stained with trichrome (magnification ×1000). (*B–D*, From the slide collection of the late Dr. Harrison Juniper.) (From Haque R, Huston CD, Hughes M, et al. Current concepts: amebiasis. *N Engl J Med*. 2003;348:1565-1573.)

complaints. By comparison, patients with bacterial causes of dysentery usually have only 1 or 2 days of symptoms (Chapter 262). Surprisingly, fever is present in only a minority of patients with amebic colitis. In young children, intussusception, perforation, peritonitis, or necrotizing colitis may develop rapidly (Fig. 323-2). Unusual manifestations of amebic colitis include toxic megacolon (0.5% of cases, usually requiring surgical intervention) and ameboma (granulation tissue in the colonic lumen mimicking colon cancer in appearance).

Amebic Liver Abscess

Amebic liver abscess (Chapter 137) is 10 times as common in men as in women and is unusual in children. The typical patient with an amebic liver abscess in the United States is a male immigrant from an endemic area, ages 20 to 40 years, with fever, right upper quadrant pain, leukocytosis, abnormal liver aminotransferase and alkaline phosphatase levels, and a defect seen on hepatic imaging studies.[9] Among travelers, the average interval between exposure and clinical presentation can be up to 18 months.[10] Most patients have 2 to 4 weeks of prior fever, cough, and abdominal pain in the right upper quadrant or epigastrium. Involvement of the diaphragmatic surface of the liver may lead to right-sided pleural pain or referred shoulder pain and an elevated right hemidiaphragm seen on chest radiography (Fig. 323-3). Hepatomegaly with point tenderness over the liver, below the ribs, or in the intercostal spaces is a typical finding.

Other Extraintestinal Infections

Thoracic amebiasis, which is the most common type of extra-abdominal amebiasis, occurs in about 10% of patients with amebic liver abscess. It develops by direct extension into the pleural cavity from the liver. Pericardial amebiasis, which is the next most common form, may result from rupture of a liver abscess in the left lobe of the liver into the pericardium or from extension of right-sided pleural amebiasis. Cerebral amebic abscesses have been found in about 0.5 to 5% of patients with amebic liver abscess. Other foci of infection are rare, but amebic rectovesical fistula formation and involvement of the pharynx, heart, aorta, and scapula have been reported. Cutaneous infection may arise from trophozoites emerging from the rectum.

DIAGNOSIS

Diagnosis of amebiasis is best accomplished by the combination of polymerase chain reaction (PCR) testing or antigen detection of the parasite in feces or at extraintestinal sites of invasion (e.g., pus obtained by fine needle aspiration of a liver abscess), often combined with serology.[11] The most sensitive diagnostic approach is the combined use of *E. histolytica*–specific antigen detection or PCR plus serology (Table 323-1). The detection of salivary IgA has a sensitivity and specificity of about 90%.[12] Examination of stool for ova and parasites should not be used to diagnose amebiasis. Amebic colitis also can be diagnosed by colonoscopy, which can show characteristic discrete ulcers or erosions with white or yellow exudates, especially in the cecum, and can identify trophozoites in about 90% of patients.

When a space-filling defect in the liver is observed, the differential diagnosis includes (1) amebiasis (most common in men with a history of travel to or residence in a developing country), (2) pyogenic or bacterial abscess (particularly

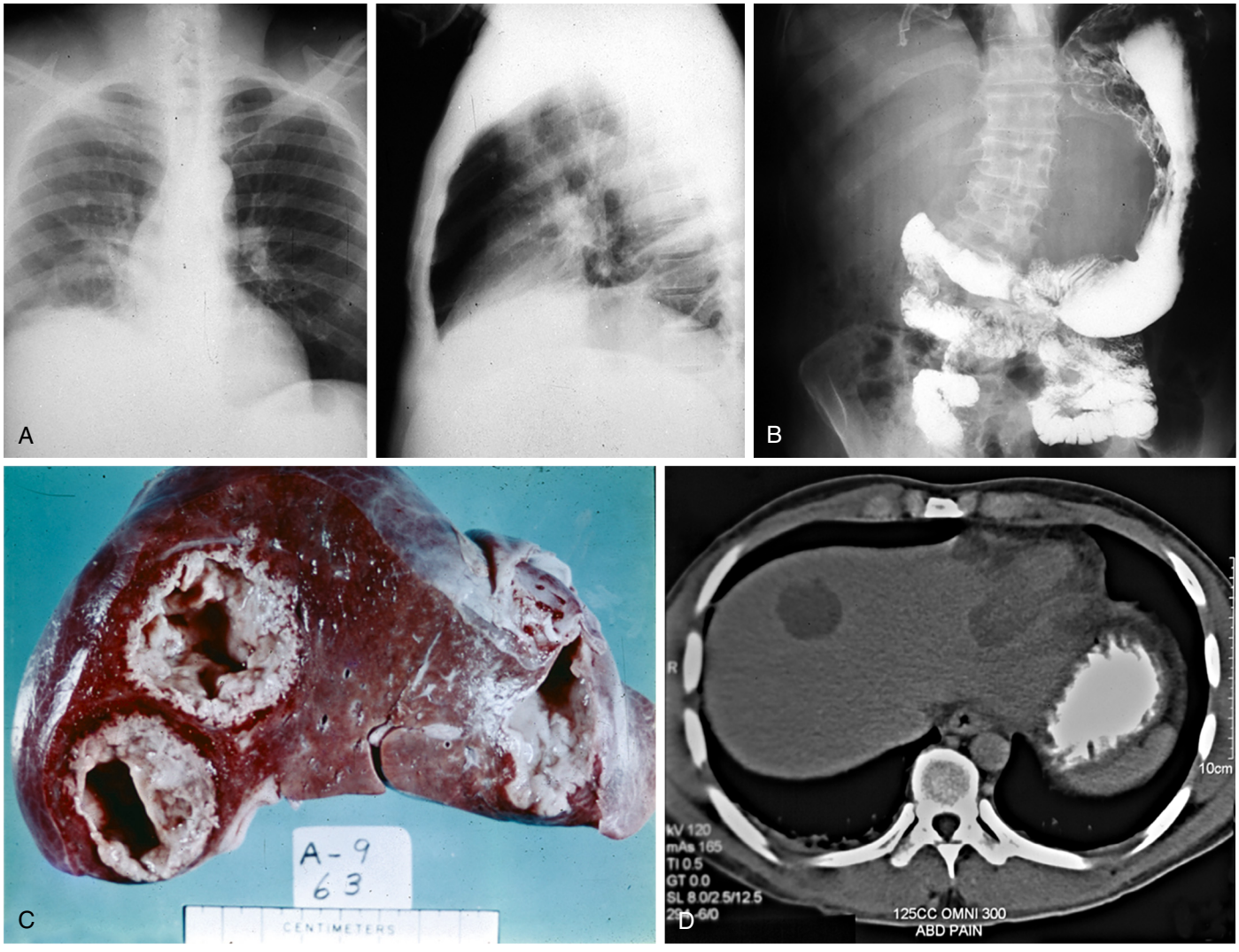

FIGURE 323-3. **Radiographic and pathologic features of extraintestinal amebiasis. A,** Left posteroanterior and right lateral chest radiographs in a patient with amebic liver abscess. The findings include an elevated right hemidiaphragm and evidence of atelectasis. **B,** Luminal narrowing revealed by barium enema examination in a patient with an ameboma. **C,** Two abscesses in the right lobe and one abscess in the left lobe of a patient with amebic liver abscess. **D,** Abdominal computed tomography showing one abscess in the right lobe and one abscess in the left lobe in a patient with amebic liver abscess. (From Haque R, Huston CD, Hughes M, et al. Current concepts: amebiasis. *N Engl J Med*. 2003;348:1565-1573.)

TABLE 323-1 SENSITIVITY OF TESTS FOR DIAGNOSIS OF AMEBIASIS

TEST	COLITIS	LIVER ABSCESS
Real-time PCR	>95%	>95%
Stool antigen detection	80%	≈40%
Microscopy: stool	25-60%	10-40%
Serum antigen detection	65%	>95%
Serologic testing (indirect hemagglutination)		
Acute	70%	70-80%
Convalescent	>90%	>90%
Microscopy: abscess fluid	N/A	≤20%

N/A = not available; PCR = polymerase chain reaction.
Modified from Haque R, Huston CD, Hughes M, et al. Current concepts: amebiasis. *N Engl J Med*. 2003;348:1565-1573.

suspected in women, patients with cholecystitis, the elderly, individuals with diabetes, and patients with jaundice; Chapter 137), (3) echinococcal abscess (which would be an incidental finding because echinococcal abscess should not cause pain or fever; Chapter 325), and (4) cancer. Most patients with amebic liver abscess will have detectable circulating antigen in serum as well as serum antiamebic antibodies.[13]

TREATMENT (ALSO SEE CHAPTER 315)

Noninvasive infection may be treated with paromomycin (Table 323-2), but invasive infections require treatment with nitroimidazoles, particularly tinidazole,[A1] metronidazole, secnidazole (2-g single dose), or ornidazole (500 mg 3 times daily for 5 days). For amebic colitis and liver abscess,[A2] tinidazole reduces treatment failure rates and adverse effects compared with metronidazole. Nitazoxanide (500 mg orally twice daily for 10 days) also appears to be superior to metronidazole for uncomplicated amebic liver abscess.[A3] In the rare case of fulminant amebic colitis, it is prudent to add broad-spectrum antibiotics to treat intestinal bacteria that may spill into the peritoneum. Parasites persist in up to 50% of patients who are treated with a nitroimidazole, so treatment should be followed with paromomycin or the second-line agent diloxanide furoate to cure luminal infection.

For liver abscesses, drainage should be considered in patients who do not show a clinical response with shrinkage of the abscess within 5 to 7 days of drug therapy, but it usually is not routinely necessary even for large abscesses. Percutaneous needle aspiration or catheter drainage is the procedure of choice for drainage of a liver abscess. Surgical intervention is occasionally required for drainage of a liver abscess, acute abdomen, gastrointestinal bleeding, or toxic megacolon.

PREVENTION

Vaccines[14] are in the late stages of preclinical development for the prevention of amebiasis in the developing world. Provision of sanitation and clean water and safe sexual practices to prevent fecal-oral transmission are of great importance but not universally effective because of the low infectious dose and chlorine resistance of the cyst.

TABLE 323-2 DRUG THERAPY FOR TREATMENT OF AMEBIASIS

DRUG	ADULT DOSAGE	SIDE EFFECTS
AMEBIC LIVER ABSCESS		
Tinidazole	2 g PO once daily × 5 days	Primarily GI side effects and disulfiram-like intolerance reaction to alcoholic beverages as for metronidazole
or		
metronidazole	750 mg PO tid × 10 days	Primarily GI side effects: anorexia, nausea, vomiting, diarrhea, abdominal discomfort, or unpleasant metallic taste
or		
secnidazole	2-g PO single dose	Disulfiram-like intolerance reaction to alcoholic beverages
or		
ornidazole	500 mg tid × 5 days	Neurotoxicity, including seizures, peripheral neuropathy, dizziness, confusion, irritability
or		
nitazoxanide	500 PO bid × 10 days	Headache, stomach pain, nausea, discolored urine
Followed by a luminal agent		
Paromomycin	30 mg/kg/day PO in 3 divided doses per day × 5-10 days	Primarily GI side effects: diarrhea, GI upset
or		
diloxanide furoate	500 mg PO tid × 10 days	Primarily GI side effects: flatulence, nausea, vomiting
		Pruritus, urticaria
AMEBIC COLITIS		
Metronidazole	750 mg PO tid × 5-10 days	Same as for amebic liver abscess
Plus a luminal agent ([e.g., paromomycin or diloxanide furoate] same as for amebic liver abscess)		
ASYMPTOMATIC INTESTINAL COLONIZATION		
Treatment with a luminal agent (e.g., paromomycin or diloxanide furoate)		

bid = twice a day; GI = gastrointestinal; PO = by mouth; tid = three times a day.
Modified from Haque R, Huston CD, Hughes M, et al. Current concepts: amebiasis. *N Engl J Med*. 2003;348:1565-1573.

TABLE 323-3 FREE-LIVING AMEBAE

ORGANISM	DISEASE	EPIDEMIOLOGY	DIAGNOSIS	CLINICAL COURSE	THERAPY
Naegleria fowleri	Primary amebic encephalitis	Warm freshwater exposure	CSF wet mount for amebae, PCR	Death within 1-2 weeks of onset	Combination therapy with amphotericin B, miltefosine, rifampin, fluconazole, and azithromycin
Acanthamoeba spp	Keratitis	Corneal trauma, usually from contact lens	Corneal scraping for amebae and cysts	Subacute	Polyhexamethylene biguanide, chlorhexidine, propamidine, hexamidine
Acanthamoeba spp	Granulomatous amebic encephalitis	Immunodeficient (organ transplants, HIV/AIDS)	Biopsy of brain or skin abscess—IFA or PCR	Subacute	Combination therapy with miltefosine, pentamidine, an azole (fluconazole or itraconazole), and/or sulfadiazine
Balamuthia mandrillaris	Granulomatous amebic encephalitis	Immunodeficient but also immunocompetent	Biopsy of brain	Subacute	Combination therapy with miltefosine, pentamidine, fluconazole, and sulfadiazine plus either azithromycin or clarithromycin
Sappinia	Amebic encephalitis	Single patient was not immunodeficient			Azithromycin, pentamidine, itraconazole, flucytosine

AIDS = acquired immunodeficiency syndrome; CSF = cerebrospinal fluid; HIV = human immunodeficiency virus; IFA = indirect fluorescent antibody; PCR = polymerase chain reaction.
Modified from Visvesvara GS, Moura H, Schuster FL. Pathogenic and opportunistic free-living amoebae: *Acanthamoeba* spp, *Balamuthia mandrillaris*, *Naegleria fowleri*, and *Sappinia diploidea*. *FEMS Immunol Med Microbiol*. 2007;50:1-26.

PROGNOSIS

Therapy for amebiasis is highly effective. Drug resistance is not reported. Even with liver abscess, the mortality is less than 1% if it is diagnosed and treated early. Death usually results from rupture of the liver abscess into the peritoneum, thorax, or pericardium, but it also may be caused by extensive hepatic damage and liver failure.

FREE-LIVING AMEBAE

Rare infections of the central nervous system can be seen with infection by free-living amebae of the genera *Naegleria, Balamuthia, Acanthamoeba,* and *Sappinia*.[15,16]

Naegleria fowleri is the agent of primary amebic meningoencephalitis,[17] which occurs in previously healthy children and young adults who have swum in fresh water 2 to 5 days before the onset of meningoencephalitis. Cerebrospinal fluid has a polymorphonuclear predominance, and motile amebae can be seen in a wet mount of cerebrospinal fluid. The disease is relentlessly progressive to death in more than 95% of patients,[18] but successful treatment has been reported with a combination of intrathecal and intravenous amphotericin B plus miconazole and oral rifampin.

Acanthamoeba can cause keratitis in individuals with corneal injuries (usually from contact lens use[19]), as well as granulomatous amebic encephalitis in immunocompromised patients. The diagnosis can best be made by a combination of PCR and culture.[20]

Granulomatous amebic encephalitis is caused by *Acanthamoeba, Balamuthia,* and *Sappinia;* it is usually associated with focal neurologic findings and has a subacute course. Miltefosine should be part of combination therapy (Table 323-3).

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For the General References and other additional features, please visit Elsevier eBooks+ at https://ebooks.health.elsevier.com.

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324 BABESIOSIS AND OTHER PROTOZOAN DISEASES

SAM R. TELFORD, III, AND PETER J. KRAUSE

BABESIOSIS

Babesiosis is a tick-borne, malaria-like disease caused by sporozoan parasites of the genus *Babesia* that infect red blood cells.

EPIDEMIOLOGY

With few exceptions, *Babesia* spp are transmitted by ixodid ticks. Thus, wherever humans are intensely exposed to hard-bodied ticks, babesiosis should be part of the differential diagnosis for a patient presenting with fever and hematologic abnormalities.

Three worldwide epidemiologic patterns are apparent. The first involves the rodent-maintained *Babesia microti*, which is a species complex distributed across the Holarctic. About 2000 cases of *B. microti* babesiosis are reported each year,[1] mostly from the northeastern United States and upper Midwestern states, compared with an average of about 26,000 cases of Lyme disease (Chapter 296), but babesiosis is thought to be underreported. The vector for both *B. microti* and Lyme disease (Chapter 296) is the deer tick, *Ixodes dammini*, also known as northern populations of *I. scapularis*.[2] As a result, concurrent babesiosis and Lyme disease is common. Immunocompetent as well as immunocompromised individuals are at risk. Within the last decade, *B. microti* has been increasingly reported in an expanded distribution in the United States from its original foci in coastal New England and the Upper Midwest, and it is possible that babesiosis cases eventually may be found wherever Lyme disease is intensely zoonotic. In addition, cases of *B. microti* or *B. microti*–like babesiosis have been reported in Australia, Canada, China, Germany, Japan, Mexico, Poland, Spain, South Africa, and Taiwan; the vectors for these have not been definitively identified.

The second pattern is represented by cases of babesiosis due to *Babesia divergens*, *B. divergens*–like, or closely related species (e.g., *Babesia venatorum*) that have been reported from Asia and Europe. Almost all clinical cases in Europe have been in splenectomized patients who reside in sites where castor bean ticks (*Ixodes ricinus*) and deer are common. *Babesia crassa and B. venatorum* babesiosis recently have been found to be endemic in northeastern China, and *B. microti* babesiosis is endemic in southern China on the Myanmar border. A few cases of *Babesia divergens*–like infections (referred to as MO-1) have been described in the United States.

The third pattern of babesiosis involves sporadic cases due to diverse *Babesia* spp, including *Babesia duncani* (WA-1) and CA-type parasites of the western United States; a *Babesia motasi*–like infection (KO-1) in Korea; and unidentified or poorly characterized *Babesia* spp from China, Colombia, Egypt, India, Mexico, Mozambique, and South Africa. Molecular phylogenetic methods provide evidence that human babesiosis may be caused by many of the known *Babesia* spp., as well as by non-*Babesia* piroplasms such as the related parasite *Anthemosoma garnhami*.

The known zoonotic tick vectors (*I. dammini, I. ricinus*) have marked seasonal periods of activity (May to August), and the majority of reported cases are acquired during these times, however, babesiosis may be diagnosed at any time of the year.

More than 250 cases of transfusion-acquired babesiosis due to *B. microti* and three due to *B. duncani* have been reported, but the actual number of cases is thought to be much greater. Babesiosis is one of the most commonly reported transfusion-transmitted diseases (Chapter 162) in the United States, and the number of such cases is increasing, including those ending in death. Cases occur throughout the year, and about 10% of cases occur in nonendemic areas because *Babesia*-infected blood is exported to nonendemic areas or persons become infected in endemic areas and subsequently donate blood in nonendemic areas.[3] A few cases of transplacentally transmitted babesiosis also have been reported.

PATHOBIOLOGY

The pathophysiology of *Babesia* infection is directly related to the development of parasitemia. Peripheral blood parasitemias of 70% or greater have been reported, although most cases sustain parasitemias on the order of 0.5 to 5%. Excessive production of pro-inflammatory cytokines seems to best explain the most common clinical manifestations, which include fever, fatigue, sweats, chills, headache, anorexia, myalgia, nausea, vomiting, and pallor. Such findings are not seen when erythrocyte lysis is due to noninfectious causes, which suggests that the release of merozoites serves as a trigger for the pro-inflammatory cascade. Elevated serum concentrations of TNF as well as of interferon-γ, interleukins 2 and 6, E-selectin, vascular cell adhesion molecule 1, and intracellular cell adhesion molecule 1 are detected during the acute phase of human *B. microti* infection and return to baseline within 3 months after resolution of infection.

Severe illness caused by infection with *Babesia* includes a complex array of metabolic abnormalities and organ dysfunction. Cardiac and pulmonary disease are the most common complications in patients who experience severe *Babesia* infection, with up to 20% of patients suffering from noncardiogenic pulmonary edema. Pro-inflammatory cytokines contribute to the pulmonary complications of *Babesia* infection. Disseminated intravascular coagulation and heart failure are even more frequently observed. It is also likely that lung and other end-organ disease is mediated, at least in part, by vascular stasis.

CLINICAL MANIFESTATIONS

About 25% of *B. microti* infections in adults and 50% of cases in children are subclinical. Most people experience a mild to moderate illness that persists for about 1 week. Manifestations include a gradual onset of malaise, anorexia, fatigue, fever (temperature as high as 40° C), sweats, and myalgia. Nausea, vomiting, headache, shaking chills, emotional lability, depression, hemoglobinuria, and hyperesthesia can also occur. Findings on physical examination may consist of fever, pallor, splenomegaly, and hepatomegaly. Laboratory abnormalities include anemia, thrombocytopenia, and leukopenia. Parasitemia generally ranges from barely detectable on blood smear to 5% in previously healthy people, but it may reach 85% in asplenic and other immunocompromised patients. Serum levels of lactate dehydrogenase, bilirubin, and aminotransferases are commonly elevated in more severe cases. Persistent relapsing illness may occur in highly immunocompromised patients who fail to clear the infection for months or more than a year despite multiple courses of antibiotics.

Severe babesiosis usually manifests as an acute onset of illness with hemoglobinuria, a persistent nonperiodic high fever (temperature of 40° to 41° C), shaking chills, intense sweats, headaches, and myalgia, as well as lumbar and abdominal pain. Vomiting and diarrhea may occur. Pulmonary, renal, or liver failure may develop rapidly. In fatal cases, patients become comatose with multiorgan failure. Severe disease occurs only in individuals with asplenia, malignancy, HIV, organ transplants, immunosuppressive treatment, or age younger than 2 months or older than 50 years. About a third of treated asplenic babesiosis patients without a history of autoimmune disease may suffer warm autoimmune hemolytic anemia (Chapter 146) that requires immunosuppressive treatment.

Cases of babesiosis caused by *B. divergens* tend to be severe, at least in part because they are primarily reported in immunocompromised patients. Almost all European patients who have experienced *B. divergens* infection have been splenectomized, and about a third died. *B. duncani, B. venatorum*, and *B. divergens*–like infections also have often been reported in immunocompromised hosts with a similarly severe course of illness. In contrast, the clinical course of *B. venatorum* infection in 48 immunocompetent patients in northeastern China was similar to that of *B. microti* infection, with full recovery of all patients, including seven patients who were admitted to the hospital.

DIAGNOSIS

The diagnosis of babesiosis is based on epidemiologic and clinical findings and confirmed by laboratory testing. It should be considered in patients who live or travel in *Babesia* endemic regions or who have received a blood transfusion within the previous 6 months and whose clinical findings are consistent with babesiosis.

The two primary laboratory tests for confirmation of babesiosis infection are microscopic visualization of parasites on a Giemsa-stained thin blood smear and the detection of *Babesia* DNA on a polymerase chain reaction (PCR) assay. Microscopy can be performed more rapidly than PCR, so it is especially useful in patients who are severely ill with parasitemia above 1% and who need immediate diagnosis and therapy. PCR has greater sensitivity and is especially useful in cases with lower degrees of parasitemia. For *B. microti* babesiosis (Fig. 324-1), examination of a slide for 10 minutes or as many fields as needed to tally 200 leukocytes (that are not infected but serve as a marker for effort) and repeated smears performed twice a day may be required. Standard Romanowsky stains (Giemsa, Wright) using malaria protocols are optimal. Artifactual inclusions are

ABSTRACT

The health burden due to human babesiosis, which causes a clinical syndrome that is similar to malaria, is increasing as it spreads further into sites where Lyme disease is endemic. Because younger infected individuals are often asymptomatic, babesia can also be transmitted through blood donation, and babesiosis is a major transfusion-transmitted disease. Molecular phylogenetic tools are better defining the global public health importance of babesiosis. Similarly, enteric disease due to other protozoa, particularly the coccidia and microsporidia, may more easily be diagnosed and characterized by molecular methods. New methods for detection are providing more information about the prevalence and incidence of trichomoniasis.

KEYWORDS

babesiosis
tick-borne
enteric protozoa
coccidian
food-borne
ixodid ticks

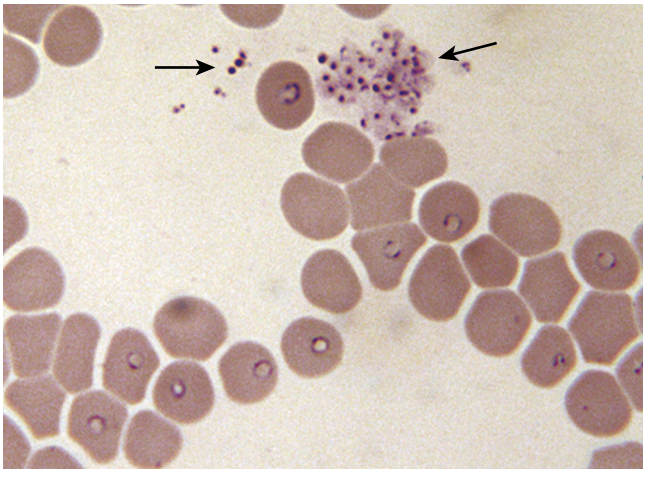

FIGURE 324-1. ***Babesia microti*. Human infection, Nantucket Island. Predominance of ring forms with a cluster of extraerythrocytic parasites (*arrow*) free in the plasma.**

limited mainly to stain precipitates (which can be determined by their presence in the plasma spaces between cells), Howell-Jolly or Heinz bodies (Chapter 143), or platelets superimposed on erythrocytes, which always have a light-colored halo when visualized this way. *Babesia* spp have clearly defined chromatin with a lighter-colored cytoplasm (Fig. 324-2A) and may be mistaken for early malarial trophozoites. Neither malarial nor babesial rings have hemozoin (malarial pigment), so this feature cannot distinguish between the two. Paired piriform parasites, arranged in a *v*, are suggestive of *B. divergens* or *B. divergens*–like infection (Fig. 324-2B). Rings of all sizes may be seen in all species. Multiple parasites may frequently be seen in single erythrocytes, as well as clumps of extracellular parasites. Tetrad forms (Fig. 324-2C) and Maltese cross forms (Fig. 324-2D), which are diagnostic but are rarely seen in *B. microti* babesiosis, seem to be more common with *B. duncani* or CA-type infections.

Serologic testing is useful to help confirm *B. microti* infection, but patients with a positive antibody test should have the diagnosis confirmed by a thin blood smear or PCR to diagnose acute infection.[4] The indirect immunofluorescence test, using antigen from infected hamster red cells, is sensitive and specific and is currently the serologic method of choice. A four-fold rise in *B. microti* antibody titer in paired acute and convalescent serum samples is most useful to corroborate *B. microti* infection. The presence of parasite-specific IgM may suggest that the patient has an acute infection even in the absence of readily demonstrable parasitemia. Serology is not generally useful for *B. divergens* babesiosis (although the immunofluorescence test is generally sensitive and specific), given its fulminant natural history.

Serology for *B. duncani* is complicated by a high rate of false positives, and specificity depends on carefully establishing a diagnostic threshold dilution. Antigens for the other *Babesia* spp infecting humans are not available. Because parasitemia occurs before an antibody response and because the doubling time of *B. divergens* can be as short as 8 hours, serologies are not helpful for prompt decision-making.

The known vectors for human babesiosis are ticks that also transmit the agents of Lyme disease (Chapter 296), human granulocytic anaplasmosis (Chapter 302), *Borrelia miyamotoi* infection (Chapter 297), *Ehrlichia muris*–like infection (Chapter 302), and tick-borne encephalitis virus (Chapter 352). Thus, coinfections should be considered in all patients with babesiosis. Acute illness in patients coinfected with Lyme disease and babesiosis is more severe and more persistent than in patients experiencing Lyme disease alone.

TREATMENT

Treatment should be initiated immediately on the basis of clinical suspicion and initial results on PCR testing or microscopy. However, incidental finding of parasites (e.g., during a manual CBC, or at a blood donation center that proactively performs screening) in an otherwise healthy individual requires monitoring but may not require treatment.

Therapy for mild to moderate *B. microti* infection, which typically occurs in immunocompetent individuals, should consist of the combination of atovaquone (750 mg orally twice daily for 7 to 10 days) and azithromycin (500 to 1000 mg initial dose followed by 250 mg orally daily for 7 to 10 days) (Table 324-1),[5,6] which clears parasitemia as effectively as the combination of clindamycin (600 mg orally every 8 hours for 7 to 10 days) plus quinine (650 mg orally every 8 hours for 7 to 10 days) with fewer side effects. For immunocompromised hosts, the azithromycin dose should be increased to 600 to 1000 mg orally daily for 7 to 10 days. For severe babesiosis (which usually occurs in immunocompromised patients or patients over age 50 years), a 7- to 10-day course of the combination of atovaquone (750 mg orally twice daily) and azithromycin (500 mg intravenously once a day) is recommended. An alternative combination is clindamycin (600 mg every 6 hours intravenously) and quinine (650 mg orally every 8 hours).

Treatment may occasionally fail in high-risk patients or in patients who must discontinue quinine because of side effects, such as severe tinnitus and gastrointestinal distress, or because of antibiotic resistance to atovaquone and azithromycin. A prolonged course of treatment may be required to clear parasitemia in certain immunocompromised patients, including patients with B-cell lymphoma (Chapter 171) or other conditions treated with rituximab, patients with malignancy who also are asplenic (Chapter 154), patients with organ or stem cell transplantation, and patients with HIV/AIDS. In such cases, expert consultation is suggested to design combination therapy for immunocompromised patients with one or more of the following regimens: atovaquone, azithromycin, and clindamycin; atovaquone plus clindamycin; atovaquone/proguanil plus azithromycin; or atovaquone, azithromycin, clindamycin, and quinine. Dosing for these antimicrobial combinations should be based on doses recommended for other infections (informed by allergic history, renal function, and other relevant considerations for the specific patient) and/or from the few case reports for which they have been used. Once an effective combination demonstrates clinical improvement and reduction in parasitemia, it should be continued for

TABLE 324-1 TREATMENT REGIMENS FOR ADULTS PATIENTS WITH BABESIOSIS

PATIENT CATEGORY	TREATMENT REGIMEN
Ambulatory patients: mild to moderate disease	Preferred: Atovaquone (750 mg orally with a fatty meal q12h) plus azithromycin 500 mg orally on day 1), then 250 mg daily for 7 to 10 days Alternative: Clindamycin (600 mg orally q8h) plus quinine sulfate (650 mg orally q8h) for 7 to 10 days*
Hospitalized patients: acute severe disease†	Preferred: Atovaquone (750 mg orally q12h) plus azithromycin (500 mg IV q24h) until symptoms abate, then convert to all oral therapy (see step-down therapy) Alternative: Clindamycin (600 mg IV q6h) plus quinine sulfate (650 mg orally q8h) until symptoms abate, then convert to all oral therapy (see step-down therapy)* If infection relapses, consider an experimental regimen (with combinations that include doxycycline, proguanil, pentamidine, or trimethoprim-sulfamethoxazole) under expert guidance
Hospitalized patients: step-down therapy (transition to oral therapy)	Preferred: Atovaquone (750 mg orally with a fatty meal q12h) plus azithromycin (250 to 500 mg orally q24h). Treatment of acute disease plus step-down therapy typically should total 7 to 10 days. A high dose of azithromycin (500 to 1000 mg orally) should be considered for immunocompromised patients Alternative: Clindamycin (600 mg orally q8h) plus quinine sulfate (650 mg orally q8h).* Treatment of acute disease plus step-down therapy typically requires a total of 7 to 10 days
Highly immunocompromised patients	Start with one of the regimens recommended for hospitalized patients with acute severe disease and follow with one of the step-down regimens, but treat for at least 6 consecutive weeks, including 2 final weeks during which parasites are no longer detected on the peripheral blood smear. When oral azithromycin is used, a 500 to 1000 mg daily dose should be considered. If infection relapses, consider an experimental regimen with combinations that include doxycycline, proguanil, pentamidine, or trimethoprim-sulfamethoxazole under expert guidance

*Clindamycin plus quinine is preferred when parasitemia and symptoms have failed to respond to atovaquone plus azithromycin.

†Exchange transfusion should be considered for patients who have high-grade parasitemia (>10%) or moderate to high-grade parasitemia plus: severe hemolytic anemia or severe pulmonary, renal, or hepatic compromise.

IV = intravenous.

Adapted from Krause PJ, Auwaerter PG, Bannuru RR, et al. Clinical practice guidelines by the Infectious Diseases Society of America (IDSA): 2020 Guideline on Diagnosis and Management of Babesiosis. *Clin Infect Dis*. 2021;72:e49-e64.

at least 6 weeks and 2 weeks beyond the time when *Babesia* can no longer be visualized on blood smear or blood samples become PCR negative. Other drugs have been demonstrated to be effective against *B. microti* in laboratory models (e.g., robenidine, primaquine, artesunate, clofazimine, tafenoquine,[7] and endochin-like quinolones) but await clinical trials.

Partial or complete red cell exchange transfusion (1 to 3 blood volumes) should be considered in addition to antibiotic treatment in severely ill patients with parasitemias in excess of 10%, evidence of severe hemolysis, or organ compromise. Apheresis reduces parasitemia and may help reduce pathogenic circulating inflammatory host factors or products liberated by the parasite, but its effect on patients' outcomes is uncertain.[8]

PREVENTION

Prevention depends on reducing the risk for tick bites. Immunocompromised individuals should be especially careful to use personal protection and may even consider avoiding highly endemic sites such as coastal New England and Long Island in the United States during May through August, when the risk is the greatest. Use of repellants such as DEET or application of permethrin to clothing will greatly reduce tick attachment. Such products should be applied to shoes, socks, and trouser cuffs. Wearing light-colored long pants and tucking the cuffs into socks will also help prevent ticks from gaining access to attachment sites. As with the agent of Lyme disease, ticks must be attached at least 36 to 48 hours before a sufficient inoculum of *Babesia* sporozoites is delivered. Daily examination for attached ticks should be performed; the best method is to feel for new bumps on a soapy body in the shower. Any attached ticks should be promptly removed by simple traction, which is best accomplished with the use of tweezers (see Fig. 302-3).

Community-level prevention should focus on public education about the risks of tick-borne infection, reducing the habitat for ticks (brush removal and landscaping around yards), or reducing the reproductive hosts for the tick. Deer reduction will reduce the abundance of the deer tick vector for *B. microti* babesiosis. Screening blood donations for *B. microti* antibodies and *B. microti* DNA (using PCR) can decrease the risk of transfusion-associated babesiosis.[9]

PROGNOSIS

The case-fatality rate for *B. microti* babesiosis has been estimated to be 6 to 9% in hospitalized patients but may be as high as 20% in immunocompromised hosts, including patients who acquire the infection through blood transfusion. Based on Medicare data, about 1% of patients older than 65 years of age die within 30 days of diagnosis.

Among survivors, long-term sequelae have not been reported if patients were adequately treated. In most patients who complete a full treatment regimen, *B. microti* DNA becomes undetectable by PCR within 3 months. Infection does not, however, imply protective immunity, although subsequent infections are usually limited in duration and intensity. Recrudescent infections have been reported, mainly in immunocompromised individuals.

ENTERIC PROTOZOA

The gastrointestinal and urogenital tracts may contain representatives of the four major groupings of protozoa (amebae, sporozoa, flagellates, and ciliates). Diarrhea and other lower gastrointestinal signs and symptoms may be caused by diverse protozoa. Specific clinical diagnosis is difficult because expert clinical parasitology support is required to determine whether an agent that has been detected in a stool sample is a pathogenic species. However, new point-of-care

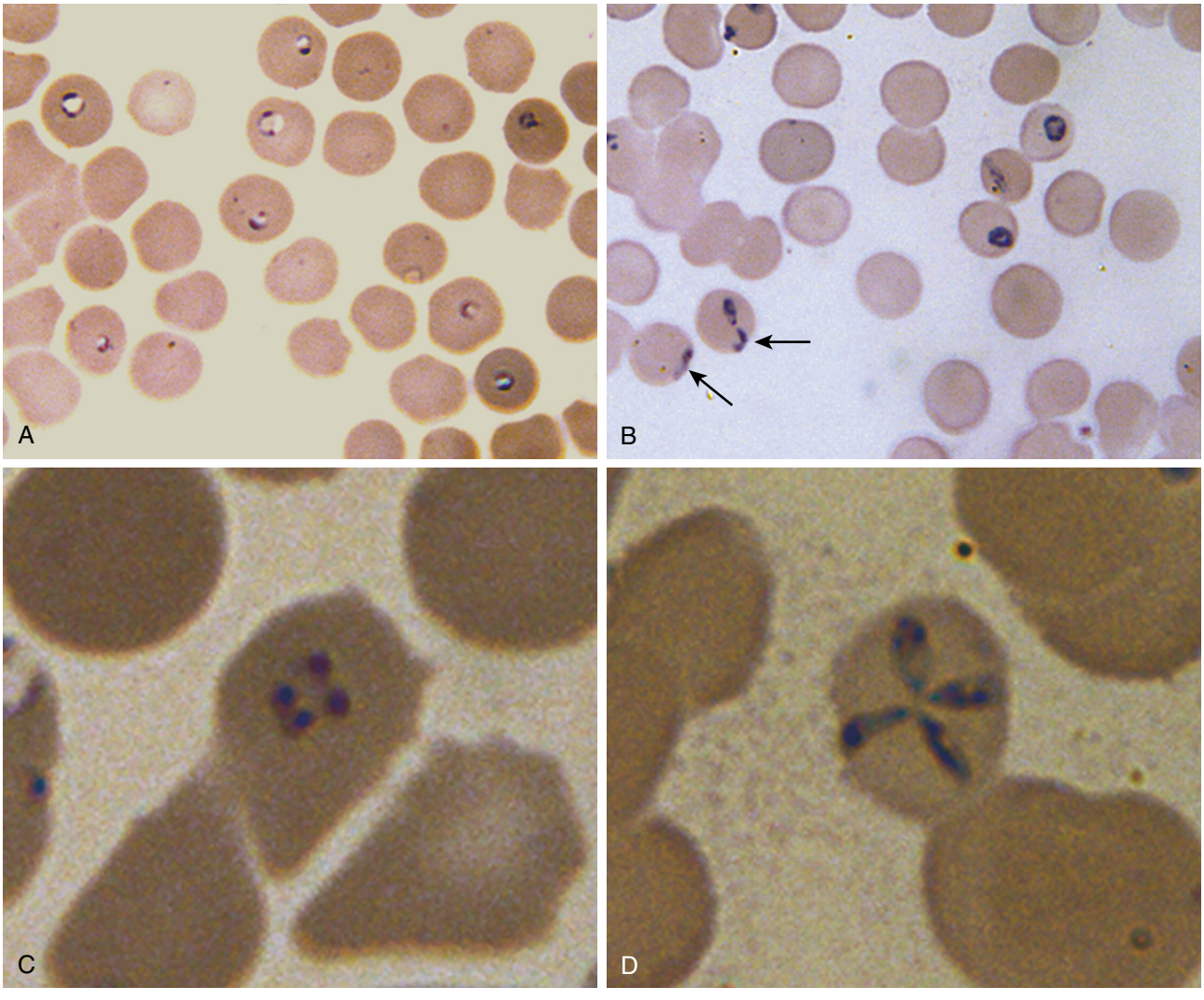

FIGURE 324-2. Diagnosis of *Babesia* infection. A, Typical thin-film field demonstrating ring forms of *B. microti* with vacuole or "whitish" cytoplasm demarcated by a dark-staining, defined chromatin. **B,** *B. divergens*–like (MO-1) with robust rings; accolé form and paired piriform parasites marked by *arrows*. **C,** Tetrad forms of *B. microti*. **D,** MO-1, classic Maltese cross. (Microscope slide from human case of MO-1 kindly provided by Dr. J. F. Beattie, Department of Pathology, The Medical Center, Bowling Green, Ky.)

antigen detection tests, or nucleic acid amplification tests (NAAT) are sensitive and specific when they can be used. Identification is necessary because treatment options differ by the agent. With the exception of *Trichomonas vaginalis* infection (sexually transmitted), all of the enteric protozoa are acquired by the ingestion of food or materials contaminated by human feces; a small subset may have extraintestinal manifestations. Given a shared mode of transmission (fecal-oral), demonstrating the presence of any one of these protozoa within a stool sample from a patient is justification for an intensified search for those that are recognized as clinically significant pathogens (*Entamoeba histolytica* [Chapter 323], *Giardia lamblia/intestinalis* [Chapter 322], *Cyclospora cayetanensis*, *Cystoisospora belli*, and *Cryptosporidium parvum/hominis* [Chapter 321]). Common luminal intestinal protists that are frequently detected during stool analyses for ova and parasites (e.g., *Blastocystis hominis, Dientamoeba fragilis, Iodamoeba bütschlii, Entamoeba coli*, and *Endolimax nana)* are thought to be microbes that interact with the intestinal microbiome (Chapter 257) and that any health impacts are likely because of their tendency to induce or serve as markers for dysbiosis, not because they themselves directly cause clinical manifestations.[10]

Cryptosporidiosis (Chapter 321), giardiasis (Chapter 322), and amebiasis (Chapter 323) are discussed in separate chapters. Trichomoniasis and coccidian enteritis are discussed here because they are relatively common infections.

TRICHOMONIASIS

EPIDEMIOLOGY

Trichomonas vaginalis is among the most prevalent of all pathogenic protozoa and is one of the most common sexually transmitted infections (Chapter 264) in the United States and likely worldwide. The World Health Organization estimates that over 150 million incident cases of trichomoniasis occur annually worldwide, thereby making trichomoniasis more common than chlamydia (about 130 million annual cases; Chapter 294) or gonorrhea (about 90 million cases; Chapter 275).[11] In the United States, the Centers for Disease Control and Prevention estimate 6.9 million incident cases per year,[12] with trichomoniasis infection rates seven-fold higher in Black women as compared with non-Hispanic White women. *T. vaginalis* can be passed from infected mothers to their newborn daughters, but it is seldom symptomatic in girls before menarche. The parasite is able to survive for some time in moist environments, and nonvenereal transmission, although uncommon, can occur. Trichomoniasis, like other sexually transmitted diseases, may increase the likelihood of transmission of HIV (Chapter 353).

PATHOBIOLOGY

T. vaginalis, known colloquially as a flagellate, is classified in the phylum Metamonada and class Parabasalia, along with another human pathogen, *Dientamoeba fragilis* (previously thought to be an ameba). The 10- to 15-µm-long trophozoites multiply by longitudinal binary fission on the epithelial surface of the vagina or urethra as well as in vaginal or urethral secretions and are thereby transmitted by sexual intercourse. No cyst form is known, and the trophozoites are easily killed by drying.

The parabasalids are a phylogenetic sister group to the class Eopharingia, which includes *Giardia* spp. The parabasalids lack mitochondria and are anaerobic; they all have a unique cellular organelle, the hydrogenosome, which is a relic of the mitochondrion and serves as the site of anaerobic pyruvate metabolism. A hemolysin is produced and may cause epithelial damage.

CLINICAL MANIFESTATIONS

As many as 50% of *T. vaginalis* infections in women and the majority of infections in men are asymptomatic. Nonetheless, trichomoniasis is one of three common causes of vaginitis or vaginosis, along with bacterial vaginosis and vulvovaginal candidiasis (Chapter 264).[13]

After an incubation period of 5 to 28 days, trichomoniasis is characterized by a thin gray to yellowish green frothy discharge; vulvovaginal erythema; ectocervical erythema or "strawberry cervix," observable mainly by colposcopy; pH higher than 4.5; increased presence of polymorphonuclear leukocytes; and a positive result of the whiff test, in which a foul fishy odor is intensified on addition of potassium hydroxide. In addition to a frothy discharge, vaginitis can be accompanied by vulvovaginal irritation, dyspareunia, abdominal pain, and dysuria. Symptoms may worsen during menstruation. *T. vaginalis* can frequently be isolated from the male partners of infected women and can produce symptomatic urethritis, generally with a scant urethral discharge. Rarely, *T. vaginalis* is associated with epididymitis, superficial penile ulcerations that are usually located under the prepuce, or prostatitis. Pharyngitis also can occur.[14] *T. vaginalis* infection is not associated with a greater risk of prostate cancer.

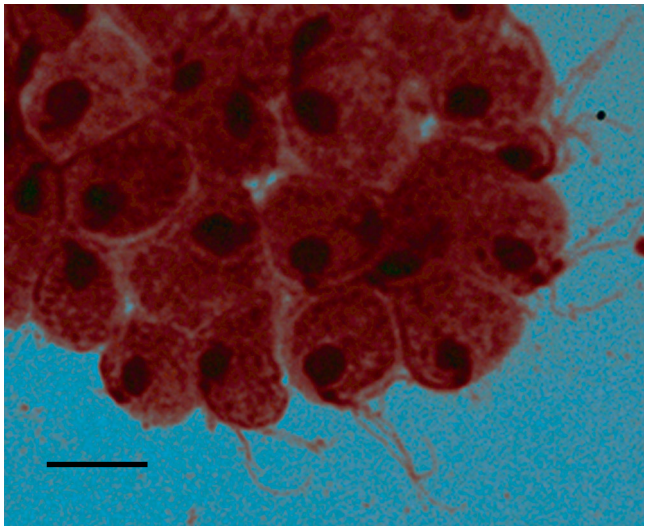

FIGURE 324-3. ***Trichomonas vaginalis*, Giemsa-stained smear of cultivated trophozoites.** (Bright-field microscopy, ×630. Scale bar is 15 µm.)

DIAGNOSIS

All women who seek health care for a vaginal discharge should be specifically tested for evidence of *T. vaginalis* infection. Rapid point-of-care nucleic acid testing of vaginal secretions or a urethral scraping has an excellent sensitivity and specificity[15,16] and is now the test of choice for diagnosis.

T. vaginalis is seen in wet mounts of vaginal secretions in approximately 60% of infected women, thus confirming the diagnosis. Live *T. vaginalis* have a twitching or tumbling motion in wet mounts, and polymorphonuclear leukocytes are usually present. For men, a wet mount of material from a platinum loop scraping of the anterior urethra reveals the organism in approximately 50% of cases. *T. vaginalis* is occasionally identified in Papanicolaou-stained smears; Giemsa stain may also be used (Fig. 324-3).Direct immunofluorescent antibody staining of vaginal secretions is another option. Culture is sensitive and useful if NAAT are not available. *T. vaginalis* is not found in the gastrointestinal tract, and the presence of trichomonads in wet fecal mounts or stained fixed fecal smears (iron hematoxylin or trichrome) most likely represents the commensal *Pentatrichomonas* (formerly *Trichomonas*) *hominis*.

Screening

Screening should be considered for women at high risk for infection (e.g., sex workers) or who are being evaluated for a sexually transmitted disease. HIV-positive women should be screened at least on an annual basis because of a *T. vaginalis*-associated risk for pelvic inflammatory disease (Chapter 264).

TREATMENT

Tinidazole (a single 2-g oral dose in adults) or metronidazole (preferably as 500 mg twice daily for 7 days rather than a single 2-g oral dose)[A1] is the treatment of choice (Chapter 315). Tinidazole is the better tolerated of the two and is more effective as single-dose therapy, which ensures adherence. Both tinidazole and metronidazole have a disulfiram-like effect, and patients who consume alcohol within 24 hours of metronidazole or 72 hours of tinidazole may experience severe nausea, vomiting, and flushing.

Because infection is associated with preterm delivery and low birth weight, pregnant women should be treated for symptomatic trichomoniasis. Metronidazole has low risk during pregnancy, with no reports of teratogenicity or mutagenicity, but tinidazole is not recommended.

Treatment failures with metronidazole and tinidazole are uncommon but well documented. HIV-positive women should be treated for 7 days with 500 mg per day of metronidazole because of frequent recrudescence with the single-dose therapy. Some instances of treatment failure in immune-intact women result from reinfection, others from poor compliance, but some are caused by resistant parasites.[17] A repeated course of metronidazole or tinidazole (2 g orally daily for 7 days) may be tried. If patients remain refractory to appropriate treatment, oral tinidazole (2 g daily for 14 days) should be added to intravaginal tinidazole (500 mg twice daily for 14 days). Clinical improvement also has been documented with intravaginal boric acid (600 mg in gelatin capsules, twice daily for one month).

PREVENTION

Condoms (male or female) reduce risk of acquiring trichomoniasis. Sexual partners should be treated concurrently to prevent reinfection because nearly 20% of male partners are coinfected.

PROGNOSIS

Rare complications include pelvic inflammatory disease (Chapter 264). Infection during gestation may lead to fetal growth retardation. There is no natural or acquired immunity, so reinfection may be common.

COCCIDIAN ENTERITIS

EPIDEMIOLOGY

The coccidia, with 43 genera and more than 1700 recognized species, are well-known veterinary pathogens. *Cyclospora cayetanensis, Cystoisospora belli*, and *Sarcocystis* spp. are causative agents of enteritis in humans. Despite their ubiquity (nearly 200 species have been described), *Sarcocystis* spp have rarely been implicated in cases of human enteritis.

Cyclospora cayetanensis may have both an animal and human reservoir, but *Cystoisospora belli* is thought to be an anthroponosis. Cyclosporiasis is a cause of gastroenteritis in tropical and subtropical areas, with Peru, Mexico, Haiti, Caribbean countries, and Nepal commonly reporting such cases. Outbreaks are invariably traced to contaminated fresh produce, such as raspberries, basil, cilantro, snow peas, or mesclun. Such outbreaks have a distinct seasonality, with most cases presenting during June and July. Cyclosporiasis is commonly diagnosed in international travelers, and large outbreaks have been reported from cruise ships. Cystoisosporiasis has mainly been reported in patients who have the acquired human immunodeficiency syndrome (AIDS)[18] or who are otherwise immunosuppressed. Food or water contaminated with human feces are the source of infection.

Sarcocystis spp are common parasites of mammals, birds, and reptiles.[19] Humans become infected by ingesting undercooked meat or food or water that has been contaminated with animal feces, usually during travel to tropical countries. Humans serve as definitive hosts for *S. suihominis* and *S. hominis*, but when pigs or cattle (intermediate hosts for the two anthroponotic species, respectively) ingest food contaminated with human feces, cysts are formed in their muscles and serve as the source for new human infections.

PATHOBIOLOGY

Oocysts are passed in feces and must sporulate for at least a day (*Cystoisospora belli*) or 5 to 11 days (*Cyclospora cayetanensis*) before attaining infectivity. Sporulated oocysts may persist in the environment for months and retain their infectivity. The infectious dose for *Cyclospora cayetanensis* is estimated to be less than 100 oocysts.

Sporozoites are liberated in the small bowel, where they penetrate enterocytes (for *Cyclospora cayetanensis*, mainly in the jejunum, whereas *Cystoisospora belli* sporozoites may also invade the bile ducts and gallbladder). Both *Cystoisospora belli* and *Cyclospora cayetanensis* have a complicated developmental cycle composed of asexual and sexual stages. The gametes fuse within enterocytes or epithelial cells, and an oocyst wall is deposited around the zygote. This sexual cycle begins about a week after infection, with oocysts sloughing into the bowel lumen and subsequently out of the body through feces. Biopsy specimens from infected patients demonstrate mononuclear and eosinophilic infiltrates in the lamina propria as well as alterations to the morphology of villi.

Humans appear to be intermediate hosts for certain *Sarcocystis* spp. after ingesting undercooked meat containing sporocysts (sarcocysts). Sporozoites are liberated from the sporocysts in the small bowel, enter the vasculature, and form cysts in muscle. The sarcocysts can acutely provoke intense inflammatory infiltrates, thereby resulting in myositis.

CLINICAL MANIFESTATIONS

After an incubation period of approximately 1 week, *Cystoisospora belli* and *Cyclospora cayetanensis* typically produce watery diarrhea, nausea, vomiting, abdominal pain, myalgias, anorexia, and fatigue. Infections may be asymptomatic, and even symptomatic illness is usually self-limited. However, symptoms can be prolonged (10 to 12 weeks) and associated with steatorrhea, flatulence, and substantial weight loss in persons who are immunocompromised, especially patients with AIDS (Chapter 358).[20] *Cystoisospora belli* has been detected in the gallbladder and apparently causes a subclinical infection in immunocompetent individuals, but is associated with acalculous cholecystitis in immunosuppressed patients.

In zoonotic sarcocystosis, parasites migrate to muscle with associated headache, fever, myalgias, weakness, and edema. With *S. nesbitti*, fever and myalgias are the dominant presentation. *Sarcocystis* spp. that appear to be anthroponotic usually colonize the intestinal epithelium but are typically not associated with disease. Rarely, a diarrheal disease may result accompanied by mild fever, chills, and vomiting.

DIAGNOSIS

The diagnosis is confirmed by identifying coccidia in stool samples stained with modified acid-fast or modified safranin preparations or by phase contrast microscopy or bright-field microscopy (using iodine as a contrast medium) of wet mounts (Fig. 324-4). *C. cayetanensis* and *C. belli* may be sensitively detected by fluorescent microscopy of wet mounts. The CDC can help confirm the identification of these enteric protozoa by telediagnosis (sending a digital image of suspicious microscopy findings). PCR is specific and can be sensitive, depending on the mode of DNA extraction. PCR support may be requested from the CDC through state public health departments. *S. nesbitti* and likely other zoonotic *Sarcocystis* spp appear to undergo an aberrant asexual cycle within humans and may

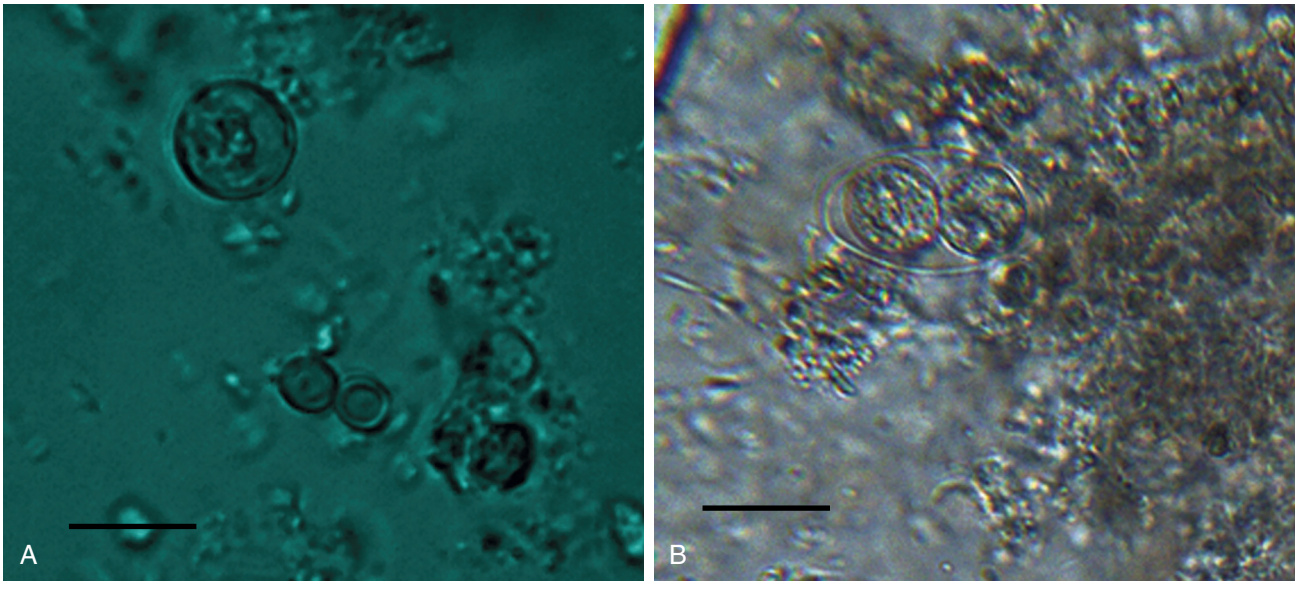

FIGURE 324-4. **Diagnosis of coccidian enteritis. A**, *Cyclospora cayetanensis*, seen on formalin-fixed human feces, unsporulated. (Bright-field microscopy, ×1000 with green contrast filter. Scale bar is 10 μm.) Note the doublet of yeast cells in lower right of the photomicrograph. **B**, *Cystoisospora belli*, seen on formalin-fixed human feces, partially sporulated. (Bright-field microscopy, ×400. Scale bar is 15 μm.)

not produce oocysts to be liberated into the bowel; as a result, diagnosis has required muscle biopsy or demonstration of eosinophilic myositis, sometimes without visualization of the sarcocyst.

TREATMENT

Rehydration is important, as it is for any severe diarrheal disease. *Cystoisospora belli* and *Cyclospora cayetanensis* disease may respond to treatment with 160 mg trimethoprim and 800 mg sulfamethoxazole taken twice daily for 7 to 10 days. HIV-infected patients may require a longer course of therapy.

No specific treatment is established for sarcocystosis, although albendazole (400 mg orally twice daily for 1 month) has been used. Symptomatic relief may be promoted by corticosteroids (e.g., oral prednisolone 100 mg daily for 5 days or intravenous hydrocortisone 100 mg three times a day for 5 days).

PREVENTION

At the community level, preventing the contamination of water and food (mainly vegetables and fruits) by animal or human feces reduces the risk of transmission. Washing vegetables and fruits in water will reduce the potential inoculum but does not eliminate all risk. *Cyclospora cayetanensis* can resist 10 ppm chlorine treatment. The widespread use of trimethoprim-sulfamethoxazole prophylaxis for *Pneumocystis* (Chapter 313) has reduced the incidence of coccidial diarrhea in patients with HIV infection. Sarcocystosis may be prevented by ensuring that meat is well cooked and by freezing meat at -20° C for at least 2 days.

PROGNOSIS

Reactive arthritis (Chapter 254), Guillain-Barré syndrome (Chapter 388), cholecystitis, and cholangitis (Chapter 141) have been reported as complications of coccidian enteritis, mainly in patients with AIDS. Otherwise, treatment appears to eradicate the organism. Whether reinfection may occur is not known. Extraintestinal development of *Cystoisospora belli* and *Cyclospora cayetanensis* suggest the possibility of reinvasion of the bowel with ensuing recrudescence of signs and symptoms, particularly in immunocompromised individuals.

OTHER ENTERIC PROTOZOANS

A number of other protozoa (also called protists) are transmitted by fecal-oral contamination and have been associated with enteric disease (Table 324-1). These enteric protozoa should be considered in the differential diagnosis of patients with persistent diarrhea and abdominal symptoms, particularly patients with a history of recent international travel (Chapter 265).

MICROSPORIDIA

Microsporidia, which have classically been considered to be protozoa but are now known to be obligately intracellular fungi (Cryptomycota), are discussed here because diagnostic parasitology laboratories continue to confirm diagnoses of these agents. Microsporidia are a diverse group of more than 300 species in 160 genera, but only 10 genera have been confirmed as causative agents in human disease. Some of these microsporidia reside in the lumen of the bowel, and others invade and multiply within enterocytes.

Chronic microsporidial diarrhea in HIV patients can contribute to wasting and cachexia. Microsporidia may disseminate to the biliary system and cause cholangitis; dissemination of these organisms in the immunosuppressed may also result in sinusitis or pulmonary disease. Some of the microsporidia cause conjunctivitis or other ocular disease.

OTHER INTESTINAL PROTISTS

Enterocytozoon bieneusi is the second most common "protozoal" cause of diarrhea in HIV patients (after *Cryptosporidium* spp.). *Enterocytozoon bieneusi* spores are shed in the feces and are environmentally resistant. Humans are thought to be the main host but diverse animals have been infected.

Balantidium (Balantioides) coli is the only ciliate known to infect humans.[21] Risk seems to be associated with pigs, which are commonly infected. Transmission is by the fecal-oral route (contaminated food or water). Both trophozoites and cysts are liberated in diarrheal stools, but only the cyst is infectious. Cysts are liberated in the small intestine, and the trophozoites colonize the lumen of the colon. Some trophozoites are invasive and may multiply in the colonic epithelium, where they cause ulceration, inflammation, and malabsorption. Most infection is asymptomatic, but persistent diarrhea and abdominal pain are the main symptoms of disease.

Dientamoeba fragilis and Blastocystis hominis have been associated with diarrhea, but causality remains disputed; indeed, *Blastocystis hominis* has been inadvertently transmitted to patients during fecal transplantation but caused no signs or symptoms.

DIAGNOSIS

A clinical diagnosis is rarely possible because of the nonspecific presentation. Laboratory tests, mainly for ova and parasites in stools, establish the diagnosis. Nucleic acid testing is more sensitive and specific but is not routinely used because primers and probes are not yet available for most of the less common enteric protozoal infections.[22] Expert microscopists are currently required because all of the enteric protozoa may be confused with fecal debris. Laboratory identification is further complicated because coccidian oocysts of animals may be found as pseudoparasites, present because they were ingested with food or water and failed to be digested. Pathogenic protozoa must also be differentiated from commensals such as *Entamoeba coli, Endolimax nana, Iodamoeba bütschlii, Pentatrichomonas hominis, and Chilomastix mesnili*.

TREATMENT

Therapy for microsporidiosis, balantidiasis, and for the signs and symptoms associated with *B. hominis* and *D. fragilis*, if indicated, includes administration of the appropriate antiprotozoal drugs (Table 324-2) (e.g., fumagillin for microsporidia)[23] and rehydration.

TABLE 324-2 TREATMENT OF PROTOZOAN DISEASES OTHER THAN BABESIOSIS

ORGANISM	EPIDEMIOLOGY	MANIFESTATIONS	THERAPY*
Microsporidia† (*Enterocytozoon bieneusi, Encephalitozoon intestinalis, Anncaliia* sp, *Tubulinosema* sp, *Nosema* sp, *Pleistophora* sp, *Vittaforma* sp)	Apparent worldwide distribution	AIDS patients with persistent diarrhea and wasting; self-limited cases in immunocompetent persons	Oral fumagillin (20 mg tid for 2-4 weeks) has been effective for *E. bieneusi*, but it has been associated with thrombocytopenia. Albendazole (400 mg PO bid for 2 weeks) has been effective for *E. intestinalis*. Treatment with HAART may lead to clinical response in HIV-infected patients with microsporidial diarrhea.
Balantidium coli	Primarily an infection of animals, especially pigs, but also affects humans	Asymptomatic or mild and self-resolving; occasionally more severe with abdominal pain, blood, and mucus in stool	Tetracycline (500 mg PO qid for 10 days) Alternative: metronidazole (750 mg PO tid for 5 days) or iodoquinol (650 mg PO tid for 20 days).
Blastocystis hominis	Probably worldwide, including North America; often found concomitantly with *Giardia lamblia*	Pathogenicity is debated; watery diarrhea has been reported but *B. hominis* is common in asymptomatic persons	The need for treatment is debated, but symptomatic improvement has been reported with metronidazole (750 mg PO tid for 10 days); trimethoprim-sulfamethoxazole (160 mg TMP/800 mg SMX PO bid for 7 days); or nitazoxanide (500 mg PO bid for 7 days).
Cyclospora cayetanensis	"Tropical" but imported in produce grown in such sites; animals may serve as reservoir	Acute: watery diarrhea, nausea, vomiting, abdominal pain, myalgias, anorexia, and fatigue. Signs and symptoms may be prolonged in immunocompromised patients and progress to steatorrhea, flatulence, and substantial weight loss.	Rehydration; 160 mg trimethoprim and 800 mg sulfamethoxazole PO bid for 7 to 10 days; immunocompromised patients may require prolonged therapy. Ciprofloxacin 500 mg PO × 7 days is an alternative.

TABLE 324-2 TREATMENT OF PROTOZOAN DISEASES OTHER THAN BABESIOSIS—Cont'd

ORGANISM	EPIDEMIOLOGY	MANIFESTATIONS	THERAPY*
Cystoisospora belli	Global, but most commonly tropical sites; no animal reservoir known	Similar to *C. cayetanensis*	Rehydration; 160 mg trimethoprim and 800 mg sulfamethoxazole orally bid for 7 to 10 days; immunocompromised patients may require prolonged therapy. Pyrimethamine 50-75 mg orally each day for 7-10 days is an alternative to those intolerant of bactrim; leucovorin 10-25 mg orally each day concurrently with the pyrimethamine should be considered to prevent bone marrow suppression
Dientamoeba fragilis	Worldwide distribution; frequently found concomitantly with the pinworm *Enterobius*	Often asymptomatic; diarrhea reported	Paromomycin (25-35 mg/kg body weight per day in 3 doses for 7 days), metronidazole (500-750 mg tid for 10 days), or iodoquinol (650 mg tid for 20 days)

*Based on CDC recommendations, www.cdc.gov/parasites/az/index.html. Accessed July 2, 2021. The dosages and durations are for adults.
†Associated with persistent, severe diarrhea in persons with AIDS.
AIDS = acquired immunodeficiency syndrome; bid = twice daily; HAART = highly active antiretroviral therapy; HIV = human immunodeficiency virus; PO = oral; tid = three times daily.

PROGNOSIS

The diverse presentations of microsporidial diseases (ocular, respiratory, gastrointestinal, biliary, respiratory complications) are influenced by immune status. In immunocompromised patients, symptoms are typically improved by treatment but may relapse when therapy is discontinued. In immune-intact individuals, treatment will usually lead to cure.

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325 CESTODES

A. CLINTON WHITE, JR., AND ENRICO BRUNETTI

DEFINITION

The Pathogens

Cestode parasites are members of the animal kingdom, subphylum Cestoda. The organisms are characterized by several life cycle stages, which typically develop in distinct hosts. The adult stage is the tapeworm, which is acquired by ingestion of uncooked tissues that harbor larval forms. After ingestion, the larvae excyst, and the scolex attaches to the intestines. Segments, termed *proglottids*, develop at the base of the scolex and are displaced from the scolex by new proglottids to form a chain or tapeworm. The host in which the tapeworm develops is termed the *definitive host*. The proglottids, which contain male and female sexual organs, produce large numbers of ova. The proglottids or their ova are shed in stools. Humans are the definitive hosts for a number of different tapeworms, including the *Taenia* species, *Dibothriocephalus* species, and *Hymenolepis nana*. Humans also can be an accidental host for the dog and cat tapeworms of the genus *Dipylidium* (Table 325-1).

The intermediate hosts harbor the larval form of the parasite. Infection follows ingestion of the ova. Under the influence of gastric and intestinal fluids, the ova hatch and release the invasive larvae (oncospheres), which migrate to tissues, forming tissue forms. The forms in tissue vary among organisms and may include the cysticercus (a bladder containing a single invaginated scolex), the coenurus (a bladder with multiple scolices), the hydatid (a cystic structure with a germinal layer, which forms numerous protoscolices), or the plerocercoid (a solid form seen in *Spirometra* species). Humans can harbor the intermediate forms of *Taenia solium* (cysticercosis), *Echinococcus granulosus* group (cystic hydatid disease), *Echinococcus multilocularis* (alveolar hydatid disease), and rarely other organisms (Table 325-2). Humans can serve as both the definitive host and an intermediate host for two species, *T. solium* and *H. nana*. In the case of *T. solium*, humans are the obligate host for the tapeworm stage (pork tapeworm) but can also harbor the cystic form (cysticercosis). In the case of *H. nana*, both stages typically develop in a single person, with the cysticercoid form in the intestinal wall and the tapeworm in the lumen.

INTESTINAL TAPEWORM INFECTIONS *DIBOTHRIOCEPHALUS* SPECIES (FISH TAPEWORMS)

Diphyllobothriid tapeworms are large segmented parasites that are acquired by ingestion of undercooked or pickled fish dishes (sushi, sashimi, ceviche, carpaccio, gefilte fish). The tapeworms develop within a few weeks and can live for more than 10 years. These organisms were formerly termed *Diphyllobotrium* species, but recent changes in taxonomy have now reclassified the organisms into several genera and multiple species,[1] including *Dibothriocephalus latus* (formerly *Diphyllobothrium latum*), *Dibothriocephalus nihonkaiensis*, and *Adenocephalus pacificum*.

EPIDEMIOLOGY AND PATHOBIOLOGY

Diphyllobothriid species are found worldwide, and perhaps 20 million people are thought to be infected. Major foci include Russia, Japan, and South America. The disease was formerly highly endemic in Scandinavia, where it is now rarely diagnosed.

In most cases, infection has little impact on the host. However, one species, *D. latus*, contains vitamin B_{12} receptors on the surface of the tapeworm and can out-compete the host, thereby leading to vitamin B_{12} deficiency (Chapter 150). This manifestation has been described only in Scandinavia.

CLINICAL MANIFESTATIONS AND DIAGNOSIS

In most infected persons, Diphyllobothriid species produce few or no symptoms. Some individuals may complain of gastrointestinal symptoms (abdominal discomfort, nausea, weight loss). The main clinical manifestation is the observation of proglottids being passed in stool. Pernicious anemia (Chapter 150) with symptoms of anemia or peripheral neuropathy may develop with *D. latus* infection. The diagnosis depends on observation of the characteristic operculated eggs in stool.

TREATMENT AND PREVENTION

A single oral dose of praziquantel (5 to 10 mg/kg) is usually adequate for therapy (Table 325-3). Niclosamide can be used as an alternative (2 g [adults] or 50 mg/kg [children] in a single dose chewed and swallowed), but it is not available in the United States. Parasites in fish can be killed by cooking (>56° C, >5 minutes) or freezing (−20° C, 24 hours). Infected fish also may be identified by inspection.

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TABLE 324-2 TREATMENT OF PROTOZOAN DISEASES OTHER THAN BABESIOSIS—Cont'd

ORGANISM	EPIDEMIOLOGY	MANIFESTATIONS	THERAPY*
Cystoisospora belli	Global, but most commonly tropical sites; no animal reservoir known	Similar to *C. cayetanensis*	Rehydration; 160 mg trimethoprim and 800 mg sulfamethoxazole orally bid for 7 to 10 days; immunocompromised patients may require prolonged therapy. Pyrimethamine 50-75 mg orally each day for 7-10 days is an alternative to those intolerant of bactrim; leucovorin 10-25 mg orally each day concurrently with the pyrimethamine should be considered to prevent bone marrow suppression
Dientamoeba fragilis	Worldwide distribution; frequently found concomitantly with the pinworm *Enterobius*	Often asymptomatic; diarrhea reported	Paromomycin (25-35 mg/kg body weight per day in 3 doses for 7 days), metronidazole (500-750 mg tid for 10 days), or iodoquinol (650 mg tid for 20 days)

*Based on CDC recommendations, www.cdc.gov/parasites/az/index.html. Accessed July 2, 2021. The dosages and durations are for adults.
†Associated with persistent, severe diarrhea in persons with AIDS.
AIDS = acquired immunodeficiency syndrome; bid = twice daily; HAART = highly active antiretroviral therapy; HIV = human immunodeficiency virus; PO = oral; tid = three times daily.

PROGNOSIS

The diverse presentations of microsporidial diseases (ocular, respiratory, gastrointestinal, biliary, respiratory complications) are influenced by immune status. In immunocompromised patients, symptoms are typically improved by treatment but may relapse when therapy is discontinued. In immune-intact individuals, treatment will usually lead to cure.

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325 CESTODES

A. CLINTON WHITE, JR., AND ENRICO BRUNETTI

DEFINITION

The Pathogens

Cestode parasites are members of the animal kingdom, subphylum Cestoda. The organisms are characterized by several life cycle stages, which typically develop in distinct hosts. The adult stage is the tapeworm, which is acquired by ingestion of uncooked tissues that harbor larval forms. After ingestion, the larvae excyst, and the scolex attaches to the intestines. Segments, termed *proglottids*, develop at the base of the scolex and are displaced from the scolex by new proglottids to form a chain or tapeworm. The host in which the tapeworm develops is termed the *definitive host*. The proglottids, which contain male and female sexual organs, produce large numbers of ova. The proglottids or their ova are shed in stools. Humans are the definitive hosts for a number of different tapeworms, including the *Taenia* species, *Dibothriocephalus* species, and *Hymenolepis nana*. Humans also can be an accidental host for the dog and cat tapeworms of the genus *Dipylidium* (Table 325-1).

The intermediate hosts harbor the larval form of the parasite. Infection follows ingestion of the ova. Under the influence of gastric and intestinal fluids, the ova hatch and release the invasive larvae (oncospheres), which migrate to tissues, forming tissue forms. The forms in tissue vary among organisms and may include the cysticercus (a bladder containing a single invaginated scolex), the coenurus (a bladder with multiple scolices), the hydatid (a cystic structure with a germinal layer, which forms numerous protoscolices), or the plerocercoid (a solid form seen in *Spirometra* species). Humans can harbor the intermediate forms of *Taenia solium* (cysticercosis), *Echinococcus granulosus* group (cystic hydatid disease), *Echinococcus multilocularis* (alveolar hydatid disease), and rarely other organisms (Table 325-2). Humans can serve as both the definitive host and an intermediate host for two species, *T. solium* and *H. nana*. In the case of *T. solium*, humans are the obligate host for the tapeworm stage (pork tapeworm) but can also harbor the cystic form (cysticercosis). In the case of *H. nana*, both stages typically develop in a single person, with the cysticercoid form in the intestinal wall and the tapeworm in the lumen.

INTESTINAL TAPEWORM INFECTIONS *DIBOTHRIOCEPHALUS* SPECIES (FISH TAPEWORMS)

Diphyllobothriid tapeworms are large segmented parasites that are acquired by ingestion of undercooked or pickled fish dishes (sushi, sashimi, ceviche, carpaccio, gefilte fish). The tapeworms develop within a few weeks and can live for more than 10 years. These organisms were formerly termed *Diphyllobotrium* species, but recent changes in taxonomy have now reclassified the organisms into several genera and multiple species,[1] including *Dibothriocephalus latus* (formerly *Diphyllobothrium latum*), *Dibothriocephalus nihonkaiensis*, and *Adenocephalus pacificum*.

EPIDEMIOLOGY AND PATHOBIOLOGY

Diphyllobothriid species are found worldwide, and perhaps 20 million people are thought to be infected. Major foci include Russia, Japan, and South America. The disease was formerly highly endemic in Scandinavia, where it is now rarely diagnosed.

In most cases, infection has little impact on the host. However, one species, *D. latus*, contains vitamin B_{12} receptors on the surface of the tapeworm and can out-compete the host, thereby leading to vitamin B_{12} deficiency (Chapter 150). This manifestation has been described only in Scandinavia.

CLINICAL MANIFESTATIONS AND DIAGNOSIS

In most infected persons, Diphyllobothriid species produce few or no symptoms. Some individuals may complain of gastrointestinal symptoms (abdominal discomfort, nausea, weight loss). The main clinical manifestation is the observation of proglottids being passed in stool. Pernicious anemia (Chapter 150) with symptoms of anemia or peripheral neuropathy may develop with *D. latus* infection. The diagnosis depends on observation of the characteristic operculated eggs in stool.

TREATMENT AND PREVENTION

A single oral dose of praziquantel (5 to 10 mg/kg) is usually adequate for therapy (Table 325-3). Niclosamide can be used as an alternative (2 g [adults] or 50 mg/kg [children] in a single dose chewed and swallowed), but it is not available in the United States. Parasites in fish can be killed by cooking (>56° C, >5 minutes) or freezing (−20° C, 24 hours). Infected fish also may be identified by inspection.

ABSTRACT

Cestode infections are neglected zoonotic infections that have widespread distributions. Neurocysticercosis is a common cause of neurologic disease in endemic countries. Diagnosis and management vary with the number of parasites and site of infection. Recent advances include the use of combination antiparasitic therapy for multiple parenchymal cysts. Cystic echinococcal disease requires careful staging, and optimal management requires attention to the stage of disease. Intestinal tapeworms are also a common infection worldwide.

KEYWORDS

tapeworm
Dibothriocephalus
Taenia
neurocysticercosis
hydatid disease
Echinococcus

TABLE 325-1 COMMON HUMAN TAPEWORM INFECTIONS

ORGANISM	INTERMEDIATE HOST	COMMON NAME	CLINICAL PRESENTATION	TREATMENT
Dibothriocephalus species	Fish	Fish tapeworm	Passing segments, pernicious anemia	Praziquantel, niclosamide
Hymenolepis nana	Humans	Dwarf tapeworm	Asymptomatic, diarrhea	Praziquantel, niclosamide
Taenia saginata	Cattle	Beef tapeworm	Asymptomatic, passing segments	Praziquantel, niclosamide
Taenia asiatica	Pigs	Asian tapeworm	Asymptomatic, passing worms	Praziquantel, niclosamide
Taenia solium	Pigs	Pork tapeworm	Asymptomatic, passing segments	Praziquantel, niclosamide
Dipylidium caninum	Fleas	Dog tapeworm	Passing segments	Praziquantel, niclosamide

TABLE 325-2 HUMAN LARVAL CESTODE INFECTIONS

ORGANISM	COMMON NAME	ORGANS INVOLVED
Taenia solium	Cysticercosis	Brain, spinal fluid, eye, muscle
Echinococcus granulosus group	Cystic hydatid disease	Liver, lung, other
Echinococcus multilocularis	Alveolar hydatid disease	Liver
Taenia multiceps, Taenia species	Coenurosis	Brain, eyes
Spirometra species	Sparganosis	Subcutaneous tissue, viscera

TABLE 325-3 ORAL THERAPY FOR INTESTINAL TAPEWORM INFECTIONS

	PRAZIQUANTEL	NICLOSAMIDE	NITAZOXANIDE
Dosage			
Adults	5-10 mg/kg for all age groups (15-25 mg/kg for *Hymenolepis nana*)	2 g (4 tablets)	500 mg
Children >34 kg		1.5 g (3 tablets)	200 mg
Children 11-34 kg		1 g (2 tablets)	100 mg
Administration	Taken as a single dose	Taken as a single dose; tablets must be chewed and swallowed	Taken twice a day for 3 days
Side effects	Mild but frequent, including dizziness, myalgias, nausea, vomiting, diarrhea, abdominal pain	Nausea, vomiting, abdominal pain, diarrhea, drowsiness, dizziness, headache, pruritus	
Pregnancy		No known mutagenic effects; considered safe if indicated	

HYMENOLEPIS NANA

Hymenolepis nana is the human dwarf tapeworm. *Hymenolepis diminuta*, a rat tapeworm, can also cause human infection.

EPIDEMIOLOGY AND PATHOBIOLOGY

H. nana is prevalent worldwide, with estimates of at least 50 to 75 million people infected. Infection follows ingestion of ova. The larvae are released, invade, and develop into cysticercoid forms in the intestinal villi. After a few days, the cysticercoids mature, invade the lumen, are transformed into a scolex, and form small tapeworms (up to 5 cm long), which begin producing eggs within 2 to 3 weeks. Autoinfection either in the intestines or by the fecal-oral route can lead to heavy infection.

CLINICAL MANIFESTATIONS AND DIAGNOSIS

Most infections are asymptomatic. However, some children may be infected by hundreds or thousands of worms, which can cause abdominal pain, loose stools, diarrhea, and malabsorption. Diagnosis depends on observation of the characteristic eggs in stool. More than one specimen may be required.

TREATMENT AND PREVENTION

Praziquantel (15 to 25 mg/kg as a single oral dose) is usually effective in treating *H. nana* infection, but it may need to be repeated in heavy infection (see Table 325-3). Nitazoxanide (100 mg by mouth twice daily for 3 days for children 1 to 3 years of age, 200 mg by mouth twice daily for 3 days for children 4 to 11 years of age, and 500 mg by mouth twice daily for 3 days for older children and adults) is a reasonable alternative therapy; efficacy is about 75 to 82%. Niclosamide also can be used as an alternative, but it must be continued for 7 days. Transmission is by the fecal-oral route and can be prevented by improved hygiene. Mass chemotherapy has been used to control infection in some populations.

DIPYLIDIUM CANINUM

Dipylidium caninum is a common tapeworm of dogs and cats. Dogs are infected by ingestion of fleas, which carry the cysticercoid form in their body cavities. The tapeworms can also develop in children who have ingested the fleas. It is widespread worldwide, but human infections are unusual.

CLINICAL MANIFESTATIONS AND DIAGNOSIS

Infection may be asymptomatic. In some cases, the motile proglottids may be noted in stool. The proglottids are similar in size and shape to rice grains. Diagnosis depends on identification of the ova in stool or identification of the proglottids.

TREATMENT AND PREVENTION

There are no controlled trials of treatment for *Dipylidium* infection, but infection is likely to respond to regimens used for other tapeworms (see Table 325-3). The main measure for prevention is treatment of pets for fleas and tapeworms.

TAENIA SAGINATA

Taeniasis refers to infection with the tapeworm form of one of three *Taenia* species. *T. solium* and *Taenia asiatica* are acquired from ingestion of undercooked pork. *Taenia saginata*, called the beef tapeworm, is a common intestinal infection worldwide; cattle, which are the intermediate hosts, harbor the tissue cysticerci in their muscle. Humans, which are the obligate definitive host, harbor the tapeworm form.

EPIDEMIOLOGY AND PATHOBIOLOGY

T. saginata is common worldwide in areas where cattle are raised and human fecal material contaminates the pastures. Approximately 45 to 60 million people are thought to be infected. Infections are found on most continents. Very high rates (>20% of the population) have been noted in east Africa, Bali, and Tibet, but infection is also endemic in the Middle East, the Americas, and Europe. *T. saginata* is also common in other parts of Asia.

T. saginata tapeworms are acquired by ingestion of undercooked beef. The scolex attaches to the intestinal wall, and proglottids form at the base of the scolex. The proglottids gradually enlarge as they are displaced from the scolex by newer proglottids. The chain of proglottids can reach a length of up to 30 feet. The terminal proglottids are shed periodically in the stool. Terminal proglottids are typically off-white, 2 to 3 cm long, 0.5 to 1 cm wide, and 1 to 2 mm thick.

CLINICAL MANIFESTATIONS AND DIAGNOSIS

Mild symptoms (e.g., nausea, abdominal discomfort, anorexia, and pruritus) may be noted. The motile proglottids may cause discomfort as they exit the anus or may be noted in stool.

Ova, which may be noted in stool, are 40 µm in diameter and are surrounded by brown radial striations; the embryos have six hooks. However, the ova of the three *Taenia* species are morphologically indistinguishable. The proglottids can be distinguished from those of *T. solium* by counting the number of uterine branches (≥14 branches suggests *T. saginata*). However, the proglottids of *T. saginata* cannot be readily distinguished from *T. asiatica*.

TREATMENT, PREVENTION, AND PROGNOSIS

Taeniasis can be treated with praziquantel in a single dose (see Table 325-3).[2] Single doses of niclosamide are effective, and nitazoxanide has also been used for *T. saginata*. Taeniasis can be prevented by inspection of beef. Also, cooking to 56° C for 5 minutes or freezing at −20° C for 7 to 10 days destroys the infective larvae. Symptoms are self-limited and resolve with or without treatment.

TAENIA ASIATICA

T. asiatica is a cause of taeniasis in Asia, termed *Asian taeniasis*. Infection is acquired by ingestion of undercooked viscera from pigs. Pigs are infected by ingestion of the ova from tapeworm carriers. *T. asiatica* has been widely described in China, Taiwan, Korea, Indonesia, and Southeast Asia. The clinical manifestations, diagnosis, treatment, and prevention of *T. asiatica* infection are similar to those noted for *T. saginata* infection.

TAENIA SOLIUM

T. solium, also known as the pork tapeworm, can cause both tapeworm infection and larval infection termed *cysticercosis*. *T. solium* tapeworm infections are caused by ingestion of infected undercooked pork.

EPIDEMIOLOGY AND PATHOBIOLOGY

T. solium is common worldwide in areas where pigs are raised and where pigs have access to human fecal material. Only a few million people are thought to harbor the tapeworm form. Pork tapeworm infection is highly endemic in Latin America, sub-Saharan Africa, south, east, and southeast Asia.

T. solium tapeworms are acquired by ingestion of undercooked pork. The scolex evaginates and attaches to the intestinal wall, and proglottids form at the base of the scolex. The proglottids gradually enlarge as they are displaced from the scolex by newer proglottids. The adult worms are often 10 to 20 feet long. Within each mature proglottids, thousands of microscopic ova develop. The terminal proglottids are shed periodically in the stool. The ova are either excreted into the stool or shed with the proglottids. By contrast, ingestion of the ova results in development of larval infection, termed cysticercosis (see later). Thus, the tapeworm carrier poses a risk of self-infection as well as infection to other people. Terminal proglottids are typically off-white, 2 cm long, 0.5 to 1 cm wide, and 1 to 2 mm thick.

CLINICAL MANIFESTATIONS AND DIAGNOSIS

Mild symptoms (e.g., nausea, abdominal discomfort, anorexia, and pruritus) may be noted. The proglottids may be seen in stool. Diagnosis is made by the finding of ova in stool. The ova are 40 µm in diameter, surrounded by brown radial striations, and embryos have six hooks and are morphologically indistinguishable from the other *Taenia* species.

TREATMENT AND PREVENTION

Taeniasis can be treated with praziquantel in a single (5 to 10 mg/kg) dose. However, praziquantel should be used with caution in areas where cysticercosis is prevalent and avoided in patients who have symptoms suggestive of neurocysticercosis because it can precipitate symptoms such as seizures. A single dose of niclosamide (see Table 325-3) is also effective and safe in those with occult cysticercercosis.

Taeniasis can be prevented by inspection of pork. Also, cooking to 56° C for 5 minutes or freezing at −20° C for 7 to 10 days destroys the infective larvae. Current control measures include mass chemotherapy for entire populations as well as chemotherapy and vaccination of pigs (see Cystercercosis below).

TISSUE CESTODE (CYST) INFECTION

Taenia solium (Cysticercosis)

DEFINITION

T. solium is the cause of human larval infection termed cysticercosis.[3] The normal hosts for the larval (cysticercus) forms are pigs. When ingested by pigs, the ova hatch, releasing the invasive larvae (termed *oncospheres*), which invade the intestines, migrate to tissues (especially muscle), and mature into cysticercus forms within the tissues. The cysticercus consists of a thin translucent bladder that contains an invaginated scolex, which is poised to form a tapeworm after being ingested by a human host. The ova are also infectious to people, including the tapeworm carrier. The sticky ova attach to the hands of the tapeworm carrier and are transmitted by the oral route to the carrier or close contacts. After ingestion, the ova can migrate to tissues and form cysts (cysticercosis). The presence of cysticerci in the central nervous system is termed *neurocysticercosis*. Neurocysticercosis includes cysticerci in the brain parenchyma (parenchymal neurocysticercosis) and cysticerci in the ventricles, subarachnoid space, spine, and eye (extraparenchymal neurocysticercosis).

EPIDEMIOLOGY

Cysticercosis is found in all regions of the world where pigs are raised with access to human fecal material. Cysticercosis is widespread in rural areas of Latin America, where more than 10% of the population in endemic villages may have neuroimaging abnormalities consistent with neurocysticercosis. Cysticercosis is also widespread in sub-Saharan Africa, India, Nepal, Southeast Asia, and parts of China. In India, the most common manifestation of neurocysticercosis is seizures and a single enhancing lesion. In the United States, over 2000 cases are diagnosed each year, with most cases occurring in immigrants from pig-raising villages in Mexico and Latin America. However, there are also imported cases from Asia and a few locally acquired infections.

PATHOBIOLOGY

For cysticercosis, the pathogenesis and pathophysiology vary with the location of the cysticerci and the host inflammatory response. Cysticerci in the brain parenchyma initially suppress the host inflammatory response. After a silent period, estimated to be several years, the cysticerci lose the ability to suppress the host inflammatory response, thereby leading to parenchymal inflammation, which typically is manifested by seizures. The cysticerci induce a granulomatous response, which gradually degrades the parasites. In some cases, the lesions resolve. In other cases, however, degradation leads to formation of calcified granulomas. These calcified lesions may intermittently become inflamed (as evidenced by edema or contrast enhancement on magnetic resonance imaging [MRI] scan) and may cause recurrent seizures during a period of years.

CLINICAL MANIFESTATIONS

The clinical manifestations vary with the location of the cysticerci and the associated host response (Fig. 325-1).[4,5] In some cases, cysticerci develop within the ventricles of the brain and can mechanically cause obstructive hydrocephalus. Cysticerci in the subarachnoid space may cause a chronic arachnoiditis, or mass effect. Cysticerci can also develop in the spine (manifested as radiculitis), eye, subcutaneous tissue, and muscle.

All forms of disease may be associated with headaches. In general, parenchymal cysticerci are associated with seizures, whereas ventricular and subarachnoid cysticercosis are associated with hydrocephalus.

Single Enhancing Lesion

A single enhancing lesion is the most common manifestation of cysticercosis in India and the United States. Patients typically present with headache or seizures, which can be focal or focal with secondary generalization. Many will have a single seizure or a few seizures during the period when the cysticercus is degenerating, but the duration of seizures is eventually self-limited in most cases. However, some cases progress to develop calcified lesions, which are a risk factor for recurrent seizures.

Multiple Parenchymal Cysticerci

In patients who have multiple lesions, the main presentation is with seizures, associated with parenchymal inflammation. In contrast to patients who have only a single lesion, seizures are more likely to recur.

Calcified Lesions

Many patients do not present until after they have calcified lesions. Patients with calcified lesions may develop recurrent seizures during a period of years. Some cases are associated with the development of mesotemporal sclerosis and refractory epilepsy (Chapter 372).[6]

Ventricular Cysticerci

The cysticerci typically are manifested by obstructive hydrocephalus.[7] The patient may present with headache, nausea and vomiting, dizziness, altered

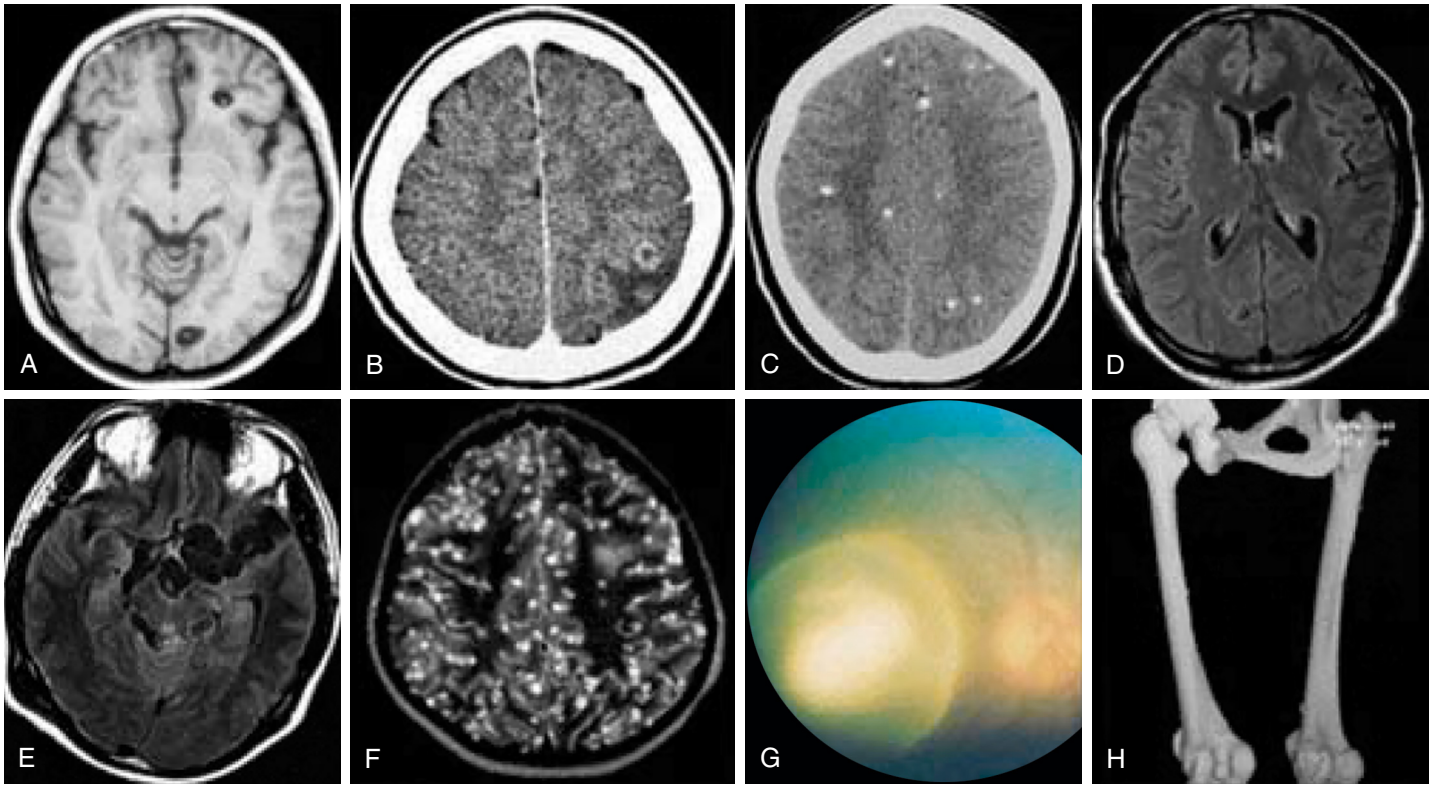

FIGURE 325-1. **Human neurocysticercosis can be classified on the basis of neuroimaging studies. A,** Multiple cystic lesions. **B,** Single enhancing lesion. **C,** Multiple calcifications. **D,** Intraventricular cysticerci. **E,** Subarachnoid cysticerci. **F,** Diffuse infection with cerebral edema, termed cysticercal encephalitis. **G,** Ocular cysticerci. **H,** Diffuse muscle calcifications. (Reprinted from Garcia HH, Del Brutto OH. Neurocysticercosis: updated concepts about an old disease. *Lancet Neurol*. 2005;4:653-661.)

mental status, or papilledema with altered vision. This presentation is a medical emergency and can be fatal if it is not treated.

Subarachnoid Cysticerci

Cysticerci in the basilar cisterns are often accompanied by cysticerci in other locations, including parenchymal cysticerci or calcifications, ventricular cysticerci, and spinal or ocular cysticerci; patients may present with disease attributable to cysticerci at these sites. Cysticerci in the basilar cisterns are particularly prone to cause arachnoiditis. Manifestations of arachnoiditis may include vascular involvement (large- or small-vessel strokes), meningeal signs, or communicating hydrocephalus (headaches, nausea, vomiting, dizziness, and altered mental status).[8] This form of neurocysticercosis is associated with a high fatality rate.[9]

DIAGNOSIS

The major clinical manifestations of neurocysticercosis (e.g., seizures and hydrocephalus) are not specific, and it is difficult to identify the parasites. The main tools used to diagnose neurocysticercosis are neuroimaging studies. Computed tomography (CT) scans are sensitive for identifying parenchymal calcifications, which appear as 2- to 5-mm nodules. CT may also reveal parenchymal cysticerci or obstructive hydrocephalus. Magnetic resonance imaging scans are more sensitive for identification of the cysticerci, especially in the subarachnoid space and ventricles. Three-dimensional sequences such as fast imaging employing steady-state acquisition are particularly effective for identifying ventricular and subarachnoid cysticerci. The cysticerci are typically round and 1 to 2 cm in diameter. The cyst fluid is usually isodense with spinal fluid. In uninflamed cysticerci, the walls may not be visible. However, most cases demonstrate enhancement of the cyst walls or surrounding tissues and associated edema. In some cases, the scolex may be visible as a 1- to 2-mm solid nodule, cylinder, or spiral on the side of the cystic lesions.

Polymerase chain reaction antigen detection assays are sensitive and specific.[10] An immunoblot assay using semipurified membrane glycoproteins is highly specific but has poor sensitivity in patients who have single enhancing lesions or just calcifications.

TREATMENT

Treatment varies with the clinical manifestations and form of infection. Seizures should be treated with antiepileptic drugs (Chapter 372). Phenytoin and carbamazepine are typically used and can control the seizures. In patients who present with hydrocephalus, surgery to re-establish cerebrospinal fluid flow is the critical initial step in management.

The role of antiparasitic drugs (Chapter 315) varies with the form of infection. Parenchymal cystic lesions resolve more rapidly with fewer generalized seizures when patients are treated with both corticosteroids (e.g., dexamethasone 0.1 mg/kg/day in three daily doses) and albendazole (15 mg/kg/day in two daily doses) for 7 to 10 days compared with placebo.[11] Praziquantel (50 to 100 mg/kg/day in three daily doses) can be used as an alternative. Data also suggest using the two drugs in combination (praziquantel 50 mg/kg/day plus albdendazole 15 mg/kg/day) in patients who have more than two parenchymal cysticerci. For a single enhancing lesion, radiologic resolution is slightly more rapid with fewer seizures when patients are treated with corticosteroids plus albendazole at doses noted above.[A1] Higher-dose corticosteroids (e.g., dexamethasone 8 mg/day in divided doses for 28 days followed by a taper) may decrease seizures near the time of antiparasitic treatment, but the differences are not dramatic. Patients who have only calcified lesions do not harbor viable parasites, so the main goal is to control symptoms (e.g., antiepileptic drugs for those with seizures; Chapter 372).

For patients with cysticerci in the ventricles, management usually involves removal by neuroendoscopy for lateral and third ventricular cysticerci and by either microsurgical dissection or neuroendoscopy for fourth ventricular cysticerci. An alternative approach for ventricular cysticerci is placement of a ventriculoperitoneal shunt. Chronic corticosteroids and antiparasitic drugs may decrease the rate of shunt failure (see doses and durations for subarachnoid disease), which usually results from clogging of the shunts by the cysticerci or proteinaceous debris. In the absence of controlled trials, expert opinion supports treatment of subarachnoid cysticercosis with prolonged courses of antiparasitic drugs (e.g., albendazole 15 mg/kg in two divided doses for months), higher doses of albendazole (up to 30 mg/kg/day in 28-day pulses), or combinations of albendazole (15 mg/kg/day in two daily doses) plus praziquantel (50 mg/kg day in three daily doses). Chronic anti-inflammatory medications (e.g., prednisone 1 mg/kg/day for at least the first month) are also critically important.[12] Patients who will be treated with chronic corticosteroids should be screened for *Mycobacterium tuberculosis* (Chapter 299) and *Strongyloides* (Chapter 327)

infections before initiation of therapy. Methotrexate (beginning at 7.5 mg/week, can be increased to a maximum of 20 mg/week) is increasingly recommended as a steroid-sparing agent. Patients with hydrocephalus should be treated by cerebrospinal fluid diversion (e.g., ventriculoperitoneal shunting). Before treatment with antiparasitic drugs, patients should undergo a funduscopic examination. Intraocular parasites may develop brisk inflammatory responses after treatment with antiparasitic drugs. Because this inflammation could lead to blindness, most authorities recommend extraction of the parasites before antiparasitic therapy. However, there are also reports of treatment of intraocular parasites with antiparasitic drugs.

PREVENTION

Although transmission of *T. solium* is potentially preventable, population-wide eradication efforts have proved very difficult. Nevertheless, transmission of *T. solium* infection can be interrupted in highly endemic regions by a program emphasizing mass antiparasitic treatment of the human population with niclosamide (2 g in a single dose) or praziquantel (5 to 10 mg/kg in a single dose), treatment of pigs with oxfendazole, plus vaccination of piglets.[A2,13] Alternatively, prevention can target rings around infected pigs.[A3]

PROGNOSIS

The prognosis varies significantly among the different forms of neurocysticercosis. Parenchymal enhancing lesions and parenchymal cystic lesions will eventually resolve over months to years. Patients who have or develop calcifications are at lifelong risk for recurrent seizures. Patients who have ventricular or subarachnoid disease are at high risk for morbidity and mortality, but can do well with optimal management.

CYSTIC HYDATID DISEASE (*ECHINOCOCCUS GRANULOSUS* GROUP)

DEFINITION

Cystic echinococcosis, also called cystic hydatidosis, is caused by the larval stage of cestodes of a number of different species (*Echinococcus granulosus, Echinococcus candadensis*) and 10 distinct genotypes of the *E. granulosus* complex.[14] In humans, the clinical manifestations range from asymptomatic infection to severe, potentially fatal disease.

EPIDEMIOLOGY AND PATHOBIOLOGY

E. granulosus species occur on all continents and in circumpolar, temperate, subtropical, and tropical zones. The highest prevalence of the parasite is found in parts of Eurasia, Africa,[15] Australia, and South America. Within the endemic zones, the prevalence of the parasites varies from sporadic to high, but only a few countries can be regarded as being free of *E. granulosus*.

It is difficult to determine the true incidence of cystic echinococcosis because of the slow rate of growth and variable clinical presentation. However, mass community-based surveys using portable ultrasound scanners suggest infection rates of up to 6.6% in endemic areas.[16] The great majority of *E. granulosus* isolates from human patients thus far have been of the sheep genotype (G1).

Echinococcal cysts consist of a periparasitic host tissue (pericyst or adventitia), which encompasses the larval endocyst, and the endocyst itself. The endocyst has an outer, acellular laminated layer and an inner, or germinative, layer that gives rise to brood capsules and protoscolices. The cyst is filled with clear fluid, numerous brood capsules, and protoscolices. Some cysts may also harbor daughter cysts of variable size. The protoscolices convert to tapeworms in the canine definitive hosts but can also form new cysts when released in mammalian tissues.

CLINICAL MANIFESTATIONS

The presentation of human cystic echinococcosis is protean.[17,18] Patients may seek medical attention when a large cyst has a mechanical effect on an adjacent organ or rupture of a cyst causes an acute hypersensitivity reaction. However, the cyst is often diagnosed incidentally during ultrasound examination, chest radiography, or body scanning performed for other clinical reasons. The liver, which is the most frequent location of echinococcal cysts, represents approximately 70% of cases (Chapter 137).[19] The lungs are the second most common location. However, cystic echinococcosis can occasionally occur in virtually any other organ.

Common symptoms are upper abdominal discomfort and pain, poor appetite, and a mass in the abdomen. Physical findings are hepatomegaly, a palpable mass on the surface of the liver or other organs, and abdominal distention. Other manifestations include jaundice, colic-like pains, portal hypertension, ascites, and compression of the inferior vena cava. If cysts in the lung rupture into the bronchi, symptoms may include intense cough, a salty taste in the mouth, or vomiting of hydatid material and cystic membranes. Patients may present with a chest mass, chest pain, chronic cough, pneumothorax, eosinophilic pneumonitis, pleural effusion, parasitic lung embolism, hemoptysis, or biliptysis. Cysts in the heart can cause a cardiac mass, pericardial effusion, and embolism. Cysts in the breast must be differentiated from neoplasms. Cysts located in the spine and in the brain can cause serious neurologic symptoms, including paralysis and seizures.

DIAGNOSIS

The diagnosis of cystic echinococcosis is based on imaging methods and on serology, but serology has only a confirmatory role. Routine laboratory tests are nonspecific. Cyst rupture into the biliary tree may cause elevation of the alkaline phosphatase level, sometimes in association with hyperamylasemia and eosinophilia (up to 60%). Unless the cyst has ruptured, eosinophilia is low grade or absent.

Imaging

Modern imaging tools (ultrasound, CT, and, to a lesser extent, MRI) are central to the diagnosis and clinical management of cystic echinococcosis. Ultrasound is the procedure of choice to diagnose asymptomatic cystic echinococcosis.[20] Ultrasound is also useful for longitudinal studies, such as monitoring the response of cysts to treatment and recording cyst growth rate, with a classification system that defines six cyst stages that are assigned to three clinical groups (Fig. 325-2). The active group comprises developing cysts, which may be unilocular (CE1) or multivesicular with daughter cysts (class CE2), and are usually found to be viable. The transitional group (class CE3), which contains cysts that are usually starting to degenerate, includes the "water lily sign" for floating membranes (subclass CE3a) and predominantly solid cysts with daughter cysts (subclass CE3b). The inactive group (classes CE4 and CE5), which exhibits involution and signs of solidification of cystic contents with increasing degrees of calcification, is nearly always found to be nonviable.

CT scanning has the advantage of inspecting any organ, detecting smaller cysts located outside the liver, locating cysts precisely, and sometimes differentiating parasitic from nonparasitic cysts. MRI may have some advantages over CT scanning in the evaluation of postsurgical residual lesions, recurrences, and selected extrahepatic infections, such as cardiac infections. Furthermore, MRI reproduces the ultrasound-defined features of cystic echinococcosis better than CT does. If ultrasound cannot be performed because of a cyst's location or because of patient-specific reasons, MRI with heavily T2-weighted series is preferable to CT. Plain radiographs are used for cysts in the lungs, bone, and muscle, as well as to detect calcified cysts.

Serology

Serologic tests are useful for confirmation of presumptive imaging diagnoses, but their sensitivity varies with the location of the cysts. Hepatic cysts are more likely to elicit an immune response than are pulmonary, brain, or splenic cysts. Serologic test results are usually positive when the endocyst is detached (CE3a) or in an active (CE1, CE2) or transitional (CE3b) stages. Serologic test results are generally negative in patients with inactive cysts (CE4 and CE5). Titers tend to decrease slowly as a cyst becomes inactive (CE4, CE5) and after radical surgery. Titers may remain positive after conservative surgery in which the antigen source (the germinal layer) is not completely removed. Antibody titers usually increase immediately after medical or percutaneous treatments because of the mobilization of the antigen following disruption of the cyst's integrity.

Other Diagnostic Procedures

Polymerase chain reaction (PCR) testing of biopsy specimens can provide rapid and accurate diagnosis.[21] Transhepatic fine-needle aspiration of the cyst under ultrasonographic guidance and anthelmintic coverage with albendazole (typically 10 to 15 mg/kg/day in two daily doses) is useful to differentiate cystic echinococcosis, malignant neoplasms, abscesses, and nonparasitic cysts. The procedure must be carried out in the presence of an anesthesiologist ready to manage the rare but possible anaphylactic reaction.

TREATMENT

The appropriate treatment depends on factors of the individual patient, the characteristics of the cyst, the therapeutic resources available, and the physician's preference. Medical treatment, percutaneous procedures, and a "watch and wait" approach have replaced surgery as the treatment of choice in selected cases.[22]

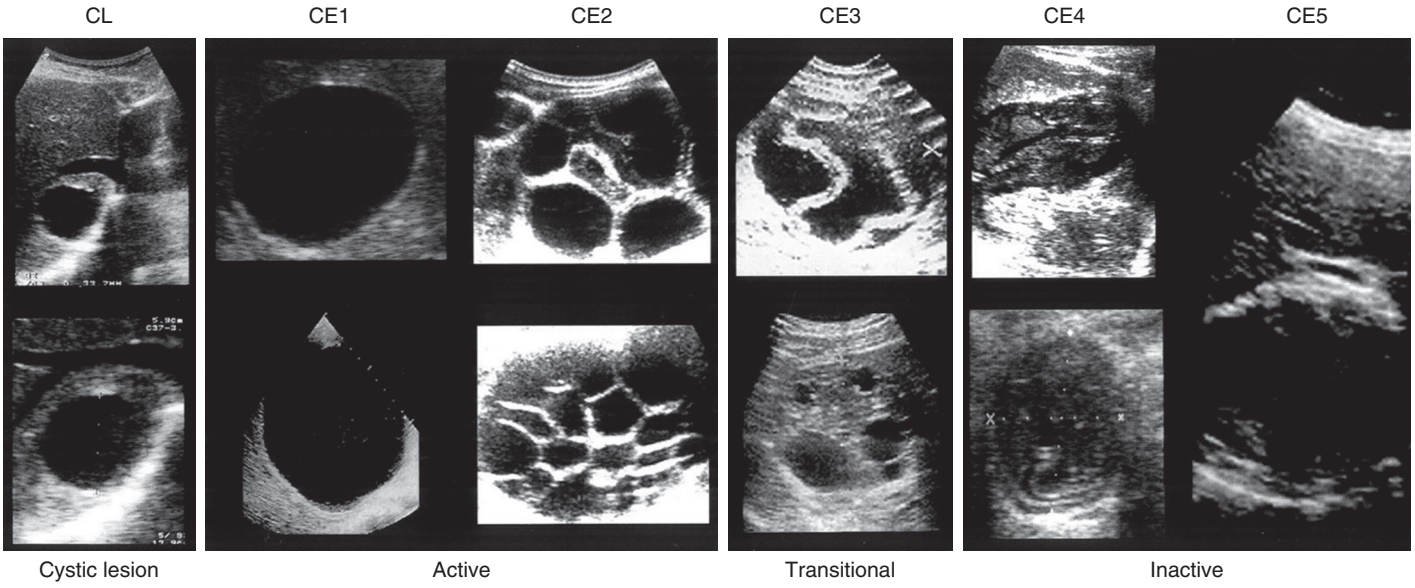

FIGURE 325-2. World Health Organization Informal Working Group on Echinococcosis standardized ultrasound classification of cystic echinococcosis. CL lesions are cystic lesions lacking a distinct wall and may have other diagnoses. CE1 lesions are cystic lesions with a visible wall that may demonstrate protoscolices ("hydatid sand"). CE2 lesions include internal septation. CE3 lesions may be detached from the wall (CE3a, *top row*) or have daughter cysts with internal thickening (CE3b, *bottom row*). CE4 lesions are heterogeneous lesions with degeneration. CE5 lesions show thick calcification.

Watch and Wait

Inactive liver cysts (CE4 and CE5) that are free of complications, such as compression on neighboring organs, are increasingly monitored without being treated.

Chemotherapy for CE1 and CE3a Cysts

Albendazole (Chapter 315), which is the antiparasitic drug of choice for cystic echinococcosis, is administered orally at a dosage of 10 to 15 mg/kg/day; administration should be continuous without treatment interruptions for at least 30 days and continued until resolution.[23] Albendazole induces solidification in small and medium-sized CE1 and CE3a cysts, whereas it has generally little effect on giant (diameter >10 cm) CE1 and CE3a cysts and is ineffective when used alone on CE2 and CE3b cysts.

Adverse effects of benzimidazoles (Chapter 315) include hepatotoxicity, leukopenia, thrombocytopenia, and alopecia. Increases in aminotransferase levels may be due to drug-related efficacy or real drug-related toxicity. Whereas teratogenic risks are theoretical, it is nonetheless good practice to avoid use during pregnancy when possible and to delay treatment until after delivery unless it is absolutely necessary.

Percutaneous Treatments for CE1 and CE3a Cysts

Percutaneous techniques either destroy the germinal layer with scolicidal agents or evacuate the entire endocyst. The most successful method aimed at destroying the germinal layer is PAIR (puncture, aspiration, injection of a scolicidal agent, and reaspiration).[A4] Many modified catheterization techniques can be used for cysts that are difficult to drain, such as multivesiculated cysts or cysts with predominantly solid content and daughter cysts. The risk of lethal anaphylaxis is 0.03%, whereas reversible allergic reactions complicate 1.7% of procedures. Prophylactic administration of albendazole (10 to 15 mg/kg/day) for at least 30 days after puncture should always accompany PAIR. PAIR is generally successful at inducing permanent solidification in CE1 and CE3a cysts, but multivesicular cysts (i.e., CE2 and CE3b) tend to relapse repeatedly after PAIR.

Surgery for Complicated Cysts and CE2 and CE3b Cysts

Surgery remains the main therapy in complicated cysts (i.e., cysts with rupture, biliary fistula, compression of vital structures, superinfection, or hemorrhage), cysts at high risk of rupture, or large cysts with many daughter vesicles that are not suitable for percutaneous treatments.[24] Surgery can be performed as an open procedure, with either radical or conservative techniques, or laparoscopically. In all hepatic cases, perioperative albendazole (10 to 15 mg/kg/day) prophylaxis, from 1 week before surgery until 4 weeks postoperatively, is recommended as a cautionary measure to minimize the risk that fluid spillage will result in secondary echinococcosis from seeding of protoscolices in the abdominal cavity. Some authorities treat with praziquantel (50 mg/kg/day or per week in divided doses) as well. Most experts recommend avoiding preoperative antiparasitic drugs for lung and intracranial disease due to increased risk of spillage.

PROGNOSIS

Follow-up is crucial to evaluate the efficacy of treatment. Long-term follow-up, generally more than 5 years, is required to evaluate local recurrences, which have been reported up to 10 years after apparently successful treatment. When the combination of imaging and serology is inconclusive, fine-needle aspiration should be performed to ascertain the viability of the cystic contents.

ALVEOLAR HYDATID DISEASE (*ECHINOCOCCUS MULTILOCULARIS*)

Alveolar hydatid disease is caused by the tissue forms of *Echinococcus multilocularis*.

EPIDEMIOLOGY AND PATHOBIOLOGY

E. multilocularis is endemic in arctic and alpine areas of the Northern Hemisphere.[25] It is highly endemic in western China, Tibet, and central Asia. *E. multilocularis* also is an important problem in alpine areas and adjacent forested areas of central Europe. Alveolar hydatid disease due to European lineage *E. multilocularis* has recently emerged in western Canada.[26]

In tissues, typically the liver, *E. multilocularis* grows as a budding mass rather than as a large cystic lesion. The tissues resemble lung tissues, hence the name "alveolar." The normal definitive hosts are canines, including wolves and foxes. The normal intermediate hosts are rodents. Humans are accidentally infected by contact with soil containing the ova.

CLINICAL MANIFESTATIONS AND DIAGNOSIS

Human *E. multilocularis* infection almost invariably involves the liver, in which it is manifested as a tumor-like mass that gradually expands during decades. The main symptoms are liver discomfort and swelling. Diagnosis is by demonstration of a characteristic mass on imaging studies (e.g. ultrasound, CT, or MRI), with the etiology confirmed by serologic tests.

TREATMENT AND PROGNOSIS

Surgery is the mainstay of treatment of *E. multilocularis*. When feasible, all infected tissues should be removed. Apparently curative therapy should be followed by a 2-year course of albendazole (10 to 15 mg/kg/day) to decrease the risk of relapse. In some cases, resection is feasible only when it is accompanied by liver transplantation. In cases that are not amenable to surgical resection, prolonged courses of albendazole continued indefinitely can suppress growth of the lesion. After treatment with benzimidazoles, mortality is similar to that of the age- and sex-matched general population.

OTHER LARVAL CESTODE INFECTIONS

Sparganosis is caused by infection with the larval (plerocercoid) stage of *Spirometra mansonoides*. Infection is acquired by ingestion or or exposure of skin to infected meat (e.g., frogs, birds, fish). After infection, plerocercoids develop in the tissues, typically presenting as subcutaneous or central nervous system nodules or occasionally larva migrans symptoms. Treatment usually involves removal of the nodule.

Coenurosis is a rare larval cestode infection caused by human infection with the larval stage of the dog tapeworms *Taenia multiceps* and *Taenia serialis*. In the tissue, the larva forms a cystic lesion that contains multiple scolices (the coenurus). The cystic lesion is usually single and most frequently identified in brain, eye, or soft tissues. Treatment usually involves removal.

Echinococcus oligarthrus and *Echinococcus vogeli* have been associated with polycystic hydatid disease in northern South America. *Taenia crassiceps* has been identified in the eye and in tissues of compromised hosts. *Hymenolepis*-like organisms have also been identified in tissues of AIDS patients.

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326 TREMATODE INFECTIONS

LUIS A. MARCOS

SCHISTOSOMIASIS

DEFINITION

Schistosomiasis, which is classified as a neglected tropical disease, is a parasitic infection caused by the trematode worms (blood flukes) of the genus *Schistosoma*. It has been reported in 78 countries worldwide, with 290 million people infected and nearly 800 million at high risk for infection. Mortality from schistosomiasis is estimated at 13,000 deaths per year, and the burden of disease at 3.3 million disability-adjusted life-years lost per year.

The Pathogen

Six major species of *Schistosoma* affect humans and cause two main forms of schistosomiasis: intestinal (*S. mansoni, S. japonicum, S. intercalatum, S. mekongi,* and *S. guineensis)* and urogenital (*S. haematobium)*. Schistosomas are long, cylindrical worms. The large male (6 to 11 mm × 2 to 4 mm) has a ventral gynecophoric canal in which the female (7 to 28 mm × 1 to 2 mm) is held during copulation.

EPIDEMIOLOGY

Schistosomiasis occurs mainly in areas with poor sanitation in rural, periurban, and urban areas in endemic countries.[1] The World Health Organization has set a goal of eliminating schistosomiasis by 2030, but schistosomiasis is still endemic in 78 countries. *S. mansoni* is found in the Arabian Peninsula, Egypt, Libya, Sudan, most countries in sub-Saharan Africa, Brazil, Suriname, and Venezuela. *S. mansoni* is found in Africa, South America (Brazil, Venezuela, and Surinam), and the Caribbean. *S. haematobium* is found in Africa and the Middle East, *S. japonicum* in China and the Philippines, *S. intercalatum* in West and Central Africa, *S. mekongi* in Southeast Asia, and *S. guineensis* in Cameroon, Equatorial Guinea, Gabon, and Sao Tomé.

The endemicity of schistosomiasis depends on the urban disposal of urine *(S. haematobium)* and feces *(S. mansoni, S. japonicum, S. intercalatum, S. mekongi, S. guineensis),* the presence of suitable snail hosts, and human exposure to cercariae. The freshwater snail intermediate hosts are *Biomphalaria* species in Africa and *Biomphalaria glabrata (Australorbis)* and *Tropicarbis* in South America and the West Indies. In some cases, the endemicity of schistosomiasis may be maintained by animal reservoirs. Such is the case with *S. japonicum,* which infects dogs and cows.[2]

Etiology and Life Cycle

Adult worms live in the mesenteric veins (*S. mansoni, S. japonicum, S. mekongi, S. intercalatum,* and *S. guineensis*) or in the venous plexus around the lower ends of the ureters and the urinary bladder (*S. haematobium*) (Fig. 326-1). In these sites, they start their sexual reproduction by releasing eggs. Once deposited in the host, eggs may stay in the mesenteric vein, be trapped in the intestines, escape to the intestinal lumen, and migrate by portal blood to the liver (*S. mansoni, S. japonicum;* Fig. 326-2). Eggs of *S. haematobium,* which

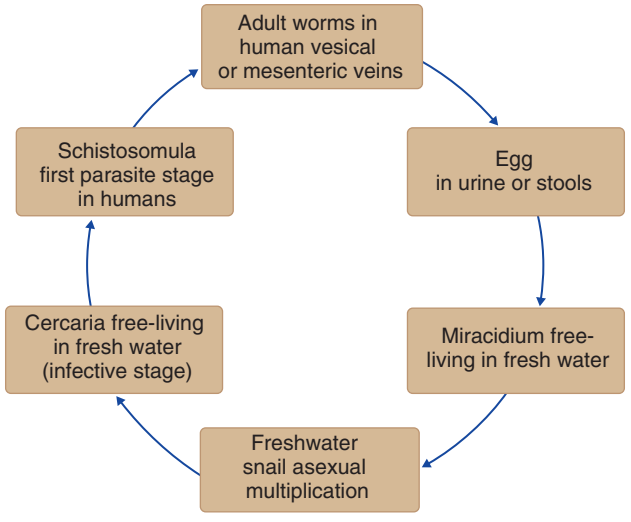

FIGURE 326-1. Schistosome life cycle.

FIGURE 326-2. Egg of *S. mansoni* (120 µm long × 50 µm wide).

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326 TREMATODE INFECTIONS

LUIS A. MARCOS

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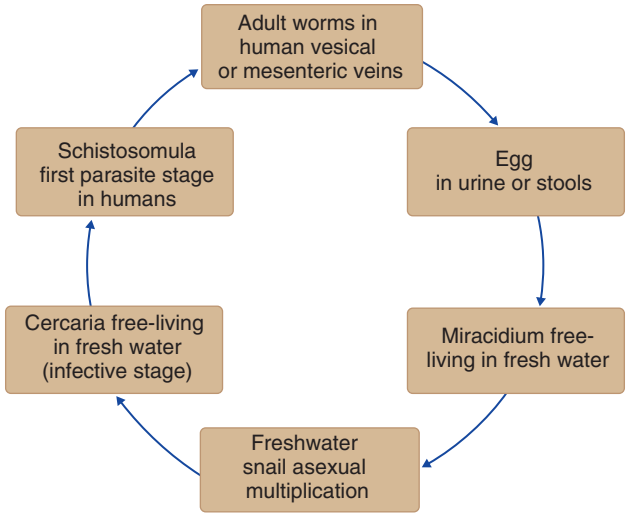

FIGURE 326-1. Schistosome life cycle.

FIGURE 326-2. Egg of *S. mansoni* (120 µm long × 50 µm wide).

ABSTRACT

The main trematode infections comprise of *Schistosoma spp*, liver flukes (*Clonorchis sinensis, Fasciola gigantica , Fasciola hepatica , Opisthorchis felineus ,* and *Opisthorchis viverrini*), lung flukes (*Paragonimus* spp), and intestinal flukes (e.g., *Echinostoma* spp, *Fasciolopsis buski,* and the heterophyids). *Clonorchis, Opisthorchis, Fasciola,* and *Paragonimus* are foodborne trematodes, whereas *Schistosoma* is transmitted by contact with contaminated water. More than 1.5 billion people are at risk for these infections. Each infection has a specific geographic distribution and affects certain organs. Management and treatment depend on the species. Trematode infections are a major public health concern, with enormous worldwide economic impact.

KEYWORDS

Schistosoma
liver flukes
Clonorchis sinensis
Fasciola gigantica
Fasciola hepatica
Opisthorchis felineus
Opisthorchis viverrini
lung flukes
Paragonimus
intestinal flukes
Echinostoma
Fasciolopsis buski
heterophyids

may be trapped in the intestines and bladder, may escape to the intestinal or bladder lumen. After being excreted with feces or urine into fresh water, the eggs hatch and release ciliated motile miracidia that penetrate into snails, which are the intermediate hosts. Following asexual multiplication in the snail, the development of cercariae, which are the infective forms for humans, requires 4 to 7 weeks. After leaving the snails, the cercariae can survive in fresh water for almost 72 hours. When penetration of the skin in the human host occurs, the cercariae lose their tails and change into schistosomula. Schistosomula migrate to the lungs and, in about 6 weeks, mature to adult worms that descend to their final habitat. Viable eggs can be seen in excretions (i.e., stool or urine) 5 to 9 weeks after cercarial penetration. The lifespan of the worms ranges from 5 to 10 years.

PATHOBIOLOGY

Four main pathophysiologic mechanisms have been proposed in acute human schistosomiasis infection: a serum sickness-like hypersensitivity reaction (Chapter 230), which is triggered by the deposition of eggs; a systemic hypersensitivity reaction against the migrating schistosomula and eggs; a toxemic and allergic reaction to the migrating and maturing larvae of *Schistosoma,* but not to eggs; and a more generalized systemic, immunologically mediated, Loeffler-like reaction, not specifically related either to larvae or to adult worms or to eggs.

In chronic schistosomiasis, tissue injury is mediated by egg-induced granulomas and the subsequent appearance of fibrosis. In *S. haematobium,* infected eggs induce the formation of granuloma in the urinary tract. Because the habitat of *S. mansoni, S. japonicum, S. mekongi, S. guineensis,* and *S. intercalatum* worms is the mesenteric blood vessels, the intestines are involved primarily, and egg embolism results in secondary involvement of the liver. Host genetics, immunologic response, and parasite load measured by egg count in the stool are associated with a greater chance for hepatosplenic involvement. Interleukin (IL)-4, IL-13, and IL-17 have been associated with granuloma formation and liver fibrosis. Enzymes and antigens released from eggs sensitize host lymphocytes, which migrate to areas of egg deposition and recruit other cell types, such as macrophages, eosinophils, and fibroblasts. The size of these granulomas and the resulting fibrosis lead to most of the characteristic chronic fibro-obstructive lesions in schistosomiasis. In the liver, the granulomas result in perisinusoidal obstruction of portal blood flow, portal hypertension, splenomegaly, esophageal varices, and portosystemic collateral circulation. Liver cell perfusion is not reduced; consequently, liver function test results remain normal for a long time.

In schistosome-infected populations, the intensity of infection increases during the first two decades of life as children accumulate worms, and then declines. Although exposure decreases with age, the lower intensities of infection in older individuals are due in part to acquired resistance. In the *S. haematobium*–infected population, immunoglobulin (Ig) E increases progressively with age, and IgE antibodies directed against adult worm antigens are associated with subsequent low intensities of reinfection. Similar associations between high IgE levels or a high IgE/IgG4 ratio and resistance to reinfection have been found among Brazilian and Kenyan subjects exposed to *S. mansoni*. In contrast, susceptibility to reinfection has been associated with IgG4, which may serve as blocking antibody that inhibits the action of IgE. A major codominant gene, called *SM1,* in the human host's genome controls the intensity of infection by *S. mansoni*.

Modulation of the immune response is a characteristic of chronic schistosomiasis, and *S. mansoni* antigens downmodulate the immune response by increasing their production of regulatory cytokines such as IL-10 and the frequency of regulatory T cells. *S. mansoni* infection attenuates the clinical manifestations of type 1 diabetes and experimental autoimmune encephalitis in mice. In humans, *S. mansoni* attenuates the clinical manifestations of asthma and is inversely associated with the development of myelopathy related to human T-cell leukemia virus type 1 (HTLV-1) infection (Chapter 360). *S. mansoni* infection may impair immunologic response to vaccines and change manifestations of other infectious diseases.

CLINICAL MANIFESTATIONS

Clinical manifestations of schistosomiasis are divided into schistosome dermatitis, acute schistosomiasis, and chronic schistosomiasis. Schistosome dermatitis, or swimmer's itch, is seen mainly when avian cercariae penetrate the skin and are destroyed. Schistosome dermatitis is a sensitization phenomenon that occurs in previously exposed persons. The cercariae evoke an acute inflammatory response with edema, early infiltration of neutrophils and lymphocytes, and later invasion of eosinophils. A pruritic papular rash occurs within 24 hours after the penetration of cercariae and reaches maximal intensity in 2 to 3 days.[3]

Acute schistosomiasis occurs usually 20 to 50 days after primary exposure. Though asymptomatic in endemic areas, acute schistosomiasis is becoming a frequent and major clinical problem when nonimmune individuals from urban regions are exposed for the first time to a heavy infection in an endemic area. The clinical syndrome (i.e., fever, chills, liver and spleen enlargement, and marked eosinophilia) originally described for *S. japonicum* infection, and still common for this species, is increasingly being diagnosed in Brazil and Africa in individuals with *S. mansoni* infection. Malaise, diarrhea, weight loss, cough, dyspnea, chest pain, restrictive respiratory insufficiency, and pericarditis are also documented in this phase. Acute disease is not observed in individuals who live in endemic areas for schistosomiasis.

S. mansoni and *S. japonicum*

In chronic schistosomiasis, intestinal involvement commonly manifests with abdominal pain, irregular bowel movements, and blood in the stool. Hepatosplenic involvement is the most important cause of morbidity with *S. mansoni* and *S. japonicum*.[4] Patients may remain asymptomatic until the manifestation of hepatic fibrosis and portal hypertension develops. Bleeding esophageal or gastric varices may cause hematemesis. Anemia and decreasing levels of serum albumin are observed. Some patients develop severe hepatosplenic disease, with jaundice, ascites, and hepatic failure.

Concomitant infection by *Salmonella* species (Chapter 284) and, to a lesser extent, other gram-negative bacteria with *S. mansoni* or *S. haematobium* leads to a picture of prolonged fever, hepatosplenomegaly, and mild leukocytosis with eosinophilia. Coinfection with *S. mansoni* and hepatitis B or C virus (Chapters 134 and 135) exacerbates liver pathology.

Glomerulonephritis (Chapter 107) and hypersplenism (Chapter 154) are other complications associated with hepatosplenic schistosomiasis. Pulmonary hypertension (Chapter 69),[5] which is increasingly recognized with the use of more advanced diagnostic technology, is detected in about 10% of patients with liver fibrosis. In countries endemic for *S. mansoni,* up to 30% of all cases of pulmonary hypertension are due to schistosomiasis.

Cerebral schistosomiasis, which is observed in patients with *S. japonicum* infection, may occur as early as 6 weeks after infection, and its most common manifestation is focal seizures. Signs and symptoms of generalized encephalitis may occur. In *S. mansoni* infection, neurologic involvement is mainly characterized by transverse myelitis.

An association between *S. mansoni* or *S. haematobium* and human immunodeficiency virus (HIV) infection has been documented in areas where both infections are present. Although the immune response of patients with schistosomiasis is altered by HIV, it has not been reported to be associated with any clear changes in the degree of infection or severity of manifestations of schistosomiasis.

S. haematobium

In *S. haematobium* infection, the main organ system involved is the urinary tract.[6] The acute granulomatous response to parasite eggs in the early stages causes urinary tract disease, such as urethral ulceration and bladder polyposis. In chronic disease, usually in older patients, granulomas at the lower ends of the ureters obstruct urinary flow and may cause hydroureter and hydronephrosis. Bladder fibrosis and calcification are also seen in this phase. Up to 70% of infected individuals have hematuria, dysuria, or urinary frequency. Radiologic findings include hydronephrosis, hydroureter, ureteral strictures, dilation or distortion, ureteral calcifications, ureterolithiasis, calcified bladder, polyps, reduction in bladder capacity, irregular contraction of the bladder wall, or a dilated bladder because of bladder neck fibrosis. An increased incidence of squamous cell urothelial carcinoma of the bladder (Chapter 182) is seen in endemic areas of *S. haematobium* infection. Female genital schistosomiasis can lead to infertility and a higher risk of HIV transmission. *S. haematobium* eggs have occasionally been found in the lungs, with subsequent focal pulmonary arteritis and pulmonary hypertension.

DIAGNOSIS

Epidemiologic risk factors such as a history of contact with contaminated water and appropriate clinical manifestations are key to raise suspicion of schistosomiasis. About 50% of infected patients have eosinophilia. Liver enzymes and

TABLE 326-1 DIAGNOSIS OF SCHISTOSOMIASIS

SCHISTOSOME	EGGS	DIAGNOSIS
S. haematobium	Mainly found in urine but may be found in stools or rectal biopsy specimens Eggs: 143 × 50 µm; spindle shaped: rounded anterior, conical posterior, tapering to a terminal delicate spine	PCR in serum: 90% of patients in acute infection are positive Obtain urine sample at midday (when eggs are excreted); more than one sample may be needed PCR in urine is more sensitive than microscopy and is highly specific Examine urine directly or by filtering 10 mL of urine through a nucleopore membrane Urine-circulating antigen test for diagnosis of light infection and serologic test to diagnose early or light infection Rectal biopsy in suspected cases with negative urine for egg and for circulating cathodic antigen
S. mansoni	Found in stool eggs: 155 × 66 µm; oval with lateral, long spine	PCR in serum: 90% of patients in acute infection are positive Examine stool for eggs PCR of stool is more sensitive than microscopy and is highly specific Use the Kato-Katz thick smear method for quantification purposes Urine-circulating cathodic antigen test, serologic testing, or rectal biopsy to diagnose stool-negative cases, particularly in lightly infected patients
S. japonicum	Found in stool Eggs: 89 × 67 µm; oval or rounded with a lateral, short, sometimes curved spine	Examine stool for eggs Kato-Katz thick smear (for quantitative assessment) Urine-circulating cathodic antigen test, serologic test or rectal biopsy for those with light infections, especially with less common manifestations (e.g., cerebral schistosomiasis) Nested PCR is promising for diagnosis in endemic areas
S. mekongi	Found in stool Eggs: 60 × 32 µm; smaller than eggs of *S. japonicum*	Examine stool for eggs
S. intercalatum	Found in stool Eggs: 180 × 65 µm; terminal spine	Examine stool for eggs

PCR = polymerase chain reaction.

the serum bilirubin level are usually normal or mildly elevated. Anemia and thrombocytopenia may occur in severe chronic schistosomiasis. Hematuria is common in *S. haematobium*.

Molecular techniques to detect schistosoma DNA in stool, urine, and blood specimens have a high sensitivity for diagnosing acute infection and are very useful in returning travelers and in individuals who may have light infection.[7] Quantification of circulating cathodic antigen (CCA) in urine also has a high sensitivity and can monitor the efficacy of antischistosome chemotherapy. A significant decrease in antigen levels is observed as early as 10 days after therapy. Serologic assays can detect antibodies to *S. mansoni* antigens but cannot distinguish between active and past exposure. As a result, they can be very useful for diagnostic purposes in travelers with suspected acute infection[8] but not for residents in endemic areas.

Despite the appeal of these molecular and immunologic tests, examination of the stool for eggs is an essential part of the evaluation, and a definitive diagnosis still often requires finding schistosome eggs in stool, urine, or a biopsy specimen, usually from the rectum (Table 326-1).[9,10] Because schistosome eggs may be few, concentration by sedimentation should be performed. All eggs from stools, urine, or tissues should be examined under high power to determine their viability by visualizing the activity of cilia of the excretory flame cells of the enclosed miracidium. Dead eggs may persist for a long time after successful therapy or natural death of the worms. The presence of only dead eggs does not necessarily require treatment. Because the intensity of infection is associated with morbidity, quantitative techniques are recommended. For *S. mansoni* and *S. japonicum*, the Kato-Katz thick smear method is used. In patients with chronic *S. mansoni* and *S. japonicum* infection and liver disease, the diagnosis is sometimes made by documentation of eggs in liver specimens. Ultrasonography allows determination of the degree of liver fibrosis. *S. mekongi* and *S. intercalatum* infections are diagnosed by examining the stool for eggs.

Urine examination for *S. haematobium* eggs can be performed by direct or concentration methods. Samples should be obtained at midday, when excretion of eggs is maximal. Assessment of urinary tract pathology by ultrasonography is recommended after the diagnosis is confirmed because of the increased incidence of carcinoma of the bladder (Chapter 182).

TREATMENT

Praziquantel, which is a pyrazinoisoquinoline derivative, is the drug of choice for the treatment of schistosomiasis. The standard recommended treatment is a single dose of praziquantel, 40 mg/kg, for *S. mansoni, S. haematobium*, and *S. intercalatum* infection. In *S. japonicum* infection, a total dose of 60 mg/kg is recommended, split into two or three doses in a single day. For *S. haematobium*, overall cure rates are similar with single-dose (40 mg/kg) and double-treatment (40 mg/kg with 2-week interval) praziquantel, but double treatment significantly reduces the intensity of infection and microhematuria, so it may reduce morbidity. *S. mekongi* may require two treatments at 60 mg/kg body weight.

Oxamniquine (40 mg/kg) is also effective as an alternative to praziquantel. Combination therapies, such as single-dose praziquantel plus dihydroartemisinin piperaquine (40 mg/320 mg), may be even more efficacious for the treatment of intestinal schistosomiasis.[A1]

The most common adverse events observed with praziquantel or oxamniquine are related to the gastrointestinal tract: abdominal pain or discomfort, nausea, vomiting, anorexia, and diarrhea. These symptoms can be observed in up to 50% of patients but are usually well tolerated.

PREVENTION

Mass drug administration with praziquantel[11] has been used as the mainstay of programs for the control and prevention of schistosomiasis morbidity,[A2] with school-based programs showing the most promising results.[A3,A4] However, this approach alone is not sufficient to eliminate or interrupt transmission of this disease. The development of anti-*Schistosoma* vaccines is necessary. Additional measures such as provision of clean water, use of molluscicides, adequate sanitation, and improvement of socioeconomic conditions also should be implemented to control the disease.[12]

PROGNOSIS

With the recommended dosages of praziquantel, recorded cure rates are 75 to 85% for *S. haematobium*, 63 to 85% for *S. mansoni*, 80 to 90% for *S. japonicum*, 89% for *S. intercalatum*, and 60 to 80% for double infections with *S. mansoni* and *S. haematobium*.[13] A decrease in the efficacy of praziquantel has been observed in patients coinfected with HTLV-1 (Chapter 360). High-risk groups for the development of liver fibrosis despite treatment include men, older individuals, and fishermen.[14]

LIVER, INTESTINAL, AND LUNG FLUKES

LIVER FLUKES

The geographic distribution, clinical manifestations, diagnosis, and treatment of liver, intestinal, and lung fluke infections are summarized in Table 326-2.[15]

FASCIOLIASIS

Fascioliasis is a zoonosis caused by *Fasciola hepatica* (adult: 30 × 13 mm) or *F. gigantica* (adult: 75 × 20 mm). The most common natural hosts are cattle, sheep, and goats.

TABLE 326-2 CLINICAL MANIFESTATIONS, DIAGNOSIS, AND TREATMENT OF LIVER, INTESTINAL, AND LUNG FLUKE INFECTIONS IN HUMANS

FLUKE, NUMBER OF PEOPLE INFECTED, AND GEOGRAPHIC DISTRIBUTION	CLINICAL MANIFESTATIONS OF ACUTE AND CHRONIC PHASES	DIAGNOSIS*	TREATMENT†
LIVER FLUKES			
Fasciola spp 17 million Cosmopolitan	Acute ‡Hepatomegaly, eosinophilia, fever, abdominal pain, metastatic-like lesions on liver CT Chronic §Biliary obstruction, gallstones, fibrosis, cholangitis	Stools are negative Serology (Fas2 ELISA) Eggs in stool Fas2 ELISA	TCZ
Opisthorchis spp 11.2 million Asia	‡Fever, malaise, arthralgia, lymphadenopathy, and rash §Jaundice, cholangitis, cholangiocarcinoma	Serology Eggs in stool	PZQ
Clonorchis spp 35 million Asia, Eastern Europe	‡Fever, rash, malaise, and RUQ abdominal discomfort §Choledocholithiasis, cholangitis, cholecystitis, liver abscess, and possible cholangiocarcinoma	Serology Eggs in stool	PZQ
INTESTINAL FLUKES			
Fasciolopsis buski and others¶ 50 million Asia and North Africa	Small bowel inflammation, ulceration, mucus secretion, protein-losing enteropathy, malabsorption	Eggs in stool	PZQ
LUNG FLUKE			
Paragonimus spp 23 million Asia, Americas, Africa	‡Abdominal pain, pleuritic pain, cough, eosinophilia §Hemoptysis, cough, chronic pleural effusions, pulmonary cysts	Abscess serology Eggs in sputum or stool	PZQ or TCZ

*For egg morphology and size, refer to text in the Diagnosis section.
†For drug regimens, refer to text in the Treatment section.
‡Acute.
§Chronic. For chronic infection, a sedimentation technique is preferred (suggested technique: rapid sedimentation technique or Kato-Katz technique).
¶Diagnosis and treatment also apply for other intestinal flukes.
CT = computed tomography; ELISA = enzyme-linked immunosorbent assay; PZQ = praziquantel; RUQ = right upper quadrant; spp = species; TCZ = triclabendazole.

EPIDEMIOLOGY

The infection is distributed globally. An estimated 2.6 million people are infected by this parasite, mainly in South America, Africa, and Asia. The highest prevalence rates (>60%) have been reported in Peru and Bolivia.

PATHOBIOLOGY AND CLINICAL MANIFESTATIONS

The life cycle begins when the parasite's eggs in stool are deposited in water; miracidia appear, develop, and hatch in 9 to 14 days and invade many species of freshwater snails (*Lymnaea* spp), in which they multiply as sporozoites, rediae, and cercariae during a period of 4 to 7 weeks. The parasite then leaves as free-swimming cercaria that subsequently attach to watercress, water lettuce, alfalfa, mint, parsley, or khat. The main source of infection is consumption of raw vegetables or water contaminated with metacercariae. Women have a higher incidence of the disease, with more severe infections and complications than seen in men.

After consumption of contaminated vegetables, the larvae excyst in the duodenum and then migrate through the bowel wall to the liver through the peritoneal cavity. In 4 weeks they reach the liver, penetrate the capsule, and cause inflammation and pain. Acute diarrhea of 2 to 5 days' duration may occur before liver invasion. During their migration through the liver, the ongoing inflammatory process is accompanied by fever, pain, and eosinophilia. In a few cases, intense hemorrhage may manifest as a subcapsular liver hematoma. Computed tomography (CT), magnetic resonance imaging, or ultrasonography can detect these initial lesions. Migration of the parasite leaves a track that can be observed in histologic sections or by imaging (CT). The flukes sometimes die and leave cavities filled with necrotic debris, which is eventually replaced by scar tissue that becomes calcified. After 3 to 5 months of migration in the liver, the juvenile larvae reach the bile ducts.

During this invasive, migratory, or acute phase the clinical manifestations are prolonged fever, hepatomegaly, abdominal pain, and eosinophilia. Multiple hypodense lesions are seen on CT, similar to metastases, but they change in position, attenuation, and shape in time because the parasites are still migrating. Acute fascioliasis is clinically similar to acute cholecystitis (Chapter 141) but with the addition of significant eosinophilia. Hyperbilirubinemia is notably absent in this phase. Other manifestations are anorexia, weight loss, nausea, vomiting, cough, diarrhea, urticaria, lymphadenopathy, and arthralgias. Occasionally, the juvenile larvae reach other ectopic or extrahepatic locations, such as subcutaneous tissue, the pancreas, eye, brain, and stomach wall. In endemic areas, the acute phase manifestations can be superimposed on chronic infection.

Arrival of the parasite in the bile ducts marks the beginning of the chronic phase. Mature flukes consume hepatocytes and duct epithelium and reside for years in the hepatic and common bile ducts and sometimes in the gallbladder. In this chronic phase, the liver contains large dilated, thick-walled, and calcareous bile ducts with yellowish-brown bile. The bile ducts have a thickened hyperplastic wall with marked fibrosis. Symptoms usually reflect biliary obstruction with colicky pain in the right upper quadrant and epigastric area. Eosinophilia is absent in half of the chronic cases. Bacterial superinfection of these cysts and consequent cholangitis can develop. Other complications are hemobilia, liver abscess,[16] and liver fibrosis. The serum alkaline phosphatase level is commonly elevated because of biliary obstruction, which sometimes requires surgical intervention. On imaging, the initial lesions often may be confused with hepatic metastases. Other findings on CT are hepatomegaly, tracklike hypodense lesions in subcapsular locations, multiple hypodense nodular areas (abscess-like lesions), or low-density, serpiginous, tortuous, tunnel-like branching lesions ranging from 2 to 10 mm. CT also can show subcapsular hematoma, enhancement of the Glisson capsule, necrotic granuloma, and cystic calcifications.

After maturation, the adult flukes start laying eggs, which are passed from the sphincter of Oddi to the intestines and evacuated to the environment along with stool. Adult parasites can live in the bile ducts for up to 13 years, where they can cause biliary obstruction, with adult parasites visible on endoscopic retrograde cholangiopancreatography (ERCP).

CLONORCHIASIS AND OPISTHORCHIASIS

Clonorchiasis is caused by *Clonorchis sinensis*, also called the Chinese or oriental liver fluke (adult: 10 to 25 mm × 3 to 5 mm). Opisthorchiasis is caused by *Opisthorchis viverrini* (adult: 5 to 10 mm × 1 to 2 mm) and *Opisthorchis felineus* (adult: 7 to 12 mm × 2 to 3 mm). The most common natural hosts are dogs, cats, pigs, and some small wild mammals.

EPIDEMIOLOGY

The global estimate for the number of people infected with both infections is 46.2 million, 35 million for *C. sinensis* (15 million in China), 10 million for *O. viverrini* (8 million in Thailand and 2 million in Laos), and 1.2 for *O. felineus*. About 600 million and 80 million people are at risk of infection with *Clonorchis* and *Opisthorchis,* respectively. Both infections are endemic in the Far East, Southeast Asia, and Eastern Europe. *C. sinensis* is endemic in northeast China, southern Korea, Japan, Taiwan, northern Vietnam, and the far eastern part of Russia, whereas *O. viverrini* is endemic in Laos, Thailand, Vietnam, and Cambodia. *O. felineus* infection is prevalent in Russia, Ukraine, and Kazakhstan.

PATHOBIOLOGY

The life cycle starts when the adult worm deposits fully developed eggs, which are then passed to the environment through feces. Eggs hatch in water, and the miracidia infect their first intermediate host, which is a freshwater snail (*Bithynia* spp or *Parafossarulus* spp), where they transform into sporocysts, rediae, and cercariae. Cercariae are released from the snail and then penetrate freshwater fish, which are the second intermediate host (*Cyclocheilichthys* spp, *Puntius* spp, *Hampala dispar*); the cercariae encyst as metacercariae in the muscles or under the scales. In general, the infection is acquired by eating raw or uncooked cyprinoid fish products in rural areas or dishes such as *koi-pla,* which is a salad made with raw fish. The metacercariae pass through the stomach and reach the small intestine unharmed. Then, through the ampulla of Vater, they reach the bile ducts, where they mature into adult worms within 4 weeks and deposit yellow, operculated eggs. The parasites may live for up to 45 years in a human host.

The pathologic and clinical consequences of these flukes are related to the intensity and duration of cumulative infestations. In general, they cause inflammation around the biliary tree, severe hyperplasia of epithelial cells, metaplasia of mucin-producing cells in the mucosa, and progressive periductal fibrosis. There are clear associations between *O. viverrini* infection and cholangiocarcinoma. Several *N*-nitroso compounds and their precursors occur at low levels in fermented food, such as preserved mud fish paste *(plara),* a condiment that is a ubiquitous component of the cuisine of northeastern Thailand and Laos. Even after treatment, the advanced periductal fibrosis that may predispose to cholangiocarcinoma may persist in one third of the patients.[17]

CLINICAL MANIFESTATIONS

Acute clonorchiasis infection caused by *C. sinensis* is usually asymptomatic, but some patients may have fever, rash, malaise, and right upper quadrant abdominal discomfort. Chronic infections may be manifested as recurrent pyogenic cholangitis, cholecystitis, obstructive jaundice, hepatomegaly, cholecystitis, multiple hepatic tumors, cholelithiasis, or pancreatitis.[18] In chronic carriers with a high load of parasites, cholangiocarcinoma may develop, especially in Thailand.

Acute opisthorchiasis infection caused by *O. viverrini* can cause right upper quadrant abdominal pain, flatulence, fatigue, and a hot sensation over the abdomen. In the chronic phase, mild hepatomegaly occurs, mainly in more heavily infected patients (egg counts >10,000/g). Jaundice and splenomegaly are not observed. Intrahepatic duct stones and recurrent suppurative cholangitis are common. Whenever jaundice and ascending cholangitis are detected, fluke-related cholangiocarcinoma should be suspected.

In opisthorchiasis caused by *O. felineus,* infestation usually follows the consumption of raw, slightly salted, and frozen fish ("stroganina"). Acute symptoms occur 2 to 4 weeks later, including high-grade fever, nausea, vomiting, abdominal pain, malaise, arthralgias, lymphadenopathy, and rash. Peripheral eosinophilia is a common finding, especially during the initial 2 to 6 weeks of the infection, together with raised liver enzyme levels. In chronic infection, the eosinophilia is usually milder. Patients may have suppurative cholangitis and liver abscesses because of biliary obstruction. Ultrasonography or CT demonstrates the pathologic changes in the liver, including intrahepatic duct dilation and periductal changes.

INTESTINAL FLUKES

The most common human intestinal trematode is *Fasciolopsis buski* (adult: 20 to 75 mm × 8 to 20 mm), which is found mainly in the central and southeast parts of Asia. *F. buski* is a common parasite in pigs. Other intestinal flukes are *Heterophyes* (adult: 1 to 2 mm in length), *Metagonimus yokogawai* (adult: 1 to 2.5 mm × 0.4 to 0.75 mm), and *Echinostoma* spp (adult: 6.5 × 1 to 2 mm).

EPIDEMIOLOGY

More than 50 species of intestinal trematodes from the Far East, Middle East, and North Africa have been reported to cause human infection. *H. heterophyes* also can be found in the Nile delta region of Egypt. An estimated 40 to 50 million people are infected with one or several species of intestinal flukes. Their life cycles are similar. The adult worm attaches to the intestinal wall of humans and produces eggs that are passed in feces. The eggs reach water, where miracidia develop and penetrate the first intermediate host, which is the snail. During the course of 6 to 7 weeks inside the host snails, the eggs develop into sporocysts, rediae, and cercariae. The cercariae leave the snails to encyst in the second intermediate host, which can be freshwater snails, fish, tadpoles, or vegetables. Humans are infected by the ingestion of raw stems, leaves (especially bamboo shoots), watercress, or water chestnuts with encysted metacercariae. In the human duodenum, the metacercariae attach to the walls and become adult worms in approximately 3 months.

PATHOBIOLOGY AND CLINICAL MANIFESTATIONS

Although the majority of intestinal fluke infections are asymptomatic, they may cause inflammation, ulceration, and mucus secretion at the site of attachment, particularly in the duodenum and jejunum. Gastrointestinal hemorrhage, perforation, and abscesses have been observed. The differential diagnoses include typhoid fever (Chapter 284), intestinal tuberculosis (Chapter 299), and amebiasis (Chapter 323). In these endemic cases, ulcerative colitis and other inflammatory diseases of the bowel are uncommon. In heavy infection, intestinal obstruction, protein-losing enteropathy, malabsorption, impaired vitamin B_{12} absorption, hypoalbuminemia, and anasarca can occur.[19] The adult worm causes traumatic, toxic, and obstructive damage to the intestinal mucosa. Some cases have been diagnosed by direct visualization of the adult parasite via esophagogastroduodenoscopy.

PULMONARY FLUKES

Paragonimiasis is a zoonosis caused by *Paragonimus* species (adult size: 10 × 5 mm). Reservoir hosts include felids, canids, viverrids, mustelids, some rodents, and pigs. At least 10 species of *Paragonimus* are known to cause human disease; of these, *Paragonimus westermani* is the most common.

EPIDEMIOLOGY

An estimated 25 or so million people are infected worldwide with *Paragonimus* species, and about 300 million are at risk. Human paragonimiasis is distributed mainly in Southeast Asia, Japan, Korea, China, and the Philippines, where *P. westermani* is the main species. In areas of low endemicity, other reported species include *Paragonimus mexicanus* in Latin America, *Paragonimus kellicotti* in North America, *Paragonimus heterotremus* in India, and *Paragonimus africanus* and *Paragonimus uterobilateralis* in West Africa.

Paragonimiasis typically results from the consumption of raw or improperly cooked crustaceans, especially crabs. Recently in the United States, some autochthonous cases have been reported in the Midwest in people who consumed raw crayfish while camping.

PATHOBIOLOGY

The life cycle starts when the eggs are excreted unembryonated in sputum, or alternatively they can be swallowed and passed in stool. In the external environment, the eggs become embryonated, and miracidia hatch. Eggs seek the first intermediate host, a snail (families Pleuroceridae and Thiaridae), and penetrate its soft tissues. Within the snail, asexual reproduction occurs for several weeks, with transformation into sporocysts, rediae, and cercariae. Cercariae emerge from the snail and invade the second intermediate host, which is a crustacean such as a crab or crayfish, where they encyst and become metacercariae, which is the infective stage for the mammalian host. Human infection occurs by eating inadequately cooked or pickled crab or crayfish that harbor metacercariae of the parasite. The metacercariae excyst in the duodenum, penetrate the intestinal wall, and migrate through the peritoneal cavity toward the lungs.

CLINICAL MANIFESTATIONS

Most infected individuals are asymptomatic and have subclinical disease. During the first month of infection, abdominal pain may represent the juvenile larvae migrating through the abdominal cavity before reaching the lungs. Irritation of the diaphragm or pleura may cause dry cough. Fever, chest pain, fatigue, and urticaria may follow, as well as eosinophilia. Pleural effusions may be seen at this stage, with significant eosinophilia noted on analysis of pleural fluid, which can be the first clue to the diagnosis. In fact,

pleural manifestations predominate early in the disease process, whereas lesions of the pulmonary parenchyma predominate later in the course of disease. Moreover, pneumothorax and mild eosinophilia may occur only 1 month after the initiation of infection. The migrating worms may cause bronchiectasis, interstitial pneumonitis, transient hemorrhage, or bronchopneumonia. Cough and recurrent hemoptysis are common clinical findings in this phase.[20]

The chronic stage occurs when the worms are paired in a cyst in the pulmonary parenchyma. Eggs are produced 6 weeks after infection, and, if there is communication with the bronchial tree, eggs may be seen in a sputum sample under microscopy, or they can be swallowed and passed with stool. The rusty discoloration of sputum is caused by the presence of the tan- to brown-pigmented *Paragonimus* eggs; the sputa of these patients have been classically described as resembling "iron filings." Charcot-Leyden crystals can be seen.

Peripheral blood eosinophilia and elevated total serum IgE levels are observed in approximately 80% of patients. Common findings on chest CT are pleural effusion, hydropneumothorax, pulmonary nodules, consolidation of air spaces, and cysts. The most common ectopic form is cerebral paragonimiasis, which is manifested as eosinophilic meningitis or meningoencephalitis, or as residual calcifications from a past infection. Infections may persist for 20 years in humans.

APPROACH TO LIVER, INTESTINAL, AND LUNG FLUKES

DIAGNOSIS

In general, transmission of food-borne trematodiases is restricted geographically, and distribution is one of the most important factors in suspecting this diagnosis. In the appropriate clinical setting, laboratory and imaging data can add information to narrow the differential diagnosis. Acute fluke infections require a high level of suspicion.

Serologic tests, direct visualization of the migrating larvae, or empirical therapy with a significant clinical response (including reduction of eosinophilia) are major criteria to confirm the diagnosis. Since these flukes are not living in blood vessels, PCR of serum has a limited role, but it can be useful for tissue, stools, or sputum when the adult parasite releases the eggs. Under the light microscope, the morphologic characteristics and size of the eggs may be sufficient to identify the specific fluke. In the chronic phase, the diagnosis is usually made by visualization of the eggs in stool or, in the case of *Paragonimus,* in sputum. A sedimentation technique must be performed on a series of at least three stool specimens from alternate days or even weeks. Immunodiagnostics is an excellent tool, particularly for patients who do not have demonstrable eggs in clinical specimens.

Fascioliasis

If acute hepatic fascioliasis is strongly suspected, cathepsin L1–based antibody enzyme-linked immunosorbent assay (ELISA) has a sensitivity of 92% and a specificity of 84%. If negative, the diagnosis is unlikely. If serology is not available, CT of the liver can visualize the characteristic track-like lesions. However, because the parasitic lesions are very similar to metastases, liver biopsy may be necessary. If serology or CT is not available, a trial of triclabendazole with clinical (including eosinophilia) resolution is the major criterion for diagnosis.

In chronic fascioliasis, the Lumbreras rapid sedimentation and Kato-Katz techniques are the tests of choice to detect the eggs in stool. At least three stool examinations are preferred. If negative, serology can be helpful. Ultrasonography and CT have low sensitivity in this phase. ERCP usually finds the adult parasites in the bile duct when performed for other reasons and can be useful to eliminate the adult parasites causing biliary obstruction.

Opisthorchiasis

In opisthorchiasis, the Ov-CP-1–based ELISA has a sensitivity of 95% and a specificity of 96%. For *C. sinensis,* ELISA has a sensitivity between 81 and 96% and a specificity between 92.6 and 96.2%. For detection of eggs and to measure the intensity of infection, the Kato-Katz technique is preferred. Intestinal fluke eggs can be detected by performing a sedimentation stool technique, preferably in consecutive stool samples.

Paragonimiasis

For paragonimiasis, an immunoblot assay performed with a crude antigen extract of *P. westermani* is the ideal first step to confirm the diagnosis, with a sensitivity of 96% and a specificity of 99%. In the acute phase, the precise location of the migrating larva is unknown, and a biopsy may not necessarily target the parasite. When serologic findings are negative (or not available), a trial of praziquantel or triclabendazole with a positive clinical response in 48 to 72 hours is a major criterion for diagnosis.

In the chronic phase, several sputum samples must be examined by a sedimentation technique to increase sensitivity. Stool examinations are complementary because the eggs can be swallowed by the host and then passed through stool. If a pulmonary cyst contains adult parasites with eggs, but they do not have communication to the main bronchi, serologic examination is indicated to confirm the diagnosis. If not available, biopsy is warranted.

TREATMENT

For fascioliasis, 10 mg/kg of oral triclabendazole on 2 consecutive days is the treatment of choice. The cure rate is higher than 90%, but failures have been reported. Cure is achieved if stool examinations remain negative for at least 3 months. Serology usually can take more than a year to resolve. In the chronic phase, the dead parasites can occasionally cause biliary obstruction, which may require surgical intervention. For drug failure, some experts recommend multiple rounds of triclabendazole, but some infections are resistant.[21,22] For intestinal flukes (i.e., *Fasciolopsis, Heterophyes,* etc.), praziquantel, 25 mg/kg orally three times daily for 1 day, is recommended and has a cure rate 90% or greater.

For *Opisthorchis viverrini,* a single oral dose of praziquantel (40 to 50 mg/kg) has a cure rate of 91 to 97%. For clonorchiasis, the recommended treatment is praziquantel (three doses of 25 mg/kg each in 1 day, for a total dose of 75 mg/kg), which has a cure rate of 83 to 85%. For *Clonorchis sinesis,* tribendimidine is as effective as praziquantel with fewer adverse events. Tribendimidine (100 to 600 mg orally) also is an efficacious alternative to praziquantel for treating *Opisthorchis viverrine,*[A5] but may or may not be quite as efficacious.[A6]

For paragonimiasis, praziquantel (25 mg/kg orally three times daily for 3 days) or triclabendazole (10 mg/kg orally once or twice) is highly effective. For ectopic cases, surgery may be necessary. In follow-up, negative stool examinations in the ensuing weeks can confirm cure. However, because the rate of reinfection is high in individuals from endemic areas, a suddenly positive stool examination is highly suggestive of a new infection rather than failure to respond to treatment.

PREVENTION

Prevention of infection with these flukes depends on several factors, including recognizing their geographic distribution and avoiding consumption of raw vegetables, fish, crayfish, or contaminated water in endemic areas. Proper medical advice must be given to individuals traveling to or planning to reside in endemic areas, not only to prevent fluke infection but also to reduce the risk for coinfections with other parasites.

For local populations in endemic areas, the challenges are greater. Control of these flukes in animals is impractical because of wild animal reservoirs. Long-established cultural, dietary, and sanitary habits are difficult to change. However, the identification of hotspots for infection[23] can guide the administration of mass chemotherapy to highly endemic populations and may reduce the infection in humans and in selected animals.

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327 NEMATODE INFECTIONS

DAVID J. DIEMERT

DEFINITION

Nematode infections are highly prevalent, affecting millions of people worldwide. Nematodes are complex, nonsegmented roundworms with specialized organs that include a protective outer coating or cuticle, a complete and functional gastrointestinal tract, and muscular, nervous, and reproductive systems. Most species are free-living in soil or water, but a few parasitize humans.

The Pathogens

Nematodes of medical importance can be categorized into those that primarily affect the gastrointestinal tract, where adult worms become established and cause disease, and those that affect other tissues and organ systems. The former includes the roundworm *Ascaris lumbricoides*, the hookworms *Ancylostoma duodenale* and *Necator americanus*, the pinworm *Enterobius vermicularis*, the whipworm *Trichuris trichiura*, and the threadworm *Strongyloides stercoralis*. Zoonotic intestinal nematodes such as *Trichostrongylus* and *Anisakis* also can incidentally infect and cause disease in humans. Nematodes that invade and cause disease primarily outside the gastrointestinal tract include those that cause lymphatic filariasis (*Wuchereria bancrofti*, *Brugia malayi*, and *Brugia timori*), *Onchocerca volvulus*, *Loa loa*, and the guinea worm *Dracunculus medinensis*, as well as *Trichinella* and *Angiostrongylus* species.

Nematodes that infect humans measure from several millimeters to more than a meter in length and often survive for months to years within their host. Except for *S. stercoralis* and *Capillaria philippinensis*, adult worms cannot complete their life cycle within a human host. Instead, sexually mature adult worms mate and produce eggs or larvae that must have at least one stage of development outside the host, either in the environment or in an intermediate host.

EPIDEMIOLOGY

Nematode infections are rarely fatal; they more commonly result in chronic morbidity such as iron deficiency anemia caused by hookworm or blindness due to onchocerciasis. For most nematodes, the severity of the clinical manifestations of infection is proportional to the number of worms harbored by a given host; although light infections with only a few worms are usually asymptomatic, heavier worm burdens often cause symptoms and clinical sequelae.

Nematode infections are prevalent in the temperate and tropical regions of Africa, Asia, and Latin America. They are transmitted by the oral ingestion of embryonated eggs or by penetration of infective larvae through the skin, either by direct contact with contaminated soil or by the bite of an arthropod vector. Nematode infections are most common in areas with poor sanitation, where the environment is contaminated by human feces, and in climates that support survival of the insect vector if one is involved in the life cycle.

FIGURE 327-1. Mass of adult *Ascaris lumbricoides* worms recovered from a child after the administration of mebendazole. (Reproduced with permission from Dickson Despommier.)

INTESTINAL NEMATODE INFECTIONS

ASCARIASIS

The Pathogen

A. lumbricoides, commonly known as roundworm, is acquired by oral ingestion of embryonated eggs that have been expelled in the feces of humans, who are the only host. Adult worms (Fig. 327-1) range in length between 15 and 50 cm and survive in the host for approximately 18 months.

EPIDEMIOLOGY

A. lumbricoides is the most prevalent nematode infection worldwide, affecting approximately 730 million people in sub-Saharan Africa, South and Southeast Asia, and Latin America, primarily in rural areas of high population density that lack adequate sanitation or treatment of sewage or where untreated human feces are used as fertilizer.[1] Climate is an important determinant of disease since warm temperatures and adequate moisture are needed for embryonation of eggs in soil. In endemic areas, the prevalence and intensity of infection increase significantly during the first 2 to 3 years of life, remain high between the ages of 4 and 15 years, and then decline during adulthood.

PATHOBIOLOGY

In the stomach, the egg's outer shell is dissolved by gastric acid, thereby releasing larvae into the small intestine, where they penetrate the intestinal wall and enter the portal circulation. The larvae migrate to the pulmonary vasculature, where they penetrate the alveoli, ascend the bronchial tree, and are swallowed back into the intestinal tract, where they develop into adult worms 9 to 11 weeks after egg ingestion.[2] Each day, a female adult *Ascaris* worm releases over 200,000 eggs that are expelled in feces. Fertilized eggs (Fig. 327-2) become infectious after embryonating in warm, moist, shady soil. Eggs are resistant to extreme temperatures and to desiccation, and they can survive up to 15 years in the environment.

Clinical manifestations are associated with heavy worm burdens and result from larval migration through the lungs and from parasitism of the gastrointestinal tract by adult worms. During the pulmonary phase of the life cycle, *A. lumbricoides* larvae can induce an intense reaction that is due to both physical disruption and a hypersensitivity response to secreted antigens. This phenomenon is more common in areas in which transmission is seasonal, such as on the Arabian Peninsula, where outbreaks of pneumonitis typically follow the rainy season because of resumption of transmission.

CLINICAL MANIFESTATIONS

Low-intensity *A. lumbricoides* infections are usually asymptomatic, but heavy worm burdens cause symptoms including sudden onset of wheezing, dyspnea, paroxysmal nonproductive cough, and high fever. Symptoms may persist for 2 to 3 weeks before resolving spontaneously. Respiratory symptoms may coincide with or be preceded by urticarial rash, angioedema, abdominal pain, and vomiting.

With moderate or heavy infections, a mass of worms can cause obstruction in the small intestine or migration of worms to the biliary tree, pancreatic duct, or appendix. Intestinal obstruction, which is more common in young children because of their smaller lumen size, is characterized by colicky abdominal

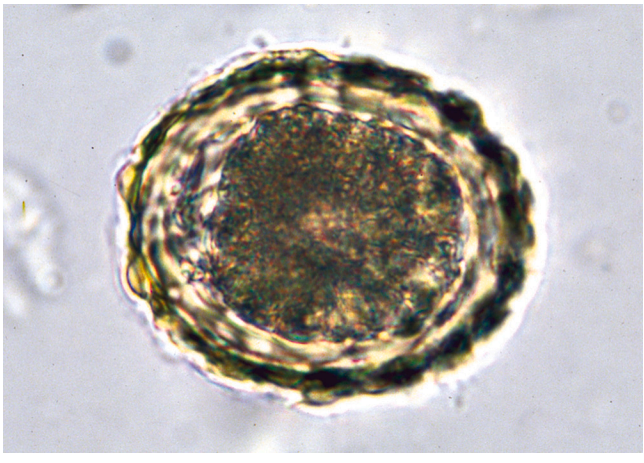

FIGURE 327-2. Fertilized, unembryonated egg of *Ascaris lumbricoides*. (Reproduced with permission from Dickson Despommier.)

ABSTRACT

Nematodes of medical importance can be categorized into those that primarily affect the gastrointestinal tract, where adult worms become established and cause disease, and those that affect other tissues and organ systems. The former group includes the roundworm *Ascaris lumbricoides*, the hookworms *Ancylostoma duodenale* and *Necator americanus*, the pinworm *Enterobius vermicularis*, the whipworm *Trichuris trichiura*, and the threadworm *Strongyloides stercoralis*. Nematodes that invade and cause disease primarily in tissues outside the gastrointestinal tract include those that cause lymphatic filariasis (*Wuchereria bancrofti, Brugia malayi*, and *Brugia timori*), *Onchocerca volvulus, Loa loa*, and the guinea worm *Dracunculus medinensis*, as well as *Trichinella* and *Angiostrongylus* species. Nematode infections are prevalent in the temperate and tropical regions of Africa, Asia, and Latin America. They are transmitted by the oral ingestion of embryonated eggs or by penetration of infective larvae through the skin, either by direct contact with contaminated soil or by the bite of an arthropod vector. Nematode infections are most common in areas with poor sanitation, where the environment is contaminated by human feces, and in climates that support survival of the insect vector if one is involved in the life cycle. Nematode infections are rarely fatal; they more commonly result in chronic morbidity such as iron deficiency anemia caused by hookworm or blindness due to onchocerciasis.

KEYWORDS

intestinal nematodes
tissue nematodes
soil-transmitted helminths
filariases
hookworm
ascariasis
cutaneous larva migrans
elephantiasis
trichinellosis/trichinosis
filariasis

pain and vomiting that may progress to signs of intestinal perforation and be confused with acute appendicitis (Chapter 128). Hepatobiliary and pancreatic ascariasis are more common in adults. Chronic intestinal infection can manifest as abdominal pain and distention, diarrhea, and nausea. More insidious effects, especially in children, include decreased protein and fat absorption, development of vitamin A and C deficiencies, and lactose intolerance, which together lead to asthenia, stunted growth, and impaired cognitive development.

DIAGNOSIS

Diagnosis of ascariasis is usually made by microscopic examination of a sample of feces for characteristic thick-shelled eggs. Polymerase chain reaction (PCR) testing, although currently available only in specialized laboratories as a research tool, is also highly sensitive and specific.[3] However, during the pulmonary phase of infection, ova will not be detectable in feces because adult worms have not yet matured and begun producing eggs; instead, larvae, as well as eosinophils or Charcot-Leyden crystals (formed from the breakdown of eosinophils), may be visualized on microscopic examination of sputum. Pulmonary disease is also usually characterized by peripheral eosinophilia and transient infiltrates on chest radiographs. The diagnosis of intestinal or biliary obstruction caused by *A. lumbricoides* is usually made by ultrasound examination or endoscopic retrograde cholangiopancreatography (ERCP).

TREATMENT

Intestinal ascariasis is usually cured with a single oral dose of albendazole (Table 327-1).[A1] Alternatives include mebendazole, ivermectin,[A2] moxidectin, tribendimidine, or pyrantel pamoate. No specific treatment is recommended for symptoms of pulmonary ascariasis since the condition is self-limited. In severe cases of biliary obstruction, including cholangitis, ERCP with or without resection of the ampulla of Vater is highly successful and may preclude the need for surgery.

PREVENTION

The definitive means of preventing *Ascaris* infection is improvement of hygiene and proper disposal of human waste.[4] In endemic communities where this is not feasible, morbidity control consists of regular (usually annual) mass administration of an anthelminthic medication such as albendazole or mebendazole to preschool and school-aged children.

TABLE 327-1 ORAL TREATMENT OF INTESTINAL NEMATODES

NEMATODE	TREATMENT
Ascaris lumbricoides	Albendazole 400 mg once. Alternatives: mebendazole 500 mg once or 100 mg bid for 3 days, ivermectin 150-200 µg/kg once, moxidectin 8 mg once, or pyrantel pamoate 11 mg/kg once with the maximum dose not to exceed 1 g
Hookworm (*Necator americanus* and *Ancylostoma duodenale*)	Albendazole 400 mg daily for 3 days. Alternatives: tribendimidine 400 mg once; mebendazole 500 mg daily or 100 mg bid for 3 days; or pyrantel pamoate 11 mg/kg for 3 days with the maximum daily dose not to exceed 1 g
Cutaneous larva migrans (*Ancylostoma caninum* and *Ancylostoma braziliensis*)	Ivermectin 200 µg/kg daily for 1-2 days. Alternative: albendazole 400 mg daily for 3 days
Trichuris trichiura	Albendazole 400 mg daily for 3 days. Alternative: mebendazole 100 mg bid for 3 days. The addition of ivermectin 200 µg/kg or moxidectin 8 mg daily for 3 days improves efficacy
Enterobius vermicularis	Pyrantel pamoate 11 mg/kg once, with a second dose 2 wk later; maximum dose of 1 g. Alternatives: mebendazole 100 mg once or albendazole 400 mg once, repeated in 2 wk
Strongyloides stercoralis	Uncomplicated infection: ivermectin 200 µg/kg daily for 2 days.* Alternative: albendazole 400 mg bid for 7 days
Trichostrongylus spp	Pyrantel pamoate 11 mg/kg once; maximum dose of 1 g. Alternatives: albendazole 400 mg daily for 10 days or mebendazole 500 mg daily for 10 days
Capillaria philippinensis	Albendazole 400 mg bid for 10 days. Alternative: mebendazole 500 mg daily for 20 days

*Treatment may need to be extended in immunocompromised patients with disseminated disease.
bid = twice daily; spp = species.

PROGNOSIS

Untreated, ascariasis may lead to chronic infection that persists for years and can result in clinical complications ranging from rarely fatal intestinal or biliary obstruction to more insidious sequelae such as malnutrition. Although treatment with albendazole is highly effective, children living in endemic communities often become reinfected within months owing to continued exposure from the contaminated environment.

HOOKWORM

The Pathogen

Hookworm infection in humans is due almost exclusively to two species: *N. americanus* and *A. duodenale*. However, incidental infection with the zoonotic hookworms *Ancylostoma caninum*, *Ancylostoma braziliensis*, *Bunostomum phlebotomum*, and *Uncinaria stenocephala* can cause self-limited dermatologic lesions known as cutaneous larva migrans (Fig. 327-3). Additionally, *Ancylostoma ceylanicum*, normally a hookworm infecting cats, has been reported to cause intestinal disease in humans, especially in Asia, whereas *A. caninum* has been implicated as a cause of eosinophilic enteritis.

EPIDEMIOLOGY

Over 400 million people are infected with hookworms worldwide. *N. americanus* is widespread, whereas infection with *A. duodenale* is more geographically restricted. The highest prevalence of infection occurs in rural areas of tropical and less developed countries, where environmental and socioeconomic conditions favor transmission. Like *A. lumbricoides*, hookworm eggs require soil of adequate moisture and warm temperature to incubate and develop into larvae. Equally important determinants of infection are poverty and lack of access to adequate sanitation and clean water. The prevalence of infection increases with age in children living in endemic areas until it plateaus by about age 10 years. By comparison, the intensity of infection rises at a slower rate during childhood, reaching a plateau by about age 20 years and then increasing again in the elderly.

Although cutaneous larva migrans is found throughout the tropics, in the United States it is diagnosed primarily in travelers who have recently returned from a tropical beach vacation, especially in the Caribbean, South and Central America, and Southeast Asia. Occasionally, autochthonous cases (originating where found) have been reported in the United States, usually from southeastern coastal states such as Florida and Texas. Cutaneous larva migrans occurs when larvae of the dog or cat hookworms (*A. caninum* or *A. braziliense*, respectively) are expelled in their feces, contaminate moist soil or sand, and then come into contact with exposed skin. Other animal hookworms such as *U. stenocephala* and *B. phlebotomum* are less common causes.

FIGURE 327-3. Typical lesion of cutaneous larva migrans. An erythematous, serpiginous track caused by intradermal migration of a dog (*Ancylostoma caninum*) or cat (*Ancylostoma braziliense*) hookworm larva is apparent. (Reproduced with permission from Gregory L. Zalar.)

PATHOBIOLOGY

Infection occurs when exposed skin comes in contact with infective filariform larvae in fecally contaminated soil or grass. Larvae penetrate the skin and enter the venous circulation. After reaching the pulmonary vasculature, larvae penetrate into alveolae, ascend the bronchial tree to the larynx, and are swallowed into the gastrointestinal tract. Larvae develop into sexually mature adult worms 5 to 9 weeks after skin penetration. Adult hookworms reside in the lumen of the small intestine, where they attach to the mucosa by means of cutting teeth (*A. duodenale*) or a rounded cutting plate (*N. americanus*). After mating, female worms produce eggs that are expelled from the body in feces; *A. duodenale* female worms lay approximately 28,000 eggs daily, whereas the output from *N. americanus* worms averages around 10,000 a day. Hookworm eggs hatch in warm, moist, sandy soil and release larvae that can infect another host. Humans are the only natural definitive hosts for these two parasites, and there are no intermediate or reservoir hosts. *A. duodenale* worms survive on average for 1 year in the human intestine, whereas *N. americanus* lives for 3 to 5 years.

The major pathology of hookworm infection is the associated gastrointestinal blood loss and resulting iron deficiency anemia. Hookworms attach to the intestinal mucosa and secrete enzymes that enable them to invade submucosal tissues and ingest villous tissue and blood. Hemoglobinases within the hookworm's digestive canal degrade host hemoglobin for use as an essential nutrient source. The amount of blood loss is directly related to the total worm burden. *A. duodenale* causes more blood loss than *N. americanus*: each *N. americanus* worm results in a daily blood loss of 0.03 to 0.1 mL, whereas the corresponding figure for *A. duodenale* is between 0.15 and 0.26 mL.

CLINICAL MANIFESTATIONS

The clinical features of hookworm infection are related to the initial larval migration through the skin and other tissues and the acute and chronic manifestations resulting from parasitism of the gastrointestinal tract by adult worms. Repeated skin exposure to hookworm larvae can result in a hypersensitivity reaction known as "ground itch," a pruritic erythematous and papular rash that appears most commonly on the hands and feet. In contrast, when zoonotic hookworm larvae penetrate the skin to produce cutaneous larva migrans, most commonly on the feet, legs, and buttocks, they are unable to complete their life cycle in the human host and eventually die after causing a typical rash consisting of intensely pruritic, erythematous serpiginous tracks (see Fig. 327-3). Tracks appear after an incubation period of a few days, can be single or multiple, and advance by millimeters to a few centimeters each day. Vesiculobullous or papular lesions may develop along the tracks, as can secondary bacterial infection because of scratching. Untreated, lesions usually heal spontaneously within weeks to months following death of the larvae in the skin.

Migration of hookworm larvae through the lungs may induce mild and transient pulmonary symptoms consisting of dry cough, sore throat, wheezing, and low-grade fever. Uncommonly, acute symptomatic disease may follow the oral ingestion of *A. duodenale* larvae, known as Wakana syndrome, which is characterized by pharyngeal irritation, cough, dyspnea, hoarseness, nausea, and vomiting.

Gastrointestinal symptoms and signs caused by hookworm infection are uncommon. Instead, the manifestations of hookworm disease occur when intestinal blood loss exceeds the nutritional reserves of the host and results in iron deficiency anemia. Usually only moderate- and high-intensity (≥2000 eggs per gram of feces) hookworm infections produce clinical disease, which resembles that of iron deficiency anemia secondary to other causes (Chapter 145). In addition, the protein losses associated with heavy hookworm infection can result in hypoproteinemia and anasarca. Clinical manifestations of iron deficiency anemia include weakness, palpitations, fainting, dizziness, dyspnea, lassitude, and headache. Uncommonly, patients may have constipation or diarrhea with occult blood in the stool or even frank melena, especially in children; there may also be an urge to eat soil (pica). Overwhelming hookworm infection may cause listlessness, coma, and even death, especially in infants. Because children and women of reproductive age have lower iron reserves, they are at increased risk of symptomatic disease.

DIAGNOSIS

The diagnosis of hookworm infection is made by microscopic identification of characteristic eggs in the stool. The eggs of *N. americanus* and *A. duodenale* cannot be distinguished because both are colorless and have a single thin hyaline shell with blunted ends; they range in size from 55 to 75 μm by 36 to 40 μm. Egg concentration techniques, such as the formalin–ethyl acetate sedimentation method, can be used to detect even light infections, although a direct wet mount examination is adequate for detecting moderate to heavy infections. As with *A. lumbricoides*, PCR testing that has been reported to be highly sensitive and specific is performed by a few specialized laboratories but is not commercially available or approved as a diagnostic test. In addition, eosinophilia is a common finding in chronic infection and during larval migration through the lungs.

TREATMENT

For intestinal hookworm infection, three daily oral doses of albendazole 400 mg is the recommended treatment (see Table 327-1). Tribendimidine, which is not FDA approved and is not available or approved in most countries, has a similar efficacy profile as albendazole as a single oral dose of 400 mg, alone or in combination with other anthelminthics, such as single-dose ivermectin or oxantel pamoate.[A3] Less effective alternatives include mebendazole, pyrantel pamoate, and single-dose albendazole. Iron supplementation is recommended in patients with significant or symptomatic anemia.

For cutaneous larva migrans, although the disease is self-limited and will resolve spontaneously within weeks to a few months, treatment with one to two daily doses of ivermectin (200 μg/kg) leads to faster resolution of symptoms and skin manifestations. Albendazole is an alternative treatment of cutaneous larva migrans.

PREVENTION

The ideal method for preventing hookworm infection is improvement in hygiene and proper disposal of human waste. In endemic communities where these public health measures have not been accomplished, control of disease consists of regular (at least annual) mass administration of single doses of an anthelminthic medication such as albendazole or mebendazole. For cutaneous larva migrans, tourists should be advised to wear shoes or sandals when walking on beaches and to avoid areas frequented by stray cats and dogs.

PROGNOSIS

Severe iron deficiency anemia caused by hookworm during pregnancy can result in adverse consequences for the mother, the fetus (spontaneous abortion, intrauterine growth restriction), and the neonate (anemia, failure to thrive). In children, the anemia and protein malnutrition (Chapter 197) associated with chronic infection cause long-term deficits in physical and cognitive development.

TRICHURIASIS

The Pathogen

T. trichiura nematodes, or whipworms, which grow to as long as 50 mm, spend their entire life cycle in the host's gastrointestinal tract.

EPIDEMIOLOGY

The estimated worldwide prevalence of trichuriasis is 465 million, most commonly in poor, rural areas of the tropics and subtropics where disposal and treatment of human waste are inadequate. Children are more frequently infected than adults and more likely to have higher worm burdens. Humans are the only host.

PATHOBIOLOGY

T. trichiura does not have a tissue migratory phase like *A. lumbricoides* and hookworm. After embryonated eggs are ingested orally, they hatch and release larvae into the proximal large intestine, where they undergo a series of molts before being carried passively to the transverse and descending colon. The adult worm's narrow anterior end embeds in the columnar epithelium, while the posterior portion protrudes into the lumen. After mating, female worms expel unembryonated eggs into the feces, which are then passed into the environment, where they must embryonate in warm, moist soil to complete the life cycle. Adult worms can survive in the host for approximately 1.5 to 2 years. The period between ingestion of eggs and detection of eggs in feces is about 90 days.

CLINICAL MANIFESTATIONS

Most *T. trichiura* infections are asymptomatic. Symptomatic disease occurs primarily in children because most heavy infections (>10,000 eggs per gram of feces) occur in this age group. Heavy infections can manifest as an acute dysentery or as a chronic colitis resembling inflammatory bowel disease with recurrent abdominal pain and diarrhea.

DIAGNOSIS

Infection is diagnosed by microscopic identification of the typical barrel-shaped eggs with bipolar plugs in direct or concentrated smears of fecal specimens. PCR testing has been reported to be highly sensitive and specific by a few specialized laboratories but is not commercially available or approved as a diagnostic test.

TREATMENT

T. trichiura responds less effectively than *A. lumbricoides* or hookworm to treatment with single-dose albendazole or mebendazole, so a 3-day course of either benzimidazole drug is recommended (see Table 327-1). The addition of ivermectin (200 µg/kg) to either drug can increase the response rate significantly.[A4] Some data also indicate that the combination of moxidectin (8 mg) plus albendazole may be more effective than albendazole alone.[A5]

PREVENTION

As for *A. lumbricoides* and hookworm, control of trichuriasis in endemic areas consists of regular mass anthelminthic drug administration, primarily to preschool and school-aged children. Although the single doses of albendazole or mebendazole that are used in most mass drug administration programs worldwide are poorly effective for this intestinal nematode, their use is still recommended by the World Health Organization.

PROGNOSIS

Chronic mucosal inflammation and edema of the colon and rectum can lead to protracted tenesmus that can result in rectal prolapse. Chronic *Trichuris* colitis can also lead to malnutrition, impaired growth, and anemia.

ENTEROBIASIS

The Pathogen

E. vermicularis, or pinworm, is transmitted by the fecal-oral route. Adult worms measure from 2 to 5 mm.

EPIDEMIOLOGY

E. vermicularis is found worldwide and is the most prevalent nematode infection in temperate climes. Transmission is frequent in primary schools and daycare centers.

PATHOBIOLOGY

After ingestion, embryonated eggs hatch in the small intestine, where larvae develop into adult worms that migrate to the large intestine, where they mate. Gravid female worms emerge nightly from the anus to deposit large numbers of eggs (11,000 per worm) on the perianal and perineal skin, where they embryonate within 6 hours. If they are still on the skin, infective larvae are released and can migrate back through the anus into the rectum (retroinfection). Alternatively, autoinfection occurs when eggs are transferred to the mouth via scratching skin on which eggs have been deposited. Larvae may also migrate into the female genital tract and establish ectopic infection.

CLINICAL MANIFESTATIONS

Although pinworm infections may be asymptomatic, perianal pruritus is the most common symptom and is due to an allergic response to worm proteins. The pruritus can be intense and result in chronic sleep deprivation in children. Rarely, adult *E. vermicularis* may precipitate appendicitis. When hatched larvae migrate into the female genital tract, vulvovaginitis, salpingitis, or peritonitis may develop.

DIAGNOSIS

Pinworm infection is diagnosed by identifying the characteristic eggs through microscopic examination of a piece of cellophane tape applied to the perianal region immediately after waking in the morning. *E. vermicularis* eggs are oval and slightly flattened on one side. Eggs are not usually found in fecal samples. Repeated examination may be necessary.

TREATMENT

Pinworm infection is treated with a single dose of pyrantel pamoate, mebendazole, or albendazole, which must be repeated 2 weeks later because the drugs do not kill eggs or developing larvae (see Table 327-1). Given the high rate of transmission, all household members and individuals in close contact with the patient (e.g., other children attending the same daycare center) should also be treated. Bedding and underclothes should be thoroughly laundered in hot water followed by a hot dryer to kill remaining eggs.

PROGNOSIS

Enterobiasis usually does not result in severe manifestations, particularly in children, and it responds rapidly to appropriate treatment.

STRONGYLOIDIASIS

The Pathogen

S. stercoralis, commonly known as threadworm, is endemic in warm climates worldwide, including parts of the United States. Adult males are about 0.75 mm long, and adult females are about 1.0 mm long.

EPIDEMIOLOGY

S. stercoralis infection is endemic in the tropical and subtropical regions of sub-Saharan Africa, Asia, Latin America, and areas of Eastern and Southern Europe, with a worldwide prevalence of up to 100 million. In the United States, *Strongyloides*-related hospitalizations are rare,[5] and infection is diagnosed most frequently in immigrants; however, strongyloidiasis is still endemic in parts of rural Appalachia. *S. stercoralis* can also be transmitted sexually through oral-anal contact, most often among men who have sex with men, or via transplantation of solid organs.

PATHOBIOLOGY

Infection occurs when exposed skin comes in contact with free-living filariform larvae in soil contaminated with human feces. Like hookworm, larvae penetrate the skin, enter the vasculature, and migrate to the pulmonary capillaries, where they penetrate into the alveoli, ascend the bronchial tree to the pharynx, and are swallowed into the gastrointestinal tract. Further development into adult worms occurs in the upper small intestine, where parasites live embedded in the mucosa. Unlike most nematodes, *S. stercoralis* reproduces by parthenogenesis, with no apparent parasitic male worm present in the human host. Within 25 to 30 days after infection, female worms begin laying eggs, which rapidly hatch in the intestinal lumen and release noninfectious rhabditiform larvae that migrate to the colon and are excreted in feces. Alternatively, larvae may penetrate the colonic mucosa or perianal skin after migrating out of the anus and enter the circulation directly, a mechanism known as autoinfection that can lead to maintenance of parasitism in the host for decades.

In the soil, infectious filariform larvae can be produced either directly via transformation from rhabditiform larvae or indirectly from eggs released by free-living adult worms that have developed from rhabditiform larvae in warm, moist, sandy soil.

In immunologically competent individuals, infection does not usually result in symptomatic disease. However, serious complications may occur in individuals with cell-mediated immunodeficiency such as patients chronically taking corticosteroids, solid organ transplant recipients, patients with hematologic malignancies, or patients infected with human T-cell lymphotropic virus type 1. In these patients, the *S. stercoralis* autoinfection cycle can become amplified and lead to a hyperinfection syndrome with a large increase in the total worm burden in the infected person. Hyperinfection can lead to life-threatening dissemination of larvae and adult worms to aberrant sites such as the brain, pancreas, and kidneys. For unknown reasons, acquired immunodeficiency syndrome (AIDS) has not been associated with hyperinfection syndrome or with disseminated strongyloidiasis.

CLINICAL MANIFESTATIONS

Most *S. stercoralis* infections, especially in immunocompetent hosts, are asymptomatic or are associated with only mild gastrointestinal symptoms such as abdominal pain, bloating, and watery diarrhea. Gastrointestinal bleeding, manifested by hematochezia or melena, occurs in less than 20% of those infected. Rare causes of morbidity include small bowel obstruction, paralytic ileus, and a malabsorption syndrome (especially in children).

During the migratory phase of larvae through the lungs, symptoms are rare in immunocompetent patients, although there may be peripheral eosinophilia. In immunocompromised persons with hyperinfection syndrome, however, pulmonary signs and symptoms can be severe and resemble those of adult respiratory distress syndrome (Chapter 90) with acute onset of dyspnea, productive cough, and hemoptysis accompanied by fever, tachypnea, and hypoxemia. Disseminated strongyloidiasis is frequently accompanied by bacterial sepsis due to translocation of enteric organisms carried by migrating larvae.

Migration of filariform larvae from the anus can lead to a dermatologic manifestation known as larva currens, which is characterized by migratory serpiginous erythematous maculopapular tracks, primarily on the skin of the buttocks, groin, and lower abdomen.

Autoinfection leading to exceptionally high worm loads (i.e., hyperinfection) and disseminated strongyloidiasis can occur in persons with deficient cell-mediated immunity. Because asymptomatic infection with *S. stercoralis* can persist for decades after initial infection, a change in immune status associated with conditions such as the administration of immunosuppressive drugs following solid organ transplantation may result in hyperinfection syndrome even though the infection was previously asymptomatic. Massive increases in the number of *Strongyloides* larvae because of hyperinfection can present as acute enteritis with severe diarrhea and ulcerative disease of the small and large intestine. During disseminated infection, larvae and sometimes adult worms penetrate the intestinal mucosa, migrate to aberrant sites, including the central nervous system, and result in metastatic abscesses and gram-negative meningitis due to enteric bacteria being carried by the migrating parasites. Less common complications of disseminated disease include glomerulonephritis and minimal-change nephrotic syndrome, acute respiratory distress syndrome, and alveolar hemorrhage.[6] Swollen belly syndrome, a less common type of strongyloidiasis seen in infants living in Central Africa and Papua New Guinea, has been attributed to infection with *Strongyloides fuelleborni*, which is normally a zoonosis of nonhuman primates.

DIAGNOSIS

Definitive diagnosis of *S. stercoralis* infection relies on microscopic identification of larvae in feces or other fluids (such as sputum) or tissues.[7] Intestinal strongyloidiasis can be diagnosed by observation of larvae in direct smears of freshly passed stool. The sensitivity of microscopy on a single fecal sample examination is as low as 30% but can be increased by examining multiple fecal specimens, by using concentration techniques, and by plating feces on an agar plate and inspecting for tracks of colonies created by bacteria being dragged by migrating larvae. Several molecular amplification techniques have been developed by various research laboratories, but none has been approved for clinical use.

Hyperinfection syndrome and disseminated strongyloidiasis can be diagnosed by detection of filariform larvae in duodenal fluid obtained by endoscopy, in sputum, or in bronchoalveolar lavage specimens. Larvae have also been recovered from cerebrospinal fluid, urine, peritoneal washings, skin, and the brains of immunocompromised persons.

Fluctuating eosinophilia is common with uncomplicated intestinal strongyloidiasis, especially during the pulmonary migration phase of initial infection. However, eosinophilia may be absent in patients with hyperinfection and dissemination. In fact, patients with hyperinfection and eosinophilia have a better prognosis than do those without eosinophilia.

Serologic diagnosis using an enzyme-linked immunosorbent assay (ELISA) that detects antibodies to filariform larvae is very sensitive, even in immunocompromised hosts with disseminated strongyloidiasis, although some false positives may occur in cases of co-infection with other nematodes, particularly filaria. Specificity is improved by using the newer luciferase immunoprecipitation system (LIPS) assays that incorporate *Strongyloides*-specific recombinant antigens. LIPS assays have the additional advantage of rapidly reverting to being seronegative following successful treatment.

TREATMENT

Uncomplicated intestinal strongyloidiasis can be treated effectively with ivermectin (200 µg/kg body weight daily for 2 days), with cure rates exceeding 90%.[A6] Albendazole is an alternative treatment (see Table 327-1),[A7] and moxidectin (8 mg) also has shown promising results.[8] Decreases in antibody titer and eosinophil count indicate a response to treatment in the absence of re-exposure. After 6 months, ELISA titers should decrease significantly, whereas LIPS assays should revert to negative.

In immunocompromised patients with hyperinfection or disseminated disease, ivermectin should be administered daily. Some experts recommend continuing treatment until 2 weeks after fecal examinations have become negative (i.e., for one autoinfection cycle). For severely ill patients who are unable to tolerate oral therapy, ivermectin enemas have been used. Combination therapy with ivermectin and albendazole may also be used to treat disseminated strongyloidiasis, but whether this combination improves prognosis over monotherapy is unknown.

PREVENTION

In endemic areas, the risk for infection can be reduced by minimizing skin contact with contaminated soil, although elimination of this infection will occur only with improvements in sanitation and treatment of human waste. To prevent hyperinfection in individuals who have unrecognized chronic infection, diagnosis should be attempted before the onset of immunosuppression if possible, such as before organ transplantation or cancer chemotherapy. Anyone who has resided in or traveled to an endemic area should undergo screening for asymptomatic infection, preferably by serology or, if not possible, by microscopic examination of at least three fecal samples for the presence of larvae. Patients with positive screening test results should be treated empirically with ivermectin. Individuals with negative screening test results but unexplained eosinophilia and a history of exposure should also be considered for empirical treatment. In patients undergoing hematopoietic stem cell transplantation, documentation of cure with at least three consecutive negative fecal examinations or a negative LIPS assay is recommended before proceeding with transplantation.

PROGNOSIS

Uncomplicated strongyloidiasis is rarely fatal and responds rapidly to effective treatment without permanent sequelae. Although hyperinfection and disseminated disease occur in only a minority of cases, mortality rates can exceed 85%, mostly due to the accompanying bacterial sepsis. However, early diagnosis and prompt initiation of treatment for this severe form of the infection are associated with improved outcomes.

UNCOMMON INTESTINAL NEMATODIASES

Humans may serve as incidental hosts for some nematodes that ordinarily parasitize the intestines of other mammals.

TRICHOSTRONGYLUS

Human infections with various species of the genus *Trichostrongylus* have been reported in Iran, the Far East, and Australia. Humans become infected when larvae are ingested with leafy vegetables that have been contaminated with soil containing the feces of herbivorous animals. *Trichostrongylus* worms are similar to hookworms in their morphology, appearance of their eggs on fecal examination, and the pathology that they induce. Heavy infections may be accompanied by diarrhea and anemia. Drugs recommended for treatment are pyrantel pamoate, albendazole, and mebendazole (see Table 327-1).

ANISAKIASIS

Anisakiasis results from ingestion of the larvae of nematodes that normally infect sea mammals such as dolphins, whales, and seals. Larvae of the genera *Anisakis*, *Phocanema*, and *Pseudoterranova* infect the flesh of several saltwater fish species as intermediate hosts. Consumption of raw or undercooked fish, often in the form of sushi or sashimi, results in release of the infective larvae into the stomach, followed by invasion of the stomach or duodenal wall, which causes upper abdominal pain that can be intense. Anisakid worms cannot further develop in humans and die within a few days; an eosinophilic granulomatous reaction that mimics a gastric tumor may result. Diagnosis and treatment are accomplished by endoscopic removal of the parasite. Infection is prevented by cooking or freezing seafood before consumption. Of note, salting, smoking, and marinating fish do not kill anisakid larvae.

CAPILLARIA PHILIPPINENSIS

C. philippinensis can cause a serious intestinal infection that has been reported primarily in the Philippines and Thailand, although cases have also been observed in Japan, Taiwan, Korea, and Egypt. Adult worms resemble those of *Trichinella spiralis*, although biologically they mimic *S. stercoralis* in that they have an autoinfection cycle of reproduction in which larvae can develop into adult worms without leaving the host. Even though the life cycle has not been completely elucidated, this nematode probably parasitizes waterfowl that feed on fish and crustaceans, which serve as intermediate hosts. Humans become infected by eating raw or undercooked infected shrimp or fish. Adult worms migrate to the mucosal crypts of the small intestine, where they deposit larvae, sometimes resulting in overwhelming infection. Clinical disease consists of severe diarrhea associated with anorexia, vomiting, and weight loss. Diagnosis depends on visualizing eggs or larvae in feces. The treatment of choice is albendazole or mebendazole (see Table 327-1). Mortality rates as high as 10% have been reported, with death resulting from severe malabsorption and protein-losing enteropathy.

TISSUE NEMATODE INFECTIONS

The tissue nematodes can be divided into organisms for which humans are the principal host (the filariases) and zoonotic organisms that usually infect

animals but can incidentally infect humans. Zoonotic nematodes such as *Toxocara*, *Trichinella*, and *Angiostrongylus* infect humans following accidental oral ingestion of eggs or larvae but are unable to complete their life cycle in the host. Clinical manifestations are primarily due to the aberrant migration of larvae through various tissues.

TOXOCARIASIS

DEFINITION

Accidental ingestion of embryonated eggs of the dog roundworm *Toxocara canis* or, less frequently, the cat ascarid *Toxocara cati* can cause the clinical syndromes of visceral larva migrans and ocular larva migrans. Symptoms, which are caused by the migration of larvae through the organs of the body, can result in serious disease and even death.

EPIDEMIOLOGY

Toxocara infections in animals are ubiquitous throughout the world. In humans, children are most frequently infected, probably due to ingestion of soil contaminated with dog or cat feces when playing outside. Visceral larva migrans occurs most commonly in children younger than 5 years, whereas ocular larva migrans typically manifests in older children between the ages of 5 and 10 years.

PATHOBIOLOGY

The life cycle of *Toxocara* in the animal host resembles that of *A. lumbricoides* in humans; larvae penetrate the intestinal wall after being released from ingested eggs, migrate through the vasculature to the lungs, enter the alveolae, and ascend the bronchial tree until they are swallowed back into the gastrointestinal tract, where they develop into adult worms that can produce eggs. However, when embryonated *Toxocara* eggs are ingested by humans, the released larvae migrate throughout the body (most commonly to the lungs, the liver, the central nervous system [CNS], and occasionally the eyes) but cannot develop into adult worms. When the larvae eventually die, they induce significant immediate-type and delayed-type hypersensitivity reactions that result in the formation of eosinophilic granulomas. Visceral larva migrans and ocular larva migrans seem to be mutually exclusive.

CLINICAL MANIFESTATIONS

Most *Toxocara* infections in humans are asymptomatic. Visceral larva migrans is characterized by low-grade fever, pulmonary symptoms (including cough and wheeze), and, less frequently, hepatosplenomegaly that sometimes causes right upper quadrant pain. Symptoms appear gradually and resolve slowly over 4 to 8 weeks. Myocarditis, nephritis, and CNS disease are less common. CNS involvement can result in seizures, encephalopathy, neuropsychiatric symptoms, or an eosinophilic meningoencephalitis.[9]

Ocular larva migrans typically presents as unilateral visual impairment that is sometimes accompanied by strabismus. Ocular larva migrans involving the retina can be difficult to distinguish from other causes of focal intraretinal lesions, such as retinoblastoma or tuberculosis.

DIAGNOSIS

Toxocariasis can be presumed based on a compatible clinical presentation and history of exposure to dogs or cats. Eosinophilia and hypergammaglobulinemia are often present. Serologic testing using an ELISA in combination with immunoblot to detect antibodies to *Toxocara* larval-stage antigens may be informative, but does not distinguish between active infection and past exposure. ELISAs incorporating recombinant larval antigens have improved sensitivity and specificity but are not yet widely available.[10] PCR testing is not currently available, and tissue biopsy to document the presence of larvae also is not recommended because of low sensitivity.

Computed tomography and fluorescein angiography may be helpful in the diagnosis of ocular larva migrans, especially to differentiate it from retinoblastoma and other causes of intraocular space-occupying lesions. Elevated levels of anti-*Toxocara* antibodies in aqueous and vitreous humor fluid relative to serum are also suggestive of this diagnosis.

TREATMENT

Albendazole (400 mg given twice daily for 5 days) is recommended for acute toxocariasis (Table 327-2). In patients who have severe pulmonary, cardiac, or neurologic involvement, corticosteroids (e.g., prednisone 60 mg daily for 5 days) may reduce the severity and duration of symptoms. Ocular larva migrans is treated by vitrectomy, corticosteroids (e.g., prednisone 30 to 60 mg daily for 2 weeks), albendazole, or a combination of these with expert supervision.

TABLE 327-2 TREATMENT OF TISSUE NEMATODE INFECTIONS

NEMATODE INFECTION	TREATMENT
Toxocariasis	Albendazole 400 mg bid for 5 days
Trichinellosis	Albendazole 400 mg bid for 8-14 days*
Angiostrongyliasis	Treatment with albendazole 15 mg/kg/day or mebendazole 10 mg/kg/day for 14 days is controversial but may relieve symptoms.
Gnathostomiasis	Albendazole 400 mg bid for 3 weeks Alternative: ivermectin 200 µg/kg/day for 2 days +/- surgical removal
Lymphatic filariasis	Diethylcarbamazine 6 mg/kg/day divided in three doses for 1 or 12† days plus doxycycline 200 mg/day for 6 weeks
Onchocerciasis	Doxycycline 200 mg/day for 6 weeks, preceded and followed by a single dose of ivermectin 150 µg/kg or moxidectin 8 mg (age >12 years) that is repeated every 3-6 months until resolution of symptoms and then annually for at least 3 years
Loiasis	Diethylcarbamazine 8-10 mg/kg/day divided in three doses for 21 days†,‡
Mansonella perstans	Doxycycline 200 mg/day for 6 weeks
Mansonella ozzardi	Ivermectin 200 µg/kg once
Mansonella streptocerca	Diethylcarbamazine 6 mg/kg/day divided into three doses for 12 days Alternative: ivermectin 150 µg/kg once
Dracunculiasis	Extraction of the adult worm

*Treatment is effective only if it is initiated during the intestinal phase of infection.
†Start at a dose of 50 mg on the first day, 50 mg three times/day on the second, 100 mg three times/day on the third, and then 8-10 mg/kg/day on day 4 onward.
‡Repeated treatment after 6 months is often necessary if symptoms and eosinophilia persist.
bid = twice daily.

PREVENTION

Visceral and ocular larva migrans may be prevented by periodic anthelminthic treatment of dogs and cats, proper disposal of pet feces, covering sandboxes, washing hands after playing with dogs or cats, and keeping children from playing in areas where animals have defecated.

PROGNOSIS

Symptoms of visceral larva migrans gradually resolve over 4 to 8 weeks, even in the absence of treatment. In ocular larva migrans, the degree of vision loss is dependent on the ocular structure involved, and permanent blindness may occur.

BAYLISASCARIASIS

Baylisascariasis is a rare zoonosis caused by infection with *Baylisascaris procyonis*, which is an ascarid parasite of raccoons and other small carnivores. In North America, infection is most associated with contact with raccoons or environments contaminated with their feces and occurs predominantly in infants and young children who ingest the embryonated eggs while playing with soil. Clinically, disease is manifested as neural larva migrans due to larval invasion of the CNS after release from ingested eggs in the gastrointestinal tract. Characteristic findings include fever, altered mental status, focal neurologic deficits, and seizures. Analysis of the cerebrospinal fluid (CSF) reveals eosinophilic meningitis. Once neural larva migrans is present, response to treatment with anthelminthics is poor, although corticosteroids may be helpful under expert supervision. *B. procyonis* has also been associated with ocular larva migrans, for which successful use of laser photocoagulation has been reported. Prophylactic albendazole (25 mg/kg/day for 20 days) started within days of an exposure may prevent clinical disease. Infection can be fatal or result in permanent neurologic or visual impairment.

TRICHINELLOSIS

DEFINITION

Trichinella infects a range of mammalian hosts, with the domestic pig serving as the most important reservoir worldwide. Humans are infected through eating raw or undercooked pork or other meats of domestic or wild animals that are contaminated with larvae that are encysted in muscle tissue. Although larvae develop into adults in the human intestinal tract, mate, and produce offspring larvae, clinical disease is characterized not so much by the intestinal infection

as by the newborn larvae that penetrate the intestinal wall and disseminate throughout the body.

EPIDEMIOLOGY

Several different species of *Trichinella* cause disease in humans, although *Trichinella spiralis* is the most common. *T. spiralis* is enzootic throughout the world in omnivorous and carnivorous wild animals, including bears, boars, and rats. *Trichinella nativa* affects predominantly carnivores (e.g., walruses, polar bears, and seals) living in the Arctic and subarctic regions of North America, Europe, and Asia. *Trichinella* is introduced into domestic animal populations, usually pigs or horses, by feeding them unprocessed meat scraps derived from infected animals, most commonly rats. Because of regulations banning this practice in the United States, Canada, and the European Union, human infection by consumption of undercooked or smoked pork products or beef contaminated with encysted larvae has been virtually eliminated, although it still occurs throughout the rest of the world. Instead, ingestion of poorly cooked wild game, especially bear or boar meat, is now the most common source of infection in these locations. In addition, an important source of infection with *T. nativa* in Alaskan and Canadian Arctic native populations is by eating uncooked walrus meat.

PATHOBIOLOGY

Trichinellosis results from ingestion of striated muscle containing encysted infective larvae. Larvae are released from muscle tissue by gastric enzymes and then migrate to the upper small intestine, where they rapidly develop into sexually mature adult worms after only 2 days. Adults live embedded in the columnar epithelium, where they grow to a length of 3 mm (females) or 1.5 mm (males). Females begin producing newborn larvae within 5 days of mating. Adult worms remain viable for an additional 3 to 5 weeks, after which acquired immunity leads to their expulsion from the host.

The oral cavity of newborn larvae possesses a swordlike stylet that permits them to penetrate the lamina propria, enter the lymphatic and blood vessels of the host, and migrate throughout the body. Larvae, which can enter all types of cells, usually die except in striated skeletal and cardiac muscle cells. Unique among nematodes, mature *Trichinella* larvae have an intracellular phase, during which they transform muscle cells into "nurse cells" that support larval growth and survival for decades (Fig. 327-4). Although nurse cells do not result in any disease in most mammals, in humans they can induce an eosinophilic granulomatous reaction that may result in significant tissue damage and symptoms.

As with most nematode infections, the severity of symptoms is related to the worm burden. Because newborn larvae are incapable of developing into adult worms within the human host, the number of encysted larvae ingested is the most important determinant of the number of larvae that invade muscle and other tissues.

CLINICAL MANIFESTATIONS

Clinical disease in humans progresses from an initial intestinal phase to a systemic or muscle phase. The initial phase of infection occurs within days after ingestion of larvae and may be associated with mild diarrhea, abdominal pain, and vomiting. This phase is self-limited and usually resolves spontaneously within 10 days.

The systemic dissemination of *Trichinella* larvae can result in myocardial, pulmonary, and focal neurologic manifestations, although usually only in heavily infected persons. This systemic phase of infection usually begins 2 to 3 weeks after ingestion of infective larvae and may persist for several weeks.

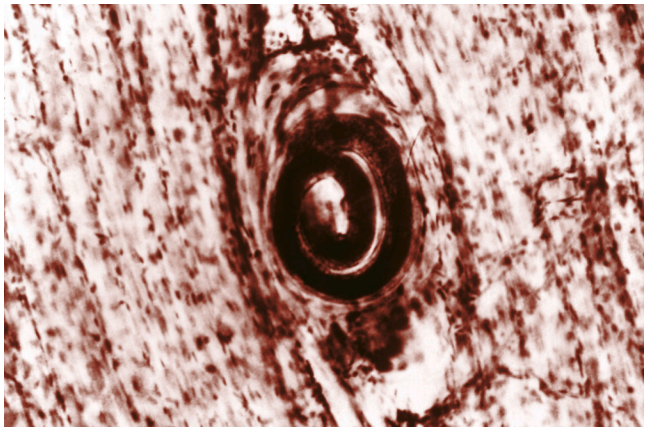

FIGURE 327-4. **Nurse cell in muscle tissue containing a larva of *Trichinella spiralis*.** (Courtesy of Dr. I. Kagan, Centers for Disease Control and Prevention.)

Clinical manifestations typically include fever, periorbital or facial edema, a diffuse inflammatory myositis (Chapter 248) that is characterized by myalgias and muscle tenderness, and petechial hemorrhages most easily observed in the subungual skin and conjunctivae. Larval invasion of the myocardium can lead to myocarditis (Chapter 47) that may result in heart failure or arrhythmias.

DIAGNOSIS

A diagnosis of trichinellosis should be suspected in individuals with a compatible clinical presentation, a history of eating raw or undercooked meat, eosinophilia, and increased muscle enzymes such as creatine kinase and lactate dehydrogenase. Definitive diagnosis depends on visualization of nurse cells in a muscle biopsy specimen or detection of *Trichinella*-specific DNA by PCR testing. Findings on muscle biopsy may be normal even in heavily infected patients because of sampling error. Detection of anti-*Trichinella* antibodies can be very useful in making a diagnosis, and antibodies can be detected as early as 12 days after initial infection.

TREATMENT

During the intestinal phase of infection, albendazole is recommended at a dosage of 400 mg given twice daily for 8 to 14 days to kill the adult worms and prevent release of newborn larvae (see Table 327-2). Administration of albendazole during the systemic phase of infection could potentially worsen symptoms by exacerbating the host inflammatory response to dying larvae, so treatment of severe systemic disease, including myocarditis and neurologic disease, should combine corticosteroids (e.g., prednisone 40 to 60 mg daily for 8 to 14 days), with albendazole. Symptomatic treatment with antipyretics and analgesics should also be considered.

PREVENTION

Trichinella infection is prevented by thoroughly cooking meat to kill encysted larvae. Freezing meat solid at –20° C for at least 3 days will kill *T. spiralis* but not all other species of *Trichinella*. Of note, curing and smoking techniques do not reliably kill this nematode.

PROGNOSIS

Although mortality due to trichinellosis is rare, larvae encysting in viscera may result in death due to cardiac, renal, hepatic, or cerebral complications. In most cases, however, fever and muscle pain usually resolve between 1 and 6 weeks after all migrating larvae have encysted in tissue.

ANGIOSTRONGYLIASIS

DEFINITION

Angiostrongylus cantonensis and *Angiostrongylus costaricensis* are nematodes that normally infect rodents, primarily rats.

EPIDEMIOLOGY

Human infections with *A. cantonensis* occur mainly in Southeast Asia and the South Pacific and less frequently in South America, the Caribbean, and in Louisiana. Abdominal angiostrongyliasis due to *A. costaricensis* has been reported mainly in Latin America, mostly in young children.

PATHOBIOLOGY

The adult worms of *A. cantonensis*, or rat lungworm, inhabit the pulmonary arteries of rodents. Larvae are produced and migrate to the pharynx, where they are swallowed, and then are passed in the feces. Mollusks such as snails, slugs, and prawns serve as intermediate hosts until they are ingested by definitive hosts. Released larvae migrate to the brain, where they develop into immature adult worms before traveling to the pulmonary vasculature to become sexually mature adults. Humans are incidentally infected after eating raw or poorly cooked mollusks or fresh vegetables contaminated with parts of infected mollusks; larvae can migrate to the CNS but cannot develop further. As opposed to *A. cantonensis*, the larvae of *A. costaricensis* can develop into sexually mature adult worms in the local lymphatics and mesenteric arterioles of humans and release eggs and larvae into the intestinal tissue, thereby causing an intense eosinophilic granulomatous reaction.

CLINICAL MANIFESTATIONS

After ingestion, *A. cantonensis* larvae penetrate the intestinal wall and migrate to the brain, the meninges, and, less commonly, the spinal cord and eye. Fever, severe headache, meningismus, nausea, vomiting, seizures, and focal neurologic deficits may develop. *A. costaricensis* infection can mimic appendicitis with right-sided abdominal pain, vomiting, and fever. Less frequently, gastrointestinal bleeding may occur.

DIAGNOSIS

Diagnosis of *A. cantonensis* infection is based on a history of ingestion of potentially contaminated food, the presence of eosinophilia, microscopic observation of eosinophils and, rarely, larvae in the CSF, and detection of the parasite by PCR in CSF.[11] In patients who have CNS and/or intestinal angiostrongyliasis, neither larvae nor eggs are found in the feces, although both may be seen in tissue specimens. Serology is not commercially available.

TREATMENT AND PREVENTION

The benefit of anthelminthics (Chapter 315) is unclear, although albendazole or mebendazole (Table 327-2), usually administered in combination with analgesics and corticosteroids (e.g., prednisone 60 mg daily for 14 days), appear to relieve symptoms. Serial lumbar punctures to remove CSF can relieve symptoms of raised intracranial pressure caused by infection with *A. cantonensis*. Proper cooking of food and washing of vegetables can prevent this infection.

PROGNOSIS

Most patients infected with either species of *Angiostrongylus* recover completely after approximately 2 weeks.

GNATHOSTOMIASIS

Gnathostoma spinigerum is an intestinal nematode of dogs and cats. Intermediate hosts include tiny crustaceans (copepods), amphibians, freshwater fish, and birds. Human infection occurs throughout the Far East, Thailand, and Latin America after eating raw or undercooked invertebrate hosts that contain infective larvae. The larvae are subsequently released into the intestine and migrate through the body without reaching sexual maturity. The most common clinical presentation is migrating painful and pruritic subcutaneous swellings. Eosinophilic meningitis and ocular larva migrans may also occur. Peripheral eosinophilia is usually present; with meningitis, eosinophils are also present in the CSF. Although serologic testing is not available in the United States, laboratories in Thailand and Japan can perform it. Treatment of cutaneous disease with either a 3-week course of albendazole or a 2-day course of ivermectin is recommended (see Table 327-2); for neurologic or ocular involvement, management is supportive, and anthelminthics are not advised because they may worsen manifestations. Gnathostomiasis may be prevented by thoroughly cooking fish. This infection may progress to potentially devastating results, including paralysis, subarachnoid hemorrhage, and permanent visual loss.

FILARIASES

DEFINITION

The filariases are arthropod-borne nematode infections in which mature adult worms live in the lymphatics or in connective tissue.

EPIDEMIOLOGY AND PATHOBIOLOGY

Eight filarial species infect humans, mostly in tropical areas of the world (Table 327-3): *Wuchereria bancrofti, Brugia malayi, Onchocerca volvulus, Brugia timori, Loa loa, Mansonella streptocerca, Mansonella perstans*, and *Mansonella ozzardi*. The first three are the most common filariases worldwide.

For all filarial nematodes, transmission to humans is via the bite of an infected arthropod vector that deposits infective larvae called microfilariae into the skin or blood. After several months, microfilariae mature into adult worms that are capable of mating to produce new microfilariae that can be ingested by another arthropod vector to complete the life cycle. Untreated, adult worms survive for 5 to 17 years in the human host; microfilariae live for between 5 months and 5 years. For most filarial nematodes except *B. malayi* and *M. perstans*, humans are the only definitive host. Most of the filariases require prolonged exposure for disease to manifest and are therefore uncommon in short-term travelers to endemic areas.

CLINICAL MANIFESTATIONS

Clinical manifestations of infection are proportional to the worm burden harbored by an individual, with relatively light infections commonly being asymptomatic. For several of the filariases, the host inflammatory response to infection becomes apparent only when the death of the adult worms or microfilariae triggers exposure to filarial antigens that were previously hidden from the immune system or the release of bacterial endosymbionts of the genus *Wolbachia* that live inside several of the filariae. *Wolbachia* are of the order Rickettsiales and are found in the hypodermis of adult worms and in oocysts, embryos, and microfilariae; they play a critical role in worm viability and fertility.

DIAGNOSIS

Diagnosis of filarial infections often is based on the microscopic examination of blood or skin specimens for characteristic microfilariae (see Table 327-3). PCR assays developed by several research laboratories are more sensitive than traditional techniques, but none are yet commercially available. Microfilariae of the different filarial species measure between 170 and 320 μm in length and can be distinguished based on the tissue source of the specimen, the presence or absence of a sheath, and the arrangement of nuclei in the tail. Serology is not useful in endemic areas because a positive result does not distinguish between previous and current infection, and there is considerable antigenic cross-reactivity between the filariae and other nematodes. Detection of antifilarial antibodies may, however, be useful in returned long-term travelers or expatriates who are not originally from endemic areas.

TREATMENT

Diethylcarbamazine, ivermectin, and albendazole are the principal antifilarial drugs, although they have varying efficacies against the different filarial species (see Table 327-2). Diethylcarbamazine is macrofilaricidal (active against the adult worm) for *W. bancrofti*, *Brugia* species, and *L. loa*, although prolonged or repeated courses are required for this effect. More commonly, the goal is to suppress microfilaria production by female adult worms using single doses of antifilarial drugs administered alone or in combination annually or biannually. Reduction of microfilariae in the blood or skin can in some cases ameliorate symptoms or prevent progression of disease as well as interrupt transmission. Furthermore, targeting the *Wolbachia* endosymbionts of some filarial species with extended courses of doxycycline can be macrofilaricidal and has been incorporated into first-line treatment recommendations.

PROGNOSIS

Although not usually fatal, infection can result in considerable disability and disfigurement, such as irreversible limb lymphedema (*W. bancrofti* and *B. malayi*) or blindness (*O. volvulus*).

LYMPHATIC FILARISIS

DEFINITION

The three principal etiologic agents of lymphatic filariasis (*W. bancrofti, B. malayi*, and *B. timori*) are transmitted to humans through the bite of an infected mosquito.

EPIDEMIOLOGY

An estimated 50 million people are affected by lymphatic filariasis worldwide; over 90% of cases are caused by *W. bancrofti*, whereas less than 4 million are

TABLE 327-3 FILARIAL PARASITES OF HUMANS

			MICROFILARIAE		
SPECIES	**DISTRIBUTION**	**VECTOR**	**PRIMARY LOCATION**	**PERIODICITY**	**PRESENCE OF SHEATH**
Wuchereria bancrofti	Tropics worldwide	Mosquitoes	Blood	Nocturnal, subperiodic	+
Brugia malayi	India, Southeast Asia	Mosquitoes	Blood	Nocturnal, subperiodic	+
Brugia timori	Indonesia	Mosquitoes	Blood	Nocturnal	+
Onchocerca volvulus	Africa, South America	*Simulium* blackflies	Skin, eye	None or minimal	–
Loa loa	West and Central Africa	*Chrysops* flies	Blood	Diurnal	+
Mansonella perstans	Africa, South America, Caribbean	Midges	Blood	None	–
Mansonella ozzardi	Central and South America, Caribbean	Midges, *Simulium* blackflies	Blood	None	–
Mansonella streptocerca	West and Central Africa	Midges	Skin	None	–

due to *B. malayi*.[12] *B. timori* is of minor importance, being restricted to southeastern Indonesia. *W. bancrofti* is widely distributed in the tropics, especially in Southeast Asia, the Indian subcontinent, Africa, South America, the Caribbean, and the South Pacific. In Europe and North America, cases are seen in returning long-term travelers and in migrants.[13] The major vectors of bancroftian filariasis are *Culex* mosquitoes in urban areas, anopheline mosquitoes in rural areas of Africa, and *Aedes* species in the Pacific.

Humans are the only definitive host for *W. bancrofti*. *B. malayi*, however, can be zoonotic, with both monkey and feline species serving as reservoir hosts. Brugian filariasis is found primarily in India, Malaysia, and other areas in Southeast Asia.

PATHOBIOLOGY

Microfilariae deposited at the mosquito bite wound subsequently migrate through the subcutaneous tissue to the lymphatic system, where adult worms develop after approximately 4 to 12 months. The worms reside coiled in lymph nodes but may extend into afferent lymph vessels and surrounding subcutaneous tissue. The lymphatics of the lower and upper extremities and male genitalia are commonly affected. After mating, female worms, which measure between 4 and 10 cm in length and are twice the length of males, release more than 10,000 microfilariae a day that migrate into the blood stream, where they may be ingested by biting mosquitos. For most lymphatic filarial species, microfilariae appear in the peripheral blood only at night, when mosquito vectors are most likely to bite. Adult filariae live between 5 and 8 years within the host, although infections persisting for decades have been reported.

The pathology of filarial infections is primarily due to obstruction of lymphatic circulation resulting from damage induced by adult worms, specifically a localized inflammatory lymphangitis. This inflammatory response is triggered by release of antigens from dead or dying worms, although evidence suggests that it can also be induced by living worms and by excreted or secreted *Wolbachia* antigens. Inflammatory damage is often exacerbated by secondary bacterial and fungal infections.

The initial inflammatory response leads to endothelial and connective tissue proliferation and vessel dilation, which impairs normal lymphatic function and results in lymphedema that is initially reversible. However, worm death results in a granulomatous reaction to released worm and *Wolbachia* antigens. The infiltration of giant cells as well as plasma cells, eosinophils, and neutrophils can completely occlude the lumen of the lymphatic vessel. Over time, progressive fibrosis and obstruction of lymph circulation result in irreversible edema. Although recanalization and collateralization of lymph vessels may occur, lymphatic function remains compromised.

CLINICAL MANIFESTATIONS

The clinical manifestations of lymphatic filariasis range from asymptomatic infection to severe chronic lymphatic obstruction accompanied by lymphedema and enlargement of the affected limb or body part (referred to as elephantiasis). Other common clinical outcomes include acute episodic lymphadenitis (also called filarial fever) and tropical pulmonary eosinophilia, usually in younger individuals. Most infected individuals living in endemic regions are clinically asymptomatic, although microfilariae can be observed in their blood. Despite the absence of a significant inflammatory response, ultrasound examination may reveal lymphatic dilation that precedes the onset of clinically apparent disease.

For unknown reasons, newly exposed individuals may develop acute inflammatory reactions that can rapidly progress to chronic or irreversible changes compared with those born in endemic areas. Severe episodes of lymphadenitis, often with genital involvement, may lead to the relatively rapid development of lymphedema and elephantiasis within a year of arrival. Findings usually resolve quickly if the individual promptly leaves the endemic area. Microfilariae are usually not detected in these patients.

Acute Lymphadenitis

Acute episodes of retrograde lymphadenitis occur most commonly in adolescents in endemic areas, often in response to dying adult worms. Painful enlargement of an affected lymph node, most commonly inguinal, with accompanying erythema of the overlying skin precedes the onset of lymphangitis and is accompanied by fever and chills. Episodes usually persist for about a week, frequently recur, and can be incapacitating. Defervescence is abrupt and associated with desquamation of the overlying skin. In men, inguinal lymphadenitis can be complicated by epididymitis and orchitis. Patients with filarial fevers may be microfilaremic but often are not.

Elephantiasis

Repeated episodes of lymphadenitis eventually lead to dilation of the lymphatic vessels, thereby resulting in chronic lymphedema over the course of months to years

FIGURE 327-5. Elephantiasis, or chronic lymphedema, due to infection with *Wuchereria bancrofti*. (Courtesy of the Centers for Disease Control and Prevention.)

(Fig. 327-5). The extremities, breasts, and genitalia are most commonly affected, although *B. malayi* infection usually involves only the lower parts of the legs. The edema is initially pitting in nature, but the subcutaneous tissue eventually loses its elasticity, thereby resulting in woody edema with thickening of subcutaneous tissue and hyperkeratosis. Secondary bacterial or fungal infection is common.

In bancroftian filariasis, hydrocele is a common manifestation of chronic filariasis in men and can occasionally become massive and debilitating. Lymphedema of the vulva is sometimes but uncommonly seen in women. Involvement of the retroperitoneal lymphatics can lead to their rupture to produce intermittent chyluria or chylocele.

Tropical Pulmonary Eosinophilia

Tropical pulmonary eosinophilia (Chapter 156) develops in a small minority of individuals with filarial infections. The syndrome is most commonly seen in young men living in southern India, although it also occurs in Pakistan, Sri Lanka, and Southeast Asia. Clinical findings include nocturnal paroxysmal cough, wheeze, and low-grade fever that is accompanied by eosinophilia. Levels of total IgE and antifilarial antibodies are typically high. Chest radiographs may show diffuse interstitial infiltrates or mottled opacities. Without treatment, chronic restrictive lung disease may develop.

DIAGNOSIS

PCR is highly sensitive for detecting filarial antigens in blood, but these tests are currently available only as research tools and not for routine clinical diagnosis. As a result, diagnosis usually relies on microscopic examination of a Giemsa-stained blood smear for microfilariae. Although thick blood smears are relatively insensitive, except in cases of high microfilaremia, concentration or filtering techniques can increase diagnostic yield. Characteristic microfilariae are 250 to 320 μm in length. Collection of blood should be timed according to the known periodicity of the microfilariae.

A rapid immunochromatographic card test is available to detect *W. bancrofti* antigen (there is no equivalent test for *Brugia* infections) and has the advantage of not requiring nocturnal collection of blood because it detects circulating antigen of the adult worm and not microfilariae. Serologic detection of antifilarial antibodies is of limited value because of extensive antigenic cross-reactivity with other nematodes. Furthermore, actively infected individuals cannot be distinguished from those previously infected or merely exposed but not infected. Ultrasound examination of the lymphatic vessels of the spermatic cord of men can be used to visualize the "filarial dance sign," which is pathognomonic for a nest of filarial parasites.

Individuals with elephantiasis may be amicrofilaremic. Diagnosis therefore depends on a compatible clinical history and physical examination in the context of the appropriate epidemiology, and it may be supported by a positive antigen test, PCR (if available) or, in men, by a suggestive scrotal ultrasonogram. It should be distinguished from podoconiosis, which is a tropical lymphedema that results from long-term barefoot exposure to red-clay soil derived from volcanic rock and that may be a T-cell–mediated inflammatory disease.

TREATMENT

Management of lymphatic filariasis differs according to whether the aim is to control or cure the disease in an individual patient. In endemic areas, annual mass drug administration with a combination of two or three[A8,A9] antifilarial drugs can reduce transmission by decreasing the number of microfilariae that are in the blood

and available to biting mosquitoes. These programs use different combinations of single-dose diethylcarbamazine (6 mg/kg), ivermectin (200 µg/kg), and albendazole (400 mg), administered at least annually. The World Health Organization recommends that all three drugs be co-administered in regions where onchocerciasis and *L. loa* are not endemic, ivermectin plus albendazole in areas where onchocerciasis is also endemic, and albendazole alone in regions with loiasis.

All individuals with active infection by a lymphatic filarial parasite, whether symptomatic or asymptomatic, should be treated with an antifilarial medication (see Table 327-2). The treatment of choice is diethylcarbamazine (6 mg/kg given once). In the United States, diethylcarbamazine is available only through the Centers for Disease Control and Prevention (CDC) drug service (http://www.cdc.gov/laboratory/drugservice/formulary.html).

Diethylcarbamazine is both microfilaricidal and partially macrofilaricidal. In individuals who will not be returning to endemic areas, repeated treatments with diethylcarbamazine every 6 to 12 months are often attempted to kill the adult worms instead of just reducing the levels of microfilariae in the blood. Although the adult worm burden is reduced in most treated individuals, all parasites are eliminated in less than 25%. In men with live adult worms visible by ultrasound in the scrotal lymphatics, serial studies may be performed to monitor the effects of therapy.

Unfortunately, lymphedema due to lymphatic filariasis is usually not reversible with diethylcarbamazine treatment, except in the very early stages. Nevertheless, the chronic sequelae of lymphatic filariasis can be limited by preventing secondary bacterial and fungal infection through meticulous hygiene and prompt treatment of suspected infections with antimicrobials. Limb elevation, physiotherapy, and use of elastic stockings may slow the worsening of lymphedema. Surgery is usually not indicated except for cases of hydrocele.

Interestingly, treatment directed against the *Wolbachia* endosymbiont is effective for killing adult *W. bancrofti* and *Brugia* worms. Doxycycline 200 mg daily for 6 weeks reduces female worm fertility with a resulting suppression of microfilaremia for up to a year and reduces the number of live adult worms. This treatment course may also prevent progression of early-stage lymphedema.[14] Given the duration of treatment, these regimens are not ideal for disease control programs in endemic countries.

Diethylcarbamazine is very effective in the treatment of tropical pulmonary eosinophilia. Treatment with 6 mg/kg/day for 14 to 21 days results in resolution of symptoms within a week, although relapse may occur even after an interval of years.

See also Chapter 315.

PREVENTION

Annual mass treatment with single doses of one to three antifilarial drugs (see Treatment) can significantly reduce the prevalence of infection within a community. In some areas, diethylcarbamazine-fortified table salt has been used to reduce the levels of microfilaremia in affected communities to interrupt transmission. Vector control through use of insecticide-treated bed nets and residual indoor spraying of insecticides may have some efficacy.

PROGNOSIS

Even when clinically asymptomatic, most individuals with microfilaremia have evidence of subclinical disease, for which early treatment can forestall additional lymphatic damage. Unfortunately, once chronic lymphedema is established, it is not usually reversible with diethylcarbamazine treatment, although progression can be limited by supportive measures such as hygiene and prompt treatment of secondary bacterial or fungal infections. Drainage of hydroceles provides temporary relief, but fluid accumulation usually recurs in the absence of surgery or drug treatment.

ONCHOCERCIASIS

DEFINITION

Onchocerciasis, or river blindness, caused by the nematode *Onchocerca volvulus*, is transmitted to humans by *Simulium* blackflies. Infective microfilariae develop into male and female adult worms over a period of several months and live for 9 to 14 years coiled within subcutaneous fibrous nodules (onchocercomas). Adult females measure between 20 and 70 cm in length and remain confined to the nodules; males are only 3 to 5 cm long and freely migrate through the subcutaneous tissues between nodules to inseminate females. Each day, mature female worms produce up to 1500 microfilariae, which leave the nodule to migrate primarily through the skin and ocular tissues. Microfilariae live within the host for 12 to 18 months.

EPIDEMIOLOGY

Onchocerciasis is endemic in equatorial Africa, with small foci in Yemen and an area on the border between Brazil and Venezuela. Approximately 20 million people are estimated to be infected, and 1 million have vision loss due to this parasite. More than 99% of cases occur in sub-Saharan Africa, with Nigeria being the most highly endemic country. Because *Simulium* blackflies require fast-flowing, well-oxygenated water for egg laying and reproduction, cases are concentrated around streams and rivers, often in the most fertile farming areas.

PATHOBIOLOGY

The pathologic changes of onchocerciasis are primarily due to an inflammatory reaction to microfilariae, mostly in the skin, eyes, and lymph nodes. Adult worms contained in nodules are relatively isolated from the host immune response. Tissue damage results when dying microfilariae precipitate a cell-mediated immune response, which becomes more pronounced as infection persists. The degree of tissue damage is directly related to the intensity of infection as well as the magnitude of the host response. Sclerosing keratitis, which is the major cause of vision loss, results from a helper T-cell type 2 (T_H2)–driven inflammatory reaction to dying intraocular microfilariae. With time, neovascularization and scarring of the cornea lead to corneal opacification and eventual blindness. In the skin, similar immune responses result in pruritus and angioedema. Ongoing low-grade inflammation in the skin can eventually lead to loss of elasticity and atrophy. Chronic inflammatory changes and fibrosis are also seen in lymph nodes.

As with the nematodes responsible for lymphatic filariasis, *O. volvulus* adult worms contain endosymbiotic *Wolbachia* bacteria that are obligatory for the development, survival, and fertility of these worms. Pro-inflammatory *Wolbachia* proteins released by dying microfilariae may be responsible for a significant amount of the immunopathology associated with onchocerciasis. For example, *Wolbachia* antigens interact with the innate immune system through a toll-like receptor 2–mediated mechanism.

CLINICAL MANIFESTATIONS

Onchodermatitis

Onchocerciasis commonly presents with a diffuse papular dermatitis that is intensely pruritic. In heavily infected individuals, the pruritus can be intractable and lead to scratching and excoriation to the point of bleeding and even suicide. Hypersensitivity reactions, scabies, insect bites, and atopic or contact dermatitis should be considered in the differential diagnosis of the acute papular dermatitis seen with onchocerciasis. The skin of affected areas becomes edematous and thickened, loses its elasticity, and takes on an orange-peel texture. A lichenified dermatitis (referred to as sowda) may occur; it consists of an intensely pruritic eruption limited to one extremity, usually a leg, with hyperpigmented papules and plaques accompanied by edema of the entire limb. Over time, the skin atrophies, and fine wrinkles appear, especially over the buttocks. Pruritus is uncommon at this point. Areas of depigmentation may occur, most commonly over the shins, a phenomenon called leopard skin.

Subcutaneous Nodules

Subcutaneous onchocercomas containing adult worms are most often palpable over bony prominences. In Africa, the nodules are often found over the hips and lower limbs; in South America, they are usually located on the head and upper part of the body. Nodules measure between 0.5 and 3 cm in diameter and are freely mobile. In lightly infected individuals, such as expatriates, palpable nodules are usually not present.

Ocular Lesions

Initial ocular involvement is characterized by conjunctivitis, excess tearing, and photophobia in response to dying microfilariae. At this point in the course of disease, punctate keratitis or snowflake corneal opacities are present. Over 20 to 30 years of chronic infection, the disease progresses to sclerosing keratitis, neovascularization, and corneal opacification. The anterior chamber of the eye may also be involved, with iritis, iridocyclitis, and secondary glaucoma. Posterior ocular disease can manifest as chorioretinitis, optic neuritis, and optic atrophy.

Neurologic Manifestations

Onchocerciasis has been linked epidemiologically to epilepsy, intellectual disability, and failure to thrive. This link has been suggested by evidence that these syndromes have declined markedly after the elimination of onchocerciasis in hyperendemic areas, such as western Uganda.[15]

Lymphadenopathy

Lymphadenopathy is frequently found in the inguinal area in Africa and in the head and neck in South America. Advanced inguinal lymphadenopathy can result in the so-called hanging groin, with elongated atrophic skin containing nontender and fibrotic lymph nodes.

DIAGNOSIS

Definitive diagnosis has traditionally been made by observing unsheathed motile microfilariae, measuring 200 to 300 µm in length, that are released from superficial

skin snips. To collect a skin snip, a thin piece of skin overlying a bony prominence that has been tented up with a needle is sliced with a scalpel blade, or a corneal-scleral punch instrument is used to obtain a small piece of skin. Avoidance of blood contamination is critical to avoid confusion with blood-borne microfilariae in cases in which patients are coinfected with other filariases. Typically, six snips are taken, one from over each scapula, iliac crest, and lateral aspect of each calf, and then incubated for up to 24 hours in warm physiologic saline and examined microscopically for motile microfilariae. PCR amplification of filarial DNA directly from skin snips is far more sensitive than direct visualization but is not widely available. With ocular disease, free microfilariae may be visible by slit lamp examination in the anterior chamber or aqueous humor.

Subcutaneous nodules can be sampled or examined by ultrasound to demonstrate the presence of adult worms. Serologic tests are usually positive for antifilarial antibodies but are not specific because of considerable antigenic cross-reactivity with other nematodes. Eosinophilia is a common but inconsistent finding.

TREATMENT

The macrocytic lactones ivermectin or moxidectin, in combination with doxycycline, are the treatments of choice for onchocerciasis (see Table 327-2). Administration of a single dose of ivermectin (150 µg/kg) or moxidectin (8 mg [age > 12 yr]) is effective in ameliorating ocular and dermatologic disease by destroying microfilariae and suppressing their release from female worms.[A10] However, since macrocyclic lactones are not active against adult worms, monotherapy with them must be repeated every 6 to 12 months, probably for at least 10 years in patients without further exposure. For unknown reasons, pruritus in lightly infected expatriates may require more aggressive and frequent treatment for the first 2 years. Within 24 hours of treatment, fever and pruritus may occur in reaction to the dying microfilariae or released *Wolbachia* antigens, especially in patients with high pretreatment levels of microfilariae.

Doxycycline 200 mg/day administered for 6 weeks, preceded by and followed by a single dose of ivermectin or moxidectin, depletes *Wolbachia* endosymbionts from adult worms, thereby resulting in a significant macrofilaricidal effect and suppression of embryogenesis and microfilaria production for up to 18 months in the remaining adult worms.[A11] This regimen is recommended if patients with onchocerciasis have departed from an endemic area and will not be re-exposed. Following initial treatment, ivermectin or moxidectin should be given every 3 to 6 months until patients are asymptomatic and then repeated annually for at least 3 years.

Ivermectin and moxidectin should be used with caution in areas where *L. loa* (see later) is coendemic because it may precipitate severe reactions, including encephalopathy in patients with high levels of microfilaremia. Diethylcarbamazine should never be used to treat onchocerciasis because of frequent serious reactions to dying microfilariae, ranging from urticaria and angioedema to hypotension and death. Although the drug suramin (available from the CDC drug service) is active against adult *O. volvulus* worms, it is used only in rare situations because of its toxicity. Nodulectomy successfully resolves the infection in some cases.

See also Chapter 315.

PREVENTION

Regular mass administration of ivermectin (150 µg/kg as a single dose) to entire communities in endemic regions forms the core of the global eradication strategy for onchocerciasis. Implementation of this program has been made easier because the drug is donated by the manufacturer. In addition to benefiting infected individuals, mass drug administration reduces the number of microfilariae available to vectors and thus interrupts transmission. For travelers to endemic areas, use of insect repellent is beneficial.

PROGNOSIS

Vision loss caused by *O. volvulus* results in significant morbidity, long-term disability, and reduced economic productivity. When untreated, onchocerciasis has been associated with a reduced life expectancy of at least 10 years compared with uninfected individuals in the same area, an effect that appears to be independent of the blindness that develops. Treatment with repeated doses of a macrocytic lactone significantly reduces the likelihood of these outcomes.

LOIASIS

DEFINITION

Loiasis is caused by infection with the filarial nematode *Loa loa*, also known as the African eye worm. *L. loa* are transmitted by flies of the genus *Chrysops* during a blood meal. Adult worms develop during a period of 1 to 4 years and can live for up to 17 years. They migrate freely in the subcutaneous tissue, including the subconjunctiva or sclera of the eye. Adult females measure between 40 and 70 mm in length; males are shorter, measuring between 25 and 35 mm. After mating, females release microfilariae into the blood. *L. loa* microfilariae exhibit a diurnal periodicity coinciding with the feeding habits of *Chrysops*, with microfilaremia peaking around midday.

EPIDEMIOLOGY

Loiasis is endemic in the rainforest regions of Central and West Africa, with the highest prevalence in Gabon, Cameroon, the Democratic Republic of the Congo, Nigeria, and the Central African Republic.[16] Symptomatic loiasis can develop after a shorter period of exposure compared with other filarial infections, so it can be seen in returning travelers or expatriates who have spent extended periods in Africa.

PATHOBIOLOGY

Neither adult *L. loa* worms nor microfilariae have any direct pathologic effects. In a subset of infected individuals, a hypersensitivity response, termed a *Calabar swelling*, develops to secretions from adult worms or released microfilariae, thereby resulting in recurrent localized angioedema that often precedes the migrating worm. These patients have high serum levels of IgE antibodies and eosinophilia. Unlike other filariae, *L. loa* does not contain *Wolbachia* endosymbionts.

CLINICAL MANIFESTATIONS

Most individuals with loiasis are asymptomatic despite being microfilaremic. Recurrent Calabar swellings and eyeworm are the most common findings.[17] Calabar swellings measure 5 to 20 cm in diameter, typically occur on the extremities and the face, and persist for a few days. The onset is often preceded by pruritus and pain. On occasion, adult worms may migrate across the subconjunctiva or sclera of the eye, thereby causing severe pain and inflammation (Fig. 327-6). Rare complications of infection include nephropathy and encephalitis, which usually develop in patients with high levels of microfilariae after receiving diethylcarbamazine or ivermectin treatment for other filarial infections. Endomyocardial fibrosis, resulting from eosinophilic infiltration of the myocardium, has been reported in association with loiasis.

DIAGNOSIS

Diagnosis depends on microscopic examination of a Giemsa-stained blood film for characteristic sheathed microfilariae. PCR testing is performed in research laboratories but is not generally available or FDA-approved. Blood should be collected between 10 AM and 2 PM because of the diurnal periodicity of the microfilariae; if someone has traveled from an endemic area, collection should be performed in relation to the time zone where the infectious bite occurred. Because individuals who are not native to endemic areas are usually not microfilaremic, diagnosis relies on a compatible history, clinical findings, peripheral eosinophilia, and elevated antifilarial antibody levels. Adult worms can sometimes be surgically removed while migrating across the eye or through subcutaneous tissues. Calabar swellings must be distinguished from onchocercomas and other causes of angioedema.

TREATMENT

Diethylcarbamazine (8 to 10 mg/kg/day for 21 days) is active against both adult *L. loa* worms and microfilariae (see Table 327-2). Treatment is usually increased from a dose of 50 mg/day on the first day to the full dose on the fourth day to minimize the likelihood of treatment-associated complications, the most

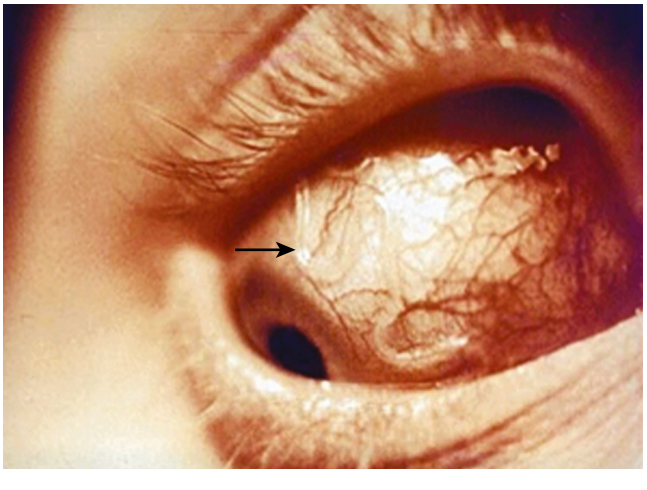

FIGURE 327-6. Adult *Loa loa* worm migrating across the eye *(arrow)*.

serious of which are glomerulonephritis and a potentially fatal encephalopathy. Treatment-associated complications, which are more common with high pretreatment microfilarial levels (>2500 microfilaria/ml), result from host allergic reactions to dying microfilariae. Corticosteroids (e.g., prednisone 40 mg daily or the equivalent for 4 to 5 days) may prevent allergic side effects. Alternatively, apheresis can be used to remove circulating microfilariae before initiation of diethylcarbamazine. Albendazole (200 mg orally twice a day for 3 weeks), which is microfilaricidal but has no activity against adult worms, can be used to reduce high-level microfilaria before treatment with diethylcarbamazine. The same albendazole regimen has shown some success in patients who have failed two rounds of diethylcarbamazine. Repeated courses of diethylcarbamazine may be necessary in about 50% of patients before clinical manifestations completely resolve. Persistent or increasing eosinophilia or levels of antifilarial antibodies 6 months after treatment should also prompt re-evaluation for repeated treatment. Adult worms in the eye may be surgically removed.

Ivermectin is microfilaricidal but has no macrofilaricidal effect and may cause toxic encephalopathy in individuals with high-level microfilaria. In areas where onchocerciasis is co-endemic, this infection should be excluded or treated before initiation of diethylcarbamazine to prevent toxicity from dying *O. volvulus* microfilariae.

See also Chapter 315.

PREVENTION

Weekly chemoprophylaxis with diethylcarbamazine administered as a 300-mg dose is effective in preventing loiasis in long-term residents of endemic areas.

PROGNOSIS

Although repeated courses of diethylcarbamazine are required in about 50% of patients before complete resolution of clinical manifestations, immunologic perturbations (e.g., eosinophilia, antifilarial antibody levels) nearly always resolve within 1 year of definitive treatment.[18]

LESS COMMON FILARIAL INFECTIONS

Mansonella perstans

M. perstans infection occurs throughout West and Central Africa, in northeastern South America, and in parts of the Caribbean. Microfilariae are transmitted by *Culicoides* midges and develop into adult worms that live in serous body cavities, such as the pleural, pericardial, and peritoneal spaces, as well as in mesenteric and retroperitoneal tissues. Most infections are asymptomatic, although painless conjunctival nodules with eyelid edema have been reported. Transient angioedema and Calabar-like swellings, fever, headache, arthralgias, and neurologic manifestations may also occur. Microfilariae do not exhibit periodicity and can be observed on stained blood films. Eosinophilia is common. *M. perstans* harbors *Wolbachia* endosymbionts, and treatment with doxycycline 200 mg/day for 6 weeks is highly effective in suppressing microfilaremia for up to 3 years, thereby suggesting that the treatment is macrofilaricidal.

Mansonella ozzardi

Infections with *M. ozzardi* occur in Central and South America and parts of the Caribbean, especially Haiti. Vectors include *Simulium* blackflies and midges. Adult worms locate to the peritoneal and thoracic cavities or the lymphatics; microfilariae circulate in the blood without periodicity. Infection usually results in asymptomatic eosinophilia, although corneal lesions and arthritis have been reported. Allergic symptoms such as urticaria and lymphadenopathy may occur in response to dying worms. *M. ozzardi* microfilariae are highly susceptible to ivermectin, and administration of a single dose of 200 µg/kg may provide long-term suppression of microfilaremia and improvement of symptoms.[19] Neither diethylcarbamazine nor the benzimidazoles are effective.

Mansonella streptocerca

M. streptocerca is endemic in the tropical forest zone of West and Central Africa and is transmitted by biting midges. Similar to *O. volvulus*, both adult worms and microfilariae reside in the subcutaneous tissues. In contrast to onchocerciasis, microfilariae do not invade the eye. Infection is usually asymptomatic, although a pruritic dermatitis with depigmentation similar to onchodermatitis can affect the trunk and upper extremities. Associated axillary or inguinal adenopathy is common. Microfilariae have characteristic hooked tails and can be visualized in skin snips. In areas where onchocerciasis is co-endemic, skin specimens must be stained to differentiate *M. streptocerca* from *O. volvulus*. Diethylcarbamazine, which is microfilaricidal and macrofilaricidal, is given as 6 mg/kg/day for 12 days. Ivermectin is not macrofilaricidal but is highly effective at eliminating microfilariae from the skin. It is likely that ivermectin-containing mass drug administration programs targeting lymphatic filariasis and onchocerciasis in Africa have significantly reduced this parasite's transmission.

ZOONOTIC FILARIAL INFECTIONS

Rare accidental filarial infections of humans with the dog heartworm *Dirofilaria immitis* occur worldwide. Transmitted by mosquitoes, *D. immitis* microfilariae cannot reach maturity in humans but embolize to the lung after dying in the right ventricle. Most infections are asymptomatic, but some people experience cough, chest pain, and hemoptysis consistent with lung infarction. Chest radiographs demonstrate typical coin lesions that may be mistaken for carcinoma. Other animal filariae, including *Dirofilaria repens* of dogs and *Dirofilaria tenuis* of raccoons, can infect humans and result in subcutaneous nodules that may be migratory. Eosinophilia and antifilarial antibodies are not usually present in zoonotic filarial infections. Surgical removal of lesions is both diagnostic and curative.

DRACUNCULIASIS

Dracunculiasis is a disfiguring disease caused by the nematode *Dracunculus medinensis*, or Guinea worm. Although previously found in the Indian subcontinent and Latin America, it is now endemic in only six countries in sub-Saharan Africa (Chad, Ethiopia, South Sudan, Angola, Mali, and Cameroon) due to concerted eradication efforts. In 2020, fewer than 30 cases were identified. Transmission to humans occurs through ingestion of copepods, tiny crustacean intermediate hosts that harbor infective larvae. Released larvae penetrate the intestinal wall and migrate to the subcutaneous tissues, where they develop into adult worms. After approximately a year, female worms induce vesicular skin lesions, usually on the lower extremities, that eventually ulcerate. On direct contact with fresh water, the female worm releases thousands of motile larvae that can then complete the transmission cycle by infecting copepods in the water. Adult worms measure up to a meter in length. Fever and allergic symptoms, including wheezing and urticaria, may precede rupture of the blister or occur upon attempted extraction of the worm. Secondary bacterial infection of the skin lesions is frequent. Although not commonly fatal, dracunculiasis can result in significant disability.

Traditionally, emerging worms are extracted by slowly winding a few centimeters of the parasite on a stick each day, taking care not to break it. Surgical removal can be attempted but may exacerbate allergic symptoms. There is no effective chemotherapy for this infection. Prevention efforts have been highly successful in interrupting transmission and have led to eradication of the parasite from many countries. Strategies include filtering of drinking water through finely woven cloth, education of infected individuals not to enter fresh water, treatment of water sources with larvicides, and provision of safe drinking water from wells.

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328 ANTIVIRAL THERAPY (NON-HIV)

JOHN H. BEIGEL AND SHYAMASUNDARAN KOTTILIL

Although some viral infections are self-limited, others can cause significant morbidity and mortality. Effective therapy is available for many of these infections. This chapter reviews currently available antiviral agents for the treatment of infections caused by viruses other than human immunodeficiency virus (HIV). Not all agents discussed are licensed in all countries.

Currently available agents can be classified into those that inhibit viral replication at the cellular level or bind the virus (antivirals), those that modify the host antiviral response to infection (immunomodulators), and those that directly inactivate viral particles (microbicides/virucides). Antiviral agents can be classified based on their mechanism of action.[1] For example, nucleic acid analogues inhibit viral DNA or RNA synthesis by competing with endogenous nucleic acids and block the viral DNA polymerase or RNA transcriptases. By comparison, protease inhibitors prevent viral replication by binding to the enzymes that cleave viral protein precursors into active proteins.

Antiviral strategies that are not covered in this chapter include local destructive measures that destroy both host tissues and virus simultaneously, such as cryotherapy, laser, and podophyllin treatment of warts. Although effective, such measures are useful only for discrete or localized mucocutaneous infections.

ANTIVIRALS FOR HEPATITIS B VIRUS INFECTIONS

Acute hepatitis B virus (HBV) infection (Chapter 134) generally does not require antiviral treatment. Currently approved antivirals for chronic hepatitis B (Chapter 135) include six nucleic acid analogues (adefovir, entecavir, lamivudine, telbivudine, tenofovir disoproxil fumarate, and tenofovir alafenamide), as well as two immune modulators (interferon-alfa-2b and pegylated [PEG]-interferon-alfa-2a) (Tables 328-1 to 328-3).[2] Treatment may be initiated with any approved antiviral medications, but tenofovir, tenofovir alafenamide, entecavir, and PEG-interferon-alfa-2a are generally the preferred agents. Tenofovir or entecavir is preferred for patients with compensated cirrhosis (Chapter 139). The goal of antiviral treatment is to suppress HBV replication and reduce the progression of liver disease and its complications.

Patients with chronic hepatitis B (hepatitis B surface antigen [HBsAg]-positive for >6 months, detectable serum HBV DNA [>2000 IU/mL for hepatitis B e antigen (HBeAg)-negative patients, >20,000 IU/mL for HBeAg-positive patients, and >200,000 IU/mL for pregnant women], and an alanine aminotransferase level more than twice the normal level) should be evaluated for treatment. Patients with clinically decompensated hepatitis B (e.g., icterus or other signs) generally require antiviral treatment. Therapy in HBeAg-positive chronic hepatitis B should be continued until the patient has achieved HBeAg seroconversion and serum HBV DNA is undetectable, followed by at least 6 months of additional treatment after the appearance of anti-HBe. Therapy in HBeAg-negative chronic hepatitis B should continue for at least a year. Patients with decompensated cirrhosis or recurrent hepatitis B after liver transplantation should receive lifelong treatment.

TENOFOVIR DISOPROXIL FUMARATE

Tenofovir, a nucleotide analogue of adenosine monophosphate, was first approved for the treatment of HIV infection. Tenofovir disoproxil fumarate is an ester prodrug of tenofovir, with an effective tenofovir bioavailability of 25%. Administration following a high-fat meal increases the oral bioavailability.

Clinical Uses

Tenofovir is approved for the treatment of chronic hepatitis B in adults with evidence of active viral replication and either persistent elevations in serum aminotransferase levels or histologically active disease. Treatment with tenofovir is more effective than adefovir or entecavir for producing histologic improvement and viral suppression in patients with HBeAg-negative or HBeAg-positive chronic hepatitis B.[A1] Tenofovir also has demonstrated efficacy in patients with lamivudine-resistant hepatitis B.

TABLE 328-1 ANTIVIRALS FOR HEPATITIS VIRUS INFECTIONS

VIRAL INFECTION	DRUG	ROUTE	USUAL ADULT DOSAGE
Chronic hepatitis B	Tenofovir disoproxil fumarate	PO	300 mg/day
	Tenofovir alafenamide	PO	25 mg/day
	Entecavir		
	Naïve virus	PO	0.5 mg daily; optimal duration of therapy unknown
	Lamivudine-resistant virus	PO	1 mg daily; optimal duration of therapy unknown
	Interferon-alfa-2b	SQ	6 MU/m² (up to 10 MU) three times weekly for 16-24 wk
	PEG-interferon-alfa-2a	SQ	180 µg weekly for 48 wk
	Adefovir	PO	10 mg/day
	Lamivudine	PO	100 mg/day
	Telbivudine	PO	600 mg/day
Chronic hepatitis C	Ledipasvir/sofosbuvir	PO	90 mg/400 mg once daily for 8-24 wk
	Sofosbuvir/velpatasvir	PO	400 mg/100 mg/day for 12 wk
	Sofosbuvir/velpatasvir/voxilaprevir	PO	400 mg/100 mg/100 mg/day for 12-24 wk
	Sofosbuvir/glecaprevir/pibrentasvir	PO	400 mg/100 mg/40 mg once daily for 12-24 wk
	Daclatasvir/sofosbuvir	PO	60 mg/400 mg/day for 12-24 wk
	Grazoprevir/elbasvir	PO	100 mg/50 mg/day for 12-16 wk
	Glecaprevir/pibrentasvir	PO	300 mg/120 mg/day for 8-16 wk
	Daclatasvir/asunaprevir	PO	60 mg/400 mg/day for 24 wk
	Sofosbuvir	PO	400 mg once daily for 12-24 wk
	PEG-interferon-alfa-2a	SQ	180 µg weekly for 48 wk
	or PEG-interferon-alfa-2b	SQ	1.5 µg/kg weekly for 48 wk
	plus ribavirin	PO	800-1200 mg/day, depending on weight

PO = orally; SQ = subcutaneously.

Toxicity

Tenofovir is generally safe and well tolerated for up to 5 years. The most common side effects are nausea, diarrhea, vomiting, and anorexia. Lactic acidosis with hepatic steatosis has been reported, primarily when it is used in combination with other nucleoside analogues. Acute exacerbations of hepatitis B have been reported after discontinuation of tenofovir in patients who are coinfected with HIV and hepatitis B.

Antiviral Resistance

Mutations in hepatitis B polymerase that confer reduced susceptibility to tenofovir occur during prolonged use (>12 months). In vitro studies showed that adefovir-resistant hepatitis B mutations are associated with three- to five-fold decrease in response to tenofovir, though clinical implications are not known.

TENOFOVIR ALAFENAMIDE

Tenofovir alafenamide, which is a prodrug of tenofovir, is a successor of tenofovir disoproxil fumarate. Tenofovir alafenamide is converted intracellularly to tenofovir. Its active diphosphate metabolite is targeted at the RNA-dependent DNA polymerase of either hepatitis B or HIV. Tenofovir alafenamide is also licensed to treat hepatitis B infection. Tenofovir alafenamide accumulates

ABSTRACT

A number of antiviral agents are available for the treatment of viral infections other than human immunodeficiency virus (HIV). Acute hepatitis B virus (HBV) and hepatitis C virus (HCV) infection generally do not require antiviral treatment. The preferred regimens for chronic hepatitis B include tenofovir disoproxil fumarate, tenofovir alafenamide, entecavir, and PEG-interferon-alfa-2a. Several direct-acting antiviral agents are highly effective against all genotypes (1-6) of HCV. Acyclovir or valacyclovir are the preferred treatments of herpes simplex and varicella-zoster virus. Ganciclovir or valganciclovir are the preferred treatments of cytomegalovirus. Oseltamivir is the preferred treatment of influenza. In nonhospitalized adults, either the combination of nirmatrelvir boosted with ritonavir or monotherapy with molnupiravir can reduce the progression of COVID-19. For patients who are hospitalized with COVID-19, remdesivir improves time to recovery and reduces mortality, primarily in patients who are receiving oxygen therapy.

KEYWORDS

hepatitis B
hepatitis C
herpes simplex
varicella-zoster
cytomegalovirus
influenza

TABLE 328-2 MECHANISMS OF EXCRETION AND THRESHOLDS FOR DOSE ADJUSTMENT

	MAJOR ROUTE OF ELIMINATION	THRESHOLD FOR ADJUSTMENT IN RENAL INSUFFICIENCY OR FAILURE	ADJUSTMENT FOR HEPATIC FAILURE	SPECIAL ADJUSTMENT FOR ELDERLY
Adefovir	Renal	CrCl <50 mL/min	No adjustment	
Entecavir	Renal	CrCl <50 mL/min	No adjustment	
Lamivudine	Renal	CrCl <50 mL/min	No adjustment	
Ledipasvir/sofosbuvir	Renal	CrCl <30 mL/min/1.73 m^2	No adjustment	
Sofosbuvir/velpatasvir	Renal	CrCl <30 mL/min/1.73 m^2	No adjustment	
Voxilaprevir	Hepatic	CrCl <30 mL/min	No adjustment	
Ribavirin	Renal	CrCl <50 mL/min	No adjustment	
PEG-interferon-alfa-2a	Renal	CrCl <50 mL/min	Progressive rise in alanine transaminase	>60 yr, consider reduction
Telbivudine	Renal	CrCl <50 mL/min	No adjustment	
Sofosbuvir	Renal	CrCl <50 mL/min	No adjustment	
Boceprevir	Hepatic	No adjustment	No adjustment	
Daclatasvir	Hepatic	No adjustment	No adjustment	
Asunaprevir	Hepatic	No adjustment	Contraindicated	
Glecaprevir/pibrentasvir	Hepatic	No adjustment	Contraindicated	
Grazoprevir/elbasvir	Hepatic	No adjustment	Contraindicated	

CrCl = creatinine clearance.

TABLE 328-3 SIGNIFICANT ADVERSE EFFECTS (U.S. FDA BLACK BOX WARNING)

DRUG	BLACK BOX SYNOPSIS
Adefovir	Severe acute exacerbations of hepatitis B may occur with cessation of therapy Nephrotoxicity may occur in patients at risk for renal dysfunction Lactic acidosis and severe hepatomegaly with steatosis
Entecavir	Severe acute exacerbation of hepatitis B may occur with cessation of therapy Lactic acidosis and severe hepatomegaly with steatosis
Grazoprevir/elbasvir	Hepatitis B virus reactivation in patients with HCV and HBV
Interferon-alfa	May cause or aggravate neuropsychiatric, autoimmune, ischemic, and infectious disorders
Lamivudine	Severe acute exacerbations of hepatitis B may occur with cessation of therapy Lactic acidosis and severe hepatomegaly with steatosis
Ledipasvir/sofosbuvir	Hepatitis B virus reactivation in patients with HCV and HBV
Voxilaprevir	Hepatic failure in patients with decompensated liver cirrhosis
Glecaprevir/pibrentasvir	Hepatic failure in patients with decompensated liver cirrhosis
Ribavirin	Monotherapy is not effective Hemolytic anemia Teratogenic and embryocidal
Sofosbuvir	Life-threatening bradycardia when administered with amiodarone Hepatic failure in patients with decompensated liver cirrhosis
Telbivudine	Severe acute exacerbation of hepatitis B may occur with cessation of therapy Lactic acidosis and severe hepatomegaly with steatosis
Tenofovir or tenofovir alafenamide	Severe acute exacerbations of hepatitis B may occur with cessation of therapy

HBV = hepatitis B virus; HCV = hepatitis C virus.

in lymphatic tissue and in the liver, and it enters cells more efficiently than tenofovir disoproxil fumarate. For these reasons, tenofovir alafenamide can be given at a lower dose, thereby resulting in lower plasma tenofovir levels and a much lower risk for kidney toxicity or bone density changes.

Clinical Uses

In clinical trials, tenofovir alafenamide was noninferior to tenofovir disoproxil fumarate in achieving HBV DNA levels below 29 IU/mL.[A2] Tenofovir alafenamide–treated patients had significantly smaller decreases in bone mineral density at the hip and spine in both HBeAg-positive and HBeAg-negative patients, and HBeAg-positive patients also had smaller mean increases in serum creatinine levels. Patients treated with tenofovir disoproxil fumarate for 96 weeks and then switched to tenofovir alafenamide had improvements in renal function and bone mineral density 24 weeks after switching.

Toxicity

Compared with tenofovir disoproxil fumarate, tenofovir alafenamide has less adverse effects on kidney (glomerular and tubular) function and bone mineral (spine, hip) density.

Antiviral Resistance

Tenofovir alafenamide leads to little or negligible emergence of drug resistance (to tenofovir). Clinical observations show a very low incidence of hepatitis B genotype resistance in treatment-naïve patients treated either with tenofovir alafenamide or tenofovir disoproxil fumarate. In patients treated with elvitegravir, cobicistat, and emtricitabine combined with either tenofovir alafenamide or tenofovir disoproxil fumarate, emergence of drug resistance did not exceed 1% for either HIV and hepatitis B.

ENTECAVIR

Entecavir, which is a deoxyguanosine nucleoside analogue with specific antiviral activity for hepadnaviruses, is more potent than lamivudine and retains some activity against lamivudine-resistant hepatitis B variants. It is well absorbed after oral administration, and its prolonged half-life (128 to 149 hours) allows once-daily dosing.

Clinical Uses

Entecavir is approved for the treatment of chronic hepatitis B in adults with evidence of active viral replication and either persistent elevations in serum aminotransferases or histologically active disease. Compared with lamivudine or telbivudine, entecavir is more efficacious in reducing hepatitis B DNA levels and normalizing serum aminotransferases, as well as in improving histologic abnormalities. Like tenofovir, entecavir can be used for lamivudine-resistant HBV infections, but higher doses and longer durations of therapy are needed.

Toxicity

Adverse effects reported during entecavir therapy include headache, fatigue, dizziness, nausea, abdominal pain, rhinitis, fever, diarrhea, cough, and myalgia. Lactic acidosis and severe hepatomegaly with steatosis have been reported.

Severe exacerbations of hepatitis B have been observed after cessation of therapy.

Antiviral Resistance

Virologic breakthrough can occur in up to 4% of patients but is usually not indicative of resistant virus. True entecavir resistance, which is caused by specific mutations in hepatitis B polymerase, is uncommon (1.2% after 5 years of treatment). In vitro studies show that entecavir-resistant mutations are susceptible to adefovir and tenofovir, but there are very few supportive clinical data.

INTERFERONS

Interferons are glycoprotein cytokines with a complex array of antiviral, immunomodulating, and antineoplastic properties. Interferons are currently classified as α, β, or γ. The natural sources of these classes in general are leukocytes, fibroblasts, and lymphocytes, but they now can be produced by recombinant DNA technology. Although the full mechanism of interferon's action is not defined, interferons generally induce synthesis of new cellular RNA and proteins that mediate antiviral effects through multiple different mechanisms.

Interferons generally must be administered daily or several times per week. However, the combination of interferon with polyethylene glycol to form PEG-interferon significantly prolongs absorption and provides higher, more sustained plasma levels that enable once-weekly administration.

Clinical Uses

In chronic active hepatitis B, treatment with interferon-alfa leads to loss of HBV DNA and biochemical and histologic improvement in about 25 to 40% of patients. Administration of PEG-interferon-alfa-2a or PEG-interferon-alfa-2b for 48 weeks converts about 30% of patients to seronegative status after 6 months of treatment. Whether combination therapy with interferons and antivirals confers an additional benefit compared with monotherapy for treating chronic hepatitis B is not known.

ADEFOVIR

Adefovir, an acyclic analogue of adenosine monophosphate, is administered orally as a prodrug, adefovir dipivoxil, which is rapidly converted enzymatically to adefovir in intestinal epithelium.

Clinical Uses

In chronic hepatitis B, prolonged administration of adefovir is effective in improving histologic abnormalities of the liver, decreasing HBV DNA levels, and normalizing biochemical markers (e.g., alanine aminotransferase) in patients with HBeAg-positive and HBeAg-negative chronic hepatitis B. Adefovir is a slightly weaker antiviral and therefore not considered first-line therapy, but it is useful for resistant viruses (effective against chronic hepatitis B resistant to lamivudine) and HIV/HBV coinfection (see later).

Toxicity

The major adverse effect is nephrotoxicity, which is manifested by increased serum creatinine levels and sometimes hypophosphatemia, both of which are usually reversible with discontinuation of the drug. Common side effects include asthenia, headache, nausea, vomiting, and diarrhea. In addition, severe exacerbations of hepatitis B have been observed after cessation of therapy.

Antiviral Resistance

Adefovir resistance due to point mutations in HBV polymerase develops in about 6% of patients after 3 years of therapy. Lamivudine generally retains activity against adefovir-resistant variants.

LAMIVUDINE

Lamivudine is a deoxycytidine nucleoside analogue active against retroviruses and hepadnaviruses. The triphosphate inhibits HBV polymerase, and its incorporation into viral DNA results in termination of the DNA chain.

Clinical Uses

Lamivudine suppresses hepatitis B viral replication, improves histologic abnormalities of the liver, reduces progression of fibrosis, and decreases the risk for late complications. Monotherapy with lamivudine appears to be inferior to the newer antivirals, as well as monotherapy with interferon, for sustained control of HBV replication. Combination therapy with lamivudine and interferon has shown inconsistent benefit compared with either drug alone. The dosing for HBV is lower than for HIV.

Toxicity

Adverse effects of lamivudine include diarrhea, headache, and elevated liver enzymes. Severe post-treatment exacerbations of hepatitis B, including fatalities, have occurred after discontinuation of lamivudine, especially in patients who are coinfected with HBV and HIV.

Antiviral Resistance

Lamivudine resistance caused by mutations in HBV polymerase is common during prolonged treatment of hepatitis B and emerges in about 20% of treated patients annually. Resistance is associated with increases in viral replication and aminotransferases.

TELBIVUDINE

Telbivudine is a synthetic thymidine nucleoside analogue with activity against HBV, including some lamivudine-resistant variants. The triphosphate form competitively inhibits the HBV DNA polymerase (reverse transcriptase).

Clinical Uses

In comparative trials against lamivudine or adefovir, telbivudine demonstrated greater virologic response at week 52 (60 vs. 40% of subjects had HBV DNA negative by polymerase chain reaction analysis). The development of resistance with telbivudine is up to 5% after 1 year and 25% after 2 years. Telbivudine-resistant viruses are cross-resistant with lamivudine. Owing to the high development of resistance and cross-resistance, telbivudine is not considered a first-line treatment for hepatitis B.

Toxicity

Common side effects include headache, nausea, and vomiting. Severe acute exacerbations of hepatitis B have been reported in patients who have discontinued anti-HBV therapy. Myopathy, manifested by muscle aches or weakness with increased serum creatine kinase levels, has rarely been reported.

Special Considerations—HIV/HBV Coinfection

Lamivudine, entecavir, tenofovir, and tenofovir alafenamide have activity against both HIV and HBV. Monotherapy treatment of HBV with these agents should not be used in HIV coinfected patients, owing to the development of HIV resistance. Emtricitabine is licensed only for the treatment of HIV but is also weakly active against HBV. Withdrawal of this medication, like withdrawal of tenofovir or lamivudine, may cause acute, sometimes fulminant, exacerbations of hepatitis B in HIV/HBV coinfected patients.

If concurrent treatment of hepatitis B and HIV is warranted, tenofovir plus emtricitabine, tenofovir plus lamivudine, or tenofovir alafenamide plus emtricitabine should be considered as the nucleoside backbone of a fully suppressive antiretroviral regimen. If tenofovir or tenofovir alafenamide cannot be used, entecavir is an alternative as part of an antiretroviral regimen. In coinfected patients who require treatment for HBV but not HIV or who are already well controlled on anti-HIV viral therapy but now need hepatitis B treatment, PEG-interferon-alfa-2a monotherapy should be considered. If the antiretroviral regimen must be changed owing to HIV virologic failure and the HBV is adequately suppressed, antiviral drugs active against HBV should be continued for HBV treatment.

ANTIVIRALS FOR HEPATITIS C VIRUS INFECTIONS

Treatment of acute hepatitis C remains symptomatic, and antiviral therapy generally is not indicated. For chronic hepatitis C (Chapter 135), however, the goal of therapy is sustained virologic response (absence of hepatitis C virus [HCV] RNA for at least 12 weeks after completion of therapy) to prevent the morbidity and mortality associated with liver disease and long-term complications, such as hepatocellular carcinoma, liver failure, transplantation, and death. Treatment has been shown to decrease liver inflammation and cirrhosis as well as reduce the risk for hepatocellular carcinoma.

Although some specific drugs are more effective for specific HCV genotypes, current therapy is based on pangenotypic oral combinations (Table 135-5), guided by whether or not patients have cirrhosis.[A3] Interferon-free regimens are preferred over interferon-based regimens (see Table 135-5 in Chapter 135 and Tables 328-1 to 328-3).[3] Direct-acting antiviral agents are highly active oral medications available to treat all genotypes of HCV. Sofosbuvir/velpatasvir glecaprevir/pibrentasvir with or without sofosbuvir, and sofosbuvir/daclatasvir are considered primary regimens for HCV regardless of genotype. Retreatment after failure of the initial regimen generally requires expert consultation.

LEDIPASVIR/SOFOSBUVIR

Ledipasvir is an HCV NS5A inhibitor. Sofosbuvir is a nucleotide prodrug that, when triphosphorylated, inhibits HCV NS5B, an RNA-dependent RNA polymerase. Both NS5A and NS5B are important for HCV viral replication. Ledipasvir/sofosbuvir is available as a combination fixed-dose once-daily oral tablet.

Clinical Uses

Ledipasvir/sofosbuvir is currently licensed in the treatment of genotypes 1, 4, 5, and 6 chronic HCV without decompensated cirrhosis and genotypes 1 and 4 with decompensated cirrhosis. For treatment-naïve patients with or without cirrhosis, treatment should continue for 12 weeks. This regimen has been associated with a sustained virologic response of 99% at 12 weeks, and the duration of treatment can be safely reduced to as low as 8 weeks in selected patients with baseline HCV RNA levels <6 million IU/mL.

Toxicity

The most common side effects are headaches and fatigue. Significant drug interactions may occur with P-glycoprotein–inducing medications such as rifampin or St. John's wort. Ledipasvir/sofosbuvir should not be given to patients who are taking amiodarone because of the risk of bradycardia.

Resistance

Resistance to the individual component drug may occur but is rare. Ledipasvir is active against sofosbuvir-resistant viruses, and sofosbuvir retains activity against ledipasvir-resistant viruses, so the clinical significance of resistance mutations is not known.

SOFOSBUVIR/VELPATASVIR

Velpatasvir is a potent pangenotypic HCV NS5A inhibitor that is approved to treat hepatitis C patients in combination with sofosbuvir, an NS5B inhibitor. Sofosbuvir/velpatasvir is available as a combination in a fixed-dose, once-daily, oral tablet.

Clinical Uses

Sofosbuvir/velpatasvir is currently licensed in the treatment of adult patients with chronic hepatitis C genotype 1, 2, 3, 4, 5, or 6 infection with any degree of liver damage, including decompensated cirrhosis. The addition of ribavirin is recommended when treating patients with decompensated cirrhosis. The duration of treatment is 12 weeks, which is associated with sustained virologic response in more than 99% of patients in real-world situations.[A4]

Toxicity

The most common adverse reactions associated with 12 weeks of sofosbuvir/velpatasvir treatment are fatigue and headaches. Significant drug interactions may occur with P-glycoprotein–inducing medications (e.g., rifampin, St. John's wort) and cytochrome P-450–inducing medications (e.g., rifampin, phenytoin). Concomitant use of sofosbuvir/velpatasvir with amiodarone is contraindicated because of the risk of bradycardia.

Antiviral Resistance

Preexisting NS5A mutants do not seem to influence the outcome of sofosbuvir/velpatasvir treatment. NS5A-resistant variants that confer in vitro resistance to velpatasvir have been isolated from the blood of the few patients who relapse. The significance of these mutants is not completely understood.

SOFOSBUVIR/VELPATASVIR/VOXILAPREVIR

Velpatasvir is a potent pangenotypic HCV NS5A inhibitor to treat hepatitis C patients in combination with sofosbuvir, an NS5B inhibitor. Voxilaprevir is a second-generation HCV serine protease inhibitor. A single fixed-dose combination tablet of sofosbuvir, velpatasvir, and voxilaprevir is approved by the U.S. Food and Drug Administration (FDA) for treatment of HCV patients who have been previously treated with other direct-acting antivirals.

Clinical Uses

Sofosbuvir/velpatasvir/voxilaprevir is currently licensed in the treatment of adult patients who have chronic hepatitis C genotype 1, 2, 3, 4, 5, or 6 infection with any degree of liver damage without cirrhosis or compensated cirrhosis and who previously have been treated with an HCV direct-acting antiviral agent regimen. The duration of treatment is 12 weeks, which is associated with sustained virologic response in more than 99% of patients.[A5]

Toxicity

The most common adverse reactions associated with 12 weeks of sofosbuvir/velpatasvir/voxilaprevir treatment are fatigue, headaches, nausea, and diarrhea. Significant drug interactions may occur with P-glycoprotein–inducing medications (e.g., rifampin or St. John's wort) and cytochrome P-450–inducing medications (e.g., phenytoin, rifampin). Significant bradycardia can occur with concomitant use of sofosbuvir/velpatasvir/voxilaprevir and amiodarone, which is contraindicated.

Antiviral Resistance

Preexisting NS5A or NS3 mutants do not seem to influence the outcome of sofosbuvir/velpatasvir/voxilaprevir treatment. NS5A-resistant variants that confer in vitro resistance to velpatasvir have been isolated from the blood of few patients who relapse. The significance of these mutants is not completely understood.

GLECAPREVIR/PIBRENTASVIR

A fixed-dose combination tablet of glecaprevir, an NS3/4A protease inhibitor, and pibrentasvir, an NS5A inhibitor, is approved for the treatment of patients with chronic HCV genotype 1, 2, 3, 4, 5, or 6 infection without cirrhosis and with compensated cirrhosis (Child-Pugh A).

Clinical Uses

Glecaprevir/pibrentasvir is currently licensed in the treatment of adult patients with chronic hepatitis C genotype 1, 2, 3, 4, 5, or 6 infection with all degrees of liver damage without cirrhosis or compensated cirrhosis (Child-Pugh A). The duration of treatment, which is 8 weeks for those without cirrhosis and 12 weeks for those with cirrhosis, is associated with sustained virologic response in more than 99% of patients.[A6] The combination pill is also indicated for the treatment of adult patients who have HCV genotype 1 infection and who previously have been treated with a regimen containing an HCV NS5A inhibitor or an NS3/4A protease inhibitor but not for those who failed both. For treatment-experienced genotype 1 patients who have failed a previous NS5A inhibitor (but not NS3)-containing HCV regimen, 16 weeks of treatment is recommended. For treatment-experienced genotype 1 patients who have failed a previous NS3 inhibitor (but not NS5A) containing HCV regimen, 12 weeks of treatment is recommended. For HCV genotype 1, 2, 4, 5, or 6 patients who have failed previous HCV regimens that did not include either an NS3 or NS5A inhibitor, either 8 weeks (those without cirrhosis) or 12 weeks (with cirrhosis) is recommended. For HCV genotype 3 patients who have failed previous HCV regimens that did not include either an NS3 or NS5A inhibitor, 16 weeks is recommended. Glecaprevir/pibrentasvir is the preferred interferon-free regimen shown to be effective in patients with stage 4 or 5 chronic kidney disease and all genotypes of HCV.[A7]

Toxicity

The most common adverse reactions associated with 12 weeks of glecaprevir/pibrentasvir treatment are fatigue and headaches in about 10% of all patients. Carbamazepine, efavirenz, and St. John's wort may decrease concentrations of glecaprevir and pibrentasvir, so coadministration of these medications is not recommended.

Antiviral Resistance

Preexisting NS5A or NS3 mutants do not seem to influence the outcome of glecaprevir/pibrentasvir treatment. NS5A- and NS3-resistant variants that confer in vitro resistance to both drugs have been isolated from the blood of few patients who relapse. The significance of these mutants is not completely understood.

DACLATASVIR

Daclatasvir is an NS5A inhibitor that can be used in combination with either sofosbuvir or asunaprevir for treatment of hepatitis C infection.

Clinical Uses

Daclatasvir is approved by the FDA to treat adult patients with HCV genotype 1 or 3 infection in combination with sofosbuvir with or without ribavirin. The duration of treatment is 12 weeks. The treatment is approved for patients with or without cirrhosis, but the response rate is reduced in patients with genotype 3 and cirrhosis. Daclatasvir is metabolized through CYP3A, so the dose must be reduced with strong CYP3 inhibitors (e.g., ritonavir or itraconazole) and increased with CYP3A inducers (e.g., rifampin and phenytoin).

Toxicity

The most common adverse reactions associated with 12 weeks of sofosbuvir/daclatasvir treatment are headaches, fatigue, and nausea. The most common adverse reactions with concomitant use of ribavirin are headache, anemia, fatigue, and nausea. Because of the risk of significant bradycardia, concomitant use of sofosbuvir and amiodarone is contraindicated.

Antiviral Resistance

For patients with genotype 1 and cirrhosis, NS5A resistance reduces the efficacy of sofosbuvir/daclatasvir, so testing for resistance should be performed in this situation. For the other genotypes, preexisting NS5A mutants do not seem to influence the outcome of sofosbuvir/daclatasvir treatment. NS5A-resistant variants that confer in vitro resistance to daclatasvir have been isolated from the blood of few patients who relapse, but the significance of these mutants is not completely understood.

DACLATASVIR/ASUNAPREVIR

Asunaprevir is an HCV NS3 (serine protease) inhibitor, and daclatasvir is a potent HCV NS5A inhibitor. The combination is licensed to treat patients with hepatitis C in Europe and Japan.

Clinical Uses

The combination is approved for treatment of adults who have hepatitis C genotype 1 infection with compensated cirrhosis, who are ineligible or intolerant to interferon-based therapy, and who have failed to respond to interferon-based therapy. The combination has resulted in high response rates for both genotype 1a and 1b patients when treated for 24 weeks.[A8]

Toxicity

Nasopharyngitis, elevated aminotransferase levels, headaches, and fatigue are the most common adverse events.

Antiviral Resistance

Preexisting NS5A and NS3 polymorphisms can lead to reduced response rates with daclatasvir/asunaprevir combination, and hence these patients are treated for an extended period of time (24 weeks). In patients with genotype 1b, the addition of ribavirin results in high sustained virologic response with only 12 weeks of treatment.

GRAZOPREVIR/ELBASVIR

Grazoprevir is a second-generation HCV NS3/4A (serine protease) inhibitor, and elbasvir is a potent HCV NS5A inhibitor. The combination is available as a fixed-dose combination single tablet and is licensed to treat patients with hepatitis C genotypes 1 and 4.

Clinical Uses

The combination grazoprevir/elbasvir is indicated with or without ribavirin for treatment of chronic HCV genotypes 1 or 4 infection in adults. For genotype 1a patients, testing of NS5A-resistant–associated polymorphisms before treatment is indicated. For treatment-naïve adult patients with hepatitis C genotype 1a (without polymorphisms), genotype 1b, and genotype 4, a total duration of 12 weeks is recommended. For treatment-experienced patients with hepatitis genotype 1, addition of ribavirin and treatment for 12 weeks is recommended. For HCV patients with genotype 1a and with the NS5A polymorphisms, addition of ribavirin for a total duration of 16 weeks is recommended. A major advantage of this combination over sofosbuvir-based combination is use in patients with significant renal impairment, including patients in hemodialysis,[A9] because both drugs are metabolized by the liver. Conversely, this combination is contraindicated in patients with decompensated liver disease. Grazoprevir/elbasvir may be used in patients with stage 4 or 5 chronic kidney disease and HCV genotypes 1 or 4.

Toxicity

The most common adverse reactions associated with 12 weeks of grazoprevir/elbasvir treatment are headaches, fatigue, and nausea. Anemia is also associated with concomitant use of ribavirin. Since grazoprevir/elbasvir is metabolized by the liver, inducers (e.g., phenytoin, rifampin) and inhibitors (e.g., ritonavir, itraconazole) of the cytochrome oxidase CYP3A system will decrease or increase levels, respectively, and should be avoided.

Antiviral Resistance

Presence of five preexisting NS5A-resistant–associated polymorphisms (M28A/G/T, Q30H/K/R/Y, L31F/M/V, H58D, Y93H/N/S) in HCV genotype 1a is associated with lower response rates when treated with grazoprevir/elbasvir alone but results in high response rates when ribavirin is added and total treatment duration is extended to 16 weeks. Hence, resistant-associated polymorphism testing is recommended for patients with HCV genotype 1a.

SOFOSBUVIR

Clinical Uses

Sofosbuvir is currently licensed as a component of a combination antiviral treatment regimen with other direct-acting antiviral medications for all HCV genotypes. Sofosbuvir and ribavirin for 24 weeks without interferon is also effective for treating HCV genotype 1. In genotypes 2 and 3, sofosbuvir in combination with ribavirin for 12 or 24 weeks also has been associated with about a 90% rate of undetectable virus 3 weeks after therapy. For patients who cannot tolerate an interferon-based regimen (autoimmune disorders, decompensated hepatic disease, leukopenia, thrombocytopenia, anemia, or preexisting cardiac disease), sofosbuvir may be used with ribavirin for 24 weeks.

Toxicity

Common side effects include headache, fatigue, anemia, and diarrhea. Severe pancytopenias, insomnia, and depression also have been reported, especially when sofosbuvir is used in combination with pegylated interferon-alfa. Sofosbuvir is a substrate of drug transporter P-gp, and drugs that are potent P-gp inducers (e.g., rifampin or St. John's wort) may decrease sofosbuvir's plasma concentration. Significant bradycardia can occur when sofosbuvir is coadministered with amiodarone.

Resistance

The emergence of resistance while on sofosbuvir treatment is extremely rare.

BOCEPREVIR

Boceprevir is a protease inhibitor that binds to the NS3/4A of hepatitis C.

Clinical Uses

Boceprevir is currently licensed only for the treatment of genotype 1 in patients with compensated liver disease. It is used in combination with PEG-interferon and ribavirin in treatment-naïve patients as well as in patients who have not responded adequately to PEG-interferon and ribavirin. Boceprevir should not be used as monotherapy. Boceprevir is started 4 weeks after initiation of therapy with PEG-interferon and ribavirin, and combination therapy is continued for an additional 24 to 44 weeks based on virologic response. Subjects with undetectable HCV RNA level at weeks 8 and 24 may be considered for a shorter duration of treatment (28 weeks in total). In patients with evidence of virologic failure (HCV RNA level is >100 IU/mL at treatment week 12 or detectable at treatment week 24), treatment with all three drugs should be stopped. Because of its inferior efficacy, boceprevir is not considered a first-line therapy for hepatitis C.

Toxicity

Common side effects include fatigue, nausea, shivering, alopecia, and dysgeusia. Patients should be monitored for serious side effects such as anemia and neutropenia, which occasionally can be dose-limiting. Patients who develop anemia on combination therapy including boceprevir may be managed by reducing the ribavirin dose. Boceprevir is a strong inhibitor of cytochrome P450 3A4/5, so drug-drug interactions (including over-the-counter and oral contraceptives) must be considered.

Resistance

Resistance to boceprevir can occur on therapy. Because boceprevir and telaprevir are structurally similar, cross-resistant mutations may emerge, and patients should not be retreated with another protease inhibitor.

PEGYLATED INTERFERON-2B AND RIBAVIRIN

Clinical Uses

Neither ribavirin nor interferon should be used as monotherapy for hepatitis C. In genotype 1, the combination of PEG-interferon and ribavirin may be considered in treatment-naïve patients who cannot be given interferon-free regimens, although sustained virologic response rates are significantly inferior. Longer durations of treatment, up to 72 weeks, may improve virologic response. PEG-interferon and ribavirin should be administered for 24 weeks for HCV genotypes 2 and 3 and for 48 weeks for HCV genotypes 4, 5, and 6.

Toxicity

Common side effects of interferon administration include influenza-like symptoms (fever, chills, headache, malaise), but these symptoms usually become

less severe with repeated treatments. Major toxicities include bone marrow suppression, especially granulocytopenia and thrombocytopenia, which are generally reversible when therapy is discontinued. Neuropsychiatric disturbances may be manifested by depression, anxiety, somnolence, confusion, and behavioral changes. Other side effects include profound fatigue and anorexia, weight loss, hypothyroidism or hyperthyroidism, alopecia, and cardiotoxicity with arrhythmias and reversible cardiomyopathy. Some side effects (e.g., hypothyroidism) can present a year or longer after therapy has finished.

Systemic ribavirin is frequently associated with hemolytic anemia (in up to 60% in some series) and sometimes with electrolyte abnormalities, including hypocalcemia and hypomagnesemia. Arrhythmias, pruritus, rash, nausea, and myalgia have been reported, as have neurologic side effects, including insomnia and irritability. Ribavirin may be gonadotoxic and teratogenic in humans.

Special Considerations—HIV/HCV Coinfection

Initial treatment regimens for HCV/HIV-coinfected patients are the same as those recommended for individuals without HIV infection. However, when treating both HCV and HIV, drug-drug interactions and additive toxicities must be considered. Grazoprevir/elbasvir, glecaprevir/pibrentasvir, and sofosbuvir/velpatasvir/voxilaprevir should not be coadministered with HIV non-nucleoside reverse transcriptase inhibitors or protease inhibitors. Ledipasvir and velpatasvir can increase tenofovir levels, and HIV regimens without tenofovir or tenofovir alafenamide should be considered.

The HIV antivirals didanosine, stavudine, and zidovudine (Chapter 357) should not be used with ribavirin. Didanosine levels and its active metabolite are increased when administered with ribavirin and can cause hepatic failure, severe peripheral neuropathy, pancreatitis, and lactic acidosis. Zidovudine administered with ribavirin can cause severe neutropenic anemia, and the combination should not be used. If ribavirin is the preferred therapy, discontinuation of didanosine and zidovudine should be considered before initiation of ribavirin.

ANTIVIRALS FOR HERPESVIRUS INFECTIONS

ACYCLOVIR AND VALACYCLOVIR

Acyclovir, an acyclic analogue of the nucleoside guanosine, is converted to its active form through initial monophosphorylation by a virus-encoded thymidine kinase. Although normal human cells possess thymidine kinase, the affinity of acyclovir for viral thymidine kinase is approximately 200 times greater than for human thymidine kinase. The monophosphate then undergoes two additional host cell enzyme-mediated phosphorylations to acyclovir triphosphate (acycloguanosine triphosphate), which preferentially inhibits viral DNA polymerase. The higher concentrations of the activated form in infected cells and its affinity for viral polymerases result in low toxicity to normal host cells.

Valacyclovir is the L-valyl ester prodrug of acyclovir. Addition of the L-valyl ester allows greater oral absorption, after which valacyclovir is converted to acyclovir; the prodrug provides three to five times greater bioavailability than oral acyclovir.

Clinical Uses

Acyclovir and valacyclovir (Tables 328-4 to 328-6) are used principally to treat infections caused by herpes simplex virus (Chapter 345) and varicella-zoster virus (Chapter 346). Depending on the country, acyclovir is available in a topical ointment and cream, oral capsules, and intravenous and ophthalmic formulations. Valacyclovir is available only as an oral capsule.

Oral acyclovir or valacyclovir decreases the duration of symptoms by approximately 50% and reduces the duration of viral shedding by about 90% in initial episodes of genital herpes. Two or 3 days of therapy appear to be sufficient for recurrent genital herpes. Chronic suppression is highly effective in reducing clinical and viral recurrences, and valacyclovir reduces the risk for transmission of genital herpes simplex between heterosexual partners by 48%. For herpes labialis (cold sores), 1 day of therapy with oral valacyclovir improves time to healing and reduces pain, whereas acyclovir ointment has no consistent clinical benefit.

Parenteral acyclovir is indicated for the initial treatment of mucosal or cutaneous herpes simplex infection in immunocompromised patients, neonatal infections, and disseminated or organ-invasive infections in immunocompetent patients. A subsequent switch to oral valacyclovir is possible in some circumstances. High-dose parenteral acyclovir is the therapy of choice for treatment of herpes simplex encephalitis. Both acyclovir chemoprophylaxis and valacyclovir chemoprophylaxis reduce the incidence of recurrent herpes simplex in recipients of stem cell and solid organ transplants, but valacyclovir is superior for prevention of cytomegalovirus disease.

Acyclovir and valacyclovir are indicated for acute varicella infection (chickenpox) in adults. Parenteral acyclovir should be used for severe acute varicella infection, including pneumonia, encephalitis, thrombocytopenia, and severe hepatitis, or in immunocompromised hosts. Acyclovir is also indicated in varicella reactivation (zoster). In adults treated within 24 hours of the development of a varicella rash, acyclovir decreases the severity of disease and number of lesions, but oral valacyclovir may be more effective than oral acyclovir. Intravenous acyclovir is warranted for zoster in immunocompromised hosts.

Toxicity

Acyclovir and valacyclovir have excellent safety profiles and are generally well tolerated. Common side effects include nausea, vomiting, and headaches. Major adverse effects include renal dysfunction and central nervous system (CNS) toxicity. Dehydration and preexisting renal dysfunction predispose to the development of renal impairment. Neurologic side effects include tremor, myoclonus, confusion, lethargy, agitation, and hallucination. Renal dysfunction predisposes to the development of neurotoxicity. Neutropenia and other signs of bone marrow toxicity also have been reported rarely.

Antiviral Resistance

Despite widespread use of acyclovir, the development of resistance to herpes simplex virus in immunocompetent patients is uncommon (prevalence <1%). However, antiviral resistance is higher in immunocompromised patients, including those with HIV infection (prevalence of 5%) or bone marrow transplants (prevalence of up to 30%). Drug-resistant refractory varicella-zoster virus infections can occur in highly immunocompromised patients. Intravenous foscarnet or cidofovir may be effective for infections caused by acyclovir-resistant viruses.

PENCICLOVIR AND FAMCICLOVIR

Penciclovir is an acyclic guanine analogue that unlike acyclovir is not an obligate chain terminator and may be incorporated into DNA. Penciclovir is phosphorylated by viral thymidine kinase to penciclovir monophosphate, which is then converted to penciclovir triphosphate. Penciclovir demonstrates in vitro activity against varicella-zoster virus and herpes simplex virus comparable to that of acyclovir. The bioavailability of penciclovir after oral administration is less than 2%, so it is useful only as a topical treatment. In contrast, famciclovir is an oral prodrug that is deacetylated and oxidized in the liver to form penciclovir; the bioavailability of penciclovir averages 77% after administration of famciclovir.

Clinical Uses

Penciclovir and famciclovir are used to treat herpes simplex and varicella-zoster infections. Penciclovir is available as a topical cream and in some countries as an intravenous formulation. Famciclovir is available as a capsule.

Topical penciclovir, which is approved for the treatment of recurrent herpes simplex labialis, reduces pain and lesions by about 1 day. Famciclovir is approved for the treatment of recurrent herpes simplex labialis and genital infections and for herpes zoster, and its effectiveness is similar to valacyclovir or acyclovir. Famciclovir also may be used for suppressive therapy. Famciclovir and acyclovir provide similar times to resolution and rates of cure.

Toxicity

Topical penciclovir is well tolerated; the majority of adverse reactions are local irritation and mild erythema. Adverse effects of oral famciclovir include headache, dizziness, nausea, and diarrhea.

Antiviral Resistance

Penciclovir resistance in herpes simplex has been uncommon in immunocompetent patients but, like acyclovir resistance, more frequent in immunocompromised hosts (2.1%). Most acyclovir-resistant herpes simplex isolates are cross-resistant to penciclovir.

GANCICLOVIR AND VALGANCICLOVIR

Ganciclovir is an acyclic deoxyguanosine analogue with antiviral activity against multiple herpesviruses, including herpes simplex, varicella-zoster, cytomegalovirus (Chapter 347), Epstein-Barr virus (Chapter 348), and human herpesvirus 8. Ganciclovir has activity against herpes simplex and varicella-zoster, but it has more adverse reactions compared with acyclovir. It is much more active than acyclovir against cytomegalovirus and Epstein-Barr virus. The bioavailability of oral ganciclovir is less than 10%. Valganciclovir, the L-valyl prodrug of ganciclovir, increases the bioavailability of ganciclovir to approximately 60% after oral administration.

Clinical Uses

Ganciclovir is available as an oral capsule, a parenteral injection, and an ocular implant; valganciclovir is available only as a tablet. Ganciclovir and valganciclovir are effective for treatment of cytomegalovirus retinitis, for which they are

TABLE 328-4 ANTIVIRALS FOR HERPESVIRUS INFECTIONS

VIRAL INFECTION	DRUG	ROUTE	USUAL ADULT DOSAGE
HERPES SIMPLEX VIRUS			
Genital herpes			
First episode	Acyclovir	PO	400 mg tid or 200 mg five times/day for 7-10 days
	Famciclovir	PO	250 mg tid for 7-10 days
	Valacyclovir	PO	1 g bid for 7-10 days
Recurrent	Acyclovir	PO	800 mg tid for 2 days, or 400 mg tid or 200 mg five times/day for 5 days
	Famciclovir	PO	1000 mg bid for 2 doses (if HIV-infected: 500 mg bid for 7 days)
	Valacyclovir	PO	500 mg bid for 3 days or 1 g/day for 5 days
Suppression	Acyclovir	PO	400 mg bid
	Famciclovir	PO	250 mg bid
	Valacyclovir	PO	500 mg/day or 1 g/day (10 or more episodes/yr)
Orolabial herpes	Penciclovir 1%	Topical	Apply cream every 2 hr while awake for 4 days
	Acyclovir 5%	Topical	Apply cream five times/day for 4 days
	Docosanol 10%	Topical	Apply cream five times/day until healing
	Valacyclovir	PO	2 g q12h × 2 doses
	Acyclovir	PO	400 mg five times/day for 5 days
	Famciclovir	PO	1500 -mg single dose
Mucocutaneous disease	Acyclovir	IV	5 mg/kg/8 hr for 7-14 days
	Acyclovir	PO	400 mg five times/day for 7-14 days
	Valacyclovir	PO	500 mg or 1 g bid for 7-10 days
Encephalitis	Acyclovir	IV	10 mg/kg/8 hr for 10 days
Neonatal	Acyclovir	IV	10-20 mg/kg/8 hr for 14-21 days
Keratoconjunctivitis	Trifluridine	Topical	1 drop of 1% solution q2h up to 9 drops/day
	Vidarabine	Topical	½-inch ribbon of 3% ointment five times daily
Acyclovir-resistant herpes simplex	Foscarnet	IV	40 mg/kg q8-12 h for 2 to 3 weeks or until healed
CYTOMEGALOVIRUS			
Cytomegalovirus retinitis	Ganciclovir	IV	5 mg/kg/12 hr for 14-21 days (maintenance: 5 mg/kg/day)
	Valganciclovir	PO	900 mg bid for 21 days (maintenance: 900 mg/day)
	Cidofovir	IV	5 mg/kg once weekly × 2 weeks (maintenance: 5 mg/kg q2wk)
	Foscarnet	IV	60 mg/kg/8 hr or 90 mg/kg q12h for 14-21 days (maintenance: 90-120 mg/kg daily)
	Fomivirsen	Intravitreal	330 µg q2 weeks × 2 weeks (maintenance: 330 µg every month)
HIV infection, cytomegalovirus colitis or esophagitis	Ganciclovir	IV	5 mg/kg/12 hr for 14-28 days (until symptoms resolved)
Prophylaxis (transplantation)	Valganciclovir	PO	900 mg daily
	Ganciclovir	IV	5 mg/kg/12 hr for 7-14 days, then 5 mg/kg IV once a day
Prophylaxis (stem cell transplantation)	Letermovir	PO or IV	480 mg/day through 100 days post-transplant
Prophylaxis (advanced HIV infection)	Ganciclovir	IV	5 mg/kg daily
VARICELLA-ZOSTER VIRUS			
Varicella	Acyclovir	PO	800 mg qid for 5 days
Varicella in immunocompromised hosts	Acyclovir	IV	10 mg/kg/8 hr for 7-10 days
Zoster (shingles) in immunocompromised hosts	Acyclovir	IV	10 mg/kg/8 hr for 7-10 days
Zoster (shingles) in normal hosts	Acyclovir	PO	800 mg five times daily for 7-10 days
	Valacyclovir	PO	1 g tid for 7 days
	Famciclovir	PO	500 mg tid for 7 days

bid = twice daily; HIV = human immunodeficiency virus; IV = intravenously; PO = orally; tid = three times daily.

TABLE 328-5 MECHANISMS OF EXCRETION AND THRESHOLDS FOR DOSE ADJUSTMENT

	MAJOR ROUTE OF ELIMINATION	THRESHOLD FOR ADJUSTMENT IN RENAL INSUFFICIENCY OR FAILURE	ADJUSTMENT FOR HEPATIC FAILURE	ADJUSTMENT FOR OBESITY
Acyclovir IV	Renal	CrCl <50 mL/min	No adjustment	Dose by ideal body weight
Acyclovir PO	Renal	CrCl <25 mL/min/1.73 m^2	No adjustment	Dose by ideal body weight
Valacyclovir	Renal	CrCl <50 mL/min	No adjustment	Unknown
Famciclovir	Renal	CrCl <60 mL/min	No adjustment	Unknown
Foscarnet	Renal	CrCl <1.4 mL/min/kg	No adjustment	Unknown
Ganciclovir IV	Renal	CrCl <70 mL/min	No adjustment	Unknown
Valganciclovir	Renal	CrCl <60 mL/min	No adjustment	Unknown
Letermovir	Hepatic	Avoid IV if CrCl <50 mL/min	No adjustment in mild or moderate impairment	Unknown
Cidofovir	Renal	CrCl <55 mL/min	No adjustment	Unknown

CrCl = creatinine clearance.

TABLE 328-6 SIGNIFICANT ADVERSE EFFECTS (U.S. FDA BLACK BOX WARNING)

DRUG	BLACK BOX SYNOPSIS
Cidofovir	Renal impairment, including renal failure; prehydrate and use probenecid Neutropenia May be carcinogenic and teratogenic and may cause hypospermia or aspermia
Foscarnet	Nephrotoxicity; prehydrate Seizures related to minerals and electrolyte disturbances
Ganciclovir	Neutropenia, anemia, thrombocytopenia May be carcinogenic and teratogenic and may cause hypospermia or aspermia
Valganciclovir	Neutropenia, anemia, thrombocytopenia May be carcinogenic and teratogenic and may cause hypospermia or aspermia

comparably active. In the absence of immune reconstitution, long-term suppression therapy is necessary. They are also used for life-threatening cytomegalovirus diseases in patients with acquired immunodeficiency syndrome (AIDS) and other immunocompromised conditions and for prevention of cytomegalovirus disease in transplant patients. For immunocompromised patients with organ-invasive cytomegalovirus infections, intravenous ganciclovir provides clinical response rates of 70 to 90%, although response rates are lower for cytomegalovirus pneumonitis after stem cell transplantation or encephalitis in patients with AIDS. Oral valganciclovir provides long-term outcomes similar to those of intravenous ganciclovir for the treatment of cytomegalovirus disease.

Long-term prophylaxis with ganciclovir or valganciclovir reduces the incidence of cytomegalovirus disease after solid organ and stem cell transplantation, but this therapy has substantial side effects, including bone marrow suppression. These drugs also can be used as preemptive therapy for patients who have cytomegalovirus viremia or antigenemia. In the prevention of cytomegalovirus disease, preemptive valganciclovir therapy may be equally effective to chronic valacyclovir prophylaxis.

Toxicity

The most common adverse effect with ganciclovir and valganciclovir is bone marrow suppression, particularly neutropenia and thrombocytopenia, which occur in up to 50% of patients given intravenous ganciclovir. Fever, edema, phlebitis, headache, neuropathy, disorientation, nausea, anorexia, rash, and myalgias have also been reported with ganciclovir therapy. Intravitreal ganciclovir implants may cause vitreous hemorrhage and retinal detachment.

Antiviral Resistance

Ganciclovir resistance secondary to mutations in cytomegalovirus kinase and sometimes DNA polymerase is related to the length of ganciclovir exposure and the degree of immunosuppression. Resistance may be associated with progressive disease during continued ganciclovir use; foscarnet and cidofovir are alternative treatments.

LETERMOVIR

Letermovir is the first agent in the non-nucleoside 3,4-dihydro-quinazoline class of antivirals that inhibits the cytomegalovirus DNA terminase complex. This enzyme is required for viral DNA processing.

Clinical Uses

Letermovir use is indicated for a specific population—prophylaxis against active cytomegalovirus infection and disease in cytomegalovirus-seropositive recipients of an allogeneic hematopoietic stem cell transplant. Although ganciclovir and valganciclovir are effective in preventing cytomegalovirus infection, their use is limited by myelosuppression. Prophylaxis with letermovir prevents significantly more cytomegalovirus infections compared with placebo. The use of letermovir for treatment of active cytomegalovirus disease or in other indications has not been evaluated and therefore cannot be recommended until additional data are available.

Toxicity

The most common side effects are nausea, vomiting, and diarrhea, but they occur at similar rates as with placebo. The cardiac adverse event rate (primarily tachycardia and atrial fibrillation) is higher in patients receiving letermovir than placebo (13% vs. 6%). Letermovir is an inhibitor of cytochrome P450 3A (CYP3A) and organic anion-transporting polypeptide 1B1 and 1B3 transporters and has numerous drug-drug interactions, including with immunosuppressants and antimicrobial agents. Consultation with an experienced clinical pharmacologist is highly recommended. In patients with creatinine clearance less than 50 mL/min and receiving IV letermovir, accumulation of the intravenous vehicle, hydroxypropyl betadex, could occur.

Antiviral Resistance

The emergence of resistance while on letermovir is rare. Letermovir is fully active against cytomegaloviruses that are resistant to cidofovir, foscarnet, or ganciclovir.

FOSCARNET

Foscarnet is a pyrophosphate analogue that acts as a noncompetitive inhibitor of many viral RNA and DNA polymerases. When a nucleotide is incorporated into a DNA or RNA strand by a polymerase, pyrophosphate is released. Foscarnet directly inhibits viral polymerases without phosphorylation, so thymidine kinase-deficient, acyclovir-resistant herpes simplex and varicella-zoster viruses are susceptible to this agent.

Clinical Uses

For extraretinal cytomegalovirus disease, foscarnet has demonstrated efficacy similar to that of ganciclovir. Foscarnet is as effective as ganciclovir for the treatment of cytomegalovirus retinitis in patients with AIDS, and combination therapy with ganciclovir may be superior to monotherapy with either agent for recalcitrant retinitis. The choice of agent may be dictated by the side effect profile. Foscarnet is also effective for the treatment of acyclovir-resistant herpes simplex and varicella-zoster infections.

Toxicity

Nephrotoxicity with azotemia and proteinuria is dose limiting and occurs in more than one third of patients. A slow infusion rate and saline hydration reduce the risk. Other common side effects include anemia (30 to 50% of patients), granulocytopenia, diarrhea, nausea, vomiting, fever, seizures, paresthesia, headache, and genital ulcers. Marked electrolyte disturbances may develop, including hypophosphatemia, hypocalcemia, hypokalemia, and hypomagnesemia. Foscarnet can prolong the QT interval and be associated with cardiac arrhythmias, including ventricular tachycardia, ventricular fibrillation, and torsades de pointes.

Antiviral Resistance

The development of cytomegalovirus resistance to foscarnet as a result of mutations in viral DNA polymerase is uncommon except after prolonged administration. In AIDS patients with retinitis, foscarnet resistance is detectable in 13% of patients at 6 months and in 37% at 12 months.

CIDOFOVIR

Cidofovir, which is an acyclic phosphonate derivative of cytosine, is phosphorylated to its active diphosphate form by host cellular enzymes. Cidofovir diphosphate competitively inhibits viral DNA polymerase and viral DNA synthesis. Despite a short serum half-life, the antiviral effects are protracted because of prolonged intracellular concentrations of the phosphorylated metabolite.

Clinical Uses

Cidofovir is commercially available as an intravenous infusion, and investigational formulations have included topical gel and intravitreal and intralesional injections. Intravenous cidofovir is licensed for the treatment of cytomegalovirus retinitis. Because of its toxicities, it is generally reserved for when ganciclovir or foscarnet therapy is failing. Limited data suggest that intravenous cidofovir may be effective in other cytomegalovirus infections (pneumonitis, gastroenteritis), acyclovir- or foscarnet-resistant herpes simplex infections, certain forms of human papillomavirus disease, invasive adenoviral infections in transplant recipients, and possibly BK virus infection in renal transplant patients. In addition, in vivo and animal data suggest efficacy of cidofovir against smallpox, vaccinia, and monkeypox infections.

Toxicity

Dose-related nephrotoxicity, characterized by increased serum creatinine, proteinuria, and tubular dysfunction, is the main side effect of intravenous cidofovir. Adequate hydration and concomitant oral probenecid reduce the risk. Other common side effects include diarrhea, asthenia, nausea, vomiting, neutropenia, fever, and rash. Iritis, intraocular pressure changes, loss of visual acuity, and uveitis have been reported with intravenous cidofovir. Intravitreal cidofovir is effective but locally toxic.

Antiviral Resistance

Sustained exposure to cidofovir does not easily induce resistance, although resistance has infrequently been described in herpes simplex virus and cytomegalovirus.

FOMIVIRSEN

Fomivirsen, which is an antisense oligonucleotide that inhibits replication of cytomegalovirus, is currently available as an intravitreal injection that is effective for both newly diagnosed cytomegalovirus retinitis and cytomegalovirus retinitis failing usual therapies, although direct comparisons with other agents are lacking. Intravitreal administration of fomivirsen may cause increased intraocular pressure, iritis, vitreitis, and cataracts in 10 to 20% of patients. Topical corticosteroids may be useful for treating inflammatory changes.

DOCOSANOL

Docosanol, which is a 22-carbon saturated fatty alcohol that inhibits intracellular penetration of lipid-enveloped viruses, is approved as an over-the-counter cream for the treatment of herpes labialis. Frequent topical applications have shown reductions in time to cessation of pain and healing, but direct comparison to other agents is lacking. Local reaction, rash, and pruritus are common side effects.

ANTIVIRALS FOR INFLUENZA VIRUS INFECTIONS

Currently approved antivirals for the treatment of influenza include two neuraminidase inhibitors (oseltamivir and zanamivir), one endonuclease inhibitor (baloxavir marboxil), and two adamantanes (amantadine and rimantadine) (Tables 328-7 and 328-8). The choice of treatment for influenza should be dictated by circulating strains, antiviral resistance within those strains, and side effect profiles.[4]

OSELTAMIVIR, ZANAMIVIR, AND PERAMIVIR (NEURAMINIDASE INHIBITORS)

Oseltamivir, zanamivir, and peramivir are sialic acid analogues that inhibit influenza virus by competitively interacting with the neuraminidases of influenza A and B viruses. Influenza neuraminidase cleaves terminal sialic acid residues and destroys the receptors recognized by viral hemagglutinin. By this mechanism, the drugs inhibit the release of virus from infected cells, thereby preventing viral aggregates and spread within the respiratory tract.

Oseltamivir is administered orally as the phosphate prodrug, which is rapidly absorbed and hydrolyzed to the active form oseltamivir carboxylate. Bioavailability exceeds 75%. Conversely, the oral bioavailability of zanamivir is poor, so it is delivered as an orally inhaled powder. Peramivir is available only as a parenterally infused solution.

TABLE 328-7 ANTIVIRALS FOR INFLUENZA VIRUS INFECTIONS

VIRUS	DRUG	ROUTE	USUAL ADULT TREATMENT DOSAGE
Influenza A and B viruses	Oseltamivir	PO	75 mg bid for 5 days
	Peramivir	IV	600 -mg single IV dose
	Zanamivir	Inhalation	10 mg bid by inhaler for 5 days
	Baloxavir marboxil	PO	40 to ≤80 kg: 40-mg single dose >80 kg: 80-mg single dose
Influenza A virus	Amantadine	PO	100 mg bid or 200 mg daily for 5 days
	Rimantadine	PO	100 mg bid for 5 days

bid = twice daily; IV = intravenously; PO = orally.

Clinical Uses

Oseltamivir and zanamivir are effective for the treatment and prophylaxis of acute influenza A and B infections. Early treatment in adults decreases the duration and severity of illness and reduces lower respiratory tract complications, antibiotic use, and, with oseltamivir, hospitalizations. In low-risk ambulatory patients, oseltamivir alleviates symptoms faster than placebo, and it also decreases the risk for lower respiratory complications. In cohort studies of hospitalized patients, treatment with oseltamivir has been associated with a significant reduction in death. Zanamivir is also effective in alleviating symptoms and decreasing the risk for lower respiratory complications. Both zanamivir and oseltamivir are also highly effective for the prevention of influenza. Peramivir is licensed as a single-dose intravenous infusion for uncomplicated influenza. However, as a once- or twice-daily infusion in patients hospitalized with influenza, its efficacy is similar to oseltamivir. Combining oseltamivir with other antivirals (amantadine and ribavirin) does not improve efficacy over oseltamivir alone.[A10]

Toxicity

The most common side effects with oseltamivir are nausea and vomiting. They also may be associated with headache, rash, and possibly abnormal aminotransferase levels. Zanamivir is generally well tolerated, but severe bronchospasm has been reported primarily in patients with underlying airway disease. The most common side effects of peramivir are nausea, diarrhea, and mild neutropenia.

Antiviral Resistance

Oseltamivir resistance can be preexisting (widespread or local) or can emerge during therapy. In the immunocompromised host and possibly in individuals with H5N1 or H1N1 influenza, the development of resistance is associated with treatment failure. Zanamivir resistance is rare, and zanamivir retains clinical effectiveness against the most common oseltamivir-resistant variants.

BALOXAVIR MARBOXIL

Baloxavir marboxil is a prodrug that is converted by hydrolysis to baloxavir. Baloxavir, which is among a novel class of antivirals for influenza, inhibits the endonuclease activity of the polymerase acidic protein, which is an influenza-specific enzyme in the viral RNA polymerase complex and is responsible for viral gene replication.

Clinical Uses

Baloxavir marboxil is indicated for the treatment of acute influenza A and B infections in adults and children older than 12 years of age. Clinical efficacy is similar to oseltamivir, but baloxavir marboxil is unique in that it is administered as a single dose.[A11] When given as post-exposure prophylaxis, it can reduce household infections by about 60% and symptomatic infection by 85%.[A12]

Toxicity

Baloxavir marboxil is well tolerated with few side effects. The most common side effects are diarrhea and bronchitis and occurred in similar rates as placebo.

Antiviral Resistance

Circulating resistance to baloxavir is currently rare, although treatment-emergent resistance is 20 to 23% in patients 1 to 11 years of age and 3 to 11% patients 12 to 64 years of age.

AMANTADINE AND RIMANTADINE (ADAMANTANES)

Currently circulating H1N1 and H3N2 viruses are highly resistant to adamantanes. Unless circulating strains are documented as susceptible, these compounds should not be used. Amantadine and rimantadine are symmetrical tricyclic amines with activity against many influenza A viruses (Chapter 332).

TABLE 328-8 MECHANISMS OF EXCRETION AND THRESHOLDS FOR DOSE ADJUSTMENTS

	MAJOR ROUTE OF ELIMINATION	THRESHOLD FOR ADJUSTMENT IN RENAL INSUFFICIENCY OR FAILURE	ADJUSTMENT FOR HEPATIC FAILURE	SPECIAL ADJUSTMENT FOR THE ELDERLY
Amantadine	Renal	CrCl <50 mL/min/1.73 m^2	No adjustment	>65 years: 100 mg daily
Rimantadine	Hepatic and renal	CrCl <10 mL/min/1.73 m^2	100 mg daily	100 mg daily
Oseltamivir	Renal	CrCl <60 mL/min	No adjustment	
Peramivir	Renal	CrCl <50 mL/min	No adjustment	
Zanamivir	Renal	No adjustment	No adjustment	
Baloxavir marboxil	Hepatic	Not evaluated on CrCl <50 mL/min	No adjustment in mild or moderate impairment	Not evaluated in patients >65 years of age

CrCl = creatinine clearance.

By inhibiting the ion channel function of the M2 protein of influenza A, they interfere with uncoating of the virus and release of the viral genome.

Clinical Uses

Amantadine and rimantadine decrease the length and severity of uncomplicated influenza A virus infection by susceptible strains if they are initiated within the first 2 days after the onset of symptoms, but it is uncertain whether they reduce the risk for complications. Both drugs are formulated for oral administration, and amantadine also has a pediatric syrup formulation. In recent years, marked increases in antiviral resistance in community isolates have limited the utility of these drugs.

When adamantine-susceptible viruses are circulating, both rimantadine and amantadine are effective when they are used for prophylaxis (overall 66% average for rimantadine and 74% for amantadine). Despite prophylaxis, subclinical infections may still develop and elicit immune responses that are protective against antigenically related viruses.

Toxicity

Amantadine causes CNS side effects in 10 to 30% of healthy young adults who take the standard adult dose; the frequency is significantly lower with rimantadine. Neuropsychiatric side effects include anxiety, nervousness, insomnia, and, particularly in the elderly or those with renal insufficiency, hallucinations, confusion, disorientation, and psychosis or coma. Amantadine (or less often rimantadine) is associated with an increased risk for seizures. Both drugs cause gastrointestinal side effects. Orthostatic hypotension occurs in 1 to 5%. Anticholinergic side effects, including dry mouth, occur in amantadine recipients.

Antiviral Resistance

Single point mutations in M2 confer high-level resistance to these drugs and make them ineffective. Such resistant variants emerge commonly during treatment and are transmissible.

ANTIVIRALS FOR CORONAVIRUS INFECTIONS

REMDESIVIR

Remdesivir is an adenosine analog prodrug that inhibits viral RNA polymerases and has activity against several viruses, including Ebola virus (Chapter 351), Marburg virus (Chapter 351), Middle East respiratory system coronavirus (Chapter 334), and severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2; Chapter 337) and the disease it causes (coronavirus disease 2019 [COVID-19]).

Clinical Uses

When used in outpatients with COVID-19, remdesivir (200 mg intravenous loading dose followed by 100 mg on days 2 and 3) can reduce the risk of hospitalization or death by 87%[A13] and reduces the time to the alleviation of symptoms. When used in hospitalized patients with evidence of lower respiratory tract infection, a 5-day course appears to be as good as a 10-day course.[A14] Despite heterogeneity in the results of various randomized trials, meta-analysis of all studies suggests a net benefit for reducing time to recovery, progression to ventilation, and mortality.[A15,A16] Remdesivir is approved in the United States and in scores of other countries for patients who are hospitalized with COVID-19 and is recommended by the National Institute of Health COVID-19 Treatment Guidelines[5] but not by the World Health Organization[6] for hospitalized patients who require oxygen therapy.

Toxicity

Remdesivir can cause an increase in hepatic aminotransferase levels as well as gastrointestinal symptoms. Respiratory distress, hypotension, atrial fibrillation, and acute kidney injury have also been reported.

Antiviral Resistance

Although remdesivir resistance can occur in vitro, remdesivir resistance does not readily occur on treatment.

NIRMATRELVIR BOOSTED WITH RITONAVIR

Nirmatrelvir is an oral protease inhibitor that is active against M^{PRO}, a viral protease that plays a role in viral replication by cleaving the two viral polyproteins. Nirmatrelvir is administered with ritonavir, a cytochrome P450 (CYP) 3A4 inhibitor, to improve its pharmacokinetics. Alone, ritonavir has no activity against coronaviruses.

Clinical Uses

In nonhospitalized adults with mild to moderate COVID-19, ritonavir-boosted nirmatrelvir given within 5 days of the onset of symptoms reduces the risk of hospitalization or death through day 28 by 90% compared with placebo.[A17] Ritonavir-boosted nirmatrelvir (twice daily for 5 days) is recommended for treatment of non-hospitalized patients aged ≥12 years and weighing ≥40 kg at high risk for severe disease within 5 days of the onset symptoms. It is not recommended for patients who are taking potent cytochrome P450 (CYP) 3A4 inducers.

Toxicity

The most common adverse effects of ritonavir-boosted nirmatrelvir are dysgeusia, diarrhea, hypertension, and myalgia. The dose should be reduced in patients with moderate renal impairment, and this compound is not recommended in patients with an estimated glomerular filtration rate <30 mL/min. It also is not recommended for patients with severe hepatic impairment and should be used with caution in patients with pre-existing liver diseases, liver enzyme abnormalities, or hepatitis.

Antiviral Resistance

Missense mutation of the viral protease can occur in circulating strains, but currently no circulating mutations confer resistance to nirmatrelvir. In individuals with uncontrolled or undiagnosed HIV-1 infection, nirmatrelvir use may also lead to an increased risk of HIV-1 viral resistance to protease inhibitors.

MOLNUPIRAVIR

Molnupiravir is the oral prodrug of beta-D-N4-hydroxycytidine, which is a ribonucleoside with activity against several RNA viruses. Uptake of beta-D-N4-hydroxycytidine by viral RNA-dependent RNA polymerases results in viral mutations and lethal mutagenesis.

Clinical Uses

In non-hospitalized, unvaccinated adults, molnupiravir reduces the rate of hospitalization or death by 30% compared with placebo when started within 5 days after the onset of signs or symptoms of mild-to-moderate COVID-19.[A18] Although the different treatment options have not been directly compared in clinical trials, molnupiravir is generally recommended only when other therapies are not available or cannot be given, because molnupiravir has lower efficacy than the other options. Molnupiravir is not recommended in children or in pregnant or lactating woman.

Toxicity

The most common adverse effects of molnupiravir are diarrhea, nausea, and dizziness.

Antiviral Resistance

Although resistance can occur in vitro, molnupiravir resistance does not readily occur on treatment.

MONOCLONAL ANTIBODIES TO SARS-COV-2

Bamlanivimab/Etesevimab

Clinical Uses

Bamlanivimab (LY-CoV555) was the first monoclonal antibody that received U.S. FDA emergency use authorization. During development, treatment was subsequently modified to add a second monoclonal etesevimab (LY-CoV016). Bamlanivimab/etesevimab treatment of outpatients with symptomatic SARS-CoV-2 infection was associated a 3 to 4% decrease in COVID-19–related hospitalizations or emergency room visits.[A19]

The combination of bamlanivimab/etesevimab is indicated for treatment of mild-to-moderate non-hospitalized COVID-19 adult and pediatric patients at higher risk for progression to severe disease (generally defined as age ≥65 years of age, BMI >25, pregnancy, or an underlying medical condition associated with poor outcomes). It is given as 700 mg bamlanivimab and 1400 mg etesevimab administered together as soon as possible after positive viral test for SARS-CoV-2 and within 10 days of the onset of symptoms. Bamlanivimab/etesevimab should not be used in patients already hospitalized with COVID-19.

Antiviral Resistance

Some circulating variants, namely B.1.351 (Beta), P.1 (Gamma), and Omicron, have decreased susceptibility to bamlanivimab/etesevimab, and its use should be guided by the susceptibility of circulating strains.

Bebtelovimab

Clinical Uses

Bebtelovimab can improve symptoms and reduce viral load in patients with mild-to-moderate COVID-19. In high-risk patients, combining it with bamlanivimab/etesevimab does not provide additional benefit. Current guidance recommends it should be used only when ritonavir-boosted nirmatrelvir or remdesivir are not available, feasible to use, or clinically appropriate.

Antiviral Resistance

Bebtelovimab retains in vitro activity against Omicron BA.1 and BA.2 subvariants. Use with future variants should be guided by the susceptibility of circulating strains.

Casirivimab/Imdevimab

Clinical Uses

In outpatients with symptomatic SARS-CoV-2 infection, the monoclonal combination casirivimab/imdevimab can reduce hospitalization or all-cause death by half (6% in treated patients compared with 3% in controls).[A20] When given to exposed family members after one family member is diagnosed with SARS-CoV-2 infection, casirivimab/imdevimab is associated with 72% protection against symptomatic infections in the first week and 93% in subsequent weeks.

Casirivimab/imdevimab is indicated for the treatment of mild-to-moderate non-hospitalized COVID-19 adult and pediatric patients at higher risk for progression to severe disease. Casirivimab and imdevimab should be dosed at 600 mg of casirivimab and 600 mg of imdevimab administered together as a single intravenous infusion or by subcutaneous injection, as soon as possible after positive results of direct SARS-CoV-2 viral testing and within 10 days of the onset of symptoms. For prophylaxis in populations in high-risk environments, such as skilled nursing and assisted living facilities, the same dose is used. Casirivimab/imdevimab should not be used in patients already hospitalized with COVID-19.

Antiviral Resistance

Casirivimab/imdevimab should not be used for the Omicron variant given its decreased susceptibility to these antibodies. Use should be guided by the susceptibility of circulating strains.

Sotrovimab

Clinical Uses

Sotrovimab reduces the risk of COVID-19 progression to hospitalization or death by 85%.[A21] Sotrovimab (VIR-7831) is indicated for the treatment of mild-to-moderate non-hospitalized COVID-19 adult and pediatric patients at higher risk for progression to severe disease. Sotrovimab should not be used in patients already hospitalized with COVID-19.

Antiviral Resistance

This antibody maintained effectiveness against the Omicron BA.1 variant but does not have efficacy against Omicron BA.2 variant.[7] Use should be guided by the susceptibility of circulating strains.

OTHER ANTIVIRALS

RIBAVIRIN

Ribavirin is a purine nucleoside with antiviral activity against some DNA viruses and many RNA viruses, including influenza A and B, parainfluenza, coronaviruses including Middle East respiratory syndrome (Chapter 334), measles (Chapter 338), respiratory syncytial virus (Chapter 330), retroviruses (Chapter 360), arenaviruses such as Lassa virus (Chapter 351), and some hantaviruses (Chapter 351) and hepatitis C virus (Chapter 135).

Clinical Uses

Aerosol administration of ribavirin has been used to treat respiratory syncytial virus bronchiolitis and pneumonia in children and to treat influenza A and B infections. Limited benefit has been seen with oral ribavirin in uncomplicated influenza. Aerosol ribavirin combined with intravenous immune globulin, particularly with the anti-respiratory syncytial virus monoclonal antibody palivizumab, appears to reduce the mortality of respiratory syncytial virus infection in bone marrow transplant and other highly immunocompromised patients.

Systemic ribavirin reduces the mortality associated with Lassa fever and Asian (Korean) hemorrhagic fever with renal syndrome (Chapter 351), although not mortality in patients with hantavirus-associated cardiopulmonary syndrome. It appears to have activity in Congo-Crimean hemorrhagic fever and in Nipah virus infections. Ribavirin is often recommended as treatment of hemorrhagic fevers of unknown etiology or secondary to arenaviruses or bunyaviruses (Chapter 351).

Given the breadth of ribavirin's activity against many viruses, it is often used for emerging infectious diseases (e.g., severe acute respiratory syndrome [SARS] and Middle East respiratory syndrome). However, the concentrations needed to show efficacy in cell cultures and animal models may be significantly higher than can be obtained in humans. Caution is therefore urged when ribavirin is suggested for treating these diseases.

Ribavirin can improve the sustained virologic response for chronic hepatitis C infection when used with pegylated interferons, but the new directly acting antiviral agents are used without ribavirin. However, ribavirin is still used in patients with viral resistance to grazoprevir/elbasvir and in patients with cirrhosis (combined with sofosbuvir plus ledipasvir for treatment-experienced patients).

IMIQUIMOD

Imiquimod and the related compound resiquimod are topical immune response modifiers that lack direct antiviral effects. Instead, these agents induce activation of immune cells (monocytes, macrophages, natural killer cells) to produce antiviral cytokines, particularly interferon-α and tumor necrosis factor-α.

Topical imiquimod cream is approved for the treatment of condyloma acuminatum (Chapter 344). In immunocompetent patients, imiquimod leads to complete clearance of warts in 37 to 52% of patients. It is administered as a topical cream three times weekly for a maximum of 16 weeks and is washed off 6 to 10 hours after application.

Side effects are primarily local and include erythema, irritation, tenderness, and (less often) erosion. The side effects usually resolve with cessation of the drug.

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329 THE COMMON COLD

BRUCE BARRETT

DEFINITION

The common cold is a clinical syndrome characterized by upper respiratory signs and symptoms (e.g., rhinorrhea, sneezing, nasal obstruction), which are frequently accompanied by sore throat, cough, and general malaise. The common cold is among the most prevalent of illness syndromes and is very costly in aggregate, especially considering the resulting absenteeism from school and work. Common cold is both a clinical and a cultural construction, and it results from a variety of etiologic agents.

The Pathogens

Human rhinoviruses are RNA viruses that infect the upper respiratory epithelium. Rhinoviruses are the most common viruses that cause upper respiratory symptoms in children and their family members.[1] The more than 150 rhinovirus genotypes are classified as species A, B, or C based on sequence homology. Rhinoviruses are important causes of exacerbations of chronic bronchitis (Chapter 76) and asthma (Chapter 75). Rhinovirus infection can cause bronchiolitis in infants and young children, and is the predominant cause of exacerbation of childhood asthma. Among elderly patients, especially those with lung disease, infection with rhinovirus and other cold viruses is an important cause of hospitalization, pneumonia, and death.[2,3]

The common cold illness syndrome also can be caused by parainfluenza viruses (Chapter 331), respiratory syncytial virus (Chapter 330), metapneumoviruses (Chapter 330), adenoviruses (Chapter 333), bocaviruses (Chapter 342), and influenza viruses (Chapter 332; Table 329-1).[4] Coronaviruses (Chapters 334 and 336), including severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) that is responsible for the coronavirus 19 (COVID-19) pandemic, also are common causes of the common cold. Bacterial pathogens such as *Mycoplasma pneumoniae* (Chapter 293), *Bordetella pertussis* (Chapter 389), group A streptococcus (Chapter 269) *Streptococcus pneumoniae* (Chapter 268), and *Haemophilus influenzae* (Chapter 277) are sometimes the only identifiable pathogen in a person who is experiencing the common cold syndrome, but the role of these organisms, which colonize the upper respiratory tract in healthy individuals, is not clear. Co-detection of more than one virus, or of a virus plus a bacterial pathogen, is fairly common.

EPIDEMIOLOGY

The incidence of common cold decreases with age, from an average of about six symptomatic episodes per year in young children to approximately two episodes per year in adults. Asymptomatic infections are also common. The incidence of illness is higher in adults who have occupational or household exposure to children and in young children who are cared for in child care centers. Common cold illnesses occur year-round in temperate climates but have a substantially increased incidence between the early autumn and late spring. Reasons for the seasonality of respiratory viruses[5] are poorly understood. In tropical climates, colds can occur year-round without defined seasonality.

TABLE 329-1 VIRUSES ASSOCIATED WITH THE COMMON COLD

VIRUS GROUP	ANTIGENIC TYPES	PERCENTAGE OF CASES
Rhinovirus	>150	30-60
Coronavirus	5	10-15
Parainfluenza virus	5	5
Respiratory syncytial virus	2	5-10
Influenza virus	3	5-15
Adenovirus	47	5
Metapneumovirus	2	5
Bocavirus	2	5-20

Based on data from: Byington CL, Ampofo K, Stockmann C, et al. Community surveillance of respiratory viruses among families in the Utah Better Identification of Germs-Longitudinal Viral Epidemiology (BIG-LoVE) study. *Clin Infect Dis*. 2015;61:1217-1224; Monto AS. Epidemiology of viral respiratory infections. *Am J Med*. 2002;112(Suppl 6A):4s-12s; and Szilagyi PG, Blumkin A, Treanor JJ, et al. Incidence and viral aetiologies of acute respiratory illnesses (ARIs) in the United States: a population-based study. *Epidemiol Infect*. 2016;144:2077-2086.

PATHOBIOLOGY

Respiratory pathogens are spread from person to person by direct contact with either infected individuals or contaminated objects in the environment, by large-particle aerosols, or by small-particle aerosols. Modes of transmission vary by agent and are influenced by a variety of factors, including distancing, mask-wearing, and handwashing. For example, respiratory syncytial virus (Chapter 330) may be spread by either direct contact or large-particle aerosols, and influenza (Chapter 332) may be spread more by small-particle aerosols. The SARS-CoV-2 virus appears to be spread more by respiratory droplets and aerosols than by direct contact.[6]

The common cold syndrome is initiated by viral infection of the epithelial cells in the nasal passageways or upper pharynx. Influenza and adenovirus produce obvious damage to the respiratory epithelium. Rhinovirus and respiratory syncytial virus, in contrast, have little or no detectable impact on the epithelium. Pathologic consequences of infection by SARS-CoV-2 are highly variable, from asymptomatic infection with minimal inflammation to highly invasive disease with a variety of pathologic manifestations and sequelae. Regardless of the histopathology, all of these viruses stimulate a nonspecific host inflammatory response that appears to be responsible for many of the symptoms associated with the common cold.

Nasal obstruction results from increased nasal blood flow and pooling of blood in the capacitance vessels of the nasal passageway. Sympathetic and parasympathetic pathways are involved. The increase in nasal secretion associated with the common cold may also contribute to nasal obstruction. Rhinorrhea is primarily a result of increased vascular permeability, with leakage of serum into the nasal secretions, which are composed of both transudates and exudates. Increased mucus production tends to contribute more to the secretions during the later stages of the illness.

Cough (Chapter 71) occurs in the majority of colds and tends to last longer than other symptoms. Cough during colds is produced by several different mechanisms, including infection-induced airway inflammation and irritation from mucus secretion or postnasal drip. Patients who smoke or who have asthma, reactive airway disease, or chronic obstructive pulmonary disease are at higher risk for cough.

The risk of infection after exposure to the respiratory viruses is primarily dependent on adaptive immune mechanisms, as indicated by the presence of specific neutralizing antibodies. Antibody responses to the rhinoviruses, adenoviruses, coronaviruses, and influenza viruses tend to be protective against subsequent infection. The frequency of infection with these viruses is a result of the large number of distinct serotypes of rhinovirus and adenovirus and the ability of the influenza viruses to behave as though there are multiple virus serotypes by virtue of the rapid mutation of surface antigens. The parainfluenza viruses, respiratory syncytial viruses, and metapneumoviruses produce very little protective immunity, so reinfection is common. As seen with SARS-CoV-2, relatively small genetic changes may result in variants that have different virulence, infectivity, and resistance to immune mechanisms.

Susceptibility to and pathogenesis of the common cold are multifactorial processes, with innate and adaptive immune mechanisms influenced by genetic predisposition, by previous antigen exposure, and by general health. Polymorphisms of mannose-binding lectin and various toll-like receptors may confer susceptibility or partial protection. Inflammatory cytokines associated with the severity of disease include various interferons, interleukins, and other factors, which rise markedly in nasal secretions but usually do not change much in the serum. Recent research suggests that the respiratory microbiome may be involved. Specific genes and epigenetic influences on the expression of those genes may predispose toward higher levels of inflammatory cytokines, and more severe respiratory illness.

Although specific mechanisms are not well understood, several decades of research have shown that susceptibility to common cold is influenced by mental health. Risk factors include perceived stress, social isolation, negative emotional style, and a history of stressful life events.

CLINICAL MANIFESTATIONS

The incubation of common cold illness is generally short, ranging from 2 to 8 days, although some adenoviruses may have an incubation of as long as 13 days. The common cold illness syndrome generally persists for 5 to 10 days, but a substantial proportion of individuals have colds that persist for longer or

ABSTRACT

Studies suggest that at least 3 of every 4 adults and 9 of 10 children will experience at least one cold in a given year, thereby making the common cold perhaps humanity's highest incidence illness. Average annual incidence deceases from five or six symptomatic episodes among very young children to one or two episodes per year among older adults. Viral infection of the upper respiratory tract stimulates immune and inflammatory mechanisms that lead to engorged blood vessels, vascular permeability, and mucus secretion, thereby producing rhinorrhea, sneezing, and nasal congestion; nociceptive stimulation that produces sore throat, headache, and myalgia; and mechanoreceptor stimulation, which involves the vagus nerve and produces cough. Generalized symptoms thought to be due to interferons and other inflammatory cytokines may lead to malaise, fatigue, headache, myalgia, or fever. Viral agents include rhinovirus, coronavirus, influenza, parainfluenza, respiratory syncytial virus, metapneumovirus, adenovirus, and bocavirus. The common cold is among the most costly of illnesses, due in large part to resulting absenteeism from school or work. Common cold symptoms may be partially alleviated with over-the-counter analgesics, decongestants, anticholinergics, and antitussives—but their effectiveness is limited, and side effects are common. For most viruses, effective antivirals do not yet exist, and antibacterial antibiotics are ineffective. Vaccinations for influenza and for severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) help prevent infection, illness, hospitalization, and death, but they are not effective against other agents. Handwashing and general health maintenance may reduce infectivity and the overall burden of the common cold.

KEYWORDS

acute respiratory infection
common cold
cough
influenza-like illness
nasal congestion
pharyngitis
sneezing
rhinovirus

shorter periods of time. A sore or scratchy throat is frequently reported as the first symptom. Sneezing is also a common early symptom. Nasal obstruction and rhinorrhea develop rapidly and are often the most bothersome symptoms. Cough generally develops later in the illness, frequently is the most bothersome symptom during the latter phases of the common cold, and may persist for several weeks after all other symptoms have resolved. When asked to rate what bothers them most about their colds, people tend to identify general malaise or interference with daily activities as more important than the presence or severity of specific symptoms.

Physical findings are generally restricted to the upper respiratory tract. Swelling of the nasal epithelia and increased nasal secretion may be obvious to the examiner. A change in the color or consistency of nasal secretions is common during the course of the illness and is not indicative of sinusitis or bacterial superinfection. The posterior pharynx may show signs of inflammation similar to streptococcal pharyngitis. Paroxysmal cough or wheezing may occur.

DIAGNOSIS

The differential diagnosis of the common cold includes noninfectious disorders as well as other upper respiratory tract infections. Allergic rhinitis (Chapter 394) has a symptom complex similar to that of the common cold, although the presence of nasal or conjunctival itching suggests allergic disease. Most patients can reliably differentiate these illnesses.

Sinus involvement is usually present in uncomplicated cold illnesses. Superimposed bacterial sinusitis (Chapter 394) may be difficult to differentiate from an uncomplicated cold. Sino-nasal symptoms that persist without improvement for more than 10 days and that are accompanied by unilateral maxillary sinus pain and purulent discharge may suggest the presence of bacterial sinusitis, which actually is a relatively rare complication that may respond to antibiotics.

When symptoms are more severe—with rapid onset, feverishness, and headache or muscle aches, accompanied by sore throat or cough—an "influenza-like illness" may be diagnosed. Although influenza-like illness is more likely to be produced by influenza, parainfluenza, or SARS-CoV-2, any of the common cold viruses can produce this more severe variant of common cold.

In general, routine laboratory studies are not helpful for the diagnosis or management of the common cold. During epidemics such as COVID-19, or perhaps during the annual winter influenza epidemic, identification of the specific pathogen can be useful for epidemiologic purposes but will rarely influence treatment unless lower respiratory symptoms develop.[7] When signs and symptoms are more severe, a white blood cell count and inflammatory markers such as C-reactive protein may be useful for assessing the likelihood of pneumonia (Chapter 85). For patients who have pharyngeal exudates, swollen cervical lymph nodes, and feverishness, a rapid test for streptococcal pharyngitis (Chapter 269) may be useful. In epidemic conditions, advice from public health authorities should be taken into account.

TREATMENT

No treatments are scientifically proven to reduce the severity or duration of common cold illness significantly,[8] but many patients are inappropriately prescribed antibiotics.[9] Several treatments, however, may confer limited symptomatic benefit, which must be balanced against the potential for side effects.

Antivirals and Antibiotics

Specific antiviral therapy is generally not useful for the treatment of common cold. For proven influenza, the oseltamivir, zanamivir, peramivir, and baloxavir (Chapter 328) have a modest ameliorating effect, but the difficulty of distinguishing influenza from common cold and the need to start treatment very early in the illness are practical limitations to the use of these agents. Antibacterial therapy is of no benefit. Despite decades of efforts to reduce antibiotic prescribing for common cold, this practice remains disturbingly common.

Nasal Congestion

Both topical and oral adrenergic agents (Table 329-2) have limited efficacy as nasal decongestants.[A1] Although direct comparison has not been performed, it is generally accepted that topical over-the-counter agents, such as intranasal xylometazoline or oxymetazoline, are more effective than oral drugs for nasal congestion. Prolonged use of the topical adrenergic agents should be avoided to prevent the development of a rebound effect when the drug is discontinued (rhinitis medicamentosa). Systemic absorption of oxymetazoline and xylometazoline have rarely been associated with bradycardia, hypotension, and coma.

The systemic side effects of the oral adrenergic agents such as pseudoephedrine include central nervous system stimulation, which can cause insomnia, jitteriness, or palpitations. As a result, adrenergic decongestants should probably be avoided, especially by patients who have hypertension or heart disease. Nasal saline is an inexpensive and safe treatment for nasal congestion, but research to date has not demonstrated substantive benefit in common cold.

TABLE 329-2 PHARMACOLOGICAL TREATMENTS FOR THE COMMON COLD

DRUG	DOSE AND DURATION	SIDE EFFECTS
Topical adrenergic agent: oxymetazoline	2-3 sprays of 0.05% solution every 12 hr as needed for up to 3 days	Rebound nasal congestion with prolonged use Nasal stinging or burning
Oral adrenergic agent: pseudoephedrine	60 mg every 4-6 hr up to 240 mg/day as needed for nasal congestion	Insomnia Agitation
Antihistamine: chlorpheniramine	4 mg orally every 4-6 hr up to 24 mg/day as needed for rhinorrhea or sneezing	Sedation
Anticholinergic: ipratropium bromide	2 sprays per nostril of 0.06% solution every 6-8 hr as needed for rhinorrhea	Nasal dryness

Rhinorrhea

Rhinorrhea (nasal drainage, runny nose) is a hallmark symptom of the common cold. Adrenergic decongestants may provide limited relief but have significant side effects.[10] Blockade of cholinergic stimulation of glandular secretion using intranasal ipratropium bromide appears to reduce rhinorrhea in colds by about 25%. The most common side effect of intranasal ipratropium is a two-fold increase in nasal irritation and bleeding. First-generation (sedating) antihistamines, owing to their anticholinergic properties, may have mild beneficial effects on rhinorrhea[A2] but also can cause drying of the eyes, mouth, and nose.

Cough

Treatment directed at an underlying condition (e.g., asthma) might be helpful (Chapters 71 and 397). For example, if cough is caused by direct irritation owing to postnasal drip, it may respond to treatment with a first-generation antihistamine or ipratropium. If a more persistent cough is the result of virus-induced reactive airway disease, patients might possibly benefit from inhaled bronchodilator therapy (Chapter 75). The evidence for nonspecific cough suppression with codeine, dextromethorphan, guaifenesin, or moguisteine is quite limited, with insufficient data to support or refute clinical effectiveness. Herbal cough formulas including *Andrographis paniculata*, *Pelargonium sidoides*, or an ivy/primrose/thyme combination may have limited efficacy, but the evidence is limited and controversial. Because of a substantive placebo effect for cough, the choice of a safe antitussive agent may be guided by a patient's belief system and prior experience.

Pain-Related Symptoms

For sore throat, ear pain, headache, and body aches (myalgias), acetaminophen (e.g., 650 to 1000 mg every 4 to 6 hours) is the preferred initial treatment. Nonsteroidal anti-inflammatory agents (e.g., ibuprofen 200 to 400 mg every 4 to 6 hours or naproxen 275 to 550 mg every 6 to 8 hours) are equally effective for pain but can cause stomach upset and increase the risk of intestinal bleeding and kidney damage.

Combination Therapies

Combination cold therapies available without a prescription (containing, for example, analgesics, decongestants, antihistamines, and/or antitussives) may have modest benefits over placebo, but any symptomatic benefits should be weighed against potential side effects. Specific therapies targeted to an individual's symptoms of nasal obstruction, rhinorrhea, or sore throat are preferred, so as to avoid the cost and side effects of unnecessary medications.

Other Remedies

Zinc lozenges (e.g., zinc acetate or zinc gluconate, dosed at ≥75mg/day of elemental zinc) may improve common cold recovery rates by 20% or more.[A3] However, zinc lozenges are associated with bad taste, sore mouth, and occasional nausea; intranasal zinc may cause nasal irritation or nosebleeds. Neither vitamin C nor Echinacea formulations are of proven benefit for treating the common cold.[11]

PREVENTION

Chemoprophylaxis or immunoprophylaxis is generally not available for the common cold.[A4] Immunization or chemoprophylaxis against influenza (Chapter 332) and SARS-CoV-2 (Chapter 336) are useful to prevent colds caused by these pathogens.

Handwashing has undeniable benefits and can prevent spread of the common cold.[A5] Physical distancing and mask-wearing are now also established as effective ways to prevent acute respiratory infections, including the common cold. Vitamin C (ascorbic acid) has not been proven to prevent the common cold,[A6] though the regular ingestion of 400 to 1000 IU per day of vitamin D may reduce its incidence.[A7] Echinacea and the regular ingestion of probiotics have at most a modest benefit as preventive therapies.[A8] Both regular exercise and meditation may help to prevent or reduce the severity of the symptoms of common cold illness.[A9,A10]

PROGNOSIS

The common cold usually has little medical significance, and complete recovery can usually be expected. However, the common cold is costly, is highly prevalent, and can be temporarily debilitating. The common cold also can be complicated by otitis media (Chapter 394), sinusitis (Chapter 394), or pneumonia (Chapter 85), which may be a direct result of the viral infection or may be due to bacterial superinfection. Exacerbations of asthma (Chapter 75) and chronic bronchitis (Chapter 76) also are important complications of the common cold. For elderly who are frail or have advanced lung disease, the common cold can even lead to hospitalization or death. Rhinovirus infection within a family also appears to facilitate within-family transmission of *S. pneumoniae*, which may then result in pneumonia.

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330 RESPIRATORY SYNCYTIAL VIRUS AND HUMAN METAPNEUMOVIRUS

H. KEIPP TALBOT AND EDWARD E. WALSH

RESPIRATORY SYNCYTIAL VIRUS

DEFINITION

Respiratory syncytial virus (RSV), which causes yearly winter outbreaks in temperate climates, is the most important cause of bronchiolitis and pneumonia in young infants, a common cause of illness in older children and young adults, and can be severe in elderly persons, adults with underlying cardiopulmonary disease, and adults who are severely immunocompromised.

The Pathogen

RSV is a single-stranded RNA-enveloped virus of the family Paramyxoviridae, genus *Pneumovirus*; it is related to human metapneumovirus. Two major transmembrane glycoproteins (G, attachment protein; F, fusion protein) carry neutralizing epitopes, and two nonstructural proteins (NS1 and NS2) block the antiviral activity of type I interferons, whereas a secreted form of G bearing a CX3C chemokine motif may modulate immune responses. Two major virus groups (A and B), each with multiple genotypes, are distinguishable.

EPIDEMIOLOGY

In the United States epidemics begin in the south in late fall, move steadily north, and peak in February and March in colder climates.[1] In tropical areas, RSV may occur throughout the year, with peaks during the rainy season. RSV annually causes approximately 100,000 hospitalizations and accounts for 60% of bronchiolitis and 25% of pneumonia cases in infants. Mortality is rare in the United States (<400 deaths annually), but deaths are substantially greater in developing countries. About half of infants become infected in their first winter and all by age 2. RSV is transmitted principally by direct contact with large-particle fomites of respiratory secretions rather than by small-particle aerosolization.

Between 1 and 3% of primary infections result in hospitalization, but lower socioeconomic status, crowding, underlying prematurity, congenital cardiac abnormalities, bronchopulmonary dysplasia, and immunosuppression are each associated with increased risk for serious disease. Severe disease is also associated with specific polymorphisms in the promoter regions of cytokine genes. Hospitalization is most frequent between the ages of 1 and 6 months, peaking at 2 months of age with a rate of 25.9 per 1000 children. However, the majority of hospitalized infants are normal healthy infants without identifiable risk factors. The overall burden of RSV in infants 0 to 6 months of age is 132 office visits, 55 emergency department visits, and 17 hospitalizations per 1000. Reinfection occurs frequently throughout life. Subsequent illness is less severe and hospitalization infrequent for persons ages 2 to 49 years, but severity increases with increasing age[2] and comorbid conditions such as diabetes, heart failure, chronic obstructive pulmonary disease, and end-stage renal disease.[3]

Though often not considered in adults, RSV infection is common and may be severe in the elderly. RSV accounts for 15 to 20% of medically attended outpatient respiratory illnesses in persons older than 45 years, and RSV-associated mortality among persons age 65 and older is about 90% as high as influenza A and greater than double that of influenza B. RSV infection is implicated in 6 to 15% of hospitalizations for acute pulmonary symptoms in the winter among community-dwelling elderly persons, numbers that are similar to those for influenza.[4]

RSV infection has been documented in up to 10% of bone marrow transplant recipients (Chapter 163), patients with acute leukemia (Chapter 168), and heart/lung transplant recipients (Chapters 46 and 87) during the winter months. In this setting, in-hospital outbreaks can develop quickly if patients are not adequately isolated.

PATHOBIOLOGY

The virus most commonly enters through the nose or eye and then spreads from the upper to the lower respiratory tract. Pathologic findings include a lymphocytic peribronchiolar infiltration with edema, obstruction, and necrosis. Bronchiolitis with multiple areas of atelectasis and pneumonia with interstitial infiltration of mononuclear cells, as well as alveoli filled by edema and necrosis, develop in infected patients.

CLINICAL MANIFESTATIONS

Infants experience upper respiratory symptoms of conjunctival injection, mucopurulent nasal discharge, cough, and low-grade fever after an incubation period of 2 to 8 days. Otitis media (Chapter 394) is often associated with secondary bacterial infection. After several days, lower respiratory tract symptoms appear in 25 to 50% of infants, with cough, wheezing, tachypnea, and use of accessory muscles as the disease progresses. Expiratory wheezes, rhonchi, and fine rales are the most common findings on lung examination. Sudden apnea may develop in the youngest infants. Hyperinflation and diffuse interstitial pneumonitis are the most frequent radiographic findings. High-titer virus shedding lasts 7 to 10 days, although immunocompromised infants may excrete virus for a month or longer, even when asymptomatic. Coinfection with other respiratory viruses occurs in up to 30% of patients, but it usually is neither clinically discernible nor definitively associated with more severe illness.

Adults with RSV typically begin with upper respiratory symptoms, but many patients have lower respiratory symptoms, including dyspnea and wheezing. Low-titer virus shedding often persists for 10 days or longer. In elderly

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330 RESPIRATORY SYNCYTIAL VIRUS AND HUMAN METAPNEUMOVIRUS

H. KEIPP TALBOT AND EDWARD E. WALSH

RESPIRATORY SYNCYTIAL VIRUS

DEFINITION

Respiratory syncytial virus (RSV), which causes yearly winter outbreaks in temperate climates, is the most important cause of bronchiolitis and pneumonia in young infants, a common cause of illness in older children and young adults, and can be severe in elderly persons, adults with underlying cardiopulmonary disease, and adults who are severely immunocompromised.

The Pathogen

RSV is a single-stranded RNA-enveloped virus of the family Paramyxoviridae, genus *Pneumovirus*; it is related to human metapneumovirus. Two major transmembrane glycoproteins (G, attachment protein; F, fusion protein) carry neutralizing epitopes, and two nonstructural proteins (NS1 and NS2) block the antiviral activity of type I interferons, whereas a secreted form of G bearing a CX3C chemokine motif may modulate immune responses. Two major virus groups (A and B), each with multiple genotypes, are distinguishable.

EPIDEMIOLOGY

In the United States epidemics begin in the south in late fall, move steadily north, and peak in February and March in colder climates.[1] In tropical areas, RSV may occur throughout the year, with peaks during the rainy season. RSV annually causes approximately 100,000 hospitalizations and accounts for 60% of bronchiolitis and 25% of pneumonia cases in infants. Mortality is rare in the United States (<400 deaths annually), but deaths are substantially greater in developing countries. About half of infants become infected in their first winter and all by age 2. RSV is transmitted principally by direct contact with large-particle fomites of respiratory secretions rather than by small-particle aerosolization.

Between 1 and 3% of primary infections result in hospitalization, but lower socioeconomic status, crowding, underlying prematurity, congenital cardiac abnormalities, bronchopulmonary dysplasia, and immunosuppression are each associated with increased risk for serious disease. Severe disease is also associated with specific polymorphisms in the promoter regions of cytokine genes. Hospitalization is most frequent between the ages of 1 and 6 months, peaking at 2 months of age with a rate of 25.9 per 1000 children. However, the majority of hospitalized infants are normal healthy infants without identifiable risk factors. The overall burden of RSV in infants 0 to 6 months of age is 132 office visits, 55 emergency department visits, and 17 hospitalizations per 1000. Reinfection occurs frequently throughout life. Subsequent illness is less severe and hospitalization infrequent for persons ages 2 to 49 years, but severity increases with increasing age[2] and comorbid conditions such as diabetes, heart failure, chronic obstructive pulmonary disease, and end-stage renal disease.[3]

Though often not considered in adults, RSV infection is common and may be severe in the elderly. RSV accounts for 15 to 20% of medically attended outpatient respiratory illnesses in persons older than 45 years, and RSV-associated mortality among persons age 65 and older is about 90% as high as influenza A and greater than double that of influenza B. RSV infection is implicated in 6 to 15% of hospitalizations for acute pulmonary symptoms in the winter among community-dwelling elderly persons, numbers that are similar to those for influenza.[4]

RSV infection has been documented in up to 10% of bone marrow transplant recipients (Chapter 163), patients with acute leukemia (Chapter 168), and heart/lung transplant recipients (Chapters 46 and 87) during the winter months. In this setting, in-hospital outbreaks can develop quickly if patients are not adequately isolated.

PATHOBIOLOGY

The virus most commonly enters through the nose or eye and then spreads from the upper to the lower respiratory tract. Pathologic findings include a lymphocytic peribronchiolar infiltration with edema, obstruction, and necrosis. Bronchiolitis with multiple areas of atelectasis and pneumonia with interstitial infiltration of mononuclear cells, as well as alveoli filled by edema and necrosis, develop in infected patients.

CLINICAL MANIFESTATIONS

Infants experience upper respiratory symptoms of conjunctival injection, mucopurulent nasal discharge, cough, and low-grade fever after an incubation period of 2 to 8 days. Otitis media (Chapter 394) is often associated with secondary bacterial infection. After several days, lower respiratory tract symptoms appear in 25 to 50% of infants, with cough, wheezing, tachypnea, and use of accessory muscles as the disease progresses. Expiratory wheezes, rhonchi, and fine rales are the most common findings on lung examination. Sudden apnea may develop in the youngest infants. Hyperinflation and diffuse interstitial pneumonitis are the most frequent radiographic findings. High-titer virus shedding lasts 7 to 10 days, although immunocompromised infants may excrete virus for a month or longer, even when asymptomatic. Coinfection with other respiratory viruses occurs in up to 30% of patients, but it usually is neither clinically discernible nor definitively associated with more severe illness.

Adults with RSV typically begin with upper respiratory symptoms, but many patients have lower respiratory symptoms, including dyspnea and wheezing. Low-titer virus shedding often persists for 10 days or longer. In elderly

ABSTRACT

Respiratory syncytial virus is a common respiratory pathogen affecting persons of all ages. The most severe illnesses occur in very young infants and frail elderly, as well as in patients with underlying cardiopulmonary disease or compromised immune systems. Clinical manifestations are dominated by upper and lower respiratory symptoms, with wheezing as a classic characteristic. Diagnosis is best made by testing respiratory secretions with molecular detection methods such as reverse transcription–polymerase chain reaction (RT-PCR). A vaccine is not currently available, and treatment options are limited. Prophylaxis with a monoclonal antibody is available for high-risk infants. Aerosolized ribavirin coupled with intravenous immunoglobulin may be efficacious in severely immunocompromised patients with lower respiratory tract disease.

Human metapneumovirus infection can range from asymptomatic carriage to fatal disease. The virus is the cause of nearly 10% of adult cases of hospitalized pneumonia. Diagnosis is by RT-PCR. Care is supportive. Most patients recover, but mortality can be high in immunocompromised patients.

KEYWORDS

bronchiolitis
COPD
ribavirin
palivizumab
respiratory syncytial virus
human metapneumovirus

persons, RSV attack rates are 3 to 5% annually; wheezing is more common than with influenza (Chapter 332), whereas fever is less common. Symptoms can progress to respiratory failure,[5] especially in frail elderly persons, nursing home residents, or patients with underlying chronic obstructive pulmonary disease or heart failure.[6] Attack rates in nosocomial nursing home outbreaks average 10 to about 90%, with crackles and wheezes evident in a third of patients and radiographically confirmed pneumonia in approximately 10%. The incidence of bacterial superinfection in hospitalized adults with RSV is about 30%, similar to that of other common respiratory viruses, including influenza.

In bone marrow transplant recipients, RSV usually presents initially with upper respiratory symptoms. In about 30% of patients, lower respiratory tract disease follows, often with severe symptoms.

DIAGNOSIS

In infants, a presumptive diagnosis is suggested by typical symptoms during the epidemic season, but the diagnosis often is not considered and therefore delayed in adults.[7] Diagnosis can be made using sensitive molecular detection methods,[8] including reverse transcription–polymerase chain reaction (RT-PCR), transcription-mediated amplification (TMA), or loop-mediated isothermal application (LAMP).[9,10] Viral culture, which can take up to 10 days, has a sensitivity of only about 30%. Neither antigen detection by immunofluorescence nor enzyme immunoassay is useful in adults.

In immunocompromised patients, chest radiographs demonstrate diffuse interstitial and alveolar infiltrates. A useful clinical clue to the presence of RSV is the frequent presence of radiographically proven sinusitis. Upper respiratory tract symptoms distinguish this illness from cytomegalovirus pneumonia (Chapter 347).

TREATMENT

Therapy is generally limited to hydration and supplemental oxygen. Neither bronchodilators nor glucocorticosteroids have shown benefit in most studies. Inhaled ribavirin (2 g administered by aerosol three times daily for 5 or so days) may be beneficial for seriously ill infants and immunocompromised adults with RSV pneumonia, especially if begun before lower respiratory symptoms develop.[11] An experimental oral RSV-entry inhibitor and an oral nucleoside analog have shown promise in reducing the viral load in experimental human challenge models of RSV infection and are currently in clinical trials.[12]

Bacterial superinfection can develop, with *Streptococcus pneumoniae* (Chapter 268) and *Haemophilus influenzae* (Chapter 277) being the most frequent organisms. For such patients, appropriate antimicrobial treatment (Chapter 85) is mandatory.

PREVENTION

Adherence to standard infection control principles (e.g., gloves, gowns, frequent handwashing) substantially reduces nosocomial spread. Vaccines can reduce RSV-associated respiratory disease by about 70 to 80% and severe diseases by up to 90%, [A1–A3] and a vaccine is approved by the U.S. Food and Drug Administration for adults ages 60 years and older. Parenteral humanized RSV monoclonal antibody (palivizumab, 15 mg/kg monthly during the RSV season) has demonstrated benefit when administered prophylactically to specific high-risk infant groups,[13] but inhaled RSV antibodies have not been shown to improve clinical outcomes despite a somewhat more rapid decline in viral load.[A4]

PROGNOSIS

RSV infection in severely immunocompromised adults such as bone marrow transplant recipients (Chapter 163) and those with acute leukemia (Chapter 168) undergoing cytotoxic chemotherapy can carry a 60% mortality rate when pneumonia develops. Lymphopenia (<100/μL) and high-dose total body irradiation are associated with more severe disease, but progression to pneumonia is very unusual in patients with an absolute lymphocyte count above 1000/μL. In lung transplant recipients, bronchiolitis obliterans syndrome may occur in 10 to 50% of patients as a late sequela of RSV infection.

Mortality is rare in otherwise healthy infants but can reach 37% in infants with cardiac disorders. In children, a link between severe bronchiolitis and subsequent asthma remains unresolved. In normal infants and healthy adults, the outcome is generally good, but the risk of mortality in adults is higher with RSV than with influenza.[14,15] Hospitalized older adults can have mortality rates of about 10%.

HUMAN METAPNEUMOVIRUS

Human metapneumovirus, which is a negative-sense single-strand RNA virus in the *Pneumoviridae* family, was first identified in 2001 in children with bronchiolitis. It is recognized primarily as a cause of upper and lower respiratory tract illness in infants and young children, with a peak age of hospitalization at 6 to 12 months.

EPIDEMIOLOGY

The virus generally circulates in late winter to early spring in the Northern Hemisphere, at the same time that the incidence of RSV is usually declining. Similar to RSV, human metapneumovirus is transmitted primarily by direct contact with respiratory secretions. Some data suggest that nearly every child will be infected, but immunity is incomplete. Reinfection is common throughout life and is generally mild, although older adults, immunocompromised individuals, and patients with chronic cardiopulmonary disease are at greatest risk of severe disease.[16] In one study, symptomatic human metapneumovirus developed in 1 to 6% of adults annually. During the same period, human metapneumovirus was identified in 8.5% of adults who were hospitalized with pneumonia and 13% of adult pneumonias that required intensive care. Chronic heart and lung disease were present in more than 50% of hospitalized patients.

PATHOBIOLOGY

Human metapneumovirus is difficult to isolate in cell culture. In response to infection, innate immunity via interferons is key to preventing viral replication. In symptomatic individuals, however, human metapneumovirus induces a poor innate immune response, because it interferes with pattern recognition and cell signaling pathways triggered by interferon-associated genes.[17]

CLINICAL MANIFESTATIONS

Infection can range from asymptomatic carriage to fatal disease. Symptoms are similar to RSV and influenza,[18,19] and wheezing is a prominent finding in hospitalized persons. Radiographic abnormalities are present in two thirds of hospitalized cases, with centrilobular nodules, ground-glass opacities, and consolidation most common.[20] In hospitalized adults, bacterial coinfection can be identified in about 25 to 40% of cases.

Human metapneumovirus can be particularly severe in immunocompromised children and adults, especially in hematopoietic cell transplant recipients (Chapter 163). Approximately 50% of stem cell recipients who have upper respiratory symptoms will develop lower tract disease, and prior exposure to antibiotics is associated with higher risk.

DIAGNOSIS

Diagnosis relies on RT-PCR, but discordance between RT-PCR results from upper and lower respiratory samples can make diagnosis difficult.[21]

PROGNOSIS

Most patients recover completely without sequelae. However, 30-day mortality is about 7% among patients who require hospitalization and can be about 40% in hospitalized stem cell transplant recipients.

TREATMENT AND PREVENTION

Care is primarily supportive, and no therapies are currently proven to be effective, even in immunocompromised patients. No vaccines are in clinical trials.

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For the General References and other additional features, please visit Elsevier eBooks+ at https://ebooks.health.elsevier.com.

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331 PARAINFLUENZA VIRAL DISEASE

GEOFFREY A. WEINBERG AND KATHRYN M. EDWARDS

EPIDEMIOLOGY

The human parainfluenza viruses are ubiquitous, with a worldwide geographic distribution.[1,2] Their transmission is principally by large-particle fomites via close person-to-person contact. Parainfluenza virus activity displays both endemic and epidemic patterns, with each serotype preferring different age groups and triggering distinct clinical syndromes but with enough overlap to preclude specific diagnosis based solely on clinical and epidemiologic grounds. In the United States, about 55% of confirmed cases are type 3, about 18% are type 1, about 14% are type 2, and about 13% are type 4.[3]

Primary infection with human parainfluenza virus occurs early in childhood. Of the parainfluenza viruses, type 3 generally infects infants first, such that 50 to 67% of infants demonstrate serologic evidence of infection by 1 year of age. Parainfluenza virus types 1 and 2 most commonly infect children between 2 and 5 years of age. Parainfluenza virus type 4 less commonly causes symptomatic respiratory infections, but it may frequently be found as a viral coinfection with other pathogens.

Until the early 1960s, type 1 human parainfluenza virus caused endemic annual disease in the United States. For the past several decades, however, type 1 human parainfluenza virus has been associated with biennial outbreaks in the fall of odd-numbered years. Infections with type 2 human parainfluenza virus largely follow this same curious pattern but occur much less commonly than type 1 human parainfluenza virus infections. Infections with type 3 human parainfluenza virus have remained endemic throughout the year, with peaks in the late spring. Biennial outbreaks of type 1 human parainfluenza virus also occur in even-numbered years in Australia. During the 2020-2021 severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) pandemic, the typical seasonal circulation patterns of human parainfluenza virus changed, but whether new seasonal patterns will emerge is not yet certain.[4,5] The incubation period for all serotypes of human parainfluenza virus is between 3 and 6 days in experimentally infected adults, but natural infections in children have incubation periods of 2 to 4 days.

The human parainfluenza viruses are second only to respiratory syncytial virus as the cause of acute upper and lower respiratory tract infections in young children in the United States. In a population-based study of children younger than 5 years hospitalized with fever or acute respiratory tract infection, 7% of children had laboratory-confirmed human parainfluenza virus infection (by cell culture and molecular amplification techniques), compared with 19% with respiratory syncytial virus and 6% with influenza A or B virus infections. The hospitalization rate for human parainfluenza virus infection in children younger than 5 years was 1.02 per 1000 children per year. Extrapolating to the entire U.S. population, these data suggest that approximately 23,000 human parainfluenza virus hospitalizations occur annually in children younger than 5 years. The rates of emergency department and outpatient health care visits attributable to human parainfluenza virus infections in young children are 10- to 50-fold greater than hospitalization rates. Further, immunity to human parainfluenza virus infection is neither complete nor durable, so older children and adults can exhibit symptomatic infection, sometimes leading to office visits and hospitalization.

PATHOBIOLOGY

The human parainfluenza virus genome encodes six structural proteins. The hemagglutinin-neuraminidase (HN) and fusion (F) proteins, which are exposed on the bilayered lipid envelope surrounding the helical nucleocapsid–RNA complex, mediate both attachment to host sialic acid–containing glycoproteins and penetration of the virus into susceptible mammalian cells. These proteins have retained their antigenic stability for many years, unlike the "drift and shift" of the hemagglutinin and neuraminidase of influenza viruses. The four serotypes of human parainfluenza virus are called types 1 to 4, including two subgroups (A and B) of type 4 virus.

The human parainfluenza viruses replicate in the ciliated epithelial cells that line the respiratory tract on its luminal surface.[6] This selective tropism is consistent with the absence of invasive disease or viremia in the immunocompetent host, although rare cases of human parainfluenza virus 3 aseptic meningitis have been described. Syncytium formation, which is noted in viral cell cultures and in the lungs of immunocompromised patients with severe pneumonia, is not thought to be important in typical infections of previously healthy individuals.

CLINICAL MANIFESTATIONS

Primary Infection

Illness associated with primary human parainfluenza virus infection varies by age and viral serotype. Underlying medical conditions such as cardiopulmonary compromise and immune disorders increase the severity of disease. Large cohort and longitudinal family studies have shown that human parainfluenza virus infections are responsible for about 65% of croup, 20 to 40% of lower respiratory infection, and 20% of upper respiratory infection in young children. The majority of children have experienced primary human parainfluenza virus infection by the time they enter elementary school. Thus, although human parainfluenza virus also causes upper respiratory infections in adults, these are reinfections rather than primary infections (see later). In general, type 1 and type 2 infections are most commonly associated with croup, whereas type 3 infection often presents as undifferentiated febrile illness, bronchiolitis, or pneumonia.

Infection typically begins with upper respiratory signs and symptoms, notably coryza, rhinorrhea, pharyngitis without cervical adenopathy, and low-grade fever. Symptoms typically persist for 3 to 5 days. About 15 to 25% of infected children develop signs of croup or progress to lower respiratory tract disease (e.g., bronchiolitis, pneumonia) indistinguishable from respiratory syncytial virus infection. Some data suggest that human parainfluenza virus may occasionally involve the myocardium and central nervous system.[7]

Croup is characterized by a raspy barking cough with notable inspiratory stridor, dyspnea, and respiratory distress. These symptoms, which are generally spasmodic, result from subglottic inflammation and edema. On occasion, severe stridor may develop and make differentiation from epiglottitis caused by *Haemophilus influenzae* type b (Chapter 277) difficult, although epiglottitis is much less common in the United States since universal Hib vaccination became routine in 1990.

Croup is very rare in adults but has been associated with human parainfluenza virus in isolated case reports. Epiglottitis is seen more often in adults, but it is more commonly associated with staphylococcal or streptococcal infection. Epiglottitis is a medical emergency for patients of all ages and must be distinguished from croup to allow proper therapy, including emergent intubation of the airway. For patients who are judged to have a stable enough airway to permit urgent radiography rather than emergent tracheostomy, the differences between these two entities are clearly shown in lateral neck radiographs, on which subglottic edema and narrowing are seen with croup, and swelling of the epiglottis is seen with epiglottitis (Figs. 331-1 and 331-2). Children with bronchiolitis or pneumonia caused by human parainfluenza virus have cough, rales, and wheezing associated with hypoxia, and their chest radiographs often exhibit air trapping.

Reinfection

Reinfection with human parainfluenza virus is less severe and typically causes rhinorrhea in normal children and adults. Reinfection with human parainfluenza virus is estimated to account for 1 to 15% of all acute respiratory illnesses in adults, with the majority of infections presenting as simple upper respiratory tract infections. However, as with respiratory syncytial virus, some adults may develop more severe disease that requires hospitalization and even ventilatory support.[8] In such patients, fever, cough, dyspnea, and wheezing are common. Radiographic changes, primarily lobar or interstitial infiltrates, are seen in more than 50% of adults hospitalized with human parainfluenza virus infection.

Elderly and Immunocompromised Patients

Parainfluenza virus infections often cause severe pneumonia in immunocompromised individuals. Nursing home outbreaks of human parainfluenza virus infection with a high incidence of pneumonia have been reported. Among healthy elderly residents of long-term care facilities, human parainfluenza virus infections are as common as infections caused by influenza A virus, influenza B virus, or respiratory syncytial virus. Ten percent of children and 2 to 7% of adults with leukemia or hematopoietic stem cell or solid organ transplant recipients develop human parainfluenza virus infections, with about 90% of those due to type 3 human parainfluenza virus.[9] Although 80 to 90% of human parainfluenza virus infections in patients with malignancy are community acquired, nosocomial outbreaks have occurred in stem cell transplant units.

ABSTRACT

Human parainfluenza viruses are important causes of a wide spectrum of respiratory illnesses, including the common cold, otitis media, croup, bronchiolitis, and pneumonia. Four viral serotypes exist, called type 1 through type 4 human parainfluenza virus. In young children, infection often occurs in the first year of life; later, all four types of human parainfluenza virus may cause initial and repeated respiratory infections, most commonly in children in years 2 to 5 but also throughout adulthood. Infection of young children with type 3 human parainfluenza virus tends to present as undifferentiated febrile illness, bronchiolitis, or pneumonia. Infections with type 1 and type 2 human parainfluenza viruses tend to present as croup—an illness characterized by a croupy, barking cough; inspiratory stridor; and respiratory distress. Reinfections are generally less severe and typically present as a common cold with rhinorrhea. However, infections with human parainfluenza virus may be severe among immunocompromised hosts, such as patients with a malignancy or after organ or stem cell transplantation. Diagnosis of human parainfluenza virus infection is best made by reverse transcription–polymerase chain reaction of respiratory tract secretions. Therapy of childhood croup is with oral dexamethasone, given as a one-time dose to reduce the need for hospitalization and intubation. Specific antiviral medications and preventive vaccines for human parainfluenza virus infection are under investigation. Less specific, supportive measures such as aerosolized ribavirin and intravenous immunoglobulin infusion may be considered for severe human parainfluenza virus infection in immunocompromised patients.

KEYWORDS

parainfluenza
virus croup
viral pneumonia

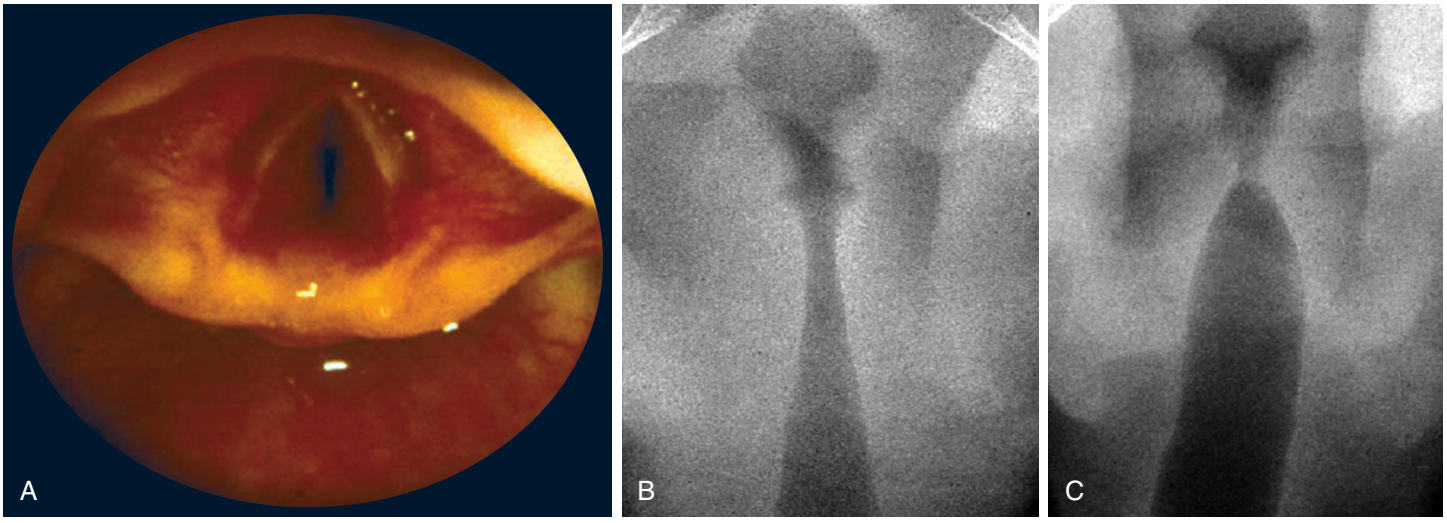

FIGURE 331-1. Subglottic edema. A, Endoscopic view of subglottic edema in viral croup. **B**, Radiologic presentation of subglottic edema in viral croup, causing narrowing ("steeple sign") of the tracheal air shadow, compared with (**C**) a normal tracheal air shadow. (From Hammer J. Acquired upper airway obstruction. *Paediatr Respir Rev*. 2004;5:25-33.)

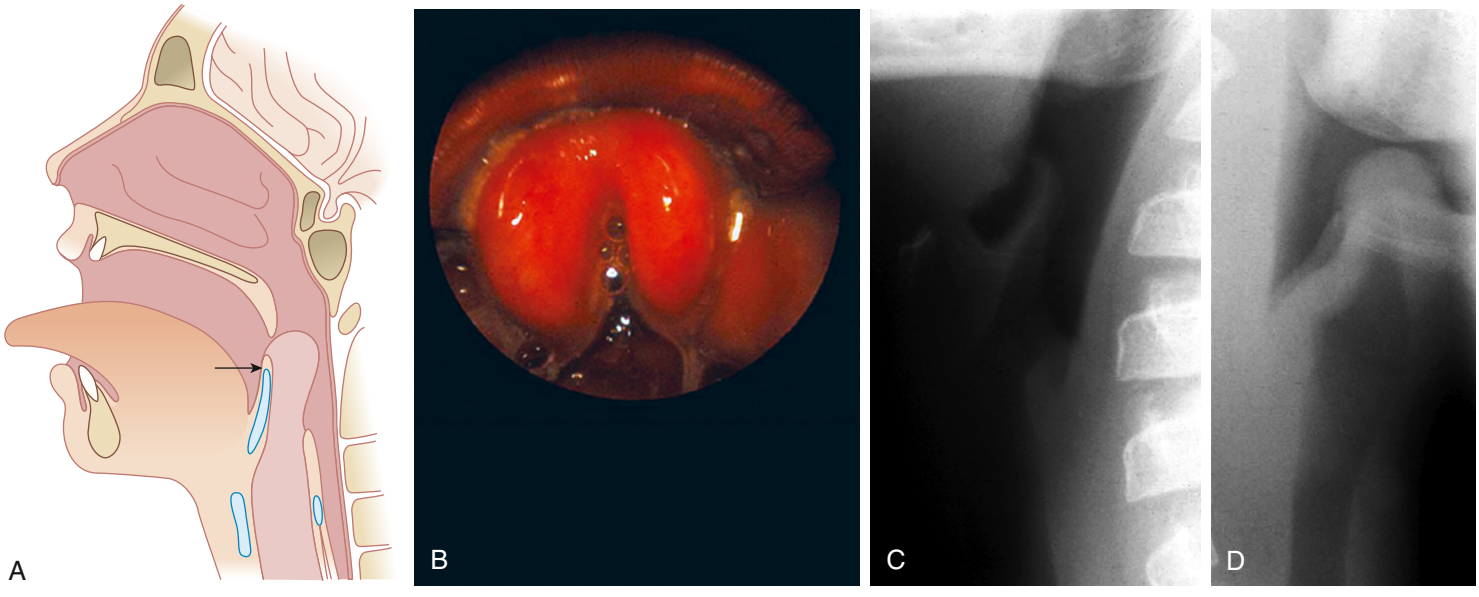

FIGURE 331-2. Epiglottitis. Schematic (**A**) and endoscopic view (**B**) of epiglottitis. **C**, The typical lateral neck radiographs of a normal child and (**D**) a child with epiglottitis ("thumb sign" of swollen epiglottis) are displayed. (From Hammer J. Acquired upper airway obstruction. *Paediatr Respir Rev*. 2004;5:25-33.)

Approximately 25% of human parainfluenza virus–infected stem cell transplant recipients develop lower respiratory disease, mostly in the first 100 days after transplantation, when lymphopenia and neutropenia are most pronounced. The strongest identified risk factors for human parainfluenza virus infection in these individuals are neutropenia, lymphopenia, more severe disease, and the use of corticosteroids, especially at higher doses.[10] Fever, cough, dyspnea, and sputum production are the most common symptoms. Coinfections with *Aspergillus* (Chapter 311) and other pathogens have been reported in hematopoietic stem cell transplant recipients with pneumonia as well.

DIAGNOSIS

Although human parainfluenza virus may be suspected on clinical and epidemiologic grounds, specific diagnosis requires isolation of the virus or detection of viral antigen or RNA in respiratory secretions. Reverse transcription–polymerase chain reaction (RT-PCR) assays are highly sensitive and specific for diagnosis. Alternatively, cultures of monkey kidney or human embryonic kidney cells can be used to grow the virus, with cytopathic effects detected in 5 to 10 days (except for type 4 human parainfluenza virus, which requires up to 3 weeks). Rapid direct or indirect immunofluorescence tests are less sensitive and specific than culture or PCR but still are used in some clinical laboratories.

Definitive diagnosis of parainfluenza infection in adults, even by RT-PCR, may be more difficult than in children, presumably because less virus is shed in partially immune adults. However, virus can usually be recovered from the nasopharyngeal secretions or bronchoalveolar lavage fluid in hematopoietic stem cell transplant recipients with pneumonia.

TREATMENT

Specific antiviral treatment of human parainfluenza virus infection is currently unavailable. Aerosolized ribavirin has in vitro activity against human parainfluenza virus and is approved for use in respiratory syncytial virus infection. Although it has shown few benefits in immunocompromised children and adults with severe human parainfluenza virus pneumonia, even when administered with concomitant intravenous immunoglobulin, some experts will offer aerosolized or intravenous ribavirin, with or without intravenous immunoglobulin, to immunocompromised patients with severe disease.[11]

For previously healthy children with croup, general comfort, which usually means sitting in the lap of a parent or caregiver, is widely recommended. Humidified air (mist) repeatedly has been shown to have no benefits and actually is associated with adverse effects, including anxiety, difficulty with cardiorespiratory monitoring, and bacterial and fungal contamination of both hot and cold mist humidifiers. Oxygen may be given by holding the end of the tubing near the nose and mouth ("blow-by" oxygen).

Children with mild to moderate croup (i.e., without stridor or significant chest wall indrawing at rest or with stridor and indrawing but without agitation) may

be given oral dexamethasone, 0.6 mg/kg body weight, and observed; if they improve, they may be discharged to home.[A1] Children with severe croup (stridor, chest wall indrawing, and agitation) may benefit from blow-by oxygen, inhaled racemic epinephrine (0.05 mL/kg body weight of a 2.25% solution of racemic epinephrine for nebulization, up to a maximum dose of 0.5 mL) or nebulized L-epinephrine (0.5 mL/kg of 1: 1000 L-epinephrine, up to a maximum dose of 5 mL) and concomitant dexamethasone. Children should be admitted to the hospital if no significant clinical improvement is seen after several hours of observation and therapy.

Oral dexamethasone is as effective as intramuscular dexamethasone or nebulized budesonide and easier to administer. Corticosteroids decrease the need for hospitalization and return visits, decrease length of stay both in emergency departments and after hospital admission, and decrease the need for intubation. In general, there are no reasons to institute either antibiotic therapy or short-acting bronchodilator therapy in children with croup.

Investigational therapies for human parainfluenza virus infection include both nonspecific and specific measures. Inhalation of heliox (helium-oxygen mixture) may decrease the work of breathing and improve gas exchange in children with moderate to severe croup, but adequately controlled clinical trial data are not yet available.[A2] The novel antiviral agent DAS181, a sialidase fusion protein with activity against both influenza and parainfluenza viruses, has shown beneficial effects in a small number of adults and children with severe human parainfluenza virus infection and is undergoing further clinical trials.[12]

PREVENTION

Clinical trials of live attenuated human parainfluenza virus vaccines are ongoing.[13] Two approaches have been taken to produce live-attenuated intranasal vaccines to type 3 human parainfluenza virus. One approach has been to attenuate a viral isolate by repeated cold-temperature passage and manipulation by recombinant technology. A second has been to use a related but nonvirulent bovine parainfluenza virus as a backbone in which to insert type 3 human parainfluenza virus genes to produce an attenuated chimeric vaccine virus. Another vaccine candidate under study uses the chimeric bovine-human type 3 parainfluenza virus but with an additional respiratory syncytial virus gene inserted into the vaccine virus genome in an attempt to prevent both of these common infections in young children. Vaccines against type 1 human parainfluenza virus infection (with or without respiratory syncytial virus components) also are under development.

PROGNOSIS

In otherwise healthy children, mortality after human parainfluenza virus infection is less than 0.1%. By comparison, mortality after human parainfluenza virus pneumonia in patients undergoing stem cell transplantation is as high as 10 to 30%.

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332 INFLUENZA

MICHAEL G. ISON AND NELSON LEE

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Influenza is an acute febrile respiratory viral illness that usually occurs in annual outbreaks of varying severity and occasionally causes worldwide epidemics (pandemics). Increasingly, sporadic zoonotic infections, sometimes associated with limited human-to-human transmission, are being reported.

Influenza viruses infect the respiratory tract, are highly contagious, and classically produce prominent systemic symptoms early in the illness. Influenza infection causes various clinical syndromes in adults, including nonfebrile common colds (Chapter 329), pharyngitis (Chapters 269 and 397), tracheobronchitis (Chapter 84), pneumonia (Chapter 85), and a range of nonrespiratory complications. Conversely, infections with other respiratory viruses, such as respiratory syncytial virus (RSV [Chapter 330]) or adenovirus (Chapter 333), may produce influenza-like illness. Influenza A viruses have caused five pandemics of varying severity within the past 120 years (E-Table 332-1). The 1918–1919 pandemic caused at least 500,000 deaths in the United States and more than 40 million worldwide,[1] whereas the 2009 H1N1 pandemic was associated with substantially less mortality. Seasonal epidemics can cause enormous morbidity, economic loss, and often substantial mortality. Each year in the United States, seasonal influenza epidemics are associated with an estimated 4.3 to 16.7 million medical visits, 140,000 to 710,000 hospitalizations, and 12,000 to 56,000 respiratory and circulatory deaths. During the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) pandemic (Chapter 336), masking and social isolation led to a decline in diagnosed cases of influenza.[2]

The Pathogen

Influenza viruses belong to the family Orthomyxoviridae and are divided into four types (A, B, C, and D) based on their protein composition and other properties (E-Table 332-2). The virion (E-Fig. 332-1) is a medium-sized enveloped pleomorphic particle covered with two types of surface glycoprotein spikes: the trimeric hemagglutinin (H or HA) and the tetrameric mushroom-shaped neuraminidase (N or NA). The envelope is composed of a lipid bilayer overlying the matrix (M1) protein that surrounds the viral genome, which consists of eight segments of single-stranded negative-sense RNA in influenza A and B viruses. Influenza C viruses have seven segments and only a single surface glycoprotein. Genomic replication occurs in the nucleus of infected cells, and multiple cellular proteins and pathways are involved during the infection of host cells.

Whereas influenza B and C viruses are principally human pathogens, influenza A viruses primarily infect aquatic birds and sometimes establish lineages that circulate in other animal hosts, including other avians, swine, horses, marine mammals, and dogs. Influenza D appears to be pathogenic in cattle and perhaps other domestic animals. Influenza A viruses are further classified into subtypes on the basis of their HA and NA glycoproteins. Sixteen HA and nine NA subtypes are currently recognized in avians, and two others are recognized in bats. Only three HAs (H1, H2, and H3) and two NAs (N1 and N2) have been documented thus far in epidemic and pandemic human influenza A viruses, although other HAs (e.g., H5, H6, H7, H9, H10) and NAs (e.g., N4, N7, N8, N9) have been found in zoonotic infections. Each strain is identified by type, subtype if influenza A, location of isolate, sample number, and year of isolation (e.g., A/California/04/2009 (H1N1)).

EPIDEMIOLOGY

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Influenza viruses are unique among the respiratory viruses with regard to their extent of genetic and antigenic variation, epidemic behavior, and frequent association with excess mortality during community outbreaks—characteristics and pathogenicity that exemplify human influenza virus's efficient host-to-host transmissibility. The changing antigenicity of the surface glycoproteins largely accounts for repeated influenza epidemics. Antibody to HA can neutralize viral infectivity and is thus the major determinant of immunity. Current vaccines are based largely on inducing hemagglutination-inhibition (HAI) or neutralizing antibodies to HA. Anti-NA antibody limits viral replication and probably reduces the severity of infection. Variation involves either relatively minor (antigenic drift) or major (antigenic shift) changes in antigenicity. Significant antigenic variation is much less frequent with influenza B or C than with influenza A.

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ABSTRACT

Influenza is an acute febrile respiratory viral illness that usually occurs in annual outbreaks of varying severity and that occasionally causes worldwide epidemics (pandemics). Increasingly, sporadic zoonotic infections, sometimes associated with limited human-to-human transmission, are being documented. Among influenza A viruses, antigenic drift and antigenic shift contribute to the annual risk of epidemics and global pandemics. Prevention is best achieved through annual vaccination. Current treatment is focused on the early use of neuraminidase inhibitors or baloxavir marboxil to reduce complications and speed recovery.

KEYWORDS

influenza
neuraminidase inhibitor
oseltamivir
zanamivir
peramivir
baloxavir
vaccine

E-TABLE 332-1 ANTIGENIC SUBTYPES OF INFLUENZA A VIRUS ASSOCIATED WITH PANDEMIC AND PANDEMIC-LIKE INFLUENZA

YEAR ONSET	INTERVAL (YR)	SUBTYPE DESIGNATION	EXTENT OF ANTIGENIC CHANGE IN INDICATED SURFACE PROTEIN†	SEVERITY OF PANDEMIC (MORTALITY)*
1889	42-59	H3N?	H+++N?	Severe
1918	29	H1N1‡	H+++N+++	Very severe
1957	39	H2N2	H+++N+++	Severe
1968	11	H3N2	H+++N–	Moderate§
1977	9	H1N1	H+++N+++	Negligible‖
2009	32	H1N1	H++N++	Mild-moderate‖

*Severity is defined as the global impact on mortality.
†Compared with antecedent or cocirculating virus.
‡Formerly designated H0N1 (swine virus prototype) or Hsw1N1.
§The population had some immunity to N2 neuraminidase.
‖The older population was largely immune because of previous infection with earlier circulating, antigenically identical (1977) or related (2009) viruses; those born after 1957 were primarily affected. The impact of the 2009 pandemic virus, based on estimated years of life lost, was comparable to that observed in the 1968 pandemic in the United States.
+ = Minor change; ++ = moderate change; +++ = major change; – = no change.

E-TABLE 332-2 INFLUENZA A VIRUS PROTEINS

DESIGNATION	LOCATION (APPROXIMATE SIZE)	FUNCTION	OTHER
Hemagglutinin (HA)	Surface, transmembrane (566 aa)	Cell attachment via sialic acid–bearing receptors and penetration; fusion of host cell and viral membranes	Type-, subtype-, and strain-specific antigens; key antigen in inactivated vaccines
Neuraminidase (NA)	Surface, transmembrane (454 aa)	Virus release and spread; enzymatic activity causes removal of sialic acid residues from receptors	Type-, subtype-, and strain-specific antigens; activity linked to risk for pneumonia; site of action of neuraminidase inhibitors
M1 or matrix	Internal (252 aa)	Major structural envelope protein; virus assembly	Type-specific antigen; conserved T-cell epitopes
M2	Surface, transmembrane (97 aa)	Ion channel; virus uncoating and budding	Influenza A only; site of action of amantadine/rimantadine; ectodomain as possible vaccine candidate
Nucleoprotein (NP)	Internal (498 aa)	Major ribonucleoprotein complex component; associated with RNA and polymerase proteins	Type-specific antigen; conserved T-cell epitopes
Polymerase proteins (PB1, PB2, PA)	Internal (PB1-757 aa, PB2-759 aa, PA-716 aa)	Viral RNA replication and mRNA transcription (RNA-dependent RNA polymerase, cap-binding, endonuclease)	Determinant of replication efficiency; specific PB2 mutations associated with mammalian adaptation; site of action of polymerase inhibitors
NS1	Nonstructural (230 aa)	Multifunctional; regulation of viral RNA and protein synthesis; host protein interactions	Interferon antagonist; inhibition of innate immune signaling
NEP (NS2)	Internal (121 aa)	Nuclear export factor	From splicing of NS1 mRNA
PB1-F2	Nonstructural (87 aa)	Pro-apoptotic factor; pro-inflammatory effects; interferon antagonist	Expressed from 1+ reading frame of PB1 of certain viruses
PA-X	Nonstructural (41-61 aa)	Endonuclease activity; inhibition of host protein synthesis	Modulation of the host response to infection; expressed by 1+ ribosomal frame-shifting

NOTE: Influenza B also has eight gene segments, one of which encodes both NA and NB proteins, the latter a membrane protein of uncertain function, and another encoding the M1 (matrix) and BM2 proteins, the latter functioning as an ion channel but not inhibited by adamantanes. Nonstructural proteins are present only in infected cells. Other small nonstructural proteins (PB1-N40) have been described in influenza A and are under study.
mRNA = messenger RNA.
Modified from Krug RA, Fodor E. Chapter 4, The virus genome and its replication. In: Webster RG, Monto AS, Braciale TJ, Lamb RA, eds. *Textbook of Influenza*. 2nd ed. Oxford: John Wiley and Sons; 2013:57-66.

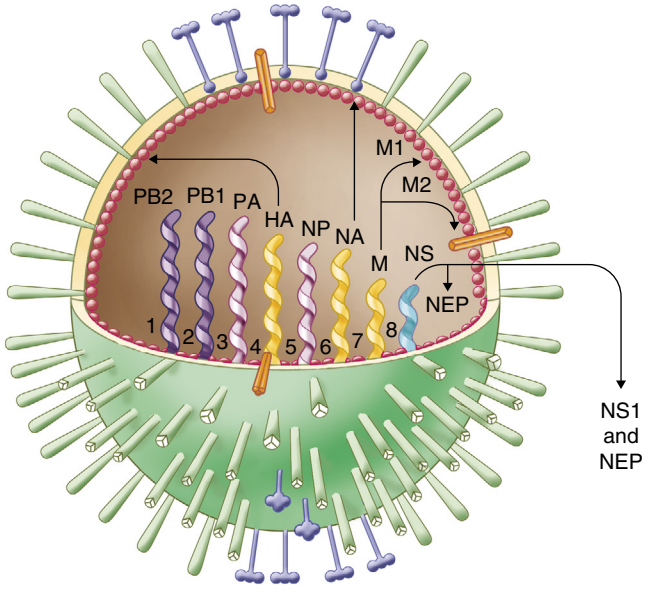

E-FIGURE 332-1. Diagram of influenza virus structure. Eight segments of viral RNA are contained within the lipid envelope and matrix (M1) shell. Each segment codes for one or more proteins that form the virus or regulate its intracellular replication. The presumed functions of each are listed in E-Table 332-2. HA = hemagglutinin; NA = neuraminidase; NEP = nuclear export protein; NP = nuclear protein; PA, PB1, PB2 = polymerase proteins. (Courtesy Dr. Robert G. Webster.)

Antigenic shift results from the appearance of a novel influenza A virus with HA, NA, or both HA and NA glycoproteins that are new to humans or that reappear after decades of absence. Because of the lack of population immunity, a new strain that is efficiently transmitted from person to person can cause pandemic disease. The origins of new pandemic strains and the basis for their subsequent seasonal circulation remain incompletely understood. Avian influenza viruses have most frequently served as the reservoir of new genes for pandemic viruses. Reassortment of gene segments may occur when two influenza viruses simultaneously infect a single cell and in reassortment events in which human viruses acquired avian genes led to both the 1957 and 1968 pandemic viruses. Because swine can support replication of both human and avian viruses, they have been postulated to serve as a mixing vessel for the generation of new strains or as the host in which avian viruses can adapt to mammals. The 2009 H1N1 pandemic virus arose as a quadruple reassortant that derived gene segments from Asian and North American swine lineage viruses that harbored genes derived from swine, avian, and human viruses.

Multiple reassortment events may occur over a period of years before a pandemic virus emerges. For example, the 1918 pandemic virus appears to have been composed primarily of avian genes that underwent adaptation in a mammalian host before causing the pandemic. Frequent intra-subtypic reassortment also occurs among seasonal human influenza A viruses and sometimes leads to new antigenic variants and sometimes to altered virulence.

Epidemic or Interpandemic Influenza

An epidemic is an outbreak of influenza confined to one geographic location. In temperate climates, community epidemics of influenza A virus infection often have a characteristic pattern, typically reaching a sharp peak in 2 or 3 weeks after initial recognition and persisting for 6 to 10 weeks. Increased numbers of schoolchildren with febrile respiratory illness are often the first indication of influenza in a community, soon followed by illnesses in adults and, 1 to 2 weeks later, by increased hospital admission of patients with influenza-related complications. Hospitalization rates in high-risk persons increase two- to five-fold during major epidemics. School and employment absenteeism increases, as does mortality from pneumonia and underlying conditions, especially in older adults during A/H3N2 epidemics. Epidemics occur almost exclusively during the late autumn and winter months in temperate areas, but activity may extend into spring months. Because of the seasonal differences between northern and southern hemispheres, seasons cycle between the hemispheres. Influenza activity may occur year-round in the tropics or display other patterns. The reasons for the distinct seasonality of influenza in temperate climates are uncertain but may include the school calendar, increased close indoor contact, and low absolute humidity, which affects airborne transmissibility. Winter holidays delay the peaks of seasonal epidemics and shift the risk of infection toward adults. Outbreaks sometimes occur in tour groups (land or ship) and in chronic care facilities during summer months, particularly after the appearance of a drift variant. Regional differences in the timing, magnitude, and causative viruses of influenza outbreaks are common. During epidemics, overall attack rates typically range from 5 to 20% in adults. Attack rates of 40 to 50% may occur in semiclosed populations, such as on hospital floors and chronic care facilities, as well as in highly susceptible age groups such as children. Influenza A and B viruses, two different influenza A subtypes, two different influenza B lineages, or two different strains within a single subtype may co-circulate or occur sequentially during one season in a given location. In addition, simultaneous outbreaks of influenza A virus and RSV or other respiratory viruses occur. Strains circulating at the end of one season's epidemic are sometimes responsible for the next season's outbreak (the so-called herald wave phenomenon).

Pneumonia- and influenza-related deaths fluctuate annually, with peaks in the winter months in temperate climates. When such deaths exceed the expected threshold, the cause is typically influenza A, but influenza B virus or RSV can occasionally be responsible. Influenza A/H3N2-dominant seasons are associated with two to three times higher mortality rates than are nonpandemic H1N1- and B-dominant seasons. Although mortality is usually greatest during pandemics, substantial mortality occurs with epidemics. During seasonal influenza, more than 85% of pneumonia- and influenza-related deaths occur in persons aged 65 years and older. Mortality risk is especially high in those aged 85 years and older. Cardiovascular events (e.g., myocardial infarction) and worsening of other chronic diseases (e.g., asthma, chronic obstructive pulmonary disease) contribute substantially to the increased mortality during influenza epidemics.

Pandemic Influenza

Pandemics of influenza A result from the emergence of a new virus capable of sustained person-to-person transmission and to which the population contains no or limited immunity. The virus spreads worldwide, often circulating outside of the usual influenza season, and usually infects persons of all ages. Preexisting immunity due to prior infection with antigenically related viruses can provide partial protection, as occurred in older adults during the 2009 H1N1 pandemic. Pandemics are associated with high morbidity rates, especially in children, and sometimes notably increased mortality rates in pregnant women and young and middle-aged adults. For example, more than 90% of deaths in the 1918 and 2009 pandemics occurred in persons younger than 65 years. In the 2009 pandemic, adults hospitalized with H1N1 were more likely to have severe pneumonia, shock, sepsis, and organ failure and to require intensive care unit (ICU) care than were patients with seasonal influenza.

The interval between pandemics is variable (10 to 40 years) and unpredictable. The most severe pandemics have been associated with major antigenic alterations in both major surface glycoproteins. Depending on population susceptibility and perhaps changes in the virus, one or more waves, sometimes with increased severity, may follow the initial one. As the level of immunity in the population increases, antigenic drift within the subtype may cause repeated epidemics in subsequent years, and excess mortality in persons younger than age 65 may continue for some years. For example, the pandemic 2009 H1N1 virus has continued to cause fatal infections at least 10 years after its initial emergence.

Zoonotic Influenza

Zoonotic infections may be acquired from swine, poultry, or rarely other animals. Although most avian influenza viruses do not cause infections directly in humans, zoonotic infections due to avian H5, H7, H9, and rarely other subtypes continue to cause outbreaks in regions where human and poultry live in close proximity (e.g., chicken farming, wet markets), thereby representing potential pandemic threats. Initially recognized by a cluster of human cases in Hong Kong in 1997, an epizootic of avian H5N1 infections has affected poultry in many areas of Asia, the Middle East, Europe, and Africa and continues to cause sporadic human illnesses with high mortality and occasional instances of nonsustained human-to-human transmission. From 2013 to 2017, repeated waves of zoonotic avian H7N9 infections have occurred during winter and early spring in China, with case-fatality rates of approximately 35% among hospitalized patients. This virus continues to evolve genetically, thereby leading to variants with altered antigenicity and increased virulence for birds and possibly humans.

In the United States infrequent zoonotic infections have been recognized for decades in people exposed to swine. Since 2012, reassortant swine H3N2 viruses that acquired the M gene and sometimes other genes from the pandemic 2009 H1N1 virus (designated variant H3N2, or H3N2v) have caused hundreds of sporadic infections, particularly in the context of agricultural fairs, sometimes followed by limited human-to-human transmission and serious infections. Other variant swine-origin viruses (H1N1v, H1N2v) have also caused zoonotic infections.

PATHOBIOLOGY

Influenza virus infection is transmitted from person to person by virus-containing respiratory secretions. Large-droplet and small-particle aerosols traveling over a short range (generally within 2 meters) appear to be the predominant route of transmission; longer-range airborne transmission may also occur rarely under unique conditions (e.g., aerosol-generating medical procedures). Other routes, including hand contamination from secretion-laden fomites followed by self-inoculation into the eye or nose, may also contribute. Infection by avian viruses can occur after direct contact with infected birds or their excreta, exposure to contaminated environments and infectious aerosols, ingestion of inadequately cooked food, and sometimes by inoculation into the conjunctiva.

The cellular receptor binding patterns and tissue tropism of influenza viruses are key determinants in transmissibility and pathogenesis. Efficient virus transmission between humans depends largely on virus attachment to and replication in cells bearing α-2,6-linked sialosaccharides in the upper respiratory tract and tracheobronchial tree. By comparison, the α-2,3-linked sialosaccharides, which are higher-affinity binding receptors for avian viruses, are distributed mostly in the distal bronchioles, alveoli, and conjunctiva. Once the virus initiates infection of the respiratory tract epithelium, successive cycles of viral replication infect large numbers of cells and result in destruction of respiratory epithelium and sometimes pneumocytes through direct cytopathic effects or apoptosis.

The incubation period averages 2 days and varies from about 1 to 4 days for seasonal influenza but may be up to 1 week and possibly longer in infections caused by avian viruses. The quantity and duration of virus replication in the respiratory tract generally correlate with the severity of illness and levels of host pro-inflammatory cytokine-chemokine responses. Rapid innate cellular responses are induced through toll-like receptors and retinoic acid inducible

gene I (*RIG-1*) that detect viral RNA and lead to the production of cytokines and interferons (IFNs). Elevated levels of mediators (e.g., IFN-α, interleukin [IL]-6, IL-8, monocyte chemoattractant protein-1 [MCP-1], macrophage inflammatory protein [MIP]–1β, and tumor necrosis factor [TNF]–α), which are frequently detected in blood and respiratory secretions, contribute to systemic symptoms, including fever, and tissue injury.[3] Deficient IFN responses have been associated with severe influenza disease.

The duration of viral replication depends on age, immune status, underlying conditions, and the viral strain. In seasonal influenza, viral RNA generally can be detected in the upper respiratory tract for 3 to 5 days in adults but for longer (7 to 10 days) in the elderly and hospitalized patients, and viral RNA may persist for weeks to months in immunocompromised hosts. By comparison, viral detection by culture, which may better reflect infectivity, is shorter. Patients who suffer from influenza pneumonia appear to have higher viral levels and more prolonged viral replication in their lower respiratory tracts. Viremia or extrapulmonary dissemination (e.g., CNS, GI) may occur in serious avian or pandemic virus infections. Detection of viral RNA in the blood is associated with a poorer prognosis in immunocompromised patients.

Nasal and bronchial biopsy specimens from persons with uncomplicated influenza reveal desquamation of the ciliated columnar epithelium and loss of cilia. The lungs in fatal influenza may show necrotizing bronchitis, diffuse alveolar damage with epithelial necrosis, alveolar edema and hemorrhage, and hyaline membrane formation, followed later by squamous metaplasia and fibrosis. Secondary bacterial infections (e.g., *Staphylococcus aureus, Streptococcus pneumoniae* [Chapter 268], *Streptococcus pyogenes* [Chapter 269]) develop as a result of altered bacterial flora, damage to bronchial epithelium with depressed mucociliary clearance, decreased polymorphonuclear and alveolar macrophage functions, accumulation of alveolar fluid, and suppression of other host immune responses.

Adaptive humoral and cell-mediated responses are important for immunity to influenza. Humoral immunity to natural influenza virus infections appears to be strain specific and largely subtype dependent. A child's first influenza A infection results in immune memory for that viral strain and its related HA subtypes within the same group ("immune imprinting"); subsequent infections or immunizations reinforce the antibody responses, which could contribute to protection against related subtypes (e.g., initial H3N2 infection reducing the risk of H7N9 illness, which is also a group 2 virus). Vaccine-induced immunity is highly strain-specific and typically short-lived (about 6 months), thereby explaining the need for annual update and administration. Protective immunity is mediated by neutralizing antibodies; the generally accepted correlates are serum-neutralizing antibody titers of 1:8 or greater, nasal-neutralizing antibody titers of 1:4 or greater, or an associated increase in the serum HAI titers of 1:40 or greater. However, considerable variability can be seen with the viral strain, in part based on the patient's age,[4] and immune status.[5] Type-specific cell-mediated immunity, which involves CD4+ and CD8+ T-lymphocytic responses, is important for the termination of viral replication and limitation of the infection. Increasing evidence suggests that human genetic factors, such as polymorphism of genes that regulate immune responses, play a role in determining the severity of influenza infection, especially in the immunologically naïve hosts. Examples include polymorphisms in the IFN-induced transmembrane 3 (*IFITM3*) protein, TMPRSS2 protease, CD55 and C1QBP complement-pathway, and SFTPA2 surfactant protein genes.

CLINICAL MANIFESTATIONS

Influenza Syndrome

An abrupt onset of feverishness, chilliness, rigors, headache, myalgia, and malaise is characteristic of influenza but occurs in less than two thirds of cases. Systemic symptoms predominate initially, and prostration occurs in more severe cases. Myalgia, arthralgia, malaise, and headache are usually the most troublesome early symptoms, and their severity is generally related to the level of fever.[6] Ocular symptoms, including photophobia, tearing, burning, and pain on moving the eyes, are sometimes present. Conjunctivitis is characteristic in some avian H7 virus infections, although not in recent zoonotic H7N9 cases. Respiratory symptoms, particularly dry cough and nasal discharge, are typical early in the illness but are overshadowed by the systemic symptoms. Nasal obstruction, hoarseness, and sore throat are likewise common. Pandemic 2009 H1N1 and avian influenza illness are associated with nausea, vomiting, and diarrhea in some adults. As systemic illness diminishes, respiratory complaints and findings become more apparent. Cough, which is the most frequent and troublesome symptom, may be accompanied by substernal discomfort or burning. Cough, lassitude, and malaise may persist for several weeks before full recovery.

Fever, a classic symptom of influenza, usually rises rapidly to a peak of 38° to 40° C within 12 hours of onset, concurrently with systemic symptoms. Fever in adults typically persists for about 3 days, but it may persist for only 1 day or for 5 or more days. Small, tender cervical lymph nodes are often present. Transient scattered rhonchi or localized areas of rales are found in less than 20% of cases.

Symptoms are more frequent and severe in smokers. Among elderly and immunosuppressed patients, particularly recipients of stem cell and solid organ transplants, fever and clinical symptoms initially may be minimal to absent. Despite the paucity of presenting symptoms, however, such patients may progress to severe lower respiratory tract disease. Older adults may less frequently have fever but more commonly have altered mental status and pulmonary complications. In zoonotic infections due to avian H5N1 or H7N9 viruses, upper respiratory complaints are less frequent, gastrointestinal complaints are more common, and progressive viral pneumonia with high mortality is much more likely. Influenza C virus generally causes sporadic upper respiratory tract illness or febrile bronchitis.

Persons at higher risk for influenza-associated complications and hospitalization (Table 332-1) include pregnant women (especially during the second and third trimesters or early postpartum period), morbidly obese patients, immunosuppressed persons, and patients with various comorbid diseases. Most adults hospitalized with seasonal influenza have exacerbations of any underlying cardiopulmonary (e.g., myocardial ischemia, heart failure, chronic obstructive pulmonary disease) or metabolic (e.g., diabetes) conditions, and about one third have pneumonia.

Respiratory Complications

Three pneumonic syndromes have been described—primary influenza viral pneumonia, secondary bacterial pneumonia, and mixed viral and bacterial pneumonia (Chapter 85)—but their clinical presentations and courses overlap considerably. Other common respiratory tract complications include exacerbations of chronic bronchitis, asthma, or cystic fibrosis; croup and bronchiolitis in young children; and otitis media and sinusitis. Bacterial tracheitis can occur, but otherwise uncomplicated influenza tracheobronchitis and airway hyperactivity can persist for weeks.

Severe primary influenza viral pneumonia and associated acute respiratory distress syndrome (ARDS [Chapter 90]) are uncommon during seasonal epidemics but account for 20 to 50% of pneumonias in hospitalized patients during pandemics. ARDS has been the principal manifestation of severe pandemic 2009 H1N1 or avian H5N1 and H7N9 infections. Severe viral pneumonia occurs predominantly in persons with underlying pulmonary and cardiac disorders, pregnancy, or immunodeficiency states,[7] although up to 25 to 40% of pandemic H1N1 and most H5N1 cases have no recognized underlying condition. After a typical onset of influenza, patients develop progressive cough, dyspnea, sometimes hemoptysis, and even cyanosis within 3 to 7 days. Bilateral pulmonary infiltrates and hypoxemia may evolve rapidly.

In patients with classic bacterial superinfection, clinical improvement for 1 to 4 days may be followed by recrudescence of fever, increased cough, sputum production, pleuritic chest pain, and a localized area of consolidation. Secondary pneumonias caused by a range of nosocomial bacterial pathogens are common in patients who are hospitalized with influenza, particularly patients who require mechanical ventilation. Staphylococcal infections may be particularly virulent and cause necrotizing pulmonary lesions. Use of high-dose corticosteroids appears to be a risk factor for bacterial suprainfection, invasive aspergillosis (Chapter 311), and increased mortality.

Nonrespiratory Complications

Severe influenza, including both pandemic 2009 H1N1 and avian H5N1 or H7N9 disease, may be associated with sepsis syndrome (Chapter 94), acute renal insufficiency (Chapter 106), and multiorgan failure. Lymphopenia and thrombocytopenia are common in severe influenza; hemophagocytic syndrome and disseminated intravascular coagulation (Chapter 161) can occur. Myositis with tender leg muscles and elevated serum creatine kinase levels is uncommon in adults, but rarely rhabdomyolysis (Chapter 99) can be severe and cause myoglobinuria. Pregnant women have increased risk of premature labor and spontaneous abortion. Toxic shock syndrome (Chapter 267) caused by respiratory tract infection with toxin-bearing *Staphylococcus aureus* or *Streptococcus pyogenes* can occur, and outbreaks of meningococcal infection (Chapter 274) have been associated with both influenza A and B virus infections. Myocarditis (Chapter 47) or pericarditis (Chapter 62) occurs uncommonly but can be severe.[8] Neurologic complications include aseptic meningitis (Chapter 381), myelitis (Chapter 380), encephalopathy (Chapter 383), necrotizing encephalitis, postinfluenzal Guillain-Barré syndrome (Chapter 388), or immune-mediated encephalitis or cerebellitis. Reye syndrome (Chapter 136), which is a well-recognized hepatic and central

TABLE 332-1 USE OF INFLUENZA VACCINE IN SPECIAL POPULATIONS AND SITUATIONS

When vaccine supply is limited, vaccination efforts should focus on delivering vaccination to persons at higher risk for influenza-related complications listed below as well as these persons:

POPULATIONS AT HIGHER RISK FOR MEDICAL COMPLICATIONS ATTRIBUTABLE TO SEVERE INFLUENZA

- All children aged 6 through 59 months;
- All persons aged ≥50 years;
- Adults and children who have chronic pulmonary (including asthma) or cardiovascular (except isolated hypertension), renal, hepatic, neurologic, hematologic, or metabolic disorders (including diabetes mellitus);
- Persons who are immunocompromised owing to any cause (including immunosuppression caused by medications or by HIV infection);
- Women who are or will be pregnant during the influenza season;
- Children and adolescents (aged 6 months through 18 years) who are receiving aspirin- or salicylate-containing medications and who might be at risk for experiencing Reye syndrome after influenza virus infection;
- Residents of nursing homes and other long-term care facilities;
- American Indians/Alaska Natives; and
- Persons who are extremely obese (BMI ≥40).

PERSONS WHO LIVE WITH OR CARE FOR PERSONS AT HIGHER RISK FOR INFLUENZA-RELATED COMPLICATIONS

- Health care personnel, including physicians, nurses, and other workers in inpatient and outpatient care settings, medical emergency-response workers (e.g., paramedics and emergency medical technicians), and employees of nursing home and long-term care facilities who have contact with patients or residents, and students in these professions who will have contact with patients;
- Household contacts (including children) and caregivers of children aged ≤59 months (i.e., aged <5 years) and adults aged ≥50 years, particularly contacts of children aged <6 months; and
- Household contacts (including children) and caregivers of persons with medical conditions that put them at high risk for severe complications from influenza.

IMMUNOCOMPROMISED PERSONS

- LAIV should be avoided in immunocompromised patients.
- Studies suggest improved immunogenicity with the use of high-dose influenza vaccine.

PERSONS WITH A HISTORY OF GUILLAIN-BARRÉ SYNDROME FOLLOWING INFLUENZA VACCINATION

A history of Guillain-Barré syndrome within 6 weeks following a previous dose of any type of influenza vaccine is considered a precaution to vaccination. Persons who are not at high risk for severe influenza complications and who are known to have experienced Guillain-Barré syndrome within 6 weeks of a previous influenza vaccination generally should not be vaccinated. Seasonal chemoprophylaxis is an option in such persons. However, the benefits of influenza vaccination might outweigh the risks for certain persons who have a history of Guillain-Barré syndrome and who also are at high risk for severe complications from influenza.

PERSON WITH A HISTORY OF EGG ALLERGY

For persons who report a history of egg allergy:

- Persons with a history of egg allergy who have experienced only urticaria (hives) after exposure to egg should receive influenza vaccine. Any licensed, recommended, and age-appropriate influenza vaccine (i.e., any IIV, RIV4, or LAIV4) that is otherwise appropriate for the recipient's health status may be used.
- Persons who report having had reactions to egg involving symptoms other than urticaria (hives), such as angioedema, respiratory distress, lightheadedness, or recurrent emesis; or who required epinephrine or another emergency medical intervention, may similarly receive any licensed, recommended, and age-appropriate influenza vaccine (i.e., any IIV, RIV4, or LAIV4) that is otherwise appropriate for their health status. If a vaccine other than ccIIV4 or RIV4 is used, administration should be done in an inpatient or outpatient medical setting (including but not necessarily limited to hospitals, clinics, health departments, and physician offices). Vaccine administration should be supervised by a health care provider who is able to recognize and manage severe allergic reactions.
- A previous severe allergic reaction to influenza vaccine, regardless of the component suspected of being responsible for the reaction, is a contraindication to future receipt of the vaccine.

Whenever possible, a vaccine recipient should be observed for 15 minutes following administration of any vaccine.

BMI = body mass index; HIV = human immunodeficiency virus; IIV = inactivated influenza vaccine; LAIV = live-attenuated influenza vaccine; RIV = recombinant influenza vaccine.

Modified from Grohskopf LA, Alyanak E, Broder KR, et al. Prevention and control of seasonal influenza with vaccines: recommendations of the Advisory Committee on Immunization Practices—United States, 2020-2021 influenza season. *MMWR Recomm Rep*. 2020;69:1-24.

nervous system complication of influenza A and B virus infections seen in children but rarely in adults, is associated with salicylate use.

DIAGNOSIS

Clinical

In an individual case, influenza often cannot be distinguished from infection with other respiratory viruses or bacterial pathogens that produce similar clinical manifestations (Chapters 84 and 397). Conversely, when public health authorities report an epidemic of influenza in a given community and an ambulatory adult patient is seen with typical febrile respiratory illness, these symptoms likely are caused by an influenza A or B virus infection. In such circumstances, the presence of fever and cough has a positive predictive value as high as 80% for laboratory-proven influenza. However, the predictive value of influenza-like illness in hospitalized patients is much lower. During evaluation, patients should also be asked about recent travel and exposures to ill persons, poultry, swine, and their environments. A positive travel history should prompt a review of the potential presence of novel or emerging respiratory viruses in the region. If risk factors for zoonotic influenza are present, specific laboratory testing is available through most health departments. When other respiratory viruses, particularly SARS-CoV-2 (Chapter 336), are also circulating, diagnostic testing is recommended to optimize management.

Laboratory

Gram staining of sputum may show abundant polymorphonuclear leukocytes but scant bacterial flora. Sputum and endotracheal aspirates usually yield high titers of influenza virus detectable by rapid (less than 60 minutes) nucleic acid amplification testing (NAAT) with a sensitivity of 92 to 95% and a specificity of >98%.[9,10] Multivirus NAAT assays that can simultaneously detect influenza A and B virus, H1, respiratory syncytial virus, rhinoviruses, parainfluenza viruses, coronaviruses,[11] and other viruses are now available to facilitate diagnosis of common pathogens when multiple viruses are circulating.[12] Viral culture, which is less sensitive than NAAT, and serologic studies are rarely useful for clinical care.

In patients who have secondary bacterial infections, Gram staining and culture of sputum or blood cultures most often reveal *Streptococcus pneumoniae* (Chapter 268), *Staphylococcus aureus* (Chapter 267) including community-acquired methicillin-resistant *S. aureus, Haemophilus influenzae* (Chapter 277), or *Streptococcus pyogenes*. NAAT can help determine the specific bacterial pathogen rapidly (Chapter 85). In hospitalized patients, a low serum procalcitonin level may help discriminate viral from mixed influenza-bacterial pneumonia and reduce antibiotic use (Chapter 85).[A1]

PREVENTION

Vaccination

Annual influenza immunization is recommended for all persons aged 6 months or older in the United States (Chapter 15).[13] Persons at higher risk for influenza-related complications or who care for or are exposed to them remain particular priorities of immunization efforts (see Table 332-1), especially when vaccine delays or shortages occur. Influenza vaccine policies differ across countries. Because influenza immunization benefits both mother and infants, the World Health Organization (WHO) has ranked pregnant women as the highest priority, followed (in no particular order) by health care workers, children 6 to 59 months of age, the elderly, and individuals with high-risk conditions.

Seasonal vaccine should be given each year in the fall as soon as available, preferably by October before the influenza season in northern temperate

areas. Quadrivalent vaccines with two A (H1N1, H3N2) and two B lineage (Yamagata, Victoria) antigens are preferred over trivalent vaccines because of their better breadth of coverage.

Egg-grown, intramuscularly administered inactivated influenza vaccines for persons 6 months of age and older; a high-dose inactivated vaccine and an MF-59 adjuvanted inactivated vaccine for persons aged 65 years and older; and a live-attenuated intranasal vaccine for otherwise healthy persons aged 2 to 49 years are currently licensed in the United States (E-Table 332-3). A mammalian cell culture–grown inactivated vaccine and a recombinant DNA–produced HA vaccine, particularly useful in individuals who have severe egg allergy, are also approved for seasonal use.

Racial and ethnic disparities in influenza vaccination rates persist,[14] and rates for key target groups, including pregnant women and health care workers, remain suboptimal. Immunization of health care personnel, which represents an important patient safety issue, can be enhanced by strategies to improve access, and especially by employer mandates.

Inactivated vaccines (Chapter 15) given by intramuscular injection provide about 50 to 70% protection against seasonal influenza illness in healthy adults,[1S] albeit with substantial year-to-year variations in effectiveness,[A2] and often much lower effectiveness in H3N2 seasons. Immunization reduces work absenteeism, use of health care resources, and antibiotics when the vaccine is well matched to the epidemic strain. On average, the effectiveness of the vaccination seems to decline by about 7% per month for at least 6 months after vaccination.

Immunogenicity and hence protection rates with inactivated seasonal vaccines are lower in elderly persons, particularly infirm nursing home residents, in immunosuppressed patients, and during circulation of H3N2 viruses. The effectiveness of influenza vaccine for prevention of medically attended acute respiratory illness among the elderly in nursing homes is estimated to average 20 to 40%. In ambulatory high-risk patients, immunization reduces hospitalizations from pneumonia, influenza, and major cardiovascular events as well as all-cause mortality during the influenza season. Both higher-dose inactivated vaccines (four-fold or three-fold more HA per strain) and adjuvanted inactivated vaccine are more immunogenic and protective than standard vaccine against seasonal influenza illness in older ambulatory adults and are the preferred vaccine for these individuals.[A3] High-dose vaccine also results in improved protection among kidney transplant patients.[A4] Immunization of children appears to reduce respiratory illness in household and community contacts.[A5] Immunization of health care providers reduces the risk of transmission to patients as well as their own risk of infection.

Experimental vaccines are using novel vaccine delivery approaches (i.e., mRNA) or alternative targets (hemagglutinin stem, neuraminidase, matrix protein 2 or nucleoprotein) with the goal of enhanced production and improving efficacy.[16] The holy grail of this effort is to develop a universal influenza vaccine that can provide coverage against a range of viruses for more than 1 year.[A6,A7]

With inactivated vaccine, fever and systemic symptoms occur at rates comparable to those of adults given placebo but are more common in young children. Among adults, 25% or more may have mild local reactions at the site of injection. Intranasal vaccine causes coryza and sore throat in adults.

Hypersensitivity reactions to residual egg proteins or other vaccine components occur rarely, and any licensed vaccine can be given to the patient. However, use of vaccines other than ccIIV4 or RIV4 should be given in a monitored clinical setting. Inactivated vaccine does not cause exacerbation of asthma but may be rarely associated with Guillain-Barré syndrome in older adults.

Medications for Chemoprophylaxis

Oral oseltamivir, single-dose baloxavir (40 mg if <80 kg [176 pounds], 80 mg if >80 kg [176 pounds]),[A8] and inhaled zanamivir are effective for chemoprophylaxis of both influenza A and B virus infections, including postexposure prophylaxis in households (Table 332-2), with each reducing the risk of symptomatic influenza infections by about 60 to 85%.[17] When an outbreak develops, unimmunized high-risk persons can be given such chemoprophylaxis and inactivated vaccine simultaneously, with cessation of chemoprophylaxis after 14 days. Alternatively, if vaccine is not available or contraindicated, is a poor match, or if the patient is highly immunosuppressed, chemoprophylaxis may be continued for the duration of the community outbreak. When given to patients and staff alike, these drugs are also helpful in managing nosocomial outbreaks.

Therapeutic doses (i.e., twice daily) should be considered for postexposure prophylaxis in immunocompromised hosts. Despite demonstrable efficacy, however, most public health authorities do not advise routine use of antiviral chemoprophylaxis, largely because of concerns regarding promotion of antiviral resistance and drug availability. In the community setting, an alternative approach is close monitoring and early initiation of antiviral treatment after suspected influenza exposures. Chemoprophylaxis is generally not recommended if more than 2 to 3 days have elapsed since exposure to a person with seasonal influenza.

Precautions

On entry to a health care facility, source control (e.g., face mask placement) and instruction in respiratory hygiene and cough etiquette should be implemented for symptomatic patients. Patients hospitalized with suspected or proven influenza should be managed with standard and droplet precautions and, when possible, private rooms. Face masks appear to provide equivalent protection compared with N95-type respirators in the outpatient setting,[A9] but compliance with a properly fitted N95-type respirator should provide better protection in the inpatient setting. An N95-type respirator should be used with other precautions (including gloves, gown, and eye protection with face shield or goggles; an airborne infection isolation room) during aerosol-generating procedures.

Early implementation and compliance with masks and hand hygiene appear to reduce the risk of secondary infections somewhat in household contacts. Physical distancing, masking, and other nonpharmaceutical interventions adopted for severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2; Chapters 335 to 337) have led to marked reductions in the circulation and impact of the influenza virus in many countries.

The risk of zoonotic infections can be reduced by avoiding exposure to potentially infectious poultry or swine and their environments. Travelers to affected countries should avoid visiting live bird markets, practice frequent hand hygiene, and not eat inadequately cooked poultry products. Closure of live bird markets and mass immunization of poultry using bivalent vaccines (to H7 and H5) have been associated with marked decrease in human cases since 2018.

TREATMENT

Hospitalized Patients

Antiviral treatment (see Table 332-2) is recommended as soon as possible for patients who have proven or suspected influenza and who manifest severe, complicated, or progressive illness; are hospitalized; or have underlying conditions that increase the risk for complications (see Table 332-1), including adults older than age 64 years and children younger than age 5 years.[18] In patients who have serious illness or high-risk conditions, decisions about initiating antiviral therapy should not wait for laboratory confirmation of influenza. Adults admitted with community-acquired pneumonia (Chapter 85) during the influenza season should initially receive both early antiviral therapy[19] and antibiotics, with subsequent therapy guided by NAAT and microbiologic testing. Although initiation of therapy is most effective if started within 2 days of the onset of symptoms, initiation within 6 hours of hospital admission is associated with reduced length of stay and death.[20]

Oral baloxavir[A10] and intravenous formulations of peramivir and zanamivir provide reliable delivery of high drug levels in seriously ill persons.[A11] A single dose of peramivir[A12] appears to be as effective as a 5-day regimen of oseltamivir in treating uncomplicated influenza, but daily dosing is advised in hospitalized patients. Intravenous zanamivir is approved for use in Europe and is available for compassionate use in a very limited number of countries, but is no more effective than oral oseltamivir in hospitalized patients with influenza.[A13]

Double doses of oseltamivir and/or combinations of anti-influenza drugs[21] do not appear to be more clinically effective than standard doses, although they may clear influenza viruses more rapidly[A14,A15] and reduce the risk of resistance during the course of therapy. Longer courses (e.g., 10 days) and perhaps higher doses are warranted in critically ill patients and immunocompromised hosts, in whom monitoring for virologic clearance is warranted.

During therapy, the emergence of resistance to oseltamivir is infrequent but highlights the need for ongoing susceptibility monitoring in high-risk patients with persistent symptomatic viral shedding after 5 to 7 days of treatment. Resistance during the course of baloxavir therapy is more common, occurring in about 10% of adults.[22] Zanamivir is inhibitory for most oseltamivir-resistant variants, and, if available, intravenous zanamivir, especially if combined with baloxavir, is generally preferred for treating severe infections that are suspected or proven to be oseltamivir-resistant.

Fulminant influenza viral pneumonia, particularly following pandemic 2009 H1N1 or avian influenza infection, requires intensive care, including ventilatory support (Chapter 91), often renal replacement therapy, and sometimes extracorporeal membrane oxygenation. Adding systemic corticosteroids for influenza-associated pneumonia or ARDS has been associated with prolonged viral replication, adverse effects including secondary bacterial infections, and increased mortality, so their routine use should be avoided.

Outpatients

Treatment with oseltamivir or single-dose baloxavir within 2 days of the onset of symptoms also may be considered in low-risk outpatients with uncomplicated febrile illness, in whom therapy reduces the duration of symptoms by 1 to 2 days, the time to functional recovery, the risk for pneumonia and hospitalization,[A16]

E-TABLE 332-3 CURRENTLY APPROVED INFLUENZA VACCINES IN THE UNITED STATES (2020-2021 SEASON)*

VACCINE TYPE	SUBSTRATE FOR PRODUCTION	NO. COMPANIES	FDA-APPROVED AGE RANGE (yr)	ROUTE	DOSE IN ADULTS
Inactivated influenza vaccine, quadrivalent, standard dose (SD-IIV4)	Eggs	Multiple	≥0.5†	IM	0.5 mL containing 15 µg per HA antigen
Adjuvanted inactivated influenza vaccine, quadrivalent, adjuvanted (aIIV4)	Eggs	1	≥65	IM	0.5 mL containing 15 µg per HA antigen
Inactivated influenza vaccine, quadrivalent, high-dose (HD-IIV4)	Eggs	1	≥65	IM	0.7 mL containing 60 µg per HA antigen
Inactivated influenza vaccine, trivalent, cell culture (ccIIV3)	MDCK cells	1	≥18	IM	0.5 mL containing 15 µg per HA antigen
Inactivated influenza vaccine, quadrivalent, cell culture (ccIIV4)	MDCK cells	1	≥18	IM	0.5 mL containing 15 µg per HA antigen
Recombinant inactivated influenza vaccine, quadrivalent (rIV4)	Insect cells	1	≥18	IM	0.5 mL containing 45 µg per HA antigen
Live-attenuated influenza vaccine, quadrivalent (LAIV4)‡	Eggs	1	2-49‡	Intranasal	0.2 mL by prefilled single-use intranasal sprayer

*Package inserts for U.S.-licensed vaccines are available at http://www.fda.gov/BiologicsBloodVaccines/Vaccines/ApprovedProducts/ucm093833.htm.

†Lower age limit of approval depends on specific vaccine product.

‡LAIV is approved only for otherwise healthy nonpregnant persons. It should be avoided in close contacts and caregivers of severely immunosuppressed persons who require a protected environment and in children and adolescents receiving concomitant aspirin therapy.

aIIV3 = adjuvanted inactivated influenza vaccine trivalent; ccIIV3 = cell culture inactivated influenza vaccine trivalent; ccIIV4 = cell culture inactivated influenza vaccine quadrivalent; HA = hemagglutinin; IIV3 = inactivated influenza vaccine trivalent; IIV4 = inactivated influenza vaccine quadrivalent; IM = intramuscular; LIV4 = live attenuated influenza vaccine quadrivalent; MDCK = Madin-Darby canine kidney; rIIV3 = recombinant inactivated influenza vaccine trivalent; rIIV4 = recombinant inactivated influenza vaccine quadrivalent.

TABLE 332-2 ANTIVIRAL DOSE RECOMMENDATIONS IN ADULTS

DRUG	ROUTE	TREATMENT	PROPHYLAXIS	DOSE REDUCTIONS	COMMENT
Baloxavir	Oral	80 or 40 mg single dose in uncomplicated illness	80 or 40 mg single dose for post-exposure prophylaxis	Weight-based dosing	Inhibitory for NAI- and adamantane-resistant viruses
Oseltamivir	Oral	75 mg bid	75 mg once daily†	CrCl ≤60 mL/min	Gastrointestinal and (very uncommonly) CNS side effects
Zanamivir	Inhaled	10 mg bid	10 mg once daily†	Avoid in those with underlying airway disease	Training in use of the inhaler device is important
Peramivir*	Intravenous	600 mg single IV dose in uncomplicated illness	Not studied	CrCl <50 mL/min	Single dose approved for uncomplicated influenza in adults in the United States
Laninamivir*	Inhaled	40 mg once in uncomplicated illness (Japan)	20 mg once daily for 2 days (Japan)	Avoid in those with underlying airway disease	Currently investigational in the United States; approved in Japan
Zanamivir*	Intravenous	600 mg q12h	Not studied	CrCl <80 mL/min	Currently investigational in the United States
Favipiravir*	Oral	1600 mg twice on day 1; 1600 mg bid (Japan) on days 2-5	Not studied	Teratogenic; avoid in pregnancy	Approved in Japan but investigational in the United States; inhibitory for NAI- and adamantane-resistant viruses; teratogenic
Amantadine	Oral	100 mg bid	100 mg bid	Age >64 yr, CrCl <50-80 mL/min	Gastrointestinal and CNS side effects Currently circulating strains are resistant
Rimantadine	Oral	100 mg bid	100 mg bid	Age >64 yr, CrCl <10 mL/min, or severe hepatic dysfunction	Lower risk of CNS side effects than with amantadine Currently circulating strains are resistant

*Oral favipiravir is approved in Japan but only for treating novel or reemerging influenza infections when other drugs are ineffective or not sufficiently effective; higher-dose regimens are being studied in the United States.

†Full therapeutic doses for postexposure prophylaxis (i.e., twice-daily dosing) are appropriate for infections due to novel influenza viruses and in immunocompromised hosts.

The standard duration of treatment in uncomplicated illness is 5 days, except for baloxavir or IV peramivir, for which single doses suffice. A longer treatment duration (e.g., 10 days) should be considered for infections in seriously ill patients, immunosuppressed hosts, or infections caused by novel viruses. Higher doses (e.g., 150 mg or 225 mg twice daily) of oseltamivir have been used in patients with serious lower respiratory illness, immunocompromise, or infections by novel viruses. The duration of prophylaxis depends on the epidemiologic setting; durations of 2 weeks after immunization or 7 to 10 days for postexposure prophylaxis are appropriate. Antiviral prophylaxis may interfere with response to intranasal live-attenuated vaccine but not to intramuscular inactivated vaccine.

bid = twice daily; CNS = central nervous system; CrCl = creatinine clearance; IV = intravenous; NAI = neuraminidase inhibitor.

and the risk for respiratory complications that lead to antibiotic use.[A17] Baloxavir appears to be the more effective option for patients with influenza B.[A18,A19]

Inhaled zanamivir may be infrequently associated with bronchospasm, sometimes severe, and nebulization of the lactose-containing commercial form is contraindicated in intubated patients. Oseltamivir is associated with nausea, vomiting, rash, and possibly rare neuropsychiatric symptoms.

Symptomatic measures include antipyretics and cough suppressants. Salicylates should not be used, especially in children younger than age 16 years, because of their association with Reye syndrome.

PROGNOSIS

Most influenza patients make a full recovery, but they may require several weeks to return to their premorbid functional status. If disease progresses despite 5 to 7 days of antiviral therapy, genotypic assays can identify drug resistance. The risk of acute myocardial infarction is increased more than six-fold in the first 7 days after diagnosis.[23] Influenza in elderly persons can cause prolonged loss of function and impairment of activities of daily living.

Approximately 90% of seasonal influenza-related deaths occur in persons who are older than 65 years or at high risk because of comorbid conditions. Mortality occurs in about 5 to 10% of adults hospitalized with seasonal influenza but is as high as 40 to 60% in zoonotic H5N1 and H7N9 infections. Bacterial infections (Chapter 85) are associated with about 20 to 40% of deaths. Detection of viral RNA in the blood is a poor prognostic finding that may reflect high viral burden in the lower respiratory tract. Once viral pneumonia progresses to respiratory failure, the mortality rate is often 50% or higher, but the risk is reduced by early antiviral therapy and high-quality intensive care.

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333 ADENOVIRUS DISEASES

MICHAEL G. ISON

DEFINITIONS

Human adenoviruses, which are members of the Adenoviridae family and the *Mastadenovirus* genus, are divided into seven species (A, B, C, D, E, F, and G; Table 333-1). Modern sequencing and molecular diagnostics have identified over 80 serotypes. Adenoviruses are double-stranded DNA, nonenveloped viruses that code for 20 early and 15 late proteins. The knobbed fiber protrudes from the fiber base (Fig. 333-1).

EPIDEMIOLOGY

Adenoviruses cause a range of infections from mild self-limited respiratory viral infections, conjunctivitis, and diarrhea to severe disseminated disease.[1] Adenoviruses have a worldwide distribution, and infections occur throughout the year without significant seasonal variability. Most infections occur as sporadic events, although local or regional epidemics have been described. Asymptomatic respiratory infection is common and is associated with prolonged carriage, particularly in feces and tonsillar tissue. Most patients with adenovirus infection are children, generally younger than 5 years, and most individuals have serologic evidence of exposure to adenovirus by age 10. Only about 25% of symptomatic cases occur in adults.[2] Adenoviruses 1, 2, and 5 are most common among children, whereas adenoviruses 3, 4, and 7 are more common in adults.

Severe outbreaks in the United States, including on college campuses, have resulted in cases requiring hospitalization, and nosocomial transmission can cause severe infections in health care workers. Adenovirus is the leading cause of respiratory viral infections among military recruits.[3] Unlike the year-round circulation of adenovirus in civilians, peaks of disease are recognized within the first 4 weeks of training exercises among military recruits. Rates of adenovirus among military recruits declined significantly with widespread use of an oral live-attenuated vaccine in 1971, increased after supplies of vaccine were depleted by 1999, then declined again after an oral live-attenuated adenovirus type 4 and 7 vaccine was approved in 2011 (E-Fig. 333-1).

PATHOBIOLOGY

Adenoviruses enter susceptible hosts by the mouth, nasopharynx, or ocular conjunctiva. The fiber protein of the virus binds to a cellular receptor that varies by serotype. On initial infection, local replication can induce considerable cellular damage owing to tissue invasive infection. Necrotizing bronchitis, bronchiolitis, interstitial pneumonia, and fibrin and hyaline membranes are seen within the alveoli during pulmonary infections. In ocular infections, exudative and mononuclear infiltrates develop beneath the epithelium. Replication results in desquamated epithelial cells, which induce hypertrophy in regional lymphatic tissue and active proliferative germinal centers. This reaction can cause swollen adenoids or intussusception (Chapter 128) associated with enlarged mesenteric lymph nodes, particularly in children.

Components of both the innate and adaptive immune responses are important for the control of adenovirus replication. Alveolar macrophages and Kupffer cells help eliminate adenovirus from the lung and liver and also secrete inflammatory cytokines such as tumor necrosis factor (TNF), interferon (IFN)–γ, interleukin (IL)–1β, IL-6, IL-8, and IL-12. $CD4^+$ and $CD8^+$ T lymphocytes play a particularly important role in the control and clearance of replicating adenovirus in humans, and the absolute lymphocyte and $CD4^+$ T-lymphocyte levels correlate inversely with adenovirus infection and the risk for developing disseminated adenoviral infections in immunosuppressed transplant patients.

Both group- and type-specific neutralizing and non-neutralizing antibodies are produced in response to infection and also play a role in limiting infection. Group-specific antibodies do not neutralize the virus but can confirm infection. Neutralizing antibodies may protect against disease manifestations in the previously infected host or against reinfection with the same serotype, but they do not eliminate the carrier state.

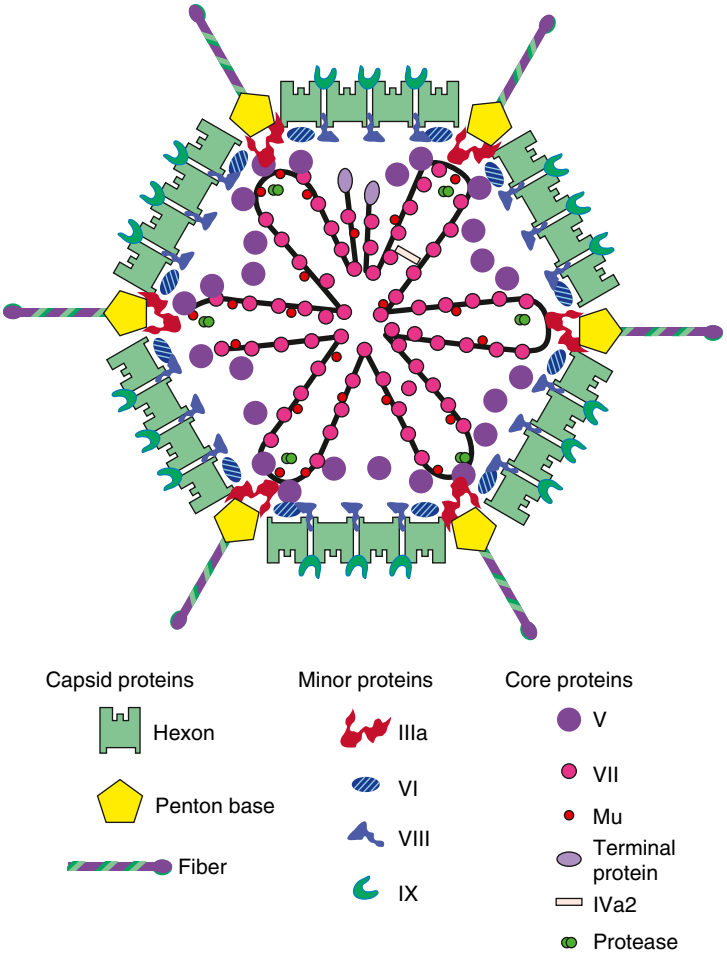

FIGURE 333-1. Adenovirus.

TABLE 333-1 CORRELATION OF ADENOVIRUS SUBGROUP AND SEROTYPE WITH MAJOR SITES OF INFECTION

SUBGROUP	SEROTYPE	MAJOR SITE OF INFECTION
A	12, 18, 31,* 61	Respiratory, urinary tract, gastrointestinal (GI)
B1	3, 7, 16, 21, 50, 68, 66, 68	Respiratory, eye (including pharyngoconjunctival fever), GI
B2	11,† 14,‡ 34,† 35,† 55,† 66	Urinary tract, respiratory
C	1, 2, 5, 6, 57	Respiratory, urinary tract, GI (especially hepatitis)
D	8§-10, 13, 15, 17, 19,§ 20, 22-30, 32-33, 36, 37§-39, 42-49, 51, 53-54, 56, 58-60, 62, 63-65, 67, 69-75	Eye, GI
E	4	Upper respiratory tract infection, pneumonia
F	40,* 41*	GI
G	52	GI

*Associated with infantile gastroenteritis.
†Associated with hemorrhagic cystitis and interstitial nephritis.
‡Associated with epidemic pneumonia with high mortality rate.
§Associated with epidemics.

CLINICAL MANIFESTATIONS

Adenovirus infections have a wide range of clinical manifestations that are linked to the virus type (see Table 333-1) as well as to the age and immunocompetence of the host. Common syndromes include infections of the respiratory tract, eye, gastrointestinal tract, genitourinary tract, and central nervous system (CNS). Disseminated infection also occurs, especially in immunosuppressed patients. Associations with adenovirus and obesity have been proposed as well.

Respiratory Tract Infections

About 10% of pneumonias in childhood and up to 5% of community-acquired pneumonias in some series of adults may be attributable to adenovirus, with

ABSTRACT

Adenovirus is a double-stranded DNA virus that causes a range of infections from mild, self-limited respiratory viral infections, conjunctivitis, and diarrhea to severe respiratory infections and disseminated disease. Military recruits, children, and the immunocompromised appear to be at greatest risk of more severe disease. Diagnosis is focused on molecular methods, including polymerase chain reaction, combined with pathology for end-organ disease. Treatment is generally supportive. Studies of cidofovir and brincidofovir show activity against adenovirus, but their use is generally limited to immunocompromised patients and patients with life-threatening infections.

KEYWORDS

adenovirus
pneumonia
pharyngoconjunctival fever
epidemic keratoconjunctivitis
diarrhea
hemorrhagic cystitis

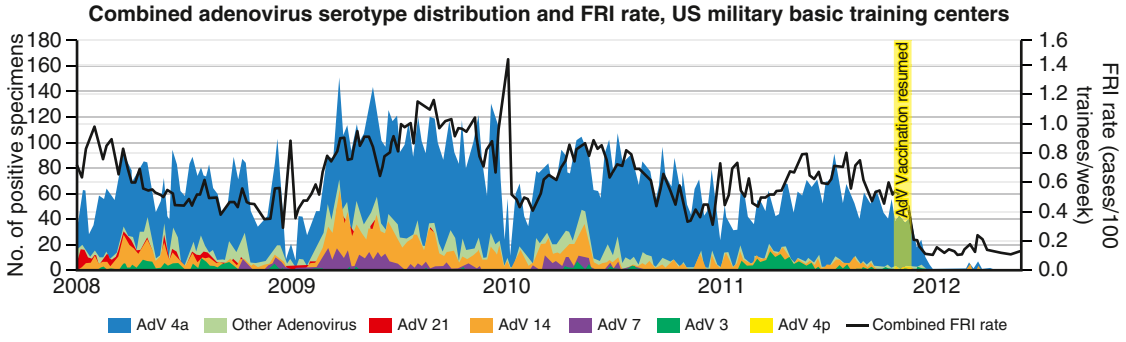

E-FIGURE 333-1. **Adenovirus serotype distribution in U.S. military basic training centers before and after reintroduction of adenovirus vaccination.** FRI = febrile respiratory illness. (From Hoke CH Jr, Snyder CE Jr. History of the restoration of adenovirus type 4 and type 7 vaccine, live oral [Adenovirus Vaccine] in the context of the Department of Defense acquisition system. *Vaccine*. 2013;31:1623-1632.)

adenovirus 7 probably carrying the highest risk for pneumonia.[4] Typical symptoms include nasal congestion, coryza, and cough, which may mimic pertussis infections (Chapter 289). Generalized malaise, fever, chills, myalgia, headache, and abdominal pain are common systemic symptoms.[5] Exudative tonsillitis and cervical adenopathy are also seen. If conjunctivitis accompanies these signs and symptoms, the disease is designated as pharyngoconjunctival fever. Otitis media is a common presentation, particularly among infants under 1 year of age. Cases in children and in adults, especially military recruits, are indistinguishable from other viral respiratory infections such as influenza (Chapter 332), parainfluenza (Chapter 331), and respiratory syncytial virus (Chapter 330). Recent outbreaks of sometimes severe and fatal adenovirus pneumonia have been described[6] and should be kept in the differential in patients with severe pneumonia.

Ocular Infections

The two most common manifestations of ocular adenovirus infection are pharyngoconjunctival fever and epidemic keratoconjunctivitis. Pharyngoconjunctival fever is typically a mild form of acute follicular conjunctivitis that accompanies febrile pharyngitis or cervical adenitis following a 6- to 9-day incubation period and may affect both eyes. Both bulbar and palpebral conjunctival involvement may occur. Swimming pools or lakes are a common source of infection. Symptoms typically resolve without treatment and without sequelae.

Epidemic keratoconjunctivitis is a more serious disease, with edema of the eyelids, pain, lacrimation, and photophobia.[7] Painful corneal opacities may occur, although they typically resolve over time. The disease typically involves just one eye and is self-limited. However, it may rarely result in permanent corneal damage, and large corneal epithelial full-layer detachment can also occur. Recovery may take up to 4 weeks. The disease is highly contagious, including nosocomial transmission to members of the health care team; as a result, diligent infection control is required even in suspected cases.

Gastrointestinal Tract Infection

Adenovirus can infect any part of the gastrointestinal tract and cause fever, nausea, vomiting, and diarrhea. Up to 10% of pediatric cases of diarrhea are caused by adenovirus, often with symptoms persisting for 8 to 12 days. Some adenoviruses can also cause mesenteric adenitis, which may clinically mimic appendicitis and rarely result in intussusception (Chapter 128). Adenovirus inclusions are seen in about one third to one half of appendices removed at surgery.

Genitourinary Tract Infections

Hemorrhagic cystitis, which typically manifests as microscopic or macroscopic blood in the urine and pain and cramping of the bladder, has been reported in children with adenoviruses 11 and 21 infection. Adults can present with urethritis with or without cystitis due to adenoviruses 19 and 37. Both diseases typically resolve over time without intervention.

Other Manifestations of Adenovirus

Acute viral hepatitis (Chapter 134),[8] meningitis (Chapter 381), and encephalitis (Chapter 383) have been reported occasionally in association with adenovirus infection. Adenovirus infection also can cause myocarditis and dilated myocardiopathy (Chapter 47).

A number of studies have found an association between detection of adenovirus in amniotic fluid associated with abnormal fetuses. In particular, echogenic liver lesions with or without hydrops and neural defects in fetuses were more common with patients with adenovirus detected in the amniotic fluid.

Adenovirus Diseases in Immunocompromised Patients

Primary adenovirus infection or reactivation of infection causes a wide range of infectious syndromes in immunocompromised children and adults. In the hematopoietic stem cell transplantation population (Chapter 163), the incidence of disease ranges from 3 to 47%.[9] Risk factors include an allogeneic transplant, T cell–depleted grafts, use of alemtuzumab, and acute graft-versus-host disease. Severe respiratory disease, hepatitis, colitis, hemorrhagic cystitis, and adenoviral keratoconjunctivitis can occur. Severe lymphopenia (<300 cells/μL) is associated with disseminated disease. Although disseminated disease only affects 1 to 7% of hematopoietic stem cell transplantation recipients, it is associated with a significant risk of mortality (8 to 26%).

Among various solid organ transplant recipients, asymptomatic adenovirus viremia is common.[10] However, progression to symptomatic disease is more common in small bowel and liver transplant recipients, pediatric transplant recipients, patients who receive antilymphocyte antibodies, and patients with donor-positive/recipient-negative adenovirus status.[11] Adenoviral hepatitis, typically caused by adenoviruses 1, 2, or 5, is most common among liver transplant recipients and can be diagnosed by detection of viremia or visualization of viral intranuclear inclusions on biopsy. Adenovirus enterocolitis occurs in small bowel transplant recipients and may mimic rejection. Adenoviral pneumonia is associated with graft loss, death, or progression to obliterative bronchiolitis for lung transplant recipients. Adenovirus causes hemorrhagic cystitis with or without interstitial nephritis in kidney transplant recipients. Such patients typically present with fever, hematuria, and new-onset renal dysfunction. Adenovirus DNA in biopsy specimens is associated with worse outcomes among pediatric heart transplant patients.

Primary adenoviral infections can cause severe, frequently fatal disease in children with primary immunodeficiency syndromes, including severe combined immunodeficiency disease (Chapter 231). Fatal cases have been reported in patients with acquired immunodeficiency syndrome (AIDS), but most are self-limited, particularly in patients on highly active antiretroviral therapy or without significant CD4 lymphopenia.

DIAGNOSIS

Diagnosis of adenovirus depends on isolation of the virus from infected tissue and either histopathologic evidence of local replication or clinical symptoms consistent with infection. Detection of virus alone is not diagnostic of an adenovirus disease, because the virus can be latent in some tissues and can be intermittently shed from the throat or in the stool for months to years after primary infection. Quantitative polymerase chain reaction (PCR) has a higher diagnostic yield than culture or direct fluorescent antigen detection. Quantitative PCR assays are also useful to predict progression to disseminated disease in pediatric and, to a lesser extent, adult hematopoietic stem cell transplantation recipients and to determine response due to therapeutic interventions.[12] It is critical to recognize that, particularly in immunocompromised patients and in patients with nonpulmonary disease, use of nasal swabs for detection of adenovirus using one of the many commercially available respiratory viral panel assays may fail to detect adenovirus infection. Testing of relevant specimens (e.g., stool for gastrointestinal disease, urine for urinary tract disease, blood for systemic or disseminated disease, and ocular swabs or fluid for ocular disease) is required for accurate detection of adenovirus.

TREATMENT

No antiviral agents are specifically approved for the treatment of adenovirus. Ribavirin is active in vitro but has not been helpful clinically. Cidofovir, which is a potent inhibitor of adenovirus in cell culture, has been used (preferably at 1 mg/kg three times a week), but data suggest that its ratio of efficacy to toxicity, predominantly nephrotoxicity, is too narrow to be clinically useful, except for severe infections.[13]

Oral brincidofovir, which is also approved for treatment of smallpox (Chapter 343) and is not nephrotoxic, is generally well tolerated and can suppress adenovirus.[A1,A2] The optimal dose of therapy has not been defined, and higher doses are associated with diarrhea that may be pathologically confused with graft-versus-host disease (Chapter 163). A newer approach using adenovirus- and multivirus-specific T cells is also being studied in prospective trials.

PREVENTION

Strict attention to contact and droplet precautions can prevent health care–associated and institutional outbreaks of adenovirus infections, including epidemic keratoconjunctivitis. An oral live-attenuated adenovirus 4 and 7 vaccine is well tolerated, with a vaccine efficacy of 99%. Currently, the vaccine is only indicated and available to U.S. military personnel, ages 17 to 50 years.

PROGNOSIS

Prognosis is strongly linked to immune competence. Immunocompetent patients typically have self-limited illnesses that generally can be managed with symptomatic care, although some epidemics, including adenovirus 7 and 14 epidemics, have resulted in high case-fatality rates. In immunocompromised adults, persistent or rising adenovirus viremia predicts progressive infection; in such cases, a reduction of immunosuppression and institution of antiviral therapy are associated with better outcomes. By comparison, patients with ongoing or predicted recovery of their lymphocyte counts may clear their viremia without specific intervention. Serial monitoring of the adenovirus load can help determine the response to therapy, which is seen in most but not all patients. Failure to reduce the viral load after 2 weeks of therapy portends a poor prognosis.

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334 PRE-2019 CORONAVIRUSES

FIONA P. HAVERS, HANNAH KIRKING, AND IAN D. PLUMB

DEFINITION

Human coronaviruses are a frequent cause of respiratory illness. Seasonal human coronaviruses (CoV) 229E, OC43, NL63, and HKU1 generally cause mild, self-limited upper respiratory tract infections (Chapter 329). However, three newer, highly pathogenic coronaviruses have caused major public health challenges: severe acute respiratory syndrome coronavirus (SARS-CoV), which was first identified in 2003; Middle East respiratory syndrome (MERS-CoV), which was identified in 2012; and SARS-CoV-2, which was identified in 2020 and which has caused the coronavirus disease 2019 (COVID-19; Chapters 335 to 337) global pandemic.

The Pathogen

The family Coronaviridae is currently divided into four genera—alpha, beta, gamma, and delta coronaviruses (Fig. 334-1). Human coronaviruses (HCoVs) are currently in two of these genera: alpha coronaviruses (229E and NL63), and beta coronaviruses (HKU1 and OC43). MERS-CoV, SARS-CoV, and SARS-CoV-2 are also beta coronaviruses but belong to different lineages than the common human coronaviruses.[1]

Coronaviruses are single-stranded positive-sense RNA viruses that contain large genomes (27 to 32kb) that can be replicated fully or can be replicated partially via subgenomic RNAs. The coronavirus genome encodes four main structural proteins: spike, membrane, nucleocapsid, and envelope; HKU1 and OC43 genomes also encode a hemagglutinin-esterase protein. Interspersed between the main structural proteins are several accessory proteins that vary among human coronaviruses and interact with the host immune response. Coronavirus genomes also encode a variety of nonstructural proteins that contribute to viral replication, proofreading, and modulation or evasion of the host response.[2]

SEASONAL CORONAVIRUS

EPIDEMIOLOGY

Seasonal coronaviruses 229E, NL63, HKU1, and OC43 are found worldwide. Seroprevalence studies indicate that exposure is common in early childhood and that a majority of adults are seropositive for at least one seasonal coronavirus. Although these viruses have been known to cause infection at any time of the year, in most temperate regions of the northern hemisphere, infections occur primarily in December through March, with peaks in January and February.[3] In a large prospective study in Norway of all hospitalized children aged 16 years or younger with respiratory tract infections, seasonal coronaviruses were present in 9% of patients. Among patients with a seasonal coronavirus, approximately two thirds had co-detection of another respiratory virus. Consistent with other studies, OC43 and NL63 were detected most frequently, with HKU1 and 229E detected much less frequently in the hospitalized patients. OC43 and NL63 infections had clear biennial peaks and alternated with HKU1, which circulated every second year when OC43 and NL63 detection rates were low.[4] By comparison, coronavirus 229E appears to be sporadic. Consistent with these findings, another recent household study showed that the proportion of acute respiratory infections associated with coronaviruses varied from 8 to 16% during annual respiratory virus season, which generally occurs from October through April in the temperate Northern Hemisphere.[5]

The incidence of symptomatic infection is highest in children below age 5 years for all seasonal coronaviruses except 229E, for which the incidence is relatively consistent across age groups. However, multiple studies indicate that all seasonal coronaviruses can infect individuals of all ages and that reinfection is common.[6]

Seasonal coronaviruses are likely spread via direct contact with respiratory droplets, aerosols, or secretions (Table 334-1). Viral shedding can frequently occur beyond 1 week in both symptomatic and asymptomatic adults and children, with viral detection typically persisting for a longer duration in children under age 5 years. Seasonal coronaviruses have a high attack rate within households; the proportion who become infected after exposure to an infected household member ranges from 7.2% for 229E to 12.6% for NL63. As a result, approximately 25% of all infections are likely acquired from an infected household contact. Children are the most frequently identified index case except for 229E, whereas adults ages 18 to 49 years comprise nearly half of the secondarily infected household contacts. Seasonal coronavirus outbreaks associated with significant morbidity have been described in babies in neonatal intensive care units and in adults in long-term care facilities.

PATHOBIOLOGY

Similar to other human coronaviruses, seasonal coronaviruses are thought to have a zoonotic origin (see Table 334-1)[7] and to attach to human cells via the receptor binding domain of the coronavirus spike protein. NL63 binds to angiotensin converting enzyme 2 (ACE-2), the same receptor as SARS-CoV and SARS-CoV-2. By comparison, 229E binds aminopeptidase N, whereas OC43 and HKU-1 bind 9-O-acetylated sialic acid. Although both ACE-2

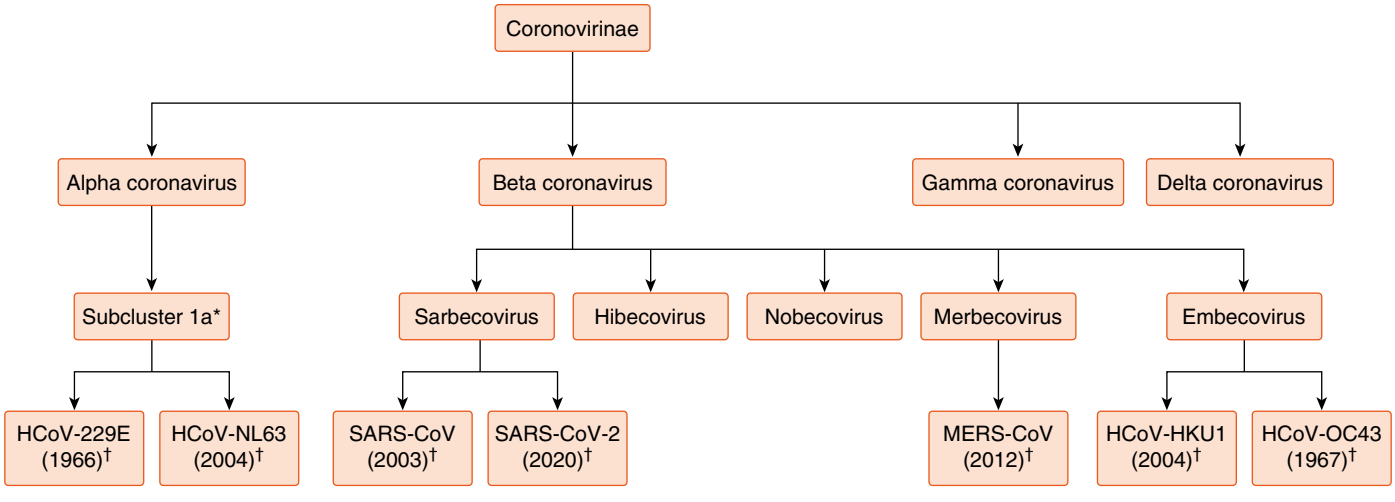

FIGURE 334-1. The four genera of coronaviruses. *Not official title. †Dates in parentheses correspond to when each human coronavirus was first reported. HCoV = human coronavirus; HKU1 = Hong Kong University 1; MERS = Middle Eastern respiratory syndrome; SARS-CoV-2 = severe acute respiratory syndrome coronavirus. (Adapted from Lu R, Zhao X, Li J, et al. Genomic characterisation and epidemiology of 2019 novel coronavirus: implications for virus origins and receptor binding. *Lancet*. 2020;395:565-574 and Cui J, Li F, Shi Z-L. Origin and evolution of pathogenic coronaviruses. *Nat Rev Microbiol*. 2019;17:181-192.)

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334 PRE-2019 CORONAVIRUSES

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DEFINITION

Human coronaviruses are a frequent cause of respiratory illness. Seasonal human coronaviruses (CoV) 229E, OC43, NL63, and HKU1 generally cause mild, self-limited upper respiratory tract infections (Chapter 329). However, three newer, highly pathogenic coronaviruses have caused major public health challenges: severe acute respiratory syndrome coronavirus (SARS-CoV), which was first identified in 2003; Middle East respiratory syndrome (MERS-CoV), which was identified in 2012; and SARS-CoV-2, which was identified in 2020 and which has caused the coronavirus disease 2019 (COVID-19; Chapters 335 to 337) global pandemic.

The Pathogen

The family Coronaviridae is currently divided into four genera—alpha, beta, gamma, and delta coronaviruses (Fig. 334-1). Human coronaviruses (HCoVs) are currently in two of these genera: alpha coronaviruses (229E and NL63), and beta coronaviruses (HKU1 and OC43). MERS-CoV, SARS-CoV, and SARS-CoV-2 are also beta coronaviruses but belong to different lineages than the common human coronaviruses.[1]

Coronaviruses are single-stranded positive-sense RNA viruses that contain large genomes (27 to 32kb) that can be replicated fully or can be replicated partially via subgenomic RNAs. The coronavirus genome encodes four main structural proteins: spike, membrane, nucleocapsid, and envelope; HKU1 and OC43 genomes also encode a hemagglutinin-esterase protein. Interspersed between the main structural proteins are several accessory proteins that vary among human coronaviruses and interact with the host immune response. Coronavirus genomes also encode a variety of nonstructural proteins that contribute to viral replication, proofreading, and modulation or evasion of the host response.[2]

SEASONAL CORONAVIRUS

EPIDEMIOLOGY

Seasonal coronaviruses 229E, NL63, HKU1, and OC43 are found worldwide. Seroprevalence studies indicate that exposure is common in early childhood and that a majority of adults are seropositive for at least one seasonal coronavirus. Although these viruses have been known to cause infection at any time of the year, in most temperate regions of the northern hemisphere, infections occur primarily in December through March, with peaks in January and February.[3] In a large prospective study in Norway of all hospitalized children aged 16 years or younger with respiratory tract infections, seasonal coronaviruses were present in 9% of patients. Among patients with a seasonal coronavirus, approximately two thirds had co-detection of another respiratory virus. Consistent with other studies, OC43 and NL63 were detected most frequently, with HKU1 and 229E detected much less frequently in the hospitalized patients. OC43 and NL63 infections had clear biennial peaks and alternated with HKU1, which circulated every second year when OC43 and NL63 detection rates were low.[4] By comparison, coronavirus 229E appears to be sporadic. Consistent with these findings, another recent household study showed that the proportion of acute respiratory infections associated with coronaviruses varied from 8 to 16% during annual respiratory virus season, which generally occurs from October through April in the temperate Northern Hemisphere.[5]

The incidence of symptomatic infection is highest in children below age 5 years for all seasonal coronaviruses except 229E, for which the incidence is relatively consistent across age groups. However, multiple studies indicate that all seasonal coronaviruses can infect individuals of all ages and that reinfection is common.[6]

Seasonal coronaviruses are likely spread via direct contact with respiratory droplets, aerosols, or secretions (Table 334-1). Viral shedding can frequently occur beyond 1 week in both symptomatic and asymptomatic adults and children, with viral detection typically persisting for a longer duration in children under age 5 years. Seasonal coronaviruses have a high attack rate within households; the proportion who become infected after exposure to an infected household member ranges from 7.2% for 229E to 12.6% for NL63. As a result, approximately 25% of all infections are likely acquired from an infected household contact. Children are the most frequently identified index case except for 229E, whereas adults ages 18 to 49 years comprise nearly half of the secondarily infected household contacts. Seasonal coronavirus outbreaks associated with significant morbidity have been described in babies in neonatal intensive care units and in adults in long-term care facilities.

PATHOBIOLOGY

Similar to other human coronaviruses, seasonal coronaviruses are thought to have a zoonotic origin (see Table 334-1)[7] and to attach to human cells via the receptor binding domain of the coronavirus spike protein. NL63 binds to angiotensin converting enzyme 2 (ACE-2), the same receptor as SARS-CoV and SARS-CoV-2. By comparison, 229E binds aminopeptidase N, whereas OC43 and HKU-1 bind 9-O-acetylated sialic acid. Although both ACE-2

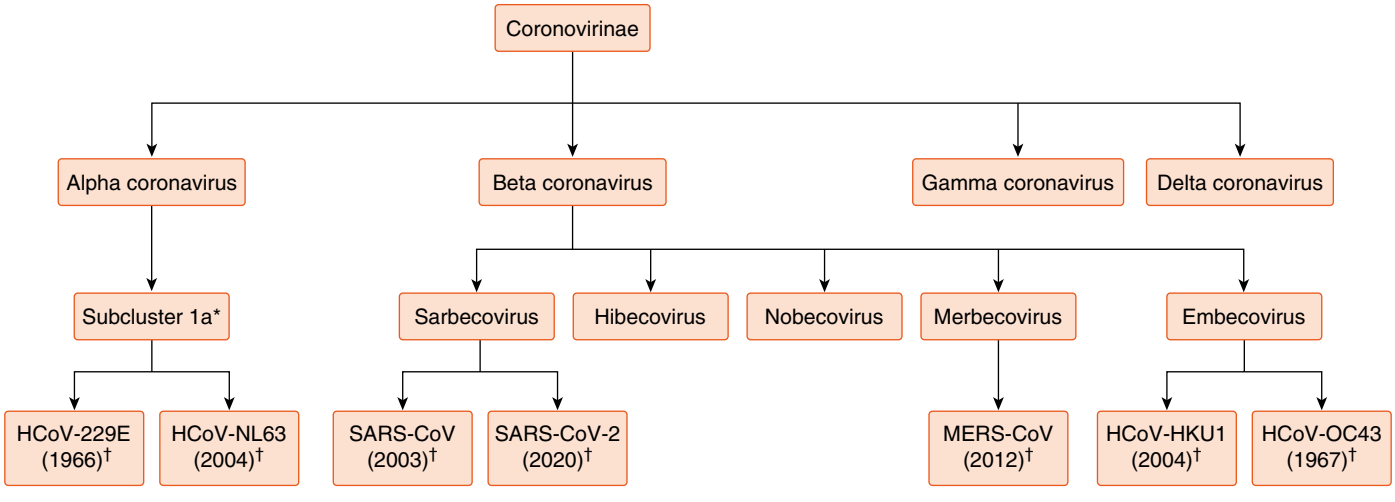

FIGURE 334-1. The four genera of coronaviruses. *Not official title. †Dates in parentheses correspond to when each human coronavirus was first reported. HCoV = human coronavirus; HKU1 = Hong Kong University 1; MERS = Middle Eastern respiratory syndrome; SARS-CoV-2 = severe acute respiratory syndrome coronavirus. (Adapted from Lu R, Zhao X, Li J, et al. Genomic characterisation and epidemiology of 2019 novel coronavirus: implications for virus origins and receptor binding. *Lancet*. 2020;395:565-574 and Cui J, Li F, Shi Z-L. Origin and evolution of pathogenic coronaviruses. *Nat Rev Microbiol*. 2019;17:181-192.)

ABSTRACT

All seven coronaviruses that are known to infect humans likely originated from animal reservoirs. Four of these human coronaviruses (HCoV-229E, HCoV-NL63, HCoV-OC43, and HCoV-HKU1) are frequent causes of relatively mild respiratory tract infections and rarely cause severe disease. In recent decades, however, three other coronaviruses have emerged to cause widespread severe disease in humans: SARS-CoV, MERS-CoV, and SARS-CoV-2 (the cause of the COVID-19 pandemic; Chapters 335 to 337). SARS-CoV was transmitted after the onset of symptoms and was successfully eliminated by a combination of public health control measures. In contrast, MERS-CoV infections continue to occur following close contact with infected persons or dromedary camels, primarily in or near the Arabian Peninsula. Infection with any of the known human coronaviruses can be confirmed using nucleic acid amplification tests, with multiplex tests increasingly available. Treatment for all non–SARS-CoV-2 human coronaviruses is supportive, although antiviral therapies and vaccines for MERS-CoV are currently being developed and evaluated.

KEYWORDS

HCoV-229E
HCoV-NL63
HCoV-OC43
HCoV-HKU1
SARS
MERS
coronaviruses

TABLE 334-1 ORIGINS, TRANSMISSION, CLINICAL FEATURES, AND INFECTIOUSNESS OF HUMAN CORONAVIRUSES IDENTIFIED BEFORE 2019

	HUMAN CORONAVIRUS		
	229E, NL63, OC43, HKU1	**SARS**	**MERS**
Postulated original animal reservoir	Bats (229E, NL63) Rodents (OC43, HKU1)	Bats	Bats
Intermediate host	Dromedary camels (229E) Unknown (NL63) Cattle (OC43) Unknown (HKU1)	Palm civet	Dromedary camels
Estimated date of first human infections	1700 (229E) 1200-1500 (NL63) 1890 (OC43) 1950s (HKU1)	2003	1980s (first case described 2012)
Source of transmission	Human infections, especially community settings	Human infections, especially health care settings (no cases reported since 2004)	Human infections, especially health care settings Contact with dromedary camels
Likely predominant route of transmission	Respiratory droplets or aerosols	Respiratory droplets or aerosols	Respiratory droplets or aerosols
Median incubation period (95% confidence interval)	3.2 days (95% CI, 2.8-3.7 days)	4.0 days (95% CI, 3.6-4.4 days); maximum 14 days	5.2 days (95% CI, 1.9-14.7 days)
Typical presentation	Upper respiratory tract infection; occasionally lower respiratory tract infections, especially if immunocompromised; croup or bronchiolitis in children	Upper respiratory tract infection, progressing to respiratory tract involvement in severe cases with multisystem involvement	Ranges from mild upper respiratory tract infection to lower respiratory tract infection with multisystem involvement
Infectious period	Typically 1-2 weeks, longer if immunocompromised; limited information on shedding of live virus	Symptom onset to 21 days Transmission usually 4-5 days after onset	Usually 1-11 days after onset of symptoms (median 7 days)

MERS = Middle East respiratory syndrome; SARS = severe acute respiratory syndrome.

and aminopeptidase N are present in a range of human tissues, host tropism of human coronaviruses is also determined by the presence of host proteases that cleave the S1 and S2 components of the spike protein, thereby permitting cell fusion and entry of viral RNA.

Seasonal coronaviruses predominantly infect cells of the upper respiratory tract. NL63, OC43, and HKU1 infect ciliary cells, whereas 229E preferentially infects nonciliary cells but can still depress ciliary function. The cytopathic effect of seasonal coronaviruses appears to be generally limited to the upper respiratory tract, although bronchiolitis, pneumonia, and acute lung injury also have been reported. The association of rare severe pulmonary disease with immunocompromise indicates the importance of the host immune response. Outside the respiratory tract, OC43 can infect neurons, and the virus has a mutation that likely enables cleavage by host cells in the nervous system. OC43 infection has been linked to neurologic syndromes including encephalitis.[8]

CLINICAL MANIFESTATIONS

Asymptomatic infections occur frequently. In human challenge studies, 72% of adults infected with 229E develop cold symptoms, with an incubation period of 2 to 5 days (median 3 days). The incubation period for the four seasonal coronaviruses is similar to other human coronaviruses (see Table 334-1) and has been estimated to be 3.2 days. Clinical manifestations of 229E, OC43, NL63, and HKU1 are generally mild and similar to those of other viral causes of the common cold (Chapter 329). Rhinorrhea, sore throat, cough, wheezing, and fever are common presenting symptoms. In a multiyear prospective household study, about 10% of infections in adults and 20% of infections in children were associated with medical consultation, with about 30% of coronavirus detections associated with moderate illness and 10% with relatively severe illness, which was defined as wheezing, dyspnea, or seeking care for the illness. Such infections are more likely in children under age 5 years and in adults age 50 years or older, and are more likely to be caused by 229E virus infection compared with the other three seasonal coronaviruses. Overall, about 5% of all hospitalized adults with acute respiratory illnesses are associated with these coronaviruses in the pre-COVID era.[9] Otitis media, gastroenteritis, an exacerbation of prior asthma, and pneumonia[10] occur more frequently in individuals who are immunocompromised or have underlying medical conditions. Rare neurologic manifestations such as meningoencephalitis and seizures have been noted in children with seasonal coronavirus infections, including fatal encephalitis in immunocompromised infants infected with OC43.

DIAGNOSIS

Given the lack of specific treatment, confirmatory diagnosis of these pathogens is generally of limited clinical utility. However, testing of nasopharyngeal samples with multipathogen respiratory viral panels using polymerase chain reaction (PCR) assays, often to exclude other pathogens such as SARS-CoV-2, is the best method for confirming the diagnosis.

TREATMENT

No specific antiviral treatment is currently recommended for seasonal coronavirus infections. Supportive care or management of complications from infection is occasionally warranted. Remdesivir, an antiviral active against SARS-CoV-2, has in vitro activity against 229E, and other compounds examined for activity against SARS-CoV-2 potentially show promise against seasonal coronaviruses, but none have been evaluated in rigorous clinical trials.

PREVENTION

During months of active circulation, transmission can be prevented by nonpharmaceutical precautions such as washing hands regularly and avoiding close contact with a person who has an upper respiratory tract infection. A decline in infections from seasonal coronaviruses during the COVID-19 pandemic showed that school closures or other precautions related to the pandemic likely prevented transmission of seasonal coronaviruses as well as SARS-CoV-2.[11] In health care settings, general infection control practices should be maintained to prevent transmission via respiratory droplets, especially for patients at extremes of age or with known immunocompromised status. COVID-19 vaccines elicit cross-reactive immune responses to seasonal coronaviruses, although it is not yet known if true cross-protection results. Prior infection with a seasonal coronavirus appears to provide limited cross-protection against SARS-CoV-2 infection.

PROGNOSIS

Although most cases are mild, severe illness has been documented in some patients, particularly patients who are immunocompromised, have underlying comorbid conditions, or are at the extremes of age.

MIDDLE EAST RESPIRATORY SYNDROME AND SEVERE ACUTE RESPIRATORY SYNDROME

EPIDEMIOLOGY

Severe Acute Respiratory Syndrome

Severe acute respiratory syndrome (SARS) is a viral respiratory illness caused by a coronavirus called SARS-associated coronavirus (SARS-CoV or SARS-CoV-1). Following reports of an atypical pneumonia in Guangdong, China, in November 2002, SARS-CoV spread to more than two dozen countries in North America, South America, Europe, and Asia, where it resulted in a sizeable international outbreak.[12] Before the SARS global outbreak of 2003 was contained, 8098 reported infections and 774 reported deaths occurred. Since mid-2004, no cases of SARS have been reported.[13]

The median incubation period for SARS was estimated to be 4 days, although incubation periods of up to 14 days were reported (see Table 334-1). SARS was spread primarily by close person-to-person contact, via respiratory droplets or aerosol, or less commonly via fomites. Likely transmission from fecal contamination was also reported.

Transmission of SARS-CoV typically occurred 4 or 5 days after onset of symptoms and was driven predominantly by more severely ill, hospitalized patients. Viral load was highest around day 10 of illness, with no virus isolated beyond 21 days. Asymptomatic and mild infections were rare, and no transmission was reported from asymptomatic individuals or from symptomatic cases before the onset of symptoms.

Middle East Respiratory Syndrome

Middle East respiratory syndrome (MERS), the illness caused by MERS-CoV-2 infection, was first reported in Saudi Arabia in September 2012. Most infected individuals with MERS have lived in the Arabian Peninsula or recently traveled from the Arabian Peninsula before they became ill, but some individuals have contracted MERS after having close contact with an infected person who had recently traveled from the Arabian Peninsula. At least 27 countries have reported cases since 2012, leading to more than 900 known deaths owing to the infection and related complications.

Transmission of MERS-CoV leading to human illness likely originates from upper respiratory tract infections among camels, specifically dromedaries (*Camelus dromedarius*).[14] Direct contact with dromedaries is a risk factor for primary human infection with MERS-CoV (see Table 334-1).

More than 80% of MERS-CoV infections are estimated to result from human-to-human transmission through close contact, most likely via respiratory droplets. Human-to-human transmission frequently occurs in health care settings. Transmission can also occur in household settings, but epidemiologic studies have not found sustained community transmission of MERS-CoV.

The majority of human-to-human transmission seems to originate from symptomatic case patients. Evidence for transmission from asymptomatic individuals is limited, but the importance of asymptomatic infections might be underappreciated, because a substantial proportion of MERS cases do not report having a known risk factor (i.e., contact with another case or a dromedary).[15]

The median incubation period for MERS is approximately 5 days (95% confidence interval, 1.9 to 14.7 days). Duration of MERS-CoV shedding in the respiratory tract is typically longer in severely ill patients compared with mildly ill patients. Shedding of cultivable virus has been detected for up to 25 days after the onset of symptoms.

PATHOBIOLOGY

After infection of epithelial cells in the upper respiratory tract, SARS-CoV and MERS-CoV can infect pneumocytes and cells in other organ systems. Tissue tropism is determined by the host receptor that binds to the coronavirus spike protein and by other factors such as host cell proteases.

Like SARS-CoV-2, the SARS-CoV spike protein binds to the ACE-2 receptor, which is abundant in epithelial, endothelial, and smooth muscle cells. Autopsy investigations of patients with SARS have noted SARS-CoV in pneumocytes, pulmonary infiltrates, the reticuloendothelial system, kidneys, gastrointestinal tract, and brain.

The MERS spike protein binds to the dipeptidyl peptidase 4 (DPP4) receptor, which is present in a variety of cell types, including epithelial cells, pneumocytes, endothelial cells, neurons, and T-cells. Autopsy after fatal MERS infection has indicated necrotizing pneumonia with diffuse alveolar damage, acute kidney injury, and other organ involvement, including hepatitis and myositis.

Pathologic damage from SARS and MERS coronavirus infections is likely caused by a combination of cytopathic effects and the host immune response. The importance of immunopathology is indicated by the typical timing of severe illness after peak viral load, and by the association of a delayed type I interferon response with severe outcomes. Conversely, an early type I interferon response and neutralizing antibody appear to be protective.

CLINICAL MANIFESTATIONS

Severe Acute Respiratory Syndrome

The clinical manifestations of SARS-CoV infection range from mild illness to severe and rapidly progressive disease. SARS-CoV infection typically begins with a fever that is sometimes associated with other nonspecific symptoms such as chills, headache, or myalgias. These nonspecific systemic symptoms progress 2 to 7 days later to pulmonary disease and a clinical syndrome indistinguishable from other causes of community-acquired pneumonia (Chapter 85). Respiratory complaints include a nonproductive cough and dyspnea, but typically do not include upper respiratory tract symptoms such as rhinorrhea and sore throat. Almost all patients with laboratory evidence of SARS-CoV infection develop radiographic evidence of pneumonia, and most (70 to 90%) develop lymphopenia. In 10 to 20% of cases, patients progress to develop acute respiratory distress syndrome (ARDS; Chapter 90) and ultimately require mechanical ventilation. Diarrhea, which is seen in approximately 10 to 20% of patients, typically develops later in the illness.

Middle East Respiratory Syndrome

Clinical features of MERS-CoV infection range from asymptomatic or mild disease (with low-grade fever, runny nose, sore throat, or muscle aches) to severe disease. In patients confirmed to have MERS-CoV infection, the disease may progress to severe respiratory illness with symptoms such as fever, cough, and shortness of breath; some patients also have diarrhea and nausea/vomiting. Chest radiographs and/or computed tomographic (CT) scans are typically normal in patients with mild illness, but severe illness can include ARDS with variable multiorgan involvement. Laboratory abnormalities commonly include leukopenia and lymphopenia; some patients also develop thrombocytopenia, anemia, and elevated aminotransferase levels. Severe MERS can progress rapidly to respiratory failure, acute kidney injury, and death.

DIAGNOSIS

Severe Acute Respiratory Syndrome

The assays most often used to diagnose SARS-CoV infection were PCR assays for viral RNA and serologic testing for virus-specific antibodies. Given the lack of any known SARS cases in the world since 2004, any decision to test for SARS should be made in conjunction with public health authorities.

Middle East Respiratory Syndrome

Individuals may be suspected of having MERS if they have both a clinical syndrome consistent with MERS (e.g., fever and respiratory symptoms) and an epidemiologic link to the Arabian Peninsula, a history of travel to the Arabian Peninsula, close contact with an ill traveler from the Arabian Peninsula, or close contact with a confirmed case of MERS.[16] Because the clinical features of MERS often do not differ from those of other acute febrile respiratory illnesses, other causes of community-acquired pneumonia should be considered with appropriate testing and/or treatment (Chapter 85).

PCR testing of respiratory secretions, done in consultation with local public health authorities, is the mainstay for diagnosis. Samples from the lower respiratory tract (collected within 7 days after the onset of symptoms) have the highest sensitivity among seriously ill patients, but multiple specimens (e.g., sputum, nasopharyngeal swabs, oropharyngeal swabs, bronchoalveolar lavage and tracheal aspirates) should be analyzed to optimize the likelihood of obtaining a positive test.

TREATMENT

No specific antiviral treatments are currently recommended for SARS or MERS. Lopinavir can limit the replication of SARS-CoV and MERS-CoV in vitro, and treatment of SARS with the combination of lopinavir plus ritonavir resulted in lower mortality compared with an untreated historical control group who were treated with ribavirin alone. Interferon is of uncertain effectiveness.

For MERS, one randomized trial found that up to 14 days of treatment with interferon beta-1b (0.25 mg on alternate days) plus lopinavir-ritonavir (400 mg

lopinavir and 100 mg ritonavir every 12hours) significantly lowered 90-day all-cause mortality from 44 to 28% compared with placebo, with the greatest effect when treatment is started during the 7 days after the onset of symptoms.[A1] Remdesivir inhibits SARS-CoV and MERS-CoV replication in vitro and in animal models. Neither monoclonal antibodies nor convalescent plasma have been tested in rigorous clinical trials.

Seriously ill patients require progressively more intense supportive care, as is recommended for pneumonia (Chapter 85) and acute respiratory failure (Chapter 90). Glucocorticoids are not recommended for MERS-CoV infections.

PREVENTION

During 2003, SARS transmission levels were dependent on super-spreader events that originated from symptomatic infections. The transmission of SARS was effectively eliminated within a few months by a combination of case detection, contact tracing, isolation, quarantine, infection control practices during health care, and temporary travel restrictions.

Prevention of MERS requires ongoing strategies because dromedaries in the Arabian Peninsula remain an important source of primary human infections. Human-to-human transmission also occurs, but human-to-human transmission chains are not sustained. Infection with MERS-CoV can elicit persistent humoral and cellular immunity.[17] Nevertheless, early identification and triage is critical to prevent onward transmission. Consistent implementation of infection control protocols can prevent health care–associated outbreaks. Handwashing and other precautions are recommended when in contact with dromedaries to prevent zoonotic transmission.

Candidate vaccines for dromedaries have been evaluated. Early studies of human vaccines against MERS are also underway, using different approaches to elicit immune responses against the spike protein.

PROGNOSIS

For patients with SARS, the overall case fatality rate was estimated to be 15%, with higher mortality among older age groups. The case fatality rate for MERS is between 20 and 40%, although the number of asymptomatic and/or mild cases may be underreported. Most people who die of MERS are older and/or have preexisting medical conditions, such as diabetes, hypertension, cardiac disease, obesity, chronic respiratory disease, end-stage renal disease, cancer, or immunosuppressive therapy. Concomitant infections, a low albumin concentration, admission to an intensive care unit, and the need for mechanical ventilation are predictors of death.

Similar to what has been observed following COVID-19 (Chapter 337), some survivors of SARS and MERS have significant long-term clinical problems, including impaired lung function and decreased exercise capacity. The prevalence of psychological sequelae, such as post-traumatic stress disorder, depression, and anxiety, is 30% or higher after more than 6 months.[18]

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335 COVID-19: VIROLOGY AND PATHOLOGY

VINCENT RACANIELLO

In December 2019, a cluster of patients with pneumonia of unknown etiology were identified in Wuhan, a city of 11 million residents in South Central China.[1] RNA extracted from bronchoalveolar fluid provided the complete genome of a novel betacoronavirus named SARS-CoV-2 (for severe acute respiratory syndrome coronavirus-2). The disease caused by this virus is called COVID-19 (for COronaVirus Infectious Disease).

SARS-COV-2: THE VIRUS AND THE GENOME

SARS-CoV-2 is classified within the Coronaviridae, a diverse family of viruses with (+) strand RNA genomes (Table 335-1). Coronaviruses, which infect not only humans but also other mammalian and avian species, may cause respiratory or enteric diseases. SARS-CoV-2 is the seventh coronavirus known to infect humans. Four of these human coronaviruses (HCoV-229E, HCoV-OC43, HCoV-NL63, HCoV-HKU1) cause mainly mild upper respiratory tract infections (Chapter 334). By comparison, severe acute respiratory syndrome coronavirus (SARS-CoV), which was identified in 2002, precipitated an epidemic that infected about 8000 humans before its circulation ceased. Middle East Respiratory Syndrome coronavirus (MERS-CoV) was first identified in 2012 and continues to infect humans, although chains of infection are very short, and only about 2500 confirmed cases have been reported.

Coronaviruses, which have the appearance of a solar corona on electron microscopy (Fig. 335-1), are enveloped, roughly spherical, and pleomorphic, with particle sizes ranging from approximately 118 to 136 nm in diameter. Embedded in the viral membrane are the spike (S), membrane (M), and envelope proteins (Fig. 335-2). The transmembrane S protein forms trimers that bind to host cell receptors and induce fusion of viral and cell membranes. The M protein monomer, which provides shape to the viral particles, is embedded in the viral membrane by three transmembrane domains. The E protein is a small (8- to 12 kDa) protein that is essential

TABLE 335-1 CLASSIFICATION OF HUMAN CORONAVIRUSES*

FAMILY: CORONAVIRIDAE	
Genus: *Alphacoronavirus*	Viruses: Human coronavirus 229E (HCoV-229E) Human coronavirus NL63 (HCoV-NL63)
Genus: *Betacoronavirus*	Viruses: Human coronavirus HKU1 (HCoV-HKU1) Severe acute respiratory syndrome coronavirus (SARS-CoV) Middle East respiratory syndrome coronavirus (MERS-CoV) Severe actute respiratory syndrome coronavirus 2 (SARS-CoV-2)

*The Coronaviridae includes five genera, of which two, the *Alphacoronavirus* and *Betacoronavirus*, include the six known human coronaviruses.

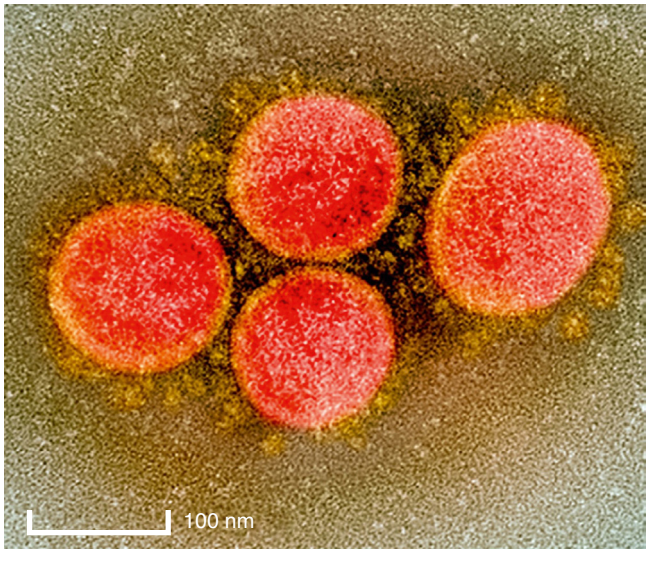

FIGURE 335-1. Transmission electron micrograph of severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2) viral particles isolated from a patient. Image captured at the NIAID Integrated Research Facility (IRF) in Fort Detrick, Maryland. (Copyright credit: NIAID. From https://www.cell.com/trends/genetics/fulltext/S0168-9525(20)30228-6#fx2.)

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lopinavir and 100 mg ritonavir every 12hours) significantly lowered 90-day all-cause mortality from 44 to 28% compared with placebo, with the greatest effect when treatment is started during the 7 days after the onset of symptoms.[A1] Remdesivir inhibits SARS-CoV and MERS-CoV replication in vitro and in animal models. Neither monoclonal antibodies nor convalescent plasma have been tested in rigorous clinical trials.

Seriously ill patients require progressively more intense supportive care, as is recommended for pneumonia (Chapter 85) and acute respiratory failure (Chapter 90). Glucocorticoids are not recommended for MERS-CoV infections.

PREVENTION

During 2003, SARS transmission levels were dependent on super-spreader events that originated from symptomatic infections. The transmission of SARS was effectively eliminated within a few months by a combination of case detection, contact tracing, isolation, quarantine, infection control practices during health care, and temporary travel restrictions.

Prevention of MERS requires ongoing strategies because dromedaries in the Arabian Peninsula remain an important source of primary human infections. Human-to-human transmission also occurs, but human-to-human transmission chains are not sustained. Infection with MERS-CoV can elicit persistent humoral and cellular immunity.[17] Nevertheless, early identification and triage is critical to prevent onward transmission. Consistent implementation of infection control protocols can prevent health care–associated outbreaks. Handwashing and other precautions are recommended when in contact with dromedaries to prevent zoonotic transmission.

Candidate vaccines for dromedaries have been evaluated. Early studies of human vaccines against MERS are also underway, using different approaches to elicit immune responses against the spike protein.

PROGNOSIS

For patients with SARS, the overall case fatality rate was estimated to be 15%, with higher mortality among older age groups. The case fatality rate for MERS is between 20 and 40%, although the number of asymptomatic and/or mild cases may be underreported. Most people who die of MERS are older and/or have preexisting medical conditions, such as diabetes, hypertension, cardiac disease, obesity, chronic respiratory disease, end-stage renal disease, cancer, or immunosuppressive therapy. Concomitant infections, a low albumin concentration, admission to an intensive care unit, and the need for mechanical ventilation are predictors of death.

Similar to what has been observed following COVID-19 (Chapter 337), some survivors of SARS and MERS have significant long-term clinical problems, including impaired lung function and decreased exercise capacity. The prevalence of psychological sequelae, such as post-traumatic stress disorder, depression, and anxiety, is 30% or higher after more than 6 months.[18]

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335 COVID-19: VIROLOGY AND PATHOLOGY

VINCENT RACANIELLO

In December 2019, a cluster of patients with pneumonia of unknown etiology were identified in Wuhan, a city of 11 million residents in South Central China.[1] RNA extracted from bronchoalveolar fluid provided the complete genome of a novel betacoronavirus named SARS-CoV-2 (for severe acute respiratory syndrome coronavirus-2). The disease caused by this virus is called COVID-19 (for COronaVirus Infectious Disease).

SARS-COV-2: THE VIRUS AND THE GENOME

SARS-CoV-2 is classified within the Coronaviridae, a diverse family of viruses with (+) strand RNA genomes (Table 335-1). Coronaviruses, which infect not only humans but also other mammalian and avian species, may cause respiratory or enteric diseases. SARS-CoV-2 is the seventh coronavirus known to infect humans. Four of these human coronaviruses (HCoV-229E, HCoV-OC43, HCoV-NL63, HCoV-HKU1) cause mainly mild upper respiratory tract infections (Chapter 334). By comparison, severe acute respiratory syndrome coronavirus (SARS-CoV), which was identified in 2002, precipitated an epidemic that infected about 8000 humans before its circulation ceased. Middle East Respiratory Syndrome coronavirus (MERS-CoV) was first identified in 2012 and continues to infect humans, although chains of infection are very short, and only about 2500 confirmed cases have been reported.

Coronaviruses, which have the appearance of a solar corona on electron microscopy (Fig. 335-1), are enveloped, roughly spherical, and pleomorphic, with particle sizes ranging from approximately 118 to 136 nm in diameter. Embedded in the viral membrane are the spike (S), membrane (M), and envelope proteins (Fig. 335-2). The transmembrane S protein forms trimers that bind to host cell receptors and induce fusion of viral and cell membranes. The M protein monomer, which provides shape to the viral particles, is embedded in the viral membrane by three transmembrane domains. The E protein is a small (8- to 12 kDa) protein that is essential

TABLE 335-1 CLASSIFICATION OF HUMAN CORONAVIRUSES*

FAMILY: CORONAVIRIDAE	
Genus: *Alphacoronavirus*	Viruses: Human coronavirus 229E (HCoV-229E) Human coronavirus NL63 (HCoV-NL63)
Genus: *Betacoronavirus*	Viruses: Human coronavirus HKU1 (HCoV-HKU1) Severe acute respiratory syndrome coronavirus (SARS-CoV) Middle East respiratory syndrome coronavirus (MERS-CoV) Severe actute respiratory syndrome coronavirus 2 (SARS-CoV-2)

*The Coronaviridae includes five genera, of which two, the *Alphacoronavirus* and *Betacoronavirus*, include the six known human coronaviruses.

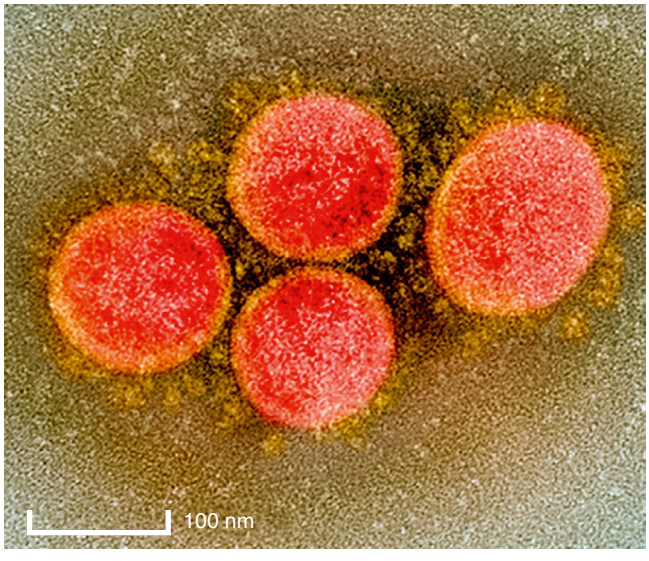

FIGURE 335-1. Transmission electron micrograph of severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2) viral particles isolated from a patient. Image captured at the NIAID Integrated Research Facility (IRF) in Fort Detrick, Maryland. (Copyright credit: NIAID. From https://www.cell.com/trends/genetics/fulltext/S0168-9525(20)30228-6#fx2.)

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ABSTRACT

A novel betacoronavirus named SARS-CoV-2 emerged in South Central China in December 2019 after a spillover from wild animals to humans at the Wuhan Huanan Seafood market. The virus particle is enveloped and harbors an RNA genome of nearly 30,000 bases in length. SARS-CoV-2 initiates infection of cells when the S protein binds to the cell receptor ACE2. In cells of the respiratory tract, the plasma membrane protease TMPRSS2 cleaves S into its S1 and S2 subunits. Upon the attachment of the receptor-binding domain to ACE2, the conformation of S2 changes to thrust the fusion peptide into the cell membrane. Consequently, fusion of viral and cell membranes occurs at the cell surface. SARS-CoV-2 is transmitted among humans by droplets that are produced by speaking, sneezing, or coughing. Virus-laden droplets are inhaled and lodge in the upper respiratory tract, where the virus attaches to and enters ciliated epithelial cells. After initial reproduction in the upper respiratory tract, virus migrates down the airways, where it may infect alveolar epithelial cells in the lungs. In the lungs, diffuse alveolar injury, exudates, and hyaline membranes are accompanied by endothelial injury with microangiopathy, microthrombosis, and vascular angiogenesis. In some cases, viral reproduction can trigger strong unregulated immune responses (cytokine storm) associated with inflammation-mediated acute lung injury, increases in vascular permeability, thrombosis, disseminated intravascular coagulation, acute respiratory distress syndrome, and generalized organ failure. SARS-CoV-2 infections have been documented in many nonhuman animal hosts, so the virus can never be eradicated.

KEYWORDS

SARS-CoV-2
COVID-19
betacoronavirus
coronavirus
ACE2
TMPRSS2
furin

for infectivity, but its function is enigmatic. The nucleocapsid (N) protein, which is the most abundant protein in the infected cell, is required for replication of the genome, coats the entire viral RNA genome, and interacts with the M protein.

Coronavirus genomes are the longest among RNA viruses, and the SARS-CoV-2 genome is nearly 30,000 bases in length (Fig. 335-3). The virion RNA is capped at the 5′-end and polyadenylated at the 3′-end and harbors 5′- and 3′-untranslated regions. The left two-thirds portion of the viral RNA encodes two overlapping open reading frames that specify proteins involved in mRNA synthesis and genome replication; no other polypeptides are translated from the viral genome RNA. The remainder of the genome, which encodes structural and accessory proteins, is expressed by means of a nested set of subgenomic RNAs.

ORIGIN OF SARS-COV-2

The closest genome to SARS-CoV-2 is a virus called RaTG13, which was obtained from a *Rhinolophus affinis* bat in 2013 in Yunnan province, China.[2] The genome of this bat virus is overall 96.2% identical to that of SARS-CoV-2, a divergence that represents about 20 years of sequence evolution. Consequently, RaTG13 cannot be a direct progenitor of SARS-CoV-2 but is clearly in its evolutionary past.

Various SARS-CoV-2–like viruses have been isolated from bats in China, Thailand, Cambodia, and Japan, but none have a spike protein that can bind angiotensin-converting enzyme 2 (ACE2) and allow entry into human cells.[3] In limestone caves in Northern Laos, however, sampling of bats has revealed the presence of three *Sarbecovirus* genomes (called BANAL-52, BANAL-103, and BANAL-236) with high sequence similarity to SARS-CoV-2 and RaTG13.[4] Of the 17 amino acids that interact with the receptor-binding domain of ACE2, 16 are conserved between SARS-CoV-2 and BANAL-52 or BANAL-103, and 15 of 17 are conserved with BANAL-236. In contrast, only 11 out of 17 receptor-binding domain amino acids are conserved among SARS-CoV-2 and RaTG13. Recombination analysis demonstrates that the SARS-CoV-2 genome is a mosaic of at least five different genomes, including BANAL-52, BANAL-103, and BANAL-236 and the previously recognized RmYN02, RpYN06, and RaTG13, the latter all discovered in China. The implication of these observations is that SARS-CoV-2 likely arose from recombination among viruses circulating in different species of *Rhinolophus* bats in the limestone caves of South China and Southeast Asia.

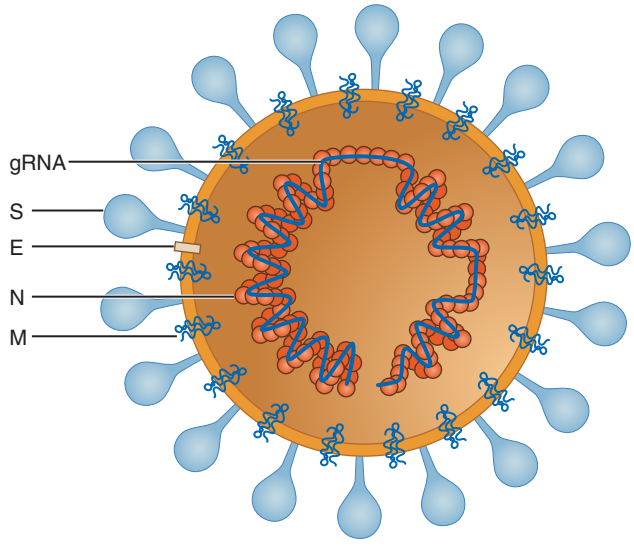

FIGURE 335-2. Schematic drawing of severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2) viral particle. The viral spike (S), membrane (M) protein, and envelope (E) proteins are shown embedded in the viral membrane. The viral RNA genome is shown as a blue line coated with orange nucleocapsid (N) protein. (Modified from https://www.cell.com/cell/fulltext/S0092-8674(20)30406-2#gr1.)

SARS-CoV-2 INFECTION OF CELLS

SARS-CoV-2 initiates infection of cells when the S protein binds to the cell receptor ACE2. This same cell protein also serves as a receptor for SARS-CoV and HCoV-NL63. The S protein is functionally divided into two parts, S1 and S2, which are separated by a protease cleavage site (Fig. 335-3). A feature of the SARS-CoV-2 S protein is the presence of a polybasic cleavage site (PRRAR) near the S1-S2 boundary (Fig. 335-4). This cleavage site allows processing by furins and enhances infectivity. A furin cleavage site has not been identified in betacoronaviruses but is present in other human coronaviruses such as HCoV-HKU1, HCoV-OC43, and MERS-CoV. The receptor-binding domain is located in S1, whereas the fusion peptide, which drives fusion of the viral and cell membranes, is located in S2. In cells of the respiratory tract, the plasma membrane protease TMPRSS2 cleaves S into its S1 and S2 subunits. After S has been proteolytically cleaved, the S1 subunit falls away. Upon the attachment of the receptor-binding domain to ACE2, the conformation of S2 changes to thrust the fusion peptide into the cell membrane. Consequently, fusion of viral and cell membranes occurs at the cell surface.

In cells that lack TMPRSS2, fusion does not occur at the plasma membrane but occurs instead from within endosomes, where cleavage of the S protein is carried out by endosomal cathepsins. These proteases are activated by low pH within endosomes, thereby explaining why hydroxychloroquine, which prevents acidification of endosomes, can block SARS-CoV-2 reproduction in kidney cells. However, hydroxychloroquine has no effect on viral reproduction in the respiratory tract because entry in these cells occurs at the plasma membrane.

Once the SARS-CoV-2 genome is released into the cytoplasm, it is engaged by ribosomes, and the ORF1a and ORF1b open reading frames are translated to form two polyproteins (see Fig. 335-3). These polyproteins are co-translationally processed by two virus-encoded proteases, PL^{pro} and M^{pro}, to produce the proteins needed for viral RNA synthesis, including the RNA-dependent RNA polymerase (RdRp). Viral RNA synthesis occurs on and within double-membrane vesicles, which are induced by viral proteins. The viral RNA genome is copied to form a full-length (−) RNA, which can be a template to produce full-length (+) RNA or for mRNA synthesis of the subgenomic RNAs that encode the structural proteins and several accessory proteins, which are thought to modulate viral pathogenesis. This latter process occurs by discontinuous synthesis and leads to the formation of multiple subgenomic mRNAs, each encoding a single polypeptide (see Fig. 335-3). Coronavirus RNA synthesis is

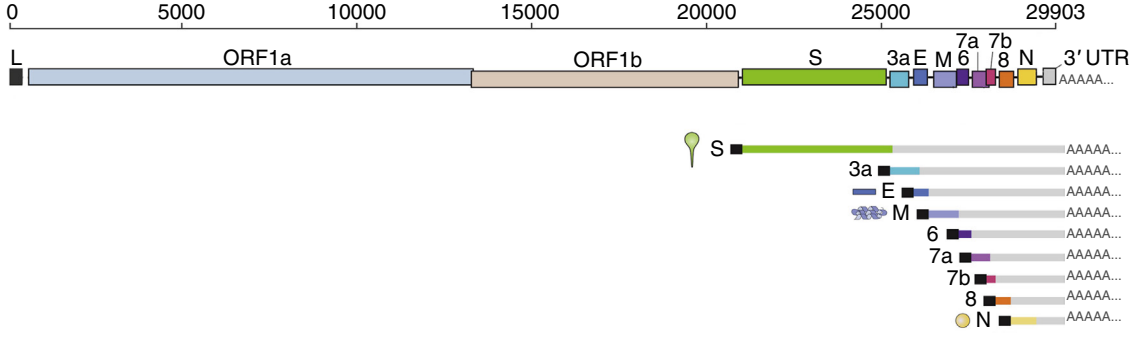

FIGURE 335-3. Open reading frames in the genome of severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2). The 29,903 nt (+) strand RNA is translated to produce polyproteins ORF1a and ORF1b, which are further processed by two virus-encoded proteases to form the viral RNA-dependent RNA polymerase and accessory proteins. The remainder of the viral proteins are translated from nine subgenomic mRNAs encoding S, E, M, N, and other accessory proteins. ORF = open reading frame. (Adapted from https://www.cell.com/cell/fulltext/S0092-8674(20)30406-2#gr1.)

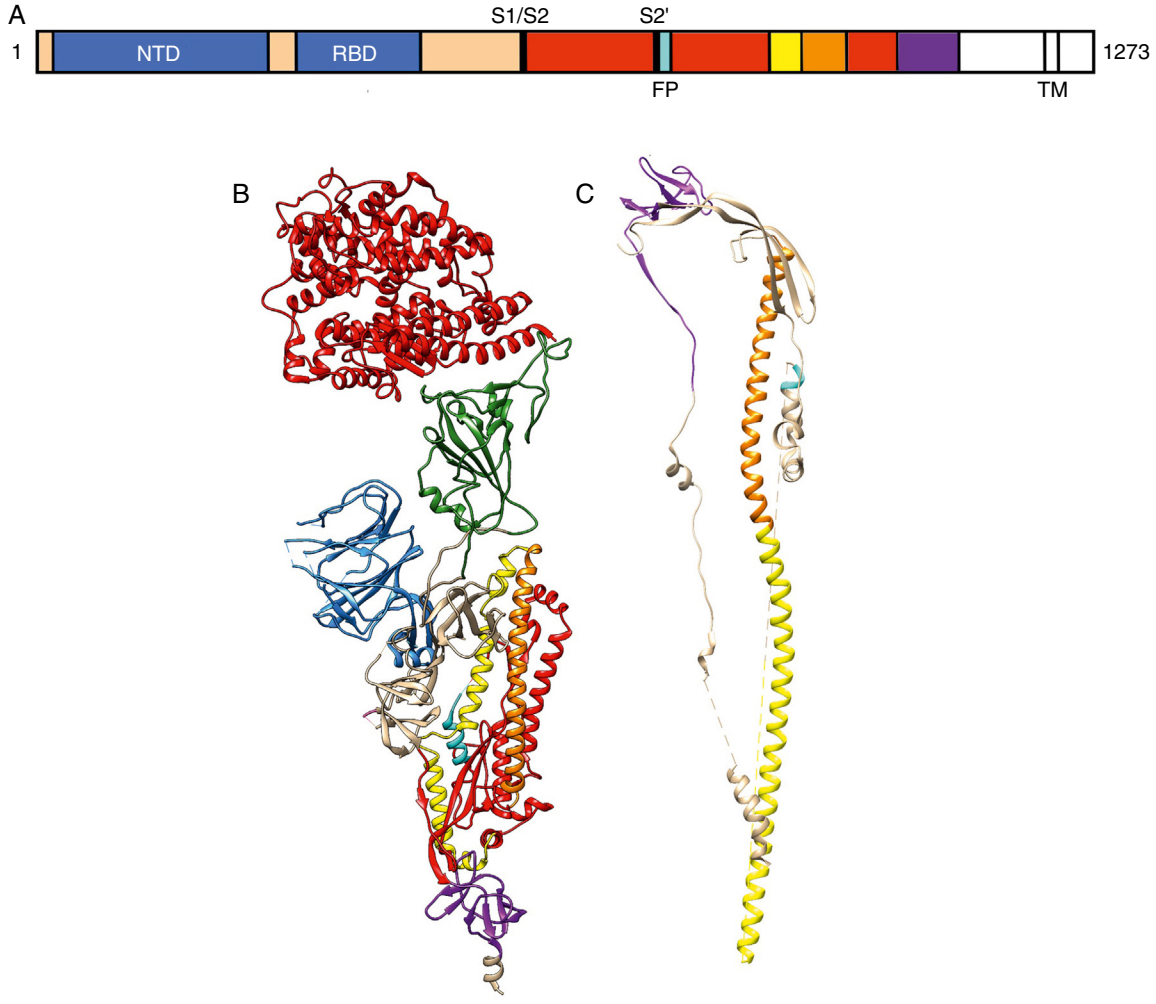

FIGURE 335-4. Functional domains of the severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2) spike protein. The box at the top shows a schematic of the 1273-amino-acid-long S protein. The N-terminal domain (NTD), receptor binding domain (RBD), fusion peptide (FP), S1/S2 and S2′ cleavage sites are labeled. Below are structural models of the S protein monomer in a prefusion state bound to the receptor ACE2 (B) and in a postfusion state (C). Domains of the S protein in (B) and (C) are colored according to the domains shown in (A). (From Protein Data Bank files 7KMS and 6XRA.)

unique among RNA viruses because the genome encodes an error-correcting endonuclease, nsp14 (ExoN), whose presence allows the correction of errors made by the RNA-dependent RNA polymerase and may have permitted the evolution of such long RNA genomes.

Two viral enzymes, RNA-dependent RNA polymerase and the M^{pro} protease, are among the many viral proteins that are targets for experimental antiviral compounds. For example, nirmatrelvir (a protease inhibitor) and molnupiravir (which targets the RNA-dependent RNA polymerase) target those enzymes.

Assembly of new infectious virus begins as the M, S, and E proteins are inserted co-translationally into the endoplasmic reticulum. These proteins then move to the site of viral assembly, which is the endoplasmic reticulum–Golgi intermediate compartment. Nucleocapsids formed by the association of the N protein with (+) viral RNA bud into the endoplasmic reticulum–Golgi intermediate compartment, thereby forming viral particles. Viral particles move to the plasma membrane within smooth-walled vesicles and are released from the cell by exocytosis.

COVID-19

SARS-CoV-2 is transmitted among humans by droplets that are produced by speaking, sneezing, or coughing. Although transmission is mainly associated with small infectious droplets, which fall to the ground within 3 to 5 feet, infection may also be spread more rarely by infectious droplet nuclei, which can remain suspended in the air and travel over 100 feet.[5] Fomites have not been demonstrated to play a role in human-to-human transmission.

Virus-laden droplets are inhaled and lodge in the upper respiratory tract, where the virus attaches to and enters ciliated epithelial cells. The incubation period, defined as the time before the onset of symptoms, ranges from 1 to 14 days (average 5 days). Large quantities of viral RNA can be detected in nasopharyngeal secretions, and expulsion of droplets containing newly synthesized virus is responsible for onward transmission. The peak production of virus in the upper respiratory tract occurs at or shortly before the onset of symptoms.[6] These kinetics, together with the observation that approximately 20% of infections are asymptomatic, contribute to widespread community transmission of the virus. This situation contrasts with SARS-CoV, for which viral shedding peaked after the onset of symptoms when over 50% of patients had already been hospitalized.

After initial reproduction in the upper respiratory tract, virus migrates down the airways, where it may infect alveolar epithelial cells in the lungs.[7] During this symptomatic viral phase, viral RNA loads in the upper respiratory tract decline rapidly, and within 7 days they are typically below the levels associated with transmission. In the lungs, diffuse alveolar injury, exudates, and hyaline membranes are accompanied by endothelial injury with microangiopathy, microthrombosis, and vascular angiogenesis. Lymphocytic myocarditis and pericarditis can also occur. These vascular findings generally distinguish SARS-CoV-2 from what is seen in equivalently sick patients with influenza (Chapter 332).

In some cases, viral reproduction can trigger strong unregulated immune responses (cytokine storm) associated with inflammation-mediated acute lung injury, increases in vascular permeability, thrombosis, disseminated intravascular coagulation (Chapter 161), acute respiratory distress syndrome (Chapter 90), and generalized organ failure. Many patients experience anosmia or ageusia, which appear to be consequences of viral reproduction in sustentacular cells of the olfactory mucosa.[8] Although SARS-CoV-2 infection can lead to signs and symptoms in diverse organ systems (e.g.,

TABLE 335-2 VARIANTS OF SEVERE ACUTE RESPIRATORY SYNDROME CORONAVIRUS-2

KEY VARIANTS	FIRST IDENTIFIED	KEY AMINO ACID CHANGES	EFFECT OF VACCINATION	NEUTRALIZATION BY ANTIBODIES
Alpha (B.1.1.7)	UK September 2020	N501Y, D614G, P681H	Two mRNA vaccine doses protect against severe disease and death	No change
Beta (B.1.351)	South Africa, May 2020	K417N, E484K, N501Y, D614G, A701V	Two mRNA vaccine doses protect against severe disease and death	Reduced in vitro susceptibility to bamlanivimab and etesevimab. Combination of casirivimab and imdevimab retains activity against the variant, as does sotrovimab.
Delta (B.1.617.2)	India, October 2020	L452R, T478K, D614G, P681R	Two mRNA vaccine doses protect against severe disease and death	Six-fold less sensitive to serum neutralizing antibodies from recovered individuals, and eight-fold less sensitive to vaccine-induced antibodies. Resistant to neutralization with bamlanivimab.
Omicron (BA.1, BA.2, BA.4, BA.5)	South Africa, November 2021		Three mRNA vaccine doses protect against severe disease and death	Bebtelovimab and tixagevimab/cilgavimab retain activity against all circulating omicron variants.

mRNA = messenger ribonucleic acid.
Monoclonal antibody data from https://www.covid19treatmentguidelines.nih.gov/tables/variants-and-susceptibility-to-mabs/ and https://www.biorxiv.org/content/10.1101/2022.05.03.490409v1.

central nervous system, circulatory system, kidneys, and gastrointestinal system), there is no convincing evidence that these symptoms are a consequence of viral reproduction. Rather, the cytokine imbalance and hypoxia associated with infection appear to be responsible for pathogenesis outside of the respiratory tract.

THE IMMUNE RESPONSE

The clinical course of COVID-19 ranges from silent infection (40% of cases) to acute respiratory distress syndrome (about 3% of cases) and death (about 1% of cases; Chapter 336). Severe COVID-19 is characterized by persistent lung infection and inflammatory cytokine production. The strongest epidemiologic predictor of death is age (Chapter 337), with risk doubling every 5 years.[9] Type I interferon (IFN) is essential for protective immunity, and an early interferon response likely occurs in the majority of patients who rapidly clear infection.[10] Patients who have inborn errors in the genes that comprise the interferon system develop lethal disease. In addition, multiple lines of evidence indicate that autoantibodies against type I interferon are strong determinants of COVID-19 death.[11] Another cause of severe disease is SARS-CoV-2 replication in lung-resident macrophages.[12] In response to infection, these cells activate inflammasomes, release the proinflammatory cytokines IL-1 and IL-18, and undergo pyroptosis, which contributes to the hyperinflammatory state of the lung[13]

VARIANTS OF CONCERN

SARS-CoV-2 variants of concern are more fit than variants that they displace in the population.[14] Viral fitness can be influenced by many factors, including the intrinsic transmissibility of the virus, its resistance to antibodies, its speed of replication, the yield of infectious virus from individual cells, and its stability in aerosols. Understanding which of these properties is responsible for the emergence of variants of concern in a population cannot be determined by epidemiologic observations, but studies in cell culture and in animal models may provide some information on what makes a particular variant more fit than others. An important issue is whether new variants of concern can be controlled by preexisting vaccines or monoclonal antibodies.

Early in 2020, a SARS-CoV-2 variant with a single amino acid change from aspartic acid to glycine (D614) at position 614 of the S protein of SARS-CoV-2 emerged and eventually was detected in isolates from all parts of the world. Laboratory and epidemiological data suggested that this new variant was inherently more transmissible than the ancestral isolate, but it is not possible to exclude a human founder effect (i.e., that the virus was simply in the right place at the right time).[15]

Later in 2020, other SARS-CoV-2 variants emerged in different locations around the world and often became the dominant local virus (Table 335-2). For example, the B.1.1.7 (alpha) variant was first observed in the United Kingdom in September 2020 and quickly became the dominant variant. It was subsequently displaced by the B.1.617.2 (delta) variant that had first been detected in India. These and multiple other variants have amino acid changes in the S protein as well as in other viral proteins. Some of the S protein changes impact antibody-mediated neutralization and receptor binding. However, displacement of one variant by another is a consequence of alterations within other viral proteins as well as the S protein.[16]

More recently, the omicron variant became the dominant cause of clinical infection worldwide. This variant of concern was unusual because its genome had more mutations than any other variant. Many of these mutations are in the spike protein gene and lead to 30 amino acid changes, three deletions, and one insertion. These changes account for the increased fitness of this variant and its ability to displace the delta variant. Amino acid changes in the spike protein also result in reduced sensitivity to neutralizing antibodies. Consequently, omicron is able to evade humoral immunity, a property that likely in part accounts for its increased fitness.[17] Whether other changes in omicron proteins, such as in the furin cleavage site, play a role in its increased fitness remains to be determined. Initial reports from South Africa, where omicron was first detected, suggested that this variant was less lethal than the delta variant.[18] However, it is now recognized that although omicron infection may be mild in immune individuals, it is just as lethal as any other SARS-CoV-2 in unvaccinated or immunocompromised patients.[19] Omicron has subsequently further evolved to other subvariants, with BA.4 and then BA.5 displacing BA.1 due to greater fitness and decreased sensitivity to neutralization by antibodies.

Two doses of COVID-19 vaccines provided strong protection against severe disease and death after infection with the ancestral SARS-CoV-2 and all variants of concern until omicron emerged, after which rates of hospitalization and death began to rise. A third vaccine dose was found to broaden the antibody response to omicron and provide stronger protection against severe disease and death (Chapter 337).[20] However, certain individuals, such as the elderly and individuals with other diseases, continue to be susceptible to severe disease and death after infection. Whether vaccine booster doses comprising BA.4 and BA.5 will enhance protection against severe disease and death after levels of antibodies and T cells have returned to homeostatic levels remains uncertain.

SPILL-BACK INFECTIONS OF WILDLIFE

SARS-CoV-2 infections have been documented in many nonhuman hosts, including dogs, cats, deer, zoo animals (tigers, lions, gorillas), and farmed mink.[21] Such infections are of concern because the animals can become reservoirs of the virus, thereby leading to new infections of humans. The transmission cycle of human-animal-human has been documented among workers on mink farms, but culling of mink has successfully limited infection in this farmed species. However, wild white-tailed deer in the United States have been found to be extensively infected with asymptomatic SARS-CoV-2, thereby establishing this species as the first wild animal reservoir of the virus.[22]

It is likely that other wild animals, such as mice,[23] also can be infected with SARS-CoV-2. Since mice represent 40% of all mammals and bats represent 20%, a vast reservoir of SARS-CoV-2 may be maintained in the wild, and such reservoirs in wildlife would mean that the virus could never be eradicated.

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336 COVID-19: EPIDEMIOLOGY, CLINICAL MANIFESTATIONS, DIAGNOSIS, COMMUNITY PREVENTION, AND PROGNOSIS

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EPIDEMIOLOGY

On December 31, 2019, the World Health Organization (WHO) was informed of a cluster of cases of pneumonia of unknown cause in Wuhan City, Hubei Province, China. On January 9, 2020, a novel coronavirus (named severe acute respiratory syndrome coronavirus-2 [SARS-CoV-2]) was identified in samples obtained from these patients,[1] whose disease is now called coronavirus 2019 (COVID-19). Although the precise source of the COVID-19 pandemic is uncertain, data suggest recombination from several related species in bats in South China (Chapter 335). SARS-CoV-2 likely jumped from a bat to an unknown animal, possibly animals being sold at wet markets to humans in Wuhan, China.[2]

Despite aggressive mitigation strategies, the infection rapidly spread and, on March 11, 2020, the World Health Organization (WHO) declared COVID-19 a global pandemic. Cases have occurred in every country.

As of March 2023, the 1.1 million COVID-19 deaths in the United States represented the second highest number of deaths per capita in the world, trailing only Brazil. Total mortality rates in the United States during the COVID epidemic have been about 20% above expected, with excess deaths higher among non-Hispanic Blacks than among other ethnic groups.[3] Overall, about one-third of the increase in all-cause U.S. deaths during the pandemic have been attributable to increases in non-COVID-19 deaths, from causes such as cardiovascular disease, cancer, Alzheimer disease, and diabetes.

The reported number of cases underestimates the overall burden of COVID-19. Seroprevalence surveys suggest that infections exceed the number of reported cases by approximately 10-fold or more.[4] By March 2023, over 6.9 million deaths worldwide were reported from COVID-19, but COVID-19 deaths are likely underreported in some countries. Moreover, up to 12 million excess deaths occurred worldwide related to other medical problems (e.g., cardiovascular disease, cancer, strokes, and other infectious diseases) not adequately treated during the pandemic as well as from other indirect consequences of the pandemic. Worldwide, these 18 million excess deaths represented about a 15% increase in global deaths.[5]

SARS-CoV-2 does not have features of an eradicable virus, because of the presence of animal reservoirs, because of its transmission from asymptomatic or presymptomatic individuals, and because its symptoms resemble those of other respiratory pathogens. The infection therefore is expected to become endemic, thereby leading to an ongoing need for vaccination and therapeutics.

The United States has the highest absolute number of documented COVID-19 deaths of any country worldwide[6] for multiple reasons, including a relatively low rate of use of available vaccines compared with other countries of similar economic status.[7] Moreover, COVID-19 has disproportionately affected racial and ethnic minority groups in the United States, with Black, Hispanic, and Native American individuals comprising a disproportionately high number of infections and deaths. As in other countries, indigenous populations (American Indian and Alaska Native) have the highest number of per capita COVID deaths in the United States. The factors that explain these disparities include more comorbid conditions, distrust of the medical system, and socioeconomic determinants of health, such as poverty, education, housing inequalities, use of public transportation, types of employment, and access to health care (Chapter 4).[8]

Transmission

SARS-CoV-2 is primarily transmitted directly from person to person through respiratory particles (droplet and, on occasion, aerosol). Transmission principally occurs when respiratory particles containing virus are released when the infected person coughs, sneezes, or talks in close contact (within approximately 6 feet or 2 meters) with an uninfected person. SARS-CoV-2 also can be airborne in enclosed, poorly ventilated spaces.[9] By comparison, COVID-19 acquisition through contact with contaminated surfaces is not thought now to be a major route of infection.[10,11] The virus is shed in stool, but the role of fecal-oral transmission is minimal even though surveillance of wastewater can track the prevalence of COVID.

The risk of transmission is higher among household contacts (above 50%) than among work or social contacts (about 1.3%). For all contacts, prolonged (>30-minute) conversations or closer contacts (e.g., sharing a bedroom or vehicle) markedly increase transmission. Asymptomatic transmission is thought to account for about 20% of all transmissions. Transmission outdoors is much less common due to ventilation. For example, a study in Wuhan, China, showed that just 1 of over 7000 infections was linked to outdoor transmission. Indeed, ventilation has emerged as one of the most important nonpharmaceutical mitigation strategies for COVID-19. Finally, global rates of human infection are somewhat lower when the maximum ambient temperature is above 52° F and when the ultraviolet light index is higher.

It is also possible for humans to transmit SARS-CoV-2 to other mammals, and infection has been documented in about 30 species of animals, including dogs, cats, gorillas, farmed mink, ferrets, hamsters, rabbits, otters, mice, lions, tigers, deer, and other mammals (Chapter 335). However, the risk these infected animals pose to humans is still being investigated.

After exposure, the incubation period for COVID-19 ranges from 2 to 14 days, with about 98% of cases having the onset of symptoms by day 12, and a relatively constant median of 5 days among persons without prior immunity or vaccination.[12] Viral shedding appears to begin about 2 to 3 days before the onset of symptoms, to be greatest in the first week of infection, to be uncommon more than 5 days after the onset of symptoms, and to be very unusual by 10 days after the onset of symptoms in mild-to-moderate disease, 15 days in severely ill or immunocompromised patients, or 2 days after clinical resolution.[13] Vaccination reduces the time of infectivity after a subsequent breakthrough infection, with implications for shortening the period of isolation when vaccinated individuals become infected.[14]

As SARS-CoV-2 has evolved, variants have arisen (Chapter 335). Most changes have little to no impact, but some mutations can change transmissibility, the severity of disease, the performance of diagnostic tests, the efficacy of therapeutics such as monoclonal antibodies, or the effectiveness of public health and social mitigation measures. If a variant demonstrates increased transmissibility, increased virulence, or immune evasion, it is classified as a "variant of concern." The alpha (B.1.1.7), beta (B.1.351), gamma (P.1), delta (B.1.617.2), and omicron (B.1.1.529) variants have been designated as variants of concern, and omicron has a number of subvariants (BA.1, BA.2 [including its offshoot BA.2.12.1], BA.3, BA.4, and BA.5). For example, the delta variant was more transmissible than the alpha variant but equally virulent.[15] The omicron variant is more transmissible than delta but less virulent.[16]

CLINICAL MANIFESTATIONS

Prior to the availability of vaccination, patients with SARS-CoV-2 infection had a wide range of clinical symptoms, from asymptomatic infection to critical illness with respiratory failure and multiorgan dysfunction. As many as 40% of infected patients may be asymptomatic,[17] and the proportion of asymptomatic infections appears to have increased since the advent of vaccines. Importantly, some individuals who are asymptomatic at the time of SARS-CoV-2 detection can subsequently develop symptoms, in which case they should be reclassified as presymptomatic. Persons with asymptomatic and presymptomatic infections are contagious, although not to the extent as those with symptomatic disease.[18] Peak transmission potential is likely to be at the onset of symptoms.

Fever, cough, anosmia, and ageusia are the most common symptoms of COVID-19 (Table 336-1).[19] Other common symptoms include fatigue, myalgias, sore throat, headache, dry cough, nasal congestion, and shortness of breath, with sputum production being rare in the early stages. Some patients may also present with nausea, vomiting, and diarrhea. With omicron variants, lower respiratory tract symptoms have become less common and gastrointestinal symptoms somewhat more common.[20]

Patients who develop symptoms are classified into four categories based on the severity of illness (Fig. 336-1): mild, moderate, severe, and

ABSTRACT

The COVID-19 pandemic that began in Wuhan, China, in December 2019, spread globally to cause an unprecedented number of infections and deaths. SARS-CoV-2, the virus that causes COVID-19, is primarily transmitted directly from person to person through respiratory particles. As SARS-CoV-2 variants have emerged, the transmissibility, clinical severity, and response to therapeutic agents, such as monoclonal antibodies, have been impacted. Prior to the availability of vaccination, patients with SARS-CoV-2 infection had a wide variety of clinical symptoms ranging from asymptomatic infection to respiratory failure with multiorgan dysfunction. The variety, magnitude, duration of symptoms, as well as the prognosis after infection are affected by age, comorbid conditions, prior infection, and vaccination status. The diagnosis of SARS-CoV-2 infection is made by the detection of viral elements by either nucleic acid amplification test or an antigen detection test. Most patients who have had COVID-19 recover completely, but some experience prolonged symptoms or develop long-term effects, a condition known as long-COVID or post-acute sequelae of SARS-CoV-2 (PASC). Prevention is best achieved by both vaccination and nonpharmacologic interventions, such as physical distancing, well-fitted masks, and ventilation.

KEYWORDS

SARS-CoV-2 epidemiology
transmission
diagnosis
prevention

critical. Among unvaccinated adults, approximately 40% have asymptomatic infection or a mild illness, defined by the presence of symptoms but the absence of hypoxia (oxygen saturation >94%) or pneumonia; 40% have moderate illness, defined by the absence of hypoxia but with evidence of lower respiratory disease based on clinical or imaging findings; 15% have severe illness, based on clinical or radiographic criteria; and 5% have critical illness, defined by the presence of respiratory failure, shock, and/or multiorgan dysfunction.

The variety, magnitude, and duration of symptoms are affected by age, comorbid conditions, prior infection, and vaccination status. Age is the most significant risk factor for progressing to severe illness, with patients over age 65 years having the highest risk. Important comorbid conditions that are more common with aging and that predispose one to severe disease and mortality include diabetes, obesity, cardiovascular disease, renal disease, chronic lung disease, and sickle cell disease. Patients who are transplant recipients, have cancer or HIV infection, or are receiving immunosuppressive therapy have defects in host defense that increase the risk of severe COVID-19. In addition, pregnant women are at increased risk for progression of infection and adverse fetal outcomes. Being unvaccinated is also a significant risk factor for severe illness (Chapter 337),[21] so at-risk groups should be prioritized for booster vaccinations, monitored closely, and prioritized for early treatment.

Extrapulmonary manifestations can affect nearly every organ.[22] Cardiac complications include thrombosis, myocardial infarction, mild to severe myocarditis[23] (in about 2% of healthy young patients), and arrhythmias. Neurologic complications can include myoclonus, seizures, delirium, and encephalitis. Loss of taste and smell appear to be locally mediated in the upper respiratory tract and not reflective of brain involvement. Renal damage is common, with about one third of the patients who require mechanical ventilation also requiring renal dialysis. Skin lesions can include maculopapular eruptions, urticarial lesions, and vesicles. Of hospitalized patients, about 15% require intensive care, about 12% require mechanical ventilation, and about 3 to 4% require renal dialysis. The severity of infections has decreased markedly with the advent of vaccinations, as well as inpatient and outpatient treatments (including remdesivir, anti-inflammatory medication, monoclonal antibodies, and antiviral agents).

TABLE 336-1 SYMPTOMS OF COVID-19 IN SYMPTOMATIC CASES

	APPROXIMATE % OF PATIENTS
Fever	70-90
Dry cough	60-85
Dyspnea	50-80
Changes in taste or smell	40-80
Fatigue	40-60
Gastrointestinal symptoms*	15-60
Myalgias	15-45
Chills	15-30
Headache	10-20
Sore throat	10-20
Rhinorrhea	5-10

*Including nausea, vomiting, diarrhea.
COVID-19 = coronavirus 19 disease.

DIAGNOSIS

The diagnosis of SARS-CoV-2 infection is made by the detection of viral elements by either a nucleic acid amplification test (NAAT; otherwise known as polymerase chain reaction [PCR] tests) or an antigen detection test.[24,25] Samples for testing can be collected from the nasopharynx, the anterior nares or mid-turbinate, oropharynx, and saliva. Estimates of sensitivity range from 80% to more than 95%, with false-negative tests more common before the onset of symptoms; test specificity is about 99%. Antigen-based testing is less sensitive than NAAT. For example, the rate of false-positive rapid antigen tests in one study of asymptomatic employees in a mass screening program was high (62%), but repeat testing significantly increased their sensitivity and specificity.[26,27] At-home testing kits using antigen-based testing are also available, although instructions must be followed to increase accuracy. Finally, patients who have recovered from COVID-19 may continue to shed inactive viral particles up to 90 days. Since inactive viral particles are not infectious, the U.S. Centers for Disease Control and Prevention (CDC) recommends a 5-day period of isolation after the onset of symptoms, but isolation can end without the need for repeat antigen or PCR testing if symptoms resolve.

The sensitivity and specificity of these tests also vary dramatically during the course of infection because of the concentration of viral material in the sample (Fig. 336-2). PCR can detect SARS-CoV-2 RNA for many days or even weeks after the person has recovered and is no longer infectious. For that reason, PCR should not be repeated in asymptomatic persons within 90 days of a confirmed SARS-CoV-2 infection. Since these tests do report replication-competent (viable) virus required for transmission, a positive rapid antigen test correlates with culture positivity only about 50% of the time, although a high PCR copy number reflected in a low number of cycles for detection (i.e., <30) is more likely to correlate with both a positive antigen test and the potential for SARS-CoV-2 transmission. However, since PCR cycles usually are not reported in a routine PCR test, the CDC recommends that isolation be guided by the maximum period of transmission (e.g., 5 days after the onset of symptoms).

Serologic tests, which can detect past infection or vaccination status, are of two types: tests that detect binding antibodies and tests that detect neutralizing antibodies. However, serologic testing is still not commercially available to measure neutralizing antibodies. In addition, serologic tests can detect IgM, IgG, IgA, or total antibodies, as well as IgG subclasses. Spike protein IgG can indicate either past infection or vaccination, whereas nucleocapsid IgG positivity is indicative of past infection since the current spike protein vaccines do not trigger this antibody. Antibody testing is not recommended for the diagnosis of acute infection but can be useful in confirming past infection when anti-nucleocapsid antibodies and anti-spike antibodies are detected. For example, a large U.S. seroprevalence survey

	Stage	Characteristics
	Asymptomatic/ presymptomatic infection	• Positive test for SARS-CoV-2 but no symptoms
~80%	Mild illness	• Varied symptoms (e.g., fever, cough, sore throat, taste/smell disturbance) but no shortness of breath or abnormal imaging
~80%	Moderate illness	• Spo_2 ≥94% and lower respiratory disease (clinical or imaging findings)
~15%	Severe illness	• Spo_2 <94%, Pao_2/Fio_2 <300, respiratory rate >30/min, or lung infiltrates >50%
~5%	Critical illness	• Respiratory failure, shock, and/or multiorgan dysfunction

FIGURE 336-1. COVID-19 clinical spectrum. SARS-CoV-2 = severe acute respiratory syndrome coronavirus-2. (Sources: Wu Z, McGoogan JM. Characteristics of and important lessons from the coronavirus disease 2019 [COVID-19] outbreak in China: summary of a report of 72 314 cases from the Chinese Center for Disease Control and Prevention. *JAMA*. 2020;323:1239-1242; and National Institutes of Health. NIH COVID-19 treatment guidelines. Clinical spectrum of SARS-CoV-2 infection. www.covid19treatmentguidelines.nih.gov/overview/clinical-spectrum/. Accessed April 25, 2022.)

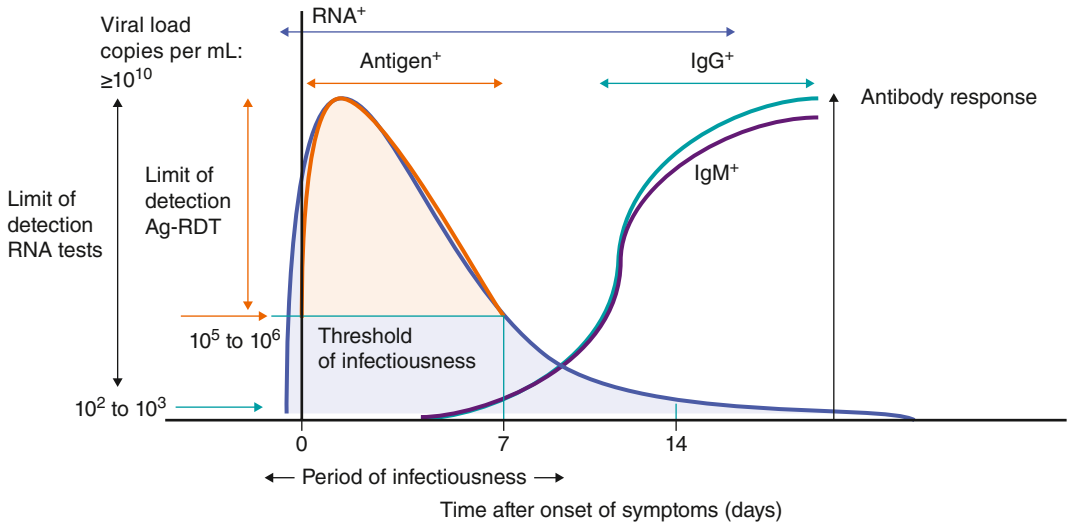

FIGURE 336-2. Timelines for optimal use of different tests for COVID-19 detection and host response. Antigen levels peak before day 4 and typically are undetectable by day 7, whereas antibody levels may not be detectable until about day 10. RNA, which is detectable by polymerase chain reaction testing, is more sensitive and long-lasting than is the detection of antigen. Ag-RDT = antigen-rapid detection test; Ig = immunoglobulin. (From Peeling RW, Heymann DL, Teo Y-Y, et al. Diagnostics for COVID-19: moving from pandemic response to control. *Lancet*. 2022;399:757-768.)

showed that almost 60% of adults and 75% of children under age 18 years had been exposed to the virus by February 2022.[28] However, serologic testing is not recommended to determine if a person is immune to SARS-CoV-2, either after infection or vaccination, because antibody titers may wane for a variety of reasons and do not reflect other potential and important immune responses, especially T-cell–mediated immunity. In addition, a positive test does not ensure immunity against reinfection and may provide a false sense of security.

Initial evaluation of symptomatic patients with SARS-CoV-2 infection and hypoxemia should include a chest radiograph or a computed tomographic (CT) scan to assess for the extent of pulmonary infiltrates. Chest radiographs may be normal in early or mild disease. Common abnormalities include ground-glass opacities and consolidation consistent with viral pneumonia (E-Figs. 72-1 to 72-6). Although chest CT may be more sensitive than plain chest radiography, chest CT is not recommended for screening or diagnosis since its findings can resemble other respiratory pathogens.[29]

Laboratory examination should include a complete blood count with differential and a metabolic profile. The measurement of serum levels of inflammatory markers (e.g., C-reactive protein, D-dimer, and ferritin) may have prognostic and therapeutic value and can be helpful in hospitalized patients at high risk of progression.[30] Common laboratory findings include lymphopenia, elevated aminotransferase levels, and elevated lactate dehydrogenase levels. Diagnostic tests such as a D-dimer test may be used to exclude deep venous thrombosis or pulmonary emboli, since clots have been an important consequence of severe SARS-CoV-2 infection.[31]

PROGNOSIS

In the first COVID-19 surge caused by the ancestral (Wuhan) strain in the pre-vaccine era, the infection fatality rate was under 1% for persons under age 65 years but increased to 15% for persons aged 85 years and older.[32] The severity of the infection has evolved as variants have appeared and as vaccinations have become available. With vaccination, the risk of hospitalization, critical illness, and death from COVID-19 is significantly decreased. For example, unvaccinated persons over age 65 years are 3.4 times more likely to be hospitalized with COVID-19 and 4.3 times more likely to die of COVID-19 than are vaccinated persons of the same age. The risk of hospitalization and mortality also have been lower with recent omicron variants than with earlier variants due to its inherently lower virulence.[33]

After recovering from COVID-19, most individuals have several months of protection from repeat infection. However, reinfection with SARS-CoV-2 has been increasingly reported,[34] either due to waning antibodies or the emergence of new variants against which antibodies do not work as well. Infections that overwhelm vaccination are referred to as breakthrough events. Reinfection and breakthrough infections have a much lower chance of progressing to hospitalization or death compared with primary infection or infection in those who remain unvaccinated.[35] For example, in a large analysis of over 1.2 million adults who completed primary vaccination by October 2021, the rate of severe COVID-19 breakthrough was 0.015% and the rate of COVID-19 death after a breakthrough was 0.0033%. Risk factors for severe outcome included over age 65 years, being immunosuppressed, and having four or more underlying comorbid conditions. These data have guided the public health community to target persons at risk of severe breakthroughs for booster vaccination and, if infected, for SARS-CoV-2 prophylaxis (e.g., with monoclonal antibodies) and antiviral treatment.

Most patients who have had COVID-19 recover completely,[36] but some patients experience prolonged symptoms or develop long-term effects.[37,38] This condition, which had been called long COVID, is now formally named post-acute sequelae of SARS-CoV-2 (PASC). The WHO defines PASC as symptoms that persist for at least 2 months after resolution of probable or confirmed acute SARS-CoV-2 infection (i.e., usually 3 months after the onset of COVID-19) and that cannot be explained by an alternative diagnosis. The CDC, by comparison, defines PASC as new, returning, or ongoing health problems 4 or more weeks after first being infected with SARS-CoV-2. Although PASC may be more common in patients who have severe COVID-19, even mild illness can lead to PASC. Risk factors for developing post-acute sequelae of SARS-CoV-2 include type 2 diabetes, SARS-CoV-2 RNAemia, and concomitant infections such as Epstein-Barr virus viremia[39] but not inflammatory markers or autoantibodies.[40] The most common symptoms include fatigue, headaches, attention disorders, anosmia, ageusia, loss of hair, persistent cough, chest pain, and memory loss.[41-43] Data suggest vaccination decreases the risk of long COVID.

COMMUNITY PREVENTION OF SARS-COV-2

As with other infectious diseases, SARS-CoV-2 prevention is best achieved by both vaccination (Chapter 337) and nonpharmacologic interventions. Prior to the availability of vaccines and monoclonal antibodies (for those who cannot respond to a vaccine), the safest behaviors include use of physical distancing, well-fitting masks, ventilation, and avoidance of indoor gatherings.[44-47] Observational data suggest that distancing at 1 meter reduces the risk of an infection by about 80%, with protection increasing as the distance is lengthened. Disposable surgical masks reduce infection by more than cloth masks, and N95, KN95, FFP2, or KF94 masks reduce the risk even more, with one-way masking serving as a form of self-protection.[48] Proper indoor air ventilation is an important mitigation procedure for SARS-CoV-2 and other respiratory pathogens.[49]

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337 COVID-19 TREATMENT AND VACCINATION

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TREATMENT OF INFECTED PERSONS

GENERAL PRINCIPLES

The approach to treating coronavirus-2019 disease (COVID-19) must first consider the severity of the patient's disease, which can range from mild to moderate respiratory or systemic symptoms, to severe disease (i.e., dyspnea, tachypnea, and hypoxia), to critical illness (i.e., respiratory failure, shock, and/or multiorgan failure; see Fig. 336-1). The second consideration is the phase of illness. The third consideration is the type of intervention: antiviral therapy, immunomodulatory medications, combination therapy, and therapies directed at preventing or treating complications, such as thrombosis.

Overview of Treatment

The pathogenesis that drives the different phases of the illness also informs treatment decisions (Fig. 337-1).[1] Viral replication is most active early in disease, whereas excess inflammation occurs later in the course of disease. Regardless of the phase of illness, it is safe to continue angiotensin-converting enzyme 2 (ACE2) inhibitors, angiotensin-receptor blockers, and therapeutic nonsteroidal anti-inflammatory drugs.

OUTPATIENTS WITH MILD TO MODERATE COVID-19

Most patients with mild to moderate COVID-19 will recover with supportive care, such as hydration, antipyretics, and analgesics.[2] However, close monitoring for clinical worsening is mandatory, particularly for patients who are at increased risk for progression, such as patients who are older, who have certain chronic conditions (e.g., cardiovascular disease, chronic lung disease, obesity, immunocompromising conditions), or who are taking immunosuppressive medications. Worsening shortness of breath, which typically occurs about 1 week after the onset of symptoms, or other severe or progressive symptoms should prompt in-person evaluation. Patients with COVID-19 may deteriorate rapidly, and hospitalization is indicated for monitoring and treatment if patients develop progressive dyspnea, weakness, lethargy, or confusion or if they become tachypneic or hypoxic or have a markedly abnormal chest radiograph.

Anti–SARS-CoV-2 Monoclonal Antibodies and Passive Immunity

Passive immunity can be induced by monoclonal antibodies that bind to the SARS-CoV-2 spike protein, block viral entry into cells, and thereby reduce replication. Monoclonal antibodies can result in more rapid viral clearance and reduce rates of hospitalization or death by approximately 70 to 85% when given within a few days of the onset of symptoms[A1–A3] to outpatients who have mild to moderate COVID-19 and are at high risk for progression (see Fig. 337-1), provided that they are infected with susceptible viral variants. However, antibodies that were successful against earlier SARS CoV-2 variants have less activity against newer variants; as a result of changing variants, anti–SARS-CoV-2 monoclonal antibodies are currently not authorized for treatment or prophylaxis in the United States. The decision to use antibodies and the doses among them should be guided by data on current variants and their susceptibility.

Convalescent plasma, which is derived from patients who previously have been infected, has shown mixed results. In one study, it reduced the risk of hospitalization in unvaccinated outpatients treated with 8 days of symptoms,[A4] but other studies showed no benefit.[A5] Currently it is authorized for use in immunocompromised individuals, but it should only be considered if the plasma is likely be active against the circulating variant.

Antiviral Medications

Antiviral medications are useful in high-risk patients who are early in their disease course (Fig. 337-2). However, none of the available drugs are currently authorized for lower risk patients.

Molnupiravir, which is an oral inhibitor of SARS-CoV-2 replication, induces mutations that compromise the virus's viability. In nonhospitalized adults who have had 5 or fewer days of mild or moderate COVID-19 symptoms plus at least one risk factor for developing severe COVID-19, molnupiravir (800 mg twice daily for 5 days) reduces the risk of hospitalization or death by about 30%.[A6] To date, the drug appears to be active against all variants, at least through Omicron.

Nirmatrelvir is an oral protease inhibitor that is coadministered with ritonavir to boost its blood level by inhibiting its metabolism by the cytochrome P-450 system. In unvaccinated nonhospitalized patients who have COVID-19 with a high risk of clinical progression and who are treated within 5 days of the onset of symptoms, nirmatrelvir/ritonavir can reduce the risk of hospitalization or death by about 90%.[A7]

Remdesivir, which is a nucleotide pro-drug, binds to the SARS-CoV-2 RNA polymerase, acts as a chain terminator, and thereby inhibits RNA synthesis and viral replication. In high-risk nonhospitalized patients treated within 7 days of the onset of symptoms, remdesivir (200 mg on day 1 and 100 mg on days 2 and 3) for 3 days can reduce hospitalization by 87%, even though it does not reduce nasopharyngeal SARS-CoV-2 levels.[A8]

Currently nirmatrelvir/ritonavir is typically the first choice in most high-risk patients. In a patient who cannot receive nirmatrelvir/ritonavir because of drug-drug interactions, remdesivir is usually the second choice. When remdesivir is not feasible or appropriate, molnupiravir should be considered.

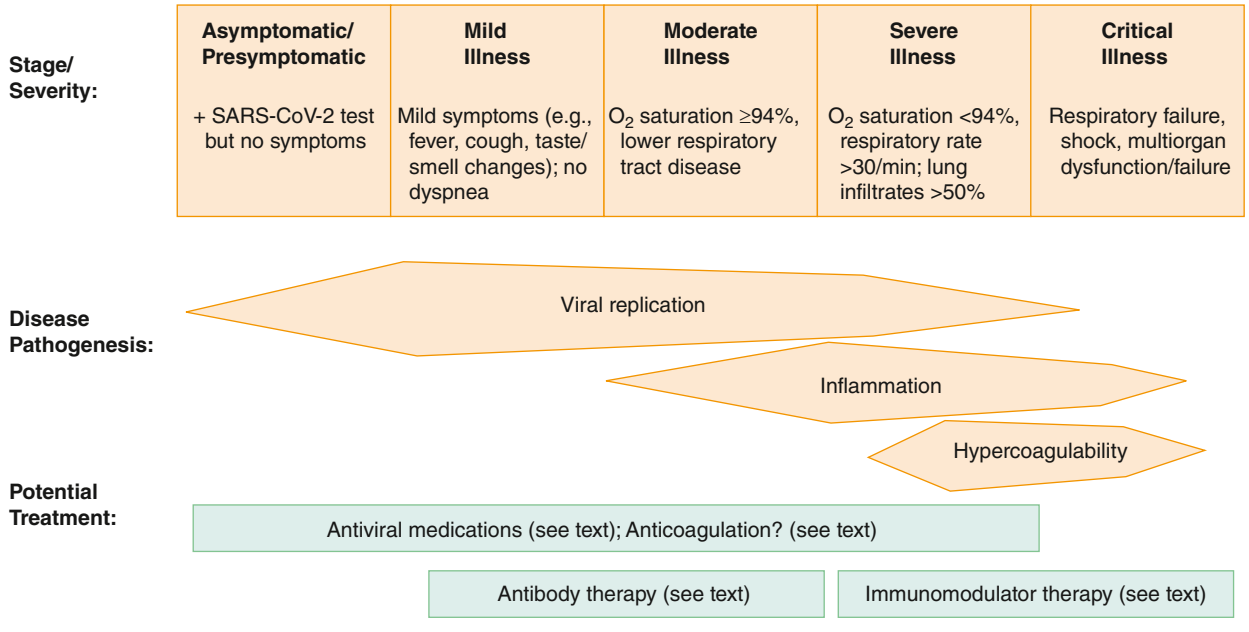

FIGURE 337-1. **Disease pathogenesis and treatment across the COVID-19 disease spectrum.** O_2 = oxygen; SARS-CoV-2 = severe acute respiratory syndrome coronavirus-2. (Adapted from Gandhi RT, Lynch JB, del Rio C. Mild or moderate Covid-19. *N Engl J Med*. 2020;383:1757-1766.)

ABSTRACT

Treatment for COVID-19 depends on the severity of the infection, the patient's characteristics, and the phase of illness. For nonhospitalized patients at high risk of progression soon after the onset of symptoms, several antiviral medications are efficacious. For patients who are hospitalized with COVID-19 and who require oxygen support, immunomodulators are the mainstay of therapy. Anticoagulation is indicated for some patients with severe COVID-19. Safe, immunogenic, and efficacious COVID-19 vaccines are approved for persons ages 6 months and older, with vaccine schedules differing by age and risk groups. Newer bivalent vaccines that contain the original and a variant strain are recommended for persons ages 5 years and older. Vaccine formulations and recommendations for use will continue to evolve over time.

KEYWORDS

COVID-19
treatment
vaccines
prevention
antivirals

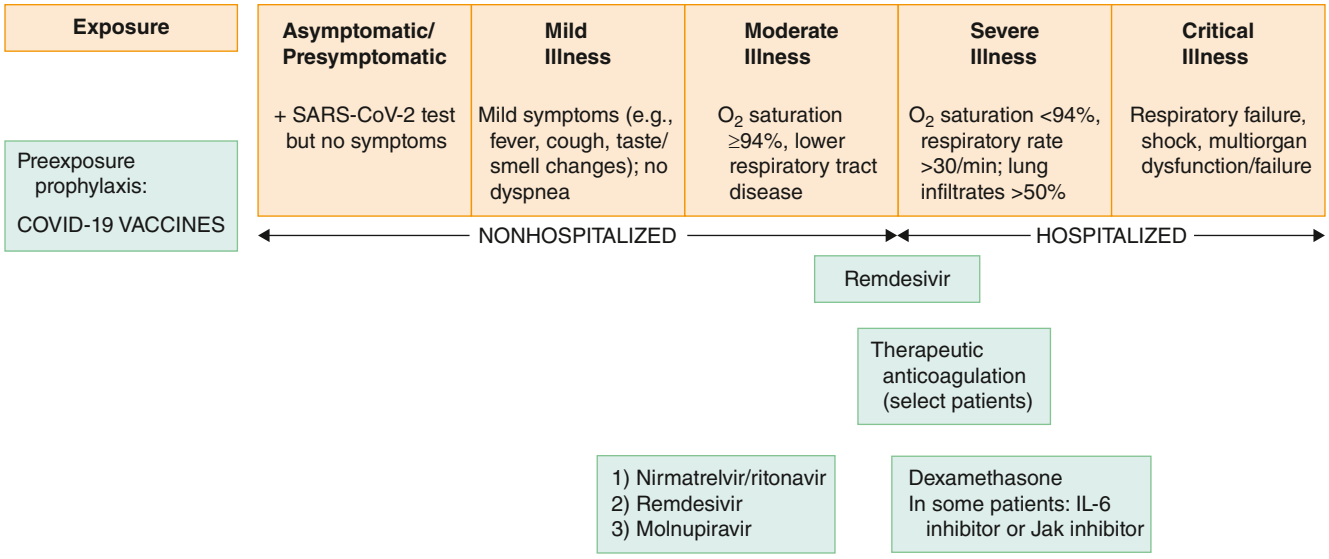

FIGURE 337-2. Approach to treatment based on severity of illness. COVID-19 = coronavirus 2019 disease; IL-6 = interleukin-6; JAK = Janus kinase; SARS-CoV-2 = severe acute respiratory syndrome coronavirus-2. (Adapted from Gandhi RT, Lynch JB, del Rio C. Mild or moderate Covid-19. *N Engl J Med*. 2020;383:1757-1766.)

Other Outpatient Medications

The role of other therapies, such as inhaled budesonide (800 μg twice daily for 14 days)[A9] and fluvoxamine, is uncertain. Ivermectin has not been shown to be of benefit. Neither anti-platelet therapy with aspirin nor anticoagulant therapy with apixaban is recommended in outpatients who do not have other indications for their use.

TREATMENT OF HOSPITALIZED PATIENTS WITH SEVERE OR CRITICAL COVID-19

Hospitalized patients with COVID-19 benefit from selected medications and from careful attention to oxygenation, intensive care, and organ support.[3] Clinicians should follow the latest guidelines (see https://www.covid19treatmentguidelines.nih.gov/about-the-guidelines/whats-new/ and https://www.idsociety.org/practice-guideline/covid-19-guideline-treatment-and-management/).

Medications

Antiviral Medications

Remdesivir (200-mg infusion on day 1 followed by a 100-mg infusion daily) appears to speed the time to recovery and improve outcomes, at least when given within 10 days of the onset of symptoms to patients who require supplemental oxygen but who are not yet intubated.[A10] Five days of therapy is as good a 10-day course. However, studies suggest that the mortality benefit of remdesivir in hospitalized paatients with COVID-19 is small and limited to patients who are not initially ventilated.[A11] Currently, guidelines in some countries, such as the United States,[4] recommend the use of remdesivir in patients with severe COVID-19 because it can hasten clinical recovery. The World Health Organization guidelines also recommend the use of remdesivir.[5]

Corticosteroids

Dexamethasone (6 mg/day, orally or intravenously, for up to 10 days or until hospital discharge if sooner) reduces mortality in hospitalized patients who require supplemental oxygen but not mechanical ventilation by nearly 20% and in patients who require mechanical ventilation by about 35%.[A12] However, it is not beneficial and may harm patients who do not require oxygen. As a result, it is recommended in all patients who require oxygen therapy but not in other patients. If dexamethasone is not available, prednisone (40 mg/day), methylprednisolone (32 mg/day), or hydrocortisone (160 mg/day) may be used.[A13]

Other Anti-Inflammatory Agents

Elevated interleukin (IL)-6 levels are associated with worse outcomes in patients with COVID-19, and IL-6 blockade with tocilizumab (8 mg/kg, up to 800 mg, intravenous infusion given once or twice in adults) reduces in-hospital mortality by about 15% in patients who are rapidly deteriorating, have excess inflammation, and are receiving corticosteroids.[A14] As a result, tocilizumab is recommended in combination with corticosteroids for recently hospitalized patients who have progressive COVID-19, rapidly worsening hypoxia, and evidence of excess inflammation or who have just been transferred to the intensive care unit. Sarilumab, another IL-6 blocker, also appears to confer benefit, although the data are more limited.[A15] IL-6 blockers should be used with caution or avoided in patients who are significantly immunosuppressed, are at high risk for gastrointestinal perforation, or who have uncontrolled serious infections other than COVID-19.

Janus kinase inhibitors reduce inflammation by reducing the production of cytokines. The Janus kinase inhibitors baricitinib (4 mg/day orally for up to 14 days or until hospital discharge)[A16] and tofacitinib (10 mg orally twice daily for up to 14 days or until hospital discharge)[A17] improve outcomes in patients who are hospitalized with COVID-19 pneumonia when added to corticosteroids. In one study, for example, baricitnib reduced mortality by day 28 by about 40% in hospitalized patients with COVID-19 pneumonia and elevation of one or more inflammatory markers (e.g., levels of C-reactive protein, D-dimer, lactate dehydrogenase, or ferritin).

Guidelines for Combined Antiviral and Anti-Inflammatory Therapies

Current guidelines recommend remdesivir plus dexamethasone in hospitalized COVID-19 patients who require supplemental oxygen but not mechanical ventilation. In a patient who requires only minimal amounts of oxygen, remdesivir alone may be used.

In hospitalized patients with progressive COVID-19, escalating oxygen requirements, rapidly worsening hypoxia, and evidence of excess inflammation or in patients who have just been transferred to an intensive care unit, augmented immunomodulation should combine dexamethasone with either an IL-6 antagonist (e.g., tocilizumab or, if unavailable, sarilumab) or a Janus kinase inhibitor (baricitinib or, if unavailable, tofacitinib). IL-6 antagonists have not been compared against Janus kinase inhibitors.

Passive Immunity

Monoclonal antibodies have had mixed success in hospitalized patients with COVID-19, even when they effectively target the viral variant. In one study, monoclonal antibodies were associated with clinical benefit in hospitalized patients who had not developed an endogenous antibody response as evidenced by their being seronegative for antispike protein antibodies.[A18] However, current variants are not expected to be susceptible to anti–SARS-CoV-2 monoclonal anitbodies, so antibodies are not being used at this time. Neither convalescent serum nor hyperimmune globulin is beneficial in unselected inpatients.

Anticoagulation

Because of the high rate of arterial and venous large vessel and microvascular thrombosis in hospitalized patients with COVID-19,[6] prophylactic anticoagulation with low-molecular-weight heparin is recommended (see Table 70-2),[7] unless contraindicated because of ongoing bleeding or severe thrombocytopenia. Anticoagulation with therapeutic doses of heparin is considered only in the subset of patients who are hospitalized with COVID-19 pneumonia, require conventional oxygen therapy, have elevated D-dimer levels, and are not at increased risk for bleeding.

Other Medications

Hydroxychloroquine, azithromycin, colchicine, interferon-β, and lopinavir/ritonavir are ineffective in hospitalized patients. Ivermectin has not been shown to

TABLE 337-1 CHARACTERISTICS OF COVID-19 VACCINES AUTHORIZED FOR USE IN THE UNITED STATES AND SPECIFIC VACCINE RECOMMENDATIONS, JULY 2022

	PFIZER-BIONTECH mRNA	MODERNA mRNA	JANSSEN AD26 VECTOR	NOVAVAX PROTEIN
Vaccine type	mRNA	mRNA	Adenovirus vector	Adjuvanted protein subunit
Target protein	Prefusion stabilized full- length S glycoprotein	Prefusion stabilized full-length S glycoprotein	Prefusion stabilized full-length S glycoprotein	Prefusion stabilized full-length S glycoprotein
Age indications	≥6 months	≥6 months	≥18 years	≥12 years
Dose	30 μg for age ≥12 years (primary series and booster) 10 μg for age 5-11 years (primary series and booster) 3 μg for age 6 months through 4 years (three-dose primary series)	100 μg primary series for ≥12 years 50 μg booster dose for ≥18 years 50 μg primary series for age 6-11 years 25 μg primary series for 6 months through 5 years (two-dose primary series)	5×10^{10} viral particles (0.5 mL)	5 μg antigen + 50 μg Matrix-M adjuvant
Dosage	0.3 mL	0.5 mL	0.5 mL	0.5 mL
Number of doses, interval, primary series	Ages 5 and over: two doses, 3-8 weeks apart Ages 6 months through 4 years: three doses, 3-8 weeks apart for doses 1 to 2 and at least 8 weeks for doses 2 to 3	Ages 6 months and older: two doses, 4-8 weeks apart	One dose	Two doses, 3-8 weeks apart
Adults who are moderately or severely immunocompromised persons	Three-dose primary series and mRNA booster doses	Three-dose primary series and mRNA booster doses	Two-dose primary series and mRNA booster doses	Two doses, 3 weeks apart and mRNA booster doses
Interval between primary and booster doses, adults	At least 5 calendar months after completing the primary series		At least 8 weeks after the first dose	Not approved for booster dose
Bivalent booster dose **should** be administered to:	All persons age 5 years and older		n/a	n/a
Interval between monovalent and bivalent booster dose	At least 2 calendar months after primary series or monovalent booster dose		n/a	n/a
Coadministration with other vaccines	COVID-19 vaccine and other vaccines may be administered on the same day, as well as any interval without respect to timing.			
Person with prior or current COVID-19	COVID-19 vaccines can be given safely to people with prior SARS-CoV-2 infection. Defer vaccination until person has recovered from the acute illness and criteria have been met for them to discontinue isolation.			
Persons who received monoclonal antibodies or convalescent plasma for COVID-19 treatment	COVID-19 vaccination can be given at any interval following receipt of passive antibody therapy. Persons should wait 2 weeks after COVID-19 vaccination before receiving tixagevimab/cilgavimab for preexposure prophylaxis.			
Interchangeability of primary series	The same vaccine product should be used for all doses in the primary series. If mixed primary series is inadvertently administered, the series is complete and doses do not need to be repeated. mRNA vaccines (Moderna, Pfizer-BioNTech) are preferred in most situations over the Janssen COVID-19 vaccine. Primary series and additional primary doses (for moderately and severely compromised people) should be with the same mRNA vaccine product. In exceptional situations, such as a contraindication to a second dose of mRNA vaccine or when a previous dose product cannot be determined or is not available, another FDA-approved or FDA-authorized COVID-19 vaccine may be used			

COVID = coronavirus disease; FDA = U.S. Food and Drug Administration; mRNA = messenger RNA; SARS-CoV-2 = severe acute respiratory syndrome coronavirus-2.
Adapted from Summary Document for Interim Clinical Considerations for Use of COVID-19 Vaccines Currently Authorized or Approved in the United States–FactSheet (cdc.gov).

confer benefit. Pegylated interferon lambda may reduce the risk of an emergency department visit or hospitalization among vaccinated outpatients who are treated within 7 days after the onset of symptoms [A19] but is currently experimental. Because clinical trials are ongoing, guidelines (https://www.covid19treatmentguidelines.nih.gov/about-the-guidelines/whats-new/ and https://www.idsociety.org/practice-guideline/covid-19-guideline-treatment-and-management/) should be consulted for the latest evidence and recommendations.[8]

General Care

Organ Support during Critical Illness

In addition to pneumonia, COVID-19 is associated with a broad range of complications (Chapter 336), including respiratory failure (Chapter 90), shock (Chapter 92), heart failure (Chapters 45 and 46), acute renal injury (Chapter 106), and hepatic failure (Chapter 140). Management is largely in accord with strategies developed for other critically ill patients. For example, treatment of shock, hypoxemic respiratory failure, and other complications is guided by general principles of critical care. High-flow oxygen therapy through a nasal cannula can significantly reduce the need for mechanical ventilation.[A20] Awake prone positioning may sometimes be useful (https://www.covid19treatmentguidelines.nih.gov/about-the-guidelines/whats-new/).

Other Complications

Coinfection with bacterial, fungal, or other viral pathogens is relatively uncommon with initial COVID-19 infection,[9] so empirical therapy for other infections is generally not warranted. However, sudden respiratory or hemodynamic deterioration, especially in a patient who has been on a ventilator for an extended period of time (Chapter 85), should raise concern about a superimposed bacterial infection or fungal pneumonia (especially aspergillosis [Chapter 311] or mucormycosis [Chapter 312]), acute heart failure, or a pulmonary embolus.

Multisystem Inflammatory Syndrome

Multisystem inflammatory syndrome is a postinflammatory condition that is seen mostly in a small proportion of children who may present with fever, elevated laboratory markers of inflammation, and multisystem organ involvement (e.g., cardiac dysfunction, gastrointestinal symptoms or signs, skin rash, and conjunctival abnormalities). Adults may develop a similar syndrome. Treatment for adults has not been well studied, so recommendations are generally extrapolated from those for children (https://www.covid19treatmentguidelines.nih.gov/management/clinical-management/hospitalized-pediatric-patients--therapeutic-management-of-mis-c/).

PREVENTION

TREATMENT OF CONTACTS OF INFECTED PERSON

Anti–SARS-CoV-2 monoclonal antibodies can prevent symptomatic COVID-19 among persons who are exposed to variants against which the antibodies are effective. Currently, however, existing antibodies for postexposure prophylaxis are not effective against the latest circulating viral variants. Preexposure prophylaxis with the combination of two long-acting anti–SARS-CoV-2 monoclonal antibodies, tixagevimab plus cilgavimab, reduced the incidence of symptomatic COVID-19 by about 80% in unvaccinated individuals.[A21] This combination had been authorized for preexposure prophylaxis in immunocompromised individuals who may not have an adequate immune response to COVID-19 vaccination or in the rare individual who cannot receive a COVID-19 vaccine due to a serious adverse event. However, current viral variants are not expected to be susceptible, and the authorization for these antibodies has been withdrawn.

VACCINATION

Vaccines for SARS-CoV-1 target the S protein, which is a trimeric fusion protein with a metastable prefusion conformation (Table 337-1). Four safe and efficacious COVID-19 vaccines are currently approved in the United States, but these vaccines have not been directly compared against each other.

A two-dose regimen of mRNA vaccines manufactured by Pfizer-BioNTech (3 weeks apart) or Moderna (4 weeks apart) was up to 95% efficacious over the short term against the original SARS-CoV-2 strain for preventing symptomatic, laboratory-confirmed COVID-19 in persons who did not have evidence of previous SARS-CoV-2 infection.[10,A22,A23] Vaccines also have been effective against serious outcomes of COVID-19 caused by viral variants, although their efficacy has declined for newer variants.[A24,A25] Vaccines are similarly effective, regardless of age, gender, ethnicity, or medical comorbid conditions, but they have not been extensively evaluated in immunocompromised patients.

Two adenovirus vector vaccines (Astra-Zeneca in a two-dose regimen 1 month apart or Janssen single dose) were about 70% protective against clinical infection due to the original vaccine strains regardless of age, sex, ethnicity, or underlying medical condition. They also appear to be 90% or more effective for preventing hospitalizations and deaths, although this effectiveness has declined for newer variants.[A26] In the United States, the Janssen vaccine is the only authorized adenovirus vector vaccine, and mRNA vaccines are preferred over Janssen COVID-19 vaccine for the primary series and booster doses.

A two-dose recombinant S protein vaccine with a saponin-based adjuvant (Novavax) is well-tolerated and has over 90% efficacy against symptomatic COVID-19 and close to 100% efficacy against severe disease.[A27] The vaccine is approved in the United States for persons ages 12 years and over as a two-dose primary series. An ASO3-adjuvanted recombinant S protein-based vaccine (Sanofi Pasteur) provides robust neutralizing antibody responses in adults, and the two-dose product is in late stages of clinical testing.

In the United States, the Pfizer-BioNTech and Moderna COVID-19 vaccines are approved in children and adolescents, beginning at 6 months of age. For children and adolescents ages 5 to 15 years[A28,A29] these vaccines are approximately 90% efficacious for preventing symptomatic, laboratory-confirmed COVID-19 in the short term. In younger children, for whom the mRNA COVID-19 vaccines were tested predominantly during circulation of variant strains, antibody levels and efficacy are similar to what is seen for similar variants in older age groups.[A30] Pediatric recommendations for dosing differ by age and manufacturer (see Table 337-1).

Over time and with new viral variants, the effectiveness of vaccines declines, more so in older adults and immunocompromised individuals, and in terms of lost protection against any infection rather than severe infection that requires hospitalization.[11] As a result, additional booster doses of mRNA vaccines are recommended to provide additional protection, including in persons who have had COVID-19.[A31,12–17] With continuing evolution of viral strains, COVID-19 vaccines have been formulated to include viral variants. The first approved bivalent formulations were mRNA formulations containing both the ancestral strain and an Omicron BA4/5 variant strain. In 2022, bivalent mRNA COVID-19 vaccine booster doses were recommended for persons ages 5 years and older, administered 2 or more months after completing the primary series or after receipt of a monovalent booster dose. Subsequently, such vaccines have been shown to improve protection against clinical illness. COVID-19 vaccines will continue to be updated on a periodic basis as directed by the Food and Drug Administration.[18,19]

Adverse Effects of Vaccination

Anaphylaxis occurs in approximately two to five people per million after COVID-19 vaccination. Most side effects are self-limiting, with pain at the injection site the most frequent and severe local reaction. Reactions tend to be more common in younger than in older age persons, and for the second dose as compared to the first.

In about 4 per 1 million persons vaccinated with the Janssen COVID-19 vaccine, a thrombosis with thrombocytopenia syndrome, with thrombosis in unusual sites such as the central venous system and splanchnic vessels, can develop approximately 1 to 2 weeks after vaccination.[20,21] Guillain-Barré syndrome, seen predominantly with the Janssen COVID-19 vaccine,[22] is also rare, with the highest risk being 16 cases per 1 million doses among 50- to 64-year-old males. Myocarditis and pericarditis can develop, principally in adolescents and young adults after either of the two mRNA COVID-19 vaccines or after the Novavax protein vaccine[23]; the clinical course is generally mild to moderate and responds to conservative treatment.[24]

Vaccine Policy

Given critical global needs, efforts continue to develop, refine, and manufacture COVID-19 vaccines at greater scale. Second-generation vaccines that increase the breadth and durability of immunity are a high priority, including vaccines against variant strains and targets other than the S protein. By June 2022, when about 80% of eligible American adults had at least one dose of a COVID-19 vaccine, only about 16% of residents of low-income countries had received one dose. Even in the United States, the poor uptake in certain segments of the population has slowed efforts to control the pandemic. Additional investments in implementation in science and public health will be needed to overcome vaccine hesitancy, to increase confidence in vaccines, and to enhance public health communications.

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338

MEASLES

MARTIN G. OTTOLINI

DEFINITION

The term *measles* is applied most appropriately to "rubeola" (also known as "morbilli"), an extremely contagious, prolonged respiratory and systemic viral illness characterized by high fever, an erythematous maculopapular rash, cough, coryza, and conjunctivitis. A member of the family Paramyxoviridae, within the genus *Morbillivirus*, the measles virus exhibits at least 24 distinct genotypes but behaves as a single serotype because natural infection or adequate immunization confers broad protection against all types.[1,2]

EPIDEMIOLOGY

Measles may be the most contagious pathogen known to humans, and it has no other reservoir. Its basic reproduction number, the R_0, which represents the number of naïve contacts potentially infected by exposure to one contagious individual, has been estimated to be 12 to 18,[3] an R_0 far higher than the R_0 of two to three for Ebola (Chapter 351) and influenza (Chapter 332). Key challenges to control of the spread of measles include the immunization status of a population, their density, and the influence of migration and travel.

In the 1950s and early 1960s, measles was ubiquitous in the United States, with more than 500,000 cases reported annually, and nearly everyone was infected by adulthood. By 2000, a two-dose, live-attenuated vaccine led to endemic measles being declared "eliminated" from the United States. From 2001 to 2016, a median of 28 imported measles case were reported annually in the United States. More recently, measles cases in the United States increased dramatically, peaking in 2019 with 1282 confirmed cases, mostly in regional outbreaks in close-knit and underimmunized communities exposed to measles brought back by international travelers.[4,5] However, the number of confirmed cases dropped dramatically to just 13 in 2020, an unexpected benefit of the restriction of social interactions and use of masks in response to the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) coronavirus disease 2019 (COVID-19) pandemic (Chapters 335, 336, and 337). This benefit may be short-lived because the pandemic's disruptions also resulted in reductions in routine immunizations by 22% in children ages 12 to 23 months and 63% in children aged 2 to 8 years. Though rates rose quickly after the lifting of the most severe SARS-CoV-2 restrictions, data so far have not shown an effective "catch up" of the deficits encountered.[6]

The global incidence of measles decreased from an estimated 145 cases per million population in 2000 to just 18 per million in 2016, subsequently rose to 120 per million in 2019, then declined again to 17 per million in 2021 during the height of the COVID-19 pandemic.[7] Annual global measles deaths decreased from over 500,000 in 2000 to 109,000 in 2017, rose to over 200,000 in 2019, and were 128,000 in 2021. The Americas are no longer free from endemic measles transmission, and the ambitious goal of eliminating measles in 5 of 6 world regions by 2020 has not been met.

Global protection by at least one measles immunization flattened after 2010, at a rate of about 86% until it fell to 81% in 2021, though the numbers of individuals receiving the required two immunizations rose from 48% in 2012 to 71% in 2019. In 2021, 47% of all WHO member countries achieved the goal of greater than 90% first-dose coverage, but an estimated 24.7 million children did not receive even an initial measles vaccine. About 60% of the missed initial doses occurred in just 10 countries, including Nigeria, India, Democratic Republic of the Congo, Ethiopia, Indonesia, Pakistan, Philippines, Angola, Brazil, and Tanzania.

Measles also can be associated with long-term complications. For example, the country of Georgia has suffered from endemic measles for years, with widespread outbreaks in 2004-2005 and 2013-2015. Between 2008 and 2017, 16 confirmed survivors developed devastating subacute sclerosing panencephalitis,[8] 92% of whom were children infected prior to 2 years of age, at a mean interval of 6 years after the infection. Other than COVID-19, measles is the fourth leading worldwide cause of death due to infectious disease, following only tuberculosis (Chapter 299), HIV/AIDS (Chapter 353), and malaria (Chapter 316).

PATHOBIOLOGY

Measles virus is spread very effectively by contact with large droplets or inhalation of aerosolized small droplets, which can remain suspended for hours after an infected individual has exited. Unlike other paramyxoviruses, which primarily infect and inflame respiratory epithelia, measles virus targets the immune system. Measles virus initially infects cells in the respiratory tract or conjunctiva, then migrates to regional lymph nodes where it infects CD150/SLAM1-expressing T and B cells.[9] Infected mononuclear cells then travel to other lymphoid tissues, including the spleen, tonsils, and other lymph nodes to propagate infection. Virus may enter the central nervous system (CNS) through infected lymphocytes, although the exact mechanism remains unclear. Systemic infection of the gastrointestinal (GI) system, kidney, liver, and skin occurs by circulation of infected immune cells. Measles virus later infects the respiratory epithelium through the Nectin-4 receptor, spreads from cell to cell to cause damage and sloughing, and then is expelled as infectious droplets by coughing to repeat the cycle.

Measles virus initially evades immune recognition by inhibiting type 1 interferons, so extensive viral replication and systemic spread precedes clinical disease. The buccal mucosal lesions (Koplik spots) and the classic rash result from infection of capillary endothelium by measles virus, with syncytial cell formation as well as local production of nitrous oxide and tumor necrosis factor-α. Measles virus–specific T-cell host-immune responses lead to eventual necrosis of infected cells with viral clearance. Poor measles virus–specific T-cell responses are observed in individuals who are severely malnourished and immunocompromised, with reduced cellular necrosis and delayed viral clearance, thereby explaining their less obvious but prolonged skin changes.

The most dramatic aspect of measles virus infection may be its transient yet profound suppression of the immune system, possibly by targeting CD150(SLAM)-expressing cells. While inducing a cytotoxic T-cell response that clears infected cells and induces measles virus–specific memory B cells, measles virus concurrently depletes subsets of both regional and circulating T and B cells, with a loss of immune memory. The depletion of lymphocytes in gut and respiratory epithelium leads to increased morbidity and mortality from other infections and explains the increase in all-cause mortality for an after-measles infection.

CNS involvement includes several clinicopathologic syndromes. The mechanism of viral entry into the CNS is poorly understood, because human neurons do not usually express the most common receptors for measles virus (SLAM or Nectin-4), though entry may be facilitated by viral binding to Nectin-4–positive nasal or meningeal epithelial cells adjacent to neuronal tissue.[10] Infection can

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338

MEASLES

MARTIN G. OTTOLINI

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CNS involvement includes several clinicopathologic syndromes. The mechanism of viral entry into the CNS is poorly understood, because human neurons do not usually express the most common receptors for measles virus (SLAM or Nectin-4), though entry may be facilitated by viral binding to Nectin-4–positive nasal or meningeal epithelial cells adjacent to neuronal tissue.[10] Infection can

ABSTRACT

Measles is an extremely contagious and prolonged respiratory and systemic viral illness characterized by high fever, an erythematous maculopapular rash, a croupy cough, coryza, and conjunctivitis. Measles infects and depletes the immune system, so patients have greater susceptibility to other pathogens long after recovery. Complications include primary viral and secondary bacterial pneumonia, otitis media, and more rarely encephalitis, a prolonged debilitating diarrhea, and corneal scarring. A small percentage of patients will develop a relentlessly progressive and fatal panencephalitis years after recovery. Vitamin A supplementation may reduce the overall morbidity and mortality, which can be as high as 30% in malnourished populations. It should be given on the first and second days of illness and repeated at 4 to 6 weeks if abnormal ophthalmic findings are present. A live attenuated vaccine has been available since the late 1960s, and a two-immunization strategy has proven safe and highly effective. Progress in reducing global infections and deaths has been significant but requires an ongoing commitment. Eradication is theoretically possible but has proven elusive due to several factors, including natural and man-made disasters, which disrupt immunization programs, and more recently by elective vaccine avoidance.

KEYWORDS

measles
rubeola
morbilliform
xeropthalmia
encephalitis
CD150(SLAM)
SSPE
vitamin A
MMR
vaccine hesitancy

cause an acute measles inclusion body encephalitis that is believed to be caused by persistent viral replication in the brain tissue of patients who are unable to mount an adequate immune response because of deficient cellular immunity.[11] The name derives from histologic evidence of viral persistence, which is seen by intracytoplasmic and intranuclear inclusions caused by nucleocapsids.

CNS infections can also trigger an immune response. In acute demyelinating encephalitis, an aberrant host response to myelin basic protein is thought to lead to brain inflammation and perivenous demyelination. In subacute sclerosing panencephalitis, patients are infected with mutated forms of the measles virus. Mutations in the M (matrix) gene may allow for long-term escape from host neutralizing antibody, and an altered F (fusion) gene leads to expression of an F protein with "hyperfusogenicity," which in turn allows for highly efficient cell-to-cell spread in neuronal tissues. Intranuclear inclusion bodies are seen in the neurons and glial cells of the white matter and neurons of the brainstem. An exaggerated host mononuclear inflammatory response occurs, with a vigorous leptomeningeal and parenchymal perivascular inflammation, which may be compounded by a degree of autoimmunity due to cross-reactivity between viral and myelin antigens. Early demyelination is followed by late stage cortical atrophy.

CLINICAL MANIFESTATIONS

Measles should be suspected in the presence of fever and a maculopapular (nonvesicular) rash. Measles has a 7- to 21-day incubation period, with onset of fever and malaise (prodrome), as well as the more specific combination of a "croupy or brassy" cough, coryza, conjunctivitis, and photophobia beginning about 10 days after exposure (Fig. 338-1). Koplik spots (Fig. 338-2),[12] which are raised bluish-white papules inside both cheeks, may appear at this time; though pathognomonic, they are often missed or misdiagnosed as thrush, and they fade as the rash emerges. The classic erythematous blanching maculopapular rash begins on the face, spreads down the body, and becomes confluent and darker in color over days (Fig. 338-3A). The rash is more subtle in dark-skinned patients (Fig. 338-3B), in whom the diagnosis may be delayed. In malnourished and immunosuppressed individuals, a prolonged desquamating dermatitis is commonly seen (Fig. 338-3C). Body temperature is high, 39° to 40.5° C, beginning with the prodrome and continuing at least 4 days into the rash. Patients are contagious to others from 4 days prior until 4 days after onset of the rash. As the rash darkens and fades, the skin will often flake and peel. In individuals with incomplete postimmunization protection, clinical symptoms may be milder, with less fever and catarrh, a later onset (12 to 16 days), and markedly reduced infectivity.[13]

Complications

Approximately one fourth of the reported measles cases identified in the United States from 2002 to 2016 resulted in hospitalization. Of these 1018 patients, reported complications included dehydration (16%), hyponatremia (14%), diarrhea (10%), thrombocytopenia (10%), pancytopenia (3%), conjunctivitis (9%), septicemia (8%), bacterial pneumonia (8%), bronchitis (4%), pleurisy (4%), and viral pneumonia (1%). One of the most specific though rare complications was encephalitis (2%).[14] By comparison, complications seen in 307 children admitted to a children's hospital in Islamabad, Pakistan from 2013 through 2017 included pneumonia (63%) and encephalitis (9%).[15]

Central Nervous System Involvement

Involvement of the CNS leads to several of the most serious complications of measles infection, with high rates of morbidity and mortality.

Acute and Subacute Encephalitis

An acute encephalitis may occur in the midst of clinical illness in 2 to 3% of infections and may explain why 5 to 10% of survivors have moderate to severe sensorineural hearing loss. A much rarer (0.1%) early, postinfectious, demyelinating encephalomyelitis occurs days after the apparent resolution of a primary infection. This syndrome, which is manifested by seizures and altered mental status, is fatal in 20% of cases, and more than one third of survivors have permanent neurologic sequelae.

Measles Inclusion Body Encephalitis

A measles inclusion body encephalitis may occur in immunosuppressed individuals, usually 1 to 6 months postinfection. Patients usually present with refractory focal seizures and rapidly progressive neurologic decline.[16]

Subacute Sclerosing Panencephalitis

Subacute sclerosing panencephalitis is a relentlessly progressive and uniformly fatal degenerative brain disorder that develops 7 to 10 years after measles infection. It occurs in 4 to 11 of every 100,000 survivors of measles infection, but rates are several times higher in resource-restrained countries, as well when measles infection occurs at a young age.[17,18] Patients typically present with cognitive and behavioral changes. A chorioretinitis may precede the more obvious CNS involvement. The result is an initial cognitive decline, followed by loss of motor skills, visual loss, and verbal difficulties, eventually leading to a persistent vegetative state and ultimately death.

DIAGNOSIS

Many diseases in children and adults have morbilliform rashes and systemic findings, including the multiorgan systemic inflammatory syndromes associated with the SARS-CoV-2 pandemic (Chapter 336), which frequently

FIGURE 338-2. Typical Koplik spots.

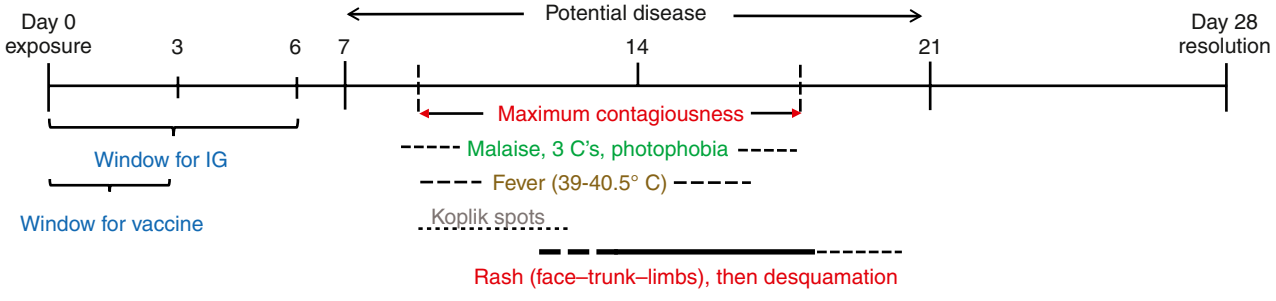

FIGURE 338-1. Clinical progression of measles. 3 Cs = cough, coryza, conjunctivitis; IG = immunoglobulin.

FIGURE 338-3. **The variable rash of measles. A,** Classic erythematous rash, conjunctivitis, and coryza. **B,** Rash is difficult to perceive on dark skin, but patient has typical conjunctivitis and coryza. **C,** Prolonged desquamating dermatitis in a malnourished child with measles.

manifest with nonspecific maculopapular or morbilliform rashes during acute illness in older adults. However, the recognition of the unique pediatric multisystem inflammatory syndrome in children (MIS-C) further complicates the diagnostic challenges presented by morbilliform rashes in the younger child, in whom a wide variety of patterns of erythematous rashes are manifest in about 50% of patients up to a month or longer after COVID-19 infection. Clinicians must use experience and judgment to decide if there is substantial risk that a patient's illness may be measles and represent the index case of a potential outbreak (Table 338-1), which may require immediate intervention.

Suspected measles infection must be confirmed by reverse transcription–polymerase chain reaction (RT-PCR) testing of samples obtained from sites of shedding, including the nasopharynx, oropharynx, conjunctiva, and even urine; or confirmatory serology. Unvaccinated infected individuals may develop an elevated measles-specific immunoglobulin M (IgM) antibody as soon as the first day of rash, whereas acute and convalescent serologies can detect a four-fold or greater rise in measles-specific antibody. Patients may have marked leukopenia and lymphopenia.

Virus recovery by PCR or culture also allows epidemiologists to genotype the isolate and to help control outbreaks. Clinicians should confer with regional or national public health experts if a case of measles is confirmed.

Neurologic Syndromes

Acute measles encephalitis is associated with a mild lymphocytic pleocytosis in the cerebrospinal fluid. Measles inclusion body encephalitis is usually diagnosed by brain biopsy. The diagnosis of subacute sclerosing panencephalitis can be confirmed by a classic pattern of periodic stereotypic sharp-slow wave discharges on electroencephalography, plus finding high titers of measles IgM and IgG in cerebrospinal fluid and serum.

TREATMENT

Treatment is supportive, with control of fever, hydration, nutrition, and observation for the serious complications of pneumonia and encephalitis (see Prognosis). Clinicians who rarely see measles may be alarmed by the prolonged high fever and malaise. Hospital admission for hydration or other concerns must be weighed against the challenge of infection control.

Vitamin A supplementation is recommended to reduce overall mortality and potentially reduce the risk for xerophthalmia, corneal scarring, and blindness, as well as the debilitating prolonged diarrhea of measles, especially in populations with vitamin A deficiency or malnutrition.[A1] Dosing is 50,000 units for infants younger than 6 months, 100,000 units for children aged 6 to 11 months, and 200,000 units for patients older than 12 months on both days 1 and 2 of presentation. An additional dose can be given 2 to 6 weeks later to patients with ophthalmic findings of vitamin A deficiency.

There are no proven therapies for any of the CNS complications of measles virus infection. Isoprinosine, ribavirin, and interferon-alpha have all been tried, with limited observational evidence that they may slow these progressive diseases. Experimental therapies include competitive antagonists and neutralizing antibodies, which may block the fusogenic properties of the mutated viral F protein in measles inclusion body encephalitis and subacute sclerosing panencephalitis.

PREVENTION

Immunization with Live Virus Vaccines

Immunization with live-attenuated measles virus vaccine, often as MMR and sometimes with varicella (MMRV), stimulates long-acting antibodies and cellular immunity.[A2] Immunization strategies are designed both to protect the individual and to ensure that least 89 to 94% of a population is protected, a level required to diminish measles propagation within the population, termed "herd immunity."

Two immunizations should be delivered, at least 1 month apart, when the protective yet also vaccine-inhibitory effects of passively transferred maternal antibody diminish (Chapter 15). The first dose is routinely administered at 9 to 12 months of age and can be given as early as 6 months if the infant is born during an outbreak or high-risk situation or is traveling to such a region. If it is given before 9 months of age, a third dose is needed to ensure that two are given after the loss of maternal antibody. The second dose can be given from 1 month to years later, often at entry to formal schooling.

As the world's population shifts to relying on vaccine immunity, further doses during adulthood may be required because the estimated waning of immunity is about 0.9%/year.[19] For example, only 82% of recent U.S. military recruits had detectable measles titers, lower than the level desired for herd immunity, and recruits older than 30 years had even lower rates, possibly suggesting waning titers. A recent systematic review found evidence of high rates of seroconversion (96 to 100%) and no additional safety concerns in recipients greater than 7 years of age.[20]

Enthusiasm has been growing for a dried measles and rubella live vaccine combination that can be delivered by a cutaneous patch microneedle intradermal delivery system.[21] This approach could overcome the current logistic challenges required by the current vaccines' requirements for strict temperature storage and need for injection.

Vaccine Safety

Measles vaccine is highly safe, with minimal side effects. Common reactions include fever 6 to 12 days after immunization in less than 15% of cases and

TABLE 338-1 DIAGNOSING MEASLES

CLINICAL PRINCIPLE	QUESTIONS TO ASK
Measles is acquired only from a person with measles	Travel to endemic areas or regions with outbreaks Warnings from health department/CDC of local measles Suspicious ill contacts with risk factors
The individual must be susceptible	Natural immunity (born before 1957, history of infection) Is the patient inadequately immunized or immunosuppressed
Most patients are ill-appearing	Ill enough to consider "admission" to a hospital (a rash in an otherwise well individual is rarely measles)
There is a predictable evolution of systemic findings	Croupy cough, coryza, and conjunctivitis (3 Cs) Relentless high fever for several days Did Koplik spots precede the rash (often unrecognized)
The rash is impressive, with a few exceptions	Previously healthy patient with lighter skin color—is there a distinct rash (see Fig. 338-3A) Hard to distinguish due to darker skin color in this previously healthy infant (see Fig. 338-3B) "Head-trunk-limb" progression, increasing confluence Is patient malnourished/immunosuppressed (rash can be absent/atypical; see Fig. 338-3C)
Other diagnoses are much more common	Enterovirus (Chapter 349), parvovirus (Chapter 342), roseola (Chapter 406), rubella (Chapter 339), EBV (Chapter 348), streptococcal/staphylococcal (Chapters 267 and 268), primary COVID-19 or MIS-C after COVID-19 (Chapters 335, 336, and 337), toxin Risk for rickettsia illnesses (Chapter 302) in region, outdoor exposure Kawasaki disease (Chapter 249), other vasculitis, or immunologic disease Risks for drug toxicity—new medications (Chapter 234)
The experience of the examining clinicians is critical	Clinicians from the 1960s-1980s, or with global experience Team consensus. This will be a public health emergency! Ability to confirm rapidly by acute IgM serology or PCR

CDC = Centers for Disease Control and Prevention; COVID-19 = coronavirus disease 2019; EBV = Epstein-Barr virus; IgM = immunoglobulin M; MIS-C = multisystem inflammatory syndrome of childhood; PCR = polymerase chain reaction.

transient rashes or lymphadenopathy in less than 5% of children and 20% of adults. The rubella component of the MMR may trigger transient arthralgia or arthritis in postpubertal girls. Febrile seizures occur in 1 in 1100 to 1400 infants at 5 to 12 days after immunization, and transient thrombocytopenia may occur in 1 in 22,000 to 40,000 individuals at 2 to 3 weeks postimmunization. Allergic reactions and anaphylaxis are rare. No evidence supports any causal relationship between receipt of measles vaccine and autism-spectrum disorders or autoimmune disorders, including Guillain-Barré syndrome, inflammatory bowel disease, and type 1 diabetes.

Immunization is encouraged for individuals with early-stage human immunodeficiency virus (HIV) who are successfully managed with antiviral therapy, and reimmunization should be considered for children who have immune reconstitution later in life. MMR vaccines are avoided in pregnant women or those who may become pregnant in the subsequent 28 days, primarily to avoid exposure to the rubella component, although vaccine-associated problems for any component are extraordinarily rare. MMR or MMRV vaccine should be avoided in patients with primary or acquired immunodeficiency (Chapters 231 and 353), including late-stage HIV or ongoing systemic immunosuppressive therapy, and in patients who have recently received antibody-containing blood products (immunoglobulin or whole blood), which might inhibit the vaccines. Measles and other immunizations should be planned around the timing of induction and recovery from immunosuppression for the growing group of patients who receive targeted immunotherapies.

Isolation of Suspected Infected Individuals and Postexposure Prophylaxis

Immediate isolation of suspected cases and quarantine of any contacts without presumptive immunity are standard practices. Hospitalized patients are ideally managed in negative-air-pressure isolation rooms using airborne precautions.

If a risk for exposure has been identified early, contacts can be screened for natural immunity or adequate immunization; if indicated, a dose of measles vaccine can be delivered within 72 hours of exposure. Passive immunoprophylaxis with human immunoglobulin preparations can achieve protective levels of antimeasles antibody in patients who were exposed between 3 and 6 days earlier, are pregnant, have late-stage HIV infection, or have other contraindications to vaccine.

Vaccine Hesitancy

Voluntary avoidance or delay of measles immunization, termed vaccine hesitancy, is a growing problem. In the resurgence of measles in the United States in 2019, 75% of cases were in small communities with high densities of underimmunized children, who were exposed to international travelers who unknowingly returned with measles infection. In the United States, the vaccine rate is about 95%, but it varies by locale. Counties with lower vaccination rates have higher rates of measles, with just 17 counties accounting for more than 50% of U.S. confirmed cases.[22] Parents under age 30 and parents with a single child are more likely to avoid vaccination. Both Internet and social media sources of information are significantly associated with vaccine hesitancy and negatively associated with correct knowledge about measles infection and vaccination.[23] The global challenge remains to eliminate barriers to timely measles immunization for all populations.

Global Strategies

In light of the failure to reach 2020 goals for eliminating measles in 5 of 6 global regions, the current global strategic plan steers away from specific numerical goals, and identifies several of the greatest current challenges, including health system weaknesses that result in immunity gaps in young infants and older age groups, inadequate mechanisms for "catch-up", inadequate surveillance, lack of resources for outbreak control, increasing vaccine hesitancy, and the recent reduction in supplemental immunization activities due to the COVID-19 pandemic.[24] Strategic planning includes tailoring programs to local challenges, implementing comprehensive and sustainable life-course immunization strategies with "catch-up" vaccination programs, using cross-border information sharing and collaboration for surveillance, and pursuit of innovative technologies that may simplify diagnostic tests and vaccines.

PROGNOSIS

Fatality rates are 2 to 3 per 1000, mostly in infants or adults older than 30 years. Among the 1018 patients admitted to hospitals in the United States from 2002 to 2016, a total of 34 deaths were noted (3.4% mortality). Fatality rates rise to 1 to 15% in populations with malnutrition and vitamin A deficiency. In the report of complications in children hospitalized in Islamabad the overall mortality was 17%, and was significantly associated with an underweight status with signs of nutritionally related growth retardation.

Patients who develop neurologic complications have a poor prognosis. Acute measles encephalitis is associated with permanent sensorineural hearing loss. Subacute demyelinating encephalitis is fatal in 20% of cases, and more than one third of survivors have permanent neurologic sequelae. Measles inclusion body encephalitis is rapidly progressive and typically fatal. Subacute sclerosing panencephalitis invariably leads to a vegetative state and death.

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339

RUBELLA (GERMAN MEASLES)

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DEFINITION

Although most cases of rubella infection lead to a mild viral illness, significant morbidity occurs when rubella virus infects the fetus, particularly during the first trimester of pregnancy, when it causes miscarriage and the congenital rubella syndrome in up to 90% of cases.[1] Humans are the only known host, so this disease is eradicable.

The Pathogen

Rubella is a single-stranded, positive-sense RNA virus that is a member of the *Togaviridae* family, in the *Rubivirus* genus. The virus has a diameter of about 60 nm and includes a core protein and two envelope proteins.

EPIDEMIOLOGY

Rubella virus is spread person to person via the respiratory route, with lifelong immunity after infection. Prior to the availability of live attenuated rubella vaccine, rubella infection was nearly ubiquitous among children, occurring in the spring season and in large epidemics every 3 to 8 years. In the prevaccine era, up to 4 infants out of every 1000 live births worldwide were born with congenital rubella syndrome, and the incidence of congenital rubella syndrome was between 0.1 to 0.2 per 1000 live births during endemic phases and 0.8–4.0 during epidemics. With widespread use of the vaccine, the number of cases has been dramatically reduced.[2] Rubella was eliminated in the United States in 2004 and in the Americas since 2015. In the United States, fewer than 10 cases occur per year among individuals infected outside of the country. Unfortunately, global plans to eliminate rubella in 5 of 6 World Health Organization regions by 2020 failed,[3] and about 50% of babies worldwide do not have access to rubella-containing vaccines. Rubella outbreaks have continued to occur related to partial vaccination strategies, lack of political commitment, disruption due to war and conflict, and the costs of elimination programs. Herd immunity thresholds, which have varied by geographic region, have generally ranged from 70 to 90%, given a basic reproductive rate that is estimated to be 3 to 8 in Western settings but as high as 12 in crowded developing settings.

PATHOBIOLOGY

Rubella virus is a respiratory pathogen that enters through the oral and/or nasal mucosa, where it initially infects the nasopharyngeal epithelial cells and spreads to regional lymph nodes. The virus then enters the bloodstream, thereby causing viremia approximately 1 week into the incubation period. In healthy children and adults, infection can involve multiple organ systems, likely due to the broad range of permissive cells with low titer viral replication and little to no cytopathic effect.[4] In pregnant women, placental infection can provide access to fetal tissues, where widespread and persistent infection can occur. Fetal infection causes widespread cell death, disruption of cell division, and damaged, delayed, and/or disrupted organogenesis, thereby leading to developmental abnormalities in up to 90% of infected fetuses. The virus can be shed from infected newborns for up to 1 year following birth, and this shedding represents an infection risk for immunologically naïve contacts.

Rubella virus is present in the skin, where direct infection or the resulting antiviral immune response may contribute to the development of the rash. Chronic joint disease is related to persistent viral infection and the presence of immune complexes in synovial fluid. In the pancreas and thyroid, rubella infection and the autoimmune response can cause endocrine dysfunction. Viral infection of the brain in congenital rubella syndrome is believed to be the cause of the neurologic sequelae of encephalitis, progressive rubella panencephalitis, and other neurologic sequelae of congenital infection.

CLINICAL MANIFESTATIONS

Acquired rubella is often a mild, self-limiting, and benign viral disease. After an incubation period of 14 to 21 days, a fever is usually followed by a maculopapular erythematous rash (Fig. 339-1) within 2 days.[5,6] The virus can be transmitted to others up to 7 days after the rash appears. During this time, patients tend to experience relatively mild symptoms, such as low-grade fever, malaise, mild conjunctivitis, sore throat, ear infection, and upper respiratory symptoms. Posterior auricular lymphadenopathy is very common.[7] Acquired rubella is usually self-limited, and the ***vast*** majority of patients fully recover. However, transient arthritis, arthralgia, and joint pain are reported in up to 70% of adults after rubella infection. Rare complications may include thrombocytopenia (in about 1 in 300 cases) and encephalitis (in about 1 in 6000 cases).

FIGURE 339-1. Rash of rubella on the skin of a child's back. The distribution is similar to that of measles, but the lesions are less intensely red. (From the Centers for Disease Control and Prevention Public Health Image Library, ID #: 712.)

The main public health concern posed by rubella is its teratogenicity. Infection during early pregnancy (8 to 10 weeks of gestation) may result in devastating consequences (e.g., fetal death, miscarriage, and fetal abnormalities), described as congenital rubella syndrome. The defects associated with congenital rubella syndrome in infants most frequently result in serious ocular (e.g., glaucoma, cataracts, retinitis, microphthalmia, chorioretinitis), hearing (e.g., cochlear deafness), brain (e.g., microcephaly, encephalitis), or cardiac disease (e.g., peripheral pulmonary artery stenosis, patent ductus arteriosus) (Table 339-1).[8]

DIAGNOSIS

Clinical specimens for the diagnosis of rubella infection in humans include blood, oral fluids, throat swabs, nasopharyngeal secretions, saliva, and urine. Amplification of rubella virus RNA from clinical specimens using the reverse transcription polymerase chain reaction (RT-PCR) method that has 100% sensitivity and 90% specificity[9] and is the preferred method for rapidly distinguishing rubella from measles (Chapter 338). The much more cumbersome alternative is to grow the virus in cultured African green monkey kidney cells.

For serologic diagnosis, a combination of laboratory methods can confirm recent rubella infection, congenital rubella infection, and congenital rubella syndrome. A four-fold increase in the level of rubella-specific IgG antibody titers between the acute and convalescent phase of illness is also used for serologic diagnosis of postnatal rubella infection. Detection of rubella virus-specific IgM antibodies can diagnose recent maternal and postnatal infection, and it is useful for the rubella and congenital rubella syndrome surveillance programs. In highly immunized populations, however, antibody-positive results are more likely to reflect prior immunization rather than recent primary infection.[10] Serum antibody levels between 10 IU/mL and 15 IU/mL indicate immunity to rubella; an antibody level of 15 IU/mL probably correlates with immune protection.

TREATMENT

Unfortunately, no rubella-specific treatments are useful for prophylactic, therapeutic, or curative purposes. Treatment is supportive and can include fluids, rest, and antipyretics for fever. For pregnant women who have been exposed to rubella, hyperimmune gamma globulin has been used but with only modest definitive evidence of benefit.[A1]

ABSTRACT

Rubella virus, which remains an important pathogen globally, is the causative agent of the disease often known as German measles. Acquired rubella infection is often typified by a rash with self-limiting and benign disease. However, infection during early pregnancy can result in devastating consequences, such as fetal abnormalities and fetal death, collectively known as congenital rubella syndrome. Nucleic acid amplification or serologic tests can diagnose rubella infection. Active immunization using live attenuated rubella virus vaccine, typically given as part of a childhood immunization schedule, prevents infection. For seronegative pregnant women, vaccine is administered postpartum, after which pregnancy should be delayed for 28 days. A strategic framework has been developed with the goal of eliminating rubella infection worldwide.

KEYWORDS

rubella
congenital rubella syndrome
rubella vaccine
elimination
pregnant women

TABLE 339-1 CLINICAL FEATURES OF CONGENITAL RUBELLA SYNDROME

FEATURE	INCIDENCE
Cataracts and microphthalmia	Permanent/Common
Retinopathy	Permanent/Common
Glaucoma	Permanent/Uncommon
Cochlear deafness	Permanent/Common
Central auditory imperception	Permanent/Developmental/Common
Patent ductus arteriosus	Permanent/Common
Peripheral pulmonic artery stenosis	Permanent/Common
Encephalitis	Transient
Microcephaly	Permanent
Mental disability	Permanent/Developmental/Common
Autism	Permanent
Intrauterine growth retardation (low birth weight)	Transient/Common
Metaphyseal rarefactions	Transient
Hepatosplenomegaly	Transient/Common
Thrombocytopenic purpura	Transient
Interstitial pneumonitis	Transient
Diabetes and hypothyroidism	Permanent/Developmental/Common

Modified from Cooper LZ, Preblud SR, Alford CA. Rubella. In: Remington JS, Klein JO, eds. *Infectious Diseases of the Fetus and Newborn Infant*, 4th ed. Philadelphia: WB Saunders; 1995:288. Cooper LZ, Buimovici-Klein E. Rubella. In: Fields BN, et al., ed. *Virology*. New York: Raven Press; 1985:1005-1020.

PREVENTION

Active immunization using live attenuated rubella virus vaccine[11] is 97% effective (range 94 to 100%) in preventing infection,[A2] including the congenital rubella syndrome. The vaccine is currently administered as a two-dose series in the United States as part of the measles-mumps-rubella (MMR-II) vaccine. Rubella vaccine is also licensed for use in children between 12 months and 12 years of age in combination with measles, mumps, and varicella (chickenpox) vaccines as the MMRV vaccine. MMR vaccines are very effective in preventing disease, although some studies have demonstrated suboptimal long-term immunity[12] and, uncommonly, seronegativity (<10 IU/mL antibody titer) in immunized persons.[13]

In newborns, passive rubella maternal antibodies disappear rapidly 2 months following birth, so the U.S. Centers for Disease Control and Prevention recommends children receive their first dose of the MMR vaccine between 12 and 15 months of age and the second dose later in childhood at age 4 to 6 years. Vaccination is recommended for high-risk groups including nonpregnant women of childbearing age, military recruits, college students, and health care workers. In the United States, a third dose of MMR vaccine may be recommended by state or local health authorities during measles or mumps outbreaks.

The estimated rate of loss of immunogenicity is about 1.2% per year.[14] Repeat vaccination is recommended in patients who are found to be seronegative. In cases of waning immunity, a repeat vaccination will raise the antibody response, but it generally wanes back to baseline. Although most vaccine-related side effects are mild (e.g., rash, fever, sore throat, lymphadenopathy, and headache), arthritis and arthralgia may occur, especially in adolescent rubella-seronegative women, but resolve over time. Rarely, the live attenuated vaccine can produce vaccine-related rubella in immunodeficient or even apparently immunocompetent patients.[15]

A third booster vaccination in seronegative and/or immunocompromised (e.g., after chemotherapy or bone marrow transplantation, or with congenital immune deficiency) children may induce immunity, but a live virus booster vaccination is not recommended for children with immunodeficiency or children who experienced thrombocytopenic purpura after MMR vaccination, due to the increased risks of adverse events after vaccination. Rubella vaccine also should not be given to individuals who had a severe allergic reaction (e.g., anaphylaxis) after a previous vaccine dose, or to patients with a known severe immunodeficiency.

Pregnancy should be avoided for 1 month after MMR vaccination, and the vaccine should be administered postpartum. MMR vaccine can be administered to breastfeeding mothers without any danger to their infant.

Worldwide eradication efforts continue.[16] However, issues with accessibility, public health infrastructure, and hesitancy have hampered such efforts.[17]

PROGNOSIS

Rubella is typically mild and transient in healthy children and adults, with nearly everyone recovering fully. Rubella encephalitis and postinfection panencephalitis, which resemble the subacute sclerosing panencephalitis that can follow measles infection (Chapter 338), occur at a rate of about 1 in 5000 infections and are associated with mortality rates as low as 0% and as high as 50%. Joint problems (e.g., polyarthralgia, polyarthritis), which are common in adults but not in children, are typically transient.[18] Treatment is limited to bed rest, adequate hydration, and mild pain relievers (e.g., acetaminophen or ibuprofen) for aches and fever.[19] The prognosis for congenital rubella syndrome is typically poor; although some specific symptoms can be treated, no cure exists.

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340 MUMPS

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DEFINITION

Mumps is an acute viral infection characterized by inflammation of the parotid and other salivary glands. Prior to the introduction of vaccination in the United States, mumps was a common childhood illness. The incidence of mumps declined dramatically after the introduction of the vaccine, but mumps remains endemic. Cases and even outbreaks can occur in previously vaccinated children and adults.

The Pathogen

The mumps virus is an enveloped, negative-strand RNA virus belonging to the Paramyxoviridae family, genus *Rubulavirus*. Twelve mumps genotypes exist, denoted by letters A to N. The diversity of genotypes in circulation in the United States is low, with the majority being genotype G.[1]

EPIDEMIOLOGY

Humans are the only natural host of mumps virus. Mumps is highly contagious and spreads by close person-to-person contact via respiratory droplets. Transplacental transmission has rarely been reported. The incubation period between exposure to the onset of illness ranges from 12 to 25 days. Infected individuals are most likely to be contagious up to 2 days before through 5 days after the onset of symptoms, but individuals who have asymptomatic infections can also transmit the disease.

The introduction of mumps vaccine into the routine childhood immunization schedule for children ages 12 months and older in 1977 led to a dramatic decline in mumps disease in the United States, from over 150,000 cases of mumps in 1968 to about 3000 cases in 1985. In 1989, a second dose of measles-mumps-rubella (MMR) vaccine for children ages 4 to 6 years was added to the routine childhood immunization schedule and led to a further reduction, with an average of fewer than 300 reported cases annually through the early 2000s.[2,3]

However, mumps remains endemic in the United States, and multiple large outbreaks of mumps continue to occur, primarily involving fully vaccinated

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TABLE 339-1 CLINICAL FEATURES OF CONGENITAL RUBELLA SYNDROME

FEATURE	INCIDENCE
Cataracts and microphthalmia	Permanent/Common
Retinopathy	Permanent/Common
Glaucoma	Permanent/Uncommon
Cochlear deafness	Permanent/Common
Central auditory imperception	Permanent/Developmental/Common
Patent ductus arteriosus	Permanent/Common
Peripheral pulmonic artery stenosis	Permanent/Common
Encephalitis	Transient
Microcephaly	Permanent
Mental disability	Permanent/Developmental/Common
Autism	Permanent
Intrauterine growth retardation (low birth weight)	Transient/Common
Metaphyseal rarefactions	Transient
Hepatosplenomegaly	Transient/Common
Thrombocytopenic purpura	Transient
Interstitial pneumonitis	Transient
Diabetes and hypothyroidism	Permanent/Developmental/Common

Modified from Cooper LZ, Preblud SR, Alford CA. Rubella. In: Remington JS, Klein JO, eds. *Infectious Diseases of the Fetus and Newborn Infant*, 4th ed. Philadelphia: WB Saunders; 1995:288. Cooper LZ, Buimovici-Klein E. Rubella. In: Fields BN, et al., ed. *Virology*. New York: Raven Press; 1985:1005-1020.

PREVENTION

Active immunization using live attenuated rubella virus vaccine[11] is 97% effective (range 94 to 100%) in preventing infection,[A2] including the congenital rubella syndrome. The vaccine is currently administered as a two-dose series in the United States as part of the measles-mumps-rubella (MMR-II) vaccine. Rubella vaccine is also licensed for use in children between 12 months and 12 years of age in combination with measles, mumps, and varicella (chickenpox) vaccines as the MMRV vaccine. MMR vaccines are very effective in preventing disease, although some studies have demonstrated suboptimal long-term immunity[12] and, uncommonly, seronegativity (<10 IU/mL antibody titer) in immunized persons.[13]

In newborns, passive rubella maternal antibodies disappear rapidly 2 months following birth, so the U.S. Centers for Disease Control and Prevention recommends children receive their first dose of the MMR vaccine between 12 and 15 months of age and the second dose later in childhood at age 4 to 6 years. Vaccination is recommended for high-risk groups including nonpregnant women of childbearing age, military recruits, college students, and health care workers. In the United States, a third dose of MMR vaccine may be recommended by state or local health authorities during measles or mumps outbreaks.

The estimated rate of loss of immunogenicity is about 1.2% per year.[14] Repeat vaccination is recommended in patients who are found to be seronegative. In cases of waning immunity, a repeat vaccination will raise the antibody response, but it generally wanes back to baseline. Although most vaccine-related side effects are mild (e.g., rash, fever, sore throat, lymphadenopathy, and headache), arthritis and arthralgia may occur, especially in adolescent rubella-seronegative women, but resolve over time. Rarely, the live attenuated vaccine can produce vaccine-related rubella in immunodeficient or even apparently immunocompetent patients.[15]

A third booster vaccination in seronegative and/or immunocompromised (e.g., after chemotherapy or bone marrow transplantation, or with congenital immune deficiency) children may induce immunity, but a live virus booster vaccination is not recommended for children with immunodeficiency or children who experienced thrombocytopenic purpura after MMR vaccination, due to the increased risks of adverse events after vaccination. Rubella vaccine also should not be given to individuals who had a severe allergic reaction (e.g., anaphylaxis) after a previous vaccine dose, or to patients with a known severe immunodeficiency.

Pregnancy should be avoided for 1 month after MMR vaccination, and the vaccine should be administered postpartum. MMR vaccine can be administered to breastfeeding mothers without any danger to their infant.

Worldwide eradication efforts continue.[16] However, issues with accessibility, public health infrastructure, and hesitancy have hampered such efforts.[17]

PROGNOSIS

Rubella is typically mild and transient in healthy children and adults, with nearly everyone recovering fully. Rubella encephalitis and postinfection panencephalitis, which resemble the subacute sclerosing panencephalitis that can follow measles infection (Chapter 338), occur at a rate of about 1 in 5000 infections and are associated with mortality rates as low as 0% and as high as 50%. Joint problems (e.g., polyarthralgia, polyarthritis), which are common in adults but not in children, are typically transient.[18] Treatment is limited to bed rest, adequate hydration, and mild pain relievers (e.g., acetaminophen or ibuprofen) for aches and fever.[19] The prognosis for congenital rubella syndrome is typically poor; although some specific symptoms can be treated, no cure exists.

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340 MUMPS

JENNIFER B. ROSEN AND JANE R. ZUCKER

DEFINITION

Mumps is an acute viral infection characterized by inflammation of the parotid and other salivary glands. Prior to the introduction of vaccination in the United States, mumps was a common childhood illness. The incidence of mumps declined dramatically after the introduction of the vaccine, but mumps remains endemic. Cases and even outbreaks can occur in previously vaccinated children and adults.

The Pathogen

The mumps virus is an enveloped, negative-strand RNA virus belonging to the Paramyxoviridae family, genus *Rubulavirus*. Twelve mumps genotypes exist, denoted by letters A to N. The diversity of genotypes in circulation in the United States is low, with the majority being genotype G.[1]

EPIDEMIOLOGY

Humans are the only natural host of mumps virus. Mumps is highly contagious and spreads by close person-to-person contact via respiratory droplets. Transplacental transmission has rarely been reported. The incubation period between exposure to the onset of illness ranges from 12 to 25 days. Infected individuals are most likely to be contagious up to 2 days before through 5 days after the onset of symptoms, but individuals who have asymptomatic infections can also transmit the disease.

The introduction of mumps vaccine into the routine childhood immunization schedule for children ages 12 months and older in 1977 led to a dramatic decline in mumps disease in the United States, from over 150,000 cases of mumps in 1968 to about 3000 cases in 1985. In 1989, a second dose of measles-mumps-rubella (MMR) vaccine for children ages 4 to 6 years was added to the routine childhood immunization schedule and led to a further reduction, with an average of fewer than 300 reported cases annually through the early 2000s.[2,3]

However, mumps remains endemic in the United States, and multiple large outbreaks of mumps continue to occur, primarily involving fully vaccinated

ABSTRACT

Mumps was a universal childhood illness in the United States prior to licensure of mumps vaccine in 1967. The national United States routine recommendation for two doses of MMR vaccine has greatly reduced the incidence of mumps, but outbreaks still occur in vaccinated populations. Mumps spreads person-to-person by respiratory droplets. Acute mumps is an infection characterized by inflammation of the parotid and other salivary glands, although 20 to 40% of infections are asymptomatic. Complications of mumps include orchitis in postpubertal males, mastitis and oophoritis in postpubertal females, pancreatitis, sensorineural hearing loss, myocarditis, nephritis, meningitis, and encephalitis. Complications are less common in previously vaccinated individuals. The differential diagnosis for parotitis is broad. Routine diagnostic testing includes a buccal swab for real-time polymerase chain reaction testing as well as serology for mumps immunoglobulin M. No specific treatment is available. Infection is usually self-limited, and treatment is supportive.

KEYWORDS

mumps
parotitis
MMR
mumps vaccine

adolescents and young adults in densely populated settings. For example, a multistate mumps outbreak in 2006 involved more than 6500 people across multiple midwestern college campuses. During 2009 to 2010, large outbreaks occurred in Guam and in New York City, where more than 3500 individuals were infected in a close-knit religious community. From 2015 to 2019, multiple large outbreaks involved schools, universities, athletic teams, and religious groups. In a large outbreak in a close-knit community in Arkansas from 2016 to 2017, approximately 3000 individuals became infected.[4] Approximately 900 mumps cases were identified across 57 detention facilities in 19 states between 2018 and 2019.[5]

Mumps cases and outbreaks among fully vaccinated persons are likely due to a combination of factors.[6] One set of factors relates to the limits of vaccination. First is the potential for a mismatch between the MMR vaccine and the mumps strains in circulation. For example, sera from vaccinated persons against genotype A strain used in vaccines in the United States fully neutralizes the genotype G strain, which is the main genotype that has circulated in the United States since 2006, but geometric mean antibody titers are lower relative to titers against the vaccine strain. In addition, the mumps component of the MMR vaccine is less effective than the measles and rubella components, with an average initial seroconversion rate of 91% and a median two-dose effectiveness of 88%. Furthermore, immunity following mumps-containing vaccine wanes over time.[7,8] A second set of issues relates to infectivity. Persons may be contagious prior to the onset of symptoms or may be asymptomatic throughout their infections. Challenges with diagnostic testing, especially in vaccinated persons, may result in delayed or missed diagnoses, thereby allowing infected individuals to spread the disease. Finally, settings with intense exposures (e.g., colleges and universities, close-knit communities with large congregate gatherings) are conducive to outbreaks.

PATHOBIOLOGY

Mumps virus is presumed to replicate initially in the upper respiratory tract, followed by spread to lymph nodes and viremia. The virus most often then spreads to glandular tissues (e.g., parotid glands, testes, breasts, pancreas) and the central nervous system. Orchitis is caused by the replication of the virus in the seminiferous tubules. Mumps virus enters the central nervous system via venous vasculature of choroidal and ependymal epithelial cells, where it replicates and can enter brain parenchyma. Hearing loss is likely due to infection of the cochlea resulting from spread from cervical lymph nodes into perilymphatic fluid, although immune-mediated damage may also play a role.

Early in the course of infection, patients develop an initial immunoglobulin M (IgM) response (see Diagnosis section), which is followed by immunoglobulin G (IgG). Elevated IgG levels peak at 3 to 4 weeks after infection and can persist for decades.

CLINICAL MANIFESTATIONS

Mumps virus infection classically causes swelling of salivary glands (Fig. 340-1). The parotid gland is most commonly affected (parotitis), but submaxillary and sublingual gland swelling can occur as well. Parotitis can be unilateral or bilateral and usually resolves within 10 days. A prodrome of nonspecific symptoms, including low-grade fever, headache, malaise, myalgia, and anorexia, may precede the parotitis. Nonspecific upper respiratory symptoms may be the only symptom, and approximately 20 to 40% of infections are asymptomatic.

Complications of mumps include orchitis in postpubertal males, mastitis and oophoritis in postpubertal females, pancreatitis, sensorineural hearing loss, arthropathy, myocarditis, nephritis, meningitis, encephalitis, and autoimmune hemolytic anemia. Complications are less common in people who were previously vaccinated against mumps (Table 340-1).

Orchitis is reported in 15 to 35% of postpubertal males but rarely in younger males. Most cases are unilateral, but about 25% may be bilateral. It usually appears about a week after the parotitis but can also occur before or without parotitis. Symptoms can be prominent, with testicular swelling and pain; these symptoms usually resolve within about a week, but tenderness may persist for several weeks. Mumps orchitis can cause testicular atrophy, with a rare risk for subsequent infertility.

In up to 10% of unvaccinated persons with mumps, symptomatic aseptic meningitis can occur and be manifested as headache, neck stiffness, vomiting, and lethargy, usually about 4 to 5 days after onset of parotitis. About 50% of cases of documented mumps meningitis can occur without parotitis. Unilateral and sometimes bilateral hearing loss can occur. Rarely, patients can develop encephalitis with obtundation and seizures, aphasia, and paresis.

DIAGNOSIS

When viral parotitis is suspected, a history of mumps vaccination or detectable mumps IgG does not exclude the possibility of mumps infection in people with clinically compatible symptoms. Mumps-specific diagnostic testing includes collection of both a buccal swab to detect mumps virus by real-time polymerase chain reaction (PCR) testing as well as serology for mumps IgM. Mumps IgM is most likely to be detectable a few days after the onset of symptoms, but it may be transient or absent and often remains undetectable in previously vaccinated individuals, thereby highlighting the importance of PCR testing. PCR is most likely to detect mumps virus when collected soon after the onset of parotitis, but it may be positive for 8 to 10 days after the onset of symptoms. The yield of PCR testing may be increased by massaging of the parotid gland for 30 seconds prior to obtaining the swab. Mumps is a nationally notifiable disease in the United States, and all cases should be reported to the state or local health departments when the diagnosis is initially considered.

The differential diagnosis for parotitis (Chapter 393) is broad, given the various infectious (e.g., bacterial, viral) and noninfectious (e.g., sialolithiasis, ductal strictures, postradiation inflammation) causes of parotitis. Nonmumps causes of viral parotitis include influenza virus (Chapter 332), human parainfluenza viruses (Chapter 331), adenoviruses (Chapter 333), Epstein-Barr virus (Chapter 348), herpes simplex viruses (Chapter 345), enteroviruses (Chapter 349), parvovirus (Chapter 342), and cytomegalovirus (Chapter 347), among others.[9] However, mumps is the only known cause of epidemic parotitis, thereby making a mumps diagnosis more likely during an outbreak.

In suspected mumps meningitis or encephalitis, cerebrospinal fluid (CSF) examination usually shows about 400 to 500 cells/μL, usually monocellular cells but sometimes polymorphonuclear cells early in the course. The CSF

FIGURE 340-1. Mumps. Child with submandibular swelling due to mumps parotitis. (From the Centers for Disease Control and Prevention Public Health Image Library, ID #: 4491.)

TABLE 340-1 FREQUENCY OF COMPLICATIONS AMONG UNVACCINATED AND VACCINATED PATIENTS WITH MUMPS

COMPLICATION	ESTIMATED FREQUENCY AMONG UNVACCINATED MUMPS PATIENTS (%)	ESTIMATED FREQUENCY AMONG VACCINATED MUMPS PATIENTS (%)
Orchitis	30	6
Oophoritis	7	≤1
Mastitis	30	≤1
Pancreatitis	4	<1
Hearing loss	4	<1
Meningitis	<1–10	≤1
Encephalitis	≤1	≤1

Adapted from Marlow M, Leung J, Marin M, et al. Mumps. In Roush SW, Baldy LM, Kirkconnell Hall MA, eds. *Manual for the Surveillance of Vaccine-Preventable Diseases*. National Center for Immunization and Respiratory Diseases, Centers for Disease Control and Prevention. Last reviewed June 30, 2021. https://www.cdc.gov/vaccines/pubs/surv-manual/chpt09-mumps.html. Accessed January 4, 2022.

protein may be mildly elevated, and the glucose level is usually normal but can be low. PCR testing may document mumps virus.

TREATMENT

No specific treatment is available. Infection is usually self-limited, and treatment is supportive based on symptoms (e.g., analgesics, cold compresses, scrotal support for orchitis).

PREVENTION

Vaccination is the most important way to prevent mumps infection. The recommendation (Chapter 15) is two doses of MMR vaccine for children, one at 12 to 15 months and one at 4 to 6 years of age. Adults ages 18 years and older who have not been previously vaccinated and are at high risk for exposure to mumps, including students in post-high school educational settings, health care personnel, and international travelers, should receive two doses of MMR; one dose is recommended for other unvaccinated adults.[10,11]

Presumptive evidence of immunity to mumps includes any one of the following four criteria: documentation of immunization, with the number of doses dependent on age and setting; laboratory evidence of immunity (i.e., detection of mumps IgG); laboratory confirmation of disease (e.g., detection of mumps virus by PCR or mumps IgM by serology); or birth before 1957. Persons who have presumptive evidence of immunity to mumps are less likely to become infected with mumps virus relative to persons without it; however, such evidence should not be used to exclude a diagnosis of mumps. Requirements for documentation of mumps-containing vaccine or laboratory evidence of immunity to mumps are required for health care workers in several states and for children attending childcare and grades kindergarten through 12 in nearly all states.[12,13]

Contraindications to MMR vaccine include a history of severe allergic reaction (e.g., anaphylaxis) to a prior dose of MMR or to any MMR vaccine component, pregnancy, immunosuppression, and congenital or hereditary immunodeficiency in a first-degree relative unless the immunocompetence of the vaccine recipient has been verified.[14] Precautions to MMR vaccine include recent (≤11 months) receipt of an antibody-containing blood product, moderate or severe illness with or without fever, and history of thrombocytopenia or thrombocytopenic purpura. If tuberculosis testing needs to be performed, it should be done either any time before, simultaneously with, or at least 4 to 6 weeks after administration of MMR vaccine. Personal or family history of seizures of any etiology is a precaution to MMR-varicella (MMRV) vaccine because of an increased risk of febrile seizures seen in 12- to 23-month-olds; however, MMR and single antigen varicella vaccine may be given, preferably at the same visit. If not, then the two live virus vaccines, MMR and single antigen varicella, should be given at least 4 weeks apart.

Individuals who have been exposed to mumps virus and who lack presumptive evidence of immunity to mumps should be brought up to date with MMR vaccination to protect them from future exposures. However, vaccination after exposure will not prevent infection from an exposure that has already occurred, and no postexposure prophylaxis exists for individuals who are exposed to mumps virus. Individuals who have been exposed, especially those who lack presumptive evidence of immunity to mumps prior to exposure, are at risk for developing infection throughout the 12- to 25-day incubation period and should monitor for symptoms. Consultation with the local public health department is recommended to determine the need for quarantine during this period.

Given repeated outbreaks among individuals who have received two doses of MMR vaccine in settings with intense, prolonged close contact (e.g., colleges, universities), a third dose of mumps-containing vaccine is recommended for persons who are identified by public health authorities as part of a group at increased risk for mumps due to an outbreak.[15] A third dose in this setting does not serve as postexposure prophylaxis to prevent infection following an exposure that already occurred, but rather aims to reduce infection and complications among people who are at risk for ongoing exposures. Data on duration of protection following a third dose of mumps-containing vaccine are limited and, at this time, use of a third dose is not recommended for routine use in the general population.

Patients who have mumps require at least 5 days of both standard precautions and droplet precautions after the onset of parotitis. Outpatients should wear a mask and be isolated from other potentially susceptible persons. Hospitalized patients require a private room, masking if transported elsewhere in the hospital, and masking for all caregivers.

PROGNOSIS

Most people with mumps infection recover fully. Bilateral mumps orchitis can lead to a temporary reduction in fertility or even transient sterility, but the risk of permanent infertility, though uncertain, appears to be rare. Mumps meningitis is usually self-limited. Hearing loss is usually transient but rarely can be permanent. Death due to mumps is exceedingly rare, with most fatalities due to mumps encephalitis.

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341 POLYOMAVIRUSES

HANS H. HIRSCH

HUMAN POLYOMAVIRUS

DEFINITION

Human polyomaviruses comprise at least 14 species, denoted human polyomavirus 1 to 14,[1] and five of these are associated with human diseases (Table 341-1). Of the types of polyomaviruses that infect humans, the principal causes of human disease are BK polyomavirus, JC polyomavirus, Merkel cell polyomavirus, human polyomavirus 7, and *Trichodysplasia spinulosa* polyomavirus.

The Pathogen

Polyomaviruses are nonenveloped virions that remain infectious for prolonged periods of time in the environment and partly resist alcoholic disinfectants. The small, circular, double-stranded DNA genome of approximately 5000 base pairs encodes for 5 to 6 major viral proteins that cannot be targeted by existing antiviral drugs. Polyomavirus genomes persist in the infected host cell nucleus as extrachromosomal DNA and are highly dependent on host cell proteins such as histones, transcription factors, and RNA- and DNA-polymerases.

EPIDEMIOLOGY

Seroprevalence studies of antibodies against the different human polyomavirus Vp1 capsid proteins indicate different exposure rates ranging from 10% for polyomavirus 9 to above 90% for BK polyomavirus (human polyomavirus 1) and human polyomavirus 10. Primary infections commonly occur independently from one another during childhood and adolescence, with smaller increases in seroconversion until the seventh decade of life. The route of transmission likely involves the respiratory, oropharyngeal, or gastrointestinal tract after direct contact or environmental exposure. There is little if any cross-neutralizing immunity against other human polyomavirus species. Ultimately, the average adult will be infected with 6 to 8 different human polyomaviruses.

PATHOBIOLOGY

The early viral gene region encodes regulatory proteins called large and small tumor antigens that interfere with the functions of pRb-retinoblastoma and the p53-protein, override the cell's control of division, and shift the host cells into S-phase to provide abundant enzymes and building blocks for efficient polyomavirus replication. The resulting hyperproliferative, transformed phenotype inactivates DNA-repair and apoptosis. Human polyomavirus-specific immunity relies upon neutralizing and opsonizing antibodies directed against receptor-binding and other domains on the viral capsid Vp1, thereby interfering with new rounds of infection and clearing circulating viral progeny and debris. Virus-specific CD4 helper and cytotoxic CD8 T cells aid in the clearance of virus-replicating cells. In immunocompetent individuals, these responses are sufficient to minimize local replication and to prevent polyomavirus diseases.

CLINICAL MANIFESTATIONS AND DIAGNOSIS

No specific symptoms or signs have been linked to primary human polyomavirus infection in the general population, presumably because of subclinical

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protein may be mildly elevated, and the glucose level is usually normal but can be low. PCR testing may document mumps virus.

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PROGNOSIS

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Human polyomaviruses comprise at least 14 species, denoted human polyomavirus 1 to 14,[1] and five of these are associated with human diseases (Table 341-1). Of the types of polyomaviruses that infect humans, the principal causes of human disease are BK polyomavirus, JC polyomavirus, Merkel cell polyomavirus, human polyomavirus 7, and *Trichodysplasia spinulosa* polyomavirus.

The Pathogen

Polyomaviruses are nonenveloped virions that remain infectious for prolonged periods of time in the environment and partly resist alcoholic disinfectants. The small, circular, double-stranded DNA genome of approximately 5000 base pairs encodes for 5 to 6 major viral proteins that cannot be targeted by existing antiviral drugs. Polyomavirus genomes persist in the infected host cell nucleus as extrachromosomal DNA and are highly dependent on host cell proteins such as histones, transcription factors, and RNA- and DNA-polymerases.

EPIDEMIOLOGY

Seroprevalence studies of antibodies against the different human polyomavirus Vp1 capsid proteins indicate different exposure rates ranging from 10% for polyomavirus 9 to above 90% for BK polyomavirus (human polyomavirus 1) and human polyomavirus 10. Primary infections commonly occur independently from one another during childhood and adolescence, with smaller increases in seroconversion until the seventh decade of life. The route of transmission likely involves the respiratory, oropharyngeal, or gastrointestinal tract after direct contact or environmental exposure. There is little if any cross-neutralizing immunity against other human polyomavirus species. Ultimately, the average adult will be infected with 6 to 8 different human polyomaviruses.

PATHOBIOLOGY

The early viral gene region encodes regulatory proteins called large and small tumor antigens that interfere with the functions of pRb-retinoblastoma and the p53-protein, override the cell's control of division, and shift the host cells into S-phase to provide abundant enzymes and building blocks for efficient polyomavirus replication. The resulting hyperproliferative, transformed phenotype inactivates DNA-repair and apoptosis. Human polyomavirus-specific immunity relies upon neutralizing and opsonizing antibodies directed against receptor-binding and other domains on the viral capsid Vp1, thereby interfering with new rounds of infection and clearing circulating viral progeny and debris. Virus-specific CD4 helper and cytotoxic CD8 T cells aid in the clearance of virus-replicating cells. In immunocompetent individuals, these responses are sufficient to minimize local replication and to prevent polyomavirus diseases.

CLINICAL MANIFESTATIONS AND DIAGNOSIS

No specific symptoms or signs have been linked to primary human polyomavirus infection in the general population, presumably because of subclinical

ABSTRACT

Polyomaviruses comprise more than 100 species that have been detected in a variety of hosts, including birds, fish, and mammals. At least 14 have been detected in humans and are denoted human polyomaviruses 1 to 14.

Seroprevalence studies of antibodies against the different human polyomavirus Vp1 capsid proteins indicate exposure rates ranging from 10% for human polyomavirus 9 to above 90% for BK polyomavirus (human polyomavirus 1) and human polyomavirus 10. Human polyomavirus infections commonly occur independently from one another during childhood and adolescence, with little if any cross-neutralizing immunity against other human polyomavirus species. Smaller increases in seroconversion are observed until the seventh decade of life. The average adult individual is ultimately infected with 6 to 8 different human polyomaviruses. The route of transmission likely involves the respiratory, oropharyngeal, or gastrointestinal tract after direct contact or environmental exposure.

No specific symptoms or signs have been linked to primary human polyomavirus infections in the general population, presumably because of its subclinical or nonspecific manifestations. In immunocompromised patients, however, human polyomaviruses, especially BK polyomavirus, JC polyomavirus, and Merkel cell polyomavirus, can cause major diseases of the renourinary tract, the central nervous system, and the skin. The specific diagnosis depends on detecting the expression of viral proteins in the affected tissues of patients who have symptoms or signs that are consistent with underlying human polyomavirus. Because of viral persistence, detection of viral genomes by PCR is not sufficient to diagnose disease. Currently available antiviral agents have no proven benefit, so the main treatment is to improve virus-specific immune functions. Such approaches are often slow, limited, or simply not feasible because of the underlying condition that provides the environment for polyomavirus disease.

KEYWORDS

polyoma
immunodeficiency
nephropathy
transplantation
immunosuppression
hemorrhagic cystitis
urothelial carcinoma

TABLE 341-1 HUMAN POLYOMAVIRUSES, THEIR DISEASE, AND POPULATION AT RISK

COMMON NAME	TAXONOMIC NAME	GENERAL TROPISM	SERO-PREVALENCE	SIGNATURE DISEASES (ORGAN)	PATHOGENIC PRINCIPLE	POPULATION AT HIGH RISK
BK polyomavirus (BKPyV)	HPyV1	Kidney, urinary tract	80-95%	Nephropathy (kidney)	Replicative—cytopathic necrosis, inflammatory	Kidney transplantation
				Hemorrhagic cystitis (bladder, ureters, renal pelvis)	Replicative—cytopathic, IRIS	Allogeneic hematopoietic cell transplantation
				Urothelial cancer (ureters, renal pelvis, metastasis)	Non-replicative transforming	Kidney transplantation (rarely other solid organ or hematopoietic cell transplantation)
JC polyomavirus (JCPyV)	HPyV2	Urinary tract, kidney, CNS	60-90%	Progressive multifocal leukoencephalopathy (cerebrum, cerebellum)	Replicative—cytopathic Replicative—cytopathic—inflammatory (progressive multifocal leukoencephalopathy, IRIS)	HIV/AIDS Multiple sclerosis (natalizumab therapy)
				Nephropathy (kidney)	Replicative—cytopathic inflammatory	Kidney transplantation
Merkel cell polyomavirus (MCPyV)	HPyV5	Skin	50-80%	Merkel cell carcinoma (skin, metastasis)		Immunocompromised patients, elderly, sun exposure, chronic hematologic malignancy, solid organ transplantation
Human polyomavirus	HPyV7	Skin	30-70%	Pruritic hyperproliferative keratinopathy (skin)		Immunocompromised patients (solid organ transplantation)
Trichodysplasia spinulosa polyomavirus (TSPyV)	HPyV8	Skin	70-90%	Trichodysplasia spinulosa (skin)		Immunocompromised patients (chronic lymphatic leukemia, solid organ transplantation)

AIDS = acquired immunodeficiency syndrome; CNS = central nervous system; HIV = human immunodeficiency virus; IRIS = immune reconstitution inflammatory syndrome.

or nonspecific manifestations. In immunocompromised patients, however, human polyomaviruses can cause major diseases of the renourinary tract, central nervous system, and skin.

BK POLYOMAVIRUS

BK polyomavirus is the main cause of nephropathy after kidney transplantation, of hemorrhagic cystitis after allogeneic hematopoietic cell transplantation, and of urothelial carcinoma (see Table 341-1). Other manifestations are rare, such as nephropathy of native kidneys, ureteritis-pyelitis, pneumonitis, meningoencephalitis, encephalopathy, and multiorgan failure. BK polyomavirus's four serotypes (I, II, III, IV) can be further divided into 12 subtypes based on their genomic sequences.[2] Seroepidemiologic evidence indicates that BK polyomavirus infects 95% of the general population during childhood, but antibody levels tend to decline during adult life. Following primary viremia, BK polyomavirus establishes a persistent infection in the renourinary tract, and about 10% of seropositive healthy persons have asymptomatic, low-level viruria (median 5000 copies/mL) but no detectable viremia.[3] Substantial weakening of the immune control by immunosuppressive drugs, chemotherapy, cortico-steroids, or lymphocyte-depleting agents typically results in high-level viruria (>10 million copies/mL) that remains clinically silent except in a subgroup of recipients of kidney transplant (Chapter 117) and allogeneic hematopoietic stem cell transplant (Chapter 163).

BK Polyomavirus–Associated Nephropathy

DEFINITION

In BK polyomavirus–associated nephropathy, the structure and function of nephrons is damaged by progressive viral replication, thereby resulting in denuded tubular basement membranes, interstitial inflammation, tubulitis, interstitial fibrosis, and tubular atrophy that cause progressive functional decline and end-stage renal failure.

EPIDEMIOLOGY

BK polyomavirus nephropathy almost exclusively affects recipients of kidney transplants and is rarely diagnosed in other immunocompromised populations despite similar or higher intensity of immunosuppression. Biopsy-proven disease develops in about 8% (range 1% to 15%) of patients in the first 2 years after kidney transplantation,[4,5] but the true rates are higher because focal early-stage involvement, especially in the medulla, is missed by needle biopsy. Given the approximately 75,000 kidney transplants annually in North America and Europe, about 7500 kidney patients per year are at risk for premature renal allograft failure and return to dialysis.

BK polyomavirus–DNAemia levels correlate with onset, extent, and resolution of proven BK polyomavirus–associated nephropathy[6] and then drop to undetectable levels with half-lives of less than 2 hours upon allograft nephrectomy. The risk of BK polyomavirus–DNAemia and nephropathy is higher with tacrolimus compared with cyclosporine immunosuppression, is lower for mTOR inhibitor combinations, and increases following treatment with high-dose corticosteroids for acute rejection (Chapter 117).

Recipient risk factors include male gender, older age, and low or undetectable levels of BK polyomavirus–specific antibodies, as well as lack of certain human leukocyte antigen (HLA)-types such as B51, B7, B8, and A24. Donor risk factors include pretransplant urinary shedding of BK polyomavirus, exposure to a BK polyomavirus subtype to which the recipient does not have detectable antibodies, and an increasing number of HLA-mismatches.

PATHOBIOLOGY

By transplanting the kidney, recipients are exposed to latent or replicating BK polyomavirus in the donor organ. Lack of sufficient BK polyomavirus–specific immunity leaves viral replication unchecked, with corresponding cytopathic changes of the renal tubular epithelial cells. Less frequently, the recipient's own virus gains access to the renal allograft by reflux from the bladder. Lytic release of intranuclear virions permits cell-to-cell spread inside the tubules and to the downstream transitional and urothelial cells, thereby further amplifying viral replication and leading to average viruria of 100 million copies/mL. Increasing cytopathic damage and necrosis induce prominent interstitial inflammation and tubulitis, which are followed by irreversible interstitial fibrosis and tubular atrophy.

CLINICAL MANIFESTATIONS

BK polyomavirus nephropathy is initially asymptomatic without affecting the function of the allograft. As damage to the allograft progresses, however, the serum creatinine concentration increases. High-level viruria develops in 20% to 40% of kidney transplant recipients, approximately 50% of whom develop BK polyomavirus–DNAemia after 0.5 to 2 months as a sign of viral replication in the allograft. Without effective interventions, increasing levels and durations of BK polyomavirus–DNAemia are associated with declining renal allograft function.

DIAGNOSIS

Differentiating acute rejection from viral nephritis is important because the treatments (increasing or reducing immunosuppression) are the opposite of each other. In kidney transplant patients with declining renal function, a biopsy of the renal allograft is commonly indicated to search for T-cell-mediated or antibody-mediated rejection, drug toxicity, and BK polyomavirus nephropathy (Chapter 117). The cytopathic and immunohistochemistry changes of BK polyomavirus nephropathy are characteristic (E-Fig. 341-1).[7] In unclear cases, other viral diseases presenting with intranuclear inclusions (e.g., adenovirus, herpes simplex, and cytomegalovirus) should be excluded.

In kidney transplant patients who present with baseline renal function and sustained or increasing BK polyomavirus–DNAemia, a biopsy is not indicated because allograft biopsy cannot exclude BK polyomavirus nephropathy. Criteria for a clinical diagnosis are: probable BK polyomavirus nephropathy, defined as sustained plasma BK polyomavirus loads of greater than 1000 copies/mL for more than 2 weeks, and presumptive BK polyomavirus nephropathy, defined as plasma BK polyomavirus loads above 10,000 copies/mL or the corresponding genome equivalent.

TREATMENT AND PREVENTION

The treatment of probable, presumptive, and biopsy-proven BK polyomavirus nephropathy consists of reducing immunosuppression.[8] The specific protocols for reducing immunosuppression vary and must be supervised by experts. In general, the options are to reduce the dose of tacrolimus or cyclosporine in one or two steps, targeting trough levels of less than 6 ng/mL and less than 125 ng/mL, respectively. The dose of the antiproliferative drug (e.g., mycophenolic acid or mycophenolate mofetil) is reduced by 50% and discontinued in one or two steps. Oral prednisone is typically tapered to 10 mg or less per day. Patients should have their serum creatinine concentrations measured at least weekly and their plasma viral loads measured at least bi-weekly. Cidofovir, leflunomide, fluoroquinolones, and intravenous immunoglobulin have been administered in addition, but their use is not supported by randomized trials.[9]

Pretransplant screening of donors and recipients for BK polyomavirus viruria or for specific antibody levels is currently not recommended because clinical studies have not assessed the risks and benefits of integrating this information into post-transplantation care. After transplantation, however, all kidney transplant recipients should be screened for BK polyomavirus–DNAemia monthly until 9 months post-transplant, followed by quarterly screening until 24 months post-transplant, to identify patients fulfilling the clinical diagnosis of BK polyomavirus nephropathy. Vaccines are lacking, and drugs with presumed antiviral activity have not proven effective for prevention.

PROGNOSIS

After reducing immunosuppression, plasma viral loads decline in 90% of kidney transplant patients within 6 to 12 months, but allograft rejection may occur in 10% of patients. Longer-term outcomes may be adversely affected by smoldering viral replication, T-cell- and/or antibody-mediated rejection, interstitial fibrosis, and tubular atrophy, all of which promote premature allograft failure within 10 years (Chapter 117). Re-transplantation has been successful after several months of reduced or discontinued immunosuppression and clearance of BK polyomavirus-DNAemia, but recurrent disease may occur.

BK Polyomavirus–Associated Hemorrhagic Cystitis

DEFINITION AND EPIDEMIOLOGY

BK polyomavirus–associated hemorrhagic cystitis describes the triad of painful macrohematuria, high-level viral replication, and denudation and inflammation of the bladder wall.[10] The disease affects 5 to 25% of patients who undergo allogeneic hematopoietic cell transplantation but rarely occurs in recipients of autologous transplants or other immunocompromised patients. Risk factors include myeloablative conditioning; exposure to cyclophosphamide or busulfan; a mismatched, unrelated, or haploidentical hematopoietic cell transplantation donor; or umbilical cord blood transplantation. The onset of the disease is typically at 2 to 8 weeks (range 1 week to 6 months) after engraftment of the allogeneic transplant.[11] In North America and Europe, the annual incidence is approximately 1000 cases per year.

PATHOBIOLOGY

Hematopoietic cell transplantation conditioning regimens abrogate BK polyomavirus–specific immune control and lead to BK polyomavirus viruria at greater than 10 million copies/mL. Of note is that such high viruria levels do not cause symptoms in other clinical settings such as kidney transplantation. When radiation or urotoxic drugs (e.g., cyclophosphamide and ifosfamide) cause subclinical damage to the bladder, BK polyomavirus causes further cytopathic damage, which leads to inflammatory exacerbation, reminiscent of the immune reconstitution inflammatory syndrome (IRIS) after engraftment.

CLINICAL MANIFESTATIONS AND DIAGNOSIS

BK polyomavirus–associated hemorrhagic cystitis presents with the clinical signs of cystitis (e.g., dysuria, urinary frequency, urgency, lower abdominal pain; Chapter 263) and macrohematuria, typically in the peri-engraftment period after allogeneic hematopoietic cell transplantation. Macrohematuria may progress to clot formation, bladder obstruction, and postrenal failure.

The clinical diagnosis of BK polyomavirus-associated hemorrhagic cystitis requires the triad of: clinical signs of cystitis, macrohematuria, and high-level viruria (>10 million copies/mL). Ultrasound or magnetic resonance imaging (MRI) can detect larger clots, urinary retention, hydronephrosis, and involvement of the ureteric and bladder wall. The differential diagnosis includes early-onset hemorrhagic cystitis owing to cyclophosphamide within 1 to 7 days of urotoxic conditioning, other bacterial infections, viruses (e.g., cytomegalovirus, herpes simplex, adenovirus), or parasites, as well as non-infectious causes such as graft-versus-host disease, bleeding disorders, irritation from catheters or stents, and primary or metastatic malignancies.

TREATMENT AND PREVENTION

The treatment of BK polyomavirus–associated hemorrhagic cystitis consists of analgesics (Table 26-4) for symptom relief and supportive therapy, hyperhydration, bladder irrigation, platelet and red blood cell transfusions, and urologic interventions for post–renal obstruction or life-threatening bleeding. Reducing immunosuppression is not recommended because it may precipitate or exacerbate graft-versus-host disease. Fluoroquinolones, leflunomide, brincidofovir, systemic or intravesical cidofovir, and hyperbaric oxygen therapy have been tried in uncontrolled studies but cannot be recommended due to side effects, toxicity, and lack of consistent responses.

Hyperhydration combined with forced diuresis to avoid volume overload can reduce early-onset hemorrhagic cystitis and diminish urotoxic damage of the bladder epithelium. No other preventive approach has evidence to support its efficacy and safety.

PROGNOSIS

About 50% of cases resolve by 3 weeks and 75% by 6 weeks. At 9 weeks, about 10% of patients have persistent disease, and another 10% will die with ongoing disease.

BK Polyomavirus–Associated Urothelial Cancer

DEFINITION AND EPIDEMIOLOGY

BK polyomavirus–associated cancers encompass carcinoma in situ, locally invasive carcinoma, metastasizing carcinoma of the urothelium (transitional cell carcinoma), or, less frequently, tumors of the collecting duct. BK polyomavirus–associated urothelial cancers affect approximately 0.1% of kidney transplant patients and arise 5 to 10 years after transplantation. A history of prolonged immunologically uncontrolled high-level BK polyomavirus–replication or BK polyomavirus nephropathy significantly increases the relative risk by approximately 10-fold.

PATHOBIOLOGY

In BK polyomavirus–associated urothelial cancer, viral tumor antigens appear to induce a phenotype similar to what is seen in BK polyomavirus–negative high-grade urothelial carcinomas (Chapter 182), with mutations in fibroblast growth factor-3 and related downstream tyrosine kinase signaling, as well as inactivation of pRB and p53 function. Subsequent genetic changes and chromosomal instability may remove the dependence on viral tumor antigens, thereby permitting the cancer to progress without expression of the viral tumor antigen.

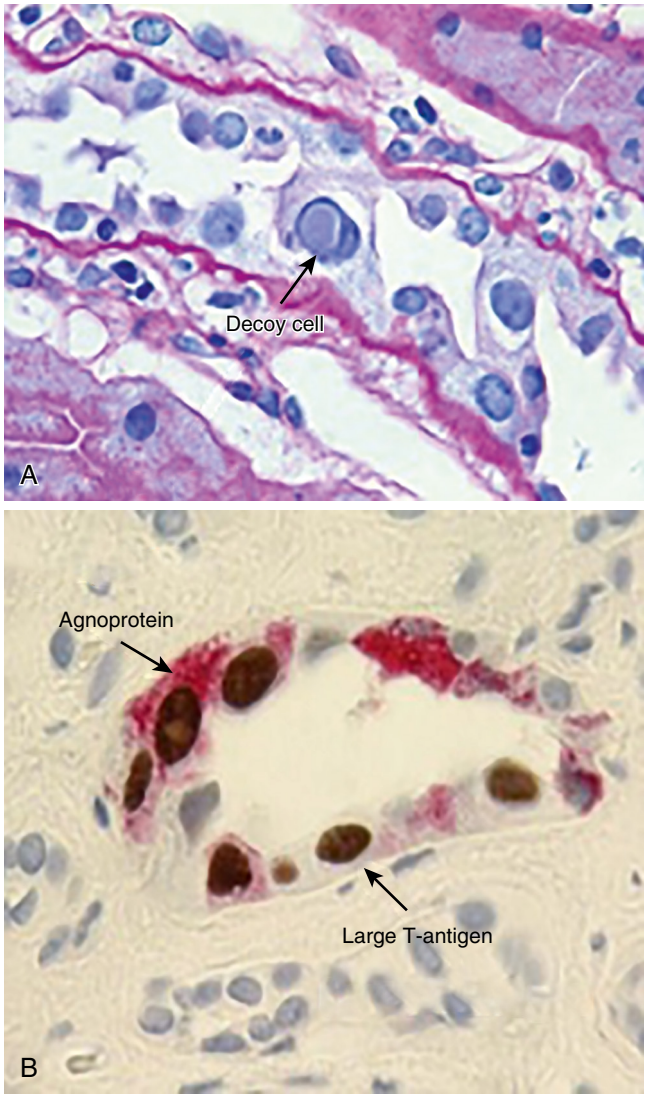

E-FIGURE 341-1. **BK Polyomavirus nephropathy in a kidney allograft biopsy. A,** Renal tubule in tangential cut showing rounded enlarged tubular cells with prominent nucleus and intranuclear ground-glass inclusions. Inflammatory infiltrates are seen in the interstitium and in the epithelial tubular lining with mononuclear cells and granulocytes. (Hematoxylin and eosin stain, magnification 1000×) **B,** Renal tubule in cross-sectional cut showing BK polyomavirus replication side-by-side in early and late phase by immunohistochemistry for the cytoplasmic agnoprotein *(red)* and the nuclear large tumor antigen *(brown),* partly displaced by intranuclear inclusions *(light brown)* (magnification 1000×). (From Leuenberger D, Andresen PA, Gosert R, et al. Human polyomavirus type 1 [BK virus] agnoprotein is abundantly expressed but immunologically ignored. *Clin Vaccine Immunol*. 2007;14:959-968.)

CLINICAL MANIFESTATIONS AND DIAGNOSIS

The clinical manifestations of BK polyomavirus–associated urothelial cancers are similar to other urothelial cancers (Chapter 182). Depending on tumor location and stage, microhematuria or macrohematuria are often accompanied by an abnormal voiding sensation, intermittent obstruction, hydronephrosis, and lymphadenopathy.

BK polyomavirus–associated cancers are diagnosed by biopsy demonstrating expression of the large viral tumor antigen. In kidney transplant patients, the BK polyomavirus–associated cancer cells are typically donor-derived, presumably because transformed cells from the renal allograft nephropathy may seed the bladder.

TREATMENT AND PREVENTION

In addition to standard therapy for the tumors (see Chapter 182), attention should focus on reducing immunosuppression, even if the allograft needs to be abandoned, to ensure the patient's survival.[12] In immunocompromised and, particularly, kidney transplant patients, occupational and leisure exposure to urotoxic substances (Chapter 106) should be avoided, and smoking should be discontinued. Avoiding prolonged high-level BK polyomavirus–replication and nephropathy should be attempted by screening kidney transplant recipients for BK polyomavirus–DNAemia and by prompt reduction of immunosuppression to restore immune control over virally induced urothelial cancers.

PROGNOSIS

The prognosis of BK polyomavirus–associated urothelial cancers in kidney transplant patients depends on tumor stage, location, and invasiveness. Recurrences are frequent, typically occur within 12 months, and often linked to the inability to reduce immunosuppression.

JC POLYOMAVIRUS

JC polyomavirus causes progressive multifocal leukoencephalopathy, which is a demyelinating, often fatal brain disease in immunocompromised patients (e.g., patients with human immunodeficiency virus [HIV]/acquired immunodeficiency syndrome [AIDS]), hematologic malignancies, and patients treated with potent biologics and small-molecule inhibitors. JC polyomavirus also has been linked to rare cases of nephropathy, encephalopathy, meningoencephalitis, and hemorrhagic cystitis. JC polyomavirus is associated with colon cancers, a variety of brain cancers, and urothelial cancer.

In the general adult population, the seroprevalence of JC polyomavirus is about 50 to 60%, but rates of more than 90% are seen in people living with HIV. Asymptomatic urinary shedding of JC polyomavirus is detectable in about one third of healthy seropositive persons at slightly higher levels than BK polyomavirus (about 50,000 copies/mL). Urine JC polyomavirus loads do not increase in immunocompromised patients to the same extent as seen for BK polyomavirus, except in kidney transplant recipients who develop JC polyomavirus nephropathy. Despite a 70% genomic homology with BK polyomavirus, there is little cross-reactivity of capsid antibodies to the two viruses, whereas cross-reactivity at the T-cell level is considerable and has been used for experimental adoptive T-cell therapies.

JC Polyomavirus–Associated Progressive Multifocal Leukoencephalopathy

DEFINITION AND EPIDEMIOLOGY

Progressive multifocal leukoencephalopathy is a demyelinating brain disease caused by lytic replication of JC polyomavirus in oligodendrocytes that produce the myelin sheath in the subcortical layers and rarely neurons of the gray matter. Nearly all patients with progressive multifocal leukoencephalopathy are seropositive for JC polyomavirus at the time of diagnosis, thereby suggesting that the disease arises despite the presence of virus-specific antibodies. Impaired cellular immune control in the brain seems to play a central role.

The incidence of progressive multifocal leukoencephalopathy in the general population is about 0.3 per 100,000 person years in North America and Europe, but it is 10 to 1000-fold higher in patients who have conditions or treatments that profoundly interfere with T- and B-cell immunity, such as lymphoproliferative diseases.[13] The incidence of progressive multifocal leukoencephalopathy among HIV-AIDS patients in the era before effective antiretroviral therapy was about 2.4 per 1000 patient years, reaching a prevalence of 1% to 7%. The incidence among patients with relapsing-remitting multiple sclerosis treated with natalizumab therapy is about 2.13 per 1000 patient years overall, increasing to 11.1 per 1000 patient years among JC polyomavirus–seropositive patients who are treated for longer than 24 months.[14] Newer potent biologicals and small molecule inhibitors that interfere with T and B cell function also are associated with progressive multifocal leukoencephalopathy.[15] Rare cases of progressive multifocal leukoencephalopathy arise in people without known immunodeficiencies, sometimes related to idiopathic CD4 lymphocytopenia or hitherto undiagnosed hematologic abnormalities.

PATHOBIOLOGY

JC polyomavirus replication in oligodendrocytes leads to cell lysis and loss of the myelin sheaths that are required for the function of neural axons. The affected oligodendrocytes lose their characteristic halo and increase in size, with prominently enlarged nuclei and eosinophilic intranuclear inclusions. On electron microscopy, intranuclear virions of 45 nm in diameter are seen. JC polyomavirus genomes in brain tissue and cerebrospinal fluid (CSF) are characterized by rearrangements of the noncoding control region that increase viral replication. As viral replication and demyelination zones expand, lesions with acellular fibrotic centers and increasing atrophy can range from less than 1 mm to several centimeters. Multiple replication zones coalesce and rapidly expand along linear axon-myelin structures in ipsilateral and contralateral subcortex. The lesions typically start in the subcortical white matter and less frequently in the cerebellum or basal ganglia. Infection of neurons defines a separate cerebellar entity called granule cell neuronopathy.

CLINICAL MANIFESTATIONS

The symptoms and signs of progressive multifocal leukoencephalopathy depend on the location and the extent of the lesions in the brain.[16] Sensory or motor deficits of the hands or visual impairments, which reflect involvement of the parietal or posterior brain, respectively, may be noticed very early. Most patients develop progressive motor weakness, followed by speech abnormalities, cognitive deficits, headache, ataxia, aphasia, and cranial nerve deficits.[17] Ophthalmologic symptoms include optic agnosia, oculomotor abnormalities, and cortical blindness. Seizures have been reported at variable rates and are more frequent in association with gadolinium enhancing cortical lesions linked to inflammation.

DIAGNOSIS

In any immunocompromised patient with new-onset focal neurologic deficits or seizures, progressive multifocal leukoencephalopathy is an important possible diagnosis. MRI is the non-invasive diagnostic procedure of choice to identify brain lesions, which are enhancing by fluid-attenuated inversion recovery (FLAIR) and/or T2-weighted imaging, revealing inflammatory signals by T1-gadolinium MRI upon immune reconstitution (Fig. 341-1). HIV/AIDS patients and rituximab-treated patients may show only little or no gadolinium enhancement. Screening of patients with multiple sclerosis can identify early stage or even presymptomatic progressive multifocal leukoencephalopathy.

Detection of the JC polyomavirus–DNA genome in the CSF is sufficient for a laboratory-confirmed diagnosis of presumptive progressive multifocal leukoencephalopathy, but 10 to 30% of eventually proven cases of progressive multifocal leukoencephalopathy remain JC polyomavirus–DNA negative despite repeated CSF sampling. Other CSF studies provide little information. Pleocytosis is absent or mild at fewer than 50 cells/μL, and levels of glucose, lactate, and protein are typically nondiagnostic. Intrathecal antibodies and oligoclonal bands may be detectable on testing performed at specialized settings. Stereotactic brain biopsies, which are rarely indicated unless an alternative diagnosis (such as recurrent multiple sclerosis, primary cerebral lymphoma, toxoplasma encephalitis or other bacterial, fungal, or parasitic diseases) is likely, can make the definitive diagnosis by showing the triad of demyelination in the white matter, compatible cytopathic alterations, and JC polyomavirus involvement by specific immunohistochemistry or in situ hybridization.

TREATMENT

No antiviral agents have proven clinical efficacy for progressive multifocal leukoencephalopathy even though some drugs (e.g., cidofovir, brincidofovir, cytarabine, topotecan, mefloquine, and mirtazapine) inhibit JC polyomavirus replication in vitro. In clinical practice, mirtazapine is frequently prescribed after consideration of drug-drug interactions and escalated from 15 mg daily to the highest tolerated dose of 45 mg daily to treat diagnosis-associated depression

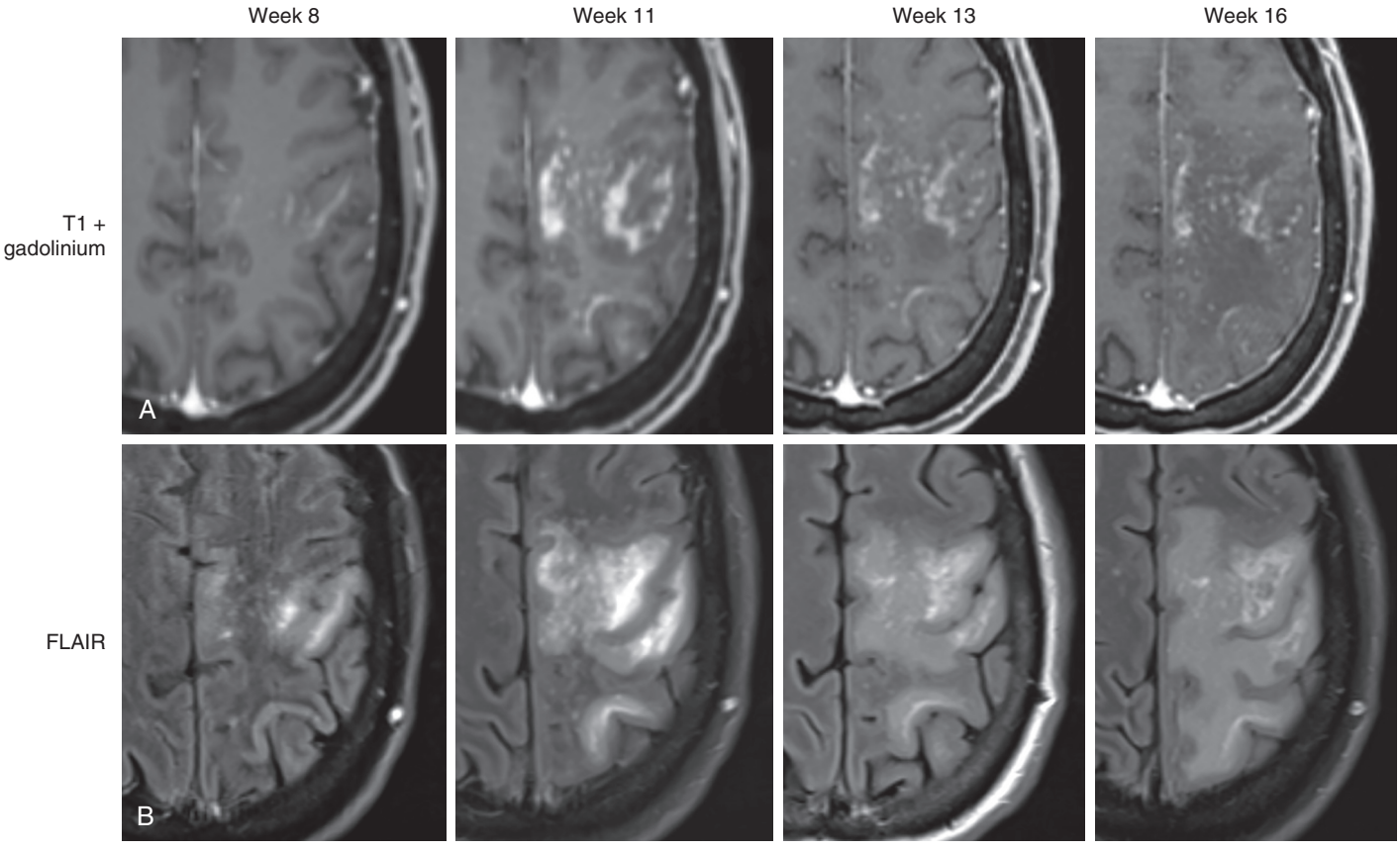

FIGURE 341-1. Cranial magnetic resonance images of progressive multifocal encephalopathy unmasked by the immune reconstitution inflammatory syndrome (PML-IRIS) in a patient with HIV/AIDS. After 8 weeks of combination viral suppressive therapy and recovery of CD4 cells from 20 to 365/μL, the lesions worsened and then improved. **A,** A T1-weighted image with gadolinium enhancement; **B,** Fluid-attenuated inversion recovery (FLAIR).

and possibly to interfere with the entry of JC polyomavirus into glial cells. The main approach to treatment is to regain JC polyomavirus–specific immune control in the brain by reversing the underlying cause of immunodeficiency by suppressing HIV-replication using combination antiretroviral therapy (Chapter 357), discontinuing natalizumab in patients with multiple sclerosis (Chapter 380), or reducing immunosuppression in solid organ transplant recipients whenever possible.[18] When immune reconstitution cannot be readily achieved, experimental approaches to enhance JC polyomavirus–specific immunity include cytokines (e.g., interleukin-2, filgrastim, interleukin-7 alone or in combination with Vp1-capsid or peptide vaccination), intravenous infusions of neutralizing monoclonal antibodies, immune checkpoint inhibitors, and adoptive transfer of related or third-party donor-derived T cells active against JC polyomavirus.[19,20]

Upon brisk recovery of CD4 and CD8 T-cell functions and their homing to the sites of JC polyomavirus replication in the brain, paradoxical clinical worsening can occur due to the immune reconstitution inflammatory syndrome (IRIS). IRIS can be seen as early as 1 to 2 weeks and up to several months after the introduction of antiretroviral treatment in 30% of HIV/AIDS patients but is encountered in nearly all multiple sclerosis patients after discontinuing natalizumab. IRIS can lead to brain swelling with mass effect, herniation, and even death. Intravenous methylprednisolone (1 g/kg for 5 to 7 days) or dexamethasone (6 to 8 mg 4 times daily for 7 to 10 days) followed by oral tapering can stabilize or improve clinical symptoms and radiologic abnormalities, but at the expense of recurring JC polyomavirus replication. Anecdotal evidence supports high-dose, steroid-saving intravenous immunoglobulin (0.5 to 2.0 g/kg 3 times per week for 3 weeks, followed by tapering).

PREVENTION

The prevention of progressive multifocal leukoencephalopathy is difficult because of its seemingly sporadic occurrence in immunocompromised patients. For HIV/AIDS patients, antiretroviral therapy (Chapter 357) to suppress HIV replication to undetectable levels has reduced the incidence of the disease to rare late presenters. For patients who have multiple sclerosis (Chapter 380) and qualify for natalizumab therapy, use of the drug requires careful patient counseling and MRI surveillance. For example, in patients who have multiple sclerosis with prior immunosuppressive treatment and JC polyomavirus–positive serology indicative of persistent infection, the risk of progressive multifocal leukoencephalopathy after 24 months of natalizumab treatment is 4 to 10 per 1000 patients, so screening MRI should be performed every 3 to 4 months. For patients without prior immunosuppressive treatment and no JC polyomavirus antibody levels, the risk of progressive multifocal leukoencephalopathy is less than 0.1 per 1000 patients, and screening patients for JC polyomavirus seroconversion is recommended to identify patients for 3- to 4-monthly MRI screening for progressive multifocal leukoencephalopathy.

PROGNOSIS

The prognosis of progressive multifocal leukoencephalopathy is closely linked to the extent and location of involvement at the time of diagnosis, the underlying cause of immunodeficiency, and the ability to revert, modify, or compensate for the missing JC polyomavirus–specific immune control. Approximately one-third of patients recover with no or only slight disabilities, one-third have significant disabilities, and one-third die within 12 months. Somewhat better outcomes are observed for natalizumab-treated patients with multiple sclerosis, especially if they are asymptomatic or have only minimal involvement at the time of diagnosis. The poorest outcomes, with fatality in more than 90% of cases, are seen in patients with hematologic malignancies or in heart or lung transplant recipients because of the inability to induce timely immune recovery. At the other extreme, the immune reconstitution inflammatory syndrome may significantly complicate the course and impair outcomes because of the need to treat with corticosteroids that facilitate viral replication. Eventually, the affected brain areas convert into fibrotic zones with progressive atrophy visible on MRI, but some functional compensation may be possible by training other domains, especially in younger patients.

JC Polyomavirus–Associated Nephropathy

JC polyomavirus–associated nephropathy describes damage to nephrons when replication of JC polyomavirus in renal tubular epithelial cells leads to progressive functional decline and irreversible end-stage renal failure. JC polyomavirus nephropathy occurs in less than 1% of kidney transplant patients. Affected patients have high-level JC polyomavirus viruria with urine viral loads greater than 10 million copies/mL.

JC polyomavirus nephropathy is asymptomatic, despite signs of declining renal function. The disease may be suspected when the more common BK polyomavirus–DNA is undetectable in blood or urine. Kidney biopsy is required to make the diagnosis.

Treatment is to reduce immunosuppression, but at the risk of precipitating acute rejection. No antiviral or vaccine is available for prevention. Notably, the risk of progressive multifocal leukoencephalopathy does not seem to be increased among patients with JC polyomavirus nephropathy.

MERKEL CELL POLYOMAVIRUS

Merkel cell polyomavirus is part of the general human skin microbiome, with a prevalence ranging from 30 to 80%. Higher rates in adults over age 60 years suggest continued life-time exposure.

Merkel Cell Polyomavirus–Associated Carcinoma

Merkel cell carcinoma is a rapidly growing, metastasizing skin malignancy with neuroendocrine and proprioceptive features. The tumors harbor chromosomally integrated Merkel cell polyomavirus genomes in 80 to 90% of cases. The incidence in the United States has increased to about 0.7 cases per 100,000 person-years. The key risk factors are fair skin, chronic sun exposure, increasing age, and immunodeficiency. More than 95% of Merkel cell carcinomas occur in persons of White ethnicity, showing an approximately three-fold rise in incidence per decade of age. Males are affected about twice as often as females. Other risk factors include immunodeficiency from HIV/AIDS, hematologic malignancies, and transplantation. For example, rates of Merkel cell carcinoma are approximately 20 times higher among recipients of solid organ transplants.

The pathogenesis of Merkel cell carcinoma is thought to involve Merkel cell polyomavirus infection of the epidermis, possibly via sites of reduced integrity or damage. Extensive viral replication in systemically immunocompromised hosts synergizes with local effects of ultraviolet light to weaken local immunity and induce chromosomal integration.[21]

CLINICAL MANIFESTATIONS AND DIAGNOSIS

Merkel cell carcinoma presents as asymptomatic, rapidly growing shiny bluish pink nodules with a smooth surface, typically located in chronically sun-exposed areas of the head, neck, and upper extremities (Fig. 341-2A),[22] and less frequently on the trunk and lower extremities. Regional lymph nodes may be enlarged.

The diagnosis is based on histopathology showing dense small uniform round cells with basophilic nuclei and minimal cytoplasm organized in trabecular, intermediate, small cell, and mixed type-denoted structures (see Fig. 341-2B).[23] Staining for Merkel cell polyomavirus large tumor antigen and cytokeratin 20 expression is often used for diagnosis. Because of its high prevalence in the general population, detecting the Merkel cell polyomavirus genome in a skin biopsy is not pathognomonic for Merkel cell carcinoma unless replication-crippling mutations or chromosomal integration are documented.

TREATMENT AND PREVENTION

Treatment is guided by staging at the time of diagnosis.[24] Stage I is defined as a tumor size of less than 2 cm without nodal or distant metastasis. Stage IIA is a larger tumor but without local invasion, whereas stage IIB is defined as a tumor of any size invading local structures but is not accompanied by nodal involvement or distant metastasis. Stage III is defined by lymph node involvement, regardless of tumor size, but without distant metastasis. Stage IV is defined by the presence of distant metastases regardless of the size of the tumor or lymph node involvement.

Complete surgical removal of the tumor and of sentinel lymph nodes is recommended for initial therapy and staging. If the primary tumor cannot be completely removed or if sentinel lymph nodes are positive, regional lymph node resection and radiation therapy is recommended. In immunosuppressed patients, immunosuppression should be reduced if possible according to the underlying condition. Immunotherapy with immune check-point inhibition (e.g., the PD-1 inhibitors nivolumab or pembrolizumab, PD-1 ligand blockade by avelumab, or the CTLA-4 inhibitor ipilimumab) under expert supervision have dramatically improved outcomes and are becoming standard of care. Chemotherapy is recommended when immunotherapy fails and for metastatic disease or recurrent disease, either alone or in combination with local radiotherapy. Experimental therapies using MCPyV-specific adoptive T cells or targeting growth factor receptors or tyrosine kinase signaling pathway are being explored in clinical trials.

Strict avoidance of sun exposure is recommended in elderly, immunosenescent, and immunocompromised patients. Correcting the underlying immunodeficiency can prevent Merkel cell carcinoma in HIV/AIDS patients but may not be feasible in other patients.

PROGNOSIS

Invasiveness and rapid growth are key determinants of outcome, and 5-year overall survival ranges from approximately 80% in stage I disease to less than 20% in stage IV disease. Lesions on the scalp tend to be larger than 5 cm and have an increased risk of distant metastasis, whereas tumors on the lips are more likely to invade local structures. Merkel cell polyomavirus–positive patients have a better prognosis presumably because expression of the viral tumor antigen enhances recognition and killing by CD8 T cells. Patients who have Merkel cell carcinoma also are at increased risk of other malignancies.

OTHER CUTANEOUS HUMAN POLYOMAVIRUS–ASSOCIATED DISEASES

Human Polyomavirus 6 and 7–Associated Pruritic Hyperproliferative Keratinopathy

The seroprevalence of human polyomavirus 7 in the general population increases substantially with age from 40% at age 20 years to more than 70% after age 70 years, whereas the seroprevalence of human polyomavirus 6 is already 80% by early adolescence. In profoundly immunocompromised patients, such as after heart or lung transplantation, a widespread maculopapular eruption has been described predominantly on the trunk and the extremities but sparing palmoplantar surfaces, facial, axillary, and inguinal areas. Skin biopsy shows dyskeratotic cells in the epidermis and layers of nucleated keratinocytes in the stratum corneum. Immunohistochemistry demonstrates replicating human polyomavirus 7 or human polyomavirus 6.

No treatment has proven efficacious. Oral antihistamines, topical pramoxine, and emollients can be used for symptomatic treatment of pruritus (Table 403-10). Systemic acitretin (25 mg daily or twice daily) has shown anecdotal success, whereas topical corticosteroids are ineffective or even deleterious. Reducing immunosuppression may be helpful. Ultraviolet light therapies should be avoided. Despite treatment, sleep-disturbing pruritus and the extensive manifestations severely decrease quality of life.

Polyomavirus-Associated Trichodysplasia Spinulosa

In the general population, the seroprevalence for trichodysplasia spinulosa polyomavirus (human polyomavirus 8) increases from 20% in children younger than age 10 years to more than 80% in adults older than age 50 years. The prevalence of trichodysplasia spinulosa polyomavirus in skin swabs or in blood samples from healthy blood donors is low, ranging from 0.3% to 3.0%. The disease is rare, with fewer than 100 cases described, mostly in patients who have hematologic malignancies or who are on chronic immunosuppressive medications and who develop primary viral infection.

Affected follicular keratinocytes are characterized by hyperproliferation with enlarged eosinophilic trichohyaline granules and enlarged cell nuclei with intranuclear inclusions of polyomavirus particles. Molecular testing reveals high loads of trichodysplasia spinulosa polyomavirus–DNA.

The key features of trichodysplasia spinulosa are painless folliculocentric papular eruptions in the face, spicule formation with distention of skin pores, loss of hair formation most prominently visible by disappearance of eyebrows and eye lashes, and progressive thickening of the skin. The clinical diagnosis is confirmed by a skin biopsy revealing dilated follicles, keratin plugs, abnormal differentiation of inner hair root sheaths, absent hair bulbs, and immunohistochemistry that detects viral protein expression.

Topical cidofovir (1 to 3%) can provide partial response, but topical steroids are ineffective. Reduced immunosuppression can be helpful, but the disease persists or progresses until immune control becomes effective. Physical removal of spicula may provide some cosmetic relief, but the risk of developing scars versus the benefit of stimulating immunity is uncertain. The disease is not life-threatening, but disfiguring skin manifestations cause significant distress.

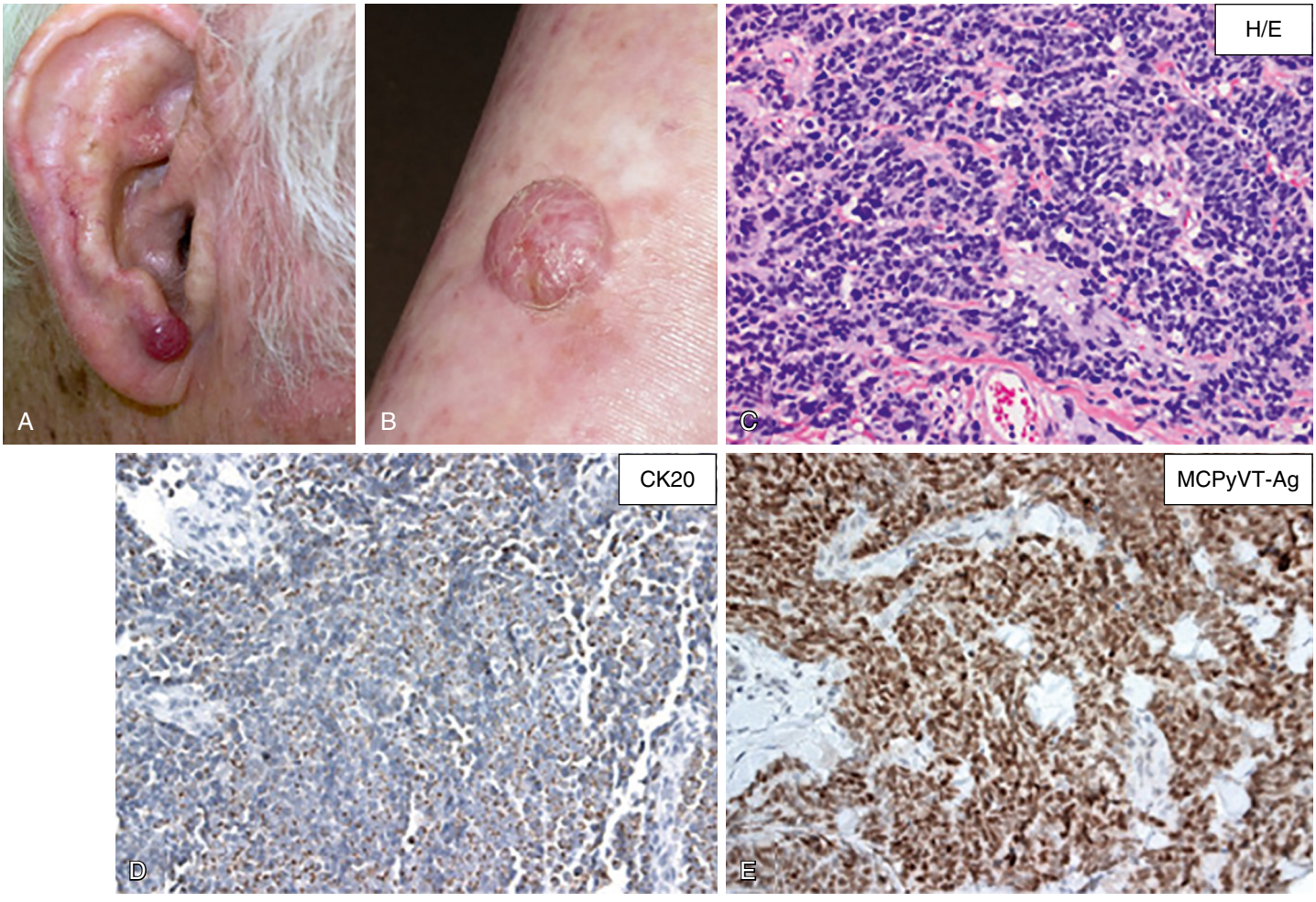

FIGURE 341-2. Merkel cell polyomavirus carcinoma. Clinical features. **A**, A 92-year-old man who presented with a rapidly growing red nodule on the right earlobe. **B**, A 77-year-old woman who presented with a 2.0 × 1.6 cm raised lesion on the anterior lower extremity. **C**, Numerous round basophilic cells, with an increased nuclear : cytoplasmic ratio and nuclear molding, are crowding out the dermal stroma (Hematoxylin and eosin stain). **D**, Immunohistochemistry staining shows the classic dot-like perinuclear expression pattern of CK20. **E**, Anti–Merkel cell polyomavirus T antigen antibody (CM2B4 clone) shows nuclear expression of Merkel cell polyomavirus oncoprotein in a virus-positive Merkel cell carcinoma. (From Akaike T, Nghiem P. Scientific and clinical developments in Merkel cell carcinoma: a polyomavirus-driven, often-lethal skin cancer. *J Dermatol Sci*. 2022;105:2-10.)

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342 PARVOVIRUS

NEAL S. YOUNG

DEFINITION

B19 parvovirus, which was discovered in the mid-1970s by electron microscopy of an anomalous precipitin reaction of a blood donor's serum (occupying position 19 in plate B), was first linked to human disease by the observation of virus-specific immunoglobulin M (IgM) antibody or the virus itself in the sera of sickle cell disease patients suffering transient aplastic crisis (Chapter 149). The common illness caused by the virus was identified later during outbreaks of fifth disease, a highly contagious rash illness of childhood long suspected of having a viral etiology. The ability of parvovirus to persist and to be manifested as an isolated hematologic syndrome was demonstrated by the presence of the virus in fetal liver at autopsy of hydropic newborns and in immunosuppressed patients with chronic pure red cell aplasia (Chapter 151).[1]

The Pathogen

The parvoviruses, which are small icosahedral capsids of about 25 nm, contain a limited genome of single-stranded DNA. The approximately 5600 nucleotides of B19 parvovirus show remarkably little sequence variation among isolates; two variants, V9 and A6, are of uncertain clinical significance.

The Parvoviridae family contains many pathogenic animal viruses: feline panleukopenia virus, the cause of a fatal agranulocytosis in cats; canine parvovirus, which probably arose from the cat virus as a host range variant in the 1970s to produce a global pandemic and can cause fatal myocarditis in puppies; Aleutian mink virus infection, a model of immune complex disease; and porcine parvovirus, responsible for fetal wastage in pig litters. Antibodies to human adeno-associated viruses, which are dependoparvoviruses that are now popular as gene therapy vectors, occur naturally in humans, but B19 is the only parvovirus known to be pathogenic in humans.

EPIDEMIOLOGY

B19 infection is global; infectivity rates, inferred from the presence of antiparvovirus IgG antibody in sera, are similar worldwide. Only isolated populations, such as Amazonian tribesman and residents of remote islands off the coast of Africa, have escaped exposure. B19 parvovirus infection is common in childhood, and half of 15-year-old adolescents have specific antiparvovirus B19 antibodies. Infection continues throughout adult life, and most elderly people are seropositive. In temperate climates, infections occur in the spring, with small epidemics every few years being typical. Transmission is respiratory by droplet spread, and secondary infection rates among household contacts are high. Nosocomial infection can occur, and B19 parvovirus has been transmitted in blood products, especially pooled components such as factor VIII and IX concentrates. Producers of plasma derivatives now voluntarily screen by quantitative measurement of B19 DNA to reduce the risk for iatrogenic transmission. The lack of a lipid envelope and the stable DNA genome make parvoviruses notoriously resistant to heat inactivation and solvent detergents.

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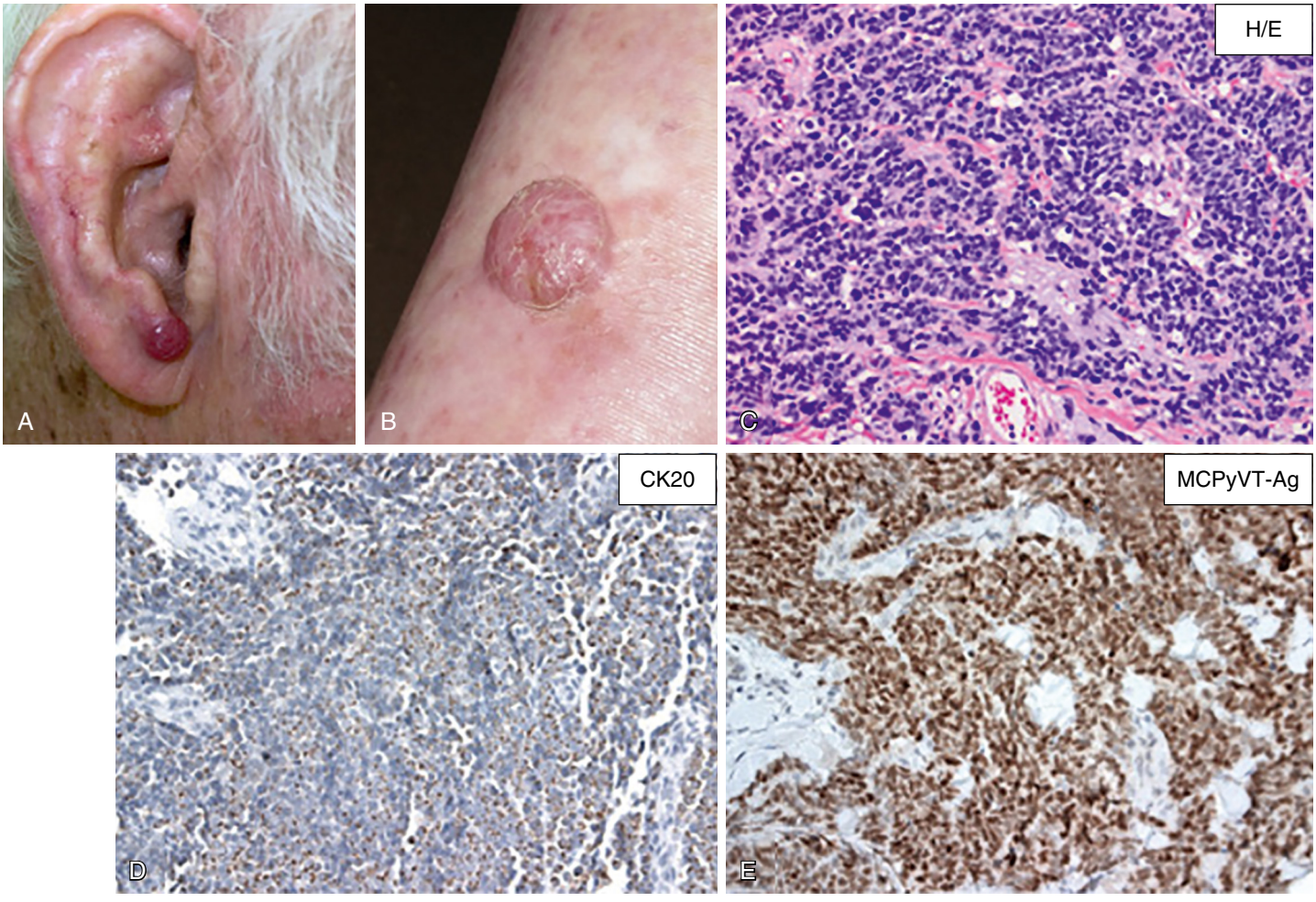

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ABSTRACT

Parvovirus B19 causes diverse important human diseases. The target of the virus is the erythroid progenitor cell, and the neutralizing antibody response dominates effective immunity. Acute infection in normal persons is fifth disease, which is a contagious rash illness in childhood and often a rheumatic syndrome in adults. Under conditions of stressed red cell production, B19 causes transient aplastic crisis, typically a severe worsening of anemia in a patient with sickle cell disease. In immunocompromised individuals, viral infection is persistent and can cause pure red cell aplasia. Infection of the mid-trimester fetus can result in hydrops fetalis.

KEYWORDS

anemia
red cell aplasia
hydrops
fifth disease
P antigen
globoside

PATHOBIOLOGY

The biology of the Parvoviridae makes them dependent on helper function from host cells or other viruses. The autonomous parvoviruses propagate in actively dividing cells; the family Parvoviridae includes many disease-causing animal parvoviruses. Adeno-associated viruses grow in tissue cultures infected with adenoviruses and herpesviruses and are popular vectors for gene transduction and therapy. B19 is the type member of the *Erythrovirus* genus, which includes similar simian viruses, all of which are best propagated in the erythroid progenitor cells that are responsible for red blood cell production in the bone marrow. Active replication of virus can be detected by the presence of double-stranded intermediate forms using simple DNA hybridization methods. The transcription map of the erythroviruses differs markedly from that of other Parvoviridae. Only a few genes produce proteins of known function. Many antigenic determinants recognized by the host immune system are located in helical loops that form the surface of each capsomere. Most of the capsid is composed of a major structural protein, called VP2, but about 5% of the capsid is the minor structural protein, VP1, which differs from VP2 by an additional 226 amino acids at the amino terminus; this VP1 unique region is located external to the capsid surface and contains linear epitopes recognized by neutralizing antibodies. VP1, which is not only immunodominant but also critical for viral entry into permissive cells, also has phospholipase A2 activity that promotes release of virions from infected cells.

The only known natural host cell of B19 parvovirus is the human erythroid progenitor. The tropism of the virus for an erythroid cell results from its cellular receptor, globoside, a neutral glycolipid also known as erythrocyte P antigen. Rare individuals with the p phenotype, who congenitally lack globoside on their erythrocytes, are genetically insusceptible to B19 parvovirus infection; they show no serologic evidence of previous infection, and their marrow erythroid progenitors proliferate normally in the presence of high concentrations of virus. Parvovirus kills erythroid progenitors by expression of its nonstructural protein, and it is possible that some cells, such as megakaryocytes, may be lysed by restricted expression of viral proteins in the absence of viral propagation. B19 can be efficiently propagated in tissue culture of primary human hematopoietic cells in which erythropoietic differentiation is stimulated by erythropoietin. There is evidence that parvovirus DNA can integrate into the genome of erythroid precursor cells in tissue culture.

The humoral immune response is dominant in B19 parvovirus infection. Levels of the chemokine CXCL-10 rise with acute viremia. Natural antibody production correlates with disappearance of the virus from blood, and the presence of IgG appears to confer lasting protection against a second infection. Parvovirus infection can persist if immunoglobulin production is defective such that antibody fails to neutralize the virus; reactivity of antibodies to the unique amino-terminal region of VP1 is especially important.

CLINICAL MANIFESTATIONS

Most B19 parvovirus infections are asymptomatic. However, infections can precipitate specific clinical syndromes such as erythema infections and pure red cell aplasia, as well as a variety of signs and symptoms that may be difficult to distinguish from other viral infections.[2-4]

Fifth Disease

The most common clinical manifestation of infection is erythema infectiosum, or fifth disease, a rash illness of childhood characterized by a "slapped cheek" appearance (Fig. 342-1).[5] In adult volunteers inoculated intranasally with B19, nonspecific influenza-like complaints occur early along with viremia, and such symptoms are also noted with natural infection.[6] The cutaneous eruption a week later corresponds with the appearance of antiviral antibodies. These more specific symptoms of B19 parvovirus infection are secondary to immune complex formation and deposition. The rash of fifth disease is typically evanescent, and recurrences can be provoked by sunlight, heat, emotion, or exercise. Fifth disease can be easily confused with rubella (Chapter 339). In adults, the rash is less characteristic, can present as palpable purpura, may be associated with pruritus in up to 50% of patients, and can be difficult to visualize in dark-skinned individuals.

B19 Arthropathy

In contrast to the mild course in children with fifth disease, acute parvovirus infection in adults, particularly immunocompetent middle-aged women, may cause significant arthropathy.[7] Not only arthralgia but also a true inflammatory arthritis can occur in older patients. Symmetrical joint involvement of the hands, ankles, knees, and wrists may resemble rheumatoid arthritis (Chapter 243), and the test result for rheumatoid factor may be positive. B19 arthropathy usually resolves within a few weeks; joint destruction does not occur. Parvovirus is not the cause of rheumatoid arthritis, but case reports suggest that B19 infection may mimic, precipitate, or worsen a variety of rheumatologic diseases, including juvenile rheumatoid arthritis, systemic lupus erythematosus, and fibromyalgia. Autoantibodies that can appear during infection may be the link between the virus and its immune-mediated manifestations.

Transient Aplastic Crisis

In patients with hematologic malignancies, a recent hematopoietic stem cell transplant, chronic hemolysis, or a high demand for erythrocytes, acute B19 parvovirus infection causes a transient aplastic crisis, which is an abrupt cessation of red blood cell production that exacerbates or, in previously compensated states, provokes severe anemia.[8] Erythropoiesis is temporarily suppressed in all B19 parvovirus infections, but hemoglobin levels remain stable because of the long lifespan of erythrocytes. The anemic crises associated with low or absent reticulocytes in hereditary spherocytosis and sickle cell disease are virtually always secondary to B19 parvovirus infection.

Parvoviremia is present in patients with transient aplastic crisis, and red cell production resumes once antibodies to the virus are produced and the infection is cleared. Transient aplastic crisis is generally a unique event in the patient's life, thereby suggesting induction of long-lasting protective immunity. Although it is self-limited, aplastic crisis often requires transfusion and can lead to severe, occasionally fatal anemia that precipitates heart failure and cerebrovascular accidents. Transient aplastic crisis is associated with a stereotypical bone marrow morphology, absence of maturing erythroid precursors, and the presence of "giant pronormoblasts" (Fig. 342-2) that are the cytopathic effect of parvovirus infection.

White blood cell and platelet counts may fall during transient aplastic crisis, especially in patients with functioning spleens. Occasional cases of agranulocytosis may be due to B19; thrombocytopenia and pancytopenia have been reported, and B19 can precipitate virus-associated hemophagocytic syndrome. In a large series of Egyptian patients with hereditary hemoglobinopathies, B19 infection documented by seroconversion was associated with reversible bone marrow failure, acute kidney injury, and extreme hyperbilirubinemia.[9]

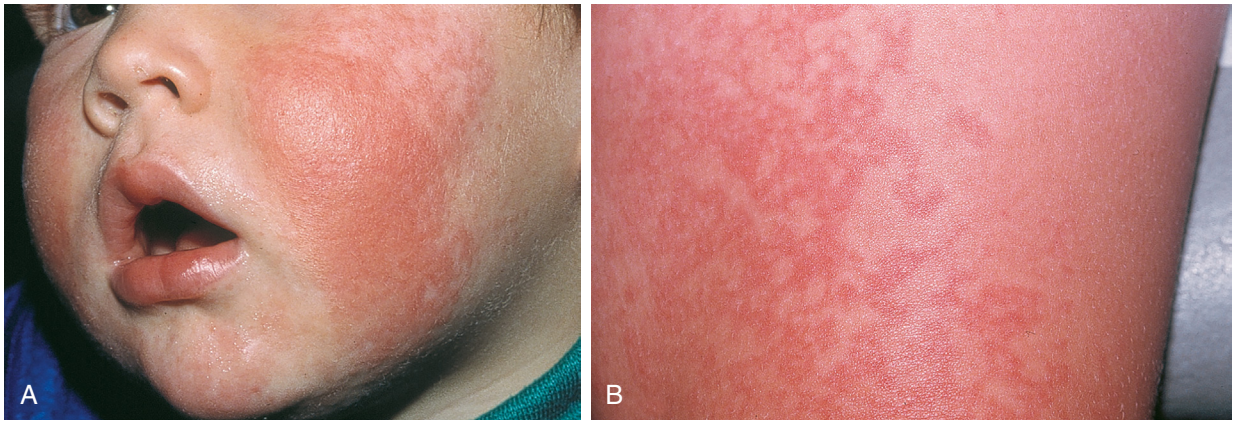

FIGURE 342-1. Erythema infectiosum. B19 infection in a child, manifesting typical prominent erythema of the cheeks ("slapped cheeks") (**A**), followed by lacelike erythema on the extremities (**B**) and buttocks. Historically denoted fifth disease, it is more appropriately termed acute parvovirus infection.

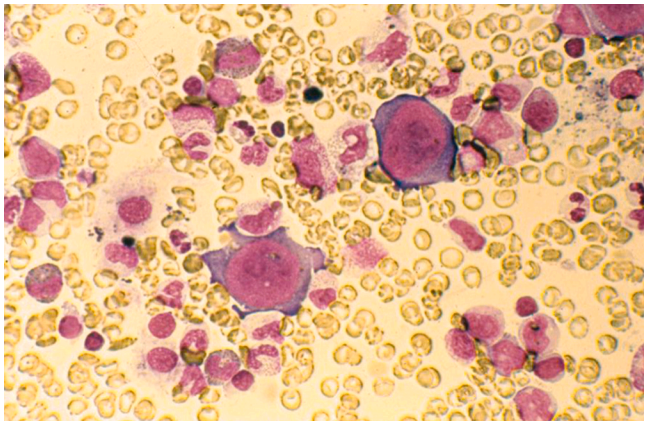

FIGURE 342-2. Bone marrow aspirate of a patient with chronic pure red cell aplasia secondary to persistent B19 parvovirus infection. Mature erythroid precursors are absent, and prominent giant pronormoblasts are typical of B19 infection.

Persistent Infection

In patients who cannot mount an appropriate host antibody response, B19 parvovirus persists in the circulation, often at extremely high levels (>10^{12} genome copies per milliliter). Patients do not develop the clinical features of fifth disease but instead have an entirely hematologic syndrome of pure red cell aplasia. The anemia is severe and requires transfusion; reticulocytes are absent from blood, and erythroid precursors are absent from the bone marrow. Observation of marrow giant pronormoblasts leads to the diagnosis. Failure to produce neutralizing antibodies to B19 parvovirus occurs in patients with congenital immunodeficiency (Nezelof syndrome), with iatrogenic immunodeficiency (from chemotherapy or immunosuppressive drugs), and with acquired immunodeficiency. Pure red cell aplasia secondary to parvovirus has been the first manifestation of acquired immunodeficiency syndrome (AIDS), but this presentation is now uncommon in the era of highly active antiretroviral therapy.

Hydrops Fetalis

B19 parvovirus infection of the pregnant mother followed by transplacental transmission to the fetus can lead to an adverse outcome, either miscarriage or hydrops fetalis.[10] Parvovirus infects the fetal liver, the site of erythrocyte production during early development. Hydrops is the result of severe anemia as well as perhaps myocarditis, contributing to congestive heart failure. Prospective studies have estimated a 30% risk for transplacental infection and 9% risk for fetal loss in women who are exposed to B19 during pregnancy. Infection during the second trimester poses the greatest risk for birth of a hydropic infant; B19 parvovirus accounts for 10 to 20% of all cases of nonimmune hydrops fetalis. The risk for spontaneous abortion resulting from first-trimester infections has been more difficult to quantitate. The likelihood of an infection increases in epidemic years and correlates with the level of contact of the pregnant woman with children. Although most B19 infections during pregnancy do not lead to either loss of the fetus or congenital anomalies, B19 infection is a cause of fetal death. Congenital malformations have not been associated with intrauterine parvovirus infection. However, severe anemia at birth with bone marrow histology consistent with either constitutional pure red cell aplasia (Diamond-Blackfan anemia) or congenital dyserythropoietic anemia has occurred in infants salvaged by in utero blood transfusions or exchange transfusion at birth.

Other Syndromes

Elevated hepatic aminotransferase levels can accompany fifth disease, and parvovirus infection has been associated with severe but usually self-limited hepatitis in some children. The presence of B19 genetic sequences in cardiac tissue has led to a diagnosis of parvovirus myocarditis.[11] Serologic and DNA evidence of B19 infection implicated parvovirus in some patients with necrotizing vasculitis, Kawasaki disease, Henoch-Schönlein purpura, and giant cell arteritis. Glove-and-sock syndrome, an exanthem localized to the hands and feet and consisting of edema, erythema, paresthesia, and pruritus, has been linked to B19. Chronic fatigue syndrome may follow parvovirus infection. Meningitis, encephalitis, and a variety of neurologic complications may occur with fifth disease and parvovirus infection.[12,13]

Subtle late effects of viral infection, not related to persistent infection, may include a worsening of the manifestations of malaria (Chapter 316), especially the severity of anemia. Previous viral infection also has been linked to cerebral infarctions in patients with sickle cell diseases[14] and to arterial ischemic strokes in pediatric populations.

However, false-positive results arise when the diagnosis of infection rests on detection of amplified B19 genome by polymerase chain reactions. Furthermore, B19 parvovirus can persist at low levels in various tissues of normal individuals for many months after infection. For example, whole genome sequencing has detected B19 in 0.12% of individuals without apparent infectious disease, usually but not always at relatively low viral abundance.

TABLE 342-1 DIAGNOSIS OF PARVOVIRUS B19

DISEASE	IgM	IgG	B19 DOT BLOT*	B19 PCR
Fifth disease	+++	++	–	+
Polyarthropathy syndrome	++	+	–	+
Transient aplastic crisis	+/–	+/–	++	++
Persistent anemia	+/–	+/–	++	++
Hydrops/congenital infection	+/–	+	+/–	++
Previous infection	–	++	–	+/–

*Sensitivity about 106 genome copies per milliliter.
Ig = immunoglobulin; PCR = polymerase chain reaction.

DIAGNOSIS

Laboratory diagnosis relies on DNA and serologic testing (Table 342-1). Although virus-specific IgM antibodies are diagnostically positive in almost all cases of fifth disease at initial evaluation and appear within a few days of the onset of transient aplastic crisis, IgM may persist for months after acute infection, IgG circulates later than IgM, generally at the end of the first week of illness. Although titers of IgG are generally highest in the year after an acute infection, substantial interindividual variation and the presence of IgG in a large proportion of the population make measurement of IgG less helpful than other tests for diagnosis of parvovirus.

DNA assays are required to diagnose persistent B19 infection, in which antibody production is absent or minimal. Parvovirus can also be found in the sera early in transient aplastic crisis. Direct hybridization methods are reliable, and they detect clinically relevant viral titers of greater than 10^6 international units (orders of magnitude below levels present in both acute and persistent infection). Gene amplification methods are more sensitive, but low positive results should be interpreted cautiously. Virus can be detected in amniotic fluid, and both virus and IgM antibody to B19 are found in umbilical cord blood; the mother's serum will show seroconversion during pregnancy, but maternal IgM may be absent at the onset of hydrops fetalis.

TREATMENT

Parvovirus infections in normal children and adults do not require specific therapy. Isolation of infected individuals is impractical, with the exception of hospitalized cases. Pure red cell aplasia and the underlying persistent B19 parvovirus infection can be dramatically terminated by discontinuation of immunosuppressive therapy or institution of effective antiretroviral drugs in patients with AIDS. Commercial immunoglobulins are a good source of antibodies to parvovirus, and persistent B19 infection responds to a 2- to 10-day course of IgG at 0.4 g/kg[15] with a prompt decline in serum viral DNA, as measured by hybridization methods, accompanied by reticulocytosis and increased hemoglobin levels. This regimen has been curative in congenital immunodeficiency, but parvovirus in AIDS patients can persist at lower levels.

Immunoglobulin therapy can precipitate fifth disease rash and arthralgia. Chronic arthropathy should be treated symptomatically with anti-inflammatory drugs (Table 26-4), and there is no established role for the administration of immunoglobulin.

PREVENTION

Effective vaccines exist for animal parvoviruses, and human B19 infection should be preventable. A recombinant immunogen for the human virus lacks DNA and is therefore noninfectious; the empty capsids have been engineered to overexpress the highly immunogenic minor structural protein VP1, and a single 2.5-μg dose of empty capsids elicited excellent neutralizing antibody responses in normal

volunteers. Vaccination would prevent transient aplastic crisis in patients with hemoglobinopathies, pure red cell aplasia in some immunodeficient individuals, and hydrops if seronegative mothers were inoculated early in pregnancy. Unfortunately, no vaccine is currently under commercial development.

PROGNOSIS

Most infections resolve without treatment. For patients with pure red cell aplasia, relapses of anemia may require repeated IgG administration. Hydrops fetalis also may resolve spontaneously, but intrauterine blood transfusions have been used with apparent success.

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343 SMALLPOX, MONKEYPOX, AND OTHER POXVIRUS INFECTIONS

BRETT W. PETERSEN AND INGER K. DAMON

DEFINITION

Human illness caused by a poxvirus is characterized by a cutaneous manifestation; illness may be localized or systemic, depending on the particular poxvirus and the route of introduction. DNA-based assays, including polymerase chain reaction (PCR) and DNA sequencing, are the most precise methods for identification and differentiation of poxvirus genera, species, strains, and variants. The guanosine plus cytosine content of orthopoxviruses, yatapoxviruses, molluscum contagiosum virus, and parapoxviruses is approximately 33%, 32%, 60%, and 63%, respectively.

The Pathogens

All poxviruses described in this chapter (Table 343-1) belong to the family Poxviridae, subfamily Chordopoxvirinae.

EPIDEMIOLOGY

Recognition of the epidemiologic characteristics of poxvirus diseases is valuable in assessing the potential etiologic agent of a particular suspected poxvirus lesion. Knowledge of zoonotic reservoirs, geographic localizations, and capacity for epidemic transmission is critical for clinical assessment and control measures. All human poxvirus infections are zoonotic in nature, with the exception of molluscum contagiosum and variola, which are solely human pathogens. Transmission of virus to humans and to animals is through direct contact with lesions, by fomites, or by inhalation of respiratory droplets.

Parapoxvirus and molluscipoxvirus infections are endemic worldwide; orthopoxvirus and yatapoxvirus infections are geographically restricted, probably by the distribution of competent reservoir hosts. Variola virus (the causative agent of smallpox, a disease declared eradicated in 1980)[1] is the only poxvirus required to be reported to public health systems under the International Health Regulations. In addition to variola virus, Congo Basin clade monkeypox viruses are considered to be select agents by the U.S. government; they must be reported and appropriately handled if discovered and if samples are maintained in the United States. Furthermore, because the availability of laboratory diagnostic testing is limited in many parts of the world, the true incidence and prevalence of poxvirus infections are uncertain.

TABLE 343-1 TAXONOMY OF POXVIRUSES KNOWN TO INFECT HUMANS

GENUS	SPECIES
Orthopoxvirus	Variola virus, vaccinia virus, cowpox virus, monkeypox virus, Akhmeta virus, and Alaskapox virus
Parapoxvirus	Orf virus, milker's node virus, bovine papular stomatitis virus, sealpox virus
Yatapoxvirus	Tanapox virus (Yaba-like disease virus), Yaba monkey tumor virus
Molluscipoxvirus	Molluscum contagiosum virus

Orthopoxvirus

Smallpox

The epidemiology of smallpox, caused by *Orthopoxvirus variola*, is understood through detailed studies conducted during the end of the eradication campaign. Interhuman transmission of variola virus generally occurred through the inhalation of large airborne respiratory droplets of infectious virus. Transmission usually required prolonged face-to-face or other close contact, although airborne transmission over longer distances had been reported.[2] Transmission by fomites or contact with infectious material from the rash also occurred. Aggregate data, collected during the smallpox eradication campaign, suggest a secondary attack rate of about 60% in unvaccinated close or household contacts and a secondary attack rate of about 4% in previously vaccinated close or household contacts. Severity of disease correlated with burden of rash and was also more severe in children and pregnant women. Variola alastrim minor, a variant of variola, had similar human-to-human disease transmission characteristics.

Vaccinia

Vaccinia is the live virus contained in preparations of the smallpox vaccines used to eradicate smallpox. In the United States, the vaccine is recommended for laboratory personnel who use replication-competent orthopoxviruses and for selected military personnel. Contacts of vaccinees occasionally develop vaccinia infections. Vaccinia viruses may have descended from horsepox virus. Vaccinia variants include buffalopox from contact with infected animals in India and vaccinia viruses in dairy cattle workers in Brazil and Colombia.[3]

Monkeypox

Monkeypox has a more complex epidemiology. The virus is zoonotic, and two genetically discrete virus clades have been described, each with apparent distinct clinical and epidemiologic parameters. In central and western Africa, the seroprevalence of anti-orthopoxvirus antibodies in unvaccinated individuals is about 20 to 25%.[4]

In the original outbreak in the Democratic Republic of Congo, the secondary attack rate in unvaccinated contacts of monkeypox cases was calculated to be about 9%. Previous smallpox vaccination (administered 3 to 19 years prior) appeared to be 85% protective against acquisition of the disease among contacts and also ameliorated the severity of disease. Overall, most identified cases acquire disease from presumed animal exposure, and about 30% of cases were ascribed to person-to-person transmission. In more recent outbreaks, however, data suggest that 50 to 90% of infections may be transmitted from human to human, with these higher rates thought to be related to the cessation of smallpox vaccination programs after that disease was eliminated.

Among primary cases, recent close zoonotic contact—through hunting, skinning, killing, cooking, or playing with carcasses—was identified with *Cercopithecus, Colobus*, and *Cercocebus* (primate); *Cricetomys* (terrestrial rodent); and *Funisciurus* and *Heliosciurus* (squirrels). The prevailing hypothesis is that one or more squirrel or rodent species is the probable reservoir of disease.

Monkeypox virus was introduced to the United States in 2003 through a consignment of animals from the West African country of Ghana. The U.S. cases had a less pronounced rash and a less severe illness, with no mortality or human-to-human transmission. These clinical data plus genomic data suggest at least two populations or clades of monkeypox virus. The apparent decreased pathogenicity and transmissibility of West African clade monkeypox virus infection led, in part, to its declassification as a U.S. select agent in 2013. An increasing number of human monkeypox cases were identified in West Africa in 2017, and human monkeypox cases subsequently were identified in the United States, United Kingdom, Israel, and Singapore among returning travelers from Nigeria.[5] More recently, monkeypox spread widely in the United States[6] and throughout the world, initially in men who have sex with men[7] but subsequently in heterosexual contacts, nonsexual contacts, and children. In the United States, cases peaked in August 2022 and eventually exceeded 30,000 cases, with about 40 deaths. Worldwide, about 90,000 cases have been reported.

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ABSTRACT

Human poxvirus infections produce both localized and systemic cutaneous manifestations. Orthopoxvirus variola, the causative agent of smallpox, is the most well-known virus in the family and caused untold deaths before being declared eradicated in 1980. It produced a systemic febrile rash illness with centrifugally distributed characteristic pustules that commonly appeared on the palms and soles. Monkeypox produces a similar clinical syndrome that is distinguished by pronounced lymphadenopathy. Vaccinia virus, which is the virus used for smallpox vaccines, produces a self-limited pustular lesion in humans. Cowpox virus infections present similarly to vaccinia virus infections in humans; both can be acquired through zoonotic transmission and cause severe disease in persons who are immunosuppressed or have skin conditions such as atopic dermatitis. Parapoxviruses (including orf virus, pseudocowpox virus, and bovine papular stomatitis virus) generally cause singular nodular lesions, which can persist for weeks after infection, after contact with ruminants (commonly cattle, sheep, or goats). Molluscum contagiosum causes smooth, dome-shaped, pearly or flesh-colored skin nodules that are often umbilicated. The clinical diagnosis of poxvirus infections can often be made based on the presentation of the disease in combination with epidemiologic characteristics. Laboratory confirmation can usually be achieved using polymerase chain reaction assays. Smallpox vaccine can prevent orthopoxvirus disease because of the development of cross-protective antibodies elicited by infection with a member of the *Orthopoxvirus* genus. Additionally, treatment with antiviral agents such as tecovirimat is available.

KEYWORDS

smallpox
monkeypox
vaccinia virus
cowpox
molluscum contagiosum
poxvirus

Cowpox

Cowpox virus is a zoonosis that is found in Europe and Asia and is maintained in rodents; in Britain, the reservoirs are bank voles and wood mice. The domestic cat is a common source of human infection. Most cases occur between July and October, with only occasional cases between January and June. In Europe, outbreaks in pet rats or feeder rats have been a source of transmission to humans. Cowpox virus also is prevalent in European zoos, where cheetahs, lions, anteaters, rhinoceros, elephants, and okapi have occasionally transmitted infection to animal handlers. No case of bovine cowpox has been detected since 1976, but two cases of a novel orthopoxvirus infection, the Akhmeta virus, were reported in 2013 in the country of Georgia in men who were exposed to ill cows. Alaskapox virus, which is a novel orthopoxvirus infection with a clinical presentation similar to cowpox, has been identified in four patients in Alaska, with wild small mammals living in peri-domestic areas as the likely source.

Parapoxvirus

Human infection with parapoxviruses such as orf[8] is an occupational hazard of farmworkers, abattoir workers, veterinary surgeons, students, and persons who participate in animal slaughter associated with religious observances. It is most common in the lambing and calving seasons and among sheep workers. A novel poxvirus with 88% similarity to *Parapoxvirus* viruses was reported in one patient in Tennessee and one in Missouri, both of whom had regular contact with horses.

Factors responsible for ongoing transmission have been attributed both to the environmental stability of orf virus in scab material and to the manifestation of chronic infections in some animals. A new parapoxvirus has been identified in deer hunters found to have cutaneous lesions after hunting and field-dressing deer.

Molluscipoxvirus

Molluscum contagiosum virus occurs worldwide and parallels cases of acquired immunodeficiency syndrome (AIDS). The disease appears to be sexually transmitted, and genital lesions are more common than lesions elsewhere on the body. Other modes of transmission are associated with mild skin trauma such as abrasions, direct contact with a lesion, and fomites (e.g., shared towels). However, children in daycare or school situations may transmit the disease to other children. Secondary spread may occur by autoinoculation (excoriation of primary lesions and spread to areas of normal skin) as well as by shaving. No known animal reservoir exists.

Yatapoxvirus

Tanapox virus, which is restricted to Africa, principally to Kenya and the Democratic Republic of Congo, probably has a simian reservoir. Direct primate-to-human transmission through a break in skin has rarely been described in animal handlers, but an insect or arthropod intermediary may be involved in the transmission of tanapox virus to humans. No human-to-human transmission has been reported. Yaba monkey tumor virus causes localized infections after contact with infected primate lesions. Little is known about the epidemiology of this virus.

PATHOBIOLOGY

Smallpox

The majority of smallpox infections were initiated by inhalation of respiratory droplets and implantation of virus on the oropharyngeal and respiratory mucosa. No primary localized site of infection was evident if the route of exposure was by inhalation. Disease could also be introduced through suspensions of virus obtained from scabs of infected patients. Transmission by fomites, such as soiled clothing or bed linens, was infrequently reported.

After entry, the virus moves to local lymph nodes and then disseminates to the reticuloendothelial system to replicate further. At this time, the individual is asymptomatic. In 10 to 14 days, secondary viremia occurs and heralds the prodrome of symptomatic illness. During this time, the virus seeds the oropharynx and epidermis. The absence of a keratinized structure in the mucosa of the oropharynx leads to ulceration and release of virus in saliva; the virus replicates in the epidermis to cause the characteristic macular, papular, vesicular, and pustular eruptions of smallpox.

In humans, the viral lesions characteristic of illness primarily develop in the epidermis, where the cells of the Malpighian layer swell and vacuolate to undergo ballooning degeneration. The cytoplasm continues to enlarge, nuclear material is lost, and the coalescence of vacuoles through cell rupture creates reticulating degeneration of the middle and upper layers of the stratum spinosum. In the next stages, the vesicle is formed. High titers of virus are found within the lesions. In mucosal surfaces, the absence of a horny layer allows the necrosis caused by proliferation of virus within the epithelium to create ulcers and leads to liberation of large quantities of virus into the oropharynx. Mild pathologic changes are seen in the lungs.

CLINICAL MANIFESTATIONS

Orthopoxvirus

Smallpox

Four main clinical types of variola can be subgrouped as: *ordinary smallpox* (about 90% of cases), which produced viremia, fever, prostration, and rash; *(vaccine) modified smallpox* (5% of cases), which produced a mild prodrome with few skin lesions in previously vaccinated people and had a mortality rate well below 10%; *flat smallpox* (5% of hospitalized cases), which produced slowly developing lesions that were difficult to ascertain because they appeared flush with the (edematous) skin at the vesicular stage and was almost always fatal; and *hemorrhagic smallpox* (<1% of cases), which induced bleeding into the skin and the mucous membranes and was invariably fatal.

Naturally acquired variola virus infection is characterized by fever and a distinctive rash, with several different clinical presentations (Table 343-2). An asymptomatic incubation period of 10 to 14 days (range: 7 to 17) was followed by a fever that quickly rose to about 103° F (38° to 40° C), sometimes with dermal petechiae. Associated constitutional symptoms included backache, headache, vomiting, and prostration. Within a day or two after incubation, a systemic rash with a characteristic centrifugal distribution (i.e., lesions present in greater numbers on the oral mucosa, face, and extremities than on the trunk) appeared. The fever typically abated as the rash developed. Lesions commonly appeared on the palms and soles. The rash lesions were initially macular and then advanced to the papular stage, at which point they enlarged and progressed to a vesicle by day 4 or 5 and a pustule by day 7. When lesions became pustular, the fever typically returned. Lesions became encrusted and scabbed by day 14 and then sloughed off. Skin lesions in the vesicular and pustular stages were deep-seated and in the same stage of development in any one area of the body (Fig. 343-1). The ordinary disease type was subgrouped into three categories based on the extent of rash on the face and the body: confluent, semiconfluent, and discrete. In *ordinary confluent disease*, no area of skin was visible between vesiculopustular rash lesions on the trunk or the face. In *ordinary semiconfluent* and *discrete disease*, patches of normal skin were visible between rash lesions on the trunk and face, respectively. Less severe manifestations (modified smallpox or variola sine eruptione) occurred in both unvaccinated and, more commonly, vaccinated individuals.

In flat smallpox, illness was heralded by the abrupt onset of fever with temperatures of 38.3° to 38.9° C and the appearance of the rash after 3 to 4 days. The oral enanthem was often confluent; rectal mucosal membranes also could be sloughed. At the papulovesicular stage of disease, lesions appeared as small indentations (day 6) with a hemorrhagic base surrounded by an erythematous ring. By day 7 or 8, the lesions appeared flat. Bullous lesions that would slough were reported. Fever persisted throughout the disease course,

TABLE 343-2 WORLD HEALTH ORGANIZATION (WHO) SMALLPOX TYPES

WHO SMALLPOX TYPE	CLINICAL DEFINITION
Variola sine eruptione	Fever, no rash
Modified	Like ordinary, with an accelerated course
Ordinary discrete	Fever, rash; areas of normal skin between pustules, even on the face
Ordinary semiconfluent	Fever, rash; pustules confluent on the face, discrete elsewhere
Ordinary confluent	Fever, rash; pustules confluent on the face and forearms
Flat	Fever, erythema, and edema of the skin; vesicles soft, flat, and bullous
Hemorrhagic, early	Fever (persistent), hemorrhages and petechiae, purpuric rash at illness onset
Hemorrhagic, late	Fever (persistent), rash, hemorrhage into the base of vesicles late in illness

FIGURE 343-1. Pustular lesions of smallpox and beginning of scarring on the face and upper part of the torso. (From the Centers for Disease Control and Prevention Public Health Image Library, ID #: 7055. Photograph by Stan Foster.)

and respiratory complications were often observed by day 7 or 8 of illness. Thrombocytopenia, neutropenia, and lymphocytosis were reported.

In hemorrhagic forms of smallpox, illness began with fever and typical prodromal symptoms, but the fever never abated. Early after the onset of fever, petechiae and purpuric rashes became apparent; subconjunctival hemorrhages, hematuria, and vaginal bleeding were also seen. Patients usually died by day 6 of illness, well before any classic vesiculopustular rash was evident, but some patients developed typical maculopapular lesions with a hemorrhagic base, bleeding in the mucous membranes, and profound thrombocytopenia before dying between days 8 and 10 of illness.

Alastrim variola minor infection results in a discrete type of the ordinary form, with a typical febrile prodrome and rash. Individuals with this form of disease are not nearly as sick as individuals with variola major infection. Previous vaccination was not necessarily protective against the hemorrhagic forms of disease; however, it seemed to be protective against flat forms of disease.

Vaccinia

Post-Vaccination Vaccinia

For laboratory personnel working with orthopoxviruses, health care personnel, and military personnel in the United States, the smallpox vaccination regimen (with vaccinia or a replication-competent smallpox) results in purposeful infection. Most commonly, the infection progresses through a standard course of events from vesicle to pustule. Major complications include progressive vaccinia, eczema vaccinatum, generalized vaccinia, post-vaccinial encephalitis, accidental infection, and myopericarditis.

Progressive vaccinia, which is a rare and often fatal vaccine complication in persons with severe deficiencies in cellular immunity, occurs in about 1 per 1 million vaccines. Progressive vaccinia is characterized by frequently painless growth and spread of the vaccine virus beyond the inoculation site, often leading to necrosis and sometimes metastases to other body sites. The possibility of progressive vaccinia should be considered if vaccinia virus infection continues to progress and expand without apparent healing more than 15 days after vaccination.

Eczema vaccinatum can occur in people with a history of atopic dermatitis (eczema), irrespective of its severity or activity, owing to local spread or dissemination from the primary vaccination site or contact with the unscabbed vaccination site of another person. A localized or generalized papular, vesicular, or pustular rash can develop anywhere on the body or be localized to previous eczematous lesions. Systemic illness with fever, malaise, and lymphadenopathy may occur. In the 1968 national U.S. surveillance of smallpox vaccination, there were 66 cases (no deaths) of eczema vaccinatum among 14.5 million vaccinees (4.6 cases/million) and 60 cases (1 death) among their several million contacts.

FIGURE 343-2. Vaccinia autoinoculation of an eye. (From the Centers for Disease Control and Prevention Public Health Image Library, ID #: 3322.)

Generalized vaccinia, which describes the vesicular rash that develops after vaccination, is estimated to occur in about 242 of every million primary vaccinations. Generalized vaccinia is believed to represent the end product of viremic spread of virus, and no predisposing factors have been identified.

Post-vaccination encephalomyelitis is a rare but serious complication that usually occurs only in primary vaccinees. Patients have variably displayed clinical and diagnostic features suggestive of a postimmunization demyelinating encephalomyelitis or direct viral invasion of the nervous system. This postvaccination reaction typically occurs 11 to 15 days after vaccination. Symptoms include fever, headache, vomiting, confusion, delirium, disorientation, restlessness, drowsiness or lethargy, seizures, and coma. Cerebrospinal fluid can demonstrate elevated pressure but generally has a normal cell count and chemistry profile. The diagnosis is one of exclusion, and no specific tests are available to confirm it.

Accidental infection occurs when virus from the vaccination site is transferred to another site or to another person through intimate skin contact. This complication generally occurs with primary vaccinees rather than revaccinees. Accidental self-inoculation, which most commonly occurs on the face, mouth, lips, or genitalia, is not usually serious and requires no specific treatment. Inoculation of the eye or eyelid is more serious and can be sight threatening if it is not evaluated and treated appropriately (Fig. 343-2). Between 1963 and 1968, ocular vaccinia was observed in 343 persons, including 22 who had evidence of corneal involvement and 11 who experienced permanent defects.

Bovine-Associated Vaccinia

With bovine-associated vaccinia virus infections (e.g., buffalopox viruses in India and vaccinia viruses in Brazil and Colombia), up to 10 lesions have been described on the hands or arms of exposed farmworkers. Fever, lymphadenopathy, backache, and fatigue are also associated symptoms. Transmission is believed to occur by unprotected contact with active lesions present on animal teats and udders. Interhuman transmission of bovine-associated vaccinia virus to family members has been reported to occur through contact with lesion exudates.

Monkeypox

After an incubation period of 7 to 17 days (mean: 12 days), a prodrome of fever, headache, backache, and fatigue begins.[9] Lesions similar to smallpox evolve in the same stage in any one part of the body from macules, papules, and vesicles to pustules, and then they crust and scar (Fig. 343-3).[10] After resolution of the rash, hypopigmentation is followed by hyperpigmentation of the scarred lesions. Pronounced cervical, postauricular, submandibular, and inguinal lymphadenopathy clinically distinguishes monkeypox from smallpox. Subclinical infection may occur in 25 to 30% of close contacts of monkeypox patients. Systemic complications can include severe pharyngitis that limits oral intake, soft-tissue superinfection, and severe anorectal pain.[11] Neurologic manifestations can include headache, mood disturbances, and even encephalitis.[12]

Cowpox

Cowpox lesions are generally restricted to the hands and face, and most patients (about 70%) have only one lesion. Multiple lesions may be caused by multiple primary inoculations, by autoinoculation, and very infrequently

FIGURE 343-3. **Rash of monkeypox of the head (A) and extremities (B) in a 7-year-old girl in central Zaire.** (From Peters W, Pasvol G. *Tropical Medicine and Parasitology*. 5th ed. New York: Mosby; 2002:238.)

by lymphatic or viremic spread. The cowpox lesion passes through macular, papular, vesicular, and pustular stages before forming a hard black crust. The lesion is generally very painful, and erythema and edema are common at the late vesicular and pustular stages. Patients usually have lymphadenitis, fever, and general malaise. About 30% of patients may be hospitalized. Most patients take 6 to 8 weeks to recover, but up to 12 weeks may be required. Scarring is usually permanent.

Parapoxvirus

Lesions, such as from the orf virus, start as erythematous papules and progress in 1 to 2 weeks to target lesions with a red center surrounded by a white halo and an outer inflamed halo. Lesions then progress to a nodular and then a papillomatous stage, which often has a "weeping" surface. In some patients, lesions may enlarge and persist for weeks before resolving by a crusting stage, which also may persist for weeks. Very large granulomatous lesions may occasionally require surgical débridement or removal.

Most patients have only one lesion, but multiple primary lesions may develop. Systemic reaction is relatively uncommon, and the lesion is often not particularly painful. Lymphadenopathy is present in some patients, and lymphangitis is relatively uncommon. Erythema multiforme (Chapter 407) can develop in up to one third of patients.

Molluscum Contagiosum Virus

The characteristic lesion begins as a small papule and, when mature, is a discrete, 2- to 5-mm-diameter, smooth, dome-shaped, pearly or flesh-colored nodule that is often umbilicated (see Fig. 407-9 in Chapter 407).[13] A cheesy, off-white or yellowish material is easily expressed from lesions. Most patients have 1 to 20 lesions, but hundreds of lesions may occasionally be present. Because of multiple simultaneous infections or mechanical spread, the lesions may become confluent along the line of a scratch, and satellite lesions are sometimes seen.

In adults, lesions tend to occur on the trunk, pubic area, and thighs, but infection can be transmitted to other areas by autoinoculation. In men infected with human immunodeficiency virus (HIV), molluscum lesions can occur along the beard line and can result in ocular involvement.

Individual lesions persist for about 2 months, but the disease usually persists for 6 to 9 months. Individuals with impaired cell-mediated immunity, including persons with HIV infection, tend to have more severe and prolonged infection.

Yatapoxvirus

Tanapox infection begins with a short febrile (38° to 39° C) illness that persists for 2 to 4 days and is sometimes accompanied by headache, backache, or prostration. The eruption of a lesion is frequently heralded by pruritus at the site of the outbreak. The lesion appears as a hyperpigmented macule, which often has central elevation and evolves to a papule with palpable induration. About 80% of patients have a solitary nodule, but as many as 10 lesions can occur. Most lesions (about 70%) occur on the lower extremities, and the fewest occur on the face and areas normally covered by clothing.

Fever and systemic symptoms wane as the lesion erupts. The papule then becomes more "pocklike" but contains no fluid; umbilication or a pseudocrust may develop. Typically, the papule evolves into a firm, deep-seated, elevated nodule. At the end of the first week, the lesion is surrounded by erythema and indurated skin, and regional lymphangitis is common. Lesions then either ulcerate or become larger nodules (up to 2 cm in diameter) within about 2 weeks, after which the local inflammatory response wanes and the lesions began to granulate. Resolution of lesions occurs within 6 weeks. Infection appears to confer lifelong immunity.

DIAGNOSIS

Smallpox and Other Orthopoxviruses

If smallpox is suspected, clinicians should follow a standardized protocol (https://www.cdc.gov/smallpox/clinicians/algorithm-protocol.html) because of the possibility of bioterrorism (Chapter 19) as well as the risk to laboratory personnel (https://www.cdc.gov/smallpox/lab-personnel/laboratory-procedures/rash-testing.html). Unlike smallpox, chickenpox (Chapter 346) produces a centripetally distributed rash and rarely appears on the palms and soles; the lesions are superficial in nature, and lesions in different developmental stages may be present in the same area of the body. Other diseases and conditions that could be confused with vesicular-stage smallpox include monkeypox, generalized vaccinia, disseminated herpes zoster or herpes simplex virus infection (Chapters 345 and 346), drug reactions (eruptions), erythema multiforme (Chapter 407), enteroviral infections (Chapter 349), scabies (Chapter 98), insect bites, impetigo (Chapter 408), and molluscum contagiosum.[14] Diseases confused with hemorrhagic smallpox included acute leukemia (Chapter 168), meningococcemia (Chapter 274), and idiopathic thrombocytopenic purpura (Chapter 158).

Nucleic acid–based tests and polymerase chain reaction (PCR) assays are the first approach to the diagnosis of orthopoxvirus infections. If the diagnosis of smallpox is being considered, viral culture requires a biosafety level 4 (BSL-4) containment facility that is sanctioned to use variola virus.

Parapoxvirus

The differential diagnosis of parapoxvirus lesions can include ecthyma gangrenosum as a result of a *Pseudomonas aeruginosa* infection (Chapter 282), vaccinia or cowpox infection, cutaneous anthrax (Chapter 272), erysipeloid (Chapter 272), tularemia (Chapter 287), and tumor. Farmworkers recognize the infection and tend not to seek medical attention for routine cases, so about 45% of reported cases may have no known contact with infected animals, and the clinical diagnosis of such cases may be difficult. Virions with the characteristic morphology of parapoxviruses are usually seen in lesion extracts on electron microscopy, thereby providing a rapid, certain diagnosis of the genus.

Molluscum Contagiosum Virus

The clinical appearance of molluscum lesions usually is sufficiently characteristic to permit a clinical diagnosis.

Yatapoxvirus

The limited geographic distribution of tanapox virus and the patient's travel history help with the diagnosis of tanapox infection. Unique clinical features that differentiate tanapox from other orthopoxvirus infections are the nodular nature of the rash lesion, the paucity of lesions, the benign disease course, and the protracted resolution of the rash. Nucleic acid testing of material from the lesions is diagnostic.

TREATMENT AND PREVENTION

Orthopoxvirus

Vaccination with smallpox vaccine is the mainstay for prevention of orthopoxvirus infection and was the primary method used to eradicate smallpox. Stockpiles of vaccine are available should smallpox recur, and guidance is available for their use in an emergency (https://www.cdc.gov/mmwr/preview/mmwrhtml/rr6402a1.htm). A replication-deficient smallpox vaccine, which has excellent immunogenicity with fewer adverse effects than prior vaccines, is licensed to prevent smallpox and monkeypox.[15] In the United States, it is being recommended for persons at risk of exposure to orthopoxviruses, including monkeypox.[16]

Early administration of vaccinia immune globulin (VIG) may reduce the mortality of eczema vaccinatum from 30 to 40% to 7%, and VIG may also be useful for other complications (e.g., progressive vaccinia, severe generalized vaccinia, or contact infection) of vaccinia (smallpox) vaccine administration and for other orthopoxvirus infections. However, VIG alone has no clear benefit for treatment of smallpox infection itself.

Tecovirimat is an effective small-molecule antiviral in animal models of systemic orthopoxvirus infection.[17] It is part of the U.S. Strategic National Stockpile and was licensed by the FDA for treatment of human smallpox disease. Brincidofovir is also licensed by the U.S. FDA for treatment of smallpox based on data in animals.[18] Tecovirimat and brincidofovir also have been used successfully to treat severe human cases of other orthopoxvirus infections, including monkeypox,[19] under expert supervision.

Antiviral compounds (Chapter 328) with in vitro and in vivo activity against poxviruses include specifically 5-iodo-2′-deoxyuridine, adenine arabinoside, and trifluorothymidine. Because of their systemic toxicity, these compounds have been used topically for the treatment of orthopoxvirus ocular infections. In vitro, cidofovir is active against cowpox, vaccinia, monkeypox, and variola. Cidofovir has known renal toxicity and is administered with hydration and probenecid.

Parapoxvirus

Treatment options are limited. Anecdotal reports have described the use of topical and intralesional cidofovir, and other options may be topical formulations of interferon-modulating compounds such as imiquimod.

Molluscum Contagiosum Virus

Molluscum contagiosum infection is benign, recovery is usually spontaneous, and no medical therapy has been consistently effective.[A1] However, treatment may be sought for cosmetic reasons, particularly for facial or multiple lesions. Cryotherapy and mechanical curettage are the most successful options.[A2] Typical chemical treatments such as podophyllin or podofilox, salicylic acid with lactic acid nitric oxide–releasing gel,[20] and 3% cidofovir antiviral cream or suspension may be helpful. Irritation has been a side effect of many of the chemical treatments. Covering of lesions and the use of proper hand hygiene after contact with lesions should prevent transmission in most situations. For individuals with AIDS and molluscum, highly active antiretroviral therapy with a resulting improvement in the $CD4^+$ cell count appears to be efficacious.

PROGNOSIS

Ordinary smallpox has a variable mortality rate ranging from 10 to 40%, which correlates with the extent and severity of the skin lesions. Flat smallpox and hemorrhagic smallpox are almost universally fatal, whereas modified smallpox in previously vaccinated patients has a mortality rate well below 10%. Variola minor variants have mortality rates of less than 1%. Vaccina virus infections after smallpox vaccination are usually self-limited, but progressive vaccinia in immunocompromised patients has a case fatality rate of about 35%. Monkeypox has a case-fatality rate of approximately 1 to 10% in persons who have not been vaccinated for smallpox, with most fatalities in children younger than age 5 years. Cowpox virus infections usually cause self-limited disease but can be severe and fatal in persons with immunosuppression or certain skin conditions such as atopic dermatitis. Parapoxvirus infections are manifested chiefly by localized symptoms, and the lesions resolve within a month or so in nonimmunocompetent hosts. Molluscum contagiosum infection is benign, usually with a spontaneous recovery, but the infection can persist for months. Yatapoxvirus infections are self-limited, and the illness resolves in the course of a few weeks.

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344 PAPILLOMAVIRUS

SEAN T. O'LEARY AND JOHN M. DOUGLAS, JR.

DEFINITION

Human papillomaviruses (HPVs) are a group of small DNA viruses that cause a variety of benign and malignant lesions of the skin and mucous membranes. The most commonly recognized HPV-associated diseases include warts (Chapter 407) at anogenital sites (condyloma acuminatum), other skin surfaces (common wart or verruca vulgaris, as well as flat wart or verruca plana), and the plantar surface of the foot (verruca plantaris). In addition, HPV infection causes squamous intraepithelial lesions, or incipient cancers, of the cervix, also known as cervical intraepithelial neoplasia, and of other anogenital sites. It is considered the etiologic agent of a variety of cancers, especially cervical (Chapter 184), anal (Chapter 131), and oropharyngeal (Chapter 176) cancers.

The Pathogen

HPV is a member of the family Papillomaviridae. Like all papillomaviruses, HPV is nonenveloped, measures 55 nm in diameter, and has a double-stranded circular DNA genome of approximately 7900 base pairs enclosed by an icosahedral capsid. The HPV genome contains three functional regions: early genes (six total—E1, E2, E4, E5, E6, E7), which are expressed soon after infection and control replication, transcription, and cellular proliferation; late genes (two total—L1, L2), which are expressed in later stages of infection and encode the structural capsid proteins; and the long control region, which contains regulatory sequences that control the replication and transcription of early and late genes. Papillomaviruses complete their life cycle only in terminally differentiated epithelial cells and thus cannot be grown in monolayer cell cultures. Papillomavirus taxonomy is based on a genotyping system involving the use of DNA sequence relatedness of the gene encoding L1, the major capsid protein, with different types defined as having less than 90% homology.

Papillomaviruses are classified taxonomically by genus (Greek letters) and species (numbered), each containing one or more types. Most HPV types are included in three large genera: alpha (primarily mucosal or genital types), beta, and gamma (both of which cause cutaneous lesions). Currently, over 200 types of HPV have been identified, over 40 of which infect genital skin and mucosa [http://pave.niaid.nih.gov/#explore/reference_genomes/human_genomes]. Of the genital types, approximately 15 are considered high risk because they are associated with high-grade squamous intraepithelial lesions and cancers of the cervix, anus, penis, vulva, vagina, and oropharynx, whereas others are considered low risk because they are largely associated with genital warts and low-grade squamous intraepithelial lesions.

EPIDEMIOLOGY

HPV infections are primarily transmitted by direct contact of skin or mucous membranes with an infected lesion. Genital HPV infection is typically contracted through sexual intercourse, although nonpenetrative genital contact, oral-genital contact, and manual-genital contact are also possible routes of transmission. In addition, genital HPV infection can be transmitted to the mouth and upper respiratory tract perinatally from infected mothers to newborns. For

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EPIDEMIOLOGY

HPV infections are primarily transmitted by direct contact of skin or mucous membranes with an infected lesion. Genital HPV infection is typically contracted through sexual intercourse, although nonpenetrative genital contact, oral-genital contact, and manual-genital contact are also possible routes of transmission. In addition, genital HPV infection can be transmitted to the mouth and upper respiratory tract perinatally from infected mothers to newborns. For

ABSTRACT

Human papillomaviruses (HPVs) are a large group of DNA viruses that typically infect the stratified epithelia of the skin and mucous membranes. They cause tumors ranging from benign to malignant according to the specific oncogenic risk of each viral genotype. The most common benign lesions are cutaneous warts found on the hands and feet, caused predominantly by HPV types 1, 2, and 4; and genital warts, caused by HPV types 6 and 11. HPV-16, -18, and several other genotypes can also infect the anus and lower genital tract causing lesions that can progress to intraepithelial neoplasias, the precursors of squamous cell carcinomas of the cervix, vagina, vulva, penis, and anus. These oncogenic HPVs are also found in some squamous carcinomas of the oropharynx. These infections are transmitted by direct contact and can remain asymptomatic, clear, or cause lesions that often can spontaneously regress. Persistent infection with oncogenic HPVs is the main determinant for progression to cancer. Available treatments that address the disease but not the infection include various chemical and physical destructive methods. Cervical cancer can be effectively prevented by screening using cervical cytology (Pap smear) or HPV DNA. Condoms offer some protection against the transmission of genital HPV infections. An available vaccine directed at nine of the most common genotypes associated with genital warts and cervical cancer has been highly effective in reducing the incidence of genital warts, oropharyngeal infection, and intraepithelial neoplasias of the cervix, vagina, vulva, and anus when administered before the initiation of sexual activity.

KEYWORDS

papillomavirus
wart
condylomata acuminate
papilloma
intraepithelial neoplasia

nongenital HPV infection, personal skin-to-skin contact also plays a primary role, whereas fomite transmission from moist surfaces is an important source of infection for plantar warts. Both genital and nongenital infection can be transmitted to new sites by autoinoculation.

Recent estimates are that 43 million males and females ages 15 to 59 years in the United States are infected with genital HPV, with about 13 million new infections occurring annually, thereby making genital HPV the most common sexually transmitted infection.[1] Acquisition of infection begins shortly after sexual debut, with risk factors related to probable exposure (e.g., younger age at onset of sexual activity, increased number of recent and lifetime partners, and number of partners of the sex partners), susceptibility (e.g., lack of circumcision for men), and absence of effective prevention (e.g., lack of consistent condom use or immunization). Most infections are asymptomatic and clear without treatment; only 10% are estimated to persist longer than 2 years. The incidence and prevalence of genital HPV infection and genital warts have been declining substantially in countries with successful immunization programs. For example, between 2003 and 2018, the prevalence of infection with the four viral types included in the original quadrivalent vaccine declined by over 80% in vaccinated women under age 25 years. Reductions of over 65% have also been seen in unvaccinated women, thereby indicating some element of indirect or herd protection.[2]

Oral HPV infection is usually asymptomatic, but when symptomatic it takes the appearance of warts or papillomas. Its prevalence in U.S. adults is lower than genital infection—approximately 3 to 7% in women and 10 to 12% in men[3], almost half of which are due to high-risk types. Risk factors for prevalent infection include number of sex partners, age, and smoking. Newly acquired oral oncogenic HPV infections are rare in healthy men, and most infections are cleared within 1 year. As with genital HPV infection, oral HPV infection has declined in the vaccine era, especially among men.[4] Cutaneous HPV infection is most typically recognized as common and plantar warts, especially in children, in whom annual incidence rates of up to 30% have been reported.

All types and manifestations of HPV infection are more common in persons with impaired cell-mediated immunity, such as those infected with human immunodeficiency virus (HIV) or receiving immunosuppressive therapy. HIV-infected persons have higher rates of intra-epithelial neoplasia at various genital and anal sites, as well as higher rates of cervical and anal cancer, although both have declined in the United States in recent years, likely as a result of widespread HIV antiretroviral therapy.[5] Evidence also suggests that genital HPV infection increases susceptibility to HIV infection.

Cervical cancer (Chapter 184) has declined in developed countries since the initiation of cytologic screening programs, although about 14,000 cases and 4300 deaths still occur in the United States annually.[6] Cervical cancer is the fourth most common and lethal cancer in women worldwide, and almost 90% of the 311,000 annual deaths occur in low- and middle-income countries. Considering all anatomic sites, almost 36,000 HPV-associated cancers occur in the United States each year, about 60% among females.[7] Oropharyngeal cancer (Chapter 176) has risen sharply over the past 20 years, particularly among men, and is now the most common HPV-associated cancer in the United States.

PATHOBIOLOGY

HPV infections cause disease by inducing proliferation of the epithelium of the skin and mucous membranes. In benign lesions, such as warts and condylomas, all epithelial layers are involved, except for the basal layer of replicating keratinocytes. The proliferation of the stratum spinosum is called acanthosis, that of the stratum granulosum parakeratosis, and that of the stratum corneum hyperkeratosis. The overall growth is called papillomatosis because it typically occurs mostly above the tissue surface but is also associated with a deepening of the rete ridges of the basement membrane. It is also accompanied by large cells with a hyperchromatic, shrunken nucleus (or nuclei) surrounded by a halo (called koilocytes) in the stratum acanthosum. For the cytopathologist, koilocytosis is the hallmark of HPV infection.

Epidermodysplasia verruciformis is an uncommon autosomal recessive disease with diffuse warts that result from the mutation of one of two adjacent genes, *EVER1/TMC6* and *EVER2/TMC8*, each coding for proteins involved in the transcription factor NF-κB that participates in the control of cell-mediated immunity.

For precancerous or cancerous lesions, dyskaryosis is caused by the proliferation of the basal layer cells, which also exhibit abnormal mitoses. This dyskaryosis progresses by replacing the upper layers of the stratified epithelium, thereby causing increasing grades 1 to 3 of intraepithelial neoplasia, according to how many thirds of the epithelium are involved. Full-thickness involvement defines carcinoma in situ. The breach of the basement membrane indicates invasive cancer. The intraepithelial neoplasias (IN) of the cervix, vagina, vulva, penis, and anus also go by the acronyms of CIN, VAIN, VIN, PIN, and AIN, respectively. For the cervix, low-grade squamous intraepithelial lesion (LSIL) is the equivalent of flat condyloma and CIN1, whereas high-grade squamous intraepithelial lesion (HSIL) regroups CIN2 and 3. To parallel these changes, low- and high-grade cervical intraepithelial neoplasia (LCIN and HCIN, respectively) are now terms also used in histology. The higher the cytologic or histologic grade of neoplasia, the higher the intralesional relative prevalence of high-risk HPV types.

At the cellular level, infection begins in the lowest and least differentiated layer of the epithelium, the basal cells, when they are exposed by microtrauma.[8] Transcription and protein expression are highly coordinated with the level of cellular differentiation. In the basal layer, the viral genome becomes established in the nucleus as an episome that replicates in tandem with cellular replication, thus maintaining a stable copy number of viral genomes. As basal cells migrate up and differentiate in the superficial layers of the epithelium, full vegetative viral DNA replication and expression of structural proteins occur, with assembly of infectious virions in the most superficial layer of the epithelium. Virions are released with the sloughing of dead cells during normal cellular turnover.

Persistent infection with various high-risk types of genital HPV is firmly established as the cause of squamous cell carcinoma and adenocarcinoma of the cervix, and HPV 16 in particular plays a causal role in other anogenital and oropharyngeal squamous cell cancers. There are also associations of beta-HPV types with squamous cell cancer of the skin. HPV DNA can be detected in more than 99% of cervical cancer cases, with 70% of cancers caused by the two most common high-risk types, HPV 16 and 18. The pathogenesis of HPV-induced cancer involves viral integration into the host genome with resulting disruption of the E2 transcription regulatory gene and increased expression of E6 and E7 proteins. These proteins have oncogenic activity and affect cell growth by binding with tumor suppressor proteins, E6 with p53 and E7 with the retinoblastoma tumor suppressor protein, thereby disrupting apoptosis and cell cycle regulation.

The oncogenic risk of HPV varies not only by type, with HPV 16 being the most oncogenic, but also according to variants (i.e., sharing between 95 and 98% of DNA homology) within a given type. A high viral load may also contribute to the risk. Although a persistent infection with a high-risk type is "necessary" for the development of cervical cancer, it is not considered "sufficient" because cancer does not develop in the majority of persistently infected women. Possible cofactors include cigarette smoking, prolonged hormonal contraceptive use, multiparity, micronutrient deficiency, immunodeficiency (e.g., HIV infection), and possibly other infections, (i.e., *Chlamydia trachomatis* and herpes simplex virus type 2). In addition, data supporting a familial risk for cervical cancer point to possible genetic factors, including genes controlling the immune response (e.g., human leukocyte antigens and tumor necrosis factor) and cell cycle (e.g., p53).

The squamous epithelium of the ectocervix and columnar epithelium of the endocervix form a squamo-columnar junction that, from birth through life, recedes towards the endocervix, traveling an area called the transformation zone, where cervical cancers (Chapter 184) arise. Squamo-columnar junctions, but without a transformation zone, also exist in the anus and larynx, and HPV benign or malignant lesions often arise in epithelium that is in close proximity (see Chapter 131 for anal cancer).

The immune response to HPV infection is less robust than for most viral infections. Viral proteins and infectious virions develop in superficial cells with limited contact with the immune system, and there is no cell lysis or viremia to trigger an inflammatory response. In addition, HPV suppresses several components of the immune response, including the interferon pathway and the expression of inflammatory cytokines and the major histocompatibility complex I. Antibody to HPV develops in only an estimated 60% of infected individuals, often as long as 6 to 12 months after infection. In contrast, the dynamics of the immune response are quite different after immunization, with almost 100% seroconversion within several months and antibody levels many-fold higher than those after natural infection. The high prophylactic efficacy of papillomavirus vaccines is due to humoral immunity and the intense production of neutralizing antibodies. Once papillomavirus infection is established, cellular immunity appears to be critical for clearance of infection.

CLINICAL MANIFESTATIONS

The clinical manifestations of HPV infection vary by anatomic site and viral type. About 2% of patients may have both oral and genital infections on initial presentation.[9]

Common warts are exophytic, hyperkeratotic papules that typically occur on the hands but can appear on any skin surface, occasionally including the genital skin; they are most commonly caused by HPV types 1, 2, 4, 27, and 57. Plantar warts, which are caused by similar types of HPV, are hyperkeratotic papules. They may present as deep plantar warts that often are very painful and endophytic in growth. They are typically associated with HPV types 1 or 63. More superficial and painless mosaic warts are typically caused by HPV types 2 or 4. In contrast, flat warts (verruca plana), which are small flat-topped papules that occur more commonly on the face, hands, and legs, are caused by a different group of nongenital HPV types (e.g., types 3, 10, 28, 38, 42, 49, 75, 76).

Epidermodysplasia verruciformis is usually manifested in childhood as diffuse warts that respond poorly to treatment. The diffuse warts of epidermodysplasia verruciformis can be associated with two types of lesions: flat warts caused by the same HPV types as in normal hosts, and scaly tinea versicolor–type lesions caused by epidermodysplasia verruciformis–associated types. The latter are associated with the development of squamous cell cancers in sun-exposed areas in 30 to 70% of persons of age 30 years and older. Similar skin lesions and, rarely, associated skin cancers can develop in other patients with acquired defects in cell-mediated immunity or who are immunosuppressed.

Bowenoid papulosis is defined by the combination of hyperpigmentation, intraepithelial neoplastic histology, and the cytoarchitecture of a condyloma. It can transform into Bowen disease (Chapter 188), which is a squamous carcinoma in situ that occurs most commonly in areas of prior skin damage.

Anogenital warts are papillomatous growths that occur throughout the anogenital skin and mucosa, typically at sites of genital friction. HPV types 6 or 11 are found in about 85% of cases, with approximately half of infected persons developing warts. Perianal warts (Chapter 131) are most common in persons with a history of anal intercourse and are often associated with intra-anal warts, but they also can occur without such contact, such as through autoinoculation when wiping. Anogenital warts can range from flat or papular lesions to the classic pedunculated, cauliflower-shaped condyloma acuminatum. Warts are typically asymptomatic, noticed either by the patient as a "bump" or inadvertently during a genital examination, although they can cause itching, burning, pain, or, rarely, bleeding. In pregnant women mechanical obstruction of the birth canal has been reported.

The most common clinical manifestations of oral HPV infection include oral squamous cell papillomas and condyloma acuminatum, which are caused by HPV types 6 and 11. Oropharyngeal precancers and cancers can present with painful ulcers, dysphagia, bleeding, and/or lymphadenopathy. Less frequent, and differentiated by histology, are common skin warts caused by cutaneous HPV. Focal epithelial hyperplasia is an uncommon disorder with a predilection for Native Americans and South Africans. It presents as round, flat papules that can be confluent and are mostly associated to HPV types 13 and 32. Warts caused by genital types can also rarely occur in the upper respiratory tract, where they produce a serious recurrent respiratory papillomatosis that can cause hoarseness and even compromise the airway.

Squamous intraepithelial lesions or intraepithelial neoplasias are most commonly found on the cervix as a result of screening for cervical cancer by cytology (Papanicolaou [Pap] test) or HPV molecular testing, with confirmation by colposcopy and biopsy. In late stages, cervical cancer can present with abnormal vaginal bleeding, pelvic pain, and dyspareunia. Potential precursors of cancer and resulting cancers also can occur at other anogenital sites (vulva, vagina, anus,[10] and penis[11]). Most squamous intraepithelial lesions are not visible on mucosal surfaces without the application of 3 to 5% acetic acid and magnification. On the external genitalia, they can appear as flat hyperpigmented papules.

FIGURE 344-1. Plantar wart. A hyperkeratotic, verrucous papule or plaque beneath a pressure point on the sole of the foot is characteristic. HPV types 1 (myrmecia), 2 (mosaic), and 4 are most common. Because plantar warts are driven into the skin by the pressure of walking or standing, they are usually the most treatment resistant.

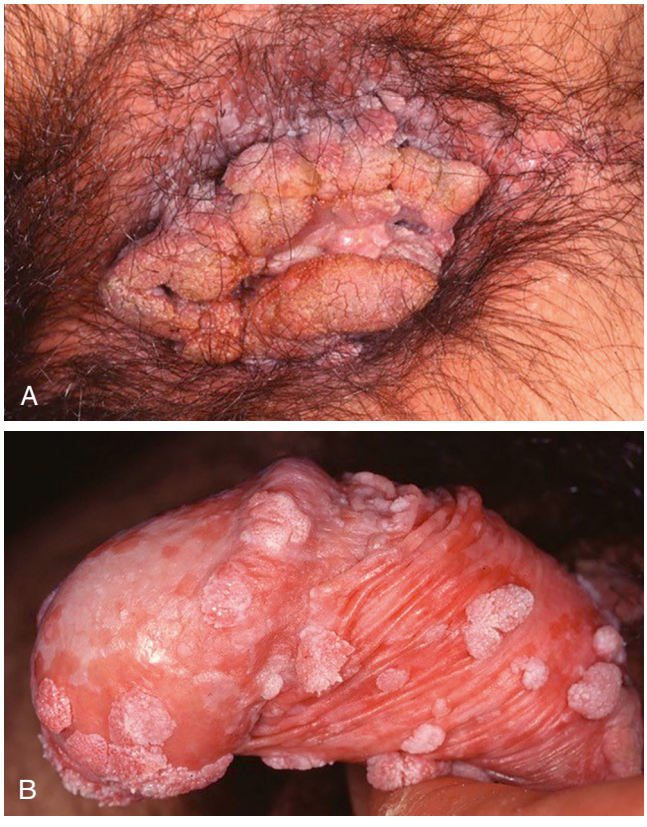

FIGURE 344-2. Genital human papillomavirus (HPV) infection. A, Perianal HPV infection. **B,** Penile HPV infection. (Courtesy CA Rietmeijer.)

DIAGNOSIS

Both cutaneous (Fig. 344-1) and genital (Fig. 344-2) warts generally present an easily recognized clinical picture and can be diagnosed by history and physical examination without laboratory testing. Oral lesions are also generally recognized by history and physical examination.

The differential diagnosis of cutaneous warts includes seborrheic and solar keratoses, nevi, irritated acrochordons, corns (also called calluses or clavi), and squamous cell carcinoma (Chapters 188 and 407), whereas plantar warts can be mimicked by lichen planus (Chapter 405) and corns of the foot. The differential diagnosis of genital warts includes benign papular lesions (e.g., seborrheic keratoses, acrochordons, and pearly penile papules) or inflammatory conditions (e.g., lichen planus, lichen nitidis). Genital warts must be distinguished from other sexually transmitted infections: the condylomata lata lesions of secondary syphilis (Chapter 295), which are typically flat-topped, moist, and kissing lesions, and molluscum contagiosum, which presents as smooth, dome-shaped papules, typically with a central dimple (Chapter 407). Biopsy for histopathologic examination may be helpful for lesions at all anatomic sites that are atypical or not responsive to therapy, those suggestive of high-grade squamous intraepithelial lesions or cancer (e.g., pigmented, indurated, fixed, bleeding, or ulcerated), or lesions in immunocompromised patients. HPV testing is not recommended for diagnosis because it cannot confirm the diagnosis and is not useful in guiding management.

Cervical squamous intraepithelial lesions have traditionally been detected by cervical cytology through Pap tests, with assessment of abnormal results by colposcopy and biopsy for histopathologic examination. However, HPV testing is more sensitive than Pap tests for detecting cervical intraepithelial neoplasia 2/3,[A1] and, used either alone or in combination with cytology (co-testing) in women over age 30 years, can permit the interval between screening to increase from every 3 years to every 5 years.[12] HPV tests are also recommended

for triage of women whose Pap test results show atypical squamous cells of undetermined significance, which is an equivocal test result. HPV testing has not been validated and is not recommended for screening for infection at other sites (e.g., anus, oropharynx), although it can assist with staging and prognosis of oropharyngeal cancer.

TREATMENT

Management of HPV infection is directed toward diagnosis and treatment of the lesions themselves because there are no virus-specific therapies. Many lesions resolve spontaneously, so the goal of treatment is amelioration or prevention of symptoms or, in the case of high-grade squamous intraepithelial lesions, prevention of progression to cancer. Treatment involves destruction of lesions by physical techniques or topically applied or injected cytotoxic agents. Because treatment does not eradicate infection in surrounding tissues, recurrent lesions are common.

Treatment of warts depends on their location and size, patient's preferences, and the clinician's experience. Recommended first-line treatment of common and plantar warts is the application of topical salicylic acid; second-line treatment of recalcitrant lesions includes cryotherapy (which also can be used for flat warts),[A2] intralesional bleomycin, pulsed dye laser therapy, and surgical excision. Recommended treatments of genital warts (Table 344-1) include patient-applied podophyllotoxin (0.5% solution or gel applied twice a day for 3 days, repeated weekly for four cycles), imiquimod, or sinecatechins, as well as provider-administered cryotherapy, trichloroacetic acid, or surgical excision; alternative treatments include laser surgery, infrared coagulation, and electrosurgery.[A3] Oral lesions can be treated by locally destructive physical techniques (cold-blade excision, cryotherapy, or laser surgery), whereas options for laryngeal papillomas include microdébridement, laser surgery, or photodynamic laser therapy.

For cervical lesions, treatment depends on histologic staging after colposcopy and biopsy and clinical context.[13] The general principles are as follows. Because cervical intraepithelial neoplasia grade 1 usually regresses spontaneously, follow-up (by cytology, HPV test, or colposcopy) without treatment is recommended. For cervical intraepithelial neoplasia grade 2/3 lesions, treatment is generally recommended, except in pregnant women, who have higher rates of spontaneous regression and a greater risk of reproductive tract complications after treatment, and in young women with cervical intraepithelial neoplasia grade 2. Treatment options include a variety of ablative and excisional techniques such as cryosurgery, loop electrosurgical excision procedure, and laser surgery. Treatment is 90 to 95% effective in preventing the recurrence of lesions, and comparative clinical trials have shown similar efficacy for different treatment modalities.

PREVENTION

Primary Prevention

Primary prevention of HPV infection depends on avoidance of contact with infectious lesions and reduction of susceptibility through immunization. For example, the use of footwear in locker rooms may prevent plantar warts. For genital HPV infection, correct and consistent condom use can reduce the risk for both HPV infection and the HPV-associated diseases of genital warts, cervical squamous intraepithelial lesions, and cervical cancer. Condom use also assists in the clearance of existing cervical HPV lesions. Male circumcision may reduce the prevalence of genital HPV infection in men, but whether it affects the transmission or clearance of these infections is unclear.[A4]

TABLE 344-1 RECOMMENDED TREATMENT OF GENITAL WARTS

PATIENT APPLIED
Podophyllotoxin (podofilox) 0.5% solution or gel; to be applied in up to 4 weekly cycles (twice daily for 3 days, followed by 4 days without treatment)
Imiquimod 3.75% cream (to be applied once daily at bedtime) or 5% cream (to be applied once at bedtime 3 times per week) for 6-10 hours for up to 16 weeks
Sinecatechins 15% ointment; to be applied 3 times daily for up to 16 weeks
PROVIDER ADMINISTERED
Cryotherapy with liquid nitrogen or cryoprobe; to be applied once every 1-2 weeks*
Trichloroacetic or bichloroacetic acid 80-90% solution; to be applied once weekly*
Office surgery* (excision, electrocautery, curettage)

*Safe for use in pregnancy.

Modified from: Workowski KA, Bolan GA. Sexually transmitted diseases treatment guidelines, 2015. *MMWR Recomm Rep.* 2015;64:1-137.

TABLE 344-2 U.S. ADVISORY COMMITTEE ON IMMUNIZATION PRACTICES RECOMMENDATIONS FOR HPV VACCINATION*

WHOM TO VACCINATE
Immunocompetent population • At age 11-12 years (but may start as early as age 9; it should start at age 9 in children with a history of sexual abuse or assault) • Catch-up HPV vaccination is recommended for all persons through age 26 years who are not adequately vaccinated • Shared clinical decision-making regarding HPV vaccination is recommended for adults ages 27 through 45 years who are not adequately vaccinated
Immunocompromised persons • 3 doses of HPV vaccine (0, 1-2, 6 months) are recommended for persons ages 9 through 26 years with immunocompromising conditions that might reduce cell-mediated or humoral immunity (e.g., B lymphocyte antibody deficiencies, T lymphocyte defects, HIV, malignancy, transplantation, autoimmune disease, or immunosuppressive therapy); the 3 dose recommendation does not apply to children ages <15 years with asplenia, asthma, chronic granulomatous disease, chronic liver disease, chronic lung disease, chronic renal disease, central nervous system anatomic barrier defects (e.g., cochlear implant), complement deficiency, diabetes, heart disease, or sickle cell disease
HOW TO VACCINATE
Recommended dosage and schedule: 0.5 mL intramuscularly • If vaccination is initiated before age 15 years, give 2-dose schedule: 0 and 6-12 months • If vaccination is initiated at age 15 years or older, give 3-dose schedule: 0, 1-2 months, and 6 months
SPECIAL CONSIDERATIONS
Schedule modifications: If the vaccination schedule is interrupted, the series does not need to be restarted but should be completed as soon as possible
Cervical cancer screening: no change in recommended interval
Special situations: females with genital warts, abnormal Pap test results, or positive HPV test results are unlikely to be infected with all vaccine types and should be immunized per other recommendations; males with genital warts should also be immunized per other recommendations
Pregnant and lactating women: not recommended for use in pregnancy based on lack of data; may be used in lactating women
Not recommended for females or males <9 and >45 years of age

*These recommendations have been adapted to reflect that (Gardasil-9) is the only available HPV vaccine in the United States.

Modified from:

Meites E, Kempe A, Markowitz LE. Use of a 2-dose schedule for human papillomavirus vaccination—updated recommendations of the Advisory Committee on Immunization Practices. *MMWR Morb Mortal Wkly Rep.* 2016;65:1405-1408.

Meites E, Szilagyi PG, Chesson HW, Unger ER, Romero JR, Markowitz LE. Human papillomavirus vaccination for adults: updated recommendations of the Advisory Committee on Immunization Practices. *MMWR Morb Mortal Wkly Rep.* 2019 Aug 16;68(32):698-702.

Of greatest importance for prevention are HPV vaccines (Chapter 15), which are composed of virus-like particles assembled from the major capsid protein, L1 (Table 344-2). Gardasil-9 is a nonavalent vaccine that includes types 6, 11, 16, and 18, 31, 33, 45, 52, 58. In addition to protecting against cervical intraepithelial neoplasia, cervical adenocarcinoma in situ, and cancer, it also protects against vulvar intraepithelial neoplasia, vaginal intraepithelial neoplasia, and cancers of the vulva or vagina in females, as well as against anal intraepithelial neoplasia[A5,A6] and anal cancer in males. In addition, vaccination protects both males and females against genital warts,[A7] and it reduces persistent oral HPV infections.[14] Cervarix, which is a bivalent (types 16 and 18) vaccine, is approved for the prevention of cervical intraepithelial neoplasia, cervical adenocarcinoma in situ, and cancer of the cervix associated with these two HPV types. Gardasil-9 is now the only vaccine available in the United States. HPV vaccination has no therapeutic benefit against existing infections or lesions but may lower the rate of disease recurrence after successful treatment. It is important to administer the vaccine before the onset of sexual activity to have the fullest benefit.

Other than transient local side effects at the site of intramuscular injection, mostly related to the adjuvant, the HPV vaccines have been very safe.[15] The longevity of protection is not yet established but has reached at least 14 years with the 3-dose regimen.[16] Two-dose regimens appear to be as good as 3-dose regimens,[17] with both regimens providing excellent and durable

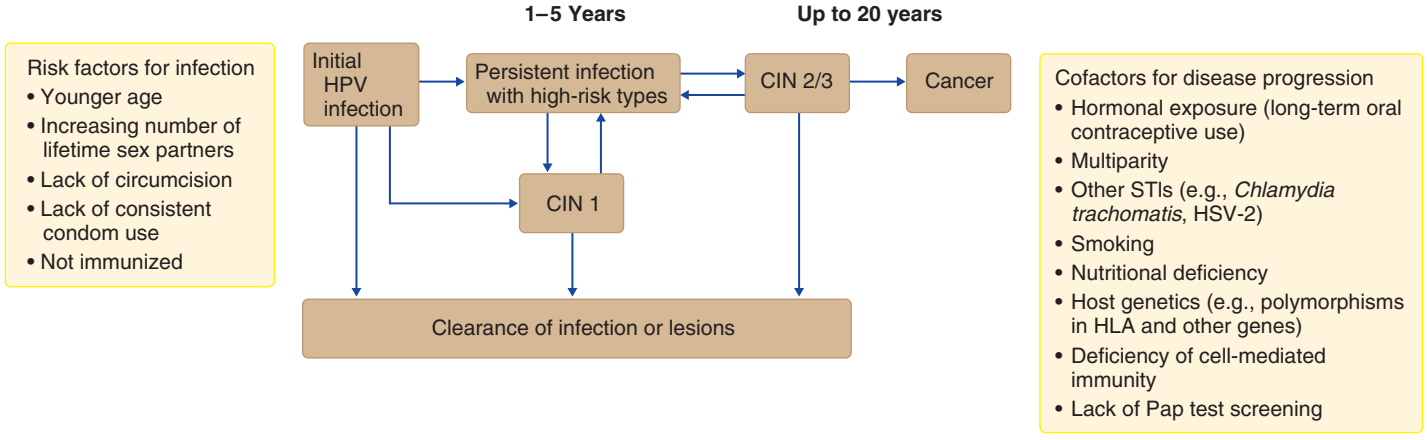

FIGURE 344-3. Natural history of genital human papillomavirus (HPV) infection and cervical cancer. CIN = cervical intraepithelial neoplasia; HSV = herpes simplex virus; STIs = sexually transmitted infections.

antibody response.[A8,A9] The HPV vaccine does not contain any live virus and can be given safely to immunocompromised persons.

Secondary Prevention

Screening plus treatment of high-grade cervical squamous intraepithelial lesions is one of the most successful of all cancer prevention strategies (see Chapter 184). HPV vaccination status currently does not alter recommendations regarding screening for cervical cancer. This recommendation could change in the future, however, if high vaccine coverage continues to lower the prevalence rates of cervical HPV infections. The value of cytologic screening for anal intraepithelial lesions (Chapter 131) in HIV-positive men who have sex with men is controversial but not currently recommended because of limited data on the natural history of these precursor lesions, the reliability of screening methods, and the safety and effectiveness of treatment.

PROGNOSIS

The large majority of HPV infections and related premalignant lesions resolve spontaneously in most immunocompetent patients based on their cell-mediated immunity. Spontaneous regression within a year is estimated to occur in 25% of genital warts and more than 50% of common warts in children. Whether infections no longer detectable have been cleared by the immune system or remain latent in the basal layer of the epithelium with the potential for reactivation is not clear, but the higher prevalence of detectable infection in advanced than in early HIV infection, as well as in immunosuppressed individuals, supports the possibility of long-term infection.

For cervical intraepithelial neoplasia, rates of regression are higher at younger ages and with lower grade lesions. The majority of grade 1 and 2 cervical intraepithelial neoplasia lesions regress spontaneously, whereas over 30% of women with grade 3 will progress to invasive cancer without treatment. The grades of cervical intraepithelial neoplasia may represent either a continuum of the same process or distinct processes, in which grade 1 cervical intraepithelial neoplasia represents a usually transient infection characterized by production of capsid protein (and probably infectious virions) and only minor cellular abnormalities, whereas grades 2 and 3 represent proliferation of immature cells as a result of the activity of oncogenic proteins of high-risk types (Fig. 344-3). Initial infection frequently leads to a transient low-grade squamous intraepithelial lesion, with persistent infection in less than 10% of cases. Persistent infection can, however, lead directly to high-grade squamous intraepithelial lesions within several years and can progress to invasive cancer after several decades, with the likelihood of cancer enhanced by cofactors such as older age and immunosuppression.[18] The natural history of squamous intraepithelial lesions at other anogenital sites is less well defined, but they may have higher rates of spontaneous regression.

The majority of patients with HPV infection have an excellent prognosis, with cancer occurring infrequently among the large number of persons infected. Treatment can hasten the resolution of cutaneous and genital warts and is highly effective for cervical lesions. Among women with cervical intraepithelial neoplasia grade 3, long-term studies indicate that the 30% risk of cancer in untreated women can be reduced to less than 1% with treatment.

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345 HERPES SIMPLEX VIRUS INFECTIONS

RICHARD J. WHITLEY AND JOHN W. GNANN, JR.

DEFINITION

The Pathogen

Among the herpesviruses, HSV-1 and HSV-2 are most closely related, with approximately 60% genomic homology. Historically, HSV-1 was more frequently associated with nongenital (especially orolabial) disease and HSV-2 with genital disease, but that distinction has become blurred with the recognition that HSV-1 causes more than half of initial genital herpes infections in some populations. These two viruses can be distinguished most reliably by DNA analysis, but differences in antigen expression and biologic properties also serve as methods for differentiation.

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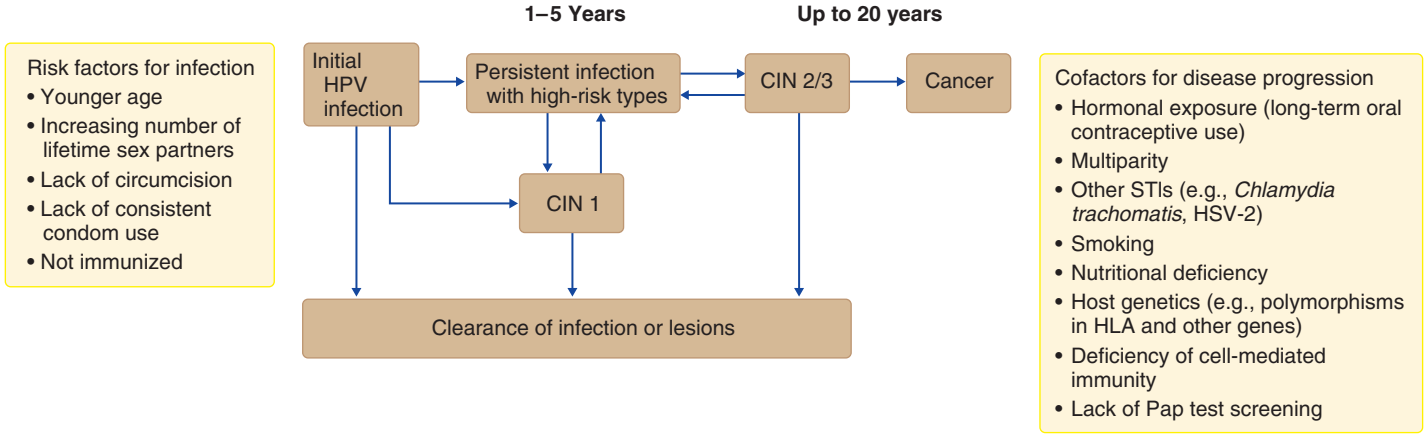

FIGURE 344-3. Natural history of genital human papillomavirus (HPV) infection and cervical cancer. CIN = cervical intraepithelial neoplasia; HSV = herpes simplex virus; STIs = sexually transmitted infections.

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PROGNOSIS

The large majority of HPV infections and related premalignant lesions resolve spontaneously in most immunocompetent patients based on their cell-mediated immunity. Spontaneous regression within a year is estimated to occur in 25% of genital warts and more than 50% of common warts in children. Whether infections no longer detectable have been cleared by the immune system or remain latent in the basal layer of the epithelium with the potential for reactivation is not clear, but the higher prevalence of detectable infection in advanced than in early HIV infection, as well as in immunosuppressed individuals, supports the possibility of long-term infection.

For cervical intraepithelial neoplasia, rates of regression are higher at younger ages and with lower grade lesions. The majority of grade 1 and 2 cervical intraepithelial neoplasia lesions regress spontaneously, whereas over 30% of women with grade 3 will progress to invasive cancer without treatment. The grades of cervical intraepithelial neoplasia may represent either a continuum of the same process or distinct processes, in which grade 1 cervical intraepithelial neoplasia represents a usually transient infection characterized by production of capsid protein (and probably infectious virions) and only minor cellular abnormalities, whereas grades 2 and 3 represent proliferation of immature cells as a result of the activity of oncogenic proteins of high-risk types (Fig. 344-3). Initial infection frequently leads to a transient low-grade squamous intraepithelial lesion, with persistent infection in less than 10% of cases. Persistent infection can, however, lead directly to high-grade squamous intraepithelial lesions within several years and can progress to invasive cancer after several decades, with the likelihood of cancer enhanced by cofactors such as older age and immunosuppression.[18] The natural history of squamous intraepithelial lesions at other anogenital sites is less well defined, but they may have higher rates of spontaneous regression.

The majority of patients with HPV infection have an excellent prognosis, with cancer occurring infrequently among the large number of persons infected. Treatment can hasten the resolution of cutaneous and genital warts and is highly effective for cervical lesions. Among women with cervical intraepithelial neoplasia grade 3, long-term studies indicate that the 30% risk of cancer in untreated women can be reduced to less than 1% with treatment.

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345 HERPES SIMPLEX VIRUS INFECTIONS

RICHARD J. WHITLEY AND JOHN W. GNANN, JR.

DEFINITION

The Pathogen

Among the herpesviruses, HSV-1 and HSV-2 are most closely related, with approximately 60% genomic homology. Historically, HSV-1 was more frequently associated with nongenital (especially orolabial) disease and HSV-2 with genital disease, but that distinction has become blurred with the recognition that HSV-1 causes more than half of initial genital herpes infections in some populations. These two viruses can be distinguished most reliably by DNA analysis, but differences in antigen expression and biologic properties also serve as methods for differentiation.

ABSTRACT

Herpes simplex virus (HSV) is one of the most common causes of human infections. The virus, which is an *alpha herpesvirus,* has the unique biologic characteristic of establishing latency in sensory ganglia and then periodically reactivating with the proper provocative stimulus and causing recurrent disease. Infection is transmitted from person-to-person via direct contact. Transmission most often occurs in the absence of clinical symptoms. There are two distinct antigenic types of HSV: HSV-1 and HSV-2. HSV-1 is usually associated with infections involving the oropharynx and lips, but the number of genital infections attributed to HSV-1 in the United States has increased significantly. HSV-2 routinely causes infections involving the genitalia and adjacent areas (pubis, buttocks, thighs, etc.). HSV disease can range from benign to life-threatening. The most severe manifestations are neonatal HSV infection (HSV-1 or HSV-2) and HSV encephalitis (usually HSV-1). Diagnosis is achieved either by polymerase chain reaction assays or by culture. Antiviral therapy is available to ameliorate the severity of the disease.

KEYWORDS

herpes simplex virus
infection
Herpesviridae
acyclovir
antivirals
encephalitis
neonatal herpes simplex virus

Inclusion in the family Herpesviridae is based on the structure of the virion (E-Fig. 345-1). HSV contains double-stranded DNA at its central core, has a molecular weight of approximately 100 million, and its 152- kb genome encodes at least 80 polypeptides. The DNA core is surrounded by a capsid that consists of 162 capsomers arranged in icosahedral symmetry. The capsid is 100 to 110 nm in diameter. Tightly adherent to the capsid is the tegument, which consists of amorphous material. Loosely surrounding the capsid and tegument is a lipid bilayer envelope derived from host cell membranes. The envelope consists of polyamines, lipids, and glycoproteins. These glycoproteins confer distinctive properties to the virus and are antigenic targets for host immune responses. Notably, glycoprotein G (gG) provides antigenic specificity to HSV, thereby resulting in an antibody response that allows serologic distinction between HSV-1 (gG-1) and HSV-2 (gG-2).

EPIDEMIOLOGY

HSV infections are very common worldwide in both developed and developing countries, without any seasonal variations. HSV is transmitted from infected to susceptible individuals during close personal contact; the virus must come in contact with a mucosal surface or abraded skin for infection to be initiated. Because over half of the world's population has HSV infections and because such infections are rarely fatal, a large reservoir of HSV exists to perpetuate person-to-person transmission. No animal vectors have been identified.

Seroprevalence studies have demonstrated that acquisition of HSV-1 infection is related to socioeconomic and behavioral factors. Antibodies, which indicate past infection, are found early in life among individuals of lower socioeconomic groups, presumably as a consequence of crowded living conditions that provide a greater opportunity for direct contact with infected individuals. Antibodies develop in as many as 75 to 90% of individuals from lower socioeconomic populations by the end of the first decade of life. In contrast, only 30 to 40% of persons in the middle and upper socioeconomic groups are seropositive by the middle of the second decade of life.

Because infections with HSV-2 are usually acquired through sexual contact, antibodies to this virus are rarely found before the onset of sexual activity, but the incidence of HSV-2 progressively increases in all populations beginning in adolescence.[1] Overall, about 15 to 20% of Americans have genital HSV-2 infection. Rates of HSV-2 infection are highest among women, non-Hispanic Blacks, men who have sex with men, and immunocompromised persons, including persons positive for human immunodeficiency virus (HIV; Chapter 358). Genital herpes infection is an important risk factor for HIV transmission. (Chapter 355). The lifetime costs of genital herpes infection are estimated to be about $1000 per treated case.[2]

Genital HSV disease occurring during gestation can result in transmission of HSV to the fetus, most frequently resulting from shedding of the virus in genital secretions at the time of delivery. Women who experience a symptomatic or asymptomatic primary infection in the third trimester of gestation have a 30 to 50% risk for transmitting infection to the child. The incidence of cervical shedding in pregnant women with asymptomatic chronic HSV-2 infection is approximately 1%. Most infants who develop neonatal disease are born to women who are completely asymptomatic for genital HSV infection at the time of delivery and who have neither a known history of genital herpes nor a sexual partner who has reported a genital rash.

PATHOBIOLOGY

Replication of HSV is a multistep process (E-Fig. 345-2). After binding of the virion to the host cell and release of the nucleocapsid into the cytoplasm, DNA is uncoated and transported to the nucleus. This release is followed by transcription of immediate-early genes, which encode the regulatory proteins, and is followed sequentially by the expression of proteins encoded by early and late genes. These proteins include structural proteins and enzymes necessary for viral replication.

Assembly of the viral core and capsid takes place within the nucleus. Envelopment at the nuclear membrane and transport out of the nucleus occur through the endoplasmic reticulum and the Golgi apparatus. Glycosylation of the viral membrane occurs in the Golgi apparatus. Mature virions are transported to the outer membrane of the host cell inside vesicles. Release of progeny virus is accompanied by cell death.

A critical factor for transmission of HSV is intimate contact between a person who is shedding virus and a susceptible host. Following inoculation onto skin or mucous membranes, HSV replicates in epithelial cells; the incubation period is 4 to 6 days (E-Fig. 345-3). Importantly, most primary infections are asymptomatic. In symptomatic patients, cell lysis and local inflammation ensue as replication continues, thereby resulting in the formation of characteristic vesicles on erythematous bases. During primary infection, lymph nodes in the area of viral replication may become enlarged. Viremia may result in visceral dissemination in immunocompromised patients. In all hosts, the virus generally ascends peripheral sensory nerves to reach the dorsal root ganglia. Replication of HSV within neural tissue is followed by spread of the virus to other mucosal and skin surfaces by means of peripheral sensory nerves. HSV replicates further in epithelial cells and reproduces the lesions of the initial infection until infection is contained through host immune responses.

The histopathologic changes induced by HSV replication are similar in both primary and recurrent infection, including ballooning of infected cells and the appearance of condensed chromatin within the nuclei of cells, followed by degeneration of cellular nuclei. Cells lose intact plasma membranes and form multinucleated giant cells. They may also demonstrate intranuclear inclusions, which are known as Cowdry type A bodies, and which are suggestive, but not diagnostic, of HSV infection. With cell lysis, clear vesicular fluid containing large quantities of virus accumulates between the epidermis and dermal layer. The dermis reveals an intense inflammatory response, more so with primary infection than with recurrent disease. As healing progresses, the clear vesicular fluid becomes pustular with the accumulation of inflammatory cells. The pustule ruptures, thereby resulting in an ulcer, which then scabs and heals; scarring is uncommon.

Vascular changes in the area of infection include perivascular cuffing and hemorrhagic necrosis. These changes are particularly prominent when organs other than skin are involved, as is the case with herpes simplex encephalitis or disseminated neonatal HSV infection. As host defenses are mounted, an influx of mononuclear cells is seen in infected tissue.

A unique characteristic of all herpesviruses is their ability to establish latent infection by persisting in an apparently inactive state for varying lengths of time and then reactivating (E-Fig. 345-4).[3] The latent viral genome may be either extrachromosomal or integrated into host cell DNA, depending on the type of herpesvirus.

Latency is established when HSV reaches the dorsal root ganglia after retrograde transmission through sensory nerve pathways. Latent virus may be reactivated and enter a replicative cycle at any point in time. Reactivation of latent virus is a well-recognized clinical phenomenon, but the molecular mechanisms remain incompletely understood. Stimuli associated with the reactivation of latent HSV include stress, fever, menstruation, and exposure to ultraviolet light. Precisely how these factors interact with latent virus at the level of the ganglia remains undefined. Reactivation is often clinically asymptomatic, but it may occasionally produce life-threatening disease.

HSV has been used for experimental gene therapy. By removal of the $\gamma_1$34.5 gene, both neurovirulence and the propensity to establish latency are ablated. These engineered viruses are being experimentally tested in patients with glioblastoma multiforme (Chapter 175) and metastatic colorectal cancer (Chapter 179).

CLINICAL MANIFESTATIONS

Gingivostomatitis

Gingivostomatitis (usually caused by HSV-1) occurs most frequently in children younger than 5 years. Illness is characterized by fever, sore throat, pharyngeal edema, and erythema, followed by the development of vesicular or ulcerative lesions on the oral and pharyngeal mucosa. Recurrent HSV-1 infections of the oropharynx, which have a significant adverse effect on quality of life,[4] are most frequently manifested as herpes simplex labialis (cold sores or fever blisters) and usually appear at the vermilion border of the lip (Fig. 345-1). Recurrences are triggered by fever, stress, physical injury, immunosuppression, menstruation, and exposure to ultraviolet light. Intraoral ulcers as a manifestation of recurrent HSV disease are uncommon.

Genital Herpes

Only 10 to 25% of persons with serologically confirmed HSV-2 infection are aware that they have genital herpes. Investigations using serial polymerase chain reaction (PCR) sampling have shown that 80 to 90% of HSV-2–infected individuals have transient episodes of asymptomatic viral shedding from the genital tract on 10 to 20% of days. Asymptomatic viral shedding from undiagnosed patients is the most common source of new transmissions.

Symptomatic initial infection in women usually involves lesions on the vulva, vagina, and cervix, whereas symptomatic men experience lesions on the glans penis, prepuce, or penile shaft. In the United States, herpes simplex

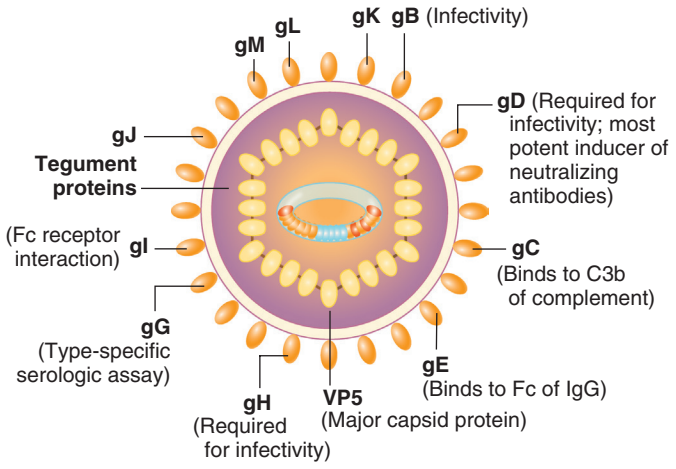

E-FIGURE 345-1. **Schematic diagram of the herpes simplex virion.** IgG = immunoglobulin G.

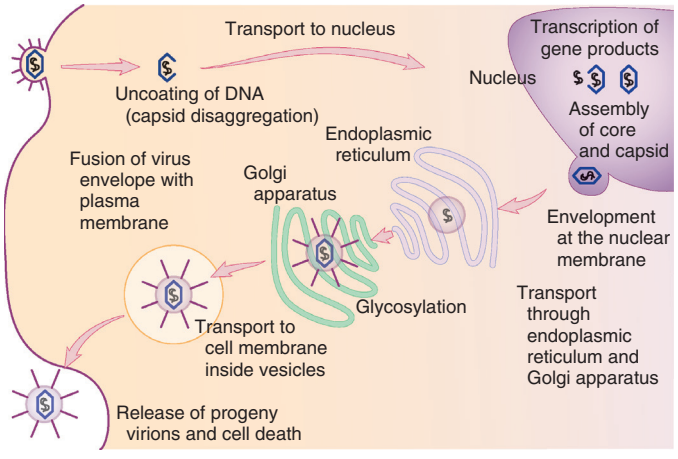

E-FIGURE 345-2. **Schematic diagram of replication of herpes simplex virus.**

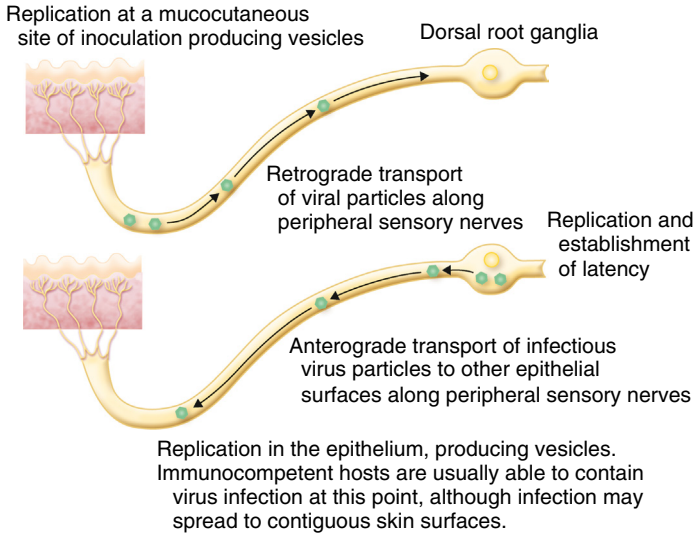

E-FIGURE 345-3. **Schematic diagram of primary herpes simplex virus infection.**

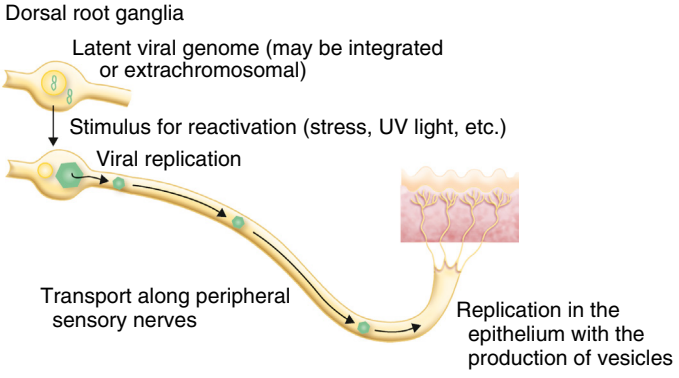

E-FIGURE 345-4. **Schematic diagram of herpes simplex virus latency and reactivation.** UV = ultraviolet.

FIGURE 345-1. Herpes labialis, classic grouped blisters.

is the most common cause of genital ulcers (Chapter 264).[5] Although genital herpes was historically attributed to HSV-2, over 50% of all initial cases in some populations (especially young women, non-Hispanic Whites, and men who have sex with men) are caused by HSV-1.

In individuals of either gender, primary disease can be associated with fever, malaise, anorexia, and bilateral inguinal adenopathy. Following initial infection, complete healing of lesions may take 2 to 3 weeks. Women frequently have dysuria and urinary retention as a result of urethral involvement. Aseptic meningitis (Chapter 381) develops in as many as 10% of individuals with primary infection. Sacral radiculomyelitis, which may occur in both men and women, results in neuralgias, urinary retention, or obstipation.

The initial episode of genital infection is less severe in individuals who have previously had HSV-1 infections at other sites. Antibodies to HSV-1 appear to ameliorate the clinical severity of initial HSV-2 infection.

Recurrent genital infections in either men or women can be particularly distressing. The frequency of recurrences varies significantly from one individual to another, but is always less frequent with HSV-1 genital disease than with HSV-2. In the first year after initial genital herpes caused by HSV-2, the median number of symptomatic recurrences is four.

Herpetic Keratitis

Herpes simplex keratitis (see Fig. 391-17), which is usually caused by HSV-1 and is often accompanied by conjunctivitis, is considered the most common infectious cause of blindness in the United States. The characteristic lesions of HSV keratoconjunctivitis are dendritic ulcers best detected by fluorescein staining of the cornea.[6] Deep stromal involvement also may result in visual impairment.

Other Cutaneous Manifestations

HSV infections can occur at any skin site. Common among health care workers are lesions on the fingers, known as herpetic whitlow. Similarly, wrestlers can develop cutaneous lesions known as herpes gladiatorum as a result of physical contact.

Herpes Meningitis

Reactivation of HSV-2 that is associated with symptomatic or asymptomatic genital herpes can cause recurrent episodes of lymphocytic meningitis (Chapter 381).[7] Symptoms include fever, meningismus, and headache, which can be severe. HSV meningitis is usually self-limited and does not progress to herpes encephalitis.

Hepatic Disease

An uncommon but potentially lethal syndrome of acute hepatic necrosis[8] caused by HSV has been described in both immunocompetent and immunocompromised patients. It occurs with increased frequency in pregnant women.

HERPES SIMPLEX VIRUS INFECTIONS IN IMMUNOCOMPROMISED HOSTS

HSV infections in immunocompromised hosts, including patients with acquired immunodeficiency syndrome, are usually due to reactivation of latent infection and are clinically more severe, may be progressive, and require a longer time to heal. Manifestations of HSV infections in this population include pneumonitis,[9] esophagitis, hepatitis, colitis, disseminated cutaneous disease, and central nervous system (CNS) infections. Individuals suffering from HIV infection may have extensive perineal or orofacial ulcerations. HSV infections can also be severe in individuals with extensive burns.

DIAGNOSIS

Definitive diagnosis of HSV infection requires detection of viral DNA by PCR testing or isolation of virus. DNA amplification has become the diagnostic method of choice in assessing cerebrospinal fluid (CSF) specimens for evidence of HSV infection of the central nervous system.[10] PCR is now widely used for confirmation of HSV as the cause of mucocutaneous or ocular infections. Viral culture is no longer frequently used, but is essential when an HSV isolate is required to assess possible resistance to antiviral drugs.

In the absence of PCR or diagnostic virologic facilities, cytologic examination of cells scraped from a clinical lesion may be useful in making a presumptive diagnosis of HSV infection (Tzanck prep), although sensitivity is low. Staining the preparation with HSV-specific monoclonal antibodies improves the sensitivity of the technique.

Type-specific serologic assays that reliably establish whether an individual is infected with HSV-1 or HSV-2 (or both) are commercially available. These tests are based on antigenic differences between HSV-1 and HSV-2 glycoprotein G.

TREATMENT

Immunocompromised Patients

For immunocompromised patients with extensive cutaneous HSV disease or with visceral organ disease, the treatment of choice is intravenous acyclovir (5 to 10 mg/kg every 8 hours, with dose adjustment for renal function). Acyclovir therapy is associated with very few adverse events. However, caution must be exercised when acyclovir is administered intravenously because the drug may crystallize in the renal tubules when infused too rapidly, especially in patients who are volume depleted or have preexisting renal dysfunction. Valacyclovir (500 to 1000 mg two or three times daily) and famciclovir (250 to 500 mg two or three times daily) are orally administered antiviral drugs that have improved pharmacokinetic profiles compared with oral acyclovir. These drugs are effective alternatives for non–life-threatening HSV infections.

Immunocompromised patients are at risk for developing infection due to acyclovir-resistant HSV. Resistance is usually due to a mutation resulting in altered or deficient expression of thymidine kinase, an enzyme essential for activation of acyclovir. Such patients can be managed with intravenous foscarnet or cidofovir, although each of these drugs can cause significant adverse effects (see Tables 328-4 and 328-5 in Chapter 328).

Immunocompetent Patients

In immunocompetent hosts with recurrent genital or bothersome labial infections,[11] oral acyclovir (800 mg twice daily for 5 days) accelerates healing of the lesion.[A1] Oral valacyclovir (1g once daily for 5 days or 500 mg twice daily for 3 days) and oral famciclovir (1 g once daily for 1 day) are equally effective[A2] and more convenient. Topical acyclovir is minimally efficacious and is not recommended,[A3] although the combination of topical therapy and photodynamic therapy (local application of methylene blue as a photosensitizer followed by laser light at a 660- nm wavelength) may reduce pain.[A4] Herpes simplex keratitis usually resolves with ganciclovir 0.15% ophthalmic gel five times daily for at least 1 week or oral acyclovir 800 mg five times daily for 7-10 days, but it can recur (Chapter 391).

Immunocompetent patients with HSV meningitis typically improve with or without specific antiviral therapy. Their treatment can focus on rehydration and analgesia rather than intravenous acyclovir therapy.

PREVENTION

Secondary Prevention

All patients with symptomatic genital HSV recurrences should be considered candidates for long-term suppressive antiviral therapy. Recommended regimens include oral acyclovir 400 mg twice daily, oral valacyclovir 500 mg or 1 g once daily, and oral famciclovir 250 mg twice daily. Suppressive therapy, which is highly effective for preventing both symptomatic recurrences and asymptomatic viral shedding, is much more efficient for genital herpes than is episodic antiviral therapy of symptomatic recurrences.

Suppressive therapy is not recommended for herpes labialis, for which the benefit of viral suppression is small. Antiviral suppressive therapy does not reliably prevent recurrent HSV-2 meningitis. Acyclovir, valacyclovir, and famciclovir are given to recipients of solid organ and bone marrow transplants in the immediate post-transplantation period to prevent reactivation of latent infection (see Tables 328-4 and 328-5).

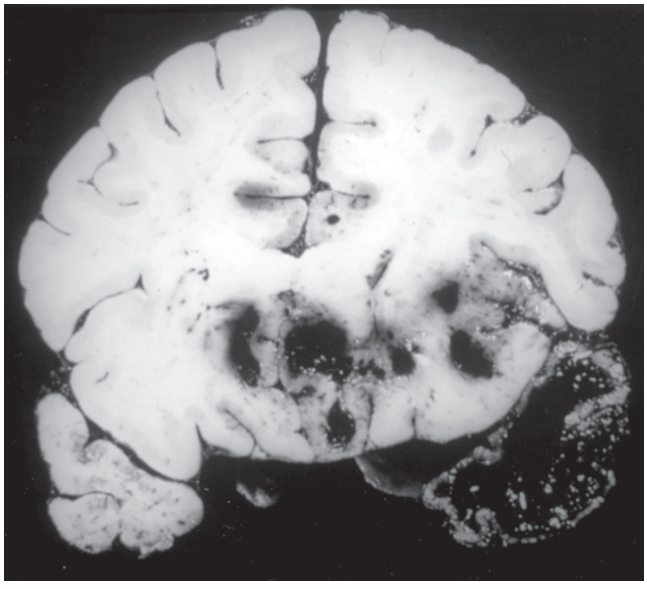

FIGURE 345-2. Hemorrhagic temporal lobe necrosis in herpes simplex encephalitis.

Primary Prevention

Screening of asymptomatic patients for genital HSV infection is not recommended. Vaccines for HSV-1 and HSV-2 remain investigational.[12] In a randomized trial, pericoital use of tenofovir gel, an antiviral microbicide, reduced HSV-2 acquisition in women by about 50%.[A5] Use of condoms also decreases transmission. Valacyclovir (500 mg daily) can decrease person-to-person transmission of HSV-2 when taken by the infected partner in a discordant couple. Suppressive therapy of an HSV-2–infected but HIV-seronegative person does not prevent HIV acquisition from HIV-seropositive partners.

HERPES SIMPLEX ENCEPHALITIS

Herpes simplex encephalitis is characterized by hemorrhagic necrosis of the temporal lobe (Chapter 383). Disease begins unilaterally and can spread to the contralateral temporal lobe (Fig. 345-2). It is the most common cause of fatal, sporadic encephalitis (Chapter 383) in the United States and occurs in approximately 1 to 2 cases per 500,000 individuals per year. More than 90% of cases in adults are caused by HSV-1. Herpes simplex encephalitis, which may follow primary or reactivated infection, can reach the temporal lobe by ascending neural pathways, such as the trigeminal tracts or the olfactory nerves. Defects in genes in the toll-like receptor 3 pathway increase risk for HSV encephalitis.

CLINICAL MANIFESTATIONS AND DIAGNOSIS

Clinical manifestations of herpes simplex encephalitis reflect temporal lobe involvement and include headache, fever, altered consciousness, behavioral changes, aphasia, and other focal neurologic abnormalities. Seizures are also common. CSF findings in these patients are variable, but usually reveal a lymphocytic pleocytosis (25 to 75 WBC/μL, 75 to 90% mononuclear cells). The protein concentration is mildly elevated (65 to 85 mg/dL), and the glucose level is usually normal. Magnetic resonance imaging (which is more sensitive than computed tomography) can suggest the diagnosis by demonstrating abnormalities of the temporal lobe, which are unilateral in the early stages of the disease.[13] Diagnosis can be confirmed detection of HSV DNA by PCR in the CSF.

TREATMENT AND PROGNOSIS

Without effective antiviral therapy, mortality is over 70%, and less than 10% of patients return to baseline neurologic function. With appropriate therapy using intravenous acyclovir (10 mg/kg every 8 hours for 14 to 21 days), the mortality rate can be reduced to 10 to 25%, with 40 to 55% of patients able to resume their activities of daily living.[14] Long-term oral valacyclovir administration has no benefit following acyclovir treatment.[A6]

Instances of recurrent HSV encephalitis have been reported, but many cases of relapsing neurologic symptoms are now thought to be due to postinfectious autoimmune phenomena, especially anti-*N*-methyl-D-aspartate receptor antibody encephalitis (Chapter 383).[15]

NEONATAL HERPES SIMPLEX VIRUS INFECTION

Neonatal HSV infection is estimated to occur in approximately 1 in 2000 to 3500 deliveries in the United States each year. Approximately 70% of cases are caused by HSV-2 and usually result from contact of the fetus with infected maternal genital secretions at the time of delivery. Manifestations of neonatal HSV infection can be divided into three categories: skin, eye, and mouth disease; encephalitis; and disseminated infection. As the name implies, skin, eye, and mouth disease is characterized by cutaneous lesions and does not involve other organ systems. Involvement of the CNS may occur with encephalitis or disseminated infection and generally results in diffuse encephalitis. Disseminated infection involves multiple organ systems and can cause disseminated intravascular coagulation, hemorrhagic pneumonitis, encephalitis, and cutaneous lesions.

Diagnosis is difficult in the absence of skin lesions, which occurs in as many as 36% of cases. CSF analysis characteristically reveals elevated protein levels and mononuclear pleocytosis.

Antiviral therapy is intravenous acyclovir, 20 mg/kg every 8 hours for 14 days for skin, eye, and mouth infections and 21 days for central nervous system or disseminated disease.[16] Six months of suppressive acyclovir therapy (300 mg three times daily) can significantly improve neurologic outcome.

Even with appropriate antiviral treatment, the mortality rate for each disease classification varies from zero for skin, eye, and mouth disease to 5% for encephalitis and up to 25% for neonates with disseminated infection. In addition to this high mortality rate, children with encephalitis or disseminated disease develop normally in only 40% of cases.

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346 VARICELLA-ZOSTER VIRUS (CHICKENPOX, SHINGLES)

JEFFREY COHEN

DEFINITION

Primary infection with varicella-zoster virus results in the rash of varicella (chickenpox). The varicella-zoster virus establishes a latent infection in the nervous system and can reactivate later in life to cause zoster (shingles).

The Pathogen

Varicella-zoster virus is a member of the alpha herpesvirus family and has a DNA core surrounded by a nucleocapsid, which is in turn surrounded by a viral envelope that is studded with glycoproteins. Antibody to viral glycoproteins is important for neutralizing the virus's infectivity and for protecting against primary infection. The virus encodes a thymidine kinase, which phosphorylates acyclovir, which in turn inhibits viral DNA replication by inhibiting the varicella-zoster virus DNA polymerase.

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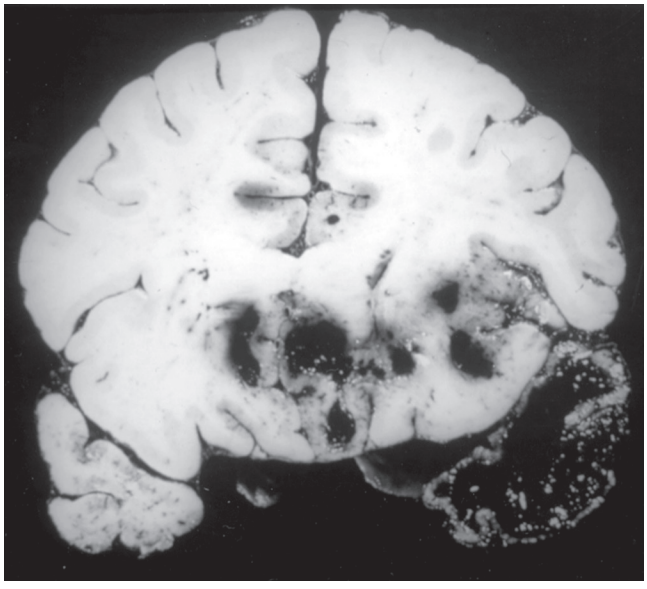

FIGURE 345-2. Hemorrhagic temporal lobe necrosis in herpes simplex encephalitis.

Primary Prevention

Screening of asymptomatic patients for genital HSV infection is not recommended. Vaccines for HSV-1 and HSV-2 remain investigational.[12] In a randomized trial, pericoital use of tenofovir gel, an antiviral microbicide, reduced HSV-2 acquisition in women by about 50%.[A5] Use of condoms also decreases transmission. Valacyclovir (500 mg daily) can decrease person-to-person transmission of HSV-2 when taken by the infected partner in a discordant couple. Suppressive therapy of an HSV-2–infected but HIV-seronegative person does not prevent HIV acquisition from HIV-seropositive partners.

HERPES SIMPLEX ENCEPHALITIS

Herpes simplex encephalitis is characterized by hemorrhagic necrosis of the temporal lobe (Chapter 383). Disease begins unilaterally and can spread to the contralateral temporal lobe (Fig. 345-2). It is the most common cause of fatal, sporadic encephalitis (Chapter 383) in the United States and occurs in approximately 1 to 2 cases per 500,000 individuals per year. More than 90% of cases in adults are caused by HSV-1. Herpes simplex encephalitis, which may follow primary or reactivated infection, can reach the temporal lobe by ascending neural pathways, such as the trigeminal tracts or the olfactory nerves. Defects in genes in the toll-like receptor 3 pathway increase risk for HSV encephalitis.

CLINICAL MANIFESTATIONS AND DIAGNOSIS

Clinical manifestations of herpes simplex encephalitis reflect temporal lobe involvement and include headache, fever, altered consciousness, behavioral changes, aphasia, and other focal neurologic abnormalities. Seizures are also common. CSF findings in these patients are variable, but usually reveal a lymphocytic pleocytosis (25 to 75 WBC/μL, 75 to 90% mononuclear cells). The protein concentration is mildly elevated (65 to 85 mg/dL), and the glucose level is usually normal. Magnetic resonance imaging (which is more sensitive than computed tomography) can suggest the diagnosis by demonstrating abnormalities of the temporal lobe, which are unilateral in the early stages of the disease.[13] Diagnosis can be confirmed detection of HSV DNA by PCR in the CSF.

TREATMENT AND PROGNOSIS

Without effective antiviral therapy, mortality is over 70%, and less than 10% of patients return to baseline neurologic function. With appropriate therapy using intravenous acyclovir (10 mg/kg every 8 hours for 14 to 21 days), the mortality rate can be reduced to 10 to 25%, with 40 to 55% of patients able to resume their activities of daily living.[14] Long-term oral valacyclovir administration has no benefit following acyclovir treatment.[A6]

Instances of recurrent HSV encephalitis have been reported, but many cases of relapsing neurologic symptoms are now thought to be due to postinfectious autoimmune phenomena, especially anti-*N*-methyl-D-aspartate receptor antibody encephalitis (Chapter 383).[15]

NEONATAL HERPES SIMPLEX VIRUS INFECTION

Neonatal HSV infection is estimated to occur in approximately 1 in 2000 to 3500 deliveries in the United States each year. Approximately 70% of cases are caused by HSV-2 and usually result from contact of the fetus with infected maternal genital secretions at the time of delivery. Manifestations of neonatal HSV infection can be divided into three categories: skin, eye, and mouth disease; encephalitis; and disseminated infection. As the name implies, skin, eye, and mouth disease is characterized by cutaneous lesions and does not involve other organ systems. Involvement of the CNS may occur with encephalitis or disseminated infection and generally results in diffuse encephalitis. Disseminated infection involves multiple organ systems and can cause disseminated intravascular coagulation, hemorrhagic pneumonitis, encephalitis, and cutaneous lesions.

Diagnosis is difficult in the absence of skin lesions, which occurs in as many as 36% of cases. CSF analysis characteristically reveals elevated protein levels and mononuclear pleocytosis.

Antiviral therapy is intravenous acyclovir, 20 mg/kg every 8 hours for 14 days for skin, eye, and mouth infections and 21 days for central nervous system or disseminated disease.[16] Six months of suppressive acyclovir therapy (300 mg three times daily) can significantly improve neurologic outcome.

Even with appropriate antiviral treatment, the mortality rate for each disease classification varies from zero for skin, eye, and mouth disease to 5% for encephalitis and up to 25% for neonates with disseminated infection. In addition to this high mortality rate, children with encephalitis or disseminated disease develop normally in only 40% of cases.

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346 VARICELLA-ZOSTER VIRUS (CHICKENPOX, SHINGLES)

JEFFREY COHEN

DEFINITION

Primary infection with varicella-zoster virus results in the rash of varicella (chickenpox). The varicella-zoster virus establishes a latent infection in the nervous system and can reactivate later in life to cause zoster (shingles).

The Pathogen

Varicella-zoster virus is a member of the alpha herpesvirus family and has a DNA core surrounded by a nucleocapsid, which is in turn surrounded by a viral envelope that is studded with glycoproteins. Antibody to viral glycoproteins is important for neutralizing the virus's infectivity and for protecting against primary infection. The virus encodes a thymidine kinase, which phosphorylates acyclovir, which in turn inhibits viral DNA replication by inhibiting the varicella-zoster virus DNA polymerase.

ABSTRACT

Primary infection with varicella-zoster virus results in the rash of varicella (chickenpox). The virus establishes a latent infection in the nervous system and can reactivate later in life to cause zoster (shingles). Varicella causes a disseminated rash, whereas zoster is usually a unilateral dermatomal rash in seemingly healthy persons, often at a time when their varicella-zoster virus-specific cellular immunity is impaired. Post-herpetic neuralgia, which is a dreaded complication of zoster, persists long after the rash has resolved. Acyclovir, valacyclovir, and famciclovir can treat varicella and zoster. Vaccines are approved to prevent both varicella and zoster.

KEYWORDS

varicella
chickenpox
zoster
shingles
post-herpetic neuralgia

EPIDEMIOLOGY

Before the advent of an effective vaccine, more than 95% of children in temperate climates were infected with varicella-zoster virus. By comparison, infection is usually delayed until adulthood in tropical climates. Varicella usually occurs in children younger than 5 years. Zoster is less common in tropical areas, probably because of a delay in acquisition of varicella. Varicella is more common in the winter and spring, whereas zoster has no seasonal predilection.

Primary varicella infection can occur after exposure to either chickenpox or zoster. The virus is spread by droplets and aerosols from patients or by contact with vesicular lesions. Persons are infectious beginning about 2 days before the rash appears and continuing until all lesions have crusted. Although 60 to 90% of susceptible household contacts develop varicella, only 20 to 30% of susceptible persons exposed to zoster become infected. More than 95% of primary infections result in the symptoms of varicella, and second episodes of varicella are rare. Varicella is more severe in persons with impaired cellular immunity, including patients who are infected with human immunodeficiency virus (HIV) and infants whose mothers present with varicella 5 days before to 2 days after delivery.

In unvaccinated immunocompetent adults over age 50 years, the risk of herpes zoster is about 0.9% per 100 person-years.[1] Before the introduction of an effective zoster vaccine, about 50% of persons who had varicella and lived to age 85 years developed zoster. The risk for zoster rises with increasing age (especially 50 years and older) and with increasing impairment of cellular immunity.[2,3] Perhaps because of advanced medical care and recognition by physicians, the reported incidence of zoster has increased by four-fold over the past six decades and continues to increase,[4] although hospitalizations for zoster have decreased in adults since 2008, apparently related to the herpes zoster vaccine.[5,6] Men who are infected with HIV and who are not taking antiretroviral therapies have a 15-fold higher risk for development of zoster than age-matched controls. Less than 5% of persons have a second episode of zoster, but recurrent zoster is more common in persons with impaired cellular immunity.

FIGURE 346-1. Child with varicella. (Courtesy of Centers for Disease Control and Prevention.)

PATHOBIOLOGY

Varicella is transmitted by the respiratory route. The virus is thought to infect epithelial cells and lymphocytes in the oropharynx and upper respiratory tract or in the conjunctiva, and then infected lymphocytes subsequently spread the virus throughout the body. The virus then enters the skin through endothelial cells in blood vessels and spreads to epithelial cells, where it causes the vesicular rash of varicella. Lesions initially are vesicular but become pustular after the infiltration of inflammatory cells. Later the lesions break open and dry to form crusts that usually heal without scarring. During primary infection, neurons in cranial nerve ganglia and dorsal root ganglia become latently infected with the virus.[7]

If varicella-zoster virus–specific cellular immunity declines, the virus can reactivate from a ganglion, travel down the axon, and replicate in epithelial cells to cause dermatomal zoster. In highly immunocompromised persons, high-grade viremia during reactivation causes disseminated zoster.

Antibodies, which usually are present at the time varicella presents clinically, persist for life. Antibody is important for protection against varicella, as evidenced by the ability of varicella immune globulin to attenuate the disease. Cytotoxic T cells are present within 2 to 3 days after the onset of varicella and limit its severity. Varicella and zoster are more severe in persons with impaired cellular immunity (e.g., HIV infection or genetic variants, particularly variants that affect interferon function)[8] but not in patients with hypogammaglobulinemia. Cellular immunity is required to prevent reactivation of virus and zoster.

CLINICAL MANIFESTATIONS

Varicella

Varicella begins with fever and malaise followed 1 to 2 days later by a disseminated, pruritic, vesicular rash (Fig. 346-1).[9] The usual incubation period for varicella is 2 weeks (range, 10 to 21 days) after exposure to an infected person. The lesions begin as papules that become vesicles, followed by pustules and then crusts. Lesions appear on the head and then spread to the trunk and then to the extremities; the mucosa also can be involved. There are typically 200 to 500 lesions in different stages on the skin. New lesions occur for up to 5 days in normal hosts, and crusting is complete within 2 weeks.

The most common complication of varicella is bacterial superinfection of skin lesions. Group A streptococcus (Chapter 269) or *Staphylococcus aureus* (Chapter 267) infections can cause cellulitis, bacteremia, and necrotizing fasciitis. Other complications include cerebellar ataxia, viral pneumonitis, hepatitis, and thrombocytopenia. Less frequent complications include viral meningitis, encephalitis, vasculopathy (which presents as a stroke),[10] disseminated intravascular coagulopathy (Chapter 161), and Reye syndrome (more common in children receiving aspirin) (Chapter 136). Complications involving the lungs and liver are more common in children with impaired cellular immunity, including those receiving systemic steroids, children with chronic pulmonary or skin disease, adults, and pregnant women during the third trimester. The fetal varicella syndrome, which occurs in fetuses infected during the first trimester, is characterized by atrophy of limbs with scarring of skin, chorioretinitis or cataracts, and central nervous system abnormalities. HIV-infected patients who have moderately reduced CD4 cell counts may develop recurrent varicella lesions in the absence of new exposures, and patients who have CD4 cell counts below 200/μL may develop progressive varicella with new lesions occurring for at least 1 month or chronic verrucous lesions.

Zoster

In healthy persons, zoster presents with localized pain and increased sensation for 1 to 3 days before the development of a dermatomal vesicular rash that does not cross the midline (Fig. 346-2).[11] Zoster most frequently presents in the dermatomes innervated by trigeminal or thoracic ganglia. The rash is usually accompanied by itching, tingling, or pain. The lesions evolve from vesicles to pustules, and crusting is usually complete by 10 days. In normal hosts, a few lesions may develop outside of the dermatome owing to low-grade viremia. Some patients with zoster sine herpete never develop a rash.

In persons with very impaired cellular immunity, reactivation is often associated with high-grade viremia with dissemination to large areas of the skin and involvement of multiple organs. As a result, patients with underlying malignancies are more likely to develop serious complications from their zoster infections, and zoster is occasionally associated with an occult hematologic malignancy.

A dreaded complication of zoster is post-herpetic neuralgia (Chapter 26), with pain persisting for at least 1 month after the rash has resolved. Risk factors include older age and severe immunosuppression. Patients may have allodynia (sensation of pain after nonpainful stimuli), paresthesias, dysesthesias, or severe neuropathic pain. Other complications of zoster include bacterial superinfection; ocular disease, involving any of the structures of the eye, due to reactivation in the ophthalmic branch of the trigeminal ganglia; facial (Bell) palsy (Chapter 388) caused by reactivation in cranial nerve VII; Ramsay Hunt syndrome, with pain and vesicles in the ear, numbness of the anterior tongue, and ipsilateral facial palsy due to reactivation in the geniculate ganglion of

FIGURE 346-2. Dermatomal zoster. (Courtesy of Centers for Disease Control and Prevention.)

cranial nerve VII; motor neuropathy; and meningitis. Zoster vasculopathy, occurring at the time of zoster or a few months later, can present with stroke due to inflammation of the cerebral arteries.

Progressive outer retinal necrosis, with few inflammatory ocular cells, occurs when varicella-zoster virus reactivates in the eye of severely immunocompromised persons, including patients who have AIDS and low CD4 cell counts. In contrast, acute retinal necrosis with a marked inflammatory response occurs when the virus reactivates in otherwise healthy persons. Patients with AIDS or recipients of hematopoietic stem cell transplants can have pancreatitis, hepatitis, and pneumonitis in the absence of or preceding a rash. Although varicella-zoster virus antigen was reported in temporal artery biopsies of some patients with giant cell arteritis, more recent studies have failed to confirm this association.

DIAGNOSIS

Most cases of varicella and zoster are diagnosed on the basis of their clinical presentation. A disseminated vesicular rash with lesions in various stages of evolution is usually sufficient for a diagnosis of varicella. The differential diagnosis includes impetigo (Chapter 408), enterovirus infections (Chapter 349), herpes simplex (Chapter 345), Stevens-Johnson syndrome (Chapter 407), and guttate psoriasis (Chapter 405). A dermatomal vesicular rash that does not cross the midline in a patient with a prior history of pain in the area is usually diagnostic of zoster. Herpes simplex is the most common disease that resembles zoster.

When the diagnosis of varicella or zoster must be confirmed definitively, polymerase chain reaction (PCR) for varicella-zoster virus from vesicular fluid is the most sensitive and specific test.[12] PCR for varicella-zoster virus in the blood can be useful for diagnosis of visceral zoster in highly immunocompromised persons before the onset of rash. PCR for varicella-zoster virus in the cerebrospinal fluid and intrathecal synthesis of varicella-zoster virus–specific antibody is useful for diagnosis of varicella-zoster virus neurologic diseases. Culture is less sensitive than PCR because the virus is very labile. Direct fluorescent antibody testing of vesicle fluid is rapid but less sensitive than PCR. Detection of multinucleated giant cells (Tzanck smear) is less specific because lesions of herpes simplex virus have a similar appearance. Biopsy specimens show eosinophilic intranuclear inclusion bodies and multinucleate giant cells.

Serology for varicella-zoster virus is useful to determine the need for postexposure prophylaxis in persons who are at high risk for disease after exposure to varicella or zoster. Enzyme-linked immunosorbent assay tests are less sensitive than latex agglutination assays and may not detect antibodies in vaccinees.

TREATMENT

Varicella

Symptomatic treatment includes acetaminophen for fever and lotion or baths for pruritus. Although acyclovir is licensed for the treatment of varicella, the drug is not recommended for otherwise healthy children because it only modestly decreases symptoms by about 1 day.

In immunocompromised persons, intravenous acyclovir (500 mg/m^2 every 8 hours for children, 10 mg/kg every 8 hours for adults) reduces visceral dissemination and is recommended for 7 to 10 days or until all lesions have crusted. Oral acyclovir (20 mg/kg four times daily for children or 800 mg five times daily for adults) given within 24 hours after the onset of rash reduces the duration of symptoms and is recommended for treatment of adolescents, adults, newborns whose mothers developed varicella near the time of delivery, mildly immunocompromised persons, children with chronic pulmonary or skin disease, and persons with complications of varicella. Acyclovir also should be considered for household contacts of persons with varicella or for pregnant women in the third trimester; these patients often have more severe disease. Oral valacyclovir is also approved for treatment of children ages 2 years to younger than 18 years with varicella (20 mg/kg three times daily with a maximum dose of 1 g). Oral valacyclovir (1 g three times daily) or famciclovir (500 mg three times daily) results in higher antiviral drug levels than does oral acyclovir and is preferred in nonpregnant adults.

Zoster

Acyclovir, valacyclovir, and famciclovir (for 7 days at the same doses as for varicella) are licensed for the treatment of zoster.[13] Oral valacyclovir and famciclovir result in higher levels of antiviral activity than oral acyclovir does. Although therapy should be started within 3 days of the rash, therapy may still be of benefit if new lesions continue to occur after this time. Because patients younger than age 50 years usually have little pain associated with zoster, antiviral therapy is often not used in these patients unless they have moderate to severe pain, have disease involving the eye, have other complications, or are immunocompromised. Antiviral drugs (see earlier) reduce the duration of lesions and zoster-associated pain but not the incidence of post-herpetic neuralgia. In severely immunocompromised persons, intravenous acyclovir (7 to 10 days or until all lesions have crusted) reduces the risk for visceral dissemination. Oral valacyclovir or famciclovir may be used in persons who are less severely immunocompromised.

Corticosteroids (e.g., prednisone, 60 mg/day and tapered over 21 days) added to acyclovir reduce acute pain and improve the quality of life in persons older than age 50 years but do not reduce the risk for post-herpetic neuralgia. Patients with severe pain often require narcotics (see Table 26-6).

Treatment of post-herpetic neuralgia is challenging. Gabapentin (initiated at a dose of 300 mg at bedtime and titrated to a maximum dose of 1200 mg three times daily) or pregabalin (initiated at a dose of 75 mg at bedtime and titrated to a maximum dose of 300 mg twice daily) may reduce pain.[A1] Additional agents include nortriptyline (initiated at a dose of 25 mg at bedtime and titrated to a maximum dose of 150 mg daily), lidocaine patches, and topical capsaicin (which itself causes pain that is not tolerated in up to one third of patients). Opioid analgesics (see Table 26-6) may be needed but must be used cautiously because of concerns about their long-term efficacy and safety.

Treatment of Varicella-Zoster Virus Complications and Acyclovir-Resistant Varicella-Zoster Virus

Intravenous acyclovir is recommended for persons with acute retinal necrosis. Corticosteroids (e.g., prednisone, 1 mg/kg per day for 3 to 5 days) and intravenous acyclovir (10 to 15 mg/kg every 8 hours for 14 days) are recommended for nonimmunocompromised persons with varicella-zoster virus vasculopathy. Zoster involving the eye should be evaluated by an ophthalmologist to assess the potential value of topical or intraocular therapy, such as the need to reduce intraocular pressure to treat glaucoma or to use mydriatics to prevent synechiae.

Acyclovir-resistant varicella-zoster virus infections are rare and are limited almost exclusively to patients who have AIDS or are recipients of transplants. Foscarnet (40 mg/kg every 8 hours) for 2 weeks or until all lesions have crusted is the treatment of choice for acyclovir-resistant varicella-zoster virus.

PREVENTION

Varicella

Patients with varicella or zoster are considered infectious until all lesions have completely crusted. Airborne and contact precautions are recommended for varicella, whereas only contact precautions are necessary for immunocompetent persons with localized zoster.

The live attenuated varicella vaccine (Chapter 15) is recommended for children aged 1 to 12 years[A2] and for persons 13 years and older without immunity to the virus. The vaccine is 92% effective in protecting against symptomatic varicella and more than 95% effective in protecting against severe disease. Two doses of vaccine are given subcutaneously. The varicella vaccine is also given as part of a combined measles, mumps, rubella vaccine (MMRV) for children 1 to 12 years of age in the United States. The rate of disease due to varicella declined by 90% in the United States during the first 13 years after the vaccine was licensed.

The most common complications of varicella vaccination are pain at the injection site, fever, and a mild rash within 2 weeks after vaccination. The rash is often localized to the area of vaccination and is often papular; in some healthy persons, the rash can be disseminated, although there are fewer lesions and symptoms are much less severe than with wild-type virus. In persons with severely impaired cellular immunity, rash is more common, can be extensive,

and may be accompanied by organ dysfunction. The varicella vaccine establishes latency and can cause zoster, although this complication occurs less commonly with vaccine virus than with wild-type virus. The vaccine strain of varicella has been transmitted to third parties only by vaccinees who developed a rash. Varicella vaccine is contraindicated in pregnant women and persons receiving high-dose immunosuppressive therapy (e.g., ≥2 mg/kg of prednisone daily) or with hematologic malignant neoplasms. Vaccination should be considered for HIV-infected children with age-specific $CD4^+$ T cells of 15% or more and adolescents and adults with $CD4^+$ T-cell counts of 200 cells/μL or higher. Serologic testing to verify immunity is not recommended for health care workers who have received two doses of vaccine because the currently available commercial antibody assays are not sensitive enough to detect protective levels of antibody.

Zoster

Two intramuscular doses of a subunit vaccine containing varicella-zoster virus glycoprotein E and the $AS01_B$ adjuvant system (called HZ/su) is about 85% effective against herpes zoster for all age groups,[I4] with a 80% efficacy in persons age 80 years and older in clinical trials[A3] and real-world experience. This vaccine is approved by the U.S. Food and Drug Administration (FDA) and recommended by the Advisory Committee for Immunization Practices (Chapter 15) for prevention of zoster and its complications in persons 50 years of age or older, and vaccination is safe and effective even in the frail elderly.[A4] The zoster subunit vaccine is safe and immunogenic in patients with hematologic malignancies,[A5] in renal transplant recipients,[A6] and in rheumatologic patients who have autoimmune diseases but are not on immunosuppressive therapies.[A7]

A live attenuated zoster vaccine is no longer available in the United States. The zoster subunit vaccine is recommended for immunocompetent individuals who previously received the live attenuated zoster vaccine[I5] because of its improved efficacy despite more local and sometimes systemic side effects than the live attenuated vaccine.

Postexposure Prophylaxis

In persons who are exposed to varicella but who have no prior history of varicella or of vaccination, three options are available. Varicella vaccine is preferred if exposure occurred within the prior 3 days and the patient is not immunocompromised. Vaccine is estimated to be 70 to 90% effective in healthy persons. VariZIG (formerly available as varicella immune globulin) prevents or attenuates varicella in 90% of susceptible persons if it is given within 4 days of exposure. The FDA has approved VariZIG for use within 10 days of exposure, but it should be given as soon as possible after exposure. VariZIG (given intramuscularly at 125 units/10 kg body weight, up to a maximum of 625 units) is indicated for susceptible persons at risk for severe varicella (e.g., pregnant women, preterm infants, neonates whose mothers have varicella between 5 days before and 2 days after delivery, immunocompromised persons) who are in close contact with patients with varicella or zoster. VariZIG has no effect in the treatment of zoster.

Oral acyclovir (40 to 80 mg/kg daily in four divided doses for 1 week beginning 7 to 9 days after exposure) is estimated to be 80 to 85% effective as postexposure prophylaxis. It is often used when the exposure occurred too long ago for vaccination or VariZIG.

PROGNOSIS

Before vaccination, about 200 children died of varicella each year in the United States. Now varicella is the underlying cause of death in an average of less than three Americans younger than 20 years annually. Of adult patients who develop zoster, the risk of post-herpetic neuralgia (Chapter 388) is about 15 to 20%.[I6]

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347 CYTOMEGALOVIRUS

GUY BOIVIN AND AJIT P. LIMAYE

DEFINITION

Cytomegalovirus (CMV) is a member of the herpesvirus family and shares, with the other members, the ability to establish a long-lived latent infection. Most of the clinical diseases caused by this virus result from reactivation of latent virus in immune-impaired patients, although primary infection in such patients can also lead to significant disease.

The Pathogen

CMV has a linear, double-stranded DNA genome with about 236,000 base pairs that encode about 167 proteins. On microscopic examination, the hallmark of tissue infection is a large (cytomegalic), 25- to 35-μm cell containing a large central, basophilic intranuclear inclusion (Fig. 347-1), referred to as an owl's eye.

EPIDEMIOLOGY

Multiple mechanisms account for the spread of this virus, including vertical (in utero, during vaginal delivery, and by breast milk) and horizontal (saliva, genital, urine, blood) contact. These routes of transmission lead, collectively, to a 15 to 20% seroprevalence by 15 years of age in developed countries, with a higher seroprevalence in lower socioeconomic settings. From that age on, there is a steady upward trend of 1 to 2% per year that is due in part to sexual transmission. As a result, approximately 50% of the general population of the United States is antibody positive by 35 years of age, and a 1% per year rate of increase occurs thereafter. In underdeveloped countries, up to 90% of persons may be seropositive by 2 years of age.[1] Presumably, crowded living conditions permit spread of the virus through close contact with body fluids. A study showed that CMV was viable on metal and wood for up to 1 hour, glass and plastic up to 3 hours, and rubber, cloth, and crackers up to 6 hours. CMV was more likely to be isolated from wet, highly absorbent surfaces. These considerations were felt to be particularly important because children may actively shed CMV in saliva and urine for months to years, and exposure to bodily fluids

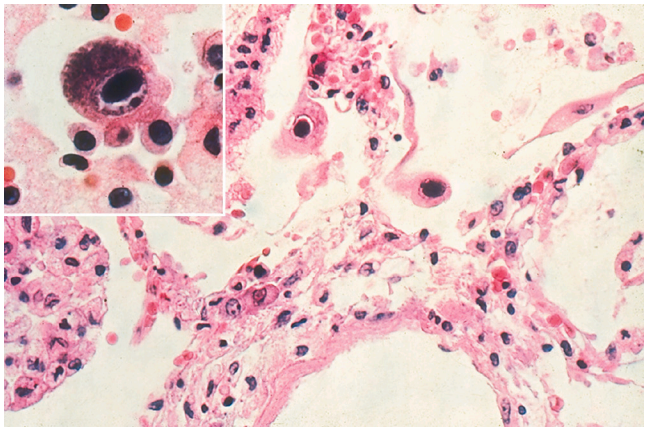

FIGURE 347-1. Cytomegalovirus (CMV) pneumonia. A lung biopsy specimen was stained with hematoxylin and eosin and magnified 250-fold. The *inset* shows a CMV "owl's eye" inclusion.

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and may be accompanied by organ dysfunction. The varicella vaccine establishes latency and can cause zoster, although this complication occurs less commonly with vaccine virus than with wild-type virus. The vaccine strain of varicella has been transmitted to third parties only by vaccinees who developed a rash. Varicella vaccine is contraindicated in pregnant women and persons receiving high-dose immunosuppressive therapy (e.g., ≥2 mg/kg of prednisone daily) or with hematologic malignant neoplasms. Vaccination should be considered for HIV-infected children with age-specific $CD4^+$ T cells of 15% or more and adolescents and adults with $CD4^+$ T-cell counts of 200 cells/μL or higher. Serologic testing to verify immunity is not recommended for health care workers who have received two doses of vaccine because the currently available commercial antibody assays are not sensitive enough to detect protective levels of antibody.

Zoster

Two intramuscular doses of a subunit vaccine containing varicella-zoster virus glycoprotein E and the $AS01_B$ adjuvant system (called HZ/su) is about 85% effective against herpes zoster for all age groups,[I4] with a 80% efficacy in persons age 80 years and older in clinical trials[A3] and real-world experience. This vaccine is approved by the U.S. Food and Drug Administration (FDA) and recommended by the Advisory Committee for Immunization Practices (Chapter 15) for prevention of zoster and its complications in persons 50 years of age or older, and vaccination is safe and effective even in the frail elderly.[A4] The zoster subunit vaccine is safe and immunogenic in patients with hematologic malignancies,[A5] in renal transplant recipients,[A6] and in rheumatologic patients who have autoimmune diseases but are not on immunosuppressive therapies.[A7]

A live attenuated zoster vaccine is no longer available in the United States. The zoster subunit vaccine is recommended for immunocompetent individuals who previously received the live attenuated zoster vaccine[I5] because of its improved efficacy despite more local and sometimes systemic side effects than the live attenuated vaccine.

Postexposure Prophylaxis

In persons who are exposed to varicella but who have no prior history of varicella or of vaccination, three options are available. Varicella vaccine is preferred if exposure occurred within the prior 3 days and the patient is not immunocompromised. Vaccine is estimated to be 70 to 90% effective in healthy persons. VariZIG (formerly available as varicella immune globulin) prevents or attenuates varicella in 90% of susceptible persons if it is given within 4 days of exposure. The FDA has approved VariZIG for use within 10 days of exposure, but it should be given as soon as possible after exposure. VariZIG (given intramuscularly at 125 units/10 kg body weight, up to a maximum of 625 units) is indicated for susceptible persons at risk for severe varicella (e.g., pregnant women, preterm infants, neonates whose mothers have varicella between 5 days before and 2 days after delivery, immunocompromised persons) who are in close contact with patients with varicella or zoster. VariZIG has no effect in the treatment of zoster.

Oral acyclovir (40 to 80 mg/kg daily in four divided doses for 1 week beginning 7 to 9 days after exposure) is estimated to be 80 to 85% effective as postexposure prophylaxis. It is often used when the exposure occurred too long ago for vaccination or VariZIG.

PROGNOSIS

Before vaccination, about 200 children died of varicella each year in the United States. Now varicella is the underlying cause of death in an average of less than three Americans younger than 20 years annually. Of adult patients who develop zoster, the risk of post-herpetic neuralgia (Chapter 388) is about 15 to 20%.[I6]

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347 CYTOMEGALOVIRUS

GUY BOIVIN AND AJIT P. LIMAYE

DEFINITION

Cytomegalovirus (CMV) is a member of the herpesvirus family and shares, with the other members, the ability to establish a long-lived latent infection. Most of the clinical diseases caused by this virus result from reactivation of latent virus in immune-impaired patients, although primary infection in such patients can also lead to significant disease.

The Pathogen

CMV has a linear, double-stranded DNA genome with about 236,000 base pairs that encode about 167 proteins. On microscopic examination, the hallmark of tissue infection is a large (cytomegalic), 25- to 35-μm cell containing a large central, basophilic intranuclear inclusion (Fig. 347-1), referred to as an owl's eye.

EPIDEMIOLOGY

Multiple mechanisms account for the spread of this virus, including vertical (in utero, during vaginal delivery, and by breast milk) and horizontal (saliva, genital, urine, blood) contact. These routes of transmission lead, collectively, to a 15 to 20% seroprevalence by 15 years of age in developed countries, with a higher seroprevalence in lower socioeconomic settings. From that age on, there is a steady upward trend of 1 to 2% per year that is due in part to sexual transmission. As a result, approximately 50% of the general population of the United States is antibody positive by 35 years of age, and a 1% per year rate of increase occurs thereafter. In underdeveloped countries, up to 90% of persons may be seropositive by 2 years of age.[1] Presumably, crowded living conditions permit spread of the virus through close contact with body fluids. A study showed that CMV was viable on metal and wood for up to 1 hour, glass and plastic up to 3 hours, and rubber, cloth, and crackers up to 6 hours. CMV was more likely to be isolated from wet, highly absorbent surfaces. These considerations were felt to be particularly important because children may actively shed CMV in saliva and urine for months to years, and exposure to bodily fluids

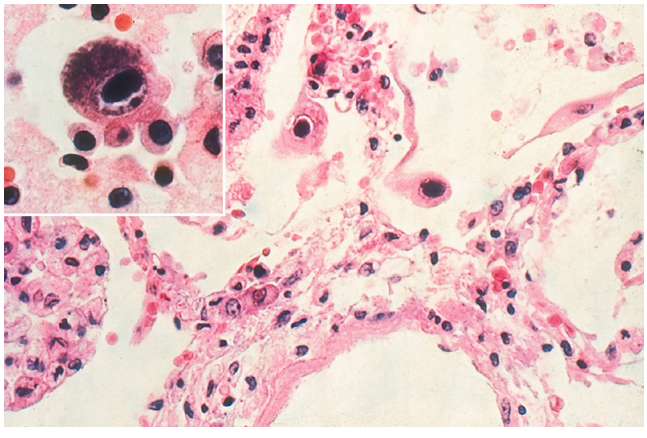

FIGURE 347-1. Cytomegalovirus (CMV) pneumonia. A lung biopsy specimen was stained with hematoxylin and eosin and magnified 250-fold. The *inset* shows a CMV "owl's eye" inclusion.

ABSTRACT

Cytomegalovirus (CMV) belongs to the Herpesviridae family. The seroprevalence of CMV is estimated to be 50% by adulthood. CMV establishes latency in host cells and may reactivate. CMV infections are generally asymptomatic in immunocompetent individuals or may be associated with mononucleosis-like syndromes. Clinical diseases result from reactivation of latent virus, primary infection or reinfections in immunocompromised patients such as transplant recipients and patients with advanced human immunodeficiency virus (HIV) infection. The virus is excreted in most biological fluids and may be transmitted through vertical and horizontal routes. Congenital infection may either be asymptomatic or lead to microcephaly, intracerebral calcifications, hepatosplenomegaly, and rash in 10% of newborns excreting CMV. Half of the survivors will develop hearing loss and/or intellectual disability. Clinical manifestations in immunocompromised hosts include a nonspecific viral illness termed "CMV syndrome" or diseases such as retinitis, pneumonitis, colitis, hepatitis, pancreatitis, and meningoencephalitis. CMV infections may increase the risks of bacterial infections and invasive fungal infections, reactivation of other herpesviruses, immunosenescence, acute or chronic allograft rejection, graft loss, and death. Diagnosis of CMV infection is performed by viral DNA quantification on whole blood, plasma, or other fluids or tissues by PCR. Candidate vaccines are being developed but remain experimental. Prophylaxis or preemptive therapy with antivirals is commonly administered to transplant recipients to prevent CMV infections and diseases. First-line antiviral therapy, which targets the viral DNA polymerase, includes ganciclovir and its prodrug valganciclovir, whereas second-line agents include foscarnet, cidofovir, and maribavir. Letermovir, a viral terminase inhibitor, is used for prophylaxis in recipients of stem cell transplants and is under study in recipients of kidney transplants.

KEYWORDS

cytomegalovirus
neonates
transplant recipients
AIDS
preemptive therapy
antiviral agents

from young children poses substantial risk for CMV exposure among women of reproductive age. Two additional mechanisms of transmission are blood transfusion and organ transplantation. A final important epidemiologic fact is that reinfection with a different strain of CMV may occur in CMV-seropositive persons, especially those who are immunocompromised or pregnant or have multiple sexual partners.

PATHOBIOLOGY

In immunocompetent individuals, CMV rarely causes clinically evident end-organ disease. When immune mechanisms are deficient, especially mechanisms mediated by $CD4^+$ and $CD8^+$ lymphocytes, latent virus replicates and causes both direct and indirect effects. Examples of direct virally mediated diseases are necrotizing CMV retinitis and esophagitis. In contrast, CMV pneumonitis is frequently manifested as subtle histologic alterations accompanied by limited viral replication, thereby suggesting that immune-mediated injury may be the primary pathologic mechanism.[2] Such injury may result from the upregulation and release of cytokines, including tumor necrosis factor-α, interferon-γ, and interleukin-2. Immune-mediated tissue injury may also be effected by $CD8^+$ cytotoxic T lymphocytes directed against CMV-infected target cells. The clinical manifestations of CMV infection, including meningoencephalitis, retinitis, enteritis, vasculitis, pneumonitis, myocarditis, lymphadenitis, hepatitis, adrenalitis, and pancreatitis, reflect the range of cell types that CMV is capable of infecting. The indirect effects of CMV include increased risks of some bacterial infections and invasive fungal diseases, reactivation of other herpesviruses, immunosenescence, rejection, graft loss, and death.

The immune response to CMV infection involves both the humoral and cell-mediated arms, and T-cell responses appear to be the most important for controlling reactivated infection. The CMV envelope glycoproteins that participate in viral entry are gB, gH/gL, and gCII, as components of the pentameric complex. Humoral immunity directed at gB has been detected in convalescent phase sera and has been shown to block viral entry, cell-to-cell transmission, and syncytium formation in CMV-infected cells. Not surprisingly, components of the pentameric complex are the primary target of experimental vaccines.

Fundamental to the pathogenesis of CMV is latency, or persistence of the viral genome in host cells without evidence of productive viral replication. It is thought that monocytes and bone marrow progenitor cells are sites of human CMV latency. Reactivation from latency has classically been associated with immunosuppression. Exposure to a rich milieu of cytokines and growth factors results in the activation of signal transduction pathways, generation of increased levels of intracellular transcription factors, and production of viable virus.

CLINICAL MANIFESTATIONS

Congenital and Neonatal Infection

In the developed world, congenital infection occurs in approximately 0.2 to 0.7% of newborns. Thus, in the United States, each year approximately 40,000 infants are born excreting CMV, and about 4000 (or ~10%) of these newborns show clinical evidence of congenital disease, such as microcephaly, intracerebral calcification, hepatosplenomegaly, and rash.[3] About 90% of these clinically infected newborns will survive, but half of the survivors will have unilateral or bilateral hearing loss, developmental delay, or both. Mothers of most infants with symptomatic CMV infection had a primary infection during pregnancy, although it is now well known that clinically evident congenital infection also occurs in infants born to mothers with past CMV infection. In mothers with a primary infection, a negative amniocentesis markedly reduces the likelihood of hearing impairment and makes more serious sequelae very unlikely. In newborns who are born to women with primary CMV infection but are initially asymptomatic, a higher viral load may increase the risk for subsequent CMV-related sequelae. Up to 14% of asymptomatic infected babies at birth will eventually develop learning problems or hearing loss.

Infection in Immunocompetent Persons

Virtually all CMV infections occurring in immunocompetent persons are asymptomatic. In some patients, a clinical illness resembling infectious mononucleosis may develop (Chapter 348), but with minimal pharyngitis and lymphadenopathy. Atypical lymphocytosis develops in these patients, similar to Epstein-Barr virus infection, but they have a negative heterophil antibody test result. Thrombocytopenia is an occasional complication.[4] CMV reactivation is more common in elderly and frail individuals and is especially common (33%) in critically ill immunocompetent patients, in whom it is associated with prolonged hospitalization and mortality, but whether it causes these effects is unclear.[5]

Infection in Transplant Recipients

When a CMV-seronegative recipient receives a solid organ from a CMV-seropositive donor, the resulting illnesses include the "CMV syndrome," characterized by fever, neutropenia, atypical lymphocytes, and sometimes by hepatosplenomegaly.[6] CMV disease may also develop in the transplanted organ. For example, CMV hepatitis in liver transplant recipients is associated with fever, hyperbilirubinemia, and elevated liver enzymes; liver failure may ensue and necessitate retransplantation. Recipients of a solid organ transplant may develop CMV disease by reactivation of latent infection, reinfection by an exogenous strain, or transmission of CMV from a seropositive donor to a seronegative individual (primary infection).[7] Disease in CMV-seropositive recipients is, fortunately, less severe than that resulting from primary infection. CMV infection occurs more commonly in recipients of lung or liver transplants than in recipients of kidney transplants.

CMV pneumonia may occur after solid organ transplantation but is most common after stem cell transplantation.[8] Fever, nonproductive cough, and dyspnea can progress rapidly. The diagnosis is suggested by interstitial to nodular infiltrates rather than by alveolar densities on chest radiographs. In contrast to solid organ transplantation, CMV disease after stem cell transplantation usually results from reactivation of latent CMV in a seropositive recipient rather than from a new, primary infection.

CMV may cause disease throughout the gastrointestinal tract. Colitis, which is a common syndrome in transplant recipients, is manifested as diarrhea, weight loss, and fever. It is characterized by diffuse submucosal hemorrhages and ulcerations.

Infection in Patients with Acquired Immunodeficiency Syndrome

In the era before highly active antiretroviral therapy, CMV retinitis occurred in approximately one third of patients with acquired immunodeficiency syndrome (AIDS), most often in those with CD4 counts below 50/μL. It usually begins unilaterally with visual blurring, floaters, decreased acuity, and loss of visual fields and progresses to blindness if it is untreated. The retinal examination is abnormal, and the finding of apparent hemorrhages and exudates is the best diagnostic test (Fig. 347-2). CMV colitis is similar to that seen in transplant recipients, but esophagitis is also common and characterized by distal ulceration, which may be single but extensive.

CMV neurologic disease occurs in multiple forms, including encephalitis and a polyradiculopathy/myelitis syndrome. The encephalitis, which usually occurs only in patients who are profoundly immunosuppressed, typically presents as a subacute encephalopathy with headache, impaired cognition, apathy, and social withdrawal. CMV transverse myelitis is indistinguishable neurologically from other forms of transverse myelitis (Chapters 369 and 380). In human immunodeficiency virus (HIV)–infected patients, CMV polyradiculomyelitis

FIGURE 347-2. Cytomegalovirus retinitis as seen by direct ophthalmoscopic examination.

presents subacutely over days to weeks with paresthesias or dysesthesias that rapidly progress to paraparesis with hypotonia.

With the efficacy of combination antiretroviral therapy, the incidence of all of these CMV syndromes has decreased dramatically, but they are still seen before HIV treatment or when such treatment is interrupted or ineffective.

Even in the current era of HIV treatment, evidence of immunoglobulin G–positive CMV infection is associated with an increased risk of severe non–AIDS-defining events and non–AIDS-related death, especially cardiovascular and cerebrovascular events, thereby suggesting a role for CMV coinfection in vascular/degenerative organ disorders in HIV-infected patients.[9]

DIAGNOSIS

Assay of viral DNA by polymerase chain reaction (PCR) testing is more sensitive than viral culture and is the best assay for the early detection of CMV disease. This assay, mainly performed on whole blood or plasma, can provide quantification that is especially helpful in supporting the diagnosis of CMV disease, enacting preemptive antiviral intervention, and monitoring therapy. PCR detection of CMV in cerebrospinal fluid is the preferred diagnostic approach to patients with suspected CMV neurologic disease. Monoclonal antibodies can quantify viremia by counting CMV antigen–positive cells directly in peripheral blood leukocytes (antigenemia). Viral culture is rarely used clinically, and culture-positivity does not prove causality, especially in immunocompromised patients. Cytologic and histologic abnormalities are not sensitive measures of CMV infection, but they are specific indicators of CMV disease.

TREATMENT

The Medications

Oral valganciclovir, intravenous ganciclovir, intravenous ganciclovir followed by oral valganciclovir, oral maribavir, intravenous foscarnet, intravenous cidofovir, and ganciclovir intraocular injection coupled with valganciclovir are all effective treatments of established CMV diseases (Table 347-1).[10] These drugs (especially ganciclovir/valganciclovir) also can be used preemptively (i.e., when the viral load reaches a predetermined level even before the development of clinical disease).[A1]

TABLE 347-1 TREATMENT OF CYTOMEGALOVIRUS DISEASE

	PREFERRED THERAPY	ALTERNATIVE THERAPY
Cytomegalovirus (CMV) retinitis* Sight-threatening lesions	Valganciclovir 900 mg bid PO ± ganciclovir intraocular injection	Ganciclovir IV; foscarnet IV; plus ganciclovir intraocular injection
Peripheral lesions	Valganciclovir 900 mg bid PO	Ganciclovir IV or foscarnet IV
Maintenance therapy	Valganciclovir 900 mg qd PO	Ganciclovir IV or foscarnet IV
CMV gastrointestinal disease	Ganciclovir IV for 3-6 wk or valganciclovir 900 mg bid PO for 3-6 wk	Foscarnet IV for 3-6 wk
CMV neurologic disease	Ganciclovir IV + foscarnet IV	
CMV viremia syndrome	Valganciclovir 900 mg bid PO or ganciclovir IV until viremia clears	Foscarnet IV
Ganciclovir resistant	Foscarnet IV ± IV ganciclovir, and intraocular injection	Maribavir or cidofovir (if only *UL97* mutation)

*If not already begun, antiretroviral therapy should be initiated concurrently with anti-CMV therapy, except possibly when treating central nervous system disease. For retinitis, anti-CMV therapy should be continued until the CD4 count has exceeded 100-150 cells/μL for ≥6 months and the retinitis is inactive. If anti-CMV therapy is discontinued, regular monthly eye examinations should be continued. Early relapses of CMV retinitis in patients treated systemically are usually due to inadequate drug penetration, and reinduction with the same drug is often effective. Drug resistance may occur in patients treated for ≥3 months. Therapy of these patients may be guided by genotyping.
bid = twice daily; IV = intravenously; PO = orally; qd = once daily.
Adapted from Drew WL, Erlich KS. Management of herpesvirus infections (cytomegalovirus, herpes simplex virus, and varicella-zoster virus). In: Volberding PA, Greene WC, Lange J, et al., eds. *HIV/AIDS Medicine Medical Management of AIDS 2012*. Philadelphia: Saunders Elsevier; 2012:433.

Ganciclovir is a nucleoside analogue given intravenously, 5 mg/kg two times daily during initial induction (2 to 3 weeks); maintenance therapy consists of 5 mg/kg once daily (Chapter 328). Ganciclovir resistance may occur as a result of mutations in the protein kinase gene (*UL97*) and/or in the DNA polymerase gene (*UL54*). Granulocyte colony-stimulating factor may be needed to offset neutropenia. Valganciclovir (an oral prodrug of ganciclovir) achieves levels comparable to intravenous ganciclovir at 5 mg/kg when it is given orally in a 900-mg dose, two times daily, and is followed by 900 mg once daily as a maintenance dose.

Foscarnet blocks the pyrophosphate-binding site of viral DNA polymerase, thereby preventing cleavage of pyrophosphate from deoxynucleotide triphosphate. The recommended initial therapy with foscarnet is 60 mg/kg intravenously every 8 hours or 90 mg/kg every 12 hours. The maintenance dose ranges from 90 to 120 mg/kg daily. Adverse effects include renal impairment, anemia, hypocalcemia (especially ionized calcium), hypomagnesemia, and hypophosphatemia. Resistance to foscarnet can develop because of mutations in the DNA polymerase gene. Although it is effective for treating CMV retinitis, its toxicity and the absence of an oral formulation make foscarnet a second choice for treatment of CMV disease.

Cidofovir is a nucleotide analogue that is active against ganciclovir-resistant CMV strains with resistance mutations only in *UL97*. The drug's extremely long half-life permits intravenous administration as infrequently as every 2 weeks during maintenance treatment. However, cidofovir is nephrotoxic, especially to the proximal renal tubule, and its toxicities make it a second- or third-line agent for treatment of CMV. Maribavir (400 mg twice daily), which inhibits the UL97 protein kinase of CMV, is effective[A2] and approved for recipients of hematopoietic or solid organ transplants who do not respond to other agents.[11] Letermovir is useful only for prevention but not treatment of established CMV infection.

Retinitis

For CMV retinitis, approximately 75% of patients treated with ganciclovir or valganciclovir respond with improvement or stabilization of vision or ophthalmoscopic appearance. CMV retinitis also can be treated locally by intraocular ganciclovir injection, but this approach should be accompanied by oral valganciclovir to treat and/or prevent extraocular end-organ disease.

Neurologic Disease

For neurologic disease, ganciclovir (5 mg/kg intravenously every 12 hours) plus foscarnet (60 mg/kg intravenously every 8 hours or 90 mg/kg intravenously every 12 hours until symptomatic improvement) is usually recommended, followed by maintenance therapy with oral valganciclovir (900 mg daily) and intravenous foscarnet (90 to 120 mg/kg intravenously during 2 hours, every 24 hours). Cidofovir is a second-line agent (5 mg/kg by intravenous infusion during 1 hour once a week for 2 consecutive weeks, with saline hydration and probenecid, 2 g orally 3 hours before the dose and 1 g orally at 2 hours and 8 hours after the dose). A maintenance dose of 5 mg/kg every other week is recommended unless and until immune reconstitution occurs. Additionally, HIV-specific antiviral therapy must be given to facilitate immune control of CMV. However, clinical deterioration due to inflammatory immune reconstitution syndrome (Chapter 357) may occur and must be closely monitored.

Post-Transplant CMV

Ganciclovir together with CMV hyperimmune globulin may reduce the mortality of CMV pneumonia after stem cell transplantation from approximately 85 to 40%, although the benefit of the antibody is unproved.

PREVENTION

Multiple vaccine approaches are being investigated to prevent or to mitigate CMV-associated complications.[12] Additionally, passive immunity (monoclonal antibodies) to pentameric complex also is being studied in high-risk transplant settings.

Because CMV is transmitted by exchange of secretions, infection can be diminished by reducing exposure to body fluids. For example, transmission by both vaginal and anal intercourse, which poses bidirectional risks, can be diminished by use of condoms. Similarly, limiting the contact of seronegative pregnant women with the secretions and excretions of children, especially preschoolers in daycare, can decrease primary infection and, in turn, congenital disease. The risk for acquiring CMV disease can be reduced in seronegative, immunosuppressed patients by using blood products or organ grafts only from CMV-seronegative donors or apheresis blood products.

Valganciclovir and ganciclovir, in the same doses used for treatment, provide effective prophylaxis in solid organ transplantation,[13] and either one is commonly administered for a 3- to 6-month period after transplantation.[A3] However, late-onset CMV end-organ disease may occur when the antiviral drug is eventually discontinued.

Prophylaxis has been uncommon for stem cell transplant recipients,[14] and these patients typically have been monitored weekly (from day 10 to day 100 after transplantation) for CMV DNA or antigenemia, with antiviral therapy

introduced preemptively if viremia occurs.[A4] With this strategy, infection is not prevented, but end-organ disease is avoided. Letermovir (a CMV terminase inhibitor 240 or 480 mg daily) can reduce the incidence of CMV infection in such patients,[A5,A6] and is replacing valganciclovir for the prevention of CMV infection and disease.[15,16] CMV hyperimmune globulin can be used prophylactically in high-risk seronegative organ transplant recipients, in whom it reduces CMV disease and mortality. It is very expensive, however, and antivirals are more commonly used alternatives.

For the prevention of vertical transmission of CMV after maternal primary infection during the first trimester of pregnancy, valacyclovir (8 g per day) may be effective in reducing the rate of fetal CMV infection by about 70%.[A7] By comparison, CMV-specific hyperimmune globulin is not effective in this setting.[A8]

PROGNOSIS

In immunocompetent patients, the mononucleosis-like CMV syndrome resolves spontaneously, and prior infection is not associated with all-cause mortality.[17] Infections in immunocompromised patients are much more serious, and patients with homozygous nitric oxide synthase 2 deficiency may have fatal primary infection.[18] CMV infection also may result in failure of a transplanted solid organ and/or systemic CMV disease. For CMV pneumonia, death often occurs even with antiviral therapy, especially after stem cell transplantation. In AIDS patients, CMV infection generally resolves when CD4 counts exceed 100/μL, but it is a grave prognostic sign if counts do not recover to those levels.

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348 EPSTEIN-BARR VIRUS INFECTION

ROBERT T. SCHOOLEY AND UPTON D. ALLEN

DEFINITION

Epstein-Barr virus (EBV), a member of the gamma human herpesvirus family, is the etiologic agent of infectious mononucleosis and of a diverse assortment of neoplastic and lymphoproliferative syndromes.

EPIDEMIOLOGY

Ubiquitous in the human population, EBV is found in 90 to 95% of adults throughout the world. As in the case of other herpesviruses, infection with EBV is lifelong. The virus resides in B lymphocytes and is intermittently shed asymptomatically in oropharyngeal secretions, which accounts for the bulk of its transmission in the human population. The virus is usually acquired during early childhood by sharing of saliva-bearing fomites or during adolescence by kissing, although it can be acquired at any decade of life. In addition to oropharyngeal spread, the virus can be transmitted by blood transfusion or by organ and tissue donation.

Most childhood EBV infections are clinically silent, but infection of adolescents and adults results in the clinical syndrome of infectious mononucleosis between 25 and 50% of the time, depending on the setting. The incidence of infectious mononucleosis is highest in the 15- to 24-year-old age group. Incidence rates in men and women are equal, but the peak incidence is 2 years earlier in women than in men. Incidence rates are lower in lower socioeconomic populations, due to the likelihood of acquisition of EBV during early childhood rather than during adolescence.

PATHOBIOLOGY

EBV infects B lymphocytes preferentially but also infects epithelial cells. For B lymphocytes, the receptor is CD21, whereas for epithelial cells, cellular entry is less well defined. Infection of B cells typically results in two pathways: lytic destruction of B lymphocytes owing to viral replication, and latency within lymphocytes. Once inside the cell, the virus expresses several nuclear proteins (termed *Epstein-Barr nuclear antigens* [EBNAs]) that activate EBV-encoded latent membrane proteins and other gene products responsible for regulation of B-cell growth. These events are associated with the transformation or immortalization of the B cell that is the phenotypic hallmark of B-cell infection.[1] EBV-transformed B cells have the potential to proliferate vigorously but are prevented from doing so in the normal host due to surveillance by T lymphocytes.

The host response to acute EBV infection consists of a vigorous and coordinated cellular and humoral immune response. The humoral immune response includes IgM and IgG antibodies directed at the viral capsid (VCA) and to EBNA, as well as "heterophile" antibodies to surface antigens of sheep red blood cells. Heterophile antibodies are useful diagnostically and are present at some point in up to 90% of adolescents and adult cases but are often not detected in children younger than 4 years of age. These antibodies are an epiphenomenon in host defense and are not cross-reactive with any known viral antigens.

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ACUTE INFECTION

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introduced preemptively if viremia occurs.[A4] With this strategy, infection is not prevented, but end-organ disease is avoided. Letermovir (a CMV terminase inhibitor 240 or 480 mg daily) can reduce the incidence of CMV infection in such patients,[A5,A6] and is replacing valganciclovir for the prevention of CMV infection and disease.[15,16] CMV hyperimmune globulin can be used prophylactically in high-risk seronegative organ transplant recipients, in whom it reduces CMV disease and mortality. It is very expensive, however, and antivirals are more commonly used alternatives.

For the prevention of vertical transmission of CMV after maternal primary infection during the first trimester of pregnancy, valacyclovir (8 g per day) may be effective in reducing the rate of fetal CMV infection by about 70%.[A7] By comparison, CMV-specific hyperimmune globulin is not effective in this setting.[A8]

PROGNOSIS

In immunocompetent patients, the mononucleosis-like CMV syndrome resolves spontaneously, and prior infection is not associated with all-cause mortality.[17] Infections in immunocompromised patients are much more serious, and patients with homozygous nitric oxide synthase 2 deficiency may have fatal primary infection.[18] CMV infection also may result in failure of a transplanted solid organ and/or systemic CMV disease. For CMV pneumonia, death often occurs even with antiviral therapy, especially after stem cell transplantation. In AIDS patients, CMV infection generally resolves when CD4 counts exceed 100/μL, but it is a grave prognostic sign if counts do not recover to those levels.

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348 EPSTEIN-BARR VIRUS INFECTION

ROBERT T. SCHOOLEY AND UPTON D. ALLEN

DEFINITION

Epstein-Barr virus (EBV), a member of the gamma human herpesvirus family, is the etiologic agent of infectious mononucleosis and of a diverse assortment of neoplastic and lymphoproliferative syndromes.

EPIDEMIOLOGY

Ubiquitous in the human population, EBV is found in 90 to 95% of adults throughout the world. As in the case of other herpesviruses, infection with EBV is lifelong. The virus resides in B lymphocytes and is intermittently shed asymptomatically in oropharyngeal secretions, which accounts for the bulk of its transmission in the human population. The virus is usually acquired during early childhood by sharing of saliva-bearing fomites or during adolescence by kissing, although it can be acquired at any decade of life. In addition to oropharyngeal spread, the virus can be transmitted by blood transfusion or by organ and tissue donation.

Most childhood EBV infections are clinically silent, but infection of adolescents and adults results in the clinical syndrome of infectious mononucleosis between 25 and 50% of the time, depending on the setting. The incidence of infectious mononucleosis is highest in the 15- to 24-year-old age group. Incidence rates in men and women are equal, but the peak incidence is 2 years earlier in women than in men. Incidence rates are lower in lower socioeconomic populations, due to the likelihood of acquisition of EBV during early childhood rather than during adolescence.

PATHOBIOLOGY

EBV infects B lymphocytes preferentially but also infects epithelial cells. For B lymphocytes, the receptor is CD21, whereas for epithelial cells, cellular entry is less well defined. Infection of B cells typically results in two pathways: lytic destruction of B lymphocytes owing to viral replication, and latency within lymphocytes. Once inside the cell, the virus expresses several nuclear proteins (termed *Epstein-Barr nuclear antigens* [EBNAs]) that activate EBV-encoded latent membrane proteins and other gene products responsible for regulation of B-cell growth. These events are associated with the transformation or immortalization of the B cell that is the phenotypic hallmark of B-cell infection.[1] EBV-transformed B cells have the potential to proliferate vigorously but are prevented from doing so in the normal host due to surveillance by T lymphocytes.

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ACUTE INFECTION

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The incubation period between exposure and the onset of symptoms is generally 30 to 50 days. The onset of symptoms may be abrupt, or it may be heralded by a several-day nonspecific prodrome of malaise and low-grade fever. Although the classic syndrome includes fever, sore throat, and adenopathy, the findings may be dominated by only one or any combination of these symptoms. Other common clinical manifestations include headache, malaise, and anorexia. On physical examination, patients are usually febrile. Pharyngeal erythema, tonsillar enlargement (see Fig. 397-4 in Chapter 397), and cervical adenopathy are generally present. Mild periorbital edema may also be observed. Abdominal findings may include splenomegaly or hepatomegaly, or both. Splenomegaly can be demonstrated by ultrasonographic examination in virtually all patients with infectious mononucleosis, although palpable splenomegaly is present in only about 20% of patients. Splenic enlargement is usually maximal in

ABSTRACT

Epstein-Barr virus (EBV), a member of the gamma human herpesvirus family, is the etiologic agent of infectious mononucleosis and of a diverse assortment of neoplastic and lymphoproliferative syndromes, including post-transplant lymphoproliferative disorder.

KEYWORDS

Epstein-Barr virus
infectious mononucleosis
post-transplantation lymphoproliferative disorder

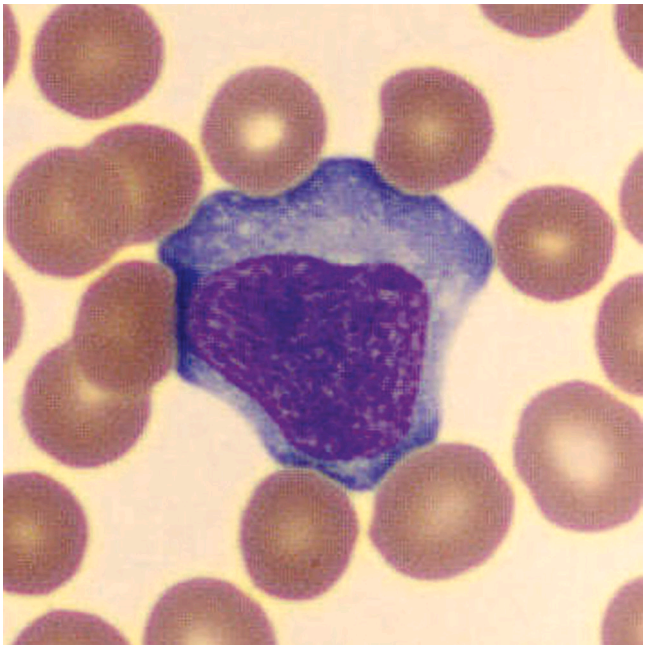

FIGURE 348-1. An atypical lymphocyte. (Courtesy of Dr. Mohamed Abdelhaleem, Hospital for Sick Children, University of Toronto.)

the second or third week of illness and might not be detectable at the initial presentation. Adenopathy may be observed in noncervical regions, but it is usually much less prominent than in cervical regions.

More serious primary infections can occur in individuals over age 30 years. Approximately 5% of patients will exhibit a rash that may be macular, scarlatiniform, or urticarial in nature. Ampicillin or its derivatives evoke a pruritic maculopapular eruption in 15 to 30% of patients with acute EBV infection in recent series, compared with a reported 80 to 100% in earlier reports. Patients with an ampicillin-induced rash during acute EBV infection generally tolerate the drug and other penicillin products when administered later in life.

Complications

Most patients have self-limited disease EBV, but a number of complications may arise. In some patients, these complications dominate the clinical findings, and seroconversion to EBV may be the only evidence of acute EBV infection.

Patients should be specifically warned about splenic rupture, a complication attributable to splenomegaly (Chapter 154) and associated stretching of the splenic capsule that occurs most frequently in the second or third week of the illness, when other symptoms of the disease are abating. It may be accompanied by trauma but may also occur without an obvious antecedent event. Left upper quadrant pain, especially pain radiating to the subscapular region, should raise this diagnostic consideration. As with other complications of acute EBV infection, splenic rupture may occur occasionally in patients without other prominent clinical manifestations of acute EBV infection. Other hematologic complications, which usually arise from a combination of self-reactive antibodies and hypersplenism, include autoimmune hemolytic anemia (Chapter 146), thrombocytopenia (Chapter 158), and neutropenia (Chapter 153).

Neurologic complications can also occur during acute EBV infection. EBV DNA has been detected in brain tissue from rare patients with clinical manifestations compatible with herpes simplex encephalitis (Chapter 383). Other neurologic complications include aseptic meningitis (Chapter 381), cerebellitis, mononeuritis multiplex (Chapter 388), Bell palsy (Chapter 388), Guillain-Barré syndrome (Chapter 388), transverse myelitis (Chapters 369 and 380), and a higher risk of multiple sclerosis.[4]

Mild hepatomegaly is common in acute infectious mononucleosis, and biochemical evidence of hepatitis (Chapter 134) is to be expected in virtually every case of acute infection. More severe hepatic complications are uncommon, however. Renal, cardiac, pulmonary, and skeletal muscle complications are rare.

X-Linked Lymphoproliferative Syndrome

The most serious complication of acute EBV infection arises in individuals with the X-linked lymphoproliferative syndrome. This syndrome occurs in males with mutations in the signaling lymphocyte activation molecule (SLAM)–associated protein (SAP) that regulates T-cells and natural killer (NK) cells. These previously healthy individuals who become immune dysregulated upon encountering EBV have severe clinical symptoms, a pronounced lymphocytosis consisting of T and B cells, and severe hepatitis. If patients survive the acute infection, the syndrome may evolve into progressive agammaglobulinemia or lymphoma in the following months. The genetic defect associated with this syndrome can be diagnosed in utero, and early bone marrow transplantation has been recommended for the prevention of the devastating clinical syndrome associated with the acquisition of EBV infection.

DIAGNOSIS

Because clinical manifestations of acute EBV infection are variable and other organisms may cause similar clinical syndromes, laboratory tools are required to confirm an etiologic diagnosis. Heterophile antibodies to sheep red blood cells are classically used to diagnose EBV-induced infectious mononucleosis. Although ultimately demonstrable in approximately 90% of symptomatic acute EBV infections, these antibodies are present in only about two thirds of patients at initial encounter. If antibodies are negative at the outset and clinical suspicion is high, repeat testing in the second or third week of the illness is warranted. EBV-specific antibodies remain the "gold standard" for the diagnosis of acute EBV infection, but if heterophile antibodies are demonstrated in a straightforward case of infectious mononucleosis, EBV-specific serologic studies are not generally required. Testing for IgM antibodies to the EBV capsid antigen (VCA) is the most useful serologic study in the diagnosis of acute EBV infection. Relatively high titers of IgG antibodies to VCA persist for life after initial infection and are not useful in making the diagnosis of acute EBV infection. Antibodies to EBNA are slower to arise than those to capsid antigens, and acute infection may be diagnosed by demonstration of seroconversion to this antigen.

Among pathogens causing clinical syndromes that can be mistaken for acute EBV infection, cytomegalovirus (Chapter 347) is the most frequent. Patients with cytomegalovirus infection are less likely to have an acute onset of illness, and pharyngitis is less frequently a prominent manifestation of the illness. *Toxoplasma gondii* (Chapter 320) infection can also present as a nonspecific febrile illness that can be confused with infectious mononucleosis. Streptococcal pharyngitis (Chapter 269), primary herpes stomatitis (Chapter 345), and adenovirus infection (Chapter 333) may occasionally cause symptoms that are mistaken for acute EBV infection. None of these syndromes is associated with heterophile antibodies or with other serologic evidence of acute EBV infection. The differential diagnosis is generally made by serologic studies directed at these organisms or by culture. Nonetheless, physicians should be cognizant that organisms such as group A β-hemolytic streptococci (Chapter 269) and herpes simplex virus are also common in the human population and may be demonstrated in people whose symptoms are nonetheless due to acute EBV infection.

TREATMENT AND PREVENTION

The clinical course is generally self-limited and does not usually require specific therapeutic intervention beyond the use of aspirin or acetaminophen for antipyresis and mild pain relief, except in the presence of specific complications such as when lymphadenopathy threatens the airway or in certain cases of autoimmune hemolytic anemia (Chapter 146) or thrombocytopenia (Chapter 158). To reduce the risk of splenic rupture, patients should be counseled against activities that might result in abdominal trauma for 6 to 8 weeks after the onset of symptoms.

Short courses of corticosteroids have been used to hasten symptomatic recovery in cases in which the symptoms are severe or refractory.[A1] For example, corticosteroids may be of benefit in more severe cases of autoimmune hemolytic anemia (Chapter 146) or thrombocytopenia (Chapter 158). Corticosteroids should not, however, be used routinely and should consist of no more than a 10- to 14-day tapering course that begins at a dose equivalent to 0.5 to 1 mg/kg of prednisone. Although EBV replication can be inhibited in vitro or in vivo by acyclovir and related antiviral agents, the symptoms of infectious mononucleosis are primarily driven by the immune response to the virus and follow the time of maximal viral replication. Antiviral agents have not been demonstrated to accelerate resolution of symptoms significantly or prevent complications of the disease.[A2] However, patients with encephalitis may be treated with parenteral ganciclovir (10 mg/kg/day intravenously for 3 weeks followed by valganciclovir 900 mg/day orally for another 3 weeks until the virus is cleared; Chapter 328).

Because the virus is usually transmitted by asymptomatic oral shedders and is so common in the human population, epidemiologic interventions directed at patients with acute infection are not warranted to prevent spread. No vaccine yet has been developed for clinical use.

PROGNOSIS

Most patients recover uneventfully from the acute symptoms and signs of infectious mononucleosis over a 2- to 3-week period, although many patients may have a variable period of malaise and fatigue that can last for another 3 to 4 weeks. Some patients may take longer to make a full recovery and experience fatigue and difficulty concentrating for up to 6 months after diagnosis. Symptoms often wax and wane and can be extremely troublesome. Reassurance is usually the best approach to these patients. Corticosteroids are not of benefit in this setting.

Recovery may be less straightforward in patients with certain specific complications of acute EBV infection. Hematologic complications are generally self-limited and resolve with the resolution of the illness. Neurologic complications may be clinically dramatic but are usually self-limited and associated with full recovery in 85% of patients without specific antiviral therapy.

Death from infectious mononucleosis is rare. When it does occur, it is most frequently associated with neurologic complications, splenic rupture, or the X-linked lymphoproliferative syndrome.

OTHER CLINICAL SYNDROMES

In addition to infectious mononucleosis, EBV is also associated with neoplasia and lymphoproliferative disorders, which are seen most frequently in patients with defects in cellular immunity but are not restricted to such patients.

POST-TRANSPLANT LYMPHOPROLIFERATIVE DISORDER

EBV-transformed B-cell proliferation that is insufficiently contained by T-cell activity is initially similar to what is seen in acute infectious mononucleosis, but then progresses to a lymphoproliferative disorder.

EPIDEMIOLOGY

This syndrome most frequently occurs in the setting of solid-organ transplantation, especially when patients acquire a primary EBV infection and/or have been immunosuppressed with agents directed specifically at T lymphocytes. This lymphoproliferative disorder also can be seen in other conditions with similar levels and durations of immunodeficiency, such as advanced HIV-1 infection (Chapter 359).

Post-transplant lymphoproliferative disorder (often simply called PTLD)[5,6] is often but not invariably EBV driven. EBV-associated post-transplant lymphoproliferative disorder is seen earlier in the post-transplant course than non–EBV-associated cases and is seen more often when the donor is EBV seropositive and the recipient is seronegative. Among recipients of solid-organ transplants, post-transplant lymphoproliferative disorder is more common in the setting of more severe immunosuppression (Chapter 38), including multiple-organ transplants, but it can occur in any recipient (Chapter 38). Among stem cell transplant recipients (Chapter 163), the most important risk factor is the level of T-cell depletion of the donor cells. However, other risk factors include the use of stem cells from HLA-mismatched donors, intensive immunosuppression, and primary immunodeficiency.

PATHOBIOLOGY

The majority of PTLD lesions are associated with EBV infection and consist of EBV-induced monoclonal or polyclonal B-cell proliferations. Monoclonal T-cell proliferation occurs less often. Among solid-organ transplant recipients, the lesions are most often of host cell origin. In contrast, PTLD lesions occurring among stem cell allograft recipients are typically of donor cell origin. Histopathologically, the four major categories of PTLD are non-destructive lesions, polymorphic PTLDs, monomorphic PTLDs, and classic Hodgkin lymphoma PTLD. Except for polymorphic PTLDs, these categories are further subcategorized. For example, Burkitt lymphoma lesions represent a subcategorization of B-cell monomorphic PTLDs, whereas plasmacytic hyperplasia, infectious mononucleosis-like lesions, and florid follicular hyperplasia represent subcategories of nondestructive PTLDs.

CLINICAL MANIFESTATIONS

Patients with post-transplant lymphoproliferative disorder can present with early-onset (within 2 years) or later onset disease (greater than 2 years after transplantation). Constitutional symptoms are typically common with the later onset syndrome. There is a predilection for the reticuloendothelial system and the transplanted organs (except heart) to be involved. Clinical manifestations may include fever, weight loss, lymphadenopathy, hepatosplenomegaly, subcutaneous nodules, tonsillar enlargement, tonsillar inflammation, signs of bowel perforation, mucocutaneous ulceration, intracranial lesions, and focal neurologic signs depending on location of lesions.[7,8]

DIAGNOSIS

Elevated levels of EBV DNA in whole blood, peripheral blood lymphocytes, or plasma are associated with an increased likelihood of post-transplant lymphoproliferative disorder, but the absence of elevated levels does not exclude the diagnosis. The diagnosis of post-transplant lymphoproliferative disorder typically requires histopathologic confirmation. Besides confirming the diagnosis, tissue examination enables the further characterization of the lesion, in terms of its immunophenotype, clonality, CD20 positivity, EBV status, and the presence or absence of tumor genetic/cytogenetic markers.

TREATMENT AND PREVENTION

Although many centers use universal CMV-like antiviral (ganciclovir or valganciclovir) prophylaxis strategies (Chapter 347) for high-risk EBV-mismatched transplant recipients, this strategy remains controversial. Antiviral agents are less useful once post-transplant lymphoproliferative disorder develops. In response to elevated EBV loads prior to the onset of post-transplant lymphoproliferative disorder, the anti-CD20 agent rituximab under expert oversight appears to be beneficial for stem cell transplant recipients. For solid-organ transplant patients, the most widely accepted preemptive strategy is to reduce immunosuppression whenever feasible.

Successful management of post-transplant lymphoproliferative disorder depends on the extent to which the immunosuppression can be reduced or even reversed before and after the development of frank post-transplant lymphoproliferative disorder. In addition to reduced immunosuppression, therapy with rituximab, with or without chemotherapy, is the treatment of choice for the majority of patients (Chapter 171). Surgical excision (e.g., adenoids or bowel), radiation, and adoptive T-cell therapies are also used, depending on the histopathology of the lesions.

BURKITT LYMPHOMA

EBV is the cause of Burkitt lymphoma. The tumor is composed of small, non-cleaved B cells and, unless aggressively treated, is rapidly fatal. This aggressive B-cell lymphoma with a predilection for the head and neck[9] is endemic in equatorial Africa and is geographically linked to *Plasmodium falciparum* malaria, which is believed to play role in the genesis of this lymphoma. EBV DNA is readily demonstrable in tumor biopsy specimens, and high titers of antibodies to EBV structural antigens are found in plasma. Sporadic cases of abdominal B-cell lymphomas with a histologic appearance compatible with Burkitt lymphoma are also observed but are associated with EBV only about 25% of the time.

The tumor is likewise seen in patients with HIV infection (Chapter 359). Although the risk for HIV-associated Burkitt lymphoma increases with advancing immunodeficiency, it may be seen in patients with relatively preserved CD4 cell counts. Antiretroviral therapy reduces but does not eliminate the risk for Burkitt lymphoma in HIV-1–infected persons. Despite the high-grade clinical behavior of the tumor, it should be vigorously treated because it is usually quite responsive to combination chemotherapy with or without radiation therapy (Chapter 171).[10]

HODGKIN LYMPHOMA

EBV is also associated with a subset of Hodgkin lymphomas (Chapter 172),[11] especially the lymphocyte-depleted or mixed-cellularity histologic subtypes. EBV DNA and proteins are detected in the Reed-Sternberg cells that are characteristic of Hodgkin lymphoma. Therapy for EBV-associated Hodgkin lymphoma is directed at the tumor. The specific approach used is based on the histology and extent of disease (Chapter 172) and is not determined in a given patient by its relationship to EBV.

CENTRAL NERVOUS SYSTEM LYMPHOMA

EBV is also associated with central nervous system (CNS) lymphoma (Chapter 171).[12] This tumor is seen in the post-transplant setting but is also now the most frequent CNS neoplasm in HIV-infected individuals. The major differential diagnostic challenge is with *T. gondii* infection (Chapter 320). Although a tissue-based diagnosis is definitive, noninvasive neurodiagnostic approaches coupled with the demonstration of EBV DNA in cerebrospinal fluid by polymerase chain reaction can strongly support the diagnosis of lymphoma over that of *T. gondii* infection. In addition to chemotherapy, radiation therapy has been used, but its effects are generally palliative.

NASOPHARYNGEAL CARCINOMA

EBV has also been associated with certain cases of nasopharyngeal carcinoma (Chapter 176).[13] This tumor is rare in Western countries, but it is much more frequent in southern China and in the Inuit population of Alaska. EBV-associated cases are generally less histologically differentiated than sporadic forms of nasopharyngeal carcinoma. EBV DNA is demonstrable in tumor tissue, and high titers of IgA and IgG antibodies to the EBV capsid antigens are found in plasma. The prognosis for this tumor is poor, although it is often treated with radiation therapy (Chapter 176).

HISTIOCYTOSES AND LYMPHOMATOID GRANULOMATOSIS

EBV DNA may be found in moderate to slowly progressive destructive midline facial angiocentric tumors of T- and NK-cell phenotypes. This neoplasm presents clinically as a syndrome that was previously known as lethal midline granuloma (Chapter 155). EBV also plays a key role in the pathogenesis of an angiocentric EBV-associated B-cell tumor, which presents clinically as lymphomatoid granulomatosis and hemophagocytic lymphohistiocytosis (Chapter 155).[14]

Lymphomatoid granulomatosis is a very rare lymphoproliferative disease that likely results from defective immune surveillance in the absence of a primary immunodeficiency.[15] It universally affects the lungs but also commonly involves skin, liver, kidneys, and the central nervous system.

TREATMENT

Treatment under expert guidance attempts to augment the immune response to EBV and may include interferon α2b for low-grade disease and immunochemotherapy (e.g., etoposide, corticosteroids, vincristine, cyclophosphamide, doxorubicin, and rituximab) for high-grade disease. Stem cell transplantation may be considered for primary refractory disease or multiple relapses. For hemophagocytic lymphohistiocytosis, which is a life-threatening hyperinflammatory syndrome, treatment must be guided by specialty experts. Etoposide and dexamethasone can induce temporary remission, but nivolumab may be preferred for relapsed or refractory disease because it can restore a defective anti-EBV response and may avoid the need for allogeneic stem cell transplants.[16]

OTHER EBV-ASSOCIATED NEOPLASMS

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CHRONIC ACTIVE EBV INFECTION

Infrequently, patients with no apparent defect in cellular immunity have been described to have chronic EBV infection, which has been associated with persistent or intermittent clinically significant infection of more than 6 months' duration. In the United States, patients most often have disease involving B or T cells, whereas the disease usually involves T or NK cells in Asia. Patients may present with fever, lymphadenopathy, splenomegaly, hepatitis, or pancytopenia. Progressive immunodeficiency may develop, and untreated patients succumb to opportunistic infections, hemophagocytosis, multiorgan failure, or EBV-positive lymphomas. Hematopoietic stem cell transplantation is the only proven therapy.

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The Pathogens

Enteroviruses are small (30 nm in diameter), nonenveloped, icosahedral-shaped viruses. The viral capsid is composed of four viral proteins (VP1 to VP4). The enteroviruses possess an approximately 7.4-kilobase positive-sense single-stranded RNA genome. The 5′ end of the genome is covalently linked to a small protein, VPg. The genome is organized into a long (about 740 nucleotides) 5′ nontranslated region that precedes a single continuous open reading frame measuring about 6.63 kilobases. The open reading frame, which is followed by a short 3′ nontranslated region and a terminal polyadenylate tail, yields a single large polyprotein that is post-translationally modified to produce four capsid proteins, seven nonstructural proteins, and several functional protein intermediates. The 5′ and 3′ nontranslated regions participate in replication of the viral genome. The 5′ nontranslated region of the enterovirus is essential for translation and contains determinants of neurovirulence in the polioviruses.

TABLE 349-1 CLASSIFICATION OF ENTEROVIRUSES

SPECIES	SEROTYPES
Enterovirus A 25 (sero)types	CV- A2-A8, A10, A12, A14, A16 EV- A71, A76, A89-A92, A114, A119-125
Enterovirus B 63 (sero)types	CV- A9 CV- B1-B6 E- 1-7, 9, 11-21, 24-27, 29-33 EV- B69, B73-B75, B79-B88, B93, B97, B98, B100, B101, B106, B107, B110-114
Enterovirus C 23 (sero)types	PV- 1-3 CV- A1, A11, A13, A17, A19-A22, A24 EV- C95, C96, C99, C102, C104, C105, C109, C113, C116-C118
Enterovirus D 5 (sero)types	EV- D68, D70, D94, D111, D120

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NASOPHARYNGEAL CARCINOMA

EBV has also been associated with certain cases of nasopharyngeal carcinoma (Chapter 176).[13] This tumor is rare in Western countries, but it is much more frequent in southern China and in the Inuit population of Alaska. EBV-associated cases are generally less histologically differentiated than sporadic forms of nasopharyngeal carcinoma. EBV DNA is demonstrable in tumor tissue, and high titers of IgA and IgG antibodies to the EBV capsid antigens are found in plasma. The prognosis for this tumor is poor, although it is often treated with radiation therapy (Chapter 176).

HISTIOCYTOSES AND LYMPHOMATOID GRANULOMATOSIS

EBV DNA may be found in moderate to slowly progressive destructive midline facial angiocentric tumors of T- and NK-cell phenotypes. This neoplasm presents clinically as a syndrome that was previously known as lethal midline granuloma (Chapter 155). EBV also plays a key role in the pathogenesis of an angiocentric EBV-associated B-cell tumor, which presents clinically as lymphomatoid granulomatosis and hemophagocytic lymphohistiocytosis (Chapter 155).[14]

Lymphomatoid granulomatosis is a very rare lymphoproliferative disease that likely results from defective immune surveillance in the absence of a primary immunodeficiency.[15] It universally affects the lungs but also commonly involves skin, liver, kidneys, and the central nervous system.

TREATMENT

Treatment under expert guidance attempts to augment the immune response to EBV and may include interferon α2b for low-grade disease and immunochemotherapy (e.g., etoposide, corticosteroids, vincristine, cyclophosphamide, doxorubicin, and rituximab) for high-grade disease. Stem cell transplantation may be considered for primary refractory disease or multiple relapses. For hemophagocytic lymphohistiocytosis, which is a life-threatening hyperinflammatory syndrome, treatment must be guided by specialty experts. Etoposide and dexamethasone can induce temporary remission, but nivolumab may be preferred for relapsed or refractory disease because it can restore a defective anti-EBV response and may avoid the need for allogeneic stem cell transplants.[16]

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ABSTRACT

The enteroviruses belong to the genus *Enterovirus* in the family Picornaviridae. Of the 15 species in the genus, four (Enterovirus A–D) are pathogenic for humans and contain more than 110 recognized strains based on phylogenetic analysis of the nucleic acid sequence of the capsid protein VP1. Enteroviruses are small, are nonenveloped, and possess an RNA genome. Worldwide, an estimated 1 billion infections occur annually, and humans are the only known reservoir. In the United States enteroviruses cause approximately 10 to 15 million symptomatic cases annually. Infections are seasonal, with the majority occurring during the summer and early autumn in temperate climates. More than 80% of infections are in individuals younger than 20 years of age, with the highest incidence in young children. The enteroviruses can affect nearly every organ system. They cause a wide spectrum of febrile exanthems and enanthems, including hand-foot-and-mouth disease and herpangina. Although poliomyelitis is on the threshold of elimination owing to effective vaccination programs worldwide, enteroviruses remain the most common cause of central nervous system infections (meningitis, encephalitis, flaccid paralysis) in the United States. Enteroviruses are responsible for approximately a third of the cases of acute viral myocarditis. Individuals with congenital or acquired B-cell immunodeficiencies may develop prolonged or chronic infections. Nucleic acid amplification is the method of choice for diagnosing enteroviruses. No specific therapy exists for the treatment of enteroviral infections, but vaccines are effective for the prevention of poliovirus and enterovirus A71.

KEYWORDS

enterovirus
poliomyelitis
central nervous system infection
myocarditis
hand-foot-and-mouth disease
enterovirus D68
enterovirus A71

EPIDEMIOLOGY

Worldwide, an estimated 1 billion or more enteroviral infections occur annually. In the United States about 30 to 50 million annual infections result in approximately 10 to 15 million symptomatic cases, with enterovirus D68, echovirus 30, coxsackievirus A6, echovirus 18, coxsackievirus B3, echovirus 9, and enterovirus 11 accounting for approximately 80% of enteroviral infections.[1]

Humans are the only known reservoir for enteroviruses. Enteroviral infections are seasonal, and the majority of infections occur during the summer and early autumn in temperate regions. For example, more than 80% of infections occur in the United States from June through October. However, winter outbreaks highlight their panseasonal occurrence. In tropical and subtropical regions, infections continue year-round, with an increased incidence during the rainy season.

Globally, the dominant circulating enterovirus serotypes may vary annually by geographic region. In the United States 7 serotypes accounted for nearly 80% of all isolates reported (Table 349-2).

The severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) pandemic has impacted enteroviral surveillance. Globally, reports of acute flaccid paralysis cases have decreased by 33%.[2] This decrease is most likely due to multiple factors including a reluctance to seek medical care as result of fear of contagion and decreased active surveillance during this period.

More than 80% of infections occur in individuals younger than age 20 years, with the highest incidence in infants and children ages 4 years and younger. Nearly 45% of all infections occur in infants younger than 1 year. Among household members of infected children, clinical or serologic evidence of secondary infection can be seen in more than 50% of susceptible individuals. A male preponderance is noted in persons younger than age 20 years (male-to-female ratio of 1.4 : 1) but not in older individuals.

Localized enteroviral outbreaks have been reported in neonatal units, nurseries, daycare centers, schools, camps, sports teams, and military facilities. Community-wide outbreaks are common. Extensive regional outbreaks of EV-A71 have occurred in the Asia-Pacific region. Occasional pandemics, such as acute hemorrhagic conjunctivitis caused by EV-D70 and CV-A24, also have occurred.

Effective antipolio immunization programs have eradicated 2 of the 3 wild-type poliovirus serotypes (serotypes 2 and 3) worldwide. Cases of serotype 1 are now restricted to only Afghanistan and Pakistan, where it remains endemic.[3]

The use of live attenuated poliovirus vaccines led to the problem of vaccine-derived polioviruses as a result of the excretion of neurorevertant vaccine (Sabin) strains from individuals who have primary humoral immunodeficiencies, but not secondary humoral or other immunodeficiencies, or as a result of natural recombination between Sabin strains and members of the Enterovirus C species.[4] Vaccine-derived polioviruses that can circulate in the environment with evidence of person-to-person transmission have been termed *circulating vaccine-derived polioviruses*. A third group, designated ambiguous vaccine-derived polioviruses, are clinical isolates from individuals without known immunodeficiency or sewage isolates whose ultimate source is unknown. Similar to wild-type poliovirus, circulating vaccine-derived polioviruses can cause acute flaccid paralysis in unimmunized or incompletely immunized individuals and have caused multiple outbreaks worldwide.

To reduce the risk for poliomyelitis owing to vaccine-derived polioviruses, all use of trivalent oral polio vaccine ceased globally in April 2016 and was replaced with a bivalent oral vaccine that contains only types 1 and 3 attenuated polioviruses. A monovalent type 2 oral polio vaccine is available for immunization in response to outbreaks. In an attempt to decrease the number of circulating vaccine-derived poliovirus outbreaks due to type 2 vaccine, a novel type 2 oral polio vaccine with a substantially lower risk of neurovirulence reversion has been approved for use by the World Health Organization.

TABLE 349-2 THE 13 MOST COMMON ENTEROVIRUS SEROTYPES REPORTED BY NATIONAL ENTEROVIRAL SURVEILLANCE SYSTEM LABORATORIES TO THE CDC, 2009–2013

ENTEROVIRUS SEROTYPE	PERCENTAGE
Enterovirus D68	55.9
Echovirus 30	5.8
Coxsackievirus A6	5.5
Echovirus 18	4.2
Coxsackievirus B3	4.0
Echovirus 9	2.4
Echovirus 11	2.3
Parechovirus A3	2.3
Coxsackievirus B4	2.0
Coxsackievirus B5	1.9
Coxsackievirus B2	1.8
Coxsackievirus A9	1.5
Echovirus 6	1.5
Total	90.9

From Centers for Disease Control and Prevention (CDC). Enterovirus and parechovirus surveillance—United States, 20014-2016. *MMWR Morb Mortal Wkly Rep*. 2018;67:515-518.

PATHOBIOLOGY

The polioviruses and the majority of the nonpolio enteroviruses are transmitted through a fecal-oral route. Notable exceptions include CV-A21 and EV-D68, which are spread by the respiratory route, and EV-D70, which may spread by contaminated fomites or ocular and respiratory secretions. Evidence also supports transplacental transmission of the enteroviruses.

Ingestion of the enteroviruses results in infection of cells of the pharynx and, because the virus is acid resistant, the lower gastrointestinal tract. Initial viral replication, which is thought to occur in the mucosal tissues of the nasopharynx and intestinal tract (i.e., tonsils and Peyer patches), leads to seeding of the deep cervical and mesenteric lymph nodes. Further replication at these sites results in a minor viremia with seeding of multiple organs, including the liver, lungs, heart, and central nervous system (CNS). Viral replication at these sites causes many of the clinical manifestations of infection and is followed by a major viremia that may infect the CNS if it was spared during the initial viremia. The virus is cleared by type-specific neutralizing antibodies directed at the capsid proteins by day 7 to 10 after infection. Immunoglobulin (Ig)A antibodies appear in the respiratory and gastrointestinal tracts 2 to 4 weeks after infection.

The host humoral immune response is pivotal in the prevention and eradication of enteroviral infections. Congenital or acquired B-cell immunodeficiencies may result in chronic or prolonged infection. Experimental evidence suggests that the interferons are important in limiting the spread of poliovirus once infection has occurred. Natural killer cells and gamma or delta T cells may play roles in regulating the host T-cell response.

Histopathologic findings in patients who died of poliomyelitis reveal neuronal necrosis in association with mononuclear and polymorphonuclear infiltrates that are initially perivascular in distribution but are later found diffusely within the gray matter of the anterior horns of the spinal cord, the reticular formation of the hindbrain, the vestibular nuclei, and the roof nuclei of the cerebellum. In nonpolio enterovirus CNS infections in immunocompetent hosts, findings include edema of the meninges and cerebral parenchyma, with microscopic perivascular lymphocytic infiltration, increased numbers of oligodendrocytes, and focal areas of necrosis and hemorrhage. In cases of enteroviral myocarditis (Chapter 47), a mononuclear cell inflammation is associated with widespread myocardial necrosis followed by fibrosis, which may be focal but results in myocardial damage.

CLINICAL MANIFESTATIONS

The incubation period for enterovirus infections is generally 3 to 6 days, with a range of 2 days to 2 weeks. Depending on serotype and the age of the patient, as many as 90% of infected individuals may have subclinical infections.[5] The enteroviruses are responsible for a wide array of clinical syndromes that affect nearly every organ system, and no enteroviral serotype is uniquely associated with a single disease or clinical syndrome (Table 349-3).

The most frequent enteroviral syndrome, seen in about 50 to 80% of cases, is nonspecific febrile illness, which occurs most commonly in infants, toddlers, and young children. The onset of illness is abrupt, with fever, poor appetite, lethargy, irritability, emesis, diarrhea,[6] and upper respiratory tract symptoms. Physical findings are minimal and consist of mild pharyngeal and conjunctival injection and lymphadenopathy. Exanthems may be present in about 25% of cases.

DIAGNOSIS

Nucleic acid amplification techniques (e.g., reverse transcription–polymerase chain reaction [RT-PCR] and nucleic acid–based sequence amplification) are

TABLE 349-3 CLINICAL MANIFESTATIONS OF NONPOLIO ENTEROVIRUS INFECTIONS*

CLINICAL SYNDROME	GROUP A COXSACKIEVIRUSES†	GROUP B COXSACKIEVIRUSES	ECHOVIRUSES	ENTEROVIRUSES
Asymptomatic infection	All serotypes	All serotypes	All serotypes	All serotypes
Undifferentiated febrile illness ("summer grippe") with or without respiratory symptoms	All serotypes	All serotypes	All serotypes	D68, D70, A71
Aseptic meningitis (often associated with an exanthem)	1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 14, 16, 17, 18, 22, 24	1, 2, 3, 4, 5, 6	1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 14, 16, 17, 18, 19, 20, 21, 25, 30, 31, 33	D70, A71
Encephalitis	2, 4, 5, 6, 7, 9, 10, 16	1, 2, 3, 4, 5	2, 3, 4, 6, 7, 9, 11, 14, 17, 18, 19, 25, 30, 33	D70, A71
Acute flaccid paralysis (poliomyelitis-like)	4, 5, 6, 7, 9, 10, 11, 14, 16, 21, 24	1, 2, 3, 4, 5, 6	1, 2, 4, 6, 7, 9, 11, 14, 16, 17, 18, 19, 30	D68?, D70, A71
Myopericarditis	1, 2, 4, 5, 7, 8, 9, 14, 16	1, 2, 3, 4, 5, 6	1, 2, 3, 4, 6, 7, 8, 9, 11, 14, 16, 17, 19, 25, 30	
Pleurodynia	1, 2, 4, 6, 9, 10, 16	1, 2, 3, 4, 5, 6	1, 2, 3, 6, 7, 8, 9, 11, 12, 14, 16, 19, 25, 30	
Herpangina	1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 16, 22	1, 2, 3, 4, 5	6, 9, 11, 16, 17, 22?, 25	A71
Hand-foot-and-mouth disease	4, 5, 6, 7, 9, 10, 16	2, 5	7	A71
Exanthems	2, 4, 5, 6, 7, 9, 10, 16	1, 2, 3, 4, 5	2, 4, 5, 6, 9, 11, 16, 18, 25	A71
Common cold	2, 10, 21, 24	1, 2, 3, 4, 5	2, 4, 8, 9, 11, 20, 25	
Lower respiratory tract infections (bronchiolitis, pneumonia)	7, 9, 16	1, 2, 3, 4, 5	4, 8, 9, 11, 12, 14, 19, 20, 21, 25, 30	D68, A71, C104
Acute hemorrhagic conjunctivitis‡	24			D70
Generalized disease of the newborn	3, 9, 16	1, 2, 3, 4, 5	3, 4, 6, 7, 9, 11, 12, 14, 17, 18, 19, 20, 21, 30	

*A great many enterovirus serotypes have been implicated in most of these syndromes, at least in sporadic cases. The serotypes listed are those that have been clearly or frequently implicated. Serotypes with a strong association are underlined.

†Because detection of many of the group A coxsackieviruses originally required suckling mouse inoculation, they are likely to be underreported as causes of illness.

‡Conjunctivitis without hemorrhage is frequently seen in association with other manifestations in patients infected with many group A and group B coxsackieviruses and echoviruses, especially coxsackieviruses A9, A16, and B1 to B5 and echoviruses 2, 7, 9, 11, 16, and 30.

From Modlin JR. Enterovirus. *Cecil Textbook of Medicine*. 23rd ed. Philadelphia: WB Saunders; 2008, with minor changes.

the preferred methods for detection and identification of all enteroviruses. RT-PCR can detect enteroviruses in cerebrospinal fluid (CSF), blood, tissue, stool, and other body fluids within hours, and their rapid results can shorten hospitalizations, decrease the use of antibiotics, and reduce health care costs.

Serologic testing is of limited use, although a four-fold change in antibody titer to a specific serotype of enterovirus in paired acute and convalescent sera can help establish the diagnosis in patients who are no longer actively infected. Cell culture is not recommended.

TREATMENT AND PROGNOSIS

Nonspecific febrile enteroviral infections generally resolve in less than 5 days without sequelae. Because of concern for possible occult bacterial infection, however, significant numbers of young infants and children are hospitalized for evaluation and empirical therapy. After infection, virus may be shed into the nasopharynx for 2 to 6 weeks and in feces for several months.

SPECIFIC CLINICAL SYNDROMES

Central Nervous System Infections

ACUTE FLACCID PARALYSIS/MYELITIS

CLINICAL MANIFESTATIONS AND DIAGNOSIS

During poliovirus epidemics, 90 to 95% of infections are subclinical. In another 4 to 8% of patients, infection results in fever, fatigue, headache, anorexia, myalgia, and sore throat, which resolve in 2 to 3 days. Paralytic polio develops in less than 1% of infected individuals.

Acute flaccid myelitis can be seen with other enteroviruses (especially CV-A7, EV-A71), and EV-D68, with sporadic cases or clusters reported worldwide.[7,8] Cases of EV-A71 associated paresis have tended to occur in the Asia-Pacific region, although cases also have been reported from the United States and Europe. Rhombencephalitis may result in autonomic dysfunction, myoclonus, and ataxia. In United States, EV-D68 is believed to be the major cause of the biennial outbreaks of acute flaccid myelitis that have occurred since 2014, with the exception of 2020, the initial year of the SARS-CoV-2 pandemic.[9] Acute flaccid myelitis predominantly affects children, the majority of whom have a prodrome of fever and respiratory symptoms. The onset of neurologic symptoms occurs within 10 days following the initiation of the prodromal phase. Early neurologic findings may include headache, nuchal rigidity, and meningismus. Weakness is preceded by pain in the involved muscles. The weakness and paralysis are flaccid in nature and asymmetric. Deep tendon reflexes in the involved extremities are decreased or absent. Upper extremities and proximal muscle groups are more frequently involved, but respiratory muscles, diaphragm, trunk, and neck can also be affected. The brainstem motor nuclei of the cranial nerves may be involved. Respiratory failure secondary to involvement of the muscles of respiration or brain stem may occur. Dysfunction of the bowel and bladder are common. Sensory pathways remain intact as does mental status.

CSF may reveal a normal cell count or a mild lymphocytic pleocytosis (<100 cells/μL) in association with mildly increased protein and normal glucose concentrations. Magnetic resonance imaging of the spinal cord demonstrates T2-weighted hyperintensity of the gray matter (anterior horn regions) that is longitudinally expansive. T2 hyperintensity can also be seen in the brainstem.

TREATMENT AND PROGNOSIS

No specific therapy exists. Efforts should focus on monitoring for the development of respiratory failure or airway compromise as well as control of pain associated with muscle spasms.

The mortality rate associated with spinal poliomyelitis is about 5%. The mortality rates for enteroviruses associated with nonpolio enteroviral acute flaccid paralysis are not known. Before modern methods of respiratory and cardiovascular support, mortality rates higher than 50% were common in patients with bulbar or medullary poliomyelitis. The ultimate outcome of the paralysis is highly variable and can range from complete resolution to lifelong persistence. The greatest gains in recovery of strength occur during the first 6 months of convalescence. Paralytic limbs become atrophic, thereby leading to skeletal deformities. In a Colorado outbreak of EV-D68, about 75% of patients had limited or no improvement of their flaccid paralysis at 30 days, and the other 25% had only partial recovery by that time. By comparison, 93% of children with EV-A71 neurologic diseases in Colorado completely recovered within 2 months.[10]

A syndrome of postpoliomyelitis muscle atrophy, which may be seen in 25 to 85% of individuals two to three decades after recovery from paralytic disease, is characterized by the gradual development of weakness, pain, and atrophy. Possible mechanisms include aging and neuronal dropout in compromised neuromuscular connections or, less likely, reactivation/ongoing poliovirus infection.

MENINGITIS

Worldwide, the enteroviruses, especially those within the Enterovirus B species, are the dominant cause of viral meningitis (Chapter 381) in all ages. About 50% of all cases of meningitis and encephalitis in the United States are documented to be enteroviral infections.

CLINICAL MANIFESTATIONS AND DIAGNOSIS

The clinical picture varies with age. In older infants and children, an abrupt onset of fever is the most frequent initial symptom. The fever may persist for 1 to 5 days and may exhibit a biphasic pattern. Irritability or lethargy is common. Other nonspecific symptoms include poor feeding, vomiting, diarrhea, and rash. Headache is present in nearly all children old enough to report it. Rash, malaise, sore throat, abdominal pain, and myalgia are common,[11] and photophobia may be reported. Seizures occur in less than 5% of cases. Examination may reveal a full fontanelle. Signs of meningeal irritation (i.e., nuchal rigidity, Brudzinski and Kernig signs) occur in less than 10% of infants younger than 3 months and increase with age.

In adolescents and adults, headache is nearly always present [12] and severe enough to require narcotic analgesics for control. Some patients report temporary relief of headache after lumbar puncture. Fever is not universal, but photophobia, signs of meningeal irritation, nausea, emesis, and neck stiffness occur in more than two thirds of patients. Myalgia is reported in 20 to 90% of patients. Less frequent findings include rash and abdominal pain.

CSF analysis generally reveals a mild to moderate lymphocytic pleocytosis (<500 cells/μL). Some patients, however, may have lymphocyte counts higher than 1000 or have neutrophilic pleocytosis early in the course of illness and then progress to a predominance of lymphocytes hours to days later. In a small percentage of patients, particularly infants, no pleocytosis is present even though enterovirus can be detected. The protein concentration may be increased. Although the glucose concentration is generally normal, hypoglycorrhachia may occur, particularly in association with group B coxsackievirus meningitis. Neuroimaging in cases of meningitis is generally unrevealing. Nucleic acid amplification testing can detect enteroviruses in CSF. The serotypes most frequently identified from CSF specimens are from the enterovirus B species.

TREATMENT AND PROGNOSIS

Treatment is supportive, with control of fever and pain. Currently available antiviral agents are not helpful. Hospitalization may not be necessary in adolescents and adults who appear well if a bacterial cause can be confidently excluded. When bacterial infection cannot be confidently excluded in adults, hospitalization and initial empirical antimicrobial therapy are advisable (Chapter 381) while awaiting the results of bacterial cultures of blood and CSF. Intravenous fluids may be required to prevent dehydration. Control of headache pain may require narcotic analgesics. Uncommon complications in all ages include coma, increased intracranial pressure, and inappropriate secretion of antidiuretic hormone.

The overwhelming majority of patients recover fully. The duration of illness in infants and children is generally less than 1 week. In adults, full recovery may take up to 3 weeks.

ENCEPHALITIS

The enteroviruses are responsible for about 20% of identifiable causes of viral encephalitis (Chapter 383). In the single largest report of enterovirus-related encephalitis, about 75% of confirmed cases occurred in individuals younger than age 20 years, including about 40% of cases in patients younger than age 10 years.

CLINICAL MANIFESTATIONS AND DIAGNOSIS

The onset of neurologic findings may be abrupt or be preceded by fever, headache, malaise, myalgia, upper respiratory symptoms, rash, nausea, emesis, or diarrhea. Somnolence, lethargy, and altered consciousness are common. Patients may exhibit irritability, changes in personality, or hallucinations. Generalized or focal seizures occur in up to 30% of patients, and a minority of patients may progress to coma. Neck stiffness and ataxia are frequent physical findings. Focal neurologic findings such as hemiplegia, hemichorea, and paresthesias are reported in nearly 30% of patients. The focal nature of the seizures and abnormal neurologic findings may be reminiscent of herpes simplex virus encephalitis (Chapter 345).

Among enteroviral encephalitides, EV-A71 is uniquely associated with severe brain stem encephalitis (rhombencephalitis), primarily in children. The initial manifestation may be a prodrome of either hand-foot-and-mouth disease or herpangina, which is followed by myoclonus that may be associated with ataxia, tremors, or cranial nerve abnormalities and a rapid onset of neurogenic pulmonary edema, shock, coma, and apnea.

Evaluation of CSF may reveal mild to moderate lymphocytic pleocytosis (<500 cells/μL), but the CSF white cell count may be normal. The protein concentration may be increased and may be the sole abnormality. The glucose concentration is generally normal. Enteroviruses may frequently be detectable by nucleic acid amplification testing of CSF.

TREATMENT AND PROGNOSIS

Management is supportive, with monitoring for the development of respiratory failure or airway compromise. Nearly 50% of patients require intensive care. In patients with focal neurologic findings, empirical acyclovir (10 to 15 mg/kg every 8 hours) is warranted until herpes simplex virus is excluded.

The median duration of hospitalization is less than 1 week, and mortality is below 10%. For severe EV-A71 rhombencephalitis, however, mortality may approach 70%. Long-term sequelae after rhombencephalitis include myoclonus, abducens nerve palsy, facial diplegia, ataxia, dysarthria, internuclear ophthalmoplegia, and central apnea.

MYOPERICARDITIS

Prior to the SARS-CoV-2 pandemic (Chapter 336), members of the Enterovirus B species, and especially the group B coxsackieviruses, were responsible for approximately a third of cases of acute myocarditis (Chapter 47), with the majority of cases occurring in young adults. Now that SARS-CoV-2 (Chapter 336) is a major cause of acute myocarditis, [13] the current contribution of enteroviruses to the burden of myocarditis remains to be determined.

CLINICAL MANIFESTATIONS AND DIAGNOSIS

An upper respiratory tract infection may precede the onset of cardiac symptoms by 1 to 2 weeks. Fever may be present, and common initial symptoms include dyspnea, chest pain, and fatigue. Physical examination may reveal a gallop rhythm or a pericardial friction rub.

Cardiomegaly may be seen on the chest radiograph. Electrocardiographic findings vary and include low-voltage QRS complexes, ST segment depression, T wave inversion, pathologic Q waves, ventricular arrhythmias, and heart block. Echocardiographic findings include a decreased ejection fraction, ventricular dilation, and pericardial effusion. Blood troponin levels are frequently elevated. Cardiac magnetic resonance imaging may help localize areas of myocarditis. Myocardial biopsy is recommended in selected patients who have refractory heart failure or suspected giant cell myocarditis (Chapter 47); enterovirus can be detected by nucleic acid amplification tests.

TREATMENT AND PROGNOSIS

Supportive treatment includes bed rest and management of heart failure (Chapter 46), arrhythmias (Chapters 52 and 53), and pericarditis with or without pericardial effusion (Chapter 62). Immunosuppressive therapy is not generally recommended (Chapter 47). In approximately a third of patients with acute myocarditis, chronic dilated cardiomyopathy develops. In patients with pericarditis, recurrent pericardial effusions or chronic constrictive pericarditis may develop in the future.

EXANTHEMS AND ENANTHEMS

Enterovirus infections may result in a wide spectrum of febrile exanthems and enanthems, including macular, papular, maculopapular, morbilliform, rubelliform, vesicular, urticarial, papulopustular, and scarlatiniform types. Exanthems are more commonly observed in children ages 15 years or younger. Any serotype is capable of causing several different rashes. With the exception of CV-A16, no serotype is associated with a unique rash. Echovirus 9 and CV-A9 can cause petechial or purpuric rashes reminiscent of meningococcemia (Chapter 274).

HAND-FOOT-AND-MOUTH DISEASE AND HERPANGINA

Hand-foot-and-mouth disease is typically associated with Enterovirus A species, particularly CV-A16, CV-A6, and EV-A71.[14] Herpangina is also most commonly caused by the group A coxsackieviruses in the Enterovirus A species, but it has also been associated with group B coxsackieviruses, echoviruses, and enteroviruses from the Enterovirus B species.

CLINICAL MANIFESTATIONS AND DIAGNOSIS

Hand-foot-and-mouth disease begins with low-grade fever, malaise, anorexia, and oral soreness. In 1 to 2 days, oral macules appear and then rapidly vesiculate and ulcerate. Oral lesions are typically distributed on the buccal mucosa and tongue, but they may also occur on the palate, uvula, anterior pillars, and gums. In approximately two thirds of patients, the enanthem is accompanied by an exanthem, with tender 3- to 7-mm vesicles on the dorsum of the hands and feet, frequently involving the palms and soles. Lesions may appear on the buttocks but tend not to be vesicular. Hand-foot-and-mouth disease associated with CV-A6 has a wider distribution of skin lesions that enlarge and vesiculate. Onychomadesis (loss of fingernails) can occur 1 to 2 months after the infection.

Herpangina begins with high fever, particularly in young patients. Additional findings include sore throat, mild cervical lymphadenopathy, sialorrhea, anorexia, dysphagia, abdominal pain, and emesis. Examination of the mouth and throat reveals 1- to 2-mm papulovesicular, grayish white lesions with an areola of erythema, primarily located on the anterior pillars of the tonsillar fauces. The soft palate, uvula, and tonsils may also be involved. Rarely, the posterior buccal surfaces and dorsal tip of the tongue may be involved. During a period of 2 to 3 days, the lesions increase to 3 to 4 mm in size. On average, five lesions are present.

TREATMENT AND PROGNOSIS

Hand-foot-and-mouth disease usually resolves in less than 1 week, and herpangina generally resolves in 10 days, both typically uneventfully and without the need for hospitalization or sequelae. Infants and young children may require hospitalization for administration of parenteral fluids. Disease associated with CV-A6 has a higher rate of hospitalization. Hand-foot-and-mouth disease due to EV-A71 may precede the development of life-threatening rhombencephalitis (see Encephalitis).

ACUTE HEMORRHAGIC CONJUNCTIVITIS

Acute hemorrhagic conjunctivitis (Chapter 391) is associated with EV-D70 and CV-A24. The illnesses caused by the two serotypes are indistinguishable from each other. However, acute hemorrhagic conjunctivitis caused by CV-A24 may be more commonly accompanied by upper respiratory and systemic symptoms and may be associated with less severe conjunctival hemorrhage. High secondary attack rates within households are common. Other enteroviruses can cause acute conjunctivitis or keratoconjunctivitis but generally without hemorrhagic manifestations.

CLINICAL MANIFESTATIONS

An incubation period of about 1 to 2 days precedes the rapid onset of palpebral swelling associated with lacrimation, photophobia, blurring of vision, and severe ocular pain. The hallmark subconjunctival hemorrhages vary in size from petechiae to large blotches. Although transient keratitis occurs frequently, it seldom results in subepithelial opacities. Preauricular adenopathy is common, but fever is not. An ocular mucopurulent discharge may occasionally be present.

TREATMENT AND PROGNOSIS

Management is supportive. The illness usually persists for 1 to 2 weeks, but complete recovery is generally the rule. A transient lumbar radiculomyelopathy and acute flaccid paralysis–like illness may develop in some patients.

RESPIRATORY TRACT SYNDROMES

The enteroviruses may cause upper and lower respiratory tract syndromes, alone or accompanying other syndromes. As determined by nucleic acid amplification testing, enteroviruses are responsible for up to 15% of upper respiratory tract syndromes. They also cause 18% of lower respiratory tract syndromes in hospitalized children and 25% of hospitalizations in patients with acute wheezing. EV-D68 and EV-C104 are being increasingly recognized as causes of respiratory tract disease. During the initial year of the SARS-CoV-2 pandemic, the incidence of enteroviral respiratory disease decreased,[15] most likely as a result of decreased transmission because of physical mitigation measures (e.g., use of face coverings, handwashing, social distancing) and school closures.[16]

CLINICAL MANIFESTATIONS AND DIAGNOSIS

The enterovirus "summer cold" (Chapter 329) consists of nasal congestion, rhinorrhea, and sneezing. Malaise and cough may be present. Fever and sore throat are typically absent or minimal.

Pharyngitis, tonsillitis, or pharyngotonsillitis begins abruptly with fever and sore throat. The nasopharynx, tonsils, uvula, and soft palate demonstrate erythema and inflammation. Petechiae may be present, and cervical lymphadenitis is common. Other syndromes associated with the enteroviruses include bronchitis (Chapter 84) and bronchiolitis.

Enteroviral pneumonias begin gradually with coryza, anorexia, and low-grade fever. A nonproductive cough, tachypnea, retractions, nasal flaring, and wheezing may be present. In severe cases, cyanosis may develop. The chest radiograph may demonstrate perihilar infiltrates, patchy consolidation, air trapping, and atelectasis.

EV-D68 has become a cause of significant respiratory disease, primarily in young children and infants but also in adolescents and adults. An underlying pulmonary condition such as asthma or wheezing has been reported in up to 70 to 80% of cases. EV-D68–associated respiratory syndromes include pneumonia, bronchiolitis, asthmatic bronchitis, asthma exacerbation, and wheezing. Signs and symptoms include nasal congestion, rhinorrhea, cough, wheezing, dyspnea, tachycardia, and inter- and subcostal retractions. Acute flaccid paralysis is a rare complication. Interestingly, fever may be absent, but hypoxia is common. The chest radiograph may show infiltrates and atelectasis.

TREATMENT AND PROGNOSIS

Treatment is supportive and consists of control of fever and pain. In older children and adults, hospitalization is not usually required. Resolution occurs in 7 days or less. Hospitalization and admission to an intensive care unit may be required for respiratory support of EV-D68 infection. Death is uncommon but does occur.

MYOSITIS

PLEURODYNIA

The group B coxsackieviruses are the major cause of sporadic and epidemic pleurodynia, but the syndrome may also be caused by a limited number of echoviruses and group A coxsackieviruses within the Enterovirus A and B species.

CLINICAL MANIFESTATIONS AND DIAGNOSIS

The onset of illness is abrupt in approximately 75% of patients. In the remainder, the onset of pleuritic chest pain is preceded by a prodrome of headache, malaise, anorexia, and vague myalgia lasting up to 10 days. Pain may be referred to the lower ribs or the sternum, and it can radiate to the shoulders, neck, or scapula. Pain is exacerbated by deep breathing, coughing, sneezing, or movement. During paroxysms, patients tend to be tachypneic and to have shallow breathing. Additional findings can include abdominal pain, headache, cough, anorexia, nausea, vomiting, and diarrhea. Fever may be biphasic.

Physical examination does not generally reveal muscle tenderness, obvious myositis, or muscle swelling. A pleural friction rub may be present in 25% of patients. The chest radiograph is typically normal.

TREATMENT AND PROGNOSIS

Treatment is supportive, with an emphasis on nonsteroidal analgesics (e.g., ibuprofen, 200 to 400 mg per dose every 4 to 6 hours) or hydrocodone (5 to 10 mg four times per day) alone or in combination with acetaminophen to control pain. The symptoms may persist for 1 to 14 days (mean of 3.5 days) and resolve without sequelae, although recurrent symptoms may occur in 25% of patients.

INFLAMMATORY MYOSITIS

Multiple enteroviral serotypes are associated with focal or generalized myositis. In patients with B-cell immunodeficiencies, a dermatomyositis-like syndrome may develop.

CLINICAL MANIFESTATIONS AND DIAGNOSIS

Nonspecific findings include fever and chills. Involved muscles may be weak, tender, and edematous. Chemical evidence of myositis may be evidenced by elevated serum levels of creatine kinase, myoglobinemia, and myoglobinuria.

TREATMENT AND PROGNOSIS

Treatment is supportive. With the exception of patients with B-cell immunodeficiencies, recovery is complete and rapid.

ENTEROVIRUS INFECTIONS IN SPECIAL POPULATIONS

PATIENTS WITH B-CELL IMMUNODEFICIENCIES

Nonpolio enteroviruses and polioviruses may result in chronic or prolonged infections in patients with congenital or acquired B-cell immunodeficiencies (Chapter 231), such as patients who have inherent immunodeficiencies (e.g., X-linked agammaglobulinemia, hyper-IgM syndrome, severe combined immunodeficiency syndrome, or common variable immunodeficiency), or acquired immunodeficiencies (e.g., because of chemotherapy or immunomodulatory therapies, especially rituximab and obinutuzumab, or because of stem cell or solid organ transplantation).

CLINICAL MANIFESTATIONS AND DIAGNOSIS

Meningoencephalitis, pulmonary infections, and severe gastroenteritis can occur. The initial symptoms may consist of only persistent headaches and lethargy. As the disease progresses, additional neurologic findings develop and may include ataxia, loss of cognitive skills and memory, dementia, emotional lability, paresthesias, weakness, dysarthria, and seizures. Non-CNS manifestations include a dermatomyositis-like syndrome, edema, exanthems, and hepatitis. CSF demonstrates a persistently elevated protein concentration and pleocytosis. Enterovirus is detectable in CSF by RT-PCR.

TREATMENT AND PROGNOSIS

Children with humoral immunodeficiency (Chapter 231) should receive lifelong immunoglobulin replacement therapy in an attempt to prevent chronic infection. However, chronic meningoencephalitis develops in some patients and is usually ultimately fatal. Severe or fatal enteroviral infections have been reported in individuals receiving rituximab.

PREVENTION

Handwashing is the primary method for the prevention of enteroviral infections. Poliovirus infections are currently preventable through vaccination. Three EV-A71 China-licensed vaccines are at least 90% effective against EV-A71-related hand-foot-and-mouth disease[A1] and appear to be 100% effective against EVA-71-associated neurologic complications,[17] but they are not currently licenced in the U.S.

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350 ROTAVIRUSES, NOROVIRUSES, AND OTHER GASTROINTESTINAL VIRUSES

MANUEL A. FRANCO AND HARRY B. GREENBERG

DEFINITION

Viruses are a principal cause of acute infectious gastroenteritis, a syndrome of vomiting, watery diarrhea, or both that begins abruptly in otherwise healthy persons. Two distinct viruses account for much of these cases. Before rotavirus vaccines were widely introduced over the last 15 years, rotaviruses accounted for over 400,000 deaths annually. Rotaviruses remain the most frequent cause of sporadic, severe gastroenteritis in young children worldwide, causing about 130,000 annual deaths in children younger than age 5 years,[1] mainly in developing countries that have not yet implemented widespread rotavirus vaccination. Noroviruses are the primary cause of epidemic infectious gastroenteritis in both infants and adults in developed countries. For example, outbreaks of gastroenteritis in closed settings, such as cruise ships and nursing homes, are a typical manifestation of epidemic norovirus infections. However, noroviruses are also an increasingly common cause of sporadic, mild to moderately severe gastroenteritis, especially in young children and adolescents,[2] and they are the leading cause of acute diarrhea in families with children in the Netherlands, even though it does not have a rotavirus vaccine program.[3] By comparison, in a birth cohort study from eight sites in South America, Africa, and Asia, rotavirus had the highest attributable burdens for sites without rotavirus vaccination.

The Pathogens

Noroviruses

Noroviruses, which are one of the five genera of the Caliciviridae family, are nonenveloped, icosahedral viruses with a relatively small, positive-sense, single-stranded RNA genome. The norovirus genus is further classified into 10 genogroups. Viruses in each genogroup are further divided into genotypes (more than 48 have been described), and a dual-typing nomenclature (genotype and P-type, depending on serology) has been proposed. Norwalk virus is a prototype genogroup I genotype 1 (GI.1) virus. The norovirus genome is approximately 7.7 kilobases in size and consists of three open reading frames, the first of which encodes the nonstructural proteins that are essential for virus replication. The second open reading frame encodes the major capsid protein, viral protein 1 (VP1). When VP1 is expressed as a recombinant protein, 180 molecules can autoassemble into virus-like particles (VLPs) that closely resemble authentic virions. These VLPs have proven to be critical to the study of noroviral epidemiology and immunity. Human noroviruses have only recently been reproducibly cultured in vitro in human enteroids,[4] so diagnosis generally depends on amplification of viral genes by polymerase chain reaction (PCR; see later) or use of VLPs as recombinant antigens for serologic analysis.

Rotavirus

Rotaviruses, which belong to the family Reoviridae, are large, icosahedral, nonenveloped viruses with a segmented, double-stranded RNA genome and a triple-layered protein coat. Rotaviruses are classified into nine species, A through I, on the basis of the presence of cross-reactive antigenic epitopes and their overall genetic relatedness. Species A rotaviruses are the most commonly encountered viral enteric pathogens of young humans and many other mammalian species. Species B viruses have been identified sporadically in outbreaks of adult diarrheal illness in China and more recently in studies of children with sporadic gastroenteritis, principally in India. Species C rotaviruses are primarily veterinary pathogens and are infrequently associated with diarrheal disease in humans and animals around the world when compared with species A. Species D through G rotaviruses have been isolated only from animals, primarily avian species. Rotaviruses are 100-nm particles that have three concentric layers of proteins: the core is composed of VP1, VP2, and VP3 and the segmented, double-stranded RNA genome; the intermediate layer is formed by VP6, the most abundant and antigenic viral protein; and the external layer is composed of VP7 and VP4. The genome, which is composed of 11 segments of double-stranded RNA that together are approximately 18 kilobases in length, encodes six structural and six nonstructural proteins. As is the case among virtually all other RNA viruses, the rotavirus RNA polymerase is error prone and, along with selective pressure such as the evolution of immunity, drives viral diversity. For rotaviruses, gene reassortment, which is the mixing of gene segments from different parental viruses in cells coinfected by two or more strains, and rearrangement of the viral genome also contributes to genetic diversity. Reassortment of gene segments between animal and human rotavirus strains also occurs in natural settings, especially in less developed countries. Recently an efficient and practical helper virus–free method was developed to recover recombinant rotaviruses, and this method will certainly lead to improved understanding of rotavirus biology as well as enhance the possibility of developing improved vaccines.[5]

Other Agents

Other viral agents that cause human acute infectious gastroenteritis that is difficult to distinguish from disease caused by rotaviruses and noroviruses include the sapovirus (like norovirus, a member of the Caliciviridae family), enteric adenoviruses (Chapter 333) belonging to types 40 and 41, and astroviruses (Table 350-1). The frequency of detection (by PCR assays) of these viruses in individuals with acute gastroenteritis depends on the setting, but

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The Pathogens

Noroviruses

Noroviruses, which are one of the five genera of the Caliciviridae family, are nonenveloped, icosahedral viruses with a relatively small, positive-sense, single-stranded RNA genome. The norovirus genus is further classified into 10 genogroups. Viruses in each genogroup are further divided into genotypes (more than 48 have been described), and a dual-typing nomenclature (genotype and P-type, depending on serology) has been proposed. Norwalk virus is a prototype genogroup I genotype 1 (GI.1) virus. The norovirus genome is approximately 7.7 kilobases in size and consists of three open reading frames, the first of which encodes the nonstructural proteins that are essential for virus replication. The second open reading frame encodes the major capsid protein, viral protein 1 (VP1). When VP1 is expressed as a recombinant protein, 180 molecules can autoassemble into virus-like particles (VLPs) that closely resemble authentic virions. These VLPs have proven to be critical to the study of noroviral epidemiology and immunity. Human noroviruses have only recently been reproducibly cultured in vitro in human enteroids,[4] so diagnosis generally depends on amplification of viral genes by polymerase chain reaction (PCR; see later) or use of VLPs as recombinant antigens for serologic analysis.

Rotavirus

Rotaviruses, which belong to the family Reoviridae, are large, icosahedral, nonenveloped viruses with a segmented, double-stranded RNA genome and a triple-layered protein coat. Rotaviruses are classified into nine species, A through I, on the basis of the presence of cross-reactive antigenic epitopes and their overall genetic relatedness. Species A rotaviruses are the most commonly encountered viral enteric pathogens of young humans and many other mammalian species. Species B viruses have been identified sporadically in outbreaks of adult diarrheal illness in China and more recently in studies of children with sporadic gastroenteritis, principally in India. Species C rotaviruses are primarily veterinary pathogens and are infrequently associated with diarrheal disease in humans and animals around the world when compared with species A. Species D through G rotaviruses have been isolated only from animals, primarily avian species. Rotaviruses are 100-nm particles that have three concentric layers of proteins: the core is composed of VP1, VP2, and VP3 and the segmented, double-stranded RNA genome; the intermediate layer is formed by VP6, the most abundant and antigenic viral protein; and the external layer is composed of VP7 and VP4. The genome, which is composed of 11 segments of double-stranded RNA that together are approximately 18 kilobases in length, encodes six structural and six nonstructural proteins. As is the case among virtually all other RNA viruses, the rotavirus RNA polymerase is error prone and, along with selective pressure such as the evolution of immunity, drives viral diversity. For rotaviruses, gene reassortment, which is the mixing of gene segments from different parental viruses in cells coinfected by two or more strains, and rearrangement of the viral genome also contributes to genetic diversity. Reassortment of gene segments between animal and human rotavirus strains also occurs in natural settings, especially in less developed countries. Recently an efficient and practical helper virus–free method was developed to recover recombinant rotaviruses, and this method will certainly lead to improved understanding of rotavirus biology as well as enhance the possibility of developing improved vaccines.[5]

Other Agents

Other viral agents that cause human acute infectious gastroenteritis that is difficult to distinguish from disease caused by rotaviruses and noroviruses include the sapovirus (like norovirus, a member of the Caliciviridae family), enteric adenoviruses (Chapter 333) belonging to types 40 and 41, and astroviruses (Table 350-1). The frequency of detection (by PCR assays) of these viruses in individuals with acute gastroenteritis depends on the setting, but

ABSTRACT

Viruses are a principal cause of acute infectious gastroenteritis, which is a syndrome of vomiting, watery diarrhea, or both that begins abruptly in otherwise healthy persons. Two distinct viruses account for much of these cases. Even after rotavirus vaccines were widely introduced, rotaviruses remain the most frequent cause of sporadic, severe gastroenteritis in young children, causing about 130,000 annual deaths in children younger than 5 years of age worldwide, mainly in developing countries that have not yet implemented widespread vaccination. Noroviruses are the primary cause of epidemic infectious gastroenteritis in both infants and adults in developed countries. For example, outbreaks of gastroenteritis in closed settings, such as cruise ships, military units, or nursing homes, are typical of norovirus infections. However, noroviruses are also an increasingly common cause of sporadic, mild to moderate gastroenteritis, mostly in young children.

KEYWORDS

acute infectious gastroenteritis
rotavirus
vaccines
noroviruses
epidemic infectious gastroenteritis
children

TABLE 350-1 EPIDEMIOLOGIC AND CLINICAL FEATURES OF NOROVIRUS AND ROTAVIRUS

	NOROVIRUS	ROTAVIRUS	ASTROVIRUS
Epidemics	Occurs year-round; outbreaks tend to peak in cold weather	Year-round in equatorial countries; winter peak in others	Winter epidemics in children and endemic year-round
Key driver of epidemics	Antigenic drift strains promoted by population-based immunologic pressure	Size of the susceptible birth cohort	Unknown
Transmission	Fecal-oral, water, and food-borne outbreaks	Fecal-oral	Fecal-oral
Severity of diarrhea in children	Mild to moderate but can be severe	Moderate to severe	Milder than rotavirus or norovirus
Reservoir	Humans are the only known reservoir of noroviruses that infect humans	Mostly humans, but rotaviruses from farm animals and pets (especially in developing countries) can rarely infect humans and very rarely spread	Humans are the only known reservoir of astroviruses that infect humans
Prevention	Viral protein 1–based vaccine in development	Several live attenuated vaccines available	No vaccine in development
Age predisposition	All ages	Primarily children <5 years; disease transmission in older family contacts is relatively low (<25%)	Generally children, but adults may also get disease

they are almost always detected much less frequently than either rotaviruses or noroviruses. Coronaviruses (Chapter 334), toroviruses, picobirnaviruses, picornavirus (Chapter 349), bocavirus, parechoviruses, and pestiviruses have also been isolated occasionally from persons with acute gastroenteritis, but their roles as causative agents of enteric disease remain unproven. Among patients with acute gastroenteritis, no etiologic agent is found in approximately 25 to 50% of cases.

EPIDEMIOLOGY

Norovirus

Over time, noroviruses appear to undergo antigenic drift in response to the acquisition of immunity in the general population. At present, gastroenteritis cases around the world are most frequently caused by strains of GII.4 norovirus, with new pandemic GII.4 strains generally appearing every 2 to 4 years.[6] However, pandemic strains seem to circulate for years prior to their worldwide distribution and do not develop from previous pandemic strains, thereby suggesting that these pandemics are driven by an interplay between pre-circulating antigenic diversity and temporal changes in host immunity. Outbreaks of gastroenteritis frequently take place in settings of close human contact, such as military establishments, cruise ships, nursing homes, and schools, especially in cold and dry weather (see Table 350-1). Viral spread is enhanced by the very high level of infectivity of noroviruses, as data suggest that 1 to 10 particles constitute an infectious dose.

Noroviruses of genotypes GII.4 and GII.3 also are currently responsible for about 12 to 20% of sporadic gastroenteritis in children younger than 5 years in both developed and developing countries.[7] In the United States, where rotavirus vaccination is now widespread, noroviruses have surpassed rotavirus as the principal cause of medically attended visits for gastroenteritis in children younger than 5 years. Among U.S. adults, norovirus may be second only to *Clostridioides difficile* (Chapter 271) as the cause of severe acute diarrhea,[8] with hospitalizations especially in individuals over age 80 years. Of note is that the prevalence of asymptomatic carriage of norovirus in adults is about 2 to 3%.[9]

Rotavirus

The incidence of rotaviral disease is similar in children in both developed and developing countries, suggesting that public hygiene measures such as access to clean water do not replace the need for an effective vaccine. In developed countries, before the implementation of highly effective vaccines, rotavirus was a major economic burden but rarely the cause of fatal disease; after the implementation of vaccines, the epidemiology of rotavirus disease changed substantially. For example in the United States, the annual winter rotavirus season was replaced by a biennial trend, with alternating low rates in even-numbered years and higher rates in odd-numbered years. Initial infections also are now being observed in older children and adolescents.[10]

In the temperate zones of the world, rotaviral illness occurs primarily during epidemic peaks in the cooler months of the year (see Table 350-1). This pattern is not seen, however, in countries within 10 degrees of the equator, where disease occurs in an endemic fashion year-round.

Antibodies against the two outer capsid proteins are the basis of serotypic classification of group A rotaviruses into G (glycoprotein, VP7) and P (protease-sensitive, VP4) serotypes. For technical reasons, P serotyping reagents are infrequently available, and classification is based on the P genotype (provided in brackets). Worldwide, most human infections are caused by just five types of group A rotavirus; P[8]G1 is by far the most common (approximately 53% of strains), followed by P[8]G3, P[4]G2, P[8]G9, and P[8]G4. In some developing areas such as India, Brazil, and Africa, P[6]G9, G5, and G8 rotaviruses, respectively, are also frequently encountered. Some human rotavirus strains may have arisen after reassortment with bovine or porcine rotavirus strains during mixed infection in susceptible children. A high prevalence of G12 viruses has recently been observed in several countries, suggesting that this serotype may be an emerging rotavirus strain. In sub-Saharan Africa and South Asia, where most of the gastroenteritis deaths in children younger than 5 years of age occur, rotavirus is the most common etiologic agent of severe diarrhea and causes an important nutritional burden in children.

PATHOBIOLOGY

Norovirus

Histo–blood group antigens (HBGAs) are the intestinal cell receptors for noroviruses and determine susceptibility to disease in a strain-specific manner. The HBGAs are complex carbohydrate oligosaccharides linked to proteins or lipids that are expressed on the mucosal epithelia of the digestive tract. All three major families of HBGA, the ABO, Lewis, and secretor families, are involved in binding noroviruses. The secretor status of an individual is controlled by the fucosyltransferase 2 (*FUT2*) gene. Secretor-negative individuals are specifically resistant to infection with the Norwalk virus (GI.1) and some GII viruses as well.

Although norovirus RNA has been detected in the bloodstream of up to 20% of patients with norovirus gastroenteritis, the site of primary viral replication is most probably in the gastrointestinal tract. Recently human noroviruses have been successfully cultivated and passaged in vitro in differentiated human stem-cell–derived intestinal epithelial cell organoid cultures. Consistent with the strong association of vomiting with norovirus disease, gastric emptying is delayed. Proximal jejunal biopsy specimens show blunting of the villi with crypt cell hyperplasia and cytoplasmic vacuolation, sometimes with an increase in epithelial cell apoptosis. A functional alteration of the epithelial barrier is likely to occur. Unknown at present is the effectiveness and persistence of long-term immunity in the context of natural infection, in which the infectious dose is generally quite low. However, both natural infection and vaccination induce both homotypic and heterotypic broadly neutralizing antibody responses, with the latter waning more rapidly.[11]

Rotavirus

For rotaviruses, HBGAs have also been recently proposed as receptors that determine susceptibility to disease in a strain-specific manner. Rotaviruses replicate in the villus tip cells of the small bowel, where the pathologic process includes shortening and atrophy of the villi, vacuolization of enterocytes, mononuclear infiltration in the lamina propria, and distention of the cisternae of the endoplasmic reticulum. However, the severity of clinical disease has not been directly related to the extent of intestinal pathology; rather, it is related to levels of viral RNA in stool.

During the initial phases of the disease, altered intestinal secretion, motility, and permeability contribute to the pathophysiologic mechanism of diarrhea.

Later during disease, malabsorption can occur. Rotaviral NSP4, encoded by rotavirus gene 10, is a viral enterotoxin that mediates, at least in part, the early secretory components of the diarrhea. It has also been postulated that viral infection increases intestinal motility by stimulating the enteric nervous system, possibly through NSP4. Whether and to what degree the enterotoxic effect of NSP4 is clinically relevant in children or other animal species remains to be fully determined. Rotavirus-infected cells release extracellular adenosine 5'-diphosphate (ADP) that activates P2Y1 purinergic receptors on neighboring bystander cells, which in turn induce intercellular calcium waves implicated in the release of serotonin and the development of diarrhea.[12] Infected individuals have a short period of viremia, but its clinical consequences are unclear other than correlating with the level of fever. However, most rotavirus-infected children have mild elevations in hepatic enzymes, thereby suggesting that low-level hepatitis may be a common occurrence.

Rotavirus serum IgA levels measured shortly after natural infection in children generally correlate with intestinal IgA levels and appear to also correlate with protection. One explanation for recurrent rotavirus (and norovirus) infections is that protection from reinfection is mediated by intestinal IgA, which is not long-lasting in humans. Another explanation is that protection is dependent on neutralizing antibodies to one or both highly variable outer-capsid rotaviral proteins. However, a widely available monovalent P[8]G1 vaccine induces significant protection against multiple strains with different serotypes, thereby supporting the conclusion that protective immunity to rotavirus infection is, in large part, heterotypic.

CLINICAL MANIFESTATIONS

Norovirus

The clinical manifestations of norovirus infection are variable and depend in part on the age of the individual infected. About one third of infections are asymptomatic, but symptoms include diarrhea, nausea, vomiting, abdominal cramps, fever, and malaise that generally persist for 1 to 3 days. In children younger than 11 years, disease typically begins with the sudden onset of vomiting and can last 4 to 6 days. Virus can be shed in low titers for up to 8 weeks from otherwise healthy individuals and for more than a year in patients with severe immunodeficiency syndromes. In neonates and premature infants, vomiting often is not a symptom, and infection has rarely been associated with necrotizing enterocolitis. To support the diagnosis of norovirus outbreaks, the following four criteria have been proposed: (1) vomiting in more than half of affected persons; (2) mean (or median) incubation period of 24 to 48 hours; (3) mean (or median) duration of illness of 12 to 60 hours; and (4) absence of bacterial pathogens in stool culture.

Rotavirus

Rotavirus diarrhea and dehydration tend to be more severe than illness caused by the other childhood enteric pathogens. Rotavirus diarrhea is watery, persists for approximately 5 days, is often preceded by the sudden onset of vomiting, and is frequently accompanied by fever and dehydration. The incubation period of rotavirus is estimated to be less than 48 hours. Viral excretion in feces persists for 10 days in most children and can persist for up to 57 days. By the age of 5 years in an unvaccinated setting, virtually all children have naturally acquired immunity to rotavirus, and very severe disease after this age is uncommon.

DIAGNOSIS

Norovirus

Reverse transcription–PCR (RT-PCR) is currently the procedure of choice to detect norovirus in clinical specimens, in food, and in water. Norovirus RNA is detected by RT-PCR in stool samples of up to 16% of healthy individuals, a finding that can substantially complicate the diagnosis of norovirus gastroenteritis and the determination of the true burden of disease. Although the relationship between disease symptoms and viral load has not been fully established, a relative threshold of positivity on a quantitative real-time RT-PCR is probably better for attributing disease to norovirus.

Rotavirus

Numerous enzyme-linked immunosorbent assays (ELISAs) for rotavirus are generally sensitive, specific, and easy to use under most conditions. PCR has the best sensitivity for detecting rotavirus and has permitted easy typing of viruses, but nearly 30% of healthy children younger than 1 year may be rotavirus positive, so it is difficult to associate gastroenteritis with the detection of viral RNA. Thus ELISA or quantitative RT-PCR (using a threshold level as for norovirus) is preferable for diagnosis of rotavirus gastroenteritis.

PREVENTION

Norovirus

The development of a norovirus vaccine for humans is likely to be a challenge owing to the antigenic heterogeneity among circulating strains, the propensity of noroviruses to undergo antigenic drift, waning immunity, and the lack of well-established correlates of protection. Nevertheless, an intramuscular bivalent norovirus GI.1/GII.4VLP-based vaccine candidate has recently shown promising efficacy in adults.[A1] Moreover a bivalent oral vaccine, which uses a nonreplicating adenoviral vector,[A2] and two parenteral tetravalent and bivalent vaccines are undergoing phase I clinical trials.

High percentage alcohol-based sanitizers (99.5% ethanol) and 10% povidone-iodine antiseptics are superior to other alcohol-based sanitizers at reducing norovirus contamination. Simple household antimicrobial hand soap and handwashing with tap water also decrease viral contamination.

Rotavirus

Two second-generation rotavirus vaccines are safe, effective, and cost-effective in developed and developing countries. The first (RV5, RotaTeq [Merck]) uses a modified pentavalent vaccine consisting of a mixture of a bovine rotavirus that expresses a variety of human rotavirus VP4 or VP7 encoding genes. The second (RV1, Rotarix [GlaxoSmithKline]) is a monovalent attenuated human rotavirus vaccine. More recently ROTAVAC[A3] (Bharat Biotech: an attenuated G9P[11] virus isolated from a human neonate) and RotaSiil (Serum Institute India: a pentavalent human-bovine reassortant vaccine) have also been licensed.

Although none of these vaccines fully prevent subsequent rotavirus infection or mild illness, all types effectively reduce the amount of severe illness, especially in developed countries. Protection rates in developed and middle-income countries for licensed rotavirus vaccines are similar, ranging from 70 to 80% against any rotavirus disease and 90 to 100% against severe gastroenteritis, but infections are still seen in children over 5 years of age.[13,14] In resource-poor settings, vaccination can safely and successfully be accomplished in neonates.[A4]

Licensed vaccines may slightly increase the risk of intussusception, although one large study in India did not find an increase.[15] Furthermore, the substantial benefits of vaccines[16] far outweigh this low-level risk. Even in the United States, where the burden of severe disease from rotavirus is lowest, the rotavirus vaccine has significantly reduced health care utilization and expenses for acute diarrhea in children.[17]

In the United States vaccination also has had an unexpected effect on reducing rotavirus-induced diarrhea among unvaccinated persons, thereby suggesting the induction of herd immunity. The U.S. Advisory Committee on Immunization Practices (Chapter 15) and the World Health Organization now recommend the routine use of these vaccines.

Currently several other rotavirus vaccine formulations are being developed,[18] mostly to reduce costs, but like current vaccines are only about 50% efficacious against severe diseases in the poorest developing countries.[A5,A6] Even with this reduced effectiveness, however, licensed vaccines are still cost-effective in the less developed world.

TREATMENT

Because both norovirus and rotavirus disease resolves within days without treatment, the basic therapeutic goal is to prevent acute dehydration. The recommended oral rehydration salts solution, which now has an osmolarity of 331 mmol/L, is as effective as higher-osmolarity solutions. After rehydration, rapid age-appropriate refeeding is recommended. Rotavirus disease induces self-limited intestinal lactase deficiency, but lactose-containing products, particularly maternal milk, should not be withheld.

Passive oral immunotherapy with diverse preparations of immunoglobulins can shorten the duration of rotavirus infection but probably is economically feasible only for immunodeficient patients or low-birthweight infants in the developed world. Recently in Bangladesh, a llama-derived, heavy-chain antibody fragment specific for rotavirus was able to reduce stool output in male infants with severe rotavirus-associated diarrhea. *Lactobacillus*, a bacterium present in yogurt, is safe and, in some, but not all, studies[A7] has been moderately effective for treatment of acute rotavirus gastroenteritis. Nonetheless, different preparations of lactobacilli vary greatly in dose of bacteria, and a general recommendation on their use has not been issued. Several studies in developing countries have shown that zinc supplementation (10 mg/day for infants younger than 6 months and 20 mg/day for older children) is useful for the treatment and prevention of diarrhea, but further studies are needed to determine whether treatment will be useful in all developing and developed countries.

At present, no pharmacologic treatment of rotavirus or norovirus diarrhea is recommended. Racecadotril (4.5 mg/kg per day), an enkephalinase inhibitor that acts on the enteric nervous system, has been shown to be useful as an

adjunct to treat rotaviral diarrhea in some, but not all, studies. Ondansetron (0.15 mg/kg per day), a serotonin antagonist, is effective in reducing the emesis from gastroenteritis during the phase of oral rehydration.[A8] In several small studies, nitazoxanide (15 mg/kg per day) was helpful in the treatment of rotavirus gastroenteritis.[A9] More studies are needed before any of these various preparations can be generally recommended for treatment of rotavirus diarrhea.

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351 VIRAL HEMORRHAGIC FEVERS

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DEFINITION

Viral hemorrhagic fever is an acute systemic illness classically involving fever, a constellation of initially nonspecific signs and symptoms, and a propensity for bleeding and shock.

The Pathogens

Viral hemorrhagic fever may be caused by more than 30 different viruses from four taxonomic families, Filoviridae, Arenaviridae, Bunyaviridae, and Flaviviridae (Table 351-1), but not every virus in these families causes the syndrome. Recently discovered viruses such as severe fever with thrombocytopenia and heartland viruses (family Phenuiviridae family)[1] have variably been considered as hemorrhagic fever viruses, thereby highlighting the extreme heterogeneity and perhaps increasing ambiguity of this categorization. All implicated viruses are single-stranded lipid-enveloped RNA viruses with small genomes (10 to 19 kilobases) that can be relatively easily inactivated in the environment.

EPIDEMIOLOGY

Maintenance in Nature and Transmission to Humans

With the exception of dengue virus, for which humans can now be considered the reservoir, all hemorrhagic fever viruses are zoonotic, maintained in nature in mammalian reservoirs that tend to be specific for each virus (see Table 351-1). Although viral hemorrhagic fevers collectively can be found worldwide, the endemic area of any given hemorrhagic fever virus is usually smaller than the extent of its natural reservoir or arthropod vector. With the exception of dengue, yellow fever, and some hantaviruses, human infection is generally infrequent and humans are usually dead-end hosts.

Depending upon the virus, primary transmission to humans may be from contact with infected animal excreta or other body fluids or from the bite of an arthropod vector. Infection may occur through direct exposure of mucous membranes or broken skin to the infected blood or excreta of an animal reservoir, which usually occurs inadvertently or, in the case of the flaviviruses and most of the bunyaviruses, by the bite of an arthropod vector. Transmissibility between humans and pathogenicity vary with the specific virus and sometimes even among strains of the same virus. The infectious dose for most hemorrhagic fever viruses appears to be low, sometimes on the order of just a few virions. Airborne transmission is not a predominant mode of spread, if it occurs at all; however, studies in nonhuman primates show that transmission of many hemorrhagic fever viruses is possible through artificially created aerosols, thereby raising the possibility of their potential use as bioweapons (Chapter 19).

Bat-Borne Viruses

The filoviruses (from the Latin *filo*, "thread," referring to their filamentous shape), Marburg and Ebola, are perhaps the most feared of all hemorrhagic fever viruses.[2,3] Fruit bats appear to be the filovirus reservoir, although more conclusive evidence is needed for Ebola virus, with transmission to humans likely from exposure to infected bat excreta or saliva. Nonhuman primates, especially gorillas and chimpanzees, and other wild animals may become infected, presumably from similar bat exposure, and transmit filoviruses to humans through contact with blood and body fluids of these animals, usually in association with hunting. Nonhuman primates, which are also dead-end hosts who develop severe and usually fatal disease similar to that seen in humans, may be easier prey for hunters when sick. Because hemorrhagic fever viruses are rapidly inactivated by heating, infection probably occurs by exposure during butchering and preparation, rather than by consumption of cooked meat. The 2013 to 2016 outbreak of Ebola virus disease in West Africa dwarfed all prior Ebola outbreaks combined, with a reported 28,616 cases and 11,310 deaths. Sporadic outbreaks continue to occur in the Democratic Republic of the Congo, West Africa, and Uganda, either through primary infection from wild animals or renewed secondary infection from persistently infected humans (see later).

Rodent-Borne Viruses

Arenaviruses (from the Latin *arena*, "sand") are divided into Old World (or lymphocytic choriomeningitis/Lassa) and New World (or Tacaribe) complexes. Lassa and Lujo viruses are found in Africa, whereas Junín, Machupo, Guanarito, Sabiá, and Chapare viruses are found in South America. Although there may be subtle differences among the syndromes produced by the New World arenaviruses, they are usually grouped together simply as the South American hemorrhagic fevers.

The genus Hantavirus of the Bunyaviridae family is similarly divided into Old and New World complexes. The Old World hantaviruses, such as Hantaan, Seoul, and Puumala, among many others, classically cause hemorrhagic fevers with prominent renal involvement across Europe and Asia. New World hantaviruses, such as Sin Nombre and Andes, among many others, cause hantavirus pulmonary syndrome, sometimes also called hantavirus cardiopulmonary syndrome to emphasize the significant cardiogenic component of this disease.

Pathogenic arenaviruses and hantaviruses are maintained in nature through chronic subclinical infection in rodents of the Muridae family, with a strict pairing between the specific virus and rodent species. Transmission between rodents may be by vertical or horizontal transmission or both, depending on the specific virus. Transmission to humans occurs through exposure to rodent excreta, either from aerosols produced when rodents urinate or by direct inoculation to the mucous membranes, although the precise modes of transmission remain to be elucidated. Secondary aerosol generation is notoriously inefficient, so disturbing shed urine is a less likely mechanism of infection. In West Africa, Lassa virus is sometimes contracted when rodents are trapped and prepared for consumption or, more rarely, through a rodent bite. Experimental data suggest that humans may also be infected with arenaviruses by the oral route.

The rodents that transmit Lassa, Machupo, and many of the Old World hantaviruses commonly invade the peridomestic environment, thereby putting housewives, children, and others who spend time at home at risk. In contrast, the reservoirs for Junín and Guanarito viruses, as well as most

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351 VIRAL HEMORRHAGIC FEVERS

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DEFINITION

Viral hemorrhagic fever is an acute systemic illness classically involving fever, a constellation of initially nonspecific signs and symptoms, and a propensity for bleeding and shock.

The Pathogens

Viral hemorrhagic fever may be caused by more than 30 different viruses from four taxonomic families, Filoviridae, Arenaviridae, Bunyaviridae, and Flaviviridae (Table 351-1), but not every virus in these families causes the syndrome. Recently discovered viruses such as severe fever with thrombocytopenia and heartland viruses (family Phenuiviridae family)[1] have variably been considered as hemorrhagic fever viruses, thereby highlighting the extreme heterogeneity and perhaps increasing ambiguity of this categorization. All implicated viruses are single-stranded lipid-enveloped RNA viruses with small genomes (10 to 19 kilobases) that can be relatively easily inactivated in the environment.

EPIDEMIOLOGY

Maintenance in Nature and Transmission to Humans

With the exception of dengue virus, for which humans can now be considered the reservoir, all hemorrhagic fever viruses are zoonotic, maintained in nature in mammalian reservoirs that tend to be specific for each virus (see Table 351-1). Although viral hemorrhagic fevers collectively can be found worldwide, the endemic area of any given hemorrhagic fever virus is usually smaller than the extent of its natural reservoir or arthropod vector. With the exception of dengue, yellow fever, and some hantaviruses, human infection is generally infrequent and humans are usually dead-end hosts.

Depending upon the virus, primary transmission to humans may be from contact with infected animal excreta or other body fluids or from the bite of an arthropod vector. Infection may occur through direct exposure of mucous membranes or broken skin to the infected blood or excreta of an animal reservoir, which usually occurs inadvertently or, in the case of the flaviviruses and most of the bunyaviruses, by the bite of an arthropod vector. Transmissibility between humans and pathogenicity vary with the specific virus and sometimes even among strains of the same virus. The infectious dose for most hemorrhagic fever viruses appears to be low, sometimes on the order of just a few virions. Airborne transmission is not a predominant mode of spread, if it occurs at all; however, studies in nonhuman primates show that transmission of many hemorrhagic fever viruses is possible through artificially created aerosols, thereby raising the possibility of their potential use as bioweapons (Chapter 19).

Bat-Borne Viruses

The filoviruses (from the Latin *filo*, "thread," referring to their filamentous shape), Marburg and Ebola, are perhaps the most feared of all hemorrhagic fever viruses.[2,3] Fruit bats appear to be the filovirus reservoir, although more conclusive evidence is needed for Ebola virus, with transmission to humans likely from exposure to infected bat excreta or saliva. Nonhuman primates, especially gorillas and chimpanzees, and other wild animals may become infected, presumably from similar bat exposure, and transmit filoviruses to humans through contact with blood and body fluids of these animals, usually in association with hunting. Nonhuman primates, which are also dead-end hosts who develop severe and usually fatal disease similar to that seen in humans, may be easier prey for hunters when sick. Because hemorrhagic fever viruses are rapidly inactivated by heating, infection probably occurs by exposure during butchering and preparation, rather than by consumption of cooked meat. The 2013 to 2016 outbreak of Ebola virus disease in West Africa dwarfed all prior Ebola outbreaks combined, with a reported 28,616 cases and 11,310 deaths. Sporadic outbreaks continue to occur in the Democratic Republic of the Congo, West Africa, and Uganda, either through primary infection from wild animals or renewed secondary infection from persistently infected humans (see later).

Rodent-Borne Viruses

Arenaviruses (from the Latin *arena*, "sand") are divided into Old World (or lymphocytic choriomeningitis/Lassa) and New World (or Tacaribe) complexes. Lassa and Lujo viruses are found in Africa, whereas Junín, Machupo, Guanarito, Sabiá, and Chapare viruses are found in South America. Although there may be subtle differences among the syndromes produced by the New World arenaviruses, they are usually grouped together simply as the South American hemorrhagic fevers.

The genus Hantavirus of the Bunyaviridae family is similarly divided into Old and New World complexes. The Old World hantaviruses, such as Hantaan, Seoul, and Puumala, among many others, classically cause hemorrhagic fevers with prominent renal involvement across Europe and Asia. New World hantaviruses, such as Sin Nombre and Andes, among many others, cause hantavirus pulmonary syndrome, sometimes also called hantavirus cardiopulmonary syndrome to emphasize the significant cardiogenic component of this disease.

Pathogenic arenaviruses and hantaviruses are maintained in nature through chronic subclinical infection in rodents of the Muridae family, with a strict pairing between the specific virus and rodent species. Transmission between rodents may be by vertical or horizontal transmission or both, depending on the specific virus. Transmission to humans occurs through exposure to rodent excreta, either from aerosols produced when rodents urinate or by direct inoculation to the mucous membranes, although the precise modes of transmission remain to be elucidated. Secondary aerosol generation is notoriously inefficient, so disturbing shed urine is a less likely mechanism of infection. In West Africa, Lassa virus is sometimes contracted when rodents are trapped and prepared for consumption or, more rarely, through a rodent bite. Experimental data suggest that humans may also be infected with arenaviruses by the oral route.

The rodents that transmit Lassa, Machupo, and many of the Old World hantaviruses commonly invade the peridomestic environment, thereby putting housewives, children, and others who spend time at home at risk. In contrast, the reservoirs for Junín and Guanarito viruses, as well as most

ABSTRACT

Viral hemorrhagic fever is an acute systemic febrile syndrome caused by over 30 viruses from four different virus families, although not all infections result in the syndrome. Microvascular instability with capillary leak and impaired hemostasis are the pathogenic hallmarks, but the mechanisms that result in these phenomena vary widely, depending on the virus. The syndrome is characterized by a short incubation period (usually 1 to 2 weeks) followed by a rapidly progressive multisystem illness that typically persists for no longer than 2 weeks. Initial signs and symptoms are usually nonspecific and include fever, headache, and myalgia, followed rapidly by gastrointestinal symptoms (nausea, vomiting and diarrhea) and, in some cases, rash and neurologic involvement. Severe cases develop hemodynamic instability, bleeding, shock, and multiorgan system dysfunction. Case-fatality rates range from less than 1% to over 80% depending on the specific infecting virus. With the exception of dengue, the causative viruses are all zoonotic, with endemic areas limited to the distribution of their mammalian reservoirs and/or arthropod vectors. Imported cases are rare but increasingly reported. The initial nonspecific manifestations of the syndrome make clinical diagnosis of isolated cases challenging. Viral hemorrhagic fever should be considered in febrile patients with a compatible clinical syndrome and history of travel and exposure. Although many hemorrhagic fever viruses may be spread person-to-person via contact with infected body fluids, secondary attack rates are generally low when routine universal precautions are maintained. For added safety, specialized viral hemorrhagic fever precautions are warranted when a confirmed or highly suspicious index case is identified. Treatment of viral hemorrhagic fever is generally supportive, but recent clinical trials have shown promising results for the treatment of Ebola virus disease. The antiviral drug ribavirin may be indicated for Lassa and other arenavirus infections, although more definitive evidence of efficacy is needed. Safe and effective vaccines exists for yellow fever and have been recently approved for Ebola virus disease.

KEYWORDS

viral hemorrhagic fever
Ebola
Marburg
Lassa
hantavirus
Congo Crimean hemorrhagic fever
Argentine hemorrhagic fever

TABLE 351-1 PRINCIPAL VIRUSES CAUSING HEMORRHAGIC FEVER

FAMILY AND VIRUS	DISEASE	GEOGRAPHIC DISTRIBUTION OF DISEASE	PRINCIPAL RESERVOIR/ VECTOR	ANNUAL ESTIMATED CASES	CASE-TO-INFECTION RATIO	HUMAN-TO-HUMAN TRANSMISSIBILITY
FILOVIRIDAE						
Ebola virus	Ebola virus disease	Central and West Africa	Fruit bat?	—*	1 : 1	High
Marburg virus	Marburg virus disease	Sub-Saharan Africa	Egyptian fruit bat *(Rousettus aegyptiacus)*	—*	1 : 1	High
ARENAVIRIDAE†,‡						
Old World Group						
Lassa	Lassa fever	West Africa	Rodent: natal mastomys or multimammate rat *(Mastomys natalensis)*	50,000-100,000	1 : 5-10	Moderate
Lujo§	Lujo HF	Zambia	Unknown, presumed rodent	Unknown	Unknown	Moderate to high
New World Group						
Junín	Argentine HF	Argentine pampas	Rodent: corn mouse *(Calomys musculinus)*	≈100	1 : 1.5	Low
Machupo	Bolivian HF	Beni Department, Bolivia	Rodent: large vesper mouse *(Calomys callosus)*	≤50	1 : 1.5	Low
Guanarito	Venezuelan HF	Portuguesa State, Venezuela	Rodent: cane mouse *(Zygodontomys brevicauda)*	≤50	1 : 1.5	Low
Sabiá‖	Brazilian HF	São Paulo and Para States, Brazil	Unknown, presumed rodent	Unknown	1 : 1.5	Low?
Chapare¶	Chapare HF	Cochabamba and La Paz Departments, Bolivia	Unknown, presumed rodent	Unknown	Unknown	Unknown
BUNYAVIRIDAE†						
Old World Complex						
Hantaan, Seoul, Puumala, Dobrava-Belgrade, others	HF with renal syndrome	Hantaan: northeast Asia. Seoul: urban areas worldwide Puumala and Dobrava-Belgrade: Europe	Rodent Hantaan: striped field mouse *(Apodemus agrarius)* Seoul: brown or Norway rat *(Rattus norvegicus)* Puumala: bank vole *(Clethrionomys glareolus)* Dobrava-Belgrade: yellow-necked field mouse *(Apodemus flavicollis)*	50,000-150,000	Hantaan: 1 : 1.5 Others: 1 : 20	None
New World Complex						
Sin Nombre, Andes, Laguna Negra, others	Hantavirus pulmonary syndrome	Americas	Rodent Sin Nombre: deer mouse *(Peromyscus maniculatus)* Andes: long-tailed colilargo *(Oligoryzomys longicaudatus)* Laguna Negra: little laucha or small vesper mouse *(Calomys laucha)*	50,000-150,000	Sin Nombre: 1 : 1 Others: up to 1 : 20	None, except for Andes virus
Rift Valley fever	Rift Valley fever	Sub-Saharan Africa, Madagascar, Saudi Arabia, Yemen	Domestic livestock/ mosquitoes (sylvatic *Aedes* and others)	100-100,000*,**	1 : 100	None
Crimean-Congo HF	Crimean-Congo HF	Africa, Balkans, southern Russia, Middle East, India, Pakistan, Afghanistan, western China	Wild and domestic vertebrates/tick (primarily *Hyalomma* species)	≈500	1 : 1-2	High
FLAVIVIRIDAE						
Yellow fever	Yellow fever	Sub-Saharan Africa, South America up to Panama	Monkey/mosquito (*Aedes aegypti*, other *Aedes* and *Haemagogus* species)	5,000-200,000††	1 : 2-20	None
Dengue	Dengue HF	Tropics and subtropics worldwide	Human/mosquito (*A. aegypti* and *albopictus*)	100,000-200,000††	1 : 10-100, depending on age, previous infection, genetic background, and infecting serotype	None
Omsk HF	Omsk HF	Western Siberia	Rodent/tick (primarily *Dermacentor* and *Ixodes* species)	100-200	Unknown	Not reported

TABLE 351-1 PRINCIPAL VIRUSES CAUSING HEMORRHAGIC FEVER—cont'd

FAMILY AND VIRUS	DISEASE	GEOGRAPHIC DISTRIBUTION OF DISEASE	PRINCIPAL RESERVOIR/ VECTOR	ANNUAL ESTIMATED CASES	CASE-TO-INFECTION RATIO	HUMAN-TO-HUMAN TRANSMISSIBILITY
Kyasanur Forest disease	Kyasanur Forest disease	Karnataka state, India; Yunnan Province, China; Saudi Arabia	Vertebrate (rodents, bats, birds, monkeys, others)/ tick (*Haemaphysalis* species and others)	≈500	Unknown	Not reported, but laboratory infections have occurred
Alkhumra HF‡‡	Proposed name: Alkhumra HF	Saudi Arabia, Egypt	Ticks?	≤50	Unknown	Not reported

*Although some endemic transmission of the filoviruses (Ebola virus > Marburg virus) and Rift Valley fever virus occurs, these viruses are most often associated with outbreaks.
†The virus families *Arenaviridae* and *Bunyaviridae* are serologically, phylogenetically, and geographically divided into Old World (i.e., Africa and Asia) and New World (i.e., the Americas) complexes.
‡In addition to the arenaviruses listed in the table, Flexal and Tacaribe viruses have caused human disease as a result of laboratory accidents. Another arenavirus, Whitewater Arroyo, has been noted in sick persons in California, but its role as a pathogen has not been clearly established.
§Only five cases (four of them fatal) from one outbreak in 2008 have been noted. The index case came to South Africa from Zambia.
‖Only five cases (three fatal) have been noted, two of them from laboratory accidents.
¶Discovered from a small outbreak in 2003 from which blood was obtained from one fatal case and Chapare virus isolated. Few other details have been reported. A cluster of five cases, three fatal, occurred on the outskirts of La Paz, Bolivia, in 2019.
**Although Rift Valley fever virus can be found throughout sub-Saharan Africa, large outbreaks usually occur in East Africa's Rift Valley region.
††Based on estimates from the World Health Organization. Significant underreporting occurs. Incidence may fluctuate widely in place and time.
‡‡Alkhumra is considered by some to be a variant of Kyasanur Forest disease virus. Disagreement exists over the proper spelling of the virus, written as Alkhurma in some publications.
HF = hemorrhagic fever.

of the New World hantaviruses, typically inhabit agricultural fields, wood lots, or other rural habitats, thereby putting outdoor workers, campers, and hikers at risk.

Mosquito-Borne Viruses

Rift Valley fever virus is maintained in domestic livestock, such as cattle, buffalo, sheep, goats, and camels, in which it often provokes spontaneous abortion. The virus may be transmitted to humans by direct exposure to these animals, especially during parturition, or by mosquitoes. Farmers, abattoir workers, and veterinarians are at particular risk.[4]

Yellow fever virus is maintained in a cycle between monkeys and forest canopy mosquitoes. Sporadic cases occur when humans are bitten by these mosquitoes, known as the sylvatic or jungle cycle. Larger outbreaks occur when humans bring the virus back to more settled environments, where the urban mosquito *Aedes aegypti* can spread the virus directly between humans (the urban cycle). *Aedes aegypti*, which typically lay eggs in artificial containers around the home and bite during the day, become infective a few weeks after feeding on a viremic monkey or human. An estimated 90% of infections occur on the African continent,[5] but large outbreaks have also been seen in South America in recent years, thereby prompting mass vaccination campaigns of millions of people and occasionally resulting in exported cases. Although *Aedes aegypti*, mosquitoes are commonly found across Asia, the Pacific, and Australia, endogenous transmission of yellow fever virus has never been recorded in these locations for unknown reasons.

Although nonhuman primates are also a reservoir for sylvatic strains of dengue, the virus is now adapted and maintained in humans, with a regular transmission cycle akin to that of urban yellow fever. Dengue virus is found in the tropics and subtropics nearly worldwide. The incidence of infection has grown dramatically in recent decades, especially in Asia and Latin America. Less than 10% of infected persons develop hemorrhagic fever, primarily children between the ages of 4 and 12 years.

Tick-Borne Viruses

The viruses that cause Crimean-Congo hemorrhagic fever,[6] Omsk hemorrhagic fever, Kyasanur Forest disease, and Alkhumra hemorrhagic fever are maintained in small mammals, such as rodents, hares, and hedgehogs, among which the viruses are spread by ticks. Humans are infected either by tick bites or by exposure to contaminated blood or excreta of the reservoir animals. Ticks also spread Crimean-Congo hemorrhagic fever virus to large mammals, including cattle and other domestic livestock, whose transient and asymptomatic viremia puts farmers, abattoir workers, and veterinarians at risk.

Human-to-Human Transmission

Secondary human-to-human transmission occurs with many of the hemorrhagic fever viruses (see Table 351-1), but attack rates are generally low (less than 15% for Ebola Zaire virus) because transmission between humans requires direct contact with contaminated blood or body fluids. Nevertheless, as evidenced by the massive 2013 to 2016 outbreak of Ebola virus disease in West Africa, the risk of transmission can increase significantly when many sick patients overwhelm fragile health systems and infection prevention and control measures break down, especially when health care workers are insufficiently trained and equipped. Human-to-human transmission probably usually occurs through oral or mucous membrane exposure, most often in the context of providing care to a sick family member (community) or patient (nosocomial transmission). Funeral rituals that entail the touching of the corpse have been a major source of infection in some outbreaks. Infection through fomites cannot be excluded. In some cases, highly infectious "super spreaders" have been suspected, but there is no evidence for natural aerosol transmission between humans. Despite modern-day travel, imported cases of viral hemorrhagic fever remain infrequent and usually do not result in secondary transmission because of the more routinely maintained infection prevention and control practices in resource-rich countries.

With the exception of hantaviruses and some of the flaviviruses, infectivity parallels the clinical state; persons are most infectious late in the course of severe disease, when viral loads are high and patients shed virus into the environment through vomiting, diarrhea, and bleeding. The risk of transmission during the incubation period or from asymptomatic persons is negligible, although a case of Argentine hemorrhagic fever occurred after blood transfusion from a donor who was asymptomatic at the time the blood was taken.

PATHOBIOLOGY

Microvascular instability and impaired hemostasis are the pathobiologic hallmarks of viral hemorrhagic fever. However, not all infections lead to these conditions, which are seen only in a subset of patients at the severe end of the disease spectrum.[7]

With the exception of disease caused by the hantaviruses and some of the flaviviruses, the pathogenesis of viral hemorrhagic fever appears to be related to unchecked viremia, with most fatal cases failing to mount an effective immune response. In these diseases, infectious virus is cleared rapidly from the blood in survivors. In dengue, yellow fever, and hantavirus infections, by comparison, viral replication is usually controlled, and virus is cleared from the blood before the most severe phase of the disease. The unique process of antibody-mediated immune enhancement, in which secondary infection with a different dengue virus serotype is more severe than the primary one, may play a role in the pathogenesis of dengue hemorrhagic fever. Data from animal models suggest that cardiac inotropy may also be directly or indirectly inhibited in some viral hemorrhagic fevers, especially Lassa fever.

After inoculation, virus first replicates in dendritic cells and other local tissues, with subsequent migration to regional lymph nodes and then

dissemination through the lymph and blood monocytes to a broad range of tissues and organs, including the liver, spleen, lymph nodes, adrenal glands, lungs, and endothelium. Migration of tissue macrophages results in secondary infection of permissive parenchymal cells. During the acute illness, virus can be found in a wide variety of body fluids, including blood, saliva, stool, and breast milk.

The interaction of virus with immune cells, especially macrophages and endothelial cells, results directly or indirectly (through soluble mediators) in cell activation and the unleashing of an inflammatory and vasoactive process consistent with the systemic inflammatory response syndrome. The synthesis of cell surface tissue factor triggers the extrinsic coagulation pathway. Impaired hemostasis may entail endothelial cell, platelet, or coagulation factor dysfunction. Disseminated intravascular coagulopathy (DIC; Chapter 161) is frequently noted, especially with Ebola, Marburg, and Crimean-Congo hemorrhagic fever viruses.

Inflammatory cell infiltrates, which are usually mild, consist of a mix of mononuclear cells and neutrophils. In some viral hemorrhagic fevers, such as Ebola virus disease, virus replication and dissemination are facilitated by virus-induced suppression of the host adaptive immune response. Failure of the immune response to adequately respond appears to be a major determinant of severity in Lassa fever.

Tissue damage may be mediated through direct necrosis of infected cells or indirectly through apoptosis of immune cells, as seen in other forms of septic shock. A dysregulated and uncontrolled host immune response leads to end-organ damage, with the most affected organs varying with the virus (Table 351-2). For example, renal tubular necrosis and retroperitoneal edema are seen in hemorrhagic fever with renal syndrome, whereas interstitial pneumonitis and myocardial depression are the hallmarks of hantavirus pulmonary syndrome. The liver is particularly affected in yellow fever, with fatty degeneration, coagulative midzonal necrosis of hepatocytes, and the presence of Councilman bodies. The brain and meninges are particularly affected in Kyasanur Forest disease and Omsk hemorrhagic fever and often in the South American hemorrhagic fevers as well. Reticuloendothelial proliferation is seen in Kyasanur Forest disease, with marked erythrophagocytosis in the spleen.

CLINICAL MANIFESTATIONS

Viral hemorrhagic fever is seen in both genders and all age groups, with a spectrum from relatively mild or even asymptomatic infection to severe vascular permeability resulting in shock, multiorgan system failure, and death. Although the clinical presentation may differ for each viral hemorrhagic fever as the disease progresses, clinical manifestations do not permit clear distinctions in most cases, especially in the early phases of disease. Dengue and Rift Valley fever viruses cause a range of syndromes, including rash and central nervous system involvement (Chapter 352). Hemorrhagic fever occurs in a minority of infections with these viruses.

After an incubation period ranging from days to weeks, most patients present with nonspecific signs and symptoms that are difficult to distinguish from many other febrile illnesses (see Table 351-2), including fever, general malaise, anorexia, headache, chest or retrosternal pain, sore throat, myalgia, arthralgia, and lumbosacral pain.[8] Conjunctival injection or hemorrhage is frequent but is not accompanied by itching, discharge, or rhinitis, thereby helping to distinguish it from viral conjunctivitis (Fig. 351-1). Relative bradycardia (Faget sign) and orthostatic hypotension may be noted, especially in yellow fever and dengue virus infections. The pharynx may be erythemic or, less frequently, exudative, especially in Lassa fever, and incorrectly lead to a diagnosis of streptococcal pharyngitis or mononucleosis. Hiccups are often seen in Ebola virus disease, although the pathogenesis of this manifestation is unclear.

After the first few days, gastrointestinal signs and symptoms readily ensue, including nausea, vomiting, epigastric and abdominal pain, abdominal tenderness, and nonbloody diarrhea or constipation. A misdiagnosis of appendicitis or other acute abdominal emergency (Chapter 128) sometimes prompts potentially hazardous surgical interventions.

Neck pain and stiffness, retro-orbital pain, photophobia, and other meningeal signs are common in Rift Valley fever, Kyasanur Forest disease, and Omsk hemorrhagic fever. A dry cough, sometimes accompanied by a few scattered rales on auscultation, is common, but prominent pulmonary symptoms are uncommon early in the course of the disease, except with hantavirus pulmonary syndrome. With the exception of yellow fever, jaundice is not typical except in patients with underlying Gilbert syndrome, drug reactions, or coinfection. Hepatosplenomegaly is frequent, but whether it is specific to the viral hemorrhagic fever or simply represents the high underlying prevalence of hepatosplenomegaly in populations in sub-Saharan Africa is unknown.

Various forms of rash, including morbilliform, maculopapular, petechial, and ecchymotic, may be seen (see Table 351-2). A maculopapular rash on the torso or face may be one early and relatively specific but insensitive indicator of Ebola or Marburg virus disease. Rash almost always occurs in fair-skinned persons with Lassa fever and Lujo hemorrhagic fever but, for unclear reasons, rarely in Blacks.

Hemorrhage is almost never present in the first few days of illness. In severe cases, however, patients progress after 7 to 10 days of illness to vascular instability, which may be manifested by conjunctival injection and hemorrhage, facial flushing, edema, bleeding, hypotension, shock, and proteinuria. Facial and neck swelling are classic and relatively specific signs of Lassa fever and Lujo hemorrhagic fever.

Sophisticated surveillance and detection methods show that clinically discernable bleeding occurs in a minority of cases, and the likelihood of hemorrhage varies with the infecting virus (see Table 351-2). Hemorrhage may be manifested as hematemesis, melena, hematochezia, metrorrhagia, petechiae, purpura, epistaxis, and bleeding from the gums and venipuncture sites (Fig. 351-2). Hemoptysis and hematuria are infrequent. Large ecchymoses are characteristic of Crimean-Congo hemorrhagic fever.

Central nervous system manifestations, including delirium, tremor, gait anomalies, convulsions, and hiccups, may be noted in end-stage disease, especially in Kyasanur Forest disease, Omsk hemorrhagic fever, and the South American hemorrhagic fevers, particularly Argentine hemorrhagic fever. Nevertheless, the cerebrospinal fluid findings are usually normal, with the exception of patients who have meningoencephalitis due to Kyasanur Forest disease or Omsk hemorrhagic fever, in which an elevated protein level is common.

Pancreatitis is often seen in severe yellow fever. Renal insufficiency or failure, which is common especially in hemorrhagic fever with renal syndrome, Lassa fever, and Ebola virus disease, is associated with a poor prognosis.

Biphasic illnesses are classically noted for the flavivirus hemorrhagic fevers, in which a quiescent period of days (yellow fever, dengue hemorrhagic fever, and Rift Valley fever) to weeks (Kyasanur Forest disease and Omsk hemorrhagic fever) precedes the most severe manifestations, including hemorrhage, shock, renal failure, and meningoencephalitis. Distinct progressive phases are classically described for hemorrhagic fever with renal syndrome (prodrome, hypotension, oliguria/renal failure, diuresis, and convalescence) and yellow fever (infection, intoxication, recovery) but are not seen in all cases. The initial manifestations for hantavirus pulmonary syndrome may be mild and nonspecific, but the disease may progress to require mechanical ventilation and pressor support within 24 hours. Sinus bradycardia and ventricular tachycardia or fibrillation may occur. Encephalitis and retinitis may develop in Rift Valley fever independently of the presence or absence of viral hemorrhagic fever.

Bilateral noncardiogenic interstitial pulmonary edema consistent with the adult respiratory distress syndrome (ARDS) is the hallmark of hantavirus pulmonary syndrome, although chest radiographs may be normal early in the disease even when the patients complain of shortness of breath. Only about 30% of patients with hantavirus pulmonary syndrome have radiographic evidence of pulmonary edema on initial evaluation, although it develops in virtually all persons within 48 hours.

Pregnant women with viral hemorrhagic fever usually present with severe disease, including spontaneous abortion and vaginal bleeding. However, initially mild symptoms that nevertheless progress to severe and even fatal disease have been noted, perhaps because the immune tolerance of pregnancy dampens the initial inflammatory clinical manifestations.

DIAGNOSIS

Because of their associated severity, risk of secondary spread, high degree of public scrutiny, and unfamiliarity to most physicians, consultation with a specialist who has experience with viral hemorrhagic fevers should be sought as soon as the diagnosis is considered. When to "sound the alarm" of viral hemorrhagic fever is a case-by-case decision left to the treating physician in consultation with experts in the field. Most viral hemorrhagic fevers are rare, and routinely practiced universal precautions are protective in most cases, at least in the early phases of disease.

TABLE 351-2 PATHOBIOLOGIC AND CLINICAL ASPECTS OF VIRAL HEMORRHAGIC FEVERS

DISEASE	INCUBATION PERIOD (DAYS)	ONSET	BLEEDING	RASH	JAUNDICE	HEART	LUNG	KIDNEY	CENTRAL NERVOUS SYSTEM	EYE	CASE-FATALITY RATIO	CLINICAL MANAGEMENT
FILOVIRIDAE												
Ebola virus disease	3-21	Variable	++	+	+	+	+	+	+	++*	40-85%†	Monoclonal antibodies
Marburg virus disease	3-21	Abrupt	++	+	+	+	+	+	+	++	22-85%‡	Supportive
ARENAVIRIDAE												
Lassa fever	5-16	Gradual	+	+§	0	++	+	++	+	0	20%	Ribavirin
Lujo HF	9-13	Abrupt	++	+	0	?	+	+	+	0	80%	Ribavirin
South American HF‖	4-14	Gradual	+++	+	0	++	+	0	+++	0	15-40%	Ribavirin, convalescent plasma
BUNYAVIRIDAE												
HF with renal syndrome	9-35	Abrupt	+++	0	0	++	+	+++	+	0	<1-50%, depending on specific virus	Ribavirin
Hantavirus pulmonary syndrome	7-35	Gradual	0 (except for Andes virus infection)	0	0	+++	+++	+	+	0	<1-50%, depending on specific virus	Supportive, consider high volume hemofiltration and ECMO
Rift Valley fever¶	2-5	Abrupt	++	+	++	+?	0	+	++	++	Up to 50% in severe forms	Ribavirin?
Crimean-Congo HF	1-12**	Abrupt	+++	0	++	+?	+	0	+	0	15-30%	Ribavirin?
FLAVIVIRIDAE												
Yellow fever	3-6	Abrupt	+++	0	+++	++	+	++	++	0	20-50%	Supportive
Dengue HF	3-15	Abrupt	++	+++	+	++	+	0	+	0	Untreated: 10-15% Treated: ≤1%	Supportive
Omsk HF	3-8	Abrupt	++	0	0	+	++	0	+++	+	1-3%	Supportive
Kyasanur forest disease	3-8	Abrupt	++	0	0	+	++	0	+++	+	3-5%	Supportive
Alkhumra HF††	3-8	Abrupt	++	+	+	+	+	0	++	+	20-25%	Supportive

*Potentially sight-threatening uveitis, early cataract formation, and other ocular sequelae are noted in up to one third of survivors.

†Four species of Ebola virus are known to cause disease in humans, with varying associated case-fatality ratios during outbreaks: Zaire, 85%; Sudan, 55%; Bundibugyo, 40%; and Tai Forest (formerly Côte d'Ivoire), 0% (only one recognized case, who survived).

‡The case-fatality ratio was 22% in the first recognized outbreak of Marburg virus disease in Germany and Yugoslavia in 1967 but has been consistently above 80% in outbreaks in central Africa, where the virus is endemic. Possible reasons for this discrepancy include differences in quality of care, strain pathogenicity, route and dose of infection, underlying prevalence of immunodeficiency and comorbid illnesses, and genetic susceptibility.

§A morbilliform or maculopapular rash almost always occurs in persons with lighter skin, who are usually expatriates, but for unclear reasons is rarely present in darker-skinned Africans from the endemic area.

‖Data are insufficient to distinguish between the syndromes produced by the various arenaviruses found in the Americas. They are thus frequently grouped as the South American hemorrhagic fevers.

¶Hemorrhagic fever, encephalitis, and retinitis may be seen in Rift Valley fever independently of each other.

**The incubation period of Crimean-Congo HF varies with the mode of transmission: typically 1 to 3 days after tick bite and 5 to 6 days after contact with infected animal blood or tissues.

††Based on preliminary observations. Fewer than 100 cases have been reported.

ECMO = extracorporeal membrane oxygenation; HF = hemorrhagic fever; 0 = sign not typically noted/organ not typically affected; + = sign occasionally noted/organ occasionally affected; ++ = sign commonly noted/organ commonly affected; +++ = sign characteristic/organ involvement severe.

The early nonspecific presentation of viral hemorrhagic fevers makes them extremely difficult to diagnose clinically, especially outside of the setting of a recognized outbreak, which is usually detected when clusters of cases occur, especially when they involve health care workers. The differential diagnosis includes a broad array of febrile illnesses that varies by geographic region (Table 351-3). A complete epidemiologic history (including details of travel, possible exposures, and occupational risks), details of the evolution of symptoms, physical examination, and preliminary basic laboratory results (Table 351-4) are critical.

A diagnosis of viral hemorrhagic fever should be considered in patients with a clinically compatible syndrome who, within the incubation period for the particular viral hemorrhagic fever in question, (1) reside in or traveled to an endemic area (see Table 351-1); (2) had potential direct contact with blood or body fluids of someone who was ill with an acute viral hemorrhagic fever, such as health care workers, persons caring for family members at home or preparing bodies for burial, and laboratory personnel; (3) had contact with live or recently killed wild animals (especially nonhuman primates) in or recently arriving from an area where a viral hemorrhagic fever is endemic (although direct contact with the animal reservoir is not usually reported even in confirmed cases); (4) worked in a laboratory or animal facility where hemorrhagic fever viruses are handled; or (5) had unprotected sex with a male who recovered from a viral hemorrhagic fever in the prior 18 months, unless his semen has been tested by polymerase chain reaction (PCR) and confirmed negative.

The index of suspicion should be especially high for persons in specific high-risk occupations, including health care workers, abattoir workers, veterinarians, farmworkers, hunters, taxidermists, and travelers who have recently returned from endemic areas, especially if an ongoing or recent outbreak

FIGURE 351-1. Subconjunctival hemorrhage and facial swelling in a boy with Lassa fever in Sierra Leone.

FIGURE 351-2. Bleeding in a patient with Ebola virus disease. (From Bausch DG. Viral hemorrhagic fevers. In: Schlossberg D, ed. *Clinical Infectious Disease*. New York: Cambridge University Press; 2008.)

has been reported.[9] ARDS (Chapter 90) or other respiratory compromise in a person living in an endemic area for New World hantaviruses should prompt consideration of hantavirus pulmonary syndrome. Risk of tick infection, including physical examination for an eschar, should be assessed if a tick-borne viral hemorrhagic fever is suspected. However, most viral hemorrhagic fevers are rare even in persons possessing one of the risk factors, so alternative diagnoses should always be aggressively sought, especially endemic malaria and typhoid fever, but also other bacterial diseases, including gram-negative sepsis (Chapter 94). Acts of bioterrorism (Chapter 19) must be considered if viral hemorrhagic fever is strongly suspected in a patient without any of the aforementioned risk factors, especially if clusters of cases occur. All cases should be immediately reported to local, state, and federal health authorities.

Laboratory Testing

Prompt laboratory confirmation, preferably using PCR assays on blood specimens, is imperative.[10] PCR assays generally have sensitivities and specificities greater than 90%, although very few have been subject to formal product validation. Robust semi-automated cartridge-based assays may be useful for some viral hemorrhagic fevers during outbreaks, but their cost is generally prohibitive for routine surveillance. Some hemorrhagic fever viruses, such as Lassa, have considerable sequence heterogeneity, so false-negative PCR results can occur owing to primer-target mismatch. False-negative results may also occur if a patient is tested very early in the course of disease when virus levels may still be below the threshold of detection. If viral hemorrhagic fever is still suspected despite a negative test, the patient should be monitored, treated empirically as needed, and, if still ill, retested a few days later when, with the exception of flavivirus infections, the viral load would normally have risen to a detectable level. Unbiased high-throughput sequencing may be helpful if PCR is repeatedly negative.

Enzyme-linked immunosorbent assays for viral antigen and immunoglobulin M antibody, virus culture, and immunohistochemistry on postmortem tissues also generally have sensitivities and specificities greater than 90%, although serologic diagnosis of flavivirus infection is complicated by cross-reactions. Rapid antigen tests for Ebola virus disease have been used effectively for community surveillance of cadavers.[11] In the United States, viral hemorrhagic fever testing can be arranged through the Centers for Disease Control and Prevention (phone 470-312-0094; email spather@cdc.gov).

TREATMENT

The rarity of most viral hemorrhagic fevers and their typical occurrence in remote and resource-poor settings make controlled studies difficult. Treatment guidelines generally follow those recommended for septic shock (Chapter 94). Consensus guidelines for supportive care for Ebola virus disease include isolation in an intensive care unit where close monitoring and critical supportive care can be provided.[12,13]

Clinical Management Guidelines

Fluid and Electrolyte Management

Severe microvascular instability, often complicated by vomiting, diarrhea, and decreased fluid intake, typically requires aggressive fluid replacement and or vasopressor support to prevent shock and dangerous electrolyte imbalances (see Chapter 94). In some cases, voluminous diarrhea may be similar to that seen in cholera (Chapter 278). Most patients require intravascular fluid administration, with careful monitoring to avoid third-spacing and pulmonary edema, especially in hantavirus pulmonary syndrome.

Blood Products and Management of Disseminated Intravascular Coagulation

Blood products should not be given empirically but only to meet defined clinical and laboratory parameters in the face of clinically significant hemorrhage. Transfusions, preferably with packed red blood cells, should be used to maintain a hemoglobin concentration above 7.0 g/dL while avoiding volume overload, taking into account that chronic anemia due to malaria and malnutrition may be frequent in patients in certain geographic areas. Whole blood is a reasonable alternative if packed cells are not available.

The possibility of DIC (Chapter 161) should be assessed by the relevant laboratory parameters (see Table 351-4), such as D-dimer levels. Platelet transfusions are generally not given to patients with DIC unless serious hemorrhage is present. When given, the platelet count should generally rise by at least 5-10 $\times$ $10^3/\mu L$ per unit of platelets transfused, although the response may be less if there is ongoing DIC and platelet consumption. Impaired platelet aggregation may promote hemorrhage in some viral hemorrhagic fevers, especially Lassa fever, even when platelet counts are not drastically low. Transfusion of fresh-frozen plasma (FFP) (15 to 20 mL/kg) should be considered when bleeding is present and fibrinogen levels are less than 100 mg/dL. Fibrinogen concentrate (total dose of 2 to 3 g) or cryoprecipitate (1 U/10 kg) may be administered instead of FFP, although FFP has the theoretical advantage of containing all coagulation factors. Vitamin K (10 mg intravenously or orally on 3 consecutive days) may be given, especially if underlying malnutrition or liver disease is suspected. Folic acid has sometimes been added to prevent the detrimental effect of acute folate deficiency on platelet production, especially in malnourished patients, although the efficacy of this treatment is unknown.

TABLE 351-3 DIFFERENTIAL DIAGNOSIS OF THE VIRAL HEMORRHAGIC FEVERS

DISEASE	DISTINGUISHING CHARACTERISTICS AND COMMENTS
PARASITES	
Malaria	Classically shows paroxysms of fever and chills; hemorrhagic manifestations less common; malaria smears or rapid test result usually positive; coinfection (or baseline asymptomatic parasitemia) common; responds to antimalarials
Amebiasis	Hemorrhagic manifestations other than bloody diarrhea generally not seen; amebic trophozoites identified in the stool by microscopy or antigen assays; responds to antiparasitics
Giardiasis	Positive stool antigen test result or identification of trophozoites or cysts in stool; responds to antiparasitics
African trypanosomiasis (acute stages)	Especially the East African form; examination of peripheral blood smear/buffy coat may show trypanosomes
BACTERIA (INCLUDING SPIROCHETES, RICKETTSIA, EHRLICHIA, AND COXIELLA)	
Typhoid fever	Hemorrhagic manifestations other than bloody diarrhea generally not seen; responds to antibiotics
Bacillary dysentery (including shigellosis, campylobacteriosis, salmonellosis, and enterohemorrhagic *Escherichia coli* and others)	Hemorrhagic manifestations other than bloody diarrhea generally not seen; responds to antibiotics
Capnocytophaga canimorsus	Associated with dog and cat bites, typically in persons with underlying immunodeficiency, notably asplenic patients; responds to antibiotics
Meningococcemia	Bacterial-induced DIC may mimic the bleeding diathesis of VHF; bleeding within the first 24-48 hours after onset of illness and rapidly progressive illness typical; large ecchymoses typical of meningococcemia are unusual in the VHFs except for Crimean-Congo HF; rapid serum latex agglutination tests can be used to detect bacterial antigen in meningococcal septicemia; may respond to antibiotics (critical to administer early)
Staphylococcemia	Bacterial-induced DIC may mimic the bleeding diathesis of VHF; may respond to antibiotics
Septic abortion	History of pregnancy and positive pregnancy test
Septicemic or pneumonic plague	Bacterial-induced DIC may mimic the bleeding diathesis of VHF; large ecchymoses typical of plague are unusual in the VHFs except for Crimean-Congo HF; pneumonic plague may mimic hantavirus pulmonary syndrome; may respond to antibiotics
Streptococcal or Epstein-Barr virus pharyngitis	May mimic the exudative pharyngitis sometimes seen in Lassa fever
Tuberculosis	Hemoptysis of advanced pulmonary tuberculosis may suggest VHF, but tuberculosis generally has a much slower disease evolution
Tularemia	Ulceroglandular and pneumonic forms more common; responds to antibiotics
Acute abdominal emergencies	Appendicitis, peritonitis, and bleeding upper gastrointestinal ulcer
Pyelonephritis and post-streptococcal glomerulonephritis	May mimic HF with renal syndrome
Anthrax (inhalation or gastrointestinal)	Prominent pulmonary manifestations and widened mediastinum on chest radiograph in inhalation form; responds to antibiotics
Atypical bacterial pneumonia (*Legionella*, *Mycoplasma*, *Chlamydophila pneumoniae*, and *C. psittaci*, others)	May mimic hantavirus pulmonary syndrome; exposure to birds; symptoms often not present until late in the illness in psittacosis; responds to antibiotics
Relapsing fever	Recurrent fevers and influenza-like symptoms, with direct neurologic involvement and splenomegaly; spirochetes visible in blood while febrile; responds to antibiotics
Leptospirosis	Jaundice, renal failure, and myocarditis in severe cases; responds to antibiotics
Spotted fever group rickettsiae (including African tick bite fever, boutonneuse fever, Rocky Mountain spotted fever)	Incubation period of 7-10 days after tick bite, compared with 1-3 days in Crimean-Congo HF; necrotic lesions (eschar) typically seen at site of tick bite in some rickettsial diseases, whereas there may be only slight bruising at the bite site in Crimean-Congo HF; rash (if present) of rickettsial infection classically involves palms and soles
Q fever (*Coxiella burnetii*)	Broad spectrum of illness, including hepatitis, pneumonitis, encephalitis, and multisystem disease with bleeding; responds to antibiotics
Ehrlichiosis	Diagnosis by serology and PCR; blood film may be useful; responds to antibiotics
Melioidosis (*Burkholderia pseudomallei*)	Highest incidence in Southeast Asia and northern Australia; systemic febrile illness or pulmonary syndrome, sometimes with central nervous system involvement; responds to antibiotics
VIRUSES	
Influenza	Prominent respiratory component to clinical presentation; no hemorrhagic manifestations; influenza rapid test result may be positive; may respond to anti-influenza drugs
Arbovirus infection (including dengue and West Nile fever)	Encephalitis unusual but when present may mimic the VHFs with significant neurologic involvement (Kyasanur Forest disease, Omsk HF); usually less severe than VHF; hemorrhage not reported
Viral hepatitis (including hepatitis A, B, and E; Epstein-Barr; and cytomegalovirus)	Jaundice atypical in HF except yellow fever; test results for hepatitis antigens positive; fulminant infection resembling VHF may be seen in persons with underlying immune deficiencies
Herpes simplex or varicella-zoster	Fulminant infection with hepatitis (with or without vesicular rash); elevated transaminases and leukopenia typical; disseminated disease may be noted in otherwise healthy persons; poor response to acyclovir drugs unless recognized early
HIV/AIDS	Seroconversion syndrome or HIV/AIDS with secondary infections, especially septicemia
Measles	Rash may mimic that seen in early stages of some VHFs and may sometimes be hemorrhagic; prominence of coryza and upper respiratory symptoms in measles should help differentiate; vaccine preventable
Rubella	Rash may mimic that seen in early stages of some VHFs; usually a mild disease; vaccine preventable
Hemorrhagic or flat smallpox	Diffuse hemorrhagic or macular lesions; in contrast to the VHFs, the rash may involve the oral mucosa, palms, and soles; smallpox in the wild has been eradicated
Alphavirus infection (including chikungunya and o'nyong-nyong)	Joint pain typically a predominant feature
FUNGI	
Histoplasmosis	Pulmonary disease may mimic hantavirus pulmonary syndrome; recent entry into mines or caves

TABLE 351-3 DIFFERENTIAL DIAGNOSIS OF THE VIRAL HEMORRHAGIC FEVERS—cont'd

DISEASE	DISTINGUISHING CHARACTERISTICS AND COMMENTS
NONINFECTIOUS ETIOLOGIES	
Heat stroke	History for extreme heat exposure; absence of sweating; bleeding not typical, but DIC may occur
Idiopathic and thrombotic thrombocytopenic purpura (ITP/TTP)	Presentation usually less acute than in VHF; may have prominent neurologic symptoms in TTP; coagulation factors normal and DIC absent; often respond to corticosteroids (ITP) or plasma exchange (TTP)
Acute glaucoma	May mimic the acute ocular manifestations of Rift Valley fever
Hematologic malignant neoplasms (leukemia, lymphoma)	May resemble leukemoid reaction occasionally seen in HF with renal syndrome
Drug sensitivity or overdose	Stevens-Johnson syndrome and anticoagulant (warfarin) overdose
Industrial and agricultural chemical poisoning	Especially anticoagulants, although other symptoms of VHF absent
Hematoxic snake bite envenomation	History of snake bite

AIDS = acquired immunodeficiency syndrome; DIC = disseminated intravascular coagulopathy; HF = hemorrhagic fever; HIV = human immunodeficiency virus; PCR = polymerase chain reaction; VHF = viral hemorrhagic fever.

TABLE 351-4 INDICATED CLINICAL LABORATORY TESTS AND CHARACTERISTIC FINDINGS IN PATIENTS WITH VIRAL HEMORRHAGIC FEVER

TEST	CHARACTERISTIC FINDINGS AND COMMENTS
Leukocyte count	Early: moderate leukopenia (except for hantavirus infection, in which early leukocytosis with immunoblasts is classically noted) Later: leukocytosis with left shift; granulocytosis more suggestive of bacterial infection
Hemoglobin and hematocrit	Hemoconcentration (especially noted in hemorrhagic fever with renal syndrome and hantavirus pulmonary syndrome)
Platelet count	Mild to moderate thrombocytopenia
Electrolytes	Sodium, potassium, and acid-base perturbations, depending on fluid balance and stage of disease
BUN/creatinine	Renal failure may occur late in disease
Serum chemistries (AST, ALT, amylase, γ-glutamyltransferase, alkaline phosphatase, creatinine kinase, lactate dehydrogenase, lactate)	Usually increased, especially in severe disease; AST > ALT A lactate level >4 mmol/L (36 mg/dL) may indicate persistent hypoperfusion and sepsis. Lactate dehydrogenase is typically markedly increased in hantavirus pulmonary syndrome
Sedimentation rate	Normal or increased
Blood gas	Metabolic acidosis may be indicative of shock and hypoperfusion
Coagulation studies (PT, PTT, fibrinogen, platelets, D-dimer)	DIC common in Ebola, Marburg, Lujo virus, Crimean-Congo HF, and New World arenavirus infections
Urinalysis	Proteinuria common; hematuria may be occasionally noted. Sediment may show hyaline-granular casts and round cells with cytoplasmic inclusions
Blood culture	Useful early to exclude VHF and later to evaluate for secondary bacterial infection. Blood should be drawn before antibiotic therapy is instituted
Stool culture	Useful to exclude VHF (in favor of hemorrhagic bacillary dysentery)
Thick and thin blood smears	May aid in the diagnosis of blood parasites (malaria and trypanosomes), bacterial sepsis (meningococcus, *Capnocytophaga*, and anthrax), and ehrlichiosis. All negative in VHF unless coinfection
Rapid test, PCR, or other assay for malaria	Negative in VHF unless coinfection with malaria

ALT = alanine aminotransferase; AST = aspartate aminotransferase; BUN = blood urea nitrogen; DIC = disseminated intravascular coagulation; HF = hemorrhagic fever; PCR = polymerase chain reaction; PT = prothrombin time; PTT = partial thromboplastin time; VHF = viral hemorrhagic fever.

Oxygenation and Ventilation

In the early phases of disease and in the absence of iatrogenic pulmonary edema, most patients can be supported with oxygen administered by nasal cannula or face mask. The exception is hantavirus pulmonary syndrome, for which early endotracheal intubation and mechanical ventilation (Chapter 91) are often life-saving. In neurologically intact patients with hypoxemia, noninvasive positive-pressure ventilation may be a useful adjunct to passive oxygenation. When mechanical ventilation is required, lung-protective tidal volumes of 6 mL/kg of ideal body weight should be employed. High-volume hemofiltration[14] and extracorporeal membrane oxygenation have been used with apparent benefit in hantavirus pulmonary syndrome.

Antibiotics and Secondary Infection

Until a diagnosis of viral hemorrhagic fever can be confirmed, patients should be immediately covered with appropriate antibacterial or antiparasitic therapy, with specific consideration of malaria (Chapter 316), tick-borne rickettsial diseases (Chapter 302), and gram-negative sepsis (Chapter 94) as appropriate based on epidemiologic risk factors. Since translocation of gut bacteria to the blood stream is a concern, antimicrobial regimens should cover enteric organisms. These drugs should then be stopped when infection with a hemorrhagic fever virus is confirmed unless there is evidence of coinfection. Secondary bacterial infection should be suspected when symptoms persist or new fever appears after about 2 weeks of illness, a time when most viral hemorrhagic fevers either have resulted in death or are resolving.

Antiviral Therapy

The single monoclonal antibody MAb114 and the triple monoclonal antibody cocktail drug REGN-E83 significantly decrease mortality from acute hemorrhagic Ebola infections.[A1] However, data are available only for the Zaire species of the virus.

Ribavirin is recommended for Lassa fever, other arenavirus infections, and hemorrhagic fever with renal syndrome, but data in support of its use are limited, and this off-label use is not approved by the U.S. Food and Drug Administration (Table 351-5).[15] Results are mixed and consensus is lacking regarding ribavirin for Crimean-Congo hemorrhagic fever. In vitro data show activity against dengue, yellow fever, Rift Valley fever, and Omsk hemorrhagic fever viruses, but clinical studies have not been performed. The main side effects of intravenous ribavirin are a mild to moderate hemolytic anemia, which infrequently necessitates transfusion and disappears with cessation of treatment, and rigors when the drug is infused too rapidly.

Favipiravir, which is licensed in many countries to treat influenza, has shown efficacy in nonhuman primate models of Lassa fever but has not yet been studied in humans.[16] The Chinese drug chongcao shenkang has been reported to have benefit for hemorrhagic fever with renal syndrome.

Transfusion of appropriately titered convalescent plasma within the first 8 days of illness has been reported to reduce the case-fatality of Argentine hemorrhagic fever from 15 to 30% to less than 1%. However, this therapy has been associated with a convalescent phase neurologic syndrome characterized by fever, cerebellar signs, and cranial nerve palsies in 10% of treated patients. Animal studies show convalescent plasma to be efficacious in Lassa fever as well but only if it contains a high titer of neutralizing antibody and if there is a close antigenic match between the infecting viruses of the donor and recipient. Convalescent plasma also appears to be efficacious for Crimean-Congo hemorrhagic fever and Rift Valley fever, but no controlled data exist. A clinical trial of convalescent plasma for Ebola virus disease did not show efficacy.

TABLE 351-5 RIBAVIRIN THERAPY FOR VIRAL HEMORRHAGIC FEVER

INDICATION	ROUTE	DOSE*	INTERVAL
Treatment	IV†	30 mg/kg (maximum 2 g)	Loading dose, followed by:
	IV†	15 mg/kg (maximum 1 g)	every 6 hours for 4 days, followed by:
	IV†	7.5 mg/kg (maximum 500 mg)	every 8 hours for 6 days
Prophylaxis	PO	35 mg/kg (maximum 2.5 g)	Loading dose, followed by:
	PO	15 mg/kg (maximum 1 g)	every 8 hours for 10 days

*Pharmacokinetic and sensitivity testing for ribavirin has not been extensively performed for each viral hemorrhagic fever. The intravenous dose used is derived from that found efficacious in Lassa fever. Oral ribavirin has also been reported to be efficacious in many viral hemorrhagic fevers, especially for Crimean-Congo hemorrhagic fever, but few controlled data are available. Intravenous administration is strongly suggested whenever possible. The dose should be reduced in persons known to have a creatinine clearance of less than 50 mL/minute.

†The drug should be diluted in 150 mL of 0.9% saline and infused slowly.

IV = intravenous; PO = oral.

Various immune modulators, including ibuprofen, corticosteroids, anti–tumor necrosis factor-α, nitric oxide inhibitors, statins, and interleukins, have not shown conclusive benefit in the treatment of sepsis. In a small study, recombinant interleukin-2 reduced the degree of acute renal insufficiency in hemorrhagic fever with renal syndrome, but further studies are needed before it can be considered the standard of care. Corticosteroids (e.g., 200 mg intravenous hydrocortisone per day, divided into two to four daily doses or administered by continuous infusion) are recommended in viral hemorrhagic fevers only when adrenal insufficiency is strongly suspected, the target blood pressure is not maintained despite adequate fluid repletion and vasopressors, or cerebral edema is suspected.

Management of Pregnancy

Uterine evacuation in pregnant patients appears to lower maternal mortality and should be considered, given the extremely high maternal and fetal mortality associated with viral hemorrhagic fever.[17] However, this procedure must be performed with extreme caution because it can be considered high risk with regard to potential nosocomial transmission. Although it is technically contraindicated in pregnancy (U.S. Food and Drug Administration Category X), considering the very high maternal and fetal mortality, ribavirin should nevertheless be considered as a life-saving measure for the mother who has a viral hemorrhagic fever for which the drug is efficacious (see Tables 351-2 and 351-5). Recent experience following this approach in the management of patients with Lassa fever in Nigeria resulted in favorable outcomes.[18]

Pain Management and Other Considerations

Oral or parenteral acetaminophen, tramadol, other nonsteroidal non-opioid analgesics (see Table 26-4), or opiates (see Table 26-6) should be used as needed for pain control, adjusting as necessary for hepatic insufficiency. Use of salicylates and nonsteroidal anti-inflammatory drugs should be avoided because of the risk of bleeding. Prophylactic therapy for gastrointestinal stress ulcers with proton pump inhibitors or histamine H_2-receptor antagonists is recommended (see Table 124-1). Antiemetics, such as the phenothiazines, are frequently warranted. Seizures can usually be managed with standard medications (Chapter 372).

Discharge and Monitoring

Because the patient's clinical status and infectivity generally correlate with the level of viremia, patients who have recovered from their acute illness can safely be assumed to have cleared their viremia and can be discharged without concern of subsequent transmission, with the exception of the risk of sexual transmission (see later) and possible transmission to infants through breast milk in women infected during pregnancy. PCR testing may detect insignificant RNA for days or even weeks after clinical recovery, so discharge should not depend on a negative PCR test.

PREVENTION

Infection Prevention and Control

The patient should be placed in an isolated room with an antechamber, if possible, for gowning of health care personnel. It is prudent to place the patient in a negative airflow room if it is available, but hermetically sealed isolation chambers are not required. Insecticide-treated bed nets and room screens should be used in open-air settings to prevent transmission of arthropod-borne hemorrhagic fever viruses. Access to the patient should be limited to a small number of designated staff with specific training regarding infection prevention and control for viral hemorrhagic fevers. Although normal barrier nursing precautions to prevent parenteral and droplet exposure to blood and body fluids are usually adequate to prevent infection, specific enhanced protection measures, including personal protective equipment, are warranted if the diagnosis of viral hemorrhagic fever is suspected.[19] Other essential components of infection prevention and control include proper staff-to-patient ratios, waste disposal, and disinfection procedures. Small-particle aerosol precautions should be used when procedures such as endotracheal intubation may generate aerosols.[20]

Contact Tracing

The early nonspecific presentation of the viral hemorrhagic fevers poses a serious challenge to effective epidemiologic surveillance. Fortunately, the low secondary attack rates afford a measure of reassurance even when cases go unrecognized as long as proper barrier nursing is maintained. Furthermore, because mild cases, which may be still more difficult to recognize, are usually not very infectious, missed or delayed diagnosis of these patients is unlikely to pose a problem from an infection control standpoint.

Persons with unprotected direct contact with a patient during the symptomatic phase of a human-to-human communicable viral hemorrhagic fever should be monitored daily for evidence of disease for the duration of the longest possible incubation period, starting after their last contact (see Table 351-2). Given the generally low secondary attack rates, especially outside of caretakers, widespread contact tracing, laboratory testing, and postexposure prophylaxis are not indicated for casual contacts. Close contacts should check their temperature daily and record the results. Despite lack of evidence for transmission during the incubation period, it is usually recommended that exposed persons avoid intimate contact with household members that might result in exposure to body fluids, such as sex, kissing, and sharing of utensils, for the duration of the incubation period. Confinement of asymptomatic persons is not warranted, but persons who develop fever or other signs and symptoms suggestive of viral hemorrhagic fever should be immediately isolated until the diagnosis can be ruled out.

Vaccines

Vaccines for viral hemorrhagic fevers are at various stages of development. The 17D live attenuated yellow fever vaccine has a generally excellent protection and safety profile despite recognition of rare serious adverse events in elderly persons. In resource-limited settings, one-fifth of the standard dose appears to be equally effective.[A2] Confirmed previous vaccination with 17D should essentially exclude the diagnosis of yellow fever unless the patient was immunocompromised at the time of vaccination.

Two vaccines have recently received regulatory approval for infection by Zaire ebolavirus. The single dose recombinant vesicular stomatitis virus–Zaire Ebola virus vaccine (rVSV-ZEBOV) has high protective efficacy and has been used extensively in recent outbreaks to vaccinate exposed health care workers, close contacts of patients, and close contacts of the close contacts themselves.[A3] Adverse effects are frequent but mostly minor, but vaccine-induced arthritis, dermatitis, and vasculitis have been reported.[A4] Ad26.ZEBOV, MVA-BN-Filo, which is a heterologous two-dose vaccine given 56 days apart with minimal adverse effects, is principally designed for primary prevention.[21] Strategies on how both vaccines should be used for optimal effect are still being debated.[22] The duration of protection, the risks of breakthrough infections, and any need for boosters remains unknown.[23] Research is underway on vaccines that would confer protection against other ebolaviruses.[24]

The live attenuated vaccine Candid 1 is highly protective against Argentine hemorrhagic fever, but it is licensed only in Argentina. Candid 1 may also be effective in Bolivian hemorrhagic fever, but it does not appear to protect against other arenavirus infections.

A tetravalent vaccine for dengue virus infection unfortunately enhances the risk of severe disease in patients who have not been previously infected.[A5] The vaccine is now recommended only for children who have previously had dengue fever or for populations in which most people have been previously infected.[25] Experimental vaccines for hantavirus,[26] Crimean-Congo

hemorrhagic fever,[27] Lassa fever,[28] Marburg virus disease,[29] Rift Valley fever, Omsk hemorrhagic fever, and Kyasanur Forest disease may be efficacious, but most have not been widely tested and are not widely approved or available.

Postexposure Prophylaxis

Postexposure prophylaxis should be considered only in persons with distinct high-risk exposure, defined as follows: (1) penetration of skin by a contaminated sharp instrument (e.g., needlestick injury), (2) exposure of mucous membranes or broken skin to blood or body secretions (e.g., blood splashing in the eyes or mouth), (3) participation in emergency procedures without appropriate personal protective equipment (e.g., resuscitation after cardiac arrest, intubation, or suctioning), (4) prolonged (i.e., hours) and continuous contact in an enclosed space without appropriate personal protective equipment, and (5) unprotected sex with a male who recovered from a viral hemorrhagic fever in the prior 18 months, unless his semen has been tested and confirmed negative. The most infectious patients are those with severe clinical conditions, usually late in the course of illness. Prophylaxis should not be used when the only exposure was during the incubation period or after acute disease has subsided.

Although no data exist, it is reasonable to use the newly approved monoclonal antibody treatments for to Ebola virus disease as postexposure prophylaxis when a high-risk exposure occurs in an unvaccinated person.[30] Postexposure prophylaxis with oral ribavirin has been recommended for Lassa fever, other arenavirus infections, and Crimean-Congo hemorrhagic fever, although no systematic data are available on its efficacy, and the frequent minor adverse events sometimes can be mistaken for the early signs of disease. When used, oral ribavirin should be started immediately after the exposure but not before counseling between the patient and the physician. The drug should be taken with food. Baseline hemoglobin, hematocrit, bilirubin, and creatinine levels should be determined, and therapy should be adjusted or reconsidered if significant anemia or renal insufficiency develops.

Convalescent plasma is given as postexposure prophylaxis for Argentine hemorrhagic fever. Numerous experimental vaccines, monoclonal antibodies, and other compounds have shown efficacy as postexposure prophylaxis in animal models, but reliable data on their efficacy in humans are not available.

Reservoir and Vector Control

Avoiding contact with bats, primarily by avoiding entry into caves and mines in endemic areas, is a key prevention measure for Ebola and Marburg viruses. Personal protective equipment may be indicated for miners and other persons who work in these environments. Humans should also avoid exposure to fresh blood, body fluids, or meat of wild animals, especially nonhuman primates.

For rodent-borne viruses, whose reservoirs often colonize human dwellings, improved "village hygiene" is recommended, such as eliminating unprotected storage of garbage and foodstuffs and plugging holes that allow rodents to enter homes. Prevention of the mosquito-borne hemorrhagic fever viruses hinges on controlling *Aedes* mosquitoes in and around the home, primarily by elimination of clean standing water containers that serve as larval habitats and use of screened windows and doors, insecticide-treated bed nets, protective clothing, mosquito repellent, and aerosol bomb insecticides in enclosed spaces. Analogous measures can help protect against tick bites.

PROGNOSIS

Mild and asymptomatic cases of even the most virulent viral hemorrhagic fevers have a benign outcome. More severe viral hemorrhagic fevers typically evolve rapidly. In fatal cases, death usually occurs within 7 to 10 days after the onset of symptoms in filovirus infection and in about 2 weeks with arenaviruses and some of the other viruses. Death usually results not from exsanguination but rather from a process akin to septic shock (Chapter 94) when insufficient effective circulating intravascular volume leads to hypotension, cellular dysfunction, acute kidney and hepatic injury, respiratory failure, and metabolic and electrolyte derangements, often in the setting of systemic inflammation and cytokine abnormalities. Less commonly, meningoencephalitis, pancreatitis, rhabdomyolysis, and cardiac arrhythmias lead to a fatal outcome. Thrombotic coronary or cerebrovascular accidents related to thrombocytosis and a hypercoagulable state have been documented during early recovery after Ebola virus disease.

Common indicators of a poor prognosis include very young or old age, hemodynamic instability and shock, bleeding, neurologic manifestations, high levels of viremia (or surrogate measurements of antigen or genome copies), neutrophilia, elevated liver enzymes and serum creatinine levels,[31] and pregnancy, especially during the third trimester, during which maternal and fetal mortality may be above 90%. Elevated levels of the biomarkers plasminogen activator inhibitor-1 and soluble thrombomodulin portend a worse prognosis in Lassa fever.[32]

Modern supportive critical care has been associated with a substantial reduction in the mortality rate for Marburg and Ebola virus disease. Whether those benefits relate to the uncontrolled use of experimental therapies, better intensive care, genetic predisposition, or fewer comorbid conditions is unknown.

Sequelae

For Ebola virus disease, convalescence can be prolonged, often with a year or more of persistent arthralgia, ocular complications (including potentially sight-threatening uveitis that may result in early cataract formation), neurologic syndromes,[33] abdominal pain, extreme fatigue, anorexia, and mental health sequelae.[34] Ebola virus can persist for months or even years in immunologically protected tissue compartments, chambers of the eye, central nervous system, and in the fetus, placenta, and amniotic sac/fluid of women infected during pregnancy. Ebola virus RNA also has been detected in the semen over a year after acute disease, with evidence of rare male-to-female sexual transmission as long as 15 months after recovery. Remdesivir may reduce the presence of Ebola virus RNA in the semen of survivors,[35] but abstinence or safe sex with condoms is recommended for at least 1 year after recovery or until virus clearance from the semen can be confirmed by laboratory testing. Ebola virus RNA has been detected in the breast milk of survivors during both acute illness and convalescence, including in one case 500 days after recovery. Furthermore, Ebola virus RNA has been found in the breast milk of some lactating women in whom acute disease was never recognized.

Ebola virus can persist and rarely be associated with organ-specific inflammatory syndromes and recrudescent disease. In one example, detectable Ebola virus RNA in the blood of a previously vaccinated survivor at 6 months after recovery led to 91 secondary cases. Ebola virus has rarely been isolated from the anterior chamber fluid of the eye (associated with panuveitis) and from the cerebrospinal fluid (associated with meningoencephalitis) months after the onset of disease; such patients eventually cleared the virus and recovered, but secondary transmission can occur.

Lassa virus can persist in the semen of survivors.[36] Hearing loss, which may be permanent, is a common sequela in of survivors of Lassa fever[37] and has also been reported after Venezuelan hemorrhagic fever. It first appears during convalescence, may be unilateral or bilateral, and is not associated with severity of the acute disease or treatment with ribavirin. Optic retinopathy with vision loss has been noted in survivors of Rift Valley fever.

Management of the sequelae of viral hemorrhagic fever is generally supportive, with the exception of uveitis, for which urgent treatment with topical steroids and atropine may be sight-saving. Breast-feeding should be avoided during convalescence unless there is no other way to support the baby. Proper infection prevention and control precautions should be taken when attending all births to women who were infected with filoviruses during pregnancy.

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For the General References and other additional features, please visit Elsevier eBooks+ at https://ebooks.health.elsevier.com.

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352 ARBOVIRUSES CAUSING FEVER, RASH, AND NEUROLOGIC SYNDROMES

J. DAVID BECKHAM

COMMON FEATURES OF ARBOVIRUSES

DEFINITION

Zoonotic viruses (Chapter 303) in animal populations infect humans. An extremely large reservoir of known and unknown viruses represents important causes of described and emerging human infectious diseases. Modes of transmission include human contact with animal bodily fluids or excrement, bite wounds, and direct exposure to an animal carcass. However, many arthropods have evolved to utilize animal blood as a food source, and viruses have exploited this adaptation as a reliable method of transmission. Infectious viruses that are transmitted through arthropod vectors are termed arthropod-borne viruses (arboviruses).

PATHOBIOLOGY

Vector Transmission Cycles

Arboviruses are transmitted to humans most commonly from the bite of a mosquito or tick species. However, other vectors include sand flies (*Phlebotomus* spp) and biting midges (*Culicoides* spp). Arboviruses infect new vectors most commonly by feeding on an intermediate host, such as small rodents, avian species, or nonhuman primates. The animal host acts as an amplifying host for the virus and can transmit to uninfected vectors. Transovarial transmission from a female to eggs and cofeeding between infected and uninfected insect vectors can contribute to the population of infectious vectors. Many arboviruses also cause persistent infection in the vector, thereby allowing for survival over the winter and transmission over multiple seasons. In general, arboviruses often exist in an enzootic (animal) or sylvatic (jungle-based) cycle of transmission between the vector and an animal host. At times, the vectors may feed on a susceptible population, such as domestic animals (epizootic cycle), or feed on humans to cause an urban cycle or epidemic. If the amount of virus in the blood of infected domestic animals or humans is not high enough or sustained enough over time to support transmission to uninfected vectors, then the host acts as a dead-end or incidental host for the virus. The endemic cycle of an arbovirus between invertebrate and vertebrate hosts determines the geographic range and epidemiology of exposure for humans. As human populations continue to expand into new regions, sylvatic arboviruses that have not yet been identified will have opportunities to develop new epidemic cycles in human populations. Thus, arboviruses represent an important source of future emerging infectious diseases in human populations.

Phylogeny of Arboviruses

Arboviruses are RNA viruses that are largely grouped into three families of viruses (*Flaviviridae, Togaviridae*, and *Reoviridae)* and one virus order (Bunyavirales).

Flaviviridae

The *Flaviviridae* are icosahedral, enveloped viruses about 50 nm in diameter with 180 membrane and 180 envelope proteins arranged in antiparallel dimers on the surface of the viral particle. The capsid protein encloses a positive-sense, single-stranded RNA genome (about 11 kb) with a single open reading frame that has an upstream 5′ untranslated region, a 5′ m7GpppRNA cap structure, and a 3′ untranslated region with conserved RNA structure and no poly-A tail. Within the *Flaviviridae* family, the genus *Flavivirus* is divided into mosquito-borne, tick-borne, arthropod-specific, and unknown vector groups. The flaviviruses circulate between mosquito and tick species and specific mammalian hosts that include avian species, small mammals, nonhuman primates, and humans.

Togaviridae

The *Togaviridae* are lipid-enveloped viruses about 60 to 70 nm in diameter with a 5′ capped positive-sense RNA genome that is 11 to 12 kb in length with a poly-A tail. The nonstructural proteins are expressed from the first open reading frame, and a subgenomic promoter drives expression of the structural genes. The enveloped virus particle consists of E1 and E2 glycoproteins as heterodimers that then form trimers to make 80 spikes. The *Alphavirus* genus makes up many of the medically important arboviruses. All *Togaviridae* are transmitted by mosquito vectors, and individual viruses are generally divided into New World and Old World alphaviruses.

Reoviridae

Reoviridae, which include Colorado tick fever virus, are nonenveloped, double-stranded RNA viruses with a segmented genome. Colorado tick fever virus genome is relatively large (~29 kb) compared with other arboviruses and has an icosahedral capsid structure about 80 nm in diameter.

Bunyavirales

The Bunyavirales order consists of 9 viral families and 13 genera. The arboviruses of human significance are largely represented by the *Orthobunyavirus*, *Phlebovirus*, and *Orthonairovirus* genera. In general, the bunyaviruses are characterized by a spherical, enveloped virus particle that is about 80 to 120 nm in diameter and is decorated with two surface glycoproteins (Gc and Gn). The negative-sense or ambisense RNA genome is divided into three segments (L, M, and S). The L segment encodes the RNA-dependent RNA polymerase, the M segment encodes the viral glycoprotein precursors, and the S segment encodes the nucleocapsid proteins.

Infectious Process

Arboviruses are generally found in the salivary glands of the associated vector, where they arrive following replication in the midgut after a blood meal from an infected, amplifying host. In some cases, an invertebrate vector can also become infected from transovarial transmission, in which the female vector transmits virus to eggs, or by cofeeding when an infected vector feeds on a previously uninfected host at the same time as an uninfected vector. Once an infected vector bites a mammalian or avian host, the salivary gland excretion, which precedes feeding, allows the arbovirus to be distributed into the subcutaneous tissue of the host. The virus replicates locally in the dermal tissue, epithelial cells, endothelial cells, or local tissue-resident immune cells such as dendritic cells. Local replication results in viral spread to draining lymph nodes, which are the site of primary viral replication, and subsequent viremia that spreads the virus to target organs, including the spleen and liver. Spread to the spleen or liver can initiate a secondary viremia that can infect the central nervous system, the placenta, or joint tissues.

CLINICAL MANIFESTATIONS

Arboviruses vary in the rate that they cause disease in humans based on many factors, including age, immune status, comorbid conditions, and prior exposure history. Exposure to an arbovirus can result in a wide range of clinical outcomes, from asymptomatic infection to severe disease. Arboviruses can cause characteristic syndromes broadly defined as a fever/rash/myalgia syndrome or a meningitis encephalitis syndrome. Fever and rash in a returning traveler (Chapter 265) from an endemic area should raise suspicion for an arboviral infection.[1] Some arbovirus members that cause fever and myalgia can also cause hemorrhagic fever syndromes (Chapter 351; Table 352-1). Other arboviruses predominantly cause infections of the central nervous system (Table 352-2) but can also cause rashes.

For individuals that develop symptoms, the initial presenting symptoms can be protean, including fever, chills, myalgias, arthralgias, and neurologic symptoms. The only differentiating features may be the geography and surrounding epidemiology of the exposure. Even in a specific region, however, clinical presentations may overlap. For example, Chikungunya virus, dengue virus, and Zika virus can co-circulate using the same vector, or coinfections may occur from *Aedes agyepti* mosquitos infected with more than one pathogen.

DIAGNOSIS

Reverse transcription polymerase chain reaction (RT-PCR) is the preferred diagnostic test when patients have viremia or active virus in the cerebrospinal fluid (CSF). Since the onset of symptoms for most patients follows clearance of active viremia, however, most patients will require virus-specific serologic testing for the presence of IgM or IgG antibodies, often with acute and convalescent titers to distinguish new infection from prior infection.[2] Many of the serologic tests used to diagnose arboviruses cross-react with co-circulating arboviruses, thereby making definitive diagnosis clinically challenging in some regions. For definitive diagnosis, virus-specific neutralizing antibody titer assays, often available through government laboratories, can help distinguish among individual arboviruses.

ABSTRACT

Arthropod-borne virus (arbovirus) infections cause a wide array of both endemic and epidemic human diseases throughout the world. With global climate change, the transmitting arthropods are rapidly expanding their geographic range. In general, arboviruses cause two predominant syndromes: fever with arthralgia/arthritis or predominantly neurologic symptoms. Some arboviruses that cause fever and arthralgia can also progress to produce hemorrhagic disease. The majority of arbovirus infections are caused by members of one of three families of viruses (*Flaviviridae, Togaviridae*, and *Reoviridae*) and one virus order (Bunyavirales). Recognition of the clinical syndrome, epidemiology, and diagnosis is essential to care for patients with potential arbovirus infections.

KEYWORDS

arbovirus
vector
zoonotic
myalgias
encephalitis
hemorrhagic

TABLE 352-1 ARBOVIRUS INFECTIONS CAUSING ARTHRALGIA AND MYALGIA SYNDROMES

VIRUS	TRANSMISSION CYCLE	GEOGRAPHIC DISTRIBUTION	CLINICAL SYNDROME	TREATMENT AND PREVENTION
TROPIC/SUBTROPICAL GLOBAL DISTRIBUTION				
Dengue *(Flaviviridae)*	Vector: *Aedes aegypti* Host: primates/humans	Global tropical distribution	Fever, headache, fatigue, myalgia, arthralgia, weakness	Vaccine
Chikungunya *(Togaviridae)*	Vector: *Aedes aegypti* Host: primates/humans	Global tropical distribution	Fever, myalgias, rash, arthralgias, arthritis, tenosynovitis	None
Zika *(Flaviviridae)*	Vector: *Aedes aegypti* Host: primates/humans	Global tropical distribution	Fever, chills, myalgias, rash, conjunctivitis	None
Yellow fever *(Flaviviridae)*	Vector: *Aedes* spp. Host: primates/humans	South America/Africa	Fever, chills, headache, nausea, vomiting, abdominal pain, jaundice	Vaccine
NORTH AMERICA				
Heartland *(Bunyavirales)*	Vector: *Amblyomma americanium* Host: unknown reservoir	Midwestern and Southern United States	Fever, headache, fatigue, myalgia, arthralgia, weakness	None
CENTRAL AND SOUTH AMERICA				
Mayaro *(Togaviridae)*	Vector: *Haemagogus* spp. Host: nonhuman primates	Central and South America	Fever, chills, headache, arthralgias, myocarditis	None
Tropical fever (Oropouche virus, *Bunyavirales*)	Vector: *Culicoides paranensis* biting midge Host: sloths, nonhuman primates	Central and South America	Mild febrile illness, myalgias, malaise; rare hemorrhagic disease	None
Bussuquara *(Flaviviridae)*	Vector: *Culex melanoconion* Host: small rodents	Central and South America	Fever, arthralgias	None
AFRICA				
O'nyong-nyong *(Togaviridae)*	Vector: *Anopheles* spp. Host: unknown host	Sub-Saharan Africa	Fever, headache, rash, conjunctivitis, large joint arthralgia, arthritis	None
Rift valley fever *(Bunyavirales)*	Vector: *Aedes* spp. and *Culex* spp. Host: wild ungulates and domesticated livestock	Sub-Saharan Africa	Fever, headache, myalgias, and severe disease with hepatitis and jaundice, hemorrhage	Vaccines for livestock to prevent epizootic outbreaks
EUROPE				
Sinbis *(Togaviridae)*	Vector: *Aedes* spp., *Culex* spp., and *Culiseta* spp. Host: bird species	Northern Europe, also in Russia, central Africa, Australia	Fever, macular rash, arthralgia of hands and small joints	None
Phlebotomus fever *(Bunyavirales)*	Vector: *Phlebotomus* spp. sandfly Host: unknown	Mediterranean area, western Europe, Turkey, Middle East, western India, Pakistan	Fever, rash, headache, photophobia, myalgia, arthralgia	None
ASIA				
Severe fever with thrombocytopenia syndrome virus *(Bunyavirales)*	Vector: *Haemaphysalis longicornis* tick Host: avian and small mammal species	Central and eastern Asia	Fever, myalgias, headache, arthralgia; can progress to bleeding diathesis	None
Crimean-Congo hemorrhagic fever *(Bunyavirales)*	Vector: *Hyalomma* spp. ticks Host: birds, small and large mammals	Asia, Africa, Middle East	Febrile illness, myalgia, vomiting and diarrhea; some progress to severe hemorrhagic disease	None
Omsk hemorrhagic fever *(Flaviviridae)*	Vector: *Dermacentor* spp. ticks Host: small mammals	Omsk, Kurgan and regions of western Siberia	Fever, headache, chills, vomiting, myalgia, photophobia, conjunctival suffusion; fatality rate < 3%	Tick-borne encephalitis vaccine may provide cross-protection
AUSTRALIA				
Ross River *(Togaviridae)*	Vector: *Aedes* spp. and multiple mosquito vectors Host: marsupials	Australia	Fever, rash, arthralgias, arthritis, myalgias	None
Edge Hill *(Flaviviridae)*	Vector: *Aedes* spp. and *Culex* spp. Host: marsupials	Australia	Fever and proximal joint arthritis	None

TABLE 352-2 ARBOVIRUS INFECTIONS CAUSING NEUROLOGIC SYNDROMES

VIRUS	TRANSMISSION	GEOGRAPHIC DISTRIBUTION	CLINICAL SYNDROME	TREATMENT AND PREVENTION
NORTH AMERICA				
West Nile *(Flaviviridae)*	Vector: *Culex* spp. mosquitoes Host: passerine birds	North America, South America, Africa, Europe, Middle East, Asia, Australia	Fever, myalgias, rash, nausea, vomiting, diarrhea, meningitis, paralysis, encephalitis	None
Powassan *(Flaviviridae)*	Vector: *Ixodes* spp. ticks Host: small mammals and white-tailed deer	North America	Fever, malaise, myalgia, nausea, rash, meningitis, encephalitis	None
Eastern equine encephalitis *(Togaviridae)*	Vector: *Culiseta melanura* mosquito Host: bird species	East coast and upper Midwest United States	Fever, chills, malaise, myalgias, arthralgias, meningitis, encephalitis	None
St. Louis encephalitis *(Flaviviridae)*	Vector: *Culex* spp. Host: avian species	Continental United States	Fever and myalgias, meningitis, encephalitis	None
Western equine encephalitis *(Togaviridae)*	Vector: *Culex tarsalis* mosquitoes Host: avian species	North America, rare cases	Fever, myalgias, meningitis, encephalitis	None
California encephalitis group *(Bunyavirales)*	Vector: *Aedes* spp. mosquitoes Host: small mammals	North America	Fever, chills, nausea, vomiting, myalgias, seizures, encephalitis	None
Colorado tick fever *(Reoviridae)*	Vector: *Dermacentor andersoni* tick Host: small mammals and rodents	North America, mountain west	Biphasic fever, chills, headache, myalgias, abdominal pain, rash, meningitis	None
CENTRAL AND SOUTH AMERICA				
Venezuelan equine encephalitis *(Togaviridae)*	Vector: *Culex, Aedes, Mansonia, Psorophora* spp. mosquitoes Host: rodents/small mammals	Central and South America	Fever, malaise, chills, myalgia, headache, encephalitis ataxia, seizures, paralysis	No licensed vaccine
Rocio *(Flaviviridae)*	Vector: *Psorophora* spp. mosquitoes Host: birds	Brazil and South America	Fever, headache, malaise, conjunctivitis; 30% of cases develop meningitis, encephalitis; 10% mortality	None
AFRICA				
Usutu *(Flaviviridae)*	Vector: *Culex pipiens* mosquitoes Host: avian species	Africa and Europe	Fever and myalgias, meningitis, encephalitis	None
EUROPE				
Tick-borne encephalitis *(Flaviviridae)*	Vector: *Ixodes* spp. ticks Host: mammals, livestock	Eastern Europe and northern Asia	Fever, myalgias, meningitis, encephalitis, poliomyelitis	Four vaccines available in endemic regions
Louping ill *(Flaviviridae)*	Vector: *Ixodes* spp. ticks Host: small rodents	Europe and Asia	Fever, myalgias, fatigue, meningitis, encephalitis	None
Toscana *(Bunyavirales)*	Vector: *Phlebotomus* spp. sandfly Host: unknown reservoir	Mediterranean Europe	Fever, headache, myalgias, meningitis, encephalitis	None
ASIA				
Japanese encephalitis *(Flaviviridae)*	Vector: *Culex tritaeniorhychnus* Host: aquatic birds and pigs	Southeast Asia, India, western Pacific Islands, northern Australia	Fever, headache, nausea, vomiting, meningitis, encephalitis	Live-attenuated vaccine
AUSTRALIA				
Murray Valley encephalitis *(Flaviviridae)*	Vector: *Culex* spp. mosquitoes Host: small mammals and marsupials	Northern Australia, New Guinea	Fever, chills, myalgias, rash, meningitis, encephalitis	None

spp = species.

TREATMENT AND PREVENTION

Specific antiviral therapeutic options are rarely available for acutely ill patients. In general, prevention is based on limiting exposure to vectors. Vaccines are available for yellow fever, dengue, tick-borne encephalitis virus, and Japanese encephalitis viruses. In endemic regions, individual prevention measures include DEET-containing repellants, permethrin-embedded clothing, long pants/sleeves, and bed nets. Vector control methods include drainage or removal of stagnant water sources where vectors reproduce.

FEVER AND MYALGIA SYNDROME

FLAVIVIRIDAE

YELLOW FEVER

DEFINITION AND EPIDEMIOLOGY

Yellow fever virus is a mosquito-borne member of the *Flaviviridae* family with characteristic, small, spherical, enveloped particles with three structural proteins that contain a positive-sense, single-stranded RNA genome. The genus, *Flavivirus* (flavi = yellow), acquired its name from the characteristic jaundice associated with yellow fever infection.

Yellow fever virus continues to cause major epidemics in tropical and subtropical regions of Africa and South America despite a safe and effective vaccine. Recent estimates report 63,000 to 158,000 severe annual infections in Africa, resulting in 29,000 to 75,000 deaths per year.[3] In South America, severe infections are estimated to be 4000 to 15,000 per year and deaths to be 2000 to 7000 per year. Yellow fever virus exhibits a sylvatic and urban transmission cycle between nonhuman primates and humans, respectively, with the *Haemagogus* spp and *Aedes aegypti* mosquitoes. Large outbreaks in densely populated urban areas are likely spillover infections from sylvatic outbreaks where large populations of *A. aegypti* mosquitoes breed in urban environments. The magnitude and duration of yellow fever viremia are sufficient to infect naïve, uninfected *A. aegypti* mosquitoes, thereby resulting in amplification of yellow fever in urban cycles of transmission.

PATHOBIOLOGY

Following a bite from a yellow fever virus–infected mosquito, the virus replicates in the dermal tissue epithelial cells and resident dendritic cells prior to spreading to a local draining lymph node. Following viral replication in the innate immune cells of the draining lymph node, yellow fever virus spreads to the liver, spleen, heart, and kidneys. Infection of Kupffer cells and hepatocytes in the liver results in liver inflammation and injury and can often cause significant liver dysfunction.

CLINICAL MANIFESTATIONS

The majority of individuals infected with yellow fever virus remain asymptomatic or mildly symptomatic. In others, however, a 3- to 6-day incubation period precedes acute yellow fever, which is characterized by the sudden onset of fever, chills, headache, myalgias, fatigue, weakness, nausea, and vomiting. Symptoms usually resolve within 1 week, but fatigue and weakness may persist. Virus is typically detectable in the serum for the first week of symptoms and clears as symptoms resolve. After a brief remission, about 12% of infected patients develop severe disease characterized by the return of fever, abdominal pain, nausea, vomiting, jaundice, and oliguria. The liver disease results in elevated levels of bilirubin and aminotransferases, with decreased hepatic synthesis of clotting factors. Some patients develop hemorrhagic manifestations of diffuse intravascular coagulation (Chapter 161), which is characterized by ecchymoses as well as bleeding from mucosal surfaces and needle puncture sites. Associated acute renal failure and hemorrhagic shock (Chapter 92) can occur.

DIAGNOSIS

The differential diagnosis is broad and includes acute viral hepatitis (Chapter 134), other arboviruses (Chapter 351), and malaria (Chapter 316). Since virus is detectable in human serum during the first 7 to 10 days following the onset of symptoms, yellow fever virus nucleic acid testing using an RT-PCR test may provide a diagnosis prior to serology. Since patients usually present later in the course of disease, laboratory diagnosis of yellow fever is generally accomplished by testing serum for virus-specific IgM antibodies and neutralizing antibodies. An elevated antibody level is diagnostic in unvaccinated patients, but a single antibody test cannot differentiate between the vaccine and natural infection, so serial serology showing a greater than four-fold increase in anti–yellow fever virus IgM or IgG between acute-phase and convalescent-phase samples is required for diagnosis in vaccinated persons.[4] Antibodies to one flavivirus can cross-react with other circulating flaviviruses, such as dengue virus, so confirmatory testing for neutralizing antibodies using plaque-reduction neutralization titers may be needed.

TREATMENT, PREVENTION, AND PROGNOSIS

Therapeutic options include supportive care with fluid resuscitation, critical care management, and renal replacement therapy when indicated (Chapter 351). Live-attenuated vaccine produces robust, long-lived neutralizing antibody and cellular immune responses,[A1] with a single lifetime dose recommended for travelers to endemic regions. Severe adverse events occur at a rate of <1 case per 100,000 doses. For severe yellow fever, the case-fatality rate is about 50% in unvaccinated individuals.

DENGUE VIRUS

DEFINITION AND EPIDEMIOLOGY

Dengue virus, which is a member of the *Flaviviridae* family (genus *Flavivirus*), causes infection by one of four serotypes. As with other flaviviruses, the lipid envelope is decorated with viral structural proteins, but its envelope protein varies by as much as 30 to 40% among the different serotypes. This large divergence is the basis for cross-reactive antibody reactions that are non-neutralizing but potentially enhance the severity of the clinical manifestations.

Dengue virus causes an estimated 390 million cases each year and continues to expand into the tropics and subtropics across the world (E-Fig. 352-1), where about 40% of the global population is at risk. Dengue virus circulates in urban cycles largely owing to the success of *A. aegypti*, its principal vector, to spread and reproduce among human dwellings in small containers of fresh water found in discarded tires, containers, jars, and other vessels. *Aedes albopictus* can also act as a vector.

PATHOBIOLOGY

All four serotypes of dengue virus cause dengue fever, and more severe dengue is typically associated with dengue virus 2 infection. The risk for developing severe dengue significantly increases in individuals who have preexisting immunity to a dengue virus serotype and then develop an acute infection with a different dengue virus serotype.[5] The mechanism, which is referred to as antibody-mediated enhancement, occurs when poorly neutralizing or low titer cross-reacting antibodies from the first dengue virus infection are enhanced by a second dengue virus infection from a different serotype or following infection with Zika virus, which is closely related to dengue virus. Human autopsy studies following severe dengue virus infection show antigen and nucleic acid in the cells of the skin, liver, spleen, lymph nodes, kidney, lung, thymus, and brain.

CLINICAL MANIFESTATIONS

Following an incubation period of 2 to 7 days, patients can exhibit asymptomatic infection (40 to 80%) or dengue fever,[6] which is characterized by sudden onset of high fever (40° C/104° F) accompanied by two or more of the following symptoms during the febrile phase: severe headache, retroorbital pain, myalgias/arthralgias, nausea, vomiting, adenopathy, and macular rash. Petechiae and epistaxis may also be present. The initial illness persists for about 7 days, whereas viremia persists for approximately 4 to 5 days, thereby allowing for transmission from humans to mosquitoes during the typical febrile period of disease. Following the initial febrile phase, most patients defervesce and begin to recover, but 1 to 5% of patients develop severe dengue, which is characterized by plasma leakage, shock, coagulation derangement, and end-organ disease resulting in hepatitis, encephalopathy, myocarditis, or severe bleeding (Chapter 351). Warning signs for severe dengue include abdominal pain, persistent vomiting, fluid accumulation, mucosal bleeding, lethargy, and liver enlargement >2 cm.

DIAGNOSIS

Laboratory testing may reveal thrombocytopenia, leukopenia, and mildly elevated liver aminotransferase levels. As patients defervesce, an increasing hematocrit, in part due to plasma leakage, and a rapid decrease in platelet count can indicate risk for development of severe dengue.

The diagnosis is best made during acute infection by RT-PCR for dengue virus nucleic acid in serum, alone or in combination with antigen testing for dengue nonstructural protein 1 by immunoassay. After about 4 days following the onset of fever, the most useful test is an IgM enzyme-linked immunoassay (ELISA), and a single serum sample strongly suggests recent dengue virus infection in regions where cross-reactive flaviviruses are not likely (E-Fig. 352-2). Plaque reduction neutralization antibody titers can be used to verify a positive dengue IgM antibody test result. The presence of IgG is indicative of past infection and not necessarily current infection. Moreover, cross-reactivity between antibodies to the individual dengue virus serotypes, other circulating flavivirus infections, or vaccines such as yellow fever virus vaccine may provide false-positive serology results.

TREATMENT, PREVENTION, AND PROGNOSIS

No specific therapy is effective for dengue virus. Ivermectin can accelerate the clearance of viral protein but has not been shown to be of clinical benefit.[A2] Supportive care includes fever reduction with acetaminophen while avoiding nonsteroidal anti-inflammatory drugs (NSAIDs) such as ibuprofen and aspirin, which can potentiate the risk for bleeding. For patients diagnosed with dengue with warning signs or severe dengue, hospitalization and close monitoring may be required with supportive care, including fluid resuscitation with infusion of crystalloid solutions and oxygen administration.

Vaccination against dengue has shown promising results.[7,8] A quadrivalent dengue virus vaccine has an 80% efficacy against infection in children ages 4 to 16 years and provides 90% protection against hospitalization.[A3,A4] Infecting *A. aegypti* mosquitoes with *Wolbachia pipientis* makes them less susceptible to dengue virus and can provide about a 75% reduction in dengue infection in endemic areas.[A5]

Severe dengue has a case-fatality rate that ranges from <1 to 5%. Appropriate supportive care in a center with experience treating severe dengue reduces overall mortality to close to 1%.

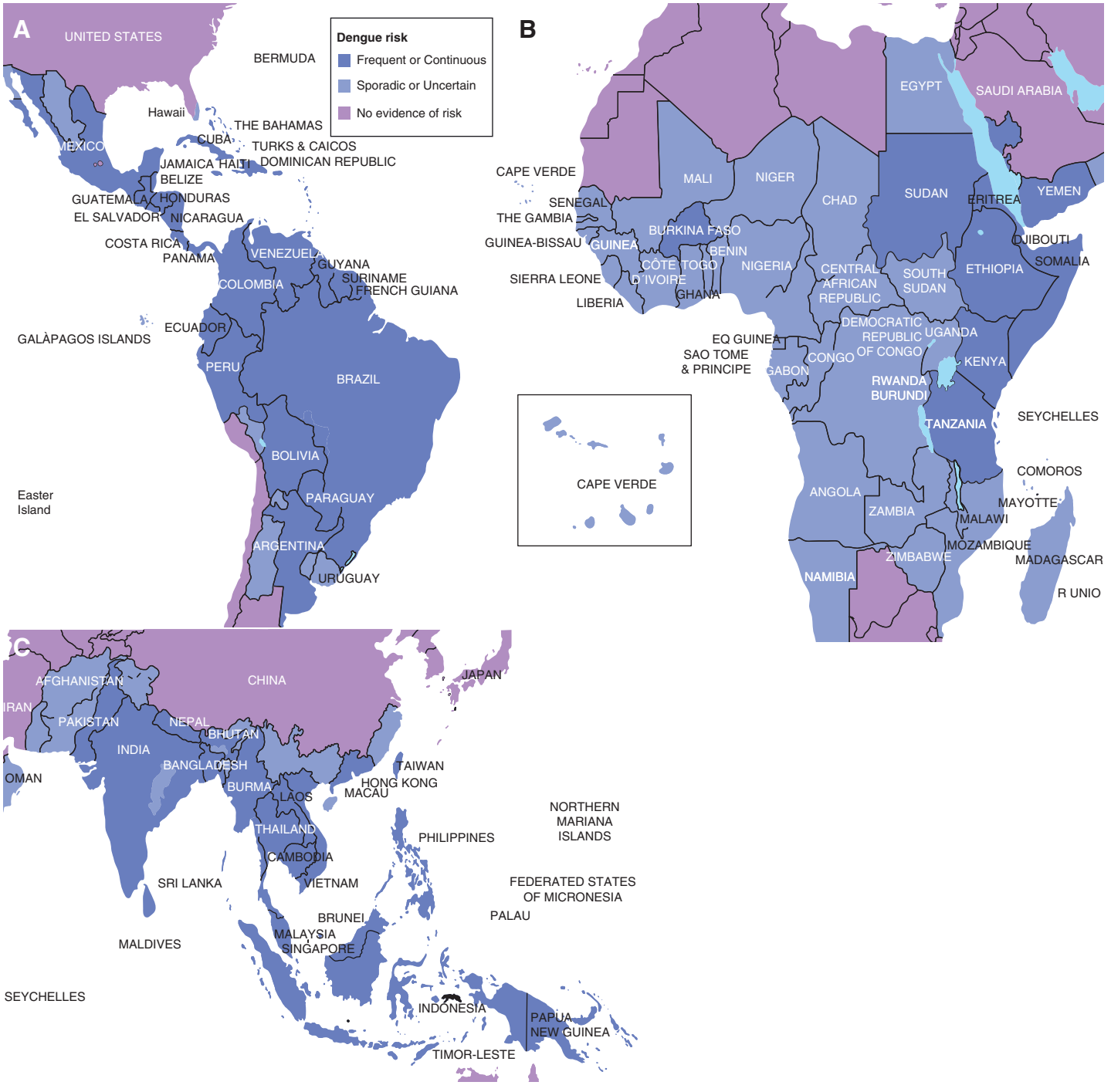

E-FIGURE 352-1. **Current distribution of the risk of transmission of dengue. A,** Americas and Caribbean Islands, Africa and Middle East (**B**), and Southeast Asia and Oceania (**C**). (Adapted from Centers for Disease Control and Prevention. *CDC Yellow Book 2020: Health Information for International Travel.* New York: Oxford University Press; 2017.)

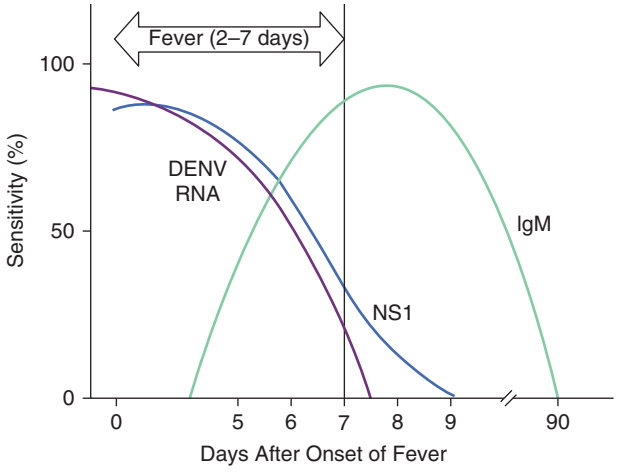

E-FIGURE 352-2. Sensitivity over time for dengue diagnostic testing. DENV RNA = dengue viral RNA; IgM = immunoglobulin M; NS1 = non-structural protein 1 antigen. (Adapted from Centers for Disease Control and Prevention. *CDC Yellow Book 2020: Health Information for International Travel.* New York: Oxford University Press; 2017.)

ZIKA VIRUS

DEFINITION AND EPIDEMIOLOGY

Zika virus is a mosquito-borne flavivirus that is closely related to dengue virus. Previously confined to Africa and Southeast Asia, Zika virus emerged in 2008 to cause large outbreaks of febrile disease with myalgias in adults in tropical and subtropical regions throughout the world. During the global outbreak, newly described Zika virus complications included postinfectious Guillain-Barré syndrome, sexual transmission, and vertical transmission of Zika virus in pregnant women, and congenital Zika virus syndrome became appreciated.

Zika virus, which was first recognized in a febrile macaque and *Aedes africanus* mosquitoes at the edge of the Zika forest in Uganda, is now an important cause of human disease throughout the world.[9] Two distinct lineages have been identified in Africa and Asia. In 2007, a large outbreak of Zika virus on Yap Island was followed by outbreaks across the Pacific Ocean and subsequently in Brazil, other countries in South America, and Central America. By 2019, 87 countries reported Zika cases. Zika is a cause of Guillain-Barré syndrome (Chapter 388), and infection of pregnant females results in significantly increased risk of fetal abnormalities, including microcephaly (termed congenital Zika syndrome). The largest recorded outbreak was a reported 2,751 cases in Brazil between 2015 and 2016, though this number is likely an undercount.[10]

PATHOBIOLOGY

Zika virus is spread principally by *A. aegypti* mosquitoes, although *A. albopictus* can also be a potential vector. The virus replicates in the dermal tissue and subsequently spreads to draining lymph nodes and the reticuloendothelial system, where it precipitates a prolonged viremia that can persist for 7 to 10 days and spread infection to end organs. The viremia can result in transmission to an uninfected mosquito that is feeding on a viremic individual in regions where competent mosquito vectors and susceptible individuals coexist. Infectious virions and viral RNA can be found in genital secretions, and sexual transmission occurs especially in nonendemic regions. In pregnant women, the virus can infect the placenta and the fetus, thereby causing placental inflammation, injury, and insufficiency, with increasingly severe fetal outcomes associated with infection earlier in pregnancy. During fetal infection, Zika virus can infect epithelial cells, thereby resulting in diffuse congenital malformations, but it also infects astrocytes and neuroprogenitor cells in fetal brain tissue, thereby resulting in developmental defects in the central nervous system and microcephaly. A significant number of infants also develop ocular disease characterized by retinal and choroid disease that results in long-term visual disturbances and blindness.

CLINICAL MANIFESTATIONS

In adults, Zika virus is asymptomatic in about 80% of cases. In symptomatic Zika virus infection, which follows an incubation period of about 7 days, patients develop a mild febrile syndrome characterized by fever, myalgias, arthralgias, a maculopapular rash, and conjunctivitis. In pregnant women, 20% of fetuses develop the severe neurologic abnormalities of congenital Zika syndrome.[11]

DIAGNOSIS

The diagnosis is suggested by the acute clinical symptoms and is made by a positive Zika virus nucleic acid amplification testing of serum or urine. Patients generally should be tested for dengue virus IgM antibody as well because of the overlap in symptoms and epidemiology.[12] If a symptomatic pregnant woman is diagnosed with acute Zika virus infection, prenatal ultrasound is often recommended.[13] If amniocentesis is completed as part of clinical care, amniotic fluid should be analyzed for Zika virus nucleic acid amplification testing.

TREATMENT, PREVENTION, AND PROGNOSIS

No approved therapy or vaccine is currently available for Zika virus, although a candidate has been shown to be safe and to produce durable immune responses.[A6] In immunocompetent adults, symptoms almost always resolve in 7 to 10 days without significant long-term complications. Less than 1% of cases develop Guillain-Barré syndrome (Chapter 388) and typically 7 to 10 days after the onset of symptoms and after the resolution of fever. Children who were exposed to Zika virus in utero are at risk for a wide range of disabilities, including long-term learning disabilities, neurocognitive defects, and abnormal visual and auditory function resulting in long-term disability.

TOGAVIRIDAE

CHIKUNGUNYA VIRUS

DEFINITION AND EPIDEMIOLOGY

Chikungunya virus, which is in the *Alphavirus* genus, is an important cause of large epidemics of fever, arthralgia, and arthritis in tropical and subtropical regions throughout the world. Similar to other alphaviruses, Chikungunya virus is an enveloped, plus-strand RNA virus with icosahedral symmetry. The virions are 60 to 70 nm in diameter, and the lipid envelope is decorated with viral glycoproteins, which form heterodimers that are grouped into trimers that form 80 projections on the virion surface.

Chikungunya virus is a mosquito-borne virus that was first characterized in Tanzania but is now transmitted globally, especially where the primary vector, *A. aegypti*, is active. In addition to occasional outbreaks in Africa and Asia, a large outbreak on Reunion Island infected about 25% of the population in 2005. Since then, Chikungunya virus has produced epidemic fever, arthralgia, and arthritic disease in 114 countries and territories in India, Southeast Asia, Africa, Oceania/Pacific islands, South America, and Central America (E-Fig. 352-3).

PATHOBIOLOGY

Transmission of Chikungunya virus is maintained in a sylvatic cycle between nonhuman primates and *Aedes* species of mosquitoes. Chikungunya virus can also maintain large urban epidemics with transmission between primarily *A. aegypti* or *A. albopictus* mosquitoes and humans. Following a bite from an infected mosquito, Chikungunya virus replicates in the dermal tissue and spreads to draining lymph nodes and the spleen, thereby resulting in viremia that may precede the onset of symptoms by 2 to 3 days. During acute viremia, direct infection of joint tissue, muscles, skin, and the central nervous system occurs, typically after 6 to 8 days of infection. The duration and magnitude of viremia are sufficient to transmit Chikungunya virus from humans to uninfected *A. aegypti* mosquitoes, thereby resulting in large urban outbreaks in tropical and subtropical regions.

CLINICAL MANIFESTATIONS

Approximately 3 to 28% of infected individuals remain asymptomatic, but the remainder develop symptomatic illness characterized by fever (>102° F/39° C) and arthralgias. A maculopapular rash, which develops 4 to 8 days after the onset of fever, involves the trunk, extremities, palms, soles of feet, and face. Other symptoms may include headache, myalgias, arthritis, conjunctivitis, nausea, and vomiting. Joint symptoms, which can be debilitating, are typically manifested as a polyarthritis involving the hands, wrists, and ankles, although more proximal joints also can be involved. Patients may also develop myocarditis, hepatitis, retinitis, acute renal disease, and meningoencephalitis.[14]

DIAGNOSIS

The differential diagnosis for Chikungunya virus includes other circulating arboviruses, such as dengue virus or Zika virus, as well as other causes of fever and arthralgias, including malaria (Chapter 316), measles (Chapter 338), enteroviruses (Chapter 349), leptospirosis (Chapter 298), and other endemic infections. Preliminary diagnosis is based on a compatible syndrome associated with exposure to a geographic region with Chikungunya virus transmission. During acute infection, diagnosis can be made using Chikungunya virus nucleic acid amplification testing of the serum. Detection of CHIKV IgM early in the course of disease or a four-fold increase in CHIKV IgG would support a diagnosis of acute CHIKV infection.

TREATMENT, PREVENTION, AND PROGNOSIS

Similar to other arboviruses, treatment is supportive with oral or intravenous fluids and with acetaminophen to reduce fever and pain. NSAIDs (Table 26-4) can be used to treat symptoms once dengue is ruled out. A safe and immunogenic vaccine is undergoing clinical trials.[15] Acute symptoms resolve in 7 to 10 days, and fatalities are rare. Some patients (5 to 80%) have chronic rheumatologic symptoms (e.g., polyarthritis, tenosynovitis, chronic arthralgias, Raynaud syndrome) and persistent and prolonged fatigue for several months after the acute infection. In some cases, the arthritis, pain, and swelling become chronic.

O'NYONG-NYONG

DEFINITION AND EPIDEMIOLOGY

O'nyong-nyong virus is an alphavirus that causes a fever-myalgia syndrome similar to Chikungunya virus, is endemic to sub-Saharan Africa, and was first identified following an outbreak of fever and arthralgia syndrome in Uganda in 1959. O'nyong-nyong virus quickly spread throughout eastern and western Africa causing outbreaks of disease with infection rates ranging from 3 to 45%. Current seroprevalence rates vary from 0.8% in inland Kenya to as high as 56% in a coastal community in Kenya.

PATHOBIOLOGY

O'nyong-nyong virus is unique among alphaviruses in that it is primarily spread by night-feeding *Anopheles* mosquitoes, including *A. funestus* and *A. gambiae*, which are also malaria vectors. O'nyong-nyong virus causes large outbreaks

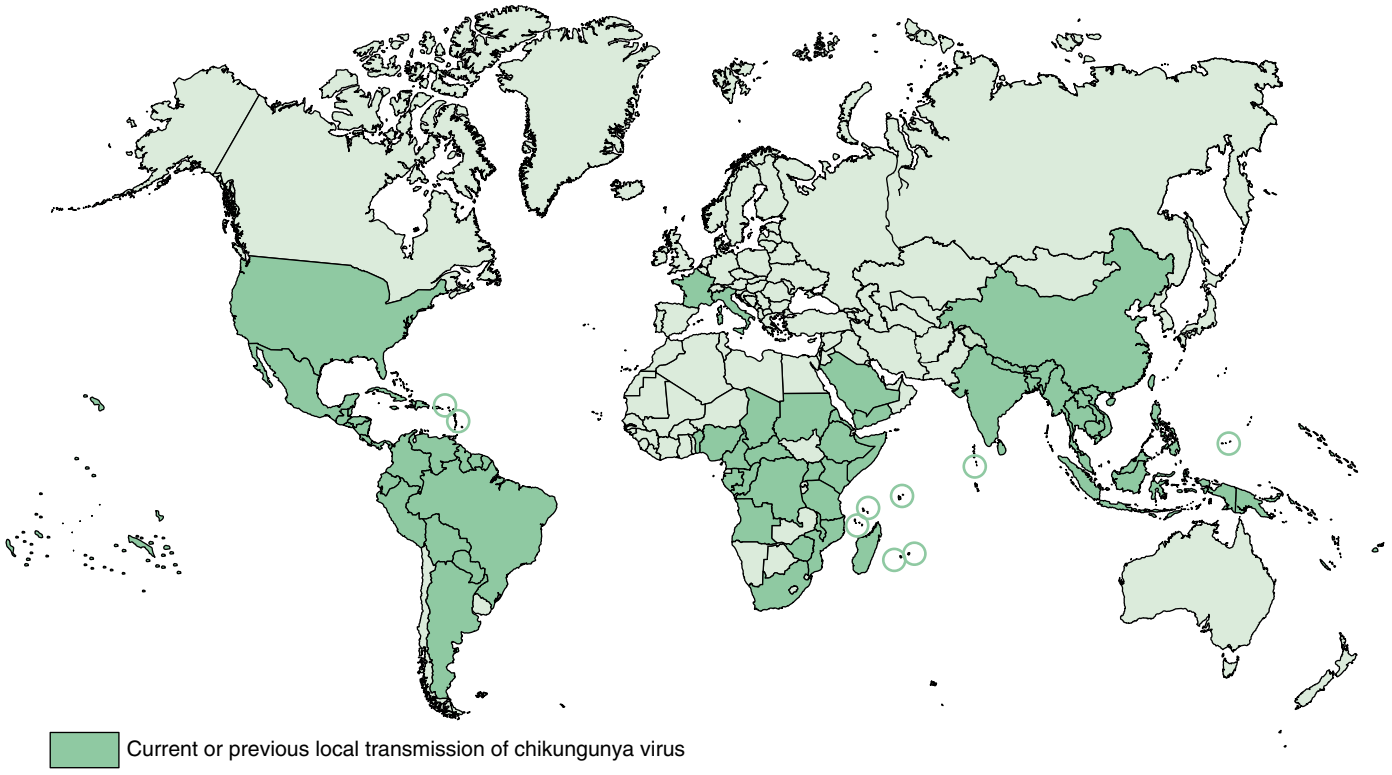

E-FIGURE 352-3. Chikungunya distribution based on past and current epidemics. (Adapted from https://www.cdc.gov/chikungunya/geo/index.html.)

of febrile disease and then will retreat, likely circulating in an enzootic cycle between vectors and natural reservoir hosts that are not currently known.

CLINICAL MANIFESTATIONS AND DIAGNOSIS

The incubation period is approximately 8 days following initial infection, and about 25% of laboratory-confirmed cases develop symptoms. O'nyong-nyong virus shares many of the clinical features of Chikungunya virus, including sudden onset of high fever, joint pains primarily in large joints,[16] headache, diffuse maculopapular rash on the chest and limbs, and conjunctivitis.

Viremia may be detected in serum in the first 7 days of illness using RT-PCR. Detectable levels of IgM antibodies appear during the second week of illness and can persist for several months.

TREATMENT, PREVENTION, AND PROGNOSIS

There is no specific therapeutic for O'nyong-nyong virus disease or vaccine available to prevent infection. The acute illness is self-limited, but patients can have prolonged large-joint arthritis that results in significant morbidity.

ROSS RIVER FEVER VIRUS (EPIDEMIC FEBRILE POLYARTHRITIS)

DEFINITION AND EPIDEMIOLOGY

Ross River fever virus, which is a member of *Togaviridae* virus, causes an acute-onset, febrile illness characterized by rash and arthralgia. The virus is seen in tropical and temperate regions in Australia (especially Queensland and New South Wales), Papua New Guinea, western New Guinea, and Pacific islands in the Australian geographic zone.

Most cases occur in spring through autumn after heavy rainfall.[17] *Aedes* mosquitoes are the major vector near saltwater, whereas *Culex annulirostris* is a freshwater vector. Intermediate hosts include domestic animals, rodents, and marsupials. Barmah Forest virus, which also is associated with epidemic febrile polyarthritis in Australia, may present in a similar fashion.

PATHOBIOLOGY

Following a bite from an infected mosquito and replication in local tissue-resident macrophages and dendritic cells, viremia results with and distribution to other tissues, including the spleen, muscle tissue, and joint tissue. Viral antigen can be detected in monocytes and macrophages early in infection, but intact virus is not identifiable by electron microscopy or cell culture. Dermal vessels show mild perivascular mononuclear cell infiltrates, mostly T lymphocytic, in erythematous and purpuric areas. Vessels in purpuric areas also show erythrocyte extravasation. Antigen can be seen in involved skin, and viral RNA can be seen in joint fluid.

CLINICAL MANIFESTATIONS AND DIAGNOSIS

The abrupt onset of arthralgia can precede or follow a rash that is typically maculopapular, predominantly on the trunk and extremities, and sometimes pruritic. The arthralgia is usually asymmetrical, migratory, and severe, with a predilection for the hands.[18] Arthralgias tend to be worse in the morning, and about 30% of patients have synovitis. Classic carpal tunnel syndrome may occur. Fever, which is usually mild to moderate and persists for several days, may also be accompanied by headache, myalgia, nausea, respiratory symptoms, photophobia, and lymphadenopathy.

Since most patients are viremic for up to 7 days after the onset of symptoms, RT-PCR can detect viral RNA in most patients. Synovial fluid shows a monocytic cell predominance.

TREATMENT AND PROGNOSIS

NSAIDs are recommended for symptomatic relief. Symptoms generally resolve over weeks to months but may persist for up to 3 years.

SINDBIS

Sindbis virus, which is a febrile illness with arthralgia and rash, has been reported primarily in Scandinavia and nearby Russia but also in southern and central Africa as well as Australia. About 3% of the population of northern Sweden is seropositive. Mosquito vectors are *Aedes, Culex*, and *Culiseta* species, and the intermediate hosts are birds.

The virus can be isolated from skin lesions. Antiviral IgM is long-lasting, thereby suggesting persistent infection or an autoimmune process.

CLINICAL MANIFESTATIONS AND DIAGNOSIS

Patients present with a macular rash and arthralgia of the hands, feet, wrists, elbows, ankles, and knees. Tendinitis can involve hand extensor and foot plantar tendons. Fever and constitutional symptoms, if present, are rarely severe. Macules on the torso, extremities, and even the palms can become papular and vesiculate.

Positive IgM titers support the diagnosis, although they can remain elevated for 3 to 4 years after infection. Molecular diagnostic techniques (RT-PCR) are not presently available for routine diagnosis.

TREATMENT AND PROGNOSIS

NSAIDs can help with symptoms. Nonerosive chronic arthropathy persists in about 50% of patients for 2.5 years after infection and may persist for up to 6 years.[19]

MAYARO FEVER

DEFINITION AND EPIDEMIOLOGY

Mayaro virus is a positive-sense, enveloped, single-stranded RNA alphavirus. It is the etiologic agent of Mayaro fever, which is an emerging virus in Central and South America. Mayaro fever is an acute febrile illness that has been seen in Trinidad, Bolivia, Brazil, and Peru. *Haemagogus* mosquitoes in tropical rainforests are the vector, and monkeys serve as the reservoir. However, Mayaro virus has infected a wide range of *Aedes* and *Culex* mosquito species and a wide range of mammalian species, thereby increasing the likelihood of future geographic spread. Imported cases have been documented in the United States and in Europe after travel to the endemic regions, and it is expected to cause more travel-related illnesses in the United States and Europe with its increased spread in the Caribbean islands and Central America.

PATHOBIOLOGY

Most human cases occur in close association with tropical rainforests. The reservoir for Mayaro virus is not known, but high-grade viremia has been found in nonhuman primates. Following the bite of a mosquito, local replication of the Mayaro virus in skin tissue likely leads to viremia and seeding of distant sites. Following dissemination, virus can cause end-organ infection and injury to joint tissue, muscles, and the spleen.

CLINICAL MANIFESTATIONS AND DIAGNOSIS

After an incubation period of 1 to 12 days, the clinical onset is sudden, with fever, chills, headache, arthralgias, and sometimes joint swelling of the hands and feet.[20] Neurologic manifestations and myocarditis have also been described. After the fever resolves in 3 to 7 days, about two-thirds of patients develop a maculopapular rash on their trunk and extremities. RT-PCR of blood has a high sensitivity and specificity for the diagnosis.

TREATMENT AND PROGNOSIS

Recovery is typically complete with supportive therapy, including NSAIDs, but arthralgias can persist for 6 months or more.

BUNYAVIRALES

RIFT VALLEY FEVER

DEFINITION AND EPIDEMIOLOGY

Rift Valley fever virus is a member of the Bunyavirales order and *Phlebovirus* family, with a virion characterized by a lipid envelope containing a tripartite, single-stranded, negative- or ambisense RNA genome. The lipid envelope is decorated with viral glycoproteins, which function as viral attachment proteins.

Rift Valley fever virus, which was first identified in sheep in the Rift Valley province of Kenya in 1931, is endemic throughout sub-Saharan Africa, where it causes epizootic animal outbreaks that result in large numbers of abortions in cattle, sheep, and other livestock, especially during periods of heavy rain, when several species of mosquitoes can spread the infection to humans. During one outbreak in Egypt, over 200,000 people were infected and over 600 died. The seroprevalence in livestock in endemic regions varies from 0.5 to 93% depending on recent epidemics, animal species, and vaccination approaches. During interepidemic periods, the seroprevalence in animals drops to about 2 to 3%.

PATHOBIOLOGY

Rift Valley fever virus is transmitted to humans by the bite of infected *Aedes* species and *Culex* species mosquitoes, but infection can also result from the ingestion of unpasteurized milk, exposure to the blood of an infected animal, or even from the aerosol from aborted material from infected livestock.[21] Following exposure to Rift Valley fever virus, the virus infects antigen-presenting cells, thereby resulting in suppression of the type 1 interferon response, death of infected macrophages and dendritic cells, and wide dissemination of the virus to kidney, liver, adrenal gland, and endothelial cells. The result is an excessive pro-inflammatory cytokine and chemokine response, microcirculatory dysfunction, and impairment of the coagulation system, sometimes resulting in edema, hemorrhage, and disseminated intravascular coagulation.

CLINICAL MANIFESTATIONS

Rift Valley fever virus can cause asymptomatic infection or a self-limited febrile illness, but severe disease occurs in approximately 1 to 2% of infections. Following an incubation period of 2 to 6 days, clinical symptoms include fever, headache, myalgias, back pain, vertigo, anorexia, and photophobia. The fever persists for 5 to 7 days, with a convalescent period that can persist for several days to a month. About 1 to 3 days after the primary symptoms resolve, some patients develop severe illness characterized by lymphopenia, hepatitis with elevated aminotransferase levels, jaundice, severe thrombocytopenia, and hemorrhage (see Chapter 351). Other manifestations of severe disease can include macular edema, miscarriage, and encephalitis.

DIAGNOSIS

Definitive diagnosis requires detection of virus RNA by RT-PCR in serum or plasma, detection of IgM and IgG antibodies, or detection of Rift Valley fever virus antigen in infected tissue. Because the periods of viremia and antigenemia are short, testing of acute and convalescent sera for IgM and IgG is often helpful. Since most human infections are asymptomatic or flulike in nature, the index of suspicion should remain high in endemic regions with increased rates of spontaneous abortions in sheep or cattle.

TREATMENT, PREVENTION, AND PROGNOSIS

No specific treatment other than general supportive care is available. Vaccines for livestock can produce long-lasting protection after a single dose and limit epizootic spread to humans, but there is no currently licensed human vaccine. Severe disease can carry a mortality rate of 5 to 70%.

PHLEBOTOMUS FEVER

DEFINITION AND EPIDEMIOLOGY

Phlebotomus fever or sandfly fever, which is an acute and self-limited febrile illness, is caused by single-stranded RNA viruses in the *Bunyaviridae* family. The virus is 80 to 120 nm in diameter with a lipid envelope and three genomic segments. The virus is transmitted by bites of *Phlebotomus* sandflies in the northern Mediterranean, western Europe, Turkey, the Middle East, western India, and Pakistan. The *Lutzomyia* fly species can transmit the virus in Central America. Sandflies exhibit hopping behavior during feeding but can still disperse widely, with travel distances up to 1 to 2 kilometers.

PATHOBIOLOGY

The pathogenesis of phlebotomus fever is not well defined. Following the bite of an infected sandfly, the virus likely replicates in tissue-resident monocyte-derived dendritic cells, thereby resulting in a viremia that seeds hepatocytes, adrenocortical cells, and renal tubular epithelial cells.

CLINICAL MANIFESTATIONS AND DIAGNOSIS

After an incubation period of 2 to 6 days, an acute febrile illness is associated with constitutional symptoms, a macular or urticarial rash, headache, altered taste, photophobia, myalgia, arthralgia, and even pleurodynia. Fever typically persists for 2 to 4 days, but about 15% of patients have recrudescence 2 to 12 weeks later. Laboratory testing is often notable for thrombocytopenia, leukopenia, and increased levels of creatinine kinase, aspartate aminotransferase, and alanine aminotransferase. Some patients develop aseptic meningitis with a mild CSF pleocytosis. The diagnosis can be made by serology for virus-specific IgG and IgM antibodies in serum. RT-PCR can detect the viral genome but is less sensitive owing to the short duration of viremia.

TREATMENT, PREVENTION, AND PROGNOSIS

Complete recovery follows supportive treatment. Sandflies, which feed in the early evening, are small enough to pass through mosquito netting. Use of insect sprays locally is effective in decreasing risk.

MENINGITIS AND ENCEPHALITIS SYNDROME

FLAVIVIRIDAE

JAPANESE ENCEPHALITIS

DEFINITION AND EPIDEMIOLOGY

Japanese encephalitis virus, which is a member of the family *Flaviviridae* and *Flavivirus* genus, is a mosquito-borne virus that causes large outbreaks of viral encephalitis, predominantly in children and young adults.[22] An estimated 60,000 annual cases occur throughout Southeast Asia, India, the western Pacific islands, and northern Australia. In endemic regions, the majority of cases occur in children, and the risk of severe disease decreases with increasing age.

PATHOBIOLOGY

Japanese encephalitis virus is transmitted by *Culex tritaeniorhychnus* and related ground-dwelling mosquitoes, principally in flooded rice fields, with pigs and aquatic birds acting as the amplifying hosts. After the bite of an infected mosquito, the virus replicates in the skin, with subsequent spread to the draining lymph nodes and spleen. Secondary viremia results in end-organ infection, including the spinal cord and brain tissue, where Japanese encephalitis virus infection causes apoptotic cell death accompanied by inflammatory immune responses.

CLINICAL MANIFESTATIONS

The majority of infected individuals are asymptomatic, but patients can develop fever, headache, nausea, vomiting, abdominal symptoms, aseptic meningitis, or encephalitis following an incubation period of 6 to 16 days. About 0.5% of infections progress to encephalitis or meningoencephalitis, which is characterized by excitability, delirium, seizures, limb tremors, and involuntary movements such as myoclonus. Cerebellar or spinal cord involvement can present with ataxia or limb paresis, including lower motor neuron–type weakness.

DIAGNOSIS

Viremia has typically resolved by the time that an immune-competent patient presents with disease, so the diagnosis is made by Japanese encephalitis virus–specific IgM antibody testing of the serum. Lumbar puncture is recommended and typically shows a CSF pleocytosis, with 10 to 500 white blood cells/μL (often with a polymorphonuclear cell predominance early in the course of disease but with a lymphocyte predominance later), an elevated protein level (50 to 100 mg/dL), and a normal glucose level. Japanese encephalitis virus–specific IgM antibodies in the CSF have a sensitivity of 65 to 70% and a specificity of 90 to 100%. An alternative is to find a four-fold increase in IgG antibody titers to Japanese encephalitis virus in convalescent as compared with acute serum samples. On MRI, Japanese encephalitis virus characteristically causes a subcortical encephalitis with a T2 hyperintense signal, most commonly in the thalamus and occasionally in the midbrain, basal ganglia, and cerebellum.

TREATMENT, PREVENTION, AND PROGNOSIS

No specific therapy is available for patients. In endemic regions, a live-attenuated vaccine is highly efficacious,[A7] even after the first dose of the two-dose regimen. Since the risk among travelers to endemic areas is approximately 1 in 5000 to 20,000 per week of travel, vaccination is recommended with two doses at 0 and 28 days. Japanese encephalitis virus has a 20% case-fatality rate and a 30 to 50% rate of long-term neurologic and neuropsychiatric complications, including parkinsonism, seizure disorders, paresis, cognitive impairment, and neuropsychiatric disorders.

WEST NILE VIRUS

DEFINITION AND EPIDEMIOLOGY

West Nile virus is a member of the *Flavivirus* genus and part of the Japanese encephalitis virus complex of viruses along with St. Louis encephalitis virus and Usutu virus. West Nile virus is widely distributed in many parts of Africa, West Asia, the Middle East, Eastern Europe, Australia, and the Americas. It is now endemic throughout the continental United States and Canada, where it is the leading cause of mosquito-borne viral encephalitis (Chapter 383), with annual outbreaks in the late summer and early fall.

West Nile virus is maintained in an enzootic transmission cycle between *Culex* spp of mosquitoes and perching birds, with resulting epizootic spillover into dead-end hosts, primarily humans and horses. Since 1999, over 50,000 reported cases of West Nile virus disease have resulted in 2390 deaths in the United States.[23] About 80% of infected individuals are asymptomatic, and the risk of developing symptoms and severe complications increases with age.

PATHOBIOLOGY

In the United States, the majority of infections follow the bite of a *Culex* mosquito, but transmission also can occur via blood transfusion or organ transplantation from viremic donors. Following infection from a mosquito bite, the virus replicates in local skin tissue and dendritic cells and then drains to regional lymph nodes, where West Nile virus infects additional macrophages and monocytes, thereby resulting in a primary viremia. Following the primary viremia, the spleen becomes infected and causes a secondary viremia, with fever and seeding of the brain, gastrointestinal neurons, and kidneys. Humans do not have a sufficient viremia to transmit West Nile virus to uninfected mosquitoes.

CLINICAL MANIFESTATIONS

Approximately 80% of infected individuals are asymptomatic. About 90% of symptomatic individuals develop only a self-limited, febrile illness termed West Nile virus fever and characterized by fever, myalgias, retrobulbar pain, headache, and a diffuse maculopapular rash on the chest and extremities.[24] Only 1 in 150 infected individuals develops meningitis or encephalitis. Meningitis is characterized by fever, photophobia, headache, and neck pain without focal neurologic abnormalities. Encephalitis is characterized by altered mental status, ataxia, tremor, myoclonus, parkinsonism, and/or varying degrees of flaccid paralysis.

DIAGNOSIS

Detection of West Nile virus RNA in the serum and CSF by RT-PCR assays is highly specific, but it is unusual to detect RNA except in immunocompromised patients (Fig. 352-1). West Nile virus–specific antibody testing detects anti–West Nile virus IgM and IgG in serum and CSF. IgG levels can be positive based on past exposure or cross-reactivity to other flaviviruses (e.g., St. Louis encephalitis virus), and West Nile virus–specific IgM sometimes can persist for up to 12 months. As a result, serum and CSF antibody testing must be interpreted with the appropriate clinical syndrome and context.

CSF exhibits a lymphocytic pleocytosis, although 30 to 45% of patients may present with a neutrophil-predominant CSF pleocytosis, particularly early in the disease. CSF protein is typically elevated, and the glucose level is normal. MRI imaging, which is positive in 40 to 50% of patients, most commonly exhibits increased T2 hyperintense signal in the thalamus, basal ganglia, midbrain, and occasionally the medial temporal lobes (see Fig. 352-1).

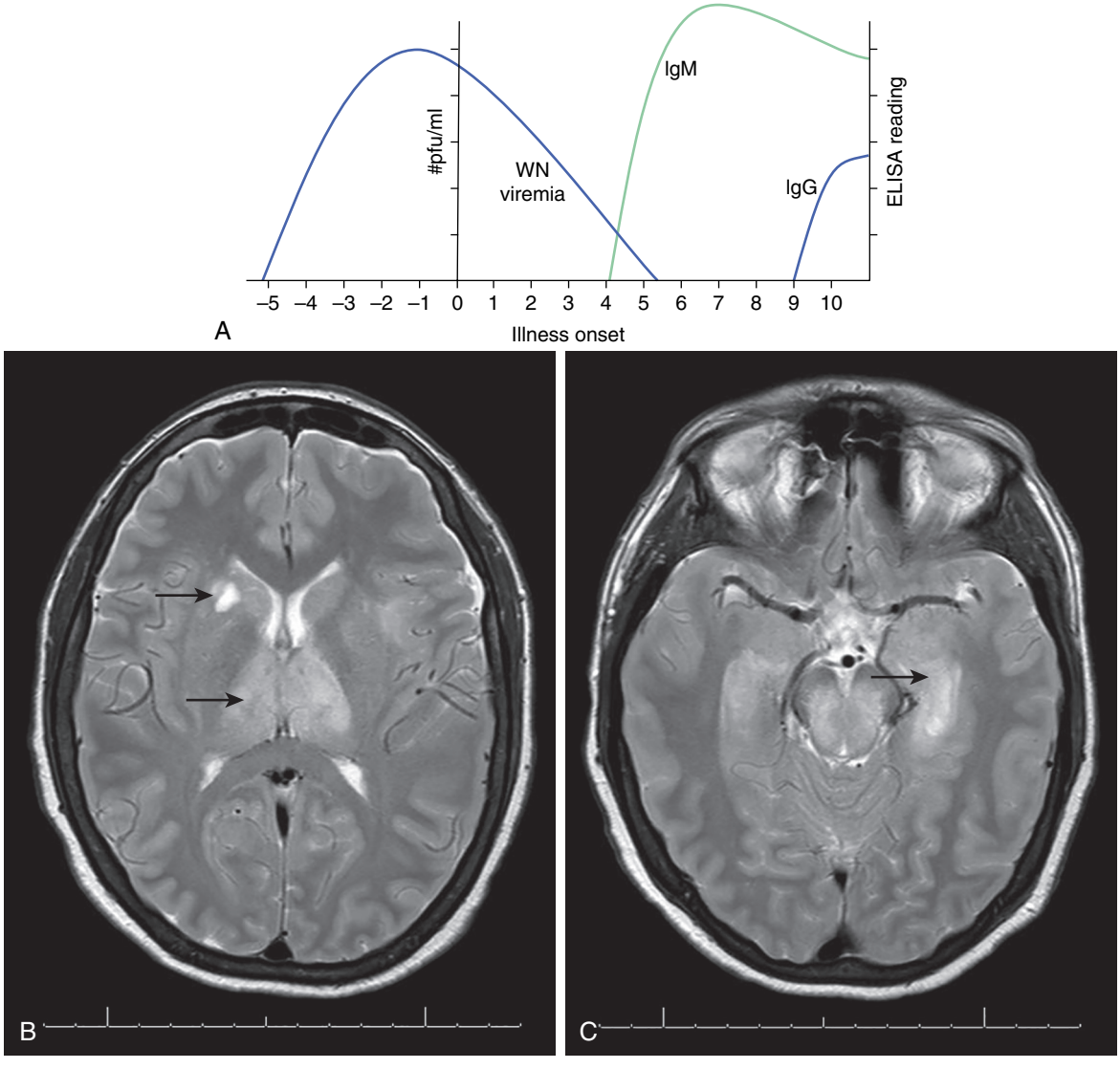

FIGURE 352-1. Diagnosis and imaging for West Nile (WN) virus disease. A, Graphic representation of timing for WNV RNA and serology detection over time. (A, Adapted from www.cdc.gov/westnile/healthcareproviders/healthCareProviders-TreatmentPrevention.html.) Magnetic resonance imaging (MRI) results from a patient with WNV encephalitis showing T2 hyperintense signal in the (B) thalamus and caudate nucleus and (C) medial temporal lobe and midbrain. *Arrows* indicate regions of increased signal. ELISA = enzyme-linked immunosorbent assay; Ig = immunoglobulin; pfu = plaque-forming unit.

TREATMENT, PREVENTION, AND PROGNOSIS

No therapy has proven efficacy. In the United States, screening of donor blood and organs using nucleic acid amplification testing has significantly decreased the risk of transmission. Following West Nile virus encephalitis or flaccid paralysis, recovery can be prolonged and associated with long-term neurologic deficits in 30 to 40% of survivors.[25] Common long-term symptoms and disabilities include fatigue, myalgias, paralysis, cognitive and memory deficiencies, and parkinsonism.

POWASSAN VIRUS

DEFINITION AND EPIDEMIOLOGY

Powassan virus is a member of the genus *Flavivirus* and an emerging cause of tick-borne viral encephalitis in the Mid-Atlantic, northeastern, and upper Midwestern regions of the United States,[26] as well as in Canada and far eastern Russia. Since 2010, the United States has reported over 180 cases of Powassan virus disease, but more than 20% were in the most recent years. Powassan virus is maintained in enzootic cycles between *Ixodes* species (*I. scapularis* and *I. cookie*) and small mammals and white-tailed deer. Two lineages, the Powassan virus and the deer-tick virus, have a 14% divergence in nucleotide sequence of their envelope glycoproteins. The apparent increase in case numbers is likely due to increased surveillance and detection, increased density and spread of tick populations, and increased human-tick contacts. Powassan virus also can be transmitted by blood transfusion and probably by organ transplantation from viremic donors.

PATHOBIOLOGY

Ixodes sp of ticks become infected by feeding on a viremic host or cofeeding with an infected tick. When infected ticks bite and secrete saliva into humans, who serve as dead-end hosts during summer months, the virus is inoculated into the skin and can replicate in the epidermis and dermal cells as well local and regional dendritic cells and macrophages. Following viral replication, the virus spreads to local lymph nodes and the spleen, before then spreading to end organs such as the CNS.

CLINICAL MANIFESTATIONS

Following infection from a Powassan virus–infected tick, the incubation period ranges from 8 to 34 days followed by a prodrome of 1 to 3 days characterized by fever (>40° C), generalized malaise, myalgia, nausea, and sometimes a maculopapular rash. The rates of asymptomatic or mild infection are unknown, but about 90% of reported cases have had neuroinvasive disease, with meningitic symptoms such as meningismus and photophobia, or with signs and symptoms of encephalitis, including altered mental status, respiratory distress, ataxia, tremor, and ocular involvement.

DIAGNOSIS

I. scapularis is able to transmit Powassan virus within 15 minutes of attachment, so a history of removal of a tick in an endemic region should indicate potential infection. Routine complete blood count may exhibit leukopenia (white blood cell count <4000/μL) and thrombocytopenia (<150,000/μL). If a patient presents early in the course of disease, PCR of blood and CSF may provide a diagnosis, particularly in immunocompromised patients. However, since the viremia has usually resolved by the time a patient presents with symptoms, serology (Powassan virus–specific IgM capture ELISA and indirect IgG ELISA) to detect antibody in the serum and IgM antibody in the CSF is the principal diagnostic approach. The CSF, as with other neuroinvasive arboviruses, typically exhibits a neutrophilic or lymphocytic pleocytosis, elevated protein level, and normal glucose level.

TREATMENT, PREVENTION, AND PROGNOSIS

There is no specific therapeutic option or vaccine for Powassan virus infection. Vaccines are available in eastern Europe and Russia for the closely related tick-borne encephalitis virus, but there is no evidence that these vaccines provide significant cross-protection against Powassan virus. An mRNA vaccine candidate for tick-borne flaviviruses exhibited protection in a murine model of Powassan virus. The reported case-fatality rate is about 10%, and about 50% of survivors have long-lasting neurologic deficits, including headaches, muscle weakness, focal paralysis, or neurocognitive deficiencies.

OTHER TICK-BORNE *FLAVIVIRIDAE*

DEFINITION AND EPIDEMIOLOGY

Louping ill, Alongshan virus, and tick-borne encephalitis are tick-borne viruses that can cause hemorrhagic fever (Chapter 351) but can also cause meningoencephalitis.[27] Louping ill virus is found in Britain and Alongshan virus in northeastern China.[28] Tick-borne encephalitis is seen in eastern Europe and far eastern Russia with more than 2000 cases reported each year. Louping ill causes sporadic cases of encephalitis in Scotland, northern England, and Ireland. Both louping ill and tick-borne encephalitis are similar to Powassan virus and other flaviviruses, with a single-stranded, positive-sense RNA genome contained in a virion that consists of a host-derived lipid envelope decorated with envelope and membrane proteins. Alongshan virus is derived from a novel emerging *Flaviviridae* group and is characterized by four positive-stranded RNA segments with poly-A tails enclosed in an enveloped virion decorated with the VP3 structural protein.

PATHOBIOLOGY

Tick-borne encephalitis virus and other tick-borne viruses are transmitted following a tick bite, most commonly of an infected *Ixodes* species tick. Ticks become infected after feeding on a vertebrate host, such as a small rodent, or can obtain the virus transtadially (transmission across tick development from larva to nymph to adult) or transovarially (from adult female to eggs). Infection may also follow consumption of unpasteurized milk or cheese from goats, sheep, or cows. During a blood meal, virus is excreted from the salivary glands of an infected tick, thereby resulting in localized infection of mononuclear cells and resident tissue macrophages in the skin. Virus replicates and spreads to regional lymph nodes and to the spleen.

CLINICAL MANIFESTATIONS AND DIAGNOSIS

Tick-borne encephalitis, which is by far the most common of these diseases, may be asymptomatic or begin with a flulike illness after a 1- to 2-week incubation period. The initial phase of the symptomatic illness is characterized by fever, myalgias, fatigue, and influenza-like symptoms during the first week. After about a week of usually mild symptoms, about 65 to 70% of patients clear the infection. However, the remaining 30% of patients develop a second phase of viremia associated with central nervous system infection that is characterized by meningitis or meningoencephalitis. The neurologic disease can be relatively mild but can also manifest as altered consciousness, bulbar paralysis, seizures, and paralysis. Louping ill and Alongshan viruses have a similar clinical course.

RT-PCR of blood can make the diagnosis in the first phase of the disease, but serologic diagnosis is required after neurologic symptoms develop.

TREATMENT, PREVENTION, AND PROGNOSIS

Treatment is supportive. A vaccine against tick-borne encephalitis is available and used in the general population in Austria and eastern Europe and in high-risk workers in Russia[29] with excellent results. Prognosis is generally benign with 1 to 2% mortality rate in Europe, but the mortality rate is 20% or so in far eastern Russia.

ST. LOUIS ENCEPHALITIS

DEFINITION AND EPIDEMIOLOGY

St. Louis encephalitis virus is closely related to Japanese encephalitis, Murray Valley encephalitis, and West Nile viruses. The virus has caused periodic epidemics of up to 2000 cases in North America (primarily in the Ohio-Mississippi River basin, eastern and central Texas and Florida, and western states, usually between July and September) as well as in the Caribbean and Argentina.[30]

PATHOBIOLOGY

The vectors are *Culex pipiens*, *Culex nigripalpus*, and *Culex tarsalis* mosquitoes that propagate in stagnant water, and the intermediate hosts are wild birds. Similar to other mosquito-borne flavivirus infections, St. Louis encephalitis virus is spread to humans as a dead-end host following a blood meal of an infected *Culex* sp mosquito. Virus replicates in tissue-resident dendritic cells and macrophages, followed by spread of virus to regional lymph nodes and the spleen. Secondary viremia following replication in splenic tissue results in infection of the central nervous system with predominant infection of neurons in basal ganglia, the thalamus, and other subcortical gray matter regions.

CLINICAL MANIFESTATIONS AND DIAGNOSIS

Over 99% of infections are asymptomatic. However, an incubation period of 4 to 21 days may precede nonspecific febrile symptoms followed by headache, drowsiness, altered consciousness, and meningeal or encephalitic signs. Seizures, which occur in 10% of patients, are a poor prognostic sign. A Guillain-Barré–like syndrome (Chapter 388) can occur acutely or during convalescence. Inappropriate antidiuretic hormone secretion

(Chapter 206) may occur. Virus in the genitourinary tract can cause incontinence, retention, microscopic hematuria, pyuria, proteinuria, and acute renal injury.

CSF shows a pleocytosis, initially neutrophilic and then lymphocytic, of up to 500 cells/μL, with an elevated protein level and normal glucose level. The electroencephalogram (EEG) typically shows frontal and temporal polymorphic delta activity, often with seizures.

Rapid diagnosis is by RT-PCR or by detecting IgM antibodies in serum and CSF. Later serologic diagnosis is made with acute and convalescent antibody titers.

TREATMENT, PREVENTION, AND PROGNOSIS

Treatment is supportive, and no vaccine is available. The case-fatality rate is negligible in persons younger than age 20 years but rises to 30% in patients over age 65 years. About 30 to 50% of adult survivors have persistent neuropsychiatric symptoms for 3 years or more.

MURRAY VALLEY AND ROCIO ENCEPHALITIS

Murray Valley encephalitis and Rocio encephalitis are caused by flaviviruses and cause clinical syndromes that are very similar to each other and to Japanese encephalitis. Murray Valley encephalitis, which is endemic in northern Australia and New Guinea, has caused limited epidemics in the Murray and Darling River valleys of Victoria and New South Wales, Australia. Rocio encephalitis in São Paulo State, Brazil, has caused epidemics of 1000 or more cases.

TOGAVIRIDAE

EASTERN EQUINE ENCEPHALITIS VIRUS

DEFINITION AND EPIDEMIOLOGY

Eastern equine encephalitis virus is a mosquito-borne virus, which is in the genus *Alphavirus* and is closely related to Western equine encephalitis virus and Venezuelan equine encephalitis virus. It has caused small, limited outbreaks (5 to 10 cases) annually in the eastern United States, but its incidence may be rising to about 40 cases per year as it spreads from its endemic areas along the Atlantic coast, Gulf Coast, and Great Lakes regions to other regions. Of its four lineages, group I causes the majority of disease in the United States, whereas groups II to IV primarily cause disease in horses in Central and South America. The virus exists in an enzootic cycle between the primary vector, *Culiseta melanura*, and birds. Multiple bridging mosquito vectors that feed on infected birds can spread the virus to a large variety of dead-end hosts, including equine species, humans, other birds, and livestock.[31]

PATHOBIOLOGY

Similar to other arboviruses, Eastern equine encephalitis virus is introduced by mosquito bite in the subcutaneous tissue with subsequent infection of epithelial cells and local dendritic cells and macrophages. The virus then drains to local lymph nodes, thereby resulting in viremia and spread to target organs like the CNS. After viremia peaks at days 2 to 4 postinfection, IgM and then IgG antibodies can be detected in the serum.

CLINICAL MANIFESTATIONS

The incubation period is 4 to 10 days, and initial symptoms include fever, chills, malaise, myalgias, and arthralgias. The initial systemic illness persists for approximately 1 to 2 weeks, followed by recovery for most patients. Clinical evidence of neuroinvasive disease, which typically develops within the first 3 to 5 days, includes headache, nausea, vomiting, weakness, and meningismus. The neuroinvasive disease is typically severe, with 25% of patients developing seizures, and 90% have a significantly altered mental status.

DIAGNOSIS

Similar to other neuroinvasive arboviruses, the CSF exhibits a lymphocytic pleocytosis, elevated protein level, and normal glucose level. However, encephalitis can cause a neutrophilic pleocytosis in the CSF, and about 75% of patients also have red blood cells in their CSF. RT-PCR testing of serum and CSF has a low sensitivity but a high specificity. The diagnosis is usually confirmed by IgG and IgM testing of the serum and CSF in specialized laboratories.

TREATMENT, PREVENTION, AND PROGNOSIS

Treatment is supportive. There are no approved therapies or vaccines. The overall mortality rate is 30 to 40%, and the majority of survivors have long-term neurologic sequelae[32] that require prolonged rehabilitation and care following infection. A new trivalent virus-like particle vaccine recently completed phase 1 trials[33] and may prove useful in the future.

WESTERN EQUINE ENCEPHALITIS

DEFINITION, EPIDEMIOLOGY, AND PATHOBIOLOGY

Western equine encephalitis is an uncommon disease with about 40 cases per year in the rural plains and Rocky Mountain areas of the United States. Cases are most frequent after snow melt or flooding, and diagnosed equine disease commonly precedes human cases. The disease has also been reported in Argentina. *Culex tarsalis* mosquitoes are the vector, and wild birds serve as the reservoir. The disease mostly affects the basal ganglia and thalami, where it causes focal necrosis.

CLINICAL MANIFESTATIONS AND DIAGNOSIS

After an influenza-like syndrome with fever, headache, and myalgia for 1 to 4 days, patients develop somnolence and lethargy that can progress to stupor, seizures, and coma, with death soon after coma develops. CSF typically shows less than 500 polymorphonuclear and then mononuclear white blood cells/μL and an elevated protein level. Diagnosis usually is achieved by IgM antibodies in serum or CSF, but RT-PCR testing of the serum and CSF is available at specialized reference laboratories.

TREATMENT, PREVENTION, AND PROGNOSIS

There is no specific therapy for Western equine encephalitis, so therapy is supportive. The case-fatality rate is 3 to 5%. Adults usually recover slowly but completely, but children are more likely to have chronic neurologic impairment.

VENEZUELAN EQUINE ENCEPHALITIS

DEFINITION, EPIDEMIOLOGY, AND PATHOBIOLOGY

Venezuelan equine encephalitis occurs in periodic outbreaks, which have been as large as 85,000 human cases in Venezuela, Colombia, Ecuador, Peru, and the Gulf Coast region of Mexico. *Aedes, Psorophora*, and *Mansonia* mosquitoes can serve as vectors, whereas equines are the principal hosts. Laboratory infections commonly occur in unvaccinated persons who work with infected animals or the virus, and the virus is a potential agent for biological warfare. Person-to-person spread can theoretically occur but seems very rare. Sporadic human disease has also been reported in Florida, where *Culex* mosquitoes are the vector and the hosts are small rodents. CNS changes include meningeal and perivascular inflammation, vasculitis, neuronal degeneration, and intracerebral hemorrhage. Hepatitis and interstitial pneumonitis also occur.

CLINICAL MANIFESTATIONS AND DIAGNOSIS

After an incubation period of 2 to 5 days, patients have a self-limited, flulike illness that subsides in 4 to 6 days. However, encephalitis develops in about 4% of infected persons, especially children, and is characterized by seizures, stupor, spastic paralysis, coma, and respiratory failure. Residual neurologic damage occurs in severe cases. The CSF has up to 500 cells/μL, predominantly lymphocytes. Virus can be detected by RT-PCR from blood or from throat swabs. The diagnosis also can be confirmed by IgM immunoassay.

TREATMENT, PREVENTION, AND PROGNOSIS

Treatment is supportive. An experimental live-attenuated vaccine provides partial immunity for adult laboratory personnel. A DNA vaccine for Venezuelan equine encephalitis is under investigation. Epidemics and epizootics can be prevented by vaccinating equines. The case-fatality rate is less than 10% in adults, but patients with severe encephalitis may have persistent neurologic deficits.

BUNYAVIRALES

CALIFORNIA ENCEPHALITIS VIRUS/LA CROSSE VIRUS/JAMESTOWN CANYON VIRUS

DEFINITION AND EPIDEMIOLOGY

California encephalitis virus, La Crosse virus, and Jamestown Canyon virus are mosquito-borne RNA viruses that are members of the California encephalitis group of viruses. These viruses exhibit shared characteristics with other

Bunyavirales members, including a lipid-enveloped virion containing a tripartite, negative- or ambisense, single-stranded RNA genome.

La Crosse virus primarily causes neuroinvasive disease in children and is the leading cause of pediatric viral encephalitis in the United States, where it results in 50 to 100 cases per year.[34] In contrast, Jamestown Canyon virus preferentially causes neuroinvasive disease in adults, with several cases every year in the United States and Canada. Jamestown Canyon virus is widely distributed throughout the United States, whereas La Crosse virus cases are most common in the Gulf Coast and Midwest regions of the United States. California encephalitis virus, which is found in the western United States, is a rare human infection. All three viruses are maintained in enzootic cycles primarily between *Aedes* or *Ochlerotatus* spp of mosquitoes and multiple mammals, including ground squirrels, chipmunks, and white-tailed deer.

PATHOBIOLOGY

La Crosse virus, Jamestown Canyon virus, and California encephalitis virus are transmitted during summer months to humans, who serve as dead-end hosts following the bite of an infected female mosquito with virus in her salivary glands. Following a mosquito bite, these viruses replicate in local cutaneous tissue and distribute via viremia to end-organ tissues such as the CNS.

CLINICAL MANIFESTATIONS AND DIAGNOSIS

Most infections are asymptomatic, but some patients can develop fever, chills, myalgias, nausea, and vomiting after a 3- to 7-day incubation period. In some patients, symptoms can progress to lethargy, aphasia, ataxia, focal weakness, and seizures. Neuroimaging is often negative, and CSF is characterized by lymphocytic pleocytosis, a high-to-normal protein level, and a normal glucose level. The EEG is abnormal in two thirds of patients with focal findings.

Detection of virus using RT-PCR assays may be helpful, especially in immunocompromised patients, but diagnosis usually relies on acute serology for virus-specific IgM in the serum and CSF. Neuroimaging is often negative, but an EEG is important to evaluate for underlying seizure activity.

TREATMENT, PREVENTION, AND PROGNOSIS

No antiviral therapy or vaccine is available for California encephalitis viruses. The mortality rate is less than 1%. Most patients recover without long-term sequelae, but some patients may have long-term complications such as seizures.[35]

REOVIRIDAE

COLORADO TICK FEVER VIRUS

DEFINITION AND EPIDEMIOLOGY

Colorado tick fever is a member of the family *Reoviridae*, a group of nonenveloped, double-stranded RNA viruses. The virions are relatively stable because of an inner icosahedral core that is surrounded by an outer capsid layer, which consists of four viral proteins.

Colorado tick fever is transmitted by the *Dermacentor andersoni* tick to humans in the western United States and western Canada at elevations of 4000 feet above sea level or higher.[36] About five cases are reported annually, predominantly from Colorado, Utah, Wyoming, Montana, Idaho, Oregon, Arizona, and California. The virus is maintained in an enzootic cycle between *D. andersoni* and small rodents and mammals. Humans come in contact with the enzootic cycle during recreational or other activities in forested regions where the virus circulates.

CLINICAL MANIFESTATIONS AND DIAGNOSIS

Following an incubation period of 1 to 14 days, symptoms include fever, chills, headache, myalgias, nausea, vomiting, abdominal pain, and a maculopapular rash on the trunk and arms. About 50% of patients develop a biphasic fever after initial improvement. About 1% of patients progress to neuroinvasive infection, most commonly characterized by meningeal symptoms, including photophobia and meningismus.

Recent outdoor exposure and tick bites in an endemic region are suggestive of infection. Most patients with biphasic illness present with leukopenia (white blood cell count <4000/μL) and thrombocytopenia (<150,000/μL). RT-PCR of blood is sensitive during the acute phase of infection.

TREATMENT, PREVENTION, AND PROGNOSIS

There is no specific therapeutic option or vaccine. Most patients recover completely, but many patients report prolonged fatigue and myalgias that may persist for several weeks. Even with neuroinvasive disease, mortality is less than 1%, and the majority of patients fully recover with no neurologic sequelae.

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353

EPIDEMIOLOGY AND DIAGNOSIS OF HUMAN IMMUNODEFICIENCY VIRUS INFECTION AND ACQUIRED IMMUNODEFICIENCY SYNDROME

LARRY W. CHANG AND THOMAS C. QUINN

Four decades after the initial recognition of acquired immunodeficiency syndrome (AIDS) in 1980 and the subsequent identification of the human immunodeficiency virus (HIV; which exists in two types: HIV-1, which is the predominant circulating type, and HIV-2), the HIV pandemic remains one of the leading causes of death worldwide. Early efforts at prevention and treatment with antiretroviral drugs tempered the spread and decreased the fatality rate in some countries. In low-income countries, however, where the social, demographic, cultural, and economic impact of the AIDS epidemic had been the greatest, these gains were initially too limited and too slow to reverse the escalating trend of the epidemic. Over the past two decades, with the increased availability of antiretroviral drugs and other prevention interventions, including voluntary medical male circumcision, the rate of new HIV infections has decreased and mortality has declined in most settings.

GLOBAL STATISTICS

Since the HIV epidemic began in the first half of the 20th century, more than 79 million people have been infected with HIV and 36 million people have died of HIV.[1] At the end of 2020, according to estimates by the Joint United Nations Program on HIV/AIDS (UNAIDS), 37.7 million people were living with HIV (Table 353-1 and E-Fig. 353-1A). Adults constituted the majority of those infected; children (persons less than 15 years of age) accounted for 1.7 million of the infected. Globally, people living with HIV were evenly divided by gender, although there was substantial regional variation. Sub-Saharan Africa continued to have the majority of persons living with HIV and the highest HIV prevalence rates, but large epidemics are present worldwide (Fig. 353-1 and see Table 353-1). The continuing rise in the population of people living with HIV infection reflects the combined effects of continued HIV transmission and the beneficial impact of antiretroviral therapy, resulting in fewer deaths.[2]

In 2020, the 1.5 million people who became newly infected with HIV globally represented a decline of 31% since 2010 and a marked decline from the more than 3 million infections per year experienced during the peak of the epidemic in the 1990s (see E-Fig. 353-1B and Table 353-1). These declines have been most prominent among children, in whom new infections have decreased by 53% since 2010; decreases in adults have occurred more slowly. Despite this progress, declines remained well short of United Nation's 2020 targets of 500,000 infections per year. Progress has also been uneven across regions, with the steepest declines in new HIV infections in eastern and southern Africa (43%) compared with a troubling 43% rise in new infections in eastern Europe and central Asia. Low- and middle-income countries constitute more than 90% of new infections, and sub-Saharan Africa alone accounts for 58% of all new HIV infections globally.

The major mode of HIV transmission globally in 2020 was heterosexual transmission, although infections continue to spread at high rates among key populations such as men who have sex with men and people who inject drugs. These and other key populations continue to play important roles in all major regional epidemics (E-Fig. 353-2). Outside of sub-Saharan Africa, key populations and their partners accounted for 93% of new HIV infections in 2020. In sub-Saharan Africa, they accounted for 39% of new HIV infections. Globally, women acquire new HIV infections at roughly the same rate as men. However, new infections in young women aged 15 to 24 years were 80% higher than in men, a figure that is a particular concern because this age group accounted for 28% of all new HIV infections in 2020 and is part of an ongoing demographic youth bulge.

HIV continues to be a major source of global morbidity and mortality, although significant progress has been made in scaling up life-saving treatment. Deaths from HIV have declined from a peak of 1.9 million deaths in 2005 to 680,000 deaths in 2020 (Fig. 353-1C), likely owing to increased HIV treatment access and fewer new HIV infections. Gender disparities in mortality are substantial, with declines in deaths about 25% lower among men compared with women, likely because of higher HIV treatment uptake among women. There have been even sharper declines in child mortality due to HIV, with less than 90,000 deaths in 2020 compared with 210,000 in 2010, a 60% decline. Similar to reductions in new HIV infections, declines in deaths due to AIDS-related illnesses have been most pronounced in eastern and southern Africa. In contrast, there have been concerning increases in AIDS-related mortality in some countries in the Middle East and North Africa and eastern Europe and central Asia.

GLOBAL IMPACT AND RESPONSE

For the first two decades of the epidemic, fatality rates from AIDS steadily increased, and the average life expectancy in some countries in sub-Saharan Africa declined from 62 to 47 years of age. For example, in Haiti, life expectancy was nearly 6 years less than it would have been in the absence of AIDS. Cambodia experienced a reduction in life expectancy of more than 4 years. In 1995 in the United States, AIDS was the leading killer of Americans aged 25 to 44 years. Globally, HIV has now claimed an estimated 36 million lives.

Beginning in 1996 in high-income countries, the advent of combination antiretroviral therapy for HIV infection led to dramatic declines in HIV-associated mortality. In low-income and most middle-income countries, the Global Fund for AIDS, Tuberculosis, and Malaria as well as the United States President's Emergency Plan for AIDS Relief (PEPFAR) continue to provide treatment and care for people living with HIV globally, as well as resources for enhancing prevention efforts to stop further transmission. WHO treatment guidelines recommend antiretroviral therapy to all people living with HIV regardless of CD4 count and encourage universal access to HIV testing and care as part of a cascade framework of prevention and care (E-Fig. 353-3).

As of 2020, an estimated 84% of people living with HIV globally were aware of their HIV status. Among those who know their status, an estimated 87%

TABLE 353-1 REGIONAL HUMAN IMMUNODEFICIENCY VIRUS AND ACQUIRED IMMUNODEFICIENCY SYNDROME STATISTICS AND FEATURES AT THE END OF 2020*

REGION	ADULTS AND CHILDREN LIVING WITH HIV/AIDS	ADULTS AND CHILDREN NEWLY INFECTED WITH HIV	ADULT AND CHILD DEATHS DUE TO AIDS	PEOPLE ACCESSING TREATMENT
Eastern and southern Africa	20,600,000	670,000	310,000	16,000,000
Western and central Africa	4,700,000	200,000	150,000	3,500,000
North Africa and Middle East	230,000	16,000	7900	96,000
Asia and the Pacific	5,800,000	240,000	130,000	3,700,000
Latin America	2,100,000	100,000	31,000	1,400,000
Caribbean	330,000	13,000	6000	220,000
Eastern Europe and central Asia	1,600,000	140,000	35,000	870,000
Western and central Europe and North America	2,200,000	67,000	13,000	1,900,000
GLOBAL	37,700,000	1,500,000	680,000	27,500,000

*Numbers are rounded estimates from the Joint United Nations Programme on HIV/AIDS.
AIDS = acquired immunodeficiency syndrome; HIV = human immunodeficiency virus.

ABSTRACT

Within years of its recognition in the 1980s, HIV disseminated rapidly throughout the world, caused a massive global pandemic, and became one of the leading causes of death worldwide. Early efforts at prevention and treatment with antiretroviral drugs tempered the spread and decreased the fatality rate in some countries. In low income countries, however, where the social, demographic, cultural, and economic impact of the AIDS epidemic had been the greatest, these gains were initially too limited to reverse the escalating trend of the epidemic. Over the past two decades, with the increased availability of antiretroviral drugs and other prevention interventions, including voluntary medical male circumcision, the rate of new HIV infections has decreased and mortality has declined in most settings.

KEYWORDS

HIV
epidemiology
AIDS
antiretrovirals
retrovirus

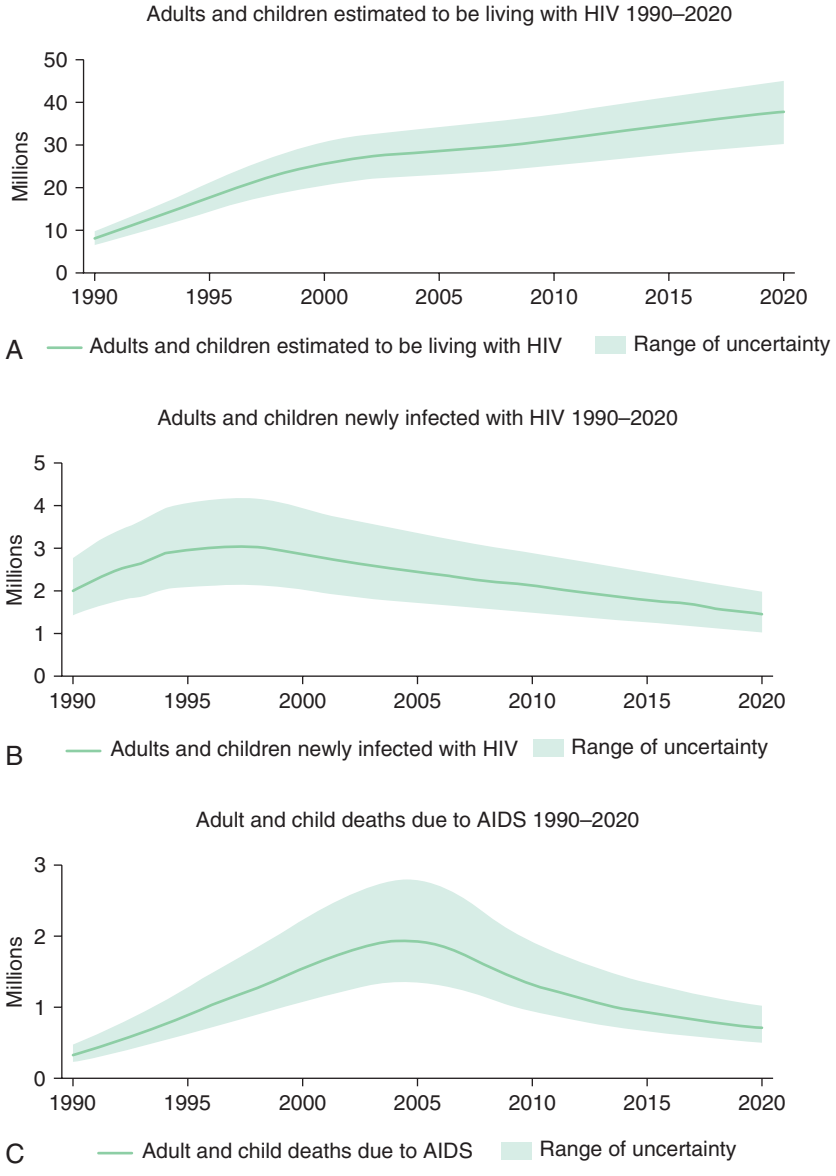

E-FIGURE 353-1. A total of 37.7 million people were living with HIV infection by the end of 2020. Global HIV trends in number of people living with HIV (A), new infections (B), and deaths (C), from 1990 to 2020. AIDS = acquired immunodeficiency syndrome; HIV = human immunodeficiency virus. (Data from UNAIDS 2021.)

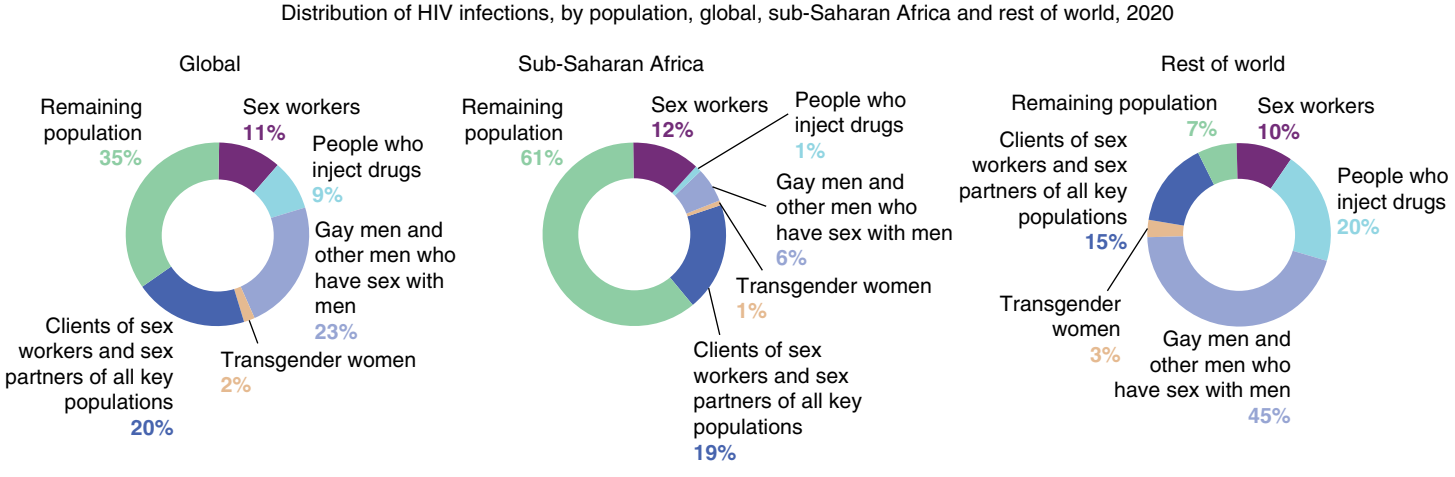

E-FIGURE 353-2. Distribution of human immunodeficiency virus (HIV) infections including key populations, 2020. (Data from UNAIDS. UNAIDS Data 2021. Geneva: UNAIDS; 2021.)

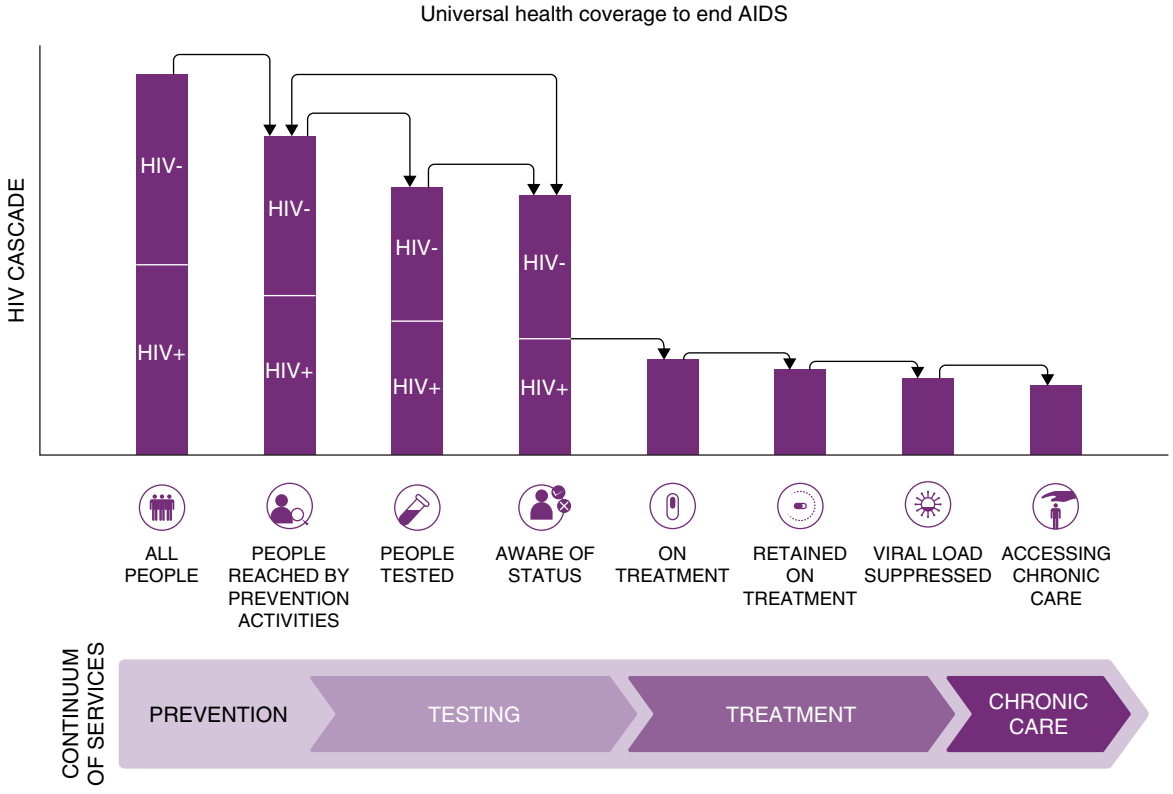

E-FIGURE 353-3. HIV prevention and care cascade describes the continuum of services for preventing and treating HIV. AIDS = acquired immunodeficiency syndrome; HIV = human immunodeficiency virus. (Data from WHO Global Health Sector Strategy on HIV, 2016-2021. Geneva: WHO; 2016.)

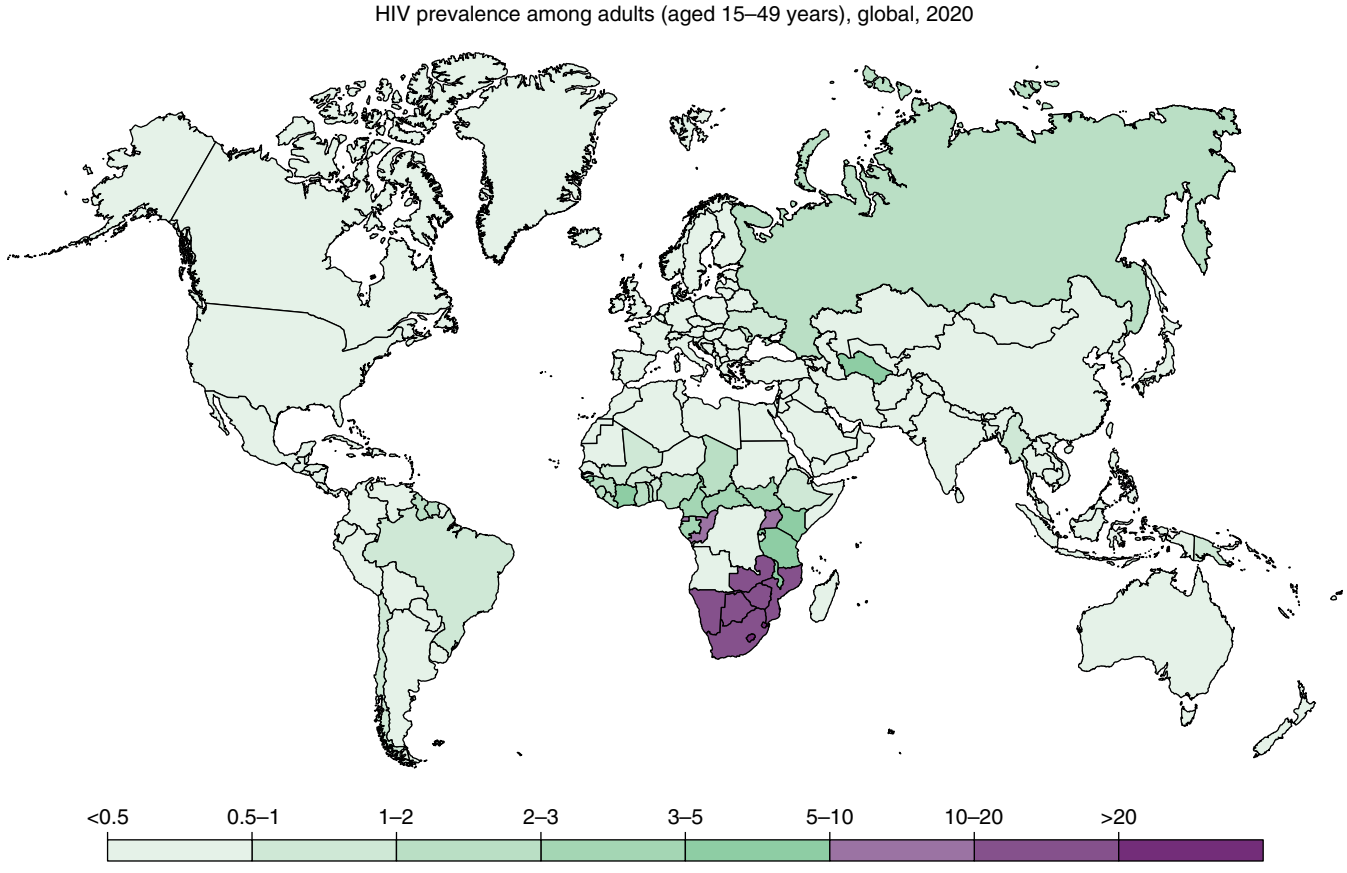

FIGURE 353-1. Prevalence of human immunodeficiency virus (HIV) among adults aged 15-49 years, 2020. (Data from UNAIDS 2021.)

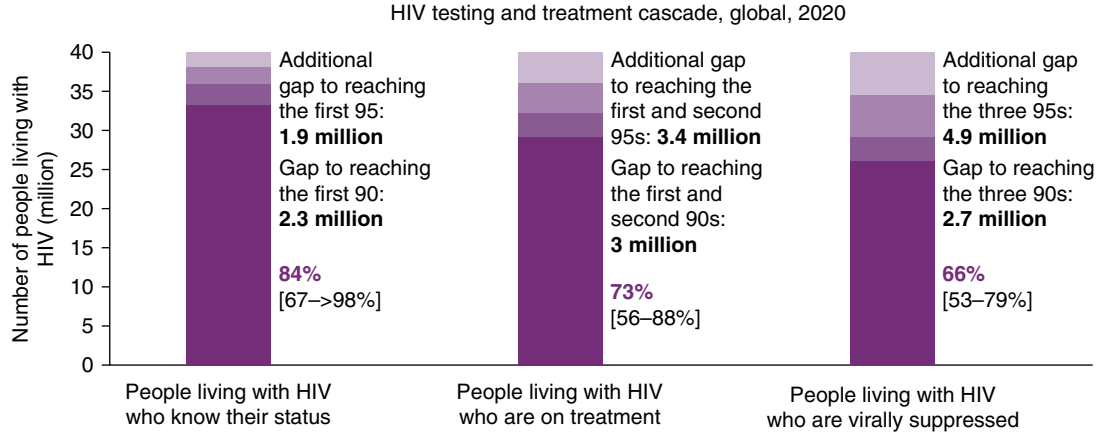

FIGURE 353-2. Global human immunodeficiency virus (HIV) testing and treatment cascade. (Data from UNAIDS. UNAIDS Data 2021. Geneva: UNAIDS; 2021.)

were on treatment, meaning that among all people living with HIV, about 73% were on treatment (Fig. 353-2). Of people on treatment, an estimated 90% were virally suppressed. Thus, in 2020, about 66% of all people living with HIV were virally suppressed. Although these figures represent remarkable progress from the early 2000s, significant gaps in testing and care remain. There is also considerable regional variation, with targets being met in some countries in western and central Europe and sub-Saharan Africa, but less so in eastern Europe and central Asia, the Middle East, and North Africa. Key success stories include Botswana, the first country in Africa to have reached UNAIDS 90-90-90 targets (90% of all people living with HIV will know their HIV status, 90% of those diagnosed are on antiretroviral therapy, and 90% of those on treatment are virally suppressed), and Eswatini, which has achieved a remarkable 97% reported viral suppression among all people living with HIV.

Regarding HIV treatment access, in 2020, an estimated 27.4 million people were on treatment, a dramatic increase from 2010 when only 7.8 million people had access to treatment (see Fig. 353-3). The trajectory of treatment access has been consistently upward for the past two decades, making the 2025 UNAIDS goals of 95% of people living with HIV on antiretroviral therapy a real possibility. People living with HIV also appear to be accessing antiretroviral therapy earlier after initial HIV infection. As a result of the rapid increases in treatment, life expectancy losses have been largely reversed in many countries (see E-Fig. 353-5). Among insured adults in the United States, life-expectancy at age 21 years is estimated to be another 57 years among HIV-treated patients compared with 64 years in uninfected people.[3] Globally, an estimated 16.6 million AIDS-related deaths have been saved due to antiretroviral therapy. Expanded treatment access to pregnant women living with HIV has already resulted in large declines in mother-to-child transmission of HIV.

Although progress in HIV prevention and treatment service access has been impressive, remaining challenges include a significant gender disparity, with men globally having lower knowledge of HIV status (82%) compared to women (88%), lower coverage of antiretroviral therapy (68%) compared with women (79%), and lower HIV viral suppression (62%) compared with women (72%). Young people living with HIV are less likely to know their HIV status, be on treatment, and have suppressed viral loads compared with older age

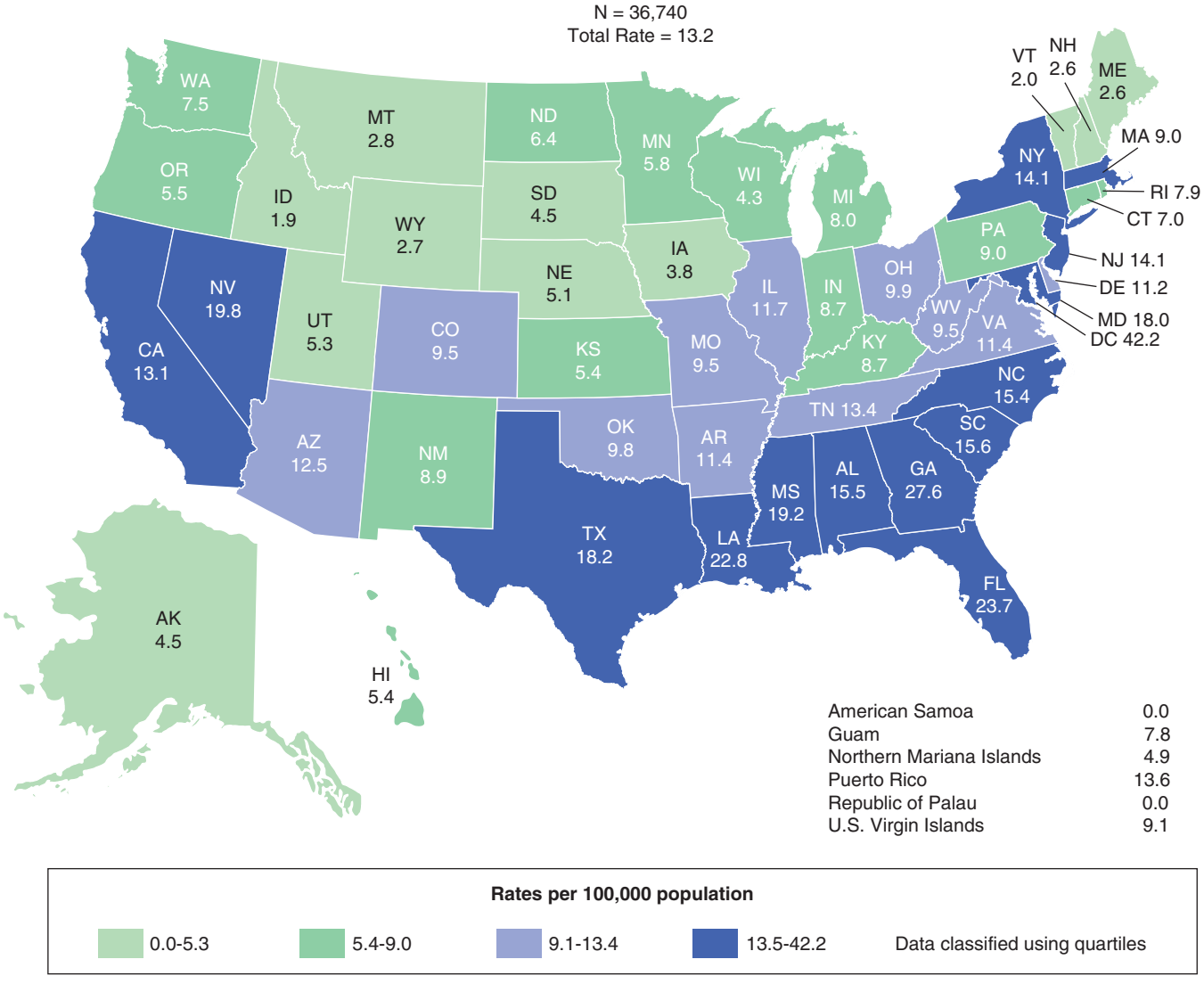

FIGURE 353-3. Rates of new diagnoses of human immunodeficiency virus infection among adults and adolescents, United States and 6 dependent areas, 2019. (Data from Centers for Disease Control and Prevention. HIV Surveillance Report, 2019.)

groups. Key populations, including sex workers, men who have sex with men, people who inject drugs, transgender people, and prisoners have additional barriers to testing and care, and resulting gaps in the HIV prevention and care cascade. HIV viral load testing access has increased rapidly, but more than half of persons on treatment remain without periodic viral load testing. In almost all target countries, global uptake of voluntary medical male circumcision, which reduces the risk for HIV acquisition among heterosexual men by about 55% and among men who have sex with men by about 20%,[A1] remains well below World Health Organization targets of 90%. Condoms, an effective HIV prevention tool, remain underused. Globally, comprehensive harm reduction programs for people who inject drugs, including needle-syringe programs and opioid substitution therapy, are also infrequently implemented. Finally, stigma, discrimination, gender-based violence, and HIV criminalization laws hinder HIV service uptake and retention, particularly among key populations.[4]

Numerous strategies can help the continuing global response to overcome existing challenges across the continuum of prevention and care. These strategies include the gradual expansion of preexposure prophylaxis (PrEP; Chapter 356),[5] either on-demand[A2] or daily[A3] among high-risk HIV-negative persons (E-Fig. 353-4),[6] as well as HIV self-testing and community-based testing to increase awareness of HIV serostatus. Differentiated care, a client-centered approach to HIV service delivery, is another approach being implemented that attempts to simplify and adapt HIV services to individual patient circumstances (e.g., stable people living with HIV on antiretroviral therapy with undetectable viral loads may need fewer provider visits, or a group of people living with HIV may form community-based treatment and support groups). In many global settings, new, less expensive, and improved antiretroviral therapy, such as integrase-based regimens, has improved access and outcomes. In the years to come, additional resources will be required to reach the additional millions of HIV-infected people who require treatment, retain those on treatment, and reach the millions of HIV-negative persons who would benefit from HIV prevention services.

REGIONAL EPIDEMICS AND RESPONSES

EASTERN AND SOUTHERN AFRICA

The 21 countries that make up eastern and southern Africa represent the epicenter of the global HIV/AIDS pandemic (see Table 353-1).[7] More than half of all people living with HIV reside in eastern and southern Africa. HIV prevalence varies widely across countries. The highest HIV prevalence rates in the world are found in Eswatini (27%). South Africa, the most populous country in this region, has an HIV prevalence of 19%. The main mode of transmission in this region is heterosexual sex. The number of new HIV infections in eastern and southern Africa has dropped from 1.1 million in 2010 to 670,000 in 2020, a 43% decline (E-Fig. 353-5). This decline has been even more pronounced in children with a 64% reduction from 2010 to 2020.

Knowledge of HIV status and HIV treatment coverage in eastern and southern Africa has risen steeply over the past decade. In 2020, about 90% of all people living with HIV in this region were aware of their HIV status (E-Fig. 353-6), 78% were on treatment, and an estimated 72% were virally suppressed. Significant progress has also been made with HIV treatment, with an estimated 16 million people on treatment in eastern and southern Africa in 2020, quadruple the number from 2010. As a result, mortality from AIDS-related deaths in this region has dropped by 50% since 2010 to a still substantial 310,000 deaths in 2020 (see E-Fig. 353-6). Continued support

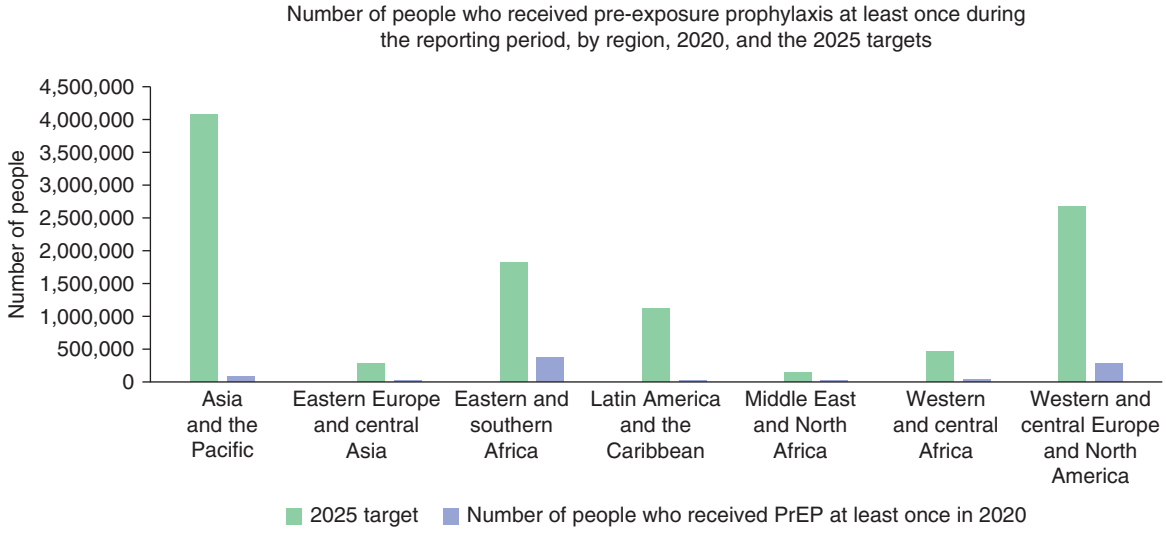

E-FIGURE 353-4. Preexposure prophylaxis coverage (PrEP) by World Health Organization regions, 2020. (Data from UNAIDS. UNAIDS Data 2021. Geneva: UNAIDS; 2021.)

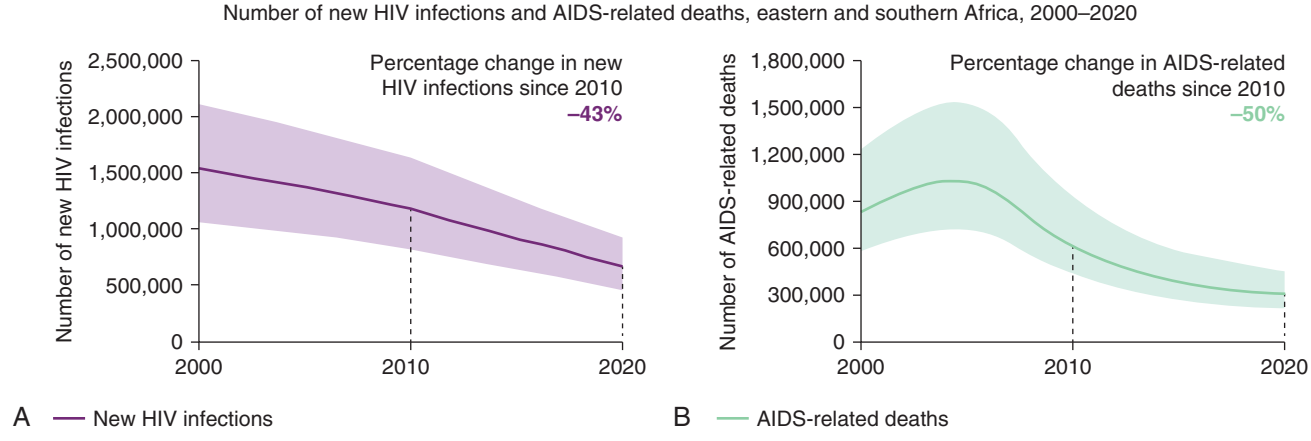

E-FIGURE 353-5. Trends in human immunodeficiency virus (HIV) infections (A) and deaths related to the acquired immunodeficiency syndrome (AIDS) (B), 2000-2020, eastern and southern Africa. (Data from UNAIDS. UNAIDS Data 2021. Geneva: UNAIDS; 2021.)

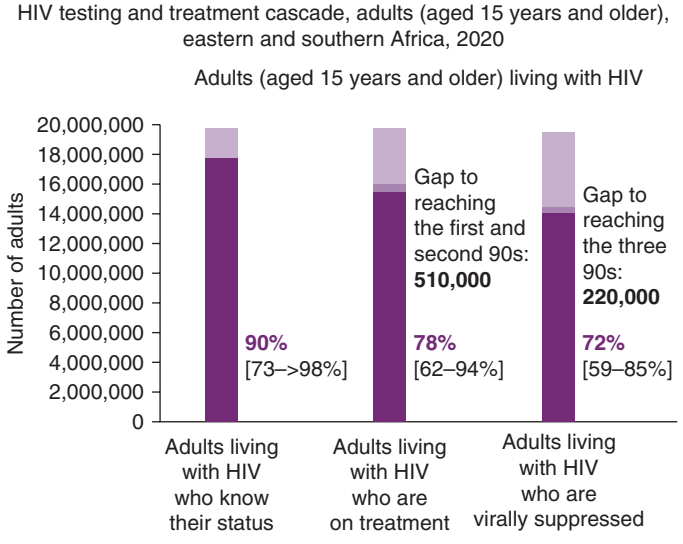

E-FIGURE 353-6. Human immunodeficiency virus (HIV) testing and treatment cascade, eastern and southern Africa in 2020. (Data from UNAIDS. UNAIDS Data 2021. Geneva: UNAIDS; 2021.)

of HIV treatment and prevention services will be needed if this region is to maintain and build on past advances.

WESTERN AND CENTRAL AFRICA

This region includes 25 countries and accounts for 12% of people living with HIV globally. Overall HIV prevalence is about 2.0% in this region, with prevalence ranging from 7.3% in Equatorial Guinea to 0.2% in Niger. The main mode of transmission is heterosexual sex. The number of new HIV infections in this region declined substantially between 2010 and 2020 from 400,000 to 200,000 (E-Fig. 353-7). Of note, Nigeria accounted for 43% of new HIV infections in this region in 2020 because of its large population, but the number of new infections decreased in Nigeria by 22% from 2010 to 2020.

Despite meaningful recent progress, knowledge of HIV serostatus remains suboptimal in this region, with 81% of people living with HIV being aware of their status, 77% being on treatment, and an estimated 62% being virally suppressed (E-Fig. 353-8), below UNAIDS 2020 goals of 73% viral suppression. AIDS-related mortality remains significant in this region, with 150,000 deaths in 2020 (see E-Fig. 353-7). HIV testing, prevention, and treatment programs must be continued in this region to address the ongoing epidemic.

NORTH AFRICA AND THE MIDDLE EAST

This region includes 20 countries and contains 230,000 people living with HIV. HIV prevalence averages less than 0.1% in countries in this region. The number of new HIV cases in North Africa and the Middle East has risen by 7% between 2010 and 2020 to around 16,000 cases annually (E-Fig. 353-9). The epidemic in this region is driven primarily by a combination of injection drug use and heterosexual transmission. Key populations and their partners contributed to almost all (95%) new infections in 2020. Three countries—Iran, Egypt, and Somalia—accounted for 60% of all new HIV infections in this region.

Despite some recent progress, knowledge of HIV status in this region in 2020 was only 61% (E-Fig. 353-10). Access to antiretroviral medications among all people living with HIV was 43%, which is very far off global goals. Viral suppression among all people living with HIV was only 37%, dramatically short of the UNAIDS 2020 goal of 73% viral suppression. In contrast to most other regions, AIDS-related deaths in North Africa and the Middle East have only decreased modestly, 17%, from 2010 to 2020 (see E-Fig. 353-9). This region needs substantial additional efforts to close major gaps in treatment and prevention cascades.

ASIA AND THE PACIFIC

After sub-Saharan Africa, Asia and the Pacific, which are home to 38 countries and 60% of the world's population, have the second largest number of HIV-positive individuals in the world, estimated at 5.8 million, which is 15% of the global total.[8] With the exception of Thailand, where HIV prevalence is 1.0%, national HIV prevalence levels remain comparatively low, well less than 1%, in most countries of Asia and the Pacific. However, low prevalences in large population bases can result in substantial HIV burdens. For example, an estimated adult HIV prevalence rate of 0.2% in India translates to 2.1 million people living with HIV—one of the highest total numbers in the world after South Africa. In 2020, there were 240,000 new infections in this region, a decline of 21% from 2010 (E-Fig. 353-11). Key populations and their partners contributed to almost all (94%) new infections in 2020.

Knowledge of HIV serostatus in Asia and the Pacific has increased steadily and in 2020 was at 76% (E-Fig. 353-12). Between countries there was significant variability, with awareness particularly high in countries such as Thailand (94%) compared with countries such as Indonesia (66%). About 3.7 million people living with HIV in this region were on antiretroviral therapy, representing 64% of this population, a remarkable increase from just 19% coverage in 2010 but still short of UNAIDS 90-90-90 goals for 2020. Viral suppression rates are estimated at 61% of all people living with HIV, a substantial gap from the 2020 73% target. With increased access to treatment, mortality has declined to 130,000 deaths in 2020, a 56% decrease from 2010 (see E-Fig. 353-11). Although progress has been made in this region, additional efforts are needed to reach key populations, address disparities in service and treatment access, and reach goals.[9]

EASTERN EUROPE AND CENTRAL ASIA

The 16 countries that make up this region contain 1.6 million people living with HIV. HIV prevalence averages about 1%, but, in contrast to other regions, the HIV epidemic in many countries of eastern Europe and central Asia is growing. An estimated 140,000 new cases of HIV occurred in 2020, a worrying 43% increase from 2010 (E-Fig. 353-13). The HIV epidemic in this region is strongly driven by people who inject drugs, who accounted for 43% of all new infections in 2020. The increase is dominated by the Russian Federation, which accounted for about 85% of all new HIV infections in this region in 2020. Ukraine accounted for another 7%. In this region, key populations and their partners contributed to almost all (91%) new infections in 2020.

Knowledge of HIV status in this region has improved slowly, with 70% aware in 2020 (E-Fig. 353-14). Access to antiretroviral therapy has improved from 2010, when only 12% of all people living with HIV were on treatment, to 53% now accessing antiretrovirals. However, the coverage rates remain well short of global goals. Among those on treatment, viral suppression is good; but, because of the low treatment access rates, only 50% of all people living with HIV in this region are virally suppressed. People who inject drugs, and who represent the population most at risk for HIV in eastern Europe and central Asia, are often least likely to receive treatment when they are medically eligible. Not surprisingly, AIDS-related deaths in this region have continued to rise. In 2020, there were 35,000 AIDS-related deaths, a 32% increase from 2010 (see E-Fig. 353-13). If more resources are not brought to bear and effective interventions are not implemented in the more severely affected countries in this region, it is likely that the epidemic in these countries will continue to worsen over the next decade.

LATIN AMERICA

An estimated 2.1 million adults and children are living with HIV in the 17 countries that make up the Latin American region. Overall HIV prevalence is 0.5% in this region. Brazil, with its large overall population, accounts for 930,000 people living with HIV. In 2020, the number of new HIV infections was 100,000, an unappreciable change from 2010 and in contrast to most other regions of the world, which have experienced declines (E-Fig. 353-15). Because of its size, Brazil accounted for about half of all new HIV infections in this region. HIV transmission in Latin America is predominantly through heterosexual or homosexual transmission. In this region, key populations and their partners contributed to almost all (92%) new infections in 2020.

Latin America has done modestly well with increasing HIV testing service access, with 81% of people living with HIV aware of their HIV status (E-Fig. 353-16). In 2020, there were 1.4 million people living with HIV on antiretroviral treatment in this region, nearly double the number from 2010; however, this figure represented only 65% of all people living with HIV. Viral suppression was estimated at 60% of all people living with HIV in 2020, still well short of 90-90-90 goals. Mortality from AIDS has modestly decreased in Latin America (see E-Fig. 353-15). From 2010 to 2020, there was a decrease of 21% to 31,000 annual deaths. Increased resources, wider access to antiretroviral therapy, and other strategies will be needed to move this region toward UNAIDS epidemic control goals.

CARIBBEAN

The 16 countries in the Caribbean region accounted for 330,000 people living with HIV in 2020. Overall HIV prevalence was about 1%. In several Caribbean countries, adult HIV prevalence rates are surpassed only by the rates experienced in sub-Saharan Africa, which makes this region the second most affected in the world. Haiti remains the worst affected, with an estimated national prevalence of 1.9%. The number of new cases in 2020 was 13,000, a 28% reduction since 2010 (E-Fig. 353-17). Homosexual and heterosexual transmission continues to be the major mode of transmission throughout the region. Key populations and their partners contributed to the majority (68%) of new infections in 2020.

Knowledge of HIV status in this region stands at 83%. Of all people living with HIV, only 67% are on antiretroviral treatment, and 60% are virologically suppressed, which remains well short of UNAIDS 2020 goals (E-Fig. 353-18). With increasing access to treatment, AIDS-related deaths have declined. In 2020, 6000 AIDS-related deaths were estimated to have occurred, a 51% decrease from 2010 (see E-Fig. 353-17). Resources for HIV treatment and prevention in this region remain limited, and additional measures and support will be needed to reach the 90-90-90 goals.

WESTERN AND CENTRAL EUROPE AND NORTH AMERICA

Thirty-nine countries make up this high-income region spread across two continents, where 2.2 million people living with HIV reside. Overall HIV prevalence is 0.3%, with no country having a prevalence higher than 0.8%. The number of new HIV infections has declined modestly (11%) from 2010 to 2020, with an estimated 67,000 new infections in 2020 (E-Fig. 353-19). The United States (see later) accounted for about half of all these new infections.

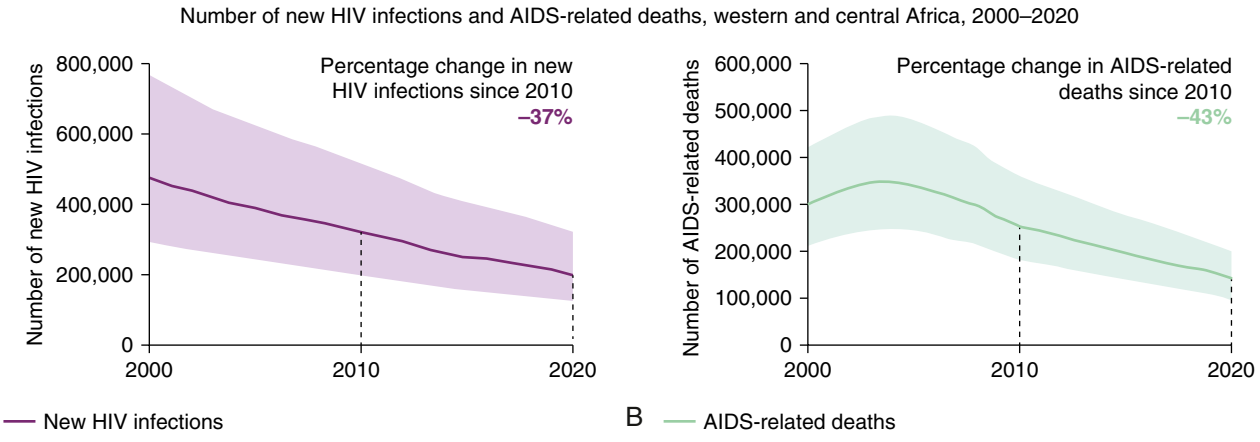

E-FIGURE 353-7. Trends in HIV infections (A) and AIDS-related deaths (B), 2000-2020, western and central Africa. AIDS = acquired immunodeficiency syndrome; HIV = human immunodeficiency virus. (Data from UNAIDS. UNAIDS Data 2021. Geneva: UNAIDS; 2021.)

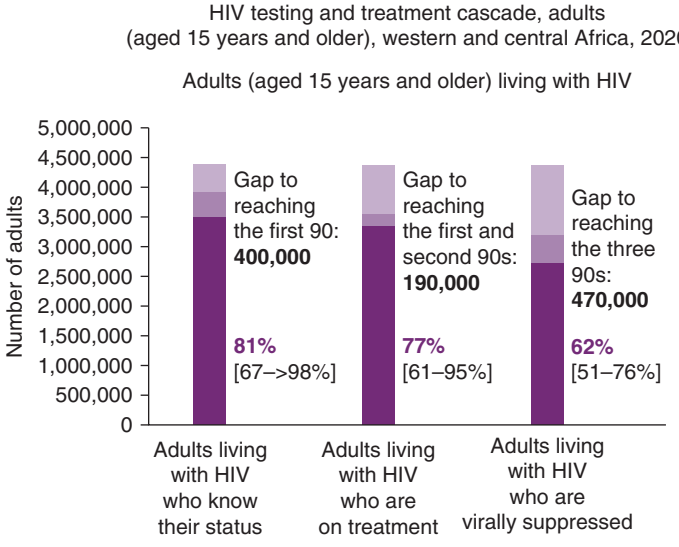

E-FIGURE 353-8. Human immunodeficiency virus (HIV) testing and treatment cascade, west and central Africa in 2020. (Data from UNAIDS. UNAIDS Data 2021. Geneva: UNAIDS; 2021.)

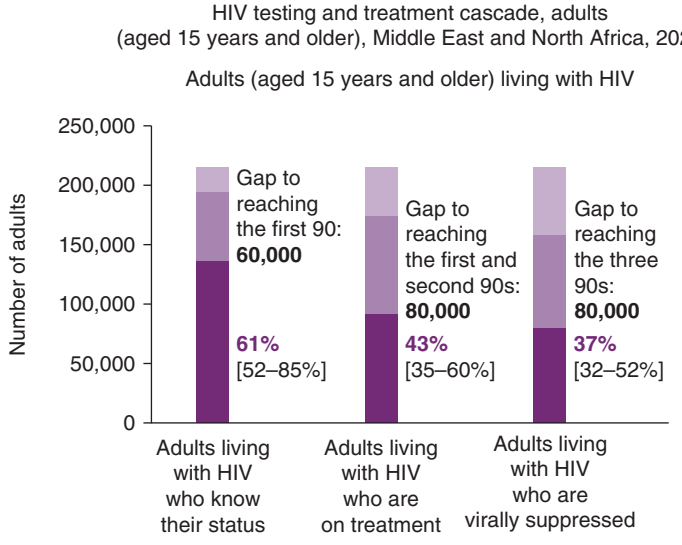

E-FIGURE 353-10. Human immunodeficiency virus (HIV) testing and treatment cascade, Middle East and North Africa in 2020. (Data from UNAIDS. UNAIDS Data 2021. Geneva: UNAIDS; 2021.)

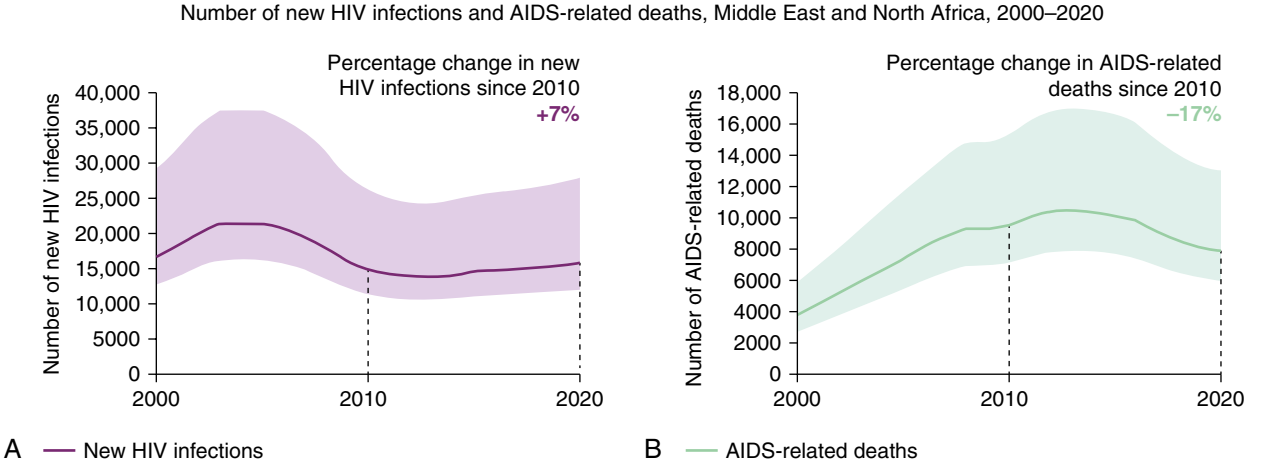

E-FIGURE 353-9. Trends in HIV infections (A) and AIDS-related deaths (B), 2000-2020, Middle East and North Africa. AIDS = acquired immunodeficiency syndrome; HIV = human immunodeficiency virus. (Data from UNAIDS. UNAIDS Data 2021. Geneva: UNAIDS; 2021.)

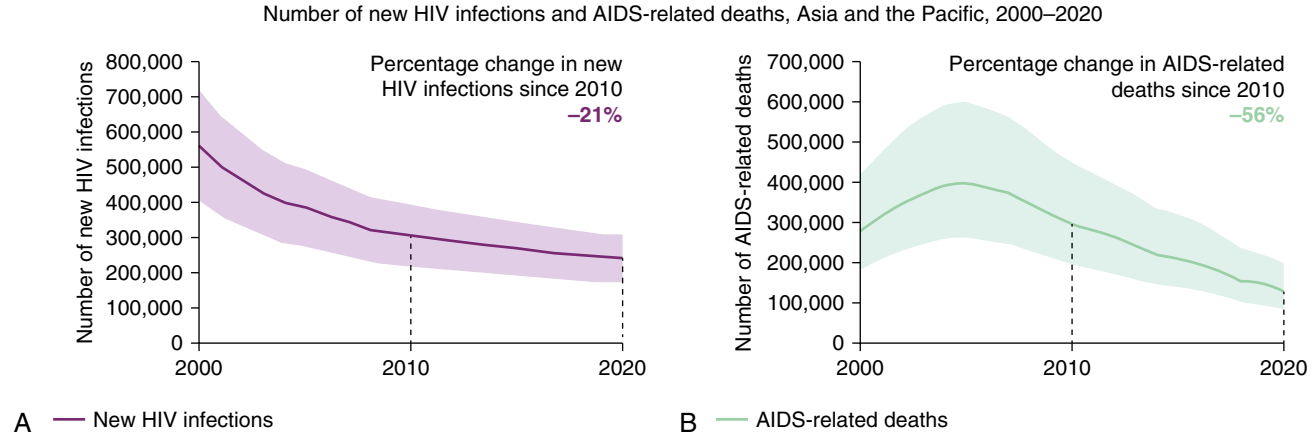

E-FIGURE 353-11. Trends in HIV infections (A) and AIDS-related deaths (B), 2000-2020, Asia and the Pacific. AIDS = acquired immunodeficiency syndrome; HIV = human immunodeficiency virus. (Data from UNAIDS. UNAIDS Data 2021. Geneva: UNAIDS; 2021.)

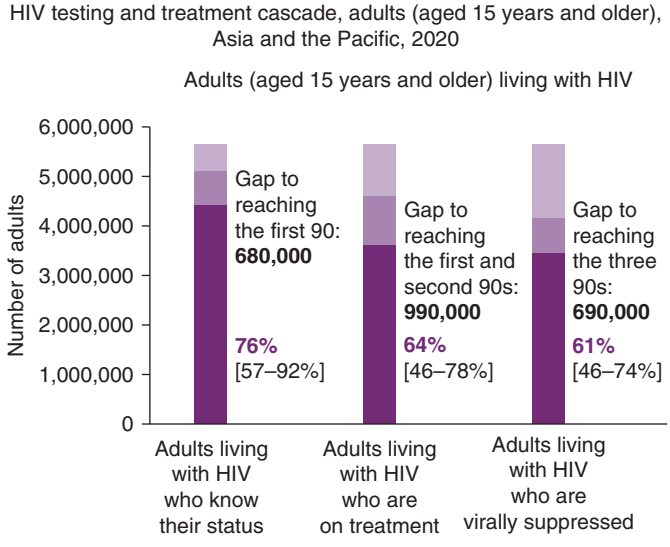

E-FIGURE 353-12. Human immunodeficiency virus (HIV) testing and treatment cascade, Asia and the Pacific in 2020. (Data from UNAIDS. UNAIDS Data 2021. Geneva: UNAIDS; 2021.)

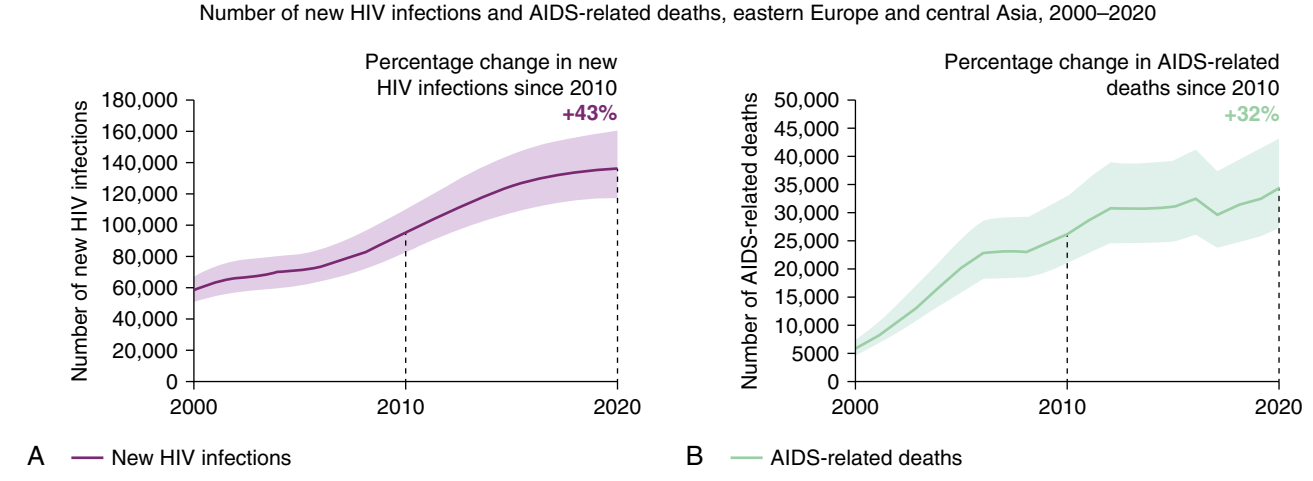

E-FIGURE 353-13. Trends in HIV infections (A) and AIDS-related deaths (B), 2000-2020, eastern Europe and central Asia. AIDS = acquired immunodeficiency syndrome; HIV = human immunodeficiency virus. (Data from UNAIDS. UNAIDS Data 2021. Geneva: UNAIDS; 2021.)

E-FIGURE 353-14. Human immunodeficiency virus (HIV) testing and treatment cascade for women (A) and men (B), eastern Europe and central Asia in 2020. (Data from UNAIDS. UNAIDS Data 2021. Geneva: UNAIDS; 2021.)

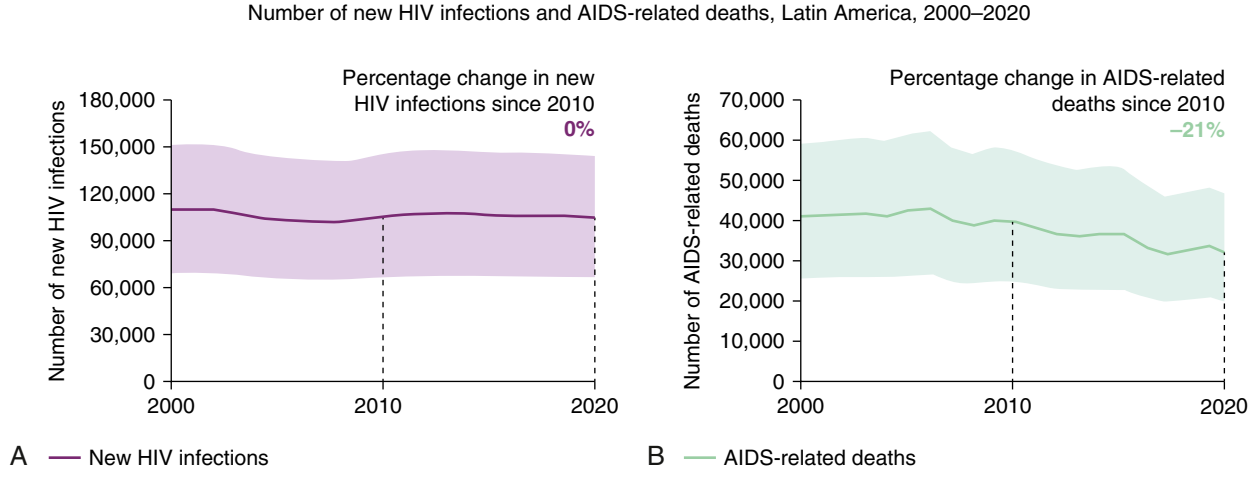

E-FIGURE 353-15. Trends in HIV infections (A) and AIDS-related deaths (B), 2000-2020, Latin America. AIDS = acquired immunodeficiency syndrome; HIV = human immunodeficiency virus. (Data from UNAIDS. UNAIDS Data 2021. Geneva: UNAIDS; 2021.)

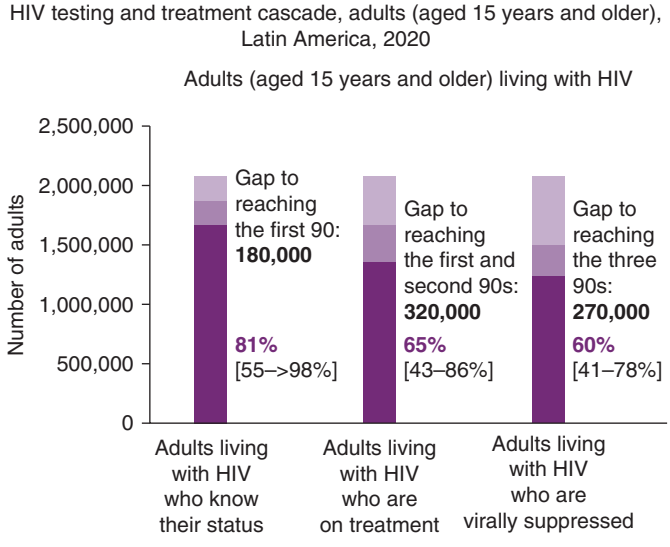

E-FIGURE 353-16. Human immunodeficiency virus (HIV) testing and treatment cascade, Latin America in 2020. (Data from UNAIDS. UNAIDS Data 2021. Geneva: UNAIDS; 2021.)

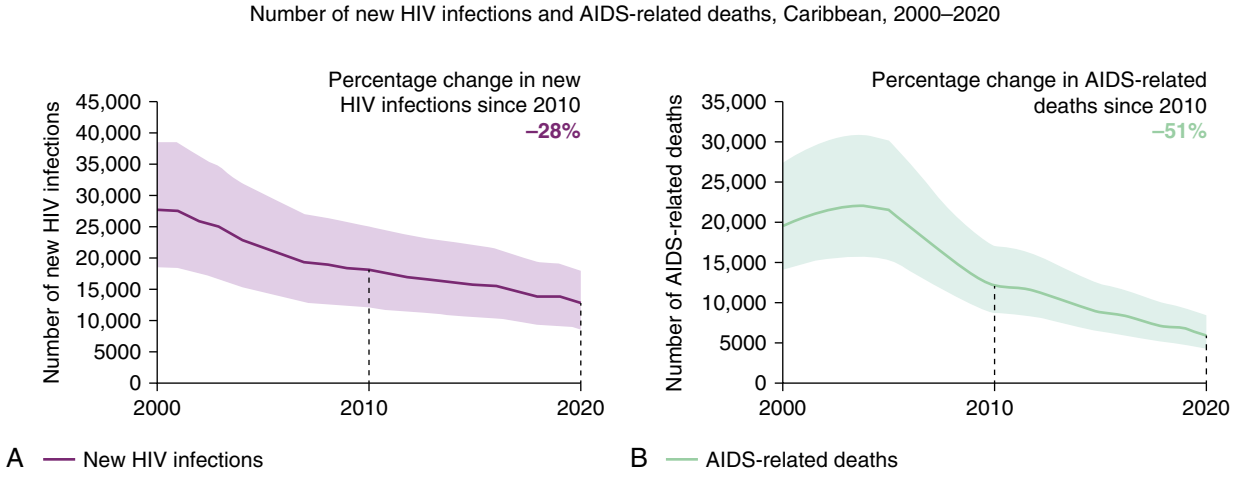

E-FIGURE 353-17. Trends in HIV infections (A) and AIDS-related deaths (B), 2000-2020, Caribbean. AIDS = acquired immunodeficiency syndrome; HIV = human immunodeficiency virus. (Data from UNAIDS. UNAIDS Data 2021. Geneva: UNAIDS; 2021.)

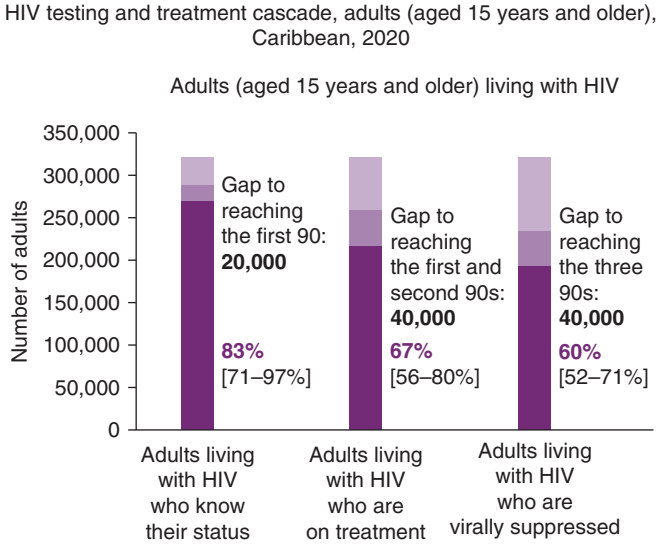

E-FIGURE 353-18. Human immunodeficiency virus (HIV) testing and treatment cascade, Caribbean in 2020. (Data from UNAIDS. UNAIDS Data 2021. Geneva: UNAIDS; 2021.)

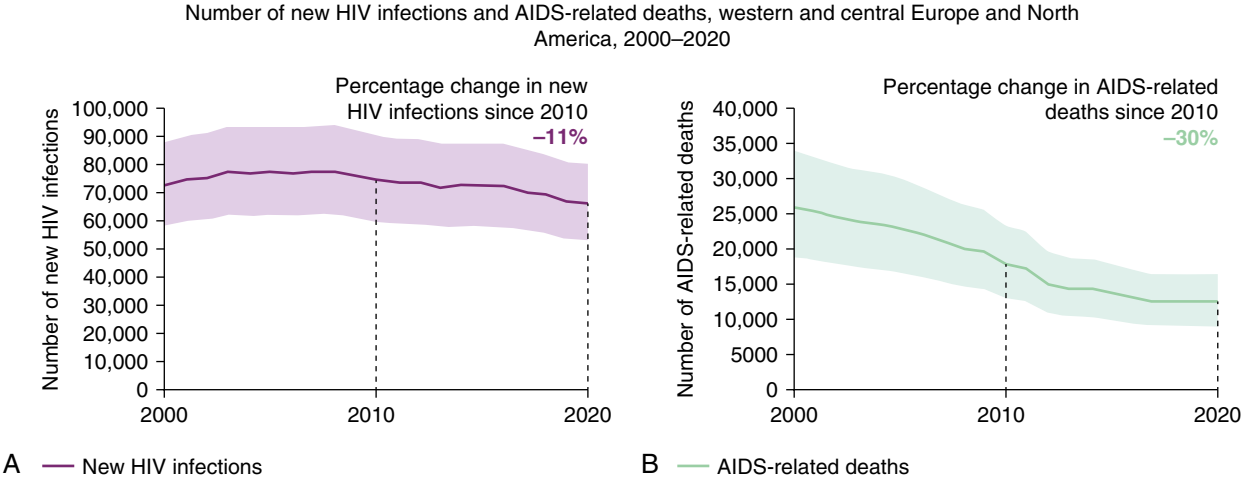

E-FIGURE 353-19. Trends in HIV infections (A) and AIDS-related deaths (B), 2000-2020, central Europe and North America. AIDS = acquired immunodeficiency syndrome; HIV = human immunodeficiency virus. (Data from UNAIDS. UNAIDS Data 2021. Geneva: UNAIDS; 2021.)

Certain countries, such as Denmark, the Netherlands, and Portugal, have experienced declines in new HIV infections of over 20% over the same time period. However, multiple countries, including Serbia, Slovakia, Czechia, and many others, have increasing new HIV infections. In this region, key populations and their partners contributed to almost all (96%) of new infections in 2020.

The HIV epidemic in western Europe is a result of a multitude of epidemics that differ in their timing, scale, and effects on populations. Unprotected sex between men remains the most important factor for spread in North America and most countries in western Europe. A large proportion of new HIV diagnoses in this region also occur through heterosexual intercourse. Injection drug use remains a major mode of transmission, particularly in the Baltic countries (Estonia, Latvia, and Lithuania). Most data from high-income countries demonstrate that the epidemic has shifted to the poor and marginalized sections of society. Recent introduction of preexposure prophylaxis (Chapter 356) has likely resulted in decreasing HIV transmission among men who have sex with men, at least in some settings.

In 2020, this well-resourced region had 90% of people living with HIV aware of their HIV serostatus (E-Fig. 353-20). In 2020, 83% of all people living with HIV were on treatment. Of all people living with HIV, an estimated 75% were virally suppressed, which met the 73% UNAIDS 2020 targets for viral suppression. As a result of expanded testing and treatment, AIDS-related deaths have decreased by about 30% from 2010 to 2020 with a current rate of 13,000 annual deaths (see E-Fig. 353-19). Despite significant successes, marginalized populations continue to share disproportionately in the burden of new infections and mortality. Continued efforts and new strategies will be needed to reach even more ambitious 2030 UNAIDS 95-95-95 targets as a region.[10]

THE UNITED STATES

By the end of 2019, an estimated 1.2 million people were living with HIV in the United States.[11] Nationally, the adult HIV prevalence was estimated to be about 0.5%. This increase in people living with HIV reflects mixed results in the United States' efforts to combat its epidemic. More people infected with HIV are living longer because of antiretroviral therapy; but, unfortunately, major gains in prevention have not been realized. Of people living with HIV, about 13% were not yet diagnosed and aware that they were infected with HIV in 2019. Of the 1.06 million who had been diagnosed, about 75% were men. Of these men, about 35% were Black, 32% were White, and 26% were Hispanic/Latino. Of the women, 57% were Black, 16% were White, and 21% were Hispanic/Latino. Of the men, most (73%) acquired infection attributable to male to male sexual contact,[12] with 10% due to heterosexual contact and 9% due to injection drug use. In contrast, among women, 77% of prevalent infections were attributable to heterosexual contact and 20% to injection drug use. Of note are the tremendous regional and state-by-state differences in the prevalence of HIV (see Fig. 353-3). The highest rates of adults and adolescents living with diagnosed HIV infection are found in southern states, the mid-Atlantic, and California.

The number of newly recorded HIV cases in the United States has varied only slightly since the late 1990s, although there has been a recent modest downward trend. In 2019, there were an estimated 34,800 new HIV infections, about an 8% decrease from 2015. About 70% of these new infections in 2019 occurred due to male to male sexual contact; 23% were attributed to heterosexual contact; and 7% were due to injection drug use. Since 2015, there has been no major change in the share of new HIV infections attributed to heterosexuals (23%). In contrast there was a 9% increase among people who inject drugs. Men accounted for 79% of all new diagnoses. Blacks accounted for 42% of all new HIV diagnoses; Hispanics/Latino accounted for 29%. Accordingly, two of the most-affected subpopulations are Black gay and bisexual men, who accounted for 26% of all new HIV infections in 2019, and Latino gay and bisexual men, who accounted for another 23%. Regarding age, in 2019, the highest rates of new HIV infections were in persons ages 25 to 29 years (31 diagnoses per 100,000 population) followed by those 20 to 24 years (27.3). Similar to HIV prevalence rates, there was also large geographic variations in new HIV diagnosis rates, with the highest rates found in the South (e.g., Georgia, Florida), the mid-Atlantic (e.g., Maryland, New York), California, Texas, and Nevada.

In the United States, more than 760,000 people with AIDS have died since the epidemic began. Mortality peaked in 1995 and has steadily declined since then with the use of increasingly effective antiretroviral therapy, although the slope of decline has been modest or flat for more than a decade now (Fig. 353-4). In 2019, there were about 15,800 deaths from any cause of persons with diagnosed HIV infection, a rate of 5.7 per 100,000. Marked racial/ethnic disparities were evident, with death rates among Black Americans (16.1/100,000) much higher compared with Hispanic/Latinos (4.5/100,000) and Whites (2.5/100,000). Black Americans accounted for about 42% of all deaths of persons with diagnosed HIV infection, Hispanic/Latinos 17%, and Whites 31%. Death rates were higher in men (8.9/100,000) compared with women (2.6/100,000), and higher in the Northeast and South compared with the Midwest and West.

An estimated 13% of people living with HIV in the United States are unaware of their HIV status. Moreover, in 2019, 34% of people living with HIV have not accessed HIV care, and only 57% of all people living with HIV were virally suppressed in the United States (Fig. 353-5). Viral suppression was particularly low in persons ages 13 to 24 years compared with persons older than 45 years. Black Americans also had the lowest rates of viral suppression compared with other races. New resources and strategies will be needed to close these disparities and gaps in the United States' HIV care continuum.[13]

With such a long-standing epidemic, complacency has increased, and some prevention efforts have dwindled as a result of declining morbidity and mortality. The increasing rate of effective viral suppression to reduce infectivity[A4] as well as the uptake of preexposure prophylaxis by mostly men who have sex with men offers hope but is tempered by increasing rates of sexually transmitted

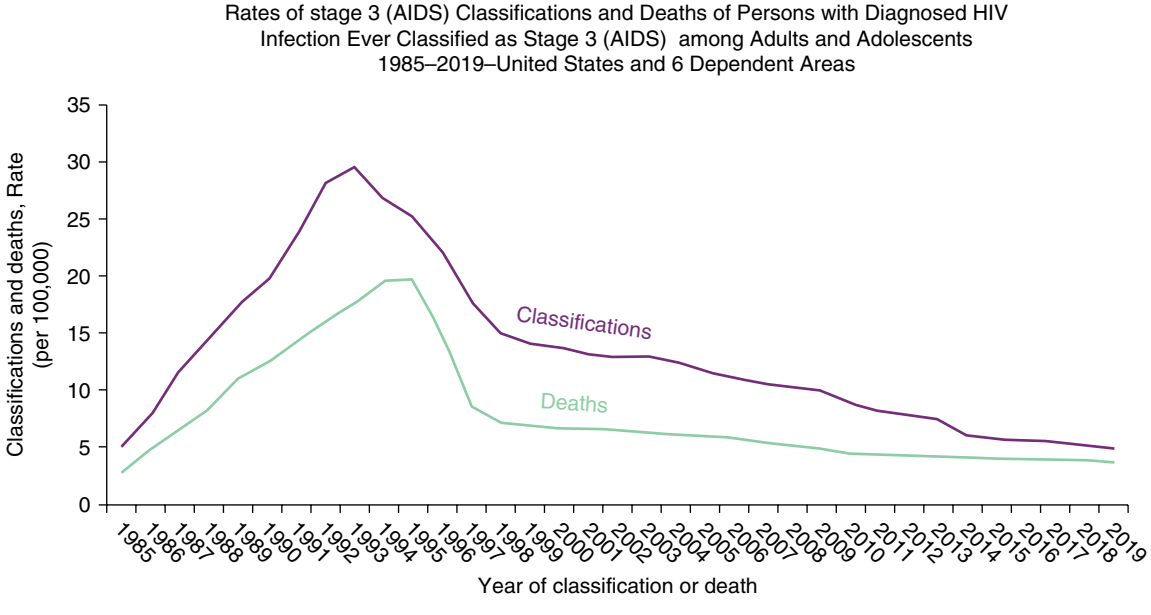

FIGURE 353-4. Trends in AIDS classifications and deaths among adults and adolescents in the United States and dependent areas, 1985-2019. AIDS = acquired immunodeficiency syndrome; HIV = human immunodeficiency virus. (Data from Centers for Disease Control and Prevention. HIV Surveillance Report, 2019.)

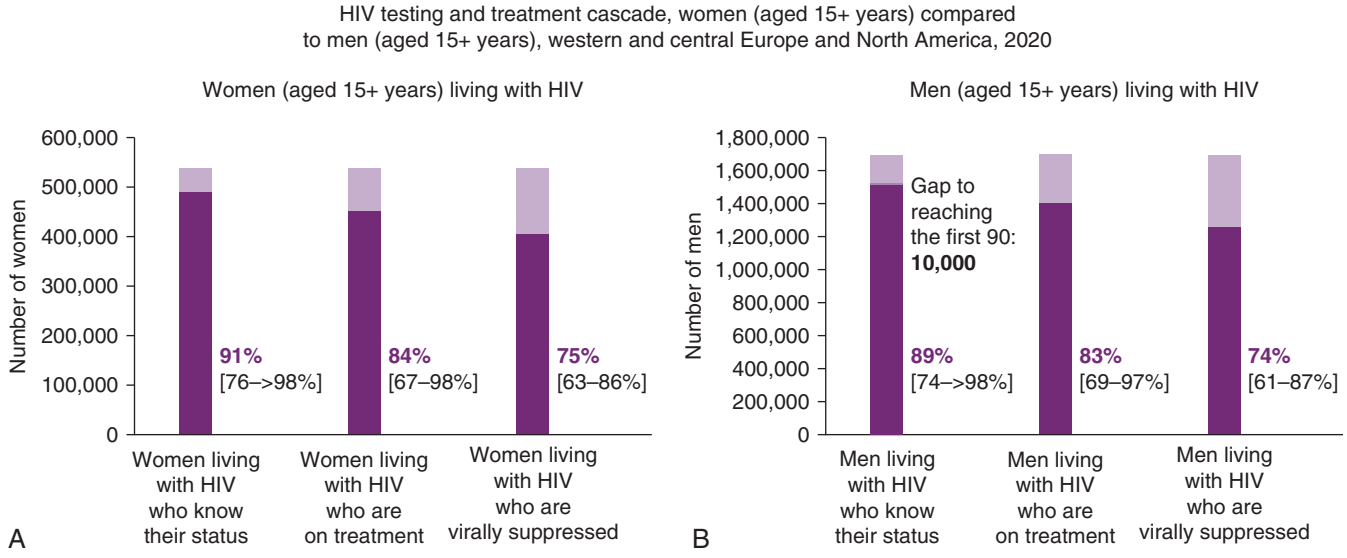

E-FIGURE 353-20. **Human immunodeficiency virus (HIV) testing and treatment cascade for women (A) and men (B), central Europe and North America, in 2020.** (Data from UNAIDS. UNAIDS Data 2021. Geneva: UNAIDS; 2021.)

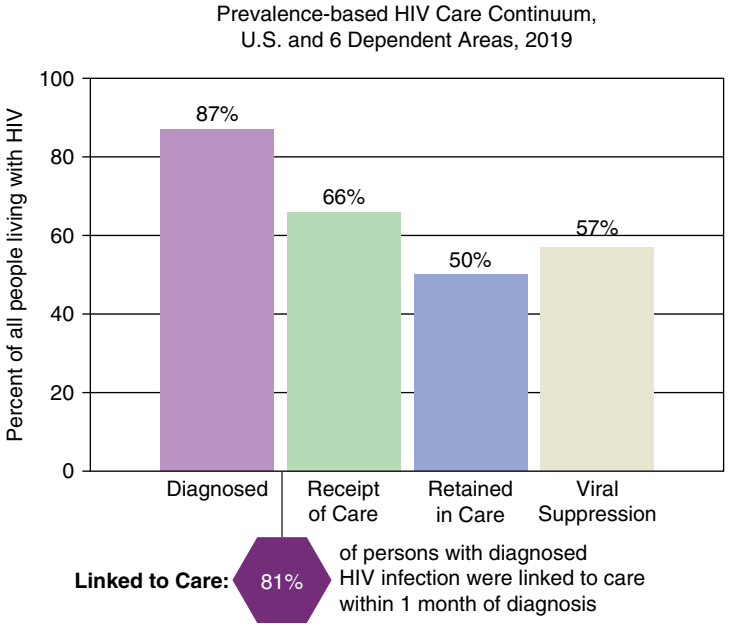

FIGURE 353-5. Human immunodeficiency virus (HIV) care continuum in the United States in 2019. (Data from Centers for Disease Control and Prevention and HIV.gov. Monitoring selected national HIV prevention and care objectives by using HIV surveillance data—United States and 6 dependent areas, 2019. HIV Surveillance Supplemental Report 2021; 26[No. 2]. Published May 2021.)

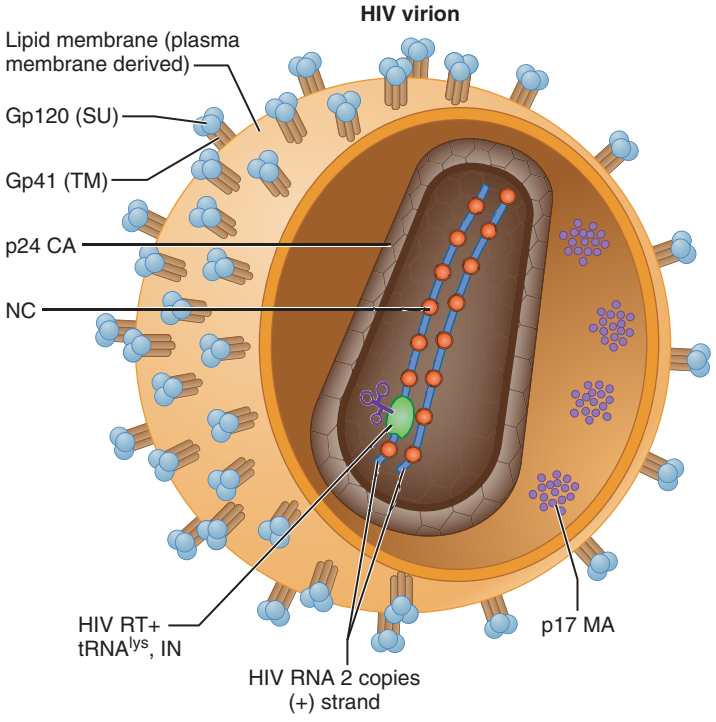

FIGURE 354-1. The HIV virion. The HIV virion contains viral gene products and cellular components essential to transmit infection and establish the proviral state. HIV virions are roughly spherical particles with a diameter of 80 to 120 nm and are composed of a viral core enveloped by a lipid membrane. The core of the mature virion is a conelike structure, composed of the HIV p24 capsid (CA), which encapsidates components necessary for replication: two copies of HIV genomic RNA template complexed with HIV p6 nucleocapsid (NC); tRNA^{lys} primer; HIV enzymes reverse transcriptase, protease, and integrase; and HIV Vif. The viral envelope, which is derived from the plasma membrane of the host cell as HIV undergoes budding, contains viral proteins Gp120 (SU) and Gp41 (TM), as well as a structural matrix protein, MA. HIV = human immunodeficiency virus; tRNA = transfer RNA.

infections and uneven access to preexposure prophylaxis for other high-risk groups.[14] The United States' Ending the HIV Epidemic goals are, by 2025, to decrease the number of new HIV diagnoses to about 9500 cases annually, to increase the percentage of people aware of their HIV diagnosis to 95%, and increase viral suppression to 95%. Renewed and novel efforts to enhance treatment and prevention will be needed to achieve these ambitious targets and drive down rates of new HIV infections and HIV-associated morbidity and mortality in the United States.[15]

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354 PATHOBIOLOGY OF HUMAN IMMUNODEFICIENCY VIRUSES

JOEL N. BLANKSON, ROBERT F. SILICIANO, AND FRANK MALDARELLI

Human immunodeficiency viruses (HIV-1, HIV-2) cause progressive immune deficiency and death from opportunistic infections or neoplastic diseases. Increased understanding of HIV pathobiology has led to significant advances in diagnosis (Chapter 355), prevention (Chapter 356), and treatment (Chapter 357) that have reduced morbidity and mortality, and tipped the balance toward control of the epidemic worldwide.

The Pathogen

HIV is a member of the lentivirus genus of the Orthoretrovirinae subfamily of the Retroviridae family of Revtraviricetes. All retroviruses contain reverse transcriptase, which catalyzes the synthesis of DNA from an RNA template. Retroviruses are widely distributed among vertebrates; lentiviruses cause chronic, recurrent, or progressive diseases, including immunodeficiencies, in various mammalian species. Several cross-species transmissions of lentiviruses from primates to humans were the source of human immunodeficiency viruses (Chapter 353).

HIV virions are enveloped particles that are approximately 100 nm in diameter (Fig. 354-1) and contain: two single-stranded (+) sense RNA copies, which code for HIV genes (E-Fig. 354-1); the tRNA primer, within a virion protein core composed of structural proteins; the viral enzymes; reverse transcriptase and integrase essential for replication; and viral factors (Vpr and Vif) that are necessary to evade intracellular restriction. The viral envelope, which is derived from the host plasma membrane at budding, contains viral proteins Gp120 (SU) and Gp41 (TM), as well as a structural matrix protein, MA.

REPLICATION CYCLE

Viral replication (E-Fig. 354-2) is initiated by direct contact of virions or infected cells with susceptible host cells (E-Fig. 354-2A)[1] mediated by surface Env glycoprotein trimers of HIV sp120 SU noncovalently bound to HIV gp41 TM. Attachment is mediated by SU, which engages two distinct cell surface proteins, a receptor, and a coreceptor. HIV initially binds the CD4 receptor, thereby resulting in conformational change in Env and facilitating binding to a coreceptor, typically either the human chemokine receptor CCR5[2] or CXCR4 (although CCR5/CXCR4 dual-tropic viruses circulate as well). Engaging both receptor and coreceptor results in conformational change in TM to drive membrane fusion. Inhibitors of SU-CD4, SU-CCR5 interactions, and TM-mediated fusion are effective treatments for HIV.

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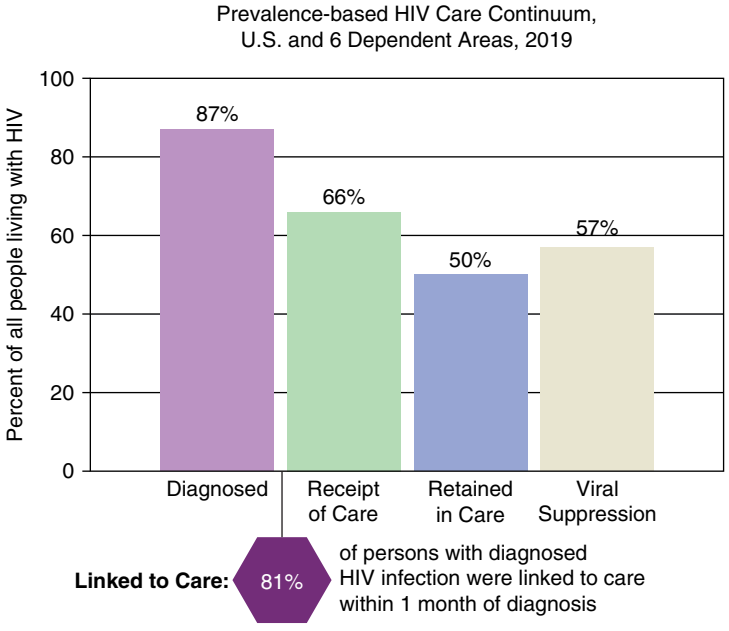

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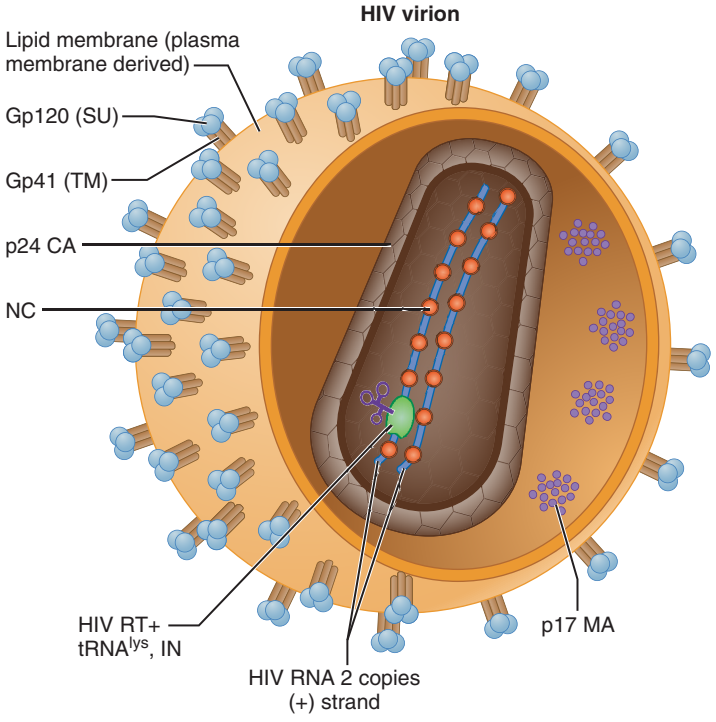

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ABSTRACT

Human immunodeficiency viruses (HIV), which are enveloped, (+)stranded RNA virus members of the retrovirus family, have infected over 37 million individuals worldwide. HIV establishes a chronic infection in anatomic compartments throughout the body. Untreated infection results in progressive lymphopenia and immunodeficiency, ultimately resulting in death from opportunistic infections or neoplasms. Replication takes place in lymphoid and myeloid cells that express the viral receptor (CD4) and a coreceptor (CCR5 or CXCR4). Replication proceeds by reverse transcription of viral RNA into HIV DNA, which is integrated into the host genome. Gene expression is controlled by viral regulatory genes and executed by host machinery; gene products traffic to the cell surface where virions assemble and bud from the cell membrane. The majority of infected cells are rapidly eliminated, but a small minority persist for prolonged periods and undergo clonal expansion, thereby maintaining a lifelong reservoir. Serologic and cellular immune responses are initiated shortly after transmission but are ineffective in most individuals, thereby resulting in the inexorable loss of CD4 cells, immune exhaustion, and impaired immune responses. In a small minority of patients known as elite controllers, HIV infection may be naturally suppressed, although persistent immune activation contributes to comorbid conditions. HIV infection is controlled but not cured through the use of combination antiretroviral therapy, which blocks active replication cycles. Ongoing immune activation persists, however, and contributes to morbidity and mortality. Studies to eradicate or control HIV without antiretroviral therapy are under active investigation.

KEYWORDS

HIV infection
acquired immunodeficiency
antiretroviral therapy
elite controllers
HIV persistence
clonal expansion

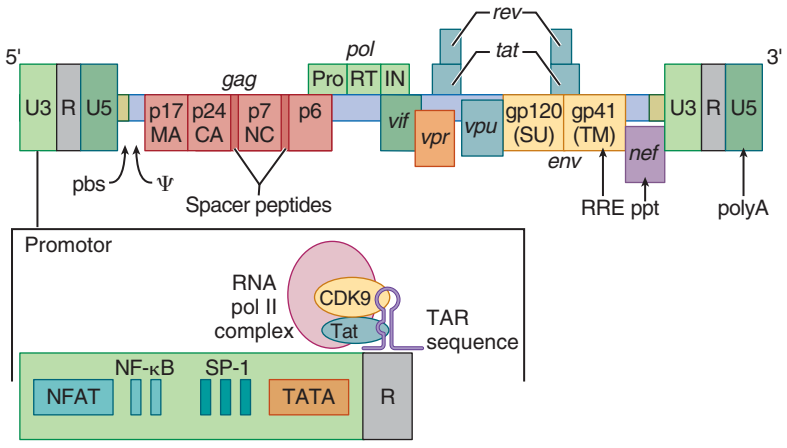

A **Proviral DNA**

HIV Gene	Rev-Dependent	Binding partner	Interaction Result	FDA Approved Inhibitor
gag **("group antigen")**	YES			
p17 Matrix MA		Host membrane	Promotes virion morphogenesis	
p24 Capsid CA		Gag	Virion structure	Late stage development
p1+p2			Virion structure	
p7 NC		HIV RNA	Facilitates reverse transcription	
p6		TSG101	Tethers GagPol precursor to lipid raft like membranes	
pol **("polymerase")**	YES			
Protease			Processes gag/pol polyprotein	YES
RT		HIV RNA and DNA	Reverse transcription of viral RNA	YES
RNase H		HIV RNA-DNA intermediate of reverse transcription	Degrades RNA from RNA: DNA hybrid	
Integrase		LEDGF/p75	Chaperone activity to integrates linear HIV DNA into areas of active transcription in host genome	YES
vpr **("viral Protein R")**	YES	CCDC137*	Cell cycle arrest	
vif **("viral Infectivity Factor")**	YES	APOBEC family of proteins*	Innate immune evasion	
tat **("trans-Activator of Transcription")**	NO	Transcription factors	Transcriptional activation	
rev **("Regulator of Expression of Viral Proteins")**	NO	CRM	RNA transport of unspliced and singly spliced RNA	
vpu/env (bicistronic mRNA)	YES			
vpu ("Viral Protein U")		CD4*	Adaptive immune evasion	
		Tetherin*	Innate immune evasion	
		Tim-3*	Increased virion production	
env ("Envelope")				
gp120 (SU)				YES
gp41^{TM}				YES
nef **("Negative Regulatory Factor")**	NO	SERINC3/5*	Increased virion infectivity	
		MHC1*	Innate immune evasion	
		CD4*	Innate immune evasion	

B

E-FIGURE 354-1. **Major HIV genes. A**, HIV proviral DNA with complete long terminal repeat (LTR). HIV encodes nine genes whose products are required for structural, enzymatic, regulatory, and innate immune neutralization functions. By convention, HIV genes (color coded, not to scale) are denoted in lower italics (*gag, pol*, etc.) with names that broadly reflect their function, location in the virion, or a historical vestige of prior viral classification (e.g., *gag*, "group antigen"). Additional genes that function in regulation or replication (*tat, rev, vpr*) or in blocking immune responses to HIV (*vif, vpu, nef*); all are critical for HIV infection in vivo. **B**, Function of HIV viral gene products. Host components interacting with each gene product are noted, and gene products are indicated for which U.S. Food and Drug Administration–approved therapeutic drugs are available. *Down-regulated by 1β HIV binding partner. DNA = deoxyribonucleic acid; FDA = U.S. Food and Drug Administration; HIV = human immunodeficiency virus; RNA = ribonucleic acid; TAR = transactivation response.

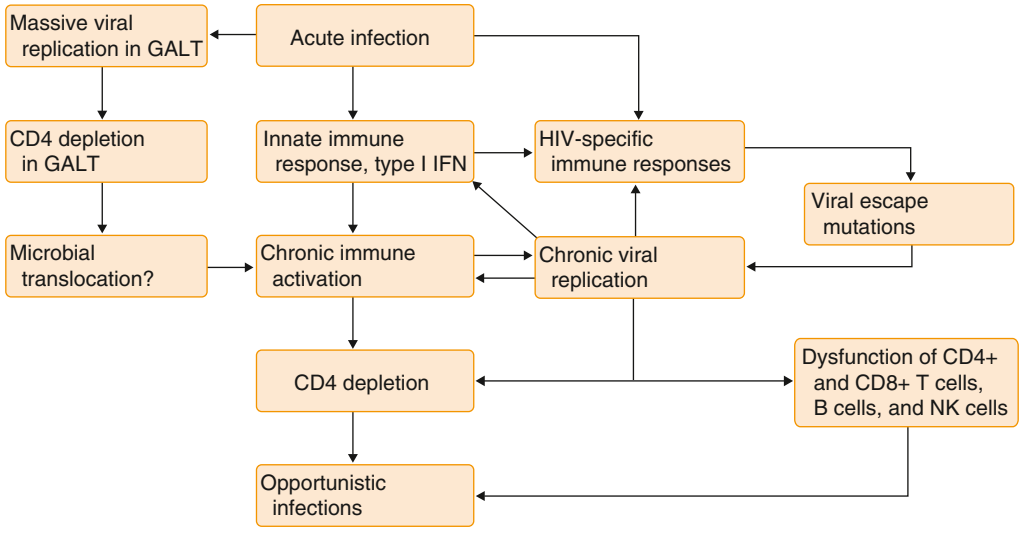

FIGURE 354-2. Parameters involved in chronic immune activation and CD4⁺ T-cell depletion. GALT = gut-associated lymphoid tissue; HIV = human immunodeficiency virus; IFN = interferon; NK = natural killer.

A key event in HIV replication is the conversion of virion RNA into double-stranded DNA by reverse transcriptase. Effective reverse transcription and uncoating occurs in the nucleus, followed directly by integration into the host's genome[3] (E-Fig 354-2B and 2C); potent inhibitors of reverse transcriptase, integrase, and uncoating are now FDA-approved (Chapter 357).

Reverse transcriptase is a highly error-prone enzyme, with only a rudimentary editing function; approximately one mutation per virion occurs per replication cycle. The HIV generation time is estimated to be relatively short (1 to 2 days), and the replicating population size is substantial. This combination of rapid and error-prone replication results in a genetically diverse population that can respond rapidly to immune- or drug-selective pressure. Thus rapid error-prone replication represents a critical pathogenic determinant for HIV. Estimates indicate that variants with single resistance mutations to individual antiretroviral agents preexist in HIV-infected patients *prior to* initiating antiretroviral therapy. As a consequence, antiretroviral therapy requires combinations of drugs with distinct resistance profiles to prevent the emergence of resistance. Combinations that inhibit one to three steps in replication can be effective (Chapter 357).

After the proviral state is established, HIV produces viral RNA and proteins using viral factors in concert with cellular mechanisms of transcription and translation.[4] HIV replicates not by dismantling cell functions but rather by using specific interactions among host factors and specific viral gene products that drive high levels of HIV RNA transcription (Tat), facilitate balanced RNA transport (Rev), and help traffic of HIV proteins to membranes for virion budding (Gag) (E-Fig. 354-3). Following budding, HIV Gag precursor proteins require proteolytic processing by the viral enzyme protease for mature core formation, which is required for viral infectivity. Potent protease inhibitors, which block this step, are important components of combination antiretroviral therapy (Chapter 357). Maturation of HIV virions represents a new target for inhibition, and several agents are under active investigation.[5]

HIV infection triggers a number of intracellular innate responses, which, if left unchecked, would arrest HIV replication. Several interferon-induced genes inhibit HIV replication, including the ABOBEC family of nucleic acid editing enzymes; the cell surface protein BST-2 (tetherin), which blocks release of virions from the cell surface; and SERINC 3/5, which incorporates into virion membranes and reduces infectivity of the produced virions. In each case, a viral factor (Vif for APOBEC, Vpu for BST-2, and Nef for SERINC 3/5) blocks these innate mechanisms by binding and redirecting corresponding host proteins to ubiquitin-induced degradation. Several HIV proteins (Vpiu, Nef) also down-modulate immune cell surface proteins CD4 and MHC molecules, thereby hindering adaptive immune responses.[6]

PHYSIOLOGY OF HIV INFECTION

UNTREATED INFECTION

FATE OF INFECTED CELLS

By the completion of the infectious cycle, HIV has produced progeny for the next round of infection, obstructed adaptive and innate immune responses, and established a proviral state in the infected cell. Despite multiple mechanisms of immune evasion, the majority of infected cells (>99%) die within 1 to 2 days of infection. Thus the virus has a strikingly short period to engage critical cell pathways to complete replication while most cells are being destroyed. A minority of infected cells survive infection and persist for prolonged periods.

The host mounts a vigorous immune response after HIV-1 infection. The virus is thought to activate plasmacytoid dendritic cells through toll-like receptors, thereby resulting in the secretion of type I interferons and other inflammatory cytokines. Whereas type I interferons have direct antiviral properties and enhance the HIV-1–specific immune response, excessive secretion may play a key role in pathogenic immune activation of CD4+ and CD8+ T cells (Fig. 354-2). Natural killer (NK) cells, which are important effector cells in the innate immune response, become activated when infection of target cells by HIV-1 or other viruses results in the downregulation of HLA molecules. Patients expressing certain NK receptor alleles are more likely to become long-term nonprogressors, thereby suggesting that these cells may play a protective role possibly by controlling early HIV-1 replication by leading to the development of an effective adaptive immune response. Myeloid dendritic cells, which play a key role in the presentation of HIV-1 antigens to HIV-1–specific CD4+ and CD8+ T cells, initiate the adaptive immune response. Dendritic cells express CD4 molecules and bind HIV-1. In the process of presenting antigen, these cells may inadvertently transmit HIV-1 to clusters of activated CD4+ T cells.

The role of the humoral response in HIV-1 infection is not clear. HIV-1–specific antibodies, which are used to diagnose HIV-1 infection, do not develop until after peak viremia occurs. A subset of the antibodies that eventually appear are capable of preventing infection by blocking the interaction of the HIV-1 envelope protein gp120 with CD4 and with coreceptor proteins on the surface of target cells. These so-called neutralizing antibodies are present at relatively low titers and have limited access to the critical regions of gp120. Although neutralizing antibodies can exert significant selective pressure on the virus, immunologic escape is common, and the bulk of evidence suggests that these antibodies do not play a major role in the control of viral replication in most long-term nonprogressors.[7]

The selective depletion of CD4+ T cells, which play a major role in the adaptive immune response, is the main reason that HIV-1 infection results in such profound immunosuppression. The ability of HIV-1–specific CD4+ T cells to proliferate and to secrete key cytokines such as interleukin-2 is lost shortly after primary infection, thereby setting up the entire HIV-1–specific response for failure. CD8+ T cells contribute to the control of HIV-1 infection by the direct lysis of infected cells and by the secretion of soluble factors, such as macrophage inflammatory protein 1β, which bind to chemokine receptors, thereby preventing HIV-1 entry into target cells. However, the HIV-1–specific CD8+ T-cell response that partially controls HIV-1 replication after peak viremia in primary infection does not achieve sterilizing immunity, partly because of a reservoir of latent virus that develops in resting memory CD4+ T cells shortly after infection. These quiescent cells probably do not make HIV-1 proteins and thus are not recognized by cytolytic T-lymphocytes. Furthermore, the cytolytic T-lymphocyte response

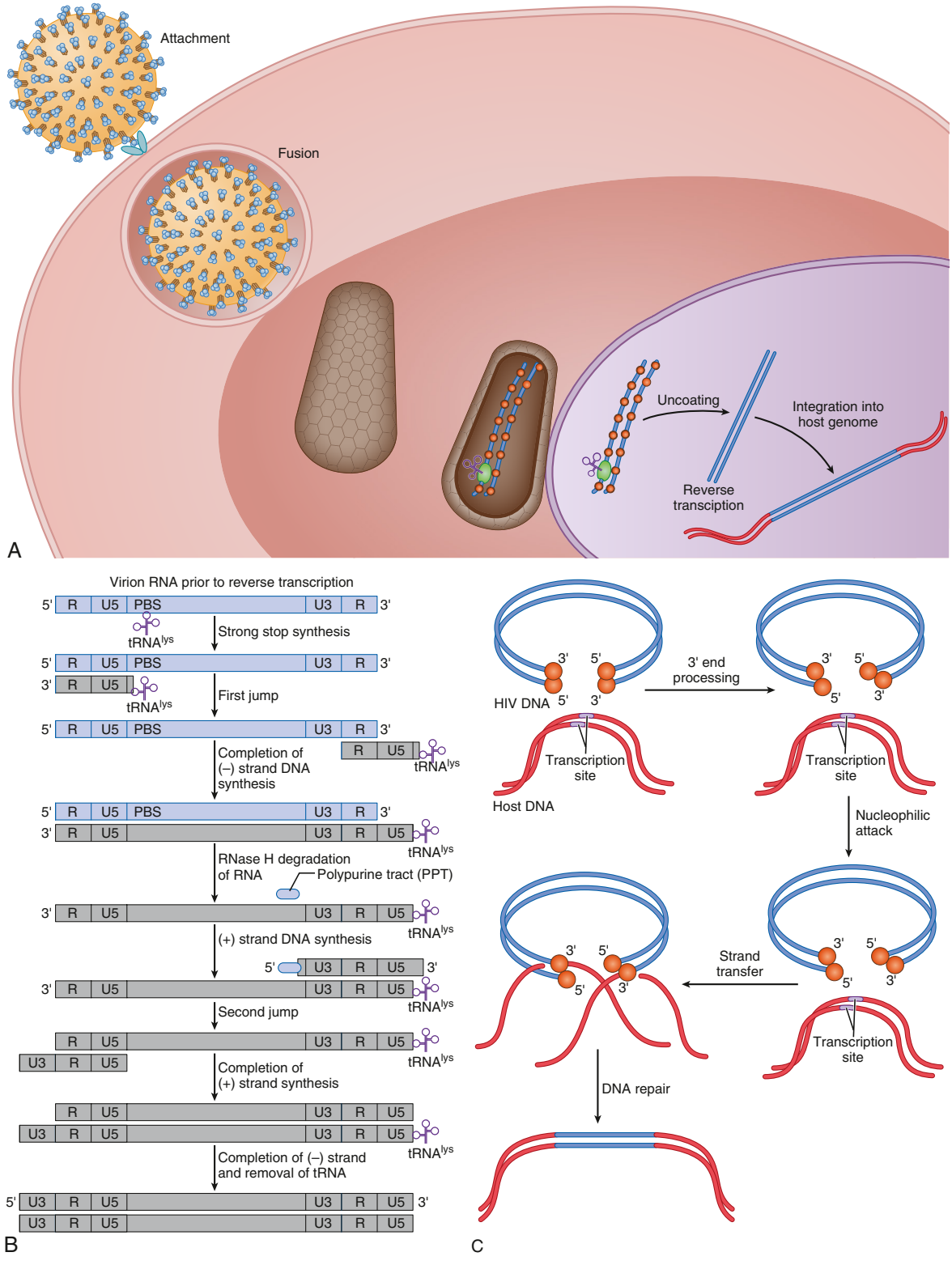

E-FIGURE 354-2. Steps in viral replication. A, Early steps in replication. Viral replication is initiated by direct contact of virions or infected cells with susceptible host cells and is mediated by surface Env glycoprotein trimeric complexes, which consist of HIV sp120 SU noncovalently bound to HIV gp41 TM. The attachment phase is mediated exclusively by SU, which engages two distinct cell surface proteins for attachment: a receptor and a coreceptor. HIV initially binds CD4, thereby resulting in conformational change in Env, which facilitates coreceptor binding. Typically, SU proteins use either the human chemokine receptor 5 (CCR5) or the human chemokine receptor 4 (CXCR4) to infect CD4+ T cells, but CCR5/CXCR4 dual tropic viruses circulate as well. Inhibition of SU-CD4 and SU-coreceptor interactions has been achieved pharmacologically (Chapter 357). Attachment results in conformational changes in TM, which reorganizes into six alpha helix bundles that drive fusion reaction; peptides that bind these alpha helices have been developed as fusion inhibitors (Chapter 357). Once membrane fusion occurs, the core is released into the cytoplasm and travels to the nucleus. **B**, Reverse transcription. The (+)-strand template strands of HIV RNA are complexed with reverse transcriptase and a specific $tRNA^{lys}$ that functions as a primer located at a specific primer binding site (see E-Fig. 354-1) near the 5′ end of the template HIV RNA. Reverse transcription is a multistep process (see E-Fig. 354-3) that first synthesizes a DNA copy of the RNA genome and then excises the RNA from the RNA-DNA hybrid using an RNase H function of reverse transcriptase; RNA removal is incomplete, and residual RNA in a region denoted the polypurine tract then serves to prime the next round of DNA synthesis. During reverse transcription a number of strand transfer events permit opportunities for frequent recombination. Reverse transcription was the first target for antiretroviral therapy, and a number of direct and allosteric inhibitors of reverse transcription have been developed (Chapter 357). All reverse transcription inhibitors inhibit RNA-dependent DNA synthesis or DNA-dependent DNA synthesis. Nucleoside and nucleotide reverse transcriptase inhibitors, which are dideoxy analogues of deoxynucleotides that are incorporated as the template is copied and act as chain terminators that block additional nucleic acid synthesis. Non-nucleoside inhibitors of reverse transcription bind to reverse transcriptase in a hydrophobic domain proximal to the active site, thereby deforming the enzyme structure and disrupting nucleic acid synthesis. **C**, Newly synthesized HIV DNA transports to the nucleus for integration into the host genome. A complex of the HIV protein integrase, newly synthesized HIV DNA, and associated proteins has been labeled an *intasome*. Structural studies have revealed that a tetramer of integrase molecules is bound to the ends of the retroviral DNA and brings the DNA ends in close proximity, poised for integration into the genome in a multistep process. Integration is a highly successful target for antiretroviral therapy, and inhibitors that block the transfer of HIV DNA strand into the host genome are now first-line antiretroviral choices in clinical practice (see Chapter 357). HIV = human immunodeficiency virus; SU = surface; TM = transmembrane; tRNA= transfer ribonucleic acid. WWW.BOOKBAZ.IR

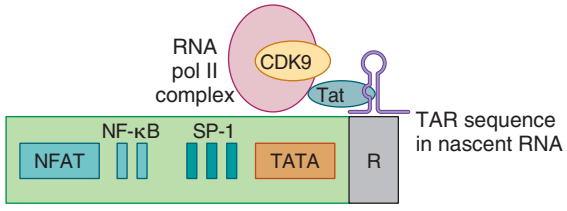

A. Proviral DNA

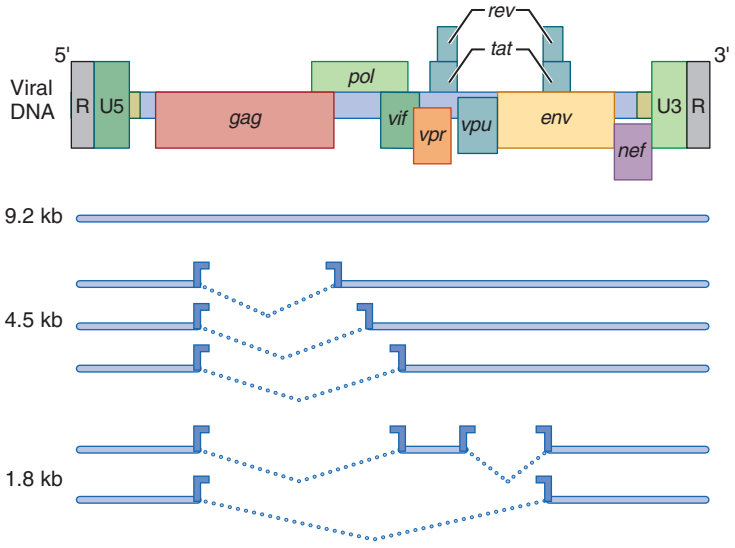

B. Post-transcriptional processing

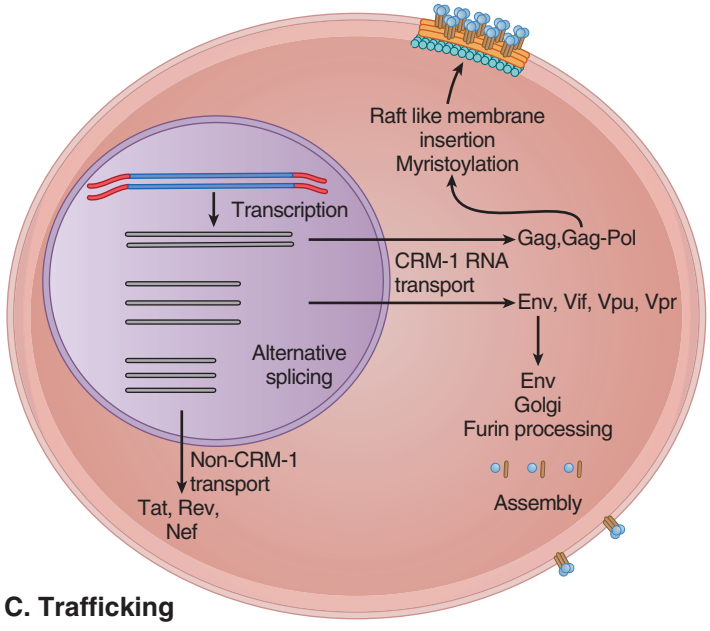

C. Trafficking

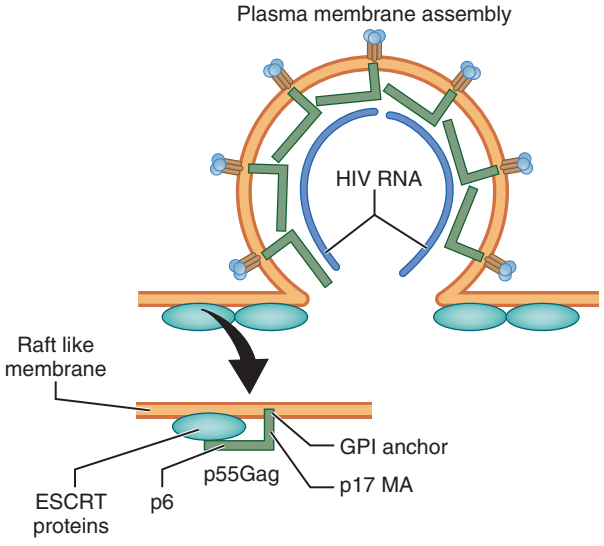

D. Budding

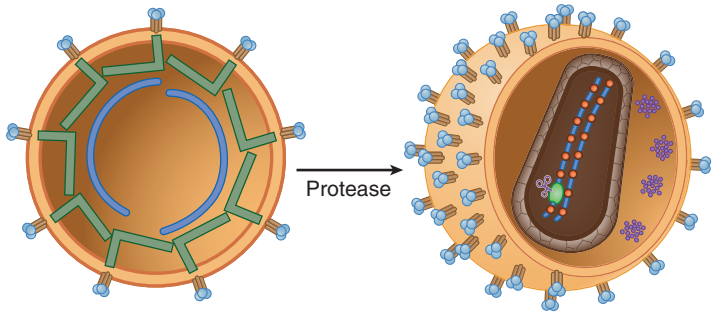

E. Generating infectious virions

E-FIGURE 354-3. Generating infectious virions: transcription and post-transcription events. A, Transcription. The integrated provirus is expressed in the context of host chromatin. Retroviruses transcribe all of their genes from a single promoter. The U3 portion of the HIV long terminal repeat contains binding sites for transcription factors common in lymphocytes and macrophage-monocyte lineages, including activator protein 1 (AP-1), specificity protein 1 (SP-1), nuclear factor kappa B (NF-κB), and nuclear factor of activated T cells (NFAT) binding sites. The presence of the viral transcription factor transactivator of transcription (Tat) markedly stimulates transcription through binding to a specific RNA enhancer, which is denoted as the transactivating region (TAR), and recruiting additional transcription factors. **B,** Post-transcription. Full-length HIV RNA is processed for expression of all nine gene products and encapsidated as the viral genome into virions. To provide sufficient mRNA species to express all HIV proteins, RNA processing is highly regulated by alternative splicing and differential RNA transport. Full-length RNA consists of a primary capped mRNA of approximately 9.2 kb that undergoes alternative splicing to produce three broad classes of RNA species: 9.2-kb unspliced RNA, responsible for translation of *gag/pol;* a number of distinct 4.5-kb singly spliced RNA species, responsible for translation of *vif, vpr*, and *vpu/env;* and 1.8-kb multiply spliced species, responsible for *tat, rev*, and *nef*. **C,** Trafficking. Multiply spliced 1.8-kb RNAs are constitutively expressed, but unspliced and singly spliced HIV mRNAs require specific transport out of the nucleus. To export unspliced and singly spliced HIV RNAs, the viral protein Rev binds to a specific region in the *env* portion of the unspliced and singly spliced RNA, denoted as the Rev responsive element (RRE); the RRE is a sequence of c.240 nt that folds into a specific structure to which Rev binds. The Rev-RNA complex then engages the nuclear host CRM-1 transport apparatus, which transports RNA out of the nucleus. Engaging appropriate host elements therefore results in a balance of 9.2-, 4.5-, and 1.8-kb mRNA species. **D,** Budding. HIV virion proteins and virion RNA species traffic to the plasma membrane, where virion assembly takes place. Gag has self-assembly properties, but correct initial assembly of the virion core into a hexagonal lattice includes incorporation of virion RNA and additional factors. Virion RNA undergoes dimerization largely through direct RNA-RNA interactions that require specialized RNA sequences, denoted psi sequences, at the 5′ region of the genome favoring incorporation of only unspliced HIV RNA species. Gag accumulates in specialized membrane microdomains enriched with sphingomyelin-saturated phospholipids and cholesterol typical of lipid rafts and binds components of the endosomal sorting complexes required for transport (ESCRT) pathway. By recruiting ESCRT to sites of HIV assembly on the plasma membrane, HIV engages a highly specialized pathway to execute budding. During processing, the core lattice begins to bend by introducing pentamers of CA at critical points of the hexagonal lattice, thereby effectively folding the structure into a fullerene-like cone that encapsidates dimeric HIV RNA-$tRNA^{lys}$ and HIV enzymes. **E,** Generating infectious virions. Nascent virions require proteolytic processing of the Gag and GagPol precursor proteins by HIV protease to become infectious. Protease is embedded as part of the GagPol precursor, cleaves itself from the precursor, and then proceeds to process Gag and GagPol into component proteins. Processing is essential for virion infectivity, and protease inhibitors are highly effective agents in HIV therapy (Chapter 357). ESCRT = endosomal sorting complex required for transport; GPI = glycosylphosphatidylinositol; HIV = human immunodeficiency virus; tRNA = transfer ribonucleic acid.

	Transmission	Acute Retroviral Syndrome	Chronic Infection	Late Stage Disease/AIDS
	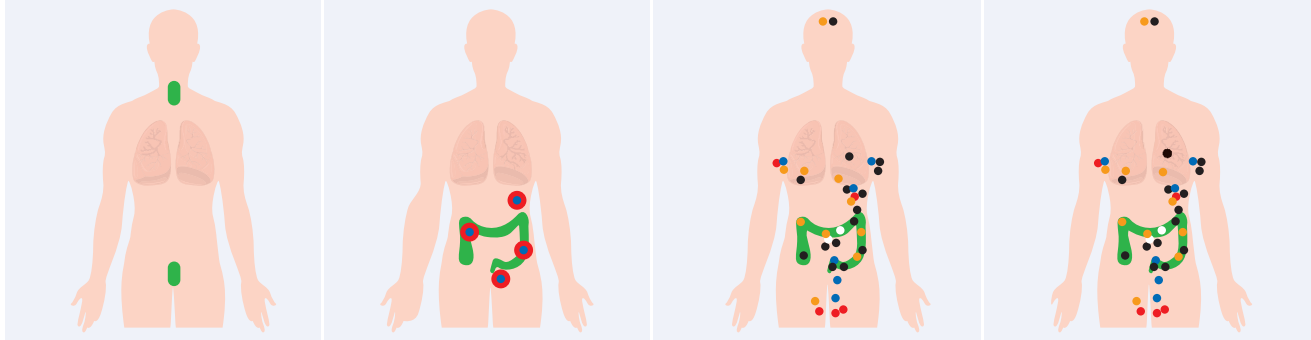			
Clinical	HIV exposure Mucous membranes Injection into blood or skin	Fever Rash Fatigue Diarrhea Headache	Lymphadenopathy Mild cognitive defects	Opportunistic infections Neoplastic diseases Dementia
Anatomic	Local spread at transmission site Rectum Genital Oropharynx	Extensive spread in GALT Destruction of gut barrier function antigen-antibody deposition in skin	Established reservoirs in lymphoid and non lymphoid tissue Elevated immune activation	Profound immune deficiency Depleted hyalinized lymph nodes Loss of Immune surveillance for neoplasms Elevated immune activation
Immune	Absent	Low avidity antibody antigen-antibody deposition in skin	Antibody (including neutralizing); interferon, cytokine response CD and CTL, NK, Brode immune activation Progressive CD4 lymphopenia T cell exhaustion	Robust antibody response CD4 responses depleted
Viral	Limited genetic variants transmitted	Ongoing cycles of HIV replication Limited genetic diversity includes CTL escape mutations CCR5 coreceptor utilizing env Interferon-resistant variants High viral load in blood Small reservoir of long-lived cells	Ongoing cycles of HIV replication High genetic diversity CCR5 coreceptor ulilizing env Interferon-sensitive variants Set point viral load in blood Clonal expansion of presistently infected long-lived cells	Ongoing cycles of HIV replication High genetic diversity CCR5 and CXCR4 coreceptor utilizing env Interferon-sensitive variants Rising viral load in blood Clonal expansion of persistently infected long lived cells

FIGURE 354-3. Pathophysiology of untreated HIV infection. Salient clinical, anatomic, immunologic, and virologic characteristics of HIV infection. AIDS = acquired immunodeficiency syndrome; CTL = cytotoxic T lymphocytes; GALT = gut-associated lymphoid tissue; HIV = human immunodeficiency virus.

in patients with progressive disease is of poor quality with limited proliferative capacity. Most important, the low fidelity of HIV-1 reverse transcriptase results in the development of mutations with each round of replication. Mutations that lead to escape from cytolytic T-lymphocyte responses have an advantage and are thus rapidly predominate.

THE EFFECT OF HIV-1 REPLICATION ON THE IMMUNE SYSTEM

Although the HIV-1–specific immune response helps limit the rate of viral replication, sterilizing immunity is never achieved and the virus has a negative impact on the immune system. Continuous viral replication results in chronic immune activation (see Fig. 354-3), but the precise mechanism is not understood. The chronic immune response to the virus may lead to nonspecific inflammation, and microbial translocation resulting from the depletion of CD4+ T cells in the gut-associated lymphoid tissue may also be important. Whatever the mechanism, immune activation appears to drive the depletion of CD4+ T cells. In untreated patients, the level of immune activation markers on CD4+ and CD8+ T cells correlates better with the rate of CD4 decline than does the magnitude of the viral load. Increased levels of activation markers are seen on NK cells, B cells, CD4+ T cells, and CD8+ T cells.[8] Activation is accompanied by an increase in the turnover rate of these cells. The compromised function of NK cells may predispose to the poor control of other viruses. B-cell defects result in hypergammaglobulinemia and the production of autoantibodies. Poor antibody responses to vaccines are also seen as CD4+ T cells decline.

The loss of infected CD4+ T cells contributes to a depletion in CD4+ T cells even though only 1% or less of these cells are infected at any given time during chronic infection. Thus, it is currently thought that chronic immune activation leading to the death of noninfected CD4+ T cells is the principal mechanism for CD4 depletion. In addition to the quantitative loss of CD4+ T cells in HIV-1 infection, marked skewing of the CD4 T-cell repertoire is seen, and there is a diminished qualitative memory response to recall antigens long before the CD4+ T-cell count drops to 200 cells/μL. The chronic activation and high turnover rate of these cells eventually result in the progressive CD4 decline that is characteristic of HIV-1 infection.

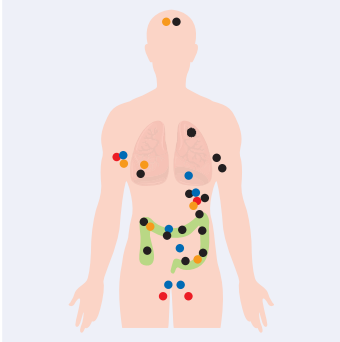

Clinical	Largely asymptomatic Elevated cardiovascular disease Complications of immune activation
Anatomic	Limited restoration of lymphoid architecture; incomplete restoration of gut barrier function Cognitive improvement
Immune	Reduced antibody response Reduced but persistent immune activation Reduced but persistent T cell exhaustion
Viral	Low level viremia (1–2 copies HIV RNA/ml plasma) Absence of viral replication cycles No molecular evolution Persistence of infected cells in resting memory subsets Clonal expansion of long-lived cells

FIGURE 354-4. Characteristics of HIV-infected individuals undergoing antiretroviral therapy. HIV = human immunodeficiency virus.

There is evidence of immune exhaustion for both CD4+ and CD8+ T cells, and there is decline in the qualitative features of the CD8+ T-cell response to other chronic viruses such as cytomegalovirus (Chapter 347) and Epstein-Barr virus (Chapter 348). This decline may be the result of anergy or depletion of the CD4+ T cells that are needed to sustain functional CD8+ T-cell responses.

CLINICAL CONSEQUENCES OF HIV INFECTION

Profound CD4+ T-cell depletion is associated with clinical immunodeficiency and a markedly increased susceptibility to a wide range of opportunistic infections (Chapter 358) in the late stages of HIV-1 infection. However, some level of immunodeficiency may be present shortly after infection because of qualitative changes in the immune response related to ongoing viral replication. As a result, patients are more susceptible to infections such as *Mycobacterium tuberculosis* (Chapter 299) before the CD4 count reaches the 200 cells/μL threshold that defines AIDS. Patients are also much more susceptible to malignant neoplasms such as non-Hodgkin lymphoma (Chapter 171) at any CD4+ T-cell count. Other opportunistic infections arise at fairly predictable CD4+ T-cell counts. For example, *Pneumocystis jirovecii* infections (Chapter 313) occur at CD4 counts below 200 cells/μL, *Cryptococcus neoformans* (Chapter 309) and *Toxoplasma gondii* infections (Chapter 320) occur at CD4 counts lower than 100 cells/μL, and *Mycobacterium avium* complex (Chapter 300) and cytomegalovirus infections (Chapter 347) occur at CD4 counts below 50 cells/μL. Although these infections are a consequence of diminished cellular immunity, there is also a marked increase in invasive pneumococcal infections (Chapter 268) in HIV-1–infected patients, possibly due to defects in humoral immunity.

ELITE CONTROLLERS

Elite controllers, who represent less than 1% of HIV-infected individuals, spontaneously suppress HIV viremia but also demonstrate chronic inflammation that may increase the risk of comorbid conditions. In these individuals, HIV-specific resident memory CD8+ T cells are abundant in lymphoid tissues, and they exhibit distinct functional properties.[9] One of the most common findings in elite controllers is the presence of human leukocyte antigen (HLA)-B*27 and or HLA-B*57 alleles.[10] Overall, elite controllers are hospitalized almost twice as frequently as persons with medically controlled HIV possibly because of residual immune activation, and cardiovascular hospitalizations are an important contributor.

TREATED HIV INFECTION

Treatment with selected combinations of antiretroviral drugs (Chapter 357) suppresses viral replication to below the limits of detection of current commercial assays (20 copies of HIV-1 RNA per milliliter of plasma). Current evidence suggests that antiretroviral therapy produces a complete or nearly complete arrest in viral replication in adherent patients, but trace amounts of viremia persist because of stable viral reservoirs, including the latent reservoir in resting CD4+ T cells. This suppression of viral replication is usually accompanied by a substantial increase in CD4+ T-cell counts. The initial rise in CD4+ T-cell counts occurs mostly as a consequence of migration of cells from lymph nodes (where 98% of all CD4 T cells reside) to the peripheral blood as inflammation diminishes in lymphoid tissue. Subsequently, the production of memory CD4+ T cells increases in most individuals. Naive T-cell production is also sometimes seen at lower levels. Clinical studies show that patients who experience significant immune reconstitution can safely discontinue prophylactic therapy for opportunistic infections.

Similar to the decline in the functional CD4+ T-cell response shortly after primary infection, CD4+ T-cell function qualitatively improves shortly after antiretroviral therapy is initiated. In some cases, an exaggerated immune response to opportunistic infections leads to the immune reconstitution inflammatory syndrome (Chapter 358), particularly in individuals with advanced HIV infection (CD4 <100 cells/μL) and when viral replication is rapidly controlled after the initiation of antiretroviral therapy.

The mechanisms that underlie the ongoing morbidity during antiretroviral therapy is not certain, but elevated immune activation, which is associated with all-cause mortality even during successful antiretroviral therapy, appears to be a key characteristic. For example, although the incidence of some neoplasms declines, the frequency of AIDS-defining cancers (Chapter 359) remains elevated during antiretroviral therapy.

ERADICATION OF HIV INFECTION

HIV-infected cells persist during antiretroviral therapy and represent the principal obstacle to HIV eradication. Forces driving persistence and expansion of HIV-infected cell populations remain uncertain. Homeostatic proliferation, antigen-induced cell proliferation, and proviral-driven clonal expansion represent potential mechanisms driving long-term persistence (Fig. 354-4).[11] HIV has been eradicated in several individuals in the setting of bone marrow transplantation using cells from donors who have a homozygous CCR5 mutation, which confers resistance to HIV isolates that use CCR5 as the coreceptor. Active studies are underway to characterize mechanisms of persistence and identify scalable strategies of HIV control or eradication.[12]

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355 ACUTE CLINICAL MANIFESTATIONS AND DIAGNOSIS OF HIV

THOMAS C. QUINN AND LARRY W. CHANG

CLINICAL MANIFESTATIONS

Symptoms and Signs of Acute HIV Infection

Different terms, including acute, recent, primary, and early HIV infection, have been used to describe initial exposure and infection with HIV. Regardless of the terminology, acute HIV infection is the period from the time of initial HIV infection until the stabilization of the viral load "set point" about 1 to 3 months later.

The usual time from any route of HIV exposure to the development of symptoms is 2 to 4 weeks, although incubation periods as long as 10 months have been observed. Typically, acute HIV infection presents with an acute retroviral syndrome, which is a constellation of nonspecific symptoms similar to a mononucleosis (Chapter 348) or a flulike illness (Chapter 331). Most symptoms associated with acute HIV infection are brief, but the severity and duration of symptoms can vary widely. Symptoms can include fever, lymphadenopathy, pharyngitis, rash, myalgia/arthralgia, diarrhea, anorexia, and weight loss (Table 355-1).[1] Headache, often described as retroorbital pain exacerbated by eye movement, frequently is reported.

No findings on physical examination are specific for acute HIV infection. Nontender lymphadenopathy, primarily involving the axillary, cervical, and occipital nodes, is common and often develops during the second week of illness. Nodes typically decrease in size following the acute presentation, but a modest degree of adenopathy may persist. Pharyngitis with pharyngeal edema and hyperemia is common, usually without tonsillar enlargement or exudate. Painful mucocutaneous ulceration is one of the most distinctive manifestations of acute HIV infection. These lesions may reflect mucocutaneous disease associated with coincident sexually transmitted infections, such as herpes simplex virus (Chapter 345), syphilis (Chapter 295), or chancroid (Chapter 276). A generalized faint rash, which is also common, typically occurs 48 to 72 hours after the onset of fever and persists for 5 to 8 days. These lesions are characteristically small (5 to 10 mm), well-circumscribed, oval or round, pink to deeply red colored macules or maculopapules.

The acute retroviral syndrome can easily be missed or misdiagnosed unless the degree of suspicion is high. The differential diagnosis of acute HIV infection includes mononucleosis (Chapter 348), toxoplasmosis (Chapter 320), rubella (Chapter 339), syphilis (Chapter 295), disseminated gonococcal infection (Chapter 275), viral hepatitis (Chapter 134), and other viral infections.

The severity of the acute syndrome is associated with a higher viral load and a stronger innate immune response.[2,3] An estimated 10 to 40% of acute HIV infections are asymptomatic and can be diagnosed only later during routine screening or when symptoms or signs of immunosuppression develop.

Opportunistic infections and central nervous system manifestations may occur in some individuals during acute HIV infection. Oral and esophageal candidiasis (Chapter 124; Figs. 310-1 and 397-5) is the most common opportunistic infection. Other infrequently reported infections include cytomegalovirus (proctitis, colitis, and hepatitis; Chapter 347), *Pneumocystis jirovecii* pneumonia (Chapter 313), and cryptosporidiosis (Chapter 321). More serious neurologic manifestations of acute HIV infection are unusual but can include aseptic meningitis, with severe headache, meningismus, photophobia, and a lymphocytic pleocytosis on cerebrospinal fluid (CSF) analysis. The presence of severe illnesses during acute infection may predict more rapid clinical progression to acquired immunodeficiency syndrome (AIDS).

Symptoms associated with acute HIV infection also can occur when patients who have well-controlled, established HIV infection discontinue suppressive antiretroviral therapy. In these cases, HIV viral levels rapidly rise from undetectable levels to as high as 1,000,000 copies/mL, CD4 counts drop appreciably, and symptoms (including fever, lymphadenopathy, and rash) develop in 10 days to 4 weeks after discontinuing all antiretroviral drugs.

Viral Load and Infectivity

In acute HIV infection, the viral RNA level is typically very high (10^5 to 10^7 copies/mL) within 2 weeks of infection, and the CD4 cell count can drop rapidly. Patients with acute HIV infection are highly contagious to others given the high HIV viral loads, which correlate with the risk of HIV transmission. In men with acute HIV infection, the viral load in semen appears to follow a similar pattern to that seen in blood, with the highest levels occurring at approximately 20 days after infection or 6 days after the onset of acute retroviral symptoms.

Concomitant with the evolution of HIV-specific immunity within the next several weeks, virus-specific CD8+ cytotoxic T lymphocytes appear, antibody seroconversion occurs, plasma HIV RNA levels fall precipitously by 2 to 3 logs, and the symptoms of the acute HIV infection resolve. In the absence of antiretroviral therapy, plasma HIV RNA levels will stabilize at an individual's given "set point" within approximately 1 to 3 months after infection. Usually, the CD4 cell counts drop in relation to the initial increase in viral load, and CD8 cell counts increase. Following peak viremia, CD4 cell counts begin to rebound, and CD8 cell counts decline but do not generally return to baseline levels, thereby resulting in a persistent inversion of the normal CD4:CD8 ratio to less than 1. Additionally, elevations of liver enzymes, mild anemia, and thrombocytopenia can occur during acute HIV infection.

Rare individuals with HIV may retain normal CD4 counts and low or undetectable plasma viremia even in the absence of antiretroviral therapy. Individuals with persistent viral suppression, who are referred to as "elite controllers," are distinguished from usual HIV patients who develop progressive disease by the persistence of HIV-specific T-helper cell proliferative responses. However, it is not clear whether these HIV immune responses directly cause or are the result of HIV control. Some data suggest that the initiation of antiretroviral therapy during acute infection protects activated HIV-specific T helper cells from infection by HIV, thereby preserving the HIV-specific cytotoxic T-lymphocyte response to virally infected cells.[4] For example, patients who become infected despite preexposure prophylaxis (Chapter 356) tend to have milder acute symptoms and lower viral loads.[5] Preservation of the immune

TABLE 355-1 FREQUENCY OF CLINICAL FEATURES OF ACUTE RETROVIRAL SYNDROME BY CATEGORY OF EXPOSURE TO HIV

FEATURES (%)	HOMOSEXUAL SEX (*n* = 280)	HETEROSEXUAL SEX (*n* = 44)	USE OF INJECTED DRUGS (*n* = 34)	OTHER OR UNKNOWN (*n* = 20)
Fever	76	79	50	80
Fatigue	71	71	50	55
Myalgia	56	23	29	30
Skin rash	51	52	21	45
Headache	49	34	30	50
Pharyngitis	45	27	18	35
Cervical adenopathy	41	39	27	35
Arthralgia	30	18	26	25
Night sweats	30	27	27	25
Diarrhea	30	14	23	10
Inguinal adenopathy	21	16	18	15

From Vanhems P, Routy JP, Hirschel B, et al. Clinical features of acute retroviral syndrome differ by route of infection but not by gender and age. *J Acqu Immune Defic Syndr*. 2002;31:318-321.
HIV = human immunodeficiency virus.

ABSTRACT

Acute HIV infection is the period of initial HIV infection until the stabilization of the viral load set point about 1 to 3 months later. The usual time from HIV exposure to the development of symptoms is usually 2 to 4 weeks, followed by an acute retroviral syndrome, which is a constellation of nonspecific symptoms similar to mononucleosis or a flulike illness. Most symptoms associated with acute HIV infection are brief, but the severity and duration of symptoms can vary widely. Symptoms can include fever, lymphadenopathy, pharyngitis, rash, myalgia/arthralgia, diarrhea, anorexia, and weight loss. The acute retroviral syndrome can easily be missed or misdiagnosed unless the degree of suspicion is high, so clinicians should have a low threshold for suspecting it. Although all patients should be questioned about HIV risk behaviors, patients may be reluctant to disclose this information. Acute HIV infection should always be considered in patients who have had a recent high-risk exposure or who have had a recent sexually transmitted infection, regardless of the presence of symptoms or signs. With the increasing sensitivity of HIV diagnostic assays, the window period wherein HIV antibodies may not be detected has gradually shortened to less than 3 to 4 weeks postexposure. The diagnosis of acute HIV infection is therefore often established by the detection of HIV viremia or the presence of HIV antibodies. It is recommended that antiretroviral therapy be started as soon as possible following the diagnosis of HIV infection, including acute HIV infection.

KEYWORDS

acute HIV
antiretroviral therapy
HIV PCR
HIV screening
HIV antibodies
HIV diagnosis

response to HIV may also shorten the duration of symptoms associated with acute infection, prevent dissemination of virus to other organs, and establish a lower virologic "set point." Unfortunately, eradication of virus is currently unlikely because replication-competent HIV can be recovered from patients with suppressed viral loads. In addition, patients with prolonged virologic suppression still experience virologic rebound when treatment is stopped.

DIAGNOSIS

Given the wide range of symptoms associated with acute HIV infection, clinicians should have a low threshold for suspecting it. Although all patients should be questioned about HIV risk behaviors, including sexual activity and injection drug use, patients may be reluctant to disclose this information or may not perceive their behavior as high risk. For example, acute HIV infection should also be considered in patients who have had a recent high-risk exposure or those who have had a recent sexually transmitted infection, regardless of the presence of symptoms or signs. Patients who have had a very recent high-risk exposure (i.e., within 72 hours) may be candidates for postexposure prophylaxis (Chapter 356) against HIV. With increasing sensitivity of these diagnostic assays, the "window period" wherein HIV antibodies may not be detected because of acute infection has gradually shortened to less than 3 weeks. The diagnosis of acute or early HIV infection is established by the detection of HIV viremia (RNA or antigen) or the presence of HIV antibodies.[6,7]

Testing Strategies

The current standard approach (Fig. 355-1)[8] starts with testing of serum by an FDA-approved fourth-generation HIV-1/HIV-2 immunoassay. Specimens that are reactive on the fourth-generation assay should be retested/confirmed with an FDA-approved second-generation antibody assay that differentiates HIV-1 antibodies from other HIV antibodies, thereby providing a definitive diagnosis of either HIV-1 or HIV-2. Specimens that are reactive on the fourth-generation assay but negative on the HIV-1/HIV-2 antibody differentiation assay should be retested with an FDA-approved nucleic acid test for HIV-1 RNA; under these circumstances, a reactive nucleic acid test indicates the presence of acute HIV infection, although RNA levels of less than 1000 copies/mL may indicate a rare false-positive result. A negative result would indicate the absence of HIV-1 and either a false-positive result on the initial fourth-generation assay or, rarely, recent HIV-2 infection. If HIV-2 infection is a possibility, an HIV-2-specific antibody or real-time polymerase chain reaction (PCR) test for HIV-2 DNA/RNA can be considered.

The preferred testing algorithm in the United States uses a fourth-generation HIV-1/HIV-2 combination immunoassay, which detects HIV p24 antigen and HIV antibodies, followed by confirmatory testing with an HIV-1/HIV-2 antibody differentiation immunoassay and HIV RNA testing as needed for indeterminate cases. The combined tests are highly accurate, with sensitivity and specificity greater than 99.5%. Results are typically available within 1 to 2 days from most commercial laboratories. In resource-limited settings, different algorithms are recommended, typically using a combination of two different rapid antibody tests.

Within weeks of exposure, many individuals will already have completely reactive immunoassays (e.g., both the combination antibody/antigen immunoassay and the antibody-only immunoassay) in addition to detectable viremia. In such cases, the timing of infection, and thus the diagnosis of acute or early versus established infection, must be inferred from the clinical presentation (e.g., symptoms consistent with acute retroviral syndrome at presentation or a very high viral RNA level suggesting established infection), exposure history, and the results of any past serologic testing. When the possibility of acute or early HIV infection is being considered, the most sensitive immunoassay available is typically performed (ideally, a combination antigen/antibody immunoassay) in addition to an HIV virologic (viral load) test. Rapid, point-of-care recency assays, which are based on the presence or absence of high-affinity antibodies that take 6 to 12 months to develop in infected patients,[9] can differentiate early infection (within about 6 months) versus established or chronic HIV infection.

Stages of Early Infection

The viral and immunologic dynamics following HIV transmission can be characterized into six stages (Table 355-2). Detection of early HIV infection is facilitated by HIV tests that detect HIV p24 antigen prior to seroconversion (i.e., prior to stage 3). In addition, confirmatory tests that use a second immunoassay instead of Western blot also improve the likelihood of diagnosing HIV in the early stages. In patients with symptoms and signs of acute HIV infection or potential recent exposure to HIV, direct testing for HIV RNA is warranted.

Rapid Tests and Home Testing Options

Rapid HIV testing, which may use either blood or oral fluid specimens,[10] can provide results as quickly as 5 minutes with a sensitivity and specificity

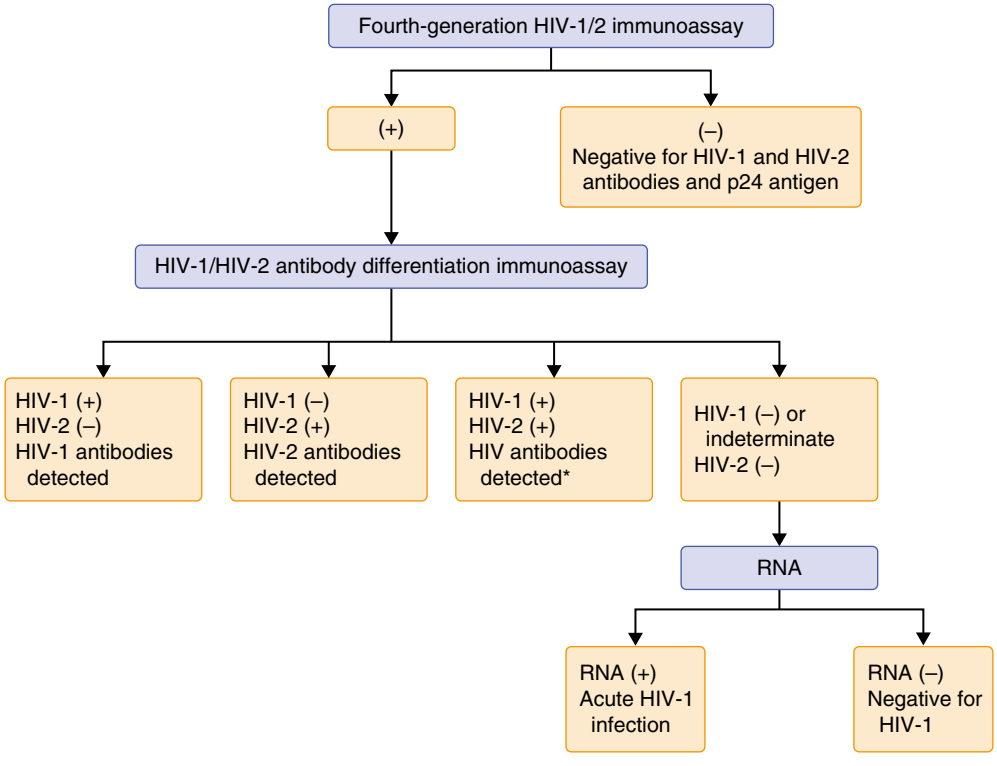

FIGURE 355-1. HIV diagnostic testing algorithm evaluated in the United States. HIV = human immunodeficiency virus. *Additional testing required to rule out dual infection with HIV-1 and HIV-2. (Modified from Centers for Disease Control and Prevention and Association of Public Health Laboratories. Laboratory Testing for the Diagnosis of HIV Infection: Updated Recommendations. Published June 27, 2014. 2018 Quick reference guide: Recommended laboratory HIV testing algorithm for serum or plasma specimens. Updated January 2018. https://stacks.cdc.gov/view/cdc/50872.)

TABLE 355-2 STAGES OF EARLY HIV INFECTION AND LABORATORY ASSAYS

STAGE	CUMULATIVE DURATION (DAYS)	HIV RNA	P24 ANTIGEN	IMMUNOASSAY	WESTERN BLOT
1	5	+	-	-	-
2	10	+	+	-	-
3	14	+	+	+	-
4	19	+	+/-	+	Indeterminate
5	88	+	+/-	+	+(p31 band negative)
6	Open-ended	+	+/-	+	+(p31 band positive)

From Fiebig EW, Wright DJ, Rawal BD, et al. Dynamics of HIV viremia and antibody seroconversion in plasma donors: implications for diagnosis and staging of primary HIV infection. *AIDS*. 2003;17:1871-1879.

greater than 99.5%. For example, early self-testing of male partners of women attending antenatal care can markedly increase the identification and early treatment of HIV-infected partners.[A1] However, initially positive results require confirmation with conventional methods (see Fig. 355-1). Rapid testing can be offered on-site in a variety of settings, including clinics, mobile vans, health fairs, and places of worship. Rapid tests are particularly important in management decisions of occupational or non-occupational exposures, when patients are unlikely to return for results and seroprevalence rates are high, such as sexually transmitted infection clinics or emergency departments, and when patients with an acute illness in which HIV-related complication is being considered but their serostatus is not known.

Home HIV tests to detect antibodies to both HIV-1 and HIV-2 are now available for consumers in stores or can be ordered online. These tests provide results within minutes after collecting an oral fluid sample. As with all rapid HIV assays, positive test results are preliminary and must be confirmed with a standard HIV antibody test. Another home testing option is kits that allow finger-prick blood samples to be taken at home and then mailed to a laboratory for screening and confirmation.

Other methods to establish HIV infection include viral isolation or qualitative or quantitative detection of HIV nucleic acid through PCR techniques, branched-chain DNA testing, or nucleic acid sequence–based amplification. Limitations of these assays include cost, the requirement for venipuncture, additional laboratory technology, and the time interval between sample collection and test results. None of these tests is considered superior to routine serologic testing. Viral detection is useful in specific situations, such as diagnosis of neonatal HIV infection when maternal antibody is passively transferred to the fetus, potentially providing a false-positive serologic result in an uninfected infant, in patients with indeterminate serologic results, or in those who may be in the window period before HIV seroconversion.

Screening for HIV

When to Screen

About 15% of HIV-infected individuals in the United States are unaware of their infection. The U.S. Preventive Services Task Force on HIV screening recommends that clinicians routinely screen for HIV infection in all adolescents and adults ages 15 to 65 years[11–13] because early diagnosis can facilitate earlier antiretroviral treatment, better outcomes, and less transmission to others (Chapter 357). All pregnant women, including those who present in labor, should also be screened for HIV if their HIV status is unknown. Men who have sex with men and individuals who are actively injecting drugs are at very high risk for new HIV infection and would qualify for increased HIV screening. Other risk factors for HIV infection include having unprotected vaginal or anal intercourse; having sexual partners who are HIV-infected, bisexual, or inject drugs; exchanging sex for drugs or money; or having or requesting testing for other sexually transmitted diseases (Chapter 264). Younger adolescents and older adults may be reluctant to disclose having HIV risk factors but should also be screened if they do.

How Often to Screen

Evidence is insufficient to determine optimum time intervals for HIV screening. A reasonable approach is a one-time screening of adolescents and adult patients to identify persons who are already HIV positive, with repeated screening of patients who are actively engaged in high-risk behaviors or live or receive medical care in a high-prevalence (HIV seroprevalence >1%) setting, such as sexually transmitted infection practices, correctional facilities, homeless shelters, or tuberculosis sites that specifically service patients with sexually transmitted infections. The approach that is supported by the U.S. Centers for Disease Control and Prevention (CDC) is to rescreen persons who are at *very high* risk for new HIV infection at least annually and individuals at *increased risk* every 3 to 5 years. Women screened for HIV during previous pregnancies should be rescreened for HIV at all subsequent pregnancies.

TREATMENT

Antiretroviral therapy (Chapter 357) should be started as soon as possible following the diagnosis of HIV infection, whether in a symptomatic patient or in the increasing number of patients whose early HIV infection is being diagnosed on routine screening. Patients should ideally be referred to a provider with experience in HIV management, preferably on the day of diagnosis, even in the setting of early HIV infection.[14,15]

Monitoring

Following initiation of antiretroviral therapy, viral RNA levels should be checked regularly to document and ensure viral suppression. If patients opt to defer antiretroviral therapy or otherwise are not ready to commit to lifelong therapy, close monitoring (i.e., every 3 months) of clinical and laboratory (e.g., CD4 cell count and viral load testing) findings should be initiated to detect any evidence of rapid immunologic decline. Behavioral counseling is vitally important, especially when viral RNA levels are very high and, as a result, so is the risk of transmission.

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356 PREVENTION OF HUMAN IMMUNODEFICIENCY VIRUS INFECTION

RAPHAEL J. LANDOVITZ, CARLOS DEL RIO, AND MYRON S. COHEN

At the end of 2020, approximately 37.6 million people worldwide were living with human immunodeficiency virus (HIV) infection and over 35 million people have died as a consequence of the acquired immunodeficiency syndrome (AIDS). Opportunities to prevent new HIV infection include behavioral modification, preexposure and postexposure prophylaxis, suppression of the viral load in already-infected individuals, and the hope for an effective vaccine (Fig. 356-1).[1]

MODES OF TRANSMISSION AND PREVENTION

SEXUAL TRANSMISSION

The primary mode of HIV transmission throughout the world is sexual contact. However, the geographic distribution of cases attributable to homosexual or heterosexual transmission varies markedly. In the United States, most sexually transmitted cases of HIV are observed in men who have sex with men (MSM), and heterosexual transmission accounts for a smaller number of new infections except among women. However, heterosexual transmission is the leading mode of transmission worldwide and remains the primary mode of disease acquisition in Africa. Sexual transmission of HIV is relatively inefficient, but behavioral and biologic factors influence the likelihood of HIV transmission in a given sexual encounter. In particular, coinfection with classic sexually transmitted infections (STIs; especially genital ulcerative diseases such as herpes simplex) greatly increases both the infectiousness and the susceptibility of an individual. Sexually transmitted infections increase the concentration of HIV in genital secretions and, as a result, increase the likelihood for transmission.

The risk for acquisition of HIV per coital act has been estimated to range from 5 per 10,000 for insertive unprotected penile-vaginal intercourse to 50 per 10,000 for receptive unprotected anal intercourse. However, the risk is not stable and varies depending on the stage of infection and other amplifying cofactors. HIV transmission risk is highest in early HIV infection and in advanced infection (Fig. 356-2), thereby demonstrating that the viral concentration in the genital secretions is the strongest predictor of the risk for transmission.

Prevention Strategies

Traditional strategies for the prevention of sexual transmission of HIV have focused on encouraging abstinence, reducing unsafe sexual behaviors (especially unprotected anal intercourse and concurrent relationships), encouraging proper use of condoms, and treating sexually transmitted infections. These interventions primarily focus on HIV-negative persons.

In situations in which a decision to engage in sexual activity has been made and the HIV serostatus of the partner is positive, unknown, or in doubt, safe sexual practices ("safe sex") should be implemented. Consistent and proper use of latex but not other types of condoms greatly reduces the transmission of HIV at both the individual and population levels. In particular, natural skin condoms should not be used because they do not prevent transmission of HIV. Petroleum-based lubricants enhance the likelihood of rupture of latex condoms and should be avoided. If needed, water-based lubricants should be used. The effectiveness of condoms in preventing heterosexual transmission of HIV has been estimated to be 87%, but it may be as low as 60% or as high as 96%. The effectiveness of condoms during anal intercourse is probably lower because the frequency of condom breakage and slippage may be considerably higher than during vaginal intercourse. The FDA has recently approved a condom specifically for anal sex.

Circumcision represents an additional strategy to protect men from HIV. Randomized clinical trials have demonstrated a protective benefit of male circumcision, with the risk for acquisition of HIV infection through heterosexual intercourse decreasing by approximately 60%, with increasing reduction in HIV acquisition over time. However, this benefit has not been confirmed for MSM.

Antiretroviral Therapy to Prevent Sexual Transmission

For people with HIV, antiretroviral therapy is a powerful tool to decrease HIV replication and thus infectivity and the subsequent risk for transmission through sexual contact.[2] For example, early antiretroviral therapy of people with HIV beginning at a CD4 count of 350 to 550 cells/μL reduces heterosexual transmission of HIV-1 by 96%.[A1] Observational data confirm a similar reduction of infectiousness for sexual transmission of HIV-1 when virus loads are suppressed among MSM.[3] The concept that if HIV is untransmittable if it is undetectable is a powerful rationale for achieving an undetectable viral load on antiretroviral therapy.

Preexposure Prophylaxis

Antiretrovirals also are effective to prevent HIV when administered prophylactically as preexposure prophylaxis (PrEP) to HIV-uninfected at-risk individuals (Table 356-1).[4–6] For example, daily administration of co-formulated tenofovir disoproxil fumarate plus emtricitabine as preexposure prophylaxis can decrease the risk for HIV infection among MSM by about 45 to 85%, with benefits varying across studies depending on adherence.[A2,A3] Subset and post-hoc analyses of the randomized studies to account for adherence to medication suggest greater than 99% efficacy against rectal acquisition and over 94% efficacy against vaginal transmission when taken as prescribed. For MSM and transgender women, daily tenofovir alafenamide in combination with emtricitabine is noninferior to daily tenofovir disoproxil fumarate plus emtricitabine, with a comparable clinical safety profile.[A4] For men, "on-demand" pericoital use of a tenofovir disoproxil fumarate plus emtricitabine (a double-dose of tenofovir disoproxil fumarate plus emtricitabine 2 to 24 hours prior

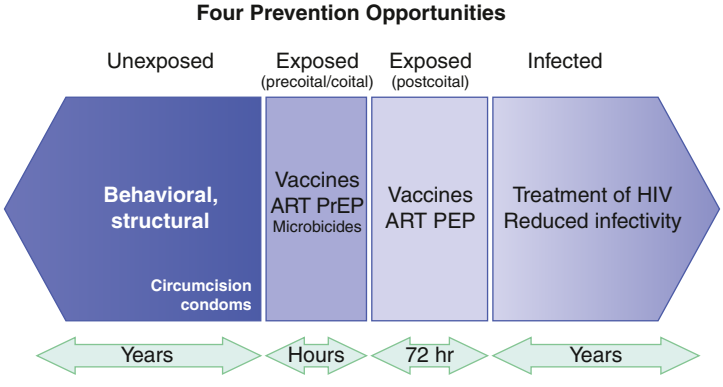

FIGURE 356-1. Opportunities for human immunodeficiency virus (HIV) prevention. ART = antiretroviral therapy; PEP = postexposure prophylaxis; PrEP = preexposure prophylaxis. (Modified from Cohen MS. Recent developments in HIV prevention. *AIDS*. 2008, Abstract TUPL0102.)

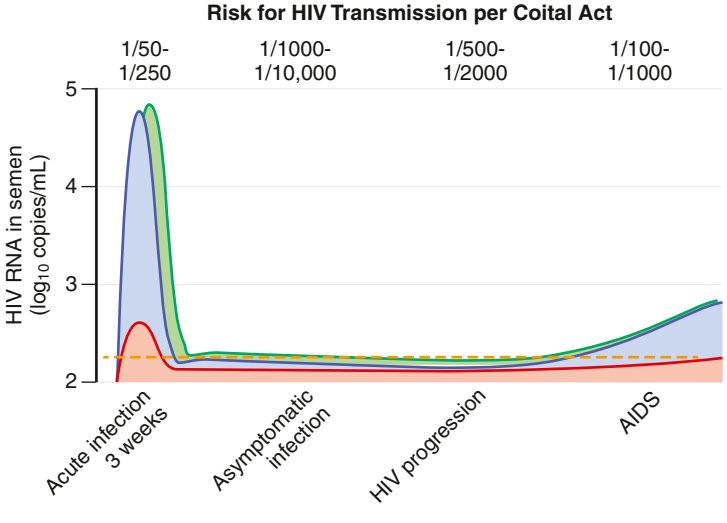

FIGURE 356-2. Prediction of the efficiency of human immunodeficiency virus (HIV) transmission according to HIV burden in the genital tract. Probability of male-to-female HIV transmission per coital act, as a function of HIV disease stage in the index case. Dashed line = a potential threshold for HIV transmission; orange = theoretical effect of a biologic intervention designed to reduce viral excretion; blue = expected distribution of viral burden in semen among men over time. AIDS = acquired immunodeficiency syndrome; HIV = human immunodeficiency virus. (Modified from Cohen MS, Pilcher CD. Amplified HIV transmission and new approaches to HIV prevention. *J Infect Dis*. 2005;191:1391-1393.)

ABSTRACT

The prevention of infection with the human immunodeficiency virus (HIV) begins with behavioral interventions, which though critical have been insufficient to reduce population-level incidence rates by themselves. The scale up of antiretroviral therapy to more than 27 million worldwide has significantly reduced the number of new infections because successful viral suppression virtually eliminates the transmission of HIV. Nevertheless, 1.5 million new infections occurred in 2020, and little progress has been made in reducing HIV incidence in the groups at highest risk. Biomedical HIV prevention strategies, such as preexposure and postexposure prophylaxis, have demonstrated efficacy in clinical trials and effectiveness in the real world and can reduce the population-level incidence of new HIV infection.

KEYWORDS

HIV prevention
preexposure prophylaxis
postexposure prophylaxis
universal precautions

TABLE 356-1 PREEXPOSURE PROPHYLAXIS REGIMENS

PrEP should be considered in the following HIV-negative persons:
- MSM or men who have sex with men and women who do not use condoms
- Transgender individuals
- Individuals from or whose partners are from any location where HIV incidence is 3% or greater
- Individuals who have traded sex for money, goods, or services
- Individuals who have multiple partners
- Individuals who have had STIs
- Individuals who have been or their partners have been incarcerated
- Individuals who share injection drug needles, syringes, or other equipment.

The preferred regimens are daily oral tenofovir disoproxil fumarate/emtricitabine or "on-demand"/pericoital tenofovir disoproxil fumarate/emtricitabine for men having planned sex and absent active HBV infection.

Cabotegravir is also recommended as first-line PrEP for all sexual risk populations.

HBV = hepatitis B; HIV = human immunodeficiency virus; MSM = men who have sex with men; PrEP = pre-exposure prophylaxis; STIs = sexually transmitted infections.

Data from *Pre-Exposure Prophylaxis* (PrEP) FOR THE PREVENTION OF HIV INFECTION IN THE UNITED STATES - 2021 UPDATE: A Clinical Practice Guide. https://www.cdc.gov/hiv/pdf/risk/prep/cdc-hiv-prep-guidelines-2021.pdf. Accessed April 5, 2023.

TABLE 356-2 POSTEXPOSURE PROPHYLAXIS REGIMENS

NUMBER OF ANTIRETROVIRAL DRUGS
A three-drug regimen for 28 days of treatment are recommended
PREFERRED ANTIRETROVIRAL REGIMEN
Tenofovir disoproxil fumarate (300 mg daily) plus emtricitabine (200 mg once daily) or lamivudine (300 mg daily) as the first two drugs
Raltegravir (400 mg twice daily) or dolutegravir (50 mg once daily) is preferred as the third drug, but darunavir (800 mg daily) boosted with ritonavir (100 mg daily) or cobicistat (150 mg daily) is an alternative

Adapted from Centers for Disease Control and Prevention, U.S. Department of Health and Human Services, Updated Guidelines for Antiretroviral Postexposure Prophylaxis after Sexual, Injection Drug Use, or Other Nonoccupational Exposure to HIV—United States, 2016. Available at https://stacks.cdc.gov/view/cdc/38856. Accessed June 19, 2021.

to planned intercourse, a single dose 24 hours later, and a final single dose 24 hours later[7] is also of proven efficacy. Individuals with ongoing exposures after the first dose should extend the daily single dosing until 48 hours after their last sexual activity. Randomized clinical trials have also demonstrated superiority of every-2-months injectable cabotegravir compared with daily oral tenofovir disoproxil fumarate plus emtricitabine as preexposure prophylaxis in MSM, transgender women who have sex with men, and cisgender women.[A5,A6] The results strongly support the adherence benefit of an injection rather than oral preexposure prophylaxis.[8] The HIV status of persons using injectable cabotegravir for preexposure prophylaxis should be monitored using the most sensitive testing assay available, ideally an HIV RNA test, owing to alterations in the biology and laboratory testing profiles of newly acquired HIV in persons who are using a long-acting product for preexposure prophylaxis.

Use of a monthly vaginal ring containing dapivirine can reduce HIV infection by about 30%. The ring has been approved by the European Medicines Agency and by the South African government, and it has been endorsed by the World Health Organization (WHO); however, if has been withdrawn from consideration before the U.S. FDA.

Postexposure Prophylaxis

Antiretroviral medications can also be given after exposure to prevent HIV acquisition (postexposure prophylaxis [PEP]) after unprotected sex, after sexual assault, injection drug use, or other nonoccupational exposures to HIV.[9] Persons who seek care 72 hours or sooner after nonoccupational exposure to the blood, genital secretions, or other potentially infected body fluids of a person known or suspected to have HIV infection should be offered a 28-day course of fully suppressive antiretroviral therapy (Table 356-2).[10]

TRANSMISSION IN INJECTION DRUG USERS

The primary mode of HIV transmission in persons with injection drug use (Chapter 365) is sharing of contaminated needles and syringes. Sharing of injection paraphernalia is commonplace among injection drug users and is reinforced by the cultural, economic, and legal environment in that community. The risk for transmission of HIV is highest in injection drug users who share needles and use drugs that are injected more frequently, such as cocaine or methamphetamines.

Prevention Strategies

The primary mode of preventing HIV transmission in persons who inject drugs is to stop the use of intravenous drugs. Education programs that are culturally sensitive and geared to young audiences have the best chance of preventing drug use. For persons with opioid use disorder, access to opioid substitution therapy with medications such as methadone, buprenorphine, and extended-release naltrexone is the best approach. However, approximately 80% of active drug users in the United States are not in substance use treatment because of either choice or the unavailability of treatment centers. For injection drug users who do not wish to seek treatment or who are unable to gain access to treatment, the most effective way to prevent HIV infection is to avoid sharing needles and paraphernalia. Some communities have adopted programs that provide free needles and syringes for injection drug users, and there is strong evidence that these programs, when implemented properly, are effective in reducing HIV transmission and do not result in increased drug use among participants. Where supplies cannot be obtained, needles and syringes should be cleaned after each use, preferably with readily accessible virucidal cleansers such as chlorine bleach (diluted 1 : 10).

As with sexual transmission, data suggest that antiretroviral prophylaxis for people who inject drugs decreases HIV infection. For example, a randomized trial conducted in Thailand demonstrated a 50% reduction in HIV acquisition when daily oral tenofovir disoproxil fumarate (as a single agent) was given as preexposure prophylaxis. The U.S. Centers for Disease Control and Prevention recommend the use of co-formulated tenofovir disoproxil fumarate (300 mg daily) plus emtricitabine (200 mg daily) rather than tenofovir disoproxil fumarate alone as the preferred preexposure prophylaxis regimen among injection drug users.

TRANSMISSION THROUGH BLOOD PRODUCTS AND OTHER TISSUES

HIV can be transmitted through the transfusion of single-donor blood and blood products, including whole blood, fresh-frozen plasma, packed red blood cells, cryoprecipitate, clotting factors, and platelets (Chapter 162). Confidential donor exclusion, screening of blood for any HIV antibodies, and nucleic acid testing have reduced the risk for HIV infection through the transfusion of blood or blood products to less than 1 in 2 million. Transmission of HIV by liver, heart, kidney, pancreas, bone, and possibly skin transplantation has been reported. In contrast, relatively avascular tissues such as corneas and processed tissues have not been associated with HIV transmission.

Prevention Strategies

The blood supply in most countries is now virtually free of HIV. For cryoprecipitate and clotting factor concentrates, heat inactivation processes have eliminated transmission of HIV. Organ and tissue donors should be evaluated and serologically screened in a manner similar to blood donors. In addition, donations of semen and bone from a living donor may be quarantined until subsequent testing has definitively excluded the possibility of delayed seroconversion in the donor.

TRANSMISSION TO HEALTH CARE WORKERS

In health care workers, occupational exposures carry a low risk for acquisition of HIV. In large surveys of health care workers, the overall risk for seroconversion after a percutaneous needlestick from a known HIV-infected source is 0.3% per exposure. The risk for transmission of HIV to a health care worker is increased when the device causing the injury is visibly contaminated with blood, when the device has been used for insertion into a vein or artery, when the device causes a deep injury, or when the source patient dies within two months after the exposure. Exposure of mucous membranes to HIV-infected blood has resulted in seroconversion only rarely, and the risk for transmission is estimated to be 0.09% per exposure.

Prevention Strategies

Universal precautions have been incorporated into health care settings to minimize exposure of health care workers to blood and body fluids that may be infected with blood-borne pathogens such as HIV. Universal precautions are based on the premise that any patient may be infected with blood-borne infectious agents, and it may be difficult, if not impossible, to differentiate patients with infection from their uninfected counterparts. All specimens containing blood or blood-tinged fluids obtained from *any* patient should be considered

hazardous and handled as such. The use of universal precautions helps minimize the transmission of many transmissible diseases in addition to HIV.

Gowns, protective eyewear, and masks are not usually needed except in circumstances in which splattering or splashing of blood-containing fluids is likely to occur. Health care workers with denuded skin, open lesions, or active dermatitis should avoid direct patient contact and should not process contaminated equipment or materials. Handling of contaminated sharp instruments ("sharps") represents the greatest risk for transmission of HIV to health care workers. Although injuries from sharps cannot be eliminated entirely, the number of exposures can be reduced substantially by adhering to universal precautions. Before a sharp instrument is used, thought should be given to where the instrument will be disposed of after use. Impervious containers should be readily available in all patient care areas and identified by the health care worker *before* the use of sharps. These containers should be checked frequently and should not be allowed to overfill. Used needles should never be manipulated, bent, broken, or recapped. Recapping of needles is the single most common activity that results in needlestick injuries. Technologic developments that do not rely on individual adherence, such as self-sheathing needles, also have been important in decreasing the risk for needlestick injury.

The essential elements of management of a health care worker after a needlestick or mucous membrane exposure include appropriately evaluating the donor (patient) and recipient (health care worker) at the time of exposure, counseling the health care worker, and providing follow-up HIV testing. A postexposure drug regimen containing three or more drugs is recommended with co-formulated tenofovir disoproxil fumarate/emtricitabine plus raltegravir or dolutegravir as the preferred postexposure prophylaxis regimen (see Table 356-2). However, the regimens for occupational exposures are interchangeable with the preferred and alternative postexposure prophylaxis regimens used for non-occupational situations. Antiretroviral postexposure prophylaxis should be initiated as rapidly as possible, but certainly within 72 hours of exposure, and it should be continued for 4 weeks. The U.S. Public Health Service has established a National Clinicians' Post-Exposure Prophylaxis Hotline (1-888-448-4911 or http://nccc.ucsf.edu/clinician-consultation/pep-post-exposure-prophylaxis/) that can provide expert consultation about the management of health care workers with potential HIV exposure.

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Antiretroviral therapy administered to HIV-infected individuals decreases the risk for HIV transmission by over 96%, so suppression of HIV replication to undetectable levels is the most effective intervention to decrease HIV transmission from an HIV-infected person (undetectable = untransmittable).[A7] U.S. guidelines recommend initiation of antiretroviral treatment regardless of the CD4 cell count, with monitoring for viral suppression. Large-scale, universal testing and then treatment of infected individuals is an appealing strategy in countries with a high prevalence of HIV, but its efficacy compared with current standard care has been mixed.[A8,A9]

In addition, the U.S. Centers for Disease Control and Prevention, Health Resources and Services Administration, National Institutes of Health, and Infectious Diseases Society of America reflect four basic priorities: (1) screening for risk behavior and STIs; (2) providing general and tailored risk reduction messages to patients; (3) when indicated, referring patients for additional risk reduction services and other services that may affect risk reduction (e.g., substance abuse treatment); and (4) ensuring that patients are provided with partner counseling and referral services. All patients with newly diagnosed HIV infection undergo screening for gonorrhea, chlamydial infection, hepatitis B and C virus infection, and syphilis. Screening for curable sexually transmitted infections (gonorrhea, chlamydial infection, and syphilis) should be performed at least annually in sexually active patients. More frequent screening for sexually transmitted infections is appropriate depending on individual risk behaviors, the local epidemiology, and whether incident STIs are detected by screening or by the presence of symptoms. Data suggest that for MSM, quarterly screening for curable sexually transmitted infections with prompt treatment for positive test results or symptoms could powerfully disrupt ongoing secondary transmission of sexually transmitted infections and reduce the risk of HIV by interrupting infectivity.

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Antiretroviral therapy should be administered and overseen by a clinician with experience and expertise whenever possible. Under such supervision, the life expectancy of an HIV-infected individual appropriately treated with antiretroviral therapy is now approaching that of the general population, in both developed[1,2] and developing countries.[3] The benefits of antiretroviral therapy have been extended to developing countries, and more than 28 million people currently are taking antiretroviral therapy worldwide.

AVAILABLE DRUGS

Each of the more than 30 antiretroviral drugs that are approved by the U.S. Food and Drug Administration (FDA; Table 357-1) is designed to block a specific step (Fig. 357-1) of the HIV life cycle (see also E-Figs. 354-2 and 354-3). Drugs must be used in combinations that block different steps so as to reduce the emergence of drug resistance, and once-daily two- or three-drug combination regimens are the standard of care.

Four kinds of HIV drugs target the first step in the HIV life cycle, which is viral entry by: (1) binding gp120 and inhibiting its attachment to the CD4 receptor (CD4 attachment inhibitors); (2) inhibiting conformational changes after gp120 attachment (CD4 post-attachment inhibitors); (3) inhibiting CCR5 chemokine receptor binding (CCR5 antagonists); or (4) inhibiting membrane

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ABSTRACT

Antiretroviral therapy suppresses human immunodeficiency virus (HIV) viremia, promotes immunologic recovery, prevents clinical progression, reduces HIV transmission, and prolongs healthy survival. First-line antiretroviral regimens consist of once-daily, one-pill therapy with two or three drugs, typically nucleoside analogue(s) combined with an integrase inhibitor. Individuals on antiretroviral therapy should be monitored regularly, and a confirmed HIV RNA level above 200 copies/mL should prompt assessment for adherence and virologic failure. With confirmed virologic failure, the patient's treatment history, adherence, and potential drug-drug interactions should be reviewed, and drug resistance testing should be conducted. These results inform the design of a new antiretroviral regimen with at least two active drugs (at least one with a high barrier to resistance), with the goal of reestablishing virologic suppression. People living with HIV, including pregnant women, who take antiretroviral therapy dramatically decrease their risk for transmitting to others. HIV-infected individuals who take antiretroviral therapy with virologic control now have a life expectancy that is approaching the life expectancy of the general population, but HIV cure remains elusive and a focus of current research.

KEYWORDS

HIV
antiretroviral therapy
entry inhibitor
nucleoside analogue reverse transcriptase inhibitor
non-nucleoside analogue reverse transcriptase inhibitor
protease inhibitor
integrase inhibitor

TABLE 357-1 ANTIRETROVIRAL DRUGS

MECHANISTIC DRUG CLASS	GENERIC NAME	ABBREVIATION(S)	TRADE NAME
HIV REVERSE TRANSCRIPTASE INHIBITORS			
Nucleoside analogues (NRTIs)	abacavir	ABC	Ziagen
	emtricitabine	FTC	Emtriva
	lamivudine	3TC	Epivir
	tenofovir		
	alafenamide	TAF	Vemlidy
	disoproxil fumarate	TDF	Viread
	zidovudine	ZDV, AZT	Retrovir
Non-nucleoside analogues (NNRTIs)	doravirine	DOR	Pifeltro
	efavirenz	EFV	Sustiva
	etravirine	ETR	Intelence
	nevirapine	NVP	Viramune
	rilpivirine	RPV	Edurant
HIV PROTEASE INHIBITORS (PIs)			
	atazanavir	ATV	Reyataz
	darunavir	DRV	Prezista
	fosamprenavir	FPV	Lexiva
	indinavir	IDV	Crixivan
	lopinavir/ritonavir	LPV/r	Kaletra
	nelfinavir	NFV	Viracept
	ritonavir	RTV	Norvir
	saquinavir	SQV	Invirase
	tipranavir	TPV	Aptivus
HIV ENTRY INHIBITORS (EIs)			
	enfuvirtide	ENF, T-20	Fuzeon
	fostemsavir	FTR	Rukobia
	ibalizumab	IBA	Trogarzo
	maraviroc	MVC	Selzentry
HIV INTEGRASE INHIBITORS (INSTIs)			
	bictegravir	BIC	Biktarvy
	cabotegravir	CAB	Vocabria
	dolutegravir	DTG	Tivicay
	elvitegravir	EVG	Vitekta
	raltegravir	RAL	Isentress
HIV CAPSID INHIBITORS (CIs)			
	lenacapavir	LEN	Sunlenca

Previously approved but no longer marketed drugs in the United States include amprenavir, delavirdine, didanosine, stavudine, and zalcitabine.
HIV = human immunodeficiency virus.

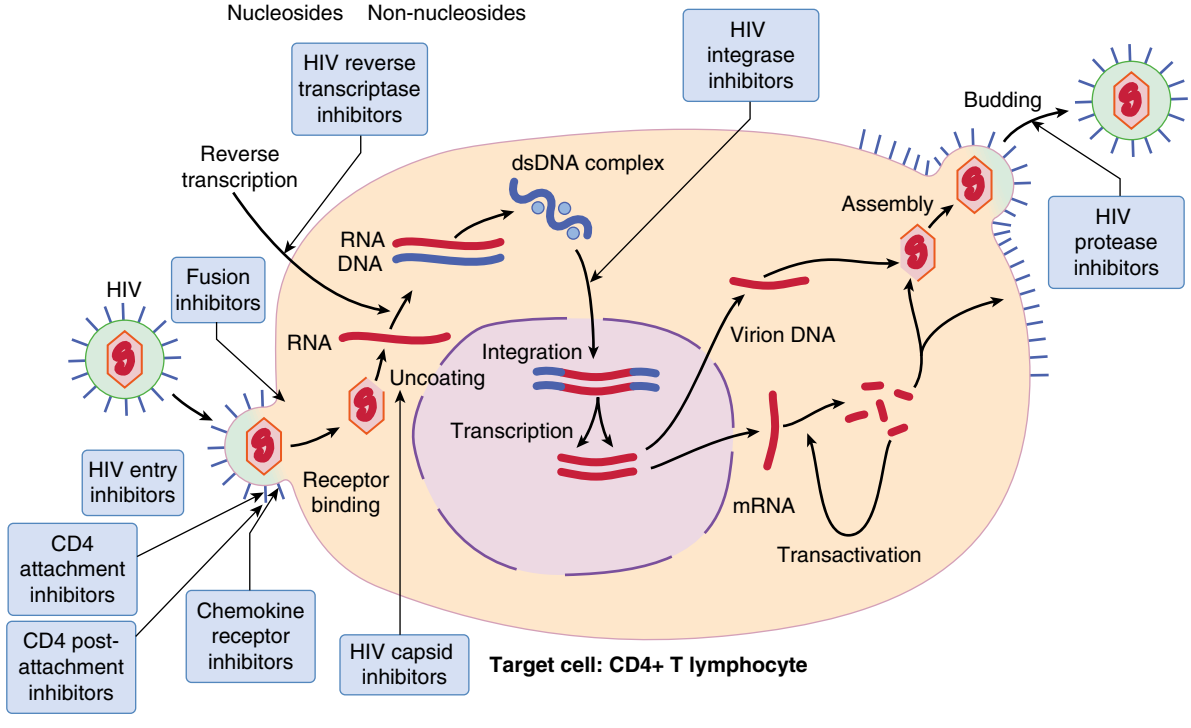

FIGURE 357-1. **Life cycle of human immunodeficiency virus *(HIV)* and mechanisms of action of the eight antiretroviral drug classes.** See text (What to Start section) for details.

fusion (fusion inhibitors). The nucleoside analogue reverse transcriptase inhibitors (NRTIs) target the viral-specific enzyme *HIV reverse transcriptase*. A second class of HIV reverse transcriptase inhibitors are the non-nucleoside analogue reverse transcriptase inhibitors (NNRTIs), which bind to a different part of the same enzyme. The capsid inhibitors (CIs) disrupt the formation of the HIV capsid that protects HIV's genetic material and enzymes. The integrase strand transfer inhibitors (INSTIs) inhibit the viral-specific enzyme *HIV integrase* by specifically targeting the transfer of viral DNA to the host cell genome. The HIV protease inhibitors (PIs) bind to the active site of the *HIV protease* enzyme and prevent precursor protein cleavage, and thereby, viral maturation, and infectivity.

WHEN TO START ANTIRETROVIRAL THERAPY

The goals of antiretroviral therapy are to suppress viral replication, prevent the emergence of drug-resistant viral strains, enhance immunologic responses, decrease clinical events, and prolong healthy life.[4-7] Antiretroviral therapy should be started as soon as possible after HIV infection is diagnosed (Chapter 355), because it reduces symptoms and signs and improves patients' outcomes compared with delayed treatment.[A1-A2] In addition, antiretroviral therapy suppresses viremia and thereby reduces the risk for transmission to others by more than 90%.[A3]

Multiple FDA-approved fixed-dose combinations include more than 10 one-pill, once-daily complete regimens. These simple regimens are popular with clinicians and patients because they are easy to use, promote adherence, and can achieve virologic suppression rates of more than 90% (Table 357-2).[A4-A8] Potency, convenience, and tolerability are essential qualities of current antiretroviral drug regimens and account for their durable clinical benefits.

WHAT TO START

Because of the risk for acquiring drug-resistant HIV, estimated to be about 17% in the United States, antiretroviral therapy should be started while awaiting the results of the HIV genotype. Guidelines recommend starting a bictegravir-, or dolutegravir-containing regimen and then adjusting when the genotypic results are available.

Currently recommended initial regimens in the United States (Table 357-3) are combinations of one or two nucleoside analogues together with a third drug (integrase inhibitor). Globally, the preferred antiretroviral regimen is co-formulated tenofovir disoproxil fumarate/lamivudine/dolutegravir.[8] However, some two-drug antiretroviral regimens (e.g., the combination of dolutegravir with lamivudine), given either as initial or maintenance therapy, are equivalent to three-drug regimens.[A9,A10] The first long-acting antiretroviral regimen is the two-drug combination of injectable cabotegravir and rilpivirine, given every other month.[A11–A13] Monotherapy, by comparison, does not appear to be adequate for chronic HIV suppression.[A14]

WHAT TO MONITOR

In a stable patient who is taking antiretroviral therapy, HIV RNA should be monitored every 3 to 6 months. In general, an adherence level of 80 to 85% can achieve effective viral suppression.[9] HIV RNA levels suppressed below the level of detection of the assay are unlikely to result in the emergence of drug-resistant viral strains. Even with initial virologic suppression rates of more than 90%, however, some patients will experience virologic failure, with a once-suppressed viral load level becoming repeatedly detectable above the limit of the HIV RNA assay (20, 40, or 50 copies/mL).

When antiretroviral therapy is started, the glomerular filtration rate should be measured at baseline, after antiretroviral therapy is started, and whenever it is changed. Even in people who are living with HIV and who are otherwise stable, it should be monitored at least twice a year. Urinalysis should be checked at baseline, when ART is initiated or changed, and at least annually in patients who are stable. Patients should be referred to a nephrologist if the glomerular filtration rate declines by more than 25% and to less than 60 mL/minute, or if proteinuria exceeds 300 mg/day or is associated with hematuria (see Fig. 359-1).

WHEN TO CHANGE ANTIRETROVIRAL THERAPY

VIROLOGIC FAILURE

Virologic failure is defined as repeated detection of HIV RNA levels in a drug-adherent patient. Repeated HIV RNA levels between the level of detection and 200 copies/mL (low-level viremia) likely represent a higher virologic set point rather than ongoing viral replication and may not necessitate treatment change. By comparison, confirmed levels greater than 200 copies/mL (and certainly >500 copies/mL) will lead to the selection of drug-resistant viral strains and result in treatment failure.

When failure is diagnosed, the first goal is to try to determine the cause of failure, so the next selected regimen can address and overcome the reason for failure. The reasons for failure can include suboptimal adherence, baseline drug resistance or cross-resistance, prior use of antiretroviral therapy, use of

TABLE 357-2 SELECTED ANTIRETROVIRAL FIXED-DOSE COMBINATIONS (LISTED IN ORDER OF U.S. FDA APPROVAL)

DRUG CLASS(ES)	GENERIC NAMES	ABBREVIATION(S)	TRADE NAMES	DOSING
2 NRTI + NNRTI	tenofovir disoproxil fumarate + emtricitabine + efavirenz*	TDF/FTC/EFV*	Atripla	Once daily
2 NRTI + NNRTI	tenofovir disoproxil fumarate + emtricitabine + rilpivirine*	TDF/FTC/RPV*	Complera	Once daily
2 NRTI + boosted INSTI	tenofovir disoproxil fumarate + emtricitabine + elvitegravir + cobicistat*	TDF/FTC/EVG/c*	Stribild	Once daily
2 NRTI + INSTI	abacavir + lamivudine + dolutegravir*	ABC/3TC/DTG*	Triumeq	Once daily
2 NRTI + boosted INSTI	tenofovir alafenamide + emtricitabine + elvitegravir + cobicistat*	TAF/FTC/EVG/c*	Genvoya	Once daily
2 NRTI + NNRTI	tenofovir alafenamide + emtricitabine + rilpivirine*	TAF/FTC/RPV*	Odefsey	Once daily
NNRTI + INSTI	rilpivirine + dolutegravir†	RPV/DTG†	Juluca	Once daily
2 NRTI + INSTI	tenofovir alafenamide + emtricitabine + bictegravir*	TAF/FTC/BIC*	Biktarvy	Once daily
2 NRTI + boosted PI	tenofovir alafenamide + emtricitabine + darunavir + cobicistat*	TAF/FTC/DRV/c*	Symtuza	Once daily
2 NRTI + NNRTI	tenofovir disoproxil fumarate + lamivudine + doravirine*	TDF/3TC/DOR*	Delstrigo	Once daily
NRTI + INSTI	lamivudine + dolutegravir†	3TC/DTG†	Dovato	Once daily
2 NRTI + NNRTI	tenofovir disoproxil fumarate + lamivudine + efavirenz 600 mg*	TDF/3TC/EFV*	Symfi (generic)	Once daily
2 NRTI + NNRTI	tenofovir disoproxil fumarate + lamivudine + efavirenz 400 mg*	TDF/3TC/EFV*	Symfi Lo (generic)	Once daily

*One pill, once-daily 3-drug antiretroviral therapy regimen.
†One pill, once-daily 2-drug antiretroviral therapy regimen.
INSTI = integrase inhibitor; NNRTI = non-nucleoside reverse transcriptase inhibitor; NRTI = nucleoside analogue reverse transcriptase inhibitor; PI = protease inhibitor; U.S. FDA = United States Food and Drug Administration.

TABLE 357-3 RECOMMENDED INITIAL ANTIRETROVIRAL DRUG REGIMENS

REGIMEN*	DRUGS
Integrase strand transfer inhibitor (INSTI)-based	bictegravir/tenofovir alafenamide/emtricitabine (co-formulated) dolutegravir/abacavir†/lamivudine (co-formulated) dolutegravir + tenofovir (alafenamide or disoproxil fumarate) + (emtricitabine or lamivudine) dolutegravir + lamivudine (co-formulated)‡

*From Panel on Antiretroviral Guidelines for Adults and Adolescents. Guidelines for the use of antiretroviral agents in adults and adolescents with HIV. Department of Health and Human Services. https://clinicalinfo.hiv.gov/en/guidelines/adult-and-adolescent-arv. September 22, 2022. Also see the International Antiviral Society—USA (IAS-USA) Guidelines (Gandhi RT, Bedimo R, Hoy JF, et al. Antiretroviral drugs for treatment and prevention of HIV infection in adults: 2022 recommendations of the International Antiviral Society-USA Panel. *JAMA*. 2023;329:63-84.), European AIDS Clinical Society (EACS) Guidelines (European AIDS Clinical Society [EACS]. European Guidelines for treatment of HIV-positive adults in Europe. October 2022, version 11.1. https://www.eacsociety.org/media/guidelines-11.1_final_09-10.pdf. Accessed April 8, 2022.), and the World Health Organization Consolidated Guidelines (World Health Organization. Policy brief: update of recommendations on first- and second-line antiretroviral regimens. July 2019. https://apps.who.int/iris/bitstream/handle/10665/325892/WHO-CDS-HIV-19.15-eng.pdf?ua=1. Accessed April 8, 2022.).

†For patients who are HLA-B*5701 negative.

‡Except for patients who have HIV RNA >500,000 copies/mL, are hepatitis B surface antigen positive, or do not have results from HIV drug resistance testing.

less potent antiretroviral drug regimens, insufficient drug levels, drug-drug interactions, and, at least theoretically, poor penetration into tissue reservoirs (e.g., genital tract, central nervous system [CNS]). More than one factor may play a role in an individual patient, and the experience of the prescribing clinician is also important.

U.S. antiretroviral therapy guidelines recommend addressing virologic failure by changing antiretroviral regimens promptly when failure is confirmed. HIV is prone to errors in gene replication, and thus an individual is infected with not just one virus but a "swarm" of related viral strains with distinct genetic mutational patterns (Chapter 354). Drug resistance is conferred by viral strains with specific amino acid substitutions in viral proteins (e.g., HIV gp120, HIV gp41, HIV reverse transcriptase, HIV integrase, HIV protease) that persist and replicate in the presence of an antiretroviral drug that inhibits the growth of susceptible strains. For example, with ongoing viral replication in the presence of the HIV nucleoside analogue emtricitabine or lamivudine, a viral strain with the substitution of valine for methionine at amino acid position 184 (denoted M184V) of HIV reverse transcriptase will be selected and confer complete resistance to these drugs. Drugs against which a single substitution confers resistance are considered to have a low barrier to resistance; such drugs include the nucleoside analogues emtricitabine and lamivudine, the non-nucleoside analogue reverse transcriptase inhibitors efavirenz and nevirapine, and the integrase inhibitors elvitegravir and raltegravir. Drugs that require multiple substitutions are considered to have a higher barrier to resistance; such drugs include the nucleoside analogue zidovudine, most of the HIV protease inhibitors, and the integrase inhibitors bictegravir and dolutegravir. Drugs with the same resistance patterns lead to cross resistance. For example, a patient who develops resistance to emtricitabine with the M184V substitution will have complete cross resistance to lamivudine, even though the patient never took lamivudine. Drug resistance can be assessed by HIV genotyping to identify amino acid substitutions that must be correlated with drug resistance, or by HIV phenotyping that assesses the in vitro growth of the virus in the presence of each of the antiretroviral drugs.[10]

IMMUNOLOGIC FAILURE

Another common clinical conundrum is immunologic failure—a patient who achieves virologic suppression on antiretroviral therapy but fails to increase their CD4 cell count. The cause of immunologic failure is not clear, but associations with various factors, including a CD4 count less than 200 cells/μL at the time of initiation of antiretroviral therapy, older age, coinfections, comorbid conditions, older medications (e.g., zidovudine; the combination of didanosine and tenofovir), persistent immune activation, and loss of regenerative potential have been reported. No accepted treatment is available for immunologic failure, and neither changing nor adding antiretroviral drugs results in an improved CD4 cell response. Immune-based therapies have been studied but also are not effective. Current management is to continue antiretroviral therapy, optimize prophylaxis against opportunistic infections, and follow the patient closely.

WHAT ANTIRETROVIRAL THERAPY TO CHANGE TO?

Changes in antiretroviral therapy should be guided by experts. The current goal for all HIV-infected patients taking antiretroviral therapy, regardless of treatment experience, is to suppress the viral load, below the level of assay detection. In a treatment-experienced patient, the choice among agents is based on a review of the antiretroviral history, with a focus on adherence, tolerability, and possible drug-drug interactions; drug-resistance testing (HIV genotype for first or second failure; HIV genotype and phenotype for more advanced failure); identification of susceptible drugs and drug classes; and, ultimately, design of a subsequent regimen with two fully active antiretroviral agents (at least one with a high barrier to resistance, e.g., darunavir or dolutegravir).

A number of antiretroviral drugs make this goal possible. Examples include drugs in the same mechanistic class (e.g., the HIV protease inhibitor darunavir, the HIV non-nucleoside analogue reverse transcriptase inhibitors doravirine and etravirine, and the HIV integrase inhibitors bictegravir and dolutegravir) and drugs with novel mechanisms of action (e.g., the CD4 attachment inhibitor fostemsavir,[A15] the CD4 post-attachment inhibitor ibalizumab,[A16] the CCR5 antagonist maraviroc, the HIV fusion inhibitor enfuvirtide, and the capsid inhibitor lenacapavir.)[A17] Some studies show that new active antiretroviral regimens result in virologic suppression in a majority of treatment-experienced patients for extended periods.[A18] Including a nucleoside analogue in subsequent regimens may not be necessary if the regimen contains more than two active antiretroviral drugs.[A19]

SIDE EFFECTS AND TOXICITY

Antiretroviral drugs, like all drugs, are associated with side effects and toxicity. Acute side effects can be troubling to the patient and can lead to suboptimal adherence. Clinicians should be in close contact with a patient who is starting a new antiretroviral regimen and have a low threshold to substitute offending drugs because of side effects or toxicities. Clinicians must also be aware of potential drug-drug interactions with specific antiretroviral drugs (Table 357-4).

Probably the most common side effect of antiretroviral therapy as a group is gastrointestinal (nausea, vomiting, diarrhea), although some drugs (e.g., zidovudine, ritonavir) are more associated than others. This side effect can be managed by taking antiretroviral therapy with food.

Other toxicities may be divided according to seriousness and drug classes. Life-threatening toxicities include drug-related hepatitis associated with non-nucleoside analogue reverse transcriptase inhibitors and protease inhibitors. Of these drugs, the non-nucleoside analogue reverse transcriptase inhibitor nevirapine is unique in causing drug-related hepatitis more frequently in patients who have higher CD4 counts (>250 cells/μL in women and >400 cells/μL in men), likely owing to an immunologic mechanism. A hypersensitivity reaction characterized by rash and constitutional symptoms that can be life-threatening is associated with the nucleoside analogue abacavir and, less commonly, with the non-nucleoside analogue reverse transcriptase inhibitors etravirine and nevirapine. For abacavir, hypersensitivity is linked to a genetic locus (HLA-B*5701) that can be detected by screening; if the drug is avoided in patients with the genetic marker, the risk for a hypersensitivity reaction is minimized.

All non-nucleoside analogue reverse transcriptase inhibitors, although structurally unrelated, are associated with rash. Stevens-Johnson syndrome (Fig. 403-8) is rarely described with etravirine or nevirapine. Although efavirenz is labeled as FDA pregnancy category D, current recommendations allow using or continuing[11] the drug in a pregnant woman. Efavirenz is linked to a small but increased risk for suicidality. Neural tube defects occur rarely in babies born to mothers who take dolutegravir at the time of conception.

Zidovudine causes anemia, neutropenia, and fatigue. Efavirenz causes CNS side effects (e.g., vivid dreams, somnolence) in up to 50% of people and should be dosed fasting at bedtime. Atazanavir causes increased indirect bilirubin by inhibiting uridine 5′-diphospho-glucuronosyltransferase, which can be associated with frank jaundice but is not associated with other liver test abnormalities.

TABLE 357-4 DRUGS THAT SHOULD NOT BE COADMINISTERED WITH SPECIFIC ANTIRETROVIRALS DUE TO PROVEN OR SUSPECTED DRUG-DRUG INTERACTIONS

ANTIRETROVIRAL	CARDIAC DRUGS	LIPID-LOWERING DRUGS	PULMONARY ARTERIAL HYPERTENSION DRUGS	COPD/ASTHMA DRUGS	ANTIPLATELET/ ANTICOAGULANT DRUGS
ALL PROTEASE INHIBITORS	Dronedarone Eplerenone Ivabradine Ranolazine	Lovastatin Simvastatin	Sildenafil	Inhaled budesonide*, fluticasone*, mometasone* Prednisone* Salmeterol	Apixaban Dabigatran if CrCl <50 mL/min Edoxaban Rivaroxaban Ticagrelor Vorapaxar
Fosamprenavir ± ritonavir	Above plus: Flecainide Propafenone				
Saquinavir/ritonavir	Above plus: Amiodarone Disopyramide Dofetilide Flecainide Lidocaine Propafenone Quinidine				
Tipranavir/ritonavir	Above plus: Amiodarone Flecainide Propafenone Quinidine				
NON-NUCLEOSIDE REVERSE TRANSCRIPTASE INHIBITOR					
Etravirine					Clopidogrel
INTEGRASE STRAND TRANSFER INHIBITOR					
Dolutegravir	Dofetilide				
Elvitegravir/ cobicistat	Eplerenone Ivabradine Ranolazine	Lovastatin Simvastatin	Sildenafil	Salmeterol	Apixaban Dabigatran if CrCl <50 mL/min Edoxaban Rivaroxaban Ticagrelor Vorapaxar

*Do not coadminister unless potential benefits outweigh the risks of systemic corticosteroid adverse effects.
Note: This table focuses on contraindications. Other medications may need to be used with caution or at lower doses based on drug-drug interactions.
COPD = chronic obstructive pulmonary disease; CrCl = creatinine clearance.
Adapted from tables from the Panel on Antiretroviral Guidelines for Adults and Adolescents. Guidelines for the use of antiretroviral agents in adults and adolescents with HIV. Department of Health and Human Services. Available at https://clinicalinfo.hiv.gov/en/guidelines/adult-and-adolescent-arv. Accessed April 21, 2022. Courtesy of Drs. Samuel Merrick, Sian Jones, and Marshall Glesby.

With the current expectation that antiretroviral therapy is lifelong, chronic and cumulative toxicities also are important. Increased cardiovascular events are associated with some, but not all, protease inhibitors[12] and, controversially, with abacavir. Indinavir and atazanavir cause renal stones. Metabolic changes, including hyperglycemia and frank diabetes, hyperlactatemia, and/or hyperlipidemia, are associated with some protease inhibitors. Morphologic changes can be very distressing for patients, including lipoatrophy (loss of fat in the face and extremities) associated with stavudine and zidovudine, and lipoaccumulation (gain of fat in the breasts, abdomen, and/or dorsocervical fat pad [buffalo hump]) associated with some protease inhibitors. Some nucleoside analogue reverse transcriptase inhibitors, including didanosine and stavudine, caused a progressive toxic peripheral neuropathy. Tenofovir disoproxil fumarate is associated with proximal renal tubular dysfunction (Fanconi syndrome) characterized by hypophosphatemia, proteinuria, glycosuria, and, eventually, elevated creatinine. Tenofovir disoproxil fumarate also is associated with loss of bone mineral density over the first year of treatment that appears to stabilize thereafter. The newer formulation of tenofovir, tenofovir alafenamide, is associated with less renal and bone toxicity. Tenofovir alafenamide and integrase inhibitors are associated with weight gain.[13] Newer antiretroviral drugs and investigational antiretroviral agents often are developed and selected for better tolerability and less toxicity.

SPECIAL POPULATIONS

ACUTE OPPORTUNISTIC INFECTION

An untreated HIV-infected patient who presents with a treatable acute opportunistic infection typically should be started on antiretroviral therapy within 48 hours to 2 weeks despite the risk of triggering the immune reconstitution syndrome (Chapter 358), particularly in patients with CD4 counts less than 50 cells/μL.[14] This syndrome, which can be worsening of an ongoing clinical infection or unmasking of a dormant subclinical infection (see Table 358-2), is not an indication to discontinue antiretroviral therapy. However, a delay of 2 to 10 weeks before starting antiretroviral therapy should be considered in patients with certain CNS opportunistic infections (e.g., cryptococcal or tuberculous meningitis), because some studies in developing countries have demonstrated increased mortality in patients who started antiretroviral therapy earlier.

PROPHYLAXIS AGAINST OPPORTUNISTIC INFECTIONS

In patients with decreased CD4 cell counts, either because antiretroviral therapy has not yet been started, has not yet been effective, or has failed, the risk for opportunistic infections such as pneumocystis pneumonia, toxoplasmosis, mycobacteria, and fungi is increased (Chapter 358). Prophylaxis is often warranted as primary or secondary prevention (see Table 358-3).

COINFECTION WITH HEPATITIS B

If treatment is started for either viral infection, both need to be treated optimally: two active drugs for hepatitis B and a third active drug added for HIV. The antiretroviral drugs emtricitabine, lamivudine, and tenofovir have activity against both viruses, so a suitable regimen to treat both infections would be tenofovir (either formulation), emtricitabine (or lamivudine), and a third antiretroviral drug. Stopping drugs with activity against hepatitis B may result in a serious hepatitis flare.

COINFECTION WITH HEPATITIS C

The optimal time to treat hepatitis C infection in a patient with HIV infection is not known. The current hepatitis C protease inhibitors are unrelated

to the HIV protease inhibitors and have no activity against HIV. Significant drug interactions can occur between antiretrovirals and hepatitis C drugs, so consultation with an expert is required.

PREGNANCY

The U.S. Perinatal Treatment Guidelines recommend antiretroviral therapy for prevention of mother-to-child transmission of HIV for all pregnant women, regardless of their CD4 cell count or HIV RNA level.[15] Based on efficacy, tolerability, convenience, and safety, preferred drugs in pregnancy include the nucleoside analogue reverse transcriptase inhibitor pairs of abacavir/lamivudine or tenofovir (either formulation)/emtricitabine (or lamivudine) combined with a third drug: the ritonavir-boosted protease inhibitors atazanavir or darunavir; or the integrase inhibitors dolutegravir[A20] or raltegravir. Other drugs are considered alternatives, and insufficient data are available on newer drugs (e.g., the integrase inhibitor bictegravir). U.S. guidelines also recommend continuing current antiretroviral therapy in a woman found to be pregnant if she is maximally virologically suppressed.

CURE

Although current antiretroviral therapy is highly effective, it is not curative. Soon after infection, HIV establishes a latent-CD4$^+$ T-lymphocyte cell reservoir that can persist for decades. Even with years of antiretroviral therapy-induced prolonged virologic suppression, the latent-cell reservoir does not decrease significantly. Strategies of intensification of antiretroviral therapy by changing or adding additional antiretroviral drugs have not been successful in decreasing the viral reservoir. HIV cure is aspirational and could be sterilizing (complete elimination of HIV) or functional (suppression of HIV without antiretroviral therapy).[16] The best documented sterilizing cure is of a man who developed acute myelogenous leukemia, underwent radiation and cytotoxic chemotherapy, and ultimately received a bone marrow transplant from a donor with a deletion in the gene that codes for the CCR5 receptor that was required for his HIV strain to enter cells. After more than 10 years off of antiretroviral therapy with no detectable HIV, he was considered to be cured of HIV, although he later died of leukemia. Three other cases have subsequently been reported. By comparison, treating a patient with HIV and acute lymphocytic leukemia with clustered regularly interspaced short palindromic repeats (CRISPR)–associated protein 9 (Cas9) edited stem cells was not successful, presumably because too many residual lymphocytes were also engrafted.[17] An example of functional cure are 14 HIV-infected individuals who were treated with antiretroviral therapy during acute infection, who subsequently discontinued antiretroviral therapy, and whose viremia remained suppressed.

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For the General References and other additional features, please visit Elsevier eBooks+ at https://ebooks.health.elsevier.com.

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358 MICROBIAL COMPLICATIONS OF HIV/AIDS

HENRY MASUR

MICROBIAL COMPLICATIONS

EPIDEMIOLOGY

Despite the widespread availability of effective antiretroviral regimens in the United States, opportunistic infections are still seen frequently at many health care facilities, especially those serving populations with poor access to health care.

The annual incidence of new diagnoses of HIV in the United States was about 34,000 cases in 2019, representing about a 17% decline since 2016. Among the estimated 1.2 million people living with human immunodeficiency virus (HIV) in the United States, nearly 87% know they are infected, about 75% have received some HIV medical care, and about two thirds are virally suppressed.

About 20% of persons diagnosed with HIV in the United States have a CD4 lymphocyte count less than 200 cells/μL at the time of diagnosis. As a result, a substantial number of people living with HIV in the United States continue to be susceptible to a wide range of opportunistic infections because either they do not know they are infected with HIV and/or they are not receiving effective care.

Globally, the prevalence of HIV is about 38 million adults, with an annual incidence of 1.5 million new infected adults. Of all people worldwide living with HIV, about 85% know their status, about 75% are accessing treatment, and about 65% are virally suppressed.[1]

Even for patients who initiate antiretroviral therapy and adhere carefully to their regimens, opportunistic infections can occur in the first few weeks or months before immunity is substantially improved, as measured by the circulating CD4 count and the HIV viral load. Immunity improves substantially as soon as the viral load is suppressed below the level of assay detection.[2] Although the level of infections risk is substantially reduced once HIV viral suppression is achieved, the absolute risk remains elevated for most opportunistic infections until the CD4 count rises above 50 to 200 cells/μL, depending on the specific opportunistic infection. In addition, some opportunistic infections (especially tuberculosis [Chapter 299], pneumococcal bacteremia [Chapter 268], and dermatomal herpes zoster [Chapter 346]) occur despite HIV viral suppression and CD4 counts above 200 cells/μL.

As patients with HIV live longer, they are developing increasing chronic morbidity and mortality due in part to latent viruses such as human papillomavirus (Chapter 344),[3] hepatitis C virus (Chapter 135),[4] hepatitis B virus (Chapter 135),[5] JC virus (Chapter 341), and human herpesvirus 8 (HHV-8) (Chapter 359).[6] The progression of hepatitis C and hepatitis B virus liver disease is accelerated in HIV-infected patients compared with HIV-uninfected patients, thereby leading to earlier development of cirrhosis, liver failure, and hepatoma. Human papillomavirus is associated with high rates of cervical carcinoma

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The U.S. Perinatal Treatment Guidelines recommend antiretroviral therapy for prevention of mother-to-child transmission of HIV for all pregnant women, regardless of their CD4 cell count or HIV RNA level.[15] Based on efficacy, tolerability, convenience, and safety, preferred drugs in pregnancy include the nucleoside analogue reverse transcriptase inhibitor pairs of abacavir/lamivudine or tenofovir (either formulation)/emtricitabine (or lamivudine) combined with a third drug: the ritonavir-boosted protease inhibitors atazanavir or darunavir; or the integrase inhibitors dolutegravir[A20] or raltegravir. Other drugs are considered alternatives, and insufficient data are available on newer drugs (e.g., the integrase inhibitor bictegravir). U.S. guidelines also recommend continuing current antiretroviral therapy in a woman found to be pregnant if she is maximally virologically suppressed.

CURE

Although current antiretroviral therapy is highly effective, it is not curative. Soon after infection, HIV establishes a latent-CD4$^+$ T-lymphocyte cell reservoir that can persist for decades. Even with years of antiretroviral therapy-induced prolonged virologic suppression, the latent-cell reservoir does not decrease significantly. Strategies of intensification of antiretroviral therapy by changing or adding additional antiretroviral drugs have not been successful in decreasing the viral reservoir. HIV cure is aspirational and could be sterilizing (complete elimination of HIV) or functional (suppression of HIV without antiretroviral therapy).[16] The best documented sterilizing cure is of a man who developed acute myelogenous leukemia, underwent radiation and cytotoxic chemotherapy, and ultimately received a bone marrow transplant from a donor with a deletion in the gene that codes for the CCR5 receptor that was required for his HIV strain to enter cells. After more than 10 years off of antiretroviral therapy with no detectable HIV, he was considered to be cured of HIV, although he later died of leukemia. Three other cases have subsequently been reported. By comparison, treating a patient with HIV and acute lymphocytic leukemia with clustered regularly interspaced short palindromic repeats (CRISPR)–associated protein 9 (Cas9) edited stem cells was not successful, presumably because too many residual lymphocytes were also engrafted.[17] An example of functional cure are 14 HIV-infected individuals who were treated with antiretroviral therapy during acute infection, who subsequently discontinued antiretroviral therapy, and whose viremia remained suppressed.

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358 MICROBIAL COMPLICATIONS OF HIV/AIDS

HENRY MASUR

MICROBIAL COMPLICATIONS

EPIDEMIOLOGY

Despite the widespread availability of effective antiretroviral regimens in the United States, opportunistic infections are still seen frequently at many health care facilities, especially those serving populations with poor access to health care.

The annual incidence of new diagnoses of HIV in the United States was about 34,000 cases in 2019, representing about a 17% decline since 2016. Among the estimated 1.2 million people living with human immunodeficiency virus (HIV) in the United States, nearly 87% know they are infected, about 75% have received some HIV medical care, and about two thirds are virally suppressed.

About 20% of persons diagnosed with HIV in the United States have a CD4 lymphocyte count less than 200 cells/μL at the time of diagnosis. As a result, a substantial number of people living with HIV in the United States continue to be susceptible to a wide range of opportunistic infections because either they do not know they are infected with HIV and/or they are not receiving effective care.

Globally, the prevalence of HIV is about 38 million adults, with an annual incidence of 1.5 million new infected adults. Of all people worldwide living with HIV, about 85% know their status, about 75% are accessing treatment, and about 65% are virally suppressed.[1]

Even for patients who initiate antiretroviral therapy and adhere carefully to their regimens, opportunistic infections can occur in the first few weeks or months before immunity is substantially improved, as measured by the circulating CD4 count and the HIV viral load. Immunity improves substantially as soon as the viral load is suppressed below the level of assay detection.[2] Although the level of infections risk is substantially reduced once HIV viral suppression is achieved, the absolute risk remains elevated for most opportunistic infections until the CD4 count rises above 50 to 200 cells/μL, depending on the specific opportunistic infection. In addition, some opportunistic infections (especially tuberculosis [Chapter 299], pneumococcal bacteremia [Chapter 268], and dermatomal herpes zoster [Chapter 346]) occur despite HIV viral suppression and CD4 counts above 200 cells/μL.

As patients with HIV live longer, they are developing increasing chronic morbidity and mortality due in part to latent viruses such as human papillomavirus (Chapter 344),[3] hepatitis C virus (Chapter 135),[4] hepatitis B virus (Chapter 135),[5] JC virus (Chapter 341), and human herpesvirus 8 (HHV-8) (Chapter 359).[6] The progression of hepatitis C and hepatitis B virus liver disease is accelerated in HIV-infected patients compared with HIV-uninfected patients, thereby leading to earlier development of cirrhosis, liver failure, and hepatoma. Human papillomavirus is associated with high rates of cervical carcinoma

ABSTRACT

Opportunistic infections continue to occur in persons living with HIV, especially patients who are unaware of their HIV infection or who do not attain durable viral suppression with antiretroviral therapy. CD4 counts are an excellent predictor of susceptibility to specific opportunistic infections. In the United States, pneumocystis pneumonia, toxoplasma encephalitis, cryptococcal and histoplasma disease, dermatomal zoster, mucosal candidiasis, mucocutaneous herpes simplex virus, and invasive pneumococcal disease continue to occur commonly as HIV-associated complications, as do Kaposi sarcoma and lymphoma. Cytomegalovirus retinitis and disseminated *Mycobacterium avium* still occur but are not recognized as frequently in patients with low CD4 counts in the United States as they were in previous decades. Outside the United States and Western Europe, tuberculosis and cryptococcosis are especially common complications. As persons with HIV infection live longer, latent viral infections are causing an increasing incidence of hepatic fibrosis and cirrhosis (e.g., hepatitis B and C), and viruses are an increasing incidence of malignant neoplastic diseases (e.g., hepatitis B and C, human papillomavirus, Epstein-Barr virus, and human herpesvirus-8).

KEYWORDS

pneumocystis
toxoplasma
Mycobacterium tuberculosis
cytomegalovirus
Kaposi sarcoma
CD4 cells
HIV
AIDS

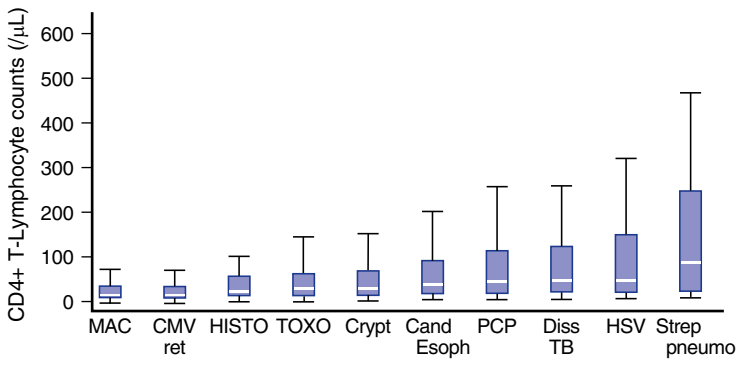

FIGURE 358-1. **Distribution of CD4+ lymphocyte counts at diagnosis of opportunistic infection.** Cand Esoph = candidal esophagitis; CMV ret = cytomegalovirus retinitis; Crypt = *Cryptococcus;* Diss TB = disseminated tuberculosis; HISTO = histoplasmosis; HSV = herpes simplex virus; MAC = *Mycobacterium avium* complex; PCP = *Pneumocystis* pneumonia; Strep pneumo = pneumococcal pneumonia; TOXO = toxoplasmosis.

and anal carcinoma, as well as oral cancers. In people living with HIV, JC virus is associated with progressive neurologic disease. Human herpesvirus-8 is associated with Kaposi sarcoma (Chapter 359), multicentric Castleman disease (Chapter 171), and primary effusion cell lymphoma (Chapter 171). The consequences of chronic inflammation related to active or latent HIV viral reservoirs also appears to be a factor causing noninfectious complications such as accelerated atherosclerotic, cerebrovascular, renal, and hepatic diseases.

PATHOBIOLOGY

The number of circulating CD4 cells is a sensitive and specific indicator of patient prognosis and of susceptibility to specific opportunistic infections for persons with HIV/AIDS[7] (Fig. 358-1). Although CD4 cells are important to host defenses in all patients, the circulating CD4 count is much more useful in predicting susceptibility to infection for patients with HIV infection than in any other patient population. The blood HIV viral load is also an independent predictor of host susceptibility to opportunistic infection, but it is not nearly as sensitive and specific for estimating survival or for assessing susceptibility to opportunistic infection as are CD4 counts.

The specific opportunistic infections that an HIV-infected person develops are influenced not only by the person's individual immunologic defects but also by environmental exposures. For instance, in areas of the world where exposure to *Mycobacterium tuberculosis* is common, tuberculosis is the major infectious cause of morbidity and mortality in people with HIV infection regardless of CD4 count, although the incidence of disease increases as the CD4 count declines. In contrast, however, in areas of the world such as the United States where tuberculosis exposure is uncommon, tuberculosis is rarely seen except in immigrants and when people living with HIV are exposed to high-risk populations, such as persons in prisons or homeless shelters. Severe manifestations of endemic fungi (e.g., cryptococcosis, histoplasmosis, and coccidiomycosis) vary in different geographic regions. Similarly, in many areas of the developing world, HIV-positive individuals are exposed to salmonella, toxoplasma, *Cryptococcus, Trypanosoma cruzi*, and *Talaromyces* more frequently than in the United States, so these diseases are more common in HIV-infected persons in those areas than in the United States.

Studies of the human microbiome provide an interesting perspective on factors that could influence the range of pathogens causing diseases among people with HIV infection.[8] For example, HIV-infected patients with lower CD4 counts have demonstrable changes in their respiratory microbiome compared to other patient populations—changes that tend to reverse with effective HIV treatment.

Behavioral factors are also important determinants of which opportunistic infections occur. Individuals who inject drugs (Chapter 365) are more likely to be infected with hepatitis C virus and hepatitis B virus than are patients without injection drug use histories; they are also more likely to develop certain non-opportunistic processes, such as *Staphylococcus aureus* (Chapter 267) soft tissue infections, bacteremia, and endocarditis. Men who have sex with men who develop proctitis or colitis are more likely to have rectal disease due to *Neisseria gonorrhoeae* (Chapter 275), *Chlamydia trachomatis* (Chapter 294; especially lymphogranuloma venereum strains), MPox (Chapter 343), or *Shigella* (Chapter 285) than individuals who are not men-who-have-sex-with-men.

TABLE 358-1 OPPORTUNISTIC INFECTIONS IN PATIENTS WITH HIV INFECTION

OPPORTUNISTIC PATHOGEN	COMMON CLINICAL MANIFESTATIONS
Bacterial enteric infection (e.g., salmonella) (Chapter 270)	Diarrhea, colitis, sepsis (salmonella)
Bartonellosis (Chapter 291)	Bacillary angiomatosis, hepatic peliosis
Candidiasis (mucocutaneous; Chapter 310)	Mucosal thrush (oral, esophageal, vaginal, rectal)
Chagas disease (Chapter 318)	Encephalitis, brain abscess
Coccidioidomycosis (Chapter 308)	Pneumonia, sepsis
Community-acquired pneumonia (Chapter 85)	Pneumonia, bacteremia
Cryptococcosis (Chapter 309)	Meningitis, sepsis, pneumonia
Cryptosporidiosis (Chapter 321)	Diarrhea, colitis
Cystoisosporiasis (Chapter 324)	Diarrhea, colitis
Cytomegalovirus (Chapter 347)	Retinitis, colitis, esophagitis
Hepatitis B virus (Chapter 135)	Hepatitis, hepatocellular carcinoma
Hepatitis C virus (Chapter 135)	Hepatitis, hepatocellular carcinoma
Herpes simplex virus (Chapter 345)	Oral mucositis, cutaneous and perirectal ulcers
Histoplasmosis (Chapter 308)	Sepsis, pneumonia, meningitis
Human herpesvirus-8 (Chapter 359)	Multicentric Castleman disease, primary effusion cell lymphoma, Kaposi sarcoma
Human papillomavirus (Chapter 344)	Cervical, anal, and oral carcinoma
JC virus (progressive multifocal leukoencephalopathy; Chapter 341)	Encephalitis
Leishmaniasis (Chapter 319)	Cutaneous, mucocutaneous, and disseminated disease
Malaria (Chapter 316)	Malaria
Microsporidiosis (Chapter 324)	Diarrhea
Mycobacterium avium complex (Chapter 300)	Lymphadenopathy, disseminated disease
Mycobacterium tuberculosis (Chapter 299)	Pneumonia, meningitis, pericarditis, lymphadenitis, disseminated disease
Pneumocystis jirovecii (Chapter 313)	Pneumonia
Syphilis (Chapter 295)	Genital ulceration, uveitis, otitis, neurologic disease
Talaromycosis (Chapter 308)	Pulmonary, cutaneous, disseminated disease
Toxoplasma gondii (Chapter 320)	Brain abscess, disseminated disease
Varicella-zoster virus (Chapter 346)	Dermatomal zoster, carotid vasculitis, stroke

The pathogens that cause active disease in persons with HIV infection (Table 358-1) may be organisms that were acquired recently or may represent reactivation of latent organisms acquired months or years previously. *Mycobacterium tuberculosis* (Chapter 299), *Pneumocystis jirovecii* (Chapter 313), *Trypanosoma cruzi* (Chapter 318), *Leishmania donovani* (Chapter 319), *Histoplasma capsulatum* (Chapter 308), *Coccidioides immitis* (Chapter 308), herpes simplex (Chapter 345), herpes zoster (Chapter 346), and cytomegalovirus (Chapter 347) are examples of pathogens that can cause acute disease either soon after exposure or after many months or years of latency as determined by molecular typing or clinical epidemiology. Thus, pathogens need to be considered as possible etiologic agents despite exposure that may have occurred in the distant past.

CLINICAL MANIFESTATIONS

Opportunistic infectious diseases in people with HIV and AIDS often have clinical manifestations and natural histories that are different than in other immunosuppressed patients. In patients with AIDS, for example, *Pneumocystis* pneumonia (Chapter 313) is much more likely to manifest with subacute symptoms over many days or weeks compared with the more acute presentation over a few days in HIV-uninfected cancer patients who are receiving chemotherapy, patients receiving high-dose corticosteroids, or transplant recipients.

TABLE 358-2 INFECTIOUS SYNDROMES, THEIR OPPORTUNISTIC AND NONOPPORTUNISTIC CAUSES, AND POTENTIAL EMPIRIC TREATMENTS IN HIV-INFECTED PATIENTS WITH CD4 COUNTS LESS THAN 50 CELLS/μL

INFECTIOUS SYNDROME	OPPORTUNISTIC OR NONOPPORTUNISTIC CAUSE	EMPIRIC THERAPY
Diarrhea/colitis	*Clostridium difficile*, *Salmonella* species, *Shigella* species, *Cryptosporidia*, *Microsporidia*	None unless persistent or severe or bloody; then consider a fluoroquinolone
Pneumonia	Pneumococcus, community-acquired viruses, atypical bacteria, pneumocystis, *Mycobacterium tuberculosis*, cryptococcus, histoplasmosis	Azithromycin plus ceftriaxone plus trimethoprim-sulfamethoxazole
Meningitis	Pneumococcus, cryptococcus, meningococcus	Ceftriaxone plus liposomal amphotericin B
Retinitis	Cytomegalovirus	IV ganciclovir, oral valacyclovir, or oral famciclovir
CNS mass lesion	Toxoplasma, lymphoma, cryptococcus, aerobic and anaerobic bacteria, *Mycobacterium tuberculosis*	Trimethoprim-sulfamethoxazole

CNS = central nervous system; HIV = human immunodeficiency virus.

When patients are diagnosed with *Pneumocystis* pneumonia, patients with AIDS at initial presentation are usually less hypoxemic and have less impressive radiographic infiltrates despite the longer duration of symptoms before diagnosis. The number of organisms found in sputum or bronchoalveolar lavage specimens is also greater in patients with AIDS than in other immunosuppressed patients, despite the less severe symptoms. Patients with AIDS also are more likely to develop treatment-limiting toxicity associated with trimethoprim-sulfamethoxazole and to have multiple relapses if they are not placed on chemoprophylaxis or chronic suppressive therapy.

For infections due to *Toxoplasma gondii* (Chapter 320), patients with HIV/AIDS characteristically develop toxoplasma encephalitis, whereas other immunosuppressed populations more often develop disseminated visceral disease involving the liver, spleen, or kidneys. Similarly, cytomegalovirus in patients with HIV/AIDS most often causes retinitis and colitis, whereas cytomegalovirus retinitis is relatively uncommon but pneumonia is frequent in patients undergoing hematopoietic stem cell or solid organ transplantation.

Some pathogens that frequently cause disease among patients with HIV/AIDS had rarely been recognized as causes of life-threatening human disease before the HIV/AIDS epidemic. Examples include *Mycobacterium avium* complex (Chapter 300), *Cryptosporidium* (Chapter 321), *Microsporidium* (Chapter 324), and *Bartonella* (Chapter 291). Conversely, some pathogens that are associated with disease in other immunosuppressed patients, including patients with compromised cell-mediated immunity, are rarely seen in patients with HIV/AIDS. Examples include *Listeria monocytogenes* (Chapter 272) disseminated herpes simplex, (Chapter 345), disseminated herpes zoster (Chapter 346), and disseminated *Strongyloides stercoralis* (Chapter 327). The reasons why some pathogens are unexpectedly frequent or unexpectedly unusual despite similar environmental exposures have not been fully elucidated.

With better antiretroviral treatment and prophylaxis against opportunistic infection, the spectrum of clinical opportunistic infections has evolved. For example, disseminated *Mycobacterium avium* complex, cytomegalovirus retinitis, cryptosporidiosis, and microsporidiosis now occur far less frequently in the United States and Western Europe than before. Much of the shift is undoubtedly due to earlier diagnosis of HIV before severe immunosuppression occurs as well as to better access to effective and durable antiretroviral therapy. In developing countries, where patients more often still present with full-blown AIDS, however, tuberculosis, cryptococcal meningitis, pneumococcal disease, and bacterial and protozoal enteritis remain major AIDS-related opportunistic complications.

DIAGNOSIS

For an infection in any patient population, management is likely to be more effective and to be associated with fewer complications if the specific microbial cause is conclusively identified, the appropriate specific therapy is started quickly, and unnecessary drugs are avoided. For patients with HIV infection, such an approach is especially appropriate given the broad range of opportunistic and nonopportunistic infections that could cause a particular syndrome (Table 358-2), as well as the noninfectious causes, including drug toxicities, that can masquerade as infections.

The diagnostic tests to identify specific opportunistic infections are usually no different in patients with HIV infection or AIDS than in other patients. For the evaluation of a febrile patient with HIV infection and a CD4 lymphocyte count less than 200 cells/μL, blood cultures for routine bacteria and fungi, a serum cryptococcal antigen test, a *Toxoplasma* IgG test, and a syphilis serologic test often provide a useful baseline. If the patient has pulmonary dysfunction, Gram stain and routine culture of expectorated or induced sputum are usually useful. If a history of appropriate geographic exposure is present, serum and urine histoplasma antigen and *Coccidioides* antibodies also can be informative.

Conversely, some clinical microbiologic tests that are useful in other immunosuppressed patient populations are not necessarily useful to diagnose opportunistic infections in patients with HIV infection. For example, blood polymerase chain reaction (PCR) for cytomegalovirus is very useful in patients who have received hematopoietic stem cell transplants, because their positive and negative predictive values are high. In patients with HIV infection, however, cytomegalovirus PCR positivity correlates mainly with the degree of immunosuppression and does not have sufficient accuracy to be useful for assessing the cause of end organ disease. Blood PCR tests for Epstein-Barr virus, varicella zoster virus, or herpes simplex virus also are not useful in most circumstances for similar reasons.

An increasing number of laboratories are offering molecular tests for opportunistic pathogens, but care must be taken to be certain that these tests are not detecting colonization rather than true infection. People living with HIV may be colonized with more pathogens and for longer periods of time than patients without HIV infection. For example, PCR for *Pneumocystis* in bronchoalveolar lavage may have excellent negative predictive value, but its positive predictive value is low because some immunosuppressed patients are asymptomatically colonized with *Pneumocystis*.

Imaging is an important aspect of patient evaluation.[9] Patients with HIV infection may have pathologic processes despite a paucity of symptoms or even normal readings on routine chest radiographs, for example. A computed tomography (CT) of the lungs may reveal unexpected pathologic findings such as diffuse interstitial infiltrates suggestive of *Pneumocystis* pneumonia despite the absence of cough, shortness of breath, or oxygen desaturation. Such a finding could lead to ordering an induced sputum or bronchoalveolar lavage and establishing the diagnosis of an infection at a time when disease is mild and the likelihood of successful treatment is high. CT of the abdomen also should be considered in patients with prolonged fever or wasting and low CD4 counts even in the absence of abdominal symptoms, because such a study may reveal unexpected adenopathy or organ infiltration that could be readily biopsied. Positron emission tomography and nuclear scans may have roles for identifying the infectious cause of clinical syndromes, but the use of such scans is not well standardized, and the results are not organism specific.

TREATMENT

Effective therapy for opportunistic infections in people living with HIV may require longer courses of treatment than in immunocompetent patients, especially if immunity is not reconstituted by antiretroviral therapy. Moreover, *Pneumocystis* pneumonia, cytomegalovirus retinitis, *Mycobacterium avium* complex bacteremia, and cryptococcal meningitis often relapse or recur if patients with HIV/AIDS are not either reconstituted immunologically with antiretroviral therapy or treated with chronic suppressive therapy for their specific opportunistic infection.

Empiric Management of Opportunistic Infections

Given the range of processes that can cause disease in patients with HIV infection or AIDS, the optimal approach is to establish the specific cause before starting therapy if such testing can be done expeditiously. However, initial empiric management of a presumed infectious process before the specific causative pathogen is definitively identified is appropriate if the patient is too sick or

deteriorating too quickly to permit delaying therapy until a specific diagnosis is established (see Table 358-2).

When assessing a patient with HIV infection with any clinical syndrome, but especially a syndrome associated with fever, the possibility of an opportunistic infection always must be considered. The likelihood of an opportunistic infection depends on the current CD4 count and the current HIV viral load. If the patient's current CD4 count is greater than 100 to 200 cells/μL, the likelihood of most opportunistic infections (other than tuberculosis and pneumococcal disease) is low (but not zero). For any patient, regardless of CD4 count, common community-acquired and hospital-acquired nonopportunistic infections also must be considered because HIV-infected patients are as susceptible to these agents as their HIV-uninfected counterparts. In addition, noninfectious syndromes, both HIV-related and HIV unrelated (Chapter 359) must be considered, especially as the patient population ages and as heart failure, pulmonary emboli, cerebrovascular disease, or chronic renal disease occur, potentially accelerated by the HIV-related inflammatory state

Patients also may have more than one process occurring concurrently. A familiar scenario, for example, is when a patient who is being treated appropriately for documented *Pneumocystis* pneumonia has respiratory deterioration because of superimposed heart failure, pulmonary hypertension, pulmonary emboli, hospital-acquired pneumonia, or ventilator-associated pneumonia rather than progressive *Pneumocystis* pneumonia. Furthermore, progressive hypoxemia may be the result of methemoglobinemia rather than progressive PCP in a patient who is being treated with dapsone or a primaquine-containing regimen.

For some syndromes, the response to empiric therapy (see Table 358-2) can plausibly suggest a presumptive diagnosis. For instance, an empiric 2-week course of pyrimethamine plus sulfadiazine (or trimethoprim-sulfamethoxazole) rather than an immediate brain biopsy would be appropriate for an HIV-infected patient who has a CNS mass lesion, a CD4 count less than 100 cells/μL, and a positive antitoxoplasma serum immunoglobulin G (IgG), because cerebral toxoplasmosis, which is the most likely diagnosis, usually improves within 14 days of treatment. A patient who failed to respond would be an appropriate candidate for brain biopsy to look for other causes. Similarly, if acute chorioretinitis in a person with HIV and a CD4 count less than 50 cells/μL improves after 2 to 3 weeks of ganciclovir, the chorioretinitis is likely due to a herpesvirus, most often cytomegalovirus, and an aqueous or vitreous diagnostic tap is not necessary.

Definitive Therapy of Opportunistic Infections

In general, HIV-infected patients are treated with the same medications as are other immunocompromised patients. However, some aspects of therapeutic management are different for AIDS patients.[10] For pneumocystis pneumonia, for example, the duration of treatment is longer and the benefit of adjunctive corticosteroids is better established (Chapter 313).

People living with HIV often have organ dysfunction that may alter absorption or excretion of drugs. These patients are also often on multiple drugs (both HIV related and HIV unrelated) that can interact pharmacokinetically with clinically important consequences for drug effectiveness or toxicity. Such therapy thus requires considerable experience and consultation with experts and up-to-date references for guidance.

Concomitant Antiretroviral Therapy

When patients who are already receiving antiretroviral therapy develop an opportunistic infection, antiretroviral therapy should be continued but the regimen should be reassessed to ensure that it is optimal in terms of antiviral activity, tolerability, potential toxicity, and drug interactions and the patient's ability to attain adequate serum levels given their ability to absorb oral drugs. When a person who has not been receiving antiretroviral therapy for HIV/AIDS develops an opportunistic infection, the patient will have longer survival and fewer HIV-related complications if put promptly on antiretroviral therapy.[A1] The general principle is to start antiretroviral therapy within 2 weeks of diagnosis of an opportunistic infection.

However, the immune reconstitution inflammatory syndrome (IRIS)[11] can be a serious complication of starting antiretroviral therapy, especially when patients have mycobacterial or endemic fungal diseases. In these instances, antiretroviral therapy is usually delayed for several weeks.[A2,A3] For tuberculosis, initiation of antiretroviral therapy is usually started within 2 weeks after tuberculosis treatment is initiated in patients who have a CD4 count less than 50 cells/mm^3. However, therapy can be delayed and initiated within 8 weeks of starting antituberculosis patients who have higher CD4 cell counts.[A4,A5] For cryptococcal meningitis, antiretroviral therapy should be started between 4 and 6 weeks after the start of antifungal therapy, with the precise starting time based on individual conditions and local experience.[A6] As clinicians develop more experience managing IRIS, some experts are not waiting for several weeks to start antiretroviral therapy, even in the face of fungal or mycobacterial disease, but evidence to support the safety of such an approach is still evolving.

PREVENTION

Immune reconstitution with antiretroviral therapy is the most effective method to prevent opportunistic infections. However, HIV-infected individuals who are immunologically vulnerable as measured by their CD4 count and viral load benefit from primary chemoprophylaxis (prevention of a first episode), chronic suppressive therapy (prevention of relapse), or secondary prophylaxis (prevention of a second or subsequent episode) for a number of opportunistic infections (Table 358-3). Patients who do not take their antiretroviral therapy reliably would theoretically benefit from prophylaxis against opportunistic infections if their CD4 counts remain low, but few if any patients will actually take prophylaxis for opportunistic infection if they will not take antiretroviral therapy. Chronic suppressive therapy of opportunistic infections (prevention of relapse) and/or secondary prophylaxis (prevention of reinfection) typically can be discontinued when patients meet the criteria for antiretroviral therapy-induced reduction in viral load and increase in CD4 counts (see https://clinicalinfo.hiv.gov/en/guidelines/adult-and-adolescent-opportunistic-infection/whats-new-guidelines?view=full).

As the management of HIV infection evolves, criteria for starting and stopping prophylaxis evolve. For instance, *Mycobacterium avium* complex disease is less and less common in the United States, so prophylaxis is no longer recommended for patients who promptly initiate antiretroviral therapy.

Optimal preventive strategies focus not only on chemoprophylaxis but also on immunization (E-Fig. 358-1) and reducing exposure to opportunistic pathogens. Examples of exposure reduction interventions likely to be effective would include immunizing household members of HIV-infected patients for pneumococcus, reducing the likelihood of cryptosporidiosis by decreasing exposure to kittens and puppies, reducing the likelihood of toxoplasmosis by avoiding exposure to feces and litter boxes of cats that forage outdoors, and limiting exposure to patients who might present with tuberculosis for HIV-infected health care workers.

Immunizations such as HPV vaccine and hepatitis B vaccine also can be important for preventing the development of neoplastic processes. Live virus vaccines must be avoided in patients with low CD4 counts, and some experts avoid them in all people living with HIV.

IMMUNE RECONSTITUTION INFLAMMATORY SYNDROME (IRIS)

The initiation of antiretroviral therapy leads to viral suppression and the restoration of immune function. In the setting of advanced HIV disease, the initiation of antiretroviral therapy may result in a robust reconstitution of immune response to opportunistic pathogen(s) that are latent or causing an acute infectious syndrome. This immune reconstitution can lead to a localized inflammatory immune response (commonly labeled as immune reconstitution inflammatory syndrome or IRIS) of the infected organs and/or to systemic manifestations similar to sepsis.

EPIDEMIOLOGY

Overall, approximately 13% of individuals develop IRIS after instituting antiretroviral therapy, with the greatest independent risk factor being CD4 count less than 50 cells/mL.[12] Currently recommended first line HIV therapy includes regimens with integrase strand transferase inhibitors that drive viral loads to undetectable levels rapidly.[A7,A8] The use of these regimens has increased the incidence of IRIS.

Nevertheless, overall incidence of IRIS has been declining, particularly as antiretroviral therapy is more often initiated at higher CD4 cell counts so patients do not develop profound immunosuppression before it is initiated. In the United States and worldwide, however, many patients still do not initiate antiretroviral therapy until they have very low CD4 counts (e.g., below 50-100 cells/mL) for a variety of reasons related to access to medical care and psychosocial issues.

PATHOBIOLOGY

In the setting of advanced HIV disease, immunodeficiency is manifest by an inability of the immune system to mount effective responses against opportunistic pathogens. Over the first few weeks after initiation of antiretroviral therapy, many patients experience a rapid increase in their CD4 cell counts. T-cell function is augmented and so are delayed hypersensitivity responses to pathogens such as *M. tuberculosis* or candida. With rapid control of HIV viremia, immune function improves, and a hyper-inflammatory localized or systemic clinical syndrome may ensue.[13]

Vaccine	All persons	How varies by age	How varies by CD4 cell count (cells/μL)	
			< 200	≥ 200
Hepatitis A	2-3 doses (varies by formulation)			
Hepatitis B	2-4 doses (varies by formulation and indication)			
Human papillomavirus (HPV)		3 doses ages 18-26*		
Influenza	1 dose annually			
Measles, mumps, rubella (MMR)			Contraindicated	2 doses if born after 1956 with no history of vaccination or positive antibody titer
Meningococcal A,C,W,Y conjugate (MenACWY)	2 doses, booster every 5 years			
Meningococcal B (MenB)	2-3 doses (varies by formulation)			
Pneumococcal conjugate (PCV15 or PCV20)	1 dose			
Pneumococcal polysaccharide (PPSV23)	1 dose (if conjugate vaccine was PCV-15)			
COVID 19	For current COVID-19 vaccination recommendations please visit *CDC.gov*		Recommendations differ with advanced or untreated HIV infection	
Tetanus, diphtheria, pertussis (Tdap/Td)	Tdap once, then Td or Tdap booster every 10 years			
Varicella (VAR)			Contraindicated	2 doses
Zoster recombinant (RZV)		2 doses for ages 18 and older		

Recommended for all adults and adolescents with HIV who meet the age requirement or lack documentation of vaccination or evidence of past infection

Recommended for adults and adolescents with HIV with another risk factor (medical, occupational, or other indication) or in select circumstances

Contraindicated

E-FIGURE 358-1. Guidelines for the prevention of opportunistic infections in adults who are infected with the human immunodeficiency virus (HIV). *HPV vaccination is not routinely recommended for persons ages 27 to 45 years with HIV infection; some people who are not adequately vaccinated in this age range might benefit from vaccination, however, and shared clinical decision making is recommended in these situations. COVID-19 = coronavirus disease 2019. (From Guidelines for the Prevention and Treatment of Opportunistic Infections in Adults and Adolescents with HIV. https://clinicalinfo.hiv.gov/en/guidelines/adult-and-adolescent-opportunistic-infection/whats-new-guidelines. Accessed August 15, 2022.)

TABLE 358-3 PROPHYLAXIS TO PREVENT FIRST EPISODE OF OPPORTUNISTIC DISEASE

OPPORTUNISTIC INFECTIONS	INDICATION	PREFERRED*	ALTERNATIVE*
Coccidioidomycosis	A new positive IgM or IgG serologic test, no sign of active coccidioidomycosis, and CD4 count <250 cells/μL	Fluconazole 400 mg PO daily	
Hepatitis A virus (HAV) infection	HAV-susceptible patients with chronic liver disease, injection-drug users, or MSM	Two-dose series of either single antigen vaccine: • Havrix: 1.0 mL IM (0, 6-12 months) *or* • Vaqta: 1.0 mL IM (0, 6-18 months) IgG antibody response should be assessed 1 month after vaccination; nonresponders should be revaccinated when CD4 count >200 cells/μL	Alternative for individuals susceptible to both HAV and HBV: • Twinrix: 1.0 mL IM Three-dose series (0, 1, 6 months) Four-dose series (0, 7, 21-30 days, 12 months)
Hepatitis B virus (HBV) infection	• Patients without chronic HBV or without immunity to HBV (i.e., anti-HBs negative) • Vaccination is recommended before CD4 count falls below 350 cells/μL • In patients with CD4 counts <350 cells/μL, vaccination should not be deferred until CD4 count reaches >350 cells/μL, because some patients even with CD4 counts <200 cells/μL respond to vaccination	• Double dose of Engerix-B (40 μg) or Recombivax (20 μg) in a three-dose series (0, 1, 6 months) *or* • Heplisav: two-dose series (0, 1 month) 20 μg in 0.5 mL IM • Combined HAV and HBV vaccine (Twinrix), 1 mL IM as a three-dose (0, 1, and 6 months) or four-dose series (days 0, 7, 21 to 30, and 12 months) Anti-HBs should be obtained 1 month after completion of a vaccine series. Patients with anti-HBs <10 international units/mL at 1-2 months are considered nonresponders **For patients with isolated anti-HBc** • Vaccinate individuals with isolated anti-HBc with one standard dose of HepB and check anti-HBs titers 1-2 months afterward. If anti-HBs ≥100 IU/mL, no further vaccination is needed, but if the titer is <100 IU/mL, then vaccinate with a complete series of HepB (double dose) followed by anti-HBs testing. If titers are not available, then give a complete vaccine series followed by anti-HBs testing	
	Vaccine Nonresponders: • Revaccinate with either: Second double dose, three-dose series of Engerix-B (40 μg) or Recombivax (20 μg) *or* Two-dose series of Heplisav-B • Delay repeat vaccination until after the CD4 count is ≥200 cells/μL		
Histoplasmosis	CD4 count ≤150 cells/μL and at high risk because of occupational exposure or live in a community with a hyperendemic rate of histoplasmosis (>10 cases/100 patient-years)	Itraconazole 200 mg PO daily	
Human Papillomavirus (HPV) infection	Females and males aged 11-26 years	• HPV recombinant vaccine 9 valent (Types 6, 11, 16, 18, 31, 33, 45, 52, 58) 0.5 mL IM at 0, 1-2, and 6 months	For patients who have completed a vaccination series with the recombinant bivalent or quadrivalent vaccine, many experts would give an additional full series of recombinant 9-valent vaccine, but there are no data to define who might benefit or how cost effective this approach might be
Influenza A and B Virus Infection	All persons with HIV	• Inactivated influenza vaccine annually (per recommendation for the season) • High-dose inactivated influenza vaccine may be given to individuals aged ≥65 years • Live-attenuated influenza vaccine is contraindicated in patients with HIV	N/A
Malaria	Travel to disease-endemic area	Recommendations are the same for HIV-infected and HIV-uninfected patients based on region of travel, malaria risks, and drug susceptibility in the region; see http://www.cdc.gov/malaria/	

TABLE 358-3 PROPHYLAXIS TO PREVENT FIRST EPISODE OF OPPORTUNISTIC DISEASE—cont'd

OPPORTUNISTIC INFECTIONS	INDICATION	PREFERRED*	ALTERNATIVE*
Mycobacterium avium complex (MAC) Disease	Not on fully suppressive ART *and* CD4 count <50 cells/mL after excluding disseminated MAC disease	• None	• Azithromycin 1200 mg PO once weekly *or* • Clarithromycin 500 mg PO bid *or* • Azithromycin 600 mg PO twice weekly *or* • Rifabutin 300 mg PO daily (dose adjustment may be necessary based on drug-drug interactions)
Mycobacterium tuberculosis infection (TB) **(i.e., treatment of latent TB infection [LTBI])**	Positive screening test for LTBI, with no evidence of active TB and no prior treatment for active TB or LTBI *or* Close contact with a person with infectious TB, with no evidence of active TB, regardless of screening test results	• Rifapentine (weight based dosing) plus INH (900 mg) plus pyridoxine (50 mg) PO once weekly for 12 weeks **Note:** Rifapentine is recommended only for persons receiving EFV, RAL, or once-daily DTG-based antiretroviral regimen • Weight-based rifapentine dose: • Weighing 32.1-49.9 kg: 750 mg PO once weekly • Weighing >50 kg: 900 mg PO once weekly *or* INH (300 mg) plus rifampin (600 mg) plus pyridoxine (25-50 mg) PO daily for 3 months	• INH (300 mg) plus pyridoxine (25-50 mg) PO daily for 9 months *or* • Rifampin 600 mg PO daily for 4 months *or* • Rifapentine (see dose below) plus INH (300 mg) plus pyridoxine (25-50 mg) PO once daily for 4 weeks • Weight-based rifapentine dose: Weighing <35 kg: 300 mg PO once daily Weighing 35-45 kg: 450 mg PO once daily Weighing >45 kg: 600 mg PO once daily
Pneumocystis pneumonia (PCP)	• CD4 count <200 cells/mm^3 *or* • CD4 <14% *or* • If ART initiation must be delayed, CD4 count ≥200, but <250 cells/mm^3 and if monitoring of CD4 cell count every 3 months is not possible **Note:** Patients who are receiving pyrimethamine/sulfadiazine for treatment or suppression of toxoplasmosis do not require additional PCP prophylaxis	• TMP-SMX 1 DS tablet PO daily *or* • TMP-SMX 1 SS tablet daily	• TMP-SMX 1 DS PO three times weekly *or* • Dapsone 100 mg PO daily or 50 mg PO BID *or* • Dapsone 50 mg PO daily with (pyrimethamine 50 mg plus leucovorin 25 mg) PO weekly *or* • Dapsone (200 mg) plus pyrimethamine (75 mg) plus leucovorin (25 mg) PO weekly *or* • Aerosolized pentamidine 300 mg via Respirgard II™ nebulizer every month *or* • Atovaquone 1500 mg PO daily *or* • Atovaquone (1500 mg) plus pyrimethamine (25 mg) plus leucovorin (10 mg) PO daily
Streptococcus pneumoniae **Infection**	For individuals who have never received any pneumococcal vaccine, regardless of CD4 count	• Administer either 15-valent pneumococcal conjugate vaccine (PCV15) or 20-valent pneumococcal conjugate vaccine (PCV20) • If PCV15 is used, a dose of 23-valent pneumococcal polysaccharide vaccine (PPSV23) should be administered at least 8 weeks later. No additional pneumococcal vaccine doses are recommended	For people with HIV who previously started or completed a pneumococcal vaccination series, there is no need to restart the series • People with HIV who previously received only the 13-valent pneumococcal conjugate vaccine (PCV13) should receive PPSV23 at least 8 weeks later • People with HIV who have received PCV13 and PPSV23 should receive a booster PPSV23 at least 5 years after the first dose. If they were <65 at the time of the second dose, they should receive a third and final dose at or after age 65, at least 5 years after the second PPSV23 dose • People with HIV who have only received PPSV23 may receive a PCV (either PCV20 or PCV15) ≥1 year after their last PPSV23 dose. When PCV15 is used in those with history of PPSV23 receipt, it need not be followed by another dose of PPSV23
Syphilis	• For individuals exposed to a sex partner with a diagnosis of primary, secondary or early latent syphilis within past 90 days, *or* • For individuals exposed to a sex partner >90 days before syphilis diagnosis in the partner, if serologic test results are not available immediately, and the opportunity for follow-up is uncertain	Benzathine penicillin G 2.4 million units IM for one dose	*For penicillin-allergic patients:* • Doxycycline 100 mg PO bid for 14 days *or* • Ceftriaxone 1 g IM or IV daily for 8-10 days *or* • Azithromycin 2 g PO for one dose—not recommended for MSM or pregnant women

TABLE 358-3 PROPHYLAXIS TO PREVENT FIRST EPISODE OF OPPORTUNISTIC DISEASE—cont'd

OPPORTUNISTIC INFECTIONS	INDICATION	PREFERRED*	ALTERNATIVE*
Talaromycosis (Penicilliosis)	Persons with HIV and CD4 cell counts <100 cells/mL, who are unable to have ART, or have treatment failure without access to effective ART options and Who reside in the highly endemic regions (particularly in highland regions during the rainy and humid months) in northern Thailand, northern or southern Vietnam, or southern China *or* Who are from countries outside of the endemic region but must travel to the region	For persons who reside in endemic areas, itraconazole 200 mg PO once daily For those traveling to the highly endemic regions, begin itraconazole 200 mg PO once daily 3 days before travel and continue for 1 week after leaving the endemic area	For persons who reside in endemic areas, fluconazole 400 mg PO once weekly For those traveling to the highly endemic regions, take the first dose of fluconazole 400 mg 3 days before travel, continue 400 mg once weekly, and take the final dose after leaving the endemic area
Toxoplasma gondii	• Toxoplasma IgG-positive patients with CD4 count <100 cells/μL **Note:** All regimens recommended for primary prophylaxis against toxoplasmosis are also effective as PCP prophylaxis	TMP-SMX 1 DS PO daily	• TMP-SMX 1 DS PO three times weekly *or* • TMP-SMX 1 SS PO daily *or* • Dapsone 50 mg PO daily + (pyrimethamine 50 mg + leucovorin 25 mg) PO weekly *or* • Dapsone (200 mg) + pyrimethamine (75 mg) + leucovorin (25 mg) PO weekly *or* • Atovaquone 1500 mg PO daily *or* • Atovaquone (1500 mg) + pyrimethamine (25 mg) + leucovorin 10 mg PO daily
Varicella (chickenpox)	CD4 count ≥200 cells/μL with no evidence of immunity to varicella	• Two-dose series of VAR 3 months apart • VAR is contraindicated if CD4 count <200 cells/mm^3	
Zoster	Age ≥18 years, regardless of past episode of herpes zoster or receipt of attenuated ZVL (Zostavax) and regardless of CD4 count	RZV IM two doses at months 0 and 2-6	• Consider delaying vaccination until the patient is virologically suppressed or until the CD4 count > 200 cells/μL to ensure a robust vaccine response

*Often depending on drug-drug interactions.

ART = antiretroviral therapy; bid = twice a day; anti-HB = hepatitis B surface antibody; anti-HBc = hepatitis B core antibody; EFV = efavirenz; DTG = dolutegravir; HIV = human immunodeficiency virus; Ig = immunoglobulin; IM = intramuscularly; INH = isoniazid; IV = intravenously; MSM = men who have sex with men; PO = orally; RAL= raltegravir; RZV = recombinant zoster vaccine; SQ = subcutaneous; TMP-SMX = trimethoprim-sulfamethoxazole; ZVL = zoster vaccine live.

From Guidelines for the Prevention and Treatment of Opportunistic Infections in Adults and Adolescents with HIV. https://clinicalinfo.hiv.gov/en/guidelines/adult-and-adolescent-opportunistic-infection/whats-new-guidelines. Accessed February 24, 2022.

For viral infections associated with IRIS, it appears that the robust cytotoxic CD8 responses aimed to control the viral infection drive the hyperinflammatory response and cause tissue pathology. This mechanism is well characterized with JC virus, for which brain biopsies demonstrate an accumulation of CD8 T cells and a concomitant decline in JC virus cells. However, the inflammatory antiviral response leads to demyelination and subsequent clinical manifestations. Host genetic factors also appear to predispose individuals to immune restoration diseases.

CLINICAL MANIFESTATIONS AND DIAGNOSIS

IRIS can present in two ways. Paradoxical IRIS is characterized by a worsening of an opportunistic infection for which specific treatment for the opportunistic infection is ongoing at the time when antiretroviral therapy is initiated. Unmasking IRIS occurs when a previously unrecognized opportunistic infection is identified when the rebound in immune function occurs following the initiation of antiretroviral therapy. The most common pathogens associated with IRIS (Table 358-4) include *Mycobacterium tuberculosis*, *Mycobacterium avium* complex, *Cryptococcal neoformans*, *Pneumocystis jirovecii*, herpes simplex virus, varicella zoster virus, cytomegalovirus, hepatitis B, human herpesvirus-8 (HHV8), and JC virus. However, many other pathogens are also potential drivers of IRIS (see Table 358-2).

IRIS has varied presentations and no definitive diagnostic criteria, but common characteristics include:

- Pre-treatment CD4 count less than 50 cells/mL
- Recent robust decline in the HIV viral load
- Temporal relationship between the initiation of antiretroviral therapy and the onset of symptoms onset, usually within 4 to 8 weeks after antiretroviral therapy is begun
- The absence of an alternative diagnosis

TREATMENT

For patients who develop IRIS, it is imperative to continue antiretroviral therapy and maintain HIV viral suppression to prevent progressive HIV disease. Since the clinical manifestations of IRIS are similar to presentations for opportunistic pathogens themselves, there often is no conclusive method to distinguish IRIS from an active infection. For any form of presumed IRIS, it is prudent to initiate a comprehensive search for an infectious or neoplastic cause, to treat any opportunistic pathogen that is detected, even though it is not certain whether such pathogen-directed therapy enhances recovery compared with continuing antiretroviral therapy without adding pathogen specific therapy. Adjunctive anti-inflammatory therapy, including corticosteroids (e.g., prednisone 1 to 2 mg/kg for 1 to 2 weeks) can be considered based on the specific pathogen and severity of symptoms.

PREVENTION

Tuberculosis IRIS can be prevented in high-risk patients with prophylactic corticosteroids.[A9] Typical doses are prednisone 40 mg daily for 14 days and then 20 mg daily for another 14 days.

PROGNOSIS

For the majority of presentations, IRIS is self-limited and resolves without any specific treatment other than for any plausible pathogen that was detected. However, morbidity and mortality are related to the involved pathogen and the anatomic location of the IRIS. For certain disease processes, particularly those that affect the CNS (e.g., cryptococcal meningitis, or tuberculous meningitis), consequences can be severe and lead to increased mortality.

TABLE 358-4 TYPICAL MANIFESTATIONS OF HIV-RELATED IMMUNE RECONSTITUTION INFLAMMATORY SYNDROME (IRIS) ASSOCIATED WITH SPECIFIC MICROBES

PATHOGEN	NOMENCLATURE	TYPICAL/CHARACTERISTICS OF THE DISEASE
Mycobacterium tuberculosis (Chapter 299)	TB-IRIS	Paradoxical exacerbation of pulmonary, lymph node, or meningeal infection
Nontuberculous mycobacteria (NTM) (Chapter 300)	NTM-IRIS	Mainly lymphadenitis, also pulmonary and abdominal diseases
Bacillus Calmette-Guérin (BCG) (Chapter 299)	BCG-IRIS	Necrotizing regional lymphadenitis
Mycobacterium leprae (Chapter 301)	Leprosy-associated IRIS	Borderline and type 1 reactional state
Cryptococcus neoformans (Chapter 309)	C-IRIS	Mainly meningitis, also lymphadenitis
Pneumocystis jirovecii (Chapter 313)	Pneumocystosis-associated IRIS	Paradoxical exacerbation of pneumonitis
Cytomegalovirus (CMV) (Chapter 347)	CMV retinitis or immune recovery uveitis	Acute retinitis or uveitis
JC polyomavirus (Chapter 341)	PML-IRIS	Multifocal leukoencephalopathy
Human herpesvirus 8 (Chapter 359)	KS-IRIS	Rapid progression of existing and/or new KS lesions
Hepatitis B or C virus (Chapter 135)	Hepatitis B or C virus-associated IRIS (that may mimic DILI)	Hepatitis flare and/or liver enzyme elevation
Varicella-zoster virus (Chapter 346)		Dermatomal or multidermatomal zoster and rarely myelitis after ART
Herpes simplex virus (Chapter 345)		Herpes Lesions with exaggerated inflammation and rarely myelitis or encephalitis
Molluscum contagiosum virus (Chapter 343)	Inflammatory molluscum contagiosum	Inflamed molluscum lesions
Malassezia spp (Chapter 405)	Inflammatory seborrheic dermatitis	Abnormally inflamed seborrheic dermatitis

ART = antiretroviral therapy; C = cryptococcosis; DILI = drug-induced liver injury; IRIS = immune reconstitution inflammatory syndrome; KS = Kaposi sarcoma; PML = progressive multifocal leukoencephalopathy; spp = species; TB = tuberculosis.
From French M, Meintjes G. Microbial complications of HIV/AIDS. In: Goldman L, Schafer AI, eds. *Goldman-Cecil Medicine*. 26th ed. Philadelphia: Elsevier; 2020.

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359 SYSTEMIC MANIFESTATIONS OF HIV/AIDS

SAMUEL T. MERRICK AND MARSHALL J. GLESBY

With the advent of early, better tolerated, less toxic, antiretroviral therapy (ART), including fixed-dose combinations and single-tablet regimens, the life expectancy among people with HIV has come closer to that of the uninfected population. However, many complications may arise that are either unique to HIV infection or occur at a younger age or with greater frequency than in HIV-negative individuals.[1] To some degree, these complications may be related to the high prevalence of traditional risk factors for systemic diseases in people with HIV, e.g., substance use, poor dietary habits, or smoking. The chronic inflammatory state and immune activation caused by HIV infection, even when fully suppressed, also may play a large role in the noninfectious systemic complications seen in people living with HIV.

In most resource-rich countries, including the United States, more than 50% of people living with HIV are now ages 50 years or older. Many comorbidities are more common in the HIV population at any given age, and aging-related syndromes, such as frailty and falls, may also occur at earlier ages than in the general population (Chapter 24).

Multimorbidity—having two or more chronic conditions—is common in older people with HIV. The higher prevalence of potentially confounding factors such as smoking, alcohol and substance use, depression, hepatitis C virus infection, poverty, and unstable housing further complicates the attribution of multimorbidity and aging-related syndromes to HIV infection per se.

NEUROPSYCHIATRIC MANIFESTATIONS OF HIV

HIV enters the central nervous system (CNS) early during infection, and aseptic meningitis may be a presenting sign of primary infection (Chapter 355). The presence of HIV in the cerebrospinal fluid (CSF) causes a pro-inflammatory state that is ameliorated but not fully resolved by combination antiretroviral therapy. People living with HIV may develop complications in any part of the neurologic axis, and the incidence of some of these manifestations may be increasing as a function of the increased survival and aging of people with HIV.

NEUROCOGNITIVE DISORDERS

Diffuse white matter changes occur more commonly in people living with HIV, become more extensive the longer the duration of HIV infection, and are associated with neurocognitive deficits. In the absence of antiretroviral therapy, up to 20 to 30% of patients develop HIV-associated dementia, which is characterized by memory deficits, psychomotor slowing, and personality changes. With effective antiretroviral therapy, the incidence is less than 5%, but a milder form of cognitive dysfunction, termed *HIV-associated neurocognitive disorder*,[2] affects about 40% of people living with HIV.[3] No effective treatment is available.

Efavirenz, a non-nucleoside reverse transcriptase inhibitor (NNRTI), has been commonly associated with neuropsychiatric side effects such as sleep disorder, depression, and seizure. Immune reconstitution inflammatory syndrome (IRIS; Chapter 358) is described with a variety of opportunistic infections

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TABLE 358-4 TYPICAL MANIFESTATIONS OF HIV-RELATED IMMUNE RECONSTITUTION INFLAMMATORY SYNDROME (IRIS) ASSOCIATED WITH SPECIFIC MICROBES

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Herpes simplex virus (Chapter 345)		Herpes Lesions with exaggerated inflammation and rarely myelitis or encephalitis
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359 SYSTEMIC MANIFESTATIONS OF HIV/AIDS

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With the advent of early, better tolerated, less toxic, antiretroviral therapy (ART), including fixed-dose combinations and single-tablet regimens, the life expectancy among people with HIV has come closer to that of the uninfected population. However, many complications may arise that are either unique to HIV infection or occur at a younger age or with greater frequency than in HIV-negative individuals.[1] To some degree, these complications may be related to the high prevalence of traditional risk factors for systemic diseases in people with HIV, e.g., substance use, poor dietary habits, or smoking. The chronic inflammatory state and immune activation caused by HIV infection, even when fully suppressed, also may play a large role in the noninfectious systemic complications seen in people living with HIV.

In most resource-rich countries, including the United States, more than 50% of people living with HIV are now ages 50 years or older. Many comorbidities are more common in the HIV population at any given age, and aging-related syndromes, such as frailty and falls, may also occur at earlier ages than in the general population (Chapter 24).

Multimorbidity—having two or more chronic conditions—is common in older people with HIV. The higher prevalence of potentially confounding factors such as smoking, alcohol and substance use, depression, hepatitis C virus infection, poverty, and unstable housing further complicates the attribution of multimorbidity and aging-related syndromes to HIV infection per se.

NEUROPSYCHIATRIC MANIFESTATIONS OF HIV

HIV enters the central nervous system (CNS) early during infection, and aseptic meningitis may be a presenting sign of primary infection (Chapter 355). The presence of HIV in the cerebrospinal fluid (CSF) causes a pro-inflammatory state that is ameliorated but not fully resolved by combination antiretroviral therapy. People living with HIV may develop complications in any part of the neurologic axis, and the incidence of some of these manifestations may be increasing as a function of the increased survival and aging of people with HIV.

NEUROCOGNITIVE DISORDERS

Diffuse white matter changes occur more commonly in people living with HIV, become more extensive the longer the duration of HIV infection, and are associated with neurocognitive deficits. In the absence of antiretroviral therapy, up to 20 to 30% of patients develop HIV-associated dementia, which is characterized by memory deficits, psychomotor slowing, and personality changes. With effective antiretroviral therapy, the incidence is less than 5%, but a milder form of cognitive dysfunction, termed *HIV-associated neurocognitive disorder*,[2] affects about 40% of people living with HIV.[3] No effective treatment is available.

Efavirenz, a non-nucleoside reverse transcriptase inhibitor (NNRTI), has been commonly associated with neuropsychiatric side effects such as sleep disorder, depression, and seizure. Immune reconstitution inflammatory syndrome (IRIS; Chapter 358) is described with a variety of opportunistic infections

ABSTRACT

With the advent of early, better tolerated, less toxic, antiretroviral therapy, including fixed-dose combinations and single-tablet regimens, the life expectancy among people with HIV has come closer to that of the uninfected population. However, many complications may arise that are either unique to HIV infection or occur at a younger age or with greater frequency than in HIV-negative individuals. To some degree, these complications may be related to the high prevalence in people with HIV of traditional risk factors for systemic diseases, such as substance use, poor dietary habits, or smoking. The chronic inflammatory state and immune activation caused by HIV infection, even when fully suppressed, also may play a large role in the noninfectious systemic complications seen in people living with HIV.

KEYWORDS

HIV
systemic manifestations
aging
noninfectious
cardiovascular
AIDS-defining malignancies
dermatologic manifestations
neuropsychiatric
blood disorders

shortly after the start of antiretroviral therapy. HIV-associated neurocognitive disorder IRIS may present as worsening of a preexisting neurocognitive disorder or may be the cause of new-onset cognitive dysfunction.

NEUROPATHIES

PERIPHERAL NEUROPATHIES

Peripheral neuropathy (Chapter 388) is the most common neurologic condition affecting people living with HIV. Distal symmetrical peripheral polyneuropathy is seen in about 30 to 70% of people living with HIV. Peripheral neuropathy may be either an indirect effect of HIV infection or a side effect of antiretroviral therapy. Patients typically present with numbness, burning pain, and paresthesias in a glove-and-stocking distribution. The diagnosis is typically made clinically, based on symptoms, absent ankle reflexes, and diminished vibratory and pinprick sensation in the feet. Nerve conduction studies and electromyography (EMG) are reserved for cases with atypical presentations.

Less commonly, patients may develop mononeuritis multiplex (Chapter 388). In the early stages of HIV infection, mononeuritis multiplex is typically due to HIV-related inflammation, whereas with more advanced immunosuppression, it is important to exclude opportunistic infections, notably cytomegalovirus.

Patients with acute HIV infection may present with unilateral or bilateral facial nerve palsy (Bell palsy; Chapter 388). Other manifestations include sensorineural hearing loss and foot or wrist drop.

Another rare complication is an inflammatory demyelinating polyneuropathy, which may present acutely as a rapidly progressive ascending, symmetrical flaccid paralysis similar to Guillain-Barré syndrome. Patients have areflexia and weakness but do not have sensory loss. They may also have autonomic dysfunction and even develop respiratory failure. Symptoms peak at about 4 weeks with recovery shortly thereafter.

Acute inflammatory demyelinating polyneuropathy typically develops early during HIV infection and may occur at the time of seroconversion. The CSF may have a mild lymphocytic pleocytosis (10 to 50 cells/μL) and a slightly elevated protein level, in distinction to Guillain-Barré syndrome, in which CSF analysis will typically show an elevated protein but no pleocytosis. Chronic inflammatory demyelinating polyneuropathy has a relapsing and remitting course over more than 8 weeks.

TREATMENT

In cases of antiretroviral toxic neuropathy, removal of the offending agent may result in improvement. Otherwise, treatment is the standard approach to peripheral neuropathy (Chapter 388).

AUTONOMIC NEUROPATHY

Autonomic neuropathy is typically seen with advanced AIDS and may be asymptomatic or a cause of orthostatic hypotension, impotence, and abnormalities in sweating. Resting tachycardia may be seen in asymptomatic individuals. After eliminating other treatable conditions, such as cardiomyopathy and adrenal insufficiency, treatment is similar to the non-HIV patient (Chapter 386).

MYELOPATHY AND MYOPATHY

Vacuolar myelopathy may occur at any stage of HIV infection but is more common with advanced disease, when it can present as a slowly progressive (over weeks to months) spastic paraparesis with loss of vibration and position sense similar to that seen with B_{12} deficiency (Chapter 150). The pathogenesis of HIV-associated myelopathy is unknown. On pathologic examination, demyelination of the dorsal and dorsolateral columns is seen with prominent vacuoles in the myelin sheaths. Virus is not thought to invade the spinal cord directly, so the changes are considered to be related to inflammatory cytokines produced by macrophages. HIV-associated myelopathy is a diagnosis of exclusion, and it is important to look for other, potentially treatable causes.

The NRTI zidovudine (AZT) has been associated with a toxic myopathy in 0.4% of patients receiving the drug. HIV-associated polymyositis is a rare condition, with an incidence of less than 1%, that can be seen at any stage of HIV infection. It presents with slowly progressive, symmetrical proximal muscle weakness similar to autoimmune polymyositis (Chapter 248).

TREATMENT

Other than discontinuing any offending drugs, the treatment is the same as in non-HIV-infected patients (Chapters 369 and 389).

STROKE

Despite antiretroviral therapy, the risk of stroke is increased by an estimated 20 to 80% in people living with HIV, even after adjusting for traditional risk factors such as diabetes, hyperlipidemia, smoking, and hypertension. Increased immune activation and chronic inflammation are likely causes.

RENAL MANIFESTATIONS

Both acute kidney injury (AKI) and chronic kidney disease (CKD) occur more commonly in people living with HIV (Fig. 359-1). AKI is most commonly a result of systemic infection, sepsis, or medication-related adverse effects. CKD, which is more common in Black patients, may be related to HIV infection itself, medications used to treat HIV, or comorbid conditions, such as diabetes mellitus, hepatitis B, hepatitis C, and hypertension.

HIV-ASSOCIATED NEPHROPATHY

HIV-associated nephropathy (Chapter 107) typically presents with nephrotic-range proteinuria.[4] Before antiretroviral therapy was available, it almost always progressed rapidly to end-stage renal disease. In contrast to nephrotic-range proteinuria from other causes, patients typically do not have peripheral edema, likely because of a concomitant salt-wasting component. It occurs predominately in individuals of African origin, related to an *APOL1* gene mutation that is protective against African trypanosomiasis (Chapter 317), and is more commonly seen with advanced AIDS. The risk for HIV-associated nephropathy has decreased by 60% in the antiretroviral therapy era. Other than antiretroviral therapy, angiotensin-converting enzyme inhibitors or angiotensin receptor blockers are useful, and corticosteroids may be helpful for persistent disease (see Chapter 107).

HIV-associated immune complex renal disease refers to a heterogeneous group of conditions characterized by immunoglobulin G (IgG) or immune complex deposition.[5] Immune complex glomerulonephropathies, IgA nephropathy, and lupus-like glomerulonephritis all fall under the umbrella of HIV-associated immune complex renal disease. The renal manifestations depend on the location and extent of the glomerular deposits. Proteinuria may be nephrotic in range. Hematuria, decreased GFR, and low serum levels of complement are also often seen.

HIV is also associated with tubular interstitial nephropathy, which is often associated with the use of tenofovir disoproxil fumarate (the pro-drug of tenofovir), and with poorly controlled HIV (Chapter 108). The diagnosis of tenofovir nephrotoxicity is based on clinical presentation and requires renal biopsy only if the presentation is atypical. If nephrotoxicity is suspected, prompt discontinuation of the drug is critical to prevent potentially irreversible damage. Another tenofovir pro-drug, tenofovir alafenamide, is less nephrotoxic.

The thrombotic microangiopathies, which include thrombotic thrombocytopenic purpura and atypical hemolytic-uremic syndrome, occur with increased frequency in people living with HIV but present similarly to HIV-uninfected individuals. Indinavir and atazanavir are associated with crystalluria and frank nephrolithiasis (Chapter 111), with the likelihood increasing with longer durations of therapy.

Rilpivirine, dolutegravir, bictegravir, and the pharmacokinetic enhancer cobicistat may artifactually raise creatinine levels by interfering with the tubular secretion of creatinine. The change is on the order of 0.14 mg/dL. However, glomerular filtration is not diminished, and measurement of a cystatin C level can clarify whether renal damage has actually occurred.

END-STAGE RENAL DISEASE

People who are living with HIV and develop end-stage renal disease are candidates for either peritoneal or hemodialysis.

NRTIs, other than abacavir, are not tightly protein bound and may be removed by dialysis, so they are administered after dialysis. Integrase inhibitors, NNRTIs, and protease inhibitors are not typically removed by dialysis.

People living with HIV also should be considered for transplantation evaluation because both graft survival and mortality compare favorably to HIV-uninfected individuals. Transplanting HIV-infected donor kidneys into recipients with HIV is safe and effective.

HEMATOLOGY AND ONCOLOGY

CYTOPENIA

Any hematopoietic cell line may be decreased in the setting of infection with HIV.[6] HIV can directly infect hematopoietic progenitor cells. In addition, the bone marrow milieu is affected by the inflammatory cytokines engendered by immune dysregulation. Cytopenias may also result from bone marrow

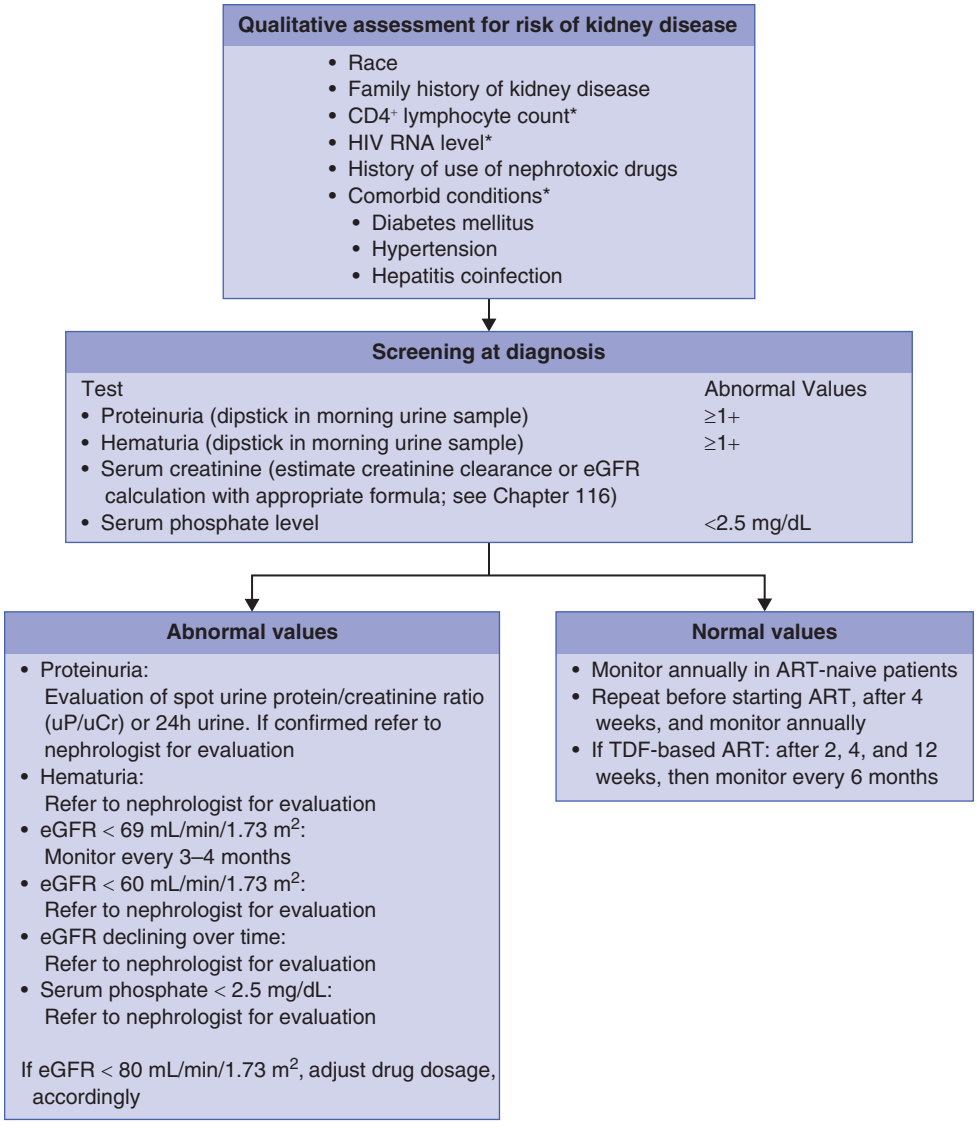

FIGURE 359-1. Guidelines for screening and management of renal disease in patients infected with HIV. *Periodic reevaluation. ART = antiretroviral therapy; CKD-EPL = Chronic Kidney Disease Epidemiology Collaboration; eGFR = estimated glomerular filtration rate; MDRD = modification of diet in renal disease; TDF = tenofovir. (Adapted from the HIV Medicine Association of the Infectious Diseases Society of America. From Maggi P, Bartolozzi D, Bonfanti P, et al. Renal complications in HIV disease: between present and future. *AIDS Rev*. 2012;14:37-53.)

infiltration from malignancy or opportunistic infection in the setting of advanced AIDS. Multicentric Castleman disease (see later) is associated with profound cytopenias, high fevers, and lymphadenopathy. Nutritional deficiencies, in particular B_{12}, folate, and iron, are more common in advanced disease, especially in resource-poor settings. Not surprisingly, cytopenias tend to increase in incidence with more advanced immunosuppression and improve after the institution of antiretroviral therapy.

Zidovudine frequently caused a macrocytic anemia as well as neutropenia. However, it is not associated with thrombocytopenia and instead is beneficial in the treatment of HIV-associated thrombocytopenia.

ANEMIA

The highest incidence of anemia is in people who are not yet on antiretroviral therapy or have symptomatic AIDS. The prevalence of anemia has decreased from 20 to 25% in the pre-antiretroviral therapy era to 4% in patients on antiretroviral therapy. Isolated anemia may result from antibody-mediated or drug-related hemolysis, infections, and bone marrow infiltration (Table 359-1).

Although about 15% of people living with HIV may have a positive direct Coombs test, clinically significant autoimmune hemolytic anemia (Chapter 146) is rare. Individuals who are glucose-6-phosphate dehydrogenase (G6PD) deficient (Chapter 147) are at risk for hemolysis with medications such as dapsone and primaquine that are used in people living with HIV.

Malaria (Chapter 316) is an important cause of anemia in coinfected patients in sub-Saharan Africa. Infection with parvovirus B19 (Chapter 342) can cause severe anemia, including aplastic crisis or pure red cell aplasia, but is readily treatable with IVIG.

LEUKOPENIA

HIV infection is associated with a decrease in endogenous granulocytic colony-stimulating factor (G-CSF), with a resultant decrease in granulocytic and macrophage progenitor cells. The risk for bacterial infection is increased with an absolute neutrophil count of less than 1000 cells/μL and, in particular, if less than 500 cells/μ. It is reasonable to consider the use of granulocyte colony-stimulating factor (Chapter 153) in patients who have profound neutropenia (<200 cells/μL) despite removal of the offending agent.

THROMBOCYTOPENIA

Thrombocytopenia was common before the availability of effective antiretroviral therapy, likely caused by cross-reactions between the HIV envelope glycoprotein gp160/120 and the platelet glycoprotein IIb/IIIa. During the later stages of AIDS, megakaryocytes can be directly infected.

TREATMENT

The treatment for HIV-associated thrombocytopenia is virologic suppression with antiretroviral therapy. For patients who do not respond, corticosteroids, IVIG, or anti-D immune globulin (if the patient is not splenectomized and is Rh positive) have all shown efficacy (Chapter 158). Corticosteroids increase platelet counts in 40 to 80% of cases, but only 10 to 20% have long-term remission. IVIG is of short-term benefit, so it is typically reserved for use before invasive procedures or in the setting of acute bleeding. Thrombopoietin receptor analogues such as eltrombopag and romiplostim (see Chapter 158) have been used with some success in cases of refractory HIV-related thrombocytopenia. Because of concerns about the potential increased risk for thrombosis, it is important to use the lowest dose of these medications needed to obtain an acceptable platelet count. Surgical splenectomy and splenic irradiation have been used in particularly refractory cases.

TABLE 359-1 EVALUATION AND MANAGEMENT OF ANEMIA IN PEOPLE WITH HIV

ETIOLOGY	EVALUATION	TREATMENT
Uncontrolled HIV infection	HIV viral load	Antiretroviral therapy
Chronic inflammation	Exclude other etiologies as below	Erythropoiesis-stimulating agents for refractory anemia
Nutritional	B_{12}, folate, iron studies Endoscopy as indicated if low iron level	Supplementation Treatment of underlying condition
Medication related	**Review medication list:** Bone marrow suppression: AZT, TMP-SMX, chemotherapy Hemolysis (see below): Dapsone, primaquine, ribavirin	Change medication where possible, support with erythropoiesis-stimulating agents
Thrombotic microangiopathy	Peripheral smear for schistocytes, ADAMTS13 level	Plasmapheresis for TTP (see Chapter 158) Eculizumab for atypical HUS (see Chapter 158)
Hemolytic anemia 1. Autoimmune 2. Medication-related	LDH, reticulocyte count, haptoglobin, indirect bilirubin Coombs test Dapsone, primaquine (G6PD deficiency)	 Corticosteroids Discontinue dapsone, primaquine Reduce ribavirin dose
Parvovirus B19	Parvovirus B19 PCR Bone marrow biopsy (pronormoblasts)	Intravenous immune globulin (see Chapter 342)
Bone marrow infiltration	Histoplasma urine/blood antigen Blood culture for MAC LDH for lymphoma Bone marrow biopsy if noninvasive tests are unrevealing	Treatment of underlying etiology

AZT = zidovudine; HIV = human immunodeficiency virus; HUS = hemolytic uremic syndrome; LDH = lactate dehydrogenase; MAC = *Mycobacterium avium* complex; PCR = polymerase chain reaction; TMP-SMX = trimethoprim-sulfamethoxazole; TTP = thrombotic thrombocytopenic purpura.

HYPERCOAGULABLE STATE

People living with HIV have a prothrombotic tendency, likely related to their pro-inflammatory state and immune activation. Other factors include antiphospholipid antibodies, such as lupus anticoagulant, and acquired protein S and C deficiency (Chapter 67). Up to about 60% of people living with HIV have anticardiolipin antibodies.

AIDS-DEFINING MALIGNANCIES

Systemic non-Hodgkin lymphoma, Kaposi sarcoma, and invasive cervical cancer are seen at substantially higher rates in people living with HIV than the general population and make up what historically have been called the AIDS-defining malignancies.[7] Before the advent of antiretroviral therapy, the risk for Kaposi sarcoma was 2800-fold higher in people living with HIV relative to the general population, and the risks for non-Hodgkin lymphoma and cervical cancer were 10-fold and 3- to 4-fold higher, respectively.

These malignancies are all associated with specific oncogenic viral infections: Kaposi sarcoma with human herpesvirus-8 (also known as Kaposi sarcoma–associated herpesvirus), non-Hodgkin lymphoma with Epstein-Barr virus, and cervical cancer with human papillomavirus (HPV). The degree of immunosuppression and the resulting lack of immunologic control of the respective oncogenic viruses is the major explanation for the increased incidence of these malignancies. Other than cervical cancer, the incidence of the other AIDS-defining malignancies has decreased significantly since the introduction of antiretroviral therapy.

Most people living with HIV will be able to tolerate standard chemotherapy regimens. However, it is important to be mindful of the potential for drug-drug interactions in patients who are on HIV protease inhibitors or a regimen that contains the pharmacokinetic booster cobicistat.

NON-HODGKIN LYMPHOMA

Non-Hodgkin lymphoma is the most common AIDS-defining malignancy. The AIDS-defining non-Hodgkin lymphomas are mature B-cell lymphomas (Chapter 171), including diffuse large B-cell lymphoma, primary CNS lymphoma, Burkitt lymphoma, primary effusion lymphoma, and plasmablastic lymphoma. Diffuse large B-cell lymphoma, which is the most common, and primary central nervous system lymphoma, which is limited to the brain and is seen in patients whose CD4 cell counts are less than 50 cells/μL, are closely associated with Epstein-Barr virus infection (Chapter 348) and advanced immunosuppression. Burkitt lymphoma, which also is associated with Epstein-Barr virus in 25 to 40% of cases, may occur earlier in the course of HIV infection and is considered highly curable. Plasmablastic lymphoma is an Epstein-Barr virus–associated CD20-negative lymphoma that typically involves the oropharynx.

Primary effusion lymphoma (Chapter 171), which is a rare B-cell non-Hodgkin lymphoma, comprises 2 to 4% of HIV-associated lymphomas and may also be associated with Epstein-Barr virus and/or human herpesvirus-8 infection. It presents as a malignant effusion involving the peritoneal, pleural, or pericardial spaces without evidence of a primary tumor mass. It is typically seen with advanced AIDS and has been associated with prior Kaposi sarcoma in about 25 to 70% of patients.

KAPOSI SARCOMA

Kaposi sarcoma in the setting of HIV infection is seen primarily in men who have sex with men (MSM) and rarely in women or individuals who have intravenous drug use as a risk factor for HIV infection. Kaposi sarcoma typically occurs at CD4 cell counts of less than 200 cells/μL, although it can occur at higher CD4 cell counts. The most common manifestation is characteristic purplish lesions on the skin, which may appear as nodules or plaques (see Fig. 359-2). Kaposi sarcoma may affect mucosal surfaces as well, and oropharyngeal lesions are most often seen on the gingiva and hard palate. In dark-skinned individuals these lesions may be harder to identify and can be confused with dermatofibromas. Bacillary angiomatosis (Chapter 291) also may be similar in appearance and require biopsy to be distinguished.

Most patients who have visceral involvement will have evidence of cutaneous disease, but it is possible to have isolated visceral disease. The most common sites are the lungs and the gastrointestinal tract. In the lungs, Kaposi sarcoma may present with parenchymal disease with or without associated effusions. Pleural effusions are characteristically bloody, carry a poor prognosis, and may require pleurodesis to control respiratory symptoms. Lesions similar to those seen on the skin may be seen on bronchoscopy but biopsy is not recommended due to their highly vascular nature. Endoscopy of the upper or lower gastrointestinal tract may also reveal the classical lesions of Kaposi sarcoma.

TREATMENT

Antiretroviral therapy is the mainstay of treatment, and decreased serum human herpesvirus-8 viral loads have been documented after the start of antiretroviral therapy.[8] Patients who have diffuse or disseminated disease or who do not respond to antiretroviral therapy may require chemotherapy with agents such as pegylated doxorubicin, liposomal daunorubicin, and paclitaxel[AT] under expert care.

When previously unrecognized Kaposi sarcoma or worsening of previously diagnosed disease occurs with the immune reconstitution inflammatory syndrome soon after starting antiretroviral therapy (Chapter 358), corticosteroids should be avoided because it increases replication of human herpesvirus-8 and can worsen Kaposi sarcoma.

FIGURE 359-2. Cutaneous Kaposi sarcoma.

MULTICENTRIC CASTLEMAN DISEASE

Multicentric Castleman disease (Chapter 171), which is a lymphoproliferative disorder with a high risk for progression to lymphoma,[9] is also associated with human herpesvirus-8 infection,[10] and up to 70% of patients may have concomitant Kaposi sarcoma. Patients typically present with fever, weight loss, diffuse lymphadenopathy, and hepatosplenomegaly. Anemia and hypergammaglobulinemia are common laboratory findings. Infection with human herpesvirus-8 is universal in HIV-associated multicentric Castleman disease. The underlying basis for these symptoms is related to the high production of the inflammatory cytokine IL-6, which is upregulated by viral products. POEMS syndrome (polyneuropathy, organomegaly, endocrinopathy, M component, and skin changes) and TAFRO syndrome (thrombocytopenia, anasarca, fever, reticulin fibrosis, and organomegaly) have also been reported in conjunction with multicentric Castleman disease.

TREATMENT

Multicentric Castleman disease in people living with HIV is thought to be associated with high rates of replication of lytic human herpesvirus-8, and these rates correlate with the severity of clinical disease (unlike the latent infection in Kaposi sarcoma). Treatment is with rituximab under expert supervision (Chapter 171), with ganciclovir added if patients have low CD4 counts or concomitant Kaposi sarcoma. Etoposide is sometimes included for patients with more aggressive disease. Biologic agents that directly target IL-6 production are sometimes effective in HIV-negative patients but are not recommended in people with HIV.

CERVICAL CANCER

Women with HIV infection are less able to clear infection with human papillomavirus (Chapter 344) and are at a three- to four-fold increased risk for cervical cancer compared with HIV-uninfected women. This risk has not decreased despite the introduction of antiretroviral therapy. Cervical cancer (Chapter 184) remains a particular problem in resource-limited settings where women do not have ready access to screening and early treatment and is a leading cause of cancer-related mortality in these countries.

The screening recommendations for women with HIV infection are slightly different from HIV-negative women.[11] In particular, it is recommended that women with HIV continue screening after age 65.

TREATMENT

Treatment for cervical dysplasia is the same as for HIV-uninfected women, although women with HIV are more likely to have persistent or recurrent dysplasia after treatment. Women with cervical dysplasia should also have anal Pap tests performed to screen for anal cancer (see later).

NON–AIDS-DEFINING CANCERS

Several malignancies that do not qualify as AIDS-defining malignancies nevertheless occur at an increased prevalence in people living with HIV.[12] The risk for developing solid tumors and non–AIDS-defining lymphomas is two- to three-fold higher than in the general population. As the average age of people living with HIV is rising, the prevalence of these non–AIDS-defining cancers is also increasing. Some are associated with underlying viral infections, whereas others may be attributed to behavioral risk factors, such as smoking and alcohol consumption. The potential role of immunosuppression or chronic inflammation related to chronic immune activation has not been well defined but is thought to be a factor.

Hodgkin lymphoma (Chapter 172) has a 5- to 20-fold higher rate in people living with HIV, and the incidence has not decreased despite the introduction of antiretroviral therapy. Hodgkin lymphoma may be more advanced and aggressive in this setting. Anal cancer (Chapter 131), which is associated with human papillomavirus infection most commonly in men who have sex with men, has a 30-fold higher incidence in people living with HIV than in HIV-uninfected individuals. Lung cancer (Chapter 177), which is the most common non–AIDS-defining cancer, has a two- to three-fold increased incidence, independent of smoking, in people living with HIV compared with the general population. Colorectal cancer (Chapter 179) develops earlier and presents with more advanced disease in people living with HIV. Hepatocellular carcinoma (Chapter 181) has a three- to six-fold increased risk in people living with HIV, likely related to high rates of coinfection with hepatitis B and C. Cancer of the head and neck (Chapter 176) occurs at a four-fold increased incidence and is also associated with human papillomavirus infection as well as smoking and alcohol consumption. Notably, breast and prostate cancer are not increased in people living with HIV.

TREATMENT

Management of non–AIDS-defining cancers does not differ substantially from that for the HIV-uninfected patient.

SCREENING AND PREVENTION

In addition to cervical Pap tests for women with HIV infection, all people living with HIV who are MSM, have a history of anogenital warts, or have abnormal cervical histology should have anal Pap tests performed to screen for anal cancer (Chapter 131). Mammograms, colonoscopy, and screening chest CT scans should be performed as per guidelines for the general population. People who have HIV and chronic hepatitis B infection and who have cirrhosis or are at high risk for hepatocellular carcinoma should be screened with an α-fetoprotein level and liver ultrasound every 6 months. Individuals who have chronic hepatitis C infection should be similarly screened if they have evidence of cirrhosis, even if they have achieved a sustained virologic response after treatment.

The importance of counseling for smoking cessation cannot be overstated. Patients should also be counseled on the use of sunblock with high SPF and have annual skin cancer screenings.

The human papillomavirus vaccine is safe and effective in people living with HIV and should be administered to individuals between the ages of 9 and 26 years for prevention of cervical and anal cancer (Chapters 15 and 358). Similarly, hepatitis B vaccine should be given to all people living with HIV who do not have serologic evidence of prior HBV infection, preferably when their CD4 counts are above 200 cells/μL.

CARDIOVASCULAR MANIFESTATIONS OF HIV

CORONARY HEART DISEASE

People living with HIV have higher rates of myocardial infarction (Chapter 58) than the general population, even after adjustment for traditional cardiovascular risk factors. This increased risk is also present in the subset of people without major cardiovascular risk factors and in those with asymptomatic, controlled HIV infection. Although data are limited, the risk for sudden cardiac death may also be increased in people with HIV.[13]

Among traditional cardiovascular risk factors, smoking accounts for a considerable proportion of the risk among people living with HIV. The prevalence of smoking is higher than the general population, and its adverse effects may be potentiated by HIV. As with certain autoimmune diseases, such as systemic lupus erythematosus, inflammation and immune activation are thought to contribute to atherosclerosis and the occurrence of cardiovascular events in HIV infection, even in the setting of virologic suppression with antiretroviral therapy.[14]

Dyslipidemia (Chapter 190) is another important modifiable cardiovascular risk factor. Advanced HIV disease is associated with low levels of total cholesterol, low-density lipoprotein (LDL) cholesterol, and high-density lipoprotein (HDL) cholesterol, as well as elevated levels of triglycerides. Initiation of antiretroviral therapy in advanced HIV disease often increases total and LDL cholesterol levels to what might be expected without HIV infection, sometimes termed a "return to health" phenomenon. Increases in HDL cholesterol are variable, however, and levels may remain persistently low in some individuals despite virologic control. Hypertriglyceridemia is the most common lipid abnormality in people with HIV, especially patients who are taking ritonavir-boosted protease inhibitors.

TREATMENT

Although management of hypertension (Chapter 64) is not fundamentally different in the setting of HIV infection, protease inhibitors may increase the concentrations of coadministered calcium-channel blockers. Furthermore, certain protease inhibitors (atazanavir, lopinavir/ritonavir, saquinavir) may prolong the PR interval, thereby necessitating caution with coadministration of calcium-channel blockers and β-blockers. Observational data suggest that current or recent use of certain antiretroviral drugs, such as abacavir and the protease inhibitors darunavir and lopinavir/ritonavir, is associated with increased risk for myocardial infarction.

Guidelines support counting HIV as a major cardiovascular risk factor when deciding about primary prevention using lipid-lowering therapy. Clinicians must be mindful that protease inhibitors, pharmacologic boosters, and cobicistat inhibit the metabolism of most statins, with some (e.g., simvastatin) being contraindicated and others (e.g., fluvastatin) being safer but requiring a lower starting dose and careful monitoring (see Table 357-4). Otherwise, the approach to prevention of cardiovascular disease mirrors that of the general population (Chapter 39).

CARDIOMYOPATHY AND HEART FAILURE

Before the availability of effective antiretroviral therapy, dilated cardiomyopathy (attributed to direct cardiac involvement by HIV, opportunistic infections, micronutrient deficiencies, or autoimmunity) was a common complication of advanced HIV disease. Echocardiography shows that diastolic dysfunction is now far more common than systolic dysfunction in people living with HIV,[15] and heart failure with preserved ejection fraction is consequently more common than heart failure with a reduced ejection fraction (Chapter 45). Cardiac steatosis and fibrosis are also more prevalent in people living with HIV.

TREATMENT

Management of impaired ventricular function and heart failure does not differ from that in the general population (Chapter 46).

PERICARDIAL DISEASE

Before the availability of effective antiretroviral therapy, pericardial disease, including symptomatic pericarditis and cardiac tamponade (Chapter 62), was an important cardiovascular issue in people living with HIV, especially patients with advanced immunodeficiency. The prevalence of pericardial effusion among people living with HIV in this era was approximately 20%. Presently, asymptomatic pericardial effusion is uncommon.

The causes of acute pericarditis in people with HIV who are not severely immunocompromised are similar to those in the general population, with approximately 80% considered idiopathic (presumed to be mostly of viral etiology). In settings with reduced access to antiretroviral therapy and in patients with advanced HIV disease, infectious causes (primarily mycobacterial) and AIDS-related malignancy predominate.

TREATMENT

Evaluation and management of pericardial disease is as per the general population.

PULMONARY ARTERIAL HYPERTENSION

The prevalence of pulmonary arterial hypertension in people living with HIV is approximately 10-fold higher than that of idiopathic pulmonary arterial hypertension in the general population (Chapter 69). Direct adverse effects of the HIV-1 viral proteins *nef, vpr,* and *tat* on the pulmonary vasculature and indirect effects of HIV through generation of proinflammatory cytokines may play important roles.

Clinicians should consider pulmonary arterial hypertension in the differential diagnosis of dyspnea on exertion in people with HIV. Secondary causes of pulmonary arterial hypertension in this population include chronic venous thromboembolic disease, obstructive sleep apnea, and portopulmonary hypertension due to chronic viral hepatitis or other causes.

TREATMENT AND PROGNOSIS

For medical management, sildenafil should not be coadministered with protease inhibitors or cobicistat, and tadalafil and bosentan must be used with caution. Otherwise, treatment is as for other causes of pulmonary hypertension (Chapter 69). The prognosis of HIV-associated pulmonary hypertension in the setting of effective antiretroviral therapy appears to be similar to that of pulmonary hypertension in the non-HIV population.

ENDOCRINE MANIFESTATIONS OF HIV

ADRENAL FUNCTION

Primary adrenal insufficiency (Chapter 208) was a common complication of AIDS before the availability of effective antiretroviral therapy. Cytomegalovirus adrenalitis was the most common identifiable cause at autopsy, although other opportunistic infections and malignancies capable of infiltrating the adrenal glands, or in some cases the hypothalamus or pituitary, were also described.

Drug-drug interactions between exogenously administered corticosteroids and antiretroviral drugs are now the primary causes of cortisol-related problems in people living with HIV. Protease inhibitors and the pharmacokinetic-boosting drug cobicistat inhibit the metabolism of commonly used corticosteroids (including fluticasone, budesonide, and triamcinolone) and can lead to systemic exposure to corticosteroids that are administered by inhalation, topically, or by injection into joint spaces. Beclomethasone is the inhaled corticosteroid of choice for patients taking protease inhibitors and, by extension, cobicistat.

THYROID DISORDERS

Clinically apparent thyroid gland dysfunction (Chapter 207) does not appear to be more prevalent in people living with HIV, but subclinical euthyroid sick syndrome may be more common, especially in advanced HIV disease. In advanced HIV disease, various pathogens and malignancies may infiltrate the thyroid gland, including *Pneumocystis jiroveci*, tuberculosis, *Cryptococcus*, *Coccidioides,* Kaposi sarcoma, and lymphoma.

Graves disease (Chapter 207) may occur in the setting of initiation of antiretroviral therapy as a manifestation of immune reconstitution inflammatory syndrome. Unlike most infectious manifestations, which occur within the initial months, Graves disease may develop up to 3 years after initiation of antiretroviral therapy.

ALTERED FAT DISTRIBUTION

Altered fat distribution, which is associated with dyslipidemia and insulin resistance, is commonly termed HIV-associated lipodystrophy syndrome. Some people with HIV have fat accumulation, some have lipoatrophy, and some have a combination of both.

People living with HIV may have abnormal fat accumulation, typically visceral abdominal fat but sometimes dorsocervical fat pad enlargement, fat accumulation in the trunk and upper chest wall, and breast enlargement. The pathogenesis of fat accumulation is unknown. No specific antiretroviral class or drug is clearly associated with fat accumulation, and switching among various types of regimens, such as protease-based to alternative regimens, has not been efficacious.

Lipoatrophy tends to be diffuse but is most visible in the face, limbs, and buttocks. It is generally attributed to mitochondrial toxicity from exposure to thymidine analogue NRTIs (stavudine or zidovudine) that have the off-target effect of inhibiting host mitochondrial DNA polymerase. Some people with HIV who were previously treated with thymidine analogues have residual lipoatrophy. With contemporary antiretroviral drug regimens, new incident cases are uncommon.

On physical examination, increased visceral abdominal fat may be difficult to distinguish from generalized obesity, although disproportionate gain of fat in the visceral compartment may result in a firmer abdomen with relatively less "pinchable" subcutaneous fat. Clinicians can measure serial waist and hip circumference.

It is important to monitor fasting glucose levels, lipid panels, and liver enzymes in patients with fat accumulation because metabolic derangements,

including dyslipidemia, prediabetes/diabetes, and nonalcoholic fatty liver disease (Chapter 138), are common.

TREATMENT

Management options for fat accumulation are limited, and switching among antiretroviral agents generally has no effect.[16] Clinicians should counsel patients on diet and exercise. Liposuction of dorsocervical fat pads may be temporarily efficacious, although fat may reaccumulate. The visceral nature of the fat accumulation precludes abdominal liposuction. Some women may benefit from reduction mammoplasty if breast enlargement causes symptoms such as low back pain.

Tesamorelin, which is a growth hormone-releasing analogue, stimulates the pituitary to release growth hormone, which increases circulating insulin-like growth factor-I (IGF-I) levels, thereby resulting in increased lipolysis. Daily subcutaneous injection of tesamorelin (1.4 mg daily) can reduce abdominal fat by approximately 15% over 26 weeks, but fat reaccumulates rapidly after its cessation.[A2] Lipid profiles tend to improve, and liver fat is reduced on tesamorelin. No long-term safety data are available, and elevated levels of IGF-I are known to be associated with an increased risk of malignancy. For lipoatrophy, two temporary injectable facial fillers are approved by the FDA (poly-L-lactic acid and calcium hydroxylapatite) and can be injected into the deep dermis at regular intervals to induce the growth of collagen.

DIABETES MELLITUS

The incidence of diabetes mellitus (Chapter 210) may be higher in people living with HIV, although epidemiologic data are conflicting. Limited data suggest that HIV itself may directly cause insulin resistance and diabetes, possibly through the effects of HIV proteins such as *vpr* on glucocorticoid sensitivity. More compelling data support an indirect role of the virus through generation of pro-inflammatory cytokines that may directly affect insulin signaling. Increased visceral adiposity (lipohypertrophy) in some people living with HIV may also contribute to insulin resistance and diabetes risk.

Guidelines recommend screening people with HIV for diabetes annually, using a fasting glucose level if a random glucose level is elevated, because some HIV drugs, especially abacavir, may falsely reduce glycosylated hemoglobin levels.

TREATMENT

The management of diabetes (Chapter 210) does not differ in people living with HIV, although attention should be paid to drug-drug interactions. For example, metformin drug levels are increased by dolutegravir.

VITAMIN D DEFICIENCY

Data are conflicting as to whether vitamin D deficiency is more common in people with HIV, but vitamin D insufficiency or deficiency is common in HIV infection. Immune activation and inflammation may play a role. Efavirenz, an NNRTI, can reduce circulating levels of the active form of vitamin D by inducing cytochrome P-450 enzymes that increase the catabolism of vitamin D to an inactive form. Protease inhibitors may inhibit the conversion of vitamin D to active metabolites. Clinicians should check 25-hydroxyvitamin D levels in patients with low bone mineral density or history of fracture.

BONE DISORDERS

HIV infection is associated with about a three-fold higher prevalence of osteoporosis (Chapter 225), with higher rates among patients on antiretroviral drugs and specifically protease inhibitors.[17] Initiation of antiretroviral therapy results in an average lost bone mineral density of 2 to 6%, akin to that seen in women going through menopause. HIV-specific risk factors for decreased bone mineral density include a low nadir CD4 cell count, HIV viremia, and use of protease inhibitors and tenofovir disoproxil fumarate. Another prodrug of tenofovir, tenofovir alafenamide, has fewer adverse effects on bone mineral density.

U.S. guidelines recommend screening for osteoporosis by dual X-ray absorptiometry scanning in men 50 years and older and postmenopausal women living with HIV. Some experts additionally advocate calculating 10-year fracture risk using the Fracture Risk Assessment Tool (FRAX; E-Fig 225-4) in men 40 to 49 years old and women older than 40 years, followed by dual X-ray absorptiometry scanning if the risk for major osteoporotic fracture exceeds 10%. Data support counting HIV as a secondary cause of osteoporosis when using this risk calculator. Patients who have had fragility fractures, are at high risk for falls, or have used glucocorticoids chronically (the equivalent of 5 mg or more per day of prednisone for more than 3 months) also should be screened by dual X-ray absorptiometry. Clinicians should evaluate patients with osteoporosis for secondary causes as in the general population. As part of routine care, patients 50 years and older should have height measured every 1 to 2 years to screen for height loss from vertebral fractures.

Criteria for initiating osteoporosis therapy (Chapter 225) in people with HIV do not differ from those for the general population.[18] Patients taking tenofovir disoproxil fumarate should be switched to tenofovir alafenamide or an alternative drug based on treatment history. Protease inhibitors also should be switched to alternative drugs when possible.

MALE HYPOGONADISM

Hypogonadism (Chapter 216) is less prevalent in the era of antiretroviral therapy, although some estimate that 15 to 20% of men with HIV are hypogonadal in the current era. Patients may present with classic symptoms and signs, including fatigue, low energy, depressed mood, decreased libido, erectile dysfunction, weight loss, testicular atrophy, and gynecomastia. Bone mineral density also may be reduced.

Although most cases of hypogonadism in men with HIV are secondary to pituitary or hypothalamic dysfunction (Chapter 205), primary hypogonadism also may be seen. In patients with CD4 cell counts less than 100 cells/μL, various opportunistic pathogens and malignancies can infiltrate the pituitary, hypothalamus, or testes. Elevations in pro-inflammatory cytokines such as tumor necrosis factor-α (TNF-α) may also contribute to hypogonadism at all stages of HIV disease.

Sex hormone–binding globulin levels are often elevated in HIV infection, which may result in normal total testosterone levels, but free testosterone levels are actually below normal (Chapter 216). Consequently, clinicians should screen symptomatic men with a morning free testosterone level. Repletion of testosterone by intramuscular injections or topical preparations may result in symptomatic improvement and improved quality of life. It is important to exclude occult prostate cancer (Chapter 186) with a prostate-specific antigen test before starting therapy with testosterone.

OVARIAN FUNCTION

Menstrual irregularities are common in women with HIV, and a low CD4 cell count has been associated with early menopause in some studies. Women living with HIV also appear to report a greater number of menopausal symptoms (Chapter 222). The prevalence of infertility is increased in women with HIV, and response rates to in vitro fertilization are also reduced.

PULMONARY MANIFESTATIONS

The epidemiology of HIV-associated pulmonary manifestations has shifted from predominantly infectious to noninfectious complications with the advent of potent antiretroviral therapy. The incidence of bacterial pneumonia, most commonly caused by *Streptococcus pneumoniae* (Chapter 268), and pneumonia caused by the fungus *P. jiroveci* (Chapter 313) has declined dramatically, although the latter remains a concern in those with low CD4 cell counts. Pulmonary tuberculosis remains prevalent in many resource-limited settings, although its incidence, too, is reduced with effective antiretroviral therapy and the use of isoniazid preventive therapy. Chronic obstructive pulmonary disease (COPD), pulmonary arterial hypertension, and lung cancer have emerged as key noninfectious complications.

CHRONIC OBSTRUCTIVE PULMONARY DISEASE

Several studies have demonstrated higher rates of COPD (Chapter 76) in people living with HIV relative to uninfected controls, even after adjustment for cigarette exposure. HIV is a risk factor for emphysema and is associated with greater severity and diffuseness of emphysema, a higher rate of ongoing lung destruction, and an accelerated decline in pulmonary function.

The management of COPD in people living with HIV does not differ fundamentally from that for the general population, except that beclomethasone is the preferred agent (see Endocrine Manifestations of HIV). Because of the potential increased risk for adverse cardiovascular events, salmeterol should not be coadministered with protease inhibitors and cobicistat.

VENOUS THROMBOEMBOLIC DISEASE

The incidence of venous thromboembolism (Chapter 68) is higher in people living with HIV relative to the general population. Risk factors include low

CD4 cell count, the presence of opportunistic infections, and the use of older protease inhibitors (indinavir, nelfinavir, ritonavir, or saquinavir). Furthermore, HIV infection predisposes to hypercoagulability that may in part be related to chronic inflammation.

TREATMENT

The management of venous thromboembolic disease in HIV infection is complicated by drug-drug interactions. Among the direct acting oral anticoagulant drugs, edoxaban and rivaroxaban should not be coadministered with protease inhibitors or cobicistat, whereas dabigatran is likely safe if the creatinine clearance rate is at least 50 mL/minute. Apixaban can be used with protease inhibitors or cobicistat at a 50% reduced dose assuming normal renal function (see Table 357-4). Warfarin sensitivity may increase with coadministration of protease inhibitors or cobicistat, thereby necessitating careful monitoring of the international normalized ratio.

PNEUMONITIS

Lymphocytic interstitial pneumonitis classically affects infants with HIV, although it may also affect adults, even at CD4 cell counts greater than 350 cells/μL. Nonspecific interstitial pneumonitis (Chapter 80) is commonly an asymptomatic finding but may present with fever, dyspnea, and cough typically in people with CD4 cell counts less than 200 cells/μL, thereby mimicking *Pneumocystis* pneumonia. Diffuse infiltrative (CD8) lymphocytosis syndrome is a chronic systemic disorder with pulmonary involvement in about 50% of patients. It shares clinical features with lymphocytic interstitial pneumonitis with the addition of Sjögren-like features, including sicca, lymphadenopathy, parotid gland enlargement (sometimes dramatic), and hepatosplenomegaly. Treatment consists of effective antiretroviral therapy (Chapter 357), although corticosteroids may rarely be required.

OTHER PULMONARY CONDITIONS

People living with HIV are not at higher risk for asthma (Chapter 75). Bronchiectasis (Chapter 78) may complicate recurrent pneumonia in people living with HIV and is typically diagnosed by high-resolution CT. Sarcoidosis (Chapter 83) may manifest as an immune reconstitution inflammatory syndrome in the setting of recently initiated antiretroviral therapy.

GASTROINTESTINAL MANIFESTATIONS OF HIV

Gastrointestinal symptoms and illnesses remain important contributors to morbidity in people living with HIV, particularly in patients who are unable to maintain viral suppression because of nonadherence or lack of access to antiretroviral therapy or who present with advanced disease at initial diagnosis. Microbial translocation due to the damaged host intestinal epithelial barrier may be a central contributor to the chronically immune-activated state seen especially during acute and early HIV infection. Early antiretroviral treatment may diminish but not interrupt this pathogenic process.[19] Most of the infectious gastrointestinal complications are seen with increasing incidence as immune suppression progresses, particularly at CD4 counts below 100 cells/μL, whereas the noninfectious complications can occur at any CD4 cell count.

Although newer first-line antiretroviral medications have very minimal gastrointestinal side effects, some patients may remain on older therapies or be on second- or third-line drugs because of acquired treatment resistance. Older antiretroviral drugs are also more commonly used in resource-constrained settings.

GASTROINTESTINAL SIDE EFFECTS OF ANTIRETROVIRAL DRUGS

REVERSE TRANSCRIPTASE INHIBITORS

Abacavir can cause a subtle hypersensitivity syndrome with low-grade fever, abdominal discomfort, nausea and vomiting, and sometimes mild rash, early after initiation of therapy. Interruption with subsequent rechallenge in patients who have manifested signs and symptoms of hypersensitivity can lead to rapid, severe non–IgE-mediated anaphylactoid reactions and death. Testing for human leukocyte antigen (HLA)-B-5701 allele positivity before initiation of therapy has largely eliminated this risk. Patients can be safely rechallenged with abacavir if they are HLA-B-5701 negative. Nevirapine, still in use in resource-poor settings, can cause elevated aminotransferase levels and rarely hepatic failure, particularly in men with a CD4 count higher than 400 cells/μL and women with a CD4 count higher than 250 cells/μL at the time of initiation of antiretroviral therapy.

PROTEASE INHIBITORS

The first-generation protease inhibitors saquinavir, indinavir, nelfinavir, and ritonavir often caused significant gastrointestinal problems. Atazanavir has been associated with cholelithiasis and almost always causes a benign mild indirect hyperbilirubinemia, similar to Gilbert disease, owing to inhibition of UDP-glucuronyltransferase and reversible on cessation of the drug. Protease inhibitors, particularly ritonavir and ritonavir-lopinavir, are more likely to cause hypertriglyceridemia, which may contribute to the risk for pancreatitis and fatty liver disease.

INTEGRASE STRAND TRANSFER INHIBITORS

The integrase inhibitors as a class are associated with weight gain. Dermatologic reaction with eosinophilia and systemic symptoms (DRESS; Chapter 407) with concomitant elevations in aminotransferase levels and liver failure can occur in patients taking raltegravir.

OTHER

Pentamidine, even in the aerosol form used to prevent *Pneumocystis* pneumonia, can cause pancreatitis. High-dose trimethoprim-sulfamethoxazole used in the treatment and prevention of *Pneumocystis* pneumonia or for the treatment of methicillin-resistant staphylococcal infections can cause a significant hepatitis.

ORAL

Patients with HIV can have a variety of noninfectious complications in the oral cavity and salivary glands (Chapter 393), often as an early indication of undiagnosed HIV infection or progression of existing disease. The prevalence of oral complications related to immune suppression has decreased with more widespread antiretroviral therapy, but other conditions related to dry mouth (xerostomia), smoking, and poor access to dental care have increased. The prevalence of HPV-related and ulcerative disease such as herpes simplex virus or idiopathic aphthous ulcers has remained stable relative to the early years of the epidemic.

The lesions of oral hairy leukoplakia (Fig. 359-3) cannot be scraped off, in contrast to the whitish coating seen with oral candidiasis or thrush (Fig. 359-4). Linear gingival erythema can present as a brightly inflamed, well-demarcated line of gingiva. Gram-negative and enteric organisms, as well as *Candida,* can be involved. Necrotizing ulcerative gingivitis or periodontitis can present as a rapid, painful destruction of bone and soft tissue with the same microbiologic flora that is present in linear gingival erythema. Kaposi sarcoma typically involves the hard palate or gingiva (Fig. 359-5) and may cause ulcerative disease.

Idiopathic oral aphthous ulceration (Fig. 359-6), which can be a severe and refractory problem in advanced HIV, places patients at nutritional risk and sometimes requires treatment. Topical steroids (e.g., triamcinolone acetonide 0.1%) for several days are useful, but more extensive disease may require systemic corticosteroids (e.g., prednisone 20 to 40 mg) for 4 to 7

FIGURE 359-3. Lesions of oral hairy leukoplakia.

FIGURE 359-4. Oral candidiasis or thrush.

FIGURE 359-5. Gingival Kaposi sarcoma.

FIGURE 359-6. Oral aphthous ulcer.

days or thalidomide (50 to 100 mg) for up to one month or until resolution. Premalignant or malignant ulcers are often painless in contrast to other ulcerative lesions.

Xerostomia can be the result of drug side effects or lymphocytic infiltration of the salivary glands manifested by painless parotid enlargement and subsequent salivary hypofunction, sometimes as part of diffuse infiltrative lymphocytosis syndrome. Diffuse infiltrative lymphocytosis syndrome is more commonly seen in advanced disease, but it can occur at any stage in the course of HIV infection. Bilateral parotid enlargement due to lymphocytic or fatty infiltration has a characteristic radiologic appearance, and biopsies are rarely necessary to establish the diagnosis. Xerostomia (Chapter 393) has a large impact on quality of life as well as tooth and gum health and can be quite difficult to treat.

TREATMENT

Typically, over-the-counter lubricating agents in the form of gels, lozenges, or mouthwash can provide some relief. Artificial salivary fluid by prescription can also be tried.

ESOPHAGEAL

Dysphagia and odynophagia, which can be common complaints in patients with HIV, are most typically related to either the common infectious complications of advanced HIV disease such as candidiasis and herpes simplex virus (CD4 <200 cells/μL) or cytomegalovirus (CD4 <50 cells/μL) and, rarely, histoplasmosis (typically CD4 <150 cells/μL with median CD4 <50 cells/μL). However, they also can be caused by idiopathic aphthous ulcerations such as those seen in the oral cavity, which may happen at any CD4 cell count but are more severe in advanced disease. Eosinophilic esophagitis (Chapter 124) is an increasingly recognized entity that can cause dysphagia and retrosternal discomfort on swallowing.

TREATMENT

For gastroesophageal reflux disease, which is a common complaint, proton pump inhibitors and histamine-2 receptor antagonists are contraindicated or must be used with caution with commonly used antiretroviral drugs such as atazanavir and rilpivirine that require an acidic environment for optimal absorption. Concomitant use of calcium- or magnesium-containing acids is contraindicated with raltegravir and can reduce the serum concentrations of the integrase inhibitors dolutegravir, bictegravir, and elvitegravir. Empirical therapy with fluconazole for typical symptoms of candidal esophagitis, which may present without oral thrush, or a trial of a proton pump inhibitor (see Table 124-1) for symptoms consistent with reflux eosinophilic esophagitis may be indicated. Persistent symptoms referable to the esophagus require endoscopic evaluation with biopsies as appropriate and treatment directed at the underlying cause.

SMALL BOWEL

The conditions for HIV enteropathy may be established early in disease, with HIV disrupting the mucosa and ultimately causing villous atrophy and reducing the effective area of small bowel. Although this complication is more typical in patients with low CD4 cell counts, patients may experience symptoms due to HIV enteropathy at any CD4 cell count. HIV enteropathy, which can cause typical symptoms of small bowel disease such as bloating, gas, abdominal pain, and watery diarrhea, is a diagnosis of exclusion after infectious causes have been excluded. Most infectious causes of diarrhea (Chapter 262) in treated HIV patients tend to be similar in their presentation and course to those seen in other immune-competent patients.

LARGE BOWEL

No major noninfectious causes of large bowel pathology are specific to HIV infection. Diagnosis of infectious diarrhea other than cytomegalovirus depends on stool studies (bacterial culture and stains for parasites, antigen tests, or, if available, multiplex PCR including for viruses) and assays for *Clostridioides difficile*. More common infectious causes of HIV-related colitis, such as cytomegalovirus, occur only at CD4 counts in the less than 50 cells/μL range and must be diagnosed by biopsy during direct examination of the colon. With antiretroviral therapy, devastating diarrheal illnesses such as cryptosporidiosis, microsporidiosis, *Cyclospora,* and *Cystoisospora belli* are rarely seen.

TREATMENT

The risk for *Salmonella* bacteremia is higher in people living with HIV, so all infected patients should receive treatment based on antibiotic susceptibility patterns (Chapter 284); recurrence is common in patients with lower CD4 cell counts and may require suppressive antibiotic therapy. For *Shigella* infection, especially in MSM, antibiotics (Chapter 285) are indicated both to shorten the duration of symptoms and potentially prevent spread to others. Patients with asymptomatic *Entamoeba histolytica* found on stool microscopy or by

PCR should receive a luminal agent such as paromomycin to clear the cysts (Chapter 323).

If no cause is found but diarrhea persists, particularly if the CD4 count is less than 50 cells/μL, colonoscopy should be performed for direct visualization and biopsy of any lesions seen. Cytomegalovirus is typically treated with a 2- to 3-week induction course of ganciclovir (5 mg/kg intravenously twice daily) followed by oral valganciclovir (900 mg daily orally) until immune reconstitution is achieved and therapy is no longer needed.

HEPATIC

Liver disease remains a major cause of morbidity and mortality in patients with HIV in part due to the high prevalence of chronic coinfection with hepatitis B and hepatitis C resulting from shared transmission routes. Acute fulminant liver failure has occurred in patients with chronic active hepatitis B (Chapter 135) in the setting of the immune reconstitution inflammatory syndrome, even while on antiretroviral therapy that is also active against hepatitis B. People with HIV and hepatitis B should have antiretroviral medication regimens that include drugs active against both viruses. Autoimmune hepatitis (Chapter 135) is uncommon in HIV infection but has been reported.

The prevalence of nonalcoholic fatty liver disease (Chapter 138) is about 35% in patients who are living with HIV and do not have hepatitis C coinfection.[20] Progression to nonalcoholic steatohepatitis with frank inflammation and fibrosis or cirrhosis appears to occur at a higher rate than in the HIV-uninfected population.

BILIARY

Atazanavir has been associated with cholelithiasis and benign indirect bilirubinemia. HIV cholangiopathy, a result of biliary strictures from opportunistic pathogens such as microsporidium or cytomegalovirus, is rarely seen in the current era of effective antiretroviral therapy.

ANORECTAL

Proctitis or proctocolitis as a result of the common sexually transmitted pathogens (Chapter 264) *Neisseria gonorrhoeae, Chlamydia trachomatis,* herpes simplex virus, and syphilis may present in the same fashion as in the general population. However, lymphogranuloma venereum (Chapter 294), formerly seen primarily in temperate regions of the world as an ulcerative proctitis with subsequent painful inguinal lymphadenopathy and occasional rupture and drainage, is seen in the population of men who have sex with men (MSM) throughout the world, predominantly in MSM with HIV. Ulcerative disease from herpes simplex virus is common; cytomegalovirus and recurrent multiple aphthous ulcerations are seen less outside of advanced HIV disease but are important causes of morbidity in patients with CD4 counts of less than 50 cells/μL. HPV-related condyloma and anal dysplasia can occur at all stages of disease and can lead to anal cancer (see Non-AIDS-Defining Cancers). Anal fissures (Fig. 131-4), fistulas (Fig. 131-3), and perirectal abscesses are also more common in MSM (Table 359-2).

DERMATOLOGIC MANIFESTATIONS OF HIV

Skin conditions may be the first presenting sign of HIV infection, and up to 90% of patients with HIV develop a skin complication in the course of their disease.[21] Skin manifestations (Table 359-3) can be broadly divided into infectious, noninfectious, and inflammatory conditions, with presentations typically similar to what is seen in immune-competent individuals but at times more severe, prolonged, and possibly requiring more intensive therapy (see Chapters 403 to 409). Some cutaneous manifestations such as oral candidiasis and secondary syphilis should always prompt consideration of HIV testing (Table 359-4).

PRURITUS WITH AND WITHOUT PHYSICAL FINDINGS

Pruritus, which is the most common dermatologic complaint in the modern antiretroviral therapy era, often has a significant impact on quality of life. Common conditions such as xerosis, seborrheic dermatitis, fungal infections, and eczema may present in a more persistent refractory fashion in patients with HIV, even at higher CD4 cell counts, and may also represent the presenting manifestation in undiagnosed HIV. Pruritus may be present with no other findings on physical examination, so a diligent search for underlying disease should be undertaken (Chapter 403).

SKIN MALIGNANCIES

People with HIV share the typical risk factors for squamous cell and basal cell carcinomas (Chapter 188) as HIV-uninfected individuals but get these cancers at a two- to three-fold higher rate, at a younger age, in multiple locations, and sometimes in areas of the skin that are not exposed to the sun.[22] Bowen disease (Chapter 188) and bowenoid papulosis, which can occur in the genital area of young sexually active males and females, present as raised, erythematous plaques associated with HPV infection. Malignant melanoma occurs at an increased frequency and is usually more advanced and aggressive in patients living with HIV. Merkel cell tumors can present at a younger age than is typically seen in immunocompetent, older, light-skinned individuals. Associated with Merkel polyomavirus, it presents as a rapidly enlarging, painless, nodular flesh-toned or bluish lesion and requires a high index of suspicion and biopsy for diagnosis. Treatment of melanoma and nonmelanoma skin cancers in people with HIV is similar to that in HIV-uninfected individuals (Chapter 188).

Kaposi sarcoma (Fig. 359-2) is discussed earlier in this chapter.

INFLAMMATORY CONDITIONS

Eosinophilic pustular folliculitis (Fig. 359-7), which can be intensely pruritic, presents as multiple papular or pustular lesions arising from hair follicles, usually on the face, neck, trunk, and upper extremities, although it may be found anywhere on the body. Papular pruritic eruption of HIV is most common in sub-Saharan Africa and is thought to be caused by an exaggerated response to arthropod bites.

Psoriasiform dermatitis and frank psoriasis (Chapter 405; see Figs. 405-13 to 405-15) with or without arthritis can occur in HIV and may be quite severe, particularly in patients with more advanced immunosuppression. It is thought to have a much higher incidence in HIV and also involves the joints in a larger percentage of patients compared with patients without HIV. It is sometimes the presenting condition of undiagnosed HIV. The ideal treatment is antiretroviral therapy because the disease will often improve or go into remission with reconstitution of the immune system.

Seborrheic dermatitis (see Fig. 405-7), presenting as reddish orange plaques with scale, typically affecting the scalp, forehead, eyebrows, nose, and cheeks, has a much higher incidence in patients with HIV than in the general population. Atopic dermatitis also has a higher incidence in patients with HIV. Photodermatitis, which presents as pruritic plaques in sun-exposed areas, is especially common in patients who are on photosensitizing drugs, such as trimethoprim-sulfamethoxazole or dapsone, for *Pneumocystis* prophylaxis.

Prurigo nodularis, which is almost exclusively seen in very advanced HIV disease, is distinguished by nodular hyperpigmented lesions and intense pruritus in skin-exposed areas. The pruritus and the skin lesions of prurigo nodularis can respond to dupilumab (600 mg subcutaneously and then 300 mg every other week)[A3] or to nemolizumab (0.5 mg/kg subcutaneously at baseline, week 4, and week 8),[A4] but only the former is approved by the U.S. Food and Drug Administration for this purpose.[23] Porphyria cutanea tarda (Chapter 194) has a strong association with chronic HCV infection.

OTHER

Diffuse alopecia and alopecia areata (Chapter 409) may occur in people living with HIV and have been seen in association with some protease inhibitors; they may be either transient or persistent. Discoloration of the nailbeds may be present with zidovudine use. Hyperpigmented areas, usually on the palms and soles and almost exclusively in Black patients, may rarely develop as a result of emtricitabine therapy.

MUSCULOSKELETAL MANIFESTATIONS OF HIV

Patients with acute HIV infection often have myalgias and arthralgias as part of their presenting complaints, but these symptoms are typically nonspecific and self-limited. HIV arthritis is a self-limited, large-joint, seronegative sterile arthritis. In Africa, the incidence of asymmetrical seronegative arthritis, sometimes termed painful articular syndrome, seems to have increased, primarily in patients naïve to antiretroviral therapy.

Another clinical entity, seen more commonly in advanced disease, is pyomyositis, which is usually caused by *S. aureus* but occasionally by other organisms. Pyomyositis typically starts as localized muscle pain, progressing to swelling, fever, and induration, and then subsequently the development of one or more abscesses in large striated muscle. The bacteria are believed to seed traumatized muscle.

TABLE 359-2 GASTROINTESTINAL MANIFESTATIONS OF HUMAN IMMUNODEFICIENCY VIRUS (HIV) INFECTION

ORAL	PRESENTATION/DIAGNOSIS	TREATMENT
Candidiasis	Clinical appearance (see Fig. 359-4) Culture and sensitivities rarely for suspected resistance	Nystatin suspension or clotrimazole troches; see Chapter 310: oral fluconazole for extensive disease; discontinue when resolved to avoid resistance
Oral hairy leukoplakia	Clinical appearance (see Fig. 359-3)	See Chapter 393: No specific treatment other than ART
Kaposi sarcoma	Clinical appearance (see Fig. 359-5) Biopsy indicated if diagnosis not established previously May have disease elsewhere	ART, intralesional injection Chemotherapy or radiation sometimes indicated for extensive cutaneous or concomitant visceral disease
Aphthous ulcerations	Clinical appearance (see Fig. 359-6) Biopsy	Topical steroids; oral steroids or thalidomide for extensive or refractory ulcers (see Chapter 345)
HSV	Clinical appearance Culture	Oral antivirals
Parotid enlargement	Clinical appearance Imaging may be helpful	ART
ESOPHAGEAL	**PRESENTATION/DIAGNOSIS**	**TREATMENT**
Candidiasis	Dysphagia, odynophagia Clinical appearance and brushings at EGD	See Chapters 124 and 310: Oral azoles
HSV	Odynophagia Biopsy at EGD	See Chapters 124 and 345: Oral antivirals
CMV	Odynophagia Biopsy at EGD	See Chapter 124: Ganciclovir, valganciclovir
Aphthous Ulcerations	Odynophagia Biopsy at EGD	Oral steroids and/or thalidomide
GASTRIC	**PRESENTATION/DIAGNOSIS**	**TREATMENT**
Infectious (CMV, MAC, *Candida*)	Advanced disease; nausea, dyspepsia Endoscopy	ART Treat underlying organism (see Chapters 347, 300, 310)
GERD, gastritis, peptic ulcer disease	Dyspepsia, abdominal pain, bleeding Endoscopy	PPI (Table 124-1) or H2RA (with attention to drug-drug interactions with ART) (see Chapters 124 and 125)
SMALL BOWEL	**PRESENTATION/DIAGNOSIS**	**TREATMENT**
Infectious (*Cryptosporidium, Microsporidium, Cyclospora, Giardia*)	Advanced disease Watery large-volume diarrhea, bloating Stool studies	Primarily immune reconstitution with ART (see Chapters 321 and 324)
Enteropathy	Weight loss, bloating, diarrhea Exclude other causes	Primarily immune reconstitution with ART Antimotility agents (see Table 123-3), nutritional support
LARGE BOWEL	**PRESENTATION/DIAGNOSIS**	**TREATMENT**
CMV	Crampy abdominal pain, small volume diarrhea Advanced disease Colonoscopy with biopsy	See Chapter 347: Ganciclovir, valganciclovir, ART
Clostridioides difficile	Crampy abdominal pain, diarrhea, fever Stool studies	See Chapter 271: Oral vancomycin
LIVER	**PRESENTATION/DIAGNOSIS**	**TREATMENT**
Chronic hepatitis B and C	Transaminitis Serologies and PCR for viremia	See Chapter 135
NAFLD, NASH	Elevated aminotransferase levels Imaging, liver biopsy	See Chapter 138
Drug toxicity	Elevated aminotransferase levels	Withdrawal or change of offending agent (see Chapter 136)
PANCREAS	**PRESENTATION/DIAGNOSIS**	**TREATMENT**
Pancreatitis	Mid-epigastric pain, nausea, vomiting, metabolic derangements	See Chapter 130
BILIARY	**PRESENTATION/DIAGNOSIS**	**TREATMENT**
Drug (atazanavir)	Indirect hyperbilirubinemia	Benign, can change ART based on patient concerns
Cholangiopathy (infectious)	Advanced disease Elevated alkaline phosphatase, RUQ discomfort ERCP	ART
ANORECTAL	**PRESENTATION/DIAGNOSIS**	**TREATMENT**
Proctitis (chlamydia, syphilis, gonorrhea)	Pain, discharge, can be asymptomatic Serologies, nucleic acid testing	See Chapter 264
Ulcerative disease	HSV; culture In advanced disease CMV, aphthous; biopsy	See Chapters 345 and 347
Anal dysplasia	Asymptomatic; Pap, HRA with acetic acid stain and biopsy	See Chapter 131
Condyloma	Clinical appearance Biopsy	See Chapters 131 and 344
Fissure, fistula, abscess	Pain, drainage	See Chapter 131

ART = antiretroviral therapy; CMV = cytomegalovirus; EGD = esophagogastroduodenoscopy; ERCP = endoscopic retrograde cholangiopancreatography; GERD = gastroesophageal reflux disease; H2RA = H_2 receptor antagonists; HBV = hepatitis B virus; HCV = hepatitis C virus; HRA = high-resolution anoscopy; HSV = herpes simplex virus; IRC = infrared cautery; MAC = *Mycobacterium avium* complex; NAFLD = nonalcoholic fatty liver disease; NASH = nonalcoholic steatohepatitis; NPO = nothing by mouth; PCR = polymerase chain reaction; PPI = proton pump inhibitor; RUQ = right upper quadrant; TAF = tenofovir alafenamide.

TABLE 359-3 APPROACH TO CUTANEOUS LESIONS ASSOCIATED WITH HUMAN IMMUNODEFICIENCY VIRUS (HIV) INFECTION

LOCALIZED VS. GENERALIZED	LESION DESCRIPTION	DIFFERENTIAL DIAGNOSIS	CLINICAL FINDINGS
Localized skin findings *Can be generalized in immunosuppressed patients	Papules and nodules	Molluscum contagiosum	2- to 3-mm skin-colored umbilicated papules
		Ecthyma	Eroded, ulcerated papules with overlying crust
		Furuncle/carbuncle	Inflammatory papules and nodules, tender
		Bacillary angiomatosis	Friable, red, purple, or flesh-colored papules and nodules
		Verruca vulgaris	Verruciform hyperkeratotic papules
		Condylomas	Skin-colored, often pedunculated verruciform papules
		Prurigo nodularis	Excoriated, often hyperkeratotic papules and nodules
		Squamous cell carcinoma	Erythematous papules with variable hyperkeratosis, crusting, and ulceration
		Basal cell carcinoma	Pearly papules with overlying telangiectasias
		Kaposi sarcoma	Red-to-brown macules, papules, and plaques
	Plaques	Cellulitis	Erythematous plaques; increased warmth, tenderness
		Intertrigo	Erythematous thin papules and plaques with superficial erosions and fine scale; skin folds
		Thrush	White plaque of the oral mucosa, can be removed by scraping
		Oral hairy leukoplakia	Nonpainful white plaque along the lateral tongue
		Other fungal or bacterial infections	Variable cutaneous presentation
		Seborrheic dermatitis	Erythematous plaques with greasy scale in a seborrheic distribution
		Psoriasis	Well-demarcated erythematous plaques with silvery scale, often on extensor surfaces
	Vesicles and bullae	Bullous impetigo	Superficial vesicles, erosions, honey-colored crust
		Folliculitis	Follicular pustules and papules
		Herpes simplex	Grouped vesicles on erythematous base
		Herpes zoster	Grouped vesicles in dermatomal distribution
		Bullous tinea or candida	Predominantly erosions and few superficial vesicles on erythematous background
	Exanthem ± enanthem	Viral diseases, acute HIV exanthem	Morbilliform macular eruptions, often associated with systemic symptoms
Generalized skin findings	Exanthem ± enanthem	Drug reaction	Often generalized morbilliform macular eruptions
	Erythema with desquamation	Stevens-Johnson syndrome, toxic epidermal necrolysis	Erythematous to dusky macules and patches; check for mucosal involvement
	Papules, plaques	Pruritic papular eruption	Widespread skin-colored to erythematous papule with signs of excoriation
	Erythema with scaling	Scabies	Widespread hyperkeratotic, scaly papules; severe pruritus
		Eczema/dermatitis, xerosis	Erythematous scaly papules and plaques, often worse in the winter

From Altman K, Vanness E, Westergaard RP. Cutaneous manifestations of human immunodeficiency virus: a clinical update. *Curr Infect Dis Rep*. 2015;17:464.

TABLE 359-4 CUTANEOUS MANIFESTATIONS THAT SHOULD PROMPT CONSIDERATION OF TESTING FOR HUMAN IMMUNODEFICIENCY VIRUS INFECTION

Oral candidiasis
Secondary syphilis
Psoriasis
Seborrheic dermatitis
Viral exanthem with or without enanthem
Herpes zoster (disseminated)

Diffuse infiltrative lymphocytosis syndrome appears to be unique to people with HIV. A Sjogrën-like syndrome, it is thought to be caused by an oligoclonal expansion of circulating $CD8^+$ lymphocytes. It results in an infiltrative disease that more commonly involves the parotids and lung, but many cases have visceral infiltration as well. The disease has decreased significantly with the introduction of effective antiretroviral therapy. Rhabdomyolysis (Chapter 99) in people with HIV has been seen with raltegravir and certain protease inhibitors with a higher risk when used in conjunction with statin therapy due to inhibition of the cytochrome pathway by the antiretroviral drugs and resultant higher circulating levels of the statin.

Osteonecrosis (Chapter 229), or avascular necrosis, most commonly affects the hip, with a higher incidence in people with HIV than in the general population. Patients may present with hip pain that radiates to the groin, and symptoms

FIGURE 359-7. Eosinophilic pustular folliculitis.

are typically progressive. Osteonecrosis may be present radiographically before the onset of symptoms.[24] Definitive treatment involves total hip arthroplasty.

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360 RETROVIRUSES OTHER THAN HUMAN IMMUNODEFICIENCY VIRUS

CHARLES R.M. BANGHAM AND LUCY B.M. COOK

DEFINITION

The human T-lymphotropic virus (HTLV) family has four members: HTLV-1, HTLV-2, HTLV-3, and HTLV-4. HTLV-1 causes two distinct types of disease: adult T-cell leukemia/lymphoma and several chronic inflammatory conditions, most notably HTLV-1-associated myelopathy/tropical spastic paraparesis (HAM/TSP).[1] HTLV-2 rarely causes neurologic symptoms and does not cause malignant disease. No disease associations have been established with HTLV-3 or HTLV-4.

The Pathogens

Within the taxa of RNA reverse-transcribing viruses, the HTLV viruses, along with bovine leukemia virus, are classified in the subfamily Retroviridae within the genus *Deltaretrovirus* (formerly termed *Oncovirus*). The molecular structure of these viruses distinguishes them from the other group of complex human retroviruses, the human immunodeficiency retroviruses HIV-1 and HIV-2 (Chapter 354), which are members of the genus *Lentivirus*. Both deltaretroviruses and lentiviruses are capable of prolonged asymptomatic infection. In vitro, however, HIV-1 and HIV-2 have cytopathic effects on human T cells, whereas HTLV-1 and HTLV-2 are noncytolytic and are capable of transforming T cells into immortalized cell lines. The HTLVs are diploid single-stranded RNA viruses that replicate through cDNA, which is a proviral intermediate, by reverse transcriptase, which is a viral polymerase.

EPIDEMIOLOGY

HTLV-1 is widely disseminated worldwide and is estimated to infect 5 to 10 million persons, with the aggressive T-cell malignant neoplasm adult T-cell leukemia/lymphoma developing in 2 to 6% and chronic inflammatory diseases, mainly HAM/TSP, developing in another 1 to 5% in their lifetime.[2] Similar to HIV, molecular epidemiology suggests that the four major subtypes of HTLV identified in humans arose from separate interspecies transmission from simians to humans.

HTLV-1 has four major geographic subtypes: cosmopolitan subtype A; central African subtype B; Australo-Melanesian (Papua New Guinea, Melanesia, and Australian aborigines) subtype C; and central African/Pygmies subtype D. Central Africa also carries a few rare subtypes (E, F, G). Within the cosmopolitan group are four subgroups: transcontinental, Japanese, West African, and North African. The virus from Australo-Melanesia differs in its genome sequence from the Japanese and African strains by 5 to 10%, owing to independent evolution of the virus in these populations separated for tens of thousands of years. The genetic stability of HTLV-1 in comparison with HIV-1 reflects the observation that HTLV persists in the host mainly by proliferation of cells that contain the HTLV-1 provirus rather than infection of new cells. The HTLV subtypes differ phylogenetically by approximately 30 to 40% among each other.

HTLV-1 is not present in all human populations but rather clusters geographically: southern Japan; Melanesia; Australia (in aboriginal peoples); western, central, and southern Africa and, by the slave trade from Africa, the Caribbean and the United States in Black Americans; Central and South America; and the Mashhad region of Iran. HTLV-1 infection in Western Europe is predominantly linked to migration patterns, but the high prevalence of HTLV-1 infection in Romania remains unexplained. HTLV-1 is found in some indigenous populations of North America as well as in persons who migrated from the endemic regions. There is evidence of HTLV-1 infection in the Indian subcontinent and the southeastern seaboard of China, but the extent is uncertain. HTLV-2 is found in Native American people throughout North, Central, and South America, as well as in West Africa. HTLV-2 infections also occur in the United States and Europe in injection drug users, in whom the virus is spread by needle sharing and other injection practices as well as by sexual contact.

HTLV-3 and HTLV-4 are closely related viruses that were originally detected in Cameroon in humans who were bushmeat hunters. They have been detected in only a few persons, and their extent in West Africa is not yet known.

Routes of Transmission

HTLV-1 is transmitted sexually, by breast-feeding, by transfusion, by injection drug use, and by solid organ transplantation (Table 360-1).

Sexual Transmission

Sexual transmission of HTLV-1 from male to female, female to male, and male to male has been documented. HTLV-1 is almost exclusively cell associated: transmission between individuals requires transfer of infected lymphocytes, and cell-free blood products are not infectious. Coincidental infection with other sexually transmitted infections, particularly those associated with ulcerative and inflammatory genital lesions, amplifies the risk for transmission. In HTLV-1 infection, elevated viral load is linked to heightened transmission. In regions endemic for the virus, there is a characteristic age-dependent rise in HTLV-1 seroprevalence. This increase first becomes evident in the adolescent years; it is steeper in women than in men and continues in women after 40 years of age, whereas rates in men plateau around the age of 40 years. This pattern reflects more efficient male-to-female transmission. For HTLV-2, the rates for both genders are equal, suggesting that the kinetics of transmission differ between the two viruses.

Transmission by Breast-feeding

Transmission of HTLV-1 through breast-feeding is more efficient than in utero or perinatal transmission. Major risk factors that increase the efficiency of

TABLE 360-1 TRANSMISSION OF HTLV-1 AND HTLV-2

MODE OF TRANSMISSION	HTLV-1	HTLV-2
MOTHER TO INFANT		
Transplacental	Yes	Not known
Breast milk	Yes	Probable
SEXUAL		
Male to female	Yes	Yes
Female to male	Yes	Yes
Male to male	Yes	Not known
PARENTERAL		
Blood transfusion	Yes	Yes
Injecting drug use	Yes	Yes
COFACTORS		
Ulcerative genital lesions	Yes	Not known
Cellular transfusion products	Yes	Yes
Sharing of "works"*	Yes	Yes
ELEVATED VIRUS LOAD		
Mother to infant	Yes	Not known
Heterosexual	Yes	Not known

*Intravenous paraphernalia, such as needles.
HTLV = human T-lymphotropic virus.

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HTLV = human T-lymphotropic virus.

ABSTRACT

Within the family of Retroviridae, the human T-lymphotropic viruses (HTLVs) belong to the genus *Deltaretrovirus*, whereas the human immunodeficiency viruses (HIVs) are in the genus *Lentivirus*. Lentiviruses are cytopathic to human T cells, but HTLVs are noncytopathic. HTLV is transmitted directly from cell to cell via the virologic synapse and subsequently maintained in the host by persistent proliferation of cell clones that harbor integrated provirus. Of the four HTLVs, HTLV-1 is a significant pathogen that causes adult T-cell leukemia and HTLV-associated myelopathy/tropical spastic paraparesis (HAM/TSP). Between 5 and 10 million people are infected worldwide, with a 2 to 6% lifetime risk of adult T-cell leukemia and a 1 to 5% lifetime risk for HAM/TSP. Transmission occurs by sexual exposure, perinatally, and by exposure to cellular blood products. Adult T-cell leukemia represents a malignant expansion of an HTLV-1–infected T-cell clone. Acute adult T-cell leukemia is highly aggressive, with a median survival of only 12 months. HAM/TSP is a chronic progressive inflammatory neurologic syndrome characterized by degeneration of the lateral and posterior columns, with loss of both myelin and axons. HAM/TSP is more frequent among females and progresses inexorably; treatment is largely symptomatic. HTLV-2 is occasionally linked to a neurologic syndrome resembling HAM/TSP. HTLV carriers should be reassured that their infection is not due to HIV. Carriers are excluded from blood donation, discouraged from breast-feeding, and encouraged to use condoms.

KEYWORDS

HTLV
adult T-cell leukemia
ATL
HTLV-associated myelopathy/tropical spastic paraparesis
HAM/TSP
retrovirus
T-cell malignancy

transmission include high proviral loads and increased duration of breast-feeding (>6 months). On average, 20% of infants breast-fed by HTLV-1-positive mothers seroconvert to HTLV-1, whereas only 1 to 2% of formula-fed infants become infected. By contrast, in utero and perinatal transmission accounts for virtually all mother-to-child HIV-1 transmission in the West, and breast-feeding accounts for an additional 15 to 20% of infant HIV infection in Africa. HTLV-2 is detectable in breast milk, and, as with HTLV-1, breast-feeding accounts for many childhood infections.

Transfusion, Solid Organ Transplantation, and Injection Drug Use

Parenteral transmission, through unscreened transfusion, solid organ transplantation, or injection drug use, is a significant source of HTLV infection. Among U.S. blood donors who are confirmed to be HTLV positive, the major risk factors are intravenous drug use, birthplace in parts of the Caribbean or Japan where the virus is endemic, and sexual contact with a person with this profile.

In the United States, more than 50% of HTLV infections among screened potential blood donors are due to HTLV-2, and effective screening can eliminate transfusion-related infection. By comparison, HTLV-1 predominates in other countries where HTLV infections are present. Among injection drug users, most HTLV infections also are due to HTLV-2.

Both HTLV-1 and HTLV-2 are transmitted only by direct cell-to-cell contact, through a specialized structure called a virologic synapse, whereas HIV-1 is transmitted either through a virologic synapse or by cell-free virus in plasma or plasma products. Approximately 50% of the recipients of cellular products of HTLV-1– or HTLV-2–positive blood seroconvert, compared with more than 95% for HIV-1.

The only documented illness linked to HTLV-1 or HTLV-2 transfusion-associated transmission is the HTLV-associated demyelinating neurologic syndrome HAM/TSP. Leukemia has not been associated with transfusion of HTLV-positive blood. Solid organ transplantation from HTLV-1–infected donors is associated with a high rate of transmission and rapid onset and progression of HAM/TSP.

Other Means of Infection

Casual contact, without sexual contact or exposure to cellular blood contents, is not a source of infection. There are limited data on health care and laboratory workers who experience a needlestick or skin or mucous membrane exposure. However, the risk of infection should be assessed from the clinical history, in particular of sexual contacts and blood transfusions, and potential seroconversion should be monitored.

Coinfection with HIV

Coinfection with HTLV-1 and HIV-1 appears to increase the progression to acquired immunodeficiency syndrome (AIDS) through unexplained mechanisms, possibly related to the cell-proliferative effects of HTLV-1 on HIV-1–infected T cells and/or coreceptor expression modulating CD4 cell permissiveness. Elevated CD4 counts due to HTLV-1 in patients with HIV/HTLV-1 coinfection can underestimate the degree of immune suppression. HAM/TSP and adult T-cell leukemia/lymphoma can occur in coinfected patients, but the clinical manifestations of HIV/HTLV coinfection in the era of early and fully suppressive antiretroviral therapy are poorly understood.

PATHOBIOLOGY

Virology

The HTLV viruses, which are single-stranded RNA viruses that contain a diploid genome, replicate through a DNA intermediary that integrates into the genome of the target T cell as a provirus, thereby resulting in lifelong infection. HTLV-1 is approximately 100 nm in diameter and has a thin, electron-dense outer envelope and an electron-dense, roughly spherical core. The total provirus genome contains 9032 nucleotides with two identical sequences termed *long terminal repeats* (LTRs) at the 5′ and 3′ ends of the genome, which contain regulatory elements that control virus expression and virion production. The retroviral structural genes (*gag* and *pol*) code for large overlapping polyproteins that are later processed into functional peptide products by virally encoded protease and cellular proteases. The viral genes are *gag* (group-specific antigen), *pol* (polymerase/integrase/protease), and *env* (envelope). In addition, HTLV-1 has a series of regulatory genes, *tax* and *rex*, and several smaller gene products that regulate infection and virus expression. A single viral gene (basic leucine zipper factor [*HBZ*]) is encoded by the minus strand of the HTLV-1 provirus and transcribed from the 3′ LTR. Tax protein plays a central role in enhancing the transcription of viral and cellular gene products that promote viral replication and transformation of human T lymphocytes. Through binding to transcription factor complexes, Tax promotes transcriptional activation of the viral genome, and by binding to key regulatory proteins of the NF-κB signaling pathway, Tax promotes cell activation and disease pathogenesis. Through binding to regulatory enhancers of the cell and through abrogation of key suppressor genes, Tax initiates the immortalization of the infected T cells. However, the *tax* gene is susceptible to genetic mutations and is expressed in only about 60% of adult T-cell leukemia/lymphoma cases. The viral protein Rex stabilizes viral mRNA and is essential for export of full-length Gag/Pol and single-spliced Env mRNA from the nucleus to the cytoplasm. *HBZ*, the only viral gene consistently expressed in all adult T-cell leukemia/lymphoma patients, appears to be essential for persistent HTLV-1 infection. HBZ inhibits the Tax-mediated activation of viral gene transcription through the 5′ LTR, which ultimately represses expression of viral proteins while simultaneously promoting the proliferation and survival of infected cells. A typical person infected with HTLV-1 carries between 10,000 and 100,000 infected T-cell clones, which appear to survive for the lifetime of the host. Most (95%) infected cells are helper ($CD4^+$) T cells; 5% of the load is carried in cytotoxic ($CD8^+$) T cells. The proviral load (the percentage of infected mononuclear leukocytes in the blood), which frequently exceeds 5%, is limited by the host's cytotoxic T-lymphocyte response. Most HTLV-1–specific cytotoxic T lymphocytes recognize the Tax protein, but it is recognition of the HBZ protein that is associated with efficient control of the virus. An individual with an efficient cytotoxic T-lymphocyte response to HBZ has a lower proviral load and consequently a lower risk for both the inflammatory and malignant diseases caused by HTLV-1.

Viral Life Cycle

The initial stage of HTLV infection involves transmission from an infected lymphocyte in contact with an uninfected cell, through a specialized structure called the virologic synapse. After infection, the viral life cycle involves membrane fusion, followed by reverse transcription from an RNA template to a circular DNA provirus that is transported to the cell nucleus and integrated into the host genome. During the long chronic phase of infection, viral replication is primarily achieved through proliferation of proviral DNA-harboring cells rather than through repeated cycles of cell-to-cell infection. However, the virus is readily reactivated in infected lymphocytes when the cell experiences stress, and it then can be transmitted to other cells. For viral entry, HTLV-1 utilizes three distinct molecules for infection of activated T cells: heparan sulfate proteoglycans, neuropilin 1, and glucose transporter 1. HTLV-2, which infects almost exclusively $CD8^+$ T cells, also uses neuropilin 1 and glucose transporter 1 for entry into the cell. After uptake and uncoating, viral RNA is transcribed into double-stranded DNA by reverse transcriptase, an RNA-dependent DNA polymerase complexed to the RNA in the core of the virus particle. This double-stranded viral DNA is integrated into the host cell nucleus by the virally encoded integrase, thereby resulting in lifelong cell infection. The viral LTR elements are essential for integration and regulation of viral genome expression, which is controlled mainly by Tax, Rex, and HBZ.

Pathogenesis of Adult T-Cell Leukemia

HTLV-1 causes adult T-cell leukemia/lymphoma through a multistage process.[3] The clonal pattern of integration of HTLV-1 in the host genome in adult T-cell leukemia/lymphoma cells indicates that the disease is derived from a single transformed tumor cell that evolved from a virus infection *before* transformation rather than afterward as a passenger virus. The integrated HTLV-1 genome is incomplete in some cases of adult T-cell leukemia/lymphoma, but it always includes an intact *HBZ* gene. Tax is an oncoprotein that interacts with numerous cellular proteins to reprogram cellular processes to alter transcription, cell cycle regulation, DNA repair, and apoptosis, thereby allowing cells with potential carcinogenic mutations to survive and to escape cell death. HBZ is also a key oncogenic protein involved in modulating cellular pathways related to cell growth and survival, immune response, and T-cell differentiation.

Of the tens of thousands of long-lived HTLV-1–infected T-cell clones in each infected person, a small number usually reach a high abundance. This oligoclonal proliferation does not necessarily presage disease. In some healthy carriers, an abnormal degree of oligoclonal T-cell proliferation can be detected before it progresses to malignant transformation, but the abnormally expanded clones also may disappear spontaneously. Morphologically abnormal "flower cells" (Fig. 360-1), which represent T cells with deeply lobulated nuclei resembling adult T-cell leukemia/lymphoma cells, are seen on peripheral blood smears of healthy carriers. Increased numbers are detected in persons with high HTLV viral loads, but such cells do not necessarily imply that malignancy will develop.

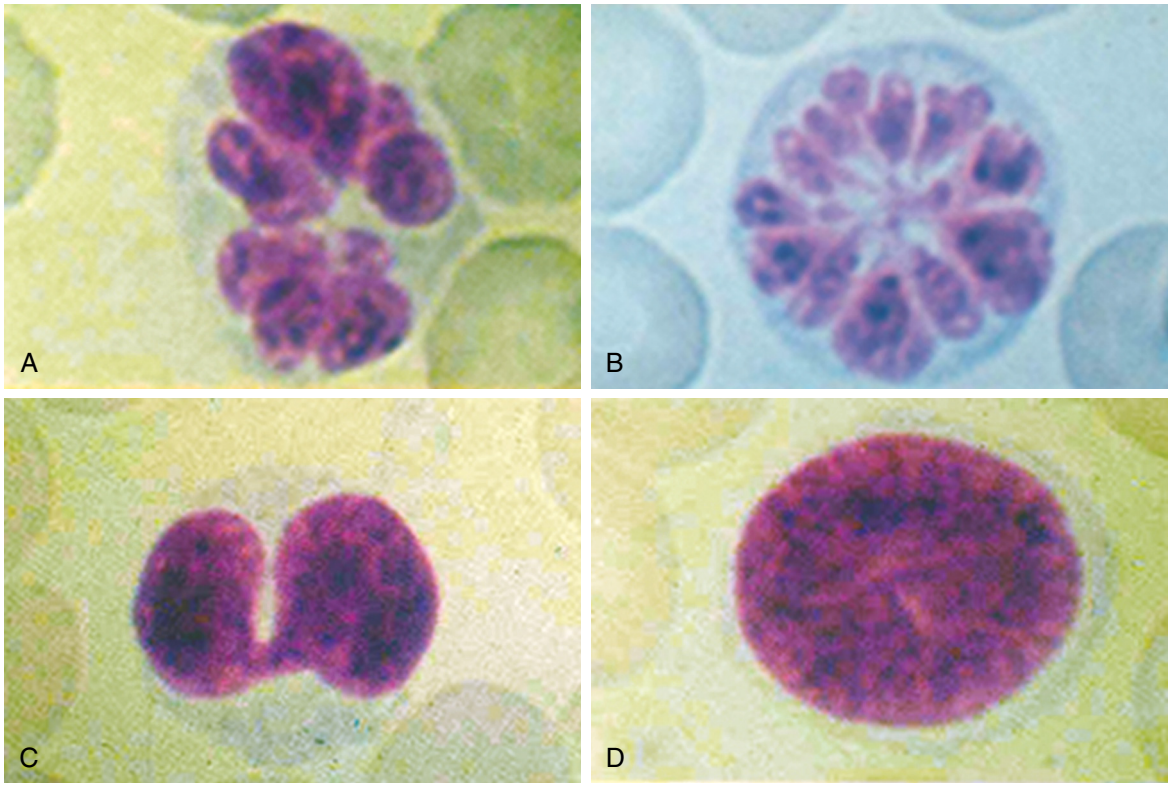

FIGURE 360-1. **Photomicrographs demonstrating the morphologic features of leukemic cells observed in different subtypes of adult T-cell leukemia/lymphoma (ATL). A and B, Polylobulated morphology of the acute type, with the highly characteristic "flower cell" shown in B. C, Typical cleaved cell seen in chronic-type ATL. D, Typical morphology of smoldering ATL. (Courtesy of K. Yamaguchi and K. Takatsuki.)**

Pathogenesis of Myelopathy/Spastic Paraparesis

HTLV-1–associated myelopathy is associated with a high proviral load that results from defective host immune responses. Local pathologic changes in neuronal tissue are thought to result from the toxic effects of cytokines released by HTLV-1–infected cells and by the local antiviral T cells. Intense mononuclear (mainly T-cell) infiltrates are associated with progressive neuronal loss. Lesions are found scattered throughout the central nervous system (CNS) but are particularly frequent in the spinal cord, where they cause most of the signs and symptoms of HAM/TSP.

ADULT T-CELL LEUKEMIA/LYMPHOMA

EPIDEMIOLOGY AND PATHOBIOLOGY

The cumulative lifetime incidence of adult T-cell leukemia/lymphoma in persons infected with HTLV-1 is between 2 and 6%, with about 2500 to 5000 cases per year in the approximately 5 to 10 million infected persons worldwide. Nearly all patients who develop this disease are infected in infancy because the disease has a long latency period.[4]

The disease typically presents in the fifth to seventh decade[5]; the risk is slightly higher in HTLV-1–infected males. The age-adjusted incidence rate of adult T-cell leukemia/lymphoma in the United States is 0.05 cases per 100,000 for men and 0.03 per 100,000 for women. In areas endemic for HTLV-1, such as southern Japan and the Caribbean Islands, adult T-cell leukemia/lymphoma accounts for half or more of adult lymphoid malignant neoplasms. Adult T-cell leukemia/lymphoma is rarely seen in children, but in one pediatric series, four of the eight patients shared a homozygous deletion in the *p16* gene locus, and deletion of exons 7 and 8 of *p53* was detected in another child, thereby suggesting that a genetic predisposition interacts with viral infection to accelerate the progression of the disease.

CLINICAL MANIFESTATIONS

The HTLV-1 disease with the highest incidence is adult T-cell leukemia/lymphoma (Table 360-2), which is a high-grade lymphoma (Chapter 171), usually of large, medium, or pleiotropic cell morphology and advanced clinical stage.[6] The acute form of adult T-cell leukemia/lymphoma, which accounts for about 55% of cases, is characterized by an aggressive, mature T-cell leukemia that presents with a high white blood cell count, hypercalcemia, and frequent cutaneous involvement. The lymphoma type (about 20% of cases) shares all the same features except for peripheral blood involvement. Other cases resemble T-prolymphocytic leukemia and are termed *chronic adult T-cell leukemia/lymphoma* (about 20% of cases). A subset of chronic cases with high serum levels of lactate dehydrogenase (LDH) and blood urea nitrogen (BUN) and low levels of albumin share the survival characteristics of the more aggressive acute and lymphoma types of adult T-cell leukemia/lymphoma, including a poor response to treatment. Smoldering adult T-cell leukemia/lymphoma (about 5%) may clinically resemble mycosis fungoides/Sézary syndrome (Chapter 171), with cutaneous involvement manifested as erythema or as infiltrative plaques or tumors (Fig. 360-2).[7] A long prodrome of signs (e.g., cutaneous rashes) and symptoms (e.g., fevers) is sometimes noted in chronic and smoldering adult T-cell leukemia/lymphoma before transformation to an acute or lymphoma type that is rapidly fatal.

DIAGNOSIS

The diagnosis should be considered in any adult who has a mature T-cell lymphoma and hypercalcemia or cutaneous involvement (or both) with characteristic "flower cells" (see Fig. 360-1). The diagnosis is established by testing of serum for HTLV-1 antibodies. Polymerase chain reaction (PCR) can detect infection, identify the type of virus, and quantify the proviral load. The cytologically distinct flower cell (a sine qua non of adult T-cell leukemia/lymphoma) is also seen in apparently healthy carriers. C-C chemokine receptor 4 (CCR4) is expressed on adult T-cell leukemia/lymphoma cells in more than 90% of cases.

TREATMENT

Treatment is based on the type of adult T-cell leukemia/lymphoma and its natural history, but it is also influenced by the patient's age and the presence of certain biomarkers.[8]

Smoldering and Chronic Adult T-Cell Leukemia/Lymphoma

About 50% of patients with symptomatic smoldering or chronic adult T-cell leukemia/lymphoma will transform to aggressive disease at a median of 18 months after diagnosis, and observational data suggest that 5-year survival is improved by the antiviral agent zidovudine (500 to 1000 mg/day in divided dosage) in combination with interferon-α (6 to 9 million units). In the absence of controlled trials, zidovudine and interferon are continued indefinitely or as long as they are tolerated.

TABLE 360-2 HUMAN T-LYMPHOTROPIC VIRUS (HTLV)-ASSOCIATED DISEASES

DIAGNOSIS	NATURE OF SYNDROME	STRENGTH OF ASSOCIATION
HTLV-1–ASSOCIATED DISEASES		
Adult T-cell leukemia/lymphoma	Aggressive lymphoproliferative malignant disease of mature T lymphocytes	Strong
HTLV-associated myelopathy/tropical spastic paraparesis (HAM/TSP)	Chronic progressive demyelinating syndrome of long motor tracts of spinal cord	Strong
Polymyositis (Chapter 248)	Degenerative inflammatory syndrome of skeletal muscles	Probable
Sporadic inclusion body myositis (Chapter 248)	Recently described HTLV-associated inflammatory muscle disease	Possible
Infective dermatitis	Chronic generalized eczema in adults and children; potential for preleukemia and immunodeficiency	Strong
Uveitis (Chapter 391)	Inflammatory infiltration of the uvea of the eye	Strong
Sjögren syndrome/keratoconjunctivitis sicca (Chapter 247)	Loss of tear production and dry eyes and dry mouth	Probable
Pulmonary lymphocyte alveolitis/cryptogenic fibrosing alveolitis	Pulmonary infiltrate involving T lymphocytosis in lungs of patients with HAM/TSP and HTLV uveitis	Possible
Bronchiectasis (Chapter 78)	Associated with repeated or chronic pulmonary infections	Probable
HTLV-associated arthritis	Large-joint polyarthropathy; rheumatoid factor positive, with HTLV-1-positive cells infiltrating the synovia	Probable
Immunodeficiency (Chapter 231)	Subclinical (e.g., decreased PPD response) or clinical (e.g., association with clinical tuberculosis and poor response to therapy for symptomatic strongyloidiasis; association of HTLV-1 with disseminated strongyloides infection [strongyloidiasis]); schistosomiasis	Probable
Miscellaneous clinical conditions	Case reports of small cell lung cancer with monoclonal HTLV-1 integration and invasive cervical cancer	Uncertain
HTLV-2–ASSOCIATED DISEASES		
HTLV-associated myelopathy	Increased numbers of cases among blood donors	Definite but rare

HAM = HTLV-1–associated myelopathy; PPD = purified protein derivative; TSP = HTLV-1–associated tropical spastic paraparesis.

Acute Lymphoma and Aggressive Chronic Adult T-Cell Leukemia/Lymphoma

A regimen of three successive drug combinations (vincristine, cyclophosphamide, doxorubicin, and prednisone [VCAP]; doxorubicin, ranimustine, and prednisone [AMP]; and vindesine, etoposide, carboplatin, and prednisone [VECP] [Chapter 171]) provides a 28% rate of progression-free survival at 1 year, a median survival time of 13 months, and a 3-year overall survival rate of 24%, but it is associated with hematologic and infectious complications when compared with less-intensive protocols. Allogenic stem cell transplantation is then recommended when feasible. Retrospective case series report a long-term survival rate of 20 to 40% after allogeneic hematopoietic stem cell transplantation (Chapter 163) but with significant treatment-related mortality.

Mogamulizumab (a humanized anti-CCR4 monoclonal antibody) has shown modest benefit for increasing remission rates when used initially or when used in combination with induction chemotherapy in patients who do not respond or relapse after conventional therapy, but it has not increased progression-free or overall survival.[A1] Other therapies, such as lenalidomide and histone deacetylase inhibitors, have shown some anecdotal promise. Whether chimeric antigen receptor T-cell (CART) therapy will be helpful remains unknown.

PROGNOSIS

The prognosis of adult T-cell leukemia/lymphoma is little changed in the past 35 years. In Japan, smoldering adult T-cell leukemia/lymphoma has a better prognosis, with a 4-year survival rate of about 50%,[9] although the presence of nodulotumoral skin lesions carries a poor prognosis. In the chronic favorable subset of patients with normal lactate dehydrogenase (LDH), blood urea nitrogen (BUN), and albumin levels, the 4-year overall survival is 60%, compared with 30% in patients with one or more of these abnormalities. In the aggressive forms of acute and lymphoma-type disease, median disease-free survival is 0.6 years and overall survival is only 0.8 years because of mortality linked to rapid tumor growth, infectious complications, and metabolic complications, especially hypercalcemia. Significant negative prognostic factors also include poor performance status at diagnosis, older age, advanced stage, and elevated serum LDH levels, as well as adverse genetic tumor profiles.[10] Death usually results from early relapse with rapid growth of tumor cells, hypercalcemia, bacterial sepsis, and opportunistic and other infectious complications.

FIGURE 360-2. Cutaneous involvement in adult T-cell leukemia/lymphoma. (From Tomita H, Fumihide O, Kuwatsuka S, et al. Attenuation of an adult T-cell leukemia lesion after treatment of a concomitant simplex infection: a case study. *Virol J*. 2012;9:224. http://www.virologyj.com/content/9/1/224. Creative Commons Attribution License.)

HTLV-ASSOCIATED MYELOPATHY/TROPICAL SPASTIC PARAPARESIS

EPIDEMIOLOGY AND PATHOBIOLOGY

HTLV-1 causes a chronic inflammatory neurologic syndrome known as HAM/TSP. The lifetime incidence is approximately half the rate for adult T-cell leukemia/lymphoma, with approximately 1 to 2% of carriers affected. HAM/

TSP is approximately two times more likely to develop in females. Most cases present in the 30- to 50-year age group, but cases have occurred in children as young as 3 years. The mean latency period before onset of HAM/TSP is shorter than that for adult T-cell leukemia/lymphoma. Both early-life and adult exposure can cause HAM/TSP, including infection with HTLV-1 by blood transfusion or solid organ transplantation. More than a dozen cases of myelopathy associated with HTLV-2 have been reported, but the occurrence is very infrequent compared with HTLV-1 carriers.

The pathogenesis results from trafficking of infected T cells into the perivascular areas and parenchyma of the spinal cord, where they cause astrocytosis. Chronic inflammation of spinal gray and white matter results in a progressive degeneration of the lateral and posterior columns, followed over time by loss of both myelin and axons in the anterior columns.

CLINICAL MANIFESTATIONS

Symptoms include stiff gait, spasticity, lower extremity weakness, back pain, urinary incontinence, impotence, and (rarely) ataxia. Patients typically present with a stiff gait that progresses (usually slowly) to increasing spasticity and weakness, with incontinence and impotence developing later, although bladder symptoms and low back pain may have been noted for months or years. In contrast to classic multiple sclerosis (Chapter 380), in which remissions may be seen, HAM/TSP is characterized by a relentlessly progressive course. Although lesions may occur anywhere in the CNS in HAM/TSP, degeneration of long motor neurons in the spinal cord accounts for the great majority of the signs and symptoms. Progression of the disease is usually slow, but some cases are acutely progressive, especially those associated with transfusion of HTLV-1–positive blood or transplantation-associated infection. Other manifestations of HTLV-1–associated "autoimmune" disease may be observed coincident with the neurologic syndrome.

DIAGNOSIS

The diagnosis is suspected in patients with unexplained loss of pyramidal tract functions and is confirmed by testing of sera for HTLV-1 antibodies. Oligoclonal immunoglobulin bands in the cerebrospinal fluid (CSF) of patients with HAM/TSP react to HTLV-1 antigens, and the CSF-to-serum ratio of HTLV-1 antibodies is greater than 1. PCR quantification of the HTLV-1 cell-associated provirus in the CSF is also diagnostic. Spinal cord lesions often appear hyperintense on T2-weighted magnetic resonance imaging.[11]

TREATMENT

Few randomized controlled trials on the therapy of HAM/TSP have been conducted. The strongest evidence of benefit is for corticosteroids: 1 g/day intravenous pulsed methylprednisolone for 3 to 5 days, followed by long-term low-dose (e.g., 5 mg daily) oral prednisolone as maintenance.[12] Higher doses of oral steroids may be required. A range of steroid-sparing therapies have been used, notably cyclosporine 2.5 mg/kg/day in divided doses, azathioprine 25 to 100 mg daily, salazopyrine 1000 to 1500 mg daily, and methotrexate 7.5 mg to 12.5 mg weekly with folinic acid recovery, but further studies are required to determine long-term efficacy. To date, there is no evidence to support the use of antiretroviral therapy alone, although the HTLV reverse transcriptase and integrase enzymes can be inhibited in vitro. There also is insufficient evidence to support the use of other therapies, although mogamulizumab has shown promising short-term results.[13]

PROGNOSIS

The prognosis of HAM/TSP is poor, with inexorable progression of neurologic deterioration. By 20 years, about 50% of patients are confined to a wheelchair.

OTHER HTLV-ASSOCIATED CONDITIONS

HAM/TSP is the archetype of a series of HTLV-1–induced inflammatory syndromes characterized by a high viral load and mononuclear cell infiltration into the tissues. Examples include skeletal muscle polymyositis, sporadic inclusion body myositis, uveitis (30 to 40% of cases in areas endemic for HTLV), lung involvement (pulmonary lymphocytic alveolitis, cryptogenic fibrosing alveolitis, bronchiectasis), Sjögren syndrome/keratoconjunctivitis sicca, and infective dermatitis, which is a pediatric syndrome characterized by inability to clear bacterial skin infections. Carriers of HTLV-1 also have elevated rates of invasive cervical cancer, tuberculosis, parasitic infestations (especially strongyloidiasis), scabies, and refractory generalized eczema associated with infective dermatitis.[14] HTLV-1 infection is associated with a 1.6-fold increase in the age-adjusted risk of death from any cause.[15] One prospective study of HTLV-2–positive drug users showed an excess of asthma-related deaths and an increased frequency of skin and soft tissue infections.

PREVENTION

Patients often seek medical attention when confronted with a positive HTLV test result based on blood bank screening. Confirmation with Western blot or PCR is needed. Three key points should be explained to the patient. First, confirmed positive patients should be told that complications related to HTLV-1 infection are uncommon and that HTLV-2 hardly ever causes disease. Second, the patient should be counseled concerning the distinction between HTLV and HIV because the greatest fear that patients may experience is that they have the "AIDS virus." Third, it should be emphasized that these viruses are not easily transmitted, but the patient should be advised how transmission can be prevented. Guidelines for prevention include:

- Condoms should be used by discordant couples. However, given the relatively low frequency of sexual transmission per sexual encounter, couples who desire a pregnancy could time unprotected sexual intercourse to coincide with periods of maximal fertility. Such decisions require careful discussion between the physician and the patient.
- HTLV-1–/HTLV-2–positive mothers should be discouraged from breast-feeding to prevent mother-to-infant transmission, except in settings in which diarrheal disease in non–breast-fed infants presents an even higher risk for morbidity and mortality.
- Blood for donation should be screened before transfusion, and positive donors should be excluded from donating. All solid-organ transplant donors should be screened for HTLV-1 infection and the use of such organs carefully considered with the potential recipient, given the high rate of HAM/TSP.

Although postexposure prophylaxis may be of theoretical benefit, it is not routinely recommended because the efficacy of such prophylaxis for HTLV infection in humans has not been established. Vaccines containing whole virus and recombinant HTLV-1 envelope antigens have successfully prevented HTLV-1 infection in monkeys and in a rabbit model. However, a vaccine for humans is unlikely to be a high priority because of the relatively low incidence of clinical disease.

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For the General References and other additional features, please visit Elsevier eBooks+ at https://ebooks.health.elsevier.com.

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361 DELIRIUM AND CHANGES IN MENTAL STATUS

SHARON K. INOUYE

EVALUATION OF CHANGE IN MENTAL STATUS

Evaluation of change in mental status requires simultaneous efforts towards (1) establishing a diagnosis; (2) identifying potential etiologies and addressing life-threatening contributors; and (3) managing symptoms to ensure patient safety. A careful history should be obtained, not only from the patient but also from a reliable informant who knows the patient's baseline functional status and can describe the time course of the change. Many features can be used to differentiate among the different potential causes of mental status change (Table 361-1). For example, delirium starts suddenly with symptoms of inattention and confusion that fluctuate throughout the day. In contrast, dementia and Alzheimer disease (Chapter 371) are characterized by an insidious decline in cognitive function, often memory, with symptoms that are chronic and typically slowly progressive over time. An acute exacerbation of a psychiatric condition, such as depression or schizophrenia (Chapter 362), is usually heralded by days or weeks of worsening symptoms. A wide range of infections, traumatic, metabolic, toxic, vascular, and space occupying lesions can cause stupor (see Table 373-2).

A careful mental status examination, including an assessment of mood, affect, and cognition, can help establish a diagnosis.[1] A targeted additional evaluation (Table 361-2) can help identify potential causes of acute deterioration in mental status and guide further diagnostic and therapeutic interventions.

Ideally, cognitive testing should evaluate at least the general domains of attention, orientation, language, memory, visuospatial ability, and conceptualization. Attention should be assessed first by asking the patient to perform a task, such as repeating digits (normal span: more than five forward or more than three backward) or reciting the months backward (allow one error maximum); the remainder of cognitive testing would not be useful in an inattentive or delirious patient. If delirium is suspected (Table 361-3), specific instruments can be used to confirm a diagnosis (Fig. 361-1). If delirium is excluded, many brief, practical screening instruments are available for further cognitive testing. Historically, the most widely used instrument has been the Mini-Mental State Examination, a 19-item, 30-point scale that can be completed in 10 minutes. This copyrighted instrument now requires a per-use fee if the official version is used. Useful, brief alternative instruments include the Mini-Cog test (Table 361-4), which can be completed in less than 5 minutes, or the Montreal Cognitive Assessment (Fig. 361-2), which provides more detailed testing but which requires 15 to 20 minutes to complete; scores less than 26 indicate cognitive impairment. If dementia is suspected, further evaluation is required (Chapter 371). The 15-item short-form Geriatric Depression Scale (Table 361-5) can identify depressive symptoms requiring further evaluation (Chapter 362).

DELIRIUM

Delirium, which can occur at any age, is one of the most common presenting symptoms in acutely ill elders, in whom it is estimated to account for 30% of emergency evaluations. Mental status change often serves as a barometer of the underlying health of an older patient and is commonly the only symptom of serious underlying disease. A broad range of medical, neurologic, and psychiatric conditions can lead to delirium (Chapters 362 and 371). A systematic approach aids in the evaluation of suspected delirium at all ages (Fig. 361-3).

TABLE 361-2 EVALUATION OF AN ACUTE CHANGE IN MENTAL STATUS

Perform cognitive testing and determine baseline cognitive functioning
Obtain a comprehensive history and perform a physical examination, including a careful neurologic examination for focal deficits and a search for occult infection
Review the patient's medication list: check the side effects of all medications
Perform a laboratory evaluation (tailored to the individual): complete blood count, electrolytes, blood urea nitrogen, creatinine, glucose, calcium, phosphate, liver enzymes, oxygen saturation
Search for occult infection: physical examination, urinalysis, chest radiography, selected cultures (as indicated)
When no obvious cause is revealed after these steps, further targeted evaluation is considered in selected patients, as follows: Laboratory tests: magnesium, thyroid function, vitamin B_{12} level, drug levels, toxicology screen Arterial blood gas analysis: indicated in patients with dyspnea, tachypnea, any acute pulmonary process, or history of significant respiratory disease (Chapter 71) Electrocardiography: indicated in patients with chest or abdominal discomfort, shortness of breath, or cardiac history Cerebrospinal fluid examination: indicated when meningitis (Chapter 381) or encephalitis (Chapter 383) is suspected Brain imaging: indicated in patients with new focal neurologic signs or with a history or signs of head trauma (Chapter 368) Electroencephalography: useful in diagnosis of occult seizure disorder (Chapter 372) and in differentiating delirium from nonorganic psychiatric disorders (Chapter 362)

TABLE 361-1 DIFFERENTIAL DIAGNOSIS FOR PATIENTS PRESENTING WITH AN ACUTE CHANGE IN MENTAL STATUS

FEATURE	DELIRIUM	ALZHEIMER DISEASE	DEPRESSION	PSYCHOTIC DISORDERS
Onset	Acute, over days to hours	Insidious, over months to years	Slow	Acute or slow
Course	Fluctuating; can be worse at night	Chronic and progressive	Episodic; can occur singly, repeatedly, or chronically	Chronic, with exacerbations
Duration	Hours to months	Months to years	Weeks to months	Months to years
Descriptive features	Confusion and inattention	Memory loss	Sadness, anhedonia	Loss of contact with reality
Consciousness	Altered	Clear	Clear	Clear
Attention	Impaired	Normal, except in late stages	May be impaired	May be impaired
Orientation	Fluctuates	Poor	Normal	Normal
Speech	Incoherent	Mild errors	Normal, slow	Normal, pressured
Thinking process	Disorganized	Impoverished	Normal	Disorganized
Illusions and hallucinations	Common (often visual)	Rare, except in late stages	Not usually	Common
Perceptions	Altered	Altered or normal	Normal	Altered
Psychomotor changes	Yes	No	Yes	Yes
Reversibility	Usually	Rarely	Possibly	Rarely
Electroencephalogram	Moderate to severe background slowing	Normal or mild diffuse slowing	Normal	Normal

Modified from Fong TG, Tulebaev SR, Inouye SK. Delirium in elderly adults: diagnosis, prevention and treatment. *Nat Rev Neurol*. 2009;5:210-220.

ABSTRACT

Delirium, which is a clinical syndrome characterized as an acute disorder of attention and global cognitive functioning, is the most frequent complication of hospitalization for elders and is a potentially devastating problem at all ages. Delirium is associated with functional decline, institutionalization, increased mortality, and high health care expenditures. Delirium is often unrecognized despite sensitive methods for its detection. The development of delirium usually involves a complex interrelationship between a vulnerable patient with pertinent predisposing factors and exposure to noxious insults or precipitating factors. Evaluation of suspected delirium should begin with a comprehensive history and physical examination, as well as brief cognitive screening, using a validated delirium tool. The most effective strategy to reduce delirium is primary prevention, including strategies designed to improve orientation, provide therapeutic activities, increase mobilization, enhance sleep with nonpharmacologic interventions, optimize vision and hearing, and manage dehydration. Preoperative medical consultation and lighter anesthesia also can reduce postoperative delirium. Pharmacologic approaches generally are not very effective for either prevention or treatment of delirium, and they should be reserved for patients whose symptoms may result in interruption of essential medical therapies or may endanger the safety of the patient or other persons.

KEYWORDS

delirium
acute confusional state
encephalopathy
multifactorial geriatric syndrome
confusion assessment method
multicomponent delirium prevention strategies

DEFINITION

Delirium is a clinical syndrome (see Table 361-3) that is characterized as an acute disorder of attention and cognitive function. Delirium is the most frequent complication of hospitalization for elders, is a potentially devastating problem at any age, and is often unrecognized despite sensitive methods for its detection. The Confusion Assessment Method and abbreviated versions of it (see Fig. 361-1) can provide quick, simple, operationalized diagnostic approaches for delirium. The Confusion Assessment Method algorithm has a sensitivity of 94%, a specificity of above 85%, and high interrater reliability. Complications of delirium may be preventable,[2] so rapid and accurate diagnosis is critical.

EPIDEMIOLOGY

The prevalence of delirium varies widely by settings and age. For older adults in a general medical setting, the prevalence of delirium is estimated to be 23%, with higher rates when frequent surveillance is performed in older, surgical, and intensive care populations. For example, delirium occurs in 8 to 58% of postoperative patients, 50 to 70% of mechanically ventilated patients, and up to 82% of patients in medical intensive care units. Delirium is also noted in up to 38% of nursing home patients and in up to 88% of patients at the end of life.

The problem of delirium in hospitalized elderly patients has assumed particular prominence because patients aged 65 years and older currently account for more than 50% of all inpatient days of hospital care. Based on U.S. vital health statistics, delirium complicates hospital stays for at least 2.6 million adults age 65 and older and accounts for more than $164 billion in health care expenditures annually. For postoperative delirium, the estimated costs are $33 billion in the United States annually.[3] Thus, delirium holds extensive economic and health policy implications.

PATHOBIOLOGY

Similar to other common geriatric syndromes (Chapter 24), delirium usually has multiple causes. A search for the many potential underlying contributors requires clinical astuteness and a thorough medical evaluation, especially because many of these factors are treatable but may result in substantial morbidity and mortality if left untreated. The process is made more challenging by the frequently nonspecific, atypical, or muted features of the underlying illness in older persons. Delirium is commonly the only initial

TABLE 361-3 DIAGNOSTIC CRITERIA FOR DELIRIUM

DSM-5 CRITERIA

- Disturbed attention (i.e., reduced ability to direct, focus, sustain, and shift attention) and awareness (reduced orientation to the environment) that have developed in a short time (usually hours to a few days) represent a change from baseline attention and awareness and tend to fluctuate in severity during the course of a day
- An additional disturbance in cognition (e.g., memory deficit, disorientation, language, visuospatial ability, or perception)
- Evidence from the history, physical examination, or laboratory findings that the disturbance is a direct physiologic consequence of another medical condition, substance intoxication or withdrawal, exposure to a toxin, or multiple causes
- No evidence for another preexisting, established, or evolving neurocognitive disorder to explain the inattention and cognitive disturbance
- No evidence for a reduced level of arousal, such as coma

DSM-5 = *Diagnostic and Statistical Manual of Mental Disorders,* 5th ed.

Modified with permission from American Psychiatric Association. *Diagnostic and Statistical Manual of Mental Disorders*, 5th ed. Washington, DC: American Psychiatric Association; 2013.

TABLE 361-4 MINI-COG TEST

1. Instruct the patient to listen carefully to and remember three unrelated words and then to repeat the words: banana, sunrise, chair.
2. Instruct the patient to draw the face of a clock, either on a blank sheet of paper or on a sheet with a large circle already drawn on the page. After the patient puts the numbers on the clock face, ask him or her to draw the hands of the clock to read a specific time, such as 11:10. These instructions can be repeated, but no additional instructions should be given. Allow up to 3 minutes to complete the clock drawing.
3. Ask the patient to repeat the three previously presented words.
4. Give 1 point for each correct word and 2 points for a correctly drawn clock. Scores <3 suggest cognitive impairment.

Modified from Borson S, Scanlan J, Watanabe J, et al. Improving identification of cognitive impairment in primary care. *Int J Geriatr Psychiatry*. 2006;21:349-355. Reprinted by permission of the copyright holder (S. Borson).

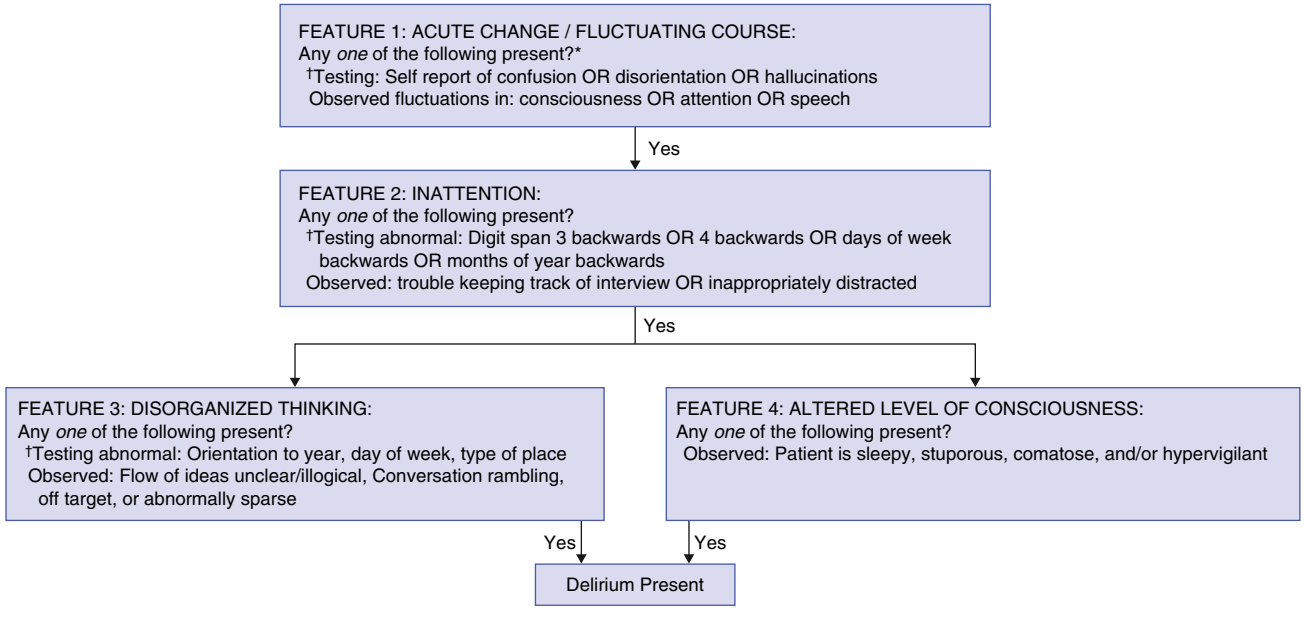

FIGURE 361-1. Overview of 3-minute Confusion Assessment Method (3D-CAM). This figure depicts the CAM diagnostic algorithm, with the 3D-CAM items and scoring summarized under each CAM diagnostic feature. *Feature 1 Supplementary Question: To be asked only if Feature 2 is present, and either Feature 3 or 4 is present, but Feature 1 is uncertain: Contact a family member, friend, or health care provider who knows the patient well and ask: "Is there evidence of an acute (sudden) change in mental status (memory or thinking) from the patient's baseline?" †It is recommended that all testing items be administered for Features 1, 2, and 3. Skip patterns have not been validated. (From Marcantonio ER, Ngo LH, O'Connor M, et al. 3D-CAM: derivation and validation of a 3-minute diagnostic interview for CAM-defined delirium: a cross-sectional diagnostic test study. *Ann Intern Med*. 2014;161[8]:554-561.)

TABLE 361-5 GERIATRIC DEPRESSION SCALE—SHORT FORM

1.	Are you basically satisfied with your life?	yes/**NO**
2.	Have you dropped many of your activities and interests?	**YES**/no
3.	Do you feel that your life is empty?	**YES**/no
4.	Do you often get bored?	**YES**/no
5.	Are you in good spirits most of the time?	yes/**NO**
6.	Are you afraid that something bad is going to happen to you?	**YES**/no
7.	Do you feel happy most of the time?	yes/**NO**
8.	Do you feel helpless?	**YES**/no
9.	Do you prefer to stay home rather than going out and doing new things?	**YES**/no
10.	Do you feel you have more problems with memory than most?	**YES**/no
11.	Do you think it is wonderful to be alive now?	yes/**NO**
12.	Do you feel pretty worthless the way you are now?	**YES**/no
13.	Do you feel full of energy?	yes/**NO**
14.	Do you feel that your situation is hopeless?	**YES**/no
15.	Do you think that most people are better off than you are?	**YES**/no

Scoring: Answers indicating depression are capitalized; six or more capitalized answers indicate depressive symptoms.

Modified with permission from Yesavage J, Brink T, Rowe T, et al. Development and validation of a geriatric depression screening scale: a preliminary report. *J Psychiatr Res*. 1983;17:37-49.

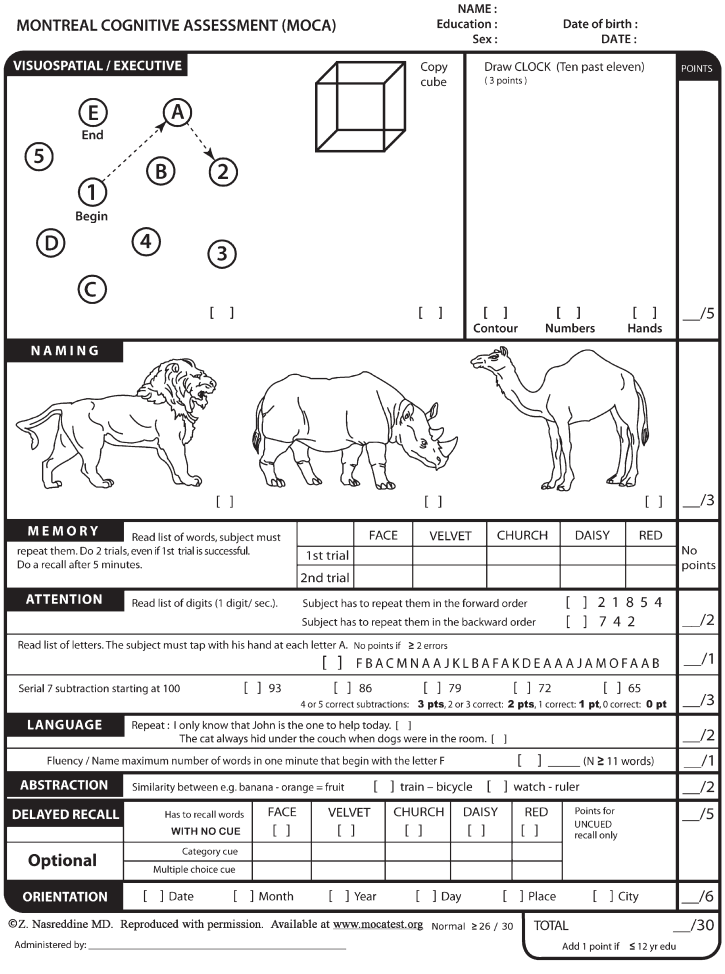

FIGURE 361-2. Montreal Cognitive Assessment. (Reproduced with permission from Nasreddine ZS, Phillips NA, Bedirian V, et al. The Montreal Cognitive Assessment, MoCA: a brief screening tool for mild cognitive impairment. *J Am Geriatr Soc*. 2005;53:695-699.)

sign of an underlying life-threatening illness, such as pneumonia (Chapter 85), urosepsis (Chapter 263), or myocardial infarction (Chapter 58), in the older population.

The basic pathogenesis of delirium remains unclear. Recent evidence suggests that interacting biologic factors result in disruption of large-scale neuronal networks in the brain, thereby leading to acute cognitive disruption and delirium. Some of the leading proposed mechanisms include disruption in neurotransmitter systems, systemic inflammation, neuronal inflammation, neuronal injury, physiologic stressors, metabolic derangements, and genetic factors.[4] Many neurotransmitter systems are potentially involved, but relative cholinergic deficiency and dopamine excess are the most frequently linked. Inflammation may play an important role, with peripheral inflammation triggering neuroinflammation and microglial activation. Whether underlying factors such as preclinical dementia impart a vulnerability for the brain to "lose" the ability to protect itself in the face of infection or trauma, with the end result being an episode of delirium, or if delirium itself causes neuronal injury and death is unknown, but both of these potential links are supported by emerging data.

The development of delirium usually involves a complex interrelationship between a vulnerable patient with pertinent predisposing factors and exposure to noxious insults or precipitating factors. Delirium may develop in vulnerable patients, such as cognitively impaired or severely ill patients, after a relatively benign insult, such as a single dose of sleeping medication. Conversely, in patients who are not vulnerable, delirium may develop only after exposure to multiple noxious insults. The effects of these risk factors may be cumulative. Recognition of this multifactorial causation is important to the clinician because the removal or treatment of one factor in isolation usually is not sufficient to resolve the delirium. The full spectrum of vulnerability and precipitating factors should be addressed.

Factors that predispose patients to delirium include preexisting cognitive impairment or dementia (Chapter 371), history of delirium, functional impairment, visual (Chapter 391) or hearing impairment (Chapter 396), multiple comorbid conditions, severe underlying illness, depression (Chapter 362), history of a stroke or transient ischemic attack (Chapter 376), alcohol use disorder (Chapter 364), and advanced age.[5] Dementia is an important and consistent risk factor for delirium; persons with dementia have a two-fold to five-fold increased risk for delirium, and 30 to 50% of delirious patients have underlying dementia.

Medications, which are the most common remediable causes of delirium,[6] contribute to delirium in 40% of cases (Chapter 361). Insufficiency or failure of any major organ system, particularly renal or hepatic failure, can precipitate delirium. Surgical procedures are leading risk factors for delirium. Hypoxemia and hypercarbia have been associated with delirium. Clinicians must be attuned to occult respiratory failure, which in the elderly often lacks the usual signs and symptoms of dyspnea and tachypnea and can be missed by the measurement of oxygen saturation alone. Acute myocardial infarction (Chapter 58) or heart failure (Chapter 45) can be manifested as delirium in an elderly patient without the usual symptoms of chest pain or dyspnea. Occult infection is a particularly notable cause of delirium. Older patients frequently fail to mount the febrile or leukocytotic response to infection, and clinicians must assess them carefully for signs of pneumonia (Chapter 85), urinary tract infection (Chapter 263), endocarditis (Chapters 61), abdominal abscess (Chapter 128 and 137), or infected joints (Chapter 251). Studies in older adults presenting to the emergency department with severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection (Chapter 336) found that delirium is a frequent presenting symptom, in some cases without typical SARS-CoV-2 symptoms or signs, such as fever or shortness of breath.[7] A variety of metabolic disorders may contribute to delirium, including hypernatremia and hyponatremia (Chapter 102), hypercalcemia (Chapter 227), acid-base disorders (Chapter 104), hypoglycemia (Chapter 211) and hyperglycemia (Chapter 210), and thyroid (Chapter 207) or adrenal disorders (Chapter 209). Immobilization and immobilizing devices (e.g., indwelling bladder catheters, physical restraints, bed alarms) are important factors in precipitating delirium. Dehydration and volume depletion and nutritional decline during hospitalization (e.g., weight loss, fall in serum albumin concentration) are well-documented factors contributing to delirium. Drug and alcohol withdrawal are important and often unsuspected causes of delirium in the elderly. Environmental factors, such as unfamiliar surroundings, sleep deprivation, deranged schedule, frequent room changes, sensory overload, and sensory deprivation, may aggravate delirium in the hospital. Psychosocial factors, such as depression, psychological stress, pain, and lack of social supports, also may precipitate delirium.

CLINICAL MANIFESTATIONS

The cardinal features of delirium include acute onset and inattention.[8] Establishing the acuteness of onset requires accurate knowledge of the

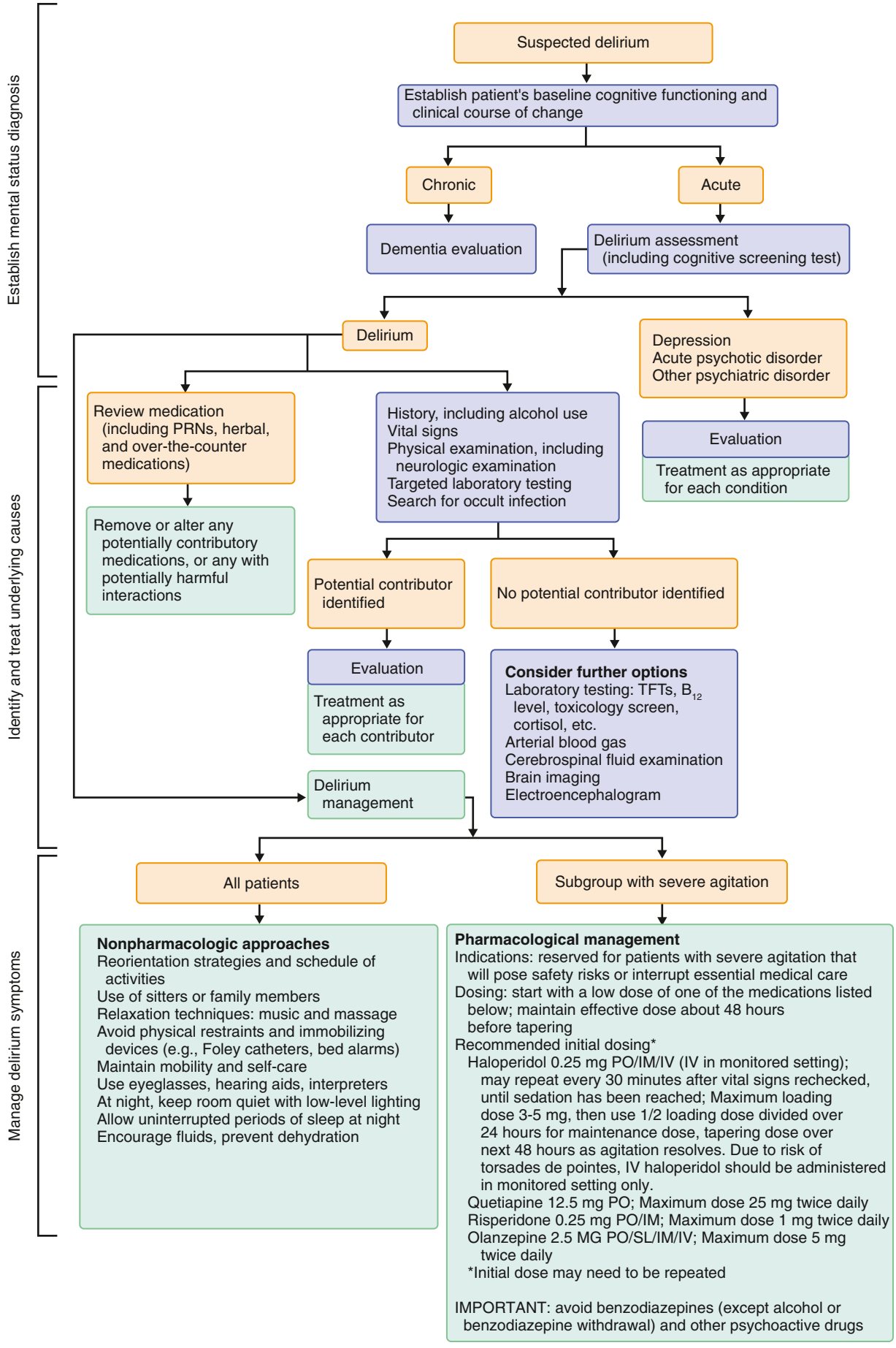

FIGURE 361-3. **Algorithm for the evaluation of suspected delirium.** IM = intramuscularly; IV = intravenous; PO = oral; SL = sublingual; TFTs = thyroid function tests.

patient's baseline cognitive function. Patients with delirium are inattentive; that is, they have difficulty focusing, maintaining, and shifting attention. They appear easily distracted and have difficulty in maintaining conversation and following commands. Objectively, patients may have difficulty with simple repetitive tasks, digit spans, and recitation of months backward. Other key features include disorganized thought processes, which are usually a manifestation of underlying cognitive or perceptual disturbances; altered level of consciousness, which typically consists of lethargy with reduced awareness of the environment; and fluctuation of cognitive symptoms. Although not cardinal elements, other features that frequently occur during delirium include disorientation, cognitive deficits, psychomotor agitation or retardation, perceptual disturbances such as hallucinations and illusions, paranoid delusions, and sleep-wake cycle reversal.

DIAGNOSIS

The cornerstone of the evaluation of delirium is a comprehensive history and physical examination (Fig. 361-3). The history, which should be obtained from a reliable informant, is targeted to establish the patient's baseline cognitive function and the time course of any mental status change and to obtain clues about potential precipitating factors, such as recent medication changes, intercurrent infection, or medical illness.

The next step is to establish the diagnosis of delirium through cognitive assessment and to determine whether the present condition represents an acute change from the patient's baseline cognitive function, such as from a family member. Because cognitive impairment may not be apparent during conversation, brief cognitive screening tests—such as the Mini-Cog test (see Table 361-4) or a short mental status questionnaire (Table 361-6)—should be used. Attention should be assessed further with other simple tests, such as a forward digit span (inattention is indicated by an inability to repeat five digits forward) or recitation of the months backward (allow maximum of one error). Specific instruments for the diagnosis of delirium, such as the Confusion Assessment Method (see Fig. 361-1) or another validated delirium tool, should be used (Video 361-1). A combination of the two-item Ultra-Brief 2 Confusion Assessment Method, which excludes delirium if negative, followed, if positive, by the 3D-CAM (https://deliriumnetwork.org/wp-content/uploads/2020/08/UB-CAM.pdf) can establish the diagnosis within a minute and is particularly useful in assessing a patient who has underlying dementia.[9] 9

Review of the patient's medication list, including over-the-counter medications and herbal remedies, is crucial, and the use of medications with psychoactive effects should be discontinued or minimized whenever possible. In the elderly, these medications may cause psychoactive effects even at doses and measured drug levels within the "therapeutic range." Consideration should also be given to the possibility that withdrawal from alcohol or other medications is a contributor to delirium. Physical examination should include a detailed neurologic examination for focal deficits and a careful search for signs of hemodynamic compromise, occult infection, or an acute abdominal process.

Laboratory Findings

Laboratory evaluation must be tailored to the individual situation (see Table 361-2). In patients with preexisting cardiac or respiratory diseases or related symptoms, electrocardiography or arterial blood gas determination may be indicated. The need for cerebrospinal fluid examination is controversial except for the clear indication of the febrile delirious patient, in whom meningitis or encephalitis is suspected. Brain imaging should be reserved for patients with new focal neurologic signs, patients with a history or signs of head trauma (e.g., upper body bruising), and patients without another identifiable cause of the delirium.[10] Electroencephalography (EEG), with a false-negative rate of 17% and a false-positive rate of 22% for distinguishing delirious from nondelirious patients, has a limited role and is most useful for detecting an occult seizure disorder and differentiating delirium from psychiatric disorders. 10

Differential Diagnosis

A crucial difficulty is distinguishing a long-standing confusional state (dementia) from delirium alone or delirium superimposed on dementia (see Fig. 361-3). The differential diagnosis also includes depression (see Table 361-5) and nonorganic psychotic disorders (see Table 361-1). Although paranoia, hallucinations, and affective changes can occur with delirium, the key features of acute onset, inattention, altered level of consciousness, and global cognitive impairment assist in the recognition of delirium. At times, the differential diagnosis can be difficult, particularly with an uncooperative patient or when an accurate history is unavailable. Because of the potentially life-threatening nature of delirium, it is prudent to manage the patient as if he or she has delirium and to search for and treat underlying precipitants (e.g., intercurrent illness, metabolic derangement, drug toxicity) until further information can be obtained.

TABLE 361-6 SHORT PORTABLE MENTAL STATUS QUESTIONNAIRE

QUESTION	RESPONSE	ERROR?
What are the date, month, and year?*	Date Month Year	
What is the day of the week?		
What is the name of this place?		
What is your phone number?		
How old are you?		
When were you born?		
Who is the current president?		
Who was the president before him?		
What was your mother's maiden name?		
Can you count backward from 20 by 3s?		

*A mistake on any part of this question should be scored as an error.
Total possible errors: 10; more than three errors indicate cognitive impairment.
From Pfeiffer E. A short portable mental status questionnaire for the assessment of organic brain deficit in elderly patients. *J Am Geriatr Soc.* 1975;23:433-441. Copyright © E. Pfeiffer 1994. Reproduced with permission of the author.

TREATMENT

Nonpharmacologic approaches and family involvement are often helpful in managing symptoms.[A1] Pharmacologic approaches should be reserved for patients whose symptoms may result in the interruption of needed medical therapies (e.g., intubation, intravenous lines) or may endanger the safety of the patient or other persons. A1

Medical Treatment

No drug is ideal for the treatment of delirium, and any drug can cloud the patient's mental status further and obscure efforts to monitor the course of the mental status change. In fact, antipsychotic medications may be ineffective or harmful by prolonging delirium and increasing adverse outcomes.[A2,A3] A2 A3

Any drug should be given at the lowest dose and for the shortest time possible. Neuroleptics are the preferred agents. Haloperidol, the most widely used agent,[A4] causes less orthostatic hypotension and fewer anticholinergic side effects than thioridazine and is available in parenteral form; however, it has a higher rate of extrapyramidal side effects and acute dystonias. Second-generation antipsychotics have not proved superior to haloperidol. If parenteral administration is required, intravenous haloperidol should be given in a monitored setting because its use results in a rapid onset of action, short duration of effect, and risk of hypotension and torsades de pointes; oral and intramuscular administration has a more optimal duration of action, and these are the preferred routes. The recommended starting dose is 0.25 mg to 0.5 mg of haloperidol orally or intramuscularly, repeated every 30 minutes after the vital signs have been rechecked, until sedation has been achieved. The end point should be an awake but manageable patient. The average elderly patient who has not been treated previously with neuroleptics should receive no more than 3 to 5 mg of haloperidol in a 24-hour period. Subsequently, a maintenance dose consisting of half the loading dose should be administered in divided doses during the next 24 hours, with doses tapered during the next 48 hours as the agitation resolves. A4

Benzodiazepines are not recommended as the first-line treatment of delirium because of their tendency to cause oversedation and to exacerbate the confusional state. They remain the drugs of choice, however, for the treatment of withdrawal syndromes from alcohol and sedative drugs (Chapters 364 and 365).

Nonpharmacologic Management

Multicomponent geriatric interventions may be effective in improving quality of life with the potential for significant cost savings. Nonpharmacologic management techniques recommended for every delirious patient include encouraging the presence of family members, using "sitters" as orienting influences, and transferring a disruptive patient to a private room or closer to the nurses' station

for increased supervision. Interpersonal contact and communication, including verbal reorientation strategies, simple instructions and explanations, and frequent eye contact, are vital. Patients should be involved in their own care and allowed to participate in decision making as much as possible. Eyeglasses and hearing aids may reduce sensory deficits. Mobility, self-care, and independence should be encouraged. Physical restraints and bed alarms should be avoided, if possible, because of their tendency to increase agitation, their lack of efficacy, and their potential to cause injury. Attention must be focused on minimizing the disruptive influences of the hospital environment. Clocks and calendars should be provided to assist with orientation. Room and staff changes should be kept to a minimum. A quiet environment with low-level lighting is optimal for delirious patients, and use of ear plugs may be helpful for management of delirium. Perhaps the most important intervention is to schedule the checking of vital signs, the administration of medications, and the performance of procedures to allow a period of uninterrupted sleep at night. Nonpharmacologic approaches to relaxation, including music, relaxation tapes, and massage, can be highly effective in managing agitation.

End-of-Life Care Management

Delirium occurs in at least 80% of patients at the end of life and is considered part of the dying process by many hospice care providers (Chapter 3). Establishing the goals for care in advance with the patient and family is critical to guide appropriate management. For example, some patients may prioritize the preservation of alertness and the ability to communicate with loved ones as long as possible; others may prioritize comfort above all else. Physicians must be aware that even in terminal patients, many causes of delirium are potentially reversible with simple interventions such as adjusting medications, providing oxygen, or treating dehydration; however, aggressive diagnostic evaluation is usually inappropriate in this population. Nonpharmacologic measures to treat agitation and delirium should be instituted in all patients (including massage, music, and relaxation therapies), but hypoactive delirium may not benefit from pharmacotherapy.[11] Haloperidol remains the first-line therapy for agitated delirium in terminally ill patients. If more sedation is indicated, a short-acting benzodiazepine such as lorazepam (starting dose 0.5 to 1.0 mg PO, IM, or SL), which is easily titrated, is recommended in this setting. The addition of lorazepam (3 mg intravenously) to haloperidol has been shown to be more effective than haloperidol alone to reduce agitation in patients who have advanced cancer with severe agitated delirium.[A5] Because sedation may result in decreased interaction and communication, increased confusion, and respiratory depression, this choice should be made in conjunction with the family while honoring the patient's preferences.

Caregiver Issues

Caring for a person with delirium can be a stressful experience. Symptoms and outcomes after delirium may force the caregiver to make significant changes in their own lifestyle and home environment, address safety issues, and provide additional supportive care. Caregivers commonly are distressed by the behaviors and symptoms of delirium, and they often do not know what to say or how to respond or behave.[12] Education should be provided to caregivers as needed to correct any misconceptions and to lessen anxiety and stress. Multicomponent delirium care, involving the family, can be effective for the prevention of delirium.

TABLE 361-7 DRUGS WITH STRONG ANTICHOLINERGIC PROPERTIES

Antiarrhythmic	Antimuscarinics (urinary incontinence)
Disopyramide	Darifenacin
	Fesoterodine
Antidepressants	Flavoxate
Amitriptyline	Oxybutynin
Amoxapine	Solifenacin
Clomipramine	Tolterodine
Desipramine	Trospium
Doxepin (>6 mg)	
Imipramine	Antiparkinsonian agents
Nortriptyline	Benztropine
Paroxetine	Trihexyphenidyl
Protriptyline	
Trimipramine	Antipsychotics
	Chlorpromazine
Antiemetics	Clozapine
Prochlorperazine	Loxapine
Promethazine	Olanzapine
	Perphenazine
Antihistamines (first generation)	Thioridazine
Brompheniramine	Trifluoperazine
Carbinoxamine	
Chlorpheniramine	Antispasmodics
Clemastine	Atropine (excludes ophthalmic)
Cyproheptadine	Belladonna alkaloids
Dexbrompheniramine	Scopolamine (excludes ophthalmic)
Dexchlorpheniramine	
Dimenhydrinate	Skeletal muscle relaxants
Diphenhydramine (oral)	Cyclobenzaprine
Doxylamine	Orphenadrine
Hydroxyzine	
Meclizine	
Clidinium-chlordiazepoxide	
Dicyclomine	
Homatropine (excludes ophthalmic)	
Hyoscyamine	
Methscopolamine	
Propantheline	

Adapted from the 2019 American Geriatrics Society Beers Criteria® Update Expert Panel. American Geriatrics Society 2019 updated AGS Beers Criteria® for potentially inappropriate medication use in older adults. *J Am Geriatr Soc*. 2019;67:674-694.

PREVENTION

The most effective strategy to reduce delirium and its associated complications is primary prevention before delirium occurs. Preventive strategies should address important risk factors and target moderate- to high-risk patients at baseline. Clinical trials document that multicomponent nonpharmacologic interventions targeted toward delirium risk factors can reduce the incidence of delirium by 30 to 40%.[A6-A8] These components typically include strategies designed to improve orientation, to provide therapeutic activities, to increase mobilization and exercise, to enhance sleep with nonpharmacologic interventions, to optimize vision and hearing, and to manage dehydration. Preoperative geriatric consultation, tailored family involvement,[A9] and lighter anesthesia also can reduce postoperative delirium, but more flexible family visitation[A10] or depth of anesthesia monitoring do not appear to be helpful.

Patients may benefit from stopping or tapering one or more of their medications and especially reducing the burden of anticholinergic drugs[13,14] (Table 361-7). However such an approach does not appear to reduce delirium in ICU patients.[A11]

Trials using melatonin[A12] or ramelteon[A13] (a melatonin receptor agonist at 8 mg nightly) to prevent delirium have shown no benefit or have been inconsistent. A meta-analysis showed a 50% reduction in delirium in surgical patients and a 34% in ICU patients but no reduction in medical patients. However, these medications did not reduce the length of hospital stay, length of ICU stay, or mortality.[A14] Prophylactic intravenous dexmedetomidine (e.g., 0.1 μg/kg/hour from intensive care unit admission on the day of surgery until 8 AM on postoperative day 1) can significantly and safely decrease the risk of delirium after noncardiac surgery and in ICU patients,[A15] but it has not been successful after cardiac surgery.[A16] By comparison, intravenous acetaminophen (15 mg/kg every 6 hours, not to exceed 750 mg/dose or 3750 mg/day, for 48 hours) combined with either propofol (20 to 100 μg/kg/min) or dexmedetomidine (bolus dose of 0.5 to 1 μg/kg IV during chest closure, followed by a maintenance infusion of 0.1 to 1.4 μg/kg/hour) can reduce delirium after cardiac surgery.[A17] No other drug treatments, including antipsychotic agents (e.g., haloperidol) or cholinesterase inhibitors (e.g., donepezil), have been shown to be consistently effective in preventing delirium.[A18-A20]

Preventive efforts require system-wide changes to educate physicians and nurses, to improve their recognition of delirium and heighten their awareness of its clinical implications, to provide incentives to change practice patterns that lead to delirium (e.g., immobilization, sleep medications, bladder catheters, physical restraints), and to create systems that enhance high-quality geriatric care (e.g., geriatric expertise, case management,

clinical pathways, quality monitoring, daily mobility, and age-friendly hospital systems).

PROGNOSIS

Delirium increases the risk of death about 2-fold, of institutionalization about 2.5-fold, and of dementia more than 12-fold even after controlling for age, sex, severity of illness, comorbid conditions, and baseline dementia. The hospital mortality rates for patients with delirium are 25 to 33%, in the same range as found with sepsis. Delirium also is associated with prolonged length of stay, increased institutional placement, and 30-day readmission.

Delirium was previously considered a reversible, transient condition, but only 20% of patients have complete resolution by 6 months, and 15% have long-term cognitive decline at 3 years. The accelerated cognitive decline following delirium can still be seen 6 years following an index episode of delirium.[15] Delirium has even more pronounced effects in patients with underlying dementia. The rate of cognitive decline in patients with dementia more than doubles after an episode of delirium, and about one in eight hospitalized patients with dementia who develop delirium will have at least one severe adverse outcome, including a markedly increased risk of death[16] and of institutionalization. The long-term detrimental effects are most likely related to the duration, severity, and underlying cause of the delirium and the vulnerability of the patients.

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For the General References and other additional features, please visit Elsevier eBooks+ at https://ebooks.health.elsevier.com.

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362 PSYCHIATRIC DISORDERS IN MEDICAL PRACTICE

JEFFREY M. LYNESS AND HOCHANG B. LEE

OVERVIEW

DISORDERS IN PSYCHIATRY

Psychiatric disorders, also known as mental illnesses, are extraordinarily common and have a profound impact on well-being and functional status. Collectively, psychiatric disorders account for more aggregate disability than do disorders involving any other organ system, with depression alone being second only to cardiovascular disorders.

Psychiatric disorders are defined as disorders of the psyche—that is, conditions that affect thoughts, feelings, or behaviors. By definition, such mental disturbances must be sufficient to produce significant distress in the patient or impairment in role or other functioning. Because the pathogeneses of most psychiatric disorders are incompletely understood, classification is based on clinical syndromes that are defined by diagnostic criteria with high interrater reliability. To achieve that reliability, the criteria emphasize discrete reportable or observable symptoms and signs. Interestingly, however, many underlying pathophysiologic mechanisms probably cut across these descriptive diagnostic categories, although current knowledge of such mechanisms rarely directly informs predictions of course or clinical decision-making.[1]

SPECIFIC SYNDROMES

Because many psychiatric disorders result from the direct influence of neurologic conditions, systemic diseases, or drugs on brain functioning, assessment of any new or worsened psychiatric condition must include evaluation for their potential contributions (Table 362-1). Delirium (Chapter 361) and dementia (Chapter 371), which are neurocognitive disorders defined by impairment in intellectual functions such as attention, memory, or language, are always the result of neurologic abnormalities, systemic illnesses, or drugs. Although intellectual impairment is the hallmark of neurocognitive disorders, these conditions also may manifest as alterations in other aspects of mental status, including mood, thought content, thought process, and behavior.

If a noncognitive psychiatric syndrome is caused by an identifiable underlying condition, it is known as a secondary psychiatric disorder (e.g., "major depression due to hypothyroidism").

TABLE 362-1 IMPORTANT CAUSES OF PSYCHIATRIC SYNDROMES

CENTRAL NERVOUS SYSTEM DISEASES
Trauma
Tumor
Toxins
Seizures
Vascular
Infections
Genetic/congenital malformations
Demyelinating diseases
Neurodegenerative diseases
Hydrocephalus
SYSTEMIC DISEASES
Cardiovascular
Pulmonary
Endocrine
Metabolic
Nutritional
Infections
Cancer
DRUGS (e.g., recreational, prescription, or over-the-counter drugs)
Drug intoxication
Drug withdrawal

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clinical pathways, quality monitoring, daily mobility, and age-friendly hospital systems).

PROGNOSIS

Delirium increases the risk of death about 2-fold, of institutionalization about 2.5-fold, and of dementia more than 12-fold even after controlling for age, sex, severity of illness, comorbid conditions, and baseline dementia. The hospital mortality rates for patients with delirium are 25 to 33%, in the same range as found with sepsis. Delirium also is associated with prolonged length of stay, increased institutional placement, and 30-day readmission.

Delirium was previously considered a reversible, transient condition, but only 20% of patients have complete resolution by 6 months, and 15% have long-term cognitive decline at 3 years. The accelerated cognitive decline following delirium can still be seen 6 years following an index episode of delirium.[15] Delirium has even more pronounced effects in patients with underlying dementia. The rate of cognitive decline in patients with dementia more than doubles after an episode of delirium, and about one in eight hospitalized patients with dementia who develop delirium will have at least one severe adverse outcome, including a markedly increased risk of death[16] and of institutionalization. The long-term detrimental effects are most likely related to the duration, severity, and underlying cause of the delirium and the vulnerability of the patients.

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362 PSYCHIATRIC DISORDERS IN MEDICAL PRACTICE

JEFFREY M. LYNESS AND HOCHANG B. LEE

OVERVIEW

DISORDERS IN PSYCHIATRY

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Psychiatric disorders are defined as disorders of the psyche—that is, conditions that affect thoughts, feelings, or behaviors. By definition, such mental disturbances must be sufficient to produce significant distress in the patient or impairment in role or other functioning. Because the pathogeneses of most psychiatric disorders are incompletely understood, classification is based on clinical syndromes that are defined by diagnostic criteria with high interrater reliability. To achieve that reliability, the criteria emphasize discrete reportable or observable symptoms and signs. Interestingly, however, many underlying pathophysiologic mechanisms probably cut across these descriptive diagnostic categories, although current knowledge of such mechanisms rarely directly informs predictions of course or clinical decision-making.[1]

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Because many psychiatric disorders result from the direct influence of neurologic conditions, systemic diseases, or drugs on brain functioning, assessment of any new or worsened psychiatric condition must include evaluation for their potential contributions (Table 362-1). Delirium (Chapter 361) and dementia (Chapter 371), which are neurocognitive disorders defined by impairment in intellectual functions such as attention, memory, or language, are always the result of neurologic abnormalities, systemic illnesses, or drugs. Although intellectual impairment is the hallmark of neurocognitive disorders, these conditions also may manifest as alterations in other aspects of mental status, including mood, thought content, thought process, and behavior.

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SYSTEMIC DISEASES
Cardiovascular
Pulmonary
Endocrine
Metabolic
Nutritional
Infections
Cancer
DRUGS (e.g., recreational, prescription, or over-the-counter drugs)
Drug intoxication
Drug withdrawal

ABSTRACT

Psychiatric disorders, also known as mental illnesses, are defined as alterations in thoughts, feelings, or behaviors sufficient to produce significant distress for the patient or impair the patient's functioning. These conditions are extraordinarily common and have a profound impact on well-being and functional status, both for affected individuals as well as their families. Because the pathogeneses of most psychiatric disorders are incompletely understood, classification is based on clinical syndromes that are defined by diagnostic criteria with high interrater reliability. These criteria emphasize discrete reportable or observable symptoms and signs. This chapter provides an overview of the major psychiatric disorders encountered in medical practice, with the exception of those disorders considered in other chapters (e.g., delirium, dementia, eating disorders, addictions).

KEYWORDS

psychiatric disorders
psychopathology
depression
bipolar disorder
anxiety disorders
schizophrenia
personality disorders

TABLE 362-2 IMPORTANT PSYCHIATRIC SYNDROMES AND DISORDER CATEGORIES

SYNDROME	MAIN SYMPTOMS AND SIGNS	MAY OCCUR AS PART OF THESE DISORDER CATEGORIES
Neurocognitive/ cognitive	Deficits in intellectual functions (e.g., level of consciousness, orientation, attention, memory, language, praxis, visuospatial, executive functions)	Neurocognitive disorders (delirium, dementia, amnesia, aphasia) Intellectual disability (if onset in childhood)
Depressive	Lowered mood, anhedonia, negativistic thoughts, neurovegetative symptoms and signs	Neurocognitive disorders Depressive disorders (primary or secondary) Bipolar disorders (primary or secondary) Psychotic disorders (schizoaffective disorder)
Manic	Elevated or irritable mood, grandiosity, goal-directed hyperactivity with increased energy, pressured speech, decreased sleep need	Neurocognitive disorders Bipolar disorder (primary or secondary) Psychotic disorders (schizoaffective disorder)
Anxiety	All include anxious mood and associated physiologic symptoms (e.g., palpitations, tremors, diaphoresis); may include various types of dysfunctional thoughts (e.g., catastrophic fears, obsessions, flashbacks) and behavior (e.g., compulsions, avoidance behavior)	Neurocognitive disorders Mood disorders (bipolar or depressive) (primary or secondary) Psychotic disorders (primary or secondary) Trauma- and stressor-related disorders Anxiety disorders (primary or secondary) Obsessive-compulsive and related disorders
Psychotic	Impairments in reality testing: delusions, hallucinations, thought process derailments	Neurocognitive disorders Depressive disorders (primary or secondary) Bipolar disorders (primary or secondary) Psychotic (schizophrenia and related) disorders
Somatic symptom syndromes	Somatic symptoms with associated distressing thoughts, feelings, or behaviors	Depressive disorders (primary or secondary) Bipolar disorders (primary or secondary) Anxiety disorders (primary or secondary) Obsessive-compulsive and related disorders Trauma- and stressor-related disorders Somatic symptom disorders
Personality pathology	Enduring patterns of dysfunctional emotional regulation, thought patterns, interpersonal behavior, impulse regulation	Neurocognitive disorders (dementia) Personality change due to another medical condition Personality disorders

Author summary based on categories and criteria from American Psychiatric Association. *Diagnostic and Statistical Manual of Mental Disorders*. 5th ed. Text Revision (DSM-5-TR). Washington, DC: American Psychiatric Association; 2022.

The major non-secondary, non-cognitive psychiatric syndromes (Table 362-2) can coexist with multiple syndromes. Mood disorders are categorized as either depressive (also termed *unipolar*, and characterized by depressive episodes only) or bipolar (characterized by manic or hypomanic episodes, typically with depressive episodes as well). For example, a patient suffering major depression with psychotic features by definition will have depressive and psychotic syndromes simultaneously, and the same patient may also manifest anxiety or other syndromes. Addictive disorders are considered in Chapters 364 and 365.

COMORBID CONDITIONS IN PSYCHIATRY

It is common for persons who suffer from mental disorders to meet the diagnostic criteria for more than one condition. Such comorbidity may reflect the limitations of current diagnostic approaches based on signs and symptoms rather than pathogenesis. At the individual level, the behavioral manifestations of psychiatric disorders are variable and could meet multiple diagnostic criteria with overlapping symptoms. Furthermore, comorbidity of psychiatric disorders overlaying other medical conditions also is common, probably reflecting complex bidirectional causal relationships between physical and mental illnesses. Such comorbidity often worsens the prognosis for both conditions.

The most common psychiatric comorbidities encountered in general medical settings are substance abuse (Chapters 364 and 365) and depressive disorders. More than 50% of patients who seek treatment for substance use disorders have past or current diagnoses of depression or an anxiety disorder. Substance abuse is also common among bipolar disorder patients. These overlapping neurobiologic conditions may be caused by a link between addictive behavior and mood disorders, or patients with mood disorders may use drugs and alcohol in an attempt to self-medicate their emotional distress. Substance abuse generally will exacerbate a mood disorder, and the overlapping clinical manifestations and mutually reinforcing clinical course often make the assessment and treatment of patients with comorbid substance use and mood disorder challenging. Generally the treatment plan should address both the mood disorder and the addictive behaviors.

Substance use is also common in patients with psychotic disorders (e.g., schizophrenia, schizoaffective disorder). Psychoactive substances such as hallucinogens and stimulants often mimic or exacerbate psychotic symptoms that are difficult to separate from underlying psychotic disorders. Regardless of cause, acute treatment of psychosis and accompanying agitation requires judicious use of antipsychotic medication. It is also crucial to ensure the cessation of active substance use while treating acute psychosis and to maintain abstinence, in part by encouraging adherence to medications and psychosocial treatments for the psychotic disorder.

TREATMENTS IN PSYCHIATRY

Acute treatments in psychiatry are intended to reduce or eliminate symptoms, thereby reducing the patient's distress and dysfunction, and, for many patients, averting suicidal behavior. Maintenance therapies reduce the frequency or severity of recurrent episodes. Pharmacotherapy is an evidence-based mainstay of the treatment of many psychiatric conditions. The evidence for a number of forms of psychotherapy administered in individual, group, or family modalities also strongly support their use as primary treatment or co-treatment of many conditions. Other psychosocial interventions, ranging from self-help groups to the use of structured treatment or residential programs, are often important components of treatment. Nonpharmacologic evidence-based somatic therapies include electroconvulsive therapy, light therapy, and vagal nerve stimulation for particular forms of major depression. Other neuromodulatory treatment methods being studied for selected patients with severe depressive or obsessive-compulsive disorders include repetitive transcranial magnetic stimulation, transcranial direct-current stimulation, and deep brain stimulation.

MAJOR DEPRESSIVE DISORDER

DEFINITION

Major depressive disorder is characterized by one or more episodes of idiopathic major depressive syndrome (Table 362-3). This disorder should be distinguished from the generally milder dysthymic, cyclothymic, and grief disorders (see later).

EPIDEMIOLOGY

In the United States, major depression has a 12-month prevalence of approximately 7%, and it is at least 1.5 times more common in females than males, partly but not

TABLE 362-3 SYMPTOMS/SIGNS OF AN EPISODE OF MAJOR DEPRESSIVE SYNDROME

DIAGNOSTIC CRITERIA ***(a minimum of five symptoms must be present for a minimum of 2 consecutive weeks)***
Depressed mood (may be irritable mood in children and adolescents) most of the day, nearly every day, *OR*
Markedly diminished interest or pleasure most of the day, nearly every day *AND*
Weight loss or gain, or change in appetite (decrease or increase) nearly every day
Change in sleep (insomnia or hypersomnia) nearly every day
Psychomotor agitation or retardation nearly every day
Fatigue or loss of energy nearly every day
Feeling of worthlessness or guilt nearly every day
Diminished concentration or indecisiveness nearly every day
Recurrent thoughts of death or suicidal ideation, or a suicide attempt, or a specific suicide plan
MNEMONIC TO AID RECALL OF DIAGNOSTIC CRITERIA: *"SIG: E CAPS" (i.e., prescribe energy capsules)* along with depressed mood
Sleep change
Interests decreased
Guilt
Energy decreased
Concentration decreased
Appetite/weight disturbance
Psychomotor changes
Suicide thoughts
DEPRESSIVE SYMPTOMS/SIGNS GROUPED CONCEPTUALLY, WITH ADDITIONAL COMMON PHENOMENA
Emotional
Depressed mood, sadness, tearfulness
Irritability (seen in all ages, perhaps most commonly in children/adolescents and the elderly)
Anxiety
Loss of interests or pleasure (anhedonia)
Ideational
Worthlessness/lowered self-esteem
Guilt
Hopelessness/nihilism
Helplessness
Thoughts of death, dying, suicide
Somatic/Neurovegetative
Change in appetite/weight
Change in sleep
Anergia
Decreased libido
Trouble concentrating
Diurnal variation in symptoms *(mornings—worst pattern is most characteristic)*
Other
Ruminative thinking (tendency to dwell on one [negativistic] theme)
Somatic symptoms or somatic worry
Psychotic symptoms (negativistic delusions most characteristic)—defines the subtype "Major Depression with Psychotic Features"

Based in part on criteria from American Psychiatric Association. *Diagnostic and Statistical Manual of Mental Disorders*. 5th ed. Text Revision (DSM-5-TR). Washington, DC: American Psychiatric Association; 2022.

2 fully explained by the 6 to 13% prevalence of postpartum depression.[3] Lifetime prevalence of depression is up to 10% in males and 20 to 25% in females. New depressive episodes have an annual incidence of approximately 3%. Depression is associated with more than twice as much disability in midlife as any other medical condition, and its overall cumulative burden is greater than that from all but cardiovascular disorders. The economic impact is also enormous, with U.S. estimates of annual costs for depression exceeding $12 billion for treatment, $8 billion for associated morbidity, and $33 billion for lost earnings and work productivity.

PATHOBIOLOGY

Major depression is not a single disease entity but rather a heterogeneous group of conditions with multiple pathogenic mechanisms. It is both multifactorial and polygenic: genetic factors account for approximately 40% of the risk for depression, but multiple gene loci, most of which are currently unknown, are probably involved in a complex interplay with developmental and environmental influences. Alterations in the brain's noradrenergic and serotonergic systems are likely related to the efficacy of current antidepressant medications. The hypothalamic–pituitary–adrenal axis is hyperactive in depression, as evidenced by a nonsuppressed response to the dexamethasone suppression test, although this test is too insensitive and nonspecific for clinical use as a diagnostic tool. Neuroimaging studies in subjects with depression show an array of findings, including smaller hippocampal volumes that may be the result of exposure to chronically elevated cortisol levels, and altered cerebral metabolic activity in regions including frontal-striatal circuitry and the anterior cingulate cortex. Cognitive psychology studies have demonstrated dysfunctional patterns of negative thinking, with distorted thoughts about self, the future, and the environment. These cognitive distortions are both risk markers for the onset of depression and manifest in worsened form during depressive episodes. Impairments in the quality or number of social relationships, and stressful life events, particularly exit events such as deaths, separations, or functional impairment, are powerfully associated with depression as well.

CLINICAL MANIFESTATIONS

The symptoms of depression (see Table 362-3) may be conceptually grouped as alterations in emotions, ideation (i.e., thought content), and somatic/neurovegetative functioning. Importantly, patients with depressive illness may be seen without a depressed mood, albeit by definition they then must have loss of interest or pleasure in their usually desired activities. In addition to the core symptoms that define the depressive syndrome, depressed patients also may exhibit prominent anxiety, irritability, or somatization. Although the mildest forms of major depression in the community may remit spontaneously within a few months without medical care, patients may have persistent symptoms for months or years, too often without seeking treatment.

DIAGNOSIS

The diagnosis is made clinically by elicitation of findings from the history and mental status examination to determine the presence of major depressive syndrome. The differential diagnosis includes other idiopathic disorders with episodes of major depression, such as bipolar disorder (distinguished by a history of manic episodes) and schizoaffective disorder (distinguished by a history of psychotic episodes in the absence of depression). Major depression may manifest as part of delirium or dementia, and secondary depression also commonly accompanies serious medical illnesses; these comorbid conditions require careful, well-coordinated care. Screening instruments (see Table 361-3 in Chapter 361) can help identify cases of depression. For example, using the two-item version of the Patient Health Questionnaire, the screener asks the patient the following questions: Over the past 2 weeks, how often have you (1) had little interest or pleasure in doing things, or (2) been feeling down, depressed, or hopeless? Responses for each question are scored as follows: 0 = not at all, 1 = several days, 2 = more than half the days, 3 = nearly every day. A score of 3 points or higher on the two-item screen is associated with 75% probability of having a depressive disorder.

TREATMENT

The approach to treatment begins with an assessment of the severity of the depression, based on the number and intensity of symptoms as well as the degree of functional impairment. Although approaches to distinguishing severe from mild to moderate major depression vary, severe depression generally produces substantial dysfunction in all aspects of the patient's life and often includes so-called melancholic features, for example, nonreactive mood and profound somatic/neurovegetative symptoms (Fig. 362-1).

The three phases of treatment are (1) acute, in which treatment is provided to resolve the major depressive episode; (2) continuation, in which the acute treatment is continued for 6 to 12 months to prevent relapse; and (3) maintenance, for those with two to three or more episodes of recurrent depression, for whom treatment is maintained indefinitely to reduce the frequency and severity of future recurrences.[3] 3

Antidepressant medications are effective for acute, continuation, and maintenance therapy. Some patients have episodes of hypomania (e.g., low-level manic symptoms without substantial functional impairment and without psychosis) accompanied by episodes of major depression. However, these patients typically seek care during depressive episodes rather than during hypomania.

Based on the patient's preference, psychotherapy rather than medication may be the initial treatment of mild to moderate depression, perhaps especially for individuals with prominent psychosocial stressors. Focused psychotherapies (Table 362-4), which are more efficacious than usual care and equivalent to medications when used for patients in primary care settings.[A1] Involvement of family members for education, support, and sometimes formal family therapy may be an important adjunctive or primary therapeutic approach. A1

Meta-analyses demonstrate that antidepressant medications (Table 362-5) are effective for treating depression.[A2] Furthermore, the combination of medications A2

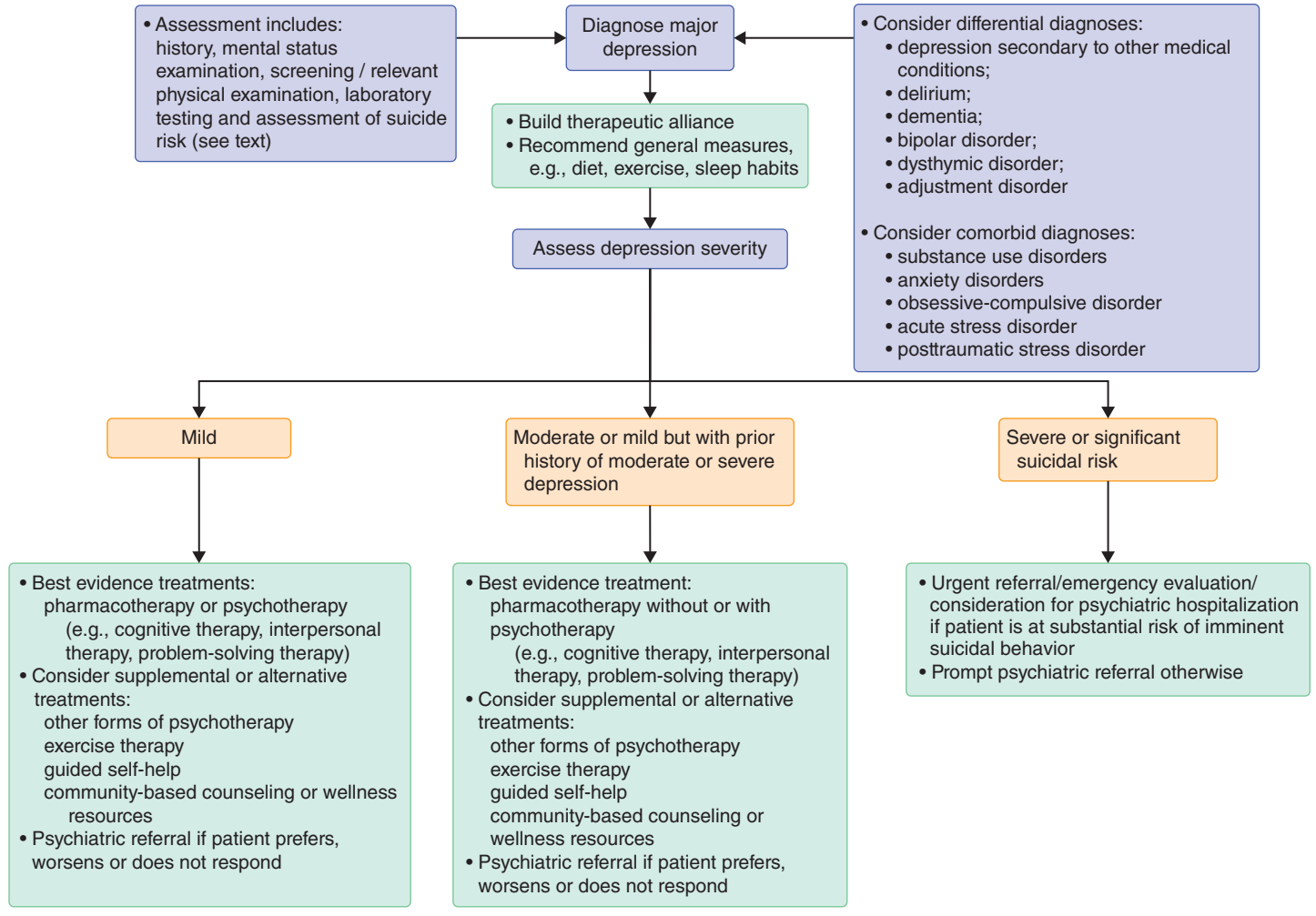

FIGURE 362-1. Approach to depressive disorders in primary care settings. (Adapted from Ng CW, How CH, Ng YP. Managing depression in primary care. *Singapore Med J*. 2017;58:459-466.)

TABLE 362-4 TREATMENTS FOR DEPRESSION

NAME OF PSYCHOTHERAPY	APPROACH
Cognitive psychotherapy	Identify and correct negativistic patterns of thinking
Interpersonal psychotherapy	Identify and work through role transitions or interpersonal losses, conflicts, or deficits
Problem-solving therapy	Identify and prioritize situational problems; plan and implement strategies to deal with problems with the best combination of high priority and high addressability
Psychodynamic psychotherapy	Use therapeutic relationship to maximize use of the healthiest defense mechanisms and coping strategies

plus psychotherapy may be more effective than medication alone for treatment-resistant major depression.[A3] Because antidepressant medications typically do not begin to improve symptoms for at least 1 to 2 weeks, with maximal benefit accruing up to at least 6 to 8 weeks, it is crucial to see patients regularly (every 1 to 2 weeks initially) to monitor their clinical status, provide support and education, and foster adherence.

In most general medical settings, it is common and reasonable practice to begin medication therapy with a selective serotonin reuptake inhibitor (SSRI) because of tolerability and straightforward dosing.[4] The choice of initial SSRI may be guided by relative side effect profiles, in particular whether to prefer or avoid sedation, although these effects may vary in individual patients. Serotonin-norepinephrine reuptake inhibitors (SNRIs) are reasonable choices for patients who do not achieve remission after an adequate trial of a SSRI and as first-line options for patients with more severe episodes. Initiation of treatment with tricyclic antidepressants or monoamine oxidase inhibitors is generally limited to patients with more severe, complex, or treatment-refractory disorders that generally require psychiatric consultation.

Antidepressant medications appear to increase the relative risk for suicidal behavior in adolescents and young adults, so such patients require careful benefit/risk assessments and close monitoring. By comparison, the relative risk for suicidal behavior is not increased by drug treatment in individuals older than age 25 years and is substantially reduced in older adults.

For severe major depression, including significant suicidality, melancholic symptoms, and substantial functional disability, psychiatric consultation is required and hospitalization may be indicated. Psychotherapies alone are insufficient for more severe forms of depression, including major depression with psychotic features, so medications should be used as initial treatment for most patients with more severe forms of major depression.[5] Overall data suggest that no second-generation agent is predictably better than others,[A4] although agents targeting noradrenergic as well as serotonergic systems may be more efficacious in more severe depression. For patients with psychotic depression, the addition of an antipsychotic medication (see Table 362-12) to an antidepressant is more efficacious than either alone.[A5]

Electroconvulsive therapy is the most effective treatment available and is the preferred approach for the most severe forms of major depression, including major depression with psychotic features, as well as depression that is refractory to other forms of treatment.[6]

A single intravenous dose of ketamine may rapidly reduce severe depressive symptoms within 24 hours,[A6] and esketamine nasal spray is effective for treatment-resistant depression. However, ketamine may not be as effective as electroconvulsive therapy[A7] and can lead to a significant increase in symptoms of psychosis in normal volunteers and people with schizophrenia. Optimal management strategies after initial improvement with ketamine or esketamine remain to be determined.

Deep brain stimulation is an investigational therapy for otherwise refractory depression. Overall evidence to date offers modest support for the efficacy of repetitive transcranial magnetic stimulation for depression. Hallucinogenic drugs such as lysergic acid diethylamide (LSD), psilocybin,[A8] and 3,4-methylenedioxymethamphetamine (MDMA) are experimental approaches that should only be considered under supervised conditions.[7]

TABLE 362-5 COMMONLY USED ORAL ANTIDEPRESSANT MEDICATIONS*

NAME OF CLASS/ SPECIFIC MEDICATION	IMMEDIATE MECHANISM OF ACTION	INITIAL ADULT DOSE	TARGET ADULT DOSE RANGE†	SIDE EFFECTS	COMMENTS
Selective serotonin reuptake inhibitors (SSRIs)	Inhibit presynaptic reuptake of serotonin			Nausea, diarrhea, sexual dysfunction, serotonin syndrome	As a class, common and reasonable first-line agents
Citalopram		20 mg daily	20-40 mg daily (maximum 20 mg daily in patients age >60 yr)	Risk of QTc prolongation/ torsades de pointes in at-risk patients	Few drug-drug interactions. May be activating
Escitalopram		10 mg daily	10-20 mg daily		Enantiomer of citalopram. May be activating
Fluoxetine		20 mg daily	20-40 mg daily (depression), up to 80 mg daily (OCD)		Long half-life; tends to be activating
Paroxetine		20 mg daily	20-50 mg daily	Anticholinergic effects	Tends to be sedating
Sertraline		25-50 mg daily	50-200 mg daily		Few drug-drug interactions. May be activating
Serotonin and norepinephrine reuptake inhibitors (SNRIs)	Inhibit presynaptic reuptake of serotonin and norepinephrine			Nausea, diarrhea, serotonin syndrome, sinus tachycardia, mild elevation in blood pressure, tremor	
Duloxetine		30-60 mg daily	30-60 mg daily on a twice-daily schedule, maximum of 120 mg/day		
Venlafaxine		37.5 mg bid	150-375 mg/day on bid schedule		XR form allows once-daily dosing
Desvenlafaxine		50 mg daily	50 mg daily, maximum of 100 mg ER daily		Metabolite of venlafaxine
Tricyclic antidepressants (TCAs)	Inhibit presynaptic reuptake of serotonin and norepinephrine (in varying proportions depending on the specific TCA)			Anticholinergic effects, sedation, orthostatic hypotension, tremor, cardiac conduction delays, ventricular arrhythmias	
Amitriptyline		25-75 mg qhs	150-300 mg qhs		Strongly anticholinergic and sedating; aim for combined amitriptyline/nortriptyline blood level of 120-250 ng/mL
Desipramine		25-75 mg daily	150-300 mg daily		Aim for blood level of 115-250 ng/mL
Doxepin		25-75 mg qhs	150-300 mg qhs		Strongly sedating
Imipramine		25-75 mg daily	150-300 mg daily		Strongly anticholinergic; aim for combined imipramine/ desipramine blood level of 180-350 ng/mL
Nortriptyline		25-50 mg qhs	50-150 mg qhs		Aim for blood level of 50-150 ng/mL; least anticholinergic of the TCAs
Monoamine oxidase inhibitors (MAOIs)	Inhibit monoamine oxidase, the enzyme that catalyzes oxidative metabolism of monoamine neurotransmitters			Need for tyramine-free diet to avoid sympathomimetic (hypertensive) crisis; sedation, anticholinergic effects, tremor, orthostatic hypotension	Initiation of any MAOI for a psychiatric indication generally should be on advice and under supervision of a psychiatrist
Isocarboxazid		10 mg bid	20-60 mg/day in bid-qid dosing		
Phenelzine		15 mg tid	45-90 mg/day in tid or qid dosing		
Selegiline	(selective MAO-B inhibitor)	5 mg bid	5 mg bid	Tyramine-free diet not required	Take with meals
Tranylcypromine		10 mg tid	30-60 mg/day in tid dosing		
Other					
Bupropion	Unknown, although it is a weak inhibitor of presynaptic reuptake of norepinephrine and dopamine	75-150 mg/day	300-450 mg/day	Activating; risk for seizures reduced by divided dosing and careful dosage titration	Divided dosing required unless using SR or XL forms. A reasonable alternative to SSRIs as a first-line agent
Mirtazapine	Antagonist at α_2 and 5-HT_2 receptors	15 mg qhs	30-45 mg qhs; maximum of 45 mg qhs	Sedation, hyperphagia	Becomes less sedating at higher doses. Often used for more severe or treatment-refractory depression
Trazodone	Inhibits presynaptic reuptake of serotonin; antagonist at 5-HT_2 and 5-HT_3 receptors	25-50 mg qhs	300-600 mg qhs for depression, 25-100 mg qhs for insomnia	Sedation, priapism	Few sexual side effects
Vilazodone	Inhibits presynaptic reuptake of serotonin; agonist at 5-HT_{1A} receptors	10 mg daily	40 mg daily	Nausea, diarrhea, sexual side effects	Dosage must be increased slowly. Reasonable second-line agent
Vortioxetine	Inhibits presynaptic reuptake of serotonin; agonist at 5-HT_{1A} receptors, antagonist at 5-HT_3 receptors	10 mg daily	20 mg daily	Nausea, diarrhea, sexual side effects	Reasonable second-line agent

*Patients on any of these medications must be monitored for suicidal thoughts.

†Target doses in the elderly may be lower.

bid = twice daily; ER = extended release; 5-HT_2 = 5-hydroxytryptamine; OCD = obsessive-compulsive disorder; qhs = at bedtime; qid = four times daily; SR = sustained release; tid = three times daily; XL = extended release; XR = extended release.

Continuation and Maintenance Therapies

After a patient achieves remission with an initial treatment, the same treatment should be continued for at least 6 months to reduce the risk of relapse. Patients who have had three or more lifetime episodes, or who develop rapidly recurrent or severe functionally disabling episodes should receive maintenance therapy. Mindfulness-based cognitive therapy, behavioral activation, and maintenance antidepressant treatment can reduce the rate of relapsing or recurrent depressive symptoms, and may have approximately equal efficacy in broad outpatient A9 populations.[A9] For highly recurrent depression, however, maintenance pharmacotherapy may have the best outcomes. Optimal care for depression in primary care and other treatment settings may be enhanced by the use of collaborative A10 care models that include on-site mental health specialists,[A10] although the lack of reimbursement mechanisms often limits their implementation.

PROGNOSIS

Optimal guideline-based treatment of major depression results in full remission in up to 80% of patients, and the expectation is that patients with major depression will return to baseline functioning after resolution of the depressive episodes. However, at least 50 to 70% of patients will suffer recurrent episodes, up to 20% may experience chronic major depression, and many more will achieve only partial remission with persistent lower-level symptoms because of a variety of factors, including limited access to care, reluctance to seek or adhere to treatment, or insufficiently assertive treatment strategies by the treating clinician. Worldwide, less than 25% of individuals with depression receive adequate treatment and are at higher risk of recurrent depressive episodes and of suicide. The life time risk of suicide among patients with untreated depression is nearly 20%.

BIPOLAR DISORDER

DEFINITION AND EPIDEMIOLOGY

Bipolar disorder, also known as bipolar I disorder, is characterized by recurrent episodes of idiopathic mania. Most persons with bipolar disorder also have recurrent episodes of major depression.

The 12-month prevalence of bipolar disorder is approximately 0.6%, with a slightly higher prevalence in males compared with females. The average age at first onset is late adolescence or early adulthood. Childhood onset is possible, but diagnosis may be difficult because of symptomatic overlap with other conditions of childhood, such as attention deficit hyperactivity disorder. First onset in midlife to late life is also possible, although late-onset mania is often secondary to other medical conditions or drugs rather than idiopathic 8 bipolar disorder.[8]

PATHOBIOLOGY

Even though the pathogenesis of bipolar disorder remains unclear, genetic factors play a greater role than in unipolar depressive conditions. Heritability has been traced to several specific loci in rare families, but genetic screening is not yet clinically useful, and the gene associations have to date revealed no unifying pathophysiologic themes. Most cases of bipolar disorder are polygenic and multifactorial, with genetic factors accounting for approximately 50% of the risk for the disorder. Dysregulation of frontostriatal systems is probably involved in the manifestations of the illness. Though not specific enough to be diagnostic, structural neuroimaging studies show increased ventricular-brain ratios suggestive of parenchymal atrophy. Phase advance of central circadian rhythms can precipitate episodes of mania in persons with bipolar disorder, so the decreased sleep need of persons with incipient mania may produce a vicious cycle in which phase-advanced circadian cycles lead to a further decreased need for sleep, thereby resulting in further phase advancement. Psychosocial stressors also often play a role in precipitating episodes of both mania and depression.

CLINICAL MANIFESTATIONS AND DIAGNOSIS

The symptoms of mania include a distinct period of abnormally and persistently elevated (euphoric) or irritable mood; goal-directed hyperactivity, often for pleasurable activities, with poor judgment that leads to long-lasting adverse financial, psychosocial, or medical consequences (e.g., sprees of spending, sexual activity, or gambling); increased energy; decreased need for sleep; pressured speech; and distractibility.

As with major depression, the diagnosis is based on findings from the history and examination revealing a pattern of recurrent manic episodes (Table 362-6) that are usually interspersed with major depressive episodes and cannot be explained by other medical conditions, medications, or other substances. Persons with bipolar disorder may become psychotic while in manic or depressed states, but a history of psychotic symptoms in the absence of mania or depression indicates a diagnosis other than bipolar disorder. Manic and depressive episodes also may be seen in the course of delirium (Chapter 361) and dementia (Chapter 371), in which case the psychiatric symptoms are accompanied by the cognitive deficits that are the hallmark of these neurocognitive conditions.

TABLE 362-6 SYMPTOMS/SIGNS OF AN EPISODE OF MANIA

DIAGNOSTIC CRITERIA
A distinct period of abnormally, persistently elevated, expansive, or irritable mood; and abnormally and persistently increased goal-directed activity or energy lasting ≥1 week and present most of the day, nearly every day, *AND*
3 or more of the following symptoms/signs (4 or more if the mood abnormality is only irritability):
Inflated self-esteem/grandiosity
Decreased need for sleep
More talkative or pressure to keep talking
Subjective experience of racing thoughts or flight of ideas observed on examination
Distractibility
Increase in goal-directed activity or psychomotor agitation
Excessive involvement in activities with a high potential for painful consequences
MANIC SYMPTOMS/SIGNS GROUPED CONCEPTUALLY, WITH ADDITIONAL COMMON PHENOMENA
Emotional
Euphoria
Irritability
Labile affect
Ideational
Grandiosity
Somatic/Neurovegetative
Increased energy
Psychomotor agitation
Decreased need for sleep
Distractibility
Other
Goal-directed hyperactivity
Pressured speech
Impaired judgment
Flight of ideas
Psychotic symptoms (may include delusions, hallucinations, or derailment of thought processes such as loose associations)—defines the subtype "mania with psychotic features"

From American Psychiatric Association. *Diagnostic and Statistical Manual of Mental Disorders.* 5th ed. Text Revision (DSM-5-TR). Washington, DC: American Psychiatric Association; 2022 with permission.

TREATMENT

The initiation of and significant alterations to treatments for bipolar disorder should be supervised by a psychiatrist. The mainstay of treatment for bipolar disorder is mood stabilizer medications to reduce the frequency and severity of recurrent manic and depressive episodes.[9,10] Mood stabilizers with substantial evidence base to support their use include lithium (typical dose of 600 to 1500 mg/day or higher given in two or three divided doses as needed to achieve plasma levels of 0.6 to 1.2 mEq/L [up to 1.4 mEq/L in acute mania]), valproic acid (typical dose of 500 to 1500 mg/day or higher as tolerated to achieve plasma levels of 50 to 100 μg/mL), and carbamazepine (typical dose of 400 to 1200 mg/day as tolerated to achieve plasma levels of 4 to 12 μg/mL). The combination of lithium plus valproate is superior to valproate alone for prevention of relapses. Lithium treatment is, however, associated with a decline in renal function, hypothyroidism, and hypercalcemia, especially in patients with higher lithium concentrations. A number of other anticonvulsants have been tried but generally with less empirical support for their use, although lamotrigine (starting at 25 mg/day, maximum dose of 200 mg/day, titrated slowly to minimize the risk for Stevens-Johnson syndrome) can be used for prophylaxis against depressive episodes. Several second-generation antipsychotic medications (e.g., olanzapine, quetiapine, and aripiprazole) are approved for bipolar I disorder maintenance by the U.S. Food and Drug Administration (FDA) for their mood-stabilizing properties, although their 9,10

potential to precipitate metabolic syndrome (and to a lesser extent tardive dyskinesia) should limit their use as maintenance medications to patients for whom other mood stabilizers are inefficacious or poorly tolerated.[11]

For acute episodes of mania (with or without coexisting psychotic symptoms), second- or first-generation antipsychotics are more rapidly efficacious than mood stabilizers, with doses similar to their use for acute psychosis (see Table 362-12). For acute treatment of bipolar depression, the evidence-based psychotherapies that are useful for unipolar depression are helpful, but antidepressants may precipitate mania. Therefore, patients in the depressive phase of illness should receive therapeutic doses of a mood stabilizer first, and antidepressant medication should used at the minimum dose for the minimum duration required. Supportive psychotherapy fosters compliance with maintenance treatments and helps patients manage psychosocial stressors, thereby minimizing their impact on precipitating mania or depression.[A11] Electroconvulsive therapy is useful for refractory mania[A12] or depression and for patients with relative contraindications to medications, such as pregnancy.

PROGNOSIS

Most patients with bipolar disorder return to baseline functioning between episodes. Some patients may experience frequent debilitating episodes (known as "rapid cycling," defined as four or more episodes per year), and others may experience deterioration in overall functioning over time.

OTHER DEPRESSIVE AND BIPOLAR DISORDERS

Although the diagnosis of chronic major depression should be made in patients with long-lasting major depressive episodes, other individuals may have chronic (≥2 years) lower-level depressive symptoms known as persistent depressive disorder (dysthymia),[12] which may be treated with a combination of antidepressant medication (Table 362-5) and psychotherapy.

Other patients may have "less than major depression" episodes of shorter duration, often referred to as subsyndromal or subthreshold depression. Broad psychotherapeutic interventions may prevent progression to full-fledged major depression in such patients. Premenstrual dysphoric disorder manifests as cyclical depressive and anxiety symptoms that resolve in the week after menses and recur in the week before the onset of menses; this is the only mood disorder that may respond to brief cyclical administration of antidepressant medication; most often an SSRI is used at usual doses (Table 362-5) for the week prior to menses.

Less severe bipolar-related disorders include bipolar II disorder, which is characterized by episodes of hypomania (i.e., low-level manic symptoms without substantial functional impairment and without psychosis) and episodes of major depression. Such patients typically seek care during depressive episodes rather than during hypomania, but antidepressant medication may worsen the manic symptoms. The clinician must ask about a history of manic or hypomanic symptoms when evaluating all patients with depression; such a history would likely change the diagnosis and require avoiding the use of antidepressants unless the patient is also on a mood stabilizer.

Cyclothymic disorder includes episodes of hypomania and low-level depression. It may be difficult to distinguish from the mood instability seen in cluster B personality disorders (see later).

ANXIETY DISORDERS

DEFINITION

The anxiety disorders (Table 362-7) are a group of conditions whose hallmark is idiopathic anxiety, typically accompanied by psychological (i.e., thought content) and somatic symptoms.[13] Anxiety is a common accompanying symptom in many other psychiatric disorders, but the primary anxiety disorders lack the neurocognitive deficits, depressive or manic symptoms, or psychosis seen in the other disorders. Trauma, stressor-related disorders, and obsessive-compulsive disorders also manifest with prominent anxiety but are classified separately from the anxiety disorders.

EPIDEMIOLOGY

Anxiety disorders are a worldwide public health problem. Panic disorder has a 12-month prevalence of 2 to 3%. Generalized anxiety disorder has a 12-month prevalence of approximately 3%, and the phobias collectively have a prevalence of 10 to 15% in the adult population. Cumulatively, anxiety disorders may have the highest prevalence of all primary psychiatric disorders in primary care settings. Clear data on incidence rates are not available.

Specific phobias often begin in childhood, although patients may not come to clinical attention until adolescence or adulthood. Most primary anxiety disorders typically begin in adolescence through the mid-30s.

Anxiety symptoms with new onset in later life are usually due to mood or neurocognitive disorders or are secondary to medical illnesses or drugs; true late-onset primary anxiety disorders are often triggered by traumatic or other stressful life events.

PATHOBIOLOGY

Anxiety may be understood in part as inappropriate triggering of the stress response system, commonly referred to as the "fight-or-flight" response. However, it is important to recognize that the responses involve a wide range of cognitive, motor, neuroendocrine, and autonomic systems and thus are not limited to manifestations of sympathetic nervous system activity. The "salience network" is thought to play a crucial role in the neurobiologic coordination of anxiety. The amygdala receives excitatory glutamatergic input from several cortical areas and from the thalamus, thereby allowing it to respond to a wide variety of stimuli, including sensory input from the external world, as well as stressors that are processed and recognized by cortical association areas. The amygdala in turn projects to the many brain regions that subserve the clinical manifestations of the anxiety response, in part through its direct projections to the important centers of monoaminergic systems: dopaminergic neurons of the ventral tegmental area in the midbrain, noradrenergic neurons in the locus coeruleus, and serotonergic neurons in the raphe nuclei.

From a cognitive psychology perspective, the pathogenesis of many anxiety disorders, particularly panic disorder, may be understood as catastrophic misinterpretations of normal somatic sensations. A vulnerable individual may become aware of a normal or minimally abnormal body sensation, which is interpreted as something concerning, thereby leading to sympathetic and other autonomic arousal, which in turn leads to further somatic sensations (e.g., tachycardia, sweating) in what becomes a vicious cycle of thoughts and somatic symptoms.

CLINICAL MANIFESTATIONS

Most individuals experience one or more somatic symptoms (Table 362-8) that accompany psychic anxiety, regardless of whether the anxiety is normal or part of a pathologic condition. Such somatic symptoms may be similar to symptoms associated with true pathophysiologic abnormalities in many other organ systems.

Many anxiety disorders include acute, discrete periods of symptoms known as panic attacks. In a panic attack, the patient experiences an abrupt surge in anxiety, fear-related thoughts, and somatic symptoms in the space of a few minutes ("crescendo onset"). The acute symptoms resolve quickly, typically within an hour or less.

TABLE 362-7 COMMON ANXIETY DISORDERS

ANXIETY DISORDER	MAJOR CLINICAL CHARACTERISTICS
Panic disorder	Recurrent unexpected panic attacks, typically with anticipatory anxiety and avoidance behavior
Generalized anxiety disorder	Excessive anxiety and worry, not meeting the criteria for other anxiety disorders, lasting ≥6 months
Agoraphobia	Anxiety about or avoidance of places or situations from which escape might be difficult or embarrassing or in which help might not be available in the event of panic symptoms
Social phobia (social anxiety disorder)	Anxiety provoked by exposure to social situations, typically with ensuing avoidance behavior; may be generalized (i.e., in response to many interpersonal situations) or specific in response to a particular social situation (e.g., using a public restroom, public speaking)
Specific phobia	Anxiety provoked by exposure to a specific feared object or (non-social) situation, typically with ensuing avoidance behavior

Author summary based on categories and criteria from American Psychiatric Association. *Diagnostic and Statistical Manual of Mental Disorders*. 5th ed. Text Revision (DSM-5-TR). Washington, DC: American Psychiatric Association; 2022.

TABLE 362-8 COMMON SOMATIC MANIFESTATIONS OF ANXIETY

CARDIORESPIRATORY
Palpitations
Chest pain
Dyspnea or sensation of being smothered
GASTROINTESTINAL
Sensation of choking
Dyspepsia
Nausea
Diarrhea
Abdominal bloating or pain
GENITOURINARY
Urinary frequency or urgency
NEUROLOGIC/AUTONOMIC
Diaphoresis
Warm flushes or chills
Dizziness or presyncope
Paresthesias
Tremor
Headache

Panic Disorder

Panic disorder consists of *recurrent panic attacks*. Although some panic attacks may be precipitated by situations known by the patient to trigger attacks, by definition at least some attacks must be *unexpected* ("out of the blue"). Faced with recurrent unexpected panic attacks, patients develop *anticipatory anxiety* in which they experience ongoing psychic distress by worrying about their next panic attack or the attack's effects (e.g., humiliation if the attack were to happen in public view). In addition, patients manifest *avoidance behavior* by staying away from known triggers or from situations in which having a panic attack might be dangerous (e.g., driving) or particularly distressing (e.g., in public spaces). For many patients, the anticipatory anxiety and avoidance behavior may be more disabling than the panic attacks themselves.

Generalized Anxiety Disorder

This more heterogeneous condition is defined by the presence of clinically significant anxiety and associated somatic symptoms for 6 or more months. For some patients, the symptoms are episodic but are not the full-fledged panic attacks seen in panic disorder, whereas for others the symptoms may be omnipresent, albeit often with waxing and waning intensity. Generalized anxiety disorder is often overridden in the diagnostic hierarchy by other conditions that produce anxiety.

Social Anxiety and Phobias

The phobias are a group of conditions defined by the consistent ability of a specific environmental stimulus to elicit a pathologic anxiety response. Exposure to such a stimulus nearly always produces this response, so the patient avoids the stimulus whenever possible (i.e., avoidance behavior) or endures the stimulus with considerable distress. The phobias are further classified based on the type of stimulus that evokes a phobic response.

Agoraphobia is defined as a distressing and disabling fear of places or situations from which escape might be difficult or embarrassing or from which help might not be available in the event of panic-like symptoms. Common agoraphobic foci include being outside one's home alone, being on bridges or in tunnels, traveling by vehicle, or being in crowds or lines. A third or more of patients with panic disorder have comorbid agoraphobia, but many patients have agoraphobia without panic disorder. In addition to agoraphobia, the other main types of phobias are social phobia (social anxiety disorder) and other specific phobias (see Table 362-7).

DIAGNOSIS

Diagnosis of anxiety disorders must rest on consideration of both syndromic and etiologic perspectives. From a syndromic perspective, a careful history and mental status examination are required to determine the pattern of anxiety and associated symptoms and to determine whether the phenomenology fits the pattern for any of the anxiety disorders as described earlier. The history and mental status examination must also assess for the presence of any other psychiatric disorder, some of which are truly comorbid with the anxiety disorder but some of which might supersede the anxiety disorder in the diagnostic hierarchy. For example, generalized anxiety may manifest as part of neurocognitive disorders (delirium or dementia), depressive or bipolar disorders, and psychotic (schizophrenia and related) disorders.

From an etiologic perspective, it is important to determine whether the anxiety disorder is primary (idiopathic) or secondary to a systemic or neurologic condition (see Table 362-1), drug intoxication, or withdrawal state. The evaluation should include physical examination and laboratory tests (e.g., toxic drug screen) as guided by the differential diagnosis generated from the history and mental status evaluation.

TREATMENT

Empirical evidence from controlled trials demonstrates the efficacy of cognitive-behavioral psychotherapies for most of the anxiety disorders. The behavioral component of such therapies uses the principles of learning theory to extinguish unhelpful behavior and positively reinforce more functional behavior. The cognitive component of the therapy helps the patient learn to identify and correct the dysfunctional patterns of thinking ("automatic thoughts") that underlie or trigger the cognitive-physiologic cascade of pathologic anxiety responses. Cognitive-behavioral therapy may be used as sole therapy, particularly for specific phobias, or in combination with pharmacotherapy for panic disorder and social phobia. Although cognitive-behavioral therapy may be administered in individual therapy with the patient, it also may be used as part of family therapy (e.g., to help family members avoid behavior that inadvertently reinforces the patient's symptoms) or in group therapy settings. When available, cognitive-behavioral therapy generally should be a first-line approach for most outpatients with most anxiety disorders.

Pharmacotherapy should be combined with cognitive behavioral therapies for more severe or treatment-refractory anxiety disorders.[14] Although anxiolytic drugs such as the benzodiazepines (Table 362-9) will usually relieve acute anxiety symptoms, for most patients they should not be the mainstay of chronic treatment because of concerns about their long-term efficacy and side effects (e.g., risk for abuse, risk for neurocognitive impairment or falls). Antidepressant medications (see Table 362-5) are the better pharmacologic agents for most anxiety disorders.[A13] In general medical settings, SSRIs including sertraline and paroxetine are often first-line choices for panic disorder, generalized anxiety disorder, and social phobia, although most antidepressants, with the probable exception of bupropion, can be helpful.[A14] β-Adrenergic blockers have been used for sympathetic symptoms of anxiety in acute situations for which benzodiazepines might unacceptably impair performance (e.g., public speaking, stage performance) but do not address other symptoms and are not recommended for longer-term use in panic disorder or phobias.

14 A13 A14

PROGNOSIS

In general, most persons with ongoing anxiety disorders tend to have a chronic course of waxing and waning symptoms. Maintenance therapies often should be used for patients with more chronic anxiety disorders, although the evidence base to support specific long-term therapies is not as robust as for depressive, bipolar, and psychotic disorders.

OBSESSIVE-COMPULSIVE DISORDER

Although anxiety is often prominent in obsessive-compulsive disorder (OCD), OCD has a distinct pathogenesis that is likely more closely related to other conditions such as body dysmorphic disorder, hoarding disorder, trichotillomania (hair-pulling), and excoriation (skin-picking) disorder.

Patients with OCD have recurrent obsessions or compulsions (Table 362-10), and most patients have both. OCD should not be confused with obsessive-compulsive personality traits or disorder, described later under "Personality Disorders." Obsessions also should not be confused with obsessing (ruminating) on a topic. Rather, obsessions are recurrent, persistent, and typically distressing thoughts that at some point during the course of the disorder are experienced as intrusive and senseless. The latter quality may be described in language such as "I don't know where this thought comes from" or "I don't know why I have this thought, I would never actually do such a thing!" Compulsions are repetitive behaviors or mental acts that the individual feels driven to perform in response to an obsession or according to rigid rules, even though they often are experienced as senseless and excessive. For example, compulsive handwashing may relate to obsessional thoughts about germs or contamination. Patients with OCD typically attempt to ignore, suppress, or neutralize their obsessions, but doing so causes great psychic distress. OCD patients may spend many hours per day related to their obsessions and compulsions. Many patients with chronic obsessions or compulsions no longer find them "senseless" and may rationalize their thoughts or behaviors.

The 12-month prevalence of OCD is approximately 1%, with onset typically in childhood, adolescence, or young adulthood. Pathogenesis probably involves

TABLE 362-9 SELECTED ORAL ANTIANXIETY AND HYPNOTIC DRUGS*

DRUG	TRADE NAME	INITIAL DOSE	TARGET DOSE RANGE†	SIDE EFFECTS	COMMENTS
Benzodiazepines				Sedation, ataxia, risk for falls	Potential for abuse/dependence
Lorazepam	Ativan	0.5 mg bid-qid	2-6 mg/day, tid-qid dosing		Reliable IM absorption; commonly used
Diazepam	Valium	2-5 mg bid-tid	10-40 mg/day, bid-tid dosing		Long half-life of drug and active metabolites limits use, although lipophilicity produces rapid-onset and fairly short duration of action for a single dose
Triazolam	Halcion	0.125 mg qhs	0.125-0.25 mg qhs	Rebound insomnia	Used in the past as hypnotic
Chlordiazepoxide	Librium	5 mg bid-tid	10-40 mg/day, bid-tid dosing		Long half-life of drug and active metabolites, limiting use
Temazepam	Restoril	7.5 mg qhs	7.5-30 mg qhs		Used in the past as hypnotic
Alprazolam	Xanax	0.25 mg tid-qid	2-8 mg/day, tid-qid dosing	Possibly greater addictive potential	Recommend limiting use
Clorazepate	Tranxene	7.5-15 mg bid-tid	15-60 mg/day, bid-tid dosing		
Flurazepam	Dalmane	15-30 mg qhs	15-30 mg qhs	Daytime somnolence	Used as hypnotic
Oxazepam	Serax	10-15 mg tid-qid	10-30 mg tid-qid		Profile similar to lorazepam
Clonazepam	Klonopin	0.5 mg bid-tid	0.5-5 mg bid-tid		Long duration of action; useful for seizure control in some patients
"Non-benzodiazepine" hypnotics					Mechanism of action, effects, and side effects generally similar to the benzodiazepines
Zaleplon	Sonata	5-10 mg qhs	5-20 mg qhs		
Zolpidem	Ambien	5-10 mg qhs	5-10 mg qhs		
Eszopiclone	Lunesta	1-2 mg qhs	1-3 mg qhs		
β-Blockers					
Propranolol	Inderal	20 mg bid	Individualize, 40-120 mg/day	Bradycardia, hypotension, potential for mental slowing	Only helps with sympathetically mediated somatic symptoms of anxiety; therefore, main use is for short-term symptomatic relief in situations where sedating effects of benzodiazepines are problematic (e.g., "stage fright")

*Antidepressants (see Table 362-5) are often first-line agents of choice for primary anxiety disorders.
†Target doses in the elderly may be lower.
bid = twice daily; IM = intramuscular; qhs = at bedtime; qid = four times daily; tid = three times daily.

TABLE 362-10 COMMON TYPES OF OBSESSIONS AND COMPULSIONS IN OBSESSIVE-COMPULSIVE DISORDER

OBSESSIONS

Aggressive (fears of harming self or others, of blurting out obscenities, or of other unwanted aggressive acts; unwanted violent or horrific images)
Contamination (concerns about dirt, germs, body waste or secretions, environmental contaminants, or animals/insects)
Sexual (concerns about unwanted sexual images or impulses)
Hoarding/saving
Religious (scrupulosity) (excessive concerns about sacrilege, blasphemy, right/wrong, morality)
Need for symmetry/exactness
Somatic (excessive concern about illness, body part, or appearance)

COMPULSIONS

Cleaning/washing (excessive or ritualized handwashing, showering, or other grooming)
Checking (checking locks, stove, appliances; checking body in relation to somatic obsessions; checking that did not or will not harm self or others)
Repeating rituals (rereading or rewriting; routine activities such as going through a door or arising from a chair)
Counting
Ordering/arranging
Hoarding/saving

Adapted from Goodman WK, Price LH, Rasmussen SA, et al. The Yale-Brown Obsessive Compulsive Scale. I. Development, use, and reliability. *Arch Gen Psychiatry*. 1989;46:1006-1011.

altered functioning of the striatofrontal systems, as well as a prominent role for central serotonergic systems. Obsessions and compulsions may represent inappropriate triggering of neural "scripts" involving thoughts and behaviors that have been analogized to the scripts involved in animal grooming and other complex stereotypical behaviors.

TREATMENT AND PROGNOSIS

Cognitive-behavioral therapies are efficacious as first-line treatments but also can be combined with pharmacotherapy. The only efficacious antidepressants in OCD are those with strong activity on serotonergic systems. SSRIs (e.g., fluoxetine, sertraline; see Table 362-5 for dosing) first-line agents, but the tricyclic clomipramine also is effective. For treatment-resistant disease, atypical antipsychotics (see Table 362-12) are an option. Deep brain stimulation targeting the ventral capsule/ventral striatum is FDA approved (as a humanitarian device exemption) for severe treatment-refractory OCD, although its precise role remains to be determined. Regional transcranial magnetic stimulation may also be useful.

Remission rates are low in adults, with most persons experiencing a chronic waxing and waning course.

ACUTE STRESS DISORDER AND POST-TRAUMATIC STRESS DISORDER

Acute stress disorder and post-traumatic stress disorder (PTSD) are specific manifestations of symptoms referable to an extremely traumatic event.[15] The event by definition must involve exposure to actual or threatened death, serious injury, or sexual violence, as reported directly by the patient or by family members or friends. The patient must have suffered the event,

witnessed it, had it reported to them by close family members or friends, or have had repeated or extreme exposure to aversive details of the event, such as first responders collecting human remains. It is important to recognize that acute stress disorder or PTSD does not develop in all individuals exposed to a traumatic event. Some individuals may instead develop an anxiety disorder, major depression, mania, or psychosis, and many may never develop diagnosable psychopathology. The 12-month prevalence of PTSD in the United States is about 3%, with projected lifetime risk approaching 9%.

PTSD symptoms by definition persist for more than 1 month after the traumatic event and include the following types of clinical phenomena: (1) intrusion, such as intrusive memories, dreams, flashbacks, or intensely distressing psychological or physiologic responses to reminders of the trauma; (2) avoidance of distressing memories or external reminders of the trauma; (3) negative cognitions and mood, such as amnesia for aspects of the event, negativistic thoughts about oneself in general or blame related to the event, persistent negative emotions, diminished interests or activities, or feelings of detachment; and (4) alterations in arousal and reactivity. Acute stress disorder by definition resolves in less than 1 month, with symptoms of intrusion, avoidance, or arousal as well as negative mood or dissociative symptoms (e.g., "in a daze").

TREATMENT AND PROGNOSIS

Trauma-focused psychotherapy with an exposure component is first-line treatment for both acute stress disorder and PTSD. Despite widespread use, psychological debriefing (e.g., critical incident stress debriefing) has not been found to be effective.[A15] A15

Medications have little role in the treatment of acute stress disorder other than short-term reduction of anxiety, insomnia, or pain. Antidepressants (see Table 362-5) have demonstrated efficacy in PTSD, with SSRIs considered first-line agents. Other agents used for PTSD include prazosin (1 mg at bedtime; may be increased by 1 to 2 mg/day every 3 to 4 days to up to 15 mg/day), primarily for nightmares and insomnia, and second-generation antipsychotics, such as risperidone and quetiapine. Early evidence suggest that ketamine also may be useful in severe cases.[A16] A16

About half of adults with PTSD have complete recovery within 3 months. However, PTSD may persist for many months or years despite treatment.

SCHIZOPHRENIA AND RELATED PSYCHOTIC DISORDERS

Psychotic disorders are defined as a loss of reality testing, include delusions (fixed false beliefs), hallucinations (false sensory perceptions), and major derailments in thought processes (e.g., loose associations). Psychotic symptoms also may be seen in the course of neurocognitive, secondary, and mood disorders. The psychotic disorders are defined by the presence of psychotic symptoms in the absence of prominent mood disturbance or of neurocognitive deficits consistent with delirium or dementia. In general, the diagnosis and treatment of patients with psychotic disorders should be conducted in mental health specialty settings, but primary care settings are common points of entry to care.

SCHIZOPHRENIA

DEFINITION AND EPIDEMIOLOGY

Schizophrenia, the prototypical psychotic disorder, necessarily includes symptoms of psychosis ("positive" symptoms) and also often includes "negative symptoms" such as affective flattening, abulia, apathy, and social withdrawal.[16] 16
The level of functioning is impaired in one or more realms (e.g., occupational, interpersonal, or self-care). The lifetime prevalence of schizophrenia is slightly less than 1%, and its chronic debilitating course takes a considerable toll on patients, families, and society. Peak onset is in late adolescence to young adulthood, slightly younger for males than females. The annual incidence is approximately 15 per 100,000, but with marked variability across study samples and populations. The condition is slightly more common in males than in females.

PATHOBIOLOGY

The pathogenesis of schizophrenia remains unknown. Twin studies show that the disease is multifactorial. Genetic factors account for up to 50% of the risk, and multiple gene loci appear to be involved. Genetically, schizophrenia is highly heterogeneous, with a large number of severe ultrarare mutations that are related to synaptic plasticity.[17] 17 Studies of postmortem brains indicate a nongliotic neuropathologic process with subtle disruptions of cortical cytoarchitecture. Considerable neuroimaging and neuropsychologic evidence supports the notion of cerebral dysfunction. Dopaminergic mesocortical and mesolimbic pathways as well as glutamatergic systems are important in the production of psychotic symptoms. It is likely that psychosocial factors and neurodevelopment interact with a nonlocalizable brain lesion that is either present at birth or acquired early in life. Psychosocial stressors also can precipitate exacerbations and worsen the overall course of schizophrenia.

DIAGNOSIS

The diagnosis of schizophrenia is based on the presence of delusions, hallucinations, and disorganized speech and behavior, often accompanied by apathy and social withdrawal and resulting in major impairment in functioning for at least 6 months (Table 362-11). Patients who have a single schizophrenia-like psychotic episode of briefer duration, with subsequent return to asymptomatic baseline functioning, are defined as having a brief psychotic disorder (<1 month) or a schizophreniform disorder (1 to 6 months). As with all psychiatric syndromes, psychosis may be due to other medical conditions that affect the central nervous system. For example, an acute first psychotic event can be the result of an autoimmune encephalitis.[18] 18

TREATMENT

Patients with psychoses require specialized psychiatric care. Antipsychotic medications (Table 362-12), often with adjunctive benzodiazepines, are used to treat acute psychotic episodes, commonly in acute inpatient settings so that the patient can be managed safely until the acute symptoms improve.[19] 19
Maintenance antipsychotic medications help reduce the severity and frequency of acute psychotic episodes. Comprehensive psychosocial rehabilitation programs are also important to improve functional outcomes; assertive use of such programs promptly at the initial onset of psychotic symptoms may improve the longer-term course of the illness.

Second-generation ("atypical") antipsychotic medications have replaced first-generation antipsychotics in common U.S. practice because of their lower rates of extrapyramidal side effects, including tardive dyskinesia, although their efficacy is generally not better than that of first-generation drugs. An exception is clozapine, which has greater efficacy, but is limited by the need for close monitoring for agranulocytosis. A large trial found that clozapine and long-acting injectable antipsychotics were associated with the greatest reduction in relapse rates.[A17] A17 Second-generation drugs contribute to the increase in obesity and metabolic syndrome in patients with chronic schizophrenia (Chapter 402). Cariprazine, a new-generation antipsychotic, might be superior to risperidone for patients with predominantly negative symptoms (withdrawal, apathy, etc.).[A18] A18 However, a systematic review concluded that there are no clear differences among antipsychotic agents for maintenance treatment and prevention of relapse.[A19] A19

PROGNOSIS

The prognosis of individuals with schizophrenia is often poor, with recurrent episodes of psychotic exacerbations superimposed on progressively deteriorating baseline functioning. However, antipsychotic drugs significantly reduce

TABLE 362-11 SYMPTOMS AND SIGNS OF MAJOR PSYCHOTIC DISORDERS

SCHIZOPHRENIA
Delusions
Hallucinations
Disorganized speech (i.e., thought process derailments)
Grossly disorganized or catatonic behavior
Negative symptoms: affective flattening, alogia, avolition
Major impairment in social or occupational functioning
Duration of at least 6 months
SCHIZOAFFECTIVE DISORDER
During the course of illness, at least one episode of schizophrenia-like psychotic symptoms *with* a mood syndrome (either major depression or mania), *AND*
During the course of illness, at least 2 weeks of schizophrenia-like psychotic symptoms *in the absence of* a mood syndrome
DELUSIONAL DISORDER
One or more delusions for at least 1 month, most often nonbizarre (i.e., potentially plausible, such as delusions of being followed, poisoned, infected, loved at a distance, deceived by a spouse or lover, or having a disease)
Not meeting full criteria for an acute episode of schizophrenia
Functioning *not* markedly impaired other than as related to the impact of the delusion(s) and its ramifications

Based on criteria from American Psychiatric Association. *Diagnostic and Statistical Manual of Mental Disorders*. 5th ed. Text Revision (DSM-5-TR). Washington, DC: American Psychiatric Association; 2022.

relapse rates. Some patients have a more favorable course, and a small proportion of individuals may recover completely. Male sex, prominent negative symptoms, younger age at first onset, and enduring psychosocial stressors and family discord all predict poorer outcomes. Average life expectancy is shortened by 10 to 15 years because of poor health behaviors, higher rates of other medical disorders (including metabolic syndrome), and a lifetime suicide risk of approximately 5 to 6%.

SCHIZOAFFECTIVE DISORDER

Schizoaffective disorder is a chronic recurrent disorder with a lifetime prevalence of approximately 0.3%. It is characterized by episodes of psychosis in the absence of mania or depression, and also by mood episodes (manic or depressed) with psychotic features. As a result, the diagnosis of schizoaffective disorder requires knowledge of the patient's course over at least two episodes and cannot be based solely on clinical findings at any one point in time. Treatment is symptomatic and involves the use of antipsychotic medications (see Table 362-12), mood stabilizers (see the Treatment box for bipolar disorders), and antidepressant medications (see Table 362-5) to target specific psychotic and mood symptoms. The outcomes of schizoaffective disorder are heterogeneous but on average intermediate between those of schizophrenia and of depressive and bipolar disorders.

DELUSIONAL DISORDER

Delusional disorder is characterized by one or more delusions in the absence of a thought process disorder, prominent hallucinations, or the negative symptoms seen in schizophrenia. The most characteristic types of delusions are potentially plausible ("nonbizarre"), such as unfounded beliefs of a partner's infidelity. Delusional disorder has a lifetime prevalence of approximately 0.2%. The pathogenesis of delusional disorder remains largely unknown. It is often only partially responsive to antipsychotic medications (see Table 362-12), but patients' functioning may be largely unimpaired if they are able, with the aid of antipsychotics and psychotherapy, to avoid acting on their delusions.

EATING DISORDERS

Eating disorders, which are quite common (up to 5% of the population), are characterized by severe and persistent disturbances in eating behaviors associated with distressing thoughts and emotions. The eating disorders seen in adults include anorexia nervosa, bulimia nervosa, binge eating disorder, and avoidant restrictive food intake disorder (see Chapter 200).

SOMATIC SYMPTOM AND RELATED DISORDERS

Formerly termed *somatoform disorders*, the *somatic symptom and related disorders* include both somatic symptoms and associated thoughts, feelings, or behaviors that are more distressing and disabling than expected with no or little medical explanation (Table 362-13). For three conditions in this category (somatic symptom disorder, illness anxiety disorder, and conversion disorder), patients are not pretending to be ill but are genuinely experiencing distressing symptoms and believe that they are sick. The three conditions are differentiated from each other by the nature of primary distress as well as the associated thoughts, feelings or behaviors. For somatic symptom disorder, one or more somatic symptoms themselves are the most distressing and result in significant disruption of daily life. For illness anxiety disorder (previously termed hypochondria), preoccupation with having or acquiring a serious illness is the main source of distress. Conversion disorder (also called functional neurologic symptom disorder) is more closely related to somatic symptom disorder because motor or sensory deficits are central to the patient's

TABLE 362-12 COMMONLY USED ANTIPSYCHOTIC MEDICATIONS*

DRUG NAME	INITIAL DOSE FOR PSYCHOSIS IN SCHIZOPHRENIA†	TARGET DOSE FOR PSYCHOSIS IN SCHIZOPHRENIA‡	SIDE EFFECTS	CHLORPROMAZINE DOSAGE EQUIVALENCE (FIRST-GENERATION DRUGS ONLY)/OTHER COMMENTS
First-generation drugs			Low-potency drugs: anticholinergic effects, orthostatic hypotension, prolongation of QT interval, cholestatic jaundice High-potency drugs: extrapyramidal side effects (dystonias, akathisia, parkinsonism, neuroleptic malignant syndrome), hyperprolactinemia with galactorrhea	High-potency drugs are reasonable first-line agents but often supplanted by second-generation drugs
Chlorpromazine	100 mg qd	300-1000 mg/day, qd-bid dosing		100 mg
Thioridazine	50-100 mg qd	300-800 mg/day, qd-bid dosing	Pigmentary retinopathy at higher doses	100 mg
Thiothixene	2-5 mg qd	5-60 mg/day, qd-bid dosing		5 mg
Trifluoperazine	2-5 mg qd	5-40 mg/day, qd-bid dosing		5 mg
Perphenazine	4-8 mg qd	8-64 mg/day, qd-tid dosing		8 mg
Haloperidol	0.5-2 mg qd	2-10 mg/day (up to 40 mg/day or higher in refractory cases), qd-bid dosing		2 mg; available in depot IM form
Fluphenazine	1-2.5 mg qd	2.5-10 mg/day (up to 40 mg/day in refractory cases), qd-bid dosing		2 mg; available in depot IM form
Second-generation drugs ("atypical antipsychotics")			Metabolic syndrome, risk for stroke and mortality in older patients with dementia, QT prolongation	Most have become reasonable first-line agents
Risperidone	0.5-1 mg qd-bid	2-4 mg/day, qd-bid dosing	Extrapyramidal side effects at higher doses	Available in depot IM form
Olanzapine	5 mg qd	5-10 mg qd (up to 20 mg/day in refractory cases)		
Ziprasidone	20 mg bid	20-80 mg bid		
Quetiapine	25-50 mg bid-tid	300-800 mg/day, bid-tid dosing		Sublingual
Asenapine	5 mg bid	5-10 mg bid		Extended-release form for qd dosing
Paliperidone	3-6 mg qd	6-12 mg qd		
Iloperidone	1 mg bid	2-12 mg bid		
Lurasidone	40 mg qd	40-160 mg qd		
Aripiprazole	10-15 mg qd	10-30 mg qd		Partial agonist/antagonist at D_2 receptors
Clozapine	12.5 mg qd-bid	300-900 mg/day, qd-bid (titrate dose slowly by 25-50 mg/day every 3-7 days)	Risk for agranulocytosis, requires ongoing monitoring of complete blood count	Efficacy superior to that of other antipsychotics, but hematologic risks and need for monitoring limit its use

*Oral unless otherwise indicated.
†Doses for other indications, such as agitation in delirium or dementia, may be much lower.
‡Target doses in the elderly may be lower.
bid = twice daily; IM = intramuscular; qd = daily; qid = four times daily; tid = three times daily.

TABLE 362-13 SOMATIC SYMPTOM AND RELATED DISORDERS

TYPE	MAIN CLINICAL MANIFESTATIONS
Somatic symptom disorder	One or more distressing somatic symptoms, together with excessive thoughts, feelings, or behaviors related to these symptoms; subsumes most of the former terms somatization disorder, pain disorder, undifferentiated somatoform disorder, and many with the former diagnosis of hypochondriasis
Illness anxiety disorder	Illness preoccupation and excessive health-related behaviors in the absence of or disproportionate to somatic symptoms; subsumes some patients with the former diagnosis of hypochondriasis
Conversion disorder (functional neurologic symptom disorder)	Neurologic somatoform symptoms (other than pain) with clinical evidence incompatible with recognized neurologic or general medical conditions (e.g., paralysis, blindness, dyscoordination, convulsion-like phenomena, memory or other neurocognitive complaints)
Psychological factors affecting other medical conditions	Psychological factors adversely affecting a (non–mental disorder) medical symptom or condition by worsening the course, interfering with treatment, adding to known health risks, or influencing underlying pathophysiology
Factitious disorder (commonly called Munchausen syndrome)	Falsification of physical or psychological signs or symptoms, with health- or help-seeking behaviors, in the absence of clear external rewards

Author summary based on criteria from American Psychiatric Association. *Diagnostic and Statistical Manual of Mental Disorders*. 5th ed. Text Revision (DSM-5-TR). Washington, DC: American Psychiatric Association; 2022.

distress. In all cases, identifiable physical disease is insufficient to explain the patient's presentation, the patient's distress and dysfunction are *not* consciously produced, and the symptoms are just as distressing and baffling to patients as would be similar symptoms produced by physical disease.

In contrast, *malingering* is the conscious feigning of illness for conscious gain (e.g., housing, financial compensation, etc.) and is not considered to be a mental disorder at all. *Factitious disorder* (often known as Munchausen syndrome) similarly involves intentional falsification of physical or psychological signs or symptoms or even self-injury. What separates factitious disorder from malingering is the absence of obvious external rewards or secondary gain other than the adoption of a sick role and attention from health care providers from this deception.

Psychological factors affecting other medical symptoms is diagnosed when a psychological factor has clinically significant effects on the course or outcome of a medical condition. For example, psychiatric symptoms (e.g., anxiety) interfering with evaluation or adherence of treatment of a potentially serious medical condition would be a common manifestation of this disorder.

TREATMENT

Management of patients with somatic symptom disorders is often difficult because physicians must simultaneously maintain an appropriate level of vigilance for undiagnosed physical illness while avoiding unnecessary interventions. Keys to ongoing care include maintaining an ongoing therapeutic alliance; setting regular office visits; conveying empathy for the patient's very real distress without colluding with the patient's belief in an identifiable physical disorder; and treating depression, anxiety, or other comorbid psychopathology. It often is helpful for one primary physician to coordinate all specialty care and to prescribe all treatments. Antidepressant medications may benefit selected patients (e.g., some chronic pain syndromes), even in the absence of other comorbid psychiatric disorders.

PERSONALITY DISORDERS

Personality is defined as the repertoire of enduring patterns of inner mental experience and behavior, including affect and impulse regulation, defense and coping mechanisms, and interpersonal relatedness. Dimensional models of personality (i.e., using multiple continuous measures of constructs such as neuroticism, extraversion, and openness to experience) likely are a more accurate representation of the spectrum of human personality, but categorical diagnostic categories (i.e., personality disorders) are more useful for clinicians to determine prognosis and treatments. Personality and personality disorders are the result of complex interactions among genetic, environmental, and developmental factors. The cumulative point prevalence of all personality disorders in the general adult population is approximately 10 to 15%, with rates as high as 50% in patients receiving care in psychiatric treatment settings.

CLINICAL MANIFESTATIONS AND DIAGNOSIS

A personality disorder is diagnosed when enduring personality traits lead to pervasive (if variable) distress or dysfunction in a range of situations (Table 362-14).[20] The cluster C personality disorders have the highest combined prevalence in the general population, but the cluster B disorders are most likely to come to clinical attention. In diagnosing personality disorders, care must be taken to distinguish personality *traits*, which by definition are enduring, from time-limited *states*. Most persons can regress to less adaptive personality styles not characteristic of their baseline personality traits in the context of substantial psychosocial stressors. [20]

TREATMENT

In many affected individuals, trying to alter the fundamental personality structure is not a realistic goal. Instead, a usually more realistic goal is to use supportive psychotherapy to help patients maximize use of their personality strengths while minimizing the harmful effects of emotional dysregulation, dysfunctional defenses, and destructive behavior. Dialectic behavior therapy is an evidence-based, focused psychotherapy based on specific cognitive-behavioral techniques that reduce self-injurious behavior and suicidality in patients with borderline personality disorder.

Although pharmacotherapy is not the mainstay of treatment for most personality disorders, drugs can be useful in selected patients. Antipsychotic drugs may be used to target escalating paranoia in paranoid personality disorder or for short-term reduction in emotional and impulse regulation with a wide range of (often cluster B, see Table 362-14) personality disorders in times of crisis (see Table 362-12, generally lower doses are used for this purpose). For longer-term treatment of emotional dysregulation in borderline and other cluster B personality disorders, a mood stabilizer, as for bipolar disorders, or antidepressant (see Table 362-5) may be used in conjunction with psychotherapy.

SUICIDE AND EVALUATION OF SUICIDALITY

Suicide is a leading cause of death worldwide. Suicide rates in the United States average approximately 11 per 100,000 per year, with considerable variability geographically and demographically. Suicide is the third leading cause of death in adolescents and young adults and the tenth leading cause of death in the population overall. Of all age-, gender-, and race-based demographic groups, the highest U.S. suicide rates occur in older White men.

Suicide attempts, which are more than 10 times more common than death by suicide, lead to considerable morbidity and utilization of health care resources. Suicide rates are higher in patients with many types of medical illness, including neurologic disorders,[21] and also in families who own guns.[22] [21] [22]

Suicide is a potentially preventable cause of death, but despite considerable research on risks for suicidal behavior, specific predictions about an individual's behavior cannot be made with certainty. The linchpin of the clinical evaluation is a methodical assessment of risks for suicide (Table 362-15),[23–25] together with direct questioning of the patient regarding thoughts of death, dying, and suicide; specific plans (in ideation or action) for suicide; and the details of any attempts. Although most persons who attempt suicide do not die, a previous history of a suicide attempt is a powerful risk for subsequent death by suicide. Suicide attempts and verbal threats should always be evaluated carefully and never dismissed as "gestures" or "attention-seeking" behavior. Patients at increased risk for suicide should be referred for psychiatric evaluation, with emergency referral if the risk is deemed to be imminent or increasing.[26] [23–25] [26]

WHEN TO REFER A PATIENT FOR PSYCHIATRIC EVALUATION

Substance abuse, somatic symptom disorders, and depressive and anxiety disorders are very common in all medical settings, and a significant proportion of health-seeking contacts in primary care are mental health-related. Although mild to moderate symptoms of these psychiatric disorders are appropriately treated in general medical settings, more severe symptoms, comorbidities

TABLE 362-14 PERSONALITY DISORDERS

TYPE OF PERSONALITY DISORDER	MAIN IDENTIFYING CHARACTERISTICS
CLUSTER A: ODD/ECCENTRIC	
Schizoid personality disorder	Detachment from social relationships, restricted emotional expression
Schizotypal personality disorder	Discomfort with close relationships, cognitive or perceptual distortions, eccentric behavior
Paranoid personality disorder	Pervasive distrust and suspiciousness of others' motives as malevolent
CLUSTER B: DRAMATIC/EMOTIONAL/ERRATIC	
Borderline personality disorder	Instability of interpersonal relationships, self-image, and affects, and marked impulsivity
Narcissistic personality disorder	Grandiosity, need for admiration, and lack of empathy
Antisocial personality disorder	Pervasive disregard for and violation of the rights of others, lack of true remorse ("conscience")
Histrionic personality disorder	Pervasive excessive emotionality (theatricality) and attention seeking
CLUSTER C: ANXIOUS/FEARFUL	
Avoidant personality disorder	Social inhibition, feelings of inadequacy, and sensitivity to negative views from others
Dependent personality disorder	Pervasive and excessive need to be taken care of, resulting in submissive and clinging behavior and fears of separation
Obsessive-compulsive personality disorder	Pervasive preoccupation with orderliness, perfectionism, and mental and interpersonal control

Author summary based on criteria from American Psychiatric Association. *Diagnostic and Statistical Manual of Mental Disorders*. 5th ed. Text Revision (DSM-5-TR). Washington, DC: American Psychiatric Association; 2022.

TABLE 362-15 SOME IMPORTANT RISKS FOR SUICIDE AND SUICIDE ATTEMPTS

- Mental disorder, particularly depressive, bipolar, substance use, psychotic, and personality disorders
- Other symptoms of acute psychic distress, particularly hopelessness and panic attacks
- Previous history of suicide attempt
- Family history of suicide or suicide attempt (and, to a lesser degree, of any mental disorder)
- Family violence, including physical or sexual abuse
- Access to firearms or other lethal methods
- Incarceration
- Exposure to suicidal behavior of others (family, peers, public figures)
- Social isolation
- Interpersonal discord or other psychosocial stressors
- Demographic factors, including male, non-Hispanic White or American Indian/Alaska Native race, older age

TABLE 362-16 GENERAL CONSIDERATIONS IN DECIDING TO REFER A PATIENT FOR PSYCHIATRIC SPECIALTY CARE

- Diagnosis or ongoing care of severe/chronic mental disorders, including bipolar disorder, psychotic disorders such as schizophrenia, and psychotic symptoms in other disorders
- Management of more severe forms of other mental disorders and those refractory to treatment, including depression, anxiety disorders, and substance use disorders
- Need for safety evaluation or management, including suicidality, homicidality or other aggressivity, or inability to care for self
- Evaluation of decision-making capacity
- Diagnostic uncertainty
- Psychiatric comorbid conditions complicating diagnosis or treatment, including personality and substance use disorders coexisting with other psychiatric disorders
- Psychiatric-medical comorbid conditions complicating diagnosis or treatment, including management of psychiatric disorders during pregnancy
- Need for expertise in psychopharmacologic treatment
- Need for expertise in other somatic therapies (e.g., electroconvulsive therapy, light therapy)
- Need for expertise in psychotherapy or other psychosocial interventions

or other complexity, or treatment refractoriness should lead to referral to a psychiatrist. Clinical decisions to refer a patient for specialty psychiatric evaluation must be made on an individual basis by taking into account the patient's clinical findings, including any previous history and immediate needs, and the clinician's own experience and expertise in assessing and managing the disorder (Table 362-16).

Unlike these milder disorders, however, patients suffering from serious mental illness, defined by the National Institute of Mental Health as "a mental, behavioral, or emotional disorder resulting in serious functional impairment, which substantially interferes in or limits one or more major life activities," are best referred for immediate specialty care. This definition encompasses conditions such as severe major depression, depression that does not respond to standard treatments, bipolar disorder, schizophrenia, schizoaffective disorder, and more severe or chronic forms of PTSD and OCD.

Emergent psychiatric referral is essential for patients with acute psychiatric symptoms that threaten their own lives (e.g., suicidal ideation, plans, or intent) or the lives of others (e.g., homicidal thoughts). Patients who pose an immediate risk to themselves or others, or who are unable to care for their own basic needs, should be seen by a psychiatric crisis clinic or emergency psychiatric service, often a part of the local emergency department. To ensure close linkage to mental health services, patients with serious mental illnesses should be referred as early as possible. For example, referral to a psychiatrist is important for the first presentation of any psychotic disorder (e.g., prodromal schizophrenia) to institute and oversee careful evaluation, assertive early treatments, and ongoing support for the patients and their families. The first presentation of many other disorders, including moderate to severe depression, bipolar disorder, PTSD, and OCD also requires prompt psychiatric expertise to develop a comprehensive evaluation and treatment plan.

A patient who suffers chronically from a serious mental illness generally requires a team of mental health professionals, led by a psychiatrist or a psychologist. This team can oversee pharmacologic interventions, provide ongoing support, implement cognitive-behavioral therapy or other specific psychotherapies, and address attendant, often complicated psychosocial issues.

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For the General References and other additional features, please visit Elsevier eBooks+ at https://ebooks.health.elsevier.com.

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363 NICOTINE AND TOBACCO

TONY P. GEORGE

DEFINITIONS

Cigarette smoking is the most frequent (>90%) method of tobacco use, although other forms, including pipe tobacco, cigars, and smokeless tobacco, are common. Nicotine, which is the active ingredient in tobacco, acts as a reinforcer for the use of all forms of tobacco. In recent years, however, vaping of nicotine through electronic nicotine delivery systems (ENDS; e-cigarettes without tobacco) now constitutes more than 30% of nicotine use in the United States.[1]

EPIDEMIOLOGY

Cigarette smoking is the leading cause of morbidity and mortality in the Western world. In the United States as of 2022, about 14% of the general population (approximately 65 million adults) are tobacco users, compared with about 47% in 1965. As the health risks of environmental tobacco smoke became increasingly clear, smoking has been banned in many public settings. However, the rate of decline has slowed in recent years, likely because the remaining smokers are refractory. Approximately 500,000 people in the United States die each year as a result of smoking-attributable medical illnesses such as lung cancer (Chapter 177), head and neck cancer (Chapter 176), bladder cancer (Chapter 182), chronic obstructive pulmonary disease (Chapter 76), cardiovascular disease (Chapter 40), and stroke (Chapter 376). The economic and health care costs of tobacco use exceed $400 billion annually. Smokeless tobacco (e.g., chewing tobacco) use has also increased and has contributed to higher rates of oral conditions, including precancerous oral lesions (Chapter 393) and cancers of the mouth and nasopharynx (Chapter 176).

Worldwide, an estimated 1.1 billion people use tobacco on a regular basis. Tobacco smoking is increasing rapidly throughout the developing world, and cigarette smoking causes about 7.7 million deaths worldwide each year.[2] In particular, the onset of smoking now occurs at a younger ages, the rates of smoking in women are increasing, and more smokers are of a lower socioeconomic status. Reducing smoking prevalence by 50% could prevent about 150 million premature deaths in the second quarter of this century. For most smokers, quitting is the single most important behavior change to improve overall health. Since the relationship between smoking and the risk of tobacco-related illness is present even at very modest daily smoking levels, sustained reductions (>25 to 75%) in daily smoking consumption are of little to no benefit, thereby substantiating the merits of quitting versus reducing smoking.

PATHOBIOLOGY

Nicotine is the primary reinforcer in tobacco, with contributions from over 400 components to the sensory (non-nicotine) aspects of cigarette smoking. Nicotine's primary site of action is the α4β2 nicotinic acetylcholine receptor (nAChR) at which acetylcholine is the endogenous neurotransmitter. nAChRs in the central nervous system (CNS) are pentameric ion channel complexes that are comprised of two α and three β subunits; the eight α subunits are designated α2 to α9, and the three β subunits are designated β2 to β4. These multiple receptors produce considerable diversity in subunit combinations, which may explain the region-specific and functional selectivity of nicotine's effects in the CNS. Activation of nAChRs leads to Na^+/Ca^{2+} ion channel fluxes and neuronal membrane depolarization. nAChRs are located presynaptically on several neurotransmitter-secreting types of CNS neurons, including mesolimbic dopaminergic neurons that project from the ventral tegmental area to the nucleus accumbens, thereby leading to the secretion of dopamine, which contributes to the reinforcing effects of smoking. Long-term smoking causes hypomethylation of the aryl hydrocarbon receptor repressor gene, but this epigenetic change is reversible after smoking cessation.[3]

At low nicotine concentrations, α4β2 nAChR stimulation of afferent gamma-aminobutyric acid (GABA)-ergic projections onto mesoaccumbal dopaminergic neurons predominates, thereby leading to reduced firing of mesolimbic neurons and reduced release of dopamine. At higher nicotine concentrations, α4β2 nAChRs desensitize, and predominant activation of α7 nAChRs on glutamatergic projections leads to increased mesolimbic neuron firing and release of dopamine. Within milliseconds of nicotine binding, nAChRs desensitize. After overnight abstinence, nAChRs resensitize, likely explaining why most smokers report that the first cigarette in the morning is the most satisfying. Interestingly, positron emission tomography (PET) neuroimaging studies show that smoking two to three puffs from a cigarette saturates nAChRs in the brain reward system, thereby suggesting that although binding to central nAChRs is an important first step in the effects of nicotine, it is not a complete explanation for persistent smoking behaviors.

In addition, the non-nicotine effects of smoking appear to reinforce the habit. Taken together, molecular and trans-synaptic nicotine effects and the biobehavioral effect of non-nicotine components appear to contribute to the high rates of smoking initiation, maintenance, and relapse in both tobacco smokers and users of e-cigarettes.

CLINICAL MANIFESTATIONS

Although a subset of cigarette smokers do not smoke every day (e.g., "chippers"), most cigarette smokers are daily users and have physiologic dependence on nicotine. Nicotine has both stimulating and anxiolytic effects depending on basal level of arousal (i.e., it is stimulating during boredom but reduces anxiety during stress). Smokers typically describe a "rush" and feelings of alertness, relaxation, and "satisfaction" when smoking.

Airway stimulation is an important aspect of smoking behavior, and the positive effects of cigarette smoking (e.g., taste, satisfaction) appear to be mediated by non-nicotine components of tobacco, such as tar, menthol, and other additives, which enhance the experience by reducing the harshness of nicotine and other components of tobacco.

In addition to the positive attributes of nicotine and other additives, smoking is stimulated by craving and withdrawal owing to the addictive properties of nicotine. Secondary effects that may contribute to both smoking maintenance and relapse include mood modulation (e.g., reduction of negative affect), stress reduction, and weight control. In addition, conditioned cues (e.g., people, places, things, emotions associated with nicotine and tobacco use) can elicit the urge to smoke even after prolonged periods of abstinence.

Nicotine may benefit smokers who hope to lose weight, and its pharmacologic actions can enhance mood and cognition while reducing stress. These secondary effects may present additional targets for pharmacologic intervention in subgroups of smokers (e.g., anxious, depressed, or weight-concerned smokers). Although nicotine is the primary reinforcer associated with tobacco smoking behaviors, the non-nicotine components (e.g., tars) that give tobacco its taste and satisfaction are polycyclic aromatic hydrocarbons that are responsible for its high risks of cancer (e.g., lung, colon, brain) and of cardiovascular and pulmonary diseases.

DIAGNOSIS

Tobacco use disorder is established clinically by historical documentation of two of the following 11 criteria:

1. Tobacco often taken in larger amounts or over a longer period than was intended;
2. Persistent desire or unsuccessful efforts to cut down or control tobacco use;
3. A great deal of time spent in activities necessary to obtain or use tobacco;
4. Presence of craving, or a strong desire or urge to use tobacco;
5. Recurrent tobacco use resulting in failure to fulfill major obligations at work, school, or home;
6. Continued tobacco use despite persistent or recurrent social or interpersonal problems caused or exacerbated by the effects of tobacco;

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363 NICOTINE AND TOBACCO

TONY P. GEORGE

DEFINITIONS

Cigarette smoking is the most frequent (>90%) method of tobacco use, although other forms, including pipe tobacco, cigars, and smokeless tobacco, are common. Nicotine, which is the active ingredient in tobacco, acts as a reinforcer for the use of all forms of tobacco. In recent years, however, vaping of nicotine through electronic nicotine delivery systems (ENDS; e-cigarettes without tobacco) now constitutes more than 30% of nicotine use in the United States.[1]

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Cigarette smoking is the leading cause of morbidity and mortality in the Western world. In the United States as of 2022, about 14% of the general population (approximately 65 million adults) are tobacco users, compared with about 47% in 1965. As the health risks of environmental tobacco smoke became increasingly clear, smoking has been banned in many public settings. However, the rate of decline has slowed in recent years, likely because the remaining smokers are refractory. Approximately 500,000 people in the United States die each year as a result of smoking-attributable medical illnesses such as lung cancer (Chapter 177), head and neck cancer (Chapter 176), bladder cancer (Chapter 182), chronic obstructive pulmonary disease (Chapter 76), cardiovascular disease (Chapter 40), and stroke (Chapter 376). The economic and health care costs of tobacco use exceed $400 billion annually. Smokeless tobacco (e.g., chewing tobacco) use has also increased and has contributed to higher rates of oral conditions, including precancerous oral lesions (Chapter 393) and cancers of the mouth and nasopharynx (Chapter 176).

Worldwide, an estimated 1.1 billion people use tobacco on a regular basis. Tobacco smoking is increasing rapidly throughout the developing world, and cigarette smoking causes about 7.7 million deaths worldwide each year.[2] In particular, the onset of smoking now occurs at a younger ages, the rates of smoking in women are increasing, and more smokers are of a lower socioeconomic status. Reducing smoking prevalence by 50% could prevent about 150 million premature deaths in the second quarter of this century. For most smokers, quitting is the single most important behavior change to improve overall health. Since the relationship between smoking and the risk of tobacco-related illness is present even at very modest daily smoking levels, sustained reductions (>25 to 75%) in daily smoking consumption are of little to no benefit, thereby substantiating the merits of quitting versus reducing smoking.

PATHOBIOLOGY

Nicotine is the primary reinforcer in tobacco, with contributions from over 400 components to the sensory (non-nicotine) aspects of cigarette smoking. Nicotine's primary site of action is the α4β2 nicotinic acetylcholine receptor (nAChR) at which acetylcholine is the endogenous neurotransmitter. nAChRs in the central nervous system (CNS) are pentameric ion channel complexes that are comprised of two α and three β subunits; the eight α subunits are designated α2 to α9, and the three β subunits are designated β2 to β4. These multiple receptors produce considerable diversity in subunit combinations, which may explain the region-specific and functional selectivity of nicotine's effects in the CNS. Activation of nAChRs leads to Na^+/Ca^{2+} ion channel fluxes and neuronal membrane depolarization. nAChRs are located presynaptically on several neurotransmitter-secreting types of CNS neurons, including mesolimbic dopaminergic neurons that project from the ventral tegmental area to the nucleus accumbens, thereby leading to the secretion of dopamine, which contributes to the reinforcing effects of smoking. Long-term smoking causes hypomethylation of the aryl hydrocarbon receptor repressor gene, but this epigenetic change is reversible after smoking cessation.[3]

At low nicotine concentrations, α4β2 nAChR stimulation of afferent gamma-aminobutyric acid (GABA)-ergic projections onto mesoaccumbal dopaminergic neurons predominates, thereby leading to reduced firing of mesolimbic neurons and reduced release of dopamine. At higher nicotine concentrations, α4β2 nAChRs desensitize, and predominant activation of α7 nAChRs on glutamatergic projections leads to increased mesolimbic neuron firing and release of dopamine. Within milliseconds of nicotine binding, nAChRs desensitize. After overnight abstinence, nAChRs resensitize, likely explaining why most smokers report that the first cigarette in the morning is the most satisfying. Interestingly, positron emission tomography (PET) neuroimaging studies show that smoking two to three puffs from a cigarette saturates nAChRs in the brain reward system, thereby suggesting that although binding to central nAChRs is an important first step in the effects of nicotine, it is not a complete explanation for persistent smoking behaviors.

In addition, the non-nicotine effects of smoking appear to reinforce the habit. Taken together, molecular and trans-synaptic nicotine effects and the biobehavioral effect of non-nicotine components appear to contribute to the high rates of smoking initiation, maintenance, and relapse in both tobacco smokers and users of e-cigarettes.

CLINICAL MANIFESTATIONS

Although a subset of cigarette smokers do not smoke every day (e.g., "chippers"), most cigarette smokers are daily users and have physiologic dependence on nicotine. Nicotine has both stimulating and anxiolytic effects depending on basal level of arousal (i.e., it is stimulating during boredom but reduces anxiety during stress). Smokers typically describe a "rush" and feelings of alertness, relaxation, and "satisfaction" when smoking.

Airway stimulation is an important aspect of smoking behavior, and the positive effects of cigarette smoking (e.g., taste, satisfaction) appear to be mediated by non-nicotine components of tobacco, such as tar, menthol, and other additives, which enhance the experience by reducing the harshness of nicotine and other components of tobacco.

In addition to the positive attributes of nicotine and other additives, smoking is stimulated by craving and withdrawal owing to the addictive properties of nicotine. Secondary effects that may contribute to both smoking maintenance and relapse include mood modulation (e.g., reduction of negative affect), stress reduction, and weight control. In addition, conditioned cues (e.g., people, places, things, emotions associated with nicotine and tobacco use) can elicit the urge to smoke even after prolonged periods of abstinence.

Nicotine may benefit smokers who hope to lose weight, and its pharmacologic actions can enhance mood and cognition while reducing stress. These secondary effects may present additional targets for pharmacologic intervention in subgroups of smokers (e.g., anxious, depressed, or weight-concerned smokers). Although nicotine is the primary reinforcer associated with tobacco smoking behaviors, the non-nicotine components (e.g., tars) that give tobacco its taste and satisfaction are polycyclic aromatic hydrocarbons that are responsible for its high risks of cancer (e.g., lung, colon, brain) and of cardiovascular and pulmonary diseases.

DIAGNOSIS

Tobacco use disorder is established clinically by historical documentation of two of the following 11 criteria:

1. Tobacco often taken in larger amounts or over a longer period than was intended;
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3. A great deal of time spent in activities necessary to obtain or use tobacco;
4. Presence of craving, or a strong desire or urge to use tobacco;
5. Recurrent tobacco use resulting in failure to fulfill major obligations at work, school, or home;
6. Continued tobacco use despite persistent or recurrent social or interpersonal problems caused or exacerbated by the effects of tobacco;

ABSTRACT

Tobacco use prevalence has diminished substantially in the United States and most Western countries but is still a leading cause of preventable morbidity and mortality. This chapter reviews the epidemiology, neurobiology, clinical features, assessment, and treatment of tobacco use disorder. There are three FDA-approved treatments for tobacco use disorder—nicotine replacement, sustained-release bupropion, and varenicline, which all double quit rates compared to placebo. They are most useful when combined with behavioral treatments, which build motivation and help smokers manage craving and withdrawal during cessation attempts. Electronic cigarettes (e-cigarettes) are increasingly common and may supplant tobacco smoking as the preferred method to deliver nicotine. Although they may be less harmful than tobacco smoking, there are still considerable concerns especially for adolescents. Nicotine and tobacco use are very problematic but also very treatable with evidence-based approaches, and thus it behooves all physicians to learn about tobacco treatment.

KEYWORDS

nicotine
tobacco
smoking cessation
e-cigarettes
nicotine replacement
bupropion
varenicline
behavioral therapy

7. Important social, occupational, or recreational activities given up or reduced due to tobacco use;
8. Recurrent tobacco use in situations in which it is physically hazardous (e.g., smoking in bed);
9. Continued tobacco use despite persistent or recurrent physical or psychological problems that are caused or exacerbated by tobacco use;
10. Tolerance, as defined by either a need for markedly increased amounts of tobacco to achieved desired effects, or markedly diminished effects with continued use of the same amount of tobacco;
11. Withdrawal, manifested by the presence of the characteristic tobacco abstinence syndrome (i.e., four of the following: irritability, anxiety, difficulty concentrating, increased appetite, restlessness, dysphoric mood, insomnia), or tobacco (or nicotine) is taken to relieve or avoid tobacco withdrawal symptoms.

The current severity of tobacco use disorder is coded as mild (two to three symptoms), moderate (four to five symptoms), or severe (six or more symptoms). For abstinent smokers, remission is classified as early (between 3 and 12 months of abstinence) or sustained (>12 months of abstinence).

Most physiologically dependent tobacco smokers state that they smoke their first cigarette of the day within the first 5 minutes of awakening. Retrospective timeline follow-back questions regarding prior use and prospective smoking diaries have been used successfully to monitor smoking consumption.

TREATMENT

Psychosocial Treatments

Behavioral therapies are based on the theory that learning processes operate in the initiation, maintenance, and cessation of smoking (Table 363-1).[4] Behavioral treatments can facilitate smoking cessation by enhancing motivation and providing an emphasis on the social and contextual aspects of smoking.[5] The primary goals of behavioral therapies to treat tobacco dependence include providing necessary skills to smokers to aid them in quitting smoking and teaching skills to avoid smoking in high-risk situations. Behavioral therapies are associated with 6-month quit rates of 20 to 25% and typically increase quit rates up to two-fold over standard medical advice.[A1]

Brief Interventions

Even brief advice can increase cessation rates.[6] Physicians should use the "5 As" with all patients (Ask patients if they smoke, Advise patients to quit, Assess patients' motivation level for quitting, Assist with quit attempts, and Arrange follow-up contacts). Providing self-help material is another brief intervention that can facilitate motivation and provide skills for smoking cessation. Minimal behavioral interventions such as community support groups, telephone counseling, and computer-generated self-help materials can augment smoking cessation rates.

Motivational Interventions

The goal of motivational interventions is to elicit change by addressing ambivalence, increasing intrinsic motivation for change, and creating an atmosphere of acceptance in which patients take responsibility and initiative for change. Brief motivational interventions can increase rates of smoking cessation.

TABLE 363-1 BEHAVIORAL TREATMENTS FOR TOBACCO DEPENDENCE

BEHAVIORAL TREATMENTS	MECHANISM OF ACTION	
Brief interventions	Increase motivation to quit and impart cessation skills (e.g., community support, telephone counseling)	2
Cognitive-behavioral and relapse-prevention therapies	Behavioral strategies are developed to manage triggers; cognitive coping strategies target maladaptive thoughts to prevent relapse	1
Motivational interviewing	Therapist promotes patient's self-motivational statements, and in turn, patient gains greater awareness of the problems with smoking; increases intention for smoking cessation	2

Effectiveness rating: 1 = Strong evidence to support efficacy; 2 = Moderate evidence to support efficacy.

Cognitive-Behavioral Therapies

In cognitive-behavioral therapy, patients learn to anticipate situations of high smoking likelihood and plan to cope with these situations using behavioral (e.g., substitution of behavior) and cognitive (e.g., challenging thoughts) techniques. Cognitive behavioral therapy has modest efficacy for smoking cessation whether delivered in individual or group counseling formats.

Online Interventions

Data suggest that online, telehealth interventions can provide smoking cessation rates that are similar to in-person behavioral interventions.[A2] Given the scalability and feasibility of online interventions, their use is likely to increase significantly.

Relapse-Prevention (Coping Skills) Therapies

A large number of smokers relapse within 6 months of quitting. Recognizing high-risk situations and coping with lapses can be included in initial smoking cessation treatment or following a quit attempt. In persons who are heavy drinkers or have coexistent alcohol use disorder (Chapter 364), an integrated approach to stop or substantially reduce alcohol intake should be undertaken before or during smoking cessation efforts.[7]

Pharmacologic Treatments

Three classes of smoking cessation pharmacotherapies are approved by the U.S. FDA: nicotine replacement therapies, sustained-release bupropion, and varenicline (Table 363-2).[8,9]

Nicotine Replacement Therapies

The goal of nicotine replacement therapy is to alleviate tobacco withdrawal, thereby allowing smokers to focus on habit and conditioning factors when attempting cessation. Because nicotine replacement therapies rely on systemic venous absorption and do not produce the rapid, high levels of arterial nicotine from inhaling cigarette smoke, individuals are unlikely to become addicted. These agents can be started safely even while individuals are still smoking, and such early use may facilitate smoking cessation compared with when they are started at the time of a quitting attempt. Commercially available forms of nicotine replacement therapy (transdermal patch, gum, and lozenge are available over the counter, whereas the nasal spray and inhaler require a prescription) increase quit rates by approximately 1.5- to 2.5-fold compared to placebo, and the results with the various delivery systems are comparable in their effectiveness.

Nicotine Gum

Nicotine ingested orally is extensively metabolized by the liver in its first pass through the portal circulation. Nicotine gum avoids the first pass hepatic degradation because 2 or 4 mg of nicotine is released from its resin for immediate buccal absorption, and blood levels peak 30 minutes after initial use. Nicotine gum should be administered by scheduled dosing (e.g., 1 piece of 2-mg gum/hour) for 3 months or longer.

Venous nicotine levels from 2-mg and 4-mg gum are about one-third and two-thirds, respectively, of the steady-state (e.g., between cigarettes) nicotine levels achieved with cigarette smoking, but nicotine delivered by cigarettes achieves arterial levels 5 to 10 times higher than those from nicotine gum because the nicotine is absorbed directly into the pulmonary arterial circulation. Nicotine absorption in the buccal mucosa is decreased by acidic conditions, and patients should not consume beverages (e.g., coffee, soda, juice) immediately before, during, or after use.

Nicotine gum is safe and effective for smoking cessation, with data supporting higher doses (4-mg pieces) in more highly dependent smokers (≥25 cigarettes per day). Rare side effects can be mechanical (e.g., difficulty chewing, sore jaw) or local pharmacologic (e.g., burning in mouth, throat irritation). Tolerance develops to most side effects over the first week, and education about proper use (e.g., do not chew too vigorously) decreases side effects.

Nicotine Lozenges

Nicotine lozenges also deliver nicotine (2-mg and 4-mg preparations) by buccal absorption but provide greater absorption of nicotine compared with nicotine gum. Nicotine lozenges significantly reduce nicotine craving and withdrawal, and they may be especially preferable to nicotine gum in more highly dependent smokers when the lozenge dose is matched to the dependence level. Mild throat and mouth irritation are the only side effects. Interestingly, the combination of nicotine lozenges with the nicotine patch may lead to higher long-term rates of smoking cessation compared with nicotine replacement monotherapies or bupropion.

Transdermal Nicotine Patch

Transdermal nicotine patches, applied daily each morning, allow for ready nicotine absorption across the skin. Three formulations are for 24-hour use and one is for 16-hour use. Initial doses are 21- to 22-mg/24-hour patch and 15-mg/16-hour patch. Nicotine is slowly absorbed from patches and, on the first day, venous nicotine levels peak 6 to 10 hours postadministration. Thereafter, nicotine levels remain fairly steady, with a decline from peak to trough of 25 to 40% with 24-hour patches. Nicotine levels obtained from patches are typically half those obtained by smoking. Patients should receive this high dose for 4 to

TABLE 363-2 PHARMACOLOGIC AND NEUROMODULATION TREATMENTS FOR TOBACCO DEPENDENCE

NICOTINE REPLACEMENT THERAPIES*		
Gum (OTC)	Slow nicotine absorption gradually reduces nicotine craving and withdrawal	1
Transdermal nicotine patch (OTC)	Slow nicotine absorption gradually reduces nicotine craving and withdrawal	1
Lozenge (OTC)	Slow nicotine absorption gradually reduces nicotine craving and withdrawal	1
Vapor inhaler (prescription)	Fast nicotine absorption leads to stimulation of nAChR, which rapidly reduces nicotine craving and withdrawal	1
Nasal spray (prescription)	Fast nicotine absorption leads to stimulation of nAChR, which reduces craving and withdrawal	1
NON-NICOTINE PHARMACOTHERAPIES		
Bupropion (sustained release)*	Blocks reuptake of dopamine and noradrenaline; high affinity, noncompetitive nAChR antagonism reduces nicotine reinforcement, withdrawal, and craving	1
Varenicline*	Acts as a partial agonist of $\alpha_4\beta_2$ nAChRs	1
Nortriptyline	Blocks reuptake of noradrenaline and 5-hydroxytryptamine; probably reduces withdrawal symptoms and comorbid depressive symptoms; side effects limit utility	1-2
Clonidine	α_2-Adrenoreceptor agonist reduces nicotine withdrawal symptoms	2
Mecamylamine	Noncompetitive, high-affinity nAChR antagonist combined with transdermal nicotine patch reduces nicotine reinforcement, craving, and withdrawal, and may increase smoking cessation rates versus transdermal nicotine patch alone	2-3
Naltrexone	Minimal evidence that this μ-opioid peptide receptor antagonist improves smoking cessation outcomes alone or in combination with transdermal nicotine patch; it may reduce alcohol use and obviate cessation-induced weight gain	3
Cytisine	Nicotinic partial agonist appears to be safe and efficacious for smoking cessation	2
Nicotine vaccine	Limited evidence of efficacy for smoking cessation in early human trials, and recent Phase III trials have been negative	3
NEUROMODULATION TECHNIQUES*		
Deep transcranial magnetic stimulation	Modest evidence; it may improve smoking cessation success rates	2

*Approved by the U.S. Food and Drug Administration.
Effectiveness rating: 1 = Strong evidence to support efficacy; 2 = Moderate evidence to support efficacy; 3 = Little evidence to support efficacy.
nAChR = nicotinic acetylcholine receptors; OTC = over-the-counter.

6 weeks, a middle dose (e.g., 14 mg/24 hours or 10 mg/16 hours) for the next 2 to 4 weeks, and the lowest dose after (7 mg/24 hours or 5 mg/16 hours) for 2 to 4 weeks before discontinuing the patches without further tapering.

A3 The benefits of nicotine patches for smoking cessation[A3] are independent of patch type, treatment duration, tapering procedures, and behavioral therapy format or intensity, but behavioral treatment enhances nicotine patch outcomes compared with nicotine patches alone. Minor side effects include skin reactions (50%), insomnia and increased or vivid dreams (15% with 24-hour patches), and nausea (5 to 10%). Tolerance to these side effects usually develops within a week. Rotation of patch sites decreases skin irritation. Insomnia reported one week postcessation appears to be due mostly to nicotine withdrawal rather than the nicotine patch itself, and a 24-hour patch can be removed before bedtime to determine if the insomnia is induced by the nicotine patch. Without treatment, insomnia usually abates after 4 to 7 days. Only 2% of patch users continue to use it for an extended period postcessation.

Nicotine Nasal Spray

Nicotine nasal spray (10 mg/mL) delivers about 1 mg nicotine per administration, and the patient administers the spray to each nostril every 4 to 6 hours. Peak nicotine levels occur within 10 minutes, a rise in nicotine between the levels produced by nicotine gum and by cigarettes. Venous nicotine levels are about two-thirds of the levels between cigarettes. Smokers may use the nasal spray as needed up to 30 times/day for 12 weeks.

Nasal spray is safe and effective for smoking cessation. Quit rates about double during its active use but decline after its cessation, thereby suggesting the need for continued use. Side effects from nicotine nasal spray are nasal and throat irritation, rhinitis, sneezing, coughing, and watering eyes. About 10% of smokers use the spray for a prolonged time, so follow-up of users is recommended.

Nicotine Inhaler

Nicotine inhalers are cartridges (plugs) of nicotine (about 1 mg of nicotine per plug) placed inside hollow cigarette-like plastic rods. The cartridges produce a nicotine vapor when warm air is passed through them. Absorption from the nicotine inhalers is primarily buccal rather than respiratory. The inhalers generally increase venous nicotine levels more rapidly than nicotine gum but less rapidly than nicotine nasal spray, with nicotine blood levels about one-third that of between-cigarette levels. Smokers are instructed to puff continuously on the inhaler (0.013 mg/puff) during the day, with recommended dosing of 6 to 16 cartridges daily. The inhaler is to be used as needed for about 12 weeks. No serious medical side effects have been reported with nicotine inhalers, though 50% of subjects report throat irritation or coughing. Nicotine inhalers increase quit rates two- to three-fold in the short term but less at follow-up periods of 1 year or longer.

Sustained-Release Bupropion

The atypical antidepressant agent bupropion, in its sustained-release formulation (Zyban), is a non-nicotine, first-line pharmacologic treatment for nicotine-dependent smokers who want to quit. Its mechanism of action likely involves dopamine and norepinephrine reuptake blockade, as well as antagonism of high-affinity nAChRs, but its exact mechanism is unclear. The goals of bupropion therapy are smoking cessation; reduction of nicotine craving and withdrawal symptoms; and prevention of cessation-induced weight gain.

The target dose of this agent is 300 mg daily (150 mg bid), but it is typically started 7 days prior to the target quit date at 150 mg daily and then increased to 150 mg bid after 3 or 4 days. Unlike the nicotine replacement therapies, there is no absolute requirement that smokers completely cease smoking by the target date, though many smokers report a significant reduction in the urge to smoke and in craving when steady-state plasma levels are reached. Some smokers gradually reduce cigarette smoking over several weeks prior to quitting.

Sustained release bupropion is a safe and effective treatment for nicotine dependence.[A4] In combination with weekly individual counseling, smoking A4 cessation rates are about 20 to 30%, and bupropion also reduces the weight gain associated with smoking cessation.

After smoking cessation, sustained-release bupropion delays smoking relapse. Bupropion's side effects, most of which occur during the first week of treatment, include headache, nausea, vomiting, dry mouth, insomnia, and activation. The main contraindication for bupropion use is a history of seizures, but de novo seizures are rare (<0.1%) at the recommended dose of 300 mg daily or less.

Varenicline

Varenicline tartrate (Chantix in United States, Champix in Europe and Canada) is an $\alpha_4\beta_2$ nicotinic acetylcholine receptor partial agonist. At an optimal dose of 2.0 mg/day, quit rates may be superior to those of sustained release bupropion (300 mg/day).[A5] Varenicline is also effective for preventing smoking relapse. A5

Varenicline is generally well tolerated and safe, even in patients with preexisting cardiovascular disease.[A6] The most common adverse events are nausea and A6 insomnia. Although it can precipitate neuropsychiatric events (including agitation, suicidal and homicidal ideation, mania, and psychosis) varenicline appears to be as safe and efficacious in smokers with comorbid psychiatric disorders as are sustained release bupropion and nicotine patches.[A7] Nevertheless, close A7 monitoring of smokers, especially those with a history of psychiatric illness, is strongly advised.

Combination Pharmacotherapies

The value of combination therapies varies. Combinations of nicotine replacement therapies can enhance smoking cessation compared with monotherapies.

However, combining sustained release bupropion with a nicotine patch or with varenicline does not appear to be any better than bupropion (or varenicline) alone for smoking cessation,[A8] though the combination may be better to prevent weight gain.

Off-Label Medications

Other medications (see Table 363-2) have demonstrated some evidence of efficacy for tobacco FDA-approved for this indication. They should be considered only by experts specializing in smoking cessation.

F2.5.1 Neuromodulation

There is modest evidence to suggest that deep repetitive transcranial magnetic stimulation directed to the insula bilaterally may promote smoking reduction and cessation. This FDA-cleared approach to smoking cessation is very promising but requires further study.

PREVENTION

Tobacco use remains one of the leading preventable causes of morbidity and mortality in the Western world, and smoking cessation therapies are among the most cost-effective and proven therapies in medicine. Yet, despite recommendations that all smokers should be approached about quitting, most health care providers do not identify tobacco use in their patients. Taxes and laws banning smoking in public places have had a substantial impact on reducing smoking rates.

PROGNOSIS

The prognosis for tobacco smokers who quit is excellent in terms of years and quality of life gained, and earlier quitting appears to be associated with increases in lifespan and quality of life. By 5 years after smoking cessation, the risk of cardiovascular disease declines by about 60%, and by 10 to 15 years the risk falls to be similar to that of never-smokers,[10] despite an average weight gain of 5 to 6 pounds.[11] Furthermore, although medication and behavioral treatments have documented efficacy in treating tobacco use disorder, it is important that these therapies be used in combination to achieve the best overall results, and ensure adequate skill acquisition and treatment adherence. The promise of novel treatment and prevention interventions such as the nicotine vaccine, and the employment of personalized medicine matching the right medications to smokers with preferential responses using pharmacogenetic (e.g., polymorphisms in genes for catecholamine-o-methyltransferase, the nicotinic receptor subunits CHRNA3 and CHRNA4, and the nicotine metabolic enzyme CYP 2A6) and neuroimaging biomarkers (e.g., PET and fMRI) are of considerable excitement for tobacco treatment. Furthermore, given the high rates of tobacco use and the lower rates of quitting in patients with psychiatric conditions, specific adaptation of tobacco treatments to this population is a challenge to be addressed.

ELECTRONIC NICOTINE DELIVERY SYSTEMS

Electronic nicotine delivery systems (ENDS; i.e. e-cigarettes) structurally consist of an e-liquid cartridge, a heating element, and a battery. The e-liquid solution, consisting of either propylene glycol itself or mixed with glycerin, nicotine (0 to 26 mg/mL), and flavoring agents, is heated and vaporized into an aerosol that is then inhaled through a mouthpiece. Electronic nicotine delivery systems constitute a global market of about $20 billion in 2022, with 55% of the world's market based in the United States. In the United States, about 13% of the adult population has used e-cigarettes, and about 4% use them regularly.

Recent estimates are that close to 6 million U.S. adults report current vaping, with about 40% being smokers, 40% being former smokers, and 20% being never smokers. E-cigarettes are most commonly used amongst adolescents, with about 3 million middle and high school students reported to be current users. Adolescents report "flavoring" as a main reason for use and, unlike adults, are not concurrent tobacco smokers.[12] Prevalence is highest among adolescents and young adults, White males, and intermediate-to-highly educated individuals.

The risk for nicotine dependence via e-cigarettes depends on the model of device, nicotine concentration, and inhalation technique, but is overall lower than the risk posed by cigarettes.[13] These devices also avoid the other harmful contents of tobacco smoke. Electronic nicotine delivery systems can potentially aid in smoking cessation,[A9–A11] but the cessation may be short-lived,[A12] and nicotine addiction in prior nonsmokers may result in a sizable number of new smokers.

Side Effects of Electronic Nicotine Delivery Systems

Toxin levels are generally lower compared to cigarette smoke apart from trace levels of metals being found at similar to higher levels in e-cigarettes. Physiologic concerns involve mouth and throat irritation, nausea, headaches, dizziness, and dry coughing. Small airway fibrosis and constrictive bronchiolitis have also been reported.[14] Topical injury from e-liquids, overly concentrated nicotine ingestion and inhalation, as well as overheating, fires, and explosions are other risks of harm to users.

E-VALI

Electronic nicotine delivery systems or vaping has been complicated by vaping-associated lung disease (E-VALI),[15] which is characterized by acute lung injury, sometimes severe and typically associated with constitutional and gastrointestinal symptoms,[16] especially in more severe cases. Vitamin E acetate, which was a common additive to vaping products containing tetrahydrocannabinol, was found in the bronchial lavage of over 90% of patients with E-VALI.[17] Cough and fever are the usual presenting symptoms. Chest radiographs usually show bilateral infiltrates.[18]

Among the first 2600 or so hospitalized patients reported, the mortality rate was 2.3%.[19] A substantial proportion of patients have residual abnormalities on their chest radiographs or pulmonary function tests. Since the removal of vitamin E acetate from vaping products, E-VALI has become very uncommon. Nevertheless, it emphasizes the potential dangers of vaping and e-cigarettes.

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For the General References and other additional features, please visit Elsevier eBooks+ at https://ebooks.health.elsevier.com.

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364 ALCOHOL USE DISORDERS

PATRICK G. O'CONNOR

DEFINITION

A variety of terms have been used to describe the spectrum of medical, psychological, behavioral, and social problems associated with excessive consumption of alcohol *(alcohol problems)*. The *Diagnostic and Statistical Manual of Mental Disorders*, 5th edition (DSM-5) replaced the terminology of *alcohol abuse* and *alcohol dependence* with the term *alcohol use disorder* (Table 364-1) to describe more clearly the spectrum of symptoms experienced by patients. Patients who meet 2 or 3 of the 11 criteria for alcohol use disorder are considered to have *mild,* 4 or 5 criteria *moderate,* and 6 to 11 criteria *severe* alcohol use disorder. Recent epidemiologic data suggest that any level of alcohol consumption increases health risks.[1]

Alcoholism, which is perhaps the most widely used term to describe patients with alcohol problems, is an often progressive and sometimes fatal chronic disease that is related to genetic, psychosocial, and environmental influences and that is characterized by preoccupation with alcohol, an impaired ability to control its intake despite the consequences, and distorted thinking, especially denial. Because the term *alcoholism* is so broad, however, it also can be imprecise in defining the entire spectrum of alcohol problems and generally should be avoided.

At-risk drinking is a level of alcohol consumption that imparts health risks (see Table 364-1). This category of drinking behavior has been identified on the basis of epidemiologic evidence that certain threshold levels of alcohol consumption are associated with increased risk for specific health problems. At-risk drinking is defined differently for men younger than age 65 years than for women of all ages because of generally lower body weights and lower rates of metabolism of alcohol in women. The definition in men older than age 65 years is the same as in women because of the age-related increased risk for alcohol problems, in part owing to changes in alcohol metabolism in older individuals. *Binge drinking* or *heavy drinking* is the episodic consumption of large amounts of alcohol, usually five or more drinks per occasion for men and four or more drinks per occasion for women. One standard drink contains 12 g of pure alcohol, an amount equivalent to that contained in 5 ounces of wine, 12 ounces of beer, or 1.5 ounces of 80-proof spirits.

Abstainers are individuals who consume no alcohol. *Moderate drinking* is defined by the U.S. National Institute on Alcohol Abuse and Alcoholism as the average number of drinks consumed daily that places an adult at low risk for alcohol problems.

TABLE 364-1 TERMS AND CRITERIA FOR PATTERNS OF ALCOHOL USE

AT-RISK DRINKING
Men: >14 drinks/week or >4 drinks/day Women: >7 drinks/week or >3 drinks/day
ALCOHOL USE DISORDER CRITERIA*
Tolerance Withdrawal More use than intended Craving Unsuccessful attempts to cut down Excessive time acquiring alcohol Activities given up because of use Use despite negative effects Failure to fulfill major role obligations Recurrent use in hazardous situations Continued use despite social or intrapersonal problems

*Mild = 2-3 criteria, moderate = 4-5 criteria, severe = 6 or more criteria.

From American Psychiatric Association. *Diagnostic and Statistical Manual of Mental Disorders*. 5th ed. Arlington, VA: American Psychiatric Publishing; 2013.

EPIDEMIOLOGY

In national surveys, 50% of American adults reported that they use alcoholic beverages (liquor, wine, or beer). The 2020 National Survey on Drug Use and Health demonstrated that among the 138.5 million Americans who were current alcohol users, 61.6 million people (or 44.4%) were classified as binge drinkers and 17.7 million people (or 13%) were classified as heavy drinkers.[2] These data emphasize that alcohol use disorders are among the most prevalent medical, behavioral, or psychiatric disorders in the general population.

Among individuals who use alcohol, many experience problems because of their drinking. An estimated nearly $250 billion is spent by American society each year to treat alcohol use disorders and to recover the costs of alcohol-related economic losses.[3] In the United States, nearly 90,000 deaths per year are attributed to alcohol use disorders,[4] and excessive alcohol consumption ranks as the third leading preventable cause of death after cigarette smoking and obesity.

Despite the high number of individuals with alcohol use disorder who by definition need treatment, only a minority (approximately 20%) have ever received treatment. In addition, individuals with alcohol use disorder are more likely to experience other substance use disorders (Chapter 365) as well as psychiatric comorbidity (Chapter 362), especially depression, bipolar disorder, antisocial disorder, and borderline personality disorder. Alcohol use disorder is prevalent throughout all sociodemographic groups. The "skid row" stereotype of the alcohol-dependent patient is much more the exception than the rule.

The prevalence of alcohol use disorders is higher in most health care settings than it is in the general population because alcohol problems often result in treatment-seeking behaviors. The prevalence of problem drinking in general outpatient and inpatient medical settings has been estimated between 15 and 40%. These data strongly support the need for physicians to screen all patients for AUD.

PATHOBIOLOGY

Beverage alcohol contains ethanol, which acts as a sedative-hypnotic drug. Alcohol is absorbed rapidly into the blood stream from the gastrointestinal tract. Because women have lower levels of gastric alcohol dehydrogenase, which is the enzyme primarily responsible for metabolizing alcohol, they experience higher blood alcohol concentrations than do men who consume similar amounts of ethanol per kilogram of body weight. The absorption of alcohol can be affected by other factors, including the presence of food in the stomach and the rate of alcohol consumption. By means of metabolism in the liver, alcohol is converted to acetaldehyde and acetate (Fig. 364-1). Metabolism is proportional to an individual's body weight, but a variety of other factors can affect how alcohol is metabolized. A genetic variation in a significant proportion of the East Asian population alters the structure of an aldehyde dehydrogenase isoenzyme, thereby resulting in the development of an alcohol flush reaction, which includes facial flushing, hot sensations, tachycardia, and hypotension.

Neurologic Effects

In the brain, alcohol affects a variety of receptors, including γ-aminobutyric acid (GABA), *N*-methyl-D-aspartate, and opioid receptors. Glycinuric and serotoninergic receptors also are thought to be involved in the interaction between alcohol and the brain. The phenomena of reinforcement and cellular adaptation are thought, at least in part, to influence alcohol-dependent

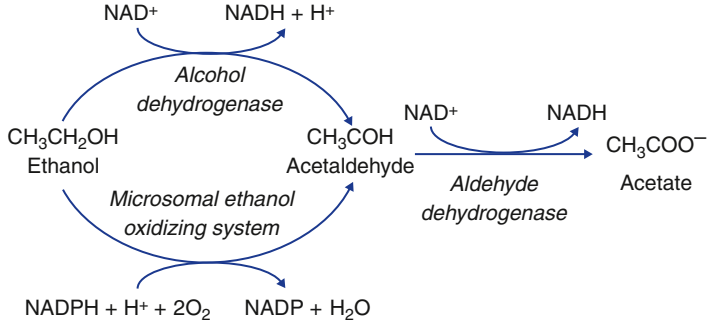

FIGURE 364-1. Ethanol metabolism. Alcohol dehydrogenase predominates at low to moderate ethanol doses. The microsomal ethanol-oxidizing system is induced at high ethanol levels of chronic exposure and by certain drugs. Aldehyde dehydrogenase inhibition (genetic or drug induced) leads to acetaldehyde accumulation, particularly in the latter group.

ABSTRACT

The prevalence of alcohol use disorder, which is associated with important medical and other health-related problems, has been rising in recent years. Clinicians should follow established approaches for screening to diagnose alcohol use disorder and prevent its complications. Individuals who are at risk but who do not meet criteria for alcohol use disorder should be counseled to reduce their alcohol consumption using brief interventions. Once alcohol use disorder is diagnosed, patients should be offered effective evidence-based treatments including counseling and pharmacotherapy.

KEYWORDS

alcohol use disorder
alcohol withdrawal syndrome
brief intervention
counseling
disulfiram
naltrexone
acamprosate

behaviors. Alcohol is known to be reinforcing because withdrawal from ethanol and ingestion of ethanol itself are known to promote further alcohol consumption. After chronic exposure to alcohol, some brain neurons seem to adapt to this exposure by adjusting their response to normal stimuli. This adaptation is thought to be responsible for the phenomenon of tolerance, whereby increasing amounts of alcohol are needed over time to achieve the same desired effects. Although much has been learned about the variety of effects alcohol can have on various brain receptors, no single receptor site has been identified. A number of neuropsychological disorders are seen in association with chronic ethanol use, including impaired short-term memory, cognitive dysfunction, and perceptual difficulties.

Because ethanol is a central nervous system depressant, the body's natural response to withdrawal of the substance is a hyperexcitable neurologic state. This state is thought to be the result of adaptive neurologic mechanisms being unrestrained by alcohol, with an ensuing release of a variety of neurohumoral substances, including norepinephrine. In addition, chronic exposure to alcohol results in a decrease in the number of GABA receptors and impairs their function.

In addition to the acute neurologic manifestations of intoxication and withdrawal, alcohol has major chronic neurologic effects. About 10 million Americans have identifiable nervous system impairment from chronic alcohol use. Individual predisposition to these disorders is highly variable and is related to genetics, environment, sociodemographic features, and gender; the relative contribution of these factors is unclear.

Liver and Pancreas

Direct liver toxicity may be among the most important consequences of acute and chronic alcohol use (Chapter 138). A variety of histologic abnormalities ranging from inflammation to scarring and cirrhosis have been described. The pathophysiologic mechanism of these effects is thought to include the direct release of toxins and the formation of free radicals, which can interact negatively with liver proteins, lipids, and DNA. The risk for pancreatitis in individuals with alcohol dependence is approximately four times that in the general population. Quantity and duration of alcohol exposure and a history of pancreatitis are predictive of future episodes.

Other Organ Systems

Alcohol also has substantial negative effects on the heart and cardiovascular system. Direct toxicity to myocardial cells can result in heart failure (Chapter 45), and chronic heavy alcohol consumption is considered to be a major contributor to atrial fibrillation and hypertension (Chapters 52 and 64). Other organ systems that experience significant direct toxicity from alcohol include the gastrointestinal tract (esophagus, stomach), immune system (bone marrow, immune cell function), and endocrine system (pancreas, gonads).

Carcinogenesis

The amount of alcohol exposure that increases the risk of cancer may vary widely and may not correlate with what might be considered to be "safe" levels of alcohol consumption. For squamous cell carcinomas of the esophagus (Chapter 178) and of the head and neck (Chapter 176), the co-occurrence of alcohol and tobacco abuse seems to be synergistic. Either heavy alcohol use or smoking individually increases the rate of oropharyngeal cancer by about six or seven times that of the general population, whereas the rate for people with both risk factors is about 40 times that of the general population. Patients with alcohol-induced liver disease who also have a history of hepatitis B or C are at particularly increased risk for hepatocellular carcinoma (Chapter 181).

CLINICAL MANIFESTATIONS

Alcohol has a variety of specific acute and chronic effects. The acute effects seen most commonly are alcohol intoxication and alcohol withdrawal. Chronic clinical effects of alcohol include almost every organ system.

Acute Effects

Alcohol Intoxication

After entering the blood stream, alcohol rapidly passes through the blood-brain barrier. The clinical manifestations of alcohol intoxication are related directly to the blood level of alcohol.[5] Because of tolerance, individuals chronically exposed to alcohol generally experience less severe effects at a given blood alcohol level than do individuals who are not chronically exposed to alcohol.

The symptoms of mild alcohol intoxication in nontolerant individuals typically occur at blood alcohol levels of 20 to 100 mg/dL and include euphoria, mild muscle incoordination, and mild cognitive impairment. In the United States, a blood alcohol level of 80 mg/dL is considered legally intoxicated, although states often enforce driving while intoxicated laws at lower levels for drivers under age 21 years. At higher blood alcohol levels (100 to 200 mg/dL), more substantial neurologic dysfunction occurs, including more severe mental impairment, ataxia, and prolonged reaction time. Individuals with blood alcohol levels in these ranges can be obviously intoxicated, with slurred speech and lack of coordination. These effects progress as the blood alcohol level rises to higher levels, to the point at which stupor, coma, and death can occur at levels equal to or greater than 300 to 400 mg/dL, especially in individuals who are not tolerant to the effects of alcohol. The usual cause of death in individuals with very high blood levels of alcohol is respiratory depression and hypotension.

Alcohol Withdrawal Syndrome

Alcohol withdrawal can occur when individuals decrease their alcohol use or stop using alcohol altogether. The severity of symptoms can vary greatly. Many individuals experience alcohol withdrawal without seeking medical attention, whereas others require hospitalization for severe illness.

The clinical manifestations of alcohol withdrawal include adrenergic hyperactivity with tachycardia and diaphoresis. Patients also experience tremulousness, anxiety, and insomnia. More severe alcohol withdrawal can result in nausea and vomiting, which can exacerbate metabolic disturbances. Perceptual abnormalities, including visual and auditory hallucinations and psychomotor agitation, are common manifestations of more moderate to severe alcohol withdrawal. Generalized seizures (Chapter 372) may occur during alcohol withdrawal.

The time course of the alcohol withdrawal syndrome can vary within an individual and by symptom complex, and the overall duration of symptoms can be a few to several days (Fig. 364-2). Tremor, which is typically among the earliest symptoms, can occur within 8 hours of the last drink. Symptoms of tremulousness and motor hyperactivity usually peak within 24 to 48 hours. Although mild tremor typically involves the hands, more severe tremors can involve the entire body and greatly impair a variety of basic motor functions.[6] Perceptual abnormalities typically begin within 24 to 36 hours after the last drink and resolve within a few days. When withdrawal seizures occur, they are typically generalized tonic-clonic seizures and most often occur within 12 to 24 hours after reduction of alcohol intake. Seizures can occur, however, at later time periods as well.

The most severe manifestation of the alcohol withdrawal syndrome is delirium tremens. This symptom complex includes disorientation, confusion, hallucination, diaphoresis, fever, and tachycardia. Delirium tremens typically begins after 2 to 4 days of last alcohol intake, and its most severe form can result in death.

The alcohol withdrawal syndrome can exacerbate existing medical conditions such as hypertension and seizure disorders. In addition, it can complicate and adversely affect inpatient admissions for conditions such as trauma, which is often associated with alcohol use disorder.

Chronic Effects

Unlike acute manifestations, including intoxication and withdrawal, which are generally stereotypical in their appearance and time course, the chronic manifestations of alcohol use disorder tend to be more varied. Many patients with alcohol dependence may have no evidence of any chronic medical manifestations for many years. Over time, however, all major organ systems can be affected, especially the nervous system, cardiovascular system, liver,

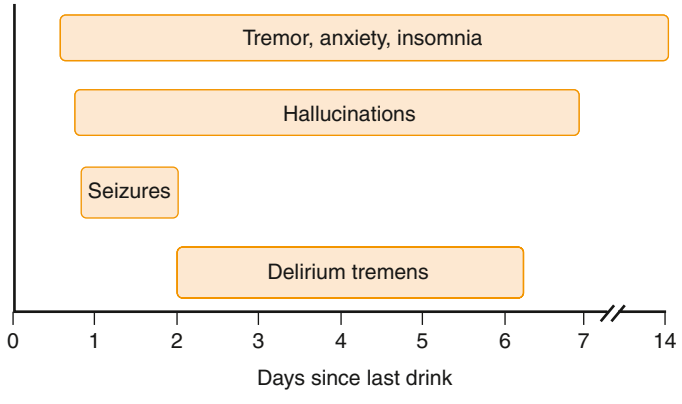

FIGURE 364-2. Time course of alcohol withdrawal.

gastrointestinal system, pancreas, hematopoietic system, and endocrine system (Table 364-2). Patients who drink are at risk for a variety of malignant neoplasms, such as head and neck (Chapter 176), esophageal (Chapter 178), colorectal (Chapter 179), breast (Chapter 183), and liver (Chapter 181) cancers. Excessive alcohol use often causes significant psychiatric and social morbidity that can be more common and more severe than the direct medical effects, especially earlier in the course of problem drinking.

Nervous System

In the central nervous system, the major effect is cognitive impairment. Patients may present with mild to moderate short-term or long-term memory problems or may have severe dementia resembling Alzheimer disease (Chapter 371). The degree to which the direct toxic effect of alcohol is responsible for these problems or the impact of alcohol-related nutritional deficiencies is uncertain (Chapter 384). The deficiency of vitamins such as thiamine may play a major role in promoting alcoholic dementia and severe cognitive dysfunction, as is seen in Wernicke encephalopathy and Korsakoff syndrome (Chapter 384). Alcohol also causes a polyneuropathy that can present with paresthesias, numbness, weakness, and chronic pain (Chapters 384 and 388). As with the central nervous system, peripheral nervous system effects are thought to be caused by a combination of the direct toxicity of alcohol and nutritional deficiencies. A small proportion (<1%) of patients with alcohol dependence may develop midline cerebellar degeneration, which presents as an unsteady gait.

Cardiovascular System

The most common cardiovascular complications of chronic alcohol consumption are cardiomyopathy (Chapters 45 and 47), hypertension (Chapter 64), and supraventricular arrhythmias (Chapter 52). Data demonstrate that excessive alcohol use increases the risk of chronic heart failure, myocardial infarction, and atrial fibrillation to a similar degree as other established "traditional" risk factors,[7] and it also increases the risk for acute cardiac decompensation.[7]

Alcoholic cardiomyopathy, which presents clinically in a manner similar to other causes of heart failure with a reduced ejection fraction (Chapter 45), is the most common cause of nonischemic cardiomyopathy in Western countries, accounting for about 45% of cases. As with other causes, alcoholic cardiomyopathy also responds to conventional treatments of heart failure (Chapter 46). Increasing levels of alcohol consumption also are associated with increasing levels of systolic and diastolic hypertension (Chapter 64). Alcoholic cardiomyopathy also is associated with arrhythmias, in particular, ventricular arrhythmias (Chapter 53).

The most common arrhythmias associated with chronic alcohol use include atrial fibrillation and supraventricular tachycardia, especially in the setting of acute intoxication and withdrawal but also with even moderate intake[8] (Chapter 52). Heavy alcohol consumption is also a risk factor for a prolonged QTc interval.

TABLE 364-2 ALCOHOL-RELATED COMPLICATIONS

SYSTEM/REALM OF PROBLEM	COMPLICATIONS
Nervous system	Intoxication Withdrawal Cognitive impairment Cerebellar degeneration Peripheral neuropathy
Cardiovascular system	Cardiac arrhythmias Chronic cardiomyopathy Hypertension
Liver	Fatty liver Alcoholic hepatitis Cirrhosis
Gastrointestinal tract, esophagus	Chronic inflammation Malignant neoplasms Mallory-Weiss tears Esophageal varices
Stomach	Gastritis Peptic ulcer disease
Pancreas	Acute pancreatitis Chronic pancreatitis
Other medical problems	Cancers: mouth, oropharynx, esophagus, colorectal, breast, hepatocellular carcinoma Pneumonia Tuberculosis
Psychiatric	Depression Anxiety Suicide
Behavioral and psychosocial	Injuries Violence Crime Child or partner abuse Tobacco, other drug abuse Unemployment Legal problems

Liver

Alcohol use is the major cause of morbidity and mortality from liver disease in the United States,[9] where an estimated 2 million or more people with known alcoholic liver disease (Chapter 138) have hepatic cirrhosis (Chapter 139). Factors that predispose to early liver disease include the quantity and duration of alcohol exposure, female gender, and malnutrition. The range of clinical manifestations includes acute fatty liver and alcoholic hepatitis (Chapter 138), as well as cirrhosis (Chapter 139). Fatty liver associated with alcohol ingestion can be asymptomatic or associated with nonspecific abdominal discomfort. Alcoholic hepatitis can present as an asymptomatic condition identified by abnormalities in liver enzymes or as an acute episode with abdominal pain, nausea, vomiting, and fever.

Alcohol-related cirrhosis is a major cause of death in the United States (Chapter 140). Although patients are often asymptomatic, patients with more advanced cirrhosis may present with a variety of symptoms and signs, including jaundice, ascites, and coagulopathy, that can benefit from management approaches tailored to this patient population. Cirrhosis is also associated with gastrointestinal bleeding from esophageal varices (Chapter 124).

Gastrointestinal Disease

Chronic alcohol use is associated with a variety of esophageal problems, including esophageal varices, Mallory-Weiss tears, and squamous cell carcinoma of the esophagus (Chapter 178). The risk for squamous cell carcinoma is increased further in patients who smoke tobacco and drink alcohol (Chapter 178). Patients with these problems can present with difficulty swallowing, chest pain, gastrointestinal blood loss, and weight loss. Acute alcoholic gastritis typically presents with abdominal discomfort, nausea, and vomiting (Chapter 118).

Pancreas

Acute alcoholic pancreatitis, which may present with severe abdominal pain, nausea, vomiting, fever, and hypotension, can be life-threatening (Chapter 130). Individuals who have recurrent acute pancreatitis may develop chronic pancreatitis, which typically presents with chronic abdominal pain, malabsorption, weight loss, and malnutrition.

Hematopoietic System

Anemia, which occurs in 10 to 60% of inpatients with alcohol dependence, can be multifactorial (e.g., blood loss, nutrient deficiency, secondary to liver disease and hypersplenism). Gastrointestinal blood loss due to Mallory-Weiss tears (Chapter 121), alcoholic gastritis (Chapter 118), or esophageal varices (Chapters 121 and 139) may be a key factor, and many patients develop subsequent iron deficiency. Dietary folate deficiency can be associated with megaloblastic anemias (Chapter 150). Alcohol's direct toxic effect on the bone marrow can lead to sideroblastic anemia that resolves after abstinence. Alcohol can suppress megakaryocyte production and cause thrombocytopenia, which may manifest as ecchymoses or bleeding (Chapter 158); the thrombocytopenia is particularly sensitive to abstinence, with platelet counts usually rebounding or returning to normal within 5 to 7 days after cessation of alcohol intake.[10] Alcohol also appears to interfere directly with platelet function. Alcohol-related immune dysfunction, as evidenced by decreased production and function of white blood cells and derangement in humoral and cell-mediated immunity, partly explains why alcohol-dependent individuals are at higher risk for infectious diseases, such as pneumonia and tuberculosis.

Malignant Neoplasms

Chronic alcohol use is associated with malignant neoplasms[11] of the head and neck (Chapter 176), esophagus (Chapter 178), breast (Chapter 183), prostate (Chapter 186), pancreas (Chapter 180), cervix (Chapter 184), lung (Chapter 177), and colon (Chapter 179). Women who have more than one

or two alcoholic drinks per day may increase their breast cancer risk 1.5-fold or more. Hormonal mechanisms and direct carcinogenic effects of alcohol have been postulated as causes of this association. The association of cervical cancer with alcohol dependence may be due to alcohol-associated high-risk sexual behaviors that are thought to increase the risk for cervical cancer.

Other Medical Issues

Gout has been associated with alcohol abuse, and flares can occur at lower serum urate levels than in nonalcoholic patients (Chapter 252). Alcoholic ketoacidosis (Chapter 104), which usually follows an alcoholic binge, presents as nausea, vomiting, abdominal pain, and volume depletion. Typically, keto-acidosis is seen with low or normal glucose readings. Mild or nonspecific abnormalities in thyroid function (Chapter 207), especially in patients with underlying liver disease, may reflect abnormalities in the clearance of thyroid-stimulating hormone or the impact of elevated circulating estrogens. Infertility and menstrual irregularities have been associated with chronic alcohol consumption, presumably due to alcohol-induced hypothalamic-pituitary dysfunction, gonadal toxicity, and impaired hepatic metabolism of circulating hormones. Hypogonadism is highly prevalent in male alcoholics with cirrhosis. Alcohol dependence is also associated with higher rates of dental and periodontal disease (Chapter 393) and with a variety of dermatologic problems, including spider angiomas and, in patients with poor hygiene, skin infestations. Both at-risk drinking and alcohol dependence have been shown to be associated with an increased risk for hospital-acquired infections, sepsis, and mortality, especially in intensive care patients. Increased alcohol consumption has been noted during the COVID-19 pandemic, and higher levels of consumption are associated with higher levels of pandemic-related mental distress.[12]

Psychiatric Issues

Psychiatric symptoms and illnesses are exceedingly common among individuals with alcohol problems. The prevalence of anxiety disorders is about 40%, and the prevalence of affective disorders is about 30%. Antisocial personality disorder is also more common in individuals with alcohol problems than in the general population. These psychiatric problems are more prevalent during periods of heavy drinking and withdrawal. All patients with alcohol use disorders require careful screening for psychiatric illnesses. Although alcohol dependence may be associated with worse outcomes in patients with common psychiatric problems such as depression and anxiety, effective treatment of underlying psychiatric disorders may result in improved drinking behaviors.

Other Behavioral and Psychosocial Issues

Alcohol commonly is the underlying cause of domestic abuse, injuries, trauma, motor vehicle crashes, and burns. For example, of all substances of abuse, alcohol and cannabis appear to have the strongest association with intimate partner violence. Patients presenting with injuries should be questioned carefully about their alcohol use. Tobacco use (Chapter 363) and other drug abuse (Chapter 365) are more prevalent in people with alcohol problems than in the general population.

DIAGNOSIS

Data from the history, physical examination, and laboratory generally are needed to provide a complete picture of the extent of alcohol problems in affected patients (Table 364-3).

History

Screening for alcohol use in combination with behavorial counseling reduces unhealthy alcohol.[A1] This process begins with a careful patient history and assessment. A four-step approach to the history of alcohol use includes comprehensive questions about alcohol use and a thorough evaluation for alcohol-related problems.[13,14]

Step 1: Ask All Patients about Current and Past Alcohol Use

A single question—Do you currently or have you ever used alcohol?—can quickly identify patients who are not lifetime abstainers and require further screening. Patients who answer yes to this question should proceed through the subsequent three steps. Patients who answer no can be classified as lifetime abstainers from alcohol and require no further questioning unless their answer changes over time. It is crucial to ask about current and past alcohol use because many patients who meet lifetime criteria for alcohol use disorder but who are currently in recovery answer no to the question about current use; unless it is specifically asked about, important past use information may be missed.

TABLE 364-3 DIAGNOSIS OF ALCOHOL PROBLEMS

HISTORY
Step 1: Ask all patients about current and past use
Do you drink alcohol (ever or currently)?
Do you have a family history of alcohol problems?
Step 2: Obtain detailed history regarding quantity and frequency of alcohol use
What types of alcohol do you consume?
How often do you drink?
How much do you usually drink?
Do you ever drink more and, if so, how much?
Step 3: Standardized questionnaire
CAGE questions:
• Have you ever felt that you should ***c***ut down on your drinking?
• Have people ***a***nnoyed you by criticizing your drinking?
• Have you ever felt bad or ***g***uilty about drinking?
• Have you ever taken a drink first thing in the morning (***e***ye opener) to steady your nerves or get rid of a hangover?
Step 4: Assess specific areas in suspected or known problem drinkers
Criteria for alcohol abuse and dependence
Evidence of medical and psychiatric problems
Evidence of behavioral or social problems
Use of other substances
• Tobacco
• Mood-altering prescription drugs
• Illicit drugs (e.g., heroin, cocaine)
• Prior alcohol or substance abuse treatment
PHYSICAL EXAMINATION
Thorough and complete examination important in all patients
Focus attention to system with identified problems
In all patients, carefully examine:
Central and peripheral nervous systems
Cardiovascular system
Liver
Gastrointestinal tract
LABORATORY STUDIES (IN SELECTED PATIENTS)
Liver enzymes
Coagulation studies
Complete blood count
Carbohydrate-deficient transferrin

Step 2: Obtain Detailed History Regarding Quantity and Frequency of Alcohol Use

A question to be asked routinely is, What type or types of alcoholic drinks (beer, wine, spirits) do you consume? Many patients do not consider the use of beer or wine "drinking." Quantity should be determined for typical use—How much do you usually drink on a typical drinking day?—and for range of use—Do you ever drink more than your usual amount and, if so, how much? This second question can be particularly important for identifying binge drinking. Quantity questions offer easy identification of at-risk drinking. Asking about the frequency of alcohol consumption—How often do you drink?—helps distinguish daily from nondaily alcohol users. Binge drinkers who drink only on weekends tend to have significant alcohol problems yet not be daily drinkers. A major goal of step 2 is to acquire a complete characterization of current alcohol use behaviors and the pattern of quantity and frequency of alcohol use during the patient's lifetime.

Step 3: Use Standardized Screening Instruments

Many standardized questionnaires have been developed to detect alcohol abuse and dependence. The two questionnaires that have been evaluated most extensively in medical settings are the CAGE (Cut down, Annoyed, Guilty, and Eye opener) questionnaire (see Table 364-3) and the Alcohol Use Disorder Identification Test (AUDIT). The CAGE questionnaire includes four questions and is scored by giving 1 point for each positive response. Given that the word *ever* is used in the CAGE questions, by definition this instrument is designed to detect lifetime alcohol problems and does not distinguish between lifetime problems and current problems. To screen for DSM-IV criteria alcohol abuse and dependence, the CAGE has a sensitivity of 43 to 94% and a specificity of 70 to 97% when a cutoff score of 2 is used to indicate a "positive" result. How this and other instruments relate to the new DSM-5 criteria for alcohol use disorder is the subject of ongoing inquiry.

The AUDIT's 10 questions cover the quantity and frequency of alcohol use, drinking behaviors, adverse psychological symptoms, and alcohol-related

problems. The AUDIT was developed by the World Health Organization to identify hazardous (e.g., at-risk) drinking and harmful (e.g., alcohol use that results in physical or psychological harm) drinking. In contrast to the CAGE questionnaire, the AUDIT focuses on recent (current to past year) drinking behaviors. Each question is scored 0 to 4 (range for total score is 0 to 40), and a total score of 8 is considered to be a positive result.

Step 4: Assess Specific Areas in Suspected or Known Problem Drinkers

Questions asked in step 4 are based on the results of the questions asked in steps 2 and 3 to obtain more detailed information in patients with potential alcohol problems. Even patients who do not screen positive on the CAGE questionnaire may warrant detailed questioning about alcohol abuse and dependence (see Table 364-1), especially if they are drinking at or above at-risk levels or there is other evidence of possible alcohol problems. A detailed review for evidence of alcohol-related medical and psychiatric problems should occur, and the need for further medical and psychiatric evaluation should be determined. The physician should look for evidence of behavioral and social problems commonly associated with alcohol use and screen for family and occupational dysfunction and other problems, such as domestic violence. Patients should be asked about their use of tobacco, mood-altering prescription medications, and illicit drugs such as heroin and cocaine.

Finally, many patients with alcohol problems have prior treatment episodes that should be detailed. The inquiry should include questions not only about formal alcohol treatment (including number of episodes, duration of treatment, and inpatient versus outpatient treatment) but also about more informal treatments, such as attendance at self-help groups like Alcoholics Anonymous (AA). For patients who require a referral for treatment, knowledge of prior treatment experience is a crucial determinant of future referral recommendations.

The Healthcare Professional's Core Resource on Alcohol. Knowledge. Impacts. Strategies (https://www.niaaa.nih.gov/health-professionals-communities/core-resource-on-alcohol) of the National Institute on Alcohol Abuse and Alcoholism (NIAAA) provides useful evidence-based strategies for the prevention and treatment of alcohol-related problems, including specific recommendations for screening, brief intervention, treatment, and referral. A recommended screening approach is the use of the NIAAA Single Alcohol Screening Questionnaire (SASQ): "How many times in the past year have you had (4 for women, or 5 for men) or more drinks a day?" If the answer is "one (or more) times," the patient is considered to have screened positive and is then asked additional questions designed to assess for alcohol use disorders.

Physical Examination

Patients with potential alcohol use disorders require a detailed physical examination to complement the history. In addition, attention should be focused on detecting common alcohol-related problems, including the nervous system, cardiovascular system, liver, and gastrointestinal system (see Table 364-2).

Laboratory Findings

A variety of laboratory tests have been proposed to aid screening for alcoholic abuse and dependence. Aminotransferase levels, red blood cell mean corpuscular volume (MCV), and carbohydrate-deficient transferrin, alone or in combination, are not as effective as screening questionnaires, such as the CAGE and the AUDIT.

Laboratory tests do have a role in diagnosis and assessment of patients with potential alcohol problems. Routine laboratory testing, including liver enzymes (Chapter 133), bilirubin, complete blood count, and prothrombin time should be obtained in all patients with alcohol problems on a regular basis so that an appropriate and complete picture of the effects of alcohol on the individual can be obtained. Patients with alcoholic hepatitis have particularly high levels of aspartate aminotransferase in the blood and elevated levels of γ-glutamyltransferase.

TREATMENT AND PREVENTION

The relationship of change in alcohol use with prevention of subsequent problems has been well established. For example, abstinence from alcohol often can result in significant improvement in cardiomyopathy. Abstinence from alcohol also reduces recurrent arrhythmia in regular drinkers with paroxysmal atrial fibrillation.[A2] Alcoholic fatty liver and alcoholic hepatitis typically improve with abstinence from alcohol. Among the hematologic abnormalities, sideroblastic anemia and thrombocytopenia respond rapidly to the cessation of alcohol.

A2

TABLE 364-4 ADVICE FOR PATIENTS WITH ALCOHOL PROBLEMS

State your medical concern:
Be specific about your patient's drinking patterns and related health risks.
Ask: How do you feel about your drinking?

Agree on a plan of action:
Ask: Are you ready to try to cut down or abstain?
Talk with patients who are ready to make a change in their drinking about a specific plan of action.

For patients who are not alcohol dependent:
Advise the patient to cut down if drinking is at or above at-risk drinking amounts (see Table 364-1) and there is no evidence of alcohol dependence.
Ask the patient to set a specific drinking goal: Are you ready to set a drinking goal? Some patients choose to abstain for a period of time or for good; others prefer to limit the amount they drink. What do you think will work best for you?
Provide patient education materials and tell the patient: It helps to think about your reasons for wanting to cut down and examine what situations trigger unhealthy drinking patterns. These materials will give you some useful tips on how to maintain your drinking goal.

For patients with evidence of alcohol dependence:
Advise to abstain if:
- Evidence of alcohol dependence
- History of repeated failed attempts to cut down
- Pregnant or trying to conceive
- Contraindicated medical condition or medication

Refer for additional diagnostic evaluation or treatment.
Procedures for patient in making referral decisions:
Involve your patient in making referral decisions.
Discuss available alcohol treatment services.
Schedule a referral appointment while the patient is in the office.

Treatment of alcohol use disorders should be based on the severity of potential or actual alcohol problems and tailored to meet the needs of individual patients.[14] Separate advice and management approaches are suggested for nondependent at-risk or problem drinkers compared with individuals who are alcohol dependent (Table 364-4). 14

Behavioral Interventions

Discussing the Diagnosis with Patients

In discussing alcohol problems, it is crucial that physicians be sensitive to the stigma and shame that may be felt by patients with alcohol problems and by their families. Alcohol-related diagnoses or problems should be discussed in a nonjudgmental manner, which forges a partnership and indicates commitment to helping with whatever problems the patient might have. Setting the stage for the discussion should include educating patients about the various levels of alcohol problems (e.g., at-risk drinking, alcohol use disorder) so that patients have an understanding of the spectrum of alcohol problems. Many patients may have a skewed view of what qualifies as problem drinking and may think that only individuals with severe alcohol problems are truly problem drinkers. The history, physical examination, and laboratory studies should be provided as "proof" that a problem may or does exist.

Treatment of At-Risk Drinkers

Evidence confirms that generalist physicians or physician extenders, in a cost-effective manner, can help patients reduce their alcohol intake and prevent subsequent alcohol-related problems by using brief, focused counseling techniques (brief interventions) that are well suited for primary care and other medical settings.[A3,A4] Data also support the use of brief interventions in general medical inpatient settings and emergency departments. Newer approaches to decreasing alcohol use in heavy drinkers include providing personalized advice by electronic interventions and using text messaging and social media. A3 A4

The brief counseling strategy includes four main components: motivational techniques, feedback about the problems with alcohol use, discussion of the adverse effects of alcohol, and setting recommended drinking limits. Motivational techniques are designed to motivate patients to change their alcohol use behavior by identifying potential or actual problems with which their alcohol use is associated. Feedback about these problems can make it clear to the patient that the problems exist. For at-risk and problem drinkers who do not meet criteria for alcohol dependence, setting recommended drinking limits below at-risk levels (e.g., less than one drink per day for women and less than two drinks per day for men) is a realistic and suitable goal. Epidemiologic evidence suggests that drinking below these levels is less likely to be associated with problems. Several randomized clinical trials confirm that patients who receive brief interventions significantly decrease their alcohol intake, often to "safe" levels, and can decrease health care use as well.

Medications

Treatment of Alcohol Use Disorders

Patients who meet criteria for an alcohol use disorder, in particular those who are dependent, usually require more intensive services than do patients who meet criteria for at-risk drinking. Most patients can be managed in outpatient treatment settings, whereas patients with a more severe alcohol use disorder or comorbid problems initially will likely require inpatient management, specific counseling programs, and pharmacologic therapy. Before entering a formal program to maintain remission, many patients first require medical management of alcohol withdrawal. Professional organizations have published practice guidelines that provide useful recommendations for how to select among treatment options for patients with alcohol dependence.

As with many other medical conditions, health disparities exist in addiction treatment, including in the treatment of alcohol use disorder.[15] Important approaches to addressing and eliminating these health disparities include educating clinicians, building community partnerships, and promoting a diverse workforce.

Management of Alcohol Withdrawal

Many patients may not present for medical management of alcohol withdrawal and try to deal with it on their own. However, a substantial subset do present for alcohol withdrawal treatment. Patients with mild to moderate withdrawal generally can be managed safely as outpatients with close follow-up.[16] Patients with moderate to severe withdrawal, as manifested by hypertension, tremor, and any mental status changes, especially patients with significant comorbid medical or psychiatric illnesses, generally are treated best as inpatients.[17] Patients who have a history of severe withdrawal in the past (e.g., delirium tremens) or who have a history of alcohol withdrawal seizures also generally should be managed as inpatients. The three major goals of medical management of alcohol withdrawal are to minimize the severity of withdrawal-related symptoms; to prevent specific withdrawal-related complications, such as seizures and delirium tremens; and to provide referral for relapse prevention treatment.

A wide variety of medications have been evaluated for their effectiveness in managing the alcohol withdrawal syndrome (Table 364-5). Longer-acting benzodiazepines are preferred because they provide a smoother withdrawal. Shorter-acting benzodiazepines, such as oxazepam, may be indicated in individuals with severe liver disease. The most common approach is to administer a standing dose of a benzodiazepine, with additional medication being given on an "as needed" basis depending on the severity of withdrawal symptoms. The specific benzodiazepine and dose often depend on the experience of the prescribing physician and the characteristics of the patient, including the severity of withdrawal (higher doses are used if withdrawal is more severe), the presence of liver disease (patients with severe liver disease should receive lower doses or shorter-acting medications), and the response to prior doses of medication (higher doses are given if symptom control is inadequate; lower doses are given if adverse effects, such as oversedation, have occurred). In general, the amount of medication per dosing period is decreased gradually as the withdrawal syndrome abates. An individualized "symptom-triggered" dosing approach, in which benzodiazepines are administered on a dose-by-dose basis as guided by withdrawal symptoms, is safe and effective in certain patients and can reduce the total doses of benzodiazepines needed to treat withdrawal. β-Blockers (atenolol and propranolol), α-agonists (clonidine), gabapentin (up to 1200 mg orally daily),[A5] and antiepileptics (carbamazepine) improve signs and symptoms of alcohol withdrawal but are viewed best as adjunctive medications to be used in addition to benzodiazepines. High-dose baclofen (a GABA-β receptor agonist at 50 to 150 mg daily) can reduce agitation-related events in patients with unhealthy alcohol use receiving mechanical ventilation, but the clinical utility of such an approach requires further trials.[A6] Thiamine supplementation (250 to 500 mg parenterally for 3 to 5 days followed by 100 to 250 mg orally daily) is routinely recommended to prevent Wernicke encephalopathy (Chapter 384).[18]

Prevention of Relapse

Counseling Strategies Used by Alcohol Treatment Programs

Three commonly used psychotherapeutic techniques are motivational enhancement therapy, 12-step facilitation, and cognitive-behavioral coping skills. Two of these techniques are designed to give patients specific tools to help them avoid relapse to alcohol use. In motivational enhancement therapy, patients identify reasons for staying away from alcohol. The 12-step facilitation therapy uses the principles of alcoholics anonymous to help patients focus their attention on abstinence. In cognitive-behavioral coping skills therapy, the patient identifies triggers to alcohol use and develops strategies to help deal with the triggers when they are present. In a controlled trial, three counseling approaches (cognitive-behavioral coping skills therapy, motivational enhancement therapy, or 12-step facilitation therapy) to treat alcohol dependence showed equivalent benefits, with most patients either remaining abstinent or significantly decreasing their alcohol use at one year.

Self-Help Groups

Self-help groups such as Alcoholics Anonymous are an important source of support and treatment for many patients with alcohol dependence.[19] Alcoholics Anonymous has the advantage of being widely available throughout the United States and free of charge, and substantial evidence supports its benefits for improving alcohol use behaviors. The overall approach to treatment is based on the 12 steps for maintaining abstinence and dealing with the various effects of alcohol. Alcoholics Anonymous meetings can be either "open" to anybody in the community or "closed" for active members only. The meetings vary in format, size, location, and demographic makeup. In

TABLE 364-5 MEDICATIONS FOR THE TREATMENT OF ALCOHOL DEPENDENCE*

MEDICATION	DOSE AND ROUTE	FREQUENCY	EFFECTS	MAJOR COMMON ADVERSE EFFECTS
ALCOHOL WITHDRAWAL				
Benzodiazepines‡				
Chlordiazepoxide*	25-100 mg, PO/IV/IM†	Every 4-6 hr	Decreased severity of withdrawal; stabilization of vital signs; prevention of seizures and delirium tremens	Confusion, oversedation, respiratory depression
Diazepam†	5-10 mg, PO/IV/IM†	Every 6-8 hr		
Oxazepam†	15-30 mg, PO†	Every 6-8 hr		
Lorazepam†	1-4 mg, PO/IV/IM†	Every 4-8 hr		
β-Blockers				
Atenolol	25-50 mg, PO	Once a day	Improvement in vital signs	Bradycardia, hypotension
Propranolol	10-40 mg, PO	Every 6-8 hr	Reduction in craving	
α-Agonists				
Clonidine	0.1-0.2 mg, PO	Every 6 hr	Decreased withdrawal symptoms	Hypotension, fatigue
Antiepileptics				
Carbamazepine	200 mg, PO	Every 6-8 hr	Decreased severity of withdrawal; prevention of seizures	Dizziness, fatigue, red blood cell abnormalities
PREVENTION OF RELAPSE				
Disulfiram†	125-500 mg, PO	Daily	Decreased alcohol use among those who relapse	Disulfiram-alcohol reaction, rash, drowsiness, peripheral neuropathy
Naltrexone†	50 mg, PO	Daily	Increased abstinence, decreased drinking days	Nausea, abdominal pain, myalgias-arthralgias
	380 mg, IM	Every 4 wk		
Acamprosate†	666 mg, PO	Three times a day	Increased abstinence	Diarrhea

*Most commonly used medications listed.
†Currently approved by U.S. Food and Drug Administration for the indication noted.
‡Dose and routes given for standard fixed-dose regimens, which include dose tapers over time.
IM = intramuscular; IV = intravenous; PO = orally.

counseling patients about attending Alcoholics Anonymous, it is important for physicians to make them aware that variations in the nature of specific meetings, especially location and demographics of participants, require patients to be willing to attend more than one meeting site on a trial basis so that they find a comfortable setting.

Pharmacotherapy to Prevent Relapse to Alcohol Use

Three medications—disulfiram, naltrexone, and acamprosate—are approved for the treatment of alcohol dependence in the United States (see Table 364-5).[20]

Disulfiram

Disulfiram is designed to prevent alcohol use by causing a severe adverse reaction when patients use alcohol. The disulfiram reaction, which includes flushing, nausea, vomiting, and diarrhea, is mediated by the inhibition of alcohol dehydrogenase and the resulting increase in serum levels of acetaldehyde and acetate after ingestion of alcohol (see Fig. 364-1). Disulfiram also affects monoamine metabolism, and the alcohol-disulfiram reaction may be related to changes in central monoamine functioning. Although disulfiram offers little benefit to most patients, it is effective in reducing alcohol intake in highly motivated patients who are supervised in an alcohol treatment program.

Naltrexone

Naltrexone is thought to decrease alcohol use by diminishing the euphorigenic effects of alcohol and by decreasing craving in alcohol-dependent patients. Randomized, placebo-controlled trials generally have shown that alcohol-dependent patients who receive naltrexone (50 mg/day) are more likely to decrease their alcohol use or remain abstinent compared with patients who receive placebo, and the effects persist after discontinuation of treatment. Naltrexone is effective in outpatient and primary care settings as well as in hospitalized patients. Side effects of naltrexone are infrequent, most notably self-limited nausea in about 10% of patients. Dose-related hepatotoxicity has been reported in patients treated for obesity with high-dose naltrexone (300 mg/day). Mild liver enzyme abnormalities are not a contraindication to naltrexone, but patients should be followed with repeated liver enzyme studies. Patients with acute hepatitis or liver failure should not use naltrexone.

In addition to oral naltrexone, injectable naltrexone, typically administered at a dose of 380 mg intramuscularly every 4 weeks, is also effective. Before beginning naltrexone, it is important to be sure that the patient is not opioid dependent in order to avoid a potentially severe opioid withdrawal reaction. Complete opioid abstinence for at least 7 to 10 days is recommended. Adverse reactions seen most commonly in patients who receive injectable naltrexone include injection site reactions (e.g., induration, itching) and symptoms such as nausea and headache, which are generally self-limited. This formulation of naltrexone may be particularly effective in individuals with more severe alcohol use disorders.

Acamprosate

Acamprosate (666 mg two times daily, 333 mg three times daily for creatine clearance 30 to 50 mL/min, not used if the creatinine clearance is <30 mL/min) is also effective for treatment of alcohol dependence. The precise mechanism of action of acamprosate is uncertain but may be related to its effects on neuroexcitatory amino acids and the inhibitory GABA system. Side effects are minimal and typically include diarrhea. Like naltrexone, acamprosate is given as an adjunctive therapy to psychological treatments for alcohol dependence. Acamprosate appears to be effective in both men and women.

Other Pharmacologic Approaches

The combination of naltrexone and acamprosate may be more effective than either medication alone, and the combination or naltrexone with behavioral interventions is better than either alone. Gabapentin is effective as a single-drug therapy for treating alcohol dependence and relapse-related symptoms, such as insomnia, and the addition of gabapentin to naltrexone improves drinking outcomes in alcohol-dependent patients. Gabapentin may be particularly effective in individuals who have a history of alcohol withdrawal symptoms.[A7]

Topiramate, a fructopyranose derivative, is an effective treatment of alcohol dependence at a dose of up to 300 mg/day and is especially effective in patients with a *GRIK1* polymorphism. Fluoxetine is useful in patients who have concurrent depression (Table 362-5), and buspirone is useful in patients who have concurrent anxiety (Table 362-9). Other medications that have shown potential promise include ondansetron, bromocriptine, and sodium valproate.

TABLE 364-6 OVERVIEW OF TREATMENT APPROACH FOR PATIENTS WITH ALCOHOL PROBLEMS

Evaluate all patients
For patterns of problem alcohol use (Table 364-1)
For alcohol-related complications, if indicated (Table 364-2)
With use of data collected from history, physical examination, and laboratory testing (Table 364-3)
For at-risk and nondependent problem drinkers
Advise to decrease alcohol use to below at-risk levels (Table 364-4)
Advise patients who cannot decrease use to below at-risk levels to abstain
For patients who are alcohol dependent
Assess for need for withdrawal management medications (Table 364-5)
Refer to an alcohol treatment program
Consider medication to prevent relapse (Table 364-5)

End-Stage Liver Disease

Despite some controversy about the use of liver transplantation to treat patients with end-stage alcoholic cirrhosis, patients in established recovery are good candidates for liver transplantation (Chapter 140). Among patients who undergo transplantation, predictors of relapse include prior relapse, continued drinking, and failure to engage in treatment.[21]

PROGNOSIS

Alcohol abuse and dependence are chronic disorders that are characterized by exacerbations and remissions. The prognosis is better for patients who seek treatment and receive it in a systematic way (Table 364-6), but it can be poor for patients with advanced liver disease and continued alcohol use. In some studies, up to 85% of patients with alcohol use disorder have been able to achieve sustained and clinically relevant reductions in alcohol consumption, even if they do not become completely abstinent.[22]

More than 25 drinks per week may shorten life expectancy by 4 to 5 years, and medical hospitalization for an alcohol use disorder is associated with over a 20 year decrease in life expectancy. Causes of death include the chronic toxicities of alcohol as well as injuries, suicide, and overdoses of alcohol or other drugs. Newer technology-based therapies, such as a smartphone application to support recovery in individuals with alcohol use disorders, hold promise for improving treatment outcomes in the future.

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For the General References and other additional features, please visit Elsevier eBooks+ at https://ebooks.health.elsevier.com.

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365 DRUG USE DISORDERS

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DEFINITION

The term *substance use disorder* has replaced *substance abuse* and *dependence* in the diagnostic lexicon. As defined by the American Psychiatric Association's *Diagnostic and Statistical Manual of Mental Disorders*, "The essential feature of a substance use disorder is a cluster of cognitive, behavioral, and physiological symptoms indicating that the individual continues using the substance despite significant substance-related problems." No single pathognomonic symptom is diagnostic of a substance use disorder. Rather, the syndrome is a series of 11 symptoms, of which the individual must meet two or more in the same 12-month period to warrant a diagnosis of a substance use disorder (Table 365-1). These 11 symptoms can be grouped into four general categories:

Impaired control: taking a substance in larger amounts or for a longer time than intended; persistent desire or unsuccessful attempts to stop or to reduce use; a great deal of time spent using a substance or recovering from the effects of its use; craving

Social impairment: failure to fulfill role obligations at home, work, or school as a result of repeated substance use; continued substance use despite experiencing interpersonal problems; or reducing or giving up important social, recreational, or occupational activities

Risky use: recurrent use in hazardous situations (e.g., driving) or despite knowledge that substance use is causing or exacerbating a physical or psychological problem

Pharmacologic criteria: tolerance and physical dependence, when relevant; not all drugs cause these symptoms

For patients who are prescribed medications that can cause tolerance and physical dependence, the diagnostic term *substance use disorder* should be used only when medication use is problematic; tolerance and physical dependence are not considered criteria for a diagnosis of a substance use disorder in patients who are taking medications such as opioids or sedative-hypnotics exclusively as part of appropriate medical care. If a patient is using legitimately prescribed medications as intended (e.g., opioids for chronic pain or benzodiazepines for panic disorder) and those medications are helping the patient to function better, that patient will not meet criteria for a substance use disorder, even if tolerant to the medication and/or physically dependent upon it.

TABLE 365-1 DSM-5 CRITERIA FOR SUBSTANCE USE DISORDERS

IMPAIRED CONTROL
1. Took larger amounts/for longer period of time than intended
2. Persistent desire or unsuccessful attempts to stop or reduce use
3. Much time spent using a substance or recovering from its effects
4. Craving
SOCIAL IMPAIRMENT
5. Failure to fulfill home, work, or school obligations because of repeated substance use
6. Continued use despite experiencing interpersonal problems
7. Reducing/giving up important social, recreational, or occupational activities
RISKY USE
8. Recurrent use in hazardous situations
9. Physical/psychological problems related to use
PHARMACOLOGIC CRITERIA
10. Tolerance, when relevant*
11. Physical dependence, when relevant*

*"When relevant" indicates that these criteria are not counted, even if the symptoms are present, when an individual is using legitimately prescribed medications as intended and those medications are helping the person to function better.

Substance use disorder is diagnosed if 2 or more of these 11 criteria are met within a 12-month period. A substance use disorder is classified as "mild if someone meets 2 or 3 criteria, "moderate" if meeting 4 or 5 criteria, and "severe" if a person meets 6 or more criteria.

Data from Hasin DS, O'Brien CP, Auriacombe M, et al. DSM-5 criteria for substance use disorders: recommendations and rationale. *Am J Psychiatry*. 2013;170:834-851.

EPIDEMIOLOGY

Use of illicit drugs and nonmedical use of prescribed drugs are common. Approximately 36 million Americans, representing approximately 13% of the population, report using an illicit drug in the previous month. When asked about their substance use in the past month, about 32 million Americans reported using marijuana (which is now legal for medical and/or recreational purposes in many states), 6.4 million reported using potentially psychoactive prescription drugs nonmedically (2.8 million of whom used prescription pain relievers nonmedically), 2.0 million people used cocaine, and 1.9 million people used hallucinogens. Among youths aged 12 to 17 years, about 9% reported using an illicit drug in the past month. The overall estimated prevalence of illicit intravenous drug use in the United States ranges between 0.24% and 0.39%.[1] Overdose deaths from opioids, cocaine, and psychostimulants continue to rise in the United States, now exceeding 100,000 per year.[2]

PATHOBIOLOGY

Drug use disorders involve complex interactions between the pharmacology of a specific drug (Chapter 27), an individual's genetic makeup, psychological strengths and weaknesses, environmental circumstances, and societal influences (such as physical and perceived drug availability, legal status and cost of the drug, religious and cultural mores, and presence of alternative rewarding activities). Thus, the etiology of drug use disorders can be conceptualized by employing the public health model frequently cited in the study of infectious disease (i.e., as an interaction among the host [which in this case is the potential drug user], the agent [a specific drug], and the environment [the person's family life and peer group, as well as the social, cultural, and religious attitudes toward use of that substance]).

The Host

A positive family history of a substance use disorder increases the likelihood of both alcohol (Chapter 364) and drug use disorders. Twin studies and adoption studies show that both genetic and environmental factors contribute to this vulnerability, although the precise nature is still unknown.[3]

Psychiatric illness (Chapter 362) influences the likelihood of developing drug use problems. For example, conduct disorder in childhood and adolescence as well as antisocial personality disorder in adulthood predispose to subsequent drug use problems. Psychiatric disorders such as mood disorders are frequently noted in people with drug use disorders. However, the presence of these two disorders in the same person does not necessarily imply causation, even if one of the disorders is manifested first.

Conversely, individual protective factors may reduce the likelihood of a substance use disorder. Individuals who have positive familial relationships, academic success, and meaningful religious affiliations have a lower likelihood for development of drug problems. The fact that many people have a mixture of risk and protective factors speaks to the complex etiologic nature of drug use disorders.

The Agent

Most drugs of misuse are inherently reinforcing; animals typically will self-administer most of the commonly misused drugs. Not all drugs are equally reinforcing, however. Some individuals like the stimulating effects of drugs such as cocaine and amphetamine, whereas others experience that level of stimulation as uncomfortable. Some individuals like the relaxation induced by drugs such as marijuana and sedative-hypnotics, whereas others feel overly slowed down by these drugs. Although some individuals gravitate toward particular drugs because of their specific pharmacologic properties, others use a variety of drugs indiscriminately, based on level of availability; some of these individuals are primarily seeking to alter their current emotional state, regardless of the direction in which it is changed. The reinforcing properties of many drugs appear to be mediated through dopaminergic pathways, although other neurotransmitters, including γ-aminobutyric acid, serotonin, and norepinephrine, are also involved in mediating drug-induced reinforcement (Chapter 27).

The Environment

The third critical factor in the development, maintenance, and perhaps cessation of drug use disorders is the environment in which the use occurs. Drug use does not occur in a vacuum. Rather, many societal factors, including legal status, availability, price, perception of dangerousness, social desirability, peer group, and religious beliefs, influence behavior relating to substance use. Drug availability is known to affect likelihood of substance use. For example, alcohol consumption (Chapter 364) increases when the hours during which alcohol

ABSTRACT

Substance use disorders are highly prevalent and are responsible for considerable morbidity and mortality. Although some symptoms of substance use disorders are drug specific, all drugs of misuse share common some combination of impaired control, social impairment, risk use, and pharmacologic symptoms, including tolerance and physical dependence. The etiology of substance use disorders is multifactorial. The public health model of disease emphasizes interactions among the individual, the drug, and the environment in which the drug is used. Medical complications from drug use disorders are often related to factors that cut across many of the drugs of misuse, including paraphernalia (e.g., unsterile needles), adulterants, and lifestyle issues. However, key drug-specific issues include opioid-induced respiratory depression and cocaine-induced ventricular tachyarrhythmias, vasoconstrictive effects, and grand mal seizures. Treatment of substance use disorders varies according to the drug. Effective pharmacotherapies are prominent in the treatment of opioid use disorders, but psychosocial treatments are emphasized for the treatment of cocaine, methamphetamine, or cannabis use disorders.

KEYWORDS

substance use disorder
addiction
withdrawal
intoxication
opioids
cocaine
methamphetamine

can be sold are extended. The restriction of alcohol availability by restricting hours of sale or by increasing its cost through taxation in turn reduces consumption. Illicit drugs are, of course, by definition less available than alcohol (Chapter 365) or tobacco (Chapter 363). A major factor that influences use of these agents is the potential user's perception of the drug's safety, social cachet (or lack thereof), likelihood of incurring legal consequences, and peer group behavior.

CLINICAL MANIFESTATIONS

Medical Complications Related to Drug Use Disorders

The medical complications of drug use disorders are often directly related to the pharmacology of the drug being used (e.g., the vasoconstrictive properties of cocaine). In addition to these drug-specific sequelae, however, many medical complications occur as a result of three factors that cut across many misused drugs: paraphernalia, particularly unsterile needles; adulterants; and lifestyle issues.

Paraphernalia

Some of the most serious medical problems that occur in individuals with drug use disorders are a result of the route of administration rather than of the actual drug being used. The use of unsterile needles, particularly if they are shared with other drug users, can lead to a variety of localized and systemic infections, some of which can be life-threatening. Skin infections and cellulitis are relatively common among injection drug users. Systemic infections related to needle use are often serious; individuals who inject drugs may develop infective endocarditis (Chapter 61) or osteomyelitis (Chapter 251). For example, between 2016 and 2018, one survey found that infection-related complications of injection opioid use increased by over 20%.[4] Other serious infections among injection drug users include hepatitis B, hepatitis C (Chapter 134), and HIV infection (Chapter 353).

Adulterants

Drugs that are purchased and sold illicitly are often adulterated or "cut" with other similar-looking products, with the intention of increasing the dealer's profit margin. For example, other white powdery substances are typically added to cocaine and heroin during the dealing process to dilute their purity. Some of these adulterants can in turn cause medical problems. At times, these complications occur because of the combined toxicity of the adulterant and the route of administration. For example, talc, which may be added to street heroin or be injected by individuals who crush talc-containing pharmaceutical tablets such as opioids, can cause granulomas in the lung or liver. Other common adulterants in street drugs include quinine (frequently used with heroin) and lidocaine or levamisole (often added to cocaine), but such toxic materials as strychnine and ground glass in street drugs can cause serious medical sequelae. The extremely powerful synthetic opioid fentanyl and its analogues, sold either as an adulterant (e.g., added to heroin) or as a substitute for other opioids, was estimated to be responsible for almost 75% of opioid overdose deaths in 2019.

Lifestyle Issues

Many patients who have drug use disorders expose themselves to multiple risks owing to intoxication, participating in dangerous illegal activities, and associating with potentially violent people. As a result, these individuals experience a high rate of traumatic injuries and are at greater risk of being victims of assault, homicide, or suicide. Suicide (Chapter 362) is far more common among people with substance use disorders than among the general population, likely related to a combination of the effects of acute intoxication, the high prevalence of depression among these individuals, and the higher rate of antisocial personality disorder, which is associated with a propensity toward impulsiveness, risk taking, and violence. Intoxication, which can lead to motor vehicle crashes, is also a factor in about one third of pedestrians who are killed by motor vehicles

DIAGNOSIS

It is often helpful to enlist the help of a family member or significant other (with the patient's permission) in obtaining historical information. In some acute medical situations (Chapter 96), drug screening can be critical for urgent diagnosis and therapy. In other situations, individuals may be screened after an event or periodically for performance issues. Routine questioning about potential unhealthy drug use is recommended by the U.S. Preventative Services Task Force,[5] although there is no confirmed evidence on its benefit.[A1]

TREATMENT

General Treatment Principles

Since drug use disorders represent a heterogeneous group of disorders, treatment requires a careful medical, social, and psychiatric assessment, including a detailed substance use history and laboratory testing. Intoxication and withdrawal syndromes need to be treated acutely; longer-term treatment involves helping the patient reduce or ideally abstain from substance use and thus improve overall functioning.

For disorders of illicit drug use, medications approved by the U.S. Food and Drug Administration (FDA) are available only for opioid use disorders. As a result, behavioral treatments are critically important. Behavioral treatments of proven benefit include cognitive-behavioral therapy, motivational enhancement therapy, contingency management (also referred to as motivational incentive) therapy, 12-step facilitation therapy, and behavioral couples therapy. For example, offering an alternative positive reward (e.g., a voucher that can be exchanged for desired goods and services such as movie tickets or clothes) in response to abstaining from drugs may help individuals with drug use disorders overcome their craving and reduce substance use. In fact, this type of treatment approach, based on the use of motivational incentives for abstinence, is one of the most powerful treatment interventions available for the treatment of drug use disorders. In addition to professional treatment, peer support groups such as the 12-step–oriented Alcoholics or Narcotics Anonymous and non–12-step groups such as SMART Recovery can be extremely helpful in facilitating recovery from drug use problems.

MAJOR DRUGS

OPIOIDS

Opioids are a core part of the medical pharmacopoeia, primarily because of their capacity to treat pain but also because of their antitussive and antidiarrheal properties. Unfortunately, opioids are also powerful euphoriants with a substantial abuse liability. Opioids can be divided into four categories: natural opium alkaloids, including opium, morphine, and codeine; semisynthetic derivatives of morphine, including heroin and oxycodone; synthetic opioids that are not derived from morphine, including methadone and fentanyl; and opioid-containing preparations, such as elixir of terpin hydrate.

EPIDEMIOLOGY

In the United States, opioid overdoses now account for about 75,000 annual deaths, representing about 75% of all overdose deaths, with about a nine-fold increase since 1999. From 1999 to 2010, prescription opioids accounted for increases in opioid overdoses, at which point heroin overdose deaths rapidly increased. Starting in 2014, illicitly produced synthetic fentanyl and its analogues were responsible for the rapid increase in overdose deaths and now represent nearly 75% of opioid overdose deaths.

Opioids are currently the most commonly misused prescription drugs. Most people who misuse opioid analgesics report that they initially obtained them from a doctor's prescription or from a friend or relative who had been prescribed them. Other factors that have led to increasing use of heroin and then fentanyl include the decreased availability of prescription opioid analgesics, as well as the increased availability and relatively low cost of heroin and fentanyl.

PATHOBIOLOGY

Opioids are readily absorbed when they are taken orally, intranasally, or by smoking or injection. Heroin and fentanyl are most commonly injected but may be smoked or used intranasally. Both are metabolized in the liver (heroin to morphine and fentanyl to norfentanyl). Fentanyl is additionally metabolized in the duodenum.

Most of the commonly abused opioids bind as agonists to the μ-receptor and typically produce the effects most commonly associated with opioids: miosis, respiratory depression, analgesia, euphoria, and drowsiness. Opioids that bind to the κ-receptor, unlike μ-receptor agonists, often produce dysphoria rather than euphoria. The other two opioid receptors, δ- and N/OFQ-receptors, do not appear to play a known significant role in opioid use disorders.

Opioid analgesics are ordinarily taken by the oral route, but they may be altered to be used through different routes. This approach is particularly common with the extended-release preparations, some of which may be altered by chewing the pill (facilitating a rapid release of the opioid medication) or by crushing the pill, dissolving it in water, and then injecting it or using it intranasally.

CLINICAL MANIFESTATIONS AND DIAGNOSIS

The initial response to the administration of heroin, particularly when it is used intravenously, is a "rush," often described as orgasmic, persisting for 30 to 60 seconds. This sensation is generally followed by a profound sense of relaxation that is sometimes referred to as being "wrapped in warm cotton." During this period, the user generally feels drowsy and may be seen to be "nodding," with mental clouding and a sense of tranquility. Associated effects include a reduction in the respiratory rate, with miosis; reduced contractility of smooth muscle; and reduced secretions in the stomach, pancreas, and biliary tract. As a result, constipation and urinary hesitancy may occur. Itching is commonly felt during opioid intoxication. Many individuals experience nausea and vomiting when they initially use opioids, but tolerance tends to develop to this effect over time. Tolerance also occurs to some other effects rather quickly, particularly the analgesic, respiratory depressant, and euphoriant properties of opioids. In contrast, relatively little tolerance occurs to constipation or to pupillary constriction, miosis is a manifestation of opioid use but is not diagnostic of opiate overuse or intoxication.

Physical Dependence

Physical dependence on opioids leads to a characteristic withdrawal syndrome, the key signs of which include elevated heart rate and blood pressure, mydriasis, abdominal cramps, sweating, gooseflesh, rhinorrhea, lacrimation, and gastrointestinal distress, particularly diarrhea, nausea, and vomiting. Insomnia, particularly difficulty in falling asleep, is common and often the most long-lasting complaint among people who experience opioid withdrawal. Yawning, muscle twitches, and difficulty with regulation of body temperature are also common. The severity of withdrawal can be highly variable, depending on the dose of opioids taken, the length of time that they have been taken, and individual factors. For short-acting opioids, such as heroin and hydrocodone, the earliest stages of withdrawal typically occur approximately 6 to 12 hours after the last use; peak symptoms tend to occur 48 to 72 hours after the last dose, and most clinical symptoms usually resolve within 7 to 10 days. For longer-acting opioids, such as methadone, each of these time periods associated with withdrawal from short-acting opioids should be approximately doubled or tripled.

Other Medical Complications

The most common serious medical complications that occur with opioid use (other than overdose and opioid use disorder itself) are typically related to factors other than the opioids themselves, particularly needle use and adulterants (see earlier). Common medical problems among heroin users include hepatitis B, hepatitis C (Chapter 134), infective endocarditis (Chapter 61), talc granulomatosis, HIV infection (Chapter 353), cellulitis (Chapter 408), and abscesses, all typically related to needle use.[6]

An important noninfectious complication is alteration of the cardiac conduction system, with a prolongation of the QT interval. This complication, which can lead to potentially serious arrhythmias, including torsades de pointes (Chapter 53), has been particularly noted with methadone, especially in high doses.

Chronic pain is commonly seen among individuals with opioid use disorders, and not just in those who have received opioids for the treatment of pain. Pain can occur in these individuals for numerous reasons, such as a predilection to experience accidents, violence, and other forms of physical trauma that can produce chronic pain. Chronic opioid use also may lead to hyperalgesia.

As with all substance use disorders, psychiatric illnesses (particularly mood disorders) are more common than in the general population. The use of multiple drugs is more the rule than the exception in patients with opioid use disorders, particularly among those using heroin and fentanyl. The use of benzodiazepines plus opioids has been linked to a higher risk of overdose.

TREATMENT

Opioid Overdose

The approach to possible or confirmed opioid overdose, which can be a life-threatening emergency, is detailed in Table 96-3.

Opioid Withdrawal

Opioid detoxification can be accomplished by switching patients from their current drug of abuse (e.g., heroin, hydrocodone) to methadone or buprenorphine and then tapering that medication.[7-9] Although detoxification regimens vary, one commonly used method in hospital settings is to administer methadone 10 mg orally whenever a patient experiences objective signs of opioid withdrawal (e.g., mydriasis, tachycardia, hypertension, and sweating). This process can be repeated every 2 to 4 hours for 24 hours after the initial dose; the total amount of methadone given in that 24-hour period is the "stabilization dose," which should not ordinarily exceed 40 mg. The stabilization dose is then reduced by 5 mg a day until the detoxification is completed.

Buprenorphine can also be used successfully for opioid detoxification.[A2] Patients who demonstrate objective signs of opioid withdrawal (often measured with a standardized withdrawal severity scale such as the Clinical Opiate Withdrawal Scale https://nida.nih.gov/sites/default/files/ClinicalOpiateWithdrawalScale.pdf) can be stabilized with buprenorphine during a 1- to 2-day period; the subsequent taper from buprenorphine may occur either right away or after a period of stabilization with buprenorphine. The dose of buprenorphine will depend on whether the medication will be used for a brief, several-day detoxification or for longer-term stabilization or maintenance treatment.

Longer-Term Treatment

Three medications are approved by the FDA for the treatment of opioid use disorder: methadone (a full opioid agonist), buprenorphine (a partial agonist), and naltrexone (an opioid antagonist). Treatment with methadone and buprenorphine treatment are associated with decreased opioid overdose and all-cause mortality.[10,11] Unlike buprenorphine and naltrexone, which can be prescribed by physicians in their offices, methadone is available for the treatment of opioid use disorder only in specially licensed treatment programs.

Methadone Maintenance

Methadone is a long-acting μ-receptor agonist with a slow onset of peak effects (typically approximately 2 to 6 hours) and a slow offset of action, thereby allowing for once-a-day administration. Methadone reduces opioid craving and induces cross-tolerance, thereby blocking or attenuating the effects of other opioids.[A3] Although the therapeutic dose of methadone for a particular individual may vary, doses of 60 mg or higher have typically been more effective than lower doses, and some evidence suggests that even higher doses (e.g., 80 mg a day or more) may be more effective than 60 mg. Methadone treatment can reduce all-cause mortality as well as reduce opioid use, increase employment, decrease criminal behavior, and reduce the rate of developing HIV infection.

When a patient who is enrolled in a methadone treatment program experiences acute pain (e.g., postoperatively) requiring opioid analgesia, the patient should continue to receive the baseline methadone maintenance treatment dose for the addiction and should receive a different opioid if needed to treat the pain (Chapter 26); or, if additional methadone is the analgesic of choice, it should be given every 6 to 8 hours in addition to the usual daily dose for the opioid use disorder. The fact that the patient is receiving methadone every day does not obviate the need for opioid analgesia. In fact, many patients receiving methadone treatment for opioid use disorder will require a dose of opioids that is relatively high as a result of cross-tolerance to other opioid drugs. Before administering methadone, however, the patient's methadone maintenance dose must be confirmed with the patient's treatment program.

Buprenorphine

Buprenorphine is a partial opioid agonist that can be administered in physicians' offices rather than exclusively in specialized opioid treatment programs. To prescribe buprenorphine, physicians must apply to the Substance Abuse and Mental Health Services Administration for a waiver that allows them to prescribe buprenorphine for up to 30 patients. To prescribe to 100 or 275 patients, prescribers must further complete 8-hour (physicians) or 24-hour (nurse practitioner or physician assistant) training before applying for eligibility.

Buprenorphine, which is a partial μ-agonist and κ-antagonist, has a more favorable safety profile than methadone because of its partial agonist properties. Respiratory depression, which can be induced by full agonists and is responsible for some overdose deaths, is far less likely to occur with buprenorphine because its partial agonist properties cause a plateau of opioid effects as the dose increases. Buprenorphine comes in sublingual form, in either tablet or film for oral use, as a depot injection that persists for 1 month,[A4] or as an implant persisting for 6 months. Longer-acting formulations provide a steady blood level. New injectable formulations with effects persisting from 1 to 4 weeks should be available soon. The sublingual forms are commonly given in a combination with naloxone to deter abuse by injection, which would precipitate withdrawal. Buprenorphine also appears to be safe and effective during pregnancy.[12]

Typical doses of 16 to 24 mg of sublingual buprenorphine per day appear to be as effective as methadone in doses up to approximately 60 mg a day. However, individuals who require much higher doses of methadone may respond better to that agent than to buprenorphine.

Extended treatment with buprenorphine-naloxone produces far better outcomes compared with short-term detoxification in opioid-addicted youths aged 15 to 21 years.[A5] Initiation of this combination in opioid-dependent patients seen in an emergency department is also better than referral to treatment or a brief intervention followed by facilitated treatment referral for reducing subsequent use of inpatient addiction treatment facilities.[A6] Buprenorphine maintenance treatment has been shown to be clearly more effective than detoxification alone.

Naltrexone

Naltrexone, which is a pure opioid antagonist, blocks the effects (including euphoria) of opioids. As a result, individuals taking naltrexone should have a reduced desire to use opioids because they will have no desired effect. When used orally (50 mg/day) or in its long-acting form (380 mg intramuscularly every 4 weeks), naltrexone is highly effective at suppressing illicit opioid use, and naltrexone maintenance is effective after buprenorphine taper. Among patients who actually take either drug, naltrexone is as safe and effective as buprenorphine.[A7] However, many patients are less interested in being treated with oral naltrexone because it requires no opioids for 7 days or until the patient is no longer withdrawing. Nevertheless, naltrexone can be a useful medication for patients who are willing (either as the result of external pressure or for internal motivation) to use it, such as those involved in the criminal justice system.

Behavioral Treatment

Methadone, buprenorphine, and naltrexone are not designed to be delivered alone but should be given in conjunction with behavioral treatment to be effective. Counseling delivered within a medical office setting can be effective in conjunction with buprenorphine treatment, thereby suggesting that general physicians who are trained to use buprenorphine can effectively treat patients with opioid use disorder in their offices with a combination of buprenorphine and counseling.

CENTRAL NERVOUS SYSTEM STIMULANTS: COCAINE AND AMPHETAMINES

The two most important central nervous system stimulants, cocaine and amphetamine (including methamphetamine), are derived from different sources. Cocaine is extracted from coca leaves, whereas amphetamine is a synthetic compound. However, both induce similar psychoactive activity when they are taken illicitly, and they both can produce similar adverse consequences. Amphetamines have been used to treat attention deficient/hyperactive disorder (Chapter 362), narcolepsy (Chapter 374), and depression (Chapter 362). Cocaine is sometimes used as a topical anesthetic for otolaryngologic surgery, where its vasoconstrictor action can reduce blood flow in the operating field.

EPIDEMIOLOGY

In 2019, approximately 2.0 million people, or 0.7% of the U.S. population, reported using cocaine in the past month. Of these past-month cocaine users, 19% (378,000) used crack (see later). Cocaine and methamphetamine each had the third highest rate of drug use disorder in 2019 (behind opioids and cannabis).

Cocaine can be used intranasally, by intravenous injection, or by smoking. Cocaine hydrochloride, which is the form of the drug used in medical therapeutics, is a water-soluble compound that can be used intranasally ("snorted") or injected. Adding an alkaline compound such as baking soda to an aqueous solution of cocaine hydrochloride produces a rocklike compound known as crack, which can be smoked.

Methamphetamine can also be used in multiple ways—orally, by smoking, or intravenously. In the United States, methamphetamine use has been particularly prevalent and worrisome, especially in the Midwestern, Southwestern, and Western states, including Hawaii.

PATHOBIOLOGY

Both cocaine and amphetamine increase the accumulation and activity of specific neurotransmitters in the synaptic cleft, including dopamine, norepinephrine, and serotonin. Cocaine is believed to exert this effect by binding to the dopamine transporter. Increased dopaminergic activity, particularly in the nucleus accumbens, is thought to be responsible for the reinforcing effects of cocaine. Amphetamines appear to increase the level of dopamine in the synaptic cleft, primarily by stimulating presynaptic dopamine release as opposed to reuptake blockade.

CLINICAL MANIFESTATIONS AND DIAGNOSIS

Both cocaine and amphetamines reliably produce euphoria, wakefulness, a sense of initiative, increased self-confidence (sometimes to the point of grandiosity), and, in some instances, sexual stimulation. With higher doses, users may feel "wired," a syndrome characterized by anxiety, irritability, and perhaps paranoia. Smoking cocaine produces the most rapid onset of intoxication (6 to 10 seconds) and the shortest period of drug effect (10 to 15 minutes). Methamphetamine effects persist much longer than those produced by cocaine; psychiatric symptoms such as paranoia that typically persist only a matter of hours in cocaine users may persist for days to weeks after methamphetamine use and occasionally may result in a chronic psychotic state. Withdrawal from either of these agents leads to opposite effects from those of intoxication: increased appetite, hypersomnia, and depression, which can occasionally be serious.

Medical complications related to cocaine use reflect a combination of cocaine's stimulant activity (increased heart rate and blood pressure) and its vasoconstrictor properties. Local complications that result from the drug's vasoconstrictor activity include ulcerations of the nasal mucosa, perforation of the nasal septum, and decreased pulmonary diffusion capacity. Systemic complications include myocardial infarction (Chapter 58), intracranial hemorrhage (Chapter 377), grand mal seizures (Chapter 372; as a result of intoxication, not withdrawal), and ventricular tachyarrhythmias (Chapter 53), which may be responsible for sudden death. Physicians seeing a patient in an emergency department for an unexplained seizure (Chapter 372) should consider drug use as a potential cause (see Table 96-2). A serum or urine toxicology can be an important diagnostic tool in such a situation.

TREATMENT

The acute treatment of cocaine or amphetamine toxicity, which can be a medical emergency, is addressed in Table 96-3.

The chronic treatment of stimulant use disorders primarily consists of behavioral therapies, including individual and group therapy as well as mutual-help groups. Specific forms of treatment, such as cognitive-behavioral therapy, individual drug counseling by a 12-step–oriented disease model, and a behavioral treatment program called contingency management, in which patients are reinforced for positive outcomes (e.g., drug-free urine screens),[A8] can be quite successful.

No medication is currently FDA-approved for the treatment of cocaine or amphetamine abuse.[13] However, two medication regimens have shown some benefit for the treatment of methamphetamine use disorder. A combination of extended-release injectable naltrexone (380 mg every 3 weeks) plus oral extended-release bupropion (450 mg daily) can result in about an 11% absolute improvement in the abstinence rate at 12 weeks.[A9] Mirtazapine (30 mg daily) has also shown benefit.[A10]

SEDATIVE-HYPNOTIC AND ANXIOLYTIC DRUGS

Benzodiazepines and other sedative-hypnotic and anxiolytic medications, such as zolpidem, are frequently prescribed for the treatment of anxiety (Chapter 362) and sleep difficulties (Chapter 374). Although these drugs have very different chemical structures, they are grouped together according to their therapeutic applications. Most of these drugs act at the γ-aminobutyric acid type A receptor and can cause physical dependence and both dispositional and pharmacodynamic tolerance.

CLINICAL MANIFESTATIONS AND DIAGNOSIS

Because the benzodiazepines are far and away the most commonly prescribed sedative-hypnotics, they are also the most widely misused. Many people who ultimately misuse these medications have initially received a legitimate benzodiazepine prescription for the treatment of anxiety or insomnia. However, a combination of tolerance, decreased effectiveness, and physical dependence over time may lead some people to increase the dose on their own. In such circumstances, attempts by the physician to taper the person off of the medication can be very difficult.

A second pattern of benzodiazepine misuse occurs among individuals who are misusing other drugs, most commonly opioids or stimulants. For example, many individuals who use heroin or other opioids may use benzodiazepines as a means of either enhancing the opioid effect or buffering symptoms of opioid withdrawal. Such individuals typically use relatively large doses of benzodiazepines intermittently, so many of these patients do not develop physical dependence on benzodiazepines.

TREATMENT

The treatment of individuals who misuse benzodiazepines depends to some extent on the pattern of use. For individuals who have an anxiety disorder and have been misusing a legitimately prescribed medication, a common approach is to taper the benzodiazepine and to institute a different type of treatment, such as an antidepressant, combined with cognitive-behavioral therapy (Chapter 362). Because benzodiazepine withdrawal in long-standing users can precipitate a seizure, tapering is often a slow process that requires careful monitoring of withdrawal symptoms (anxiety, agitation, insomnia, tachycardia, palpitations). Most patients initially tolerate a reduction in the benzodiazepine dose with relatively little difficulty but experience their greatest discomfort toward the

end of the taper, perhaps because the percentage dose reduction is greater at the low end of a taper regimen.

For patients who are misusing benzodiazepines as part of a pattern of multiple substance use, medical detoxification from the benzodiazepine itself will often be unnecessary; for this population, psychosocial approaches that advocate abstinence from all substances, in conjunction with appropriate pharmacotherapy as needed (e.g., in the case of opioid use disorder), are preferred. However, the parenteral combination of buprenorphine and benzodiazepines can be hazardous, so physicians who are treating patients who are misusing both opioids and benzodiazepines must be mindful of this issue when considering the use of buprenorphine.

MARIJUANA

Marijuana, which refers to the dried leaves and flowers of the plant *Cannabis sativa*, is now legal in some circumstances and states, but it is still illicit in other settings. The psychoactive substance responsible for the marijuana "high" is Δ^9-tetrahydrocannabinol (THC). The concentration of THC in available cannabis plant material increased from 1 to 3% in the 1970s to 4% in 1995 and to nearly 14% in 2019. Some forms of cannabis use (e.g., "dabbing") involve much higher concentrations of THC.

EPIDEMIOLOGY

Marijuana is the most commonly used drug in the United States, with nearly 130 million Americans reporting lifetime marijuana use and about 30 million reporting use in the past month. As of 2021, 37 states have legalized medical marijuana and 18 states have legalized recreational marijuana. Other states have legalization legislation under consideration. This legalization has been associated with a rise in the use of marijuana, including a higher percentage of youths using marijuana products.[14]

The association of adolescent marijuana use with other substance use can be explained by a common liability model, where common environment and genetic factors predispose to substance use, rather than marijuana serving as a gateway to hard drugs such as heroin and cocaine. About 9% of past-year and 20% of daily marijuana users meet criteria for cannabis use disorder.[15]

PATHOBIOLOGY

Marijuana and other cannabinoids such as hashish (dried cannabis resin) exert their effects by binding to the cannabinoid receptors, of which two are currently known. Binding to the CB1 receptor, which is located primarily in the brain, appears to be responsible for the psychoactive effects of THC, whereas the CB_2 receptor may be associated with immune system responses.

CLINICAL MANIFESTATIONS AND DIAGNOSIS

When marijuana is smoked, its psychoactive effects occur almost immediately, with peak intensity approximately 30 minutes later; effects tend to disappear within 3 hours. Oral administration of marijuana leads to a delayed onset of action, but the effects of the drug persist for a longer time. Physiologic effects of marijuana intoxication include increased heart rate and conjunctival injection. Psychological effects include a sense of euphoria and well-being, friendliness, increased appetite, a distorted sense of time, impaired short-term memory, and sometimes a feeling of having achieved special insights.

The recent increase in the potency of cannabis has increased the likelihood of adverse reactions. The most common acute adverse event that occurs with marijuana use is a sense of acute panic, most common in inexperienced users, when the user's level of intoxication is greater than expected and the individual feels out of control. Cannabis hyperemesis syndrome, a cause of cyclical vomiting syndrome, may be misdiagnosed without knowledge of heavy cannabis use, thereby leading to an unnecessary diagnostic evaluation. Cannabis use, particularly during adolescence, may increase the likelihood of developing neuropsychological deficits and, in some cases, a psychotic disorder such as schizophrenia later in life.

Cannabis has the capacity to cause tolerance in regular users, and some regular heavy users experience withdrawal symptoms on cessation of use, including irritability, difficulty in sleeping, and anxiety. Because THC is highly soluble in lipids, it can be stored in fat depots of regular users for several weeks, sometimes longer, with resultant positive urine test results for THC.

TREATMENT

Cessation of cannabis will cure the hyperemesis syndrome. Acute panic induced by marijuana can be best managed with reassurance that the effects will resolve as the drug wears off.

Compared with alcohol, opioids, and stimulants, cannabis users uncommonly seek treatment of cannabis use disorder itself, but increased rates of use likely will lead to an increasing number of people seeking treatment because of difficulty in stopping marijuana use. No medications are approved by the FDA for the treatment of cannabis use disorder. Psychosocial approaches similar to the treatment of other substance use disorders are currently the treatment of choice.

HALLUCINOGENS

Hallucinogens are a group of plant-based and synthetic drugs that lead to primarily visual perceptual alterations, such as illusions and hallucinations. External normal stimuli also often are experienced in unusual ways, and ordinary events can appear profound to people while they are under the influence of these agents. The most common hallucinogens are lysergic acid diethylamide (LSD), mescaline, and psilocybin. Methylene dioxymethamphetamine (MDMA), also known as ecstasy, has both mild stimulant and potentially hallucinogenic properties and is thus sometimes categorized with the hallucinogens and sometimes as a stimulant.

EPIDEMIOLOGY

Approximately 1.9 million individuals in the United States report having used a hallucinogen in the previous month; LSD and MDMA are the most commonly used hallucinogens. Although illicit throughout the United States, these drugs are currently being studied for their potentially therapeutic effects in a variety of mental health and addictive disorders.

PATHOBIOLOGY

LSD is thought to exert its action through serotonin agonist activity, particularly at the $5\text{-}HT_{2A}$ receptor. Other neurotransmitters may be involved in hallucinogenic activity as well. Hallucinogens can produce tolerance in a matter of days, but they do not produce physical dependence.

CLINICAL MANIFESTATIONS AND DIAGNOSIS

In addition to their effects on perception and behavior, hallucinogens can produce sympathomimetic effects, such as tachycardia, increased blood pressure and body temperature, and pupillary dilation. Hyperreflexia and muscle weakness can also be seen. The most commonly seen medical consequence of hallucinogen use is hyperthermia, which can occur most commonly in users of MDMA.

The most common acute psychological adverse event, similar to marijuana, is a feeling of panic over the sense of loss of control that a person may feel as a result of intoxication. As is the case with marijuana, this is most likely to occur in inexperienced users. Some hallucinogen users will develop psychotic symptoms that fail to remit after the drug has worn off. Some hallucinogen use can also lead to longer-term perceptual difficulties. When these occur, a spontaneous return of very brief hallucinogen-induced symptoms long after the drug has worn off is known as a flashback. People who have perceptual difficulties that are much more pervasive may be said to have *hallucinogen persisting perception disorder*, which can occasionally be quite disabling.

TREATMENT

Symptomatic treatment is focused on the specific adverse medical and psychiatric sequelae. If a psychotic episode that occurs after use of a hallucinogen persists over time, it would be treated as any other psychotic disorder (Chapter 362). No specific treatment is available for hallucinogen use disorder, and it is uncommon for people to seek treatment specifically because they want to stop using hallucinogens.

PHENCYCLIDINE

Phencyclidine (PCP) use is reported by approximately 120,000 Americans. Low doses of PCP can lead to symptoms that resemble alcohol intoxication, with slurred speech, ataxia, and a subjective feeling sometimes described as "feeling dead." PCP intoxication typically is accompanied by increased muscle tone, hyperreflexia, nystagmus, and ataxia.

When taken in high doses, PCP can have serious medical and psychiatric consequences. High-dose users may experience psychosis, catatonia, and extremely violent behavior. Medical sequelae of PCP intoxication can include muscle rigidity, seizures, hyperthermia, coma, and occasionally death.

TREATMENT

Treatment of patients with a PCP-related substance use disorder consists of the usual behavioral approaches used for other substance use disorders. No specific FDA-approved medications are available for this disorder.

ANABOLIC-ANDROGENIC STEROIDS

Anabolic-androgenic steroids, such as testosterone and its synthetic analogues, are typically used for their physical rather than behavioral effects. Anabolic-androgenic steroids can have a legitimate medical purpose to treat testosterone deficiency (Chapter 216). Misuse of anabolic-androgenic steroids has traditionally been primarily to enhance strength and athletic performance, although an increasing number of individuals have used these drugs primarily in an attempt to improve their physical appearance.

Misuse of anabolic-androgenic steroids can cause a number of medical and psychiatric problems, including hypertension, elevated low-density lipoprotein cholesterol levels, cardiomyopathy, hepatotoxicity, acne, feminization (gynecomastia and reduced testicular size) in men, and masculinization (hirsutism, reduction in breast tissue, deeper voice) in women. Behavioral effects include aggressiveness (sometimes leading to violence) and an increased prevalence of mood disorders.

No specific treatment is available to help people stop abusing anabolic steroids. Behavioral treatment approaches that are commonly used to treat other substance use disorders should be used with this population.

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366 APPROACH TO THE PATIENT WITH NEUROLOGIC DISEASE

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INTRODUCTION

Neurologic symptoms and diseases are encountered in all spheres of clinical practice. Many symptoms of nervous system diseases are a part of everyday experience for healthy people, whether it be slips of the tongue, headache, numbness, muscle twitches, tremors, or mood swings with feelings of elation and depression. The challenge is to decipher whether symptoms fall within the spectrum of normal health or warrant further investigation. Neurology demands a pragmatic and skillful ap-proach embedded in core principles of clinical medicine.

CLINICAL MANIFESTATIONS

Knowledge of the structure and function of the nervous system is essential to the diagnostic method in neurology. Through a careful history and neurologic examination, even if performed virtually,[1] the clinician can elicit the key symptoms and signs to formulate problems within an anatomic and pathophysiologic framework, thereby targeting appropriate evaluation. The seasoned clinician can often swiftly arrive at the neurologic diagnosis by extracting the most relevant historical details and generating a hypothesis that can be tested and refined through a reliable neurologic examination. In evaluating a patient's symptoms and signs, it is valuable to arrive at a clinical diagnosis without reference to neurodiagnostic laboratory findings, which can often be normal when symptoms first appear. Furthermore, the widespread availability of neurodiagnostic imaging and electrophysiologic, biochemical, and genetic testing can lead to the detection of incidental "abnormalities" that often cause unnecessary concern, wasteful extraneous evaluation, and potentially harmful treatment. In general, the adage that it is difficult to improve an asymptomatic patient should be kept in mind.

A practical approach to understand the basis of a patient's neurologic symptoms involves addressing three key questions:

1. *Are the symptoms neurologic?*
   A patient may present with a constellation of symptoms that masquerade as neurologic (such as "dizziness" in a patient with cardiovascular disease, or perioral tingling in a patient with panic attacks) or as non-neurologic (such as intractable hiccups in a patient with a lesion in the area postrema of the medulla, or abdominal discomfort caused by a thoracic myelopathy). It is important to allow patients to describe symptoms in their own words, but direct questions are often necessary to characterize the problem fully. Terms such as weakness, numbness, heaviness, cramps, and tiredness may each mean pain, weakness, or alteration of sensation to some patients. Clarification of described symptoms provides critical clues to ascertain whether there is an underling neurologic basis for their presentation.
   Context is also relevant, because a history of general medical and psychiatric problems may lead one to consider a non-neurologic cause. A history of physical abuse (Chapter 223) or alcohol use (Chapter 364) and drug misuse (Chapter 365) can add a challenging layer of complexity to the interpretation of symptoms.
2. *Where is the lesion?*
   The organization of the nervous system is such that diseases affecting a neuroanatomic structure usually give rise to specific constellations of neurologic symptoms and signs in keeping with the disrupted function of that structure. For this reason, the clinician should formulate a diagnostic opinion in anatomic terms. The neurologic history and clinical examination are best viewed as a search to detect a pattern of dysfunction where symptoms suggest a lesion of particular neuroanatomic units. The clinician should aim to discern which level of the nervous system is involved—the central nervous system (supratentorial [Videos 366-1 through 366-4], posterior fossa [Videos 366-5 and 366-6], spinal cord/column [Video 366-7]) or the peripheral nervous system (anterior horn cell [Video 366-8], nerve root, plexus [Video 366-9 and E-Fig. 366-1], peripheral nerve [Video 366-10 and E-Fig. 366-2], neuromuscular junction [Video 366-11], muscle [Videos 366-12 and 366-13 and E-Figs. 366-3 through 366-6])—and whether the process is focal (midline or lateralized) or diffuse. Relevant questions include the following: Can one disease account for all of the symptoms and signs? A second issue is whether the history is suggestive of a single focus (e.g., stroke or tumor) or multiple sites of nervous system involvement (e.g., multiple sclerosis), or part of a systemic disease (e.g., vitamin B_{12} deficiency, myopathy, or polyneuropathy).
3. *What is the lesion?*
   In neurologic diagnosis, the history usually indicates the nature of the disease or the diagnosis, whereas the neurologic examination localizes it and quantitates its severity. In arriving at a diagnosis, the following points are useful: consider the patient's entire medical history; consider the tempo and duration of the symptoms; determine whether the symptoms have been progressive without remission, or whether there have been plateaus or periods of return to normal. Symptoms with an acute onset suggest a vascular cause (Chapter 375) or seizure (Chapter 372); symptoms that are subacute in onset suggest a mass lesion, such as tumor (Chapter 175) or abscess (Chapter 382); symptoms that have a waxing and waning course with exacerbations and remissions suggest a central demyelinating cause (Chapter 380); and symptoms that are chronic and progressive suggest a degenerative disorder. Toxic and metabolic syndromes (Chapter 384) are typically diffuse and can manifest acutely or chronically.

DIAGNOSIS

History

The neurologic history is the most important component of neurologic diagnosis. For many diseases, the history is almost the only avenue to explore. Examples of such disorders include headaches (Chapter 367), seizures (Chapter 372), developmental disorders (Chapter 385), memory disorders (Chapter 371), and behavioral diseases (Chapter 362). A careful history frequently determines the cause. When a neurologic problem is suspected, the physician should begin to try to localize the lesion, a process that aids in establishing whether the disease is diffuse or focal.

The history is often the only way of diagnosing neurologic illnesses that typically have normal or nonfocal findings on neurologic examination. Such illnesses include paroxysmal disorders (such as many seizure disorders [Chapter 372], narcolepsy [Chapter 374], migraine, and most other headache syndromes [Chapter 367], as well as the various causes of dizziness) and most types of dementia. The neurologic history often provides the first clues that a symptom is psychological (Chapter 362) in origin.

To guide the clinician in obtaining a meaningful neurologic history, the following are points to consider:

- *Carefully identify the chief complaint or problem.* Not only is the chief complaint important in providing the first clue to the physician about the differential diagnosis, but it is also the reason the patient is seeking medical advice and treatment. If the chief complaint is not properly identified and addressed, the correct diagnosis may be missed and an inappropriate diagnostic evaluation may be undertaken. Establishing a diagnosis that does not incorporate the chief complaint frequently focuses attention on a coincidental process irrelevant to the patient's concerns.
- *Begin with open-ended questions and listen carefully to the patient as long as necessary*. The patient often volunteers the most important information at the start of the history. A good rule of thumb is to listen initially for at least 5 minutes without interrupting the patient. During this time, insight into the patient's mental status (including level of alertness, cognitive function, and behavior), cranial nerve function (e.g., ocular movements [Video 366-5], facial asymmetry [Video 366-13], speech disturbances [Video 366-11]), and motor function (e.g., increase or paucity of spontaneous movements as seen with movement disorders [Video 366-4]) can be gleaned. This period of intent listening and observation allows the physician to follow up with focused and relevant questions and clinical examination maneuvers to formulate an accurate diagnostic opinion.
- *Clarify the timing of symptoms*. In addition to the nature of the onset of the symptom (i.e., acute, subacute, chronic), the timing of symptoms also can provide clues. For example, symptoms may relate to the time of day. Early morning headaches may suggest an underlying sleep disorder, such as obstructive sleep apnea, a psychiatric condition such as anxiety or depression, or an intracranial mass lesion. Abnormal movements at night may point to restless legs syndrome, rapid eye movement (REM) sleep behavior disorder, or frontal lobe epilepsy. The timing of medications is important when evaluating "on"/"off" periods with dopaminergic agents in Parkinson

ABSTRACT

Neurologic diseases are encountered in all spheres of clinical practice. Although their broad range of symptoms, complexity of anatomy, and diverse pathophysiologies make neurologic conditions challenging to diagnose and manage, a systematic approach can be helpful. By conducting a careful history and neurologic examination, the clinician can elicit the key symptoms and signs to formulate problems within an anatomic and pathophysiologic framework that facilitates appropriate investigation. This chapter reviews the core aspects of the neurologic history and examination. Common complaints of possible neurologic origin are presented. The indications, strengths, and pitfalls of investigations commonly used in clinical neurology are provided with illustrative examples. Clinical pearls are embedded throughout to help the clinician utilize the diagnostic formulation process that is central to clinical neurology.

KEYWORDS

neurology
history
examination
investigations
symptoms
diagnosis

E-FIGURE 366-1. Left brachial plexopathy. A 52-year-old woman with a left idiopathic brachial plexopathy. Atrophy of abductor digiti minimi (ADM) *(solid arrow with open arrowhead)* and dorsal interossei (*asterisk*) muscles (**A**, dorsal view) and marked wasting of the thenar eminence (*dashed arrow*) of the left hand are shown (**B**, palmar view). Scapular winging (*solid arrow with closed arrowhead*) is demonstrated on the left with shoulder flexion due to serratus anterior muscle weakness (**C**). The involvement of multiple nerve root and peripheral nerve territories of the left upper limb is consistent with a left-sided brachial plexus lesion (see below for innervation of above muscles) (Video 366-9). *Innervation of above muscles*:
ADM—C8 and T1, lower trunk, deep branch of ulnar nerve
Dorsal interossei—C8 and T1, lower trunk, ulnar nerve
Thenar eminence—C8 and T1, lower trunk, median nerve
Serratus anterior—C5, C6, C7, long thoracic nerve

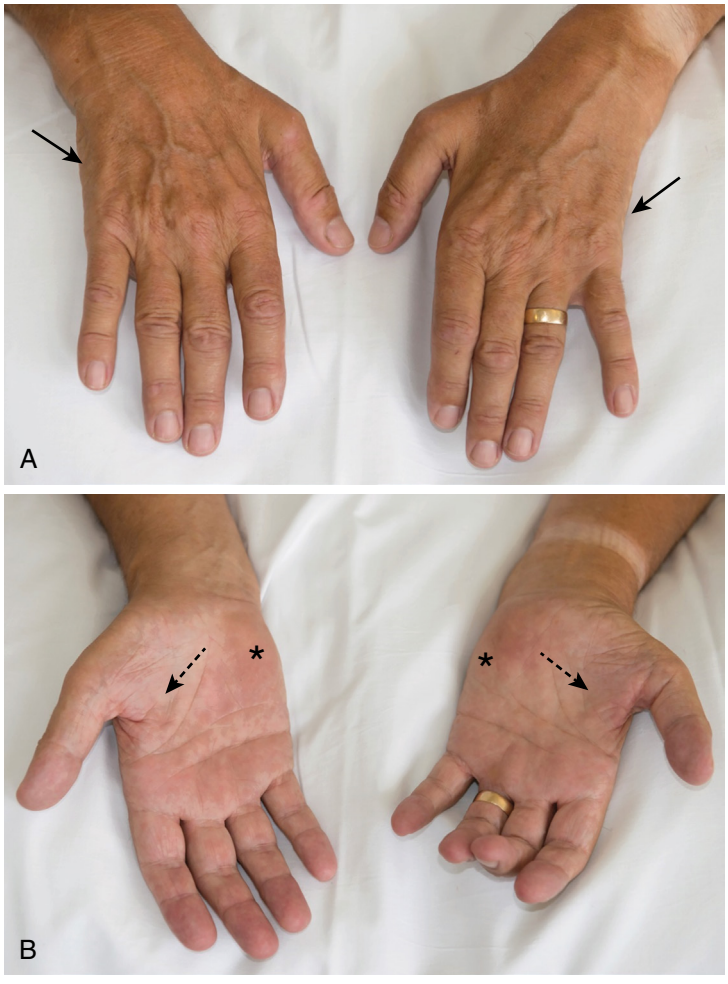

E-FIGURE 366-2. Charcot-Marie-Tooth disease. A 69-year-old man with Charcot-Marie-Tooth disease. Atrophy of abductor digiti minimi (ADM) (*solid arrow with open arrowhead*) of both hands (**A**, dorsal view), and thenar eminence (*dashed arrow*) and hypothenar eminence (*asterisk*) of both hands (**B**) are shown. These upper limb findings along with foot deformities, such as hammer toes and pes cavus, and changes to the appearance of the lower limbs (i.e., "inverted champagne bottle") (not shown) and a steppage gait (Video 366-10) are classic features of a symmetrical, length-dependent peripheral neuropathy as is seen in Charcot-Marie-Tooth disease.

E-FIGURE 366-4. Facioscapulohumeral dystrophy. An 80-year-old man with facioscapulohumeral dystrophy. Asymmetrical facial weakness, wasting of pectoral muscles with prominent axillary creases and upper arm wasting (with forearm sparing, not shown) (**A**) accompanied by scapular winging (**B**) are pathognomonic features of facioscapulohumeral dystrophy. A protuberant abdomen and the presence of Beevor sign are also classic features of this diagnosis (Video 366-13).

E-FIGURE 366-3. Myotonic dystrophy. A 58-year-old man with myotonic dystrophy type 1. Facial features such as frontal balding, ptosis, and temporal muscle atrophy (**A**) and orbicularis oculi weakness (demonstrated by inability to bury eyelashes with forced eye closure) (**B**) are typical for myotonic dystrophy. These facial characteristics along with the presence of clinical myotonia are pathognomonic of the diagnosis (Video 366-12).

E-FIGURE 366-5. Inclusion body myositis. A 66-year-old man with inclusion body myositis. Inclusion body myositis is an inflammatory myopathy that is typically refractory to immunosuppressant medicines. Atrophy of the ventromedial forearm muscles (**A**, anterior view; **B**, lateral view). Preservation of flexion at metacarpophalangeal joints with complete paralysis of flexion at proximal and distal interphalangeal joints (**C**). These findings (**A-C**) in combination with quadriceps atrophy (especially vastus medialis and lateralis) (**D**) and ankle dorsiflexor weakness (not shown) are highly distinctive features of inclusion body myositis. Other commonly involved muscles include biceps brachii, triceps, and wrist flexors.

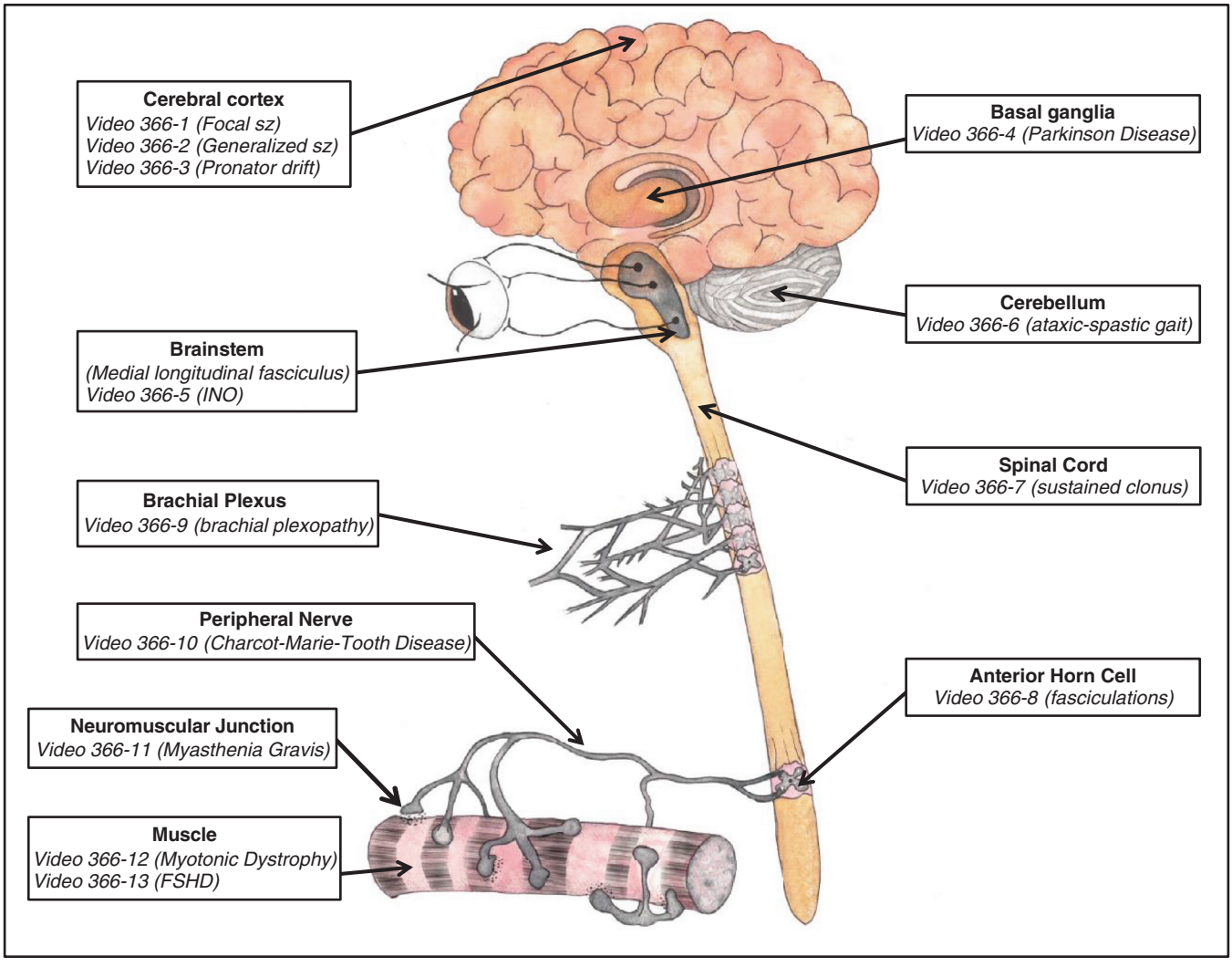

E-FIGURE 366-6. **Videos illustrating neurologic findings.** FSHD = facioscapulohumeral muscular dystrophy; sz = seizure.

disease or the relationship of chemotherapy to length-dependent sensory/motor peripheral neuropathy. Symptoms may also follow a specific precipitant such as the loss of muscle tone with emotional triggers in cataplexy, the electric-shock–like sensation with neck flexion in cervical demyelination, the numbness and weakness when prolonged focal pressure in a limb causes a compression neuropathy, or new-onset seizures after the use of alcohol or recreational drugs. The muscle weakness of hypokalemic period paralyses typically is exacerbated after a carbohydrate-rich meal.

- *Obtain a collateral history from surrogate historians*. Surrogate historians often provide key or missing information about the onset and evolution of neurologic disorders that alter mental status, whether episodic (e.g., loss of consciousness in syncope [Chapter 49] or epilepsy [Chapter 372, Videos 366-1 and 366-2]) or progressive (e.g., degenerative dementia [Chapter 371] or cerebral tumor [Chapter 175]) or influence a patient's awareness of disease (e.g., anosognosia in nondominant hemispheric lesions). Importantly, surrogate historians can provide real-life context that casts light onto the severity and impact of the patient's symptoms on his or her functional status.
- *Take a complete past medical, medication, psychiatric, family, and social and occupational history*. Many neurologic illnesses are complications of underlying medical disorders or are due to adverse effects of drugs. For example, posterior reversible encephalopathy syndrome can be a complication of renal disease (Chapter 100) and encephalopathy after bariatric surgery can be secondary to thiamine deficiency (Chapter 384). Parkinsonism (Chapter 378) is a frequent complication of the use of antinausea medicines (e.g., metoclopramide or prochlorperazine) and many neuroleptic agents (Chapter 402). A large number of neurologic disorders have a hereditary component, so a positive family history often can help establish the diagnosis. Occupational exposures play a role in various neurologic disorders, such as carpal tunnel syndrome (e.g., repetitive injury in machine operators or people who use keyboards), peripheral neuropathy (e.g., lead or other toxin exposure), and parkinsonism (e.g., heavy metal exposure).
- *Summarize the history for the patient*. A summary of the history is an effective way to ensure that all details were covered sufficiently for a tentative diagnosis to be made. This summary provides an opportunity for the physician to fill in historical gaps not apparent when the history was initially taken, as well as for the patient or surrogate to correct any historical misinformation.
- *End by asking if the patient had considered or was concerned about a particular diagnosis and what the patient's expectations are for the visit*. These questions allow the physician to evaluate the patient's concerns about and insight into his or her symptoms and/or condition. Some patients have a specific diagnosis in mind that spurs them to seek medical attention. Multiple sclerosis (Chapter 380, Videos 366-5 and 366-6), amyotrophic lateral sclerosis (Chapter 387, Video 366-8), Alzheimer disease (Chapter 371), and brain tumors (Chapter 175) are diseases that patients often suspect may be the cause of their neurologic symptoms. The discussion will also help guide how to discuss prognosis, especially in patients with advanced neurologic disease.
- *Avoid referral bias and keep an open mind*. Often patients come to a consultation with a neurologic diagnosis already in mind, whether it be self-generated or from the referring physician. In these situations, it is important to steer the patient away from discussions of previous diagnostic test results and the opinions of previous health care professionals. Clinicians can sometimes be influenced by the opinion of their colleagues and, as a result, potentially overlook key historical elements that may prove central to the diagnosis.
- *Do not be misled by incidental findings on neurodiagnostic studies*. Lesions such as congenital anomalies of the brain or spinal cord, small meningiomas, subarachnoid cysts, small cavities in the spinal cord, degenerative changes of the spine, and small cerebral aneurysms detected by CT or MRI scanning are often incidental findings or even normal variants rather than the causes of current symptoms. A good rule to remember is "never order (or look at) a test until you have decided what you are looking for."

Important Considerations: Physical Abuse and Substance Abuse

Traumatic injury (Chapter 368) and substance misuse (Chapters 364 and 365) are usually difficult to detect by the medical history and examination. Physically, sexually, and/or emotionally abused individuals are often unable or unwilling to report abuse even though such harm may cause or contribute to symptoms. People who abuse alcohol (Chapter 364) or toxins (Chapters 365) do not typically give an accurate account of their use of these agents, which themselves may cause a host of neurologic disorders. Therefore, a systematic and sensitive consideration of the possibility of these frequent causes of neurologic symptoms is important in every patient. Awareness of and attention to the often-subtle signs that suggest physical trauma (Chapter 223) is of paramount importance.

ACUTE NEUROLOGIC DISORDERS REQUIRING IMMEDIATE DIAGNOSIS AND TREATMENT

Most neurologic diagnoses are made by a careful, thorough history and an appropriately complete examination. However, the tempo of illness and the availability of life-saving treatment that is effective only if administered within minutes of evaluating a patient dictate rapid action in several specific circumstances. Coma (Chapter 373), repetitive seizures (Chapter 372), acute stroke (Chapters 376 and 377), suspected meningitis and encephalitis (Chapters 381 and 383), head and spine trauma (Chapter 368), and acute spinal cord compression are diagnosed by clinical and laboratory assessment, and urgent treatment must be instituted as soon as ventilation and cardiac status are stabilized.

For acute spinal cord compression, the differential diagnosis includes transverse myelopathy (Chapter 380), spinal shock (Chapter 368), central cord syndrome (Chapter 368), hemicord (Brown-Séquard) syndrome (Chapter 368), conus medullaris syndrome (Chapter 369), and cauda equina syndrome (Chapter 369). The cause may be acute spinal trauma (Chapter 368), a spinal epidural abscess (Chapter 382), or a spinal epidural hematoma (Chapter 369). Emergent imaging is indicated and should be followed, if possible, by targeted surgical therapy.

NEUROLOGIC EXAMINATION

The neurologic examination is an extension of the history that can affirm the presence of disease; detect unsuspected or subclinical findings; localize the process when there is a fixed lesion; and provide a clue to etiology. For these reasons, many tests of neurologic function are routinely indicated in all patients. For practical purposes, however, there is no "complete" neurologic examination; the skilled clinician implements a core examination and adds or subtracts layers, as clinically indicated.

The neurologic examination should be tailored to the clinical setting of the patient. The approach to an ambulatory office patient is considerably different than the approach to a critically ill patient. The examination of a patient with specific complaints focuses on findings pertinent to that patient. Thus, more detailed testing of cognition is indicated in patients with behavioral or memory disturbance, and more detailed testing of sensation should be performed in patients with complaints of pain, numbness, or weakness. It is important to perform all routine tests in patients with abnormalities in one sphere of neurologic dysfunction; otherwise, erroneous localization of a lesion or disease process can occur. For deviations from normal to be recognized and quantitated, a physician must have extensive experience in the routine assessment of healthy individuals.

THE GENERAL EXAMINATION

Specific neurologic symptoms or signs should prompt a general physical examination focused on conditions that may have neurologic significance. Examination of the scalp and skull should focus on any abnormalities of the contour or symmetry. Localized thickening of the skull or a cluster of abnormal blood vessels could suggest an underlying meningioma (Chapter 175) or arteriovenous malformation (Chapter 377); depressions in the skull may represent the consequence of fracture (Chapter 368). An enlarged head circumference in an adult (greater than 55 to 60 cm) is occasionally a normal, often hereditary variant but could point toward a long-standing anomaly of the brain or spinal cord in a patient with underlying central nervous system disease. Neck range of motion, straight-leg raising, and spinal curvature (scoliosis; Chapter 86) should be assessed. Deformities of the spinal column or extremities may suggest the cause of presenting neurologic signs or provide an adequate non-neurologic explanation for the chief complaint.

The skin should be inspected for neurofibromas and café au lait maculae (e.g., neurofibromatosis type I; Chapter 385), adenoma sebaceum (e.g., tuberous sclerosis; Chapter 385), lipomas (e.g., lipomatosis), vascular nevi (e.g., Sturge-Weber syndrome [Chapter 385] if in trigeminal nerve distribution), and brown hair nevi/pad of fat or skin dimple (e.g., spina bifida or myelodysplasia when found over the sacral region). Peripheral nerve lesions may be associated with vasomotor or trophic changes to the overlying skin and/or irregular hair or nail growth.

Assessment of blood pressure and heart rate (with orthostatic measurements, where indicated) should be routinely performed. Carotid auscultation for

bruits is indicated in older adults, especially in the presence of focal neurologic symptoms or signs. Evaluation of peripheral pulses may provide important clues relevant to sensory or motor complaints.

In patients with bladder, bowel, or leg symptoms, evaluation of rectal sphincter tone is usually indicated. Limitation of joint range of motion or painless swelling of joints may be a sign of an unsuspected neurologic lesion. The presence of enlarged lymph nodes should raise suspicion of underlying infection or malignancy affecting not only those nodes but also parts of the nervous system.

COMPONENTS OF THE NEUROLOGIC EXAMINATION

The neurologic examination begins with the first sight of the patient and continues throughout the consultation. The handshake, manner of walking and seating, nature of clothing, and general comportment can provide useful clues that help guide the history and examination. Facial features may direct clinicians to specific lines of inquiry and examination, such as with prominent supraorbital ridges and jaw (acromegaly; Chapter 205), protruding ocular globes and eyelid retraction with staring expression (exophthalmic goiter; Chapter 207), frontal balding, ptosis, and drooping mouth (myotonic dystrophy; Chapter 389, Video 366-12, E-Fig. 366-3), fatigable ptosis and snarling expression (myasthenia gravis; Chapter 390, Video 366-11), and expressionless facies with reduced blink frequency (Parkinson disease; Chapter 378, Video 366-4).

The various aspects of the detailed neurologic examination are considered in specific symptom and disease sections noted later. The major components of the examination include mental status, cranial nerves, motor (including reflexes), sensory, cerebellar/coordination, and gait and should form part of the clinician's "core" examination and be assessed in all patients.

A careful medical history often provides an adequate assessment of mental status: level of consciousness, orientation, memory, language function, affect, and judgment. Abnormalities in any of these functions demand more detailed testing. Detailed mental status testing is also indicated when the chief complaint suggests a cognitive problem.

Cranial nerve function that should be tested in all patients includes visual acuity (with and without correction); optic fundi; visual fields; pupils (size and reactivity to direct and consensual light); ocular motility (Video 366-5); jaw, facial, palatal, neck, and tongue movement (e.g., tongue fasciculations, Video 366-8); and hearing.

Examination of motor function (Chapter 389) is essential in all patients. The patient should be observed for tremor (Chapter 379, Videos 366-4 and 366-10) and other abnormal movements, and the muscles inspected for fasciculations (Video 366-8). Muscle bulk (atrophy or hypertrophy), tone (flaccid, spastic, or rigid), and strength can be assessed rapidly. The distribution of weakness often sheds light on localization based on the pattern (e.g., upper motor neuron, myotomal, peripheral [Videos 366-9 through 366-11 and 366-13]). Strength testing should include assessment of specific functional activities, including the ability to sit up from a supine position, to rise from a deep knee bend or deep chair, to walk on heel and toe, to lift the arms over the head, and to make a tight fist.

Muscle stretch reflexes are the most objective component of the motor examination and are useful in confirming the localization (i.e., central versus peripheral) of motor dysfunction. Reflexes and plantar responses should take into account right-left symmetry and disparity between proximal and distal reflexes in a limb or between arm and leg reflexes. Biceps, triceps, brachioradialis, quadriceps, and ankle reflexes should be quantitated from 0 to 4 (0 = absent; 1 = hypoactive; 2 = normal; 3 = brisk; 4 = clonus).

Sensory testing (Chapter 388) need not be detailed unless there are sensory symptoms. However, the evaluation of at least one large fiber (e.g., vibration or joint position sense with use of tuning fork or by moving a distal joint, respectively) and one small fiber (e.g., pain or temperature with respective use of a single-use pin or warmed tuning fork) should be performed. If sensory changes do not follow a peripheral pattern, cortical sensory function should be tested (i.e., two-point discrimination, graphesthesia, stereognosis).

Appendicular (finger-nose-finger, heel to shin) and truncal (station) function (Video 366-6) should be assessed. Rapid alternating movements of the tongue, hands, fingers, and feet can point to a pyramidal, extrapyramidal, or cerebellar lesion if the rate, amplitude (Video 366-4), or rhythm, respectively, is affected. Asymmetry of movement should be noted. A pronator drift is a sensitive sign of upper motor neuron weakness.

The assessment of a patient's ability to stand and walk provides important clues about motor, sensory, and cerebellar function. The patient should be instructed to walk across the room normally, then on his or her heels, then toes, and then in tandem (heel to toe) (Videos 366-4, 366-6, and 366-10). If an ambulatory patient is able to rise from a deep knee bend and walk on heels and toes, lower limb strength is likely normal and may preclude the need for individual muscle testing. Postural instability should be evaluated (Videos 366-4 and 366-6).

THE COMATOSE PATIENT

In the patients with reduced level of consciousness, lesions in the ascending reticular activating system, thalamus, or diffuse injury to the cerebral hemispheres should be considered. To evaluate these possibilities, a rapid examination that differs considerably from an alert, aware individual is required (Chapter 373). In such patients, many aspects of the neurologic examination cannot be tested, but considerable information can still be gleaned. On inspection, attention should focus on the examination of the level of consciousness, respiratory pattern, position of eyelids and eyes in primary gaze, size of pupils, and spontaneous eye and limb movements. Signs of injury related to seizures, including tongue biting, should be sought. Assessment of the optic fundi should look for hemorrhage (see Fig. 391-28 in Chapter 391) or papilledema (see Fig. 391-25 in Chapter 391),[2] and examination of cranial nerve reflexes, including pupillary, corneal, vestibulo-ocular, and gag reflexes, can provide valuable insight into possible contributory intracranial processes and brainstem function. The nature and distribution of motor responses to (painful) stimuli assist localization. Muscle stretch reflexes when obviously asymmetrical suggest dysfunction of the motor unit. However, minor asymmetries are much less important than in an awake patient, especially given that reflexes are likely to fluctuate from one moment to the next. Particular elements of the general examination must also be assessed quickly: evidence of cranial and spinal trauma, tenderness of the skull to percussion, nuchal rigidity (but not in patients with head or neck trauma), and evidence of physical abuse.

COMMON COMPLAINTS OF POSSIBLE NEUROLOGIC ORIGIN

SPONTANEOUS MOVEMENTS

Muscle tremors, jerks, twitches, cramps, and spasms (Chapter 379) are frequent symptoms. The cause of spontaneous movements can reside at any level of the nervous system. In general, movements that occur in an entire limb or in more than one muscle group concurrently are caused by central nervous system disease. Movements confined to a single muscle are likely to be a reflection of disease of the motor unit (including the motor neurons of the brainstem and spinal cord; Video 366-8). When spontaneous movements of a muscle are associated with severe pain, patients often use the term "cramp." Cramp is a medically defined disorder that reflects the intense contraction of a large group of motor units. Leg cramps are occasionally a sign of an underlying disease of the anterior horn cell, nerve roots, or peripheral nerve; however, cramps are frequent in normal persons, particularly in the elderly, and they are usually benign. When cramps are severe, they can produce such intense muscle contraction that muscle injury is caused and muscle enzyme (e.g., creatine kinase) levels are elevated in blood.

The rare muscle diseases in which an enzyme deficiency interferes with substrate use as fuel for exercise (e.g., McArdle disease; Chapter 389) are often associated with severe exercise-provoked muscle contractures. These contractures are electrically silent on electromyography, in contrast to the intense motor unit activity seen with cramps. Such contractures should not be confused with the limitation of joint range of motion resulting from long-standing joint disease or long-standing weakness, also termed *contractures*.

The intense muscle contractions of tetany are frequently painful. Although tetany is usually a reflection of hypocalcemia (Chapter 227), it can occasionally be seen without demonstrable electrolyte disturbance. Tetany results from hyperexcitability of peripheral nerves. Similarly, in the syndrome of tetanus produced by a clostridial toxin (Chapter 271), intensely painful life-threatening muscle contractions arise from hyperexcitable peripheral nerves. A number of toxic disorders, such as strychnine poisoning and black widow spider envenomation, produce similar neurogenic spasms.

MUSCLE PAIN

Acute muscle pain in the absence of abnormal muscle contractions is an extremely common symptom. When such pain occurs after strenuous exercise or in the context of an acute viral illness (e.g., influenza), it probably reflects muscle injury. In such patients, the serum creatine kinase level is often raised. It is uncommon for this frequent and essentially normal sign of muscle injury to be associated with weakness or demonstrable ongoing muscle disease. Chronic muscle pain is a common symptom but is seldom related to a definable

disease of muscle. Muscle pain in the presence of progressive proximal muscle weakness should suggest an underlying inflammatory or immune-mediated myopathy (Chapters 248 and 389).

WEAKNESS

Patients typically have motor signs before motor symptoms and, conversely, sensory symptoms before sensory signs. Thus, patients with even severe weakness[3] may not report symptoms of weakness. Somewhat paradoxically, patients who complain of "weakness" often do not have confirmatory findings on examination that document the presence of weakness.

When weakness is confirmed to be a symptom of underlying neurologic disease, a lesion of the peripheral nervous system (i.e., motor unit) is the frequent culprit (Chapters 387, 389, and 390).[4] The pattern of weakness (i.e., upper motor neuron versus lower motor neuron) and associated neurologic signs and symptoms help localize the responsible lesion (Videos 366-3 and 366-6 through 366-13; E-Figs. 366-1 through 366-6). The symptom of weakness in the absence of objective weakness on neurologic examination is more likely to be a symptom of disease outside of the nervous system altogether (Table 366-1) than to be attributable to neuromuscular disease.

EPISODIC AND INTERMITTENT WEAKNESS

The complaint of attacks of severe weakness or paralysis in a patient with normal baseline strength is uncommon and suggests an underlying ion channelopathy (e.g., periodic paralysis; Chapter 389) or neuromuscular junction disorder (e.g., myasthenia gravis [Video 366-11] or the myasthenic syndrome; Chapter 390). Patients with narcolepsy also occasionally complain of intermittent paralysis as a reflection of sleep paralysis (Chapter 374). Exposure to heat in a patient with a demyelinating disease such as multiple sclerosis (Chapter 380) also may cause intermittent weakness, but other features of an underlying upper motor neuron lesion are typically seen (Videos 366-6 and 366-7).

DIZZINESS

Dizziness is a vague term that can mean one of many things to a patient (Fig. 366-1), including vertigo (illusion of world spinning; Chapter 396), unsteadiness (imbalance without abnormal head sensation), lightheadedness (sense of impending faint; Chapter 49), or a sensation of wooziness (a difficult-to-describe floating sensation; Chapter 49).[5] Vertigo (see Fig. 396-3 in Chapter 396) suggests disease of the labyrinth, vestibular nerve, brainstem, or cerebellum as a probable cause. When unsteadiness and loss of balance are not associated with vertigo, particularly if the unsteadiness appears to be out of proportion to other symptoms of the patient, a widespread disorder of sensory or motor function is likely (e.g., multiple sclerosis [Video 366-6] or Charcot-Marie-Tooth disease [Video 366-10]). In the unsteady patient, one should also consider extrapyramidal (Video 366-4) (e.g., Parkinson disease), cerebellar, and endocrine (e.g., hypothyroidism) disorders. Lightheadedness is typically not from a focal neurologic disorder and should prompt the clinician to consider cardiac dysrhythmias, neurally mediated syncope (e.g., vasovagal), endocrine, or autonomic causes (Chapter 49).

ABNORMAL GAIT AND POSTURE

The ability to stand and walk in a well-coordinated, effortless fashion requires integrity of the entire nervous system.[6] Relatively subtle deficits localized to one part of the nervous system produce characteristic abnormalities (Table 366-2 and Videos 366-4, 366-6, and 366-10).

TABLE 366-1 DISORDERS COMMONLY ACCOMPANIED BY WEAKNESS

NEUROLOGIC CAUSES

Central Nervous System

- Upper motor neuron lesions—spasticity (e.g., amyotrophic lateral sclerosis, multiple sclerosis, stroke)
- Basal ganglia disorders—rigidity (e.g., Parkinson disease)

Peripheral Nervous System

- Disorders of the motor unit (e.g., peripheral neuropathy, myopathy)

NON-NEUROLOGIC CAUSES

- Heart failure
- Respiratory insufficiency
- Renal, hepatic, and other metabolic disease
- Alcoholism and other toxin-related disease
- Functional disorders
- Psychiatric disorders (e.g., depression, factitious disorders, malingering)

SENSORY SYMPTOMS AND PAIN

Sensory symptoms, which can be negative or positive, and pain are among the most common neurologic complaints. Negative symptoms refer to a loss of sensation, such as numbness, whereas positive symptoms, which can occur either spontaneously or when evoked by stimulation of sensory receptors, include paresthesias and dysesthesias. Paresthesias refer to a feeling of tingling, crawling, itching, compression, tightness, cold, or heat. Dysesthesias refer to abnormal, unpleasant sensations, often tingling, discomfort, or pain. Dysesthesias include hyperalgesia (increased pain from a stimulus that normally provokes pain) and allodynia (pain evoked by innocuous stimuli). In contrast, hypoesthesia denotes decreased sensitivity to stimulation (e.g., loss or impairment of touch), with hypoalgesia specifically referring to a diminished pain response to a normally painful stimulus.

For pain (Chapter 26), the initial goal is to ascertain whether the pain is secondary to a lesion in the nervous system (neuropathic pain), disease of visceral or somatic structures (nociceptive pain), or without identifiable organic cause (idiopathic pain). Neuropathic pain most commonly originates from lesions of the peripheral nerves and spinal roots, but interruption of sensory fibers in the central nervous system are also an important cause.

Peripheral neuropathies lead to sensory disturbances that depend on the population of affected nerves (Chapter 388). In large-fiber predominant neuropathies, paresthesias are common; on examination, vibration and joint position sense are impaired. In contrast, pain and temperature appreciation are relatively preserved. Movement can become clumsy and ataxic, and tendon reflexes are lost early. With severe loss of proprioception, patients may develop pseudoathetoid movements of the outstretched hands, sensory ataxia, or postural and action tremors (Video 366-10). In contrast, small-fiber predominant neuropathies commonly present with spontaneous pain that may be burning, lancinating, or aching in quality. Pain and temperature are disproportionately affected in these neuropathies, and autonomic dysfunction may be a feature. Examples of small-fiber neuropathies include diabetes and alcoholism. Most sensory neuropathies have sensory loss that begins distally and is dependent on the distance of the nerve ending from the spinal cord. By comparison, lesions affecting the dorsal root ganglia, which give rise to sensory neuronopathies, may also involve the trunk and face. Sensory changes in a radiculopathy owing to a nerve root lesion (Chapter 369) conform to a dermatome. Root pain is typically aggravated or intensified by maneuvers that stretch the involved nerve root, such as the straight-leg raising test or by bending forward via traction on the sciatic nerve. With distal nerve root involvement, as in the cauda equina syndrome,[7] sensory deficits involve multiple roots and may lead to saddle anesthesia and reduced sensation associated with the passage of urine or feces.

Spinal cord lesions can lead to sensory symptoms, the nature of which depends on the part of the cord affected. With involvement of the dorsal columns, such as occurs in multiple sclerosis (Chapter 380), vitamin B_{12} deficiency (Chapter 384), and cervical spondylosis (Chapter 369), patients commonly report a feeling of compression or bandlike tightness in the affected region. They may also experience Lhermitte sign (paresthesia radiating down the back and/or limbs on neck flexion). Examination reveals ipsilateral impairment of vibration and joint position senses, with relative sparing of pain and temperature sensation. Conversely, with involvement of the spinothalamic tracts in the anterolateral columns (as in cordotomy) or central cord where spinothalamic fibers decussate (as in syringomyelia; Chapter 385), patients will have impaired pain and temperature sensation with relative preservation of vibration, joint position sense, and light touch. Thalamic lesions cause dense hemibody (i.e., face, arm, trunk, and leg) sensory loss and can be associated with a thalamic pain syndrome. Somatosensory cortical lesions cause contralateral sensory loss of varying distribution; lateral cortical involvement leads to sensory alteration in the face and arm compared with medial cortical involvement, which causes predominant leg symptoms. Dysfunction of cortical sensory modalities, including trouble with two-point discrimination, graphesthesia, and stereognosis, is a typical feature. For both central and peripheral lesions, motor deficits may also be present and help localize the lesion.

HEAD PAIN

Head pain is usually primary (benign) but can be debilitating (Chapter 367). A comprehensive history combined with general and neurologic examinations typically yield important clues. Secondary causes must always be considered, identified, and treated early as they can be life-threatening. Headache features that should raise concern for a secondary cause include thunderclap onset (e.g.,

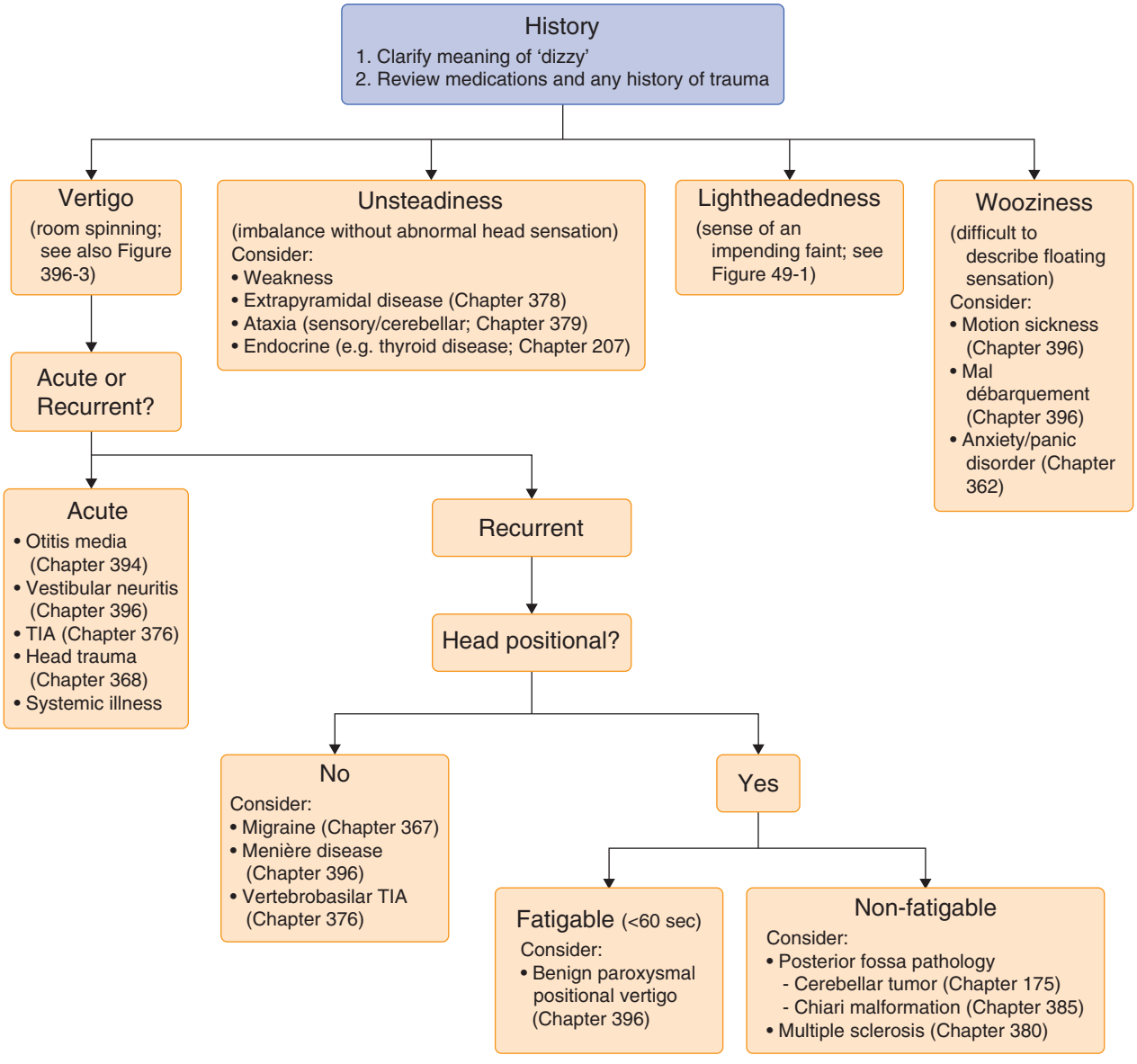

FIGURE 366-1. Approach to the patient complaining of dizziness. TIA = transient ischemic attack.

subarachnoid hemorrhage); precipitation by Valsalva maneuver or cough (e.g., Chiari type I malformation) or postural/positional change (CSF hypotension); change in pattern or progressive worsening of prior headaches (e.g., brain tumor); and pregnancy (e.g., vasculopathy). An older age of onset (i.e., >50 years), presence of systemic features (e.g., fever, malaise, unintentional weight loss), and accompanying neurologic symptoms (especially if unilateral) should be considered red flags that prompt urgent further evaluation (e.g., inflammatory markers, neuro-imaging, lumbar puncture). Medications, recreational exposures (e.g., alcohol, caffeine, and illicit drugs), and sleep disturbance (e.g., obstructive sleep apnea) are a commonly overlooked contributors of headache.

FATIGUE

Complaints of fatigue, tiredness, and lack of energy are usually symptoms of disease outside the nervous system. Medical conditions associated with a complaint of "weakness" (e.g., anemia, endocrine dysfunction, or inflammatory disease) and psychiatric and behavioral disorders (Chapter 362) are all frequent causes of fatigue. Chronic fatigue syndrome and many cases of fibromyalgia (Chapter 253) have fatigue as a predominant and disabling symptom. These disorders are defined in part by the absence of consistent neurologic findings and lack of demonstrable disease in the nervous system.

Neurologic disorders associated with fatigue through mechanisms that are not known include multiple sclerosis (Chapter 380; Videos 366-6 and 366-7), Parkinson disease (Chapter 378; Video 366-4), and motor neuron disease (Chapter 387; Video 366-8). Sleep disorders (Chapter 374) may also include fatigue as a prominent symptom. Following recovery from the many acute bacterial or viral infections, a patient's energy level may only slowly return to normal; infectious mononucleosis (Chapter 348) and coronavirus-2019 (Chapter 337) infections are particularly prone to such chronic fatigue.

COGNITIVE IMPAIRMENT AND MEMORY LOSS

Problems with cognition and memory warrant a systematic approach to arrive at the appropriate diagnosis (Chapter 371). The distinction between non-neurologic contributors and neurodegenerative disease is essential and aided by obtaining a careful history and functional assessment. Delirium, depression, and reversible causes should be excluded. Delirium (Chapter 361) is characterized by acute onset, fluctuating course, prominent inattention, and presence of disordered thinking and/or altered level of consciousness. Patients require prompt evaluation and correction of any underlying causes (e.g., medications, metabolic disturbances, infection, or occult organ failure). Depression (Chapter 362) may mimic or exacerbate dementia. The history and/or physical examination may point to reversible causes, such as nutritional deficiency or endocrine disturbance (Chapter 207), and the presence of focal neurologic symptoms or signs should raise suspicion of structural brain disease, including tumors (Chapter 175) or traumatic encephalopathy (Chapter 368).

Aging is the greatest risk factor for memory difficulties, which lie on a continuous spectrum ranging from "normal" cognitive aging and mild cognitive impairment to dementia with functional impairment (Chapter 371). Common types of dementia include Alzheimer disease (gradual onset, early episodic memory loss), vascular dementia (stepwise decline, early executive dysfunction, presence of vascular risk factors and/or a history of stroke), and

TABLE 366-2 CHARACTERISTIC GAIT DISORDERS

SPECIFIC DISORDER	LOCATION OF LESION	CHARACTERISTICS
Spastic gait	Bilateral corticospinal pathways within the thoracic or cervical cord or in the brain	Legs stiff, feet turning inward, "scissoring"
Hemiparetic gait	Unilateral central nervous system, cervical cord, or brain	Affected leg circumducted, foot extended, arm flexed
Sensory ataxia	Posterior columns of the spinal cord or peripheral nerve	Wide-based, high steps; Romberg sign present
Cerebellar ataxia	Brainstem or cerebellum	Wide-based steps; Romberg sign absent
Parkinsonian gait	Basal ganglia	Shuffling, small steps
Dystonic gait	Basal ganglia; also corticospinal pathways	Abnormal posture of the arms, head, neck
Gait disorder of the elderly	Multifactorial: bihemispheric disease, spinal cord disease, impaired proprioception, muscle weakness	Stooped posture, wide-based steps; often retropulsion
Steppage gait	Distal muscle weakness	High steps ("steppage")
Waddling gait	Proximal muscle weakness	Both legs circumducted to allow locking of the knees
Antalgic gait	Non-neurologic; reflects disease of joints, bones, or soft tissue	Minimizes pain in the hip, spine, leg
Hysterical gait	Psychiatric or behavioral disorder	Reeling side to side, associated astasia-abasia, bizarre arm and trunk movements

mixed dementia (Alzheimer plus vascular pathology). Rarer forms of dementia should be considered when cognitive decline is rapid (e.g., paraneoplastic/immune-mediated, Creutzfeldt-Jakob disease) or is accompanied by atypical features, such as early prominent parkinsonism and visual hallucinations (e.g., Lewy body dementia) or behavioral and/or language disturbance (e.g., frontotemporal dementia).

NEUROLOGIC DIAGNOSTIC PROCEDURES

IMAGING

Computed tomography (CT) and magnetic resonance imaging (MRI) are complementary techniques, each with its own strengths and weaknesses. CT is much faster and less costly than MRI, less susceptible to motion artifact, and sufficient to exclude many neurologic disorders, thereby making it the study of choice in trauma and other acute neurologic emergencies. CT provides detailed evaluation of cortical bone, allows accurate detection of calcification and foreign bodies, and can be performed at no risk to patients with implantable medical devices. MRI demonstrates superior soft-tissue contrast, so it allows higher resolution of anatomy and increased sensitivity and specificity for funding abnormalities in the brain, spinal cord, peripheral nervous system, and muscle. As MRI does not use ionizing x-rays, it is the preferred modality in situations in which multiple imaging studies are required. The addition of intravenous contrast media to either CT or MRI allows better characterization of the vasculature (e.g., via angiography) and detection of conditions in which blood-brain-barrier function is compromised (e.g., primary brain tumor, brain metastases, and infection/abscess).

On the basis of the relative advantages and disadvantages of CT and MRI, different clinical entities can and should be assessed differently (Table 366-3). In acute ischemic stroke (Chapter 376) without bleeding, CT abnormalities typically appear within 4 to 12 hours and are seen even earlier with larger infarctions and embolic infarctions (E-Fig. 366-7). The addition of CT angiography in acute ischemic stroke helps guide the need for thrombectomy. CT detects hemorrhagic stroke (Chapter 377) acutely and can estimate its age. CT is also the preferred initial imaging modality for detection of intraparenchymal hemorrhage and subarachnoid hemorrhage, and it often suggests whether an aneurysm is the likely cause. Either CT angiography or magnetic resonance

TABLE 366-3 STRENGTHS AND WEAKNESSES OF SELECTED IMAGING MODALITIES

MODALITY	STRENGTHS	WEAKNESSES
Computed tomography (CT)	Fast; good at bony pathology; preferred for trauma, acute neurologic symptoms, and decreased level of consciousness	Poorer soft tissue contrast resolution than MRI; ionizing radiation exposure
Conventional angiography	Best spatial resolution for vessels, useful in aneurysms, vascular malformations, and vasculitis; provides information about flow and arteriovenous shunting	Invasive and often lengthy; risk of stroke and other complications
CT myelography and cisternography	Useful in CSF leaks with intracranial hypotension to identify point of leak	Invasive, with risk of complications from lumbar puncture and instillation of contrast material
Magnetic resonance imaging (MRI)	Noninvasive; no radiation; multiplanar; high soft tissue contrast resolution	Less sensitive for bony pathology; contraindicated in patients with ferromagnetic devices or foreign bodies; patient must be able to cooperate and tolerate confined space; time-consuming relative to CT
Magnetic resonance angiography (MRA)	Noninvasive; good for screening extracranial and intracranial vascular disease; may be performed with or without contrast agent	Technically demanding; noncontrast MRA may overestimate the degree of vascular stenosis
Magnetic resonance spectroscopy (MRS)	May help differentiate tumor grade or tumor from nontumor (e.g., tumefactive demyelination); may help diagnose and classify dementias such as Alzheimer disease	Low spatial resolution; low specificity; time-consuming
Positron emission tomography (PET)	Provides information as to metabolic activity dependent on the tracer used; fludeoxyglucose (FDG) most commonly used—can help in diagnosis of Alzheimer disease, epilepsy, and radiation necrosis	Requires a cyclotron to generate radioisotopes with a short half-life; lower resolution and less available than MRI and CT; high radiation exposure
Single-photon emission computed tomography (SPECT)	Occasionally useful in epilepsy; sensitive for diffuse pathologic processes	Lower resolution than PET, MRI, or CT
Ultrasonography	Fast; easy to use; can be performed at the bedside to assess vessel patency	Limited field of view due to bone; cannot visualize vessels in the upper neck and cranial base; operator dependent
Transcranial Doppler (TCD)	Fast; easy to use; assesses vascular velocities quantitatively; can assess cerebral vasospasm and occluded vessels	Does not provide images of vessels

CSF = cerebrospinal fluid.

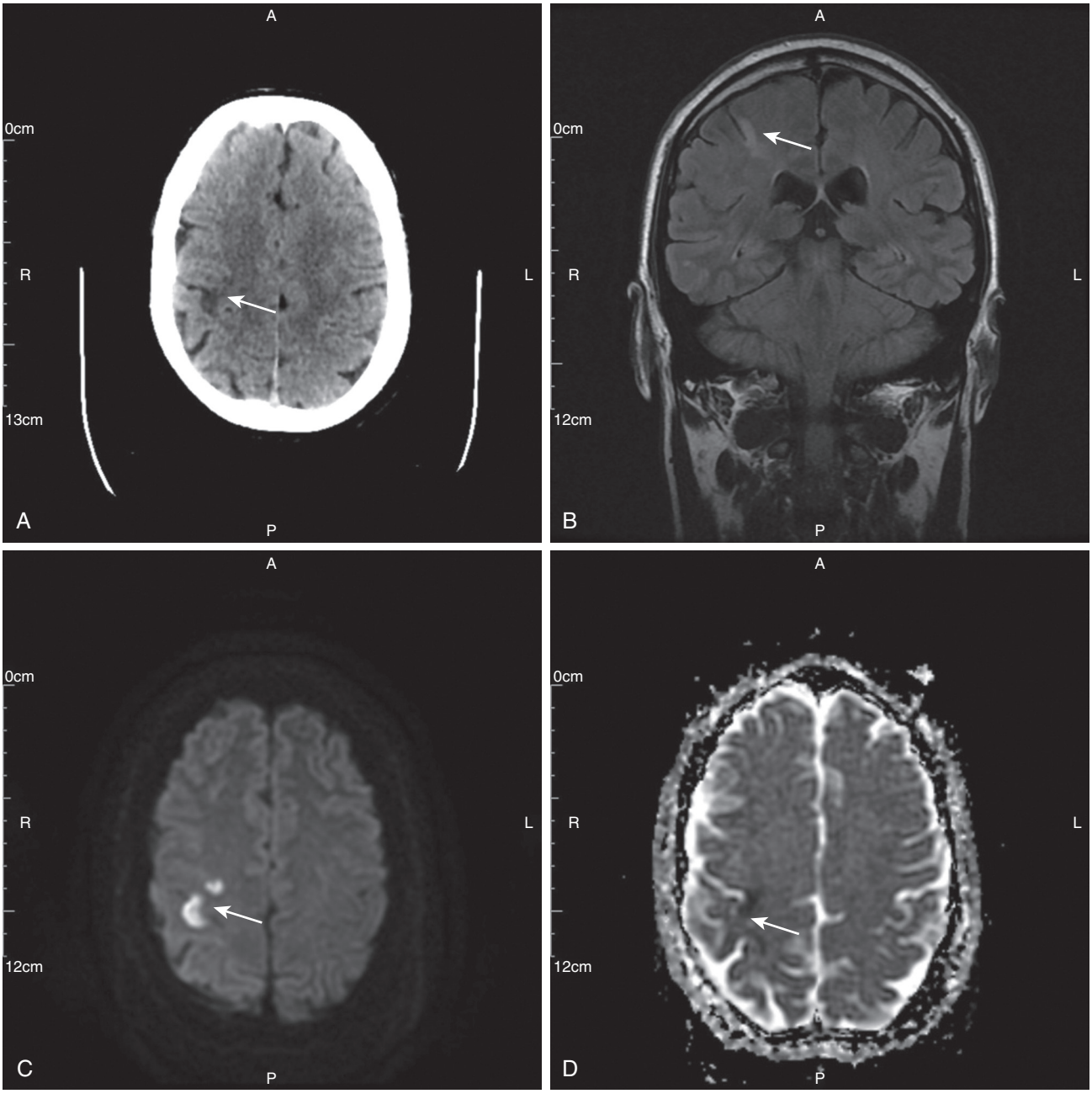

E-FIGURE 366-7. Radiographic changes of acute ischemic stroke. A 54-year-old man with left pronator drift secondary to a right middle cerebral artery territory ischemic stroke. Head computed tomographic scan without contrast (axial view) demonstrates an area of low attenuation involving the cortex and subcortical white matter of the right "precentral knob" (**A**), which corresponds to the hyperintense region seen on magnetic resonance imaging (head fluid-attenuated inversion recovery sequence; T2-FLAIR) (**B**). Hyperintensity on diffusion-weighted imaging (DWI) (**C**) and reduced apparent diffusion on the apparent diffusion coefficient (ADC) map (**D**) are in keeping with an acute ischemic infarct in the hand-motor cortical homunculus, which accounts for the patient's symptoms (Video 366-3). Areas of ischemic lesion are indicated by *white arrows* (**A-D**).

angiography can display the three-dimensional anatomy of aneurysms with sufficient detail for therapy to be planned, but surgical/endovascular treatment generally requires catheter arteriography. CT is the first-line method for evaluation of brain trauma and diagnosis of subdural or epidural hematoma (Chapter 368), usually without requiring intravenous contrast material. Many brain tumors are initially recognized on CT scans, but MRI is the preferred modality for detection and characterization of all brain tumors (Chapter 175), including those that might be the cause of new-onset seizures in adults.

Imaging often detects asymptomatic findings,[8] including subclinical cerebrovascular lesions of unclear immediate importance. However, diffusion-weighted imaging lesions on MRI are associated with a three-fold increased risk of clinical abnormalities, and even very small (<3 mm) subclinical cerebrovascular lesions portend about a three-fold increased risk of a subsequent stroke.

LUMBAR PUNCTURE

Lumbar puncture accesses cerebrospinal fluid (CSF) in the lumbar cistern of the subarachnoid space for both diagnostic and therapeutic purposes. A patient's discomfort is usually only slightly greater than for a blood draw.[9] Ultrasonography[10] can help identify the optimal site for the procedure,[A1] and atraumatic needles can reduce pain and the incidence of post–lumbar puncture headache.[A2]

Laboratory evaluation of CSF is crucial for the accurate diagnosis of meningeal infections and carcinomatosis and is useful in the assessment of inflammatory and demyelinating diseases. CSF analysis is also helpful to evaluate for hemorrhage, particularly when imaging studies are inconclusive (Fig. 366-2). For example, the combination of less than 2000 red blood cells/μL and the absence of xanthochromia excludes the diagnosis of aneurysmal subarachnoid hemorrhage with a sensitivity of 100% and a specificity of 91%. The measurement of β-amyloid-42/total tau and β-amyloid-42/hyperphosphorylated tau can identify early Alzheimer disease with high accuracy. In terms of therapeutic uses, lumbar puncture allows removal of CSF to lower intracranial pressure (as seen in idiopathic intracranial hypertension; Chapter 367) and access to the CSF for drug delivery.

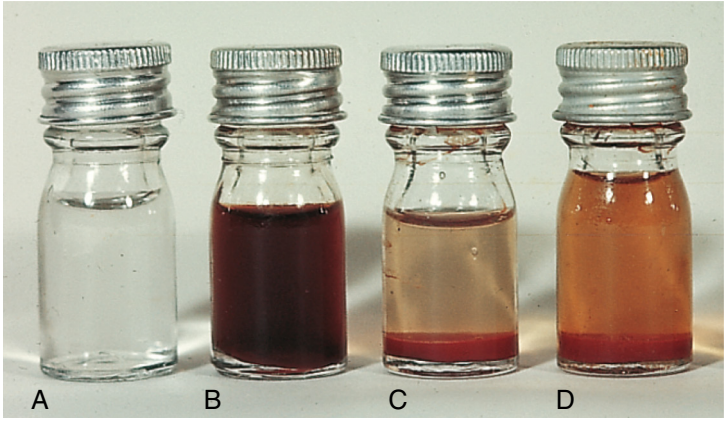

FIGURE 366-2. Cerebrospinal fluid (CSF) examination. A, Normal crystal-clear CSF. **B,** Blood in the CSF, which could result from a traumatic (bloody) tap or from subarachnoid hemorrhage. In a traumatic tap, subsequent tubes of CSF are usually less bloody. **C,** Centrifuged CSF in a traumatic tap. The supernatant is nearly clear. **D,** CSF from a patient with subarachnoid hemorrhage. There is blood at the bottom of the tube and the supernatant is yellow (xanthochromic) as a result of breakdown of blood cells in the CSF before the lumbar puncture. (From Forbes CD, Jackson WD. *Color Atlas and Text of Clinical Medicine*. 3rd ed. London: Mosby; 2003, with permission.)

Lumbar puncture is otherwise contraindicated in patients with evidence of raised intracranial pressure (e.g., secondary to obstructive noncommunicating hydrocephalus, focal mass lesion, or hemorrhage), local skin infection, or developmental anomaly (e.g., myelomeningocele). It is also contraindicated in patient with a bleeding diathesis (e.g., marked thrombocytopenia or a very prolonged international normalized ratio [INR]), but it can be performed safely in patients with a mild coagulopathy.[11] In patients with suspected meningitis or encephalitis, emergent lumbar puncture is critical. However, the administration of empiric antibiotic or antiviral therapy should not be delayed if the lumbar puncture is delayed to obtain brain imaging in patients who have focal findings or papilledema or if there are technical difficulties in performing the lumbar puncture itself.[12] Neuroimaging should be performed before lumbar puncture in patients who are over age 60 years; are immunocompromised; or have papilledema, a reduced level of consciousness, or focal findings on the neurologic examination.

The CSF formula often provides an important clue to the pathologic process involved (Table 366-4). An elevated white blood cell count is seen with infections and other inflammatory diseases, as well as with carcinomatosis. The differential white blood cell count may point to a specific class of pathogen; polymorphonuclear leukocytes suggest a bacterial process, whereas mononuclear cells suggest a viral, fungal, or immunologic cause. The CSF glucose concentration is typically reduced to less than 50% of a simultaneous serum concentration in bacterial and fungal infections, as well as with certain viral infections (e.g., mumps virus) and sarcoidosis. The CSF protein concentration is elevated in a variety of disorders, including most infections and demyelinating neuropathies. If malignancy is being considered, CSF cytology is useful in the detection of primary brain tumors, metastatic lesions, and lymphomas.

CSF polymerase chain reaction (PCR) is a rapid, sensitive, and specific test that is useful for suspected viral infections, including herpes simplex types 1 and 2, varicella zoster, Epstein-Barr virus, cytomegalovirus, and enterovirus.[13] PCR for tuberculosis is more specific than a smear for acid-fast bacilli, but its lack of sensitivity makes cultures the diagnostic gold standard. The CSF Venereal Disease Research Laboratory (VDRL) assay is a relatively specific although insensitive test for neurosyphilis (Chapter 295).

Specialized CSF tests for oligoclonal bands that are more abundant in the CSF than a paired serum sample are found in most patients with multiple sclerosis (Videos 366-6 and 366-7) but are not specific to this disease and can be seen in other inflammatory and noninflammatory conditions, including systemic lupus erythematosus, neurosarcoidosis, cerebral angiitis, paraneoplastic disorders, human immunodeficiency virus infection, and stroke. The detection of antibodies in the CSF is helpful to diagnose an expanding number of autoimmune neurologic diseases and encephalitides (Chapter 380).

ELECTROENCEPHALOGRAPHY

Electroencephalography, which is the recording and measurement of scalp electrical potential, provides useful information about baseline brain function and paroxysmal brain electrical activity suggestive of a seizure disorder.[14] A standard electroencephalograph (EEG) typically records around 30 minutes

TABLE 366-4 CHARACTERISTIC CEREBROSPINAL FLUID FORMULAS

	TURBIDITY AND COLOR	OPENING PRESSURE	WBC COUNT	DIFFERENTIAL CELLS	RBC COUNT	PROTEIN	GLUCOSE
Normal	Clear, colorless	70-180 mm H_2O	0-5 cells/μL	Mononuclear	0	<60 mg/dL	>½ serum
Bacterial meningitis	Cloudy, straw colored	↑	↑↑	PMNs	0	↑↑	↓
Viral meningitis	Clear or cloudy, colorless	↑	↑	Lymphocytes	0	↑	Normal
Fungal and tuberculous meningitis	Cloudy, straw colored	↑	↑	Lymphocytes	0	↑↑	↓↓
Viral encephalitis	Clear or cloudy, straw colored	Normal to ↑	↑	Lymphocytes	0 (herpes ↑)	Normal to ↑	Normal
Subarachnoid hemorrhage	Cloudy, pink	↑	↑	PMNs and lymphocytes	↑↑	↑	Normal (early); ↓ (late)
Guillain-Barré syndrome	Clear, yellow	Normal to ↑	0-5 cells/μL	Mononuclear	0	↑	Normal

PMN = polymorphonuclear leukocyte; RBC = red blood cell; WBC = white blood cell.

of brain activity, both in the awake state and in the first two stages of sleep. Activation procedures, including hyperventilation and photic stimulation, are routinely performed to increase the frequency of epileptogenic discharges. Electroencephalographic frequencies are divided into four categories: delta (<4 Hz), theta (4 to 7 Hz), alpha (8 to 13 Hz), and beta (>13 Hz). The presence of spikes (20 to 70 ms) and sharp waves (70 to 200 ms) may indicate a seizure focus.

In the occipital leads, the normal awake EEG contains an alpha rhythm that attenuates with eye opening. In normal sleep, EEG activity shows typical features of different stages of light, deep, and rapid eye movement (REM) sleep. Abnormalities seen on EEG can be broadly classified into changes in background activity or paroxysmal discharges (Table 366-5).

Electroencephalography plays a major role in the diagnosis and categorization of a seizure disorder and can aid in determining the probability of recurrent seizures. EEG is neither highly sensitive nor completely specific (78-98%) for diagnosing a seizure. Only about 50% of patients with seizures show epileptiform activity on a single EEG recording. Repeating the EEG with provocative maneuvers such as sleep deprivation, hyperventilation, and photic stimulation may increase this percentage to 90%. Conversely, about 1% of adults and 3.5% of children who are neurologically normal and who have never had a seizure have pseudoepileptiform activity on EEG.

An EEG also can provide important clues about the diagnosis and prognosis in patients with disorders of consciousness, such as coma (Chapter 373) and encephalopathy, and can be a useful adjunct in the determination of brainstem death (Chapter 373) and diagnosing sleep disorders (Chapter 374). In addition, specific EEG patterns lend support to specific neurologic diagnoses (see Table 366-4; Videos 366-1 and 366-2). More recently, a wearable EEG device has shown promise for objectively recording seizures in ambulatory patients.[15]

NERVE CONDUCTION STUDY

Nerve conduction can be measured in motor and sensory nerves. A nerve conduction study, which is the recording and measurement of the compound nerve and muscle action potentials elicited in response to an electrical stimulus, can glean information only from medium- to large-diameter myelinated fibers, which include motor fibers and sensory fibers that convey sensation to vibration and joint position sense. Small unmyelinated fibers responsible for pain and temperature are not assessed.

Abnormalities on a nerve conduction study can document a neuropathy and demarcate its distribution (i.e., whether it is distal, proximal, or diffuse). In addition, it can decipher the modality involved (i.e., motor versus sensory or both) and whether the underlying process is predominantly axonal or demyelinating (E-Fig. 366-8 and Table 366-6).

TABLE 366-5 ELECTROENCEPHALOGRAPHIC ABNORMALITIES

ELECTROENCEPHALOGRAPHIC ABNORMALITY	CLINICAL CORRELATE
BACKGROUND RHYTHM ABNORMALITIES	
Generalized slowing	Most metabolic encephalopathies
Triphasic waves	Hepatic, renal, and other metabolic encephalopathies
Focal slowing	Large mass lesions (tumor, large stroke)
Electrocerebral inactivity with lack of response to all stimuli	Neocortical death, hypothermia, drug overdose
PAROXYSMAL ABNORMALITIES	
3-Hz spike and wave, augmented by hyperventilation	Primary generalized epilepsy (e.g., childhood absence epilepsy)
3- to 4-Hz spike and wave in light sleep or with photic stimulation	Primary generalized epilepsy (e.g., juvenile myoclonic epilepsy)
Central to midtemporal spikes	Benign epilepsy with centrotemporal spikes
Anterior temporal spikes or sharp waves	Focal epilepsy (e.g., mesial temporal lobe seizures)
Periodic lateralizing epileptiform discharges	Stroke, herpes simplex encephalitis
Generalized periodic sharp waves	Creutzfeldt-Jakob disease
Burst suppression	Severe anoxic brain injury, barbiturate coma

REPETITIVE STIMULATION STUDY

To diagnose disorders that affect the neuromuscular junction, repetitive stimulation repeatedly delivers a supramaximal electrical stimulus to a nerve and serially records the amplitude of the compound muscle action potential. In myasthenia gravis (Chapter 390), these amplitudes become progressively smaller with repetitive stimulation in affected muscles (Video 366-11). In contrast, fast repetitive stimulation evokes an increment in these amplitudes in presynaptic myasthenic syndromes.

ELECTROMYOGRAPHY

Electromyography (EMG) assesses the properties of the motor unit by recording variations of electrical potential detected by a needle electrode inserted into skeletal muscle. During EMG, the electrical activity of muscle is studied in four settings: insertional activity (occurs within the first second of needle insertion), spontaneous activity (electrical activity at rest), voluntary activity (electrical activity with muscle contraction), and recruitment pattern (change in electrical activity with maximal contraction; Table 366-7). EMG can help support or exclude a diagnosis, but no EMG findings are pathognomonic for a specific disease.[16] If a patient has weakness, EMG is helpful in localizing the abnormalities to determine whether the weakness is due to disease of the anterior horn cell (e.g., motor neuron disease; Video 366-8), nerve root (radiculopathy), plexus (plexopathy; Video 366-9), an individual peripheral nerve (mononeuropathy), or multiple peripheral nerves (polyneuropathy; Video 366-10). EMG can also detect muscle disease by distinguishing active (inflammatory) myopathies (e.g., dermatomyositis, polymyositis, inclusion body myositis; E-Fig. 366-5) from chronic myopathies (e.g., congenital

TABLE 366-6 NERVE CONDUCTION STUDY ABNORMALITIES

ABNORMALITY	CLINICAL CORRELATE
Reduced CMAP amplitude	Axonal neuropathy
Prolonged terminal latency	Demyelinating neuropathy Distal compressive neuropathy
Conduction block	Severe focal compressive neuropathy Severe demyelinating neuropathy
Slowed conduction velocity	Demyelinating neuropathy

CMAP = compound muscle action potential.

TABLE 366-7 ELECTROMYOGRAPHIC ABNORMALITIES

ABNORMALITY	CLINICAL CORRELATE
INSERTIONAL ACTIVITY	
Prolonged	Acute denervation Active (usually inflammatory) myopathy
SPONTANEOUS ACTIVITY	
Fibrillations and positive waves	Acute denervation Active (usually inflammatory) myopathy
Fasciculations	Chronic neuropathies Motor neuron disease (rare fasciculations may be normal)
Myotonic discharges	Myotonic disorders Acid maltase deficiency
VOLUNTARY ACTIVITY	
Neuropathic potentials: large-amplitude, long-duration, polyphasic potentials	Chronic neuropathies and anterior horn cell diseases
Myopathic potentials: small-amplitude, short-duration, polyphasic potentials	Chronic myopathies Neuromuscular junction disorders
RECRUITMENT	
Reduced	Chronic neuropathic disorders
Rapid	Chronic myopathies

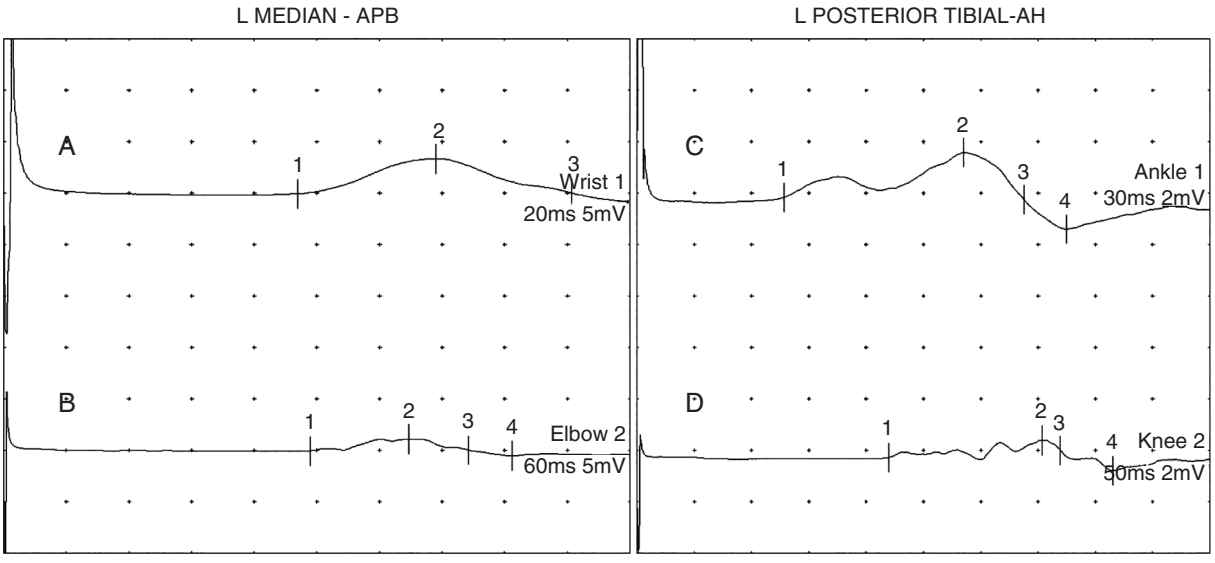

Nerve / Sites	Latency	Duration	Amp	Velocity	Dist.
	ms	ms	mV	m/s	cm
L MEDIAN - APB					
Wrist	9.40	26.95	4.4		
Elbow	29.35	34.30	1.7	11.4	22.8
R MEDIAN -APB					
Wrist	8.55	28.80	4.7		
Elbow	28.70	36.10	2.5	11.4	23
L ULNAR-ADM					
Wrist	7.95	30.25	6.3		
above el	29.10	70.85	5.2	13.2	28
L COMM PERONEAL- EDB					
Ankle	NR				
L POSTERIOR TIBIAL - AH					
Ankle	7.70	29.75	3.0		
Knee	21.95	29.60	1.2	26.0	37
R POSTERIOR TIBIAL - AH					
Ankle	NR				

E-FIGURE 366-8. **Abnormal nerve conduction studies in a patient with chronic inflammatory demyelinating polyneuropathy. A,** With stimulation of the median nerve at the wrist and recording over the belly of the abductor pollicis brevis (APB) muscle, the normal latency should be less than 4.5 msec; here, the distal motor latency is 9.4 msec, which is significantly prolonged, indicating demyelination. **B,** Stimulation of the median nerve at the elbow and recording at APB. The motor conduction velocity in the forearm can be calculated as the distance between elbow and wrist stimulation points divided by the difference in latency between the two stimulation points (i.e., 22.8 cm/(29.35 to 9.4 msec) = 11.4 m/sec). Normal conduction velocities in the upper limbs are >50 m/sec; here, there is evidence of significant slowing indicating demyelination in the forearm. Further, the CMAP duration with elbow stimulation is significantly prolonged (marker 4-marker 1), which corresponds to temporal dispersion, also a marker of demyelination. **C,** Stimulation of the posterior tibial nerve at the medial malleolus recording over the belly of the abductor hallucis (AH) muscle. **D,** Stimulation of the tibial nerve behind the knee with recording at the AH muscle. Conduction velocity in the leg is normally greater than 40 m/sec; here, it is 26.0 m/sec, indicating demyelination in the leg. The amplitude of the response at the knee (1.2 millivolts) is significantly lower than the amplitude at the ankle (3.0 millivolts; marker 2-marker 4), indicating conduction block, another feature of demyelination. ADM = abductor digiti minimi; CMAP = compound motor action potential; EDB = extensor digitorum brevis; NR = not reported.

myopathies and some metabolic myopathies). Myotonic discharges on EMG may point to certain muscle diseases, including myotonic dystrophy (Video 366-12 and E-Fig. 366-3), myotonia congenita, or paramyotonia. It is important to note that it may take several weeks for a muscle to develop EMG signs of acute degeneration after nerve transection. For this reason, EMG performed in the acute setting after nerve injury should be interpreted with caution, and it may need to be repeated at a later date.

EVOKED POTENTIALS

Evoked potentials measure conduction velocities of sensory pathways from the periphery through the central nervous system. Three types of evoked potentials are routinely performed in clinical practice: visual, brainstem auditory, and somatosensory.

Pattern Reversal Visual Evoked Potentials

The function of the anterior visual pathway, particularly the optic nerve, is assessed by the pattern reversal visual evoked potential. A prolonged latency in the absence of ocular disease implies slowed conduction velocity in the optic nerve and suggests underlying demyelination optic nerve and suggests underlying demyelination (E-Fig. 366-9). When multiple sclerosis is suspected, evoked potential testing is helpful to document the presence of a demyelinating lesion that may not be clinically evident.[17]

Brainstem Auditory Evoked Potentials

The electrophysiologic response to auditory stimuli is measured by brainstem auditory evoked potentials.[18] Brainstem auditory evoked potential testing is helpful in the diagnosis of acoustic neuroma (Chapter 175) and other cerebellopontine angle tumors.

Somatosensory Evoked Potentials

The somatosensory evoked potential assesses conduction after stimulation of a mixed or cutaneous peripheral nerve. The recorded responses reflect activity of large-diameter, myelinated cutaneous and muscle afferents in the peripheral nervous system and the dorsal columns of the spinal cord, medial lemniscus of the brainstem, ventroposterior lateral nucleus of the thalamus, and somatosensory cortex of the contralateral cerebral hemisphere. Somatosensory evoked potential testing is helpful when multiple sclerosis (Chapter 380) is suspected clinically, and it is necessary to document the presence of a demyelinating lesion in the central nervous system that may not be clinically or radiographically evident.

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367 HEADACHES AND OTHER HEAD PAIN

KATHLEEN B. DIGRE

DEFINITION

Headache, which is a very common symptom, can be secondary to an underlying abnormality but is usually a primary headache disorder such as migraine headache, tension-type headache, cluster headache, and paroxysmal hemicrania.

EPIDEMIOLOGY

About 90% of all adults experience headache at some time in their lives, and over 75% of children have complained of headaches by the age of 15 years. In the United States, the direct and indirect costs associated with migraine are over $27 billion annually. The World Health Organization lists migraine in the top 10 most disabling conditions. Patients at most risk for lost days of employment are those with chronic migraine and daily headache.

In large population-based studies, the relative risk of having migraine, tension-type headaches, or cluster headaches increases up to four times if a first-degree relative has the same kind of headaches. Studies of twins, especially identical twins, also show a similar susceptibility.

PATHOBIOLOGY

Headache pain is initiated by primary trigeminal afferents that innervate the blood vessels, mucosa, muscles, and tissues. Fibers from these sources coalesce in the trigeminal ganglion, especially the first division. The trigeminal afferents terminate in the primary sensory nucleus of cranial nerve V and its spinal nucleus, which has several small subnuclei, the most important of which is the subnucleus caudalis. This subnucleus receives afferents from meningeal vessels, dura-sensitive neurons, and even the upper cervical cord and then projects them to the lateral and medial thalamus by way of the spinothalamic tract and to diencephalic and brain stem regions that are involved in the regulation of autonomic functions. Thalamic nociceptive information ascends to the sensory cortex, as well as to other areas of the brain.

Although secondary headaches may stimulate the pathway by way of processes such as inflammation and compression, primary headache disorders occur spontaneously by means of chemical mediators such as calcitonin gene–related peptide. The sequence of events commences with peripheral activation caused by neurogenic plasma extravasation activated spontaneously or by cortical spreading depression. The trigeminocervical complex, especially the nucleus caudalis, is then activated, and patients can experience allodynia, a condition in which a non-noxious stimulus is sensed as painful.

Aura is defined as a focal visual, sensory, or motor neurologic disturbance that may occur with or without headache. Aura is thought to occur when cortical spreading depression causes depolarization of membranes. Both neurons and glia can mediate both constriction and dilation of blood vessels. Migraine headache clearly has a genetic component. Familial hemiplegic migraine can be caused by mutations in the *CACNA1A* gene, which is located on chromosome 19p13.2-p13.1 and encodes for voltage-gated neuronal calcium channels. Mutations in the *CACNA1A* gene also cause episodic ataxia and epilepsy. Another mutation is in *ATP1A2*, also called the familial hemiplegia migraine 2 (*FHM2*) gene, which is located on chromosome 1q21-q23 and encodes for the sodium-potassium adenosine triphosphatase (Na^+, K^+-ATPase) transport protein. A third genetic locus is the *SCN1A* gene on chromosome 2q24.3, which is a voltage-gated sodium channel. In addition, many single-nucleotide polymorphisms have been associated with migraine. Although there are linkages to many genetic loci for more common forms of migraine, migraine and other headaches also probably have multiple epigenetic interactions[1] with environmental factors, and it is clear that the genetic contributions are complex.

CLINICAL MANIFESTATIONS

Patients with headache may describe the pain as throbbing, band-like, or aching. The pain is frequently unilateral but can be bilateral. Migraine headache is often associated with nausea, vomiting, photophobia, and phonophobia. It is invariably moderate to severe and interferes with activities. Other autonomic manifestations that can accompany migraine, cluster, and other headache variants include ptosis, conjunctival injection, tearing, rhinorrhea, Horner syndrome, and facial edema. Secondary headaches sometimes may appear to be similar to tension-type or migraine headaches, but "red flags" may suggest a secondary rather than a primary headache disorder (Table 367-1). Particular attention should be paid to the sudden onset of severe thunderclap headaches (Table 367-2), which frequently have an urgent underlying secondary cause.[2]

DIAGNOSIS

Five elements of the history are key for evaluating headaches. The family history helps determine whether a person has a genetic predisposition to headache. The life history of headache determines whether the headache is new or has evolved over the course of a lifetime. The attack history provides the clinical features of the headache or headaches. The medical and psychiatric history determines whether there are comorbid conditions that can cause or worsen the headache. The medication and drug history determines whether the headache could be caused by or worsened by medications or drugs the person has ingested.

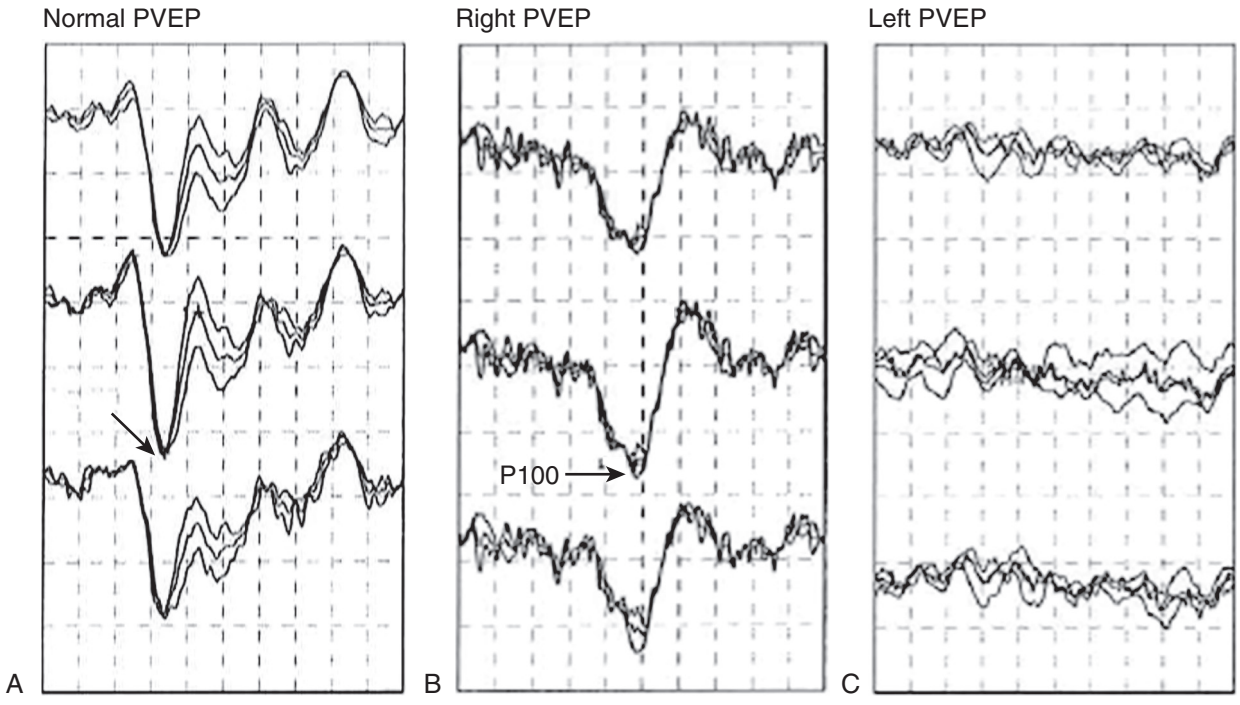

Right PVEP

Wave	Electrode	Latency (ms)								Stim.	Ave.
		N75	P100	N145							
C2	-	104.40	143.40	189.30							162

Mark Pair	Pair1	Pair2	Pair3	Pair4
Amplitude	N75-P100			
C2	7.700uV			

D

Left PVEP

Wave	Electrode	Latency (ms)								Stim.	Ave.
		N75	P100	N145							
D2	-	118.80	134.40	148.20							286

Mark Pair	Pair1	Pair2	Pair3	Pair4
Amplitude	N75-P100			
D2	1.400uV			

E

E-FIGURE 366-9. **Normal and abnormal pattern reversal visual evoked potentials. A**, Pattern reverse visual evoked potentials (PVEP) in a normal patient; the P100 wave response is at 100 msec. **B-E**, PVEPs in a patient with optic nerve demyelination secondary to anti–myelin oligodendrocyte glycoprotein (MOG) antibodies. The P100 wave latencies are prolonged in both eyes (**B and D**, right is at 143.4 msec; **C and E**, left [which is barely recordable] is at 134.4 msec). These findings suggest a conduction defect in both optic nerves. The severe attenuation of amplitude of the P100 responses on the left suggests axonal loss in the left optic nerve. Pattern reversal responses are generated by averaging between 65 and 100 pattern reversal sweeps for each trace. Three separate runs are overlaid to demonstrate consistency of responses (top, middle, and bottom traces correspond to O1, Oz, and O2 electrodes in each of **A, B,** and **C**). Each horizontal division represents 30 msec.

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The electrophysiologic response to auditory stimuli is measured by brainstem auditory evoked potentials.[18] Brainstem auditory evoked potential testing is helpful in the diagnosis of acoustic neuroma (Chapter 175) and other cerebellopontine angle tumors.

Somatosensory Evoked Potentials

The somatosensory evoked potential assesses conduction after stimulation of a mixed or cutaneous peripheral nerve. The recorded responses reflect activity of large-diameter, myelinated cutaneous and muscle afferents in the peripheral nervous system and the dorsal columns of the spinal cord, medial lemniscus of the brainstem, ventroposterior lateral nucleus of the thalamus, and somatosensory cortex of the contralateral cerebral hemisphere. Somatosensory evoked potential testing is helpful when multiple sclerosis (Chapter 380) is suspected clinically, and it is necessary to document the presence of a demyelinating lesion in the central nervous system that may not be clinically or radiographically evident.

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367 HEADACHES AND OTHER HEAD PAIN

KATHLEEN B. DIGRE

DEFINITION

Headache, which is a very common symptom, can be secondary to an underlying abnormality but is usually a primary headache disorder such as migraine headache, tension-type headache, cluster headache, and paroxysmal hemicrania.

EPIDEMIOLOGY

About 90% of all adults experience headache at some time in their lives, and over 75% of children have complained of headaches by the age of 15 years. In the United States, the direct and indirect costs associated with migraine are over $27 billion annually. The World Health Organization lists migraine in the top 10 most disabling conditions. Patients at most risk for lost days of employment are those with chronic migraine and daily headache.

In large population-based studies, the relative risk of having migraine, tension-type headaches, or cluster headaches increases up to four times if a first-degree relative has the same kind of headaches. Studies of twins, especially identical twins, also show a similar susceptibility.

PATHOBIOLOGY

Headache pain is initiated by primary trigeminal afferents that innervate the blood vessels, mucosa, muscles, and tissues. Fibers from these sources coalesce in the trigeminal ganglion, especially the first division. The trigeminal afferents terminate in the primary sensory nucleus of cranial nerve V and its spinal nucleus, which has several small subnuclei, the most important of which is the subnucleus caudalis. This subnucleus receives afferents from meningeal vessels, dura-sensitive neurons, and even the upper cervical cord and then projects them to the lateral and medial thalamus by way of the spinothalamic tract and to diencephalic and brain stem regions that are involved in the regulation of autonomic functions. Thalamic nociceptive information ascends to the sensory cortex, as well as to other areas of the brain.

Although secondary headaches may stimulate the pathway by way of processes such as inflammation and compression, primary headache disorders occur spontaneously by means of chemical mediators such as calcitonin gene–related peptide. The sequence of events commences with peripheral activation caused by neurogenic plasma extravasation activated spontaneously or by cortical spreading depression. The trigeminocervical complex, especially the nucleus caudalis, is then activated, and patients can experience allodynia, a condition in which a non-noxious stimulus is sensed as painful.

Aura is defined as a focal visual, sensory, or motor neurologic disturbance that may occur with or without headache. Aura is thought to occur when cortical spreading depression causes depolarization of membranes. Both neurons and glia can mediate both constriction and dilation of blood vessels. Migraine headache clearly has a genetic component. Familial hemiplegic migraine can be caused by mutations in the *CACNA1A* gene, which is located on chromosome 19p13.2-p13.1 and encodes for voltage-gated neuronal calcium channels. Mutations in the *CACNA1A* gene also cause episodic ataxia and epilepsy. Another mutation is in *ATP1A2*, also called the familial hemiplegia migraine 2 (*FHM2*) gene, which is located on chromosome 1q21-q23 and encodes for the sodium-potassium adenosine triphosphatase (Na^+, K^+-ATPase) transport protein. A third genetic locus is the *SCN1A* gene on chromosome 2q24.3, which is a voltage-gated sodium channel. In addition, many single-nucleotide polymorphisms have been associated with migraine. Although there are linkages to many genetic loci for more common forms of migraine, migraine and other headaches also probably have multiple epigenetic interactions[1] with environmental factors, and it is clear that the genetic contributions are complex.

CLINICAL MANIFESTATIONS

Patients with headache may describe the pain as throbbing, band-like, or aching. The pain is frequently unilateral but can be bilateral. Migraine headache is often associated with nausea, vomiting, photophobia, and phonophobia. It is invariably moderate to severe and interferes with activities. Other autonomic manifestations that can accompany migraine, cluster, and other headache variants include ptosis, conjunctival injection, tearing, rhinorrhea, Horner syndrome, and facial edema. Secondary headaches sometimes may appear to be similar to tension-type or migraine headaches, but "red flags" may suggest a secondary rather than a primary headache disorder (Table 367-1). Particular attention should be paid to the sudden onset of severe thunderclap headaches (Table 367-2), which frequently have an urgent underlying secondary cause.[2]

DIAGNOSIS

Five elements of the history are key for evaluating headaches. The family history helps determine whether a person has a genetic predisposition to headache. The life history of headache determines whether the headache is new or has evolved over the course of a lifetime. The attack history provides the clinical features of the headache or headaches. The medical and psychiatric history determines whether there are comorbid conditions that can cause or worsen the headache. The medication and drug history determines whether the headache could be caused by or worsened by medications or drugs the person has ingested.

ABSTRACT

Headache is an extremely common symptom, which can have multiple causes. Although secondary causes of headache should be considered, the most common types of headache are migraine, tension, cluster, and medication-overuse headaches. Each type of headache has different treatments, so accurate diagnosis is critical. Patients with trigeminal autonomic cephalalgias should undergo imaging at the time of diagnosis, because many secondary headaches mimic this phenotype. Two common secondary headaches are idiopathic intracranial hypertension (seen in obese women in their child-bearing years) and intracranial hypotension (or hypovolemia). Both conditions have imaging characteristics that can be helpful in making the correct diagnosis.

KEYWORDS

headache
migraine
tension-type headache
cluster headache
idiopathic intracranial hypertension
intracranial hypotension
trigeminal neuralgia

Diagnosis of the type of headache is based on the type of pain, the duration of headache, and accompanying features (Table 367-3).[3] Secondary headaches are usually due to an underlying condition such as a brain tumor (Chapter 175), increased or low intracranial pressure, sinus disease (Chapter 394), or a vascular malformation (Chapter 377); on removing the cause, the headache generally improves. Headaches that occur at a frequency of less than 15 days a month are called episodic, whereas headaches that occur more than 15 days a month are considered chronic.

TABLE 367-1 REASONS FOR FURTHER EVALUATION TO LOOK FOR SECONDARY HEADACHES

Beginning of headaches at an older age, without a previous history or a positive family history
Unexplainable and abnormal worsening of previously existing migraines
Dramatic or unusual change in character of the prodrome or the headache previously present
Headaches awakening the patient in the middle of the night (except for a cluster headache)
Headaches much worse when recumbent, only when upright, or with coughing, sneezing, or the Valsalva maneuver
Unusually severe headache of sudden onset ("worst headache of my life")
Focal deficits that do not disappear after the headache is over
Any abnormal neurologic or new psychiatric finding on examination
A new headache in a patient with human immunodeficiency virus infection, malignancy, or pregnancy

TABLE 367-2 THUNDERCLAP HEADACHE

Defined as sudden-onset severe headache reaching maximum intensity immediately or within 1 minute.
Causes:
- Subarachnoid hemorrhage
- Intracerebral hemorrhage
- Transient ischemic attack or stroke
- Cerebral venous thrombosis
- Unruptured vascular malformation (mostly aneurysm)
- Arterial dissection (intra- and extra-cranial)
- Reversible cerebral vasoconstriction syndrome
- Pituitary apoplexy
- Meningitis
- Colloid cyst of the third ventricle
- Spontaneous intracranial hypotension (CSF leak)
- Acute sinusitis (particularly with barotrauma)
- Primary headache with sexual activity (diagnosis of exclusion)
- Primary thunderclap headache (diagnosis of exclusion)

The diagnostic evaluation for headache depends on the clinical findings. If the history is typical and if the neurologic examination is completely normal, no further evaluation is needed. The features of the history that are most likely to predict migraine headache without a secondary disorder include photophobia, nausea, and disabling nature. However, if there are atypical features of the history or any abnormality on neurologic examination, further evaluation is indicated. Patients with cluster headache types and headaches of undetermined cause need imaging to exclude secondary causes.

In patients with acute-onset headache, computed tomography (CT) is best for assessing possible acute hemorrhage as the cause of the headache. By comparison, magnetic resonance imaging (MRI) is best for assessing most persistent headaches to look for mass lesions, evidence of intracranial hypertension or hypotension, hemosiderin (old hemorrhage), and congenital abnormalities (e.g., Chiari malformation). If reversible cerebral vasoconstriction is a concern, either CT angiography or MR angiography should be obtained. In individuals older than 60 years with an unexplained new or unusual headache, the erythrocyte sedimentation rate (ESR) and/or C-reactive protein (CRP) level should be measured to evaluate for giant cell arteritis (Chapter 63). Cerebrospinal fluid (CSF) analysis, including opening pressure, protein, glucose, cells, culture, and cytology, is indicated in patients with suspected intracranial hypertension or meningitis.

TREATMENT

Treatment of acute headache depends on the type and severity of the headache. For mild headaches, simple analgesics such as acetaminophen[A1] (500 to 1000 mg), acetaminophen with caffeine, aspirin (250 to 1000 mg),[A2] and nonsteroidal anti-inflammatory drugs[A3] ([NSAIDs]; e.g., ibuprofen, 400 to 800 mg; naproxen sodium, 220 to 500 mg, diclofenac 50 mg) will suffice.

PREVENTION

Preventive medications are recommended when headaches are frequent or severe enough to interfere with quality of life. The choice of medications should be based on the type of headache (migraine, tension-type), their side effect profiles, and the patient's comorbid conditions (Table 367-4). In general, treatments aimed at the calcitonin gene–related peptide are reserved for patients who have not responded to two to three other classes of medication.

PROGNOSIS

The natural history of headache depends on many factors, including the type of headache, comorbid conditions that accompany the headache, and success of treatment. Risk factors for chronic headache include female sex, migraine-type headaches, frequent headaches, obesity, low education and

TABLE 367-3 DIFFERENTIAL DIAGNOSIS OF HEADACHE

HEADACHE TYPE	GENETICS	EPIDEMIOLOGY	CHARACTERISTIC FEATURES	LENGTH	ACCOMPANYING SYMPTOMS
Migraine headache	Complex genetics but usually a family history	More frequent in women	Unilateral, bilateral; throbbing; moderate to severe; worsens with activity	Hours to days	Photophobia, phonophobia, nausea and/or vomiting
Tension-type headache	Usually a family history	Equal frequency in men and women	Tight band–like pain; bilateral; pain may be mild to moderate; improves with activity	Hours to days	No nausea or vomiting; small amount of light or sound sensitivity, but not both
Cluster headache	May have a family history	More frequent in men but also occurs in women	Unilateral severe pain in the face	Minutes to hours	Ipsilateral ptosis, miosis, rhinorrhea, eyelid edema, tearing
Paroxysmal hemicrania	Usually no family history	More frequent in women	Unilateral pain in the face	Minutes	Ipsilateral ptosis, miosis, rhinorrhea, eyelid edema, tearing; responds to indomethacin
Short unilateral headache with conjunctival injection, tearing	No family history	More frequent in men	Unilateral eye pain; orbit pain	Seconds to 240 seconds	Conjunctival injection, tearing
Hemicrania continua	No family history	More frequent in women	Unilateral continuous headache with episodic stabbing pains	Continuous	Ipsilateral autonomic features: ptosis, miosis, rhinorrhea, eyelid edema, tearing; responds to indomethacin

TABLE 367-4 PREVENTIVE MEDICATIONS FOR HEADACHE

DRUG	RATIONAL USE	DOSAGE	SIDE EFFECTS	CONTRAINDICATIONS/ CAUTION
β-Blockers (e.g., propranolol, nadolol, timolol)	Migraine, anyone with elevated blood pressure	Propranolol, 20-80 mg; may increase	Lethargy, depression	Asthma, low blood pressure
Calcium-channel antagonists: verapamil, amlodipine	Cluster headache, elevated blood pressure	Verapamil, 120-480 mg/day	Low blood pressure	
Nonsteroidal anti-inflammatory drugs:				
naproxen, ibuprofen	Migraine, tension-type, and menstrual migraine	Naproxen, 200-600 mg/day; ibuprofen, 600-800 mg bid-tid	Gastrointestinal	Ulcers, sensitivity, allergy
indomethacin	Paroxysmal hemicrania, hemicrania continua	Indomethacin, 25-50 mg tid	Gastrointestinal	Ulcers; renal insufficiency
Tricyclic antidepressants: amitriptyline, nortriptyline, imipramine	Migraine, tension-type headache, anyone with poor sleep	10-25 mg qhs; may increase	Dry mouth, orthostatic hypotension, weight gain	Sensitivity to tricyclic antidepressants
Anticonvulsants: topiramate valproate	Migraine, cluster headache	Topiramate, 25-50 mg bid; valproate, 250-500 mg bid	Topiramate: weight loss, kidney stones, intraocular hypertension Valproate: weight gain	Pregnancy—both U.S. FDA classification D
Calcitonin gene–related peptide antibodies: eptinezumab, erenumab, fremanezumab, galcanezumab	Migraine, chronic migraine, cluster (galcanezumab)	Eptinezumab 100-300 mg IV every 3 months; erenumab 70-140 mg SQ monthly; fremanezumab 225 mg SQ monthly; galcanezumab 240 mg SQ loading dose, then 120 mg SQ monthly	Injection site redness; nasal symptoms; constipation	Unknown pregnancy effect
Calcitonin gene–related peptide antagonists: rimegepant, atogepant	Migraine	Rimegepant 75 mg qod oral dissolving; atogepant 10-30 mg orally daily	Abdominal pain; indigestion	Unknown pregnancy effect

bid = twice daily; FDA = Food and Drug Administration; IV = intravenously; qhs = at bedtime; qod = every other day; SQ = subcutaneously; tid = three times daily.

socioeconomic level, overuse of medication, depression, anxiety, stressful life events, and sleep apnea.

MIGRAINE HEADACHE

DEFINITION

Migraine is an inherited headache disorder that is typically unilateral but sometimes bilateral, moderate to severe, worsens by routine physical activity, associated with nausea and/or vomiting, and accompanied by photophobia and phonophobia. The headache occurs anytime and persists from 4 to 72 hours. It may occur with an aura (a focal neurologic symptom that may be visual, sensory, motor, or language) or without an aura. Visual auras may have positive (photopsias) and negative (scotomas) features.

EPIDEMIOLOGY

The prevalence of migraine is 15 to 20% in women and 4 to 7% in men, and migraine headaches are estimated to afflict 1 billion people worldwide.[4] In children the prevalence may be as high as 17% and is equal in boys and girls. At puberty, the prevalence rises in girls and remains higher throughout their lifespan. The highest prevalence occurs between the ages of 25 and 55. Migraine with aura affects 5% of the adult population, and 90% of auras are visual. Migraine is more prevalent in White persons and in those with a lower socioeconomic status or income.

Comorbid conditions and lifestyle factors[5] that may be associated with migraine headache include epilepsy, stroke, depression, anxiety, asthma, myocardial infarction, patent foramen ovale, Raynaud phenomenon, irritable bowel syndrome, and pain disorders such as fibromyalgia. Menstruation and ovulation may increase the frequency of headache.

PATHOBIOLOGY

The aura of a migraine headache is thought to be due in part to cortical spreading depression, which is associated with a brief reduction in blood flow followed by hyperemia. These changes do not seem to correlate with the phase of the headache. Pain occurs when trigeminal afferents of the dura are stimulated.

CLINICAL MANIFESTATIONS

Migraine headache often begins with a prodrome that may persist for hours to days, when patients note difficulty concentrating or fatigue without headache.[6] An aura may or may not occur but is generally present before the headache begins. The headache may be unilateral or bilateral, throbbing, moderate to severe, and worsened with activity. Accompanying clinical features include nausea, vomiting, and sensitivity to light and sound. Other clinical features may include neck pain, dizziness, osmophobia (sensitivity to odors), and difficulty thinking clearly.

The migraine aura is generally visual but can be sensory or include aphasia or vertigo. Migraine aura without headache begins with a neurologic disturbance (e.g., a visual phenomenon) but without a subsequent headache. Although an aura is traditionally thought to precede the headache, it can be present during the headache phase.

DIAGNOSIS

The diagnosis of migraine is based on the history. The differential diagnosis includes tension-type headache, but most moderate to severe headaches are migraine.[7] In patients with a history suggestive of a secondary headache (see Table 367-1), further evaluation with an MRI should be considered (Fig. 367-1). However, if the headache is typical of migraine and the findings on neurologic examination are normal, no further studies are needed.

TREATMENT

Treatment of migraine[8] is divided into treatment of the acute headache and prevention of subsequent migraine attacks (see Fig. 367-1 and https://americanheadachesociety.org/flowchart/). Acute treatment is most effectively accomplished with migraine-specific care: a nonspecific analgesic agent or combination analgesic therapy for milder migraine and, most frequently, aggressive migraine-specific therapy for migraine. Stratification of care, including tailoring the treatment according to the type of headache, results in fewer days of disability and use of medications.[9] Which migraine-specific drug will work for any individual patient depends on the patient. It is important to avoid overuse of analgesic and other medications (especially opiates) because overuse can cause chronic daily headache in susceptible individuals. Prompt treatment improves the outcome of headache when compared with late treatment.

Mild attacks can generally be treated successfully with over-the-counter analgesics such as acetaminophen (suggested dose, 650 to 1000 mg) or NSAIDs (aspirin, 250 mg to 1000 mg; ibuprofen, 400 to 600 mg; naproxen, 500 to 825 mg; diclofenac, 50 mg; or ketoprofen, 75 mg).

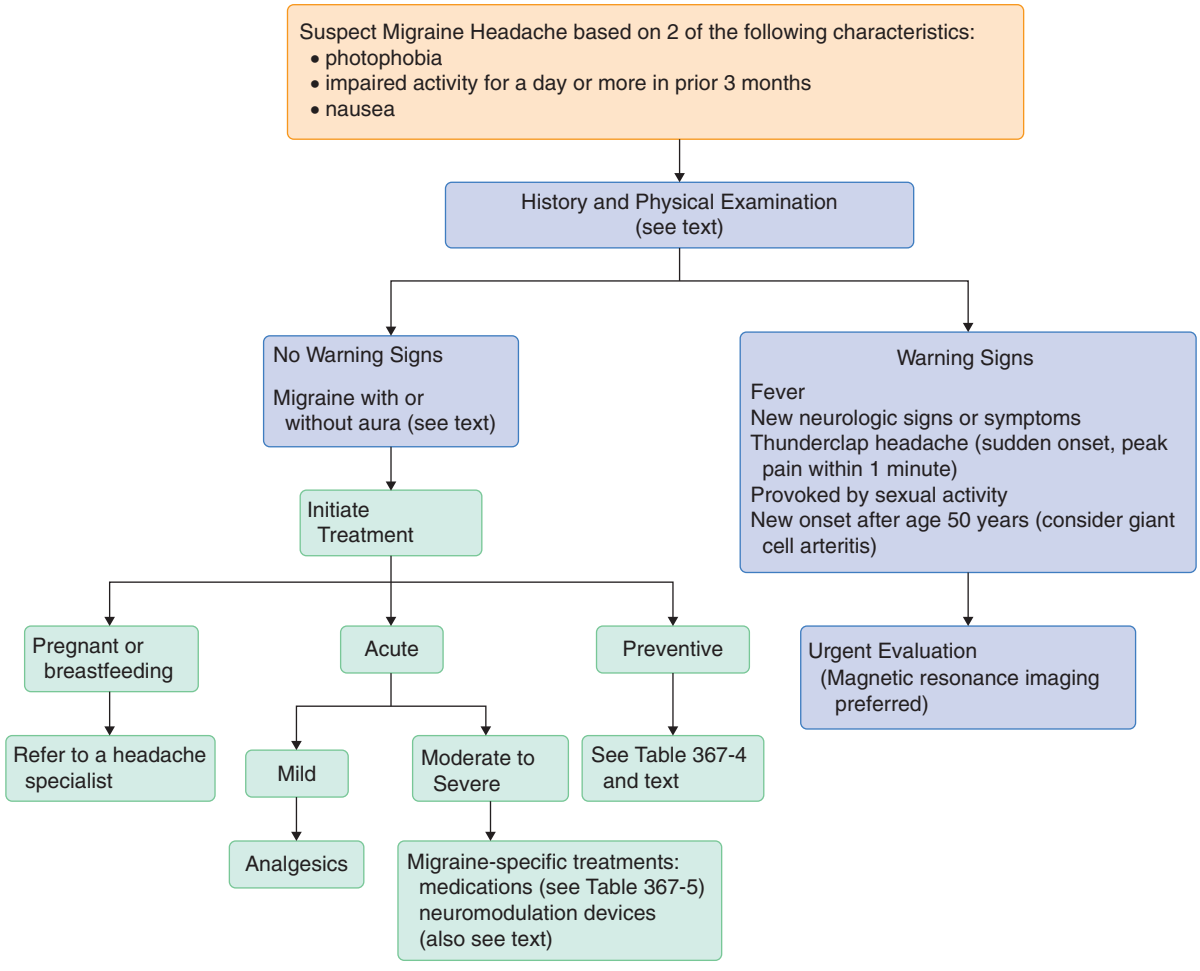

FIGURE 367-1. Approach to possible migraine headaches. (Based on data reviewed in https://americanheadachesociety.org/flowchart/.)

For *moderate to severe* migraine headaches, patients benefit from migraine-specific triptans (see Table 367-5), ergotamines (dihydroergotamine 1 to 2 mg intranasally or subcutaneously; ergotamine tartrate, 2 mg sublingually or 1 to 2 mg orally), the combination of naproxen and a triptan, or a formulary combination of isometheptene (65 mg), dichlorphenazone (100 mg), and acetaminophen (325 mg).[A4] Contraindications to use of triptans include uncontrolled hypertension, clinical evidence of ischemic heart disease, and Prinzmetal angina. Ergotamine given early in the migraine attack can be effective if the associated nausea and peripheral vasoconstriction are tolerable. Lasmitidan (50 to 200 mg) is a serotonin receptor agonist that does not have the vasoconstrictive side effects of triptans and that is safe and effective for patients who have contraindications to triptans[A5]; however, it is sedating, so driving is contraindicated for at least 90 minutes and perhaps up to 8 hours after its administration. Small-molecule, calcitonin gene–related peptide receptor antagonists are also helpful for treating migraine attacks. Both rimegepant (75 mg orally) or ubrogepant (50 to 100 mg) can provide about a 10% absolute increase in pain freedom within 2 hours compared with placebo,[A6,A7] have few side effects, and are useful when triptans are not successful or are contraindicated.

For *very severe* attacks, dihydroergotamine (1 mg subcutaneously or 0.5 to 1 mg intravenously [IV]) is usually effective but generally requires an antiemetic (e.g., promethazine, 25 mg) before intravenous use. Ketorolac (60 mg intramuscularly [IM] or 30 mg IV), prochlorperazine (10 to 25 mg IM or 10mg IV[A8] delivered over a 5-minute period), metoclopramide (10 mg IV), or celecoxcib solution (120 mg orally)[A9] is useful for patients who are nonresponsive or have contraindications to vasoactive abortive agents.

Opioids should not be used except as a last resort. Nevertheless, opioids (e.g., acetaminophen [325 mg] with codeine [30 mg]; N-acetyl-p-aminophenol [APAP] with codeine [30 mg]; or butorphanol [1 mg per spray]) may benefit some patients who have contraindications to triptans and ergotamines. Meperidine is not effective. Oral opiates should not be used for chronic recurrent, primary headaches. When opiates are used, caution is required.

Noninvasive Neuromodulation

Noninvasive neuromodulation is an important new approach for treating acute migraine headaches.[10] For example, randomized trials have supported FDA approval for electrical non-invasive vagus nerve stimulation, trigeminal nerve stimulation, occipital nerve stimulation, transcranial magnetic stimulation, and remote electrical neuromodulation via a smartphone-controlled wireless device.[A10–A12] These devices should be avoided or used with great caution in patients who have cardiac pacemakers.

Pregnant Patients

During pregnancy, mild to moderate attacks can be treated with acetaminophen. Moderate headaches may respond to the combination of acetaminophen, isometheptene mucate (a mild vasoconstrictor, 65 mg), and dichloralphenazone (a mild sedative, 100 mg). Antinausea agents include prochlorperazine (10 to 25 mg) and metoclopramide (2.5 to 10 mg). The combination of metoclopramide (5 to 10 mg) with diphenhydramine (25 mg) is superior to codeine in pregnancy.[A13] In pregnant patients, noninvasive neuromodulation device therapy is an especially attractive alternative.

PREVENTION

Preventive treatment (see Table 367-3) is often recommended when headaches interfere with activities on 3 or more days per month or when the headaches are severe or prolonged.[11] Prophylactic options include β-adrenergic blockers, calcitonin gene–related peptide antibodies and small-molecule inhibitors, calcium-channel antagonists, NSAIDs, tricyclic antidepressants, valproate, and topiramate. Other alternatives include the serotonergic drug cyproheptadine (4 to 20 mg) or the monoamine oxidase inhibitor phenelzine (30 to 60 mg).

Calcitonin gene–related peptide antibody options for prevention[A14,12] include erenumab (70 to 140 mg subcutaneously monthly),[A15] fremanezumab (225 mg subcutaneously monthly or 675 mg quarterly),[A16] eptinezumab (100 to 300 mg intravenously at baseline and week 12),[A17] and galcanezumab (240 mg loading and 120 mg monthly).[A18] Small-molecule inhibitors include rimegepant (75 mg orally every other day) and atogepant (10 mg once daily to 60 mg once daily).[A19]

Acupuncture and biofeedback have been used successfully. OnabotulinumtoxinA injection is also effective for prophylaxis of chronic migraine.[A20] FDA-approved devices for the prevention of migraines include vagus nerve stimulation, transcutaneous direct current stimulation,[A21] trigeminal

TABLE 367-5 SPECIFIC TRIPTAN MEDICATIONS FOR THE TREATMENT OF ACUTE MIGRAINE WITH GRADE A EVIDENCE FROM TWO OR MORE RANDOMIZED TRIALS

	SUMATRIPTAN	ZOLMITRIPTAN	NARATRIPTAN	RIZATRIPTAN	ALMOTRIPTAN	FROVATRIPTAN	ELETRIPTAN
Trade name	Imitrex, Zecuity	Zomig	Amerge	Maxalt	Axert	Frova	Relpax
Forms	SQ, nasal (NS), oral	Oral: tablet/ ZMT, NS	Oral	Oral: tablet/MLT	Oral	Oral	Oral
Dose	Oral: 50-100 mg (200 mg/24 hr max.) SQ: 4-6 mg (12 mg/ 24 hr max.) NS: 5-20 mg (40 mg/ 24 hr max.) Nasal delivery device (22 mg)	2.5-5 mg (10 mg/ 24 hr max.) 5 mg (10 mg/24 hr max.)	1-2.5 mg (5 mg/ 24 hr max.)	5-10 mg (30 mg/ 24 hr max.)	6.25-12.5 mg (25 mg/24 hr max.)	2.5 mg (7.5 mg/ 24 hr max.)	20-40 mg (80 mg/24 hr max.)
Half-life	2-3 hr	3-4 hr	6-8 hr	2-3 hr	3-4 hr	26 hr	4-6 hr
Crosses blood-brain barrier	–	+	+	+	+	+	+
Use with monoamine oxidase inhibitor (MAOI)	–	–	+	–	+	+	–
Good for recurrence	–	–	+	–	–	+	–
Rapid response	SQ, 10-15 min NS, 15-20 min Oral, 30 min	30 min	1-4 hr	30 min	60 min	1-4 hr	20-30 min
Other	In combination with naproxen (Treximet)			Decrease dose by half with propranolol			Do not use with CYP3A4 drugs (ketoconazole and some macrolide antibiotics)

max. = maximum; MLT = rizatriptan melting tablet; NS = nasal spray; SQ = subcutaneous; ZMT = zolmitriptan melting tablet.

nerve stimulation, and transcranial magnetic stimulation.[13] As with acute therapy, these devices should be avoided or used with great caution in patients with cardiac pacemakers.

PROGNOSIS

The prognosis for patients with migraine is variable. In many patients, headaches decrease in severity with age, but migraine aura without headache becomes more frequent with older age. Modification of inciting factors such as avoiding dietary triggers (tyramine, phenylethylamine, ethanol), ameliorating or preventing insomnia, and averting environmental triggers (light, sound, odor) may improve outcome. Migraines may become chronic, defined as more than 15 days per month, especially when associated with obesity, snoring, depression, frequent headaches, and low socioeconomic status. Since there appears to be shared genetic susceptibility to migraine with aura and ischemic stroke, careful attention to cardiovascular risk factors is important. Closure of an associated patent foramen ovale (Chapter 55) is of modest if any benefit.[A22]

TENSION-TYPE HEADACHE

DEFINITION

Tension-type headache is defined as a mild or moderate holocranial headache without nausea or vomiting. Patients may have either photophobia or phonophobia but not both, and the headache does not worsen with activity.

EPIDEMIOLOGY

The 1-year prevalence is 14 to 93 per 100,000 individuals for episodic tension-type headache and 8.1 per 100,000 for chronic tension-type headache. Tension-type headaches are more common in women than in men, regardless of age, race, and educational level. Tension-type headaches are more common in Western countries and less frequent in Asian countries, and they are more common in White persons than in African Americans.

PATHOBIOLOGY

The pathophysiology of tension-type headache is less well understood than that of the other types of headache. Myofascial tenderness is increased, especially in chronic tension-type headache. Genetic factors are uncertain. Migraine and tension-type headache often coexist. Although tension-type headaches are not due to emotion or muscle contraction, triggers of a tension-type headache are similar to those associated with migraine: stress, fatigue, and lack of sleep. Comorbid conditions in patients with tension-type headache include depression and anxiety in more than 50% of individuals.

CLINICAL MANIFESTATIONS

Tension-type headaches are usually mild to moderate in severity, and most individuals do not seek care. Tension-type headache can be episodic (occurring <15 days per month) or chronic (occurring >15 days per month). In many patients headaches remain episodic, but about 25% progress to chronic headache. Of the patients with chronic tension-type headache, about a quarter to a third continue as chronic, half can improve to episodic, and in about a quarter medication overuse headache can develop. Episodic tension-type headaches can last minutes, hours, or days.

DIAGNOSIS

Headaches that can be misdiagnosed as tension-type headache include migraine, hemicrania continua, new daily persistent headache, and headaches caused by brain tumors, elevated or low intracranial pressure, or giant cell arteritis. A careful history is the best way to distinguish other types of headaches.

TREATMENT

Episodic tension-type headaches are generally treated successfully[14] with acetaminophen (650 to 1000 mg) or NSAIDs (aspirin, 250 to 1000 mg; naproxen, 250 to 500 mg; ibuprofen, 200 to 800 mg; or ketoprofen, 12.5 to 75 mg). However, analgesic use for more than 3 days per week can worsen headaches and lead to medication-induced headache.

PREVENTION

Chronic tension-type headaches may benefit from prophylactic treatment with amitriptyline (starting with 10 mg at bedtime and increased slowly up to 100 mg until the patient improves or intolerable side effects develop), nortriptyline (25 to 100 mg each evening), doxepin (25 to 75 mg/day), maprotiline (10 to 25/mg/day), or fluoxetine (10 to 20mg/day). Tricyclics are generally more

efficacious than serotonin reuptake inhibitors.[A23] Muscle relaxants, physical therapy, localized botulinum toxin injection, and acupuncture can be useful.

PROGNOSIS

Tension-type headache has a variable prognosis. Adolescents with tension-type headache and two or more psychiatric factors (e.g., depression and anxiety) have a worse prognosis.

CLUSTER HEADACHE AND OTHER TRIGEMINAL AUTONOMIC CEPHALALGIAS

DEFINITION

Trigeminal autonomic cephalalgias, including cluster headaches, are unilateral headaches associated with ipsilateral autonomic features. Other trigeminal autonomic cephalalgias include paroxysmal hemicrania, which is characterized by bouts of headache that persist for 5 to 30 minutes, is generally unilateral, and usually occurs in women; they typically respond to indomethacin. Hemicrania continua, another indomethacin-responsive headache seen in both men and women, is characterized by continuous unilateral pain and mild associated autonomic features; it frequently coexists with a form of chronic daily headache. Short unilateral neuralgiform headache with conjunctival injection and tearing is a rare trigeminal autonomic cephalalgia that occurs in men; individual headaches persist for only a short time (seconds to 2 minutes) but occur frequently.

EPIDEMIOLOGY

Cluster headache occurs in 56 to 401 per 100,000 persons and is more frequent in men (3 : 1 to 7 : 1). Attacks usually begin between 20 and 30 years of age. Paroxysmal hemicrania occurs in 56 to 381 per 100,000 persons; it affects women more often (2 : 1) and can begin at any age but usually commences at 34 to 41 years. Short unilateral neuralgiform headache with conjunctival injection and tearing is rare, with a slight male preponderance (2 : 1).

PATHOBIOLOGY

Cluster headache may have a genetic predisposition. Imaging studies such as positron emission tomography and functional MRI show inferior posterior hypothalamic activation at the onset of cluster headache and other trigeminal autonomic cephalalgias. In addition, the trigeminovascular complex and the cranial autonomic system are activated. The pathophysiology of hemicrania continua is unknown, and there is debate whether it is associated with hypothalamic involvement or whether it resembles migraine.

CLINICAL MANIFESTATIONS

Cluster headache is almost always unilateral, rarely bilateral, and has characteristic ipsilateral autonomic features, commonly including lacrimation and conjunctival injection and occasionally nasal congestion, rhinorrhea, ptosis, miosis, flushing, and eyelid edema (Table 367-6).[18] The location of the pain is usually behind or above the eye or in the temple but can include the forehead, cheek, teeth, or jaw. The pain reaches its maximum intensity in about 9 minutes and tends to end abruptly. Attacks occur one to eight times a day and are usually described as "boring" or "stabbing" excruciating pain that persists for 15 minutes to 2 hours. Migraine symptoms may coexist, including unilateral photophobia, phonophobia, and, rarely, an aura. Unlike migraine patients, who usually try to rest, patients with cluster headaches pace and are unable to sit or lie down. Cluster headaches, often precipitated by alcohol, histamine, or nitroglycerin, have a daily periodicity and may also have a seasonal periodicity. For example, episodic cluster headache may occur annually or every 2 years, often in the same season each time. Chronic cluster headache occurs without a remission.

Paroxysmal hemicrania is pain of short duration, usually 2 to 30 minutes, and occurs unilaterally around the eye, temple, or maxillary region. Autonomic features similar to cluster headache can occur. The usual attack rate is up to 40 episodes each day. Bouts of pain may be episodic, separated by a remission, but most patients have daily chronic paroxysmal hemicrania without a remission.

Short unilateral neuralgiform headache with conjunctival injection and tearing attacks are unilateral and consistently on the same side. Although the pain is excruciating, the attack is brief, usually seconds; most patients are free of pain between attacks, although a dull ache can be present. Associated autonomic features include ipsilateral conjunctival injection and tearing.

DIAGNOSIS

The diagnostic criteria for cluster headache include severe unilateral orbital, supraorbital, or temporal pain persisting for 15 to 180 minutes with at least one of the following: ipsilateral conjunctival injection or lacrimation, nasal congestion or rhinorrhea, eyelid edema, forehead and facial sweating, miosis with or without ptosis, and restlessness or agitation.[16] Attacks occur between once and as often as eight times each day. There is no other cause of the disorder.

Paroxysmal hemicrania is defined by unilateral pain persisting for 2 to 30 minutes, about five times each day, with one or more autonomic features such as conjunctival injection, nasal congestion, eyelid edema, forehead and facial sweating, and miosis or ptosis (or both). Complete prevention may be achieved with indomethacin.

Hemicrania continua is a unilateral headache that occurs daily and continuously without pain-free periods; its intensity is moderate, with exacerbations of severe pain. During the exacerbations, at least one ipsilateral autonomic feature is present: conjunctival redness, lacrimation, nasal congestion, ptosis, or miosis. It responds to indomethacin.

Short unilateral neuralgiform headache with conjunctival injection and tearing is diagnosed by unilateral orbital, supraorbital, temporal stabbing pain persisting for 5 to 240 seconds at a frequency of three to 200 per day. It is associated with conjunctival injection and tearing.

An imaging procedure such as MRI is indicated for all patients at the onset of cluster headaches or other trigeminal autonomic cephalalgias because they can be the result of infection (Chapters 381 to 383), vascular malformation (Chapter 377), carotid dissection, or neoplasm, especially a pituitary tumor (Chapter 175). Other possibilities in the differential diagnosis include migraine,

TABLE 367-6 DISTINGUISHING CHARACTERISTICS OF THE TRIGEMINAL AUTONOMIC CEPHALALGIAS

CHARACTERISTIC	CLUSTER	PAROXYSMAL HEMICRANIA	HEMICRANIA CONTINUA	SHORT UNILATERAL NEURALGIFORM HEADACHE WITH CONJUNCTIVAL INJECTION AND TEARING
Sex—F:M	1 : 3-7	2 : 1	2 : 1	1 : 2
Unilateral	+	+	+	+
Attack frequency	1-8/day	1-40/day	3-200/day	3-200/day
Attack duration	15-80 min	2-30 min	Continuous with episodic exacerbations	5-240 sec
Autonomic features	+	+	+ with exacerbations	+
Indomethacin effect	–	+++	+++	–
Acute treatment at onset	Oxygen, sumatriptan SQ, DHE nasal spray; sumatriptan or zolmitriptan nasal spray (A-level evidence)	None	None	None
Preventive medications	Verapamil, lithium, corticosteroids, anticonvulsants, galcanezumab (A level)	Indomethacin (A level)	Indomethacin (A level)	Lamotrigine, topiramate, gabapentin (B level)

DHE = dihydroergotamine; SQ = subcutaneous.

hypnic headache (rare short-lasting headaches exclusively during sleep in the elderly), and trigeminal neuralgia.

TREATMENT

Because the course of the headache is brief, oral medications take too long to work to be effective. The use of 100% oxygen at 7 to 10 L/minute for 15 to 30 minutes in a nonrebreathable mask benefits some patients.[A24] Sumatriptan or zolmitriptan nasal spray or sumatriptan subcutaneously (4 to 6 mg) can be helpful. Dihydroergotamine can be helpful when given nasally, IM, or even IV. Vagal nerve stimulation was recently approved for acute cluster headache. Refractory cases may respond to sphenopalatine ganglion and occipital nerve stimulation. Chronic paroxysmal hemicranias and hemicrania continua are characterized by a response to indomethacin, 25 to 50 mg three times daily. Short unilateral neuralgiform headache with conjunctival injection and tearing attacks is so brief that there are no medications to treat it acutely.

PREVENTION

Preventive medications should be started at the beginning of a cluster bout. Verapamil, 240 to 480 mg, is the drug of choice. Lithium (300 mg twice daily) is an alternative. Corticosteroids (e.g., prednisone, 40 to 100 mg/day for 5 days then tapered over 3 days, or dexamethasone, 4 mg twice daily for 2 weeks) act rapidly as a bridge to prevent cluster headache while other preventive medications are started.[A25] Galcanezumab, a monoclonal antibody to calcitonin gene–related peptide (300 mg subcutaneously once per month), may significantly reduce the frequency of cluster headaches.[A26] Valproic acid (500 to 1500 mg/day in divided doses), topiramate (50 to 100 mg/day), melatonin (4 mg at bedtime), and gabapentin (300 mg three times daily) are sometimes beneficial. Other approaches, including suboccipital steroid injections, noninvasive vagus nerve stimulation, occipital nerve stimulators,[A27] sphenopalatine ganglion stimulation, hypothalamic stimulation, and destructive procedures, are sometimes necessary for this disabling headache.

Paroxysmal hemicrania and hemicrania continua respond to daily indomethacin (25 to 50 mg three times daily). If the patient cannot tolerate indomethacin, celecoxcib, calcium-channel blockers (e.g., verapamil, 240 to 480 mg/day), or melatonin may be helpful. Preventive treatment of short unilateral neuralgiform headache with conjunctival injection and tearing includes lamotrigine (100 to 400 mg/day), topiramate (50 to 100 mg), gabapentin (300 to 900 mg), or intravenous lidocaine (starting at 1 to 2 mg/minute with cardiac monitoring).

PROGNOSIS

Cluster headache is often a lifelong problem, but remissions may persist for longer periods as the patient ages. The other trigeminal autonomic cephalalgias are probably lifelong; nevertheless, symptomatic treatment combined with preventive medications is helpful.

CHRONIC DAILY HEADACHE

DEFINITION

Though not a specific disorder, chronic daily headache, defined as a headache that is present on more than 15 days per month, is challenging for both patients and physicians.[I6] These headaches may be chronic migraine, chronic tension-type headache, new daily persistent headache, hemicranias continua, or chronic cluster headache, with or without overuse of medications.

EPIDEMIOLOGY

Up to 5% of the population suffers from chronic daily headache, most commonly chronic migraine or chronic tension-type headache. Trigger factors such as a previous infection, mild head injury, or stressful life event are present in 40 to 60% of patients with new daily persistent headache. Risk factors for chronic daily headache include medication overuse, history of migraine headache, frequent headache, depression, female sex, obesity, snoring, stressful life events, and low educational level.

PATHOBIOLOGY

Chronic daily headache is probably related to migraine, with both central and peripheral abnormalities. Once migraine has been prolonged and headache occurs on a daily basis, patients may develop allodynia, a sense that a usually nonpainful stimulus is painful. Use of an opiate for more than 8 days per month, especially in men; use of barbiturates for more than 5 days per month, especially in women; or use of triptans for more than 10 to 14 days per month can often lead to chronic migraine headache with medication overuse.

CLINICAL MANIFESTATIONS

New daily persistent headache is characterized by daily occurrence, onset at specific time, and an unrelenting course. It is generally bilateral, nonpulsating, mild to moderate, and associated with features of migraine, photophobia, phonophobia, or nausea. Severe nausea or vomiting is rare. New daily persistent headache can be disabling and is difficult to treat. Chronic daily headache is often associated with profound psychiatric comorbidity, especially depression and anxiety; such psychiatric comorbidity predicts intractability.

DIAGNOSIS

Diagnosis of chronic daily headache is based on the history.[I7] It is important to identify the underlying type of primary chronic daily headache: chronic migraine, chronic tension-type headache, new daily persistent headache, or hemicrania continua. Headaches of less than 4 hours' duration can also be chronic and daily: cluster headache, paroxysmal hemicrania, hypnic headaches occurring every night (usually in the elderly), and episodic stabbing headache. It is most important to exclude secondary headaches (including post-traumatic headache), headaches associated with vascular disorders (e.g., giant cell arteritis, arteriovenous malformations, carotid and vertebral artery dissections), and headaches associated with nonvascular disorders (e.g., intracranial hypertension or hypotension, infections). MRI and laboratory studies (e.g., ESR in an elderly individual) are commonly recommended. Lumbar puncture (LP) to assess intracranial pressure also may be indicated in selected patients.

TREATMENT

The most common cause of chronic daily headache is overuse of medications, so patients must be weaned off the overused symptomatic medication and start a preventive medication. Underlying depression and anxiety also should be addressed. Occasionally, hospital admission is necessary to break the headache cycle.

PREVENTION

Medications that are helpful in preventing chronic daily headache include tricyclic antidepressants, selective serotonin reuptake inhibitors if patients are depressed, anticonvulsants, β-blockers, and calcium-channel blockers (see Tables 367-3 and 367-4). For hemicrania continua, indomethacin (25 to 50 mg three times daily) is the preferred treatment.

PROGNOSIS

The prognosis depends on the underlying headache diagnosis. Depression, anxiety, poor sleep, stress, medication overuse, and poor self-efficacy are associated with a worse prognosis among patients with chronic headaches. If medication overuse is the cause and the patient is successfully detoxified, about 75% of patients improve when treated with preventive medications. Treatment may fail if the diagnosis is incorrect or because of continued overuse of medications, overuse of caffeine, lack of sleep, dietary or other life triggers, hormonal factors, or psychiatric factors. Explaining medication overuse headache to the patient, inpatient and outpatient detoxification, and multidisciplinary care treatments have been found helpful. New daily persistent headache often does not respond to medical therapy.

SECONDARY CAUSES OF HEADACHES

SINUS HEADACHE

Rhinosinusitis (Chapter 394) is characterized by inflammation or infection of the nasal mucosa and sinuses. The sinuses themselves are relatively insensate, but ducts, turbinates, blood vessels, and ostia are the painful structures.

Headaches attributed to rhinosinusitis are frontal headaches with pain in the face, ears, or teeth. The onset of pain is simultaneous with the rhinosinusitis, and the headache and face pain resolve within 7 days after successful treatment. The diagnosis requires imaging and clinical evidence that support the diagnosis of acute rhinosinusitis. Many acute and most chronic headaches that are initially thought to result from sinus disease are found to be migraine or tension-type headache.

The headache should resolve with treatment of acute sinusitis (Chapter 394). If it does not, an underlying primary headache disorder is likely.

TEMPORAL (GIANT CELL) ARTERITIS

Temporal arteritis (Chapter 250) is an inflammatory process seen almost exclusively in elderly individuals. Headache, especially pain in the jaw when chewing, is one of the most common features. Its incidence is approximately 12 per 100,000 and increases with age to 51 per 100,000 in individuals older than 80. It affects women more often than men (3 : 1) and is more common in White individuals, especially those of Scandinavian and British descent. It is associated with polymyalgia rheumatica.

The headache has no specific feature, but the pain is usually continuous, generalized, and occasionally throbbing. The temples are generally painful, and patients complain of pain when performing certain activities of daily living, such as chewing food or combing hair. Transient monocular blindness, permanent blindness, and diplopia can occur.

Elevation of the ESR and CRP occurs almost invariably. The diagnosis is made by finding giant cells in a temporal artery biopsy specimen. Immediate treatment with corticosteroids, sometimes before the biopsy result is available, is necessary in doses between 40 and 80 mg daily, with the dose then titrated downward while monitoring the ESR or CRP. Used early enough, corticosteroids (Chapter 250) generally prevent the complications of temporal arteritis, including blindness. Tocilizumab (162 mg subcutaneously weekly or every other week) can provide sustained corticosteroid-free remission in patients with temporal arteritis.[A28] The disorder can be long lasting.

INTRACRANIAL HYPERTENSION AND PSEUDOTUMOR CEREBRI

Intracranial hypertension can be primary and idiopathic or secondary to cerebral venous thrombosis (Chapter 376), a mass in the brain (Chapter 175), hydrocephalus, or other intracranial processes. *Pseudotumor cerebri* is an all-encompassing term referring to increased intracranial pressure without obvious mass lesions. Primary idiopathic intracranial hypertension occurs in obese women of childbearing age. Secondary pseudotumor cerebri causes a similar syndrome but is due to an offending agent such as medications (e.g., tetracycline, minocycline, lithium, fluoroquinolones, vitamin A–related medications, growth hormone), endocrine disorders (e.g., parathyroid dysfunction), and sleep apnea.

Idiopathic increased intracranial pressure occurs in 1 to 2 per 100,000 individuals but in 19 to 20 per 100,000 individuals (15 to 55 years of age) who are obese. Women are affected more frequently than men (6 to 8 : 1). Onset is usually in young adulthood.

The cause of the increased pressure is poor CSF absorption, as is thought to be the problem in idiopathic intracranial hypertension; venous hypertension, as is seen in venous thrombosis; or a mass that causes an increase in pressure. A genetic component is also likely because there are reports of the condition occurring in families.

CLINICAL MANIFESTATIONS

Idiopathic intracranial hypertension is characterized by headache in more than 90% of individuals, about 90% of whom are obese. The headache may be pulsatile and is frequently felt behind the eyes. Patients often report neck pain, upper back pain, or even radicular pain. The intensity of headache does not correlate with the height of the intracranial pressure. Pulse-synchronous tinnitus is a frequent accompaniment, as are transient visual obscurations and diplopia. Vision-specific quality of life is often reduced.

On examination, papilledema (Chapter 391, Fig. 391-25) may be found. The remainder of the general and neurologic examination is usually normal in patients with idiopathic intracranial hypertension, but abnormalities on examination may point to a secondary cause, such as underlying venous sinus thrombosis (Chapter 376), ischemic stroke, central nervous system infection (Chapters 381 and 382), or brain tumor (Chapter 175). Although idiopathic intracranial hypertension often persists for years, the condition can be self-limited.

DIAGNOSIS

The diagnosis of intracranial pressure is made by the symptoms and signs such as papilledema (Chapter 391, Fig. 391-25), but up to 40% of cases of presumptive intracranial hypertension are not confirmed by specialist evaluation, usually because of an initially inaccurate diagnosis of papilledema. MRI is necessary to exclude secondary causes of increased intracranial pressure. MR or CT venography is often needed to exclude venous sinus thrombosis (Chapter 376). LP must be performed unless patients have a contraindication such as an intracranial mass lesion, and CSF pressure should be measured. The diagnosis can be made if the pressure is elevated (CSF >250 mm H_2O) and the fluid itself is normal in terms of its protein level, glucose level, and cell count. Visual fields must be examined formally because visual acuity is not affected until late in the course of the disorder.

TREATMENT

Acetazolamide (doses ranging from 500 to 4000 mg daily) combined with a weight loss program is more efficacious for individuals with idiopathic intracranial hypertension and mild to moderate visual loss than is placebo.[A29] Any underlying secondary cause should also be treated (e.g., stopping an offending medication, treatment of sleep apnea [Chapter 374]). Weight loss is beneficial in obese subjects. If visual loss progresses, surgical procedures should be considered. Optic nerve sheath fenestration allows CSF to escape through slits or windows in the orbit; sometimes the treatment of one side decreases the optic disc swelling on the other side as well. Complications include visual loss or diplopia, so visual fields must be followed carefully to anticipate and prevent visual loss. Lumbar or ventricular peritoneal diversion procedures also reduce intracranial pressure, but their complications include infection and shunt obstruction. Venous sinus stenting has occasionally been used for fixed stenoses.[18]

PROGNOSIS

The prognosis of patients with idiopathic intracranial hypertension is good with treatment, but up to a third of inadequately treated patients can experience permanent defects of visual fields or loss of visual acuity from papilledema. Individuals are susceptible to recurrence if they suddenly gain weight.

INTRACRANIAL HYPOTENSION

Intracranial hypotension (or CSF hypovolemia) causes a headache that is characteristically better when the patient is supine and worse when the patient is upright. It can be primary (spontaneous) or secondary to another underlying cause, most commonly a previous LP.

Intracranial hypotension was once considered rare, but modern imaging techniques suggest an incidence of about five per 100,000 per year; it is slightly more common in women than men. The onset is usually at about 40 years of age, but it can occur in children and the elderly. Post-LP headaches occur more commonly but only infrequently persist.

PATHOBIOLOGY

The cause of primary intracranial hypotension is thought to be a small leak or tear in the dura, usually in the thoracic or lumbar region around cystic structures called Tarlov cysts. The cause of intracranial hypotension may not be the tear itself but rather the low CSF volume and low epidural venous pressure that assists in development of the lower pressure and hence the leak. The leaks frequently occur in the thoracic and cervicothoracic junction spine. Previous trauma history is reported in only one third of cases. Genetic and connective tissue disorders (e.g., Ehlers-Danlos syndrome, Marfan syndrome [Chapter 239]) may predispose individuals to have these leaks.

CLINICAL MANIFESTATIONS

Intracranial hypotension is characterized clinically by a positional headache, which is reported by 92% of patients.[19] The location of the pain is variable, and the most constant characteristic is the orthostatic change in the pain. If the leak is untreated for a long time, the headache may lose the orthostatic characteristic. Posterior neck pain can also occur. Changes in hearing, taste, and balance, as well as blurred vision and diplopia, can develop if hindbrain herniation occurs. If very severe hindbrain herniation occurs, changes in consciousness, subdural hygromas, ataxia, and pseudo-frontotemporal dementia can occur.

DIAGNOSIS

The diagnosis of intracranial hypotension is made by MRI showing pachymeningeal enhancement, venous engorgement, dural thickening, pituitary fossa enlargement, and herniation of the hindbrain (Fig. 367-2). Hindbrain herniation appears as a downward descent of the posterior fossa along with loss of the prechiasmatic cistern, flattening of the pons against the clivus, and descent of the cerebellar tonsils, which is often misconstrued as a Chiari I malformation. LP may also show low (<50 mm H_2O) CSF pressure, but it also may be normal. The diagnosis is most commonly made by clinical characteristics and imaging, so the decision as to whether or not to do an LP should be made on a case-by-case basis because there is at least a theoretical risk of more hindbrain herniation. The differential diagnosis includes new daily persistent headache, chronic migraine, or another secondary headache. The diagnosis is confirmed if a CSF leak is demonstrated by isotope studies, CT myelography, or MR myelography.[20]

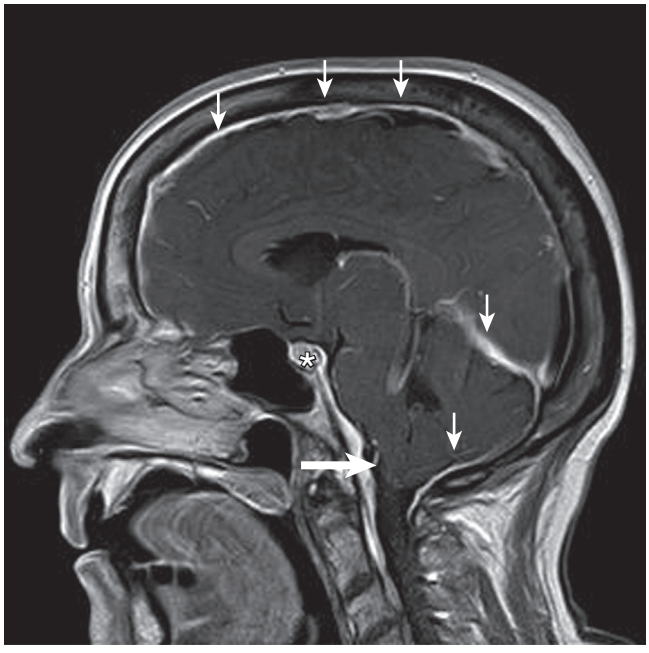

FIGURE 367-2. Intracranial hypotension. This 56-year-old woman had headaches that initially were positional. Gadolinium-enhanced magnetic resonance imaging shows characteristic findings of engorgement of the pituitary (*), slumping of the posterior fossa with tonsillar herniation (*large arrow*), and meningeal enhancement (*smaller arrows*).

TREATMENT AND PROGNOSIS

For spontaneous intracranial hypotension, the recommended treatment is bed rest and an epidural blood patch (blind or directed). Treatment of CSF leaks includes bed rest, caffeine (200 to 300 mg two to three times daily), an abdominal binder wrapped around the abdomen to increase central pressure, and generous intake of oral fluids. For post–dural puncture headache and most spontaneous episodes, an epidural blood patch usually improves the symptoms within days.[21] Surgical repair is rarely required. With treatment, the symptoms and MRI findings should resolve completely. Recurrence is infrequent.

REVERSIBLE CEREBRAL VASOCONSTRICTION

Reversible cerebral vasoconstriction syndrome is characterized by thunderclap headache (sudden onset and reaching peak intensity within ≤1 minute) that is associated with reversible vasospasm, benign or postpartum angiopathy, migrainous vasospasm, drug-induced cerebral arteritis, and sexual headache without primary angiitis or aneurysm.[22]

DIAGNOSIS

MR angiography, CT angiography, or digital subtraction angiography shows transient (<2 months) vasospasm. About 70% of patients have symptoms precipitated by drugs (e.g., cannabis, selective serotonin reuptake inhibitors, nasal decongestants, binge alcohol, steroids, ergots, triptans, cocaine, nicotine patches, other antidepressants), the postpartum period, strenuous physical exercise, or sexual activity.

TREATMENT AND PROGNOSIS

Prognosis is generally favorable, but seizure, hemorrhage, and brain infarction can occur. Acute treatment with intra-arterial calcium-channel blockers (e.g., nimodipine) or with oral verapamil (180 mg daily extended release, can titrate up to 480 mg daily) may be helpful.[23]

TRIGEMINAL NEURALGIA

Trigeminal neuralgia is a distinct, excruciatingly painful condition provoked by sensory stimuli in the distribution of the trigeminal nerve.[24] Trigeminal neuralgia occurs in 4 per 100,000 individuals, most commonly in persons between 50 and 70 years of age and in women slightly more than in men (1.5 : 1).

In younger individuals, multiple sclerosis (Chapter 380) can be associated with the condition. In older individuals, an ectatic artery in the vertebrobasilar system often causes the syndrome. The trigeminal nerve root entry zone is thought to be the site of pathology. Either demyelination or compression of this region increases the firing of trigeminal afferents. When a specific cause can be defined, the term *symptomatic trigeminal neuralgia* is often used.

CLINICAL MANIFESTATIONS

Trigeminal neuralgia pain is characteristically sharp, lancinating (shooting), and electric shock–like in the distribution of the trigeminal nerve: cheek (V2), chin or lower teeth (V3), and around the eye (V1). A combination of V2 and V3 is the most common. The paroxysms are brief—usually seconds but up to 2 minutes. Some patients have a dull and continuous interictal pain, whereas most have only staccato-like volleys of pain. Pain is usually triggered by stimuli such as touching the face, brushing the teeth, air moving across the face, or masticating food. Once a volley of pain is triggered, there is usually a refractory period in which pain will not occur.

DIAGNOSIS

Diagnostic criteria include paroxysmal attacks of pain persisting for a second to 2 minutes and affecting one or more divisions of the trigeminal nerve. To make the diagnosis, the pain must be intensely sharp, stabbing, or precipitated by a trigger. Each attack is stereotypical, and there are usually no other neurologic defects. Idiopathic trigeminal neuralgia by definition has no causative lesion, whereas symptomatic trigeminal neuralgia has a cause such as vascular compression of the trigeminal nerve root exit zone. The differential diagnosis includes trigeminal autonomic cephalgia, which has autonomic accompaniments that are not associated with trigeminal neuralgia. Atypical facial pain, idiopathic stabbing headache, and Tolosa-Hunt syndrome, an inflammatory syndrome of the anterior cavernous sinus, are also included in the differential. MRI is recommended to evaluate possible secondary causes of trigeminal neuralgia, such as demyelination, tumors, and vascular loops on the trigeminal nerve exit zone.

TREATMENT

Trigeminal neuralgia is treated with medications or surgery.[25,26] Carbamazepine (400 to 1200 mg) is considered the first-line agent for the neuralgia. Phenytoin (200 to 300 mg), baclofen (50 to 60 mg), clonazepam (2 to 6 mg), valproic acid (500 to 1500 mg), lamotrigine (100 to 400 mg), gabapentin (900 to 1800 mg), oxcarbazepine (300 to 1800 mg), levetiracetam 2 to 4 g), and topiramate (50 to 200 mg) are also used. Botulinum toxin may be effective for this disorder. Surgical treatments include microvascular decompression, which may alleviate the symptoms and preserve sensory function. Other treatments include partial destruction of the trigeminal nerve with heat (radio frequency lesions) or with glycerol (chemical destruction).

PROGNOSIS

Patients with trigeminal neuralgia can have spontaneous or medication-induced remissions. Microvascular decompression is often curative. In patients whose pain is triggered by mastication, weight loss and inanition may develop; prompt treatment is essential.

GLOSSOPHARYNGEAL NEURALGIA

Less common than trigeminal neuralgia, glossopharyngeal neuralgia is unilateral pain in the distribution of the glossopharyngeal and vagal nerves in the ear, jaw, throat, and base of the tongue. This neuralgia is rare, with a prevalence of less than 1 per 100,000. The cause is thought to be compression of the glossopharyngeal nerve by blood vessels, tumor, or aneurysm and demyelination or infection.

The pains are paroxysmal and persist for less than seconds to 2 minutes, but patients can experience 30 to 40 attacks in a day. As in trigeminal neuralgia, the pain is triggered by chewing, swallowing, or talking.

The diagnosis is made clinically. MRI should be done to evaluate the glossopharyngeal nerve to exclude a tumor or vascular abnormality. The differential diagnosis includes trigeminal neuralgia, geniculate neuralgia, and atypical pain syndrome.

Pharmacologic therapy is similar to that for trigeminal neuralgia, and carbamazepine (200 to 800 mg) is usually the drug of choice. Surgical therapy and microvascular decompression or radio frequency ablation should be considered in patients whose weight loss does not respond promptly to medication.

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368 TRAUMATIC BRAIN INJURY AND SPINAL CORD INJURY

JEFFREY J. BAZARIAN

ACUTE BRAIN AND SPINAL INJURY

EPIDEMIOLOGY

Traumatic brain injury and traumatic spinal cord injury are common preventable diseases. The majority of patients with traumatic brain and spinal cord injuries are young adult males. Hospitalization for traumatic brain injury is more common in urban areas, whereas brain injury-related deaths are more common in rural areas.[1]

An estimated 54 to 60 million people sustain a traumatic brain injury worldwide each year, and it is projected to become the third largest cause of disease burden worldwide by 2020. Low- and medium-income countries have nearly three times more traumatic brain injuries per capita than do high-income countries, with the greatest overall burden in Southeast Asia and the Western Pacific. The predominant mechanism of injury varies geographically, from road traffic accidents in Africa and Southeast Asia (both 56%) to violence in South America, the Caribbean, and sub-Saharan Africa. In the United States, traumatic brain injury results in over 2.5 million emergency department visits and 52,000 deaths each year, thereby making it the single leading cause of traumatic death and disability (Chapter 97). Between 2000 and 2015, over 300,000 soldiers were diagnosed with traumatic brain injury, and estimates of sports-related traumatic brain injury range from 1.6 to 3.8 million annually. The prevalence of traumatic brain injury in the U.S. population is estimated at 5 million, but the magnitude is likely greater because this injury is often underreported by patients and overlooked by acute care providers. Over 85% of all traumatic brain injuries are mild injuries, commonly known as concussions. The majority of traumatic brain injuries are due to falls (Chapter 24), motor vehicle accidents, and assaults.

The prevalence of spinal cord injury in the United States is estimated at about 240,000 to 350,000, with approximately 12,500 new severe spinal cord injuries occurring each year. About one third of all spinal cord injuries result in complete paraplegia or tetraplegia. Spinal cord injuries most commonly result from motor vehicle collisions, falls, assaults, and sports-related injuries (Chapter 97).

PATHOBIOLOGY

Primary Injury Phase

In traumatic brain injury, this phase refers to parenchymal injuries that result from the mechanical forces acting on the brain. These forces include direct linear acceleration as well as rotational acceleration due to movement of the head on the neck, which acts as a fulcrum for this rotation. Direct acceleration results in direct impact, which can damage parenchymal structures beneath the impact (with or without skull fracture), as well as structures on the opposite side as the brain recoils and strikes the inner aspect of the skull (coup-contrecoup lesion). Rapid head rotation puts stretch forces (i.e., strain) on neuronal axons and blood vessels, which are uniquely susceptible owing to their elongated microstructure. The result of these mechanical forces is axonal injury, intracranial hemorrhage, and disruption of the blood-brain barrier, all of which can contribute to an increase in the volume of intracranial contents. Because the brain is enclosed within the confines of a rigid skull, even a small increase in volume can raise intracranial pressure and result in reduced cerebral perfusion pressure, unless there is a compensatory increase in mean arterial blood pressure. This relationship is expressed by the following equation: cerebral perfusion pressure equals mean arterial pressure minus intracranial pressure.

In the uninjured brain, cerebral autoregulation keeps cerebral perfusion pressure relatively constant over a range of mean arterial pressures (50 to 170 mm Hg) to meet the brain's high metabolic demands. Autoregulation is accomplished primarily through dynamic control of cerebral blood flow and cerebrovascular resistance, which are related to cerebral perfusion pressure in the following way: cerebral blood flow equals cerebral perfusion pressure divided by cerebral vascular resistance. In the injured brain, this autoregulatory process is often impaired, such that sudden increases in mean arterial pressure may be directly translated to spikes in cerebral perfusion pressure, which can worsen existing hemorrhage or contribute to secondary hemorrhage. By comparison, decreases in mean arterial pressure can reduce cerebral perfusion pressure, thereby resulting in neuronal ischemia and necrosis, as well as brain edema.

Uncontrolled increases in intracranial pressure can cause swollen sections of brain tissue to herniate around or through rigid skull structures, such as the falx cerebri, the tentorium cerebelli, and the foramen magnum. High pressure contact with these structures compromises local blood flow and leads to tissue death. The most common brain herniation is uncal herniation, which results when the innermost aspect of the temporal lobe swells over the free edge of the tentorium cerebelli, thereby compressing the midbrain pyramidal tract and parasympathetic fibers in the oculomotor nerve. Herniation of the cerebellar tonsils through the foramen magnum compresses the medulla or pons against the odontoid process and can result in sudden death.

In spinal cord injury, this phase refers to injury to the cord and blood vessels as a result of direct mechanical forces on the vertebral column. These forces cause hemorrhage and edema at the site of injury.

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368 TRAUMATIC BRAIN INJURY AND SPINAL CORD INJURY

JEFFREY J. BAZARIAN

ACUTE BRAIN AND SPINAL INJURY

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PATHOBIOLOGY

Primary Injury Phase

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In spinal cord injury, this phase refers to injury to the cord and blood vessels as a result of direct mechanical forces on the vertebral column. These forces cause hemorrhage and edema at the site of injury.

ABSTRACT

Traumatic brain injury and spinal cord injury are potentially devastating injuries with far-reaching consequences for patients, families, and society at large. In this chapter, we review the epidemiology and pathobiology of both injuries and describe their clinical manifestations and diagnosis. The indications for plain radiography, computed tomography, and magnetic resonance imaging for each injury are presented. We also review the emerging role of blood-based biomarkers in the management of traumatic brain injury. The latest recommendations for monitoring and treating mild traumatic brain injury, severe traumatic brain injury, and spinal cord injury are presented. Finally, we review the prognosis and long-term outcomes for each injury.

KEYWORDS

spinal cord injury
traumatic brain injury
mild traumatic brain injury
concussion
severe traumatic brain injury

Secondary Injury Phase

The secondary injury phase of traumatic brain injury involves progression of axonal injury, a neuroinflammatory response, and reduced glymphatic clearance of potentially toxic metabolites, all taking place over days to weeks and even months post-injury. Progression of axonal injury involves shifts in ionic flux, destruction of intra-axonal structures, axonal swelling, and mitochondrial failure, with resulting loss of axonal transport and altered neurotransmission (E-Fig. 368-1). Affected neurons may undergo demyelination and/or apoptosis (programmed cell death). A neuroinflammatory response involving microgliosis starts within hours of injury and may continue for months or even years.

The secondary injury phase of traumatic spinal cord injury involves vasospasm and thrombosis of small arterioles, thereby resulting in extension of cord edema. After spinal cord injury, the process of neuronal degeneration is similar to what happens with traumatic brain injury. Injury-induced disruption of the blood-brain barrier allows elements of the peripheral immune system to instigate and sustain persistent abnormal neuroinflammation. The destruction of intra-axonal structures can result in release of neurotoxic proteins, such as beta-amyloid and phosphorylated tau, which accumulate because of reduced glymphatic clearance.

CLINICAL MANIFESTATIONS

Traumatic Brain Injury

The clinical hallmark of acute traumatic brain injury is an alteration in the level of consciousness, as indicated by a loss of consciousness, amnesia, confusion, and/or disorientation at the time of injury. Clinical manifestations vary depending on the severity of the injury.

Patients with mild traumatic brain injury (concussion) may experience a brief loss of consciousness (<30 minutes) or have a period of amnesia (repeating questions to providers) or confusion persisting for less than 24 hours.[2,3] The physical examination is notable for the absence of signs of increased intracranial pressure or brain herniation. Vomiting, seizures, or signs of skull fracture should raise suspicion for intracranial hemorrhage, which can occur in up to 5 to 10% of patients with mild traumatic brain injury.

Patients with moderate to severe traumatic brain injury have readily recognizable reductions in the level of consciousness, ranging from confusion to agitation to somnolence persisting for at least 24 hours.

More severe brain trauma is typically assessed by the Glasgow Coma Scale (Table 368-1), which measures eye opening, verbal response, and motor responses to spoken commands or tactile stimulation. The physical examination may reveal signs of elevated intracranial pressure such as Cushing reflex (increased blood pressure, bradycardia, and irregular respiratory rate), vomiting, and decorticate or decerebrate posturing. Signs of uncal herniation include an ipsilateral fixed and dilated pupil with contralateral motor paralysis, whereas cerebellar tonsillar herniation results in midsized unreactive or pinpoint pupils and flaccid paralysis. Signs of open/depressed skull fracture or basilar skull fracture (hemotympanum, cerebrospinal fluid rhino/otorrhea, periorbital ecchymosis, postauricular ecchymosis) are often associated with intracranial hemorrhage. Focal cerebral injury may manifest as seizures or focal limb weakness/numbness.

After resolution of the acute alteration in consciousness, most patients with traumatic brain injury experience one or more symptoms such as headache,[4] dizziness, difficulty with memory and concentration, difficulties with balance, and fatigue. These symptoms reflect axonal injury to functional brain networks regulating head and neck pain, sleep, mood, attention, short-term memory, vestibular function, and near vision. On physical examination, patients with traumatic brain injury may display abnormal postural stability, unsteady tandem gait, abnormal smooth pursuit or saccadic eye movements, abnormal vestibulo-ocular reflex, convergence insufficiency, or accommodative insufficiency. Neurocognitive testing may reveal deficits in immediate and delayed recall, concentration, information processing, executive functioning, and reaction time. In addition, patients who survive moderate-severe traumatic brain injury can have deficits of motor function, sensation, and language.

Traumatic Spinal Cord Injury

The three main spinal cord syndromes are Brown-Séquard, central cord, and anterior cord syndromes. In Brown-Séquard syndrome, the deficits are referable to a lesion of a lateral half of the cord; findings consist of loss of ipsilateral motor, touch, proprioception, and vibration sensation, as well as contralateral loss of pain and temperature sensation. Central cord syndrome is manifested as bilateral loss of motor function involving the upper extremities but sparing the lower extremities and is sometimes referred to as "man in a barrel syndrome." Proximal weakness is greater than distal weakness. Pain and temperature sensation is reduced, whereas proprioception and vibration are usually spared. Anterior cord syndrome is manifested by deficits referable to bilateral anterior and lateral spinal cord columns or funiculi. There is loss of touch, pain, and temperature sensation and motor function below the level of the lesion, but the posterior column functions of proprioception and vibratory sensation remain intact.

After acute traumatic spinal cord injury, patients may suffer from spinal shock or temporary loss of spinal reflexes below the level of injury, including loss of muscle stretch reflexes, the bulbocavernosus reflex, and the anal wink. In high cervical injuries, the lower reflexes (bulbocavernosus reflex and anal wink) may be preserved. Some patients demonstrate the Schiff-Sherrington phenomenon, in which reflexes are affected above the level of injury. Patients with spinal shock also may lose autonomic reflexes, thereby leading to neurogenic hypotension, peripheral vasodilation, ileus, and urinary retention. If the lesion is at T3 or above, sympathetic tone to the heart is compromised. In this setting, hypotension is accompanied by bradycardia, thus producing dysautonomia and the neurogenic shock triad of bradycardia, hypotension, and peripheral vasodilation.

DIAGNOSIS

Traumatic Brain Injury

The diagnosis of traumatic brain injury is primarily clinical. Two necessary elements are experiencing an injury and having an alteration in the level of consciousness (confusion, disorientation, amnesia, loss of consciousness) at the time of injury.[5] Physical examination and neuroimaging can substantiate the initial clinical impression and determine the severity of the injury, but neither is sensitive enough to exclude traumatic brain injury. Alterations in the level of consciousness are readily recognized in severe traumatic brain injury but are more difficult to detect in milder forms. A standardized protocol (Table 368-2) can help first responders identify more subtle alterations in the level of consciousness.

TABLE 368-1 GLASGOW COMA SCALE SCORE

BEST MOTOR RESPONSE	BEST VERBAL RESPONSE	BEST EYE OPENING
1 = No motor response	1 = No verbal response	1 = No eye opening
2 = Extension to pain	2 = Incomprehensible sounds	2 = Eye opening to pain
3 = Flexion to pain	3 = Inappropriate words	3 = Eye opening to verbal command
4 = Withdrawal from pain	4 = Confused	4 = Eyes open spontaneously
5 = Localizes pain	5 = Oriented	
6 = Obeys commands		

To calculate the score, sum the numbers from each of the three columns. A score of 3-8 indicates a severe head injury, 9-12 indicates moderate injury, and 13-15 is classified as mild injury.

TABLE 368-2 STANDARDIZED ASSESSMENT OF CONCUSSION

TASK	POSSIBLE SCORE
ORIENTATION	
Month, date, day of week, year, time (1 point for each correct answer)	0-5
IMMEDIATE MEMORY	
Patient repeats a five-word list spoken by examiner; three trials (1 point for each word correctly remembered)	0-15
CONCENTRATION	
Digits backward; three-, four-, five-, and six-digit strings (1 point for each digit string correctly repeated backward)	0-4
Months of the year in reverse order (1 point for repeating backward in correct sequence)	0-1
DELAYED MEMORY RECALL	
Patient repeats the five words from Immediate Memory test (1 point for each word correctly recalled)	0-5
TOTAL SCORE	0-30

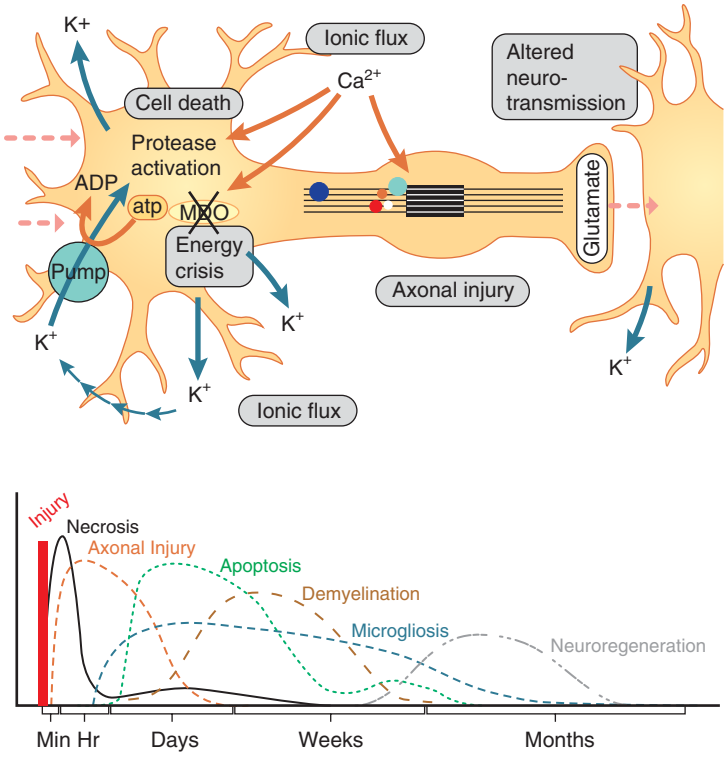

E-FIGURE 368-1. **Axonal injury (*top*) and time course of traumatic brain injury pathobiologic events (*bottom*).**

The Glasgow Coma Scale score (see Table 368-1) should be calculated to estimate the severity of the traumatic brain injury.

Biomarkers and Imaging

All patients with a Glasgow Coma Scale score (see Table 368-1) below 15 should have a noncontrast computed tomography (CT) scan of their head to detect clinically important intracranial injuries such as trauma-related fractures, hemorrhage, and brain tissue swelling. Early detection of expanding hemorrhage is key for rapid neurosurgical decompression, which can be lifesaving. For patients with a Glasgow Coma Scale score of 15, in whom the prevalence of intracranial injury is less than 10%, clinical decision rules can be used to identify high-risk patients in need of head CT scanning (Table 368-3). Typical postinjury CT findings include subdural hematoma (Fig. 368-1), epidural hematoma, intraparenchymal hemorrhage, contusion, and traumatic subarachnoid hemorrhage (Chapter 377). An associated skull fracture, especially at the temporoparietal junction, increases the likelihood of epidural hematoma, usually by disruption of the middle meningeal artery. Magnetic resonance imaging (MRI) is a more sensitive test that can detect subtle changes not visible on CT. Most patients with mild traumatic brain injury will have normal neuroimaging, because axonal injury is largely invisible on CT and standard MRI. However, susceptibility weighted MRI can detect microhemorrhages, and diffusion tensor imaging can visualize disrupted white matter tracts.

Elevations in blood-based brain biomarkers (e.g., ubiquitin carboxyl-terminal hydrolase isozyme L1 precursor and glial fibrillary acid protein) can aid in the decision to obtain a head CT scan in patients with mild traumatic brain injury.[6] Used in combination (i.e., a positive test is defined by an elevation of either or both proteins, whereas a negative test is defined by neither protein being elevated), these proteins have a sensitivity of about 98% and specificity of 99.6% for predicting the presence of traumatic intracranial lesions on CT.

Traumatic Spinal Cord Injury

A detailed neurologic examination is needed to identify the level of the injury and the severity of any deficits, as well as to document the degree of neurologic dysfunction at the earliest time possible. The level of the injury is the lowest spinal cord segment with intact motor and sensory function. Normal neurologic findings in patients with a clear sensorium obviate the need for imaging studies. However, any complaints of pain over the spine, numbness, tingling, or weakness should raise suspicion of spinal cord injury. In particular, a complaint of "burning hands" suggests traumatic spinal cord injury.

The time of injury should be recorded as accurately as possible. The prognosis for neurologic improvement is better if the lesion is incomplete as opposed to complete. During the acute period, serial examinations must be performed frequently.

If spinal cord injury is suspected, the patient should be appropriately immobilized, such as with a rigid collar and back board. In patients who are able to cooperate with a neurologic examination, are not intoxicated, and do not have painful distracting injuries (e.g., femoral fracture, which would interfere with the leg motor and sensory examination), normal neurologic findings effectively exclude cervical spinal cord disease.

TABLE 368-3 DECISION RULES FOR DETERMINING THE NEED FOR A COMPUTED TOMOGRAPHY (CT) SCAN IN HEAD-INJURED ADULTS

INDICATION FOR CT SCANNING	CANADIAN	NEW ORLEANS	ACEP
GCS	<15 at 2 hr	<15	<15
Amnesia	Retrograde >30 min	Anterograde	Any
Suspected skull fracture	Yes	Yes	Yes
Vomiting	Recurrent	Any	Any
Age	≥65	>60	>60*
Coagulopathy	—	—	Yes
Focal deficit	—	—	Yes
Seizure	—	Any	Yes
Loss of consciousness	If GCS = 14	—	Yes?
Visible trauma above the clavicles	—	Any	Any
Headache	—	Yes	Yes
Dangerous injury mechanism†	Yes	—	Only if no LOC
Suspected intoxication	—	Drug, alcohol	Drug, alcohol
Sensitivity/specificity‡	0.99/0.51	0.99/0.33	Unknown

*Age >65 if no loss of consciousness; otherwise, positive only if loss of consciousness or amnesia.
†Pedestrian vs. motor vehicle, ejection from motor vehicle, fall from height >1 m or five stairs.
‡For detection of traumatic intracranial injury on head CT scan.
ACEP = American College of Emergency Physicians; GCS = Glasgow Coma Scale; LOC = loss of consciousness.

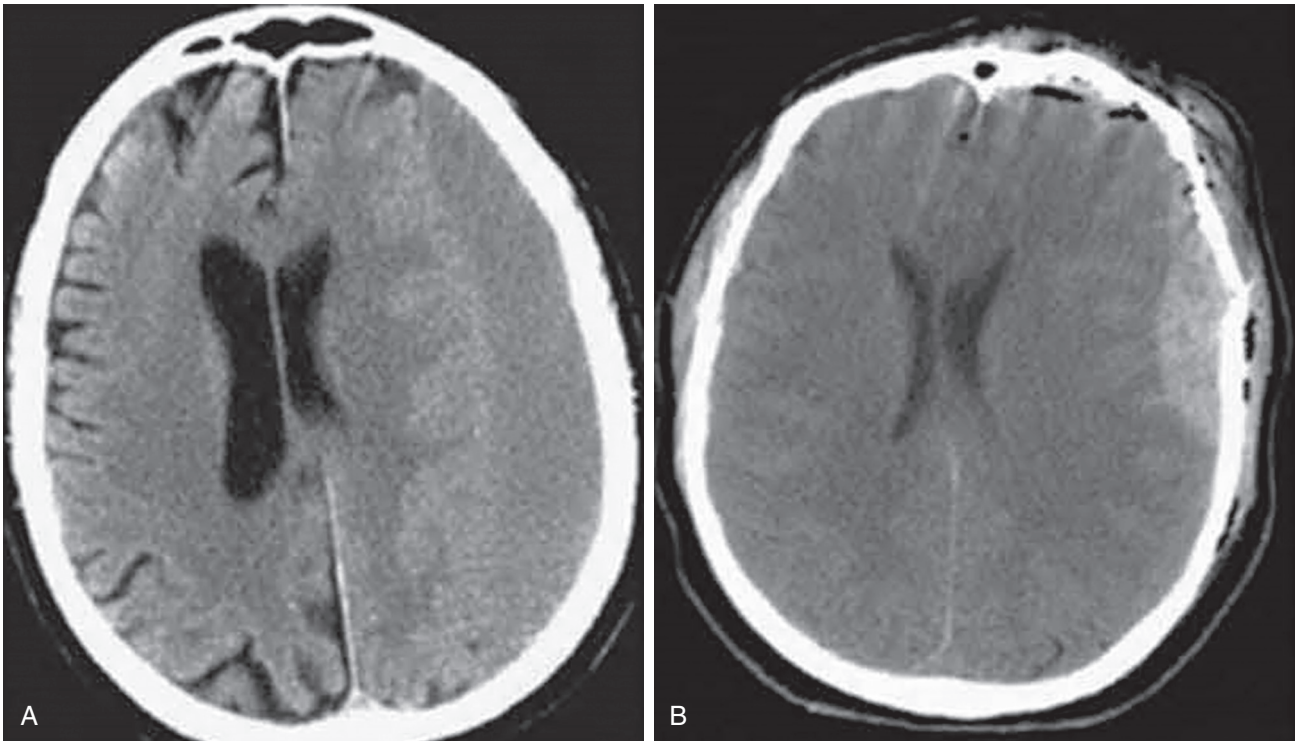

FIGURE 368-1. Computed tomography image of (A) subdural hematoma and (B) epidural hematoma.

Spine Imaging

In patients who are alert and stable, the Canadian C-Spine Rule (Fig. 368-2) can be used to reduce unnecessary spinal imaging without any adverse effect on patients' outcomes. In other patients, the radiologic evaluation should begin with plain radiographs of the bony spine, with further neuroimaging of any abnormalities that are found. Bony vertebrae should be examined with CT, whereas the spinal cord and intervertebral and paravertebral soft tissue are best studied with MRI. After blunt trauma, negative results from a well-interpreted, high-quality CT scan is probably a safe and efficient way to exclude cervical spine injury in obtunded patients. A chest radiograph is usually indicated to provide images of the lower cervical and thoracic vertebrae; the presence of a pleural effusion in the setting of a possible thoracic spine injury suggests a hemothorax.

Ligamentous Injury versus Spinal Cord Injury

If plain radiographs and CT of the cervical spine are normal but the patient still complains of neck pain, a ligamentous injury should be considered. Patients should be kept in a rigid cervical collar until one of the following conditions is met: (1) pain and muscle spasm resolve, (2) dynamic flexion/extension radiographs are normal, or (3) MRI obtained within 48 hours of injury is normal. Abnormal imaging or persistent pain warrant surgical evaluation to determine whether further immobilization or surgical correction is necessary.

TREATMENT

Traumatic Brain Injury

The approach to treatment varies based on the severity of the injury.[7]

Mild Traumatic Brain Injury

For mild traumatic brain injury, the acute treatment priority is identification of those at risk for traumatic intracranial injuries such as hemorrhage or edema. Patients who have intracranial injury on head CT scan should be evaluated by a neurosurgeon and observed in a hospital setting for neurologic deterioration or expansion of the hematoma. Patients without intracranial injury or at low risk for it can be managed as an outpatient but should be removed from play or work for 1 to 2 days if they have persistent symptoms.[8,9] Patients who have had a concussion should not return to work or school until a detailed evaluation with written authorization can be made by an appropriately experienced physician. Postacute treatment is focused on managing symptoms and returning patients to their baseline activity level.[A1] Most patients with mild traumatic brain injury will experience one or more postconcussive symptoms such as headache, dizziness, difficulty with memory and concentration, difficulties with balance, and fatigue. Despite a common belief that mild traumatic brain injury is not a treatable injury, targeted, symptom-based treatments (Table 368-4) can improve head and neck pain, cognition, vestibular function, near vision, and overall recovery.[A2]

Moderate to Severe Traumatic Brain Injury

For moderate to severe traumatic brain injury, early appropriate management must begin in the prehospital and emergency department settings.[10] The goals of initial treatment are to maintain cerebral perfusion pressure and to limit secondary injury phase insults such as hypotension, hypoxia, and hypercapnia.[11,12] Even a single episode of hypotension or hypoxia can increase mortality by 2.5-fold, whereas adherence to guidelines is associated with improved outcomes.[13]

Immediate treatment begins with stabilization of the airway, breathing, and circulation. Patients with a Glasgow Coma Scale score <8 should undergo rapid sequence intubation to protect the airway and to provide adequate ventilation (Pco_2 35 to 45 mm Hg) and oxygenation. Hypotension should be aggressively corrected. Because rapid identification and neurosurgical evacuation of intracranial hemorrhage can be lifesaving, immediate transport to a facility with a CT scanner and providers capable of managing traumatic brain injury is recommended. Not all patients with intracranial hemorrhage require neurosurgery, and indications for surgical decompression vary depending on the type of hemorrhage. A small proportion (<10%) of patients (especially patients with a history of alcohol abuse, multiple falls, or use of anticoagulants) who do not meet criteria for urgent surgery require delayed surgical intervention when they later develop increased intracranial pressure or have a new seizure.

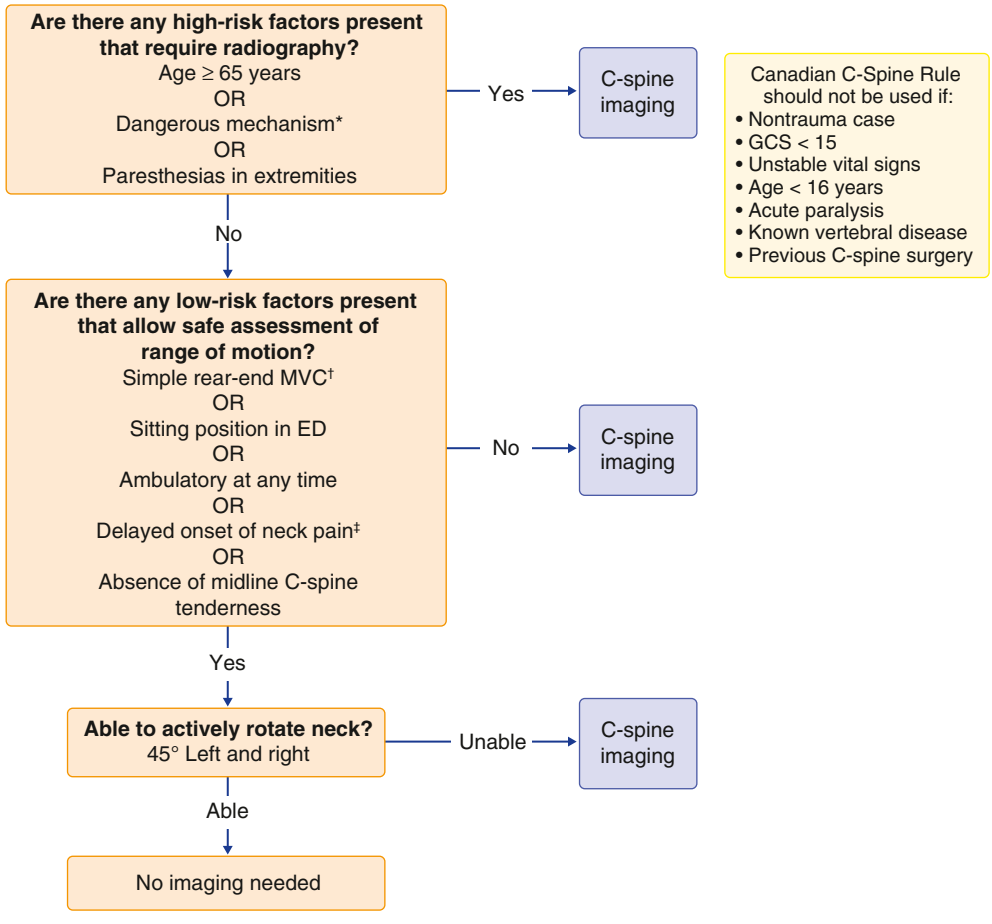

FIGURE 368-2. **Canadian C-Spine Rule, for alert (Glasgow Coma Scale ≥15) and stable trauma patients in whom cervical spine injury is a concern.** *Dangerous mechanism: fall from elevation ≥3 ft/5 stairs, axial load to head (e.g., diving), MVC high speed (>100 km/hr), rollover, ejection, motorized recreational vehicles, bicycle struck or collision. †Simple rear-end MVC excludes: pushed onto incoming traffic, hit by bus/large truck, rollover, hit by high-speed vehicle. ‡Delayed: i.e., not immediate onset of neck pain. ED = emergency department; GCS = Glasgow Coma Scale (see Table 368-1); MVC = motor vehicle collision. (Modified from Stiell IG, Clement CM, McKnight RD, et al. Comparative validation of the Canadian C-Spine Rule and the NEXUS low-risk criteria in alert and stable patients. *N Engl J Med*. 2003;349:2510-2518; Stiell IG, Wells GA, Vandemheen KL, et al. The Canadian C-Spine Rule for radiography in alert and stable trauma patients. *JAMA*. 2001;286:1841-1848.)

TABLE 368-4 ASSESSMENT AND TREATMENT RECOMMENDATIONS FOR MILD TRAUMATIC BRAIN INJURY

FUNCTION	ASSESSMENT	TREATMENT
Overall recovery	Standardized symptom checklist	Physical rest 1-2 days followed by subsymptomatic aerobic exercise
Headache	Determine the type (Chapter 367)	HA persisting more than 3-4 days may require abortive treatment tailored to phenotype (e.g., migraine, tension-type, occipital neuralgia) (Chapter 367)
Vertigo	Romberg test, dynamic standing, tandem gait (see Chapter 396)	If Dix Hallpike test (see Chapter 396) is normal or if Epley maneuver (Fig. 396-4) does not relieve symptoms, consider physical therapy for vestibular rehabilitation
Eye movements	Examine cranial nerves III, IV, VI for tracking, saccades, diplopia, nystagmus (Chapter 392)	Physical therapy evaluation for vestibular rehabilitation
Near vision	Near-point accommodation and binocular convergence	Ophthalmologic evaluation for vision therapy
Cognitive function	Symptoms, cognitive testing, neuropsychology evaluation (Chapters 361 and 371)	Sleep hygiene, neuropsychology evaluation for cognitive rehabilitation

HA = headache.

The goals of the postimmediate injury phase, regardless of the need for neurosurgery, are to maintain adequate cerebral perfusion pressure in an intensive care setting by monitoring and treating elevated intracranial pressure (as well as hypotension, hyperglycemia, hyperthermia, and anemia) and to avoid secondary medical complications (Table 368-5). Despite major research efforts, current clinical treatment is largely confined to supportive measures: maintaining cerebral perfusion pressure, minimizing intracranial pressure, and indirectly treating edema with mannitol or hypertonic saline.[A3] However, a continuous infusion of hypertonic saline does not improve 6-month outcomes compared with standard care.[A4] Elevated intracranial pressure that does not respond to these interventions is an ominous sign. In such cases, bifrontotemporoparietal craniectomy can reduce intracranial pressure and the length of stay in an intensive care unit but has not been shown to improve outcomes significantly,[A5] with about a 20% increase in overall survival but only about a 10% increase in survival without severe disability at 24 months.[A6] Neither prehospital tranexamic acid[A7] nor postinjury prophylactic hypothermia are beneficial.[A8]

Traumatic Spinal Cord Injury

Initial Management

As with traumatic brain injury, early appropriate management of spinal cord injuries in the prehospital and emergency department settings can play a critical role in outcome.[14] A key principle in early management is to presume that patients with a trauma mechanism and neck pain or altered level of consciousness have an unstable spinal injury. The goal of initial treatment is to prevent movement of potentially unstable vertebral column elements, such as bone fractures or herniated intervertebral discs that can compress and damage the spinal cord. Immediate care for spinal injuries involves stabilization of airway, breathing, and circulation while simultaneously immobilizing the entire spine with a rigid cervical or manual in-line spine stabilization. A long back board is typically used to provide additional spinal stability.

Cervical lesions above C5 and sometimes below C5 are associated with impaired respiratory capability, so rapid sequence intubation with manual in-line cervical spinal stabilization is required if there is any concern that ventilatory effort is compromised. Hypotension can be the result of either neurogenic shock or hypovolemia. In patients who are hypotensive but warm and bradycardic because

TABLE 368-5 MONITORING AND TREATMENT RECOMMENDATIONS FOR SEVERE TRAUMATIC BRAIN INJURY*

MONITORING	INDICATION AND/OR RECOMMENDATION
Intracranial pressure (ICP)	GCS ≤8 *AND* abnormal head CT† *OR* any two of the following: age >40, motor posturing, SBP <90 mm Hg. Treatments should aim to keep ICP ≤22 mg Hg.
Cerebral perfusion pressure (CPP)	Treatments should aim for a CPP of 60-70 mm Hg.
Advanced cerebral monitoring	Jugular bulb monitoring of AV oxygen difference. Treatments should aim to keep venous saturation ≥50%.
Systolic blood pressure (SBP)	Treatments should aim to keep SBP ≥110 mm Hg in those 18-49 and >70 yr old, ≥100 mm Hg in those 50-69 yr old.
TREATMENT	
Decompressive craniectomy	Not recommended to improve outcome, but may shorten ICU stay and result in fewer ICP-targeting interventions.
Prophylactic hypothermia	Does not improve outcome.
Hyperosmolar therapy	Mannitol for signs of herniation or progressive neurologic deterioration.
CSF drainage	Within first 12 hr in those with GCS <6. Continuous drainage is better than intermittent.
Ventilation	Short-term hyperventilation can be used to reduce elevated ICP, but avoid in the first 24 hr after injury. Prolonged hyperventilation with $Paco_2$ ≤25 mm Hg is not recommended; if used, monitor jugular venous saturation.
Sedation	Propofol to control ICP. High-dose barbiturate administration is restricted to ICP refractory to standard surgical and medical treatments.
Corticosteroids	Not recommended (high-dose methylprednisolone is associated with increased mortality risk).
Nutrition	Achieving basic caloric replacement by postinjury day 5-7 to reduce mortality risk. Transgastric jejunal feeding tube reduces ventilator-associated pneumonia.
Prophylactic antibiotics	Povidone-iodine oral care does not reduce ventilator-associated pneumonia. Antimicrobial-impregnated catheters may prevent catheter-related infections during external ventricular drainage.
DVT prophylaxis	LMWH or low-dose unfractionated heparin may be used (in combination with compression stockings) if the traumatic brain injury is stable and the benefit outweighs the increased risk of intracranial hemorrhage expansion.
Seizure prophylaxis	Phenytoin to prevent early post-traumatic seizures (within 1 wk of injury), although early seizures are not associated with worse outcome; antiepileptic drugs are not recommended to prevent late seizures.

*Brain Trauma Foundation Guidelines.
†Hematoma, contusion, swelling, herniation, or compressed basal cisterns.
AV = arteriovenous; CSF = cerebrospinal fluid; CT = computed tomography; DVT = deep venous thrombosis; GCS = Glasgow Coma Scale; ICU = intensive care unit; LMWH = low-molecular-weight heparin.

of neurogenic shock from the loss of sympathetic innervation to peripheral arteries and the heart, vasopressive agents such as phenylephrine (beginning as a continuous IV infusion at 100 µg/min with titration to clinical effect) may be needed. Patients who are hypotensive because of hypovolemia are cold and tachycardic, and they require fluid resuscitation (Chapter 92). Methylprednisolone is no longer advocated for the treatment of acute spinal cord injury.[A9]

The goals of treatment in the postimmediate injury phase are to preserve the structural integrity of as much of the spinal cord as possible by alleviating cord compression, establishing spinal stability, and preventing secondary injury. Spine imaging, which is required to determine the need for surgical intervention, should only take place after the airway, breathing, and circulation have been stabilized. Surgical intervention within 8 hours or, at most, 24 hours[15] is targeted to provide stability of the anterior column (anterior half of the vertebral body and the vertebral disc), middle column (posterior half of the body and disc), and posterior column (the arch, facets, and ligaments). In general, if two of the three columns are damaged, surgical stabilization is needed.

If immediate surgery is not indicated, the patient should be admitted to the intensive care unit for further management. The subacute management of patients with severe spinal cord injury involves close cardiovascular and ventilatory care, supportive care for bladder and bowel function, approaches to avoid pressure ulcers,[16] and general measures similar to those used for patients with traumatic brain injury.

Supportive Care

Ventilatory Support

Not all patients intubated during the immediate postinjury phase require long-term ventilatory support. However, if the patient does not show signs of ventilatory recovery within 2 weeks of intubation, a tracheostomy should be considered. For patients with intact diaphragm function, as determined by a positive "sniff" test under fluoroscopy, pressure support ventilation may be sufficient (Chapter 91).

Thromboembolic Disease

Thromboembolic disease (Chapter 68) is a leading cause of morbidity and mortality after traumatic spinal cord injury. Prolonged immobility of the lower extremities leads to deep venous thrombosis in up to 70% of spinal cord–injured patients. Patients should receive prophylaxis with low-molecular-weight heparin (e.g., enoxaparin 30 mg twice daily subcutaneously) within 72 hours of injury (Chapter 70). Anticoagulation can be held on the day of surgery but should be resumed 24 hours after surgery. A less effective alternative is intermittent compression devices (e.g., pneumatic stockings) with low-dose unfractionated heparin. Early prophylactic placement of an inferior vena cava filter does not reduce the risk of pulmonary embolism, even in patients with contraindications to anticoagulation, and the potential benefit of a prophylactic inferior vena cava filter is uncertain in patients who cannot be anticoagulated within 1 week.[A10]

Visceral Function and Nutrition

For ileus, a nasogastric tube should be placed to decompress the stomach. Parenteral nutrition (Chapter 198) should be started as soon as possible and continued until gastrointestinal motility returns, usually within 2 to 3 weeks, and enteral feeding can begin.

Decubitus Ulcers

Patients with traumatic spinal cord injury often develop decubitus ulcers and pressure sores (Chapter 24). Mechanical kinetic beds, regular log rolling (every 2 hours), and padded orthotics are all useful for minimizing this complication.

PROGNOSIS

Traumatic Brain Injury

Mild Traumatic Brain Injury

Most patients with mild traumatic brain injury make a full recovery within 3 months. However, symptoms persist for longer than 3 months in 15 to 20% of such patients, with some experiencing symptoms for several years. These persisting postconcussion symptoms, which are similar to the subacute symptoms of concussion, include headaches,[17] altered mood, and sleep disturbances.

Even a single mild traumatic brain injury is associated with increased risk of later development of symptoms resembling Alzheimer disease. Individuals who have sustained moderate to severe traumatic brain injury are four times more likely to develop dementia than are people without traumatic brain injury.[18] Mounting evidence indicates a clear association between repetitive head hits sustained in contact sports and a form of early-onset dementia called chronic traumatic encephalopathy. For example, recurrent subclinical brain trauma in military personnel[19] and soccer players is associated with neurodegeneration. Symptoms of chronic traumatic encephalopathy include memory loss, confusion, impaired judgment, impulse control problems, aggression, depression, anxiety, suicidality, parkinsonism, and, eventually, progressive dementia. As with Alzheimer disease–like dementia, the symptoms of chronic traumatic encephalopathy often begin years after the last head impact. Individuals with one or more E4 alleles of the apolipoprotein E genes may be at particular risk for postinjury neurodegenerative disease.

Moderate to Severe Traumatic Brain Injury

The most useful prognostic indicators after traumatic brain injury are the Glasgow Coma Scale and the neurologic examination at the initial evaluation. For patients with moderate to severe traumatic brain injury, the lower the initial Glasgow Coma Scale score, the less likely a patient will have meaningful neurologic or functional recovery; 40% of patients with a score of 8 have a good recovery versus only 7% when the score is 3. Furthermore, only 27% of patients with a score of 3 survive versus 88% of patients with a score of 8. Patients in whom the Glasgow Coma Scale score remains the same or worsens over a period of 6 hours do worse clinically than those whose score improves. Further prognostic stratification at 24 hours can be based on pupillary responses, motor responses, and age (Chapter 373), as well as on biomarkers such as ubiquitin C-terminal hydrolase levels.[20] Among unresponsive patients, the detection of brain activation on EEG portends about a 45% chance of regaining independent function at 12 months. Of patients who survive for 3 to 5 years after traumatic brain injury, approximately 6% will have severe disability, 18% will have moderate disability, and 75% will have a good recovery. Most clinical recovery occurs during the first 6 months, although significant recovery can take place up to 2 years after the injury.

Traumatic Spinal Cord Injury

After traumatic spinal cord injury, the completeness of the injury is the most useful prognostic predictor (Table 368-6), and complete motor and sensory deficit below the lesion has a poor prognosis.[21] If a complete paralysis persists more than 72 hours, there is little likelihood of meaningful recovery.

Conversely, even severe partial injuries have a higher probability of recovery. If some sensory function is preserved, the chance that the patient will eventually be able to walk is >50%. Most patients initially show some improvement but usually do not continue to improve after 2 years.[22] Ultimately, 90% of spinal cord injury patients return to their homes and regain independence.

POST-TRAUMATIC HEMATOMAS

SUBDURAL HEMATOMA

Acute Subdural Hematoma

EPIDEMIOLOGY AND PATHOBIOLOGY

Acute subdural hematoma is caused by sudden deceleration of brain parenchyma with subsequent tearing of the bridging veins extending from the cerebral cortex to the dural-venous sinuses. Blood, which collects between the dura mater and the arachnoid mater, can gradually expand, thereby raising intracranial pressure and compressing vital brain structures. Acute subdural hematomas occur in approximately 11% of all traumatic brain injuries and are more common in males and adults between 31 and 47 years of age. Other risk factors include alcohol use disorder, cerebral atrophy, and impaired blood clotting, particularly the use of anticoagulant or antiplatelet medications. Motor vehicle collisions and falls are the most common injury mechanisms.

TABLE 368-6 AMERICAN SPINAL INJURY ASSOCIATION IMPAIRMENT SCALE

GRADE	INJURY TYPE	DEFINITION	LIKELIHOOD OF RECOVERY*
A	Complete	No motor or sensory function below the lesion	15.5% (cervical) and 7% (thoracic)
B	Incomplete	Sensory but no motor function	47%
C	Incomplete	Some motor strength (<3)	84%
D	Incomplete	Motor strength >3	84%
E	None	Sensory and motor function normal	100%

*Data from Coleman WP, Geisler FH. Injury severity as primary predictor of outcome in acute spinal cord injury: retrospective results from a large multicenter clinical trial. *Spine J*. 2004;4:373-378.

CLINICAL MANIFESTATIONS AND DIAGNOSIS

Up to 80% of patients with acute subdural hematoma present with an initial Glasgow Coma Scale score <8 (see Table 368-1), and up to half have pupillary abnormalities. Most patients present with symptoms within minutes of injury, but sometimes symptoms can be delayed for up to 2 weeks after injury.

Diagnosis is made by head CT scan showing a hyperdense, crescent-shaped mass with the concave surface away from the skull, most frequently located around the sides and top of the frontal and parietal lobes (see Fig. 368-1A).

TREATMENT AND PROGNOSIS

Surgical decompression is recommended for hemorrhage thickness >10 mm or associated with a midline shift >5 mm on CT scan, regardless of the Glasgow Coma Scale score, or a smaller hemorrhage associated with a Glasgow Coma Scale score <9 but accompanied by one or more of the following criteria—a 2-point decrease in the Glasgow Coma Scale score, an intracranial pressure >20 mm Hg, or signs of herniation (pupillary asymmetry).[23] Postoperative seizures are relatively common. A nonsurgical approach can be considered in patients who do not meet criteria for surgery, but a small proportion (about 6%) may later require surgery, usually for raised intracranial pressure or progression of the hematoma.

Acute subdural hematomas have a relatively high mortality rate, ranging from 50 to 90%. Because they are often associated with underlying parenchymal brain injury, only about 20 to 30% of patients recover full or partial brain function after an acute subdural hematoma.

Chronic Subdural Hematoma

EPIDEMIOLOGY AND PATHOBIOLOGY

Signs and symptoms of subdural hematoma developing 2 weeks or more after injury are referred to as a chronic subdural hematoma, but no obvious antecedent injury is identified in about 50% of patients.[24] Chronic subdural hematomas are thought to result from an initial mechanical insult (such as trauma) that splits open the dural border cell layer, thereby leading to reactive inflammation and the release of angiogenic factors. These processes in turn lead to the creation of an inflammatory membrane containing fragile blood vessels that exude blood, fibrinolytic factors, and inflammatory mediators. Risk factors include age over 65, alcohol abuse disorder, and use of anticoagulant or antiplatelet medication.

CLINICAL MANIFESTATIONS AND DIAGNOSIS

Symptoms, which can be vague or subtle but usually reflect gradually increasing intracranial pressure, include headache, new seizures, confusion, drowsiness, and difficulty walking. Diagnosis is made by CT scan with intravenous contrast or MRI. On CT, a chronic subdural hematoma appears hypodense (dark) because the iron in the blood has been metabolized (Fig. 368-3).

TREATMENT AND PROGNOSIS

Surgical evacuation is recommended for symptomatic patients with clinical or radiographic evidence of cerebral compression, and 10 to 20% of patients will require repeat surgery because of recurrent hemorrhage. Irrigation with fluids at body temperature is superior to irrigation with fluids at room temperature for reducing recurrences.[A11] Asymptomatic patients with and without cerebral compression can often be managed without surgery. Corticosteroids are not beneficial,[A12] and prophylactic anti-epileptic drugs are not recommended.[25] Embolization of the middle meningeal artery,[26] antifibrinolytic agents, and statins are currently under investigation as potential adjuvant therapies but are not currently recommended for routine clinical use. Mortality rates from chronic subdural hematomas vary but are generally less than 30%. Over 80% of survivors will have good or complete 6-month functional recovery.

EPIDURAL HEMATOMA

Intracranial Epidural Hematoma

EPIDEMIOLOGY AND PATHOBIOLOGY

An epidural hematoma results from mechanical disruption of the middle meningeal artery or dural venous sinus by a temporal bone fracture. Blood, which collects in the potential space between the inner table of the skull and the outer layer of the dura mater, can expand rapidly and compress vital brain structures. This life-threatening injury, which requires rapid diagnosis and surgical evacuation for a good outcome, occurs in approximately 2% of all traumatic brain injuries and is more common in males as well as in adolescents and young adults. Unlike subdural hematomas, epidural hematomas are uncommon after the age of 50 years.

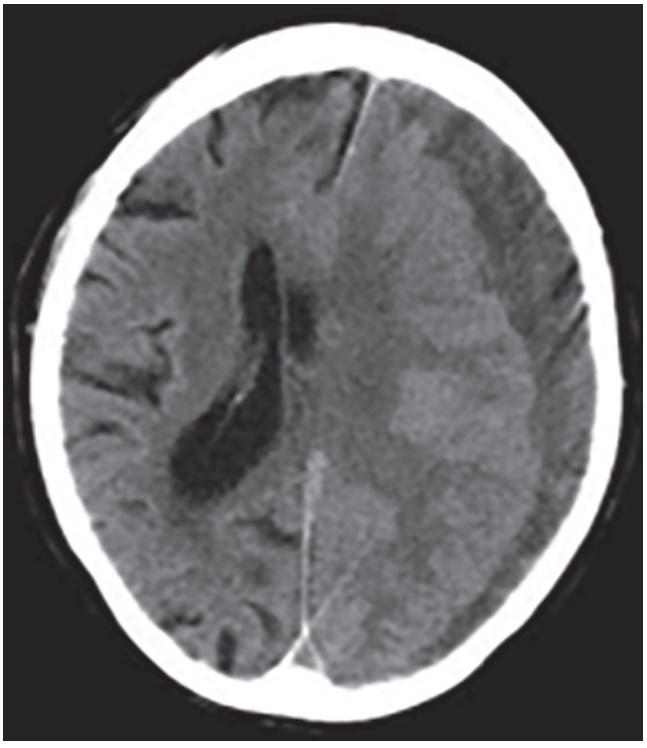

FIGURE 368-3. Left temporal-parietal chronic subdural hematoma, appearing hypodense on a computed tomographic scan. Ventricular compression and midline shift can also be seen. (Reproduced from Kotwica Z, Saracen A, Dziuba I. Chronic subdural hematoma [CSH] is still an important clinical problem. Analysis of 700 consecutive patients. *Transl Neurosci*. 2019;10:260-263.)

CLINICAL MANIFESTATIONS AND DIAGNOSIS

The typical clinical presentation involves an initial loss of consciousness followed by a lucid period and subsequently by rapid neurologic deterioration. However, this presentation occurs in less than 20% of all patients with epidural hematomas. Patients may also display signs of raised intracranial pressure, such as vomiting, ipsilateral pupillary dilatation, elevated blood pressure, slowed heart rate, and irregular breathing. The high-pressure arterial bleeding of an epidural hematoma can lead to herniation within hours of injury. The diagnosis is based on head CT scan showing a biconvex or lens-shaped mass, typically in the temporal region (see Fig. 368-1B).

TREATMENT AND PROGNOSIS

Early surgical evacuation can reduce morbidity and mortality. A nonsurgical approach can be considered in patients who have all of the following findings: hematoma volume <30 cc, clot diameter <15 mm, midline shift <5 mm, Glasgow Coma Scale score >8, and nonfocal neurologic examination. Unlike subdural hematomas, epidural hematomas typically do not result in injury to the underlying brain parenchyma. Complete neurologic recovery may be expected if the hematoma is evacuated prior to herniation or the development of neurologic deficits.

Traumatic Spinal Epidural Hematoma

EPIDEMIOLOGY AND PATHOBIOLOGY

Traumatic spinal epidural hematoma is a relatively uncommon injury that results from the mechanical disruption of blood vessels in the epidural space by vertebral fracture fragments or dislocation.[27] Traumatic spinal epidural hematomas can cause cord compression that requires immediate surgical decompression. This injury occurs in 0.5 to 7.5% of all spinal injuries, typically in adults over 40 years of age after an injury involving high energy, such as a motor vehicle collision. Traumatic spinal epidural hematomas can occur anywhere along the spinal cord, but most commonly occur in the cervical and proximal thoracic spine. Risk factors include ankylosing spondylitis, rheumatoid arthritis, and impaired blood clotting, the latter most often due to anticoagulant medications or neoplasia. Spinal epidural hematomas also

FIGURE 368-4. Ventral epidural hematoma *(arrows)* compressing and deforming the spinal cord on T2-weighted magnetic resonance image. Acute fractures of C5 and T6 *(asterisks)* can also be seen. (Reproduced from Bennett DL, George MJ, Ohashi K, et al. Acute traumatic spinal epidural hematoma: imaging and neurologic outcome. *Emerg Radiol*. 2005;11:136-144.)

can occur after a traumatic lumbar puncture or a spinal cord procedure, and they rarely can occur apparently spontaneously in patients on chronic oral anticoagulation.

CLINICAL MANIFESTATIONS AND DIAGNOSIS

In the setting of traumatic injury to the spine, no specific symptoms or signs suggest the presence of a traumatic spinal epidural hematoma, so these injuries are typically detected serendipitously on MRI obtained to define the extent of vertebral fracture or dislocation seen on CT or plain radiographs or to investigate signs of cord compression. MRI usually reveals a collection of blood extending two to three vertebral segments, primarily isointense on T1 and hyperintense on T2 (Fig. 368-4).

TREATMENT AND PROGNOSIS

Immediate surgical decompression is usually recommended in patients with neurologic deficits, but patients without neurologic deficits may be treated without surgery. Conservative management consists of correction of any underlying coagulopathy and close inpatient observation of the hematoma by serial neurologic examinations and repeat CT imaging. Six-month neurologic outcomes are similar for patients who are treated with indicated surgical decompression and for patients who are able to be treated conservatively. Regardless of treatment approach, the presence of a traumatic spinal epidural hematoma does not appear to alter the long-term outcome of spinal cord injury.

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For the General References and other additional features, please visit Elsevier eBooks+ at https://ebooks.health.elsevier.com.

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369 MECHANICAL AND OTHER LESIONS OF THE SPINE, NERVE ROOTS, AND SPINAL CORD

J.D. BARTLESON

Disorders of the spine, nerve roots, and spinal cord are common and frequently disabling. At any one time, 1% of the U.S. population is chronically disabled by lower back pain and another 1% temporarily disabled. Lower back pain is the number one cause of years lived with disability in the United States, and neck pain is the number six cause.[1] Low back and neck pain also are the leading causes of disability in most countries and for most age groups and have increased over the past 25 years. Although the natural prognosis for acute and even chronic spine and limb pain is good, expensive, and sometimes hazardous, imaging studies and treatments are often prescribed.

PATHOBIOLOGY

The 7 cervical vertebrae, 12 thoracic vertebrae, 5 lumbar vertebrae, the sacrum, and the coccyx comprise the spine (Fig. 369-1). Each vertebra has an anterior cylinder-shaped body, which is flattened posteriorly and held together by intervertebral discs, as well as by anterior and posterior longitudinal ligaments (Fig. 369-2A and B). Each disc consists of an outer annulus fibrosus, which receives some blood supply, and an inner, softer nucleus pulposus, which is avascular. The vertebral arch is composed of two short, round, rodlike bones called pedicles, which project backward from the dorsolateral surface of a vertebral body. Each pedicle meets a broad lamina. At one level, two laminae are angled posteriorly and medially to meet in the midline behind the vertebral (or spinal) foramen, where they fuse and form the posteriorly projecting spinous process. The ligamenta flava connect vertically to adjacent laminae. At the junctions of the pedicles and laminae, superior and inferior articular processes articulate with similar processes from above and below. These so-called zygapophyseal joints are true synovium-covered joints that help to protect the spine while permitting a limited amount of movement. The overlapping facet joints and multiple sets of longitudinal ligaments give the spine stability during its ranges of motion and prevent excess motion. The posterolaterally placed intervertebral or neural foramina allow the exit of spinal nerves.

The spinal cord has 31 spinal segments, with one more cervical cord segment (8) than vertebra. Each segment gives rise to a bilateral pair of spinal nerves. Spinal nerves C1 to C7 exit the canal above their corresponding vertebral bodies, whereas the C8 nerve exits below the C7 vertebra. Spinal nerves in the thoracic and lumbar spine exit below the vertebra with the same number.

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FIGURE 368-4. Ventral epidural hematoma *(arrows)* compressing and deforming the spinal cord on T2-weighted magnetic resonance image. Acute fractures of C5 and T6 *(asterisks)* can also be seen. (Reproduced from Bennett DL, George MJ, Ohashi K, et al. Acute traumatic spinal epidural hematoma: imaging and neurologic outcome. *Emerg Radiol*. 2005;11:136-144.)

can occur after a traumatic lumbar puncture or a spinal cord procedure, and they rarely can occur apparently spontaneously in patients on chronic oral anticoagulation.

CLINICAL MANIFESTATIONS AND DIAGNOSIS

In the setting of traumatic injury to the spine, no specific symptoms or signs suggest the presence of a traumatic spinal epidural hematoma, so these injuries are typically detected serendipitously on MRI obtained to define the extent of vertebral fracture or dislocation seen on CT or plain radiographs or to investigate signs of cord compression. MRI usually reveals a collection of blood extending two to three vertebral segments, primarily isointense on T1 and hyperintense on T2 (Fig. 368-4).

TREATMENT AND PROGNOSIS

Immediate surgical decompression is usually recommended in patients with neurologic deficits, but patients without neurologic deficits may be treated without surgery. Conservative management consists of correction of any underlying coagulopathy and close inpatient observation of the hematoma by serial neurologic examinations and repeat CT imaging. Six-month neurologic outcomes are similar for patients who are treated with indicated surgical decompression and for patients who are able to be treated conservatively. Regardless of treatment approach, the presence of a traumatic spinal epidural hematoma does not appear to alter the long-term outcome of spinal cord injury.

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PATHOBIOLOGY

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ABSTRACT

Spine disorders are common and affect most people at some time in their lives. Spondylosis (i.e., degenerative wear-and-tear changes in the spine) is the most common cause of spine and limb pain. Spine pain alone occurs more frequently than myelopathy, radiculopathy, or the cauda equina syndrome. This chapter reviews the anatomy and physiology of the spine. It describes symptoms and signs of stenosis and radiculopathy that affect the cervical and lumbar regions. Worrisome "red flag" findings that prompt investigation and intervention are included. Without these red flags, patients with acute spine and/or limb pain can be treated conservatively for 4 to 6 weeks. MRI is the diagnostic test of choice for patients with pain and neurologic dysfunction. However, MRI often shows incidental findings that can mislead the clinician. Ancillary tests include neurophysiologic studies, which help to exclude neural impingement, nerve injury, or a peripheral nerve disorder unrelated to the spine. Treatment for acute and chronic symptoms is presented. Medications and physical treatments are commonly used. Spine surgery is a consideration for compression of the spinal cord or nerves with persistent or worsening neurologic deficits and/or pain. In general, the prognosis for patients with spondylosis is favorable. Most patients do well with conservative, nonoperative treatment.

KEYWORDS

myelopathy
radiculopathy
spondylosis
spinal stenosis
spine and limb pain
herniated intervertebral disc
cauda equina syndrome

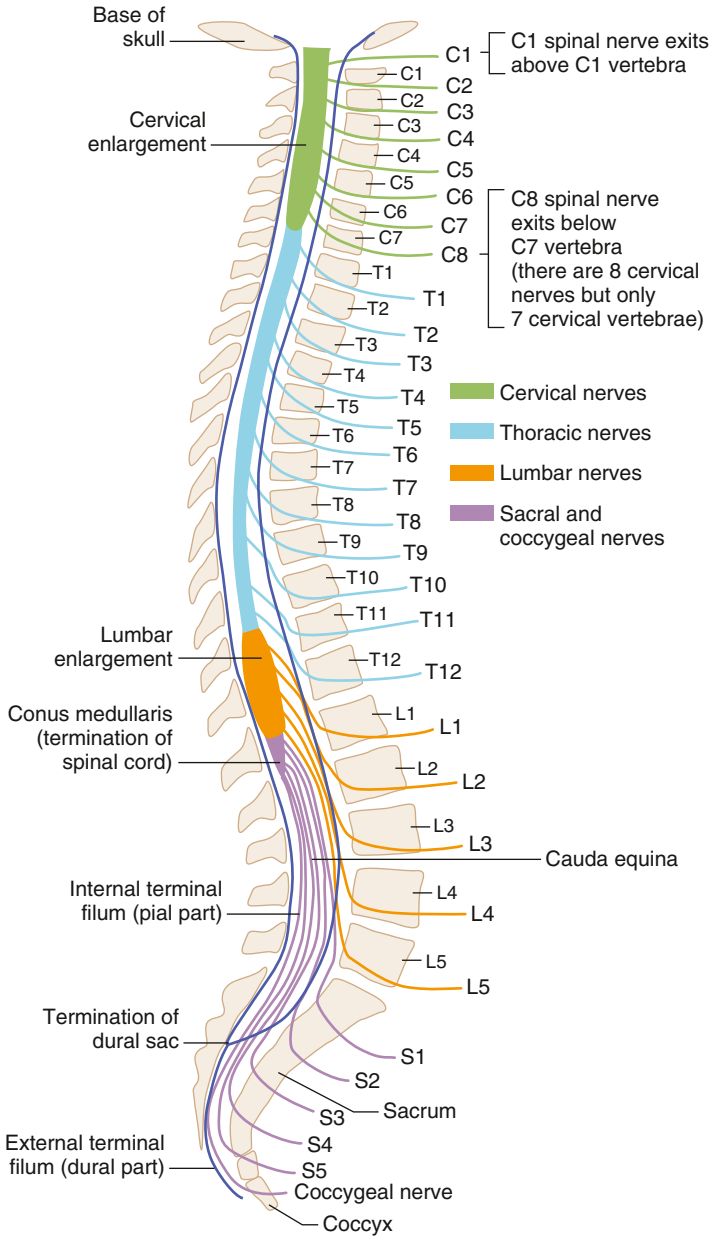

FIGURE 369-1. **Anatomy of the spine and spinal cord.**

Spinal cord segments lie progressively superior to the vertebrae, so that the end of the spinal cord and conus medullaris is at about the L1 vertebral level in adults. Below this level, the spinal nerves travel in a bundle as the cauda equina within the subarachnoid space before exiting through their respective foramina. The spinal cord is wider in the cervical and lumbar cord segments because of the increased number of motor and sensory neurons supplying the upper and lower extremities.

Spinal nerves are formed by joining of the anterior (or ventral) and posterior (or dorsal) spinal nerve roots, which directly enter and exit the spinal cord (Fig. 369-2B). The anterior or ventral root is derived from axons of the anterior horn cells and lateral columns. The posterior or dorsal root mostly derives axons from the dorsal root ganglion. The sensory root is twice as thick as the motor root. The spinal nerves exit and enter the spinal canal through the intervertebral or neural foramina formed by the upper and lower pedicles, the vertebral body, and the laminae (Fig. 369-2A).

CLINICAL MANIFESTATIONS

Most spine disorders are related to spondylosis, which results from wear and tear that takes place in the vertebrae, intervertebral discs, facets, and other true joints of the spine, associated ligaments, and secondarily the paraspinal and other muscles. Pain-sensitive structures in the spine include the periosteum of the bony spine (vertebrae); the dura, facet, and other true joints; the annulus fibrosus (but not the nucleus pulposus); blood vessels; ligaments; and paraspinal muscles.

The most frequent complaint related to spondylosis is axial spine pain affecting the low back more than the neck and more than the midback. With compression or irritation of the spinal nerves, patients can develop tingling, prickling, or burning sensations (termed paresthesias if they occur spontaneously or dysesthesias if they are provoked by stimulation); pain; loss of sensation; weakness; and sometimes autonomic dysfunction (most commonly difficulty with bowel or bladder control).

When it affects a myotome (the group of muscles served by motor neurons of a single spinal cord segment), the motor deficit associated with a spinal root disorder is of the lower motor neuron type. Typical findings are weakness, hypotonia, depressed or absent reflexes, fasciculations, and, if the syndrome has persisted for at least several weeks, muscle atrophy (Table 369-1 and Table 369-2). Sensation at the spinal nerve level is diminished or absent for all modalities in a characteristic dermatomal pattern (Fig. 369-3). Sensation below and above the affected root is intact.

Conversely, disorders of the spinal cord produce a "level" below which sensation is abnormal and motor deficits are of the upper motor neuron type, with weakness without atrophy (unless caused by disuse), hypertonia, and increased reflexes. At the level of a spinal cord lesion, the motor deficits can be of the lower motor neuron type owing to injury to anterior horn cells or nerve roots; but below this level, an upper motor neuron syndrome will predominate. As with strokes (Chapter 375) and other central nervous system (CNS) insults, the full upper motor neuron syndrome of spasticity and hyperreflexia may be absent in the acute phase of spinal cord injury.

DIAGNOSIS

Knowledge of the usual patterns of the sensory, motor, and reflex innervation of the spinal nerves greatly aids in diagnosis of the patient with possible radiculopathy. The history of sensory loss or motor weakness may be more important than findings on the physical examination. The patient should be asked about, and the neurologic examination focus on, sensory, motor, and reflex functions. Careful side-to-side comparisons can help detect subtle deficits. All muscles receive innervation from more than one spinal nerve and all nerve roots innervate multiple muscles, so individual muscles are rarely profoundly weak when a single root is affected. Give-way weakness, when a patient does not give a full effort, can be due to pain, lack of understanding, the patient trying to help the provider, conversion disorder, and malingering. In this setting it may be best to interpret strength as being at least as good as when it gave way, but the presence or absence of some weakness cannot be known. Overlap of sensory dermatomes explains why sharp demarcations and complete sensory loss rarely occur. All sensory loss is subjective, thereby making the sensory examination less reliable. Typical symptoms and signs associated with cervical and lumbosacral radiculopathies are shown in Tables 369-1 and 369-2.

DISORDERS OF THE SPINE

Neck and Low Back Pain

DEFINITION

Most neck and low back pain is mechanical and attributable to the structural elements of the spine. Pain referred to the spine can arise from internal structures in the neck, upper chest, abdomen, or pelvis. Pain of spinal origin may be referred to the upper or lower extremity or the torso. In the lower limbs, conditions affecting the upper lumbar spine tend to refer pain to the groin and/or anterior thigh (from the hip to the knee). Conditions affecting the lumbar spine tend to cause referred pain in the buttock, posterior thigh, leg (from the knee to the ankle), or foot. Referred pain can be unilateral or bilateral. Pain that follows a dermatomal distribution is likely to be due to nerve root pathology.

EPIDEMIOLOGY

Low back pain is more common and more disabling than neck pain. The thoracic spine, possibly because of rib attachments and limited range of motion, is a less common location for spine pain. An exception to this rule is the condition of diffuse idiopathic skeletal hyperostosis (Chapter 252), which is a noninflammatory, age-related condition of unknown etiology, characterized by ossification of paravertebral ligaments and peripheral entheses. It is more common in men and increases with age. Pain in the thoracic spine region occurs in up to 80% of patients with diffuse idiopathic skeletal hyperostosis.

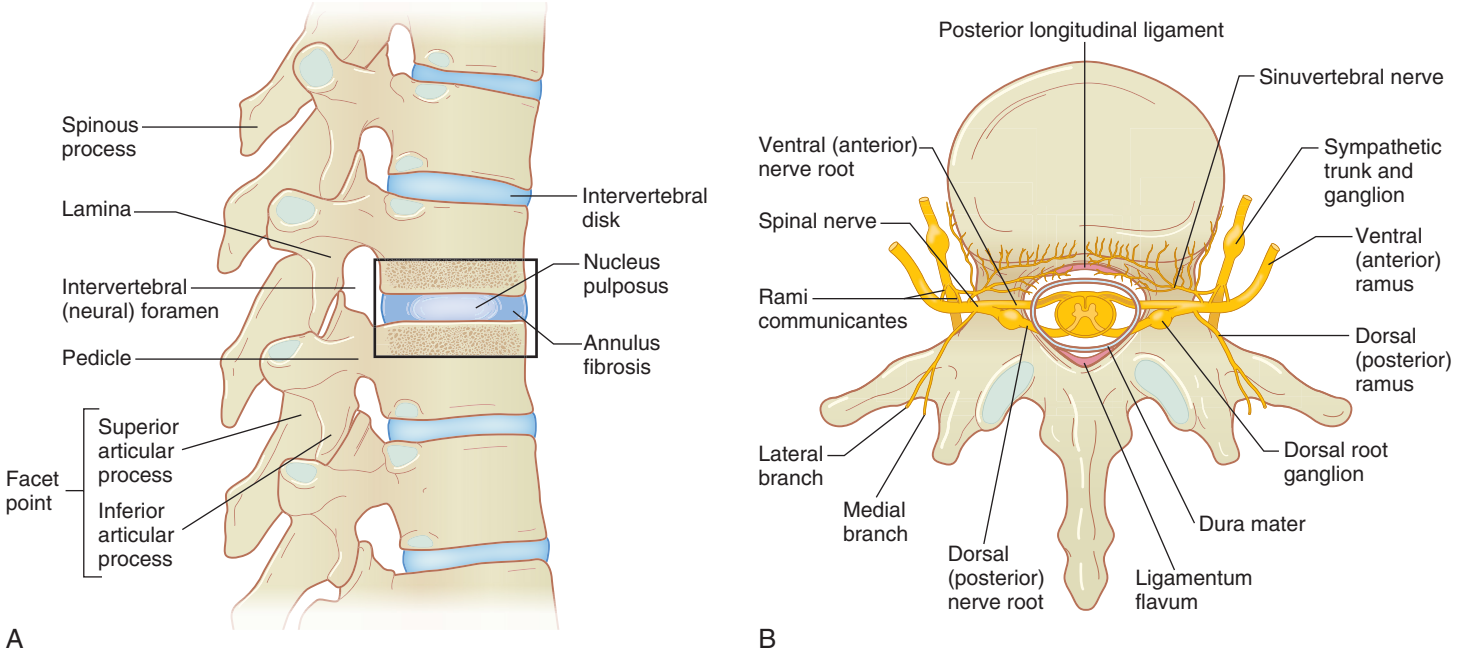

FIGURE 369-2. **Anatomy of the thoracic spine. A, Lateral view. B, Cross-section of the spine, spinal cord, spinal nerves, and nerve roots. (From *Spine Disorders: Medical and Surgical Management* by JD Bartleson and HG Deen; Cambridge University Press, 2009. Copyrighted and used with permission of Mayo Foundation for Medical Education and Research.)**

TABLE 369-1 SYMPTOMS AND SIGNS ASSOCIATED WITH SPONDYLOTIC CERVICAL AND HIGH THORACIC RADICULOPATHY

	USUAL LOCATION OF:			
DISC LEVEL/ROOT	**PAIN**	**SENSORY ABNORMALITIES**	**WEAKNESS**	**AFFECTED REFLEX**
C3-4/C4	Neck	Suprascapular, supraclavicular, and top of shoulder	Usually none	None
C4-5/C5	Neck, scapula, shoulder, anterior arm	Lateral arm and forearm	Shoulder abduction and elbow flexion	Biceps, brachioradialis
C5-6/C6	Neck, scapula, shoulder, lateral arm, and forearm	Anterolateral arm, forearm, hand, thumb, and forefinger	Shoulder abduction, elbow flexion, and forearm pronation	Biceps, brachioradialis
C6-7/C7	Neck, shoulder, lateral arm, medial scapula, extensor surface of forearm	Dorsolateral forearm and hand, forefinger, and long finger	Extension of elbow, wrist, and fingers	Triceps
C7-T1/C8	Neck; medial scapula, arm, and forearm	Medial forearm and hand, ring, and little fingers	Finger abduction, adduction, and flexion	None or finger flexor
T1-2/T1	Anterior chest, medial arm, and forearm	Medial arm and forearm	Finger abduction, adduction, and flexion	None or finger flexor

Adapted from *Spine Disorders: Medical and Surgical Management* by JD Bartleson and HG Deen; Cambridge University Press, 2009. Copyrighted and used with permission of Mayo Foundation for Medical Education and Research.

TABLE 369-2 SYMPTOMS AND SIGNS ASSOCIATED WITH SPONDYLOTIC LUMBOSACRAL RADICULOPATHIES

	USUAL LOCATION OF:			
DISC LEVEL/ROOT	**PAIN**	**WEAKNESS**	**AFFECTED REFLEXES**	**SENSORY ABNORMALITIES**
L1-2/L1	Inguinal	None	Cremasteric	Inguinal
L2-3/L2	Inguinal and anterior thigh	Hip flexion, hip adduction, some knee extension	Cremasteric, thigh adductor	Proximal anterior thigh
L2-3/L3	Anterior thigh and knee	Knee extension, hip flexion, hip adduction	Knee, thigh adductor	Anterior and anteromedial thigh including knee
L3-4/L4	Anterior thigh, anteromedial leg	Knee extension, hip flexion, hip adduction	Knee	Anterior knee and medial leg
L4-5/L5	Posterolateral thigh, lateral leg, medial foot	Foot dorsiflexion, inversion and eversion, knee flexion, hip abduction, toe extension and flexion	Internal hamstring	Lateral leg, dorsal foot, and great toe
L5-S1/S1	Posterior thigh and leg, heel, and lateral foot	Foot plantar flexion, toe flexion, knee flexion, hip extension	Ankle, external hamstring	Posterolateral leg and lateral foot, heel
L5-S1/S2	Buttock	Foot plantar flexion, hip extension	Anal reflex, ankle	Posterior leg and thigh, medial buttock

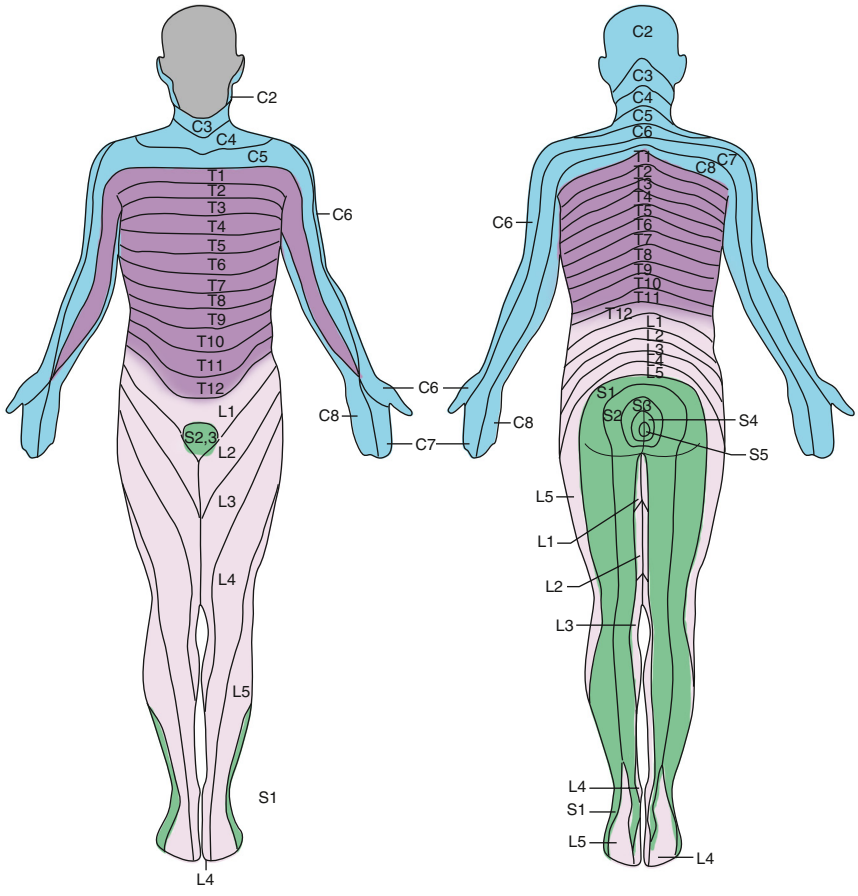

Levels of principal dermatomes

C5	Clavicles
C5,6,7	Lateral parts of upper limbs
C8, T1	Medial sides of upper limbs
C6	Thumb
C6,7,8	Hand
C8	Ring and little fingers
T4	Level of nipples
T10	Level of umbilicus
T12	Inguinal or groin regions
L1,2,3,4	Anterior and inner surfaces of lower limbs
L4,5 S1	Foot
L4	Medial side of great toe
S1,2, L5	Posterior and outer surfaces of lower limbs
S1	Lateral margin of foot and little toe
S2,3,4	Perineum

FIGURE 369-3. Schematic demarcation of levels of principal dermatomes shown as distinct segments. There is considerable overlap between any two adjacent dermatomes.

In the general population, the incidence of self-reported neck pain is 213 per 1000; the 12-month prevalence of any neck pain is typically between 15 and 50%, and pain severe enough to limit activity is between 1.7 and 11.5%. The prevalence is higher in women. Risk factors for neck pain include heredity, poor psychological health, occupations such as dentistry, and tobacco use. The presence of disc degeneration does not correlate with the incidence of neck pain.

More than 70% of people will experience lower back pain significant enough to inhibit their participation in daily activities at some time in their life.[2] The highest prevalence is in the 45- to 64-year age group, without a gender difference. Tobacco use is an associated risk factor. Physical work–related factors (e.g., heavy lifting, prolonged sitting, repetitive twisting) increase risk. Prospective studies show that psychosocial issues such as work monotony, job dissatisfaction, and depression also are major predisposing factors for chronic lower back pain.

PATHOBIOLOGY

Neck and lower back pain can occur with or without radicular pain. In the low back, radicular lower limb pain usually affects the L5 or S1 nerve root. In the cervical spine, the C7 nerve root is most affected. Radicular upper or lower limb pain is usually caused by compression and irritation of the spinal nerve, typically by a protruding disc or osteoarthritic change. The precise cause of axial neck and lower back pain is often difficult to determine. The degenerative process of spondylosis, including facet joint pathology, is thought to be responsible for both acute and chronic axial spine pain, whereas the intervertebral disc is thought to account for a minority of symptoms. Intervertebral disc degeneration has a genetic predisposition with heritability estimates in the range of 35 to 75%.

Spondylosis is accompanied by disc degeneration, the formation of osteophytes, ligamentous hypertrophy, facet joint arthropathy, and vertebral subluxation (spondylolisthesis) of one vertebral body forward (anterolisthesis) or backward (retrolisthesis) on its mate below. The vast majority of people develop spondylosis, which includes disc desiccation and loss of elasticity of the annulus fibrosus. Congenital or acquired fractures of the pars interarticularis on both sides of one lumbar spinal level, termed spondylolysis, promote the development of spondylolisthesis. Spondylolisthesis is graded by the amount of maximal shift in quartiles from 0 being normal to 5 being total dissociation of the vertebral body with an adjacent vertebra. Stability of spondylolisthesis is estimated by plain radiographs of the spine with the patient in flexion and extension.

Whiplash, an acute flexion or extension injury (or both) of the cervical spine, is common, especially after motor vehicle accidents. The acute whiplash syndrome is thought to be a result of mechanical irritation of pain-sensitive mostly musculoskeletal structures in the cervical spine, typically without spinal cord or spinal nerve injury. More severe trauma can cause fracture and vertebral instability, which often require urgent surgical intervention.

CLINICAL MANIFESTATIONS

Acute neck pain and lower back pain are commonly limited to the axial region, although radicular signs and symptoms can occur in the presence of nerve root irritation. The most common radicular pain occurs in the distribution of a dermatome. Other radicular signs and symptoms can include dysesthesias or sensory loss in the affected dermatome, decreased strength in muscles of the affected myotome, and one or more decreased reflexes. Cranial nerve findings, diffuse weakness throughout a limb or in more than one limb, hemisensory symptoms, autonomic symptoms, and diffuse increase

in reflexes are not typical manifestations of spine disease in the absence of spinal cord compression; these signs and symptoms should prompt evaluation for other conditions that affect the brain, brain stem, or spinal cord. Bowel and bladder symptoms should prompt urgent evaluation for cauda equina compression or a myelopathy.

Acute spine problems can also cause referred pain at sites other than their anatomic source. More often, the term referred pain denotes the situation in which other structures, usually internal organs, refer pain to the spine or limbs. Areas of referred pain usually share the same embryologic origin and the same sensory pathways. Differentiation of referred pain from localized spine pain is aided by the history and examination. Mechanical pain is often exacerbated by spinal movement, whereas referred pain tends to be independent of such activities. Sciatica, which is defined as pain in the distribution of the sciatic nerve, often includes pain in the back as well as the buttock, posterior thigh, leg, and foot. Although sciatica can be caused by a lesion anywhere along the course of the sciatic nerve, it is most commonly caused by injury to one of the exiting spinal nerves that contribute to the sciatic nerve (L4-S2).

DIAGNOSIS

A structured approach can improve outcomes while avoiding unnecessary diagnostic tests and ineffective therapies (Fig. 369-4).

History and Clinical Examination

The history and physical examination are essential for the initial evaluation and triage of patients with neck and lower back pain, with or without possible radicular upper or lower limb pain. "Red flags" help identify patients who may have a serious underlying cause for their spinal pain (e.g., fracture, infection, hemorrhage, tumor, serious neurologic disease) and generally warrant very prompt diagnostic evaluation and possibly earlier medical or surgical intervention (Table 369-3). Red flags for neck or upper limb pain are similar to those for lower back pain with the addition of conditions unique to the cervical spine (rheumatoid arthritis, spondyloarthropathy, and Down syndrome); neck pain associated with chest pain, diaphoresis, or dyspnea, which can occur with myocardial ischemia (Chapter 57); and signs or symptoms of myelopathy. However, most patients do not present with red flags, and guidelines for patients without red flags usually recommend a wait-and-see approach for at least 4 to 6 weeks after the onset of neck or lower back pain.

On clinical examination, inspection should assess for evidence of trauma, muscle wasting, fasciculations, erythema, rashes, and scars. Palpation should look for areas of point tenderness, muscle spasm, and masses. If light percussion of the spinous process evokes significant pain, a focal lesion, such as fracture, tumor (Chapter 175), or infection (Chapter 382), should be considered. Active and passive range of motion for flexion, extension, rotation, and side-to-side bending should be tested.

Many provocative tests have been described for the evaluation of spine and limb pain, but few have undergone formal evaluation of their diagnostic accuracy. For neck and upper limb pain, an increase in symptoms with contralateral rotation of the neck and extension of the arm and fingers (Video 369-1) suggests cervical root involvement, as does the Spurling maneuver, in which the patient's head is bent backward and flexed (bent) laterally to the symptomatic side. Provocation of radicular pain or paresthesias with or without downward pressure on the top of the patient's head suggests cervical nerve root impingement or irritation (Video 369-2). Diagnostic tests also can reduce symptoms. In the cervical distraction test, the examiner's hands are placed under the jaw and occiput. Gentle upward pulling of the head can temporarily reduce or alleviate the symptoms of cervical spinal nerve impingement (Video 369-3).

Provocative tests that can be helpful in the patient with low back and lower limb pain include straight leg raising performed with the patient supine. The examiner flexes the thigh at the hip while the leg is held in extension at the knee. The test is positive if pain along the course of the sciatic nerve is provoked. Further increase in pain with foot dorsiflexion provides additional evidence of lumbosacral nerve root impingement.

Straight leg raise (Video 369-4) has sensitivity of 0.85 to 0.91 but a specificity of only 0.26 to 0.52 for the diagnosis of sciatica due to a herniated disc. A positive crossed straight leg raise test (Video 369-5), which has a lower sensitivity of 0.23 to 0.34 but a much higher specificity of 0.86 to 0.90, is often positive in the presence of a disc extrusion. Positive seated straight leg raising when the knee is fully extended is about as useful as a positive test at 65 degrees elevation when the patient is supine (Video 369-6). In reverse straight leg raising, the examiner maximally flexes the knee while the patient is prone; provocation of same-sided pain, usually in the anterior thigh, is highly

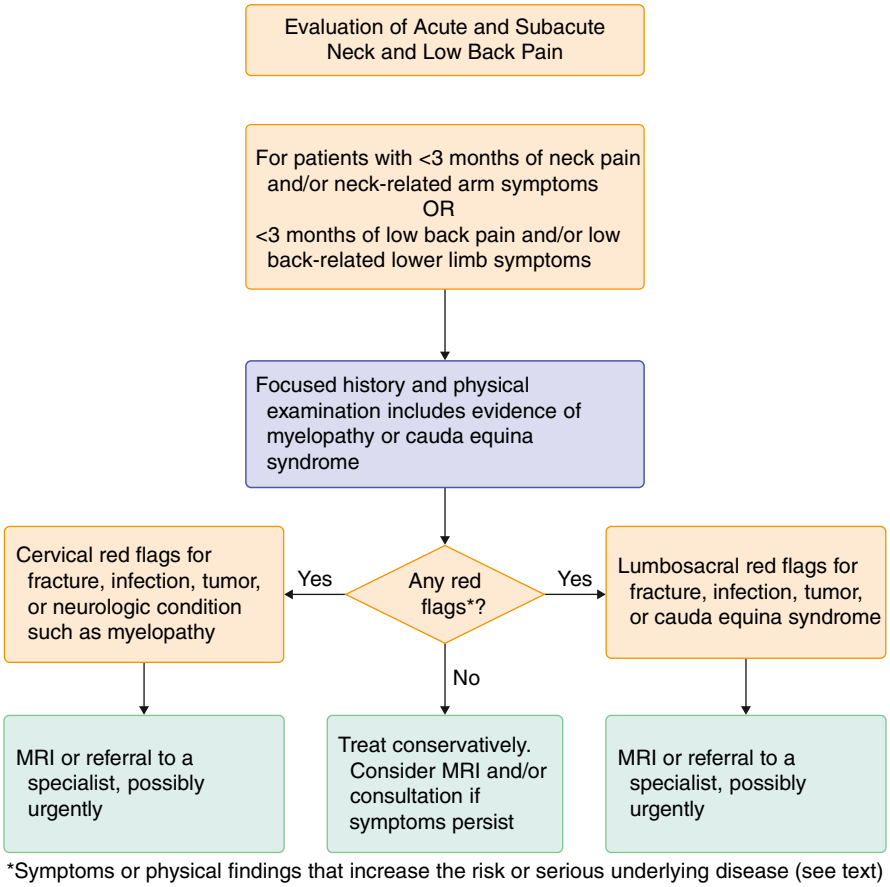

FIGURE 369-4. Evaluation of acute and subacute neck and low back pain. MRI = magnetic resonance imaging.

TABLE 369-3 "RED FLAGS" IN THE EVALUATION OF SPINE PAIN

History of trauma
Unexplained weight loss
Unexplained fever
Immunosuppression
History of cancer
History of recent surgery
Systemic disorder
Intravenous drug use
Osteoporosis
Prolonged use of corticosteroids
Age <20 or >50 years
Significant or progressive neurologic deficit
Myelopathy
Possible cauda equina syndrome
Duration > 6-12 weeks
Uncontrollable pain

suggestive of impingement of the L2, L3, or L4 nerve roots, which contribute to the femoral nerve and are stretched by this maneuver.

Ancillary Testing

For acute and subacute neck and lower back pain, observation and conservative treatment are recommended if no red flags are present.[3] If the patient's symptoms are unchanged after 4 to 6 weeks, then further investigation can be considered. Magnetic resonance imaging (MRI) is the diagnostic test of choice for patients with neck and lower back pain, especially if they have radicular pain or evidence of myelopathy. MRI is recommended only in patients who have major or progressive neurologic deficits, in whom a serious underlying condition is suspected, or in whom surgery or epidural corticosteroid injections are being considered. Even in patients age 65 years and older, the value of early diagnostic imaging in patients without radiculopathy is uncertain. However, MRI abnormalities are common in asymptomatic patients, so MRI has a very high false-positive rate when imaging the cervical or lumbar spine. Frequent asymptomatic findings include loss of disc signal intensity, disc protrusion, narrowing of the disc space, facet arthropathy, and central or foraminal stenosis.

The need to correlate the patient's presentation with their imaging findings cannot be overemphasized. More than half of asymptomatic patients will have more than one potentially symptomatic cervical or lumbar finding on MRI. This number approaches 100% with age older than 50 to 60 years. Modic changes in the vertebrae, spondylolisthesis, and lumbar disc extrusion are more strongly associated with low back pain than is disc degeneration without end plate changes. Discography is an invasive procedure that can be of some help in diagnosing lumbar internal disc disruption, which is a condition that may cause low back pain but for which there is no known effective treatment. Discography is not recommended in the cervical spine.

Computed tomography (CT), usually with the instillation of contrast (CT myelography), is not as accurate as MRI but is the test of choice for patients who are intolerant of or unable to undergo MRI. CT myelography can be complementary to MRI, and one imaging study may be positive when the other is not. Otherwise, with few exceptions, MRI is the test of choice given its superiority in evaluating soft tissue structures and its lack of radiation exposure.

For stress fracture (Chapter 225), plain CT and single-photon emission computed tomography (SPECT) are more sensitive than MRI. CT can also be used to evaluate scoliosis, bone graft integrity, implanted instrumentation, and union of surgical fusion.

Plain radiography is of some use for judging the presence of spondylosis, vertebral enumeration, congenital abnormalities, normal cervical and lumbar lordosis and alignment, and absence of gross fracture and spinal instability. For patients in whom only a benign lumbar compression fracture is suspected, plain radiography may suffice if the results are normal and no other abnormalities are present.

Electrodiagnostic testing is not usually helpful in axial spine pain without neurologic symptoms. It can, however, be useful in documenting the presence and activity of radiculopathy and in diagnosing other conditions (e.g., brachial plexus neuritis, carpal tunnel syndrome, and sciatic neuropathy). Furthermore, it is a lagging indicator and may not become abnormal until 4 weeks have elapsed from the onset of nerve injury.

TABLE 369-4 MAJOR CAUSES OF NECK PAIN

SPONDYLOTIC DEGENERATIVE DISEASE
Joints: facet, uncovertebral
Discs: herniation, degeneration
Bone: fracture, hypertrophic spurring
Muscle: acute strain, chronic pain
CONGENITAL/ACQUIRED DEFORMITY
Klippel Feil syndrome (congenital fusion of two or more cervical vertebrae)
Iatrogenic fusion
Craniocervical subluxation
Cervical spinal stenosis
RHEUMATOLOGIC
Rheumatoid arthritis (Chapter 243)
Ankylosing spondylitis (Chapter 244)
Other spondyloarthropathy (Chapter 244)
Polymyalgia rheumatica (Chapter 250)
Fibromyalgia (Chapter 253)
TRAUMA (CHAPTER 368)
Sprain (e.g., from whiplash)
Fracture
TUMOR (CHAPTERS 175 AND 176)
Bony spine
Spinal cord
Head and neck
INFECTION
Osteomyelitis (Chapter 251)
Disc space infection
Epidural abscess (Chapter 382)
Meninges
Spinal cord
NEUROGENIC (CHAPTER 366)
Spinal nerves
Spinal cord
Meninges
REFERRED FROM VISCERA
Lung tumor, especially at the apex (Pancoast tumor; Chapter 177)
Upper esophagus (Chapter 124)
Carotid or vertebral artery dissection (Chapter 376)
Myocardial ischemia (Chapters 56 to 58)
Thyroid (Chapter 207), throat (Chapter 397), and laryngeal disease (Chapter 397)
PSYCHOGENIC (CHAPTER 362)
With or without an additional source of pain
Malingering

Differential Diagnosis

The differential diagnosis of neck pain (Table 369-4)[4] and lower back pain (Fig. 369-5)[5,6] is very broad. Acute mechanical neck pain is most often caused by neck muscle strain, a herniated nucleus pulposus, or whiplash. Up to 97% of cases of low back pain are due to mechanical causes or are idiopathic. For neck pain of gradual onset, osteoarthritis and cervical spinal stenosis are leading causes. For low back pain, muscle strain and a herniated nucleus pulposus are possible acute causes, whereas insidious causes include osteoarthritis, lumbar spinal stenosis, spondylolisthesis, sacroiliitis (Chapter 244),[7] and scoliosis (Fig. 369-5).[8] The presence of red flags will help identify serious and nonmechanical causes of neck and low back pain.

Abdominal and pelvic structures can refer pain to the low back. Abdominal aortic aneurysms (Chapter 63) can present with mid- or low back pain that may radiate to the hips or anterior thighs. Dissection of the thoracic aorta (Chapter 63) can cause sudden severe pain in the front and back of the chest, including the spine. Cholecystitis (Chapter 141) can cause pain in the midthoracic area. Pancreatic disease (Chapter 130) can cause pain in the L1 region. Diverticulitis (Chapter 128) can cause lower abdominal and diffuse low back pain. Genitourinary disorders (Chapter 111) can cause colicky pain referred to the flank and costovertebral angle. Bladder disorders can occasionally refer pain to the sacral area, as can prostate conditions (Chapter 114). Pelvic disorders in women that can cause referred low back pain include endometriosis (Chapter 218), ectopic pregnancy, and pelvic inflammatory disease (Chapters 275 and

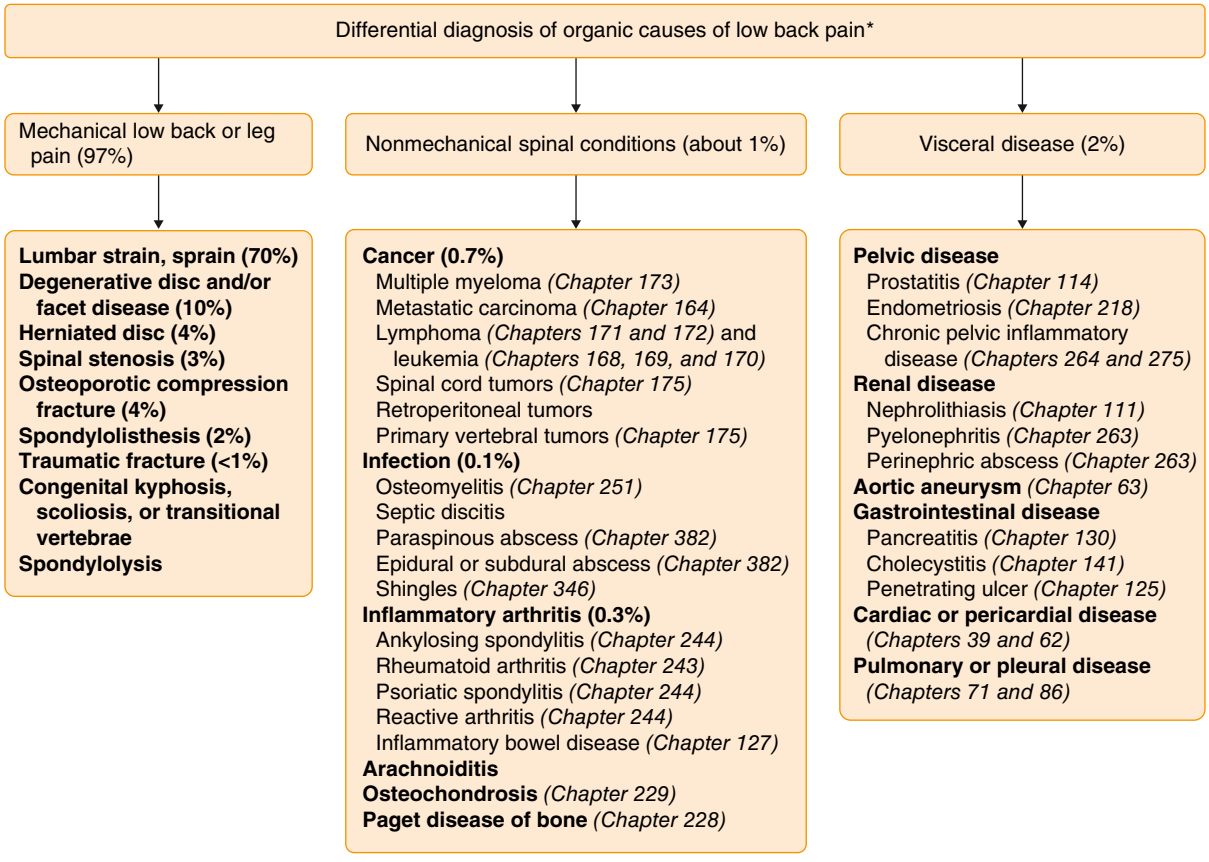

FIGURE 369-5. Differential diagnosis of organic causes of low back pain. *Percentages are approximations and may vary substantially in different practices. (Data from Deyo RA, Weinstein JN. Low back pain. *N Engl J Med*. 2001;344:363-370.)

294). Most of these disorders have additional signs and symptoms to aid in the diagnosis.

Myocardial ischemia (Chapters 56 to 58) can be associated with anterior neck pain, although less commonly than with left arm or jaw pain. Arterial dissections (Chapter 63) are more commonly associated with neck pain. For example, about 25% of patients with carotid dissections (Chapter 376) complain of anterolateral neck pain, and about 50% of patients with vertebral dissections have posterior neck pain. Patients with arterial dissections can have signs and symptoms of stroke (Chapter 376). Disorders of the esophagus (Chapter 124) and mass lesions of the neck and throat (Chapters 176 and 397) can present with neck pain.

Acute radicular pain can precede the rash in herpes zoster (Chapter 346). Sickle cell anemia can cause severe pain in almost any location, including the spine (Chapter 149). Infections of the disc (Chapter 382) can cause severe back pain worsened by movement. Arachnoiditis (Chapter 381), an inflammatory process of the arachnoid membrane, can cause chronic back and radicular pain, often after spine surgery or the introduction of a foreign substance into the intrathecal space. Twenty to 50% of patients with depression (Chapter 362) will complain of back pain that is often diffuse and described in emotionally laden terms. Complaints of low back pain are also common in malingering patients.

TREATMENT

Patients with neck or lower back pain, with or without limb pain, should try to continue routine activities insofar as possible.[9,10]

Medications

Medication options include nonsteroidal anti-inflammatory drugs (NSAIDs) (e.g., ibuprofen 600 mg three times daily for up to a few weeks)[A1] and skeletal muscle relaxants (e.g., cyclobenzaprine 5 to 10 mg three times daily, tizanidine 2 to 6 mg three times daily, or carisoprodol 250 to 350 mg three times daily for up to a few weeks). Muscle relaxants are of short-term help for acute pain with muscle spasm, but can cause sedation. Duloxetine (60 mg once daily) can be helpful for chronic low back pain. Acetaminophen is not helpful for low back pain and is of uncertain benefit for neck pain.[A2] Systemic corticosteroids do not seem to be effective. The use of opioid analgesics is controversial and of uncertain benefit for chronic low back pain.

Nonsurgical Interventions

No data support corticosteroid injections into facet joints for axial neck or lower back pain, although transforaminal and interlaminar epidural corticosteroid injections are indicated for radicular pain. Temporary pain relief with medial branch nerve blocks can help determine which facet joints are responsible for axial neck and lower back pain. If medial branch blocks are helpful, radiofrequency ablation of the identified nerves can provide months of pain relief, especially for chronic neck pain.

Heat, massage, physical therapy,[A3] acupuncture, and spinal manipulation are helpful for acute and subacute lower back and possibly for axial neck pain, but bed rest is not recommended for acute neck or low back pain. For chronic neck pain, yoga therapy provides modest to significant pain relief. Cervical collars and traction are not of established benefit. Chiropractic or osteopathic manipulation is more helpful for low back pain than for neck pain and better for acute than chronic pain, but its benefit is small.[A4]

Helpful therapies for chronic low back pain include tai chi, mindfulness-based stress reduction, and yoga.[A5] Psychological and physical therapies, multidisciplinary rehabilitation, massage, cognitive-behavioral therapy, and acupuncture also are helpful for chronic low back pain. Closed-loop spinal cord stimulation may be helpful in otherwise refractory cases of back and leg pain,[A6] but its benefit is limited.[11] Stem cell therapy is also being evaluated for the treatment of chronic discogenic pain.

Surgery

Referral to a spine surgeon is appropriate if an operation may be indicated, for confirmation of advice not to have surgery, or if the patient or family requests a consultation. Even in the absence of radicular pain or myelopathy, surgical intervention for neck pain is indicated in cases of vertebral instability, such as caused by fracture, tumor, or infection. For neck pain that is accompanied by signs or symptoms of radiculopathy, surgery should be considered but is not usually the initial treatment. If a cervical spine lesion is causing spinal cord compression, evaluation for possible surgery is indicated.

When persistent nonradicular lower back pain is accompanied by degenerative spine changes, surgical fusion is often performed. However, randomized controlled studies have shown that lumbar spinal fusion is only modestly helpful compared with no treatment, and lumbar fusion is not beneficial compared with an active physical therapy program.[A7] Total disc arthroplasty (artificial disc) can be used for cervical radiculopathy or myelopathy but not for neck pain alone. Total lumbar disc arthroplasty is available, but little used for chronic lower back pain.

PROGNOSIS

Between 50 and 85% of patients who have neck pain that persists for more than a day report recurrence of symptoms in 1- and 5-year follow-up. About 50% of patients recover within 3 months. Patients who remain symptomatic generally have relatively mild pain and disability. Factors that increase the likelihood of developing persistent or recurrent neck pain include prior neck injury, psychopathology, low work satisfaction, poor workplace environment, female gender, concomitant low back and other pain disorders, poor coping skills, neck trauma, sedentary lifestyle, and weight gain. Patients with neck pain following a whiplash injury are especially likely to experience protracted symptoms.

Mechanical low back pain, even with radicular symptoms, resolves without specific intervention within 30 days in most patients and within 3 months in 90% of patients. Exercise alone or in combination with education is effective for preventing low back pain.[A8] Recurrence is frequent, however, and about 50% of patients will experience another episode within 1 year. Many patients will have lingering fluctuating or intermittent low back pain, but only a minority develop significant chronic low back pain.

Long-term disability is more common with obesity, low education level, tobacco use, high levels of pain at the onset, tendency to somatization, job dissatisfaction, lack of availability of light-duty employment, and need to perform heavy lifting at work. Genetic variability, such as in polymorphisms of catechol *O*-methyltransferase, also may play a role in the development of chronic pain.

LUMBAR SPINAL STENOSIS

DEFINITION

Lumbar spinal stenosis occurs when narrowing of the lumbar spinal canal, its lateral recesses, or neural foramina causes symptomatic or asymptomatic compression of the lumbosacral nerve roots. L4-5 is the most common level of stenosis, followed by L3-4, L2-3, L5-S1, and L1-2; most patients have stenosis at more than one vertebral level.

EPIDEMIOLOGY

Congenital spinal stenosis occurs in about 7% of the general population, and midsagittal degenerative stenosis occurs in about 30%. More severe stenosis is associated with older age and more low back pain. About 10% of patients have spinal stenosis in both the cervical and lumbar levels. Patients with diffuse idiopathic skeletal hyperostosis are especially likely to develop spinal stenosis.

PATHOBIOLOGY

Primary lumbar spinal stenosis is caused by congenital narrowing of the spinal canal, whereas causes of secondary stenosis include degenerative spondylotic changes, which increase with age. Patients with congenital lumbar spinal stenosis typically do not have symptoms until they develop additional degenerative changes in the spine. Structures that can hypertrophy and lead to canal narrowing include disc bulging and vertebral osteophytic spurring, enlargement of the facet joints, thickening of the ligamenta flava, thickening of the posterior longitudinal ligament, and spondylolisthesis.

In addition to static narrowing of the lumbar spinal canal, dynamic narrowing accounts for the postural provocation of symptoms. With extension, the inferior articular processes, which form the upper half of facet joints, slide backward and downward on the superior articular processes, which form the lower half of the facet joints. Movement of the facet joints narrows the lumbar spinal canal and intervertebral foramina. The lumbar discs and posterior longitudinal ligaments may bulge posteriorly into the spinal canal, and the ligamenta flava can buckle forward into the canal. These mechanical changes further narrow the lumbar spinal canal and compress the spinal nerves. Intervertebral foramina also narrow when the lumbar spine is extended, thereby causing compression of individual lumbosacral spinal nerves.

CLINICAL MANIFESTATIONS

Lumbar spinal stenosis causes a syndrome of pseudoclaudication, which can mimic the symptoms of lower limb vascular claudication (Chapter 65). Pseudoclaudication typically affects the entire lower limb, usually the posterior aspect bilaterally, but can affect the thigh alone or leg alone. Patients report lower limb numbness, weakness, or pain, with or without back pain, when standing or walking. The absence of pain when seated and the improvement of symptoms when bending forward at the waist are typical. Patients also can develop fixed neurologic deficits, usually in the distribution of the L5 and S1 nerve roots, especially if they have a concomitant peripheral neuropathy. Bowel and bladder function are usually unaffected.

DIAGNOSIS

Plain CT can be used as a screening test, but MRI is the diagnostic test of choice. CT myelography has the advantage of allowing imaging with the patient in an upright position (Fig. 369-6). Plain lumbar spine radiographs with the patient in flexion and extension can detect any spondylolisthesis. Electromyography (EMG) typically shows evidence of radiculopathy rather than peripheral neuropathy (unless the patient has both). Vascular laboratory testing of the lower extremity arteries can help exclude peripheral arterial disease. The differential diagnosis includes any mass that affects the thecal sac (e.g., large lumbar disc, tumor), vascular claudication (usually due to atherosclerosis), osteoarthritis (Chapter 241) of the hips and/or knees, arteriovenous malformation of the spinal cord, multiple sclerosis (Chapter 380), and peripheral neuropathy (Chapter 388).

TREATMENT AND PROGNOSIS

Treatment includes pharmacologic, physical, and surgical approaches.[12] Medications are not particularly helpful or needed. Exercises to strengthen the abdominal muscles and reduce lumbar lordosis may be helpful. Use of a short cane or walker can allow the patient to stand longer and walk farther. Lumbar corsets and braces may help to reduce lumbar lordosis when standing and delay the onset of symptoms. Very substantial weight loss in the obese patient can reduce the degree of lumbar lordosis that occurs with standing and reduce the axial load on the lumbar spine. Analgesics are not very helpful because pain is intermittent and can be relieved by changing posture. Epidural corticosteroid injections, though often given, are of no benefit.[A9]

Without surgery, most patients gradually worsen, although some stabilize, and a small percentage improve. For patients who have appropriate symptoms for more than 3 months, have symptoms that interfere with their work or leisure activities, have progressive neurologic deficits, and have stenosis at one or more levels, the mainstay of treatment is elective surgical decompression, typically consisting of laminectomy with or without medial facetectomies at one or more levels. Lumbar fusion is of no incremental benefit,[A10] even in patients with spondylolisthesis of 3 mm or more.[A11] About 80% of patients improve after surgery, but postural low back pain may persist. Despite adequate decompression, about 30% of patients develop recurrent lumbar stenosis at another level after several years, and this risk is higher in patients with diffuse idiopathic skeletal hyperostosis.

In patients unable to tolerate laminectomy or with a shortened life expectancy, an alternative to laminectomy is an interspinous distraction device, which consists of a titanium rod that can be placed between adjacent spinous processes at one or two lumbar levels to prevent lumbar extension and provide symptomatic benefit for pseudoclaudication.[A12] The device is placed in an outpatient procedure under local anesthesia.

CERVICAL SPINAL STENOSIS AND SPONDYLOTIC MYELOPATHY

DEFINITION

Cervical spinal stenosis is narrowing of the cervical spinal canal due to congenital factors, acquired conditions (mostly spondylosis), or a combination of the two. Cervical spondylotic myelopathy occurs when cervical spondylosis causes spinal cord injury.

EPIDEMIOLOGY

The prevalence of cervical spondylosis is 95% in men and 89% in women over age 60 years. In one autopsy study of presumably asymptomatic patients, 7.5% were found to have spondylotic compression of their spinal cord. Risk factors include repeated trauma, male gender, older age, stenosis at another spinal level, and a positive family history.

PATHOBIOLOGY

Narrowing of the cervical spinal canal is due to bulging discs, which generate osteophytic spurring in the vertebral bodies, thickening of the posterior longitudinal ligament anterior to the spinal canal, thickening of the ligamenta flava posterior to the canal, enlargement of the uncovertebral processes, and enlargement of the facet joints. When the disc or hypertrophic spur projects posteriorly, the spondylotic bar compresses the spinal cord. The C5-6 level is most commonly affected, followed by C6-7 and then by C4-5, but more than one level is characteristically involved. Compression of one or more spinal nerves causes radiculopathy. In addition to static narrowing of the spinal canal, neck flexion (when the spinal cord is pulled over the spondylotic osteophytes and bulging discs) and neck extension (when the spinous process may get close to the most posterior aspect of the vertebral disc osteophyte complex and pinch the spinal cord) can cause a dynamic component. The mechanism of cord and nerve root injury is a combination of direct mechanical compression and impaired circulation.

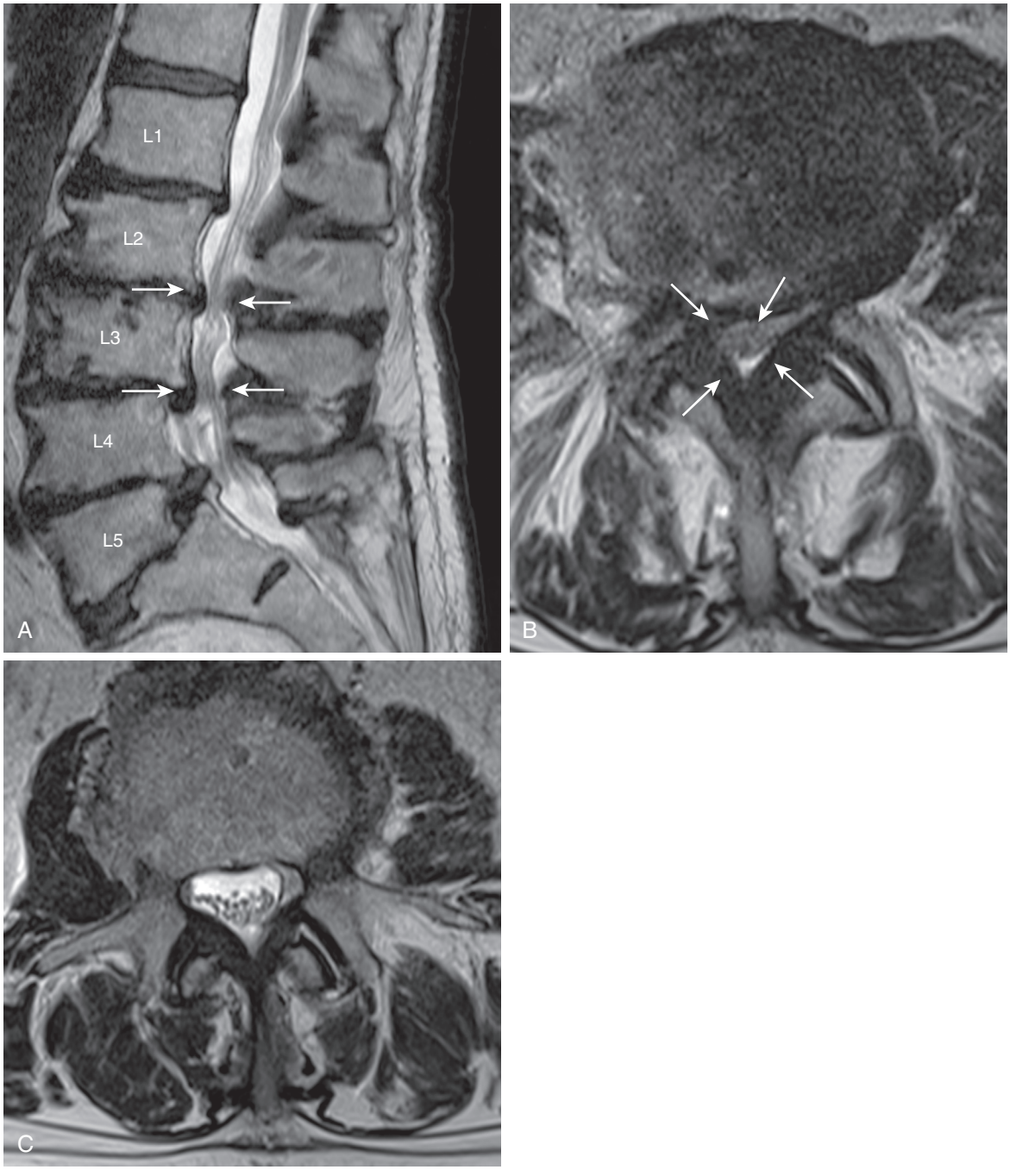

FIGURE 369-6. **Lumbar spinal stenosis. A**, Sagittal T2-weighted magnetic resonance image (MRI) of the lumbar spine shows severe stenosis at L2-3 and L3-4 (*arrows*). **B**, Axial T2-weighted MRI of lumbar spine shows severe stenosis at L3-4 level (*arrows*). **C**, Axial T2-weighted MRI of lumbar spine shows no significant stenosis at L1-2 level.

CLINICAL MANIFESTATIONS

Symptoms include neck pain; unilateral or bilateral upper limb pain; upper limb weakness, numbness, and loss of dexterity; lower limb stiffness, weakness, or sensory loss; urgency of bladder more likely than bowel; and the Lhermitte sign (electric-like pain or tingling down the spine or limbs with neck flexion or extension). The condition may be painless, and severe pain is uncommon. Neurologic symptoms are typically steady and persistent rather than transient or fluctuating.

On physical examination, the patient can have increased or reduced upper limb reflexes, increased lower limb reflexes, upper or lower limb weakness or sensory loss, abnormal reflexes, gait disturbance, and lower more often than upper limb spasticity.

DIAGNOSIS

MRI of the cervical spine is the diagnostic test of choice (Fig. 369-7) followed by CT myelography. The physician must recognize that cervical spondylosis and cervical spinal stenosis are common, often asymptomatic, and not necessarily the cause of a patient's symptoms. Signal abnormality within the spinal cord on MRI indicates that some cord injury has occurred. EMG can be helpful in excluding carpal tunnel syndrome, brachial plexus neuritis, and motor neuron disease and in documenting the presence of one or more cervical radiculopathies. Blood and cerebrospinal fluid (CSF) testing may be helpful to exclude, for example, tabes dorsalis (Chapter 295) and neuromyelitis optica (Chapter 380).

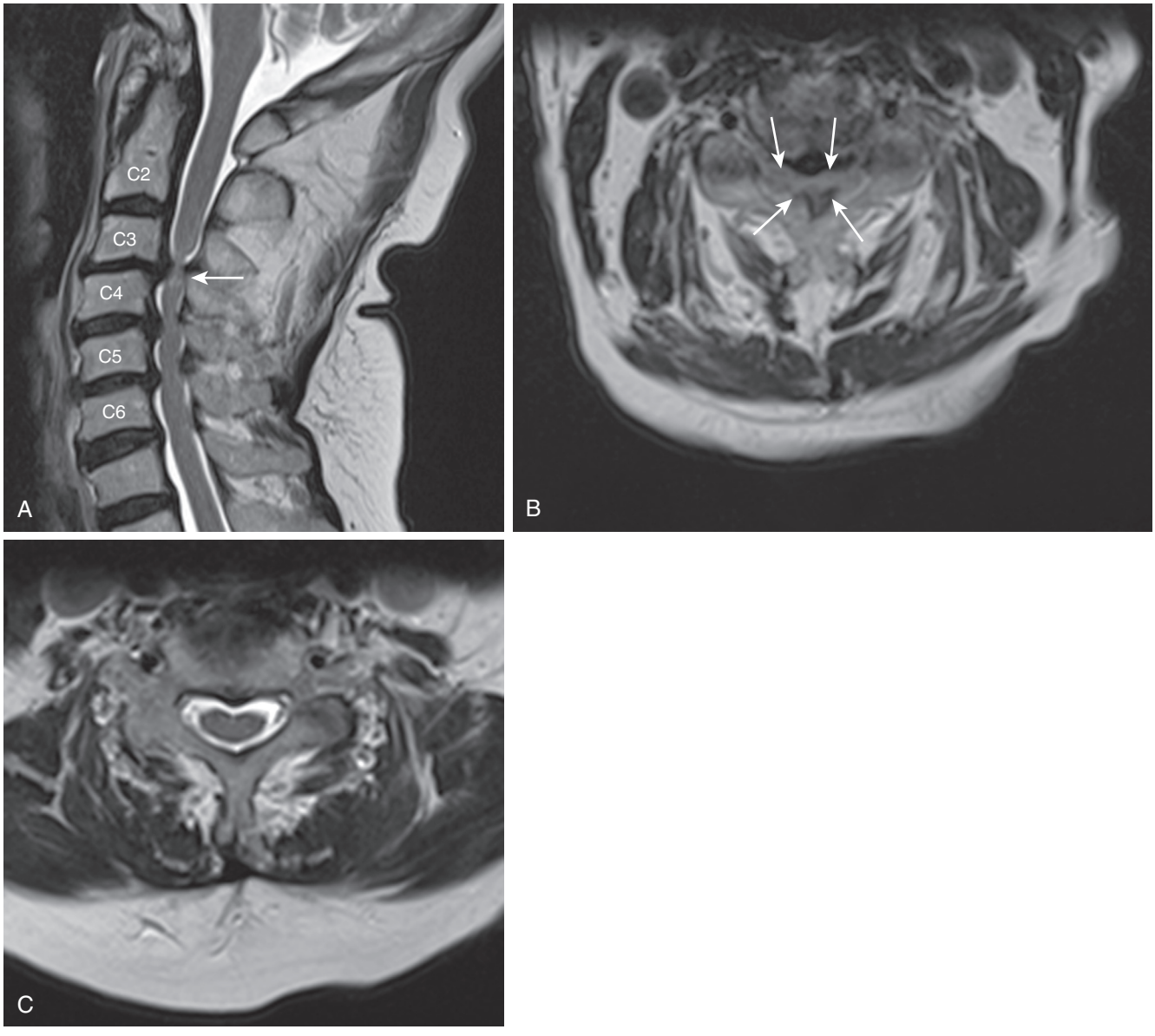

FIGURE 369-7. Cervical spinal stenosis. A, Sagittal T2-weighted magnetic resonance image (MRI) of the cervical spine shows multilevel spinal stenosis worse at C3-4 than at C4-5 than at C5-6. There is increased T2 signal within the spinal cord just below the C3-4 level indicating myelomalacia (*arrow*). **B,** Axial T2-weighted MRI of cervical spine at C3-4 level shows severe cord compression and deformity (*arrows*). **C,** Axial T2-weighted MRI of cervical spine at C6-7 level, away from severe stenosis shows a nearly normal appearance.

TREATMENT AND PROGNOSIS

Conservative treatment is aimed at controlling any pain, maintaining function (e.g., physical therapy, a gait aid), protecting the spinal cord from additional injury by avoiding head and neck trauma, and monitoring for neurologic worsening. Nonoperative therapy with little or no evidence includes a cervical collar during the day and a cervical pillow at night. Physical therapy should be directed at neurologic signs and symptoms (e.g., imbalance, weakness). Vigorous neck range-of-motion exercises should be avoided.

Medical treatments include NSAIDs (e.g., naproxen 400 mg twice daily) if pain control is needed (Chapter 26). Cervical epidural corticosteroid injections can be tried for radicular pain.[13]

Decompressive surgery, which is indicated for moderate to severe neurologic deficits or progressively worsening myelopathy,[14] results in neurologic improvement in 50 to 70% of patients. Recovery is typically incomplete and plateaus at about 6 months. Some patients have late deterioration with or without recurrent spinal stenosis. Surgery can be performed from an anterior or posterior approach with equal benefit.[A13] Anterior surgery includes discectomy and fusion. Posterior decompression, which is usually needed at more than one level, includes laminectomies or laminoplasty. Placement of an artificial cervical disc is an option for one- or two-level stenosis. Patients who have iatrogenic or congenital fusion develop new spondylotic degeneration at a level above or below their fusion at a rate of 3% per year and may require additional surgery.

PROGNOSIS

Without surgery, a small number of patients with cervical spondylotic myelopathy improve, 20 to 60% worsen either gradually or in a stepwise fashion, and many are stable for long periods.

DISORDERS OF THE NERVE ROOTS

DEFINITION

Disorders of the spinal nerve or nerve root, which is the short segment of nerve after the ventral and dorsal nerve roots have joined and before the spinal nerve divides into its ventral and dorsal rami, are termed radiculopathies. Symptoms depend on the specific spinal level and the side(s) involved.

EPIDEMIOLOGY

The average annual age-adjusted incidence rate for cervical radiculopathy is about 83/100,000. Men are affected nearly twice as often as women, and the peak age is 50 to 54 years. The annual incidence of new-onset lumbosacral radicular pain ranges from about 1.5% to 18.5%. The estimated prevalence of cauda equina syndrome among all patients with lower back pain is about 1 in 2500. Strenuous physical activity, cigarette smoking, and genetic factors are thought to increase the risk of disc herniation.

PATHOBIOLOGY

Irritation of the spinal sensory nerve root or dorsal root ganglion causes symptoms referable to that dermatome. Mechanical compression of the nerve contributes to the syndrome. In addition, inflammatory cytokines can leak from the nucleus pulposus into the epidural space, where they result in endoneurial edema and pain. The pro-inflammatory cytokine TNF-α is a likely key contributor. Herniation of the nucleus pulposus releases phospholipase A_2, which also plays an important role in the inflammatory process. The inflammatory process itself can cause pain in the absence of frank root compression.

Sciatica is pain in the distribution of the sciatic nerve, which receives contributions from the L4, L5, S1, and S2 nerve roots and innervates the ipsilateral buttock, posterior thigh, leg, and foot. Disc herniations, which are a frequent cause of sciatica, are most common at L4-5 and L5-S1. A herniated disc characteristically protrudes posterolaterally and impinges on the nerve that is migrating laterally to exit beneath the pedicle of the next lower vertebral segment. For this reason, a disc rupture usually compresses the nerve root that is one higher in number (and one lower in the spine). Hence, an L4 disc typically impinges on the L5 nerve, and an L5 disc compresses the S1 nerve. A far lateral disc protrusion can compress the spinal nerve at the same level as the protruded disc, and a large disc can compress more than one nerve root. In addition to disc herniation, sciatica can be caused by direct sciatic nerve injury anywhere along its course. The cauda equina syndrome results from disease involving multiple roots of the lower lumbar and sacral spinal levels as they travel downward within the spinal canal on their way to exit through their respective intervertebral (or neural) foramina.

CLINICAL MANIFESTATIONS

The symptoms of radiculopathy depend on the affected root (see Tables 369-1 and 369-2). Root involvement is likely if pain radiates beyond the shoulder or the knee. In the thoracic region, root involvement often produces symptoms that "wrap around" the trunk. Radicular pain is often worsened by activities that increase intraspinal pressure, such as coughing, sneezing, straining, and other Valsalva maneuvers. The character of the pain varies, but it is often described as sharp, shooting, electrical, or tingling. When reporting symptoms, patients may point to or rub the dermatome where they are experiencing discomfort. Patients also may report specific positions that increase or decrease pain; for example, sitting will often worsen the pain of acute lumbar disc herniation, and neck extension can produce radiating pain in cervical disc herniation or other processes that narrow the intervertebral foramen. Radicular pain often worsens when the patient is supine and frequently wakes the patient from sleep. Referred cervical root pain may affect only the scapula.

Patients often note hypesthesia (diminished sensation), which often follows a dermatome but also can be described as affecting a limb diffusely. Complaints of weakness may be difficult to localize to a particular muscle, except when the patient complains of a weak grip (C8 or T1) or a foot drop (L5).

Weakness can be asymptomatic (especially the triceps, C7, and the gastrocnemius, S1, muscles). Side-to-side strength testing aids in the detection of weakness. Mild weakness is more readily appreciated if the muscle is placed in a position of mechanical disadvantage (e.g., testing the triceps with the elbow flexed at ≥90 degrees). Slight weakness can also be identified by asking patients to walk on their toes, walk on their heels, and go up and down stairs or a stepstool. Sensory examination should test all potential root distributions. Testing pinprick is often sufficient. Hyperreflexia is not expected in a spinal nerve disorder and should raise questions about pathology in the spinal cord or brain (Chapter 368). Patients who are older than 65 years or who have a peripheral neuropathy (Chapter 388) can have reduced or even absent ankle and knee reflexes.

Cauda equina syndrome manifests as unilateral or bilateral leg weakness, saddle anesthesia, sexual dysfunction, urinary dysfunction with hesitancy or retention, and, less commonly, bowel dysfunction. Depending on the cause, it is frequently accompanied by low back pain. The syndrome can be accompanied by severe sciatica, which can be unilateral or bilateral and include perineal pain. Lower limb weakness, which may be asymmetrical, is of the lower motor neuron type.

DIAGNOSIS

The history and physical examination for suspected radiculopathy is similar to the evaluation of neck and lower back pain (see earlier), with special emphasis on finding evidence of nerve root deficits.

The patient should be asked about bowel and bladder dysfunction. Frank incontinence (Chapter 115) suggests either the cauda equina syndrome or a myelopathy. If the patient reports any loss of perineal sensation, such as might be noted during or after voiding or passing stool, the examination should test perianal sensation, anal sphincter strength and tone, and the anal reflex. Because the cauda equina syndrome involves nerve roots, reflexes should be normal or decreased; hyperactive reflexes or a Babinski sign suggest myelopathy.

For most patients with suspected spondylotic radiculopathy, no diagnostic testing is recommended for 4 to 6 weeks because symptoms may resolve with conservative treatment. Imaging to evaluate a potential radiculopathy is similar to the evaluation for neck and back pain (see earlier), and MRI (Fig. 369-8) is the best test in almost all instances. However, many imaging findings are asymptomatic and should be ignored. EMG can help determine whether a finding on MRI is truly associated with neurologic signs and symptoms, localize radicular abnormalities, judge their severity, and find comorbid or alternative neurologic disease, such as diffuse peripheral or focal entrapment neuropathies. EMG may not show abnormalities for 3 to 4 weeks following nerve root injury but has a high sensitivity and specificity for identifying chronic denervation when the motor component of the root is involved. EMG is less sensitive (about 30 to 70%) if only the sensory component of the root is involved by the lesion. An EMG is unnecessary if the diagnosis is clear from the history, physical examination, and MRI. In other situations, its high specificity complements the high sensitivity of MRI.

Many of the conditions that cause neck and low back pain can also cause radiculopathy including sciatica (Table 369-5). Spondylosis is the most common cause of radiculopathy, sciatica, and cauda equina syndrome, but the same symptoms and signs can be caused by infections (e.g., herpes zoster; Chapter 346), tumor (e.g., mass effect or leptomeningeal spread; Chapter 175), and scarring (e.g., post-surgical arachnoiditis). Disorders of the brachial plexus (e.g., brachial plexus neuritis) and lumbosacral plexus (e.g., diabetic radiculoplexus neuropathy; Chapter 388) also can simulate spondylotic radiculopathy.

Non-neurologic disorders, such as fibromyalgia (Chapter 253) and polymyalgia rheumatica (Chapter 250), can cause pain that mimics radiculopathy. Cervical radiculopathy also can be mimicked by acromioclavicular joint arthropathy, shoulder bursitis, rotator cuff disease, thoracic outlet syndrome,

FIGURE 369-8. Magnetic resonance imaging of a large lumbar disc herniation. (From *Spine Disorders: Medical and Surgical Management* by JD Bartleson and HG Deen; Cambridge University Press, 2009. Copyrighted and used with permission of Mayo Foundation for Medical Education and Research.)

TABLE 369-5 DIFFERENTIAL DIAGNOSIS OF LOWER LIMB PAIN SUGGESTIVE OF SCIATICA

Neurogenic within the spine
- Spondylotic
  - Herniated nucleus pulposus
  - Stenosis of central canal, lateral recess, or intervertebral foramen
  - Synovial cyst
- Arachnoid or perineural cyst
- Sterile inflammatory arachnoiditis
- Tumor: primary (e.g., neurofibroma, ependymoma) or metastatic (bone or epidural space, meningeal)
- Infection: disc, epidural, herpes zoster, Lyme disease
- Inflammatory radiculopathy (e.g., sarcoidosis, paraneoplastic)

Neurogenic outside of the spine (e.g., lumbosacral plexus, sciatic neuropathy, peripheral neuropathy)

Non-neurogenic
- Musculoskeletal
- Peripheral vascular disease

and the shoulder impingement syndrome. Lumbar radiculopathy can be mimicked by hip arthritis, trochanteric bursitis, sacroiliac joint disease, piriformis syndrome, iliotibial band syndrome, and hamstring tendinitis (Chapter 242).

The most common cause of cauda equina syndrome is a very large L4-5 or L5-S1 disc herniation. Other causes include tumor, abscess, epidural hematoma, and scarring. Depending on the rate of progression, cauda equina syndrome should be considered an emergency. Unless the onset is gradual, emergent or possibly urgent lumbar spine MRI and neurosurgical consultation should be obtained.

TREATMENT

Acute radicular symptoms are usually self-limited and resolve on their own. Treatment with medications and physical therapies are as for neck and lower back pain. Pregabalin is not helpful for acute or chronic sciatica.[A14]

If radiculopathy is associated with an underlying lesion other than spondylosis, such as infection (Chapter 382) or tumor (Chapter 175), treatment should be directed toward that process. Surgery is indicated for spinal instability, severe or progressive neurologic deficits, myelopathy, neurologic deficits critical to the patient's vocation or avocation, or uncontrollable severe radicular pain in the presence of root compression.

In cervical radiculopathy, transforaminal epidural corticosteroid injections can provide short-term pain relief with an acceptable risk. In cervical spondylotic radiculopathy, surgery provides more rapid pain relief than does physical therapy, but little or no long-term benefit. Anterior cervical discectomy with fusion or with placement of an artificial disc (arthroplasty) provides equivalent symptomatic benefit.[A15] Cervical laminectomy and discectomy from a posterior approach are also effective.[A16]

For lumbar radiculopathy, epidural corticosteroid injections may provide relatively minor short-term pain relief for 2 to 6 weeks, but they do not improve function or relieve pain beyond 3 months.[A17] In some cases, temporary relief of symptoms may help confirm a causal link with an injected anatomic site. There is no evidence that epidural injections avoid eventual surgical intervention. For symptomatic lumbar radiculopathy due to a herniated disc, either open surgical discectomy or microdiscectomy (Video 369-7) is superior to nonsurgical therapy[A18] in the short term (6 months), but not necessarily in the medium or long term. If the condition is isolated to a single disc and no significant degenerative changes are present, longer duration of benefit is more likely. Patients who derive a greater benefit from surgery include those in whom MRI shows a herniated disc with compression of the thecal sac of one third or more, or those with nerve root compression. Minimally invasive procedures are not clearly better than standard approaches.[A19]

DISORDERS OF THE SPINAL CORD

DEFINITION AND OVERVIEW

A disorder of the spinal cord is termed a myelopathy. A myelopathy can be intramedullary, as the result of a disorder intrinsic to the cord, or extramedullary, as the result of an abnormality that is extrinsic to the cord but compressing it. Extramedullary lesions can be further divided into intradural (within) and extradural (outside) the dura.

TABLE 369-6 CAUSES OF MYELOPATHY

Extramedullary and Compressing the Spinal Cord
- Cervical stenosis (spondylosis, congenital)
- Cervical disc herniation
- Diffuse idiopathic skeletal hyperostosis
- Tumor
- Synovial or arachnoid cyst
- Infection (e.g., epidural abscess [Chapter 382], osteomyelitis [Chapter 251])
- Epidural hematoma (Chapter 368)
- Trauma (Chapter 368)
- Rheumatoid arthritis (Chapter 243), ankylosing spondylitis (Chapter 244)
- Other: Paget disease (Chapter 228), epidural lipomatosis, ossification of posterior longitudinal ligament

Intramedullary and Intrinsic to Spinal Cord
- Tumor (Chapter 175)
- Infection (e.g., syphilis [Chapter 295]; HIV-associated [Chapter 359], HTLV-1 [Chapter 360])
- Demyelinating (e.g., multiple sclerosis [Chapter 380], neuromyelitis optica [Chapter 392], acute disseminated encephalomyelitis [Chapter 380]), acute transverse myelitis [Chapter 380]
- Inflammatory (e.g., systemic lupus erythematosus [Chapter 245], Sjögren syndrome [Chapter 247], Behçet disease [Chapter 249], sarcoidosis [Chapter 83], paraneoplastic [Chapter 164])
- Metabolic: Deficiency of vitamin B_{12}, folic acid, vitamin E, copper
- Postradiation myelopathy
- Hereditary spastic paraparesis (Chapter 379)
- Vascular (e.g., spinal cord infarction, vascular malformation)
- Syringomyelia (Chapter 385)
- Nitrous oxide
- Sarcoidosis (Chapter 83)
- Motor neuron disease (Chapter 387)

HIV = human immunodeficiency virus; HTLV = human T-lymphotropic virus.

EPIDEMIOLOGY AND PATHOBIOLOGY

Spinal cord disorders can be caused by a wide range of conditions (Table 369-6), but cervical spondylotic myelopathy is the most common cause.

The functional elements of the spinal cord (Fig. 369-9) include tracts descending to motor and autonomic neurons, as well as ascending sensory tracts. The anterior horn cell motor neuron is the cell body for the axon that will become the anterior nerve root and continue directly to innervate skeletal muscle. The cell bodies for the primary sensory neurons reside in the dorsal root ganglia outside the spinal cord itself.

CLINICAL MANIFESTATIONS

The clinical manifestations of myelopathy correlate with the spinal level of the lesion and the affected columns or tracts. Myelopathies typically affect both sides of the spinal cord, but they can be asymmetric or unilateral. In general, all three major functions—motor, sensory, and autonomic (e.g., bowel and bladder control)—are affected.

The anterior cord syndrome is manifested as lower motor neuron weakness at the level of the lesion (anterior horn damage); upper motor neuron weakness and spasticity below the lesion (corticospinal tracts); autonomic dysfunction below the level of the lesion (lateral horn); and loss of pain and temperature sensation below the level of the lesion (spinothalamic tract). Vibration and joint position sense remain intact (posterior columns). The major causes of this syndrome are vascular, such as an anterior spinal artery occlusion, or an anteriorly impinging mass lesion, such as a disc or vertebral body mass.

The central cord syndrome is characterized by lower motor neuron signs and symptoms at the level of the lesion (anterior horn cells), upper motor neuron signs and symptoms below the lesion (corticospinal tracts), urinary retention, and a band of loss of temperature and pain sensation at the level of the lesion (anterior white commissure decussation of these fibers). In the mid-cervical level, this syndrome is typical of syringomyelia (Chapter 385). Other major causes include cervical trauma (Chapter 368), especially when patients with preexisting cervical spondylosis sustain a hyperextension injury, and intramedullary tumors (Chapter 175).

The posterior cord syndrome is manifest by imbalance, especially in the dark or with eyes closed, and an examination notable for sensory ataxia, presence of the Romberg sign, and loss of vibration and position sense below

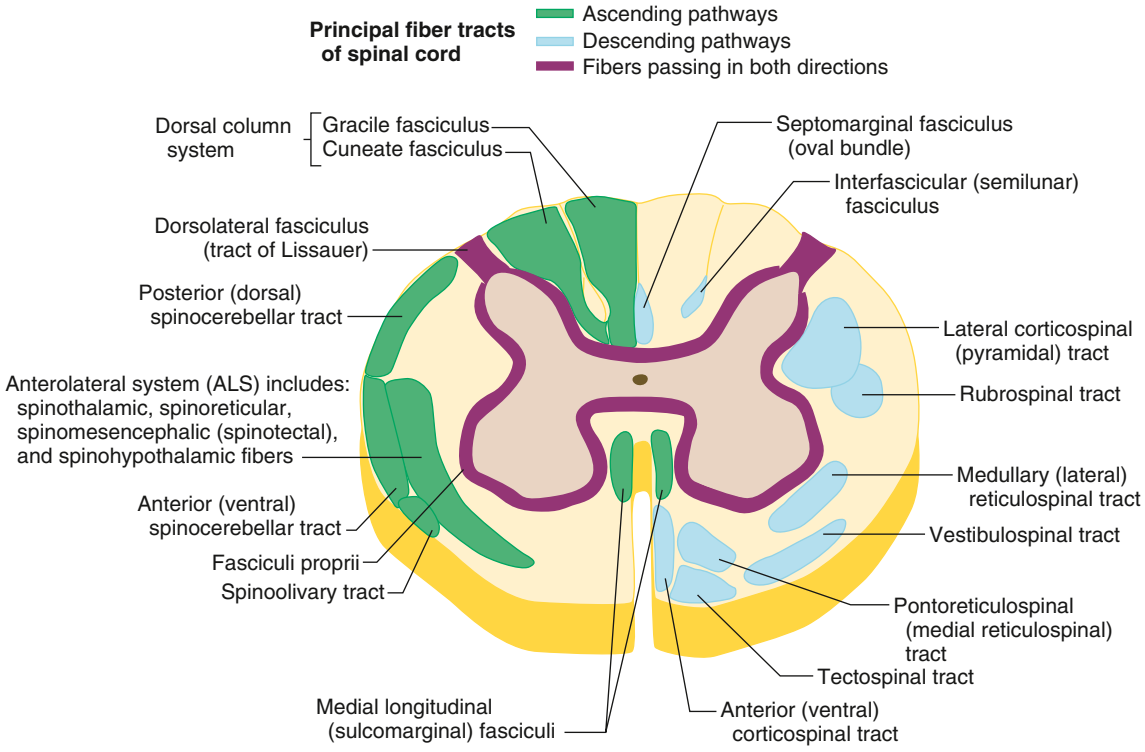

FIGURE 369-9. **Principal fiber tracts of the spinal cord.**

the level of the lesion (posterior columns), with preservation of pain and temperature sensation. Patients are seldom weak. Posterior cord dysfunction may be caused by spondylotic disease, but other causes include deficiency of vitamin B_{12}, copper deficiency (which can be caused by excess zinc intake), vitamin E deficiency (Chapters 199 and 384), syphilis (Chapter 295), AIDS-associated vacuolar myelopathy (Chapter 359), and nitrous oxide inhalation (Chapter 400).

The Brown-Séquard (cord hemisection) syndrome combines features of these syndromes. At the level of the lesion, patients exhibit ipsilateral lower motor weakness (anterior horn) and loss of all sensation (posterior root entry zone). Below the level of the lesion, patients have ipsilateral upper motor neuron weakness and spasticity (corticospinal tract) and ipsilateral loss of vibration and joint position sense (posterior columns), with contralateral loss of pain and temperature (spinothalamic tract, the fibers of which have crossed from the opposite side through the anterior white commissure). The Brown-Séquard syndrome is often caused by trauma (Chapter 368) or eccentric compression.

The conus medullaris syndrome refers to dysfunction of the distal-most tapered portion of the spinal cord, which anatomically lies at approximately the T12-L1 vertebral spine level. The arms are normal; weakness in the legs is variable but often symmetrical when it is present. The main signs and symptoms are sexual dysfunction, loss of bowel and bladder control, and perianal anesthesia with loss of the anal reflex. The major causes are disc herniation, lumbar stenosis, trauma, and neoplasm.

With high cervical spine lesions, paresis or paralysis of the diaphragm and respiratory failure can occur. In lesions of the thoracic level or above, interruption of the lateral column autonomic pathways can lead to autonomic instability, including labile blood pressure. At any level, but especially at the conus and cauda equina levels, acute urinary retention can occur.

Spinal epidural hematoma (Chapter 368) is a relatively uncommon condition that can cause very rapidly progressive (hours to days) spine and radicular pain, myelopathy, and/or the cauda equina syndrome depending on the location of epidural bleeding. The hematoma often extends over several spinal segments. The condition is typically caused by trauma including lumbar puncture, spinal manipulation, and spine surgery, and it often occurs in patients with a congenital or acquired coagulopathy. MRI is the diagnostic test of choice.

DIAGNOSIS

Symptoms of bilateral involvement of the arms or legs suggest a myelopathy, although bilateral lower limb involvement can be seen in lumbar spinal stenosis and the cauda equina syndrome. Complaints of leg stiffness or incoordination suggest spasticity from myelopathy. Other symptoms include a recent change in bowel or bladder function, erectile dysfunction, imbalance (especially in the dark or with eyes closed), and catching of the feet when walking. These central symptoms can also reflect lesions of the brain stem and higher, so the patient should be asked about cortical and brain stem symptoms (e.g., cognitive function, vision, facial strength, sensation, and swallowing). Focal cervical or thoracic spine pain supports a myelopathy.

Examination for a potential myelopathy must include an evaluation of anal tone and perineal sensation. The patient's gait should be tested fully clothed. Then, the patient should be examined in a gown to allow inspection of the spine and overlying skin. A sensory level, which represents a point where distal sensation is altered, should also be sought but is not always found. Joint position sense can be reduced if the posterior columns are involved. Tandem gait testing identifies possible ataxia. Finally, the patient should be examined for spasticity by testing limb muscle tone and deep tendon reflexes. In acute spinal cord lesions, however, a state of "spinal shock" can cause hyporeflexia or even flaccid paralysis.

Ancillary Testing

MRI is the test of choice because it provides anatomic detail of the spine and subarachnoid space as well as the spinal cord. MRI can also show evidence of demyelination or metastatic disease. If MRI is normal, lumbar puncture and blood tests can be useful for diagnosing conditions that resemble or cause myelopathy (e.g., neuromyelitis optica; Chapters 380 and 392), infectious or carcinomatous meningitis (Chapter 381), syphilis, herpes simplex, varicella-zoster virus, deficiency states, and paraneoplastic conditions.

Differential Diagnosis

Many causes of myelopathy can occur at any spinal level, but certain conditions predominate at specific spinal levels. Any lesion that has an upper cervical localization must be evaluated for disorders of the craniocervical junction, especially disorders that can produce atlantoaxial instability, such as rheumatoid arthritis, ankylosing spondylitis (Chapter 243), and Down syndrome (Chapter 385). After trauma, cervical or odontoid fracture must be excluded. Disorders at the base of the skull, such as Chiari I and other congenital malformations (Chapter 385), can sometimes affect the upper cervical cord. Syringomyelia (Chapter 385), which may or may not be associated with Chiari malformation, also has a predilection for the cervical cord.

The thoracic cord is the most common site for metastatic cord compression. Transverse myelitis most commonly affects the thoracic level, and the thoracic cord also is particularly vulnerable to a watershed ischemic myelopathy due to severe hypotension. Epidural lipomatosis is most symptomatic at the thoracic

level. Ossification of the posterior longitudinal ligament has a predilection for the cervical spine.

The rapidity of onset helps in diagnosis. Acute or relatively acute myelopathy suggests a vascular cause, disc herniation, trauma, demyelinating lesions, or a pathologic fracture. In a young person with no other comorbid illnesses, a demyelinating illness, such as multiple sclerosis, neuromyelitis optica (Chapters 380 and 392), or acute disseminated encephalomyelitis (Chapter 383), is suggested. In older persons or patients with known vascular risk factors, hypotension or onset in the immediate postoperative period, spinal cord infarction is possible. Sudden sharp back pain suggests a mechanical disorder (e.g., pathologic fracture, sudden worsening of spondylolisthesis) or spinal cord infarction, whereas demyelinating lesions are often painless.

Myelopathy developing subacutely, especially accompanied by back pain, can be caused by metastatic disease (Chapter 175) and epidural abscess (Chapter 382). Both conditions must be evaluated and treated as emergencies to prevent permanent paralysis. Subacute or chronic myelopathies include vitamin B_{12} deficiency (Chapter 384), syringomyelia (Chapter 385), and slowly growing tumors, such as meningiomas (Chapter 175), ependymomas, and neurofibromas (Chapter 385).

In the setting of known malignant disease or unexplained weight loss, metastatic cord compression (Chapter 175) must be considered.[15] Weight loss, back pain, and fever can be seen in infection (Chapters 381 and 382) and occasionally with spondyloarthropathies (Chapter 244). Infectious causes include tropical spastic paraparesis (human T-lymphotropic virus type 1 [HTLV-1; Chapter 360]). Syphilis (Chapter 295) is the cause of tabes dorsalis; patients may have lancinating pains, gait ataxia, depressed lower limb reflexes, and Argyll Robertson pupils. Myelopathies that follow an infectious illness include acute disseminated encephalomyelitis and transverse myelitis (Chapter 380). Myelopathy accompanied by evidence of multifocal central nervous system dysfunction suggests multiple sclerosis or acute disseminated encephalomyelitis (Chapter 380). An accompanying peripheral neuropathy is seen in vitamin B_{12} deficiency myelopathy (Chapter 384), which causes gait ataxia. Rheumatoid arthritis (Chapter 243) and ankylosing spondylitis can cause atlantoaxial instability and C1-C2 subluxation. Other systemic illnesses, such as systemic lupus erythematosus (Chapter 245), Behçet syndrome (Chapter 249), and sarcoidosis (Chapter 83), can also cause myelopathies. In patients with exogenous or endogenous hypercortisolemia (Chapter 208), epidural deposition of fat can cause dorsal epidural lipomatosis that can compress the spinal cord. A remote history of cord trauma raises the possibility of post-traumatic syringomyelia.

TREATMENT AND PROGNOSIS

Depending on the rate of worsening, patients with spinal cord lesions may need urgent or emergent assessment and treatment to prevent further deterioration and hopefully to restore lost function. Surgery may be needed for cord compression (e.g., disc, tumor, abscess). For a spinal epidural hematoma, the recommended treatment is reversal of anticoagulant therapy, evacuation of the blood clot, and emergent laminectomy if needed. Other specific causes require targeted treatment.

Prognosis depends on the diagnosis, severity of the condition, and the patient's response to appropriate treatment. Long-term complications of spinal cord injury include osteoporosis (Chapter 225), orthostatic hypotension (Chapter 49), deep vein thrombosis (Chapter 68), decubitus ulcers, autonomic dysreflexia (Chapter 386), and chronic neuropathic pain (Chapter 26).

SPECIFIC CAUSES OF MYELOPATHIES

VASCULAR MYELOPATHIES

Like the brain, the spinal cord is intolerant of ischemia. Vascular myelopathy occurs when there is loss of blood flow to the spinal cord, whether it is acute or chronic and whether the cause is ischemic or hemorrhagic.[16]

Blood supply to the spinal cord comes from one anterior and two posterior spinal arteries that run longitudinally along the length of the spinal cord (Fig. 369-10). The paired posterior spinal arteries arise rostrally as branches of the vertebral arteries at the level of the medulla and run inferiorly along the posterolateral surface of the spinal cord. The anterior spinal artery is formed superiorly when branches of the vertebral artery join to form a single anterior spinal artery, which then runs down the midline of the anterior surface of the spinal cord. The main caudal anterior spinal blood supply is from a large artery of Adamkiewicz that enters the spinal canal through an intervertebral foramen somewhere between T5 and L1, usually on the left, and supplies most of the lower spinal cord and conus medullaris.

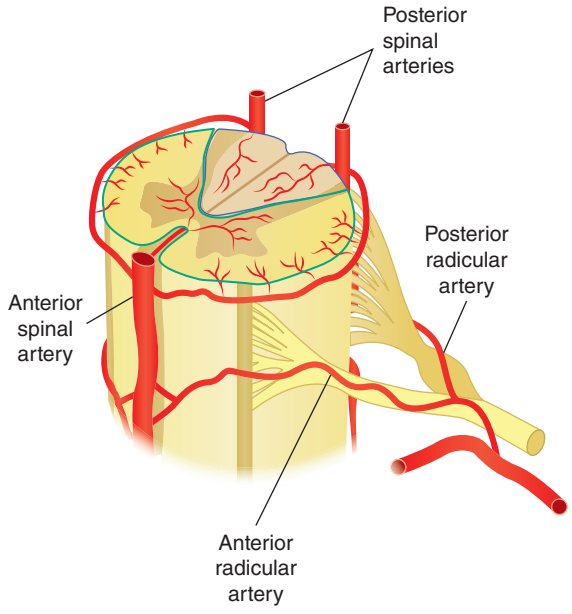

FIGURE 369-10. Blood supply of the spinal cord: section through the thoracic level, anterosuperior view. The anterior spinal artery supplies the anterolateral two-thirds of the cord. (From *Spine Disorders: Medical and Surgical Management* by JD Bartleson and HG Deen; Cambridge University Press, 2009. Copyrighted and used with permission of Mayo Foundation for Medical Education and Research.)

Spinal cord compression and compromise of the microvascular supply to the cord underlie the gliotic changes in many slowly progressive myelopathies such as spondylotic myelopathy. Overt ischemic causes include hypotension, atherosclerotic disease, embolic events, vasculitis (Chapter 249), decompression sickness (Chapter 82), and vascular steal.

Spinal dural arteriovenous fistulas are the most common type of spinal cord vascular malformation. Vascular malformations can cause myelopathy by acting as mass lesions that compress local structures, by interfering with normal venous drainage, by diverting blood as part of a vascular steal with exercise of muscles that compete for blood flow, or by bleeding. Spinal cord hemorrhage, which is rare, can be caused by trauma, bleeding into a tumor, an intramedullary vascular malformation, or a complication of anticoagulant therapy. Epidural hematomas cause cord compression and can occur as a complication of surgery or lumbar puncture, especially in patients with a bleeding diathesis.

CLINICAL MANIFESTATIONS

Occlusion of the artery of Adamkiewicz usually presents with signs of thoracic watershed ischemia—paraplegia with relative sparing of the sacral roots and dorsal columns. Infarction in the anterior spinal artery distribution results in dysfunction of the anterior two thirds of the cord, including the anterior horns, spinothalamic tracts, and corticospinal tracts. Patients usually present with acute paraparesis and impaired bowel and bladder function. Below the level of the lesion, temperature and pain sensation are lost, but vibration and joint position sense are preserved.

Infarction in the distribution of the posterior spinal arteries is less common because of better collateral circulation. Clinical manifestations include loss of vibration and joint position sense, ataxia, gait disturbance, and positive Romberg sign. Reflexes may be depressed at the level of infarction.

Vascular malformations most often have a chronic or stepwise progressive clinical course. Pain is common. Arteriovenous fistulas frequently occur in the thoracic cord and present with progressive paraplegia.

DIAGNOSIS

Vascular malformations are initially evaluated by MRI. If embolization or surgery is being considered, spinal angiography is needed to identify feeding and draining vessels. When imaging is equivocal, lumbar puncture can be considered; an elevated leukocyte count (>10 cells/μL of CSF) suggests an inflammatory myelopathy rather than a vascular lesion.

TREATMENT AND PROGNOSIS

Treatment options for spinal cord ischemia are limited and include reversal of the cause of ischemia, such as by correcting hypotension (Chapter 92). Prognosis for most cases of spinal cord infarction is poor unless blood flow is restored rapidly. In one study 3-year mortality was 23%, 42% of survivors needed wheelchairs, but 40% of those in wheelchairs at hospital discharge were able to walk 3 years later.

Arteriovenous fistulas are treated by occluding the shunt with embolization or surgery. Successful treatment may arrest worsening and improve symptoms. Patients with suspected epidural hematomas (Chapter 368) require emergency surgery if they have severe or progressive neurologic dysfunction.

INFLAMMATORY, METABOLIC, AND INFECTIOUS MYELOPATHIES

Transverse myelitis,[17] multiple sclerosis, neuromyelitis optica, and other demyelinating diseases are considered in Chapter 380. Metabolic myelopathies can be caused by vitamin B_{12}, vitamin E, folate, and copper deficiencies (Chapter 199).

Acute disseminated encephalomyelitis is mostly a monophasic disorder of demyelination of the spinal cord and brain. If it is isolated to the spinal cord, it is termed transverse myelitis. Extensive evaluation of presumed idiopathic transverse myelitis frequently leads to a more precise diagnosis, such as multiple sclerosis (Chapter 380) or sarcoidosis (Chapter 83) affecting the spinal cord.

Connective tissue diseases can infrequently cause myelopathy. Systemic lupus erythematosus (Chapter 245) with or without antiphospholipid antibody can cause myelitis in 1 to 3% of patients. Sjögren syndrome (Chapter 247), Behçet syndrome (Chapter 249), sarcoidosis (Chapter 83), mixed connective tissue disease (Chapter 249), and systemic sclerosis (Chapter 246) can be associated with inflammatory myelitis.

HIV can cause a vacuolar myelopathy that is not always symptomatic. Human T-lymphotropic virus type 1 (HTLV-1)–associated myelopathy, also known as tropical spastic paraparesis (Chapter 360), is a chronic progressive myelopathy that can cause leg weakness, spasticity, loss of vibratory sense, and bladder dysfunction. Transformation to myelopathy, which occurs in less than 10% of infected patients, is thought to be largely related to the host's immune response. Tertiary syphilis (Chapter 295) affecting the spinal cord is called tabes dorsalis and is rarely seen today.

DIAGNOSIS

In general, diagnosis of these myelopathies is based on the history, clinical examination, MRI, analysis of the CSF, and blood tests. With inflammatory myelopathies, MRI often shows increased T2 signal and focal enlargement of the spinal cord.

TREATMENT

Intravenous corticosteroid infusions (e.g., methylprednisolone 1 g intravenously daily for 5 days) are used to treat acute attacks of inflammatory myelopathy. In patients who do not respond to corticosteroids, plasma exchange can be effective. About 60% of patients show improvement at 6 months. Factors predicting improvement are initiation of treatment within 15 days of the onset of symptoms and evidence of early improvement. Disease-modifying therapies are indicated for inflammatory demyelinating disease.

Metabolic deficiencies can be replaced. Aggressive antiretroviral therapy can lead to improvement in HIV myelopathy. No effective treatment is available for HTLV-1–associated myelopathy (Chapter 360).

METASTATIC SPINAL CORD COMPRESSION

When metastatic cancer invades the spine or epidural space, the resultant destruction and tumor growth compress the spinal cord and lead to myelopathy. The prevalence of metastatic spinal cord compression may be as high as 5% in patients with cancer, depending on the type of malignant neoplasm and its tendency to metastasize to bone. Prostate (Chapter 186), breast (Chapter 183), and lung (Chapter 177) cancers each account for approximately 15 to 20% of cases, and non-Hodgkin lymphoma (Chapter 171), renal cell cancer (Chapter 182), and multiple myeloma (Chapter 173) account for about 5 to 10% each.

Metastatic cancer usually causes compression because of an extradural tumor, although metastatic lesions can be intradural-extramedullary. Intramedullary metastases are rare. Symptoms can be caused by direct compression of the cord and roots in the epidural space as a result of direct extension from a hematogenous metastasis to the vertebral body. However, some tumors (e.g., lymphomas) may grow through the intervertebral foramina without causing significant bone destruction. Vertebral destruction can make the spine unstable and cause pathologic fractures that lead to damage of the cord and root.

CLINICAL MANIFESTATIONS

About 90% of patients present with pain that is classically worse on lying down and increases with the Valsalva maneuver. If the nerve root is involved, the pain will have a radicular component; if there is bone collapse, pain can be made worse by movement. At the time of diagnosis, muscle weakness is present in 35 to 75% of patients, sensory deficits in 50 to 70% of patients, and autonomic dysfunction in 50 to 60% of patients. Signs and symptoms depend on the level of compression.

DIAGNOSIS

Spinal cord compression must be suspected when any patient with a history of cancer complains of new spine pain. Even in the absence of neurologic signs or symptoms, suspected compression is a neurologic emergency. MRI is the test of choice because of its ability to detect soft tissue masses, spinal cord and nerve root damage, and bone pathology. CT myelography should be used if MRI cannot be performed. Because up to 35% of patients have more than one site of metastasis, the entire spine should be imaged.

Differential Diagnosis

For metastatic extradural tumors, the differential diagnosis includes lipoma, neurofibroma (Chapter 385), meningioma (Chapter 175), chordoma, vascular malformation, and abscess. For intradural-extramedullary lesions the possibilities include neurofibroma (Chapter 385), neurinoma, meningioma, vascular malformation, and arachnoid cyst. The differential diagnosis for intramedullary lesions includes vascular malformation, ependymoma, astrocytoma, and syringomyelia.

TREATMENT

Prompt initiation of corticosteroids (e.g., dexamethasone, loading dose of 10 to 16 mg followed by tapering over 10 to 14 days) and radiation therapy are the mainstays of initial therapy. Patients with an unstable spine, limited disease burden, and a relatively favorable prognosis may benefit from decompressive resection and spinal stabilization. Vertebroplasty and kyphoplasty may provide symptomatic help for patients who are not candidates for radical spine surgery.

PROGNOSIS

Metastatic spinal cord compression usually occurs in the setting of metastases to multiple locations, and the expected prognosis for survival is generally less than 6 months. Prognosis is improved in patients with neoplasms that are sensitive to corticosteroid therapy (especially lymphoma and leukemia) or are radiosensitive (e.g., multiple myeloma, small cell lung cancer). Patients who are ambulatory at the time of diagnosis, have a single site of compression, and have a slower onset of symptoms also have a better prognosis.

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370 REGIONAL CEREBRAL DYSFUNCTION: HIGHER MENTAL FUNCTIONS

DAVID S. KNOPMAN

DEFINITION

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The evaluation of higher mental function presupposes that the patient has intact arousal and alertness. Higher mental function is not a unitary entity, and these functions are not homogenously distributed throughout the brain. Human cognitive functioning can be decomposed into several domains (memory, language, visuospatial cognition, and executive cognitive functioning), each with a regional anatomic localization in the brain.

CLINICAL MANIFESTATIONS AND DIAGNOSIS

In the vast majority of encounters with patients in the practice of adult medicine, the default approach to patients should be that they have no cognitive impairment, defined by the absence of evidence of cognitive dysfunction. No cognitive impairment implies that the clinician believes that the patient possesses sufficient mental capacity to understand the nature of their own health, to acquire and retain new information, to appreciate the consequences of most choices related to their well-being, and to be able to weigh different options on their merits and risks. Thus, a determination of no cognitive impairment means that a patient must be treated as a competent adult and afforded the agency to engage in medical and other decisions. This determination may be based on the clinician's own observations of the patient, on the patient's own statements regarding their thinking and memory, or on presumably reliable family members or close companions of the patient.

By comparison, a provisional impression of cognitive impairment cannot be based on an informal conversation. Rather, it requires further attention (Fig. 371-1, Chapter 371), including a history from the patient, a family member, or companion regarding the patient's capabilities in instrumental and basic activities of daily living, as well as a more formal examination of cognition. The purpose of the formal cognitive assessment is to gain an objective measure from which the clinician can judge whether the responses meet expectations for cognitive normality.

Bedside evaluations of orientation, memory, language, reasoning, and visuospatial function can be used to derive an impression of cognitive function using relatively brief but validated instruments (see Chapter 361). Performance on these brief examinations of cognition must be evaluated in the context of the patient's alertness, cooperation, education, native language, sensorimotor function, and mood (i.e., in light of the totality of the medical and psychosocial condition of the patient). If uncertainty exists as to whether a patient has cognitive impairment after careful consideration of the findings from the history and examination, more detailed cognitive testing by a neuropsychologist may be indicated.

MEMORY FUNCTION AND AMNESIC DISORDERS

DEFINITION

Amnestic disorders almost always involve impairment in learning new information and involve dysfunction in the episodic memory system.[1] Episodic memory refers to learning and recall of specific events. Retention of information for more than a few seconds in the face of exposure to additional facts, details, or events requires a person to encode, store, and organize the information suitable for later recall. Anterograde amnesia is the clinical manifestation of disturbances in episodic memory. Anterograde refers to failure to learn, and hence recall, new information on an ongoing basis. Some conditions that cause acute brain injury also lead to retrograde amnesia, a disturbance of the ability to retrieve information that was acquired some time prior to the brain injury.

Immediate recall of information with zero delay and zero intervening information is a very short-term memory function. Immediate memory is capable of storing an image of an auditory message in exact form, but only a small amount and for a short period. The fidelity of immediate memory recall accuracy drops off dramatically over seconds, particularly if intervening sensory stimuli attract attention. A comparable system exists in the visual modality in that the memory acts like a photograph that fades rapidly. From a clinical perspective, immediate memory is separate from episodic memory. Immediate recall is generally used as a marker of attention and alertness and not memory per se.

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The hippocampal formations are the anatomic structures of importance for the declarative episodic memory system. The hippocampal formations are imaged well with magnetic resonance imaging (MRI). The principal input to the hippocampus comes through the entorhinal cortex from multimodal association areas in the frontal, parietal, and temporal neocortices. A second important input is a cholinergic pathway that originates in the septum of the medial-orbital frontal lobe. There are two principal output circuits of the hippocampal formations. One is via the subiculum back to multimodal association areas. The other hippocampal efferent pathway projects via the fornix to the mammillary bodies. The projection from the mammillary bodies passes through the medial thalamus to the ventral anterior nucleus of the thalamus, then to the posterior cingulate, and then back to the entorhinal cortex. The hippocampal circuit is believed to facilitate the formation of memory in association neocortices. The hippocampus does not store a particular learned fact, but rather it enables the appropriate region in a multimodal association cortical region to do so.

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ABSTRACT

Cognitive dysfunction is subdivided into four key domains: memory, language, visuospatial, and executive functioning, each with a unique brain localization. Disorders of memory are especially linked to the hippocampal formations. Disorders of language are typically localized to the peri-Sylvian cortex of the dominant hemisphere, its underlying fiber pathways, and its related subcortical nuclei. Visuospatial disturbances are localized to the nondominant parieto-occipital regions. Executive dysfunction is diffusely represented, with lesions of the frontal or anterior temporal lobes being the most discrete loci, but many other cortical regions and pathways are also involved.

KEYWORDS

memory
executive function
visuospatial function
language function
aphasia
amnesia
visual agnosia

more evident to the family and acquaintances of patients with the disorder than they are to the patients themselves. Anosognosia (lack of awareness) for the deficit of anterograde amnesia is very common, though not universal. In contrast, many patients with milder amnestic disorders can recall information from years or decades earlier, as those memories are more permanently stored.

Objective testing of short-term memory is a critical diagnostic step in the evaluation of persons with memory complaints. Testing of memory can be performed at the bedside in alert patients. The patient is asked to learn three or four words and recall them after 1 or 2 minutes. A patient with severe anterograde amnesia will recall none or, at most, one of the words, whereas individuals with normal memory can recall all of the words or all but one.

In patients with questionable memory difficulties, assessment by an experienced neuropsychologist can be helpful. Standardized tests of memory have greater precision and reliability than bedside tests and involve the use of lengthier material to be remembered and a longer delay between learning and recall.

Determining the Cause

Anterograde Amnesia

Alzheimer disease is the most common context in which anterograde amnesia occurs (Chapter 371). In Alzheimer disease, anterograde amnesia is usually the dominant cognitive symptom, not only as the earliest symptom but also as a very prominent symptom across the duration of the disease. Hippocampal atrophy is common (Chapter 371, Fig. 371-3). Anterograde amnesia also occurs in other dementing illnesses, such as vascular dementia and dementia with Lewy bodies.

Strokes (Chapters 375-377) can damage regions involved in episodic memory. Occlusion of the medial temporal branch of the posterior cerebral artery causes infarction of the hippocampus. Infarction in the territory of penetrating branches of the tip of the basilar artery causes bilateral medial thalamic infarcts.

Anterograde amnesia may be a major residual deficit after herpes simplex encephalitis (Chapter 345). Herpes simplex encephalitis has a predilection for damaging structures at the base of the cerebral hemispheres; frequently, the temporal lobes are severely damaged. Korsakoff syndrome, the residual of the encephalopathy of thiamine deficiency (Chapter 384), is characterized by profound anterograde amnesia. Hemorrhagic necrosis of the mammillary bodies occurs in Korsakoff syndrome. Survivors of closed head injuries (Chapter 368) may have anterograde amnesia because the medial temporal lobes are vulnerable to trauma as a result of their close proximity to the temporal bone. Survivors of an episode of anoxic-ischemic encephalopathy may also have dense anterograde amnesia. The pyramidal neurons of the CA1 region of the hippocampus are particularly vulnerable to hypoxic injury.

Transient Global Amnesia

The syndrome of transient global amnesia involves anterograde amnesia, but the duration of the amnesia is a matter of 6 to 12 hours rather than the weeks or months seen in post-traumatic amnesia or the permanent deficits in patients with Alzheimer disease or Korsakoff syndrome.[2] Patients with transient global amnesia remain alert, though inattentive; the key element of the syndrome is that they lay down no new memories during the event. As a consequence, they are amnestic for the several hours of the episode. Transient global amnesia generally affects middle-aged or elderly individuals. Its cause is not known, although it is not usually due to typical cerebrovascular disease or epilepsy. Electroencephalography is typically not specifically abnormal, but diffusion-weighed MRI often shows distinctive abnormalities of the hippocampus a day or more after the onset of transient global amnesia. Data suggest that the relapse rate is low, the risk of stroke and seizures is not considerably increased, and cognitive outcome is generally good.

LANGUAGE FUNCTION AND APHASIC DISORDERS

DEFINITION

Aphasia is a disorder of language at the conceptual level. Aphasics may have difficulty producing language, comprehending language, or both.

PATHOBIOLOGY

In more than 99% of right-handed individuals, language is localized to the left hemisphere. In left-handed individuals, language is also predominantly localized to the left hemisphere, although varying degrees of bilateral or, rarely, right hemispheric dominance may be seen. The hemisphere involved in language is referred to as the dominant hemisphere. Anatomic differences in the temporal and parietal lobes of the dominant hemisphere versus the other hemisphere also reflect its specialization for language.

Different aspects of language processing can be localized to specific regions within the dominant hemisphere. Lesions in the dominant hemisphere's auditory association areas cause receptive language dysfunction. The critical regions are located in the superior temporal lobes adjacent to the primary auditory cortex and in the adjacent supramarginal and angular gyri of the inferior parietal lobule. Lesions in the dominant hemisphere's lateral inferior posterior frontal lobes result in expressive language deficits. Loss of access to one's vocabulary for either understanding spoken language or expressing oneself results from lesions in any portion of the region around the sylvian fissure of the dominant hemisphere, including the lateral posterior inferior frontal lobe, the inferior parietal lobule, and the superior and middle temporal gyri.

CLINICAL MANIFESTATIONS AND DIAGNOSIS

The language comprehension difficulties in persons with aphasia must be distinguished from hearing disorders (Chapter 396), and the motor speech dysfunction in aphasia must be distinguished from dysarthria. Errors of articulation in persons with aphasia reflect altered conceptual selection of what is to be said. In aphasia, mispronunciation of a sound within one word may be followed by perfect pronunciation of the same sound in a different word. In dysarthria, by comparison, the errors in articulation or phonation are consistent.

Aphasia has three principal components: impaired verbal comprehension, disordered verbal expression, and impaired naming. Disorders of reading, writing, and sentence repetition are additional elements of the aphasia syndrome.

In expressive aphasic syndromes, written material and spoken speech are most often, but not always, affected in parallel. Speech is labored in the expressive aphasias, and it lacks the normal melody and variation in intonation that characterizes normal speaking. Melody and intonation are referred to as the prosody of speech. Speech is often grammatically impoverished. The number of words per utterance is greatly reduced, thus giving the speech a choppy, staccato character. These features are referred to as speech apraxia. *Nonfluency* is a related term that describes the reduced number of words and the terseness of verbal output. In some aphasic syndromes, speech is often degraded by anomia and paraphasic errors (word or syllable substitutions), even when fluency, melody, and intonation are preserved. Focal lesions of the dominant posterior inferior frontal lobe, its connected subcortical nuclei, or its white matter tracts produce an expressive (or nonfluent) aphasia (Fig. 370-1).

The disordered verbal comprehension may range from mild to profound. When profound, patients are unable to grasp the meaning of single words. In milder forms of disordered comprehension, patients may be able to follow one-step but not two- or three-step commands. Usually, the difficulty in comprehension involves both spoken and written language, but each can be affected separately.

Focal lesions of the dominant superior temporal lobe (Fig. 370-2) may produce a syndrome in which impaired comprehension of spoken and written language is accompanied by fluent speech that sounds normal to the ear but contains nonsense words (paraphasias) or lacks relevant nouns and therefore has little information content.

Anomia, which is an inability to produce names of people or objects, is common in almost all isolated aphasic syndromes and is common in persons with delirium or dementia. Naming can be tested by asking the patient to name a series of common objects, such as the parts of the hand and arm (e.g., thumb, palm, knuckles, wrist, elbow). In general, the more commonly a word is used in language, the easier it will be to name, whereas infrequent words are harder for patients with aphasias.

Ideomotor apraxia is a disorder at the interface between comprehension and execution of motor actions. Patients with ideomotor apraxia have no paresis of the face or limb musculature and are able to carry out simple tasks, but they are unable to execute more complex tasks or commands. For example, in a woman who is able to name a comb and use her right hand to point to parts of her body, ideomotor apraxia can be demonstrated if she is unable to indicate through her actions how she would use the comb.

Stuttering is usually a developmental disorder. The left pars opercularis is a locus where the intrinsic functional architecture of speech-language processes is altered in patients with persistent developmental stuttering.

DIAGNOSIS

The diagnosis of a disorder of language is made by listening to the patient speak and by examining comprehension, naming ability, reading, and writing in a

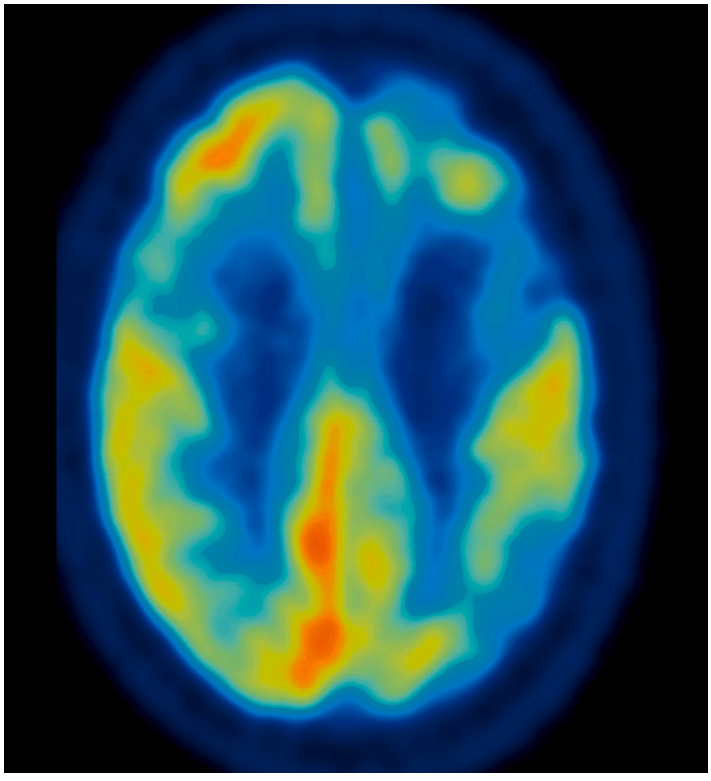

FIGURE 370-1. Progressive nonfluent aphasia. An axial ^{18}fluorodeoxyglucose positron emission tomographic scan slice of a patient with progressive nonfluent aphasia showing hypometabolism that was especially marked in the left frontal region. There was also less substantial hypometabolism in the left parietal and right frontal regions. He presented with difficulties with expressive speech and severe word-finding problems.

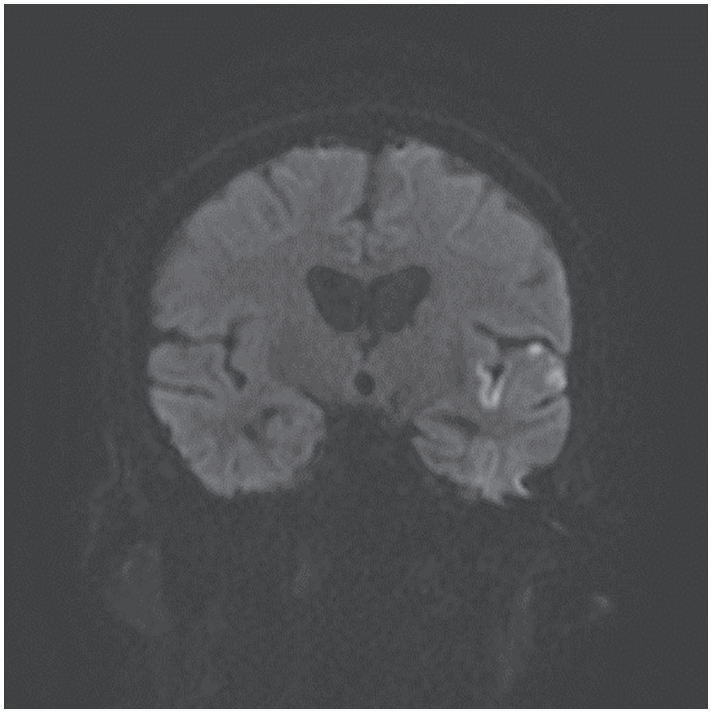

FIGURE 370-2. Fluent aphasia due to stroke. Diffusion images from a coronal magnetic resonance imaging scan of a patient who had an acute ischemic stroke, regained some expressive speech 72 hours after it, but whose fluent speech was associated with word-finding problems and the use of neologisms (nonsense words) and paraphasias. He also had severe difficulties with auditory comprehension, so that 3 weeks after his stroke, he could follow only one-step commands consistently. The scan shows diffusion abnormalities limited to the left superior temporal gyrus and adjacent insular cortex.

standardized fashion. Frequently the diagnosis of aphasia is suggested during attempts to obtain a history from the patient. It is helpful to prompt patients to speak about a neutral topic such as what they had for their last meal or what they did the previous day. Listening to their spontaneous speech allows the examiner to characterize its fluency, grammatical form, articulation, melody, and intonation, as well as difficulty finding words, the presence of paraphasias, and the overall information content.

Disorders of comprehension may be apparent during the interview when the patient cannot follow commands or understand questions being posed. Comprehension should be examined formally by asking the patient to perform tasks that range from one to at least three steps.

Determining the Cause

Portions of the language circuits in the dominant hemisphere may be damaged by infarction (Chapters 375 to 377), hemorrhage, and other space-occupying brain lesions such as neoplasms (Chapter 175) and abscesses (Chapter 382). Aphasia secondary to stroke has an abrupt onset, usually with some subsequent improvement. Aphasia due to stroke is often, but not always, accompanied by other neurologic signs, such as hemiparesis or hemianopia.[3] Recovery from aphasia after a stroke may occur as ischemic zones around an infarction eventually regain function. Regions remote from the infarction may also be synaptically depressed acutely after a stroke (diaschisis) but eventually regain function. Finally, regions in the nondominant hemisphere may become more active over the course of recovery. Aphasia that has a gradual and slowly progressive onset occurs in the neurodegenerative syndromes of primary progressive aphasia (Chapter 371). Degeneration in the anterior portion of the dominant temporal lobe produces a syndrome called semantic variant primary progressive aphasia (see Fig. 371-9); the pathoanatomy of this disorder illustrates the localization of access to the meaning of words.

TREATMENT

Speech therapy may be helpful for patients in the first few months after a brain injury that causes aphasia.[4] For example, 3 weeks of intensive speech and language therapy can significantly improve verbal communication in stroke survivors under age 70 years with chronic aphasia.[A1] Speech therapy initiated later than 6 months after a brain injury is of uncertain value.

CORTICAL DISORDERS OF VISUAL FUNCTION AND HEMISPATIAL NEGLECT

DEFINITIONS

Cortical disorders of vision and spatial cognition are caused by lesions in the occipitoinferotemporal or occipitoposteroparietal lobes. The principal disorders of cortical visual functioning are alexia (impaired reading), object agnosia (impaired recognition of visual forms), and prosopagnosia (impaired face recognition). The principal disorders of spatial cognition are geographic disorientation, simultanagnosia (impaired integration of complex visual scenes), dressing apraxia, and visual hemispatial neglect (lack of awareness of the personal or extrapersonal hemispace). In order to consider a cortical visual disorder diagnostically, a clinician should verify the integrity of primary visual function from the cornea to the lateral geniculate nuclei.

PATHOBIOLOGY

Higher visual function is localized to a network centered in the occipital lobe and includes the inferior temporal and posterior parietal lobes. From area 17, processing of visual information passes to visual association areas 18 and 19. From there it proceeds in several directions. Disorders of higher visual function can be related to a ventral or dorsal pathway. The ventral pathway from the visual centers to the medial temporal lobe links visual information to meaning ("What is the object?"). The dorsal visual processing pathway has several target regions. One links the visual centers to the parietal lobes and is concerned with locating objects in space and determining spatial relationships among objects in order to grasp a complete visual scene ("Where is the object?"). Another integral part of the dorsal visual processing stream is the cortical control of the extraocular muscles in the parietal and prefrontal regions, whereby the eyes are directed to various elements of a visual scene so that the individual elements are synthesized into a coherent ensemble. Yet a third part of the dorsal visual pathway leads to premotor areas that, in conjunction with eye movement control, facilitate visually guided limb motor actions.

Alexia occurs as a result of lesions in the ventral pathway of the dominant hemisphere. Object agnosia may also occur with lesions, usually bilateral, in the ventral pathway. Alexia and object agnosia occur with neurodegenerative diseases that affect the parieto-occipital cortex. Geographic disorientation,

simultanagnosia, dressing apraxia, and hemispatial neglect are syndromes caused by lesions in the dorsal pathway. Limb apraxia and impaired visuomotor activities may result from disruption of the premotor pathways that interact with the dorsal visual system. Simultanagnosia usually requires bilateral posterior parietal lesions. Dressing apraxia and hemispatial neglect arise from unilateral lesions, most often in the nondominant hemisphere. Cortical blindness is a consequence of bilateral occipitoparietal pathology.

CLINICAL MANIFESTATIONS AND DIAGNOSIS

Alexia may occur as an isolated deficit, or it may occur in the context of other evidence of aphasia. Patients may be able to recognize individual letters but are unable to recognize a string of letters as a word. Geographic disorientation is a common manifestation of a disturbance of the cortical visual system. Patients will become unable to travel to previously familiar locations and will get lost in familiar surroundings, eventually including even their own homes. Operating a motor vehicle is particularly challenging and risky to persons whose pathology in the cortical visual system causes difficulties with integrating a complex visual scene, because safe driving requires the rapid integration of multiple visual events. Patients with cortical disorders usually have difficulty with visuoconstructional tasks such as copying figures or drawing simple objects such as a flower, house, or clock. Dressing apraxia represents a deficit of practical significance in which patients are unable to comprehend the orientation of articles such as a shirt or a blouse and to manipulate them. The most severe form of a cortical disorder of visuospatial processing is cortical blindness. In this condition, in which the anterior visual pathways can be reasonably believed to be intact, patients appear functionally blind.

Hemispatial neglect occurs in the setting of acute strokes involving the nondominant perisylvian region. Even when there is no hemianopia as measured by single visual stimuli, presentation of double simultaneous stimuli to the patient reveals unawareness in the nondominant field. Hemispatial neglect can be demonstrated at the bedside with a task such as drawing a clock. A patient with hemispatial neglect will fail to place the numbers on the nondominant side (i.e., the left side in a right-handed person). Patients with hemispatial neglect may sometimes deny that their paretic limb belongs to them.

Bedside tests that screen for visuospatial deficits include either copying a simple geometric design or drawing an object. Intersecting pentagons and a cube are objects used clinically. Clock drawing is a brief but informative exercise. Reading of words or commands and naming of objects can be done at the bedside as well. Formal testing of visuospatial function in the neuropsychology laboratory involves the use of specially designed instruments to characterize visual processing.

Determining the Cause

The etiology of lesions that cause deficits in cortical vision and spatial cognition ranges from focal cerebrovascular disease, neoplasms, infectious processes, and brain trauma to neurodegenerative disorders. Patients with posterior cortical atrophy, which is usually due to Alzheimer disease, show marked atrophy and dysfunction of the occipital and parieto-occipital lobes (Fig. 370-3).

EXECUTIVE COGNITIVE DYSFUNCTION AND THE CONTROL OF INTERPERSONAL BEHAVIOR

DEFINITIONS

Higher mental integrative abilities that are broadly referred to as executive cognitive function include mental agility, abstract reasoning, and problem solving. Executive cognitive function represents processes that support mental flexibility, adaptability, focus, and tenacity. Mental flexibility refers to the ability to be able to manipulate simultaneously more than one stream of mental

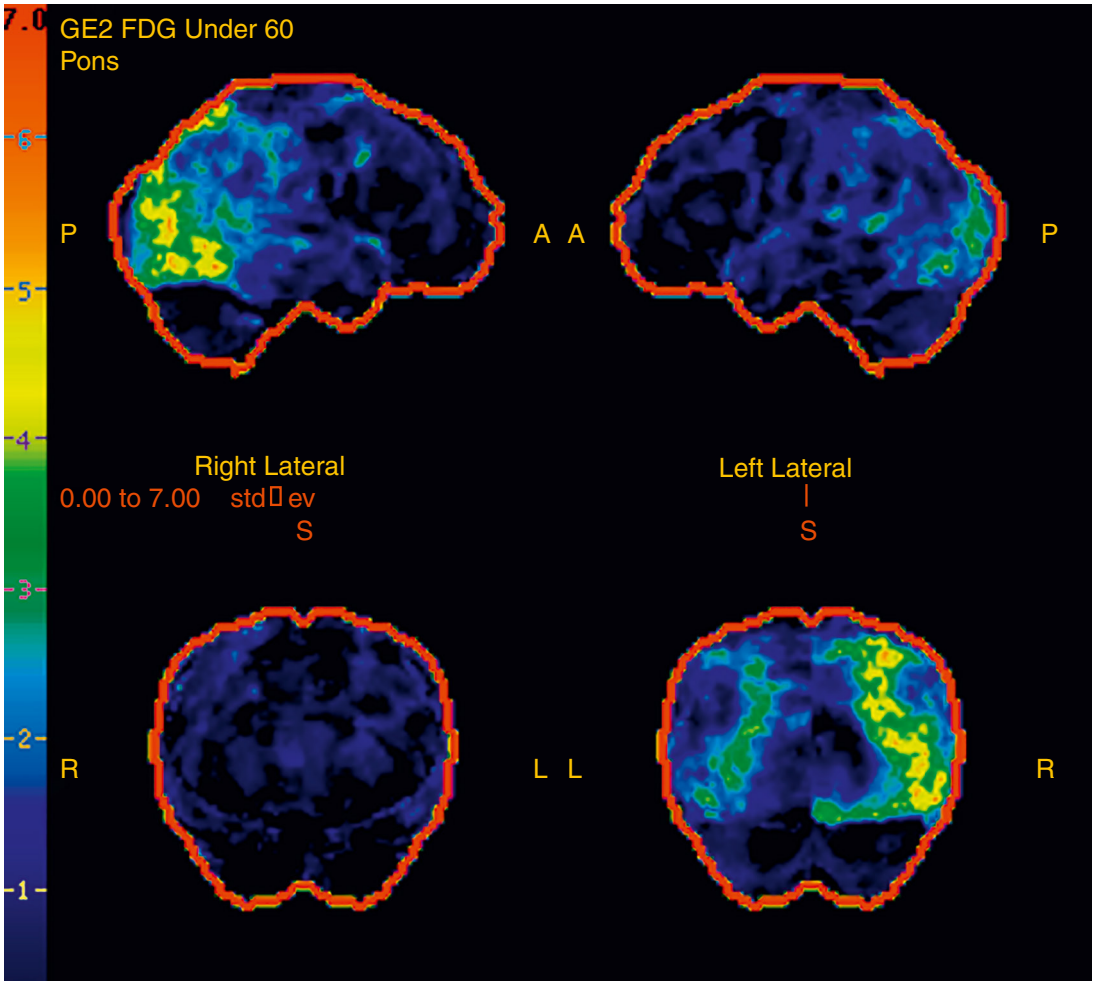

FIGURE 370-3. Posterior cortical atrophy. Lateral surface reconstruction of an ^{18}fluorodeoxyglucose positron emission tomographic scan of a patient with visuospatial difficulties that were due the Alzheimer disease variant referred to as posterior cortical atrophy. The scan shows prominent hypometabolism in the posterior parietal lobes, much more so in the right hemisphere. The patient presented with difficulties with dressing (dressing apraxia). She also had difficulties with writing.

activity and is sometimes labeled as working memory. Adaptability refers to the ability to shift mental activity rapidly from one topic to another. Focus and tenacity refer to the ability to concentrate on a topic while simultaneously ignoring extraneous distractions. Speed of mental processing is a necessary function that supports all cognitive functions and especially executive functions. Control of personal actions and regulation of interpersonal relationships are also major functions that are part of integrative abilities. The term *comportment* denotes how a person behaves, particularly in interactions with other people.

PATHOBIOLOGY

Executive cognitive functioning utilizes a network of brain regions anchored in the prefrontal neocortex, but involving wide swaths of the frontal, temporal, and parietal neocortex. The control of personal actions and behavior also is centered in the prefrontal regions as well as the anterior temporal lobes. These regions receive input from multiple cortical and subcortical regions. Although psychomotor speed, executive function, and maintenance of comportment and interpersonal relationships are often referred to as frontal lobe functions, the anatomic basis of these alterations is often more broadly distributed throughout the temporal and parietal gray and white matter, as well as subcortical nuclei such as the caudate.[5]

CLINICAL MANIFESTATIONS AND DIAGNOSIS

Psychomotor slowing, executive cognitive dysfunction, and alteration in the control and regulation of behavior often occur concurrently. Patients with executive dysfunction are deficient in goal-oriented behavior; they lose the ability to predict the consequences of their actions or words. Patients with executive dysfunction also exhibit poor mental agility and inflexibility in their thinking and control of their actions. They are easily distracted and exhibit a tendency to perseverate, in which the answer to a prior question is repeated in response to subsequent questions. They are disinhibited; as a consequence, when asked to recall a specific event, they may glibly answer with a fabrication, a phenomenon referred to as confabulation.

Patients with lateral prefrontal pathology exhibit poor performance on tests of abstract reasoning and mental agility. In a test such as verbal similarities, they tend to be very concrete and narrowly focused. They become easily distracted and are slow in performing tasks that require sustained attention. Because of their mental rigidity and difficulty in set shifting, they do poorly on tests that require the ability to vary their response strategies, such as verbal fluency tests.

Patients with medial frontal lesions are often profoundly apathetic and lack initiative and motivation. They may be laconic and completely unable to express emotion, whether it be anger, sadness, or elation. They tend to be indifferent to their surroundings, a state referred to as abulia. The majority of patients with substantial prefrontal or anterior temporal lobe pathology lack insight into the extent of their inappropriate behavior.

Patients with diseases of the frontal lobes or of the anterior portions of the temporal lobes often exhibit changes in personality and dysregulation of personal actions and interpersonal behavior. These alterations may include difficulty controlling impulsivity, poor social graces (manifested as rude behavior or caustic comments), a disregard for the feelings of others (loss of empathy), and a general failure to understand what constitutes acceptable behavior in a particular social context. If the underlying disease is progressive, gross alterations in table manners and loss of interest in maintaining personal hygiene may appear. Inappropriate sexual behavior may occur. Patients with prominent disease of the frontal lobes may also exhibit hyperorality, which is a compulsion to put nonfood objects into their mouths. Hyperorality can be life-threatening, depending on the substance ingested.

Bedside testing of executive cognitive dysfunction provides only a superficial view of the cognitive domain. Assessment in the neuropsychology laboratory gives a more refined estimate of the degree of psychomotor slowing and executive dysfunction.

Determining the Cause

Space-occupying lesions of the frontal lobes (e.g., neoplasms, brain abscesses) can lead to the cognitive and behavioral syndromes of frontal lobe dysfunction.

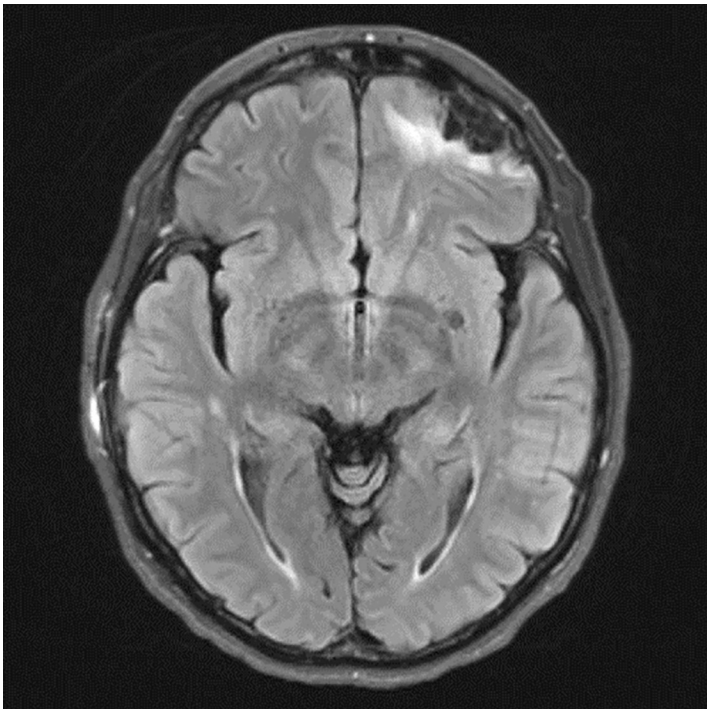

FIGURE 370-4. Brain trauma. Axial magnetic resonance imaging scan showing left frontopolar encephalomalacia in a patient who had suffered a traumatic brain injury. During the recovery process, she had exhibited irritability, increased libido, other changes in personality, and pressured speech, but those symptoms had largely resolved 2 years later.

With these diseases, executive cognitive dysfunction and alteration of control of personal behavior develop over a period of weeks.

In patients with acute brain trauma (Fig. 370-4) (Chapter 368), brain imaging at the time of initial medical and surgical evaluation will reveal whether the brain suffered acute traumatic lesions.[6] Chronically, traumatic brain injury may later lead to encephalomalacia of the frontal lobes.

Strokes[7] and neurodegenerative diseases such as frontotemporal lobar degeneration (Chapter 371) are associated with dysfunction and brain loss in the prefrontal and anterior temporal lobes (Chapter 371, Fig. 371-8). These disorders may produce the entire spectrum of executive cognitive dysfunction and altered control of personal behavior over a period of a year or longer.

Some diseases that do not directly damage the frontal or anterior temporal neocortex may cause executive cognitive dysfunction and alteration of control of personal behavior because of the interconnectedness of the frontal and anterior temporal lobes with other cortical and subcortical regions. Multiple sclerosis (Chapter 380), a disorder of white matter pathways, may cause abnormalities in cognition and behavior of the frontal type. Similarly, Huntington disease (Chapter 379) and progressive supranuclear palsy, which affect the caudate nuclei, may also resemble a frontal cognitive and behavioral syndrome and result in executive cognitive dysfunction and alterations in comportment.

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371 COGNITIVE IMPAIRMENT AND DEMENTIA

DAVID S. KNOPMAN

THE SPECTRUM OF MILD COGNITIVE IMPAIRMENT TO DEMENTIA

DEFINITION

Dementia is a cognitive disorder that leads to interference with daily functioning and results in loss of independence (Table 371-1). Dementia can range in severity from mild, when a patient may still be independent in a few activities, to severe, when total dependence occurs. Mild cognitive impairment is the term that describes the earlier phase of symptomatic cognitive impairment that precedes mild dementia (Table 371-2). The definitional boundary between mild cognitive impairment and dementia is based on the preservation or loss of independence in daily life. Given the diversity of life experiences and circumstances, the concept of the distinction between mild cognitive impairment and dementia has more conceptual clarity than operational precision. Indeed, the spectrum of symptomatic cognitive impairment is a continuum.

The majority of conditions that result in symptomatic cognitive impairment are of gradual onset, are progressive in course, and occur in persons with previously normal cognition. Some diseases that lead to dementia, such as those caused by an acute neurologic illness secondary to stroke (Chapter 375), encephalitis (Chapter 383), or head trauma (Chapter 368), may begin abruptly and then remain static for long periods. Conversely, a small subset of dementias, such as Creutzfeldt-Jakob disease, has a rapid onset and a course that can run for less than a year. Dementia may also occur in persons with developmental disabilities and long-standing cognitive deficits.

TABLE 371-1 DEFINITION OF DEMENTIA

Dementia is a persistent cognitive impairment that interferes with the ability to function at work or at usual activities; *and* • It represents a decline from prior levels of functioning and performing; *and* • The cognitive impairment and impaired functioning are not explained by delirium or major psychiatric disorder
The cognitive impairment of dementia is detected and diagnosed through a combination of: • History-taking from the patient and a knowledgeable informant; *and* • Objective cognitive assessment, either a "bedside" mental status examination or neuropsychological testing
The cognitive or behavioral impairment of dementia involves *at least two* of the following domains: • Impaired ability to acquire and remember new information • Impaired reasoning and handling of complex tasks; poor judgment • Impaired visuospatial abilities • Impaired language functions (speaking, reading, writing) • Changes in personality, behavior, or comportment

Adapted from McKhann GM, Knopman DS, Chertkow H, et al. The diagnosis of dementia due to Alzheimer's disease: recommendations from the National Institute on Aging-Alzheimer's Association workgroups on diagnostic guidelines for Alzheimer's disease. *Alzheimers Dement*. 2011;7:263-269.

TABLE 371-2 DIAGNOSTIC CRITERIA FOR AMNESIC MILD COGNITIVE IMPAIRMENT

The presence of a new memory complaint, preferably corroborated by an informant
Objective evidence of an impairment in episodic memory (for age)
Normal general cognitive functioning as measured by a brief cognitive assessment
No substantial interference with work, usual social activities, or other activities of daily living
No dementia

Adapted from Albert MS, DeKosky ST, Dickson D, et al. The diagnosis of mild cognitive impairment due to Alzheimer's disease: recommendations from the National Institute on Aging-Alzheimer's Association workgroups on diagnostic guidelines for Alzheimer's disease. *Alzheimers Dement*. 2011;7:270-279.

EPIDEMIOLOGY

The prevalence and incidence of mild cognitive impairment and dementia increase with advancing age. Both are uncommon before 50 years of age. In individuals older than age 65 years, who comprise 95 to 97% of all patients with dementia, the prevalence of dementia of all types is about 7%. In the age range of 65 to 69, the prevalence of dementia is only 1 to 2%, but it increases to 20 to 25% in the 85- to 89-year age range and continues to rise steadily thereafter. The incidence of new cases of dementia is about 1 per 100 per year at the age of 70 and rises to about 2 to 3 new cases per 100 per year by about the age of 80. Incidence rates continue to rise into the ninth and tenth decades of life. The incidence and prevalence of mild cognitive impairment are roughly the same as those of dementia. This means, for example, that the prevalence of symptomatic cognitive impairment after age 65 years is about 14%. With the dramatic increase in longevity, the societal burden of dementia has risen substantially. Interestingly, however, the incidence rate of dementia has declined over the past three decades, likely related to better and earlier treatment of cardiovascular risk factors.[1,2]

In absolute numbers, far more women than men have dementia because women live longer. However, men and women have an equal age-adjusted risk for the development of dementia. Blacks and Latinx adults are at greater risk of dementia, probably because of disparities in socioeconomic status and medical care. Risk factors include the *APOE* ε4 allele, current depressive symptoms, exposure to anticholinergic drugs,[3] midlife onset of diabetes, hypertension or hyperlipidemia, and vascular diseases such as atrial fibrillation or stroke. Normal blood pressure reduces the risk of dementia,[4] and targeting a systolic blood pressure below 120 mm Hg versus 140 mm Hg reduces the combined risk of mild cognitive impairment and dementia.[A1] A parental history of dementia before age 80 years increases the risk for dementia by about two- to six-fold independent of all currently known genetic risk factors. A healthy lifestyle may protect against dementia,[5] and intellectual engagement raises cognitive performance and may be associated with a slower decline in cognitive function.[6]

PATHOBIOLOGY

Symptomatic cognitive impairment is the culmination of dysfunction in the cerebral hemispheres, especially the association cortices, hippocampal formations, their supporting subcortical nuclear structures (e.g., caudate nuclei, thalamus), and their white matter interconnections. Specific diseases that cause mild cognitive impairment and dementia do so by affecting particular parts of the cerebral cortex, subcortical nuclei, or the underlying white matter pathways linking different cortical regions. Especially in patients over the age of 75 to 80 years of age, most dementia has a multifactorial basis rather than representing a single biologic process. The failure to remove the waste products of brain metabolism, either through endosomal recycling or through clearance via bulk transport into cerebrospinal fluid pathways, is thought to be a final common pathway to dementia in neurodegenerative diseases.[7,8]

CLINICAL MANIFESTATIONS

Any of the major domains of cognition—episodic memory, executive cognitive functioning, visuospatial function, or language—may be affected in dementia (Chapter 370). Because Alzheimer disease is the most common cause of mild cognitive impairment and dementia, anterograde amnesia is typically present first and most intensely in the majority of dementia patients. In other dementing illnesses, deficits in the other cognitive domains may be dominant. Although persons with mild cognitive impairment often retain some sense of their loss of cognitive capacities, a pervasive and nearly invariant aspect of dementia is a loss of insight (anosognosia) into the extent of one's cognitive and functional losses.

Neuropsychiatric symptoms are also common in dementia. Apathy and loss of initiative are almost always present. Depression and anxiety are frequent, as are irritability, paranoia, delusional thinking, and hallucinations. Daily functioning of patients with dementia is compromised. In early dementia, difficulty is likely to be present in management of finances and medications, independent travel, preparation of meals, and keeping of appointments. In more advanced disease, difficulty becomes evident in basic activities of daily living such as bathing, dressing, toileting, and feeding oneself. Dementias secondary to cerebrovascular or Lewy body disease are often associated with specific abnormalities in strength, coordination, gait, or balance. Alzheimer disease typically has no associated motor abnormalities.

DIAGNOSIS

Clinical Examination

Mild cognitive impairment and dementia are strictly clinical diagnoses based on evidence of cognitive dysfunction in both the history and the mental status examination. The key elements of the history flow from their definitions: What

ABSTRACT

The spectrum of cognitive impairment ranges from mild cognitive impairment to dementia. The four major classes of diseases that cause cognitive impairment and dementia are Alzheimer disease, cerebrovascular disease, dementia with Lewy bodies, and the frontotemporal degenerations, each with its own specific epidemiology, pathobiology, clinical manifestations, diagnostic criteria, prognosis, and management.

KEYWORDS

Alzheimer disease
vascular cognitive impairment
dementia with Lewy bodies
behavioral variant frontotemporal dementia
primary progressive aphasia
normal pressure hydrocephalus
hippocampal sclerosis
mild cognitive impairment
dementia

is the evidence for impairment in one or more domains of cognition? What is the evidence that daily functioning is affected? The mental status examination is necessary to establish that alertness is preserved (i.e., the patient does not have delirium [Chapter 361]) and to determine what specific areas of cognition exhibit directly observable impairment. For diagnosis of the syndrome of dementia, no laboratory test supersedes the clinical history and mental status examination. Laboratory testing is critical, however, to determine the cause of the cognitive disorder.

Bedside testing of mental status is based on the principles of cognitive neurology (Chapter 370). For moderate or severe dementia to be distinguished from normal cognitive states, a bedside mental status examination such as the Mini-Cog test (see Table 361-5 in Chapter 361) is accurate. However, for mild cognitive impairment and mild dementia, bedside mental status examinations lack sensitivity (i.e., they fail to diagnose some cases at the milder end of the spectrum). For patients with suspected mild cognitive impairment or dementia, neuropsychometric testing is a useful adjunct to the bedside examination. The neurologic examination is also important for evaluation of signs of specific diseases, including signs of cerebrovascular disease (e.g., hemiparesis [Chapter 375]) and signs of extrapyramidal disease (e.g., rigidity, bradykinesia, resting tremor [Chapter 378]).

Differential Diagnosis

Mild cognitive impairment and dementia must be distinguished from other disorders of cognition (Fig. 371-1).[9] Delirium (Chapter 361) also affects cognition directly; key features distinguishing it from dementia include impaired arousal and attention. Delirium is almost always of sudden onset, whereas the majority of cases of dementia are of gradual onset.

Primary psychiatric diseases (Chapter 362) such as major depression, bipolar disorder, and schizophrenia may also impair cognition. In mild cognitive impairment and dementia, however, the impairment in cognition is typically equivalent to or more pervasive than the changes in mood and behavior.

The principal diseases that cause mild cognitive impairment and dementia are three neurodegenerative diseases—Alzheimer disease, Lewy body disease, and frontotemporal lobar degeneration—and cerebrovascular disease (Fig. 371-2).[10] The neurodegenerative diseases are typically slow and insidious in onset and inexorably progressive. Mild cognitive impairment and dementia secondary to cerebrovascular disease may be of either sudden or gradual onset.

Many much less common secondary causes account for less than 2% of all dementias. Drug intoxication (Chapters 365 and 384), metabolic disorders (Chapter 189), central nervous system infections (Chapters 381 to 383), and brain structural lesions (Chapter 370) are typically subacute in onset; if they are diagnosed and treated early, the cognitive deficits improve or resolve completely. A number of medications such as sedatives, pain medications, corticosteroids, digoxin, and others cause mental confusion, particularly but not always at toxic levels (Chapter 96). Metabolic disorders that may also cause subacute confusion and produce a cognitive disorder include hypothyroidism or hyperthyroidism (Chapter 207), vitamin B_{12} deficiency (Chapter 384), chronic liver disease (Chapter 139), chronic renal failure (Chapter 116), and hypocalcemia or hypercalcemia (Chapter 227). Chronic viral infections of the brain, especially human immunodeficiency virus infection, frequently cause dementia (Chapter 359). Chronic meningitides in the differential diagnosis of dementia include cryptococcal meningitis (Chapter 309), tuberculous meningitis (Chapter 299), and tertiary syphilis (Chapter 295). Finally, structural lesions of the brain, including primary and metastatic tumors (Chapter 175), chronic subdural hematomas (Chapter 368), and normal-pressure hydrocephalus, can cause a syndrome resembling dementia that consists of a subacute or slowly progressive decline in cognition with few or no other neurologic symptoms or signs.

PROGNOSIS

Except for the secondary causes of mild cognitive impairment and dementia and the rare dementing illnesses caused by single episodes of brain injury (e.g., severe head trauma, anoxic encephalopathy), dementia is a condition that invariably leads to worsening of cognition and function. Almost all patients who have more than mild cognitive impairment worsen over the course of several years if they do not die from other causes. The rate of cognitive decline is variable among individuals and, of course, also varies with the specific disease. In general, dementia can be said to decrease life expectancy by half compared with the life expectancy of nondemented individuals.

End-of-Life Care

The terminal stage and end-of-life care issues (Chapter 3) associated with the common dementias are usually similar.[11] Dementia itself does not directly cause death, but it is strongly linked to reduced survival. Patients with dementia typically die of the same illnesses that affect debilitated individuals, such as sepsis, pneumonia, pulmonary embolism, or heart disease.

Most patients with dementia experience their terminal illnesses in hospitals or extended care facilities. Given the inexorably progressive nature of most dementing illnesses and their likelihood of producing severe and completely disabling cognitive and functional impairment, it is widely accepted that patients with end-stage dementia should receive conservative care. Feeding tubes and ventilatory support should not generally be considered.

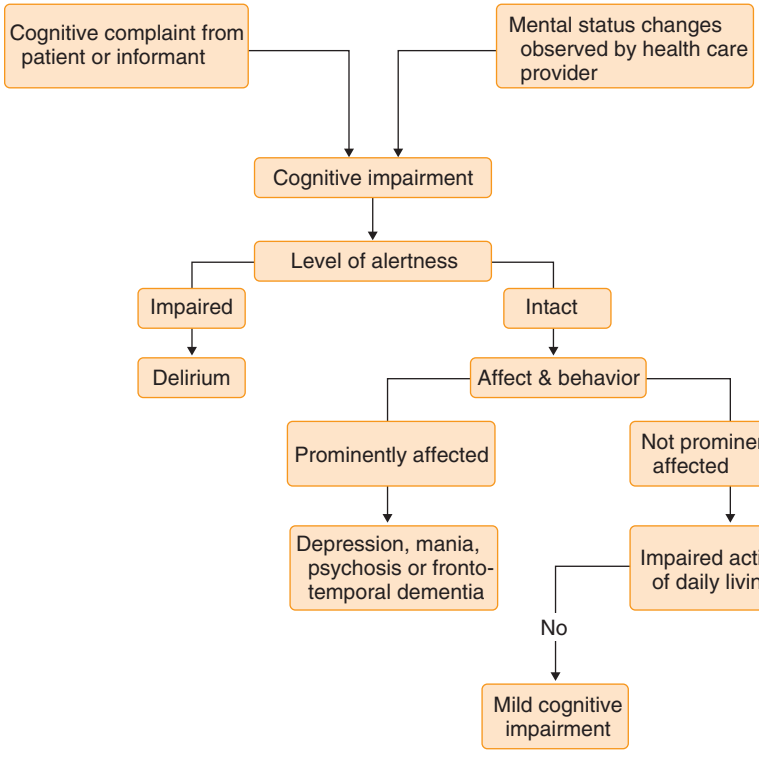

FIGURE 371-1. Flow diagram to establish the diagnosis of dementia.

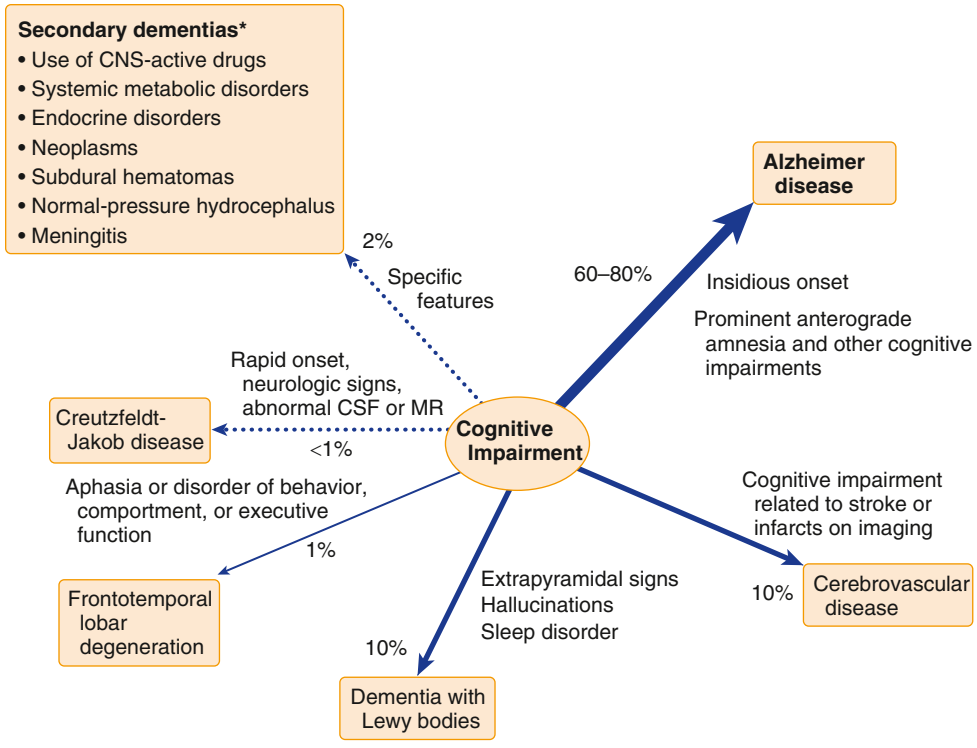

FIGURE 371-2. **Flow diagram for the differential diagnosis of mild cognitive impairment and dementia.** The percentage contributions of various diagnoses are approximate. *The list of secondary causes of dementia is not exhaustive. CNS = central nervous system; CSF = cerebrospinal fluid; MR = magnetic resonance imaging.

MANAGEMENT OF PERSONS WITH MILD COGNITIVE IMPAIRMENT OR DEMENTIA

Pharmacologic treatment of persons with mild cognitive impairment or dementia should be focused on the specific disease causing the cognitive disorder. Unfortunately, symptomatic treatments are currently available only for Alzheimer disease dementia. Management of persons with symptomatic cognitive impairment, on the other hand, involves issues that are common to all etiologies. Principles of care include disclosure of the diagnosis, education and support of caregivers, assessment of functional status, screening and management of behavioral and psychiatric symptoms, addressing safety concerns, assessing driving status, advance care planning, pain assessment, and pharmacologic treatment of dementia.

ALZHEIMER DISEASE

DEFINITION

Alzheimer disease, which is a pathophysiologic process involving β-amyloidosis and limbic and isocortical neurodegeneration with tauopathy, produces a cognitive disorder that usually progresses to severe dementia in which anterograde amnesia is the initial dominant symptom (Table 371-3).[12] The clinical diagnosis implies that the causative pathologic process is of the Alzheimer type, whereas the pathologic diagnosis rests on the findings of characteristic histopathologic features.

EPIDEMIOLOGY

Between 60 and 80% of all dementing illness is due to Alzheimer disease. Among all individuals older than 65 years, the prevalence of Alzheimer disease is estimated to be about 5%. As with dementia in general, the prevalence doubles in every 5-year interval after age 65, and the incidence continues to rise into the 10th and 11th decades of life. Men and women may be equally affected, although on an absolute basis, far more women have prevalent Alzheimer disease because women live longer than men. There are no ethnic or racial differences in the predilection for Alzheimer disease.

Risk Factors

Established risk factors for Alzheimer disease include advancing age and a family history. Most patients with Alzheimer disease have other comorbid brain pathologies, which may effectively lower the threshold for dementia in persons who also have Alzheimer pathology. For example, midlife vascular risk factors and elevated low-density lipoprotein (LDL) levels specifically may be associated with elevated brain β-amyloid later in life. Low educational achievement is a consistent risk factor, likely in part because it is associated with less cognitive reserve, but educational level also may be a proxy for other factors, such as socioeconomic status or the early childhood medical and psychosocial environment, that raise the risk of concomitant cerebrovascular disease. Head injury may be a risk factor for Alzheimer disease, but head injury acts mainly through chronic traumatic encephalopathy (Chapter 368).

PATHOBIOLOGY

The histopathologic diagnosis of Alzheimer disease is based on the joint presence of a substantial cerebral burden of neuritic plaques and neurofibrillary tangles. Neuritic plaques consist of a core of aggregated β-amyloid peptide surrounded by degenerating neurites, which are fragments of axons and dendrites. β-Amyloid contains 39 to 42 amino acids and is proteolytically derived from a larger protein, the amyloid precursor protein. Neurofibrillary tangles are intracellular aggregations of an excessively phosphorylated form of the microtubule-associated protein tau. The altered tau protein self-aggregates and forms neurofibrillary tangles. In a low-powered microscopic section of frontal, temporal, or parietal cortex, at least six neuritic plaques and neurofibrillary tangles should be visible for the diagnosis of Alzheimer disease to be made.

Pathophysiology

The progression of changes of β-amyloidosis follows a roughly predictable pattern in Alzheimer disease. Positron emission tomography (PET) imaging with ligands that bind to β-amyloid shows that β-amyloid begins to accumulate in the neocortex as long as 20 years before dementia occurs. Soluble aggregates of β-amyloid in oligomeric (consisting of a small number of monomers) forms may be the key pathogenic molecules that eventually induce or accelerate neuronal injury. By the time clinical dementia due to Alzheimer disease is present, large numbers of β-amyloid peptide–containing deposits invariably are found in neuritic plaques in the neocortex. Neuritic plaques represent the end stage of the Alzheimer process. Because β-amyloidosis begins well before clinical symptoms appear and probably reaches a plateau in terms of abundance, the amount of β-amyloidosis does not closely mirror the severity of dementia in Alzheimer disease.

The regional extent of neurofibrillary tangles in Alzheimer disease anticipates and parallels the clinical progression of the disease from an amnestic disorder to a multidomain cognitive disorder. Neurofibrillary tangles appear in the medial temporal lobe and brain stem in cognitively normal persons by the fourth decade of life. In persons destined to develop Alzheimer disease, a critical part of the pathophysiology involves transsynaptic spread of neurofibrillary tangle pathology to cortical association areas. At the time clinical symptoms develop, neurofibrillary tangles are found in association neocortices of the frontal, parietal, and temporal lobes. It is only in the most severe and final stages that neurofibrillary tangles are found in the occipital lobes and primary motor and sensory cortices. The location of neurofibrillary

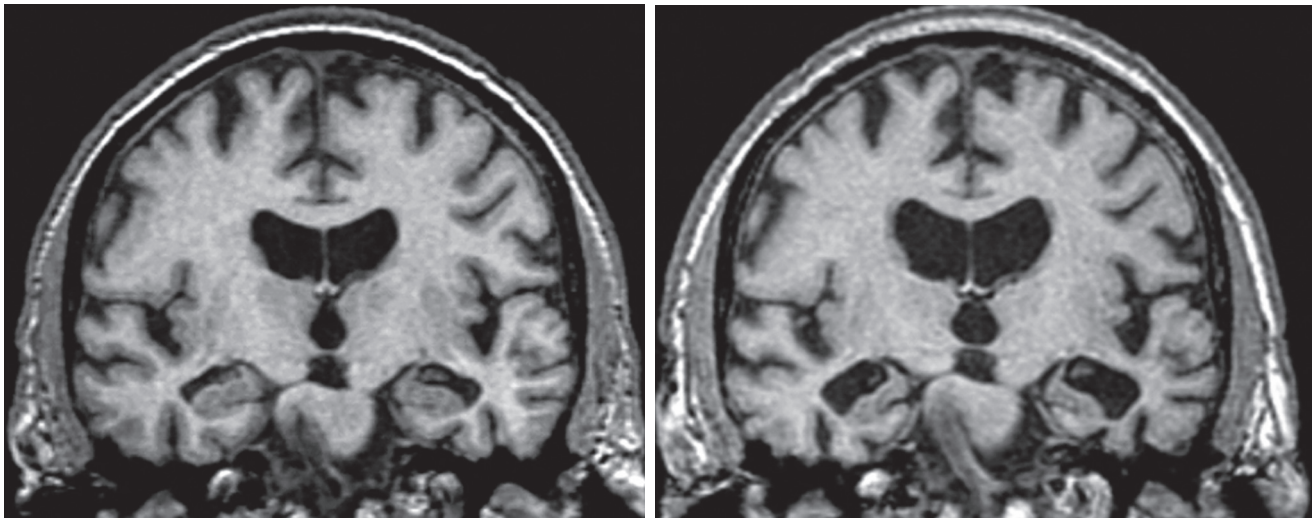

FIGURE 371-3. Serial coronal images from magnetic resonance imaging of a patient with Alzheimer disease. The scan on the *left* was performed when the patient was clinically normal. The scan on the *right* was performed 11 years later when the patient was demented. Hippocampal atrophy has increased dramatically from the first to the subsequent scan. (Courtesy Maria Shiung and Clifford Jack.)

tangles corresponds faithfully to the clinical evolution of specific symptoms and severity of Alzheimer disease. In mild cognitive impairment, the earliest clinical manifestation of Alzheimer disease, the most intense burden of neurofibrillary tangles is in the entorhinal cortex and hippocampi, precisely the regions involved in declarative episodic memory. Hippocampal atrophy is characteristic, and reductions in hippocampal volumes may be observed on magnetic resonance imaging (MRI; Fig. 371-3). Involvement of the association neocortices with neurofibrillary tangles represents the histopathologic correlate of the progression to dementia. Quantitative MRI in patients with mild cognitive impairment who later progress to dementia shows increasing atrophy of key cortical association areas, such as the lateral temporal lobes, inferior parietal lobes, posterior cingulate cortex, and lateral frontal lobes. Reflecting the spread to association neocortex, language functions, visuospatial functions, and executive cognitive functions typically become impaired some time after declarative episodic memory dysfunction occurs.

The most consistent neurotransmitter deficit in Alzheimer disease is in cholinergic neurotransmission. The cells of origin of hippocampal and neocortical cholinergic projections are located in the septum, diagonal band, and nucleus basalis. Neurofibrillary tangles accumulate in the neurons in these regions as Alzheimer disease develops, but there is also neurochemical evidence that these neurons are stressed much earlier in the disease.

Genetics

The overwhelming majority of Alzheimer disease is due to sporadic (not genetic) disease. However, in a very small number of instances, Alzheimer disease occurs as an autosomal dominant disease. The three known genes involved in autosomal dominant Alzheimer disease all are directly involved in the production of β-amyloid peptide. The first is the amyloid precursor protein *(APP)* gene, located on chromosome 21q21.3. Over 60 known mutations in this gene lead to excess production of β-amyloid and are reliably associated with a very early onset (20 to 50 years of age) of Alzheimer disease. Another line of evidence implicating the *APP* gene in Alzheimer disease is the invariable appearance of the pathologic process of Alzheimer disease in individuals with Down syndrome (trisomy 21 [Chapter 32]) who have an extra copy of the *APP* gene as a result of the trisomy.

The other two genes associated with autosomal dominant Alzheimer disease are the presenilin 1 and 2 genes, located on chromosomes 14q24.3 and 1q31.42. Over 300 presenilin 1 mutations account for the majority of autosomal dominant Alzheimer disease; mutations in presenilin 2 are least common. Both genes code for a similar protein known as presenilin. Presenilin is involved in the proteolysis of the APP molecule at the gamma cleavage site. Presenilin mutations alter the balance of APP cleavage products, including β-amyloid and other peptides that may influence synaptic functioning. The presenilin mutations are almost always associated with early-onset (age 40 to 60 years) Alzheimer disease.

Studies of the familial aggregation of Alzheimer disease have shown that later-onset disease also displays genetic risks, but only a few genes have been definitively linked to later-onset Alzheimer disease. The most prominent gene related to later-onset Alzheimer disease, located on chromosome 19q13.2, encodes apolipoprotein E (apo E), a protein involved in lipid transport. In humans, three allelic variants of apolipoprotein gene *(APOE)* are determined by differences in the amino acids cysteine and arginine at positions 112 and 158 of the 299–amino acid protein. One of the allelic variants, with arginine at both positions, designated the ε4 variant, is strongly associated with a 14-fold increased risk for Alzheimer disease in homozygotes and a 3-fold increase in heterozygotes. In many series, almost 50% of Alzheimer disease dementia patients, but only about 25% of nondemented controls, have at least one copy of the *APOE* ε4 allele. The presence of an *APOE* ε4 allele does not always cause Alzheimer disease in that the disease never develops in some carriers of the genotype. The mechanism by which the *APOE* ε4 allele predisposes to Alzheimer disease is not established, but the tertiary structure of the APOE protein with arginine at positions 112 and 158 may lead to impaired binding to β-amyloid, which in turn reduces the clearance of β-amyloid from cells.

A very rare missense mutation in the *TREM2* gene also increases the risk for Alzheimer disease. The R47H variant of *TREM2* increases the risk for Alzheimer disease three-fold. The pathophysiology appears to be impaired containment of inflammatory processes rather than a direct effect on neurologic function. Rare loss-of-function mutations in *ABCA7* uniformly lead to classical Alzheimer disease, but with a widely variable age of onset.

CLINICAL MANIFESTATIONS

The early course of symptomatic cognitive impairment due to Alzheimer disease is dominated by difficulties with anterograde amnesia. Some of the usual complaints include forgetting recent events and conversations, misplacing items, problems with keeping track of the date, getting lost in familiar surroundings, and problems with remembering to complete tasks. The frequency and severity of the memory lapses progress from occasional difficulty to more pervasive and consistent failure.

In mild cognitive impairment and mild dementia due to Alzheimer disease, episodic memory function may be lost. Familiarity and access to previous knowledge may allow patients to function in their usual daily routines as long as nothing out of the ordinary is required of them. They may still retain the ability to prepare simple meals and take walks in their neighborhood without getting lost. However, even in mild Alzheimer disease, medication-taking errors and difficulty managing money or balancing a checkbook are likely to occur. Traveling to unfamiliar places often accentuates confusion. Changes in personality commonly accompany the cognitive losses. Apathy, loss of initiative, and loss of interest in previous hobbies and pastimes are ubiquitous in early symptomatic Alzheimer disease.

As the disease progresses, the ability to perform necessary daily tasks becomes more and more difficult to the point that the patient will need assistance preparing meals, paying bills, taking transportation, and keeping house. As the disease moves into the severe stages, assistance and supervision in basic activities such as bathing, dressing, toileting, and eating become necessary.

In the terminal stages of the disease, all communicative abilities may be lost. Mobility may still be preserved until late in the disease. Alzheimer disease dementia patients commonly die of illnesses that strike other debilitated elderly individuals, such as sepsis, pneumonia, and heart failure.

The duration of the course of dementia due to Alzheimer disease is long but variable. The time from mild dementia to death may be as short as 2 to 3 years or may be well over a decade. For patients in whom mild dementia is diagnosed, about 10% per year reach the stage of severe dementia.

Rarely, Alzheimer disease is associated with prominent symptoms in cognitive domains other than memory. The most common of the atypical syndromes is one in which profound visuospatial deficits occur without the typical severe anterograde amnesia. This syndrome is referred to as posterior cortical atrophy. Patients with posterior cortical atrophy have a slower course compared with the typical amnestic dementia of Alzheimer disease, and, until the severe stages, have a relative preservation of short-term memory function. Some patients with other variants may have more dysfunction in language and executive tasks than in memory per se.[13]

DIAGNOSIS

The diagnosis of mild cognitive impairment or dementia due to Alzheimer disease is largely a clinical one based on the history and examination.[14] The key elements in the history are a gradual onset and insidious progression of cognitive impairment, especially anterograde amnesia. The mental status examination should demonstrate impairment in short-term memory and other cognitive deficits. The clinical diagnosis of Alzheimer disease should be thought of as a diagnosis of inclusion: if the history and examination are compatible with Alzheimer disease and if certain exclusions can be verified, the diagnosis can be made with moderate confidence. Recent PET imaging studies have shown that non-Alzheimer disease etiologies can sometimes mimic the amnestic syndrome of Alzheimer disease.

Cerebrospinal fluid (CSF) protein markers (β-amyloid and tau) (see Table 371-3)[15] and brain imaging (structural MRI, ^{18}fluorodeoxyglucose PET [Fig. 371-4], amyloid positron emission tomography [Fig. 371-5], and tau positron emission tomography [Fig. 371-6][16]) are being used in research settings to enhance the precision of a diagnosis of Alzheimer disease as a cause of symptomatic cognitive impairment. For example, amyloid PET scanning and CSF Aβ42/t-tau and Aβ42/p-tau can identify early-stage Alzheimer disease with sensitivities of about 97% and specificities of about 83% and may be alternatives to more invasive and expensive tests such PET scanning. In the future, such tests may be used in clinical practice to help discriminate Alzheimer disease from other neurodegenerative diseases.[17] For experimental therapeutics, efforts are now underway to use CSF or biomarkers to diagnose Alzheimer disease before individuals develop symptoms.

TABLE 371-3 DIAGNOSTIC CRITERIA FOR PROBABLE ALZHEIMER DISEASE DEMENTIA

The clinical diagnosis of probable Alzheimer disease dementia is made when:
Criteria for dementia met (see Table 371-1), and the illness has the following characteristics: Insidious onset: symptoms have a gradual onset over months to years; *and* Clear-cut history of worsening of cognition by report or observation; *and* The initial and most prominent cognitive deficits are evident on history and examination consistent with an amnestic disorder (most common) or a nonamnestic cognitive disorder (less common) (aphasia, visuospatial disorder, or behavioral/dysexecutive disorder)
The diagnosis of probable Alzheimer disease dementia should not be applied when there is substantial evidence for another neurodegenerative disease, extensive cerebrovascular disease, or a non-neurologic medical comorbidity or medication use that could have a substantial impact on cognition
Research criteria for probable Alzheimer disease dementia with higher certainty when imaging or cerebrospinal fluid biomarkers are available:
Alzheimer disease is considered the cause of cognitive impairment when β-amyloid markers (in cerebrospinal fluid or by PET imaging) are abnormal and tau markers (cerebrospinal fluid phospho-tau or tau PET) are abnormal
Alzheimer disease pathophysiology is considered present but of uncertain etiologic significance when β-amyloid markers (in cerebrospinal fluid or by PET imaging) are abnormal but tau markers are normal

PET = positron emission tomography; MR = magnetic resonance.

Adapted from McKhann GM, Knopman DS, Chertkow H, et al. The diagnosis of dementia due to Alzheimer's disease: recommendations from the National Institute on Aging-Alzheimer's Association workgroups on diagnostic guidelines for Alzheimer's disease. *Alzheimers Dement*. 2011;7:263-269; and Jack CR, Jr., Bennett DA, Blennow K, et al. NIA-AA research framework: toward a biological definition of Alzheimer's disease. *Alzheimers Dement*. 2018;14:535-562.

Differential Diagnosis

A number of other conditions that bear similarity to Alzheimer disease must be excluded on clinical or laboratory grounds (see Fig. 371-2). One is dementia with Lewy bodies, which is suggested by the presence of parkinsonism, prominent visual hallucinations, and a specific sleep disorder. At autopsy, the pathologic processes of Lewy body disease and Alzheimer disease often coexist, thus suggesting that the diagnoses overlap. Frontotemporal lobar degeneration is suggested by prominent behavioral and personality changes or by prominent language difficulties early in the course. Hippocampal sclerosis has unique neuropathologic findings but is difficult to distinguish from Alzheimer disease by clinical features. The combination of a slowly progressive amnestic disorder coupled with prominent hippocampal atrophy and the absence of elevated brain amyloid may suggest the diagnosis. Other neurodegenerative conditions in the differential diagnosis of Alzheimer disease include Huntington disease (Chapter 379), progressive supranuclear palsy (Chapter 379), corticobasal degeneration (Chapter 379), amyotrophic lateral sclerosis (Chapter 387), and Wilson disease (Chapter 195); however, these diseases invariably have prominent motor manifestations early in their course. Normal-pressure hydrocephalus (see later) is a rare cause of dementia associated with a gait disorder.

It is particularly challenging to distinguish dementia caused by cerebrovascular disease from Alzheimer disease (see later). The fact that Alzheimer disease and cerebrovascular disease often coexist requires clinicians to consider both simultaneously.

PREVENTION AND TREATMENT

There are no established preventive therapies for mild cognitive impairment or dementia due to Alzheimer disease.[A2] Although a healthy diet, physical exercise, and stimulating cognitive leisure activities are sensible, evidence supporting their value in the prevention of dementia is limited. There also currently is insufficient evidence to recommend any diet, physical activity program, or cognitive activities program for the treatment of symptomatic cognitive impairment. A multidomain intervention has been shown to delay cognitive decline in an elderly Finnish population who had existing cardiovascular risk factors. However, another intervention trial in France (including cognitive training, physical activity, and nutrition) failed to show any benefits.

Evidence-Based Treatments

Two classes of drugs have long been approved by the U.S. Food and Drug Administration (FDA) for the treatment of Alzheimer disease: cholinesterase inhibitors and memantine, a glutamate receptor antagonist.[18] The rationale for use of cholinomimetic drugs (donepezil, 5 or 10 mg/day; immediate-release galantamine, 16 or 24 mg/day) or rivastigmine (6 to 12 mg/day orally or 4.5 to 9 mg/day by skin patch) is the reduced levels of cholinergic markers in the neocortex of patients dying of Alzheimer disease. All three agents delay the progression of symptoms to a statistically significant but clinically marginal extent at 6 to 12 months in patients with mild to moderate dementia due to Alzheimer disease.[A3] For example, donepezil shows some benefits in reducing the development of dementia among patients with mild cognitive impairment at 1 year but not at 3 years. Furthermore, community-dwelling patients whose moderate or severe Alzheimer disease had been treated with donepezil for at least 3 months and who continue donepezil at 10 mg daily may have functional benefits over the next 12 months compared with patients who discontinue it.[A4] Higher doses of donepezil and rivastigmine are marketed, but in neither case has efficacy superior to standard dosages been demonstrated. Memantine, which is a low- to moderate-affinity uncompetitive *N*-methyl-D-aspartate receptor antagonist that acts on glutamate neurotransmission, appears to delay the progression of functional decline in patients with moderate to severe Alzheimer disease at a dose of 10 mg twice daily. Individual patients, however, often do not show any clear benefits of treatment.

In 2023, the FDA approved the anti-amyloid antibody lecanemab for the treatment of Alzheimer disease based on its ability to lower the amount of beta-amyloid seen in PET scanning over 18 months in patients with mild cognitive impairment or mild dementia owing to Alzheimer disease. In a randomized clinical trial, lecanemab delayed decline in function and cognition by roughly 27% compared with placebo, but it also has been associated with brain edema and hemorrhage.[A5] Aducanumab, another anti-amyloid antibody, was FDA-approved in 2021, but its status is uncertain. Another anti-amyloid antibody, donanemab, has shown similar results.[A6]

Except in patients who have folate or vitamin B_{12} deficiency, vitamin B supplementation is not effective in slowing cognitive decline. Treatment of diabetes (Chapter 210) and hypertension (Chapter 64) is beneficial for other reasons, but it is not clear that such treatment alters the course of Alzheimer disease.

One study of patients with moderately severe Alzheimer disease showed that vitamin E was effective in delaying progression, and it may also benefit patients with mild to moderate Alzheimer disease.[A7] Multivitamins are not efficacious,

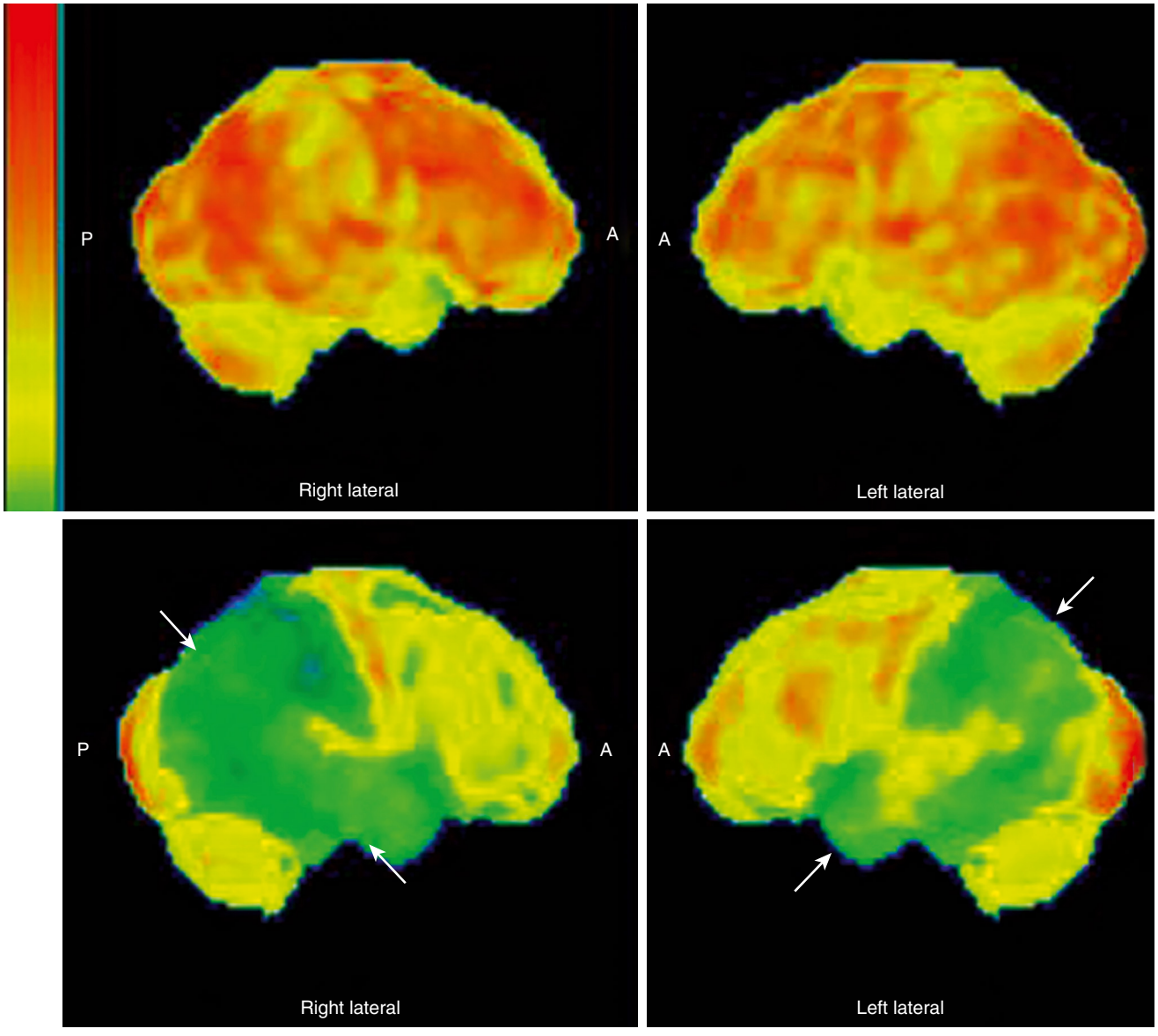

FIGURE 371-4. **^{18}Fluorodeoxyglucose positron emission tomographic scan of a patient with Alzheimer disease dementia.** Computerized reconstructions of the regional glucose uptake ratio (using pons as reference) of the cortical surface show hotter colors (*yellow* and *orange*) in areas of normal glucose uptake, whereas cooler colors (*green* and *blue*) indicate hypometabolism. The scan on the top is from a normal individual of the same age. The scan on the bottom is from a patient with typical Alzheimer disease dementia, and it shows hypometabolism in the temporal and parietal cortical regions *(arrows)*.

and trials of drugs to bind β-amyloid peptides or block the 5-hydroxytryptamine 6 receptor have been unsuccessful.[A8] Antidepressants generally are ineffective and increase adverse events when used to treat patients with Alzheimer disease.

Exercise is not helpful for preventing cognitive impairment or for slowing progression after Alzheimer disease becomes symptomatic.[A9,A10] Support for family caregivers is a critical intervention that cannot be overemphasized. Support groups through the Alzheimer Association (available at http://www.alz.org) can benefit families coping with the disease.

Important safety issues include supervision of medications, supervision of finances, and close scrutiny of motor vehicle operation. Operation of other potentially dangerous tools, firearms, appliances, and equipment should also be carefully monitored or avoided. Patients with Alzheimer disease often wander and can become lost long distances from home. Identification of patients can prevent tragic occurrences.

PROGNOSIS

Persons who have elevated amyloid and elevated tau on PET scanning have a much higher risk for becoming cognitively impaired compared with persons who have lesser degrees of Alzheimer abnormalities by PET.[19] Alzheimer disease is inevitably progressive, and severe cognitive impairment and complete dependence on others develop in virtually all patients unless they die prematurely. Alzheimer disease also contributes to premature death; the mortality rate in patients with Alzheimer disease is about 10% per year. In patients with advanced dementia, the 6-month mortality rate is about 55%; pneumonia, fever, and eating problems are associated with poor prognosis.

COGNITIVE IMPAIRMENT DUE TO CEREBROVASCULAR DISEASE

DEFINITION

Cerebrovascular disease makes an important contribution to late life cognitive impairment. For a cognitive disorder to be attributed to cerebrovascular disease from a neuropathologic perspective, there must be sufficient cerebral infarction in locations known to be responsible for the cognitive deficits in the absence of other neurodegenerative neuropathologic changes (Table 371-4). When cerebrovascular disease produces cognitive impairment that is not severe enough to meet the criteria for dementia, it is referred to as vascular cognitive impairment.

EPIDEMIOLOGY

In clinical studies, as many as 20% of dementia patients have cerebrovascular disease. Like Alzheimer disease, it is less common in patients younger than 65 years and increases steadily thereafter. In neuropathologic studies, about 25% of all cases of dementia have some vascular component. Roughly half that number are relatively pure vascular dementia; the remainder consists of vascular disease mixed with Alzheimer disease. Men and women are equally affected.

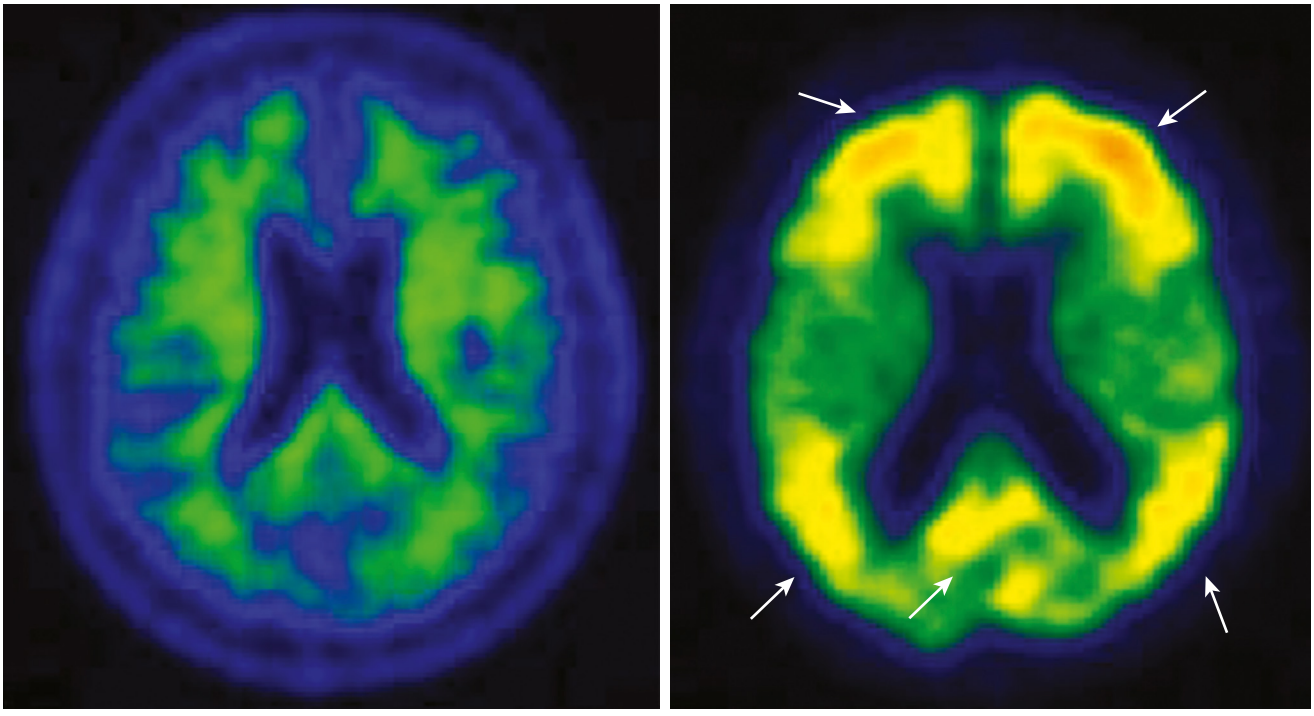

FIGURE 371-5. Amyloid positron emission tomographic (PET) scan of a patient with Alzheimer disease dementia. On this axial image of a ^{11}C Pittsburgh compound B PET scan, the *left* scan is from an individual with no cortical amyloid retention. The *green* signal represents low levels of nonspecific white matter binding. On the *right*, a scan of a patient with Alzheimer disease dementia shows the prominent retention of the amyloid imaging agent in the frontal, parietal, and posterior cingulate cortices *(arrows)*.

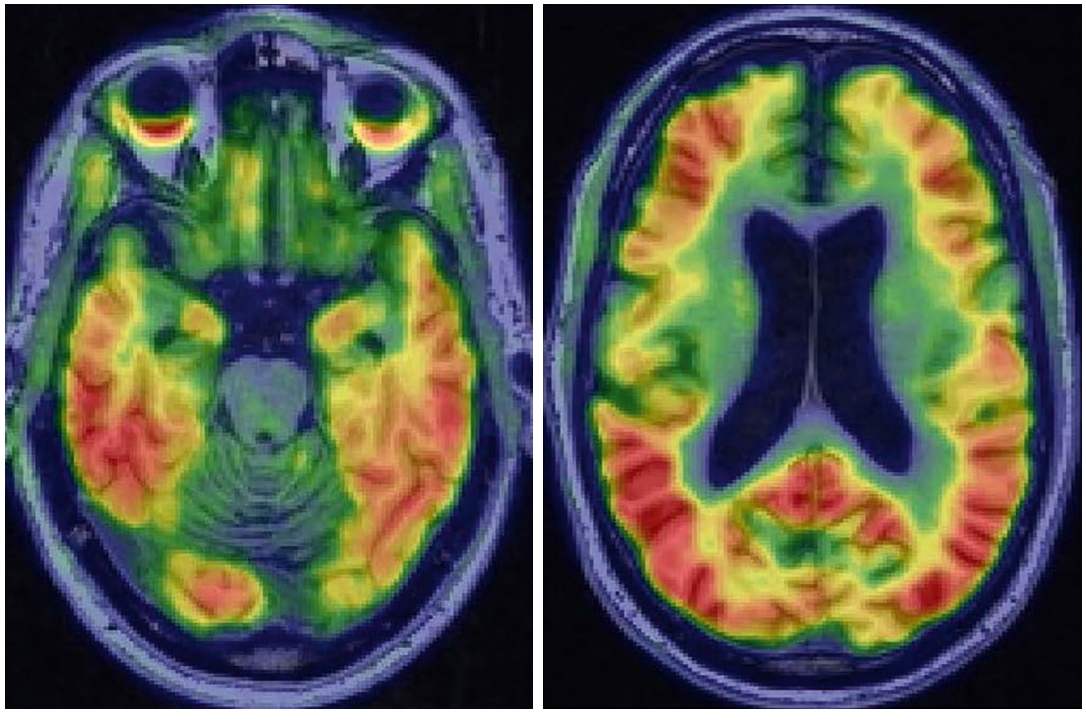

FIGURE 371-6. AV1451 (tau) positron emission tomographic (PET) scan of a patient with Alzheimer disease dementia. On axial images, the tau PET signal can be seen in the temporal and parietal lobes. The *left* scan at the level of the temporal lobes shows the increased signal (*red* and *yellow*) representing tau deposition. The *right* scan at the level of the lateral ventricles shows the tau deposition to be widespread in the parietal lobes, including the precuneus in the medial parietal lobes and lateral frontal lobes.

Risk Factors

Risk factors for vascular cognitive impairment include cardiovascular disease, atrial fibrillation, higher glucose levels, diabetes, and hypertension. There are no known protective factors other than treatment of these risk factors. Populations with high rates of generalized vascular disease should have higher rates of vascular dementia, but competing mortality from cardiovascular disease may obscure part of the relationship to brain health. Microinfarcts contribute to brain atrophy and cognitive impairment, particularly before dementia is clinically evident. In the first year after a stroke, the risk for development of dementia is about nine-fold higher than the rate in persons without a stroke, with the risk correlating with the severity of stroke-related deficits.[20] The risk remains about two-fold higher in subsequent years.

PATHOBIOLOGY

The majority of vascular disease causing cognitive impairment is due to atherosclerosis. One mechanism is by large territorial infarctions, such as those secondary to occlusive disease in major cerebral vessels, including the carotid arteries and the anterior, middle, and posterior cerebral arteries (Chapter 376). A second mechanism, which is at the arteriolar level, typically causes infarctions that are much smaller in volume than are territorial infarctions and are

typically located in the thalamus, basal ganglia, and subcortical white matter. Both of these processes can be detected by brain MRI. Smaller territorial infarctions or larger arteriolar-related infarcts in the hippocampal formations, medial thalamus, caudate nuclei, and parietal association areas are highly likely to produce cognitive impairment but not necessarily dementia. Smaller territorial infarctions or arteriolar-related infarcts outside of those strategic locations may not result in cognitive consequences. Microinfarcts, which are small zones of infarction that are not visible to the naked eye but can be observed with light microscopy, may also contribute to the dementia. Lacunar infarction and microinfarcts are far more commonly represented in series of patients with vascular dementia than are large infarctions. The simultaneous presence of Alzheimer disease is common in vascular dementia.

There are other uncommon causes of vascular cognitive impairment. Cerebral autosomal dominant arteriopathy with subcortical infarcts and leukoencephalopathy (CADASIL) is a very rare inherited disease that usually becomes clinically evident between the ages of 30 and 50 years and causes severe white matter disease, headaches, and dementia. The cause of CADASIL is mutations in the *notch3* gene on chromosome 19q12. Cerebral amyloid angiopathy, a β-amyloidosis in which the β-amyloid peptide accumulates in the media of small to medium-sized arteries in the leptomeninges and superficial cortex, causes cerebral hemorrhages that may lead to dementia if it occurs in sufficient number and in critical locations. Cerebral amyloid angiopathy is also seen in Alzheimer disease, but its hemorrhagic manifestations may occur in individuals with little evidence of Alzheimer disease clinically and modest evidence pathologically. Cerebral vasculitis (Chapter 249) is a very rare cause of dementia.

CLINICAL MANIFESTATIONS

The spectrum of cognitive changes in patients with cerebrovascular disease is broad. The more common cognitive syndromes in cerebrovascular disease include mild cognitive impairment, a dementia with prominent anterograde amnesia, and a dementia with prominent changes in personality and executive function. Some patients with vascular cognitive impairment without dementia may have deficits in only one domain (Chapter 370). A number of aphasia syndromes are a result of cerebral infarction or hemorrhage in the perisylvian regions of the dominant hemisphere. Infarction or hemorrhage in the occipitotemporal or occipitoparietal regions may produce one of the disorders of visual cognition, such as alexia or visual agnosia. Infarcts in the caudate nuclei, particularly if they are bilateral, may produce a cognitive syndrome that includes both amnesia and disordered executive function, thus mimicking dementia. Large infarcts in the right parietal lobe can also produce dementia. Infarcts in the medial thalami or in the hippocampal formations can produce isolated amnesia.

The evolution of symptoms in vascular cognitive impairment does not follow a stereotypical pattern. In some, the cognitive syndrome may remain static. In others, new strokes may lead to substantial declines in cognition and function. Some patients with vascular cognitive impairment may experience a gradually declining illness. Patients with vascular cognitive impairment without dementia or vascular dementia may also have other neurologic signs typical of patients with cerebrovascular disease, such as hemiparesis, hemianopia, hemisensory changes, or cranial nerve abnormalities.

TABLE 371-4 DIAGNOSTIC CRITERIA FOR THE SYNDROME OF DEMENTIA CAUSED BY CEREBROVASCULAR DISEASE (VASCULAR COGNITIVE IMPAIRMENT)

Mild cognitive impairment as defined in Table 371-1 or dementia as defined in Table 371-1
Clinically important cerebrovascular disease is demonstrable by *either* of the following:
Onset of the cognitive disturbance or dramatic worsening of an existing disturbance that occurred within 3 months of a stroke, where stroke is defined as a focal neurologic deficit of acute onset due to brain infarction in which the symptoms and signs persist for more than 24 hours
Neuroimaging evidence of bilateral brain infarctions rostral to but including the thalamus

DIAGNOSIS

The diagnosis of vascular cognitive impairment is based on the neurologic history and examination. Brain imaging, preferably with MRI, is essential to establish the presence of infarcts. The cardinal diagnostic features of vascular cognitive impairment are that (1) the cognitive disorder should have begun within 3 months of a clinical stroke event and (2) there should be multiple bilateral infarcts in the cerebral hemispheres visible on brain imaging studies (Fig. 371-7). A temporal link between the onset or worsening of cognitive impairment and a stroke is important in demonstrating that cerebrovascular disease is etiologically relevant to the cognitive impairment. Brain imaging of infarcts in the cerebral cortex, basal ganglia, thalamus, and cerebral white matter has obvious value for establishment of cerebrovascular disease. In contrast to actual infarcts on imaging, the presence of white matter hyperintensities without infarcts on brain MRI is much less specific.

The accuracy of the clinical diagnosis of cerebrovascular disease as a cause of cognitive impairment is generally lower than that of Alzheimer disease. The combination of (1) a temporal relationship between dementia and a stroke and (2) imaging evidence of bilateral infarcts is diagnostically specific for vascular dementia but is insensitive. Broader diagnostic criteria (see Table 371-4) are more sensitive but less specific. The usual alternative diagnosis is Alzheimer disease, and there is typically no way to be certain whether and how much Alzheimer disease is simultaneously present.

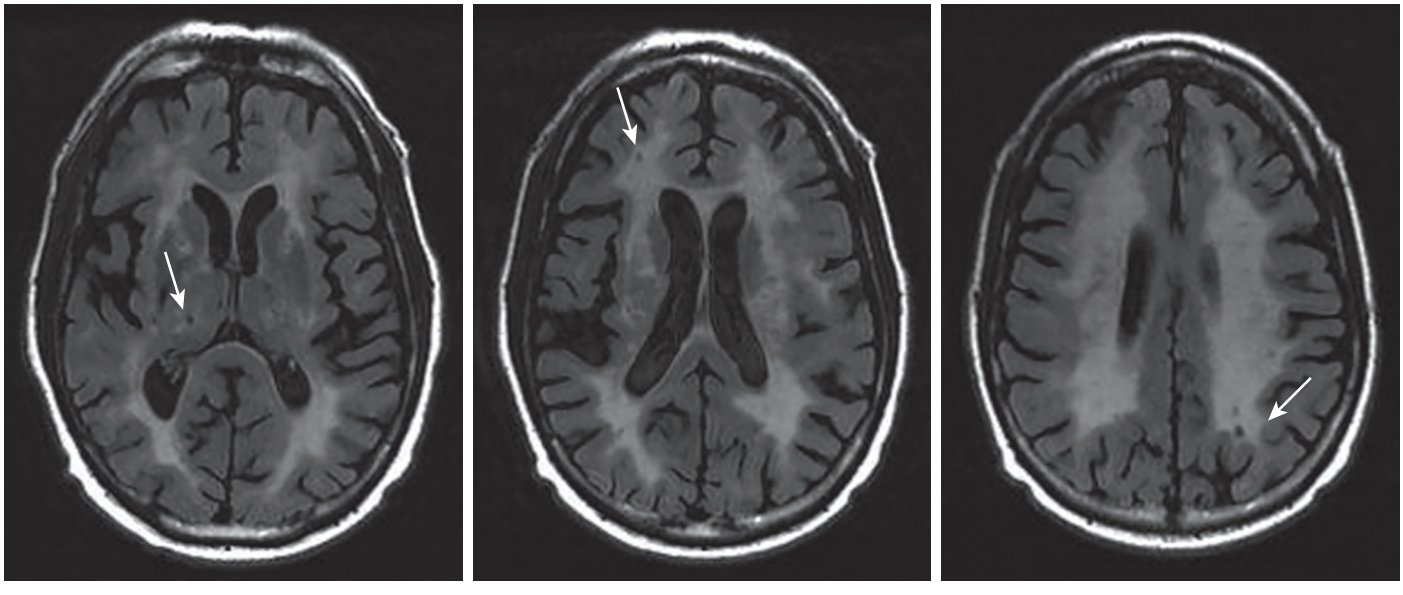

FIGURE 371-7. Axial magnetic resonance images of a patient with extensive cerebrovascular disease. The images show extensive white matter hyperintensities bilaterally. There are also lacunar infarcts *(arrows)*.

PREVENTION AND TREATMENT

The burden of cerebrovascular disease in later life can be mitigated by treatment of vascular risk factors in midlife. With early lifelong aggressive treatment of diabetes (Chapter 210), hypertension (Chapter 64), and hyperlipidemia (Chapter 190), as well as the use of prophylactic anticoagulation in patients with atrial fibrillation (Chapter 52), the number of cerebral infarcts should be reduced, with a corresponding reduction in the number of cases of vascular dementia. Evidence for this link comes from large-scale studies in which the treatment of hypertension reduced the frequency of strokes and incident dementia.[A11] After vascular dementia develops, cholinesterase inhibitors have shown some purely symptomatic benefits. A more important goal, however, is to mitigate ongoing cerebrovascular damage by addressing the same vascular risk factors that caused the cognitive decline.

PROGNOSIS

Patients with vascular dementia can often be expected to have severe cardiovascular disease and a greater likelihood of future strokes and cardiac ischemic events. Survival of patients with vascular dementia is poorer than that of patients with Alzheimer disease dementia.

DEMENTIA WITH LEWY BODIES

DEFINITION

Dementia with Lewy bodies is a multifaceted dementing disorder in which the underlying pathologic process includes Lewy bodies in limbic and cortical structures (Table 371-5). Some clinicians make a distinction between patients in whom parkinsonism preceded the cognitive disorder and those in whom the cognitive disorder occurred either simultaneously with or before the movement disorder. This distinction may be somewhat useful in clinical practice, but there are few clinical or neuropathologic differences based on different sequences of signs and symptoms. The diagnosis of dementia with Lewy bodies is similar in principle to diagnosis of both dementia and Parkinson disease (Chapter 378) in the same individual, but *dementia with Lewy bodies* is a term with broader connotations because of other features (hallucinations, fluctuations, and sleep disorder) that may be more apparent than the movement disorder.

TABLE 371-5 DIAGNOSTIC CRITERIA FOR THE DEMENTIA SYNDROME ASSOCIATED WITH LEWY BODY PATHOLOGY

Mild cognitive impairment as defined in Table 371-1 or dementia as defined in Table 371-1
Core clinical features (The first three typically occur early and may persist throughout the course.) 1. Fluctuating cognition with pronounced variations in attention and alertness 2. Recurrent visual hallucinations that are typically well formed and detailed 3. REM sleep behavior disorder, which may precede cognitive decline 4. One or more spontaneous cardinal features of parkinsonism: bradykinesia (defined as slowness of movement and decrement in amplitude or speed), rest tremor, or rigidity
Supportive clinical features Severe sensitivity to antipsychotic agents; postural instability; repeated falls; syncope or other transient episodes of unresponsiveness; severe autonomic dysfunction, such as constipation, orthostatic hypotension, urinary incontinence; hypersomnia; hyposmia; hallucinations in other modalities; systematized delusions; apathy, anxiety, and depression
Indicative biomarkers Reduced dopamine transporter uptake in basal ganglia demonstrated by SPECT or PET Abnormal (low uptake) ^{123}iodine-MIBG myocardial scintigraphy Polysomnographic confirmation of REM sleep without atonia
Probable dementia with Lewy bodies can be diagnosed if: a. Two or more core clinical features of dementia with Lewy bodies are present, with or without the presence of indicative biomarkers, or b. Only one core clinical feature is present, but with one or more indicative biomarkers
Probable dementia with Lewy bodies should not be diagnosed on the basis of biomarkers alone.

MIBG = meta-iodobenzylguanidine; PET = positron emission tomography; REM = rapid eye movement; SPECT = single-photon emission computed tomography.

From McKeith IG, Boeve BF, Dickson DW, et al. Diagnosis and management of dementia with Lewy bodies: fourth consensus report of the DLB Consortium. *Neurology*. 2017;89:88-100.

EPIDEMIOLOGY

Mild cognitive impairment or dementia with Lewy bodies is about one fourth as common as Alzheimer disease dementia. Lewy body disease becomes more common with advancing age, and the prevalence of dementia with Lewy bodies increases with advancing age as well. As with the other dementias, there are no known ethnic or racial differences, but dementia with Lewy bodies may be more common in men. There are no known risk factors for dementia with Lewy bodies. Dementia develops in up to 30% of patients with Parkinson disease, and advancing age is the major risk factor.

PATHOBIOLOGY

The pathology of dementia with Lewy bodies is a mixture of Lewy body disease and Alzheimer disease. In general, the more intense the Lewy body disease, the less abundant the Alzheimer disease. Lewy bodies, which are intraneuronal inclusions that contain α-synuclein, are found in the nucleus basalis, pars compacta of the substantia nigra, locus caeruleus, other brain stem structures, amygdala, cingulate gyrus, and neocortex. The earliest locations of Lewy bodies are the brain stem, where they affect nuclei involved in sleep and arousal, and the substantia nigra, the locus caeruleus, and cranial nerve nuclei IX and X. Typically, the nucleus basalis, transentorhinal cortex, cingulate gyrus, and neocortex become involved later.

In Lewy body disease, the α-synuclein protein becomes misfolded and aggregates intraneuronally. Mutations in the α-synuclein gene have been seen in a few families with autosomal dominant Parkinson disease, but most cases of dementia with Lewy bodies are sporadic. Mutations in the glucocerebrosidase gene *(GBA1)* confer increased risk for dementia with Lewy bodies and Parkinson disease.[21]

CLINICAL MANIFESTATIONS

The clinical manifestations of mild cognitive impairment and dementia with Lewy bodies include four major abnormalities: the cognitive disorder, the neuropsychiatric disorder, the motor disorder, and the disorder of sleep and wakefulness. The cognitive disorder may differ from Alzheimer disease dementia, although there is considerable overlap.[22] In a typical patient with dementia with Lewy bodies, visuospatial deficits, impaired concentration, and impaired attention dominate the picture. In some patients, the deficits in executive functions may be similar to what is seen in frontotemporal lobar degeneration. Anterograde amnesia is usually present but milder than in Alzheimer disease dementia. Language deficits are not prominent. The neuropsychiatric manifestations of dementia with Lewy bodies, including prominent apathy, loss of initiative, and depression, may be more disabling than the cognitive symptoms. The motor manifestations include bradykinesia, gait disturbances, postural disturbances, and rigidity. Rest tremor is less common in dementia with Lewy bodies in patients in whom the cognitive disorder appears before the parkinsonism. Visual hallucinations, fluctuations in alertness, and REM sleep disorders are part of a broader disorder of the regulation of sleep and wakefulness. Visual hallucinations are often graphic, detailed, and bizarre, perhaps because the sleep phenomenon of dreaming intrudes into wakefulness. Patients with dementia with Lewy bodies have large fluctuations in their alertness and arousal from day to day.

REM sleep behavior disorder (Chapter 374) is a parasomnia in which patients exhibit dream enactment behavior, often with violent, threatening overtones. Patients typically relate that they feel as though they are being chased by something or someone. Their behavior while they are asleep consists of excessive talking, calling out or shouting, and thrashing about, often to the point of striking a bed partner or falling out of bed. The REM sleep behavior disorder may precede the development of Parkinson disease and dementia with Lewy bodies by years.

DIAGNOSIS

The diagnosis of dementia with Lewy bodies is based on clinical information that corroborates the presence of abnormalities in cognition, motor function, neuropsychiatric behavior, and regulation of sleep and wakefulness. Formal neuropsychologic testing is often helpful in evaluating memory, executive function, and visuospatial function in a detailed manner. Neuroimaging has only a limited role in the diagnosis of dementia with Lewy bodies, but reduced uptake of dopamine transporter in the basal ganglia on single photon emission computed tomography (SPECT) increases the likelihood of the diagnosis when motor deficits are subtle.

Differential Diagnosis

Other disorders that must be considered in patients with dementia and a movement disorder include progressive supranuclear palsy (Chapter 379), which

can resemble dementia with Lewy bodies in terms of both the dementia and the motor disorder. In progressive supranuclear palsy, patients are much less likely to have disorders of arousal and typically have other distinctive signs and symptoms, including the characteristic supranuclear gaze palsy and other brain stem findings. The corticobasal degenerations, which are members of the family of frontotemporal lobar dementias (see later), may also produce a movement disorder and dementia. Huntington disease (Chapter 379) is associated with dementia and a movement disorder, but the movement disorder of Huntington disease includes prominent chorea and athetosis, neither of which is present in dementia with Lewy bodies.

Normal-Pressure Hydrocephalus

Normal-pressure hydrocephalus, which is rare relative to dementia with Lewy bodies and Alzheimer disease, is typically characterized by the triad of a gait disorder, dementia, and urinary incontinence.[23] Altered dynamics of CSF flow in the ventricular system appear to reduce periventricular metabolism and also induce damage in periventricular axons. Normal-pressure hydrocephalus can be suspected when computed tomography or MRI shows ventricular enlargement, widened Sylvian fissures, convex CSF pockets, and tight sulci at the vertex. Treatment is placement of a ventriculoperitoneal shunt, but it is difficult to predict which patients will respond. Imaging studies to measure CSF flow through the aqueduct of Sylvius or to measure the flow of radiolabeled CSF have not been useful. Clinical response to the removal of a high volume (e.g., 30 mL) of CSF through lumbar puncture is sometimes used to select patients for surgery, although its positive and negative predictive values are unclear. Only about one third of patients who initially respond to shunting have persistent benefits at 3 years.

TREATMENT

Management of patients with cognitive impairment with Lewy bodies is challenging because of the simultaneous appearance of a cognitive disorder, a neuropsychiatric disorder, a motor disorder, and a sleep and wakefulness disorder.[24] Treatment of the motor disorder is accomplished with antiparkinsonian drugs such as levodopa-carbidopa to 25/100 2 tablets 3 times a day (Chapter 378). Treatment with levodopa should be instituted for dementia with Lewy bodies if there are prominent gait or balance problems that threaten safety and interfere with independence. Levodopa may worsen hallucinations and exacerbate confusional states, but this concern should not preclude a treatment trial if the motor symptoms pose safety risks or interfere with independence.

Cholinesterase inhibitors (e.g., donepezil in a maintenance dose of 10 mg daily or rivastigmine patch in a maintenance dose of 9.5mg daily), which do not exacerbate parkinsonian symptoms, have a beneficial effect on neuropsychiatric symptoms and perhaps on the cognitive disorder.[A12] Autonomic disturbances such as urinary incontinence can be challenging to treat in persons with cognitive impairment due to Lewy body disease because the usually prescribed medications have anticholinergic pharmacologic profiles. Anticholinergic drugs have a definite risk for increasing confusion.

Hallucinations and agitation impair quality of life for the patient and family and often require treatment. Some antipsychotic agents that might otherwise control these symptoms dramatically exacerbate the parkinsonism in dementia with Lewy bodies. Atypical antipsychotics are usually recommended, but there is insufficient experience from controlled clinical trials. Many movement disorder specialists prefer to use quetiapine in doses of 25 to 200 mg/day or clozapine at 6.25 to 50 mg/day because these agents appear to have the lowest rate of extrapyramidal side effects. However, it is not possible to make any strong statements about the relative efficacy of atypical antipsychotics in treating the hallucinations in dementia with Lewy bodies, especially in view of the possibility that atypical antipsychotic agents may be associated with higher than expected mortality.

REM sleep behavior disorder (Chapter 374) can be disabling, but there are no controlled clinical trials to inform treatment. Some sleep disorder specialists typically use either melatonin, 3 to 12 mg, or clonazepam, 0.5 to 2 mg, at bedtime.

Treatment of depressive symptoms may substantially improve a patient's functioning. Use of one of the newer generation antidepressants, such as sertraline (25 to 100 mg/day) or citalopram (10 to 20 mg/day), may be beneficial and does not necessarily interfere with management of the other symptoms (Chapter 362).

PROGNOSIS

As opposed to patients with Alzheimer disease dementia, some studies show that patients with dementia with Lewy bodies have a more rapidly progressive course and poorer survival. As a result of the combination of manifestations, patients with dementia with Lewy bodies may become disabled sooner in their course.

TABLE 371-6 DIAGNOSTIC CRITERIA FOR BEHAVIOR-VARIANT FRONTOTEMPORAL DEMENTIA

The following symptom must be present to meet criteria for behavior-variant frontotemporal dementia: Shows progressive deterioration of behavior and/or cognition by observation or history (as provided by a knowledgeable informant)
Three of the following behavioral/cognitive symptoms that are persistent or recurrent must be present **within 3 years of onset** to meet criteria for **possible** behavior-variant frontotemporal dementia: Early behavioral disinhibition such as socially inappropriate behavior, loss of manners or decorum, or impulsive, rash, or careless actions Early apathy or inertia Early loss of sympathy or empathy Early perseverative, stereotyped, or compulsive/ritualistic behavior Hyperorality and dietary changes such as altered food preferences, binge eating, increased consumption of alcohol or cigarettes, or oral exploration or consumption of inedible objects Neuropsychological profile exhibits executive/generation deficits with relative sparing of memory and visuospatial functions
Probable behavior-variant frontotemporal dementia is diagnosed when **all of the following** are present: Criteria met for possible behavior-variant frontotemporal dementia Significant functional decline present by caregiver report Imaging results that demonstrate frontal and/or anterior temporal atrophy on MRI or CT, or frontal hypoperfusion or hypometabolism on PET or SPECT
The diagnosis of behavior-variant frontotemporal dementia **should not** be applied when the pattern of deficits is better explained by a psychiatric diagnosis, other nondegenerative nervous system disorders, or medical disorders.

CT = computed tomography; MRI = magnetic resonance imaging; PET = positron emission tomography; SPECT = single-photon emission computed tomography.

Adapted from Rascovsky K, Hodges JR, Knopman D, et al. Sensitivity of revised diagnostic criteria for the behavioural variant of frontotemporal dementia. *Brain*. 2011;134:2456-2477.

FRONTOTEMPORAL LOBAR DEGENERATION

DEFINITION

The frontotemporal lobar degenerations are a group of neurodegenerative disorders with distinctive clinical manifestations and a predilection for the prefrontal and anterior temporal neocortices. The most common clinical syndrome is a disorder of behavior and personal relationships (comportment) with a loss of executive functions (Table 371-6). This syndrome is referred to as behavior-variant frontotemporal dementia. Other syndromes in the clinical spectrum of frontotemporal lobar degeneration involve different aspects of language or motor dysfunction of the limbs.

EPIDEMIOLOGY

Unlike Alzheimer disease, the frontotemporal lobar degenerations have a peak age at onset in the 50- to 70-year range, and the incidence declines after the age of 70. In patients with dementia who are younger than 70 years, frontotemporal lobar degeneration makes up 10 to 20% of cases. However, across the entire age spectrum, the frontotemporal lobar degenerations are much less common than Alzheimer disease dementia, dementia with Lewy bodies, or vascular dementia. Both men and women are affected equally. There are no known risk factors for the frontotemporal lobar degenerations except a family history.

PATHOBIOLOGY

The clinical syndrome in frontotemporal lobar degeneration is determined by the lobar location of the pathologic process. Right prefrontal or anterior temporal disease and brain atrophy produce behavioral syndromes like frontotemporal dementia. Left frontal involvement tends to produce progressive nonfluent aphasia. Predominant left anterior temporal lobe involvement may produce semantic dementia.

On histopathologic grounds, patients with frontotemporal lobar degeneration can be divided into three groups: those whose inclusions contain the microtubule-associated protein tau, those whose inclusions contain the TAR DNA-binding protein 43 (TDP-43), and those whose inclusions contain the fused in sarcoma protein, another ribonucleic acid–binding protein. The latter is much less common than the first two. Each type includes both genetically determined and sporadic forms.

Among the tau-positive varieties are Pick disease, in which intracellular tau-positive inclusions known as Pick bodies are seen. Several other pathologic tau-positive subtypes occur, including progressive supranuclear palsy,

corticobasal degeneration, and the disorder associated with mutations in the tau gene. Over 65 mutations in the *MAPT* gene on chromosome 17q21 are almost always associated with autosomal dominant frontotemporal lobar degeneration syndromes, each with a slightly different clinical and neuropathologic phenotype.[25] The most common is a proline-to-leucine mutation at codon 301, located in exon 10. The tau gene undergoes alternative splicing, resulting in six isoforms of the tau protein. Pathologic mutations appear to disrupt splicing of alternative isoforms of tau protein, which in turn adversely affects the binding of tau to microtubules in neurons. Reduced binding of tau to microtubules is deleterious to microtubule function and neuronal integrity.

The TDP-43–positive frontotemporal lobar degenerations are almost equally common. Immunostaining shows that there are distinctive TDP-43–containing inclusions. Mutations in the granulin *(GRN)* gene, also located on chromosome 17q21, cause familial autosomal dominant forms of frontotemporal lobar degeneration with TDP-43–positive inclusions with nearly 100% penetrance. Currently, 130 different mutations in the granulin gene have been linked to frontotemporal lobar degenerations. All of the mutations lead to premature degradation of the messenger RNA—a process termed *nonsense-mediated* decay that leads to a roughly 50% reduction in progranulin protein, referred to as *haploinsufficiency*. The normal function of granulin in the brain is unclear, and the pathophysiologic basis for dementia in persons with granulin gene mutations is unknown. The link between alterations in TDP-43 and *GRN* mutations is also unknown at this time.

A third important gene mutation involved in frontotemporal lobar degenerations associated with TDP-43 inclusions is the highly penetrant hexanucleotide repeat expansion in *C9ORF7* gene located on chromosome 9p21. This latter mutation is the most common of the mutations causing frontotemporal lobar degeneration and amyotrophic lateral sclerosis (Chapter 387).

Frontotemporal lobar degenerations caused by mutations in the fused in sarcoma (*FUS*) gene are much less common. Such cases have the behavioral variant of frontotemporal dementia.

CLINICAL MANIFESTATIONS

The clinical manifestations of the syndrome of frontotemporal dementia begin insidiously. Apathy, loss of initiative, and flattening of affect are common early symptoms. As the disease progresses, the entire spectrum of behavioral changes associated with dysfunction of the frontal and anterior temporal lobes appears. On cognitive assessments, patients may have preserved memory functions, but they typically have difficulty with tests of executive cognitive function. When frontotemporal dementia progresses to moderate or severe stages, the behavioral changes remain prominent, but the disease becomes more difficult to distinguish from other dementias such as Alzheimer disease. The neuropathology of behavior-variant frontotemporal dementia may be either tau positive or TDP-43 positive.

In some patients with frontotemporal lobar degeneration, signs and symptoms of motor neuron disease (Chapter 387) develop, such as weakness, atrophy, and fasciculation in the limbs or the bulbar musculature. In other patients with frontotemporal lobar degeneration, asymmetrical limb apraxia develops that is part of the corticobasal syndrome. Features of progressive supranuclear palsy may also appear in patients with behavior-variant frontotemporal dementia.

Aphasic disturbances are often the presenting manifestation of patients with frontotemporal lobar degeneration. The two most characteristic syndromes are a nonfluent/agrammatic variant of primary progressive aphasia or the semantic variant of primary progressive aphasia. The nonfluent/agrammatic primary progressive aphasia variant is seen in patients who exhibit hesitancy in selecting words in their speech, a problem that may be difficult for others to appreciate at first. Anomia is an early sign. Gradually, the patient's speech becomes laconic and labored. Eventually, a nonfluent, apractic, agrammatic speech develops. In other cognitive domains, patients often have no deficits. Other nonfluent/agrammatic primary progressive aphasic patients may eventually become virtually mute even though they may appear to have preserved memory and visuospatial functions. Patients with nonfluent/agrammatic primary progressive aphasia often have tau-positive neuropathologic findings.

The semantic variant of primary progressive aphasia, previously known as semantic dementia, is a disorder that involves dissolution of the meaning of words or objects. A patient with semantic variant primary progressive aphasia may also become unable to access knowledge about objects (object agnosia) and people's faces (prosopagnosia). The most striking demonstration of the deficit in semantic variant primary progressive aphasia is when a patient can produce the name of an object—a watch, for example—but then cannot say what a watch is for when asked. Often, patients with semantic variant primary progressive aphasia have preservation of the ability to learn a list of words, even if their knowledge of the meaning of the words is diminished. Patients with semantic variant primary progressive aphasia usually have TDP-43–positive neuropathologic findings.

Not all patients with primary progressive aphasia fit neatly into a well-delineated syndrome. Although the semantic and nonfluent/agrammatic variants of primary progressive aphasia are almost always due to frontotemporal lobar degenerations, other variants, especially one in which word-finding problems predominate (the logopenic variant of primary progressive aphasia), may be due to Alzheimer disease.

DIAGNOSIS

Frontotemporal lobar degeneration must first be suspected as a cause for a cognitive or behavioral disorder on clinical grounds, based on the appearance of one of the distinctive clinical syndromes such as frontotemporal dementia (see Table 371-6) or one of the aphasic subtypes.[26] Neuropsychological testing can also aid in the diagnosis by detecting abnormalities in executive function and verifying that memory function is preserved, as it often is. For all frontotemporal lobar degeneration syndromes, MRI showing focal atrophy of the frontal (Fig. 371-8) or temporal lobes (Fig. 371-9) is highly likely to be diagnostic. Imaging with fluorodeoxyglucose PET also can be useful when the clinical diagnosis is uncertain and MRI is nondiagnostic.

TREATMENT

There is no symptomatic therapy specifically for frontotemporal lobar degeneration. In patients with agitation, paranoia, delusions, or obsessive behavior, atypical antipsychotics (e.g., quetiapine, 25 to 200 mg/day) are used, but no controlled clinical trials are available.[27] There are no preventive or disease-modifying treatments of frontotemporal lobar degeneration.

PROGNOSIS

Specific frontotemporal lobar degeneration syndromes have dramatic differences in their clinical course and outcome. In patients with motor neuron signs and symptoms, the prognosis is usually poor, with survival of only about 2 years from the time of diagnosis. Patients with semantic variant and nonfluent variant primary progressive aphasia have much more protracted and gradual trajectories; survival for more than 10 years is not uncommon. Behavior variant frontotemporal dementia itself can also exhibit a more protracted course.

CREUTZFELDT-JAKOB AND OTHER CLASSIC PRION DISEASES

Prion diseases are neurodegenerative conditions of humans and other mammals. In prion diseases, a normal brain protein known as the prion protein (PrP) aggregates in an abnormal conformation that can act as an infectious agent called a prion and transmit disease to another host. Most human forms of prion disease are termed Creutzfeldt-Jakob disease (CJD).

EPIDEMIOLOGY

Prion diseases have an incidence of 1 to 2 cases per million annually.[28] About 90% of cases are sporadic, and most of the remainder are genetic, with dietary and iatrogenic causes accounting for fewer than 1% of cases in most human populations.

Sporadic disease can occur at any age but with a peak incidence in the eighth decade. Genetic forms peak in the sixth decade.

Infectious prion disease formerly included Kuru, which was seen in the Fore group in New Guinea, and spread by the practice of ritual cannibalism. Variant CJD, caused by eating meat from cattle infected with prion disease, probably caused fewer than 250 cases of spongiform encephalopathy, predominantly in Great Britain. That outbreak has not recurred since the 1990s. Other animal prion diseases (scrapie in sheep and chronic wasting disease in deer) have not been transmitted to humans. Iatrogenic transmission of variant CJD can rarely occur with contaminated surgical instruments and corneal transplants.

PATHOBIOLOGY

In prion disease, an abnormally aggregated form of PrP, termed PrP^{Sc}, accumulates in the brain and recruits the normal form of PrP into the pathologic aggregate, so the normal PrP loses its α-helical structure and forms β-sheets. Inherited forms are caused by more than 20 autosomal dominant mutations of high penetrance in the PrP coding sequence of the gene *PRNP*.

CLINICAL MANIFESTATIONS

The typical age of onset of sporadic and inherited CJD is in the 50s to 70s. The initial presentation may be with: neuropsychiatric symptoms such as

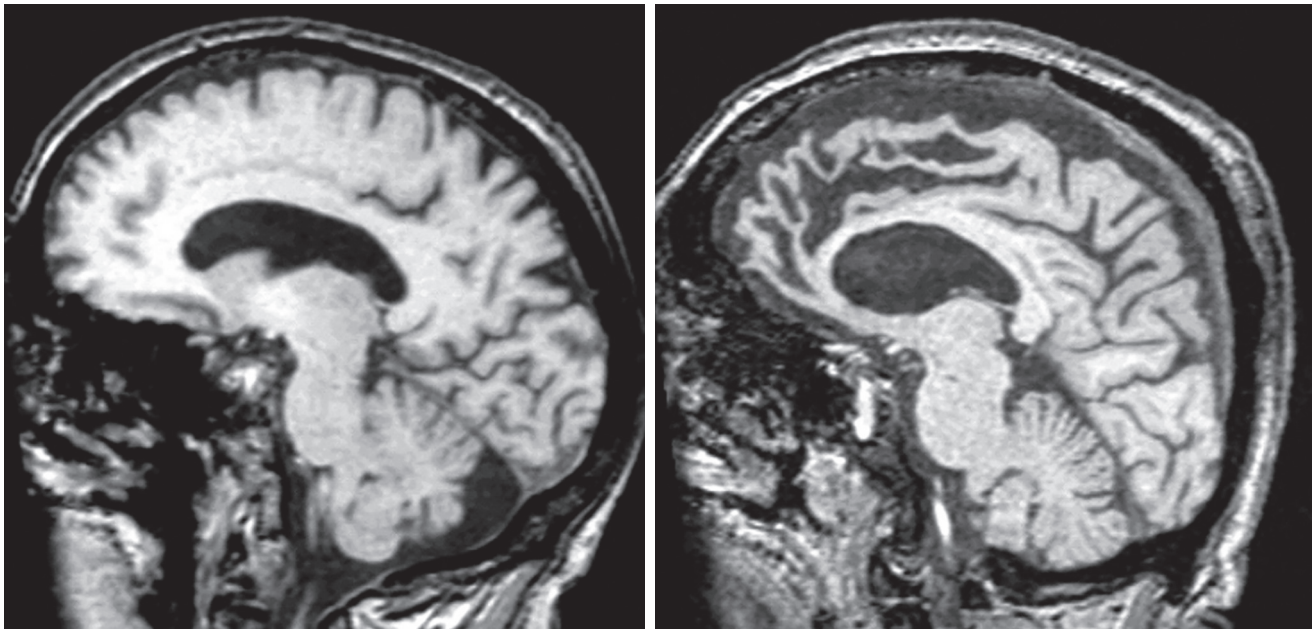

FIGURE 371-8. Parasagittal image from magnetic resonance imaging of a patient with frontotemporal dementia *(right).* Atrophy of the frontal lobes is dramatic compared with the brain of a normal individual *(left).* (Courtesy Maria Shiung and Clifford Jack.)

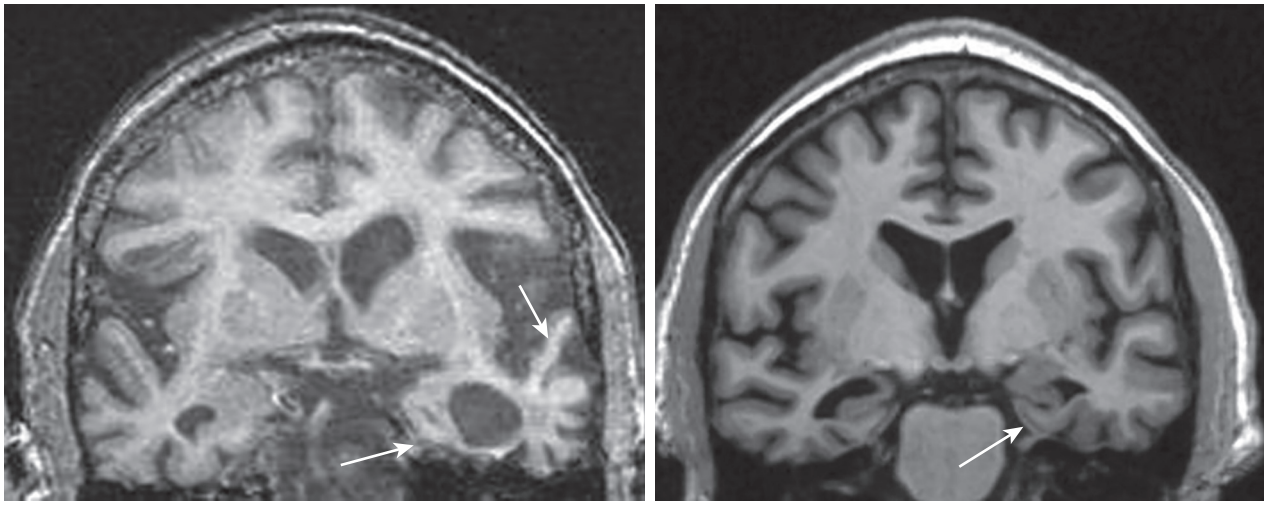

FIGURE 371-9. Coronal images from magnetic resonance imaging of a patient with semantic variant of primary progressive aphasia *(left).* There is prominent asymmetrical atrophy of the left anterior temporal lobe involving the amygdala, head of the hippocampus, and the lateral temporal lobe neocortex. By comparison, on the scan of a patient with Alzheimer disease dementia *(right),* the neocortex is preserved even though there is atrophy involving the amygdala and head of the hippocampus *(arrows).*

depression, apathy, or altered sleep; motor symptoms such as cerebellar ataxia, parkinsonism, myoclonus, or spasticity; or cognitive deficits in any domain. Once symptomatic, the illness typically is inexorably and rapidly progressive, with the majority of patients dying within 12 to 18 months. In some families, however, prion disease progresses slower and can mimic Alzheimer disease or Huntington disease (Chapter 379).

Iatrogenic CJD usually resembles sporadic CJD. Variant CJD tended to have more prominent psychiatric and sensory signs.

Some prion diseases cause specific syndromes. In Gerstmann-Straüssler-Scheinker syndrome, which is a very rare genetic disorder caused by mutations in the prion gene, ataxia predominates and dementia occurs late, with progression over 5 to 6 years from onset to death. The fatal familial insomnia syndrome begins with anxiety, depression, and sleep disturbance followed by ataxia and other motor signs; dementia occurs relatively late.

DIAGNOSIS

The diagnosis can be strongly suspected on clinical grounds based on the rapid progression of symptoms over weeks to months, in combination with the neuropsychiatric, motor, and cognitive deficits. Polymerase chain reaction testing of CSF has a specificity and sensitivity approaching 99%[29] and is available through the National Prion Disorders Pathology Service Center (available at http://www.cjdsurveillance.com). Elevated levels of the neuronal proteins 14-3-3 and tau in the CSF are also suggestive. However, in patients with a family history, exome sequencing that finds a consistent mutation in the protein-coding region can be diagnostic.

The clinical diagnosis is also supported by MRI changes that are both specific and sensitive for CJD (Fig. 371-10). Periodic sharp wave complexes on EEG support the diagnosis. In rare cases, definitive diagnosis may require brain tissue, obtained by biopsy or at autopsy.

TREATMENT AND PROGNOSIS

No treatment alters the natural history of prion disease. For sporadic CJD, progression to akinetic mutism and death typically occurs within 1 year. Patients with other genetic or variant forms may live longer.

PREVENTION

Sporadic prion disease cannot be prevented. Genetic cases can potentially be prevented by genetic counseling and prenatal testing (see below). Infectious cases can be prevented by avoidance of surgical transmission and protecting the human food supply from contaminated meat products.

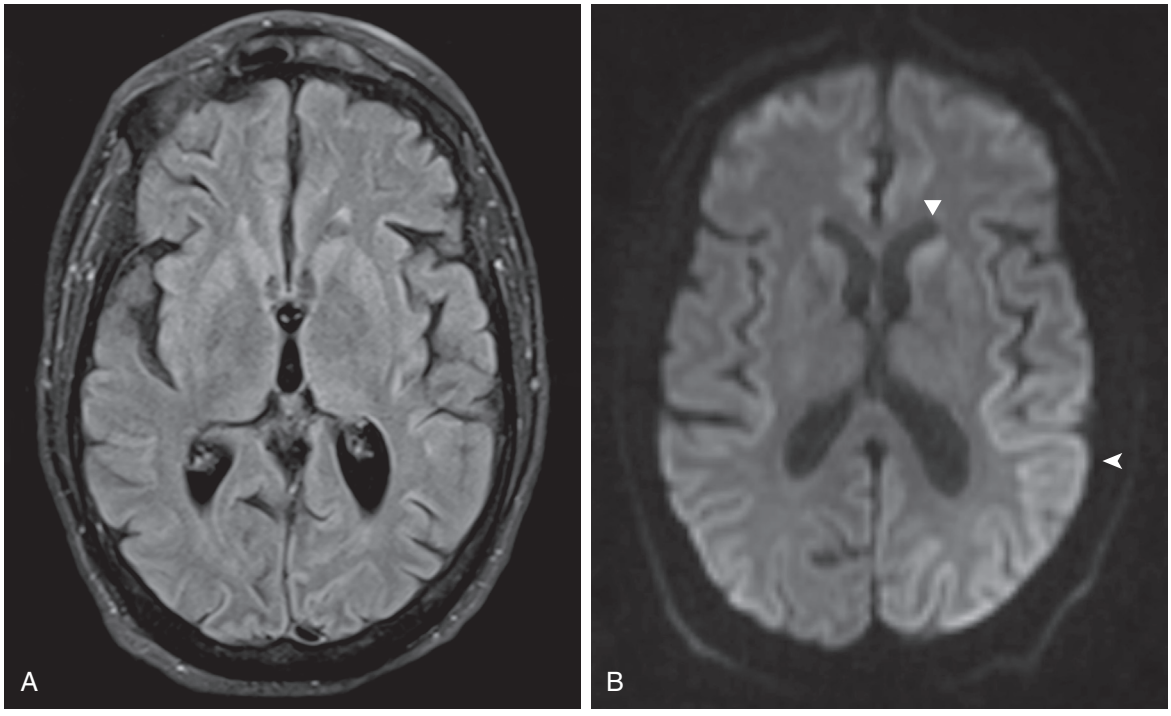

FIGURE 371-10. Magnetic resonance imaging appearance of sporadic Creutzfeldt-Jakob disease. The figure depicts fluid-attenuated inversion recovery (FLAIR) (A) and diffusion weighted images (B) of the brain of a patient with sporadic Creutzfeldt-Jakob disease. An excess of brightness is barely detectable in the FLAIR image but is readily apparent in the diffusion weighted image in several regions of cortical gray matter, particularly in the left parietal region *(notched arrowhead)*. Also, the left caudate *(triangular arrowhead)* is abnormally bright. (From Bosque P. Prion Diseases. In: Goldman L, Schafer AI, eds. *Goldman-Cecil Medicine*, 26th ed. Philadelphia: Elsevier; 2019.)

TABLE 371-7 DIFFERENTIAL DIAGNOSIS OF RAPIDLY PROGRESSIVE DEMENTIA

Neurodegenerative diseases that may mimic CJD	Alzheimer disease, diffuse Lewy body disease, frontotemporal dementia, corticobasal ganglion degeneration, progressive supranuclear palsy
Treatable diseases that mimic CJD	**Autoimmune:** autoimmune encephalitis (Chapter 383), CNS vasculitis (Chapter 249), limbic encephalitis (Chapter 383), Hashimoto encephalopathy (Chapter 383), anti–voltage-gated potassium channel encephalopathy, sarcoidosis (Chapter 83), steroid-responsive autoimmune encephalopathy (Chapter 383) **Infections:** viral encephalitis (Chapter 383), chronic meningitis (Chapter 381), Whipple disease (Chapter 254) **Neoplasms:** primary CNS lymphoma (Chapter 171), intravascular lymphoma (Chapter 171) **Vascular:** dural arteriovenous fistula **Nutritional:** Wernicke encephalopathy (Chapter 384) **Toxicities:** lithium, bismuth, methotrexate

CJD = Creutzfeldt-Jakob disease; CNS = central nervous system.
From Bosque P. Prion Diseases. In: Goldman L, Schafer AI, eds. *Goldman-Cecil Medicine*, 26th ed. Philadelphia: Elsevier; 2019.

TABLE 371-8 EVALUATION OF RAPIDLY PROGRESSIVE DEMENTIA

Initial screening	**History:** review for exposure to tricyclic antidepressants, lithium, bismuth, methotrexate, etc.; consider blood levels if toxicity suspected **Blood tests:** levels of glucose, sodium, calcium, blood urea nitrogen, creatinine, hepatic aminotransferases, albumin, vitamin B_{12}, thyroid stimulation hormone; international normalized ratio, antinuclear antigen, HIV testing, and syphilis serology **Imaging:** brain MRI, including DWI sequences **CSF:** glucose, protein, cell counts, VDRL
Further tests to consider	**Serum:** antibodies against thyroglobulin, thyroid peroxidase, voltage-gated potassium channel, Hu (ANNA-1) **CSF:** cytology, flow cytometry, Alzheimer biomarkers **EEG** **Brain biopsy (only if a non-CJD potentially treatable disorder is strongly suspected)**
Test findings supporting a diagnosis of prion disease	**CSF:** Prion amplification assay (e.g. RT-QuIC)* Levels of 14-3-3 and tau proteins* **MRI:** T2 hyperintensity in the basal ganglia, sometimes in the cortex **EEG:** Periodic sharp wave complexes

*In the United States, available through National Prion Disorders Pathology Service Center.
CJD = Creutzfeldt-Jakob disease; CSF = cerebrospinal fluid; DWI = diffusion-weighted imaging; EEG = electroencephalography; HIV = human immunodeficiency virus; MRI = magnetic resonance imaging; TSH = thyroid-stimulating hormone; VDRL = Venereal Disease Research Laboratory test.
From Bosque P. Prion Diseases. In: Goldman L, Schafer AI, eds. *Goldman-Cecil Medicine*, 26th ed. Philadelphia: Elsevier; 2019.

RAPIDLY PROGRESSIVE DEMENTIA

Most dementias are very slowly progressive over a matter of years. In a limited number of disorders, however, cognitive decline evolves subacutely over weeks to months. Sporadic CJD is the most common disorder among the rapidly progressive dementias. However, it is itself very uncommon, occurring with an incidence of about 1 per million persons per year.

Rapidly worsening cognitive impairment also can be caused by potentially treatable conditions (Table 371-7) such as autoimmune encephalitis,[30] viral encephalitis (Chapter 383), or central nervous system neoplasms (Chapter 175). Inflammation in the CSF should prompt additional testing (Table 371-8) to search for rare but treatable conditions.

FAMILY TESTING

When a family member has had dementia of any age of onset, patients often ask about their own risk and may request genetic testing.[31] However, genetic testing must be approached deliberately for later life cognitive disorders. The clinician should not simply order a battery of genetic tests but rather should engage the

patient in a detailed discussion about the limited benefits and potential emotional risks associated with the knowledge a mutation may cause disease many years in the future.[32] Several key questions should be asked to understand how to proceed. First, how old was the affected family member at the time of disease onset and at death? Second, what was the clinical diagnosis and how and by whom was the diagnosis made (i.e., was the diagnosis made by a dementia specialist) and on the basis of what clinical features and what laboratory tests? Third, was a brain autopsy performed, and is the written report available. Fourth, are any other first-degree relatives affected? And fifth, did any of the parents, siblings, or children of the affected person also have the same or similar disorder? Persons for whom genetic testing would be reasonable have a multigenerational family history of dementia before age 65 years, or if the affected family member had been proved or strongly suspected of harboring a relevant mutation. Persons in whom genetic testing is not justified on the basis of very low risk would be those in whom the affected family member was over age 70 years at onset and in whom there were no other affected family members. In between those two ends of the spectrum, risk is low, but the physician and patient may choose to pursue genetic testing after a discussion that takes into account the strengths and weaknesses of the available family history.

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372 THE EPILEPSIES

SAMUEL WIEBE

DEFINITION

A seizure is defined by transient focal or generalized signs or symptoms due to abnormal excessive or synchronous neuronal activity in the brain. Focal seizures, which originate within neuronal networks limited to one cerebral hemisphere, produce signs and symptoms corresponding to the specific region of the brain affected by the seizure. Generalized seizures rapidly affect extensive neuronal networks on both cerebral hemispheres, and their signs and symptoms are consistent with substantial involvement of both sides of the brain.

Seizures are not synonymous with epilepsy. The epilepsies should be distinguished from situations in which acute brain insults (e.g., infections, trauma, intoxication, metabolic disturbances) cause one or more seizures without a resulting chronic seizure tendency. Acute symptomatic seizures, or provoked seizures, constitute about 40% of all incident cases of nonfebrile seizures, typically respond to treatment of the provoking factor, and do not require long-term treatment with antiseizure medications.

The epilepsies are a group of conditions in which an underlying neurologic disorder results in a chronic tendency to have recurrent unprovoked seizures. The diagnosis of epilepsy is established if one of the following three criteria is met: two or more unprovoked or reflex seizures occurring more than 24 hours apart; a single unprovoked or reflex seizure in a person whose risk of recurrence is at least 60% over the next 10 years (e.g., brain tumor, hemorrhage, or infection); or a known epilepsy syndrome (e.g., self-limited epilepsy with centrotemporal spikes).

The causes, types, and clinical expression of the epilepsies are numerous and varied. However, some of the epilepsies conform into identifiable epileptic syndromes, which consist of clusters of clinical and electroencephalographic (EEG) features that have specific causes, respond to particular treatments, and may have specific prognostic implications.

EPIDEMIOLOGY

Incidence and Prevalence

Seizures are common in the general population, and about 1 in 10 people will experience a seizure in their lifetime. Most of these seizures are provoked by acute events and are not related to epilepsy. The overall annual incidence of acute symptomatic seizures, excluding febrile seizures, in developed countries is about 39 per 100,000 people. The incidence is higher in men and follows a bimodal age distribution, with its highest peak in the first year of life (up to 300 per 100,000), a nadir of 15 per 100,000 in the third and fourth decades of life, and a second peak rising to 123 per 100,000 after 75 years of age. These differences are attributable to the high incidence of acute symptomatic seizures associated with metabolic, infectious, and encephalopathic causes during the neonatal period and of cerebrovascular, neoplastic, and degenerative diseases in elderly persons.

After headache, the epilepsies are the most frequent chronic neurologic condition seen in general practice worldwide. In developed countries, the prevalence of active epilepsy ranges from 5 to 7 per 1000 persons, and the median annual incidence is 45 per 100,000 (range, 30 to 67), varying by age and socioeconomic status. One in 26 people will develop epilepsy during their lifetime (1 in 21 males and 1 in 28 females). The incidence of epilepsy peaks in children younger than 5 years at 60 to 70 per 100,000, decreases throughout adolescence to 30 per 100,000 in early adulthood, and rises again after the sixth decade, reaching a peak of 150 to 200 per 100,000 persons older than 75 years. The overall incidence of epilepsy appears to be increasing in recent decades because of a larger proportion of elderly persons in the population and an increasing incidence rate of epilepsy within the elderly population. Overall, the incidence and prevalence of the epilepsies are higher in developing countries, largely owing to a higher frequency of perinatal insults, trauma, and infectious disorders of the brain and to suboptimal treatment. In these countries, the median prevalence of active epilepsy is 12.5 per 1000 (range, 5 to 57 per 1000), and the annual incidence ranges from 78 to 190 per 100,000.[1] Furthermore, the patterns of age-specific incidence are quite different in developing countries, where incidence peaks in young adults, not in elderly persons.

Risk Factors

Among all age groups, the top five risk factors for developing acute symptomatic seizures are head trauma (16%),[2] stroke (16%), infectious disorders (15%), toxic-metabolic disorders (15%), and drug and alcohol withdrawal (14%) (Table 372-1).

The risk factors for developing epilepsy differ in adults and children. In childhood, excluding inherited epilepsies, the risk is increased by febrile seizures, head trauma, infections of the brain, intellectual disability, cerebral palsy, brain malformations, and attention-deficit/hyperactivity disorder. Perinatal insults do not carry an increased risk for epilepsy unless they are accompanied by intellectual disability or cerebral palsy.

In adults, risk factors for developing epilepsy can be identified in about one third of patients, in whom head trauma, brain infections, stroke, brain tumor, and dementia are the most common causes. In surgical specimens, the most common causes are mesial temporal sclerosis, cortical dysplasias,

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patient in a detailed discussion about the limited benefits and potential emotional risks associated with the knowledge a mutation may cause disease many years in the future.[32] Several key questions should be asked to understand how to proceed. First, how old was the affected family member at the time of disease onset and at death? Second, what was the clinical diagnosis and how and by whom was the diagnosis made (i.e., was the diagnosis made by a dementia specialist) and on the basis of what clinical features and what laboratory tests? Third, was a brain autopsy performed, and is the written report available. Fourth, are any other first-degree relatives affected? And fifth, did any of the parents, siblings, or children of the affected person also have the same or similar disorder? Persons for whom genetic testing would be reasonable have a multigenerational family history of dementia before age 65 years, or if the affected family member had been proved or strongly suspected of harboring a relevant mutation. Persons in whom genetic testing is not justified on the basis of very low risk would be those in whom the affected family member was over age 70 years at onset and in whom there were no other affected family members. In between those two ends of the spectrum, risk is low, but the physician and patient may choose to pursue genetic testing after a discussion that takes into account the strengths and weaknesses of the available family history.

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372 THE EPILEPSIES

SAMUEL WIEBE

DEFINITION

A seizure is defined by transient focal or generalized signs or symptoms due to abnormal excessive or synchronous neuronal activity in the brain. Focal seizures, which originate within neuronal networks limited to one cerebral hemisphere, produce signs and symptoms corresponding to the specific region of the brain affected by the seizure. Generalized seizures rapidly affect extensive neuronal networks on both cerebral hemispheres, and their signs and symptoms are consistent with substantial involvement of both sides of the brain.

Seizures are not synonymous with epilepsy. The epilepsies should be distinguished from situations in which acute brain insults (e.g., infections, trauma, intoxication, metabolic disturbances) cause one or more seizures without a resulting chronic seizure tendency. Acute symptomatic seizures, or provoked seizures, constitute about 40% of all incident cases of nonfebrile seizures, typically respond to treatment of the provoking factor, and do not require long-term treatment with antiseizure medications.

The epilepsies are a group of conditions in which an underlying neurologic disorder results in a chronic tendency to have recurrent unprovoked seizures. The diagnosis of epilepsy is established if one of the following three criteria is met: two or more unprovoked or reflex seizures occurring more than 24 hours apart; a single unprovoked or reflex seizure in a person whose risk of recurrence is at least 60% over the next 10 years (e.g., brain tumor, hemorrhage, or infection); or a known epilepsy syndrome (e.g., self-limited epilepsy with centrotemporal spikes).

The causes, types, and clinical expression of the epilepsies are numerous and varied. However, some of the epilepsies conform into identifiable epileptic syndromes, which consist of clusters of clinical and electroencephalographic (EEG) features that have specific causes, respond to particular treatments, and may have specific prognostic implications.

EPIDEMIOLOGY

Incidence and Prevalence

Seizures are common in the general population, and about 1 in 10 people will experience a seizure in their lifetime. Most of these seizures are provoked by acute events and are not related to epilepsy. The overall annual incidence of acute symptomatic seizures, excluding febrile seizures, in developed countries is about 39 per 100,000 people. The incidence is higher in men and follows a bimodal age distribution, with its highest peak in the first year of life (up to 300 per 100,000), a nadir of 15 per 100,000 in the third and fourth decades of life, and a second peak rising to 123 per 100,000 after 75 years of age. These differences are attributable to the high incidence of acute symptomatic seizures associated with metabolic, infectious, and encephalopathic causes during the neonatal period and of cerebrovascular, neoplastic, and degenerative diseases in elderly persons.

After headache, the epilepsies are the most frequent chronic neurologic condition seen in general practice worldwide. In developed countries, the prevalence of active epilepsy ranges from 5 to 7 per 1000 persons, and the median annual incidence is 45 per 100,000 (range, 30 to 67), varying by age and socioeconomic status. One in 26 people will develop epilepsy during their lifetime (1 in 21 males and 1 in 28 females). The incidence of epilepsy peaks in children younger than 5 years at 60 to 70 per 100,000, decreases throughout adolescence to 30 per 100,000 in early adulthood, and rises again after the sixth decade, reaching a peak of 150 to 200 per 100,000 persons older than 75 years. The overall incidence of epilepsy appears to be increasing in recent decades because of a larger proportion of elderly persons in the population and an increasing incidence rate of epilepsy within the elderly population. Overall, the incidence and prevalence of the epilepsies are higher in developing countries, largely owing to a higher frequency of perinatal insults, trauma, and infectious disorders of the brain and to suboptimal treatment. In these countries, the median prevalence of active epilepsy is 12.5 per 1000 (range, 5 to 57 per 1000), and the annual incidence ranges from 78 to 190 per 100,000.[1] Furthermore, the patterns of age-specific incidence are quite different in developing countries, where incidence peaks in young adults, not in elderly persons.

Risk Factors

Among all age groups, the top five risk factors for developing acute symptomatic seizures are head trauma (16%),[2] stroke (16%), infectious disorders (15%), toxic-metabolic disorders (15%), and drug and alcohol withdrawal (14%) (Table 372-1).

The risk factors for developing epilepsy differ in adults and children. In childhood, excluding inherited epilepsies, the risk is increased by febrile seizures, head trauma, infections of the brain, intellectual disability, cerebral palsy, brain malformations, and attention-deficit/hyperactivity disorder. Perinatal insults do not carry an increased risk for epilepsy unless they are accompanied by intellectual disability or cerebral palsy.

In adults, risk factors for developing epilepsy can be identified in about one third of patients, in whom head trauma, brain infections, stroke, brain tumor, and dementia are the most common causes. In surgical specimens, the most common causes are mesial temporal sclerosis, cortical dysplasias,

ABSTRACT

In general clinical practice, seizures and epilepsy are the second most common neurologic condition after headache. This chapter discusses the most relevant and latest evidence pertaining to the epidemiology, pathobiology, clinical manifestations, diagnosis, treatment, and prognosis of seizures and epilepsy, as well as the most recent seizure classification system. The cornerstone of the management of epilepsy is a correct diagnosis. Because both overdiagnosis and underdiagnosis of epilepsy are common and carry serious consequences, clinicians must first determine whether the clinical signs and symptoms correspond to seizures or to one of its many mimics, notably psychogenic nonepileptic seizures and physiologic events such as syncope. Subsequently, the type of seizures (focal or generalized) must be determined based on their earliest signs and symptoms. This essential step guides the type of drug that is most effective for an individual patient. In about two-thirds of patients, seizures can be well controlled with antiseizure medications. Patients whose seizures are not controlled with two or more drugs are considered to be pharmacoresistant and should be referred to specialized centers for possible surgical therapy, which can result in freedom from seizures in about 60% of such patients. In women, hormonal interactions, pregnancy, and teratogenesis require individualized attention. Special issues in the elderly include frailty, multimorbidity, and drug interactions.

KEYWORDS

epilepsy
seizures
antiseizure medications
epilepsy surgery
prognosis
management

low-grade tumors, and vascular malformations. The risk of developing epilepsy is increased more than 500-fold by a history of a military head injury; 30-fold by a severe civilian head injury (Chapter 368); 20-fold each by stroke (Chapter 376) and brain infection (Chapter 381 to 383); and 10-fold each for Alzheimer disease (Chapter 371), migraine (Chapter 367), and hypertension. In Latin America, the most frequently identified risk factor is brain infection. In endemic areas, neurocysticercosis (Chapter 325) accounts for about 10% of all newly diagnosed cases of epilepsy.

Pathobiology

Pathogenesis

The pathologic substrates and mechanisms underpinning initiation and propagation differ for focal and generalized seizures. In focal seizures, an aggregate of cortical or subcortical neurons develop high-frequency bursts of sodium-dependent action potentials caused by a shift in calcium conductance, thereby resulting in the typical EEG spike discharge (Fig. 372-1). Spread of bursting activity to other neurons is normally prevented by surrounding inhibitory mechanisms, such as hyperpolarization and inhibitory interneurons. When a sufficient number of neurons are engaged in sustained bursting, further excitatory phenomena ensue, including the increased release of excitatory neurotransmitters owing to presynaptic accumulation of Ca^{2+}, depolarization of surrounding neurons owing to increased extracellular K^+, and further neuronal activation caused by depolarization-induced activation of *N*-methyl-D-aspartate (NMDA) receptors. As excitation increases and inhibition decreases, additional neurons are recruited regionally and distantly, thereby resulting in seizure propagation. The mechanisms by which neurons develop a tendency toward anomalous bursting activity include alterations in neurotransmitters, membrane receptors, ion channels, second-messenger systems, and gene expression of various proteins.

Considerably less is known about the basic mechanisms underlying generalized seizures, which depend prominently on thalamocortical circuits. In absence seizures, the classic generalized spike-and-wave discharges seen on EEG (Video 372-1) are related to alterations in oscillatory rhythms generated by circuits that connect the thalamus and cortex and that involve T-type Ca^{2+} channels, which are located in the reticular nucleus of the thalamus. In generalized convulsive seizures, cortical neurons exhibit prolonged depolarization during the tonic phase, followed by rhythmic depolarization and repolarization during the clonic phase. Activation of NMDA receptors increases calcium Ca^{2+} influx, thereby leading to further neuronal excitation. The initiation and modulation of generalized convulsive seizures involve cholinergic, noradrenergic, serotonergic, and histaminergic afferents from the brain stem and basal forebrain structures, which modulate excitability of hemispheric motor mechanisms.

TABLE 372-1 COMMON CAUSES OF ACUTE SYMPTOMATIC (PROVOKED) SEIZURES

METABOLIC
Hypernatremia, hyponatremia, hypocalcemia, hypoxia, hypoglycemia, nonketotic hyperosmolar hyperglycemia, renal failure
DRUG INDUCED
Theophylline, meperidine, tricyclic antidepressants, ephedra, ginkgo, phenothiazines, quinolones, β-lactams, isoniazid, antihistamines, cyclosporine, interferons, tacrolimus, cocaine, lithium, amphetamines
DRUG WITHDRAWAL
Alcohol, benzodiazepines, barbiturates
ENDOCRINE
Hyperthyroidism, hypothyroidism, peripartum
OTHER SYSTEMIC CONDITIONS
Sickle cell crisis, hypertensive encephalopathy, systemic lupus erythematosus, polyarteritis, eclampsia, high fever
CENTRAL NERVOUS SYSTEM DISORDERS
Trauma, stroke, intracerebral hemorrhage, encephalitis, abscess, bacterial meningitis

Genetics

One or more genetic factors play a role in 70% of people with epilepsy, and the risk of epilepsy is higher in first-degree relatives of patients with epilepsy than in the general population. For example, about 15% of patients have one or more first-degree relatives who also suffer from epilepsy, and 75% of those have just one affected relative. In a large population-based study, the cumulative incidence of epilepsy to age 20 years was 2.5-fold higher in siblings and 3.4-fold higher in offspring of patients with epilepsy. Transcranial magnetic stimulation shows increased cortical excitability in siblings of patients with epilepsy, even when these epilepsies are acquired.

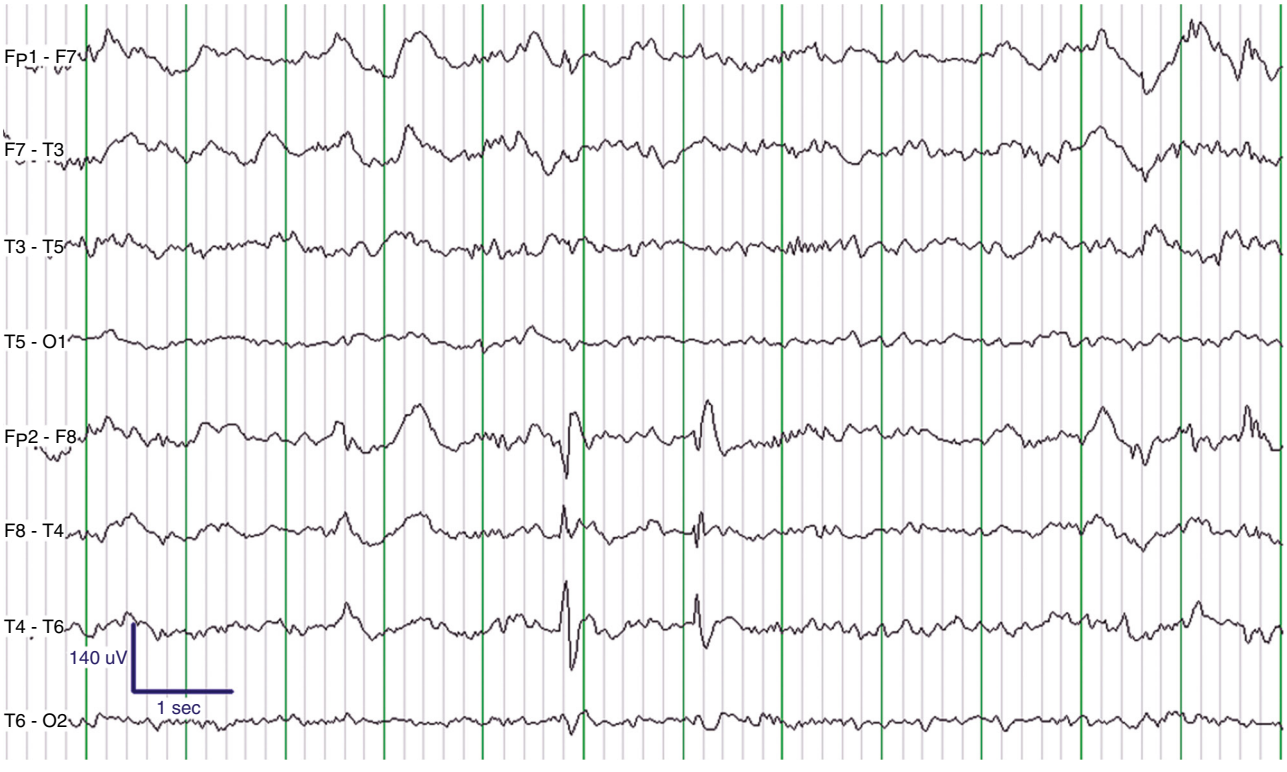

FIGURE 372-1. Selected electroencephalogram channels showing a typical right anterior temporal spike, the archetypal interictal footprint of temporal lobe epilepsy. The patient had right hippocampal sclerosis.

Genetic causes of epilepsy may arise at a chromosomal or molecular level. Important chromosomal disorders producing epilepsy include the following syndromes: Angelman (15q11-q13), Down (trisomy 21), Klinefelter (XXY), Miller Dieker (17p), Pallister Killian (12p), Wolf-Hirschhorn (4p), and Ring 14 and 20.

All modes of inheritance are involved in epilepsy: mendelian epilepsy genes, which are rare but carry a high risk of epilepsy; rare variants associated with an intermediate risk and frequency of epilepsy; and common variants, which occur frequently but have a low independent risk of epilepsy.[3] In addition, epigenetic mechanisms, which can also be inherited, are increasingly recognized in epilepsy.[4]

1. Conditions in which epilepsy or seizures form part of a mendelian disorder (e.g., autosomal dominant, autosomal recessive, X-linked) comprise over 1000 rare conditions with a high risk. These conditions include neurocutaneous disorders (Chapter 385), neurodegenerative disorders, inherited malformations of cortical development (Chapter 385), and inherited metabolic disorders. For example, genes have been identified in progressive myoclonic epilepsies (e.g., Unverricht-Lundborg disease, Lafora disease, and the neuronal ceroid lipofuscinosis), X-linked myoclonic epilepsy with intellectual disability, and cortical malformation syndromes (e.g., polymicrogyria, pachygyria, periventricular nodular heterotopia).
2. Epilepsies that can be directly explained by single gene mutations are rare and account for only about 1% of all epilepsy cases. Over 30 genes have been identified in at least 15 focal and generalized epilepsy syndromes, including genetic epilepsy with febrile seizures plus, severe myoclonic epilepsy of infancy and related syndromes, benign familial neonatal convulsions, benign familial neonatal-infantile seizures, benign familial infantile seizures, juvenile myoclonic epilepsy, childhood absence epilepsy, West syndrome, early infantile epileptic encephalopathy with suppression burst, malignant migrating partial seizures of infancy, autosomal dominant nocturnal frontal lobe epilepsy, familial infantile myoclonic epilepsy, epilepsy + paroxysmal exercise-induced dyskinesia, familial lateral temporal lobe epilepsy, and familial focal epilepsy with variable foci. Genetic mutations may affect neuronal excitability, neuronal metabolism, synaptic function, or network development. Although most of these gene mutations affect ion channels (*SCN1A, SCN1B, SCN2A, KCNQ2, KCNQ 3, KCNT1, KCTD7*), other cellular functions affected include neurotransmitter release (*STXBP1*), neurotransmitter receptors (*CHRNA, CHRNB, GABRD, GABRG2, GRIN2A, GRIN2B*), synaptic function (*SYN1*), glutamate transport (*SLC25A22*), gene regulation and transcription (*ARX*), cell adhesion (*PCDH19*), cell membrane function (*PRRT2, TBC1D24, DEPDC5*), protein kinase and cell energy function (*CDKL5, BCKDK, ATP1A2*), glucose transporter GLUT1 deficiency (*SLC2A1*), the mTOR pathway for cell growth and differentiation (*TSC1, TSC2*), and neuronal signaling (*EFHC1, LGI1, PLCB1*). An increased genetic predisposition for epilepsy is associated with specific genotypes (*MTHFR, C677T*) in patients who develop posttraumatic epilepsy.
3. In some patients, the epilepsy is associated with "complex" disease genes. In this large group, which constitutes about 50% of all patients with epilepsy, multiple genes (common variants) with individually small but additive effects act in combination with environmental factors to produce an increased risk for epilepsy. Genes associated with generalized epilepsy in this category include *CHRM3, VRK2, ZEB2, SCN1A*, and *PNPO*.

CLINICAL MANIFESTATIONS

The clinical expression of seizures varies widely depending on the type of seizure and the areas of the brain involved by the epileptic activity. Accurate identification of the specific type of seizures is crucial because it dictates the type of medication the patient should receive. The signs and symptoms at the onset of individual seizures describe three categories: focal, generalized, and unknown onset (Fig. 372-2 and www.epilepsydiagnosis.org).

Focal seizures are further subclassified according to their clinical expression. If awareness is impaired at any point, they are referred to as *focal impaired awareness seizures*. For example, patients who formerly were classified as having simple partial seizures are now classified as having *focal aware seizures*. Focal seizures are also subclassified by the presence or absence of motor phenomena at the onset into *focal motor or nonmotor seizures*. More granular categorization of motor and nonmotor seizures are then provided according to the clinical expression.

Generalized seizures are classified primarily into *motor* (e.g., tonic, tonic-clonic, myoclonic seizures) and *nonmotor* (absence seizures). Finally, when it is not possible to determine whether the onset of seizures is focal or generalized because of lack of information or ambiguous features, seizures are termed *unknown-onset seizures*.

Focal Seizures

The seizure warning often consists of sensory, autonomic, or emotional symptoms that are experienced at the start of an observable seizure. The warning symptom is a focal seizure itself, and it is often missed because patients and clinicians focus on the more dramatic aspects of awareness or convulsion that follow. Careful inquiry about the occurrence of a warning is of crucial importance for three reasons. First, it points to a focal as opposed to a generalized onset, thereby implying an underlying focal structural or functional brain abnormality (e.g., a tumor) that requires further investigation. Second, focal seizures have important implications for therapy and for prognosis (see later). Third, the nature of the symptoms points to the area of the brain that gives rise to the seizure and that could be a target for surgical treatment (Table 372-2).

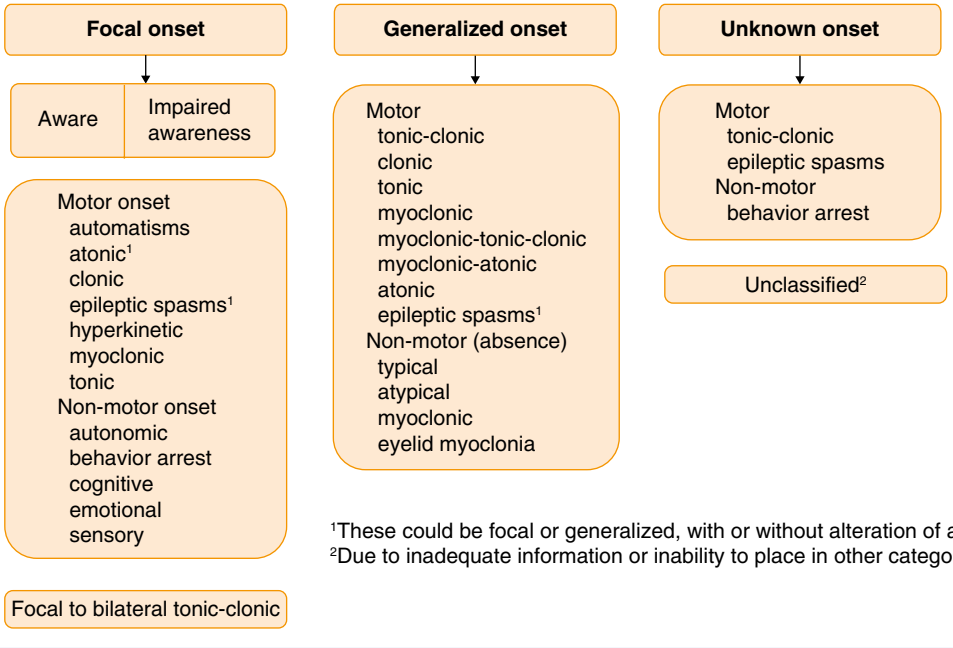

FIGURE 372-2. International League Against Epilepsy Classification of Seizures. Seizures are classified by the earliest clinical signs and symptoms. The first question is whether the onset is focal, generalized, or unknown. *Focal* seizures can be described based on whether the most prominent feature at the onset consists of motor or nonmotor phenomena or whether awareness is impaired at any point during the seizure. *Generalized* seizures are divided into motor and nonmotor.

The neuronal discharge causing the focal seizure may remain confined to the region where it began (as a warning symptom or more objective focal event), or it may spread to involve additional brain areas. Thus a focal seizure originating in the cortical area that represents sensation of the hand (rolandic area) may begin with contralateral hand tingling and then progress to involve additional cortical regions ipsilaterally, producing more extensive sensory symptoms as well as clonic motor signs. Seizures of rolandic origin in particular exhibit a peculiar type of propagation, in which the seizure activity "marches" from hand to arm to leg area ipsilaterally, a process referred to as a jacksonian march. After the clonic motor activity ends, patients are often weak; a postictal or Todd paralysis may last hours or even a day or two, with gradual resolution (Video 372-2). The seizure may also propagate to distant ipsilateral or contralateral regions along known anatomic pathways.

In focal impaired awareness seizures, the person is not aware of self or environment during the seizure because of sufficient propagation of seizure activity to limbic and bilateral structures to cause alteration of awareness (Videos 372-3 and 372-4). Focal seizures originating from any region can impair awareness, and unilateral focal seizures can progress to involve bilateral brain areas and cause a bilateral convulsive seizure (Video 372-5). Such convulsive seizures usually take the form of bilateral tonic-clonic events rather than another type of generalized seizure (Table 372-3).

The evolution of the focal clinical seizure reflects the evolution of the EEG changes, which in turn reflects the pathophysiology of the process. A simultaneous rhythmic, localized discharge (often in the 4- to 7-Hz range) becomes higher in amplitude and lower in frequency as the seizure continues (see Video 372-5). Some seizures that begin in the association cortex (e.g., frontal or

TABLE 372-2 CLINICAL MANIFESTATIONS OF DIFFERENT TYPES OF FOCAL SEIZURES AND AREAS OF THE BRAIN INVOLVED

SEIZURE TYPE	AREAS OF BRAIN INVOLVED	CLINICAL EXPRESSION
MOTOR		
Clonic	Precentral rolandic	Contralateral regional clonic jerking, usually rhythmic and sustained, may spread to other body segments in jacksonian motor march; often accompanied by sensory symptoms in the same area
Tonic and Dystonic	Supplementary sensory-motor	Unilateral or bilateral tonic contraction of limbs causing postural changes; may exhibit classic fencing posture; may have speech arrest or vocalization
	Frontal	Contralateral head and eye version, salivation, speech arrest or vocalization; may be combined with other motor signs (as noted earlier) depending on seizure spread
NONMOTOR		
Somatosensory	Postcentral rolandic; parietal	Contralateral intermittent or prolonged tingling, numbness, sense of movement, desire to move, heat, cold, electric shock. Sensation may spread to other body segments
	Parietal	Contralateral agnosia of a limb, phantom limb, distortion of size or position of body part
	Second sensory; supplementary sensory-motor; insula	Ipsilateral or bilateral facial, truncal or limb tingling, numbness, or pain. Often involve lips, tongue, fingertips, feet
Gustatory	Parietal; rolandic operculum; insula; temporal lobe	Often unpleasant taste, acidic, metallic, salty, sweet, smoky
Olfactory	Mesial temporal; orbitofrontal	Often unpleasant, often with gustatory symptoms
Vestibular	Occipitotemporal-parietal junction; frontal lobe	Sensation of body displacement in various directions
Visual	Occipital	Contralateral static, moving, or flashing colored or uncolored lights, shapes, or spots. Contralateral or bilateral, partial or complete loss of vision
	Temporal; occipitotemporal-parietal junction	Formed visual scenes, faces, people, objects, animals
Autonomic, Cognitive, and Emotional	Limbic structures: amygdala, hippocampus, cingulum, olfactory cortex, hypothalamus	Autonomic: abdominal rising sensation, nausea, borborygmi, flushing, pallor, piloerection, perspiration, heart rate changes including asystole, chest pain, shortness of breath, cephalic sensation, lightheadedness, orgasm Cognitive: déjà vu, jamais vu, depersonalization, derealization, dreamlike state, forced memory or forced thinking, apraxia, aphasia Emotional: fear, elation, sadness, anxiety, pleasure, crying, laughing, anger
Impaired Awareness	Usually extensive or bilateral involvement of limbic structures (see earlier)	Previously known as "complex partial seizures," characterized by lack of perception, knowledge, or memory of events occurring during the seizure

Note: Focal seizures may evolve into bilateral tonic-clonic seizures.

TABLE 372-3 GENERALIZED SEIZURES: CLASSIFICATION AND CLINICAL EXPRESSION

TYPE OF SEIZURE	SUBTYPE	CLINICAL EXPRESSION
MOTOR		
Tonic		Sustained increase in muscle contraction persisting for a few seconds to minutes
Clonic		Sustained regularly repetitive contractions involving the same muscle groups at a rate of 2-3 cycles per second
Tonic-clonic		A sequence consisting of a tonic followed by a clonic phase
Myoclonic	Myoclonic	Sudden, brief (<100 msec), shocklike, involuntary single or multiple contractions of muscle groups of various locations
	Myoclonic atonic	A sequence consisting of a myoclonic followed by an atonic phase
	Myoclonic-tonic-clonic	A sequence consisting of a few myoclonic jerks followed by a tonic-clonic seizure, commonly seen in juvenile myoclonic epilepsy
Atonic		Sudden loss or diminution of muscle tone persisting for 1-2 seconds, involving the head, trunk, jaw, or limb muscles
NONMOTOR		
Absence	Typical	Abrupt cessation of activities, motionless, blank stare, and loss of awareness persisting about 10 seconds; attack ends suddenly, and patient resumes normal activities immediately
	Atypical	Longer duration than typical absence, gradual onset and offset, often accompanied by myoclonic, tonic, atonic, and autonomic features as well as automatisms
	Myoclonic absence	Absence seizure with rhythmic three-per-second myoclonic movements, causing ratcheting abduction of the upper limbs, progressive arm elevation, and associated with three-per-second generalized spike-wave discharges
	Myoclonic atonic absence	Absence seizure with brief jerking of limbs or trunk, followed by a limp drop

parietal lobes) have bizarre or extremely brief clinical manifestations without postictal deficits and create diagnostic challenges (Videos 372-6, 372-7, and 372-8). The stereotyped nature of the clinical events, with identification of EEG changes if present, may be the only way to make an appropriate diagnosis. The diagnosis can be even more challenging if the seizure spreads to different cortical regions during different seizure episodes, thereby producing variable constellations of clinical findings at different times.

Focal seizures with or without impaired awareness can also occur as a series of single events without intervening normal behavior, thereby resulting in focal status epilepticus. Focal status epilepticus with impaired awareness seizures is characterized by prolonged confused behavior. EEG findings may be normal in a focal seizure without altered awareness, even in patients with status epilepticus, but the diagnosis is usually evident from the clinical features. In status epilepticus of focal impaired awareness seizures, EEG recordings show continuous abnormalities that are different than those seen in single seizures in that individual. The most common are a slow background with superimposed rhythmic high-amplitude sharp waves or repetitive rhythmic seizure discharges (Fig. 372-3). This type of status epilepticus is most frequent with frontal lobe seizures but can occur in temporal lobe or other seizures as well. The factors that precipitate status epilepticus are not well defined, nor are the implications for treatment or prognosis.

Nonconvulsive status epilepticus consists of a state of confusion or impaired mental status in patients with various neurologic diagnoses (e.g., trauma, stroke) in the acute intensive care unit setting (Video 372-9). It also denotes a condition that can occur de novo in older adults without a precipitating cause and that is characterized by prolonged confusional episodes, which are caused by generalized slow spike-and-wave status epilepticus. Clinical suspicion should prompt an EEG study, which is essential for diagnosis.

Generalized Seizures

Generalized seizures rapidly affect both cerebral hemispheres, and their clinical expression is consistent with substantial involvement of both sides of the brain (see Table 372-3). Convulsive seizures, which were previously termed grand mal seizures, consist of excessive abnormal muscle contractions that may be sustained or interrupted and usually are a combination of tonic and clonic phases (generalized tonic-clonic seizures). This type of seizure may involve both hemispheres at the onset or may result from propagation of a focal seizure. These dramatic seizures often frighten witnesses and cause severe disruption of social interaction and development. They may begin with a "cry" as a result of abrupt air movement across the glottis from sudden tonic muscle contraction. The patient becomes diffusely stiff, usually with limb and body extension (Video 372-10). Breathing is suspended, cyanosis occurs, and urinary incontinence is common. After 15 to 45 seconds, the tonic activity gives way to clonic, rhythmic, sometimes asymmetrical jerking of all four extremities (Video 372-11). The rhythmic contractions gradually become slower in frequency until the event stops; the patient is apneic, comatose, and diaphoretic, but breathing with stridor and gasping begins within 60 seconds. Patients who have generalized tonic-clonic seizures in public often prompt bystanders to initiate resuscitation efforts, although such patients begin spontaneous respiration within 1 minute or so. Postictal stupor persists for a variable length of time. The patient generally sleeps for 2 to 8 hours and then complains of severe headache, sore muscles, a bitten tongue, and the inability to concentrate for a day or more. After generalized tonic-clonic seizures, some individuals have severe memory loss that gradually improves, sometimes over a period of weeks. Generalized tonic-clonic seizures also are a common expression of many metabolic, toxic, traumatic, or ischemic insults (see Table 372-1), but these provoked seizures do not qualify for the diagnosis of epilepsy.

Absence seizures, which are the second most common type of generalized seizure, are classified as typical or atypical (see Table 372-3). In typical absence seizures, patients experience an abrupt onset and termination of a momentary lapse of awareness. Patients have no perception of any aspect of the event and may or may not realize that some time was lost, although individuals often lose their train of thought. Because consciousness is abruptly lost and immediately regained, there is neither an initial symptom nor residual postictal symptoms. These seizures begin in childhood, and school teachers are often the first to notice them. In absence seizures, patients stop abruptly, stare vacantly, may have brief eye blinking or myoclonic movements, particularly if the event extends beyond 10 seconds (as judged by EEG), and regain

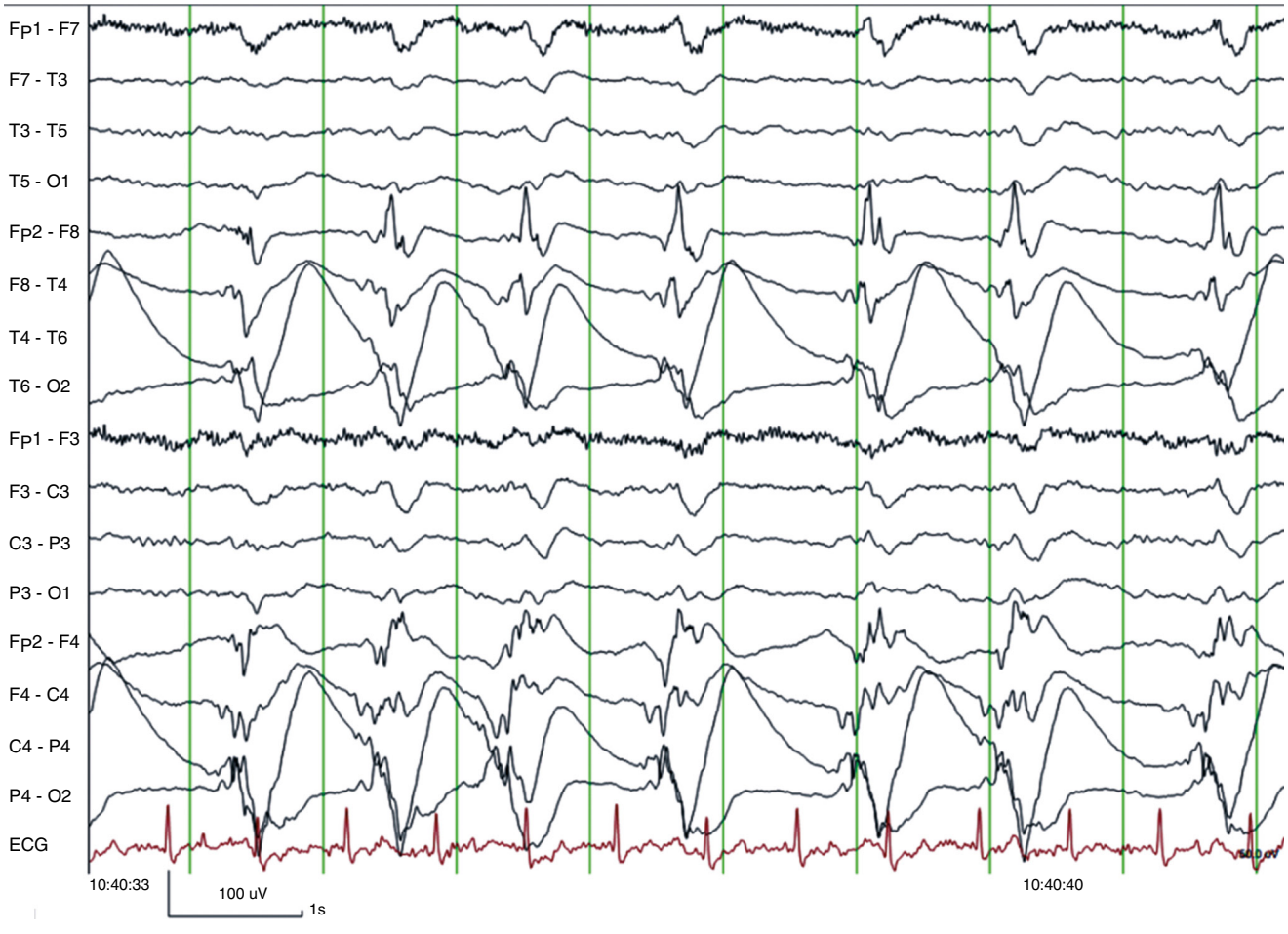

FIGURE 372-3. Focal right hemisphere nonconvulsive status epilepticus in a comatose patient with a large right hemisphere infarct.

function instantly (see Video 372-1). These seizures can occur many times a day but are not associated with progressive neurologic disease. Absences can also occur in a more continuous form as nonconvulsive status epilepticus with resultant confusion.

Atypical absence seizures occur in patients with extensive bilateral brain disease. The events are similar to typical absence seizures in terms of loss of contact, but the onset and termination are gradual instead of abrupt; the duration is longer; and there is more motor, autonomic, or automatic activity.

Myoclonic seizures consist of brief, irregular, unsustained episodes of sudden motor contraction (see Table 372-3) that can be focal (Video 372-12), with one limb involved, or bilateral and massive, with involvement of the face, both upper extremities, and the trunk. Consciousness may be preserved but can be difficult to evaluate because of the brevity of these seizures. Myoclonic seizures form part of three main clinical entities: juvenile myoclonic epilepsy, which starts in childhood or adolescence and often persists into adulthood; epilepsy with various combinations of absence and myoclonic seizures; and progressive myoclonic epilepsy, which occurs in the setting of degenerative or inherited syndromes with bilateral cerebral involvement and abnormal cerebral function. Myoclonic seizures most commonly occur in the morning after awakening and often increase in frequency to culminate in a generalized tonic-clonic seizure.

Atonic and tonic seizures are brief but extremely disabling motor events that are characterized by a sudden increase or decrease in muscle tone. They can result in falls and injuries with variable impairment of awareness. Such seizures frequently begin in children with diffuse central nervous system (CNS) disease and multiple types of seizures, but they persist during adulthood (Videos 372-13 and 372-14).

DIAGNOSIS

The basic diagnosis of seizures is established by the clinical history.[5] Although EEG, imaging, and laboratory studies are commonly required to determine the type of epilepsy, epilepsy syndrome, site of origin of focal seizures, and occurrence of nonepileptic seizures, the answer to the basic question of whether the patient's episodes are seizures or not rests almost entirely on a careful clinical history and descriptions from eyewitnesses. The diagnosis of epilepsy can also be established by history, because epilepsy is defined as the occurrence of two unprovoked seizures or one unprovoked seizure in the context of a high underlying risk of recurrence or an epileptic syndrome.[6]

Differential Diagnosis

The first question facing clinicians is whether the episodes under consideration are indeed seizures. The diverse clinical expression of seizures encompasses a large differential diagnosis among conditions that produce episodic neurologic dysfunction (Table 372-4). Common conditions resembling seizures include syncope (Chapters 39 and 49), transient ischemic attacks (Chapter 376), migraine (Chapter 367), movement disorders (Chapter 379), and psychogenic nonepileptic seizures (see Table 372-4).[7]

A number of historical elements dramatically change the likelihood of this diagnosis. Three essential elements help determine whether an episode is a seizure (Table 372-5) and distinguish seizures from other causes of temporary loss of consciousness, especially syncope (Chapters 39 and 49).

1. The clinical context, including medical and family history and circumstances under which the episode occurred. For example, a strong family history of seizures and an event after sleep deprivation support a diagnosis of epileptic seizures. Conversely, a family history of syncope and an event occurring upon standing or with painful stimuli support a diagnosis of syncope.
2. Specific triggers or provoking factors. For example, events occurring with exposure to bright or flashing lights support a diagnosis of epileptic seizures.
3. A stereotypical evolution of the event, including four key components:
   - What is the first symptom or sign (presence and type of warning symptom, evidence of focal seizure at onset)?
   - How does it evolve after onset (what happens during the seizure proper, what are the signs or symptoms, how long does it last)?
   - How does it end (gradually or abruptly)?
   - Are there any neurologic deficits after the seizure ends?

Because patients have limited or no recall, the history from others is crucial. Observers can contribute important information about the patient's activity, responses, and appearance, including changes in color, diaphoresis, respirations, vocalization, and muscle tone. Cell-phone videos obtained by witnesses can be very helpful in this regard. This information is required to characterize the type of seizure and to distinguish seizures from conditions that resemble seizures.

TABLE 372-4 DISORDERS RESEMBLING SEIZURES

VASCULAR AND PERFUSION DISORDERS
Migraine, syncope, transient ischemic attack, transient global amnesia, arrhythmia/hypoperfusion
PSYCHIATRIC DISORDERS
Psychogenic nonepileptic seizures, panic disorder, dissociative disorder
MOVEMENT DISORDERS
Tics, paroxysmal dystonia, paroxysmal choreoathetosis, paroxysmal ataxia
SLEEP DISORDERS
Night terrors, sleep walking, sleep myoclonus, narcolepsy/cataplexy, rapid eye movement sleep intrusions
METABOLIC DISTURBANCES
Alcoholic blackouts, delirium tremens, hypoglycemia, hallucinogenic drugs, renal or hepatic encephalopathy
OTHER
Breath-holding spells in children, paroxysmal vertigo, migraine with recurrent abdominal pain and cyclic vomiting

TABLE 372-5 CLINICAL FEATURES THAT HELP DISTINGUISH A BILATERAL TONIC-CLONIC SEIZURE FROM SYNCOPE

	SEIZURE	SYNCOPE
Clinical context and circumstances	Neurologic or systemic conditions that predispose to seizures, family history of seizures. Mental fatigue, sleep deprivation, alcohol use or withdrawal, systemic illness	Cardiovascular disorders, dehydration, anemia. Family history of syncope
Triggers	Usually none (unless reflex epilepsy)	Orthostatic hypotension, venipuncture, painful and noxious stimuli, emotional stress, micturition, Valsalva maneuver
Clinical features		
• Onset	No warning unless there is a warning symptom. Abrupt loss of consciousness, generalized stiffening, and fall. Occurs in any position	Tiredness, nausea, diaphoresis, tunneling of vision. Loss of consciousness over a few seconds and falls. Occurs usually standing
• Course	Prominent tonic phase then clonic movements lasting about 1 minute, cyanosis, labored breathing, may bite tongue or cheeks, sometimes urinary incontinence	Usually loss of tone, pallor, multifocal myoclonic jerks lasting <15 seconds, sometimes urinary incontinence, usually no tongue or cheek biting
• Offset	Postictal sleepiness and confusion lasting up to hours, headache, myalgia	Rapid recovery over seconds to less than a few minutes, no confusion, headache, or myalgia. May have fatigue

Migraine (Chapter 367) and focal seizures not only resemble each other but also coexist as comorbid conditions and share genetic susceptibility loci. Features that favor a diagnosis of seizures over classic migraine include an inconsistent occurrence of headache during the event, a brief duration, and the occurrence of more severe seizures. Myoclonus (Chapter 379) occurs in a variety of settings (e.g., metabolic encephalopathies) without any association with epilepsy or the EEG changes seen in myoclonic epilepsy.

Frontal lobe seizures arise predominantly during sleep and can have dramatic motor expression. They can be confused with nonepileptic psychogenic

seizures, sleep disorders (Chapter 374), or movement disorders (Chapters 378 and 379). Video EEG monitoring may be necessary for diagnosis (see Videos 372-7 and 372-8).

Patients with panic attacks (Chapter 362) can experience events that mimic focal seizures with autonomic and emotional features. However, panic attacks usually have a longer duration, do not progress to more severe seizures, and can be linked to specific circumstances. Nevertheless, focal seizures with emotional symptoms are often misdiagnosed as panic attacks.

Psychogenic nonepileptic seizures are behaviors that resemble seizures and are part of a functional neurologic disorder (Chapter 362) that often leads to misdiagnosis. Psychogenic seizures can be difficult to diagnose because they can mimic almost any type of epileptic seizure, and they often coexist with epilepsy in the same patient. An erroneous diagnosis of nonepileptic seizures poses a risk for inappropriate discontinuation of medication, resulting in status epilepticus. Conversely, an erroneous diagnosis of epileptic seizures in a patient with psychogenic seizures can result in complications of unnecessary therapy, excessive sedation, and consequent cardiorespiratory depression, often requiring intubation and respiratory support. Features suggesting nonepileptic psychogenic seizures include variable clinical manifestations across episodes, frequent and prolonged episodes, lack of response to antiseizure medication, out-of-phase upper and lower body movements, prominent pelvic thrusting, eye closure during convulsive movements, and lack of rigidity. Patients may have a history of sexual or physical abuse.[8] Nevertheless, the peculiarities of these attacks may require continuous video EEG monitoring for diagnosis.

Diagnostic Investigations

A detailed history, EEG recordings, and magnetic resonance imaging (MRI) can lead to a definitive diagnosis of epilepsy and can identify a cause in up to 50% of patients. In other patients, the information is insufficient or inconsistent, but the physiologic and CNS abnormalities surrounding the actual event allow it to be placed provisionally into a specific diagnostic category in about another 30% of patients. Continuous video EEG monitoring in an inpatient epilepsy unit can increase diagnostic accuracy.

Single Seizures

Single seizures can be classified as *unprovoked* (with no apparent immediate cause) or *acute symptomatic* (see Table 372-1), which are the known consequence of an acute condition, and investigations should be directed at the possible cause of these seizures. Evaluation of patients who present with a first unprovoked seizure, which may be an indicator of the onset of epilepsy,[9] includes either brain computed tomography (CT) or preferably MRI, which reveals a possible cause in about 10% of patients. An EEG obtained after the seizure will demonstrate abnormalities with prognostic significance in 20 to 25% of these patients. Blood tests (including levels of serum electrolytes, glucose, calcium, and magnesium; tests of liver and kidney function; a complete blood cell count; and screening for suspected toxins) will reveal abnormalities in up to 15% of these patients but are often nonspecific. Lumbar puncture is indicated if CNS infections are suspected and in all patients infected with human immunodeficiency virus (HIV), even in the absence of clinical findings suggestive of infection.

Epilepsy

Electroencephalogram

The EEG is the keystone investigation in all patients with seizures and epilepsy. Between seizures, the EEG can assess overall brain function and the type, location, and amount of epileptiform (spike) discharges (see Fig. 372-1). The EEG is crucial in determining the epilepsy syndrome and choosing appropriate antiseizure medications. In focal epilepsies, the EEG often demonstrates focal slowing and spike discharges in the area of abnormality.

The EEG can establish the definitive diagnosis of epilepsy if electrical changes consistent with a seizure are recorded during a clinical seizure. However, the EEG may fail to demonstrate electrical changes during a typical clinical seizure if the seizure focus is too small (at least 10 cm^2 of cortical involvement is needed to create an EEG epileptiform change), if the seizure focus is deep or in the mesial or inferior surfaces of the brain, or if the event in question is not an epileptic seizure. The EEG is always abnormal during bilateral tonic clonic and absence seizures.

The interictal initial EEG is normal in up to 60% of people with known epilepsy. However, epileptiform abnormalities occur in more than 80% of individuals with focal epilepsy if three or more EEG studies are performed. Interictal epileptiform discharges are more common and are easier to capture on the EEG when they are a manifestation of generalized rather than focal epilepsies (see Video 372-1).

The type of abnormality points to the epilepsy syndrome. For example, the EEG can show hypsarrhythmia in West syndrome (see later) or the classic 3-Hz generalized spike wave in generalized epilepsies with absence seizures (see Table 372-3 and Video 372-1). In atypical absence seizures, the EEG demonstrates discharges that are slower than the 3-Hz spike and wave of typical absence seizures.

In some circumstances, it is imperative to record seizures with video EEG, such as in the evaluation of patients for epilepsy surgery and when the diagnosis of seizures is in question (Video 372-15; also see Video 372-7). Continuous video EEG monitoring for prolonged periods has made it possible to capture these events. Continuous EEG is also used in comatose patients in the intensive care unit setting when nonconvulsive seizures or status epilepticus are suspected and to monitor the effect of treatment.

Magnetoencephalography

Magnetoencephalography measures the small magnetic fields that are generated by electrical activity in the brain and approximates their location using mathematical models. Its use is largely restricted to the evaluation of patients for epilepsy surgery, in whom it is used for mapping interictal discharges and the localization of brain function when superimposed on brain MRI.

Imaging Studies

Brain MRI, which can demonstrate lesions in most patients whose epilepsy is associated with a structural cause, should be performed in essentially all patients with new-onset seizures. The most common lesions in adults with new-onset focal seizures are post-stroke or post-traumatic gliosis or encephalomalacia (50%), tumors (15%), vascular abnormalities (15%), developmental abnormalities (15%), and mesial temporal sclerosis (9%). The use of fluid-attenuated inversion recovery (FLAIR) (Fig. 372-4A) sequences increases the sensitivity to detect abnormalities of cortical development as well as hippocampal sclerosis, which point to the need for chronic anticonvulsant therapy or possible surgical treatment. Functional imaging procedures such as positron emission tomography (PET) for analysis of metabolism and single-photon emission computed tomography (SPECT) (see Fig. 372-4B) for determination of blood flow are also used to help localize areas of the brain to be targeted with epilepsy surgery.

Genetic Testing

The decision to perform genetic testing should be guided by the clinical syndrome or phenotype and the high likelihood of benefit from counseling or treatment. The yield is highest (5%) in patients whose epilepsy is accompanied by intellectual disability, autism, and dysmorphic features. The genetic epilepsies for which testing is most useful are early infantile developmental and epileptic encephalopathy, X-linked infantile spasms, Dravet syndrome, epilepsy and intellectual disability limited to females, early-onset absence epilepsy, autosomal dominant nocturnal frontal lobe epilepsy, and epilepsy with paroxysmal exercise-induced dyskinesia. Before testing, however, the ethical aspects, the potential harms and benefits, and the need for pre- and post-testing counseling must be carefully considered.

Specific Epilepsy Syndromes

Of the large number of age-related epilepsy syndromes, all but six begin or occur in infancy and childhood (E-Table 372-1). Some syndromes represent diagnostically meaningful forms of epilepsy, with specific implications for treatment, especially surgery (e.g., mesial temporal lobe epilepsy with hippocampal sclerosis, Rasmussen encephalitis). The diagnosis of epilepsy syndromes is based on the types of seizures, the setting in which seizures occur, the patient's neurologic and cognitive status, age at onset, family history, and results of diagnostic studies, including EEG, MRI, and genetic studies. The epilepsy syndrome and type of seizure determine the selection of specific drugs and surgical treatment (Table 372-6). The need for lifelong treatment, the risk for genetic transmission, the likelihood of concurrent neurologic diseases, the risk for comorbid conditions, and the long-term prognosis are critical factors that can be addressed only with knowledge of the specific epilepsy syndrome.

Idiopathic Generalized Epilepsies

Idiopathic generalized epilepsies include four syndromes: childhood absence epilepsy, juvenile absence epilepsy, juvenile myoclonic epilepsy, and epilepsy

E-TABLE 372-1 EPILEPSY SYNDROMES BY AGE AT ONSET

	FREQUENCY*
NEONATAL PERIOD AND INFANCY	
Self-limited	
Self-limited familial neonatal epilepsy	5/100,000
Self-limited familial infantile epilepsy	14/100,000
Genetic epilepsy with febrile seizures plus	Common
Myoclonic epilepsy of infancy	Rare
With Encephalopathy	
Early-infantile developmental and epileptic encephalopathy	10/100,000
Epilepsy of infancy with migrating focal seizures	<1/100,000
Infantile spasms (West) syndrome	30/100,000
Dravet syndrome	7/100,000
With Specific Etiology	
KCNQ2 developmental epileptic encephalopathy	Unknown
Pyridoxine-dependent epilepsy	1/65,000
CDKL5 developmental epileptic encephalopathy	1/60,000
PCDH19 clustering epilepsy	1/42,000
Glucose transporter-1 deficiency syndrome	1/24,000
Sturge Weber syndrome	1/50,000
Gelastic seizures with hypothalamic hamartoma	<1/100,000
CHILDHOOD	
Self-limited Focal Epilepsies	
Self-limited epilepsy with centrotemporal spikes	6/100,000
Self-limited epilepsy with autonomic seizures	Common
Childhood occipital visual epilepsy	Infrequent
Photosensitive occipital lobe epilepsy	Infrequent
Genetic Generalized Epilepsies	
Epilepsy with eyelid myoclonia	Rare
Epilepsy with myoclonic absence	Rare
With Encephalopathy	
Myoclonic atonic epilepsy	1/100,000
Lennox-Gastaut syndrome	1/100,000
Epilepsy with spike-wave activation in sleep	Rare
Febrile infection-related epilepsy syndrome	Rare
Hemiconvulsion-hemiplegia-epilepsy syndrome	Rare
VARIABLE AGE	
Focal Epilepsies	
Sleep-related hypermotor epilepsies	2/100,000
Familial focal epilepsy with variable foci	Rare
With Specific Etiology	
Mesial temporal lobe epilepsy with hippocampal sclerosis	3/100,000
Rasmussen encephalitis	Rare
Progressive myoclonic epilepsies	Variable
IDIOPATHIC GENERALIZED EPILEPSIES	
Childhood absence epilepsy	8/100,000
Juvenile absence epilepsy	Common
Juvenile myoclonic epilepsy	Common
Epilepsy with generalized tonic-clonic seizures alone	Common

*Annual incidence unless otherwise specified.

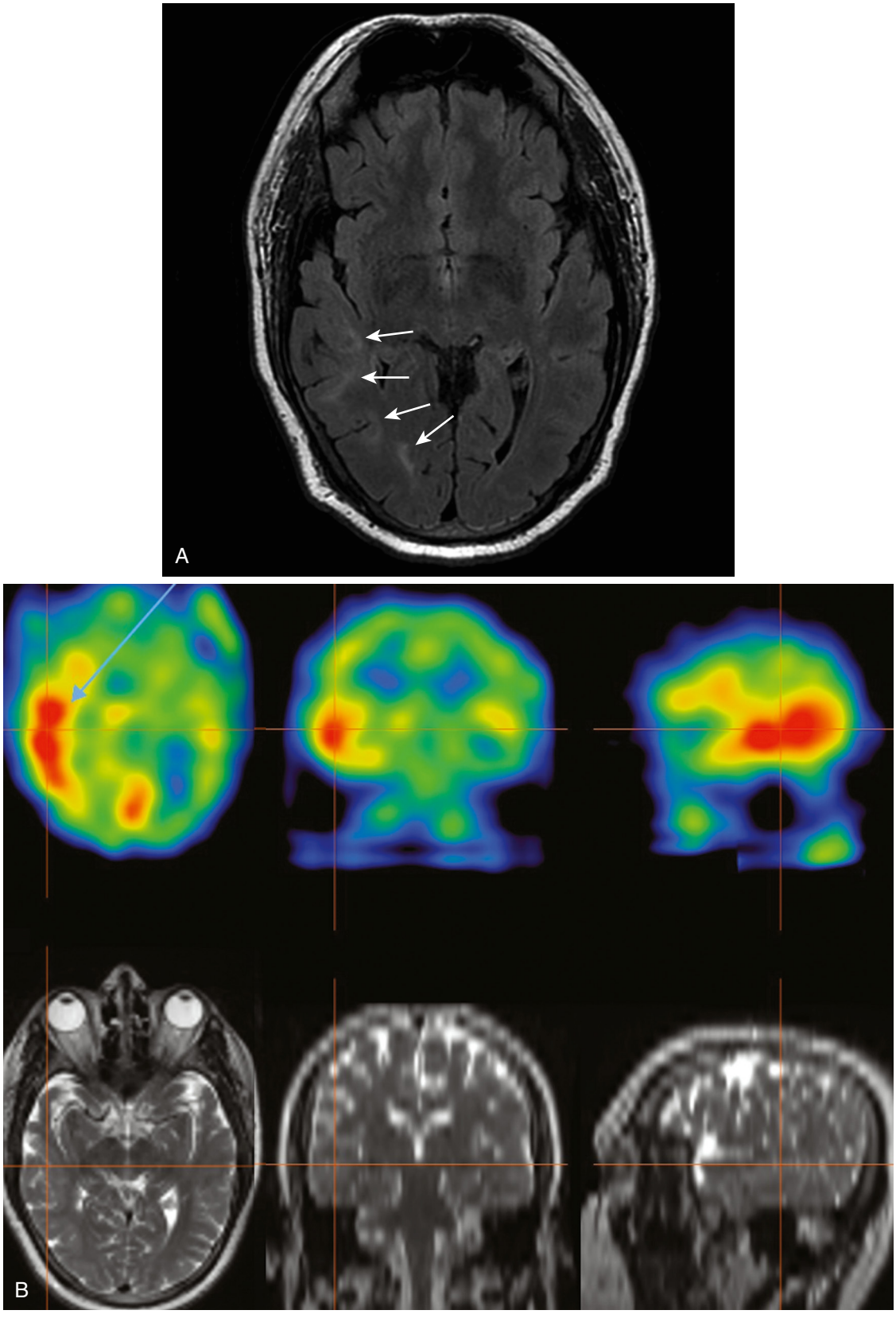

FIGURE 372-4. **Imaging studies from a patient with dramatic motor seizures that were initially attributed incorrectly to psychogenic nonepileptic events (see Video 372-7). A, Fluid-attenuated inversion recovery (FLAIR) axial magnetic resonance image (MRI) demonstrating a large developmental cortical abnormality involving the midposterior right temporal lobe. B, Ictal SPECT during a seizure demonstrating an area of hyperperfusion that corresponds to the abnormality seen on the MRI and confirms the area where the seizure originated.**

with generalized tonic-clonic seizures alone. These syndromes account for 15 to 20% of all epilepsies and about 50% of all generalized epilepsies.[10]

Childhood absence epilepsy begins between 4 and 12 years of age, and its onset peaks at age 5 to 7 years, with a strong genetic tendency. It is more common in girls than in boys and is characterized by very frequent daily absence seizures (up to hundreds per day), rarely with other types of generalized seizures. It occurs in the setting of otherwise normal brain structure and function, and it remits by adolescence in about 60% of cases. However, generalized tonic-clonic seizures may develop and herald evolution to another syndrome. The seizures are accompanied by a characteristic 3-Hz spike-and-wave EEG discharge, which appears in short bursts between seizures and in continuous runs during seizures. In early-onset absence epilepsy, mutations have been found in genes related to GABA receptors (*GABRA1, GABRG2*) and GLUT1 glucose transporter (*SLC2A1*).

TABLE 372-6 ANTISEIZURE MEDICATION SELECTION BY TYPE OF SEIZURE

		EFFECTIVENESS (GRADE A RECOMMENDATION)	
SEIZURE TYPE	**COMMONLY USED**	**NEW-ONSET SEIZURES**	**REFRACTORY SEIZURES**
Focal seizures with or without impaired awareness or evolution to bilateral tonic-clonic seizures	***Carbamazepine*** ***Eslicarbazepine*** ***Lacosamide*** ***Lamotrigine*** ***Levetiracetam*** ***Oxcarbazepine*** Clobazam Gabapentin Phenytoin Tiagabine Topiramate Valproate	Carbamazepine*† Gabapentin*† Lamotrigine*† Levetiracetam† Oxcarbazepine*† Phenobarbital* Phenytoin*† Topiramate* Valproate* Zonisamide†	Carbamazepine‡ Gabapentin* Lamotrigine* Levetiracetam* Oxcarbazepine* Phenobarbital‡ Phenytoin‡ Tiagabine* Topiramate* Valproate‡ Zonisamide*
Generalized tonic-clonic seizures (or unknown whether focal or generalized onset)	***Lamotrigine*** ***Levetiracetam*** ***Valproate*** Carbamazepine Oxcarbazepine Topiramate	Carbamazepine‡ Lamotrigine* Levetiracetam* Phenytoin‡ Valproate*	Carbamazepine‡ Lamotrigine* Levetiracetam* Phenytoin‡ Topiramate* Valproate*
Absence seizures	***Ethosuximide*** ***Valproate*** Lamotrigine* Topiramate	Ethosuximide*† Lamotrigine* Valproate*†	
Myoclonic seizures	***Clonazepam*** ***Levetiracetam*** ***Valproate***	Valproate‡	

*Supported by class I evidence, American Academy of Neurology.
†Supported by class I evidence for initial monotherapy, International League Against Epilepsy.
‡Often the "standard" of comparison, without evidence of effectiveness by randomized controlled trials.
Bold italics indicate medications commonly used as "first-line" therapy (online tool available at www.epipick.org).

Juvenile myoclonic epilepsy is one of the most common generalized genetic epilepsies. It usually starts in the second decade with myoclonic seizures in cognitively intact males and females. Generalized tonic-clonic and absence seizures may also occur. Earlier onset or cognitive decline after onset suggest a different diagnosis. Twin studies demonstrate a strong familial aggregation, but genetic variants (involving γ-aminobutyric acid [GABA] receptors [*GABRA1, GABRAD*] as well as in genes related to neuronal signaling [*EFHC1*]) have been found infrequently. Seizures typically occur in the morning immediately after awakening. The seizures are especially linked to sleep deprivation. A proportion of these patients have absence seizures as well. The EEG typically shows fast (4 to 6 Hz) generalized spike and wave. Medications control seizures in the majority of patients, but lifetime treatment is generally needed.

Epilepsy with generalized tonic-clonic seizures alone is a syndrome that presents with infrequent seizures in the second or third decade in cognitively normal individuals, often triggered by sleep deprivation or alcohol. It accounts for 30% of all idiopathic generalized epilepsies in adolescence, responds to medications, and usually requires lifelong treatment.

Epilepsy Syndromes with Specific Etiologies

Mesial temporal lobe epilepsy with hippocampal sclerosis is the most common cause of focal, impaired-awareness seizures in adults. It is characterized by recurrent seizures with autonomic, emotional, and cognitive features (see Table 372-2), with and without impaired awareness, that originate in mesial temporal and limbic structures. Up to 70% of patients have a risk factor such as lengthy and complicated seizures before the age of 4 years, frequently associated with fever or encephalitis, meningitis, or trauma. However, the characteristic seizures generally begin some years later. Although most cases are sporadic, familial forms have been associated with a susceptibility locus on chromosome 18(P11.31).

Mesial temporal sclerosis, also called hippocampal sclerosis, is characterized by neuronal loss and gliosis, mostly in the CA1 and CA3 regions of the hippocampus. Whether hippocampal sclerosis is the cause or the result of seizures (or both) is not known. However, up to 12% of children with febrile status epilepticus have MR evidence of hippocampal injury, thereby suggesting a causal association. The seizures of mesial temporal lobe epilepsy often begin at 5 to 15 years of age. Typical seizures with impaired awareness and emotional symptoms predominate, often starting with a warning of a rising epigastric sensation or a feeling of déjà vu, followed by oral and alimentary automatisms and later by contralateral arm dystonia and ipsilateral arm automatisms. The seizures persist for several minutes, rarely generalize, and typically occur several times a month. Warning symptoms without subsequent seizures are common. Hippocampal atrophy and increased hippocampal signal are best seen on T2-weighted and FLAIR coronal MRI sequences, and interictal hypometabolism is seen in the temporal lobe on PET. Verbal or visual memory impairment corresponds to primary involvement of the dominant or nondominant hippocampus, respectively. EEG recordings show temporal lobe spikes interictally as well as rhythmic 4- to 7-Hz rhythmic discharges over the appropriate temporal lobe during seizures.

Progressive myoclonus epilepsies comprise a heterogeneous group of rare genetic disorders that affect previously normal individuals of all ages but usually before age 50 years. This syndrome is characterized by the presence of myoclonus and myoclonic seizures, progressive deterioration of motor cognitive and cerebellar function, and an abnormal EEG. Treatment is largely symptomatic.

Reflex epilepsies are not considered a specific syndrome; however, they are triggered reliably by specific simple (e.g., flashing lights, sound) (see Video 372-15) or elaborate (e.g., reading) stimuli. The mechanisms are diverse, and most patients have no structural abnormalities. Visual-sensitive seizures (triggered by light or visual patterns) are the most common type of reflex seizures. They occur most commonly in females, and their incidence peaks around puberty, when they represent 4% to 7% of all new cases of epilepsy. Other triggers of reflex seizures include specific thoughts, actions, reading, tactile stimuli, adopting certain positions, eating, listening to music, startle, and contact with hot water. The triggered seizures can be myoclonic, convulsive, atonic, or focal, depending on the triggering stimulus. Avoiding the offending stimulus is crucial to avoid seizures, emphasizing the importance of careful questioning about seizure triggers in patients with epilepsy.

TREATMENT

The treatment of seizures and epilepsy is guided by accurate knowledge of the type of seizure and epilepsy syndrome, the probability of recurrent seizures, the likelihood and severity of psychosocial or physical consequences with further seizures, and whether the benefit from treatment substantially outweighs the risks for side effects.[11] It is important to identify and correct any environmental, physiologic, or lifestyle factors, such as sleep deprivation and irregular sleep habits, and alcohol abuse, all of which can lower the seizure threshold and trigger seizures in patients with epilepsy.

Single Unprovoked Seizures

The decision about whether to prescribe chronic antiseizure medication after a single, unprovoked, focal or generalized seizure should be made by an expert based on the likelihood of recurrence and on the patient's profile and preference. Antiseizure medications reduce the short-term absolute risk of having a second seizure by 33% and may be the preferred course of action in many scenarios. The risk of recurrence (20 to 45%)[12] is highest in the first 2 years and is higher in patients with prior brain insults or abnormalities on EEG or MRI. However, at least two randomized trials have shown that deferring antiseizure medications until additional seizures occur achieves a similar long-term seizure outcome, as does treating the first seizure.[A1] Therefore the decision to treat the first seizure should be individualized based on the patient's preference, the risk for and impact of recurrent seizures (e.g., driving and employment), and the risk for medication side effects, which occur in 7 to 30% of patients (Table 372-7).

Acute Symptomatic Seizures

Seizures that are provoked by specific exposures are usually self-limited and not associated with an enduring seizure tendency, so the primary therapeutic consideration should be identification and treatment of the underlying disorder (see Table 372-1). However, the risk of developing epilepsy after febrile seizures is about 10 times that of the general population. If antiseizure medications are needed to treat seizures acutely, they usually can be discontinued after the patient has recovered from the primary illness. Some acute conditions like stroke (Chapter 376), brain infections (Chapter 381 to 383), and trauma (Chapter 368) can produce both acute provoked seizures and a higher than 60% risk of recurrent seizures (which establish the diagnosis of epilepsy), thereby warranting the consideration of long-term antiseizure medications to prevent or reduce future seizures. For example, patients with post-stroke seizures have up to a 60% risk of recurrence within 1 year if the stroke was severe, the patient has large vessel atherosclerosis, the cortex in the territory of the middle cerebral artery territory was affected, and seizures occurred within 7 days of the stroke. To date, however, randomized controlled trials have not been able to demonstrate that antiseizure medications prevent the development of epilepsy in these conditions.

Self-Limited Epilepsy Syndromes

In syndromes such as childhood epilepsy with centrotemporal spikes and some types of childhood occipital epilepsy, seizures are mild, infrequent, or exclusively nocturnal, and they remit spontaneously, thereby making treatment generally unnecessary. In selected cases, treatment may be desirable to prevent recurrences and to help alleviate parental concerns. In such cases, drug treatment is usually limited to 1 to 2 years regardless of interictal EEG abnormalities, which can persist long after seizures have remitted. The recommended antiseizure medications are those used in focal epilepsy in children, including oxcarbazepine, carbamazepine, valproate, gabapentin, lamotrigine, and topiramate. Some patients with reflex seizures may require antiseizure medication, which should be chosen according to seizure type (see Table 372-7).

TABLE 372-7 CHARACTERISTICS OF MAJOR ANTISEIZURE MEDICATIONS

NAME	TOTAL MILLIGRAMS PER DAY (USUAL SCHEDULE)	THERAPEUTIC RANGE (μg/ML)	PROMINENT SIDE EFFECTS	OTHER EFFECTS	OTHER ISSUES
Brivaracetam	50-200 (bid)	Not well established	Mood change, irritability, lethargy	Serum concentration is decreased by phenytoin and carbamazepine	Can be up-titrated rapidly
Cannabidiol	10-20 mg/kg/day (bid)	Not well established	Sedation, irritability	Elevated liver enzymes	Enzyme inhibitor
Carbamazepine	400-2400 (bid)	4-12	Diplopia, fatigue, hyponatremia	Mood stabilizer	Enzyme inducer
Clobazam	10-40 (od, bid)	0.25-0.75	Sedation, depression	Metabolite desmethylclobazam has significant clinical effect	
Eslicarbazepine	800-1600 (daily)	Not well established	Sedation, ataxia		Risk for Stevens-Johnson syndrome
Ethosuximide	750-1250 (daily, bid)	40-100	Ataxia, lethargy	Rash, bone marrow suppression	
Gabapentin	600-1800 (tid, qid)	2-12	Fatigue	Treatment of pain	No drug interactions
Lacosamide	200-400 (bid)	Not well established	Dizziness, diplopia, tremor	Minor prolongation of PR interval	Low risk of drug interaction
Lamotrigine	100-600 (bid),100-200 (bid) if used with valproate	4-18	Insomnia, headache, tremor, anxiety	Mood stabilizer	Risk for Stevens-Johnson syndrome; slow start-up
Levetiracetam	500-3000 (bid)	3-63	Mood change, irritability, lethargy		No drug interactions
Oxcarbazepine	1200-2400 (bid, tid)	6-40	Diplopia, hyponatremia, sedation	Mood stabilizer	
Perampanel	4-12 (od)	Not well established	Psychiatric and behavioral adverse reactions	Serum concentration is decreased by phenytoin and carbamazepine	Hormonal contraceptives may be less effective
Phenobarbital	60-240 (at bedtime)	15-40	Fatigue, depression, sedation	Joint pain	Enzyme inducer
Phenytoin	200-600 (bid)	10-20	Fatigue, hirsutism, gingival hypertrophy	Treatment of some pain	Enzyme inducer
Rufinamide	400-3200 (bid)	5-48	Mood change, irritability, lethargy	Contraindicated in familial short QT syndrome	Hormonal contraceptives may be less effective
Topiramate	50-400 (bid)	2-12	Anorexia, weight loss, kidney stones, speech disturbance, distal paresthesias	Headache prophylaxis, mood stabilizer	Enzyme inducer
Valproate	1000-3000 (bid or tid)	50-100	Weight gain, hair loss, tremor	Headache prophylaxis, mood stabilizer	Enzyme inhibitor, parkinsonian effects in elderly patients
Zonisamide	400-600 (at bedtime)	10-40	Anorexia, kidney stones, dizziness, distal paresthesias	Mood stabilizer	

Choice of Antiseizure Medications

The ultimate goal of treatment is to obtain complete freedom from seizures without side effects.[13] Some of the newer antiseizure medications (see Table 372-7) are better tolerated and have better pharmacokinetics than older drugs, but there is no evidence to support superior efficacy of one drug over another. The choice of medication depends on the type of seizure and epilepsy syndrome (thereby making a correct diagnosis crucial) and the medication's side effects, cost, and ease of use.[A2] Specific drugs are effective for specific types of seizures, and some drugs can worsen other types of seizures. Knowledge of individual drugs as they relate to age, sex, comorbid conditions, drug interactions, sedation, tolerance, mood, and withdrawal is critical in the drug selection process (see Table 372-7). For example, levetiracetam is increasingly used for focal and generalized seizures, but it can cause adverse psychiatric effects.

Drugs that cause enzyme induction (e.g., carbamazepine, phenytoin, phenobarbital, rufinamide) or inhibition (e.g., valproic acid) can be difficult to manage when additional medications, such as oral contraceptives and warfarin are used for independent conditions. For these clinical settings and in elderly patients, drugs such as gabapentin, levetiracetam, brivaracetam, and lacosamide are particularly useful because they have fewer drug interactions.

Newly Diagnosed Epilepsy

Among patients who present with a new diagnosis of epilepsy of any type, about 65% achieve a complete remission on antiseizure medications. Of these patients, about 45 to 50% achieve remission with the first antiseizure medication, 10 to 15% with the second, 1% with the third, and 3% with a combination of two or more antiseizure medications. Valproate is superior to levetiracetam for patients with newly diagnosed generalized epilepsy.[A3]

In patients with newly diagnosed focal epilepsy, the underlying cause influences the response to antiseizure medications. The likelihood of achieving freedom from seizures is higher for patients with vascular malformations, stroke, and tumors (63 to 78%) and lower for patients with hippocampal sclerosis and malformations of cortical development (40 to 50%).[A4] In this setting, lamotrigine is superior to levetiracetam or zonisamide.[A5]

Antiseizure medications also can be chosen based on specific targets and mechanisms. For example, the mTOR inhibitor everolimus reduces seizures by 25% compared with placebo in patients with tuberous sclerosis (Chapter 385).[A6] Cannabidiol can significantly reduce seizures in patients with Dravet syndrome and Lennox-Gastaut syndrome.[A7,A8] Stiripentol, a lactate dehydrogenase inhibitor in astrocytes and neurons, also may be useful in epilepsy.[A9]

Drug-Resistant Seizures

Because the likelihood of achieving subsequent seizure remission is small if two drug trials fail, the 35% or so of patients who fail adequate trials of two antiseizure medications are considered to be drug resistant. The first consideration in managing apparently drug-resistant patients is to ensure that the diagnosis is correct and the antiseizure medication is appropriate. Other common causes of a poor response to drugs include poor adherence to antiseizure medications, sleep deprivation, alcohol use, fatigue, emotional stress, systemic illnesses, use of concurrent medications, and nonepileptic seizures. After addressing these factors, patients who remain drug resistant should be considered potential candidates for surgical therapy.[14]

Procedures and Surgeries

Surgical treatment entails resection or disconnection of the cerebral region that contains the seizure focus.[15] Removal of an epileptogenic region requires accurate identification of the region as well as documentation of a lack of functional consequences after its removal. Video EEG monitoring with seizure recording from scalp electrodes, MRI protocols with special attention to areas commonly associated with refractory seizures (e.g., the medial temporal and frontal lobes), and functional neuroimaging, including PET and SPECT, are used to make the assessment. In temporal lobe epilepsy, neuropsychological evaluation is essential to localize dysfunction and establish the level of function in the region considered for resection. EEG localization of the region of seizure onset and mapping of brain function may require the surgical implantation of intracranial electrodes for recording and for stimulating cortical tissue. These procedures are performed by multidisciplinary teams in specialized epilepsy centers.

Epilepsy surgery interventions that have been subjected to rigorous randomized trials include temporal lobe resection compared with medical therapy for mesial temporal lobe epilepsy,[A10] radiosurgery ablation, and neurostimulation (of the vagal nerve, trigeminal nerve, thalamus, hippocampus, or cerebral cortex). The most dramatic surgical effect is seen for temporal lobe resection compared with medical therapy. In one randomized trial, 64% of surgical patients and only 8% of medical patients became seizure free at 1 year. In another randomized trial of patients with drug-resistant temporal lobe epilepsy, surgery plus continued antiseizure medications was successful in eliminating seizures in 70% of patients at 2 years, whereas all medically treated patients continued to have seizures at 2 years. Since better outcomes are obtained when surgery is performed earlier in the course of the disease,[16] patients with drug-resistant temporal lobe epilepsy should be evaluated for epilepsy surgery as soon as possible. Nonrandomized studies demonstrate enduring freedom from seizures at 10 years or more after hemispheric disconnection (61%), temporal lobe resection (64%), parieto-occipital resection (46%), and frontal lobe resection (27%). In the long term, about 65% of patients undergoing surgery achieve sustained seizure freedom (40 to 50% immediately after surgery and 15% after a period of initial seizures), 16% have a fluctuating course of relapsing-remitting seizures, and 18% never become seizure free.

Promising less invasive surgical therapies for epilepsy include various types of electrical brain stimulation,[A11] which can provide a 75% median reduction in the number of seizures.[17] Other options include laser interstitial therapy and focused ultrasound. However, standard surgical resection may be preferable to radiosurgery in patients with temporal lobe epilepsy.[A12] Palliative surgical procedures such as callosotomy and multiple subpial transections have lower success rates and are used when surgical resection of the seizure focus is not possible.

Status Epilepticus

Status epilepticus is a medical emergency in which seizures occur continuously or repeatedly without intervening resumption of consciousness. The diagnosis is established after 5 minutes in generalized tonic-clonic seizures and 10 minutes in focal impaired awareness seizures, although long-term neurologic consequences are not likely to occur unless status epilepticus persists for 30 minutes for generalized tonic-clonic seizures or 60 minutes for focal impaired awareness seizures. Most episodes of status epilepticus are caused by an acute brain insult in persons without underlying epilepsy, so a cause should be sought promptly. In one study, the most common cause was autoimmune encephalitis, but 50% remained cryptogenic even after detailed evaluation.

After securing the airway and stabilizing cardiovascular function, immediate intervention with parenteral agents is needed to stop the seizures.[18] In adults in status epilepticus treated before arriving at the hospital, 10 mg of intramuscular midazolam is more effective and at least as safe as 4 mg of intravenous (IV) lorazepam for stopping seizures. Early status epilepticus (first 5 to 10 minutes) can be controlled in about 70% of patients with IV lorazepam (0.1 mg/kg given at 2 mg/min), diazepam (5 to 10 mg IV bolus given at 5 mg/min), clonazepam (1 mg IV bolus, given at 0.5 mg/min), or phenobarbital (10 mg/kg, given at 100 mg/min). Established status epilepticus (10 to 30 minutes) that does not respond to such treatment can be successfully treated in about 45% of patients with fosphenytoin (15 to 20 mg/kg at a rate of 150 mg/min), valproate (30 to 40 mg/kg at 5 mg/kg/min), or levetiracetam (30 to 60 mg/kg over 10 minutes).[A13] Patients who do not respond to these measures have refractory status epilepticus and require treatment in an intensive care unit with respiratory support and IV sedation sufficient to suppress the epileptic EEG discharges, using continuous IV infusion of midazolam (0.1 to 0.4 mg/kg/hour), propofol (1 to 3 mg/kg/hour), pentobarbital (0.5 to 3 mg/kg/hour), or thiopental (3 to 5 mg/kg/hour). Ketamine infusion (2.2 mg/kg/hour) also may be effective in highly refractory status epilepticus. Therapeutic hypothermia is not beneficial.

Activity Restrictions in Epilepsy

Complete prevention of seizures is the goal of treatment. Patients with even infrequent seizures are at risk for harm to themselves or others while driving, operating machinery, working near depths or heights, swimming, or engaging in activities that entail risk of injuries. Patients with inadequately controlled seizures should be advised to avoid such activities. Some jurisdictions require patients or physicians to notify authorities if they have a condition that alters consciousness to determine if patients can operate vehicles. The duration of restriction of activities after seizures are controlled varies among jurisdictions, and physicians must be aware of these requirements. Once seizures are controlled, these restrictions are unnecessary, and it is important to encourage normal activities to avoid stigmatization.

Considerations in Women

Changes in hormone levels during the menstrual cycle may aggravate seizures perimenstrually in some women (i.e., catamenial epilepsy). The administration of oral contraceptives (Chapter 220), Depo-Provera, acetazolamide (250 to 500 mg/day), or clobazam (10 to 20 mg/day around the time of menses) may reduce perimenstrual seizures. Enzyme-inducing antiseizure medications (see Table 372-7) that reduce estrogen levels by enhancing its metabolism require patients to be treated with higher doses of estrogen or alternative methods of contraception.

Pregnancy poses challenges with regard to seizure control, teratogenesis, and outcomes of pregnancy.[19] Nevertheless, pregnancy itself has no consistent effect on the frequency of seizures, and more than 90% of pregnancies in women with epilepsy are safe and successful. Freedom from seizures for at least 9 months preceding pregnancy is associated with a high probability of freedom from seizures during the pregnancy. Serum levels of lamotrigine, phenytoin, carbamazepine, levetiracetam, topiramate, and oxcarbazepine may decrease during pregnancy and should be monitored. Valproate carries a higher risk for major congenital malformations and an enduring reduction in cognitive abilities in children exposed to this medication in utero; therefore its use should be avoided during pregnancy if seizure control permits it. Similarly, polytherapy and high doses of antiseizure medications should be avoided if possible, but they should not be discontinued. There is no increased risk for cesarean section or premature contractions, and maternal epilepsy itself does not increase the risk for cognitive impairment in the child. Supplementation with at least 0.4 to

1 mg of folic acid daily should be given before conception and during pregnancy to reduce the risk of neural tube defects.

Considerations in the Elderly

The incidence and prevalence of epilepsy in the elderly are rising, and its management poses special considerations because of increased frailty, multiple coexisting conditions, and polypharmacy with potential for adverse drug interactions,[20,21] for example, between antihypertensives, lipid-lowering drugs, anticoagulant drugs, and enzyme-inducing antiseizure medications. Antiseizure medications with fewer interactions (e.g., lamotrigine, levetiracetam, and lacosamide) may be better tolerated in the elderly.[A14]

Discontinuing Antiseizure Medications

About 60% of patients have seizures that are easy to control with antiseizure medications. Medications may be slowly tapered over 4 to 6 months in patients who have remained free of seizures for 2 years or longer, have had few seizures before treatment started, and who have a normal neurologic examination and EEG and do not have a condition that entails a high risk of recurrent seizure (e.g., brain malformations, high-risk stroke). However, the increased absolute risk for recurrent seizures after withdrawal of medication is about 20% (number needed to harm of 5). The consequences of a recurrent seizure, the costs and side effects of drugs, and aspects such as personal preferences influence the decision to withdraw antiseizure medications in patients who have been free of seizures. Evidence-based algorithms can assist in estimating the risk of recurrence after the withdrawal of medications.[22]

PROGNOSIS

The prognosis is favorable in the majority of patients who experience either unprovoked seizures or one of the epilepsies.

Prognosis after Febrile Seizures

Febrile seizures are common and usually consist of generalized tonic-clonic seizures. They are provoked by fever and therefore are not considered epilepsy. The seizures begin after 6 months of age and stop before 6 years of age. Usually, febrile seizures are left untreated because the prognosis is benign. When febrile seizures occur in the setting of a neurologic abnormality or are prolonged or complicated, the risk for later epilepsy is increased.

Prognosis after a Single Unprovoked Seizure

The risk of experiencing recurrent seizures after a first unprovoked seizure ranges from 21 to 69% at 2 years and from 34 to 70% at 5 years. The risk is lower in the general population than in hospital-based studies (36% at 1 year and 45% at 2 years). The probability of a relapse decreases with time; about 50% of recurrences occur within 6 months of the initial seizure, and 76 to 96% occur within 2 years. The two most consistent predictors of recurrence are the presence of a neurologic cause for the seizure, which is often uncovered on brain MRI or by the neurologic examination and history, and an epileptiform or slow EEG. The 2-year risk for recurrence is lowest for patients without an identified neurologic cause and with a normal EEG (about 25%), intermediate for patients with an identified neurologic cause or without a cause but with an abnormal EEG (48%), and highest for those with a neurologic cause and an abnormal EEG (about 65%). The risk rises dramatically if more than one seizure has occurred; after a second unprovoked seizure, the risk for a third seizure is 73%, and after a third seizure, the risk for a fourth seizure is 76%.

Prognosis of Epilepsy

The natural history of untreated epilepsy, mostly in developing countries, shows that 30 to 40% of patients obtain 5- to 10-year remissions without treatment. In developed countries, where treatment is generally started early after the diagnosis of epilepsy, the likelihood of 5-year remission is about 60% when patients are followed for 10 years and about 70% when patients are followed for 20 years.[23] The rate of 5-year remission in children is about 75%. In the long term, sustained freedom from seizures is achieved in about 60% of patients (early remission in about 35 to 40% of patients and late remission in about 20 to 25%), about 16% of patients fluctuate between relapses and remissions, and about 25% never achieve seizure remission. Epilepsy is considered to be resolved in patients who had an age-dependent epilepsy syndrome and are now past the applicable age or in patients who have been seizure free for at least 10 years, with no seizure medications for the last 5 years.

Conversely, the duration of active epilepsy before achieving control is one of the most powerful predictors of remission. If seizures remain uncontrolled during the first year after diagnosis, the chance of ever achieving control is about 60%. If the period of uncontrolled seizures extends to 4 years, the chance of ever achieving control is only 10%. The presence of multiple seizure types and frequent generalized tonic-clonic seizures is associated with a lower likelihood of remission. From 40% to 60% of patients with newly diagnosed epilepsy due to structural brain abnormalities (e.g., tumors, cortical malformations, vascular malformations, mesial temporal sclerosis) will be controlled with medications.

Children whose seizures remain uncontrolled are at risk of developing cognitive impairment, especially at a younger age, thereby emphasizing the importance of prompt seizure control. In children with absence epilepsy, the 12-month probability of seizure control on medication is about 35 to 40% overall, but it is higher for ethosuximide (45%) and valproic acid (44%) than for lamotrigine (21%). In longitudinal population studies of children with newly diagnosed epilepsy, quality of life improves over time in about 50%, remains stable in 30%, and deteriorates in 20%.

Patients with epilepsy are at risk for poor psychosocial outcomes, depression, and increased mortality. The risk for death is two to three times higher in epilepsy than in the general population, and it can be up to five times higher in patients with frequent generalized convulsions and drug-resistant epilepsy. The major causes of death are underlying conditions such as stroke and pneumonia, although unnatural deaths from unintentional injury and poisoning are also more common.[24] Sudden unexpected death in epilepsy occurs in about 1 per 1000 patient-years in adults and is particularly devastating because it affects young individuals with frequent uncontrolled seizures. Complete control of seizures is a major way to decrease mortality in epilepsy. Patients who undergo successful epilepsy surgery, the most effective treatment for drug-resistant focal epilepsy, have a 66% decrease in mortality compared with medically treated patients, and receiving treatment in specialized epilepsy centers also decreases the risk of mortality.[25]

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373 COMA, DISORDERS OF CONSCIOUSNESS, AND BRAIN DEATH

DAVID M. GREER AND JAMES L. BERNAT

Disorders of consciousness and limited responsiveness (Table 373-1) encompass a range of conditions, from mild encephalopathy or confusion to coma and brain death. Although not all causes of encephalopathy lead to poor outcomes, the rapid and comprehensive evaluation of a patient with altered consciousness remains one of the most important goals in all of medicine. Depending on the cause, a patient with altered mental status or coma may suffer irreversible brain injury or even death; conversely, with prompt diagnosis and treatment, many if not most patients will recover, often fully.

Consciousness arises from the ascending reticular activating system, an ill-defined group of neurons that originates in the rostral portion of the brain stem tegmentum and projects to the thalami and then to both cerebral cortices. For consciousness to be disrupted, the underlying pathologic process must affect the brain stem or thalami primarily (e.g., a structural injury such as an intracerebral hemorrhage or ischemic stroke), affect both cerebral cortices simultaneously (e.g., global anoxic brain injury or encephalitis), or both (e.g., drug intoxication or toxic-metabolic insult).

Consciousness comprises two elements: wakefulness and awareness. Wakefulness represents the ability to establish an alertness response to internal need or external stimulation. Awareness of the self and environment is established by a diffuse network of thalamocortical and corticocortical circuits. Patients in coma have neither wakefulness nor awareness. Patients in persistent vegetative state (or unresponsive wakefulness syndrome as it is also called) have wakefulness, including sleep-wake cycles, but no awareness.

COMA

Coma is a state of pathologic unresponsiveness from which the patient cannot be aroused by any form of stimulation.[1]

EPIDEMIOLOGY

The most common causes of coma include trauma, toxic-metabolic, global anoxia, and lesions that result in herniation and compression of the brain stem (Table 373-2).

PATHOBIOLOGY

Wakefulness arises from the ascending reticular activating system, which is a neural network that originates in the central tegmentum of the pons and midbrain in the rostral brain stem, receiving input at each level as it ascends into the central basal forebrain, thalami, and cerebral cortices. Arousal can be affected by damage or dysfunction anywhere along these pathways, but thalamic and cortical neurons are more susceptible to damage because of their higher metabolic demands. The classic scenario is a global anoxic insult from

TABLE 373-2 CAUSES OF STUPOR AND COMA

Traumatic brain injury*
Contusion
Intracerebral, epidural, subdural, or subarachnoid hemorrhage
Diffuse axonal injury
Raised intracranial pressure
Neoplasms and other mass lesions
Infections
Meningitis
Encephalitis
Brain abscess or empyema
Sepsis or other infection, especially in the elderly or a demented patient*
Cerebrovascular disease
Intracerebral hemorrhage
Infarction in the brain stem or cerebellum or large hemispheric infarction
Hemorrhage in the brain stem or cerebellum or large hemispheric hemorrhage
Vasculitis, disseminated intravascular coagulation, thrombotic thrombocytopenic purpura
Seizures
Status epilepticus
Spike-wave stupor
Postictal state
Metabolic encephalopathies*
Hypoglycemia, hyperglycemia
Hypercalcemia
Hyponatremia, hypernatremia
Hypoxemia, including anoxia after cardiac arrest
Acidosis
Organ system failure: hepatic, renal, pulmonary, cardiac
Endocrinopathy (e.g., myxedema coma)
Toxic encephalopathies
Drug intoxications*: alcohol, barbiturates, benzodiazepines, opioids, stimulants, salicylates, anticonvulsants, anticholinergics, psychotropic drugs, or others
Poisoning: carbon monoxide, industrial toxins
Other encephalopathies
Hypertensive encephalopathy
Acute hydrocephalus
Pituitary apoplexy
Other
Conversion, malingering, functional neurologic disorder

*Most common causes.

TABLE 373-1 COMPARISON OF DISORDERS OF CONSCIOUSNESS* AND LIMITED RESPONSIVENESS

	AWARENESS	WAKEFULNESS	BRAIN STEM/ RESPIRATORY	MOTOR	EEG	EVOKED POTENTIALS	PET/fMRI	PROGNOSIS
Brain death	Absent	Absent	Absent	Absent	ECS	Absent	Absent cortical metabolism	The person has died
Coma	Absent	Absent	Depressed, variable	Reflex or posturing	Polymorphic delta, burst suppression	BAER variable; cortical ERPs often absent	Resting <50%	Variable
Unresponsive wakefulness syndrome	Absent	Present, intact sleep-wake cycles	Intact	Reflex, nonpurposeful	Delta, theta, or ECS	BAER preserved; cortical ERPs variable	Resting <50%; primary areas stimulatable	Poor, when chronic
Minimally conscious state	Intact but poorly responsive	Intact	Intact	Variable with purposeful movements; may follow some commands	Nonspecific slowing	BAER preserved; cortical ERPs often preserved	Reduced; secondary areas also stimulatable	Variable
Locked-in syndrome	Intact but communication difficult	Intact	Intact breathing; often brain stem signs	Quadriplegia, pseudobulbar palsy	Usually normal	BAER variable; cortical ERPs normal	Normal or nearly normal	Poor

*The table lists typical findings, which are not necessarily present in all patients. Locked-in syndrome may be mistaken for a disorder of consciousness.
BAER = brain stem auditory evoked response; ECS = electrocerebral silence; EEG = encephalography; ERP = event-related potential; fMRI = functional magnetic resonance imaging; PET = positron emission tomography.
From Bernat JL. *Ethical Issues in Neurology.* 3rd ed. Philadelphia: Lippincott Williams & Wilkins; 2008:292.

ABSTRACT

Disorders of consciousness encompass a range of conditions, from mild encephalopathy or confusion to coma and brain death. Consciousness is an emergent function that arises from the ascending reticular activating system, an ill-defined group of neurons that originates in the rostral portion of the brain stem tegmentum and projects to the thalami and then to both cerebral cortices. For consciousness to be disrupted, the underlying pathologic process must (1) affect the brain stem or thalami primarily (e.g., a structural injury such as an intracerebral hemorrhage or ischemic stroke), (2) affect both cerebral cortices simultaneously (e.g., global anoxic brain injury or encephalitis), or (3) both 1 and 2 (e.g., drug intoxication or toxic-metabolic insult). Consciousness comprises two elements: wakefulness and awareness. Awareness of the self and environment is established by a diffuse network of thalamocortical and corticocortical circuits. Patients in coma have neither wakefulness nor awareness. Patients in persistent vegetative state (also called unresponsive wakefulness syndrome) have wakefulness, including sleep-wake cycles, but no awareness. Although not all causes of encephalopathy lead to poor outcomes, the rapid and comprehensive evaluation of a patient with altered consciousness remains one of the most important goals in all of medicine. Depending on the cause, a patient with altered mental status or coma may suffer irreversible brain injury or even death; conversely, with prompt diagnosis and treatment, many patients will recover, often fully. Brain death is a state of complete and irreversible loss of all brain function; core components include coma, brainstem areflexia, and apnea in the setting of a carbon dioxide and acidosis challenge. Ancillary testing may be necessary when a complete clinical determination cannot be performed fully or safely.

KEYWORDS

coma
brain death
unresponsive wakefulness syndrome
vegetative state

a cardiac arrest, which selectively injures specific cortical laminae, the thalami, basal ganglia, and the hippocampus owing to their high oxygen demands and relatively high metabolic activity. By comparison, phylogenetically older and less metabolically demanding neurons of the ascending reticular activating system are relatively spared. This selective injury helps explain the unresponsive wakefulness syndrome (also called the vegetative state), which is characterized by wakefulness without awareness.

Coma can be caused by (1) structural damage as a result of trauma, edema, inflammation, ischemia, hemorrhage, or mass lesions or (2) diffuse toxic and/or metabolic effects on neurons. Structural lesions can affect the ascending reticular activating system directly by neuronal damage or indirectly by extrinsic pressure or displacement, thereby causing ischemia and/or edema. Metabolic and toxic encephalopathies diffusely affect all brain neurons but preferentially the metabolically sensitive neurons in the cortex and thalamus. However, several acute metabolic derangements or toxicities can also cause structural brain injury by altering blood pressure or oxygenation (e.g., opioid toxicity [Chapter 365]), brain edema (e.g., acute hepatic failure [Chapter 140] with hyperammonemia), or acute demyelination (e.g., central pontine myelinolysis owing to rapid osmolar shifting, such as seen in rapid correction of chronic hyponatremia [Chapter 102]).

Structural lesions causing coma typically present with clinically recognizable herniation syndromes, in which shifts in intracranial pressure produce caudal and lateral displacement and ischemia of the midbrain and medial temporal lobe through the tentorial incisura. Herniation results in dysfunction of cranial nerves (pupillary dilation followed by more complete third nerve palsy), breathing, and motor systems. Most commonly, central herniation occurs with global events such as meningoencephalitis (Chapter 383), global anoxic brain injury, massive brain swelling from toxic-metabolic insults, or hydrocephalus. Uncal herniation results from rapidly expanding and laterally placed lesions that trap the ipsilateral oculomotor nerve against the uncus of the temporal lobe. Lateral displacement of brain structures can match or exceed downward displacement. Brain stem compression can also result from structural lesions in the posterior fossa. The ascending reticular activating system also can be damaged directly by primary brain stem injuries, such as from hemorrhage or infarction, or indirectly by downward-directed pressure produced by hemispheric mass lesions, such as from brain trauma (Chapter 368), neoplasms (Chapter 175), abscesses (Chapter 382), hemorrhages (Chapter 377), or large infarctions (Chapter 376).

Encephalopathy in the setting of metabolic disturbances results from perturbation of the neuronal microenvironment by altering the precise metabolic conditions necessary for normal neuronal conduction and excitability. These disturbances can occur due to changes in blood flow, oxygen delivery, glucose concentration, temperature (hyperthermia or hypothermia), electrolyte concentrations, and intracranial pressure. Other causes include meningitis, seizures, and organ failure. The severity of the insult matches the impact: more profound metabolic insults cause greater encephalopathy. The rapidity of onset also is an important factor. Sudden metabolic changes, such as in serum sodium concentration, may result in seizures and coma, whereas a slow decline, even to a low level, may cause little clinical impact (Chapter 102). Toxic encephalopathies, with indistinguishable clinical manifestations, can result from exogenous poisoning with illicit (e.g., opiates, hallucinogenics) or therapeutic (e.g., antidepressants, anticholinergics) substances, or endogenous toxins that result from renal or hepatic failure. Acute meningoencephalitis, with inflammation of both the meninges and cerebrum, causes coma by direct inflammation, vascular insults, cerebral edema, and hydrocephalus.

CLINICAL MANIFESTATIONS

A patient in coma displays neither wakefulness nor awareness. There is no purposeful response to noxious stimulation. Reflexive posturing may be present. The eyes are typically closed, except in the rare situation of "eyes open coma,[2]" which occasionally follows cardiac arrest (Chapter 50) with global anoxic brain injury. The eyes do not open in response to noxious stimulation. The patient does not express any interpretable sounds reflective of responsiveness, only sounds associated with attempts at breathing.

Coma should be differentiated from stupor, in which the patient is able to be aroused temporarily during vigorous stimulation but then immediately resumes unresponsiveness once stimulation is stopped. However, this differentiation serves only to distinguish levels of brain stem dysfunction and does not imply reversibility, which depends on the underlying etiology. The pattern of brain stem dysfunction usefully localizes the anatomic extent of a structural injury or impingement.

TABLE 373-3 SOME INITIAL CLINICAL CLUES TO THE DIAGNOSIS OF STUPOR AND COMA

STRUCTURAL CAUSES
History
Abrupt onset of unconsciousness
Sudden headache
Vomiting
Examination
Focal neurologic signs (hemiparesis, posturing, asymmetrical reflexes)
Abnormal pupillary light reflexes
METABOLIC OR TOXIC CAUSES
History
Gradual onset of unconsciousness
Preceding confusional state
Seizures
Known cognitive impairment
Taking insulin or illicit drugs
Examination
Absence of focal neurologic signs
Presence of frontal release signs
Intact pupillary light reflexes
Tremor, asterixis, or multifocal myoclonus
Evidence of systemic infection
Needle tracks
MENINGITIS
History
Worsening headache
Neck stiffness and pain
Fever, chills
Progressive stupor and coma
Examination
Fever, rigors
Nuchal rigidity and signs of meningeal inflammation

DIAGNOSIS

Rapid diagnosis of the etiology of coma is crucial for expeditious and targeted treatment (Table 373-3).[3] A detailed history, physical examination, laboratory testing, and neuroimaging should be performed in a parallel manner. Immediate attention should be focused on whether the patient has signs of trauma (cranial or cervical), meningitis (fever, nuchal rigidity), drug intoxication (which may be rapidly reversed), seizures (including nonconvulsive status epilepticus, which may manifest only with eye deviation), or focal findings suggestive of a mass lesion or vascular event.[4]

The history should focus on any witnessed events or recent history according to others, such as feeling unwell or suffering any trauma or medication changes. Information should be obtained regarding any preceding headache, vomiting, confusional state, prescription and illicit drug use, alcohol use, fever, metabolic disturbances (including a history of diabetes), seizure history, abnormal recent behavior, and preexisting medical conditions, particularly atrial fibrillation or prior neurologic events (e.g., stroke, hemorrhage).

The general physical examination should include assessment of vital signs, otoscopy, funduscopic examination, and a search for physical signs of head trauma, nuchal rigidity, or needle track marks. The respiratory rate and pattern should be carefully noted (Table 373-4). Cheyne-Stokes respiration is a periodic breathing pattern whose amplitude forms a sine wave, with 5- to 45-second periods of apnea alternating with periods of hyperpnea. It can be seen in patients with primary cardiac/respiratory disorders or in patients with metabolic encephalopathy, and it is typically reversible by treating the underlying cause. Central neurogenic hyperventilation consists of continuous hyperpnea and tachypnea that leads to a pure respiratory alkalosis; it occurs with lesions of the rostral brain stem tegmentum at the level of the midbrain, or damage to the central pons. Kussmaul respiration, which consists of rapid deep breathing, is seen as a compensatory mechanism in the setting of severe metabolic acidosis, often with hyperglycemia (Chapter 210). Ataxic or irregular breathing patterns, with or without apneic periods, are associated with lower brain stem dysfunction and can represent an agonal pattern.

A detailed neurologic examination is important to discern if there are localizing signs that may point to a structural etiology to assess the level of brain function and to look for evidence of trauma or drug use.

The patient's limbs should be uncovered to view any movements, either spontaneously or in response to stimulation. Responsiveness should be checked

TABLE 373-4 BRAIN FUNCTIONAL LEVELS DETERMINED BY FINDINGS IN CLINICAL SYSTEMS

FUNCTIONAL LEVEL	CONSCIOUSNESS	RESPIRATION	PUPILS	VESTIBULO-OCULAR REFLEXES	MOTOR RESPONSES
CENTRAL TRANSTENTORIAL HERNIATION					
High diencephalic	Light stupor	Eupnea, yawning, post-hyperventilation apnea	Small, reactive	Loss of checking component	Paratonia, grasp
Low diencephalic	Deep stupor	Cheyne-Stokes	Small, reactive	Loss of checking component	Decorticate posturing
Midbrain	Coma	Central neurogenic hyperventilation	Midposition, fixed	Loss of medial rectus function	Decerebrate posturing
Upper pons	Coma	Central neurogenic hyperventilation	Midposition, fixed	Loss of medial rectus function	Decerebrate posturing
Lower pons	Coma	Ataxic	Midposition, fixed	Absent	Flaccid
Medulla	Coma	Apnea	Midposition, fixed	Absent	Flaccid
UNCAL TRANSTENTORIAL HERNIATION					
Early third nerve	Unreliable	Normal	Ipsilateral dilated, fixed	Normal	Contralateral hemiparesis
Late third nerve	Coma	Cheyne-Stokes or central neurogenic hyperventilation	Ipsilateral dilated, fixed; contralateral dilated, fixed	Medial rectus dysfunction	Ipsilateral hemiparesis and contralateral decerebrate posturing
Midbrain-pons	Coma	Central neurogenic hyperventilation or ataxic	Midposition, fixed	Absent	Bilateral decerebrate posturing

by increasingly noxious stimulation, starting with loud auditory stimulation. Noxious physical stimulation should include not only stimulation of the extremities (typically starting with pressure on the nail bed), but also on the cranium, including the supraorbital ridge and temporomandibular joint. Only when adequate stimulation has been provided can one say that the patient is truly unresponsive and comatose.

Cranial Nerve Examination

In a detailed cranial nerve examination, the eyes should be held open, and any spontaneous eye movements, deviation, nystagmus, or dysconjugation should be noted. The patient should be asked to look up and down, so that pseudocoma from a locked-in state can be detected. A blink to visual threat should be tested with the hand flat (so as to avoid creating a wind wave that would stimulate a corneal reflex) approaching the eye, first laterally (to test the visual field), and then centrally if there is no response laterally. The pupillary light reflex should be tested with a bright light, and a magnifying glass or pupillometer may be helpful to evaluate questionable responsiveness or briskness and degree of response. A corneal reflex may be tested initially with a squirt of water or saline and then a light cotton wisp; however, if these minor stimuli are not successful, a more potent stimulus, such as pressing on the eye with a cotton-tipped applicator, may be necessary.[5]

Pupillary responses to bright light and darkness assess the pathways of the optic nerve, oculomotor nerves, midbrain, and sympathetic nerves. Pupillary reactivity helps distinguish structural from toxic-metabolic causes of coma. Pupils remain reactive to light and usually symmetrical through varying depths and causes of toxic-metabolic coma, whereas pupillary reflexes are abnormal, and often asymmetrical, with structural causes of coma such as transtentorial herniation with compression of the third nerve. With asymmetrical pupils, it is important to distinguish which eye is the abnormal one; the larger pupil may not necessarily be the abnormal side, such as in the setting of Horner syndrome, in which there is loss of sympathetic input. However, in the setting of a compressive lesion or other cause of third nerve dysfunction, pupillary enlargement occurs before ophthalmoplegia because the parasympathetic pupilloconstrictor fibers course on the outside of the nerve and are compressed first. With progressive herniation, the brain stem sympathetic tracks are also damaged, so the pupil may return to be midposition and remain unreactive. Primary structural injuries to the pons (e.g., hemorrhage or infarction) cause "pinpoint" pupils owing to loss of sympathetic tracts; however, they are typically still reactive with a magnifying glass or pupillometer. Pinpoint pupils are not simply the result of loss of sympathetic tone; pontine lesions stimulate adjacent intact parasympathetic tracts, thereby making the pupils even smaller than by pure sympathetic denervation alone.

The examiner should consider the potential for preexisting pupillary abnormalities (e.g., diabetes, postsurgical), as well as locally applied medications that can impair pupillary reflexes.

A dilated funduscopic examination is helpful to look for ocular pathology as well as evidence of increased intracranial pressure. However, if pharmacologic dilation is performed, it is important that all caregivers know that it has been performed so erroneous conclusions do not result.

Spontaneous eye movements may have localizing value. Horizontally and conjugately deviated eyes owing to a hemispheric lesion follow the rules of "look toward a stroke, look away from a seizure" because of ablation or stimulation of the frontal lobe gaze center. With lesions in the brain stem, however, the eyes often will deviate in the opposite direction because of damage to the parapontine reticular formation. Tonic downward eye deviation is sometimes seen in patients with global anoxic brain injury. Ocular bobbing, with rapid downward movement followed by a slow return upward, can occur with pontine lesions. "Reverse" ocular bobbing with slow downward but rapid upward movement ("ocular dipping") may be seen after primary brain stem insults or with global anoxia or toxic-metabolic states. "Ping-pong" gaze with alternative conjugate horizontal movements is nonspecific, but a slower and similar disorder of periodic alternating gaze can be seen with hyperammonemia owing to portosystemic encephalopathy.

Horizontally dysconjugate gaze should be placed in the clinical context because it may be from a brain stem injury or it may simply be an uncovering of a preexisting esotropia or exotropia. However, vertical dysconjugation ("skew") is almost always abnormal and should signal a structural problem at the level of the rostral brain stem.

The vestibulo-ocular reflex can be tested using ice-water caloric stimulation of the external auditory canals. Before doing the ice-water test, otoscopic evaluation should reveal an intact tympanic membrane and a clear auditory canal, and the head of the bed should be elevated to 30 degrees. Ice water is instilled in one ear at a time for 60 seconds continuously, and the eyes are observed for any movement. With an intact brain stem, the eyes will tonically deviate toward the cold-irrigated ear, sometimes with nystagmus in the opposite direction. Both ears should be tested, but there should be an interval of at least 5 minutes before testing the second ear. If a cervical spine computed tomography (CT) scan shows cervical spine stability, it also can be tested using sudden head movements. For this test, the head is briskly rotated, laterally as well as vertically to elicit the oculocephalic reflex. In an intact brain stem, the eyes move in the opposite direction from which the head is turned.

Facial movement is tested as above with noxious stimulation, which can also include stimulation of the nasal hair and septum with a cotton-tipped swab, which may elicit a grimace response. Lower cranial nerve function is tested with posterior pharyngeal stimulation to test for a gag reflex, and deep bronchial suctioning to test for a cough reflex.

Motor Examination

The motor response can give a clue to localization. The motor examination includes observing the patient for spontaneous movements, testing tone, and

TABLE 373-5 FOUR SCORE COMA ASSESSMENT SCALE*

EYE RESPONSE
E4 = Eyelids open or closed, tracking or blinking to command
E3 = Eyelids open but not tracking
E2 = Eyelids closed but open to pain
E1 = Eyelids remain closed with pain stimuli
MOTOR RESPONSE
M4 = Thumbs up, fist, or peace sign
M3 = Localizing to pain
M2 = Flexion response to pain
M1 = Extension response to pain
M0 = No response to pain or generalized myoclonic status epilepticus
BRAIN STEM REFLEXES
B4 = Pupillary and corneal reflexes present
B3 = One pupil dilated and unreactive to light
B2 = Pupillary or corneal reflexes absent
B1 = Pupillary and corneal reflexes absent
B0 = Absent pupillary, corneal, or cough reflexes
RESPIRATION
R4 = Regular breathing pattern
R3 = Cheyne-Stokes breathing pattern
R2 = Irregular breathing pattern
R1 = Triggers or breathes above the ventilator rate
R0 = Apnea or breathes at the ventilator rate

*For nontraumatic coma and other disorders of consciousness.
From Wijdicks EFM. *The Comatose Patient*. 2nd ed. New York: Oxford University Press; 2014.

testing responses elicited by noxious stimulation of the extremities, typically starting with deep nail bed pressure, and then with noxious stimulation more proximally on the limb. The movement in response to stimulation in both locations should be noted, including whether they are symmetrical. Stereotyped responses are most consistent with a posturing reflex. Responses can be graded as localization, purposeful withdrawal, reflex flexor (decorticate) posturing, reflex extensor (decerebrate) posturing, and none.

Decorticate or flexor posturing suggests a lesion above the level of the red nucleus in the brain stem, whereas decerebrate or extensor posturing suggests a brain stem lesion. Symmetrical findings are more consistent with a toxic-metabolic or global insult, whereas asymmetrical findings suggest a focal structural injury. However, exceptions include hypoglycemia and hyponatremia, which notoriously can cause focal neurologic findings in the absence of a structural injury and which are often reversible. Other motor findings include tonic or clonic movements consistent with seizure, or myoclonic (nonrhythmic) jerking, which is a nonspecific finding associated with many disease states. Unrelenting myoclonic jerking (myoclonic status epilepticus) in the setting of a global anoxic brain injury tends to carry a poorer prognosis.

Grading Coma

Multiple scales are helpful for grading and evaluating coma, estimating prognosis, and assessing changes over time. The Glasgow Coma Scale (Table 368-1) is widely used, especially to evaluate patients with traumatic brain injury; its components include verbal, motor, and eye responses. The more recent FOUR score (Table 373-5) is more comprehensive for brain stem function (including respiratory patterns) and responsiveness, and it is useful in evaluating all causes of coma.

Laboratory Testing

Emergency laboratory testing should include a complete blood count, electrolytes, serum glucose, liver and kidney function tests, a coagulation profile, thyroid function tests, an ammonia level, arterial blood gas analysis, a blood alcohol concentration, and blood and urine drug screens. If intoxication is likely, particularly in the absence of ketones, uremia, or an elevated lactate level, anion and osmolar gaps should be measured. Urine or blood serum for opioids, benzodiazepines, and other toxins (e.g., pesticides, heavy metals, and atypical alcohols) should be obtained. Blood, urine, and sputum cultures should be obtained, as should an electrocardiogram and chest radiograph.

Expeditious neuroimaging often starts with a noncontrast head CT, but a CT angiogram should be performed if a vascular lesion is suspected. If the patient was found unconscious or if there is any question of trauma, a cervical spine CT can be obtained concomitantly. Magnetic resonance imaging (MRI) typically is not helpful in the acute setting and may be contraindicated in an unstable patient in whom close monitoring is required. The one exception would be a possible acute brain stem or posterior fossa infarction, which may not be seen on noncontrast head CT but should be detected by MRI with diffusion-weighted imaging.

If the head CT shows no evidence of mass lesion or edema, a lumbar puncture should be performed to exclude meningitis (Chapter 381) or other causes of central nervous system inflammation. An urgent electroencephalogram (EEG) should be considered to exclude nonconvulsive seizures or status epilepticus, but continuous EEG monitoring does not appear to improve outcomes in patients without clinical seizures, even though it can detect subclinical seizure activity.[A1]

TREATMENT

Management of coma requires simultaneous diagnostic, supportive, and treatment measures (Table 373-6). Specific treatments relate to the underlying cause, and some conditions require urgent attention, such as head trauma (Chapter 368), cerebrovascular events (Chapter 375), severe hypoglycemia or hypoglycemia (Chapter 210), meningitis (Chapter 381), and encephalitis (Chapter 383). Emergency stabilization of respiratory and circulatory functions is paramount for all patients. Early treatment of seizures (Chapter 372) can prevent progression to status epilepticus.

In patients without focal findings or obvious meningitis, 50% dextrose (25 g IV for potential hypoglycemia), empiric thiamine (100 mg IV to prevent glucose-induced Wernicke-Korsakoff syndrome), naloxone (0.4 to 2 mg IV for potential opioid overdose), and flumazenil (0.2 mg IV to reverse the action of benzodiazepines) can be administered during the diagnostic evaluation. If fever, nuchal rigidity, or leukocytosis are present, the patient should empirically be treated for bacterial meningitis (Chapter 381) and viral encephalitis (Chapter 383) while awaiting the results of polymerase chain reaction testing and/or cultures of the cerebrospinal fluid.

Raised intracranial pressure must be treated urgently. Hyperventilation by bag or ventilator to a goal Pco_2 of 30 mm Hg will rapidly lower the intracranial pressure, but the effect is transient. If this maneuver is undertaken, care must be given to reestablish normocapnia slowly and at the appropriate time. Hyperosmolar therapy with mannitol (0.5 to 1.5 g/kg every 6 hours) or hypertonic saline (1.5 to 7% as a continuous drip or 23.4% as a bolus) has a more durable effect. Glucocorticoids may be used in patients with brain tumors (Chapter 175) or bacterial meningitis (Chapter 381), but they are not effective in traumatic brain injury, vascular insults, or metabolic causes of coma. For refractory elevations in intracranial pressure, barbiturates (typically pentobarbital, with the dose titrated based on EEG findings) may be helpful; but at that stage (or earlier), a surgical craniectomy should be considered for decompression[A2] or evacuation of any mass lesion. For global anoxic brain injury after cardiac arrest, therapeutic normothermia is recommended.[A3]

PROGNOSIS

The prognosis of coma, which is highly variable, depends on its cause, stage, duration, degree of structural brain damage, and potential reversibility. Regular repeat evaluation (Table 373-7) must be performed to assess progress and to help predict potential recovery. Prediction rules apply only to specific causes, and common sense must prevail. For example, patients with isolated respiratory arrest who never lose perfusion may be comatose for extended periods of time but usually achieve a good neurologic recovery.

For global anoxic brain injury owing to cardiac arrest, however, reliable predictors of poor outcome include absent pupillary or corneal reflexes 72 hours after arrest (or 72 hours after rewarming if the patient undergoes therapeutic hypothermia),[6,7] as well as bilateral absence of cortical responses on somatosensory evoked potential testing 48 hours after arrest (or 48 hours after rewarming if the patient undergoes therapeutic hypothermia). Other potential prognostic factors include malignant patterns (burst-suppression, severe attenuation) on the EEG, elevated serum biomarker levels (including neuron-specific enolase, neurofilament light chain, tau protein, and glial fibrillary acidic protein), and evidence of severe anoxic injury on CT or MRI. Caution should be used to avoid premature withdrawal of life-sustaining therapies, because patients with an indeterminant predicted outcome may achieve good functional outcomes after delayed recovery.

Some patients may recover within the first few days after a hypoxic event but then regress days to weeks later with a syndrome of delayed post-hypoxic leukoencephalopathy, which is thought to be a demyelinating process. This outcome is more common in patients with prolonged hypoxia/anoxia followed by cardiac arrest with ischemia. Neuroimaging shows diffuse bilateral

TABLE 373-6 EMERGENCY MANAGEMENT OF COMATOSE PATIENTS

1. Ensure oxygenation
2. Maintain circulation
3. Administer 50% dextrose, 25 g IV, and control blood glucose levels
4. Lower raised intracranial pressure
5. Stop seizures with lorazepam, 1-2 mg IV
6. Search for and treat infections
7. Restore acid-base and electrolyte balance
8. Normalize body temperature
9. Administer thiamine, 50 mg IV, and multivitamins
10. Consider administration of opioid antagonists (naloxone, 0.4-2 mg IV)
11. Consider administration of benzodiazepine antagonists (flumazenil, 0.2 mg IV)
12. Control agitation
13. Protect the eyes
14. Consider inducing therapeutic hypothermia for neuroprotection following cardiac arrest

Modified from Posner JB, Saper CB, Schiff ND, Claassen J. *Plum and Posner's Diagnosis of Stupor and Coma*. 5th ed. New York: Oxford University Press; 2019.

TABLE 373-7 SERIAL TESTING IN COMATOSE PATIENTS AFTER CARDIAC ARREST

TEST	NO HYPOTHERMIA	HYPOTHERMIA
Clinical Exam	Pupillary and corneal reflex testing for prognosis at 72 hours after complete rewarming	Pupillary and corneal reflex testing for prognosis at 72 hours after complete rewarming
EEG	Daily, continuous if possible. If not, repeat EEG after discontinuing sedating medications	Daily, continuous if possible. If not, repeat EEG during and following rewarming, and after discontinuing sedating medications
SSEP	48-72 hours after complete rewarming	48-72 hours after complete rewarming
NSE	Trend daily over first 3-5 days after complete rewarming	Same
CT	On admission; repeat on day 2-3 after complete rewarming for prognosis	Same
MRI	Consider on day 2-7 after complete rewarming if CT unrevealing	Same

CT = computed tomography; EEG = electroencephalogram; MRI = magnetic resonance imaging; NSE = neuron specific enolase blood level; SSEP = somatosensory evoked potentials.

hemispheric demyelination that spares the cerebellum and brain stem. Some patients can recover slowly over 3 to 12 months, but often with substantial neurologic sequelae. Others may be left in a vegetative or minimally conscious state.

UNRESPONSIVE WAKEFULNESS SYNDROME

The unresponsive wakefulness syndrome, formerly known as the vegetative state, is a disorder of consciousness in which wakefulness is achieved but awareness of the self or environment is absent on clinical testing (Table 373-8).[8] The unresponsive wakefulness syndrome can be transient or permanent, depending on the underlying cause and degree of injury. It is a state into which comatose patients may emerge, but it also may be the final state. Adjectives such as "persistent" or "permanent" should be avoided, because they are arbitrary and lead to confusion by confounding the diagnosis and prognosis.

EPIDEMIOLOGY

The unresponsive wakefulness syndrome is caused by diffuse or multifocal brain lesions that disrupt the thalamocortical pathways but spare the brain stem and hypothalamus. Its prevalence is unknown, but the prevalence of a chronic, stable unresponsive wakefulness syndrome is about 19 per million population.

PATHOBIOLOGY

Causative lesions can be located in the bilateral thalami, diffusely in the cerebral cortices, or diffusely in the white matter that connects the thalami to the cortex. The two most common underlying causes are hypoxic-ischemic injury to the thalami and cortex in the setting of cardiac arrest (Chapter 50) and diffuse axonal injury caused by traumatic brain injury (Chapter 368) with torque force. These causes have different pathologies. Hypoxic-ischemic injury affects cortical, thalamic, basal ganglia, and cerebellar neurons, whereas diffuse axonal injury shears and disconnects the axons at the gray matter–white matter junctions diffusely and multifocally, often with profound white matter injury that includes the brain stem.

TABLE 373-8 DIAGNOSIS OF THE UNRESPONSIVE WAKEFULNESS SYNDROME

I. Absence of:
- Awareness of self or environment
- Purposeful or voluntary behavioral response to all stimuli
- Language comprehension or expression

II. Presence of:
- Intermittent wakefulness manifested by the presence of sleep-wake cycles
- Autonomic functions
- Cranial nerve and spinal reflexes

III. Potential behavioral repertoire:
- Breathe spontaneously
- Spontaneous roving eye movements
- Utter sounds but no words
- Grimace to pain, make facial expressions
- Yawn, make chewing jaw movements, swallow saliva
- Move limbs nonpurposefully, arch back, decorticate limb posturing
- Flexion withdrawal from noxious stimuli
- Move head or eyes briefly toward sound or movement
- Auditory startle

CLINICAL MANIFESTATIONS AND DIAGNOSIS

Patients have wakefulness but no evidence of responsiveness. A careful clinical examination is mandatory to search for any evidence of awareness, because up to 40% of patients diagnosed with the unresponsive wakefulness syndrome are actually in a minimally conscious state (see later).

As a clinical syndrome, unresponsive wakefulness presents as a spectrum of severity. Most patients have slow wave activity on EEG, but the most severely affected patients may have nearly flat EEGs. However, some patients in the unresponsive wakeful state can generate appropriate EEG responses to distinct commands, thereby suggesting residual cognitive function and conscious awareness. A subset of patients who are thought to have the unresponsive wakefulness syndrome possess awareness based on their ability to perform ideational tasks on command with corresponding changes on functional MRI. Such findings identify patients who are more appropriately categorized as minimally conscious.

TREATMENT AND PROGNOSIS

There are no proven treatments to reverse or improve the chronic, stable unresponsive wakefulness syndrome.[9] Aggressiveness of treatment should ideally be guided by a patient's previously stated wishes (Chapters 2 and 3),[10] which unfortunately are often unknown. Patients in the unresponsive wakefulness state often require nearly the same nursing, physical therapy, and nutritional care as patients in coma. Referral to specialized neurorehabilitation centers may be appropriate.

Patients who have some recovery from unresponsive wakefulness usually have initially preserved pupillary light reflexes and nociceptive responses, paroxysmal sympathetic hyperactivity, and preserved cortical somatosensory evoked potential responses. If patients with unresponsive wakefulness from nontraumatic causes do not regain awareness within 3 months of the insult, they have only a small chance of experiencing neurologic improvement. The prognosis in patients with unresponsive wakefulness caused by head trauma (Chapter 368) is less clear, and patients typically require at least a year or two to provide a similar level of certainty. Functional neuroimaging is a promising but as yet unproven way to help to identify patients who may be destined to recover awareness, particularly after traumatic brain injury.

MINIMALLY CONSCIOUS STATE

The minimally conscious state, which is a profound disorder of consciousness, is more common than the unresponsive wakefulness syndrome and must be distinguished from it. The minimally conscious state is defined by clear

TABLE 373-9 DIAGNOSIS OF THE MINIMALLY CONSCIOUS STATE

Globally impaired responsiveness
Limited but discernable evidence of awareness of self and environment as demonstrated by the presence of one or more of the following behaviors that occur in a contingent relationship to relevant environmental stimuli and are not simply reflexive movements:
- Follow simple commands
- Gesture yes/no answers
- Make intelligible vocalizations or gestures in direct response to a question's linguistic content
- Reach for objects that demonstrates a clear relationship between object location and direction of reach
- Touch and hold objects in a manner that accommodates the size and shape of the object
- Sustain visual pursuit to moving stimuli
- Smile or cry appropriately to linguistic or visual content of emotional but not to affectively neutral topics or stimuli

partial or intermittent evidence of awareness of self and environment (Table 373-9). Patients with the minimally conscious state have necessarily suffered a less severe injury than patients with unresponsive wakefulness syndrome.

The minimally conscious state has now been separated into two categories. Minimally conscious+ denotes the presence of at least an intermittent ability to follow commands, whereas minimally conscious– lacks that ability.

Disruptions in an underlying functionally connected network that is involved in consciousness, the "default mode network," can be explored by neuroimaging as well as by EEG. Some patients have behaviors that imply preservation of language function, which may be evidenced by the reproducible ability to follow commands after object recognition or intelligible verbalization.

TREATMENT AND PROGNOSIS

Patients in the minimally conscious state may respond to environmental and sensory stimuli in a nonreflexive manner. They also respond to stimulants, such as levodopa/carbidopa (25/100 mg, which stimulates thalamic dopaminergic neurons, thereby likely leading to improvement in consciousness and responsiveness) and amantadine.[11] Amantadine (100 mg twice daily initially, later increased to 200 mg twice daily) can accelerate the pace of early recovery but may not ultimately affect overall prognosis.

Patients in the minimally conscious state require extensive rehabilitation services, and their prospects of recovery are better than for patients with unresponsive wakefulness syndrome, likely because of their ability to participate, at least at a minimal level.

Prognostic data are limited for the minimally conscious state, other than for recovery in the subset of patients with traumatic brain injury (Chapter 368). Both fluorodeoxyglucose-positron emission tomography and functional MRI are useful tools for evaluating patients, and the EEG may also provide information about the extent of brain injury and likelihood of recovery.

THE LOCKED-IN SYNDROME

The locked-in syndrome, a state of profound paralysis, is not a disorder of consciousness but may be mistaken for one.[12] In its classic form, it is produced when a large infarction or hemorrhage in the pontine tegmentum and base produces quadriplegia, pseudobulbar palsy, and paralysis of horizontal eye movements. Once the acute encephalopathy resolves, locked-in patients usually remain awake and alert, breathe spontaneously, and have normal consciousness and cognition, to the extent that they can be tested accurately. Inexperienced examiners may incorrectly diagnose locked-in patients as being comatose because of their profound paralysis, pinpoint pupils, and seeming unresponsiveness. A similar state of profound global paralysis with intact cognition can be produced by advanced amyotrophic lateral sclerosis (Chapter 387), Guillain-Barré syndrome (Chapter 388), or critical illness polyneuropathy (Chapter 388).

Patients can be taught to communicate with voluntary vertical eye movements and eyelid movements, which are typically their only retained volitional movements, because they are controlled rostral to the pons. Most affected patients, particularly older patients with comorbid illnesses, die within a few months, but some otherwise healthy young patients who have become locked in as a result of basilar artery occlusion have survived for many years. Occasional patients may recover function to become independent. Computerized systems targeting remaining voluntary eye movements and other intact voluntary movements can help patients communicate.

TABLE 373-10 TESTS FOR BRAIN DEATH IN ADULTS

I. Preconditions showing irreversibility: all necessary
- Presence of a structural brain lesion sufficient to produce all the clinical signs
- No neuromuscular blockade (use electroneurography if uncertain)
- Absence of reversible significant toxic or metabolic encephalopathy:
  - No depressant drug intoxication
  - No severe acid-based, electrolyte or endocrine disorders, or severe hyperammonemia
  - Temperature at least 36° C
  - Systolic blood pressure at least 100 mm Hg

II. Signs showing complete cessation of all clinical brain functions: all necessary
- Coma: no spontaneous movements, no response to any stimuli, and no brain-mediated movements
- Brain stem areflexia: all necessary
  - Absent pupillary light and dark reflexes
  - Absent corneal reflexes
  - Absent facial movement to noxious stimuli, both on corpus and cranium
  - Absent oculocephalic reflexes (only tested in patients with integrity of the cervical spine)
  - Absent vestibulo-ocular reflexes tested by caloric irrigation of the external auditory canal with ice water for 60 seconds continuously
  - Absent pharyngeal and tracheal reflexes to pharyngeal stimulation and deep bronchial suctioning
- Apnea: no breathing or respiratory effort when the $Paco_2$ ≥60 mm Hg while preserving the Pao_2

III. Ancillary tests: performed only when the clinical examination cannot be adequately or confidently completed
- Neuroimaging showing complete absence of intracranial blood flow (preferred over electrophysiology testing):
  - Conventional angiography
  - Transcranial Doppler ultrasound
  - Single-photon emission computed tomography (SPECT)

BRAIN DEATH

Brain death is not only a state of unconsciousness, it is a state of complete and irreversible loss of all brain function that constitutes legal death in the United States and most of the developed world.[13,14] Diagnosis of brain death is a medical imperative, with medical, legal, and ethical implications, as well as a potential for organ donation (Chapter 2). It is a diagnosis that must be made with 100% accuracy.

EPIDEMIOLOGY AND PATHOBIOLOGY

The most common causes of brain death include traumatic brain injury (Chapter 368), global anoxic brain injury (e.g., cardiac arrest, Chapter 50), intracranial hemorrhage (including subarachnoid hemorrhage [Chapter 377] and primary intracerebral hemorrhage), meningitis (Chapter 381), or ischemic stroke (Chapter 376). Cerebral edema and/or hydrocephalus leads to severely elevated intracranial pressure. When the mean arterial pressure equals the intracranial pressure, the cerebral perfusion pressure is thus zero, meaning that there is no effective forward intracranial flow, which is incompatible with life. Widespread ischemic neuronal death ensues.

CLINICAL MANIFESTATIONS AND DIAGNOSIS

Before clinical testing for brain death, strict criteria must be met (Table 373-10).[15] The cause of the neurologic catastrophe must be known, and the state must be known to be completely irreversible. If there is any question as to the potential for reversibility, the patient should not be tested for brain death. There must be an absence of confounding, including from drug/alcohol intoxication; metabolic, acid-base, or endocrine disturbances; or pharmacologic paralysis. The patient must be normotensive (adult systolic blood pressure at least 100 mm Hg) and normothermic (at least 36° C).

Brain dead patients have no clinical evidence of brain function whatsoever. There are three cardinal clinical features: coma, brain stem areflexia, and apnea. The patient must have complete unresponsiveness, with the testing methods as described earlier, including both cranial and corporeal noxious stimulation, which should produce only spinally mediated responses, if any. The pupils are typically midposition (3 to 7 mm) and fixed, even when checked with an arduous method, such as a magnifying glass or pupillometer; small pupils should alert the clinician to the possibility of intoxication or a pontine lesion.

The corneal reflex, likewise, should be tested with a potent stimulus, such as pressing the cornea at the iris-sclera junction with a cotton-tipped applicator and with enough pressure to see the eye move. Oculocephalic and maximal oculovestibular testing should show no eye movement in brain death, and no gag or cough reflexes should be present.

A number of motor signs of spinal origin can be seen in brain death, such as intact deep tendon reflexes, triple flexion (stereotyped flexion at the ankle, knee, and hip to noxious stimulation at multiple locations), and Babinski sign, as well as other movements that fall under the term "Lazarus signs" (including head turning, arching of the back, and crisscrossing of the arms across the body). However, decorticate posturing and decerebrate posturing are brain-mediated responses and are not consistent with brain death.

To test for apnea, the ventilator should be adjusted to achieve normocarbia and preoxygenation to a Pao_2 of greater than 200 mm Hg. The patient is observed for at least 8 to 10 minutes off the ventilator for any respiratory effort, and the test should be aborted if a breath is observed or if the patient develops hypotension (systolic blood pressure <90 mm Hg) or hypoxia (O_2 saturation <85% for at least 30 seconds). The Pco_2 must rise to 60 mm Hg or greater (or at least 20 mm Hg above baseline for a patient who chemically retains CO_2 owing to lung disease). The time of death is when an arterial blood gas value consistent with apnea is reported by the laboratory.

If clinical testing, including the apnea test, cannot be performed or is precluded by hemodynamic instability, currently accepted alternative tests include intracranial blood flow studies (conventional angiography, transcranial Doppler, or single-photon emission computed tomography [SPECT]). When alternative testing is required, the time of death is the time the study is formally interpreted and signed by the attending physician.

TREATMENT

Once brain death is diagnosed, the patient is legally dead. Further management is pursued only in the setting of possible organ donation. Otherwise, the ventilator is removed and all lines and monitors are discontinued. Physicians should be aware of local laws or policies that may restrict diagnosing death by brain criteria in patients who belong to certain religious groups that do not adhere to the concept of brain death.

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374 SLEEP DISORDERS

BRADLEY V. VAUGHN AND ROBERT C. BASNER

DEFINITION

Sleep is an active state of decreased responsiveness during which multiple vital functions occur to promote higher cognitive functioning and overall good health. During this physiologic state, the brain restores several metabolic processes, clears waste products, and furthers synaptic reorganization to promote alertness, memory, and learning. To achieve these goals, the brain cycles through discrete stages of sleep that allow progressive revitalization to support neuronal function. The non–rapid eye movement (non-REM) sleep stages appear to affect the glia and neurons in functions such as replenishing of energy stores and recycling of neurotransmitters. In addition, the glymphatic system clears protein waste products of brain metabolism, predominantly during slow wave sleep. Synapses are pruned and reinforced during the cycling of slow wave and rapid eye movement (REM) sleep.[1] Conversely, the disruption of sleep is associated with a variety of health issues, as well as impaired performance and psychosocial interactions. Second in frequency only to pain, sleep-wake complaints lead one in three individuals to seek medical attention. Untreated sleep disorders and disruption may also exacerbate symptoms of other diseases by worsening a preexisting disorder or impairing the ability to cope with or counter the symptoms of the original disease. Thus, clinicians should recognize that such signs and symptoms may be related to dysfunctional sleep.

PATHOBIOLOGY

Complex humoral, neurochemical, and neuronal networks determine the sleep-wake state. Dynamic in organization, sleep is composed of REM and non-REM sleep (denoted as stage R). Non-REM is divided into three stages (N1, N2, and N3). Each stage has a distinct physiologic regulation, and each contributes to health and improved brain function.

Wakefulness involves activation of the monoaminergic neuronal groups, basal forebrain cholinergic neurons, and the brainstem reticular activating system (E-Fig. 374-1). The reticular activating system promotes the relay of sensory information to the cerebral hemispheres, and the forebrain cholinergic and monoaminergic neurons promote attention of the hemispheric networks to sensory information.

With the onset of sleep, information from two major drives (homeostatic, the chemicals that build during wakefulness; and circadian, the internal body clock) influence the ventral lateral preoptic nucleus to actively suppress the networks of wakefulness and allow the initiation of non-REM sleep (E-Fig. 374-2). Non-REM sleep typically starts as stage N1, with slowing of the electroencephalogram (EEG), and slow eye movements (Table 374-1). Stage N1, which is associated with the feeling of drowsiness, accounts for about 5% of nocturnal sleep time. Although minimal sensory processing can occur, memory is not typically stored. Blood pressure may decrease slightly, and breathing becomes more periodic.

The hallmark of stage N2 sleep is an EEG with sleep spindles and K complexes. N2 typically represents about 50% of a night's sleep for an adult. Although stage N2 is considered light sleep, it is associated with less responsiveness to stimuli and to changes in CO_2 and O_2 than stage N1. Stage N3 is characterized by slow waves (0.5 to 2.0 Hz, >75 μV) in the EEG. These slow waves are more prominent in brain areas that are more heavily used during the preceding awake period. In stage N3, which constitutes 20% of nocturnal sleep, the individual is difficult to arouse and has rhythmic breathing that is less responsive to elevated CO_2 and low O_2 than during stage N2. This stage is most associated with metabolic rebalancing of the neurons and glia, as well as the pruning of lesser used synapses.

REM sleep (stage R) is generated by cholinergic neurons in the subcoeruleus nucleus in the brain stem, which then activate other neuronal groups to produce the associated rapid eye movements, active theta and alpha frequency EEG waveforms, skeletal muscle paralysis, and reduced temperature regulation. Most vivid dreaming occurs in stage R, but dreams can occur in other stages. Because most skeletal muscles, including accessory respiratory muscles, are paralyzed in stage R, ventilation is solely dependent on the diaphragm. This stage is associated with the least amount of responsiveness to low O_2 and elevated CO_2. Stage R typically encompasses about 20% of the night's sleep and is ended by activation of norepinephrine and serotonergic neurons (E-Fig. 374-3). Age influences the distribution of sleep stages: REM sleep occupies 50% of sleep at birth and then gradually declines to 25% by age 3 years. Similarly, slow wave sleep is prominent in children and declines in men in their 30s and in women by age 40 to 50 years.

Sleep stages graphed through the night demonstrate the dynamic interplay of the various stages. As seen in an idealized hypnogram (Fig. 374-1), sleep has repeating cycles of approximately 90 minutes. These cycles show a predominance of stage N3 in the first two cycles, and a gradual lengthening of the periods of stage R through the night. This cycling and progression of sleep stages appear to aid in the revitalization of the brain.

Many models that consider the array of neurochemical pathways that influence sleep can theoretically explain its physiologic regulation. The most accepted two-driver model uses the homeostatic and circadian drivers to explain sleep-wake state. Other issues such as psychological status also play a role. The homeostatic drive is the accumulation of substances that promote

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ABSTRACT

Sleep is essential to good health and a sense of well-being. This normal state of decreased responsiveness restores bodily processes, and it also promotes alertness, memory, and learning. Conversely, the disruption of sleep is associated with a variety of health issues, as well as impaired performance and psychosocial interactions. This chapter reviews normal sleep physiology, common sleep disorders (including sleep-related breathing disorders), and their daytime manifestations. This chapter also reviews common therapies used to treat these disorders. Thus, the goal of the chapter is to help clinicians recognize the signs and symptoms related to dysfunctional sleep and the method to approach sleep issues.

KEYWORDS

sleep
sleep disorders
sleep apnea
insomnia
restless legs syndrome
parasomnia

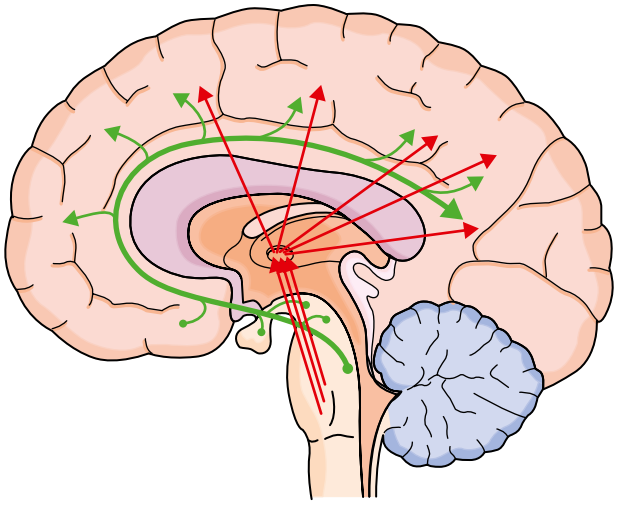

E-FIGURE 374-1. **The two components that produce wakefulness are the reticular activating system (*red*), which permits sensory input to be relayed by the thalamus, and the monoaminergic nuclei and basal forebrain cholinergic system, which promote responsiveness of the cerebral hemispheres.** (Adapted from Saper CB, Scammell TE, Lu J. Hypothalamic regulation of sleep and circadian rhythms. *Nature*. 2005;437:1257-1263.)

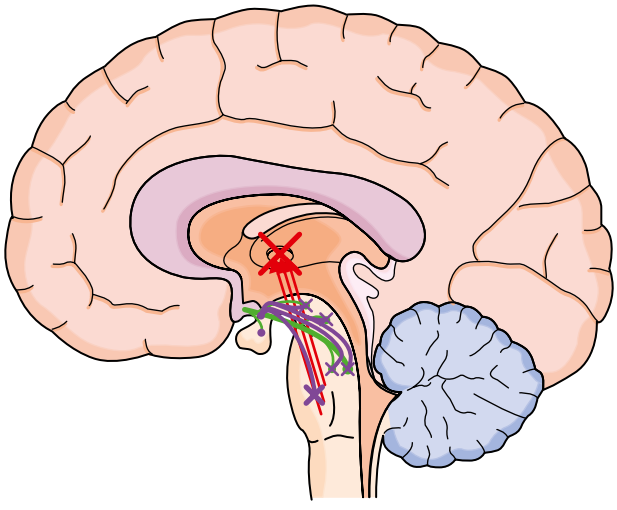

E-FIGURE 374-2. **Activation of the ventral lateral preoptic nucleus subsequently inhibits (*purple arrows*) the reticular activating system (*red*) and the monoaminergic nuclei (*green*), thereby producing non–rapid eye movement sleep and blocking sensory input to the hemispheres.** (Adapted from Saper CB, Scammell TE, Lu J. Hypothalamic regulation of sleep and circadian rhythms. *Nature*. 2005;437:1257-1263.)

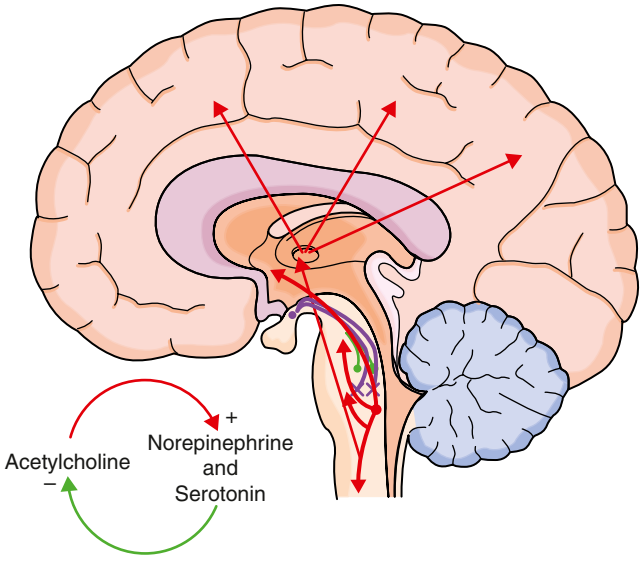

E-FIGURE 374-3. **Rapid eye movement sleep (REM) sleep is activated from the subcoeruleus nucleus, which uses acetylcholine (*red arrows*), and further deactivation (*purple arrows*) of norepinephrine- and serotonin-producing neurons (*green*).** The reciprocal relationship of REM on (cholinergic neurons) and REM off (norepinephrine and serotonin neurons) is depicted in the lower corner. (Adapted from Saper CB, Scammell TE, Lu J. Hypothalamic regulation of sleep and circadian rhythms. *Nature*. 2005;437:1257-1263.)

TABLE 374-1 SLEEP STAGE PARAMETERS*

STAGE	EEG FINDINGS	EYE MOVEMENTS (EOG)	SUBMENTAL EMG	ASSOCIATED PHYSIOLOGY
Wakefulness (W)	**More than 50% of an epoch has the posterior dominant rhythm present**	**Rapid eye movements** to slow movements. **Blinking** may be present	**Normal to high muscle tone**	Memory registration, voluntary control over breathing
Stage N1	**Attenuation of the posterior dominant rhythm with mixed theta frequency low-amplitude background activity**	*Slow rolling eye movements*	*Variable but less than wake*	Automatic behavior can occur; diminished cognitive processing, periodic breathing
Stage N2	**K-complexes and/or sleep spindles.** *Low-amplitude mixed-frequency EEG*	*No eye movements, but slow eye movements may persist*	*Variable amplitude, typically lower than W and higher than R*	No memory, decreased arousal to stimuli, less response to elevated CO_2 and low oxygen
Stage N3	**Slow wave activity (0.5-2 Hz, >75 μV) for >20% of an epoch.** Sleep spindles and K complexes may persist	*No eye movements seen*	*Variable amplitude, typically lower than N2 and can be as low as R*	No memory, rhythmic breathing pattern with less responsiveness to elevated CO_2 and low O_2
Stage R (REM sleep)	**Low-amplitude mixed-frequency EEG.** *Sawtooth waves*	**Rapid eye movements**	**Low muscle tone**	Similar response to stimuli as light sleep, irregular breathing pattern, least response to elevated CO_2 and low O_2

*Sleep staging requirements. **Boldfaced** items are requirements for staging. *Italicized* items are nonrequired associated findings that may be present in that stage.
CO_2 = carbon dioxide; EEG = electroencephalogram; EMG = electromyogram; EOG = electro-oculogram; O_2 = oxygen.
Adapted from the American Academy of Sleep Medicine. *The AASM Manual for the Scoring of Sleep and Associated Events*. 2nd ed. version 2.4. Westchester, IL: American Academy of Sleep Medicine; 2017.

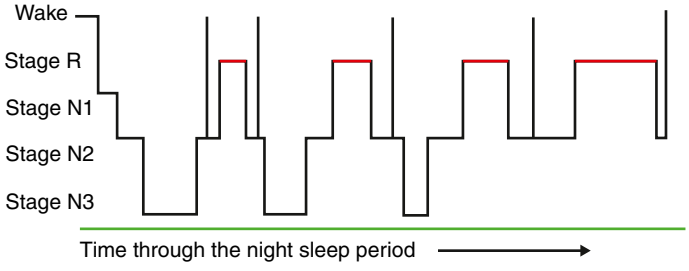

FIGURE 374-1. **Hypnogram showing sleep stages across a sleep period.**

sleepiness and increase while the person is awake. Once asleep, these substances are metabolized. Mental and physical activities increase this drive by producing neuronal byproducts (e.g., adenosine), whereas caffeine blunts this drive by blocking adenosine. In contrast, the circadian rhythm drive promotes wakefulness and, through its predictable cycle, prepares the body for anticipated activities. The circadian rhythm is a naturally occurring rhythm that is slightly longer than 24 hours but is readjusted each day to maintain alignment with the natural day-night cycle. This cycle is driven by a genetic transcription-translation feedback loop that occurs in every cell of the body. These cells are synchronized by a master clock in the suprachiasmatic nucleus by complex chemical signaling, including through the hormone melatonin, which is released in response to darkness. The circadian rhythm is primarily adjusted by bright light and to a lesser extent by exercise, food, and social interactions. When the circadian rhythm is stronger than the homeostatic drive, the person is awake, and when the homeostatic drive is stronger than the circadian rhythm, the person is sleepy (E-Fig. 374-4). This theoretical model helps explain aspects of sleep-wake regulation, such as the periods of postlunch sleepiness or evening wakefulness.

CLINICAL MANIFESTATIONS

Most patients who seek medical help for sleep issues present with one of three complaints: (1) excessive sleepiness, (2) difficulty attaining or sustaining sleep, (3) or unusual events associated with sleep. Excessive sleepiness, which is the propensity to fall asleep, should be distinguished from fatigue or lack of energy. Insomnia, the difficulty initiating or maintaining sleep at night with resulting daytime sequelae, may be a clue to daytime issues, and nocturnal events may be a clue to possible neurologic issues. Other common presenting symptoms include morning headaches, lapses of attention, or diffuse muscle aches.

DIAGNOSIS

Both subjective information and objective tests are used to investigate sleep complaints. Questionnaires such as the Pittsburgh Sleep Quality Index provide a broad overview of sleep symptoms, including bedtime, wake time, activities, medications, and other substances that could influence sleep. Sleep diaries can also give a subjective report of the daily schedule (Fig. 374-2).

Objective testing of sleep includes polysomnography, actigraphy, multiple sleep latency testing, and maintenance of wakefulness testing. Polysomnography (Fig. 374-3) assesses both sleep stage and associated physiology. Sleep stage is determined by three parameters: EEG, electro-oculogram, and submental electromyogram activity. Measures assessing associated physiology include respiratory function (airflow, effort, and gas exchange), limb muscle activity, and the electrocardiogram. Polysomnography, which assesses sleep-stage–associated physiology, is most useful for evaluating sleep disruption, including sleep apnea, excessive movements, and parasomnias (Table 374-2). More limited overnight recordings may focus on strictly respiratory measurements. Actigraphy monitors movement, typically of a nondominant extremity, over 7 to 28 days to assess patterns of activity (Fig. 374-4). When combined with a sleep diary, actigraphy estimates total sleep time and assesses the sleep-wake schedule. Many wearable and nonwearable consumer devices claim to provide an assessment of sleep, but these typically are much less accurate than medical grade devices and are not currently reliable as diagnostic tools.[2]

Two daytime tests can help estimate the degree of physiologic sleepiness. The multiple sleep latency test quantifies objective sleepiness based on the time to onset of sleep across five daytime naps; it is validated for diagnosing narcolepsy when paired with a polysomnogram and clinical criteria. The maintenance of wakefulness test, which quantifies the propensity to stay awake across four 40-minute epochs, can provide objective evidence of a person's ability to stay awake.

HYPERSOMNIA

Sleepiness is normal just before a typical sleep period or after prolonged wakefulness. About 5 to 20% of adults have hypersomnia, in which sleepiness occurs in inappropriate settings and affects quality of life due to lapses of attention, decreased mood, or diminished cognitive abilities.[3] After chronic sleep deprivation, the perception of sleepiness is reduced such that individuals become accustomed to their impairment and fail to recognize their degree of sleepiness.

DIAGNOSIS

Clinicians should question hypersomnic patients for clues about sleep restriction, sleep disruption, neurologic issues, medication effect, or medical or psychiatric causes (Fig. 374-5). Information regarding sleep habits, including week and weekend schedules, as well as environment, may disclose important contributing factors. Patients with sleep apnea, narcolepsy, excessive periodic limb movements, circadian rhythm disorders, and parasomnias may have excessive daytime sleepiness as their main complaint. A history of snoring, observed apnea, morning headaches, cataplexy, sleep paralysis, hypnogogic hallucinations, or altered sleep schedule suggests other specific sleep disorders. Excessive sleepiness can also result from many medical disorders and medications. Patients with heart (Chapter 45), kidney (Chapter 117), or liver failure (Chapter 139), rheumatologic disease, or endocrinologic disorders such as

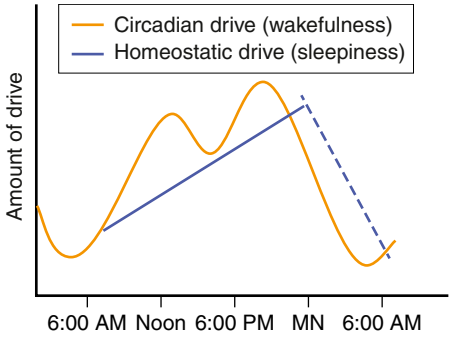

E-FIGURE 374-4. Idealized graph depicting the two-process model. The circadian driver promotes wakefulness (*orange*), and the homeostatic drive promotes sleep (*blue*). The dynamic interaction of the two drives is shown.

TWO WEEK SLEEP DIARY

INSTRUCTIONS:
1. Write the date, day of the week, and type of day: Work, School, Day Off, or Vacation.
2. Put the letter "C" in the box when you have coffee, cola or tea. Put "M" when you take any medicine. Put "A" when you drink alcohol. Put "E" when you exercise.
3. Put a line (I) to show when you go to bed. Shade in the box that shows when you think you fell asleep.
4. Shade in all the boxes that show when you are asleep at night or when you take a nap during the day.
5. Leave boxes unshaded to show when you wake up at night and when you are awake during the day.

SAMPLE ENTRY BELOW: On a Monday when I worked, I jogged on my lunch break at 1 PM, had a glass of wine with dinner at 6 PM, fell asleep watching TV from 7 to 8 PM, went to bed at 10:30 PM, fell asleep around Midnight, woke up and couldn't go back to sleep at about 4 AM, went back to sleep from 5 to 7 AM, and had coffee and medicine at 7:00 in the morning.

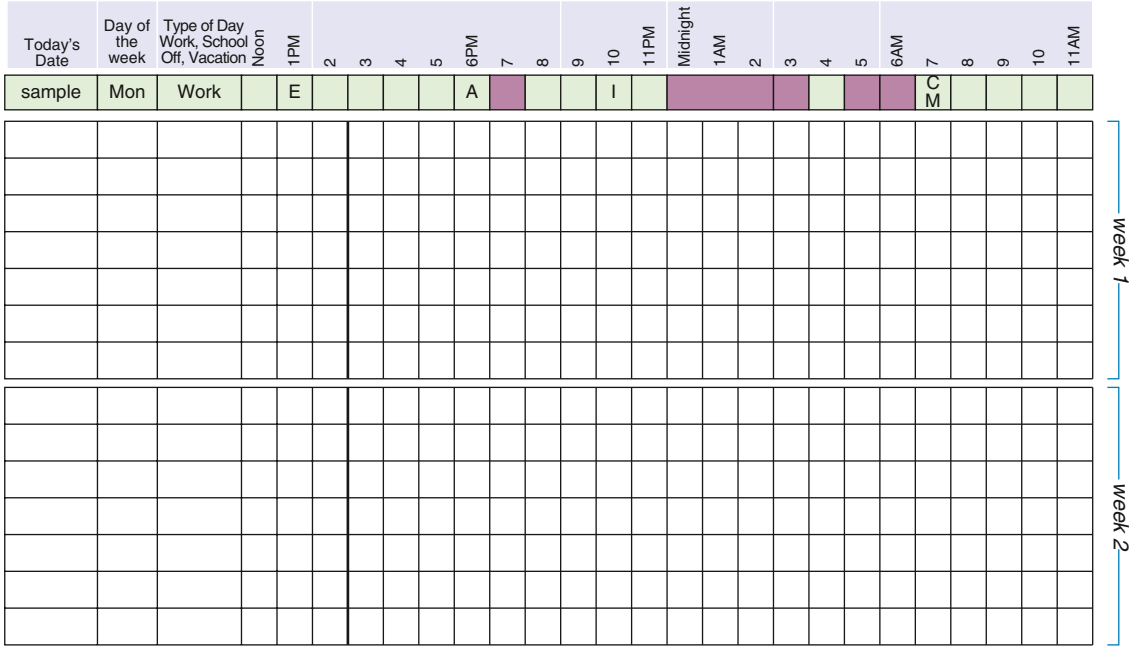

FIGURE 374-2. Example of a sleep diary. Patients record their daily schedule, work, and medications. (With permission from the American Academy of Sleep Medicine, Darien, Illinois.)

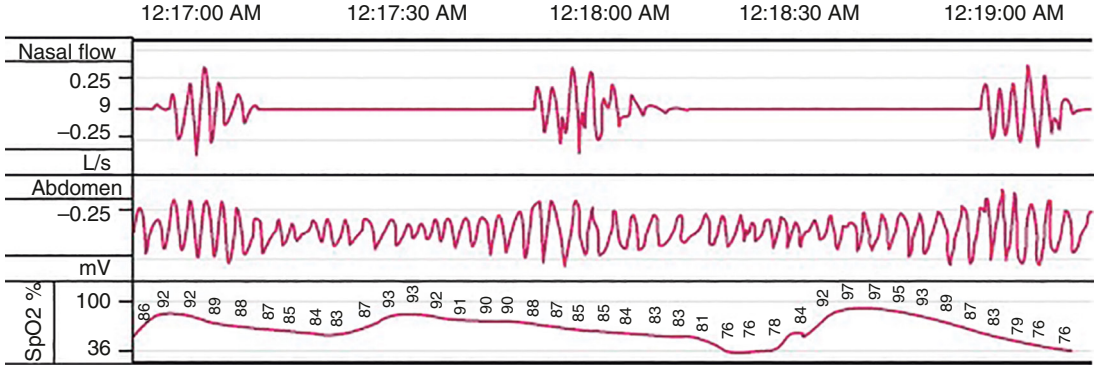

FIGURE 374-3. Polysomnographic tracing of a patient with obstructive sleep apnea during 2 minutes of non–rapid eye movement sleep. Displayed are airflow in the upper airway ("nasal flow"), recorded with a nasal pressure transducer; respiratory effort ("abdomen"), recorded by inductance plethysmography; and oxygen saturation of hemoglobin (Spo_2), recorded with pulse oximetry. The tracing shows characteristic periodic respiratory effort, waning at the onset of the apnea (absent airflow) and crescendoing through the apnea to the resumption of airflow.

hypothyroidism (Chapter 207) and diabetes (Chapter 210) may note sleepiness and fatigue. Neurologic disorders such as stroke (Chapter 376), degenerative diseases (Chapters 371 and 378), tumor (Chapter 175), demyelinating disease (Chapter 380), and head trauma (Chapter 368) can cause excessive sleepiness.

Sleepiness can be quantified subjectively by questionnaires or by physiologic measures such as a multiple sleep latency test. The Epworth Sleepiness Scale quantifies sleepiness by asking the subject to rate on a scale of 0 to 3 (0, no chance; 3, high likelihood) the chance of dozing in eight situations (Table 374-3). A score of 7 is considered average, whereas a score of 10 or more is consistent with subjective sleepiness. This score has a modest correlation with objective measures of sleepiness and better correlation with the severity of obstructive sleep apnea. Other objective tests, such as the multiple sleep latency test, give clues to the degree of sleepiness and possible sleep-onset REM, whereas the maintenance of wakefulness test gives a snapshot of the patient's ability to stay awake.

NARCOLEPSY

DEFINITION

Narcolepsy includes a tetrad of excessive sleepiness, cataplexy, sleep paralysis, and hypnogogic hallucinations. Narcolepsy has been divided into patients with low neurotransmitter hypocretin-1 (also known as orexin) or cataplexy (type 1), and patients without cataplexy or low hypocretin-1 (type 2).

EPIDEMIOLOGY

Narcolepsy type 1 affects 1 in 2000 to 6000 individuals; 40 to 80% have the complete tetrad, and approximately 50% complain of sleep disruption.

TABLE 374-2 INDICATIONS FOR POLYSOMNOGRAPHY

POLYSOMNOGRAPHY IS ROUTINELY INDICATED FOR:
Diagnosis of sleep-related breathing disorders, including suspected obstructive sleep apnea in patients with daytime sleepiness, unrefreshing sleep, or insomnia
Patients with a sleep-related breathing disorder and heart, brain (stroke), neuromuscular, lung, or other major organ disease
Positive airway pressure (PAP) titration in patients with sleep-related breathing disorders
A preoperative clinical evaluation to evaluate for the presence of obstructive sleep apnea before upper airway surgery or oral appliance therapy
Patients suspected of nocturnal movement disorders
Patients suspected of narcolepsy or unexplained excessive daytime sleepiness may require polysomnography and multiple sleep latency test on the ensuing day
Follow-up Polysomnography:
After titration of oral appliance treatment or final fitting in patients with obstructive sleep apnea
Following surgical treatment of patients with moderate to severe obstructive sleep apnea
A patient whose symptoms return after surgical or dental treatment of a sleep-related breathing disorder
Substantial weight gain or loss in patients on PAP
Insufficient clinical response to PAP therapy
Patient with sleep behaviors that are potentially injurious or suggestive of unusual or atypical parasomnias or in which specific motor patterns are in question
POLYSOMNOGRAPHY IS *NOT* ROUTINELY INDICATED FOR:
Patients whose symptoms resolve with continuous positive airway pressure (CPAP) treatment
Diagnosis of a sleep-related breathing disorder in a patient with chronic lung disease
Diagnosis of typical, uncomplicated, and noninjurious parasomnias when the diagnosis is clearly delineated
Patients with a seizure disorder who have no specific complaints consistent with a sleep disorder
Diagnosis or treatment of restless legs syndrome, except where diagnostic uncertainty exists
Establishing the diagnosis of depression
Diagnosis of circadian rhythm sleep disorders

Over 90% of individuals in the United States with cataplexy have the HLA-DQB1*0602 gene. Narcolepsy type 2 occurs in about 2 per 1000 individuals; approximately 40% have the HLA-DQB1*0602 gene, and some exhibit intermediate cerebrospinal fluid (CSF) hypocretin-1 levels. Despite the connection to a gene, the risk to first-degree relatives is only 1 to 2%, or about a 10- to 50-fold increased risk compared with the general population.

PATHOBIOLOGY

Narcolepsy type 1 reflects the loss of hypocretin-producing neurons in the lateral hypothalamus. This neurotransmitter is important for stabilizing the sleep-wake state and for motor control. Thus the manifestations of the disease are related to frequent stage shifts and intrusion of fragments of REM sleep into wakefulness. An immune mechanism is postulated, potentially through a T-cell–mediated response and the loss of orexin-producing neurons.[4] Narcolepsy type 2 appears to be a more diverse group of mechanisms that most likely do not share a common pathophysiology.

CLINICAL MANIFESTATIONS

The tetrad of excessive sleepiness, cataplexy, hypnogogic hallucinations, and sleep paralysis is the major clinical manifestation. Cataplexy is abrupt loss of muscle tone triggered by strong emotional stimuli such as laughter, surprise, or anger. Patients are aware of their surroundings but lose muscle control, first in the face and neck, followed by the arms and then the trunk and legs. Hypnogogic (sleep-onset) and hypnopompic (sleep-offset) hallucinations are vivid and often frightening visual or auditory events. Sleep paralysis is an inability to move or speak, typically during the transition out of sleep when individuals have complete or partial awareness of their surroundings. Patients may describe a strong feeling of impending doom or having to escape imminent danger. Patients with narcolepsy often feel brief naps are refreshing. Frequently, their sleep is fragmented, with sleep intruding into daily activities and wakefulness interrupting nighttime sleep. Sleep paralysis and hypnogogic hallucinations can occur in normal individuals, especially after sleep deprivation, but cataplexy is virtually pathognomonic for narcolepsy.

DIAGNOSIS

The diagnosis of narcolepsy type 1 and type 2 is based on a mean sleep latency of less than 8 minutes and the presence of REM sleep on at least two of the five naps of a multiple sleep latency test. The multiple sleep latency test is predicated on the documentation of at least 6 hours of sleep before the study. The previous night's polysomnography must also not show other sleep pathologies. Low CSF hypocretin level in the setting of excessive sleepiness can also confirm of the diagnosis of narcolepsy type 1.

TREATMENT

Treatment of narcolepsy focuses on improving symptoms of excessive sleepiness, cataplexy, and REM sleep intrusion into wakefulness (Table 374-4). Narcolepsy requires a three-pronged approach of improving the quality of sleep, prescribing stimulants, and controlling cataplexy. Nighttime sleep may be improved with sodium oxybate or the mixed salt oxybate (both at 4.5 to 9.0 g in divided nighttime doses or as the single-dose formulation), which improves daytime alertness and reduces cataplexy.[A1,A2] Planned naps may help some patients, and stimulants such as modafinil (100 to 600 mg/day), armodafinil (50 to 250 mg/day), methylphenidate (5 to 60 mg/day), and dextroamphetamine (5 to 60 mg/day) can improve but do not eliminate daytime sleepiness.[5] Solriamfetol (a selective dopamine and norepinephrine inhibitor at 75 to 150 mg daily)[A3] and pitolisant[A4] (a central histamine H_3 receptor inverse agonist, starting at 8.9 mg and increasing to 17.8 to 35.6 mg daily) also promote wakefulness. To avoid further sleep disruption, patients should not use stimulants in the evening and night hours. Selective serotonin reuptake inhibitors (SSRIs) (Chapter 362, Table 362-5) and combined serotonin-norepinephrine reuptake inhibitors (SNRIs) (Chapter 362, Table 362-5) also reduce cataplexy, as well as sleep paralysis and hallucinations.

PROGNOSIS

Narcolepsy is a lifelong disorder. Patients who present in adolescence or young adulthood may progress to more severe symptoms, but the disorder does not affect longevity.

OTHER HYPERSOMNIAS

Idiopathic hypersomnia is a disorder in which hypersomnia cannot be explained by another disorder, is characterized by unrelenting hypersomnia, and is only minimally improved with therapy. Patients find that their symptoms persist despite sleep periods of longer than 10 to 12 hours.[6] These patients have average sleep latencies of less than 8 minutes, typically do not display REM sleep, but may have stage N3 on their multiple sleep latency test studies. Periodic hypersomnia can also occur in in Kleine-Levin syndrome (a syndrome of periodic hypersomnia, hyperphagia, and hypersexuality) and in perimenstrual hypersomnia.

TREATMENT

Treatment of sleepiness should focus on correcting the underlying cause. One early step is to extend the total sleep time for at least a 3-week period to see if sleep deprivation plays a role. Stimulants such as modafinil (100 to 400 mg) should be tried in individuals who are impaired by the symptoms and in whom other therapies have failed to correct the hypersomnia. In some patients, sodium oxybate can improve daytime symptoms. Some patients with Kleine-Levin syndrome respond to lithium.

SLEEP-RELATED BREATHING DISORDERS

Sleep-related breathing disorders in adults include obstructive sleep apnea, the central sleep apneas (including Cheyne-Stokes breathing), and the sleep-related hypoventilation disorders (including obesity-hypoventilation, congenital and idiopathic central alveolar hypoventilation, and hypoventilation due to medical disorders and respiratory suppressants). These categories and clinical disorders can overlap, but each has distinctive features. Obstructive sleep apnea and Cheyne-Stokes breathing are common in patients with heart failure (Chapters 45 and 46). Patients with brain stem dysfunction may have central apneas, whereas patients with obesity (Chapter 201), chest wall (Chapter 86), neuromuscular (Chapter 390), and central nervous system disorders with hypoventilation will often manifest sleep-related exacerbation of awake hypoventilation and hypoxemia.

SLEEP APNEA

Obstructive sleep apnea is characterized by episodes of absent (apnea) or attenuated (hypopnea) upper airway airflow for at least 10 seconds with continued,

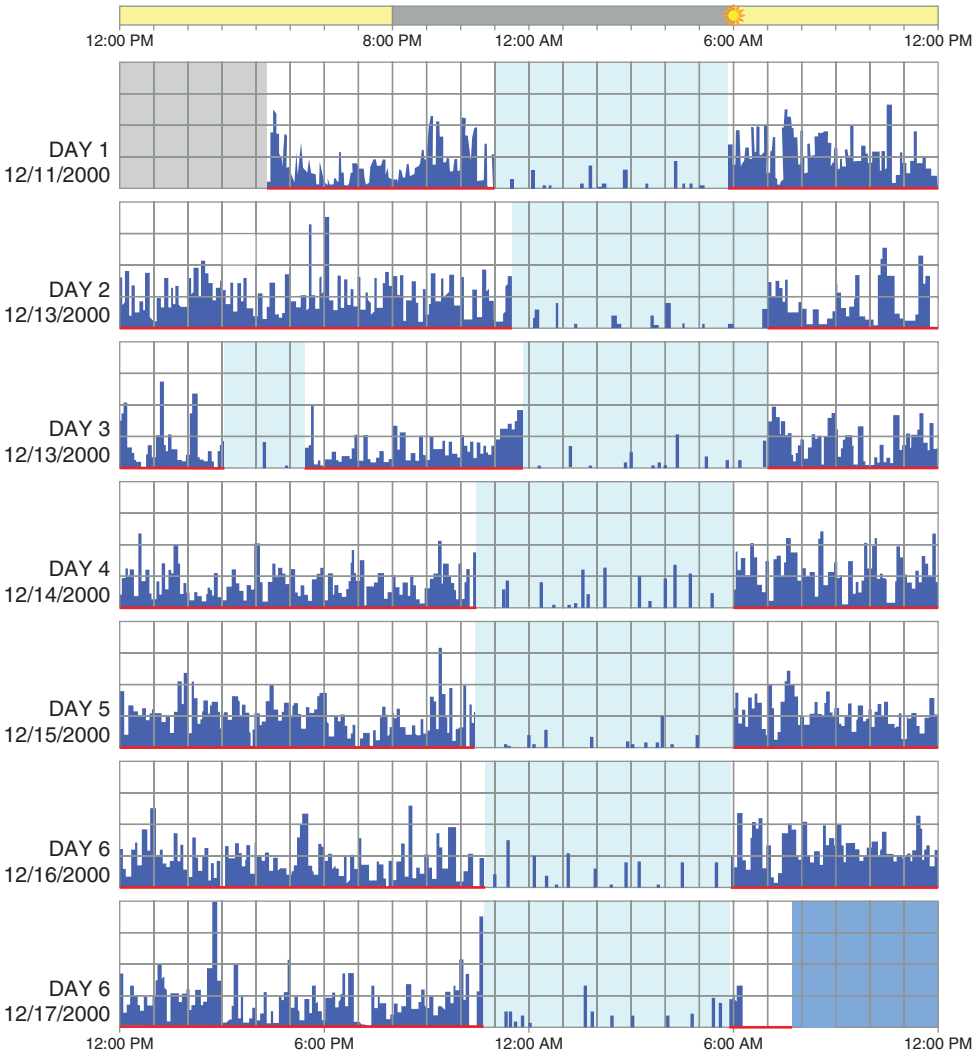

FIGURE 374-4. Actigraphy report. The *shaded* areas are scored as rest time; in this instance, the bedtime is 11 PM to 12 midnight, and wake time about 6 AM. One nap is observed on day 3 in the middle of the afternoon.

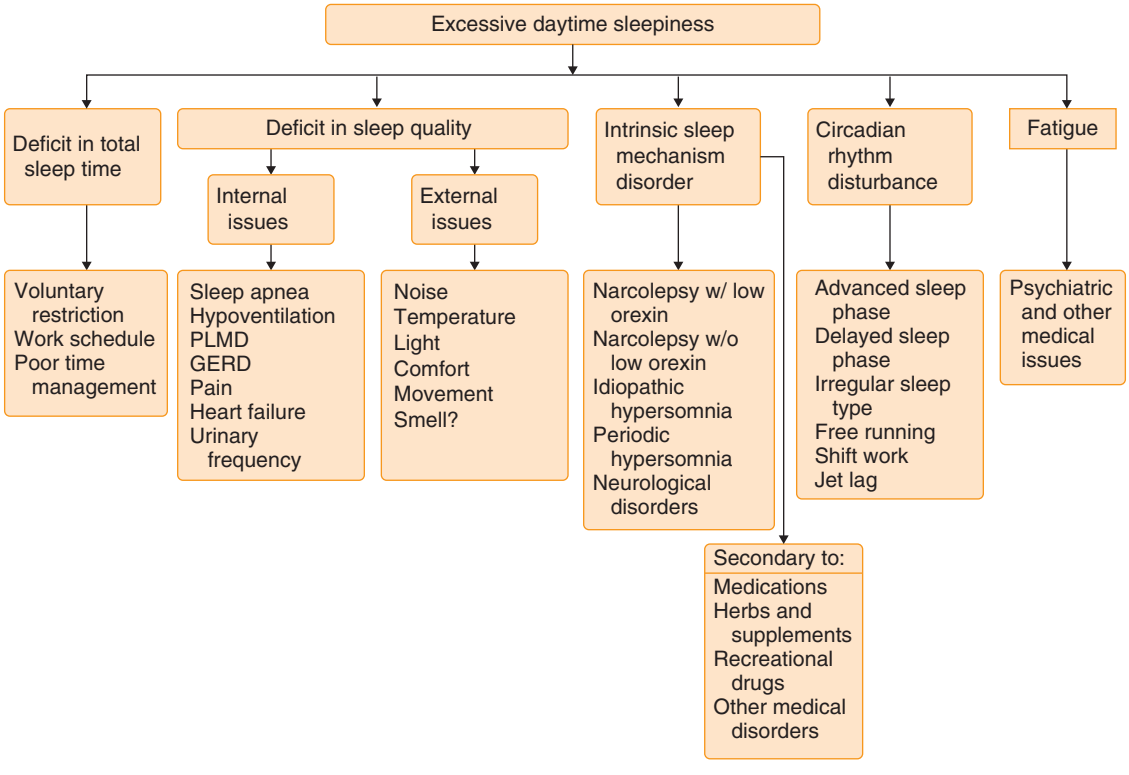

FIGURE 374-5. Differential diagnosis of excessive daytime sleepiness. GERD = gastroesophageal reflux disease; PLMD = periodic limb movement disorder.

TABLE 374-3 EPWORTH SLEEPINESS SCALE

How likely are you to doze off or fall asleep in the following situations, in contrast to just feeling tired? This refers to your usual way of life in recent time. Even if you have not done some of these things recently, try to work out how they would have affected you. Use the following scale to choose the most appropriate number for each situation.

0 = would never doze
1 = slight chance of dozing
2 = moderate chance of dozing
3 = high chance of dozing

SITUATION	CHANCE OF DOZING
Sitting and reading	
Watching TV	
Sitting and inactive in a public place (theater or meeting)	
As a passenger in a car for an hour without a break	
Lying down to rest in the afternoon when circumstances permit	
Sitting and talking to someone	
Sitting quietly after lunch (without alcohol)	
In a car, while stopped for a few minutes in traffic	
Total	

Adapted from Johns MW. A new method for measuring daytime sleepiness: the Epworth Sleepiness Scale. *Sleep*. 1991;14:540-545.

and typically increasingly forceful, ventilatory effort followed by arousal and resumption of ventilation (E-Fig. 374-5) Repetitive, often cyclic, asphyxia and sleep fragmentation is the hallmark of this disorder. *Central sleep apnea* is defined by repetitive episodes, periodic, cyclic, intermittent, or erratic, of at least 10 seconds of absent respiratory effort.

SLEEP-RELATED HYPOVENTILATION

Sleep-related alveolar hypoventilation is defined by intermittent or sustained elevation of arterial P_{CO_2} levels—either >55 mm Hg, or ≥10 mm Hg above awake—with or without associated central or obstructive apnea or hypopnea.

PATHOBIOLOGY

In patients with obstructive sleep apnea, particularly those with obesity, chest wall movement is restricted, with resultant mechanical and reflex upper airway narrowing, increased upper airway compliance, ventilatory instability, and an impaired ability to compensate for increased upper airway resistance. All these abnormalities may contribute to the obstruction of the upper airway during sleep, as well as predominantly non-REM sleep-wake cycling and respiratory periodicity. During REM sleep, erratic neural drive and descending neural inhibition of accessory ventilatory and upper airway muscles may lead to severe alveolar hypoventilation, hypoxemia, and/or obstructive apnea.

With each obstructive event, the combination of progressive asphyxia, increasingly negative intrathoracic pressure, and autonomic and behavioral arousal leads to acute cardiac and cerebrovascular perturbations, including increased afterload of both the left and right ventricles, decreased left ventricular compliance, increased pulmonary artery pressure, decreased coronary artery blood flow, and increased myocardial oxygen demand (see Fig. 374-3). The abrupt arousal at the termination of obstructive events is associated with peripheral vasoconstriction and an increase in the heart rate and in systemic blood pressure, even as cardiac output continues to fall.

Central sleep apnea of the Cheyne-Stokes breathing type is common in patients who have heart failure, mediated by interacting physiologic variables, including lung volume changes, circulatory timing, and a higher than normal gradient between inspired and arterial carbon dioxide tensions (P_{CO_2}). The ventilatory response to a change in blood gases is augmented. The net effect is oscillation of ventilation between central apnea and hyperpnea, as sleep and awake states oscillate. Central apneas in other circumstances may be linked to dysfunctional neural chemosensitivity responses resulting in subsequent apnea, as is seen in the idiopathic, medication-related, and central alveolar hypoventilation syndromes.

Sleep-related hypoventilation without central or obstructive apnea is pathogenetically linked to neural inhibition of postural respiratory muscles and/or perturbed respiratory mechanics, and it tends to be most prominent during REM sleep.

CLINICAL MANIFESTATIONS

Obstructive Sleep Apnea

The cardinal manifestations of obstructive sleep apnea include loud, chronic snoring; excessive daytime somnolence; and witnessed sleep-related choking or gasping. Excessive daytime somnolence is present in approximately 50% of patients with obstructive sleep apnea and may be quantified by laboratory tests that monitor the propensity to fall asleep during the day or by questionnaires or subjective scales that assess sleepiness or decrements in quality of life. Resolution of obstructive sleep apnea does not necessarily resolve excessive daytime somnolence, thereby suggesting the possibility of sustained neurologic perturbation from chronic intermittent hypoxemia and/or arousal, and highlighting the common association of obstructive sleep apnea with metabolic, neurocognitive, respiratory, and cardiovascular abnormalities. Mood disorders, including depression and irritability, as well as perturbations in visual memory and working memory appear to be related to the severity of sleep fragmentation and hypoxemia. Morning dry mouth is a common symptom, as is morning headache. Insomnia may be associated with the repetitive interruption of sleep characteristic of sleep apnea. Transient arousals during N3 sleep may result in confusional parasomnias, such as sleepwalking and sleep talking. Arousals and increased work of breathing may result in restless sleep and night sweats. Nocturia, possibly mediated via atrial natriuretic receptors, may resolve with treatment.

Upper airway abnormalities associated with obstructive sleep apnea include nasal congestion, rhinitis, chronic sinusitis, nasopharyngeal anatomic abnormalities, and craniofacial abnormalities such as micrognathia and retrognathia. Large tonsils, redundant soft palate tissue, and a large tongue may all be associated with a "crowded" oropharynx, but the precise role of these upper airway abnormalities in the pathogenesis of the disorder is unclear.[7] Reductions in the volume of tongue fat account for some of the association between weight loss and a decreased apnea + hypopnea index in patients with obstructive sleep apnea.[8] Obstructive sleep apnea is commonly associated with major medical disorders, including cardiovascular (e.g., heart failure [Chapters 45 and 46], systemic [Chapter 64][9] and pulmonary hypertension [Chapter 69], dysrhythmias including atrial fibrillation [Chapter 52][10] and coronary artery disease), cerebrovascular (e.g., stroke and transient ischemic attack [Chapter 376]), pulmonary (e.g., chronic obstructive pulmonary disease [COPD; Chapter 76], asthma [Chapter 75], and interstitial lung disease [Chapter 80]), and metabolic (e.g., metabolic syndrome) disorders. These conditions tend to have a worse prognosis when concomitant obstructive sleep apnea is not treated. Untreated severe obstructive sleep apnea also has been associated with increased risk for adverse cardio/cerebrovascular events within 30 days following major non-cardiac surgery.[11] In adults diagnosed with severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2; Chapter 336), obstructive sleep apnea is independently associated with an increased risk of severe infection independent of its association with obesity or other comorbid conditions.[12]

Central Sleep Apnea

Central sleep apnea is prevalent in patients who use opiates (Chapter 365), during which cluster breathing with central apneas is characteristic, and in patients with congenital and acquired central nervous system and/or cervical spine disorders, in which noncyclic central apneas, or outright Biot-type breathing is characteristic (E-Fig. 374-6). Cheyne-Stokes breathing, the most common form of central sleep apnea, is manifested as a crescendo-decrescendo breathing pattern with central apnea or hypopnea as the nadir of the breathing effort cycle (E-Fig. 374-7). Central sleep apnea with Cheyne-Stokes breathing is prevalent in patients with heart failure (Chapter 45), in which it is an independent predictor of increased mortality. Patients with heart failure and Cheyne-Stokes breathing tend to have lower awake arterial carbon dioxide tensions (P_{aCO_2}) than other patients who have heart failure. The increased mortality in this setting has been correlated with the severity of the associated nocturnal hypoxemic burden.

Sleep-Related Hypoventilation

Patients with sleep-related hypoventilation may note daytime sleepiness, fatigue, morning headache, or unrefreshing sleep. Sleep-related hypoventilation is common in individuals with central obesity, often in association with obesity-hypoventilation syndrome, neuromuscular and chest wall disease, central hypoventilation disorders (with disordered respiratory control), COPD, and opioid use.

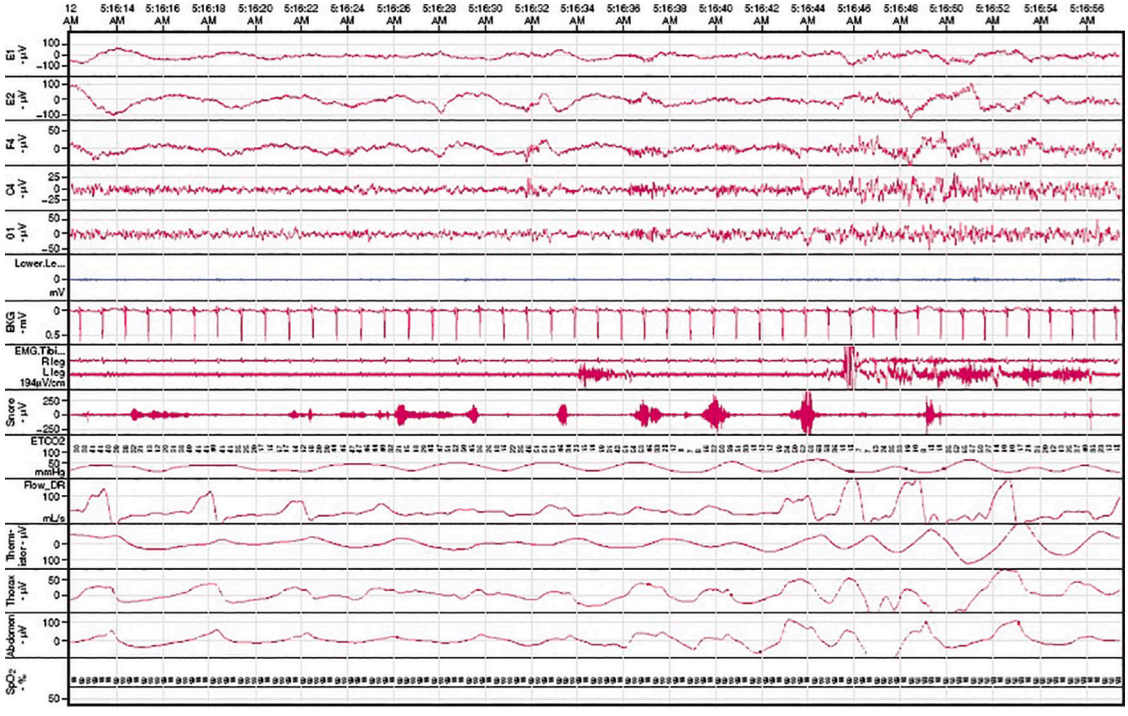

E-FIGURE 374-5. **A 45-second epoch of non–rapid eye movement sleep, demonstrating an obstructive hypopnea in a patient with obstructive sleep apnea.** There is a > 10 second attenuation of the nasal and oronasal airflow in both the nasal pressure transducer (Flow DR) and oronasal thermistor (Thermistor), accompanied by inspiratory flattening/flow limitation of the airflow (as seen in the nasal pressure transducer), increasing thoracic and abdominal respiratory effort (inspiration upward deflection), and crescendo snoring (Snore). Note the consistently increasing end-tidal P_{CO_2} ($ETCO_2$) throughout the hypopnea. Thoraco-abdominal paradoxic breathing effort is, however, not seen on this tracing. The event is terminated with an abrupt electroencephalographic arousal (F4, C4, C3) and abrupt leg movements seen in the anterior tibialis electromyogram (EMG Tib).

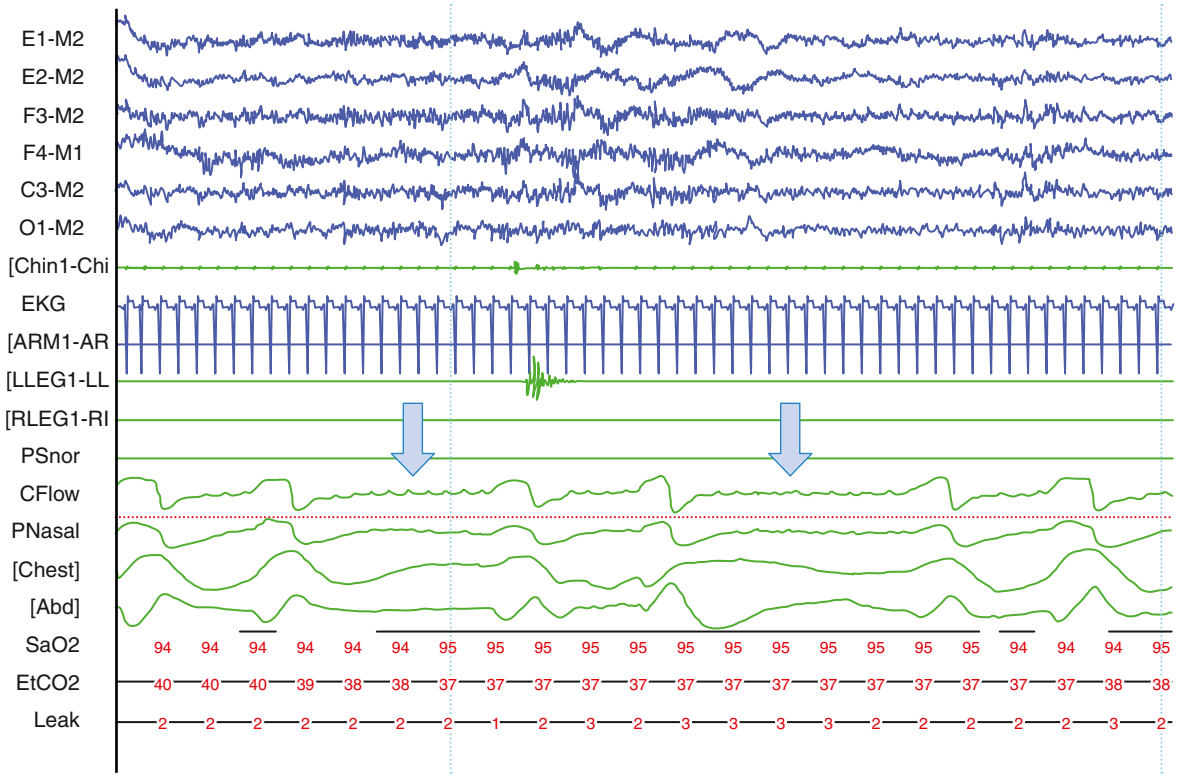

E-FIGURE 374-6. **This polysomnographic recording in a patient with Arnold-Chiari malformation shows repetitive, noncyclic central sleep apnea events (*blue arrows*).** The apneas are without chest or abdominal respiratory effort, thereby indicating that these apneas are central in nature.

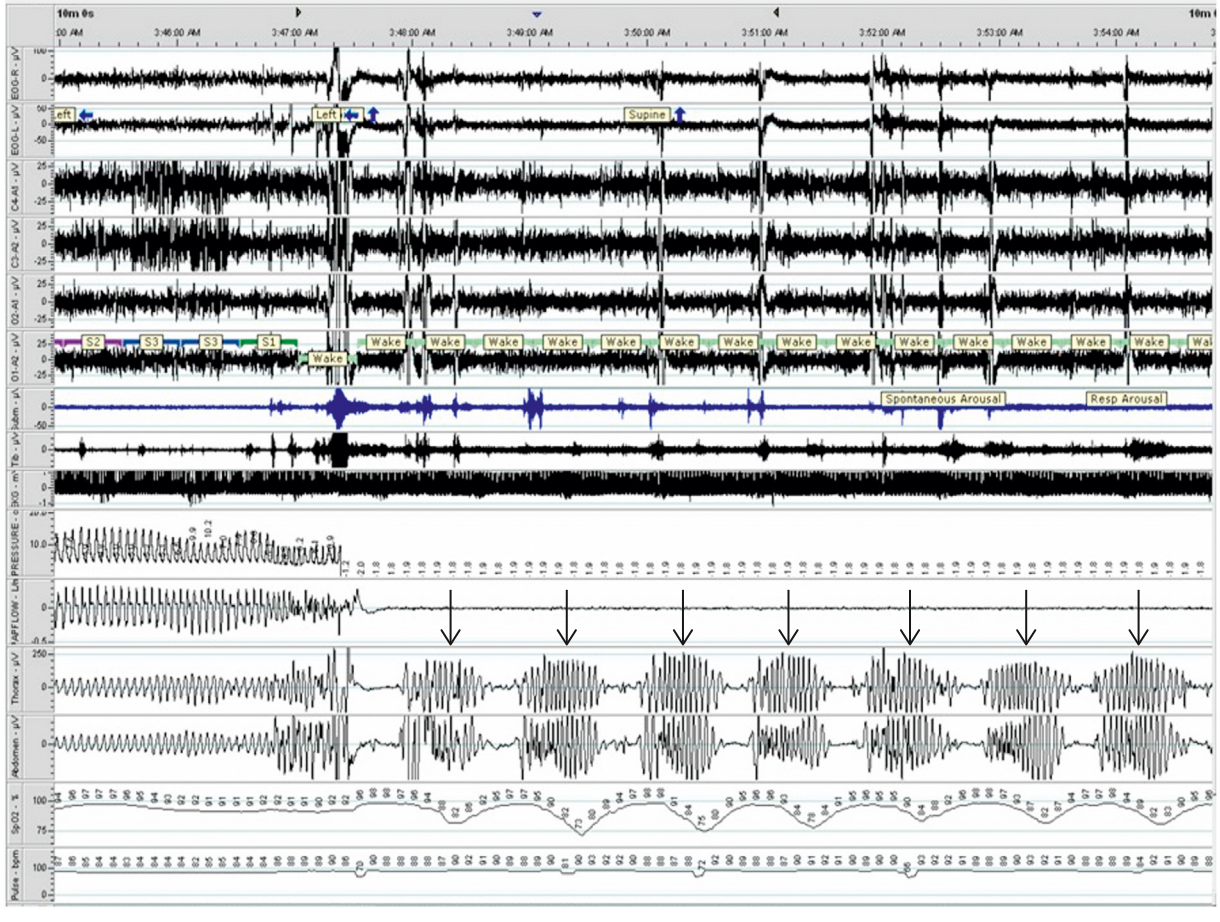

E-FIGURE 374-7. **This epoch from a polysomnographic recording shows a patient with heart failure and Cheyne-Stokes breathing in sleep, with typical waxing and waning of respiratory effort, airflow, and O_2 saturation, with repetitive central apneas (*blue arrows*).** Cheyne-Stokes breathing is seen on termination of the servo-ventilation used at the beginning of the recording.

TABLE 374-4 THERAPIES FOR NARCOLEPSY

MODALITY	STARTING DOSE	HIGHEST DAILY DOSE	DOSE AT
Scheduled naps	10-15 minutes	1-3 naps	Just before time needing to be awake
OVER-THE-COUNTER STIMULANT			
Caffeine	25 mg	300 mg	AM
WAKE PROMOTING			
Modafinil	100-200 mg	400 mg	AM and noon
Armodafinil	50-150 mg	250 mg	AM
Methylphenidate	5-10 mg	120 mg	AM and noon
Methylphenidate ER	10-20 mg	120 mg	AM
Dextroamphetamine	5-10 mg	60 mg	AM and noon
Combination dextroamphetamine/amphetamine	5-10 mg	60 mg	AM and noon
Pitolisant	8.9 mg	35.6 mg	AM
Solriamfetol	37.5-75 mg	150 mg	AM
IMPROVE NIGHTTIME SLEEP, DAYTIME ALERTNESS, AND CATAPLEXY			
Sodium oxybate	2.25 g	9 g	Bedtime and 4 hr into sleep
Calcium, magnesium, potassium, sodium oxybate	2.25 g	9 g	Bedtime and 4 hr into sleep
Once nightly sodium oxybate	4.5 g	9 g	Not currently FDA-approved
THERAPIES FOR CATAPLEXY (NOT FDA APPROVED)			
Fluoxetine	10-20 mg	40 mg	AM
Venlafaxine	75 mg	225 mg	AM at lower dose or divided
Protriptyline	5 mg	30 mg	AM at lower dose or divided

FDA = U.S. Food and Drug Administration.

DIAGNOSIS

Screening for obstructive sleep apnea with polysomnography is not indicated in asymptomatic patients. Formal screening questionnaires add little to careful clinical assessment. In symptomatic patients with a high degree of clinical suspicion, and particularly in patients with concomitant cardiac, respiratory, metabolic, or neurologic disorders, polysomnography is indicated.[13] Polysomnography generally involves all-night monitoring at home or in a sleep laboratory (or at the bedside in hospitalized patients).

In a sleep laboratory or hospital setting, data are gathered via electroencephalography, electro-oculography (primarily to determine rapid eye movements characteristic of REM sleep), electrocardiography, leg and chin electromyography, and measures of respiratory effort (airflow, hemoglobin oxygen saturation, and alveolar or arterial carbon dioxide levels). Audiovisual recordings can identify crescendo snoring and thoracoabdominal paradoxical breathing efforts to help differentiate obstructive from nonobstructive hypopnea. Home sleep studies, which monitor only basic respiratory parameters, are as good for making the diagnosis at a lower cost in patients who are suspected of having obstructive sleep apnea without major hypoventilation, cardiovascular, or cerebrovascular comorbidities.[A5] In-laboratory polysomnography has the advantages of recording more parameters, such as carbon dioxide, in a controlled setting, and of allowing for objective titration of positive airway pressure and/or oxygen during the same night as the diagnostic portion of study—an approach that is of particular importance in patients with sleep-related hypoventilation (e.g., obesity hypoventilation syndrome, COPD, and neuromuscular disorders).

TREATMENT

For obstructive sleep apnea, weight loss and avoidance of supine sleep are important components of treatment.[14] The mainstay of immediate and effective reversal of the disorder is positive airway pressure (PAP), usually in a continuous mode (continuous positive airway pressure [CPAP]).[15] This therapy requires a significant commitment for compliance, and the physician must closely monitor and work with the patient to ensure its usage, which is easy to measure objectively with current CPAP devices. Both continuous and bilevel PAP are effective in improving sleep-related and awake hypoventilation and quality of life in the obesity hypoventilation syndrome[A6,A7] particularly in patients with severe obstructive sleep apnea, although bilevel PAP with assured volume appears to provide optimal benefit in terms of cardiovascular function.[16] Noninvasive ventilation alone should *not* be considered safe therapy in patients with central alveolar hypoventilation, in whom tracheostomy-assisted, 24-hour assured ventilation should be considered the standard of care.

Positive airway pressure can improve symptoms[A8] and ambulatory blood pressure in patients with obstructive sleep apnea. However, it has not been definitively shown to reduce future cardiovascular events or death,[A9] despite suggestive data from observational studies.[17]

Weight loss (Chapter 201), maintained via lifestyle intervention or medications in overweight or obese patients with obstructive sleep apnea, is associated with sustained improvement in apnea + hypopnea indices,[A10] and CPAP plus weight loss is superior to weight loss alone or CPAP alone in improving hypertension in obese patients with obstructive sleep apnea.

Unfortunately, neither supplemental oxygen alone nor medication provides optimal benefit in obstructive sleep apnea. A mandibular advancement device may be effective therapy[A11]; conversely, surgical uvulopalatopharyngoplasty, radiofrequency volumetric tissue reduction of the palate or tongue (or both), and laser-assisted uvuloplasty are not recommended as first-line therapy to treat symptomatic patients. However, combined therapies may be helpful in selected patients. In adults who have moderate or severe obstructive sleep apnea and who failed or refused CPAP, combined uvulopalatopharyngoplasty[18] and minimally invasive tongue volume reduction can reduce the number of apnea and hypopnea events and patient-reported sleepiness at 6 months compared with virtually no ongoing therapy for sleep apnea. Nevertheless, such surgically treated patients continue to have a clinically significant apnea-hypopnea and do not improve in terms of their objective measures of sleepiness.[A12] Promising evolving therapeutic modalities include proprietary implantable neurostimulation of the hypoglossal nerve for obese patients[A13] and nasal or oral/nasal expiratory positive airway pressure, alone or in combination with a mandibular advancement device.[19] Solriamfetol, a selective dopamine and norepinephrine reuptake inhibitor with robust wake-promoting effects at 75 to 300 mg, can significantly increase wakefulness and reduce sleepiness in patients with excessive daytime sleepiness, usually with tolerable side effects.[A14] Pitolisant (titrated up to 20 mg/day over 12 weeks), which is a selective histamine H_3 receptor antagonist with wake-promoting effects, can significantly reduce daytime sleepiness and fatigue in patients who refuse or are nonadherent to CPAP.[A15]

In patients with heart failure (Chapter 46), the increased mortality associated with Cheyne-Stokes breathing can be reduced if there is an effective response to CPAP. Adaptive servo-ventilation can improve Cheyne-Stokes breathing, quality of life, and functional status in patients with heart failure but has not been shown to reduce mortality, and in one study was shown to increase mortality.[A16]

Transvenous phrenic nerve stimulation can normalize moderate to severe elevations in central apnea indices and improve oxygen saturation during sleep in patients with and without heart failure. However, its effects on mortality in central sleep apnea syndromes and in Cheyne-Stokes breathing specifically remain to be determined.[A17]

INSOMNIA

DEFINITION

Insomnia is the complaint of difficulty initiating or maintaining sleep, or of unrefreshing sleep that results in daytime symptoms of excessive fatigue or impairment of performance.[20] Some individuals may need less sleep and have no daytime sequelae, thereby differentiating them from individuals with insomnia. Chronic insomnia is defined by symptoms that persist more than 3 months regardless of the underlying cause or associations.

EPIDEMIOLOGY

Many individuals have occasional nights with difficulty falling asleep or maintaining sleep, often provoked by psychological challenges or sudden changes in their environment. Approximately 35% of individuals complain of intermittent insomnia, and approximately 10% have chronic insomnia.[21] Women, older individuals, and patients with psychiatric or chronic medical illness are predisposed to develop insomnia. Insomnia is also more common in individuals with lower socioeconomic status and poor education. Patients with behavioral traits such as obsessive-compulsive tendency, frequent rumination, or poor coping strategies are also at greater risk for insomnia.

PATHOBIOLOGY

Patients with insomnia frequently give historical clues directed toward the mechanisms behind their insomnia. Studies of patients with insomnia show that these individuals are in a state of hyperarousal with increased brain metabolic rates during non-REM sleep. Most patients have multiple factors that contribute to the insomnia, including features that predispose them to insomnia, events that precipitated the insomnia, and maladaptive behaviors that perpetuate the insomnia. Many patients have a coincident psychiatric disorder (Chapter 362) or psychological or medical issues. Patients with depression or anxiety may have insomnia for years before other characteristics of affective disorders. Patients with organ failure, such as heart failure, commonly complain of insomnia and may note difficulty remaining in bed owing to breathing issues. Restless legs syndrome, pain of any origin, and diseases that limit mobility (e.g., muscular dystrophy [Chapter 389] or Parkinson disease [Chapter 378]) can interrupt sleep. Sleep schedules also may be influenced by diseases (e.g., dementia [Chapter 371], Parkinson disease [Chapter 378], cancer in which circadian rhythm abnormalities promote nighttime awakenings).

CLINICAL MANIFESTATIONS

The patient and bed partners may give clues to a poor sleep environment, maladaptive behaviors, psychological stress, psychiatric or neurologic disease, primary sleep disorders, or other medical issues that cause insomnia. Insomnia may be initiated by events that shift schedules or by a change in medications. Initiating events may play little role in long-term insomnia, but these also give important clues to preventing further recurrence of the insomnia. When insomnia persists, many patients adopt behaviors that help perpetuate poor sleep. Maladaptive behaviors that may occur during the day or night include heavy daytime caffeine or alcohol use, watching television or using electronic devices near or while in bed, or eating or exercising near the sleep period. Similarly, having electronic devices such as televisions, computers, and cell phones in the bedroom disrupt sleep. A subgroup of patients may develop mental rumination or even sleep phobias. This expectation of poor sleep promotes apprehension about sleep and may perpetuate counterproductive sleep rituals. These maladaptive behaviors become the predominant feature of the subtype of psychophysiologic insomnia (Table 374-5).

Some patients may not perceive that they are asleep. Individuals with the subtype of paradoxical insomnia have normal physiologic sleep but do not recognize that they have been asleep. Other patients may have the unrealistic expectation that sleep should not be interrupted by any arousals or that they must sleep a set number of hours.

The less common subtype of idiopathic insomnia starts in childhood and continues as a lifelong difficulty of sleep. These patients may have impaired inherent sleep mechanisms. Noting the timing of the insomnia during the sleep period also may be helpful. Difficulty with the onset of sleep suggests a possible underlying delayed sleep phase or sleep phobia, and insomnia with early morning arousal suggests possible underlying depression or advanced sleep phase. Documentation of schedule changes (e.g., from jet lag or shift work) can be useful in determining links to circadian rhythm issues.

DIAGNOSIS

The diagnosis of insomnia is based on the patient's history that difficulty with sleep results in daytime sequelae (Fig. 374-6). Although a patient may have more than one insomnia subtype, evidence is lacking that subtypes should direct therapy.

The history should include a review of the patient's 24-hour schedule, meals, and caffeine, tobacco, and medicine intake; sleep environment; attitudes about sleep; and the sleep experience. In addition, a thorough history from the bed partner may disclose features the patient is unaware of, such as snoring, limb movements, and sleep habits. Patients should be asked to keep a 2-week diary of their daily events, which often will show specific patterns or provide clues that can guide interventions. Polysomnography should be considered only if the patient has symptoms of sleep apnea or has failed multiple therapeutic trials.

TABLE 374-5 CLASSIFICATION OF ADULT INSOMNIA

INSOMNIA
Subtypes:
Psychophysiologic insomnia—maladaptive behaviors conditioned in response to associating the bed environment or thoughts of bedtime with heightened arousal; patients typically sleep better in a different environment, such as away on vacation.
Idiopathic insomnia—insomnia beginning in infancy or childhood, with a persistent unremitting course and no improvement with change in environment
Paradoxical insomnia (sleep state misperception)—insomnia characterized by a marked mismatch between the patient's description of sleep duration and objective polysomnographic findings
INSOMNIA ASSOCIATED WITH
Adjustment insomnia—associated with an acute or active psychosocial stressor
Inadequate sleep hygiene—associated with lifestyle habits that impair the ability to sleep
Insomnia comorbid with a psychiatric disorder—associated with an active psychiatric disorder such as anxiety or depression
Insomnia comorbid with a medical condition—associated with a condition such as renal failure, hepatic failure, chronic pain, nocturnal cough or dyspnea, or hot flashes
Insomnia caused by a drug or substance—secondary to consumption or discontinuation of medications, drugs of abuse, alcohol, or caffeine

TREATMENT

Insomnia is generally treated as a single disorder even though it has been divided into subtypes (Table 374-6), but effective treatment requires identifying factors that contribute to insomnia.[21] Treatment is multipronged and includes improving behaviors that promote sleep, addressing the perpetuating factors, and deciding if hypnotic medication is appropriate.[22] Every patient with insomnia should practice routines that appropriately promote good sleep and wake habits. Cognitive behavioral therapy provides long-term success for insomnia (see Table 374-6).[A18] The cognitive portion focuses on restructuring beliefs about sleep, whereas behavioral therapies focus on actions that may mitigate maladaptive behaviors and promote better sleep behaviors: progressive relaxation techniques, stimulus control, or sleep or time-in-bed restriction (Table 374-7). Cognitive behavioral therapies for insomnia delivered through an internet-based system can be clinically effective and less costly than face-to-face therapies.

Hypnotics are best used for short-term treatment in conjunction with cognitive behavioral therapy (see Table 374-7).[A19] Agents with rapid onset and a short half-life are typically used to address difficulties initiating sleep, whereas agents with a longer half-life or continuous-release are used to improve sleep maintenance. Benzodiazepines are preferred first-line agents, but a melatonin receptor agonist (ramelteon, 8 mg) and antidepressant medications (Chapter 362, Table 362-5) also may be used for insomnia. Newer agents, suvorexant (10 to 20 mg) and daridorexant (25 to 50 mg), improve sleep by blocking hypocretin to promote sleep maintenance.[A20] In patients with insomnia and coexisting depression or anxiety, the combination of the short-term use of a hypnotic, such as a benzodiazepine, and long-term antidepressant or anxiolytic is better for both the insomnia and the affective disorder than either therapy alone.[A21]

PROGNOSIS

Most patients will improve, although some will relapse. Cognitive behavioral therapy is key to long-term success. Long-standing insomnia can herald an affective disorder (Chapter 362) and is associated with a higher risk of dementia in older ages. Except for very rare patients with the prion-induced fatal familial insomnia (Chapter 371), patients with insomnia have only a slightly lower life expectancy.

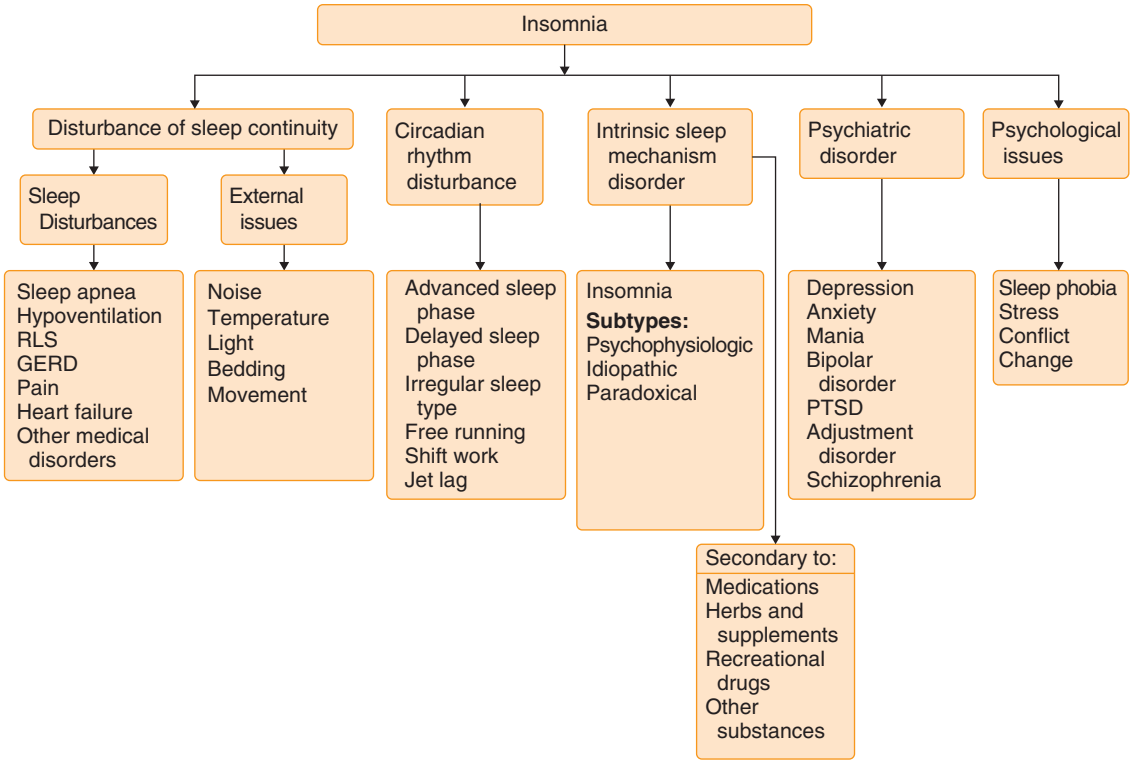

FIGURE 374-6. **Differential diagnosis of insomnia.** GERD = gastroesophageal reflux disease; PTSD = post-traumatic stress disorder; RLS = restless legs syndrome.

TABLE 374-6 NONPHARMACOLOGIC THERAPIES FOR INSOMNIA

COGNITIVE-BEHAVIORAL THERAPY with or without relaxation therapy (Standard)
The combination of multiple modalities noted below
STIMULUS-CONTROL THERAPY (Standard)
Go to bed only when sleepy.
Use the bedroom only for sleeping and sex.
Go to another room when unable to sleep in 15-20 minutes, read or engage in other quiet activities, and return to bed only when sleepy; repeat if necessary.
Have a regular wake time regardless of the duration of sleep.
Avoid daytime napping.
SLEEP-RESTRICTION THERAPY (Guideline)
Reduce time in bed to the estimated total sleep time (minimum, 5 hr).
Increase time in bed by 15 minutes every week when the patient estimates the sleep efficiency is at least 85% (ratio of time asleep to time in bed).
RELAXATION THERAPY (Standard)
Physical component: progressive muscle relaxation, autogenic training
Mental component: reducing intrusive thoughts through imagery training, meditation, or hypnosis
PARADOXICAL INTENTION (Guideline for sleep-onset difficulties)
Instruct the patient to remain passively awake in bed and avoid any effort to fall asleep.
COGNITIVE THERAPY (Insufficient evidence as a single therapy)
Education to alter maladaptive or unrealistic beliefs and attitudes about sleep, such as that a minimum of 8 hours of sleep per night is required for health
SLEEP HYGIENE EDUCATION (Insufficient evidence as a single therapy)
Correction of extrinsic factors and behaviors that affect sleep, such as environmental disruption (pets, music, or television); bedroom temperature; fixation on the bedside clock; use of alcohol, nicotine, or caffeine; lack of exercise or exercise too close to bedtime

CIRCADIAN RHYTHM DISORDERS

DEFINITION

Circadian rhythm disorders cause misalignment of the person's sleep-wake cycle and the naturally occurring day-night cycle. Pathologic symptoms must be persistent or recurrent, and the patient must incur some social, occupational, or additional impairment.[23] Individuals may note insomnia, excessive daytime sleepiness, or both. Circadian rhythm sleep-wake disorder is typically classified by comparing the patient's rhythm to the naturally occurring day. Circadian rhythm sleep-wake disorders are subtyped into advanced sleep-wake phase disorder (early to bed and rise), delayed sleep-wake phase disorder (late to bed and rise), irregular sleep-wake rhythm disorder (no clear pattern), and non–24-hour sleep-wake rhythm disorder (a rhythm that is free running and not entrained to the environment). Induced disorders include jet lag and shift work. Another disorder related to circadian rhythm involves the gastrointestinal cycle: nocturnal eating syndrome, in which individuals consume over half of their caloric intake after 9 PM.

EPIDEMIOLOGY

Approximately 3% of the adult population experiences a circadian rhythm disorder, and approximately 28% of the population works a rotating or night shift. Some patterns of sleep are inherent in specific age groups. Advanced sleep phase issues are more common in the elderly, and delayed sleep phase issues are more common in adolescents. Purposeful shifting of the circadian rhythm, such as with shift work or jet lag, is common. Although about 30% of the U.S. workforce works nights or rotating shifts, only one third of these individuals have a clinical circadian rhythm disorder. A non–24-hour sleep-wake rhythm disorder is more common among blind persons, of whom about 25% have the disorder. Irregular sleep-wake disorder appears more commonly in patients with neurodegenerative diseases, in which it may be an early symptom.

PATHOBIOLOGY

Circadian rhythm sleep-wake disorders may be more prevalent in today's "24-hour society," which offers constant stimuli to remain awake. Teens are more vulnerable to the phase-delaying effects of light in the evening. The human "master clock," which resides in the suprachiasmatic nucleus of the hypothalamus, synchronizes the body's peripheral tissue clocks, possibly mediated by melatonin. About 10 to 30% of genes are expressed with circadian rhythmicity. Abnormalities in genetic clock genes may contribute to circadian rhythm disorders. Variations in the *Clock, Per2,* and *Per3* genes appear to influence the morning/evening preference. Advance sleep-wake phase disorder has been associated with the *Per2* S662G mutation and the *Ck1d* T44A mutation, whereas delayed sleep-wake phase disorder is associated with the *Per3* V647G and *Ck1e* S408N mutations. The latter mutation is also associated with non–24-hour sleep-wake rhythm disorder. Non–24-hour sleep-wake rhythm disorder in individuals who are blind appears to be related to the loss of the photoreceptive ganglion cell input to the hypothalamus and not into the retina itself.

TABLE 374-7 MEDICATIONS FOR INSOMNIA

NAME	DOSE	TIME OF DOSE	FDA INDICATION	COMMON SIDE EFFECTS	HALF-LIFE	MECHANISM
Zolpidem SL	1.75-10 mg	Bedtime	Yes	Sleepiness, amnesia, falls, parasomnias	1-2 hr	Benzodiazepine receptor agonist (BZRA)
Zolpidem reg	5-10 mg	Bedtime	Yes	Sleepiness amnesia, falls, parasomnias	1-2 hr	BZRA
Zolpidem CR	6.25-12.5 mg	Bedtime	Yes	Sleepiness, amnesia, falls	1-2 hr but continued release	BZRA
Temazepam	7.5-30 mg	Bedtime	Yes	Sleepiness, dizziness	8-10 hr	Benzodiazepine
Zaleplon	5-20 mg	Bedtime	Yes	Sleepiness, dizziness, parasomnias	1 hr	BZRA
Eszopiclone	1-3 mg	Bedtime	Yes	Sleepiness, dizziness	4-8 hr	BZRA
Doxepin	3-6 mg	Bedtime	Yes	Drowsiness, dizziness, nausea	17 hr	Histamine receptor antagonist
Mirtazapine	7.5-15 mg	Bedtime	No	Drowsiness, dizziness, weight gain	20 hr	Histamine receptor antagonist
Ramelteon	4-8 mg	Bedtime	Yes	Sleepiness, headache	1-2 hr	Melatonin receptor agonist
Suvorexant	10-20 mg	Bedtime	Yes	Sleepiness	12 hr	Blocks orexin

FDA = U.S. Food and Drug Administration.

CLINICAL MANIFESTATIONS

Patients with circadian rhythm disorders typically complain of insomnia and/or excessive sleepiness, and they may incur sleep deprivation by trying to maintain schedules that are not consistent with their inherent clocks. Some individuals "catch up" on the weekends by sleeping during their preferred times. A key feature of a circadian rhythm disturbance is that once asleep on their inherent cycle, the patient sleeps well; the sleep period is just misaligned with the environment. Circadian rhythm sleep-wake disorders are associated with an increased risk of accidents and impaired quality of life.[24]

Delayed sleep-wake phase disorder patients typically have trouble falling asleep and may not fall sleep for over 2 hours later than the conventional bedtime (E-Fig. 374-8A). They then have trouble arousing in the morning, preferring later wake times. These patients typically complain of inability to fall asleep or not feeling refreshed in the morning. Advanced sleep-wake phase disorder patients fall asleep early in the evening and awaken several hours earlier than the conventional morning awakening (E-Fig. 374-8B). Patients complain of early morning awakening and the inability to maintain wakefulness during evening activities. Individuals with non–24-hour sleep-wake rhythm disorder have a circadian rhythm that continues to run on the 24.3- to 25-hour cycle. In this disorder, patients have alternating episodes of insomnia and excessive sleepiness, depending on the phase of the endogenous sleep-wake cycle. This disorder can be confused with a periodic hypersomnia. Irregular-sleep-wake rhythm disorder patients have both excessive sleepiness and insomnia, with at least three periods of sleep each 24 hours, associated with decreased functioning and a decreased sense of well-being during the waking period.

DIAGNOSIS

The diagnosis of a circadian rhythm disorder is made by history and a 2- to 3-week sleep diary or actigraphy recording. Normal individuals have a tendency toward "morningness" or "eveningness," so the diagnosis requires documentation of a negative impact of circadian rhythm on quality of life.

TREATMENT

Most therapy is directed toward aligning the disordered circadian rhythm with the desired sleep-wake schedule.[25] Shifting the schedule, known as chronotherapy, can be accomplished by allowing a gradual delay or advancing of the inherent schedule to the desired time, and then using clues (bright light, exercise, food, and social interaction) to maintain the schedule.

The circadian rhythm is susceptible to time clues only if such clues are given at an appropriate time of the endogenous circadian rhythm. Using the temperature cycle nadir (which typically occurs approximately 2 hours before the natural wake up time) as a reference, bright light, exercise, food, and social interactions delivered before the temperature nadir will delay the cycle, whereas these stimuli delivered after the temperature nadir will advance the cycle. Melatonin has an opposite effect and typically advances the cycle if given 4 to 6 hours before the onset of sleep. Melatonin therapy may delay the cycle if used after the temperature nadir. For patients who have non–24-hour sleep-wake rhythm disorder, tasimelteon (20 mg in the evening) improves the sleep-wake cycle.[A22]

Once the circadian rhythm is realigned, patients benefit from strictly maintaining their schedule and time clues to reinforce the new circadian timing. Although short-term hypnotics and stimulants are commonly used to help adjustment, these medications do not realign the circadian rhythm.

PARASOMNIA

DEFINITION

Parasomnias are undesirable behavioral events or experiential phenomena occurring during entry into, within, or as part of arousal from sleep. These events include abnormal movements, behaviors, emotions, perceptions, dreaming, and activities of the autonomic nervous system. Parasomnias are typically subdivided into those arising from non-REM sleep, REM sleep–related parasomnias, and other parasomnias. Non-REM events include sleep-related eating disorder and disorders of arousal (sleepwalking, sleep terrors, and confusional arousals). REM-related parasomnias include nightmare disorder, REM sleep behavior disorder, and recurrent sleep paralysis.

EPIDEMIOLOGY

Approximately 3% of adults and 15% of children have a sleep-related abnormal behavior. Although some parasomnias, such as disorders of arousal from NREM sleep (sleepwalking, sleep terrors, and confusional arousals), are more common in children, REM-related parasomnias, such as nightmare disorder, are common among all ages and are especially common in individuals with post-traumatic stress disorder (Chapter 362). REM sleep behavior disorder, which is another REM sleep–related parasomnia, is more common in the elderly and may predate other features of synucleinopathy neurodegenerative disorders such as Parkinson disease (Chapter 378), dementia with Lewy bodies (Chapter 371), and multiple-system atrophy (Chapter 378).

CLINICAL MANIFESTATIONS AND DIAGNOSIS

The history is the mainstay of the diagnosis of most parasomnias. Key features include age of onset, time of night of the events, memory for the events, and family history (Table 374-8). Because non-REM parasomnias are a mixture of deep non-REM sleep with the awake state, these events are more common in the first third of the night, are associated with no or little memory for the event, and the behaviors are not stereotypical. Events are more likely to occur with sleep deprivation, alcohol ingestion, sleeping in strange environments, and coincidental conditions that predispose to arousals, such as sleep apnea. Patients are neurologically and psychiatrically normal during wakefulness.

REM sleep behavior disorder typically begins in late adulthood, but it can occur in children. In this disorder, patients lose the muscle atonia of REM sleep and thus act out during their dreams, sometimes injuring themselves or bed partners. This nonstereotypical motor activity is often associated with vivid recall of a dream that correlates with the witnessed behavior. Patients can have multiple events typically in the latter half of the night. This behavior disorder can be provoked by medications such as tricyclic antidepressants, monoamine oxidase inhibitors, and serotonin reuptake inhibitors or more acutely with alcohol withdrawal.

The diagnosis is based on the documented excessive electromyographic activity during REM sleep and the history of dream enactment. Because chronic REM sleep behavior disorder has been linked to the subsequent development of Parkinson disease (Chapter 378), multiple system atrophy (Chapter 378), and Lewy body dementia (Chapter 371), patients should have a detailed neurologic examination to look for subclinical features. If the patient demonstrates stereotypic sleep motor behavior, rather than the characteristic nonstereotypical

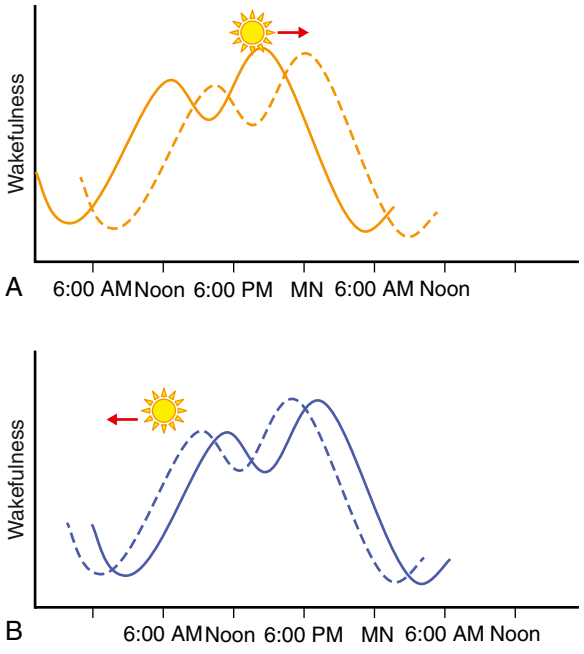

E-FIGURE 374-8. **A,** An idealized graph of the circadian rhythm (*solid orange curve*), shows the phase shift delay (*dotted curve*) caused by bright light given before the temperature nadir. **B,** This idealized graph of the circadian rhythm (*solid blue curve*), shows the phase shift advance (*dotted curve*) caused by bright light given after the temperature nadir.

TABLE 374-8 KEY FEATURES OF NOCTURNAL EVENTS

DISORDER	SYMPTOMS	TIME OF NIGHT	DURATION	FREQUENCY	STEREOTYPICAL	MEMORY	POLYSOMNOGRAPHIC FINDINGS
Sleepwalking	Slow, deliberate, complex behaviors	First half of sleep period	Seconds to minutes	Less than one per night to fewer	No	No or partial vague memory	Arousal from slow wave sleep
Sleep terrors	Piercing scream, followed by fight or flight response	First half	Seconds to minutes	Less than one per night or fewer	No	No or partial vague memory	Arousal from slow wave sleep
Confusional arousals	Variety of unusual behaviors upon sudden awakening	Anytime	Seconds to minutes	Less than one per night or fewer	No	No or partial vague memory	Arousal from slow wave sleep
Sleep-related eating	Eating of high-calorie or strange foods in a messy manner	First half	Minutes	May occur nightly	No	No or partial vague memory	Arousal typically from non-REM sleep
Nightmares	Frightening dreams associated with anxiety	Latter half	Seconds to minutes	Variable	No, but may have a common theme	Yes	Events occur in REM sleep
REM sleep behavior disorder	Dream enactment, may be violent	Latter half	Seconds	Multiple times per night	No	Yes	Excessive EMG activity in REM sleep
Rhythmic movement disorder	Rocking, head banging	Near sleep onset but may be throughout the night	Minutes to hours	Multiple times per night	Yes	Yes	Rhythmic movement in transition from waking to sleeping
Catathrenia	Nocturnal prolonged moaning	Intermittent throughout the night	Minutes to hours	Multiple times per night	Yes	No	Prolonged expiratory moans and groans, with slowed respiratory rate
Exploding head syndrome	Loud painless sound of explosion inside the head	Near the onset of sleep	Seconds	Rare, typically infrequent	Yes	Yes	Typically events are close to sleep onset

EMG = electromyogram; non-REM = non–rapid eye movement; REM = rapid eye movement.

behavior in non-REM or REM sleep, the possibility of epilepsy (Chapter 372) should be considered.

Other nocturnal events can present as sensory phenomena or sleep-related movements. Nightmares are emotionally disturbing dreams associated with fear, anxiety, anger, or sadness. Nightmares most commonly occur after a psychologically disturbing event, but may also occur as a result of antihypertensive medications, antidepressants, or dopamine agonists. Exploding head syndrome is the painless perception of a loud sound or sense of an explosion, typically in light sleep. Bruxism is a disorder of jaw clenching or grinding that can cause tooth damage and headaches. Rhythmic movement disorder is associated with body rocking or head banging in the transition from wake to sleep.

Patients who have nocturnal events with atypical features, a risk of harm, signs or symptoms of other sleep disorders, or excessive daytime sleepiness should undergo in-laboratory video polysomnography, with extended EEG recording if seizures are being considered.

TREATMENT

Therapy first should focus on ensuring safety for individuals who may injure themselves or others (e.g., placing the bed on the floor, blocking windows, or moving the patient's bedroom to the ground floor), decreasing factors that may provoke events such as NREM parasomnia by causing arousals, and avoiding inciting factors such as sleep deprivation, alcohol, and short-acting hypnotic agents. Pharmacologic treatment with clonazepam (0.5 to 2 mg) and tricyclic antidepressants (Chapter 362, Table 362-5) has been tried for non-REM parasomnias with varying success. Treatment of sleep apnea reduces both non-REM and REM events. For REM sleep behavior disorder, most patients respond well to melatonin (3 to 20 mg) or clonazepam (0.25 to 3 mg). Rhythmic movement disorder is typically refractory to medication therapy. Nightmares may respond to removal of the provocative substance or may require imagery rehearsal therapy, which helps patients create nonfrightening endings to recurrent nightmares.

RESTLESS LEGS SYNDROME

Restless legs syndrome (Chapter 388) is characterized by four essential features: discomfort or urge to move the legs, worsening with rest, improvement with movement, and worsening in the evening. Patients with restless legs syndrome may report that the discomfort can be torturously debilitating and cause them to walk or continuously move their legs until the early morning hours. Some patients note that their legs will move on their own, thereby indicating periodic limb movements in wakefulness. About 85 to 90% of restless legs syndrome patients will have periodic limb movements in sleep, but only a minority of patients with periodic limb movements in sleep will meet the clinical criteria of restless legs syndrome.

Therapies for restless legs syndrome[26] include dopamine agonists (pramipexole 0.125 to 1.5 mg or ropinirole 0.25 to 3 mg), transdermal rotigotine (1 to 3 patch/24 hours), and gabapentinoid medications (e.g., gabapentin-encarbil 600 to 1800 mg).[A23] Dopamine agonists are now avoided because they augment the intensity and duration of daily symptoms; in such patients the agent should be carefully withdrawn and another agent, such as gabapentin or pregabalin (25 to 300 mg daily), can be tried. In some patients, restless legs syndrome has been linked to low iron levels in the central nervous system and may improve with iron replacement.[A24] More intractable symptoms may require chronic narcotics (Chapter 26, Table 26-6).

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For the General References and other additional features, please visit Elsevier eBooks+ at https://ebooks.health.elsevier.com.

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375

APPROACH TO CEREBROVASCULAR DISEASES

LARRY B. GOLDSTEIN

DEFINITION

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Globally, age-adjusted stroke mortality decreased by 14% between 2007 and 2017,[5] but the annual decrease gradually slowed over that time. In the United States, age-adjusted stroke-related mortality decreased by 6.6% between 2009 and 2019, but the total number of stroke deaths increased by 16%.

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About 60% of stroke deaths occur in women, but the rates are actually highest in Black men. It is estimated that someone in the United States has a stroke about once every 40 seconds. In addition, Blacks, people with lower levels of education, individuals who reside in the southeastern portion of the country (the "Stroke Belt"), and individuals with a first-degree relative who had a stroke before the age of 65 years have a higher risk for stroke and stroke-related mortality. Poor diet, lack of exercise (Chapter 14), cigarette smoking (Chapter 363), exposure to environmental tobacco smoke, obesity (Chapter 201), and excess alcohol consumption (Chapter 364) are lifestyle factors that greatly increase the risk for stroke. Of the medical conditions that increase the risk for stroke, hypertension (Chapter 64) has the highest population-attributable risk. Other stroke risk factors include atrial fibrillation (Chapter 52), diabetes (Chapter 210), dyslipidemia (Chapter 190), inflammatory states, elevated homocysteine levels, high lipoprotein (a), carotid artery stenosis, patent foramen ovale (Chapter 55), other congenital heart defects, sleep apnea (Chapter 374), and chronic kidney disease. Coagulation disorders (Chapter 67), oral contraceptive agents (Chapter 220), and migraine headache with aura (Chapter 367) also may contribute to the risk. For many of these risk factors, primary or secondary prevention can substantially reduce the risk of a first or recurrent stroke.[9,10]

Mendelian diseases associated with stroke include sickle cell disease (Chapter 149); mitochondrial encephalopathy, lactic acidosis, and stroke (MELAS); cerebral autosomal dominant arteriopathy with subcortical infarcts and leukoencephalopathy (CADASIL; Chapter 371); Fabry disease (Chapters 192 and 254); and Marfan syndrome (Chapter 239). In addition, autosomal dominant polycystic kidney disease (Chapter 112) is associated with intracranial aneurysms and fibromuscular dysplasia. Ehlers-Danlos type IV (Chapter 239) is also associated with intracranial aneurysms as well as cervical arterial dissection. Several genetic polymorphisms also have been associated with stroke, but these genetic markers are not yet clinically relevant.

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An understanding of vascular anatomy and its normal variants as well as their relationships to functional neuroanatomy can provide important clues for identifying the cause of cerebrovascular symptoms and signs in individual patients and can also help guide treatment.

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Paired carotid and vertebral arteries normally supply the brain (Fig. 375-1). The right common carotid artery arises from the brachiocephalic trunk (innominate artery), which then gives rise to the right subclavian artery. The

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375

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ABSTRACT

Cerebrovascular disease leads to parenchymal brain injury resulting from pathophysiological processes affecting vascular structures supplying, within, or draining the brain. These diseases are a leading cause of morbidity and mortality worldwide. Understanding vascular anatomy and its normal variants must be integrated with a knowledge of functional neuroanatomy and physiology to provide important clues for identifying the cause of stroke in individual patients, to help guide diagnostic evaluations, and to direct rational treatment.

KEYWORDS

ischemic stroke
brain hemorrhage
epidemiology
vascular anatomy
diagnosis
pathophysiology

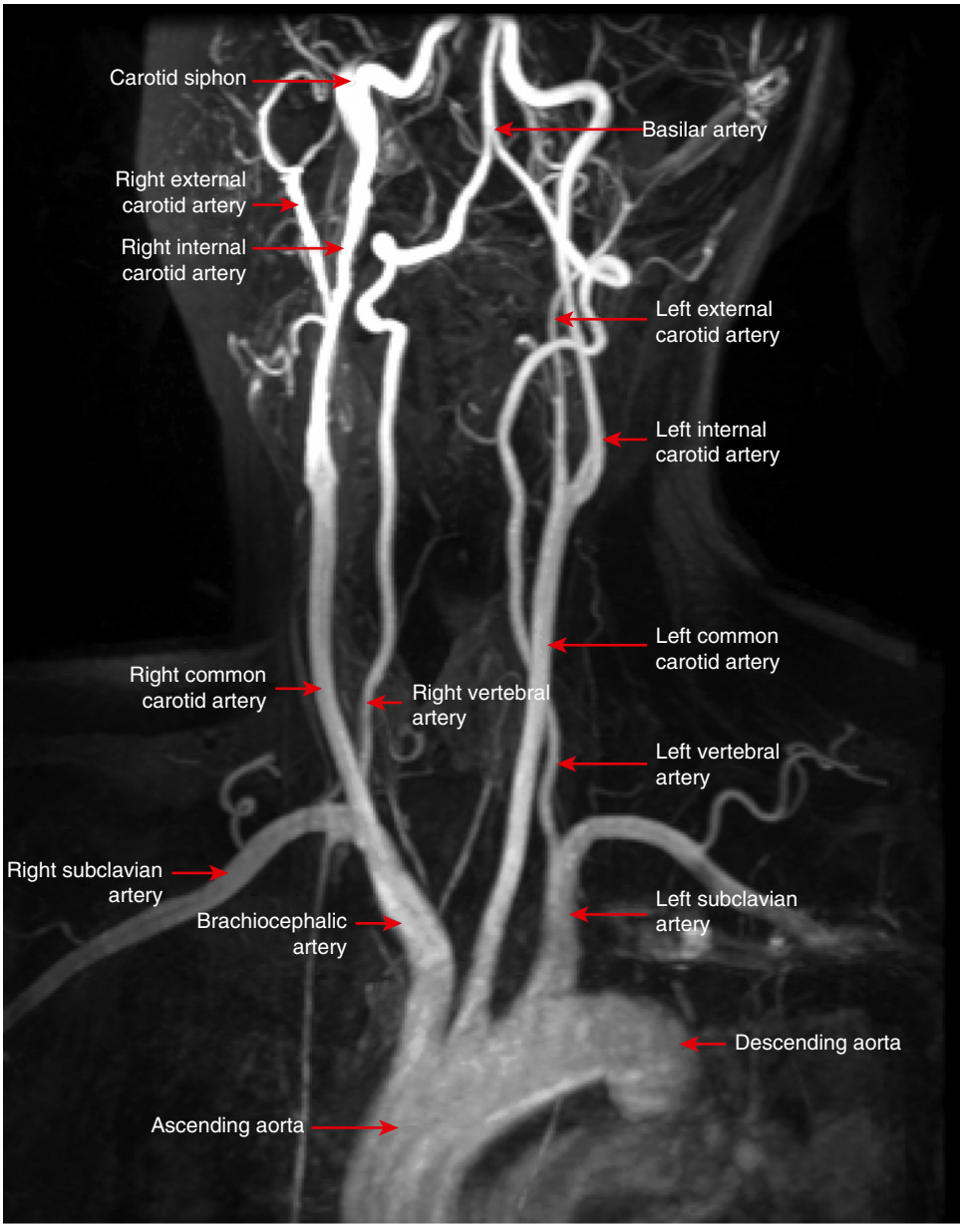

FIGURE 375-1. **Magnetic resonance angiogram of normally configured aortic arch.**

right vertebral artery generally arises from the proximal portion of the right subclavian artery. The left common carotid artery usually arises directly from the aortic arch; but in some individuals, it may arise from the proximal portion of the brachiocephalic trunk ("bovine" anatomy). The left subclavian artery originates from the aortic arch distal to the left common carotid artery and also supplies the left vertebral artery.

Internal Carotid Arteries

The common carotid arteries bifurcate into the internal carotid artery and external carotid artery in the neck, generally at the level of the thyroid cartilage. The bifurcation may less commonly occur above the lower level of the mandible or lower in the neck. The internal carotid artery enters the skull through the foramen lacerum and travels through the petrous bone adjacent to the inner ear. It then enters the cavernous sinus, ascends in an S shape (carotid siphon), penetrates the dura, and finally divides into the anterior cerebral artery and middle cerebral artery (Fig. 375-2). The ophthalmic artery can originate from the internal carotid artery in the carotid siphon, but it more commonly arises from the supraclinoid internal carotid artery, followed by the posterior communicating and anterior choroidal arteries.

External Carotid Arteries

The external carotid arteries have extracranial branches, thereby distinguishing them from the internal carotid arteries. The superficial temporal arteries (palpable anterior to the ears) and facial arteries can anastomose with the intracranial circulation through branches of the ophthalmic artery and can be clinically important, potentially supplying the intracranial circulation in the setting of a proximal internal carotid artery occlusion.

Vertebral Arteries

Although the vertebral arteries generally arise from the subclavian arteries, they can also originate from the aortic arch or thyrocervical trunk. They most commonly enter the C6 transverse process but may also enter at the C4, C5, or C7 levels. They exit the transverse processes at C1, turn posteriorly behind the atlantoaxial joint, and then pass through the dura at the foramen magnum. Intracranially, they typically join at the pontomedullary junction to form the single basilar artery, although the vertebral artery can end in the posterior inferior cerebellar artery in some individuals (Fig. 375-3). The portion of the vertebral artery between its origin and its entry into the transverse process is referred to as the V1 segment. The V2 segment refers to the portion of the artery traveling through the transverse foramina; the V3 segment, the portion between where the artery exits the transverse foramina and penetrates the dura; and the V4 segment, the intracranial portion of the artery. One vertebral artery may be hypoplastic (E-Fig. 375-1). Clues are that the ipsilateral transverse foramina are generally smaller on the side of the hypoplastic artery and that the proximal portion of the basilar artery can be displaced ipsilateral to the hypoplastic artery. The V3 segment is particularly vulnerable to mechanical

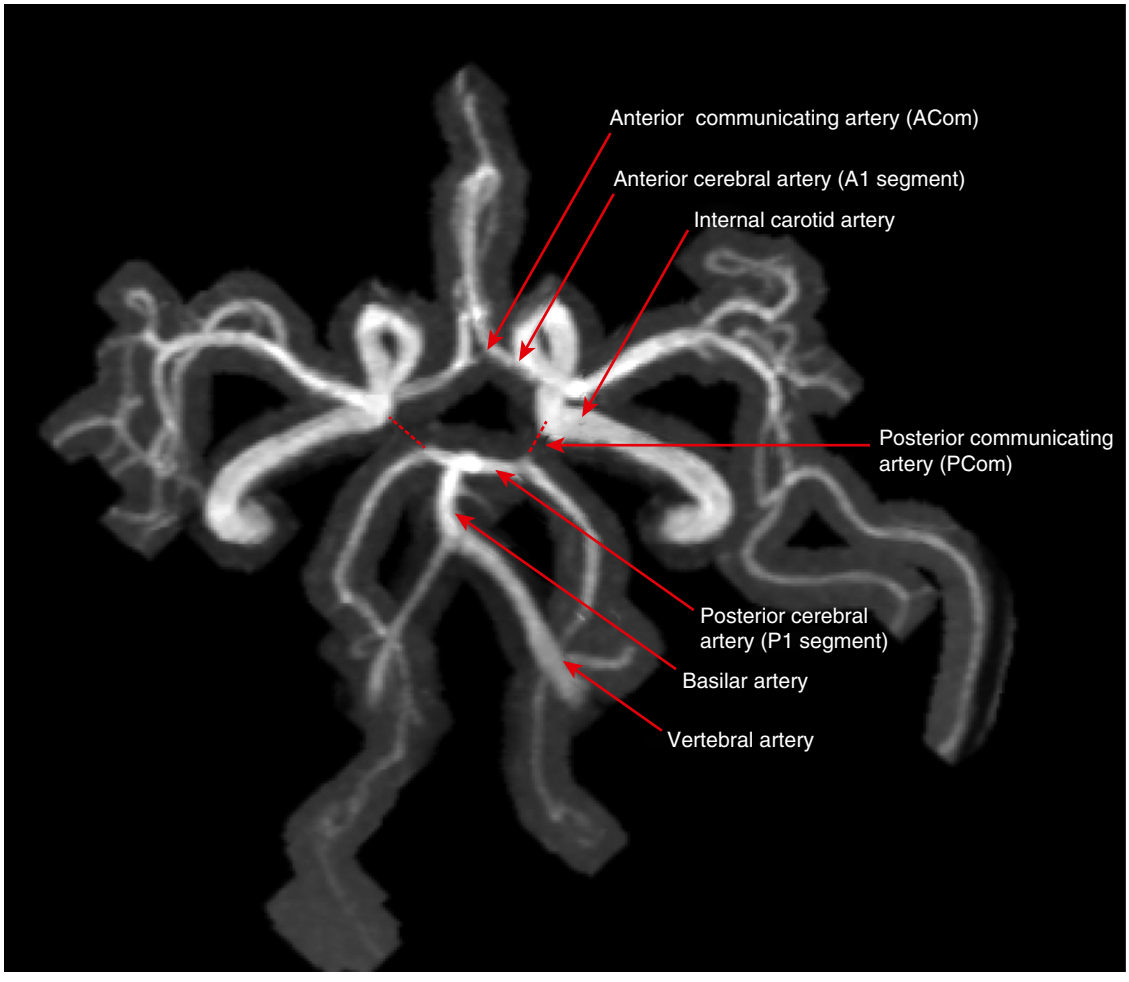

E-FIGURE 375-1. Magnetic resonance angiogram of the circle of Willis. The approximate positions of the posterior communicating arteries are shown with *dotted lines*.

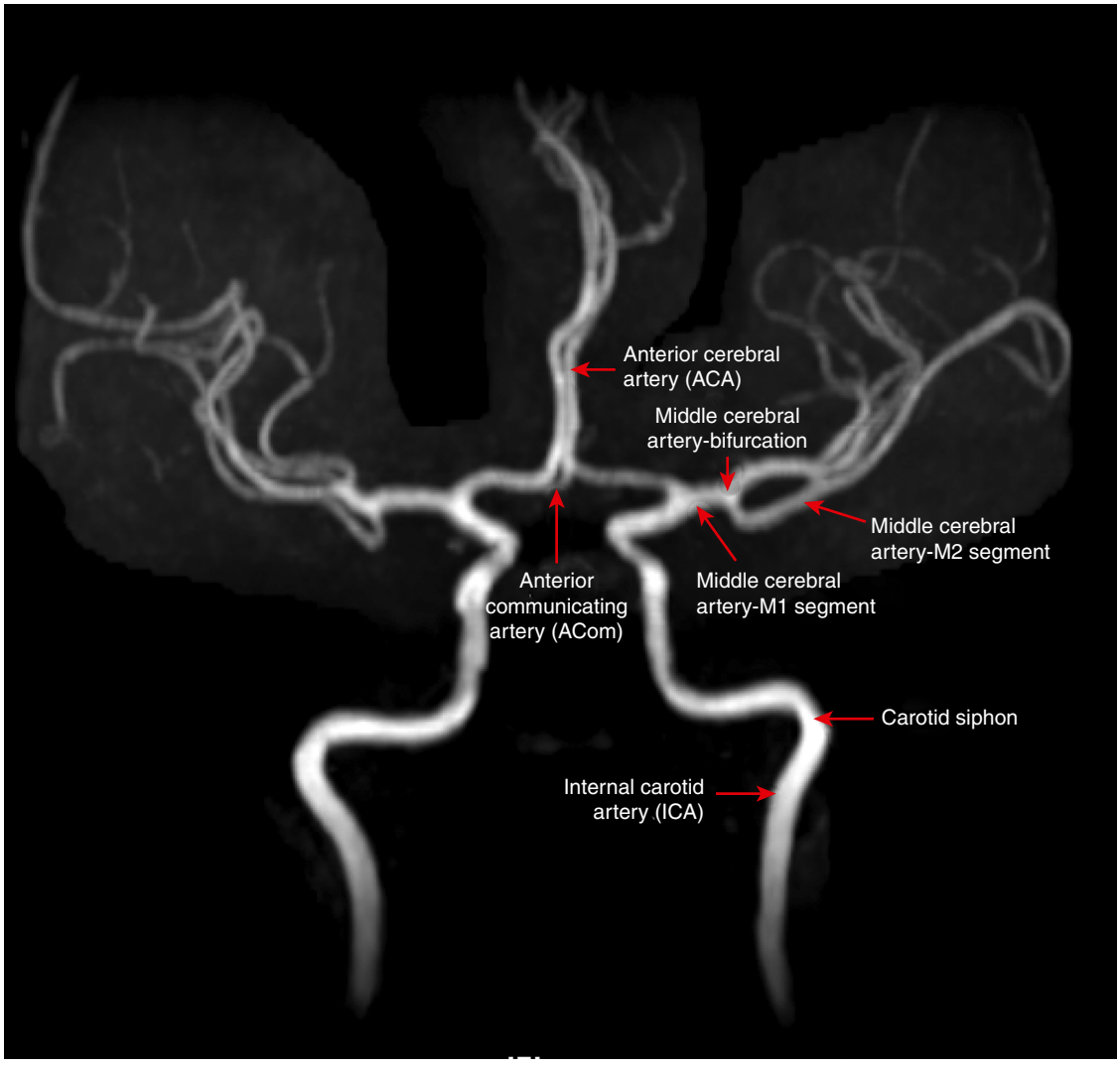

FIGURE 375-2. **Magnetic resonance angiogram of the intracranial portion of the internal carotid artery and its main branches.**

injury that can lead to dissection. The vertebral arteries have medial branches that unite to form the anterior spinal artery and lateral branches that supply the dorsolateral medulla and inferior portion of the cerebellum, which also supplies the vestibular nuclei (Fig. 375-4). Other medial branches of the vertebral artery supply the medullary pyramid, inferior olivary nucleus, medial lemniscus, and hypoglossal nerve fibers. Longer circumferential branches from the vertebral arteries and posterior cerebral arteries supply the spinothalamic tracts and sympathetic fibers as they traverse the medulla, the sensory nuclei, and the descending tracts from cranial nerve V as well as emerging fibers from the vagus and glossopharyngeal nerves.

Basilar Artery

The basilar artery has small penetrating branches supplying the dorsal portions of the pons and midbrain (see Figs. 375-3 and 375-4). The anterior inferior cerebellar arteries originate from the mid-basilar artery. They supply portions of the cerebellar hemispheres in addition to the lateral pons; cranial nerves V, VII, and VIII; and pontine portions of the spinothalamic tracts and sympathetic fibers. The two superior cerebellar arteries arise from the distal basilar artery at the level of the midbrain proximal to the common origin of the two posterior cerebral arteries. The oculomotor nerves exit the midbrain between the superior cerebellar artery and posterior cerebral artery. The superior cerebellar arteries give branches supplying the dorsal midbrain, including the colliculi and the superior portions of the cerebellar hemispheres and vermis. The long circumferential vessels also supply the dorsolateral brain stem.

In addition to the anterior inferior cerebellar artery and superior cerebellar artery, the basilar artery has paramedian vessels supplying the middle portion of the basis pontis and midline pontine structures, including the corticospinal tracts, medial longitudinal fasciculus, and pontine reticular nuclei. At the midbrain level, paramedian branches of the basilar artery supply the cerebral peduncles, cranial nerve III nuclei and fibers, and medial portions of the red nucleus and medial lemniscus. Short circumferential branches supply the ventrolateral pons and midbrain.

Circle of Willis

The arterial anastomosis at the base of the brain is termed the circle of Willis (see E-Fig. 375-1). The two anterior cerebral arteries are connected by the anterior communicating artery. The posterior communicating arteries connect the supraclinoid internal carotid arteries with the proximal posterior cerebral arteries. In persons with an intact circle of Willis, the entire intracranial circulation can be supplied by a single patent internal carotid artery or vertebral artery.[11] The majority of individuals, however, have an incomplete circle of Willis (see Fig. 375-2). One common variant is for the portion of the anterior cerebral artery between the internal carotid artery and the anterior communicating artery (A1 segment) to be hypoplastic or absent. In this case, both anterior cerebral arteries can be supplied from a single internal carotid artery. Another common variant is for the portion of the posterior cerebral artery between its normal origin from the basilar artery and the posterior communicating artery (P1 segment) to be absent or hypoplastic (termed a "fetal" posterior cerebral artery). In these individuals, the distal posterior cerebral artery territory is supplied by the carotid rather than by the vertebrobasilar arteries.

Anterior Cerebral Arteries

The anterior cerebral arteries travel anteriorly and then turn posteriorly with leptomeningeal branches supplying the medial portions of the frontal and parietal lobes (Figs. 375-5 to 375-7; see also Fig. 375-2). In about half of

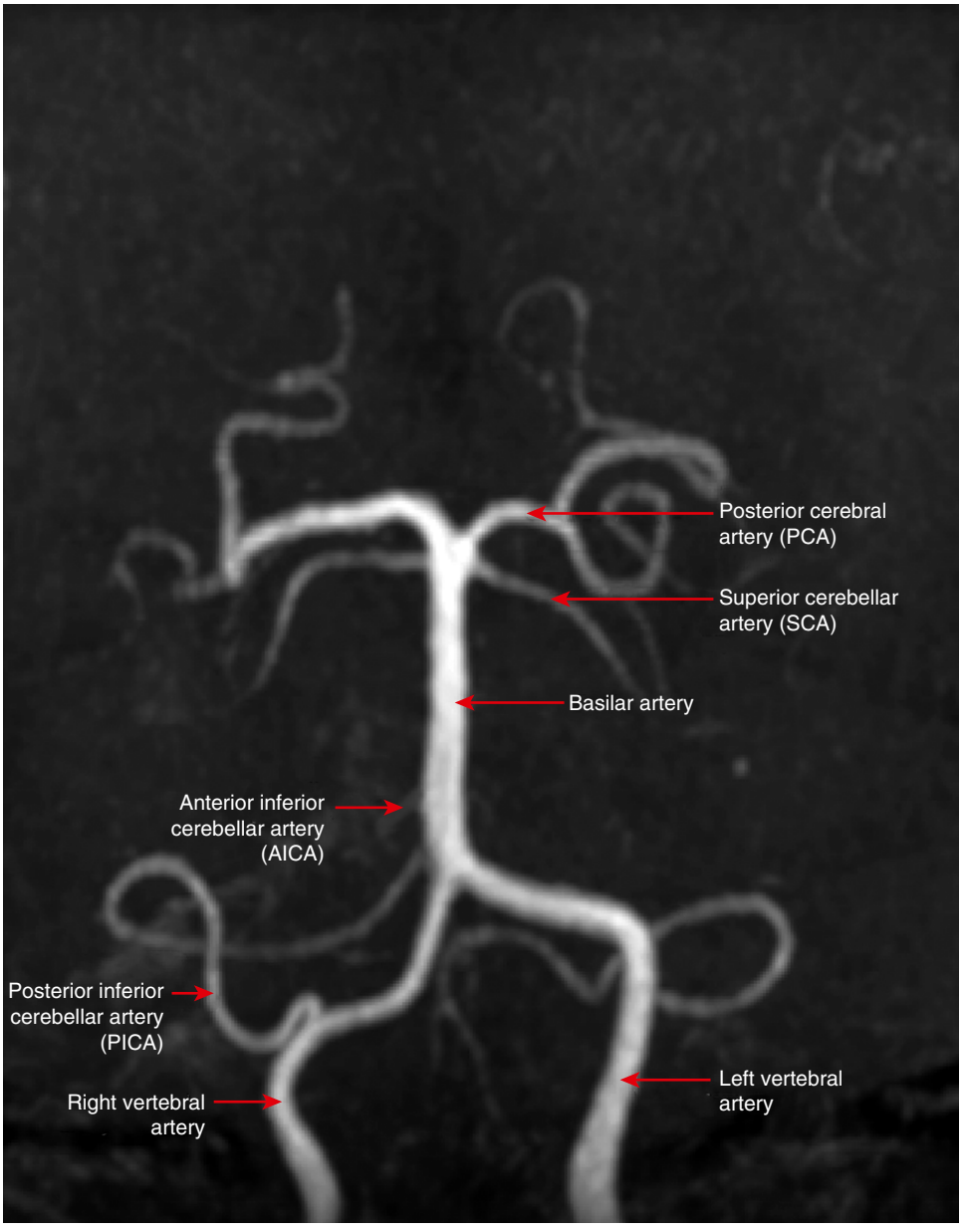

FIGURE 375-3. **Magnetic resonance angiogram of the intracranial portion of the vertebrobasilar system.**

people, the anterior cerebral artery divides into pericallosal and callosal marginal branches. Terminal portions of the latter artery supply the medial cortex between the parietal and occipital lobes. Damage to this area can be confused with "watershed" hypoperfusion injury. A series of small lenticulostriate arteries originate from the A1 and A2 (between the anterior communicating artery and corpus callosum) segments of the anterior cerebral artery. The recurrent artery of Heubner is a large, important medial striate artery that provides blood supply to the anterior and inferior portions of the anterior limb of the internal capsule, anterior and inferior portions of the caudate nucleus, anterior globus pallidus, putamen, hypothalamus, olfactory bulbs and tracts, and uncinate fasciculus. It can be inadvertently damaged during surgical clipping of an anterior communicating artery aneurysm.

Anterior Choroidal Artery

The anterior choroidal artery (medial striate artery) commonly arises from the supraclinoid internal carotid artery distal to the posterior communicating artery. It travels posteriorly over the medial optic tract and enters the brain at the choroidal fissure. It gives branches to the optic tract, anterior hippocampus, amygdala, tail of the caudate nucleus, geniculate body, and inferior portion of the posterior limb of the internal capsule (see Fig. 375-7). Ischemic lesions in this area can be confused with lesions arising from the middle cerebral artery.

Middle Cerebral Artery

The middle cerebral artery supplies the bulk of the frontal, parietal, and lateral portions of the temporal lobes (Figs. 375-8 and 375-9; see also Figs. 375-6 and 375-7). The M1 segment refers to the portion of the middle cerebral artery between its origin from the supraclinoid internal carotid artery and its distal branches (see Fig. 375-2). The middle cerebral artery bifurcates in the Sylvian fissure in 20 to 30% of individuals and trifurcates in about 70% of individuals. The superior division supplies the frontal and parietal lobes, and the inferior division supplies the lateral portion of the temporal lobe. The M1 segment gives rise to some medial and all of the lateral lenticulostriate arteries. These arteries supply the head and body of the caudate nucleus, the putamen, and the globus pallidus as well as the anterior limb, genu, and superior portions of the posterior limb of the internal capsule (see Fig. 375-7).

Posterior Cerebral Artery

The distal portion of the posterior cerebral artery divides into an anterior and a posterior division (see Fig. 375-3). The anterior division supplies the inferior and medial portions of the temporal lobe in the middle cranial fossa, with distal branches anastomosing with those of the middle cerebral artery (see E-Fig. 375-1). The posterior division supplies the occipital lobe, including the calcarine cortex, with terminal branches anastomosing with those of the middle cerebral artery and anterior cerebral artery. The proximal portions of both the posterior cerebral artery and

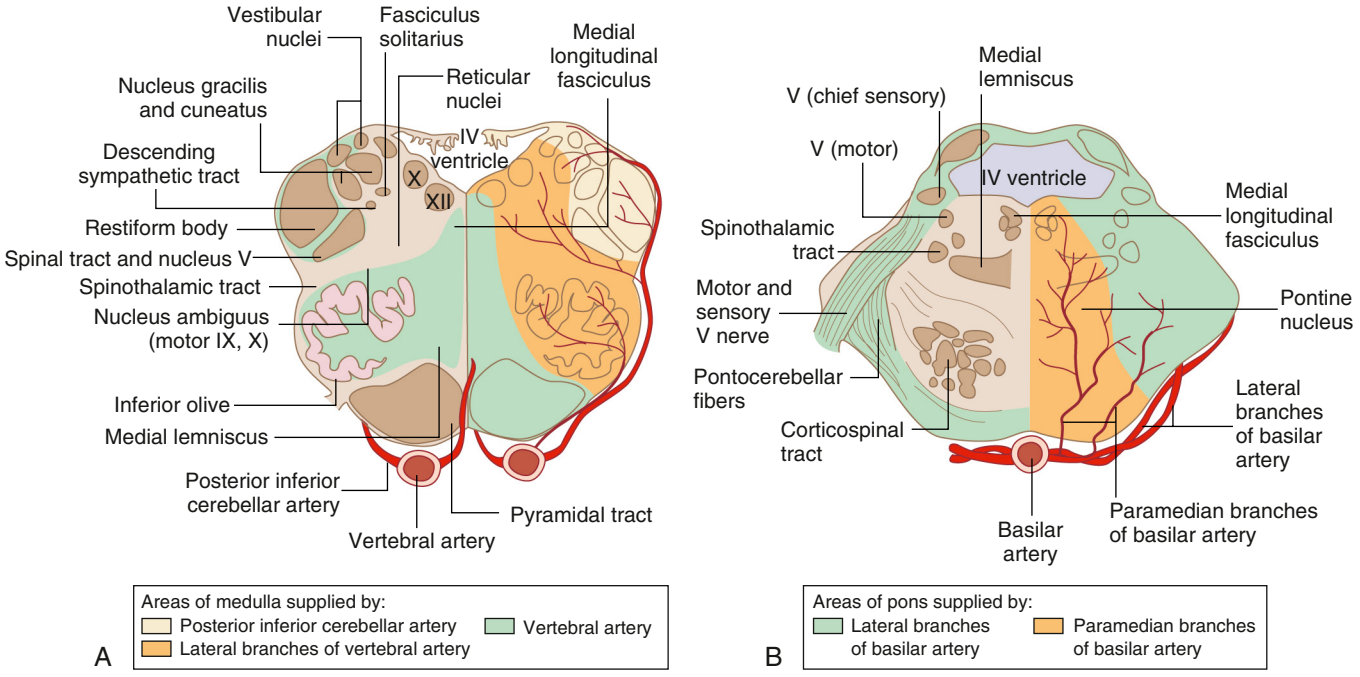

FIGURE 375-4. **Brain stem blood supply. A,** Cross section of the medulla oblongata at the level of the hypoglossal nuclei (cranial nerve XII). Short branches of the vertebral and anterior spinal arteries supply the medulla. Longer circumferential branches, including the posterior inferior cerebellar artery, supply the lateral portions of the medulla. **B,** Cross section of the midpons region. The medial portion receives blood supply from short, perforating basilar artery branches. More laterally, the blood supply comes from lateral basilar artery branches. (From Zivin JA. Approach to cerebrovascular diseases. In: Goldman L, Schafer AI. *Goldman's Cecil Medicine*. 24th ed. Philadelphia: Elsevier Saunders; 2012.)

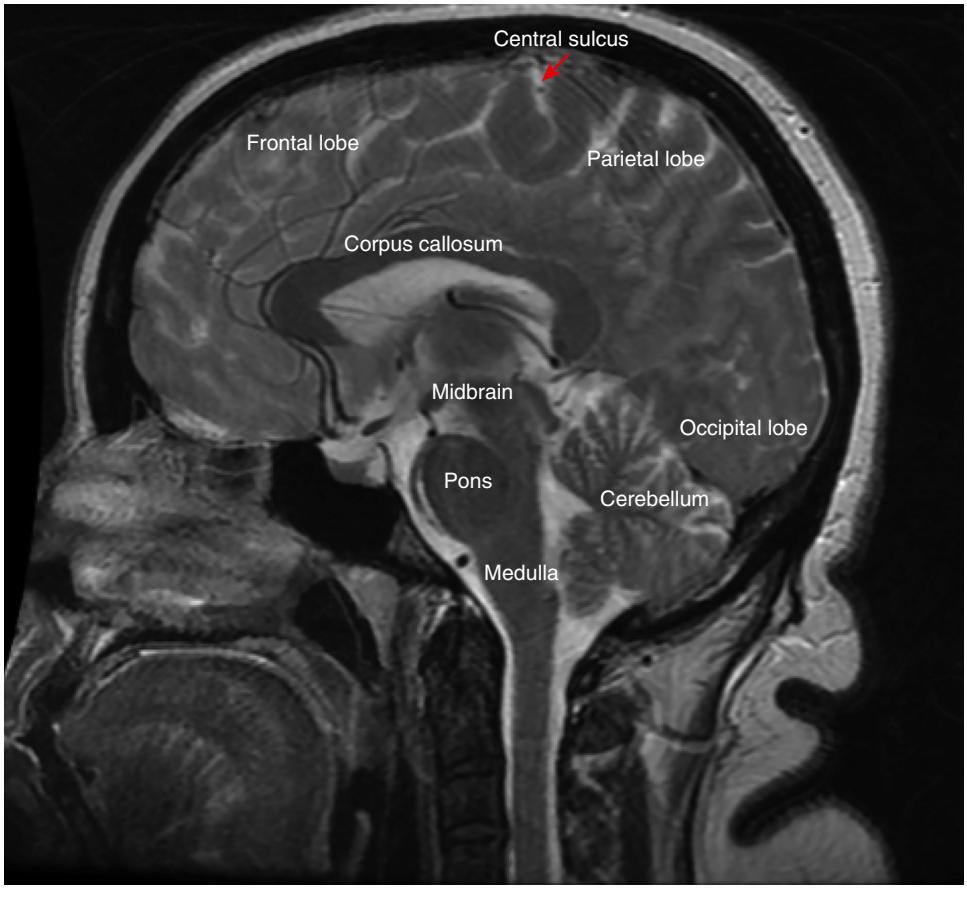

FIGURE 375-5. **Parasagittal T2-weighted magnetic resonance image showing midline structures.**

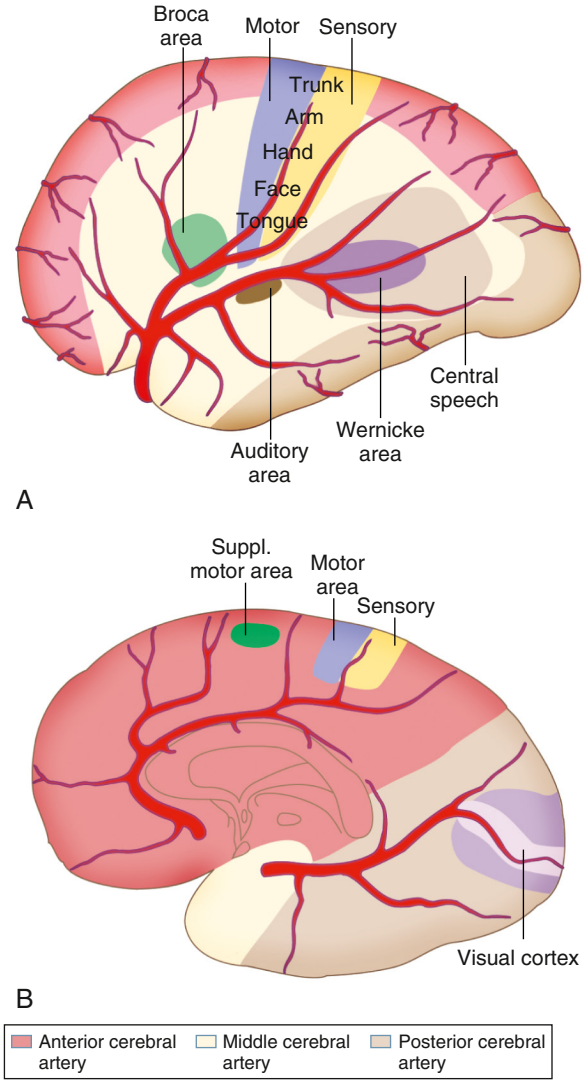

FIGURE 375-6. Surface cerebral arterial anatomy. Lateral (**A**) and medial (**B**) views of the cerebral hemisphere show the surface distributions of the anterior, middle, and posterior cerebral arteries. (From Zivin JA. Approach to cerebrovascular diseases. In: Goldman L, Schafer AI. *Goldman's Cecil Medicine*. 24th ed. Philadelphia: Elsevier Saunders; 2012.)

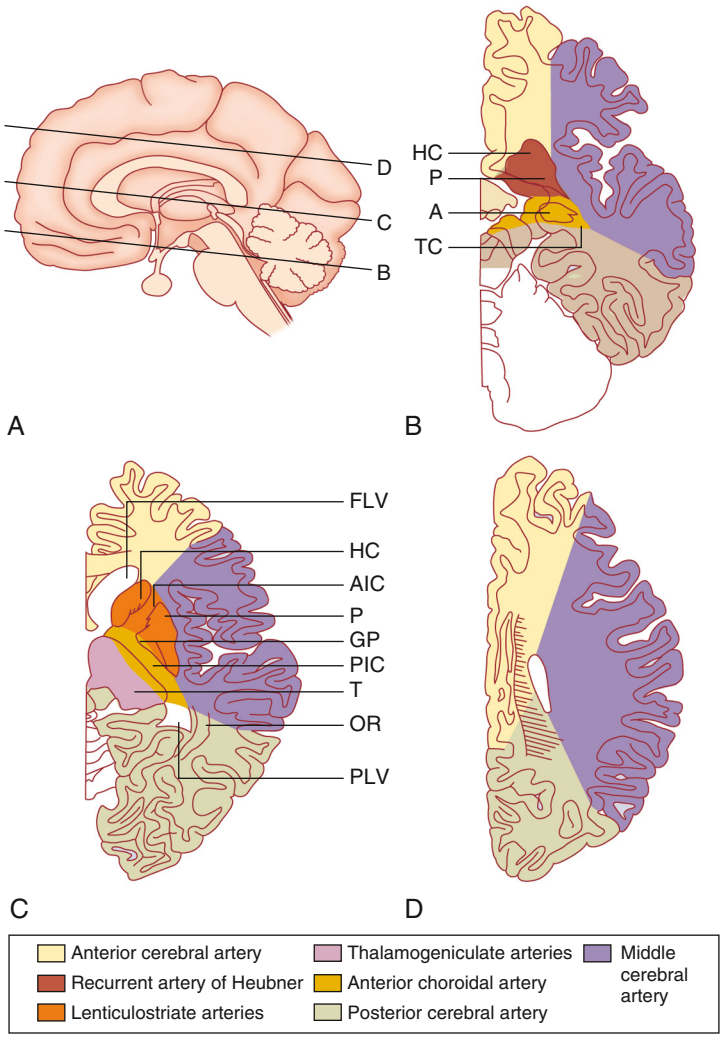

FIGURE 375-7. Arterial supply of the deep brain structures. A, Sagittal view of the brain showing the computed tomographic (CT) planes through which views **B**, **C**, and **D** were taken. **B**, CT plane through the head of the caudate nucleus (HC), putamen (P), amygdala (A), tail of the caudate nucleus (TC), hypothalamus, temporal lobe, midbrain, and cerebellum. **C**, CT plane through the frontal horn of the lateral ventricle (FLV), head of the caudate nucleus (HC), anterior and posterior limbs of the internal capsule (AIC, PIC), putamen (P), globus pallidus (GP), thalamus (T), optic radiations (OR), and posterior horn of the lateral ventricle (PLV). **D**, CT plane through the centrum semiovale. (Modified from De Armond S, Fusco MM, Dewey MM. *Structure of the Human Brain, a Photographic Atlas*. 3rd ed. New York: Oxford University Press; 1989, with permission.)

the posterior communicating artery give off small penetrating arteries to the thalamus (thalamoperforators). In some individuals, a single common artery arising from the P1 segment (artery of Percheron) can supply both thalami. Unless the posterior cerebral artery has a fetal-type origin from the internal carotid artery, thalamic strokes are generally related to the vertebrobasilar circulation. Two posterior choroidal arteries arise separately from the posterior cerebral artery and supply the choroid plexus, posterior thalamus, fornix, and midbrain tectum. Posterior cerebral artery perforators also supply the medial portions of the cerebral peduncles, substantia nigra, red nuclei, hippocampus, and posterior hypothalamus.

Venous System

The venous drainage of the brain is divided into superficial and deep systems (Figs. 375-10 and 375-11). Deep structures drain into the inferior sagittal sinus and vein of Galen that join to form the straight sinus, which runs along the tentorium to join the superior sagittal sinus at the torcula. The cerebral veins drain into the sagittal sinus. The two transverse sinuses extend laterally from the torcula into the sigmoid sinus, which then forms the jugular vein. Often, one hypoplastic transverse sinus can cause confusion if a sinus thrombosis is suspected. In these cases, the jugular notch in the occipital bone and jugular foramen may be smaller on the side of the hypoplastic transverse sinus. Each cavernous sinus surrounds the ipsilateral internal carotid artery. Fibers from cranial nerve VI run within the cavernous sinus inferior to the carotid artery, with fibers from cranial nerves III, IV, V1, and V2 running in its lateral wall. The two cavernous sinuses connect to each other and drain into the petrosal sinus and then the sagittal sinus.

Physiology

Cerebral Blood Flow

The brain, which is among the body's most metabolically active tissues, receives about 14% of resting cardiac output. Normal resting metabolism of brain tissue requires 140 µmol of oxygen and 24 µmol of glucose per 100 g of tissue per minute. Although total blood flow to the brain remains constant in normal conditions, regional flow changes with mental activity, often manifested by changes in synaptic activity, and provides the basis for functional magnetic resonance imaging or positron emission tomography imaging studies. Approximately 80% of glucose is used to generate energy, with the remainder metabolized to lactate or used for synthetic activities. Little glucose is stored in the brain, and the brain's high metabolic demand makes it particularly vulnerable to reductions in oxygen and blood supply. Cerebral blood flow at rest averages 50 to 100 mL per 100 g of brain tissue per minute. If blood flow falls below this level, normal neuronal function is suppressed (i.e., neurons become electrically quiescent). If the deficit persists, irrevocable neural injury can result.

Cerebral blood flow is regulated though a variety of mechanisms in addition to mental activity. Constant, overall cerebral blood flow is maintained through autoregulation. This autoregulatory relationship is reflected in the equation cerebral blood flow = cerebrovascular resistance/mean arterial pressure. If the mean arterial pressure is decreased, there is a compensatory decrease in

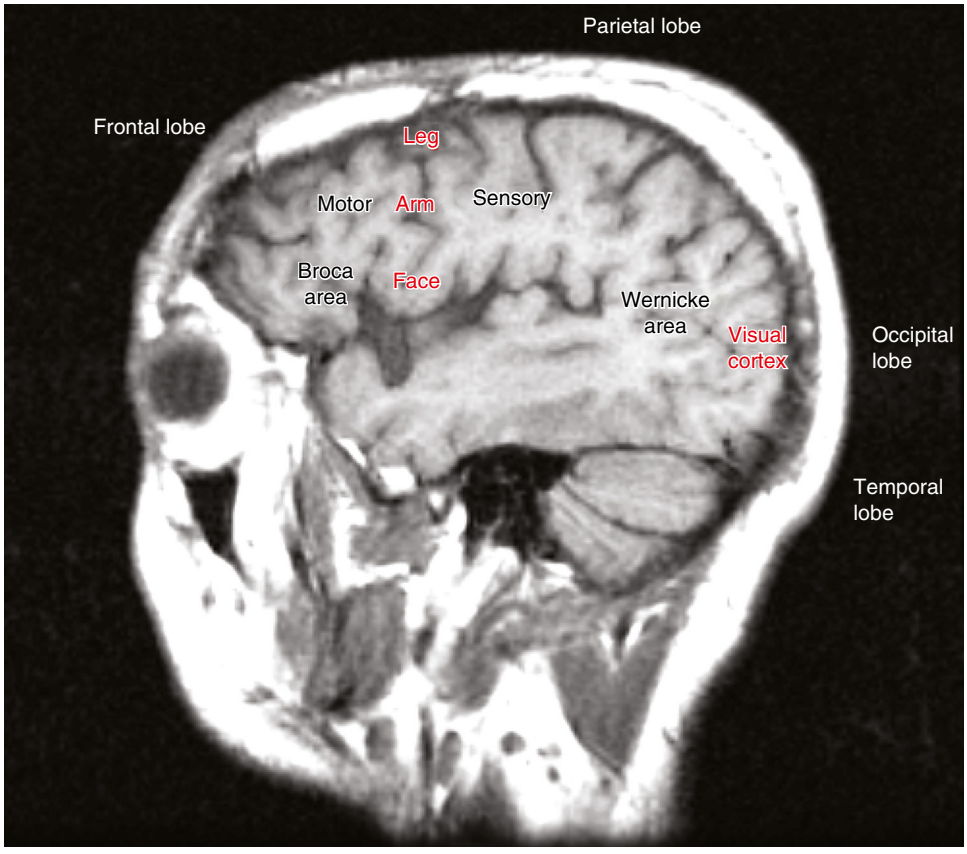

FIGURE 375-8. Sagittal, lateral T1-weighted magnetic resonance image showing cortical motor, sensory, visual, and language areas.

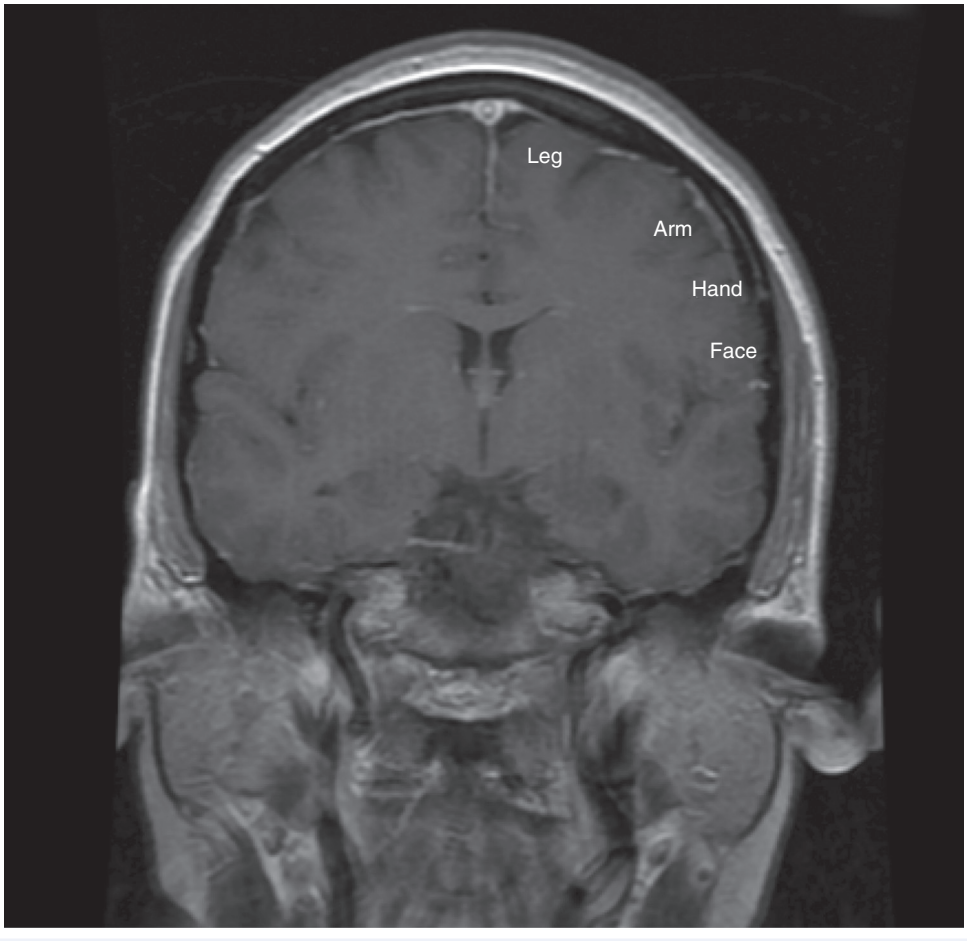

FIGURE 375-9. Coronal T1-weighted magnetic resonance image showing cortical areas for the leg, arm, hand, and face.

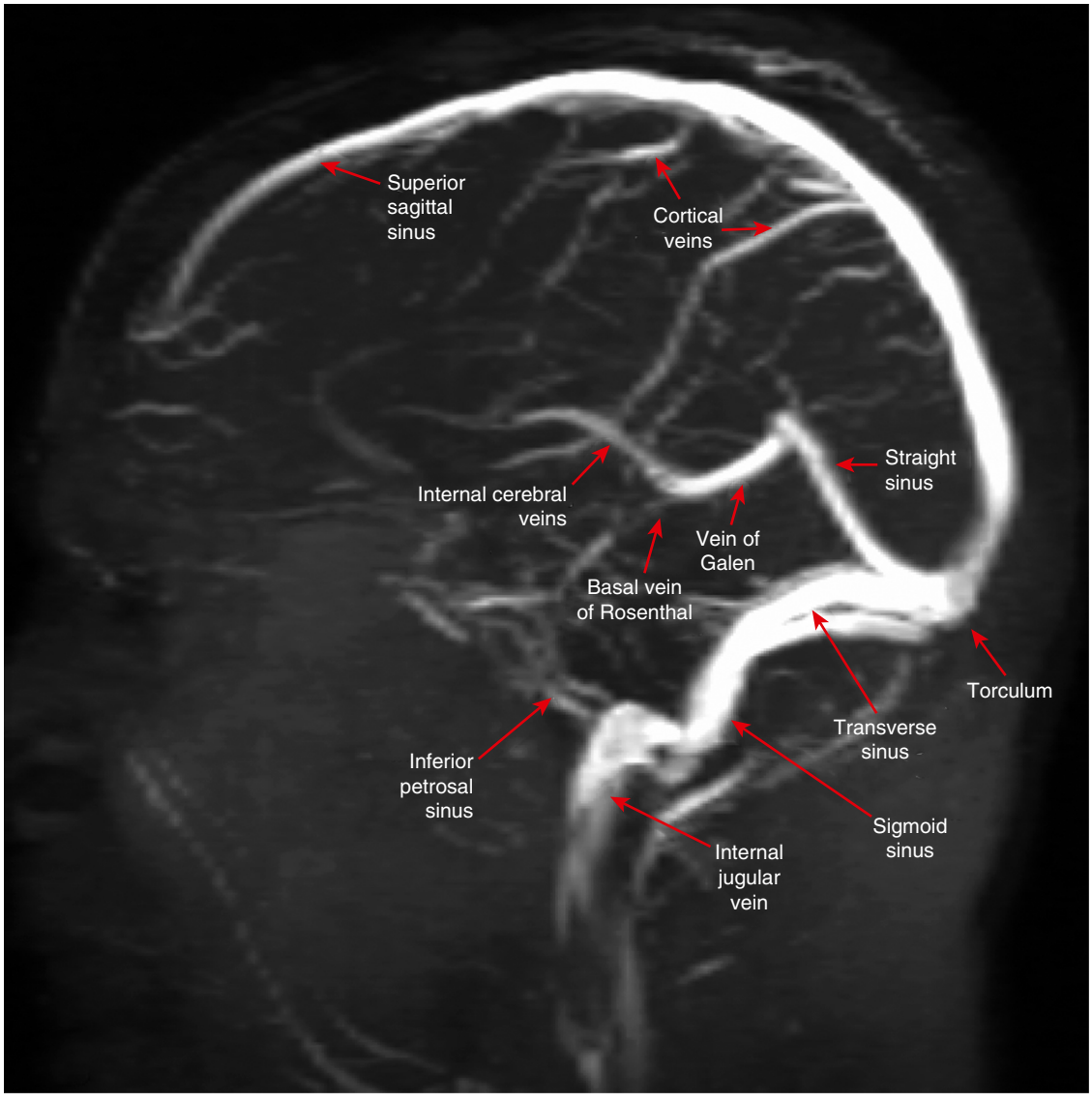

FIGURE 375-10. **Parasagittal magnetic resonance venogram showing venous structures.**

cerebrovascular resistance (through dilation of cerebral arterioles) to maintain cerebral blood flow constant. If the mean arterial pressure is increased, there is a compensatory increase in cerebrovascular resistance (through constriction of cerebral arterioles). There are, however, limits to cerebral autoregulation. At mean arterial pressures greater than about 150 mm Hg, cerebral arterioles are maximally constricted, and cerebral blood flow rises. At mean arterial pressures below about 50 mm Hg, cerebral arterioles are maximally dilated, and cerebral blood flow falls. In the setting of chronic hypertension, the autoregulatory relationship between cerebrovascular resistance and mean arterial pressure is shifted to higher critical mean arterial pressures (i.e., cerebral blood flow falls at a higher mean arterial pressure).

Metabolic factors can also affect cerebral blood flow. Hypercapnia causes cerebral vasodilation, and hypocapnia causes cerebral vasoconstriction that is mediated by changes in the pH of the brain's extracellular fluid. Cerebral blood flow declines by approximately 2% for every 1 mm Hg decline in P_{CO_2}. In patients who have increased intracranial pressure and threatened herniation, a short period of hyperventilation (target arterial P_{CO_2} of 30 to 35 mm Hg) can be used as a temporary measure until more definitive treatment can be instituted. The response is only transient because of compensation by the choroid plexus, and a rebound increase in P_{aCO_2} can lead to a rise in intracranial pressure when hyperventilation is discontinued.

Blood-Brain Barrier

The triggering of a neuronal action potential depends on the relative concentrations of Na^+, K^+, and Ca^{2+}, and it is also modulated by Mg^{2+} and a variety of neurotransmitters. The blood-brain barrier is critical for maintaining the environment necessary for normal neuronal function. The blood-brain barrier consists anatomically of the capillary endothelial cells, a basement membrane with pericytes, and astrocytic perivascular footplates. The brain's vascular endothelial cells, which are the principal component of the blood-brain barrier, are joined by tight junctions and generally lack the transport channels found elsewhere in the body. As a result, the blood-brain barrier prevents hydrophilic polar and large molecules in the blood from entering the brain. By comparison, oxygen and carbon dioxide rapidly cross the blood-brain barrier. Nutrients, toxins, and drugs can cross the blood-brain barrier by simple diffusion, by transport through carrier molecules based on concentration gradients (facilitated transport), or by energy-dependent mechanisms (active transport). Glucose is the brain's sole source of energy. Glucose transport into the brain is through non–energy-dependent facilitated transport (glucose transporter isotype 1 [Glut1]). In the setting of ischemia, endothelial cell function can be compromised, and the blood-brain barrier can fail.

The Neurovascular Unit

The concept of the neurovascular unit is important for understanding the complex relationships between anatomic structures and the integrity of brain function. The term reflects the physiologic interrelatedness of the brain's various components, including endothelial cells, vascular smooth muscle, adventitial cells, glia, and neurons. The concept reflects the observation that local pH as well as neural activity can affect local cerebral blood flow. In addition to linking neural activity with blood flow and maintaining the blood-brain barrier, the neurovascular unit can secrete a variety of immunologic and neurotrophic factors that further affect both normal function and the brain's response to injury.

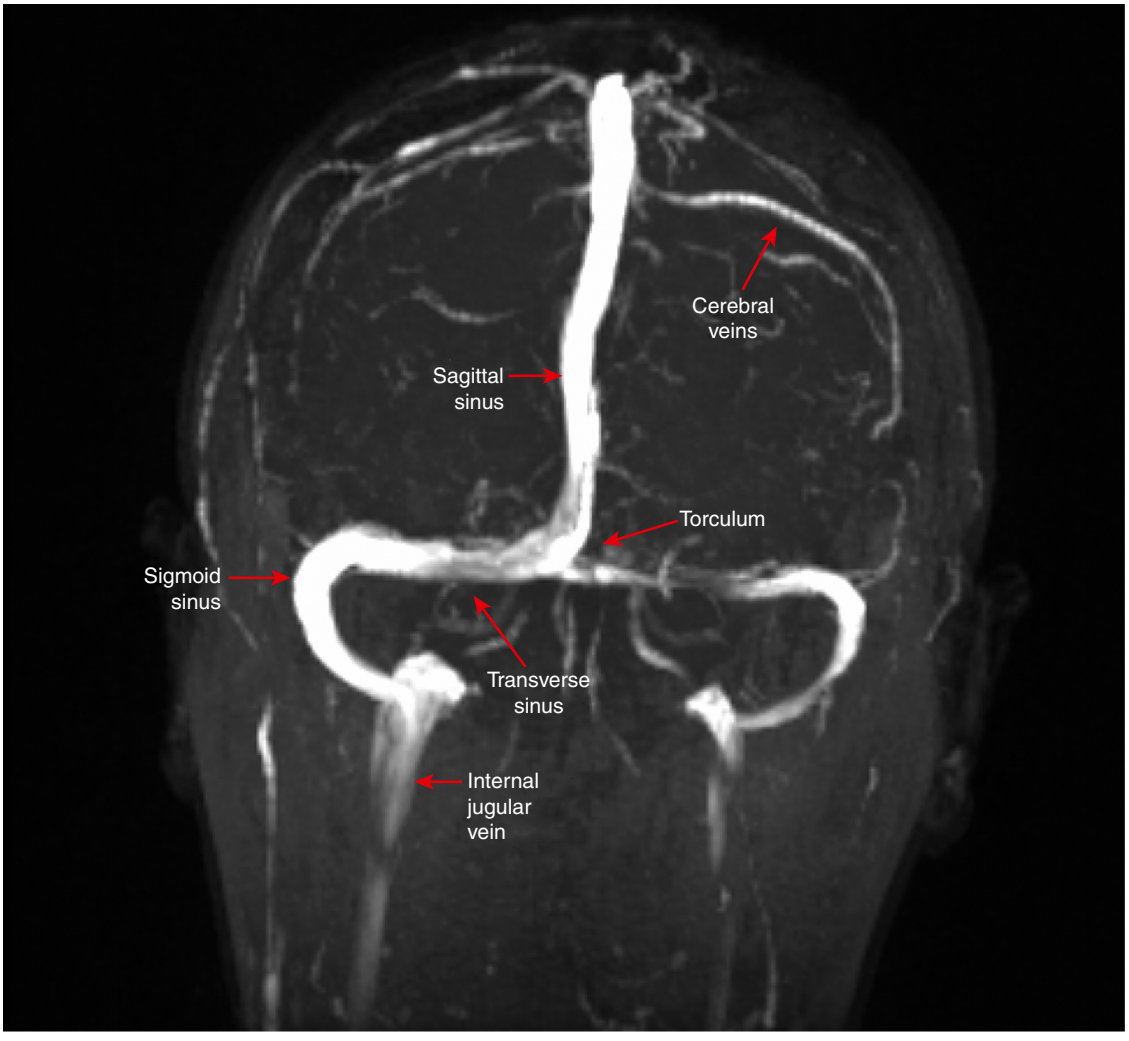

FIGURE 375-11. Anteroposterior magnetic resonance venogram showing venous structures.

CEREBRAL ISCHEMIA

Because of its high metabolic demands, brain function is completely dependent on its supply of blood and oxygen. Clinical symptoms ensue when global or regional blood supply falls below the critical 50 mL per 100 g per minute. Permanent neural injury does not occur if the supply of blood and oxygen is quickly restored, such as with a faint (Chapter 49) in the setting of a global reduction in the supply of blood or oxygen or a transient ischemic attack (Chapter 376) with brief, local reductions in cerebral blood flow. Certain groups of neurons may be particularly vulnerable to hypoxic-ischemic injury (i.e., regions of the hippocampus, cerebellar Purkinje cells, and neocortical layers III, V, and possibly VI). Hypoxic-ischemic injury can be global, diffuse, or focal. In stable patients who are not hypoxemic, supplemental oxygen administration is not helpful.

GLOBAL ISCHEMIC INJURY

Global ischemic injury occurs in the setting of complete cardiovascular collapse, such as with ventricular fibrillation, electromechanical dissociation, and asystole (Chapter 50). Some neurons are particularly vulnerable to ischemic injury and will be selectively damaged, whereas neurons only millimeters away may be spared. In the setting of hypotension, areas of brain between the territories of major arteries (i.e., between the anterior cerebral artery and middle cerebral artery in the frontal cortex and adjacent subcortical white matter), between the middle cerebral artery and posterior cerebral artery (in the parieto-occipital cortex and adjacent subcortical white matter), and between penetrating arteries from distal branches of the middle cerebral artery and lenticulostriate arteries (deep hemispheric white matter, centrum semiovale) are especially vulnerable and are termed watershed areas.

The duration of anoxia, the duration of cardiopulmonary resuscitation (CPR), and the cause of cardiac arrest are related to outcome after CPR (Chapters 50 and 373), but none of these factors accurately discriminate between patients who will have a poor or a favorable outcome. Prognosis also cannot be based on the circumstances of CPR or on elevated body temperature alone. Myoclonic status epilepticus within the first day after cardiac arrest implies a poor prognosis, as does the absence of pupillary or corneal reflexes or extensor motor responses 3 days after cardiac arrest in patients who remain comatose. Bilateral absence of cortical somatosensory evoked responses within 1 to 3 days also portends a poor prognosis.

Out-of-hospital cardiac arrest carries a poor prognosis if effective CPR is not rapidly instituted. A period of therapeutic temperature control to less than 37.8° C may improve neurologic outcome after resuscitated cardiac arrest if it can be instituted rapidly after hospital admission (Chapter 50), and such therapeutic hypothermia may be preferred over cooling to a lower temperature.[A1] If the cerebral cortex is irreversibly damaged but the relatively resistant brain stem control of respiration and cardiovascular regulation is preserved, the patient can enter a persistent vegetative state (Chapter 373).

DIFFUSE HYPOXIC INJURY

Diffuse hypoxia can alter cognition, cause confusion, impair consciousness, and lead to coma, which can be irreversible. Causes include travel to high altitudes, severe anemia, and pulmonary disease. Symptoms are generally present when the Pao_2 abruptly falls to less than 40 mm Hg. Increases in cerebral blood flow can partially compensate for slow declines in Pao_2, which may still cause symptoms with further or rapid reductions.

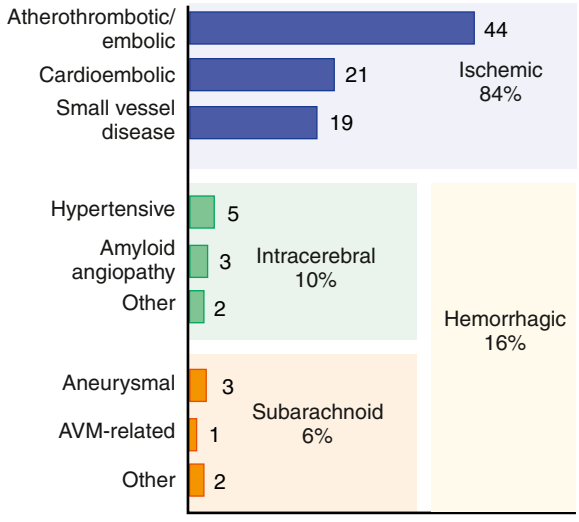

FIGURE 375-12. Classification of cerebrovascular disease by cause. AVM = arteriovenous malformation. (From Zivin JA. Approach to cerebrovascular diseases. In: Goldman L, Schafer AI. *Goldman's Cecil Medicine*. 24th ed. Philadelphia: Elsevier Saunders; 2012.)

FOCAL ISCHEMIC INJURY

Focal ischemic injury is caused by occlusion of a cervical or intracranial artery that supplies the brain. Although this injury can occur from many causes (including infection, inflammation, metabolic disorders, trauma, and hematologic disorders), the majority of strokes are related to thrombotic or embolic occlusion (Fig. 375-12). If flow is not restored within minutes, a core area of irreversible brain injury is commonly produced. A surrounding area of variable size, depending on the artery involved and the integrity of collaterals in which blood flow is reduced, will suffer injury that is not irreversible. The brain in this area, termed the penumbra, is electrically quiescent and contributes to the resulting neurologic deficit. Because the pH of the extracellular fluid in the penumbral zone is low, vessels are maximally dilated and the cerebral autoregulatory response is inoperative. Because cerebrovascular resistance in the penumbral zone is fixed, any decline in mean arterial pressure can further reduce its cerebral blood flow, thereby extending the volume of infarcted brain tissue. A variety of neuroimaging techniques can help distinguish penumbral from infarcted brain tissue (i.e., magnetic resonance diffusion-perfusion mismatch, computed tomographic perfusion imaging) but have not been standardized and have not yet been proved essential for clinical decisions regarding the use of intravenous thrombolytic therapy. Identification of viable tissue in areas of reduced perfusion can guide the use of endovascular thrombectomy in the setting of large vessel occlusions.[12] Many putative neuroprotective strategies aimed at preserving ischemic brain tissue until it can be reperfused through collateral flow have failed in clinical trials.

PATHOBIOLOGY

Permanent occlusion of a cerebral artery results in necrosis of its supplied neurons, glia, and endothelial cells (pan-necrosis). In gross appearance, the area of infarcted brain may be pale or hemorrhagic if secondary bleeding occurred. Over time, the lesion becomes cavitary (encephalomalacia). On microscopic examination, ischemic neurons initially appear small and angular. The cytoplasm becomes homogeneously eosinophilic, and the nucleus becomes dark and pyknotic. As endothelial cells die, associated areas of petechial hemorrhage may appear. An initial inflammatory reaction may lead to microvascular occlusions, such that flow to ischemic tissue may not be restored even if a proximal thrombus is removed (no-reflow phenomenon). Leukocytes that infiltrate ischemic tissue can also release interleukins and cytokines, which can contribute to cytotoxic injury. Blood macrophages begin to reach the infarcted tissue, and neovascularization peaks after about 2 weeks. Macrophage-mediated removal of cellular debris peaks at about 3 to 4 weeks after the infarct. Astrocytes then form a glial scar around the area of infarction.

Because the brain has no reserve energy supply, energy-dependent neuronal and glial processes stop soon after acute deprivation of blood and oxygen. Calcium ions enter depolarized neurons and glia, where they activate second messengers, including lipases and proteases, thereby releasing free fatty acids and generating free radicals that degrade cellular organelles and membranes. Depolarized neurons also release high levels of excitatory neurotransmitters, such as glutamate into synapses, which leads to further neuronal depolarization and calcium entry. Once this cascade has been initiated, neurons may still degenerate over time by apoptosis (programmed cell death) even if blood flow is restored.

CEREBRAL HEMORRHAGE

Subarachnoid hemorrhage, which is bleeding between the pial and arachnoid coverings over the brain, is most commonly related to a ruptured aneurysm (Chapter 377).[13] Cerebral aneurysms may occur spontaneously or be acquired as a result of infection or trauma. They are more common in first-degree relatives of patients who have a cerebral aneurysm and with certain conditions, such as autosomal dominant polycystic kidney disease (Chapter 112) and type IV Ehlers-Danlos syndrome (Chapter 239). Noninfectious aneurysms are typically situated at branch points of major cerebral arteries: anterior cerebral artery–anterior communicating artery, internal carotid artery–posterior communicating artery, middle cerebral artery bifurcation, and basilar artery tip. Initial brain injury can be caused by an acute increase in intracranial pressure, with delayed ischemic injury related to the development of vasospasm after 7 to 10 days. Interference with the absorption of cerebrospinal fluid through the arachnoid granulations can lead to communicating hydrocephalus. Clot within the third or fourth ventricle or cerebral aqueducts can cause obstructive hydrocephalus.

The most common causes of intracerebral parenchymal brain hemorrhages are hypertension (Chapter 64) and cerebral amyloid angiopathy.[14] Myriad other potential vascular and nonvascular causes, including vascular malformations, vasculitis (Chapter 249), venous sinus thrombosis, and coagulopathies (Chapters 158, 159, and 160), are less common. Some tumors (e.g., melanoma [Chapter 188] and renal cell carcinoma [Chapter 182]) can initially present as an intracerebral hemorrhage. Hypertension-related intracerebral hemorrhage occurs in typical areas of the brain (i.e., basal ganglia, thalamus, basis pontis, and cerebellum). In contrast, intracerebral hemorrhage related to cerebral amyloid angiopathy is typically lobar and located closer to the cortical surface. Without sequential neuroimaging studies showing an initial area of ischemic injury, lobar hemorrhages may be difficult to distinguish from a hemorrhagic infarction. Susceptibility-weighted brain magnetic resonance imaging sequences may reveal prior microhemorrhages at the gray-white junction in patients with cerebral amyloid angiopathy.

CEREBRAL EDEMA

When neurons and glia are injured by ischemia, energy metabolism fails and the cells can no longer maintain normal ion gradients between the intracellular and extracellular compartments. The result is cytotoxic edema, in which cells swell soon after the injury. Neurons, glia, and endothelial cells can be affected. Vasogenic edema, which may occur as a result of disruption of the blood-brain barrier due to injury to the endothelium, allows large molecules to pass through the blood-brain barrier and gain access to the brain. Edema generally peaks between 48 and 72 hours after the onset of ischemic injury. In patients with ischemic stroke, the development of cytotoxic edema can lead to an increase in intracranial pressure and, when severe, herniation. In selected patients, craniotomy can be considered to relieve the pressure until the edema subsides.

Neurons, glia, and endothelial cells are also damaged in the setting of intracerebral hemorrhage. The hemorrhage itself is a space-occupying lesion that also can be associated with both cytotoxic and vasogenic edema. Mass effect from cerebellar hemorrhages can compress the fourth ventricle (thereby leading to obstructive hydrocephalus), compress the brain stem (thereby compromising the reticular activating system and impairing consciousness), or cause herniation. Emergent evacuation of cerebellar hemorrhages can be life-saving and leave surviving patients with little or no long-term functional impairment. By comparison, surgical evacuation of intracerebral hemorrhage is not of proven value (Chapter 377), although minimally invasive surgery shows promise.

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Grade A **Grade A Reference**

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376 ISCHEMIC CEREBROVASCULAR DISEASE

LARRY B. GOLDSTEIN

DEFINITION

Ischemic cerebrovascular disease is caused by a reduction of blood supply to the brain. The injury may be focal (related to occlusion of a single artery), multifocal (related to occlusion of several arteries), or global. Although certain clinical features (e.g., severe hypertension, headache, impaired consciousness) may suggest brain hemorrhage (Chapter 377) rather than ischemia, it is not possible to differentiate the two types of conditions without a brain imaging study. In the absence of an inflammatory disease such as vasculitis or other rare conditions, simultaneous involvement of more than one vascular distribution suggests a proximal source of embolism (i.e., a cardiogenic or a proximal arterial source). Involvement of a single vascular territory may be due to either local steno-occlusive disease (e.g., atherosclerosis) or a proximal source of embolism. Involvement in the distribution of a single penetrating artery suggests small-vessel type intracranial disease, but ischemic strokes in this distribution may also be caused by proximal arterial steno-occlusive disease or embolism.

The definition of ischemic stroke is brain, spinal cord, or retinal cell death attributable to ischemia with neuropathologic, neuroimaging, or clinical evidence of permanent injury. Overall, approximately 85% of strokes are related to ischemic disease, with 44% attributable to atherosclerosis, 21% to cardiogenic embolism, and 20% to small-vessel disease.

Transient ischemic attack (TIA) is defined as a brief episode of neurologic dysfunction resulting from focal cerebral ischemia with no evidence of corresponding tissue injury. Symptoms are similar to those of ischemic stroke. Previously characterized as a transient deficit with symptoms persisting for less than 24 hours, evidence of corresponding tissue injury can be found on brain magnetic resonance imaging (MRI) in 30 to 40% of patients who otherwise fulfill the clinical definition of TIA.

EPIDEMIOLOGY

Stroke (ischemic and hemorrhagic) is the third leading cause of death worldwide and the fifth leading cause of death in the United States.[1] It is also a leading cause of adult disability. In addition to age, race or ethnicity, and family history, certain lifestyle factors and medical conditions increase the risk of stroke (Chapter 375; Table 376-1). Of these, hypertension is the single most important treatable risk factor (Chapter 64; Table 376-1), and the risk of stroke increases with increasing blood pressure without a threshold effect. Diabetes (Chapter 210) is associated with a doubling of the risk of stroke (Table 376-1). Atrial fibrillation (Chapter 52; Table 376-1) is associated with up to 25% of ischemic strokes, with the absolute risk varying by concomitant risk factors.

TABLE 376-1 COMMON STROKE RISK FACTORS

FACTOR	POPULATION-ATTRIBUTABLE RISK	RISK REDUCTION WITH TREATMENT
LIFESTYLE		
Cigarette smoking	12-14%	50% within 1 yr of quitting
Physical inactivity	30%	None proven
Excess alcohol consumption	7%	None proven
MEDICAL		
Hypertension	>90%	32%
Diabetes	5-27%	None proven
Atrial fibrillation	2-24%	64%
Carotid stenosis	2-7%	50%
Sickle cell disease	—	91% with transfusion therapy in children

Data from Goldstein LB, Bushnell CD, Adams RJ, et al. Guidelines for the primary prevention of stroke: a guideline for healthcare professionals from the American Heart Association/American Stroke Association. *Stroke*. 2011;42:517-584.

Extracranial carotid artery stenosis is found in 5 to 10% of individuals older than 65 years and is associated with about 10% of all ischemic strokes. Untreated asymptomatic carotid stenosis carries only a 1 to 2% annual risk of stroke, and the risk is decreased to as low as 0.5% annually with standard medical therapy.[2] Stroke is also a complication of sickle cell disease (Chapter 149), although this risk is dramatically reduced by transfusion therapy in high-risk children. Unlike with coronary heart disease, the overall association between high cholesterol concentration and the risk of stroke is less certain. In the general population, the risk of ischemic stroke is associated with higher levels of total and low-density lipoprotein cholesterol, whereas the risk of hemorrhagic stroke has been associated with lower levels.

Other factors associated with the risk of stroke include migraine headaches with aura (Chapter 367), particularly in women who smoke and are receiving oral contraceptives; elevated homocysteine level; high lipoprotein (a) level; postmenopausal hormone replacement therapy (Chapter 222); coagulation disorders (Chapter 67); systemic infection (Chapter 61); renal impairment (Chapter 116); low vitamin D levels (Chapters 199 and 226); and environmental factors, including air pollution.

PATHOBIOLOGY

For patients who have a TIA and who are by definition at increased risk of having an ischemic stroke during the next few days or weeks or those who had an ischemic stroke, distinguishing among the major pathophysiologic causes (i.e., atherothrombotic, cardioembolic, small vessel) is critical to guide secondary prevention.[3] Atherothrombosis due to atherosclerosis is the most common cause of a TIA or stroke that is related to steno-occlusive disease in the distribution of a single artery. The ischemia may be caused when progressive stenosis at the site of an atherosclerotic plaque leads to hemodynamic compromise affecting distal brain tissue. Sometimes bleeding into the plaque can lead to abrupt arterial occlusion, and sometimes a thrombus that has formed on an ulcerated plaque may embolize and occlude a distal artery. Occlusion of a cerebral artery, however, does not necessarily lead to ischemic brain injury. Blood may still reach the supplied territory through collaterals, either through the circle of Willis or from extracranial-intracranial anastomoses (see E-Fig. 375-1 in Chapter 375).

Arterial dissection is now recognized frequently on the basis of noninvasive vascular imaging such as MR angiography or computed tomography (CT) angiography. Other arteriopathies, such as fibromuscular dysplasia (Chapters 64, 66, and 110), may also lead to single, large-vessel distribution, ischemic stroke. Atherosclerosis of the ascending aorta or aortic arch can lead to the formation of thrombus, which can then embolize to a cerebral artery.

Atrial fibrillation is the single most common cause of cardioembolic stroke, with annual risks of 3 to 5% if it is not treated with anticoagulation but declining to about one fourth of that risk with anticoagulation (Chapter 52). Other cardiac causes of cerebral embolism include clots or vegetations in patients with valvular heart disease (Chapter 60), such as mechanical prosthetic heart valves (Chapter 60), infectious endocarditis (Chapter 61), nonbacterial endocarditis (Chapter 61); and mural thrombi in patients with a cardiomyopathy (Chapter 47) or myocardial infarction (MI), particularly anteroseptal MI (Chapter 58). Paradoxical embolism of a venous clot across a congenital heart defect, such as a patent foramen ovale or an atrial septal defect (Chapter 55), is another cause of embolic stroke. Intracranial atherosclerotic plaque in a nonstenotic artery can also be a source of embolic stroke.[4]

Small-vessel intracranial disease may result in ischemic stroke in the distribution of a single penetrating vessel. These strokes commonly affect deep structures (e.g., centrum semiovale, basal ganglia, thalamus, internal capsule, pons) and occur more frequently in patients with hypertension and diabetes. Classically, small-vessel strokes are caused by lipohyalinosis, which is a thickening of the vessel wall resulting in a diminished luminal area, but they also can be caused by atherothrombosis or embolism.

Symptoms of ischemic stroke may worsen during the first hours or days through various mechanisms. For example, decreases in systemic blood pressure may decrease cerebral blood flow to marginally perfused, ischemic brain. In the setting of atherothrombotic disease, a partially occluded artery may progress to complete occlusion. Recurrent embolism may occur from a proximal arterial or cardiac source. Cerebral edema may develop during the first few days after an ischemic stroke, and the resulting mass effect can lead to clinical deterioration (Chapter 375). Secondary bleeding can occur in an area that was primarily the site of an ischemic injury when reperfusion, either through collateral vessels or as the result of a therapeutic intervention, restores blood flow into vessels in which the endothelium was damaged by the original ischemic insult.

ABSTRACT

Ischemic stroke can have a variety of causes, but the most effective approach is primary prevention. Symptoms depend on the involved vascular territory. Selected patients with acute ischemic stroke benefit from treatment with endovascular thrombectomy and/or intravenous thrombolysis. Secondary prevention is aimed at general risk factors and specific therapies depending on stroke etiology.

KEYWORDS

ischemic stroke
thrombolysis
endovascular thrombectomy
risk factors
prevention

CLINICAL MANIFESTATIONS

Neurologic deficits that occur in the setting of ischemic stroke depend on the involved vascular territory (Table 376-2) and underlying cause. Embolic stroke is generally characterized by the presence of a maximal deficit at onset, whereas the onset may be more gradual or stuttering in the setting of an atherothrombotic stroke. The distinction, however, is not of great use for diagnosis in individual patients. Transient symptoms in the same distribution can be caused by TIA if there is no permanent tissue injury.

Internal Carotid Artery

The bifurcation of the common carotid artery into the internal and external carotid arteries in the neck is a common site of atherosclerotic disease (see Fig. 375-1 in Chapter 375). With occlusion of the internal carotid artery, patients who have an incomplete circle of Willis can have a profound contralateral loss of motor and sensory function affecting the face, arm, and leg. In patients with an intact anterior communicating artery that can supply the ipsilateral anterior cerebral artery (see Fig. 375-2 in Chapter 375), the leg may be relatively spared, and an internal carotid artery occlusion may be clinically indistinguishable from a middle cerebral artery occlusion. If the A1 segment of the anterior cerebral artery is absent on the side opposite an internal carotid artery occlusion in a patient with an intact anterior communicating artery, the ipsilateral leg may also be affected, and the presentation may be confused with a cardioembolic cause because both hemispheres are involved. Occlusion of the ipsilateral ophthalmic artery can lead to blindness in that eye. Transient symptoms of retinal ischemia, classically described by patients as a "shade coming down over my vision," indicate amaurosis fugax. Other common symptoms of transient monocular visual loss include a darkening or blurring of vision in the affected eye. Transient hypoperfusion ipsilateral to a high-grade internal carotid artery stenosis can cause limb-shaking TIAs that can be confused with seizures. Systemic hypotension in the setting of a high-grade carotid stenosis can lead to ischemic injury in watershed zones between the major intracranial arteries and in the border zone between the distal territories of cortical and lenticulostriate penetrating vessels (Chapter 375).

TABLE 376-2 CLINICAL MANIFESTATIONS OF ISCHEMIC CEREBROVASCULAR DISEASE

OCCLUDED ARTERY	TYPICAL MAJOR CLINICAL MANIFESTATIONS*
Internal carotid artery	Loss of vision in the ipsilateral eye Ipsilateral middle cerebral artery syndrome
Anterior choroidal artery	Contralateral hemiparesis Contralateral sensory impairment Contralateral visual field defect
Anterior cerebral artery	Contralateral leg > arm paresis Contralateral leg > arm sensory deficit
Middle cerebral artery	Contralateral hemiparesis affecting face and arm > leg Contralateral sensory deficit affecting face and arm > leg Contralateral visual field defect Aphasia (dominant hemisphere) Contralateral hemispatial neglect (nondominant or dominant hemisphere)
Posterior cerebral artery	Contralateral homonymous hemianopia (or homonymous superior or inferior quadrantanopia) Contralateral sensory deficits (thalamic involvement)
Basilar artery tip	Bilateral central visual loss Confusion
Basilar artery	Ipsilateral cranial nerve deficit Contralateral hemiparesis Contralateral sensory impairment affecting arm and/or leg Coordination deficit
Vertebral artery, posterior inferior cerebellar artery	Ipsilateral sensory impairment over the face Dysphagia Ipsilateral Horner syndrome Ataxia
Superior cerebellar artery	Gait ataxia Ipsilateral limb ataxia Variable contralateral limb weakness

*Note: Not all may be present.

Anterior Choroidal Artery

The anterior choroidal artery generally arises from the supraclinoid portion of the internal carotid artery. Causes of occlusion of the anterior choroidal artery are similar to those of occlusion of the small intracranial arteries. Symptoms can include contralateral motor and sensory deficits and contralateral visual field deficits, the latter of which can occur in isolation.

Cerebral Arteries

About 2% of strokes are related to isolated occlusion of the anterior cerebral artery (see Figs. 375-6 and 375-7 in Chapter 375). Occlusion of the A1 segment in patients in whom the contralateral A1 segment is hypoplastic or absent can lead to bilateral leg involvement, abulia, and urinary incontinence because of infarction of both frontal lobes.

The middle cerebral artery is the most common artery involved in occlusions related to cardiogenic embolism. It supplies the lateral portions of the frontal, parietal, and temporal lobes as well as the basal ganglia and the anterior limb and genu of the internal capsule. Middle cerebral artery occlusions are characterized by involvement of the contralateral face and arm to a greater extent than of the leg (see Figs. 375-6, 375-7, and 375-8 in Chapter 375), often accompanied by a contralateral hemispatial neglect. When the dominant hemisphere is involved, the patient may have an aphasia. With frontal lobe involvement, patients often have an ipsilateral conjugate deviation of the eyes, which can be forced past the midline with vigorous encouragement, oculocephalic maneuvers, or caloric stimulation.

Branch middle cerebral artery occlusions can result in partial syndromes. For example, a branch middle cerebral artery occlusion with intact collaterals can cause a global aphasia without an accompanying motor deficit (i.e., "global aphasia without hemiparesis"). Anterior branch dominant hemisphere middle cerebral artery occlusions can cause an expressive cortical-type motor (Broca) aphasia with sparing of comprehension. Occlusion of the angular branch of the middle cerebral artery can cause receptive cortical-type (Wernicke) aphasia. Border zone infarcts can result in transcortical aphasias, characterized by relatively preserved repetitions.

Both posterior cerebral arteries arise from the basilar artery in about 75% of people (see Fig. 375-3 in Chapter 375). In the other 25%, one or both P1 segments are hypoplastic or absent, with the posterior cerebral arteries arising from the ipsilateral internal carotid artery (so-called fetal circulation). Without vascular imaging, it is not possible to determine if a posterior cerebral artery distribution infarct (see Figs. 375-6 to 375-8 in Chapter 375) is related to carotid or vertebrobasilar circulation disease. The posterior cerebral artery and posterior communicating arteries supply the thalamus. Thalamic infarctions can result in contralateral hemianesthesia and ataxia. Contralateral hemiballismus can result if the subthalamic nucleus is damaged. Infarction of the ipsilateral occipital lobe causes a contralateral homonymous hemianopia that can be partial, depending on the extent of injury. The visual field deficit tends to become more congruous in the two eyes as the area of injury becomes more posterior (i.e., the closer to the occipital pole).

Vertebral and Basilar Arteries

Occlusion of the basilar artery (see Figs. 375-3 and 375-4B in Chapter 375) can lead to "locked-in syndrome" (Chapter 373) in which the patient is awake and alert, because the periaqueductal gray can receive a separate blood supply, but is unable to move or to communicate except for vertical eye movements, because of sparing of the collicular nuclei in the midbrain. The top of the basilar artery is a common location for embolic occlusion. Symptoms can include visual field defects due to unilateral or bilateral occipital injury and confusional states due to thalamic involvement.

Occlusions of penetrating and circumferential branches of the basilar artery and vertebral artery can produce a variety of symptoms (see Table 376-2) depending on the portion of the artery involved, several of which constitute eponymic midbrain (E-Fig. 376-1), pontine (E-Fig. 376-2), or medullary (E-Fig. 376-3) syndromes. Occlusion of the superior cerebellar artery can cause truncal ataxia because of infarction of the cerebellar vermis, with or without ataxia of the ipsilateral limbs, which can be caused by infarction of the ipsilateral cerebellar hemisphere.

Small Vessels

Occlusion of a small penetrating intracranial vessel can result in one of the classic lacunar syndromes (Table 376-3). These syndromes are not otherwise localizing and can occur with occlusions of small penetrating vessels in either the anterior or vertebrobasilar circulations. Lacunar syndromes are not pathognomonic of small-vessel intracranial disease and can be caused by

Claude Syndrome

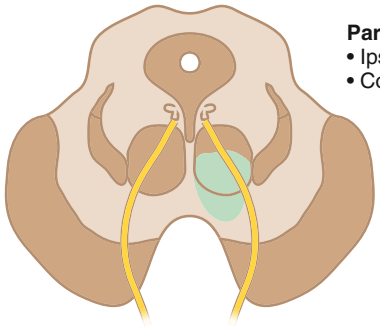

Paramedian infarction
- Ipsilateral 3rd nerve
- Contralateral ataxia

Benedikt Syndrome

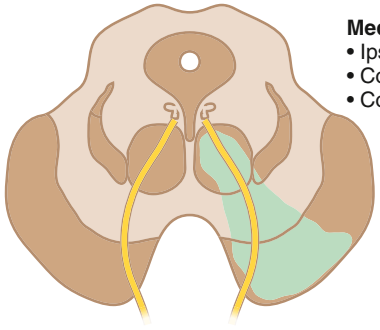

Medial infarction
- Ipsilateral 3rd nerve
- Contralateral ataxia
- Contralateral hemiparesis

Weber Syndrome

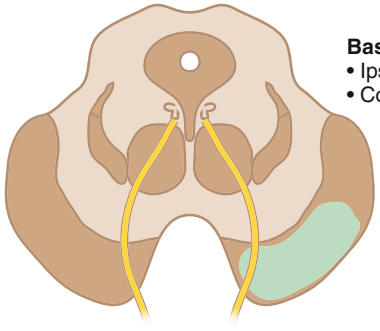

Basal infarction
- Ipsilateral 3rd nerve
- Contralateral hemiparesis

E-FIGURE 376-1. **Midbrain stroke syndromes.**

Raymond Syndrome

Mediolateral infarction
- Ipsilateral internuclear ophthalmoplegia
- Contralateral hemiparesis
- Contralateral UMN 7th nerve
- Contralateral light touch, proprioception
- +/– Contralateral pain/temperature (with ipsilateral Horner)

Foville Syndrome

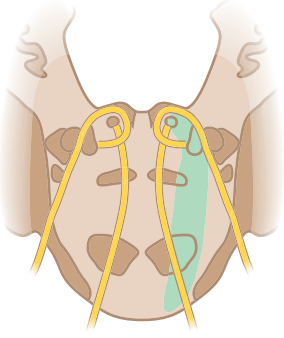

Mediolateral infarction
- Ipsilateral LMN 7th nerve
- Ipsilateral conjugate gaze palsy
- Contralateral hemiparesis

Millard-Gubler Syndrome

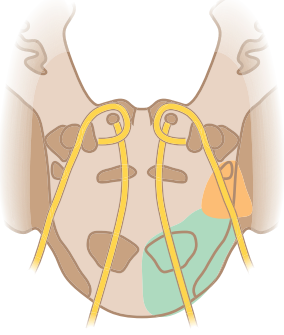

Basal infarction
- Ipsilateral LMN 7th nerve
- Ipsilateral 6th nerve
- Contralateral hemiparesis
- +/– Contralateral pain/temperature

Locked-in Syndrome

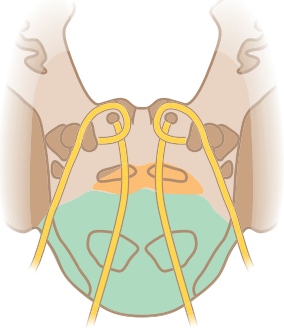

Bilateral basis pontis infarction
- Bilateral LMN 7th nerve
- Bilateral 6th nerve
- Quadriplegia
- +/– Bilateral light touch/proprioception

E-FIGURE 376-2. **Pontomedullary and pontine stroke syndromes.** LMN = lower motor neuron; UMN = upper motor neuron.

Dejerine Syndrome

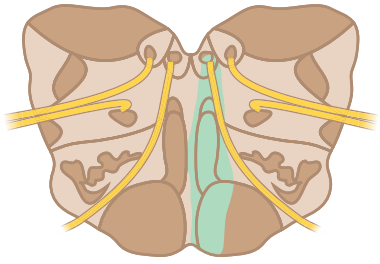

Medial infarction
- Ipsilateral XII nerve
- Contralateral hemiparesis
- Contralateral light touch, proprioception

Jackson Syndrome

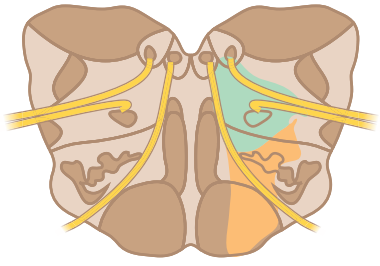

Lateral median infarction
- Ipsilateral IX, X nerve
- Ipsilateral XII nerve
- Variable contralateral hemiparesis

Avellis Syndrome

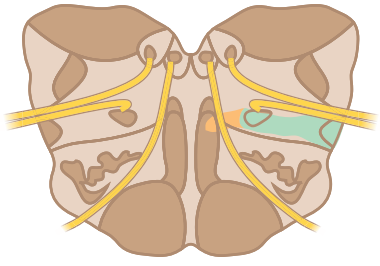

Lateral infarction
- Ipsilateral IX, X nerve
- Contralateral pain, temperature (ipsilateral Horner)
- +/– Contralateral hemiparesis

Wallenberg Syndrome

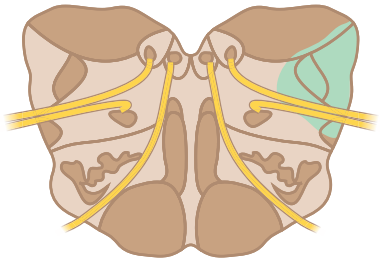

Dorsolateral infarction
- Ipsilateral facial anesthesia
- Contralateral pain, temperature
- Ipsilateral Horner
- Ipsilateral IX, X
- Ipsilateral ataxia (olivocerebellar tract)

E-FIGURE 376-3. **Medullary stroke syndromes.**

TABLE 376-3 LACUNAR SYNDROMES

Pure motor stroke
Pure sensory stroke
Ataxic hemiparesis
Clumsy hand–dysarthria

a variety of other conditions, including emboli from a more proximal arterial or cardiac source or a brain hemorrhage (Chapter 377).

DIAGNOSIS

The diagnosis of ischemic stroke depends on acquiring an accurate history, eliciting key findings on general and neurologic examinations, and obtaining supporting data from selected laboratory studies (Fig. 376-1). An initial anatomic and pathophysiologic differential diagnosis is usually established based on the patient's history. Findings on physical and neurologic examinations can support or refute initial conclusions based on the history and can further refine the differential diagnosis.[5]

History

The abrupt onset of a focal neurologic deficit in the distribution of a specific vascular territory is the hallmark of acute ischemic stroke. The differential and most likely diagnosis can often be determined on the basis of history alone. For example, a patient with a history of atrial fibrillation who abruptly develops word-finding difficulties associated with a right hemiparesis and sensory impairment most likely had a cardiogenic embolus to the left middle cerebral artery. A patient with the acute onset of diplopia, vertigo, and a hemiparesis most likely has a lesion in the brain stem.

Goals of the immediate history include determining the time when symptoms began or the last time the patient was known to be well, concomitant medical illnesses, risk factors, medications, allergies, and other potential causes for symptoms that might mimic acute stroke. Because a stroke may affect a patient's ability to communicate, the history may require input from a witness. Additional details of the patient's past medical, family, and social history may need to be deferred in the emergent setting, but these issues can be explored if the information is important for acute treatment decisions.

Physical Examination

Severely elevated blood pressures in the setting of neurologic deficits referable to the basal ganglia, thalamus, pons, or cerebellum increase the likelihood of a brain hemorrhage (Chapter 377). In a patient with transient vertigo associated with left arm movement, a reduced blood pressure in that arm suggests subclavian steal syndrome. Detection of an anterior cervical bruit contralateral to symptoms and signs indicative of a middle cerebral artery distribution infarct increase the likelihood of symptomatic carotid stenosis. An irregularly irregular heart rhythm with or without a cardiac murmur may indicate atrial fibrillation and a cardioembolic etiology. Finding a cholesterol embolus on funduscopic examination can be consistent with a proximal source of atheroembolism. Funduscopy can also show evidence of a small-vessel disease related to diabetes or hypertension (see Figs. 391-22 and 391-24 in Chapter 391).

A general neurologic examination (Chapter 366) including evaluations of cognition, language, spatial neglect, cranial nerves, motor function, sensation, coordination, gait, and reflexes is important both for documenting stroke-related deficits and for providing information critical for determining the area of the brain affected by the stroke and the extent of the injury. The use of a standardized graded neurologic impairment assessment provides a tool for measuring the severity of the stroke, determining the risks and benefits of treatment interventions, assessing prognosis, and observing patients objectively over time. The National Institutes of Health Stroke Scale, which is the most commonly used approach, is both reliable and well validated. The individual items are summed to provide a total score.

Initial Laboratory Tests

Laboratory testing can help exclude conditions that may mimic, complicate, or lead to an acute ischemic stroke (Table 376-4). Tests that should be obtained in all patients with suspected stroke include a complete blood count and platelet count, prothrombin time/international normalized ratio (INR), activated partial thromboplastin time, blood glucose level, serum electrolytes, tests of renal function, troponin level, and oxygen saturation. An electrocardiogram should be obtained urgently.

The patient should be sent for a CT brain scan or MRI as soon as possible. CT or MR angiography should be obtained in patients suspected of having a large-vessel occlusion. In many stroke centers, patients are taken for

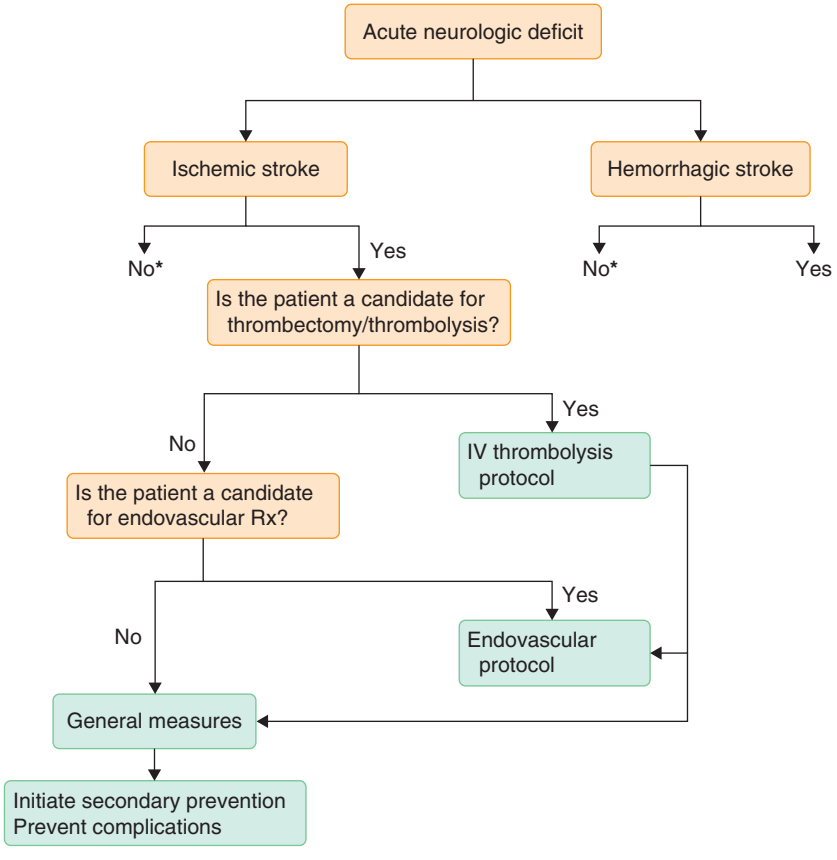

FIGURE 376-1. Approach to ischemic stroke. *If both No, search for conditions that mimic stroke (see text). IV = intravenous; Rx = therapy. (Modified from Goldstein LB. Modern medical management of acute ischemic stroke. *Methodist DeBakey Cardiovasc J.* 2014;10:99-104. See Chapter 377 for hemorrhagic stroke.)

TABLE 376-4 IMMEDIATE DIAGNOSTIC STUDIES: EVALUATION OF A PATIENT WITH SUSPECTED ACUTE ISCHEMIC STROKE

ALL PATIENTS
Noncontrast CT brain or MRI brain
Blood glucose
Oxygen saturation
Serum electrolytes/renal function tests*
Complete blood count, including platelet count*
Markers of cardiac ischemia (troponin)*
Prothrombin time/INR*
Partial thromboplastin time*
ECG*
SELECTED PATIENTS
Thrombin time and/or ecarin clotting time or anti-Xa level if it is suspected the patient is taking direct thrombin inhibitors or direct factor Xa inhibitors
Hepatic function tests
Toxicology screen
Blood alcohol level
Pregnancy test
Arterial blood gas tests (if hypoxia is suspected)
Chest radiography (if lung disease is suspected)
Lumbar puncture (if meningitis is suspected or subarachnoid hemorrhage is suspected but the CT scan is negative for blood)
Electroencephalogram (if seizures are suspected)

*Although it is desirable to know the results of these tests before giving intravenous recombinant tissue-type plasminogen activator, fibrinolytic therapy should not be delayed while awaiting the results unless (1) there is clinical suspicion of a bleeding abnormality or thrombocytopenia, (2) the patient has received heparin or warfarin, or (3) the patient has received other anticoagulants (direct thrombin inhibitors or direct factor Xa inhibitors).

CT = computed tomography; ECG = electrocardiogram; INR = international normalized ratio; MRI = magnetic resonance imaging.

From Jauch EC, Saver JL, Adams HP Jr, et al. Guidelines for the early management of patients with acute ischemic stroke: a guideline for healthcare professionals from the American Heart Association/American Stroke Association. *Stroke*. 2013;44:870-947.

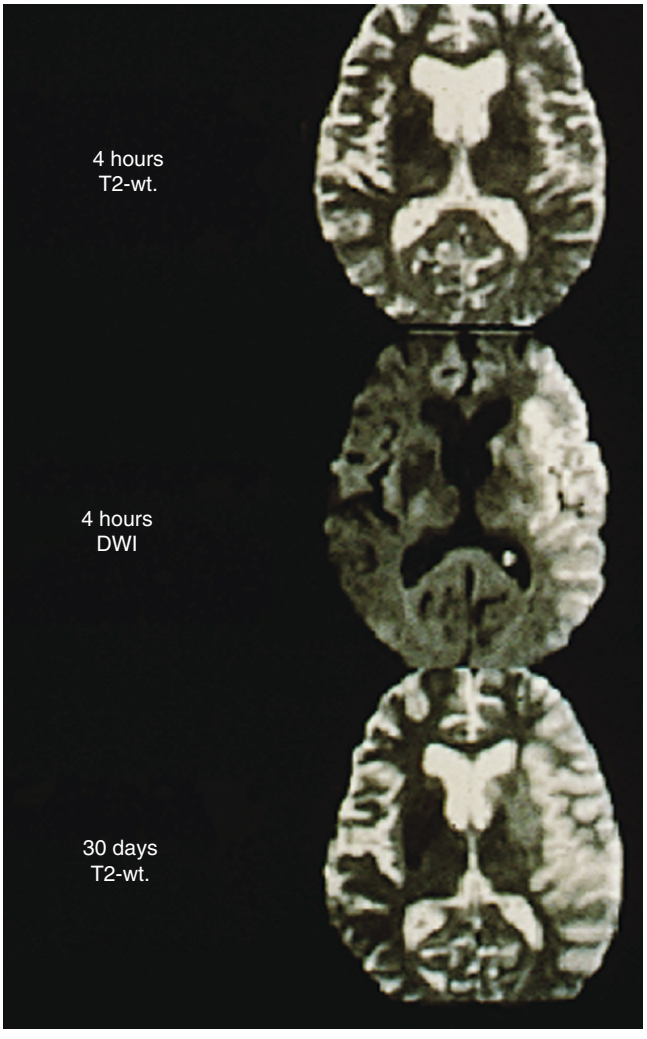

FIGURE 376-2. **Magnetic resonance imaging (MRI) showing possible advantages of diffusion-weighted imaging (DWI) relative to conventional MRI at early times after vascular occlusion.** ***Top*****, Conventional T2-weighted MRI 4 hours after symptom onset that appears normal.** ***Middle*****, At the same time, a DWI scan shows abnormalities in the left hemisphere.** ***Bottom*****, Repeated T2-weighted MRI 1 month later showed an infarction in the same location as the initial DWI scan. (Courtesy Gregory W. Albers, Stanford University, Stanford, Calif.)**

neuroimaging directly from the ambulance after a very brief assessment. Mobile stroke units with CT brain scans also are being used in some communities.

Additional tests are indicated in selected patients. For example, women of childbearing age should have a pregnancy test. A toxicology screen and blood alcohol levels should be obtained if drug or alcohol abuse is suspected. In patients who may be receiving a direct thrombin inhibitor or a factor Xa inhibitor, a thrombin time, ecarin clot time, or anti–factor Xa level may be helpful in determining whether the patient is anticoagulated. An elevated erythrocyte sedimentation rate may point to an inflammatory cause or systemic infection.

The complete blood count can provide information about both the potential cause of the stroke and possible therapeutic interventions. An elevated white blood cell count may indicate an infectious cause of stroke, such as infective endocarditis (Chapter 61). Systemic infection may also cause a recrudescence of prior stroke symptoms in a patient who had previously recovered or in whom a stroke had not been previously recognized. Polycythemia (Chapter 152) can cause hyperviscosity that leads to occlusion of small intracranial vessels. Thrombocytopenia, either primary or secondary, can lead to platelet thrombi. The prothrombin time/INR and activated thromboplastin time provide indices that may reveal an underlying coagulation disorder, and thrombocytopenia and coagulation disorders may preclude treatment with intravenous recombinant tissue plasminogen activator (rtPA) or tenecteplase.

Both hypoglycemia (Chapter 211) and hyperglycemia (Chapter 210) may cause strokelike symptoms. Impaired renal function (Chapter 116) is a risk factor for ischemic stroke and may increase the risks of using thrombolytic and anticoagulant medications. Abnormalities of other serum electrolytes (e.g., hyponatremia; Chapter 102) can also cause neurologic symptoms.

The electrocardiogram may reveal changes suggestive of acute myocardial ischemia as well as atrial fibrillation, the most common cause of embolic stroke. Stroke may also cause a variety of cardiac arrhythmias. Acute MI, especially anteroseptal MI, is associated with a higher risk of cardiogenic embolism, and an acute stroke may also precipitate an MI. A troponin level is usually adequate for this purpose, especially because it remains elevated for several days after the MI when embolism from a mural thrombus is most likely to occur. Patients with acute stroke should be placed on telemetry monitoring. Urgent echocardiography is used selectively.

Brain Imaging

CT or MRI brain imaging is an essential part of the evaluation of all patients with suspected ischemic stroke. Imaging can locate the area of damage, distinguish a brain hemorrhage from an ischemic stroke, and identify mass lesions such as tumor (Chapter 175), abscess (Chapter 382), or subdural hematoma (Fig. 368-1) that can present acutely and mimic a stroke. Brain CT is widely and rapidly available and provides the information necessary for the treatment of most patients with acute stroke. Brain MRI can detect areas of acute ischemic injury not apparent on CT brain imaging (Fig. 376-2), but it cannot be performed in patients who have metal implants or devices such as older non–MRI-compatible cardiac pacemakers, and it is a challenge to perform in unstable patients.

The changes on brain CT, such as loss of gray-white distinction, loss of the insular ribbon, and blurring of the borders of the basal ganglia, can be subtle. The area of ischemic injury on brain CT scan appears as a relative hypodensity (Fig. 376-3), in contrast to brain hemorrhage, which appears hyperdense compared with the surrounding brain parenchyma (see Fig. 377-5 in Chapter 377). CT can also show acute hemorrhage in the subarachnoid space, which can be indicative of aneurysmal rupture (see Fig. 377-3 and 377-4 in Chapter 377). The dense middle cerebral artery sign or the dot sign, in which an artery in the Sylvian fissure may appear dense, can indicate thrombus in these vessels.

The findings on CT are often normal in the acute phase of ischemic stroke, and MRI is more sensitive for demonstrating acute ischemic injury (Fig. 376-4). Because brain CT imaging of posterior fossa structures is often obscured by a beam-hardening artifact from the petrous bones, MRI is also more sensitive for visualizing the brain stem and cerebellum. MRI signal patterns also can

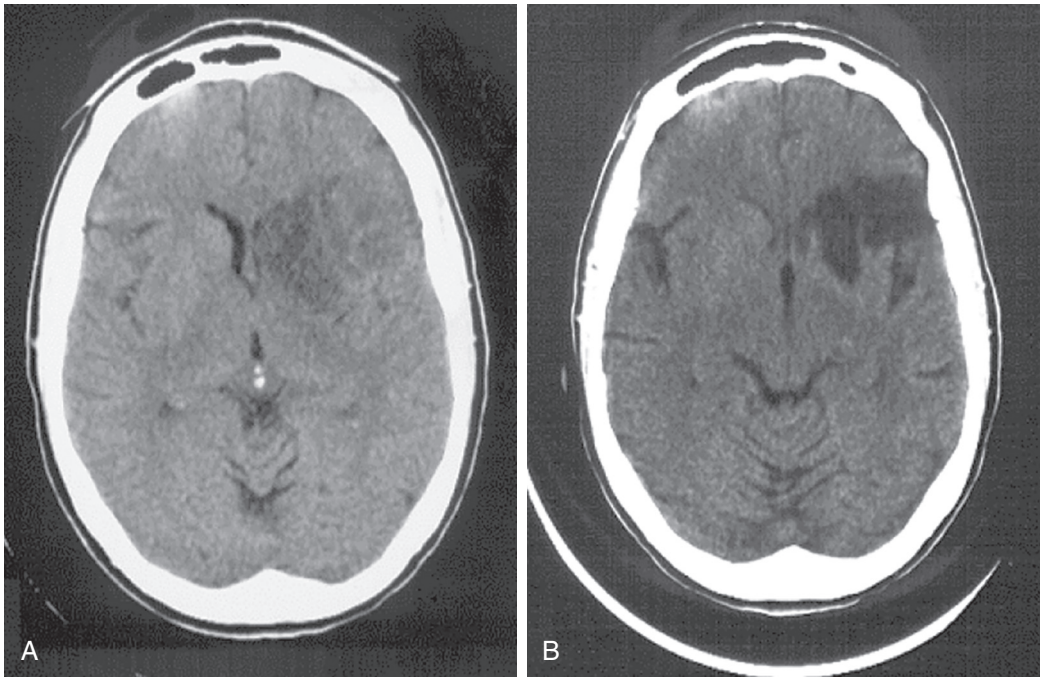

FIGURE 376-3. Computed tomographic imaging. A, A computed tomography (CT) scan of a patient with a left hemisphere infarction 6 to 24 hours after the onset of symptoms shows a hypodense area in the basal ganglia region and compression of the frontal horn of the lateral ventricle. **B,** A CT scan shows the chronic infarction 1 year later; atrophy and loss of tissue volume are visible. (Courtesy Gregory W. Albers, Stanford University, Stanford, Calif.)

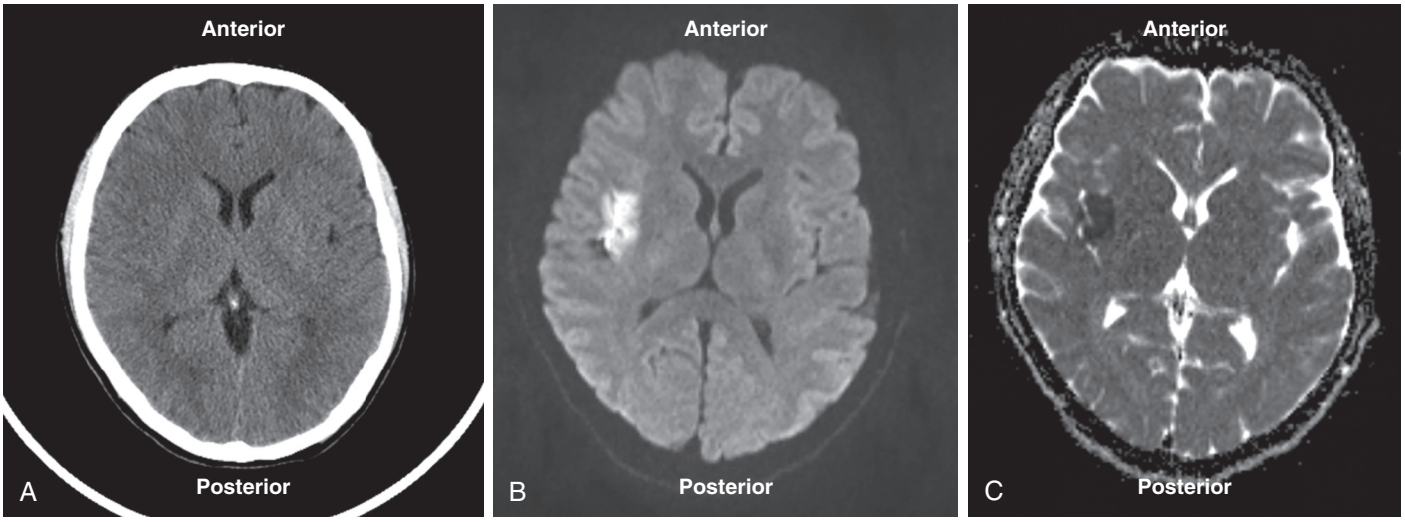

FIGURE 376-4. A, Computed tomographic imaging. **B,** Magnetic resonance imaging, diffusion sequence. **C,** Magnetic resonance imaging, apparent diffusion coefficient (ADC) map. Computed tomography shows no evidence of ischemic injury. There is an obvious area of restricted diffusion in the right frontotemporal cortex that is dark on the ADC map, consistent with an area of acute ischemic injury.

distinguish acute from subacute and remote ischemic injury, differentiate acute and remote brain hemorrhage, and identify other nonvascular conditions. However, MRI is not required before treatment with an intravenous thrombolytic agent because CT can reliably exclude parenchymal brain hemorrhage and can detect other common conditions that may mimic a stroke, such as a mass lesion. CT or MR perfusion can also help identify patients who might benefit from endovascular clot removal.

Lumbar Puncture

Lumbar puncture is rarely necessary in the evaluation of patients with acute stroke. In occasional patients, meningitis, especially septic meningitis from cardiogenic embolism in a patient with infective endocarditis, may cause stroke or strokelike symptoms and be an indication for an urgent lumbar puncture. Brain CT usually demonstrates blood in the subarachnoid space in patients presenting with symptoms and signs of subarachnoid hemorrhage (Chapter 377), such as headache and meningismus. If, however, brain CT fails to visualize a subarachnoid hemorrhage in a patient in whom the clinical suspicion of subarachnoid hemorrhage is high, lumbar puncture should still be obtained.

Other Imaging

Carotid duplex ultrasonography, which combines B-mode vascular imaging with measures of blood flow velocity, is commonly used to screen for extracranial carotid artery stenosis but is rarely indicated in the acute setting. Both CT and MR angiography provide noninvasive vascular imaging of the extracranial and intracranial cerebral circulation, and one of these studies should be obtained emergently in patients who have suspected large-vessel occlusion and who might be candidates for endovascular thrombectomy. CT or MR angiography may be helpful in identifying cervical artery dissections in a patient with headache, neck pain, and symptoms and signs consistent with ipsilateral ischemic injury. Venous sinuses should be imaged if a sinus thrombosis is being considered. Transcranial Doppler ultrasonography is an alternative for evaluating the proximal cerebral vessels, but it cannot be obtained in some patients because of inadequate sonographic windows.

Diagnostic catheter angiography carries about a 0.5 to 1.5% risk of causing a stroke. For screening for large-vessel occlusion in the acute setting, it has largely been supplanted by noninvasive vascular imaging. Catheter angiography is, however, superior to CT or MR angiography for visualizing smaller intracranial vessels and for detecting intracranial vasculopathies such as vasculitis (Chapter 249).

Differential Diagnosis

The hallmark of acute ischemic stroke is the abrupt onset of a focal neurologic deficit, frequently attributable to an area of brain supplied by a specific artery or arteries. In some patients, however, the onset of ischemic stroke may be stuttering, and stroke symptoms may have been heralded by a prior TIA. The detection of an ipsilateral cervical artery bruit may also support the diagnosis. Embolic stroke typically has its maximal severity at onset, but it can involve multiple vascular territories. The diagnosis of an embolic stroke may be further suggested by finding a cardiac murmur, an irregularly irregular heart rhythm, or signs of emboli of similar age in other vascular territories.

A variety of other neurologic conditions may also be manifested acutely. Migraine with aura (Chapter 367) can be associated with focal neurologic deficits, including speech impairment, visual changes, vertigo, weakness, numbness, and imbalance. Partial seizures (Chapter 372) may have negative symptoms, including aphasia and paresis, and a patient with a postictal Todd paralysis may appear to have had a stroke. As a further challenge in diagnosis, seizures may occur in patients who are having an acute stroke. In a patient without a previous diagnosis, the first episode of multiple sclerosis (Chapter 380) can mimic a stroke. Mass lesions such as neoplasms (Chapter 175) and abscesses (Chapter 382) are generally associated with a slowly progressive worsening of neurologic symptoms but may occasionally be manifested acutely. Metabolic disorders such as hypoglycemia (Chapter 211) or hyperglycemia (Chapter 210), toxin exposures (Chapters 20 and 96), and drug intoxications (Chapter 365) can cause focal symptoms similar to stroke. Strokelike symptoms may also be a manifestation of malingering, a conversion disorder, or other psychiatric illness.

TREATMENT

Rapid transfer of stroke victims to an appropriate hospital is critical.[6] After initial respiratory and hemodynamic stabilization (Chapter 92), the management of patients with acute ischemic stroke is directed at determining expeditiously (Table 376-5) whether treatment with intravenous rtPA (total dose 0.9 mg/kg, maximum 90 mg, 10% bolus with the remainder given over 1 hour) or endovascular thrombectomy is appropriate (Table 376-6; see also Fig. 376-1). Current guidelines recommend treatment with an intravenous thrombolytic even if intra-arterial treatments are available, but endovascular therapy is recommended and considered usual therapy in selected patients who have an emergent large-vessel occlusion and who can be treated at centers with such capabilities.[7–9]

Intravenous Thrombolysis

Intravenous rtPA, administered within 4.5 hours of the onset of symptoms, does not reduce mortality but results in higher odds of a better neurologic outcome at 3 months compared with placebo. The benefit of rtPA declines over time within this 4.5-hour treatment window (E-Fig. 376-4), with the odds ratio for a favorable 3-month outcome declining from 2.55 for treatment within 0 to 90 minutes, to 1.64 for 91 to 180 minutes, to 1.26 for 181 to 270 minutes, and to no statistical benefit for treatment beyond 4.5 hours except that patients with ischemic but not yet infarcted brain tissue on imaging can still benefit if their symptoms began between 4.5 and 9 hours or if they awoke with symptoms.[A1] Treatment with rtPA is efficacious and safe among patients who are chronically treated with warfarin, provided their INR is 1.7 or lower, and is contraindicated with an INR higher than 1.7. The prothrombin time may be normal in patients who have received a direct oral anticoagulant (direct thrombin inhibitor or direct factor Xa inhibitor), and rtPA should not be administered unless appropriate assays are normal. Tenecteplase (single IV bolus of 0.25 mg/kg, maximum 25 mg) may be considered as a simpler, one-dose alternative to alteplase,[A2] especially in patients who have minor neurologic impairment without a major intracranial occlusion or who are to undergo mechanical thrombectomy (see later), but it is not approved by the U.S. Food and Drug Administration (FDA) for this purpose as of March 2022.

Treatment with a thrombolytic agent increases the risk of intracranial hemorrhage, but the overall benefit includes these adverse events, which do not significantly increase in frequency during the 4.5-hour treatment window. Treatment with intravenous rtPA is contraindicated in some patients (Table 376-7), with additional relative contraindications for treatment between 3 and 4.5 hours (Table 376-8). In patients without contraindications, treatment should begin as soon as possible in either treatment window. Prehospital magnesium sulfate is of no benefit.

TABLE 376-5 TIME GOALS FOR EVALUATION AND TREATMENT OF PATIENTS WITH ACUTE ISCHEMIC STROKE

TIME AFTER EMERGENCY DEPARTMENT ARRIVAL	GOALS
10 min	Assess ABCs, vital signs Provide oxygen if hypoxemic Obtain intravenous access Obtain laboratory studies CBC, coagulation, electrolytes Check glucose level, treat if indicated Perform screening neurologic assessment Activate stroke team Order "stroke code" brain CT* or MRI Obtain 12-lead ECG
25 min	Review history Establish time at onset or last known normal Perform neurologic examination NIH Stroke Scale
45 min	Review laboratory studies Review brain CT or MRI results Evaluate inclusion and exclusion criteria (see Tables 376-7 and 376-8)
60 min	Review risks and benefits Obtain consent Begin infusion

*CT/CT angiography should be obtained if emergent large vessel occlusion that may be amenable to endovascular treatment is suspected.

ABCs = airway, breathing, circulation; CBC = complete blood count; CT = computed tomography; ECG = electrocardiogram; MRI = magnetic resonance imaging; NIH = National Institutes of Health.

TABLE 376-6 ADMINISTRATION OF rtPA FOR ACUTE ISCHEMIC STROKE*

Infuse 0.9 mg/kg (maximum dose 90 mg) over 60 min, with 10% of the dose given as a bolus over 1 min
Admit the patient to an intensive care or stroke unit for monitoring
If the patient develops severe headache, acute hypertension, nausea, or vomiting or has a worsening neurologic examination, discontinue the infusion (if IV rtPA is being administered) and obtain emergent CT scan
Measure blood pressure and perform neurologic assessments every 15 min during and after IV rtPA infusion for 2 hr, then every 30 min for 6 hr, then hourly until 24 hr after IV rtPA treatment*
Increase the frequency of blood pressure measurements if systolic blood pressure is >180 mm Hg or if diastolic blood pressure is >105 mm Hg; administer antihypertensive medications to maintain blood pressure at or below these levels
Delay placement of nasogastric tubes, indwelling bladder catheters, or intra-arterial pressure catheters if the patient can be safely managed without them
Obtain a follow-up CT or MRI scan at 24 hr after IV rtPA before starting anticoagulants or antiplatelet agents

*Although not approved by the U.S. Food and Drug Administration for this indication, tenecteplase (0.4-mg/kg single IV bolus) can be considered.

CT = computed tomography; IV = intravenous; MRI = magnetic resonance imaging; rtPA = recombinant tissue plasminogen activator.

Endovascular Therapy

Strokes caused by large proximal occlusions tend to benefit less from treatment with intravenous rtPA compared with more distal or small-vessel obstructions. Although some additional benefit can be obtained from infusing rtPA directly into a proximal intracranial occlusion in the anterior circulation, mechanical thrombectomy has become usual care in eligible patients who are treated at stroke centers for proximal intracranial occlusions with potentially salvageable tissue, including if they had already received thrombolysis, and even if they have large infarcts.[A3–A7] Overall data for mechanical thrombectomy indicate improved functional outcomes but no significant difference in symptomatic intracranial hemorrhage or all-cause mortality at 90 days and 2 years compared with standard care (including intravenous rtPA). Improvement is more likely if endovascular therapy is provided earlier, but functional benefit is seen even when patients with middle cerebral artery or internal carotid artery occlusion are treated between 6 and 16 hours after the onset of symptoms if the affected brain is ischemic but not infarcted.[A8]

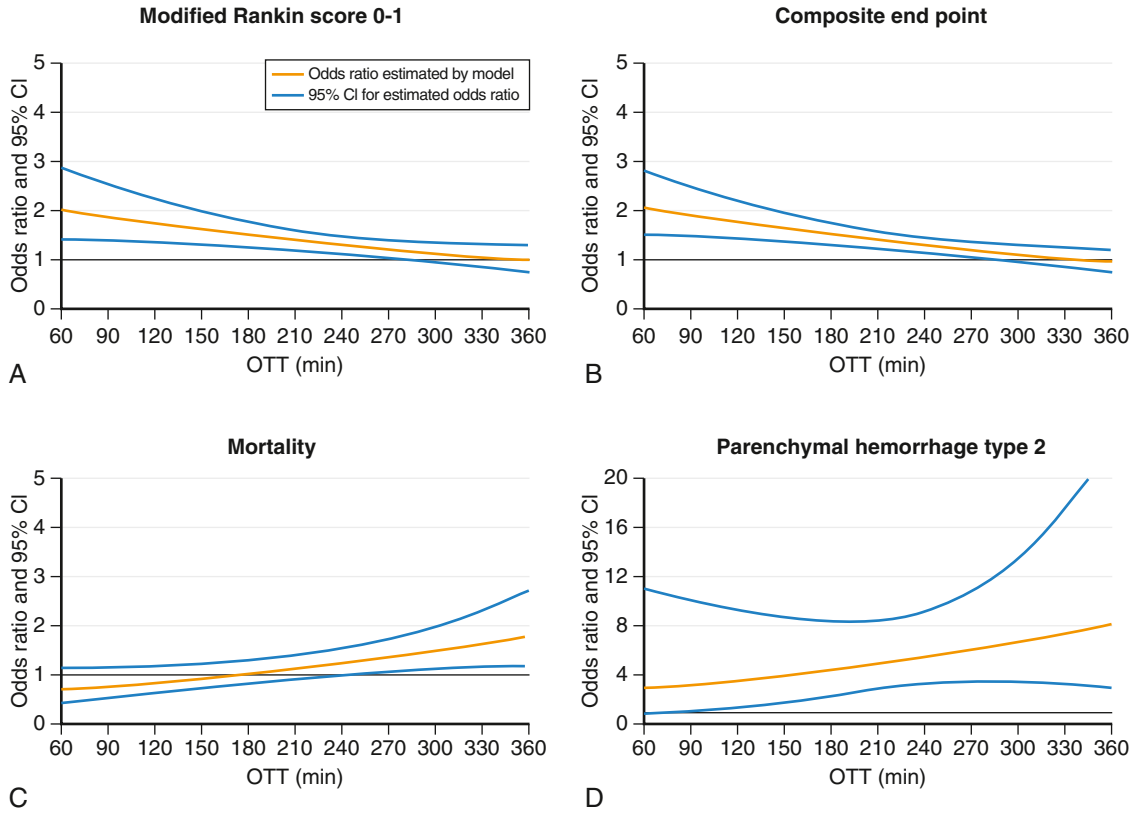

E-FIGURE 376-4. Relation of onset to treatment delay with treatment effect with intravenous rtPA. Relation of stroke onset to start of treatment (OTT) with treatment effect after adjustment for prognostic variables assessed by (**A**) day 90 modified Rankin score 0-1 versus 2-6 (interaction $P = 0269$, n = 3530 [excluding EPITHET7 data $P = 0116$, n = 3431]); (**B**) global test that incorporates modified Rankin score 0-1 versus 2-6, Barthel Index score 95-100 versus 90 or lower, and NIHSS score 0-1 versus 2 or more (interaction $P = 0111$, n = 3535 [excluding EPITHET7 data $P = 0049$, n = 3436]); (**C**) mortality (interaction $P = 0444$, n = 3530 [excluding EPITHET7 data $P = 0582$, n = 3431]); and (**D**) parenchymal hemorrhage type 2 (interaction $P = 4140$, n = 3531 [excluding EPITHET7 data $P = 4578$, n = 3431]). Thus, for parenchymal hemorrhage type 2, the fitted line is not statistically distinguishable from a horizontal line. For each graph, the adjusted odds ratio is shown with the 95% confidence interval (CI). CIs from the models will differ from those shown in the tables because the model uses data from all patients treated within 0 to 360 minutes, whereas the categorized analyses in the tables are based on subsets of patients; the modeled CIs are deemed to be more reliable. (From Lees KR, Bluhmki E, von Kummer R, et al. Time to treatment with intravenous alteplase and outcome in stroke: an updated pooled analysis of ECASS, ATLANTIS, NINDS, and EPITHET trials. *Lancet*. 2010;375:1695-1703.)

TABLE 376-7 INCLUSION AND EXCLUSION CHARACTERISTICS OF PATIENTS WITH ISCHEMIC STROKE WHO COULD BE TREATED WITH IV rtPA WITHIN 3 HR FROM SYMPTOM ONSET

INCLUSION CRITERIA
Diagnosis of ischemic stroke causing measurable neurologic deficit
Onset of symptoms <3 hr before beginning treatment
Aged ≥18 yr
EXCLUSION CRITERIA
Significant head trauma or prior stroke in previous 3 mo
Symptoms suggest subarachnoid hemorrhage
Arterial puncture at noncompressible site in previous 7 days
History of previous intracranial hemorrhage
Intracranial neoplasm, arteriovenous malformation, or aneurysm
Recent intracranial or intraspinal surgery
Elevated blood pressure (systolic >185 mm Hg or diastolic >110 mm Hg)
Active internal bleeding
Acute bleeding diathesis, including but not limited to:
Platelet count <100,000/μL
Heparin received within 48 hr, resulting in aPTT greater than the upper limit of normal
Current use of anticoagulant with INR >1.7 or PT >15 sec
Current use of direct thrombin inhibitors or direct factor Xa inhibitors with elevated sensitive laboratory tests (such as aPTT, INR, platelet count, and ECT; TT; or appropriate factor Xa activity assays)
Blood glucose concentration <50 mg/dL (2.7 mmol/L)
CT demonstrates multilobar infarction (hypodensity > ⅓ cerebral hemisphere)
RELATIVE EXCLUSION CRITERIA
Recent experience suggests that under some circumstances—with careful consideration and weighting of risk to benefit—patients may receive fibrinolytic therapy despite one or more relative contraindications. Consider risk to benefit of IV rtPA administration carefully if any of these relative contraindications are present:
Only minor or rapidly improving stroke symptoms (clearing spontaneously)
Pregnancy
Seizure at onset with postictal residual neurologic impairments
Major surgery or serious trauma within previous 14 days
Recent gastrointestinal or urinary tract hemorrhage (within previous 21 days)
Recent acute myocardial infarction (within previous 3 mo)
NOTES:
• The checklist includes some FDA-approved indications and contraindications for administration of IV rtPA for acute ischemic stroke. Recent guideline revisions have modified the original FDA-approved indications. A physician with expertise in acute stroke care may modify this list.
• Onset time is defined as either the witnessed onset of symptoms or the time last known normal if symptom onset was not witnessed.
• In patients without recent use of oral anticoagulants or heparin, treatment with IV rtPA can be initiated before availability of coagulation test results but should be discontinued if INR is >1.7 or PT is abnormally elevated by local laboratory standards.
• In patients without history of thrombocytopenia, treatment with IV rtPA can be initiated before availability of platelet count but should be discontinued if platelet count is <100,000/μL.

aPTT = activated partial thromboplastin time; CT = computed tomography; ECT = ecarin clotting time; FDA = U.S. Food and Drug Administration; INR = international normalized ratio; IV = intravenous; PT = partial thromboplastin time; rtPA = recombinant tissue plasminogen activator; TT = thrombin time.

TABLE 376-8 RELATIVE CONTRAINDICATIONS TO IV rtPA IN PATIENTS WITHIN 3 TO 4.5 HR AFTER ONSET OF SYMPTOMS OF ACUTE ISCHEMIC STROKE

National Institutes of Health Stroke Scale >25
Age >80 yr old
Taking an oral anticoagulant regardless of INR
History of diabetes *and* a prior ischemic stroke

INR = international normalized ratio; IV = intravenous; rtPA = recombinant tissue plasminogen activator.

For vertebrobasilar occlusion, functional outcomes also appear to be better with endovascular compared with medical therapy.[A9,A10] Pre-thrombectomy thrombolysis can further improve outcomes.[A11] Despite the benefits of thrombectomy, thrombolysis at the closest stroke center is as good as transfer to a thrombectomy-capable center for patients in nonurban areas.[A12]

Other Treatments

Regardless of whether the patient received intravenous thrombolytic therapy, with rtPA or tenecteplase, and with or without endovascular therapy, care in a comprehensive specialized stroke unit that incorporates rehabilitation is associated with better patient outcomes.[10] Urgent anticoagulation to prevent recurrent stroke, to prevent worsening, or to improve functional outcome of patients with acute ischemic stroke is not recommended. Aspirin generally should not be started within 24 hours of treatment with an intravenous thrombolytic agent unless its benefit for the treatment of concomitant conditions outweighs the risk of bleeding. For patients with high-risk TIA or a minor, nondisabling ischemic stroke, 21 days of dual antiplatelet therapy with clopidogrel (600 mg loading dose on day 1, followed by 75 mg per day) plus aspirin (50 to 325 mg per day) or with ticagrelor (180 mg loading dose followed by 90 mg twice daily) plus aspirin (300 to 325 mg on the first day followed by 75 to 100 mg daily) for 30 days decreases the risk of recurrent stroke by 30% compared with monotherapy, but it increases the risk of major bleeding by about 40% (and by substantially more if ticagrelor is used instead of clopidogrel).[A12–A15] In patients with a major stroke, aspirin 325 mg daily should be started within 24 hours after the onset of stroke.[A16] Long-term dual or triple antiplatelet therapy either increases bleeding without reducing the risk of recurrent stroke or reduces recurrent stroke without reducing long-term disability and is not recommended.

Some patients have space-occupying cerebral infarctions that compress normal brain tissue. In such patients, decompression decreases the likelihood of death and increases the likelihood of a favorable outcome.[A17]

Antihypertensive medications to reduce blood pressure acutely by 10 to 25% in the first 24 hours with a goal of blood pressure to below 140/90 mm Hg by 1 week does not improve outcomes compared with discontinuation of all antihypertensive medications.[A18] Current guidelines recommend that antihypertensive medications not be given unless the blood pressure rises to more than 220/120 mm Hg or higher in the absence of other indications. An exception is that blood pressure can be lowered in patients who are otherwise candidates for intravenous rtPA with a goal of maintaining blood pressures below 180/105 mm Hg after treatment (Fig. 376-5). Disability after acute stroke is similar for patients who lie flat for the first 24 hours compared with those who sit up with the head elevated to at least 30 degrees for 24 hours. Tight glucose control using intravenous insulin is no better than using subcutaneous insulin with a goal of 80 to 179 mg/dL.[A19]

Several potential complications of acute stroke can often be avoided. Patients with stroke in any vascular distribution are at risk of aspiration pneumonia (Chapter 85). Stroke patients should not receive oral medications or nutrition until their ability to swallow safely has been assessed. Urinary tract infections (Chapter 263) are a potential complication; indwelling bladder catheters should not be placed routinely and, if needed, should be removed as soon as feasible. Any infectious complications should be treated aggressively, and antipyretics should be used to maintain euthermia because fever is associated with more ischemic injury and poorer outcomes. Immobilized patients should receive deep venous thrombosis prophylaxis with subcutaneous unfractionated heparin or low-molecular-weight heparin (see Table 70-3 in Chapter 70) if it is not contraindicated, with mechanical intermittent pneumatic compression if anticoagulation is contraindicated, or with both.

Recovery/Rehabilitation

The process of recovery begins even before the sequelae of acute brain injury have resolved. Multidisciplinary physiotherapy should include assessments by speech pathologists, physical therapists, and occupational therapists.[11] Organized inpatient multidisciplinary rehabilitation is associated with a 34% lower odds of death, a 30% lower odds of death or institutionalization, and a 35% lower odds of death or dependency for patients with deficits warranting these services, and telehealth home-based rehabilitation also may be beneficial.[A20] However, neither aggressive mobilization within 24 to 48 hours nor robotic-assisted training is of benefit compared with usual care. All patients with stroke-related deficits should be assessed for rehabilitative interventions. Vagus nerve stimulation paired with rehabilitation is a potential treatment for upper limb weakness.[A21] Because depression can complicate stroke and affect recovery, all patients should be screened for depression. Prophylactic antibiotics are not effective for preventing post-stroke pneumonia, even in patients with dysphagia.

UNUSUAL CAUSES OF STROKE

Ischemic strokes may be caused by a variety of rare conditions. Specific treatments, many of which are not supported by extensive clinical trial data, vary accordingly (E-Table 376-1).

E-TABLE 376-1 UNUSUAL CAUSES OF ISCHEMIC STROKE

CAUSE	SETTING	NOTES	POSSIBLE TREATMENT
Vasculitis (Chapter 249)	Patients commonly, but not always, have a prior known vasculitic condition	Vasculitis can be manifested with headache, cognitive impairment, multiple areas of infarction, or hemorrhage. Vasculitis affecting the cerebral vasculature can occur in the setting of systemic vasculitis or be confined to the central nervous system (primary vasculitis of the central nervous system). Diagnosis is supported by evidence of an inflammatory response in the spinal fluid, meningeal enhancement on MRI, and a typical pattern of focal stenoses on cerebral angiography. Brain/meningeal biopsy is often necessary to exclude other causes.	Steroids, immunosuppression
Sickle cell disease (Chapter 149)	Patients with known sickle cell disease; persons of African, Indian, and Mediterranean descent	Sickle cell disease can cause stroke by occlusion of small brain vessels or by intimal fibrosis leading to large-vessel occlusion. Patients with sickle cell disease can be monitored with transcranial Doppler ultrasound.	Transfusions to reduce hemoglobin S to <30% to 50% of total hemoglobin, hydroxyurea
Atrial myxoma (Chapter 47)	Usually not previously diagnosed; may be suspected on physical examination but usually otherwise asymptomatic and discovered on echocardiography	Atrial myxoma is the most common primary cardiac tumor and can lead to emboli.	Surgical removal of the tumor
Coagulation disorders (Chapter 67)	Young people with stroke of unknown cause or history suggesting coagulopathy, such as prior venous thrombosis, pulmonary embolism, multiple (particularly late) miscarriages	Prothrombotic coagulopathies can be inherited or acquired. These are more commonly associated with venous thrombosis and can lead to stroke in patients with a right-to-left shunt as paradoxical emboli. Late miscarriages in women or unprovoked deep venous thrombosis may be clues to an underlying coagulopathy. In addition to abnormalities of fibrinogen occurring in patients with cancer, anticardiolipin/antiphospholipid antibodies, and lupus anticoagulants are most commonly associated with ischemic stroke. Coagulopathies need to be considered in all patients with a cerebral venous sinus thrombosis.	Platelet antiaggregants or anticoagulation
Hyperviscosity	Usually caused by polycythemia vera, macroglobulinemia, or multiple myeloma	Hyperviscosity can cause ischemic stroke through occlusion of small intracranial vessels.	Treatment of underlying hematologic disorder
Cervical artery dissection	Often in otherwise healthy younger individuals	Dissections can be caused by trauma or occur spontaneously. Underlying causes include fibromuscular dysplasia (which can also affect renal arteries), Marfan syndrome, Ehlers-Danlos type IV, and tuberous sclerosis.	Dissections often heal spontaneously with no evidence of residual vascular injury. A period of anticoagulation is commonly used in patients with stroke related to dissection; however, data showing the benefit of the approach are lacking.
Aortic dissection (Chapter 63)	Marfan syndrome, Ehlers-Danlos syndrome	Aortic dissection can be manifested with chest pain radiating to the back.	Emergency surgical repair
Moyamoya	Usually discovered with intracranial vascular imaging, such as CT angiography, MR angiography, or catheter angiography	Moyamoya refers to neovascularization in patients with occlusion of the distal intracranial internal carotid arteries or proximal middle cerebral arteries. Moyamoya can be the result of other conditions (moyamoya syndrome) or occur without identifiable cause (moyamoya disease). Moyamoya can be associated with both ischemic stroke and brain hemorrhage.	Extracranial-intracranial bypass
Fabry disease (Chapter 192)	Stroke in the setting of typical historical features and physical examination findings; may be considered in young persons with stroke of unknown cause	Fabry disease is an X-linked disorder causing reduction in α-galactosidase. In addition to stroke, Fabry disease can cause angiokeratomas, acroparesthesias, hypohidrosis, corneal opacities, and renal and cardiac disease.	Enzyme replacement therapy is available but has not been shown to reduce stroke risk.

CT = computed tomography; MRI = magnetic resonance imaging.

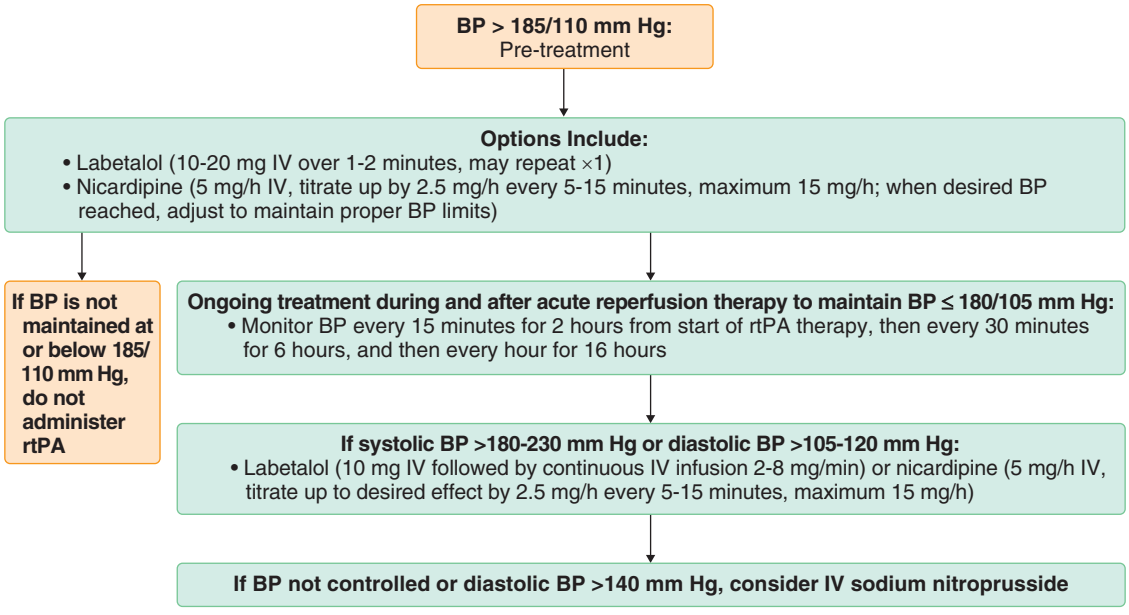

FIGURE 376-5. Potential approaches to arterial hypertension in acute ischemic stroke patients who are candidates for acute reperfusion therapy. BP = blood pressure; IV = intravenously; rtPA = recombinant tissue plasminogen activator. (Adapted from Jauch EC, Saver JL, Adams HP Jr, et al. Guidelines for the early management of patients with acute ischemic stroke: a guideline for healthcare professionals from the American Heart Association/American Stroke Association. *Stroke*. 2013;44:870-947.)

CEREBRAL VENOUS THROMBOSIS

Thrombosis of a cerebral venous sinus can cause headache, focal strokelike manifestations, seizures, altered mental status, and papilledema owing to raised intracranial pressure.[12] It is a rare (incidence rate about 0.08% among hospitalized patients) complication of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection (Chapter 337).[13]

With superior sagittal sinus obstruction (see Fig. 375-10 in Chapter 375), patients can develop bilateral leg weakness and sensory changes. Obstruction of a transverse sinus or one of the major veins over the cerebral convexity (see Fig. 375-11 in Chapter 375) can also produce symptoms, depending on the area of the brain that is injured. Cerebral venous sinus thrombosis is an uncommon condition that usually occurs in patients with coagulopathies, disseminated cancer, or a prior inner ear infection. It can also occur in the peripartum period. Venous obstruction can mimic an ischemic arterial stroke, but symptoms and signs often extend beyond a single arterial territory and can be more diffuse, resembling encephalitis (Chapter 383) or meningitis (Chapter 381). The diagnosis can be suspected on routine CT or MRI and confirmed by CT or MR venography (Fig. 376-6). Initial acute treatment options include either body weight–adjusted subcutaneous low-molecular-weight heparin (see Table 70-3 in Chapter 70) or dose-adjusted intravenous heparin (see Table 68-6 in Chapter 68), even if patients have some degree of hemorrhage. One small randomized trial found that treatment with low-molecular-weight heparin was associated with lower mortality compared with unfractionated heparin. Limited data preclude conclusions regarding the efficacy of systemic thrombolysis for acute cerebral venous sinus thrombosis, and a small trial found no benefit with endovascular therapy added to medical therapy compared with medical therapy alone.

Patients should be anticoagulated for at least 3 months, and longer periods of anticoagulation may be considered, depending on the cause of the sinus thrombosis. Data are limited, but a clinical trial in children with venous thromboembolism (about 25% of whom had cerebral venous sinus thrombosis) found no appreciable differences in recurrence or bleeding between patients treated with body-weight-adjusted doses of rivaroxaban (see Table 70-6) compared with standard oral warfarin to an INR target of 2.0 to 3.0.[A22]

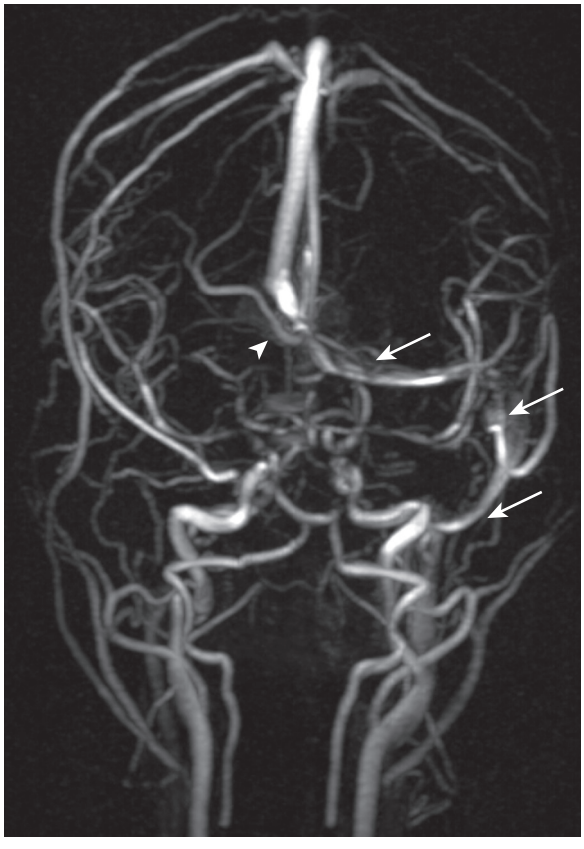

FIGURE 376-6. Magnetic resonance venogram showing absent flow in the right transverse sinus (*arrowhead*) and sigmoid sinus and intact flow in the left transverse sinus and sigmoid sinus (*arrows*).

CERVICAL ARTERY DISSECTION

A cervical artery dissection or cerebral artery dissection, each of which can be associated with the formation and subsequent longitudinal extension of an intramural hematoma, can narrow or obstruct the arterial lumen. These dissections can be spontaneous, or they can be associated with major neck injury, relatively minor trauma (such as a chiropractic neck manipulation or neck hyperextension), or otherwise innocuous activities, such as coughing, sneezing, or lifting. Patients may have underlying fibromuscular dysplasia (Chapter 66); inherited conditions such as Marfan syndrome (Chapter 239), Ehlers-Danlos syndrome, or tuberous sclerosis (Chapter 385); an elevated blood homocysteine level; or no identified underlying cause. The diagnosis can be challenging but should be considered especially in an otherwise healthy young patient who has neck or facial pain in conjunction with a stroke. MR angiography may show a hyperintense mass adjacent to a flow void, and MR angiography or catheter angiography can show a tapered lumen leading

to an obstruction or even a double lumen. Acute treatment may include thrombolysis or endovascular or surgical repair, depending on individual circumstances. Although one randomized trial found that antiplatelet and anticoagulation therapy provided equivalent outcomes,[A23] a subsequent trial found that anticoagulation with a vitamin K antagonist (phenprocoumon, acenocoumarol, or warfarin to a target INR of 2.0 to 3.0 for 90 days) to be superior to aspirin.[A24]

VASCULITIS

Vasculitis (Chapters 245, 249, and 250) can cause focal or multifocal cerebral ischemia due to local inflammation, stenosis, and even necrosis of extracranial or intracranial blood vessels. Patients can have preexisting or concurrent headaches, cognitive changes, and seizures. Because vasculitis often involves multiple arteries, multiple foci of ischemic injury on neuroimaging studies may mimic multiple emboli. Catheter angiography classically shows multiple areas of beadlike segmental narrowing, but findings may be normal. Similar findings may occur with other causes of intracranial vasculopathy, and the angiographic appearance is not specific. The diagnosis may require leptomeningeal/cortical biopsy, which may be negative because the inflammatory process can be multifocal rather than diffuse. Examples of vasculitides that can cause strokelike symptoms include primary central nervous system vasculitis, systemic lupus erythematosus (Chapter 245), rheumatoid vasculitis (Chapter 243), Behçet disease (Chapter 249), Takayasu arteritis (Chapters 63 and 249), temporal arteritis (Chapter 250), fibromuscular dysplasia (Chapters 61 and 66), granulomatosis with angiitis (Chapter 249), sarcoidosis (Chapter 83), meningovascular syphilis (Chapter 295), and lymphomatoid angioendotheliomatosis, among others.

SICKLE CELL DISEASE

Strokes occur in about 8 to 17% of patients with sickle cell disease and in about 2% of individuals with sickle cell trait (Chapter 149). Ischemic strokes are more common in children, whereas hemorrhagic strokes are more common in adults. Transfusion therapy can markedly reduce the risk of a first or recurrent stroke. When adults with sickle cell disease have an acute ischemic stroke, treatment with IV rtPA can be beneficial.

DRUG-RELATED CAUSES OF STROKE

A variety of legal and illicit drugs (Chapter 365) can precipitate an ischemic stroke. Intravenous drug users are more likely to develop bacterial endocarditis (Chapter 61), which can cause embolic stroke and lead to mycotic aneurysms that can cause subarachnoid hemorrhage. Solid adulterants in injected material can reach the brain through an existing shunt, such as a patent foramen ovale, or they can cause local pulmonary arteriolitis that damages the endothelium and results in arteriovenous shunts through which microemboli can reach the brain. Potent vasoconstricting drugs (e.g., cocaine, ephedrine, phenylpropanolamine, and fenoxazoline) and dietary supplements (e.g., ephedra) may precipitate cerebral vasospasm and ischemic stroke, although hemorrhagic strokes are more common (Chapter 377). These drugs have been used in high doses as appetite suppressants, and case reports suggest that stroke may occur even after the first use of these products.

RARE GENETIC CAUSES

Several relatively rare genetic diseases can cause ischemic stroke. *Cerebral autosomal dominant arteriopathy with small subcortical infarcts and leukoencephalopathy* (CADASIL) can cause multiple deep infarcts and dementia in patients without other risk factors for stroke. A mutation in the Notch3 receptor gene on the short arm of chromosome 19 leads to an accumulation of Notch3 protein in vascular smooth muscle cells. The mean age at onset is about 40 years, although migraine with aura often antedates strokes by several years. Dementia usually develops within 10 to 15 years. Antenatal diagnosis is recommended in affected families. Treatment is symptomatic, with CADASIL-associated headaches potentially responding to acetazolamide (125 to 500 mg daily).

Moyamoya disease (see E-Table 376-1) is linked to variants in the *RNF213* gene and is more common in East Asian countries.[14] X-linked Fabry disease (angiokeratoma corporis diffusum) (Chapter 192) frequently includes cerebrovascular occlusion due to the accumulation of glycolipids in small and medium-sized arteries. Enzyme replacement therapy is recommended, although it is not proven to reduce the risk of stroke. *Neurofibromatosis* (Chapter 385) can occlude the internal carotid arteries or the proximal part of the anterior cerebral circulation. Marfan syndrome (Chapter 239) can cause ischemic stroke due to dissection of the carotid arteries or related valvular heart disease.

FAT EMBOLISM

Fat embolism (Chapter 68) after trauma to the long bones (Chapter 97), orthopedic procedures, and severe trauma to large fat deposits can cause a stroke, usually several days later. Diffuse embolization can produce encephalopathy or seizures, but more focal emboli can be manifested as an ischemic stroke.

CRYPTOGENIC STROKE

When the cause of the stroke is uncertain, and especially when an embolic source is suspected, prolonged electrocardiographic monitoring and echocardiography are indicated. The use of extended cardiac rhythm monitoring (i.e., 30-day event-triggered loop monitoring or an implanted monitor; Chapter 49) reveals occult atrial fibrillation in up to 25% of patients with an otherwise cryptogenic stroke.[A25,A26] Transesophageal echocardiography in adult patients with embolic stroke of undetermined source may positively affect the selection of an appropriate therapeutic strategy in approximately one in seven patients by detecting a patent foramen ovale (Chapter 55), bacterial endocarditis (Chapter 291), left atrial clot, or other abnormalities. If patent foramen ovale is the presumed cause of paradoxical embolization and a cryptogenic stroke,[15] especially in the presence of a moderate to large right to left shunt, devise closure is often preferable to chronic anticoagulation.[A27] Other cryptogenic strokes may be due to embolism from either a cardiac or other proximal arterial source. In these patients, neither dabigatran nor rivaroxaban is preferable to aspirin prophylaxis. Despite a comprehensive evaluation (Fig. 376-7), however, no definitive cause of stroke is found in 15 to 40% of patients with strokes.

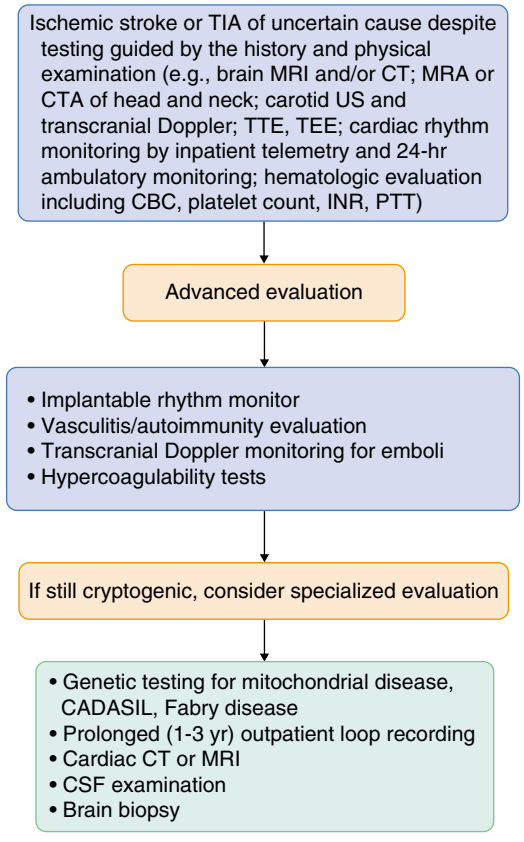

FIGURE 376-7. Diagnostic evaluation of patients with cryptogenic ischemic stroke or transient ischemic attack. CADASIL = cerebral autosomal dominant arteriopathy with subcortical infarcts and leukoencephalopathy; CBC = complete blood count; CSF = cerebrospinal fluid; CT = computed tomography; CTA = computer tomographic angiography; INR = international normalized ratio; MRA = magnetic resonance angiography; MRI = magnetic resonance imaging; PTT = partial thromboplastin time; TEE = transesophageal echocardiography; TIA = transient ischemic attack; TTE = transthoracic echocardiography; US = ultrasound. (Data from Saver JL. Clinical practice. Cryptogenic stroke. *N Engl J Med.* 2016;374:2065-2074.)

PREVENTION

Primary Prevention

Because more than 75% of strokes are first events, primary prevention of stroke is of paramount importance.[16] Following a healthy lifestyle (not smoking, following a diet low in sodium and rich in fruits and vegetables, getting at least 30 minutes of moderate or vigorous physical activity daily, having a body mass index below 25 kg/m^2, and consumption of no more than one alcoholic drink per day for women and one or two for men) is associated with an 80% lower risk of a first stroke compared with people who do not follow these lifestyles. The effect is graded, with increasing benefit depending on the number of healthy lifestyles an individual follows. There is no evidence that prophylactic treatment with aspirin or other antiplatelet drugs reduces the risk of stroke in low-risk individuals.

Risk factors that are amenable to treatment (see Table 376-1) include hypertension, diabetes, atrial fibrillation, and carotid artery stenosis. Treatment of hypertension dramatically reduces the risk of stroke. Regular blood pressure screening and treatment of hypertension (see Tables 64-7 and 64-9 in Chapter 64) are recommended, and aggressive treatment (goal systolic blood pressure less than 120 mm Hg) may prevent an additional 100,000 deaths in the United States each year compared with a goal of 140/90 mm Hg (Chapter 64). Blood pressure treatment and the use of a statin in patients with diabetes (Chapter 210) are recommended to lower the risk of a first stroke. Statins (Chapter 190) are also recommended to prevent a first ischemic stroke in patients with coronary heart disease. Although microvascular complications of diabetes are reduced with adequate glycemic control (target glycated hemoglobin level <7%), there is no evidence that tight control reduces the risk of stroke or coronary heart events.

Screening by electrocardiography or a loop recorder can detect asymptomatic atrial fibrillation, but the benefit for reducing stroke is only about 1% over the next 5 to 7 years.[A28,A29] Patients who have atrial fibrillation and are at increased risk of embolism benefit from treatment with a direct oral anticoagulant or warfarin (Chapter 52). In patients with a mechanical prosthetic heart valve (Chapter 60), direct oral anticoagulants are contraindicated, and anticoagulation with warfarin is recommended to prevent stroke. The U.S. Preventive Services Task Force recommends against screening for asymptomatic carotid artery stenosis. Folic acid does not prevent stroke in Western countries, but it may reduce the risk of stroke in Chinese adults with hypertension, among whom absolute or relative folate deficiency is more common.

Prevention of Stroke in the Patient with Asymptomatic Carotid Stenosis

The current benefit of carotid endarterectomy for patients with asymptomatic carotid stenosis is uncertain[17] because of advances in medical therapy, since early randomized trials found about a 50% reduction in the risk of stroke in patients with stenoses >70%. The risk of ipsilateral stroke associated with an asymptomatic carotid stenosis is now about 1.5% per year based on observational studies and clinical trials, and the benefits of carotid revascularization, which are equivalent with endarterectomy and stenting,[A30] may be less than 1% over 5 years.[18] Clinical trials are in progress comparing carotid revascularization with current best medical therapy in asymptomatic patients. Population screening for asymptomatic carotid stenosis is not recommended.

Secondary Prevention after a Transient Ischemic Attack or Stroke

A transient ischemic attack increases the risk of a subsequent stroke by over five-fold.[19] Although clinical trials demonstrating the efficacy of lifestyle interventions for secondary stroke prevention are generally unavailable, the same lifestyle behaviors associated with a reduced risk of a first stroke are an essential part of secondary stroke prevention. Patients should routinely be prescribed an antiplatelet agent unless there are contraindications. The exception is the patient who has a specific indication for treatment with an anticoagulant, such as atrial fibrillation or a prosthetic heart valve, or in whom antithrombotic therapy is contraindicated. The choice of agent needs to be individualized, but aspirin (50 to 325 mg daily), clopidogrel (75 mg daily), ticagrelor (180 mg loading dose on day 1 followed by 90 mg twice daily), or aspirin plus sustained-release dipyridamole (25/200 mg twice daily) are options. Ticagrelor alone is no better than aspirin in reducing the rate of stroke, myocardial infarction, or death at 90 days. As noted earlier, short-term dual antiplatelet therapy with aspirin and clopidogrel may be more efficacious than single-agent therapy, but long-term therapy increases the risk of serious bleeding.

Blood pressure reduction is recommended to lower the risk of recurrent stroke and other vascular events. The precise timing of initiation of antihypertensive therapy after ischemic stroke is not established, but it can begin once the patient is stabilized after the acute period, generally after at least 24 hours. An average reduction of 10/5 mm Hg is associated with about a 25% reduction in the risk of recurrent stroke. In patients with MRI-defined symptomatic lacunar infarctions, reducing systolic blood pressure to a target of less than 130 mm Hg starting 2 weeks later significantly reduces the rate of intracerebral hemorrhage and insignificantly reduces all subsequent stroke compared with a target of 130 to 149 mm Hg. The choice of a specific antihypertensive regimen for secondary prevention should be individualized (see Tables 64-7 and 64-9 in Chapter 64). Treatment recommendations are for a diuretic, calcium channel antagonist, angiotensin-converting enzyme inhibitor, or angiotensin receptor blocker.

Patients with a prior stroke or TIA and known atherosclerotic disease, diabetes, or hyperlipidemia meeting criteria for statin therapy should be treated with a high-potency statin (e.g., 40 to 80 mg of atorvastatin or 20 to 40 mg of rosuvastatin daily; see also Table 190-2 in Chapter 190)[A31] or a PCSK9 inhibitor[A32] (see Chapter 190), unless contraindicated, to reduce the risk of recurrent stroke and of other cardiovascular events. A target LDL cholesterol level of <70 mg/dL can reduce subsequent major cardiovascular events and all recurrent strokes by about 20% compared with a target of 90 to 110mg/dL, despite a nonsignificantly higher risk of hemorrhagic stroke.[A33] Stopping a statin in the setting of an acute ischemic stroke is associated with increased morbidity and mortality.

In one randomized trial of patients who had a recent history of ischemic stroke or TIA and who also had insulin resistance but not diabetes, the subsequent risk of stroke or myocardial infarction was lower among patients who received pioglitazone (target dose, 45 mg daily) than among patients who received placebo. Additional data are necessary before such treatment is recommended for routine use. In addition to these general measures, additional specific treatment for secondary stroke prevention depends on the cause of the stroke. Atrial fibrillation–related stroke is associated with a high risk of recurrence (i.e., 6 to 10% annually). Patients with atrial fibrillation–related stroke should be treated with a direct oral anticoagulant or warfarin. Anticoagulation with warfarin is indicated in patients with stroke related to acute MI and in those with valvular heart disease.

Procedures and Devices

The rate of recurrent stroke after stroke or TIA related to a high-grade (70 to 99%) extracranial carotid artery stenosis may be as high as 25% during the ensuing 2 years, with the highest risk in the first weeks after the index event. Because this risk of recurrence is decreased by 50% with successful carotid revascularization, selected patients with stroke associated with 70 to 99% extracranial carotid artery stenosis within the prior 6 months benefit from carotid revascularization, provided the procedure can be performed with less than 6% morbidity. Patients with a 50 to 69% symptomatic stenosis also appear to benefit, but with about a 16% relative reduction in subsequent events.[A34] Patients with less than 50% carotid stenosis do not benefit from carotid revascularization.

For a combined end point of stroke, MI, and death, carotid stenting appears to be as efficacious as endarterectomy in patients with a symptomatic or asymptomatic extracranial carotid artery stenosis,[A35] but stenting tends to be associated with a higher risk of stroke. Younger patients seem to do somewhat better with stenting, whereas patients over age 70 years seem to do better with endarterectomy. Extracranial-intracranial bypass does not reduce the risk of recurrent strokes in patients with complete occlusion of an extracranial carotid artery and may be associated with a higher risk of stroke than medical therapy. Similarly, angioplasty/stenting for a symptomatic intracranial arterial stenosis has no benefit compared with medical therapy,[A36] and vertebral artery angioplasty or stenting is not beneficial even in symptomatic patients.[A37]

PROGNOSIS

TIA is a major risk factor for stroke and requires urgent evaluation to detect specific causes that may require immediate treatment.[20,21] Overall, approximately 10% of patients who have a TIA will have a stroke within 90 days, with almost half occurring within 2 days. The strokes that occur are frequently fatal or associated with disabling deficits (E-Table 376-2). Factors associated with higher risk include age older than 60 years, diabetes, impaired speech or weakness, symptoms lasting more than 10 minutes, and evidence of ischemic injury on brain MRI. After the acute period, about 20% of patients who had a TIA will have a stroke during the next 10 years.

E-TABLE 376-2 DISABLING DEFICITS

The following typically should be considered disabling deficits:

- Complete hemianopsia (≥2 on NIHSS question 3) or severe aphasia (≥2 on NIHSS question 9), or
- Visual or sensory extinction (≥1 on NIHSS question 11), or
- Any weakness limiting sustained effort against gravity (≥2 on NIHSS question 6 or 7), or
- Any deficits that lead to a total NIHSS score >5, or
- Any remaining deficit considered potentially disabling in the view of the patient and the treating practitioner. Clinical judgment is required.

NIHSS = National Institutes of Health Stroke Score. (See Table 376-4.)

Levine SR, Khatri P, Broderick JP, Grotta JC, Kasner SE, Kim D, Meyer BC, Panagos P, Romano J, Scott P. Review, historical context, and clarifications of the NINDS rt-PA stroke trials exclusion criteria: Part 1: rapidly improving stroke symptoms. *Stroke*. 2013;44:2500-2505.

Stroke-related mortality varies by age. The 30-day stroke mortality rate is estimated to be 9% for patients aged 65 to 74 years, 13% for patients aged 74 to 84 years, and 23% for patients older than 85 years. About 30% of patients who have had a stroke will have a recurrent stroke within 5 years. Stroke is also a leading cause of disability. Among stroke survivors, approximately 45% have cognitive deficits, 30% are unable to walk without assistance, 25% are institutionalized, and 25% are dependent in activities of daily living after 6 months.

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377 HEMORRHAGIC CEREBROVASCULAR DISEASE

SEEMANT CHATURVEDI AND MAGDY SELIM

In the United States, about 13%[1] of strokes are caused by intracranial hemorrhage, but the worldwide percentage is about 20% because of countries where hypertension is common but atherosclerosis is less common.[2,3] Intracerebral hemorrhage, which accounts for about 75% of cases, usually occurs when small penetrating arteries rupture and produce a focal collection of blood within the parenchyma. Subarachnoid hemorrhage, which accounts for about 25% of cases, occurs when a vessel ruptures on the surface of the brain, and blood enters into and spreads throughout the cerebrospinal fluid (CSF). In both of these bleeds, extension of blood into the cerebral ventricles occurs in about 40% of cases.

SPONTANEOUS SUBARACHNOID HEMORRHAGE

In subarachnoid hemorrhage, the hemorrhage occurs in the space between the innermost (pia mater) and middle layer (arachnoid mater) of the meninges that cover the surface of the brain.

EPIDEMIOLOGY AND PATHOLOGY

Subarachnoid hemorrhage represents approximately 25% of hemorrhagic strokes and 5% of all strokes. Trauma (Chapter 368) is by far the most common cause of subarachnoid hemorrhage, accounting for perhaps 70% or more of cases. Nontraumatic, spontaneous subarachnoid hemorrhages are commonly caused by rupture of an intracranial aneurysm, almost 80% of which are saccular or berry aneurysms that most often occur at the bifurcations of the major branches of the circle of Willis (Fig. 377-1).[4] Other causes of spontaneous subarachnoid hemorrhage include peri-mesencephalic subarachnoid hemorrhage, cerebral amyloid angiopathy,[5] cerebral venous sinus thrombosis (Chapter 376), cerebral arteriovenous malformation, cerebral vasculitis, mycotic aneurysms, coagulopathies (Chapter 157), dissection of the intracranial carotid or vertebral arteries (Chapter 376), or extension of an intracerebral hemorrhage into the subarachnoid space (Table 377-1).

Population-based studies indicate that the incidence of spontaneous subarachnoid hemorrhage varies by geographic region. The world age-standardized incidence is approximately 3.3 per 100,000 person-years. The annual incidence of aneurysmal subarachnoid hemorrhage in the United States is about 1 in

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377 HEMORRHAGIC CEREBROVASCULAR DISEASE

SEEMANT CHATURVEDI AND MAGDY SELIM

In the United States, about 13%[1] of strokes are caused by intracranial hemorrhage, but the worldwide percentage is about 20% because of countries where hypertension is common but atherosclerosis is less common.[2,3] Intracerebral hemorrhage, which accounts for about 75% of cases, usually occurs when small penetrating arteries rupture and produce a focal collection of blood within the parenchyma. Subarachnoid hemorrhage, which accounts for about 25% of cases, occurs when a vessel ruptures on the surface of the brain, and blood enters into and spreads throughout the cerebrospinal fluid (CSF). In both of these bleeds, extension of blood into the cerebral ventricles occurs in about 40% of cases.

SPONTANEOUS SUBARACHNOID HEMORRHAGE

In subarachnoid hemorrhage, the hemorrhage occurs in the space between the innermost (pia mater) and middle layer (arachnoid mater) of the meninges that cover the surface of the brain.

EPIDEMIOLOGY AND PATHOLOGY

Subarachnoid hemorrhage represents approximately 25% of hemorrhagic strokes and 5% of all strokes. Trauma (Chapter 368) is by far the most common cause of subarachnoid hemorrhage, accounting for perhaps 70% or more of cases. Nontraumatic, spontaneous subarachnoid hemorrhages are commonly caused by rupture of an intracranial aneurysm, almost 80% of which are saccular or berry aneurysms that most often occur at the bifurcations of the major branches of the circle of Willis (Fig. 377-1).[4] Other causes of spontaneous subarachnoid hemorrhage include peri-mesencephalic subarachnoid hemorrhage, cerebral amyloid angiopathy,[5] cerebral venous sinus thrombosis (Chapter 376), cerebral arteriovenous malformation, cerebral vasculitis, mycotic aneurysms, coagulopathies (Chapter 157), dissection of the intracranial carotid or vertebral arteries (Chapter 376), or extension of an intracerebral hemorrhage into the subarachnoid space (Table 377-1).

Population-based studies indicate that the incidence of spontaneous subarachnoid hemorrhage varies by geographic region. The world age-standardized incidence is approximately 3.3 per 100,000 person-years. The annual incidence of aneurysmal subarachnoid hemorrhage in the United States is about 1 in

ABSTRACT

Approximately 20% of all strokes are due to spontaneous intracranial hemorrhage, with about 25% being subarachnoid and about 75% being intracerebral. The most common cause of nontraumatic subarachnoid hemorrhage is a ruptured brain aneurysm, whereas intracerebral hemorrhage is usually caused by rupture of penetrating arteries in the brain parenchyma. Subarachnoid hemorrhage typically presents with a sudden and severe headache, often accompanied by nausea, vomiting, loss of consciousness, and nuchal rigidity. Rapid diagnosis with computed tomographic (CT) angiography or conventional angiography is critical. Major treatment goals are to limit brain injury, prevent rebleeding, and prevent vasospasm. Treatment for a ruptured berry aneurysm is either surgical clipping or endovascular coiling. Intracerebral hemorrhage, which typically presents with a headache and focal neurologic deficits, may be difficult to distinguish from an ischemic stroke. Early unenhanced CT imaging is critical to identify the location and extent of the hemorrhage. Treatment is focused on blood pressure control, limiting brain edema, and reversal of any prior anticoagulation treatment. Brain vascular malformations may present with a headache, seizure, or cerebral hemorrhage. Treatment includes direct surgical resection, embolization, or radiation. For patients with an unruptured vascular malformation, conservative treatment is frequently recommended.

KEY WORDS

subarachnoid hemorrhage
intracerebral hemorrhage
brain aneurysm
arteriovenous malformation
intraventricular hemorrhage
hemorrhagic stroke
intraparenchymal hemorrhage

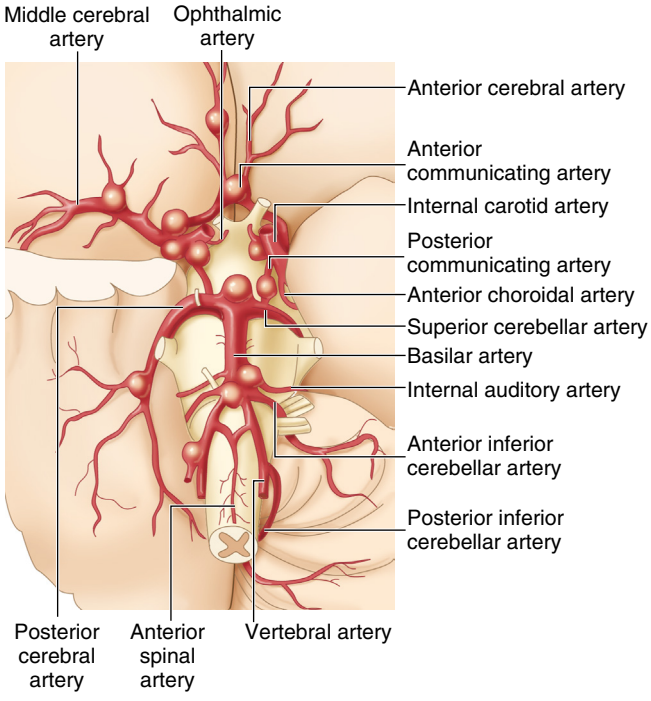

FIGURE 377-1. Saccular aneurysms. Saccular, or berry, aneurysms typically develop at the bifurcations of arteries on the undersurface of the brain. (Courtesy Dr. Justin Zivin.)

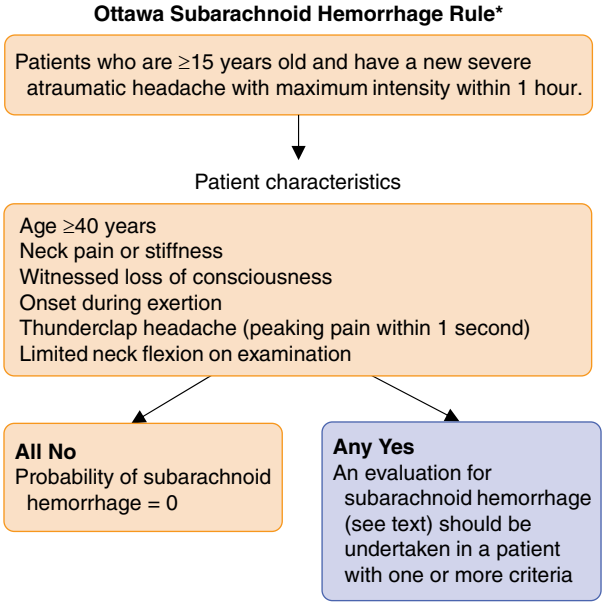

FIGURE 377-2. The Ottawa Subarachnoid Hemorrhage Rule. *Should not be used in patients with new neurologic deficits, a prior aneurysm, prior subarachnoid hemorrhage, known brain tumors, or chronic recurrent headaches.

TABLE 377-1 NON-ANEURYSMAL CAUSES OF SUBARACHNOID HEMORRHAGE

Trauma (Chapter 368)
Idiopathic perimesencephalic subarachnoid hemorrhage
Arteriovenous malformation
Intracranial arterial dissection (Chapter 376)
Cocaine and amphetamine use (Chapter 365)
Mycotic aneurysm (Chapter 61)
Pituitary apoplexy (Chapter 205)
Moyamoya disease (Chapter 376)
Central nervous system vasculitis (Chapter 249)
Sickle cell disease (Chapter 149)
Coagulation disorders (Chapters 158, 160, and 161)
Primary or metastatic neoplasm (Chapter 175)

Causes are listed in approximate order of frequency.
From Mayer SA. Hemorrhagic cerebrovascular disease. In: Goldman L, Schafer AI, eds. *Goldman-Cecil Medicine*. 26th ed. Philadelphia: Elsevier; 2020.

13,000, thereby resulting in about 25,000 cases per year, with the highest rates among women ages 40 to 60 years and Black Americans.[6]

The risk factors for aneurysmal subarachnoid hemorrhage include a family history in first-degree relatives, autosomal dominant polycystic kidney disease (Chapter 112), history of prior aneurysmal subarachnoid hemorrhage, and connective tissue or moyamoya disease. Additional modifiable risk factors are smoking (Chapter 363), poorly controlled hypertension (Chapter 64), excessive alcohol use (Chapter 364), and use of sympathomimetic drugs such as cocaine (Chapter 365) or adrenergic stimulants.

CLINICAL MANIFESTATIONS

The classic presentation of subarachnoid hemorrhage is a "thunderclap headache." The headache starts suddenly with maximum intensity, and most patients describe it as the worst headache of their lives. The headache is often associated with nausea, vomiting, photophobia, neck stiffness, and back or leg pain. Abrupt elevation of intracranial pressure at the time of aneurysmal rupture may result in brief loss of consciousness, with or without tonic posturing that mimics a seizure.

A sentinel or warning event can occur days to weeks before an overt aneurysmal subarachnoid hemorrhage in about 15 to 40% of cases. This warning event, which often implies minor leaks of blood from the aneurysm or aneurysmal expansion, dissection, or thrombosis, typically is not associated with nuchal rigidity, and the headache tends to be milder.

Mental status may vary from normal to coma depending on the severity of the subarachnoid hemorrhage. The physical examination may reveal meningismus and/or preretinal hemorrhages as a result of abrupt increase in intracranial pressure. Most patients do not have focal neurologic deficits, but focal neurologic deficits can occur based on the location of the aneurysm and hemorrhage. For example, cranial nerve III (oculomotor nerve) palsy suggests a posterior communicating artery aneurysm.

DIAGNOSIS

All patients who present with a new atraumatic headache with a maximum intensity within 1 hour should be questioned about characteristics that could be consistent with a subarachnoid hemorrhage (Fig. 377-2) and further evaluated if such characteristics are present.[7] The utility of diagnostic tests for subarachnoid hemorrhage is time-dependent. A noncontrast computed tomographic (CT) scan of the brain is the preferred initial diagnostic test, with an overall sensitivity of 97.5% for detecting subarachnoid hemorrhage (Fig. 377-3). The sensitivity is even higher during the first 6 hours after the onset of symptoms (97% to 99%) but declines substantially (to about 75% by day 3) if the scan is delayed for 24 to 72 hours after the onset of symptoms.

If the CT scan is negative for subarachnoid hemorrhage but the index of suspicion is high, a lumbar puncture should be performed as soon as possible to examine CSF for cell counts and xanthochromia (a yellow-tinged appearance owing to hemolysis and usually indicative of a bleed 2 hours to a week or more earlier of the supernatant fluid after centrifugation. The classic findings in subarachnoid hemorrhage are an elevated opening pressure, an elevated red blood cell count typically greater than 100,000 cells/μL that does not decrease from tube 1 to 4, and xanthochromia. However, xanthochromia may take up to 12 hours to appear. Other conditions that can result in xanthochromia include systemic hyperbilirubinemia, a traumatic lumbar puncture with more than 100,000 red blood cells/μL, and increased concentrations of protein in the CSF.

About 15% of subarachnoid hemorrhages are initially overlooked, particularly in less symptomatic patients, and about 40% of these misdiagnosed patients experience subsequent complications such as vasospasm, rebleeding, hydrocephalus, or even death before returning for further evaluation. Therefore, a high degree of suspicion and vigilance is required to obtain a head CT scan and lumbar puncture in all patients who present with a thunderclap headache.

Laboratory testing including a complete blood count, platelet count, partial thromboplastin time, and international normalized ratio (INR) should be performed to evaluate for an underlying coagulopathy (Chapter 157). An electrocardiogram showing peaked T-waves with QTc segment prolongation or an elevated troponin level can diagnose sympathetically mediated cardiac injury, which warrants an echocardiogram, and a chest

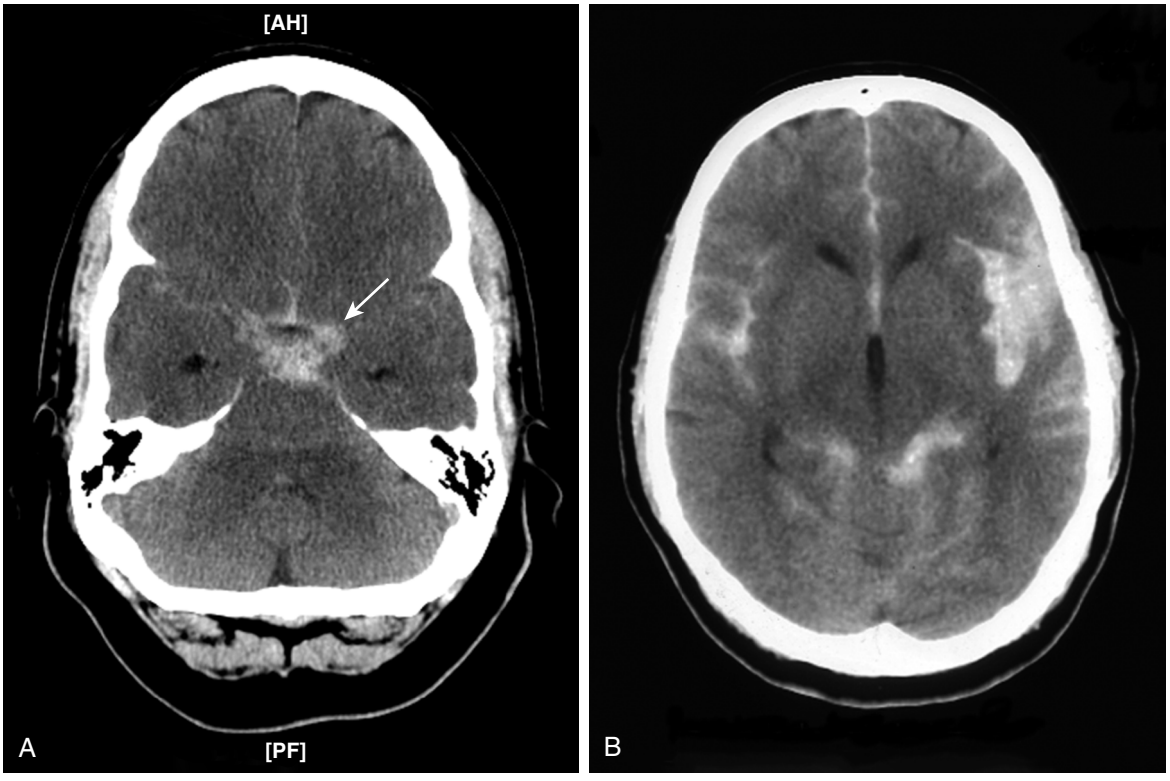

FIGURE 377-3. Two CT images of subarachnoid hemorrhage. A, Diffuse thick subarachnoid hemorrhage is seen in the anterior interhemispheric and bilateral sylvian fissures and the quadrigeminal cistern (*arrow*). A left middle cerebral artery aneurysm was identified. **B**, Perimesencephalic subarachnoid hemorrhage; only a small focus of blood in the interpeduncular cistern is identified. No aneurysm was identified. (Part A Courtesy of Dr. Larry B. Goldstein; Part B Courtesy of Dr. Stephan A. Mayer.)

radiograph can assess for possible aspiration pneumonitis or neurogenic pulmonary edema.

Causes of Subarachnoid Hemorrhage

Once the diagnosis of subarachnoid hemorrhage is established, its cause must be determined (see Table 377-1). Aneurysmal subarachnoid hemorrhage is always the primary consideration in patients who present with a sudden nontraumatic headache.[8] A CT angiogram or brain magnetic resonance image (MRI) with and without gadolinium and susceptibility-weighted imaging often can detect the bleed or a thrombosed aneurysm. However, the gold-standard for diagnosis of an aneurysm (Fig. 377-4) is a four-vessel cerebral angiogram, which is indicated if noninvasive imaging is not revealing. Even with cerebral catheter-based angiography, a cause for the subarachnoid hemorrhage may not be evident on the initial study in 14 to 22% of cases. If the initial angiogram is negative, a repeat angiogram within 14 days should be considered. Angiography can also reveal an arteriovenous malformation, which is more likely to cause intracerebral than subarachnoid hemorrhage (see later) or features suggestive of CNS vasculitis.[9]

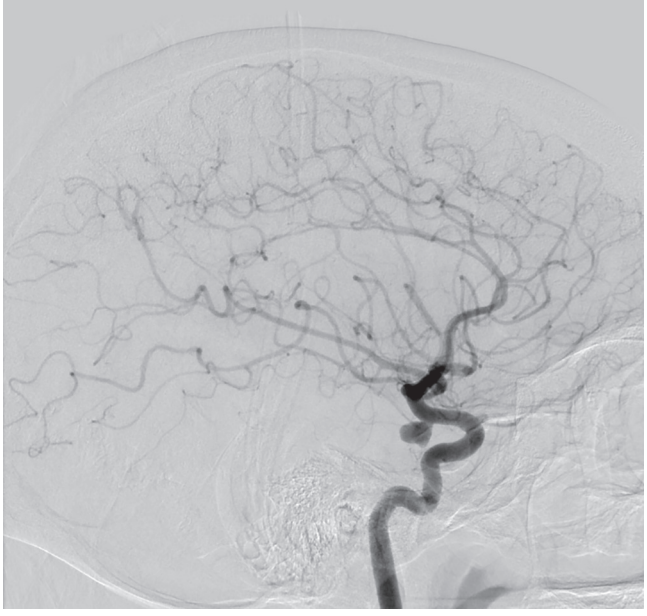

FIGURE 377-4. Cerebral aneurysm. Cerebral angiography showing an outpouching typical of an aneurysm.

TREATMENT

The goals of treatment are to minimize early brain injury, prevent rebleeding, perform definitive surgical or endovascular interventions quickly, and prevent and treat secondary complications.[10] Management of subarachnoid hemorrhage begins with early diagnosis and, if feasible, transfer to a high-volume, specialized center for emergency management and subsequent neurocritical care (Table 377-2).

Supplemental oxygen should be given to maintain normocapnea, and an oxygen saturation greater than 90%. Intubation should be considered if the patient's Glasgow Coma Scale score (see Table 368-1) is less than 8, or if there is concern about patient's ability to protect the airway (e.g., if excessive secretions or vomiting are present, or if gag or cough reflexes are absent). Maintenance of the circulation begins with establishing peripheral venous access and administration of isotonic fluids to maintain a mean blood pressure of 90 mm Hg.

Prevention and Treatment of Complications

To prevent rebleeding, the targeted systolic blood pressure should be less than 160 mm Hg, with a preferred goal of 140 to 160 mm Hg.[11] The timing and need for vasopressors, central access, and invasive blood pressure monitoring should be individualized.[12] To avoid rapid and large fluctuations in blood pressure, continuous intravenous infusions of labetalol or nicardipine (see Table 377-2) can be titrated. Vasodilators such as nitroprusside or nitroglycerin should be avoided because of their propensity to increase cerebral blood volume and intracranial pressure. Desmopressin (0.3 μg/kg intravenous push) may be beneficial in patients who have been taking antiplatelet agents. Epsilon aminocaproic acid (4 g followed by 1 g/hour for up to 72 hours) may be of modest benefit.

Environmental stimuli should be minimized to decrease the risk of rebleeding. Bed rest, low lighting, minimizing stress/pain-inducing interventions, use of antiemetics, and adequate pain control are important supportive measures to achieve this goal.

Emergent endovascular coiling or surgical clipping of a ruptured aneurysm is usually required to prevent rebleeding, except in patients with extremely

TABLE 377-2 MANAGEMENT PROTOCOL FOR ACUTE SUBARACHNOID HEMORRHAGE

Blood pressure	• Control elevated blood pressure during the preoperative phase (systolic BP <160 mm Hg) with IV labetalol (starting at 2-10 mg/min) or nicardipine (starting at 5-15 mg/hr) to prevent rebleeding
Rebleeding prophylaxis	• ε-Aminocaproic acid 4 g IV upon diagnosis followed by 1 g/hr until aneurysm repair, for a maximum of up to 72 hr after ictus
Intravenous hydration	• Normal (0.9%) saline at 1.0-1.5 mL/kg/hr
Laboratory testing	• Periodically check complete blood count and electrolytes • Obtain serial ECGs and check admission cardiac troponin level to evaluate for cardiac injury; perform echocardiography in poor-grade patients (i.e., Hunt-Hess IV-V), ECG findings, or elevated cardiac troponin level
Seizure prophylaxis	• Levetiracetam (2000 mg IV loading dose followed by 1000 mg IV twice daily); or discontinue on postoperative day 1 unless patient has seized, is poor grade, or has focal cortical pathology or is otherwise unstable
Vasospasm prophylaxis	• Nimodipine 60 mg PO every 4 hr until day 21 or discharge
Physiologic homeostasis	• Cooling blankets to maintain temperature ≤37.5° C • Insulin drip if needed to maintain glucose 100-120 mg/dL • Transfuse to maintain hemoglobin >7.0 g/dL (in the absence of active cerebral or cardiac ischemia)
Ventricular drainage	• Emergent external ventricular drain placement in all stuporous/comatose patients (Hunt-Hess IV/V), as well as lethargic patients with hydrocephalus • Begin trials of clamping external ventricular drain and monitoring intracranial pressure on day 3 after placement • Perform ventriculoperitoneal shunting during subacute phase of illness in patients with persistent cognitive dysfunction and ventriculomegaly
Vasospasm diagnosis	• Transcranial Doppler sonography every 1 to 2 days until the 10th day after subarachnoid hemorrhage • Computed tomographic angiography and perfusion on day 4-8 after subarachnoid hemorrhage or for neuroworsening
Therapy for symptomatic vasospasm	• Place patient in Trendelenburg (head down) position. • Infuse 1 L normal saline over 30 min. • If the deficit persists, raise the systolic blood pressure with phenylephrine or norepinephrine until the deficit resolves (target 180-220 mm Hg) • If refractory, monitor cardiac output and add dobutamine or milrinone to maintain cardiac index ≥4.0 L/min/m^2 • Transfuse to maintain hemoglobin >10.0 g/dL • Emergency angiogram for intra-arterial verapamil or cerebral angioplasty unless the patient responds well to the above measures

BP = blood pressure; ECG = electrocardiogram; IV = intravenous; L = liter; PO = oral.
Modified from Mayer SA. Hemorrhagic cerebrovascular disease. In: Goldman L, Schafer AI, eds. *Goldman-Cecil Medicine*. 26th ed. Philadelphia: Elsevier; 2020.

poor prognoses. For small- to medium-sized anterior circulation aneurysms in patients with good Hunt-Hess grades of 3 or less (Table 377-3), endovascular coiling provides better results than surgical clipping.[A1]

Vasospasm

Vasospasm, manifested by focal ischemic findings and diminished consciousness, is a common complication that may occur 5 to 14 days after an aneurysmal subarachnoid hemorrhage when blood degradation products irritate the walls of an artery, thereby leading to spasm with subsequent reduction in blood flow and cerebral ischemia (Table 377-4). Transcranial Doppler ultrasonography is the primary noninvasive method to detect vasospasm by measuring elevations of mean cerebral blood flow velocities within the cerebral arteries. CT angiography also can be helpful to establish the diagnosis, but catheter-based cerebral digital subtraction angiography remains the gold standard to diagnose radiographic vasospasm.

Careful control of blood pressure and fluid status are important to prevent and treat vasospasm. After the aneurysm has been secured, blood pressure can be liberalized to a mean arterial pressure of 100 to 110 mm Hg to maintain adequate cerebral perfusion pressure of 60 to 80 mm Hg. Intravascular fluid management should focus on avoiding hypovolemia and maintaining euvolemia with isotonic fluid resuscitation (0.9% normal saline at 1 to 1.5 mL/kg/hour). Nimodipine (60 mg every 4 hours for 21 days orally or via nasogastric tube) is also indicated beginning within 48 hours of the hemorrhage and continuing for 21 days to reduce the risk of delayed cerebral ischemia.[A2] Some data suggest that local administration of an antifibrinolytic drug at the site of the clot might reduce the risk of symptomatic vasospasm and its adverse effects,[A3] but the treatment is not widely advocated. If hypotension or symptomatic vasospasm occurs, bolus doses of isotonic fluid can be given in combination with pressors, (e.g., norepinephrine, phenylephrine, or milrinone) to elevate systolic blood pressure above 180 mm Hg. In refractory symptomatic cases, intra-arterial infusion of verapamil or nicardipine may be beneficial, and sometimes intraluminal balloon angioplasty may be warranted.

Hydrocephalus

Obstructive or nonobstructive hydrocephalus can develop acutely after subarachnoid hemorrhage and result in increased intracranial pressure or herniation. Initial life-saving treatment requires placement of an external ventricular drain to remove CSF and to monitor intracranial pressure. Many patients with acute hydrocephalus will develop chronic hydrocephalus and require placement of a permanent ventriculoperitoneal shunt.

TABLE 377-3 MORTALITY ACCORDING TO THE HUNT-HESS GRADING SCALE FOR ANEURYSMAL SUBARACHNOID HEMORRHAGE

GRADE	CLINICAL FINDINGS	HOSPITAL MORTALITY (%)
I	Asymptomatic or mild headache	3
II	Moderate to severe headache or oculomotor palsy	3
III	Confused, drowsy, or mild focal signs	9
IV	Stupor (localized to pain)	24
V	Coma (posturing or no motor response to pain)	70
TOTAL		18

Data are from 580 patients treated at Columbia University Medical Center. From Mayer SA. Hemorrhagic cerebrovascular disease. In: Goldman L, Schafer AI, eds. *Goldman-Cecil Medicine*. 26th ed. Philadelphia: Elsevier; 2020. (Courtesy of Stephan A. Mayer, MD.)

Seizures

Patients who suffer an aneurysmal subarachnoid hemorrhage are at high risk of seizures, which can raise intracranial pressure and increase the risk of rebleeding. To reduce the risk of seizures, prophylactic therapy with levetiracetam (2000 mg IV loading dose followed by a maintenance dose of 1000 mg IV twice daily) is commonly started at the time of diagnosis. In the absence of acute seizures, antiepileptic therapy can be safely discontinued in good-grade (Hunt-Hess grade 3 or less) patients after the ruptured aneurysm has been repaired. In poor-grade, comatose or stuporous patients, continued antiepileptic therapy and continuous EEG monitoring may be considered to evaluate for subclinical seizures. A benzodiazepine or propofol may be used to treat seizures (Table 372-6).

Medical Complications and Special Considerations

Patients who suffer a subarachnoid hemorrhage are at risk for medical complications. Hyponatremia (Chapter 102) is common and may be caused by the syndrome of inappropriate antidiuretic hormone (SIADH) or by cerebral salt

TABLE 377-4 MODIFIED FISHER COMPUTED TOMOGRAPHIC RATING SCALE FOR THE PREDICTION OF SYMPTOMATIC VASOSPASM

		PERCENTAGE OF AFFECTED PATIENTS		
GRADE	CRITERIA	FREQUENCY	DELAYED CEREBRAL ISCHEMIA*	INFARCTION
0	No subarachnoid hemorrhage or intraventricular hemorrhage	5%	0%	0%
1	Minimal/thin subarachnoid hemorrhage, no biventricular intraventricular hemorrhage	30%	12%	6%
2	Minimal/thin subarachnoid hemorrhage, *with* biventricular intraventricular hemorrhage	5%	21%	14%
3	Thick subarachnoid hemorrhage,† no biventricular intraventricular hemorrhage	43%	19%	12%
4	Thick subarachnoid hemorrhage,† *with* biventricular intraventricular hemorrhage	17%	40%	28%
	All patients	100%	20%	12%

*Defined as symptomatic deterioration, cerebral infarction, or both resulting from vasospasm.
†Thick subarachnoid hemorrhage is defined as completely filling at least one cistern or fissure.
Adapted from Claassen J, Bernardini GL, Kreiter K, et al. Effect of cisternal and ventricular blood on risk of delayed cerebral ischemia after subarachnoid hemorrhage: the Fisher scale revisited. *Stroke*. 2001;32:2012-2020. From Mayer SA. Hemorrhagic cerebrovascular disease. In: Goldman L, Schafer AI, eds. *Goldman-Cecil Medicine*. 26th ed. Philadelphia: Elsevier; 2020.

wasting. Sodium levels should be monitored closely, and hyponatremia should be corrected slowly at a rate not to exceed 1.3 mEq/L or more than 10 Eq/L in 24 hours. Unlike hyponatremia in other settings, fluid restriction should be avoided in patients who have a subarachnoid hemorrhage because it may result in increased blood viscosity and predispose to cerebral ischemia from vasospasm. Early treatment with fludrocortisone (0.05 mg per day) is recommended to prevent natriuresis and hyponatremia, and small doses (e.g., 250 to 500 mL) of hypertonic saline may be considered.

Fever, which is common after subarachnoid hemorrhage, may be related to loss of autoregulation or to a systemic inflammatory response. Acetaminophen (650 mg every 6 hours as needed) is preferred over agents that may aggravate bleeding. Surface or intravascular cooling may be considered as a second-line option if needed.

Massive sympathetic outflow after subarachnoid hemorrhage, particularly in poor-grade patients, may lead to neurogenic pulmonary edema (Chapter 45), cardiac dysfunction, electrocardiographic changes, an elevated cardiac troponin level, and a reduced left ventricular ejection fraction with wall motion abnormalities. These consequences are usually reversible with supportive treatment.

PREVENTION

Preventive screening for intracranial aneurysms is reasonable in first-degree relatives of patients who have suffered an aneurysmal bleed and in patients with polycystic kidney disease (Chapter 112).[13] Intracranial aneurysms that show growth on serial studies have about a 2.5% risk of rupture within the next year and may be appropriate for definitive treatment (coiling or clipping).[14] Otherwise, however, intervention appears to be no better than careful monitoring and control of risk factors, such as hypertension (Chapter 64), and cessation of smoking (Chapter 363) and heavy alcohol use (Chapter 364),[A4] probably even in patients with polycystic kidney disease (Chapter 112).

OTHER CAUSES OF SUBARACHNOID HEMORRHAGES

FUSIFORM ANEURYSMS

Fusiform aneurysms, which are elongated, atherosclerotic ectasias of large arteries, are most common in the basilar artery but can occur in the internal, middle, and anterior cerebral arteries. These aneurysms can cause focal neurologic signs and symptoms as they dilate and compress surrounding structures. Rupture is rare but should be treated with total occlusion because surgical clipping is technically difficult.

MYCOTIC ANEURYSMS

When an infected embolism in a patient who has infective endocarditis (Chapter 61) lodges in a distal branch of a cerebral artery,[15] it can cause microinfarction or microabscesses. The result may be an acute arterial rupture or focal arteritis with the formation of one or more mycotic aneurysms. These aneurysms are almost always initially asymptomatic and rarely diagnosed unless they rupture. Unfortunately, up to 10% of mycotic aneurysms eventually rupture, although some may be amenable to coiling if discovered before rupture.

TRAUMA

The cause of traumatic subarachnoid hemorrhage is uncertain, but probably includes blood extravasating from an adjacent brain contusion, an arterial dissection, direct damage to small vessels, or rupture because of a sudden change in intravascular pressure. Treatment is generally as for other traumatic brain injuries (Chapter 368). Nimodipine is not beneficial. Outcomes are generally more favorable than with spontaneous hemorrhage.

OTHER CAUSES

For most other causes (see Table 377-1), treatment is targeted at the underlying disease. Arteriovenous malformations, which more frequently cause intracerebral or intraventricular hemorrhage rather than subarachnoid hemorrhage, are discussed later in this chapter.

PROGNOSIS

The prognosis for patients with non-aneurysmal subarachnoid hemorrhage is generally better than for those with an aneurysmal subarachnoid hemorrhage, although cognitive and psychosocial difficulties are common. Aneurysmal subarachnoid hemorrhage is a devastating disease. About 10% of patients die before reaching the hospital. In-hospital mortality from an aneurysmal subarachnoid hemorrhage varies widely based on the clinical severity (see Table 377-3) and age, and 50% of patients die within 30 days. One-third of survivors have residual moderate-to-severe disability.[16] The most important prognostic factors are neurologic status at presentation and age, but an elevated troponin level also carries a worse prognosis.[17] The risk of rupture is nearly zero for aneurysms 3 mm and smaller, less than 0.5% per year for aneurysms 5 mm or smaller, and less than 1% per year for aneurysms 7 mm and smaller.

INTRACEREBRAL HEMORRHAGE

Intracerebral hemorrhage is a deadly form of stroke with limited evidence-based treatments.[18]

EPIDEMIOLOGY

Worldwide, an estimated two million individuals suffer an intracerebral hemorrhage annually. The incidence of intracerebral hemorrhage is about 43 per 100,000 person-years, rising to 176 per 100,000 person-years in individuals age 75 years and over.[19] Incidence rates are about 50% higher in men and are also higher in Black Americans, Mexican Americans, and individuals of Chinese or Japanese descent. Hypertension is the key risk factor for intracerebral hemorrhage, especially in communities with suboptimal management. Black Americans and Hispanic Americans also have higher rates of small vessel disease and hypertensive arteriopathy.[20]

PATHOBIOLOGY

In patients over age 70 years, common causes are hypertensive hemorrhages, cerebral amyloid angiopathy, oral anticoagulant medications, and hemorrhages due to tumors. In the 50- to 70-year-old age range, hypertensive hemorrhages predominate. In individuals younger than age 50 years, causes include arteriovenous malformations, illicit use of sympathomimetic agents (e.g., cocaine,

TABLE 377-5 CAUSES OF INTRACEREBRAL HEMORRHAGE BY AGE

AGE GROUP	>70 YEARS	50-70 YEARS	<50 YEARS
	Hypertensive hemorrhage Cerebral amyloid angiopathy Oral anticoagulants Tumors	Hypertensive hemorrhage Oral anticoagulants	Arteriovenous malformations Sympathomimetic use Cerebral venous sinus thrombosis Reversible cerebral vasoconstriction syndrome

methamphetamine [Chapter 365]), cerebral venous sinus thrombosis (Chapter 376), and the reversible cerebral vasoconstriction syndrome (Table 377-5).

Most hypertensive hemorrhages do not have a known strong genetic component. However, mutations in the gene *KRIT1,* which encodes a microtubule-associated protein, have been documented in familial cases of intracerebral hemorrhage due to cavernous malformations. Rare familial forms of cerebral amyloid angiopathy also have been described. For patients with sporadic cerebral amyloid angiopathy, the Apo E2 and E4 alleles are linked to recurrent hemorrhage. In patients with Alzheimer disease (Chapter 371), severe cerebral amyloid angiopathy is more common in carriers of the Apo E4 allele.

CLINICAL MANIFESTATIONS

Intracerebral hemorrhage typically presents because the blood is a clinically significant space-occupying lesion that causes the acute onset of focal neurologic symptoms, such as hemiparesis, language disturbances, or ataxia. Clinical features rarely distinguish an intracerebral hemorrhage from an ischemic stroke (Chapter 376) on clinical grounds, but the presence of severe headache, vomiting, and markedly elevated blood pressure are more common in patients with intracerebral hemorrhage.

Massive bleeding can cause rapid death. The most commonly affected site is the putamen, where the hematoma typically causes a dense contralateral hemiparesis and hemianopia. Larger hemorrhages can result in a dense contralateral sensorimotor deficit, aphasia, hemi-spatial neglect, contralateral gaze paresis, and a contralateral visual field deficit. Lobar hemorrhages, typically the junctions between gray and white matter, are often caused by cerebral amyloid angiopathy and may present with dementia, gait disturbances, and complex partial seizures. Deep parenchymal bleeding with rupture into the ventricular system can occlude the third or fourth ventricles and result in acute hydrocephalus and intracranial hypertension, which can rapidly progress to massive intraventricular hemorrhage.

Cerebellar or pontine hemorrhages typically begin abruptly with vomiting and severe ataxia, which usually prevents standing and walking. It may be misdiagnosed as an ischemic infarction but often can be distinguished by dysarthria, adjacent cranial nerve dysfunction, and paralysis of conjugate ipsilateral gaze. If untreated, it can progress to quadriparesis, disconjugate ocular motility disorders, and coma.

Seizures occur in about 10% of patients. Expansion of a hematoma because of continued bleeding causes abrupt neurologic deterioration, especially in the first 6 hours.

DIAGNOSIS

Early performance of brain imaging (typically with a CT scan without contrast) can establish the volume, location, and extension of the hemorrhage (Fig. 377-5). Imaging can distinguish between cortically based "lobar" hemorrhages as compared with "deep" hemorrhages that typically originate from gray matter structures, such as the putamen or thalamus, and determine whether the hemorrhage extends to either the intraventricular system or the subarachnoid space. Brain MRI can be useful to identify areas of asymptomatic cerebral microbleeds (Fig. 377-6). Cerebral digital subtraction angiography and venography should be considered to exclude an underlying macrovascular lesion (Fig. 377-7) in patients who are younger than age 70 years and who have lobar intracerebral hemorrhage, especially if they do not have hypertension, and in patients who are younger than age 45 years and have a deep or infratentorial intracerebral hemorrhage and negative imaging (MRI and magnetic resonance angiography or CT angiography).

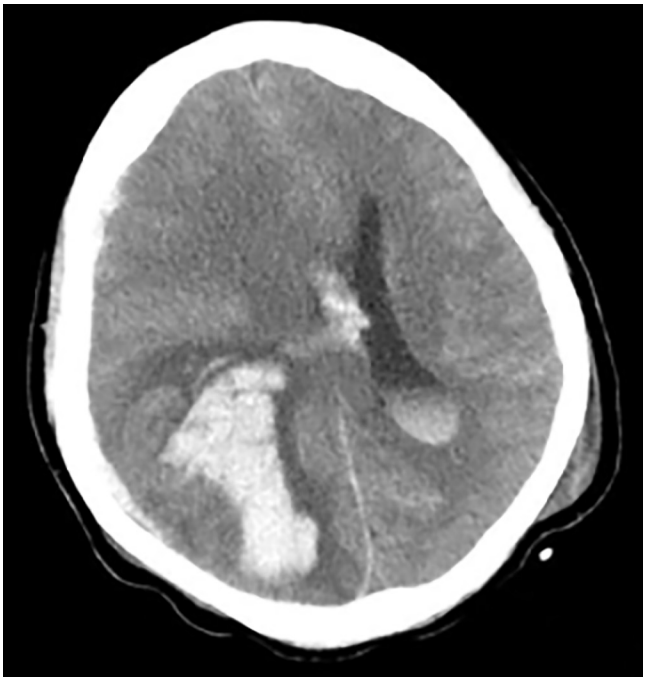

FIGURE 377-5. Intracerebral hemorrhage. Computed tomographic scan showing an intracerebral hemorrhage.

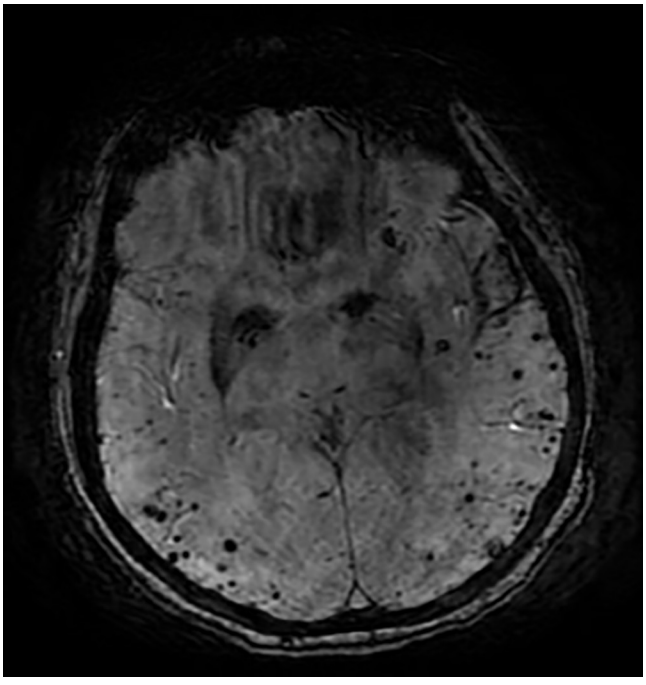

FIGURE 377-6. Cerebral microbleeds. Magnetic resonance imaging showing cerebral microbleeds from amyloid angiopathy.

The pattern of the hemorrhage on brain imaging can help identify potential etiologies. In some patients the history of chronic, poorly controlled hypertension is obvious, and evidence of end organ damage (e.g., left ventricular hypertrophy, hypertensive renal disease, or hypertensive retinopathy) can be easily ascribed to it when blood is located in areas such as the putamen, thalamus, deep cerebellar nuclei, or pons. In the absence of clear evidence of hypertension, the clinician should more vigorously pursue the possibility of secondary causes, such as vascular malformations (Fig. 377-8) and tumors. In patients who suffer intracranial hemorrhage while taking antithrombotic agents, additional vascular imaging is typically not needed unless they have an intraventricular hemorrhage or combined intracerebral plus subarachnoid hemorrhage.

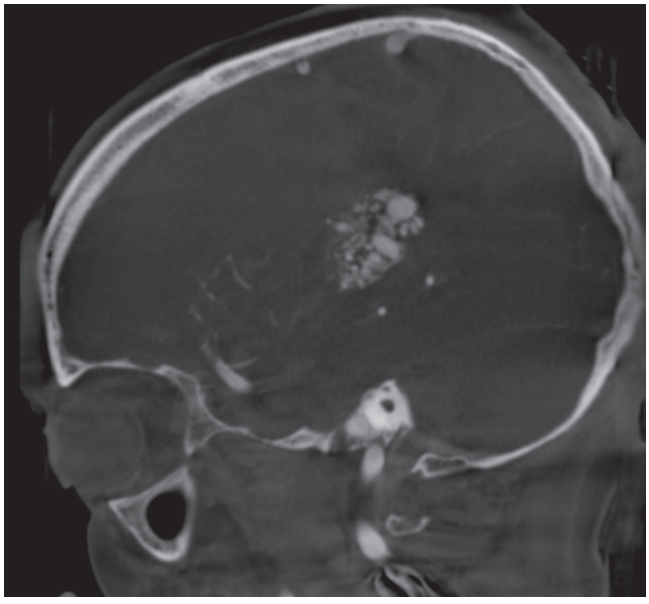

FIGURE 377-7. Arteriovenous malformation. Sagittal digital subtraction computed tomographic scan showing an abnormal tangle of vessel suggestive of an arteriovenous malformation.

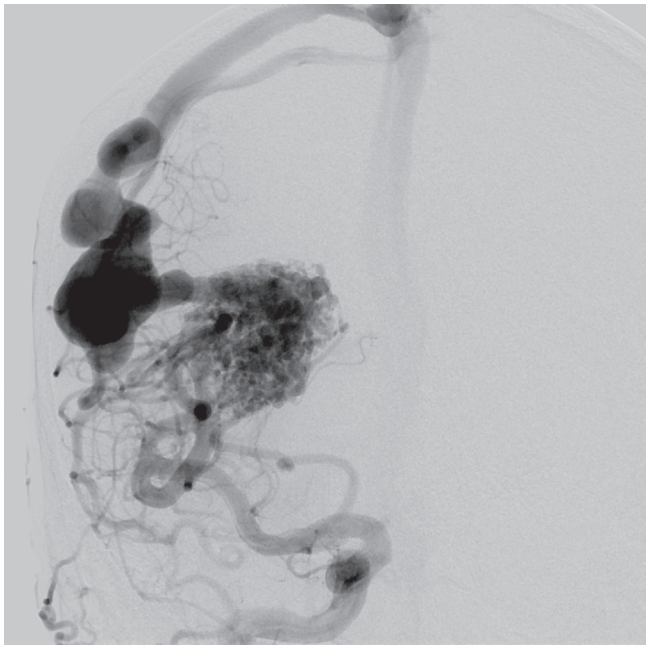

FIGURE 377-8. Arteriovenous malformation. Cerebral angiography showing an arteriovenous malformation.

In approximately 30 to 40% of intracerebral hemorrhage cases, the hemorrhage will enlarge in the first 6 to 12 hours (Fig. 377-9). Imaging features, such as the CT "spot sign" (visualized as punctate hyperdensity within or at the periphery of the hemorrhage on CT angiography) seen after contrast infusion is one feature that can potentially delineate patients with higher risk for hemorrhagic expansion.

The presence and pattern of microbleeds can provide useful clues to the clinician. If all the microbleeds are confined to deeper, gray matter nuclei, hypertension is the likely cause of an intracerebral hemorrhage. If the microbleeds are predominantly cortical, other conditions such as cerebral amyloid angiopathy are more likely.

TREATMENT

Acute Treatment

In the acute period after detection of an intracerebral hemorrhage, meticulous intensive care is needed (Table 377-6).[21,22] Blood pressure must be carefully monitored using either a cuff or arterial line to reduce the likelihood of expansion of the hematoma and worsening of neurologic status. In patients who present with acute intracerebral hemorrhage of mild severity (intracerebral hemorrhage volume 6 to 19 mL) and systolic blood pressure between 150 to 220 mm Hg, systolic blood pressure should be lowered to a target of 140 mm Hg to improve 3-month functional outcomes and quality of life. Additional lowering to a systolic blood pressure of 110 to 139 mm Hg does not add benefit and is associated with an increased risk of renal adverse events.[A5] Preferred antihypertensive agents (see Table 377-6) should have a rapid onset and short duration of action to avoid blood pressure lability.

In anticoagulation-associated intracerebral hemorrhage, anticoagulation should be discontinued immediately, and rapid reversal of anticoagulation is recommended in most patients (see Table 377-6). In patients who have coagulopathy due to coagulation factor deficiency (Chapter 160) or severe thrombocytopenia (Chapter 158), replacement of the deficient factor or platelet transfusion (Chapter 162) are recommended, but platelet transfusions should be avoided in patients who have been taking anti-platelet agents.[A6]

The one exception to avoiding or reversing antithrombotic agents in the acute period after an intracerebral hemorrhage is for patients who have cerebral venous sinus thrombosis, in which anticoagulants (e.g., intravenous heparin [Chapter 70] or low-molecular-weight heparin [Table 70-3]) should be administered even in the acute stage. For the intermediate term (typically 5 to 10 days after the intracerebral hemorrhage) treatment of cerebral venous sinus thrombosis, direct acting oral anticoagulants (e.g., rivaroxaban 20 mg daily; see Table 70-6) are recommended for 3 to 6 months, with venous sinus patency monitored using techniques such as MR venography or CT venography.

Several in-hospital complications must be anticipated and prophylactic treatment considered. For patients with clinically apparent seizures, treatment with antiepileptic drugs (see Table 377-6) must be initiated. However, prophylactic use of antiepileptic medications in patients without evidence of seizures does not improve outcomes.[A7]

In patients whose intracerebral hemorrhage extends into the ventricular system, the risks of a decline in mental status and for the development of hydrocephalus are higher. In these patients, an intraventricular drainage catheter can be useful to promote clearance of blood from the ventricular system.

Because many patients with intracerebral hemorrhage will have prolonged hospital stays, deep venous thrombosis is a common complication. For immobile patients, pneumatic compression devices are recommended, but low-molecular-weight heparin (Table 70-3) can be safely administered to stable patients. Other complications include acute renal failure and myocardial infarction, both of which are associated with increased in-hospital mortality.

Brain edema adjacent to the intracerebral hemorrhage is very common and can lead to neurologic deterioration. Hypertonic saline or mannitol can be considered, but high-quality evidence for the benefit of these treatments is limited. Glucocorticoids should be avoided because they not only are not beneficial but also are associated with an increased risk of infections and diabetic complications.[A8]

Surgical Treatment

Immediate evacuation of the hematoma is recommended in deteriorating patients who have cerebellar hemorrhages of 15 mL or greater associated with brainstem compression and/or hydrocephalus.[23] In other patients admitted within 48 hours of the onset of a supratentorial intracerebral hemorrhage, however, routine surgical drainage of the hematoma via an open craniotomy procedure is not beneficial but can be considered as a life-saving measure on an individual basis in patients who are deteriorating. For patients with intraventricular hemorrhage, administration of low-dose alteplase to accelerate clearance of the blood does not improve outcomes.[A9]

An emerging option is urgent minimally invasive drainage with endoscopic devices that can be placed into the hemorrhage with stereotactic guidance.[24] Randomized trials are ongoing to evaluate the utility of this approach.

Recovery and Secondary Prevention

A commonly used prognostic scale is the intracerebral hemorrhage score, which assigns points for worse Glasgow Coma Scale, age 80 years or older, intracerebral hemorrhage volume of 30 mL or greater, intraventricular extension of the hemorrhage, and infratentorial location (Table 377-7). Although such scales can assist in advising families and guiding transfer of patients to a comprehensive stroke center, they should not be used to withhold care prematurely. Current guidelines recommend full support for at least 72 hours in the majority of patients with intracerebral hemorrhage to avoid a self-fulfilling prophecy of poor prognosis owing to early termination of life-sustaining care.

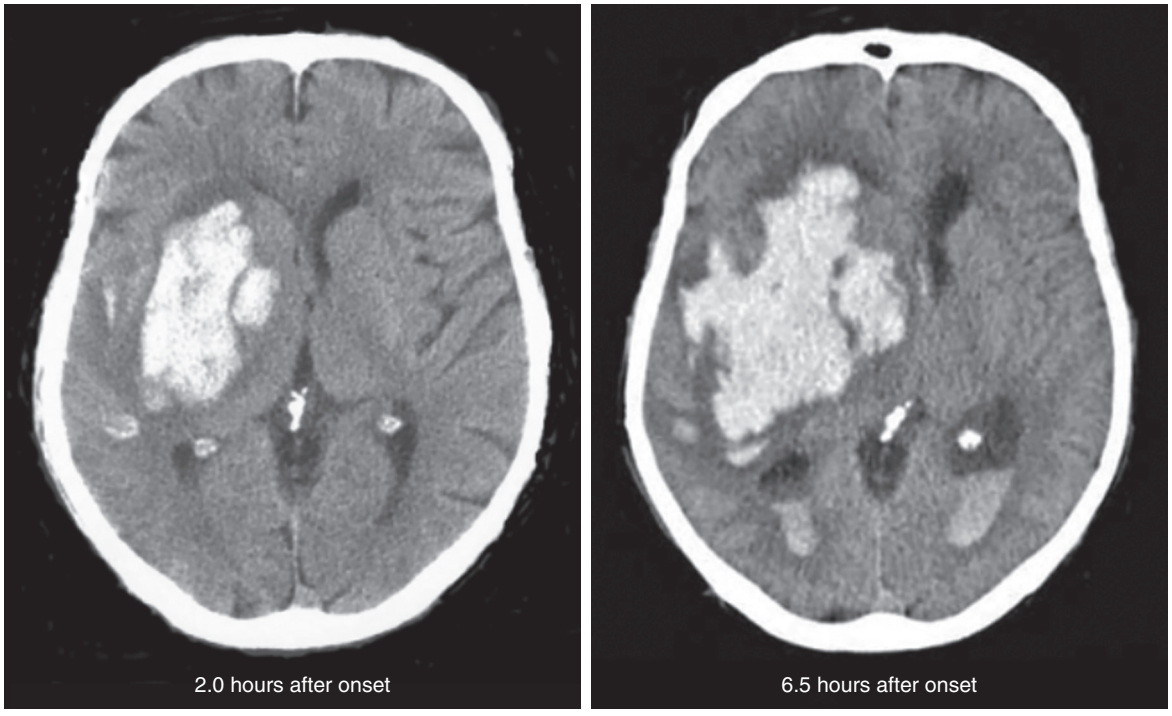

FIGURE 377-9. Early hematoma growth in a 48-year-old chronically hypertensive woman. *Left*, The baseline computed tomography scan shows a moderate-sized intracerebral hemorrhage in the right putamen. At this point, she is stuporous with a left hemiparesis. *Right*, A follow-up computed tomography scan performed after she deteriorated to coma with bilateral decerebrate posturing shows massive expansion of the hematoma as well as new intraventricular hemorrhage and obstructive hydrocephalus. Within 24 hours, she was declared brain dead. (From Mayer SA, Rincon F. Treatment of intracerebral haemorrhage. *Lancet Neurol*. 2005;4:662-672.)

TABLE 377-6 MEDICAL MANAGEMENT PROTOCOL FOR ACUTE INTRACEREBRAL HEMORRHAGE

Blood pressure	• Maintain mean arterial pressure <140 mm Hg with continuous infusion labetalol (2-10 mg/min), nicardipine (5-15 mg/hr), or clevidipine (2-6 mg/hr) • If stuporous or comatose, measure ICP and maintain CPP >70 mm Hg
Reversal of anticoagulation	• For elevated INR: Vitamin K 10 mg IV push and 4F-PCC INR 2 to <4: 25 units/kg; not to exceed 2500 units INR 4-6: 35 units/kg; not to exceed 3500 units INR >6: 50 units/kg; not to exceed 5000 units • For heparin: protamine sulfate 10 to 50 mg slow IV push (1 mg reverses approximately 100 units of heparin) • For dabigatran: Idarucizumab 5 g IV (Praxbind) • For the factor Xa inhibitors (rivaroxaban, apixaban and edoxaban): Andexanet-alpha IV. Low dose (≤10 mg rivaroxaban or ≤5 mg apixaban per dose): 400 mg IV bolus, followed by 4 mg/kg for 2 hr. High dose (higher doses given within 8 hr): 800-mg bolus, followed by 8 mg/kg for 2 hr. • For thrombocytopenia or platelet dysfunction: Desmopressin 0.3 µg/kg intravenous push. Platelet transfusion is reasonable in the setting of thrombocytopenia but is not effective and may be harmful when given to patients on NSAIDs or other antiplatelet agents • Expedited INR reversal for life-saving neurosurgical intervention: recombinant activated factor VII 40-80 µg/kg (approximately 3.0-6.0 mg) intravenous push
Intracranial hypertension	• Elevate head of bed to 30° • Mannitol 1.0-1.5 g IV • Hyperventilate to P_{CO_2} of 30 mm Hg
Fluids and nutrition	• Normal (0.9%) saline at 1.0 mL/kg/hr • Begin enteral feeding via nasoduodenal tube within 24 hr
Seizure prophylaxis	• For coma with intracranial hypertension or acute seizures: fosphenytoin or phenytoin IV load (15-20 mg/kg); 300 mg IV daily for 7 days
Physiologic homeostasis	• Cooling blankets to maintain temperature ≤37.5° C • Insulin drip as needed to maintain glucose 120-180 mg/dL

CPP = cerebral perfusion pressure; FEIBA = factor VIII inhibitor bypass activity; 4F-PCC = four-factor prothrombin complex concentrate, containing factors II, VII, IX, and X; ICP = intracranial pressure; INR = international normalized ratio; IV = intravenous; NSAIDs = nonsteroidal anti-inflammatory drugs.

From Mayer SA. Hemorrhagic cerebrovascular disease. In: Goldman L, Schafer AI, eds. *Goldman-Cecil Medicine*. 26th ed. Philadelphia: Elsevier; 2020.

TABLE 377-7 THE INTRACEREBRAL HEMORRHAGE SCORE

COMPONENT	SCORE POINTS
GCS Score (see Table 368-1)	
3-4	2
5-12	1
13-15	0
Intracerebral hemorrhage (volume, cm^3)	
≥30	1
<30	0
Intraventricular hemorrhage	
Yes	1
No	0
Infratentorial intracerebral hemorrhage	
Yes	1
No	0
Age, years	
≥80	1
<80	0

Estimated 30-day mortality is 0% for a score of 0, 13% for a score of 1, 26% for a score of 2, 72% for a score of 3, 97% for a score of 4, and 100% for a score of 5+.

GCS = Glasgow Coma Scale.

From: Hemphill JC 3rd, Bonovich DC, Besmertis L, et al. The ICH score: a simple, reliable grading scale for intracerebral hemorrhage. *Stroke*. 2001;32:891-897.

After the acute period, multidisciplinary rehabilitation can be helpful. For prevention of recurrent intracerebral hemorrhage, strict blood pressure control is beneficial. Survivors of intracerebral hemorrhage also have a high frequency of arterial ischemic events, including a three-fold higher risk of subsequent ischemic stroke and two-fold increased risk of subsequent myocardial infarction.[25] As a result, long-term cardiovascular prevention efforts (Chapter 40) must be focused on both reducing the risk of recurrent ischemic and hemorrhagic events.

For patients with an intracerebral hemorrhage related to oral anticoagulant therapy, the optimal timing for restarting oral anticoagulants is uncertain,[A10] but antiplatelet therapy can be restarted safely at about 2 to 3 months after the bleed.[A11] Most clinicians wait at least 10 days before restarting antithrombotic medication, but the discussion must be individualized. For patients who developed an intracerebral hemorrhage while on treatment with a vitamin K antagonist, switching treatment to a direct oral anticoagulant is recommended, because such medications are associated with a 40 to 60% lower relative rate of brain hemorrhage (Chapter 70).

If patients who have suspected cerebral amyloid angiopathy, concomitant atrial fibrillation, or high-risk MRI features for recurrent intracerebral hemorrhage (e.g., a large number of cerebral microbleeds or presence of cortical superficial siderosis) are deemed ineligible for anticoagulation, left atrial appendage closure may be considered to reduce the risk of thromboembolic events. The role of amyloid-depleting treatments in patients with cerebral amyloid angiopathy is uncertain.

PROGNOSIS

Intracerebral hemorrhage is more deadly than ischemic stroke, with 1-month mortality of 20 to 35%. Short-term mortality (within 30 days) tends to be higher in patients who have larger hematomas and in the elderly (see Table 377-7). In addition, hemorrhage related to oral anticoagulant medications (Chapter 70) has a higher mortality compared with intracerebral hemorrhage in the absence of antithrombotic medication.[26]

VASCULAR MALFORMATIONS

Vascular malformations in the brain are space-occupying lesions that are typically asymptomatic until they expand and compress surrounding brain tissue or rupture to cause an intracerebral hemorrhage, an intraventricular hemorrhage, or less commonly a subarachnoid hemorrhage.[27]

EPIDEMIOLOGY AND PATHOBIOLOGY

Vascular malformations cause about 10% of intracerebral hemorrhages but only about 1% of strokes. The prevalence of a malformation is about 0.5%, and the incidence of hemorrhage is about 1 to 3 cases per 100,000 person-years, mostly in the second through fourth decades of life. The risk of an acute rebleed is about 7%, then the risk falls to about 2% per year for the next 5 years and to about 1 to 2% per year thereafter. As a result, the cumulative lifetime incidence of a rebleed is 50 to 60%, with each rebleed associated with about a 10 to 15% mortality. Unlike with some causes of cerebral hemorrhage, preexisting hypertension does not seem to be a risk factor.

PATHOBIOLOGY

The most common intracerebral vascular malformation is an arteriovenous malformation, in which dysplastic vessels are fed by arteries and drained by veins without intervening capillaries. In over 60% of patients with arteriovenous malformation, an activating *KRAS* mutation appears to be pathogenic.[28] The resulting low-resistance, high-flow shunt leads to progressive arterial and especially venous dilatation. A subarachnoid hemorrhage is usually caused by bleeding from an aneurysm in the feeding artery, whereas an intracerebral hemorrhage usually emanates from bleeding at the nidus itself. Intraventricular hemorrhage usually results when a draining vein bleeds. Other vascular malformations include cavernous angiomas or hemangiomas and dural arteriovenous fistulas.

CLINICAL MANIFESTATIONS

Arteriovenous malformations may be diagnosed at an asymptomatic or minimally symptomatic stage when a patient with a headache (Chapter 367) has a brain CT or MRI (see Fig. 377-8), whether or not the arteriovenous malformation is truly causally related. When arteriovenous malformations become truly symptomatic, the common manifestations are intracranial hemorrhage (about 50%), seizures (about 30%), and progressive neurologic dysfunction (about 20%). An increasing proportion, however, are now detected by brain imaging as part of the evaluation of headaches.

The bleeding from an arteriovenous malformation can be subarachnoid, intracerebral, or intraventricular, with symptoms and signs depending on the severity and location of the bleed. Post-bleeding cerebral vasospasm occurs in fewer than 5% of cases. Arteriovenous malformations typically cause focal seizures (Chapter 372) or focal neurologic deficits when a thrombosis or shunting of blood through the malformation reduces perfusion to normal brain tissue.

DIAGNOSIS

A noncontrast CT scan may show bleeding, but contrast-enhanced CT angiography or MRI is preferred to identify the feeding arteries and draining veins (see Fig. 377-8). However, catheter-based angiography is usually required to delineate its size, gross morphology, feeding arteries, and draining veins in preparation for surgical intervention.

TREATMENT

If the patient survives the initial hemorrhage, the therapeutic goals are to avoid neurologic deterioration and to remove the arteriovenous malformation completely. General medical treatment measures are the same as for intracerebral hemorrhage (see Table 377-6). Treatment options include curative surgical resection. Microsurgical removal can be performed in stages until an angiogram shows no residual malformation. Selective embolization can reduce the size of the malformation but rarely can obliterate it completely. Stereotactic radiosurgery[29] is used only for small lesions.

PREVENTION AND PROGNOSIS

The prognosis of an unruptured arteriovenous malformation varies by location, size, and morphology. For nonbleeding malformations, medical management emphasizing control of hypertension, avoidance of anticoagulation, and anticonvulsant medications as needed for seizures is superior to prophylactic intervention with surgery and/or endovascular embolization in terms of subsequent symptomatic stroke or death.[A12] For familial cerebral cavernous malformations, propranolol 20 to 300 mg daily may reduce the incidence of future clinical events.[A13]

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For the General References and other additional features, please visit Elsevier eBooks+ at https://ebooks.health.elsevier.com.

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378 PARKINSONISM

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Parkinsonism is a clinical syndrome that consists of four cardinal signs: tremor, rigidity, akinesia, and postural disturbances. Parkinson disease is a common cause of the syndrome, but there are numerous other causes (Table 378-1).

TABLE 378-1 DIFFERENTIAL DIAGNOSIS OF PARKINSONISM

PARKINSON DISEASE
Sporadic
Genetic
Autosomal dominant (e.g., α-synuclein gene mutations, duplications, triplications; *LRRK2* mutations)
Autosomal recessive (e.g., *parkin, DJ1, PINK1*)
Other genetic mutations that increase risk (e.g., glucocerebrosidase deficiency)
SECONDARY PARKINSONISM
Neurodegenerative diseases (sporadic or genetic)
Progressive supranuclear palsy* (Videos 378-3 through 378-6)
Multiple system atrophy* (Videos 378-7 through 378-9)
Corticobasal degeneration* (Videos 378-10 and 378-11)
Dementia with Lewy bodies*
Alzheimer disease*
ALS-parkinsonism-dementia complex of Guam
Huntington disease
Rapid-onset dystonia-parkinsonism
Pallidopyramidal degeneration (including PARK9 and PARK15)
Neuroacanthocytosis
Spinocerebellar ataxias (e.g., SCA-3, SCA-2)
Wilson disease
Pantothenate kinase–associated neurodegeneration (Hallervorden-Spatz syndrome)
Neuroferritinopathy
Calcification of the basal ganglia (Fahr disease)
Dopa-responsive dystonia (not a degenerative disorder)
Drugs*
Neuroleptics, metoclopramide, prochlorperazine, tetrabenazine, reserpine, cinnarizine, flunarizine, α-methyldopa, lithium
Toxic
MPTP, manganese (including illicit use of ephedrone), carbon monoxide, mercury
Copper (Wilson disease)
Infectious
Encephalitis lethargica
Other encephalitis, including HIV associated
Subacute sclerosing panencephalitis
Creutzfeldt-Jakob disease
Vascular*
Atherosclerosis
Amyloid angiopathy
Neoplastic
Brain tumor
Other mass lesions
Normal-pressure hydrocephalus*
Head trauma
Multiple sclerosis

*See Table 378-4 for additional details.

ALS = amyotrophic lateral sclerosis; HIV = human immunodeficiency virus; MPTP = 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine.

Modified from Cloutier M, Lang AE. Movement disorders: an overview. In: Factor SA, Lang AE, Weiner WJ, eds. *Drug Induced Movement Disorders*. Malden, Mass: Blackwell; 2005:3-19.

PARKINSON DISEASE

EPIDEMIOLOGY

Parkinson disease, which is the second most common neurodegenerative disorder after Alzheimer disease (Chapter 371), occurs in approximately 1 in 1000 in the general population and in at least 1% of persons older than 65 years. Men are affected slightly more often than women (3 : 2). The prevalence of Parkinson disease is thought to be increasing greatly as the world's population ages. For example, the age-adjusted mortality from Parkinson disease increased by 2.4% per year between 1999 and 2019.[1]

PATHOBIOLOGY

The cause of Parkinson disease is believed to be a variable combination of poorly understood genetic and environmental factors. Environmental exposures such as pesticides or heavy metals and traumatic brain injury severe enough to cause an emergency department visit are associated with increased risk of developing Parkinson disease.[2] Both autosomal dominant and recessive genes can cause syndromes that appear like classic Parkinson disease. The protein α-synuclein, which is the chief constituent of the hallmark cytoplasmic inclusion, the Lewy body (Chapter 371), is critical in the pathogenesis of Parkinson disease. Abnormal aggregation of the protein, either from mutations in the α-synuclein gene or as a result of excessive production of the normal protein because of gene duplications or triplications, is associated with varying disease phenotypes. Other defined genetic abnormalities may be associated with classic later-onset Parkinson disease, including *LRRK2*,[3] which is currently the most common cause of autosomal dominantly inherited Parkinson disease. Early-onset parkinsonism is typically found in the autosomal recessive forms associated with *parkin, DJ1,* and *PINK1*. The *PARK10* haplotype on chromosome 1 also is strongly associated with Parkinson disease. Other genes in which mutations may increase the risk for developing of Parkinson disease include the glucocerebrosidase gene, which appears to be associated with higher rates of dementia and faster progression of motor symptoms.[4]

Since known genetic causes account for only about 10% of cases, environmental triggers are also likely. Strong support for the environmental hypothesis of sporadic Parkinson disease relates to the observation that the selective neurotoxin 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP) causes acute parkinsonism due to loss of dopamine neurons in the substantia nigra pars compacta. MPTP is oxidized to the active toxin MPP^+, which is a selective inhibitor of complex I of the mitochondrial electron transport chain. This observation, combined with recognition of the importance of dopamine (see later), has implicated the role of oxidative stress in the pathogenesis of Parkinson disease. Other proposed pathogenetic factors include mitochondrial dysfunction, protein misfolding and aggregation, excitotoxicity, inflammation, apoptotic cell death, and loss of trophic support.

Pathology

Many of the features of Parkinson disease are due to loss of dopamine in the neostriatum (especially the putamen) secondary to loss of pigmented dopaminergic neurons in the substantia nigra pars compacta of the midbrain. Approximately 60% of these dopaminergic neurons will have degenerated before classic motor features of the disease develop.

In addition to the prominent degenerative changes in the substantia nigra pars compacta (cell loss, gliosis, abnormal deposition of aggregated α-synuclein as Lewy bodies and Lewy neurites), pathologic changes are also evident in other brain stem nuclei, in cortical regions, and in peripheral autonomic neurons. Parkinson disease may begin in the lower brain stem and the olfactory system, where it causes early loss of the sense of smell and only later involve the substantia nigra. Independent of the order of involvement, it is likely that the widespread extranigral neurodegenerative changes account for the many symptoms that do not respond to dopamine replacement and that become increasingly problematic as the disease progresses. How the disease progresses and spreads in the nervous system is unknown. Cell to cell transmission of toxic forms of α-synuclein induce abnormal protein misfolding and aggregation in a "permissive templating" fashion similar to prion diseases (Chapter 371).[5]

CLINICAL MANIFESTATIONS

Patients typically receive a diagnosis of Parkinson disease after parkinsonism symptoms become notable.[6] However, the disease begins years earlier in what is now termed the premotor or prodromal phase of the disease, when patients have minimal motor signs or symptoms but early evidence of neurodegeneration. In this phase of the disease, common signs or symptoms include disorders in rapid eye movement (REM) sleep, loss of olfaction, autonomic dysfunction, and depression.[7]

Motor Symptoms

In most patients with Parkinson disease, the symptoms begin in one limb or one side of the body. This asymmetry often persists into later stages of the disease.

ABSTRACT

Parkinsonism is a clinical syndrome that consists of four cardinal signs: tremor, rigidity, akinesia, and postural disturbances. Parkinson disease is a common cause of this syndrome, but numerous other sporadic and genetic causes also exist. Secondary parkinsonism can be due to neurodegenerative diseases, genetic causes, drug reactions, toxins, infections, vascular disease, tumors, head trauma, multiple sclerosis, and normal pressure hydrocephalus.

KEYWORDS

Parkinson disease
parkinsonism
progressive supranuclear palsy
multiple system atrophy
Lewy body dementia
drug-induced parkinsonism

Tremor

The classic resting tremor of Parkinson disease has characteristic clinical features but occurs in only one in five patients. The tremor has a slow frequency of 4 to 6 cycles per second, typically with a "pill-rolling" character when it involves the hand; but its characteristics, including frequency, can be widely variable.[8] The tremor generally is present with the limb in complete repose and typically subsides when the limb moves and takes up a new position, although the tremor may reemerge ("reemergent tremor") within a short time after maintaining the new position (Video 378-1). Because resting tremor diminishes or subsides with action, it may not be disabling but can be embarrassing and may be associated with aching or fatigue of the affected limb. Resting tremor is usually accentuated by stress (e.g., by asking the patient to perform mental calculations). It is also characteristically present in the upper limbs while walking. A higher-frequency (e.g., 7 to 10 Hz) postural and kinetic tremor is also common in patients who have various causes of parkinsonism, and younger patients tend to have a higher frequency tremor.

Rigidity

Rigidity is a form of increased muscle tone appreciated best on slow passive flexion and extension movements across a joint. Rigidity may be characterized as "cogwheel" when a tremor is superimposed or as "lead pipe" when it is not. Rigidity is activated or accentuated on examination by asking the patient to move the limb opposite the one being tested. Patients may complain of stiffness, but the rigidity usually is not disabling.

Akinesia

Akinesia or bradykinesia comprises a variety of disturbances in movement, including slowness, reduced amplitude, fatiguing, and interruptions in ongoing movement. This aspect of parkinsonism interferes with all voluntary activities and accounts for many of the well-known features of parkinsonism: lack of facial expression with reduced blinking (hypomimia or masked facies—the "reptilian stare"), soft monotonous speech (hypophonia), impaired swallowing resulting in drooling (sialorrhea), small handwriting (micrographia), reduced arm swing while walking, shortened stride and shuffling gait, difficulty arising from a low chair, and problems turning over in bed. Arrest in ongoing movement (motor block) can interfere with a variety of activities, but it is best appreciated as freezing of gait (Video 378-2). Bradykinesia is evident on inspection and elicited by testing rapid repetitive and alternating movements: finger tapping, opening and closing the fist, pronating and supinating the wrist, and toe and heel tapping.

Postural Disturbances

Postural disturbances include a flexed posture in the limbs and trunk (stooped posture) as well as postural instability resulting in imbalance and falls.[9] Patients may complain of being unable to stop themselves from going forward (propulsion, festination) or backward (retropulsion). Assessment of postural instability includes the pull test, in which the examiner stands behind and abruptly pulls the patient by the shoulders while protecting the patient from a fall.

Other Symptoms

Premotor symptoms often include olfactory dysfunction, REM sleep behavioral disorder (Chapter 374), constipation, restless leg syndrome (Chapter 374), and neuropsychiatric symptoms. As the disease progresses, nonmotor symptoms commonly include pain; sensory disturbances; dysautonomic complaints (e.g., urinary urgency and frequency; orthostatic hypotension; constipation; male erectile dysfunction); anxiety; fatigue; depression; and cognitive disturbances, including dementia.[10]

Complications

In addition to the manifestations of the disease itself, complications of chronic drug therapy include motor- and nonmotor-related fluctuations and psychiatric or behavioral disturbances. In the later stages of the disease, the clinical picture often fluctuates from hour to hour as patients exhibit a mixture of the classic features of parkinsonism (which may improve considerably in response to medication), symptoms that persist despite the peak benefit of medication, and symptoms that occur as a complication of dopaminergic medication (Table 378-2).

TABLE 378-2 PROBLEMS IN LATER-STAGE PARKINSON DISEASE

PROBLEM	SYMPTOMS
LATER TREATMENT-RESISTANT SYMPTOMS	
Motor	Dysarthria Dysphagia Freezing of gait (on-period freezing) Postural instability with falls
Nonmotor	Dysautonomia, weight loss Sensory symptoms, including pain (some may be responsive to levodopa) Changes in mood or behavior (depression, anxiety), apathy, sleep disturbances (excessive daytime sleepiness often caused by or aggravated by dopaminergic medication) Rapid eye movement sleep behavior disorder (may develop before parkinsonism) Fatigue Cognitive dysfunction and dementia
RELATED TO TREATMENT AND DISEASE	
Motor fluctuations	Wearing off of drug effect (predictable end-of-dose deterioration, morning akinesia), increased latency to benefit ("delayed-on"), dose failures ("no-on") On-off phenomenon, more rapid and unpredictable fluctuations Concomitant fluctuations of nonmotor-related symptoms ("nonmotor fluctuations") that may be as disabling as motor symptoms (or more so)
Dyskinesia (abnormal involuntary movements)	Peak-dose dyskinesia: chorea, athetosis, and, less often, more prolonged dystonia, typically worse on the initially affected side (Video 378-12) Diphasic dyskinesia ("beginning-of-dose" and "end-of-dose" dyskinesias): mixtures of choreoathetosis, ballism, dystonia, alternating movements (especially in the legs) Off-period dystonia: most often involving the legs and feet (including morning foot dystonia)
Psychiatric disturbances	Vivid dreams and nightmares Visual hallucinations with a clear sensorium Hallucinations with confusion Mania, impulse control disorders (e.g., hypersexuality, problem gambling), dopaminergic drug addiction Paranoid psychosis

Modified from Lang AE, Lozano AM. Parkinson's disease—second of two parts. *N Engl J Med.* 1998;339:1130-1143.

TABLE 378-3 CLINICAL CLUES TO AN ALTERNATIVE (NON–PARKINSON DISEASE) CAUSE OF PARKINSONIAN SIGNS AND SYMPTOMS

Extraocular movements—e.g., nystagmus, limitation of vertical gaze, especially with slowing of downward saccadic eye movements (see Video 378-4)
Early and prominent dysarthria or dysphagia
Prominent or early abnormal neck postures: flexion or extension (see Video 378-8)
Ataxia—limb, gait (impaired tandem gait)
Lower body distribution with relative sparing of upper limb function
Early postural instability, falls, or freezing (see Video 378-3)
Dysautonomia (early and prominent), prominent hypotensive response to dopaminergic medication
Pyramidal tract signs—very brisk reflexes, clonus, extensor plantar responses
Peripheral nerve dysfunction—loss of reflexes, distal sensory loss, weakness
Apraxia and cortical sensory changes
Early severe dementia
Poor response to levodopa

DIAGNOSIS

Testing for genetic forms of Parkinson disease is available and should be considered in patients with a strong family history of Parkinson disease, early-onset disease, and in patients with interest in knowing.[11] To date, however, genetic diagnosis has not changed therapeutic approaches, and the diagnostic evaluation focuses largely on excluding other causes of parkinsonism (Table 378-3).[12]

Early-onset patients should have Wilson disease excluded by determination of 24-hour urine copper excretion, a serum ceruloplasmin, and slit lamp examination (Chapter 195). Findings on magnetic resonance imaging (MRI) are generally normal in Parkinson disease, but MRI can be useful to exclude other diagnoses (Table 378-4): multiple-system atrophy that is characterized

TABLE 378-4 DISEASES THAT MUST BE DISTINGUISHED FROM PARKINSON DISEASE

DIAGNOSIS	IMPORTANT DISTINGUISHING CLINICAL FEATURES	RESPONSE TO LEVODOPA/COMMENTS (INCLUDING IMAGING)
Multiple-system atrophy (MSA) (includes older terms: striatonigral degeneration, sporadic olivopontocerebellar atrophy, and Shy-Drager syndrome) (a "synucleinopathy")	Early dysautonomia (including orthostatic hypotension and sexual impotence) and bladder dysfunction (with autonomic and nonautonomic components) Cerebellar dysfunction	Good response initially evident in 20% and sustained partial response in ≈15% Dyskinesias or motor fluctuations possible; cranial dystonia may be prominent (see Video 378-7) Patient is wheelchair bound despite response to levodopa (early loss of postural reflexes, with or without ataxia)
MSA-P, a predominant parkinsonian manifestation	Pyramidal tract signs Stimulus-sensitive myoclonus of the hands and face	MRI (including diffusion-weighted imaging and gradient-echo sequences) often shows diagnostic changes in the striatum in MSA-P and "hot cross bun sign" in the pons and hyperintensity in middle cerebellar peduncles in MSA-C
MSA-C, a predominant cerebellar manifestation (mixed features are common)	Extreme forward neck flexion (anterocollis) Mottled, cold hands Inspiratory stridor (see Video 378-9) Prominent dysarthria	
Progressive supranuclear palsy (a "tauopathy")	Supranuclear vertical ophthalmoplegia (see Video 378-4) Other oculomotor and eyelid disturbances (see Video 378-6) Axial rigidity greater than limb rigidity Early falls, speech and swallowing disturbances Nuchal extension Cognitive or behavioral changes Progressive nonfluent aphasia Possibly a higher incidence of hypertension than in Parkinson disease and other neurodegenerative causes of parkinsonism	Good response rarely evident; benefit only for classic parkinsonian features, such as limb rigidity, classic bradykinesia with fatiguing of amplitude of repetitive movements, and rare examples of tremor at rest MRI often demonstrates profound midbrain atrophy ("hummingbird sign" on a midline sagittal view, "morning glory sign" on axial view)
Corticobasal degeneration (a "tauopathy")	Apraxia, cortical sensory loss, alien limb phenomenon (see Video 378-10) Pronounced asymmetrical rigidity Limb dystonia Stimulus-sensitive myoclonus (see Video 378-11) Aphasia (progressive nonfluent aphasia) Cognitive dysfunction (frontotemporal dementia)	Usually negligible MRI may show pronounced asymmetrical cortical atrophy
Vascular parkinsonism	"Lower-half" parkinsonism with gait disturbances predominating, often with minimal or much milder upper body involvement Additional neurologic deficits (e.g., pyramidal tract signs, pseudobulbar palsy)	Usually poor, but some respond well Imaging demonstrates multiple infarcts involving the basal ganglia and subcortical white matter
Dementia with Lewy bodies (a "synucleinopathy")	Early dementia (cognitive profile somewhat different from that of Alzheimer disease) Spontaneous hallucinations, fluctuating cognitive status, falls, orthostatic hypotension, RBD Pronounced sensitivity to the extrapyramidal side effects of neuroleptic drugs Parkinsonism may be similar to typical Parkinson disease, although rigidity may be more prominent than bradykinesia or tremor	Motor features may respond well; psychiatric side effects of dopaminergic drugs are typically dose limiting
Alzheimer disease	Early dementia (memory loss, apraxia, aphasia) Tremor uncommon Spontaneous hallucinations less common than in dementia with Lewy bodies	Poor
Normal-pressure hydrocephalus	"Lower-half" parkinsonism ("gait apraxia") Urinary complaints (frequency, urgency, incontinence) Cognitive disturbances	Generally poor Imaging demonstrates ventriculomegaly out of proportion to cortical atrophy
Drug-induced parkinsonism	All the classic features of parkinsonism (tremor may be less common than in Parkinson disease) Usually symmetrical signs and symptoms Other drug-induced movement disorders (e.g., tardive dyskinesia with neuroleptics)	Usually poor because of ongoing dopamine receptor blockade; may aggravate movements of tardive dyskinesia

MRI = magnetic resonance imaging; RBD = rapid eye movement sleep behavior disorder.

by progressive autonomic failure with parkinsonian, cerebellar, and pyramidal features in various combinations; progressive supranuclear palsy with midbrain atrophy; and vascular parkinsonism. Positron emission tomography, which can assess the presynaptic and postsynaptic sides of the nigrostriatal dopamine system, does not reliably distinguish Parkinson disease from many other neurodegenerative diseases that mimic it.

TREATMENT

Early treatment in a patient with little or no disability may entail only education, psychological support, strong encouragement to remain active and to become involved in an exercise program,[13] and ongoing follow-up. For example, tai chi training improves balance and lowers the incidence of falls in patients with mild to moderate Parkinson disease. Regular cardiovascular exercise,[14] both endurance and resistance, are very beneficial.[A1]

Early treatment, even when patients are only mildly symptomatic, may preserve quality of life, and therapy should be initiated before or when quality of life is impaired or when there is a risk of physical injury.[15,16] Such treatment currently is directed at improving symptoms, typically by restoring dopaminergic tone medically or by correcting basal ganglia neurophysiology surgically. Management of later-stage Parkinson disease requires neurologic expertise, skill in polypharmacy, and an understanding of the complicated benefit-risk ratios of the many drugs needed.[17]

Medical Treatment

Levodopa

Levodopa (which is a dopamine precursor) given with carbidopa (which reduces its peripheral side effects) is the most effective symptomatic treatment of Parkinson disease. No data support delaying treatment with levodopa, but it does not alter the course of the disease[A2] and is associated with a variety of side effects (see Table 378-2).

In early disease, the benefit of levodopa persists throughout the day with little symptomatic variability. However, in time, the duration of benefit declines, with worse symptoms upon awakening in the morning (morning akinesia) and for a variable time before scheduled daytime doses (wearing-off/end-of-dose akinesia). Within 2 to 5 years after the initiation of treatment, up to 50% of patients may also experience involuntary movements (chorea, athetosis, dystonia), most often when the medication level peaks in the bloodstream. These complications are generally more prominent and develop earlier in the disease course in patients who have early-onset Parkinson disease. Motor complications (wearing off and dyskinesia), which reflect the short half-life of levodopa combined with the underlying progressive loss of presynaptic dopamine neurons, result in nonphysiologic pulsatile stimulation of striatal dopamine receptors, which then induce neuroplastic changes in postsynaptic striatal neurons. Even as Parkinson disease progresses, however, most of the classic motor features continue to respond after 20 years or more of treatment.

There is no clear advantage to starting initial treatment with a controlled-release rather than with an immediate-release preparation of levodopa or combining levodopa with a catechol *O*-methyltransferase inhibitor (see Table 378-5). When motor fluctuations develop during levodopa therapy, however, they can be managed by a number of approaches (see Table 378-5), including increasing the frequency of the dose, using a controlled-release preparation, or prolonging the action by blocking metabolism (monoamine oxidase B[A3] or catechol *O*-methyltransferase inhibition).

Newer oral levodopa formulations can provide more sustained and reliable plasma levels.[A4] Fast-acting inhaled levodopa is effective within 10 minutes for morning symptoms and sudden "off" symptoms.[A5] Continuous subcutaneous infusion of levodopa prodrugs is a promising option.[A6] For more severe cases, a formulation that provides continuous infusion into the duodenum can significantly improve symptoms during "off" time without increasing dyskinesias compared with immediate-release levodopa.[18]

Dopamine Agonist Therapy

In patients who are younger than age 65 years and who are cognitively intact and lack other major medical problems, initial therapy with a dopamine agonist may be reasonable. In older patients, in patients with cognitive dysfunction (more prone to hallucinations with dopamine agonists), and in circumstances that require a more rapid improvement of pronounced disability, levodopa should be the initial drug of choice. Installation of a dopamine agonist (see Table 378-5) rather than levodopa may be associated with a delay in the onset of motor complications, but the clinical benefit is generally less than with levodopa.[19] If a dopamine agonist does not provide adequate clinical benefit or has intolerable side effects, levodopa should be initiated. All patients eventually require the addition of levodopa to control symptoms.

When motor fluctuations develop or symptoms become more pronounced, combination therapy is often used and can also include the addition of a dopamine agonist. These drugs more often result in excessive sleeping, leg edema, impulse-control disorders (such as pathologic gambling, hypersexuality, binge eating, and shopping), and hallucinations compared with levodopa monotherapy. Impulse control disorders occur in one of six patients, so monitoring by a family member is highly recommended.

For "off" symptoms, options include a sublingual dopamine agonist dissolvable film,[A7] apomorphine injections, and in Europe, a continuous subcutaneous infusion of apomorphine via a pump.

Other Anti-Parkinsonism Medications

Dyskinesia improves when doses of dopaminergic medications are reduced, but the parkinsonism may then worsen to an intolerable level. Amantadine (see Table 378-5) may improve the dyskinesia without worsening the parkinsonism. Istradefylline, which is an antagonist of the adenosine A_{2A} receptor, also improves the wearing-off phenomenon.[A8]

Mildly effective drugs such as a monoamine oxidase B inhibitor or amantadine may provide adequate benefit in mildly symptomatic patients (see Table 378-5). Although anticholinergics may be used for tremor, their cognitive side effects make them a less desirable choice.[20]

Other Medical Issues

Cognitive impairment is a troublesome symptom that eventually affects most patients with Parkinson disease.[21] Cognitive impairment can be treated with acetylcholinesterase inhibitors including donepezil and rivastigmine (see Table 378-5). Antipsychotic medications quetiapine, clozapine, and pimavanserin[A9] (see Table 378-5) are options for treating psychosis related to Parkinson disease.[22]

Medical management of Parkinson disease often includes a variety of other agents, including medications directed at the treatment of orthostatic hypotension (Chapters 49 and 386), depression (Chapter 362), anxiety (Chapter 362), urinary frequency and urgency (Chapters 114 and 115), and male erectile dysfunction (Chapter 216).[23]

Since no current therapy can slow or reverse the pathologic process and clinical decline in Parkinson disease, experimental gene and cellular therapies are directed at either modifying neurotransmitter function or inducing neuroregeneration.[24] Trials of monoclonal antibodies targeting pathologic α-synuclein have been unsuccessful.[A10,A11] Future treatments must also address the widespread, multisystemic nature of the disease, especially symptoms that are unrelated to nigrostriatal dopamine deficiency and that fail to respond to current therapies.

Interventional Treatment

Bilateral deep brain stimulation of the subthalamic nucleus or globus pallidus improves the symptoms of Parkinson disease, often permits lower doses of antiparkinsonism medications to be used, and it improves self-reported quality of life[A12] and symptoms for at least 5 years.[A13] Earlier use of subthalamic nucleus deep brain stimulation, at a time when patients are just beginning to develop motor complications (mean duration of disease, 7.5 years), provides significantly greater benefit than best medical therapy, but there is no consensus as to the most appropriate time to intervene surgically.[25] Thalamic deep brain stimulation is of limited utility because it is effective only for tremor. The best predictor of a good response to deep brain stimulation of the subthalamic nucleus or globus pallidus internus is the patient's ongoing clinical response to levodopa. Apart from tremor, which may be resistant to the highest tolerable dose of levodopa but generally responds well to surgery, symptoms that are resistant to the peak effect of levodopa (e.g., dysarthria, postural instability with falls) also fail to respond to deep brain stimulation. The typical good candidate for deep brain stimulation of the subthalamic nucleus or globus pallidus is an otherwise healthy, relatively young, cognitively intact, and psychiatrically stable patient who still responds well to levodopa (apart from tremor) but is suffering from disabling tremor, "off" time, motor fluctuations, and dyskinesias. High-frequency focused ultrasound is being explored to treat unilateral Parkinson disease,[A14,A15] but it can result in slurred speech, weakness, and dyskinesia, so its best role remains to be determined. Transplantation of fetal substantia nigra tissue into the striatum was not shown to be beneficial overall.

PROGNOSIS

Parkinson disease progresses inexorably during a period of many years, with the speed and course of progression varying considerably from patient to patient. Some patients maintain an excellent response to treatment, including medications and deep brain stimulation, and seem to change very little during prolonged follow-up, but most patients note increasing disability, with the development of many symptoms that are poorly responsive to medications. Factors such as poor postural stability, falls, dysarthria, dysphagia, dysautonomia, excessive daytime sleepiness, apathy, and dementia contribute to the disability and increased mortality. Approximately half of patients who have normal cognition at baseline develop cognitive impairment within 6 years, and patients who develop mild cognitive impairment commonly progress to dementia within 5 years. Most Parkinson patients die of causes directly related to Parkinson disease, often from complications of reduced mobility, falling, and from general physical decline.

OTHER CAUSES OF PARKINSONISM

The numerous causes of parkinsonism (see Table 378-1) are sometimes termed *akinetic-rigid syndrome, Parkinson syndrome, atypical parkinsonism,* or *Parkinson-plus syndrome* to emphasize that these patients commonly demonstrate additional clinical features indicative of the more widespread and particularly more severe pathologic involvement of areas beyond the dopaminergic substantia nigra pars compacta. These other parkinsonism conditions are generally associated with "postsynaptic" changes that result in a poor or unsustained response to levodopa, and this unresponsiveness serves as one of the most important of

TABLE 378-5 DRUGS FOR PARKINSON DISEASE

	INDICATION	DOSE*	COMMON SIDE EFFECTS	OTHER
DOPAMINE PRECURSOR – LEVODOPA BASED MEDICATIONS				
Carbidopa/levodopa (immediate release)	Monotherapy in early disease and in combination with adjunctive therapies in fluctuating disease	25/100 mg three times a day, increase as needed for frequent dose adjustments	Peripheral and central dopaminergic side effects Peripheral: nausea, vomiting, and orthostatic hypotension Central: motor fluctuations, dyskinesia, psychiatric disturbances	
Carbidopa/levodopa (orally disintegrating)	As above	Same but dissolves in the mouth	As above	
Carbidopa/levodopa (controlled release) or (sustained release)	As above	50/200 mg twice a day, increase as needed	As above	Does not reduce "off" time versus IR
Carbidopa/levodopa (extended release)	As above; can reduce "off" time and increase "on" time without troublesome dyskinesia	23.75 mg/95 mg 3 caps three times a day in levodopa naïve patients. In patients already taking immediate release carbidopa/levodopa, conversion is generally 2× daily dose divided 3, 4, or 5 times daily (see package insert)	As above	
Levodopa inhalation powder	Rapid and reliable relief from debilitating motor fluctuations ("off" episodes)	One dose (84 mg) = two 42 mg capsules up to 5 times	Cough, nausea, upper respiratory tract infection, discolored sputum	
Carbidopa/Levodopa (enteral suspension)	Motor fluctuations in advanced disease	Enteral suspension: 4.63 mg carbidopa and 20 mg levodopa per mL Maximum recommended daily dose 2000 mg of levodopa (i.e., one cassette per day) over 16 hours; titrate dose based on clinical response	Similar to levodopa above plus complications of the device and at the infusion site (e.g., infection/dislodged tube)	Administered into jejunum through percutaneous endoscopic gastrostomy with jejunal tube under expert supervision
MONOAMINE OXIDASE TYPE B INHIBITORS				
Selegiline	Adjunct to levodopa in fluctuating diseases; reduces "off" time and increased on time without troublesome dyskinesia	5 mg twice a day	Dizziness, nausea, insomnia, headache, dyskinesia	Contraindicated in patients taking meperidine, tramadol, methadone, propoxyphene, dextromethorphan, St. John's wort, cyclobenzaprine, or another (selective or non-selective) potent MAO inhibitor
Rasagiline	Monotherapy in early disease; adjunct to levodopa in motor fluctuations; reduces "off" time and increases "on" time without troublesome dyskinesia	0.5-1 mg once a day	Flu syndrome, arthralgia, depression, dyspepsia, peripheral edema, fall, arthralgia, cough, insomnia, dyskinesia, weight loss, postural hypotension, nausea	Similar to above
Safinamide (plus channel inhibitor)	Adjunct to levodopa in fluctuating disease with "off" episodes; reduces "off" time; increases "on" time without troublesome dyskinesia	50-100 mg once a day	Dyskinesia, falls, nausea, insomnia	Similar to above
CATECHOL-O-METHYLTRANSFERASE (COMT) INHIBITORS- INHIBITS PERIPHERAL CONVERSION OF LD AND ALLOWS MORE LD TO ENTER CNS				
Entacapone	Adjunct to levodopa to treat wearing off; reduces "off" time; increases "on" time without troublesome dyskinesia	200 mg with each dose of levodopa, up to a maximum of 1600 mg/day Combined Carbidopa/levodopa/entacapone tablet formulation: 25 mg/100 mg/200 mg tab then titrate up per package insert	Dyskinesia, nausea, diarrhea	
Tolcapone	Adjunct to levodopa/carbidopa treatment and symptoms fluctuations	100 mg three times a day, can increase to 200 mg three times a day	Dyskinesia, nausea, diarrhea, insomnia, rare hepatotoxicity	Contraindicated in patients with liver disease Need to monitor liver enzymes
Opicapone	Adjunctive treatment to levodopa/carbidopa in patients experience "off" episodes	25-50 mg once at night	Dyskinesia, constipation, elevated creatine kinase levels, hypotension, syncope, decreased weight	

TABLE 378-5 DRUGS FOR PARKINSON DISEASE—cont'd

	INDICATION	DOSE*	COMMON SIDE EFFECTS	OTHER
NON-ERGOT DOPAMINE RECEPTOR AGONISTS				
Pramipexole	Monotherapy in early disease; may delay motor complications; adjunct to levodopa; reduces "off" time; increases on time without troublesome dyskinesia	Immediate release: 0.125 mg tid, increase as needed Extended release: 0.375 mg qd, increase as needed Maximum dose = 4.5 mg qd	Impulse control disorders, excessive and sudden daytime sleepiness, nausea, dizziness, headache, dyskinesia, hallucinations, lower extremity edema	
Ropinirole	As above	Immediate release: 0.25 mg three times a day Extended release: 2 mg each day increase as needed Maximum dose = 24 mg qd	As above	
Rotigotine	Adjunct to levodopa in fluctuating disease; reduces "off" time; increased "on" time without troublesome dyskinesia	2 mg/24 hours Increase gradually to max 8 mg/24 hours	As above	Application site reaction
Apomorphine injections	Acute, intermittent treatment of "off" episodes	2-6 mg injections up to 5× day	Yawning, postural hypotension, rhinorrhea (+ above)	
Apomorphine sublingual film		10-30 mg sublingual film up to 5× day	Nausea, somnolence, dizziness, oropharyngeal effects	
NMDA RECEPTOR ANTAGONIST				
Amantadine (immediate release)	Monotherapy in early disease or as an adjunct to levodopa; reduces dyskinesia	50-100 mg up to three times a day	Nausea, dizziness, lightheadedness, insomnia, hallucinations, livedo reticularis, orthostatic hypotension	Commonly used but not FDA approved for Parkinson disease
Amantadine (extended release capsules)	Dyskinesia from levodopa-based therapy, with or without concomitant dopaminergic medications Adjunctive treatment to carbidopa/levodopa in patients experiencing "off" episodes	137 mg at bedtime, can increase to 274 mg	Hallucinations, dizziness, dry mouth, edema, constipation, falls, orthostatic hypotension	
Amantadine (extended release tablets)	Monotherapy in early disease or as an adjunct to levodopa	129 mg in AM, can increase to 322 mg in AM	Nausea, dizziness, lightheadedness, insomnia, hallucinations	
ADENOSINE A_{2A} RECEPTOR ANTAGONIST				
Istradefylline	Combination therapy with carbidopa/levodopa for "off" episodes	20-40 mg once a day	Dyskinesia, insomnia, hallucinations, dizziness	
ANTICHOLINERGIC AGENTS				
Trihexyphenidyl HCL	Early treatment of tremor	1-2 mg twice or three times a day	Dry mouth, blurred vision, constipation, difficulty with urination, confusion, memory issues	Contraindicated in the elderly and in patients with cognitive disturbances
NEUROLEPT AGENTS				
Clozapine	Psychosis	Start at 12.5 mg once at bedtime; wide range of doses (6.25-150 mg/day), usually <75 mg/day	Agranulocytosis, sedation, hypotension, sialorrhea	Very low risk of worsening parkinsonism; agranulocytosis rare (<1%) and reversible if discovered early (requires regular monitoring of complete blood count)
Quetiapine	Psychosis	12.5-25 mg once at bedtime 25-150 mg/day	Sedation, may worsen parkinsonism	Probably less effective than clozapine
Pimavanserin	Hallucinations and delusions	34 mg once a day (2-17 mg tabs)	Peripheral edema, confusion, prolonged QT interval on the electrocardiogram	
ACETYLCHOLINESTERASE INHIBITORS				
Donepezil	Cognitive impairment	5-10 mg/day	Nausea, vomiting, diarrhea, syncope, bradycardia, increased tremor, worsening of other Parkinson features	
Rivastigmine	Cognitive impairment	Oral dose: 1.5 mg twice a day, increased as needed - 3-12 mg/day Transdermal patch: 4.6 mg/24 hours up to 13.3 mg/24 hours	As above	Patch formulation for transdermal administration—may be better tolerated than the oral formulation

*Dose is oral unless otherwise noted.

CNS = central nervous system; FDA = U.S. Food and Drug Administration; HCL = hydrochloride; IR = immediate release; LD = levodopa; MAO = monoamine oxidase; NMDA = N-methyl-D-aspartate; PO = orally or by mouth; qd = once daily; SQ = subcutaneous; tid = three times a day.

several clues that the parkinsonism features are caused by conditions other than Parkinson disease (see Table 378-4) (e.g., "parkinsonism minus," a levodopa response; see Table 378-3).

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379 OTHER MOVEMENT DISORDERS

MICHAEL S. OKUN AND JILL L. OSTREM

DEFINITION

Movement disorders are first divided into hypokinetic and hyperkinetic categories. *Hypokinetic disorders*, which are characterized by akinesia, bradykinesia, and rigidity, are parkinsonian syndromes and are discussed in Chapter 378. The common *hyperkinetic movement* disorders (Table 379-1) are defined by specific clinical phenomena.

TABLE 379-1 HYPERKINETIC MOVEMENT DISORDERS

Tremor
Chorea
Ballism
Dystonia
Athetosis
Tics
Myoclonus
Startle
Stereotypies
Miscellaneous

CLINICAL MANIFESTATIONS AND DIAGNOSTIC APPROACH

The traditional approach to a neurologic symptom is first to address localization within the nervous system (i.e., "Where is the lesion?"), followed by an evaluation of the origin ("What is the lesion?"). The neurologic examination is critical in determining the localization of the lesion, and generally the history, including the nature of onset and the progression of the symptoms, will determine the most likely diagnosis. However, when a movement disorder is the predominant problem, the approach is somewhat different. The pathophysiology of most movement disorders is complex. Many of these disorders are the result of dysfunction of different circuits in the brain, and it is often impossible to ascertain a specific anatomic localization. Instead, an accurate appreciation of the clinical phenomena is the first important step in evaluation. The clinician must observe and examine the patient to define the type of movement disorder that best describes the clinical picture. This accurate characterization then allows the generation of a differential diagnosis for the specific movement disorder. The age and nature of onset, the distribution, the progression of symptoms, a family history of similar or related symptoms, and the presence of other neurologic and systemic signs aid in determining the most likely explanation.

TREMOR

Tremor, which is a rhythmic, sinusoidal movement of a body part, is caused by regular, either synchronous or alternating, contractions of reciprocally innervated muscles. Tremors are classified based on whether they occur at rest (weight fully supported against gravity) or in action. Resting tremors are typically seen in Parkinson disease and other parkinsonism syndromes, but this is not an absolute rule[1] (see Table 378-1 in Chapter 378). Action tremors are further divided into postural, kinetic, or intention tremors. A postural tremor is seen with the maintenance of a posture against gravity (e.g., when the arms are outstretched in front of the body). A *kinetic tremor* is seen with a voluntary movement of the limb (e.g., a tremor in an upper limb when performing the finger-to-nose test). An intention tremor increases in amplitude on approaching a target.

CLINICAL MANIFESTATIONS

Most action tremors (Table 379-2) combine postural and kinetic components. Most tremors worsen with stress, including performing an affected activity in public. Initially, a tremor may be evident only when one attempts fine, dexterous tasks such as threading a needle, soldering, or using a screwdriver. More severe tremors interfere with activities such as handwriting, fastening buttons, shaving, eating soup with a spoon, or drinking from a cup. Patients often adapt or use compensatory measures, such as switching an activity to a less affected hand (e.g., shaving with the nondominant hand), using two hands to drink, drinking only from an incompletely filled glass or cup, or completely avoiding more challenging feeding activities in public. Severe action and intention tremors can cause handwriting to become completely illegible and can result in dependence on others for care.

Head tremors, which may be side to side, up and down, or mixed, are rarely disabling but are often a source of embarrassment. Tremor of the larynx, which causes the voice to quaver, is best appreciated by asking the patient to sustain a note. Action tremor of the lower limbs is assessed by having the patient hold the foot up to a target (e.g., the examiner's hand) and then perform a heel-knee-shin test.

Most upper limb action tremors affect many activities to a similar extent. Less commonly, tremors can affect a single task in isolation (task-specific tremors), the most common being a primary writing tremor. Orthostatic tremor is apparent in the legs and in antigravity muscles only when the patient is standing in one spot and subsides during walking or leaning against a wall; these patients commonly complain of a tremendous sense of insecurity while standing and a fear of falling. Electrophysiologic assessment demonstrates a very characteristic high-frequency tremor (14 to 18 Hz).

ENHANCED PHYSIOLOGIC TREMOR

A 7- to 12-Hz tremor is detectable by electrophysiologic recordings in all humans. This physiologic tremor is enhanced and may become symptomatic

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ENHANCED PHYSIOLOGIC TREMOR

A 7- to 12-Hz tremor is detectable by electrophysiologic recordings in all humans. This physiologic tremor is enhanced and may become symptomatic

ABSTRACT

This chapter addresses hyperkinetic movement disorders that are easy to distinguish clinically from the parkinsonian hypokinetic disorders, which are characterized by akinesia, bradykinesia, and rigidity. The common hyperkinetic movement disorders, which are defined by specific clinical phenomena, include tremor, chorea, ballism, dystonia, athetosis, tics, myoclonus, startle, and other stereotypies. This chapter provides a comprehensive review of these disorders with current treatment options.

KEYWORDS

hyperkinetic disorders
tremor
chorea
ballism
dystonia
tics
myoclonus

in a variety of circumstances, including fatigue, anxiety, and excitement. This same tremor may be accentuated by drugs and systemic processes.

ESSENTIAL TREMOR

Essential tremor affects up to 5% of the general population after the age of 60 years.[2,3] Essential tremor is often inherited in an autosomal dominant fashion, with the phenotype showing genetic heterogeneity from at least six different genes, as well as environmental influences. Recent pathology studies have variably demonstrated microscopic abnormalities of cerebellar decreased Purkinje cells, changes in axon thickness, and decreased axonal branching. The age of onset may be as early as the first or second decade of life, but senile tremor may be delayed until the mid-60s. Patients first become aware of a mild postural and action tremor in the hands, which is indistinguishable from an enhanced physiologic tremor and may result in little functional impairment for many years until it gradually interferes with activities. Older patients with large-amplitude, lower frequency tremors can have a resting component that is often misdiagnosed as Parkinson disease (see Table 378-1 in Chapter 378; Video 379-1).

TABLE 379-2 DIFFERENTIAL DIAGNOSIS OF TREMOR AND RHYTHMIC MOVEMENT DISORDERS

ENHANCED PHYSIOLOGIC TREMOR
Metabolic disorders
Hyperthyroidism
Hyperparathyroidism
Hypoglycemia
Pheochromocytoma
Drugs
Caffeine
Theophylline
Amphetamines
Lithium
Valproic acid
Antidepressants
Amiodarone
β-Agonists
Others
Withdrawal of drugs
Benzodiazepines
Alcohol
Others
Fever, sepsis
Anxiety, stress, fatigue
PRIMARY OR IDIOPATHIC TREMOR
Essential tremor
Task-specific tremor
Orthostatic tremor
Idiopathic palatal tremor
TREMOR ASSOCIATED WITH CENTRAL NERVOUS SYSTEM DISEASES
Tremor with parkinsonian syndromes
Idiopathic Parkinson disease
Multiple system atrophy
Progressive supranuclear palsy
Corticobasal degeneration
Neuroleptic-induced parkinsonism
Wilson disease
Multiple sclerosis
Fragile X premutation-tremor/ataxia syndrome
Stroke
Arteriovenous malformation
Tumor
Head trauma
Midbrain tremor (Holmes tremor)
TREMOR ASSOCIATED WITH PERIPHERAL NEUROPATHIES
PSYCHOGENIC TREMOR
OTHER RHYTHMIC MOVEMENT DISORDERS
Rhythmic movements in dystonia (dystonic tremor)
Rhythmic myoclonus (including myoclonic tremor)
Asterixis
Clonus
Epilepsia partialis continua
Hereditary chin quivering
Spasmus nutans
Head bobbing with hydrocephalus
Nystagmus

Modified from Cloutier M, Lang AE. Movement disorders: an overview. In: Factor SA, Lang AE, Weiner WJ, eds. *Drug Induced Movement Disorders*. Malden, Mass: Blackwell; 2005:3-19.

TREATMENT

Treatment of essential tremor does not influence the course of the illness and therefore is justified only when the tremor interferes with function. At least 50% of patients note improvement or complete amelioration of tremor following the ingestion of a small amount of ethanol.

First-line drug treatment includes trials of a noncardioselective β-adrenergic blocker (e.g., propranolol, ≤320 mg/day), primidone (starting in a low dose of 25 to 62.5 mg at night and increasing to 250 and sometimes 500 to 750 mg/day if tolerated), or topiramate (≤400 mg/day).[4] Other drugs that have been shown probably to be effective in double-blind crossover trials include gabapentin (1200 to 1800 mg/day), atenolol (50 to 150 mg/day), alprazolam (0.125 to 3 mg/day), and sotalol (75 to 200 mg/day). However, sotalol is associated with ventricular arrhythmias and dose-related QT interval prolongation, so it is not routinely considered as treatment of essential tremor. The medications that have been shown to be of possible benefit include nadolol (120 to 240 mg/day), nimodipine (120 mg/day), and clonazepam (0.5 to 6 mg/day), but many patients remain resistant to all drugs. Botulinum toxin may be effective, but it also may result in dose-dependent weakness and pain at the injection site. If disability is substantial, thalamic deep brain stimulation[A1] or focused ultrasound thalamotomy[A2] can be of major benefit, with significant reductions following unilateral or bilateral treatment.

However, a few patients suffer permanent neurologic sequelae such as speech and gait dysfunction even with unilateral procedures, and even more suffer such problems after bilateral procedures.

CHOREA

Chorea (Table 379-3) consists of irregular, random, brief, flowing movements that often flit from one body part to another in an unpredictable and purposeless sequence. Patients may incorporate choreiform movements into a voluntary movement to mask them. The severity varies from the appearance of being slightly fidgety or restless, to striking, continuous movements involving the whole body. Many patients with chorea seem unaware of their movements, whereas others can be very troubled and disabled.

HUNTINGTON DISEASE

DEFINITION AND EPIDEMIOLOGY

Huntington disease is a fully penetrant autosomal dominant neurodegenerative disorder caused by an expanded trinucleotide (CAG) repeat in the gene for the protein huntingtin located on chromosome 4. The worldwide 2.71 per 100,000[5] prevalence ranges from 5.7 per 100,000 for individuals of European descent to 0.4 per 100,000 for Asians. The age at diagnosis is driven by the longest expanded allele and as yet unidentified genetic or environmental factors.

PATHOBIOLOGY

Huntington disease is characterized neuropathologically by neuronal loss accompanied by intraneuronal inclusions and gliosis, especially in the caudate nucleus and putamen (the striatum) and the cerebral cortex. Although symptoms do not begin until later in life, early neurodevelopment is likely altered. Understanding how these changes result from the expanded polyglutamine tract in the mutated huntingtin protein is the goal of current research.

CLINICAL MANIFESTATIONS

Symptoms typically begin between the ages of 30 and 55 years, but 5 to 10% of patients have an onset before the age of 20 years (juvenile Huntington disease) and a few patients begin to have symptoms late in life. Symptoms include a combination of a movement disorder, psychiatric disturbances, and cognitive dysfunction. Early on, the movement disorder is predominantly chorea, but parkinsonism and dystonia develop later (Video 379-2). Some patients, especially those with juvenile onset, have a more rapidly progressive akinetic-rigid and dystonic form (the Westphal variant). Psychiatric manifestations, which are universal but widely variable, include personality changes, impulsiveness, aggressive behavior, depression, and paranoid psychosis. These psychiatric symptoms may precede the motor manifestations, and psychotropic drug therapy may be incorrectly blamed for the subsequent development of the movement disorder. Cognitive changes result in progressive subcortical

TABLE 379-3 DIFFERENTIAL DIAGNOSIS OF CHOREA

GENETIC DISORDERS
Benign hereditary chorea
Huntington disease
Huntington-like conditions
Neuroferritinopathy
Neuroacanthocytosis, including McLeod syndrome
Dentatorubropallidoluysian atrophy
Wilson disease
Neurodegeneration with brain iron accumulation 1 (NBIA 1) (previously Hallervorden Spatz disease)
Spinocerebellar ataxias
Ataxia-telangiectasia
Ataxia-oculomotor apraxia type 1
Tuberous sclerosis
INFECTIONS/PARAINFECTIOUS CAUSES
Sydenham chorea
Acquired immunodeficiency syndrome (including complications)
Encephalitis and postencephalitic disorders
Creutzfeldt-Jakob disease
DRUGS
Levodopa
Dopaminergic agonists used for Parkinson disease
Amphetamines
Anticholinergics
Anticonvulsants (especially phenytoin)
Neuroleptics
Tricyclic antidepressants
Selective serotonin reuptake inhibitors (occasionally)
Oral contraceptives (typically in patients with a prior history of Sydenham chorea)
Antihistamines
ENDOCRINOLOGIC/METABOLIC CONDITIONS
Hyperthyroidism
Hypoparathyroidism
Chorea gravidarum
Acquired hepatolenticular degeneration
IMMUNOLOGIC DISORDERS
Systemic lupus erythematosus
Antiphospholipid syndrome
Henoch-Schönlein purpura
VASCULAR DISORDERS
Stroke
Hemorrhage
Arteriovenous malformation
Polycythemia rubra vera
OTHER CONDITIONS
Cerebral palsy
Kernicterus
Head trauma
Cardiopulmonary bypass with hypothermia
Neoplastic and paraneoplastic syndromes
Paroxysmal dyskinesias

Modified from Cloutier M, Lang AE. Movement disorders: an overview. In: Factor SA, Lang AE, Weiner WJ, eds. *Drug Induced Movement Disorders*. Malden, Mass: Blackwell; 2005:3-19.

dementia with disturbed attention, concentration, judgment, and problem solving that differs from the typical cortical dementia of Alzheimer disease. Oculomotor dysfunction, most often manifested by difficulties with refixating the gaze and a resulting tendency to use blinks and head thrusts, is another common feature.

DIAGNOSIS

The diagnosis is confirmed by genetic testing. Normal alleles of the *IT15* gene have fewer than 30 CAG repeats, whereas 40 or more repeats invariably result in clinical illness.[6] An earlier age of onset correlates with larger numbers of CAG repeats. Patients with intermediate alleles (27 to 35) have more behavioral abnormalities, such as apathy and suicidal ideation, than unaffected individuals. Mutant huntingtin protein levels, detected by ultrasensitive single-molecule counting, are associated with the onset of symptoms and diminished cognitive and motor function.

TREATMENT AND PROGNOSIS

Current care for patients with Huntington disease involves a multidisciplinary team of clinical geneticists, neurologists, psychiatrists, psychologists, social workers, occupational and physical therapists, speech therapists, nutritionists, and nurses.[7] Genetic counseling for patients and family members is critical. Chorea may be extremely responsive to drugs that reduce central dopamine activity, especially tetrabenazine, starting at 12.5 mg two or three times daily and gradually increasing to up to 100 to 200 mg/day, or deutetrabenazine (starting at 6 mg/day and increasing weekly by 6 mg/day until chorea is adequately controlled or up to maximum 48-mg daily dose).[A3] Patients should be monitored for depression, parkinsonism, and weight gain. Other agents should be reserved for patients with disabling chorea because they may be associated with increased parkinsonism, postural instability, depression, sedation, and other adverse effects; these options include amantadine (300 to 400 mg/day) and possibly riluzole (200 mg/day). Other potential agents that work by blocking dopamine receptors include haloperidol (3 to 30 mg/day), pimozide (0.5 to 10 mg/day), fluphenazine (0.5 to 20 mg/day), and reserpine (0.75 to 5 mg/day). Data suggest that RAN proteins could be future therapeutic targets.

Unfortunately, physical function may not improve significantly even when the chorea is controlled. Psychiatric symptoms (e.g., anxiety, psychosis, depression) can be managed effectively with the same strategies as in other psychiatric diseases (Chapter 362).

Disease-modifying strategies are under active development. Unfortunately, neither the intrathecal administration of an antisense oligonucleotide to reduce the concentration of the mutant huntingtin protein nor the transplantation of normal human fetal cells is helpful.[8,9]

Progression can be monitored by clinical changes and by following changes in gray matter volumes on brain magnetic resonance imaging (MRI) in both premanifest and early-stage patients. Patients inexorably decline at a relatively constant rate, and the disease progresses to institutionalization and death over the course of approximately 15 years. However, this prognosis is variable depending largely on the burden of disease.

OTHER CHOREAS

Most of the non-neurodegenerative causes of chorea (see Table 379-3) can be established or excluded by a careful history (including a detailed drug history) and a focused set of investigations, including, in appropriate circumstances, wet preparation of peripheral blood for acanthocytes (which are associated with neurodegeneration), immunologic studies (including anticardiolipin antibodies), endocrine assessment (hyperthyroidism, pregnancy), neuroimaging, and genetic testing. Mutations in the *NKX2-1* gene and the *ADCY5* gene can cause benign hereditary chorea.[10] Heterozygous hexanucleotide expansions in the *C9orf72* gene or in the *RNF216* gene can cause a Huntington-like disorder, and *C9orf72* may co-occur with the Huntington gene.[11] Among 36 adult cases of autoimmune chorea seen at one institution in 5 years, 50% had a coexisting autoimmune disorder, especially systemic lupus erythematosus (Chapter 245), and most of the remainder had a paraneoplastic cause, especially small cell carcinoma of the lung and adenocarcinoma.

Sydenham chorea, which is a late component of rheumatic fever (Chapter 269), is presumably the result of immunologic cross-reactivity between the causative group A β-hemolytic streptococcus and the basal ganglia. However, not all patients with Sydenham chorea have a history of rheumatic fever. This disorder is infrequently seen in North America but is more common in developing countries. Sydenham chorea usually affects children and young adults, and it is more common in girls before puberty. Adults with a history of Sydenham chorea in childhood may develop chorea during pregnancy or in response to taking oral contraceptive agents or estrogen preparations. They also may have a higher rate of subsequent psychiatric disturbances and impaired executive neurologic function even when in remission.

Drugs that can cause chorea should be withdrawn if possible. Tetrabenazine and deutetrabenazine, as prescribed for Huntington disease, may be useful for these other choreas.[12]

BALLISM

Ballism, which is considered an extreme form of chorea, involves large-amplitude, random, often violent flinging movements of the proximal limbs (Table 379-4). It is most often a consequence of an acute cerebral insult, such as a stroke, and it usually involves one side of the body, particularly the arm, hence the term *hemiballism* (Video 379-3). When a causative lesion can be demonstrated, it typically involves the region of the subthalamic nucleus, the thalamus, or the striatum. When the condition is caused by a stroke, movements usually subside spontaneously over days to weeks, although they may persist indefinitely in some patients. Ballism also may be a side effect after deep brain stimulation or ablative procedures that target the subthalamic region.

TABLE 379-4 DIFFERENTIAL DIAGNOSIS OF BALLISM

Focal lesions in basal ganglia
Vascular: Stroke (including infarction and hemorrhage), cavernous angioma, post-surgical complications
Neoplastic: Metastases, primary central nervous system tumors
Infections: Cryptococcosis, toxoplasmosis, tuberculoma
Inflammatory: Multiple sclerosis
Iatrogenic: Subthalamotomy, thalamotomy
Immunologic: Systemic lupus erythematosus, scleroderma; Behçet disease
Nonketotic hyperglycemia (high-intensity lesions in striatum on T1 MRI)
Hypoglycemia
Sydenham chorea
Head injury
Drugs
Anticonvulsants
Oral contraceptives
Levodopa

MRI = magnetic resonance imaging.
Modified from Cloutier M, Lang AE. Movement disorders: an overview. In: Factor SA, Lang AE, Weiner WJ, eds. *Drug Induced Movement Disorders*. Malden, Mass: Blackwell; 2005:3-19.

Treatment often requires the use of medication that antagonizes the effects of dopamine in the brain, including dopamine receptor blockers (neuroleptics such as haloperidol, 3 to 30 mg/day) or dopamine depleters (e.g., tetrabenazine, 50 to 200 mg/day). Functional neurosurgery (e.g., pallidotomy, deep brain stimulation) can be considered in patients with refractory, persistent symptoms.

DYSTONIA

DEFINITION AND PATHOBIOLOGY

In dystonia, sustained muscle contractions, often initiated or worsened by voluntary action, result in repetitive twisting and sometimes tremulous movements and abnormal postures. Dystonia can be classified as primary dystonia, dystonia-plus, secondary dystonia, and heredogenerative dystonia (Table 379-5). One classification uses five descriptors to specify the clinical characteristics: age at onset, body distribution, temporal pattern, and whether dystonia occurs in isolation (or only accompanied by tremor; "pure dystonia") or coexists with other movement disorders (typically parkinsonism and myoclonus). *Etiology* is defined as the presence or absence of degenerative or structural nervous system pathologic process and by whether the mode of inheritance is autosomal dominant, autosomal recessive, X-linked recessive, mitochondrial, or acquired. Probable or causal monogenic variants are found in about 20% of cases. A commonly used classification scheme for the genetic dystonias involves applying the "DYT" prefix followed by a number (e.g., 1 to 25); however, several shortcomings have encouraged an active re-evaluation

TABLE 379-5 CLASSIFICATION AND CAUSES OF DYSTONIA

PRIMARY (ISOLATED) DYSTONIAS
Familial (several genetic causes and types)
Sporadic (idiopathic), usually adult onset, focal, or segmental
DYSTONIA-PLUS
Dystonia with parkinsonism
Dopa-responsive dystonia
Dopamine agonist–responsive dystonia (e.g., aromatic acid decarboxylase deficiency)
Myoclonus dystonia
SECONDARY DYSTONIAS
Perinatal cerebral injury
Athetoid cerebral palsy
Delayed-onset dystonia
Pachygyria
Kernicterus
Encephalitis
Reye syndrome
Subacute sclerosing leukoencephalopathy
Wasp sting
Creutzfeldt-Jakob disease
Human immunodeficiency virus infection
Head trauma
Thalamotomy
Brainstem lesion
Primary antiphospholipid syndrome
Stroke
Arteriovenous malformation
Hypoxia
Brain tumor
Multiple sclerosis
Central pontine myelinolysis
Cervical cord injury
Peripheral injury
Drugs
Toxins
Hypoparathyroidism
Psychogenic conditions

HEREDODEGENERATIVE DYSTONIAS
X-linked
Lubag disease
Deafness-dystonia-optic atrophy (Mohr-Tranebjaerg) syndrome
Pelizaeus-Merzbacher disease
Lesch-Nyhan syndrome
Autosomal dominant
Rapid-onset dystonia-parkinsonism
Juvenile parkinsonism (e.g., from mutations in the *parkin* gene)
Huntington disease
Machado-Joseph disease (SCA3) and other SCAs
Dentatorubropallidoluysian atrophy
Autosomal recessive
Wilson disease
Niemann-Pick disease type C
GM_1 gangliosidosis
GM_2 gangliosidosis
Metachromatic leukodystrophy
Homocystinuria
Glutaric acidemia
Triose-phosphate isomerase deficiency
Hartnup disease
Ataxia-telangiectasia
Neurodegeneration with brain iron accumulation (NBIA 1) (previously Hallervorden-Spatz disease)
Juvenile neuronal ceroid lipofuscinosis
Neuroacanthocytosis
Intranuclear hyaline inclusion disease
Hereditary spastic paraplegia with dystonia
Probably autosomal recessive
Familial basal ganglia calcifications (also dominantly inherited)
Progressive pallidal degeneration
Rett syndrome
Mitochondrial
Leigh disease
Leber disease
Other mitochondrial cytopathies
Sporadic, with parkinsonism
Parkinson disease
Progressive supranuclear palsy
Multiple system atrophy
Corticobasal degeneration

SCA = spinocerebellar ataxia.
Modified from Cloutier M, Lang AE. Movement disorders: an overview. In: Factor SA, Lang AE, Weiner WJ, eds. *Drug Induced Movement Disorders*. Malden, Mass: Blackwell; 2005:3-19.

of this approach. Acquired causes include drugs, toxins, infections, vascular disease, neoplasia, trauma, and psychogenic.

CLINICAL MANIFESTATIONS

Common forms of dystonia include eyelid closure (blepharospasm), jaw opening or closing (oromandibular dystonia), pulling or turning of the neck in any one or combination of directions (cervical dystonia: rotatory torticollis, laterocollis, retrocollis, anterocollis), hyperadduction and less often excessive abduction of the vocal cords (laryngeal dystonia or spasmodic dysphonia), abnormal posturing and tightness of the hand while writing or using the hand for other tasks (writer's cramp, manual dystonia), abnormal posturing of the trunk or pelvis (axial dystonia), or abnormal posturing of the lower limb, including plantar flexion and inversion of the foot (Videos 379-4, 379-5, 379-6, and 379-7). The movements are often slow and sustained, although they also may be rapid (dystonic spasms). Slower, sinuous writhing dystonic movements, particularly present in the distal limbs, are referred to as *athetosis*. Dystonia is often made worse by activity (action dystonia), and a unique aspect of dystonia is that only selected acts may be affected, with complete sparing of all other activities in the same limb (task-specific dystonia, including writer's cramp and musician's cramp) (Video 379-8). Task specific dystonia (e.g., golfing, running) may occur only during specific activities. In some patients, dystonia remains isolated and action specific over many years; in others, it progresses to involve adjacent muscles (overflow dystonia) and may eventually be present at rest, in which case joint contractures may result. Another common feature of dystonia is its transient improvement with the use of a sensory trick (geste antagoniste), such as lightly touching the chin to relieve severe cervical dystonia or the lid to relieve disabling blepharospasm (Video 379-9). Patients with dystonia, independent of cause, often have additional postural and action tremors, phenotypically similar to those in essential tremor. Some patients also demonstrate more irregular, coarse, lower frequency rhythmic movements called *dystonic tremor*.

Dystonia is often classified according to the site of involvement: focal, only one body part (e.g., blepharospasm, cervical dystonia, writer's cramp); segmental, two or more contiguous body parts; multifocal, two or more noncontiguous body parts; generalized, trunk and at least two other sites (with or without leg involvement); and hemidystonia, unilateral (generally a causative focal brain lesion is found most often involving the putamen).

DIAGNOSIS AND PROGNOSIS

For diagnostic and prognostic purposes, dystonia also may be distinguished by age of onset as childhood-onset, adolescent-onset, or adult-onset dystonia.[13] The younger the age of onset, the more likely a cause can be defined. Conversely, isolated dystonia beginning in adult life is most often an idiopathic disorder; further investigations are typically unrewarding and are usually not indicated. Likewise, independent of the cause, dystonia beginning in childhood commonly progresses to segmental or generalized involvement whereas adult-onset dystonia usually remains focal or segmental.

SPECIFIC DYSTONIAS

PRIMARY (IDIOPATHIC) OR ISOLATED DYSTONIAS

Primary dystonia accounts for up to 90% of patients with a pure dystonic syndrome, in which dystonia either is the only motor feature or is accompanied only by tremor. To date, no consistent neuropathologic changes have been found in the small numbers of brains affected by primary dystonia that have been studied.

When symptoms begin in childhood, a definable genetic cause is often identified, one of the most common being DYT1, usually resulting from the autosomal dominant inheritance of a GAG deletion in the *torsin A* gene (Oppenheim dystonia). This disorder is more common in persons of Ashkenazi Jewish descent. The dystonia often begins in the first decade of life and can progress to severe disability, although the spectrum of disease, even within the same family, can be quite varied and penetrance is relatively low (about 40%; Video 379-10). Other genetic forms of dystonia include *THAP1* mutations for DYT6 and *TUBB4A* mutations for DYT4 or "whispering dystonia." Genetic testing is available but in the case of DYT1 is recommended only when the age of onset in the patient or another affected family member is less than 26 years. Among the many other potential genes and gene variants are the rare *KMT2B* missense mutation in generalized dystonia.[14]

ADULT-ONSET IDIOPATHIC DYSTONIA

Adult-onset idiopathic dystonia is the most common type of dystonia seen in general neurologic practice. The dystonia typically begins in the face, neck, or arm and may remain focal and nonprogressive or spread only to contiguous muscles after many years. The cause of this disorder is not known, although a positive family history may be noted if multiple family members can be examined. Genetic forms of adult-onset focal or segmental dystonia include *ANO3* and *GNAL* mutations for craniocervical dystonia and possibly *CIZ1* mutations for cervical dystonia.

DYSTONIA-PLUS

The term *dystonia-plus* refers to a small number of disorders characterized by dystonia with other neurologic signs that result from a known or presumed genetic defect without an underlying progressive neurodegenerative process. In the newer classification, these conditions are included in the group of disorders with dystonia combined with other neurologic features.

Dopa-responsive dystonia, which usually results in dystonia beginning in the first decade of life, most often in the lower limbs, sometimes can be mistaken for hereditary spastic paraplegia or cerebral palsy. Most patients with dopa-responsive dystonia have a mutation in the *GCH1* gene, which results in reduced production of dopamine. Approximately 75% of patients have notable worsening of dystonia as the day progresses (diurnal variation). Exercise often aggravates the dystonia. Patients commonly demonstrate some degree of bradykinesia (especially in the legs) and postural instability. Rare adult-onset disease may result in a pure parkinsonian phenotype. Dopa-responsive dystonia should be considered in all children with dystonia. Symptoms are exquisitely sensitive to low doses of levodopa (typically as little as 50 mg/day of levodopa), and this treatment allows patients to live a normal life without the usual complications seen in Parkinson disease (Chapter 378).

Myoclonus dystonia, which usually begins within the first decade of life, combines dystonia with separate multifocal myoclonic jerks. Myoclonus dystonia is genetically heterogeneous; the most common definable cause is a mutation in the *epsilon-sarcoglycan* gene. The dystonia in these patients most often involves the neck or upper limbs, is mild, and is often overlooked. The disorder also can include psychopathology, such as obsessive-compulsive behavior. A characteristic feature of this disorder is the marked ameliorative effect of ethanol on both the myoclonus and the dystonia, a feature that sometimes results in alcohol abuse.

OTHER DYSTONIAS (SECONDARY)

Dystonia may be a symptom of many diseases. The nature and extent of the investigations undertaken depend on such factors as age at onset, clues provided on the history, and additional neurologic or systemic features on examination. Wilson disease (Chapter 195) is an important consideration in the diagnosis of dystonia beginning in children and young adults. Another potentially treatable form of dystonia is caused by a mutation in the *SLC30A10* gene, which codes for a manganese transporter. The phenotype is similar to that of Wilson disease, with generalized dystonia, cirrhosis, and hyperintensities in the basal ganglia on T1 MRI scans.

Some patients with dystonia, chorea, or a mixture of the two (choreoathetosis) have intermittent symptoms (paroxysmal dyskinesias) and may be normal between episodes. The duration of symptoms can be as brief as a few seconds to a few minutes or persist for several hours. Symptoms triggered by sudden movement, which are termed *kinesigenic*, are typically brief; prolonged episodes are commonly triggered by exercise, stress, fatigue, caffeine, or alcohol. Paroxysmal dyskinesias may be genetically determined, idiopathic, the manifestation of another disorder (e.g., head injury, brain tumor, or stroke), or even psychologically based. A mutation of the *PRRT2* gene has been described in a large proportion of genetically determined paroxysmal kinesigenic dystonia.

TREATMENT

Ideally, treatment is directed at the underlying cause, such as dopa-responsive dystonia, which is treated with levodopa (usually up to 300 mg/day) or Wilson disease by copper chelation (Chapter 195). Patients with mutations in the manganese transporter gene may benefit from chelation with ethylenediaminetetraacetic acid (EDTA) (see Table 20-2 in Chapter 20). Unfortunately, cause-specific treatment usually is not possible, so a variety of symptomatic treatments may be tried, often unsuccessfully, in an attempt to reduce disability.

Focal injections of botulinum toxin are now usually the first choice for treatment of focal and segmental dystonias.[15] This approach can improve symptoms of patients with cranial (blepharospasm, oromandibular dystonia) and cervical dystonia. Patients with task-specific limb dystonias (e.g., writer's cramp) often benefit less because weakness of the treated muscles, which is the most common side effect of this therapy, can impair other important upper limb functions.

Young patients in particular can tolerate and benefit from high doses of anticholinergic drugs such as trihexyphenidyl (6 to 40 mg/day, but sometimes as much as 100 mg/day). However, high doses may affect school performance. Muscle relaxants, including benzodiazepines (diazepam, 5 to as much as 100 mg/day) and baclofen (40 to 120 mg/day), may provide some benefit. Dopamine-depleting (e.g., tetrabenazine, 50 to 200 mg/day) and dopamine-blocking (e.g., haloperidol, 3 to 30 mg/day) agents are occasionally helpful (more often effective in tardive dystonia than in other types). Paroxysmal kinesigenic dyskinesia usually responds well to anticonvulsant drugs. Paroxysmal exercise-induced dyskinesias are associated with mutations in the *SLC2A1* gene, which encodes the glucose transporter GLUT1, and may respond to a ketogenic diet. Deep brain stimulation of the internal segment of the globus pallidus, thalamus, and the subthalamic nucleus,[16] can be considered in medically refractory, disabling dystonia, especially in patients with idiopathic dystonia (e.g., DYT1, adult-onset cervical dystonia). However, the target should be chosen based on symptoms as well as clinical findings, and not all dystonias respond to deep brain stimulation.

TICS

EPIDEMIOLOGY AND PATHOBIOLOGY

Tics are repetitive, stereotyped movements (motor tics) or vocalizations (vocal tics). Transient tics are extremely common in childhood, and simple tics may begin in childhood and persist throughout adult life. Most tics (Table 379-6) are primary or idiopathic and have no identifiable cause. Secondary tics are caused by a defined underlying brain disease or environmental factor.

TABLE 379-6 ETIOLOGIC CLASSIFICATION OF TICS

PRIMARY OR IDIOPATHIC TICS
Transient motor or phonic tics
Chronic motor or phonic tics
Adult-onset tics
Tourette syndrome
SECONDARY TICS
Genetic disorders
Neuroacanthocytosis
Huntington disease
Neurodegeneration with brain iron accumulation 1 (NBIA 1) (previously Hallervorden-Spatz disease)
Idiopathic dystonia*
Tuberous sclerosis*
Chromosomal disorders
Infections
Sydenham chorea
PANDAS†
Encephalitis and postencephalitic disorders
Creutzfeldt-Jakob disease
Neurosyphilis
Drugs
Methylphenidate
Amphetamines
Cocaine
Levodopa
Carbamazepine
Phenytoin
Phenobarbital
Lamotrigine
Neuroleptics
Developmental disorders
Mental retardation
Pervasive developmental disorders/autism
Other causes
Head trauma
Stroke
Carbon monoxide poisoning
Cardiopulmonary bypass with hypothermia
RELATED DISORDERS
Mannerisms, stereotypies
Compulsions
Self-injurious behavior

*Tics have been described with these conditions but may simply be coincidental.
†Pediatric autoimmune neuropsychiatric disorders associated with streptococcal infections.
Modified from Cloutier M, Lang AE. Movement disorders: an overview. In: Factor SA, Lang AE, Weiner WJ, eds. *Drug Induced Movement Disorders*. Malden, Mass: Blackwell; 2005:3-19.

The tics of Tourette syndrome are now classified as a neurodevelopmental disorder.

CLINICAL MANIFESTATIONS

Tics vary in terms of complexity, from abrupt, brief, meaningless movements or sounds (simple motor tics such as eye blinking, nose wrinkling, or head jerking; simple vocal-phonic tics such as sniffing, throat clearing, or grunting) to more sustained, more deliberate, almost meaningful gestures or utterances (complex motor tics such as touching, hand shaking, and jumping; complex vocal tics such as echolalia [repeating others], palilalia [repeating oneself], and coprolalia [uttering profanities]). The frequency of the tics in an individual patient varies markedly over minutes, hours, days, weeks, and years.

DIAGNOSIS

Various characteristics help to differentiate tics from other abnormal movements.[17] Tics are often described by patients as being "semivoluntary" in response to an inner, irresistible urge. Premonitory sensory symptoms occasionally precede the tic, usually in the same general anatomic area as the tic itself. Relief is often associated with the production of the tic. Tics can be partially or completely voluntarily suppressed for variable periods, but often at the expense of mounting inner tension and psychological discomfort. Performing the tic or sometimes even substituting another more acceptable behavior for the socially inappropriate tic alleviates the tension. Many patients report that some tics occur in response to a typical urge, whereas the same or different tics may be unexpected and totally involuntary.

TOURETTE SYNDROME

EPIDEMIOLOGY AND PATHOBIOLOGY

The exact relationship between childhood tics and Gilles de la Tourette syndrome remains uncertain. Tourette syndrome is a common disorder, with an overall prevalence of 7.7 per 1000 children. There is a male preponderance of 3 : 1 for the classic syndrome, but female patients manifest obsessive-compulsive features more often than tics. A functional mutation in the *HDC* gene encoding L-histidine decarboxylase can be a rare cause of Tourette syndrome, thereby suggesting a role for histaminic neurotransmission in its pathogenesis (Video 379-11). Two new copy number variants, NRXN1 and CNTN6, increase the risk of Tourette syndrome.

CLINICAL MANIFESTATIONS AND DIAGNOSIS

The criteria for this disorder include the presence of multiple motor and at least one vocal tic beginning before the age of 21 years (typically between ages 2 and 10 years) and lasting for more than 1 year, waxing and waning symptoms over time (new tics replacing old ones; previous tics sometimes recurring years after they had originally resolved), and the absence of other explanatory medical conditions. Involuntary swearing (coprolalia), a highly publicized feature of the syndrome, is present in fewer than 10% of patients. Patients commonly exhibit a variety of comorbid disorders, including obsessive-compulsive disorder, attention-deficit disorder (with or without hyperactivity), impulse control problems, and other behavioral disturbances.

TREATMENT

Most patients who fulfill diagnostic criteria for Tourette syndrome have mild symptoms that do not require drug treatment; education, reassurance, behavioral therapy,[18] and follow-up are often sufficient. When tics (isolated or as part of Tourette syndrome) interfere with social and physical function, low-dose clonazepam (0.5 to 4 mg/day) may be effective. Clonidine (0.05 to 0.5 mg/day) is variably effective in controlling tics and may be useful for impulse control and symptoms of attention-deficit/hyperactivity disorder (ADHD); alternatively, guanfacine (0.5 to 4 mg/day) can be used. The most effective treatments for disabling tics are the dopamine receptor blockers such as risperidone (0.5 to 16 mg/day), haloperidol (0.5 to 20 mg/day), pimozide (0.5 to 10 mg/day), fluphenazine (0.5 to 20 mg/day), and aripiprazole (5 to 15 mg/day), but caution is required in view of the potential for important side effects, rarely including tardive dyskinesia, with long-term use. The dopamine-depleting drugs tetrabenazine (50 to 200 mg/day) and deutetrabenazine (6 to 72 mg twice daily) have been tried by experts but are not of proven benefit,[A4] and they should be used only by experts. Injected botulinum toxin may be effective for simple motor tics of the

face and neck and may also reduce the urge to perform the tic. More aggressive use of botulinum toxin in neck muscles should be considered in patients with very forceful neck tics, which have rarely been associated with complications such as noncompressive myelopathy and vertebral artery dissection. Comorbid ADHD can be treated safely with stimulant therapy (e.g., methylphenidate, 2.5 to 60 mg/day) without increasing the severity of tics. Obsessive-compulsive symptoms may respond well to selective serotonin reuptake inhibitors (e.g., clomipramine, 25 to 250 mg/day; paroxetine, 10 to 60 mg/day; or citalopram, 10 to 40 mg/day). Behavioral disorders, which remain a major therapeutic challenge, may require a variety of psychotherapeutic or behavioral modification approaches. Even in the absence of behavioral disturbances, comprehensive behavioral intervention therapy, which incorporates habit reversal training, can be very effective as first-line therapy for tic disorders. Promising preliminary reports of deep brain stimulation require confirmation in controlled clinical trials.

PROGNOSIS

The natural history of Tourette syndrome is to stabilize and in the majority of cases to improve in adolescence. Approximately half of patients have a complete or partial remission at this time.

MYOCLONUS

DEFINITION

Myoclonus (or myoclonic jerks) consists of sudden, brief, shock-like, involuntary movements that result from both active muscle contraction (positive myoclonic jerks) and brief inhibition of ongoing muscle activity (negative myoclonic jerks).[19] The most common form of a negative myoclonic jerk is asterixis.

PATHOBIOLOGY

Myoclonus generally arises in the central nervous system, although rare peripheral causes are described, and it is distinct from abnormal muscle activity associated with peripheral nervous system diseases, such as fasciculations or myokymia. Myoclonus can be classified according to origin (E-Table 379-1), including physiologic, essential, epileptic, and symptomatic forms. Physiologic myoclonus, such as hypnic (sleep) jerks and hiccups, occurs in normal healthy subjects. Patients with essential myoclonus, which may be sporadic or inherited, often have additional postural tremor or dystonia, and this disorder is probably the same as what is now referred to as myoclonus dystonia (see Dystonias, earlier). Epileptic myoclonus arises in the context of seizures (Chapter 372), including many inherited generalized epileptic syndromes and the progressive myoclonic epilepsies. Symptomatic myoclonus occurs in association with a large number of encephalopathic states.

CLINICAL MANIFESTATIONS

Myoclonic jerks are very short, typically persisting for less than 100 msec, although occasional patients have longer muscle bursts. Myoclonus can be spontaneous, action induced, reflex (induced by various sensory stimuli), or a combination. Spontaneous myoclonus occurs at rest, without any provocation. Action myoclonus occurs during purposeful movement and is often very disabling owing to its interference with volitional activity. Reflex myoclonus can be triggered by visual, auditory, or somesthetic stimuli. The distribution of myoclonus may be focal, segmental, multifocal, or generalized. When myoclonus involves more than one body area, the movements may be synchronous or asynchronous. Myoclonus can be intermittent or repetitive, and it sometimes is rhythmic (e.g., usually originating in the brainstem or spinal cord). Palatal myoclonus, now referred to as palatal tremor, is a rhythmic movement disorder originating in the brainstem and involving the soft palate as well as the eyes, facial muscles, neck, and limbs; it is commonly the result of a focal lesion (e.g., stroke, demyelination) in the connections between the dentate nucleus of the cerebellum and the inferior olives of the medulla (symptomatic palatal tremor), and it may persist during sleep.

DIAGNOSIS

Myoclonus can be classified according to the anatomic site of origin, usually with the assistance of detailed electrophysiologic assessments. These sites may be cortical, subcortical (e.g., thalamic, lower brainstem [reticular myoclonus]), or spinal (two types: spinal segmental and propriospinal).

TREATMENT

Management of myoclonus, when possible, should be directed specifically at the underlying cause. Drug treatment includes a variety of anticonvulsant medications, most notably clonazepam (1.5 to 15 mg/day), valproic acid (10 to 15 mg/kg/day), carbamazepine (600 to 1200 mg/day), and levetiracetam (1000 to 4000 mg/day). Lacosamide (200 to 400 mg/day) is also effective in select patients. Postanoxic action myoclonus (the Lance-Adams syndrome) in some patients who survive severe cerebral anoxia also may respond to 5-hydroxytryptophan (400 to 2800 mg/day) given with carbidopa (75 to 300 mg/day). Acetazolamide (250 to 1000 mg/day) may be useful for patients with action myoclonus. Zonisamide (300 mg/day) improves myoclonus and related disability in patients with myoclonus-dystonia.[A5]

HYPEREXPLEXIA

Hyperexplexia, which is a disorder related to myoclonus, manifests as an excessive startle response to tactile, visual, and/or auditory stimulations. Genetic causes are mainly abnormalities in synaptic transmission of the inhibitory neurotransmitter glycine, including glycine receptor α_1 gene (*GLRA1*), glycine receptor subunit gene (*GLRB*), and the presynaptic glycine transporter 2 gene *SLC6A5*. Some patients demonstrate only generalized body jerking or an exaggerated startle response that habituates poorly after repeated stimuli. By comparison, other patients experience disabling stiffness in response to sudden unexpected stimuli, such as a loud sound. The disorder typically responds well to clonazepam (1.5 to 15 mg/day) therapy. Additional medications that have been tried with mixed results include clobazam, levetiracetam, valproic acid, and phenobarbital.

OTHER MOVEMENT DISORDERS

DRUG-INDUCED MOVEMENT DISORDERS

All the movements listed in Table 379-1 can be induced by medications. Neuroleptic drugs, which block postsynaptic dopamine receptors, particularly the D2 subtype, can result in a variety of movement disorder syndromes, including acute dystonic reactions, akathisia, drug-induced parkinsonism (including the "rabbit syndrome" with perinasal and perioral rest tremor), the neuroleptic malignant syndrome, and a variety of later-onset, often persistent, movements referred to as tardive dyskinesia. Metronidazole also rarely can cause an encephalopathy that typically manifests as dysarthria and gait instability.

ACUTE DYSTONIC REACTIONS

Acute dystonic reactions (Chapter 402) are most often seen in young patients who are receiving potent antipsychotic agents (e.g., young male patients receiving high doses of haloperidol for acute psychosis), but they also occur in patients receiving dopamine receptor blockers, including metoclopramide as antiemetic therapy. Symptoms range from overt dystonic postures of the face and neck, to involuntary prolonged deviation of the eyes (oculogyric crises), to simple slurring of speech and difficulty coordinating the tongue. Symptoms often vary from moment to moment and can increase with anxiety and improve with relaxation or reassurance. Acute dystonic reactions are self-limited and respond rapidly to a parenteral injection of an anticholinergic drug such as benztropine (2 mg intravenously [IV] followed by 2 mg orally [PO] three times daily for a variable duration depending on neuroleptic use) or an antihistaminic such as diphenhydramine (50 mg IV followed by oral benztropine).

AKATHISIA

Akathisia refers to a sense of restlessness and a need to move. Typically, the patient performs a variety of purposeful or semipurposeful, often complex, movements in response to an uncomfortable subjective restlessness, including pacing when standing, marching in place, rocking, shifting weight, moving legs when sitting, picking at clothing or hair, rubbing body parts with hands, and other similar movements. Akathisia is most often a side effect of medications, especially neuroleptic drugs and selective serotonin reuptake inhibitors (Chapter 362). Symptoms occur in a dose-related fashion and usually resolve on drug withdrawal. Akathisia is a common reason for psychiatric patients to comply poorly with their medications; management includes adjustment of the dose or type of antipsychotic agent and trials of β-blockers (e.g., propranolol, 80 mg/day) or antiparkinson agents, such as anticholinergics (e.g., benztropine (6 mg/day) or amantadine (200 to 300 mg/day). Rare patients experience a very disabling and persistent form referred to as tardive akathisia. Akathisia is also sometimes seen in patients with Parkinson disease.

E-TABLE 379-1 CLASSIFICATION AND CAUSES OF MYOCLONUS

PHYSIOLOGIC MYOCLONUS

Sleep myoclonus
Anxiety-induced myoclonus
Exercise-induced myoclonus
Hiccups
Benign infantile myoclonus during feeding

ESSENTIAL MYOCLONUS

Essential myoclonus*
- Hereditary
- Sporadic

Myoclonus dystonia*

EPILEPTIC MYOCLONUS

Fragments of epilepsy
- Isolated epileptic myoclonic jerks
- Photosensitive myoclonus
- Myoclonic absences
- Epilepsia partialis continua
- Idiopathic stimulus-sensitive myoclonus

Childhood myoclonic epilepsies
- Infantile spasms
- Lennox-Gastaut syndrome
- Cryptogenic myoclonus epilepsy
- Juvenile myoclonic epilepsy of Janz

Benign familial myoclonic epilepsy
Baltic myoclonus (Unverricht-Lundborg)

SYMPTOMATIC MYOCLONUS

Storage disease
- Lafora body disease
- Lipidoses
- Neuronal ceroid lipofuscinosis
- Sialidosis

Spinocerebellar degeneration
- Friedreich ataxia
- Ataxia-telangiectasia
- Other spinocerebellar degenerations

Basal ganglia degenerations
- Wilson disease
- Idiopathic torsion dystonia
- Neurodegeneration with brain iron accumulation 1 (NBIA 1)
- Progressive supranuclear palsy
- Corticobasal degeneration
- Parkinson disease
- Multiple-system atrophy
- Huntington disease
- Dentatorubropallidoluysian atrophy

Mitochondrial cytopathies
Dementias
- Alzheimer disease
- Creutzfeldt-Jakob disease
- Dementia with Lewy bodies
- Frontotemporal lobar degeneration with TDP-43 positive inclusions

Viral encephalopathies
- Subacute sclerosing panencephalitis
- Encephalitis lethargica
- Herpes simplex encephalitis
- Arbovirus encephalitis
- Human immunodeficiency virus infection
- Postinfectious encephalitis

Metabolic disorders
- Hepatic failure
- Renal failure
- Dialysis dysequilibrium syndrome
- Hyponatremia
- Hypoglycemia
- Nonketotic hyperglycemia
- Infantile myoclonic encephalopathy
- Multiple carboxylase deficiency
- Biotin deficiency

Toxins
- Bismuth
- Heavy-metal poisoning
- Methylbromide, dichlorodiphenyltrichloroethane (DDT)
- Drugs (multiple)

Physical encephalopathies
- Posthypoxic myoclonus (Lance-Adams)
- Post-traumatic status
- Heat stroke
- Electric shock
- Decompression injury

Focal central nervous system damage
- Stroke
- Post-thalamotomy status
- Tumor
- Trauma
- Spinal cord lesions

Peripheral myoclonus (lesions of peripheral nerve, plexus, or nerve root)
Whipple disease
Paraneoplastic syndromes
Psychogenic myoclonus

*Probably represents the same entity.
TDP-43 = TAR DNA-binding protein 43.
Modified from Cloutier M, Lang AE. Movement disorders: an overview. In: Factor SA, Lang AE, Weiner WJ, eds. *Drug Induced Movement Disorders*. Malden, Mass: Blackwell; 2005:3-19.

NEUROLEPTIC MALIGNANT SYNDROME

The neuroleptic malignant syndrome (Chapters 400 and 402) is an uncommon but severe, sometimes fatal, complication of neuroleptic therapy. Patients usually manifest a combination of features including fever, marked rigidity, changes in level of arousal, and autonomic instability. Laboratory abnormalities include a marked increase in the serum creatine kinase level and the blood leukocyte count. Management involves early recognition, withdrawal of the causative agent, systemic supportive therapy, a dopamine agonist (most experience has been with the older agent bromocriptine, ≤60 mg/day), and, when necessary, dantrolene sodium (50 to 600 mg/day PO or ≤10 mg/kg/day IV) to reduce muscle contraction.

TARDIVE DYSKINESIA

EPIDEMIOLOGY AND PATHOBIOLOGY

The term *tardive dyskinesia* encompasses a wide variety of abnormal movements caused by chronic neuroleptic therapy (Chapter 402). The cumulative 5-year incidence rate in patients taking classic neuroleptics is approximately 25%, and the incidence may continue to increase almost linearly beyond that point. The annualized risk is estimated to be 5% in haloperidol-treated patients compared with 2% in patients treated with atypical neuroleptics (Video 379-12). The pathophysiology commonly has been attributed to hypersensitivity or upregulation of dopamine D2 receptors induced by chronic blockade. However, this explanation is generally felt to be inadequate, especially for more persistent symptoms, and other proposed mechanisms include oxidative stress from increased dopamine turnover and a maladaptive synaptic plasticity.

CLINICAL MANIFESTATIONS

Tardive dyskinesia generally begins after a minimum of 6 weeks of treatment. One of the most common forms involves the lower facial muscles and has been given a variety of names, including orobuccolinguomasticatory dyskinesia.[20] The movements generally include repetitive chewing and smacking movements with the tongue either protruding between the lips (fly-catching movements) or pushing into the cheek (bonbon sign). Although the movements are somewhat choreic, they are not as random as true chorea. The more stereotypical, repetitive nature of the movements, involving not only face but also the limbs (e.g., piano playing movements of the fingers, rocking or thrusting of the pelvis), has encouraged the more recent term *tardive stereotypies*. This term, however, fails to fulfill the definition of stereotypy owing to the lack of distractibility and the unpredictability of the sequence of movements. Many patients with classic orofacial tardive dyskinesia seem unaware of the presence of the movements and are not disabled by them, but others are embarrassed or otherwise impaired.

Tardive akathisia and tardive dystonia are less common but particularly disabling subtypes of tardive dyskinesia. Rarer forms include tardive tics (tourettism), tardive tremor, tardive myoclonus, and even tardive oral or genital pain.

TREATMENT AND PROGNOSIS

Treatment is often unsatisfactory, but the dopamine depleters deutetrabenazine (starting at 6 mg daily and increasing up to 48 mg daily),[21] valbenazine (40 mg daily for the week, then 40 mg or 80 mg daily), and tetrabenazine (50 to 200 mg/day) can be very effective. Other drugs that possibly provide benefit include amantadine, propranolol, zolpidem, ginkgo biloba, and clonazepam. Consideration should be given to discontinuing concurrent anticholinergic medications. Prevention is the most important consideration. The physician must regularly reassess the need for ongoing neuroleptic therapy, consider switching to an atypical agent when possible (particularly quetiapine and clozapine; Chapter 362), and routinely evaluate the patient for the presence of early subtle clinical features, such as mild pursing of the lips or rolling movements of the tongue in the mouth. Unfortunately, tardive dyskinesia may persist for many years despite withdrawal of neuroleptic treatment in up to 50% of patients. Several atypical neuroleptics, such as risperidone and olanzapine, nevertheless block dopamine D2 receptors sufficiently to cause drug-induced parkinsonism and tardive dyskinesias.

RESTLESS LEGS SYNDROME

EPIDEMIOLOGY

Restless legs syndrome (Chapter 374) is now recognized as an extremely common disorder affecting between 3 and 29% of the general population.[22] Women are affected more frequently than men. Although the incidence increases with age, it also can affect children, in whom it may be confused with "growing pains" or ADHD.

PATHOBIOLOGY

Restless legs syndrome is most often primary or idiopathic, in which case it is frequently inherited in an autosomal dominant fashion. Eight genetic loci associated with restless legs syndrome include variants in *MEIS1, BTBD9, MAP2K5/LBXCOR1, PTPRD,* and *PCDHA3,* as well as loci on 2p14 and 16q12.1. Restless legs syndrome also may be secondary to other causes, including peripheral neuropathy, uremia, pregnancy, and iron deficiency, and it may occur more commonly than by chance in some neurodegenerative disorders such as Parkinson disease. The pathophysiology of restless legs syndrome is uncertain, but central iron dysregulation may somehow alter central dopamine. Serum ferritin levels are often low, even in the presence of normal values of hemoglobin, hematocrit, iron, and iron-binding capacity.

CLINICAL MANIFESTATIONS AND DIAGNOSIS

In restless legs syndrome, as in akathisia, movements occur because of the subjective need to move. However, unlike in akathisia, the patient typically complains of a variety of sensory disturbances in the legs, including pins and needles, creeping or crawling sensations, aching, itching, stabbing, heaviness, tension, burning, or coldness. Occasionally, similar symptoms are appreciated in the upper limbs or other areas of the body. These symptoms are usually experienced during periods of prolonged inactivity, especially with recumbency in the evening, and are often associated with insomnia (Chapter 374). The discomfort appears particularly during the transition from wake to sleep in the evening and often follows a circadian pattern, peaking between midnight and 4 AM. Symptoms are typically relieved only by movement or stimulation of the legs; although these maneuvers are effective while they are being performed, the discomfort usually returns as soon as the individual becomes inactive or returns to bed to try to sleep. Patients often have significant problems with immobility during long automobile drives or plane flights.

In approximately 80% of patients, this condition is associated with another movement disorder, periodic leg movements in sleep, sometimes inappropriately called nocturnal myoclonus. These periodic, slow, sustained (1 to 2 seconds) movements range from synchronous or asynchronous dorsiflexion of the toes and feet to triple flexion of one or both legs. In 15% of patients, more rapid myoclonic movements or slower, prolonged dystonic-like movements of the feet and legs are present while patients are awake. In the absence of evidence of a secondary cause of restless legs syndrome, the only useful routine test is a serum ferritin level.

TREATMENT

Dopamine agonists (e.g., pramipexole, 0.125 to 1.5 mg at bedtime), ropinirole (0.25 to 3 mg at bedtime), and transdermal rotigotine (1 to 3 mg/24 hours) are the treatments of choice in moderate-to-severe restless legs syndrome and can be very effective. Impulse control disorders are an occasional side effect. Levodopa preparations (100 to 300 mg of levodopa at bedtime; consider controlled-release preparation) are also effective but are more often associated with disabling rebound symptoms early in the morning or during the day (augmentation). Gabapentin enacarbil (a gabapentin prodrug at 600 to 1200 mg/day) is also effective and approved in the United States at the 600-mg dose.[A6] Patients with milder symptoms may respond to gabapentin (300 to 2400 mg/day). Opiate agonists (e.g., oxycodone, 5 mg at bedtime; codeine, 30 mg at bedtime; propoxyphene, 65 mg or N-100 mg at bedtime) and less often benzodiazepines (e.g., clonazepam, 0.5 to 2 mg at bedtime) also may be effective. Oxycodone-naloxone (40/20 mg) twice daily is also effective, and methadone has also shown effectiveness in non-blinded studies; however, these options are less attractive because of their addictive potential. Tolerance or loss of original benefit may occur with all these treatments. Iron replacement is indicated in patients with reduced serum ferritin levels (325 mg ferrous sulfate two or three times per day for 3 to 4 months until ferritin levels exceed 50 mg/L and iron saturations exceed 20%). Deep brain stimulation may be effective but is rarely required.

PAINFUL LEGS AND MOVING TOES

Another uncommon but well-defined movement disorder of the lower limbs has been termed *painful legs and moving toes.* Patients typically complain of a deep pulling or searing pain in the lower limbs, associated with continuous involuntary wriggling or writhing of the toes. Occasionally, the ankle and less commonly more proximal muscles of the legs are involved. Rarely, a similar problem is seen in the upper limbs as well. Although a peripheral nerve trigger, such as a radiculopathy, may be evident, the pain and movements probably are generated centrally in the spinal cord or brainstem. Various treatments have been tried without much benefit to the pain, which is typically the major concern of the patient.

OTHER ABNORMAL MOVEMENTS

Numerous abnormal movements are caused by dysfunction of the peripheral nerves (e.g., fasciculations, myokymia); these movements are usually easily separated from the movement disorders described earlier. *Hemifacial spasm* is a common disorder in which irregular clonic and tonic movements involve

TABLE 379-7 DIFFERENTIAL DIAGNOSIS OF ADULT-ONSET ATAXIA

Inherited
Autosomal dominant, including the spinocerebellar ataxias (SCAs)
Autosomal recessive, including Friedreich ataxia
X-linked, including fragile X tremor ataxia syndrome (FXTAS)
Mitochondrial
Episodic ataxias
Ataxia telangiectasia
Autoimmune (e.g., paraneoplastic, anti-GAD antibodies, postinfectious)
Degenerative (e.g., multiple system atrophy [MSA-C])
Demyelinating (e.g., multiple sclerosis)
Infectious
Metabolic (e.g., hypothyroidism, vitamin E deficiency)
Stroke
Trauma (e.g., closed head injury)
Toxic (e.g., alcoholic cerebellar degeneration, lithium)
Tumor: Primary and secondary brain tumors

GAD = glutamate decarboxylase.

the muscles innervated by the facial nerve, usually owing to compression of the seventh nerve as it exits the brainstem, most often by a normal small artery or vein and less often by a mass lesion or inflammatory process. Eyelid twitching is usually the first symptom, followed at variable intervals by lower facial muscle involvement. MRI with careful assessment of the posterior fossa is necessary to exclude secondary causes. Treatment usually involves injections of botulinum toxin into selected facial muscles, although surgical decompression can be curative (Video 379-13).

CEREBELLAR ATAXIAS AND SPASTIC PARAPLEGIAS

There are an extremely large number of causes of cerebellar ataxia (Table 379-7). Many are hereditary, with the full spectrum of possible inheritance patterns. Sporadic or noninherited ataxias are common; in many cases, a cause can be defined and treatment may be effective in halting or even reversing the process. However, a large proportion of ataxias in adults are progressive, presumably owing to a degenerative cause, many of which remain to be determined.

HEREDITARY CEREBELLAR ATAXIAS

The hereditary cerebellar ataxias, which may begin in childhood or adulthood, can progress at widely varying rates. During the preclinical stage, subtle abnormalities may be detected on a careful clinical examination.[23] These ataxias are divided into early-onset ataxias, which are usually inherited as autosomal recessive disorders, and adult-onset ataxias, which are usually autosomal dominant. A small number are X-linked.[24] Because most of these ataxias are untreatable, it is important to recognize the rare causes of treatable or preventable progressive ataxias.

Friedreich Ataxia

EPIDEMIOLOGY AND PATHOBIOLOGY

The most common progressive inherited ataxia in children is Friedreich ataxia. Friedreich ataxia is a trinucleotide-repeat disorder that affects the central and peripheral nervous systems, the heart, and many other organs. Friedreich ataxia is an autosomal recessive disorder with no anticipation. It has an estimated carrier frequency in the population of approximately 1 in 100 and a resulting disease prevalence of approximately 1 per 50,000.

The normal length of the GAA repeat on the long arm of chromosome 9 (9q13-q21) is 10 to 21 copies, but expansion in individuals with Friedreich ataxia results in 200 to 900 copies and disrupts the expression of the protein frataxin. GAA unstable expansion, which occurs on an intron, leads to gene silencing rather than to the production of an abnormal protein. Higher numbers of copies correlate with more severe neurologic deficits. Frataxin appears to be critical for iron export and mitochondrial function. Because accumulation of mitochondrial iron affects the production of oxygen radicals, loss of frataxin may lead to oxidative mitochondrial damage. The pathology of Friedreich ataxia includes spinal cord atrophy, which often is evident on MRI, with loss of neurons in Clarke columns and the dorsal root ganglia. Degeneration occurs in spinocerebellar tracts, pyramidal tracts, dorsal column tracts, and peripheral nerves, with minor cell loss in the brainstem and cerebellum. Cardiomyopathy is associated with ventricular hypertrophy and chronic interstitial myocardial fibrosis.

CLINICAL MANIFESTATIONS AND DIAGNOSIS

Typical Friedreich ataxia first manifests clinically during puberty with progressive ataxia, loss of lower extremity deep tendon reflexes, and extensor plantar responses (i.e., Babinski signs). Other common clinical features include nystagmus, dysarthria, stocking-glove sensory loss, and weakness in the lower extremities. Patients frequently have kyphosis, scoliosis, and pes cavus. Interstitial myocardial disease may cause a typical hypertrophic cardiomyopathy (Chapter 47). A small number of patients have a later onset and a less severe and progressive course, sometimes with retained or even brisk reflexes.

The diagnosis is made by genetic testing for the trinucleotide repeat expansion, which usually is present on at least one allele. Point mutations are sometimes present in the other allele and are more difficult to detect. Potentially treatable conditions with similar clinical manifestations include vitamin B_{12} deficiency (Chapter 199), abetalipoproteinemia (Chapter 126), and a selective defect in vitamin E absorption (Chapter 199).

TREATMENT AND PROGNOSIS

No effective disease-modifying treatments are available, so treatment consists of supportive measures. Intensive inpatient rehabilitation can improve overall function. Nicotinamide can increase frataxin concentrations, but whether it alters the clinical course of the disease is unproven. Future treatments may include histone deacetylase inhibitors that may increase frataxin gene expression.[25] The disorder is progressive,[26] and patients usually are wheelchair bound by their mid-20s. The average age at death is 37 years, and the major cause of death is hypertrophic cardiomyopathy (Chapter 47).

Other Spinocerebellar Ataxias

The hereditary spinocerebellar ataxias are routinely classified by their specific molecular diagnosis. At least 20 autosomal recessive and more than 35 autosomal dominant cerebellar ataxias have been identified. Clinical features, ethnic origin, and family history may suggest an autosomal recessive, autosomal dominant, or X-linked inheritance and often narrow the search for the genetic mutation. As the molecular pathogenesis of many of the hereditary ataxias is unraveled, the current numerical classification, which largely reflects the chronology of the identification of causative mutations, is likely to be replaced by a gene-specific or pathophysiologic approach. Spinocerebellar ataxias 1, 2, 3, 6, 7, and 17 are caused by trinucleotide expansions in or adjacent to a protein-coding region of a gene. These expansions result in polyglutamine expansions in the protein product, which likely results in a toxic gain of function in a manner analogous to the pathogenesis of Huntington disease. Approximately 40 spinocerebellar ataxias have been described, but clear genotype-phenotype associations have not been confirmed for every type.[27]

CLINICAL MANIFESTATIONS AND DIAGNOSIS

The predominant clinical features of the spinocerebellar ataxias are ataxia and dysarthria. Other cerebellar signs include titubation, dysdiadochokinesia, and dysmetria. With increasing ataxia, patients can become wheelchair bound. Additional clinical signs include ophthalmoplegia, dementia, optic atrophy, retinal pigmentary degeneration, deafness, dysphagia, and peripheral neuropathy. Extrapyramidal features include masked facies, cogwheel rigidity, dystonia, athetosis, and chorea. Levodopa-responsive parkinsonism (Chapter 378) may be seen in some patients, particularly in spinocerebellar ataxias 2 and 3. Pyramidal dysfunction includes spastic limbs, especially legs; hyperreflexia; and Babinski response. Diagnosis is based on genetic testing.

TREATMENT AND PROGNOSIS

In a small randomized trial, varenicline (a partial agonist of 24β2 neuronal nicotinic acetylcholine receptors, at 1 mg/day for 2 weeks, then 2 mg/day) improved gait, stance, and timed 25-foot walk but did not improve appendicular function, except for rapid alternating movements, in adults with genetically confirmed SCA3. However, these results have not been reproduced, and the drug is often poorly tolerated. Docosahexaenoic acid (600 mg daily) is effective for spinocerebellar ataxia 38, in which polyunsaturated fat metabolism is altered.[28] No treatment is currently available for the other spinocerebellar ataxias, although preliminary data indicate that physiotherapy may improve gait and balance. Cerebello-spinal direct current stimulation is a potential new option for the neurodegenerative ataxias.[A7] The spinocerebellar ataxias are progressive, with worsening gait, hand coordination, speech, and eye movements, but with preserved mental function in most forms. Pneumonia is a common cause of death.

HEREDITARY SPASTIC PARAPLEGIAS

Hereditary spastic paraplegias, also known as Strümpell disease, are a group of clinically and genetically heterogeneous monogenic neurodegenerative disorders. The prevalence is approximately 1 per 10,000 in the population. Over 70 different genetic loci have been identified; approximately 20 autosomal dominant, over 45 autosomal recessive, 5 X-linked, and 1 a maternal trait of inheritance. The most common forms of hereditary spastic paraplegia are autosomal dominant mutations in one of four proteins: spastin (SPG4), atlastin-1 (SPG3A), *REEP1* (SPG31), and reticulon-2 (SPG12). These proteins are involved in the endoplasmic reticulum network, whose morphology and distribution in neurons has a special importance for their normal function. Defects of ganglioside biosyntheses and defects in glucocerebrosidase functions are present in some forms. At autopsy, patients with hereditary spastic paraplegia have axonal degeneration of the pyramidal tracts and dorsal column tracts with lesser involvement of the spinocerebellar tracts. The neurons of origin are intact. The peripheral nervous system is unaffected.

CLINICAL MANIFESTATIONS

Patients with hereditary spastic paraplegia have a progressive gait disturbance with spasticity of lower extremities, hyperreflexia, clonus, and extensor plantar responses. Cranial nerves, speech, swallowing, and upper extremities remain normal. Although patients can experience weakness of their lower extremities, spasticity is usually the disabling component. The progressively increased leg spasticity results in tripping and an inability to run. Pain is infrequent, and sensation is normal. Other clinical features include pes cavus (30 to 50%), decreased vibratory sensation, and urinary frequency, urgency, and hesitancy. Pure hereditary spastic paraplegia is limited to symptoms and signs of spasticity, whereas complex or complicated hereditary spastic paraplegia can include cognitive impairment, dementia, epilepsy, extrapyramidal disturbances, cerebellar involvement, retinopathy, optic atrophy, deafness, polyneuropathy, or skin lesions.

DIAGNOSIS

Hereditary spastic paraplegia is diagnosed when patients meet clinical criteria and when other causes of spasticity are excluded. MRI may show spinal cord atrophy, but cerebrospinal fluid analysis and nerve conduction studies are normal. The differential diagnosis of spastic paraplegia includes other genetic conditions, spinal cord disease from structural lesions, multiple sclerosis, and vitamin deficiencies or retroviral infections (Table 379-8). Even a positive family history does not obviate the need to exclude potentially treatable alternative diagnoses.

TREATMENT AND PROGNOSIS

No specific treatment is available. Symptomatic therapy is aimed at decreasing disability and preventing complications, such as contractures. Antispastic agents, such as oral baclofen (usually 10 to 20 mg three times daily), improve spasticity but should be used with caution because they may worsen weakness. Some reports suggested an improved therapeutic response to intrathecal baclofen, but no controlled trials have addressed this issue. Preliminary data also raise the possible utility of injected botulinum neurotoxin type A injections for improving spasticity. Most patients become nonambulatory between 60 and 70 years of age. Patients with complicated hereditary spastic paraplegia often have other disabling features. Some patients with parkinsonism may benefit from dopaminergic therapies such as levodopa.

TABLE 379-8 DIFFERENTIAL DIAGNOSIS OF SPASTIC PARAPLEGIAS

- Hereditary
  - Dopa-responsive dystonia
  - Spinocerebellar ataxias
  - Adult-onset adrenoleukodystrophy (Chapters 208 and 380)
- Structural lesions of the spinal cord (Chapter 369)
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- Infections
  - Human immunodeficiency virus (Chapter 359)
  - Human T-lymphotropic virus type 1 (Chapter 360)
  - Tertiary syphilis (Chapter 295)

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380 MULTIPLE SCLEROSIS AND DEMYELINATING CONDITIONS

PETER A. CALABRESI

The disorders of myelin encompass a wide range of diseases in which myelin is not produced (hypomyelination), myelin is not formed in a normal fashion (dysmyelinating disease), or normally formed myelin is destroyed or not maintained appropriately (demyelinating disease and myelinolysis) (Table 380-1). Hypomyelinating and dysmyelinating diseases are uncommon and include an array of leukodystrophies that have a genetic basis and may affect the formation of myelin as a primary or secondary result. Demyelinating diseases are much more common and include multiple sclerosis, which represents more than 95% of all types of disorders of central nervous system (CNS) myelin.

Some disorders of myelin have a distinct pathogenesis in which the disruption of myelin is secondary. Further, in many of the diseases of myelin, the axon degenerates as a result of decreased trophic support from loss of myelin, impaired health of the oligodendrocyte, or increased susceptibility to injury in the absence of myelin. This observation led to the recent hypothesis that axonal loss is the underlying substrate for permanent disability in multiple sclerosis, adrenoleukodystrophy, and perhaps other diseases of myelin.

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EPIDEMIOLOGY

The annual incidence of multiple sclerosis varies by location, and estimates range between 1.5 and 11 per 100,000 people. Multiple sclerosis is second only to trauma as the most common cause of neurologic disability in young adults. Recent studies suggest that the incidence rate has increased, in part because of recognition of more cases at an earlier stage, but probably also because of a truly rising incidence, especially in women. The prevalence is

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HEREDITARY SPASTIC PARAPLEGIAS

Hereditary spastic paraplegias, also known as Strümpell disease, are a group of clinically and genetically heterogeneous monogenic neurodegenerative disorders. The prevalence is approximately 1 per 10,000 in the population. Over 70 different genetic loci have been identified; approximately 20 autosomal dominant, over 45 autosomal recessive, 5 X-linked, and 1 a maternal trait of inheritance. The most common forms of hereditary spastic paraplegia are autosomal dominant mutations in one of four proteins: spastin (SPG4), atlastin-1 (SPG3A), *REEP1* (SPG31), and reticulon-2 (SPG12). These proteins are involved in the endoplasmic reticulum network, whose morphology and distribution in neurons has a special importance for their normal function. Defects of ganglioside biosyntheses and defects in glucocerebrosidase functions are present in some forms. At autopsy, patients with hereditary spastic paraplegia have axonal degeneration of the pyramidal tracts and dorsal column tracts with lesser involvement of the spinocerebellar tracts. The neurons of origin are intact. The peripheral nervous system is unaffected.

CLINICAL MANIFESTATIONS

Patients with hereditary spastic paraplegia have a progressive gait disturbance with spasticity of lower extremities, hyperreflexia, clonus, and extensor plantar responses. Cranial nerves, speech, swallowing, and upper extremities remain normal. Although patients can experience weakness of their lower extremities, spasticity is usually the disabling component. The progressively increased leg spasticity results in tripping and an inability to run. Pain is infrequent, and sensation is normal. Other clinical features include pes cavus (30 to 50%), decreased vibratory sensation, and urinary frequency, urgency, and hesitancy. Pure hereditary spastic paraplegia is limited to symptoms and signs of spasticity, whereas complex or complicated hereditary spastic paraplegia can include cognitive impairment, dementia, epilepsy, extrapyramidal disturbances, cerebellar involvement, retinopathy, optic atrophy, deafness, polyneuropathy, or skin lesions.

DIAGNOSIS

Hereditary spastic paraplegia is diagnosed when patients meet clinical criteria and when other causes of spasticity are excluded. MRI may show spinal cord atrophy, but cerebrospinal fluid analysis and nerve conduction studies are normal. The differential diagnosis of spastic paraplegia includes other genetic conditions, spinal cord disease from structural lesions, multiple sclerosis, and vitamin deficiencies or retroviral infections (Table 379-8). Even a positive family history does not obviate the need to exclude potentially treatable alternative diagnoses.

TREATMENT AND PROGNOSIS

No specific treatment is available. Symptomatic therapy is aimed at decreasing disability and preventing complications, such as contractures. Antispastic agents, such as oral baclofen (usually 10 to 20 mg three times daily), improve spasticity but should be used with caution because they may worsen weakness. Some reports suggested an improved therapeutic response to intrathecal baclofen, but no controlled trials have addressed this issue. Preliminary data also raise the possible utility of injected botulinum neurotoxin type A injections for improving spasticity. Most patients become nonambulatory between 60 and 70 years of age. Patients with complicated hereditary spastic paraplegia often have other disabling features. Some patients with parkinsonism may benefit from dopaminergic therapies such as levodopa.

TABLE 379-8 DIFFERENTIAL DIAGNOSIS OF SPASTIC PARAPLEGIAS

- Hereditary
  - Dopa-responsive dystonia
  - Spinocerebellar ataxias
  - Adult-onset adrenoleukodystrophy (Chapters 208 and 380)
- Structural lesions of the spinal cord (Chapter 369)
- Cervical spondylosis (Chapter 369)
- Tumor (Chapter 164)
- Arteriovenous malformation (Chapter 377)
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Some disorders of myelin have a distinct pathogenesis in which the disruption of myelin is secondary. Further, in many of the diseases of myelin, the axon degenerates as a result of decreased trophic support from loss of myelin, impaired health of the oligodendrocyte, or increased susceptibility to injury in the absence of myelin. This observation led to the recent hypothesis that axonal loss is the underlying substrate for permanent disability in multiple sclerosis, adrenoleukodystrophy, and perhaps other diseases of myelin.

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ABSTRACT

Multiple sclerosis remains by far the most common demyelinating condition and should be considered in any young adult with episodic neurologic symptoms referable to the central nervous system (CNS) in whom no better explanation can be ascertained. Although the diagnosis of multiple sclerosis can be made on clinical grounds alone, diagnostic criteria now incorporate the results of MRI, exclusionary criteria, and sometimes cerebrospinal fluid analysis to avoid misdiagnosis. Several new therapies exist for reducing relapses and one of these strategies, B-cell depletion with anti-CD20 monoclonal antibody (Ocrelizumab), became the first treatment approved for primary progressive multiple sclerosis. Side effects, including infections secondary to immune suppression, mandate vigilance in treatment monitoring for all of the new-high potency drugs. Leukodystrophies, which can cause dysfunction of any types of cells in the CNS, have a variable prognosis, with late-onset forms having milder phenotypes, but remain largely untreatable.

KEYWORDS

demyelination
multiple sclerosis
leukodystrophy
neuromyelitis spectrum disorder
immune suppression
CSF
MRI

TABLE 380-1 DISEASES OF MYELIN

IDIOPATHIC
Recurrent or chronic progressive demyelination (multiple sclerosis and its variants)
Monophasic demyelination (may be the first clinical episode of multiple sclerosis)
Optic neuritis
Acute transverse myelitis
Acute disseminated encephalomyelitis; acute hemorrhagic leukoencephalopathy, neuromyelitis optica spectrum disorder
VIRAL INFECTIONS
Progressive multifocal leukoencephalopathy
Subacute sclerosing panencephalitis (Chapter 338)
NUTRITIONAL AND METABOLIC DISORDERS (CHAPTER 384)
Combined systems disease (vitamin B_{12} deficiency)
Copper deficiency (dorsal columns and subacute optic neuropathy)
Demyelination of the corpus callosum (Marchiafava-Bignami disease)
Central pontine myelinolysis
ANOXIC-ISCHEMIC SEQUELAE (CHAPTER 373)
Delayed postanoxic cerebral demyelination
Progressive subcortical ischemic encephalopathy
LEUKODYSTROPHIES PRIMARILY AFFECTING CENTRAL NERVOUS SYSTEM MYELIN
Adrenoleukodystrophy (Schilder disease)
Pelizaeus-Merzbacher disease (sudanophilic leukodystrophies)
Spongy degeneration
Vanishing white matter disease
Others (Alexander disease, Canavan disease)
Leukodystrophies of the central and peripheral nervous system
Metachromatic leukodystrophy
Globoid cell leukodystrophy (Krabbe disease)

estimated at 309 per 100,000 in the adult U.S. population, which translates to about 730,000 cases in the United States and approximately 2.8 million worldwide, but these numbers may be underestimates owing to incomplete recognition of the disease, even in developed countries, and the higher incidence in young people.

Multiple sclerosis occurs 2- to 2.5-fold more frequently in women than in men, a sex predilection that is common in autoimmune diseases. The disease most often manifests in the third to fourth decades of life, but with an incidence age range from postpubertal teenagers to persons in their 50s. Rare cases occur in infants or in patients in their 60s, but extreme caution is warranted in these situations to exclude alternative processes. In many of the late-onset multiple sclerosis cases, symptoms were present in younger years and were attributed to other causes.

In many areas of the world, multiple sclerosis is more prevalent in temperate latitudes (approaching 1 in 500 in some locations) and becomes less common toward the Equator (1 in 20,000 or rare case reports only in some locations), perhaps explained in part by migration patterns of people with the same gene pools. However, the absence of complete genetic penetrance in monozygotic twin studies and recent increases in incidence in genetically stable populations strongly suggest an environmental component to the disease. Indeed, an outbreak of multiple sclerosis was documented on the Faroe Islands following World War II, and numerous other clusters have been reported, although a single environmental trigger has not been identified.

Several studies have linked cigarette smoking and childhood obesity with an increased risk for multiple sclerosis. High levels of vitamin D and early exposure to excessive sunlight (sunburns) have been linked with lower risk for multiple sclerosis, possibly related to the beneficial effects of cholecalciferol (vitamin D) on regulating immune cell responses.

PATHOBIOLOGY

Genetics

Monozygotic twins with multiple sclerosis show a concordance rate of between 15 and 50%, compared with only 3 to 5% concordance in dizygotic twins, consistent with a strong but incomplete role for genes in causing multiple sclerosis. The lifetime risk is increased to 2 to 4% in individuals with a first-degree relative with multiple sclerosis, compared with the general population risk of 0.1%. In addition, between 10 and 20% of patients have a first-degree relative with another autoimmune disease, commonly rheumatoid arthritis, systemic lupus erythematosus, or autoimmune thyroid disease. Psoriasis (Chapter 405) and inflammatory bowel disease (Chapter 127) also may be more common in patients with multiple sclerosis. Genetic modeling of the disease strongly argues against a single gene and suggests that many different genes predispose to multiple sclerosis and account for its many phenotypes and its overlap with other autoimmune diseases.[1] Linkage and association studies have identified the human leukocyte antigen (HLA) or major histocompatibility complex (MHC) region on chromosome 6p21 as one genetic determinant for multiple sclerosis. The MHC class II region, involved in presentation of antigen to $CD4^+$ T cells, is the most strongly associated locus. The HLA-DR2 allele and, more specifically, the molecular haplotype HLA-DRB1*1501 allele have repeatedly been implicated. Multiple single-nucleotide polymorphisms (SNPs) in the interleukin-2 (IL-2) receptor-α gene and the IL-7 receptor-α gene also appear to be associated with a higher risk for multiple sclerosis. Over 200 other gene SNPs have been identified, most of which are related to immune function. Although patterns are emerging to suggest dysregulation of differing immune cell subsets, the associations to date are not strong enough to have clinical predictive value.

Pathology

Most cases are characterized by multifocal areas of demyelination and gross gliotic scar in the brain and spinal cord. Classic locations of these lesions, called *plaques* are the optic nerves, periventricular white matter, deep white matter, juxtacortical white matter, corpus callosum, cerebellar peduncles, and dorsolateral spinal cord. However, there is a bias toward recognition of lesions in white matter because of the relative ease of detecting demyelination and inflammation in white compared with gray matter by magnetic resonance imaging. Indeed, more recent pathologic studies have confirmed demyelination, neuritic damage, and atrophy in the cerebral cortex (pial surface and intracortical or juxtacortical) and deep gray matter structures, especially the thalamus. At the microscopic level, one usually sees multiple areas of perivenular inflammatory cell infiltrates with extravasation into the surrounding tissue parenchyma. In the acute active plaque, CD4 helper T (T_H) cells are prominent in the perivenular areas. Pro-inflammatory cytokines released from T_H1 (interferon-γ [IFN-γ]) and T_H17 (IL-17, tumor necrosis factor [TNF], and granulocyte-macrophage colony-stimulating factor [GM-CSF]) cells are thought to mediate damage. Increasingly, large numbers of CD8 cytotoxic T cells have been documented in brain tissue, especially in the parenchyma, and these cells may mediate direct damage to axons and oligodendrocytes through release of proteases such as granzyme B. Most parenchymal inflammatory cells, especially in chronic plaques, are $CD68^+$ macrophages and microglia. In addition to the influx of circulating immune cells, prominent astroglial activation and in some cases oligodendrocyte precursor cell differentiation occur in response to injury. Over time, the inflammation becomes less prominent in the center of the plaque, but a chronic active rim of inflammation with microglial activation exists at a well-demarcated border between abnormal and normal unharmed myelin. This characteristic of multiple sclerosis is seldom seen in other disorders of myelin. Although oligodendrocytes may survive, proliferate, and result in partial remyelination (shadow plaques) in some early cases, this process is hardly ever complete in multiple sclerosis. Over time, remyelination is less successful, and oligodendrocyte precursor cells appear unable to differentiate into mature myelinating oligodendrocytes.

The number of damaged axons correlates with the extent of inflammation. Further, axonal damage and even neuronal apoptosis and loss are seen in the cortex and retina. Atrophy of both the brain and spinal cord, which occurs more rapidly in multiple sclerosis than in normal aging, reflects loss of both myelin and axons.

Seroconversion, especially to Epstein-Barr virus,[2] has been associated with a 32-fold increased risk of developing multiple sclerosis, and it may be a necessary trigger, perhaps through molecular mimicry, but is not sufficient for disease. Differential expression of human herpesvirus type 6, which is acquired by most people in childhood, has been noted in oligodendrocytes of patients with multiple sclerosis, but whether this virus is a cofactor in demyelination or just a bystander remains unclear. Evidence suggests the possibility that the earliest event may be an insult to the oligodendrocytes, with subsequent activation of resident immune cells and secondary recruitment of other immune cells only at later stages.

Some pathologists think that four distinct subtypes of multiple sclerosis can be discerned, thereby allowing patients to be classified with differing pathologic categories rather than just describing the evolution of lesions over time. Type I lesions are characterized by typical perivenular inflammatory infiltrates consisting mainly of T cells, with early preservation of oligodendrocytes. Type II lesions are similar to type I but have an additional humoral

component with immunoglobulin G (IgG) deposition and complement activation. Type III lesions are distinguished by not being based around venules and by prominent loss of myelin-associated glycoprotein, with evidence for oligodendrocyte apoptosis. Type IV lesions have inflammatory infiltrates more similar to those in types I and II but also have oligodendrocyte loss as in type III. These varying pathologic features may begin to explain clinical subtypes of the disease.

Pathogenesis

It remains possible that the autoimmune hypothesis is wrong and that the inflammation observed in multiple sclerosis is secondary to an as yet uncharacterized primary degenerative process. Proponents of this theory cite evidence from pathologic features of hyperacute cases, in which the oligodendrocytes appear to die before any systemic immune response occurs, as well as recent data revealing neuronal and axonal death or demyelination in the absence of inflammation.

Macrophages and microglia, which make up the majority of cells within the parenchymal infiltrate in chronic multiple sclerosis plaques, are potent antigen-presenting cells and express HLA and costimulatory molecules. Activated macrophages and microglia also have effector functions, including release of cytokines that are partly (IL-6, TNF-α) or completely distinct from the T cells (IL-1β, IL-12, and IL-23). In high concentrations, these cytokines may damage oligodendrocytes and neurons and activate T cells. Reactive astrogliosis, which is also a hallmark of multiple sclerosis plaques, is characterized by loss of homeostatic astrocytic function and gain of neurotoxic properties.

CLINICAL MANIFESTATIONS

Presenting Symptoms

Multiple sclerosis, which can manifest in many ways across a broad age range, may initially masquerade as a variety of different illnesses (Table 380-2; see Table 380-1).[3] In a classic presentation, a young person, more often a woman, will have the acute to subacute onset of impaired vision or sensation. Fatigue, depression, bladder urgency, weakness, impaired balance, and impaired coordination also are common symptoms. The often remarkably mild nature of the first symptoms frequently dissuades the patient from seeking medical attention or is insufficiently impressive to stimulate the physician to order diagnostic tests. Furthermore, patients may initially have few objective neurologic findings, especially between attacks.

Paresthesias of a limb that are circumferential and do not follow a dermatome suggest a spinal cord lesion; these symptoms often manifest distally and then ascend to involve more proximal parts of the limb, spread to the contralateral limb, or progress from a leg to an arm. Similarly, bandlike painful sensations around a limb or the torso also suggest a myelopathic process.

Incomplete transverse myelitis is a focal (partial) spinal cord syndrome that is usually inflammatory and does not follow vascular territories. It is a common presentation of multiple sclerosis.

Lhermitte sign, an electrical sensation moving down the spine into the limbs on flexion of the neck, is characteristic of cervical myelitis from any cause, including multiple sclerosis. Frank loss of sensation is less common as an early symptom or sign but is seen in more advanced cases. Burning, electrical, or deep aching sensations are also common in multiple sclerosis.

Sensory Abnormalities

On examination, the most common sensory findings are loss of vibration perception, most prominent in the feet, and incomplete spinal cord levels to pinprick or vibration, which are often more notable in a graded fashion rather than at a distinct level. Such sensory levels may be asymmetrical and differ by sensory modality because of isolated demyelination in the dorsal columns compared with the spinothalamic tracts. Patchy or seemingly nonanatomic focal areas of impaired sensation can occur, and some patients describe bizarre sensations such as water dripping or bugs crawling on an area of the body.

Visual Effects

Optic neuritis (Chapter 392) is a classic manifesting syndrome, typically with visual symptoms in one eye. In optic neuritis, patients often complain of pain over the temporal eyebrow and worsening on lateral eye movement. The visual impairment may be described as looking through frosted glass or a veil. The scotoma or area of greatest loss often can be mapped in a centrocecal distribution (central focal point to the blind spot laterally), which in mild cases may be evident only as desaturation to red color using the head of a pin. More severe cases may result in total loss of light perception. In most acute cases of optic neuritis, the inflammation is retrobulbar (behind the disc), so no immediate changes are visible on the optic disc, thereby leading to the aphorism "the patient sees nothing, and the doctor sees nothing." However, there should be a relative afferent papillary defect (Marcus-Gunn pupil; Chapter 392) with paradoxical dilation of the affected eye to direct light on swinging a flashlight from the unaffected eye in which consensual constriction was induced. In cases of bilateral optic neuritis (new or old), this abnormality may not be seen. Patients usually spontaneously recover substantial vision after weeks to months. Later, the optic disc may become pale, especially in the temporal region, a finding reflecting damage to the axons following inflammation and demyelination, even with recovery of normal visual acuity. Patients often have more subtle chronic visual impairment for colors, low-contrast visual acuity, and contrast sensitivity. Visual testing using low-contrast letter acuity charts commonly reveals substantial visual loss after clinical optic neuritis, which manifests clinically as nyctalopia (night blindness).

Visual impairment from impaired tracking of eye movements owing to brain stem or cerebellar disease most commonly occurs in the setting of an acute lesion affecting the medial longitudinal fasciculus, which is the neurologic pathway that yokes the eyes together on lateral saccades. Patients may experience frank diplopia or just blurred vision, especially when they look off to one side rapidly, such as when looking over one's shoulder while driving. The neurologic sign of this problem is called *internuclear ophthalmoplegia* (Chapter 392) and manifests as slowed or absent adduction of one eye with abducting nystagmus of the other eye. It may occur bilaterally or may exist in milder forms, such that the adduction lag is imperceptible to the

TABLE 380-2 CONDITIONS THAT CAN BE MISTAKEN FOR MULTIPLE SCLEROSIS AND OTHER DISEASES OF MYELIN

VASCULAR DISEASE
Small-vessel cerebrovascular disease
Vasculitides
Arteriovenous malformation
CADASIL, CARASIL, COL4A1
Antiphospholipid antibody syndrome
STRUCTURAL LESIONS
Craniocervical junction, posterior fossa, or spinal tumors
Cervical spondylosis or disc herniation
Chiari malformation or syrinx
DEGENERATIVE DISEASES
Hereditary myelopathy
Hereditary neuropathy
Spinocerebellar degeneration
INFECTIONS
HTLV-1 infection
HIV myelopathy or HIV-related cerebritis
Neuroborreliosis (e.g., Lyme disease)
JC virus/progressive multifocal leukoencephalopathy
Neurosyphilis
OTHER INFLAMMATORY CONDITIONS
Systemic lupus erythematosus
Sjögren syndrome
Sarcoidosis
Autoimmune encephalitis
MONOFOCAL OR MONOPHASIC DEMYELINATING SYNDROMES
Transverse myelitis
Optic neuritis
Neuromyelitis optica spectrum disorder and MOG antibody disorder
Acute disseminated encephalomyelitis
OTHER CONDITIONS
Hashimoto thyroiditis with or without encephalopathy
Nonspecific MRI abnormalities related to migraine, aging, or trauma
Leukodystrophy

CADASIL = cerebral autosomal dominant arteriopathy with subcortical infarcts and leukoencephalopathy; CARASIL = cerebral autosomal recessive arteriopathy with subcortical infarcts and leukoencephalopathy; COL4A1 = collagen type IV alpha 1 chain gene mutation; HIV = human immunodeficiency virus; HTLV = human T-cell lymphotropic virus; MOG = myelin oligodendrocyte glycoprotein; MRI = magnetic resonance imaging.

human observer. Blurred vision from cerebellar damage with nystagmus is very common and is often worse on extreme lateral or vertical gaze. *Oscillopsia,* which is the sensation that the environment is moving when it actually is not, is another symptom of impaired cerebellar coordination of the eyes. Saccadic eye movement or loss of smooth pursuit is common in multiple sclerosis and also can be seen in numerous neurologic conditions or with aging.

Motor Symptoms

The most common motor symptoms of multiple sclerosis are weakness and impaired coordination, in a leg, with ascending involvement from distal to proximal and commonly spreading to the contralateral leg or ipsilateral arm. The lesion causing these symptoms is more commonly in the cervical spinal cord rather than the thoracic spinal cord, even when the first sign is partial footdrop. It is likely that axons that must conduct impulses over the longest distance (entire length of the spinal cord) from a site of inflammatory demyelination will become symptomatic before axons delivering signals to closer synapses (adjacent anterior horn cells in the cervical cord). Clinically, the weakness may be severe and may result in an obvious paralysis or be so subtle as to be undetectable. Heat-induced fatigue and weakness, as manifested by focal symptoms (slapping of a foot or dragging a leg) occurring after 15 to 20 minutes of exercise and resolving with rest, are characteristic of early demyelinating disease. The early absence of associated hyperreflexia and plantar extensor responses (Babinski sign) may make it difficult to document corticospinal tract involvement. Later, in more established multiple sclerosis, classic corticospinal tract signs are often evident and manifest clinically as spastic gait (either hemiparetic or paraparetic), muscle cramps, and clonus (sustained reflex loop), sometimes occurring with positional changes and mistaken for signs of a cerebellar tremor. Some patients will lose reflexes.

Ataxia may occur as a result of impaired delivery of sensory information up the spinal cord or from demyelination of cerebellar pathways in the brain stem or cerebellum. Often, the two are mixed and may be confounded further by visual loss and impaired ability to compensate by fixing on the environment; this combination commonly causes dizziness in crowds, in which fixation may be further obscured. Appendicular dysmetria resulting in tremor on reaching for an object is a common cause of impaired coordination and dexterity. Lower extremity and truncal ataxia may result in a wide-based (drunk) gait. Other movement disorders, such as postural tremor and titubation (head tremor), are much less common. *Myokymia* (wormlike muscle movements) under the skin, especially around the face, however, is fairly common. Pseudoathetosis and parkinsonism can be seen in severe cases.

Cognitive and Behavioral Symptoms

Over 50% of patients with multiple sclerosis experience bouts of moderate-to-severe depression (Chapter 362). There is also increased incidence of bipolar disease, which may manifest after treatment of depression or treatment with corticosteroids. Pseudobulbar affect, either pathologic laughing or crying, is seen in patients with more advanced disease. Numerous cognitive symptoms, including short-term memory loss, word-finding difficulty, trouble with multitasking, and cognitive fatigue, may be mistaken for depression but are well-recognized primary symptoms of multiple sclerosis pathology. Most patients do not progress to dementia (Chapter 371), but cognitive and behavioral impairments are major causes of loss of employment and quality of life.

Organ Dysfunction

Bladder symptoms are extremely common, but often are not volunteered, so specific questions must be asked concerning urinary frequency, urgency, incontinence, or retention. Careful discrimination of a spastic bladder (detrusor muscle spasm) causing incontinence from an atonic bladder or spasm of the external sphincter (the latter two causing retention) leading to overflow incontinence is critical to designing treatment (Chapter 115). Urinary tract infections (Chapter 263) owing to bladder dysfunction may aggravate symptoms of multiple sclerosis.

Bowel dysfunction commonly manifests as constipation (Chapter 122), which may be primary (related to spinal cord involvement) or secondary (related to self-induced dehydration to manage urinary frequency or to side effects of anticholinergic drugs). Bowel incontinence secondary to an incompetent anal sphincter is less common and most often occurs as an isolated episode of fecal urgency, sometimes related to dietary change or diarrheal illness, or as a sequela of prolonged compaction.

Sexual dysfunction is common and underdiscussed in multiple sclerosis. In men, erectile dysfunction is frequent. In women and men, loss of libido and inability to achieve orgasm can occur as a result of medication, loss of sensation, heat-induced worsening of symptoms, physical barriers to intercourse (impaired mucosal moisture, spasticity, and pain), depression, or disorders of body image.

Systemic Symptoms

Fatigue, which is common, may be linked to depression but often occurs independently and can be the most disabling symptom of the disease. A sleep history is important to exclude daytime fatigue resulting from disrupted sleep secondary to pain, cramps, bladder frequency, sleep apnea, periodic limb movements, depression, or disrupted sleep-wake cycles. Daytime fatigue even after a good night of sleep may occur in mid-afternoon and may be described as being "unplugged" or completely drained. Many patients obtain benefit from a short daytime nap.

Sensitivity to heat, which is a classic symptom of multiple sclerosis, occurs only in some patients. Even minor elevations of the body temperature can dramatically worsen symptoms (Uhthoff phenomenon). Some patients complain of worsened symptoms in cold weather, likely related to increased dysfunction of already stiff muscles or signal blockade consistent with the known physiology of nerve conduction, which has an inverted U-shaped temperature versus conduction curve.

Pregnancy

Women with multiple sclerosis may have children, and the activity of disease typically lessens during the course of pregnancy, especially by the third trimester, when the frequency of exacerbations is reduced by approximately two thirds. Relapses are more frequent in the first 6 postpartum months, but no evidence indicates that pregnancy changes the natural history of the disease. Whether breast-feeding alters the course of multiple sclerosis is unclear, but it is contraindicated for patients who resume disease-modifying drugs following delivery.

Types of Multiple Sclerosis

The three major clinical types of multiple sclerosis are relapsing remitting, secondary progressive, and primary progressive. Approximately 85 to 90% of patients present with relapsing-remitting multiple sclerosis, characterized by acute or subacute episodes of new or worsening old neurologic symptoms that increase in severity, plateau, and then partly or completely remit. Patients may have no detectable residual deficit, or they may accumulate significant permanent disability from an attack. Many patients with relapsing-remitting multiple sclerosis will convert to secondary progressive multiple sclerosis after 20 to 40 years. This stage of the disease, which is characterized by at least 6 months of progressive worsening without evidence of a relapse, can be diagnosed with confidence only retrospectively. Some patients with secondary progressive multiple sclerosis also have interposed relapses (called active secondary progressive multiple sclerosis) distinct from their periods of progressive worsening, although these episodes become less frequent with time. Primary progressive multiple sclerosis, which is characterized by progressive deterioration from the onset for at least 1 year without a history of distinct relapses, occurs in approximately 10 to 15% of patients. It is more common in middle-aged men and typically has more involvement of the spinal cord and fewer inflammatory brain lesions.

Acute progressive multiple sclerosis (Marburg disease) causes acute or subacute progressive neurologic deterioration leading to severe disability within days to a month in a patient with no prior history of multiple sclerosis. This rare form of the disease may progress to a quadriplegic, obtunded state with death as a result of intercurrent infection, aspiration, or respiratory failure from brain stem involvement.

DIAGNOSIS

The diagnosis of multiple sclerosis rests on demonstrating evidence of at least two inflammatory demyelinating lesions referable to different locations within the CNS, occurring at different times (usually ≥1 month apart), and for which no better explanation exists. Diagnostic criteria allow for the diagnosis to be made on clinical grounds alone as long as appropriate exclusionary testing is performed (Table 380-3).[4] Clinical evidence of a lesion requires objective findings on examination, not just a symptom. Further, repeated episodes of neurologic dysfunction that could be explained based on one lesion (e.g., a cervicomedullary junction lesion causing brain stem, cerebellar, and corticospinal tract dysfunction) is not enough evidence to diagnose multiple sclerosis.

Magnetic Resonance Imaging

No definitive diagnostic laboratory test exists for multiple sclerosis, but magnetic resonance imaging (MRI) of the brain is extremely useful and should

be performed in all patients in whom multiple sclerosis is a diagnostic consideration.[5] More than 95% of patients with clinically definite multiple sclerosis have an abnormal brain MRI, and the presence of T2-weighted high-signal, bright lesions is so characteristic that a normal brain MRI should suggest an alternative diagnosis. Brain MRI is also useful in predicting future multiple sclerosis at the time of a clinically isolated demyelinating syndrome. Specific MRI findings allow for confirmation of disease disseminated in time and space (different parts of the brain or spinal cord) and fulfilling evidence for dissemination in time (see Table 380-4). Multiple sclerosis plaques typically appear as high-signal (white) areas on fluid attenuation inversion recovery (FLAIR) T2-weighted images, which allow for the best discrimination of the supratentorial lesions by suppressing high signal from cerebrospinal fluid (CSF) in the ventricles (Fig. 380-1). Lesions generally range in size from 2 mm to 2 cm; larger plaques occasionally resemble a tumor. Features of an MRI lesion suggesting multiple sclerosis include an elliptical shape, discrete borders, lack of mass effect, and gadolinium enhancement. Typical locations include the periventricular area (perpendicular to or abutting the walls of the ventricles) (Fig. 380-2), the corpus callosum, the cerebellar peduncles, the

TABLE 380-3 2017 REVISIONS TO THE MCDONALD DIAGNOSTIC CRITERIA FOR MULTIPLE SCLEROSIS

CLINICAL PRESENTATION	ADDITIONAL DATA NEEDED FOR DIAGNOSIS OF MULTIPLE SCLEROSIS
Two or more attacks; objective clinical evidence of two or more lesions; or one lesion with a prior attack	None*
Two or more attacks; objective clinical evidence of one lesion	Dissemination in space, demonstrated by: 1. MRI (see Table 380-4), or 2. Two or more MRI-detected lesions consistent with MS plus positive CSF specific oligoclonal bands, or 3. Await further clinical attack implicating a different site
One attack; objective clinical evidence of two or more lesions	Dissemination in time, demonstrated by: 1. MRI (see Table 380-4), or 2. Second clinical attack
One attack; objective clinical evidence of one lesion (monosymptomatic presentation; clinically isolated syndrome)	1. Dissemination in space, demonstrated by: a. MRI (see Table 380-4), or b. Two or more MRI-detected lesions consistent with MS plus positive CSF-specific oligoclonal bands, and 2. Dissemination in time, demonstrated by: a. MRI (see Table 380-4), or b. Second clinical attack or c. Demonstration of CSF-specific oligoclonal bands

*Must rule out other causes (e.g., see Table 380-2).
CSF = cerebrospinal fluid; MRI = magnetic resonance imaging; MS = multiple sclerosis.
Modified from Thompson AJ, Banwell BL, Barkhof F, et al. Diagnosis of multiple sclerosis: 2017 revisions of the McDonald criteria. *Lancet Neurol.* 2018;17:162-173.

TABLE 380-4 MAGNETIC RESONANCE IMAGING CRITERIA IN MULTIPLE SCLEROSIS (INTERNATIONAL PANEL RECOMMENDATIONS: 2017)

DISSEMINATION

Dissemination in space can be demonstrated by one or more T2-hyperintense lesions that are characteristic of multiple sclerosis in two or more of four areas of the CNS: periventricular, cortical or juxtacortical, and infratentorial brain regions, and the spinal cord.

Dissemination in time can be demonstrated by the simultaneous presence of gadolinium-enhancing and nonenhancing lesions at any time or by a new T2-hyperintense or gadolinium-enhancing lesion on follow-up MRI, with reference to a baseline scan, irrespective of the timing of the baseline MRI.

DIAGNOSIS OF PRIMARY PROGRESSIVE MULTIPLE SCLEROSIS

Primary progressive multiple sclerosis can be diagnosed in patients with:
- 1 year of disability progression (retrospectively or prospectively determined) independent of clinical relapse

Plus two of the following criteria:
- One or more T2-hyperintense lesions characteristic of multiple sclerosis in one or more of the following brain regions: periventricular, cortical or juxtacortical, or infratentorial
- Two or more T2-hyperintense lesions in the spinal cord
- Presence of CSF-specific oligoclonal bands

CNS = central nervous system; CSF = cerebrospinal fluid; MRI = magnetic resonance imaging.
From Thompson AJ, Banwell BL, Barkhof F, et al. Diagnosis of multiple sclerosis: 2017 revisions of the McDonald criteria. *Lancet Neurol.* 2018;17:162-173.

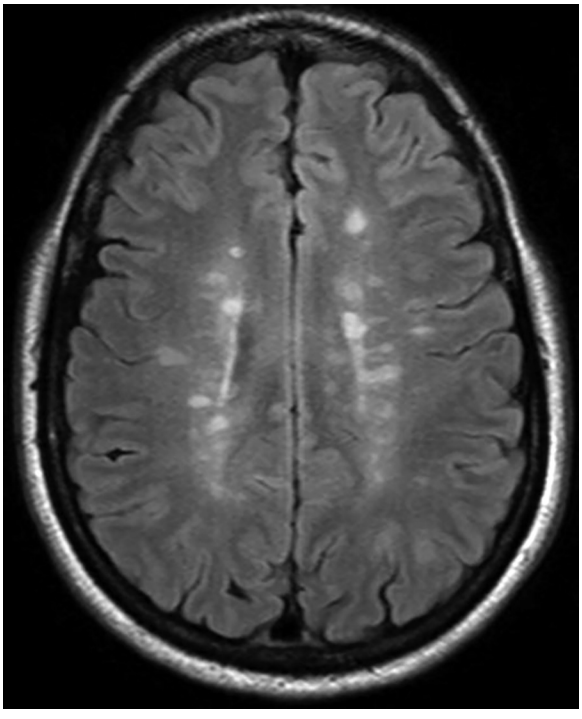

FIGURE 380-1. Axial fluid attenuation inversion recovery image of the brain from a patient with multiple sclerosis revealing classic multiple periventricular and deep white matter high-signal lesions.

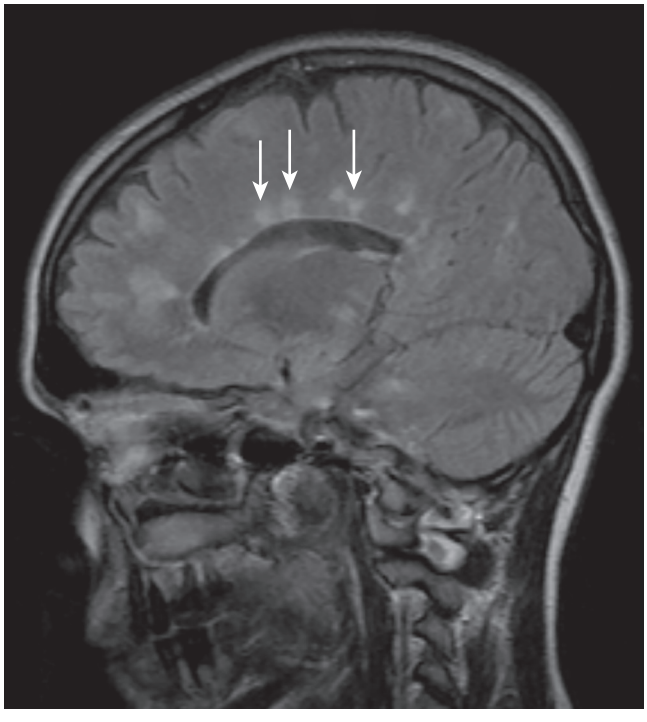

FIGURE 380-2. Sagittal fluid attenuation inversion recovery image of the brain from a patient with multiple sclerosis revealing classic periventricular lesions radiating outward from the ventricles *(arrows)*.

brain stem, the juxtacortical area, and the dorsolateral spinal cord (Fig. 380-3). Cortical and deep gray matter lesions also occur but are less clearly seen on conventional MRI. Gadolinium enhancement, which suggests permeability of the blood-brain barrier, is correlated with new or active inflammation in lesions (Fig. 380-4). Lesions that enhance on a T1-weighted sequence usually have a concomitant lesion in the same location on a T2-weighted image. However, T2-weighted lesions may form without evident enhancement. Gadolinium enhancement may be homogenous, central, or in a ring pattern; it typically persists for 2 to 8 weeks and thus may be missed on intermittent scans. Persistent areas of low signal on T1-weighted images before contrast ("black holes") correlate with pathologic evidence of axonal loss and atrophy (Fig. 380-5).

Cerebrospinal Fluid

Examination of the CSF is useful in many cases but is not mandatory in patients with a typical clinical presentation and MRI evidence of disseminated disease. CSF evaluation includes cell counts, total protein, glucose, IgG index, and electrophoresis to assess for an oligoclonal banding pattern with a paired serum sample. The presence of myelin basic protein is not specific for multiple sclerosis because it can be elevated secondary to any disruption of CNS tissue. Oligoclonal IgG bands in the CSF or an elevated IgG index provides evidence for intrathecal production of immunoglobulins. However, although oligoclonal bands are common in multiple sclerosis, they also can occur with infection or other immune-mediated processes. As a result, the test lacks specificity and has a sensitivity of only approximately 85 to 90% of patients with clinically definite multiple sclerosis. In clinically isolated demyelinating syndromes (see later), the sensitivity is even lower (~50%). Further, the sensitivity depends on local laboratory techniques. Oligoclonal mirror bands, in the serum and CSF, may signal a systemic immune process with CNS involvement.

CSF evaluation is generally recommended if an alternative diagnosis is considered, especially if one suspects an infectious or neoplastic process (e.g., fever, sweats, unusual travel history, tick bite, or rash). CSF analysis also may

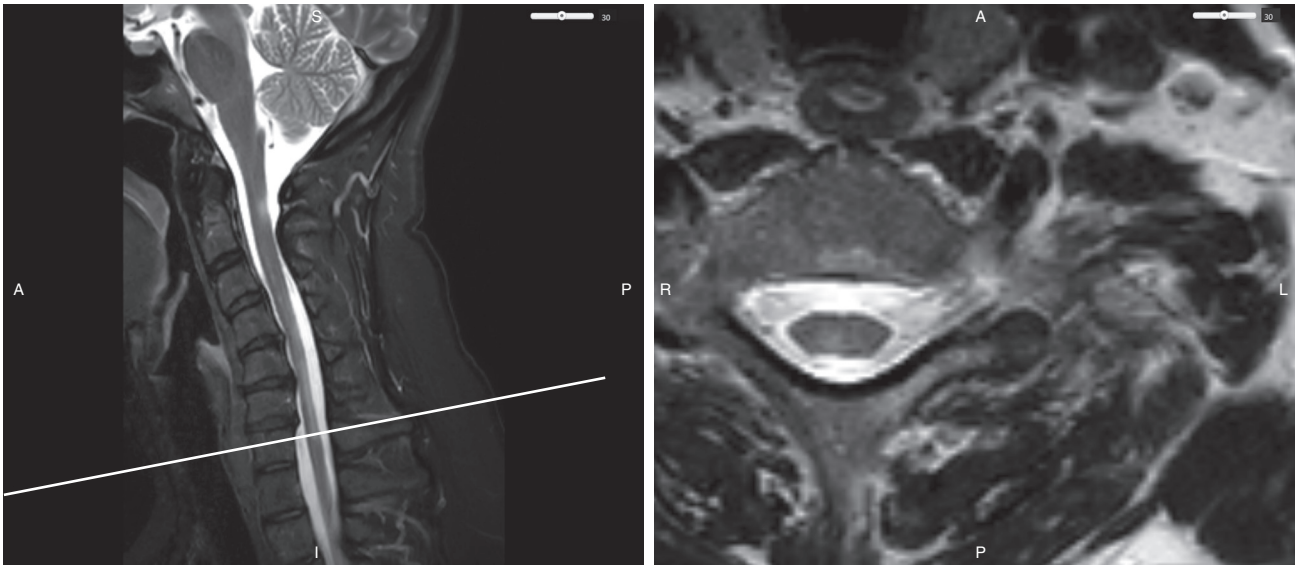

FIGURE 380-3. Sagittal T2-weighted image of the brain and cervical spine from a patient with multiple sclerosis.

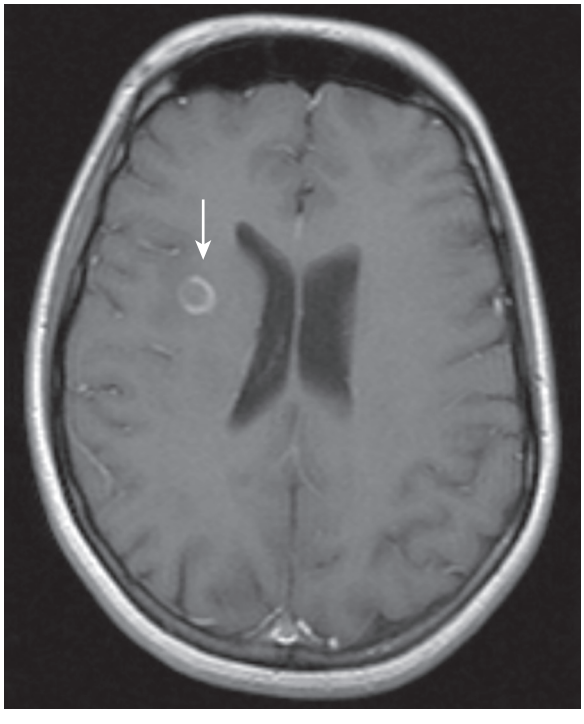

FIGURE 380-4. Axial T1-weighted image after gadolinium contrast showing an actively inflamed ring-enhancing lesion *(arrow)* in a patient with multiple sclerosis.

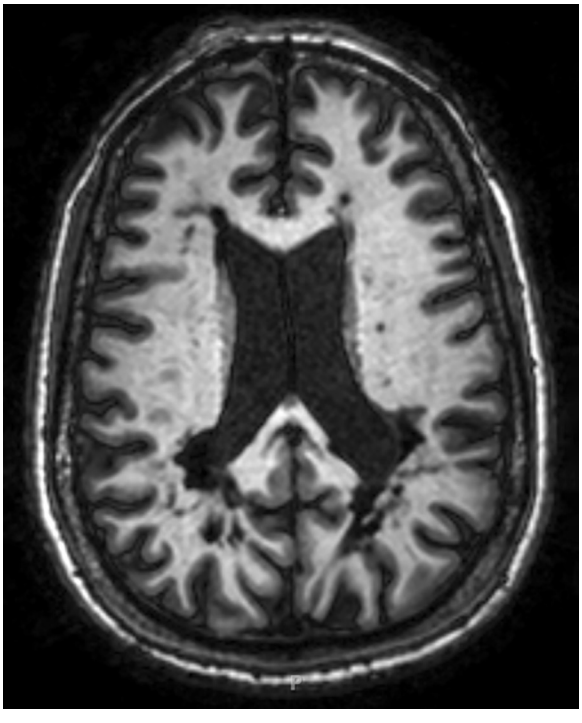

FIGURE 380-5. Axial T1-weighted image showing numerous areas of T1 low signal ("black holes"), ventricular enlargement, and diffuse atrophy.

be useful if clinical or MRI criteria are incomplete to provide confirmation of the diagnosis.

Evoked Potential Tests

Evoked potentials (Chapter 366) may be useful in some situations to document objective evidence of slowed conduction owing to demyelination in locations different from those recognized clinically. However, visual evoked potentials (VEPs), brain stem auditory evoked potentials, and somatosensory evoked potentials are less sensitive and less specific for multiple sclerosis than is high-resolution MRI. Multifocal VEPs may be more sensitive than global VEPs in revealing focal areas of abnormal conduction along the optic nerve.

Optical Coherence Tomography

Optical coherence tomography is performed with an office-based device that uses the reflection of infrared light (from an exogenous source directed through the pupil) off the back of the eye to quantify the thickness of retinal tissues, including the peripapillary retinal nerve fiber layer and macular layers. This test, which has been widely used in glaucoma, can monitor axonal and retinal ganglion cell damage, both in the setting of acute optic neuritis and in detecting subclinical neuroaxonal damage (E-Fig. 380-1). Retinal nerve fiber layer thinning correlates with brain atrophy and may be useful as a surrogate marker of more global neurodegeneration in multiple sclerosis.

Differential Diagnosis

The diagnosis of multiple sclerosis may be so clear that it is recognized by the patient and is readily confirmed by the primary physician or so obscure that even experienced specialists disagree.[6] Many processes (see Table 380-2) can mimic the clinical, radiologic, and CSF findings associated with multiple sclerosis, and no diagnostic test is 100% sensitive and specific for the disease. The incorporation of MRI T2-weighted high-signal white matter lesions in the diagnostic criteria for multiple sclerosis has improved diagnostic sensitivity but must be used with caution so as not to compromise specificity. Nonspecific white matter lesions have numerous causes, especially vascular. On MRI, multiple sclerosis lesions are more likely to have a central vein sign, which is characterized by a thin (<2 mm) hypointense line or dot in the center of a white matter lesion on T2*-weighted images.

The most common conditions misdiagnosed as multiple sclerosis in one study were migraine (Chapter 367), fibromyalgia (Chapter 253), and conversion or psychogenic disorders (Chapter 362).[7] Other processes that mimic multiple sclerosis include structural lesions, especially of the base of the brain and of the spinal cord, in which one lesion can cause symptoms referable to many different tracts and at different perceived locations in the body. Chiari malformations with or without syrinx (Chapter 385), disc herniation (Chapter 369), cervical spondylosis, and low-grade tumors (Chapter 175) can produce symptoms of multiple sclerosis both in newly presenting patients and in patients who truly have multiple sclerosis but who also have a second process.

Various infectious diseases can mimic multiple sclerosis. Examples include human T-cell lymphotropic virus types I and II (virally associated myelopathy or tropical spastic paraparesis; Chapter 360), human immunodeficiency virus (neuropathy, myelopathy, cognitive impairment, CNS white matter changes; Chapter 359), neuroborreliosis (Lyme disease; Chapter 296), neurosyphilis (Chapter 295), Epstein-Barr virus (Chapter 348), cytomegalovirus (Chapter 347), herpes simplex virus (Chapter 345), varicella-zoster virus myelitis (Chapter 346), and JC virus (progressive multifocal leukoencephalopathy; Chapter 341).[8]

Inflammatory diseases that usually involve other parts of the body can concomitantly affect or, rarely, manifest in the CNS. Examples include sarcoidosis (Chapter 83), systemic lupus erythematosus (Chapter 245), Sjögren syndrome (Chapter 247), and vasculitides (Chapter 249). Autoimmune encephalitis, although usually more fulminant and with distinguishing features such as seizures and behavioral disturbance, may be mistaken for multiple sclerosis. Ischemic vascular disease secondary to any cause also can resemble multiple sclerosis. Metabolic and nutritional disorders that can mimic multiple sclerosis include vitamin B_{12} deficiency and methylmalonic acidemia (in some cases distinct from cyanocobalamin deficiency). Rarely, central pontine myelinolysis (Chapters 102 and 384) is mistaken for multiple sclerosis. Thyroid disease (Chapter 207) may mimic the fatigue of multiple sclerosis and may cause dysesthesias and disorders of the optic nerve and muscles. Nutritional deficiency (Chapter 197) and malabsorption have been associated with demyelination and may mimic multiple sclerosis. Copper deficiency can cause dorsal column pathology, neuropathy, anemia, and optic neuropathy. Vitamin D deficiency (Chapter 226), which is becoming increasingly common, can cause proximal weakness, fatigue, asthenia, bone loss, and impaired immune function. Vitamin A deficiency, although not common in industrialized countries, can cause night blindness and immune dysfunction.

Monophasic demyelinating syndromes with or without multiple other lesions often, but not always, progress to become multiple sclerosis (see later). Spinocerebellar atrophy and hereditary myelopathy cause slowly progressive disease but do not cause sensory and visual abnormalities.

Hereditary diseases are increasingly recognized as mimicking multiple sclerosis. Spinocerebellar atrophy (Chapter 379) may manifest as progressive myelopathy and ataxia. A variety of genetic neuropathies (type 2 CMT mitofusinopathies, adult-onset polyglucosan body disorder; Chapter 388), ataxias (Friedreich, ataxia telangiectasia; Chapter 379), mitochondrial diseases (progressive optic atrophy, Leber, mitochondrial encephalopathy, lactic acidosis, and stroke-like episodes [MELAS], myoclonic epilepsy with ragged red fibers [MERRF]; Chapter 389), and metabolic diseases (urea cycle disorders; Chapter 189) can have CNS manifestations that could lead to misdiagnosis.

TREATMENT

The treatment of multiple sclerosis can be divided into drugs designed to relieve symptoms, drugs designed to modify the course of the disease, and nondrug measures.[9] Numerous drugs target specific aspects of multiple sclerosis: depression, fatigue, muscle spasticity, pain, insomnia, and bladder, bowel, and sexual dysfunction. Before considering a symptomatic therapy, the patient should be educated about the purpose of the drug and its side effect profile. Symptomatic therapies are best started at low doses and frequently require titration to obtain the optimal balance between efficacy and side effects.

Treatment of Specific Symptoms

Depression and emotional lability are common symptoms of multiple sclerosis. In addition to appropriate supportive care and counseling, antidepressant therapy with one of the "activating" serotonergic or noradrenergic drugs (fluoxetine, sertraline, citalopram, escitalopram, venlafaxine, desvenlafaxine, or bupropion) can be of benefit for depression as well as for anxiety and panic symptoms (see Tables 362-5 and 362-7 in Chapter 362). Most patients do not seem to tolerate paroxetine well long term; fluoxetine and sertraline work for panic and anxiety. Patients with pain or insomnia may benefit more from a sedating antidepressant (amitriptyline, nortriptyline, or trazodone) given at bedtime, which may have the added anticholinergic benefits on urinary bladder urgency.

Spasticity can be managed by physical therapy, stretching, and institution of either baclofen (5 to 160 mg in divided doses) or tizanidine (2 to 32 mg in divided doses). Either drug should be started as a single agent at a low dose at bedtime, gradually increasing to three to four times daily, with a larger dose at bedtime to target nocturnal symptoms. Decreasing muscle tone can result in weakness. Baclofen should never be discontinued abruptly because of the potential for a severe withdrawal reaction.

Bladder urgency resulting from detrusor muscle spasm can be managed effectively with anticholinergics (antimuscarinic) such as oxybutynin (5 to 20 mg in divided doses) or tolterodine (1 to 4 mg) or with B3 adrenergic receptor agonist mirabegron (25 to 50 mg daily) or focal intravesicular injections of botulinum toxin, but these agents can cause temporary urinary hesitancy or retention. Bladder ultrasonography permits accurate bedside assessment of postvoid residual volume to determine whether a patient is retaining excessive amounts of urine (>50 mL is abnormal but >300 mL requires intervention). Urinary retention may be improved by removing drugs known to induce it (e.g., anticholinergics and opioids). Primary urinary retention is difficult to treat with drugs, but external sphincter spasm can be treated with α_{1a}-adrenergic receptor blockers such as tamsulosin (0.4 to 0.8 mg) and doxazosin (1 to 8 mg). Bethanechol (10 to 150 mg in divided doses) may be tried for an atonic bladder, but intermittent catheterization is often required. Alternative causes of bladder symptoms such as urinary tract infections, prostatic enlargement, or anatomic changes following pregnancy should be considered and managed separately. Prolonged urinary retention predisposes to infections, structural damage to the bladder and kidneys, and malignancy. Persistent postvoiding residual volumes greater than 300 mL should be treated medically, with intermittent straight catheterization recommended for patients with large volume retention refractory to medical therapy.

Painful dysesthesias and paroxysmal dystonic spasms may be managed effectively with antiepileptic drugs (gabapentin, 300 to 5400 mg/day in divided doses; pregabalin, 75 to 600 mg/day in divided doses; or oxcarbazepine, 300 to 2400 mg/day in divided doses) or tricyclic antidepressants (amitriptyline, 10 to 150 mg; nortriptyline, 10 to 50 mg, or duloxetine, 20 to 90 mg). Patients with trigeminal neuralgia (Chapter 367) may respond to these drugs or to baclofen, misoprostol, botulinum toxin, or decompression surgery; consideration of intravenous loading with an antiepileptic drug (Chapter 372) is worthwhile for severe acute pain attacks.

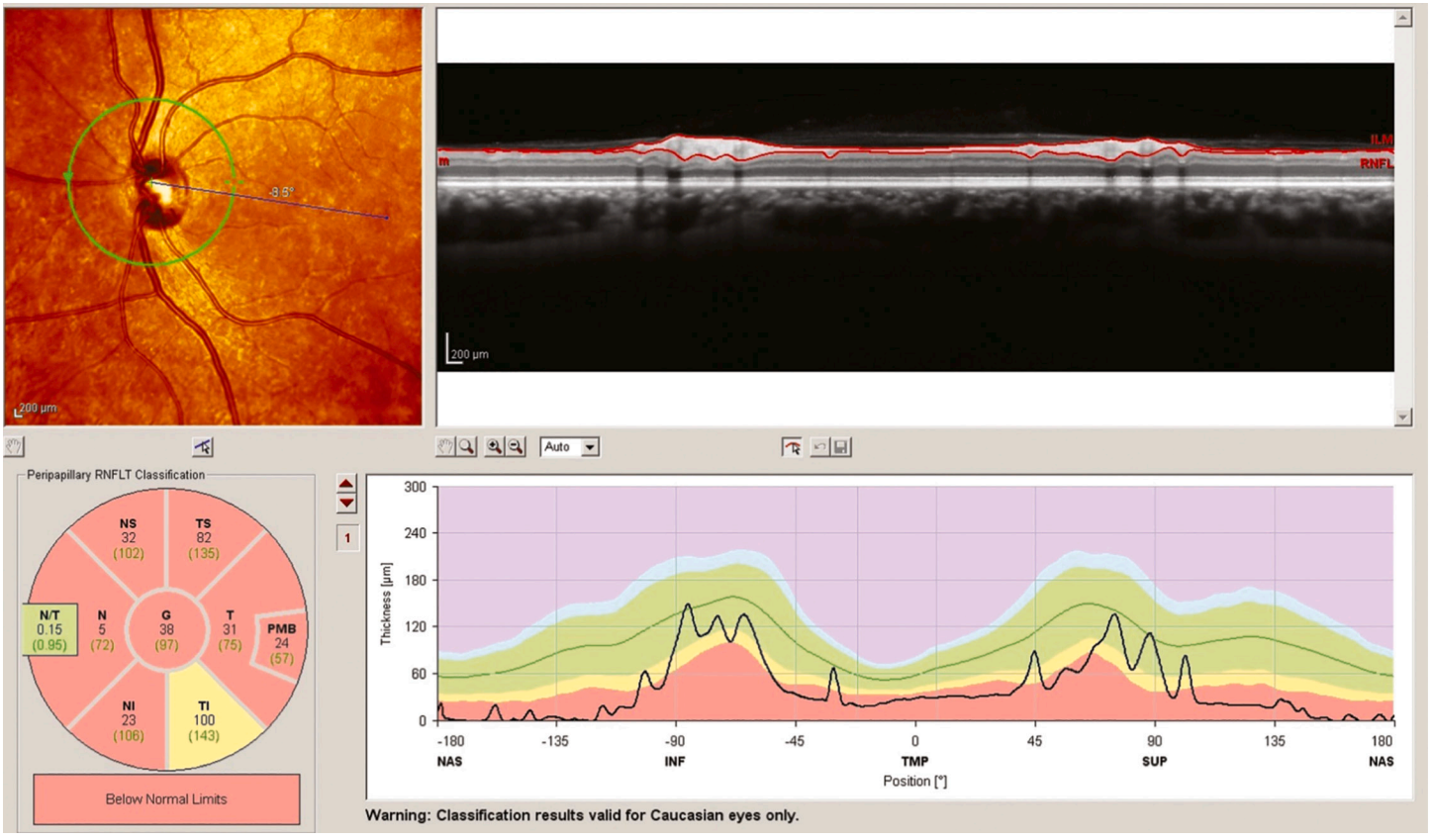

E-FIGURE 380-1. High-resolution spectral domain optical coherence tomography scan. The scan is from the retina of a patient with multiple sclerosis and history of optic neuritis in the scanned eye. The *upper left* is a fundus photo; the *upper right* is the tomogram map of the peripapillary retinal nerve fiber layer. *Lower panels* show regional quantitative data and color maps based on percentile compared to age- and sex-matched healthy controls (*green* is fifth to 95th percentile, *yellow* is fifth percentile, and *red* is first percentile). INF = inferior; N = nasal; NAS = nasal; NI = inferior-nasal; NS = superior-nasal; PMB = papillomacular bundle; RNFLT = retinal nerve fiber layer thickness; SUP = superior; T = temporal; TI = inferior-temporal; TMP = temporal; TS = superior-temporal.

TABLE 380-5 MEDICATIONS FOR MULTIPLE SCLEROSIS

GENERIC	TRADE NAME(S)	DOSE	ROUTE/ FREQUENCY	INDICATION	MAJOR MECHANISM	NUISANCE SIDE EFFECTS	RARE POSSIBLE SERIOUS SIDE EFFECTS	CONSIDERATIONS
Interferon Beta1b	Betaseron, Extavia	250 μg	SQ 3 times weekly	RRMS	Modestly inhibits many peripheral immune pathways	Injection site reactions, influenza-like side effect, depression, elevated aminotransferase level	Cytopenia, hepatitis, cardiomyopathy	First line, but less commonly used now
Interferon Beta1a	Avonex	30 μg	IM weekly	RRMS	Modestly inhibits many peripheral immune pathways	Injection site reactions, influenza-like side effect, depression, elevated aminotransferase level	Cytopenia, hepatitis, cardiomyopathy	First line, but less commonly used now
Interferon Beta1a	Rebif	22-44 μg	SQ 3 times weekly	RRMS	Modestly inhibits many peripheral immune pathways	Injection site reactions, influenza-like side effect, depression, elevated aminotransferase level	Cytopenia, hepatitis, cardiomyopathy	First line, but less commonly used now
Interferon Beta 1a pegylated	Plegridy	125 μg	IM every 2 weeks	RRMS	Modestly inhibits many peripheral immune pathways	Injection site reactions, influenza-like side effect, depression, elevated aminotransferase level	Cytopenia, hepatitis, cardiomyopathy	First line, but less commonly used now
Glatiramer acetate	Copaxone, Glatopa, or generic	20-40 mg	SQ daily (20 mg) or 3 times weekly (40 mg)	RRMS	T_H2 immune deviation, induction of brain-derived neurotrophic factor	Injection site reactions, lipoatrophy, allergies, immediate post-injection reactions		First line, Pregnancy Category B (no risk in animal studies, insufficient data in humans)
Ofatumumab	Kesimpta	Initial 20 mg SQ at weeks 0, 1, and 2, followed by 20 mg SQ once monthly starting at week 4	Every 4 weeks	RRMS	Anti-CD20 monoclonal antibody depletes B cells	Increased risk of urinary tract infections and common upper respiratory infection infections	Uncertain if below listed risks of anti-CD20 mitigated by lower dose	First line in highly active disease, lower dose may be safer but more frequent injections
ORALS								
Fingolimod	Gilenya	In pediatric patients 10 yr and older weighing less than or equal to 40 kg, the recommended dose is 0.25 mg orally once daily	Oral daily	RRMS	Sphingosine 1 phosphate receptor (S1PR) modulator thereby blocking egress from lymph nodes	First dose bradycardia, retinal monitoring	Macular edema, type 2 heart block, class associated with HTN, PML, and other rare opportunistic infections	First line
Siponimod	Mayzent	2 mg (titration to start)	Oral daily	RRMS and active SPMS	S1P1 and 5 receptor modulator, blocking egress from lymph nodes	First dose bradycardia, retinal monitoring	S1P1 selectivity diminishes risk of cardiac arrhythmia but first dose bradycardia seen; same likely with newer drugs of same category	First line
Ozanimod	Zeposia	0.92 mg (titration to start)	Oral daily	RRMS	S1P1R modulator, blocking egress from lymph nodes	Dose titration, but avoids first dose monitoring	Same infection risk likely with newer drugs of same category	First line
Ponesimod	Ponvory	20 mg (titration to start)	Oral daily	RRMS and active SPMS	S1P1R modulator, blocking egress from lymph nodes		Same infection risk likely with newer drugs of same category	First line
Dimethylfumarate	Tecfidera, generic	120 mg twice a day orally. After 7 days, the dose should be increased to the maintenance dose of 240 mg	Oral twice daily	RRMS	Nrf2 transcription factor agonist, inhibits glycolytic metabolism in immune cells	Gastrointestinal side effects, flushing, lymphopenia	PML and other rare opportunistic infections	First line
Diroximel fumarate	Vumerity	231 mg twice a day orally. After 7 days, the dose should be increased to the maintenance dose of 462 mg (administered as two 231-mg capsules) twice a day orally	Oral twice daily	RRMS	Monomethylfumarate, Nrf2 agonist, unclear if entirely the same as dimethylfumarate	Gastrointestinal side effects (reduced), flushing, lymphopenia	Same likely with newer drugs of same category	First line

TABLE 380-5 MEDICATIONS FOR MULTIPLE SCLEROSIS—cont'd

GENERIC	TRADE NAME(S)	DOSE	ROUTE/ FREQUENCY	INDICATION	MAJOR MECHANISM	NUISANCE SIDE EFFECTS	RARE POSSIBLE SERIOUS SIDE EFFECTS	CONSIDERATIONS
Monomethylfumarate	Bafiertam	95 mg twice a day orally for 7 days. After 7 days, the dose should be increased to the maintenance dosage of 190 mg (administered as two 95-mg capsules) twice a day orally	Oral twice daily	RRMS	Monomethylfumarate, Nrf2 agonist, unclear if entirely the same as dimethylfumarate	Gastrointestinal side effects, flushing, lymphopenia	Same likely with newer drugs of same category	First line
Teriflunomide	Aubagio	7-14 mg	Oral daily	RRMS	Blocks dihydro-orotate dehydrogenase (de novo pyrimidine synthesis) in lymphocytes	Diarrhea and other gastrointestinal side effect, elevated aminotransferase levels	Peripheral neuropathy, hepatitis, contraindicated in pregnancy (for women and men)	First line, Pregnancy Category X (contraindicated in pregnancy)
2-Chlorodeoxyadenosine (cladribine)	Mavenclad	3.5 mg/kg body weight administered orally and divided into 2 yearly treatment courses (1.75 mg/kg per treatment course)	Oral daily for 5 days month 1 and month 2 of yearly cycle	RRMS and active secondary progressive disease		Cytopenia, common infections	Increased risk of serious infections	Second line, treatment failures
INFUSIONS								
Natalizumab	Tysabri	300 mg	IV every 4-6 weeks	RRMS	Anti-CD49d Mab block alpha-4 integrin mediated cell adhesion/trafficking	Infusion reactions in first few doses, frequent blood tests for JC viral antibody	PML risk-escalates after 2 years and in patients who are elderly, have high titer JC viral antibodies, or a prior history of chemotherapy	First line in highly active disease, beware of potential for rebound if stopped
Ocrelizumab	Ocrevus	600 mg	IV every 6 months	RRMS and PPMS	Anti-CD20 Mab depletes B cells	Infusion reactions, increased risk of urinary tract infections and common upper respiratory infections	Rare reports of PML and cancer being investigated, mammograms and Pap smears recommended	First line in highly active disease, breast cancer risk screening
Alemtuzumab	Lemtrada	12 mg up to 60 mg in year 1	Year 1 is IV daily for 5 days in a row, then wait a year and reassess		Anti-CD52 Mab depletes leukocytes	Infusion reactions, monthly monitoring for ITP, herpes prophylaxis	Autoimmune disease in 50%, fungal, viral, bacterial infections	Second or third line for treatment failures, secondary autoimmune disease in 50%
Ublituximab	Briumvi	150 mg on day 1 then 450 mg on day 15 and at weeks 24, 48, and 72	IV every 24 weeks	RRMS	binds to B-cell-specific cell surface antigen CD20	Fever, chills, headaches, respiratory symptoms, PML	Neutropenia, anaphylaxis	Can reactivate hepatitis B infection
Mitoxantrone	Novantrone	12 mg/m^2 up to 120 mg/m^2	IV every 3 months	RRMS and active PMS	Type 2 isomerase inhibitor disrupts DNA synthesis	Cytopenia, infections, frequent blood draws	Cardiotoxicity, lymphoma	Rarely used
ACUTE SYMPTOMS SYMPTOMATIC								
Dalfampridine	Ampyra	10 mg	Oral twice daily	Ambulatory	Kv1.4 channel blocker enhances nerve conduction	Insomnia, dizziness, increased neuropathic pain	Seizures in <1%	Avoid if history of seizures, <40% of patients respond
ACTH	Acthar gel	80-120 units	SQ or IM daily for 2-3 weeks	Acute relapses	Induces cortisol, there may be additional effects of ACTH	Infections, insomnia, gastrointestinal, behavioral change	Possibly same as corticosteroids	Not for chronic use

ACTH = adrenocorticotropic hormone; BID = twice daily; HTN = hypertension; IM = intramuscularly; ITP = immune thrombocytopenic purpura; IV = intravenously; PML = progressive multifocal leukoencephalopathy; PMS = progressive multiple sclerosis; PPMS = primary progressive multiple sclerosis; RRMS = relapsing remitting multiple sclerosis; SPMS = secondary progressive multiple sclerosis; SQ = subcutaneously.

Sexual dysfunction in multiple sclerosis is often multifactorial. Patients with erectile dysfunction usually respond well to the phosphodiesterase type 5 inhibitors, which enhance penile vasodilation (Chapter 216). Education regarding the use of lubrication, alternative sensory stimulation, and the adverse effect of heat can improve sexual function. Tadalafil 5 mg once daily also can ameliorate symptoms of an overactive bladder in older men.

Symptoms related to heat sensitivity may improve on cooling. Cooling devices can prevent this phenomenon, but there is no persistent benefit of inducing hypothermia.

Systemic Treatments

Corticosteroids (e.g., methylprednisolone, 1 g/day orally or intravenously [IV] for 3 to 5 days) are equivalent[A1] to each other for shortening the duration and severity of symptoms from an acute exacerbation, but they have no proved effect on long-term disability. Similarly, adrenocorticotropin-releasing hormone injected daily intramuscularly or subcutaneously at doses of 80 to 120 units for 2 to 3 weeks shortens the duration of acute exacerbations. Intravenous immunoglobulin (IVIG) and plasma exchange may occasionally benefit steroid-refractory patients, but large randomized placebo-controlled trials in relapsing multiple sclerosis have failed to show consistent benefits, perhaps because only patients with type II pathology (humoral component) are likely to respond.

Approved Disease-Modifying Treatments

Multiple disease-modifying agents have been approved by the U.S. Food and Drug Administration (FDA) (Table 380-5).[10,11] All of these agents are approved for relapsing-remitting multiple sclerosis, and mitoxantrone is indicated for worsening forms of multiple sclerosis and for secondary progressive multiple sclerosis. Ocrelizumab is the only drug approved for primary progressive multiple sclerosis.[12]

The five IFN-β drugs reduce the relapse rate by approximately one third.[A2] IFN-β1b (8 million international units [IU], subcutaneously [SQ] every other day [Betaseron and Extavia]) and IFN-β1a (30 μg intramuscularly [IM] weekly [Avonex] or 22 to 44 μg SQ three times weekly [Rebif]) and pegylated IFN-β1a (125 μg every 14 days, SQ [Plegridy]) appear to have a more rapid onset of action, perhaps based on their dosing regimen, compared with weekly IFN-β1a (30 μg IM weekly). However, weekly IFN-β1a (Avonex) and pegylated IFN-β1a (Plegridy) are less immunogenic and result in only a 3 and 1% incidence of neutralizing antibodies, respectively, which reduce efficacy, compared with 20 to 30% for the other IFN-β1b preparations. The major side effects of IFN-β are a flulike reaction (low-grade fever, chills, and myalgias 6 to 24 hours after the injection), local reactions at the injection site (pain, erythema, and rarely necrosis), and elevated aminotransferase levels (rarely severe hepatitis). These side effects can be managed by initiating the drug slowly and by prophylaxis with acetaminophen and nonsteroidal anti-inflammatory agents, and they improve in most patients after 3 to 6 months. An advantage of pegylated IFN-β1a is its less frequent dosing, but side effects can be more severe than with other IFN-β1a preparations.

Glatiramer acetate is a copolymer of four amino acids designed to mimic myelin basic protein; given as 20 mg/day SQ or as 40 mg SQ three times a week, it also reduces relapses by about one third and is well tolerated by most patients.[A3] Major side effects are local reactions at the injection site (swelling, hives, and delayed lipoatrophy) and a rare, self-limited (15 to 20 minutes) systemic reaction consisting of chest pain, palpitations, and anxiety. No monitoring of blood tests is required for this medication. The effect of glatiramer acetate on MRI T2-weighted and gadolinium-enhancing lesions is less dramatic than for the IFNs (30% reduction), perhaps because its primary effect is not at the blood-brain barrier.

Natalizumab is a monoclonal antibody directed against the α_4-integrin chain of the leukocyte adhesion molecule VLA-4. At a dose of 300 mg IV every 4 weeks, it reduces relapses by about 70% compared with placebo and reduces gadolinium-enhancing lesions by 90%.[A4] It also may slightly reduce progression in secondary progressive multiple sclerosis.[A5] However, approximately 1 in 1000 patients develop JC virus brain infection (Chapter 341) after 24 months of exposure, which causes progressive multifocal leukoencephalopathy. The risk for progressive multifocal leukoencephalopathy appears to be significantly higher in patients with JC virus serum antibody titers greater than 0.9 (1 in 100 to 200) compared with low-titer or seronegative patients, in whom the risk is less than 1 in 1000. Such data can help guide the safety of long-term usage; however, the results may change over time, so patients require repeated testing.

Alemtuzumab, a monoclonal antibody that targets CD52 on lymphocytes and monocytes, reduces annualized relapse rates by approximately 50% and also can reduce the progression of disability compared with IFN-β1a.[A6] The drug is given as yearly courses at 12 or 24 mg daily for 5 consecutive days in year 1 and for 3 days in years 2 and 3. Serious side effects associated with alemtuzumab include a 20 to 25% risk for developing autoimmune thyroid disease and rare cases of immune thrombocytopenic purpura (Chapter 158), autoimmune hemolytic anemia (Chapter 146), autoimmune neutropenia (Chapter 153), and Goodpasture syndrome (Chapter 107). Severe infections and vascular events (e.g., myocardial infarction and stroke) are associated with use of this medication.

Fingolimod is a sphingosine-1 phosphate receptor modulator that is given orally once daily at 0.5 mg. Fingolimod reduces relapse rates and the progression of disease compared with placebo and compared with IFN therapy.[A7] It generally is not considered first-line therapy because its risks, including type 2 heart block and herpes encephalitis, are concerning, especially in young, otherwise healthy people with multiple sclerosis. Fingolimod side effects include first-dose bradycardia, macular edema, and respiratory infections. More selective sphingosine-1 phosphate receptor modulators reduce the risk of serious cardiac arrythmias but still can cause bradycardia and hypertension. For example, siponimod (2 mg daily), can reduce the risk of progressive disability in patients with active secondary progressive multiple sclerosis.[A8]

Teriflunomide is approved as an oral agent for multiple sclerosis based on two phase 3 trials in which the annualized relapse rate was reduced by 31% compared with placebo, and disability also was reduced.[A9] It is dosed at 7 or 14 mg/day orally and requires monitoring of blood tests for rare liver and kidney toxicities.

Oral dimethyl fumarate (240 mg twice daily)[A10] reduces the annualized relapse rate and disease progression in addition to suppressing active MRI lesions with an efficacy similar to that of teriflunomide.[A11] Rare cases of progressive multifocal leukoencephalopathy have been reported in patients with prolonged severe lymphopenia (<500/μL), and close monitoring is recommended. Generic dimethylfumarate and its active metabolite, monomethylfumarate, have comparable efficacy.

Ofatumumab (a subcutaneous anti-CD20 monoclonal antibody, at 20 mg on days 1, 7, and 14 and then every 4 weeks) is more effective than oral teriflunomide for preventing relapses.[A12]

The only approved therapy for primary progressive multiple sclerosis is ocrelizumab (600 mg IV every 6 months), which is a humanized anti-CD20 monoclonal antibody that rapidly depletes B cells. Ocrelizumab reduces the rate of progression of disability by about 25% in patients with primary progressive multiple sclerosis, whereas ocrelizumab reduces the annualized relapse rate by about 45% compared with IFN-β1a.[A13,A14] In addition, ocrelizumab reduces gadolinium-enhancing lesions by about 95%. Infusion-related side effects are common but can be managed with corticosteroids (e.g., prednisone 100 mg before the infusion) and antihistamines (e.g., diphenhydramine 50 mg before infusion).

Several other B-cell–depleting strategies are being tested in multiple sclerosis. Atacicept, a targeted B-cell therapy, has no effect on multiple sclerosis or actually worsens it, thereby raising questions regarding the subset of memory B cells that might be pathogenic. Furthermore, the long-term side effects of sustained B-cell depletion remain unclear. Bruton tyrosine kinase inhibitors may have efficacy in relapsing multiple sclerosis.[13,A15]

Other Therapies

Rituximab (1000 mg IV 2 weeks apart repeated every 6 months) is a monoclonal antibody that depletes B-cell lymphocytes and can significantly reduce inflammatory brain lesions and relapse by approximately 50% for up to 48 weeks in patients with relapsing-remitting multiple sclerosis.[A16] However, it has not been effective in primary progressive multiple sclerosis. Ublituximab is a monoclonal antibody that depletes B cells and that is effective for relapsing multiple sclerosis.[A17] Cladribine (2-chlorodeoxyadenosine, 3.5 or 5.25 mg/kg/day) given as a short course once per year reduces the annualized relapse rate by 55% and disease progression by one third compared with placebo.[A18] Both of these drugs may have a role in treating multiple sclerosis, but they also have global immunosuppressive effects that increase the risk for serious infections and possibly other systemic complications.

Sustained-release dalfampridine, a potassium-channel Kv1.4 blocker at 10 mg twice daily, improves walking in 35% of patients compared with only 8% of patients receiving placebo. It is approved by the FDA as a symptomatic therapy for multiple sclerosis.[A19] Only a subset of patients appears to benefit, and dalfampridine is contraindicated in patients with a history of seizures and may cause dizziness, insomnia, and an increase in painful paresthesias.

Mitoxantrone, which is an anthracenedione antineoplastic agent with potent immunosuppressive activity, is approved to slow the progression of neurologic disability and reduce the relapse rate in patients with relapsing-remitting multiple sclerosis and secondary progressive multiple sclerosis. However, it is rarely used because of the availability of safer, more effective alternatives.

Other forms of immunosuppression, including laquinimod, methotrexate, azathioprine, mycophenolate mofetil, and cyclophosphamide, may have some efficacy in multiple sclerosis, although either no definitive clinical trials have been done with these agents or safety profiles have outweighed risks, and none is as yet approved for multiple sclerosis by the FDA.

Choosing the Best Treatment Options

No specific treatment algorithm can be recommended because the disease is heterogeneous, there are few head-to-head studies between medications, and reported effect sizes of the approved drugs versus placebo depend on the

varying characteristics of patients in different trials.[14] As a result, the treatment decision is best made in conjunction with the patient based on the patient's disease, the side effect and safety profiles of the various drugs, and the physician's assessment of severity and prognosis.[15] Older drugs such as IFN-β or glatiramer acetate are safe but have provided variable responses, with the average benefit being less than is seen with newer therapies. The availability of effective safe oral therapies has modified treatment practice. For the typical newly diagnosed patient with relapsing multiple sclerosis but no early signs of poor prognosis (e.g., high relapse rate with early accrual of disability, Black ancestry, high lesion load, T1 black holes on MRI, multiple spinal cord lesions), a reasonable strategy is to start with one of the oral agents and then switch to a higher efficacy monoclonal antibody medication if the patient experiences a severe relapse, multiple small relapses, or new MRI lesions.[16]

Prevention

Patients who present with a first demyelinating event such as optic neuritis, transverse myelitis, or another brain stem, cerebral, or cerebellar myelopathy are at risk for developing full-blown multiple sclerosis and several studies have documented efficacy for multiple sclerosis disease-modifying therapy at the time of a clinically isolated syndrome.

Other Approaches to Well-Being

Patients with multiple sclerosis are at high risk for developing osteopenia or osteoporosis (Chapter 225), so prophylaxis with vitamin D and calcium and treatment with bisphosphonates or other proved approaches should be considered. Patients with suboptimal 25-OH vitamin D levels (<30 ng/mL) on standard 1000-IU cholecalciferol replacement therapy should consider increasing to 4000 to 5000 IU/day or 50,000 IU every other week or, in some cases, weekly, with appropriate monitoring of vitamin D and serum plus urine calcium levels. If osteoporosis has already been diagnosed, bisphosphonate therapy, such as alendronate (10 mg/day or 70 mg/week) or a similar drug, is generally indicated.

Nonmedical treatment is a critical part of managing multiple sclerosis. Patients derive benefit from a health care team approach consisting of an experienced multiple sclerosis physician, nurse, social worker, therapist, and counselor, with appropriate referral to other subspecialties as needed. Alternative and complementary therapies (Chapter 30) are commonly used by patients with multiple sclerosis, and the risks and benefits of these approaches must be discussed with the patient. No diet has yet proved effective in multiple sclerosis.

PROGNOSIS

The annual risk of death for patients with multiple sclerosis is about twice as high as in the overall population, and the average lifespan of patients with multiple sclerosis is approximately 8 years less than normal, a finding reflecting a bimodal distribution in which many patients live a normal lifespan and a few die earlier owing to aggressive disease, severe disability, infection, or suicide. About 85% of patients commence with a relapsing and remitting pattern of disease, whereas 15% progress from what is initially thought to be primary progressive multiple sclerosis. Many patients presenting with relapsing-remitting multiple sclerosis convert to secondary progressive multiple sclerosis after 20 to 40 years. Only one third of patients will require use of a wheelchair, but 50% may need assistive devices and nearly two thirds will have disability that prevents them from working. African Americans and men of all races tend to have a more aggressive course and are more likely to become disabled. Immunomodulating therapy early in the course of the disease appears to slow progression of disability, but long-term follow-up data are open-label and uncontrolled, so it is difficult to quantify the extent of this benefit.

OTHER DISEASES OF MYELIN

Monofocal and Monophasic Demyelinating Processes

OPTIC NEURITIS AND TRANSVERSE MYELITIS

Optic neuritis (Chapter 392) and transverse myelitis are inflammatory processes that can occur as entities distinct from multiple sclerosis or as part of multiple sclerosis (see earlier). In addition, optic neuritis and transverse myelitis can occur together in the syndrome called *neuromyelitis optica* or myelin oligodendrocyte glycoprotein antibody disorder (MOGAD).

Optic Neuritis

Optic neuritis (Chapter 392) is an inflammatory disease that usually involves the retrobulbar portion of the optic nerve and sometimes parts of the optic chiasm.[17] Although optic neuritis is most often associated with multiple sclerosis (50 to 75%), it also can be seen as an isolated idiopathic disorder (25 to 50%), as part of neuromyelitis optica, myelin oligodendrocyte glycoprotein antibody disorder, or associated with other inflammatory and infectious diseases such as chronic relapsing inflammatory optic neuropathy, systemic lupus erythematosus, Sjögren syndrome, sarcoidosis, Lyme disease, syphilis, and human immunodeficiency virus infection.[18] The pathobiologic features are thought to be similar to those of multiple sclerosis and are characterized by idiopathic inflammatory demyelination followed by secondary axonal injury. Hereditary optic neuropathies may be unmasked during periods of stress and manifest as an acute monocular visual loss.

CLINICAL MANIFESTATIONS AND DIAGNOSIS

The clinical presentation, which typically is monocular visual loss with pain over the brow that worsens with lateral eye movement, is similar regardless of whether it manifests as part of multiple sclerosis (see the earlier discussion of the visual effects of multiple sclerosis) or not. Retinal axonal and neuronal damage develops over the course of weeks after the onset of acute optic neuritis. When it involves the optic nerve head, it is called *papillitis* and, in bilateral cases, can be impossible to differentiate from papilledema. Optic neuritis also can be mimicked by anterior segment, choroidal, or retinal diseases. Optic neuritis is distinguished from optic neuropathy, which is a chronic, generally noninflammatory condition of the optic nerve caused by tobacco or nutritional amblyopia, ischemia, Leber disease, Charcot-Marie-Tooth type 2a (mitofusinopathy; Chapter 388), or a number of other rare hereditary diseases (Chapter 392). Subclinical optic neuropathy in the absence of painful monocular visual loss resulting in retinal nerve fiber layer and ganglion cell layer thinning over time and appears to be common in most cases of multiple sclerosis independent of acute optic neuritis

TREATMENT

Among patients with optic neuritis, the 15-year risk for developing multiple sclerosis is 25% in patients without lesions on their baseline brain MRI but 72% in patients with one or more baseline MRI lesions. Treatment with intravenous methylprednisolone as in multiple sclerosis or with bioequivalent doses of oral corticosteroids[A20] may shorten the duration and severity of the attack, but no definitive evidence indicates that it changes the long-term outcome. In patients whose optic neuritis is at high risk for conversion to multiple sclerosis (one or more typical brain MRI lesions), data support the use of therapies that modify the course of multiple sclerosis.

Transverse Myelitis

Transverse myelitis is a rare (approximately 1 in 100,000 people) monophasic inflammatory process of the spinal cord that is usually distinct from multiple sclerosis in that it either involves the entire cross section or is longitudinally extensive along three vertebral body segments rostrocaudally.[19] Transverse myelitis or myelopathy may be idiopathic or associated with inflammatory diseases (neuromyelitis optica, systemic lupus erythematosus, Sjögren syndrome, vasculitis, or multiple sclerosis), infectious diseases, or vascular diseases (antiphospholipid antibody syndrome or dural venous fistula).

CLINICAL MANIFESTATIONS AND DIAGNOSIS

In its fulminant form, transverse myelitis causes complete loss of motor and sensory function below the affected level of the spinal cord and causes concomitant bowel, bladder, and sexual dysfunction. Autonomic involvement can be seen in cervical and high thoracic spine cases. Longitudinally extensive transverse myelitis (a lesion extending across three vertebral body lengths) should prompt consideration of neuromyelitis optica. Transverse myelitis also may manifest in an incomplete or partial form, which is more commonly associated with multiple sclerosis. In older patients, patients with vascular risk factors, or patients with central cord edema pattern on MRI, spinal angiography should be considered to exclude spinal cord ischemia or infarction (Chapter 369).

TREATMENT AND PROGNOSIS

Treatment of the inflammatory process is usually with methylprednisolone (1000 mg IV for 3 to 5 days), followed by specific treatment of any identifiable underlying disease process. The prognosis is worse than in multiple sclerosis in that significant recovery is seen in fewer than 50% of patients and many patients remain completely paralyzed after the initial attack. Plasma exchange, IVIG, or cyclophosphamide may be considered in steroid-refractory cases.

NEUROMYELITIS OPTICA SPECTRUM DISORDERS

Neuromyelitis optica (Chapter 392) is now recognized as an entity distinct from multiple sclerosis and is characterized by an optic neuritis, often bilateral and temporally associated with a fulminant multilevel transverse myelitis.[20] A specific serum IgG (NMO-IgG) directed against aquaporin 4 is diagnostic of this process, although seronegative patients with similar clinical presentations exist and are part of what is now called NMO spectrum disorder. Brain lesions may be seen on MRI and have a predilection for the brain stem. Neuromyelitis optica may be similar to what is called *opticospinal multiple sclerosis* in Japan, although the latter overlaps with multiple sclerosis. Several biologic agents (satralizumab [a humanized monoclonal antibody targeting the interleukin-6 receptor at 120 mg subcutaneously at 0, 2, and 4 weeks, then every 4 weeks thereafter], eculizumab [a terminal complement inhibitor at 900 mg intravenously weekly for 4 doses followed by 1200 mg every 2 weeks], and tocilizumab [an interleukin-6 receptor inhibitor at 8 mg intravenously every 4 weeks]) can reduce the risk of relapse (see Chapter 392) in aquaporin-4–positive neuromyelitis optica and may be preferred over azathioprine 3 mg/kg/day or rituximab 1000 mg IV 2 weeks apart every 6 months.[A21–A23] However, most patients develop sustained disabling visual loss and weakness.

MYELIN OLIGODENDROCYTE GLYCOPROTEIN ANTIBODY DISORDER

Myelin oligodendrocyte glycoprotein IgG associated disorder can mimic neuromyelitis optica but also can present as isolated optic neuritis. It tends to have a milder course with fewer attacks and resolution of some MRI lesions.[21] In addition to therapies used for neuromyelitis optica, IVIG appears to be effective in myelin oligodendrocyte glycoprotein antibody disorder.[22]

ACUTE DISSEMINATED ENCEPHALOMYELITIS

Acute disseminated encephalomyelitis and its hyperacute form, acute necrotizing hemorrhagic encephalopathy, are thought to be forms of monophasic immune-mediated inflammatory demyelination. They differ from multiple sclerosis in that they are typically monophasic, whereas multiple sclerosis is by definition multiphasic or chronically progressive. However, no reliable clinical or pathologic criteria are available to differentiate the two processes, which may represent a continuum. Patients may present with fever, headache, meningeal signs, and altered consciousness, which are exceedingly rare in multiple sclerosis. There is no known effective treatment. Large numbers of patients, especially children, make remarkable recoveries, but the necrotizing form can be severely disabling or fatal. Relapsing forms of the disease in children are more likely to become multiple sclerosis.

LEUKODYSTROPHIES

The leukodystrophies represent a variety of diseases characterized by progressive hereditary CNS white matter degeneration thought to be related to abnormal production or maintenance of myelin. Many of these diseases now have a defined biochemical and genetic basis, are caused by primary pathology in other CNS components (including astrocytes, microglia, axons, and blood vessels), and are no longer considered exclusively to be primary myelin disorders.

ADRENOLEUKODYSTROPHY AND ADRENOMYELONEUROPATHY

Adrenoleukodystrophy and adrenomyeloneuropathy, which are caused by impaired ability of the peroxisomes to metabolize very-long-chain fatty acids, represent different phenotypes resulting from the same X-linked, incompletely recessive genetic defect. Impaired oxidation of very-long-chain fatty acids results from deficient function of the enzyme lignoceroyl–coenzyme A ligase. The defective gene maps to Xq28 and codes for a peroxisomal membrane protein (ALDP), which is a member of a large family of proteins referred to as the adenosine triphosphate–binding cassette (ABC) transporters, specifically *ABCD1*.

Childhood cerebral adrenoleukodystrophy, which is the most common form of the disorder, represents 45% of all cases; it is seen only in male patients, with an onset at ages 4 to 11 years. Adolescent (5%) and adult (3%) cerebral forms progress at a similar or slower rate than the childhood form.

CLINICAL MANIFESTATIONS

Adrenomyeloneuropathy begins in young men as slowly progressive paraparesis with hypogonadism, impotence, sphincter disturbances, variable adrenal insufficiency, and axonal neuropathy affecting mainly the lower extremities. A rare acute inflammatory form with rapid progression and dementia may occur. A similar, but usually milder, disorder can be seen in up to 20% of women who are hemizygous for the disease.

DIAGNOSIS

Diagnosis is established in male patients by finding elevated very-long-chain fatty acids in the plasma. DNA-based diagnosis in carriers is reliable and is recommended in women because of false-negative results using the plasma assay.

TREATMENT

Treatment has been unsatisfactory. A 4:1 mixture of glyceryl trioleate and glyceryl trierucate (i.e., "Lorenzo oil") normalizes plasma very-long-chain fatty acids within 4 weeks and has few side effects. Although clinical trials suggested that treatment in presymptomatic patients delayed or prevented the onset of disease, this treatment is ineffective after symptoms have begun and the disease progresses relentlessly.

Elivaldogene autotemcel gene therapy, which has breakthrough FDA approval for cerebral adrenoleukodystrophy, is designed to add functional copies of the *ABCD1* gene into a patient's own hematopoietic (blood) stem cells.[23] In one study, 90% of treated patients were alive and free of major functional disabilities at 24 months follow-up.

PELIZAEUS-MERZBACHER DISEASE

Pelizaeus-Merzbacher disease is a rare, chronic, familial leukodystrophy usually caused by a genetic defect in the X-linked myelin proteolipid protein *(PLP)* gene. In classic Pelizaeus-Merzbacher disease, age at onset varies between 3 months and 9 years, and the age at death varies between 6 years and 25 years. However, milder forms of spastic paraplegia 2 are now well recognized in adults. The disease manifests as a slowly progressive myelopathy, often with cerebellar and cognitive involvement, and the diagnosis is established by genetic testing for mutations in the *PLP* gene. A variety of different types of *PLP* mutations account for the variability in clinical phenotypes. An autosomal recessive disease called Pelizaeus-Merzbacher–like disease 1 and the less severe spastic paraplegia 44, caused by mutations of the gap junction protein gamma-2 gene *(GJC2)*, are recognized variants. No specific treatment exists beyond supportive therapy.

METACHROMATIC LEUKODYSTROPHY

Metachromatic leukodystrophy usually results from a recessively inherited defect in the lysosomal enzyme arylsulfatase A. Absence of arylsulfatase A results in the accumulation of sulfatide in both central and peripheral myelin and myelin-forming cells; instability of the myelin membranes results in the breakdown of myelin. Metachromatic leukodystrophy is generally divided into four subtypes: congenital, late infantile (most common), juvenile, and adult. It appears in all ethnic groups and has an overall frequency of one in 40,000.

The clinical manifestations are variable and may include progressive spastic paraparesis, extrapyramidal signs, seizures, and peripheral neuropathy. Brain MRI usually shows large confluent symmetrical high-signal areas in the cerebral white matter, brain stem, and cerebellum, but a more patchy appearance resembling multiple sclerosis is occasionally seen in adult cases. At present, no satisfactory treatment exists. A case series suggests that hematopoietic stem cell gene therapy can potentially prevent the onset of symptoms in presymptomatic patients and may slow or even halt progression of the disease. In this approach, hematopoietic stem cells are transduced ex vivo using a lentiviral vector encoding the human *arylsulfatase-A (ARSA)* gene to produce the ARSA enzyme that breaks down sulfatides that accumulate in nerve and other cells. The treatment is indicated in children with asymptomatic late infantile or early juvenile disease, or juveniles who have early clinical manifestations but still can walk independently and have not yet experienced cognitive decline.

GLOBOID CELL LEUKODYSTROPHY

Globoid cell leukodystrophy (Krabbe disease; Chapter 192) is characterized biochemically by accumulation of galactocerebroside in cerebral white matter as a result of deficient galactocerebroside β-galactosidase activity. The disease is transmitted as an autosomal recessive trait and affects infants in the first 2 to 3 months of life, initially manifesting with behavioral changes and failure to achieve developmental milestones. Rare late-onset cases manifest with progressive motor impairment and, less frequently, visual failure. Neuropathologic examination reveals marked loss of myelin throughout the brain, with the presence of round or oval macrophages and large, irregular, multinucleated cells, termed *globoid cells,* that are filled with galactocerebroside. Accumulation of galactosylsphingosine (psychosine) is thought to cause destruction of oligodendrocytes and marked reduction of myelin formation.

CANAVAN DISEASE

Canavan disease is a fatal, progressive leukodystrophy with an autosomal recessive inheritance, caused by mutations in the gene for aspartoacylase, an enzyme that hydrolyzes *N*-acetylaspartate into L-aspartate and acetate. Aspartoacylase deficiency results in elevated levels of its substrate molecule, *N*-acetylaspartate, brain edema, and dysmyelination. Clinically, the disease manifests with developmental delay, seizures, and diffuse, symmetrical white matter degeneration in the subcortical areas, with involvement of the globus pallidum on MRI. No treatment is available.

VANISHING WHITE MATTER DISEASE

Vanishing white matter disease is an increasingly recognized autosomal recessive disorder with a broad range of clinical manifestations from rapidly progressive presentations in infants to slowly progressive disease in adults. The disease is caused by mutations in the eukaryotic translation initiation factor 2B *(eIF2B)* genes 1 to 5, which code for proteins involved in the integrated stress response of cells. Pathologic characteristics include vacuolated myelin with cystic appearance on MRI. No specific therapy, other than avoidance of stress, is known.

CHRONIC AUTOIMMUNE SYNDROMES

Chronic autoimmune neurologic syndromes with either cerebral or extracerebral symptoms and signs include stiff person syndrome, which is characterized by chronic progressive axial rigidity and spasticity and is associated with high-titer anti-GAD65, antiamphiphysin (women), and anti–glycine receptor antibodies. Stiff person syndrome, which may be mistaken for progressive supranuclear palsy (Chapter 378), is associated with diabetes and other endocrine disorders. Progressive encephalomyelitis with rigidity and myoclonus is a distinct process that may be confused with stiff person syndrome but is often more acute in onset and rapidly progressive; patients also may have brain stem features such as ataxia, dysphagia, dysarthria, and ophthalmoparesis. Rasmussen encephalitis is a refractory epilepsy syndrome with hemispheric dysfunction associated with CD8 T-lymphocyte infiltration.

Autoimmune encephalitis is discussed in Chapter 383.

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For the General References and other additional features, please visit Elsevier eBooks+ at https://ebooks.health.elsevier.com.

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381 MENINGITIS: BACTERIAL, VIRAL, AND OTHER

AVINDRA NATH

BACTERIAL MENINGITIS

DEFINITION

Meningitis is an inflammation of the arachnoid membrane, the pia mater, and the intervening cerebrospinal fluid (CSF). The inflammatory process extends throughout the subarachnoid space around the brain and spinal cord and involves the ventricles. Pyogenic meningitis is usually an acute bacterial infection that evokes a polymorphonuclear response in CSF. By comparison, tuberculous meningitis (Chapter 299) is often subacute and characterized initially by a modest polymorphonuclear pleocytosis that rapidly evolves to lymphocytic predominance.

EPIDEMIOLOGY

The incidence of bacterial meningitis has dropped dramatically to about 0.5 to 1.5 cases per 100,000 adults in developed countries largely because of vaccines against bacterial pathogens such as *Haemophilus influenzae* type b (Chapter 274), *Streptococcus pneumoniae* (Chapter 268), and *Neisseria meningitidis* (Chapter 306). Since the advent of the *Haemophilus* vaccine, *S. pneumoniae* has become the most common pathogen, accounting for about 70% of cases, and the disease is now more common in older adults than children. Unfortunately, mortality rates (~15%) have not changed. Worldwide, the incidence of bacterial meningitis is related to poverty and remains a major cause of mortality and morbidity. Although all human microbes have the potential to cause meningitis, only a few organisms cause most cases of bacterial meningitis.

The clinical setting in which meningitis develops may provide a clue to the specific bacterial cause. *H. influenzae* (Chapter 277) affects primarily children,

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GLOBOID CELL LEUKODYSTROPHY

Globoid cell leukodystrophy (Krabbe disease; Chapter 192) is characterized biochemically by accumulation of galactocerebroside in cerebral white matter as a result of deficient galactocerebroside β-galactosidase activity. The disease is transmitted as an autosomal recessive trait and affects infants in the first 2 to 3 months of life, initially manifesting with behavioral changes and failure to achieve developmental milestones. Rare late-onset cases manifest with progressive motor impairment and, less frequently, visual failure. Neuropathologic examination reveals marked loss of myelin throughout the brain, with the presence of round or oval macrophages and large, irregular, multinucleated cells, termed *globoid cells,* that are filled with galactocerebroside. Accumulation of galactosylsphingosine (psychosine) is thought to cause destruction of oligodendrocytes and marked reduction of myelin formation.

CANAVAN DISEASE

Canavan disease is a fatal, progressive leukodystrophy with an autosomal recessive inheritance, caused by mutations in the gene for aspartoacylase, an enzyme that hydrolyzes *N*-acetylaspartate into L-aspartate and acetate. Aspartoacylase deficiency results in elevated levels of its substrate molecule, *N*-acetylaspartate, brain edema, and dysmyelination. Clinically, the disease manifests with developmental delay, seizures, and diffuse, symmetrical white matter degeneration in the subcortical areas, with involvement of the globus pallidum on MRI. No treatment is available.

VANISHING WHITE MATTER DISEASE

Vanishing white matter disease is an increasingly recognized autosomal recessive disorder with a broad range of clinical manifestations from rapidly progressive presentations in infants to slowly progressive disease in adults. The disease is caused by mutations in the eukaryotic translation initiation factor 2B *(eIF2B)* genes 1 to 5, which code for proteins involved in the integrated stress response of cells. Pathologic characteristics include vacuolated myelin with cystic appearance on MRI. No specific therapy, other than avoidance of stress, is known.

CHRONIC AUTOIMMUNE SYNDROMES

Chronic autoimmune neurologic syndromes with either cerebral or extracerebral symptoms and signs include stiff person syndrome, which is characterized by chronic progressive axial rigidity and spasticity and is associated with high-titer anti-GAD65, antiamphiphysin (women), and anti–glycine receptor antibodies. Stiff person syndrome, which may be mistaken for progressive supranuclear palsy (Chapter 378), is associated with diabetes and other endocrine disorders. Progressive encephalomyelitis with rigidity and myoclonus is a distinct process that may be confused with stiff person syndrome but is often more acute in onset and rapidly progressive; patients also may have brain stem features such as ataxia, dysphagia, dysarthria, and ophthalmoparesis. Rasmussen encephalitis is a refractory epilepsy syndrome with hemispheric dysfunction associated with CD8 T-lymphocyte infiltration.

Autoimmune encephalitis is discussed in Chapter 383.

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The clinical setting in which meningitis develops may provide a clue to the specific bacterial cause. *H. influenzae* (Chapter 277) affects primarily children,

ABSTRACT

Inflammation within the meningeal space can result from a myriad of infectious agents and noninfectious causes. Proper diagnosis is dependent not only on detection of the offending organism, but also on a proper understanding of the risk factors, clinical manifestations, and laboratory findings, including the host immune response and the features on neuroimaging. In a substantial proportion of cases, the organism may be elusive and initial empirical therapy may be required. In many cases in which antimicrobial therapy alone may not be optimal, modulation of the host immune response and management of the associated complications can have a major impact on the patient's prognosis. This chapter provides a detailed description of the various causes of meningitis as well as how to diagnose and treat them.

KEYWORDS

bacterial meningitis
viral meningitis
CSF
pleocytosis
meningeal signs

whereas *S. pneumoniae* (Chapter 268) affects predominantly adults older than age 50 years with comorbid conditions. Meningococcal meningitis (Chapter 274) often occurs in outbreaks. In developed countries, *Listeria monocytogenes* (Chapter 272) is emerging as the most common cause of bacterial meningitis, with peak frequencies in neonates and in persons older than 60 years of age. Simultaneous mixed bacterial meningitis is rare but may occur after neurosurgical procedures, penetrating head injury, head trauma with fracture of the cribriform plate, erosion of the skull or vertebrae by adjacent neoplasm, extension of osteomyelitis, or intraventricular rupture of a cerebral abscess. Isolation of anaerobes should strongly suggest the latter two of these situations. In approximately 10% of patients with pyogenic meningitis, the bacterial cause cannot be defined.

Over the past several decades, gram-negative bacillary meningitis has doubled in frequency in adults, a change reflecting more frequent and extensive neurosurgical procedures, as well as other nosocomial factors. *L. monocytogenes* (Chapter 272) has increased 8- to 10-fold as a cause of bacterial meningitis. *Listeria* infections are often food-borne via dairy products, processed meats, uncooked vegetables, and pre-cut salads. Although *Listeria* meningitis may occur in immunocompetent individuals, it occurs most frequently in individuals who are immunocompromised owing to organ transplantation, hemodialysis, corticosteroid therapy, chemotherapy for cancer or autoimmune diseases, liver disease, alcoholism, uncontrolled diabetes, and pregnancy. Meningitis caused by coagulase-negative staphylococci, which represents approximately 3% of cases in large urban hospitals, occurs as a complication of neurosurgical procedures and is often caused by methicillin-resistant strains.

In large tertiary care hospitals, approximately 40% of cases of bacterial meningitis in adults are of nosocomial origin. The leading causes are gram-negative bacilli (primarily *Escherichia coli* and *Klebsiella*), which account for approximately 40% of nosocomial episodes, as well as various streptococci, *Staphylococcus aureus*, and coagulase-negative staphylococci, each responsible for approximately 10% of nosocomial cases.

Meningococcal disease (Chapter 274), including meningitis, may occur sporadically and in cyclic outbreaks. High-risk groups include individuals who live in close quarters such as crowded classrooms, college dormitories, military barracks, or jails. It is carried in the nasopharynx and spread by nasal or oral secretions. With the introduction of the meningococcal vaccine, the incidence of meningococcal meningitis has decreased dramatically, although vaccinated populations remain vulnerable to the serotypes that are not covered by the vaccine. Antibiotic-resistant strains of meningococcus also have emerged.

Predisposing factors for the development of pneumococcal meningitis include acute otitis media (Chapters 268 and 394), with or without mastoiditis, in approximately 20% of adult patients. Pneumonia is present in approximately 15% of patients with pneumococcal meningitis, a much higher frequency than in meningitis caused by *H. influenzae* or *N. meningitidis*. Acute pneumococcal sinusitis (Chapter 394) is occasionally the initial focus from which infection spreads to the meninges. A recent or remote major head injury (Chapter 368) precedes approximately 10% of episodes of pneumococcal meningitis, and CSF rhinorrhea (usually caused by a fracture in the cribriform plate) is present in approximately 5% of patients. Occasionally, meningitis caused by *S. pneumoniae* develops in patients with central nervous system (CNS) shunts. Splenectomy or splenic dysfunction, as in sickle cell anemia (Chapter 149), cirrhosis (Chapter 139) with portal hypertension, or defects in humoral immunity also predispose patients to pneumococcal meningitis. Alcoholism (Chapter 364) is an underlying risk factor in 10 to 25% of adults with pneumococcal meningitis in urban hospitals.

The estimated annual incidence of bacterial meningitis (primarily pneumococcal) in untreated patients infected with human immunodeficiency virus (HIV; Chapter 353) and untreated with antiretrovirals is 150-fold higher than in the general population. However, cryptococcal meningitis and tuberculous meningitis are much more common in HIV-infected patients.

S. aureus (Chapter 267) meningitis may occur from a neurosurgical procedure, after penetrating skull trauma, or occasionally with staphylococcal bacteremia, and methicillin-resistant forms are increasing in frequency. Meningitis caused by group A streptococci is uncommon but occasionally occurs after acute otitis media, more often in children than in adults.

Meningitis caused by gram-negative bacilli takes one of two forms in adults: meningitis after trauma or neurosurgery (e.g., shunt infections), or spontaneous meningitis in adults (e.g., bacteremic *Klebsiella* meningitis in a patient with diabetes mellitus, sinusitis, or otitis media). The most common causes of gram-negative bacillary meningitis in adults are *E. coli* (≈30%) and *Klebsiella-Enterobacter* (≈40%), but *Bacteroides* (Chapter 273), *Fusobacterium* (Chapter 273), *Clostridioides* (Chapter 271), *Actinomyces* (Chapter 304), and *Propionibacterium* (Chapter 272) species also can cause meningitis. *H. influenzae* type b meningitis in an adult suggests an underlying anatomic or immunologic defect.

PATHOBIOLOGY

Pathology

On gross examination, purulent exudate in the subarachnoid space is most abundant in the cisterns at the base of the brain and over the convexities of the Rolandic and Sylvian sulci, which are expansions of the subarachnoid space. Although neither the infecting organism nor the inflammatory exudate directly invades cerebral tissue, the subjacent brain becomes congested and edematous. The pial barrier generally prevents bacterial meningitis from causing a cerebral abscess; when these two processes coexist, the sequence is usually that an initial abscess leaks its contents into the ventricular system or the subarachnoid space, where it produces secondary ventriculitis and/or meningitis.

The inflammatory exudate can extend around the perivascular spaces to adjacent structures, especially the arteries and veins that carry a layer of pia mater and arachnoid membrane as they enter the brain from the cortical surface. *Cortical thrombophlebitis* results from venous stasis and adjacent meningeal inflammation. Infarction of cerebral tissue may follow. *Involvement of cortical and pial arteries* by peripheral aneurysm formation and vascular occlusion or narrowing (related to spasm, arteritis, or both) of the supraclinoid portion of the internal carotid artery at the base of the brain occurs in approximately 15% of patients with meningitis. The anterior and middle cerebral arteries may also develop stenosis or spasm. In fulminating cases, particularly meningococcal meningitis, *cerebral edema* may be marked even though the pleocytosis is only moderate. Rarely, temporal lobe herniation through the tentorium develops in such patients and compresses the midbrain, thereby leading to ipsilateral third nerve palsy and contralateral hemiparesis; or cerebellar herniation through the foramen magnum with compression of the medulla, which results in apnea, hemodynamic instability, and coma. *Damage to cranial nerves* occurs in areas where dense exudate accumulates around the nerves; the third and sixth cranial nerves are also vulnerable to damage by increased intracranial pressure. *Ventriculitis* accompanies most cases of bacterial meningitis and may rarely progress to *ventricular empyema*. As the exudates accumulate, obstruction of the flow of CSF may result in *hydrocephalus*. Obstruction of the cerebral aqueduct or foramina of Magendie and Luschka at the base of the fourth ventricle results in noncommunicating or obstructive hydrocephalus, whereas obstruction at the level of the arachnoid granulations in the venous sinuses results in communicating hydrocephalus. *Subdural effusions* are sterile transudates that develop over the cerebral cortex and can be demonstrated readily by computed tomography (CT) as low-density areas about the cerebrum. On magnetic resonance imaging (MRI), they appear as high signal intensity lesions of T2 or fluid-attenuated inversion recovery (FLAIR) sequences. Rarely, such an effusion becomes an infected subdural empyema.

Pathogenesis

Bacteria may gain access to the meninges by several routes: (1) hematogenous spread from a distant site; (2) direct ingress from the upper respiratory tract or skin through an anatomic defect (e.g., skull fracture, meningocele, sequela of surgery); (3) passage intracranially through venules in the nasopharynx; or (4) spread from a contiguous focus of infection (infection of the paranasal sinuses, leakage of a brain abscess). Bacteremic spread of *H. influenzae, N. meningitidis*, and *S. pneumoniae* is probably the most frequent path of infection. Bacteremia is usually initiated by pharyngeal adhesion and colonization by an infecting strain. Adhesion of such strains, as well as of *S. pneumoniae*, to mucosal surfaces is abetted by their capacity to produce proteases that cleave immunoglobulin A, thus inactivating this local antibody defense. Adhesion of *N. meningitidis* to nasopharyngeal cells is affected by fimbriae or pili and promoted by previous damage to ciliated cells such as from smoking or viral infections. Meningococci invade the nasopharyngeal mucosal cells by means of endocytosis and are transported to the abluminal side in membrane-bound vacuoles. *H. influenzae*, in contrast, invades intercellularly by causing separation of the apical tight junctions between columnar epithelial cells. When these meningeal pathogens gain access to the blood stream, their intravascular survival is aided by the presence of polysaccharide capsules that inhibit phagocytosis and confer resistance to complement-mediated bactericidal activity.

Bacteria also may travel along nerve tracts to invade the brain. For example, *L. monocytogenes* invades the intestine, and animal models suggest that these bacteria can travel along the vagus nerve to the brain stem, from where they also may invade the meninges in the posterior fossa.

Bacteria can gain access to the subarachnoid spaces from blood cells, either by disruption of the blood-brain barrier or via the choroid plexus, also termed the blood-CSF barrier. Once established in any part of the meninges, infection quickly extends throughout the subarachnoid space. Bacterial replication proceeds relatively unhindered because the low CSF levels of immunoglobulin and complement early in meningeal inflammation result in minimal or no opsonic or bactericidal activity and because surface phagocytosis of unopsonized organisms is meager in such a fluid environment. During meningitis, the concentrations of immunoglobulins in CSF increase but still remain relatively low. Secondary bacteremia may follow meningeal infection and may itself contribute to continuing further inoculation of CSF.

Bacterial meningitis following head trauma occurs because of a dural fistula from the nasal cavity, paranasal sinuses, or middle ear to the subarachnoid space. The most frequent site is at the cribriform plate, where the bone is thin and the dura is tightly adherent to the bone. Leakage of CSF results in CSF rhinorrhea and loss of smell.

Cerebral blood flow, which depends on mean arterial pressure, is increased in the early stages of meningitis, but it subsequently decreases, substantially in some patients, which may cause ischemic neurologic injury. Localized regions of marked hypoperfusion, attributable to focal vascular inflammation or thrombosis, can occur in patients with normal blood flow. Impairment of cerebral blood flow autoregulation, as measured by transcranial Doppler ultrasonography of the middle cerebral artery, occurs early in acute bacterial meningitis and causes cerebral blood flow to correspond directly to mean arterial blood pressure, with attendant hyperperfusion or hypoperfusion of the brain. On recovery, the ability of the cerebral vasculature to maintain a constant level of perfusion despite variations in mean arterial pressure is restored.

Genetics

Patients with defects in cell-mediated immunity are susceptible to the development of CNS infections with intracellular organisms such as *L. monocytogenes*. Patients with defective humoral immunity and an inadequate antibody response are particularly vulnerable to meningitis with *S. pneumoniae* and *H. influenzae*. For example, deficiencies in the complement system predispose patients to meningitis, and 50 to 60% of adults with pneumococcal meningitis may have C2 deficiency. Mutation in the intron of UBE2U, which is involved in antigen presentation, is also linked to severity of pneumococcal meningitis. Meningococcal meningitis is associated with polymorphisms in CD32, CD16, mannose-binding lectin, toll-like receptor 4 (TLR4), and the B-2 adrenoceptor gene. Patients with neutropenia are at higher risk for meningitis with *Pseudomonas aeruginosa* and members of the Enterobacteriaceae family.

CLINICAL MANIFESTATIONS

History

Acute-onset fever, generalized headache, vomiting, and stiff neck are common to many types of meningitis (Table 381-1). Most patients with community-acquired pyogenic meningitis have had an antecedent or accompanying upper respiratory tract infection or nonspecific febrile illness, acute otitis (or mastoiditis), or pneumonia. Myalgia, particularly in patients with meningococcal disease, backache, and generalized weakness are common symptoms. The illness usually progresses rapidly, with the development of confusion, obtundation, and loss of consciousness. Occasionally, the onset may be less acute, with meningeal signs being present for several days to a week.

General Physical Findings

Evidence of meningeal irritation is usually present, as evidenced by a stiff neck, Kernig sign (inability to straighten the leg when the hip is flexed to 90 degrees), and Brudzinski sign (involuntary flexion of the hip and knee when the neck is passively flexed). Neck stiffness, Kernig sign, and Brudzinski sign each have sensitivities of approximately 30% or lower for diagnosing acute bacterial meningitis in adults. Although the classic triad of fever, stiff neck, and change in mental status is initially present in only about 45% of episodes, a combination of two of four symptoms (headache, fever, stiff neck, and altered mental status) is found in 95% of patients. The findings of meningitis may be easily overlooked in infants, obtunded patients, elderly patients with heart failure or pneumonia, or immunosuppressed individuals, who may have meningitis without prominent meningeal signs; in such patients, lethargy should be investigated carefully, meningeal signs should be sought, and examination of CSF is indicated if any doubt exists. In elderly patients, neck stiffness may be difficult to evaluate because of osteoarthritis in the neck or stiffness of neck muscles secondary to basal ganglia disorders. When neck stiffness is caused by meningitis, the neck resists flexion but can be rotated passively from side to side; with cervical spine disease, however, resistance is present in all directions of neck movement. Neck stiffness disappears during coma.

TABLE 381-1 SYMPTOMS AND SIGNS OF BACTERIAL MENINGITIS*

CHARACTERISTIC	EPISODES OF MENINGITIS
Duration of symptoms <24 hr	48%
Predisposing conditions	
Otitis or sinusitis	25%
Pneumonia	12%
Immunocompromise†	16%
Symptoms at initial evaluation	
Headache	87%
Nausea	74%
Neck stiffness	83%
Triad of fever, neck stiffness, and change in mental status	44%
Focal neurologic deficits	33%
Aphasia	23%
Hemiparesis	7%
Indices of CSF inflammation	
Opening pressure (mm H_2O)‡	370 ± 130
White cell count§	
Mean (cells/μL)	7753 ± 14,736
<100/μL	7%
100-999/μL	14%
>999/μL	78%
Protein (g/L)	4.9 ± 4.5
CSF/blood glucose ratio	0.2 ± 0.2
Positive blood culture‖	66%
Blood tests	
ESR (mm/hr)¶	46 ± 37
C-reactive protein (g/L)**	225 ± 132
Platelet count (platelets/μL)††	198,000 ± 100,000

*Data from 696 cases reported in van de Beek D, de Gans J, Spanjaard L, et al. Clinical features and prognostic factors in adults with bacterial meningitis. *N Engl J Med*. 2004;351:1849-1859. The study included 671 patients who had a total of 696 episodes of community-acquired meningitis. Plus-minus values are means ± standard deviation.

†Immunocompromise was defined by the use of immunosuppressive drugs, a history of splenectomy, or the presence of diabetes mellitus or alcoholism, as well as patients infected with human immunodeficiency virus.

‡CSF pressure was measured in 216 patients.

§The CSF leukocyte count was determined in 659 patients; CSF specimens from 14 patients had too many leukocytes for an exact count to be performed.

‖Blood culture was performed in 611 patients.

¶The ESR was determined in 549 patients.

**C-reactive protein levels were determined in 394 patients.

††The thrombocyte count was determined in 653 patients.

CSF = cerebrospinal fluid; ESR = erythrocyte sedimentation rate.

The presence of a petechial or ecchymotic rash (see Fig. 274-2 in Chapter 274) in a patient with meningeal findings almost always indicates meningococcal infection and requires prompt treatment because of the rapidity with which this infection can progress (Chapter 274). Rarely, extensive petechial and ecchymotic lesions occur in meningitis caused by *S. pneumoniae, H. influenzae,* or echovirus type 9. Very rarely, skin lesions almost indistinguishable from those of meningococcal bacteremia occur in patients who have acute *S. aureus* endocarditis (see Fig. 61-1 in Chapter 61) and who also have meningeal signs and pleocytosis (secondary to either staphylococcal meningitis or embolic cerebral infarction). Usually, one or two of the lesions in such a patient represent purulent purpura; aspiration of material reveals staphylococci on Gram staining. In the summer, viral aseptic meningitis may produce meningeal signs, macular and petechial skin lesions, and a pleocytosis of several hundred cells, sometimes with neutrophils predominating initially.

Fulminant meningococcal septicemia may cause hemorrhages within the adrenal glands and result in Waterhouse-Friderichsen syndrome (Chapter 208), a condition characterized by the sudden onset of a febrile illness, large petechial hemorrhages in the mucous membranes and skin, cardiovascular collapse, and disseminated intravascular coagulation. In contrast, hyponatremia and the syndrome of inappropriate secretion of antidiuretic hormone may develop in patients with meningitis attributable to *H. influenzae*. A concurrent

respiratory tract infection or acute otitis media may be present with either *H. influenzae* or *S. pneumoniae*.

In patients with a basilar skull fracture, the potential for development of a dural fistula and bacterial meningitis is indicated by the presence of CSF rhinorrhea, periorbital ecchymoses, bruising behind the ear (Battle sign), hemotympanum, or blood in the external auditory canal. Meningitis complicating neurosurgical procedures may be insidious in onset and difficult to distinguish from the altered consciousness and signs of meningeal irritation that are expected in the postoperative period. However, fever or prolonged obtundation is an indication for evaluation of CSF.

Neurologic Findings and Complications

Neurologic abnormalities in patients with inadequately treated bacterial meningitis can be severe and disabling.[1] Cranial nerve abnormalities, involving principally the third, fourth, sixth, or seventh nerve, occur in 5 to 10% of adults with community-acquired meningitis and usually disappear shortly after recovery. The most likely sites of involvement in patients with persistent sensorineural deafness appear to be the inner ear (infection or toxic products possibly spreading from the subarachnoid space along the cochlear aqueduct) and the acoustic nerve.

Seizures (focal or generalized; Chapter 372) occur in 20 to 30% of patients and may result from reversible causes (high fever or hypoglycemia in infants, penicillin neurotoxicity when large doses are administered intravenously [IV] to patients with renal failure) or, more commonly, from focal cerebral injury related to arterial hypoperfusion and infarction, cortical venous thrombosis, or focal edema and cerebritis. Seizures can occur during the first few days or can appear with associated focal neurologic deficits caused by vascular inflammation some days after onset of the meningitis. In adults with seizures accompanying meningitis, *S. pneumoniae* is more commonly the cause, but alcohol withdrawal is a confounding factor.

Increased CSF pressure, which can be caused by brain swelling or hydrocephalus, is associated with seizures, vomiting, sixth and third nerve dysfunction, abnormal reflexes, reduced consciousness or coma, dilated and poorly reactive pupils, and the Cushing response of decerebrate posturing, hypertension, bradycardia, and irregular respirations. In approximately a fourth of fatal cases of community-acquired meningitis in adults, cerebral edema accompanied by temporal lobe herniation is observed at autopsy.

Papilledema (see Fig. 391-25 in Chapter 391) occurs in less than 1% of patients with bacterial meningitis, even with high CSF pressure, probably because the patient is seen early in the process before changes in the nerve head have occurred. The presence of this sign should indicate the possibility of another associated or independent suppurative intracranial process, such as subdural empyema or brain abscess or a more chronic process such as fungal or tuberculous meningitis. Marked central hyperpnea sometimes occurs in patients with severe bacterial meningitis; CSF acidosis, which is principally due to increased lactic acid levels, provides much of the respiratory stimulus.

Focal cerebral signs (principally hemiparesis, dysphasia, visual field defects, and gaze preference) occur in approximately a third of adults with community-acquired bacterial meningitis. These signs may develop because of arterial or venous occlusion or concurrent development of brain abscess (Chapter 382), subdural empyema or cerebral edema. In addition, cerebral blood flow velocity may be decreased in patients with increased intracranial pressure and may lead to temporary or lasting neurologic dysfunction. It is important to distinguish these vascular effects from postictal changes (Todd paralysis), which usually persist for less than a day. Meningitis may cause the syndrome of inappropriate secretion of antidiuretic hormone.

DIAGNOSIS

Bacterial meningitis is a medical emergency that requires immediate diagnosis and rapid institution of antimicrobial therapy.[2] Delay in treatment is the most critical factor in determining the morbidity and mortality of patients with bacterial meningitis. The diagnosis of bacterial meningitis is not difficult in a febrile patient with meningeal symptoms and signs developing in the setting of a predisposing illness. The diagnosis may be less obvious in an elderly, obtunded patient with pneumonia or a confused alcoholic patient in impending delirium tremens.

When the diagnosis of bacterial meningitis is entertained, blood cultures should be performed, CSF examined and cultured and antimicrobial therapy instituted promptly. Observational data suggest that the prompt performance of a lumbar puncture before CT scanning is associated with significantly earlier treatment and favorable outcomes.[3] If a mass lesion (cerebral abscess, subdural empyema) is suspected from the history (e.g., recent seizure), clinical setting (e.g., coma), or physical findings (e.g., papilledema, focal cerebral signs, decorticate or decerebrate posturing, abnormal breathing pattern, or fixed or dilated pupils), CT with or without contrast enhancement or MRI should be performed because of the danger of brain herniation with lumbar puncture.

Antibiotics can and should be started immediately, with the goal of a door to antibiotics time of less than 1 hour, even before performing lumbar puncture, because it takes approximately 2 hours for antibiotics to affect CSF cultures. Empiric corticosteroids (see Treatment) also should be given at this same time. Diagnostic lumbar puncture should not be delayed to perform CT or MRI except in patients who have focal neurologic findings suggestive of a parameningeal collection or other intracranial mass lesions; in such patients, it is critical to initiate antimicrobial therapy for meningitis of unknown origin or brain abscess before CT or MRI is performed. Patients with community-acquired meningitis rarely have important abnormalities detected on CT in the absence of focal neurologic findings.

Laboratory Findings

Cerebrospinal Fluid Examination

Initial CSF pressure is usually moderately elevated (200 to 300 mm H_2O in adults). Striking elevations (≥450 mm H_2O) occur in occasional patients with acute brain swelling complicating meningitis in the absence of an associated mass lesion. Findings on CSF analysis are strikingly abnormal in patients with meningitis, and such findings help suggest the cause even before the results of culture are available (Table 381-2).[4] In patients with skull fractures, CSF rhinorrhea can be distinguished from nasal secretions by the presence of glucose.

Gram-Stained Smear

By the time of hospitalization, most patients with pyogenic meningitis have large numbers (≥10^5/mL) of bacteria in their CSF. Careful examination of the Gram-stained smear of the spun sediment of CSF reveals the etiologic agent in 60 to 80% of cases. In most instances in which gram-positive diplococci (or short-chain cocci) are observed on a stained CSF smear, they are pneumococci. *Enterococcus*, an occasional cause of nosocomial meningitis, is detected by latex particle agglutination. Rarely, three species may morphologically mimic

TABLE 381-2 COMMON CEREBROSPINAL FLUID FINDINGS IN PATIENTS WITH MENINGITIS

MICROORGANISM	CSF OPENING PRESSURE (cm H_2O)	CELL COUNT (CELLS/μL)	PROTEIN (mg/dL)	GLUCOSE (mg/dL)
Normal	10-20	<5	20-40	40-60
Bacteria*	>20	>1000	>100	<10
Mycobacterium tuberculosis	>20	100-500	>100	10-45
Borrelia burgdorferi	<20	100-500	50-150	10-45
Treponema pallidum	<20	5-500	50-150	10-45
Fungi	<20	5-500	>100	10-45
Viruses	<20	5-500	50-150	Normal

*Group B streptococci, *Escherichia coli, Listeria monocytogenes, Streptococcus pneumoniae, Neisseria meningitidis*, and *Haemophilus influenzae* type b.
Ranges of biochemical tests may vary in different laboratories.
CSF = cerebrospinal fluid.
Modified from Kim KS. Acute bacterial meningitis in infants and children. *Lancet Infect Dis*. 2010;10:32-42.

Neisseria in CSF or may suggest a mixed infection with short gram-negative rods and meningococci: *Acinetobacter baumannii, Moraxella* sp, and *Pasteurella multocida*.

Rapid Bacteriologic Diagnosis

Broad-range polymerase chain reaction (PCR) testing, which can be performed on CSF within 1.5 hours, can diagnose bacterial meningitis in patients in whom cultures will be negative. Overall reported sensitivities in various studies range from 87 to 100%, with specificities of 98 to 100%. PCR also can rapidly diagnose viral meningitis, which overall is far more common than bacterial meningitis, thereby establishing an alternative diagnosis so that antibiotics can be discontinued because a combined viral and bacterial meningitis is highly unlikely.[5] However, because a totally negative PCR result does not exclude bacterial meningitis, other tests (cell count; glucose, protein, and lactic acid levels), which served as proxies while awaiting culture results in an earlier era, still remain very useful in such patients. Metagenomic testing or DNA sequencing also may be useful for diagnosing rare organisms. In resource-poor countries, a urine reagent strip that detects cells, proteins, and glucose in CSF has a sensitivity of 92% and a specificity of 98% for diagnosing bacterial meningitis. Such an approach may be especially useful for distinguishing bacterial meningitis from cerebral malaria (Chapter 316).

Culture of CSF reveals the etiologic agent in 80 to 90% of patients with bacterial meningitis if CSF is obtained before or within 1 to 2 hours of the initiation of antibiotics, but its sensitivities decline to less than 50% with longer delays. For therapeutic decisions, a positive PCR or a positive culture mandates a full course of antibiotic treatment.

Cell Count

Cell counts should be determined promptly because the cells will begin to lyse after 90 minutes. The normal CSF white blood cell count is less than 5/μL (all mononuclear). The cell count in untreated meningitis usually ranges between 100 and 10,000/μL, with polymorphonuclear leukocytes predominating initially (>80%) and lymphocytes appearing subsequently.

Extremely high cell counts (>50,000/μL) should raise the possibility of intraventricular rupture of a cerebral abscess. Cell counts as low as 10 to 20/μL may be observed early in bacterial meningitis, particularly that caused by *N. meningitidis* and *H. influenzae*. Occasionally, in granulocytopenic patients or in elderly persons with overwhelming pneumococcal meningitis, CSF may contain very few leukocytes and yet may appear grossly turbid because of the presence of a myriad of organisms and an elevated protein level. Meningitis caused by several bacterial species (*Mycobacterium tuberculosis, Borrelia burgdorferi, Treponema pallidum, Leptospira* sp, *Francisella tularensis, Brucella* sp) is characteristically associated with a lymphocytic pleocytosis. *L. monocytogenes* meningitis usually elicits a polymorphonuclear response, but rarely lymphocytes may predominate.

Glucose

CSF glucose is reduced to values of 40 mg/dL or less (or <50% of the simultaneous blood level) in 50% of patients with bacterial meningitis; this finding helps distinguish bacterial meningitis from most viral meningitides or parameningeal infections. However, a normal CSF glucose value does not exclude the diagnosis of bacterial meningitis. The blood glucose level should be determined simultaneously because patients with diabetes mellitus (or those who are receiving intravenous glucose infusions) have an elevated CSF glucose level that can be appreciated only by comparison with the simultaneous blood level; however, it may take 90 to 120 minutes for equilibration to occur after major shifts in the level of glucose in the circulation.

Protein

The level of protein in lumbar CSF is usually elevated to greater than 100 mg/dL, and higher values are more commonly observed in pneumococcal meningitis. Extreme elevations, 1000 mg/dL or greater, may indicate subarachnoid block with obstruction of CSF flow. Values higher than 15 mg/dL in ventricular CSF are considered abnormal. If the lumbar puncture is traumatic, the CSF protein level is corrected by subtracting 1 mg/dL for every 1000 red blood cells.

Lactic Acid

Elevated levels of lactic acid occur in pyogenic meningitis. The diagnostic accuracy of a CSF lactate level is at least as good as a cell count for differentiating bacterial from aseptic meningitis; a value above 3.0 mmol/L has a sensitivity and specificity of 94 to 95% for bacterial meningitis. However, the CSF lactate level is less useful in patients who have received antibiotics, and it also may be increased in other conditions such as cerebral ischemia, stroke, and head trauma.

Blood and Respiratory Tract Cultures

Bacteremia is demonstrable in approximately 80% of patients with *H. influenzae* meningitis, 50% of patients with pneumococcal meningitis, and 30 to 40% of patients with meningococcal meningitis. Hence, blood cultures should be performed routinely in patients suspected of having bacterial meningitis. Cultures of the upper respiratory tract are not helpful in establishing an etiologic diagnosis.

Determination of serum creatinine and electrolyte levels is important in view of the gravity of the illness, the occurrence of specific abnormalities secondary to the meningitis (syndrome of inappropriate secretion of antidiuretic hormone), and problems with therapy in patients with renal dysfunction (seizures and hyperkalemia with high-dose penicillin therapy). In patients with extensive petechial and purpuric skin lesions, evaluation for coagulopathy is indicated.

Radiologic Studies

Because of the frequency with which pyogenic meningitis is associated with primary foci of infection in the chest, nasal sinuses, or mastoid, radiographs of these areas should be taken when clinically indicated at the appropriate time after antimicrobial therapy is begun. Initial head CT or MRI is not indicated in most patients with bacterial meningitis. For example, in patients who undergo head CT or MRI before lumbar puncture for suspected meningitis, only approximately 5% have a mass effect identified on CT. Baseline clinical features associated with abnormal findings on CT include age older than 60 years, history of CNS disease, seizure within the previous week, abnormal level of consciousness, abnormal visual fields, limb drift, and aphasia. In patients without any of these clinical findings, only approximately 1% have a mass effect identified on CT or MRI that would raise concern regarding lumbar puncture.

Specific changes that may be observed on CT or MRI during meningitis include cerebral edema and enlargement of the subarachnoid spaces, contrast enhancement of the leptomeninges and the ependyma, or patchy areas of diminished density as a result of associated cerebritis and necrosis. In patients with meningitis whose clinical status deteriorates or fails to improve, CT or MRI may help demonstrate suspected complications—that is, sterile subdural collections or empyema; ventricular enlargement secondary to communicating or obstructive hydrocephalus; prominent persisting basilar meningitis; extensive areas of cerebral infarction resulting from occlusion of major cerebral arteries, veins, or venous sinuses; or marked ventricular wall enhancement suggesting ventriculitis or ventricular empyema. MRI is superior to CT for visualizing these abnormalities. Rarely, cerebral hemorrhage identifiable on CT may complicate acute bacterial meningitis in adults. In approximately 10% of adults with bacterial meningitis, findings on cranial CT (mastoid or sinus wall defect, eroding retrobulbar mass, pneumocephalus) are indicative of disruption of the dural barrier.

Rarely, paraparesis or tetraparesis resulting from myelitis may complicate bacterial meningitis. In this situation, T2-weighted or short tau inversion recovery (STIR) sequences on MRI can be helpful to exclude spinal cord compression by an extramedullary mass.

Differential Diagnosis

Headache, fever, stiff neck, confusion, vomiting, and pleocytosis are features of meningeal inflammation and are common to many types of meningitis (e.g., bacterial, fungal, viral, chemical) and also some parameningeal processes. The CSF findings are most helpful in distinguishing among these processes (Chapters 382 and 383), and PCR can usually provide a rapid diagnosis.

In most modern studies of adults, viral meningitis or encephalitis is about four times more common than bacterial meningitis (Table 381-3). Although

TABLE 381-3 CAUSES OF NON-NOSOCOMIAL MENINGITIS AND ENCEPHALITIS IN U.S. ADULTS

Enterovirus	51%
Unknown cause	19%
Bacterial	14%
Herpes simplex	8%
Noninfectious	3%
Fungal	3%
Other viruses	2%

Hasbun R, Rosenthal N, Balada-Llasat JM, et al. Epidemiology of meningitis and encephalitis in the United States, 2011-2014. *Clin Infect Dis*. 2017;65:359-363.

a lymphocyte-predominant pleocytosis without hypoglycorrhachia is characteristic of viral (usually enteroviral or herpes simplex virus type 2 [HSV-2]) meningitis or meningoencephalitis (HSV-1), the initial CSF finding may be a polymorphonuclear response (of ≤60%) that quickly becomes mononuclear. HSV-1 encephalitis is suggested by neurologic findings (dysphasia, hemiparesis, olfactory hallucinations, other temporal lobe signs, seizures), abnormalities in the orbitofrontal and medial temporal lobes on MRI, and distinctive electroencephalographic changes in the temporal lobe or lobes.

The rash, fever, and headache of Rocky Mountain spotted fever (Chapter 302) may suggest meningococcal infection, but the geographic and seasonal predilections of the former can provide clues. Approximately 10% of patients hospitalized with Rocky Mountain spotted fever have CSF cell counts higher than 100/μL (>70% polymorphonuclear), and thus the condition initially may be confused with bacterial meningitis. The rash associated with enteroviral infections typically consists of erythematous macules and papules on the face, neck, and trunk.

Acute subarachnoid hemorrhage (Chapter 377) may be confused with bacterial meningitis because of headache, stiff neck, and vomiting. However, subarachnoid hemorrhage usually has a more abrupt onset without a prodromal fever but with evidence of subarachnoid blood on CT or CSF examination. In patients with neuroleptic malignant syndrome (Chapters 379 and 386), fever, generalized rigidity, and a fluctuating level of consciousness with autonomic instability and leukocytosis may develop. The most specific laboratory abnormality in these patients is a markedly elevated creatine kinase level.

In patients who have meningitis but whose CSF does not reveal the etiologic agent on a Gram-stained smear or PCR test, particularly when the CSF glucose level is normal and the polymorphonuclear pleocytosis is atypical, certain treatable processes that can mimic bacterial meningitis should be considered in the differential diagnosis:

1. *Parameningeal infections*. The presence of infections (chronic ear or nasal accessory sinus infections, lung abscess) predisposing to brain abscess (Chapter 382), epidural (cerebral or spinal) abscess, subdural empyema, or pyogenic venous sinus phlebitis should be considered (Chapter 382). Neurologic symptoms may appear in the course of primary bacterial meningitis, but their presence may indicate the presence of a space-occupying infectious process in the CNS. Neurologic symptoms or findings antedating the onset of meningeal symptoms may suggest a parameningeal infection. Isolation of an anaerobic organism should suggest the possibility of intraventricular leakage of a cerebral abscess.
2. *Bacterial endocarditis*. Bacterial meningitis may occur during bacterial endocarditis (Chapter 61) caused by pyogenic organisms such as *S. aureus* and enterococci. In subacute bacterial endocarditis, sterile embolic infarctions of the brain may produce meningeal signs and a pleocytosis consisting of several hundred cells, including polymorphonuclear leukocytes. A history of dental manipulation, fever, and anorexia antedating the meningitis should be sought; careful examination for heart murmurs and peripheral stigmata of endocarditis is indicated.
3. *"Chemical" meningitis*. The clinical and CSF findings (polymorphonuclear pleocytosis and even reduced glucose level) of bacterial meningitis may be produced by chemically induced inflammation. Acute meningitis after diagnostic lumbar puncture or spinal anesthesia may result from bacterial or chemical contamination of equipment or anesthetic agent. Chemical meningitis, characterized by polymorphonuclear pleocytosis, hypoglycorrhachia, and a latent period of 3 to 24 hours, occurs after 1% of metrizamide myelograms. Endogenous chemical meningitis resulting from material from an epidermoid tumor or a craniopharyngioma leaking into the subarachnoid space, a glioblastoma invading the ventricles (Chapter 175), or carcinomatous meningitis (see later) can produce polymorphonuclear pleocytosis and hypoglycorrhachia.

TREATMENT

Antimicrobial Agents

Antimicrobial therapy should be initiated promptly in this life-threatening emergency, even before performing an emergent lumbar puncture and within 1 hour of hospital arrival.[6] Subsequent management should be undertaken with close monitoring, often in an intensive care unit. Treatment should be aimed at the most likely causes based on clinical clues, such as the age of the patient, the presence of a petechial or purpuric rash, a recent neurosurgical procedure, and CSF rhinorrhea. If the infecting organism is observed on examination of a Gram-stained smear of the CSF sediment, specific therapy is initiated. If the etiologic agent is not seen on a smear from a patient with suspected bacterial meningitis or if lumbar puncture is delayed because head CT is needed, empirical antimicrobial therapy should be initiated (Table 381-4).

Adequate CSF bactericidal activity, which is critical to cure the meningitis, depends on the ability of the antibiotic to penetrate CSF and maintain its activity in the purulent exudate, as well as on its metabolism and rate of clearance from CSF. With the exception of rifampin and chloramphenicol, the commonly used antimicrobial agents do not readily penetrate the normal blood-brain barrier, but the passage of penicillin and other antimicrobial agents is enhanced in the presence of meningeal inflammation (Table 381-5). Antimicrobial drugs should be administered intravenously throughout the treatment period; the dose should not be reduced as the patient improves because normalization of the blood-brain barrier during recovery reduces the achievable CSF drug levels. Bactericidal drugs (penicillin, ampicillin, third-generation cephalosporins) are preferred whenever possible, and CSF levels of antibiotics at least 10 to 20 times the minimal bactericidal concentration are needed for optimal therapy.

Empiric Treatment

Initial treatment of presumed bacterial meningitis when the etiologic agent cannot be identified on a Gram-stained smear of CSF is based on the available clinical clues. In adults, therapy with vancomycin and a third-generation cephalosporin (cefotaxime or ceftriaxone) is recommended (see Table 381-4). In adults older than 50 years and in high-risk groups, ampicillin is also added because of the possibility of the presence of *L. monocytogenes*, which is susceptible to ampicillin or amoxicillin but not to third-generation cephalosporins. In a penicillin-allergic individual, trimethoprim-sulfamethoxazole is a suitable alternative for *Listeria* meningitis. In special settings, such as nosocomial meningitis associated with neurosurgical procedures or penetrating head trauma, more resistant species such as methicillin-resistant *S. aureus* (MRSA), coagulase-negative staphylococci, and *P. aeruginosa* may be responsible; in these situations, options for initial therapy include vancomycin plus a β-lactam (such as cefepime, ceftazidime, or meropenem). If β-lactams are contraindicated, linezolid, aztreonam, or ciprofloxacin is recommended for gram-negative coverage.

Meningitis of Specific Bacterial Cause

Pneumococcal Meningitis

Antimicrobial susceptibilities should be determined for all pneumococcal isolates from CSF, blood, or sterile body fluids (see Table 381-5). If the minimal inhibitory concentration for cefotaxime or ceftriaxone (≤1.0 μg/mL) indicates a susceptible isolate, cefotaxime or ceftriaxone is the drug of choice. If the isolate is highly penicillin resistant or is resistant to 1 μg/mL ceftriaxone or cefotaxime, alternative therapy (vancomycin with or without rifampin IV) is indicated. Because of the increasingly wide distribution of highly resistant strains, initial therapy (pending susceptibility testing) with cefotaxime (or ceftriaxone) in addition to vancomycin IV is recommended. When initial adjunctive therapy with dexamethasone is used (see later) along with vancomycin, CSF vancomycin levels may be reduced by concomitant corticosteroid use.

The β-lactam antibiotic meropenem is as effective as cefotaxime for meningitis caused by *S. pneumoniae, N. meningitidis*, and *H. influenzae*. Cefepime is also similar to ceftriaxone and cefotaxime for infection with *S. pneumoniae, N. meningitidis*, and *H. influenzae*, and it has greater activity than these antibiotics against *Enterobacter* sp and *P. aeruginosa* (Table 381-6).

Meningococcal Meningitis

Intravenous administration of penicillin G and ampicillin successfully treats *N. meningitidis* meningitis resulting from susceptible strains. Meningococci resistant to penicillin have occasionally been isolated, but most are only intermediately resistant to penicillin (minimal inhibitory concentration of 0.1 to 1.0 μg/mL), so "meningitis doses" of penicillin or ampicillin may provide sufficient CSF levels. However, rare strains have high-level resistance and require third-generation cephalosporins such as ceftriaxone. A 7-day course of antibiotics usually is sufficient.

Haemophilus influenzae Meningitis

For *H. influenzae* meningitis,[7] cefotaxime or ceftriaxone is the initial therapy of choice (see Table 381-6). Alternatives include cefepime or the combination of chloramphenicol and ampicillin; if the isolate proves susceptible to ampicillin, chloramphenicol may be discontinued. A 10-day course of antibiotics is usually sufficient.

Staphylococcal Meningitis

For methicillin-susceptible *S. aureus*, nafcillin or oxacillin is recommended. For MRSA or in a penicillin-allergic patient, vancomycin is the treatment of choice (Tables 381-7 and 381-8). Because penetration of vancomycin into CSF is limited, adjunctive intrathecal (or intraventricular) therapy with vancomycin (without preservative) is occasionally used when CSF cultures have remained positive after 48 hours of intravenous therapy alone and CSF levels can be monitored. If β-lactam agents or vancomycin cannot be used, linezolid, daptomycin, or trimethoprim-sulfamethoxazole is recommended. In severe or refractory cases, the addition of rifampin is warranted. Rifampin is also recommended as part of combination therapy for patients with intracranial or spinal hardware such as a CSF shunt or drain.

TABLE 381-4 INITIAL EMPIRICAL THERAPY FOR COMMUNITY-ACQUIRED AND NOSOCOMIAL PURULENT MENINGITIS BASED ON AGE AND CLINICAL SETTING (SEE TABLE 381-8 FOR DOSING SCHEDULES)

PREDISPOSITIONS	LIKELY PATHOGENS	PREFERRED ANTIMICROBIALS	ALTERNATIVE ANTIMICROBIALS
Age			
<50 yr	*N. meningitidis, S. pneumoniae*	Vancomycin* plus ceftriaxone or cefotaxime	Meropenem (? plus vancomycin*)
>50 yr	*S. pneumoniae, N. meningitidis, L. monocytogenes,* aerobic gram-negative bacilli	Vancomycin* plus ceftriaxone or cefotaxime plus ampicillin	Vancomycin* plus ceftriaxone or cefotaxime plus trimethoprim-sulfamethoxazole
Impaired immunity	*L. monocytogenes,* gram-negative bacilli, *S. pneumoniae, Staphylococcus, Salmonella*	Ampicillin plus cefepime or meropenem plus vancomycin*	Trimethoprim-sulfamethoxazole plus meropenem
Cerebrospinal fluid leak or basilar skull fracture	*S. pneumoniae,* various streptococci, *H. influenzae*	Vancomycin* plus cefotaxime or ceftriaxone	Vancomycin* plus meropenem
After neurosurgery or penetrating trauma	*S. aureus,* coagulase-negative staphylococci, aerobic gram-negative bacilli (including *P. aeruginosa*)	Vancomycin* plus cefepime	Vancomycin* plus ceftazidime or vancomycin* plus meropenem
Cerebrospinal fluid shunts (external or internal)	Coagulase-negative staphylococci, *S. aureus,* aerobic gram-negative bacilli (including *P. aeruginosa*), *Propionibacterium acnes*	Vancomycin* plus cefepime	Vancomycin* plus ceftazidime or vancomycin* plus meropenem

*If dexamethasone is also administered, consideration should be given to the addition of rifampin.
Modified from van de Beek D, Brouder MC, Thwaites GE, et al. Advances in treatment of bacterial meningitis. *Lancet.* 2012;380:1693-1702.

TABLE 381-5 PERMEABILITY OF ANTIBIOTICS INTO CEREBROSPINAL FLUID

GOOD CONCENTRATIONS IN CSF WITH AND WITHOUT MENINGITIS	ADEQUATE CONCENTRATIONS IN CSF IN MENINGITIS	FAIR TO POOR CONCENTRATIONS IN CSF IN MENINGITIS
Chloramphenicol	Penicillin	Early cephalosporins
Sulfonamides	Ampicillin	Cephalothin
Cephalosporins	Methicillin	Cefoxitin
Cefotaxime	Oxacillin	Aminoglycosides
Ceftriaxone	Nafcillin	Gentamicin
Ceftazidime	Carbenicillin	Tobramycin
Moxalactam	Ticarcillin	Amikacin
Cefepime	Tetracycline	Clindamycin
Metronidazole	Erythromycin	Benzathine penicillin
Trimethoprim-sulfamethoxazole	Ethambutol	
Isoniazid	Rifampin	
Linezolid	Vancomycin	
Fluconazole	Meropenem	
Fluoroquinolones		

CSF = cerebrospinal fluid.
Courtesy Allen Aksamit, Mayo Clinic, Rochester, MN.

TABLE 381-6 ANTIMICROBIAL THERAPY FOR COMMUNITY-ACQUIRED BACTERIAL MENINGITIS OF KNOWN CAUSE (SEE TABLE 381-8 FOR DOSING SCHEDULES)

ORGANISM	PREFERRED ANTIMICROBIAL THERAPY	ALTERNATIVE ANTIMICROBIAL THERAPY
Streptococcus pneumoniae		
Penicillin MIC <0.1 μg/mL	Penicillin G or ampicillin	Cefotaxime, or ceftriaxone, or vancomycin, or chloramphenicol
Penicillin MIC 0.1-1 μg/mL	Ceftriaxone or cefotaxime	Vancomycin,* or meropenem, or cefepime
Penicillin MIC ≥2.0 μg/mL	Vancomycin* (plus cefotaxime or ceftriaxone)	Moxifloxacin or gatifloxacin
Cefotaxime or ceftriaxone MIC ≥1.0 μg/mL	Vancomycin* (plus cefotaxime or ceftriaxone)	Moxifloxacin or gatifloxacin
Neisseria meningitidis		
Penicillin MIC <0.1 μg/mL	Penicillin G or ampicillin	Ceftriaxone, or cefotaxime, or chloramphenicol
Penicillin MIC 0.1-1.0 μg/mL	Ceftriaxone or cefotaxime	Chloramphenicol, or meropenem, or gatifloxacin, or moxifloxacin
Haemophilus influenza		
β-Lactamase negative	Ampicillin	Ceftriaxone, or cefotaxime, or cefepime, or chloramphenicol
β-Lactamase positive	Ceftriaxone or cefotaxime	Cefepime, or chloramphenicol, or gatifloxacin, or moxifloxacin
Listeria monocytogenes	Ampicillin† or penicillin G† (plus vancomycin)	Trimethoprim-sulfamethoxazole or meropenem
Streptococcus agalactiae (group B streptococci)	Ampicillin† or penicillin G†	Cefotaxime or ceftriaxone

*Addition of rifampin should be considered. Consider intrathecal (or intraventricular vancomycin, 5 to 20 mg/day) if not responding to intravenous therapy.
†Addition of intravenous gentamicin should be considered.
MIC = minimal inhibitory concentration.

TABLE 381-7 THERAPY FOR NOSOCOMIAL MENINGITIS OF KNOWN BACTERIAL CAUSE IN ADULTS

ORGANISM	THERAPY OF CHOICE	ALTERNATIVE THERAPY
Staphylococcus aureus		
Methicillin susceptible	Nafcillin or oxacillin; in difficult cases may add rifampin	Vancomycin or meropenem
Methicillin resistant	Vancomycin; in difficult cases may add rifampin	Daptomycin, linezolid, or trimethoprim-sulfamethoxazole
Coagulase negative	Vancomycin; may consider addition of rifampin	Daptomycin
Enterococcus species		
Ampicillin susceptible	Ampicillin plus gentamicin	
Ampicillin resistant	Vancomycin plus gentamicin	Vancomycin plus gentamicin
Ampicillin and vancomycin resistant	Daptomycin	Daptomycin
Escherichia coli and other	Cefotaxime, ceftriaxone, or cefepime	Meropenem, aztreonam, ampicillin, or trimethoprim-sulfamethoxazole
Enterobacteriaceae*		
*Pseudomonas aeruginosa**	Cefepime or ceftazidime	Meropenem, aztreonam, or ciprofloxacin
Acinetobacter species		
Meropenem susceptible	Meropenem	
Meropenem resistant	Colistimethate or polymyxin B	

*Selection of specific antimicrobial drug should be based on in vitro susceptibility results, with consideration given to the addition of an aminoglycoside (e.g., tobramycin, gentamicin, or amikacin).
Modified from van de Beek D, Drake JM, Tunkel AR. Nosocomial bacterial meningitis. *N Engl J Med*. 2010;362:146-154.

Listeria Meningitis

Ampicillin is the drug of choice for *Listeria* meningitis. When combined with gentamicin, it can have a synergistic bactericidal effect. Third-generation cephalosporins and vancomycin are not effective. In patients allergic to ampicillin, intravenous trimethoprim-sulfamethoxazole may be used, followed by oral trimethoprim alone.

Gram-Negative Bacillary Meningitis

Cefotaxime or ceftriaxone (see Tables 381-7 and 381-8) is used to treat meningitis known to be caused by susceptible gram-negative bacilli (e.g., *E. coli, Klebsiella, Proteus*), but they should not be used to treat meningitis caused by less susceptible species such as *P. aeruginosa* and *Acinetobacter*. After identifying the specific pathogen and determining its drug susceptibilities, alterations in antimicrobial therapy may be indicated. If the organism is *P. aeruginosa*, ceftazidime or cefepime is recommended and may be combined with vancomycin (see Tables 381-7 and 381-8). An alternative is aztreonam or a fluoroquinolone with in vitro activity. For *Acinetobacter* species, meropenem is recommended; for strains that demonstrate carbapenem resistance, colistimethate sodium or polymyxin B (see Table 381-8) administered by the intravenous or intraventricular routes is recommended. Intraventricular administration of polymyxin B is recommended at a dose of 50,000 U once daily for 3 to 4 days, then every other day for 2 weeks after the CSF cultures are negative. Concomitant use of muscle relaxants should be avoided.

Zoonotic Bacterial Meningitis

Brucella meningitis (Chapter 286) is a subacute or chronic process that is often accompanied by other manifestations of neurobrucellosis (encephalitis, polyradiculitis, myelitis). Infection is transmitted to humans in endemic areas (Central and South America, Mediterranean littoral, Arabian peninsula) from the ingestion of unpasteurized milk or cheese or direct contact with domestic animals. Neurobrucellosis occurs in 2 to 5% of patients with brucellosis. CSF findings consist of a lymphocytic pleocytosis (<500 cells/μL), hypoglycorrhachia, and an elevated protein level, findings that could mistakenly suggest tuberculous meningitis. The diagnosis is based on demonstration of antibody in serum and CSF or by isolation of *Brucella* from blood; the microorganism is isolated from CSF in only a minority of cases. Treatment is a three-drug combination of doxycycline (200 mg/day), rifampin (600 mg/day), and trimethoprim-sulfamethoxazole (20 mg/kg/day IV, based on trimethoprim component, in 6-hour aliquots) for several months, depending on the clinical and CSF responses.

Streptococcus suis is an uncommon cause of meningitis seen in pig breeders, butchers, and abattoir workers in Europe, Canada, and China. *S. suis* meningitis, which is an acute illness with a brisk neutrophilic pleocytosis, is often initially mistaken for pneumococcal meningitis on the basis of Gram stain of CSF. Treatment is penicillin (12 to 24 million units [U]/day in 4-hour aliquots) or ampicillin (12 g/day in 4-hour aliquots) IV for 10 to 14 days.

Bacillus anthracis (Chapter 272) is a rare cause of meningitis that most often develops as a complication of inhalation anthrax following exposure to aerosols of anthrax spores in the setting of large-scale processing of wool and hides or a bioterrorism attack (Chapter 19). Anthrax meningitis is an acute process characterized by hemorrhagic or serohemorrhagic CSF with a neutrophilic predominance (several thousand cells per cubic millimeter), hypoglycorrhachia, an elevated protein level, and prominent large gram-positive bacilli on stained smear. Treatment initially includes ciprofloxacin (400 mg at 12-hour intervals) in addition to penicillin (24 million U/day in 4-hour aliquots) and chloramphenicol (4 g/day in 6-hour aliquots) IV. Alternatively, treatment could substitute levofloxacin or moxifloxacin for ciprofloxacin, meropenem for penicillin, and linezolid or chloramphenicol (Chapter 257). Whether all drugs are continued (or treatment is narrowed to one or two antimicrobials) and the duration of treatment depend on whether the meningitis is of suspected bioterrorist origin (Chapter 19) or caused by cutaneous anthrax resulting from animal (or animal product) exposure (Chapter 272). Consultation with infectious disease and public health authorities should be sought.

Repeat CSF Examination and Duration of Therapy

The frequency of CSF examination depends on the clinical course, but examination should be repeated in 24 to 48 hours if there has not been satisfactory improvement or if the causative microorganism is a more resistant gram-negative bacillus or a highly penicillin-resistant (or cephalosporin-resistant) *S. pneumoniae* strain, especially in patients who are receiving adjunctive dexamethasone therapy. Routine "end-of-treatment" CSF examination is unnecessary in most patients with the common types of community-acquired bacterial meningitis.

Treatment of adults with meningococcal meningitis should be continued for 4 to 7 days after the patient becomes afebrile. *H. influenzae* meningitis should be treated for 7 to 10 days. For pneumococcal meningitis, antimicrobial treatment should be continued for 10 to 14 days, and follow-up examination of CSF should be performed, particularly when the patient has coexistent mastoiditis. More prolonged therapy is indicated with concomitant parameningeal infection. Meningitis caused by *L. monocytogenes* should be treated for 21 days.

Treatment of gram-negative bacillary meningitis with parenteral antimicrobials is prolonged, usually for a minimum of 3 weeks (particularly in patients after a recent neurosurgical procedure) to prevent relapse. Repeated examinations of CSF are necessary both during and at the conclusion of treatment to determine whether bacteriologic cure has been achieved.

Other Aspects of Treatment

Adjunctive Corticosteroids

In adults with community-acquired bacterial meningitis, adjunctive dexamethasone therapy (10 mg every 6 hours IV for 4 days) significantly reduces the proportion of patients with an unfavorable neurologic outcome from 25% to 15% or a fatal outcome from 15% to 7%, with the beneficial effect most evident in patients with pneumococcal meningitis. In a study of adolescents and adults with bacterial meningitis in Vietnam, dexamethasone significantly reduced death and disability by approximately 54% at 6 months in patients with confirmed disease. By comparison, adjunctive corticosteroids were not effective in treating bacterial meningitis in a large trial of predominantly HIV-positive patients in sub-Saharan Africa. Based on these data, adjunctive dexamethasone (0.15 mg/kg every 6 hours for 2 to 4 days, with the initial dose given 10 to 20 minutes before or simultaneously with the initial dose of antimicrobial therapy) is recommended in adults with suspected or demonstrated pneumococcal meningitis and perhaps routinely in all cases of bacterial meningitis, at least in non–HIV-infected patients in high-income countries,[A1] and its benefits extend for at least 13 years after the event (see Table 381-5).

Elevated Cerebrospinal Fluid Pressure (Brain Swelling)

Occasional patients with acute bacterial meningitis experience marked brain swelling (CSF pressure >450 mm H_2O), which may lead to temporal lobe or cerebellar herniation after lumbar puncture. To decrease the possibility of this

TABLE 381-8 INTRAVENOUS DOSES OF ANTIMICROBIAL DRUGS FOR TREATMENT OF BACTERIAL MENINGITIS IN ADULTS*

ANTIMICROBIAL DRUG	24-HR DOSE
β-LACTAMS	
Penicillin G	24 million U, q4h aliquots
Ampicillin	12 g, q4h aliquots
Nafcillin	10-12 g, q4h aliquots
Oxacillin	10-12 g, q4h aliquots
Aztreonam (a monobactam)	6-8 g, q6-8h aliquots
Meropenem (a carbapenem†)	6 g, q8h aliquots
CEPHALOSPORINS	
Cefotaxime	12 g, q4h aliquots
Ceftriaxone‡	4 g, q12h aliquots
Ceftazidime	6 g, q8h aliquots
Cefepime	6 g, q6-8h aliquots
Ceftaroline	600 mg, q12h aliquots
AMINOGLYCOSIDES	
Gentamicin§	5 mg/kg, q8h aliquots
Tobramycin§	5 mg/kg, q8h aliquots
Amikacin§	15 mg/kg, q8h aliquots
FLUOROQUINOLONES	
Ciprofloxacin	800-1200 mg, q8-12h aliquots
Gatifloxacin‖	400 mg, q24h dosing
Moxifloxacin‖	400 mg, q24h dosing
OTHERS	
Chloramphenicol	4-6 g, q6h aliquots
Vancomycin¶	2-3 g, q6-8h aliquots
Rifampin	600 mg, q24h dosing
Trimethoprim-sulfamethoxazole**	20 mg/kg, q6h aliquots
Daptomycin	8-10 mg/kg, q24h dosing
Polymyxin B*	7,500-12,500 U/kg, q12h dosing
Colistimethate*	1.25 mg/kg, q6-12h dosing
Linezolid	1200 mg, q12h dosing

*Dosages are intravenous and for patients with normal renal and hepatic function.
†Use may be associated with seizures, but much less so than with imipenem.
‡Four-gram maximum daily dose.
§Peak and trough serum levels should be monitored.
‖No data are available on the optimal dosage required for bacterial meningitis.
¶Monitoring of trough serum levels is advisable; they should be maintained at concentrations of 15 to 20 μg/mL. If the patient is not responding well, one may need to monitor cerebrospinal fluid levels and, if low, temporarily increase the daily dose accordingly or add adjuvant intrathecal vancomycin (5 to 20 mg), as for the treatment of methicillin-resistant *Staphylococcus aureus* meningitis.
**Dosage based on the trimethoprim component of the combination.

complication when the pressure is found to be this high, only a small amount of CSF should be removed for analysis (the amount present in the manometer), and a 20% solution of mannitol (0.25 to 0.5 g/kg IV) should be infused over a period of 20 to 30 minutes while monitoring (if possible) for a decline in CSF pressure to a lower level before the spinal needle is removed. Continued control of increased intracranial pressure, if needed thereafter, may be effected with additional mannitol; dexamethasone (10 mg IV, followed by 0.15 mg/kg every 6 hours) should be used in patients with brain swelling regardless of the suspected bacteriologic cause of meningitis.

In a stuporous patient or one with respiratory insufficiency and markedly increased intracranial pressure, use of a ventilator to reduce the arterial carbon dioxide pressure to between 25 and 32 mm Hg is reasonable, and the patient's head should be elevated 30 to 45 degrees. Intubation should be performed with minimal stimulation to avoid an appreciable further rise in pressure; pharmacologic aids to intubation are recommended, such as succinylcholine and opioids, with the possible use of adjunctive intravenous lidocaine. Subsequently, transient increases in intracranial pressure associated with hyperactive airway reflexes can be mitigated by intratracheal instillation of lidocaine before vigorous suctioning. With continued marked and fluctuating elevations in intracranial pressure, use of a continuous intracranial monitoring device may be warranted. Induced hypothermia is not beneficial and may be harmful.

Hypotension

Initial hypovolemia or hypotension, if present, should be treated with fluid to prevent significantly decreased cerebral blood flow. Over the next 24 to 48 hours, inappropriate secretion of antidiuretic hormone may contribute to further brain swelling; in such cases, fluid should be restricted to 1200 to 1500 mL daily in adults if possible, although a study in children suggests that routine fluid restriction does not improve outcome and that the resulting decrease in extracellular water may increase the likelihood of hypovolemia and an adverse outcome.

Supportive Care

Patients with acute bacterial meningitis should receive constant nursing attention in an intensive care unit to ensure prompt recognition of seizures and to prevent aspiration. If seizures occur, they should be treated acutely in adults with diazepam (administered slowly IV at a dose of 5 to 10 mg) or lorazepam (4 to 8 mg). Maintenance anticonvulsant therapy can be continued thereafter with intravenous phenytoin (Chapter 372) until the medication can be administered orally (PO). Sedation should be avoided because of the danger of respiratory depression and aspiration.

Surgery

Surgical treatment of an accompanying pyogenic focus such as mastoiditis should be undertaken when recovery from the meningitis is as complete as possible but under continuing antibiotic administration. Rarely, the mastoid infection (e.g., Bezold abscess) is so hyperacute that early drainage may be required after 48 hours or so of antibiotic therapy when the acute meningeal process has subsided somewhat.

Complications

Non-neurologic Complications

Shock

When shock occurs in patients with pyogenic meningitis, it is usually a manifestation of the accompanying intense bacteremia, as in fulminant meningococcemia, rather than a manifestation of the meningitis itself. Management is guided by the principles of septic shock therapy (Chapter 94), with appropriate modifications in patients with heart failure (Chapter 46).

Coagulation Disorders

Coagulopathies (Chapter 160) are frequently associated with the intense bacteremia (usually meningococcal, occasionally pneumococcal) and hypotension that can accompany meningitis. The changes may be mild, such as thrombocytopenia (with or without prolongation of the prothrombin and partial thromboplastin times), or more marked, with clinical evidence of disseminated intravascular coagulation (Chapter 161).

Septic Complications

Endocarditis

In patients with pneumococcal meningitis, particularly those with concomitant bacteremia and pneumonia, acute endocarditis (Chapter 61) can develop, most commonly on the aortic valve. In such patients, febrile relapse and a new cardiac murmur may appear shortly after the completion of antimicrobial therapy for meningitis.

Pyogenic Arthritis

Septic arthritis may result from the bacteremia associated with meningitis caused by *S. pneumoniae, N. meningitidis*, or *H. influenzae*.

Prolonged Fever

With appropriate antimicrobial treatment of community-acquired bacterial meningitis, patients become afebrile within 2 to 5 days. Sometimes, however, the fever persists or recurs after an afebrile period. In a patient with persisting headache, obtundation, and cerebral findings, inadequate drug therapy or neurologic sequelae (cortical venous thrombophlebitis, ventriculitis, subdural collections) are important considerations. Re-evaluation of CSF, particularly Gram-stained smear and culture, is essential in these circumstances. Drug-induced fever (Chapters 234 and 259) should be suspected in patients who continue to show clinical improvement in all other respects. Metastatic infection (septic arthritis, purulent pericarditis, thoracic empyema, endocarditis) may be the cause of continuing or recurrent fever. A syndrome, probably immunologic, consisting of fever, arthritis, and pericarditis 3 to 6 days after the initiation of effective antimicrobial therapy for meningococcal meningitis occurs in approximately 10% of patients (Chapter 274).

Recurrent Bacterial Meningitis

Repeated episodes of bacterial meningitis generally indicate a host defect, either in local anatomy or in antibacterial and immunologic defenses (e.g., recurrent *N. meningitidis* infections in patients with congenital or acquired deficiencies of complement, particularly the late-acting components). Approximately 10%

of episodes of pneumococcal meningitis in adults are recurrent meningitis, but only 0.5% of patients with community-acquired meningitis caused by other microorganisms have recurrent attacks. *S. pneumoniae* is the cause of a third of episodes of community-acquired recurrent meningitis; various streptococci, *H. influenzae*, and *N. meningitidis* are the cause of another third of episodes. In contrast, in nosocomial recurrent meningitis, gram-negative bacilli and *S. aureus* are the cause of approximately 60% of episodes.

A history of head trauma is frequent in patients with recurrent meningitis. Organisms may enter the subarachnoid space directly, through a defect in the cribriform plate (the most common site), in association with the empty sella syndrome, by means of a basilar skull fracture, through an erosive sequestrum of the mastoid, through congenital dermal defects along the craniospinal axis (usually evident before adult life), or as a consequence of penetrating cranial trauma or neurosurgical procedures. The anatomic defect may produce a frank CSF leak (rhinorrhea or, less commonly, otorrhea) or may entrap a vascular cuff of meninges that may subsequently serve as a direct route for organisms to reach the meninges. CSF rhinorrhea may be intermittent, and meningitis may occur months or years after head injury.

The presence of CSF rhinorrhea should be sought at admission and subsequently (rhinorrhea may clear during active meningitis only to recur when the inflammation has resolved). Clinical clues suggesting the presence of a CSF fistula through the cribriform plate, pericranial air sinuses, or temporal bone include (1) a salty taste in the throat; (2) positionally dependent rhinorrhea (rhinorrhea only in the lateral recumbent or prone position suggests an otic or sphenoid origin); (3) anosmia (cribriform plate leak); and (4) hearing loss or full feeling in the ear, often with a finding of fluid or bubbles behind the tympanic membrane (leakage into the middle ear). Quantitative determination of the glucose and chloride content of nasal secretions and detection of a transferrin band unique to CSF by protein electrophoresis can definitively establish the presence of CSF rhinorrhea.

Recurrent pneumococcal meningitis may develop without apparent predisposing circumstances, and cryptic CSF leaks should be sought actively in such patients by CT of the frontal and mastoid regions and by radioisotope techniques. Radioiodine-labeled albumin is introduced intrathecally, and pledgets of cotton placed in the nares are subsequently examined for the radionuclide. Intrathecal introduction of fluorescein as a visual tracer (under ultraviolet light) can similarly be used to detect active leaks.

TREATMENT

In most patients with CSF otorrhea and rhinorrhea after an acute head injury, the leak ceases in 1 or 2 weeks. Persistent rhinorrhea for more than 4 to 6 weeks is an indication for surgical repair. Prolonged administration of penicillin does not prevent pneumococcal meningitis and may encourage infection with more drug-resistant species. CSF fistulas should be closed surgically to prevent further episodes of meningitis.

PROGNOSIS

Prompt treatment of bacterial meningitis usually results in rapid recovery of neurologic function. Persistent or late-onset obtundation and coma without focal findings suggest brain swelling, subdural effusion, hydrocephalus, loculated ventriculitis, cortical thrombophlebitis, or sagittal sinus thrombosis. The last three conditions are commonly associated with fever and continuing pleocytosis.

The mortality rate for community-acquired bacterial meningitis in adults varies with the etiologic agent and clinical circumstances. With current antimicrobial therapy, the mortality rate for *H. influenzae* meningitis is less than 5% and that for meningococcal meningitis is approximately 10%. The highest mortality is seen with pneumococcal (20%)[8] and *L. monocytogenes* (20 to 30%) meningitis.

The mortality rate for gram-negative bacillary meningitis, commonly nosocomial in origin, has been 20 to 30% in adults, but may be decreasing. The mortality rate for recurrent community-acquired meningitis in adults (≈5%) is lower than the 20% rate for nonrecurrent episodes. Poor prognostic factors include advanced age, the presence of other foci of infection, underlying diseases (leukemia, alcoholism), obtundation, seizures within the first 24 hours, and delay in instituting appropriate therapy.

Residual neurologic damage is seen in up to 30% of patients who recover from bacterial meningitis.[9] Approximately 25% of adults considered clinically well recovered (expected to function independently and resume activities of daily life, including work) from pneumococcal meningitis show neuropsychological abnormalities, mainly loss of cognitive speed, when they are examined 6 to 24 months after hospital discharge.

PREVENTION

Vaccination

Adherence to recommended vaccination (Chapter 15) substantially reduces the risk of bacterial meningitis. For example, effective vaccines for *H. influenzae* (Chapter 332) have nearly eliminated this formerly common cause of meningitis. The meningococcal vaccine is approximately 85% protective against four of the strains that cause illness. The MenB vaccine is currently recommended only for immunocompromised individuals or those exposed during an outbreak (Chapter 15). At age 65 years, all adults should receive pneumococcal PCV13 vaccination, followed about 1 year later by PPSV23 vaccination. For people who smoke, have underlying lung disease, or are immunosuppressed, vaccination is recommended after age 19 years (Chapter 15). Immunocompromised patients may remain at high risk for infection despite vaccination.

Chemoprophylaxis

Prompt prophylaxis of close contacts (individuals who frequently slept and ate in the same household with the patient, girlfriend, or boyfriend) is warranted because up to a third of secondary cases of meningococcal disease develop within 2 to 5 days of illness in the initial case. Only hospital personnel who were in close contact with a patient (mouth-to-mouth resuscitation, initial examination before institution of respiratory precautions) are at special risk. Commonly, oral rifampin is used for prophylaxis: for adults (other than pregnant women), 600 mg twice daily for 2 days; for children, 10 mg/kg twice daily for 2 days. Alternatively, for adults, ciprofloxacin (500 mg), ofloxacin (400 mg), or azithromycin (500 mg), each given PO as a single dose, may be used. Another choice is ceftriaxone intramuscularly as a single dose in adults (250 mg) or children (125 mg).

Widespread use of *H. influenzae* type b polysaccharide protein-conjugate vaccine in developed countries has largely eliminated the need for chemoprophylaxis of close childhood contacts of patients with *H. influenzae* meningitis or invasive infection. However, prophylaxis would be indicated for unimmunized close household contacts of an index patient (e.g., recent immigrant) younger than 6 years. If two or more cases of invasive *H. influenzae* type b disease occur in children at a daycare center, prophylaxis of other unimmunized attendees is warranted with rifampin (20 mg/kg/day PO) for 4 days.

VIRAL MENINGITIS

DEFINITION

The nonspecific term *aseptic meningitis* describes an inflammatory process involving the meninges, usually accompanied by a mononuclear pleocytosis, without evidence of pyogenic bacterial infection on Gram stain or culture. The definition encompasses various processes that produce similar clinical pictures and inflammatory responses: viral meningitis, atypical and nonpyogenic bacterial and fungal meningitis, chemically induced meningitis, drug-induced meningitis, neoplastic meningitis, meningeal inflammation caused by adjacent pyogenic infections, and meningitis associated with autoimmune hypersensitivity diseases. Aseptic meningitis, which is usually an acute or subacute process, can be further divided into types by the duration of illness (chronic versus chronic-intermittent) and distinctive cellular responses in CSF (e.g., eosinophilic meningitis).

Many of the viruses causing meningitis also may cause infection of the brain parenchyma (encephalitis; Chapter 383) or spinal cord. Sometimes, parenchymatous involvement and meningeal involvement occur simultaneously in the same patient and are referred to as meningoencephalitis and meningomyelitis.

EPIDEMIOLOGY

Most cases of community-acquired aseptic meningitis are the result of viruses, principally enteroviruses, which account for more than 60% of viral meningitides and for 90% of those for which an etiologic agent is identified (Table 381-9). Enteroviruses are members of the Picornaviridae (small RNA) family, which consists of more than 60 serotypes: 28 echoviruses, 23 group A and 6 group B coxsackieviruses, four numbered enteroviruses (68 to 71), and three polioviruses. The most common serotypes implicated in viral meningitis from year to year have been echoviruses 4, 6, 9, 11, 13, 16, 30 and 33 and coxsackie B serotypes 2 to 5. Currently, poliovirus infections (Chapter 349) are limited to parts of Asia and Africa, although rare cases occur secondary to attenuated vaccine strains. Outbreaks of EV-D68 (Chapter 349), which can cause meningitis as well as a polio-like syndrome in children, have been recorded worldwide.

Many viruses that produce the clinical picture of aseptic meningitis, such as arthropod-borne viruses, HSV-1, enterovirus 71, lymphocytic choriomeningitis virus, mumps virus, HIV-1, cytomegalovirus, and Epstein-Barr virus, also can produce the clinical picture of meningoencephalitis and encephalitis (Chapter

TABLE 381-9 AGENTS OF VIRAL MENINGITIS

COMMON
Nonarthropod Viruses
Picornavirus (RNA)
Enterovirus
Enterovirus 70, 71, 68, D68
Coxsackie A, B
Echovirus
Herpes simplex virus type 2 (HSV-2) (DNA)
LESS COMMON
Arthropod-Borne Viruses (Arboviruses)
Togavirus (alphavirus, RNA)
Eastern equine encephalitis
Western equine encephalitis
Venezuelan equine encephalitis
Flavivirus (RNA)
West Nile virus (WNV)
Dengue
St. Louis encephalitis
Japanese encephalitis
Zika virus
Chikungunya
Bunyavirus (RNA)
California encephalitis
UNCOMMON
Arenavirus (RNA)
Lymphocytic choriomeningitis
Paramyxovirus (RNA)
Mumps
Retrovirus (RNA)
Human immunodeficiency virus (HIV-1)
RARE
Enterovirus—poliovirus
Parechovirus
Herpesvirus (DNA)
Herpes simplex virus type 1 (HSV-1)
Epstein-Barr virus
Cytomegalovirus
Varicella-zoster virus
Human herpesvirus type 6 (HHV-6)
Adenovirus (DNA)
Coltivirus (RNA)
Colorado tick fever
Bunyavirus (RNA)
Toscana virus (a Phlebovirus)
Filoviruses
Ebola virus

383). In addition, some viruses involve the spinal cord, including the anterior horn cells (poliovirus, West Nile virus) or the dorsal root ganglia (HSV-2).

Enterovirus

An estimated 10 to 15 million clinical enteroviral infections (Chapter 349) occur annually in the United States, and these include an estimated 50,000 to 75,000 cases of enteroviral meningitis. In temperate climates, enteroviral meningitis peaks during the summer and fall. Serotypes tend to cycle with varying periodicity, and outbreaks are related to lack of previous exposure to a particular serotype. Serotype-specific protective antibodies develop following infection, so subsequent episodes of enteroviral meningitis are uncommon and are caused by a different serotype.

Humans are the only known reservoir of enteroviruses. Enteroviral infection is spread predominantly by the fecal-oral route and occasionally by the respiratory route.

Herpes Viruses

HSV (Chapter 345) accounts for 1 to 3% of all episodes of aseptic meningitis and occurs most commonly in sexually active adults or adolescents. In individuals with primary genital herpes (HSV-2) infection, up to 36% of women and 13% of men have symptoms of aseptic meningitis. Recurrences of genital herpes are common and are sometimes accompanied by recurrent aseptic meningitis. More than 80% of cases of benign recurrent aseptic meningitis are caused by HSV-2 (Chapter 345). In contrast, HSV-1 CNS infection almost always manifests as encephalitis (Chapter 383) rather than aseptic meningitis. Herpesviruses, such as Epstein-Barr virus (Chapter 348), cytomegalovirus (Chapter 347), varicella-zoster virus (Chapter 346), and human herpesvirus type 6 (Chapter 345) also may be reactivated in patients taking immunomodulatory drugs to treat autoimmune diseases or chemotherapeutic agents.

Arboviruses

Although the most common form of CNS infection caused by arboviruses (Chapter 352) is encephalitis (Chapter 383), aseptic meningitis also may occur. These vector-borne viruses are introduced subcutaneously by a mosquito (e.g., West Nile virus, Japanese encephalitis), tick (e.g., Colorado tick fever), or sandfly (e.g., Toscana virus). Birds, which are vectors of mosquito-borne arboviruses, may not be obviously sick, although West Nile virus may cause prominent die-offs of corvine species, especially crows and blue jays, which can provide clues to an outbreak affecting humans.

The geographic spread of alphavirus infections (Eastern equine encephalitis, Western equine encephalitis, Venezuela equine encephalitis) in the United States is determined by the range of their individual mosquito vectors. Eastern equine encephalitis occurs sporadically or as focal outbreaks in the summer in the eastern and Gulf coasts, most frequently in children and elderly persons. Western equine encephalitis occurs predominantly in the western states, and Venezuela equine encephalitis is found in Florida. St. Louis encephalitis infections were originally recognized in the Midwest, but sporadic cases and outbreaks have occurred more recently in most parts of the United States; it is the most common arbovirus causing aseptic meningitis in the United States. West Nile virus infections first appeared in the United States in 1999 and now account for approximately 3000 cases of meningitis and another 3000 cases of encephalitis annually. Meningitis is also a rare manifestation of Zika, Chikungunya and dengue virus (Chapter 352) infections.

Other Viruses

Lymphocytic choriomeningitis virus which is infrequently a cause of aseptic meningitis, is transmitted to humans by rodents through direct contact, through ingestion of animal-contaminated food, or via aerosol or an animal bite. Cases tend to occur in early winter when mice seek shelter in homes. Outbreaks have occurred following exposure to pet or laboratory hamsters.

Mumps virus (Chapter 340) is now an uncommon cause of viral meningitis in the United States, but still occurs worldwide in areas with inadequate vaccinations.

PATHOBIOLOGY

The two basic routes for virus to gain access to the CNS are hematogenous (enteroviral infection) or neuronal (HSV infection). Enteroviruses pass through the stomach, where they resist the acid pH, and proceed to the lower gastrointestinal tract. Some virus also undergoes replication in the nasopharynx and spreads to regional lymphatics. A minor enterovirus viremia then seeds the CNS, heart, liver, and reticuloendothelial system. Following extensive replication at the latter sites, a major viremia ensues, often accompanying the onset of clinical illness. The mechanism by which enterovirus enters the CNS is presumed to involve crossing the blood-CSF barrier's tight endothelial junctions and then entering CSF, probably at the choroid plexus.

In contrast, HSV infections may reach the CNS via the neuronal route: in HSV-1 encephalitis, from oral sites via the trigeminal and olfactory nerve; in HSV-2 (and the rare HSV-1) aseptic meningitis, by spread from a primary genital lesion and ascent along the sacral nerve roots to the meninges. After subsidence of the primary infection, HSV-1 may remain dormant in the trigeminal or olfactory root ganglia only to reactivate at a later date, enter the temporal lobe, and produce encephalitis. Similarly, HSV-2 may remain latent in the sacral root ganglia until subsequent reactivation causes later episodes of aseptic meningitis.

CLINICAL MANIFESTATIONS

Enteroviral Meningitis

The clinical features of enteroviral meningitis (Chapter 349) in older children and adults often begin abruptly with headache (85 to 100%), fever (80 to 100%), and stiff neck (50 to 80%).[10] In some patients the course is biphasic, with the initial prodromal phase being characterized by low-grade fever and nonspecific symptoms (malaise, sore throat, diarrhea), followed by a second phase at which time the meninges are seeded, with the development of higher fever, nausea, vomiting, myalgia, photophobia, and stiff neck. Other enteroviral syndromes may coexist, particularly pleurodynia or pericarditis resulting from coxsackieviruses. Rash may be a manifestation of infections caused by echoviruses, particularly echovirus type 9, coxsackieviruses A9 and A16, and enterovirus 71; the latter three cause hand-foot-and-mouth disease, which

may occur alone or accompany aseptic meningitis. Echovirus 9 epidemics often produce syndromes of exanthem, enanthem (small, grayish-white lesions resembling Koplik spots on the buccal mucosa), and aseptic meningitis, either alone or in combination; a macular and petechial rash in the presence of a meningitic syndrome must be differentiated from meningococcal meningitis.

The clinical course of enteroviral meningitis is usually benign, even in the minority of patients in whom the onset is acute and even fulminant. Symptoms typically subside within a week in children but may continue for several weeks in adults.

However, some patients have encephalitis or meningoencephalitis, rather than enteroviral meningitis, with neurologic abnormalities affecting the cerebrum. In agammaglobulinemic individuals in whom enteroviral CNS infection develops, meningitis may progress to a chronic meningoencephalitis with multiple neurologic features, including headache, seizures, ataxia, weakness, hearing loss, obtundation, and coma. Enterovirus D68 is associated with an acute flaccid myelitis.

Herpes Simplex Virus Type 2 Meningitis

Aseptic meningitis is a common complication of primary genital HSV-2 infection (Chapter 345)[11]; up to about 35% of women and 15% of men have headache (developing over 2 to 3 days), stiff neck, and photophobia. Clinical features of meningitis occur 3 to 12 days after the appearance of genital lesions and usually last for 4 to 7 days. Neurologic complications occur in up to about 40% of patients and include dysesthesia or paresthesia in the perineum or sacral area, urinary retention, and constipation; evidence of transverse myelitis with motor weakness in the lower extremities, hyporeflexia, and paraparesis occasionally ensues. Recurrent episodes of HSV-2 meningitis may occur at intervals of months or years in 20% of patients. In recurrent HSV-2 meningitis, fever may develop but is not as prominent as in bacterial or acute enteroviral meningitis. Recurrent vesicular lesions, paresthesia, or dysesthesia in areas of previous genital herpes may or may not precede individual recurrences of meningitis. Between recurrences, CSF findings and clinical manifestations return to normal. In patients who have had neurologic complications with a first episode of HSV-2 meningitis, the findings subside within 6 months.

Mumps Meningitis

Symptomatic CNS disease, principally meningitis or meningoencephalitis, occurs in 1 to 10% of patients with mumps parotitis (Chapter 340), but pleocytosis occurs in more than 50% of patients with mumps, most of whom lack CNS symptoms. When meningitis occurs in patients with mumps, it usually follows parotitis by 4 to 10 days, but it may precede parotitis by up to 1 week. The typical features of viral meningitis (headache, fever, vomiting) are each present in 50 to 100% of patients. Stiff neck (40 to 90%) is common, and abdominal pain (perhaps complicating pancreatitis or oophoritis) or orchitis (in ≤20% of men with mumps) may be present. Other complications of mumps may involve the nervous system (eighth nerve damage, transient facial nerve paralysis, and rarely, fifth nerve palsy) but are usually independent of mumps meningitis or meningoencephalitis. The incubation period for mumps is 18 to 21 days. When mumps meningitis occurs in the absence of clinical parotitis, it is difficult to distinguish it from other forms of viral meningitis.

When meningitis complicates mumps, fever, which had been low grade, rises to 103°F or higher and persists at this level for 3 or 4 days. Most cases are uncomplicated, with approximately a 10-day duration of illness and then complete recovery. However, symptomatic mumps meningitis may persist for more than 14 days in some patients.

Meningitis Caused by Lymphocytic Choriomeningitis Virus

Lymphocytic choriomeningitis virus infections are uncommon, and clinical illness occurs after an incubation period of 1 to 3 weeks. Illness begins with a grippe-like syndrome of fever, rigors, malaise, myalgia, anorexia, and photophobia. Sore throat and arthralgia or arthritis of the digits are noted by some patients. Orchitis or parotitis occurs rarely. This grippe-like illness lasts 1 to 3 weeks in humans, but 15% of patients have a biphasic illness consisting of transient improvement and then recrudescence, 1 to 2 days later, of fever, photophobia, and more prominent headache. Meningeal signs are observed during the second phase. The duration of meningitis caused by lymphocytic choriomeningitis virus, like that of mumps meningitis, tends to be longer than the 7 to 10 days for enteroviral meningitis.

Meningitis Caused by Human Immunodeficiency Virus

Initial infection with HIV-1 (Chapter 353) is symptomatic in 40 to 90% of patients but is frequently overlooked. The interval between exposure and onset of symptoms is 2 to 4 weeks. This acute illness resembles mononucleosis, with fever, malaise, lymphadenopathy, arthralgia, myalgia, anorexia, nausea, headache, and morbilliform rash. A few patients with this initial syndrome have manifestations of aseptic meningitis (headache, photophobia, nausea, vomiting, and stiff neck). Occasionally, encephalopathy or cranial nerve palsies (seventh, eighth, and fifth) develop. Symptoms of the initial HIV-1 aseptic meningitis syndrome last several weeks and then subside. Occasionally, manifestations similar to those of the initial infection may appear later in the course of untreated infection.

DIAGNOSIS

Cerebrospinal Fluid Examination

Neuroimaging with an MRI or CT scan can be helpful if there is accompanying encephalitis as manifested by focal neurologic signs or to look for obstructive hydrocephalus prior to performing a lumbar puncture. CSF findings in all types of viral meningitis are similar and consist of a predominantly lymphocytic pleocytosis (usually 50 to 1000/μL but occasionally higher), a normal glucose concentration, and a mildly elevated protein level (usually <150 mg/dL). During the first 24 to 48 hours of enteroviral meningitis, a predominance of neutrophils (55 to ≤90%) is observed in approximately 50% of patients; subsequently, the principal cells in CSF change to lymphocytes. Occasionally, no pleocytosis is noted in patients proved by culture or PCR to have early enteroviral meningitis. Rarely, meningitis resulting from mumps or lymphocytic choriomeningitis virus is associated with a low CSF glucose level.

Polymerase Chain Reaction versus Culture or Antibody Detection

Rapid PCR testing of the CSF has a sensitivity for detecting viruses of 85 to 100%, with a specificity of 95 to 100%, depending on the laboratory, and has been standardized for a select number of clinically relevant pathogens in the same sample.[12] For example, reverse-transcription PCR for enteroviruses can reduce detection time to 5 hours or less, thereby shortening hospital stay and minimizing the unnecessary use of antimicrobial agents. By comparison, viral culture of enterovirus from CSF has a sensitivity of only 65 to 75% and takes 4 to 8 days. PCR for HSV-2 DNA is usually positive in the CSF of patients with initial episodes of meningitis and is positive in approximately 80% of patients with benign recurrent meningitis caused by lymphocytic choriomeningitis virus. Metagenomic next-generation sequencing may be particularly useful for identification of rare and unusual organisms when routine testing fails to identify a cause.

The diagnosis also can be made retrospectively by demonstrating seroconversion in HSV-2 meningitis, mumps, or lymphocytic choriomeningitis virus.

Differential Diagnosis

The most important process to distinguish from viral meningitis is bacterial meningitis. A predominance of CSF neutrophils, hypoglycorrhachia, and bacteria on Gram-stained smear or culture indicate bacterial meningitis. An early neutrophilic predominance in CSF combined with a macular and petechial rash in enteroviral meningitis may mimic meningococcemia with meningitis. Occasional bacteria and fungi cause meningitis with a predominantly lymphocytic pleocytosis similar to that of most viral meningitides (Table 381-10). Epidemiologic considerations and clinical findings aid in distinguishing leptospiral (Chapter 298), Lyme *Borrelia* (Chapter 297), and syphilitic meningitis (Chapter 295), whereas hypoglycorrhachia suggests tuberculous and cryptococcal meningitis.

PREVENTION AND TREATMENT

Most cases of viral meningitis are self-limited and require only supportive treatment. The introduction of live attenuated mumps vaccine in the United States reduced mumps from the leading cause of aseptic meningitis and meningoencephalitis to the point at which it occurs only rarely. Chronic enteroviral meningitis and meningoencephalitis in agammaglobulinemic patients have been controlled by parenteral (even intrathecal) administration of immune globulin.

No approved antiviral chemotherapy is available for enteroviral meningitis. Pleconaril, a drug that prevents attachment of virus to host cells, can produce clinical improvement in agammaglobulinemic patients with chronic enteroviral meningoencephalitis.

Intravenous acyclovir (5 to 10 mg/kg three times daily) is used to treat hospitalized, symptomatic patients with HSV-2 meningitis, particularly when the disease is associated with primary genital herpes, although it has not been shown in clinical trials to alter the course of illness. In patients with frequent recurrences of HSV meningitis, it is reasonable to attempt prophylaxis with oral antivirals: valacyclovir (500 mg/day), famciclovir (250 mg twice daily), or acyclovir (400 mg twice daily).

TABLE 381-10 NONVIRAL INFECTIOUS CAUSES OF ASEPTIC MENINGITIS

UNCOMMON	RARE
BACTERIAL	
Leptospira interrogans serovars	*Mycoplasma pneumoniae*
Borrelia burgdorferi	*Ehrlichia chaffeensis*
Treponema pallidum	*Listeria monocytogenes*
Mycobacterium tuberculosis	*Borrelia recurrentis* and *Borrelia hermsii*
Brucella species	*Chlamydia psittaci*
Parameningeal infections	Staphylococcal enterotoxin or TSST-1
Subacute bacterial endocarditis	*Rickettsia rickettsii* and *Rickettsia prowazekii*
Partially treated bacterial (pyogenic) meningitis	
FUNGAL	
Cryptococcus neoformans	*Blastomyces dermatitidis*
Coccidioides immitis	*Sporothrix schenckii*
Histoplasma capsulatum	*Candida* species
PROTOZOAN	
	Trypanosoma brucei species
	Toxoplasma gondii
	Acanthamoeba species

TSST-1 = toxic shock syndrome toxin 1.

TABLE 381-11 NONINFECTIOUS CAUSES OF ASEPTIC MENINGITIS

Drug hypersensitivity
Systemic disease
Systemic lupus erythematosus
Familial Mediterranean fever
Behçet syndrome
Granulomatosis with polyangiitis (formerly Wegener)
Cogan syndrome
Sarcoidosis
Still disease
Kawasaki disease
Lead poisoning
Neoplastic disease
Metastatic carcinomatous meningitis
Central nervous system tumors (meningeal gliomatosis, dysgerminomas, ependymomas)
Tumors that leak inflammatory material into cerebrospinal fluid (squamous cells in epidermoid tumors of the posterior fossa, cholesteatomas)
Inflammatory processes involving central nervous system structures primarily
Chemical meningitis following myelography (water-soluble nonionic contrast material)
Continuous spinal and epidural anesthesia, inflammation after neurosurgery
Granulomatous cerebral vasculitis
Vogt-Koyanagi-Harada syndrome

PROGNOSIS

The course and outcome in patients with enteroviral meningitis are almost always benign, although approximately 1% of patients have subsequent abnormalities, probably reflecting a meningoencephalitic process. Most viral meningitides are self-limited, but some cause chronic or recurrent illness. Persistent meningitis or meningoencephalitis, sometimes fatal, can occur in individuals with hereditary (usually X-linked agammaglobulinemia or common variable immunodeficiency) deficiencies in B-lymphocyte function. HIV-1 may produce a prolonged meningeal inflammation. HSV-2 infection is the most common viral cause of recurrent episodes of aseptic meningitis.

OTHER MENINGITIDES

NONVIRAL INFECTIOUS CAUSES OF ASEPTIC MENINGITIS

Categories of aseptic meningitis other than the viral meningitides include nonviral infectious processes (see Table 381-10), noninfectious processes (Table 381-11), chronic meningitides (Table 381-12), recurrent meningitis (Table 381-13), and eosinophilic meningitis (Table 381-14). Nonviral infectious causes are uncommon or rare in comparison to viral or acute suppurative meningitis. Some of the bacterial causes (e.g., *Leptospira* serovars, *B. burgdorferi, Brucella* sp, *T. pallidum*) produce a lymphocytic pleocytosis; others (partially treated bacterial meningitis, subacute bacterial endocarditis with embolic cerebral infarcts) produce a mixed neutrophilic-mononuclear pleocytosis; and *M. tuberculosis*, though producing a lymphocytic response with developing hypoglycorrhachia, may show a predominantly neutrophilic response in a minority of patients early in the disease. Although patients with *L. monocytogenes* infection usually have neutrophilic pleocytosis, this infection may suggest aseptic meningitis because of its sometimes indolent onset. Fungal (e.g., *Cryptococcus neoformans, Coccidioides immitis, Histoplasma capsulatum*) meningitides are associated with a predominantly mononuclear response, sometimes with a small percentage of eosinophils, particularly in coccidioidal meningitis (Chapter 308). Patients with Rocky Mountain spotted fever (Chapter 302), an acute disease with a macular and petechial rash, may exhibit confusion. When examined, the CSF in approximately 20% of such patients shows a pleocytosis of 10 to 100 or more cells/μL, with either a neutrophilic or lymphocytic predominance. The clinical picture may suggest either enteroviral or meningococcal disease.

Epidemiologic factors are important in raising suspicion for nonviral aseptic meningitis. Leptospirosis (Chapter 298) may be suggested by a history of recent direct or indirect exposure to animals (e.g., dogs, rodents, dairy cattle) and their urine. Neurobrucellosis (Chapter 286) is suggested by the recent ingestion of unpasteurized cheese from the Mediterranean littoral, Middle East, or Mexico or by work as a veterinarian or in an abattoir. Specific endemic mycoses may be a consideration with residence in the southwestern United States (coccidioidomycosis; Chapter 308) and the Mississippi River valley (histoplasmosis; Chapter 308). The setting of immunosuppression by drugs or illness such as acquired immunodeficiency syndrome would raise the possibility of *C. neoformans* (Chapter 309) or *L. monocytogenes* (Chapter 272). Sexual promiscuity and the macular rash of secondary syphilis could suggest *T. pallidum* (Chapter 295) as the cause in a patient with lymphocytic meningitis.

NONINFECTIOUS CAUSES OF ASEPTIC MENINGITIS

Noninfectious causes fall into four principal categories (see Table 381-11): drug hypersensitivity; systemic processes such as systemic lupus erythematosus and other collagen-vascular diseases; neoplastic disease, primary or metastatic, infiltrating the leptomeninges; and inflammatory processes primarily involving the CNS. Although a mononuclear cell predominance is found in the CSF in most noninfectious aseptic meningitides, there are several important exceptions. Drug hypersensitivity (e.g., from trimethoprim-sulfamethoxazole) meningitis usually causes a neutrophilic response, although occasionally mononuclear cells or eosinophils predominate. In systemic lupus erythematosus (Chapter 245), the pleocytosis may be predominantly lymphocytic or neutrophilic (sometimes several thousand per cubic millimeter) with a normal CSF glucose level. Hypoglycorrhachia is a feature of few noninfectious aseptic meningitides and suggests malignant disease or sarcoidosis (Chapter 83).

CHRONIC MENINGITIS

Chronic meningitis is defined by the clinical syndrome of headache, stiff neck, altered mental status, nausea and vomiting, evidence of myelopathy or radiculopathy with or without cranial nerve palsies (e.g., III, IV, VI, VII, VIII), and an inflammatory response in the CSF for 4 weeks or longer.[13] Obstruction of CSF flow may produce hydrocephalus and papilledema.

Infectious Causes

Among the more common bacterial causes of chronic meningitis, *M. tuberculosis* (Chapter 299) is the most important to identify because if untreated, it is almost always fatal within 4 to 8 weeks (see Table 381-12).[14,15] Tuberculosis should be suspected in patients with a previous history of a tuberculous illness, a history of recent exposure, HIV infection or another immunosuppressed state, particularly the use of drugs and biologics that block TNF-α and that are often used to treat autoimmune diseases. Clinical manifestations include fever and night sweats, sixth cranial nerve palsies, stroke related to arteritis, or lesions on the chest radiograph. The purified protein derivative skin test may be negative in patients who are severely immunosuppressed or who have recently acquired or overwhelming disease. Acid-fast smear and culture of concentrated CSF can provide the diagnosis, and modern PCR testing has a sensitivity above 90% and a specificity close to 100%.[16,17] Measurement of CSF levels of adenosine deaminase has both a sensitivity and specificity of about 90%.

When clinical and CSF testing findings suggest the diagnosis, treatment (Chapter 299) should be initiated while awaiting the culture results. There is no benefit from adding levofloxacin (10 mg/kg, maximum 500 mg/day) or using moderately high-dose rifampicin (15 mg/kg as compared with 10 mg/kg) routinely,[A2] but very high-dose rifampicin (20 mg/kg/day intravenously or 35 mg/kg/day orally) can be effective,[A3] and such therapy can improve survival in drug-resistant cases.[A4] Drug resistance and coinfection with HIV infection can be major impediments to adequate treatment. Rifampicin resistance can

TABLE 381-12 INFECTIOUS CAUSES OF CHRONIC (PERSISTENT) LYMPHOCYTIC MENINGITIS

CAUSATIVE CONDITIONS	OTHER CSF FINDINGS
BACTERIAL	
Mycobacterium tuberculosis	Usually <500 white blood cells/μL, low glucose, high protein
Borrelia burgdorferi (Lyme disease)	Normal glucose, elevated protein
Treponema pallidum (secondary syphilitic meningitis, tertiary meningovascular syphilis)	Elevated protein; Venereal Disease Research Laboratory positive in CSF and serum
Brucella species (uncommon)	Often low glucose; elevated protein
Tropheryma whippelii (rare)	Cells positive for periodic acid–Schiff on meningeal biopsy
Partially treated bacterial meningitis	Mixture of PMNs and lymphocytes, bacteria on Gram stain and culture
Parameningeal infections	Lymphocytes or mixed lymphocytic-PMN response, normal glucose
FUNGAL	
Cryptococcus neoformans	Low glucose, elevated protein, budding yeast on fungal wet mount, antigen detectable
Coccidioides immitis	Often low glucose, may have 10-20% eosinophils, elevated protein, presence of complement-fixing antibody
Histoplasma capsulatum	Low glucose; complement-fixing antibodies in CSF; antigen detectable in urine, CSF, serum
Blastomyces dermatitidis	Low glucose
Candida species	Low glucose, may have PMN or lymphocyte predominance, fungal stain may be positive
Aspergillus species	Lymphocytes or PMNs predominate
Sporothrix schenckii (sporotrichosis)	Low glucose; protein, 200-800 mg/dL
PROTOZOAL	
Toxoplasma gondii	Usually, picture is that of an encephalitis; often in patients with AIDS; pleocytosis is mild (<60 cells/μL) and protein is mildly elevated
Trypanosoma gambiense or *rhodesiense*	Meningoencephalitis is stage II of disease, elevated protein and immunoglobulin M, trypanosomes on Giemsa-stained smear
VIRAL	
Mumps	Rarely, low glucose
Lymphocytic choriomeningitis	Rarely, low glucose
Echovirus (in patients with congenital agammaglobulinemia)	Occasionally, low glucose
HIV-1	Cell counts lower (10-20/μL) than in acute self-limited meningitis at clinical onset of HIV infection or may develop during course of AIDS

AIDS = acquired immunodeficiency syndrome; CSF = cerebrospinal fluid; HIV = human immunodeficiency virus; PMN = polymorphonuclear leukocyte.

TABLE 381-13 CAUSES OF CHRONIC (RECURRENT) MENINGITIS

Infections
Herpes simplex virus type 2
Leakage of contents from central nervous system tumors (chemical meningitis)
Epidermoid tumors
Craniopharyngiomas
Cholesteatomas
Drug hypersensitivity with repeated use of agent
Inflammatory processes
Behçet syndrome
Systemic lupus erythematosus
Mollaret meningitis
Vogt-Koyanagi-Harada syndrome

TABLE 381-14 CAUSES OF EOSINOPHILIC MENINGITIS*

CAUSATIVE CONDITIONS	SOURCE
PARASITIC DISEASE	
Angiostrongylus cantonensis	Ingestion of raw shellfish; Pacific
Taenia solium (cysticercosis)	Fecal-oral transmission of *T. solium* eggs
Gnathostoma spinigerum	Ingestion of raw fish; Japan, Southeast Asia
Baylisascaris procyonis	Accidental ingestion of *B. procyonis* eggs from raccoon feces
Trichinella spiralis (trichinosis)	Ingestion of poorly cooked pork
Schistosoma species	Exposure of skin to fresh water; Africa, Middle East
Echinococcus granulosus	Contact with infected dogs passing eggs in feces
Toxoplasma gondii	Ingestion of meat containing cysts or food contaminated with oocysts from cat feces
Toxocara canis (visceral larva migrans)	Ingestion of infective eggs from dog feces
FUNGAL INFECTIONS	
Coccidioides immitis	Southwestern United States
NEOPLASTIC DISEASE	
Lymphoma, leukemia, metastatic carcinoma	
Hypereosinophilic syndrome (myeloproliferative disorder)	
INFLAMMATORY PROCESSES	
Sarcoidosis	
Drug hypersensitivity	
Presence of foreign body in the central nervous system	

*The percentage of eosinophils varies from as little as 6% to the majority of cells.

be easily detected by PCR, because almost all the mutations that confer rifampicin resistance are contained within a well-defined segment of the *rpoB* gene. Resistance to other drugs is less easily detected by these methods.

Adjunctive corticosteroids (e.g., dexamethasone 0.3 to 0.4 mg/kg IV daily for 1 week, then 0.2 to 0.3 mg/kg IV for another week, then a taper from 4 mg daily to 1 mg daily PO over 4 weeks) reduce mortality by about 25%, but do not significantly alter the risk of neurologic sequelae among survivors.[A5]

Parameningeal infections (Chapter 382) should be suspected when chronic meningitis with focal neurologic signs develops in the setting of chronic otitis media or sinusitis, pleuropulmonary infection, or right-to-left cardiopulmonary shunting. Contrast-enhanced CT or MRI of the head is important to delineate brain abscess, sinus infection, and epidural or subdural infections.

Meningitis may accompany the skin, mucous membrane, and lymph node features of secondary syphilis (Chapter 295), or it may occur alone. Individual cranial nerves (II to VII) may be involved; visual abnormalities, hearing loss, and facial palsy are most frequent. The fluorescent treponema antibody absorption test or microhemagglutination *T. pallidum* serologic studies are helpful in distinguishing the process from biologic false-positive Venereal Disease Research Laboratory (or rapid plasma reagent) results in serum.

Lyme disease meningitis (Chapter 297) should be suspected on the basis of epidemiologic grounds (geographic location, season, tick exposure) and associated clinical features (erythema migrans rash, Bell palsy, radiculopathy). The diagnosis is made by enzyme-linked immunosorbent assay with Western blot confirmation.

A variety of fungal infections can cause a chronic meningitis. Cryptococcal meningitis (Chapter 309)[18,19] is common in immunosuppressed individuals and can be diagnosed by detection of cryptococcal antigen in the CSF. Histoplasmosis (Chapter 308) should be suspected in endemic regions. Aspergillosis (Chapter 311) is angiocentric and can cause associated cerebral infarcts. Mucormycosis (Chapter 312) is common in patients with poorly controlled diabetes mellitus. Flucytosine is superior to fluconazole when used with amphotericin B for treatment of cryptococcal meningitis (Chapter 309). Unlike bacterial and tuberculous meningitis, adjunctive corticosteroids are not beneficial and even seem to be detrimental,[A6] except in patients with immune reconstitution inflammatory syndromes (Chapter 358), in which corticosteroids may be beneficial if given concomitantly with antimicrobial agents.

Noninfectious Causes

Noninfectious causes of meningitis include malignant disease (from both hematologic and solid tumors),[20] chemical meningitis, and primary inflammatory

conditions (Table 381-15). Malignant disease may be diagnosed by cytologic examination of large volumes of CSF. Contrast-enhanced MRI may disclose thickening of the meninges and nerve roots, but meningeal biopsy may be required for diagnosis. Chemical meningitis from previous subarachnoid injection may persist, with xanthochromia noted in CSF; meningeal inflammation may be identified on contrast-enhanced CT or MRI.

Meningeal or CNS sarcoid (Chapter 83) may be isolated or occur with other organ involvement, such as pulmonary granulomas, lymphadenopathy, or myopathy. Neurologic findings can include diabetes insipidus and cranial nerve palsies. Granulomatosis with polyangiitis (Chapter 249) may produce meningeal inflammation and cranial nerve palsies, often in association with air sinus disease. The diagnosis is suggested by lesions on the chest radiograph, microscopic hematuria, skin lesions, peripheral neuropathy, and serum antineutrophil cytoplasmic antibodies. Aseptic meningitis associated with systemic lupus erythematosus (Chapter 245) may be accompanied by other neurologic manifestations (seizures, encephalopathy, stroke, transverse myelopathy), systemic manifestations (rash, arthritis), and antinuclear and anti-DNA antibodies.

Chronic Meningitis with a Predominantly Neutrophilic Pleocytosis

Chronic persistent neutrophilic meningitis (E-Table 381-1) is defined by the following combination: (1) clinical features consistent with meningitis; (2) initial CSF examination showing greater than 50% neutrophils, hypoglycorrhachia, and elevated protein concentration; (3) prior or no response to antimicrobial therapy that would be appropriate for the usual causes of bacterial meningitis; (4) negative smears and cultures for bacteria on the initial CSF specimen; and (5) repeated CSF examination 7 days or more after initial analysis showing 50% or greater neutrophils, hypoglycorrhachia, and elevated protein concentration.

Among the bacterial causes (see E-Table 381-1) are organisms (*Actinomyces israelii* and *Arachnia propionica* [Chapter 304]) that can be isolated by culture only under anaerobic conditions. Coexisting pulmonary lesions may suggest *Nocardia* (Chapter 306) or *M. tuberculosis* (Chapter 299) as the cause, although the initial polymorphonuclear pleocytosis present in some cases uncommonly persists much beyond a week before changing to a lymphocytic predominance. *Brucella* (Chapter 286) and endemic invasive mycotic infections would be suggested by epidemiologic considerations. Other fungal causes may be diagnosed, particularly in immunocompromised patients, by antigen testing with enzyme-linked immunosorbent assay (*Aspergillus* sp galactomannan; Chapter 311), or meningeal biopsy may be required.

Occasionally, exogenous chemical meningitis secondary to intrathecal injection of antimicrobials, chemotherapeutic agents, or contrast media may produce persisting pleocytosis and hypoglycorrhachia resulting from sclerosing arachnoiditis well after the inciting medication has been withdrawn. Systemic lupus erythematosus (Chapter 245) can produce a variety of meningitides, including acute lymphocytic or neutrophilic aseptic meningitis, as well as chronic persistent lymphocytic or neutrophilic CSF responses.

CHRONIC INTERMITTENT MENINGITIS

In chronic intermittent meningitis, all clinical and CSF abnormalities resolve completely between episodes without antimicrobial therapy (see Table 381-12). Uncommonly, a patient may have several episodes resulting from different viral agents. The major causes of recurrent aseptic meningitis are infections (almost always viral and resulting from HSV-2), endogenous chemical meningitis, drug hypersensitivity (including the use of intravenous immunoglobulins) with meningitis following each use, and inflammatory and autoimmune diseases.

In HSV-2 recurrent meningitis, lymphocytes predominate, with the cell numbers being approximately 40% higher in the initial episode than in recurrences. Leakage of material from intracranial epidermoid cysts produces 1000 to 5000 cells/μL (≈80% polymorphonuclear leukocytes) initially, with a subsequent mononuclear cell predominance. Occasionally, polarizing microscopy may demonstrate keratin and cholesterol crystals in the CSF of patients with endogenous chemical meningitis. In Behçet syndrome (Chapter 249), the CSF may have predominantly mononuclear cells or polymorphonuclear leukocytes. Mollaret meningitis, a syndrome of benign recurrent meningitis usually caused by HSV-2, is initially associated with neutrophils and monocytes in the CSF without hypoglycorrhachia but subsequently transitions to a predominantly lymphocytic pleocytosis. However, prolonged treatment with valacyclovir 1 g/day does not prevent recurrences of HSV-2–associated meningitis. Vogt-Koyanagi-Harada syndrome, a rare uveomeningoencephalitis, consists of recurrent meningitis/meningoencephalitis and anterior or posterior uveitis, followed by vitiligo, poliosis, alopecia, and dysacousia; the CSF cellular response is mononuclear, and an autoimmune origin, directed against a melanocyte antigen, has been suggested.

TABLE 381-15 NONINFECTIOUS CAUSES OF CHRONIC (PERSISTENT) LYMPHOCYTIC MENINGITIS

CAUSATIVE CONDITIONS	OTHER CSF FINDINGS
NEOPLASMS	
Metastatic: Lung, breast, stomach, pancreas, lymphoma, melanoma, leukemia	Low glucose; elevated protein, cytologic examination; polarizing microscopy; clonal lymphocyte markers
Central nervous system: Meningeal gliomatosis, meningeal sarcoma, cerebral dysgerminoma; epidermoid tumors/cysts	
CHEMICAL INFLAMMATION	
Endogenous: Epidermoid tumor, craniopharyngioma	Low glucose, elevated protein
Exogenous: Recent injection into the subarachnoid space	Low glucose, elevated protein
PRIMARY INFLAMMATORY PROCESSES	
Central nervous system sarcoid	Often low glucose, elevated protein, elevated angiotensin-converting enzyme levels in CSF (and serum)
Granulomatosis with polyangiitis (formerly Wegener)	Elevated protein
Behçet syndrome	Elevated protein
Isolated granulomatous angiitis of the central nervous system	Elevated protein
Systemic lupus erythematosus	Elevated protein
?Chronic idiopathic benign meningitis	Elevated protein

CSF = cerebrospinal fluid.

EOSINOPHILIC MENINGITIS

The presence of 5% or greater eosinophils in CSF is uncommon and suggests parasitic disease, certain fungal infections such as coccidioidal or candidal meningitis, neoplastic diseases, or a few inflammatory processes (see Table 381-14).[21] In most cases, eosinophils are mixed with lymphocytes, which predominate; the highest percentage of eosinophils is seen with meningitis caused by migrating larvae of the raccoon ascarid *Baylisascaris procyonis* (Chapter 327) and the rat lung worm *Angiostrongylus cantonensis* (Chapter 327). In fungal meningitides, particularly those resulting from *C. immitis* (Chapter 308), the CSF response is primarily mononuclear with 6 to 20% eosinophils; hypoglycorrhachia may be a feature of *C. immitis* and *Candida* meningitis (Chapter 310) and of neoplastic processes and sarcoid.

Most patients with eosinophilic meningitis, except those with cases resulting from trichinosis (Chapter 327) or drug hypersensitivity, have prolonged symptoms suggesting chronic meningitis. Most patients with meningitis of parasitic or neoplastic origin have evidence of cerebral involvement as well.

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For the General References and other additional features, please visit Elsevier eBooks+ at https://ebooks.health.elsevier.com.

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E-TABLE 381-1 CAUSES OF CHRONIC (PERSISTENT) MENINGITIS WITH NEUTROPHIL PREDOMINANCE

UNCOMMON	OTHER CSF FINDINGS
BACTERIAL	
Nocardia asteroides	Low glucose, markedly elevated protein, culture positive
Actinomyces israelii	Low glucose, elevated protein, anaerobic culture positive
Arachnia propionica	Low glucose, elevated protein, anaerobic culture positive
FUNGAL	
Candida species	Low glucose, elevated protein, culture positive
Aspergillus species	Low glucose, elevated protein, enzyme immunoassay or enzyme-linked immunosorbent assay for *Aspergillus* galactomannan
Zygomycetes	Low glucose, elevated protein
Dematiaceous fungi	Low glucose, protein may be markedly elevated
NONINFECTIOUS	
Systemic lupus erythematosus	Low glucose, elevated protein
Chemical meningitis	Low glucose, protein may be markedly elevated
VERY RARE	
Bacterial	
Brucella species	Low glucose, elevated protein
Mycobacterium tuberculosis	Low glucose, elevated protein, polymerase chain reaction positive for *M. tuberculosis* DNA
Fungal	
Pseudallescheria boydii	Low glucose, protein may be markedly elevated
Coccidioides immitis	Low glucose, elevated protein, presence of complement-fixing antibody
Blastomyces dermatitidis	Low glucose, protein elevated, antigen detection possible in CSF and urine
Histoplasma capsulatum	Low glucose; protein mildly elevated; complement-fixing antibodies in CSF; antigen detectable in CSF, urine, serum

CSF = cerebrospinal fluid.

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382 BRAIN ABSCESS AND PARAMENINGEAL INFECTIONS

AVINDRA NATH AND JOSEPH R. BERGER

A brain abscess affects the brain's parenchyma directly, whereas parameningeal infections produce suppuration in potential spaces covering the brain and spinal cord (epidural abscess and subdural empyema) or produce occlusion of the contiguous venous sinuses and cerebral veins (cerebral venous sinus thrombosis).

BRAIN ABSCESS

EPIDEMIOLOGY

The frequency of various causes of brain abscess (Table 382-1) in the population is difficult to ascertain because of wide variations among case series, in part owing to referral patterns. Improvements in health care have lowered the incidence to about 3 per 100,000 person years.[1] Brain abscesses account for less than 1% of intracranial mass lesions in developed countries but are significantly more common in developing countries. Males predominate in virtually all series of brain abscess.

On average, 90% of brain abscesses are a consequence of a focus of suppuration elsewhere in the body, with the remainder due to introduction of the infection from head wounds or neurosurgical procedures.[2] Disease of the paranasal sinuses, middle ear, and mastoid cells account for approximately 40% of brain abscesses.[3] Dental infections of the upper molars can be a source of infection,[4] but invasive dental procedures otherwise are not.[5] Cyanotic congenital heart disease (Chapter 55), a patent foramen ovale, and pulmonary arteriovenous malformations (as are seen in hereditary hemorrhagic telangiectasia; Chapter 159), also are risk factors for bacterial brain abscess, apparently because venous infection bypasses the pulmonary circulation and spreads directly to the systemic circulation. Fungal brain abscesses are rare in immunocompetent adults but can be caused by aspergillosis in immunocompromised patients.[6] Brain abscesses caused by *Toxoplasma* species (Chapter 320) usually occur in immunocompromised patients, and especially in patients with advanced human immunodeficiency virus (HIV) infection.[7]

PATHOBIOLOGY

Brain abscesses are collections of purulent material (neutrophils and necrotic tissue) caused by infection with bacterial, fungal, or parasitic organisms. When contiguous to the brain, infection enters by direct extension or by traveling along veins with associated thrombophlebitis of pial veins and sinuses. Brain abscesses arising from sinus or ear infection, or those from penetrating injury, are generally proximate to the site of the originating infection. For instance, abscesses originating from the frontal and sphenoid sinuses typically affect the frontal and temporal lobes, whereas those originating from the ear affect the anterolateral cerebellar hemispheres or middle and inferior temporal lobes.

More commonly, the brain is seeded hematogenously by the offending microorganism from a distant site. Hematogenous dissemination typically results in lesions located at the junction of white and gray matter.

Within the brain, the infection begins as a cerebritis with perivascular infiltrates and infiltration of neutrophils into the brain parenchyma. With time, the developing abscess is characterized by a purulent exudate that includes necrotic brain tissue as well as viable and necrotic neutrophils. Granulation tissue develops at the interface between necrotic and viable tissue, and eventually, the abscess is walled off by a fibrous capsule. Formation of the capsule depends on the virulence of the organism and the immune status of the individual. More virulent organisms cause larger lesions, more necrosis, earlier ependymitis, and a greater degree of inflammation outside the collagen capsule.

TABLE 382-1 CONDITIONS THAT PREDISPOSE TO THE DEVELOPMENT OF BRAIN ABSCESS

Otogenic
Otitis media
Mastoiditis
Dental infections
Cardiac
Cyanotic heart disease
Tetralogy of Fallot
Patent foramen ovale
Infective endocarditis
Pulmonary
Pulmonary arteriovenous fistula
Lung infection
Esophageal stricture dilatation
Cerebral infarcts and tumors
Penetrating and nonpenetrating head injury
Postoperative neurosurgical procedure
Dermal sinus tracts
Sepsis
Immunosuppression

CLINICAL MANIFESTATIONS

The clinical picture reflects a triad of the infectious nature of the lesion, focal brain involvement, and an increasing intracranial mass effect (Table 382-2). One or two elements may be absent, particularly early in the course. Among infectious symptoms, fever is present at onset or early in the course in only about 60% of cases. Neck stiffness is an infrequent complaint, and meningeal signs are elicited in about 30% of cases. The absence of classical signs may delay diagnosis.

Focal neurologic deficits depend on the site and size of the lesion, which in turn will be determined by the causative agent and any underlying condition that may predispose to the development of brain abscess. In some patients, seizures precede the diagnosis. Temporal lobe abscess, often caused by spread of an otogenic infection, may manifest as contralateral homonymous superior quadrantic visual field defects and, if in the dominant hemisphere, with aphasia. Motor deficits eventually occur in 40 to 50% of supratentorial abscesses. Cerebellar abscesses, which are often caused by aural-mastoid infections, are characterized by ipsilateral limb ataxia; there may also be abnormal head positioning (forward and away from the side of the lesion) and nystagmus that is slow and coarse on gaze to the side of the abscess and rapid in the opposite direction. Patients with multiple brain abscesses may have multifocal signs or encephalopathy. Patients with *Toxoplasma* species (Chapter 320) brain abscesses often have movement disorders because these abscesses frequently localize to the basal ganglia. In fact, nearly all patients with HIV infection in whom hemiballism or hemichorea is present have *Toxoplasma* species brain abscesses.

Headache is an important initial symptom in 80 to 90% of patients with bacterial abscess but is less frequent in patients with fungal abscesses. Symptoms of increased intracranial pressure, such as nausea, depressed level of consciousness, and papilledema, occur less often. The development of headache in a patient with a known chronic anaerobic infection, such as aural-mastoid, paranasal sinus, or pulmonary suppuration, suggests the possibility of brain abscess. Similarly, the development of headache in a child with cyanotic congenital heart disease is often related to a brain abscess. Tetralogy of Fallot (Chapter 55) is the most common congenital heart anomaly associated with brain abscess.

DIAGNOSIS

Examination of the cranium, ears, paranasal sinuses, oral cavity, heart, and lungs may provide important clues to the etiology, as may overt signs of

TABLE 382-2 INITIAL CLINICAL FEATURES IN BRAIN ABSCESS

Fever	60%
Headache	55%
Disturbed consciousness	50%
Hemiparesis	50%
Nausea, vomiting	30%
Nuchal rigidity	30%
Dysarthria	20%
Seizures	20%
Visual disturbance	15%

ABSTRACT

Brain abscesses occur when bacterial, fungal, or parasitic organisms directly invade the brain, whereas parameningeal infections are caused by infection in the subdural or epidural space or in the venous sinuses. Early recognition, which is key for effective management, can be challenging, and aggressive treatment is required.

KEYWORDS

brain abscess
subdural abscess
epidural abscess
bacterial
fungal
parasitic abscess

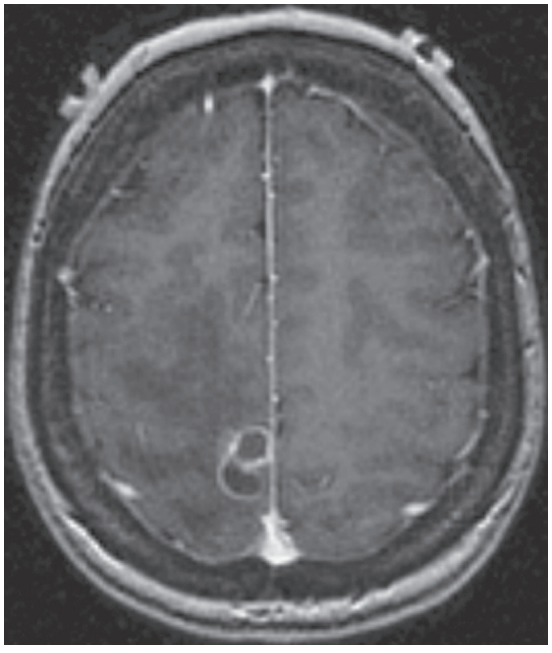

FIGURE 382-1. Brain abscess. Magnetic resonance imaging with gadolinium shows a multiloculated ring-enhancing lesion caused by *Nocardia* species infection.

infection at other sites. Laboratory examination often, but not invariably, reveals a leukocytosis, an elevated erythrocyte sedimentation rate, and an increased C-reactive protein level. Cultures of blood and sputum may identify the organism and its antimicrobial sensitivity. Lumbar puncture, generally contraindicated in the setting of brain mass lesions because of concern about the risk of brain herniation from increased intracranial pressure, reveals a moderately increased cerebrospinal fluid (CSF) pressure with early abscess. A mild to moderate CSF pleocytosis and protein levels <100 mg/dL may be observed. CSF glucose is normal, and the CSF is sterile unless there is a concomitant meningitis.

Magnetic resonance imaging (MRI) can detect early changes such as brain edema and is preferable to computed tomography (CT). In the early cerebritis stage, T2-weighted MRI shows abnormally high signal intensity corresponding to low signal intensity on the T1-weighted images. The fluid-attenuated inversion recovery (FLAIR) sequence provides superior visualization of brain edema. On T1-weighted images, the area of cerebritis that is seen initially as a low-signal-intensity, ill-defined area later progresses to a central cavity with slightly higher signal intensity than CSF, surrounded by edema that is slightly hypointense in comparison to brain parenchyma. Later stages of infection show central necrosis and formation of a rim of slightly high-signal intensity on T1-weighted images (Fig. 382-1). With gadolinium administration, a ring-enhancing lesion owing to leakage of the contrast material at the rim of the lesion is seen where there is breakdown of the blood-brain barrier. Diffusion-weighted imaging helps differentiate abscesses from brain tumors (Chapter 175); pus in the abscess cavity demonstrates high signal with decreased apparent diffusion coefficient values, whereas necrotic tumor cavities demonstrate the opposite.

Surgical aspiration or excision of the lesion may be necessary to establish a microbial diagnosis. Multiplex polymerase chain reaction testing can rapidly identify bacterial organisms and may be able to detect antibiotic-resistance genes. Gram stain and culture from abscess fluid, with proper handling, have high yield, with or without previous antibiotic therapy. If immediate surgery is planned, antibiotics can be deferred until culture material has been acquired.

TREATMENT

Brain abscess requires urgent intervention. Surgical intervention has the advantage of establishing a definitive diagnosis, identifying the causative organism, and determining antibiotic susceptibility.[8]

Because of the risk for cerebral herniation with large lesions, treatment of cerebral edema (intravenous [IV] dexamethasone 16 to 24 mg/day in four divided doses) may be needed even while initiating surgical intervention.

TABLE 382-3 COMMON PATHOGENS AND EMPIRICAL THERAPY FOR BRAIN ABSCESS

PREDISPOSING CONDITION	COMMON PATHOGENS	ANTIMICROBIAL AGENTS*
Dental abscess	Streptococci, *Bacteroides fragilis*	Penicillin + metronidazole
Chronic otitis	*Bacteroides fragilis; Pseudomonas, Proteus, Klebsiella* species	Cefotaxime or ceftriaxone + metronidazole; ceftazidime or cefepime for *Pseudomonas* species
Sinusitis	Streptococci; *Haemophilus, Staphylococcus* species	Cefotaxime, ceftriaxone, or nafcillin + metronidazole
Penetrating trauma or postsurgical	*Staphylococcus, Pseudomonas, Enterobacter* species; streptococci	Nafcillin or vancomycin + ceftriaxone or cefotaxime + metronidazole
Bacterial endocarditis or drug use	Mixed flora, streptococci, *Staphylococcus* species	Nafcillin or vancomycin + ceftriaxone or cefotaxime + metronidazole
Congenital heart disease	Streptococci	Cefotaxime or ceftriaxone
Pulmonary infection	*Nocardia* species, *Bacteroides fragilis*, streptococci, mixed flora	Penicillin + metronidazole + trimethoprim-sulfamethoxazole
Gastrointestinal infection	*Listeria monocytogenes*	Ampicillin + gentamicin
HIV infection	*Toxoplasma gondii*	Pyrimethamine + sulfadiazine + folinic acid
Diabetes/ immunosuppression	*Fungal species*	Amphotericin, voriconazole or fluconazole

*See Table 266-4 in Chapter 266 for dosing schedules.
HIV = human immunodeficiency virus.

Corticosteroids often decrease edema within 8 hours but may retard the formation of a capsule around the brain abscess, suppress the immune response to the infection, and decrease penetration of antibiotics. Hence, they should be used for short periods, usually only until surgical decompression by needle drainage or surgical removal is possible.

Toxoplasma brain abscesses are not accompanied by capsule formation and hence respond well to antibiotic therapy alone. As a result, patients with acquired immunodeficiency syndrome and suspected cerebral toxoplasmosis (Chapter 320) should initially receive antimicrobial therapy, and the abscess does not need to be drained.

For other abscesses, empirical antibiotic therapy (Table 382-3) is recommended prior to surgery, based on the likely source of infection, knowledge of proved or suspected pathogens, as well as familiarity with a drug's spectrum of activity and penetration into the central nervous system.[9] Because abscesses may include multiple organisms, antibiotic coverage should include both aerobic and anaerobic bacteria.

However, antibiotics may not penetrate the cavity of more advanced brain abscesses owing to the absence of blood supply in the necrotic lesion. Therefore, surgical drainage is usually the treatment of choice. Fungal brain abscesses may require aspiration and intracavitary antifungal drugs in addition to prolonged systemic antifungal therapy.

When surgery cannot be performed (e.g., in a remote location where neurosurgical expertise may not be available), empirical antibiotic therapy is the only alternative. A trial of nonsurgical treatment may also be considered in patients with (1) small lesion size; (2) an already identified pathogen; (3) no symptoms or signs of increased intracranial pressure requiring neurosurgical intervention; (4) a deep or inaccessible lesion; (5) multiple abscesses; (6) a contraindication to surgery (e.g., a bleeding diathesis); (7) a short duration of symptoms, which suggests that the lesion is in the cerebritis stage; and (8) availability of monitoring with MRI.

In patients who are suspected of having a brain stem abscess, the possibility of listerial infection (Chapter 272) should be considered (Fig. 382-2), even in the absence of documented immunodeficiency. Empirical parenteral antibiotics to cover *Listeria* species should be started (Chapter 272).

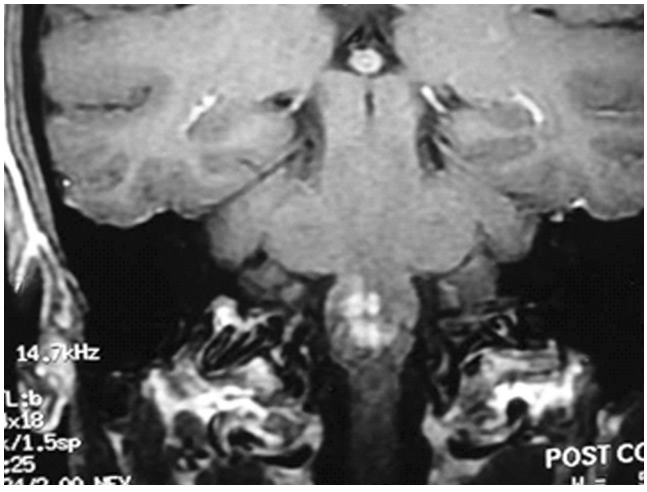

FIGURE 382-2. Brain stem abscess. Magnetic resonance imaging with gadolinium shows an enhancing lesion in the brain stem caused by *Listeria* species infection.

PROGNOSIS

Before the CT scan era, the mortality of brain abscesses ranged from 40 to 60%, and even in the era of modern neuroimaging, the mortality rate remains about 20%.[10,11] About 70% of patients recover fully. In post-transplantation patients and those with deep hemispheric or brain stem abscesses, mortality rates may exceed 80%. Other factors associated with a poor prognosis include extremes of age, multiple abscesses, and diagnostic delay in the absence of systemic signs of infection. An impaired level of consciousness is a poor prognostic sign even with early hospitalization and rapid diagnosis. Anaerobic and gram-negative organisms and culture-negative cases also have a poor prognosis. Seizures (Chapter 372) develop in up to 50% of patients, sometimes after latencies as long as 5 years.

SPINAL EPIDURAL ABSCESS

DEFINITION

Infection within the epidural space around the spinal cord is an uncommon, but often readily treatable, potential cause of paralysis and death. The epidural space surrounds the dural sac and is limited by the posterior longitudinal ligament anteriorly, the ligamenta flava and the periosteum of the laminae posteriorly, and the pedicles of the spinal column and the intervertebral foramina containing their neural elements laterally. The space communicates with the paravertebral space through the intervertebral foramina. Superiorly, the space is closed at the foramen magnum. Caudally, the space is closed by the sacrococcygeal ligament. The epidural space contains loose areolar connective tissue, semiliquid fat, lymphatics, arteries, an extensive plexus of veins, and the spinal nerve roots.

EPIDEMIOLOGY

Spinal epidural abscesses can result from hematogenous spread of infection; risk factors include IV drug use, organ transplantation, chronic steroid use, malignancy, and diabetes. Local infection after acupuncture for back pain or epidural analgesia can also cause epidural abscesses. Cutaneous sites of infection are the most common remote sources, especially in IV drug users. Abdominal, respiratory tract, and urinary sources are also common. Osteomyelitis may be a cause of either direct extension or hematogenous spread, particularly when associated with sepsis. Contiguous spread may occur from epidurally placed catheters, psoas abscesses, decubitus ulceration, perinephric and retropharyngeal abscesses, or surgical sites. Minor back trauma has been implicated in causing a paraspinal hematoma, which may be seeded hematogenously. *Staphylococcus aureus* is the most common organism isolated from spinal epidural abscesses,[12] followed by streptococci, gram-negative bacilli, and anaerobic organisms.

PATHOBIOLOGY

Because the dura mater around the cord is adherent to the vertebral column anteriorly, more epidural abscesses lie posteriorly, and because no anatomic barriers separate the spinal segments in the posterior epidural space, such abscesses usually extend over several vertebral segments. Spinal cord dysfunction can be a result of local inflammation, compression and edema of the spinal cord, thrombophlebitis, or ischemic injury from venous thrombosis or from compression of the spinal arteries.

CLINICAL MANIFESTATIONS

The presence of a risk factor such as intravenous drug use, an indwelling vascular catheter, or an infection at another site (>80% of patients) in the setting of neurologic deficits or back or radicular pain should suggest a spinal epidural abscess.[13,14] The clinical manifestations can be divided into four stages (E-Table 382-1). Back pain (in about 70% of patients) and fever (in about 65% of patients) are common. With focal percussion, pain over the spine can be elicited in about 20% of patients. Radicular pain can be mistaken for sciatica, a visceral abdominal process, chest wall pain, or cervical disc disease. Clinical signs are often substantially greater than would be predicted from the anatomic extent of pus or granulation tissue.

DIAGNOSIS

The differential diagnosis includes compressive and inflammatory processes involving the spinal cord: transverse myelitis (Chapter 380), herniation of an intervertebral disc (Chapter 369), epidural hemorrhage (Chapter 369), or metastatic tumor (Chapter 175), none of which are associated with evidence of systemic infection. Blood leukocytosis may not be present, but the sedimentation rate is often elevated. Other infectious processes that may produce back or neck pain or tenderness must be excluded: bacterial meningitis (Chapter 381), perinephric abscess, disc space infection, and bacterial endocarditis (Chapter 61).

Lumbar puncture should be avoided in patients suspected of having a spinal epidural abscess, for fear of spreading the infection to the subarachnoid space and causing meningitis. Gadolinium-enhanced MRI (Fig. 382-3) is the method of choice for diagnosis,[15] and paraspinal edema on MRI is the most sensitive feature for a spinal epidural abscess, but MRI findings in patients undergoing epidural analgesia can resemble those of epidural spinal abscess even when no infection is present.

Unfortunately, as many as 75% of patients with spinal epidural abscess are misdiagnosed at the time of initial presentation. If the condition goes unrecognized, symptoms can evolve over a period of hours to days to paralysis below the spinal level of infection.

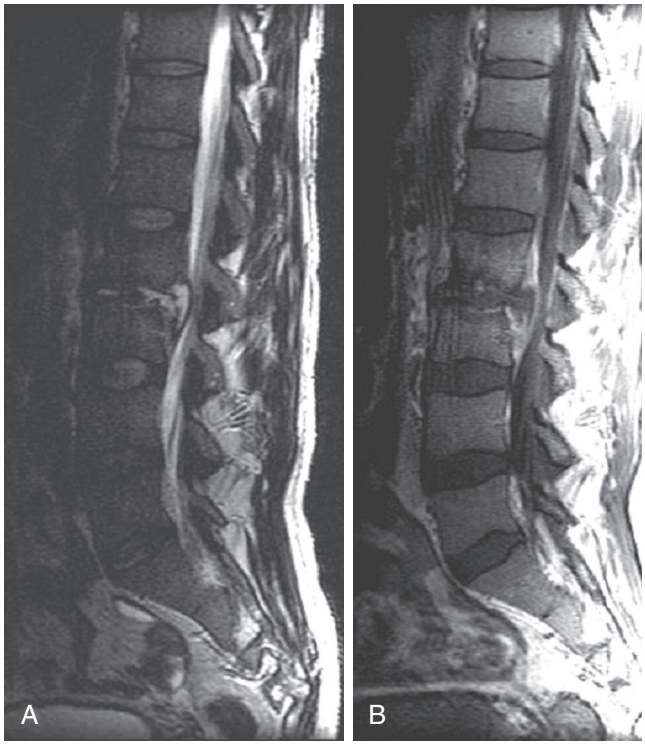

FIGURE 382-3. Spinal epidural abscess. A and B, Magnetic resonance images of the lumbosacral spine show a lesion in the epidural space compressing the thecal sac.

E-TABLE 382-1 INITIAL CHARACTERISTICS OF 915 PATIENTS WITH SPINAL EPIDURAL ABSCESS

STAGE 1	
Back pain	71%
Fever	66%
STAGE 2	
Radicular pain	20%
STAGE 3	
Muscle weakness	26%
Sphincter incontinence	24%
Sensory deficits	13%
STAGE 4	
Paralysis	31%
Quadriplegia	3%

From Reihsaus E, Waldbaur H, Seeling W. Spinal epidural abscess: a meta-analysis of 915 patients. *Neurosurg Rev*. 2000;23:175-204.

TREATMENT

Patients with a progressing neurologic deficit should undergo urgent surgical drainage, because medical management often fails.[16,17] CT-guided aspiration may be useful, and antibiotics plus percutaneously guided needle aspiration may be as therapeutically effective as antibiotics plus surgery. Unless culture results and sensitivities dictate otherwise, empirical therapy should cover *S. aureus* (nafcillin 2 g every 6 hours; vancomycin 1 g every 12 hours for methicillin-resistant strains). Additional gram-negative coverage with a third-generation cephalosporin (e.g., cefotaxime 2 g every 6 hours or ceftriaxone 2 g every 12 hours) or a quinolone (e.g., ciprofloxacin 400 mg every 12 hours) should be considered for severe disease. Rifampin (300 mg every 12 hours) may be added because of its ability to penetrate the abscess cavity. IV therapy should be continued for 3 to 4 weeks except in the presence of osteomyelitis (6 to 8 weeks).

PROGNOSIS

The mortality rate of spinal epidural abscess is about 15%. Approximately 50% of survivors have residual neurologic deficits. More severe preoperative neurologic deficits and deficits of longer duration are associated with a worse prognosis. In general, patients who develop paralysis that persists for longer than 36 hours do not recover function.

SUBDURAL EMPYEMA

Subdural empyema is an infection in the space between the dura and the arachnoid. It usually results from infected paranasal sinuses and rarely from infected mastoid sinuses by extension of thrombophlebitis from the sinuses into the subdural space. The infection is often unilateral because bilateral spread is prevented by the falx. The empyema may result in cortical vein thrombosis, cerebral abscesses, or purulent meningitis.

CLINICAL FEATURES AND DIAGNOSIS

The most common symptoms are headache, fever, a neurologic deficit, and a stiff neck. However, subdural empyema may progress and cause signs of raised intracranial pressure, such as vomiting, altered level of consciousness, seizures, and papilledema. A high degree of suspicion is needed to establish the diagnosis early in the course of the illness. In patients with sinusitis (Chapter 394), the symptoms of subdural empyema may be incorrectly attributed to the sinusitis.

MRI with gadolinium enhancement and diffusion-weighted images is useful in visualizing the subdural infection as a crescent-shaped mass with an enhancing rim over the cerebral convexities and below the inner table of the skull (Fig. 382-4). CSF evaluation is useful only if there is accompanying meningitis. In a patient with signs of raised intracranial pressure, lumbar puncture should be avoided because of the risk for herniation.

TREATMENT

Surgical drainage of the empyema is mandatory. IV antibiotic therapy is also necessary and is based on the organisms isolated at the time of craniotomy.

PROGNOSIS

The mortality rate is about 25%, with severe residual neurologic sequelae in about 20% of survivors. Accompanying venous sinus thrombosis or brain abscess carries a poor prognosis.

VENOUS SINUS THROMBOSIS SECONDARY TO INFECTION

The venous sinus system (Fig. 382-5) lacks valves, thereby permitting retrograde propagation of clots or infections that emanate from structures located in the central portion of the face or the middle ear.

SEPTIC CAVERNOUS SINUS THROMBOSIS

DEFINITION

The cavernous sinuses, which are the most caudal dural venous chambers at the base of the skull, lie on either side of the pituitary fossa immediately above the midline sphenoid sinus. The cavernous sinus encloses the "cavernous portion" of the internal carotid artery as well as the third, fourth, and sixth cranial nerves.

EPIDEMIOLOGY AND PATHOBIOLOGY

The infection usually spreads from the paranasal sinuses, dental abscesses, or other infections affecting the orbit or middle third of the face. *S. aureus* is the most common organism. Streptococci, pneumococci, and gram-negative bacilli are less common; anaerobic infection has also been reported.

CLINICAL MANIFESTATIONS

Cavernous sinus thrombosis may be manifested as an acute fulminant disease or have an indolent subacute manifestation. Fever and other systemic symptoms from sepsis may be present. Clinical symptoms and signs are related to anatomic structures within the cavernous sinuses or drained by them: unilateral periorbital edema, headache, photophobia, proptosis, ophthalmoplegia, pupillary dilation, decreased corneal reflex, and periorbital sensory loss. Obstruction of venous drainage from the retina can result in papilledema, retinal hemorrhages, and visual loss. The infection can spread rapidly (24 to 48 hours) through the intercavernous sinuses to the contralateral cavernous sinus. Thrombus can extend to other dural venous sinuses, adjacent vascular structures, or the brain parenchyma.

DIAGNOSIS

The diagnosis is made on clinical findings and confirmed by radiographic studies.[18] Radiologic evaluation includes sinus imaging, particularly the sphenoid and ethmoid sinuses. MRI using flow parameters and MR venogram is sensitive and

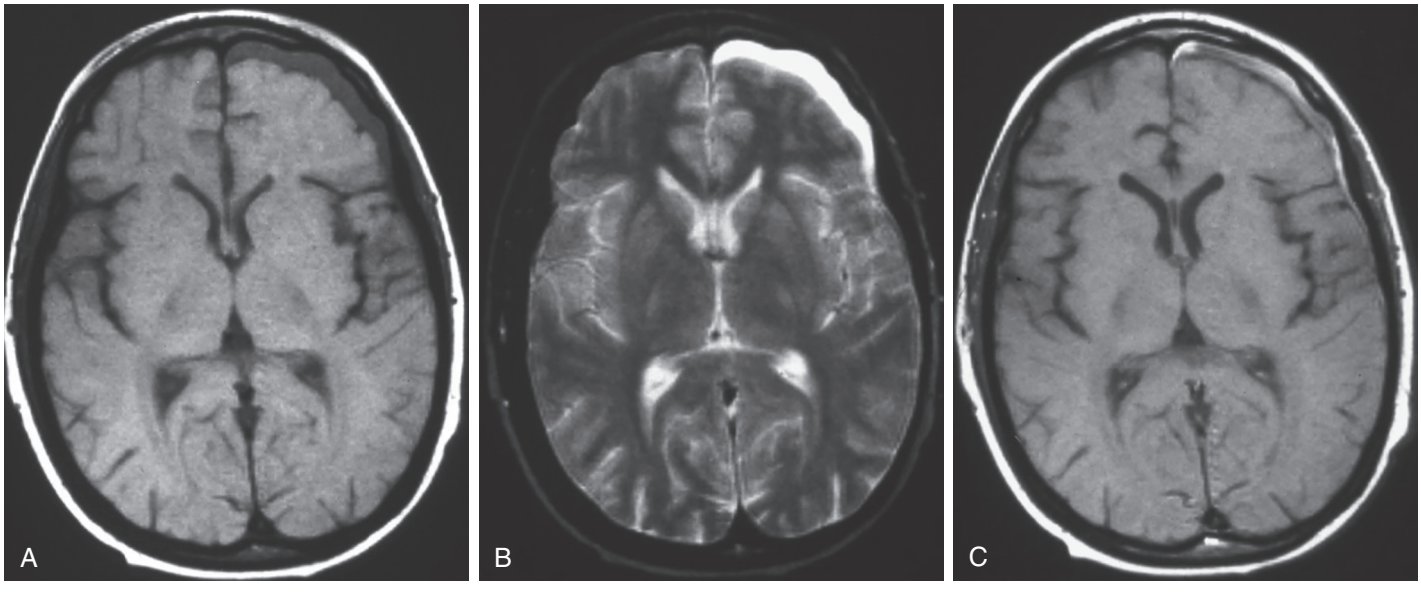

FIGURE 382-4. **Subdural abscess. A,** T1-weighted magnetic resonance imaging shows a hypodense area in the left frontal region. **B,** T2-weighted image shows increased signal intensity in the same region. **C,** A contrast scan shows enhancement in the same region.

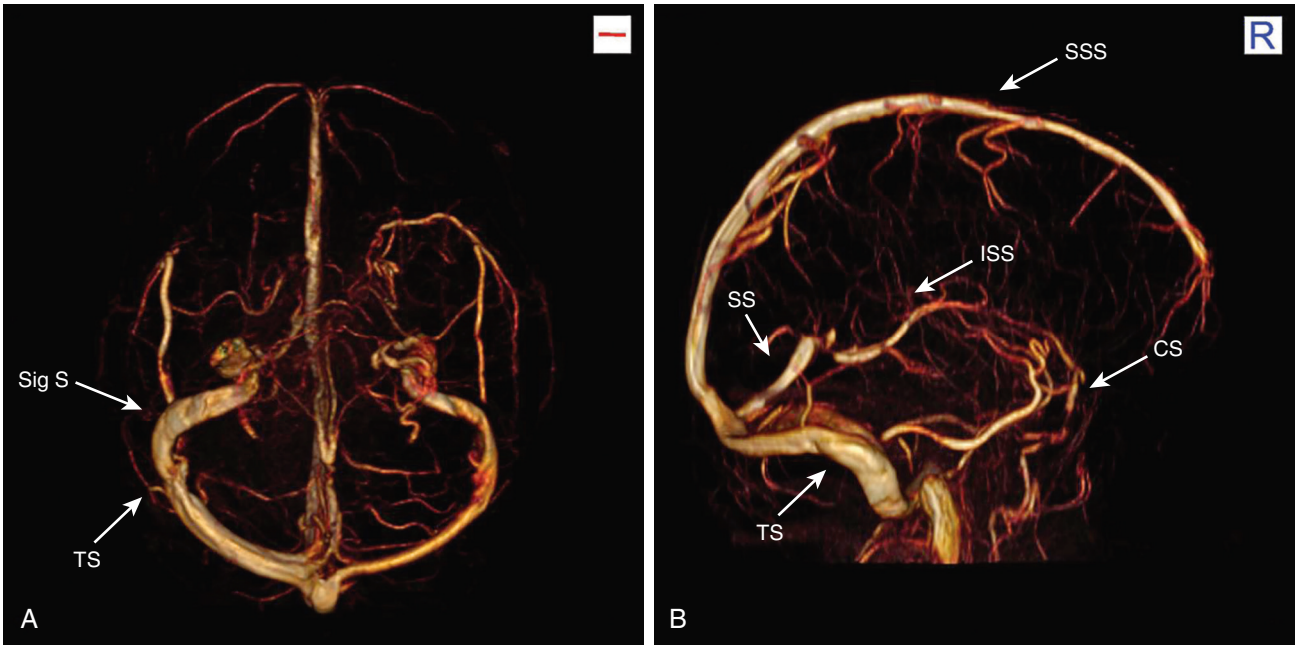

FIGURE 382-5. Anatomy of major venous sinuses. Magnetic resonance venography of the brain shows the normal venous sinuses. **A** shows sigmoid sinus (Sig S) and transverse sinus (TS). **B** shows superior sagittal sinus (SSS), inferior sagittal sinus (ISS), straight sinus (SS), transverse sinus (TS), and cavernous sinus (CS).

may reveal deformity of the cavernous portion of the internal carotid artery, a heterogeneous signal from the abnormal cavernous sinus, and an obvious hyperintense signal of thrombosed vascular sinuses. MRI with IV gadolinium can demonstrate venous thrombosis by illustrating a lack of the normal "flow void" within vascular structures. Cranial CT scans are less helpful but may show a subtle increase in the size and enhancement of the thrombosed sinus. MR angiography may demonstrate extrinsic narrowing of the intracavernous portion of the internal carotid artery.

TREATMENT AND PROGNOSIS

Blood cultures are often negative, so delays in diagnosis are common. Even when the diagnosis is established, empirical antimicrobial treatment may not provide full coverage.

Treatment consists of prompt drainage of infected paranasal sinuses or other identifiable source of infection, as well as specific antistaphylococcal agents (Chapter 267). Heparin anticoagulation without a loading dose is sometimes initiated to reduce morbidity from associated brain ischemia, but experience in septic venous thrombosis is limited compared with the more frequent use of anticoagulation in nonseptic venous thromboses. Hemorrhage caused by anticoagulation is rare in this setting. Despite modern therapy, mortality rates may approach 50%.

LATERAL SINUS THROMBOSIS

Septic thrombosis of the lateral sinus results from acute or chronic infections of the middle ear.

CLINICAL MANIFESTATIONS AND DIAGNOSIS

Symptoms consist of ear pain and fever followed by headache, nausea, vomiting, loss of hearing, and vertigo, usually evolving over a period of several weeks. Symptoms or signs suggestive of otitis media (Chapter 394), including mastoid swelling, may be seen. Sixth cranial nerve palsies can occur, but other focal neurologic signs are rare. In some patients with nonseptic lateral sinus thrombosis, headache may be the only symptom. Papilledema occurs in 50% of cases, and elevated CSF pressure is present in most, especially with occlusion of the right lateral sinus, which is the major venous conduit from the superior sagittal sinus (Fig. 382-6).

CSF is usually normal, although a parameningeal inflammatory profile (mild pleocytosis, slight elevation in protein level, and a normal glucose level) may be seen. The diagnosis is confirmed by MR venography.

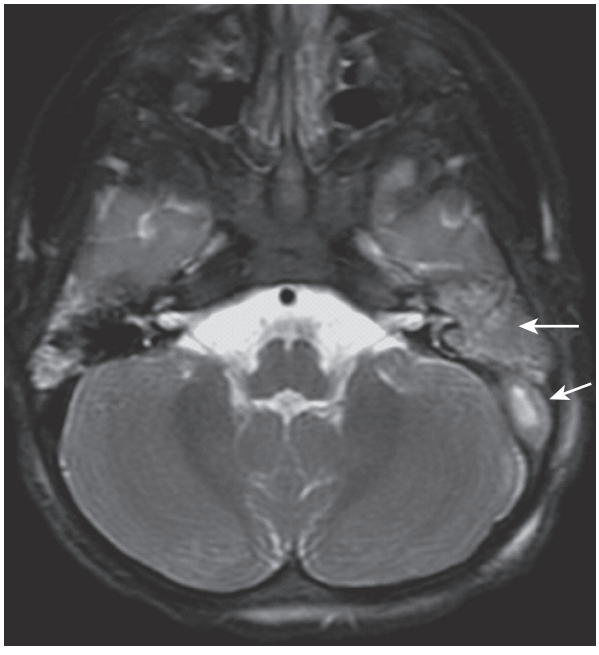

FIGURE 382-6. Lateral sinus thrombosis. Magnetic resonance imaging shows a thrombus in the lateral sinus (*short arrow*) with accompanying mastoiditis (*long arrow*).

TREATMENT

Treatment includes IV antibiotics to cover staphylococci, anaerobes, and gram-negative bacilli such as *Proteus* species and *Escherichia coli* (nafcillin 2 g every 6 hours or vancomycin 1 g every 12 hours; plus cefotaxime 2 g every 6 hours or ceftriaxone 2 g every 12 hours; plus metronidazole 7.5 mg/kg every 6 hours or clindamycin 300 mg every 6 hours; plus ciprofloxacin 400 mg every 12 hours). Surgical drainage (mastoidectomy or tympanoplasty) may be required to eradicate the nidus of infection and determine the antibiotic susceptibility of the organism. If the sinus contains pus, it must be opened so the septic thrombus can be removed. Unless vision is compromised, increased intracranial pressure seldom requires drainage or placement of a shunt.

PROGNOSIS

Broad IV antibiotic coverage and eradication of the perisinus infection, which may require surgical drainage, early in the course of the illness lead to a good prognosis. Neurologic sequelae may include a sixth nerve palsy, ataxia, and hearing loss.

SEPTIC SAGITTAL SINUS THROMBOSIS

Although superior sagittal sinus thrombosis is the most common form of venous sinus thrombosis and is frequently associated with the use of oral contraceptives, septic sagittal sinus thrombosis is an uncommon condition that occurs as a consequence of purulent meningitis, infections of the ethmoid or maxillary sinuses spreading through venous channels, compound infected skull fractures, or (rarely) neurosurgical wound infections.

CLINICAL MANIFESTATIONS AND DIAGNOSIS

Symptoms are primarily related to the elevated intracranial pressure and can evolve rapidly to stupor and coma. Seizures and hemiparesis may result from cortical infarction. Early recognition and treatment are necessary because septic sagittal sinus thrombosis carries a high mortality rate. The rate of progression, severity of symptoms, and prognosis are all related to the location of thrombosis. Obstruction of the anterior third of the sinus produces less intense symptoms and evolves more slowly.

CSF abnormalities are frequent, including enough red blood cells that the CSF can sometimes be mistaken for a subarachnoid hemorrhage; the opening pressure is increased in proportion to the extent of sagittal sinus involvement. A septic sagittal sinus is best visualized during the venous phase of cerebral angiography or MR venography. The diagnosis can also be made by MRI, which demonstrates an abnormal increase in signal intensity (absent flow void) within the affected venous sinus. Contrast-enhanced CT scanning may reveal a contrast void lying at the junction of the transverse and sagittal sinuses (the region of the torcular); this so-called delta sign is an intraluminal clot surrounded by contrast material.

TREATMENT

IV antibiotics should be directed at organisms recovered from the meningeal process or the meningeal site. *S. aureus* (Chapter 267), β-hemolytic streptococci (Chapter 269), pneumococci (Chapter 268), and gram-negative aerobes such as *Klebsiella* species (Chapter 282) are the most common organisms. Associated paranasal sinusitis should be drained surgically.

PROGNOSIS

If the thrombosis progresses to involve the middle and posterior thirds of the sinus, deterioration progresses rapidly. The prognosis is poor, with a mortality rate of nearly 30%.

NEUROLOGIC COMPLICATIONS OF INFECTIOUS ENDOCARDITIS

Neurologic complications develop in nearly one third of patients with infective endocarditis (Chapter 61), and neurologic manifestations are the initial symptom in 20% of patients with infective endocarditis. In nearly 30% of patients, the neurologic complications occur within 2 weeks after the initiation of treatment. Ischemic stroke owing to cerebral embolization is the most common[19] manifestation of infectious endocarditis. Stroke may occur in 20 to 40% of cases, and it is the presenting manifestation in about 20% of patients. Hemorrhagic stroke is much less common in patients with infectious endocarditis. Infective endocarditis should always be considered in a patient with a fever and stroke.

PATHOBIOLOGY

Cerebral embolization occurs as a result of dislodgement or disruption of the cardiac vegetations and frequently causes occlusion of cerebral blood vessels. Emboli occurring before the initiation or completion of treatment with antibiotics may contain microorganisms capable of causing metastatic infections such as abscesses, arteritis, meningitis, or mycotic aneurysms. Most cerebral emboli involve small or moderate-sized blood vessels, and multiple cerebral emboli are common. Intracranial hemorrhage is usually due to rupture of a mycotic aneurysm (Chapter 377), septic erosion of the arterial wall without the formation of an aneurysm, or hemorrhagic transformation of a large cerebral infarct. Mycotic aneurysms occur in approximately 2 to 3% of patients with infective endocarditis. About 20% of patients have multiple aneurysms; involvement of the middle cerebral artery and its branches occurs in more than 75% of patients, unlike congenital aneurysms, which occur predominantly in the circle of Willis. Mycotic aneurysms develop as a result of either septic embolization into the vasa vasorum or direct penetration of the microorganism into the wall of the artery. Streptococci and staphylococci account for nearly 90% of all mycotic aneurysms.

CLINICAL MANIFESTATIONS

Embolic stroke typically causes an acute onset of a focal neurologic deficit. Seizures may also occur. Multiple microemboli result in an altered or fluctuating level of consciousness not adequately explained by other abnormalities.

Most patients with mycotic aneurysms have a sudden, often fatal, subarachnoid or intracerebral hemorrhage without warning signs. Warning signs, if present, include severe localized headache, ischemic events, seizures, and cranial nerve abnormalities. In some patients, mycotic aneurysms may be asymptomatic and resolve with antibiotic therapy. Other neurologic complications of infective endocarditis include micro- or macroabscesses, septic or aseptic meningitis (Chapter 381), or a generalized toxic metabolic encephalopathy.

DIAGNOSIS

MRI is the modality of choice for the diagnosis of cerebral infarcts and brain abscesses related to endocarditis. Gradient echo sequences on the MRI may be more sensitive than a CT scan for detecting intracranial hemorrhage and can also detect microbleeds. MRI should include diffusion-weighted sequences for detection of infarcts. An MR angiogram is preferred for diagnosing an aneurysm. CSF evaluation is useful if accompanying meningitis or a slow leak from an aneurysm is suspected but not visualized with these imaging tests.

TREATMENT

Treatment of patients with infective endocarditis and cerebral emboli requires prevention of embolization with appropriate antibiotic therapy and sometimes cardiac surgery (Chapter 61). Anticoagulation is contraindicated in patients with cerebral infarcts and septic emboli because of the high risk for complications from intracerebral bleeding.

Patients with unruptured aneurysms smaller than 7 mm in diameter, proximal aneurysms, multiple aneurysms, ruptured aneurysms without an intracerebral hematoma, and aneurysms for which excision is likely to cause a neurologic deficit can be monitored conservatively with serial MRI and MR angiography. All other aneurysms require surgical excision of the aneurysm and the adjacent septic vessel wall. Patients who cannot undergo surgery may be candidates for endovascular embolization of the aneurysmal vessel.

PROGNOSIS

Mortality rates in patients with infective endocarditis and cerebral emboli range from 30 to 80%. Mortality is high if there is hemorrhagic transformation of the infarct. Mortality in patients with ruptured mycotic aneurysms is 80%, and even patients with unruptured aneurysms have a mortality rate of 30%.

VIRALLY MEDIATED CEREBRAL VENOUS THROMBOSIS

Cerebral venous thrombosis, especially of the transverse and sigmoid sinuses, can be a complication of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection or of vaccination to prevent it (Chapters 336 and 337).[20] It is also seen in acute varicella zoster infection (Chapter 346). However, these thromboses do not appear to reflect local infection, but rather an immune-mediated thrombotic process (Chapter 336).

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383 ENCEPHALITIS

ALLEN J. AKSAMIT, JR.

DEFINITION

Encephalitis is a diffuse or focal inflammation of the parenchyma of the brain. The term *encephalitis* indicates that the predominant clinical syndrome arises from infection and inflammation in the parenchyma of the brain rather than in the leptomeninges. When both the leptomeninges and brain parenchyma are involved, the term *meningoencephalitis* is used.

In the United States, about 50% of cases of encephalitis are viral in origin and about 25% are autoimmune.[1,2] The remaining 25% are currently of unknown cause, although advances in diagnostic technology may reduce this percentage in the future.

VIRAL ENCEPHALITIS

EPIDEMIOLOGY

Viral encephalitis has an estimated incidence of 7 per 100,000 per year. Many viruses (Table 383-1) are implicated, and testing by nucleic acid identification (by polymerase chain reaction [PCR]) or by serology is required to identify the specific virus. The epidemiology of each virus responsible for central nervous system infection (see Table 383-1) is distinct in terms of the populations at highest risk, geographic distribution, and seasonal occurrence, especially the arboviruses (Chapter 352) and enteroviruses (Chapter 349), which are covered in separate chapters.

In the United States, the most common cause of nonepidemic encephalitis is herpes simplex encephalitis, which is caused by herpes simplex virus type 1 (Chapter 345). The most common epidemic virus in the United States is now West Nile virus (Chapter 352), which is a mosquito-transmitted Flavivirus related to St. Louis encephalitis virus and to its Asian counterpart, Japanese encephalitis virus, all of which share serologic cross reactivity (Chapter 352). Emerging infections that can cause encephalitis in the United States are Chikungunya and Zika (Chapter 352).[3,4] In Eastern Europe and Asia, tick-borne encephalitis (Chapter 352) can occur. A zoonotic borna disease virus encephalitis has been associated with fatal human encephalitis in Germany,[5,6] and Nipah virus is a zoonosis in India with a case fatality rate of about 80%.[7]

PATHOBIOLOGY

In general, gross pathologic inspection of an encephalitic brain does not reveal purulence visible to the naked eye. If focal purulence is present, *cerebritis* is the more correct term. If frank necrosis and purulence are present, the correct pathologic term is *brain abscess* (Chapter 382). Encephalitis, however, can be associated with substantial necrosis pathologically, and patients with severe acute viral encephalitis frequently have microscopic evidence of necrosis. Certain viral encephalitides, such as herpes simplex encephalitis, can be both focal and hemorrhagic.

Viruses that cause acute encephalitis often also may cause meningitis (Chapter 381). Indeed, patients with encephalitis virtually always have some microscopic inflammatory changes in the leptomeninges. Conversely, patients with viral meningitis will inevitably have some component of microscopic encephalitis. The degree of inflammatory change present in the brain is determined by the individual viral pathogen and by host immune factors, which are responsible for the reaction to the invading virus.

CLINICAL MANIFESTATIONS

The clinical findings in patients with acute viral encephalitis start with a subacute prodrome of fever, headache, malaise, myalgia, and nonspecific symptoms. Nausea, vomiting, diarrhea, cough, sore throat, and rash can precede the neurologic symptoms as part of the systemic initial manifestations of the infection. Invasion of the nervous system is typically accompanied by headache, photophobia, and altered consciousness, with symptoms progressing over a period of a few days. Seizures are a common heralding symptom. Signs of meningeal irritation may be present but are an unreliable finding in encephalitis.

Focal brain dysfunction is seen with some viruses. For example, West Nile virus (Chapter 352) can cause a brain stem encephalitis with an early onset of coma. Herpes simplex virus (Chapter 345) tends to cause focal cortical neurologic deficits, including hemiparesis, aphasia, and seizures. Limbic parts of the brain commonly involved by herpes simplex encephalitis, human herpesvirus-6 or rabies can lead to prominent behavioral changes at the beginning of the illness before the patient's level of consciousness is depressed. Focal or generalized seizures are particularly common when encephalitis affects the cerebral cortex, especially the hippocampus and limbic system. Rabies is typically associated with brain stem–mediated laryngospasm, hydrophobia, and depressed consciousness. Because of spinal cord anterior horn cell involvement, West Nile virus, St. Louis encephalitis virus, Japanese encephalitis virus, poliovirus (Chapter 349), and rabies virus infections can cause focal or asymmetrical weakness with areflexia.

TABLE 383-1 COMMON CAUSES OF VIRAL ENCEPHALITIS

I. Causes of viral encephalitis
- A. Nonseasonal
  - Herpes simplex virus type 1 (herpes simplex encephalitis)
  - Herpes simplex virus type 2 (neonatal encephalitis or adult meningoencephalitis)
- B. Seasonal—summer and fall—arboviruses (arthropod borne)
  - West Nile virus
  - St. Louis encephalitis virus
  - Eastern equine encephalitis virus
  - Western equine encephalitis virus
  - La Crosse/California encephalitis virus
  - Powassan encephalitis virus
- C. Seasonal—non–arthropod borne
  - Summer and fall: enteroviruses (including coxsackieviruses, echoviruses, polioviruses, and enterovirus 71)
  - Winter: influenza virus
- D. Immunosuppressed patients
  - Human immunodeficiency virus (chronic HIV encephalitis)
  - Varicella-zoster virus (subacute encephalitis)
  - JC virus (progressive multifocal leukoencephalopathy)
  - Cytomegalovirus (ventriculitis or encephalitis)
  - Human herpesvirus 6 (subacute encephalitis)
  - Epstein-Barr virus (subacute encephalitis)

II. Uncommon causes in the United States
- Powassan encephalitis virus
- Zika virus
- Chikungunya virus
- Cache Valley virus disease
- Jamestown Canyon virus
- Borna virus
- Lymphotropic choriomeningitis virus
- Rabies
- Measles (subacute sclerosing panencephalitis)
- Mumps
- Adenovirus
- Herpes B virus (of monkeys)
- Rubella (progressive rubella panencephalitis)

III. Causes outside the United States
- Zika virus (Africa, Asia, Caribbean, Central America, Pacific Islands, South America)
- Chikungunya virus (Africa, Asia, Central America, Pacific Islands, South America, Western Europe)
- Tick-borne encephalitis virus (Russia, Asia)
- Borna disease virus
- Japanese encephalitis virus (Japan, Southeast Asia, Malaysia)
- Venezuelan equine encephalitis virus (Central and South America)
- Dengue virus (Southern Asia, Africa, South America)
- Rift Valley fever virus (east central Africa)
- Murray Valley encephalitis virus (Australia)
- Powassan encephalitis virus (Canada)
- Nipah virus (Malaysia and Bangladesh)

DIAGNOSIS

In patients with coma or focal deficits, computed tomography (CT) of the head usually should be performed before spinal fluid analysis to exclude substantial mass effect and to avoid the risk of herniation with lumbar puncture. In patients without focal findings, however, lumbar puncture should be performed immediately to establish the diagnosis; distinguish viral from bacterial, fungal, and parasitic causes; and guide early empirical treatment. Opening pressures should be measured because increased intracranial pressure can occur with all forms of viral encephalitis and may need additional treatment.

ABSTRACT

Encephalitis is a diffuse or focal inflammation of the parenchyma of the brain. The term *encephalitis* indicates that the predominant clinical syndrome arises from infection *or* inflammation in the parenchyma of the brain rather than in the leptomeninges. When both the leptomeninges and brain parenchyma are involved, the term meningoencephalitis is used. This chapter covers encephalitis.

KEYWORDS

viral encephalitis
autoimmune encephalitis
herpes simplex encephalitis
rabies
MRI of head in encephalitis
spinal fluid PCR
acyclovir

TABLE 383-2 SELECTED TESTS FOR VIRAL ENCEPHALITIS

ORGANISM/ SYNDROME	TEST	COMMENT
WEST NILE VIRUS		
West Nile encephalitis	IgM in CSF	Diagnostic of CNS invasive disease, including encephalitis or acute flaccid paralysis
HERPES SIMPLEX VIRUS TYPE 1		
Herpes simplex encephalitis	PCR in CSF	Sensitive and specific in the acute phase
HERPES SIMPLEX VIRUS TYPE 2		
Neonatal encephalitis Primary or relapsing meningitis	PCR in CSF PCR in CSF	Confirmatory, high sensitivity Sensitive and specific in first 3 days of illness
HUMAN HERPESVIRUS 6		
Limbic encephalitis	PCR in CSF	Confirmatory, sensitivity unknown, possible false positives
VARICELLA-ZOSTER VIRUS		
Meningoencephalitis	PCR in CSF	Confirmatory when used with clinical and spinal fluid findings; sensitivity unclear
JC VIRUS		
Progressive multifocal leukoencephalopathy	PCR in CSF	Diagnostic but incompletely (70%) sensitive
CYTOMEGALOVIRUS		
CMV ventriculitis	PCR in CSF	Sensitive and specific

CMV = cytomegalovirus; CNS = central nervous system; CSF = cerebrospinal fluid; IgM = immunoglobulin M; PCR = polymerase chain reaction.

Spinal fluid analysis typically reveals an elevated protein level, which usually is less than 2 g/dL. The cerebrospinal fluid (CSF) glucose level is typically normal and greater than 40% of the coincident serum value, but rare patients may have a low CSF glucose level similar to what is seen in patients with bacterial infection (Chapter 381). The CSF white blood cell count is typically elevated, usually in the range of 10 to 500 cells/μL, and often with a lymphocytic predominance. However, a polymorphonuclear predominance is seen in some cases, especially in some patients with West Nile encephalitis (Chapter 352) or cytomegalovirus ventriculitis (Chapter 347).

PCR testing of spinal fluid (Table 383-2) has the advantage of proving direct viral infection within the central nervous system, but serologic testing is more sensitive for some infections, such as West Nile virus encephalitis, which is best confirmed by an immunoglobulin M (IgM) antibody response in spinal fluid. Next-generation sequencing can detect viral pathogens for which PCR assays are insensitive, not established, or not readily available,[8,9] such as Cache Valley viral encephalitis.

Magnetic resonance imaging (MRI) of the brain is the most sensitive technique for defining structural abnormalities in patients with viral encephalitis.[10] Herpes simplex encephalitis often has a characteristic pattern involving the mesiotemporal, inferofrontal, and insular cortices, usually unilateral or asymmetrically bilateral (Fig. 383-1). However, no imaging characteristics reliably distinguish among the various causes, and frank viral encephalitis can occur with normal findings on MRI.

Differential Diagnosis

Among children and adults with acute encephalitis, about 50% have a confirmed viral cause, 25% have an autoimmune cause, and 25% have no identifiable cause. A systematic approach (Fig. 383-2) can usually detect the identifiable causes.

Several nonviral pathogens can cause encephalitis that is clinically and pathologically indistinguishable from viral encephalitis. Examples include *Rickettsia* (Chapter 302), Lyme disease (Chapter 296), *Borrelia* (Chapter 297), Whipple disease (Chapter 305), *Toxoplasma* (Chapter 320), *Mycoplasma* (Chapter 293), and *Acanthamoeba* (Chapter 323), tuberculosis (Chapter 299), and listeria (Chapter 272). Other forms of infectious nonviral causes mimicking viral encephalitis include meningovascular syphilis (Chapter 295) and cerebral cysticercosis (Chapter 326).

Purulent bacteria and fungal reactions in the brain are referred to as cerebritis, which is the first stage of infection of the brain before frank abscess develops with parenchymal necrosis and purulence, but can also mimic encephalitis. Additionally, opportunistic Epstein-Barr virus related lymphoma or lymphoproliferative disorder (Chapter 348) can behave like an encephalitis.

Additionally, autoimmune encephalitides (see later) can mimic viral encephalitis. Examples include limbic paraneoplastic encephalitis, especially associated with antibodies against antigens associated with the voltage-gated potassium channel complex, Hashimoto encephalopathy associated with autoimmune thyroiditis (Chapter 207), and encephalitis associated with anti–*N*-methyl-D-aspartate (NMDA) receptor antibodies.

In parainfectious encephalitis, a systemic viral infection is associated with a febrile encephalopathy, sometimes with inflammatory spinal fluid but without direct evidence of brain invasion by the virus. Examples of parainfectious encephalitis include infection and encephalopathy associated with influenza virus (Chapter 332), varicella virus (Chapter 346), and Epstein-Barr virus (Chapter 348). Monkeypox (Chapter 343) is the latest virus recognized to produce this syndrome.[11] Furthermore, primary demyelinating disease (Chapter 380), particularly in the form of acute disseminated encephalomyelitis, overlaps clinically with viral encephalitis. In children, a syndrome associated with streptococcal infection has been labeled pediatric autoimmune neuropsychiatric disorders associated with streptococcal infections (PANDAS), which is thought to represent a postinfectious streptococcal autoimmunity directed against the brain.[12]

TREATMENT

Effective antiviral therapy does not exist for most forms of viral encephalitis,[13] except for herpes simplex encephalitis. However, because of the usual delay in establishing or excluding the diagnosis of herpes simplex encephalitis, patients suspected of having encephalitis should start acyclovir therapy (10 mg/kg intravenously every 8 hours for 2 weeks) while spinal fluid PCR analyses and specific serologic studies are being performed to make a diagnosis.

Supportive measures for patients with encephalitis typically include intensive care unit treatment in the initial phases of the illness. Seizures are common and frequently refractory to antiepileptic drugs; however, the seizures themselves can increase morbidity and mortality, so vigorous treatment attempts are required (Chapter 372).

In patients who are immunosuppressed (see Table 383-1), the spectrum of possible infections is broader and potentially more treatable. Examples include varicella-zoster virus (Chapter 346), with acyclovir administered at doses similar to those used for herpes simplex virus, and cytomegalovirus (Chapter 347), with ganciclovir administered at 5 mg/kg intravenously every 12 hours for 2 weeks or cidofovir administered at 5 mg/kg intravenously weekly for 2 weeks, although some patients require long-term oral valganciclovir (900 mg every 24 hours) or intravenous cidofovir (5 mg/kg every 2 weeks). HIV encephalitis (Chapter 359) responds in variable degree to triple antiretroviral therapy. By comparison, no specific treatments are currently effective for Epstein-Barr virus (Chapter 348). JC virus (progressive multifocal leukoencephalopathy [Chapter 341]) can be treated with PD-1 immune inhibitors, or by using BK virus sensitized T-cell immune therapy, with limited success.[14] Variable success has been reported for treatment of human herpesvirus 6 encephalitis in hematopoietic stem cell transplant recipients using ganciclovir, foscarnet, or valganciclovir alone or in combination (Chapter 328, Table 328-4).

PROGNOSIS

The prognosis of viral encephalitis is dependent on the cause, with an overall mortality rate of about 6 to 10% in the United States. Herpes simplex encephalitis, even with adequate treatment, has a 20% mortality, and the likelihood of major persistent morbidity with seizures or defects in memory and behavior is 35 to 40%. Each of the arboviruses (Chapter 352) has a different mortality rate, with eastern equine encephalitis virus associated with the highest mortality. La Crosse encephalitis virus has the lowest mortality.

About 50% of survivors will have significant clinical sequelae. Some forms of viral encephalitis have specific sequelae, such as sensorineural deafness or hydrocephalus associated with mumps encephalitis. In one large observational study of acute viral encephalitis, factors that portended a worse prognosis included advanced age, immunocompromised state, coma, mechanical ventilation, and acute thrombocytopenia. Conversely, the specific viral cause of encephalitis, the development of seizures or a focal neurologic deficit, and MRI findings were not associated with clinical outcomes.

SELECTED SPECIFIC VIRUSES

HERPES SIMPLEX ENCEPHALITIS

EPIDEMIOLOGY

Herpes simplex (Chapter 345) encephalitis, which is the most common form of sporadic encephalitis in the United States, has an annual incidence of two to four cases per million people per year. There is no seasonal or gender predisposition. The encephalitis can strike children but is most commonly a disease of adults.

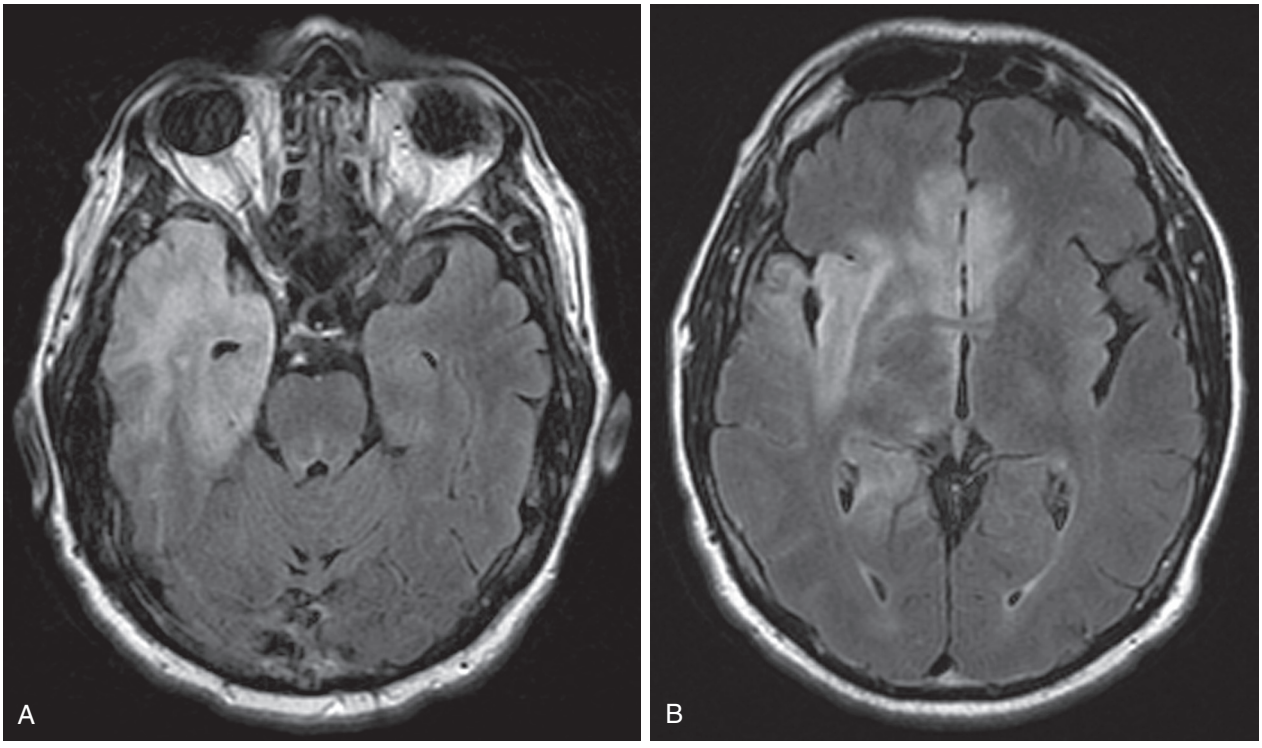

FIGURE 383-1. Magnetic resonance imaging (MRI) in herpes simplex encephalitis. Fluid-attenuated inversion recovery (FLAIR) MRI scan of the brain, showing increased signal in the right mesiotemporal lobe (including the amygdala, hippocampus, and uncus) (**A**) and in the bilateral inferofrontal lobes (cingulate gyrus and orbital frontal cortex) and the right insular cortex (**B**).

PATHOBIOLOGY

Herpes simplex encephalitis usually occurs in immunocompetent patients, but immunosuppressed patients also may be affected. Patients (especially children) who are deficient in toll-like receptor 3 in the immune system, may be selectively vulnerable to herpes simplex encephalitis.

Herpes simplex virus type 1 infects and establishes latency in the trigeminal ganglion in most of the population. Whether herpes simplex encephalitis arises from reactivation of a latent viral infection or is a primary nasopharyngeal infection that ascends into the olfactory nervous system is uncertain.

The pathology of herpes simplex encephalitis is a necrotizing hemorrhagic inflammatory encephalitis in a characteristic pattern affecting the mesiotemporal, inferofrontal, and insular cortices, with gray matter predominance. Even if the brain is affected bilaterally, the pathologic features are usually asymmetrical, a pattern that helps distinguish herpes simplex from other forms of limbic encephalitis.

CLINICAL MANIFESTATIONS

The clinical manifestations of herpes simplex encephalitis usually begin with a nonspecific febrile prodrome that is followed within hours to days by the symptoms of headache, malaise, nausea, and vomiting. A reduced level of consciousness may occur early. Seizures may be the first manifestation of this encephalitis. Focal neurologic deficits, such as hemiparesis or aphasia, appear early and can be mistaken for stroke. More specific manifestations of herpes simplex encephalitis are symptoms of limbic system–associated behavioral changes, such as behavioral or emotional lability and inappropriateness. Memory is affected early if consciousness is preserved. As the encephalitis progresses, symptoms of increased intracranial pressure, lethargy, and coma are usual. Focal findings alone in the context of clinical encephalitis are not sufficient to confirm a diagnosis of herpes simplex encephalitis.

DIAGNOSIS

Spinal fluid analysis is necessary in the diagnosis of herpes simplex encephalitis. In a patient with focal encephalitis or coma, however, CT of the brain should be performed before spinal fluid analysis to avoid the risk of herniation. Elevation of the CSF protein level and the white blood cell count, with a predominance of lymphocytes, is the most frequent pattern; red blood cells are also commonly seen. The CSF glucose level is usually normal but is less than 50% of the blood glucose level in about 5% of patients.

The most accurate test for proof of herpes simplex encephalitis is the presence of herpes simplex virus type 1 DNA amplified by PCR of the spinal fluid. Herpes simplex virus type 1 can be distinguished from herpes simplex virus type 2, which also can cause encephalitis in neonates and meningoencephalitis in adults.

MRI typically shows characteristic focal involvement with increased T2 and fluid-attenuated inversion recovery (FLAIR) signal in the mesiotemporal lobes (including the amygdala, hippocampus, and uncus), the inferofrontal lobes (cingulate gyrus and orbital frontal cortex), and the insular cortex (see Fig. 383-1). MRI abnormalities are often unilateral but can be bilateral and asymmetrical. Focal MRI abnormalities must be distinguished from brain abscess (Chapter 382), cerebral infarction (Chapter 376), cerebral hemorrhage (Chapter 377), brain tumors (Chapter 175), and paraneoplastic limbic encephalitis. Radiographically detected involvement of the mesiotemporal rather than the lateral temporal areas and involvement of the gray matter rather than the white matter suggests herpes simplex encephalitis as the diagnosis. Early gadolinium contrast enhancement may occur but is not universal.

CT of the head is less sensitive than MRI for detecting mild cases of herpes encephalitis. However, because herpes simplex encephalitis can be hemorrhagic, CT may sometimes identify the hemorrhage more accurately than MRI can.

TREATMENT

When suspicion for herpes simplex encephalitis is raised in the acute setting by the presence of focal signs or symptoms, early empirical treatment is recommended even while the diagnostic evaluation is proceeding. Intravenous acyclovir (10 mg/kg every 8 hours for 14 to 21 days) is the therapy of choice.[15] Autoimmune post–herpes simplex encephalitis may respond to corticosteroids, intravenous immunoglobulin, or plasma exchange, but no randomized trials are available.

PROGNOSIS

With prompt treatment with intravenous acyclovir, the mortality of herpes simplex encephalitis has been reduced from approximately 70 to 10%, but survivors are commonly left with significant neurologic impairment. Less than 20% of patients are able to return to work, and about 50% are classified as moderate to severely disabled.

Late autoimmune encephalitis can occur 1 to 7 weeks after herpes simplex encephalitis. This encephalitis is associated with NMDA-receptor antibodies in the spinal fluid. The clinical picture is relapse of the initial symptoms, with worsening of the MRI findings. Treatment is with high-dose corticosteroids (typically methylprednisolone, 1 g intravenously daily for 5 days).

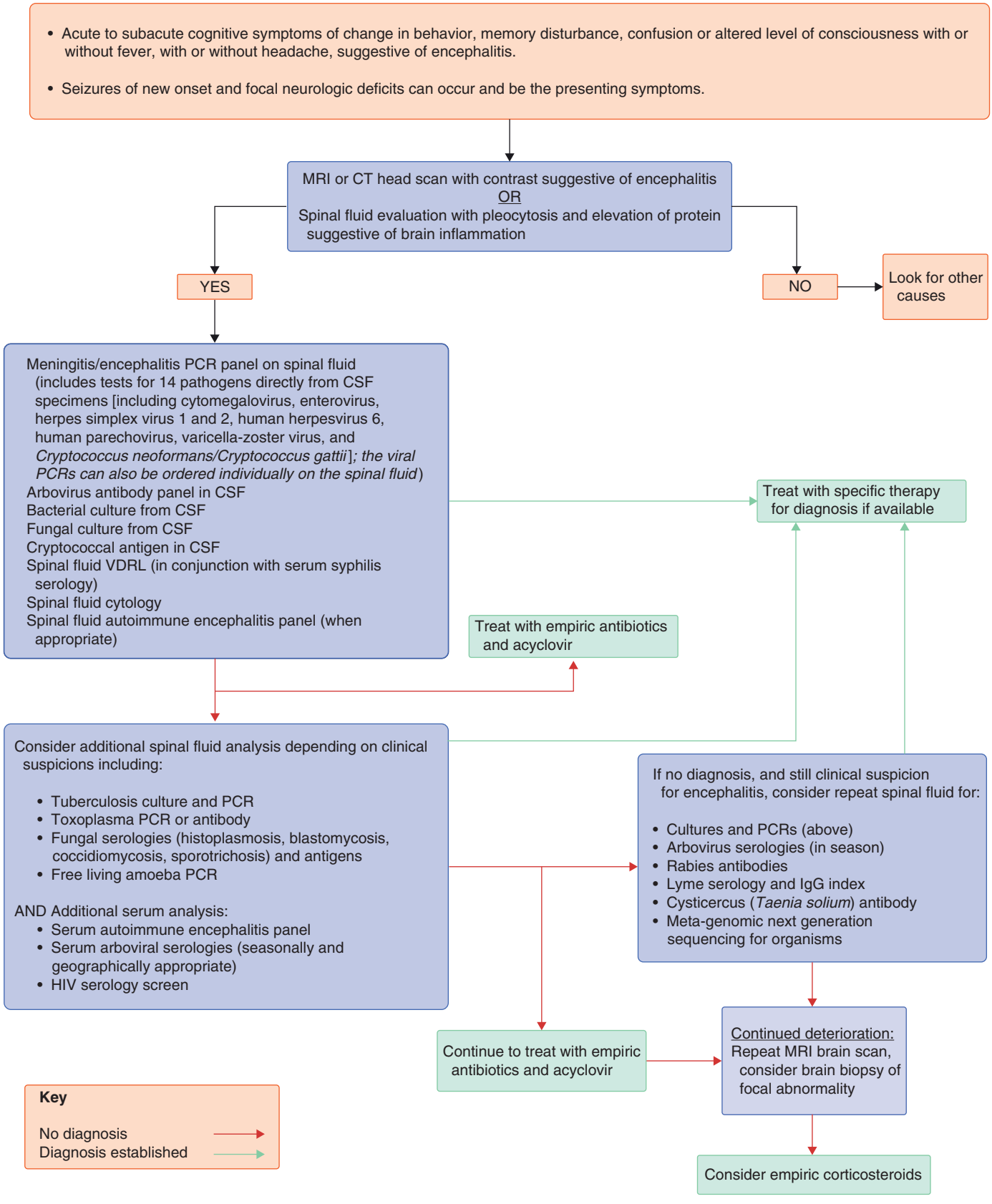

FIGURE 383-2. Diagnostic approach to encephalitis. CSF = cerebrospinal fluid; CT = computed tomography; HIV = human immunodeficiency virus; IgG = immunoglobulin G; MRI = magnetic resonance imaging; PCR = polymerase chain reaction; VDRL = Venereal Disease Research Laboratory.

RABIES

Human rabies is an encephalitic illness caused by the rabies virus, usually transmitted by an animal bite. It produces a fatal encephalitis, although the long latency between animal bite exposure and occurrence of neurologic symptoms may sometimes obscure the diagnosis.[16]

EPIDEMIOLOGY AND PATHOBIOLOGY

Rabies is a rare illness in the United States and developed world. However, initially unsuspected cases have been transmitted via trivial bites by infected bats, which are widely distributed in every state in the United States except Hawaii. Rabies virus variants in bats are now responsible for most recent human cases in the United States and Canada.

Canine rabies is still endemic in much of the developing world, including Africa, Latin America, Eastern Europe, and Asia, and most human rabies cases worldwide occur because of untreated dog bites from endemic areas. Rare cases of transmission of rabies to transplant organ recipients have occurred in the United States.

The presence of Negri bodies (intracytoplasmic viral inclusions) in neurons of the brain stem, cerebellum (especially the Purkinje cells), or hippocampus defines rabies pathologically. These inclusions are often not present, and more sensitive detection of antigen by immunohistochemistry aids in the pathologic diagnosis.

CLINICAL MANIFESTATIONS

Human rabies usually develops 20 to 90 days after a bite, although rarely disease develops after only a few days or after a year or more following bite exposure. Multiple bites and facial bites are associated with shorter incubation times.

Nonspecific prodromal symptoms include fever, chills, malaise, fatigue, insomnia, anorexia, headache, and irritability. In most patients, migratory pain or paresthesias will develop in the limb that was affected by the bite. Following the prodromal illness, an encephalitic form develops in about 80% of patients and causes behaviors ranging from episodes of agitated arousal to quiet lethargy. Fever is a common accompaniment but not universal at this phase. Disinhibition of brain stem reflexes leads to hydrophobia with laryngospasm and an inability to deal with salivation, swallowing of water, or other oral intake. When the brain stem encephalitis affects the bulbar, cardiovascular, and respiratory centers, autonomic dysfunction, cardiopulmonary complications, and respiratory failure occur.

Another form of rabies that affects up to a third of patients is known as paralytic rabies. This form of rabies is manifested as acute flaccid paralysis, which may be multifocal and affect the limbs and the bulbar musculature, thereby resembling poliomyelitis (Chapter 349) because of its multifocality. It can be confused with Guillain-Barré syndrome (Chapter 388). Paralytic rabies typically occurs in conjunction with febrile encephalitis.

DIAGNOSIS

Findings on spinal fluid analysis may be abnormal in human rabies. A lymphocytic pleocytosis, usually less than 100 white cells/μL, is found in more than 50% of patients in the first week of illness. The CSF protein concentration usually is mildly elevated, and the glucose level is usually normal.

Imaging of patients with rabies is sometimes useful. MRI may show gray matter involvement, particularly involvement of the brain stem and deep gray matter structures, with increased T2 signal, commonly without enhancement. Spinal cord MRI in patients with paralytic rabies may show multifocal increased T2 signal mimicking acute disseminated encephalomyelitis. Involvement of brain gray matter, including the hippocampus and basal ganglia structures, indicates the gray matter predilection and often bilateral involvement of supratentorial structures. However, MRI cannot be relied on to exclude rabies.

Rabies RNA can be detected by PCR testing of spinal fluid, saliva, or brain tissue. A positive result confirms the diagnosis, but the exclusionary value of negative results is unknown. Serum antibodies against rabies virus are not usually present in unimmunized patients until the second week of illness, and patients can die before having a detectable serum antibody level in serum or in spinal fluid, but its absence is unreliable in excluding the diagnosis. Staining of a skin biopsy sample taken from an area near the nape of the neck for rabies antigen in the sensory nerves can confirm the diagnosis of rabies.

TREATMENT

Rabies postexposure prophylaxis includes local wound cleansing, passive immunization with immunoglobulin, and active immunization with rabies vaccine. Once rabies encephalitis is manifested, however, it is unclear whether vaccination, although regularly used, has any role in improving outcome. Antiviral therapy and a variety of immunotherapies, including ribavirin and interferon alpha, have been tried in the treatment of rabies, usually without success.

Health care workers can occasionally have high-risk exposures related to broken skin contact or mucosal splash with the patient's secretions. Given the lack of documented human-to-human rabies transmission, postexposure prophylaxis for contacts of patients with rabies is rarely indicated but can be decided on a case-by-case basis after consultation with local or state health officials. An mRNA vaccine is currently being tested for primary prophylaxis in high-risk individuals.

PROGNOSIS

Although one patient has survived with the use of therapeutic coma without vaccination, subsequent reports of patients treated in similar fashion have been associated with a fatal outcome. Treatment is otherwise supportive, and outcome is essentially always fatal.

COVID ENCEPHALITIS

EPIDEMIOLOGY AND PATHOBIOLOGY

Coronavirus-2019 disease (COVID-19; Chapter 335) from infection with the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) can cause encephalitis, especially in patients with serious COVID infection.[17] The incidence of encephalitis as a complication of COVID-19 is about 0.2%,[18] However, several autopsy studies of patients with encephalopathy as a consequence of COVID infection have revealed little evidence of direct viral infection of the brain.[19] Instead, prominent microglial activation, particularly affecting the brain stem, has been noted without evidence of direct viral infection or damage. This phenomenon has been referred to as parainfectious (inflammation occurring at the time of the infection without viral infection of brain cells) or postinfectious (viral-directed immunity cross-reacting with nervous system tissue), thereby suggesting immune mechanisms and possibly vascular mechanisms as the cause. One concept is that the microvasculature is affected by the cytokine storm, thereby leading to microthrombosis, hemorrhage, and ischemic infarcts from small-vessel disease in the brain.

DIAGNOSIS

The spinal fluid may show a low-grade pleocytosis, and virus may be detected by PCR. A small percentage of patients have frank focal clinical and imaging abnormalities suggesting acute necrotizing encephalopathy, limbic encephalitis, acute disseminated encephalomyelitis, and acute hemorrhagic leukoencephalitis on a parainfectious or postinfectious basis.[20]

TREATMENT

Post-COVID encephalitis may treated as for autoimmune encephalitis (see later).

PROGNOSIS

Many COVID-19 patients will have prolonged neurologic symptoms, including include brain fog, cognitive symptoms, headache, anosmia, and fatigue. It is unclear whether these phenomena are related to encephalitis or to consequences of microvascular disease and cytokine effects on the brain.

RARE VIRAL CAUSES OF ENCEPHALITIS

Lymphocytic choriomeningitis (Chapter 381) virus is a human infection acquired from mice. Typically, humans acquire the infection by contact with food or dust that is contaminated by excreta of the common house mouse. Most commonly, human disease occurs in winter, when the natural host tends to move indoors. It also can be acquired due to laboratory exposure by human caretakers.

The mumps virus (Chapter 340) is typically acquired by the respiratory route. Infection can occur throughout the year, but the incidence is higher during the spring. Although mumps virus infects both sexes equally, meningoencephalitis develops in males three times more frequently than in females. Vaccination programs in the United States have made mumps encephalitis rare, though unvaccinated populations may bring this disorder back to prominence.

AUTOIMMUNE ENCEPHALITIS

Autoimmune encephalitis is increasingly recognized as a treatable cause of brain dysfunction distinct from infectious encephalitis. It can be caused by a number of autoantibodies and is also an infrequent complication of treatment with programmed cell death-1 checkpoint inhibitors.

EPIDEMIOLOGY AND PATHOBIOLOGY

Autoimmune encephalitides are responsible for about 25% of all cases of encephalitis. Autoimmune encephalitis is a complex series of disorders that can mimic infectious encephalitis or present with neurocognitive disorders and seizures alone. An ever-increasing list of autoantibodies has been associated with encephalitis (Table 383-3).[21] Some disorders are paraneoplastic disorders,[22] with autoimmunity directed against cancer also affecting the nervous system. However, primary autoimmune encephalitis without detectable cancer can be associated with similar autoantibodies, and autoimmune encephalitis can be a complication of treatment with programmed cell death-1 checkpoint inhibitors.[23] Encephalitis also can occur with autoimmune antibodies associated with systemic disease, including Hashimoto encephalopathy (Chapter 207), encephalopathy associated with Sjögren syndrome (Chapter 247), and rheumatoid arthritis–associated meningoencephalitis (Chapter 243).

In general, the autoimmune encephalitides can be divided into primary, in which the autoantibody is directed against a central nervous system antigen, or secondary, in which the autoantibody associated with the encephalitis is directed against a systemic antigen and associated with systemic autoimmune disease. In both types, the antibody may either be pathogenic or be a marker

TABLE 383-3 AUTOIMMUNE ENCEPHALITIS AND ASSOCIATED NEURAL ANTIGEN TARGETS

NEURAL ANTIGEN	ASSOCIATED NEOPLASIA OR SYSTEMIC DISEASES	ENCEPHALITIS CLINICAL PHENOTYPE
Hu or ANNA-1	Small cell lung carcinoma	Limbic encephalitis
Ri or ANNA-2	Breast, gynecologic, lung, or bladder cancer	Brain stem/cerebellar encephalitis
Ma2	Testicular seminoma	Limbic encephalitis, brain stem encephalitis
GAD65	Thymoma, small cell lung cancer, breast cancer, diabetes	Cerebellar encephalitis, stiff person syndrome
NMDA-R	Ovarian teratoma	Encephalitis
AMPAR	Thymoma, small cell lung cancer	Limbic encephalitis
GABA A receptor	Infrequent, thymoma	Limbic encephalitis
GABA B receptor	Small cell lung cancer	Limbic encephalitis
mGluR5	Hodgkin lymphoma	Encephalitis
GlyR	Infrequent thymoma	Limbic encephalitis, PERM
VGKC (voltage-gated potassium channel complex)		
LGI-1	Neuroendocrine tumor, thymoma	Limbic encephalitis, faciobrachial seizures
CASPR 2		Limbic encephalitis, Morvan syndrome
DPPX	Megacolon, rare B cell neoplasm	Encephalitis, PERM
KLHL11	Testicular seminoma	Cerebellar encephalitis, hearing loss
CRMP 5	Small cell lung cancer, thymoma	Encephalomyelitis; limbic encephalitis
Amphiphysin	Breast cancer, small cell lung cancer	Limbic encephalitis, encephalomyelitis
PCA-1	Small cell lung, breast, or ovarian cancer	Cerebellar/brain stem encephalitis
MOG	Rare ovarian teratoma	Encephalomyelitis
AQP4	Rare adenocarcinoma	Neuromyelitis optica, brain stem encephalitis
GFAP	Rare ovarian teratoma	Encephalomyelitis

AMPAR = α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid receptor; ANNA = antineuronal nuclear antibody; AQP4 = aquaporin 4; CASPR 2 = contactin-associated protein-like 2; CRMP 5= collapsin response-mediator protein 5; DPPX = dipeptidyl peptidase-like protein; GABA A receptor = ɣ-aminobutyric acid-a receptor; GABA B receptor = ɣ-aminobutyric acid-b receptor; GAD65 = glutamic acid decarboxylase 65-kilodalton isoform; GFAP = glial fibrillary acidic protein; GlyR = glycine receptor; KLHL11 = Kelch-like protein 11; LGI 1 = leucine-rich glioma-inactivated protein 1; mGluR5 = metabotropic glutamate receptor type 5; MOG = myelin oligodendrocyte glycoprotein; NMDA-R = NMDA receptor; PCA-1 = Purkinje cell cytoplasmic antibody; PERM = progressive encephalomyelitis with rigidity; VGKC = voltage-gated potassium channel complex.

of autoimmunity associated with encephalitis. Additionally, the typical phenotype of autoimmune encephalitis can occur with no identifiable autoantibody.

CLINICAL MANIFESTATIONS

The three characteristic clinical syndromes of autoimmune encephalitis are limbic encephalitis, a cerebral cortical generalized encephalitis similar to what is associated with *N*-methyl-D-aspartate (NMDA)-receptor antibodies, and brain stem encephalitis. Other clinical phenotypes associated with paraneoplastic autoimmunity include rapidly progressive cerebellar encephalitis, neuromyelitis optica, and opsoclonus myoclonus.[24] Less well-defined encephalitis with encephalopathy, behavioral abnormalities, neurocognitive changes,[25] and evidence of brain inflammation identified by spinal fluid pleocytosis can also occur.

The clinical presentation is typically acute or subacute alteration of mental status characterized by change in behavior, memory, and awareness. Seizures also are common.

NMDA receptor can be paraneoplastic in association with ovarian carcinoma, but it can be found after apparently successful treatment of viral encephalitis and in other patients as an autoimmune disorder without known cancer. Otherwise unexplained NMDA-receptor autoimmune encephalitis has been associated with a female predominance, psychosis, and abnormal behavior in adults. Because of the frequent psychiatric symptoms at onset, correct diagnosis may be delayed. The diagnosis requires specialized testing with detection of NMDA-receptor antibodies in the spinal fluid of affected patients.

DIAGNOSIS

An expanding number of IgG autoantibodies can help in the definitive diagnosis of the specific type of autoimmune encephalitis and also for guiding subsequent evaluation, including the search for an occult malignancy and the potential escalation of immunotherapy.[26] Such testing is critical because a variety of psychiatric, neurodegenerative, and functional disorders can be misdiagnosed as autoimmune encephalitis.[27] In limbic encephalitis, the CSF often shows lymphocytes (5 to 100/μL) but no identifiable infection. Antibody testing of CSF and often blood can identify the underlying antibody.[28]

Malignancy is the cause in at least 95% of patients who have anti-Hu (small cell lung carcinoma [Chapter 177]) or Ma2 (testicular seminoma [Chapter 185]) antibodies and in about 25% of patients who have high-titer anti-glutamic acid decarboxylase (GAD) antibodies (thymomas [Chapter 390] or small cell lung carcinoma [Chapter 177]). GAD antibodies are also found in patients with diabetes (Chapter 210) and other endocrine disorders. Other antibodies with a moderately high risk of malignancy include γ-aminobutyric acid (GABA) B (small cell lung cancer; Chapter 177), mGlu-R5 (Hodgkin lymphoma; Chapter 172), and α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid receptor (thymomas [Chapter 390] and small cell lung cancer [Chapter 177]). In patients who have autoantibodies that are potentially linked to occult malignancy, whole-body computed tomography (CT) and, if possible, positron emission tomography (PET) should be performed.

In NMDA-receptor encephalitis, the CSF contains antibodies against the GluN1 subunit of the NMDA receptor. However, serum can have false-negative results. Some patients have underlying ovarian teratomas (Chapter 184). Neuroimaging with a brain MRI scan of the head may show focal areas of encephalitis or be normal. Because NMDA receptor encephalitis is treatable, it is important to recognize when it has been triggered by viral injury, such as prior herpes simplex encephalitis.

Some systemic antibodies that are associated with autoimmune encephalitis (e.g., GAD65 and TPO antibodies) are common in the population at large and are not a sign of disease by themselves. Hashimoto encephalopathy is most controversial because of frequent occurrence of thyroid peroxidase (TPO) antibodies in the population (Chapter 207), and the nonspecificity of the encephalopathy.[29] However, patients with laboratory signs of spinal fluid inflammation and high serum levels of TPO antibodies probably have autoimmune encephalitis. Sjögren syndrome (Chapter 247) can cause a variety of neurologic consequences, one of which is meningoencephalitis associated with behavioral change. Rheumatoid arthritis (Chapter 243) affects the pachymeninges as well as the leptomeninges and brain in selected patients.[30]

TREATMENT

No standardized treatment exists for autoimmune encephalitis.[31] The goal of initial treatment is to provide the maximum response that can be obtained with an immunotherapy regimen.[32] The intensity and duration of the initial phase of treatment depends on the clinical syndrome, presence or absence of underlying cancer, and severity of illness. Patients who are clinically unstable may require a rapid escalation of treatment strategies.[33]

Most experts recommend intravenous methylprednisolone (1000 mg intravenously daily for 5 days). Intravenous immunoglobulin (400 mg/kg every other day for 5 days) may be used in patients who do not tolerate steroids. Therapy can be continued with weekly methylprednisolone or immunoglobulin for 6 to 12 weeks in an ambulatory setting.[34] Some experts will use a course of oral corticosteroids tapered over weeks to months instead. Other options include rituximab (1000 mg twice, 2 weeks apart) or tocilizumab (4 mg/kg every 4 weeks, then increased to as much as 8 mg/kg every 4 weeks based on the clinical response). Other regimens with anecdotal reports include cyclophosphamide, azathioprine, mycophenolate, methotrexate, anti-B cell antibodies, or anti-CD19 monoclonal intravenous antibodies. Plasma exchange may be used in patients with treatment-refractory disease or in patients with contraindications to other treatments.

PROGNOSIS

Prognosis for autoimmune encephalitic diseases vary widely, and no single statement can apply to this series of disorders.

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384 NUTRITIONAL AND ALCOHOL-RELATED NEUROLOGIC DISORDERS

BARBARA S. KOPPEL, LOUIS H. WEIMER, AND MICHAEL DARAS

Vitamins and minerals, which are essential to cellular function, must be obtained from the environment because the body cannot produce them. They are necessary for embryonic and early development as well as the subsequent maintenance of metabolic function of both the central and peripheral nervous systems. Deficiencies can cause a variety of neurologic syndromes (Table 384-1), each with a well-described constellation of symptoms that are dependent on the location of the pathology within the nervous system, the duration of the deficiency, and the potential presence of multiple deficiencies or other risk factors, such as excess alcohol use.

Acquired vitamin deficiency (Chapter 199) can be caused by malnutrition (Chapter 197), malabsorption (Chapter 126), or increased demand owing to stress, sepsis (Chapter 94), chronic inflammatory conditions, renal dialysis (Chapter 117), infection, or other disease states. Even with adequate supply, inherited (genetic) conditions can produce neurologic dysfunction through various pathophysiologic mechanisms, including aberrant production of a necessary cofactor; impaired transport of a vitamin from the intestine, in the blood, or within the cell that needs it (e.g., mitochondria, neuron, glial cell); production of an enzyme from a vitamin cofactor, thereby resulting in metabolic dysfunction; or an epiphenomenon in a vitamin pathway. These gene disorders generally present early in life, even in neonates, although somewhat different presentations can occur in adolescence or adulthood. By comparison, acquired deficiency states may occur at any age and usually take months to years to develop. Exposure to alcohol, chemotherapy, cassava, or other neurotoxins in the setting of certain vitamin deficiencies (usually B_1) synergistically contributes to neuropathology. Genetic predisposition to variable metabolic rates also may explain why not all patients who consume the same food or ingest the same amount of alcohol develop deficiencies.

Malnutrition is the most common cause of vitamin deficiency in economically disadvantaged geographic locations, especially in seasons of famine due to drought or disease-induced crop failure or times of conflict or warfare. Overreliance on a single food source, particularly one that has lost its nutritional value—such as polished rice, untreated corn, or spoiled grain—can precipitate disease. In contrast, attempts to deal with obesity, such as consuming empty calories with little other nutritional value, following a fad diet, or undergoing restrictive bariatric surgery without guidance on the need for supplemental vitamins, can cause disease. Even when sufficient food supplies are readily available, malnutrition may be caused by inadequate consumption owing to mechanical obstruction from cancer of the mouth or gastrointestinal tract, unbalanced diets, fasting, anorexia, chronic nausea, or recurrent or persistent vomiting.

Iatrogenic causes include failure to feed patients who are comatose, patients who are not self-sufficient (from dementia [Chapter 371], brain injury [Chapter 368], or psychiatric illness [Chapter 362]), or patients who have dysphagia, as can occur following a stroke or spinal cord injury. Vitamin deficiency can also result from failure to include adequate amounts of vitamin and mineral supplements when parenteral or liquid enteral diets are used for an extended period (Chapter 198).

Malabsorption (Chapter 126) over long periods can cause deficiency of fat-soluble vitamins such as vitamin E and even substances with higher body stores, such as vitamin B_{12} and copper. As bariatric surgery has become more common in the treatment of morbid obesity (Chapter 201), patients who do not maintain their vitamin supplementation after bypass-type procedures or who continue to limit intake after undergoing restrictive procedures ("lap band," sleeve gastrectomy) are at high risk of vitamin deficiency syndromes, primarily early thiamine deficiency but also delayed cases of copper and B_{12} deficiency.

DEFICIENCY OF WATER-SOLUBLE VITAMINS

THIAMINE (VITAMIN B_1) DEFICIENCY

Thiamine is converted to thiamine pyrophosphate, which is a coenzyme required in glucose and lipid metabolism for energy production and in the synthesis of neurotransmitters from branched-chain amino acids (Chapter 199). Storage is exhausted after 2 to 3 weeks, and even sooner in conditions of high demand, such as pregnancy, lactation, or infection. Daily requirements of about 1 mg (0.33 mg per 1000 calories) can be obtained from food sources such as whole grains, legumes, meat, and fortified bread or cereals. Inherited dysfunction of thiamine transport mechanisms also can produce the same deficiency.

BERI-BERI

In developing countries, the most common manifestation of thiamine deficiency is beri-beri, which is characterized by a peripheral sensorimotor axonal neuropathy with numbness, paresthesias, or burning pain, occasionally accompanied[1] by peripheral edema from heart failure ("wet beri-beri"). Other causes of thiamine deficiency include reliance on foods in which the vitamin has been inactivated by processing (e.g., polished rice) or overcooking, or eating foods that contain thiaminase-producing bacteria (e.g., raw fish). Deficiency also contributes to the neuropathy caused by chemotherapy.

"Dry" beri-beri does not produce heart failure but has a prominent neuropathy that affects all nerve types (motor, sensory and autonomic) and produces subacute distal (because of its length-dependent process) weakness and burning pain that can mimic Guillain-Barré syndrome (Chapter 388). Progression usually occurs over weeks and can become advanced; rarely, a more insidious presentation can develop over months. Alcohol abuse can contribute to the nutritional deficiency but is not a required prerequisite.

WERNICKE ENCEPHALOPATHY

Thiamine deficiency also can result in Wernicke encephalopathy,[2] a syndrome characterized by the development and progression over days to weeks of confusion or delirium, abnormal eye movements, and ataxia as early as 2 weeks after thiamine stores have been depleted, especially in seriously ill patients. Wernicke encephalopathy occurs most often in the setting of poor nutrition or prolonged vomiting in patients with chronic alcohol abuse. Based on pathologic changes discovered at autopsy, only about 25% of cases are detected before death. Other at-risk patients include those with excessive vomiting from any cause,[3] including bariatric surgery[4]; patients with the acquired immunodeficiency syndrome (AIDS) or cancer; patients with cachexia and poor nutrition; or people who are chronically malnourished.[5] The symptoms and signs of Wernicke encephalopathy reflect the preferential dysfunction of brain regions that have a high demand for thiamine, a cofactor in energy-producing cycles, including the blood-brain barrier, anterior and centromedian thalamus, mamillary bodies, periaqueductal gray matter, superior and inferior colliculi, and floor of the fourth ventricle. The most common pathologic changes in these regions include neuronal swelling and microscopic hemorrhages, followed by gliosis. Rarely, the cerebral cortex and hypothalamus may be involved as well. Deficiency of α-ketoglutamate dehydrogenase activity in astrocytes leads to microglial activation and glutamatergic toxicity.

CLINICAL MANIFESTATIONS AND DIAGNOSIS

The full triad of mental status change (delirium or coma), abnormal eye movements,[6] and ataxia occurs in only about one-third of cases. Acute symptoms may be provoked if intravenous (IV) glucose or food is given before thiamine has been replaced. Because a medical history may be unobtainable until the patient's confusion clears, physical signs of chronic alcoholism (e.g., gynecomastia, skin angiomata, palmar erythema, Dupuytren contractures, ascites, jaundice; Chapters 132 and 138) or of cachexia must be sought.

Mental status changes range from mild memory impairment and inattention to delirium and coma, often with apathy or abulia. Eye movement abnormalities include nystagmus, dysconjugate gaze, and gaze palsies (Video 384-1 and Video 384-2). Especially in alcoholic patients, ataxia can affect the limbs (legs more than arms), trunk, and gait. Nonalcoholic patients are more likely to have ocular dysfunction. Patients with Wernicke encephalopathy also can have autonomic and hypothalamic dysfunction, with bradycardia and hypothermia, as well as papilledema, optic neuropathy, seizures, and myoclonus.

In symptomatic patients, T2-weighted magnetic resonance imaging (MRI) can be normal but often demonstrates symmetrical increased signal owing to edema or hemorrhage in affected areas, most often periventricular thalamus, periaqueductal regions in the floor of the fourth ventricle or cerebellum, and in the mamillary bodies (Fig. 384-1). Low thiamine levels (<50 mg/mL) are common, although levels may be normal in about 10% of cases. Because thiamine deficiency disrupts carbohydrate metabolism, serum levels of lactate and pyruvate can be elevated.

ABSTRACT

Neurologic syndromes have been described in many vitamin deficiency states, with specific symptoms related to the site of the nervous system affected and the vitamin responsible. Examples include Wernicke-Korsakoff (thiamine, B_1), neuropathy (pyridoxine, B_6), myelopathy (B_{12} or copper), and ataxia (tocopherol, E). Alcohol causes neurotoxicity leading to dementia, seizures, neuropathy, and ataxia and can contribute to damage from vitamin deficiencies.

KEYWORDS

neurologic complications of alcohol
neurologic complications of vitamin deficiencies
toxicities
alcohol neuropathy
alcohol dementia
Wernicke encephalopathy
ataxia

TABLE 384-1 VITAMIN AND MINERAL DEFICIENCIES

VITAMIN AND MINERAL DEFICIENCIES	NEUROLOGIC SYNDROME(S)	SUPPORTING TESTS	TREATMENT* REPLETION/SUPPLEMENTATION	CAUSES (OTHER THAN MALNUTRITION)
A (retinol)	Blindness from retinal or corneal damage, especially at night; ageusia	Visual fields, visual acuity Serum level <30-65 µg/dL	30,000 IU vitamin A daily × 1 wk or 60,000 µg × 2 days, repeated in 2 wk; then 5000-10,000 IU daily	Hypothyroidism, diabetes, renal or liver failure, bariatric surgery
B_1 (thiamine)	Wernicke encephalopathy: ataxia, nystagmus, ophthalmoparesis, confusion, delirium Korsakoff syndrome: amnesia, confabulation, impaired learning Beri-beri: axonal neuropathy with paresthesias, numbness, loss of distal reflexes	MRI: symmetrical lesions of midbrain (periaqueductal area), pons, hypothalamus, thalamus, cerebellum MRI: necrosis of mamillary bodies, dorsomedial and anterior thalamus Nerve conduction tests: decreased amplitude Serum thiamine level <20 ng/dL Decreased erythrocyte transketolase	Prevent by 100 mg PO daily before and after bariatric surgery, 100 mg IV before glucose administration or refeeding after starvation Treat Wernicke encephalopathy with 5 days of thiamine, 500-1000 mg IV or IM daily, until improvement stabilizes, then 250 mg daily for 3-5 days; then PO 100 mg daily or 100 mg IM monthly	Alcoholism, bariatric or other major GI surgery, prolonged vomiting, hemodialysis, diuretic treatment of heart failure, cachexia, 5-fluorouracil, other blockers of thiamine phosphate production
B_3 (niacin)	Pellagra: confusion, dementia, weakness, ataxia, spasticity, myoclonus, glossitis, dermatitis, photosensitivity	Erythrocyte NAD, plasma niacin, urinary N1-methylnicotinamide	Nicotinic acid, 50 mg PO tid or 25 mg IV tid; nicotinamide, 50-100 mg IM or 250-500 mg daily PO	Alcoholism, corn- or cereal-based diet, Hartnup syndrome, carcinoid syndrome
B_5 (pantothenic acid)	Dysesthesias, foot paresthesias, cramps, poor coordination	Deficient coenzyme A	5 mg PO daily	Severe malnutrition
B_6 (pyridoxine)	Neuropathy, sensory ataxia, depression, irritability Infantile and adult pyridoxine-deficient epilepsy	Plasma PLP <27 nmol/L; urinary 4-pyridoxic acid <3 nmol ↑ Homocysteine after methionine loading challenge ↑ α-AASA in urine, plasma, CSF	50-100 mg PO daily for neuropathy (preventive use if taking B_6 antagonist) 100 mg IV; then 15-30 mg/kg lifelong PO daily for infants, 100-200 mg PO daily for adult epilepsy	Diverticulosis, isoniazid, some anti-seizure medications, cycloserine, other antagonists Genetic defects in *ALDH7A1* gene for antiquitin (aldehyde dehydrogenase), pyridoxal synthesis Renal failure, homocystinuria
B_{12} (cobalamin)	Myelopathy with spastic paraparesis and sensory ataxia, peripheral neuropathy, optic neuropathy, memory loss, dementia; indirect contributor to stroke	Blood level <200 pg/mL ↑ Methylmalonic acid >145 nmol/L Intrinsic factor antibodies Megaloblastic anemia (bone marrow) Delayed somatosensory evoked potentials ↑ Homocysteine, total >12.5 µmol/L	IM B_{12}, 1000 µg daily for 1 wk, then weekly for 1 mo, then monthly; or oral B_{12}, 1000 µg daily; or nasal B_{12}, 500 µg weekly for lifetime if abnormal absorption, 50-100 µg daily if normal absorption	Achlorhydria, pernicious anemia, gastric or ileal resection, blind loop syndrome, sprue, HIV infection, nitrous oxide anesthesia (especially abuse), fish tapeworm, vegan diet
D (calciferol)	Proximal myopathy, often painful; cognitive impairment Secondary compression of spinal cord, plexus, or peripheral nerves from rickets or osteomalacia	25-(OH) vitamin D_3 level <10 ng/mL in urine Serum calcium ↑ PTH >54 pg/mL Osteopenia/osteoporosis on bone densitometry	Daily supplementation with 400 IU cholecalciferol (D_3) or 50,000 IU ergocalciferol (D_2) 1-3 times per week if malabsorption; use blood level to guide dosing or urine calcium excretion (should be >100 mg/day)	Lack of exposure to sunlight, including sunblock protection; chronic antiepileptic drug use
E (tocopherol)	Spinal and cerebellar ataxia, Babinski sign, ophthalmoplegia, peripheral neuropathy, retinitis pigmentosa	Vitamin E level <2.5 mg/L (normal, 6-15 with normal lipid level) ↑ A-β-lipoprotein levels, antigliadin antibodies Genetic analysis to rule out other spinocerebellar ataxias such as Friedreich ataxia	Supplement with 6-800 IU or 10-40 mg/kg daily, for ataxia of genetic causes. Water-soluble 20 mg/kg/day PO or 50-100 mg/wk IM α-tocopherol to normal serum level for malabsorption; 300 mg PO daily after bariatric surgery	Biliary atresia, celiac sprue, Genetic: ↓ α-tocopherol transport protein (8q13), microsomal triglyceride transfer protein
Folate	Dementia, B_{12} deficiency, stroke	↑ Homocysteine, plasma level <2.5 µg/L	1 mg 3 times daily until normal level, then maintenance of 1 mg/day Pregnancy: 1-4 mg/day during first trimester if taking a folate antagonist or at risk of neural tube defects	Malabsorption or use of antagonist (methotrexate) or antiepileptic medication
K (phytonadione)	Intracranial hemorrhage	INR or PT elevation	IM phytonadione at birth, maternal vitamin K for last month of pregnancy	Medication use that increases metabolism (e.g., phenytoin)
Copper	Myelopathy, neuropathy	Serum Cu <75 µg/dL, ↓ urinary Cu, ceruloplasmin <23 mg/dL MRI: ↑ T2 signal in cervical cord, dorsal column Mutation in *ATP7A* gene (Menkes disease)	Elemental Cu, 8 mg/day PO or 2 mg/day IV wk 1, 6 mg/day wk 2, 4 mg/day wk 3, 2 mg/day ongoing malabsorption Menkes disease: 250 mg copper histidine SQ bid, 1-2 mg in a multivitamin postbariatric surgery	Wilson disease, Menkes disease, alcoholism, malabsorption, gastric bypass, zinc toxicity
Magnesium	Seizures, encephalopathy	Serum magnesium <1.5 mg/dL, correct for low albumin	Magnesium sulfate IV or PO to normal level Avoid magnesium-wasting drugs	Alcoholism, especially beer Diuretic use
Potassium	Muscle weakness, chronic, acute	Serum potassium <3.5 mEq/L, ECG	IV or PO KCl until normalized	Diuretic use, bulimia

*Treatment doses not same as RDA, recommended daily intake.

AASA = aminoadipic semialdehyde; bid = twice daily; CSF = cerebrospinal fluid; Cu = copper; ECG = electrocardiography; GI = gastrointestinal; HIV = human immunodeficiency virus; IM = intramuscular; INR = international normalized ratio; IV = intravenous; KCl = potassium chloride; MRI = magnetic resonance imaging; NAD = nicotinamide adenine dinucleotide; PLP = pyridoxal-5-phosphate (active coenzyme of pyridoxine); PO = by mouth; PT = prothrombin time; PTH = parathyroid hormone; SQ = subcutaneous; tid = three times daily.

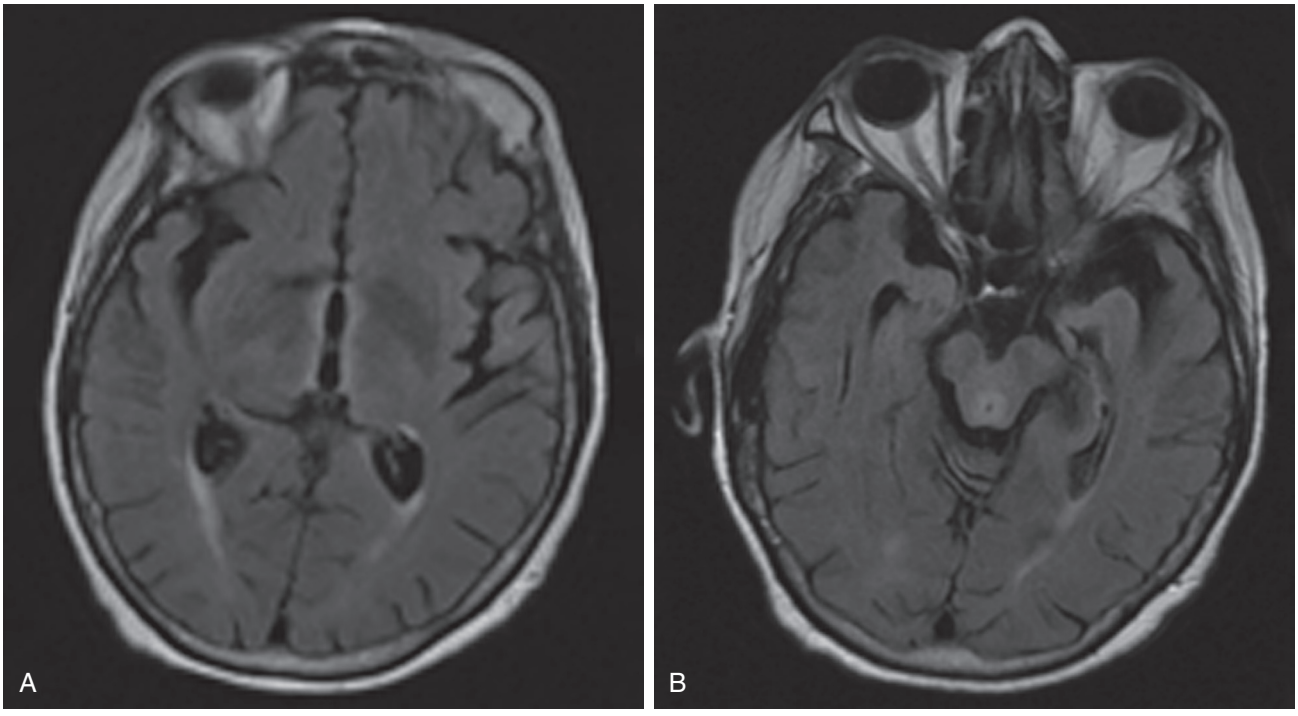

FIGURE 384-1. **Wernicke encephalopathy. A,** Magnetic resonance imaging axial FLAIR images show abnormal hyperintensity of bilateral medial thalami/periventricular third ventricle. **B,** Hyperintensity of tectum of the midbrain periaqueductal region.

KORSAKOFF SYNDROME

Korsakoff syndrome becomes apparent in up to 80% of patients who survive Wernicke encephalopathy. It is more likely to follow in the setting of alcoholism than in pure nutritional deficiency, thereby implying a synergistic mechanism that may be due to repeated episodes of alcohol withdrawal with associated glutamate neurotoxicity, compounded by lack of thiamine. The primary pathologic findings occur in the limbic system, especially the mamillary bodies, amygdala, and dorsomedial and anterior thalamus. Cortical involvement may be related to alcohol neurotoxicity rather than thiamine deficiency.

As the mental status changes of Wernicke syndrome improve, the delirious, confused state is followed by an amnestic state in which patients are often unaware of their memory impairment. Korsakoff syndrome can be reliably identified only when patients can cooperate with neuropsychological testing. It is characterized by retrograde and anterograde episodic amnesia, confabulation, and hallucinations. Occasionally, Korsakoff psychosis is present clinically or pathologically without documented episodes of Wernicke encephalopathy, perhaps because Wernicke encephalopathy went unrecognized.

The memory deficit, which precludes learning new information or acquisition of new memories, is disproportionately severe in relation to other aspects of cognitive function. For example, alertness, attention, social interactions, and motor learning (procedural memory) are generally well preserved. There may be mild disorientation with respect to time and place, and sometimes apathy and other emotional changes are present. Confabulation, in which the intrusion of errors in response to questions leads to fabrication of answers without the intention to deceive, is sometimes present spontaneously in the first weeks after Wernicke encephalopathy. Since it is most likely a compensatory mechanism, it usually lessens over time. Neuropsychological testing frequently demonstrates emotional changes and mild problems in executive function, which are indicative of frontal lobe involvement.

TREATMENT

Prophylactic treatment (i.e., >100 mg daily of thiamine replacement) of anyone at risk due to vomiting, starvation, bariatric surgery, and dialysis (see Table 384-1) can prevent Wernicke encephalopathy as well as beri-beri. In the acute setting, especially in intensive care units, all patients should receive replenishment with high-dose IV or IM thiamine (500 to 1000 mg daily for 3 to 5 days) prior to any glucose administration to circumvent any problems with swallowing or absorption. Treatment will lead rapidly, often within hours, to complete resolution of nystagmus and oculomotor paresis, followed by resolution of the ataxia and eventually of the mental status changes attributable to thiamine deficiency. Magnesium (Chapter 105) and sodium also must be replaced if deficient.

PROGNOSIS

The cognitive function in Korsakoff tends to be stable,[7] but many alcoholic patients may have residual ataxia and cognitive impairment, including memory dysfunction, owing to the toxic effects of alcohol itself. As a result, about 50% of treated patients die within 8 years. Because Korsakoff syndrome does not respond to thiamine replacement, prevention by timely recognition of Wernicke encephalopathy is essential. Untreated, Wernicke encephalopathy is fatal in 90% of cases, and the mortality rate can be as high as 20% even in treated patients.

COBALAMIN (VITAMIN B_{12}) DEFICIENCY

Cobalamin is involved in methionine pathways that regulate the formation of myelin during development and maintain myelin throughout life (Chapter 199).[8] Deficiency results in combined system disease (peripheral neuropathy and spinal cord degeneration) or subacute combined degeneration of the dorsal (sensory) and lateral (motor) tracts (i.e., myelopathy). The spinal cord tracts that are dysfunctional result in impaired position and vibratory sensation and spastic paraparesis. Impairment of cognitive function is not as closely correlated with B_{12} deficiency.

Cobalamin deficiency is rarely due to inadequate dietary intake (e.g., a vegan diet for several years), because it is stored in fat and found in many foods, although more in animal proteins than vegetables. Failure to absorb the vitamin results in its deficiency, especially in individuals over age 60 years (Chapter 150) because the prevalence of atrophic gastritis (Chapter 125) with lack of intrinsic factor and achlorhydria rises in older individuals. Long-term use of proton pump inhibitors can also cause the same lack of gastric acid required for B_{12} absorption. A more common cause in recent years is failure to maintain supplement use after bariatric surgery, with a higher risk after bypass (i.e., Roux-en-Y) than after restrictive surgery (i.e., sleeve gastrectomy or balloon placement). Reduced absorption can also occur with bacterial overgrowth, inflammatory bowel disease (Chapter 127), and rarely, tapeworm infestation (Chapter 315). Nitrous oxide ("laughing gas") toxicity, usually from illicit use rather than administration as an anaesthetic, can cause cobalamin deficiency by inactivating the cobalamin-dependent enzyme methionine synthase. Long-term treatment of diabetes with metformin can lower B_{12} levels. Low vitamin B_{12} levels have been associated with increased homocysteine levels, but a relationship to vascular disease or vascular dementia is not established.

CLINICAL MANIFESTATIONS

Demyelination of the dorsal columns causes proprioceptive loss that can result in sensory ataxia owing to loss of position sense in the feet. A positive Romberg sign (failure to maintain balance only after the eyes are closed) distinguishes sensory from cerebellar ataxia. A non–length-dependent axonal peripheral

neuropathy[9] causing numbness and tingling in the hands and feet is often present, but spinal cord disease is more prominent and less amenable to recovery. Motor nerve function eventually becomes impaired as well. The optic nerve is the most commonly involved cranial nerve, but vagal neuropathy also can occur. Signs of cerebral involvement include memory loss, personality changes, and occasionally hallucinations and psychosis. Although encephalopathy and dementia may be present, B_{12} deficiency may be a secondary phenomenon in a patient with another cause of memory impairment, or both conditions may coexist without a causative relationship. Neurologic abnormalities may precede or be present without anemia, although the anemia is severe in 20% of patients with vitamin B_{12} deficiency. Symptoms generally progress slowly, but they can appear rapidly after exposure to nitrous oxide anaesthesia in individuals who have preexisting subclinical cobalamin deficiency.

DIAGNOSIS

Serum vitamin B_{12} levels are usually low (<300 pg/mL) but can be normal in symptomatic patients. In such cases, serum levels of methylmalonic acid and homocysteine are useful ancillary tests because these levels are increased as a result of impaired cobalamin-dependent reactions. Pernicious anemia (Chapter 150), an autoimmune disease diagnosed by measuring intrinsic factor antibodies, is severe in about 20% of patients. However, both the hematocrit and mean corpuscular volume are sometimes normal because the hematologic effects of cobalamin deficiency can be partially masked by folate supplementation. Inactivated cobalamin from nitrous oxide exposure cannot be detected by most assays; despite the normal B_{12} level, methylmalonic acid levels are elevated.

Low cobalamin levels are sometimes present in normal people, especially the elderly, in which dementia, peripheral polyneuropathy, and myelopathy may be due to a myriad of unrelated causes. Therefore, a low cobalamin level may reflect poor nutrition or absorption rather than being the cause of these conditions. Causality is definitively confirmed by clinical improvement after cobalamin replacement, which usually begins only after several weeks and may continue for up to a year.

The myelopathy (Chapter 369) may be difficult to distinguish from other causes. However, a magnetic resonance image (MRI) showing an increased T2 signal in the posterior and lateral columns of the spinal cord and in periventricular white matter can help exclude other causes of myelopathy.

TREATMENT

Treatment begins by repleting low B_{12} levels with subcutaneous or IM injections of 1000 to 2000 μg of cobalamin daily for 1 week and then weekly for 1 month. After that time, oral supplementation continued indefinitely with 1000 μg daily of cyanocobalamin usually suffices in patients with achlorhydria, a history of bariatric surgery, pernicious anemia, or other causes of malabsorption.[A1] If no response in serum levels is seen with oral treatment, intramuscular monthly injections should be continued instead. Sublingual, transdermal patch, and nasal gel forms (500 μg weekly) have not been adequately studied. The anemia can be corrected by high-dose folate replacement, but the neurologic damage will progress unless vitamin B_{12} is administered.

PROGNOSIS

Neurologic symptoms, especially paresthesias, typically improve to some extent within 3 months of achieving adequate B_{12} serum levels. Numbness and areflexia often persist, especially if treatment is delayed. If there is no improvement whatsoever, causes other than vitamin B_{12} deficiency are likely, such as copper deficiency or human immunodeficiency virus (HIV)–associated myelopathy. Similarly, vitamin B_{12} supplementation does not affect cognitive performance in hyperhomocysteinemic elderly people without clinical signs of B_{12} deficiency.

FOLATE DEFICIENCY

Folate is an important coenzyme in the metabolism of nucleic and amino acids (Chapter 199). Maternal deficiency accounts for 50% of babies born with neural tube defects and may cause more subtle neurologic problems, including autism.[10] Inborn errors of folate metabolism cause seizures and intellectual disability. Other signs include psychomotor retardation, autism, dyskinesias, and irritability. In adults, neurologic symptoms of folate deficiency overlap with those of B_{12} deficiency and include peripheral neuropathy,[11] cognitive impairment, depression, and rarely, retrobulbar optic neuropathy. Folate deficiency also results in elevated levels of homocysteine, which is associated with an increased risk for ischemic heart disease and stroke, although replacement to correct homocysteine level does not prevent cardiovascular disease.[12] Patients with genetic folate deficiency due to lack of methylenetetrahydrofolate reductase, which converts ingested folate to the active metabolic cofactor, have an increased risk of intracerebral hemorrhage.

The supplementation of flour with folate has greatly reduced the risk of folate deficiency, and pregnant women are now generally prescribed supplemental folate. Women of childbearing age should be treated even before pregnancy if they have any conditions that predispose to folate deficiency, such as the use of antiepileptic or other medications that induce folate metabolism.

Folate deficiency also can lead to megaloblastic anemia (Chapter 150). Before correction of megaloblastic anemia with folate alone, vitamin B_{12} levels should be checked to avoid ongoing neurologic injury from unrecognized cobalamin deficiency.

TREATMENT AND PROGNOSIS

Folate deficiency is treated orally with 1 mg three times daily for 1 month, followed by 1 mg daily; improvement takes many months. Return of folate and homocysteine serum levels to normal has not shown benefit for preventing progressive cognitive impairment, for preventing stroke, or for reducing adverse vascular events except in patients with classic homocysteinemia (Chapter 193).

PYRIDOXINE (VITAMIN B_6) DEFICIENCY AND TOXICITY

Pyridoxine is a coenzyme in multiple reactions that involve gluconeogenesis, biosynthesis of neurotransmitters, and the metabolism of amino acids, nucleic acids, and lipids. Pyridoxine deficiency can be caused by genetic defects, such as defective antiquitin, that lead to increased utilization of pyridoxine. In adults, low serum pyridoxine levels are well tolerated, so symptomatic deficiency is rare, but it can occur in the setting of renal failure (Chapter 116) or dialysis (Chapter 117), cirrhosis (Chapter 139), or with medications such as isoniazid for antitubercular therapy (Chapter 299) or hydralazine for heart failure (Chapter 46) if patients do not receive concurrent supplementation. Deficiency is also seen with extreme malnutrition, especially diets consisting predominantly of white rice. Pyridoxine deficiency in pregnancy can be caused by hyperemesis gravidarum (Chapter 221).

CLINICAL MANIFESTATIONS AND DIAGNOSIS

Pyridoxine Deficiency

Prolonged pyridoxine deficiency causes a painful peripheral axonal neuropathy that leads to weakness and sensory ataxia. Genetic defects can rarely present in adolescence or adulthood with neuropathy,[13] but adult pyridoxine deficiency is almost always acquired, not genetic. Some patients have skin thickening, seborrheic dermatitis, or glossitis, which can resemble pellagra.

Serum levels of the active form of pyridoxine, pyridoxal 5′-phosphate, and urine levels of the metabolite 4-pyridoxic acid are low. Ancillary tests include nerve conduction studies, which show significantly reduced amplitudes in sensory and motor action potentials with normal conduction velocity times, typical of an axonal neuropathy. In the setting of seizures, which is predominately a neonatal manifestation, electroencephalography shows a highly disorganized pattern with excessive slow frequency activity and abundant multifocal and generalized spikes, similar to hypsarrhythmia.

Pyridoxine Toxicity

Toxicity occurs due to excess pyridoxine intake (usually ≥200 mg daily). A competition between the inactive pyridoxine form and the active form of pyridoxal-5′-phosphate, which is a cofactor in a myriad of enzyme actions, can occur in patients who take large amounts of vitamin supplements (which require no prescription) or after accidental intravenous overdose (Table 384-2). In the United States, a 100 mg daily supplement is thought to be safe, despite controversial isolated reports of toxicity at lower doses. Toxicity is characterized by a ganglioneuropathy with purely sensory symptoms, including sensory loss, ataxia, areflexia, and prominent Romberg sign. Blood pyridoxine levels are typically more than 10 times the normal upper limit.

TREATMENT

Patients in whom symptoms of pyridoxine deficiency develop or who take pyridoxine antagonists should receive supplemental pyridoxine (50 to 100 mg daily). Children with pyridoxine-dependent epilepsy require immediate and lifelong supplementation with at least 100 mg of pyridoxine daily. Antisense therapy against the mutant gene is being tested.

For pyridoxine toxicity, simply stopping excess oral vitamin intake can improve damage. After intravenous exposure to toxic doses, however, ganglion cell death is mostly irreversible.

TABLE 384-2 VITAMIN AND MINERAL TOXICITIES

VITAMIN AND MINERAL TOXICITY	NEUROLOGIC SYMPTOMS	SUPPORTING TESTS	CAUSES	TREATMENT
Vitamin A	Idiopathic intracranial hypertension (pseudotumor cerebri): headaches, papilledema, blindness Embryotoxic effects	Lumbar puncture: elevated opening pressure (>250 mm H_2O); normal composition	• Excessive intake of vitamin A • Use of tretinoin for acne • Excessive consumption of liver from fish-eating animals (polar bear, seal, walrus) • Consumption of >10,000 IU/day during pregnancy	Stop the use
Vitamin B_3 (Niacin, Nicotinamide)	Flushing, headaches, lightheadedness			Stop the use
Vitamin B_6	Sensory ganglioneuropathy: sensory loss, areflexia, ataxia, Romberg sign, chorea, Lhermitte sign	Nerve conduction study: slow sensory conduction with normal motor velocities	Excess intake (>200 mg daily)	Stop the use
Vitamin E	Muscle weakness, intracranial hemorrhage	Level >23.3 μg/mL		
Vitamin D	Hypercalcemia Muscle and bone pain Confusion	Levels 150-2000 ng/mL with calcium >11 mg/dL	• Overcorrection of deficiencies • Accidental ingestion • Prolonged use of high doses	Stop the use
Copper	Psychiatric symptoms, dementia, chorea, tremor, dystonia	Kayser-Fleischer rings Low ceruloplasmin level		Chelation with penicillamine or zinc
Oxalyl diaminopropionic acid	Spastic paraparesis		Excess consumption of grass peas or chick peas	
Cassava tubers (Konzo)	Sensory ataxia, optic atrophy, sensorineural deafness (men), spasticity (women and children)		Potentiates cyanate and glucoside neurotoxicity	
Cycad toxins	Amyotrophic lateral sclerosis/parkinsonism in Guam			

Other B Vitamins

B_2 (Riboflavin)

Oxidation-reduction reactions require flavins, which are present in dairy products, meat, fish, vegetables, and fortified cereal and bread. Deficiencies are rare, but some inherited mitochondrial myopathies, mostly motor neuropathies and multisystem conditions caused by riboflavin electron transfer mitochondrial defects, can respond to supplementation with this vitamin.

B_3 (Niacin)

Pellagra is a symptom complex of photosensitive dermatitis, delirium or dementia, neuropathy, and diarrhea. It occurs in patients with malabsorption of niacin or in patients undergoing dialysis. The syndrome can be confused with alcohol withdrawal (delirium tremens) or psychosis. Pellagra is also seen in Hartnup syndrome, a recessively inherited failure to transport tryptophan, which is converted to niacin. In utero genetic deficiencies cause malformations of many organ systems, but it is often difficult to isolate the effects of niacin from other B vitamins.

B5 (Pantothenic Acid)

Deficiency of vitamin B_5 is rare, and disease associated with it is hard to prove, because it is often accompanied by deficiencies of other B vitamins. Also this vitamin is found in many different foods and is produced by colonic bacteria. The neurologic syndrome associated with B_5 deficiency is presumed to be a small-fiber neuropathy with dysesthesias and paresthesias that result in "burning feet." Treatment is with B complex vitamins. Treatment with gabapentin (Table 26-5) may help relieve neuropathic symptoms.

B_7 (Biotin)

Biotin (B_7) deficiency is caused by lack of protein in the diet, accidentally failing to add it to total parenteral nutrition, and an autosomal recessive disorder affecting biotinidase, which prevents biotin from being removed from proteins and recycled, so as to be accessible for metabolic use. Genetic causes result in developmental delay, seizures or myoclonus, ataxia, and deafness if supplementation is not begun in the newborn period. Biotinidase deficiency causes a combination of optic atrophy and spinal cord pathology that clinically resembles neuromyelitis optica (Chapter 392). Dietary deficiencies lead to lethargy, myalgias, and paresthesias, along with rash. Treatment is with B complex vitamins. Gabapentin (Table 26-5) may help with symptoms.

DEFICIENCY OF FAT-SOLUBLE VITAMINS

VITAMIN E (TOCOPHEROL) DEFICIENCY

Although vitamin E is composed of several tocopherols, it is the α form, which is found in plants such as leafy vegetables and vegetable oils, that is biologically active in humans.[14] Because it is so widely available, deficiency in adults (who require 15 mg/day) is almost never due to inadequate dietary consumption (malnutrition). Rather, vitamin E deficiency is the result of prolonged malabsorption of lipids in the setting of biliary and pancreatic disease (Chapters 141 and 130), cystic fibrosis (Chapter 77), celiac disease (Chapter 126), Crohn disease (Chapter 127), extensive small bowel resection, and blind loop syndrome (Chapter 126). In inherited forms, decreased availability of vitamin E is caused by faulty intracellular transport owing to structural defects in the α-tocopherol transfer protein, which is produced by a gene on chromosome 8q12.3, whose product binds the vitamin to protein, or to decreased absorption of lipids (hypolipoproteinemia and abetalipoproteinemia).

CLINICAL MANIFESTATIONS AND DIAGNOSIS

Neurologic manifestations of vitamin E deficiency include a spinocerebellar syndrome with ataxia of gait or limbs (dysmetria)[15]; abnormal eye movements (nystagmus or dysconjugate gaze); loss of vibration and position senses (sometimes causing sensory ataxia or pseudoathetosis); distal sensory neuropathy with hyporeflexia; and, rarely, cognitive dysfunction, myopathy, or blindness owing to retinopathy. A normal blood vitamin E level is considered to be 11 to 37 μM/L in adults, but serum levels of vitamin E can vary with the serum lipid level. Especially in patients with extreme hyperlipidemia, such as cholestasis, the ratio of vitamin E to cholesterol will be more reliable than the absolute vitamin E level.

Although generally not toxic, excessive intake of vitamin E causes bleeding, including hemorrhagic infarcts, in adults, probably from its effects on platelets. Myalgia, mild proximal weakness, and elevated serum creatine kinase levels can also occur. During pregnancy, high doses of vitamin E can interfere with oxidation in the fetus and cause growth retardation.

TREATMENT

Treatment depends on the cause of the deficiency. Malabsorption syndromes require 1000 to 2000 mg daily (where 1 mg is equivalent to 1.49 IU) for infants and 100 mg/kg/day (10 to 20 g) for adults, with 300 mg daily considered adequate supplementation after bariatric surgery. Genetic causes can be treated with 5 to 10 g/day.

VITAMIN D (CALCIFEROL) DEFICIENCY

Vitamin D deficiency is often diagnosed in asymptomatic adults because of frequent screening, despite the U.S. Preventive Services Task Force's recommendations against screening (Chapter 199).[16] Although there is no absolute

cutoff, serum levels of 25(OH) D below 30 nmol/L can cause parathyroid dysfunction with subsequent dysregulation of calcium and serum electrolytes (Chapter 227). Deficiency results from impaired skin synthesis owing to inadequate exposure to sunlight, dietary insufficiency, intestinal malabsorption; or sequestration of the vitamin as it is stored in fat cells of obese patients. The average multivitamin contains 400 IU of combined D_2 (ergocalciferol) and D_3 (cholecalciferol), whereas 20 minutes of full-body summer sun exposure provides 10,000 IU of D_3, the form used in the body.

CLINICAL MANIFESTATIONS

Vitamin D deficiency causes rickets in children and osteomalacia (Chapter 226) in adults. Bone remodelling and degenerative changes in vertebral end plates near intervertebral discs may lead to vertebral collapse and resulting compression of the spinal cord or nerve roots (Chapter 369). Abrupt extreme lack of vitamin D causes hypocalcemia with secondary hyperparathyroidism (Chapter 227). Hypocalcemia, in turn, can cause tetany, encephalopathy, and generalized seizures. Deficiency also causes a proximal myopathy (owing to impaired calcium influx or actin and troponin production), which is worse in the legs and pelvic girdle than the arms and which can lead to peculiar patterns of gait as a result of weakness and fear of falling. This myopathy is associated with sleep disorders and fibromyalgia without weakness. Vitamin D deficiency is also associated with an increased incidence of Alzheimer and all-cause dementia.[17] Low levels of vitamin D also may adversely affect postural stability in Parkinson patients.

Vitamin D plays a role in immune modulation of regulatory T cells, which may explain the relationship of vitamin D deficiency to an earlier onset, higher prevalence, higher relapse rate, and more severe manifestations of multiple sclerosis (Chapter 380). Other autoimmune diseases, such as narcolepsy (Chapter 374), also are more common in patients with low levels of vitamin D.

DIAGNOSIS

Normal serum levels of 25(OH)D are 20 to 40 ng/mL. Measurement of 1.25 (OH)D is not useful.

TREATMENT

Individuals whose dietary absorption is normal require 400 to 600 IU (10 to 15 µg) of vitamin D_3 daily, but persons with malabsorption may need more than twice that amount. Supplementary doses depend on the degree of deficiency, with high doses (50,000 units, 1.25 mg) of ergocalciferol (D_2) given weekly for no more than 8 weeks to patients whose 25-OH calciferol level is very low (<20 ng/mL), followed by daily 400 to 800 IU of cholecalciferol (D_3). In patients with malabsorption, 1000 IU should be given daily, indefinitely. Serum levels should be monitored after reaching at least 20 ng/mL.

Supplementation of vitamin D in patients with normal 25-OH D levels is ineffective and may lead to fatigue and weakness from toxicity (see Table 384-2). Toxicity (serum levels of 150 to 1220 ng/mL) is extremely rare and generally iatrogenic because of overcorrection, accidental injection, or prolonged use of high-dose supplements. However, excess absorption of vitamin D is seen in sarcoidosis (Chapter 83) and other granulomatous conditions. The most dangerous symptom is hypercalcemia. Like deficiency states, vitamin D toxicity causes muscle and bone pain (Chapter 227) or mental confusion related to hypercalcemia. Very high doses also have been associated with an increased risk of falls.

VITAMIN A DEFICIENCY

Vitamin A is required to bind opsin to produce the retinal transmitter rhodopsin. It also plays a role in endothelial stability, especially in bone and smooth muscle. Vitamin A is found in animal products (retinol, retinoids) or as a provitamin in colorful plants such as carrots (beta-carotenoid). In adults, the absence of vitamin A impairs vision in conditions of low light ("night blindness"). In abetalipoproteinemia, in which vitamin E is also lacking, complete blindness may occur (Chapter 190). The ability to taste is also impaired, and hyperkeratinization of skin and cornea can occur.

Malabsorption must be very prolonged to produce vitamin A deficiency because this fat-soluble vitamin has large body stores. Repletion in patients with corneal changes requires intramuscular doses of 50 to 100,000 units for up to 2 weeks.

Vitamin A toxicity is rare but can occur in patients who use isotretinoin for acne or have excessive dietary intake owing to the consumption of liver (especially from fish-eating mammals such as polar bear, seal, and walrus). Vitamin A in large amounts can cause idiopathic intracranial hypertension (Chapters 175 and 367) with headache and papilledema that leads to diminished vision or even blindness in severe cases. Excess vitamin A is also highly teratogenic (Table 384-2).

VITAMIN K DEFICIENCY

Vitamin K deficiency, a rare consequence of malabsorption, also can be seen in patients taking high doses of vitamin A or E. It is most often seen in patients who have compromised storage or synthesis in the liver or who are taking the antagonist warfarin (Chapter 199). Adequate intake is 90 µg daily for adult women and 120 µg daily for adult men. Vitamin K deficiency causes excessive bleeding and increases the risk of intracerebral hemorrhage. Hemorrhagic disease of the newborn (now known as vitamin K deficiency bleeding) can occur in offspring of mothers who take hepatic enzyme-inducing anticonvulsants (such as phenytoin) that increase vitamin K metabolism or any broad-spectrum antibiotics that kill the gut bacteria that are required to make vitamin K. This outcome is better prevented by routinely giving all newborns an injection of vitamin K rather than by maternal supplementation using 5 mg daily for the last month of pregnancy. Because vitamin K levels are difficult to obtain, functional testing of clotting with the international normalized ratio is typically used to guide replacement dose adjustments. Toxicity is not reported.

DEFICIENCY OF MISCELLANEOUS ELEMENTS AND NUTRIENTS

COPPER DEFICIENCY

Acquired copper deficiency (Chapter 199) is rare and can be difficult to recognize. It occurs most often in premature or malnourished infants and in patients with very prolonged malabsorption owing to celiac disease (Chapter 126), cystic fibrosis (Chapter 77), Crohn disease (Chapter 127), or intestinal blind loops after surgery (e.g., a Whipple procedure for pancreatic or other malignancy, or bypass surgery for weight loss). It can also occur in patients with nephrotic syndrome (Chapter 107) and intestinal bacterial overgrowth (Chapter 126). Copper deficiency is also a well-recognized consequence of excessive intake of zinc (from denture paste, wound cream, eating pennies, or herbal therapy for colds) or as a consequence of parenteral overload during hemodialysis (Chapter 117), which competitively upregulates copper loss in the intestine.

The most common neurologic complication of copper deficiency is a myelopathy that is clinically very similar to that of cobalamin deficiency. The most prominent features are spastic paraparesis and sensory ataxia. An insidious peripheral polyneuropathy, initially sensory and eventually motor, of the axonal type is usually present as well. Optic neuropathy with hallucinations or visual loss, wrist drop, and foot drop have also been reported. Copper levels, including excreted urinary copper, should be measured in patients who have symptoms suspicious for vitamin B_{12} deficiency but have normal vitamin B_{12} levels or who fail to respond to cyanocobalamin replacement. Treatment consists of oral copper supplementation, 8 mg/day tapering by 2 mg weekly over 3 weeks, followed by maintenance of 2 mg/day for life. Zinc overexposure should be sought and stopped. A ratio of 8 to 15 mg of zinc to 1 mg of copper should be supplied after bariatric surgery.

Menkes disease, an X-linked recessive copper deficiency caused by mutations in the *ATP7A* gene needed for absorption, is characterized by severe intellectual disability and kinky hair. The diagnosis is made by finding low serum copper levels or changes in the ratio of dopamine to norepinephrine. Large doses of copper histidine (250 mg twice daily until age 1, then daily until age 3) must be delivered subcutaneously, but improvement is variable. Patients survive to adulthood only if persistent copper injections are begun in the neonatal period.

Toxicity from copper is indirectly caused by Wilson disease (Chapter 195, Table 384-2), which is an autosomal recessive disorder caused by a mutation in the *ATP7B* gene that encodes ceruloplasmin, a copper-transporting protein (Chapter 195). Psychiatric features such as personality change, disinhibition, depression, and psychosis sometimes overshadow neurologic manifestations such as dementia, dysarthria, chorea, tremor, and dystonia. Deposition of copper in the eye's Descemet membrane causes the characteristic Kayser-Fleischer ring (Fig. 195-2), which is seen in the iris in over 95% of patients. Serum ceruloplasmin levels are low. Accumulation of copper in the liver leads to chronic liver failure. Wilson disease is treated by copper chelation with penicillamine or zinc (Chapter 195) along with minimization of dietary intake.

OTHER NUTRITIONAL DISORDERS

Iodine deficiency leads to hypothyroidism (Chapter 207), which causes varying degrees of congenital iodine deficiency syndrome (formerly cretinism) in the

offspring of mothers with insufficient thyroid hormone. Selenium deficiency leads to skeletal and cardiac muscle dysfunction; supplementation with at least 100 μg daily after bariatric surgery is necessary.

Overreliance on one hardy food source (e.g., grass peas, chick peas) may lead to spastic paraparesis from lathyrism owing to oxalyl diaminopropionic acid, which is a neurotoxic glutamate agonist. In older Nigerian men who consume excess cassava tubers (konzo) or tapioca (which contains the cyanide-like product cyanogenic glycoside), neurotoxicity (Chapter 96) symptoms include sensory neuropathy, ataxia, optic atrophy, and sensorineural deafness. In contrast, women and children develop spasticity, presumably from the same toxin. Amyotrophic lateral sclerosis (Chapter 387) and Parkinson-dementia (Chapter 378) complex in Guam are probably caused by cycad toxins in flour (see Table 384-2). Occasional epidemics that combine toxins such as alcohol or smoking with malnutrition and respond clinically to vitamin B supplementation are presumed to reflect deficiencies of various nutrients. Examples are Strachan Jamaican neuropathy and Cuban tobacco-alcohol amblyopia with optic neuropathy.

ALCOHOL-RELATED DISORDERS

Alcohol (Chapter 364) is responsible for a wide spectrum of neurologic disorders.[18] At one extreme, it can cause irreversible dementia, cerebellar degeneration, optic neuropathy, and peripheral polyneuropathy. Syndromes are "dose dependent" in the sense that greater durations and amounts of alcohol use produce more serious complications.[19] Binge drinking, combined with B-vitamin deficiencies and electrolyte derangements, also contribute to neurologic disease. Intoxication and withdrawal states may obscure other serious conditions such as osmotic demyelination syndromes and Wernicke encephalopathy, thereby delaying treatment.

Acute intoxication can range from mild euphoria to vestibular and cerebellar dysfunction to coma and death. Intoxication may also affect judgment and coordination, thereby contributing to subsequent vehicular accidents, falls, traumatic brain injury, violence, and other unsafe behaviors. After chronic excessive alcohol intake, cessation or lowering of alcohol consumption can lead to withdrawal, which presents with overexcitation syndromes such as seizures, tremors, and autonomic overload. Untreated withdrawal can lead to fatal delirium tremens. Sleep homeostasis is disrupted by binge drinking,[20] thereby making rebound of rapid eye movement (REM) sleep a possible contributor to the hallucinations of alcohol withdrawal.

Alcohol-induced liver toxicity results in hepatic encephalopathy (Chapter 139) and, rarely, acquired hepatocerebral (lenticular) degeneration. Coagulopathy caused by liver disease or suppressed platelet production and function raises the risk for subdural or intracranial hematoma (Chapter 368). Fetal alcohol syndrome reflects the vulnerability of the developing nervous system to the toxic effects of alcohol, especially during the first two trimesters.[21]

Signs of intoxication correlate with blood alcohol levels: 50 mg/dL for personality changes and disinhibition of behavior; 150 mg/dL for ataxia, vestibular dysfunction, and nystagmus; 300 mg/dL for stupor; 400 mg/dL for coma; and 500 mg/dL for respiratory depression or apnea. Owing to slower rates of metabolism, women require fewer drinks than men to reach equivalent serum levels. However, the effects of alcohol intake vary greatly depending on the chronicity of intake (tolerance) and the rate at which high levels develop. Intoxication alone should never be assumed to be the sole cause of a depressed mental state because people with alcohol use disorder are at increased risk for other treatable causes of coma (Table 373-2), such as repeated seizures and herniation from hemorrhage (Fig. 384-2).

SPECIFIC CLINICAL ALCOHOL-RELATED SYNDROMES

Seizures and Status Epilepticus

Seizures and status epilepticus (Chapter 372) can be a direct consequence of intoxication or of withdrawal, or they can be a result of associated electrolyte derangements, including hyponatremia (Chapter 102), hypomagnesemia (Chapter 105), and hypoglycemia (Chapter 211).[22] Patients with preexisting epilepsy (Chapter 372), possibly from epileptogenic foci owing to previous head trauma (Chapter 368) or stroke (Chapter 376), have an increased risk that alcohol will lower their seizure threshold, interfere with their adherence to anti-seizure medication, or disrupt their sleep. Patients with prior withdrawal-related seizures are at increased risk for recurrence. However, imaging by CT or MRI is always indicated to exclude other causes of seizures.

TREATMENT AND PROGNOSIS

Alcohol-related seizures, which may be focal or generalized, require treatment with antiseizure medication (Table 372-7). Withdrawal seizures, which precede the autonomic excitation of delirium tremens by several hours, warrant observation and benzodiazepine therapy at the time of the seizure (e.g., lorazepam 2 mg intravenously) followed by a tapering dose to suppress withdrawal symptoms (e.g., oxazepam, usually starting at 30 mg every 4 hours and then reducing the dose as the patient's response dictates) for about 3 days.

Consideration should be given to non-GABAergic seizure medications, such as levetiracetam or phenytoin (Table 372-7), instead of medications with dual purposes, such as barbiturates or gabapentin.

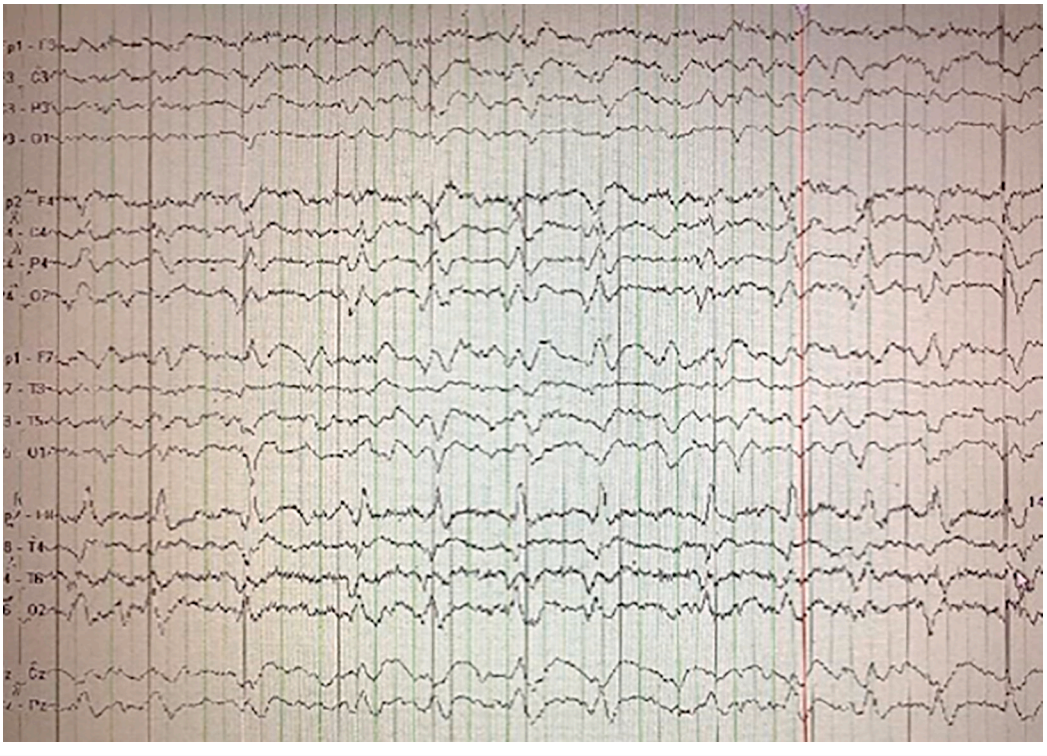

FIGURE 384-2. Hepatic encephalopathy. Electroencephalography of patient with alcohol use disorder and hepatic encephalopathy demonstrating triphasic waves and background slowing.

Hepatic Encephalopathy

Hepatic encephalopathy is most often seen in patients with end-stage alcoholic cirrhosis (Chapter 139). The characteristic manifestations are irritability alternating with depressed mental status, somnolence, seizures, tremor, and asterixis. Protein loads, including bleeding from esophageal varices or gastritis, can trigger decompensation. Encephalopathy also can be iatrogenic in patients treated for alcohol withdrawal with protocol-driven benzodiazepines instead of dosing in response to symptoms of withdrawal.

DIAGNOSIS AND TREATMENT

Electroencephalography demonstrates slowing and triphasic waves (Fig. 384-3). Although temporary reversal of encephalopathy with flumazenil (2 mg IV) can confirm the diagnosis, treatment focuses on trying to reduce the serum ammonia level, usually with lactulose (15 to 30 mL orally twice daily) or polyethylene glycol 3350-electrolyte solution (4 L orally or by nasogastric tube over 4 hours; see Chapter 139) to speed gastrointestinal transit time. Nonabsorbable antibiotics such as rifaximin (550 mg twice daily), neomycin (500 mg to 1 g three times daily), or metronidazole (250 mg two to four times daily) can be used chronically. Closure of spontaneous portosystemic shunts by embolization may be effective for reducing intractable encephalopathy in some patients.

Dementia and Other Encephalopathies

Headache (hangover) is probably due to low CSF pressure found in dehydrated binge drinkers.[23] Wernicke encephalopathy and Korsakoff syndrome (see earlier) are seen in alcoholic patients, especially binge drinkers, owing to thiamine deficiency. Dementia, not the memory disorder of Korsakoff syndrome, can develop even when nutrition is well maintained because of alcohol's direct and irreversible neurotoxic effects owing to glutamate excitotoxicity and oxidative stress. The absolute amounts of alcohol necessary to produce dementia are unclear and vary among patients. In younger patients with dementia, 10 to 25% of cases may be attributable to alcohol. Alcohol may also exacerbate Alzheimer disease.

Frontal lobe dysfunction results in deficits of executive function (planning, abstract reasoning) rather than the amnesia that is prominent in Korsakoff syndrome. Additional damage from head injury, status epilepticus, and cerebrovascular disease can contribute to cognitive dysfunction.

The appearance of cerebral atrophy is further evidence of alcohol's deleterious effect on cortical and white matter fibers. Abstinence is advised to limit degeneration. Standard dementia therapies are not very effective.

Cerebellar Degeneration

Cerebellar degeneration and ataxia result from alcohol-induced loss of Purkinje cells, mainly in the anterior superior part of the cerebellar vermis; the cerebellar hemispheres are less affected. As a result, the clinical picture is one of mainly truncal and gait ataxia, with a wide-based unsteady gait and inability to walk tandem. The arms are usually spared, with no intention tremor; nystagmus and dysarthria are rare when the patient is not intoxicated. Findings are exacerbated by concurrent thiamine deficiency. Alcohol may activate antibodies against Purkinje cells in individuals with gluten intolerance.

No treatment is available other than adaptive physical therapy. Prognosis for recovery of function is poor.

Alcoholic Neuropathies

Optic Neuropathy

Optic neuropathy, which occurs with severe chronic alcohol abuse, is manifested as progressive painless visual loss and sometimes visual hallucinations as a result of damage to the optic nerve fibers. The macular region is most affected. The prognosis is poor.

Alcoholic Peripheral Neuropathy

Peripheral neuropathy (Chapter 388) ("alcoholic neuropathy") is the most common neurologic complication of chronic alcoholism. It is an axonal sensorimotor neuropathy that causes dysfunction of small nerve fibers, thereby producing painful sensory symptoms such as burning and paresthesias of the feet. Numbness develops in a stocking-glove distribution, with loss of ankle reflexes. Mild distal weakness eventually occurs in some patients. Involvement of the autonomic nervous system frequently causes impotence as well as urinary or bowel complaints. Neurophysiologic testing reveals primarily axonal patterns. Concurrent thiamine deficiency should be excluded or treated. Although supplements of thiamine and pyridoxine may lead to some improvement, especially in the painful paresthesias, complete resolution is rare. If abstinence from alcohol is not also achieved, the symptoms persist, thereby implying that a direct toxic effect of alcohol is likely.

Compressive Neuropathies

Compressive neuropathies, especially of the radial nerve ("Saturday night palsy") or fibular nerve, can result after prolonged pressure on a nerve while the patient is obtunded from heavy alcohol consumption. Recovery takes many weeks but is generally complete.

Alcoholic Myopathy

Alcoholic myopathy (Chapter 389) occurs in binge drinkers, in whom severe muscle injury with rhabdomyolysis (Chapter 99) can develop, especially in the setting of fasting and prolonged absence of movement. Myoglobinuria can result in kidney damage. Heavy alcohol consumption is also associated with cardiomyopathy (Chapter 47), which can lead to arrhythmias even in the absence of hypokalemia. Chronic steady (not binge) alcohol use causes a symmetrical proximal weakness (Chapter 389) and muscle loss that is not

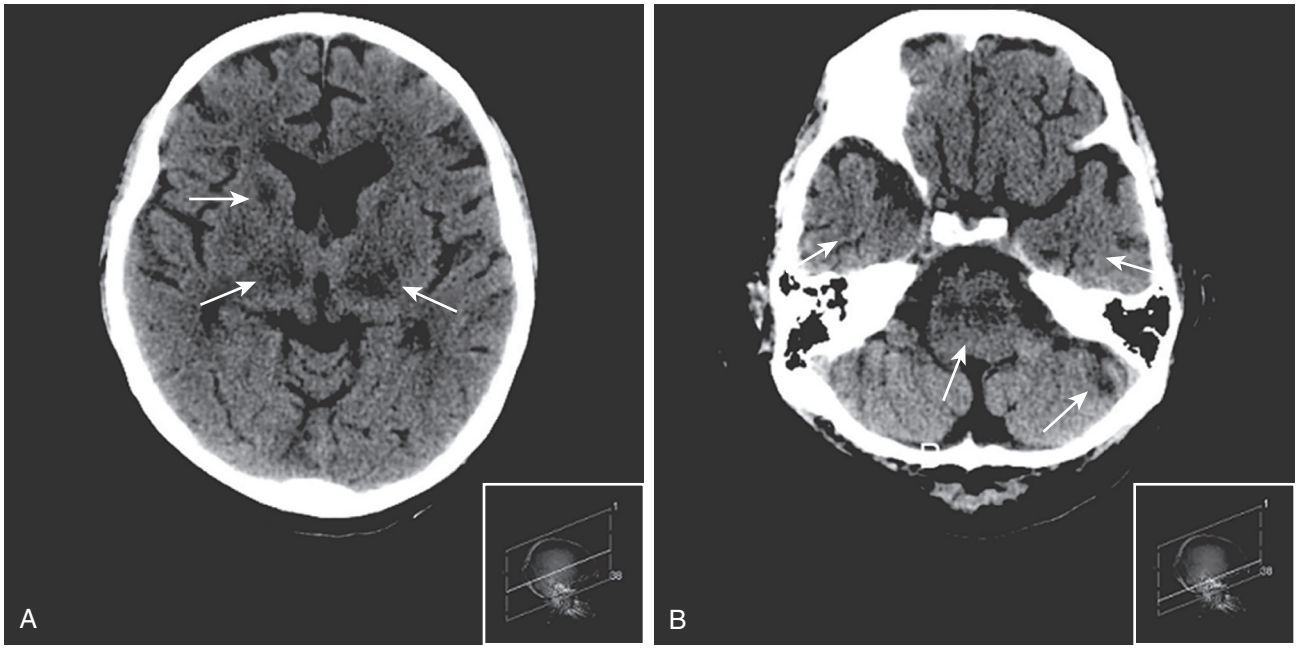

FIGURE 384-3. **Osmotic demyelination syndrome: computed tomographic imaging. A,** Cerebral atrophy and hypodensities in bilateral thalami as well as right caudate. **B,** Hypodensity in center of pons, left and right temporal lobes, and left cerebellum.

usually severe enough to prevent walking or standing. It can be detected in up to 50% of heavy users and is more prevalent in women.

Fetal Alcohol Syndrome

Fetal alcohol syndrome is recognized at birth in infants whose mothers consumed significant amounts of alcohol in the early stages of pregnancy.[24] The quantity required to place a fetus at risk has not been definitively determined, so abstinence is generally recommended throughout pregnancy. Rates as high as 55 per 1000 births have been described.

The characteristic findings are growth retardation, microcephaly, hypotonia, skeletal and cardiac anomalies, and characteristic facial features (micrognathia, small palpebral fissures). Exposure of the developing brain to alcohol can also lead to subtle or severe neurocognitive defects and attention-deficit disorder, which may not be detected until later in childhood. Although malnutrition and excess alcohol have synergistic deleterious effects, the teratogenic effects of alcohol are not prevented by adequate amounts of thiamine, folate, and other vitamins.

OSMOTIC DEMYELINATION

Osmotic demyelination syndrome (formerly called central pontine myelinolysis)[25] most commonly involves the pons, with or without the basal ganglia and thalamus, and sometimes also involves the corpus callosum, where it is also known as Marchiafava-Bignami syndrome. Chronic hyponatremia (Chapter 102) with cerebral edema leads to depletion of osmoles in the brain areas where gray and white matter intermingle. Abrupt correction of the hyponatremia precipitates central dehydration; separation of axons from their surrounding myelin and apoptosis of oligodendrocytes lead to noninflammatory demyelination. Beer drinkers are at increased risk due to the antidiuretic hormone effect of beer.

Signs and symptoms include dysarthria and dysphagia, with abnormal eye movements (Video 384-3) and ataxia (pons), delirium or coma (thalami), and neuropsychiatric syndromes reflecting "split brain" disconnection of hemispheres (corpus callosum). Symptoms also can occur during recovery from Wernicke encephalopathy, thereby suggesting contributions from thiamine deficiency, malnutrition, and alcoholism. CT is easier to obtain in very ill patients (Fig. 384-3), but MRI can identify milder cases in which recovery can occur.

TREATMENT PREVENTION AND PROGNOSIS

See Chapter 102.

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385 DEVELOPMENTAL AND NEUROCUTANEOUS DISORDERS

E. STEVE ROACH

The understanding of many neurodevelopmental disorders has improved dramatically because of high-resolution neuroimaging, which can detect structural defects that previously went unrecognized, genetic testing, and a better grasp of molecular mechanisms. As a result, targeted treatments are now available for some conditions.

NEURAL TUBE DEFECTS

The worldwide incidence of neural tube defects is about 1 to 10 per 1000 live births. In the United States, neural tube defects occur in about 3500 births per year, with anencephaly and spina bifida being the two most common forms.

Neural tube defects are developmental anomalies resulting from failure of the anterior and posterior neuropore to close during gestation. Depending upon the embryologic stage at which the neuropore closure is disrupted, neural tube defects can manifest as anencephaly, encephalocele, and myelomeningocele with Chiari II malformation. Both genetic and environmental factors may play a role in neural tube defects. Although these lesions occur with increased frequency with chromosomal anomalies, single gene mutations are uncommonly associated with neural tube defects. In utero exposure to medications such as valproic acid is associated with neural tube defects. Folic acid deficiency also is associated with neural tube defects, and folate supplementation (6 mg/day) during pregnancy can reduce the risk of a neural tube defect by about 50 to 60%[1] (Chapter 221).

SPINAL MALFORMATIONS

Developmental anomalies of the vertebral bodies are common and cause pain and neurologic symptoms when they result in scoliosis (Chapter 86) or accelerated degenerative changes of the spine. Neurologic disability is likely when spine anomalies compress neural structures or alter the flow of cerebrospinal fluid.

SPINA BIFIDA

Spina bifida describes a spectrum of congenital defects, ranging from isolated, usually asymptomatic, bony defects of vertebral arch closure (spina bifida occulta) to a myelomeningocele, which is characterized by herniation of the spinal cord and meninges through a defect of the posterior spine. A myelocele is an open midline lesion with exposed neural elements that are flush with the adjacent skin (Fig. 385-1). The uncommon meningocele is characterized by herniation of leptomeninges and cerebrospinal fluid through a spinal defect without nerve tissue involvement.[2] Myeloceles and myelomeningoceles are visible at birth as midline back lesions.

EPIDEMIOLOGY

The incidence of myelomeningocele and other neural tube defects has been decreasing in recent years, probably because of folate supplementation in bread and the routine prescription of perinatal folic acid. It occurs at a rate of 1 per 1000 births worldwide. In the United States, the incidence is about 0.6 per 1000 births. Females are affected slightly more often than males.

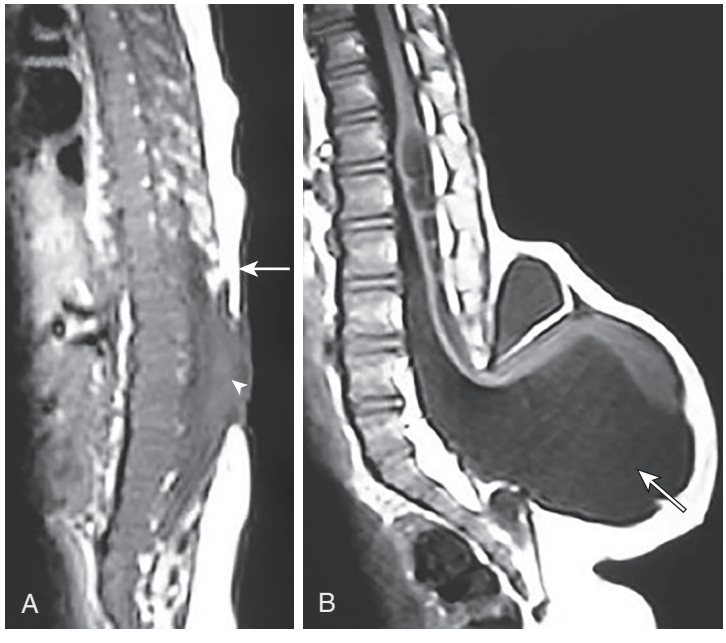

FIGURE 385-1. Sagittal T1-weighted images of a myelocele (A) and a myelomeningocele (B). With a myelocele, the neural tissue *(arrowhead)* is even with the adjacent skin surface *(arrow)*. With the myelomeningocele (B), the lesion extends beyond the skin surface and contains nerve tissue and cerebrospinal fluid *(arrow)*. (Reprinted with permission from Kumar J, et al. Imaging spectrum of spinal dysraphism on magnetic resonance: A pictorial review. *World J Radiol*. 2017;9:178-190.)

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385 DEVELOPMENTAL AND NEUROCUTANEOUS DISORDERS

E. STEVE ROACH

The understanding of many neurodevelopmental disorders has improved dramatically because of high-resolution neuroimaging, which can detect structural defects that previously went unrecognized, genetic testing, and a better grasp of molecular mechanisms. As a result, targeted treatments are now available for some conditions.

NEURAL TUBE DEFECTS

The worldwide incidence of neural tube defects is about 1 to 10 per 1000 live births. In the United States, neural tube defects occur in about 3500 births per year, with anencephaly and spina bifida being the two most common forms.

Neural tube defects are developmental anomalies resulting from failure of the anterior and posterior neuropore to close during gestation. Depending upon the embryologic stage at which the neuropore closure is disrupted, neural tube defects can manifest as anencephaly, encephalocele, and myelomeningocele with Chiari II malformation. Both genetic and environmental factors may play a role in neural tube defects. Although these lesions occur with increased frequency with chromosomal anomalies, single gene mutations are uncommonly associated with neural tube defects. In utero exposure to medications such as valproic acid is associated with neural tube defects. Folic acid deficiency also is associated with neural tube defects, and folate supplementation (6 mg/day) during pregnancy can reduce the risk of a neural tube defect by about 50 to 60%[1] (Chapter 221).

SPINAL MALFORMATIONS

Developmental anomalies of the vertebral bodies are common and cause pain and neurologic symptoms when they result in scoliosis (Chapter 86) or accelerated degenerative changes of the spine. Neurologic disability is likely when spine anomalies compress neural structures or alter the flow of cerebrospinal fluid.

SPINA BIFIDA

Spina bifida describes a spectrum of congenital defects, ranging from isolated, usually asymptomatic, bony defects of vertebral arch closure (spina bifida occulta) to a myelomeningocele, which is characterized by herniation of the spinal cord and meninges through a defect of the posterior spine. A myelocele is an open midline lesion with exposed neural elements that are flush with the adjacent skin (Fig. 385-1). The uncommon meningocele is characterized by herniation of leptomeninges and cerebrospinal fluid through a spinal defect without nerve tissue involvement.[2] Myeloceles and myelomeningoceles are visible at birth as midline back lesions.

EPIDEMIOLOGY

The incidence of myelomeningocele and other neural tube defects has been decreasing in recent years, probably because of folate supplementation in bread and the routine prescription of perinatal folic acid. It occurs at a rate of 1 per 1000 births worldwide. In the United States, the incidence is about 0.6 per 1000 births. Females are affected slightly more often than males.

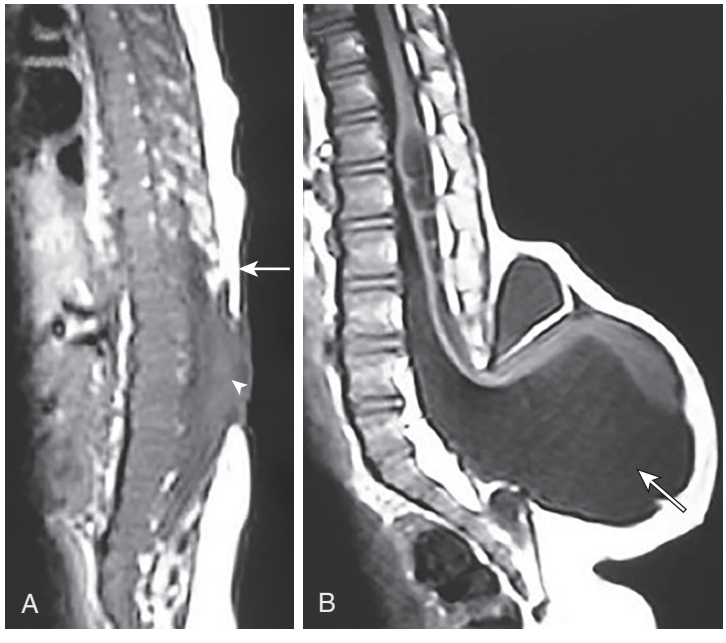

FIGURE 385-1. Sagittal T1-weighted images of a myelocele (A) and a myelomeningocele (B). With a myelocele, the neural tissue *(arrowhead)* is even with the adjacent skin surface *(arrow)*. With the myelomeningocele (B), the lesion extends beyond the skin surface and contains nerve tissue and cerebrospinal fluid *(arrow)*. (Reprinted with permission from Kumar J, et al. Imaging spectrum of spinal dysraphism on magnetic resonance: A pictorial review. *World J Radiol*. 2017;9:178-190.)

ABSTRACT

Our understanding of many neurodevelopmental disorders has improved owing to high-resolution imaging procedures and more precise genetic techniques. This chapter summarizes selected congenital disorders of the brain and spinal cord, such as neural tube defects, Chiari malformation, syringomyelia, holoprosencephaly, and agenesis of the corpus callosum. Also included are genetic and developmental disorders such as autism, Down syndrome, fragile X syndrome, and Rett syndrome. Several neurocutaneous disorders presented in detail include tuberous sclerosis complex, neurofibromatosis types 1 and 2, Sturge-Weber syndrome, and von Hippel-Lindau disease. Disease-modifying therapy is available for tuberous sclerosis, neurofibromatosis type 1, and possibly fragile X and Rett syndromes. For other conditions, improved identification and treatment of disease complications has greatly improved longevity and quality of life.

KEYWORDS

spina bifida
anencephaly
Down syndrome
tuberous sclerosis
neurofibromatosis
Sturge-Weber syndrome
autism

PATHOBIOLOGY

A myelocele results from failure of posterior neuropore closure by day 26 of embryogenesis. Chromosomal deletions, duplications, and trisomy can lead to neural tube defects, but single gene mutations are uncommon. Low serum folate levels promote neural tube defects, and vitamin A deficiency may play a role in some individuals. The use of valproic acid during pregnancy increases the likelihood of neural tube defects.

CLINICAL MANIFESTATIONS

The manifestations of spina bifida depend primarily on the location of the lesion on the spinal axis and the extent of spinal cord involvement. Spina bifida occulta is typically asymptomatic and often discovered as an incidental finding on imaging studies. Myelomeningoceles and myeloceles can affect any portion of the spinal column, but the lumbosacral region is by far the most common site. Lumbosacral lesions typically cause less devastating dysfunction than lesions in the thoracic or cervical region. Loss of sensation and motor weakness typically occur below the level of spinal cord lesion, thereby contributing to the development of ulcers or other injuries. Bowel and bladder control are generally impaired regardless of the affected level. Frequent urinary tract infections can promote renal failure.

Myelomeningoceles are often associated with other conditions, such as a tethered cord, a Chiari II malformation, or agenesis of the corpus callosum. Epilepsy is common, particularly among individuals with an associated brain malformation or hydrocephalus. Kyphosis, clubfoot, and extremity contractures are frequent complications. Although the mechanism is incompletely understood, latex allergy is common, and its frequency tends to increase with age.

DIAGNOSIS

Abnormalities are often detected on prenatal ultrasound studies. In addition to prenatal ultrasound studies, prenatal detection of myelomeningoceles is aided by elevated concentrations of alpha-fetoprotein and acetylcholinesterase; the latter normally occurs in the cerebrospinal fluid but not in amniotic fluid. Ultrasound and magnetic resonance imaging can help define the extent of the abnormalities.

TREATMENT

A baby with an open neural tube defect should begin antibiotics after birth and undergo surgical closure within three days. Individuals with hydrocephalus usually require a ventriculoperitoneal shunt. Prenatal closure of the spinal lesion may reduce the incidence of hydrocephalus. Myelomeningocele is a static lesion, so any deterioration in neurologic function could signal worsening hydrocephalus, a tethered cord, or a syrinx. Proper attention to skin care and bladder training may limit the number of pressure ulcers and urinary tract infections, and neuropsychologic care can help patients deal with the disease.[3]

CHIARI MALFORMATION

A Chiari malformation denotes the downward displacement of structures in the posterior fossa through the foramen magnum. A Chiari I malformation, which is characterized by the displacement of the cerebellar tonsils more than 5 mm below the foramen magnum, occurs in about 1% of patients who undergo cranial magnetic resonance imaging (MRI).[4] A Chiari II malformation typically occurs in association with a myelomeningocele and hydrocephalus. It is characterized by downward displacement of cerebellar vermis, tonsils, fourth ventricle, and medulla, with "beaking" of the midbrain, in which the posterior midbrain appears elongated in sagittal images.

Most Chiari I malformations remain asymptomatic, although some individuals with more severe displacement develop occipital headaches, particularly with straining, or lower cranial neuropathies that manifest as tongue weakness, vocal cord paralysis, or recurrent aspiration. Since Chiari II malformations typically occur in conjunction with a myelomeningocele (see Spina Bifida) and hydrocephalus, affected individuals often experience seizures, cognitive delay, paraplegia, and sphincter dysfunction. Diagnosis is confirmed by magnetic resonance imaging (MRI) without contrast showing displacement of the cerebellar tonsils more than 5 mm below the foramen magnum (Fig. 385-2). Given the high frequency of asymptomatic Chiari I malformations, it can be difficult to determine whether the malformation is responsible for the patient's symptoms, particularly when the tonsillar displacement is not severe.

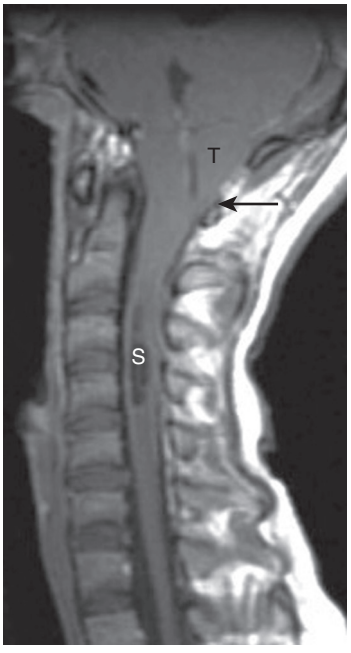

FIGURE 385-2. Chiari I malformation. A sagittal magnetic resonance image shows low, pointed cerebellar tonsils (i.e., Chiari I malformation, T) that extend to the level of C1 *(arrow)* and a dilated central canal of the spinal cord (i.e., syringohydromyelia [S]). (From Barkovich AJ, Kuzniecky RI. Congenital, developmental, and neurocutaneous disorders. In Goldman L, Ausiello D, eds. *Cecil Textbook of Medicine*. 23rd ed. Philadelphia: Saunders Elsevier; 2008:2790.)

TREATMENT

Patients with a symptomatic Chiari I malformation may require a posterior fossa decompression. Surgery is not usually necessary for mildly symptomatic or asymptomatic patients, and expert consultation is required to assess the potential benefit of decompressive surgery.[5] Individuals with a Chiari II lesion typically require surgical repair of the associated myelomeningocele and shunting of the hydrocephalus. Bladder dysfunction may necessitate intermittent catheterization and treatment of urinary tract infections (Chapter 263) and genitourinary reflux. Prognosis in Chiari II patients depends greatly on the severity of the brain abnormalities and myelomeningocele.

TETHERED SPINAL CORD

A tethered spinal cord results from abnormal fixation of the filum terminale to the lower spinal structures. Tethering can represent a developmental anomaly or occur in association with a myelomeningocele, intraspinal tumor, or infection. Common associated spinal anomalies include diastematomyelia (split cord), spinal lipomas, dermal sinuses, and fibrolipomas of the filum terminale. Progressive cord dysfunction can occur when repeated flexion and extension of the spine results in stretching of the tethered cord.

Symptoms can occur in either children or adults. Clinical manifestations vary with the patient's age and whether there is progressive dysfunction. Cutaneous findings can include a lumbar cutaneous lipoma, skin dimple, dermal sinus, or tuft of hair.[6] Associated orthopedic abnormalities include scoliosis and leg length discrepancy. Urologic manifestations include poor bladder control, loss of previously attained urinary continence, and recurrent urinary tract infections. Infants may have diminished spontaneous leg movements, whereas older children exhibit delayed walking, an abnormal gait, and poor bladder control. Adolescents and adults may experience difficulty walking, sensory loss, and back and leg pain. Sexual dysfunction and urinary incontinence are common. Many individuals with a tethered cord syndrome have a latex allergy, possibly due to recurrent latex exposures during procedures. The diagnosis is confirmed by an MRI showing a conus medullaris below the bottom of the L-2 vertebral border or thickened or fat-containing filum terminale.

TREATMENT

For symptomatic patients, surgical release of the tethered cord is recommended. For asymptomatic individuals, the value of surgery is uncertain, in part because the cord often retethers following surgery.

SYRINGOMYELIA

Syringomyelia is a cystic cavitation of the central portion of the spinal cord, whereas hydromyelia results from dilatation of the central spinal canal. Both lesions are typically located in the cervical cord but may extend into the medullary region (syringobulbia) or into the lower cord segments. Syringomyelia may develop in association with Chiari malformations (see Fig. 385-2), trauma, a spinal cord tumor, or a tethered cord. The classic presentation is a dissociated sensory loss (pain and temperature loss with preservation of light touch, vibration, and proprioception) in the neck and arms. Symptoms classically appear in late adolescence or early adulthood and progress sporadically with intermittent stable periods.[7] A cervical lesion produces a cape-like pattern of sensory loss of the arms and shoulder, sometimes accompanied by atrophy of the hands and arms, with hypertonia and hyperreflexia in the legs. Extension into the medulla may cause lower cranial neuropathies. The diagnosis is best confirmed by MRI.

TREATMENT

Patients with an associated Chiari II malformation may require posterior fossa decompression and shunting of secondary hydrocephalus. Occasionally, a large syrinx unassociated with a Chiari malformation may require shunting of the syrinx.

BRAIN MALFORMATIONS

DISORDERS OF VENTRAL INDUCTION

Brain malformations develop during the first trimester. Disorders of ventral induction include holoprosencephaly, septo-optic dysplasia, and agenesis of the corpus callosum. Holoprosencephaly results from failure of the prosencephalon to divide, thereby resulting in alobar holoprosencephaly (cortex with a single ventricle) or lobar holoprosencephaly (cerebral hemispheres are mostly separated except for the frontal lobes).

HOLOPROSENCEPHALY

Holoprosencephaly occurs in some individuals with trisomy 13 or 18 or in association with single gene mutations (e.g., *SHH, ZIC2,* and *SIX3*). Holoprosencephaly is often associated with facial dysmorphism. Abnormal temperature regulation and disrupted sleep cycles are common. Central diabetes insipidus occurs in about two thirds of patients with classic holoprosencephaly, whereas deficiencies of growth hormone, thyrotrophic hormone, or adrenocorticotrophic hormone occur less frequently.

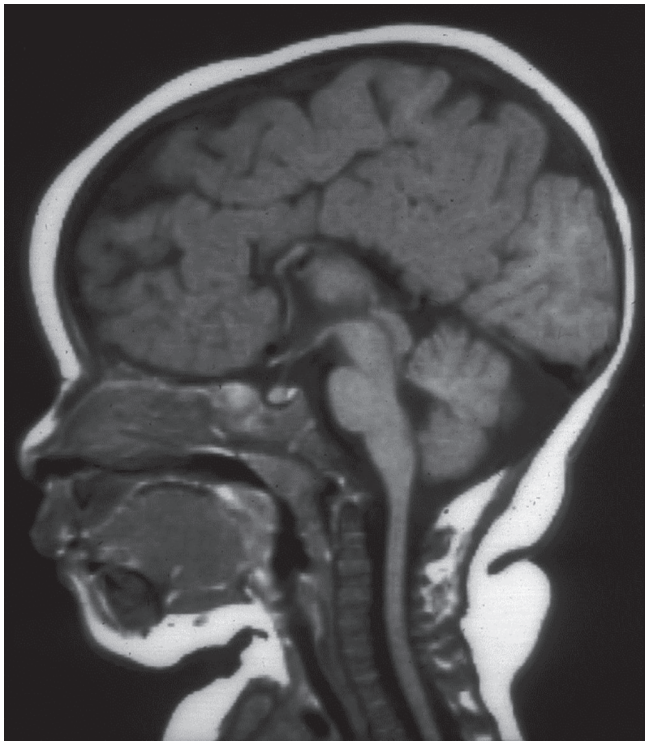

FIGURE 385-3. Midline sagittal view magnetic resonance scan from a child with a near-complete absence of the corpus callosus. Note also the abnormal gyral pattern of the interhemispheric cortex.

Although lobar holoprosencephaly may have a milder phenotype than alobar holoprosencephaly, all patients will experience substantial cognitive impairment and many will develop intractable epilepsy. It is important to identify and treat any associated endocrine dysfunction.

SEPTO-OPTIC DYSPLASIA

Septo-optic dysplasias characterized by optic nerve hypoplasia with visual impairment and variable absence of the septum pellucidum and corpus callosum. It is often associated with pituitary aplasia.[8] Septo-optic dysplasia arises from a variant of *HESX1* on chromosome 3p14. As with holoprosencephaly, septo-optic dysplasia is often associated with endocrine abnormalities, most notably growth hormone deficiency and less frequently hypothyroidism, central diabetes insipidus, and adrenal insufficiency.

AGENESIS OF THE CORPUS CALLOSUM

Complete congenital agenesis of the corpus callosum is rare, but partial absence or hypoplasia of the structure are relatively common. Disruption of brain development by an intrauterine infection or exposure to alcohol can alter the formation of the corpus callosum. Agenesis can be inherited as either an autosomal dominant or an autosomal recessive trait, or it can occur as a component of disorders such as septo-optic dysplasia or the X-linked dominant condition Aicardi syndrome. Often, however, a specific cause of aberrant development of the corpus callosum is not apparent.

An abnormal or missing corpus callosum (Fig. 385-3) is usually discovered on neuroimaging performed to evaluate seizures or developmental delay. Isolated absence or hypoplasia of the corpus callosum can cause few symptoms, but it is often a harbinger of more widespread defects in brain development.[9] Consequently, many individuals with callosal abnormalities have epilepsy, impaired cognition and development, or motor dysfunction.

DISORDERS OF NEURONAL MIGRATION

Disrupted neuronal migration during the second to the fourth month of gestation causes a spectrum of anomalies, including lissencephaly, polymicrogyria, and pachygyria. These disorders also are often associated with hypoplasia of the corpus callosum. Migrational abnormalities have been documented with intrauterine infections, multiple different single gene mutations (e.g., *FLNA DCX, TUBA1A, APC2*), or antenatal exposure to alcohol.

Lissencephaly is characterized by a thickened, smooth-appearing cortex with scant gyral and sulcal development. Band heterotopia and periventricular nodular heterotopia represent less complete migrational abnormalities featuring less severe manifestations than those of lissencephaly. As the name suggests, polymicrogyria is characterized by the occurrence of an excessive number of very small gyri, whereas pachygyria describes a small number of gyri that are too broad. When affecting the entire cortex, all of these anomalies are associated with severe neurologic dysfunction with marked cognitive impairment and often refractory epilepsy. However, very localized migrational abnormalities may allow near normal function, and such focal lesions lend themselves to surgical treatment of epilepsy. Interestingly, subtle migrational anomalies are often identified microscopically in cortical tissue that has been removed during epilepsy surgery, even in individuals whose neuroimaging was unremarkable.

Brain malformations and migrational abnormalities can usually be confirmed with MRI. However, less severe migrational abnormalities may not be obvious on routine neuroimaging.

TREATMENT

Epilepsy resulting from migrational abnormalities is often medically intractable, but some patients respond to antiseizure medications (Chapter 372), vagus nerve stimulation, or a low-glycemic diet. Individuals with very localized cortical dysplasia may benefit from resective epilepsy surgery.

CEREBRAL PALSY

Cerebral palsy is a nonprogressive developmental abnormality that causes permanent disorders of movement and posture. This syndrome presents in infants and often follows an obvious perinatal insult (e.g., asphyxia, intrauterine infection, hemorrhage, prematurity, or brain infarction) or is associated with anatomic abnormalities (e.g., congenital absence of the corpus callosum). However, about 20% of cases are idiopathic, and about one third of such patients have clinically significant, usually de novo, copy number variants.[10] The clinical syndrome is demonstrated by exaggerated reflexes, involuntary movements, and spasticity. About 50% of patients have cognitive impairment, sometimes severe.

TREATMENT

Treatment focuses on managing the hypertonia with oral or intrathecal baclofen, exercise training,[11] intramuscular botulism injections, deep brain stimulation, and selective dorsal rhizotomy.

COGNITIVE DISORDERS

AUTISM SPECTRUM DISORDERS

Autism spectrum disorders are characterized by early-onset impaired social communication and interactions along with repetitive patterns of behavior, interests, or activities. Although autism spectrum disorder is increasingly diagnosed, it is unclear whether this increased prevalence stems from increased recognition and diagnosis or from a truly increased incidence. The cause of autism in most patients is not usually known, but it commonly occurs with genetic conditions such as Rett syndrome, fragile X syndrome, and tuberous sclerosis complex. Other gene variants are less commonly associated with autism spectrum disorder, and the recurrence risk of autism in subsequent siblings is about 5 to 6%.

Prenatal exposure to chemicals such as lead, mercury, toluene, and polychlorinated biphenyls may increase the risk of autism, but it is often difficult to establish causation in a specific individual. However, the administration of childhood vaccines has been definitively shown not to increase the risk of autism.

CLINICAL MANIFESTATIONS AND DIAGNOSIS

Symptoms can range from mild to severe. Children typically have impaired nonverbal communication, poor eye contact, and an apparent lack of empathy. Affected individuals crave a predictable routine, often becoming upset at the slightest deviation from their expectations; they often exhibit repetitive stereotypical motor mannerisms such as arm flapping or walking in circles. The diagnostic criteria for autism spectrum disorder require evidence of impaired communication and social interaction, as well as two examples of persistent repetitive behaviors or an overly restricted range of interests (Table 385-1).

TREATMENT

Early therapy tends to be more effective, although complete obliteration of the symptoms is not usually feasible.[12] Behavioral therapy can reduce the undesirable behaviors and facilitate more appropriate behaviors. Speech therapy is indicated for individuals with language delay. Most children with autism spectrum disorder require an individualized educational plan. Pharmacotherapy does not effectively reduce the primary manifestations of autism spectrum disorder, but drug therapy may help comorbid conditions such as attention deficit disorder (Chapter 362), aggression, anxiety, oppositional behavior, and obsessive-compulsive behaviors (Chapter 362).

PROGNOSIS

Autism spectrum disorder is a chronic condition, and symptoms persist into adulthood. The severity largely determines the patient's functional outcome. Individuals with mildly impaired social communication and interaction can often function with targeted support, whereas children with little language, limited social adaptability, and great difficulty adjusting to change typically respond less effectively to treatment. The presence of comorbid conditions such as cognitive impairment, psychiatric disorders, or epilepsy can further worsen the prognosis.

RETT SYNDROME

With a prevalence of 1 in 10,000 female births, Rett syndrome is one of the most common monogenetic causes of cognitive impairment. Rett syndrome is an X-linked dominant disorder caused by variant in the *MECP2* gene.[13] The vast majority of affected individuals arise via a spontaneous mutation. The MeCP2 protein is particularly abundant in the brain, where it likely facilitates the development and maintenance of synaptic connections. Mutational analysis has allowed the recognition of a broad spectrum of clinical severity, ranging from learning disability to severe encephalopathy.

CLINICAL MANIFESTATIONS AND DIAGNOSIS

Girls with classic Rett syndrome develop normally for the first 6 to 18 months, then undergo deceleration of head growth and rapid loss of previously acquired developmental skills. Function eventually stabilizes, with residual microcephaly, loss of language, and diminished purposeful hand movements. Patients often exhibit stereotypical hand wringing (or "hand washing") movements. Epilepsy and behavioral abnormalities are common. With the typical loss of language, the manifestations of Rett syndrome resemble those of autism, although with notable preservation of eye contact. Late manifestations include spasticity, gait apraxia, and scoliosis. Live-born hemizygous males have earlier and more severe symptoms, typically presenting with neonatal epileptic encephalopathy, microcephaly, abnormal tone, irregular breathing, and macroorchidism.

Diagnosis of Rett syndrome is confirmed by mutational analysis. An electrocardiogram should be obtained because QTc prolongation is common.

FIGURE 385-4. A young woman with the characteristic facial appearance of Down syndrome.

TABLE 385-1 DIAGNOSTIC CRITERIA FOR AUTISM SPECTRUM DISORDER

1. Deficits in Social Communication/Interaction (must have all three criteria):
   a. Problems reciprocating social or emotional interaction, including difficulty establishing or maintaining back-and-forth conversations and interactions, inability to initiate an interaction, and problems with shared attention or sharing of emotions and interests with others
   b. Severe problems maintaining relationships—ranges from lack of interest in other people to difficulties in pretend play and engaging in age-appropriate social activities, and problems adjusting to different social expectations
   c. Nonverbal communication problems such as abnormal eye contact, posture, facial expressions, tone of voice, and gestures, as well as an inability to understand these
2. Restricted and Repetitive Behavior (at least two criteria must be met):
   a. Stereotyped or repetitive speech, motor movements, or use of objects
   b. Excessive adherence to routines, ritualized patterns of verbal or nonverbal behavior, or excessive resistance to change
   c. Highly restricted interests that are abnormal in intensity or focus
   d. Hyperreactivity or hyporeactivity to sensory input or unusual interest in sensory aspects of the environment

Symptoms must be present in early childhood but may not become fully manifest until social demands exceed capacities. Symptoms need to be *functionally impairing* and not better described by another DSM-5 diagnosis.

DSM-5 = *Diagnostic and Statistical Manual of Mental Disorders*. 5th ed.

From American Psychiatric Association. *Diagnostic and Statistical Manual of Mental Disorders*. 5th ed. Arlington, VA: American Psychiatric Publishing; 2013.

TREATMENT AND PROGNOSIS

In one study, trofinetide (an analogue of neuropeptide (1-3) IGF at 200 mg twice daily) significantly improved functional status but did not restore normal function.[A1] Treatment of epilepsy (Chapter 372) and spasticity is beneficial. An annual electrocardiogram to monitor for prolonged QTc is appropriate. Early death is common in hemizygous males. Affected females often live well into middle age and beyond, although information about survival beyond middle age is limited.

FRAGILE X SYNDROME

Fragile X syndrome is another common genetic cause of intellectual disability. Most instances of fragile X syndrome are due to expanded trinucleotide (CGG) repeats in the first exon of the X-linked *FMR1* gene. Individuals with more than 200 CGG repeats have a high likelihood of exhibiting the classic manifestations of fragile X syndrome, whereas those with 55 to 200 repeats may remain asymptomatic or exhibit a milder phenotype.[14] Similarly, female carriers typically exhibit less severe cognitive and behavioral symptoms.

Affected individuals have a distinctive phenotype, characterized by macrocephaly, a long narrow face, prominent ears, pubertal macroorchidism, and joint laxity. Cognitive impairment, autism spectrum disorder, and attention deficit disorder are common. Diagnosis is confirmed by genetic testing.

TREATMENT AND PROGNOSIS

A recent small randomized trial of oral trofinetide (70 mg/kg twice daily) yielded encouraging preliminary results.[A2] The severity of fragile X syndrome manifestations varies, in part because of the number of CGG repeats in a given individual. Most males have marked cognitive and behavioral dysfunction. Manifesting females typically experience milder symptoms than male patients. Longitudinal studies suggest that cognitive development plateaus in adolescence and then tends to decline by adulthood. The mechanism for this decline is incompletely understood, and it is not yet clear whether trofinetide can prevent this decline.

DOWN SYNDROME (TRISOMY 21)

With a frequency of 1 in 700 newborns, Down syndrome is the most common chromosomal anomaly as well as the most common genetic cause of intellectual disability.[15] The incidence of Down syndrome increases with advanced maternal age at the time of conception. Down syndrome results from complete or partial duplication of chromosome 21. Approximately 95% of the individuals with Down syndrome have trisomy 21. The remaining cases are related to a translocation (4%) or mosaicism (1%) involving chromosome 21.

Individuals with Down syndrome exhibit a characteristic phenotype (Fig. 385-4), although both the findings and their severity vary. Newborns typically exhibit hypotonia, a short neck, an upward slant of the eyes, and a single deep crease across the palms. Delayed motor and cognitive milestones are apparent early, and variable intellectual disability is characteristic, although most individuals are able to attend school with the appropriate accommodations and manage some activities of daily living.

Down syndrome is associated with a variety of complications, many of which result in neurologic dysfunction. Affected individuals have an increased risk of hypothyroidism (Chapter 207), epilepsy (Chapter 372), and acute lymphocytic leukemia (Chapter 168). Many individuals with Down syndrome have congenital heart anomalies (especially endocardial cushion defects, atrial septal defects, and ventricular septal defects; Chapter 55), which in turn introduce a risk of cerebral embolism and stroke. Stroke can also arise from progressive carotid vasculopathy (moyamoya syndrome). About 10 to 20% of individuals with Down syndrome have atlantoaxial instability, and about a third of such individuals later develop premature cervical spondylosis, thereby further increasing the risk of spinal cord dysfunction. Approximately 1 to 2% of individuals with Down syndrome develop symptomatic spinal cord dysfunction.

The gene encoding amyloid precursor protein is on chromosome 21, and a mutation of this gene is responsible for a hereditary form of Alzheimer disease (Chapter 371). By age 40, many individuals with Down syndrome have beta amyloid brain plaques and tau tangles. An estimated 30% of individuals with Down syndrome develop dementia by age 60 years and 50% by age 70 years. The baseline cognitive impairment of individuals with Down syndrome can make early diagnosis of dementia challenging. Many people initially present not with memory loss but with diminished attention, loss of enthusiasm, behavior change, or withdrawal.

The diagnosis is usually clinically evident, but it should be confirmed by chromosomal analysis.

TREATMENT

No targeted therapy currently exists for Down syndrome. Nevertheless, the prognosis for these individuals has improved considerably owing to improved recognition and management of conditions such congenital heart disease, spine defects, and leukemia.[16] Screening for cervical spine instability is recommended before general anesthesia and before allowing participation in activities that might aggravate atlantoaxial instability. It is important to eliminate potentially treatable causes of cognitive change, particularly hypothyroidism (Chapter 207). Appropriate educational programs, good medical care, and a supportive environment allow most patients to lead enjoyable lives.

NEUROCUTANEOUS DISORDERS

Neurocutaneous syndromes are congenital, often hereditary, disorders that feature lesions of both the skin and the nervous system.[17] Although these disorders have distinctive clinical findings and unique pathogenic mechanisms (Table 385-2), the term neurocutaneous syndrome has persisted in part because it facilitates recognition of these rare conditions.

TUBEROUS SCLEROSIS COMPLEX

The incidence of tuberous sclerosis complex is about 1 in 6000. Tuberous sclerosis complex is inherited as an autosomal dominant trait, although sporadic mutations account for up to 75% of the affected patients. The two tuberous sclerosis complex genes are *TSC1* at 9q34.3 (coding for hamartin) and *TSC2* at 16p13.3 (coding for tuberin). A mutation of either gene leads to upregulation of the mammalian target of rapamycin (mTOR), which promotes cell growth, proliferation, neuronal migration, and angiogenesis.[18] Although the clinical manifestations are similar, *TSC2* mutations tend to cause a more severe phenotype than *TSC1* mutations.

CLINICAL MANIFESTATIONS AND DIAGNOSIS

Multiple organs can be affected, including the brain (cortical tubers, subependymal giant cell astrocytomas), heart (cardiac rhabdomyomas), skin (facial angiofibromas, hypomelanotic ["ash leaf"] macules, shagreen patches, and ungual fibromas), kidneys (renal angiomyolipomas), eye (retinal hamartomas), and lung (lymphangioleiomyomatosis; Chapter 78).[19] Brain imaging typically shows subependymal nodules and cortical tubers (Fig. 385-5). The manifestations of tuberous sclerosis complex are highly variable, even among affected members of the same family, and many of its complications are age-related. Cardiac rhabdomyomas typically present as obstructive heart failure in neonates. Seizures, often infantile spasms, usually begin during the first year of life, then persist. Lymphangioleiomyomatosis often presents with a spontaneous pneumothorax (Chapter 86) and, if untreated, can progress to respiratory failure. It is strikingly more common among women and usually remains asymptomatic until adolescence or adulthood.

The diagnosis of tuberous sclerosis complex is generally apparent from the clinical manifestations (Table 385-3), but genetic testing is useful in atypical cases and for genetic counseling.

TREATMENT

The mTOR inhibitors everolimus and sirolimus have dramatically altered the natural history of tuberous sclerosis complex. Everolimus (10 mg/day) reduces the size of angiomyolipomas in about 40% of treated patients, and everolimus (titrated to 5 to 15 ng/mL) also reduces the size of subependymal giant cell astrocytomas by at least 50% in about one third of treated patients.

Unfortunately, lesions promptly regrow when the medication is halted. Topical rapamycin can shrink facial angiofibromas,[A3] and the topical combination of 0.1% rapamycin plus 0.0003% calcitriol may be even better.[A4] Sirolimus (under expert supervision at a typical adult maintenance dose of 2 mg/day) is also approved for use in individuals with lymphangioleiomyomatosis.

Everolimus is also approved for treatment of intractable epilepsy due to tuberous sclerosis complex,[A5] but it is used infrequently due to its cost and limited effectiveness. Increasing evidence supports starting treatment of tuberous sclerosis complex-related epilepsy even before the onset of clinical seizures to reduce the severity of the epilepsy and the associated cognitive impairment.[A6] Vigabatrin is recommended for the initial treatment of infantile spasms due to tuberous sclerosis complex. If the onset of seizures can be localized to one or two areas of cortical dysplasia, surgical resection may be effective.

TABLE 385-2 SELECTED NEUROCUTANEOUS DISORDERS

DISORDER	INHERITANCE	GENE/CHROMOSOME	CLINICAL MANIFESTATIONS
Tuberous sclerosis	AD	*TSC1*/9q34.4 *TSC2*/16p13.3	Cutaneous: Hypomelanotic macules, facial angiofibromas, periungual fibromas, shagreen patch, ungual fibromas Neurologic: Epilepsy (often infantile spasms), multiple subependymal nodules, multifocal cortical dysplasias, cognitive impairment, autism spectrum disorder; giant cell astrocytoma Other: Lymphangioleiomyomatosis, renal angiomyolipomas, retinal hamartomas, cardiac rhabdomyomas
Neurofibromatosis 1	AD	*NF1*/17q11.2	Cutaneous: Café-au-lait spots, axillary freckling, cutaneous neurofibromas Neurologic: Learning disorders, attention deficit disorder, cerebral vasculopathy, optic nerve glioma, and other cerebral tumors Other: Lisch nodules of the iris, pheochromocytoma, renal artery stenosis, macrocephaly, skeletal anomalies
Neurofibromatosis 2	AD	*NF2*/22q12.2	Cutaneous: Plaque-like intracutaneous tumor; nodular nerve tumors; café-au-lait macules (in about 40%) Neurologic: Bilateral cranial nerve VIII schwannomas with progressive deafness; other tumors, including meningiomas, ependymomas, and astrocytomas Other: Cataracts
Sturge-Weber syndrome	Sporadic (SM)	*GNAQ*/9q21	Cutaneous: Upper facial port-wine nevus Neurologic: Leptomeningeal angioma, epilepsy, variable cognitive impairment Other: Glaucoma
Hereditary hemorrhagic telangiectasia (Chapter 159)	AD	*ENG*/9q34.11 *ALK1*/12q13 Rare other loci	Cutaneous: Telangiectasias of nasal mucosa, tongue, earlobes, extremities Neurologic: Cerebral arteriovenous malformation; paradoxical embolism with stroke; cerebral abscess Other: Pulmonary arteriovenous fistulas; nosebleeds; gastrointestinal hemorrhage
Ataxia telangiectasia (Chapter 231)	AR	*ATM*/11q22.3	Cutaneous: Telangiectasias especially of the sclera, face and the antecubital and popliteal fossa Neurologic: Early-onset progressive ataxia and oculomotor apraxia; later onset of chorea and dystonia Other: Deficient immunoglobulins with frequent infections; risk of leukemia, lymphoma and other malignancies
PHACE syndrome	Sporadic (Likely SM)	Unknown	Cutaneous: Hemangiomas of face and scalp Neurologic: Cerebellar anomalies; anomalies of the brain arteries Other: Female predominance; anomalies of the heart, eye, and sternum
Pseudoxanthoma elasticum (Chapter 239)	AR	*ABCC6*/16p13.11	Cutaneous: Plaque-like yellowish lesions of the neck, axillae, and popliteal or antecubital fossae Neurologic: Cerebral vasculopathy with single or multiple infarctions, intracranial aneurysms Other: Angioid retinal streaks with retinal hemorrhage or retinal detachment, gastrointestinal hemorrhage
Neurocutaneous melanosis	Sporadic (SM)	*NRAS*/1p13.2	Cutaneous: Giant melanocytic nevus, often with satellite nevi that occasionally undergo transformation to melanoma. Neurologic: Melanosis of CNS, occasional hypotonia and epilepsy, rare melanoma
Incontinentia pigmenti	XLD	*IKBKG*/Xq28	Cutaneous: Inflammatory vesicular rash (neonates) evolving to verrucous lesions, then a swirling marbled hyperpigmentation pattern in older patients Neurologic: Recurrent neonatal strokes with cystic encephalomalacia, variable epilepsy and cognitive impairment Other: Dental anomalies, thin hair, retinal vascular changes and risk of retinal detachment
Menkes disease	XLR	*ATP7A*/Xq21.1	Cutaneous: Sparse fragile hair with characteristic kinky appearance Neurologic: Severe epileptic encephalopathy and profound cognitive impairment Other: Arterial tortuosity, growth failure

AD = autosomal dominant; AR = autosomal recessive; CNS = central nervous system; PHACES = **P**osterior fossa malformations, **H**emangiomas of face and scalp, **A**rterial anomalies (cerebral or cervical vessels), **C**ardiac anomalies, **E**ye anomalies, **S**ternal anomalies; SM = somatic mosaicism; XLD = X-linked dominant; XLR = X-linked recessive.

NEUROFIBROMATOSIS TYPE 1

Neurofibromatosis type 1 is an autosomal dominant disorder with a prevalence of 1 in 3000 births. Almost 50% of the cases arise from sporadic mutations. The *NF1* gene (chromosome 17q11.2) expresses neurofibromin, a tumor suppressor protein. Loss of neurofibromin expression leads to dysregulation of cell growth and differentiation.[20] There is no consistent genotype-phenotype correlation.

About 50% of affected patients have learning disabilities. Subcutaneous neurofibromas may be disfiguring and can be painful. Patients may have plexiform neurofibromas, tibial dysplasia, and vasculopathy. Affected patients also have an increased risk of malignant peripheral nerve sheath tumors and central nervous system gliomas, as well as other tumors, with a 60% lifetime risk of cancer. Other manifestations include attention deficit disorder, macrocephaly, and epilepsy. Important complications include scoliosis, gastrointestinal neurofibromas, pheochromocytomas (Chapter 209), and renal artery stenosis (Chapter 110).

The criteria for the diagnosis of neurofibromatosis type 1 include two or more of the following: (1) six or more café-au-lait macules (Fig. 385-6) larger than 5 mm in prepubertal patients or more than 15 mm in postpubertal individuals, (2) two or more neurofibromas (Fig. 385-7) of any type or one plexiform neurofibroma, (3) axillary or inguinal freckling, (4) sphenoid bone dysplasia, (5) optic nerve glioma, (6) Lisch nodules (pigmented hamartomas in the iris), and (7) a family history of neurofibromatosis type 1. Mutational analysis is not required for diagnosis but may be useful in individuals with less severe or atypical manifestations.

TREATMENT

Many individuals with neurofibromatosis type 1 do not require treatment, and many others need treatment only for low-level symptoms. However, all patients require periodic surveillance because of these associated risks (Table 385-4). Genetic counseling is recommended for all patients and their families.

Surgery can be successful for subcutaneous, intraspinal, or intracranial lesions. The MEK inhibitor selumetinib (25 mg/m^2 twice daily in 28-day cycles)[21] can reduce the size of inoperable plexiform neurofibromas.[A7] Optic nerve gliomas may be treated with cisplatin or temozolomide. Radiation is not recommended. Selumetinib and other MEK inhibitors have also shown promise in individuals with low-grade astrocytoma, spinal neurofibromas, and even cognitive dysfunction.[22]

NEUROFIBROMATOSIS TYPE 2

Neurofibromatosis type 2 is inherited as autosomal dominant trait and occurs in approximately 1 in 50,000 individuals, with clinical onset usually in young adulthood. Although classified as a subtype of neurofibromatosis and usually included with the neurocutaneous disorders, neurofibromatosis type 2 bears little resemblance to neurofibromatosis type 1. The *NF2* gene, which is located on chromosome 22q, codes for merlin, a cytoskeletal protein. Most patients eventually develop bilateral cranial nerve VIII nerve schwannomas (Fig. 385-8), although these tumors often begin as unilateral lesions. Multiple meningiomas are also common,[23] whereas ependymomas and gliomas occur less frequently.

Skin lesions are present in a minority of patients with neurofibromatosis type 2, and the diagnosis is based on the following criteria: (1) bilateral cranial nerve VIII nerve tumors detected by MRI, (2) a family member with either neurofibromatosis type 2 or unilateral cranial nerve VIII nerve schwannoma, and (3) juvenile posterior subcapsular lens opacities.

TREATMENT

Removal of the schwannomas and other tumors is usually indicated, although preservation of hearing is challenging even with early surgery. Bevacizumab (a vascular endothelial growth factor inhibitor at 5 mg/kg intravenously every 2 weeks) can improve hearing in some patients who have vestibular schwannomas, but its role remains uncertain.[24] Family genetic counseling is often helpful.

STURGE-WEBER SYNDROME

Sturge-Weber syndrome is characterized by an upper facial vascular nevus (port-wine stain; Fig. 385-9), a leptomeningeal angioma, and variable ocular abnormalities (glaucoma and choroidal hemangioma). The disorder occurs sporadically in approximately 1 in 20,000 births. The syndrome results from a somatic mutation of *GNAQ* on chromosome 9q21.[25]

CLINICAL MANIFESTATIONS AND DIAGNOSIS

The clinical manifestations of Sturge-Weber syndrome are highly variable. Only individuals with a port-wine stain of the upper face and periorbital area develop the leptomeningeal angioma, but only about 15% of people with an upper facial nevus have brain involvement. Glaucoma can occur even in the absence of neurologic involvement. Neurologic manifestations most often include focal-onset epilepsy and variable cognitive impairment. Less common features include hemiparesis, hemianopia, or other focal finings. Calcium deposition within the cerebral cortical layers explains the classic "trolley track" radiographic calcification pattern of Sturge-Weber syndrome, although this finding is often absent, especially in infants.

The diagnosis of Sturge-Weber syndrome rests on the clinical findings because the somatic mosaic gene mutation is not detectable on blood-based

TABLE 385-3 DIAGNOSTIC CRITERIA FOR TUBEROUS SCLEROSIS COMPLEX

Definite—Two major features or one major feature plus two minor features
Probable—One major feature plus one minor feature
Possible—One major feature or two or more minor features

MAJOR FEATURES
Facial angiofibromas or forehead plaque
Nontraumatic ungual or periungual fibromas
More than three hypomelanotic macules (ash leaf spots)
Shagreen patch (connective tissue nevus)
Multiple retinal nodular hamartomas
Cortical tuber
Subependymal nodule
Subependymal giant cell astrocytoma
Cardiac rhabdomyoma, single or multiple
Lymphangiomyomatosis
Renal angiomyolipoma
MINOR FEATURES
Multiple dental enamel pits
Hamartomatous rectal polyps
Bone cysts
Cerebral white matter radial migration lines
Gingival fibromas
Nonrenal hamartoma
Retinal achromic patch
"Confetti" skin lesions
Multiple renal cysts

Reproduced with permission from Northrup H, Aronow ME, Bebin EM, et al. Updated international tuberous sclerosis complex diagnostic criteria and surveillance and management recommendations. *Pediatr Neurol.* 2021;123:50-66.

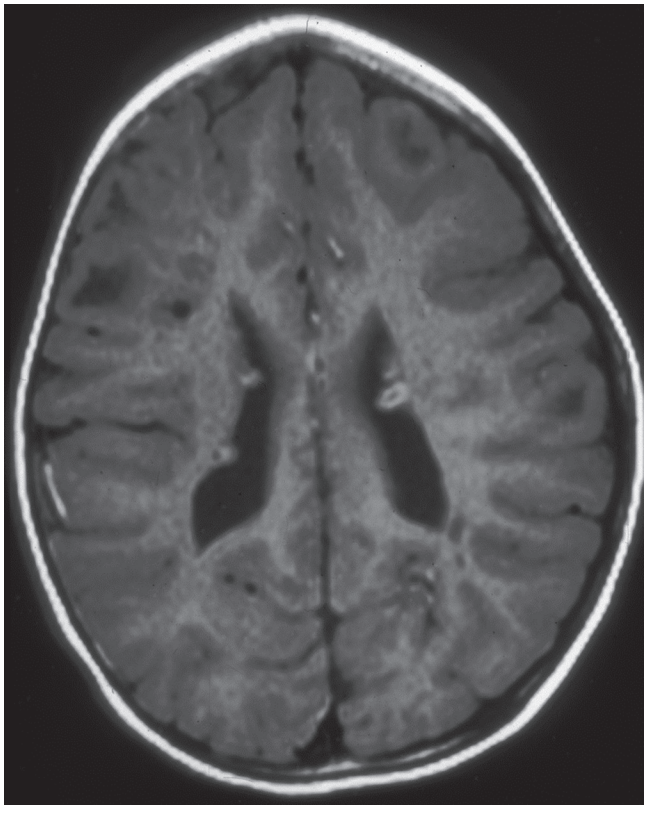

FIGURE 385-5. Magnetic resonance imaging depicts subependymal nodules and multiple cortical tubers in a patient with tuberous sclerosis complex.

FIGURE 385-6. Café-au-lait macules in a child with neurofibromatosis type 1. Note also the presence of axillary freckling.

FIGURE 385-7. **Multiple neurofibromas covering the back of a patient with neurofibromatosis type 1.**

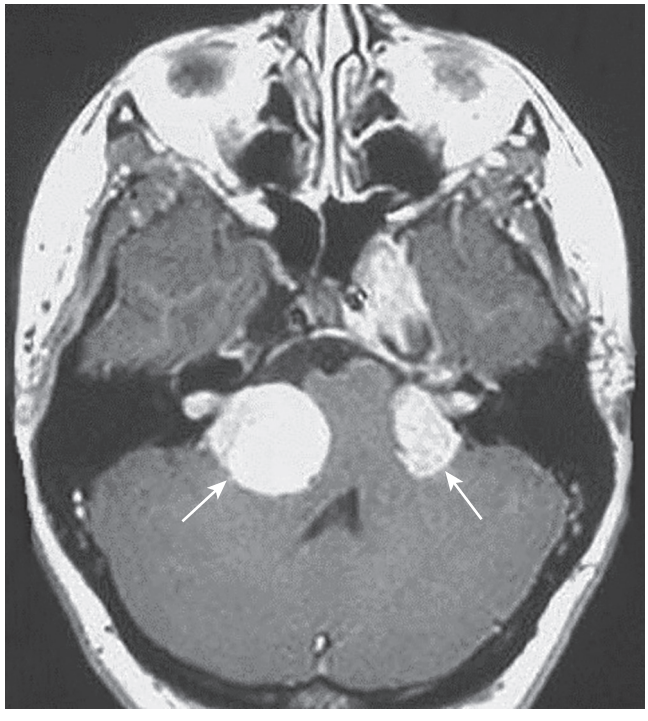

FIGURE 385-8. **Bilateral cranial nerve VIII nerve schwannomas *(arrows)* due to neurofibromatosis type 2.**

TABLE 385-4 RECOMMENDED SURVEILLANCE IN PATIENTS WITH NEUROFIBROMATOSIS TYPE 1

Annual physical examination by a physician who is familiar with the individual and with the disease
Annual ophthalmologic examination in early childhood, less frequent examination in older children and adults
Regular developmental assessment by screening questionnaire (in childhood)
Regular blood pressure monitoring
Other studies only as indicated on the basis of clinically apparent signs or symptoms
Monitoring of those who have abnormalities of the central nervous system, skeletal system, or cardiovascular system by an appropriate specialist

Adapted from Miller DT, Freedenberg D, Schorry E, et al. Health supervision for children with neurofibromatosis type 1. *Pediatrics*. 2019;143:e20190660.

FIGURE 385-9. **Sturge-Weber syndrome.** This man has a classic capillary hemangioma affecting the right face and extending posteriorly beneath the hairline. The hemangioma often thickens as the patient ages, thereby resulting in the nodular appearance shown here.

gene testing. The upper facial nevus is obvious at birth. Neuroimaging can identify brain involvement prior to the onset of neurologic symptoms. Computed tomography can demonstrate the brain calcification, but MRI with contrast more reliably demonstrates the intracranial vascular lesion.

TREATMENT

Laser treatments can render the nevus less obvious. Periodic screening for glaucoma is essential, even into adulthood. Uncontrolled epilepsy likely contributes to long-term cognitive impairment; if antiepileptic drugs are ineffective, surgical excision of epileptogenic region may be considered.

PROGNOSIS

The prognosis of individuals with Sturge-Weber syndrome varies depending on the severity of their manifestations. Patients with good seizure control and near-normal cognition function normally and can have a normal lifespan. Individuals with intractable epilepsy and severe intellectual disability, in contrast, have a shorter life expectancy but can still live well into adulthood.

VON HIPPEL-LINDAU DISEASE

Von Hippel-Lindau disease is an autosomal dominant disorder caused by a defective tumor suppressor *(VHL)* at chromosome 3p25-p26.[26] Clinical manifestations, which usually begin in the third or fourth decade, include retinal angiomas (with retinal inflammation and detachment), hemangioblastomas of the brain (usually cerebellar) and spinal cord, angiomas of the liver and kidney, renal cell carcinomas (Chapter 182), pheochromocytomas (Chapter 209), endolymphatic sac tumors, and cysts of the pancreas, kidney, liver, and epididymis. Retinal and cerebellar symptoms (headache, vertigo, vomiting, ataxia, and dysmetria) are common.

Clinical diagnosis is suggested based on the presence of more than one brain hemangioblastoma, one hemangioblastoma with a visceral manifestation of the disease, or one disease manifestation plus a known family history. Genetic testing detects mutations in the *VHL* gene in essentially all affected individuals.

TREATMENT

Recommended surveillance includes an annual ophthalmologic examination, annual blood pressure monitoring, screening for pheochromocytoma (Chapter 209) every 5 years in affected families, and annual abdominal ultrasound examination beginning at age 16 years. Treatment is symptomatic for retinal detachments. Brain tumors (Chapter 175), renal cell carcinomas (Chapter 182), pheochromocytomas (Chapter 209), epididymal tumors (Chapter 185), and endolymphatic sac tumors should be treated surgically, but smaller central nervous system tumors may be treated by gamma knife. Pazopanib (a tyrosine kinase inhibitor that inhibits angiogenesis) at 800 mg per day may be useful in patients who have progressive lesions,[27] and belzutifan (120 mg daily) has shown promise for treating renal cell carcinomas in this syndrome.[28]

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386 AUTONOMIC DISORDERS

EDUARDO E. BENARROCH AND ROY FREEMAN

SYSTEMIC AUTONOMIC DISORDERS

DEFINITION

Autonomic dysfunction, which is an important cause of disability, accompanies many diseases that affect the central or peripheral nervous system. It may manifest as autonomic failure or autonomic hyperactivity, may be generalized or focal, and may have a subacute, chronic progressive, or intermittent temporal profile.[1] The prognosis of autonomic disorders depends on the underlying condition.

EPIDEMIOLOGY

The most common causes of autonomic failure are neurodegenerative disorders and autonomic neuropathies. Multiple system atrophy (Chapters 378 and 379), which is the most common central neurodegenerative disorder associated with severe autonomic failure,[2] has an estimated incidence of 0.6 per 100,000 persons per year and a prevalence of 3 per 100,000 in persons older than age 50 years. Autonomic failure may also occur in the other central neurodegenerative diseases, such as Parkinson disease (Chapter 378) and Lewy body dementia (Chapter 371), associated with deposition of the protein alpha-synuclein.

By comparison, the most common cause of autonomic neuropathy in the developed world is diabetes mellitus[3] (Chapter 210), but clinically important peripheral neurodegenerative disease is also seen with amyloid deposition (Chapter 174) as well as inherited neuropathies (Chapter 388). After 10 years with type 2 diabetes (Chapter 210), autonomic impairment is detected by abnormal heart rate variability in 65% of patients, and orthostatic hypotension is seen in about 25% of patients. The incidence of light chain (AL) amyloidosis (Chapter 174) is approximately 12 cases per million persons per year, with an estimated prevalence of 30,000 to 45,000 cases per million persons; peripheral nerve involvement occurs in 22% of cases.[4] The incidence of variant amyloid transthyretin (ATTR) amyloidosis is estimated at 0.3 cases per million persons per year, with an estimated prevalence of 5.2 cases per million persons. Although rare, an important cause of hereditary autonomic neuropathy is hereditary sensory and autonomic neuropath type III (HSAN-III), also known as familial dysautonomia or Riley-Day syndrome. This autosomal recessive disorder is seen primarily in Ashkenazi Jewish children, with an incidence of 1 in 3700 live births and a carrier frequency of 1 in 32 individuals in this population.

PATHOBIOLOGY

The three components of the autonomic system are the sympathetic, parasympathetic, and enteric nervous systems.[5] The sympathetic and parasympathetic outputs are mediated by preganglionic neurons located in the spinal cord or brainstem, as well as by neurons that are located in autonomic ganglia and project to the target organs. Preganglionic neurons activate the autonomic ganglion neurons by releasing acetylcholine, which acts via ganglion-type nicotinic acetylcholine receptors. Sympathetic output depends on preganglionic neurons that are located at the T1-L2 segments of the spinal cord and that activate neurons in the paravertebral and prevertebral ganglia, as well as in the adrenal medulla. The sympathetic division is critical for maintenance of arterial blood pressure, regulation of regional blood flow, thermoregulation, the response to exercise, homeostatic challenges, and external stressors.[6] The primary sympathetic neurotransmitter, which is norepinephrine, acts via $\alpha 1$ receptors to elicit vasoconstriction, pupillary dilation, and smooth muscle contraction in the bladder detrusor muscle and vas deferens; $\beta 1$ receptors to elicit cardiac stimulation (tachycardia and increased stroke volume); and $\beta 2$ receptors to elicit relaxation of vascular and visceral smooth muscle. The sympathetic output to the sweat glands is mediated by acetylcholine acting via muscarinic M3 receptors.

Parasympathetic output is critical for reflex control of organs via their effects on local ganglia that are close to or within the target organ. Output from the Edinger-Westphal nucleus, mediated by the oculomotor nerve via the ciliary ganglion, controls accommodation and the pupillary light reflex. Outputs from the salivatory nuclear complex—mediated by the facial and glossopharyngeal nerves via the sphenopalatine, submaxillary, submandibular, and otic ganglia—control lacrimation and salivation. The vagus nerve provides the most widespread preganglionic parasympathetic output to local respiratory, cardiac, and enteric ganglia. The dorsal motor nucleus of the vagus controls motility and secretion in the respiratory and gastrointestinal tracts and also contributes to control of the heart. Neurons located in the nucleus ambiguus provide vagal output to the heart (cardiovagal output) that is critical for the beat-to-beat control of the heart rate. Vagal outputs inhibit heart rate and atrioventricular conduction via M2 receptors. The parasympathetic output is also mediated by noncholinergic neurons that trigger smooth muscle relaxation and vasodilation primarily via release of nitric oxide and vasoactive intestinal polypeptide.

The sacral preganglionic nucleus innervates the pelvic organs and promotes bladder detrusor contraction for micturition, rectal contraction for defecation, and vasodilation of erectile tissues. The enteric nervous system mediates local reflexes for peristalsis and secretion, both independently and under sympathetic and parasympathetic modulation. The primary neurotransmitter of most parasympathetic and enteric neurons is acetylcholine, which acts via M3 receptors, which in turn promote smooth muscle contraction and glandular secretion.

The two main influences controlling sympathetic and parasympathetic output are reflexes triggered by visceral afferent nerves and the descending modulatory influence from the hypothalamus and brainstem. The baroreceptor reflex (baroreflex) is a critical feedback mechanism for buffering changes in arterial pressure. Inputs from the carotid sinus and baroreceptors in the aortic arch, activated by an increase in pulse pressure, reach the nucleus of the solitary tract, which triggers two responses that reduce blood pressure: activation of vagal output to the heart, thereby leading to decrease of the heart rate; and inhibition of sympathetic output to splanchnic and muscle blood vessels leading to a decrease of total peripheral resistance. Upon standing, unloading of the baroreceptors triggers sympathetically mediated vasoconstriction that limits venous pooling in the abdomen and lower limbs. Failure of this efferent baroreflex sympathetic vasoconstrictor response results in neurogenic orthostatic hypotension (Chapter 49). The primary causes are lesions that affect sympathoexcitatory neurons in the rostral ventrolateral medulla, preganglionic sympathetic neurons, and/or noradrenergic ganglion neurons or their

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386 AUTONOMIC DISORDERS

EDUARDO E. BENARROCH AND ROY FREEMAN

SYSTEMIC AUTONOMIC DISORDERS

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By comparison, the most common cause of autonomic neuropathy in the developed world is diabetes mellitus[3] (Chapter 210), but clinically important peripheral neurodegenerative disease is also seen with amyloid deposition (Chapter 174) as well as inherited neuropathies (Chapter 388). After 10 years with type 2 diabetes (Chapter 210), autonomic impairment is detected by abnormal heart rate variability in 65% of patients, and orthostatic hypotension is seen in about 25% of patients. The incidence of light chain (AL) amyloidosis (Chapter 174) is approximately 12 cases per million persons per year, with an estimated prevalence of 30,000 to 45,000 cases per million persons; peripheral nerve involvement occurs in 22% of cases.[4] The incidence of variant amyloid transthyretin (ATTR) amyloidosis is estimated at 0.3 cases per million persons per year, with an estimated prevalence of 5.2 cases per million persons. Although rare, an important cause of hereditary autonomic neuropathy is hereditary sensory and autonomic neuropath type III (HSAN-III), also known as familial dysautonomia or Riley-Day syndrome. This autosomal recessive disorder is seen primarily in Ashkenazi Jewish children, with an incidence of 1 in 3700 live births and a carrier frequency of 1 in 32 individuals in this population.

PATHOBIOLOGY

The three components of the autonomic system are the sympathetic, parasympathetic, and enteric nervous systems.[5] The sympathetic and parasympathetic outputs are mediated by preganglionic neurons located in the spinal cord or brainstem, as well as by neurons that are located in autonomic ganglia and project to the target organs. Preganglionic neurons activate the autonomic ganglion neurons by releasing acetylcholine, which acts via ganglion-type nicotinic acetylcholine receptors. Sympathetic output depends on preganglionic neurons that are located at the T1-L2 segments of the spinal cord and that activate neurons in the paravertebral and prevertebral ganglia, as well as in the adrenal medulla. The sympathetic division is critical for maintenance of arterial blood pressure, regulation of regional blood flow, thermoregulation, the response to exercise, homeostatic challenges, and external stressors.[6] The primary sympathetic neurotransmitter, which is norepinephrine, acts via $\alpha 1$ receptors to elicit vasoconstriction, pupillary dilation, and smooth muscle contraction in the bladder detrusor muscle and vas deferens; $\beta 1$ receptors to elicit cardiac stimulation (tachycardia and increased stroke volume); and $\beta 2$ receptors to elicit relaxation of vascular and visceral smooth muscle. The sympathetic output to the sweat glands is mediated by acetylcholine acting via muscarinic M3 receptors.

Parasympathetic output is critical for reflex control of organs via their effects on local ganglia that are close to or within the target organ. Output from the Edinger-Westphal nucleus, mediated by the oculomotor nerve via the ciliary ganglion, controls accommodation and the pupillary light reflex. Outputs from the salivatory nuclear complex—mediated by the facial and glossopharyngeal nerves via the sphenopalatine, submaxillary, submandibular, and otic ganglia—control lacrimation and salivation. The vagus nerve provides the most widespread preganglionic parasympathetic output to local respiratory, cardiac, and enteric ganglia. The dorsal motor nucleus of the vagus controls motility and secretion in the respiratory and gastrointestinal tracts and also contributes to control of the heart. Neurons located in the nucleus ambiguus provide vagal output to the heart (cardiovagal output) that is critical for the beat-to-beat control of the heart rate. Vagal outputs inhibit heart rate and atrioventricular conduction via M2 receptors. The parasympathetic output is also mediated by noncholinergic neurons that trigger smooth muscle relaxation and vasodilation primarily via release of nitric oxide and vasoactive intestinal polypeptide.

The sacral preganglionic nucleus innervates the pelvic organs and promotes bladder detrusor contraction for micturition, rectal contraction for defecation, and vasodilation of erectile tissues. The enteric nervous system mediates local reflexes for peristalsis and secretion, both independently and under sympathetic and parasympathetic modulation. The primary neurotransmitter of most parasympathetic and enteric neurons is acetylcholine, which acts via M3 receptors, which in turn promote smooth muscle contraction and glandular secretion.

The two main influences controlling sympathetic and parasympathetic output are reflexes triggered by visceral afferent nerves and the descending modulatory influence from the hypothalamus and brainstem. The baroreceptor reflex (baroreflex) is a critical feedback mechanism for buffering changes in arterial pressure. Inputs from the carotid sinus and baroreceptors in the aortic arch, activated by an increase in pulse pressure, reach the nucleus of the solitary tract, which triggers two responses that reduce blood pressure: activation of vagal output to the heart, thereby leading to decrease of the heart rate; and inhibition of sympathetic output to splanchnic and muscle blood vessels leading to a decrease of total peripheral resistance. Upon standing, unloading of the baroreceptors triggers sympathetically mediated vasoconstriction that limits venous pooling in the abdomen and lower limbs. Failure of this efferent baroreflex sympathetic vasoconstrictor response results in neurogenic orthostatic hypotension (Chapter 49). The primary causes are lesions that affect sympathoexcitatory neurons in the rostral ventrolateral medulla, preganglionic sympathetic neurons, and/or noradrenergic ganglion neurons or their

ABSTRACT

The autonomic nervous system is affected by many diseases of the central and peripheral nervous systems. Although this involvement is often mild or subclinical, autonomic involvement sometimes is prominent and a source of major disability. Autonomic dysfunction may manifest as autonomic failure or autonomic hyperactivity, may be generalized or focal, and may have a subacute, chronic progressive, or intermittent temporal profile. The presenting features include impairment of cardiovascular, gastrointestinal, urogenital, thermoregulatory, sudomotor, and pupillomotor function. The accurate diagnosis of the autonomic dysfunction is enhanced by imaging studies, physiologic tests, body fluid biomarkers, and structural studies of autonomic cutaneous innervation.

KEYWORDS

sympathetic nervous system
parasympathetic nervous system
enteric nervous system
central autonomic neurodegeneration
peripheral autonomic neuropathy

axons, and disorders that affect norepinephrine synthesis (e.g., dopamine-β-hydroxylase deficiency) or α1 receptor blockade.

The sympathetic output to the skin is critical for thermoregulatory sweating in response to heat and vasoconstriction in response to cold. Lesions that affect the descending pathway from the hypothalamus to the intermediolateral cell column, cholinergic sympathetic neurons or their axons, or that cause muscarinic receptor blockade impair sweating, thereby leading to anhidrosis and heat intolerance.

Cranial parasympathetic failure manifests with an impaired pupillary response to light as well as impaired lacrimation and salivation. Causes include involvement of individual cranial nerves, parasympathetic ganglion neurons, or muscarinic receptor blockade.

The vagus nerve is frequently affected in length-dependent neuropathies. Vagal impairment primarily affects upper gastrointestinal motility and beat-to-beat control of heart rate. The sacral preganglionic nucleus, which promotes contraction of the bladder detrusor or rectal sphincters, participates in reciprocal inhibitory interactions with the Onuf nucleus that is located at the S1-S3 levels and that innervate the external sphincter and pelvic floor. These interactions, which are controlled by descending inputs from the pons, allow coordination of bladder or rectal contraction and external sphincter relaxation. A neurogenic bladder (Chapter 115) can manifest with detrusor overactivity, detrusor-sphincter dyssynergia, or detrusor activity with urinary retention, depending on the level of the lesion.

Motility in the gut involves peristaltic reflexes that are mediated by the enteric nervous system under the excitatory parasympathetic and inhibitory sympathetic modulation. Disorders affecting enteric ganglia or their extrinsic control primarily result in constipation (Chapter 118) but are occasionally associated with diarrhea (Chapter 126) and fecal incontinence (Chapter 131).

Pathogenesis

Autonomic disorders, which can affect the sympathetic, parasympathetic, or enteric nervous systems, either in isolation or in various combinations, can be classified on the basis of their localization and underlying pathologic substrate (Table 386-1). The main causes of autonomic disorders include neurodegenerative synucleinopathies, autonomic ganglionopathies, small fiber peripheral neuropathies, and focal lesions.

Neurodegenerative synucleinopathies that may manifest with prominent progressive autonomic failure[7] include multiple system atrophy, Parkinson disease (Chapter 378), and dementia with Lewy bodies (Chapter 371). These conditions are characterized by the accumulation of abnormally misfolded α-synuclein aggregates that propagate in a prion-like fashion between neighboring cells, thereby leading to progressive disease in the central and peripheral nervous systems.

A second major group of disorders associated with generalized autonomic failure are the autoimmune ganglionopathies.[8] Damage to the autonomic ganglia, which are a major target of autoimmune disorders, produces subacute, generalized autonomic failure. The prototypical example is autoimmune autonomic ganglionopathy, which is caused by antibodies directed against ganglion-type nicotinic acetylcholine receptors and affects transmission at sympathetic, parasympathetic, and enteric ganglia.[9]

The third major group of disorders associated with autonomic failure are small fiber neuropathies[10] (Chapter 388), which affect unmyelinated and small myelinated axons from nociceptors as well as autonomic ganglionic neurons. Autonomic impairment is commonly associated with neuropathic pain and loss of sensation to pain and temperature. Some of these autonomic neuropathies are hereditary, such as hereditary transthyretin-related amyloidosis (hATTR) polyneuropathy (formerly known as familial amyloid polyneuropathy), which is due to mutations of the transthyretin (*TTR*) gene (Chapter 174). Less frequent examples are hereditary sensory and autonomic neuropathies (HSANs), such as HSAN type III (familial dysautonomia) associated with mutations of the *ELP1/IKBKAP* gene; sodium channelopathies such as those associated with variants in the genes encoding sodium channels $Na_V1.7$ (*SCN9A*); and Fabry disease associated with mutations of the *GLA* gene that encodes α-galactosidase (Chapter 192). Focal disorders affecting the central or peripheral nervous system may produce local autonomic manifestations.

CLINICAL MANIFESTATIONS

The classical clinical manifestations of autonomic disorders are related to autonomic failure, but other types of autonomic dysfunction may dominate the clinical picture.

TABLE 386-1 CLASSIFICATION OF AUTONOMIC DISORDERS

CENTRAL NERVOUS SYSTEM DISORDERS
Neurodegenerative disorders (synucleinopathies)
Multiple system atrophy
Parkinson disease
Dementia with Lewy bodies
Autoimmune encephalitis
Focal brain disorders
Traumatic brain injury
Insular stroke
Temporal lobe seizures
Hypothalamic disorders
Wernicke encephalopathy
Brainstem stroke
Syringobulbia
Focal spinal cord disorders
Spinal cord injury
Multiple sclerosis
Neuromyelitis optica
Syringomyelia
GANGLIONOPATHIES
Pure autonomic failure
Autoimmune ganglionopathies
Autoimmune autonomic ganglionopathy
Paraneoplastic ganglionopathy
Sjögren syndrome
PERIPHERAL NEUROPATHIES
Autoimmune neuropathies
Autoimmune sensory and autonomic neuropathy
Guillain-Barré syndrome
Lambert-Eaton myasthenic syndrome
Diabetic autonomic neuropathy
Generalized diabetic autonomic neuropathy
Treatment-induced neuropathy
Amyloid neuropathy
Light chain (AL) amyloidosis
Hereditary amyloid neuropathy including hATTR amyloidosis
Hereditary neuropathies
Hereditary sensory and autonomic neuropathies (HSANs)
Sodium channelopathies
Fabry disease
Metabolic neuropathies
Thiamine deficiency
Vitamin B_{12} deficiency
Toxic neuropathies
Alcohol
Chemotherapeutic agents (e.g., vincristine, taxanes, bortezomib)
Hydrocarbons, organic solvents
Infectious neuropathies
Human immunodeficiency virus
Chagas disease
Severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2)
OUTPUT-SELECTIVE DISORDERS
Horner syndrome
Adie pupil
Harlequin syndrome
Trigemino-autonomic cephalalgia
Ross syndrome
Essential hyperhidrosis
Chronic idiopathic anhidrosis
Complex regional pain syndrome
ORTHOSTATIC INTOLERANCE WITHOUT AUTONOMIC FAILURE
Postural tachycardia syndrome
Reflex (vasovagal) syncope

Autonomic Failure

The most disabling manifestation of autonomic failure is orthostatic hypotension, defined as a sustained reduction in systolic blood pressure of at least 20 mm Hg or a reduction in diastolic blood pressure of at least 10 mm Hg, usually within the first 3 minutes of standing or a head-up tilt on a tilt table.[11] Orthostatic hypotension indicates volume depletion, impaired peripheral vasoconstriction, or both. Symptoms reflect hypoperfusion of the brain (lightheadedness, cognitive slowing, syncope), retina (blurry or dimmed vision), upper body

muscles ("coat hanger pain"), lungs (dyspnea owing to apical hypoperfusion), and, rarely, the heart (angina). These symptoms are typically more severe in the morning and worsen during exercise, after meals (postprandial hypotension) due to splanchnic vasodilation, upon exposure to heat (owing to skin vasodilation), and with prolonged bed rest that results in physical deconditioning. Patients with cognitive impairment may not accurately identify symptoms of organ hypoperfusion. Supine hypertension, defined as systolic blood pressure 140 mm Hg or higher and/or diastolic blood pressure 90 mm Hg or higher, measured after at least 5 minutes of rest in the supine position, occurs in about 50% of patients with neurogenic orthostatic hypotension (Chapter 64). Supine hypertension promotes overnight natriuresis, thereby causing intravascular volume depletion that predisposes to symptomatic orthostasis in the morning.

A second major manifestation of sympathetic failure is widespread anhidrosis, which produces heat intolerance that manifests with lightheadedness, fatigue, and facial flushing upon exposure to a hot environment. Anhidrosis in the feet and hands occurs in small fiber peripheral neuropathies, whereas patchy, non-length-dependent anhidrosis in the trunk and limbs occurs in autonomic ganglionopathies. Focal or regional anhidrosis is associated with compensatory hyperhidrosis, which occurs either adjacent or distant to areas of anhidrosis and leads patients to seek medical attention.

Cranial parasympathetic failure manifests as intolerance to light, dry eyes (xerophthalmia), and dry mouth (xerostomia) (Chapter 393). Upper gastrointestinal dysmotility (Chapter 122) manifests with dysphagia and delayed gastric emptying, thereby producing early satiety, anorexia, nausea, bloating, belching, postprandial vomiting, and pain (Chapter 122). Lower gastrointestinal dysmotility usually manifests with constipation and impaired defecation, but it also can occasionally cause diarrhea. Detrusor overactivity produces urinary urgency with or without incontinence, urinary frequency, and nocturia (Chapter 115). Reduced detrusor activity leads to incomplete bladder emptying, increased postvoid residual, and eventually urinary retention and overflow incontinence.

Orthostatic Intolerance without Autonomic Failure

A frequent cause of orthostatic intolerance is postural tachycardia syndrome (POTS; Chapter 49), which is a heterogeneous condition that is defined by a sustained heart rate increment of more than 30 beats per minute within 10 minutes of standing or head-up tilt, associated with symptoms of cerebral hypoperfusion (e.g., lightheadedness) and sympathetic activation (e.g., palpitations and chest pressure). The standing heart rate is typically greater than 120 beats per minute. Some patients have evidence of a mild autonomic neuropathy affecting the lower limbs. Other mechanisms include hypovolemia, venous pooling, cardiovascular deconditioning, and hyperadrenergic states, which may occur in combination.

Neurally mediated (reflex) syncope (Chapter 49) can be triggered by orthostatic stress as well as by visceral stimuli (e.g., deglutition, micturition, or defecation), cough, pain, and emotional states. It may be preceded by manifestations of sympathetic hyperactivity, such as pallor and diaphoresis. Rarely it may be due to carotid sinus hypersensitivity or a manifestation of glossopharyngeal neuralgia (Chapter 367).

Afferent Baroreflex Failure

Afferent baroreflex failure manifests with wide fluctuations of arterial pressure (Chapter 64). The main causes are prior neck radiation or bilateral neck surgery affecting the carotid sinus, familial dysautonomia (HSAN-III), Guillain-Barré syndrome (Chapter 388), and medullary lesions. Baroreflex failure can result in acute hypertensive crisis immediately following a lesion, but it most commonly manifests with fluctuating hypertension that may develop several months or years after surgical or radiation injury. The hypertensive surges are typically associated with tachycardia, diaphoresis, severe headache, and anxiety, thereby resembling a pheochromocytoma (Chapter 209). Patients may experience hypotension during sedation and sleep, or they may experience orthostatic hypotension in the setting of volume depletion or treatment with vasodilators or sympatholytic drugs. Less frequently, patients may have episodes of hypotension and bradycardia or episodes of orthostatic tachycardia.

Autonomic Hyperactivity

Autonomic hyperactivity, which is a life-threatening manifestation of some neurologic, iatrogenic, and toxic disorders,[12] typically manifests with excessive sympathetic output that leads to tachycardia, hypertension, diaphoresis, piloerection, and pupillary dilatation. Sympathoadrenal hyperactivity may lead to intracerebral hemorrhage (Chapter 377), hypertensive encephalopathy (Chapter 376), posterior reversible encephalopathy syndrome (Chapter 392), takotsubo cardiomyopathy (Chapter 47), pulmonary edema (Chapter 45), and supraventricular or ventricular arrhythmias (Chapters 50, 51, 52, and 53). Major causes include traumatic brain injury (Chapter 368), subarachnoid hemorrhage (Chapter 377), status epilepticus (Chapter 372), autoimmune encephalitis (Chapter 383), autonomic dysreflexia after spinal cord injury (Chapter 368), Guillain-Barré syndrome (Chapter 388), and severe emotional stress (Chapter 362). In some conditions, such as severe traumatic head injury (Chapter 368), tetanus (Chapter 271), malignant hyperthermia (Chapter 400), neuroleptic malignant syndrome (Chapter 402), and serotonin syndrome (Chapter 213), sympathetic hyperactivity is associated with hyperthermia, muscle rigidity, and myoclonus. In isolation, excessive parasympathetic activity is rare, except when temporal lobe seizures cause bradycardia, heart block, or asystole.

Sweating Disorders

Sweating disorders (sudomotor dysfunction) may be the sole manifestation of autonomic disorder.[13] Essential or primary generalized hyperhidrosis is typically most pronounced over the face, neck, and upper trunk. Secondary generalized hyperhidrosis is often associated with drugs or systemic illness. Primary focal hyperhidrosis affects palms, soles, axilla, and sometimes the craniofacial region; it may be exacerbated by anxiety, physical exertion, or heat exposure. Anhidrosis, which refers to the absence of sweating, may occur in central or peripheral autonomic disorders or as a side effect of drugs, most commonly anticholinergic agents. Sympathetic vasomotor and sudomotor dysfunction, which are associated with neuropathic pain, hypesthesia, and allodynia affecting one limb, is the typical manifestation of chronic regional pain syndrome (Chapter 388).

Cranial Autonomic Dysfunction

Cranial autonomic disorders reflect abnormalities in sympathetic outputs via the superior cervical ganglion or parasympathetic outputs via the ciliary, sphenopalatine, or other cranial ganglia. Horner syndrome (Chapter 392), which is a unilateral deficit of sympathetic innervation of the eye and face, results in miosis, mild ptosis, and facial anhidrosis (Chapter 392). It is an important clue to carotid artery dissection (Chapter 376), apical lung neoplasm (Pancoast syndrome; Chapter 177), cervical myelopathy (Chapter 369), or brainstem stroke (Chapters 375, 376 and 377). Hemifacial flushing or sweating in response to heat stress, emotion, or exercise, known as harlequin syndrome, indicates a contralateral sympathetic sudomotor deficit caused by a lesion that affects the superior cervical ganglion.

Lesions affecting the ciliary ganglion produce an Adie pupil (Chapter 392), which is an unreactive pupil that eventually develops a tonic response to light and accommodation. An Adie pupil may occur in isolation, in association with symmetrical or asymmetrical loss of muscle stretch reflexes (Holmes-Adie syndrome), or in Ross syndrome, which is a chronic autonomic disorder consisting of the triad of ipsilateral or bilateral tonic pupils, tendon hyporeflexia, and segmental body anhidrosis. Trigemino-autonomic cephalalgias, including cluster headache, are typically associated with ipsilateral miosis, conjunctival congestion, lacrimation, and rhinorrhea (Chapter 367).

Gustatory hyperhidrosis primarily affecting the face is triggered by hot or spicy foods. One example is Frey syndrome, which may develop after injury of the auriculotemporal nerve in the parotid region and reflects aberrant reinnervation of sweat glands by facial nerve branches destined to the salivary glands. Gustatory sweating may also occur in diabetic autonomic neuropathy (Chapter 210).

DIAGNOSIS

Clinical Evaluation

The mainstays of evaluation of patients with autonomic failure are a careful history as well as a general physical and neurologic examination to determine the type, distribution, and temporal profile of autonomic symptoms, as well as the presence of associated neurologic symptoms and signs (Fig. 386-1). The history should include a careful review of the patient's comorbid conditions and medication list (Table 386-2). Acute or subacute autonomic failure suggests an autoimmune ganglionopathy or a toxic cause. Chronic and progressive generalized autonomic failure suggests one of the neurodegenerative synucleinopathies, which are typically associated with and may be preceded by rapid eye movement (REM) sleep behavior disorder characterized by movements during sleep triggered by dreams (Chapter 374). Patients with suspected neurodegenerative disorders should be assessed for impaired olfaction (Chapter 395), which is an early symptom in Lewy body disorders but not of multiple system atrophy. Both patients and caregivers should be

instructed about recognition of inspiratory laryngeal stridor, which occurs in multiple system atrophy. The presence of sensory and autonomic symptoms suggests an autonomic neuropathy. Patchy, diffuse, or non-length-dependent sensory symptoms, and/or sensory ataxia suggests an immune ganglionopathy. A positive family history may be a clue to hereditary transthyretin amyloidosis (Chapter 174) or Fabry disease (Chapter 192).

The autonomic neurologic examination includes measurements of blood pressure and heart rate after 5 minutes of rest in the supine position and after 1 and 3 minutes of standing. A transient increase in heart rate during the first 15 to 30 seconds of standing is normal. In patients who have orthostatic hypotension, an increase in heart rate of less than 0.5 beats per minute for each mm Hg fall of systolic arterial pressure may indicate a neurogenic cause. The examination should also include assessment of the pupils (for size, symmetry, and reactivity with both bright and dim light), vasomotor signs, and sweat. Distal arteriolar vasoconstriction, which may manifest with cold hands and feet, can be seen in some patients with autonomic neuropathies or as "blue hands" in multiple system atrophy. Anhidrosis can be detected by palpation or a sense of resistance when sliding a tuning fork; hyperhidrosis is visualized by shining a bright light perpendicularly to the skin in a dimly lit room. Neurologic examination should include testing for parkinsonism, cerebellar ataxia, and both large and small fiber sensory loss (Chapter 366).

TABLE 386-2 DRUGS AFFECTING AUTONOMIC FUNCTION

SYMPTOM	DRUG (EXAMPLE)
Orthostatic hypotension	Diuretics Alpha-1 adrenoreceptor antagonists (e.g., terazosin) Calcium channel blockers Phosphodiesterase 4 inhibitors Nitrates Alpha-2 adrenoreceptor agonists (e.g., clonidine, tizanidine) Neuroleptics (e.g., clozapine)
Dry mouth Constipation Urinary retention	Anticholinergic drugs (e.g., trihexyphenidyl) Tricyclic antidepressants (e.g., amitriptyline)
Impaired sweating	Anticholinergic drugs (e.g., trihexyphenidyl) Tricyclic antidepressants (e.g., amitriptyline) Bupropion Antihistamines (e.g., doxepin, diphenhydramine, hydroxyzine) Neuroleptics (e.g., prochlorperazine) Carbonic anhydrase inhibitors (e.g., acetazolamide, topiramate) Central alpha-2 adrenoreceptor agonists (e.g., clonidine) Botulinum toxin
Excessive sweating	Serotonin reuptake inhibitors Opioids Acetylcholinesterase inhibitors (e.g., pyridostigmine)

Laboratory Evaluation

General laboratory tests in patients with autonomic failure should include a complete blood count; levels of serum glucose, hemoglobin A_{1c}, vitamin B_{12}, methylmalonic acid, thyroid-stimulating hormone, and creatinine, as well as serum and urine protein electrophoresis with immunofixation. Patients who have a subacute onset of autonomic symptoms should undergo testing for antibodies associated with autonomic failure or autonomic hyperactivity (Table 386-3).[14] Determination of forearm venous catecholamines after 30 minutes of supine rest and 10 minutes of standing may be helpful in some cases. Low basal norepinephrine levels indicate a disorder affecting autonomic ganglia or peripheral sympathetic nerves; normal supine norepinephrine levels suggest a central autonomic disorder, and low or undetectable noradrenaline levels associated with increased dopamine levels indicate a deficit of dopamine-β-hydroxylase, which normally transforms dopamine into norepinephrine.

Autonomic Function Tests

Autonomic laboratory evaluation is indicated to determine the presence, extent, and severity of autonomic failure; evaluate patients with orthostatic intolerance; and assess disease progression or therapeutic response. Sudomotor function tests include the thermoregulatory sweat test, which assesses the integrity of central and peripheral sudomotor pathways, as well as tests that assess peripheral innervation of the sweat glands, such as the quantitative sudomotor axon reflex test or the quantitative direct and indirect test of sudomotor function. Tests that assess vagal control of the sinus node (cardiovagal function) include the heart rate response to deep breathing (respiratory sinus

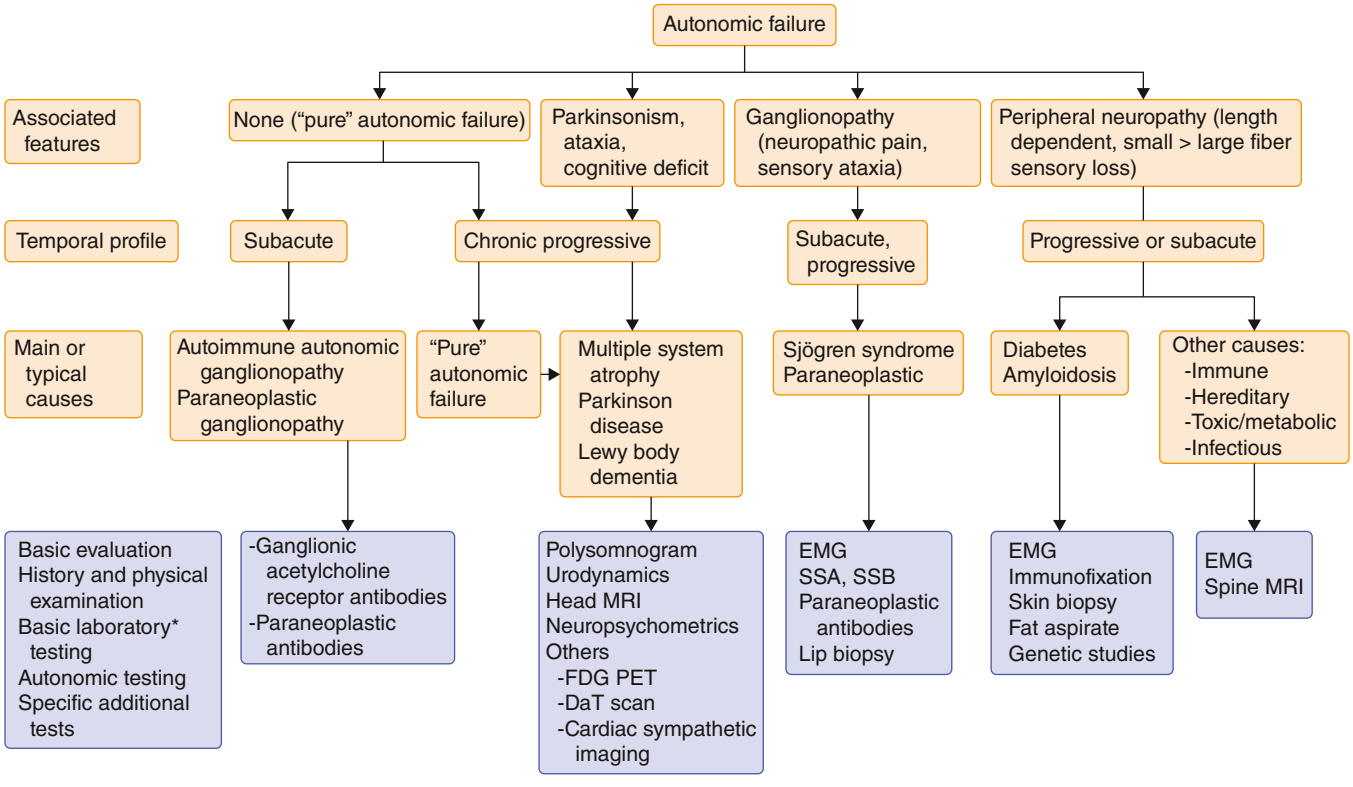

FIGURE 386-1. Approach to the diagnosis of a patient with signs or symptoms of autonomic failure. *Complete blood count, fasting blood glucose, vitamin B_{12}/methylmalonic acid, protein electrophoresis with immunofixation, plasma norepinephrine levels (supine and standing). DaT scan = dopamine transporter scan; EMG = electromyelogram; FDG/PET = fluorodeoxyglucose positron emission tomography; MRI = magnetic resonance imaging; SSA = Sjögren syndrome type A antibody (anti-Ro); SSB = Sjögren syndrome type B antibody (anti-La).

TABLE 386-3 ANTIBODIES ASSOCIATED WITH AUTOIMMUNE AUTONOMIC DISORDERS

ANTIBODY	DISORDERS	ASSOCIATED CONDITION
DISORDERS ASSOCIATED WITH AUTONOMIC FAILURE		
Ganglionic AChR	Autoimmune autonomic ganglionopathy	Typically none May occur in association with other paraneoplastic autoantibodies
Hu (ANNA1)	Paraneoplastic autonomic neuropathy Intestinal pseudoobstruction	Small cell lung carcinoma, rarely thymoma
CRMP5	Paraneoplastic autonomic neuropathy	Small cell lung carcinoma, thymoma, renal cell carcinoma, thyroid carcinoma
SSA, SSB	Autoimmune sensory and autonomic ganglionopathy	Sjögren syndrome
P/Q VGCC	Lambert-Eaton myasthenic syndrome	Small cell lung carcinoma
DISORDERS ASSOCIATED WITH AUTONOMIC HYPERACTIVITY		
LGI	Limbic encephalitis	Typically, non-paraneoplastic, but <20% of cases may have small cell lung carcinoma, thymoma, or adenocarcinoma of the breast or prostate
CASPR2	Limbic encephalitis Morvan syndrome	Typically, non-paraneoplastic, but <20% of cases may have small cell lung carcinoma, thymoma, or adenocarcinoma of the breast or prostate
NMDAR	NMDAR encephalitis	Ovarian teratoma
DPPX	Encephalomyelitis with rigidity and myoclonus	Hematologic malignancies (<20% of patients)

AChR = acetylcholine receptor; CASPR2 = contactin-associated protein; DPPX = dipeptidyl peptidase X; LGI1 = leucine-rich glioma inhibited 1; NMDAR = N-methyl D-aspartate; SSA = Sjögren syndrome type A; SSB = Sjögren syndrome type B; VGCC = voltage-gated calcium channel.

arrhythmia) and the heart rate response to the Valsalva maneuver (Valsalva ratio). The beat-to-beat blood pressure profile during the Valsalva maneuver and the blood pressure response to head-up tilt indirectly assess the integrity of sympathetic vasomotor output in response to the baroreflex. The orthostatic stress in head-up tilt differs from that of active standing, as it does not involve contraction of calf muscles (which increases venous return). In patients who report typical orthostatic symptoms but do not have a fall in blood pressure within 3 minutes of standing, a more prolonged tilt-table test (Chapter 49) may detect delayed orthostatic hypotension, which can be seen with milder or earlier forms of autonomic failure.

Gastrointestinal motility studies assess gastric emptying, colonic transit, and defecatory function (Chapter 122). Urodynamic studies are necessary to assess bladder storage and emptying as well as detrusor sphincter dyssynergia (Chapter 115). Determination of postvoid residual volume is valuable to assess for impaired bladder emptying owing to impaired detrusor contractility.

Additional Tests in Specific Conditions

Electromyography and nerve conduction studies are indicated in all patients who are suspected of having peripheral autonomic nervous system dysfunction. Skin biopsy with assessment of intraepidermal nerve fiber density and immunocytochemical quantification of the innervation density of sweat gland and pilomotor nerves can be useful in the evaluation of small fiber neuropathy. Alpha-synuclein may also be detected in the cutaneous autonomic nerves in patients with or at risk for a synucleinopathy. Abdominal fat aspirate, skin biopsy, or sural nerve biopsy are indicated to evaluate for amyloidosis (Chapter 174); immunostaining, laser microdissection, and mass spectrometry–based proteomic analysis allow identification of the specific subtype of amyloid protein. Salivary gland or lip biopsy can support a diagnosis of Sjögren disease (Chapter 247). Genetic testing for transthyretin mutations of amyloidosis (Chapter 174) or determination of α-galactosidase for Fabry disease (Chapter 192) is indicated when these diseases are suspected.

Polysomnography is indicated in all patients who have progressive autonomic failure to detect REM sleep without atonia, which may manifest as REM sleep behavior disorder and which is often a premotor manifestation in the alpha-synucleinopathies (Chapter 374). Polysomnography may also detect laryngeal stridor in patients with multiple system atrophy before it manifests during wakefulness. Magnetic resonance imaging (MRI) is indicated in patients with a presentation suggestive of limbic encephalitis, a focal lesion, or a neurodegenerative disorder. Other imaging modalities, such as [^{18}F] fluorodeoxyglucose positron emission tomography, dopamine transporter imaging, or imaging of cardiac sympathetic innervation with [^{123}I] metaiodobenzylguanidine (MIBG) or 6-[^{18}F] fluorodopamine may help differentiate among different neurodegenerative disorders associated with autonomic failure.

TREATMENT

Regardless of the cause, the bothersome and sometimes life-threatening clinical manifestations of autonomic disorders require symptomatic treatment.

Orthostatic Hypotension

The goal of treatment for orthostatic hypotension is to improve the patient's symptoms rather than to achieve a target blood pressure.[15] Patient education about mechanisms and factors that worsen orthostatic hypotension is critical. The steps of management include correcting aggravating factors, nonpharmacologic measures, and pharmacologic therapies (Fig. 386-2). Patients who have asymptomatic neurogenic orthostatic hypotension usually require only education and nonpharmacologic measures.

Drugs that exacerbate orthostatic hypotension (see Table 386-2) should be reduced or discontinued if possible. Levodopa or dopaminergic agonists used to treat the Parkinsonism associated with the central synucleinopathies may also lower blood pressure, and their doses should be adjusted if possible.

Management of orthostatic hypotension requires lifestyle and dietary modifications.[16] Patients should be instructed to change positions gradually, briefly sit before standing, avoid Valsalva-like maneuvers, and use a urinal or urinate in the sitting position. They should also avoid exposure to hot and humid environments that cause vasodilatation. Patients should not stop exercising because of the adverse effects of cardiovascular deconditioning, but exercise is preferred in the recumbent or seated position or in a swimming pool.

Many patients have postprandial hypotension within 2 hours after a meal because of insulin-triggered splanchnic vasodilation, so patients should be instructed to eat smaller, more frequent meals that are low in carbohydrates. Alcohol, which is a powerful vasodilator, should be reserved for the evening, prior to bedtime. Fluid intake should be 2 to 2.5 L of water per day, and patients should increase their salt intake,[A1] such as by adding 1 to 2 teaspoons of salt to a healthy diet. Salt tablets (e.g., 0.5 g or 1.0 g tablets) can be used but may cause abdominal discomfort.

As a rescue measure for acute symptoms, bolus water drinking (0.5 L, 16 oz) produces a rapid increase in blood pressure owing to a reflex sympathoexcitatory response, presumably triggered by portal osmoreceptors. This pressor response occurs within 5 to 10 minutes and peaks in about 30 minutes, and it may persist for hours. Other physical countermaneuvers (e.g., leg crossing, standing on tiptoes, stooping, squatting, and buttock clenching) can help maintain blood pressure and reduce orthostatic symptoms during daily activities. High-waist stockings that produce at least 15 to 20 mm Hg compression or an abdominal binder can reduce venous pooling and thereby increase venous return and blood pressure.

When these interventions fail, pharmacologic strategies, which are aimed to expand intravascular volume and promote vasoconstriction, should be introduced (Table 386-4).[17] Stepwise pharmacologic treatment usually begins with low-dose fludrocortisone (0.1 mg/day).[A2] This long-acting synthetic mineralocorticoid, which increases renal sodium and water re-absorption, thereby expanding intravascular volume, usually requires at least 7 days of treatment to exert significant clinical effect. Midodrine (5 to 10 mg three times a day) is an oral prodrug converted peripherally into the active metabolite desglymidodrine, a selective α_1-adrenoceptor agonist that elicits arteriolar and venous constriction; it is an effective treatment for symptomatic orthostatic hypotension.[A3,A4] Droxidopa (100 to 600 mg three times a day), which is an oral synthetic amino acid that is decarboxylated to norepinephrine by the enzyme aromatic amino acid decarboxylase in the remaining sympathetic postganglionic terminals and in non-neuronal tissues, improves neurogenic orthostatic hypotension.[A5] Midodrine or droxidopa should be taken before getting out of bed, before lunch, and no later than 3 to 4 hours before bedtime to avoid supine hypertension. Norepinephrine reuptake inhibitors, such as atomoxetine (10 to 18 mg, twice a day), increase norepinephrine availability at the neurovascular junction and may be effective in patients who have preserved peripheral sympathetic function, as occurs in multiple system atrophy. Pyridostigmine (30 to 60 mg two to three times daily) is an inhibitor of cholinesterase; it potentiates cholinergic neurotransmission in autonomic ganglia and may increase sympathetic output "on demand" upon standing, without the risk of supine hypertension.

Other drugs can be used as adjunctive treatment in specific conditions (Fig. 386-2). The α-glucosidase inhibitor acarbose (50 to 100 mg before meals), which decreases gastrointestinal absorption of glucose and release of the vasodilator insulin, is useful to treat postprandial hypotension. The somatostatin analog octreotide (0.2 to 0.4 μg/kg, subcutaneously) induces splanchnic vasoconstriction and is very effective to attenuate postprandial hypotension. In patients who have anemia of chronic disease (Chapter 144), treatment with erythropoietin increases standing blood pressure and improves orthostatic tolerance.

Neurogenic supine hypertension poses a therapeutic challenge in patients who have orthostatic hypotension. During daytime, avoiding the supine position is the best treatment. During the night, tilting the head of the bed to achieve a 30- to 45-degree angle (reverse Trendelenburg position) lowers blood pressure and prevents the nocturnal polyuria and natriuresis that worsen orthostatic hypotension the next morning. Eating high-glycemic carbohydrate snacks or drinking a glass of wine right before going to bed also can decrease supine nocturnal hypertension. In patients who have prolonged and severe supine hypertension, short-acting drugs, such as captopril (25 mg), losartan (50 mg), nifedipine (1 to 2 mg), amlodipine (2.5 to 5 mg), or a nitroglycerine patch (0.1 mg), can be considered. Because these drugs increase the risk of hypotension and falls upon standing up from recumbency (e.g., to urinate), the use of a urinal or bedside commode should be encouraged.

Other Manifestations of Autonomic Failure

The care of patients with severe gastrointestinal or urologic symptoms requires referral to a specialist. Treatment of constipation (Chapter 118) includes increased water and fiber intake, bulking agents (e.g., psyllium), osmotic laxatives (e.g., polyethylene glycol and magnesium citrate), emollients (e.g., docusate), and gastrointestinal tract stimulants (e.g., cascara). More recently approved novel therapies include the guanylate cyclase C activator, linaclotide, and the chloride channel type 2 activator, lubiprostone.

Potential treatments of overactive bladder (Chapter 115) include antimuscarinic drugs (e.g., oxybutynin, tolterodine, trospium, darifenacin, solifenacin fesoterodine) or the β_3 receptor agonist mirabegron. Patients with detrusor hypoactivity and large (>100 mL) postvoid residual should practice intermittent self-catheterization. Erectile dysfunction (Chapter 216) is typically managed with oral phosphodiesterase 5 inhibitors, such as sildenafil, tadalafil, and vardenafil—all of which may worsen orthostatic hypotension—or with local treatment.

Hyperhidrosis

Initial treatment for palmar hyperhidrosis begins with tap water iontophoresis, which blocks the sweat ducts at the stratum corneum. Endoscopic transthoracic sympathotomy or sympathectomy can produce long-term benefit but may lead to compensatory hyperhidrosis at other sites. Intradermal botulinum toxin injections can be used for palmar or axillary hyperhidrosis and for gustatory sweating. Topical antiperspirants are the initial treatment for generalized hyperhidrosis. Pharmacologic treatment includes anticholinergic drugs such as glycopyrrolate (1 to 2 mg one to three times daily), which typically produces dry mouth; topiramate (beginning at 25 mg twice daily); and clonidine (0.1 mg three times daily).

SPECIFIC AUTONOMIC DISORDERS

NEURODEGENERATIVE SYNUCLEINOPATHIES

In synucleinopathies, slowly progressive generalized failure may occur either in isolation or in association with different motor and cognitive manifestations.[18] Pure autonomic failure is a sporadic, gradually progressive disorder of adult onset primarily characterized by orthostatic hypotension, in many cases associated with progressive loss of sweating, constipation, bladder disturbances and erectile dysfunction. Approximately one third have or may eventually develop multiple system atrophy or a Lewy body disorder.

Multiple system atrophy is characterized by prominent autonomic failure associated with Parkinsonism, cerebellar ataxia, or both (Chapters 378 and 379). The pathologic hallmark of multiple system atrophy is the accumulation α-synuclein containing glial cytoplasmic inclusions and loss of neurons in the striatum, substantia nigra, cerebellum, pons, and other brain regions. The prominent involvement of brainstem areas critical for cardiovascular control, micturition, and respiration explains the early and severe orthostatic hypotension, neurogenic bladder, and respiratory complications that characterize multiple system atrophy. Early and severe orthostatic hypotension and urinary retention with large postvoid residual (>100 mL) and incontinence typically differentiates this multiple system atrophy from Lewy body disorders. Laryngeal stridor is a typical manifestation, and its early development predicts shorter survival. A thermoregulatory sweat test typically shows global anhidrosis. Normal supine plasma norepinephrine levels and preserved cardiac sympathetic innervation on cardiac imaging reflect a relative preservation of autonomic ganglia at early disease stages. Survival in multiple system atrophy is poor, with a median survival from onset to death ranging from 6 to 10 years.

Autonomic failure in Parkinson disease and dementia with Lewy bodies reflects accumulation of α-synuclein in neurons and axons of the sympathetic, parasympathetic, and enteric ganglia. The pathologic hallmark of these disorders is accumulation of α-synuclein containing Lewy bodies and Lewy neurites.

In Parkinson disease (Chapter 378), involvement of the enteric nervous system typically occurs before that of the central nervous system and precedes the motor manifestations, thereby suggesting that Lewy neuropathology extends from the peripheral autonomic to the central nervous system. Autonomic manifestations, such as constipation, may precede the development of motor symptoms by over two decades. Impaired gastric emptying may contribute to variable absorption of levodopa and motor fluctuations. Orthostatic hypotension occurs in 50% of cases, may be detected early in the course of the disease, and may be aggravated by dopaminergic agonists. Urinary symptoms, which affect up to 85% of patients, reflect detrusor overactivity. Patients may be intolerant to heat or cold and may have intermittent episodes of hyperhidrosis, which more frequently occur during "off" periods in patients with motor fluctuations. Symptoms may be ameliorated temporarily by adjusting anti-Parkinsonism medication, and the prognosis is determined by the progression of the underlying disease.

Lewy body dementia is characterized by progressive dysfunction in attention and executive tasks, accompanied by visual processing deficits, fluctuating cognition, recurrent visual hallucinations, REM sleep behavior disorder, and Parkinsonism (Chapter 371). Autonomic dysfunction, neuroleptic sensitivity, postural instability, repeated falls, and neuropsychiatric manifestations are supportive clinical features. In Lewy body disorders, autonomic manifestations are primarily due to involvement of peripheral autonomic ganglia, as reflected by low supine plasma norepinephrine and cardiac sympathetic denervation on cardiac imaging. No specific treatments are available, and the prognosis is poor (Chapter 371), usually with rapid progression of symptoms and death within 5 to 7 years.

AUTOIMMUNE AUTONOMIC DISORDERS

Several autoimmune disorders may manifest with either autonomic failure or autonomic hyperactivity. Recognition of these disorders is critical because they may respond to immunomodulatory therapy, including high-dose corticosteroids, intravenous immunoglobulin or plasma exchange, and, in some cases, mycophenolate mofetil, cyclophosphamide, or rituximab.

Autoimmune autonomic ganglionopathy is an important cause of subacute panautonomic failure. Orthostatic hypotension and constipation occur in 70% of patients. Prominent cholinergic failure, manifested by dry mouth, dry eyes, impaired pupil responses, and urinary retention, is a typical feature. About 50% of patients have ganglionic acetylcholine receptor antibodies, whose levels correlate with severity of the disease; levels greater than 1.0 nmol/L are fairly specific. Intermediate levels of ganglionic acetylcholine receptor antibodies (0.1 to 1.0 nmol/L) can be associated with limited forms of autonomic failure, such as gastrointestinal dysmotility (including chronic intestinal pseudo-obstruction). Low titers are found in some cases of idiopathic anhidrosis, which may respond to corticosteroids under expert supervision.

Paraneoplastic antibodies (Chapter 164) can be associated with autonomic or enteric neuropathy. Small cell lung cancer (Chapter 177), which is the most commonly associated tumor, is especially associated with ANNA-1 (anti-Hu) and CRMP5 antibodies. Among patients with anti-Hu antibody, 18% present with an autonomic neuropathy, and 12% may initially present solely with enteric neuropathy.

Primary Sjögren syndrome[19] (Chapter 247) is characterized by sicca symptoms (dry mouth and dry eyes) and may manifest with sensory ganglionopathy or small fiber neuropathy. More than half of patients with neuropathy report symptoms of autonomic dysfunction. The diagnosis may be confirmed by the presence of SSA and SSB antibodies and/or lymphocyte infiltrates in salivary gland biopsy. Treatment is largely symptomatic, and prognosis depends on the response to treatment of Sjögren syndrome.

Seronegative idiopathic subacute autonomic and sensory neuropathy disorder is characterized by subacute onset of autonomic failure associated with prominent sensory manifestations. Symptoms include orthostatic hypotension, gastrointestinal dysmotility, neuropathic pain, and sensory ataxia with objective evidence of small or large fiber sensory neuropathy. MRI of the spinal cord may reveal increased T2 signal in the posterior columns. Lambert-Eaton myasthenic syndrome (Chapter 390), which is a neuromuscular junction disorder due to antibodies directed against the P/Q type voltage-gated calcium channel, results in impaired release of acetylcholine at both the neuromuscular junction and autonomic synapses. It manifests with proximal weakness, fatigability,

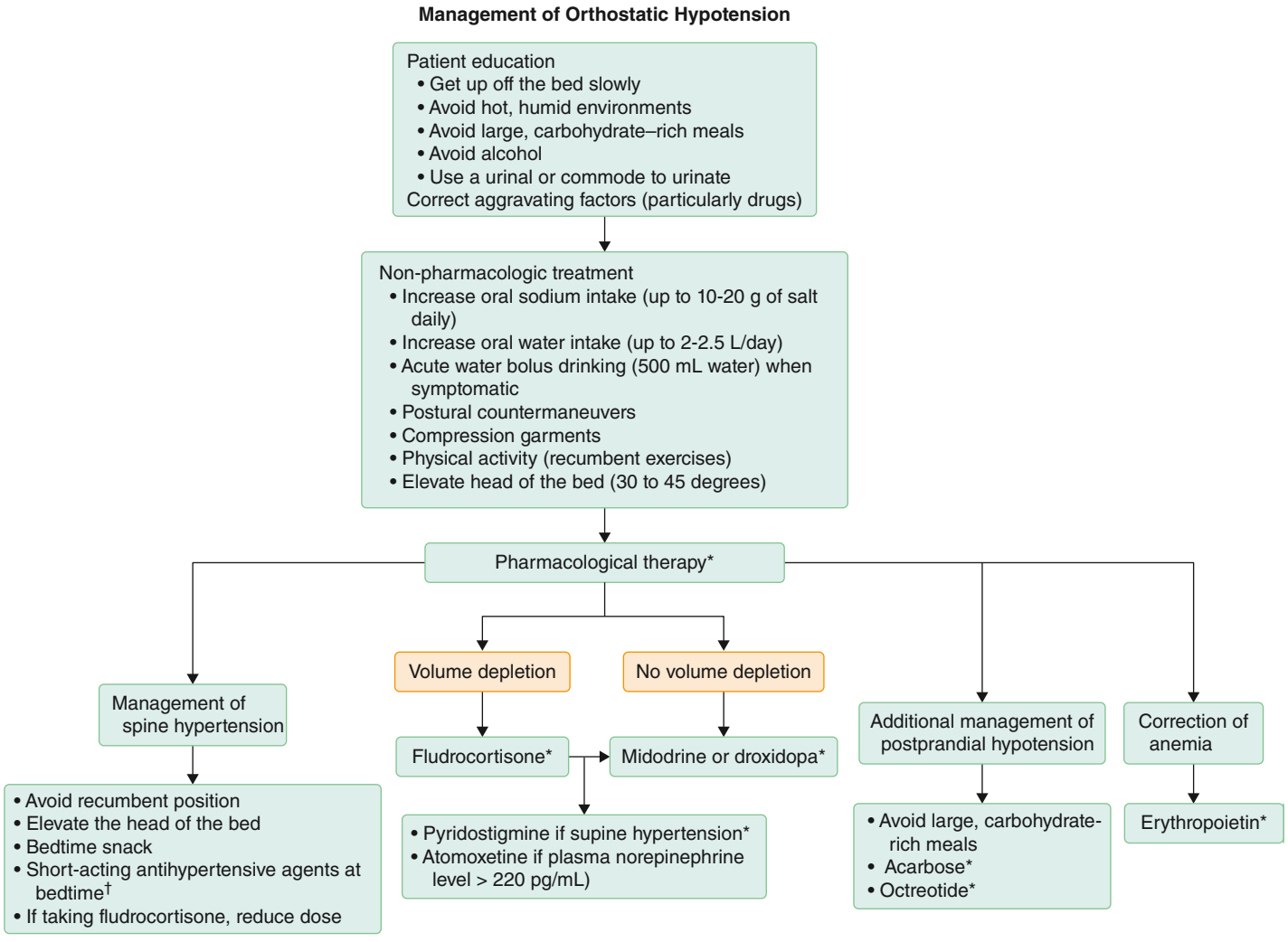

FIGURE 386-2. Approach to the management of orthostatic hypotension. *See Table 386-4 for drug doses. †See text for drugs and doses.

TABLE 386-4 DRUG MANAGEMENT OF ORTHOSTATIC HYPOTENSION

DRUG	DOSE	SIDE EFFECTS	COMMENTS
Fludrocortisone	0.1-0.2 mg orally daily	Supine hypertension, hypokalemia, ankle edema	Potential nephrotoxic effect, left ventricular hypertrophy
Midodrine	5-10 mg orally three times daily	Piloerection Scalp itching Urinary retention Supine hypertension	Take before getting out of bed, before lunch, and no later than 3-4 hr before bedtime
Droxidopa	100-600 mg orally three times daily	Supine hypertension	Take before getting out of bed, before lunch, and no later than 3-4 hr before bedtime
Pyridostigmine	30-60 mg orally three times daily	Bradycardia, abdominal cramps, diarrhea, sialorrhea, urinary incontinence	Increase standing blood pressure without risk of orthostatic hypotension Can be administered together with each dose of midodrine
Atomoxetine	10-18 mg orally twice daily	Insomnia, irritability decreased appetite	May be more helpful in patient with preserved sympathetic terminals
Acarbose	50-100 mg orally before meals		Adjuvant treatment of postprandial hypotension
Octreotide	0.2-0.4 mcg/kg, SQ	Nausea, abdominal pain	Adjuvant treatment of postprandial hypotension
Erythropoietin	25-75 U/kg SQ three times a week until hematocrit normalizes, then 25 U/kg three times weekly	Hypertension	Treatment of anemia of chronic disease worsens hypotension; iron supplementation also may be required

SQ = subcutaneous.

and areflexia (Chapter 390). Autonomic symptoms include dry mouth, constipation, and erectile dysfunction. This disorder is typically associated with small cell lung carcinoma. Treatment focuses on the underlying malignancy, but the prognosis is poor.

In Guillain-Barré syndrome (Chapter 388), up to two thirds of patients may have autonomic dysfunction, which can be life-threatening. Manifestations include labile blood pressure and heart rate, paralytic ileus, and urinary retention. These manifestations resolve as the neuropathy resolves.

Several autoimmune disorders affecting the central nervous system may be associated with autonomic hyperactivity.[20] For example, autonomic encephalitis due to antibodies against the voltage-gated potassium channel complex proteins LGI1 (leucine-rich glioma inactivated protein 1) or CASPR2 (contactin-associated protein–like 2) may manifest with episodes of hyperhidrosis, tachycardia, labile blood pressure, and hypersalivation. In N-methyl-D-aspartate (NMDA) receptor encephalitis (Chapter 383), the prominent psychiatric, cognitive, and motor manifestations may be accompanied by tachyarrhythmias, labile blood pressure, and central hypoventilation. Antibodies against dipeptidyl peptidase X (DPPX) produce a disorder characterized by profuse diarrhea and weight loss, followed by confusion, psychosis, myoclonus, exaggerated startle responses, and, in some cases, cardiac arrhythmias. Neuromyelitis optica spectrum disorder (Chapter 392), which is associated with aquaporin 4 antibodies, may manifest with intractable hiccups and vomiting, owing to involvement of the area postrema, and with hypothalamic dysfunction, including the syndrome of inappropriate secretion of antidiuretic hormone and narcolepsy. In these autoimmune disorders, the prognosis depends on the progression of the underlying disease.

PERIPHERAL AUTONOMIC NEUROPATHIES

Autonomic dysfunction may be a prominent manifestation of a variety of peripheral neuropathies.

DIABETES

Autonomic neuropathies in diabetes (Chapter 210) include generalized autonomic neuropathy, treatment-induced neuropathy, autonomic neuropathy of prediabetes, and hypoglycemia-associated autonomic impairment.[21] Generalized autonomic neuropathy typically occurs in the setting of a generalized diabetic polyneuropathy but may occur in isolation. About 65% of patients develop impaired cardiac vagal function, manifested by reduced heart rate variability on autonomic testing, and about 25% develop orthostatic hypotension. Rigorous glycemic control can delay the appearance and slow the progression of neuropathy in type 1 diabetes[A6] Cardiovascular autonomic neuropathy in diabetes is associated with a significant morbidity and mortality, ranging from 27 to 56% over 5 to 10 years.

Gastrointestinal tract dysfunction in diabetic autonomic neuropathy reflects abnormalities in the enteric nervous system, the parasympathetic vagal and pelvic nerves, and the sympathetic mesenteric nerves, in various combinations.[22] Hyperglycemia may also slow gastric emptying. Gastroparesis (Chapter 122) may occur in 20 to 50% of patients, and constipation may be found in up to 50% of patients, frequently associated with diarrhea. Fecal incontinence, due to anal sphincter incompetence or reduced rectal sensation, may be exacerbated by diarrhea. Voiding dysfunction occurs in up to 80% patients with diabetic autonomic neuropathy. Erectile failure, which is present in up to 75% of men with diabetes, may be the earliest symptom of autonomic neuropathy. Ejaculatory failure may precede the appearance of erectile dysfunction. Impaired bladder neck closure during ejaculation results in retrograde ejaculation. Impaired vaginal lubrication may also occur in diabetic patients. Sweating is typically impaired in a length-dependent fashion.

Treatment-induced neuropathy should be considered in patients who have diabetes and who present with the sudden onset of neuropathic pain and autonomic dysfunction. This reversible diabetic peripheral neuropathy is associated with rapidly instituted glycemic control, typically in patients who had a high pretreatment hemoglobin A_{1c} level, and may occur in patients with type 1 or type 2 diabetes treated with oral hypoglycemic agents or insulin. Symptoms of autonomic dysfunction, particularly orthostatic intolerance and gastrointestinal manifestations, are particularly prominent in patients with type 1 diabetes. Autonomic symptoms and test results tend to improve over time.

AMYLOIDOSIS

Peripheral autonomic neuropathy is a prominent feature of both primary (AL) and hereditary ATTR amyloidosis[23,24] (Chapter 174). Amyloid neuropathy results from abnormal deposition of insoluble beta-fibrillar proteins in the epi-, peri-, and endoneurium; the perineuronal tissues; and the neural vasculature.

Peripheral neuropathy, which is present in at least 20% of patients with AL amyloidosis, may be the presenting feature or an incidental finding. The most common manifestations are a length-dependent polyneuropathy associated with neuropathic pain and generalized autonomic failure.

Familial amyloid polyneuropathy is due to mutations of the transthyretin (*TTR*) gene on chromosome 18, most commonly a substitution of methionine for valine at position 30 (Val30Met). Hereditary ATTR amyloidosis with neuropathy is a progressive, debilitating, multisystem, life-threatening disease that typically has an insidious onset in the third to fifth decade. Autonomic manifestations are prominent and may be the presenting feature of the neuropathy.

The major diagnostic tools to diagnose amyloidosis are serum and urine immunoelectrophoresis; evaluation for cardiac amyloidosis (e.g., echocardiogram, cardiac MRI, and scintigraphy); subcutaneous fat aspirate, bone marrow biopsy, or lip biopsy with Congo red staining; amyloid typing with tissue mass spectrometry or immunocytochemistry; and germline DNA testing.[25] Cardiac biomarkers, such as troponin and N-terminal fragment of brain natriuretic peptide, are used for staging.

TREATMENT AND PROGNOSIS

For AL amyloidosis, high-dose chemotherapy followed by autologous stem cell transplant is usually the treatment of choice in eligible patients (Chapter 174). The addition of bortezomib to melphalan/prednisone regimens significantly improves both progression-free and overall survival in AL amyloidosis.[A7] Daratumumab, which is a monoclonal antibody directed to the CD38 antigen, is approved for treatment of multiple myeloma and is being studied in newly diagnosed patients with AL amyloidosis. Prognosis is linked to the outcome of treatment for the underlying disease.

For ATTR amyloidosis, effective treatments are now available for both the cardiac and neuropathic complications. Options to slow the progression of polyneuropathy include the small interfering RNA patisiran (30 mg intravenously every 3 weeks; see Chapter 174),[A8] diflunisal (a nonsteroidal anti-inflammatory agent at 250 mg twice daily), and the antisense nucleotide inotersen (284 mg subcutaneously weekly).[A9] Tafamidis (80 mg daily) slows the progress of cardiac disease and reduces all-cause mortality in patients with variant ATTR amyloidosis.[A10] The major determinant of prognosis in patients with amyloidosis is the extent of cardiac involvement, which portends a 1-year mortality of 40% and a median survival ranging from 22.2 to 96.5 months.

HEREDITARY SENSORY AND AUTONOMIC NEUROPATHIES

Many mutations affecting proteins critical for development and survival of sensory and autonomic nerves cause hereditary sensory and autonomic neuropathies. These conditions, which present in infancy and childhood, are autosomal recessive disorders with abnormal development of primary sensory nerves.

Variants in the genes encoding sodium channels selectively expressed in nociceptive afferents and autonomic axons have been linked to small fiber neuropathy associated with autonomic dysfunction. Gain-in-function variants in the genes encoding sodium channels $Na_v1.7$ (*SCN9A*), Nav 1.8(*SCNA10*), and $Na_v1.9$ (*SCN11A*) that are expressed in nociceptive neurons have been found in some patients with small fiber neuropathy. Gain-in-function *SCN9A* mutations have been linked to familial paroxysmal pain syndromes, including familial erythromelalgia, whereas loss-of-function *SCN9A* mutations have been linked to insensitivity to pain. Autonomic features, which include dry mouth and eyes, reduced urinary sensation, urinary hesitancy, orthostatic dizziness, hyperhidrosis, palpitations, and alternating constipation and diarrhea, can be present in some patients who harbor the *SCN9A* mutations affecting $Na_v1.7$ channel function. Similar, although less prominent, autonomic manifestations have been reported in patients harboring *SCN10A* and *SCN11A* mutations. No treatments are currently available.

Fabry disease, which is an X-linked, recessively inherited disorder associated with deficiency of alpha-galactosidase A (Chapter 192), manifests with a painful peripheral neuropathy associated with pain crises, hypohidrosis, and gastrointestinal symptoms. Typical features include angiokeratomas in the lower abdomen and genital regions; corneal dystrophy; hearing loss; vertigo; and renal, coronary, and cerebrovascular disease. Enzyme replacement therapy (agalsidase) and in some cases adjuvant treatment with migalastat may reduce complications, particularly when used early in the course of the disease.

METABOLIC, TOXIC, AND INFECTIOUS CAUSES

Several metabolic, toxic, and infectious neuropathies may manifest with prominent autonomic features. Thiamine deficiency (Chapter 199), like alcoholic

neuropathy (Chapter 384), may manifest with early involvement of the vagus nerve, followed by late development of orthostatic hypotension. Vitamin B_{12} deficiency may occasionally be associated with orthostatic hypotension. Replacement of vitamin deficiencies is important. Alcoholic neuropathy is usually permanent and will progress if drinking continues.

Toxins that may produce peripheral autonomic neuropathy include chemotherapeutic agents, such as vinca alkaloids, platinum derivatives, taxanes, thalidomide, lenalidomide, and bortezomib. Industrial and environmental toxins potentially causing autonomic neuropathy include organic solvents, arsenic, mercury, acrylamide, and thallium (Chapter 20). Organophosphate poisoning (Chapter 96) produces life-threatening cholinergic muscarinic hyperactivity with bradycardia and increased lacrimal, salivary, and bronchial secretions, owing to their inhibition of acetylcholinesterase. Botulinum toxin (Chapter 271) prevents the release of acetylcholine, thereby producing neuromuscular weakness, dilated and unreactive pupils, dry mouth, anhidrosis, constipation, and urinary retention. In contrast, tetanus toxin (Chapter 271) prevents release of γ-aminobutyric acid and glycine in the brain stem and spinal cord, thereby leading to sympathetic hyperactivity that results in tachycardia, hypertension, fever, and profuse sweating.

Some infectious neuropathies may also affect autonomic function. Human immunodeficiency virus (HIV) infections (Chapter 359) may be associated with orthostatic hypotension, tachycardia, cardiac conduction defects, diarrhea, and genitourinary dysfunction. Chagas disease (Chapter 318) affects enteric ganglia, thereby producing megaesophagus and megacolon, as well as causing a cardiomyopathy. Leprosy (Chapter 301) may be associated with focal anhidrosis in areas of hypopigmented and hypoesthesic skin. Autonomic dysfunction has also been observed in some survivors of severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2) infection (Chapter 336).[26]

FOCAL CENTRAL NERVOUS SYSTEM DISORDERS

Autonomic dysfunction may be a prominent feature of focal lesions of the brain or spinal cord. Strokes involving the insula (Chapter 376) can be complicated with cardiac arrhythmia, myocardial injury, or, in rare cases, contralateral hyperhidrosis. Temporal lobe seizures (Chapter 372) may manifest with ictal tachycardia or bradycardia (including asystole), ipsilateral piloerection or hypersalivation, episodic abdominal pain and vomiting, and ictal apnea. Paroxysmal hypothermia with hyperhidrosis is a rare hypothalamic disorder characterized by episodic hypothermia associated with excessive sweating, flushing or pallor, bradycardia, weakness, ataxia, and confusion. It may rarely associate with agenesis of the corpus callosum (Shapiro syndrome), but in most cases the cause is unknown. Wernicke encephalopathy (Chapter 384) may be associated with hypothermia. Strokes or neoplasms involving the medulla may manifest with orthostatic hypotension, paroxysmal hypertension, cardiac arrhythmias, vomiting, and respiratory dysfunction, in several combinations.

Disorders of the spinal cord, such as multiple sclerosis (Chapter 380), neuromyelitis optica (Chapter 392), syringomyelia (Chapter 385), and spinal cord injury (Chapter 368), may affect autonomic function. The manifestations and severity of autonomic dysfunction depend on the spinal segment involved, extent of the lesion, and time since the acute injury. Neurogenic bladder, bowel, and sexual dysfunction are a frequent feature. Acute spinal cord injury results in severe hypotension and areflexic bladder, ileus, and impaired response to thermal stimuli. Autonomic dysreflexia, which occurs in patients with spinal cord lesions above the T5 spinal level, consists of reflex sympathoexcitation characterized by severe hypertension, headache, flushing, piloerection, sweating about the level of the lesion, and bradycardia. These episodes can be triggered by bladder distension, fecal impaction, or nociceptive stimuli below the lesion and may result in hypertensive encephalopathy, cerebral or retinal hemorrhage, and cardiac arrhythmias.

REGIONAL SYMPATHETIC DYSFUNCTION

Regional sympathetic dysfunction can be a manifestation of complex regional pain syndrome. This condition, which is often a result of injury, is characterized by pain, hyperalgesia (an exaggerated response to normally painful stimuli), and allodynia (pain in response to stimuli that normally are not painful, such as light touch). These painful symptoms are accompanied by varying combinations of motor, sensory, autonomic, and trophic features. Complex regional pain syndrome can be subdivided into two clinical subtypes: type I, the more common, in which the intensity, duration, and extension of pain are out of proportion to an originally minor or inapparent injury; and type 2, which develops after major nerve damage. The warm subtype of autonomic features is characterized by a warm, red, edematous, and sweaty extremity, whereas the cold subtype manifests as a cold, blue extremity. Most cases are in the upper limbs, and about 80% of cases are in females.[27] The underlying pathobiology is unclear. The sudomotor findings can range from regional hyperhidrosis to anhidrosis. Local dystrophic changes include dry atrophic skin, sparse or coarse hair, brittle nails, and osteopenia.

Early in the syndrome, mobilization of the affected limb may be important, but the evidence base in support of any intervention is limited.[28] Analgesic medications and regional anesthesia may help facilitate physical therapy, which can be helpful.[A11] Improvement has been reported in small studies with interventions such as bisphosphonates (e.g., alendronate), ketamine infusions, corticosteroids (e.g., prednisone or methylprednisolone), epidural clonidine, intrathecal baclofen, and epidural spinal cord stimulation under expert supervision. However, the level of evidence for these interventions is low, and none of these treatments are well established. Most patients improve within 12 months, but a significant proportion of patients have persisting symptoms, ongoing disability, and impaired quality of life.

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387 AMYOTROPHIC LATERAL SCLEROSIS AND OTHER MOTOR NEURON DISEASES

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DEFINITION

The motor neuron diseases (Table 387-1) are a heterogeneous group of disorders in which selective loss of function of upper motor neurons, lower motor neurons, or both results in impairment of the nervous system's control of voluntary movement. The most common acquired motor neuron disease, amyotrophic lateral sclerosis (ALS), is a combined upper and lower motor neuron disorder. The features of lower motor neuron involvement are muscle wasting, fasciculations, and flaccid weakness, with normal or depressed tendon reflexes. Upper motor neuron dysfunction may cause increased muscle tone, brisk reflexes, clonus, weakness in a pyramidal distribution, and extensor plantar responses. Recent advances in the molecular genetics of hereditary motor neuron diseases have improved their classification and enhanced the careful diagnosis that is essential for genetic counseling, guidance, treatment, and advising patients about prognosis.

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neuropathy (Chapter 384), may manifest with early involvement of the vagus nerve, followed by late development of orthostatic hypotension. Vitamin B_{12} deficiency may occasionally be associated with orthostatic hypotension. Replacement of vitamin deficiencies is important. Alcoholic neuropathy is usually permanent and will progress if drinking continues.

Toxins that may produce peripheral autonomic neuropathy include chemotherapeutic agents, such as vinca alkaloids, platinum derivatives, taxanes, thalidomide, lenalidomide, and bortezomib. Industrial and environmental toxins potentially causing autonomic neuropathy include organic solvents, arsenic, mercury, acrylamide, and thallium (Chapter 20). Organophosphate poisoning (Chapter 96) produces life-threatening cholinergic muscarinic hyperactivity with bradycardia and increased lacrimal, salivary, and bronchial secretions, owing to their inhibition of acetylcholinesterase. Botulinum toxin (Chapter 271) prevents the release of acetylcholine, thereby producing neuromuscular weakness, dilated and unreactive pupils, dry mouth, anhidrosis, constipation, and urinary retention. In contrast, tetanus toxin (Chapter 271) prevents release of γ-aminobutyric acid and glycine in the brain stem and spinal cord, thereby leading to sympathetic hyperactivity that results in tachycardia, hypertension, fever, and profuse sweating.

Some infectious neuropathies may also affect autonomic function. Human immunodeficiency virus (HIV) infections (Chapter 359) may be associated with orthostatic hypotension, tachycardia, cardiac conduction defects, diarrhea, and genitourinary dysfunction. Chagas disease (Chapter 318) affects enteric ganglia, thereby producing megaesophagus and megacolon, as well as causing a cardiomyopathy. Leprosy (Chapter 301) may be associated with focal anhidrosis in areas of hypopigmented and hypoesthesic skin. Autonomic dysfunction has also been observed in some survivors of severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2) infection (Chapter 336).[26]

FOCAL CENTRAL NERVOUS SYSTEM DISORDERS

Autonomic dysfunction may be a prominent feature of focal lesions of the brain or spinal cord. Strokes involving the insula (Chapter 376) can be complicated with cardiac arrhythmia, myocardial injury, or, in rare cases, contralateral hyperhidrosis. Temporal lobe seizures (Chapter 372) may manifest with ictal tachycardia or bradycardia (including asystole), ipsilateral piloerection or hypersalivation, episodic abdominal pain and vomiting, and ictal apnea. Paroxysmal hypothermia with hyperhidrosis is a rare hypothalamic disorder characterized by episodic hypothermia associated with excessive sweating, flushing or pallor, bradycardia, weakness, ataxia, and confusion. It may rarely associate with agenesis of the corpus callosum (Shapiro syndrome), but in most cases the cause is unknown. Wernicke encephalopathy (Chapter 384) may be associated with hypothermia. Strokes or neoplasms involving the medulla may manifest with orthostatic hypotension, paroxysmal hypertension, cardiac arrhythmias, vomiting, and respiratory dysfunction, in several combinations.

Disorders of the spinal cord, such as multiple sclerosis (Chapter 380), neuromyelitis optica (Chapter 392), syringomyelia (Chapter 385), and spinal cord injury (Chapter 368), may affect autonomic function. The manifestations and severity of autonomic dysfunction depend on the spinal segment involved, extent of the lesion, and time since the acute injury. Neurogenic bladder, bowel, and sexual dysfunction are a frequent feature. Acute spinal cord injury results in severe hypotension and areflexic bladder, ileus, and impaired response to thermal stimuli. Autonomic dysreflexia, which occurs in patients with spinal cord lesions above the T5 spinal level, consists of reflex sympathoexcitation characterized by severe hypertension, headache, flushing, piloerection, sweating about the level of the lesion, and bradycardia. These episodes can be triggered by bladder distension, fecal impaction, or nociceptive stimuli below the lesion and may result in hypertensive encephalopathy, cerebral or retinal hemorrhage, and cardiac arrhythmias.

REGIONAL SYMPATHETIC DYSFUNCTION

Regional sympathetic dysfunction can be a manifestation of complex regional pain syndrome. This condition, which is often a result of injury, is characterized by pain, hyperalgesia (an exaggerated response to normally painful stimuli), and allodynia (pain in response to stimuli that normally are not painful, such as light touch). These painful symptoms are accompanied by varying combinations of motor, sensory, autonomic, and trophic features. Complex regional pain syndrome can be subdivided into two clinical subtypes: type I, the more common, in which the intensity, duration, and extension of pain are out of proportion to an originally minor or inapparent injury; and type 2, which develops after major nerve damage. The warm subtype of autonomic features is characterized by a warm, red, edematous, and sweaty extremity, whereas the cold subtype manifests as a cold, blue extremity. Most cases are in the upper limbs, and about 80% of cases are in females.[27] The underlying pathobiology is unclear. The sudomotor findings can range from regional hyperhidrosis to anhidrosis. Local dystrophic changes include dry atrophic skin, sparse or coarse hair, brittle nails, and osteopenia.

Early in the syndrome, mobilization of the affected limb may be important, but the evidence base in support of any intervention is limited.[28] Analgesic medications and regional anesthesia may help facilitate physical therapy, which can be helpful.[A11] Improvement has been reported in small studies with interventions such as bisphosphonates (e.g., alendronate), ketamine infusions, corticosteroids (e.g., prednisone or methylprednisolone), epidural clonidine, intrathecal baclofen, and epidural spinal cord stimulation under expert supervision. However, the level of evidence for these interventions is low, and none of these treatments are well established. Most patients improve within 12 months, but a significant proportion of patients have persisting symptoms, ongoing disability, and impaired quality of life.

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For the General References and other additional features, please visit Elsevier eBooks+ at https://ebooks.health.elsevier.com.

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387 AMYOTROPHIC LATERAL SCLEROSIS AND OTHER MOTOR NEURON DISEASES

PAMELA J. SHAW AND MERIT E. CUDKOWICZ

DEFINITION

The motor neuron diseases (Table 387-1) are a heterogeneous group of disorders in which selective loss of function of upper motor neurons, lower motor neurons, or both results in impairment of the nervous system's control of voluntary movement. The most common acquired motor neuron disease, amyotrophic lateral sclerosis (ALS), is a combined upper and lower motor neuron disorder. The features of lower motor neuron involvement are muscle wasting, fasciculations, and flaccid weakness, with normal or depressed tendon reflexes. Upper motor neuron dysfunction may cause increased muscle tone, brisk reflexes, clonus, weakness in a pyramidal distribution, and extensor plantar responses. Recent advances in the molecular genetics of hereditary motor neuron diseases have improved their classification and enhanced the careful diagnosis that is essential for genetic counseling, guidance, treatment, and advising patients about prognosis.

ABSTRACT

The neurodegenerative motor neuron disorders affect the upper and/or lower motor neurons, thereby resulting in symptoms of limb and/or bulbar weakness. Accurate diagnosis of these conditions is essential to guide treatment options and to allow informed communication of the prognosis and genetic advice. In amyotrophic lateral sclerosis (ALS), cell death of upper and lower motor neurons results in progressive failure of the neuromuscular system affecting limb, bulbar, and respiratory muscles. Average life expectancy is only 2 to 3 years from the onset of symptoms, with death usually resulting from respiratory failure. Characteristic clinical features are of combined upper and lower motor neuron signs in the bulbar, upper, and lower limb regions. Recent progress has been made in the genetic subclassification of ALS and in establishing the value of symptomatic measures such as noninvasive ventilation. Neuroprotective agents such as riluzole, edaravone, and the combination of sodium phenylbutyrate plus taurursodiol have only modest effects on survival and function, but emerging trials of genetic therapy hold promise. Spinal muscular atrophy (SMA) is an autosomal recessive lower motor neuron disorder with four grades of clinical severity (SMA types I to IV), most commonly caused by a deletion in the *SMN1* gene and resulting deficiency of the survival motor neuron protein. Recent gene therapy and antisense oligonucleotide trials to increase SMN protein levels have shown evidence of efficacy and have improved the prognosis. Kennedy disease is an X-linked lower motor neuron disorder caused by a CAG expansion in exon 1 of the androgen-receptor gene. Features of androgen insensitivity are likely to be present as well as mild distal sensory abnormalities. The disease course is relatively indolent compared with ALS.

KEYWORDS

motor neuron
ALS
mimic syndromes
spinal muscular atrophy
Kennedy disease

TABLE 387-1 CLASSIFICATION OF MOTOR NEURON DISORDERS

COMBINED UPPER AND LOWER MOTOR NEURON DISORDERS
Amyotrophic lateral sclerosis (ALS)
Familial adult onset
Familial juvenile onset
Sporadic
ALS-plus syndromes
ALS with frontotemporal dementia
Western Pacific ALS–parkinsonism-dementia complex
UPPER MOTOR NEURON DISORDERS
Primary lateral sclerosis
Hereditary spastic paraplegias
Neurolathyrism
Konzo
LOWER MOTOR NEURON DISORDERS
Hereditary
Spinal muscular atrophies (SMAs)
Proximal autosomal recessive SMA (associated with *SMN* mutations) types I to IV
Other forms of SMA not associated with *SMN* mutations
Distal SMAs/hereditary motor neuronopathies
Kennedy disease (X-linked spinobulbar neuronopathy)
Hexosaminidase deficiency (GM2 gangliosidosis)
Acquired
Monomelic focal and segmental SMAs
Multifocal motor neuropathies
Acute motor axonal neuropathy (AMAN)
Post-polio syndrome
Post-irradiation syndrome
Infective disorders
Acute poliomyelitis
West Nile fever
Other viral infections (e.g., enterovirus 71 and rabies virus)
Human immunodeficiency virus–associated motor neuron disorder
Lyme disease
Creutzfeldt-Jakob disease (amyotrophic form)
DISORDERS OF THE BULBAR MOTOR SYSTEM
Kennedy disease (X-linked bulbospinal neuronopathy)
Brown-Vialetto-Van Laere syndrome
Fazio-Londe disease
TOXIC DISORDERS OF THE MOTOR NEURON
Neurolathyrism
Konzo
Heavy metal toxicity (lead, mercury)
Western Pacific ALS–parkinsonism-dementia complex
Post-irradiation motor neuron injury
DISORDERS OF MOTOR NEURON OVERACTIVITY
Neuromyotonia
Stiff person syndrome
MISCELLANEOUS MOTOR NEURON DISORDERS
Endocrinopathies (e.g., hyperthyroidism, hyperparathyroidism, hypoglycemia)
Copper deficiency syndrome
Benign cramp-fasciculation syndrome

AMYOTROPHIC LATERAL SCLEROSIS

EPIDEMIOLOGY

ALS is a neurodegenerative disorder that causes progressive injury and cell death of lower motor neurons in the brain stem and spinal cord, as well as upper motor neurons in the motor cortex.[1] ALS has an incidence of about 2 per 100,000 and a prevalence of 6 to 8 per 100,000. The global incidence is fairly uniform, with the exception of a few high-incidence foci such as the Western Pacific island of Guam. The disease affects predominantly middle-aged and elderly individuals, with a mean age at onset of 55 to 60 years, although younger individuals can also be affected. Increasing age, male sex (male/female ratio ≈ 1.6 : 1), and genetic susceptibility are the only proven risk factors, although strenuous physical exercise, head trauma, and lead exposure may also be potential environmental risk factors[2,3] Approximately 90% of cases of ALS occur sporadically, but 5 to 10% are familial, usually with an autosomal dominant mode of inheritance.

PATHOBIOLOGY

The process of neuronal degeneration in ALS is complex, and more than 40 ALS susceptibility genes have been identified. GGGGCC hexanucleotide intronic expansions in the chromosome 9 *C9ORF72* gene are the most common genetic cause of ALS identified to date, accounting for up to 40 to 50% of familial ALS cases and 7 to 10% of sporadic ALS.[4] Accumulating evidence suggests that defective RNA processing likely plays a key role in the pathogenesis of *C9ORF72* ALS as well as other genetic subtypes. The pathobiology of C9-ALS is not yet completely understood, but the sequestration of RNA binding proteins by RNA foci and altered nucleocytoplasmic transport that allows the expansion RNA to translate into dipeptide repeat proteins in the cytoplasm are clearly of key importance.

The subtype of disease caused by *SOD1* mutations accounts for 20% of familial ALS cases and 2% of ALS cases overall. Mutant *SOD1* appears to transmit templated propagation in a prion-like (Chapter 378)[5] fashion, with these aggregates then triggering a complex interplay of multiple pathogenic processes, including oxidative stress, protein aggregation, mitochondrial dysfunction, excitotoxicity, and impaired axonal transport. Non-neuronal cells in the vicinity of motor neurons may contribute importantly to neuronal injury. Genetically engineered mouse models of *SOD1*-related ALS have shown that normal astrocytes can protect motor neurons expressing mutant *SOD1* and that removing the expression of mutant *SOD1* from microglia or astrocytes slows the progression of disease in these murine models. Astrocytes expressing mutant *SOD1* exert toxic effects on neighboring motor neurons through as yet undefined mechanisms.

Familial motor neuron disease has been linked to mutations involving alsin, senataxin, angiogenin, *VAPB*, dynactin, *TARDBP, TBK1, FUS/TLS*, and multiple other genes.[6] Intermediate-length polyQ expansions (27-33Q) in ataxin 2 are found as a risk factor for ALS in approximately 5% of patients. Associations have been reported with alterations in at least eight other genes in cases that appear sporadic. Large combined genome-wide association studies suggest that rare genetic variants underpin 15 to 20% of cases of sporadic ALS.

Pathology

At autopsy, the gross pathologic features of ALS consist of atrophy of the cerebral precentral gyrus, as well as sclerosis and pallor of the corticospinal tracts of the spinal cord. Thinning of the hypoglossal nerves and ventral spinal roots may be observed, and muscle atrophy is obvious. Microscopically, ALS patients will typically have lost at least 50% of their spinal motor neurons and have diffuse astrocytic gliosis in the spinal gray matter. By comparison, motor neurons in Onuf nucleus in the sacral spinal cord (which innervate the pelvic floor muscles) and the motor nuclei of cranial nerves III, IV, and VI (which control eye movements) are relatively preserved. A cardinal feature in residual motor neurons is the presence of ubiquitinated proteinaceous inclusions, which may be compact or skeinlike. TDP-43 has been recognized as a major protein constituent of these aggregates. In the motor cortex, there is variable loss of upper motor neurons and astrocytic gliosis. In the descending corticospinal tracts, axonal loss, myelin pallor, and gliosis are seen. The atrophied skeletal muscle shows clusters of angular atrophic fibers and fiber-type grouping that results from serial denervation and reinnervation. The selectivity of the disease process for the motor system is now recognized to be relative, and involvement of extra-motor parts of the central nervous system can be found, especially in the sensory and spinocerebellar pathways, substantia nigra neurons, and dentate granule cells in the hippocampus. In the ALS variant caused by *C9ORF72* expansions, the characteristic extra-motor system pathology demonstrates cerebellar and hippocampal inclusions that are P62+ and TDP-43-negative by immunostaining. Some of these inclusions comprise dipeptide proteins generated by aberrant translation of the hexanucleotide repeats.

CLINICAL MANIFESTATIONS

ALS is characterized by a combination of upper and lower motor neuron degeneration. Lower motor neuron degeneration causes weakness, atrophy, and fasciculation of the limb and bulbar musculature. Features of upper motor neuron dysfunction include the incongruous presence of active or brisk tendon reflexes in a wasted limb, increased muscle tone, and sometimes the presence of the Babinski sign. Upper motor neuron bulbar disease causes pseudobulbar palsy, with emotional lability, a brisk jaw jerk, slowing of repetitive tongue movements, and strained effortful speech. Fatigue and weight loss are also common symptoms. At end-stage disease, most patients will have features of upper and lower motor neuron dysfunction affecting all four limbs and the bulbar musculature.

In approximately 75% of patients, the disease starts distally, focally, and asymmetrically in an upper or lower limb (Video 387-1), followed by progressive spread of pathology in an anatomically logical progression to contiguous groups of motor neurons. Affected individuals may notice weakness, wasting or clumsiness of one hand, or unilateral footdrop. Muscle cramps may precede other clinical features, and fasciculations are most noticeable in the large proximal limb muscles. In the upper limbs, the thenar and intrinsic hand muscles tend to be severely affected, whereas the triceps and finger flexors are relatively spared until late in the disease. In the lower limbs, the pattern of weakness is often in a pyramidal distribution (flexors weaker than extensors), with early weakness of hip flexion and ankle dorsiflexion and severe involvement of the distal muscles.

Bulbar symptoms, which are the initial feature in approximately 25% of patients, are especially common in elderly women with ALS (Video 387-2). The first problem is usually slurring of speech, initially apparent only when the individual is tired. Patients often have a mixed spastic/flaccid dysarthria in which speech develops a tight strangled quality because of the upper motor neuron component, with a superimposed nasal quality as a result of the flaccid lower motor neuron weakness of the palate and nasopharynx. In patients with bulbar disease, examination often reveals weakness of the facial muscles; a spastic, weak, wasted, and fasciculating tongue; and a brisk jaw jerk. Dysphagia, initially more pronounced for liquids than for solids, usually follows the dysarthria within a few weeks or months (Video 387-3). Complications include weight loss and prolonged and arduous meal times with frequent episodes of coughing, drooling of saliva, and aspiration pneumonia.

Respiratory muscle weakness is rarely the initial feature of ALS. More commonly, respiratory muscle weakness develops insidiously and causes dyspnea and orthopnea. Diaphragmatic weakness may be apparent from the paradoxical movement of the abdominal wall during inspiration and a marked decline in forced vital capacity in the supine position. Symptoms of nocturnal carbon dioxide retention may develop, including interrupted sleep, morning headaches, anorexia, and daytime somnolence.

Neck muscle weakness, which is common later in the course of the disease, causes difficulty holding the head upright (dropped head syndrome). Eye movements tend to be spared even in advanced disease, thereby permitting limited communication by movements of the eyes. Similarly, the strength of the pelvic floor muscles is relatively preserved, so patients with ALS usually remain continent throughout the course of the disease.

Overt features of frontotemporal dementia (Chapter 371), with progressive deterioration in personality and behavior,[7] will develop in approximately 5% of patients with ALS. Cognitive dysfunction may precede, follow, or coincide with the features of motor dysfunction. Up to 50% of ALS patients without overt dementia may show more subtle features of frontal lobe dysfunction. The C9ORF72-ALS variant causes both ALS and/or frontotemporal dementia (Chapter 371), and patients with this subtype of ALS are more likely to have cognitive disturbances as well as a family history of dementia or psychosis.

About 5 to 10% of ALS patients have the progressive muscular atrophy variant, with clinical features reflecting only degeneration of lower motor neuron groups in the spinal cord. In primary lateral sclerosis, patients have pure upper motor neuron degeneration. Although severe spastic spinobulbar paresis ultimately develops in these patients, the duration of survival is commonly 10 to 15 years after the onset of symptoms. The progressive bulbar palsy variant usually progresses to involve the limbs, although limb signs may not be present initially.

Several ALS variants follow a more segmental pattern than is typical in ALS. Up to 10% of patients with ALS have flail arm syndrome, which is more common in men and is associated with a longer median survival than seen in those with typical ALS. A similar focal manifestation in the lower limbs, flail leg syndrome, is another recognized segmental variant.

DIAGNOSIS

The diagnosis of ALS is essentially clinical, and there currently is no specific diagnostic test. Nevertheless, biomarkers of motor neuron injury, including elevated levels of neurofilament light and phosphorylated neurofilament heavy in cerebrospinal fluid (CSF), and plasma have promise for the future.[8]

Diagnosis requires evidence of lower motor neuron degeneration by clinical, electrophysiologic (Chapter 366), or neuropathologic examination; upper motor neuron degeneration by clinical examination; and progressive spread of symptoms or signs within a region or to other regions, as determined by the history or examination. The diagnosis also requires the absence of other disease processes as determined by electrophysiologic testing, neuroimaging, and blood tests. Generally accepted criteria (Table 387-2) classify patients as having definite, probable, or possible ALS. However, a number of other conditions may mimic ALS (Table 387-3), and about 8% of patients in whom ALS is initially diagnosed have other lower motor neuron syndromes, such as multifocal motor neuropathy with conduction block, Kennedy disease, or mixed spinal cord and nerve root compression (Chapter 369). Conversely, 10 to 15% of patients in whom ALS is ultimately diagnosed may first undergo inappropriate surgery for presumed spinal cord or root compression abnormalities.

TABLE 387-2 AWAJI-SHIMA CONSENSUS CRITERIA FOR DIAGNOSING AMYOTROPHIC LATERAL SCLEROSIS

The diagnosis of ALS requires:
1. Evidence of LMN loss (reduced interference pattern on full contraction and increased firing rate)
2. Evidence of reinnervation (motor units of large amplitude and longer duration)
3. Fibrillation and sharp waves or fasciculation potentials (fibrillation and sharp waves are required in weak limb muscles)

Number of muscles affected by region:
- Cervical and lumbo-sacral region: a minimum of 2 muscles innervated by different roots and nerves
- Bulbar and thoracic region: a minimum of 1 muscle

Diagnostic classification: Awaji-Shima Consensus Recommendations and the Revised El Escorial Criteria
- Clinically definite ALS:
  - Clinical or electrophysiologic evidence of the presence of LMN as well as UMN signs in the bulbar region and at least 2 spinal regions or the presence of LMN and UMN signs in 3 spinal regions
- Clinically probable ALS:
  - Clinical or electrophysiologic evidence of LMN and UMN signs in at least 2 regions, with some UMN signs necessarily rostral to (above) the LMN signs
- Clinically possible ALS:
  - Clinical or electrophysiologic signs of UMN and LMN dysfunction are found in only 1 region, or UMN signs are found alone in ≥2 regions, or LMN signs are found rostral to UMN signs

ALS = amyotrophic lateral sclerosis; LMN = lower motor neuron; UMN = upper motor neuron.
UMN signs: clonus, Babinski sign, brisk tendon reflexes, absent abdominal reflexes, hypertonia, loss of dexterity.
LMN signs: atrophy, weakness. If only fasciculation, search with electromyography (EMG) for active denervation. Regions reflect segmental motor neuron pools: bulbar, cervical, thoracic, and lumbosacral.
Adapted from Costa J, Swash M, de Carvalho M. Awaji criteria for the diagnosis of amyotrophic lateral sclerosis: a systematic review. *Arch Neurol*. 2012;69:1410-1416.

Blood tests that may be helpful in distinguishing ALS from mimic syndromes (see Table 387-3) include a complete blood count and serum calcium level, thyroid function tests, parathyroid hormone, serum protein electrophoresis, Venereal Disease Research Laboratory test, creatine kinase level, inflammatory markers (erythrocyte sedimentation rate and C-reactive protein), and levels of anti-GM1 ganglioside and anti–myelin-associated glycoprotein (MAG) antibodies. Further testing, which is guided by the patient's clinical findings, might include acetylcholine receptor antibody; mutation screening in patients with familial disease, suspected Kennedy disease, or spinal muscular atrophy (SMA); heavy metal screening; urinary porphyrins; serum hexosaminidase A and B levels; *Borrelia* titers; and testing for human immunodeficiency virus.

Typical features of ALS on electromyography (EMG) include evidence of active denervation (i.e., positive sharp waves, fibrillation, and fasciculation potentials) and chronic denervation, as evidenced by large motor unit potentials that cannot be explained by a single nerve, root, or plexus lesion. Neuroimaging of the brain and spinal cord is usually needed to exclude structural pathology.

Baseline respiratory function tests should be performed on all patients. Muscle biopsy is indicated only in atypical cases when diagnostic uncertainty persists.

In the current era of emerging trials of genetic therapy, a case can be made for offering genetic panel screening to patients with both sporadic and familial ALS.[9]

TREATMENT

ALS is best managed in specialized centers that offer multidisciplinary care. Teams typically include a neurologist, nurse specialist, occupational therapist, physical therapist, speech and language therapist, and dietitian. During the course of the disease, patients frequently require referral for placement of a gastrostomy tube[10] and for provision of respiratory support.

TABLE 387-3 DISORDERS THAT CAN MIMIC AMYOTROPHIC LATERAL SCLEROSIS/MOTOR NEURON DISEASE

FORM OF MOTOR NEURON DISEASE	MIMIC SYNDROMES	CLINICAL CLUES
Progressive muscular atrophy (PMA)/LMN-predominant phenotype	Multifocal motor neuropathy	Weakness out of proportion to wasting. Neurophysiology identifies conduction block. Anti-GM1 antibodies may be raised.
	Kennedy disease	Gynecomastia, distal sensory features, perioral fasciculation, indolent progression.
	SMA	SMA can be adult onset. Pure LMN syndrome. Slower progression than PMA. Probably no family history.
	Chronic idiopathic demyelinating polyneuropathy	Electrophysiology identifies peripheral nerve demyelination. CSF protein likely to be raised.
	Benign cramp-fasciculation syndrome	Predominantly middle-aged men. Largely calf involvement. Failure to progress. No active denervation on EMG.
	Post-polio syndrome	Pure LMN syndrome. Past history of an illness compatible with poliomyelitis. Indolent progression.
	Lead poisoning	Extramotor clinical features (e.g., constipation, nail and buccal signs).
	Acute motor axonal neuropathy (AMAN—a Guillain-Barré syndrome variant)	Acute onset, with progression ceasing after a few weeks. Nerve conduction studies show features of motor axonopathy.
	Hereditary motor neuropathies	Pure LMN syndrome. Family history, clinical signs indicating chronicity, slower rate of progression.
	Porphyria	Extramotor clinical features, family history, episodic exacerbations.
	Compressive focal motor neuropathies	Pure motor disorders can result from compression of the deep palmar branch of the ulnar nerve and posterior interosseous branch of the radial nerve. Failure to extend beyond territory of one nerve. Electrophysiology with or without imaging helpful.
ALS	Multilevel spinal cord and root compression by discs, osteophytes, or tumor	Sensory symptoms and pain are common. UMN signs often caudal to LMN signs.
	Thyrotoxicosis	Systemic symptoms and signs.
	Combined peripheral neuropathy and cervical myelopathy	MRI of the spine and electrophysiology will differentiate.
	Inclusion body myositis	Rarer than ALS. Characteristic pattern of weakness with early involvement of the long finger flexors and quadriceps.
	Paraneoplastic syndromes, especially lymphoma	History of malignancy or systemic features.
	Sjögren syndrome	Non–motor-related symptoms.
	Radiation myelopathy	History of radiotherapy.
	Structural lesions of the bulbar region (e.g., tumor of the tongue base)	Pain, failure of features to extend outside the bulbar territory.
Primary lateral sclerosis	Hereditary spastic paraplegia	Family history. Symptoms rarely extend beyond the lower limb territory. Prominent bladder dysfunction.
	Multiple sclerosis	Non–motor-related symptoms and signs (e.g., eye, bladder, cerebellar, and sensory involvement).
	Spinal cord compression by disc or tumor	Pain and sensory involvement usually present.

ALS = amyotrophic lateral sclerosis; CSF = cerebrospinal fluid; EMG = electromyography; LMN = lower motor neuron; MRI = magnetic resonance imaging; SMA = spinal muscular atrophy; UMN = upper motor neuron.

Riluzole, a sodium channel blocker whose primary mechanism of action is to reduce excitotoxicity through inhibition of presynaptic glutamate release, prolongs survival by approximately 3 months when given at 50 mg twice daily.[11] It may cause fatigue, nausea, and dizziness, but these effects are frequently transient. Liver function tests should be performed at baseline and monthly for the first 3 months of therapy. Edaravone (an intravenous injection, initially daily for 14 days, then 14 days off, and then given as cycles thereafter) is an antioxidant that is approved in Japan, South Korea, and the United States; it can slow the progression of disease by approximately one third in patients who have early ALS and preserved vital capacity.[A1] Sodium phenylbutyrate (3 g) and taurursodiol (1 g) administered orally (daily for 3 weeks and then twice daily) to reduce neuronal death by mitigating endoplasmic reticulum stress and mitochondrial dysfunction can slow functional decline and prolong survival by a median of 6.5 months compared with placebo.[A2,A3]

For patients with mutations in *SOD1*, antisense nucleotide technology and gene therapy are potential options.[12] Intrathecal tofersen, which is an antisense oligonucleotide that catalyses the degradation of SOD1 messenger RNA and reduces synthesis of the SOD1 protein, substantially decreases CSF SOD1 protein levels and neurofilament light levels and results in clinical benefit at 12 months.[13] Intrathecal infusion of an adeno-associated virus encoding a microRNA targeting SOD1 also has shown promise.[14]

Other phase III trials of potential neuroprotective therapies have so far proved negative. Experimental approaches include troponin activators to improve muscle contraction.

Good clinical care must focus on symptoms and preservation of independence and quality of life. Mexiletine (300 mg/day) can significantly reduce the frequency and severity of muscle cramps.[A4] In patients with progressive bulbar problems, optimal positioning, attention to food and fluid consistency, and protective swallowing techniques are helpful. Nuedexta (a combination of 20 mg dextromethorphan and 10 mg quinidine once daily) can improve symptoms of pseudobulbar affect (inappropriate tearfulness and laughter) and is also currently under study for symptoms of swallowing and speech dysfunction.[A5] If weight loss continues, high-calorie nutritional supplements are added between meals. In ALS patients with dysphagia due to upper motor neuron impairment of the upper esophageal sphincter, local injection of botulinum toxin type A can significantly improve the dysphagia and may represent an alternative to percutaneous endoscopic gastrostomy. Placement of a gastrostomy tube via endoscopy or under radiologic guidance is recommended in patients in whom dehydration, weight loss of 10 to 15%, frequent distressing choking episodes, prolonged and tiring mealtimes, or aspiration pneumonia develop. Tube placement is higher risk in patients with respiratory insufficiency. Tubes should ideally be placed before the patient's forced vital capacity falls below 50% of predicted. Some evidence suggests that radiologically guided gastrostomy insertion may be safer in frail patients in the late stages of ALS.

Respiratory muscle weakness, which can develop insidiously during the course of ALS, causes breathlessness, orthopnea, daytime somnolence, morning headaches, and interrupted sleep. Aerobic exercise,[A6] especially if combined with strength training,[A7] can significantly slow the decline of respiratory function. Management must emphasize detection and prevention of aspiration pneumonia, assistance in clearing of secretions by agents to reduce saliva production (e.g., anticholinergic drugs such as transdermal hyoscine, amitriptyline, glycopyrrolate, or intrasalivary botulinum toxin injections), providing a suction machine, use of a mucolytic agent such as carbocisteine (in a dose of up to 750 mg three times daily), adoption of a semi-upright position for sleep, and aggressive antibiotic therapy for chest infection (Chapters 84 and 85). A small dose of sublingual lorazepam (0.5 to 1 mg) may be useful if dyspnea is accompanied by extreme anxiety; opiate therapy (e.g., morphine, diamorphine, fentanyl [Chapter 26, Table 26-4]) may be given orally, transdermally, or by subcutaneous infusion to relieve respiratory distress during the later stages of the disease.

As respiratory function worsens, noninvasive ventilation[15] can alleviate symptoms of chronic hypoventilation, significantly improve quality of life, and prolong survival,[A8] especially in patients with orthopnea, daytime hypercapnia,

and nocturnal oxygen desaturation. Full 24-hour ventilation via a tracheostomy is an option that is chosen uncommonly by fully informed patients. Diaphragm muscle pacing appears to worsen the course of the disease in ALS.[A9] Ongoing clinical research is evaluating the value of cough assist devices, as well as the optimal way to manage respiratory symptoms at the end of life. An experimental fully implanted brain-computer interface has allowed communication at the equivalent of two letters per minute in a locked-in patient with ALS.

Multidisciplinary teams can improve symptoms and perhaps survival.[16] Palliative care teams and hospices can contribute substantially to the care of ALS patients in the later stages of the disease. In the absence of ventilatory support, ALS patients will almost always die in their sleep from hypercapnic coma. In the terminal phases (Chapter 3), the aim of treatment is to ensure comfort by prescribing opiates and anxiolytic medications as required to alleviate discomfort or distress.

PROGNOSIS

Clinical features associated with a worse prognosis include older age at onset of symptoms, compromise of respiratory function, bulbar symptoms, and more rapid presentation to medical attention. The mean duration from the onset of symptoms to death in patients with sporadic ALS ranges from 27 to 43 months. The average 5-year survival rate is 25%, and approximately 5% of patients will survive for more than 10 years. The usual cause of death is respiratory failure, which may be accompanied by bronchopneumonia.

SPINAL MUSCULAR ATROPHIES

DEFINITION

The term *spinal muscular atrophy* encompasses a group of pure lower motor neuron disorders that cause progressive symmetrical muscle weakness and wasting.[17] Because the bulbar musculature may be affected, an alternative term, *hereditary motor neuronopathy*, has been proposed. The time of onset is variable and ranges from in utero to adult life.

EPIDEMIOLOGY AND PATHOBIOLOGY

The most common type of SMA is caused by mutations in the survival motor neuron (*SMN*) gene and is inherited as an autosomal recessive disorder. The estimated carrier frequency of an *SMN* mutation is 1 in 50. Type 1 SMA (Werdnig-Hoffmann disease) has an incidence of 1 in 8000 births. SMA is divided into subtypes I to IV according to age at onset and severity of the phenotype.

The human *SMN* gene on chromosome 5q13 exists in two forms, with five base-pair differences between *SMN1* and its centromeric homologue *SMN2*. A change in exon 7 of *SMN2* leads to skipping of exon 7, and as a result, 80% of the protein encoded by *SMN2* is truncated and nonfunctional rather than full length. The majority of patients with SMA have homozygous absence of *SMN1* exon 7, but *SMN1* may be replaced by a copy of *SMN2* during DNA replication by a process known as gene conversion. An individual may have one to four copies of *SMN2*, with a proportional increase in the amount of full-length SMN protein. A molecular basis for the wide variation in the phenotypic severity of SMA, which can range from in utero onset (SMA type I) to adult onset (SMA type IV), is the number of copies of *SMN2* and the SMN protein levels, although other disease-modifying factors have also been implicated.

The SMN protein oligomerizes and associates with other proteins to form the SMN complex, which in turn has an important role in the assembly of spliceosomal small nuclear ribonucleoproteins that have a function in pre-mRNA splicing in the nucleus. These cellular processes are ubiquitous, so either the clinical features of SMA may be caused by a particular susceptibility of lower motor neurons to defects in RNA processing or SMN may have additional functions that are specific to the motor neuron, including axonal transport of mRNA molecules essential for the health of the distal axon. Recent work has highlighted the role of dysregulation of ubiquitin homeostasis and β-catenin signaling, as well as genes involved in motor neuron synaptogenesis in the pathophysiology of SMA.

At autopsy, patients with SMA have atrophic spinal cords with loss of α-motor neurons and evidence of motor neuron degeneration and gliosis. The ventral roots are atrophic, and muscle atrophy is apparent, with microscopic evidence of denervation and reinnervation.

CLINICAL MANIFESTATIONS

Type I SMA (Werdnig-Hoffman disease) is characterized by severe generalized muscle weakness and hypotonia at birth or by the age of 6 months; affected children never sit or walk. Type II is an intermediate form with an onset of muscle weakness before the age of 18 months; patients can sit but are never able to walk unaided. Type III SMA (Wohlfart-Kugelberg-Welander disease) appears after 18 months of age; patients acquire the ability to stand and walk but often become wheelchair dependent in adolescence or adult life, although life expectancy is normal. Patients with type IV SMA have onset of muscle weakness in adult life.

DIAGNOSIS

The diagnosis of SMA caused by changes in *SMN* can be made by genetic testing in a patient with appropriate clinical signs and symptoms; 95% of affected individuals have *SMN* deletions. Prenatal diagnosis is available. Electrophysiology and muscle biopsy reveal evidence of denervation.

Other disorders can present in infancy or childhood as hypotonia, and a pattern of weakness similar to *SMN*-related SMA can be distinguished by associated clinical features such as early respiratory distress or vocal cord paralysis, or an atypical distribution of motor features such as upper limb–or lower limb–predominant or scapulo-peroneal involvement. The etiologic relationship of these disorders to classic SMA can be clarified by testing for *SMN* mutations.

It is important to distinguish SMA type I from infantile botulism, which can have a similar initial clinical picture. EMG with high-frequency repetitive nerve stimulation shows a decrement in botulism, and testing for the presence of botulinum toxin can confirm the diagnosis (Chapter 271). SMA II and SMA III can be distinguished from chronic inflammatory demyelinating polyneuropathy (Chapter 388) by the presence of normal CSF protein and normal nerve conduction studies in SMA. Patients with SMA type III can have clinical features that are similar to those of the hereditary motor and sensory neuropathies, but it can be distinguished by neurophysiologic assessment and genetic testing.

TREATMENT AND PROGNOSIS

Approaches to upregulate expression of the SMN protein include the intravenous infusion of an adenoviral vector that contains the DNA that codes for SMN. Nusinersen (an antisense oligonucleotide drug that modifies the pre–messenger RNA splicing of the *SMN2* gene) promotes increased production of full-length SMN protein and improves motor function in infants and children with spinal muscular atrophy[A10,A11] for at least 3 years.[18] Risdiplam (an oral small molecule with actions similar to nusinersen) also can increase blood levels of SMN protein and potentially improve function.[A12,19,20] Similar results have also been reported for onasemnogene abeparvovec.[21,22]

Children with SMA may benefit from passive and active physical therapy, lightweight braces, surgical correction of scoliosis, and respiratory support measures. Untreated patients with type I SMA usually die by the age of 2 years, untreated patients with type II SMA typically survive into adolescence, and patients with type III and type IV have a normal life expectancy. New treatments appear to hold great promise for improving this prognosis.

SPINOBULBAR MUSCULAR ATROPHY/ KENNEDY DISEASE

EPIDEMIOLOGY

Kennedy disease, or spinobulbar muscular atrophy, is an X-linked degenerative disorder of the lower motor neurons.[23] Though rare, it is important not to miss the diagnosis because of the genetic implications for the family and a more benign course than occurs with ALS. The diagnosis should be considered in any male patient with a pure lower motor neuron disorder, particularly when the disease course is relatively indolent, gynecomastia is present, or there is evidence of a mild accompanying sensory neuropathy.

PATHOBIOLOGY

Spinobulbar muscular atrophy is a trinucleotide repeat disorder in which a CAG expansion encodes for a polyglutamine tract in the first exon of the androgen receptor gene on chromosome Xq11-12. The androgen receptor, which contains three functional domains, is transported to the nucleus, where it binds to DNA and acts as a transcription factor. Expansion of the polyglutamine tract results in reduced target gene transactivation, and neurodegeneration occurs when the polyglutamine tract reaches a critical length of approximately 40 repeats. The neurodegeneration in patients with spinobulbar muscular atrophy is considered to result from a ligand-dependent toxic gain of function of the mutant androgen receptor protein. Complete loss of its function, as seen in testicular feminization syndrome (Chapter 214), does not lead to motor neuron degeneration. The toxicity

has not been fully characterized, but protein aggregation, impairment of protein degradation pathways, disruption of gene transcription, impairment of axonal transport, and altered neurotrophic factor signaling may all contribute.

Pathologic examination reveals mild spinal cord atrophy with ventral horn gliosis and loss of α-motor neurons. Misfolding of the polyglutamine (Q)–expanded protein leads to the formation of nuclear inclusions that contain the amino-terminal epitopes of the mutant androgen receptor within motor neurons and certain non-neuronal tissues.

CLINICAL MANIFESTATIONS AND DIAGNOSIS

The mean age at onset of spinobulbar muscular atrophy is 30 years, with a range of 15 to 60 years, and the severity of the disease and its age at onset correlate with the size of the repeat expansion. Initial symptoms consist of hand tremors, fasciculations, and muscle cramps, followed by progressive weakness and atrophy of the limb and bulbar muscles. Limb muscle weakness tends to be proximal and predominantly involves the lower limbs. There are no clinical signs of upper motor neuron dysfunction. Weakness of the lower facial and tongue muscles causes dysarthria, and jaw weakness may cause the mouth to hang open. The presence of perioral fasciculations with quivering of the chin is a characteristic feature. Pharyngeal involvement can cause dysphagia, and respiratory muscle weakness causes breathlessness. Mild distal sensory loss is frequently present in the lower limbs. Features of mild androgen insensitivity are frequent: gynecomastia, testicular atrophy, and erectile dysfunction. Heterozygous female carriers of spinobulbar muscular atrophy may show mild clinical manifestations of the disease.

EMG and muscle biopsy, which is often performed because the creatine kinase level tends to be elevated, reveal evidence of chronic denervation. Genetic screening for the CAG repeat expansion in exon 1 of the androgen receptor gene is diagnostic.

TREATMENT AND PROGNOSIS

Because there are no established disease-modifying therapies for spinobulbar muscular atrophy, current therapy consists of supportive care to prevent complications. The course of the disease is slowly progressive in comparison to ALS and is compatible with normal life expectancy, although some patients may die of respiratory failure. Patients may become wheelchair dependent over a period of 2 to 3 decades, but some remain ambulatory until late in life.

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388

PERIPHERAL NEUROPATHIES

A. GORDON SMITH AND MICHAEL E. SHY

APPROACH TO PERIPHERAL NEUROPATHY

The term *peripheral neuropathy* is used to describe a group of disorders that are caused by injury to the peripheral nervous system, which encompasses the final pathways of motor, sensory, and autonomic function.

EPIDEMIOLOGY

As a group, peripheral neuropathies are among the most common neurologic problems encountered in medical practice. The prevalence of peripheral neuropathy increases with age from 2 to 3% in individuals who are 50 to 60 years of age to 13% among individuals who are 70 to 80 years of age and greater than 30% among individuals over age 80 years. The population prevalence of peripheral polyneuropathy in the United States is 2.4% overall but rises to as high as 50% among individuals over 85 years of age. The most common cause of polyneuropathy is diabetes, which accounts for approximately 50% of cases. Most of the remainder have cryptogenic sensory peripheral neuropathy, although over 50% of this population has prediabetes. Other common causes of neuropathy include genetic, inflammatory, metabolic, and toxic etiologies.

PATHOBIOLOGY

Motor neurons extend from their cell body in the ventral horn of the spinal cord through the ventral nerve roots and peripheral nerves to the neuromuscular junctions at the muscle that they innervate. The cell bodies of primary sensory neurons lie outside the spinal cord in the dorsal root ganglia, where they extend peripherally to specialized sensory end organs, including nociceptors (pain receptors), thermoreceptors, and mechanoreceptors. Central projections from dorsal root ganglia enter the spinal cord through the dorsal roots to carry sensory information to the central nervous system (CNS). At each spinal segment, the ventral roots, which carry motor axons, and the dorsal roots, which carry sensory axons, join to form mixed sensorimotor nerves. In the proximal upper and lower extremities, the mixed spinal nerves form the brachial and lumbar plexuses from which arise the major anatomically defined limb nerves. Each mixed nerve is composed of a spectrum of nerve fibers, damage to which causes specific but overlapping symptoms and signs. Large-diameter myelinated fibers are responsible for motor function, proprioception, and touch sensation, whereas small-diameter lightly myelinated and unmyelinated axons are responsible for pain and autonomic function. Preganglionic sympathetic autonomic fibers begin in the intermediolateral column of the spinal cord and synapse in ganglia of the sympathetic trunk. Preganglionic parasympathetic fibers travel long distances from their cell bodies in the brain stem or sacral spinal cord to reach terminal ganglia near the organs that the parasympathetic fibers innervate.

Although positive sensory symptoms occur with injury to both large- and small-diameter fibers, severe painful sensations, particularly burning, usually suggests preferential injury to small-diameter axons. Because motor axons are capable of reinnervating denervated muscle fibers via collateral sprouting, weakness does not develop in axonal neuropathies until about 50% of axons have been injured.

CLINICAL MANIFESTATIONS

The clinical features of a peripheral neuropathy are dependent on the involved regions. Most patients with peripheral neuropathy have a chronic axonal sensory greater than motor peripheral polyneuropathy and present with slowly progressive sensory symptoms.

Sensory and motor symptoms may be divided into negative (loss of function) and positive (abnormal function). Common negative sensory symptoms include a general sense of numbness or loss of sensation, such as feeling as if feet are "walking on pebbles" or "ice cold," difficulty determining whether bath water is hot or cold with the foot, and loss of balance, particularly in the dark when visual compensation is difficult. Positive symptoms include painful dysesthesias, such as feeling as though the feet are "on fire," "on hot coals," or "stuck with pins." If severe, the symptoms may reach the level of the knee, at which point the fingers may become involved. Motor symptoms

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388

PERIPHERAL NEUROPATHIES

A. GORDON SMITH AND MICHAEL E. SHY

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As a group, peripheral neuropathies are among the most common neurologic problems encountered in medical practice. The prevalence of peripheral neuropathy increases with age from 2 to 3% in individuals who are 50 to 60 years of age to 13% among individuals who are 70 to 80 years of age and greater than 30% among individuals over age 80 years. The population prevalence of peripheral polyneuropathy in the United States is 2.4% overall but rises to as high as 50% among individuals over 85 years of age. The most common cause of polyneuropathy is diabetes, which accounts for approximately 50% of cases. Most of the remainder have cryptogenic sensory peripheral neuropathy, although over 50% of this population has prediabetes. Other common causes of neuropathy include genetic, inflammatory, metabolic, and toxic etiologies.

PATHOBIOLOGY

Motor neurons extend from their cell body in the ventral horn of the spinal cord through the ventral nerve roots and peripheral nerves to the neuromuscular junctions at the muscle that they innervate. The cell bodies of primary sensory neurons lie outside the spinal cord in the dorsal root ganglia, where they extend peripherally to specialized sensory end organs, including nociceptors (pain receptors), thermoreceptors, and mechanoreceptors. Central projections from dorsal root ganglia enter the spinal cord through the dorsal roots to carry sensory information to the central nervous system (CNS). At each spinal segment, the ventral roots, which carry motor axons, and the dorsal roots, which carry sensory axons, join to form mixed sensorimotor nerves. In the proximal upper and lower extremities, the mixed spinal nerves form the brachial and lumbar plexuses from which arise the major anatomically defined limb nerves. Each mixed nerve is composed of a spectrum of nerve fibers, damage to which causes specific but overlapping symptoms and signs. Large-diameter myelinated fibers are responsible for motor function, proprioception, and touch sensation, whereas small-diameter lightly myelinated and unmyelinated axons are responsible for pain and autonomic function. Preganglionic sympathetic autonomic fibers begin in the intermediolateral column of the spinal cord and synapse in ganglia of the sympathetic trunk. Preganglionic parasympathetic fibers travel long distances from their cell bodies in the brain stem or sacral spinal cord to reach terminal ganglia near the organs that the parasympathetic fibers innervate.

Although positive sensory symptoms occur with injury to both large- and small-diameter fibers, severe painful sensations, particularly burning, usually suggests preferential injury to small-diameter axons. Because motor axons are capable of reinnervating denervated muscle fibers via collateral sprouting, weakness does not develop in axonal neuropathies until about 50% of axons have been injured.

CLINICAL MANIFESTATIONS

The clinical features of a peripheral neuropathy are dependent on the involved regions. Most patients with peripheral neuropathy have a chronic axonal sensory greater than motor peripheral polyneuropathy and present with slowly progressive sensory symptoms.

Sensory and motor symptoms may be divided into negative (loss of function) and positive (abnormal function). Common negative sensory symptoms include a general sense of numbness or loss of sensation, such as feeling as if feet are "walking on pebbles" or "ice cold," difficulty determining whether bath water is hot or cold with the foot, and loss of balance, particularly in the dark when visual compensation is difficult. Positive symptoms include painful dysesthesias, such as feeling as though the feet are "on fire," "on hot coals," or "stuck with pins." If severe, the symptoms may reach the level of the knee, at which point the fingers may become involved. Motor symptoms

ABSTRACT

Peripheral neuropathies are among the most common neurologic disorders encountered in general medical practice. Common causes include inflammatory, inherited, toxic, and metabolic disorders, with diabetes being the most common etiology. Effective treatments are available for many forms, and promising therapeutics are in development for others.

KEYWORDS

polyneuropathy
Guillain-Barré syndrome
diabetic neuropathy
Charcot-Marie-Tooth disease
neurotoxicity

and signs are typically mild and limited to subtle weakness of toe extension and flexion, with atrophy of foot muscles. There may be mild gait instability that does not require the use of assistive devices. Foot ulceration is absent. Gait imbalance owing to a sensory ataxia (instability worse with eyes closed) indicates large fiber involvement or dysfunction of the dorsal columns of the spinal cord. Sensory ataxia involving the upper extremities is manifest by impaired coordination and finger-nose-finger testing that is worse with eyes closed, when there are often writhing, "pseudoathetoid" movements of the fingers with arms outstretched.

Involvement of motor nerves results in muscle weakness and, over time, atrophy. In peripheral polyneuropathies weakness involves distal muscles in the legs more than the arms. Deep and superficial muscles that are innervated by the peroneal nerve, such as the tibialis anterior and peroneus brevis and longus muscles, are usually affected first. As a result, tripping on a carpet or curb and ankle sprains are frequent symptoms. In the hands, symptoms typically involve fine movements, such as using buttons or zippers and inserting and turning keys in locks.

Peripheral neuropathies that involve nerve roots (polyradiculopathies, such as acute inflammatory demyelinating polyradiculoneuropathy, the most common cause of the Guillain-Barré syndrome) usually cause proximal muscle weakness that results in difficulty arising from a chair, climbing stairs, or working with the arms over the head (e.g., washing or combing hair). Positive motor symptoms, which are less common, include cramps and fasciculations, which are characteristic of disorders involving the motor neuron (e.g., amyotrophic lateral sclerosis) but also may be seen in peripheral neuropathies.

Careful examination of deep tendon reflexes is an important part of the clinical examination. Absence of reflexes often reflects a demyelinating neuropathy. In patients with acute numbness or weakness, this finding suggests Guillain-Barré syndrome. Length-dependent reduction or loss of reflexes (e.g., in Achilles tendons) is common in peripheral polyneuropathies. Because both the afferent and efferent limbs of the deep tendon reflexes involve large myelinated fibers, reflexes are often normal in neuropathies that preferentially involve small-diameter lightly myelinated and unmyelinated axons.

Autonomic symptoms (Chapter 386) are frequent in neuropathies associated with diabetes (Chapter 210) or amyloidosis (Chapter 174) and include urinary retention or incontinence, abnormalities of sweating, constipation alternating with diarrhea, and lightheadedness when standing. Erectile dysfunction is frequent in men.

DIAGNOSIS

A Systematic Approach to Patients with Neuropathy

Diagnosis of peripheral neuropathies is founded on neuroanatomical localization (Table 388-1).[1] The pattern of involvement is often appreciable with a careful history. The most common form of neuropathy is peripheral polyneuropathy. Polyneuropathies cause length-dependent, "stocking glove" symptoms and signs. Most polyneuropathies are sensory predominant, although some forms, particularly inherited polyneuropathies, cause more weakness than sensory loss. Multifocal and asymmetrical distal predominant motor and sensory signs and symptoms usually suggest a disorder involving multiple individual peripheral nerves ("mononeuritis multiplex"). Polyradiculopathies, which involve multiple nerve roots, cause non–length-dependent motor and sensory signs and symptoms that involve both proximal and distal locations. Recognition of a specific pattern can suggest a diagnosis. For example, a patient with stepwise development of asymmetrical distal weakness, pain, and numbness likely has a mononeuritis multiplex, which is usually caused by a vasculitis (Chapter 249).

Approximately 50% of patients with an acquired peripheral polyneuropathy have diabetes (Chapter 210), and most of the remainder have cryptogenic sensory peripheral neuropathy. Over half of patients with cryptogenic sensory peripheral neuropathy have prediabetes or previously unrecognized mild diabetes, and up to 80% have the metabolic syndrome. Every patient with this pattern of polyneuropathy should be evaluated for diabetes and prediabetes, paraproteinemia (Chapter 173), and vitamin B_{12} deficiency (Chapter 199). In the absence of clinical evidence of a systemic disorder or history of toxic exposure associated with peripheral polyneuropathy (Table 388-2), additional diagnostic evaluation is usually unhelpful.

Disorders of the peripheral nervous system usually conform to one of ten patterns, which reflect the underlying neuroanatomic pattern of impairment of sensory, motor, and/or autonomic function caused by the specific disorder. Recognition of a specific pattern narrows the differential diagnosis and focuses the diagnostic evaluation (Table 388-3).

Any pattern other than typical neuropathy, or the presence of any atypical "red flag" (e.g., an acute onset suggestive of inflammatory, infectious, or toxic causes; proximal involvement; motor predominance; significant ataxia; or asymmetry), should prompt additional diagnostic evaluation to assess the neuroanatomic localization, underlying physiology (demyelinating versus axonal), and structural changes (Fig. 388-1).

Nerve Conduction Studies and Electromyography

Nerve conduction studies and electromyography (Chapter 366) should be performed in all patients with diagnostic red flags or patterns other than distal, symmetrical, sensory-predominant polyneuropathy. On nerve conduction studies, axonal polyneuropathies reduce the action potential amplitudes of sensory nerves and, if there is motor axonal involvement, muscle action potential amplitudes as well; however, conduction velocities and latencies remain normal. Demyelinating neuropathies slow conduction velocities and prolong distal latencies. Genetic demyelinating polyneuropathies cause uniform conduction slowing, but acquired demyelinating neuropathies cause nonuniform slowing.

On electromyography, abnormal insertional and spontaneous activity, such as fibrillations or positive sharp waves, suggests acute or active axon injury. The presence of large, polyphasic motor units suggests partial reinnervation of muscle by regenerating axons (i.e., a more chronic process). Recruitment of motor units (firing too few motor units at a higher than normal frequency) is reduced in patients with demyelinating and axonal neuropathies.

Nerve and Skin Biopsy

The most common indications for biopsy of a distal sensory nerve, usually the sural or superficial peroneal sensory nerve, is peripheral nerve vasculitis (Fig. 388-2). Among patients referred for suspected peripheral nerve vasculitis, a simultaneous muscle biopsy increases diagnostic yield from approximately 50% to 60 to 70%. The second most common indication for nerve biopsy is evaluation for suspected light chain amyloidosis (Chapter

TABLE 388-1 TYPES OF NEUROPATHIES

PERIPHERAL NERVOUS SYSTEM LOCALIZATION	SYSTEMS INVOLVED	ANATOMIC DISTRIBUTION	EXAMPLES
Acquired peripheral polyneuropathy	Positive sensory symptoms and sensory signs; usually less motor involvement	Symmetrical and length dependent ("stocking glove") sensory loss and weakness	Diabetes, cryptogenic sensory peripheral neuropathy, chemotherapy-induced peripheral neuropathy
Genetic peripheral polyneuropathy	Motor often greater than sensory, with primarily negative sensory symptoms (numbness), high arched feet, and hammer toes	Symmetrical and length-dependent ("stocking glove") weakness and sensory loss	Charcot-Marie-Tooth disease
Mononeuritis multiplex	Motor and sensory, often painful	Asymmetrical, usually distal predominant	Vasculitis (systemic and primary peripheral nervous system)
Polyradiculopathy	Motor greater than sensory involvement	Proximal and distal; usually symmetrical but may be asymmetrical	Acute or chronic inflammatory demyelinating polyradiculoneuropathy (symmetrical); diabetic radiculoplexus neuropathy (asymmetrical)
Sensory neuronopathy (dorsal root ganglionopathy)	Sensory only, usually with ataxia and often painful	Proximal and distal, and asymmetrical	Sjögren syndrome, paraneoplastic (anti-Hu), idiopathic

174).[2] Nerve masses usually require a biopsy to diagnose a potential tumor. Rarely, nerve biopsy may be useful in the diagnosis of other infiltrative or inflammatory disorders.

Skin biopsies are routinely performed to confirm the presence of a small fiber neuropathy in patients with distal symmetrical sensory loss with neuropathic pain (Fig. 388-3), in which nerve conduction studies are usually normal, with an antibody that binds to all axons (PGP 9.5). The diagnosis of small fiber neuropathy is based on demonstrating a reduced density of intraepidermal nerve fibers.

Laboratory Testing

A hemoglobin A_{1c} level is usually the best first test in all patients with distal symmetrical polyneuropathy, but 2-hour glucose tolerance may be performed when the suspicion for prediabetes is high (Chapter 210). Paraproteinemia is most easily evaluated by measuring serum globulin levels and performing a serum protein electrophoresis (Chapter 173). The vitamin B_{12} level should also be measured; if it is borderline, a methylmalonic acid level may be required to confirm deficiency. Other common disorders associated with polyneuropathy include hepatitis C (Chapter 135) and HIV (Chapter 359). Heavy alcohol users (Chapters 364 and 384) are also at risk for polyneuropathy owing to a combination of direct ethanol toxicity and associated vitamin deficiency, particularly vitamin B_1 (thiamine).

TABLE 388-2 SELECTED CAUSES FOR TOXIC NEUROPATHIES

TOXIN CATEGORY	SPECIFIC AGENTS
Antineoplastic agents	Paclitaxel, cisplatin, oxaliplatin, bortezomib, thalidomide
Antimicrobials	Chloroquine, dapsone, isoniazid, metronidazole, nitrofurantoin
Cardiac medications	Amiodarone, perhexiline, hydralazine
Other medications	Colchicine, gold salts, phenytoin, disulfiram, pyridoxine
Heavy metals	Lead (wrist drop), arsenic, thallium (alopecia), mercury
Organic solvents	Hexane, acrylamide, vacor

In selected patients, electrodiagnostic studies will suggest the need to test for specific antibodies, such as antibodies reacting to ganglioside GM_1 (multifocal motor neuropathy) or myelin-associated glycoprotein (MAG—distal demyelinating neuropathy with weakness and tremor).[3] Genetic testing is most cost-effective when the selection of candidate genes is based on the patient's nerve conduction studies, inheritance pattern, and clinical findings.

INHERITED NEUROPATHIES

Inherited neuropathies can be divided into those that affect the peripheral nervous system in isolation, such as Charcot-Marie-Tooth (CMT) disease, and those that involve multiple organ systems.

CHARCOT-MARIE-TOOTH DISEASE

EPIDEMIOLOGY AND PATHOBIOLOGY

Charcot-Marie-Tooth disease has a prevalence of 1 : 2500 and is caused by mutations that affect myelin formation. Autosomal dominant Charcot-Marie-Tooth is subdivided into demyelinating (CMT1) and axonal (CMT2) forms based on electrophysiologic criteria. Many patients have de novo mutations. X-linked (CMTX) and autosomal recessive demyelinating (CMT4) and axonal (CMT-AR2) forms are also seen. Each type is further subdivided by the specific genetic cause. The most common form, CMT1A, is caused by a duplication of a fragment of chromosome 17 containing the peripheral myelin protein 22-kD *(PMP22)* gene. The most common form of CMT2 is a mutation in the mitofusin gene (CMT2A). Overall, CMT1A accounts for roughly 50% of all cases of Charcot-Marie-Tooth disease, CMT1X accounts for 10 to 20%, CMT1B for less than 5%, and CMT2 for 20%. However, mutations have been identified in more than 100 genes, and this number is likely to increase substantially in the future.

CLINICAL MANIFESTATION

Classic Charcot-Marie-Tooth disease causes slowly progressive distal weakness and sensory loss, often beginning in the first 2 decades of life, but an increasing number of patients are being identified well into adulthood and even in later years of life.[4] Children are often slow runners and have impaired balance (e.g., skating, walking across a log). Ankle-foot orthoses are frequently required by the third decade. Fine hand movements (e.g., fastening jewelry, turning a key, or using buttons and zippers) may be impaired. Most patients have distal leg atrophy (inverted champagne bottle) with high arched feet (pes cavus) and hammer toes (Fig. 388-4). Nevertheless, many patients remain ambulatory

TABLE 388-3 TEN TYPICAL PATTERNS OF NERVOUS SYSTEM DISORDERS

ANATOMIC PATTERN	NEUROANATOMIC LOCALIZATION	DIFFERENTIAL DIAGNOSIS
1. Symmetrical proximal and distal weakness with sensory loss	Polyradiculoneuropathy	Acute inflammatory demyelinating polyradiculoneuropathy if acute and maximal involvement within the first 4 weeks, chronic inflammatory demyelinating polyneuropathy if progressive over >8 weeks
2. Symmetrical distal sensory loss with or without distal weakness	Peripheral polyneuropathy	Cryptogenic sensory peripheral neuropathy, diabetes or other metabolic disorders, toxic, hereditary such as Charcot-Marie-Tooth
3. Asymmetrical distal weakness with sensory loss	Mononeuritis multiplex	Vasculitis, hereditary neuropathy with predisposition to pressure palsies, multifocal acquired demyelinating sensory and motor neuropathy, infections (e.g., leprosy)
	Mononeuropathy or radiculopathy	Compression, trauma, or tumor
4. Asymmetrical proximal and distal weakness with sensory loss	Polyradiculopathy	Polyradiculopathy or plexopathy due to diabetes (diabetic lumbosacral radiculoplexus neuropathy) or a meningeal disorder (carcinoma, lymphoma, sarcoidosis, chronic infection)
5. Asymmetrical distal weakness without sensory loss	Motor neuronopathy with upper motor neuron signs (brisk reflexes, spasticity, Babinski responses)	Amyotrophic lateral sclerosis Progressive muscular atrophy, multifocal motor neuropathy, monomelic amyotrophy (Hirayama disease)
	Motor neuronopathy (lower motor neurons) or motor neuropathy	
6. Symmetrical sensory loss with distal areflexia with upper motor neuron findings	Mixed myelopathy and polyneuropathy	Severe combined degeneration due to vitamin B_{12} or copper deficiency or to inherited disorders (adrenomyeloneuropathy, metachromatic leukodystrophy, Friedreich ataxia)
7. Symmetrical weakness without sensory loss	Motor neuronopathy	Proximal and distal: spinal muscular atrophy or progressive muscular atrophy
	Motor neuropathy	Distal predominant: hereditary motor neuropathy
8. Focal midline proximal weakness	Motor neuronopathy, neuromuscular junction disorder, myopathy	Neck extensor weakness (head drop): amyotrophic lateral sclerosis, myasthenia gravis, myopathy
		Bulbar weakness: amyotrophic lateral sclerosis, myasthenia gravis
9. Asymmetrical sensory loss with sensory ataxia without weakness	Sensory neuronopathy/ganglionopathy	Sjögren, paraneoplastic (anti-Hu antibody), idiopathic
	Sensory polyradiculoneuropathy	Chronic immune sensory polyradiculoneuropathy
10. Autonomic symptoms and signs	Autonomic neuropathy	Diabetes, amyloid, autoimmune autonomic neuropathies

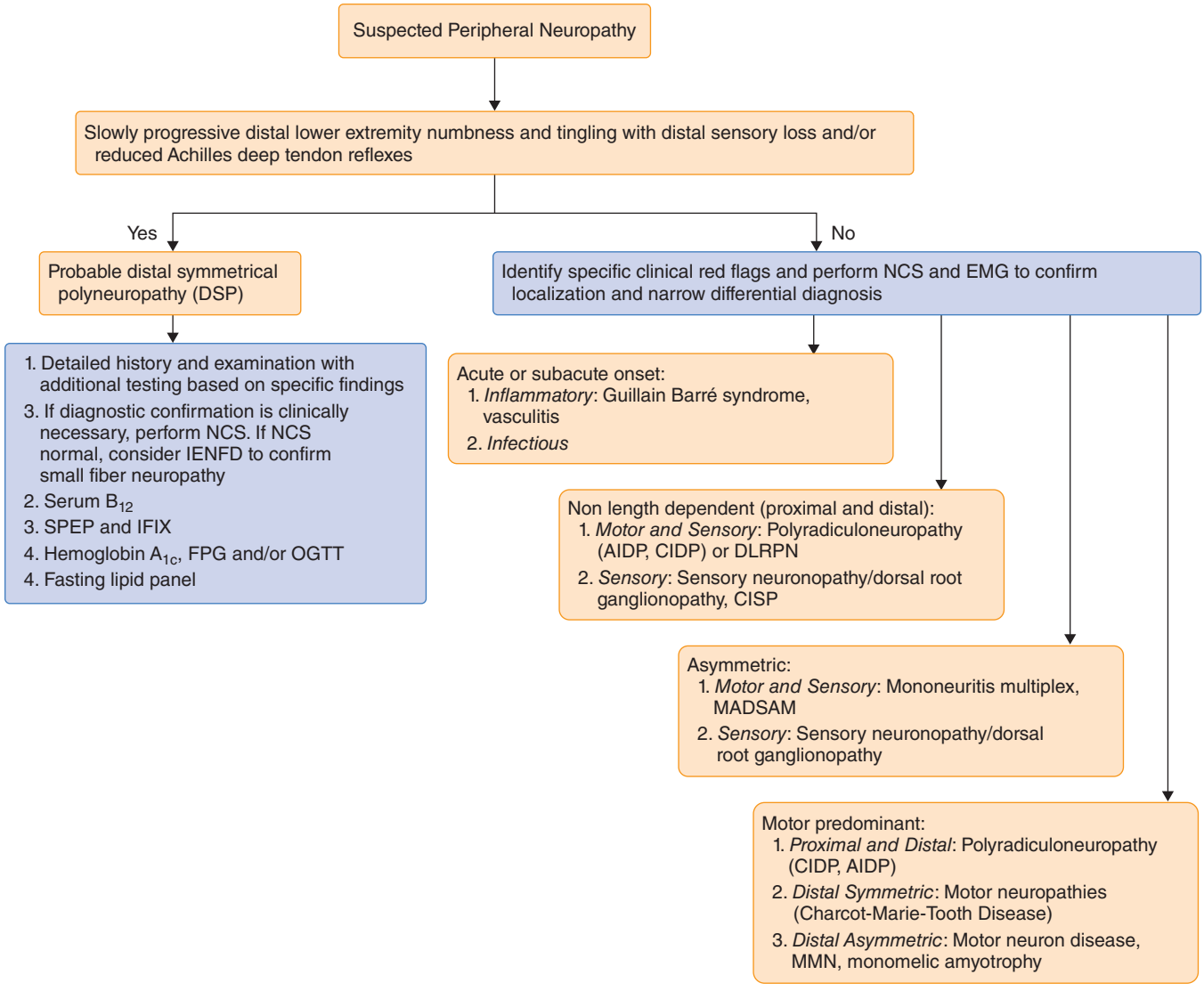

FIGURE 388-1. Diagnostic flow diagram for suspected peripheral neuropathy. AIDP = acute inflammatory demyelinating polyradiculoneuropathy; CIDP = chronic inflammatory demyelinating polyradiculoneuropathy; CISP = chronic inflammatory sensory polyradiculoneuropathy; DLRPN = diabetic lumbosacral radiculoplexus neuropathy ("diabetic amyotrophy"); DSP = distal symmetric polyneuropathy; EMG = electromyography; FPG = fasting plasma glucose; IENFD = intraepidermal nerve fiber density; IFIX = immunofixation; MADSAM = multifocal acquired demyelinating sensory and motor neuropathy; MMN = multifocal motor neuropathy; NCS = nerve conduction studies; OGTT = oral glucose tolerance test; SPEP = serum protein electrophoresis.

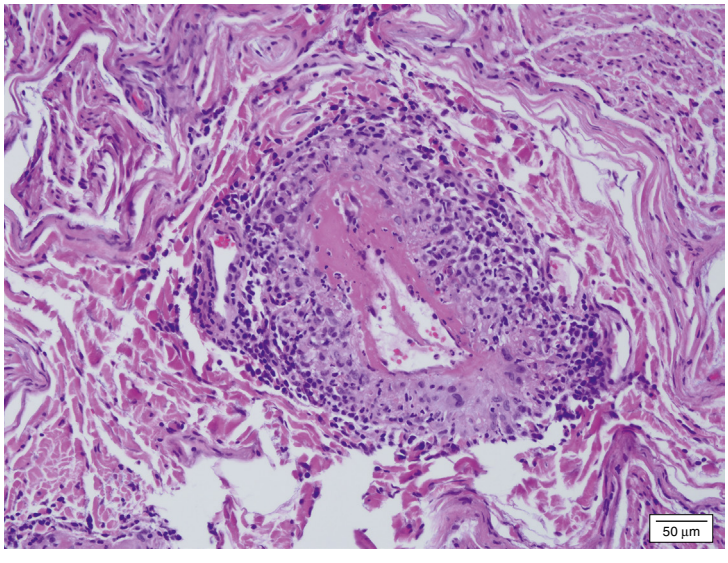

FIGURE 388-2. Nerve biopsy from a patient with mononeuritis multiplex reveals vasculitis involving the full thickness of the vessel wall with fibrinoid necrosis.

throughout life, and most have a normal lifespan. A minority of patients have a more severe phenotype with delayed motor milestones and onset in infancy (Dejerine-Sottas neuropathy).

Patients with hereditary motor neuropathies sometimes have mild sensory abnormalities, and patients with hereditary sensory and autonomic neuropathies usually have some weakness. The extent of motor or sensory loss can sometimes alter the classification. For example, the same mutations in the same gene (*GARS*) may cause both CMT2D and hereditary motor neuropathy type V (Video 388-1).

DIAGNOSIS

Genetic testing is the gold standard for accurately diagnosing patients with inherited neuropathies, but it should be combined with a careful family history, clinical examination, and neurophysiologic testing. The diagnostic yield of genetic testing is highest among patients with clinical onset at a young age and a positive family history. For CMT1A, which comprises about 50% of cases of Charcot-Marie-Tooth disease, genetic testing must specifically search for a PMP22 duplication, which will not be diagnosed by next-generation sequencing. If this test is negative or in patients with axonal variants (CMT2), next-generation sequencing is typically performed. Since not all variants are pathogenic and many are described as variants of uncertain significance, it is essential to determine, if possible, whether a given variant tracks with neuropathy in a family, whether the variant is common in population databases, and whether it is predicted to be pathogenic in animal or *in silico* models.

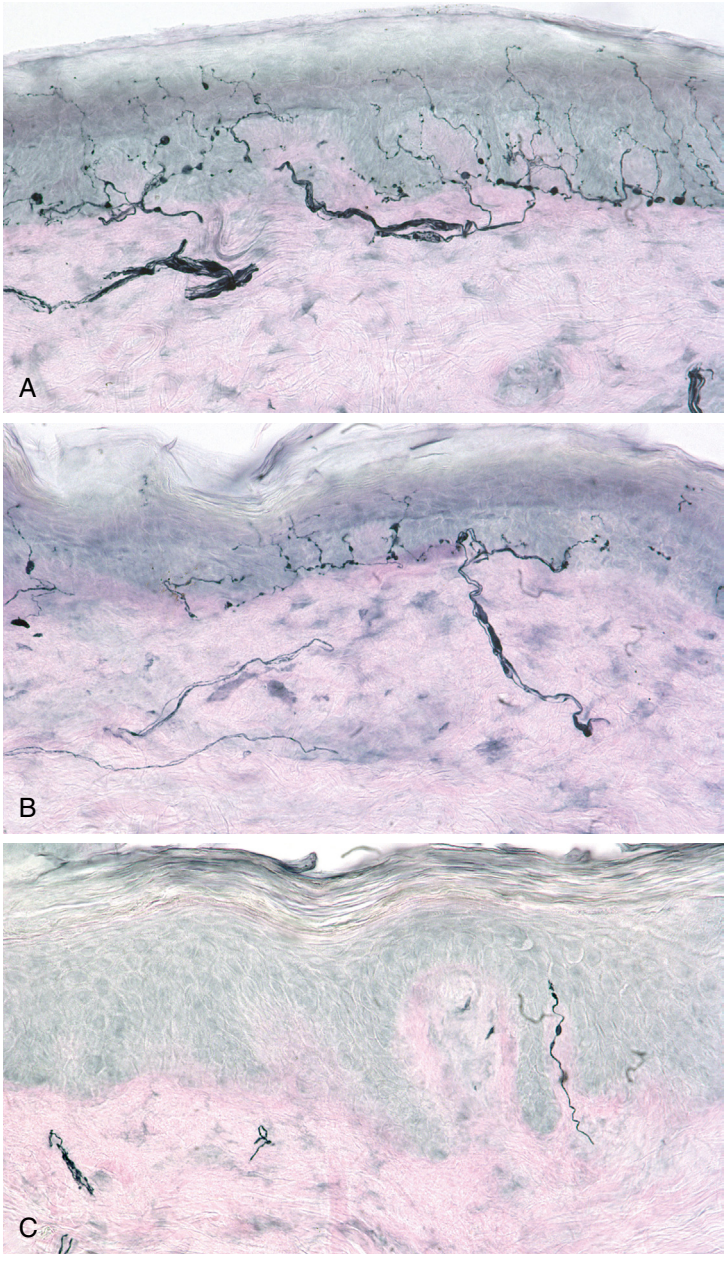

FIGURE 388-3. Skin biopsies from the proximal thigh (A), distal thigh (B), and distal leg (C) of a patient with suspected small fiber neuropathy were stained with PGP 9.5, a pan-axonal marker.

Differential Diagnosis

Inherited neuropathies must be distinguished from acquired neuropathies. Clinical clues that a neuropathy is likely to be genetically based are slow progression beginning in early childhood, abnormal foot structure, and uniform slowing of upper extremity nerve conduction velocities in CMT1. CMT2 is characterized by axonal loss as reflected by reduced compound muscle action potential and sensory nerve action potential amplitudes. Other genetic disorders, such as hereditary spastic paraplegia (Chapter 379) or leukodystrophies (Chapter 380), may mimic inherited neuropathies by causing distal weakness, sensory loss, and foot deformities such as pes cavus; these patients often have upper motor neuron signs and may have clinical and neurophysiologic evidence of neuropathy.

TREATMENT

Ankle-foot orthoses may return gait and balance to normal for years. Foot surgery to correct inverted feet, pes cavus, and hammer toes can sometimes improve walking, alleviate pain over pressure points, and prevent plantar ulcers. Experimental molecular treatments are emerging for inherited neuropathies. For example, antisense oligonucleotides and RNA inhibition have proven effective in mouse and rat models.

FIGURE 388-4. Distal leg atrophy and high arched feet (pes cavus) in a patient with Charcot-Marie-Tooth disease.

PROGNOSIS

A detailed family history and examination of family members may be required for prognosis and genetic counseling. In general, Charcot-Marie-Tooth is a slowly progressive disorder that does not affect longevity, although many patients experience progressive gait difficulties with aging. The prognosis and degree of disability vary among specific forms.

FAMILIAL AMYLOID POLYNEUROPATHY

Familial amyloid polyneuropathy (Chapter 174) is caused by dominantly inherited mutations in one of at least three genes: transthyretin, apolipoprotein A1, and gelsolin. Pathogenic mutations in transthyretin cause a conformational change that destabilizes its normal tetramers, thereby resulting in intracellular aggregates that form amyloid deposits in peripheral nerve, heart, and other tissues.

Familial amyloid polyneuropathy typically presents as a painful sensory neuropathy in mid to late adulthood, with prominent autonomic features, including sexual dysfunction, gastrointestinal disturbances, and cardiac arrhythmias, followed by weakness, weight loss, and inanition. Certain mutations commonly cause neuropathy (Val30Met), whereas others (Val122Ile) usually present with heart disease.

Diagnosis is based on genetic testing supported by tissue evidence of amyloid because mutations are not always penetrant.[5]

TREATMENT

Tafamidis (20 mg daily) acts to stabilize the variant transthyretin polymer to prevent its dissociation and can delay progression of the polyneuropathy.[A1] Other effective options for polyneuropathy include patisiran (a small interfering RNA at 30 mg intravenously every 3 weeks)[A2] and inotersen (an antisense oligonucleotide at 284 mg subcutaneously weekly).[A3] Diflunisal (250 mg twice daily), which is a generic nonsteroidal anti-inflammatory drug that complexes to the thyroxine binding sites on the tetrameric form of transthyretin, stabilizes it, and thus inhibits the release of the transthyretic monomer required for amyloidogenesis, can slow the rate of progression of familial amyloidosis-associated polyneuropathy.[A4] Gene editing using clustered regularly interspaced short palindromic repeats and associated Cas9 endonuclease (CRISPR-Cas9) is an experimental approach to lowering the transthyretin protein concentration.

PROGNOSIS

Death has typically occurred within a decade of diagnosis owing to cardiac or autonomic failure unless patients underwent liver transplantation. As noted earlier, however, new molecular therapies, including inotersen and patisiran, can substantially slow progression, with their long-term benefits still to be determined.

INFLAMMATORY AND IMMUNOLOGIC NEUROPATHIES

Autoimmune disorders of the peripheral nervous system include primary inflammatory neuropathies (Guillain-Barré syndrome and chronic inflammatory demyelinating polyneuropathy) as well as neuropathies related to vasculitis and other systemic autoimmune disorders.

GUILLAIN-BARRÉ SYNDROME

DEFINITION

Guillain-Barré syndrome refers to acquired, inflammatory polyradiculoneuropathies that share an acute onset, elevated cerebrospinal fluid (CSF) protein levels with low cell counts (cytoalbuminologic dissociation), and a monophasic course.[6] Guillain-Barré syndrome is subdivided into demyelinating (acute inflammatory demyelinating polyradiculoneuropathy), and axonal (acute motor and sensory axonal neuropathy and acute motor axonal neuropathy) variants, and the Miller-Fisher syndrome.

EPIDEMIOLOGY

The annual incidence of Guillain-Barré syndrome is 1 to 2 per 100,000, although in some areas the incidence may be higher. Acute inflammatory demyelinating polyradiculoneuropathy accounts for 97% of cases in North America and Europe with an incidence of 0.6 to 1.9 cases per 100,000. Men are more often affected than women (1.4 : 1). In 60% of patients, a respiratory tract infection or gastroenteritis precedes Guillain-Barré syndrome. Patients with axonal variants are particularly likely to have had a prior *Campylobacter jejuni* diarrheal illness.[7] In Belgium and the Netherlands, 5 to 10% of patients have a preceding hepatitis E infection (Chapter 134), thereby emphasizing the regional variability in infectious triggers. Guillain-Barré syndrome does not appear to be substantially associated with severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection or vaccination (Chapters 335 to 337), aside from a slight increase in risk of 0.6 cases/100,000 doses for the ChADOx1nCoV-19 vaccine,[8] and the incidence of Guillain-Barré syndrome actually declined during the pandemic likely due to a reduced incidence of communicable diseases known to provoke Guillain-Barré syndrome.[9] In contrast, Zika virus (Chapter 352) has been associated with a significantly increased risk of all forms of Guillain-Barré syndrome,[10] as well as a transient polyneuritis pattern of mild distal sensory symptoms (acute peripheral polyneuropathy).

PATHOBIOLOGY

All forms of Guillain-Barré syndrome probably result from postinfectious molecular mimicry, in which the immune system attacks peripheral nerve antigens because they resemble antigens presented by microbes, in particular, *C. jejuni*. For example, the HS/0:19 serotype of *C. jejuni* is common in patients with the acute motor axonal neuropathy form of Guillain-Barré syndrome in northern China and other countries. However, it is not clear that molecular mimicry causes acute inflammatory demyelinating polyradiculoneuropathy, which is the most common form in the United States and Europe.

CLINICAL MANIFESTATIONS

Weakness is the most common initial symptom. It can be mild, such as difficulty walking, or severe, with total quadriplegia and respiratory failure. The most common manifestation is leg weakness that progresses into the arms. Bilateral facial weakness occurs in 50% of patients and may lag behind limb weakness. Although Guillain-Barré syndrome has been described as an "ascending paralysis," proximal weakness is common, and 5% of patients have isolated cranial nerve involvement that subsequently descends into the limbs. Slight sensory loss occurs in most patients. The autonomic nervous system is involved in about 65% of cases.

Acute motor sensory axonal neuropathy is clinically similar to acute inflammatory demyelinating polyradiculoneuropathy except it is typically more severe because of primary injury to axons rather than to myelin. Autonomic dysfunction is more common. Weakness without sensory loss develops in acute motor axonal neuropathy, including cranial nerve involvement in about 25% of patients.

The Miller-Fisher syndrome consists of the triad of ophthalmoplegia, ataxia, and areflexia. Facial weakness, ptosis, and pupillary abnormalities may be present. Nerve conduction velocities in Miller-Fisher syndrome are normal, unlike acute inflammatory demyelinating polyradiculoneuropathy.

DIAGNOSIS

The diagnosis of acute inflammatory demyelinating polyradiculoneuropathy and acute motor sensory axonal neuropathy is based on the history, physical examination, CSF evaluation, and nerve conduction studies.[11] Weakness is symmetrical, and deep tendon reflexes are decreased or absent. The presence of other CNS abnormalities should cast doubt on the diagnosis.

CSF analysis typically reveals high protein with a paucity of white blood cells (WBCs). The CSF should have fewer than 5 WBCs/mL; a CSF cell count greater than 50 WBCs/mL suggests HIV seroconversion (Chapters 355 and 359) or infections such as Lyme disease (Chapter 296). Acute inflammatory demyelinating polyradiculoneuropathy is distinguished from acute motor sensory axonal neuropathy by nerve conduction studies. Because elevated CSF protein and abnormal nerve conduction studies may not be apparent in the first 7 to 10 days of the illness and because CSF protein remains normal in up to 10% of cases, the initial treatment decision often must be made based on clinical judgment. Most Miller-Fisher syndrome patients (>85%) have polyclonal antibodies that react to the ganglioside GQ_{1b}.

Differential Diagnosis

Guillain-Barré syndrome usually causes symmetrical proximal and distal weakness with milder sensory loss that reaches maximum severity in less than 4 weeks. A number of warning signs suggest further evaluation for an alternative diagnosis (Table 388-4). Other causes for symmetrical acute weakness include acute toxic neuropathies; fulminant myopathies, particularly immune-mediated necrotizing myopathy (the serum creatine kinase level is usually markedly elevated); and myasthenia gravis (ptosis, diplopia and dysphagia/dysarthria; Chapter 390). Botulism (Chapter 271) causes ophthalmoplegia, unreactive pupils, bulbar weakness, dry mouth, constipation, and orthostatic hypotension, without sensory symptoms. Asymmetrical weakness can be seen with viral encephalomyelitis (Chapter 383). In North America, polio has been eradicated, but other viral illnesses may induce polio-like syndromes including ECHO 70, coxsackievirus (Chapter 349), and West Nile virus (Chapter 352). Though very rare, rabies (Chapter 383) also may present with rapidly progressive paralysis. Tick paralysis, caused by a toxin within the tick, can mimic Guillain-Barré syndrome, particularly in children. Usually, removal of the tick is associated with improvement within hours, although progression can occur, particularly in Australia, where the toxin differs from that found in North America.

Acute myelopathies such as transverse myelitis (Chapter 380), neuromyelitis optica (Chapter 392), and vascular myelopathies (Chapter 248) may also cause rapidly progressive symmetrical weakness and sensory loss. Brisk reflexes and a sensory level are often observed, and bowel and bladder dysfunction are apparent. Carcinomatous or lymphomatous meningitis can also cause a rapidly developing quadriparesis owing to an acute polyradiculopathy.

Nerve conduction studies and electromyography are helpful in excluding myopathies and disorders of the neuromuscular junction. Other acute neuropathies cause axonal injury, so neurophysiologic findings share features with axonal variants of Guillain-Barré syndrome. CSF analysis can be helpful in excluding infectious causes.

TREATMENT

Patients with Guillain-Barré syndrome require hospitalization because of the risk of respiratory compromise, and the decision to admit a patient to an intensive care unit should be based on the trajectory of change in respiratory function and clinical assessment. A vital capacity of less than 1 L or a negative inspiratory force of less than −70 cm water suggests the need for ventilator support (Chapter 91) in an intensive care unit. Autonomic and swallowing function should also be monitored. Guillain-Barré syndrome can be treated within 2 weeks of onset with either intravenous immunoglobulin (IVIG, 2g/kg divided over 2 days or longer if necessary because of the patient's cardiac function or fluid status) or therapeutic plasma exchange of 5 plasma volumes over 10 days.[A5] Patients are significantly more likely to complete a full course of IVIG, so this treatment is generally preferred. Methylprednisolone (500mg/day for 5 days) plus IVIG has a slight initial advantage but no long-term benefit compared with IVIG alone;[A6] given its risks, it generally is not recommended. A second dose of IVIG does not improve outcomes, is associated with a higher risk of complications, and should not be given.[A7] The prognosis of Miller-Fisher syndrome is generally excellent, and there is controversy regarding the necessity of treatment with IVIG or plasma exchange

TABLE 388-4 WARNING SIGNS SUGGESTING AN ALTERNATIVE DIAGNOSIS IN PATIENTS WITH SUSPECTED GUILLAIN-BARRÉ SYNDROME

WARNING SIGN	DIFFERENTIAL DIAGNOSIS
Sensory predominant	Sensory neuronopathy
Prominent bowel and bladder symptoms	Myelopathy
Spinal sensory level	Myelopathy
Persistently asymmetrical weakness	Viral encephalomyelitis (enteroviral), mononeuritis multiplex (vasculitis), radiculoplexus neuropathy (diabetic amyotrophy)
Distal predominant weakness and sensory loss (peripheral polyneuropathy pattern)	Toxic neuropathies (e.g., arsenic)
Slow progression	Chronic inflammatory demyelinating polyradiculoneuropathy
CSF: >50 WBCs/μL	HIV seroconversion

CSF = cerebrospinal fluid; HIV = human immunodeficiency virus; WBC = white blood cell.

PROGNOSIS

Fifty percent of patients progress to maximum disability within 2 weeks of the onset of symptoms, 75% within 3 weeks, and greater than 90% within 4 weeks. With supportive care, mortality is 3% at 6 months, primarily in the elderly and severely affected patients, and especially during the recovery phase. After a brief period of stabilization, slow recovery occurs over weeks to months. Most patients recover completely or are left with minor sequelae; 20% have a persistent disability. The prognosis is poorer in patients who present with weakness, have axonal variants, or have acute inflammatory demyelinating polyradiculoneuropathy with significant axonal loss as reflected by reduced compound muscle action potential amplitudes in the upper extremities. Other predictors of a poor prognosis include older age, preceding diarrheal illness, and the severity of weakness.

CHRONIC INFLAMMATORY DEMYELINATING POLYRADICULONEUROPATHY

DEFINITION

Chronic inflammatory demyelinating polyradiculoneuropathy is usually slowly progressive but may be monophasic or relapsing. By definition, it develops over at least 2 months and more slowly than acute inflammatory demyelinating polyradiculoneuropathy, which it otherwise resembles.

EPIDEMIOLOGY

Chronic inflammatory demyelinating polyradiculoneuropathy[12] occurs in all age groups, with a mean age of 30 to 50 years. Women are more likely to be affected. Antecedent events in about 30% of patients include upper respiratory infections, gastrointestinal infections, vaccinations, surgery, and trauma. In some patients it is a paraneoplastic phenomenon, especially with non-Hodgkin lymphoma (Chapter 171).[13]

PATHOBIOLOGY

Chronic inflammatory demyelinating polyradiculoneuropathy is considered an autoimmune disorder based on its pathology and experimental models, in which a similar disorder follows immunization with peripheral nervous system myelin components and Freund adjuvant. Nerve biopsy shows macrophage-mediated segmental demyelination, occasional endoneurial lymphocytic T-cell infiltrates, and endoneurial edema. Major histocompatibility complex class I and II antigens are upregulated, and there are often deposits of immunoglobulins and complement on the outer Schwann cell membranes or myelin sheaths. Chronic inflammatory demyelinating polyradiculoneuropathy can be passively transferred to animals by patient sera, but no clear autoantigen has been identified.

CLINICAL MANIFESTATIONS

Weakness and sensory loss begin insidiously and progress over a period of months to years. Weakness, which involves both proximal and distal muscles, is usually symmetrical. The absence of proximal weakness suggests a polyneuropathy. Patients often require assistance with ambulation. Loss of proprioception from damage to large-diameter sensory nerves may affect balance. Deep tendon reflexes are usually absent or markedly decreased. Facial weakness (15%), ptosis, or ophthalmoparesis (5%) may occur. Variants include pure motor, pure sensory, and multifocal forms (multifocal acquired demyelinating sensory and motor neuropathy).

DIAGNOSIS

Diagnosis is based on clinical symptoms and signs, CSF examination, and electrodiagnostic studies.[14] CSF results resemble those of acute inflammatory demyelinating polyradiculoneuropathy: WBC counts are usually fewer than 10 cells/μL, and the level of protein is greater than 60 mg/dL. A CSF WBC count greater than 50/μL suggest another diagnosis, such as HIV infection or hematologic malignancy.

Nonuniform, asymmetrical slowing of motor nerve conduction velocity with prolonged minimal F wave latencies is typical. Compound muscle action potential amplitudes are generally reduced because of secondary axonal degeneration. Sensory nerve action potential amplitudes are usually reduced or absent.

Many patients, however, do not meet formal electrophysiologic criteria for chronic inflammatory demyelinating polyradiculoneuropathy. The combination of symmetrical onset of weakness involving all four limbs with proximal weakness in at least one limb has a comparable diagnostic accuracy (sensitivity 83%, specificity 97%).

A subset of patients with severe disability, subacute onset, tremor, sensory ataxia, and poor response to IVIG have antibodies reactive against contactin or neurofascin.[15] These antibodies, which are usually of the immunoglobulin (Ig) G4 isotype, bind to the nodal and paranodal region.

Differential Diagnosis

Chronic inflammatory demyelinating polyradiculoneuropathy, which is distinguished from acute demyelinating polyneuropathy by its time course, may be associated with monoclonal gammopathies (Chapter 173). However, it does not appear to be related to diabetes.

Different clinical patterns should suggest a broader differential diagnosis, and up to 50% of patients initially diagnosed with chronic inflammatory demyelinating polyneuropathy may be incorrectly diagnosed. Overdiagnosis is often related to misinterpretation of nerve conduction study data, a mild to moderate elevation of CSF protein, or reliance on a subjective response to immunotherapy rather than on objective evidence of improvement.[16]

TREATMENT

A standard approach is oral prednisone (1 mg/kg/day) for 6 to 8 weeks, followed by slow tapering over a 3- to 12-month period to a maintenance level of about 0.1 mg/kg/day.[A8] A response to prednisone may take months to occur, and occasional patients may worsen before they respond. Other alternatives are pulsed dexamethasone (6 cycles of 40 mg/day orally for 4 days) or short-term prednisolone (60 mg/day for 5 weeks, then tapering to zero). IVIG at a dose of 1 g/kg every 3 weeks is also effective. Most patients respond within the first three treatments, and a failure to do so suggests a low likelihood of future response. IVIG is more frequently effective than corticosteroids initially, but it may have a less durable benefit. Subcutaneous injections of immunoglobulin are another therapeutic option. Although plasma exchange also is effective, it is difficult to use as a chronic therapy. Because of the side effects of long-term corticosteroids, azathioprine 2 mg/kg and mycophenolate mofetil 1000 to 1500 mg in divided doses twice daily are often used as steroid-sparing agents.

Patients with contactin or neurofascin antibodies may respond to corticosteroids or IVIG; however, these patients may respond better to rituximab, often administered at a dose of 325 mg/m^2 weekly for four doses. New therapeutic agents under active investigation include inhibitors of FcRn (neonatal Fc receptor) and complement.

MULTIFOCAL MOTOR NEUROPATHY

DEFINITION

Multifocal motor neuropathy is characterized by progressive, distal more than proximal, asymmetrical limb weakness, mostly affecting the upper limbs with minimal or no sensory impairment.

EPIDEMIOLOGY

The prevalence of multifocal motor neuropathy is estimated at 2 per 100,000. Men are more frequently affected than women (2.6 : 1). Initial symptoms develop in 80% between 20 and 50 years, with a mean age at onset of 40 years.

PATHOBIOLOGY

Multifocal motor neuropathy is considered to be an autoimmune neuropathy based on clinical improvement with immunotherapies and because patients often have serum antibodies that react with ganglioside GM_1 and because this antibody titer decreases during effective treatment. GM_1 is highly represented in neural membranes at the nodes of Ranvier, compact myelin, and the motor end plate at the neuromuscular junction.

CLINICAL MANIFESTATIONS

The usual pattern is progressive, distal, asymmetrical arm weakness, often in the distribution of a single nerve. In a minority of patients, weakness may start proximally or in the legs. Multifocal motor neuropathy frequently affects multiple nerve distributions, occasionally with a crossed distribution (i.e., one arm and the contralateral leg). Asymmetry and predominance of arm weakness may become less evident over time. Localized muscle atrophy, which may be mild or absent initially, becomes prominent later as a result of axonal degeneration.

DIAGNOSIS

The diagnosis is established by the presence of multifocal, persistent, partial conduction block on motor but not sensory nerve conduction studies. Conduction block can be hard to find, however, and multifocal motor neuropathy should be considered in patients with a typical clinical pattern in the absence of upper motor neuron signs. Anti-GM_1 ganglioside antibodies are detectable in 50% of patients with multifocal motor neuropathy.

Differential Diagnosis

Multifocal motor neuropathy shares many diagnostic features with amyotrophic lateral sclerosis (Chapter 387), including distal asymmetrical upper extremity weakness and atrophy. Key differentiating features include the time course (multifocal motor neuropathy is slowly progressive whereas amyotrophic lateral sclerosis progresses rapidly) and the absence of respiratory or bulbar weakness and of upper motor neuron features. Magnetic resonance imaging or ultrasound of peripheral nerve may be useful in differentiating multifocal motor neuropathy without GM_1 antibodies or conduction block from amyotrophic lateral sclerosis.[17] Multifocal motor neuropathy also may be confused with multifocal chronic inflammatory demyelinating polyradiculoneuropathy, which causes sensory loss as well as motor weakness and is associated with more severe sensory abnormalities on nerve conduction studies.

TREATMENT

IVIG (2 g/kg) is the initial treatment for multifocal motor neuropathy, and almost 80% of patients respond within a week. However, improvement is typically brief (3 to 6 weeks), so repeated treatments are required indefinitely. Clinical improvement is often accompanied by a reduction or resolution of motor conduction block in some nerves, but it does not consistently correlate with a reduction in GM_1 titers. In patients who may eventually become refractory to IVIG, either pulse cyclophosphamide (1 g/m^2 monthly for 6 months) or rituximab (e.g., 375 mg/m^2 weekly for 4 weeks) have been effective in case reports. Mycophenolate and corticosteroids are ineffective.

PROGNOSIS

Long-term follow-up data of patients with multifocal motor neuropathy show impairment of hand function (reduced dexterity and grip strength) and ankle stability with reduced walking speed. Although patients have greater fatigue than age-matched control subjects, their mood, working capacity, and aerobic capacity are not affected.

VASCULITIC NEUROPATHIES

Vasculitic neuropathies typically present as a subacute painful mononeuritis multiplex with acute motor and sensory loss in multiple nerve territories.

EPIDEMIOLOGY

Systemic vasculitic neuropathy is more common than nonsystemic vasculitic neuropathy, but about 10% of patients who initially have nonsystemic peripheral nerve vasculitis ultimately develop a systemic vasculitis. Peak age at onset of both are between the ages of 40 and 70 years, but vasculitis can occur at any age. Rheumatoid arthritis (Chapter 243) evolves into systemic rheumatoid vasculitis in 5 to 15% of patients, and vasculitic neuropathy develops in about 50% of these cases. More than 50% of patients with Churg-Strauss syndrome, 40 to 50% with granulomatosis with polyangiitis (Chapter 137), 35 to 75% with polyarteritis nodosa (Chapter 249), and a majority with mixed cryoglobulinemia have neuropathy. Patients with Sjögren syndrome (Chapter 247) are often initially found to have sensory neuronopathy (ganglionopathy). By comparison, neuropathies are uncommon in systemic lupus erythematosus (Chapter 245).

PATHOBIOLOGY

In patients with mononeuritis multiplex, axonal degeneration develops as a result of nerve ischemia. Inflammation and necrosis of blood vessel walls occlude the lumen, thereby resulting in ischemic damage. Peripheral nerve vasculitides can be divided into those that affect large-diameter arterioles (75 to 300 μm), small-diameter arterioles (<40 μm), and capillaries.[18]

The immune-mediated inflammation is associated with antibody-antigen complexes that are deposited in the vessel wall. Antibodies also bind directly to endothelial cell antigens. In both circumstances, complement is activated. Chemotactic factors then recruit neutrophils, which release proteolytic enzymes and generate toxic oxygen free radicals.

The sensory neuropathy of Sjögren syndrome (Chapter 247) probably results from the infiltration of dorsal root ganglia by cytotoxic T cells. Some patients with systemic vasculitis have symmetrical neuropathies rather than mononeuritis. The pathogenesis of such cases is not defined.

CLINICAL MANIFESTATIONS

Patients typically have a relatively sudden onset of painful focal or multifocal weakness or of sensory loss. These symptoms reflect ischemia anywhere along the length of the nerves, most often in the lower extremities. Up to 30% of patients have a progressive symmetrical pattern of involvement. Patients with large arteriole systemic vasculitis often have systemic symptoms, including fatigue, myalgias, fevers, and arthralgias in addition to the organ involvement that is typical for the specific disorder (Table 388-5). For example, certain forms of vasculitis may affect cranial nerves (polyangiitis with granulomatosis and Sjögren syndrome) or cause autonomic neuropathy (Sjögren syndrome). Mononeuritis multiplex can occur in systemic vasculitis that involves other organ systems, in association with underlying viral infection, or as an organ-specific (nonsystemic) peripheral nerve vasculitis.

DIAGNOSIS

Diagnostic clues are the subacute and progressive time course, as well as the presence of distal weakness and pain. The number of nerves involved may be extensive enough to make the distinction between a multifocal and diffuse neuropathy difficult, and many patients have a mildly asymmetrical or symmetrical confluent mononeuritis multiplex.

Nerve biopsy of clinically affected sensory nerves (sural, superficial peroneal, or superficial radial) is the gold standard for diagnosis, especially because aggressive, long-term therapy may be required. Diagnostic pathologic features of vasculitis are seen in about 50% of patients referred for suspected vasculitis, including destruction of the vessel and inflammation within the vessel wall, and the addition of muscle biopsy may increase diagnostic yield to 60 to 70%. Fibrinoid necrosis, vessel wall scarring, recanalization, neovascularization, and hemosiderin are common but not essential histopathologic features (see Fig. 388-2).

Electrophysiologic findings can also suggest the diagnosis. For example, electromyography and nerve conduction studies can distinguish between mononeuritis multiplex and a symmetrical neuropathy.

Differentiation of systemic versus isolated peripheral nervous system vasculitis depends on clinical and serologic evaluation. The erythrocyte sedimentation rate is usually elevated in systemic vasculitis but is often normal in nonsystemic vasculitis. Perinuclear and cytoplasmic antineutrophil cytoplasmic antibodies (p-ANCA and c-ANCA) suggest granulomatosis with polyangiitis or eosinophilic granulomatosis with polyangiitis (Churg-Strauss syndrome; Chapter 249). Hepatitis C (Chapter 135) is usually associated with cryoglobulinemia. Serum complement levels, extractable nuclear antigen, angiotensin-converting enzyme levels, serum protein electrophoresis, and HIV serology are generally indicated. CSF analysis may be needed to exclude infectious (e.g., Lyme disease; Chapter 296) or other inflammatory causes.

Differential Diagnosis

Acute or subacute mononeuritis multiplex may also result from diabetic and nondiabetic lumbosacral radiculoplexus neuropathy, which usually causes proximal greater than distal weakness in the legs, sarcoidosis (Chapter 83), Lyme disease (Chapter 296), and malignant infiltration of nerves. Multifocal

TABLE 388-5 CLINICAL AND SEROLOGIC FINDINGS OF SYSTEMIC AND NONSYSTEMIC VASCULITIS INVOLVING THE PERIPHERAL NERVOUS SYSTEM

DIAGNOSIS	SEROLOGIC FEATURES	ASSOCIATED CLINICAL FEATURES	USUAL TYPE OF NEUROPATHY	PREVALENCE OF NEUROPATHY
Rheumatoid arthritis (Chapter 243)	RF (80-90%)	Arthritis frequent; multiple organs often affected	Mononeuritis multiplex and sensorimotor neuropathy	50%
Eosinophilic granulomatosis with polyangiitis (formerly Churg-Strauss syndrome) (Chapter 249)	c-ANCA (<30%), p-ANCA (<50%), eosinophilia (100%), elevated ESR (85%)	Eosinophilia, asthma, sinusitis (60-80%), skin lesions (50-70%)	Mononeuritis multiplex	20%
Granulomatosis with polyangiitis (Chapter 249)	c-ANCA (75-90%) p-ANCA (<20%)	Pulmonary and renal involvement	Mononeuritis multiplex	15%
Polyarteritis nodosa	Elevated ESR (85%), positive serology, hepatitis B (30%), ANCA (<10%)	Multiple organs (skin, joints, renal, gastrointestinal)	Mononeuritis multiplex	60%
Mixed cryoglobulinemia (Chapter 173)	Hepatitis C (80-90%), reduced complement (70-90%), RF (70-90%), elevated ESR (70%).	Skin (purpura, livedo), joints, Raynaud phenomenon	Mononeuritis multiplex	20-90%
Sjögren syndrome (Chapter 247)	α-Ro/SS-A (60%), α-La/SS-B (50%)	Dry eyes, dry mouth; 90% are women	Multiple patterns	25%
Nonsystemic peripheral nerve vasculitis	Elevated ESR (50%), positive ANA (25%), reduced complement (5%)	Muscle disease (25%)	Mononeuritis multiplex	100%

ANCA = antineutrophil cytoplasmic antibodies; α-Ro/SS-A = anti–Sjögren's-syndrome–related antigen A autoantibodies; c-ANCA = cytoplasmic antineutrophil cytoplasmic antibodies; ESR = erythrocyte sedimentation rate; La/SS-B = La/Sjögren syndrome antigen B; p-ANCA = perinuclear antineutrophil cytoplasmic antibodies; RF = rheumatoid factor.

motor neuropathy and multifocal acquired demyelinating sensory and motor neuropathy cause asymmetrical weakness, but neither causes pain; furthermore, multifocal motor neuropathy does not cause sensory loss. Asymmetrical isolated sensory loss occurs in some forms of sensory neuronopathy that are caused by dorsal root ganglionopathy.

TREATMENT

Treatment for vasculitic neuropathy should be based on the specific form and clinical situation. Patients with large arteriole systemic vasculitis are at risk for rapid progression and disability, so treatment should be more aggressive, for example, oral prednisone (1 mg/kg) or intravenous methylprednisolone (1000 mg/day for 3 to 5 days) as induction therapy. Oral prednisone is continued at this dose for 1 to 2 months before instituting a slow taper. Maintenance cyclophosphamide (1 g/m^2 IV monthly for 6 months, or 2 mg/kg orally daily) is usually required for 3 to 6 months. If ongoing therapy is needed, cyclophosphamide may be replaced with oral methotrexate (e.g., starting at 7.5 to 15 mg/week) or azathioprine (e.g., starting at 2 to 3 mg/kg/day), with the dose ultimately decreased if the treatments prove effective. Patients with refractory vasculitis may benefit from rituximab (usually at a dose of 325 mg/m^2 weekly for four doses), IVIG (typically 1 g/kg every 3 to 4 weeks), or plasma exchange.

Because patients with nonsystemic vasculitic neuropathy usually have a more benign course than do patients with systemic vasculitis, alternate-day oral prednisone (e.g., 60 to 80 mg every other day) is often adequate therapy. Azathioprine or weekly methotrexate can be used as a glucocorticoid-sparing agent.

Patients with viral-induced peripheral nerve vasculitis, such as hepatitis C–associated cryoglobulinemia, require treatment of the underlying viral illness. Clinically significant vasculitic neuropathy can be treated as previously outlined.

PROGNOSIS

Most systemic and nonsystemic vasculitis cases respond at least partially to treatment. For systemic vasculitic neuropathy, the prognosis is linked to that of the causative disease, whereas isolated peripheral nervous system vasculitis has a better prognosis.

NEUROPATHIES ASSOCIATED WITH MONOCLONAL GAMMOPATHIES AND MULTIPLE MYELOMA

Monoclonal gammopathy and multiple myeloma (Chapter 173) are associated with multiple patterns of neuropathy, including a distal symmetrical polyneuropathy; polyneuropathy, organomegaly, endocrinopathy, myeloma protein, and skin changes (POEMS) syndrome; light chain amyloidosis; and distal acquired demyelinating syndrome, which is a variant of chronic inflammatory demyelinating polyradiculoneuropathy characterized by antibodies to myelin-associated glycoprotein in 50% of patients.[19] Multifocal motor neuropathy may occur with IgM gammopathies with specificity for GM_1 ganglioside (reviewed earlier). Patients with typical chronic inflammatory demyelinating polyradiculoneuropathy have a monoclonal gammopathy in the absence of the specific syndromes reviewed later; however, treatment and the response to it are similar to patients without gammopathy.

MONOCLONAL GAMMOPATHY OF UNCERTAIN SIGNIFICANCE

Monoclonal gammopathy refers to the presence in the β-γ region of serum protein electrophoresis of an abnormal spike (variably termed a paraprotein, monoclonal protein, or M protein) consisting of immunoglobulins of the same isotype, all produced by a single clone of abnormally proliferating lymphocyte/plasma cells. In some cases, the M protein is part of a malignant lymphoproliferative disease such as multiple myeloma, solitary plasmacytoma (IgG and IgA), Waldenström IgM macroglobulinemia (Chapter 173), chronic lymphocytic leukemia (Chapter 169), primary light-chain amyloidosis (Chapter 174), or cryoglobulinemia (Chapter 173). In most instances, however, monoclonal gammopathy is not initially associated with any of these disorders and is classified as a monoclonal gammopathy of uncertain significance (MGUS; Chapter 173),[20] although patients with MGUS have a 1 to 2% per year risk of progressing to myeloma or another hematologic disease.

EPIDEMIOLOGY

Monoclonal gammopathy is seen in 5 to 8% of patients with peripheral neuropathy of unknown etiology. However, MGUS is frequent, being found in 1% of the population older than 50 years and in 3% older than 70 years, and most subjects with MGUS do not have neuropathy. In some cases, the co-occurrence of neuropathy and M protein may be a coincidence.

The prevalence of neuropathy is higher in patients with IgM versus IgG or IgA M proteins. The prevalence of symptomatic neuropathy associated with IgM monoclonal gammopathy in patients older than 50 years is approximately 20 per 100,000. In half of such patients, the M protein reacts with either the HNK1 carbohydrate moiety of MAG or with other glycoproteins (MPZ, PMP22) and glycolipids (sulfoglucuronylparagloboside [SGPG] and lactosaminylparagloboside [SGLPG]). IgM M proteins associated with neuropathy may also bind to other neural antigens.

In patients with IgG monoclonal gammopathy and neuropathy, the relationship is less clear than with IgM. Although about 10% of patients with multiple myeloma have neuropathy, in most cases, the M protein does not react with a neural antigen, and the neuropathy does not improve with therapy (see later).

PATHOBIOLOGY

The underlying pathobiology of neuropathy associated with MGUS and multiple myeloma is unknown.

CLINICAL MANIFESTATIONS

Patients with MGUS typically present with a slowly progressive distal symmetrical peripheral polyneuropathy that is clinically indistinguishable from cryptogenic sensory peripheral neuropathy. Patients with multiple myeloma also typically have a slowly progressive sensory greater than motor peripheral polyneuropathy, although motor-predominant forms have been described.

DIAGNOSIS

Diagnosis is based on demonstration of a monoclonal gammopathy on serum protein electrophoresis or immunoelectrophoresis. Immunoelectrophoresis has a higher sensitivity than serum protein electrophoresis, but serum protein electrophoresis is required to define the heavy- and light-chain of MGUS. Patients with a non-IgG gammopathy, anemia, constitutional symptoms, or a high weight gammopathy (>15 g/L) require a full hematologic evaluation (Chapter 173). Patients with a distal symmetrical sensory polyneuropathy, a low level of monoclonal IgG or IgM, and normal hematologic values can be followed with yearly paraprotein measurements. The presence of distal weakness, tremor, severe pain, autonomic dysfunction, or rapid progression should prompt a more extensive evaluation for another cause for neuropathy, either related to the monoclonal gammopathy (e.g., POEMS, see later) or as a distinct disorder.

TREATMENT

Treatment of MGUS neuropathy is largely symptomatic, because treatment of the underlying monoclonal gammopathy does not improve the neuropathy. In contrast, treatment of multiple myeloma may improve the neuropathy.

PROGNOSIS

In patients whose myeloma responds to treatment, more than 50% have improvement in neuropathy. Patients with MGUS usually have a disease course similar to cryptogenic sensory peripheral neuropathy, with slow progression and minimal disability.

POEMS SYNDROME

The component features of POEMS syndrome are *P*olyneuropathy, *O*rganomegaly, *E*ndocrinopathy, *M*yeloma protein, and *S*kin changes. POEMS syndrome is a rare paraneoplastic neuropathy associated with osteosclerotic myeloma or Castleman disease (Chapters 171 and 359).[21]

EPIDEMIOLOGY

Approximately 50% of patients with the osteosclerotic form of myeloma have neuropathy.

PATHOBIOLOGY

The underlying mechanism of neuropathy in POEMS syndrome is unknown, although the very frequent elevation of vasoactive growth factors such as vascular endothelial growth factor (VEGF), the levels of which correlate with disease severity, suggest vascular permeability as a contributing mechanism.

CLINICAL MANIFESTATIONS

Neuropathy typically presents with distal numbness and pain progressing to weakness that is often in the pattern of a length-dependent polyneuropathy. The progressive nature and severity of weakness often suggest chronic inflammatory demyelinating polyradiculoneuropathy, although proximal weakness is less common in POEMS. The general physical examination should evaluate possible organomegaly (hepatomegaly, splenomegaly, or lymphadenopathy), features of volume overload (edema, ascites, or pleural effusions), endocrinopathy (diabetes, hypothyroidism, gynecomastia, amenorrhea, and hypogonadism), and skin changes.

DIAGNOSIS

The monoclonal protein usually has a lambda light chain, and any patient with a progressive neuropathy or suspected chronic inflammatory demyelinating polyradiculoneuropathy with a lambda monoclonal gammopathy should be carefully examined and evaluated for POEMS syndrome, as should patients who are thought to have chronic inflammatory demyelinating polyradiculoneuropathy but fail to respond to immunotherapy. Important diagnostic clues include common skin changes such as hyperpigmentation or hypertrichosis, edema, gynecomastia, and papilledema (Fig. 388-5). However, most patients do not manifest the full syndromic spectrum of POEMS (Table 388-6).

Nerve conduction studies often demonstrate some features of demyelination, although axon loss is common. Blood levels of VEGF are elevated to greater than 200 pg/mL in many patients (sensitivity of 68% and specificity of 95%), and the concentration increases as the disease progresses.

TREATMENT

Treatment of POEMS syndrome is based on directing therapy at the clonal plasma cell expansion. Modalities include radiation of osteosclerotic lesions, systemic chemotherapy (Chapter 173), and autologous stem cell transplantation. Treatments typically recommended for chronic inflammatory demyelinating polyradiculoneuropathy are usually ineffective.

LIGHT CHAIN AMYLOIDOSIS

Light chain amyloidosis (Chapter 174), which shares many features with hereditary forms of amyloidosis, affects peripheral nerve in about 20% of patients. The heart and kidney are commonly affected.

FIGURE 388-5. Optic disc edema in a patient with polyneuropathy, organomegaly, endocrinopathy, myeloma protein, skin change (POEMS) syndrome.

TABLE 388-6 DIAGNOSTIC CRITERIA FOR POLYNEUROPATHY, ORGANOMEGALY, ENDOCRINOPATHY, MYELOMA PROTEIN, SKIN CHANGE (POEMS) SYNDROME

Mandatory major criteria (both must be present)	Polyneuropathy Monoclonal plasma cell-proliferative disorder (almost always lambda)
Other major criteria (1 required)	Castleman disease Sclerotic bone lesions Elevated vascular endothelial growth factor
Minor criteria (1 required)	Organomegaly (splenomegaly, hepatomegaly, or lymphadenopathy) Extravascular volume overload (edema, pleural effusion, ascites) Endocrinopathy (diabetes, hypothyroidism, gynecomastia, amenorrhea, and hypogonadism) Skin changes (hyperpigmentation, hypertrichosis) Papilledema Thrombocytosis or polycythemia

EPIDEMIOLOGY

Light-chain amyloidosis is more common in men (2 : 1 ratio) and has a median age at onset in the seventh decade.

PATHOBIOLOGY

Monoclonal light chains, either lambda or kappa, misfold and aggregate into beta-pleated sheets, which deposit in susceptible tissues. The most commonly involved tissues are kidneys, liver, heart, the carpal tunnel, and the peripheral nervous system.

CLINICAL MANIFESTATIONS

Patients typically present with a relentlessly progressive, distal, symmetrical polyneuropathy that is usually painful and associated with autonomic dysfunction, often with fatigue and unexplained weight loss. Orthostatic hypotension is common, and men often note erectile dysfunction. A minority of patients have a painless neuropathy or do not have prominent autonomic symptoms (Chapter 386). Other organ systems are usually involved, most often leading to renal failure and heart failure.

DIAGNOSIS

Most patients with light chain amyloidosis have free light chains in the urine. Confirmation requires tissue diagnosis, usually with bone marrow biopsy and fat pad biopsy or aspiration (Chapter 174). Biopsy of other affected tissues may be necessary.

TREATMENT

Treatment (Chapter 174) consists of systemic chemotherapy and, for patients who are candidates, stem cell transplantation. When successful, treatment may result in stabilization of the neuropathy.

DISTAL ACQUIRED DEMYELINATING SYMMETRIC SYNDROME

Distal acquired demyelinating symmetric syndrome, which is an uncommon variant seen in only about 7% of patients with chronic inflammatory demyelinating polyradiculoneuropathy, preferentially affects the distal nerve segments, where it results in distal weakness and numbness, often with tremor.[22]

PATHOBIOLOGY

Approximately 50% of patients have an IgM monoclonal protein that immunoreacts with myelin associated glycoprotein (MAG). Nerve biopsy demonstrates segmental demyelination, with deposits of M protein and complement in patients with anti-MAG related distal acquired demyelinating symmetric syndrome. The myelin lamellae are often widened on sural nerve biopsies, but a biopsy is not necessary for diagnosis. High titers (>1 : 10,000) of anti-MAG IgM antibodies are associated with neuropathy, and intraneural or systemic injection of anti-MAG IgM M proteins causes complement-mediated demyelination of nerves in animals.

CLINICAL MANIFESTATIONS

Most patients are initially seen in their sixth to seventh decade of life with dysesthesias and paresthesias in their legs and unsteadiness while walking because of loss of proprioception. Distal weakness subsequently ensues, and many patients develop a coarse postural and action tremor. Disability and reduced quality of life are determined by weakness, tremor, ataxia, and fatigue. Physical examination shows a length-dependent large fiber sensory neuropathy.

DIAGNOSIS

Nerve conduction studies demonstrate evidence of distal demyelination with markedly prolonged motor distal latencies. The presence of an IgM monoclonal gammopathy with high titer anti-MAG antibodies is observed in 50% of patients.

TREATMENT

Patients with anti-MAG neuropathy and distal acquired demyelinating syndrome do not respond as well to immunotherapy as do patients with typical chronic inflammatory demyelinating polyradiculoneuropathy. One small trial of rituximab failed to show substantial improvement although case series data suggest up to 30% of patients may have benefit, particularly patients with high antibody titers. Multiple other agents have been tried without success.

PARANEOPLASTIC NEUROPATHIES

DEFINITION

Paraneoplastic neuropathies (Chapter 164) are a remote effect of cancer not caused by metastatic invasion of neural tissue; radiation therapy or chemotherapy; metabolic, vascular, or hormonal disturbances; or opportunistic infections.[23] Neural injury is the result of the host immune responses to a tumor antigen or antigens that are also present in neural tissues. Paraneoplastic peripheral neuropathy is also termed a sensory neuronopathy or ganglionopathy.

EPIDEMIOLOGY

Paraneoplastic syndromes occur in less than 1% of patients with cancer; peripheral neuropathy is only one of the paraneoplastic syndromes. Although more than 25% of patients with cancer have evident neuropathy on neurologic examination, the relationship to malignancy is unclear in most. Paraneoplastic neuropathy may develop before, during, or after the tumor is diagnosed. Certain patterns of neuropathy, such as a non–length dependent sensory neuronopathy (dorsal root ganglionopathy), suggest a paraneoplastic etiology and should prompt a thorough investigation for an underlying cancer. Small cell carcinoma of the lung is by far the most common underlying neoplasm, followed by carcinoma of the stomach, breast, colon, rectum, ovary, and prostate. A similar neuronopathy/ganglionopathy can be seen in Sjögren syndrome (Chapter 247), rarely with HIV infection, as a complication of platin chemotherapy or checkpoint inhibitor therapy, and with pyridoxine toxicity.[24]

PATHOBIOLOGY

Subacute sensory neuronopathy, the most characteristic paraneoplastic neuropathy, results from an immune-mediated ganglionitis that destroys sensory neurons in the dorsal root ganglia. Mononuclear inflammatory infiltrates composed of CD4+ and prominent CD8+ T cells, along with plasma cells, are found in the stroma surrounding the dorsal root ganglion neurons. Other findings include atrophy of the dorsal roots; loss of sensory neurons, which appear to be replaced by a proliferation of satellite cells (Nageotte nodule); axonal degeneration; and secondary degeneration of the dorsal column of the spinal cord. Inflammatory infiltrates can also be found in peripheral nerves or muscle. Sural nerve biopsies typically reveal only loss of myelinated nerve fibers and are not useful for diagnosis.

CLINICAL MANIFESTATIONS

Subacute sensory neuronopathy is characterized by subacute, progressive impairment of all sensory modalities and is associated with severe sensory ataxia and areflexia. Subacute sensory neuropathy may precede the diagnosis of tumor by months or even years. At onset, patients may have shooting pain and burning sensations. Other symptoms include numbness, tingling, and a progressive sensory loss that may be asymmetrical. Symptoms usually progress rapidly to involve all four limbs, the trunk, and face. Findings may then stabilize, although by this time the patient is often totally disabled. Occasional patients have an indolent course.

Neurologic examination reveals loss of deep tendon reflexes and involvement of all modalities of sensation; large fiber modalities such as vibration and joint position sense are most severely affected. The loss of position sense may lead to severe sensory ataxia with pseudoathetoid movements of the hands and an inability to walk despite normal strength. Cranial nerve involvement includes sensorineural deafness, loss of taste, and facial numbness. The asymmetrical pattern of symptoms sometimes suggests a radiculopathy or plexopathy.

A paraneoplastic encephalomyelitis characterized by patchy, multifocal neuronal loss in regions of the cerebral hemispheres, the limbic system, the cerebellum, the brain stem, the spinal cord, and autonomic ganglia often develops in patients with subacute sensory neuropathy. Autonomic symptoms include impotence, dry mouth, and constipation.

DIAGNOSIS

The diagnosis is based on recognizing the typical neuropathy in the setting of malignancy. The results of routine laboratory studies are generally normal. The diagnosis is supported by finding serum polyclonal IgG anti-Hu antibodies, also called antineuronal antibodies type 1, or by indirect immunofluorescence or immunohistochemistry and confirmed by Western blot analysis.

Subacute painful, asymmetrical neuropathy or neuronopathy in an elderly patient should prompt a search for carcinoma of the lung because small cell lung cancer accounts for more than 80% of the associated tumors. Subacute sensory neuropathy also has been reported in patients with adenocarcinoma of the lung, breast, ovary, stomach, colon, rectum, and prostate, as well as

Hodgkin and non-Hodgkin lymphoma. In patients with no evidence of cancer, detection of anti-Hu antibodies should prompt a computed tomography study of the chest with special attention to the mediastinal lymph nodes. The use of whole-body positron emission tomography with fluorodeoxyglucose has been advocated for early diagnosis in patients with anti-Hu antibodies or clinical suspicion of subacute sensory neuropathy because it may reveal neoplastic adenopathy months before computed tomography or magnetic resonance imaging.

TREATMENT

Subacute sensory neuropathy responds poorly to plasma exchange, IVIG, or immunosuppressant medications, even when such treatment is started early in the course of the disease. Successful treatment of the tumor rarely induces remission of subacute sensory neuropathy, but it may stabilize symptoms.

THE DIABETIC NEUROPATHIES

Diabetes causes a broad spectrum of neuropathies that can be divided into chronic (distal symmetrical polyneuropathy and autonomic neuropathy) and acute forms (diabetic amyotrophy, acute cranial mononeuropathies and truncal radiculopathy, and treatment-induced neuropathy of diabetes).[25] Patients with prediabetes, obesity, and the metabolic syndrome are at risk for cryptogenic sensory peripheral neuropathy.

EPIDEMIOLOGY

Diabetes (Chapter 210) is the most common cause of neuropathy in the world. Distal symmetrical polyneuropathy, which occurs in about 50% of patients, is one of the most costly and disabling diabetic complications. Autonomic neuropathy is also common (erectile dysfunction develops in 20 to 60% of diabetic men), but widespread autonomic dysfunction (Chapter 386) develops in less than 5% of patients.

DISTAL SYMMETRICAL AND AUTONOMIC POLYNEUROPATHY

PATHOBIOLOGY

The pathogenesis of diabetic distal symmetrical and autonomic polyneuropathy involves both microvascular and metabolic abnormalities. In type 1 diabetes, increased blood glucose levels are clearly linked to the risk of neuropathy. In type 2 diabetes, other metabolic features, including hyperlipidemia and obesity, are important contributors to the risk of neuropathy. Specific pathogenic mechanisms, ultimately leading to mitochondrial injury and axon loss in both types of diabetes, include activation of the polyol pathway, formation of advanced glycation end products, altered diacylglycerol/protein kinase activity, and oxidative stress.

CLINICAL MANIFESTATIONS

Distal symmetrical polyneuropathy can be symptomatic or asymptomatic. Patients with symptoms develop numbness, tingling, and, in 20% of cases, neuropathic pain in the feet that over time progresses proximally toward the knees. In type 2 diabetes, small-diameter axons responsible for pain sensation are injured first. With time, injury to large-diameter fibers results in loss of proprioception and touch sensation, leading to gait instability and risk of ulceration and amputation. Patients with asymptomatic neuropathy often present later in the disease with large-fiber neuropathy and severely reduced sensation in the feet. Weakness is minimal, even in the distal foot muscles. Once numbness reaches the knees, the fingers and hands may become involved. Ankle reflexes are generally absent, although patellar reflexes may be present.

Autonomic neuropathy (Chapter 386) typically presents after years of diabetes with gastroparesis (Chapters 122 and 210), constipation that may alternate with diarrhea, orthostatic hypotension, anhidrosis, cardiac arrhythmias, and erectile dysfunction. Autonomic abnormalities, which can be the most disabling component of diabetic neuropathy, pose a significant risk of cardiac mortality.

DIAGNOSIS

Diagnosis is based on a combination of symptoms and signs of polyneuropathy. Distal symmetrical polyneuropathy may be the first symptom of diabetes, with the diagnosis apparent only after careful evaluation. Nerve conduction studies or skin biopsy can confirm the diagnosis if there is diagnostic uncertainty but are not routinely recommended.[26]

TREATMENT

Aggressive glycemic control reduces the risk of neuropathy in type 1 diabetes but not in type 2 diabetes, in which control of other metabolic risk factors may be equally important.[27] Several studies suggest diet and exercise may reduce neuropathic symptoms, including pain, and slow their progression. Gabapentin (up to 3600 mg/day in divided doses 3 to 4 times per day), pregabalin (150 to 300 mg/day in two or three divided doses), duloxetine (60 to 120 mg/day), and tricyclic antidepressants (e.g., amitriptyline, desipramine, or nortriptyline at doses of 25 to 100 mg daily) may be partially effective for treatment of neuropathic pain.[28,A9] Patients with loss of touch and protective sensation are at risk for foot ulceration and amputation.

DIABETIC LUMBOSACRAL RADICULOPLEXUS NEUROPATHY

Diabetic lumbosacral radiculoplexus neuropathy, commonly referred to as "diabetic amyotrophy," develops acutely or subacutely, most commonly in type 2 diabetes, with asymmetrical proximal leg pain that is typically severe. Atrophy and weakness of proximal thigh muscles ensues, and symptoms often spread to the contralateral side. Distal leg weakness is common, and some patients develop hand weakness. Diagnosis is based on clinical features. Nerve conduction studies and electromyography demonstrate an axonal polyradiculoneuropathy with frequent denervation in paraspinal muscles. CSF examination reveals an elevated protein with normal cell counts. Although not necessary for diagnosis, cutaneous sensory nerve biopsy demonstrates a small vessel vasculitis, thereby suggesting an autoimmune etiology. Half of patients require opiate analgesia and a wheelchair to assist with ambulation. Spontaneous recovery is typical, although up to 50% of patients do not regain baseline function. It is unclear if immunosuppressant therapy can alter the natural history, although a brief course of corticosteroids (e.g., 1 g solumedrol 3 times weekly with a tapering dose over 12 weeks) may improve pain.

TREATMENT-INDUCED NEUROPATHY OF DIABETES

Treatment-induced neuropathy of diabetes develops after rapid correction of severe hyperglycemia. Patients present with a subacute painful neuropathy with autonomic features. The distribution and severity of symptoms are proportional to the magnitude of rapid decline in the hemoglobin A_{1c} level. Patients whose hemoglobin A_{1c} drops by 2 to 3% over 3 months have a 20% risk of a distal predominant painful neuropathy, and patients with a drop of 4% or more have an 80% risk, often with more proximal involvement and severe pain. Treatment-induced neuropathy of diabetes is often associated with worsening diabetic retinopathy, suggesting a common microvascular mechanism, although the time course is also consistent with an inflammatory etiology. Neuropathy improves gradually, although most patients require symptomatic pain management.[29]

ACUTE FOCAL NEUROPATHIES

Truncal radiculopathy is characterized by the subacute onset of focal pain and sensory loss over a region of the trunk, with some patients developing segmental abdominal weakness appreciable as a bulge. Symptoms are similar to those of post-herpetic neuralgia. As with diabetic lumbosacral radiculoplexus neuropathy, many patients require aggressive pain management, and at least partial improvement occurs after a period of months.

Cranial neuropathies classically manifest as an acute oculomotor nerve palsy in which retro-orbital pain is followed by diplopia and ptosis. Pupillary fibers are often spared, thereby distinguishing the disorder from lesions that compress the oculomotor nerve and cause a dilated pupil. Similar findings may occur with the trochlear or abducens nerves. Bell palsy is more frequent in diabetic patients and is less likely to involve taste than in patients without diabetes.

INFECTIOUS NEUROPATHIES

NEUROPATHIES ASSOCIATED WITH HIV INFECTION

The peripheral nervous system may be involved in all phases of HIV infection (Chapters 355 and 359). The most common peripheral neuropathy is a distal, painful, sensory axonal polyneuropathy that is similar to the toxic neuropathy caused by nucleoside reverse transcriptase inhibitors (NRTIs), including zidovudine, zalcitabine, didanosine, stavudine, and lamivudine. When an iatrogenic neuropathy is suspected, discontinuation of NRTIs may improve symptoms. A neuropathy caused by HIV is likely to stabilize or improve with antiretroviral treatment.

Inflammatory neuropathies such as chronic or acute inflammatory demyelinating polyradiculoneuropathy can also occur in the early stages of HIV infection at the time of seroconversion; the CSF cytoalbumin dissociation usually seen with these conditions may not be evident in these patients because of a mild CSF mononuclear pleocytosis. The response of these neuropathies to plasma exchange or IVIG is generally good. In later stages of HIV infection, cytomegalovirus (Chapter 347) may cause either an acute lumbosacral polyradiculopathy as a result of direct invasion of nerve roots or a mononeuritis multiplex through a vasculitic mechanism.

NEUROPATHIES ASSOCIATED WITH HERPES ZOSTER

Varicella-zoster virus (Chapter 346) usually remains latent in cranial or spinal ganglia after resolution of a systemic infection. Reactivation, which is more frequent in elderly and immunocompromised patients, causes a vesicular skin eruption accompanied by pruritus and dysesthesias. Herpes zoster resolves spontaneously but is frequently followed by post-herpetic neuralgia, which is characterized by severe pain persisting for more than 6 weeks after the rash appears. Early treatment with oral acyclovir (800 mg, five times daily for 7 days) may reduce both the duration of the acute phase and the risk for post-herpetic neuralgia. The use of concomitant corticosteroids in addition to acyclovir improves acute pain without exacerbating viral spread but does not reduce the incidence or severity of post-herpetic neuralgia. Vaccination with the herpes zoster subunit vaccine reduces the risk of post-herpetic neuralgia (Chapter 346).

NEUROPATHY ASSOCIATED WITH LYME DISEASE

Borrelia burgdorferi (Chapter 296) causes a disease with three stages. In the first stage, shortly after and in the same area of a tick bite, a nonpruritic rash (erythema migrans) appears and spontaneously disappears after a few weeks. The second stage is frequently associated with neurologic complications such as lymphocytic meningitis and focal and multifocal peripheral and cranial neuropathies; characteristic manifestations are unilateral or bilateral facial palsy and radiculitis. The third stage is associated with severe neurologic complications, including encephalopathy, encephalomyelitis, and a predominantly sensory axonal polyneuropathy. A lymphocytic pleocytosis in CSF and demonstration of *B. burgdorferi* infection in serum or CSF are the main laboratory findings. Treatment is discussed in Chapter 296.

NEUROPATHY ASSOCIATED WITH LEPROSY

Leprosy (Chapter 301) is infrequent in the United States but is a common cause of peripheral neuropathy in some developing countries. Leprosy presents in different forms, depending on the host's immune system. Patients with normal cell-mediated immunity are more likely to have a tuberculoid form characterized by hypopigmented skin lesions associated with decreased sensation. In patients with abnormal cell-mediated immunity, the more severe lepromatous form with large disfiguring lesions may develop. A mononeuritis multiplex pattern with prominent superficial sensory loss is the most typical clinical manifestation of leprosy. If treated early, neuropathies in leprosy improve. World Health Organization recommendations call for combination therapy that includes dapsone (50 to 100 mg/day or 200 to 250 mg/week), rifampicin (600 mg monthly), and clofazimine (100 mg/day).

NEUROPATHY ASSOCIATED WITH DIPHTHERIA

Vaccination has made diphtheria (Chapter 272) rare in developed countries, but it is an important cause of subacute neuropathy in developing countries. Some strains of *Corynebacterium diphtheriae* produce a potent neurotoxin that causes palatal weakness, lens accommodation deficits, and extraocular palsies. These acute manifestations are followed by limb paralysis that resembles acute inflammatory demyelinating polyradiculoneuropathy (see earlier). The neuropathy caused by the neurotoxin usually resolves with resolution of the infection. The diphtheria organism can be eradicated by therapy with antibiotics such as erythromycin (2 g/day intravenously divided twice daily for adults) or penicillin (procaine penicillin G, 1.2 million U/day intramuscularly divided twice daily for 14 days). However, the neuropathy, as with other manifestations of the disease, generally requires treatment with diphtheria antitoxin, a hyperimmune antiserum produced in horses. Depending on the severity of the disease, antitoxin is administered intramuscularly or intravenously (80,000 to 120,000 units for extensive disease for 3 or more days; Chapter 272).

TOXIC AND DEFICIENCY SYNDROMES

In Western countries, toxic neuropathies are frequently the side effects of a medication[30] rather than a result of environmental exposure (see Table 388-2). In most cases, iatrogenic neuropathy is manifested as a length-dependent or "dying-back" axonal neuropathy. Treatment requires a correct diagnosis and discontinuation of the drug. The most common category of drugs associated with neuropathy are antineoplastic agents (especially paclitaxel and oxaliplatin). In some cases, the neuropathy progresses for weeks following discontinuation of exposure (hexane and cisplatin), a phenomenon referred to as "coasting," and improvement often requires many months.

Treatment is symptomatic. Duloxetine (30 mg orally once daily for 1 week, then 60 mg daily for 4 weeks) improves pain in chemotherapy-induced peripheral neuropathy.[A10]

Peripheral polyneuropathy may also develop with deficiency of a number of vitamins and nutrients (Chapter 199).[31] Deficiency of vitamin B_{12} results in severe combined degeneration of the spinal cord and peripheral nerves, accompanied by tingling feet and a sensory ataxia. Copper deficiency (Chapter 199), often due to zinc overload, causes a similar syndrome. Vitamin E deficiency causes ataxia and a phenotype similar to Friedreich ataxia (Chapter 379). Vitamin B_1 (thiamine) deficiency may cause a severe sensorimotor axonal neuropathy in addition to the classic triad of Wernicke encephalopathy (ataxia, ophthalmoparesis, and encephalopathy; Chapter 384). Vitamin B_6 (pyridoxine) is unique in that neuropathy may develop with either deficiency or overload. Excessive doses of B_6 result in a sensory neuronopathy (ganglionopathy) that ranges in severity from mild distal numbness and tingling with modest exposure to severe sensory ataxia with higher doses.

An acute axonal sensorimotor peripheral polyneuropathy with ataxia and areflexia in the setting of nutritional deficiency has been described in alcoholic patients and in patients who fail to follow the recommended nutritional supplementation plan following bariatric surgery. Some patients develop significant weakness. Serum thiamine and vitamin B_6 levels are often reduced,[32] and most patients respond to nutritional repletion.

CRITICAL ILLNESS NEUROPATHY

Critical illness polyneuropathy is an acute or subacute axonal length–dependent axonal neuropathy that occurs in critically ill patients with sepsis. It is often associated with critical illness myopathy (Chapter 389), which has resulted in some confusion regarding the extent to which clinical symptoms are attributable to the neuropathy or the myopathy. Up to 70% of critically ill patients with sepsis (Chapter 94) develop some degree of critical illness neuropathy, and patients with the systemic inflammatory response syndrome are at particular risk. Treatment is directed at the underlying systemic disorder that led to critical illness and sepsis. Most patients experience at least some degree of recovery, with the ultimate disability determined by the degree of persistent weakness.

NEURALGIC AMYOTROPHY (IDIOPATHIC BRACHIAL PLEXITIS)

Neuralgic amyotrophy, also known as idiopathic brachial plexitis, typically presents with acute severe shoulder and proximal arm pain followed by rapidly progressive arm weakness and atrophy within several days. Hereditary neuralgic amyotrophy is due to autosomal dominant mutations in the *SEPT9* gene, which encodes the Septin 9 protein. Idiopathic neuralgic amyotrophy is thought to be inflammatory because 50% of patients describe a preceding infection.

Initially thought to be very uncommon, recent data suggest the incidence may be as high as 1 : 1000. Although 70% of patients have a typical presentation, the remainder present with other focal variants, including involvement of individual upper extremity peripheral nerves, including the phrenic and laryngeal nerves. Recurrent episodes occur in 25% of idiopathic cases. Treatment is focused on management of neuropathic pain (Chapter 26).

COMPRESSIVE MONONEUROPATHIES

Peripheral nerves are vulnerable to compression at specific anatomic sites. The most common are median nerve compression at the wrist within the carpal tunnel (carpal tunnel syndrome), ulnar nerve compression at the elbow (cubital tunnel syndrome), and peroneal nerve compression over the lateral fibular head.

CARPAL TUNNEL SYNDROME

Carpal tunnel syndrome, which is caused by compression of the median nerve at the wrist, is the most common compressive mononeuropathy.[33] The carpal tunnel is bounded by the carpal bones and carpal ligament, and it is traversed by the median nerve and flexor tendons. Risk factors include repetitive motion of the wrist and fingers, as well as structural abnormalities within the tunnel such as osteoarthritis, synovial cysts, myxedema, and (rarely) amyloid deposition. Carpal tunnel syndrome is also common during pregnancy, but it usually resolves following delivery.

Symptoms typically include paresthesias of the first three fingers, often at night, and are relieved by shaking or elevating the hand. Patients also commonly

FIGURE 388-6. Bell palsy is characterized by a lower motor neuron pattern of weakness. At rest, there is slight widening of the right palpebral fissure (**A**). With smiling, there is deviation of the corner of the mouth towards the normal side on the left (**B**). There is weakness of eye closure on the right while closing the eyes (**C**). When the patient is asked to look surprised, there is weakness (or flattening) of the frontalis muscles on the right (**D**). Upper motor neuron facial weakness, such as is seen with a stroke, would not cause forehead weakness.

experience subjective numbness in a broader distribution including the medial hand (ulnar distribution) and as proximal as the shoulder. In severe cases, patients have objective sensory loss in the median nerve distribution as well as atrophy and weakness of median-innervated thenar muscles (abduction and opposition). Provocative maneuvers such as the *Tinel* (tapping the carpal tunnel) and *Phalen* (sustained flexion of the wrist) signs have poor diagnostic utility compared with nerve conduction studies. Neutral splinting of the wrist during sleep is effective for most patients. Subacute painful, asymmetrical neuropathy or neuronopathy in an elderly patient should prompt a search for carcinoma of the lung because small cell lung cancer (Chapter 177) accounts for more than 80% of the associated tumors. Methylprednisolone injections can provide temporary relief,[A11] as can injection of 5% dextrose,[A12] but patients who fail to respond or whose symptoms recur usually obtain relief from endoscopic or open decompressive surgery, with the endoscopic approach generally preferred.[A13]

CUBITAL TUNNEL SYNDROME

Cubital tunnel syndrome is manifested by numbness and tingling of the fifth finger and the outer half of the fourth finger. The approach is as for carpal tunnel syndrome, except that exercises may be helpful. If symptoms warrant, treatment is by decompression surgery.[34]

BELL PALSY

Unilateral facial paralysis of acute onset frequently occurs on an idiopathic basis (Bell palsy). The diagnosis is one of exclusion. Facial nerve palsies also occur in the setting of *herpes zoster oticus* and are associated with otalgia and varicelliform lesions affecting the external ear, ear canal, or tympanic membrane. Facial paralysis of a lower motor neuron type can be caused by carcinomatous meningitis (Chapter 381), sarcoidosis (Chapter 83), Lyme disease (Chapter 296), and HIV infection (Chapters 355 and 359). Lower motor neuron facial weakness is characterized by weakness of the lower face and frontalis muscle (Fig. 388-6), whereas upper motor neuron weakness (such as is seen with a stroke) involves only the lower face.

Primary tumors of the facial nerve can cause rapidly developing facial paralysis. Facial paralysis can also occur in *CNS disease* affecting the pontomedullary junction, such as stroke or multiple sclerosis (Chapter 380).

CLINICAL MANIFESTATIONS AND DIAGNOSIS

Most cases of facial paralysis are idiopathic. Patients typically notice facial paralysis on inspection in the mirror in the morning. Facial paralysis may be heralded or accompanied by pain behind the ear. The severity of paralysis varies widely.

TREATMENT

Ten days of oral corticosteroids (prednisolone 25 mg twice daily for 10 days) administered early in the course increases the return of facial function from 63 to 83% at 3 months in patients with idiopathic Bell palsy.[35] Acyclovir is of no independent benefit, but adding it (at a dose of 400 mg five times daily for 7 days, or twice this dose for varicella zoster) to corticosteroid therapy appears to improve outcomes in severe cases. In severe cases, protection of the cornea from drying and injury is essential.

PROGNOSIS

Most patients improve, but about 10% of patients have little recovery. Aberrant regeneration of the facial nerve can cause synkinesis, such as "jaw winking" (when the eye is closed) or tearing accompanying salivation (syndrome of crocodile tears).

TRIGEMINAL NEURALGIA (TIC DOULOUREUX)

Trigeminal neuralgia and other painful cranial neuralgias are discussed in Chapter 367.

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389 MUSCLE DISEASES

DUYGU SELCEN

DEFINITION

Muscle diseases, which are also called myopathies, are disorders of skeletal muscle structure or function. Myopathies can be primary and occur in isolation, or they can be part of a multisystem disorder.

EPIDEMIOLOGY

Many muscle diseases (Table 389-1) are inherited as autosomal dominant, autosomal recessive, X-linked, or maternal (mitochondrial) conditions.[1] Environmental factors that may precipitate myopathies include recent infection, foreign travel, exposure to medications such as statins, and alcohol abuse (Chapter 364). Exercise commonly precipitates symptoms in patients with metabolic myopathies, whereas exposure to cold and high-carbohydrate or potassium-rich food can precipitate weakness in muscle channelopathies.

The prevalence of muscle disease is estimated to be about 1 per 1000 people, including acute and transient disorders (e.g., myositis owing to infectious or toxic causes) and chronic inflammatory or genetic disorders that cause substantial morbidity over decades or a lifetime. Myopathies can cause premature death owing to neuromuscular weakness and secondary respiratory infections or to involvement of other organs in multisystem diseases. Myocardial involvement, which is particularly common in some muscle diseases, can cause heart failure or life-threatening arrhythmias.

PATHOBIOLOGY

Muscle disease can result from a perturbation in the anatomy or any of the physiologic processes required for muscle contraction or the genes that control them. Skeletal muscle is part of a motor unit, which is defined as the anterior horn cell body, its axon, the neuromuscular junction, and the skeletal muscle fibers innervated by the one axon. The motor unit is coordinated in a manner that allows efficient muscle contraction and function. The number of muscle fibers innervated by each motor unit varies from a few (e.g., in muscles controlling very precise movements, such as extraocular muscles) to more than 1000 (e.g., large and powerful but less precise muscles, such as the quadriceps).

Skeletal muscle is composed of myriad muscle fibers. Muscle fibers, which are multinucleated cells formed by fusion of myoblasts during development, are surrounded by a plasma membrane, the sarcolemma, which is surrounded by a basal lamina and endomysial connective tissue. Groups of muscle fibers compose the fascicles, which are surrounded by perimysium, and the groups of fascicles in turn are surrounded by epimysium. Nerve branches, blood vessels, muscle spindles, and fat cells lie within the connective tissue of the muscle.

Each muscle fiber is composed of myofibrils, which themselves are composed of repeat units a few microns long called sarcomeres. The sarcomere consists of a highly organized protein network that gives the muscle fiber its characteristic striated appearance. Each sarcomere is flanked by two Z discs. Z discs are composed of multiple proteins, including α-actinin. Emanating from the Z disc are thin filaments, composed of actin, troponin, and tropomyosin. Thick filaments consist of myosin. Other structures comprise subcellular organelles, including the mitochondria, which are the principal energy source, the endoplasmic reticulum, and the transverse tubules that communicate with the extracellular space.

Muscle function (E-Fig. 389-1) is dependent on chemical energy from adenosine triphosphate (ATP). In the first 30 minutes of sustained activity, ATP is produced by the breakdown of glycogen (glycolysis), and after 30 minutes ATP is produced by fatty acid β-oxidation and oxidative phosphorylation within the mitochondria. The process that leads to muscle contraction begins with the generation of the muscle fiber action potential (Chapter 41), which initiates muscle contraction after it is propagated into the interior of muscle fiber through the transverse tubular system. The release of calcium from the endoplasmic reticulum triggers a coordinated series of events that lead to the coupling of excitation to contraction. Calcium binds to troponin, which interacts with tropomyosin and results in actin-myosin binding. The repeated formation and cleavage of actin-tropomyosin cross-bridges, in an ATP-dependent process, results in sliding of thick and thin filaments and shortening of the sarcomere.

The structural integrity of the muscle fiber surface membrane is maintained by a network of proteins within the muscle. Dystrophin is a key component of the subsarcolemmal cytoskeleton. In combination with several glycoproteins called sarcoglycans (α, β, δ, γ), dystroglycans (α, β), and syntrophins (α,β1, β2), which form the dystrophin-sarcoglycan complex, it anchors the contractile elements of the muscle fiber to the sarcolemma and to the extracellular basal lamina. The basal lamina contains several important proteins, such as collagen, fibronectin, and laminin, which includes merosin and related proteins. The intermediate filament proteins, including desmin, connect the Z disc and other organelles to the subsarcolemmal cytoskeleton.

TABLE 389-1 CLASSIFICATION OF MYOPATHIES

HEREDITARY
Muscular dystrophies
Congenital myopathies
Myotonia and channelopathies
Metabolic myopathies
Mitochondrial myopathies
ACQUIRED
Inflammatory myopathies
Endocrine myopathies
Myopathies associated with systemic illness
Drug-induced/toxic myopathies

Adapted from Chinnery PF. Muscle diseases. In: Goldman L, Schafer AI, eds. *Goldman's Cecil Medicine*, 24th ed. Philadelphia: Elsevier; 2012.

CLINICAL MANIFESTATIONS

Muscle diseases often present with localized or diffuse muscle weakness, reduced exercise tolerance, resting or exercise-induced muscle pain, muscle enlargement or atrophy, cramps, delayed relaxation, or, rarely, myoglobinuria. These symptoms and signs can be masked by other neurologic or systemic features in patients with multisystem diseases.

History

The assessment of patients with neuromuscular diseases begins with a careful history, general physical examination, and detailed neurologic examination. The age of onset, the rate of progression, and whether the process is episodic, static, or progressive can provide important clues. Congenital and childhood-onset myopathies can be associated with reduced fetal movements, breech delivery, weak cry or suck, and the delayed acquisition of motor milestones. Weakness is the most common presenting symptom, but other symptoms of muscle disease include muscle pain, reduced exercise tolerance, change in the muscle bulk (hypertrophy or atrophy), abnormal spontaneous muscle activity, delayed relaxation, fatigue, or myoglobinuria. Weakness may be relatively static as in some congenital myopathies, progressive as in muscular dystrophies, intermittent as in periodic paralysis, fluctuating as in neuromuscular junction disorders (Chapter 390), or exercise related as in metabolic myopathies. The most common distribution of weakness is proximal or limb-girdle weakness, which results in difficulties in getting out of low chairs, a bathtub, or a car seat; climbing up and down stairs; arising from a squat; or getting off the floor. Proximal arm weakness manifests as difficulty reaching to shelves, washing or brushing hair, or raising arms to put on a shirt. Distal leg weakness can lead to difficulty walking on uneven surfaces, tripping over curbs, difficulty standing on the toes, or slapping feet owing to footdrop. Distal upper limb weakness results in difficulty opening jars, typing at a keyboard, writing, or buttoning clothes. Bilateral facial weakness can result in difficulty whistling, blowing up balloons, or drinking through a straw. Predominant involvement of ocular muscles can produce ptosis and diplopia. Weakness of the bulbar muscles manifests as difficulties with speech and swallowing, neck weakness that can lead to a dropped head, and respiratory muscle weakness that can lead to symptoms suggestive of nocturnal hypoventilation or respiratory failure. The early recognition of progressive respiratory failure is essential because it is treatable with noninvasive positive-pressure ventilation.

Fatigue and exercise intolerance can be presenting symptoms of muscle diseases, but they can also be multifactorial and nonspecific. In isolation, these symptoms usually do not indicate a primary muscle disease.

Muscle pain is another nonspecific symptom that can arise from many systemic and psychiatric conditions. Sometimes patients describe aching, stiffness, numbness, or burning as pain. Muscle diseases rarely cause diffuse, generalized, or persistent muscle pain. Muscle pain without muscle weakness

ABSTRACT

Muscle diseases, which are also called myopathies, are disorders of skeletal muscle structure or function. Myopathies can be primary and occur in isolation, or they can be part of a multisystem disorder. Many muscle diseases are inherited as autosomal dominant, autosomal recessive, X-linked, or maternal (mitochondrial) conditions. Environmental factors may precipitate myopathies. Myopathies often present with localized or diffuse muscle weakness, reduced exercise tolerance, resting or exercise-induced muscle pain, muscle enlargement or atrophy, cramps, delayed relaxation, or rarely, myoglobinuria. Exercise commonly precipitates symptoms in patients with metabolic myopathies, whereas exposure to cold and high-carbohydrate or potassium-rich food can precipitate weakness in muscle channelopathies. Neurophysiologic testing, measurement of serum creatine kinase, muscle biopsy, and genetic testing help guide the diagnosis of muscle diseases. Myopathies can cause premature death owing to neuromuscular weakness and secondary respiratory infections or to involvement of other organs in multisystem diseases. Myocardial involvement, which is particularly common in some muscle diseases, can cause heart failure or life-threatening arrhythmias.

KEYWORDS

skeletal muscle
congenital myopathy
muscular dystrophy
metabolic myopathy
mitochondrial myopathy
inflammatory myopathy
channelopathy

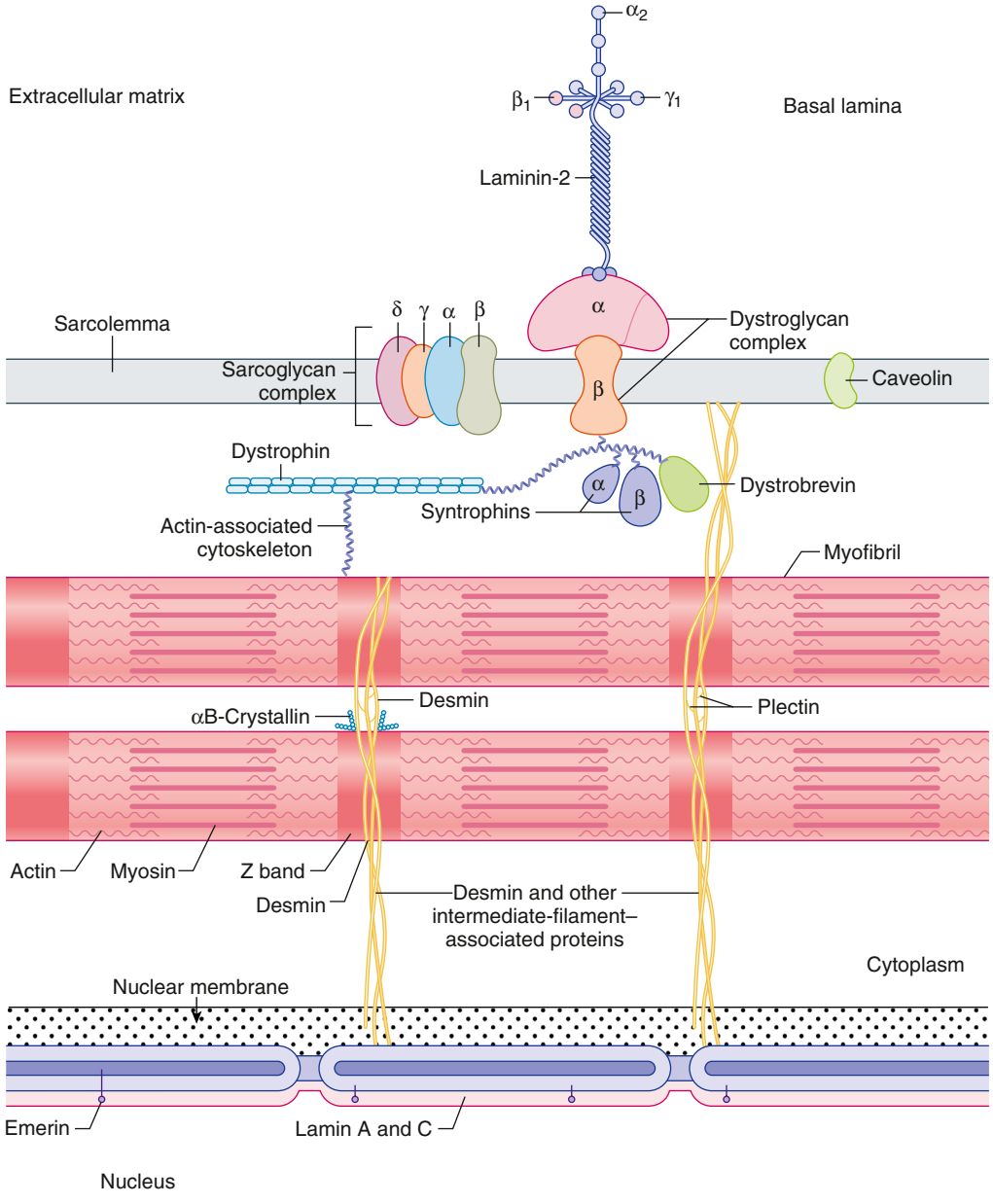

E-FIGURE 389-1. **Muscle structure.** (From Chinnery PF. Muscle diseases. In: Goldman L, Schafer AI, eds. *Goldman's Cecil Medicine,* 24th ed. Philadelphia: Elsevier; 2012.)

is often a feature of fibromyalgia (Chapter 253) or chronic fatigue syndrome. Diffuse myalgia can occur in inflammatory muscle disease such as polymyositis or dermatomyositis, vasculitis, or viral or parasitic myositis. Muscle pain precipitated by exercise usually suggests a metabolic myopathy.

Muscle cramps are involuntary painful contractions that may occur in healthy individuals. Dehydration, renal failure (Chapter 116), and electrolyte imbalances (Chapters 102, 103, 105, and 227) can also produce muscle cramps. Muscle stiffness can occur in inflammatory, metabolic, and ion-channel diseases as well as in conditions such as multiple sclerosis (Chapter 380), polymyalgia rheumatica (Chapter 250), and connective tissue diseases (Chapter 236).

Fasciculations are caused by spontaneous firing of muscle fibers that are innervated by a single motor unit. Fasciculations may occur in normal persons, in whom they are usually exacerbated by stress and increased caffeine intake. Fasciculations in association with muscle weakness suggest anterior horn cell disease. Myotonia, often described as muscle stiffness, is characterized by prolonged contraction and delayed relaxation of muscle.

Myotonia can affect limb, facial, or bulbar muscles, and it can lead to persistent limb muscle contraction, eyelid closure, or dysphagia. Myotonic dystrophy is the most common muscle disease associated with myotonia, but patients usually complain more of weakness than the myotonia. Conversely, the myotonia associated with sodium and chloride channelopathies can be disabling. Patients who describe locking of their hands but do not have objective myotonia rarely have a physical explanation for their symptoms.

Tetany is the most severe form of sustained muscle contraction. Tetany occurs in patients with hypocalcemia and hypomagnesemia (Chapter 105), and it is aggravated by metabolic or respiratory alkalosis (Chapter 104).

Severe acute muscle damage, termed *rhabdomyolysis* (Chapter 99), results in myoglobinuria that presents as dark brown or red urine. Such discoloration must be distinguished from other causes of pigmenturia (Chapter 100) such as hemolysis or porphyria.

The detailed family history should include questions about muscle disease, including specific questions about the use of canes, braces, or wheelchairs. It also should assess whether family members have had a cardiomyopathy, unexpected sudden death, diabetes, or cataracts.

Physical Examination

A full physical examination must look for signs that may suggest any of the systemic diseases that are associated with myopathies. The skin examination can give clues to systemic illness, such as the heliotrope rash of dermatomyositis (Chapter 248).

A comprehensive neurologic examination should be performed in each patient to exclude possible central or peripheral nervous system disorders (Table 389-2). Once the muscle disease is confirmed, further testing and diagnosis can be guided by the history and physical examination (Fig. 389-1). The examination begins as soon as the patient enters the examination room. Proximal leg muscle weakness may be evident if patients push themselves up on their thighs or have a waddling gait. Patients should be examined for possible facial muscle weakness or wasting, ptosis, or characteristic dysmorphic features, such as with myotonic dystrophy (Fig. 389-2), that can lead to an immediate clinical diagnosis.

Patients should be asked to rise from a squatting position and walk on their toes to assess possible calf weakness and on their heels to assess ankle dorsiflexion weakness. Patients should be asked to stand to assess posture and any evidence of rigidity or scoliosis. Joints should be moved passively to assess for contractures.

All muscle groups should be inspected for evidence of involuntary movements, atrophy, or hypertrophy. Muscles should be palpated for tenderness or unusual texture. Myotonia can be assessed by the inability to relax the muscle belly after percussion with a reflex hammer or the inability to relax the fingers from a firm grip.

Strength should be graded (Table 389-3) in each muscle group. Observing children and infants when they play with toys and how they stand up and walk usually reveals more than formal manual muscle strength testing. The pattern of muscle involvement can provide clues for the diagnosis of a specific myopathy.

DIAGNOSIS

Neurophysiologic testing, measurement of serum creatine kinase (CK), muscle biopsy, and genetic testing help guide the diagnosis of muscle diseases (see Fig. 389-1 and Table 389-4).

A complete blood count and serum levels of alanine aminotransferase, aspartate aminotransferase, and creatinine can assess possible systemic involvement. An elevated erythrocyte sedimentation rate or C-reactive protein level is found in some inflammatory myopathies and is typical of connective tissue disorders (Chapters 236 and 237). Additional tests to evaluate patients suspected of having inflammatory myopathy or connective tissue disease can include antinuclear antibodies, extractable nuclear antigens, rheumatoid factor, and antineutrophilic cytoplasmic antibodies, as well as anti-Jo-1, anti-Mi2, anti-MDA5, anti-centromere, anti-SCL-70, anti-PM/Scl-100, anti-Ku, anti-PL-7, anti-PL-12, anti-MDA5, anti-NXP-2, anti-TIF-1gamma, anti-U1 RNP, anti-U2 RNP, anti-U3 RNP, anti-SAE1, anti-SAE2, anti-EJ, anti-OJ, anti-SSA, anti-SSB, anti-3-hydroxy-3-methylglutaryl-coenzyme A reductase, or anti–signal recognition particle antibodies (Chapter 237).

The muscle isoform (MM) of CK is frequently elevated in patients with muscle disease, although a normal level is seen in metabolic myopathies and in some chronic myopathies. A mild to moderate increase in the serum CK level can occur in patients with peripheral neuropathy, radiculopathy, and anterior horn cell diseases. The serum CK level is markedly increased in dystrophinopathies, dysferlinopathy, some of the sarcoglycanopathies, α-dystroglycanopathies, and during rhabdomyolysis (Chapter 99). However, it can decline later in muscular dystrophies as the disease progresses. When the serum CK level exceeds the upper limit of normal by about 10-fold, levels of alanine aminotransferase, aspartate aminotransferase, and lactate dehydrogenase also can be elevated, and some patients can be initially misdiagnosed as having hepatitis (Chapters 133 and 134) before the serum CK level is measured. The blood lactate level can be increased in patients with a mitochondrial myopathy, but a normal value does not exclude this diagnosis. In patients with acute muscle pain and/or weakness, electrolytes and thyroid function tests should be checked.

In patients who are diagnosed with dermatomyositis (Chapter 248), the evaluation should include a search for an underlying malignancy. In patients with suspected mitochondrial cytopathy, a serum and/or spinal fluid lactate level may be useful for diagnosis. In patients with suspected fatty acid β-oxidation defects, blood acylcarnitine profile may be useful for the diagnosis.

Electromyography

Electromyography (EMG) consists of nerve conduction studies, repetitive nerve stimulation, and needle examination of muscles (Chapter 366). Nerve

TABLE 389-2 CLINICAL FINDINGS DIFFERENTIATING MUSCLE FROM NERVE DISEASE

FINDING	MYOPATHY	ANTERIOR HORN CELL DISEASE	PERIPHERAL NEUROPATHY	NEUROMUSCULAR JUNCTION DISEASE
Distribution	Usually proximal and symmetrical but can be distal or asymmetrical at onset	Proximal, asymmetrical, and bulbar	Distal, symmetrical	Extraocular, bulbar, proximal limb, but sometimes distal
Atrophy	Slight early, marked late	Marked early	Moderate	Occasionally
Fasciculations	Absent	Frequent	Sometimes present	Absent
Reflexes	Lost late	Variable, can be hyperreflexic	Lost early	Normal or hyporeflexic
Pain	Variable	Absent	Variable, distal when present	Absent
Cramps	Rare	Frequent	Occasional	Absent
Sensory loss	Absent	Absent	Usually present	Absent
Serum creatine kinase	Usually elevated	Occasionally mildly elevated	Normal	Occasionally mildly elevated

Adapted from Chinnery PF. Muscle diseases. In: Goldman L, Schafer AI, eds. *Goldman's Cecil Medicine,* 24th ed. Philadelphia: Elsevier; 2012.

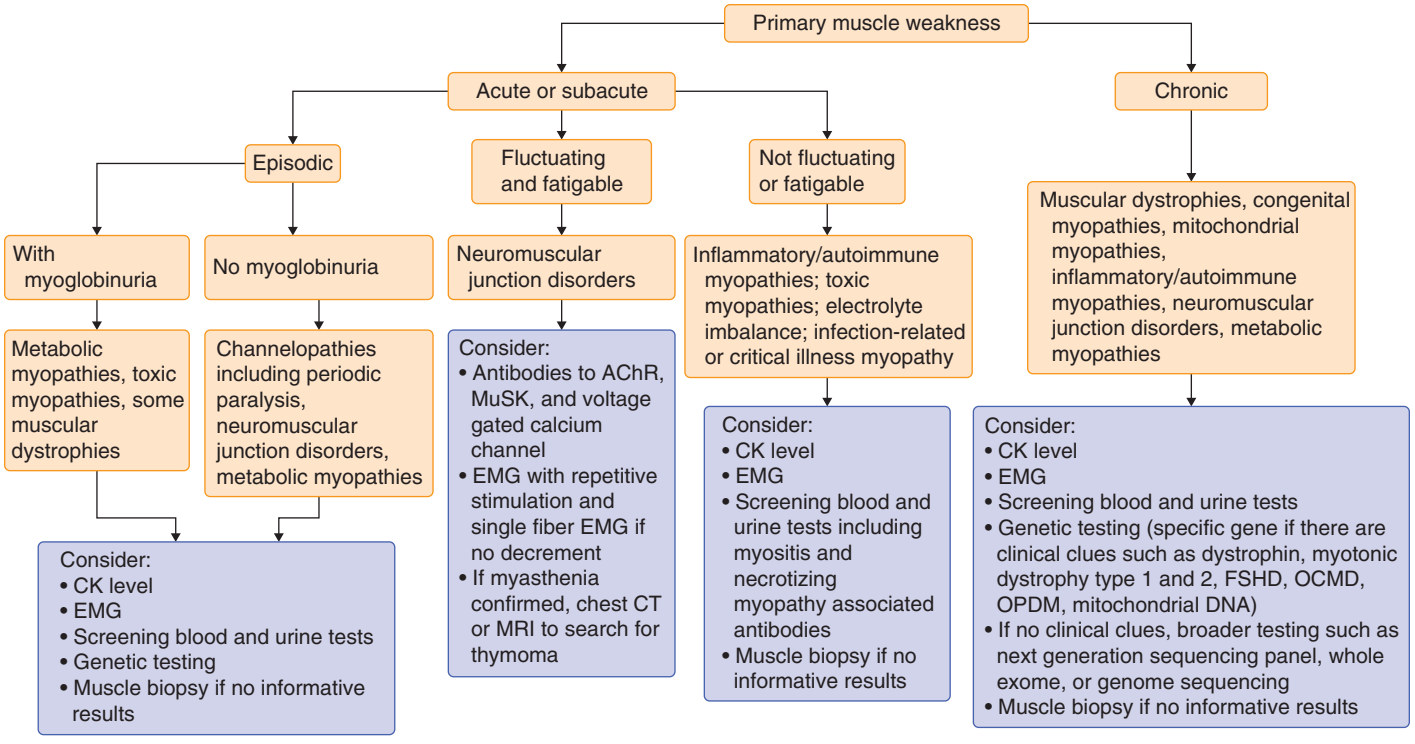

FIGURE 389-1. Approach to weakness of muscle origin. AChR = acetylcholine receptor; CK = creatine kinase; CT = computed tomography; EMG = electromyogram; FSHD = facioscapulohumeral dystrophy; MRI = magnetic resonance imaging; MuSK = muscle-specific kinase; OCMD = oculopharyngeal muscular dystrophy; OPDM = oculopharyngeal myopathy.

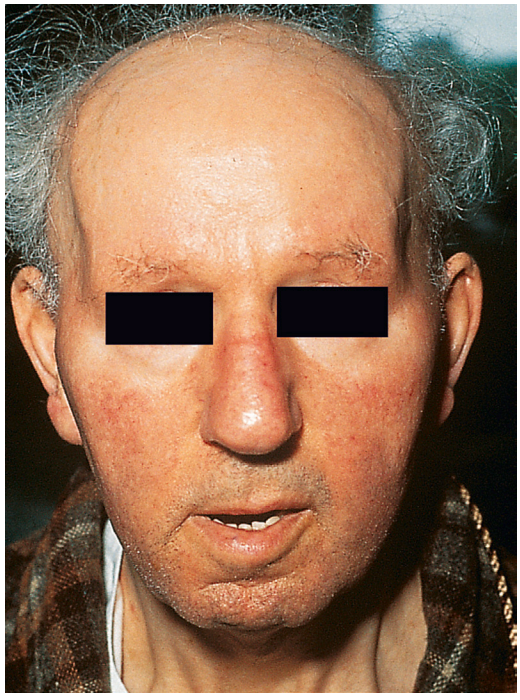

FIGURE 389-2. Myotonic dystrophy in a 50-year-old man. His appearance is typical with facial weakness, atrophy of the temporal muscles and sternocleidomastoids, and frontal baldness, which gives a monklike appearance. (From Chinnery PF. Muscle diseases. In: Goldman L, Schafer AI, eds. *Goldman's Cecil Medicine,* 24th ed. Philadelphia: Elsevier; 2012.)

conduction studies (Chapter 388) are normal in patients with myopathies. In myopathies, the needle examination typically shows complex, polyphasic, low-amplitude motor unit potentials. Myotonia is caused by recurrent depolarization of the muscle fiber surface membrane and has characteristic waxing and waning rhythmical discharges or fibrillation potentials during the needle examination on an EMG. Contractures are electrically silent on EMGs, but muscle cramps are associated with high-amplitude, high-frequency bursts of motor unit activity. The EMG can be normal in some focal myopathies (such as inflammatory myositis), in metabolic myopathies, and in some congenital myopathies.

TABLE 389-3 MEDICAL RESEARCH COUNCIL SCALE OF MUSCLE STRENGTH

GRADE	DEGREE OF STRENGTH
5	Normal power
4	Active movement against gravity and resistance (often subdivided into 4–, 4, and 4+)
3	Active movement against gravity, but not against resistance
2	Active movement, with gravity eliminated
1	Observable muscle contraction, but not capable of initiating movement
0	No contraction

Adapted from Chinnery PF. Muscle diseases. In: Goldman L, Schafer AI, eds. *Goldman's Cecil Medicine,* 24th ed. Philadelphia: Elsevier; 2012.

Genetic Testing

The widespread availability of molecular genetic testing with commercial panels and whole-exome and -genome sequencing has revolutionized the approach to patients who are suspected of having hereditary muscle disease. Dystrophin genetic testing can identify the defects in dystrophin in 90 to 95% of the patients with Duchenne and Becker muscular dystrophy. The sensitivity of the whole-exome sequencing is higher if multiple affected and some unaffected family members and more than one family are analyzed at the same time. Novel genes causing muscular dystrophies are still being discovered.

Muscle Biopsy

Despite advances in genetics and molecular biology, muscle biopsy remains a key component in the diagnosis of most muscle diseases. The biopsy site should be carefully chosen from a clinically affected but not too severely involved muscle. Fresh-frozen sections of the specimens should be used for histochemical studies because even marked morphologic alterations may be

TABLE 389-4 GUIDING PRINCIPLES FOR ASSESSING MUSCLE DISEASES

1. **History**
   - Age of onset (most inherited and acquired disorders have a characteristic age of onset)
   - Rate of progression (acute suggests an acquired, often inflammatory cause)
   - Fluctuating weakness (may indicate a neuromuscular junction disorder, metabolic myopathy, or a channelopathy)
   - Relationship to exercise (may indicate metabolic myopathy or channelopathy)
   - Muscle pain (may indicate inflammatory or metabolic myopathy)
   - Relevant multisystem involvement (may indicate a mitochondrial cytopathy or myotonic dystrophy)
   - Family history (may indicate a genetically determined chronic muscle disease)
2. **Pattern of weakness**
   - Limb-girdle weakness is relatively nonspecific.
   - Inherited disorders often have specific patterns of muscle involvement.
   - Fluctuating weakness may indicate a neuromuscular junction disorder, metabolic myopathy, or channelopathy.
3. **Testing**
   - The serum creatine kinase can be normal.
   - Electromyography is often normal in metabolic myopathies.
   - All patients with muscular dystrophy should have an electrocardiogram and echocardiogram to look for cardiomyopathy and/or conduction defect.
   - Muscle magnetic resonance imaging is increasingly being used to guide muscle biopsy and may sometimes reveal diagnostic patterns of muscle involvement.
   - Some inherited muscle diseases can be diagnosed clinically and confirmed by genetic testing without requiring other investigations (e.g., myotonic dystrophy; Duchenne, Becker, and facioscapulohumeral dystrophy).
   - Muscle biopsy may reveal the cause in most cases; it identifies specific inflammatory myopathies and muscular dystrophies and often provides diagnostic clues for other muscle and neurogenetic disorders.

Adapted from Chinnery PF. Muscle diseases. In: Goldman L, Schafer AI, eds. *Goldman's Cecil Medicine*, 24th ed. Philadelphia: Elsevier; 2012.

undetected in paraffin-embedded tissue. Immunocytochemical localization of specific proteins is useful and diagnostic in some forms of muscular dystrophies. Specific enzyme histochemistry and biochemistry can be used for metabolic myopathies. Genetic analysis of the muscle specimen can be more informative than blood specimens for mitochondrial myopathies.

Imaging

Muscle computed tomography (CT) and magnetic resonance imaging (MRI) are of limited utility for evaluating muscle diseases but can be very useful in excluding spinal cord abnormalities that may cause weakness. Some inherited myopathies are associated with patterns of atrophy and the replacement of muscle with fat. In patchy or focal inflammatory myopathy, MRI can guide muscle biopsy. Functional MRI is sometimes useful in patients with suspected mitochondrial disorders.

SPECIFIC MUSCLE DISEASES

INHERITED MUSCLE DISEASES

The four main categories of inherited muscle diseases are muscular dystrophies (E-Table 389-1), congenital myopathies (E-Table 389-2), muscle ion-channel disorders (E-Table 389-3), and metabolic myopathies (E-Table 389-4). Some gene defects cause specific phenotypes that are instantly recognizable at the bedside by an experienced clinician, but less specific phenotypes can be caused by defects in more than one gene. A systematic approach is critical for an efficient and successful investigation of these disorders.

MUSCULAR DYSTROPHIES

The term *muscular dystrophy* refers to the primary degeneration of the muscle fiber, usually associated with an increase in fatty and fibrous connective tissue.[2] The common clinical presentation is progressive muscle weakness.

DYSTROPHINOPATHIES

Duchenne and Becker muscular dystrophies are caused by mutations in the dystrophin gene, which is located on the X chromosome. Female carriers can develop variable phenotypes, including a severe Duchenne-like presentation, mild adult-onset limb-girdle weakness, asymptomatic CK elevation, and cardiomyopathy.

Duchenne Muscular Dystrophy

Duchenne muscular dystrophy is the most common inherited muscle disease, with an incidence of about 1 in 5000 male births. About one third of patients carry a de novo mutation without a family history. In most patients, a frameshift mutation in the dystrophin gene results in a complete absence of the dystrophin protein. This absence of dystrophin disrupts the mechanical link between the sarcomere and the sarcolemma, thereby causing a calcium leak that leads to necrosis of muscle fibers.

CLINICAL MANIFESTATIONS

Duchenne dystrophy typically presents in young boys who are between 2 and 5 years of age with delayed motor milestones, difficulty running, increasing falls, and enlarged calves. The disorder is relentlessly progressive and can cause a cardiomyopathy (Chapter 47) that leads to heart failure and fatal arrhythmias. Intellectual disability, learning disorders, autism, and attention-deficit/hyperactivity disorder can be associated features. By 12 years of age, most affected individuals can no longer ambulate. By the age of 20 years, most patients develop joint contractures and kyphoscoliosis that lead to further respiratory compromise.

DIAGNOSIS

Affected individuals have a 20- to 100-fold elevation of their serum CK level. Confirmation of diagnosis requires DNA analysis of the dystrophin gene. Genetic testing is positive in about 90 to 95% of patients. If genetic testing is negative, a muscle biopsy is indicated. The pathologic features are typical of a chronic myopathy. Immunostaining shows an absence of dystrophin except in revertant fibers that express dystrophin (E-Fig. 389-2).

TREATMENT

Management requires a multidisciplinary team approach,[3,4] including physical therapy to prevent contractures, the timely provision of appropriate devices and wheelchairs, and indicated medical therapies.[5]

Several phosphorodiamidate morpholino oligomers can induce exon skipping and improve symptoms in Duchenne muscular dystrophy. Eteplirsen, which is designed to skip DMD exon 51, slows the rate of decline in ambulation on a 6-minute walk test compared with placebo over 3 years of treatment compared with nonrandomized controls and has been conditionally approved by the Food and Drug Administration (FDA) to be administered once weekly as 30 mg/kg intravenous infusion.[A1] Golodirsen and viltolarsen, which are designed to induce DMD exon 53 skipping, increase dystrophin protein expression, are well tolerated, and have been conditionally approved by the FDA: golodirsen as a once-weekly 30 mg/kg intravenous infusion[A2] and viltolarsen as a once-weekly 80 mg/kg intravenous infusion.[A3] Casimersen, which is designed to induce DMD exon 45 skipping, also is beneficial and conditionally FDA-approved as a once-weekly 30 mg/kg intravenous infusion.[A4] The choice among these four options requires expert neurologic consultation.

Prednisone (0.75 mg/kg/day) prolongs the ability to ambulate despite its significant side effects (Chapter 28) and is preferable to intermittent prednisone.[A5] Both prednisone (0.75 mg/kg/day) and deflazacort (0.9 mg/kg/day) improve muscle strength, with less weight gain from deflazacort. Prednisone may also help respiratory function and slow the progression of scoliosis.

The cardiomyopathy is typically managed by using β-blockers and angiotensin-converting enzyme inhibitors (Chapter 46), the latter of which can slow the progression of myocardial fibrosis,[A6] which in turn is associated with a poorer prognosis. An orthopedic surgeon should help with monitoring of scoliosis and spinal fusion if indicated. A pulmonologist should assess and follow respiratory function, including the initiation and monitoring of noninvasive ventilation. An endocrinologist should help with monitoring bone health.

Additional gene-therapy approaches are being developed.[6] For example, removal of the mutation in the gene encoding the dystrophin protein in mice using CRISPR-Cas9 technology delivered to muscle by an adeno-associated virus can initially correct about 2% of the protein but then apparently spreads enough over time to improve strength. Recombinant AAV9 capsid carrying a truncated or shortened version of the human dystrophin gene (mini-dystrophin) under the control of a human muscle-specific promotor showed promising results in a phase Ib study.

PROGNOSIS

With ventilatory support, patients often live well into the third or even fourth decade. Chronic respiratory failure is the primary cause of death in the late 20s or early 30s, with most patients succumbing to pneumonia, heart failure, or arrhythmias.

E-TABLE 389-1 MUSCULAR DYSTROPHIES

X-LINKED

Dystrophinopathies (Duchenne/Becker muscular dystrophy)
Emery-Dreifuss (Emerin)
FHL1-related (*FHL1*)

AUTOSOMAL DOMINANT

Facioscapulohumeral dystrophy (D4Z4 repeat deletions in 4q35 subtelomeric region in 95%; toxic gain of function in *DUX4* in 5%) and with *SMCHD1* mutation
Myotonic dystrophy, type 1 (CTG repeats in *DMPK*)
Myotonic dystrophy, type 2 (CCTG repeats in *ZNF9*)
Oculopharyngeal muscular dystrophy (*PABPN1*)
Myotilinopathy* (*MYOT*)
Laminopathy (*LMNA*)
Caveolinopathy (*CAV3*)
DNAJB6opathy* (*DNAJB6*)
Desminopathy* (*DES*)
Zaspopathy* (*ZASP*)
Bag3opathy* (*BAG3*)
Filaminopathy* (*FLNC*)
α-B-crystallinopathy* (*CRYAB*)
Titinopathy* (*TTN*)
VCPopathy† [valosin-containing protein] (*VCP*)
MYH7-myopathy†,‡ [Laing myopathy] (*MYH7*)
MYH2-myopathy† (*MYH2*)
Nesprinopathy (*SYNE1, SYNE2*)
TIA1opathy [Welander distal myopathy] (*TIA1*)
KLHL9opathy [kelch-like homologue-9] (*KLHL9*)
LUMA related (*TMEM43*)
TNPO3opathy (*TNPO3*)
HNRNPDLopathy (*HNRNPDL*)
CollagenVIopathy§ (*COL6A1, COL6A2, COL6A3*)
Collagen 12-related§ (*COL12A1*)
Calpainopathy (*CAPN3*)
HSPB8 related (*HSPB8*)
Oculopharyngodistal myopathy (trinucleotide repeats in *LRP12, GIPC1, NOTCH2NLC*)

AUTOSOMAL RECESSIVE

Calpainopathy (*CAPN3*)
Dysferlinopathy (*DYSF*)
Anoctaminopathy (*ANO5*)
α-sarcoglycanopathy (*SGCA*)
β-sarcoglycanopathy (*SGCB*)
δ-sarcoglycanopathy (*SGCD*)
γ-sarcoglycanopathy (*SGCG*)
Telethoninopathy§ (*TCAP*)
TRIM32opathy (*TRIM32*)
α-Dystroglycanopathies§ (*FKRP, POMT1, POMT2, FKTN, POMGNT1, POMGNT2, LARGE1, DAG1, DPM1, DPM2, DPM3, GMPPB, ISPD, B3GNT1, ALG13, B3GALNT2, B4GAT1, TMEM5, POMK, POGLUT1, MPDU1, RXYLT1, GOSR2*)
Titinopathy (*TTN*)
Laminopathy§ (*LMNA*)
Plectinopathy (*PLEC*)
Merosin deficiency§ (LAMA2)
Selenoproteinopathy†,§ (*SELENON*)
CollagenVIopathy§ (*COL6A1, COL6A2, COL6A3*)
Collagen 12-related§ (*COL12A1*)
With generalized lipodystrophy (*PTRF*)
Integrinα7opathy§ (*ITGA7*)
Integrinα9opathy§ (*ITGA9*)
With mitochondrial structural abnormalities§ (*CHKB*)
GNE-opathy† [glucosamine (UDP-*N*-acetyl)-2-epimerase/*N*-acetylmannosamine kinase] (*GNE*)
Pompe disease (*GAA*)
Matrin3opathy (*MATR3*)
LAP1Bopathy (*TOR1AIP1*)
Desminopathy (*DES*)
TRAPPC11opathy§ (*TRAPPC11*)
BVESopathy (*BVES*)
CHKBopathy¶ (*CHKB*)
VCP related (*VCP*)
POPDC3 related (*POPDC3*)
LIMS2 related (*LIMS2*)
PYROXD1 related (*PYROXD1*)

*Associated with pathologic features of myofibrillar myopathy.
†Associated with pathologic features of inclusion body myopathy.
‡Can also cause congenital myopathy.
§Can also cause congenital muscular dystrophy.
¶Causes congenital muscular dystrophy with mitochondrial structural abnormalities (megaconial type).

E-TABLE 389-2 CONGENITAL MYOPATHIES

Central core, multi-minicore disease (*RYR1, SELENON, MYH7, ACTA1, LMNA, MEGF10, TTN, FXR1, ACTN2*)
Centronuclear myopathy (*MTM1, DNM2, RYR1, BIN1, TTN, SPEG, CCDC78*)
Nemaline rod myopathy (*NEB, ACTA1, TPM3, TPM2, TNNT1, CFL2, KLHL40, KLHL41, KBTBD13, LMOD3, MYPN, MYO18B, RYR3*)
Congenital fiber-type disproportion (*ACTA1, SELENON, RYR1, MYH7, TPM3, MYH7, MYL2, ZAK*)
Myosin storage myopathy (*MYH7*)
Other structural and nonspecific myopathies: cap myopathy, zebra body myopathy, sarcotubular myopathy, spheroid body myopathy, fingerprint body myopathy, trilaminar myopathy, cylindrical spiral myopathy, myopathy with muscle spindle excess, myopathy with tubular aggregates, Danon disease, myopathy with excessive autophagy, SCN4A related

E-TABLE 389-3 CHANNELOPATHIES AND RELATED DISORDERS

DISORDER	PATTERN OF CLINICAL FEATURES
Thomsen disease (*CLCN1*)	Myotonia
Becker disease* (*CLCN1*)	Myotonia and weakness
Paramyotonia congenita (*SCN4A*)	Paramyotonia
Hyperkalemic periodic paralysis (*SCN4A*)	Periodic paralysis, sometimes with myotonia and paramyotonia
Hypokalemic periodic paralysis (*SCN4A, ATP1A2, CACNA1S, KCNE3, KCNJ18*)	Periodic paralysis
Andersen-Tawil syndrome (*KCNJ2*)	Periodic paralysis, cardiac arrhythmias, skeletal abnormalities
Potassium-aggravated myotonias (myotonia fluctuans, myotonia permanens, and acetazolamide-sensitive myotonia) (*SCN4A*)	Myotonia
Schwartz-Jampel syndrome* (Chondrodystrophic myotonia) (*HSPG2*)	Pseudomyotonia, dysmorphism, blepharospasm
Rippling muscle disease (*CAV3*)	Muscle mounding/stiffness
Brody disease* (*ATP2A1*)	Delayed relaxation, no myotonia on electromyogram
Malignant hyperthermia (*RYR1, STAC3, CACNA1S*)	Anesthetic-induced excessive calcium release by sarcoplasmic reticulum

*Autosomal recessive; all other listed diseases are autosomal dominant.
Adapted from Chinnery PF. Muscle diseases. In: Goldman L, Schafer AI, eds. *Goldman's Cecil Medicine*, 24th ed. Philadelphia: Elsevier; 2012.

E-TABLE 389-4 METABOLIC AND MITOCHONDRIAL MYOPATHIES

DISORDERS OF GLYCOGEN METABOLISM
Type II: α-1,4-Glucosidase (acid maltase) (*GAA*)
Type III: Debrancher (*AGL*)
Type IV: Branching (*GBE1*)
Type V: Myophosphorylase (*PYGM*)
Type VII: Phosphofructokinase (*PFKM*)
Type VIII: Phosphorylase b kinase (*PHBK*)
Type IXd: Phosphorylase kinase, alpha 1 subunit (*PHKA1*)
Type IX: Phosphoglycerate kinase (*PGK*)
Type X: Phosphoglycerate mutase (*PGAM-M*)
Type XI: Lactate dehydrogenase (*LDHA*)
Type XII: Aldolase A (*ALDOA*)
Type XIII: β-Enolase (*ENO3*)
Type XIV: Phosphoglucomutase 1 (*PGM1*)
Type XV: Glycogenin 1 (*GYG1*)
Type 0: Glycogen synthetase 1 (*GYS1*)
DISORDERS OF LIPID METABOLISM
Carnitine palmitoyltransferase II (*CPT2*)
Primary systemic carnitine deficiency (*SCL22A5*)
Carnitine/acyl-carnitine translocase deficiency (*SLC25A20*)
Secondary carnitine deficiency
Very-long-chain acyl coenzyme A dehydrogenase deficiency (*ACADVL*)
Long-chain acyl coenzyme A dehydrogenase deficiency (*ACADL*)
Medium-chain acyl coenzyme A dehydrogenase deficiency (*ACADM*)
Short-chain acyl coenzyme A dehydrogenase deficiency (*ACAD5*)
Long-chain hydroxyl/acyl coenzyme A dehydrogenase deficiency (*LCHAD*)
Multiple acyl coenzyme A dehydrogenase deficiency (*ETFA, ETFB, ETFDH*)
Mitochondrial complex I deficiency (*ACAD9*)
Triglyceride storage disease with ichthyosis (*ABHD5*)
Neutral lipid storage with myopathy (*PNPLA2*)
Acute recurrent myoglobinuria (*LPIN1*)
Flavin adenine dinucleotide synthetase deficiency (*FLAD1*)
Medications (valproic acid)
MITOCHONDRIAL MYOPATHIES
Chronic progressive external ophthalmoplegia
Kearns-Sayre syndrome
Mitochondrial encephalopathy, lactic acidosis, and strokelike episodes (MELAS)
Mitochondrial neurogastrointestinal encephalomyopathy (MNGIE)
Myoclonic epilepsy with ragged red fibers (MERRF)
Infantile myopathy and lactic acidosis
Cytochrome c oxidase deficiency

Adapted from Chinnery PF. Muscle diseases. In: Goldman L, Schafer AI, eds. *Goldman's Cecil Medicine*, 24th ed. Philadelphia: Elsevier; 2012.

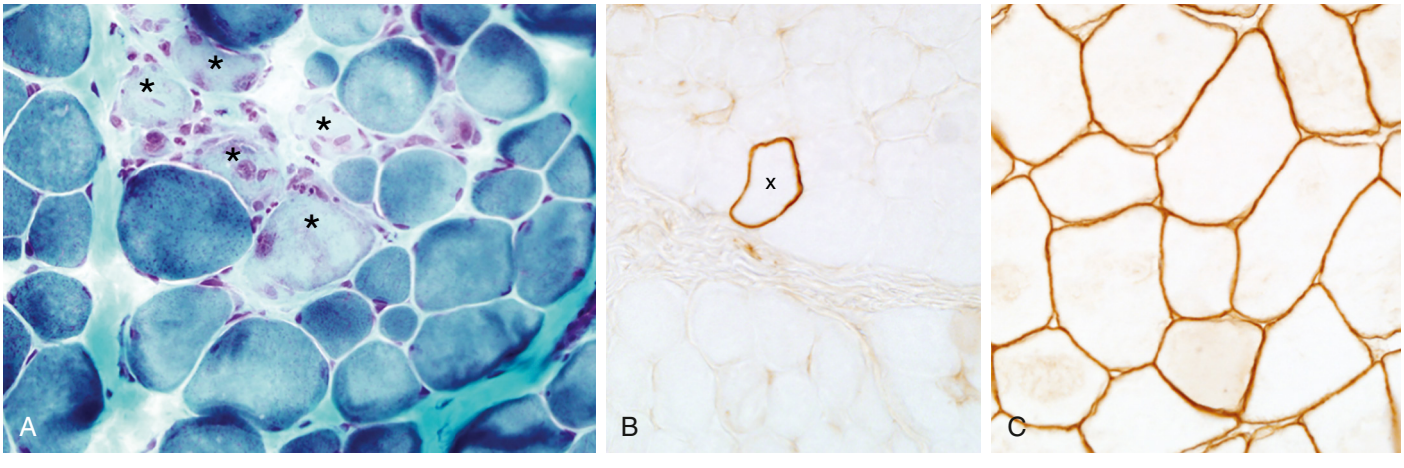

E-FIGURE 389-2. Duchenne muscular dystrophy. A, Trichromatically stained section of a specimen from a patient with Duchenne dystrophy displaying necrotic fibers (*) and increased endomysial and perimysial connective tissue. **B,** Dystrophin immunostain shows absent dystrophin reactivity in all fibers except for a revertant fiber (x). **C,** Normal sarcolemmal dystrophin reactivity in a control section.

Becker Muscular Dystrophy

Becker dystrophy is a milder form of Duchenne dystrophy caused by an in-frame mutation in the dystrophin gene.

CLINICAL MANIFESTATIONS AND DIAGNOSIS

Becker dystrophy can present in boys older than age 5 years, teenagers, or even in adults. Typical findings are symmetrical proximal weakness and prominent calf hypertrophy. Heart failure is common and may be the initial manifestation in some patients. The CK is elevated, although not to the same degree as seen in Duchenne dystrophy. Muscle biopsy findings are similar to those of Duchenne dystrophy but less severe: immunohistochemistry shows decreased dystrophin expression, and immunoblotting reveals decreased expression and/or a lower-molecular-weight dystrophin protein.

TREATMENT AND PROGNOSIS

Management is largely supportive. Corticosteroids are rarely used. Similar to Duchenne dystrophy, screening for respiratory function and cardiac monitoring is indicated. Heart transplantation (Chapter 46) has been performed in patients with severe restrictive cardiomyopathy (Chapter 47).

Many patients have a normal lifespan, although some develop respiratory failure and have a shortened lifespan owing to respiratory complications. Heart failure and arrhythmias occur late in the course of disease.

Female Carriers of Duchenne or Becker Dystrophy

Female carriers of a dystrophin gene mutation are usually totally asymptomatic. However, about 2.5 to 10% of carriers can develop symptoms, including myalgias, proximal muscle weakness, and cardiomyopathy. Rarely, they present with a Duchenne phenotype owing to an XO karyotype (Turner syndrome) or skewed X-chromosome inactivation. If a specific mutation is identified in the family, targeted DNA analysis can confirm the diagnosis. Immunostaining of the muscle specimens shows a mosaic pattern, in which some fibers express dystrophin normally and others show decreased or even absent expression. Management of symptomatic carriers is similar to the management of Duchenne and Becker dystrophy patients with similar disease severities.

Facioscapulohumeral Muscular Dystrophy

Facioscapulohumeral muscular dystrophy is an autosomal dominant disorder with variable penetrance. It is the third most common dystrophy after the dystrophinopathies and myotonic muscular dystrophy, with a prevalence of about 1 in 15,000. About 95% of patients have a truncated D4Z4 tandem repeat region in chromosome 4q35.[7] The other 5% have hypomethylation of the D4Z4 region along with a mutation in the *SMCHD1* gene, which is critical for the structural maintenance of chromosome-flexible hinge-domain-containing protein 1.

CLINICAL MANIFESTATIONS

Facioscapulohumeral muscular dystrophy has a highly variable penetrance within the same family. Some gene carriers never present with clinical symptoms or signs. The muscle weakness initially affects the face, where it causes difficulty smiling or whistling. Patients then develop scapular, humeral, truncal, and lower limb weakness leading to footdrop. Scapular winging is a typical feature. Muscle involvement is often asymmetrical.

Associated symptoms can include high-frequency hearing loss and retinal telangiectasia. Rare patients with retinal vascular abnormalities can develop retinal exudation leading to retinal detachment (Chapter 391). Infants with profound facial diplegia can also have intellectual disability and intractable epilepsy.

DIAGNOSIS

The CK level ranges from normal to mildly elevated. EMG shows typical myopathic features. Muscle biopsy shows chronic myopathic changes, sometimes with an inflammatory exudate. Definite diagnosis is based on genetic testing.

TREATMENT AND PROGNOSIS

Management is supportive, and corticosteroids are of no benefit. Patients do benefit, however, from physical therapy for motion exercises for the shoulder girdle, molded ankle-foot orthoses for the footdrop, hearing aids for patients with hearing loss, and scapular fixation surgery to improve shoulder range of motion.[8] Cardiac features are not prominent, and respiratory muscle weakness is a late feature. The prognosis is highly variable, depending on the severity and age of onset. Many patients have a normal lifespan.

MYOTONIC DYSTROPHIES

Myotonic dystrophies,[9] which are the second most common inherited muscle disease, affect about 1 in 8000 of the population. The two types, DM1 and DM2, are inherited in an autosomal dominant manner. Both cause multisystem disease and can be difficult to distinguish from each other. DM1 is caused by an abnormal expansion of CTG nucleotide repeats in an untranslated region of the dystrophia myotonica protein kinase (*DMPK*) gene on chromosome 19q. DM2 is caused by an abnormal expansion of CCTG nucleotide repeats in intron 1 of the zinc finger protein 9 (*ZNF9*) gene on chromosome 3q.

CLINICAL MANIFESTATIONS

Patients typically have frontal balding, ptosis, and temporal and masseter muscle wasting. Speech is nasal in quality, and patients display a high-steppage gait owing to their distal myopathy. On neurologic examination, myotonia is seen with percussion (inability to relax the muscle after percussion with a reflex hammer), after a grip (inability to relax the fingers after a firm grip), and in the eyelids (inability to open forcibly closed eyelids). Weakness in DM1 predominantly affects facial, oropharyngeal, forearm flexor, and foot dorsiflexor muscles. In DM2, weakness is predominantly proximal, although deep finger flexors are frequently affected. Muscle pain and stiffness are common in DM2 but can be seen in DM1 as well. Systemic features include premature subcapsular lens cataracts, testicular atrophy, intellectual disability, impotence, and hypersomnolence mediated by both central and neuromuscular mechanisms. Endocrine dysfunction is common, including diabetes mellitus and thyroid abnormalities. Dysphagia and constipation are common. Progressive cardiac conduction defects can lead to sudden death. Patients may require ventilation support after general anesthesia. Women who transmit DM1 are at high risk for having a child with a severe congenital form, including hypotonia at birth, respiratory failure, failure to thrive, and globally delayed developmental milestones with mild to severe intellectual disability.

DIAGNOSIS

Classical myotonic dystrophy usually can be diagnosed clinically by a patient's essentially pathognomonic facial features (see Fig. 389-2). The CK may be normal or mildly elevated. EMG, which is useful when the diagnosis is unsuspected or unclear, reveals myopathic features and myotonic discharges. Molecular genetic analysis of the nucleotide repeats confirms the diagnosis.

TREATMENT

All patients should have an annual electrocardiogram and a Holter monitor to detect conduction system abnormalities (Chapter 49). An echocardiogram should be performed at diagnosis and repeated about every 2 to 4 years. Respiratory function testing also is usually recommended about every 2 to 4 years, and a sleep study is useful to detect nocturnal hypoventilation for symptomatic patients.

Mexiletine (150 to 200 mg three times daily) is well tolerated and can improve muscle relaxation, but it does not improve walking distance or patients' perceptions of the severity of their disease.[A7] Hypersomnolence (Chapter 374) can be treated with overnight positive-pressure ventilation. Methylphenidate (20 mg daily) may be preferable to modafinil (200 mg daily) for excessive daytime sleepiness, but neither provides dramatic results. Cardiac pacing (Chapter 54), which is frequently required, can reduce the incidence of paroxysmal atrial fibrillation. Physical therapy can help to prevent contractures.

OTHER MUSCULAR DYSTROPHIES

Limb-girdle muscular dystrophies are a diverse group of myopathies caused by gene defects or deficiencies of muscle proteins that are critical for the normal function of the muscle cell membrane and especially the dystrophin-sarcoglycan complex. Inheritance can be autosomal dominant or recessive. Although most patients have classical limb-girdle muscle weakness at the onset, some can present with distal leg muscle involvement that may initially be misdiagnosed as sensorimotor neuropathy. Some causes can be identified clinically by an experienced clinician. However, EMG can help to differentiate these conditions from neuropathies, and muscle biopsy, immunohistochemistry studies, and genetic analysis are often required to make a precise diagnosis.

Myofibrillar myopathies present with progressive distal or proximal muscle weakness and characteristic morphologic features on muscle biopsy (E-Fig. 389-3). Cardiomyopathy and neuropathy can be associated features.

Emery-Dreifuss muscular dystrophy was originally described as X-linked and was initially shown to be caused by mutations in the emerin gene, a nuclear membrane protein. However, mutations in other genes can cause a similar

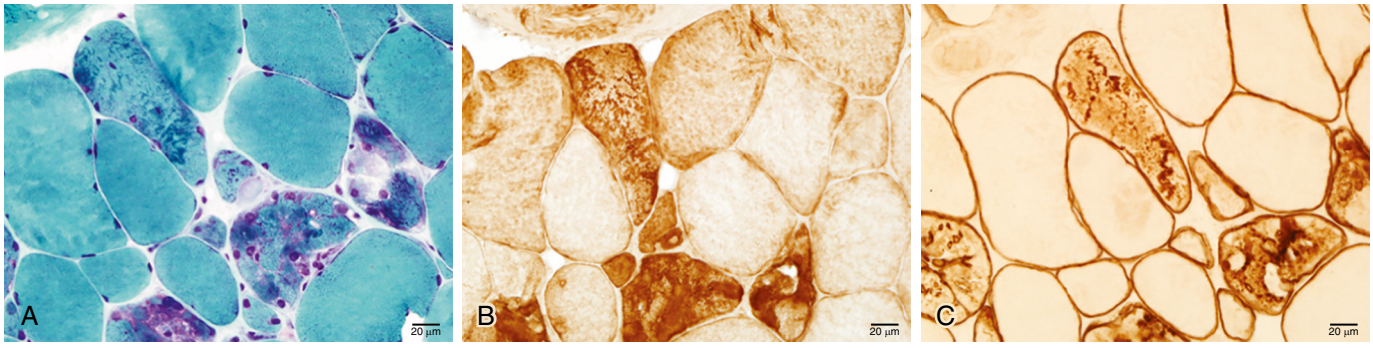

E-FIGURE 389-3. **Myofibrillar myopathy. A,** Trichromatically stained section of a specimen from a patient with myofibrillar myopathy displaying abnormal fibers with hyaline deposits or amorphous material and vacuoles. Abnormal fibers show abnormal and ectopic expression for desmin (**B**) and dystrophin (**C**).

phenotype. Patients have a distinctive phenotype, including progressive joint contractures, scapuloperoneal distribution weakness, and cardiomyopathy with a progressive cardiac conduction disorder. The CK is often elevated but can be normal. Cardiac function needs to be monitored periodically. As with the dystrophinopathies, female carriers of the X-linked forms may develop weakness and cardiac disease.

Oculopharyngeal muscular dystrophy is an autosomal dominant myopathy caused by a trinucleotide repeat expansion of the poly(A)-binding protein, nuclear 1 (*PABPN1*) gene. Onset typically occurs in the fifth or sixth decade of life with dysphagia and marked ptosis. Marked distal and proximal weakness occurs later in the disease course. Surgical correction of ptosis often yields excellent results, but the dysphagia can be more difficult to manage. Patients often have a normal lifespan.

CONGENITAL MUSCULAR DYSTROPHIES

Congenital muscular dystrophies (see E-Table 389-2) are a rare group of autosomal recessive muscle diseases that present in infancy or childhood with hypotonia and muscle weakness. The main differential diagnosis is spinal muscular atrophy (Chapter 387) and congenital myasthenia (Chapter 390). Affected infants can have joint contractures, which can be severe at birth. Some have a pure muscle phenotype and survive into adulthood. Others have severe central nervous system and eye involvement, which are associated with hypoglycosylation of α-dystroglycan that may be fatal in early childhood.

CONGENITAL MYOPATHIES

Congenital myopathies (see E-Table 389-2) are rare inherited muscle diseases that are generally less severe than congenital muscular dystrophies. Most patients present at birth with hypotonia, myopathic facies, and delayed motor milestones. The weakness is usually slowly progressive. Respiratory muscle weakness can occur, and patients can present with ventilator failure at birth or insidiously in adult life. The most severely affected patients present in utero with reduced fetal movements and polyhydramnios. Muscle biopsy is diagnostic (E-Figs. 389-4 to 389-6). Patients with central core myopathy can develop malignant hyperthermia (Chapter 400).

No specific treatments are available. Management requires a multidisciplinary team approach similar to muscular dystrophies.

ION CHANNELOPATHIES

Ion channelopathies (see E-Table 389-3) are genetically determined disorders in which the muscle membrane functions abnormally. The combined prevalence of the various skeletal muscle channelopathies is about 1.1 per 100,000.[10] Each has a specific molecular cause, but the phenotypes overlap.

CHLORIDE CHANNELOPATHIES

Mutations in the muscle chloride-channel gene *CLCN1* cause autosomal dominant (Thomson) and autosomal recessive (Becker) myotonia congenita. Patients present with painless myotonia, muscle stiffness that may be slightly worse in the cold and improves with exercise (the warm-up phenomenon), muscle hypertrophy, and grip and percussion myotonia. EMG shows myotonic discharges. The myotonia responds to mexiletine (150 to 200 mg up to three times a day). Patients have a normal lifespan.

SODIUM CHANNELOPATHIES

Mutations in *SCN4A*, which is the voltage-gated sodium-channel gene, cause a range of autosomal dominant phenotypes, including hyperkalemic periodic paralysis, paramyotonia congenita, and potassium aggravated myotonia. Periodic paralysis is typically precipitated by sustained exercise that leads to weakness during the rest period, by potassium-rich food, or sometimes by emotional stress or cold. The attacks can persist for hours, during which the patient can be quadriplegic with depressed tendon reflexes but normal sensation, eye movements, and respiration. The serum potassium level may be high or normal during the attack. The physical examination is usually normal between attacks, but some patients develop fixed proximal weakness later in the disease. In patients with paramyotonia, the muscle stiffness paradoxically increases with exercise and is often painful. Cold sensitivity is typically more extreme than that seen in myotonia congenita, and cold can precipitate the muscle weakness. The diagnosis is made clinically, although patients with fixed proximal muscle weakness, which can be confused with other myopathies, have vacuolar changes and sometimes tubular aggregates on muscle biopsy. For both phenotypes, management involves avoidance of precipitating factors such as cold or strenuous exercise. If the myotonia is disabling, medications that act on sodium channels such as dichlorphenamide (50 to 200 mg daily), acetazolamide (250 mg twice daily), mexiletine (150 mg three times a day), phenytoin (300 to 600 mg daily), and carbamazepine (400 to 800 mg daily) can be considered. Life expectancy is normal.

CALCIUM CHANNELOPATHIES

Hypokalemic periodic paralysis is usually caused by autosomal dominant mutations in the voltage-dependent calcium channel gene *CACNA1S* but in about 10% of cases is caused by dominant mutations in *SCN4A*. The attacks of weakness, which are usually more severe and prolonged than in hyperkalemic period paralysis, generally persist for hours to days before gradually resolving. Attacks occur spontaneously or during prolonged rest after vigorous exercise and also can be precipitated by a high-carbohydrate meal. The serum potassium level is reduced or low-normal during the attack. Avoidance of high carbohydrate loads and treatment with acetazolamide (125 to 1000 mg/day) or dichlorphenamide (50 to 200 mg/day)[A8] are effective in hypokalemic periodic paralysis. Patients may develop permanent muscle weakness if they have frequent attacks.

OTHER FORMS OF PERIODIC PARALYSIS AND MUSCLE STIFFNESS

Periodic paralysis can occur in a wide range of metabolic and electrolyte disorders (Table 389-5).[11] Mutations in the *KCNJ2* gene, which encodes the inward rectifier potassium channel Kir2.1, cause *Andersen-Tawil syndrome*, an autosomal dominant, usually hypokalemic, periodic paralysis that is associated with distinctive facial features, including hypertelorism and low-set ears, as well as a propensity for cardiac arrhythmias. Treatment includes acetazolamide (250 mg twice daily) and dichlorphenamide. For patients with sulfa allergy, potassium-sparing diuretics such as spironolactone (25 to 100 mg/day) or triamterene (25 to 100 mg/day) can be used. The patients should be treated as indicated for the cardiac arrhythmia and prolonged QT interval (Chapter 53). Despite successful treatment, many patients have long-term changes with fat replacement detectable by MRI.[12]

Brody disease, an autosomal recessive disorder caused by mutations in the SR calcium ATPase gene (*ATP2A1*), is characterized by exercise-induced muscle stiffness that is electrically silent on EMG. There are case reports of treatment with dantrolene, verapamil, or nifedipine with varying success.

Neuromyotonia (Isaac syndrome) is an autoimmune disorder associated with peripheral nerve hyperexcitability. It is caused by voltage-gated potassium-channel antibodies and is part of a spectrum of disorders, including limbic encephalitis. Oral immunomodulatory therapy, intravenous immunoglobulin, plasmapheresis, and symptomatic therapy with carbamazepine or phenytoin have been used with varying response. *Rippling muscle syndrome*, which can be caused by mutations in the *CAV3* gene, is characterized by rippling muscles triggered by exercise or percussion. Rippling muscle syndrome and neuromyotonia

TABLE 389-5 SECONDARY CAUSES OF PERIODIC PARALYSIS

HYPOKALEMIC
Thyrotoxicosis
Primary hyperaldosteronism (Conn syndrome)
Renal tubular acidosis (e.g., Fanconi syndrome)
Juxtaglomerular apparatus hyperplasia (Bartter syndrome)
Gastrointestinal potassium wastage
Villous adenoma
Pancreatic non–insulin-secreting tumors with diarrhea
Nontropical sprue
Barium intoxication
Potassium-depleting diuretics
Amphotericin B
Licorice
Corticosteroids
Toluene toxicity
p-Aminosalicylic acid
Carbenoxolone
HYPERKALEMIC
Addison disease
Hypoaldosteronism
Excessive potassium supplementation
Potassium-sparing diuretics
Chronic renal failure

From Barohn RJ. Muscle diseases. In: Goldman L, Ausiello DA, eds. *Cecil Medicine*, 23rd ed. Philadelphia: Elsevier; 2008.

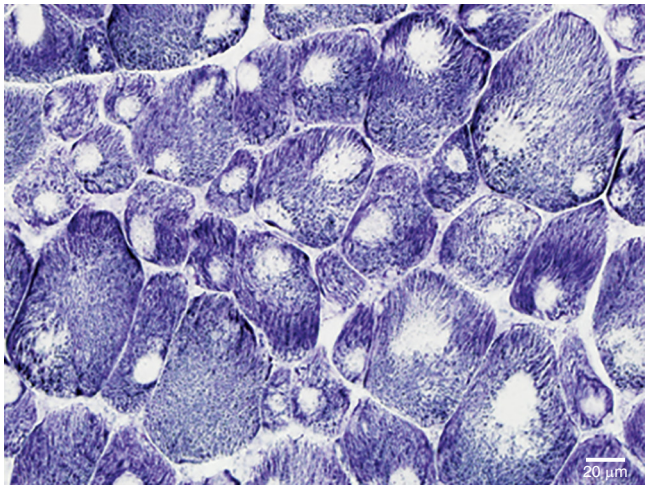

E-FIGURE 389-4. Core myopathy. NADH dehydrogenase–reacted section displaying cores in almost all fibers in a patient with central core disease. NADH = nicotinamide adenine dinucleotide.

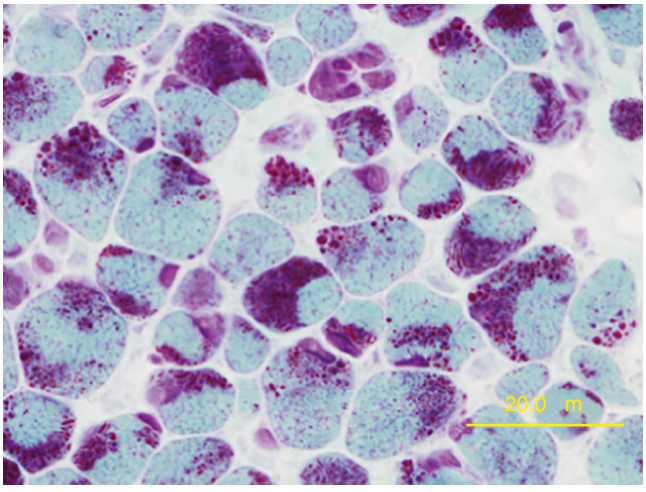

E-FIGURE 389-6. Nemaline rod myopathy. Trichromatically stained section showing myriad small nemaline rods in a patient with nemaline rod myopathy.

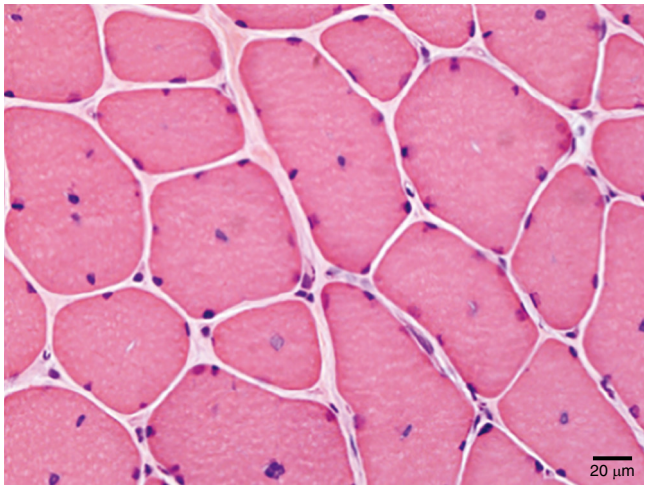

E-FIGURE 389-5. Centronuclear myopathy. Hematoxylin and eosin–stained section displaying central nuclei in almost all fibers in a patient with centronuclear myopathy.

can be paraneoplastic phenomena, and a search for malignancy should be considered in these patients.

METABOLIC MYOPATHIES

Metabolic myopathies (see E-Table 389-4) are caused by enzyme defects that affect the three principal stages of muscle metabolism: (1) carbohydrate disorders due to a defect of glucose-glycogen metabolism; (2) disorders of fatty acid oxidation; and (3) disorders of mitochondrial oxidative phosphorylation. Muscle dysfunction can be acute, recurrent, and reversible, but the exercise intolerance can cause progressive weakness or even rhabdomyolysis (Chapter 99).

DISORDERS OF CARBOHYDRATE METABOLISM

Because glucose and glycogen are the primary energy sources for muscle contraction, any defects of glucose-glycogen metabolism cause muscle pain, cramps, contracture, and weakness within the first 30 minutes of exercise. The most common form is myophosphorylase deficiency (Chapter 191), and other forms are extremely rare. Most of these disorders are inherited autosomal recessively, although phosphoglycerate kinase deficiency is X-linked. Patients also note exercise intolerance and become deconditioned. Severe episodes are associated with very high CK levels, rhabdomyolysis, and myoglobinuria.

Phosphorylase Deficiency

Phosphorylase deficiency (McArdle disease, type IV glycogenosis) typically presents with muscle pain or cramps after short bursts of exercise. Some patients present with recurrent rhabdomyolysis. Persistent exercise beyond 30 minutes leads to the "second-wind" phenomenon, when fatty acids become the primary source of muscle energy. Clinical examination and the CK can be normal between the attacks, although some patients develop fixed proximal muscle weakness with myopathic features on EMG. Histochemical and enzyme analysis of muscle confirms the diagnosis. A high-protein diet and 37 g or 75 g of oral sucrose shortly before exercise and graded exercise may improve symptoms, but patients are at risk for developing contractures. The life expectancy is normal.

Acid Maltase Deficiency

Acid maltase deficiency (type II glycogenosis, α-1,4-glucosidase), also called Pompe disease, may present in infancy as a very severe generalized muscle disease that is fatal before age 2 years, as a juvenile variant that causes muscle weakness and death by the second or third decade owing to respiratory failure, or as an adult-onset form that presents with limb-girdle muscle weakness or sometimes with respiratory failure (Chapter 192). In each type, EMG reveals myotonic discharges. Abnormal glycogen storage and acid phosphatase–positive vacuoles are seen on muscle biopsy. The disorder can be diagnosed by measuring the enzyme activity in leukocytes or in muscle, but the use of dried blood samples to measure enzyme activity is increasingly becoming the standard practice. Mutation analysis is also clinically available. Enzyme replacement therapy appears promising in children and in the late-onset form.[A9]

DISORDERS OF FATTY ACID METABOLISM

After about 30 minutes of exercise, when the muscle glycogen reserves become exhausted, fatty acids become the principal source of muscle energy. Fatty acid metabolism involves the transport of fatty acids from the serum into the muscle and mitochondria, where both carnitine and carnitine palmitoyltransferase are key components of the β-oxidation pathway.

Fatty acid oxidation disorders can present with a proximal myopathy, exercise intolerance, muscle pain, rhabdomyolysis, and cardiomyopathy. Other features can include neuropathy, pigmentary retinopathy, recurrent hypoketotic hypoglycemia, seizures, and intellectual disability. There may be a family history of sudden unexpected death syndrome. The most common fatty acid oxidation defect is *medium-chain acyl-CoA dehydrogenase (MCAD) deficiency. Carnitine palmitoyltransferase I deficiency* presents in childhood with an encephalopathy and liver failure associated with hypoglycemia and a high blood ammonia during metabolic crises. *Carnitine palmitoyltransferase II deficiency* can present as a fatal infantile-onset form or, more commonly, between the first and sixth decade of life with muscle pain, exercise intolerance, and myoglobinuria, typically after a long period of fasting or sustained exercise.

Carnitine deficiency can be primary or secondary. *Primary carnitine deficiency* causes myopathy, cardiomyopathy, and encephalopathy in association with hypoketotic hypoglycemia, although pure muscle presentations have been described. The diagnosis can be made by finding a low blood level, although prominent fat deposition in muscle is another clue. Other metabolic myopathies that can cause a secondary carnitine deficiency include disorders of β-oxidation and mitochondrial oxidative phosphorylation and may cause similar symptoms as the primary carnitine deficiency. Analysis of serum acylcarnitines, urine organic acids, and urine acylglycines and specific enzyme assays in fibroblasts can help to pinpoint the enzyme defect.

TREATMENT

The general treatment approach is avoidance of precipitating factors, such as prolonged fasting or prolonged exercise. Carbohydrate intake is advised before exercise, and patients should be prescribed a high-carbohydrate, low-fat diet with frequent feedings. Both primary and secondary carnitine deficiencies respond well to oral carnitine replacement (50 to 200 mg/kg/day in divided doses). Some patients have a multiple acyl-coenzyme A dehydrogenase deficiency (also called trifunctional enzyme deficiency, or glutaric aciduria type II), which responds well to riboflavin (100 mg daily).

DISORDERS OF MITOCHONDRIAL OXIDATIVE PHOSPHORYLATION

Disorders of mitochondrial oxidative phosphorylation (see E-Table 389-4), which are among the most common causes of inherited metabolic diseases, can present with isolated myopathy but often are multisystemic with cardiac involvement, diabetes mellitus, and both central and peripheral neurologic features.[13] Abnormal fatigability or exercise intolerance is a frequent complaint. Common CNS manifestations include epilepsy, migraine, strokelike episodes, myoclonus, ataxia, neuropathy, pigmentary retinopathy, dementia, and psychomotor regression.

Mitochondrial oxidative phosphorylation requires five respiratory chain complexes that are located on the inner mitochondrial membrane. Mitochondrial dysfunction results in energy deficits, which can lead to organ failure. Mitochondrial proteins can be coded by mitochondrial DNA (mtDNA), which is maternally inherited, and nuclear DNA, which can be inherited in an autosomal dominant, recessive, or X-linked manner. Phenotypic presentation of mtDNA defects depends on heteroplasmy, which is the amount and tissue distribution of the mutant mtDNA. If the amount of heteroplasmy exceeds a certain threshold, symptoms become apparent. Mitochondrial DNA disorders affect the structure or amount of the respiratory chain proteins, whereas nuclear DNA disorders can affect the proteins, the assembly of the respiratory chain, or the maintenance of mtDNA.

CLINICAL MANIFESTATIONS

Mitochondrial diseases should be considered in all patients who have a complex multisystemic myopathy, especially patients with neuromuscular, ocular, and endocrine involvement.[14]

Mitochondrial encephalomyopathy with lactic acidosis and strokelike episodes (MELAS) is most frequently caused by a point mutation of mtDNA (m.3243 A>G). Patients can have myopathy, cardiomyopathy, strokelike attacks, and encephalopathy. Some patients have one or only a few of these characteristics, some only have diabetes and deafness, and some only have cardiomyopathy.

Myoclonic epilepsy with ragged-red fibers (MERRF) is usually caused by a point mutation of mtDNA (m.8344 A>G). It presents with a proximal myopathy associated with slowly progressive ataxia, epilepsy, peripheral neuropathy, and myoclonus.

Leber hereditary optic neuropathy (Chapter 392) predominantly affects young adult men, more than 95% of whom have mtDNA point mutations in m.3460 G>A, m.11778 G>A, or m.14484 T>C. Patients develop subacute bilateral visual failure in both eyes within 2 to 3 months.

Chronic progressive external ophthalmoplegia with ptosis and gradual limitation of eye movements is seen in up to 20% of mitochondrial disorders.[15] About 95% of patients have sporadic mtDNA point mutations or deletions, but the disease can be inherited as either an autosomal dominant or recessive trait. Mutations in the *POLG* gene, which encodes the mitochondrial polymerase γ, are the most common causes of autosomal dominant or recessive progressive external ophthalmoplegia. *Kearns-Sayre syndrome* (Chapter 392) is characterized by the triad of external ophthalmoplegia, retinitis pigmentosa, and onset before the age of 20 years plus at least one of the following: heart block, cerebellar ataxia, or cerebrospinal fluid protein greater than 100 mg/dL. Kearns-Sayre syndrome is usually sporadic and caused by a single deletion of mtDNA.

Mitochondrial DNA depletion syndromes can present in the neonatal period or infancy with subacute necrotizing encephalomyopathy (*Leigh syndrome*), hepatorenal failure, cardiomyopathy, and severe lactic acidosis. Children with

Pearson syndrome, which is caused by accumulation of mtDNA deletions, typically present with pancytopenia, sideroblastic anemia, and exocrine pancreatic failure. *Primary coenzyme Q10 (ubiquinone) deficiency* is a rare autosomal recessive disorder that can present with encephalopathy, lipid storage myopathy, myoglobinuria, seizures, and cerebellar ataxia or as an isolated nephrotic syndrome or an isolated myopathy.

DIAGNOSIS, TREATMENT, AND PROGNOSIS

The investigation of suspected mitochondrial disorders involves a systematic screen for multisystem complications, especially diabetes and cardiomyopathy; muscle biopsy to look for ragged red fibers, cytochrome c oxidase deficiency, or biochemical evidence of respiratory chain dysfunction; search for mitochondrial deletion or depletion in muscle; and molecular genetic tests. Some primary mtDNA defects are not detectable in blood, so skeletal muscle is often required for the biochemical and genetic tests. For example, diagnosis of primary coenzyme Q10 (CoQ10) deficiency is made by measuring CoQ10 in muscle but not in blood.

Patients with primary CoQ10 deficiency can respond dramatically to CoQ10 supplementation (30 mg/kg/day in children and up to 2400 mg/day in adults in three divided doses). Vitamins and cofactors, including thiamine, riboflavin, and CoQ10, have shown varying degrees of benefit in different mitochondrial diseases. Management is largely supportive with monitoring and treatment of complications. Prognosis varies depending on the phenotype, ranging from the relatively normal life expectancy with chronic external ophthalmoplegia to a relatively rapid demise with Leigh syndrome.

OTHER METABOLIC AND TOXIC MYOPATHIES

Myopathy can complicate many metabolic disorders, including hypothyroidism (Chapter 207), Addison disease (Chapter 208), hyperaldosteronism (Chapter 208), hyperparathyroidism (Chapter 227), vitamin D deficiency (Chapter 226), and liver and renal failure (Chapters 116 and 139). The myopathy is often subtle, the CK level and EMG are often normal, and the muscle biopsy may be nonspecifically abnormal.

Alcohol (Chapters 364 and 384) and many drugs cause myopathy (Table 389-6) with proximal muscle weakness, muscle pain, and exercise intolerance. The CK and EMG can be normal, and muscle biopsy findings may be nonspecific. The diagnosis may depend on the resolution of symptoms after the toxic agent is removed. Perhaps the most commonly incriminated medications are statins (Chapter 190), which can cause mild muscle symptoms or a severe autoimmune myopathy with a symmetrical proximal weakness, muscle pain, a markedly increased CK level, and, rarely, myoglobinuria. The presence of anti-HMG-CoA reductase antibodies is diagnostic.[16] Steroid-induced myopathy (Chapter 28) is characterized by symmetrical weakness predominantly of proximal muscles.[17]

INFLAMMATORY MUSCLE DISEASES

Inflammatory or immune myopathies are a heterogeneous group of acquired muscle diseases (E-Table 389-5) that usually present with muscle weakness and exercise intolerance, with or without pain (Chapter 248).[18,19] Careful evaluation can help distinguish among the most common possible causes (Table 389-7). Most patients have an elevated CK level and an abnormal EMG. Muscle biopsy shows an inflammatory infiltrate. However, the inflammatory process can be patchy and missed on the EMG or muscle biopsy, especially if the specimen is small or if a clinically unaffected muscle is biopsied. Similarly, a short period of corticosteroid therapy can mask the findings. MRI guidance can help to identify high-yield locations for muscle biopsy. Inflammatory exudates are usually mild or absent in necrotizing autoimmune myopathies.

Systemic diseases associated with an inflammatory myopathy[20] include polymyositis, dermatomyositis, inclusion body myositis (Chapter 248),[21] systemic lupus erythematosus (Chapter 245), mixed connective tissue disease (Chapter 62), Sjögren syndrome (Chapter 247), rheumatoid arthritis (Chapter 243), and sarcoidosis (Chapter 83). Systemic viral illnesses and other infectious microorganisms frequently cause muscle pain and an elevated CK, which rarely are major clinical problems.

SARCOPENIA AND MUSCLE WASTING

Muscle wasting is a common problem in elderly people (Chapter 24), partly related to hormonal changes and largely related to underuse. Critically ill patients rapidly lose muscle owing to inactivity and reduced protein synthesis, with some potential to slow this process with protein-calorie nutrition (Chapter 97).[22] Sarcopenia is also a prominent feature of many cancers, end-stage heart failure (Chapter 45), renal failure (Chapter 117), and eating disorders (Chapter 200).

TABLE 389-6 TOXIC MYOPATHIES

INFLAMMATORY	**MALIGNANT HYPERTHERMIA**
Cimetidine	Halothane
D-Penicillamine	Ethylene
Procainamide	Diethyl ether
L-Tryptophan	Methoxyflurane
L-Dopa	Ethyl chloride
NONINFLAMMATORY NECROTIZING OR VACUOLAR	Trichloroethylene
Statins	Gallamine
Chloroquine	Succinylcholine
Colchicine	**MITOCHONDRIAL**
Emetine	Zidovudine
ε-Aminocaproic acid	**MYOTONIA**
Labetalol	2,4-d-Chlorophenoxylacetic acid
Cyclosporine	Anthracene-9-carboxylic acid
Tacrolimus	Cholesterol-lowering agents
Isoretinoic acid (vitamin A analog)	Chloroquine
Vincristine	Cyclosporine
Alcohol	**MYOSIN LOSS**
Immune checkpoint inhibitors	Nondepolarizing neuromuscular blocking agents*
RHABDOMYOLYSIS AND MYOGLOBINURIA	Intravenous glucocorticosteroids*
Statins	**CORTICOSTEROID INDUCED**
Alcohol	
Heroin	
Amphetamine	
Toluene	
Cocaine	
ε-Aminocaproic acid	
Pentazocine	
Phencyclidine	

*In the setting of critical illness.

Adapted from Barohn RJ. Muscle diseases. In: Goldman L, Ausiello DA, eds. *Cecil Medicine*, 23rd ed. Philadelphia: Elsevier; 2008.

E-TABLE 389-5 CLASSIFICATION OF INFLAMMATORY OR IMMUNE MYOPATHIES

IDIOPATHIC
Polymyositis
Dermatomyositis
Inclusion body myositis
Necrotizing autoimmune myopathy
Overlap syndromes with other connective tissue disease (scleroderma, systemic lupus erythematosus, mixed connective tissue disease, Sjögren syndrome, rheumatoid arthritis, polyarteritis nodosa)
Inflammatory myopathy with abundant macrophages
With perifascicular necrosis (associated with anti-Jo-1 antibody)
Sarcoidosis and other granulomatous myositis
Behçet disease
Inflammatory myopathies and eosinophilia
Eosinophilic polymyositis
Diffuse fasciitis with eosinophilia
Focal myositis
Benign acute childhood myositis
Myositis ossificans
INFECTIOUS
Bacterial: *Staphylococcus aureus*, streptococci, *Escherichia coli, Yersinia* spp., *Legionella* spp., gas gangrene (*Clostridium welchii*), leprous myositis, Lyme disease (*Borrelia burgdorferi*)
Viral: acute myositis after influenza or other viral infections (adenovirus, coxsackievirus, echovirus, parainfluenza virus, Epstein-Barr virus, arbovirus, cytomegalovirus), retrovirus-related myopathies (HIV, HTLV-1), hepatitis B and C, COVID-19
Parasitic: trichinosis (*Trichinella spiralis*), toxoplasmosis (*Toxoplasma gondii*), cysticercosis, sarcosporidiosis, trypanosomiasis (*Taenia solium*)
Fungal: *Candida* spp., *Cryptococcus* spp., sporotrichosis, actinomycosis, histoplasmosis

COVID = coronavirus disease; HIV = human immunodeficiency virus; HTLV-1 = human T-lymphotrophic virus 1; spp = species.

Adapted from Barohn RJ. Muscle diseases. In: Goldman L, Ausiello DA, eds. *Cecil Medicine,* 23rd ed. Philadelphia: Elsevier; 2008.

TABLE 389-7 CRITERIA SUPPORTING THE DIAGNOSIS OF INFLAMMATORY MYOPATHIES

CRITERION	DERMATOMYOSITIS	POLYMYOSITIS	NECROTIZING AUTOIMMUNE MYOPATHY	INCLUSION-BODY MYOSITIS
Pattern of muscle weakness	Subacute symmetrical proximal weakness with characteristic skin rash	Subacute symmetrical proximal weakness	Acute or subacute severe proximal weakness	Slow onset of proximal and distal weakness after age 50; atrophy of quadriceps, forearms, and facial muscles; frequent falls
Creatine kinase level	Usually elevated, up to 50-fold	Elevated up to 50-fold	Elevated more than 50-fold	Usually elevated up to 10-fold
Autoantibodies	Anti-MDA-5, anti-Mi-2; anti-TIF-1 and anti-NXP-2 in cancer-associated dermatomyositis	Antisynthetase antibodies associated with interstitial lung disease, arthritis, and fever	Anti-SRP and anti-HMGCR	Anti-cN1A
Electromyography	Active and chronic myopathic units	Active and chronic myopathic units	Active myopathic units	Active and chronic myopathic units
Magnetic resonance imaging	May show active inflammation	May show active inflammation	May show active inflammation	Shows selective muscle involvement
Muscle biopsy	Perivascular, perimysial, and perifascicular inflammation; necrotic fibers in "wedge-like" infarcts; perifascicular atrophy; reduced capillaries	$CD8^+$ cells invading healthy fibers; widespread expression of MHC class I antigen; no vacuoles	Scattered necrotic fibers with macrophages; no $CD8^+$ cells or vacuoles; deposits of complement on capillaries	CD8+ cells invading healthy fibers; widespread expression of MHC class I antigen; autophagic vacuoles

Anti-cN1A = anti–cytosolic 5′-nucleotidase 1A; anti-HMGCR = anti–3-hydroxy-3-methylglutaryl–coenzyme A reductase; anti-MDA-5 = anti–melanoma differentiation–associated protein-5; anti-NXP-2 = anti–nuclear matrix protein 2; anti-SRP = anti–signal recognition particle; anti-TIF-1 = anti–transcriptional intermediary factor 1; MHC = major histocompatibility complex.
Adapted from Dalakas MC. Inflammatory muscle diseases. *N Engl J Med.* 2015;372:1734-1747.

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390 DISORDERS OF NEUROMUSCULAR TRANSMISSION

HENRY J. KAMINSKI

DEFINITION

The clinical recognition of neuromuscular transmission disorders (Table 390-1) is critically important because all are treatable. Afflicted patients have the potential to improve substantially or even return to normal function, whereas undiagnosed or untreated disease leads to severe morbidity and death. Each of these disorders compromise the postsynaptic potential, thereby reducing the force generated by muscles. Myasthenia gravis and Lambert-Eaton syndrome are autoimmune diseases. The much less common genetic disorders mimic the autoimmune diseases clinically but do not respond to immunotherapies. Toxic and infectious disorders of neuromuscular transmission can be more easily identified because of coexistent autonomic findings and a history of exposure, which sometimes is obvious but sometimes requires a detailed evaluation.

EPIDEMIOLOGY

All neuromuscular transmission disorders are rare. Myasthenia gravis has an estimated annual incidence of about three to four per million, with a prevalence of 200 to 400 per million. Myasthenia gravis occurs more commonly after age 50 years[1] and in women, but at least 30% of patients, especially older patients, are men. Japanese and Chinese populations appear to have higher frequencies of myasthenia gravis restricted to the ocular muscles, whereas muscle-specific kinase myasthenia gravis appears to be more common in Blacks compared with Whites and is more common in European countries closer to the equator. The estimated prevalence of Lambert-Eaton syndrome is about one-tenth that of myasthenia gravis. Congenital myasthenic syndromes have an estimated prevalence of 10 per million. Botulism cases depend on outbreaks of foodborne infections, with 100 cases, about 25% of which are foodborne, reported annually in the United States.[2] Toxic exposures to organophosphates and other chemicals are sporadic and vary based on the scale of exposure. Except for myasthenia gravis, these diseases are sufficiently uncommon that most information is based on expert opinion, retrospective studies, or small case series.

PATHOBIOLOGY

Neuromuscular transmission involves propagation of an action potential along a motor nerve, thereby leading to an electrical potential change at the nerve terminal and the triggering of calcium influx through voltage-gated calcium channels. The calcium influx signals a series of synaptic proteins to fuse the synaptic vesicles that contain acetylcholine to the neuronal cell membrane, thereby allowing their contents to be released into the narrow cleft between the nerve ending and the postsynaptic muscle surface. Acetylcholine rapidly diffuses across the cleft and binds to highly concentrated acetylcholine receptors, which trigger the ion channel to open and generate an end plate potential that, if of adequate magnitude, activates an action potential, which then propagates along the muscle fiber to prompt muscle contraction. The postsynaptic folds and concentration of sodium channels at their base serve to increase the postsynaptic potential. Diffusion of acetylcholine and its hydrolysis by acetylcholinesterase, which is anchored to the basal lamina of the synaptic cleft, serve to terminate postsynaptic activation (E-Fig. 390-1).

Disorders of neuromuscular transmission produce clinical manifestations by compromising or eliminating the difference between the postsynaptic potential

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Disorders of neuromuscular transmission produce clinical manifestations by compromising or eliminating the difference between the postsynaptic potential

Known targets for autoantibodies

- Acetylcholine receptor (AChR)
- Muscle-specific kinase (MuSK)
- Lipoprotein-related receptor protein 4 (LRP4)
- Voltage-gated calcium channel (VGCC)
- Voltage-gated potassium channel (VGKC)

Main targets for genetic defects

- Acetylcholine receptor (AChR)
- Receptor aggregating protein at the synapse (Rapsyn)
- Choline acetyltransferase (CHAT)
- Acetylcholinesterase (AChE)
- DOK7

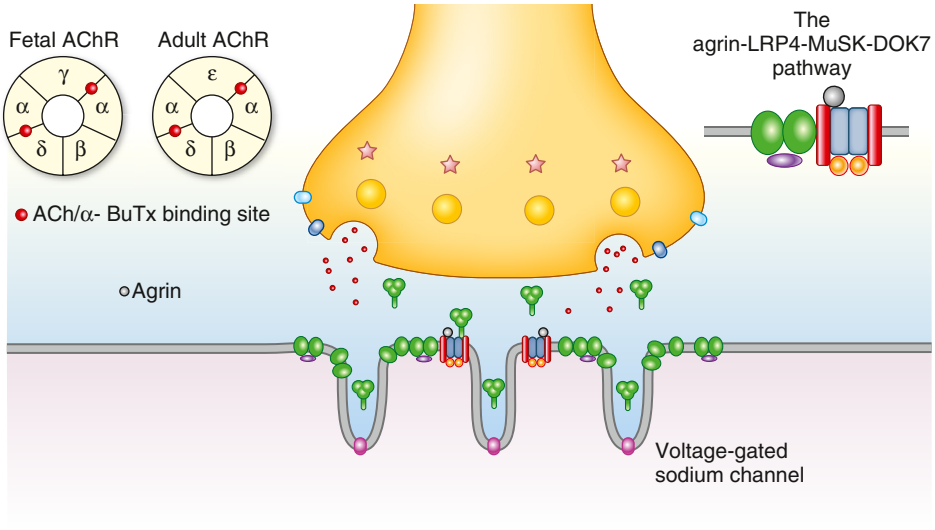

FIGURE E-E- 390-1. Diagrammatic representation of the neuromuscular junction, indicating the ion channels, receptors, enzymes, and associated proteins that are the most frequent targets for autoimmune diseases (left) or mutations in genetic disease (right). The acetylcholine (ACh) receptor (AChR) exists in fetal and adult isoforms as illustrated at *top left*. The replacement of the fetal form by the adult form takes place toward the end of gestation in humans. The agrin-lipoprotein–related receptor protein 4–muscle-specific kinase–downstream of kinase 7 (DOK7) pathway associated with AChRs on the postsynaptic membrane is illustrated at *top right*. α-BuTx = α-bungarotoxin, the snake toxin that binds with high specificity to the two ACh binding sites on the AChRs. (Reproduced from Evoli A, Vincent A. Disorders of neuromuscular transmission. In: Goldman L, Schafer AI [Eds.]. *Goldman-Cecil Medicine*. Philadelphia: Elsevier; 2020:2509-2515.)

ABSTRACT

Disorders of neuromuscular transmission can be caused by autoimmune, genetic, infectious, and toxic conditions. The clinical presentations of each share common features of fatigable weakness, which may be life-threatening, and have a propensity to involve the ocular muscles. The most common of these rare diseases is myasthenia gravis, which is caused by autoantibodies directed against the nicotinic acetylcholine receptor and other postsynaptic proteins of the neuromuscular junction. In Lambert-Eaton syndrome, autoantibodies attack presynaptic voltage-gated calcium channels and compromise the release of acetylcholine. For both of these disorders, immunotherapies can moderate the severity of the weakness but also can have serious adverse effects. Neuromyotonia, which is phenotypically distinct, manifests as hyperexcitable muscles caused by antibodies to potassium-gated potassium channels. A range of mutations lead to congenital myasthenic syndromes, which are phenotypically similar to myasthenia gravis and Lambert-Eaton syndrome and can be treated by drugs that enhance neuromuscular transmission. Botulism, which manifests as rapidly progressive weakness in association with autonomic disturbances, requires rapid identification to institute antitoxin therapy. A number of neurotoxins can compromise neuromuscular transmission and produce rapid paralysis and death. The challenge for the clinician lies in recognition of these rare diseases so that tailored treatments can be instituted.

KEYWORDS

neuromuscular transmission
myasthenia gravis
Lambert-Eaton syndrome
congenital myasthenia
botulism
organophosphates

TABLE 390-1 DISORDERS OF NEUROMUSCULAR TRANSMISSION

DISEASE	TARGET	PATHOBIOLOGY
AUTOIMMUNE		
Myasthenia gravis	AChRs	Antibodies to AChR in 85% reduce AChR numbers and EPP amplitude
Transient neonatal myasthenia	MuSK	Antibodies to MuSK in 5 to 8% reduce MuSK–LRP4 binding
	LRP4	Antibodies to LRP4 in a small proportion of patients reduce LRP4–agrin binding
	AChRs MuSK	Maternal antibodies cause transient disease in neonate
Arthrogryposis	Fetal AChR	Maternal antibodies that inhibit fetal AChR function resulting in paralysis in the fetus in utero, leading to multiple joint contractures
Lambert-Eaton myasthenic syndrome	VGCCs	Antibodies to VGCC in 90% reduce VGCC numbers, acetylcholine release and EPP amplitude
Acquired neuromyotonia	VGKC-complex	Antibodies to VGKC-complex (mainly CASPR2) in 40% lead to increased and spontaneous ACh release
GENETIC		
Presynaptic	ChAT, ChT, SYT2, SNAP25	Different mutations (mostly recessive) reduce acetylcholine release. ChAT mutations are the most common
Synaptic	ColQ, laminin ß2	Mutations in the collagen tail (*COLQ*) that anchor AChE at the neuromuscular junction cause absence of AChE Rare mutations of LAMB2 reduce ACh release and EPP amplitude
	AChR	Recessive mutations in AChR-subunits (mostly in the ε-subunit) cause reduced AChR expression
Postsynaptic	AChR	Dominant or recessive mutations in AChR-subunits cause kinetic defects: "slow" and "fast" channel syndromes
	$Na_v1.4$	Mutations in SCN4A sodium channel reduce muscle fiber excitability
Defects in end-plate development and maintenance	Rapsyn, DOK7, agrin, MuSK, LRP4	Recessive mutations cause structural alterations of the end plate. DOK7 and rapsyn defects are the most common
Glycosylation defects	GFPT1, DPAGT1, ALG2, ALG14	Recessive mutations cause glycosylation defects of end-plate proteins. GFPT1 defect is the most common
Arthrogryposis, multiple pterygium, Escobar syndrome	Rapsyn, AChR δ- and γ-subunits, DOK7, MuSK, GFPT1	Recessive mutations cause a prenatal defect of neuromuscular transmission with fetal akinesia
NEUROTOXIC		
Botulism	SNARE (SNAP) receptor) proteins	Botulinum toxin gains entry into the presynaptic motor nerve and cleaves proteins involved in ACh release mechanism
Envenomation following bites from snakes, spiders, scorpions, etc.	Varied sites of action	Neurotoxins specific for VGCCs, VGKCs, AChE, AChRs, voltage-gated sodium channels, and other targets are frequent in many animal venoms and generally inhibit function
Drugs and insecticides (unintentional or intentional poisoning)	Varied sites of action	Muscle relaxants and other drugs Many antibiotics and quinine-related drugs can alter neuromuscular transmission at high dose Organophosphates block AChE and have complicated acute and chronic actions (Novichok, common pesticides)

AChE = acetylcholinesterase; AChR = acetylcholine receptor; ALG2 = alpha-1,3-mannosyl transferase; ALG14 = uridine diphosphate-*N*-acetylglucosaminyl-transferase subunit; CASPR2 = contactin-associated protein 2; ChAT = choline acetyltransferase; ChT = high-affinity choline transporter 1; ColQ= collagen-like tail of acetylcholinesterase; DOK7 = downstream of kinase 7; DPAGT1 = dolichyl-phosphate *N*-acetylglucosaminephosphotransferase 1; EPP = end-plate potential; GMPPB = guanosine diphosphate mannose pyrophosphorylase B; GFPT1 = glutamine fructose-6-phosphate transaminase; LRP4 = low-density lipoprotein-related receptor protein 4; MuSK = muscle-specific kinase; $Na_v1.4$ = muscle sodium channel; SCN4A = sodium voltage-gated channel alpha subunit 4; SNAP25 = synaptosomal nerve-associated protein 25; SYT2 = synaptotagmin 2; VGCC = voltage-gated calcium channel; VGKC-complex = voltage-gated potassium channel and associated proteins.

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and the minimum magnitude action potential that is necessary to signal muscle contraction. In myasthenia gravis, autoantibody–mediated injury of the postsynaptic surface leads to a reduction of acetylcholine receptors; if severe enough, this reduction will lead to such a low postsynaptic potential that an action potential cannot be generated. In contrast, Lambert-Eaton syndrome and botulinum toxin reduce the release of acetylcholine, thereby leading to a compromised activation of the normal postsynaptic surface. Congenital myasthenic syndromes and toxins compromise neuromuscular transmission by a variety of mechanisms.

MYASTHENIA GRAVIS

PATHOBIOLOGY

Myasthenia gravis is an autoimmune disorder caused by antibodies that are directed at postsynaptic proteins, primarily the skeletal muscle nicotinic acetylcholine receptors, muscle-specific kinase, lipoprotein receptor–related protein-4, and perhaps other autoantigens. Antibodies to the acetylcholine receptor act through activation of complement, thereby leading to destruction of the post-junctional membrane; antigenic modulation by cross-linking receptors and removal of the acetylcholine receptors from the muscle membrane; and blockade of the function of the acetylcholine receptors (E-Fig. 390-2). Antibodies to muscle-specific kinase are primarily immunoglobulin (Ig)G4 and act by inhibiting the signals that lead to the concentration of acetylcholine receptors on the postsynaptic surface. The activity of low-density lipoprotein receptor-related protein 4 antibodies is less well understood, but they likely also interfere with signals that maintain the integrity of the neuromuscular junction. Other putative antigenic targets include agrin, cortactin, and other proteins that are concentrated in the neuromuscular junction.

Myasthenia gravis consists of distinct subgroups: acetylcholine receptor antibody-positive, early-onset disease; acetylcholine receptor antibody–positive, late-onset disease, which generally occurs after age 50 years; muscle-specific kinase antibody-positive; thymoma-associated myasthenia gravis; and seronegative myasthenia gravis without detectable autoantibodies. Patients with early-onset myasthenia gravis are more often women with thymic hyperplasia, whereas the late-onset patients skew toward being men with an atrophic thymus. In about 10% of patients, and especially in men, thymomas trigger myasthenia gravis, but removal of the thymoma does not cure the myasthenia gravis. Women with early-onset myasthenia gravis are more likely to be human leukocyte antigen (HLA)-A1, B8, or DRw3-positive, whereas men with late-onset disease are more likely to have HLA-A3, B7, or DRw2.1.

Myasthenia gravis has a genetic predisposition, with close to 5% of patients having a family member with the disease. Twin studies indicate a heritability index of 0.65 for myasthenic gravis, similar to that of Alzheimer disease. Little is understood about whether environmental factors lead to myasthenia gravis.

Across all subgroups, autoantibodies are produced by B cells, supported by T cells and pro-inflammatory cytokines, but with largely unknown triggers, and the mechanisms that maintain autoreactive B cells are poorly characterized. In patients with early-onset disease, thymic hyperplasia with active germinal centers suggests that the breakdown in immune tolerance is initiated in the thymus, but the autoimmune reaction persists after thymectomy. Thymoma-associated myasthenia gravis is marked by a deficiency of the autoimmune regulatory protein AIRE, which appears to lead to a deficiency of regulatory T cells and a resultant increase in autoreactivity. Some autoreactive T cells may be activated in association with the thymoma because of local expression of muscle antigens, including the acetylcholine receptors, and the lack of AIRE. These autoreactive T cells can then stimulate peripheral B cells to

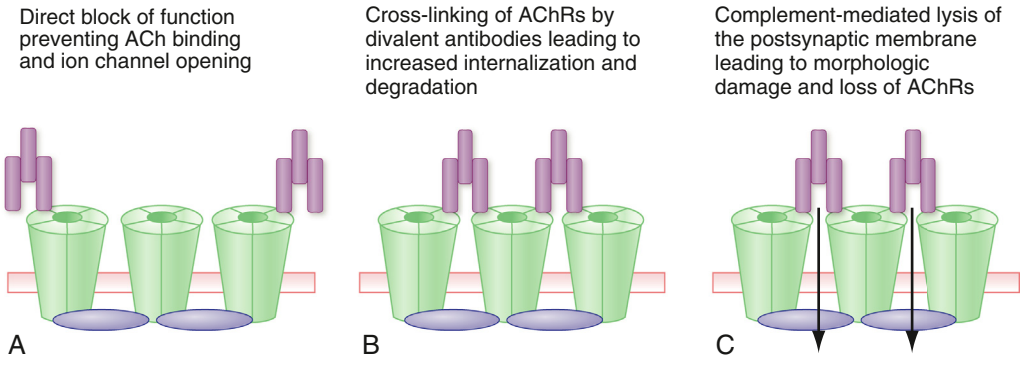

E-FIGURE 390-2. Effects of antibodies on the acetylcholine (ACh) receptor (AChR). In myasthenia gravis, complement-dependent lysis is likely to be the most important mechanism overall. Interestingly, there is no evidence of complement-dependent mechanisms in either the Lambert-Eaton myasthenic syndrome or acquired neuromyotonia, in which cross-linking of the respective ion channels with increased internalization seems to be the main mechanism. (Reproduced from Evoli A, Vincent A. Disorders of neuromuscular transmission. In: Goldman L, Schafer AI [Eds.]. *Goldman-Cecil Medicine*. Philadelphia: Elsevier; 2020:2509-2515.)

produce antibodies. Triggers for non–acetylcholine receptor antibody myasthenia gravis are not known. Patients with muscle-specific kinase antibodies have a normal-appearing thymus.

CLINICAL MANIFESTATIONS

Myasthenia gravis is characterized by fluctuating, painless muscle skeletal weakness, which can worsen over minutes to hours. Symptoms can vary across muscle groups and over time, with spontaneous remissions. This variability can lead to diagnostic challenges, especially when patients lack findings during clinical examinations. The majority of patients present with ocular muscle involvement that causes drooping eyelids or double vision (Fig. 390-1).[3] Ptosis may be unilateral or bilateral, and it often is asymmetrical. The pupils are always normal, an important finding that distinguishes myasthenia gravis from other ocular motility disorders and causes of ptosis, (e.g., third nerve palsy and Horner syndrome). Some patients have only isolated ocular muscle weakness (so-called ocular myasthenia), some patients have isolated weakness of bulbar muscles (which manifests as slurred speech, difficulty swallowing, and facial weakness), but the majority of patients will develop general weakness, especially in the proximal arms and legs and in respiratory muscles. Isolated bulbar weakness is particularly seen in patients who have muscle-specific kinase antibodies and who also may have muscle atrophy; these presentations can be confused with motor neuron disease (Chapter 387). Some patients have remarkably acute, lateralized weakness that mimics a stroke (Chapters 376 and 377) or distal weakness that may be confused with peripheral nerve injury (Chapter 388). Myasthenic crisis is defined as the need for ventilatory support for respiratory muscle weakness.[4]

Patients do not have sensory abnormalities, reflexes are normal, and bladder function is normal. Nevertheless, patients typically report a more substantial decrement in their quality of life than their physicians suspect.

DIAGNOSIS

Serologic testing is indicated when the clinical diagnosis of myasthenia gravis is suggested by ocular findings, especially when coupled with weakness or fatigue as documented by asking patients to maintain upgaze or hold their arms outstretched for 30 seconds to a minute. Provocative testing with edrophonium, ice packs, and rest tests should be performed only by individuals with extensive experience to avoid false positives.

Myasthenia gravis can be confirmed by serologic detection of acetylcholine receptor antibodies in about 50% of patients with isolated ocular myasthenia and upwards of 90% of patients with generalized disease. Muscle-specific kinase antibodies are present in about one-third of patients who do not have acetylcholine receptor antibodies, and very occasional patients may have both antibodies. False positives are exceedingly rare, but acetylcholine receptor antibodies can be detected in patients with thymoma and in asymptomatic family members of patients with myasthenia gravis. Low-density lipoprotein receptor–related protein 4 antibodies may be present in 1 to 4% of patients without other autoantibodies, but they are also detected in patients with motor neuron disease (Chapter 387).

In patients without serologic evidence of myasthenia gravis, electrodiagnostic studies can confirm a disorder of neuromuscular transmission. Approximately 75% of patients will have a decremental response to repetitive nerve stimulation. Single-fiber electromyography, which records action potentials generated by individual muscle fibers, has an estimated sensitivity over 95% when performed by experts (but is not likely to be that high in general practice).[5] However, single fiber examination is so sensitive that it will detect abnormalities produced by previous therapeutic botulinum toxin, thereby leading to the potential for a false positive evaluation. All patients should have chest imaging to detect a possible thymoma.

FIGURE 390-1. Marked ocular and facial muscle weakness in a young female with myasthenia gravis. (From Evoli A, Vincent A. Disorders of Neuromuscular Transmission. In: Goldman L, Schafer A, eds. *Goldman-Cecil Medicine*. 26th ed. Philadelphia: Elsevier; 2020.)

TREATMENT

If found on imaging, a thymoma should be removed. Postoperative radiation is recommended for completely resected stage II or III thymomas.[6] Unfortunately, this procedure does not eliminate the autoimmune disease and is not effective in reducing symptoms. For patients who do not have a thymoma, who are acetylcholine receptor antibody–positive, and who are younger than 65 years of age, thymectomy reduces weakness and the cumulative required medication dose over time.[A1,A2] Video-assisted thoracoscopic removal is as good as open surgery.[7] For patients who have muscle-specific kinase antibodies or do not have serum autoantibodies, thymectomy is not indicated.

For severe exacerbations of myasthenia gravis or myasthenia crisis, an immunoglobulin infusion (intravenous immunoglobulin [IVIG] 1 to 2 g/kg given over 2 to 5 days) or plasmapheresis can provide rapid improvement. The duration of response is usually only 4 to 6 weeks, so chronic therapy also must be instituted.

Consensus treatment guidelines[8] emphasize a trial of cholinesterase inhibitors (e.g., pyridostigmine [starting at 30 to 60 mg four times daily]) as first-line therapy to enhance neuromuscular transmission and reduce symptoms over the 3 to 4 hours after treatment. Unfortunately, cholinesterase inhibitors typically do not eliminate weakness, and they may cause gastrointestinal side-effects (bloating, nausea, and diarrhea) as well as increased respiratory secretions that can worsen reactive airway disease. Furthermore, they are much less effective in patients with muscle-specific kinase antibodies.

The most consistently effective treatment is high-dose prednisone (e.g., prednisone escalating to a maximum of 60 mg daily) that then should be tapered to the lowest effective dose, which may be maintained for years.[9] All patients have some adverse effects (Chapter 28), with 30% being severe, ranging from weight gain, diabetes, and hypertension to severe insomnia and osteoporosis. For the 20% or so of patients who do not respond to prednisone or have unacceptable adverse effects, immunosuppressive treatments[10] are warranted and can permit tapering of the prednisone dose.[A3] Rituximab (e.g., 375 mg/m^2 repeated weekly for 4 weeks) eliminates CD20 cells and appears to be effective for patients who have muscle-specific kinase antibodies, but its efficacy in patients with acetylcholine receptor antibodies is less clear.[11] Efgartigimod (an IgG1 antibody at 10 mg/kg as four weekly intravenous infusions, with a maximum dose of 1200 mg for patients who weigh more than 120 kg) is effective for generalized myasthenia gravis.[A4] Other immunosuppressive options include azathioprine (e.g., 2.5 mg/kg/day), mycophenolate (e.g., 2000 mg/day), tacrolimus (e.g., 3 mg/day), and less commonly methotrexate (e.g., 5 to 15 mg weekly). Each of these agents may require many months of therapy before they have biologic and clinical efficacy and may have significant toxicity. Intravenous eculizumab (e.g., 1200 mg every 2 weeks), which inhibits the activation of complement, is effective and well-tolerated in patients with acetylcholine receptor antibodies,[A5] but it is currently reserved for patients who have not responded to prednisone or immunosuppressive agents, in part because of its very high price. Other currently experimental immunotherapies[12] include zilucoplan (a complement inhibitor, given subcutaneously at 0.3 mg/kg daily for 2 weeks).[A6] The precise roles of these newer therapies continues to evolve, but these drugs do not eliminate the production of autoantibodies and, therefore, are unlikely to provide a continuous remission of weakness after they are discontinued. Experimental treatments include B cell ablation, cytokine inhibitors, and CAR-T cells.

Patients should be advised to be as physically active as possible once severe weakness is effectively treated. Exercise limits corticosteroids and may have further positive effects on the immune system.

PROGNOSIS

If not recognized and treated, myasthenic crisis will lead to death. There is no cure for myasthenia gravis. Effective therapies can eliminate symptoms in most patients, but more than 30% of patients have a poor response or intolerable adverse effects to first-line therapy. Patients suffer significant disability, with limitations in employment and compromised quality of life. With modern treatment, however, the lifespan of patients with myasthenia gravis is similar to that of the general population.

LAMBERT-EATON SYNDROME

PATHOBIOLOGY

Lambert-Eaton syndrome is caused by autoantibodies against the voltage-gated calcium channel on the presynaptic nerve terminal. The antibodies cross-link the calcium channels, thereby leading to increased internalization, which reduces the influx of calcium when the nerve terminal depolarizes and, as a result, reduces the vesicular release of acetylcholine. If the amount of acetylcholine is insufficient to activate the required number of acetylcholine receptors, no action potential will be generated to signal muscle contraction. If a nerve is repetitively stimulated during electrophysiologic testing, calcium will accumulate in the nerve terminal, can reach a level that is sufficient to overcome the defect, and will allow the release of acetylcholine. This accumulation is the basis of the incremental response observed in diagnostic testing, a response that is just the opposite of the fatigue seen with myasthenia gravis.

About 60% of patients with Lambert-Eaton syndrome have small cell lung cancer (Chapter 177), which expresses calcium channels that become the target of autoantibodies, whereas the remainder of patients have a primary autoimmune disorder. These latter patients tend to be younger, are more likely to be female, and often to have other autoimmune diseases. The specific stimulus that produces Lambert-Eaton syndrome in these patients is not known.

CLINICAL MANIFESTATIONS

Lambert-Eaton syndrome mimics myasthenia gravis in producing weakness and fatigue, but Lambert-Eaton syndrome tends to be characterized by more prominent proximal muscle involvement with comparatively limited ocular and bulbar muscle weakness. Patients often complain of proximal muscle aches, which are not common in myasthenia gravis.[13] Fluctuations in strength are often less obvious, and progressive weakness may be confused with a myopathy (Chapter 389). Autonomic disturbances, such as xerostomia, hypohydrosis, reduced lacrimation, constipation, and orthostasis, are common. In men, impotence and urinary retention also occur.

On examination, in addition to the expected weakness, pupillary reflexes may be slowed. Deep tendon reflexes are usually reduced but improve after exercise.

DIAGNOSIS

Serum antibodies to the voltage-gated calcium channel are detected in more than 95% of patients and are highly specific for Lambert-Eaton syndrome. On nerve stimulation testing, the compound muscle action potential may be reduced at baseline, which can lead to confusion with a motor neuropathy (Chapter 387), but rapid repetitive nerve stimulation or stimulation performed after brief exercise will lead to an incremental increase in the compound muscle action potential in about 90% of patients.

All patients must be screened for small cell lung cancer (Chapter 177) with a computed tomographic (CT) scan of the chest. If the CT scan is negative in a patient who smokes or is over age 40 years, fluorodeoxyglucose positron emission tomography (PET) scanning is recommended, with a CT scan every 6 months for up to 4 years. SOX1 antibodies are found in about two-thirds of patients with paraneoplastic Lambert-Eaton syndrome but are never positive in patients with the autoimmune form.

TREATMENT

For an acute crisis, plasmapheresis and IVIG (1 g/kg for 2 days) can provide improvement. First-line chronic treatment is with 3,4-diaminopyridine/amifampridine (10 to 20 mg four times daily, either in its base form or a phosphate version),[A7] which blocks potassium channels, prolongs the presynaptic potential, and increases the calcium concentration so that more acetylcholine is released from the nerve terminal.[14] The drug is contraindicated in patients with epilepsy. Paresthesias are common at the start of treatment. If patients do not respond well, pyridostigmine (60 mg three times daily and then increased as tolerated) should be added.

In patients with persistent symptoms, both the primary autoimmune and paraneoplastic forms of Lambert-Eaton syndrome should be treated with immunotherapy. Chemotherapy for small cell lung cancer (Chapter 177) or any other underlying tumor will often ameliorate the symptoms. Otherwise, options, as in myasthenia gravis, include prednisone, mycophenolate mofetil, azathioprine, and rituximab.

PROGNOSIS

Prognosis depends on the underlying condition.[15] For patients with the nonmalignant form, a normal lifespan can be expected but quality of life is reduced. With treatment, weakness can stabilize and gradually improve. For Lambert-Eaton syndrome associated with a malignancy, prognosis is dependent on the tumor's response to treatment.

CONGENITAL MYASTHENIC SYNDROMES

PATHOBIOLOGY

Congenital myasthenic syndromes are caused by rare genetic mutations of the presynaptic, synaptic, or postsynaptic machinery of neuromuscular transmission (see Table 390-1). Because these defects are not exclusive to the lower motor neuron, patients may have a broad range of neurologic manifestations in addition to abnormal neuromuscular transmission.

CLINICAL MANIFESTATIONS

Severe forms of congenital myasthenic syndromes typically present at birth with general weakness manifest with poor sucking and respiratory insufficiency. Progressive weakness and muscle atrophy can be confused with a primary myopathy. Mutations of presynaptic proteins and glycosylation defects can cause intellectual disability and seizures, which may mask identification of the neuromuscular transmission defect. In contrast to such severe forms, the slow channel syndrome and cholinesterase deficiency often are recognized in adulthood when patients develop fatigue, ocular findings, and progressive weakness.

DIAGNOSIS

Differentiation of congenital myasthenic syndromes from seronegative myasthenia gravis is critical so that ineffective immunosuppressive therapies can be avoided. The long history of progressive weakness in congenital myasthenic syndromes can help, but genetic analysis is the key diagnostic test and also guides drug therapy.[16]

TREATMENT

Treatment is guided by the genetic cause and should be managed at a specialized center.[17] Many patients will improve with pyridostigmine (60 mg three times daily and then increasing dose and frequency to maximal tolerated effect) as used for myasthenia gravis or with 3,4-diaminopyridine (250 mg/kg four times daily). Adrenergic receptor agonists, such as salbutamol (0.5 to 2 mg three times daily), improve several forms of congenital myasthenic syndromes, not only by an immediate effect but also over months to years. For the slow channel syndrome, open channel blockers such as fluoxetine (60 to 100 mg/day) normalize synaptic currents.

PROGNOSIS

Congenital myasthenic syndromes vary in severity from death in early childhood to mildly symptomatic disease with limited disability presenting in adulthood. Treatments may improve strength and limit disability.

NEUROMYOTONIA

DEFINITION AND EPIDEMIOLOGY

Neuromyotonia manifests as spontaneous muscle contractions from peripheral nerve hyperexcitability. Its prevalence is poorly defined, but it is even less common than Lambert-Eaton syndrome.

PATHOBIOLOGY

Voltage-gated potassium channels and an associated complex of proteins on the nerve surface are rapidly activated during the propagation of the motor nerve action potential. Antibodies primarily against the contactin-associated protein-2 (CASPR2) part of this system lead to repetitive discharges, which activate muscle.[18] These antibodies are acquired, often as part of a more generalized autoimmune disorder, but sometimes after infection, after an allergic reaction, or with a tumor (especially a thymoma or small cell lung cancer).[19] Mutations of the *HINT1* gene produce neuromyotonia with associated axonal neuropathy. Gene defects of calcium and potassium channels may also produce neuromyotonia.

CLINICAL MANIFESTATIONS

Beginning at any age, patients complain of irregularly undulating muscle movements, called myokymia, and stiffness, usually of limb muscles but also sometimes involving the face, tongue, and muscles of respiration. Fasciculations,

cramps, and pain are typical. The severity of neuromyotonia varies considerably from minor to profound disability.

On examination, typical findings include weakness; delayed muscle relaxation after voluntary contraction (pseudomyotonia), a positive Chvostek sign (contraction of the facial muscle with percussion in the area of the facial nerve), and a positive Trousseau sign (carpopedal spasm induced with restriction of blood flow, as with a blood pressure cuff). Muscular hypertrophy may be found in patients with long-standing disease. Sensory nerve involvement may lead to paresthesias and numbness. Constipation, tachycardia, and hyperhidrosis indicate involvement of the autonomic nervous system. Cognitive manifestations can range from personality alterations and insomnia to psychosis.

DIAGNOSIS

Confirmation of the clinical impression of muscular hyperexcitability is straightforward when electromyography shows characteristic spontaneous discharges, which are also present after contraction. Antibodies directed to voltage-gated potassium channels are found in the serum of some patients. Acquired neuromyotonia can be differentiated from genetic causes by a more abrupt onset and by the presence of autoantibodies. Genetic screening can be performed for known mutations.

TREATMENT

For autoimmune neuromyotonia, plasmapheresis or IVIG (as for myasthenia gravis) can provide short-term benefit for severe symptoms. Drugs that stabilize hyperexcitability, such as carbamazepine (up to 800 to 1000 mg daily), lamotrigine (up to 100 mg daily), or phenytoin (up to 300 mg daily), provide symptomatic relief. Immunotherapies, such as those used to treat myasthenia gravis, are sometimes useful. Treatment of any underlying malignancy may improve symptoms.

PROGNOSIS

Some patients have spontaneous resolution of symptoms, especially if the symptoms were precipitated by an infection. Most others respond to medications. For the paraneoplastic forms, prognosis depends on the underlying cancer.

BOTULISM

PATHOBIOLOGY

Clostridium botulinum (Chapter 271) and, rarely, other species of clostridium will produce toxin under anaerobic and acidic conditions. All strains of botulinum toxins are endopeptidases, which cleave proteins critical for synaptic vesicular fusion at cholinergic neuromuscular junctions and cholinergic synapses of the sympathetic and parasympathetic nerves.

CLINICAL MANIFESTATIONS

Foodborne botulism, which occurs with ingestion of a range of inappropriately home-processed foods and much more rarely commercially processed foods, including food in restaurants, can occur sporadically in an individual or as a cluster from a shared source. Wounds can be contaminated with *C. botulinum* in users of intravenous drugs but also may occur postoperatively.

Botulinum toxin can be aerosolized and used as a weapon or for bioterrorism (Chapter 19). Therapeutic administration of botulinum toxin for a wide range of disorders can have systemic adverse effects, particularly in patients who have preexisting disorders of neuromuscular transmission.

Symptoms of botulism typically begin with dysphagia, dysarthria, ptosis, and diplopia. Subsequent bilateral limb weakness and respiratory insufficiency can be fatal.[20] Weakness progresses over hours to days and is dependent on the amount of toxin. Additional autonomic features include constipation, diarrhea, and urinary retention. Gastrointestinal complaints, which include nausea and vomiting, should alert the clinician to the possibility of botulism because they are distinctly unusual in myasthenia gravis and Guillain-Barré syndrome (Chapter 388), which are the most common misdiagnoses. Absent pupillary reflexes, which also suggest botulism, never occur in myasthenia gravis and are exceedingly rare in Guillain-Barré syndrome.

DIAGNOSIS

Botulism can be confirmed by detection of the toxin by molecular testing (in serum, stool, or lavage fluid, or the food consumed by the patient) or culture of *Clostridium* species that produce the toxin from stool or wounds.[21] Repetitive nerve stimulation may demonstrate a defect of neuromuscular transmission, but normal findings do not exclude botulism, especially early in the course of the disease. In uncertain cases, neurophysiologic testing and analysis of the cerebrospinal fluid, (which is normal in botulism) can identify alternative diagnoses, such as the Guillain-Barré syndrome (Chapter 388) or myasthenia gravis.

TREATMENT AND PROGNOSIS

Outstanding critical care support is the most important determinant of outcome because affected individuals may require months of hospitalization for prolonged paralysis before the infection and toxin are cleared. Equine antiserum, which will not reverse weakness but can eliminate the toxin in circulation, should be instituted within 48 hours of the onset of suspected botulism and should not be delayed for confirmation of the diagnosis. Any wounds may be a source of infection and should undergo debridement. Specific antibiotic therapy is generally not recommended for botulism because antibiotics can lead to release of toxin.

The outcome of botulism depends on recognition and rapid institution of appropriate care, with about 50% of hospitalized cases resolving completely.[22]

OTHER NEUROTOXINS

Neurotoxins (see Table 390-1), which poison neuromuscular transmission, are produced by a variety of pharmaceutical agents, plants, and animals. Onset of weakness develops rapidly after exposure and may lead to death within minutes to hours. Recognition of such intoxication is usually straightforward if the encounter is with a snake or spider (Chapter 98), but is more challenging if a toxin, such as Novichok, is being used to poison an individual. The key to saving a patient is rapid institution of supportive care until the toxin is metabolized. In the case of tick bite, the exceedingly small tick, which is often found at the hairline, needs to be removed.

Organophosphate poisoning (Chapter 96) may occur with accidental exposure to a pesticide, intentional suicide, or intentional delivery in the form of a gas to produce widespread death or focused exposure to an individual by injection or inhalation. Patients will experience severe weakness in combination with manifestations of cholinergic excess: hypersalivation, pupillary constriction, diarrhea, and sweating. Treatment (see Table 96-3) is with atropine (1 to 2 mg, initial intravenous bolus, doubled every 5 minutes as needed and followed by a titrated infusion) and magnesium sulfate (4 g intravenously over 30 minutes).[23]

Many commonly used drugs may reduce the safety factor for neuromuscular transmission. This side-effect (Table 390-2) is not relevant in individuals with a normal neuromuscular junction but can have devasting consequences for patients who have an existing neuromuscular transmission disorder. Checkpoint inhibitors, now used widely in oncology (Chapters 164 and 166), can worsen

TABLE 390-2 DRUGS THAT WORSEN OR INDUCE NEUROMUSCULAR TRANSMISSION DISORDERS*

COMPROMISE SAFETY FACTOR	INDUCE AUTOIMMUNE REACTION
Aminoglycosides, macrolides	Penicillamine
Fluoroquinolones, clindamycin, telithromycin	Nivolumab, pembrolizumab, ipilimumab, tremelimumab, durvalumab
Hydroxychloroquine	
Procainamide, propranolol, propafenone	
Verapamil, quinidine	
Phenytoin, trimethadione, lithium	
Botulinum toxin	
Intravenous magnesium	

*This list is not exhaustive, and the clinician should consult myasthenia.org for a complete list of medications to use with caution in patients with disorders of neuromuscular transmission.

or even induce myasthenia gravis.[24] Penicillamine has long been known to induce myasthenia gravis by induction of an immune reaction, which often resolves with discontinuation of treatment.

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For the General References and other additional features, please visit Elsevier eBooks+ at https://ebooks.health.elsevier.com.

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391 DISEASES OF THE VISUAL SYSTEM

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The eye is a compact, complicated structure (Fig. 391-1) that is remarkably stable throughout life. Once the growth of the eye is complete, at approximately age 7 to 8 years, the structure of the eye changes very little throughout one's life.

The eyelids physically protect the eye. The pathway of light through the eye, termed the *visual axis*, ideally contains no opaque structures such as blood vessels. Light passes through the tear film, cornea, aqueous humor, crystalline lens, vitreous, and inner retina, all of which, except for the crystalline lens, remain essentially transparent throughout life. Delicate intraocular structures are protected by a tough collagenous "eye wall" composed of the cornea and sclera. The optic nerve, which is primarily composed of axons from the retinal ganglion cells, is enveloped by dura, arachnoid, and pia mater, which are contiguous with the dural layers of the brain. The myelination of the neural elements of the optic nerve begins at the posterior aspect of the eye. The orbital portion of the optic nerve is long enough to allow free excursions of the eye through a 100-degree arc under the influence of six coordinated and critically placed rectus muscles. All these functional components are housed in a bony cavity, the orbit, which protects the eye from external injury.

The eyelid skin, only loosely connected to underlying structures, is among the thinnest of the body. The eyelid is unique because it contains the highest density of sebaceous glands in the body. These meibomian glands produce a sebaceous (lipid) material that is the principal evaporation retardant for the tear film. Malorientation of the eyelid margin or malorientation of the lashes (trichiasis) may cause scarring of the anterior surface of the eye, even to the point of blindness, owing to diminished transparency of the cornea. The upper eyelid is opened by contraction of the levator muscle. The tendon of the levator tends to degenerate over time to produce mechanical ptosis ("drooping eyelids"). The soft tissue of the eyelid is separated from the soft tissue of the orbit by the orbital septum, a major collagenous barrier that protects intraorbital soft tissue from extension of preseptal eyelid inflammation and infection. Extension of inflammation from preseptal cellulitis or ethmoiditis may cause orbital cellulitis, thereby resulting in potential consequences such as cavernous sinus thrombosis. The elastic tissue supporting the skin of the anterior eyelid is reduced over time, thereby causing dermatochalasis ("baggy eyelids"). Redundant tissue of the superior eyelid may be sufficient in quantity to restrict the visual field.

The conjunctiva is a mucous membrane with an outer layer of stratified, nonkeratinizing squamous epithelium containing goblet cells. The epithelium is supported by delicate fibrovascular tissue that contains lymphatic channels. The conjunctival epithelium also contains melanocytes. Squamous carcinoma or malignant melanoma originating in the conjunctiva may extend through these channels to regional lymph nodes or beyond. Immune processing cells are present in the epithelium (Langerhans cells) and in the stroma as collections of non-nodal B and T lymphocytes. Non-nodal primary lymphomas, which tend to have an indolent course in this location, may arise from this tissue. The aqueous portion of tears is formed constantly by accessory lacrimal glands in the conjunctiva as well as by reflex action from the lacrimal gland. Symptoms of itching and burning, as well as periodic disturbance of vision, may result from inadequacies of the tear film layer.

Tears drain through two puncta located at the nasal eyelid margin (one in the upper lid and one in the lower lid) into the nasolacrimal duct, which exits into the nasal cavity under the inferior turbinate. The epithelium of the nasolacrimal duct also contains melanocytes and is supported by a resting lymphocyte population. Neoplasms including lymphoma, concretions (dacryoliths), and tissue injury from trauma may occlude the puncta and nasolacrimal system in adults.

The cornea is avascular and lined anteriorly by epithelial cells and posteriorly by endothelial cells. Lack of an adequate tear film (dry eye syndrome) may seriously alter the ability of the cornea to transmit light, thereby affecting visual acuity. The posterior cellular lining of the cornea is a single layer of highly modified corneal endothelial cells that maintain tissue dehydration. Lack of effective pumping by the endothelial cells will allow excess hydration of the corneal stroma—that is, corneal edema—which diminishes the transmission of light. The corneal stroma is particularly sensitive to proteolysis from collagenases found with certain inflammatory conditions, such as herpes simplex and zoster keratitis. The cumulative effect of multiple episodes of corneal inflammation may be thinning and even perforation of the cornea or, alternatively, thickening and scarring.

The anterior chamber is bounded by the posterior surface of the cornea, the anterior surface of the iris, and the anterior surface of the crystalline lens within the pupillary space. The posterior chamber is bounded by the posterior surface of the iris, the ciliary body circumferentially, and the anterior surface of the vitreous. Aqueous humor normally flows from the posterior chamber into the anterior chamber through the pupil and exits into the general circulation through the trabecular meshwork and a series of collector veins. Most causes of pathologically increased intraocular pressure and optic nerve damage (e.g., glaucoma) are due to abnormalities of filtration through the trabecular meshwork. The crystalline lens is located entirely in the posterior chamber.

The anterior segment is composed of the cornea and the anterior and posterior chambers. Most of the anterior segment is derived from the skin and neural crest tissue. The posterior segment is the remainder of the eye. Most of the posterior segment structures are derived from the central nervous system and neural crest tissue.

When first formed, the crystalline lens is a totally cellular structure bounded by a true basement membrane. Throughout life, the new cells that are continuously added from the outer-layer epithelial cells compress the central cells, thereby resulting in cell degeneration in the central core (nucleus). The lens doubles in volume from birth to age 70 years at the cost of both pliability (presbyopia) and clarity (cataract). The lens is suspended in the posterior chamber by fibers (zonules) attached to the ciliary body.

The ciliary body comprises the middle layer of the eye wall, the uveal tract. The uveal tract extends under the retina as a vascular plexus, the choroid, and the iris. The surface cells of the ciliary body produce aqueous humor, and its muscles function in accommodation.

The vitreous is composed primarily of water and type II collagen. The vitreous makes up the majority of the volume and weight of the eye. It functions as a biochemical sink as well as to maintain neural retinal attachment. With time, the vitreous shrinks and separates from the retina (posterior vitreous detachment). Condensed vitreous opacities, which cast shadows on the retina, are perceived by the patient as "floaters."

The retina is the site of photochemical conversion of light to electrical energy. Ganglion cells and their axons in the internal retina aggregate at the optic disc to form the optic nerve. Only the inner half of the retina is supplied by intraretinal vessels that are seen by ophthalmoscopy. The outer half of the retina is supplied by large-caliber capillary vessels in the choroid (the choriocapillaris). Extensive biochemical support and control of stray light are performed by the retinal pigment epithelium located between the choriocapillaris and the photoreceptor outer segments. The density of photoreceptor cells (rods and cones) varies across the retina. Only a 500-μm area of the posterior retina, the central macula (about 3 to 5% of the total retina), has a high enough density of photoreceptor cells, primarily cones, to allow images to be resolved to 20/20. The remainder of the retina has much less sensitive image resolution owing to a lower density of photoreceptor cells. The blood-retinal barrier, which protects the biochemical integrity of the retina, is composed of anatomic attachments between neighboring retinal pigment epithelial cells, as well as attachments between vascular endothelial cells of the retinal circulation. The retina is held in place by physiologic forces that may be compromised by holes in the retina (rhegmatogenous retinal detachment) or by fluid accumulating in the subretinal space without a retinal hole (nonrhegmatogenous retinal detachment).

The optic nerve is composed of approximately 1 million axons from retinal ganglion cells. Axons are separated into bundles by pial septa, which are in turn enclosed in an arachnoid layer. The dura is contiguous with the posterior sclera and the periosteum of the optic canal. Delicate vessels extending from the dura across the arachnoid to the pial septa supply the optic nerve. The central retinal artery is present in the axial layer of the optic nerve near the eye but does not supply blood to the optic nerve itself. The optic nerve axons travel through a collagenous sieve in the plane of the posterior sclera, the lamina cribrosa. The choroid is that portion of the uveal tract external to the retina. This layer is composed of various calibers of blood vessels that ultimately supply blood for the choriocapillaris.

The sclera is composed of dense, relatively disorganized collagen. It is opaque because of the nonhomogeneous structure of the collagen and the degree of hydration relative to the cornea. There are multiple scleral ostia for the passage of arteries, veins, and nerves, both posteriorly and anteriorly.

ABSTRACT

The structure and function of the eye is affected by normal aging and local and systemic diseases. Although the detection of the loss of vision and disease screening typically require use of specialized equipment and personnel, the eye examination may reveal neurologic, cardiovascular, endocrinologic, and inflammatory disease that aids in systemic disease diagnosis and management across all fields of medicine.

KEYWORDS

cataract
macular degeneration
retinopathy
glaucoma
neurodegeneration
visual function

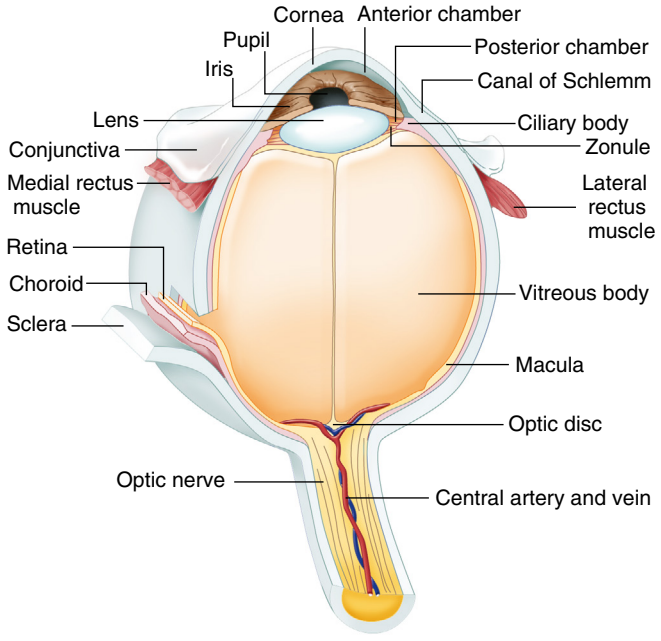

FIGURE 391-1. **Anatomy of the eye.**

The orbit is composed of bones of the facial skeleton. Sutures between major bones exist in the superior nasal and superior temporal quadrants. Multiple vessels and nerves extend through the thin ethmoid bone from nasal sinus tissue medially. The orbital floor, which is a relatively thin layer of bony support over the maxillary sinus, may rupture with increased intraorbital pressure or after blunt trauma to the inferior orbital rim. The nasolacrimal duct travels through a portion of the lacrimal bone. Portions of the sphenoid bone protect the optic nerve. Major cranial nerves travel through the adjacent superior orbital fissure, also a portion of the sphenoid bone. There is no normal lymphoid tissue in the orbit outside of the lacrimal gland. The rectus muscles may be enlarged by inflammation in thyroid eye disease, but the tendinous insertion into the sclera is usually not inflamed early in the course of the disease.

CLINICAL MANIFESTATIONS AND DIAGNOSIS

Patients may present with complaints of diminished vision, eye pain, redness, or pain around the eye. The causes may be primarily ophthalmic (e.g., cataract) or systemic (e.g., diabetic retinopathy). A comprehensive ophthalmologic examination also should evaluate for possible asymptomatic local (e.g., choroidal melanoma) or systemic (e.g., hypertensive retinopathy) abnormalities in patients with normal acuity and no subjective complaints.

Functional Evaluation

The most objective and common measure of ocular function is line letter acuity, with normal vision (Table 391-1) defined as the ability to see at 20 feet what a normal person sees at 20 feet, known as 20/20 vision (E-Fig. 391-1). Less than 20/20 vision can be caused by an abnormality anywhere from the tear film to the visual cortex of the occipital lobe (see Fig. 391-1). However, normal vision also includes other functions, such as the perception of color, motion, contrast, brightness, field, and depth, for which there is greater variation among individuals. Normal visual acuity is potentially achievable in essentially all individuals, either naturally or with the correction of the refractive error. Although effective treatments are available for refractive errors, cataracts, glaucoma, and other eye conditions, there is no evidence that routine screening for impaired visual acuity is associated with improved clinical outcomes.[A1]

Correction of vision is based on the refraction of light (Fig. 391-2). The diopter (D) is the unit of measurement of the ability of an optical system to refract (bend) light. The normal human eye has a refractive capacity of approximately 60 D, which is accomplished by the cornea and the crystalline lens. This refractive capacity is needed to focus light onto the central retina, the macula. If the eye is too short, light will be focused behind the eye (hyperopia). If the eye is too long, light will be focused in the vitreous cavity in front of the retina (myopia). Normally, a person can involuntarily control the crystalline lens, alternating between near and distant tasks. During the fourth and fifth decades of life, the lens becomes less pliable and the eye loses its ability to alter its shape (presbyopia). Refraction is the method of determining the amount of optical correction (strength of glasses) needed to establish 20/20 vision.

TABLE 391-1 VISUAL ACUITIES REQUIRED FOR COMMON DAILY TASKS

20/20	Physiologic vision
20/30-20/100	Driver's license, varies by state
20/50	Newspaper print
20/70	Large-print *Reader's Digest*
20/100	Check writing
20/200	Legal blindness
20/400	Paper currency

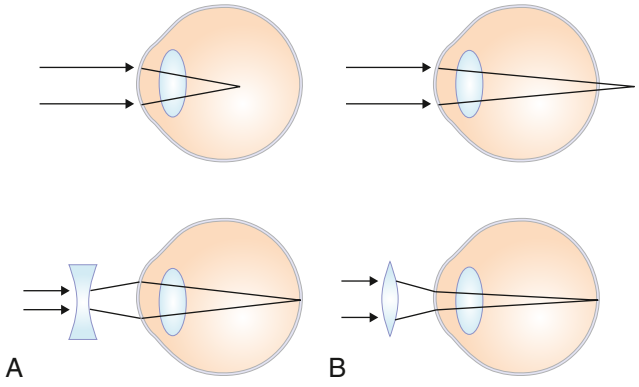

FIGURE 391-2. **Myopia/hyperopia. A,** In the myopic eye, parallel rays of light are focused anterior to the retina. A divergent lens can be used to compensate for the mismatch between refracting power and axial length. **B,** The hyperopic eye requires the additional power of a convergent lens to bring images into focus on the retina.

Examination of pupillary response assesses whether neural function is intact (see Figs. 392-2 and 392-4). Confrontational visual field testing (see Fig. 392-1 in Chapter 392) should be performed in each eye to detect gross quadrantic defects. Extraocular motility should be assessed to exclude nerve or muscle abnormalities (see Table 392-6). Color vision testing plates are a sensitive indicator of optic nerve function and for detecting genetic variations that result in deficiencies of color perception.

Diagnostic testing during a routine eye examination also includes external examination of the lids and adnexa, applanation tonometry to determine intraocular pressure, biomicroscopy (slit lamp examination) of the anterior segment, and ophthalmoscopic examination of the ocular fundus (the retina and associated structures). Other tests include exophthalmometry (measurement of proptosis), visual field and electrophysiologic testing and imaging (fluorescein angiography, mainly in diabetic patients; optical coherence tomography [OCT] to investigate retinal disease and glaucomatous damage), and corneal topography.

The conjunctiva, cornea, lens, and anterior chamber are evaluated using a slit lamp biomicroscope. The slit lamp is composed of a binocular microscope with variable magnification (40× and 80×) in conjunction with adjustable light sources. An increased concentration of protein can be detected in the anterior chamber because of the Tyndall (flare) effect, indicating vascular incompetence associated with either inflammation or ischemia. Even individual inflammatory cells can be resolved with the slit lamp. A cobalt blue filter can be used to detect fluorescein dye that accumulates in regions of abnormal epithelium (dendrite of herpes simplex keratitis or a corneal abrasion). The slit beam is used to examine the crystalline lens to determine the depth of the anterior chamber and the degree of opacification from a cataract. By using a green filter with the 90-D lens, the retinal vessels and retinal vascular abnormalities such as microaneurysm can be seen.

COMMON CLINICAL CONDITIONS

Chronic Abnormal Vision

MYOPIA

Nearsightedness (myopia; see Fig. 391-2) is usually discovered during childhood when children cannot perform distant tasks during school (reading the

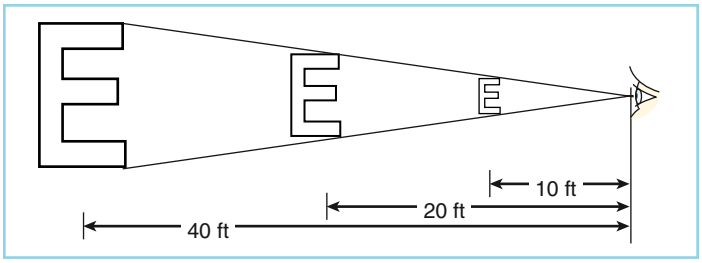

E-FIGURE 391-1. Snellen visual acuity. The most common test for visual acuity measures the eye's ability to resolve linear images at a test distance of 20 feet, approximating infinity (parallel rays of light). A 20/20 E subtends 5 minutes of arc at a distance of 20 feet, with each segment of the E subtending 1 minute of arc. The larger letters (e.g., 20/30, 20/40) are determined by the distance at which they subtend an angle of 5 minutes. Thus, an E that subtends 5 minutes at 40 feet, if viewed clearly at 20 feet, indicates 20/40 visual acuity.

blackboard) or during school screening. Myopia usually progresses until age 20 to 25 years. Rapidly progressing myopia at any time after age 25 years requires evaluation for diabetes mellitus (reversible metabolic changes in the crystalline lens), trauma (development of a cataract), or use of corticosteroids (development of a cataract). Nonpathologic forms of myopia are usually fully correctable with eye glasses or contact lenses or can be corrected to a visual acuity of 20/40 or better in 95% or more of patients by various forms of laser-assisted in situ keratomileusis (LASIK).[A2] Complications of LASIK include glare symptoms, dry eye, and undercorrection or overcorrection.[1] Rare but serious complications include epithelial ingrowth, diffuse keratitis, and flap dislocation.

Pathologic myopia is a partly heritable condition causing progressive weakening of the posterior sclera and resulting increases in the axial length of the eye. Localized areas of deformation arise where there is an abrupt increase in the posterior radius of curvature of the eye (posterior staphyloma). The axial length of a normal eye is typically between 20 and 24 mm, whereas it can increase to above 25 mm in pathologic myopia and may be as high as 40 mm in severe cases. Abnormal physical forces in pathologic myopia may lead to retinal hole formation, retinal detachment, choroidal neovascularization, or intraocular hemorrhage. Associated systemic conditions include Cornelia de Lange syndrome, Stickler syndrome, and Marfan syndrome. Clinical surveillance is important to identify treatable complications such as retinal holes and detachment. Pathologic myopia is treated palliatively with eye glasses or contact lenses. Refractive procedures are less successful in pathologic myopia because of the severity of the refractive errors and the presence of posterior segment abnormalities. Surgical and laser procedures may be required to treat retinal and choroidal lesions.

HYPEROPIA

In hyperopia (farsightedness; see Fig. 391-2), in contrast to myopia, the eye tends to have a shorter than average axial length. Shorter axial lengths are associated with narrow-angle glaucoma and angle-closure glaucoma. Compensatory mechanisms of the crystalline lens may functionally correct small degrees of hyperopia until age 40 years, when the crystalline lens loses its pliability. The initial pair of glasses may have to correct for both distance and near tasks (bifocals). Refractive surgical procedures can correct up to 5 D of hyperopia.

PRESBYOPIA

Presbyopia typically presents in the fourth to sixth decades of life and manifests as a progressive decrease in the ability to focus clearly on near objects. Presbyopia results when the crystalline lens loses its pliability, thereby preventing light rays from close objects from focusing onto the retina. The lens is suspended by fibers (zonules) attached to the ciliary body. In youth, the musculature of the ciliary body, acting via the zonules, alters the shape of the lens to provide increased near focusing power. As the lens hardens and presbyopia ensues, symptoms include difficulty reading small print, eyestrain, headaches, and the inability to read material unless it is farther away. Treatment is typically with eye glasses, such as bifocals, to provide adequate magnification to replace the lost ability of the eye.

ASTIGMATISM

Astigmatism derives from changes in the radius of curvature of the cornea and from the lens. Symptoms are predominantly blurry vision with "shadowing" and difficulty seeing fine detail. Regular astigmatism is not a pathologic state but rather a variation in anatomy; most people have some degree of regular astigmatism that can be corrected with eye glasses or contact lenses. Irregular astigmatism is usually from changes on the cornea (e.g., from scarring owing to infections or trauma) or from adjacent tissue on the cornea (e.g., pterygia or limbal masses that induce changes in the corneal curvature). Some forms of regular astigmatism can be corrected with corneal laser ablation, but irregular astigmatism often requires correction with rigid contact lenses.

KERATOCONUS

Keratoconus is an acquired thinning of the cornea that induces irregularities of the corneal surface and irregular astigmatism; its cause is controversial but probably is partly genetic. Chronic eye rubbing has been associated with progressive disease. Onset generally is during adolescence, and the process often evolves over 5 to 10 years. The prevalence in the United States is approximately 55 cases per 100,000, but this figure may underestimate subclinical cases. Corneal surface mapping allows earlier and more precise diagnosis.

Patients with keratoconus typically report a progressive worsening of vision, sometimes severe. The condition is usually bilateral but not symmetrical. Mild degrees of early keratoconus can be corrected with glasses or contact lenses. The condition is typically progressive, but corneal collagen cross-linking can halt the progression in early to moderate cases and provide a sustained improvement in vision. For severe cases with significant corneal scarring and intolerance to contact lenses, corneal transplantation (graft) is the primary therapy.

STRABISMUS

The control of simultaneous orientation of the two eyes to ensure that the visual axes of both eyes are aligned is not complete until 6 to 12 months following birth. Misalignments of the two eyes (strabismus) may be the result of abnormalities in the central oculomotor nuclei of the brain, malfunction of one or several oculomotor nerves, or intrinsic abnormalities of the rectus or oblique muscles (see Fig. 392-6). If the eyes are not simultaneously stimulated with the images of the same degree of clarity or complexity, there is a risk that only one eye will develop normal vision (amblyopia). In most cases, only the central vision is affected, so the peripheral vision in both eyes is likely to be normal. Binocular vision can be disrupted with amblyopia, with a loss in depth perception that may become permanent if the normal eye alignment is not restored.

Amblyopia also may be caused by a marked difference in refractive error between the two eyes (anisometropic amblyopia), congenital cataracts, or eyelid ptosis (deprivational amblyopia). Ptosis may be neurogenic or mechanical (e.g., congenital eyelid hemangioma). To avoid amblyopia, it is extremely important to refer a child with strabismus to an ophthalmologist as soon as the strabismus is noted.

Treatment options include patching or atropine eye-drops (1%, typically daily but effective if used as infrequently as twice per week) to blur the better-seeing eye, thereby strengthening the amblyopic eye. These therapies have been shown to be equally effective in providing good vision if patients are treated before age 7 years. The outcome of treatment is more favorable if amblyopia is detected before age 2 to 3 years but may be occasionally successful into the teenage years depending on the severity. Success is directly related to compliance and the timeliness of diagnosis.

Esotropia is a deviation of one eye inward ("crossed eyes"). Although intermittent esotropia may be a normal finding in infancy, it should not be present beyond 6 months of age. Delay in facial maturation (underdeveloped nasal bridge) may give the appearance of esotropia, even though the visual axes are correctly aligned. In true strabismus, the corneal light reflex will be in the center of one cornea and decentered in the other.

Exotropia is deviation of one eye outward. Exotropia is often intermittent and less likely to result in amblyopia compared to esotropia. Like esotropia, intermittent exotropia may also be a normal developmental finding in infancy.

In some cases, esotropia or exotropia may be treated by using appropriate corrections of refractive error with glasses (occasionally bifocals). It is critically important to recognize that strabismus may be the presenting sign of vision loss due to other causes (e.g., retinoblastoma). Extraocular muscle surgery may be necessary to correct alignment.

DIPLOPIA (DOUBLE VISION)

Acute onset of diplopia is an ominous sign suggestive of a cranial nerve palsy (i.e., III, IV, or VI) or pathology in the orbit (Chapter 392). Diplopia of any kind is usually an intolerable symptom, which is often worse with vertical deviations than horizontal deviations.

COLOR VISION CHANGE

Most cases of congenital color blindness are genetically determined and go undetected for many years. Acquired color deficiency at any age may be caused by a cataract or optic nerve disease.

CHANGE IN VISION

If only one eye has a change in vision, the problem, such as a cataract or retinal detachment, is most likely in that eye. If both eyes have a change in vision, the problem generally is outside of the eye, such as homonymous hemianopia (Chapter 392). Improvement of near vision in middle age may be a sign of cataract ("second sight") or hyperglycemia. Transient complete or partial unilateral or bilateral loss of vision may be caused by vascular abnormalities inside or outside of the eye (Table 391-2).

ACUTE EYE ABNORMALITIES

PAIN

The most severe eye pain (Table 391-3), typically associated with a red eye, is caused by acute angle-closure glaucoma. Sharp, intermittent pain is usually

caused by ocular surface abnormalities (e.g., corneal foreign body). Burning pain that clears with blinking generally relates to tear film abnormalities (dry eyes). Deep boring pain most often is associated with an ocular abnormality (e.g., uveitis).

RED EYE

A red or inflamed eye can be caused by conjunctivitis (allergic, inflammatory, or infectious), iritis (anterior uveitis), acute glaucoma, ocular trauma, or infection (Table 391-4).[2] All of these causes are typically painful to varying degrees.

DISTORTED VISION

Distorted vision (metamorphopsia), which is the perception that straight lines are distorted or bowed, results from macular dysfunction. Causes include fluid under the retina; macular degeneration, which tends to elevate the retina; and an epiretinal membrane, which tends to contract the retina.

NIGHT BLINDNESS

Retinitis pigmentosa, vitamin A deficiency, and systemic medications such as phenothiazines can cause true night blindness, in which patients have difficulty seeing any stars in the sky on a clear night and may be unable to ambulate without assistance in a dark environment. Patients with cataracts may have difficulty driving at night because of excessive glare and visual distortion. Gene therapy using adeno-associated virus vectors carrying the *RPE65* gene has been shown to increase retinal sensitivity and to improve night vision in patients with retinitis pigmentosa.

TABLE 391-2 DIFFERENTIAL DIAGNOSIS OF SUDDEN VISUAL LOSS

UNILATERAL	BILATERAL
Amaurosis fugax (carotid artery stenosis or vascular occlusion)	Eclampsia
Central retinal artery occlusion	Vertebrobasilar infarct
Occipital lobe infarct	Trauma
Temporal arteritis	
Nonarteritic anterior ischemic optic neuropathy	
Hemorrhage	
Preretinal (high altitude, Valsalva)	
Vitreous	
Aqueous (hyphema)	
Trauma	

TABLE 391-3 CAUSES OF EYE PAIN

Blepharitis	Glaucoma
Blocked tear duct	Hordeolum (stye)
Chalazion	Iritis
Conjunctivitis	Keratoconus
Corneal abrasion	Optic neuritis
Dry eyes	Scleritis
Ectropion	Trauma
Entropion	Uveitis
Foreign object	

SENSATION OF FLASHING LIGHTS

The sudden onset of flashes (photopsia) in the peripheral visual field suggests traction of the vitreous on the peripheral retina, sometimes with a resulting retinal tear. The flashes, which may be more pronounced in the dark and with rapid eye movement, may be associated with the sudden onset of floaters, which can indicate debris or blood in the vitreous cavity. Because a tear in the retina can lead to a retinal detachment, urgent consultation with an ophthalmologist is required.

Flashing light with a migraine (Chapter 367) is described as scintillations or zigzagging lights that march across the visual field for a few minutes or as long as 30 minutes, sometimes associated with transient visual field loss. Headache is not universal.

FLOATERS

Floaters, which are caused by small aggregates or opacities in the vitreous cavity, result from the normal aging of the vitreous. The acute onset of vitreous floaters may be associated with uveitis or with the sudden onset of bleeding in the vitreous cavity owing to diabetes or vascular occlusions. Acute floaters, however, particularly if associated with flashing lights, may indicate a posterior vitreous detachment and/or a retinal tear with an impending retinal detachment. Urgent ophthalmic referral is essential.

PHOTOPHOBIA

Photophobia, particularly if associated with eye pain, redness, and decreased vision, is a symptom of intraocular inflammation (uveitis) from trauma or other causes. Photophobia is also typical of acute migraine and meningeal irritation. Prompt ophthalmologic referral is prudent.

HALOS AROUND LIGHTS

Patients with cataracts commonly see halos around lights, particularly when driving at night. Episodic decreased vision, redness, and halos around lights may be symptoms of impending angle-closure glaucoma owing to increased intraocular pressure with resulting corneal edema and loss of corneal clarity. Halos also can occur as a complication of refractive eye surgery.

FOREIGN BODY SENSATION

A foreign body sensation is commonly caused by ocular surface diseases such as dry eye syndrome (see later). Entropion (see Fig. 391-3) or misdirected lashes (trichiasis) also can cause a foreign body sensation. Most corneal abrasions cause severe pain, but minor corneal abrasions may be associated with a foreign body sensation rather than the severe pain. An arc welder burn causes a punctate corneal keratopathy, and foreign body sensation may be a prominent symptom. A true conjunctival or corneal foreign body also may be present.

EXCESSIVE TEARING (EPIPHORA)

Tearing can occur because of the overproduction of tears or impairment of tear drainage. Any abnormalities in upper or lower lid laxity, position, or closure can impair the lacrimal pump system. The most common cause of epiphora is

TABLE 391-4 DIFFERENTIAL DIAGNOSIS OF COMMON CAUSES OF INFLAMED EYE*

FEATURE	ACUTE CONJUNCTIVITIS	ACUTE IRITIS†	ACUTE GLAUCOMA‡	CORNEAL TRAUMA OR INFECTION
Incidence	Extremely common	Common	Uncommon	Common
Discharge	Moderate to copious	None	None	Watery or purulent
Vision	No effect on vision	Slightly blurred	Markedly blurred	Usually blurred
Pain	None	Moderate	Severe	Moderate to severe
Conjunctival injection	Diffuse: more toward fornices	Mainly circumcorneal	Mainly circumcorneal	Mainly circumcorneal
Cornea	Clear	Usually clear	Steamy	Change in clarity related to cause
Pupil size	Normal	Normal or small	Moderately dilated and fixed	Normal or small
Pupillary light response	Normal	Normal or reduced	None	Normal
Intraocular pressure	Normal	Variable	Elevated	Normal
Smear	Causative organisms	No organisms	No organisms	Organisms found only in corneal ulcers related to infection

*Less common causes of red eyes include endophthalmitis, foreign body, episcleritis, and scleritis.
†Acute anterior uveitis.
‡Angle-closure glaucoma.

chronic or acute irritation that results in the overproduction of reflex tearing from ocular dryness (dry eye syndrome). Ocular surface irritants, such as trichiatic eyelashes touching the cornea, also can stimulate excessive tear production. Obstruction of the nasolacrimal tear drainage system owing to age, inflammation, infection, trauma, or neoplasm can prevent appropriate tear drainage. Treatment depends on the underlying condition.

EYELID TWITCHING

Any irritation of the conjunctiva or cornea can cause the eyelids to twitch. Occasional twitching of the lids usually is associated with stress or adrenergic stimulation. Benign essential blepharospasm is severe spasm of the lids leading to functional impairment. Multiple sclerosis (Chapter 380) also can cause lid spasm.

CONJUNCTIVITIS

Any ocular inflammation, including corneal ulcers, angle-closure glaucoma, endophthalmitis, and uveitis, can be associated with secondary conjunctival hyperemia. Conjunctivitis usually involves the entire conjunctiva, is associated with a discharge, and may or may not be associated with pain (see Table 391-4).

PTOSIS (DROOPY EYELID)

Ptosis (Fig. 391-4) is typically due to age-related degeneration and even disinsertion of the levator palpebrae superioris muscle. However, it also can be caused by a third nerve palsy, Horner syndrome, myasthenia gravis (Chapter 390), or other neurologic conditions. Third nerve palsy is usually associated with diplopia and a large pupil. Horner syndrome (see Fig. 392-5) is associated with a small pupil and ipsilateral anhydrosis. With myasthenia gravis (Chapter 390), other typical features of muscle weakness and fatigability are usually present or can be elicited. Non-neurologic causes of ptosis include age-related dehiscence of the levator muscle.

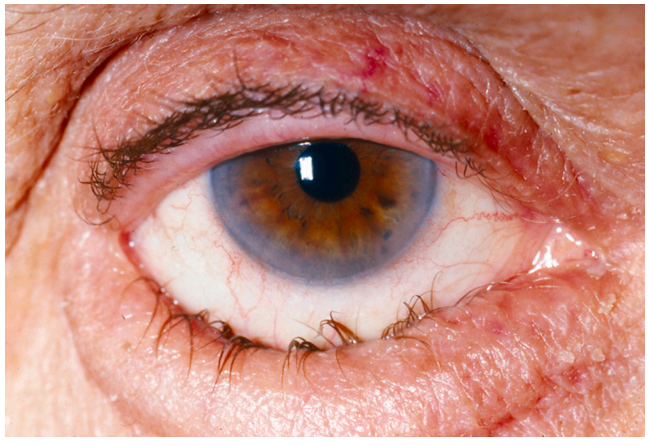

FIGURE 391-3. Involutional entropion of the lower lid with trichiasis. (From Palay DA, Krachmer JH. *Primary Care Ophthalmology*, 2nd ed. Philadelphia: Elsevier Mosby; 2005.)

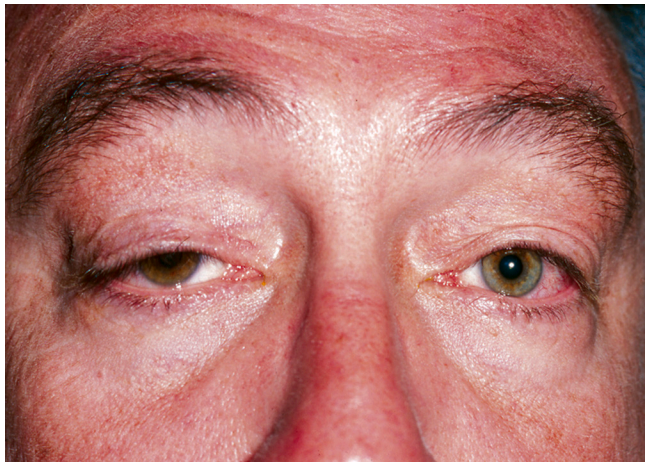

FIGURE 391-4. Ptosis of the right upper lid. (From Palay DA, Krachmer JH. *Primary Care Ophthalmology*, 2nd ed. Philadelphia: Elsevier Mosby; 2005.)

PROPTOSIS (EXOPHTHALMOS)

Proptosis, or a prominent globe, can be a manifestation of thyroid eye disease, which in turn is associated with thyroid abnormalities, especially Graves disease (Chapter 207). In this setting, proptosis can be subacute and asymmetrical. Any orbital inflammation, infection, or neoplasm can cause unilateral proptosis; in the case of inflammation or infection, proptosis is typically acute in onset. All orbital processes can affect orbital cranial nerves, with associated diplopia or optic neuropathy. Orbital infection, or cellulitis, typically presents with concurrent severe eye redness, pain, sinusitis, and an elevated white blood cell count (Fig. 391-5). Idiopathic orbital inflammation can cause acute, usually unilateral proptosis, with severe pain, particularly with eye movement, and often with decreased vision. An optic nerve tumor causes chronic, unilateral proptosis associated with a slow onset of visual field loss. Acute cellulitis can be associated with unilateral proptosis, severe redness, and moderate to severe pain, commonly with sinusitis and an elevated white blood cell count.

SMALL PUPIL

A unilateral small pupil is best detected in dark conditions. Causes include Horner syndrome, associated with ptosis on the same side; the bilaterally small, poorly reacting pupils of tertiary syphilis (Argyll Robertson pupils), which accommodate with normal constriction to a near object; miotic drops (e.g., pilocarpine); traumatic iritis; uveitis; and opioids.

LARGE PUPIL

Any α-adrenergic or anticholinergic agent placed into the eye can cause a large pupil. With eye trauma, the iris sphincter muscle can be damaged, and an abnormally large pupil can result. Tears in the iris sphincter can sometimes be appreciated on slit lamp examination. Third nerve palsy may cause a dilated pupil associated with ptosis and decreased elevation, depression, and medial eye movement. Adie pupil (see Fig. 396-3) is an idiopathic, unilateral large pupil that is hypersensitive to weak cholinergic stimulation. Recent eye surgery with pharmacologic dilation, uveitis, an acute angle-closure glaucoma attack, and traumatic iritis can cause a large pupil.

LEUKOCORIA

Leukocoria (white pupil) in a young child is critically important, because it may be a sign of retinoblastoma. Some of the more common non-retinoblastoma conditions presenting with leukocoria (Table 391-5) include cataracts, retinal detachment, persistent fetal vasculature (a developmental anomaly of the vitreous resulting in intraocular fibrosis and retinal detachment), Coats disease (a developmental vascular malformation of the retina leading to exudative retinal detachment), and ocular toxocariasis (a parasitic intraocular nematode infection that leads to intraocular scarring and retinal detachment).

FIGURE 391-5. Thyroid eye disease (Graves) with characteristic exophthalmos and eyelid retraction.

TABLE 391-5 DIFFERENTIAL DIAGNOSIS OF LEUKOCORIA

Retinoblastoma
Cataract
Persistent hyperplastic primary vitreous
Retinopathy of prematurity (retrolental fibroplasia)
Coats disease (retinal telangiectasia)
Retinal detachment
Toxocariasis
Familial exudative vitreoretinopathy (FEVR)

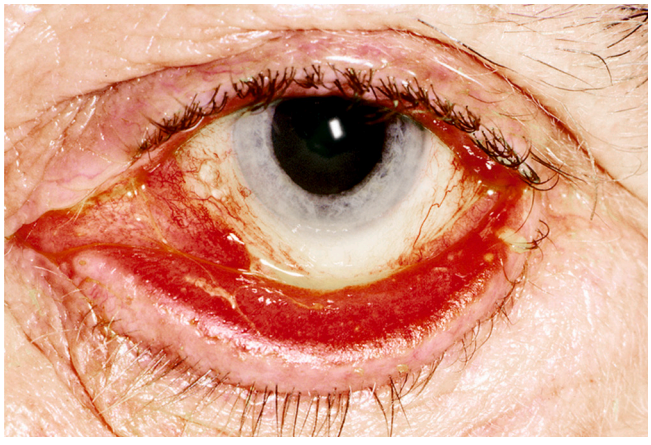

FIGURE 391-6. Involutional ectropion. (From Palay DA, Krachmer JH. *Primary Care Ophthalmology*, 2nd ed. Philadelphia: Elsevier Mosby; 2005.)

EYELID ABNORMALITIES

ECTROPION AND ENTROPION

An ectropion is an out-turning of the eyelid, typically the lower lid (Fig. 391-6), with exposure of the undersurface of the lid. Causes include aging, scarring, a mass on the eyelid, and seventh nerve (Bell) palsy. Common symptoms, which derive from corneal exposure and drying, include burning, itching, tearing, and the sense of a foreign body. Treatment is surgical, although mild symptoms may be managed conservatively with lubrication.

An entropion, which is an in-turning of the eyelid (see Fig. 391-3), is usually age related and associated with irritation, burning, and a foreign body sensation because the eyelashes touch the cornea. If it leads to trichiasis, in which the eyelashes rub or abrade the cornea, the lashes can be removed with forceps or surgery to correct the eyelid malposition. Botulinum toxin can be injected into the orbicularis muscle to temporarily correct the entropion.

CHALAZION

A chalazion (Fig. 391-7) is a localized lipogranulomatous inflammation owing to an occluded sebaceous (meibomian) gland. The retained, lipid-rich sebaceous material acts as a foreign material that stimulates a lipogranulomatous foreign body inflammatory reaction. A painless or slightly tender, nonmobile nodule forms under the eyelid skin. Most lesions resolve over days to weeks with warm compresses or without specific treatment. If the chalazion persists, it may be surgically débrided. Some individuals may have recurrent chalazia. A recurrent chalazion in the same spot may point to an underlying carcinoma.

HORDEOLUM (STYE)

A hordeolum (stye) (Fig. 391-8) is a painful abscess in a hair or eyelash follicle or in a sebaceous gland. Styes are usually self-limited infections that respond to warm compresses and topical antibiotics (e.g., bacitracin or erythromycin ointment or moxifloxacin or gatifloxacin drops). An ophthalmologist may perform incision and drainage if symptoms do not improve within 48 hours.

BLEPHARITIS

Blepharitis (Fig. 391-9) is a common, nonspecific inflammation of the eyelid margin or skin. The condition is usually bilateral and symmetrical. Rosacea (Chapter 406) is the most common associated cutaneous condition, and *Staphylococcus aureus* is the most common infectious agent. If untreated, blepharitis becomes chronic and may lead to corneal and conjunctival inflammation (blepharoconjunctivitis). Effective supportive care for blepharitis includes warm compresses and maintenance of good lid hygiene. Ophthalmic antibiotic ointment (e.g., bacitracin or erythromycin) is more efficacious than eye-drops, but systemic antibiotics (e.g., minocycline, 50 to 100 mg; doxycycline, 100 mg, once daily; tetracycline, 250 mg twice daily; or erythromycin, 250 mg three

FIGURE 391-7. Bilateral chalazion in the upper eyelids.

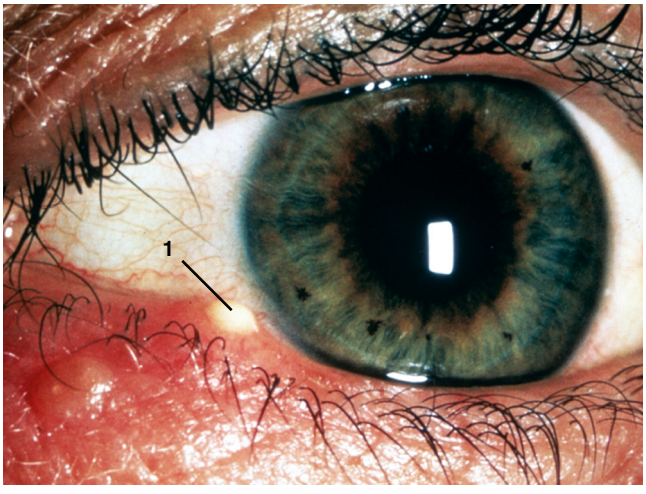

FIGURE 391-8. A lower lid stye *(1)*. (From Palay DA, Krachmer JH. *Primary Care Ophthalmology*, 2nd ed. Philadelphia: Elsevier Mosby; 2005.)

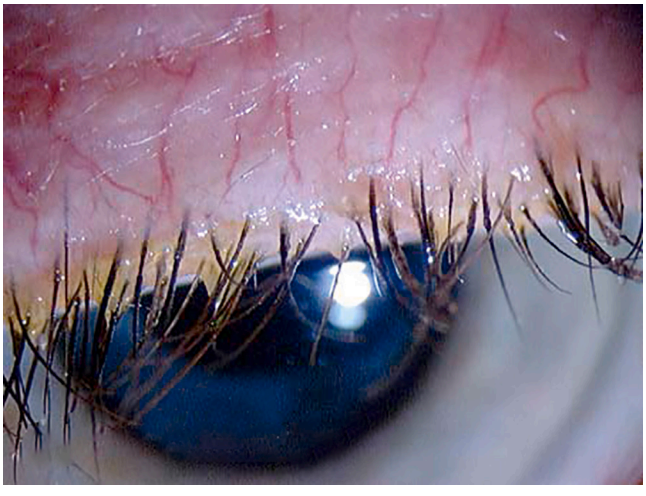

FIGURE 391-9. Blepharitis. The lid margins are very red and under high magnification demonstrate tiny ulcerations. (Courtesy of Edward S. Harkness Eye Institute, Columbia University.)

times daily) infrequently may be recommended, particularly if there is any evidence of inflammation of the cornea or conjunctiva.

In seborrheic blepharitis, exfoliated keratinous debris accumulates along the eyelid margin, particularly at the follicles of the eyelashes, and irritates the conjunctiva. Treatment of this chronic condition is directed at mechanically removing the keratinous debris by scrubbing the eyelid and eyelashes daily with a mild detergent ("baby shampoo") in warm water applied with a soft cloth.

BENIGN EYELID NEOPLASMS

Skin tags, also known as acrochordons, are the most common benign skin lesions of the lids and periocular region. Other skin lesions include seborrheic keratitis, actinic keratitis, inverted follicular keratitis, papillomas, and benign lesions of the eccrine and apocrine systems. Most of these benign lesions are cured by simple excision.

SEBACEOUS CARCINOMA

Sebaceous carcinoma originates from sebaceous glands either in the tarsal plate (meibomian gland) or associated with eyelashes (glands of Zeis) and is capable of producing widespread metastasis resulting in death. Muir-Torre syndrome is a syndrome of sebaceous tumors associated with visceral malignancy. Except for chronic, unilateral blepharitis, owing to the peculiar manner of spread of this tumor in the plane of the skin epithelium (pagetoid spread) without causing the formation of nodules, few symptoms occur early in the course of the disease. The tumor may progress to involve the tarsal conjunctiva, the bulbar conjunctiva, and even the corneal epithelium. A characteristic sign is regional loss of eyelashes. When the mass thickens, it may have the appearance of a chalazion; a history of multiple chalazia in the same region of the eyelid is suggestive of sebaceous carcinoma and warrants a diagnostic biopsy. Diagnostic delay is common because the lesion often has only modest clinical features.

Treatment is complete surgical excision. Map biopsies to determine the extent of tumor spread can be useful for definitive surgical planning. Topical mitomycin C has been suggested as treatment for pagetoid invasion of the conjunctiva. Cryotherapy also can be a useful adjuvant to surgery for eyelid and conjunctival lesions. In advanced cases, removal of the eyelids, eye, and orbital contents (exenteration) may be necessary. Imaging for local and distant metastases is critical.

BASAL CELL CARCINOMA

Basal cell carcinoma (E-Fig. 391-2), which originates from the basal cell layer of the epithelium, is the most common cutaneous malignancy (Chapter 188). The lesion, which usually is asymptomatic, is often a well-demarcated, elevated nodule that may have a central region of ulceration and fine cutaneous vascular channels (telangiectasias). Occasionally, lesions may be more subtle and present only with eyelid margin thickening, a focal loss or disruption of the eyelashes, or a mild out-turning (ectropion) of the eyelid. A common benign cutaneous lesion, sometimes confused clinically with basal cell carcinoma, is seborrheic keratosis (Chapter 407), which tends to be soft and appear hyperpigmented; the most common site is the lower eyelid, especially in the nasal quadrant. Basal cell carcinoma, particularly near the medial canthus, may extend posteriorly into the soft tissues of the orbit. Imaging before surgical excision for medial canthal lesions may be necessary to determine the true extent of the tumor. Basal cell carcinoma is treated by surgical excision, using the Mohs technique with intraoperative histologic evaluation to determine adequate margins of excision, if possible.

Metastasis is extremely rare. With early detection and adequate excision of the local lesion, the prognosis is excellent.

EYELID SQUAMOUS CELL CARCINOMA

Eyelid squamous cell carcinoma, which is much less common than basal cell carcinoma, arises from the surface squamous epithelium. Ultraviolet light exposure is the major risk factor. In contrast to basal cell carcinoma, squamous cell carcinoma can metastasize, most often to regional lymph nodes. It also can invade the orbit and cavernous sinus via perineural spread from untreated lesions on the eyelids. Treatment is surgical excision, often with the Mohs micrographic surgical technique. Except in rare circumstances, such as in immunosuppressed patients or patients with xeroderma pigmentosa, the prognosis is excellent.

OCULAR SURFACE ABNORMALITIES

DRY EYES

Even minor disturbances in the tear film can cause itching, burning, a foreign body sensation, and transient changes in vision.[3] Dry eyes that cause conjunctival hyperemia without purulent discharge particularly disturb some patients. Paradoxically, decreased tearing can result in irritation and secondary increased (reflux) tearing.

Most daily tear production is not by the lacrimal gland but by small collections of lacrimal glands, mucus-producing glands, and sebaceous glands located throughout the conjunctiva, eyelid, and anterior orbital soft tissue. Over time, particularly in women, production of tear film diminishes. Because tear film production is lower during sleep, patients often note symptoms on awakening followed by slow resolution over minutes or hours. Wind and low-humidity environments, such as in commercial airliners, can exacerbate symptoms. The reduction in aqueous components of tears is often associated with a compensatory increase in mucus production, which tends to blur vision until the patient blinks or uses supplemental tears. These symptoms are particularly prominent in persons who have autoimmune diseases, including rheumatoid arthritis (Chapter 243), Sjögren syndrome (Chapter 247), Stevens-Johnson syndrome (Chapter 407), and ocular cicatricial pemphigoid.

Dry eye disease can be divided by etiology into aqueous tear deficiency and evaporative tear dysfunction. Evaporative tear dysfunction is most commonly secondary to tear film instability and is the result of meibomian gland dysfunction (Fig. 391-10).

Treatment is not definitive and is often not satisfactory.[4] No medication increases the production of tears. Low-viscosity artificial tears (e.g., polyethylene glycol 400 0.4%), which do not tend to blur vision but have a short duration of action, are best used during visually important tasks. High-viscosity tears (e.g., carboxymethylcellulose sodium) have a longer duration of action but tend to blur vision; they are best used at bedtime to maintain lubrication of the ocular surface during sleep. When artificial tears do not control symptoms, occlusion of the nasolacrimal duct with synthetic plugs or permanent surgical occlusion tends to retain the tears that are produced. Anti-inflammatory drugs (e.g., cyclosporine 0.05% drops, every 12 hours indefinitely) can preserve glandular tissue that may be affected by local inflammation. Topical lifitegrast, given topically twice daily indefinitely, is also thought to work through anti-inflammatory mechanisms by inhibiting T-cell activation. For patients with systemic disease associated with dry eyes, effective treatment of the systemic disease sometimes improves the eye abnormalities.

PINGUECULA AND PTERYGIUM

A pinguecula (Fig. 391-11) consists of a limbal (at junction of cornea and sclera) and bulbar conjunctival degenerative process caused by ultraviolet light damage to the subepithelial tissue. It is very common and rarely causes symptoms. If the supportive tissue degeneration extends into the cornea, it becomes a pterygium (Fig. 391-12), which may cause corneal astigmatism and require surgical excision. About 2 to 10% with a pterygium have a coexisting squamous carcinoma, which often is clinically unsuspected and diagnosed only by histopathologic examination.

RECURRENT EROSION

Recurrent corneal erosion most often manifests as a delayed reaction to a minor traumatic corneal abrasion. The abrasion heals abnormally, resulting in a weakness of the epithelial attachment to its underlying tissue. Weeks to months to years later, the patient awakens with ocular pain on opening the eye, sometimes with recurrent episodes of pain every morning. The epithelium has become "stuck" to the overlying upper lid and is mechanically abraded. The condition is treated with hyperosmotic drops as well as lubrication with either wetting drops or ointment. If the erosions continue to occur despite drops and ointment, surgical options include superficial keratectomy (in which the epithelium is mechanically débrided), phototherapeutic keratopathy, or stromal micropuncture. All three techniques work by trying to strengthen the adherence of the weak epithelium to the underlying cornea.

ACCIDENTAL TRAUMA

With ocular trauma, many tissues of the eye can be easily disrupted, and the effects of trauma may not be manifest for months or even years after the episode of trauma. If the traumatic episode disrupts the eye wall (cornea and sclera), surgical repair is necessary, usually urgently. If the eye wall is intact, surgical treatment is often not necessary, at least initially.

CORNEAL ABRASION

The corneal epithelium is very delicate, and contact by any object can result in shearing or irregularity of the epithelium. Corneal abrasion is one of the most common forms of ocular injury. Symptoms are often intense and intolerable. Healing (i.e., re-epithelialization) of the cornea occurs within 24 to

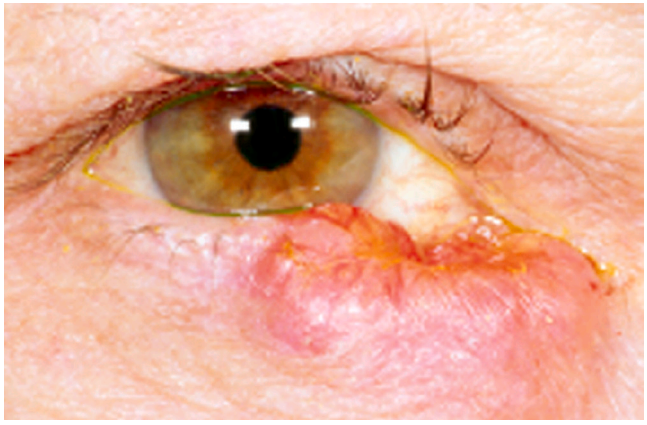

E-FIGURE 391-2. A typical nodular basal cell carcinoma. (From Palay DA, Krachmer JH. *Primary Care Ophthalmology*, 2nd ed. Philadelphia: Elsevier Mosby; 2005.)

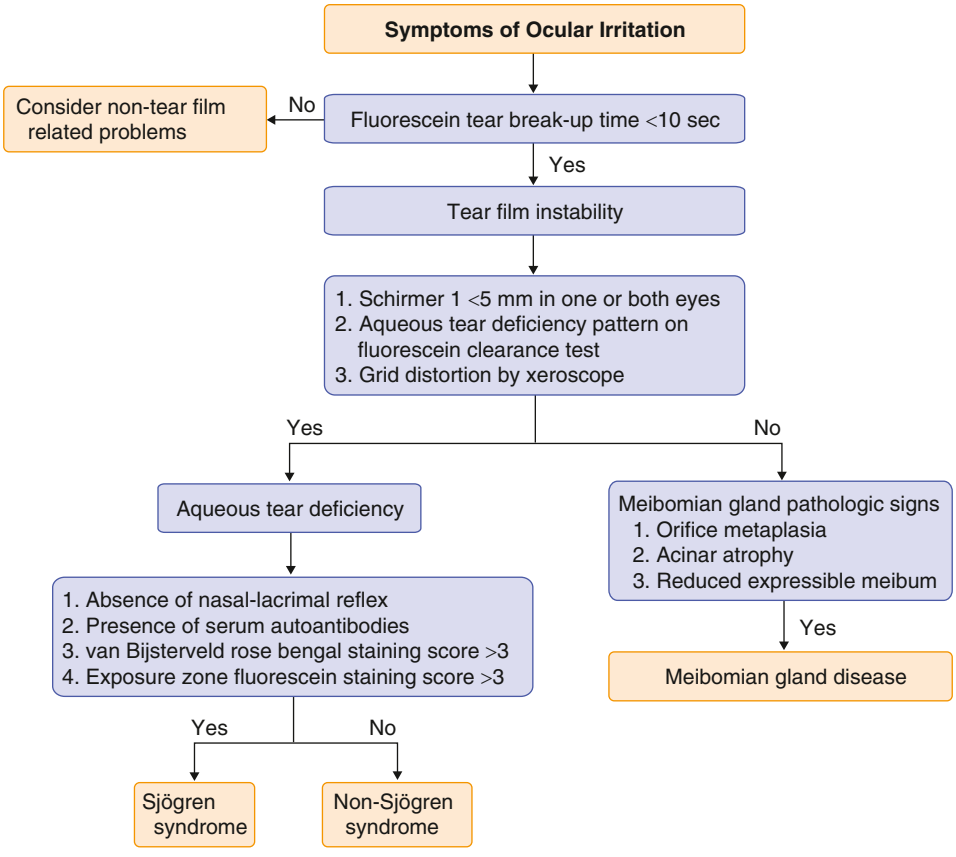

FIGURE 391-10. Diagnostic algorithm for ocular irritation. (Modified from Pflugfelder SC, Tseng SC, Sanabria O, et al. Evaluation of subjective assessments and objective diagnostic tests for diagnosing tear-film disorders known to cause ocular irritation. *Cornea*. 1998;17:38-56.)

FIGURE 391-11. Pinguecula. These lesions are found at the 3-o'clock and 9-o'clock positions and are extremely common, especially in older patients. (From Palay DA, Krachmer JH. *Primary Care Ophthalmology*, 2nd ed. Philadelphia: Elsevier Mosby; 2005.)

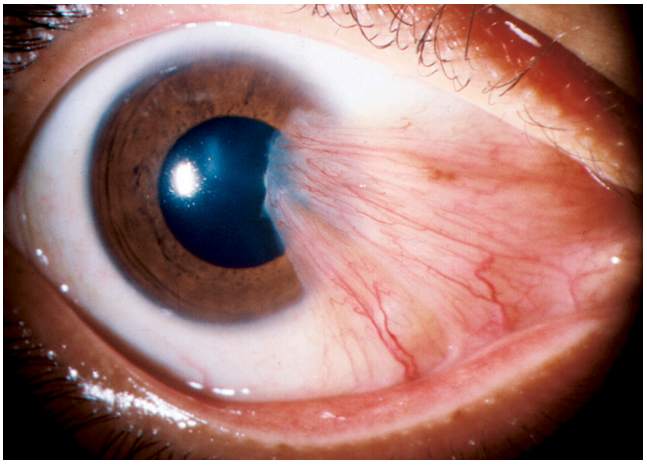

FIGURE 391-12. Pterygium. These lesions are found in the horizontal meridian, most common nasally. (From Palay DA, Krachmer JH. *Primary Care Ophthalmology*, 2nd ed. Philadelphia: Elsevier Mosby; 2005.)

48 hours. Rust from metallic fragments is toxic to the epithelium and should be removed. Bacterial or fungal keratitis may complicate injuries from fingernails or vegetable matter, such as tree branches. Treatment usually consists of a topical antibiotic (e.g., fluoroquinolone antibiotics or antibiotic ointment, four times daily for 10 to 14 days) to prevent bacterial keratitis. Subsequent scarring usually does not occur unless deeper structures, such as the Bowman membrane, are affected. Topical anesthetics never should be prescribed to control pain because they increase the risk for microbial keratitis and scarring and may delay healing.

MAJOR OCULAR TRAUMA

Hyphema (Fig. 391-13) is hemorrhage into the anterior chamber usually caused by blunt trauma. If the patient is supine, such as in an intensive care unit, the blood will distribute uniformly over the iris to cause the appearance of increased pigmentation of the iris (heterochromia iridis). If the patient has been sitting, the blood may settle by gravity to form an aqueous-blood interface with the blood in the dependent portion of the anterior chamber. Hyphema, which is a sign of serious ocular damage, may lead to secondary glaucoma and blood staining of the cornea. It requires prompt evaluation by an ophthalmologist.

The most common site of rupture of a globe is at the limbus (junction of cornea and sclera), where a pigmented mass may be noted. The mass may be either a blood clot or an anteriorly displaced uveal tract (usually iris). Any manipulation of the globe may force the remaining intraocular tissue through the wound and may make the injury irreparable. Emergent surgical repair is usually indicated.

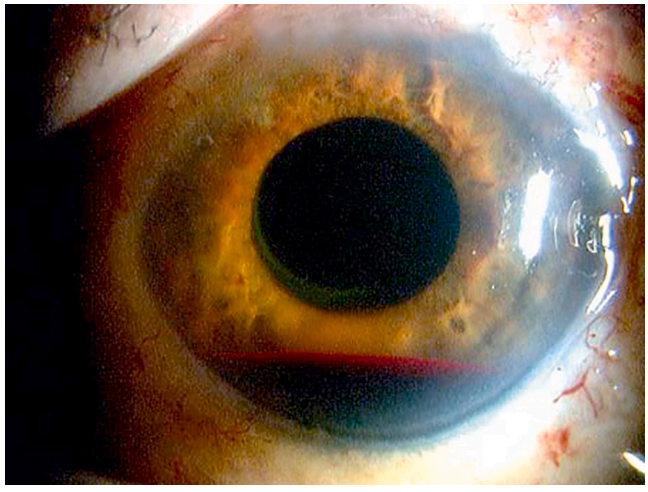

FIGURE 391-13. Hyphema. (Courtesy of Edward S. Harkness Eye Institute, Columbia University.)

Cataract and retinal detachment are not common except in severe accidental trauma. A unilateral cataract or unilateral glaucoma may occur decades after the injury, even when an injury is too minor to be recalled. Traumatic cataract and traumatic glaucoma are treated in the same manner as other forms of these conditions.

INFLAMMATORY EYE DISORDERS

UVEITIS

Inflammation of any part or parts of the uveal tract (iris, ciliary body, and choroid) is called uveitis, iritis, iridocyclitis, or choroiditis, depending on the extent of the involvement of the anterior and posterior segments of the eye. Symptoms include a red eye (see Table 391-4), decreased vision, and photophobia. The inflammation may be acute or chronic, and an underlying systemic cause is found in approximately 50% of cases. Uveitis accompanies many autoimmune diseases, often without correlation to the activity of the systemic inflammation. Anterior uveitis or conjunctivitis is nearly universal in patients with reactive arthritis (Chapter 244). About 25% of patients with ankylosing spondylitis (Chapter 244) develop acute, recurrent anterior uveitis. Two to 12% of patients with inflammatory bowel disease (Chapter 127) develop anterior uveitis, which is also common with psoriatic arthritis but not with psoriasis alone (Chapters 244 and 405). Treatment with topical corticosteroids (e.g., prednisolone acetate 1%, one drop in the affected eye or eyes every 1 to 6 hours while awake) is often sufficient to control ocular disease, but some patients will require more aggressive local therapy, including intravitreal or periocular steroid injections. Systemic immunosuppression[5,6] with oral corticosteroids (e.g., 10 to 35 mg prednisone daily)[A3] or steroid-sparing immunosuppressive agents (e.g., methotrexate 25 mg weekly, mycophenolate mofetil 39 mg daily,[A4] or adalimumab 80 mg loading dose then 40 mg every 2 weeks)[A5,A6] is an effective alternative that also may be necessary to reduce flares and visual loss in patients with chronic disease.

ENDOPHTHALMITIS

Endophthalmitis is extensive inflammation within the eye from any cause. Most cases of endophthalmitis involve a breach in the eye wall (cornea and sclera), associated with either trauma or surgical procedures (incidence of approximately <0.03%). The initial symptom is usually decreased vision followed by ocular pain. The initial sign is often evidence of inflammatory cells either within the aqueous (anterior uveitis) or within the vitreous (vitritis). The cells can be seen only by slit lamp biomicroscopy. Common microbial organisms include toxin-producing gram-positive species and gram-negative species that are often associated with rapidly destructive course. Other organisms of relatively low virulence, *Propionibacterium acnes* and *Staphylococcus epidermidis*, follow a more indolent course with less potential destruction. Metastatic endophthalmitis infection from a primary source outside of the eye is an unusual cause.

Diagnosis is established by sampling anterior chamber fluid or preferably vitreous fluid (vitreous tap) and evaluation of that fluid by Gram stain and culture. Prophylaxis against endophthalmitis includes preoperative topical instillation of povidone-iodine, perioperative topical antibiotics, and intracameral antibiotic injection at the end of cataract surgery.

Systemic antibiotics are not generally effective. Initial management is with intravitreal antibiotics (e.g., commonly used, but not limited to, vancomycin 1 mg/0.1 mL and ceftazidime 2.25 mg/0.1 mL) and, in certain instances, corticosteroids. If there are external signs of infection (e.g., corneal ulcer), topical antibiotics are also used simultaneously. Severe cases may require surgical debulking of the infection (vitrectomy) to reduce the microbial and inflammatory debris burden and to treat associated vitreoretinal pathology.

ALLERGIC CONJUNCTIVITIS

Allergic conjunctivitis (Table 391-6) is commonly associated with atopy, hay fever, and allergic rhinitis.[7] Itching, a foreign body sensation, and a watery discharge are common. Treatment includes cool compresses and topical antihistamines (e.g., olopatadine, once to twice per day until symptoms resolve). Long-term treatment with mast cell stabilizers (e.g., pemirolast drops, four times daily during the allergic season) or the combination of an antihistamine plus a mast cell stabilizer (e.g., olopatadine drops, two times daily during the allergic season) can be extremely effective in treating chronic symptoms. Oral antihistamines (e.g., cetirizine 5 to 10 mg per day until symptoms resolve) can also be useful.

INFECTIOUS EYE DISORDERS

CELLULITIS

Preseptal cellulitis (Fig. 391-14) is soft tissue inflammation of the eyelid anterior to the orbital septum. The orbital septum divides the soft tissues of the eyelid from the soft tissues of the orbit. Orbital tissue is more susceptible to damage by the inflammation than is the preseptal tissue.

The clinical signs of preseptal cellulitis include soft tissue swelling, hyperemia, and conjunctival edema (chemosis). Movement of the eye is not restricted. Extension of inflammation posterior to the orbital septum is indicated by proptosis of the globe and ophthalmoplegia (restricted ocular motility). Treatment of preseptal cellulitis includes oral antibiotics (e.g., commonly used, but not limited to, amoxicillin-clavulanate, 500 mg orally every 8 hours for 10 days, or Bactrim, 500 mg orally twice a day for cases of suspected methicillin-resistant *S. aureus* [MRSA]). Treatment of orbital cellulitis, which can lead to septic optic neuritis, intracranial spread, and cavernous sinus thrombosis, may require intravenous antibiotics and surgical drainage of a paraorbital abscess.

ADENOVIRAL CONJUNCTIVITIS

Viral conjunctivitis (Fig. 391-15) is commonly (see Table 391-6) caused by adenoviruses (especially subtypes 7, 11, and 18). The condition is highly contagious through direct contact or inhalation of respiratory particles. After an incubation period of 3 to 7 days, the patient presents with red eyes (see Table 391-4), itching, burning, foreign body sensation, and often a watery discharge, which persist for 5 to 15 days. Preauricular lymphadenopathy may be present, and a history of upper respiratory tract infection is common. The disease is self-limited, and treatment is aimed at patients' comfort. Cool compresses are often soothing. Patients are advised to wash their hands frequently to prevent spread to others. Topical antibiotics are not required.

BACTERIAL CONJUNCTIVITIS

About 5 to 15% of cases of conjunctivitis in adults are caused by bacteria, mostly *Staphylococcus, Haemophilus*, or *Streptococcus* species.[8] Patients have a mucoid or purulent discharge (Fig. 391-16), often with crusting and edema of the conjunctiva (chemosis) and lids. Bacterial conjunctivitis responds to broad-spectrum antibiotic solutions or ointments (e.g., topical erythromycin ointment three times daily for 2 weeks) (Table 391-7).

CHLAMYDIAL CONJUNCTIVITIS

Adult inclusion conjunctivitis is a chronic conjunctivitis caused by sexual transmission of *Chlamydia trachomatis* (Chapter 294). Patients often have preauricular lymphadenopathy. Oral erythromycin (500 mg orally, four times daily for 7 days) or azithromycin (1 g orally twice daily for 7 days) is required. Trachoma, which is a chronic cicatricial conjunctivitis after repeated chlamydial infection (Chapter 294), is the world's leading cause of corneal blindness. It causes an entropion, inversion of the eyelashes (trichiasis), corneal vascularization, and opacification. Topical erythromycin or tetracycline, twice daily for 3 to 4 weeks, can be effective, but epilation or surgical eyelid reconstruction may be required.

TABLE 391-6 OPHTHALMIC DISORDERS ASSOCIATED WITH CONJUNCTIVITIS

DISORDER	ACUTE OR CHRONIC	UNILATERAL OR BILATERAL	KEY SYMPTOMS	DEGREE OF INJECTION	DISCHARGE TYPE	OTHER FEATURES
Viral conjunctivitis	Acute	Bilateral, possibly asymmetrical	Itching, burning, soreness	4+	Watery	Preauricular lymphadenopathy
Bacterial conjunctivitis	Acute	Unilateral or bilateral	Burning	3+	Heavy, mucopurulent	Lids possibly adherent
Chlamydial conjunctivitis	Subacute, chronic	Usually unilateral	Burning, irritation	2+	Scant, mucopurulent	Usual occurrence in young, sexually active adults
Herpes simplex conjunctivitis	Acute	Unilateral	Photophobia, irritation	1-2+	None	Dendritic ulcer on the cornea or vesicles on the lid possible
Allergic conjunctivitis	Chronic	Bilateral	Itching	2+	Stringy, mucoid	Usual occurrence in atopic persons, possible seasonal symptoms
Blepharitis	Chronic	Bilateral	Itching, burning, foreign body sensation	1-2+	Usually none	Inflammation and crusting of lid margins
Dry eye	Chronic	Bilateral	Foreign body sensation	1+	Mucoid in severe cases	Punctate fluorescein staining of the cornea

Adapted from Palay DA, Krachmer JH. *Primary Care Ophthalmology*, 2nd ed. Philadelphia: Elsevier Mosby; 2005.

FIGURE 391-14. Eyelid abscess. Preseptal cellulitis, commonly resulting from minor penetrating trauma, may evolve into an abscess. Treatment requires incision and drainage followed by systemic antibiotics.

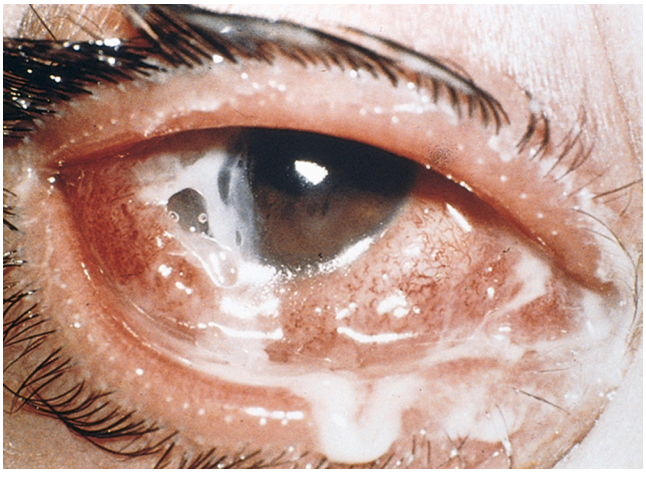

FIGURE 391-16. Bacterial conjunctivitis. Purulent discharge and conjunctival hyperemia suggest bacterial conjunctivitis. Viral conjunctivitis produces watery discharge, foreign body sensation, preauricular lymphadenopathy, and conjunctival follicles seen on slit lamp examination. (Reproduced with permission from the American Academy of Ophthalmology.)

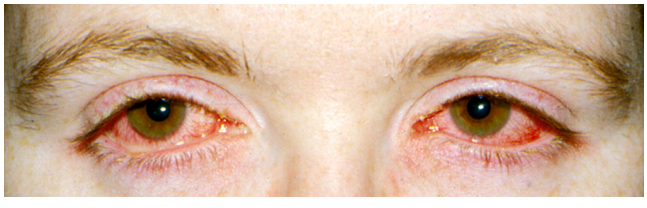

FIGURE 391-15. Diffuse injection of the conjunctiva with a watery discharge is evident in this case of viral conjunctivitis. (From Palay DA, Krachmer JH. *Primary Care Ophthalmology*, 2nd ed. Philadelphia: Elsevier Mosby; 2005.)

TABLE 391-7 TOPICAL ANTIBIOTICS FOR EYE INFECTIONS

DRUG	TYPE	CONCENTRATION	DOSE
Moxifloxacin	Drops	0.5%	1 drop bid × 7 days
Gatifloxacin	Drops	0.5%	1 drop q2h × 24 hours; then qid × 6 days
Ciprofloxacin	Drops	0.3%	1 drop q2h × 48 hours; then q4h × 5 days
Gentamicin	Drops	0.3%	1 drop four times daily
Ofloxacin	Drops	0.3%	1 drop q2h × 48 h; then qid × 5 days
Bacitracin	Ointment	500 U/g	Put in eye, for several days
Tobramycin	Ointment	0.3%	Put in eye, for several days
Erythromycin	Ointment	0.5%	Put in eye, for several days

bid = twice a day; qid = four times a day.

HERPES SIMPLEX KERATITIS

Herpes simplex keratitis is the most common cause of a central corneal ulcer (Fig. 391-17).[9] Herpes simplex virus also can cause vesicular eyelid dermatitis. Initially, the main signs of primary herpes simplex keratitis are a red eye and a corneal epithelial dendritic ulcer. With appropriate antiviral therapy (e.g., ganciclovir 0.15% ophthalmic gel five times daily for at least 1 week or oral acyclovir 800 mg five times per day for 7 to 10 days), the keratitis usually heals without scarring. Herpes simplex keratitis can recur and may extend into the corneal stroma and cause a red eye, ocular discomfort, blurred vision, and corneal scarring. Patients with recurrent disease may benefit from chronic low-dose antivirals (e.g., oral acyclovir 800 mg per day indefinitely) for suppression. Stromal involvement is multifactorial and can be recalcitrant. Corneal transplantation is occasionally needed for scarring, but success is often limited by recurrence in the donor tissue.

HERPES ZOSTER OPHTHALMICUS

Herpes zoster ophthalmicus (shingles, Chapter 346) has a propensity to involve one or more branches of the trigeminal nerve. The virus also can affect the

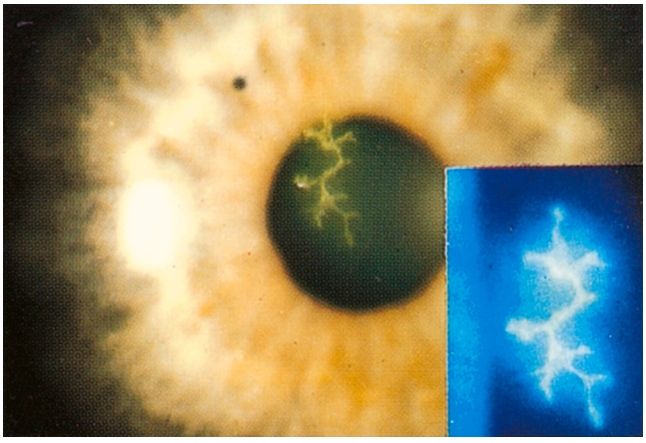

FIGURE 391-17. Herpes simplex corneal epithelial keratitis in diffuse light and in light passed through a cobalt blue filter after fluorescein staining *(inset)*. Note the dendritic staining pattern characteristic of herpes simplex.

uveal tract and, in immunosuppressed patients, the retina (i.e., acute retinal necrosis). When the trigeminal nerve is involved, spread to the inside of the eye (uveitis) is most likely if vesicles are present in the inner corner of the eyelids or on the nose, especially the tip of the nose (Hutchinson sign). If the uvea is not involved, the skin lesions heal with some scarring but no long-term effects. In patients with moderate to severe skin involvement, treatment can be started with oral acyclovir (800 mg orally five times per day for 7 to 10 days) or valacyclovir (1 g three times a day for 10 to 14 days). If uveitis develops, the treatment (e.g., prednisolone acetate drops 1% four times daily and atropine 1.0% once or twice daily) can be extended and difficult. Like herpes simplex virus, herpes zoster can affect the cornea, and patients should be monitored for recurrent disease.

PSEUDOMONAL AND GONOCOCCAL KERATITIS

Keratitis, which is inflammation of the corneal stroma, can be caused by spread of pathogens internally from a corneal ulcer. *Pseudomonas aeruginosa* (Chapter 282), which causes a particularly virulent keratitis, is the most common gram-negative pathogen and is especially common in people who wear contact lenses. To avoid intraocular spread, urgent and aggressive antibiotic treatment is necessary (e.g., fortified tobramycin [9 mg/mL] or a fourth-generation fluoroquinolone (e.g., moxifloxacin), every hour for 3 to 7 days. The dosage and duration of the treatment depend on the response.

Another gram-negative cause of a virulent keratitis is *Neisseria gonorrhoeae* (Chapter 274), especially in neonates. Corneal infection is accompanied by copious tearing and a characteristic hyperpurulent discharge. Prompt treatment with topical irrigation (normal saline to remove mucopurulent material) and penicillin G (100,000 units/kg/day given intravenously in four divided doses for 7 days) is essential to prevent corneal perforation.

CYTOMEGALOVIRUS RETINITIS

Cytomegalovirus retinitis (Chapter 347) is unusual except in immunosuppressed patients and human immunodeficiency virus (HIV) infection but is increasing among patients who have undergone solid organ or hematopoietic stem cell transplantation. Clinically, a central retinochoroiditis is seen. The presumptive diagnosis is made on the characteristic intense, wedge-shaped reaction in the retina, with considerable exudates and hemorrhages, giving the terms "pizza pie retinitis" and "hemorrhagic cottage cheese retinitis" to the entity. Treatment is with antiviral drugs: ganciclovir (5 mg/kg intravenously twice daily, two to three times per week), foscarnet (90 mg/kg intravenously twice daily, twice per week), or cidofovir (5 mg/kg intravenously, weekly for 3 weeks) with follow-up maintenance. Intravitreal injections with an appropriately reduced dose are also used in selected cases.

ACANTHAMOEBA KERATITIS

Acanthamoeba species (Chapter 323) can cause a severe, blinding keratitis. The wearing of contact lenses is a major risk factor. A characteristic stromal ring infiltrate develops, and uveitis may occur. When patients are examined early in their disease course, they may only have a slight epitheliopathy and have pain out of proportion to findings on examination. A history of swimming or using fresh water to cleanse or store contact lens often can be elicited. Using a confocal microscope, the acanthamebic parasite can be observed clinically as a pear-shaped cyst (11 to 15 μm). Numerous treatment protocols exist (e.g., polyhexamethyl biguanide 0.02% drops every hour). The duration and dose depend on the response. Corneal transplantation may be necessary in cases of severe corneal scarring.

TOXOPLASMIC RETINITIS

Toxoplasma gondii (Chapter 320) causes both a congenital and an acquired retinochoroiditis, which is more common in immunosuppressed patients. The lesions begin as an acute retinitis that atrophies centrally and pigments peripherally as it heals (Fig. 320-2). The protozoa are found both in free and encysted forms within the retina. The condition may be self-limited and diagnosed as a healed incidental finding that does not need treatment. Standard treatment of vision-threatening toxoplasmosis remains controversial. When active lesions are in the macula or a severe vitritis causes at least a two-line decrease in vision, 4 to 6 weeks of quadruple therapy (pyrimethamine, 200 mg oral loading dose, then 25 mg orally daily; folinic acid, 10 mg orally every other day; sulfadiazine, 2 g oral loading dose, then 1 g four times daily; and oral corticosteroids; e.g., prednisone, 20 to 60 mg orally daily beginning at least 24 hours after antibiotic therapy is started and tapered 10 days before stopping antibiotics) usually produces good results. Alternative regimens may include trimethoprim-sulfamethoxazole (800/160 mg orally twice daily), clindamycin (150 to 450 mg orally three to four times daily), or atovaquone (1 g oral loading dose, then 500 mg daily).

FUNGAL ENDOPHTHALMITIS

Fungal endophthalmitis is infrequent (7% of microbial endophthalmitis) but is a potentially disastrous infection of the inside of the eye, often leading to blindness. The primary organisms are *Candida, Coccidioides*, and *Aspergillus* species, which can gain access inside the eye either by traumatic introduction or through hematogenous spread. The patient presents with floaters and/or decreased vision. In advanced cases, the patient develops red eye and ocular pain. Multiple abscesses tend to be caused by fungi, whereas a solitary abscess is more likely caused by bacteria. Systemic antifungal agents (e.g., fluconazole 100 to 200 mg daily for 2 months) are often effective in treating localized fungal abscesses, but if the infection has progressed into the vitreous body, vitrectomy and intravitreal antifungal therapies are indicated.

TUBERCULOSIS

About 1% of patients with pulmonary tuberculosis (Chapter 299) have uveal involvement, usually as iridocyclitis or diffuse choroiditis. Painless progressive visual loss is the most common symptom. Small yellow choroidal lesions may be seen, and retinal periphlebitis may occur secondarily. Treatment is as for the primary disease.

SYPHILIS

About 5% of patients with secondary syphilis (Chapter 295) develop anterior uveitis or neuroretinitis. In tertiary syphilis, the miotic Argyll Robertson pupil reacts poorly to light but briskly to accommodation. Treatment is as for the systemic disease.

STRUCTURAL AND AGE-RELATED DISORDERS

CATARACT

A cataract is an opacification of the crystalline lens. The lens doubles in volume between birth and age 70 years as new lens "fiber cells" are laid down on the external aspect of the lens cortex, beneath the lens capsule. The older fibers in the center of the lens cannot be desquamated into the surrounding aqueous and thus are compressed into the center of the lens. At birth, the lens is pliable and totally transparent. By age 45 years, the lens loses its pliability, which compromises near vision. As the process progresses, the lens loses its transparency, beginning at the center of the lens (nuclear sclerosis). The concurrent change in density of the lens nucleus may alter the optical characteristics of the eye to cause acquired nearsightedness ("second sight"). Ultimately, the cataract may become so dense that cataract surgery is necessary to restore vision.

Symptoms are typically loss of vision, especially at night, and glare.[10] Cataract surgery, performed as an outpatient, is elective and depends on how much the decreased vision interferes with the normal lifestyle of the patient. A synthetic intraocular lens implant is inserted into the eye during surgery. Standard phacoemulsification provides results as good as femtosecond laser treatment.[A7]

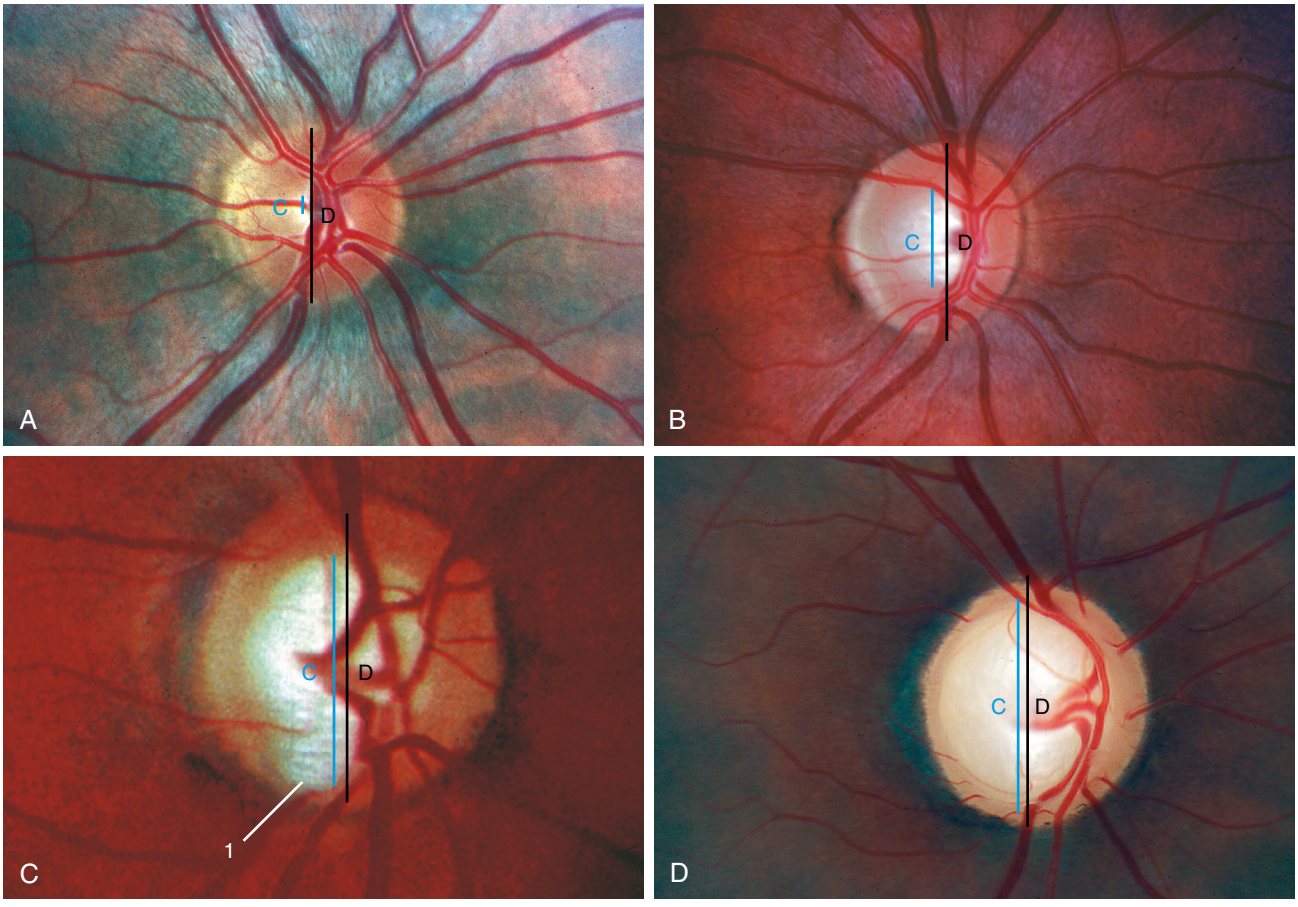

FIGURE 391-18. **Cup-to-disc ratios. A,** Normal cup-to-disc (C/D) ratio of 0.1. **B,** Likely normal C/D ratio of 0.5. **C,** C/D ratio of 0.8 vertically with inferior notching (1) of the nerve (glaucomatous change). **D,** C/D ratio of 0.90 vertically (glaucomatous change). C = cup; D = disc. (From Palay DA, Krachmer JH. *Primary Care Ophthalmology*, 2nd ed. Philadelphia: Elsevier Mosby; 2005.)

Prognosis for restoration of vision is excellent, depending on the function of the retina. In general, cataracts develop asymmetrically, and the worst eye (vision-wise) should have surgery first. As the second eye's cataract worsens, decreasing vision and monocularity are indications for cataract surgery in the second eye.

GLAUCOMA

Glaucoma is an optic neuropathy in which progressive damage to retinal ganglion cells and their axons results in the characteristic loss of optic nerve tissue and damage to the peripheral and central visual field.[11] The primary site of damage is at the lamina cribrosa, where the axons of the optic nerve leave the eye.

Aqueous humor is produced by the nonpigmented ciliary epithelium of the pars plicata of the ciliary body. Aqueous fluid leaves the eye through the trabecular meshwork and uveoscleral pathways into the venous circulation. If the drainage function does not match production, the intraocular pressure increases. If the elevated intraocular pressure is high enough or is present long enough, ganglion cells in the retina are damaged, causing loss of their axons. Loss of axons can best be appreciated clinically at their normal exit from the eye, the optic disc. Bulk loss of axons will lead to enlargement of the optic cup, which is recorded as increase in the cup-to-disc ratio.

Intraocular pressure is the principal risk factor for the onset and progression of glaucoma. In general, the higher the pressure, the greater is the risk. An intraocular pressure greater than 2 standard deviations above the population mean (21 mm Hg) is termed *ocular hypertension,* but no intraocular pressure is fully protective, and many individuals develop glaucoma despite a statistically normal intraocular pressure. Additional risk factors for glaucoma include African ancestry, older age, low blood pressure, genetic predisposition, myopia, hemorrhages on the anterior surface of the optic nerve (disc hemorrhage), and anterior segment abnormalities.

In open-angle glaucoma, there is apparent free anatomic access to the trabecular meshwork. In closed-angle glaucoma, there is a relative or absolute anatomic barrier to the flow of aqueous. For most individuals, glaucoma is asymptomatic until late in the disease, and the only way to detect it is by an ophthalmologic examination.

PRIMARY OPEN-ANGLE GLAUCOMA

The most common type of glaucoma in elderly people is primary open-angle glaucoma. For many patients, the first symptom may be difficulty reading, loss of contrast sensitivity, or glare. Peripheral visual fields may be reduced considerably before the patient notes loss of function. Most cases of primary open-angle glaucoma are identified during routine eye examinations, either by discovery of abnormally high intraocular pressure or by the presence of a high cup-to-disc ratio (Fig. 391-18). Although the U.S. Preventive Services Task Force has determined that evidence is insufficient to assess the benefits of screening for open angle glaucoma,[A8] testing is routine during most ophthalmologic examinations in adults. Average intraocular pressure is generally at or below 21 mm Hg, but exceptions exist depending on corneal thickness (causing artifacts of measurement in patients with excessively thin or thick corneas) and genetic disposition. The diagnosis of glaucoma is confirmed by characteristic visual field loss as determined by automated perimetry.

The treatment goal is to reduce intraocular pressure, initially with pharmacologic agents: β-blockers (e.g., timolol drops 0.5% twice daily), carbonic anhydrase inhibitors (e.g., dorzolamide drops three times daily), α-agonists (e.g., brimonidine drops three times daily), prostaglandin analogues (e.g., travoprost 0.004% or latanoprost 0.005% drops once daily), and rho-kinase inhibitors (e.g., netarsudil 0.02% drops once daily). Generally, the drops are taken for a lifetime. Applying energy to the structures of the trabecular meshwork with a laser (laser trabeculoplasty) often results in years of control of intraocular pressure, and this procedure may be considered first-line therapy, because it can maintain normal pressure without medications.[A9] In resistant cases, mechanical filtration is accomplished surgically by bypassing the trabecular meshwork either by creating a fistula (trabeculectomy) between the anterior chamber and the episcleral tissue or by implanting a synthetic filtration device (a tube-shunt)[A10] from the anterior chamber through the sclera into a collection reservoir located behind the equator of the eye in the soft tissues of the orbit.

SECONDARY OPEN-ANGLE GLAUCOMA

Secondary causes of elevated intraocular pressure also can lead to glaucomatous nerve damage. The most common is pseudoexfoliation syndrome, a genetically

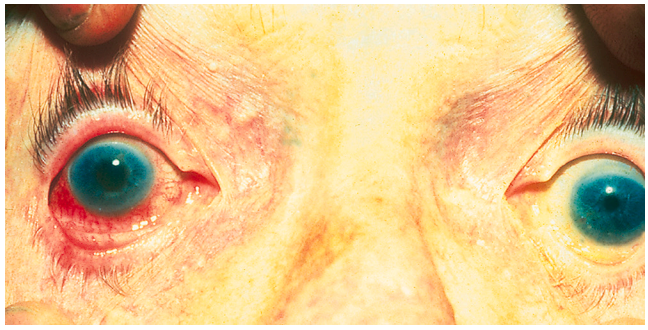

FIGURE 391-19. Acute angle-closure glaucoma. The left eye is normal. The red right eye has a nonreactive, mid-dilated pupil. (Courtesy of Dr. Myron Yanoff.)

determined biochemical abnormality of the basement membrane protein, fibrillin. The syndrome occurs among people throughout the world but is especially prominent in Scandinavians and Saudi Arabians. Affected individuals are identified by accumulation of abnormal fibrillogranular material (exfoliative material) on the surface of the crystalline lens, most easily seen in the pupillary space or pupillary border. Pseudoexfoliative glaucoma greatly increases the risk for developing open-angle glaucoma. Treatment is as for open-angle glaucoma.

ANGLE-CLOSURE GLAUCOMA

An acute attack of angle-closure glaucoma (Fig. 391-19) may occur over a short period of time and cause extreme, debilitating symptoms. Alternatively, symptoms may develop over a long period of time with few specific symptoms.

The risk factors for angle-closure glaucoma are based on the anatomic configuration of the components of anterior chamber. Persons who are farsighted (hyperopia) have a shortened anterior-to-posterior axis of the eye, indicated clinically by a shallow anterior chamber that may be noted with penlight illumination but often requires slit lamp examination. As the crystalline lens increases in volume with time, the iris is displaced anteriorly. At some point, the posterior surface of the iris may come in relatively tight contact with the anterior surface of the lens. Aqueous flow is restricted, and fluid accumulates in the posterior chamber, where it displaces the diaphanous peripheral iris anteriorly. When the peripheral iris comes in contact with the posterior cornea, the anterior chamber angle is suddenly occluded, thereby preventing egress of aqueous humor via the trabecular meshwork. Acute angle-closure may be precipitated by pharmacologic dilation of the pupil. Patients who are farsighted (hyperopia) or have cataracts should be dilated with caution. The intraocular pressure may increase from normal levels (10 to 20 mm Hg) to greater than 60 mm Hg (nearly equaling diastolic arterial pressure). The symptoms of acute angle closure may include extreme pain, which may be poorly localized to the eye, as well as nausea and vomiting. Persistent vomiting may cause abdominal pain, thereby simulating an acute abdomen.

Initial treatment is with topical (e.g., timolol 0.5% in one dose) and systemic pressure-lowering agents (e.g., carbonic acetazolamide, 250 to 500 mg intravenously or two 250-mg tablets orally in one dose if intravenous access or drug is not available), followed by creation of a fistula in the peripheral iris with a laser (laser iridotomy) between the posterior chamber and the anterior chamber to bypass the obstruction. Most patients require a laser iridotomy prophylactically in the second eye to prevent angle-closure glaucoma. Another potential option is lens extraction because age-related growth in the lens contributes to angle closure.

Secondary glaucoma may also occur after intraocular hemorrhage, intraocular trauma, and intraocular inflammation. Some developmentally related secondary glaucomas, such as the iridocorneal endothelial syndrome, may not become evident until adulthood.

RETINAL DETACHMENT

A retinal detachment is a separation of the neural (sensory) retina from the underlying retinal pigment epithelium. The main types are rhegmatogenous, caused by a retinal tear or hole, as typically occurs with a posterior vitreous detachment; tractional, caused by fibrosis, such as in advanced proliferative diabetic retinopathy; or serous, when fluid accumulates under neural retina because of breakdown of the blood-retinal barrier in conditions such as malignant hypertension or eclampsia of pregnancy.

The classic symptoms are a sensation of flashes of light, floaters in the involved eye owing to the causative vitreous detachment, and a shadow in the field of vision. Urgent treatment usually is needed to prevent macular involvement or deterioration. Most cases require a scleral buckle and/or vitreous surgery, although select cases may be successfully treated by in-office procedures such as laser photocoagulation and pneumatic tamponade. The latter involves the intravitreal injection of a gas bubble that, with proper head positioning on the part of the patient, effectively closes a retinal break; permanent sealing of the break is accomplished laser photocoagulation. In contrast, serous retinal detachments generally resolve without direct intervention when the underlying cause is successfully treated.

AGE-RELATED MACULAR DEGENERATION

Age-related macular degeneration is a neurodegenerative disease that initially affects the retinal pigment epithelium of the macula, mainly in the sixth to ninth decades of life.[12–14] About 8.5% of the world's blindness is caused by age-related macular degeneration, mainly in industrialized countries. In the United States, age-related macular degeneration affects more than 1.75 million persons, and its prevalence increases with each decade after the age of 55 years. The exact genetic influence has not yet been determined, but abnormalities of complement factor H appear to play a role. Environmental factors such as smoking are known to accelerate this degenerative process.

Two forms of age-related macular degeneration predominate: the "dry" or nonexudative type and the "wet" or neovascular type. The dry form usually precedes the wet form, which usually causes the most profound vision loss, especially if untreated.

The first clinical sign of age-related macular degeneration is an attenuated or mottled appearance of the retinal pigment epithelium in the macula, usually accompanied by *drusen,* which are abnormal lipoprotein deposits within the retinal pigment epithelial basement membrane complex (Bruch membrane). Lipofuscin, a complex mixture composed mainly of the oxidation products of polyunsaturated fatty acids and vitamin A dimers, accumulates in stressed retinal pigment epithelial cells. Significant macular degeneration is typically characterized by soft drusen that are greater than 60 μm and appear on examination as deep, hypopigmented spots. This nonexudative age-related macular degeneration may antedate subjective alteration in vision by years to several decades.

Symptoms of age-related macular degeneration are confined to deterioration of central visual function, because the peripheral retina is not involved. As the process progresses, individuals with advanced disease will be able to walk down a street without apparent difficulty (a peripheral retinal function) but will not be able to recognize facial features of people whom they meet (a macular retinal function). Visual aids and other devices, such as special glasses and video-based magnification aids, often allow patients to continue with daily functions and to continue to live independently.

Dry age-related macular degeneration advances at a variable rate (months to decades), during which patients develop retinal features of well-defined pigment loss (geographic retinal atrophy; Fig. 391-20). No current treatment exists for the dry phase of the disease, except for a possible positive influence of dietary supplements (antioxidants). Vitamin supplementation with vitamins C and E, lutein, zeaxanthin, zinc, and copper may retard the progression of moderate age-related macular degeneration to severe age-related macular degeneration. β-Carotene (a vitamin A precursor) of this quantity is not recommended for cigarette smokers because of an increased risk for lung cancer. Cessation of smoking, control of blood sugar, control of blood lipid levels, and control of systemic blood pressure are particularly important behavioral modifications. Patients with dry age-related macular degeneration who are at higher risk for developing choroidal neovascularization should be advised to monitor themselves by means of Amsler grid or similar testing strategies and urgently seek treatment if new visual symptoms develop.

In the "wet phase" of age-related macular degeneration (Fig. 391-21), frail neovascular channels originating from the established vascular system of the choroid may extend through a breach in Bruch membrane into the subretinal space (subretinal or choroidal neovascularization). Spontaneous hemorrhage of the vessels adds to the loss of photoreceptors. Hemorrhage is accompanied by acute, and often permanent, loss of central visual acuity (i.e., the wet phase of age-related macular degeneration). Both eyes are typically affected to a similar degree. Neovascularization can be identified by fluorescein angiography and ocular coherence tomography. Intraocular injections of antivascular endothelial growth factors (e.g., ranibizumab, bevacizumab, or aflibercept)[A11] or a dual inhibitor of angiopoietin-2 and vascular endothelial growth factor A (faricimab)[A12] reduce the risk for visual loss in patients with neovascular age-related macular degeneration and can result in gains in vision, especially when administered on a timely basis. Other treatments include photodynamic therapy or, in advanced cases, vitrectomy to remove massive subretinal hemorrhage.

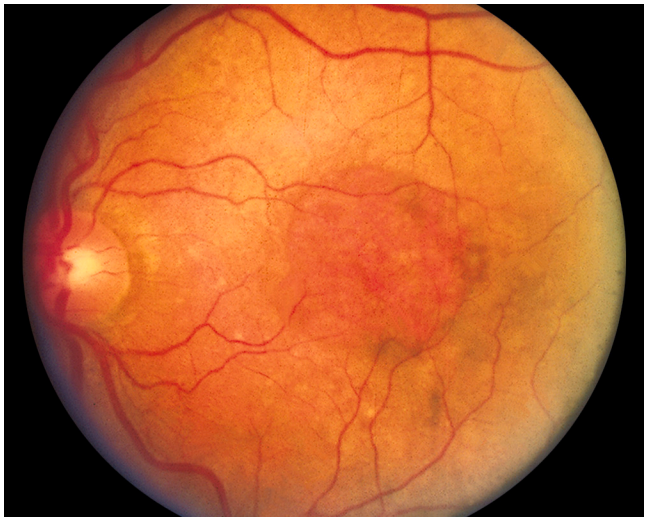

FIGURE 391-20. Dry age-related macular degeneration. Drusen are present in the posterior pole around a large area of geographic atrophy of the retinal pigment epithelium.

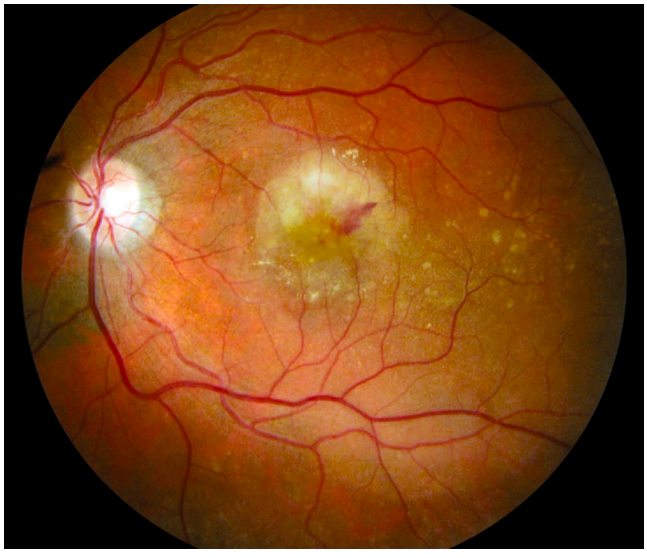

FIGURE 391-21. Wet age-related macular degeneration. A "dirty gray" neovascular membrane is present under the central macular area.

FIGURE 391-22. Background diabetic retinopathy. Exudates, microaneurysms, and small hemorrhages are seen in the posterior pole (left eye).

FIGURE 391-23. Severe nonproliferative diabetic retinopathy with cotton-wool spots, intraretinal microvascular abnormalities, and venous beading. (From Yanoff M, Duker JS, eds. *Ophthalmology*. Philadelphia: Mosby Elsevier; 2009.)

SYSTEMIC DISEASES WITH OCULAR SYMPTOMS DURING ADULTHOOD

DIABETES MELLITUS

Diabetic retinopathy is one of the leading causes of blindness in the United States. Background diabetic retinopathy, with microaneurysms, hemorrhages, exudates (Fig. 391-22), and macular edema, accounts for most cases of decreased vision but rarely causes profound vision loss.[15] With acute hyperglycemia, accumulation of sorbitol may lead to swelling of the lens; secondary refractive errors may persist for 6 to 8 weeks. Most diabetic patients never develop the more severe proliferative diabetic retinopathy (Fig. 391-23), which generally occurs only after 15 years or more of diabetes and causes a profound loss of vision.

Diabetic retinopathy is closely correlated with the duration of diabetes mellitus (Chapter 210). The prevalence of diabetic retinopathy is approximately 27% among patients who have had type 1 diabetes for 5 to 10 years, 70 to 90% among patients who have had diabetes for more than 10 years, and 95% among patients who have had diabetes for 20 to 30 years. In patients with type 2 diabetes (Chapter 210), the prevalence of diabetic retinopathy is about 23% after 12 years and 60% after 16 years. Tight control of blood glucose greatly reduces the risk for the development of diabetic retinopathy.

The treatment of diabetic retinopathy includes control of the diabetes and any hyperlipidemia (Chapter 190). Intensive diabetes therapy (Chapter 210) reduces the risk of future ocular surgery in type 1 diabetes. Antiangiogenic therapy (e.g., ranibizumab, bevacizumab, aflibercept, or faricimab[A13–A17]) is generally as good as or superior to laser therapy for diabetic macular edema and has often replaced it as first-line therapy.[16] However, laser photocoagulation remains particularly useful for proliferative diabetic retinopathy, for clinically significant macular edema that does not involve the foveal center, or when antiangiogenic therapy does not provide a complete response. Intravitreal steroid injection may also be beneficial.

HYPERTENSION

In chronic systemic hypertension (Chapter 64), the characteristic retinal vascular findings can assess the severity of hypertension. As the severity increases, patients develop arterial narrowing, arteriovenous nicking (Fig. 391-24), nerve fiber layer infarcts, and intraretinal hemorrhages. Moderately sclerosed arterioles have a "copper wiring" appearance, whereas severely sclerosed vessels demonstrate "silver wiring." Acute hypertension may cause optic nerve edema ("papilledema"; Fig. 391-25) and serous retinal detachments that usually resolve without significant sequelae if blood pressure is controlled.

OTHER SYSTEMIC DISEASES

In bacterial endocarditis (Chapter 61), emboli may cause retinal hemorrhages or the characteristic Roth spot (Fig. 391-26). Accumulation of copper in the posterior cornea may aid in the diagnosis of Wilson disease (Chapter 195), although its clinical diagnosis usually precedes the characteristic Kayser-Fleischer ring (see Fig. 195-2), which fades after treatment. Tay-Sachs and Niemann-Pick diseases (Chapter 192) are associated with a foveal cherry-red spot owing to the accumulation of gangliosides within perifoveal ganglion cells. Pseudoxanthoma elasticum (Chapter 239) is often associated with characteristic angioid streaks of the retina.

FIGURE 391-24. Hypertension retinopathy with narrowed arterioles whose sclerosed walls create the appearance of "nicking" when the arterioles cross venules. (From Yanoff M, Duker JS, eds. *Ophthalmology*. Philadelphia: Mosby Elsevier; 2009.)

FIGURE 391-25. Papilledema. (Courtesy of Dr. Kathleen Digre.)

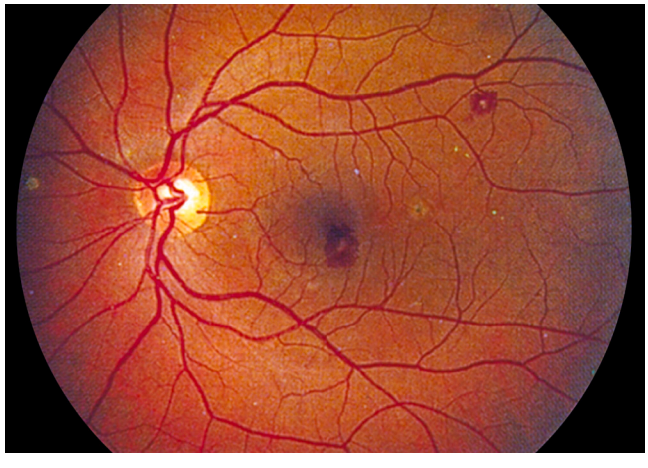

FIGURE 391-26. Roth spots. Multiple white-centered hemorrhages in a man with recurrent subacute bacterial endocarditis. White-centered hemorrhages are also seen with leukemia and diabetes. The small white scars are probably the residua of previous episodes.

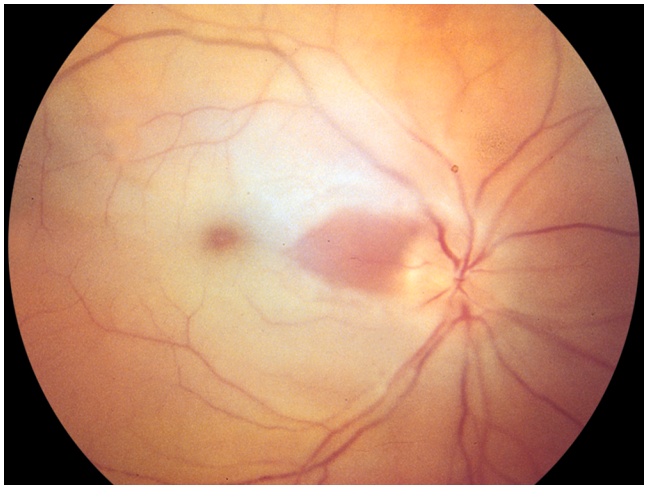

FIGURE 391-27. Central retinal artery occlusion. Fundus photograph shows the fovea, which lacks inner retinal layers, as a cherry-red spot, in contrast to extrafoveal retina, which appears white because of inner retinal infarction. In this case, a small area of retina adjacent to the optic disc is spared, owing to the presence of a cilioretinal artery.

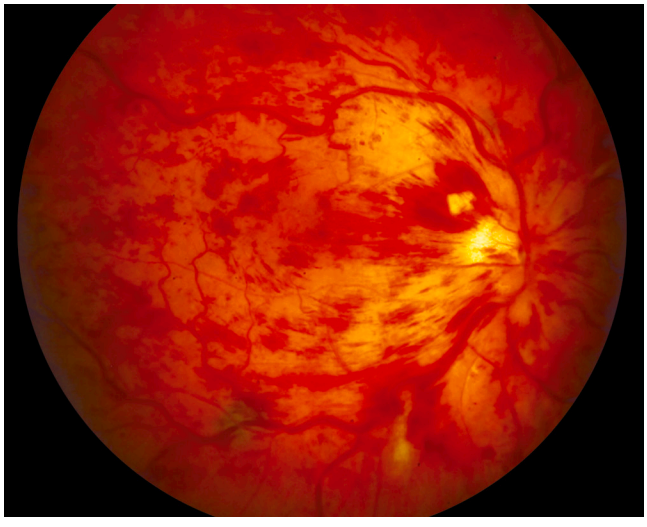

FIGURE 391-28. Central retinal vein occlusion with diffuse intraretinal hemorrhages in all four quadrants.

VASCULAR ABNORMALITIES OF THE EYE

The major vessels of the retina enter the eye at a point of relative constriction in the tissues of the lamina cribrosa of the optic disc. In persons who have generalized vascular disease, particularly systemic hypertension, occlusion of either the artery or vein may lead to a sudden loss of vision.[17] Partial occlusion of either the artery or vein is associated with less visual loss but still increases the risk for developing neovascular glaucoma.

Occlusion of the central retinal artery (Fig. 391-27) presents as painless acute loss of vision. The ischemic retina generally has a pale gray appearance except at the fovea, where the normal color is preserved (cherry-red spot). The clinical appearance of edema resolves over time, but vision generally does not recover.

Venous occlusion of the central retinal vein (Fig. 391-28) presents as painless loss of vision. The appearance of the fundus is characterized by extensive intraretinal hemorrhages and a variable degree of retinal ischemia. Macular edema is common, but intravitreal anti–vascular endothelial growth factor injections can provide significant and sustained visual improvement.[A18] Ischemic central vein occlusion is a major risk factor for developing secondary neovascular glaucoma.

Giant cell arteritis (temporal arteritis [Chapter 250]) can occlude the blood supply of the optic disc by inflammation of the short posterior ciliary arteries. This occlusion causes acute, painless loss of vision. Presenting symptoms before visual loss often include scalp tenderness or jaw claudication, which may be accompanied by weight loss and a vague sensation of fatigue. Diagnostic suspicion is further raised by an elevated erythrocyte sedimentation rate and/or C-reactive protein level. Temporal artery biopsy showing granulomatous inflammation in the region of the internal elastic lamina confirms the diagnosis. Because of the significant risk of visual loss in the initial and contralateral eye, even before laboratory or pathologic studies are known, systemic corticosteroid

therapy (e.g., oral prednisone 40 to 60 mg per day) should be administered for a protracted period until the sedimentation rate normalizes and symptoms are relieved (Chapter 250). Unfortunately, treatment usually does not restore lost vision in the presenting eye.

Nonarteritic ischemic optic neuropathy is caused by occlusion of the posterior ciliary arteries and infarction of the optic disc, resulting in acute, usually unilateral, painless loss of vision. There often are no antecedent symptoms except those systemic signs and symptoms associated with systemic nonarteritic vascular disease such as systemic hypertension. Occlusion is thought to be due to atherosclerosis or some other lumen-compromising mechanism. No treatment restores vision. There is a risk for the same process affecting the second eye.

IDIOPATHIC INFLAMMATORY AND AUTOIMMUNE DISORDERS

Ocular or periocular tissues may be the primary focus of isolated idiopathic or autoimmune inflammation. Pain is common, and changes in vision may occur.

KERATOCONJUNCTIVITIS SICCA

Keratoconjunctivitis sicca, or the dry eye syndrome, results from deficiency of any of the tear film layers. Symptoms include gritty, foreign body sensations, burning, photophobia, and decreased visual acuity. Idiopathic inflammation in keratoconjunctivitis sicca and xerostomia represents Sjögren syndrome (Chapter 247). Recurrent corneal erosion, keratitis, and corneal opacification can occur. Both systemic (e.g., β-blockers, α-agonists, antihistamines, anticholinergics) and topical (e.g., retinoids) medications can also cause dry eyes.

Artificial tears, up to four times daily, and lubricating ointments are helpful. Corticosteroids (e.g., loteprednol 0.5% eye-drops four times a day) are also effective as an initial treatment. Cyclosporine eye-drops (0.05%, one drop in each eye every 12 hours) are useful when other measures fail. In cases of severe tear deficiency, surgical closure of the lacrimal puncta may be performed to prevent drainage of tears into the nasal cavity.

SCLERITIS

Episcleritis, which is an inflammation immediately underlying the conjunctiva, is distinguished from conjunctivitis because its radially oriented vessels do not move with the conjunctiva. Mild pain may be present. Episcleritis is self-limited. Instillation of 10% phenylephrine is helpful in making the diagnosis because it causes blanching in episcleritis but not in scleritis. Oral or topical nonsteroidal anti-inflammatory medications such as flurbiprofen or diclofenac may hasten resolution.

Scleritis, which presents as severe pain and redness, is associated with infectious or autoimmune connective tissue disease in about 50% of cases. Vision may be reduced if the posterior sclera is involved. Diffuse or sectoral hyperemia is nonmobile and does not blanch with instillation of phenylephrine. Secondary uveitis and keratitis may occur. Diagnostic evaluation includes ultrasonography or magnetic resonance imaging and laboratory tests to identify potential underlying conditions. Treatment may require topical or oral nonsteroidal anti-inflammatory medications or corticosteroids.

MOOREN ULCER

Mooren ulcer is idiopathic, progressive, peripheral corneal thinning, likely autoimmune. It can be unilateral or bilateral, and pain is common. Topical corticosteroids, mucolytics, and cytotoxic agents have been used. Bandage contact lenses and conjunctival recession or advancement also have been used with variable success.

ORBITAL PSEUDOTUMOR

Nonspecific, idiopathic orbital inflammation involving the lacrimal gland (dacryoadenitis), extraocular muscles (myositis), orbital fat, sclera, or optic nerve sheath (optic perineuritis) can be caused by orbital pseudotumor. Some of the cases of idiopathic orbital inflammation have been recently associated with immunoglobulin G4 autoimmune disease. Pain is frequent. Patients may present with proptosis, limited ocular movements, or decreased acuity. Orbital ultrasonography or magnetic resonance imaging excludes a mass lesion. Patients respond dramatically to systemic corticosteroids within 24 hours, but the steroids must be tapered slowly over months to prevent recurrence.

IRITIS

Iritis presents with pain, photophobia, and blurred vision, with about 50% of cases related to systemic disease. Slit lamp examination shows inflammatory cells and protein exudate in the anterior chamber. Symptomatic treatment is with prednisolone acetate 1% suspension four times a day and cycloplegic drugs (cyclopentolate 1 or 2% twice daily) is usually effective, but repeated episodes require evaluation for autoimmune and infectious causes.

RHEUMATOID ARTHRITIS

Juvenile rheumatoid arthritis (Chapter 243) is the most common specific childhood entity associated with uveitis. In adults, the ocular manifestations of rheumatoid arthritis mainly affect the anterior part of the eye, cornea, and sclera. Nearly 50% of patients who have peripheral ulcerative keratitis of the cornea have an associated systemic disease, mainly collagen vascular disease, and especially rheumatoid arthritis. Similarly, almost half of patients who have scleritis have an associated systemic disease, and about 15% of these are connective tissue diseases. Scleromalacia perforans, which is aseptic necrosis of the sclera, is associated with rheumatoid arthritis about 46% of the time.

SYSTEMIC LUPUS ERYTHEMATOSUS

Systemic lupus erythematosus (Chapter 245) causes eye manifestations from both the primary disease and its treatment with derivatives of chloroquine. Patients may have retinal vasculitis and can develop an ischemic or nonischemic optic neuritis, both of which can result in severe and permanent loss of vision. Hydroxychloroquine therapy can cause a toxic retinal degeneration, but this complication is rare during the first 10 years of use and lower at a dose of 5 mg/kg per day. Screening with visual fields or retinal imaging can detect toxicity before the patient complains of visual loss or any signs are seen on examination of the fundus.

SARCOIDOSIS

About 25% of patients with sarcoidosis (Chapter 83) develop chronic uveitis. Sarcoid also can involve the lids, conjunctiva, optic nerve, cranial nerves, and lacrimal glands. Anterior uveitis is treated topically with prednisolone acetate in decreasing doses, depending on degree of inflammation, and with daily cycloplegics (cyclopentolate 2%, atropine 1%). Posterior uveitis, dacryoadenitis, and neurologic manifestations require systemic corticosteroids, but the doses have not been standardized.

SYMPATHETIC OPHTHALMIA

Sympathetic ophthalmia is an autoimmune disease characterized by bilateral granulomatous uveitis following trauma to one eye. The condition is very rare, occurring in fewer than 1 per 10,000 cases of ocular surgical procedures and 1 per 1000 cases of accidental trauma.

The identified antigen within the eye is thought to be located in the outer retina. The disease is recognized clinically by signs of inflammation in the uninjured eye, generally 2 weeks or longer after the injury. Generally, removal of the injured eye within these 2 weeks will protect against the development of sympathetic ophthalmia in the uninjured eye, but once the uninjured eye is involved, removal of the originally injured eye is not likely to influence the process. Left untreated, inflammation may destroy the function of both eyes. When sympathetic ophthalmia is established, the patient will require anti-inflammation treatment (e.g., prednisolone, 1.0 to 1.5 mg/kg orally per day), most likely for an extended period. Most patients retain useful vision if treated at an early stage.

GENETICALLY DETERMINED DISEASES THAT MAY BECOME SYMPTOMATIC DURING ADULTHOOD

CORNEAL STROMAL DYSTROPHY

Most corneal dystrophies are autosomal dominant and bilateral, progress slowly, and primarily affect one layer of an otherwise normal cornea. Common types of dystrophies are anterior basement membrane, macular, granular, lattice, and Fuchs endothelial. Some result from mutations within the same gene. For example, the *BIGH3* on 5q31 is associated with granular and lattice dystrophy and corneal dystrophy of Bowman. The main symptom, caused by opaque corneal deposits, is blurred vision. If the decreased vision interferes with activities of normal living, a corneal transplantation can be performed.

CHOROIDAL DYSTROPHY

Choroidal dystrophies are progressive, inherited disorders characterized by atrophy of the retinal pigment epithelium and choroid. The main entities are central areolar choroidal sclerosis (autosomal dominant or recessive), gyrate atrophy (deficiency of the mitochondrial matrix enzyme ornithine-δ-aminotransferase), and choroideremia (deficiency of component A of Rab

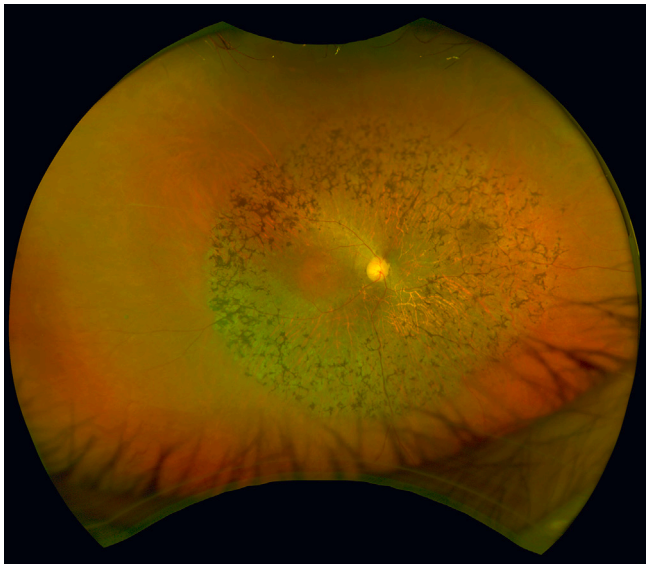

FIGURE 391-29. Retinitis pigmentosa. Fundus photograph shows "bone spicule" pigmentation of the midperipheral fundus, waxy pallor of the optic disc, and attenuated retinal vessels, the most consistent finding in retinitis pigmentosa.

geranylgeranyl transferase). No treatment exists for central areolar choroidal sclerosis or choroideremia. An arginine-restricted diet may be helpful in treating gyrate atrophy, and gene therapy trial has shown promising results for choroideremia. An arginine-restricted diet may also be helpful in treating gyrate atrophy.

RETINITIS PIGMENTOSA

Retinitis pigmentosa (Fig. 391-29) is bilateral and symmetrical, starts in early adult life, and is progressive. Retinitis pigmentosa can be an autosomal dominant or recessive disease, X-linked, digenic, mitochondrial, or sporadic. The primary defect, apoptotic in nature, appears to be in the neural retinal receptors. The main findings consist of the tetrad of bone-corpuscular retinal pigmentation; a pale, waxy optic nerve; attenuation of retinal arterioles; and a posterior subcapsular cataract. Night blindness is the primary symptom. The electroretinogram usually shows no electrical evidence of retinal function. Vitamin A palmitate supplementation (15,000 IU daily) may slow the rate of progression. Gene therapy is under investigation.

COMMON PEDIATRIC OR ADOLESCENT DISEASES THAT MAY PERSIST INTO ADULTHOOD

RETINOPATHY OF PREMATURITY

Retinal vascular development is not complete until 40 weeks of gestational age, so a premature infant is at risk of developing retinopathy of prematurity, in which blood vessels of the immature retina may leave the plane of the retina and grow into the adjacent vitreous body. The resulting tractional forces can cause total, irreversible retinal detachment and, ultimately, blindness. Myopia, strabismus, and amblyopia also are sequelae of retinopathy of prematurity. The primary risk factors for retinopathy of prematurity are early gestational age, low birth weight, and the use of supplemental oxygen. Early recognition and treatment (typically with laser photocoagulation) of retinal neovascularization are essential to halt progressive disease and prevent blindness.

HEMANGIOMA OF THE EYELID

Hemangioma of the eyelid is a hamartomatous (tissue normally found in the area) malformation of vessels in the soft tissues of the eyelid. The abnormal vascular lesion is usually insignificant at birth but grows in size over the first several months of life. The expanding hemangioma may cause astigmatism or mechanical ptosis, placing the infant at risk of amblyopia. The lesions rarely grow beyond 1 year of age and typically involute over time. If hemangiomas are small and not visually significant, observation is appropriate. Oral propranolol (1.5 to 3 mg/kg per day in two divided doses for up to 1 year), which is the treatment of choice for larger lesions or those at risk of causing amblyopia, can result in complete regression of the hemangioma.

CONGENITAL CATARACT

Congenital cataracts, which can be inherited as an autosomal dominant trait, are opacifications of the crystalline lens at birth. In congenital rubella (Chapter 339), the opacity is relatively limited to the fetal nucleus and has a pearl-like appearance. The cataract of galactosemia (Chapter 189) is potentially reversible with dietary restriction of galactose. Small cataracts can be observed, whereas dense cataracts that obstruct vision should be excised at an early age to prevent amblyopia.

TUMORS OF THE EYE

RETINOBLASTOMA

Retinoblastoma, the most common intraocular malignant tumor of childhood, results from uncontrolled proliferation of retinoblasts, which are pluripotential neuroectodermal cells that will differentiate into the various components of mature retina. A genetic deletion of the *Rb* (retinoblastoma) gene occurs in the chromosomal region 13q14. The tumor initially proliferates in the plane of the retina but is capable of involving all structures within the eye. Retinoblastoma may spread to the central nervous system through the optic nerve and vasculature to tissues at distant sites.

Approximately 40% of cases of retinoblastoma are heritable germline tumors generally diagnosed before the age of 12 months. In 80% of heritable retinoblastomas, tumors are bilateral and multiple in each eye. These patients also have a significant risk for developing a secondary primary malignant tumor (e.g., osteogenic sarcoma).

The nonheritable sporadic retinoblastomas arise spontaneously and represent about 60% of cases. The average age at presentation is 24 months, and patients generally have only a single tumor in one eye. Except in patients with mosaicism, the absence of germline mutations means that the risk for retinoblastoma in succeeding generations is low and the risk for a second primary tumor is the same as in the general population.

Retinoblastoma is often discovered by parents or relatives who notice a light reflex in one eye relative to the other either (white pupil or "cat's eye" reflex; leukocoria). Children with retinoblastoma also may present with strabismus, pseudocellulitis, iris neovascularization, dilated fixed pupil, secondary glaucoma, or tumor accumulation in the anterior chamber (neoplastic hypopyon). More advanced cases may present with signs of intraocular inflammation or ruptured globe with orbital extension. In some cases of spontaneously regressed retinoblastoma, the sole clinical sign may be a small, calcified tumor in the plane of the retina with surrounding retinal pigment epithelial scarring. Magnetic resonance imaging is the diagnostic test of choice.

Most children are treated with chemotherapy, sometimes with intraocular laser or cryotherapy. Enucleation is used for advanced cases in eyes with no visual potential.

MALIGNANT MELANOMA

Malignant melanoma (Chapter 188) of the conjunctiva is rare. Individuals at risk are middle aged and lightly pigmented. Melanoma of the conjunctiva arises most commonly from primary acquired melanosis but can occur as a de novo lesion and, rarely, from a preexisting conjunctival nevus. The regions of greatest risk are in the conjunctiva at the limbus (junction of cornea and sclera), in the conjunctival fornix (deep peripheral recesses of the conjunctiva), and in the caruncle (elevated nodule between the nasal lid margins). Extensions onto the corneal surface or formation of a nodule or loss of pigmentation are indications for excisional biopsy. Proliferation and hyperpigmentation of melanocytes without nuclear or cellular atypia is not associated with progression to melanoma, whereas associated nuclear or cellular atypia, particularly coupled with mitotic activity, is highly linked with progression to melanoma. Frank melanoma with a thickness of more than 0.8 mm is a risk factor for metastatic melanoma. Treatment is surgical excision, often supplemented with cryoablation. The long-term outcome is less favorable than for cutaneous melanoma because the tumor may metastasize early when the primary tumor is very small (e.g., 2 mm).

Malignant melanoma of the uveal tract[18] is the most common primary intraocular malignancy of adults, but its incidence is only 2 to 6 per 1 million per year in high-risk populations (blue-eyed, light-skinned persons). The tumor, which arises from preexisting nevi or dendritic melanocytes anywhere in the uveal tract, is almost always unilateral, unicentric, and nodular and is usually diagnosed at an asymptomatic phase during routine screening examination of the dilated fundus. Symptomatic tumors arise near sensitive portions of the retina (e.g., the macula) or cause retinal detachment or cystoid macular edema. Iris tumors (Fig. 391-30) are generally pigmented and elevated above the surrounding contour, where they are recognized early in their course.

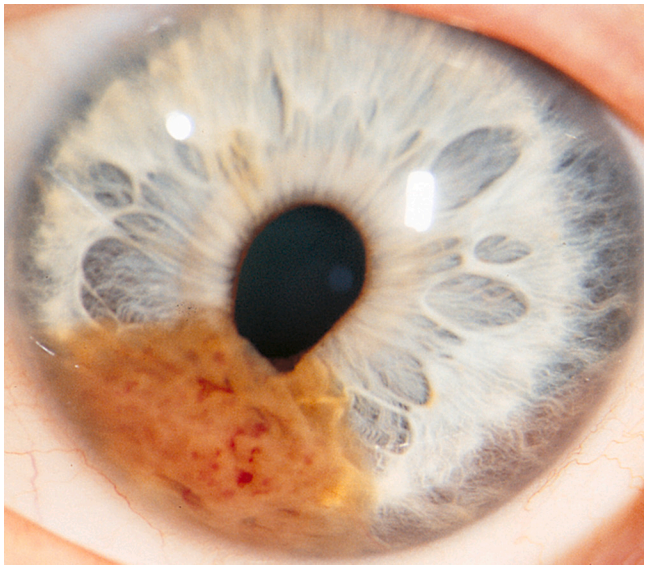

FIGURE 391-30. **Iris melanoma that has prominent intrinsic blood vessels. Note peaking of the pupil toward the tumor. (From Yanoff M, Duker JS, eds. *Ophthalmology*. Philadelphia: Mosby Elsevier; 2009.)**

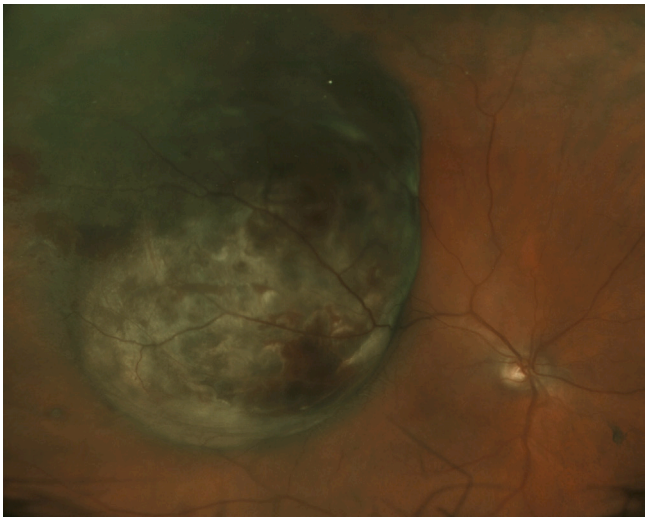

FIGURE 391-31. **Posterior choroidal melanoma.**

Posterior tumors, which originate under the retina, may extend into the vitreous cavity, be completely amelanotic, and occasionally may have a bilobed appearance (Fig. 391-31). Accuracy in diagnosing melanoma of the uveal tract by clinical means alone is greater than 98%. Treatment is controversial; options include enucleation of the eye, proton beam and plaque (iodine-125) radiation,[19] thermal laser ablation, photodynamic therapy, and en bloc resection. For metastatic uveal melanoma, intravenous tebentafusp (a bispecific protein with a T-cell receptor fused to an anti-CD3 effector at 20 μg on day 1, 30 μg on day 8, and 68 μg on day 15 and weekly thereafter) can significantly prolong survival.[A19] The survival rate can be as low as 50% at 15 years for large lesions. Risk factors for metastasis, most commonly to the liver, include tumor size, cell type, angiogenic mimicry, the presence of monosomy 3, and other genetic markers.

ORBITAL TUMORS

Primary tumors in the orbit of adults include cavernous hemangioma, schwannomas, and various proliferations of fibrous tissue (solitary fibrous tumor). Rhabdomyosarcoma may arise from ectopic rests of mesenchyme rather than from mature rectus muscle. Orbital tumors usually are diagnosed by imaging techniques. The treatment is orbital exploration and surgical removal.

LYMPHOMA

Orbital and conjunctival lymphomas are usually small (marginal zone B-cell lymphomas; Chapter 171). Approximately 50% of cases ultimately include systemic disease that may not be clinically diagnosed. External beam radiation is used to treat isolated periocular disease, whereas systemic chemotherapy (Chapter 171) is required for symptomatic, systemic involvement.

Large-cell B-cell lymphoma may present in the eye as a form of vitreitis (cells suspended in the vitreous) or a subretinal or intraretinal infiltrate before it is discovered in the central nervous system. The diagnosis may be verified by cytologic examination of vitrectomy specimens. Treatment is generally systemic (Chapter 171), but the outcome is usually poor.

The eye may infrequently be involved in multiple myeloma (Chapter 173). Retinal hemorrhages and vitreous opacification may occur. Periorbital osteolytic lesions of bone may be present.

TABLE 391-8 SYSTEMIC MEDICATIONS WITH OCULAR EFFECTS

AGENT	EFFECT
Chloroquine	Dyschromatopsia, visual field defects
Hydroxychloroquine	Dyschromatopsia, visual field defects; bull's-eye maculopathy
Thioridazine	Blurred vision
Chlorpromazine	Blurred vision
Digoxin	Yellow vision
Ethambutol	Optic neuritis
Amiodarone	Corneal whorls, pigmentary retinopathy
Corticosteroids	Glaucoma, cataract
Tamoxifen	Maculopathy
Neuroleptics	Nystagmus
Compazine	Oculogyric crisis
Vitamin A	Pseudotumor cerebri
5-Fluorouracil	Canalicular stenosis (tearing)
Isotretinoin	Severe dry eye (long-term effect)

LACRIMAL GLAND TUMORS

The lacrimal gland contains a resting population of non-nodal lymphocytes and is a common site for lymphomas. Epithelial neoplasms may arise from components of the acini and ducts of the lacrimal gland. Malignant epithelial tumors (adenoid cystic carcinoma) may metastasize at an early stage through perineural spaces of large peripheral nerves to adjacent bone. Most epithelial tumors are treated with total surgical removal of the lacrimal gland because of the risk for recurrence and malignant transformation of residual tumor. The prognosis for malignant lacrimal gland tumors is generally poor.

OCULAR METASTASIS

Metastasis to the orbit in adults is very uncommon because of its relatively small vascular volume. Metastasis to the rectus muscles present with adult-onset strabismus. Metastasis to the orbit is more common in childhood leukemia than adult leukemia.

Metastasis to the uveal tract is common, especially from primary breast and lung tumors. Metastatic lesions often grow rapidly and disturb visual function; serous retinal detachment is common. Treatment of the underlying malignancy can be effective on the choroidal lesions, but supplemental radiation or photodynamic therapy can be used to try to restore or preserve vision.

OCULAR EFFECTS OF SYSTEMIC MEDICATIONS

Innumerable medications may cause ocular side effects (Table 391-8). Therefore, patients taking systemic medications often require periodic surveillance to identify ocular toxicity.

The most common cause of drug-induced glaucoma is topical corticosteroid therapy of more than 4 to 6 weeks' duration in the 5 to 6% of the population who are genetically predisposed. Nonsteroidal drugs usually cause narrow-angle glaucoma. Sulfa-containing drugs may induce glaucoma as an idiosyncratic reaction in persons with either narrow or open anterior chamber configuration. Treatment is the same as for non–drug-induced glaucoma.

Chloroquine and *hydroxychloroquine* may cause decreased color vision and visual field defects at high doses. Chloroquine toxicity is thought to occur after a cumulative dose of 300 g, whereas hydroxychloroquine may cause symptoms after long-term maintenance of 750 mg/day. The macular portion of the fundus

develops a typical bull's-eye pattern of pigment disturbance. Corneal whorls composed of epithelial intracellular pigment may be seen. Vision loss from retinal toxicity is not reversible and tends to progress even after cessation of hydroxychloroquine treatment. Annual fundus examination with color testing, macular function tests, and automated visual field test may be indicated.

Ethambutol is often used for chronic pulmonary infection. The dose of drug is dependent on body weight. Toxic optic neuropathy is rare but unpredictable in incidence and outcome. Careful follow-up with close ophthalmic clinical surveillance is required.

Any of the commonly used antituberculous medications may cause optic neuropathy, although *ethambutol* carries the greatest risk. Pupillary response, color vision, acuity, and visual fields are the clinical parameters used to assess optic nerve function.

Cornea verticillata may be seen in patients taking *amiodarone* because of lysosomal accumulations within the epithelial basement membrane. *Fabry disease* produces similar changes, as can other medications. Corneal whorls are usually reversible when caused by drug toxicity, and they rarely interfere with vision.

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For the General References and other additional features, please visit Elsevier eBooks+ at https://ebooks.health.elsevier.com.

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392 NEURO-OPHTHALMOLOGY

ROBERT W. BALOH AND JOANNA C. JEN

A mechanistic understanding of vision impairment along with disturbances in pupillary and oculomotor control is often critical for diagnosing neurologic disorders. Although all physicians should be able to recognize neuro-ophthalmologic abnormalities,[1] precise diagnosis and treatment commonly requires specialty consultation.[2]

VISION

One of the most difficult diagnostic problems is vision loss that cannot be explained by obvious abnormalities of the eye. To evaluate such a patient properly, the examining physician must be familiar with the anatomy and physiology of the afferent visual system. The afferent visual pathways cross the major ascending sensory and descending motor systems of the cerebral hemispheres and in their anterior portion are intimately related to the vascular and bony structures at the base of the brain. Not surprisingly, localization of lesions within the afferent visual pathways has great value in neurologic diagnosis.

ANATOMY OF THE VISUAL PATHWAYS

Light entering the eye falls on the retinal rods and cones, which transduce the stimulus into neural impulses to be transmitted to the brain. The distribution of visual function across the retina takes a pattern of concentric zones increasing in sensitivity toward the center, the fovea. The fovea consists of a "rod-free" central grouping of approximately 100,000 slender cones. The ganglion cells subserving these cones send their axons directly to the temporal aspect of the optic disc, where they form the papillomacular bundle. Axons originating from ganglion cells in the temporal retina curve above and below the papillomacular bundle and form dense arcuate bands.

The arteries supplying the optic nerve and retina derive from branches of the ophthalmic artery. The central retinal artery approaches the eye along each optic nerve and pierces the inferior aspect of the dural sheath about 1 cm behind the globe to enter the center of the nerve. The artery emerges in the fundus at the center of the nerve head, from which it nourishes the inner two thirds of the retina by superior and inferior branches. Anastomotic branches derived from the choroidal and posterior ciliary arteries, the ciliary system, supply the choroid, optic nerve head, and outer retinal layers, including the photoreceptors. In about 10% of the population, the macula is supplied by a retinociliary artery, a branch of the ciliary system. Venous drainage from the retina and nerve head flows primarily through the central retinal vein, whose course of exit from the eye parallels that of entry of the artery.

What each eye "sees" is termed its *visual field* (Fig. 392-1). The nasal side of the left retina and the temporal side of the right see the left side of the world, and the upper half of each retina sees the lower half of the world. Behind the eyes, the optic nerves pass through the optic canal to form the optic chiasm. In the chiasm, nerves from the nasal half of each retina decussate and join the fibers from the temporal half of the contralateral retina. From the chiasm, the optic tracts pass around the cerebral peduncles to reach the lateral geniculate ganglia. The orientation of the visual field is rotated 90 degrees in the lateral geniculate such that images from the inferior visual field project to the medial half, whereas images from the superior visual field project to the lateral half. The geniculocalcarine radiation initially fans out into superolateral and inferolateral projections, the latter passing around the lateral ventricle and for a short distance into the temporal lobe (Meyer loop) before turning posteriorly to reach the striate cortex of the occipital lobe. In the occipital lobe, the striate cortex (area 17) lies along the superior and inferior bands of the calcarine fissure, with macular fibers projecting most posteriorly to the occipital pole and more peripheral retinal projections lying more anteriorly.

LOCALIZATION OF LESIONS WITHIN VISUAL PATHWAYS

Monocular vision loss is due to a lesion in one eye or optic nerve. Binocular visual loss, on the other hand, can result from disease located anywhere in

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develops a typical bull's-eye pattern of pigment disturbance. Corneal whorls composed of epithelial intracellular pigment may be seen. Vision loss from retinal toxicity is not reversible and tends to progress even after cessation of hydroxychloroquine treatment. Annual fundus examination with color testing, macular function tests, and automated visual field test may be indicated.

Ethambutol is often used for chronic pulmonary infection. The dose of drug is dependent on body weight. Toxic optic neuropathy is rare but unpredictable in incidence and outcome. Careful follow-up with close ophthalmic clinical surveillance is required.

Any of the commonly used antituberculous medications may cause optic neuropathy, although *ethambutol* carries the greatest risk. Pupillary response, color vision, acuity, and visual fields are the clinical parameters used to assess optic nerve function.

Cornea verticillata may be seen in patients taking *amiodarone* because of lysosomal accumulations within the epithelial basement membrane. *Fabry disease* produces similar changes, as can other medications. Corneal whorls are usually reversible when caused by drug toxicity, and they rarely interfere with vision.

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392 NEURO-OPHTHALMOLOGY

ROBERT W. BALOH AND JOANNA C. JEN

A mechanistic understanding of vision impairment along with disturbances in pupillary and oculomotor control is often critical for diagnosing neurologic disorders. Although all physicians should be able to recognize neuro-ophthalmologic abnormalities,[1] precise diagnosis and treatment commonly requires specialty consultation.[2]

VISION

One of the most difficult diagnostic problems is vision loss that cannot be explained by obvious abnormalities of the eye. To evaluate such a patient properly, the examining physician must be familiar with the anatomy and physiology of the afferent visual system. The afferent visual pathways cross the major ascending sensory and descending motor systems of the cerebral hemispheres and in their anterior portion are intimately related to the vascular and bony structures at the base of the brain. Not surprisingly, localization of lesions within the afferent visual pathways has great value in neurologic diagnosis.

ANATOMY OF THE VISUAL PATHWAYS

Light entering the eye falls on the retinal rods and cones, which transduce the stimulus into neural impulses to be transmitted to the brain. The distribution of visual function across the retina takes a pattern of concentric zones increasing in sensitivity toward the center, the fovea. The fovea consists of a "rod-free" central grouping of approximately 100,000 slender cones. The ganglion cells subserving these cones send their axons directly to the temporal aspect of the optic disc, where they form the papillomacular bundle. Axons originating from ganglion cells in the temporal retina curve above and below the papillomacular bundle and form dense arcuate bands.

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What each eye "sees" is termed its *visual field* (Fig. 392-1). The nasal side of the left retina and the temporal side of the right see the left side of the world, and the upper half of each retina sees the lower half of the world. Behind the eyes, the optic nerves pass through the optic canal to form the optic chiasm. In the chiasm, nerves from the nasal half of each retina decussate and join the fibers from the temporal half of the contralateral retina. From the chiasm, the optic tracts pass around the cerebral peduncles to reach the lateral geniculate ganglia. The orientation of the visual field is rotated 90 degrees in the lateral geniculate such that images from the inferior visual field project to the medial half, whereas images from the superior visual field project to the lateral half. The geniculocalcarine radiation initially fans out into superolateral and inferolateral projections, the latter passing around the lateral ventricle and for a short distance into the temporal lobe (Meyer loop) before turning posteriorly to reach the striate cortex of the occipital lobe. In the occipital lobe, the striate cortex (area 17) lies along the superior and inferior bands of the calcarine fissure, with macular fibers projecting most posteriorly to the occipital pole and more peripheral retinal projections lying more anteriorly.

LOCALIZATION OF LESIONS WITHIN VISUAL PATHWAYS

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ABSTRACT

Understanding neuro-ophthalmology is of great value in neurologic diagnosis. The afferent visual pathways cross the major ascending sensory and descending motor pathways of the cerebral cortex, and oculomotor control involves large parts of the cerebral cortex, cerebellum, and brain stem. The neuro-ophthalmologic examination requires a systematic assessment of both afferent and efferent pathways. Examination of the afferent system should include ophthalmoscopic visualization of the retina, visual acuity, visual fields, and pupillary responses. Examination of the efferent system should include assessment of the extraocular muscles, a search for ocular oscillations including nystagmus, and assessment of each of the supranuclear control systems—saccade, smooth pursuit, vergence, and vestibular.

KEYWORDS

visual loss
optic neuritis
papilledema
visual field
anisocoria
gaze palsy
strabismus

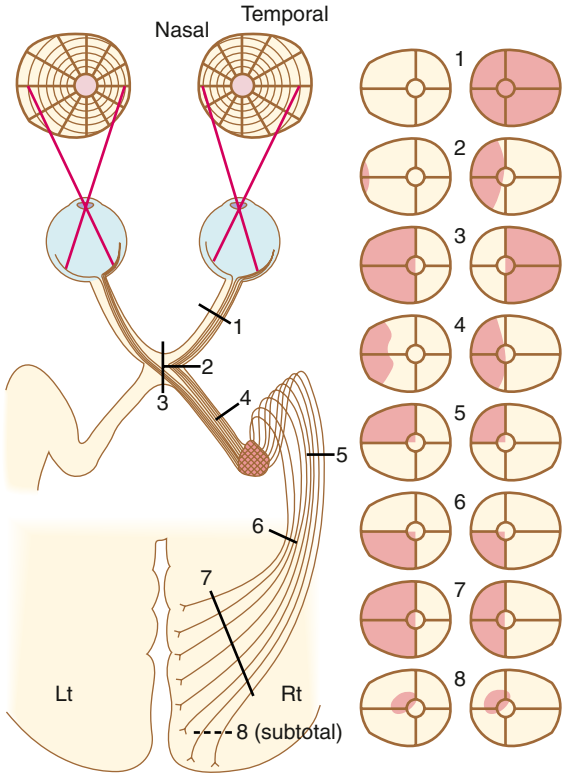

FIGURE 392-1. **Visual fields that accompany damage to the visual pathways.** *1*, Optic nerve: unilateral amaurosis. *2*, Lateral optic chiasm: grossly incongruous, incomplete (contralateral) homonymous hemianopia. *3*, Central optic chiasm: bitemporal hemianopia. *4*, Optic tract: incongruous, incomplete homonymous hemianopia. *5*, Temporal (Meyer) loop of the optic radiation: congruous partial or complete (contralateral) homonymous superior quadrantanopia. *6*, Parietal (superior) projection of the optic radiation: congruous partial or complete homonymous inferior quadrantanopia. *7*, Complete parieto-occipital interruption of the optic radiation: complete congruous homonymous hemianopia with psychophysical shift of the foveal point, often sparing central vision and resulting in "macular sparing." *8*, Incomplete damage to the visual cortex: congruous homonymous scotomas, usually encroaching at least acutely on central vision. Lt = left; Rt = right.

the visual pathways from the corneas to the occipital poles. Lesions involving the optic chiasm produce nonhomonymous visual abnormalities (e.g., the bitemporal hemianopia illustrated by lesion 3 in Fig. 392-1). Optic tract abnormalities are comparatively rare but produce characteristic visual changes. The fibers serving identical points in the homonymous half-fields do not fully commingle in the optic tract, so lesions damaging this structure produce incongruous homonymous hemianopia. Lesions of the geniculate nuclei, optic radiations, or visual cortex produce congruent hemianopic field defects that may go unrecognized unless the hemianopia intrudes on macular vision. Postgeniculate visual loss can be differentiated from pregeniculate visual loss by (1) a normal funduscopic appearance, (2) intact pupillary light reactions, and (3) appropriate lesions on brain imaging.

EXAMINATION OF THE AFFERENT VISUAL SYSTEM

Visual function is most commonly assessed by "best-corrected visual acuity" (Chapter 391). If visual acuity is not normal, it must be determined whether acuity can be improved with lenses or at least with the use of a pinhole. The normal reference is recognition of letters at an idealized 20 feet, and acuity charts are designed with even larger letters that are normally recognized at proportionally greater distances. Thus, if one reads letters at 20 feet no better than those normally perceived at 40 feet, vision is recorded as 20/40. Small visual charts that are easily carried in the physician's case permit quick and fairly accurate bedside appraisal of acuity.

Visual fields can be tested at the bedside by confrontation, and rough estimates of their integrity can be made even in patients with reduced alertness. The fields should be tested individually for each eye because the pattern of visual field defects can provide important localizing information. A quick screen of the visual fields can be made by having the patient fixate on the examiner's nose and identify the number of fingers flashed in each of the four visual field quadrants.

COMMON CAUSES OF VISUAL LOSS

Eye

The cause of monocular vision loss secondary to ocular and retinal lesions can often be detected by ophthalmoscopic examination or by measurement of intraocular pressure (Chapter 391). *Glaucoma* caused by impaired absorption of aqueous humor results in a high intraocular pressure that usually produces gradual loss of peripheral vision, "halos" seen around lights, and occasionally, pain and redness in the affected eye. *Retinal tears* and *detachments* give rise to unilateral distortions of the visual image seen as sudden angulations or curves of objects containing straight lines (metamorphopsia). *Hemorrhages* into the vitreous humor or infections or inflammatory lesions of the retina can produce scotomas that resemble those resulting from primary disease of the central visual pathway.

Binocular vision loss secondary to retinal disease in younger subjects is often due to *heredodegenerative conditions*. Vascular diseases, diabetes (Chapter 210), and age-related macular degeneration are causes in older patients. In most cases of *pigmentary retinal degeneration*, visual loss begins peripherally and slowly proceeds centrally. By contrast, *macular degeneration* (see Figs. 391-20 and 391-21) impairs central vision early in its course. A common variant in the complement factor H (*CFH*) gene is associated with a markedly increased risk for the development of age-related macular degeneration.

Optic Nerve

Acute or subacute monocular vision loss (Table 392-1) as a result of optic nerve disease is most commonly produced by demyelinating disorders, vascular obstruction, neoplasm, or hereditary optic neuropathy.[3] Demyelinating disease of the nerve head (*optic neuritis* or *papillitis*) produces disc edema along with loss of central vision in the affected eye only; subjectively unrecognized scotomas may sometimes be found in the other eye. Demyelination of the optic nerve behind the point where the retinal vein emerges (*retrobulbar neuritis*) initially leaves a normal-looking disc but a central or paracentral scotoma. With chronic demyelinating disorders, the optic disc becomes pale and atrophic.

Optic neuritis can be an isolated syndrome or a manifestation of systemic diseases.[4,5] The clinical course and therapeutic response of optic neuritis depend on the underlying inflammatory mechanism. In more than 50% of patients initially seen with optic neuritis, typical symptoms and signs of multiple sclerosis eventually develop (Chapter 380). Optic neuritis caused by multiple sclerosis is not responsive to steroids,[A1] but the underlying multiple sclerosis should be treated promptly. Some data suggest that phenytoin may be neuroprotective in patients with acute optic neuritis when used in doses of 4 to 6 mg/kg/day.[A2] Optic neuritis related to systemic lupus erythematosus (Chapter 245),[6] vasculitis (Chapter 249), or sarcoidosis (Chapter 83) may be steroid responsive.

Optic neuritis with an associated transverse myelitis is the clinical hallmark of *neuromyelitis optica*,[7] which is a severe demyelinating disease often mistaken for multiple sclerosis but now recognized to be caused by anti–aquaporin 4 autoantibodies. Standard treatment options include rituximab (1-g infusions at an interval of 2 weeks) or azathioprine (3 mg/kg/day orally). More recently, satralizumab (a humanized monoclonal antibody targeting the interleukin-6 receptor at 120 mg subcutaneously at 0, 2, and 4 weeks, then every 4 weeks thereafter), eculizumab (a terminal complement inhibitor at 900 mg intravenously weekly for 4 doses followed by 1200 mg every 2 weeks), and tocilizumab (an interleukin-6 receptor inhibitor at 8 mg intravenously every 4 weeks) have been shown to reduce the risk of relapse.[A3–A6] Doses should be adjusted based on response and immune suppression.[8]

Intraocular arterial occlusion may produce either central visual loss or an altitudinal field defect (*ischemic optic neuropathy*). Nonarteritic anterior ischemic optic neuropathy results from disease of the small vessels supplying the anterior portion of the optic nerve. The most common systemic disorders associated with it are hypertension (present in 50% of patients) and diabetes mellitus (present in 25%). Arteritic ischemic optic neuropathy is most commonly caused by giant cell arteritis (Chapters 63 and 250) and should be considered in all patients who are older than 50 years of age. Oral glucocorticoids are the cornerstone of treatment for giant cell arteritis but are not helpful in patients with nonarteritic anterior ischemic optic neuropathy.[A7]

Tumors (Chapter 175) invading the optic nerve or space-occupying lesions compressing it anywhere between the orbit and chiasm cause gradually decreasing central vision or a sector defect of the peripheral visual field. With such chronic lesions, the affected optic nerve becomes visibly atrophic.

Acute binocular vision loss resulting from bilateral optic nerve disease is most often caused by demyelinating disease or by toxic (methanol, tobacco, isoniazid) or nutritional factors (B vitamin deficiency, particularly of thiamine;

TABLE 392-1 COMMON CAUSES OF TRANSIENT MONOCULAR VISION LOSS

CATEGORY (TYPICAL DURATION)	CAUSES	DIFFERENTIAL FEATURES
Thromboembolism (1-5 min)	Atherosclerosis	Other atherosclerotic vascular disease, associated contralateral hemiparesis, angiography (carotid atheroma)
	Cardiac	Valvular disease, mural thrombi, atrial fibrillation, recent myocardial infarction
	Blood dyscrasia	Blood tests positive for sickle cell anemia, macroglobulinemia, multiple myeloma, polycythemia, other
Vasospasm (5-30 min)	Migraine	Ipsilateral headache, other classic aura, family history
Vascular compression (few seconds)	Increased intracranial pressure	Precipitated by position change, Valsalva maneuver, or pressure waves
	Tumor	Associated with slowly progressive monocular visual loss
Vasculitis (1-5 min)	Temporal arteritis	Associated with headache, polymyalgia rheumatica, palpable temporal artery, elevated sedimentation rate

TABLE 392-2 DIFFERENTIATION OF OPTIC NEURITIS FROM PAPILLEDEMA

	OPTIC NEURITIS	PAPILLEDEMA
Central-cecocentral vision loss	Present	Absent
Distribution	Usually unilateral	Usually bilateral
Ocular pain on movement	Present	Absent
Direct light reflex	±Reduced	Intact
CT and MRI of head	White matter plaques	Tumor, venous occlusion, etc.
Visual evoked responses	Abnormal	Normal
Lumbar puncture pressure	Normal	Elevated

CT = computed tomography; MRI = magnetic resonance imaging.

Chapter 384). In younger persons and those lacking a clear history of toxic exposure, demyelinating lesions overwhelmingly predominate. Symptoms are of abrupt or subacute onset with visual blurring, which may progress rapidly to blindness within hours or days. There may be pain about the eyes, particularly with movement. *Leber optic neuropathy*, caused by a mutation in mitochondrial DNA, typically begins painlessly and centrally in one eye, with the second eye affected weeks to months later. Gene therapy can modestly improve vision in both the treated and untreated eye,[A8] albeit only for 3 years or so.

Papilledema is disc edema secondary to increased intracranial pressure (Table 392-2). Vision is normal except under one of two circumstances: (1) acute transient episodes of amaurosis lasting a few seconds and attributable to acute increases in intracranial pressure (plateau waves); and (2) progressive loss of peripheral vision with long-standing, severe papilledema caused by compression of the optic nerve head. Idiopathic intracranial hypertension (Chapter 175)[9] is commonly seen in overweight women of childbearing age. Optical coherence tomography can help establish the diagnosis and differentiate papilledema from other optic disc abnormalities.[10] Subacute or chronic binocular vision loss secondary to optic nerve disease can result from *toxic* and *nutritional* causes or from *inherited optic atrophy*. Visual loss is painless and primarily affects central vision; ophthalmoscopy shows optic atrophy.

Chiasm and Optic Tract

Patients with lesions of the optic chiasm or optic tract are often unaware of visual impairment until the deficit encroaches on central vision in one or both eyes. Intrinsic or extrinsic neoplasms and parachiasmal arterial aneurysms are the most common lesions in this location. Gliomas that arise within the chiasm or optic tract are rare in adulthood. Extrinsic lesions compressing the chiasm or tract include *pituitary adenomas* (Chapter 205), *dysgerminomas, craniopharyngiomas, meningiomas* (Chapter 175), and large *aneurysms* of the carotid or basilar artery (Chapter 377). The diagnosis rests on finding the characteristic visual field abnormalities (bitemporal hemianopia for chiasm and incongruous homonymous hemianopia for optic tract lesions) and identifying the lesion with computed tomography or magnetic resonance imaging. Pituitary apoplexy secondary to acute hemorrhage into the gland (Chapter 205) can result in sudden vision loss; prompt neurosurgical intervention under steroid coverage is required for most patients.

Visual Radiations and Occipital Cortex

Lesions involving the postgeniculate visual pathways most often result from *vascular damage, traumatic injuries, neoplasms*, or rarely, *inflammatory* or *degenerative disorders* involving the cerebral white matter. Their localization can be deduced by the resulting visual field defects. Vascular disease of the occipital lobes is the most common cause of homonymous visual field defects in middle-aged and elderly people. *Anton syndrome* refers to cerebral visual loss with denial of a visual defect. Affected patients not only deny that they are blind but also confabulate details of their visual environment from memory. Anton syndrome results from bilateral lesions involving the parieto-occipital lobes or in the setting of metabolic encephalopathy. The reversible *posterior leukoencephalopathy syndrome*, which is characterized by headache, seizures, confusion, and cortical visual loss, is associated with an abrupt increase in blood pressure, such as may be seen with eclampsia and with immunosuppressive therapy after transplantation.

PUPILLARY CONTROL

The neuromechanisms that control pupil size and reactivity are complex, yet they can be evaluated by simple clinical procedures. The diameter of the pupil is determined by the antagonistic actions of the iris sphincter and dilator muscles, with the latter playing a minor role. If the sphincter muscle is severed or ruptured, it does not retract toward one quadrant but rather continues to function, except in the altered segment. Therefore, pupillary response can be evaluated even in the presence of significant damage to the iris.

ANATOMY AND LOCALIZATION OF LESIONS WITHIN PUPILLARY PATHWAYS

The size of the pupil is governed by tonic balance between sympathetic and parasympathetic innervation of the muscles of the iris. Sympathetic stimulation dilates the pupil, whereas parasympathetic stimulation constricts it. In the normal resting state, light entering the eye provides the major stimulus governing the size of the pupil (Fig. 392-2). Light activates the retinal rods and cones, with maximal sensitivity in the macular area. The optic nerve fibers follow the crossed and uncrossed visual pathways to the pregeniculate portion of the optic tracts, where the receptor fibers for light diverge to the pretectal nucleus located at the midbrain-diencephalic junction. Interneurons project from this nucleus to the Edinger-Westphal nuclei atop the midbrain third nerve nuclear complex of either side. From that point, paired parasympathetic efferents leave the midbrain in the third nerves, travel in the interpeduncular space across the petroclinoid ligament and edge of the tentorium, traverse the cavernous sinus, and then enter the orbit through the superior orbital fissure. In the orbit, the parasympathetic efferents synapse in the ciliary ganglion, from which ciliary nerves enter the eye to reach the pupillary muscles.

The principal sympathetic control of the pupil originates in the ventral lateral hypothalamus (first-order neuron), from which fibers descend ipsilaterally through the brain stem tegmentum and thence to the cervical cord, where they synapse with preganglionic neurons in the intermedial lateral column of the upper three thoracic segments. Preganglionic fibers (second-order neurons) emerge with the ventral roots of C8, T1, and T2 and ascend in the neck to synapse in the superior cervical ganglion adjacent to the base of the skull. Postganglionic (third-order neurons) pupillary fibers accompany the internal carotid artery through the skull and then leave it to follow the ophthalmic branch of the trigeminal nerve to reach the pupillodilator muscle of the eye.

EXAMINATION OF THE PUPIL

The pupillary response to light should be examined in a dimly lighted room, where the pupils are naturally dilated. First, the size and symmetry of the pupils are assessed by shining a dim light onto the face from below so that both pupils are seen simultaneously in the indirect illumination. To test light reactivity, gaze is directed at a distant object (so that constriction secondary to

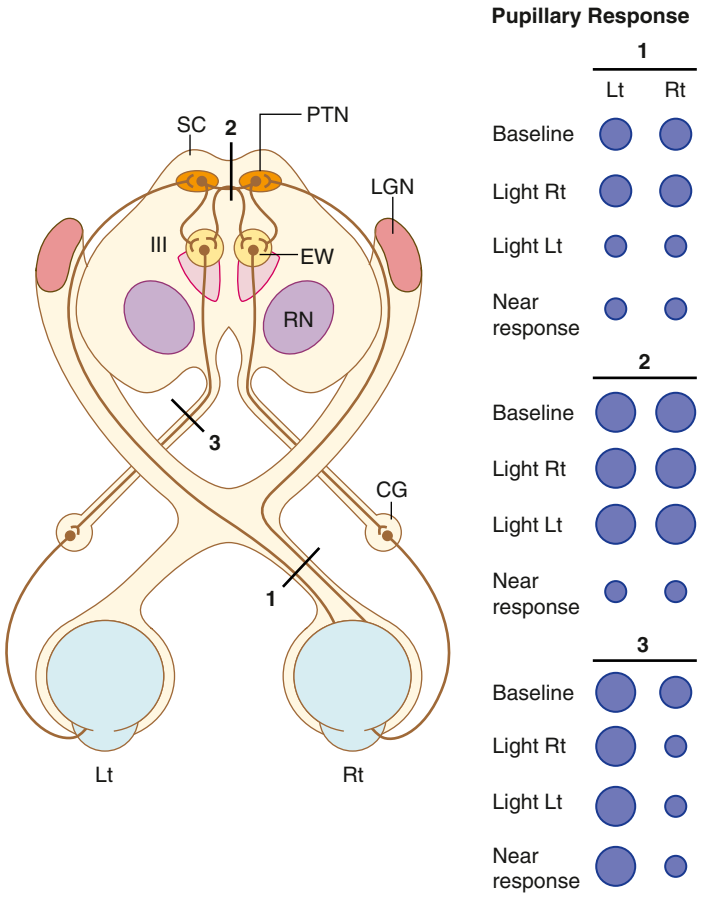

FIGURE 392-2. **Pupillary responses associated with lesions of the *(1)* optic nerve, *(2)* pretectum, and *(3)* oculomotor nerve.** Baseline is obtained with fixation on a distant target and the near response with a target in front of the nose. CG = ciliary ganglion; EW = Edinger-Westphal nucleus; LGN = lateral geniculate nucleus; Lt = left; PTN = pretectal nucleus; RN = red nucleus; Rt = right; SC = superior colliculus.

FIGURE 392-3. **Adie tonic pupil in the right eye of a young woman.** The affected pupil is "tonic"; that is, it responds slowly to light and accommodation but on rapid testing appears unresponsive. The site of the lesion is usually obscure, but the condition is benign. There may be associated areflexia. (From Forbes CD, Jackson WF. *Color Atlas and Text of Clinical Medicine*, 3rd ed. London: Mosby; 2003.)

convergence is minimal), and first one and then the other pupil is illuminated with a bright light source. If a pupil reacts poorly to direct light, it is observed as the opposite eye is illuminated (consensual response). Pupils that react poorly to light should be tested for reactivity to the near reflex by first having the patient gaze at a distant object and then quickly fixate on an object just in front of his or her nose. *Light-near dissociation* refers to a pupil that does *not* react to light but does accommodate by constricting to a near target.

COMMON CAUSES OF PUPILLARY ABNORMALITIES

With so-called benign pupillary dilation, or *physiologic anisocoria*, a long-standing difference in the size of the two pupils is associated with normal reflex reactions; the disparity remains constant during constriction and dilation. Lesions compressing or damaging the pretectal region interrupt the afferent light reflex bilaterally to produce dilated and light-fixed pupils (e.g., lesion 2; see Fig. 392-2).[11] Pupillary constriction to the near response is preserved until late stages. Tumors of the pineal gland (e.g., dysgerminomas) and *localized infarctions* are the most common lesions in this location. *Adie tonic pupil* (Fig. 392-3) is a medium to large (3 to 6 mm) pupil that constricts little or not at all to light and very slowly to accommodation but constricts with the instillation of dilute (0.125%) pilocarpine (Fig. 392-4). The condition usually affects one eye (occasionally both), is more common in women 25 to 45 years of age, and carries no serious implications. It most likely results from postviral denervation of the pupillary muscles. Unexplained unilateral or bilateral dilated pupils as an isolated finding can result from *accidental or intentional instillation of mydriatic drugs*. Transdermal scopolamine is a common cause. Failure of the pupil to constrict promptly with pilocarpine (1%) gives the diagnosis if the history is unclear. Interruption of the emerging third nerve in the ventral midbrain or along the proximal part of its course produces a dilated pupil 6 to 7 mm in diameter. Important causes of compression of the third nerve in this region are *aneurysms* (Chapter 377), *neoplasia* (Chapter 175), and *brain herniation* (Chapter 175) as a result of increased intracranial pressure. In nearly all cases, the pupillary involvement is associated with other signs of third nerve involvement (see later text).

Sympathetic paralysis of the eye with ptosis, anhidrosis, and miosis (Horner syndrome; Fig. 392-5) can result from lesions anywhere along the pathway of the sympathetic innervation to the eye (Table 392-3). The diagnosis can sometimes be made by identifying associated signs in the brain stem or neck or along the carotid artery. *Argyll Robertson pupils* are small (1 to 2 mm), unequal, irregular, and fixed to light; they constrict minimally to accommodation. Their principal cause is tertiary neurosyphilis (Chapter 295).

OCULOMOTOR CONTROL

Abnormal eye movements can result from disturbances at several levels. Disconjugate eye movements result from lesions in the individual ocular muscles, the myoneural junctions, the oculomotor nerves and their three paired nuclei in the brain stem, and the internuclear medial longitudinal fasciculus (MLF), which yokes the eyes in horizontal movements. Supranuclear lesions typically produce disorders of conjugate gaze (gaze palsies).

ANATOMY AND LOCALIZATION OF LESIONS WITHIN THE OCULOMOTOR PATHWAYS

Nuclear and Internuclear Pathways

The abducens (sixth) nerve supplies the lateral rectus muscle. Selective involvement of the abducens nerve anywhere along its pathway leads to isolated weakness of abduction of the affected eye. Destruction of the abducens nucleus in the brain stem results in a conjugate gaze paralysis (ipsilateral) because, in addition to oculomotor neurons, the nucleus contains interneurons destined for the contralateral medial rectus nucleus. The trochlear (fourth) nerve supplies the contralateral superior oblique muscle, which turns in and depresses the eye. Patients with superior oblique weakness note an increase in diplopia with head tilt toward the side of weakness and often tilt their head in the opposite direction. At rest, there is slight upward deviation of the involved eye, and downward movement is impaired when the affected eye is turned in. Patients typically complain of diplopia when reading or going down stairs. The third (oculomotor) cranial nerve supplies the remaining ocular muscles. Involvement of the third nerve nucleus in the midbrain always produces at least some bilateral oculomotor weakness; the superior rectus division of the nucleus supplies the contralateral superior rectus muscle (all other divisions supply ipsilateral muscles). Peripheral third nerve paralysis can result from lesions damaging the structure anywhere from its course within the ventral midbrain to where it enters the orbit through the superior orbital fissure. When complete, third nerve palsy produces a widely dilated pupil, severe ptosis, and an externally deviated eye held in position by unopposed contraction of the lateral rectus muscle. In such conditions, the continued trochlear action reveals itself by intorsion of the eye when the subject attempts to look down.

The MLF interconnects the abducens nucleus in the pons with the contralateral oculomotor nuclear complex in the midbrain. It terminates cephalad in the interstitial nucleus in the rostral midbrain and can be traced as far caudad as the thoracocervical region of the spinal cord (coordinating nuchal-ocular control). Lesions involving the MLF characteristically produce internuclear ophthalmoplegia, in which the eyes are conjugate in the primary position but disconjugate on lateral gaze. With fully developed internuclear ophthalmoplegia on lateral gaze away from the side of the lesion, the contralateral eye abducts and shows nystagmus, whereas the ipsilateral adducting eye does not move

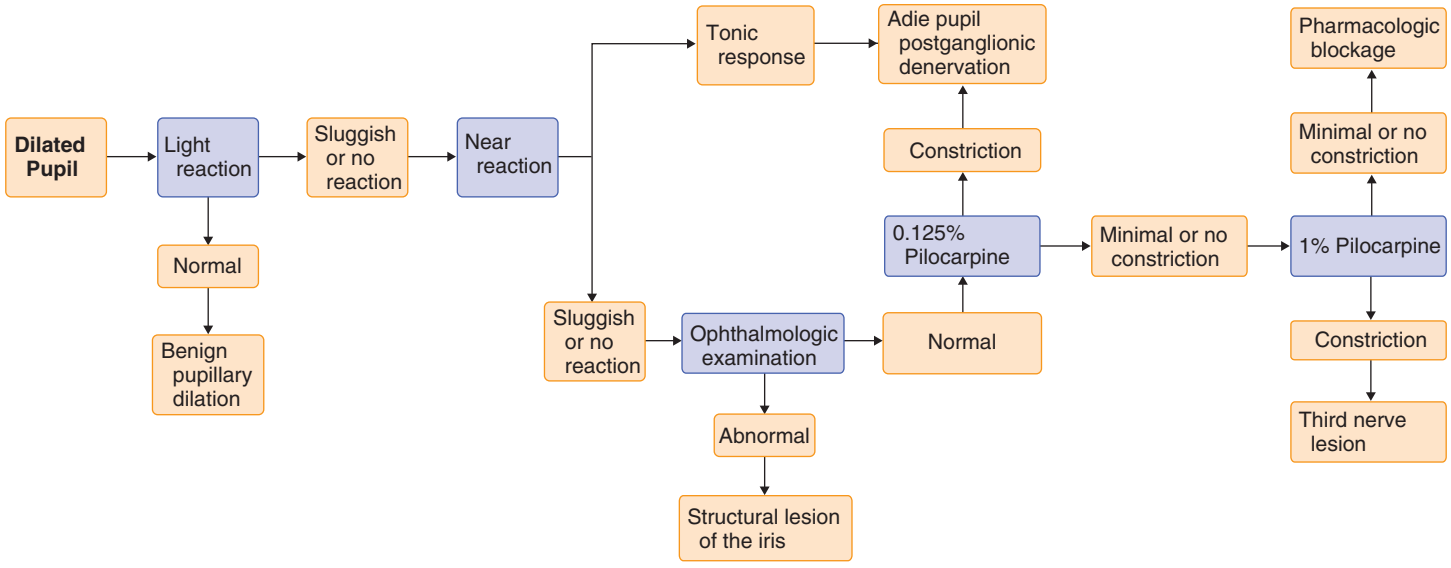

FIGURE 392-4. **Use of pilocarpine to help differentiate among different causes of a dilated pupil.**

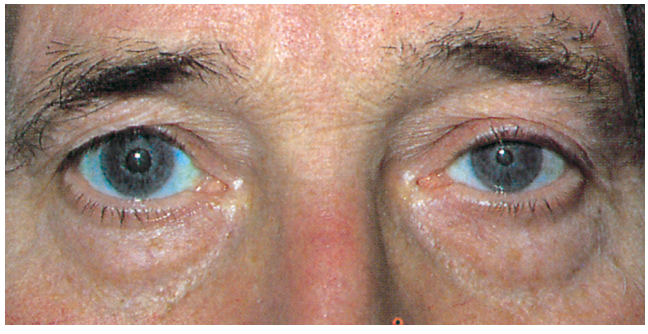

FIGURE 392-5. **Horner syndrome.** Note the characteristic ptosis of the left eye associated with constriction of the pupil (miosis). This patient had syringomyelia, but Horner syndrome has many possible causes. (From Forbes CD, Jackson WF. *Color Atlas and Text of Clinical Medicine*, 3rd ed. London: Mosby; 2003.)

TABLE 392-3 HORNER SYNDROME RESULTS FROM LESIONS IN MULTIPLE LOCATIONS

LOCATION OF LESION	NEURON INVOLVED	TYPE OF LESION	ASSOCIATED SYMPTOMS AND SIGNS
Lateral brain stem	1st order	Infarction, glioma	Vertigo, nystagmus, imbalance, numbness, weakness
Apex of lung	2nd order	Lung cancer, trauma	Often none
Neck	3rd order	Carotid dissection or inflammation	Pain, monocular visual loss, hemiparesis

nasally because of failure of ascending impulses to reach the medial rectus division of the third nerve nucleus. Adduction for convergence is usually relatively maintained.

Supranuclear Pathways

Pathways descending from the frontal eye fields in the frontal lobe through the superior colliculi to the contralateral brain stem regulate rapid voluntary eye movements (*saccades*; E-Table 392-1).[12] Pathways descending from the parieto-occipital and frontal regions to the ipsilateral brain stem subserve slow visual tracking (smooth pursuit—foveal target; optokinetic—full-field target). For the vestibulo-ocular reflex, primary afferent neurons in the inner ear synapse with neurons in the vestibular nuclei, which in turn synapse with appropriate oculomotor neurons to produce compensatory eye movements. The *convergence* center is located in the rostral-dorsal midbrain near the vertical gaze center.

EXAMINATION OF EYE MOVEMENTS

Fixation and gaze holding are tested by having the patient look center, right, left, up, and down. Each position should be held steady and unwavering with the observer carefully documenting abnormal movements or ocular disconjugacies. Each supranuclear oculomotor control system is examined separately. *Saccades* are tested by having the patient alternately fixate on two targets such as the examiner's finger and nose; the speed and accuracy are noted. *Smooth pursuit* is tested by slowly moving a target back and forth and up and down and observing the patient's ability to produce smooth tracking movements. If the target velocity is low, normal subjects should be able to pursue without requiring catch-up saccades. The *vestibulo-ocular reflex* is evaluated with the head-thrust test (Chapter 396). *Convergence* is tested by having the patient follow a target moving from far to near. The degree of convergence depends to some extent on the cooperation of the patient. A clear sign that the patient is attempting to converge is simultaneous pupillary constriction.

COMMON CAUSES OF ABNORMAL OCULOMOTOR CONTROL

Strabismus (Ocular Misalignment)

A comitant (same in all directions of gaze) strabismus present since childhood is usually a benign *congenital disorder*. Latent congenital strabismus can become manifested in adulthood in association with a systemic illness. An acquired skew deviation (vertical displacement of the ocular axes) indicates a lesion within the otolith-ocular pathways (generally the brain stem). Incomitant strabismus can result from restrictive disease of the orbit or from abnormal muscle or oculomotor nerve function. The presence of mechanical restriction is confirmed by the use of forced duction testing (Fig. 392-6; after a topical anesthetic is applied to the eye, the ophthalmologist grasps the muscle insertion with large blunt-toothed forceps. Failure of the eye to deviate fully in the pulled direction implies restriction). Common causes of *orbital restrictive disease* include dysthyroid ophthalmopathy (Chapter 207), orbital pseudotumor, trauma, and orbital mass lesions (Chapter 391). Variable strabismus that increases with fatigue suggests *myasthenia gravis* (Chapter 390). A Tensilon test can usually confirm the diagnosis (see Fig. 392-6). If both restrictive disease and myasthenia gravis (Chapter 390) have been excluded, most patients with incomitant strabismus have processes affecting the oculomotor nuclei, their fascicles, or the cranial nerves themselves. Common causes of an *isolated third nerve palsy* in an adult include aneurysm (Chapter 377), small-vessel occlusive disease (including diabetes mellitus [Chapter 210]), trauma (Chapter 368), and neoplasm. Typically, third nerve lesions secondary to vascular disease spare the pupil. Vascular disease and trauma are by far the most common causes of *isolated trochlear nerve palsy*. The abducens nerve is particularly vulnerable to isolated traumatic involvement because of its long pathway outside the brain stem. Lesions that produce increased intracranial

E-TABLE 392-1 SUPRANUCLEAR OCULOMOTOR CONTROL SYSTEMS

SYSTEM	DESCRIPTION	FUNCTION	KEY ANATOMIC STRUCTURES
Saccade	Fast conjugate voluntary movements	Move the fovea to a new target of interest	Frontal eye field, superior colliculus, pretectum—vertical, pontine—horizontal cerebellar dentate nucleus
Smooth pursuit/ optokinetic	Slow conjugate tracking	Match eye velocity to target velocity	Occipital, parietal, pons, cerebellar flocculus
Vestibulo-ocular	Slow conjugate compensatory eye movements	Keep eyes stable when head moves	Pontomedullary region
Vergence	Slow disconjugate tracking	Focus on near and far targets	Pretectum, tectum

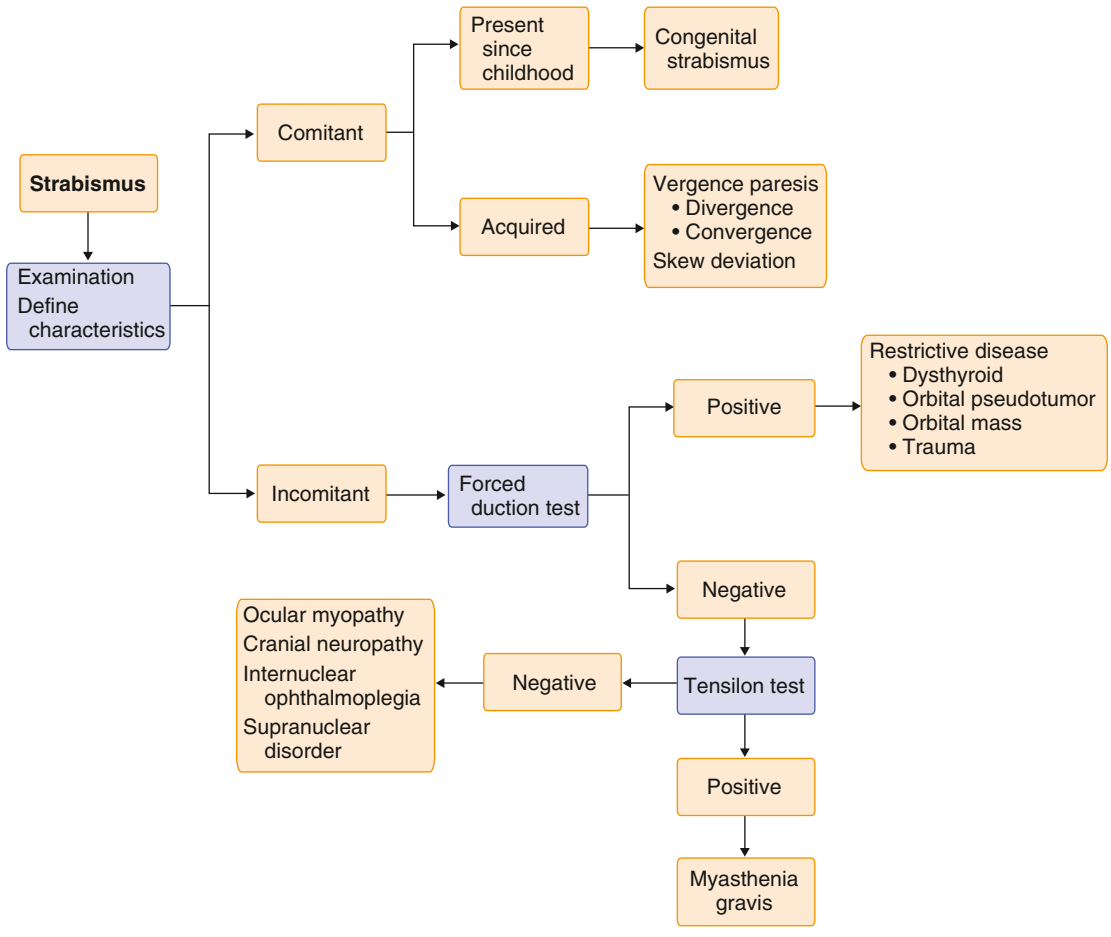

FIGURE 392-6. **Diagnostic tests that help differentiate among common causes of strabismus.**

pressure (Chapter 175) can lead to abducens nerve dysfunction regardless of the location and produce a "false localizing sign." Other common causes of *isolated sixth nerve palsy* are vascular disease (Chapter 376), trauma (Chapter 368), and neoplasm. Progressive external ophthalmoplegia, with worsening bilateral ptosis and diffuse reduction in ocular motility, is a manifestation of a mitochondrial myopathy.[13]

Internuclear Ophthalmoplegia

Internuclear ophthalmoplegia (Fig. 392-7) may be unilateral or bilateral, partial or complete, depending on the location of the lesion and the degree of damage to the MLF. *Demyelinating* and small *vascular lesions* are the most common causes of unilateral internuclear ophthalmoplegia unaccompanied by other ocular palsies or brain stem signs. Myasthenia gravis (Chapter 390) can produce an ophthalmoparesis resembling internuclear ophthalmoplegia as a result of greater involvement of the medial rectus than the lateral rectus. Demyelinating diseases (Chapter 380) are the most common causes of bilateral internuclear ophthalmoplegia involvement.

Disorders of Conjugate Gaze

Acute lesions involving a frontal eye field (e.g., hemorrhage or infarction [Chapters 376 and 377]) result in a transient inability to direct the eyes contralaterally. Vertical eye movements are not affected by unilateral lesions. Bilateral damage to the frontal eye fields or their descending pathways may produce an inability to move the eyes voluntarily (horizontally or vertically) despite preserved reflex eye movements, a condition called *oculomotor apraxia*. Lesions involving the horizontal gaze center in the pons produce an ipsilateral paralysis of conjugate gaze and tonic deviation of the eyes to the contralateral side (Chapter 391). Lesions of the pretectum selectively impair vertical gaze, with the vertical upgaze center being slightly rostral and dorsal to the vertical downgaze center. Patients with the *dorsal midbrain syndrome* (Parinaud syndrome) have a conjugate upgaze paresis. When they attempt to make upward saccades, convergence retraction nystagmus develops. As noted earlier, impaired convergence and light-near dissociation of the pupillary reflexes are also part of the syndrome. The most common causes of the dorsal midbrain syndrome include tumors of the pineal gland (Chapter 204; dysgerminomas), hydrocephalus (Chapter 175), and localized infarction.

Nystagmus

Spontaneous nystagmus can be congenital or acquired.[14] *Congenital nystagmus* typically has a high frequency and variable waveform (usually pendular) and is highly fixation dependent. It generally remains horizontal in all positions of gaze. The lifelong history and lack of symptoms confirm the diagnosis. Spontaneous nystagmus resulting from a *peripheral vestibular* lesion (i.e., in the labyrinth or vestibular nerve) usually has combined horizontal and torsional components (Table 392-4). The nystagmus resolves within a few days of the acute lesion. Acquired persistent spontaneous nystagmus indicates a lesion in the brain stem or cerebellum, or both. The latter is often purely vertical, horizontal, or torsional. Spontaneous *downbeat nystagmus*[15] is commonly seen with lesions of the cerebellum or cervicomedullary junction (e.g., Arnold-Chiari malformation [Chapter 385]).

Gaze-evoked nystagmus is always in the direction of gaze and is usually present with and without fixation. It is most commonly produced by the ingestion of *drugs* such as phenobarbital, phenytoin, alcohol, and diazepam (Chapter 96). It can also occur in patients with such varied conditions as myasthenia gravis (Chapter 390), multiple sclerosis (Chapter 380), and cerebellar atrophy. Asymmetrical horizontal gaze-evoked nystagmus is caused by a structural brain stem or cerebellar lesion (particularly at the cerebellopontine angle), with the lesion generally being on the side of the larger-amplitude nystagmus (Bruns nystagmus). *Rebound nystagmus* is a type of gaze-evoked nystagmus that either disappears or reverses direction as the eccentric gaze position is held. When the eyes are returned to the primary position, nystagmus occurs in the direction of the return saccade. Rebound nystagmus occurs in patients with cerebellar atrophy and focal structural lesions of the cerebellum; it is the only variety of nystagmus thought to be specific for cerebellar involvement. *Disconjugate gaze–evoked nystagmus* most commonly results from lesions of the MLF (see earlier discussion), but it can also occur with other lesions

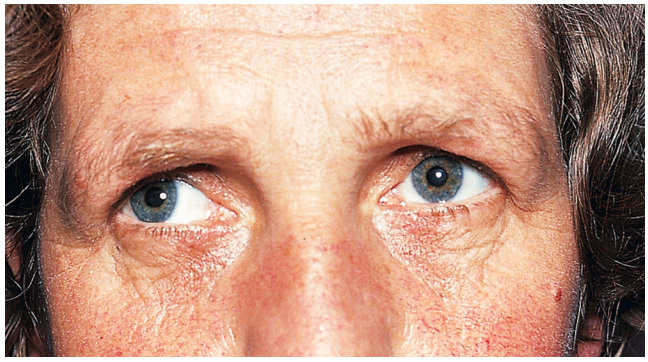

FIGURE 392-7. Internuclear ophthalmoplegia may be an initial feature of brain stem involvement in multiple sclerosis. On lateral gaze to the right, adduction of the left eye is incomplete. On convergence, eye movement was normal. The lesion is in the left medial longitudinal bundle, between the nucleus in the pons and the third nerve nucleus on the opposite side. (From Forbes CD, Jackson WF. *Color Atlas and Text of Clinical Medicine*, 3rd ed. London: Mosby; 2003.)

TABLE 392-4 KEY DISTINGUISHING FEATURES OF PERIPHERAL AND CENTRAL TYPES OF SPONTANEOUS AND POSITIONAL NYSTAGMUS

TYPE OF NYSTAGMUS	PERIPHERAL (END ORGAN AND NERVE)	CENTRAL (BRAIN STEM AND CEREBELLUM)
Spontaneous	Unidirectional, fast phase away from the lesion, combined horizontal torsional, inhibited with fixation	Bidirectional or unidirectional; often pure horizontal, vertical, or torsional; *not* inhibited with fixation
Static positional	Fixed or changing direction, inhibited with fixation	Fixed or changing direction, *not* inhibited with fixation
Paroxysmal positional	Vertical-torsional, occasionally horizontal-torsional, vertigo prominent, fatigability, latency	Often pure vertical, vertigo less prominent, no latency, nonfatigable

of the brain stem involving the oculomotor nuclei. Positional nystagmus is discussed in Chapter 396.

Other Ocular Oscillations

Ocular bobbing consists of a fast conjugate downward eye movement followed by a slow return to the primary position. The phenomenon accompanies severe displacement or destruction of the pons or, less often, metabolic central nervous system depression. *Ocular myoclonus* consists of continuous rhythmic pendular oscillations, most often vertical, at a rate of one to three beats per second; it often accompanies palatal myoclonus and has a similar pathogenesis. *Square-wave jerks* and *ocular flutter* consist of brief, intermittent, horizontal oscillations (back-to-back saccades) arising from the primary gaze position. These types of ocular oscillation are most commonly seen with cerebellar disease but can also accompany more diffuse central nervous system disorders. *Opsoclonus* consists of rapid, chaotic, conjugate, repetitive saccadic eye movements (dancing eyes). Opsoclonus accompanies the cerebellar dysfunction, with the most chaotic varieties associated with brain stem encephalitis or the remote effects of systemic neoplasm, especially neuroblastoma in children. *Ocular dysmetria* refers to overshooting and undershooting of saccadic eye movements, often followed by multiple attempts at refixation. It reflects cerebellar dysfunction.

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393 DISEASES OF THE MOUTH AND SALIVARY GLANDS

RICHARD C. JORDAN

More than 200 primary lesions or diseases occur in the oral mucosa, gingiva, teeth, jaws, and minor or major salivary glands. In addition, secondary abnormalities of the oral mucosa or salivary glands can be caused by systemic diseases or drugs. The most common or important of these diseases may be observed during physical examination.[1]

ORAL MUCOSAL DISEASES

ACUTE ULCERATIONS

Painful, short-lasting ulcerations can be caused by mechanical trauma, immunologic mechanisms, or bacterial or viral infections (Table 393-1). Soon after formation, oral mucosal ulcers become covered by a white to gray pseudomembrane, analogous to the yellow scabs on dry skin. Pseudomembrane-covered ulcers are distinguished from white hyperkeratotic lesions by their clinical features: pseudomembranes are removeable and painful, and they have a flat surface with an erythematous periphery. Traumatic ulcers are characteristically located on the tongue or inside the cheeks or lips close to the chewing surfaces of the teeth.

APHTHOUS STOMATITIS ("CANKER SORES")

These idiopathic recurrent ulcers are common, afflicting up to 20% of the population and can be found on nonkeratinized mucosa: the buccal mucosa, ventral tongue, lips, and alveolar mucosa (Fig. 393-1). They form well-defined, usually shallow, circular ulcers that may be single or multiple. There are three clinical forms: (1) minor, which are flat and less than 0.5 cm in diameter and last 5 to 10 days; (2) major, which have raised borders, are deeper, solitary, greater than 0.5 cm, and often last for weeks or months; and (3) herpetiform, which are usually clusters of very small ulcers that resemble recurrent herpetic lesions but are not preceded by vesicles and do not occur on keratinized mucosa. A viral or bacterial pathogenesis has not been established for any of these forms. Lesions clinically indistinguishable from minor aphthae occur in Behçet syndrome (Chapter 249). Aphthae are rarely associated with anemias or gluten-sensitive enteropathy (Chapter 126) and may become more frequent and severe in association with human immunodeficiency virus (HIV) infection (Table 393-2).

Minor or herpetiform aphthous ulcers are generally self-limiting within a week or two and may not require treatment unless they occur frequently.[2] Topical steroids, such as fluocinonide gel or ointment, can reduce the severity and duration of the lesions only if applied with prodromal symptoms or earliest signs. A freshly prepared suspension of tetracycline or doxycycline in water used as a mouth rinse at the onset of symptoms also reduces the severity and duration of disease.[A1] Unfortunately, none of these treatments prevent recurrent ulcers. Major aphthae usually require treatment with prednisone (e.g., 40 mg daily for 3 days); failure to respond significantly should prompt incisional biopsy to exclude neoplasia. Unfortunately, no treatment will cure a patient of recurrent aphthous stomatitis.[A2] Laser therapy may promote healing and pain relief in patients with recurrent aphthous stomatitis, although this approach has not been proven in clinical trials.

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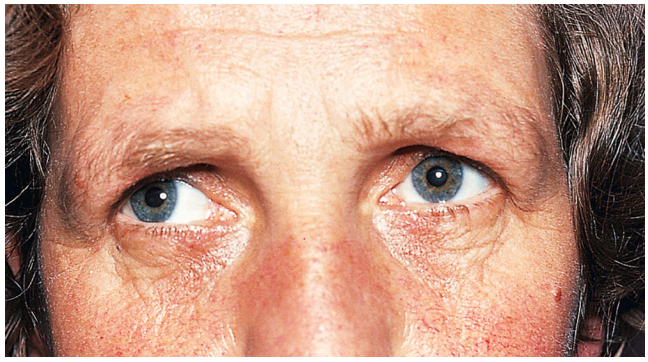

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393 DISEASES OF THE MOUTH AND SALIVARY GLANDS

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More than 200 primary lesions or diseases occur in the oral mucosa, gingiva, teeth, jaws, and minor or major salivary glands. In addition, secondary abnormalities of the oral mucosa or salivary glands can be caused by systemic diseases or drugs. The most common or important of these diseases may be observed during physical examination.[1]

ORAL MUCOSAL DISEASES

ACUTE ULCERATIONS

Painful, short-lasting ulcerations can be caused by mechanical trauma, immunologic mechanisms, or bacterial or viral infections (Table 393-1). Soon after formation, oral mucosal ulcers become covered by a white to gray pseudomembrane, analogous to the yellow scabs on dry skin. Pseudomembrane-covered ulcers are distinguished from white hyperkeratotic lesions by their clinical features: pseudomembranes are removeable and painful, and they have a flat surface with an erythematous periphery. Traumatic ulcers are characteristically located on the tongue or inside the cheeks or lips close to the chewing surfaces of the teeth.

APHTHOUS STOMATITIS ("CANKER SORES")

These idiopathic recurrent ulcers are common, afflicting up to 20% of the population and can be found on nonkeratinized mucosa: the buccal mucosa, ventral tongue, lips, and alveolar mucosa (Fig. 393-1). They form well-defined, usually shallow, circular ulcers that may be single or multiple. There are three clinical forms: (1) minor, which are flat and less than 0.5 cm in diameter and last 5 to 10 days; (2) major, which have raised borders, are deeper, solitary, greater than 0.5 cm, and often last for weeks or months; and (3) herpetiform, which are usually clusters of very small ulcers that resemble recurrent herpetic lesions but are not preceded by vesicles and do not occur on keratinized mucosa. A viral or bacterial pathogenesis has not been established for any of these forms. Lesions clinically indistinguishable from minor aphthae occur in Behçet syndrome (Chapter 249). Aphthae are rarely associated with anemias or gluten-sensitive enteropathy (Chapter 126) and may become more frequent and severe in association with human immunodeficiency virus (HIV) infection (Table 393-2).

Minor or herpetiform aphthous ulcers are generally self-limiting within a week or two and may not require treatment unless they occur frequently.[2] Topical steroids, such as fluocinonide gel or ointment, can reduce the severity and duration of the lesions only if applied with prodromal symptoms or earliest signs. A freshly prepared suspension of tetracycline or doxycycline in water used as a mouth rinse at the onset of symptoms also reduces the severity and duration of disease.[A1] Unfortunately, none of these treatments prevent recurrent ulcers. Major aphthae usually require treatment with prednisone (e.g., 40 mg daily for 3 days); failure to respond significantly should prompt incisional biopsy to exclude neoplasia. Unfortunately, no treatment will cure a patient of recurrent aphthous stomatitis.[A2] Laser therapy may promote healing and pain relief in patients with recurrent aphthous stomatitis, although this approach has not been proven in clinical trials.

ABSTRACT

More than 200 primary lesions or diseases occur in the oral mucosa, gingiva, teeth, jaws, and minor or major salivary glands. In addition, secondary abnormalities of the oral mucosa or salivary glands can be caused by systemic diseases or drugs. The most common or important of these diseases may be observed during physical examination.

KEYWORDS

oral cavity
ulcers
pigmented lesions
cancer
salivary glands

TABLE 393-1 ORAL MUCOSAL ULCERS

TYPE/DISEASE	CLINICAL FEATURES
INSIDIOUS ONSET, CHRONIC	
Multiple or Bilateral	*Shallow ulcers on mucosa, skin, or both*
Pemphigus vulgaris	Begin as fragile, short-duration blisters
Mucous membrane pemphigoid	Begin as short-duration blisters
Lichen planus	Bilaterally symmetrical lesions (white lacelike with or without erythema)
Lupus erythematosus	Asymmetrical lesions, with or without systemic lupus (white with or without erythema)
Lichenoid drug reaction	Variable lesions; often unilateral; history of medication use
Epidermolysis bullosa	Begin as blisters; lifelong history
Solitary	*Indurated or cratered ulcers*
Squamous cell carcinoma	Most common on tongue, oropharynx, lip, mouth floor
Adenocarcinomas, various	Salivary tumors most common; on palate, cheeks, mouth floor
Tuberculosis	Usually painful
Actinomycosis	Often associated with draining sinus tract
Deep mycoses (particularly histoplasmosis, coccidioidomycosis)	Associated with systemic infection; can resemble carcinoma clinically
Midline (lethal) granuloma	Associated with necrosis, may perforate palate; usually an NK/T-cell lymphoma or granulomatosis with polyangiitis
Bony osteonecrosis	Associated with prior cancer, radiation therapy or bisphosphonate/antiresorptive agent use
ACUTE ONSET, OFTEN SELF-LIMITING	
Clusters	*Usually small and shallow ulcers; history of blisters*
Primary herpes simplex	Any oral mucosal site, associated with fever, malaise; often widespread
Recurrent herpes simplex	Unilateral, only on keratinized mucosa (gingiva, hard palate, or lip)
Varicella-zoster	Unilateral lesions along neural distribution
Herpangina	Usually bilateral on soft palate
Measles (rubeola)	Precede skin rash; associated with fever, malaise
Solitary or Multiple (without Clustering)	*Variable, usually without history of blisters*
Traumatic ulcers	Usually solitary; history of trauma
Aphthous stomatitis (canker sores)	Circular, often multiple, shallow, only on nonkeratinized mucosa
Behçet syndrome	Oral lesions similar to recurrent aphthae
Erythema multiforme	Multiple lesions, often involve lower labial mucosa with hemorrhagic crust
Drug reaction	Appropriate history of drug use
Necrotizing sialometaplasia	Deep ulcers, usually on palate; can be associated with trauma
Primary syphilis	Solitary, indurated, painless, any site
Gonorrhea	Painful, surrounded by erythema, usually in oropharynx

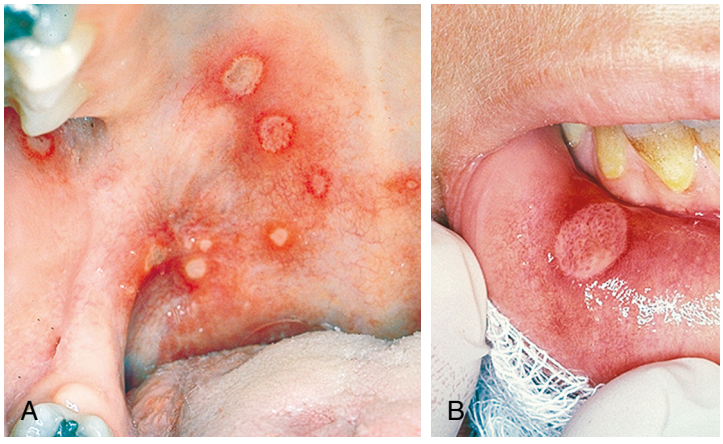

FIGURE 393-1. Aphthous ulcers. A, A cluster of minor aphthae on the soft palate and buccal mucosa, present about 1 week. **B,** A major aphthous ulcer on the labial mucosa, present about 3 weeks.

TABLE 393-2 ORAL LESIONS ASSOCIATED WITH HUMAN IMMUNODEFICIENCY VIRUS INFECTION

Kaposi sarcoma (human herpesvirus type 8)
Candidiasis (pseudomembranous, hyperplastic, and/or erythematous lesions)
Other opportunistic fungal infections (e.g., histoplasmosis or coccidioidomycosis)
Aphthous ulcers (increased frequency, duration, or size)
Virus-associated epithelial hyperplasias Hairy leukoplakia (Epstein-Barr virus) Oral wart (human papillomavirus type 6, 11, and other types) Focal (multifocal) epithelial hyperplasia (Heck disease) (human papillomavirus types 13 and 32) Condyloma acuminatum (human papillomavirus types 6 and 11)
Herpes zoster (varicella-zoster virus)
Exaggerated forms of gingivitis and inflammatory periodontal disease
Decreased salivary gland function
Parotid gland enlargement (lymphoepithelial lesion)
Non-Hodgkin lymphoma (e.g., plasmablastic lymphoma)

VIRAL ULCERS

Several types of virus (most commonly herpes simplex type 1; Chapter 345) cause multiple oral mucosal vesicles that last only a few hours or days and then become irregular shallow ulcers. In the initial infection by herpes simplex virus, usually in children, numerous vesicles may appear on any oral mucosal site (called primary herpetic gingivostomatitis), accompanied by malaise, headache, fever, and cervical lymphadenopathy. Patients previously exposed to this virus may develop recurrent (secondary) lesions that appear as clusters of small vesicles, most commonly on the lips (herpes labialis) and less commonly on the keratinized mucosa of the gingiva or hard palate (Fig. 393-2). Such lesions contain live virus and tend to recur at the same site but less frequently with increasing age.

Although widespread vaccination has reduced the incidence, similar mucosal vesicles may also accompany the initial infection by the varicella-zoster virus in children with chickenpox (Chapter 346), and unilateral lesions may occur if herpes zoster (Chapter 346) affects branches of the trigeminal nerve. Uncommonly, oral mucosal ulcers may be caused by different types of coxsackievirus (Chapter 349), appearing on any oral site in hand-foot-and-mouth disease or on the soft palate or pharynx in herpangina. After infection by the measles (rubeola) virus, small ulcers (Koplik spots; see Fig. 338-2 in Chapter 338) may form on the inside of the cheeks 1 to 2 days before development of the skin rash (Chapter 338). Patients with severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection (Chapter 336) may have a variety of oral manifestations, including erosions, ulcers, bullae, vesicles, and pustules.[3]

MUCOSITIS ASSOCIATED WITH CANCER TREATMENT

Patients who receive radiation therapy for cancers where the radiation fields include the oral cavity are at risk for the development of oral mucositis (Chapters 18 and 176). Oral mucositis is also common in patients who receive intensive chemotherapy for malignancies, such as patients who have leukemia (Chapters 168 to 170) or undergo hematopoietic stem cell transplantation (Chapter 163). Oral mucositis also occurs in about 20 to 40% of patients treated with chemotherapy for other solid tumors. Risk factors include smoking, poor oral hygiene, a lower pretreatment neutrophil count, and the depth of treatment-induced neutropenia. Agents with higher risks include anti-angiogenic tyrosine kinase inhibitors (e.g., axitinib, cabozantinib, pazopanib, sorafenib, and sunitinib) and mammalian target of rapamycin (mTOR) inhibitors (e.g., everolimus), as well as etoposide, fluorouracil, and methotrexate. The pathobiology is cytotoxic damage to rapidly dividing cells, predominantly basal cells of the mucosal epithelium, by chemotherapy and radiation.

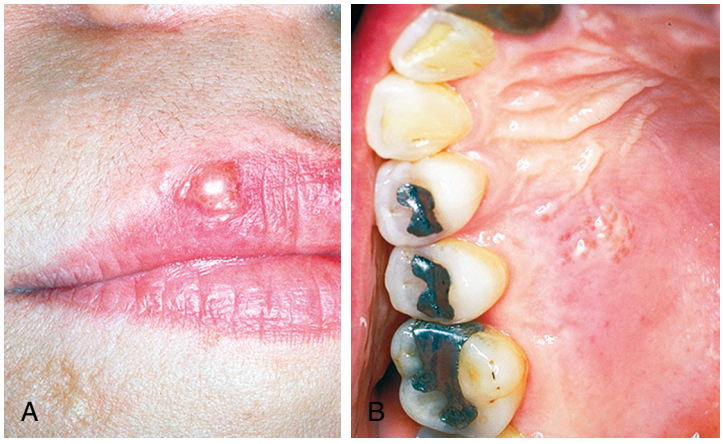

FIGURE 393-2. Clusters of recurrent herpes simplex vesicles. A, On the lip; B, on the hard palate, both present 2 to 3 days, in different patients.

Patients can develop pain and sensitivity to irritating substances, which can be avoided by the patient. Mild mucositis may be difficult to confirm on examination, but oral ulceration is the hallmark of the condition. Bleeding occurs with more severe mucositis. A complete blood count with differential is helpful, and the patient should also be assessed for any signs of dehydration (Chapter 7).

For patients with mild symptoms, a bland mouthrinse (e.g., normal saline or sodium bicarbonate in water) as a "swish and spit" can be symptomatically helpful. For moderate pain that does not interfere with oral intake, patients should avoid hard-consistency, rough, or sharp foods; alcohol; and smoking. A 2% oral lidocaine solution can be added to a normal saline or sodium bicarbonate mouthrinse. For more severe mucositis, topical agents include a doxepin mouthrinse and "Magic" mouthwashes. For more severe pain that interferes with eating, dehydration, neutropenia, or suspected systemic infection, expert consultation and typically hospitalization must be considered. For radiation-induced mucositis, a diphenhydramine/lidocaine/antacid mouthwash can reduce the incidence and severity of mucositis, and dexamethasone mouthwash can provide analogous benefits for patients receiving mTOR inhibitors.[4]

ERYTHEMA MULTIFORME

In this potentially recurrent disease, painful oral mucosal ulcerations develop rapidly, with or without target-like skin lesions. It may be associated with a previous viral infection or hypersensitivity to a food or drug. The affected patients, usually young adults with minimal or no systemic symptoms, have irregularly shaped ulcers that can be small and few or involve large areas of the mucosa; the most common sites are the lower labial mucosa and vermilion. On the vermilion of the lips, bilateral hemorrhagic crusting is a characteristic finding. These lesions can be distinguished from those of primary herpes by the absence of oral vesicles and systemic symptoms or by the presence of characteristic skin lesions (Chapter 406). A major variant of this disease is Stevens-Johnson syndrome, in which ocular, genital, and other lesions may accompany the oral lesions.

VENEREAL INFECTIONS

Primary syphilis may arise as a solitary, indurated, painless ulcer on the oral mucosa that resolves spontaneously in 4 to 6 weeks (Chapter 295). Uncommonly, *Neisseria gonorrhoeae* (Chapter 275) may cause oral ulcers, usually in the soft palate and pharynx, which may be confused with oral ulcers of other causes.

ORAL SQUAMOUS CELL CARCINOMA

About 4% of all cancers occur in the mouth, most commonly as squamous cell carcinomas of the mucosal epithelium (Chapter 176). Oral carcinoma occurs usually in the fifth decade or beyond, in men twice as frequently as in women, and is associated with long-term use of tobacco in more than 80% of cases.

Oral carcinoma usually arises as a chronic, indurated, cratered ulcer, but white (leukoplakia) and especially red (erythroplakia) macular lesions (Table 393-3; Fig. 393-3) frequently exhibit premalignant epithelial dysplasia or early carcinoma. Oral carcinomas spread to cervical lymph nodes. The overall 5-year survival rate is about 50%, but early treatment of small, localized lesions can lead to survival rates as high as 90%. Nevertheless, current guidelines find insufficient evidence to recommend for or against screening in asymptomatic adults.

TABLE 393-3 WHITE AND RED/BLUE ORAL MUCOSAL LESIONS

WHITE LESIONS (PLAQUES)
Squamous cell carcinoma (early)
Frictional keratosis (buccal mucosa at dental occlusal line)
Leukoplakia (with or without dysplasia)
Smokeless tobacco–associated lesions
Nicotine stomatitis (palate)
Lichen planus (reticular and plaque types)
Pseudomembranous candidiasis (thrush)
Hyperplastic candidiasis (candidal leukoplakia)
Hairy leukoplakia (immunosuppression related, often with HIV infection; usually on lateral tongue)
Geographic tongue (benign migratory glossitis)
Mucous patch or condyloma latum of secondary syphilis
Pseudomembrane-covered ulcers (see Table 393-1)
RED OR BLUE LESIONS (MACULAR, MACULOPAPULAR)
Squamous cell carcinoma (early)
Erythroplakia (epithelial dysplasia)
Erythematous (atrophic) candidiasis
Median rhomboid glossitis
Mucocutaneous diseases (see Table 393-1)
Angular cheilitis
Telangiectasias and purpuras (red to blue)
Kaposi sarcoma (blue to purple)

HIV = human immunodeficiency virus.

FIGURE 393-3. Squamous cell carcinoma. Biopsy of this area of erythroplakia with slight induration in the anterior mouth floor exhibited squamous cell carcinoma.

Over the past two decades, there has been a rapid increase in a type of head and neck cancer associated with human papillomavirus (HPV) type 16 (Chapter 344).[5] Occurring primarily at the base of the tongue and tonsillar region of the oropharynx, this form of nonkeratinizing squamous cell carcinoma is seen in younger patients who typically lack the history of smoking and alcohol. Other features of the disease include advanced stage at presentation and its favorable response to radiation and chemotherapy (Chapter 176). In the absence of concurrent tobacco use, the 5-year survival rate is over 80%.

OTHER CHRONIC ULCERATIONS

Prescription drugs that can be responsible for chronic oral mucosal ulcerations include barbiturates, β-blockers, nonsteroidal anti-inflammatory drugs, allopurinol, isoniazid, and many others. Several mucocutaneous diseases can cause chronic multifocal oral mucosal lesions composed of ill-defined areas of erythema and ulceration. They are among the most difficult oral lesions to diagnose and are discussed later with the red lesions (see Table 393-3). Several microbial infections or underlying osteonecrosis (e.g., with the use of bisphosphonates and other antiresorptive medications) can lead to indurated, chronic oral mucosal ulcerations with moderate symptoms (see Table 393-1).

WHITE LESIONS

White plaques are commonly found in the mouth and, like ulcerations, have a wide variety of causes and outcomes (see Table 393-3). The clinical descriptor term *leukoplakia* applies to a white plaque that does not rub off and whose appearance does not indicate another disease. Leukoplakia can occur in any

area of the mouth and usually exhibits benign hyperkeratosis on biopsy.[6] On long-term follow-up, 2 to 6% of these lesions undergo malignant transformation into squamous cell carcinoma. Leukoplakias that are shown on biopsy to contain epithelial dysplasia have a higher rate of transformation to cancer than those that do not, thereby emphasizing the important role of biopsy for these lesions. Areas of leukoplakia with a corrugated surface or mixed with areas of erythema are often found in the lower labial or buccal vestibule of patients who use smokeless tobacco.

Frictional keratoses are often found posterior to the lower molar teeth as irregular white plaques and on the buccal mucosa as white lines adjacent to the dental occlusion. Unlike leukoplakia, these lesions rarely become malignant.

LICHEN PLANUS

Oral lesions of lichen planus (Chapter 405) occur in about 1% of the population, usually as multiple, bilaterally symmetrical reticular (lattice-like) white lesions, with or without adjacent areas of erythema (atrophy or erosion) or irregular ulcers (Fig. 393-4). The presence of mucosal atrophy, erosion, or ulceration usually causes pain and sensitivity to certain foods. Most lesions can be adequately controlled by topical application of fluocinonide or clobetasol gel or ointment (0.05%, three times a day) for periods of several weeks,[A3] although recurrence is common.

ORAL CANDIDIASIS

This common fungal disease (Chapter 310) has three clinical forms: pseudomembranous (thrush), erythematous (atrophic), and hyperplastic (candidal leukoplakia).[7] Pseudomembranous candidiasis, usually of relatively short duration, occurs on any site and consists of white fungal plaques that can be rubbed off, leaving a red or bleeding base. Lesions of hyperplastic candidiasis are white, have fungal hyphae within the surface layers of hyperkeratotic epithelium, do not rub off, and are most often found on the anterior buccal mucosa or on the tongue. Erythematous candidiasis is discussed under Red Lesions. All forms of oral candidiasis represent overgrowth or superficial infection by *Candida* species from the oral flora, induced by a variety of causes, including suppression of bacterial flora by systemic antibiotics, chronic salivary dysfunction, uncontrolled diabetes mellitus or anemia, and immunosuppression (especially in HIV-infected patients). The condition can be managed with topical or systemic antifungal agents, although acquired resistance to fluconazole (discussed later) therapy can occur.

HAIRY LEUKOPLAKIA

The lesion of hairy leukoplakia, which is caused by Epstein-Barr virus, is a white plaque occurring most frequently on the lateral surfaces of the tongue bilaterally in immunosuppressed persons, usually but not always HIV infected (Fig. 393-5). Hairy leukoplakia also is purported to occur rarely in immunocompetent patients.[8] *Candida* may be present in the surface layers, but the lesion is not eliminated by effective antifungal therapy. The diagnosis of hairy leukoplakia by biopsy should raise suspicion of HIV infection or other forms of systemic or local immunosuppression.

GEOGRAPHIC TONGUE

Also called *benign migratory glossitis*, this common, benign, idiopathic condition affects the dorsal tongue of about 2% of the population. It is characterized by well-defined areas of atrophied filiform papillae bordered by arcs of normal or hyperplastic filiform papillae and by gradual changes in the location of these lesions over time (Fig. 393-6). Lesions that appear to be geographic tongue on other oral sites should prompt consideration of concurrent inflammatory bowel disease (Chapter 127). Treatment is usually ineffective and not necessary.

SECONDARY SYPHILIS

Secondary syphilis may manifest as a well-defined white plaque on the labial or palatal mucosa, called *condyloma latum* (or "split papule," because of its lobulated periphery), or as a mucous patch.

RED LESIONS

Solitary red macules or plaques (*erythroplakia*) are less common in the mouth than white lesions but should be viewed with concern because they may exhibit premalignant dysplasia, carcinoma in situ, or squamous cell carcinoma (see Table 393-3 and Fig. 393-3). One exception is a red macule occurring in the midline of the posterior dorsal tongue, called *median rhomboid glossitis*, which is uniformly benign and usually associated with localized overgrowth of *Candida* species.

ERYTHEMATOUS (ATROPHIC) ORAL CANDIDIASIS

Erythematous (atrophic) oral candidiasis is a chronic condition characterized by erythema and atrophy of the filiform papillae on the dorsal tongue or by

FIGURE 393-5. Hairy leukoplakia. These white plaques on the lateral border of the tongue were the first visible sign of human immunodeficiency virus infection.

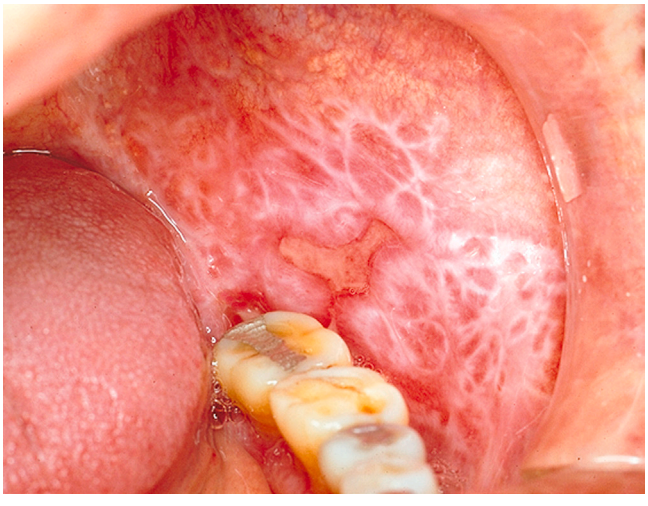

FIGURE 393-4. Lichen planus. A similar-appearing lesion is also present on the right buccal mucosa. Note central pseudomembrane-covered shallow ulceration.

FIGURE 393-6. Geographic tongue. The distribution of these changes on the dorsal tongue may change over time, but they are asymptomatic and diagnosed by their characteristic appearance.

patchy, ill-defined erythema on the palate, tongue, or buccal mucosa (Fig. 393-7). It is usually accompanied by symptoms of oral mucosal burning and sensitivity to spicy foods. It occurs most commonly in patients with chronic salivary hypofunction (e.g., Sjögren syndrome or anticholinergic drug effects), but it also occurs in patients who wear removable dentures infected with *Candida*, in whom mucosal erythema is confined to the denture-bearing area.

For acute or chronic oral candidal infections, systemic or topical antifungal drugs are necessary to resolve the associated lesions. In patients who have clinically apparent salivary production, fluconazole (200 mg on the first day, then 100 mg daily for 2 weeks) is the drug of choice. However, systemic antifungal drugs may not be effective in patients who have severe salivary hypofunction and insufficient saliva to convey the drug from the blood stream to oral mucosa. In such patients, with remaining natural teeth, *oral* antifungal preparations (troches or pastilles), all of which contain cariogenic amounts of sucrose or glucose, *must not be used* to avoid enhancing dental caries. Instead, slow oral dissolution (15 to 20 minutes for 2 weeks) of vaginal nystatin tablets (twice daily) or miconazole tablets (50 mg daily), which contain little or no caries-supporting carbohydrates, is safe and effective; xerostomic patients usually need frequent sips of water to aid in dissolving the tablets. Effective topical or systemic treatment significantly improves oral symptoms. Treatment of denture-associated candidiasis requires that the denture be effectively disinfected and fit well.

The treatment end point is reached when mucosal burning symptoms cease, the patient can again tolerate acidic or spicy foods, and filiform papillae on the dorsal tongue have returned to normal; this recovery takes 2 to 12 weeks, depending on the patient's salivary production and treatment compliance. Recurrence is common in patients with chronic salivary hypofunction or immunosuppression, which necessitates recurring or long-term treatment using a noncariogenic topical antifungal drug that provides a sufficient duration of oral mucosal contact (e.g., nystatin or miconazole tablets).

ANGULAR CHEILITIS

Erythema or crusting of the labial angles is usually caused by *Candida* species (see Fig. 393-7) and is usually associated with intraoral candidiasis. In such cases, topical treatment of the angular cheilitis with clotrimazole (0.75% cream) should be accompanied by intraoral or systemic antifungal treatment, as described previously.

MUCOCUTANEOUS DISEASES

The mucocutaneous diseases of pemphigus vulgaris, mucous membrane pemphigoid, atrophic or erosive lichen planus, and lupus erythematosus can cause similar-appearing oral lesions. Their diagnosis requires examination of a biopsy specimen by routine histopathology and by direct immunofluorescence to identify characteristic deposits of various inflammatory proteins.

The first lesions of pemphigus vulgaris are usually oral mucosal vesicles that rapidly rupture, leaving painful erosions or ulcerations. These are followed by development of skin lesions. Rarely, the lesions remain confined to the mouth (Chapter 406).

Lesions of mucous membrane (cicatricial) pemphigoid are usually confined to the oral mucosa or conjunctivae and occur in patients older than 60 years. They begin as vesicles that quickly rupture, leaving ulcers that are chronic but only moderately symptomatic. Use of topical fluocinonide or clobetasol (0.05% gel or ointment, three times a day, 4 to 12 weeks) for several months, as described for lichen planus, is sometimes sufficient to treat the oral lesions, but most patients also need systemic treatment (Chapter 406). Eye care is also important to prevent ocular damage.

Oral mucosal lesions of lupus may occur in patients who have systemic lupus erythematosus (SLE), in patients who do not have SLE but later develop that disease, or in patients who do not develop SLE (Chapter 245). In this last group, the lesions of mucosal lupus may be analogous to the skin lesions of chronic discoid lupus. They take the form of ulcers with surrounding, radiating hyperkeratotic lines associated with erythema, often resembling lichen planus, but unlike lichen planus are usually solitary or bilaterally asymmetrical. They can be controlled by topical fluocinonide (0.05%, three times a day, 2 to 4 weeks) or intralesional triamcinolone suspension (5 mg/mL), or respond to systemic treatment of SLE.

PIGMENTATIONS

Brown or gray-black macules on the oral mucosa are relatively common and range from benign to highly malignant. They may be caused by localized increase in melanin production, proliferation of melanin-producing cells, or deposition of local or systemically distributed pigmented substances (Table 393-4). Mucosal pigmentation may occur after long-term administration of hydroxychloroquine, minocycline, ketoconazole, methyldopa, or cyclophosphamide. Malignant melanomas can occur at any oral mucosal site, but about 85% develop on the hard palatal mucosa or gingiva, or both. Diagnosis of any of these conditions is established by biopsy and knowledge of relevant underlying conditions.

Lesions of Kaposi sarcoma associated with HIV infection often appear first on the oral mucosa, especially the palate. They begin as macules with a blue or purple color, at which time they must be distinguished from purpura. Later, they spread radially and expand vertically (Chapter 359).

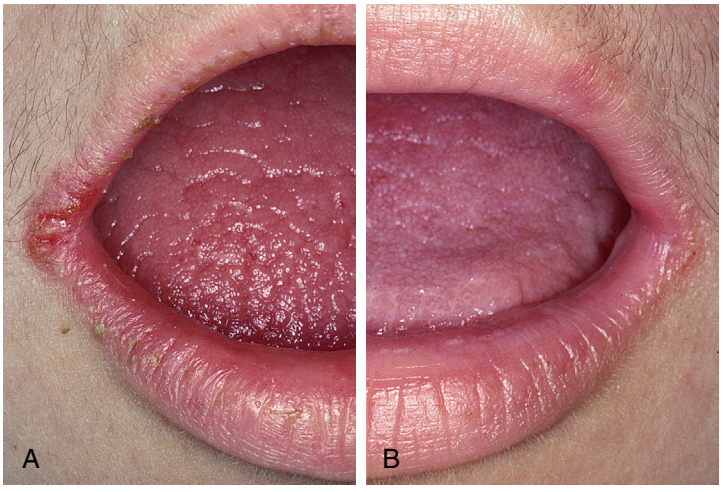

FIGURE 393-7. **Erythematous oral candidiasis. A,** Erythematous candidiasis in a 26-year-old woman with primary Sjögren syndrome, exhibiting symptomatic angular cheilitis, atrophic mucositis, and lingual papillary atrophy. **B,** Asymptomatic and normal-appearing mucosa after treatment with appropriate topical antifungal drugs (see text).

TABLE 393-4 PIGMENTATIONS OF THE ORAL MUCOSA (BROWN OR GRAY-BLACK IN COLOR)

INCREASED MELANIN PRODUCTION (FLAT LESIONS)
Oral melanotic macule
Ephelis (vermilion border)
Systemic diseases: Addison disease, von Recklinghausen disease of skin, Albright syndrome, Peutz-Jeghers syndrome; Laugier-Hunziker syndrome
PROLIFERATION OF MELANIN-PRODUCING CELLS (FLAT OR RAISED LESIONS)
Melanocytic nevi
Melanoma in situ
Malignant melanoma
NONMELANIN PIGMENTATION
Amalgam tattoo
Focal deposition of systemically distributed metal (lead, bismuth, mercury, others) usually at sites of chronic inflammation
Systemically administered drugs (chloroquine, minocycline, ketoconazole, cyclophosphamide)

ORAL SOFT TISSUE TUMORS

A range of oral benign soft tissue tumors should be treated by excisional biopsy.

CONNECTIVE TISSUE HYPERPLASIAS

The most common oral soft tissue tumors are small, pedunculated masses of hyperplastic fibrous connective tissue covered by normal-appearing mucosa (Table 393-5). Solitary lesions are usually found on the inside of the cheeks or lips. Similar lesions may be present at the border of an ill-fitting denture or may occur in clusters on the hard palate under an ill-fitting denture (palatal papillomatosis).

Generalized or multifocal enlargement of the gingiva (gingival hyperplasia) may be caused by chronic administration of phenytoin, cyclosporine, and many of the calcium-channel blocking drugs (e.g., diltiazem, verapamil, or nifedipine; Fig. 393-8). It can also be associated with a hereditary defect or be caused by an infiltration of atypical white blood cells in some types of leukemia (particularly acute monocytic leukemia; Chapter 168) or by uncontrolled diabetes mellitus (Chapter 210).

TABLE 393-5 ORAL SOFT TISSUE TUMORS

CONNECTIVE TISSUE HYPERPLASIA (NORMAL-APPEARING OVERLYING MUCOSA)
Irritation fibroma Denture-associated hyperplasia (fibrous epulis) Palatal papillomatosis (papillary hyperplasia) Generalized gingival hyperplasias Drug-induced (phenytoin, nifedipine, cyclosporine) Hereditary
REACTIVE HYPERPLASIA (ERYTHEMATOUS OVERLYING MUCOSA)
Pyogenic granuloma/pregnancy tumor Peripheral giant cell granuloma Inflammatory gingival hyperplasia Hyperplastic lingual tonsil
EPITHELIAL MASSES (USUALLY IRREGULAR WHITE SURFACE)
Papilloma/oral wart Squamous cell carcinoma Verrucous carcinoma Focal (multifocal) epithelial hyperplasia (Heck disease) Condyloma acuminatum (venereal wart) Keratoacanthoma (on skin aspect of lips)
SALIVARY DUCT OBSTRUCTION (MINOR SALIVARY GLANDS)
Mucocele/ranula (usually fluctuant) Salivary stone (sialolith)
SUBEPITHELIAL NEOPLASMS
Primary connective tissue or salivary gland tumors Metastatic lesions (especially in the mandible) Lymphoma (especially in the palate or posterior mandible) Focal or generalized leukemic infiltrates in the gingiva (especially with acute monocytic leukemia)

FIGURE 393-8. Drug-induced gingival hyperplasia. Similar clinical lesions may occur with prolonged use of various drugs or as a hereditary condition (see text).

REACTIVE HYPERPLASIAS

Small masses with surfaces that are ulcerated or only partially covered by normal-appearing mucosa usually represent reactive lesions in the form of pyogenic granulomas (whose frequency increases during pregnancy), peripheral giant cell granulomas, peripheral ossifying fibroma, or lymphoid hyperplasia of the lingual or other tonsillar tissue. The granulomas are most often located on the gingiva. Rarely, such lesions may represent a metastatic neoplasm.

EPITHELIAL PROLIFERATIONS

Small, white, wartlike epithelial masses are common and can occur in any area of the oral mucosa (Fig. 393-9). They are occasionally classified as epithelial neoplasms, but most do not continue to grow. Human papillomavirus types 2, 6, 11, 13, 32, and 57 have been identified in these wartlike lesions, which are usually classified generically as squamous papillomas. A large wartlike lesion on the oral mucosa or gingiva should raise suspicion of verrucous carcinoma.

SALIVARY MUCOUS RETENTION LESIONS (MUCOCELES)

Mucoceles are small, chronic, or recurring vesicles or bullae that occur commonly on the inside of the cheeks and lips, the posterior soft palate, and the floor of the mouth. They are caused by injury to one of the many submucosal minor salivary glands, resulting in extravasation of mucus, which causes inflammation or blockage of the excretory duct, leading to cyst formation. Mucoceles require conservative surgical excision because simple incision and drainage are usually followed by recurrence.

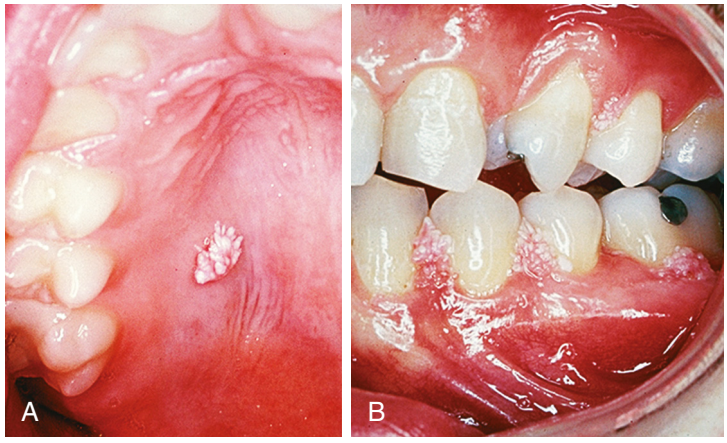

FIGURE 393-9. Papillary epithelial tumors. A, A solitary squamous papilloma. **B,** Multiple gingival papillomas, occurring in all quadrants, from condyloma acuminatum, associated with papillomavirus subtype 6 or 11.

SALIVARY GLAND DISEASES

PRIMARY DISEASES OF SALIVARY GLANDS

Unilateral major salivary gland enlargement that is markedly painful or tender to palpation and has a purulent exudate or nothing expressible from the duct suggests bacterial sialadenitis. Any exudate should be cultured, and initial treatment should be with an oral penicillinase-resistant antibiotic, such as cloxacillin or dicloxacillin 500 mg, every 6 hours.

Painful sialolithiasis usually occurs in submandibular gland ducts, less commonly in the parotid gland, and much less commonly in sublingual and minor salivary glands. Peak incidence is in the third to sixth decades, almost always with pain but occasionally with painless swelling. Diagnosis is clinical, supplemented by ultrasound or computed tomography. Small stones may be expressible or treated by extracorporeal shock wave lithotripsy or endoscopic removal. Larger stones require incisional surgery.

More than 30 types of benign or malignant neoplasms appear as firm and nontender unilateral or bilateral enlargement of a major gland or as a firm submucosal nodule on the palate or the labial or buccal mucosa (Table 393-6). Their causes are unknown, except for Warthin tumor (papillary cystadenoma lymphomatosum) that has a strong association with cigarette smoking. Uncommonly, unilateral major gland enlargement may be reactive—for example, chronic sialadenitis from duct obstruction or inadequately treated bacterial sialadenitis.

Salivary gland tumors (Chapter 176) are relatively uncommon and present as a swelling in one of the major paired salivary glands or in one of the minor glands of the mouth. Most occur in the major glands, with approximately 90% developing in the parotid. The most common benign salivary gland tumor is the pleomorphic adenoma (mixed tumor). Most salivary gland tumors in the parotid gland are benign, in contrast to the sublingual gland, where more than 90% are malignant. Approximately half of tumors in the submandibular and minor glands are malignant. Benign tumors are generally slowly growing, not fixed to the skin, and do not show ulceration of the overlying epithelium. Malignancies generally grow more quickly, are often fixed to the skin or adjacent normal structures, and tend to show ulceration. Adenoid cystic carcinoma has a characteristic local infiltration with prominent perineural spread. Detection of any salivary gland mass lesions should be followed by appropriate imaging, cytology, and biopsy. Both benign and malignant tumors typically are initially treated by surgery.[9]

SECONDARY DISEASES OF SALIVARY GLANDS

BILATERAL SALIVARY GLAND ENLARGEMENT AND DECREASED SALIVARY SECRETION ASSOCIATED WITH SYSTEMIC DISEASES

The best-known cause of bilateral salivary gland enlargement is infection by the mumps virus (Chapter 340) in children. However, the prevalence of mumps decreased in the United States by more than 98% after the introduction of an effective vaccine in 1967, and now there are only a few hundred to a few

TABLE 393-6 CAUSES OF SALIVARY GLAND ENLARGEMENT

USUALLY UNILATERAL
Benign or malignant salivary gland neoplasms (more than 30 different histopathologic types)
Bacterial infection
Chronic sialadenitis (single gland)
USUALLY BILATERAL AND ASSOCIATED WITH SALIVARY HYPOFUNCTION
Viral infection (mumps, cytomegalovirus, influenza, Coxsackie A)
Sjögren syndrome
Chronic granulomatous diseases (sarcoidosis, tuberculosis, leprosy)
Recurrent parotitis of childhood
Human immunodeficiency virus infection/acquired immunodeficiency syndrome
BILATERALLY SYMMETRICAL, SOFT, NONTENDER, PAROTID ONLY
Sialadenosis (asymptomatic parotid enlargement), idiopathic or associated with:
Diabetes mellitus
Hyperlipoproteinemia
Hepatic cirrhosis
Anorexia/bulimia
Chronic pancreatitis
Acromegaly
Gonadal hypofunction
Phenylbutazone use

TABLE 393-7 CAUSES OF DECREASED SALIVARY SECRETION

TEMPORARY
Effects of short-term drug use (e.g., antihistamines)
Virus infections (e.g., mumps)
Dehydration
Psychogenic conditions (e.g., anxiety)
CHRONIC
Effects of chronically administered drugs (particularly antidepressants, monoamine oxidase inhibitors, neuroleptics, parasympatholytics, some combinations of drugs for treating hypertension)
Chronic diseases
Sjögren syndrome
Sarcoidosis
Human immunodeficiency virus or hepatitis C infection
Depression
Diabetes mellitus (uncontrolled)
Amyloidosis (primary or secondary)
Central nervous system diseases
Other effects of treatment
Therapeutic radiation to the head and neck
Graft-versus-host disease
Absent or malformed glands (rare)

thousand cases per year. Uncommonly, a less acute, mumpslike illness may occur in adults in association with cytomegalovirus (Chapter 347), influenza (Chapter 332), or Coxsackie A (Chapter 349) virus infection.

About 15% of patients who meet the criteria for Sjögren syndrome (Chapter 247) may gradually develop chronic bilateral enlargement of major salivary glands that feel firm and nontender or only slightly tender to palpation. Histologically, the tumors begin as a benign lymphoepithelial lesion but after several years of chronicity may transform into an extranodal marginal zone B-cell lymphoma (Chapter 171).

In most patients with Sjögren syndrome, gradually progressive salivary hypofunction can impair speech and swallowing and cause a characteristic pattern of progressive dental caries that leads to excessive tooth loss if not actively prevented. In severe cases, the oral mucosa becomes dry and sticky, saliva is not expressible from the major ducts, and about one third of patients have signs and symptoms of chronic erythematous candidiasis (see earlier discussion and Fig. 393-7).

The salivary component of Sjögren syndrome is diagnosed from a labial salivary gland biopsy specimen that contains three to five minor glands (>10 mm^2 of salivary tissue) and exhibits focal lymphocytic sialadenitis in the absence of nonspecific chronic sialadenitis or another disease, such as noncaseating granuloma. A patient's symptoms of oral dryness (xerostomia) can be caused by a wide variety of conditions (Table 393-7).

Several chronic granulomatous diseases, such as sarcoidosis (Chapter 83), tuberculosis (Chapter 299), and leprosy (Chapter 301), can cause bilateral enlargement and decreased function of salivary glands. The clinical and serologic features of sarcoidosis may occasionally closely mimic those of Sjögren syndrome, and the distinction is best made by minor salivary gland biopsy supplemented with chest radiography.

A few adult patients with HIV infection and most children who are infected in utero develop major salivary gland enlargement and reduced salivary secretion that are caused by lymphocytic infiltration. Parotid gland enlargement usually represents a solid or cystic lymphoepithelial lesion (see Table 393-2).

Recurrent parotitis of childhood includes episodes of unilateral or bilateral parotid enlargement. During flares of this illness, salivary secretion may be reduced, but usually without prominent secondary symptoms or signs. This condition, of unknown cause, usually subsides after puberty.

ASYMPTOMATIC PAROTID ENLARGEMENT (SIALADENOSIS, SIALOSIS)

Parotid glands can develop bilateral, symmetrical enlargement that is soft and nontender to palpation and associated with normal salivary function (see Table 393-6). Diagnosis is established by this clinical presentation and the presence of one of the systemic diseases known to be associated with it: diabetes mellitus (Chapter 210), hyperlipoproteinemia (Chapter 190), hepatic cirrhosis (Chapter 139), anorexia or bulimia (Chapter 200), chronic pancreatitis (Chapter 130), acromegaly (Chapter 205), and gonadal hypofunction. It can also result from use of phenylbutazone or be a reaction to iodine-containing contrast media. Biopsy of the affected glands is not indicated for diagnosis.

IMPAIRED SALIVARY SECRETION WITHOUT GLAND ENLARGEMENT

The common symptom of dry mouth (xerostomia) is most often a side effect of chronically administered drugs. Many classes of drugs reduce unstimulated salivary secretion through anticholinergic or other mechanisms (see Table 393-7). Patients experience these symptoms soon after beginning to use the drug but produce enough saliva during a meal for normal chewing and swallowing. However, the symptoms and associated dental caries are dose dependent and gradually increase with prolonged use of the drug. The classes of drugs producing the most profound effects are most tricyclic antidepressants, most neuroleptics, monoamine oxidase inhibitors, and all anticholinergics. A combination of drugs for treatment of hypertension may also cause symptoms of dry mouth.

Several systemic diseases affect salivary secretion. As noted earlier, most patients with Sjögren syndrome, some with sarcoidosis, and a few patients with HIV infection experience symptoms of dry mouth to various degrees, with or without salivary gland enlargement. In addition, patients who have primary or secondary *amyloidosis* with salivary gland amyloid deposits may develop impaired secretion. The symptom of xerostomia is more prevalent in individuals who exhibit symptoms of depression, even in those not taking drugs for its treatment. Studies done before the availability of antidepressant drugs showed that symptoms of depression were associated with decreased salivary secretion.

Irradiation of the head and neck region to treat a malignancy usually produces profound dry mouth during and after therapy.[10] Secretory capacity recovers only slightly in the months after treatment for patients with solid tumors but recovers significantly for those with multifocal tumors (e.g., Hodgkin disease).

TREATMENT

Significant chronic salivary hypofunction from any cause produces a risk for dental caries (decay) in approximate proportion to the secretory impairment, but caries can largely be prevented if appropriate measures are taken as soon as the hypofunction begins. Remaining teeth should be protected by a comprehensive dental caries prevention program, monitored by a dentist and include daily application of appropriate topical fluorides, removal of dental plaque, counseling on control of cariogenic dietary carbohydrates, and placement of appropriate dental restorations as necessary.

Symptomatic treatment of mild to moderately severe salivary hypofunction can include sialagogs such as sugar-free hard candies or chewing gum, regular sips of water, and use of saliva substitutes at night, but no topical therapy is reliably helpful.[11] If not contraindicated, symptoms of severe hypofunction can be improved by prescribing pilocarpine (5 mg four times a day).[12] Such treatment alone, however, will not prevent dental caries.

Chronic erythematous oral candidiasis is a frequent sequela of chronic salivary hypofunction, and its treatment and retreatment, as noted earlier, substantially improve the patient's oral symptoms.

PERIODONTAL DISEASE

Periodontal diseases are a group of oral infections that affect the periodontium, which are the hard and soft tissues that support and maintain teeth in the jaws. A worldwide problem, it is the most common cause of tooth loss. Periodontal disease in its most prevalent form is associated with excessive build-up of plaque and calculus on teeth and roots. Most cases of periodontal disease begin with inflammation of the gingiva—termed *gingivitis*—that may progress to loss of the supporting bone around the roots of the teeth. Other subtypes of periodontal disease are recognized with differing risk factors and natural histories. The mainstay of treatment is the removal of subgingival calculus and biofilm deposits using mechanical methods (tooth brushing, flossing, scaling, and root planing). Referral for appropriate dental care is indicated. Despite ongoing concerns, there is no current evidence that periodontal disease is an independent risk factor for coronary artery disease.

ACUTE DENTAL INFECTIONS

Localized dental infections respond well to local surgical treatment. Analgesia and nonsteroidal anti-inflammatory drugs are helpful. Antibiotics should be prescribed only in patients with signs of local or systemic spread or in patients who are moderately or severely immunocompromised. Amoxicillin (250 mg three times daily for 3 days) is the first-choice medication, and clindamycin (150 mg four times daily for 3 days) is an alternative in patients who are allergic to it. Spreading dental infections require evacuation of pus without delay, including exploration of all affected fascial spaces and removal of necrotic debris. Parenteral broad-spectrum antibiotics are indicated (e.g., a broad spectrum β-lactam, metronidazole, or gentamicin; see Chapter 258).

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394 APPROACH TO THE PATIENT WITH NOSE, SINUS, AND EAR DISORDERS

ANDREW H. MURR AND STEVEN D. PLETCHER

Patients with nose, sinus, and ear disorders may have a variety of chief complaints. Nasal symptoms, including rhinorrhea and congestion, may be due to allergic, infectious, inflammatory, neoplastic, or structural causes. Sinus disorders generally result in concomitant nasal inflammation, so the term rhinosinusitis is preferred. Patients who have rhinosinusitis are more likely to present with purulent rhinorrhea, facial pressure, loss of smell, and pain or headache (Chapter 367). Common ear complaints include pain, tinnitus, loss of hearing (Chapter 396), and vestibular symptoms (Chapter 396). Epistaxis, which is bleeding from the nose, is usually easy to distinguish from hemoptysis from the bronchial tree (Chapter 71) or hematemesis from the gastrointestinal tract (Chapter 121).

NASAL AND SINUS COMPLAINTS

RHINITIS AND RHINOSINUSITIS

DEFINITION

Rhinitis is generally defined as any inflammatory process in the nose, with the common result being a sensation of excess mucous or nasal congestion. Anterior nasal drainage may be perceived by the patient as being accompanied by an activity such as eating (gustatory rhinitis) and may be visible to an observer. Posterior nasal drainage is more nebulous and subjective, but it is very common and is referred to as postnasal drip. Rhinitis and rhinosinusitis can have allergic or nonallergic causes.

Both rhinitis and rhinosinusitis may be categorized as acute, subacute, or chronic, and they can resolve or recur. In general, acute rhinitis and sinusitis describe inflammatory conditions of the nose and sinuses that persist for less than 4 weeks. Chronic rhinitis and sinusitis persist for more than 12 weeks despite treatment. Subacute rhinitis and sinusitis define symptoms that persist between 4 and 12 weeks and resolve completely with treatment. Recurrent acute rhinitis and sinusitis are defined by episodes that occur four or more times per year and persist for 7 to 10 days per episode, but symptoms clear completely between episodes.

EPIDEMIOLOGY

The most common reason for a patient to seek the advice of a physician in the United States concerns problems relating to rhinitis and sinusitis. More than 30 million patient visits per year are devoted to this complaint, and billions of dollars are spent on medications that are expected to improve the condition.

Acute rhinosinusitis accounts for 2 to 10% of U.S. primary care visits. Allergic rhinitis, which is estimated to be the sixth most common chronic illness in the United States, affects between 10 and 20% of adults. Each year, nearly 80 million people in the United States experience 7 days or more of nasal or ocular symptoms as a result of allergic rhinitis, with an estimated annual direct and indirect medical cost of $5 to 8 billion and $11 billion, respectively. The incidence of allergic rhinitis has been increasing, perhaps related to fewer exposures to allergens in early life. The impact of allergic rhinitis also reflects its association with a variety of comorbid conditions, including asthma (Chapter 75), acute and chronic rhinosinusitis, nasal polyposis, secretory otitis media, and sleep disorders (Chapter 374).

PATHOBIOLOGY

Humans normally produce about 2 L of mucus per day from their nasal lining. The nose functions primarily as a humidification and filtration system, with a clean and refreshed nasal mucous blanket serving to trap particulate matter and organisms. The nasal and sinus lining consists of ciliated respiratory epithelium; the cilia function in a highly organized and orderly fashion under normal circumstances to transport particulate matter trapped in the mucous blanket in a consistent fashion so that the mucus can be swallowed, thereby avoiding deposition in the bronchi. The nose also serves as the organ of olfaction (Chapter 395) to allow patients to discern tastes and avoid spoiled foods that could cause illness.

The nose represents the entry site for the majority of respired air, which is warmed, humidified, and filtered in the nose in preparation for the lower respiratory tract. Deposition of allergens, microbes, and other inspired materials presents a challenge to the immune system at this interface with the outside world. The mucosal barrier of the nasal and sinus cavities includes a ciliated respiratory epithelium, where coordinated mucociliary clearance transports particulate matter out of the respiratory tract and into the gastrointestinal tract. The normal microbiome (Chapter 257) of the sinonasal mucosa is thought to contribute to host defense against pathogenic microbes.

Insults to the mucosal barrier, infection, and immune response to inspired particulate matter may result in inflammation of the sinonasal mucosa. The resultant hypersecretion of mucus and tissue edema manifest as the common symptoms of congestion and rhinorrhea. This process may be limited to the nasal cavity (rhinitis) or include both the sinuses and the nasal cavity (rhinosinusitis).

Alterations in the parasympathetic control of vascular tone in the nose may also lead to vascular engorgement and the secretion of mucus. The parasympathetic nervous system controls both vascular tone and mucus production in the nose. Inflammatory conditions, such as the common cold, can cause the nasal and sinus lining to swell, thereby highlighting the nasal cycle governed by parasympathetic neural control. In a normal state, one side of the nose is relatively decongested and one side is relatively congested because of vascular engorgement. This vascular dilation allows humidification and warming of inspired air and can also affect the ability to discern odors in the process of olfaction. During rhinitis, the inflammation exaggerates the normal relative comparison between the decongested and congested sides of the nose and can be perceived as an uncomfortable nasal stuffiness that shifts from side to side over a period of several hours.

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Alterations in the parasympathetic control of vascular tone in the nose may also lead to vascular engorgement and the secretion of mucus. The parasympathetic nervous system controls both vascular tone and mucus production in the nose. Inflammatory conditions, such as the common cold, can cause the nasal and sinus lining to swell, thereby highlighting the nasal cycle governed by parasympathetic neural control. In a normal state, one side of the nose is relatively decongested and one side is relatively congested because of vascular engorgement. This vascular dilation allows humidification and warming of inspired air and can also affect the ability to discern odors in the process of olfaction. During rhinitis, the inflammation exaggerates the normal relative comparison between the decongested and congested sides of the nose and can be perceived as an uncomfortable nasal stuffiness that shifts from side to side over a period of several hours.

ABSTRACT

Common sinonasal symptoms, including nasal congestion, nasal obstruction, and nasal drainage, may be secondary to isolated rhinitis (inflammation of the nasal cavity) or inflammation centered in the sinuses with associated nasal involvement (rhinosinusitis). A detailed history and physical examination, including endoscopy, are the mainstays of clinical evaluation. Imaging, specifically computed tomographic scans, are often helpful in evaluating patients who have chronic rhinosinusitis or complications of acute rhinosinusitis. The initial treatments for both disorders include nasal saline irrigations and intranasal corticosteroid sprays. Successful treatment of refractory or severe disease requires a more nuanced understanding of the pathophysiology of nasal and sinus disorders.

Epistaxis, or bleeding from the nose, and ear pain also are common complaints. A systematic approach to the evaluation of these symptoms is described.

KEYWORDS

acute sinusitis
chronic sinusitis
nasal polyp
allergic rhinitis
epistaxis
otitis externa
otitis media

Rhinitis

Allergic respiratory diseases result from a hypersensitivity immune reaction to airborne allergens (Table 394-1).[1] Perennial allergic rhinitis may occur year-round. The most common causes include indoor fungi, animal dander, and dust mites. Cat dander is the most common animal allergen, but rodents (mice, rats, guinea pigs, ferrets, hamsters), rabbits, dogs, and birds also may be significant. Dust mites, which live in bedding, pillows, and stuffed animals, are semiseasonal with maximal impact from August to December. Cockroaches and other insects, including gypsy moths, crickets, ladybugs, spiders, and beetles, may be locally important sources of allergen. Seasonal allergic rhinitis is most often triggered by pollens from trees and grasses.

Exposure to allergies results in both early- and late-phase reactions in the nasal cavity. IgE subunits in the surface of mast cells and basophils recognize specific allergens, thereby triggering degranulation of the immune cells with release of histamine and other inflammatory mediators. Within minutes of exposure to the allergen, this process results in tissue edema, nasal congestion, and nasal irritation, frequently associated with sneezing. Approximately 4 to 8 hours after the exposure, chemoattractants and adhesion molecules released in response to the inflammatory mediators promote infiltration of leukocytes, eosinophils, basophils, CD4+ lymphocytes, and monocytes. Activation of these cells results in release of a second wave of inflammatory mediators. Nasal congestion is generally the dominant symptom during the late-phase reaction.

The severity of allergic disease is mediated not only by the current pollen count and exposure to allergens, but also by the cumulative exposure for a given allergy season. Priming is not an allergen-specific phenomenon—patients report increased sensitivity to nonspecific nasal irritants such as perfume and smoke following exposure to allergens. The increased reactivity is thought to be secondary to recruitment of mast cells and basophils as well as neural hyperresponsiveness. Because of this phenomenon, patients may continue to experience symptoms of severe seasonal allergy even after the pollen count of their triggering allergens falls.

Asthma (Chapter 75) and allergic rhinitis share a common pathophysiology and strong epidemiologic association. About 80% of patients with allergic asthma also suffer from allergic rhinitis, and the presence of allergic rhinitis is a risk factor for the development of asthma.

TABLE 394-1 ALLERGENS CAUSING ALLERGIC RHINITIS

COMMON NAME	SEASON IN UNITED STATES
SEASONAL ALLERGENS	
Trees	
Birch	March–May
Cottonwood	April–May
Elm	February–May
Cedar	March–May
Oak	May–June
Maple	March–May
Grasses	
Kentucky blue	Mid-May–June
Timothy	Mid-May–June
Orchard	Mid-May–June
Sweet vernal	Mid-May–June
Fescue	Mid-May–June
Bermuda	Mid-May–June
Weeds	
Ragweed	August–September
Kochia	July–September
Russian thistle	July–September
Sage	July–September
Marsh elder	July–September
English plantain	July–September
Outdoor Molds	
Alternaria	Spring–fall
Cladosporium	Spring–fall
PERENNIAL ALLERGENS	
Household Allergens	
Cockroaches (German and American)	
Dust mites: *Dermatophagoides farinae, D. pteronyssinus, Blomia tropicalis*	More active in summer and humid months
Other insects (spiders, ladybugs)	
Animals	
Cats	
Dogs	
Other pets (guinea pigs, ferrets, hamsters, horses)	
Rodents	
Indoor Molds	
Aspergillus	
Cladosporium	
Penicillium	

Rhinosinusitis

Sinusitis differs from rhinitis in that the term implies an infectious cause rather than physiologic dysfunction. Nevertheless, many different mechanisms of inflammation besides infection may give rise to what is currently generally termed sinusitis.

Acute rhinosinusitis is most frequently caused by a viral infection. Acute bacterial rhinosinusitis may develop secondarily, owing to virus-induced tissue edema and mucus stasis. Odontogenic infection (Chapter 393) may progress to acute or chronic bacterial rhinosinusitis and is a common cause for unilateral infection of the maxillary sinus.

Chronic rhinosinusitis includes both the neutrophilic and eosinophilic drivers of inflammation. Isolated or unilateral disease may occur secondary to chronic suppurative infections, including odontogenic disease and fungal processes, such as a fungus ball or mycetoma.[2] The microbiology of chronic rhinosinusitis differs from that of acute rhinosinusitis, with *Staphylococcus aureus* (Chapter 267), *Pseudomonas aeruginosa* (Chapter 282), and anaerobic bacteria (Chapter 273) commonly cultured. Although the precise role of microbes in the pathophysiology of chronic rhinosinusitis remains unclear, chronically inflamed sinuses are characterized by a loss of bacterial diversity and overgrowth of a pathologic bacterial species.

CLINICAL MANIFESTATIONS

When normal nasal mucosal function is lost, patients often complain of nasal crusting or obstruction, hypersecretion or postnasal drip, coughing, facial pressure, and fatigue. Nasal obstruction that shifts from side to side during the day is common in many types of rhinitis and may be considered an exaggeration of normal physiology.

Rhinitis

Rhinitis is characterized by sneezing, which is often paroxysmal; rhinorrhea with clear, watery secretions; nasal congestion; and itching in the nares and palate. In allergic rhinitis, these symptoms are generally associated with allergic conjunctivitis manifested by ocular itching, lacrimation, and conjunctival injection. Severe conjunctivitis is less common in perennial allergic rhinitis than in seasonal allergic rhinitis. Lethargy, fatigue, arthralgias, myalgias, and cognitive impairment frequently accompany allergic rhinitis. Fever is not a feature of allergic rhinitis, even though the lay term for this condition is hay fever, which reflects the influenza-like nature of this disease. The natural history of allergic rhinitis is for symptoms to worsen inexorably during several weeks in the presence of ongoing allergen exposure. Symptoms often do not peak until well after the peak in pollen counts, and then they persist after pollen counts have declined.

Rhinosinusitis

Cardinal symptoms of acute rhinosinusitis (Table 394-2) include purulent nasal drainage; nasal obstruction; and facial pain, pressure, or fullness. Additional signs and symptoms include fever, cough, fatigue, reduced or absent sense of smell, dental pain, and ear symptoms such as pressure and fullness. The sign with the highest diagnostic value is purulent nasal discharge or posterior pharyngeal discharge. The presence of purulent nasal drainage generally supports the diagnosis of acute bacterial sinusitis, but culture of the drainage does not necessarily correlate well with actual pathogenic bacteria found on direct sinus culture.

TABLE 394-2 CARDINAL SYMPTOMS OF ACUTE SINUSITIS

CARDINAL SYMPTOMS	OTHER SIGNS/SYMPTOMS
Facial pain, pressure, or fullness	Hyposmia/anosmia
Nasal obstruction	Fatigue
Nasal purulent discharge	Dental pain
	Fever
	Cough
	Ear pressure or fullness

In chronic rhinosinusitis, typical symptoms include nasal obstruction or congestion, drainage, diminished sense of smell, and facial pressure. Acute pain and fever are uncommon with chronic disease. Patients with chronic sinusitis often note a dull facial pressure that seems to worsen with dependency. Other factors favoring a diagnosis of bacterial sinusitis over viral sinusitis include length of illness beyond 10 days or when a patient's symptoms worsen within 10 days after an initial improvement in symptoms.

DIAGNOSIS

History

A thorough history should probe whether patients have tried over-the-counter or prescription medications, including antihistamines, decongestants, mucolytics, analgesics, mast cell stabilizers, and even steroids, and whether they have helped improve the condition. In addition, other prescription medications have side effects that affect nasal physiology, including antihypertensive medications that cause systemic vasodilation, aspirin, corticosteroids, and antibiotics. Specific questions regarding allergies are important, including seasonality or environmental triggers, the presence or absence of pets, food sensitivities, recent changes in environment, and living conditions, with a focus on old or new carpets, mattresses, furnace filters, or freshly painted interior walls. A patient should be questioned about past allergy skin testing or other testing.

A recent history of other family members or coworkers being ill with an upper respiratory viral infection suggests an infectious over an environmental process. A careful past medical history should allow one to determine whether relevant conditions such as previous nasal surgery or trauma, granulomatous diseases, cystic fibrosis (Chapter 77), rheumatologic conditions, immune deficiencies (Chapter 231), or other problems may be contributing factors. Unilateral nasal congestion raises concern for either an anatomic abnormality, such as septal deviation, perhaps related to previous trauma, a polyp or other neoplastic mass, or perhaps even a foreign body.

Physical Examination

The nose should be inspected with a nasal speculum to assess nasal septal anatomy (Fig. 394-1), the most caudal aspect of the inferior turbinates (Fig. 394-2), and the possibility of large nasal polyps (Fig. 394-3 and 394-4) or other masses. In patients with allergic rhinitis, the physical examination may reveal pale and swollen inferior turbinates, whereas copious nasal secretions are more apparent with viral infections. By spraying the nose with a topical decongestant such as phenylephrine (Neo-Synephrine) or oxymetazoline, the middle meatus, which is the air space between the middle turbinate and lateral nasal wall, can often be visualized to assess for nasal polyps or purulent discharge. Examination of the mouth and oropharynx, including the posterior pharyngeal wall, with a tongue blade if necessary, can sometimes identify a stream of postnasal discharge or pus. Sinus palpation and transillumination, although part of the art of medicine, are not sufficiently reliable for diagnosis. The patient's ability to open the mouth without limitation helps exclude trismus, which can sometimes be caused by a dental infection or a deep neck infection.

A complete examination of the head and neck should be performed to look for signs of recent or old trauma such as ecchymosis under the eyelids, swelling of the soft tissue of the face, or deviation of the nasal dorsum. The neck should be palpated for adenopathy (Chapter 154) or other masses.

A basic eye examination should be performed to assess pupillary function, extraocular movements, and possible nystagmus (Chapter 392). An ear examination should be conducted to assess the tympanic membranes bilaterally. In patients with an abnormality of the tympanic membrane or concomitant complaints of hearing loss or disequilibrium (Chapter 396), pneumatoscopy using an air bulb attached to the otoscope can be used to insufflate the ear canal and assess for mobility of the tympanic membrane; decreased mobility suggests a middle ear effusion. Weber and Rinne testing using a 512-Hz tuning fork screens for conductive hearing loss, especially unilateral loss.

Endoscopic examination of the nose, almost always performed by a specialist, is the "gold standard" for evaluating rhinitis and sinusitis. A flexible or rigid fiberoptic scope can allow fine inspection of the septum, turbinates, middle meatus, and sphenoethmoid recess, as well as direct inspection of the

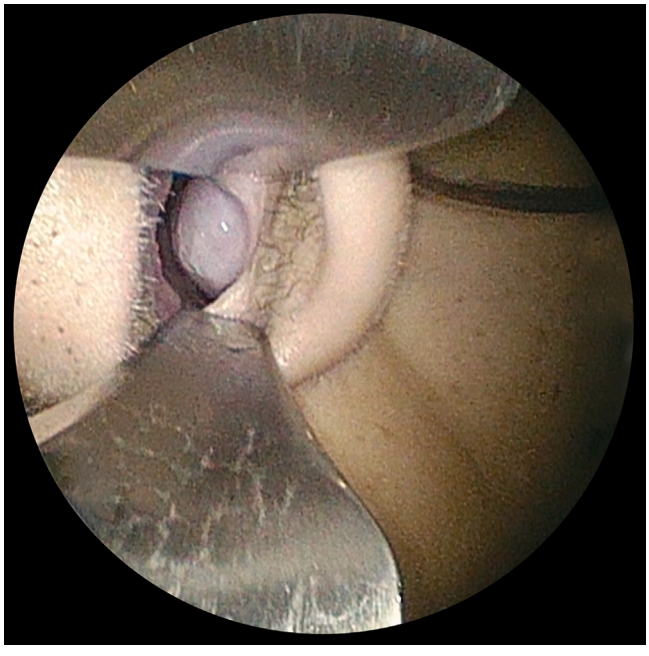

FIGURE 394-2. Examination of the left nasal cavity using a nasal speculum demonstrates an edematous, pale inferior turbinate consistent with allergic rhinitis.

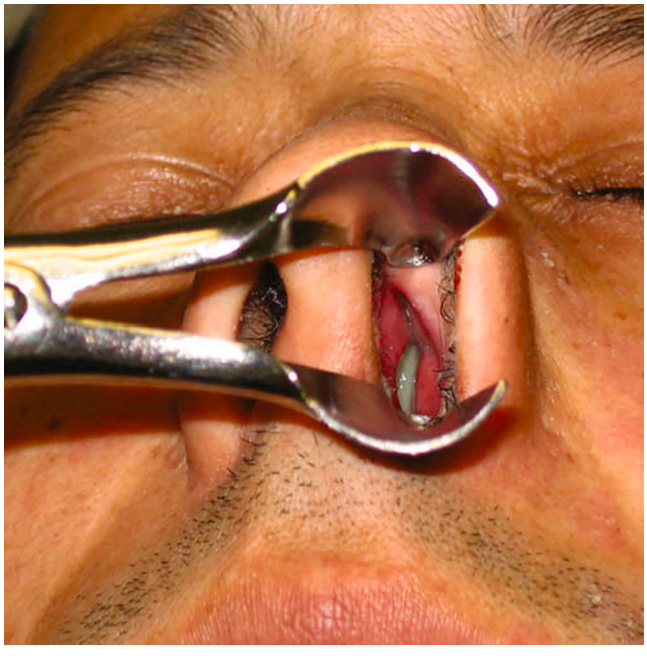

FIGURE 394-1. Purulent drainage from the middle meatus seen on anterior rhinoscopy.

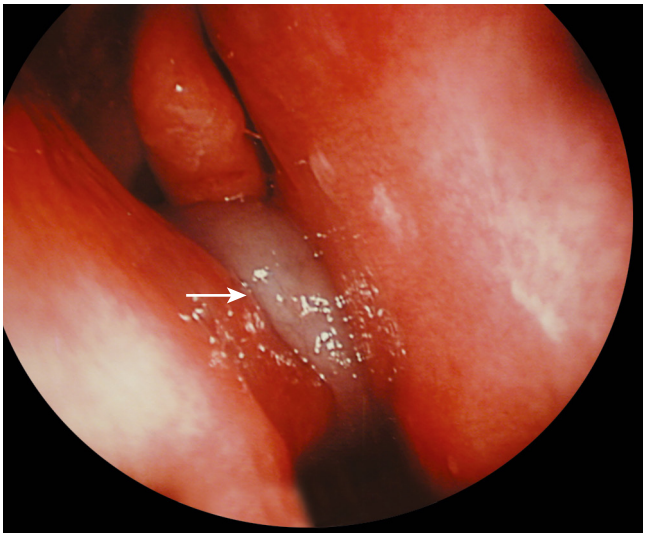

FIGURE 394-3. Nasal polyp in the right nasal cavity. A polyp is seen on the right side just inferior to the middle turbinate, next to the nasal septum. It is paler than the surrounding tissue.

nasopharynx, orifice of the eustachian tube, and fossa of Rosenmüller, which is just rostral to the Eustachian tube in the nasopharynx and is often the site of origin of nasopharyngeal carcinoma (Chapter 176). Flexible endoscopy can be used to further inspect the oropharynx, larynx, and most of the hypopharynx (Chapter 397). Mucus samples can be obtained for culture.

Laboratory Findings

Cultures

Cultures of the nostril or lower nasal cavity are not typically useful and are not recommended. An endoscopically guided culture of the middle meatus by a specialist may help guide treatment for acutely ill immunocompromised patients, for patients suspected of having acute bacterial rhinosinusitis, for patients with refractory chronic rhinosinusitis, or for those whose sinusitis is suspected of causing secondary meningitis, epidural or subdural abscess, brain abscess, orbital involvement, or cavernous sinus thrombosis.

FIGURE 394-4. Nasal polyp clearly visible on physical examination.

Other Tests

A nasal smear can reveal eosinophils, which is consistent with allergic rhinitis. Likewise, skin testing or radioallergosorbent testing can help pinpoint allergic triggers (Chapter 230). In patients with acute sinusitis, a white blood cell count with differential may be useful. In patients with chronic sinusitis, serum immunoglobulin levels can be helpful: highly elevated IgE levels can raise suspicion for allergic fungal sinusitis, whereas low levels of IgG and other subclasses suggest immunodeficiency (Chapter 231). If the patient has chronic nasal crusting as a primary complaint, screening serologic tests for sarcoid (Chapter 83), granulomatosis with polyangiitis (Chapter 249), T-cell lymphomas (Chapter 171), syphilis (Chapter 295), tuberculosis (Chapter 299), Sjögren syndrome (Chapter 247), and other chronic inflammatory diseases can be considered. Relatively rare infections such as rhinoscleroma also may be present, so biopsy and cultures may be indicated to help reveal a diagnosis. Use of illicit substances should be considered because cocaine and other illicit drugs may cause chronic nasal crusting. Toxicology screening can be useful if substance abuse (Chapter 365) is suspected. In a patient with a lifelong history of sinusitis since childhood, cystic fibrosis should also be considered (Chapter 77).

Imaging

Imaging is not indicated for routine rhinitis, acute rhinosinusitis without suggestion of complications, or chronic rhinosinusitis when objective evidence of inflammation is confirmed on nasal endoscopy (Fig. 394-5). Computed tomography (CT) is frequently used to provide objective evidence of inflammation in patients whose symptoms are suggestive of chronic rhinosinusitis (Fig. 394-6), in patients who have nasal polyps (Fig. 394-7), to identify the extent of disease, to exclude impending complications. A CT scan also is required to define anatomy before endoscopic sinus surgery. The additional of intravenous contrast is helpful in patients with suspected complications of sinusitis, including orbital or intracranial spread of infection.

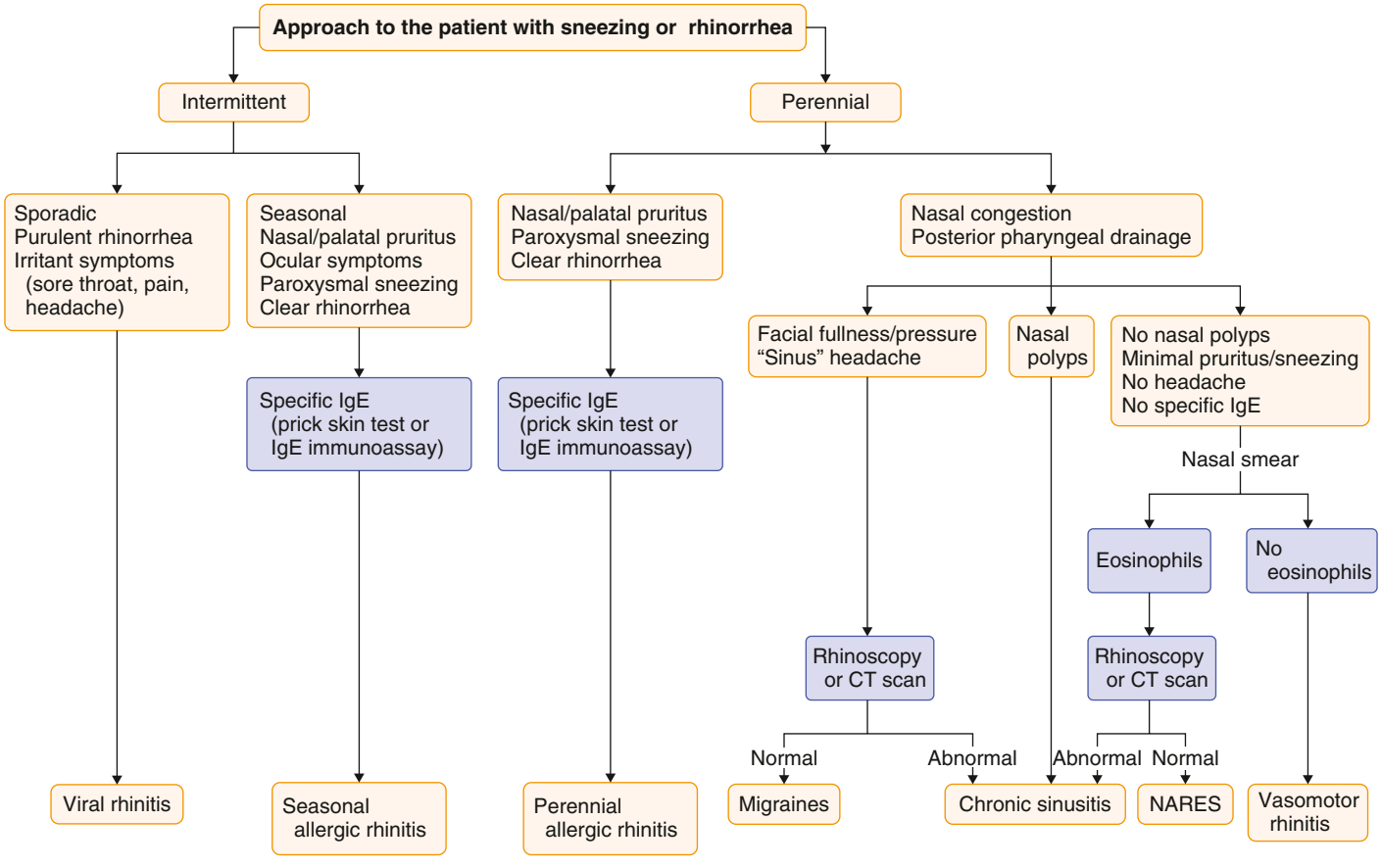

FIGURE 394-5. Approach to the patient with rhinitis symptoms. CT = computed tomography; HA = headache; IgE = immunoglobulin E; NARES = nonallergic rhinitis with eosinophilia syndrome.

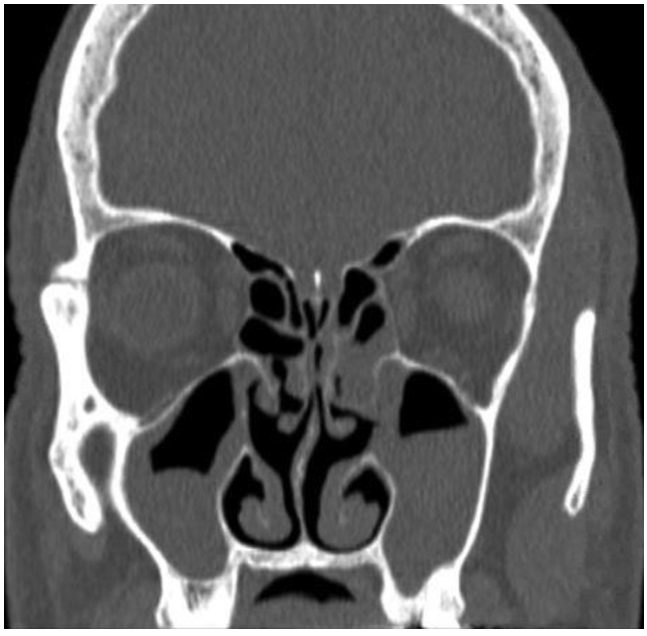

FIGURE 394-6. Coronal noncontrast computed tomographic image of a patient with chronic sinusitis. There is partial opacification of the maxillary sinuses bilaterally. Also noted is partial opacification of a left ethmoid cell.

Plain films have little utility and are not generally recommended given the superiority of CT imaging. Magnetic resonance imaging (MRI) is occasionally helpful, especially when there is a concern for a sinonasal tumor, invasive fungal sinusitis, or an encephalocele.

Differential Diagnosis, Rhinitis

Rhinitis is primarily a clinical diagnosis with multiple specific causes (see Fig. 394-5 and Table 394-3) based on symptoms and exposure history. The diagnosis of allergic rhinitis[3] may be confirmed by the demonstration of specific IgE antibodies reactive to the relevant allergen through either positive allergy skin test responses or IgE immunoassays (Video 394-1). Prick skin testing is safe, specific, and rapid, and it is the diagnostic test of choice for identifying relevant allergens. IgE immunoassays are an appropriate alternative when skin testing is not available. However, a negative IgE immunoassay with a strong clinical suspicion suggests the need for a specialty referral.

Viral rhinitis[4] may be difficult to distinguish from seasonal allergic rhinitis. In contrast to the pervasive eosinophilia in allergic rhinitis, viral rhinitis often produces thicker, purulent secretions, with neutrophils present on the nasal smear. Conjunctival symptoms are less pronounced, and on physical examination, the nasal mucosa is erythematous and swollen.

Abuse of topical nasal decongestants (e.g., oxymetazoline), with chronic reflex vasodilation, has historically been the most common cause of rhinitis medicamentosa; however, cocaine and nasal narcotic abuse is another frequent cause of this condition. Chronic unilateral nasal blockage suggests an anatomic defect, often a deviated septum, but such blockage can also result from polyps, foreign bodies, and tumors. This history necessitates referral for rhinoscopy (Video 394-2).

An abnormal neurogenic response to irritants (e.g., cold air, pollutants, cigarette smoke, strong odors, alcohol, foods) is the predominant feature of vasomotor rhinitis. Patients with vasomotor rhinitis typically have chronic nasal congestion and posterior pharyngeal drainage, but they lack the paroxysmal sneezing, rhinorrhea, pruritus, conjunctivitis, and systemic complaints typical of patients with allergic rhinitis. In addition, eosinophils are absent in their nasal mucus.

Laryngopharyngeal reflux is another possible cause of nasal congestion and posterior pharyngeal drainage that often occurs in association with cough and hoarseness. These patients are often otherwise asymptomatic from "silent" gastroesophageal reflux (Chapter 124), thereby making recognition challenging. Because symptoms may not resolve until after several months of aggressive reflux treatment and because proton pump inhibitors by themselves may not prevent reflux of digestive enzymes (e.g., pepsin) or other stomach-derived irritants, proper diagnosis can be daunting.

Atrophic rhinitis is characterized by atrophy of the nasal epithelium and is associated with complaints of nasal congestion and a perceived bad odor. It is observed in elderly patients, but the most common cause is devascularization secondary to nasal surgery or trauma.

A disease termed nonallergic rhinitis with eosinophilia syndrome[5] presents with symptoms similar to those of vasomotor rhinitis. The syndrome is diagnosed by performing a nasal smear for eosinophils; however, a CT scan or rhinoscopy is required to exclude chronic sinusitis or nasal polyposis because the symptoms of these conditions may overlap. In contrast to vasomotor rhinitis, nonallergic rhinitis with eosinophilia syndrome is more responsive to intranasal cromolyn and intranasal corticosteroids.

Cerebrospinal fluid (CSF) rhinorrhea may be misdiagnosed as chronic rhinitis. CSF leaks are typically unilateral and may occur spontaneously[6] or secondarily following sinonasal surgery or trauma. Patients with spontaneous CSF leaks often have underlying intracranial hypertension (Chapter 367) and comorbid obesity (Chapter 201). Patients with CSF leaks are generally able to demonstrate their unilateral rhinorrhea as a flow or individual clear droplets from the affected nasal cavity when leaning over or bearing down with a Valsalva maneuver. This fluid may be collected and sent for beta-2 transferrin testing to confirm the CSF origin.

Rhinitis and atrophic rhinitis may be the presenting symptom of a systemic disorder. Granulomatosis with polyangiitis (Chapter 249), sarcoidosis (Chapter 83), and T-cell lymphomas (Chapter 171) may affect the nasal cavity, most commonly resulting in nasal congestion, epistaxis, and pain. Granulomatosis with polyangiitis and T-cell lymphomas are frequently destructive within the nasal cavity, where they lead to erosion of the septum (septal perforation) and inferior turbinates. Intranasal drug use (Chapter 365) can also cause local tissue destruction.

Differential Diagnosis, Rhinosinusitis

Rhinosinusitis must be differentiated from rhinitis. Rhinosinusitis may be caused by viral infection, bacterial infection, fungal infection, and allergy (Table 394-4).

Rhinosinusitis

Acute rhinosinusitis requires the presence of either nasal obstruction/congestion or nasal drainage (anterior or posterior) combined with either facial pain/pressure or loss of smell. From a clinical perspective it is important to distinguish between allergic versus infectious causes and, if infectious, between acute viral rhinosinusitis (common cold; Chapter 329) from acute bacterial rhinosinusitis. An acute onset of inhalant allergy is often seasonal or can be traced to a particular precipitant. A rapid onset of sinus-related symptoms suggests a viral upper respiratory infection, especially if the patient also has typical systemic symptoms, such as arthralgia, myalgia, fever, chills, gastrointestinal symptoms, and cough in addition to nasal congestion, postnasal drip, and headache. Viral disease can progress to a secondary bacterial infection; patients with symptoms that persist without evidence of improvement for at least 10 days or have acute worsening of symptoms following an initial improvement are diagnosed clinically as having acute bacterial rhinosinusitis.[7] Rare complications of acute rhinosinusitis include spread of infection to the orbit, intracranial space, soft-tissues are associated with fulminant bacterial infection. Acute bacterial rhinosinusitis causes facial pressure and purulent postnasal discharge.

Chronic rhinosinusitis encompasses multiple pathophysiologic mechanisms and implies a prolonged course of sinus symptoms that have been refractory to symptomatic treatment over a period of at least 12 weeks.[8] Chronic sinusitis presents with nasal congestion, nasal drainage, facial pressure, and sometimes anosmia (see Table 394-2). In contrast to acute (infectious) sinusitis, headaches are an unusual manifestation of either perennial rhinitis (allergic or nonallergic) or chronic sinusitis, and virtually all patients who complain of "sinus headaches" suffer from atypical migraine headaches (Chapter 367) that occur in a bilateral distribution involving the maxillary or ophthalmic branches of the trigeminal nerve. This distribution, especially when it is combined with vasomotor symptoms such as nasal congestion, rhinorrhea, and conjunctival injection, often leads to misdiagnosis as chronic sinusitis or rhinitis. Because of this overlap in symptoms among chronic sinusitis, perennial rhinitis, and atypical migraine headaches, as well as their synergistic influences on each other, objective evaluation with either CT or rhinoscopy is usually required to establish the diagnosis of chronic sinusitis (Table 394-5).

Endoscopically guided culture techniques combined with CT are the best way to diagnose or exclude infectious rhinosinusitis. CT can reveal mucoceles, which are blocked individual sinuses that continue to secrete mucus and can slowly erode bone, expand to involve the eye and brain, or become acutely infected. Mucus retention cysts, often present in the maxillary sinus, are

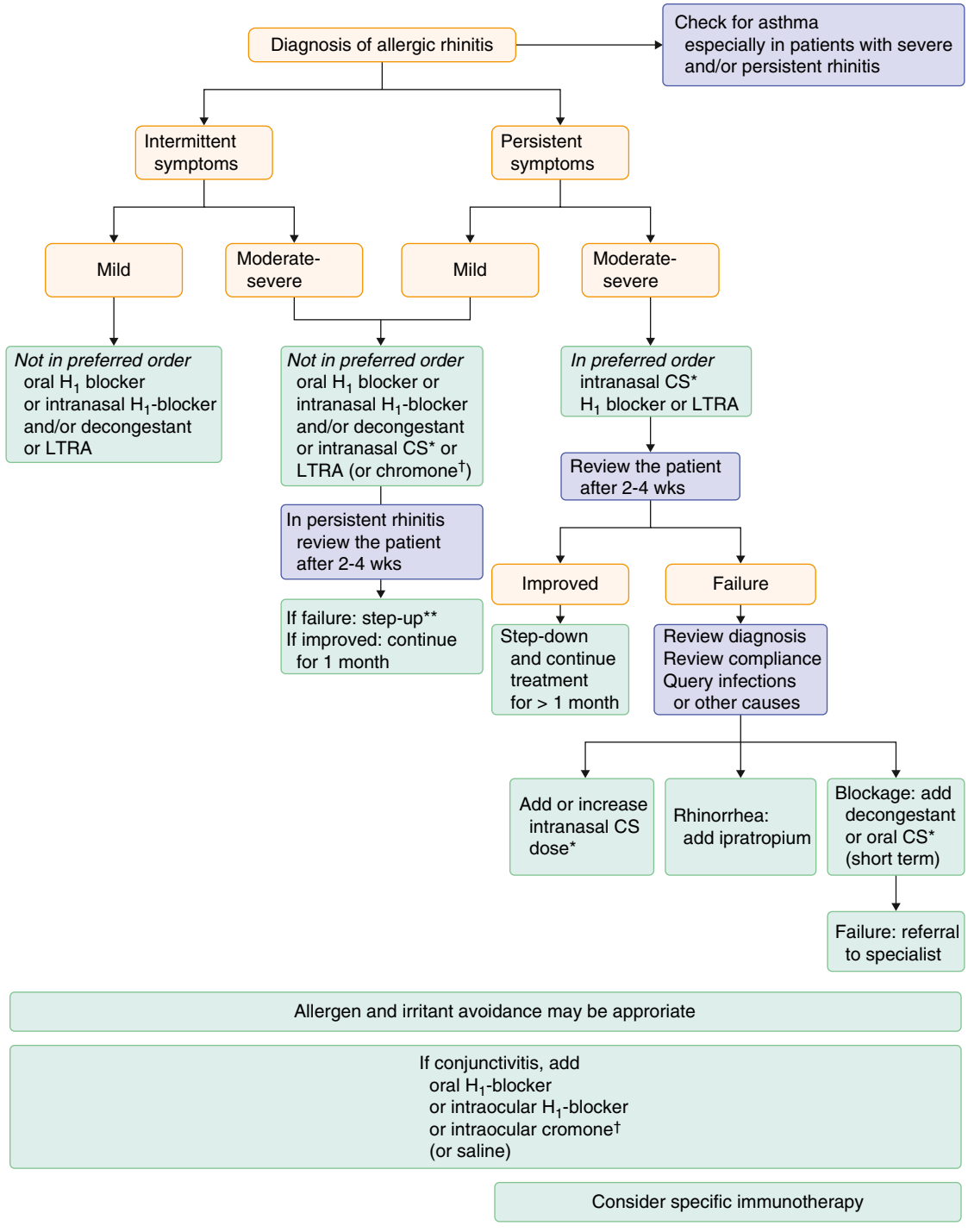

FIGURE 394-7. Algorithm for the management of allergic rhinitis. See text for specific drugs and doses. CS = corticosteroids; LTRA = leukotriene-receptor antagonist. *Total dose of topical and oral corticosteroids should be considered if inhaled corticosteroids are used for concomitant asthma. **Step-up with an LTRA or cromolyn (see text). †Chromone is available as cromolyn. (From Bousquet J, Schünemann HJ, Samolinski B, et al. Allergic rhinitis and its impact on asthma [ARIA]: achievements in 10 years and future needs. *J Allergy Clin Immunol*. 2012;130:1049-1062.)

manifested as a spherical opacification; an estimated 10% of the population has a mucus retention cyst, which is usually asymptomatic.

Immunosuppressed patients are at risk for invasive fungal sinusitis,[9] a life-threatening acute infection of the sinuses. The fulminant version of invasive fungal disease typically occurs with severe neutrophilic dysfunction in patients who have a hematologic malignancy or poorly controlled diabetes. Chronic invasive fungal disease may be seen with long-term use of systemic corticosteroids, after solid organ transplantation, or with chronic immunodeficiency syndromes

A mycetoma, which is an isolated "fungus ball" in a sinus, has a characteristic hyperdensity within a sinus opacification. Mycetomas (Chapter 314) are noninvasive but may erode bone because of pressure necrosis over a long period of time.

TREATMENT

Medical Therapy

Allergic Rhinitis

The three categories of treatment for allergic rhinitis are avoidance of allergens, pharmacotherapy, and immunotherapy.[10] The severity and duration of symptoms, as well as patient's preference, help determine the appropriate treatment options. Antihistamines (oral or intranasal) are the primary treatments for seasonal, mild disease, whereas intranasal corticosteroids are preferred for perennial, severe disease (see Fig. 394-7). If an antihistamine is to be added to an intranasal corticosteroid, an intranasal antihistamine is preferred.[A1] Second-generation antihistamines have a long duration of action and are nonsedating. These once-daily agents include cetirizine (10 mg), levocetirizine (5 mg), fexofenadine (180 mg), desloratadine (5 mg), and loratadine (10 mg). The intranasal

TABLE 394-3 DIFFERENTIAL DIAGNOSIS OF RHINITIS

ALLERGIC
Seasonal allergic rhinitis
Perennial allergic rhinitis
INFLAMMATORY
Infectious rhinitis (viral)
Nonallergic rhinitis with eosinophilia syndrome
Chronic sinusitis with or without nasal polyposis
Laryngopharyngeal reflux
HORMONAL
Pregnancy, oral contraceptives, perimenopause
Hypothyroidism
Hyperthyroidism
RHINITIS MEDICAMENTOSA
Topical or, less commonly, oral decongestants
Antihypertensives
Antidepressants
Cocaine
VASOMOTOR
Irritant induced (pollution, cigarette smoke)
Cold air induced
Gustatory (food induced)
ANATOMIC
Nasal septal deviation
Tumor, neoplasm
Foreign body
Cerebrospinal fluid leak
Atrophic (postsurgical or trauma)

TABLE 394-4 HETEROGENEITY OF CHRONIC SINUSITIS

PHENOTYPE	CHARACTERISTIC
Infectious	Very unusual as a cause of chronic sinusitis
Inflammatory	Develops secondary to anatomic obstruction of the sinus ostia; often resolves after surgical correction Bacterial biofilms contribute to presence and severity Infrequently associated with nasal polyps
Hyperplastic eosinophilic	Prominent eosinophilic infiltrate with systemic eosinophilia Frequent association with allergies and asthma Usually associated with nasal polyps
Allergic fungal	Often unilateral; presents as expansive, dense infiltrate on CT scan Associated with elevated total IgE and specific IgE to colonizing fungi
Aspirin-exacerbated respiratory disease	Intense eosinophilic infiltrate Usually associated with nasal polyps and asthma Exacerbations of upper and lower respiratory disease (asthma) after ingestion of aspirin and nonselective COX1 inhibitors

COX1 = cyclooxygenase 1; CT = computed tomography; IgE = immunoglobulin E.

antihistamines azelastine and olopatadine, have a more rapid onset of action than oral antihistamines and also are effective for nonallergic forms of rhinitis. The benefit of antihistamines diminishes in patients with continuous allergen exposures, such as perennial allergic rhinitis caused by indoor allergens or after several days of continuous exposure to seasonal allergens; in such settings, these drugs often prove to be little better than placebo.

Oral decongestants such as pseudoephedrine (30 to 60 mg every 4 to 6 hours; not more than 240 mg per 24 hours) treat nasal stuffiness but are mild stimulants and may produce rebound congestion and headaches. These drugs are usually used in combination with antihistamines to control the full spectrum of allergic rhinitis symptoms. Antihistamines and decongestants alone generally do not provide satisfactory relief in patients with moderate to severe allergic rhinitis.

Intranasal corticosteroids, including triamcinolone acetonide (two sprays [55 μg] to each side of the nose every day), mometasone furoate (two sprays [50 μg] to each naris every day), fluticasone propionate (two sprays [50 μg] to each naris every day), and budesonide (two sprays [32 μg] to each naris every day) (Table 394-6), are the treatments of choice for patients with moderate to severe seasonal allergic rhinitis or perennial allergic rhinitis.[A2] Intranasal corticosteroids provide a 50 to 90% reduction in symptoms compared with 20 to 30% for oral antihistamines.

TABLE 394-5 DIAGNOSTIC CRITERIA FOR CHRONIC SINUSITIS

Symptoms for more than 3 months:
Mucopurulent nasal drainage
Nasal obstruction
Reduced sense of smell
Facial pressure, or fullness
Supported by an objective finding:
Nasal or middle meatus polyps
Edema or purulence in middle meatus
Paranasal *sinusitis* on endoscopy or CT scan

CT = computed tomography.

Data from Fokkens WJ, Lund VJ, Mullol J, et al. EPOS 2012: European position paper on rhinosinusitis and nasal polyps 2012. A summary for otorhinolaryngologists. *Rhinology*. 2012;50: 1-12; Desrosiers M, Evans GA, Keith PK, et al. Canadian clinical practice guidelines for acute and chronic rhinosinusitis. *Allergy Asthma Clin Immunol*. 2011;7:1-38; Rosenfeld RM, Piccirillo JF, Chandrasekhar SS, et al. Clinical practice guideline (update): adult sinusitis. *Otolaryngol Head Neck Surg*. 2015;152:S1-S39.

Leukotriene antagonists (zileuton [1200 mg twice daily], zafirlukast [20 mg twice daily], montelukast [10 mg once daily])[A3] have a confirmed efficacy in allergic rhinitis that is comparable to that of antihistamines but do significantly improve sneezing, rhinorrhea, nasal congestion, ocular symptoms, and quality of life in patients with seasonal allergic rhinitis and perennial allergic rhinitis. For otherwise refractory symptoms, a 6-day course of oral corticosteroids (e.g., methylprednisolone, 8 mg four times daily for 1 day, 4 mg four times daily for 2 days, 4 mg three times daily for 1 day, 4 mg twice daily for 1 day, 4 mg once daily for 1 day) can be tried. Nasal cromolyn stabilizes mast cells and mediates additional anti-inflammatory activities. Although it is not as effective as intranasal corticosteroids, cromolyn provides relief in patients with mild to moderate symptoms. The value of cromolyn is mitigated by the need for frequent doses (four times/day), a lack of efficacy in approximately 30 to 40% of recipients, and the superior efficacy of intranasal corticosteroids in controlled studies. Cromolyn may be especially useful preventively (e.g., immediately before cat exposure). Ocular cromolyn has been especially useful in the treatment of allergic conjunctivitis. No significant side effects are associated with its use.

Infectious Rhinitis

Viral rhinitis is treated with supportive care, including fluid replacement and treatment of the febrile component of the syndrome with acetaminophen or nonsteroidal anti-inflammatory medications. Steam has a mild decongestant effect, and vitamin C and good nutrition may help hasten the resolution of symptoms. Oral decongestants (e.g., pseudoephedrine, 120 mg every 12 hours for several days), mucolytics (e.g., guaifenesin, 200 to 400 mg every 4 to 6 hours for several days), and ipratropium bromide (0.03 or 0.06%, two sprays on each side of the nose every 12 hours for several days) are of potential benefit.

Acute Rhinosinusitis

Acute rhinosinusitis, including acute bacterial rhinosinusitis, may be managed with supportive care, including saline irrigations, nasal steroid sprays, antipyretics, decongestants, and analgesics. The best clinical predictors of the presence of acute bacterial rhinosinusitis rather than viral rhinosinusitis include persistent symptoms for 7 or more days without evidence of clinical improvement; high fever (>39° C [102° F]) with purulent nasal discharge or facial pain for at least 3 to 4 consecutive days; or the onset of worsening symptoms more than 5 days after the onset of an apparent viral upper respiratory tract infection. Even for patients who meet the clinical criteria for acute bacterial rhinosinusitis,[11] however, the impact of antibiotic treatment is modest; about 85% of patients will have complete resolution of symptoms at 10 to 14 days; watchful waiting is a reasonable alternative.[A4] Engaging patients in a discussion of the modest impacts of antibiotics and potential risks of treatment is recommended to determine a patient-specific treatment plan.

Patients with a suspected complication of acute bacterial sinusitis (e.g., infection involving the orbit, intracranial cavity, or other adjacent soft tissues) should be treated immediately with antibiotics and referred to an otolaryngologist for urgent evaluation. Patients who have refractory disease, who are immunocompromised, or who require intensive care may benefit from procedures to decompress the maxillary sinus and sample its contents for culture to guide antibiotic therapy.

The preferred antibiotic regimen is amoxicillin (500 mg three times daily), or amoxicillin-clavulanate (875 mg/125 mg orally twice daily),[A5] with no evidence that higher doses are more beneficial, except perhaps for increasing to 2000 mg/125 mg orally twice daily in patients who have fever greater than 39° C (102° F), are immunocompromised, or have recently received antibiotics. In patients who are allergic to penicillin, alternatives include doxycycline (100 mg orally twice daily), trimethoprim-sulfamethoxazole (160/800 mg orally twice daily), or a fluoroquinolone (e.g., levofloxacin 500 mg orally daily or moxifloxacin 400 mg orally daily). By

TABLE 394-6 INTRANASAL CORTICOSTEROIDS*

GENERIC NAME	DOSE (PER ACTUATION)	MINIMUM APPROVED AGE	USUAL DOSING
Beclomethasone AQ	42 µg	6 yr	Twice daily
Beclomethasone HFA	80 µg	12 yr	Once daily
Flunisolide	25 µg	6 yr	Twice daily
Triamcinolone	55 µg	2 yr	Once daily
Budesonide	32 µg	6 yr	Twice daily
Fluticasone furoate	27.5 µg	2 yr	Once daily
Fluticasone propionate	50 µg	4 yr	Once daily
Mometasone	50 µg	2 yr	Once daily
Ciclesonide	50 µg	6 yr	Once daily
Ciclesonide HFA	37 µg	12 yr	Once daily

*Intranasal corticosteroids are generally administered at 2 sprays per nostril.

comparison, macrolides and second- and third-generation oral cephalosporins are not recommended because of high levels of resistance. The usual course of therapy is 7 days, regardless of the medication chosen. Patients who initially choose watchful waiting should be treated with antibiotics if their symptoms do not resolve within 1 week. Intranasal saline irrigations, using either physiologic or hypertonic saline, may be a useful adjunct in patients with acute bacterial rhinosinusitis, but neither topical decongestants nor antihistamines are useful.

If patients worsen despite 72 hours of antibiotic treatment or do not improve after 5 to 7 days of treatment, further evaluation should include a CT scan to localize the infection and detect complications, as well as cultures—either by direct sinus aspiration or endoscopically guided cultures of the middle meatus. Other cultures are unreliable.

Chronic Rhinosinusitis

The mainstays for treating the symptoms of chronic rhinosinusitis are saline irrigation[A6] and intranasal corticosteroids,[A7] (e.g., triamcinolone acetonide, two 55-µg sprays to each side of the nose every day; mometasone furoate, two 50-µg sprays to each naris every day; fluticasone propionate, two 50-µg sprays to each naris every day; or budesonide, two 32-µg sprays to each naris every day) for 6 weeks.[12] Unfortunately, relief may be limited, and patients frequently require oral corticosteroids (e.g., prednisone 40 mg per day for 5 days, 30 mg per day for 5 days, 20 mg per day for 5 days, and 10 mg per day for 5 days) to achieve appreciable improvement. Oral antibiotics are of little value,[13] except in patients who are experiencing an acute exacerbation. Endoscopically obtained cultures of the middle meatus can help define which patients may improve with culture-guided antibiotic treatment. Antifungal agents, including itraconazole in an oral or aerosolized form and amphotericin B in an aerosolized form, do not appear beneficial in the treatment of typical chronic sinusitis.

Biologic treatments initially designed to treat asthma (Chapter 75) hold promise for the treatment of chronic rhinosinusitis with type 2 inflammation, but the precise integration of biologic treatments into the care of patients with chronic rhinosinusitis and nasal polyps remains in evolution.[14] Because of their cost and the need for indefinite treatment, most recommendations suggest limiting their use to patients who have recurrent disease following endoscopic sinus surgery or who have comorbid conditions that preclude surgery.[15] Dupilumab[A8] (300 mg subcutaneous injection every 2 weeks), omalizumab (subcutaneous injection, dosing dependent upon weight and total IgE count), and mepolizumab (100 mg subcutaneous injection every 4 weeks) are approved for the treatment of chronic rhinosinusitis associated with nasal polyps.

Surgical Therapy

Patients who have severe symptoms, who fail to respond to therapy, or who have unusual, or resistant, or recurrent infections should be sent to a specialist for further evaluation and treatment (Table 394-7). Surgery is recommended in patients with benign neoplasms, mucoceles, juvenile nasopharyngeal angiofibroma, and some types of malignancies. Surgery can correct septal deviations and anatomically related nasal obstruction.[A9]

Surgery on the inferior turbinates may be beneficial for refractory allergic rhinitis.[A10] For patients who have chronic rhinosinusitis and who do not receive adequate benefit from medical treatment, endoscopic sinus surgery may be considered. Surgery allows removal of inflammatory tissue and mucus along with enhanced access for future topical treatments and clinic interventions. Patients should be monitored following surgery to tailor their medical regimen and maintain the benefits of surgery. Even with aggressive medical therapy and appropriate surgical intervention, patients with severe type 2 inflammation may experience early recurrence of inflammatory sinonasal disease with nasal polyps. Functional endoscopic surgery, which is designed to preserve mucociliary function and is performed with endoscopes through the nostril without skin incisions, can be useful for recurrent acute sinusitis and chronic rhinosinusitis.

TABLE 394-7 WHEN TO REFER A PATIENT WITH PRESUMED BACTERIAL RHINOSINUSITIS TO AN EAR, NOSE, AND THROAT SPECIALIST

Temperature >39° C (>102° F); orbital edema; severe headache, visual disturbance, altered mental status, meningeal signs
Failure to respond to more than two courses of antimicrobial therapy
Nosocomial infection, anatomic abnormalities
Immunocompromise or multiple comorbidities
Unusual or resistant pathogens
Fungal sinusitis or granulomatous disease
Recurrent episodes suggesting chronic sinusitis

Adapted from Chow AW, Benninger MS, Brook I, et al. IDSA clinical practice guideline for acute bacterial rhinosinusitis in children and adults. *Clin Infect Dis*. 2012;54:e72-e112.

PREVENTION

Avoidance and Environmental Control

When feasible, avoidance or elimination of the source of the allergen is the treatment of choice for patients with allergic rhinitis. Dust mite avoidance involves removing reservoirs for mite growth (i.e., use allergen-impermeable mattress and pillow covers), keeping the relative humidity lower than 50%, washing bedding in hot water (130° F) to kill mites, and wearing a simple mask when dust is being disturbed. Many of the measures suggested for mites are also helpful for fungi, especially dehumidification. Windows, shower curtains, and indoor plants are important sites for fungal growth and can be treated with mild fungicides (dilute household bleach).

In some houses, and particularly urban apartment blocks, large numbers of cockroaches are present, and IgE sensitivity is common. Although it may be difficult to kill cockroaches in an apartment, it is usually possible to keep a house clear of cockroaches by using chemical sprays and traps. Air-conditioning with closed windows is useful for reducing seasonal allergens, and the dehumidification provided by air-conditioning also mitigates the mite and indoor mold load.

Pets, especially cats and dogs, are the most preventable source of allergic diseases. The dominant rodent allergen is a urinary protein, and rodents, like cats, can deposit large quantities of allergen in a house.

Immunotherapy

Immunotherapy may be used for prevention in patients who have refractory disease or in patients with moderate to severe symptoms who want to de-escalate pharmacotherapy. This immunomodulatory approach is the only known option to affect the natural history of disease and may limit the future development of asthma. Subcutaneous immunotherapy regimens generally involve weekly antigen injections with a gradual escalation of the antigen dose. Efficacy depends on delivery of the correct antigen, regular injections for 3 to 5 years, and administration of an adequate dose of the allergen (10 to 15 µg, a dose much higher than that used historically). Immunotherapy is associated with a small risk of fatal anaphylaxis (about 3 fatalities/year in the United States, of 2 million people receiving this form of treatment) and must be administered in a facility where resuscitation equipment and trained personnel are available. The effects of subcutaneous immunotherapy persist for many years after a 3- to 5-year course of treatment has been discontinued, and they could be lifelong.

Sublingual immunotherapy provides significant clinical benefit along with reduced need for pharmacologic therapy for numerous allergens including grass,[A11] ragweed, and dust mites.[A12,A13] Sublingual immunotherapy treatments are FDA approved for timothy grass or cross-reactive grass pollens, for a panel of different grass pollens, for dust mites, and for ragweed pollen.[16] For example, administration of a house dust mite sublingual allergen immunotherapy tablet (6 or 12 development units) is an experimental option for reducing asthma exacerbations in patients who are allergic to house dust mites. As with subcutaneous immunotherapy, long-term clinical benefits are observed after it is discontinued, although recurrences are common after 5 to 10 years and some sublingual preventive treatments may lose efficacy within 3 years.[A14]

Severe responses to immunotherapy are exceedingly rare, but the potential for anaphylaxis and even death requires vigilance. Practitioners who perform skin testing and administer allergy shots require appropriate training and access to emergency protocols and medications. In comparison to subcutaneous

administration, sublingual immunotherapy is sufficiently safe to permit home administration.

NASAL POLYPS

During the evaluation of symptoms of rhinitis or sinusitis, the physical examination may reveal nasal polyps. Nasal polyps typically begin near the ethmoid sinuses in the middle meatus and extend into the nose, where they block the nasal airway and/or the sinuses. Most chronic rhinosinusitis with polyps is associated with type 2 inflammation, which is an inflammatory pathway that involves interleukin (IL)-4, IL-5, IL-13, and IgE and that is strongly associated with tissue eosinophilia, comorbid asthma, and severe sinus disease.[17] However, some patients with chronic rhinosinusitis and polyps demonstrate a predominately neutrophilic inflammatory response mediated by IL-17. A subset of patients with nasal polyps will be found to have aspirin sensitivity[18] and asthma related to arachidonic acid metabolism and upregulation of leukotriene production. Human papillomavirus (Chapter 344) may cause an inverted papilloma, which presents as a polyp causing unilateral nasal obstruction. This initially benign neoplasm responds to surgical excision but can transform to frank malignancy. Polyps are also seen in patients with cystic fibrosis, especially patients with the delta F508 mutation (Chapter 77). They are also seen in allergic fungal sinusitis, which is manifested by an elevated IgE level, positive fungal cultures (usually for aspergillosis), Charcot-Leyden crystals on histopathology, characteristic densities on CT, and nasal polyposis that is often, but not always, unilateral. Antral choanal polyps may extend into the nasal cavity or nasopharynx and cause obstruction.

CLINICAL MANIFESTATIONS

Nasal polyps often present with symptoms of nasal blockage and anosmia along with typical symptoms of rhinitis. When polyps are present, the nasal congestion is often unrelenting. Sometimes, patients with prolonged symptoms will present with a visible mass in their nostril. Rarely, facial asymmetry or orbital involvement will be the presenting sign of long-ignored nasal polyps. Patients with nasal polys may be more likely to complain of facial or ear pain than patients with rhinitis without polyps.

DIAGNOSIS

Nasal polyps will be visible in a careful examination (see Fig. 394-3 and 394-4), and their extent can be shown on a CT scan (Fig. 394-8). Unilateral nasal polyposis is suggestive of an antral choanal polyp, malignancy, inverted papilloma, or allergic fungal sinusitis; early biopsy is recommended.

TREATMENT

Benign inflammatory nasal polyps frequently respond to oral steroids, either in a tapered burst dose or, in rare cases, in small amounts of titrated daily oral steroids such as prednisone (40 mg per day for 5 days, followed by 30 mg per day for 5 days, followed by 20 mg per day for 5 days, followed by 10 mg per day for 5 days) or methylprednisolone (beginning with 24 mg the first day and tapering by 4 mg each subsequent day for 6 days).[19] The combination of systemic steroids with doxycycline (e.g., 100 mg twice daily) may be even more effective, and the leukotriene antagonist montelukast (10 mg once daily) can be helpful as well.[A15] Topical steroids are also efficacious for treating nasal polyps.[A16] In adults with symptomatic chronic sinusitis and nasal polyps that are refractory to intranasal corticosteroids, the addition of subcutaneous dupilumab (300 mg every 2 weeks),[A17] omalizumab (dosing depending upon weight and total IgE count) under expert guidance,[A18] or mepolizumab (100 mg subcutaneously every 4 weeks)[A19] to a corticosteroid nasal spray can reduce polyp burden and symptoms as well as the need for systemic corticosteroids in patients with chronic sinusitis and nasal polyps.[20] For patients with aspirin allergy, desensitization to aspirin or biologics may be helpful.[21]

Surgery for benign nasal polyposis can improve symptomatic control and reduce the need for oral steroids.[A20] Surgery is always recommended for inverted papillomas, antral choanal polyps, and most mucoceles, and surgery is likely to be helpful if acute sinusitis has caused central nervous system complications such as meningitis (Chapter 381), epidural abscess, subdural abscess, brain abscess (Chapter 382), or orbital abscess. Occasionally, surgery will be required when an untreated and aggressively growing polyp causes orbital or skull base erosion. Allergic fungal sinusitis is often treated with a combination of surgery, corticosteroids, and sometimes immunotherapy.

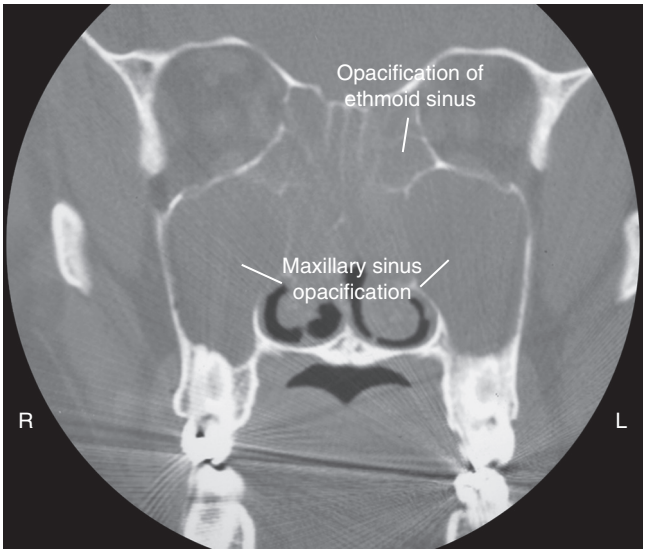

FIGURE 394-8. Computed tomography showing bilateral nasal polyposis of a chronic nature.

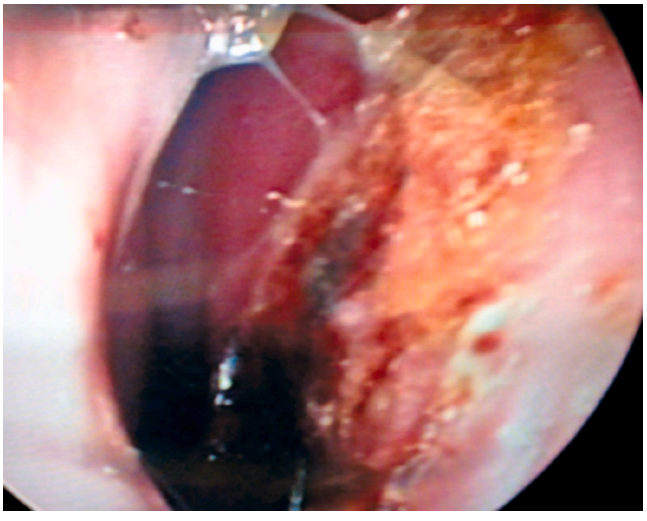

FIGURE 394-9. Dilated nasal vessels and crusting typical of a patient with epistaxis.

EPISTAXIS

Epistaxis (a bloody nose) can be an isolated or recurrent problem. Patients with nosebleeds frequently have systemic conditions that contribute to the severity of their bleeds. Persistent bleeding may result from hypertension,[22] oral anticoagulants, antiplatelet agents, or any underlying platelet disorder (Chapters 158 and 159) or clotting deficiency (Chapter 160).

DIAGNOSIS

For a patient with epistaxis, it is first critical to determine the severity of the blood loss. Physical examination should focus on inspection of the anterior septum, which is the most frequent point of origin for epistaxis. Frequently, dilated blood vessels on the caudal septum can be seen with anterior rhinoscopy (Fig. 394-9). Rarely, recurrent bleeding may be a sign of a sinonasal neoplasm. Bleeding in combination with unilateral nasal obstruction, epiphora, facial numbness, pain, ipsilateral serous otitis media, and/or cervical adenopathy are all concerning findings that warrant referral to a specialist. Lesion such as nasopharyngeal carcinoma (Chapter 176), juvenile nasopharyngeal angiofibroma, found in young men, may present with recurrent epistaxis and associated findings. A family history of nosebleeds in patients with recurrent epistaxis and multiple small visible vascular lesions on the fingers, lips, or tongue should raise concern for hereditary hemorrhagic telangiectasia (Fig. 394-10; Chapter 159).[23]

FIGURE 394-10. **Telangiectasias on the lower lip in a patient with recurrent nosebleeds and a diagnosis of hereditary hemorrhagic telangiectasias (HHT).**

TREATMENT AND PREVENTION

Epistaxis can be treated by local pressure, packing (using nasal sponges, balloons, or by ½-inch by 72-inch gauze impregnated with petroleum jelly), humidification, and hydration.[24–26] Hospitalization and transfusion are rarely required. Offending anticoagulation medications should be reduced in dose or discontinued temporarily if possible. Topical vasoconstrictive medication such as oxymetazoline spray, two sprays on each side of the nose every 12 hours for 3 days, can help limit persistent epistaxis.[27] Hemostatic agents such as Gelfoam-thrombin combination products also can be useful in treating refractory epistaxis or epistaxis in the presence of coagulopathy. Topical bevacizumab, estriol, and tranexamic acid are not routinely recommended, but topical tranexamic acid can reduce the need for nasal packing.[A21]

Patients with refractory bleeding may be treated with surgical arterial clipping or interventional neuroradiologic arterial occlusion. If a focal vascular lesion or exposed vessel is identified, it may be cauterized with silver nitrate, bipolar cautery, or laser treatment.

Dry airflow often precipitates nosebleeds in susceptible patients; maintaining a moist nasal environment through the use of topical ointments, gels, or viscous sprays helps limit bleeding. Humidifiers also may be used to reduce dryness.

EAR PAIN

DEFINITION

Ear pain (otalgia; Table 394-8) is discomfort perceived by a patient in the area of the lateral temporal bone. Although the discomfort often can be localized by the patient, at times the cause of the discomfort may in fact be distant from the site where the pain is felt. This referred pain can be due to problems in the oral cavity, oropharynx, hypopharynx, or larynx.

PATHOBIOLOGY

The ear is well supplied with sensory nerves and is positioned on the side of the skull. The ear is divided into the outer ear, or pinna, and the ear canal; the middle ear, which encompasses the tympanic membrane and ossicles; and the inner ear, which consists of the cochlea and the vestibular canals, including the utricle and saccule. In general, otalgia is due to problems in the outer or middle ear. The trigeminal nerve innervates the anterior-superior quadrant of the pinna, whereas the C2 and C3 cervical cutaneous nerves innervate the rest of the majority of the outer ear. However, there are contributions by the 9th and 10th nerves in the ear canal and even a small patch of sensory innervation by the 7th nerve in the posterior superior ear canal. It is the overlap in distribution of the 9th and 10th cranial nerves that establishes the anatomic basis for referred otalgia in diseases of the oral cavity, oropharynx, and larynx. Additionally, otalgia may be caused by disorders of the temporal mandibular joint, which is located just anterior to the external auditory canal. Therefore, ear pain may be due to inflammatory conditions of the skin of the outer ear, the ear canal, or the middle ear, or it may be due to disease processes unrelated to the ear itself.

CLINICAL MANIFESTATIONS

Patients with ear pain often have complaints referable directly to the ear itself. In cases of otitis externa, obvious erythema and swelling of the skin of the ear canal may be present. Limited physical manipulation of the ear may be excruciating for the patient with acute otitis externa. In chondritis of the pinna, which may be related to rheumatologic disorders, infection, or trauma, the entire pinna may be swollen and painful (Fig. 394-11). Hearing loss accompanying otalgia may indicate middle ear disease, especially otitis media. Patients sometimes complain of pain in the ear after air travel or driving from a mountainous region. Quick changes in pressure, such as encountered in scuba diving, may indicate barotrauma (Chapter 82), in which the Eustachian tube is unable to compensate rapidly enough for the changes in pressure that are encountered. Pain also may be a post-traumatic symptom from relatively minor percussion injury, more severe head trauma, or percussion injury related to a blast. Pain related to noise exposure may also indicate damage to the middle ear or even the inner ear. Deep-seated boring pain over the temporal area accompanied by retro-orbital pain can be due to petrous apex disease, including petrous apicitis.

TABLE 394-8 CAUSES OF OTALGIA

CAUSES OF OTALGIA	EXTERNAL EAR	MIDDLE EAR	UPPER AERODIGESTIVE TRACT
Likely	Otitis externa Herpes zoster oticus Chondritis Foreign body	Acute otitis media Acute eardrum perforation Barotrauma Chronic otitis media with impending complication	Tonsillitis Tonsillar abscess Deep neck abscess Tumor (especially base of the tongue, tonsil, hypopharynx, larynx, nasopharynx)
Unlikely	Malignant otitis externa Tumor	Tumor	

DIAGNOSIS

History

A patient with ear pain should be asked to reveal the location of the discomfort, the duration of the symptoms, and any activities related to onset of the condition. As an example, recent swimming would make otitis externa ("swimmer's ear") more likely, whereas a recent upper respiratory infection with hearing loss would suggest otitis media. Questions should address possible hearing loss, vertigo, otorrhea, hoarseness, voice change, dysphagia, odynophagia, dyspnea, hemoptysis, hematemesis, and weight loss. A social history with specific concentration on tobacco and alcohol use should be obtained. A possible family history of upper aerodigestive tract and nasopharyngeal carcinoma should be sought. A surgical history can reveal distant ear or throat surgery.

Physical Examination

A complete head and neck examination, including general assessment for trauma and a basic eye examination, is required. The outer ear and pinna should be examined first. The ear canal should first be palpated and then inspected. An otoscope with a pneumatic bulb attachment is critical to establish the presence or absence of a middle ear effusion. Inspection of the tympanic membrane should be accomplished with notations made about translucency of the eardrum, position and definition of the malleus (Fig. 394-12), presence or absence of a perforation (Fig. 394-13), and the eardrum's mobility with the ear canal sealed and a puff of air delivered by the pneumatic bulb (pneumotoscopy). A middle ear effusion (Fig. 394-14) may be seen in patients with resolving infection or chronic dysfunction of the eustachian tube. Blood may be seen especially after barotrauma but also with the secretory otitis media (Fig. 394-15). Examination with a 512-Hz tuning fork should be performed to differentiate conductive (diseases of the auditory canal and middle ear) from sensorineural (diseases of the inner ear) hearing loss by the lateralization of midline bone conduction (Weber test) and whether air conduction is superior to bone conduction (Rinne test) (see Chapter 396).

Facial nerve function should be assessed (Chapter 366) by determining whether the patient can raise the eyebrows, close the eyes, wrinkle the nose, and purse the lips. The presence or absence of nystagmus should be recorded. Inspection of the nose, oral cavity, oropharynx, and neck should be accompanied by cranial nerve examination (Chapter 366). Palpation of the tongue and tonsils is especially important if the ear pain is intense and persistent. A careful neck examination should be performed to look for masses. Oral cavity infections (Chapter 393), such as a peritonsillar abscess or severe tonsillitis,

FIGURE 394-11. Swollen ear pinna in a patient with chondritis.

FIGURE 394-12. This view of a normal tympanic membrane shows a right ear with a translucent drum, a prominent umbo of the malleus and just posteriorly the incudostapedial joint is visible. There is no evidence of effusion, but pneumotoscopy would be necessary to ascertain that finding. (Image courtesy of Dr. Jeffrey Sharon.)

may arise as ear pain, and the physical examination should reveal trismus, erythema, mass effect, and other common signs of pharyngitis.

Laboratory

An audiogram can assess hearing loss (Chapter 396). A tympanogram measures compliance of the middle ear system and is an accurate method for diagnosis of a middle ear effusion, often as a result of otitis media. Cultures are rarely performed because they require tympanocentesis, and cultures of the external ear can reveal a vast variety of organisms that are often treated empirically with antibiotics. If a fever and middle ear effusion are present and neck stiffness is found on physical examination, lumbar puncture may rarely be recommended because of the small chance that otitis media can cause central nervous system complications such as meningitis.

Imaging

In general, imaging is indicated if complications of acute or chronic otitis media are suspected or to look for occult causes of otalgia in the upper

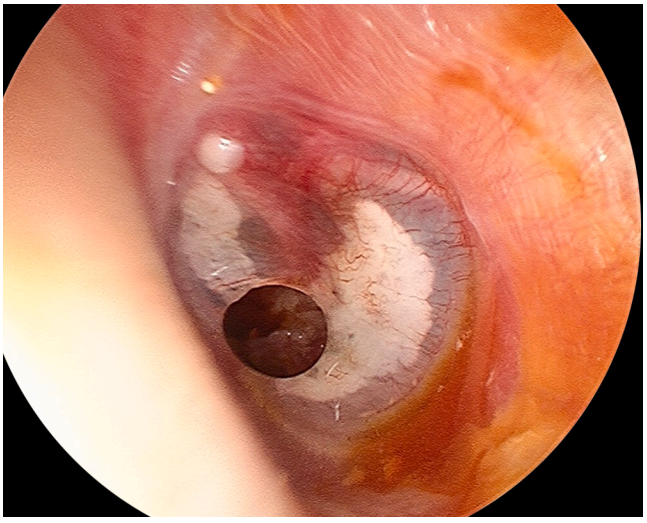

FIGURE 394-13. This left tympanic membrane has a small perforation surrounded by white plaque-like dystrophic calcification, which is referred to as tympanosclerosis.

FIGURE 394-14. A fluid meniscus of straw-colored effusion can be seen filling the middle ear space behind the left tympanic membrane. (Image courtesy of Dr. Jeffrey Sharon.)

aerodigestive tract. If a patient is suspected of having meningitis, epidural or subdural abscess, brain abscess, or sagittal sinus thrombosis, contrast imaging is mandatory. Imaging is also useful for operative planning in patients with chronic otitis media or (rarely) to evaluate for the presence of tumors in the middle or external ear.

Differential Diagnosis

Otitis externa, which is an infection of the skin of the ear canal, is often due to manipulating the ear after swimming or trying to scratch an ear canal that itches because of skin irritation. Patients exhibit erythema and edema of the canal skin often accompanied by a purulent exudate (Fig. 394-16). Patients with otitis externa and may experience extreme pain on manipulation of the ear canal. In the presence of concomitant cranial neuropathies, especially in diabetic or otherwise immunocompromised patients, malignant otitis externa with osteomyelitis should be suspected. Inspection of the tympanic membrane may reveal fluid consistent with otitis media; the tuning fork examination should support the presence of conductive hearing loss. Vesicles on the conchal portion of the pinna, especially when accompanied by facial nerve paralysis, strongly suggest herpes zoster oticus with Ramsay Hunt syndrome (Chapter 346). Perforation of the eardrum suggests either acute or chronic otitis media, traumatic perforation, or possibly cholesteatoma (Chapter 396) if the perforation is in the posterior-superior quadrant. Chronic draining otorrhea

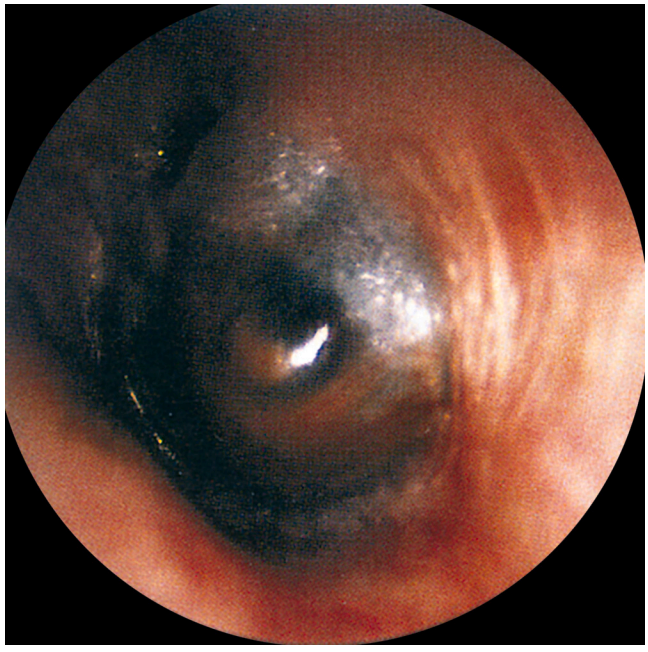

FIGURE 394-15. Blood in the middle ear (hemotympanum). Causes include otitic barotrauma, secretory otitis media, and a high jugular bulb. (From Dhillon RS, East CA, eds. *Ear, Nose and Throat and Head and Neck Surgery*, 2nd ed. Edinburgh: Churchill Livingstone; 1994:26.)

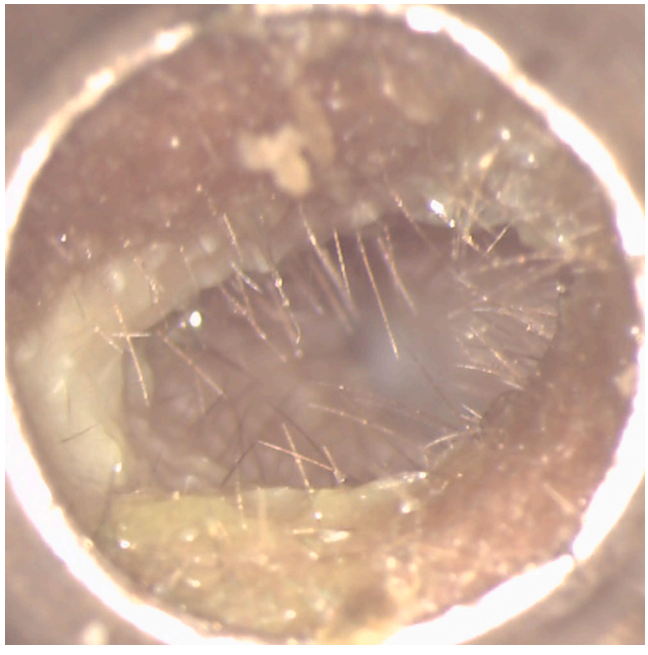

FIGURE 394-16. This view through a speculum shows an erythematous external auditory canal with exudate consistent with otitis externa. The fine hairs of the lateral external auditory canal are visible. The bright ring is a reflection from the speculum as seen through a microscope. Treatment is with topical antibiotic drops with or without topical corticosteroids.

of long standing with a deep boring pain and perforation of the tympanic membrane suggests a complication of otitis media.

If findings on ear and cranial nerve examination are negative but the patient's complaints of otalgia are persistent, special effort needs to be made to visualize the upper aerodigestive tract, including the nasopharynx, oral cavity, oropharynx, larynx, and hypopharynx, to be sure that infection or tumor is not present in these hard-to-examine areas. Flexible fiberoptic nasopharyngoscopy is a standard examination in these circumstances, and imaging such as MRI with contrast also can be very useful.

TREATMENT

Otitis externa is often treated with meticulous office debridement using a microscope and the application of antibiotic drops (ciprofloxacin, tobramycin, neomycin, polymyxin B), with or without hydrocortisone in various combinations.[28,29] In patients who are suspected of having a perforation of the tympanic membrane, aminoglycosides, which can be toxic to the inner ear, should be avoided. In patients who have substantial edema of the ear canal with narrowing of its lumen, a small wick or sponge is placed in the ear canal to help maintain patency of the canal and allow facile application of the medications.[30]

For acute otitis media, oral antibiotic treatment is directed at eradicating *Haemophilus influenzae* (Chapter 277), *Moraxella catarrhalis* (Chapter 277), *Streptococcus pneumoniae* (Chapter 268), and *Staphylococcus aureus* (Chapter 267) with amoxicillin, with or without clavulanate (e.g., amoxicillin 500 mg three times daily for 7 days or amoxicillin clavulanate [875 mg/125 mg] twice daily for 7 days), as for sinusitis. In general, antibiotics provide somewhat better short-term outcomes but at the expense of significantly more diarrhea and rashes. In patients with middle ear effusions, antimicrobial treatment may effectively reduce the duration of effusion, but whether it improves hearing is unknown.[A22] In some patients, the natural history of acute otitis media is acute perforation of the eardrum, which often results in otorrhea, relief of pain, and spontaneous healing of the perforation. Most middle ear effusions clear spontaneously within 3 months regardless of whether they are treated. A persistent effusion in an adult should prompt evaluation of the nasopharynx to exclude the presence of a mass impacting the eustachian tube. Chronic suppurative otitis media responds to oral antibiotics and probably to topical antibiotics.[A23,A24]

Traumatic perforations of an eardrum usually heal without surgical intervention, but if an eardrum perforation persists for more than about 3 months, surgical closure and the use of tympanoplasty with or without mastoidectomy can be contemplated, although tympanostomy tubes do not prevent recurrent otitis media in children.[A25] Chronic draining perforations, especially if located in the posterior-superior quadrant of the tympanic membrane, may portend the presence of cholesteatoma and may require tympanomastoid surgery. Earwax, which may cause reduced hearing (Chapter 396) or ear pain, may be treated with removal of the wax and over-the-counter ceruminolytic agents.

In patients in whom herpes zoster is suspected, acyclovir can be started at 800 mg by mouth five times per day for 7 days, with or without prednisone (Chapter 346). Intracranial complications of otitis media, though rare, require urgent evaluation and surgical intervention.

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395 SMELL AND TASTE

ROBERT W. BALOH AND JOANNA C. JEN

EPIDEMIOLOGY

Loss of smell is increasingly being recognized by the fifth decade of life, and an inability to smell or a diminished sense of smell is present in 3 to 20% of the population.[1] Nevertheless, these disorders are often neglected because they are not fatal and, unlike abnormalities of vision and hearing, are not considered serious handicaps. Recently, however, loss of taste and smell has been identified as a common and very bothersome symptom in patients with coronavirus disease 2019 (COVID-19; Chapters 335 to 337),[2] in which changes in smell occur in up to 50% of cases,[3,4] usually several days after the onset of other symptoms

PATHOBIOLOGY

The sensory receptor for taste, the taste bud, is made up of 50 to 150 cells arranged to form a pear-shaped organ. The lifespan of these cells is 10 to 14 days, and they are constantly being renewed from dividing epithelial cells surrounding the bud. Taste buds are located on the tongue, soft palate, pharynx, larynx, epiglottis, uvula, and upper third of the esophagus. The taste buds located on the anterior two thirds of the tongue and on the palate are innervated by the chorda tympani branch of the seventh cranial nerve.[5] The ninth cranial nerve innervates the posterior third of the tongue. The ninth and tenth nerves innervate taste buds in the pharynx and larynx. Afferent signals from the taste buds project to the nucleus of the solitary tract in the medulla and then through a series of relays to the thalamus and postcentral somatosensory cerebral cortex (primary ipsilateral). Free nerve endings of the fifth cranial nerve are found on the tongue and in the oral cavity, and lesions involving these pathways can also alter taste perception.

Olfactory receptors lie in a roughly dime-sized area of specialized pigmented epithelium that arches along the superior aspect of each side of the nasal mucosa. Specialized bipolar sensory cells in this region thrust short receptor hairs into the overlying mucosa to detect aromatic molecules as they dissolve. Like taste buds, the specialized receptor portion of the bipolar neuron undergoes continuous renewal, with turnover occurring approximately every 30 days. Thin axons of the bipolar neurons course through small holes in the cribriform plate of the ethmoid bone to form connections in the overlying olfactory bulb on the ventral surface of the frontal lobe. From there, second- and third-order neurons project directly and indirectly to the prepiriform cortex and parts of the amygdaloid complex of both sides of the brain, which represents the primary olfactory cortex.

Genes that encode chemoreceptor proteins belong to the G protein–coupled receptor superfamily, which accounts for up to 1% of mammalian genomes. Sequence diversity in these genes encodes unique structural motifs that bind to different ligands signaling different odors and tastes. Distinct and dedicated taste receptor cells express unique receptors to detect each of the five basic tastes: sweet (sensed by the heterodimers T1R1 and T1R3), umami (detected by the heterodimers T1R2 and T1R3), bitter (sensed by an estimated 30 T2Rs), sour (sensed by PKD2L1, with membrane-tethered carbonic anhydrase IV sensing carbonation), and salty (epithelial sodium channel). The taste receptor cells transform and transmit information to primary afferents through multiple cranial nerves (VII, IX, and X) that project to the solitary tract nucleus in the brain stem, with relay in the thalamus, and then onward to the primary cortex (Fig. 395-1).

Disorders of taste and smell can be divided into local, systemic, and neurologic categories (Table 395-1). The taste buds and the specialized receptor portion of the bipolar olfactory cells are constantly being renewed, and the process of renewal can be affected by nutritional, metabolic, and hormonal states as well as by therapeutic radiation, drugs, and age. For example, with interruption of mitosis by antiproliferative agents, return of normal taste function takes a minimum of 10 days, whereas return to normal olfactory function takes more than 30 days. Diuretics can block apical ion channels on a taste bud, and antifungal drugs inhibit cytochrome P-450–dependent enzymes at the level of the receptors. Numerous local conditions, such as colds and allergies, chronic sinusitis, and nasal polyposis, can influence the sense of smell by restricting airway patency. Accidental blows to the head can shear the fine axons of the bipolar olfactory neurons and result in loss of smell. Lesions of the fifth, seventh (chorda tympani), and ninth nerves can lead to disordered taste sensation. Kallmann syndrome (Chapter 216) is anosmia associated with male infertility owing to defects in the secretion or action of gonadotropin-releasing hormone. By comparison, the loss of smell and taste in COVID-19 appears to be centrally mediated via immune inflammation.[6]

CLINICAL MANIFESTATIONS

Disorders of taste and smell can cause poor appetite and suboptimal intake of micronutrients, such as zinc, but do not directly contribute to overall protein-calorie undernutrition.[7] Disorders of taste interfere with digestion because taste stimulants alter salivary and pancreatic flow, gastric contractions, and intestinal motility. Smell also contributes to the anticipation and ingestion of food because much of what is tasted is derived from olfactory stimulation during ingestion and chewing. An inability to detect noxious tastes and odors can result in food or gas poisoning, particularly in elderly subjects. In the extreme, chemosensory disorders can lead to overwhelming stress, anorexia, and depression.

DIAGNOSIS

Olfaction can be tested grossly at the bedside with a few easily recognized odors, such as coffee, chocolate, and the roselike aroma of the compound phenylethyl alcohol.[8] Nasal irritants should be avoided. Each nostril is tested separately to determine whether the problem is unilateral or bilateral. Gustatory sensation is typically tested with weak solutions of sugar, salt, and acetic acid or vinegar. The patient must keep the tongue protruded and respond to questions by nodding the head or by pointing to names of the tastes written on cards. The anterior two thirds and posterior third of the tongue should be tested separately.

The most frequently encountered causes of loss of smell are local obstructive disease, viral infections, head injuries (Chapter 368), and normal aging (Chapter 24). Patients can lose their sense of smell not only from chronic allergies and sinusitis[9] (Chapter 394) but also from the nasal sprays and drops that they use to treat these conditions.

The most common causes of loss of the sense of taste are viral infections and drug ingestion, particularly antirheumatic and antiproliferative drugs (see Table 395-1).[10] Many of the systemic disorders that lead to loss of taste probably produce their effect by decreasing the rate of turnover of sensory receptors on the tongue and olfactory epithelia. In pregnancy (Chapter 221), taste is often altered, perhaps because taste buds express receptors for hormones that are altered during pregnancy.

Viral illnesses, such as influenza (Chapter 332), COVID-19 (Chapter 336), viral hepatitis (Chapter 134), and allergic rhinitis, are the most common causes of loss of both taste and smell. Olfactory and gustatory disturbances also can serve as important diagnostic signs for focal neurologic lesions from a neoplastic (e.g., frontal lobe tumors) inflammatory process. Multifocal neurologic disorders such as multiple sclerosis (Chapter 380) and traumatic head injuries (Chapter 368) can affect the central olfactory and gustatory pathways at multiple levels; as a result, abnormalities in taste and smell are common in such patients. Hallucinations of smell and taste occur in persons with epileptogenic lesions affecting the mesial temporal lobe and insular region, respectively. Olfactory disturbances and hallucinations also occur with a number of psychiatric illnesses (particularly depressive illness and schizophrenia), and especially

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395 SMELL AND TASTE

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DIAGNOSIS

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The most frequently encountered causes of loss of smell are local obstructive disease, viral infections, head injuries (Chapter 368), and normal aging (Chapter 24). Patients can lose their sense of smell not only from chronic allergies and sinusitis[9] (Chapter 394) but also from the nasal sprays and drops that they use to treat these conditions.

The most common causes of loss of the sense of taste are viral infections and drug ingestion, particularly antirheumatic and antiproliferative drugs (see Table 395-1).[10] Many of the systemic disorders that lead to loss of taste probably produce their effect by decreasing the rate of turnover of sensory receptors on the tongue and olfactory epithelia. In pregnancy (Chapter 221), taste is often altered, perhaps because taste buds express receptors for hormones that are altered during pregnancy.

Viral illnesses, such as influenza (Chapter 332), COVID-19 (Chapter 336), viral hepatitis (Chapter 134), and allergic rhinitis, are the most common causes of loss of both taste and smell. Olfactory and gustatory disturbances also can serve as important diagnostic signs for focal neurologic lesions from a neoplastic (e.g., frontal lobe tumors) inflammatory process. Multifocal neurologic disorders such as multiple sclerosis (Chapter 380) and traumatic head injuries (Chapter 368) can affect the central olfactory and gustatory pathways at multiple levels; as a result, abnormalities in taste and smell are common in such patients. Hallucinations of smell and taste occur in persons with epileptogenic lesions affecting the mesial temporal lobe and insular region, respectively. Olfactory disturbances and hallucinations also occur with a number of psychiatric illnesses (particularly depressive illness and schizophrenia), and especially

ABSTRACT

Chemosensory disorders are not life-threatening, but they reduce the enjoyment and quality of life and are very important to patients who have them. Disorders of taste and smell can be divided into local, systemic, and neurologic categories. The most common causes of loss of smell are local obstructive disease, viral infections, head injuries, and normal aging. The most common causes of loss of the sense of taste are viral infections and drug ingestion, particularly antirheumatic and antiproliferative drugs. Drugs known to affect taste or smell should be discontinued if possible to see whether patients improve. Vitamin and mineral therapies have been recommended but are of unproven benefit.

KEYWORDS

taste buds
olfactory receptors
chemoreceptor genes
chorda tympani nerve
olfactory hallucinations

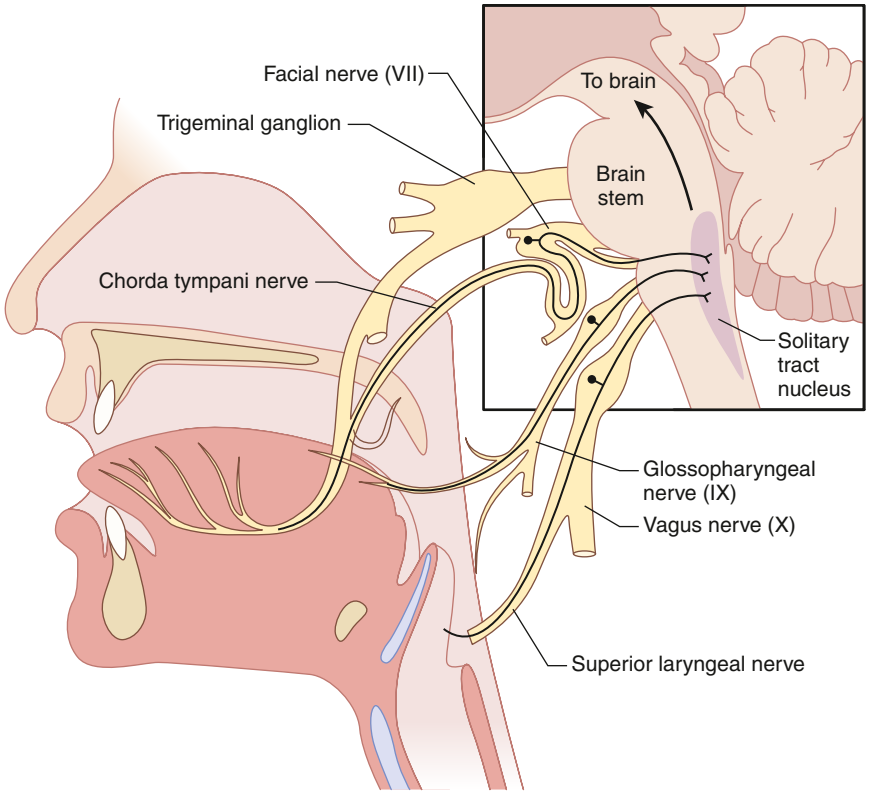

FIGURE 395-1. Anatomy of peripheral taste pathways. Taste information is transmitted from the mouth and the pharynx through multiple cranial nerves that project to the solitary tract nucleus in the brain stem, with relay in the thalamus before reaching the cortex. (Copyright 1999-2000 David Klemm. Reproduced from Bromley SM. Smell and taste disorders: a primary care approach. *Am Fam Physician*. 2000;61:427-436, 438.)

TABLE 395-1 COMMON CAUSES OF LOSS OF TASTE AND SMELL

	TASTE	SMELL
Local	Radiation therapy, oral infections, dentures, dental procedures	Allergic rhinitis, sinusitis, nasal polyposis, upper respiratory infection
Systemic	Cancer, renal failure, hepatic failure, nutritional deficiency (vitamin B_3, zinc), Cushing syndrome, hypothyroidism, diabetes mellitus, infection (viral), drugs (antirheumatic and antiproliferative, e.g., corticosteroids, cisplatin, carboplatin, cyclophosphamide, doxorubicin, and methotrexate)	Renal failure, hepatic failure, nutritional deficiency (vitamin B_{12}), Cushing syndrome, hypothyroidism, diabetes mellitus, infection (viral hepatitis, influenza), drugs (nasal sprays, antihistamines, decongestants, antibiotics, and antirheumatic and antiproliferative drugs that affect taste)
Neurologic	Bell palsy, familial dysautonomia, multiple sclerosis	Head trauma, multiple sclerosis, Parkinson disease, Alzheimer disease, frontal tumor

in patients with depression[11] and in the early stages of many neurodegenerative disorders, including Parkinson disease, motor neuron disease, Huntington disease, Alzheimer dementia,[12] and even mild cognitive impairment.[13]

TREATMENT AND PROGNOSIS

Treatment of olfactory dysfunction secondary to nasal disease is aimed at opening the air passageways while preserving the olfactory epithelium (Chapter 394). Intranasal steroids for rhinosinusitis (Chapter 394),[14] antibiotics as needed for sinusitis, and therapies for seasonal allergies are useful in selected cases,[15] but nasal corticosteroids are not effective for anosmia related to COVID-19.[A1] Drugs known to affect taste or smell (see Table 395-1) should be discontinued for a trial. Vitamin and mineral therapies are of unproven benefit.[A2] The treatment of taste and smell disorders in cancer patients is usually unsatisfactory, and no options are currently supported by firm data.[16] After COVID-19 and other viral infections, smell and taste typically return in 1 to 2 weeks,[17] but some patients have persistent defects.[18] Impaired odor identification, particularly in the anosmic range, is associated with increased mortality in older adults[19] even after controlling for dementia and medical comorbidity.

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396 HEARING AND EQUILIBRIUM

ROBERT W. BALOH AND JOANNA C. JEN

DISORDERS OF THE AUDITORY SYSTEM

DEFINITION

The normal ear can detect sound frequencies ranging between 20 and 20,000 Hz; the upper range drops off fairly rapidly with advancing age. The ear is most sensitive between 500 and 4000 Hz, which roughly corresponds to the frequency range most important for understanding speech. The hearing level in this range has several practical implications in terms of the degree of handicap and the potential for useful correction with amplification. A 30- to 40-dB hearing level in the speech range would impair normal conversation, whereas an 80-dB hearing level would make everyday auditory communication almost impossible (the social definition of deafness).

EPIDEMIOLOGY

About 5% of the world population suffers from disabling hearing loss (defined by the World Health Organization as greater than 40 dB in the better hearing ear in adults and greater than 30 dB in the better hearing ear in children). The prevalence of disabling hearing loss is twice as high in poorer countries compared with richer countries. The prevalence increases with every age decade, and it is higher in men than in women across all age decades. Even subclinical hearing loss is independently associated with accelerated cognitive decline, incident cognitive impairment, and a higher risk of accidental injury in community-dwelling older adults.[1,2]

PATHOBIOLOGY

Localization of Lesions within the Auditory Pathways

Conductive hearing loss results from lesions involving the external or middle ear. It is typically characterized by an approximately equal loss of hearing at all frequencies and by well-preserved speech discrimination once the threshold for hearing is exceeded. Patients with conductive hearing loss can hear speech in a noisy background better than in a quiet background because they can understand loud speech as well as anyone.

Sensorineural hearing loss results from lesions of the cochlea or auditory division of the eighth cranial nerve, or both. With sensorineural hearing loss, the hearing levels for different frequencies are usually unequal, typically resulting in better hearing for low- than for high-frequency tones. Patients with sensorineural hearing loss often have difficulty in hearing speech that is mixed with background noise and may be annoyed by loud speech. Three important manifestations of sensorineural lesions are diplacusis, recruitment, and tone decay. Diplacusis and recruitment are common with cochlear lesions; tone decay usually accompanies eighth nerve involvement.

Central hearing disorders result from lesions of the central auditory pathways. As a rule, patients with central lesions do not have impaired hearing for pure tones, and they can understand speech as long as it is clearly spoken in a quiet environment. If the listener's task is made more difficult with the introduction of background noise or competing messages, performance deteriorates more markedly in patients with central lesions than in normal subjects.

DIAGNOSIS

Evaluation

Bedside Test

A quick test for hearing loss in the speech range is to observe the response to spoken commands at different intensities (whisper, conversation, shouting). Tuning fork tests permit a rough assessment of the hearing level for pure tones of known frequency. The clinician can use his or her own hearing level as a reference standard. In the Rinne test, nerve conduction is compared with bone conduction by holding a tuning fork (preferably 512 Hz) against the mastoid process until the sound can no longer be heard. It is then placed 1 inch from the ear and, in normal subjects, can be heard about twice as long by air as by bone. If bone conduction is better than air conduction, the hearing loss is conductive, but care must be taken to ensure that the bone conduction is not heard in the normal ear. In the Weber test, the tuning fork is placed on the patient's forehead or upper teeth. Normally, this sound is referred to the center of the head. If it is referred to the side of unilateral hearing loss, the hearing loss is conductive; if it is referred away from the side of unilateral hearing loss, the loss is sensorineural.

Audiometry

Pure tone testing is the cornerstone of most auditory examinations. Pure tones at selected frequencies are presented through either earphones (air conduction) or a vibrator pressed against the mastoid portion of the temporal bone (bone conduction), and the minimal level that the subject can hear (threshold) is determined for each frequency. Two speech tests are routinely used. The *speech reception threshold* is the intensity at which the patient can correctly repeat 50% of the words presented. The speech reception threshold is a test of hearing sensitivity for speech and should reflect the hearing level for pure tones in the speech range. The *speech discrimination test* is a measure of the patient's ability to understand speech when it is presented at a level that is easily heard. In patients with eighth nerve lesions, speech discrimination scores can be severely reduced, even when pure tone thresholds are normal or nearly normal; by comparison, in patients with cochlear lesions, discrimination tends to be proportional to the magnitude of hearing loss.

Brain stem auditory evoked responses can be recorded from scalp electrodes at 0 to 10 msec (early), 10 to 50 msec (middle), and 50 to 500 msec (late) following a click (a high-frequency stimulus). The early potentials reflect electrical activity at the cochlea, eighth cranial nerve, and brain stem; the later potentials reflect cortical activity. Computer averaging of the responses to 1000 to 2000 clicks separates the evoked potential from background noise. Early evoked responses may be used to estimate the magnitude of hearing loss and to differentiate among cochlea, eighth nerve, and brain stem lesions.

Differential Diagnosis

Conductive Hearing Loss

The history, examination, and audiometry usually provide the key differential features for identifying common causes of hearing loss (Fig. 396-1). Asymmetrical hearing loss in adults is usually idiopathic.[3]

Otosclerosis commonly produces progressive conductive hearing loss by immobilizing the stapes with new bone growth in front of and below the oval window. The hearing loss is typically conductive, although in some persons the cochlea may be invaded by foci of otosclerotic bone, producing an additional sensorineural hearing loss. Otosclerosis usually stabilizes when the hearing level reaches 50 to 60 dB and rarely progresses to deafness.

The most common cause of reversible conductive hearing loss is *impacted cerumen* in the external canal. This benign condition is usually first noticed after bathing or swimming when a droplet of water closes the remaining tiny passageway. The most common serious cause of conductive hearing loss is inflammation of the middle ear, *otitis media*, either infective (suppurative) or noninfective (serous). Chronic otitis media with perforation of the tympanic membrane can result in an invasion of the middle ear and other pneumatized areas of the temporal bone by keratinizing squamous epithelium (*cholesteatoma*). Cholesteatomas can produce erosion of the ossicles and bony labyrinth, thereby resulting in a mixed conductive and sensorineural hearing loss. Barotrauma to the middle ear arises with otalgia and hearing loss and can be associated with serous effusion or hematotympanum (see Fig. 394-15 in Chapter 394). Other causes of conductive hearing loss include trauma, congenital malformations of the external and middle ear, and glomus body tumors.

Sensorineural Hearing Loss

Hereditary Deafness

Genetically determined deafness, usually from hair cell aplasia or deterioration, may be present at birth or may develop in adulthood. The diagnosis of *hereditary deafness* rests on the finding of a positive family history. Mutations in connexin 26, a key component of gap junctions in the inner ear, account for most cases of recessively inherited deafness. *Intrauterine factors* resulting in congenital hearing loss include infection (especially rubella); toxic, metabolic, and endocrine disorders; and anoxia associated with Rh incompatibility and difficult deliveries.

Cochlear Damage

Acute unilateral deafness usually has a cochlear basis. *Bacterial or viral infections* of the labyrinth, *head trauma* with fracture or hemorrhage into the cochlea, or *vascular occlusion* of a terminal branch of the anterior inferior cerebellar artery can extensively damage the cochlea and the vestibular labyrinth. An isolated sudden unilateral sensorineural hearing loss is presumed to reflect a

ABSTRACT

The neural pathways subserving hearing and those most important for equilibrium and spatial orientation are anatomically proximate in much of their course from their end organs in the inner ear to their termination in the superior portion of the temporal lobe. Because of the close anatomic linkage, disorders that affect hearing often affect equilibrium, and vice versa. Nevertheless, substantial pathophysiologic differences make clinical examination of the two systems different. The auditory system is relatively isolated physiologically, so that function and dysfunction can be tested independently of other neural systems. In contrast, the vestibular system has many close physiologic links with other neural systems (particularly the visual-oculomotor, somatosensory, and autonomic systems) and can be difficult to test in isolation of these other systems. Abnormalities of the auditory system lead to only a few well-defined and unique symptoms (i.e., hearing loss or tinnitus). Abnormalities of the vestibular system can mimic disorders of other neural structures when they cause dizziness, visual distortion (oscillopsia), imbalance, nausea, vomiting, and even syncope.

KEYWORDS

hearing loss
sudden deafness
tinnitus
vertigo
benign paroxysmal positional vertigo
Meniere disease
acoustic neuroma

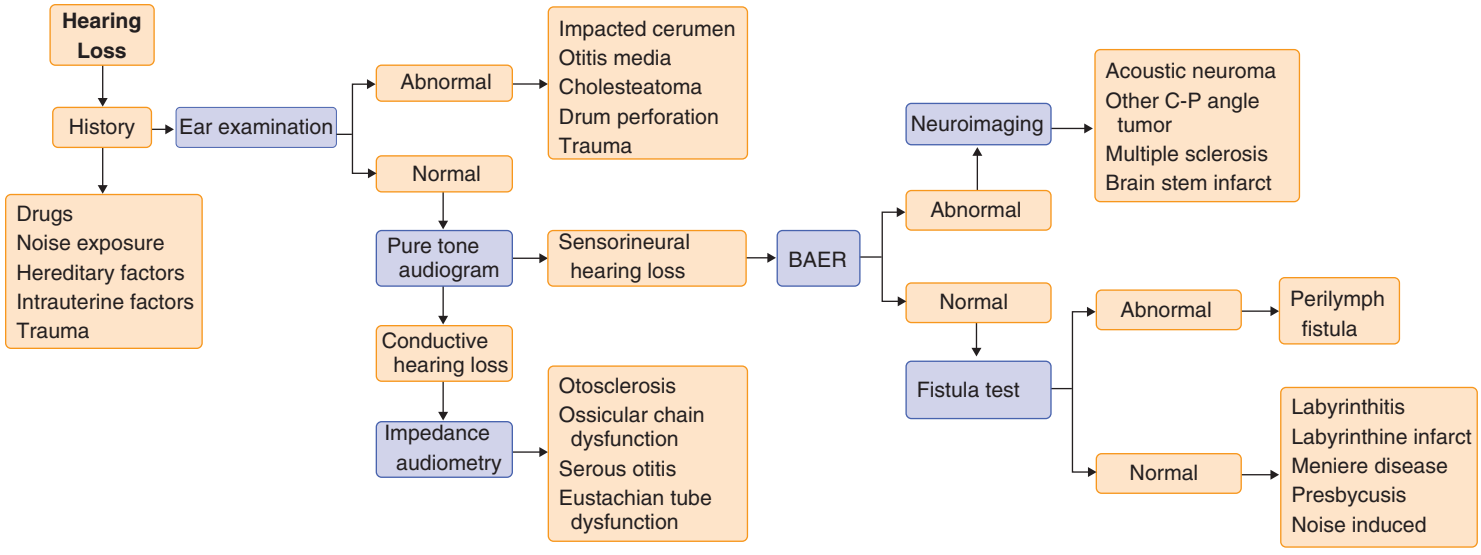

FIGURE 396-1. Evaluation of hearing loss. BAER = brain stem auditory evoked response; C-P = cerebellopontine.

viral infection of the cochlea and auditory nerve terminals. High-dose steroids followed by a rapid taper is recommended (see Treatment).

Sudden unilateral hearing loss often associated with vertigo and tinnitus can result from a *perilymphatic fistula*. Such fistulas may be congenital or may follow stapes surgery or head trauma.

Drugs

Drugs cause acute and subacute bilateral hearing impairment. Salicylates, furosemide, and ethacrynic acid have the potential to produce transient deafness when they are taken in high doses. More toxic to the cochlea are aminoglycoside antibiotics (gentamicin, tobramycin, amikacin, kanamycin, streptomycin, and neomycin). These agents can destroy cochlear hair cells in direct relation to their serum concentrations. Some antineoplastic chemotherapeutic agents, particularly cisplatin, cause severe ototoxicity.

Meniere Disease

Subacute relapsing cochlear deafness occurs with Meniere disease, a condition associated with fluctuating hearing loss and tinnitus, recurrent episodes of abrupt and often severe vertigo, and a sensation of fullness or pressure in the ear. Recurrent endolymphatic hypertension (hydrops) is believed to cause the episodes. On pathologic examination, the endolymphatic sac is dilated, and the hair cells become atrophic. The resulting deafness is subtle and reversible in the early stages but subsequently becomes permanent and is characterized by diplacusis and loudness recruitment. The disorder is usually unilateral, but in about 20 to 40% of patients, bilateral involvement eventually occurs.

Presbycusis

The gradual, progressive, bilateral hearing loss commonly associated with advancing age is called presbycusis. Presbycusis is not a distinct disease entity but rather represents multiple effects of aging on the auditory system. It may include conductive and central dysfunction, although the most consistent effect of aging is on the sensory cells and neurons of the cochlea. The typical audiogram of presbycusis is a symmetrical high-frequency hearing loss gradually sloping downward with increasing frequency. The most consistent pathologic finding associated with presbycusis is degeneration of sensory cells and nerve fibers at the base of the cochlea.

Noise

The recurrent trauma of *noise-induced hearing loss* affects approximately the same region at the base of the cochlea and is also common, particularly among those with exposure to loud explosive or industrial noises. Loud, blaring, modern music has become a recent offender. The loss almost always begins at 4000 Hz and does not affect speech discrimination until late in the disease process. With only brief exposure to loud noise (hours to days), there may be only a temporary threshold shift, but with continued exposure, permanent injury begins. The duration and intensity of exposure determine the degree of permanent injury, but estimates suggest that nearly 25% of American adults have some degree of noise-induced hearing damage or loss.

Acoustic Neuroma

Progressive unilateral hearing loss, which arises insidiously, initially in the high frequencies, and worsens by almost imperceptible degrees, is characteristic of benign neoplasms of the cerebellopontine angle, most commonly *acoustic neuromas*. In about 10% of cases, the hearing loss can be acute, apparently due to either hemorrhage into the tumor or compression of the labyrinthine vasculature. Magnetic resonance imaging (MRI) with contrast enhancement reliably identifies small acoustic neuromas.

Central Hearing Loss

Central hearing loss is unilateral only if it results from damage to the pontine cochlear nuclei on one side of the brain stem from conditions such as *ischemic infarction* of the lateral brain stem (e.g., occlusion of the anterior inferior cerebellar artery [Chapter 376]), a plaque of *multiple sclerosis* (Chapter 380), or, rarely, invasion or compression of the lateral pons by a *neoplasm* or *hematoma* (Chapters 175 and 368). Bilateral *degeneration* of the cochlear nuclei accompanies some of the rare recessive inherited disorders of childhood. As noted, clinically important unilateral hearing loss never results from neurologic disease arising rostral to the cochlear nucleus. Although bilateral hearing loss could, in theory, result from bilateral destruction of central hearing pathways, in practice this is rare because involvement of neighboring structures in the brain stem or hemisphere would usually produce overwhelming neurologic disability.

TREATMENT

If an underlying disorder has not yet destroyed the auditory system and can be ameliorated medically or surgically, hearing may be improved or preserved. Most patients with otosclerosis respond to stapedectomy. Closure of a perilymph fistula may improve hearing. Antibiotic and decongestive treatment of otitis media (Chapter 394) should prevent permanent hearing loss. Removal of ear wax can restore hearing when impacted cerumen is the cause.[4]

A brief course of high-dose steroids is commonly used for patients with idiopathic sudden unilateral sensorineural deafness, but the evidence to support this approach is limited. Intratympanic corticosteroid treatment (four doses of 40 mg/mL of methylprednisolone during 2 weeks) is not inferior to oral treatment (60 mg/day of oral prednisone followed by a 5-day taper) for idiopathic sudden sensorineural hearing loss, and combination oral and intratympanic therapy may be better than either alone.[A1] Hyperbaric oxygen therapy may also be helpful.[A2] A low-salt diet and diuretics are effective in selected cases of Meniere disease.

Folic acid supplementation appears to reduce the rate of hearing loss in the elderly. Hearing aids amplify sound, usually with the goal of making speech intelligible. Patients with conductive hearing loss require simple amplification, but those with sensorineural hearing loss often need frequency-selective amplification to make hearing aids useful. Hearing aids can also blunt the decline in cognitive function in the elderly.[5] Community health care workers can accelerate access to sound amplification devices.[A3]

Cochlear implants can markedly help patients of all ages with profound hearing loss if they have some intact auditory nerve fibers.[6] Intense postoperative speech recognition training is required.

PREVENTION

Noise-induced hearing loss can be prevented with the use of ear plugs and other noise-reducing interventions.[A4] Recent evidence also suggests that ebselen (a glutathione peroxidase 1 mimic at 400 mg twice daily 2 days before and 2 days after a noise challenge) can prevent noise-induced damage.[A5] However, the absence of interventions to blunt age-related hearing loss argues against routine hearing screening even in older adults.[7]

PROGNOSIS

Prognosis depends on the cause of hearing loss. For sudden idiopathic sensorineural hearing loss, about 40% of patients regain hearing but only about 15% have a complete recovery.[8]

TINNITUS

DIAGNOSIS

As many as 10% of U.S. adults may complain of tinnitus. The evaluation of common causes of tinnitus (Fig. 396-2) begins with a careful history to identify common offending drugs.[9]

Objective Tinnitus

With objective tinnitus, the patient hears a sound arising external to the auditory system, a sound that can usually be heard by the examiner with a stethoscope. Objective tinnitus usually has benign causes, such as noise from temporomandibular joints, opening of eustachian tubes, or repetitive muscle contractions. Sometimes, in a quiet room, the patient can hear the pulsatile flow in the carotid artery or a continuous hum of normal venous outflow through the jugular vein. The latter can be obliterated by compression of the jugular vein or extreme lateral rotation of the neck. Pathologic objective tinnitus occurs when patients hear turbulent flow in vascular anomalies or tumors (e.g., glomus jugulare tumor). Objective tinnitus also may be an early sign of increased intracranial pressure. Such tinnitus, which probably arises from turbulent flow through compressed venous structures at the base of the brain, is usually overshadowed by other neurologic abnormalities.

Subjective Tinnitus

Subjective tinnitus can arise from sites anywhere in the auditory system. The sounds most frequently reported are metallic ringing; buzzing; blowing; roaring; or, less often, bizarre clanging, popping, or nonrhythmic beating. Tinnitus heard as a faint, moderately high pitched, metallic ring can be observed by almost anyone who concentrates attention on auditory events in a quiet room. Sustained louder tinnitus accompanied by audiometric evidence of deafness occurs in association with both conductive and sensorineural hearing loss. Tinnitus observed with otosclerosis tends to have a roaring or hissing quality, and that associated with Meniere disease often produces sounds that vary widely in intensity with time and quality, sometimes including roaring or clanging. Tinnitus with auditory nerve lesions tends to be higher pitched and ringing in quality. Audiometric and brain stem evoked response testing can help distinguish between lesions involving the conducting apparatus, the cochlea, and the auditory nerve. Tinnitus without observable deafness appears sporadically and for variable lengths of time in many persons without other evidence of an ongoing pathologic process.

TREATMENT

Most patients with tinnitus can be helped by a careful evaluation to exclude serious underlying conditions and by subsequent reassurance when appropriate.[10] Often, exacerbating factors such as chronic anxiety and depression can be treated. In patients with hearing loss and tinnitus, a hearing aid may improve tinnitus because the amplification of ambient sound may effectively mask the tinnitus. This mechanism probably explains the frequent observation that removal of cerumen from the external auditory canal to improve ambient hearing also improves tinnitus. Also, when cerumen is attached to the tympanic membrane, tinnitus may result from local mechanical effects on the conductive system. For patients who find their tinnitus most obtrusive when trying to sleep, recorded masking sounds (e.g., white noise, rainfall, mountain stream) can be helpful. A careful drug history should be taken (see Fig. 396-2), and a drug-free trial period should be considered when possible.

No medications are approved for the treatment of tinnitus in the United States or Europe. Benzodiazepines (e.g., diazepam, 2 to 5 mg every 8 hours) or tricyclic amines (e.g., amitriptyline, 25 to 75 mg at bedtime) may provide temporary symptomatic relief of tinnitus, but cognitive-behavioral therapy, which can be administered face-to-face or via the Internet, is a more effective long-term approach that can significantly decrease tinnitus and improve health-related quality of life,[A6,A7] and group cognitive behavioral treatment may be better than individual therapy.[A8] Furthermore, some patients have varying degrees of spontaneous improvement. In patients with concomitant profound bilateral sensorineural hearing loss, cochlear implants can improve hearing and often decrease tinnitus.

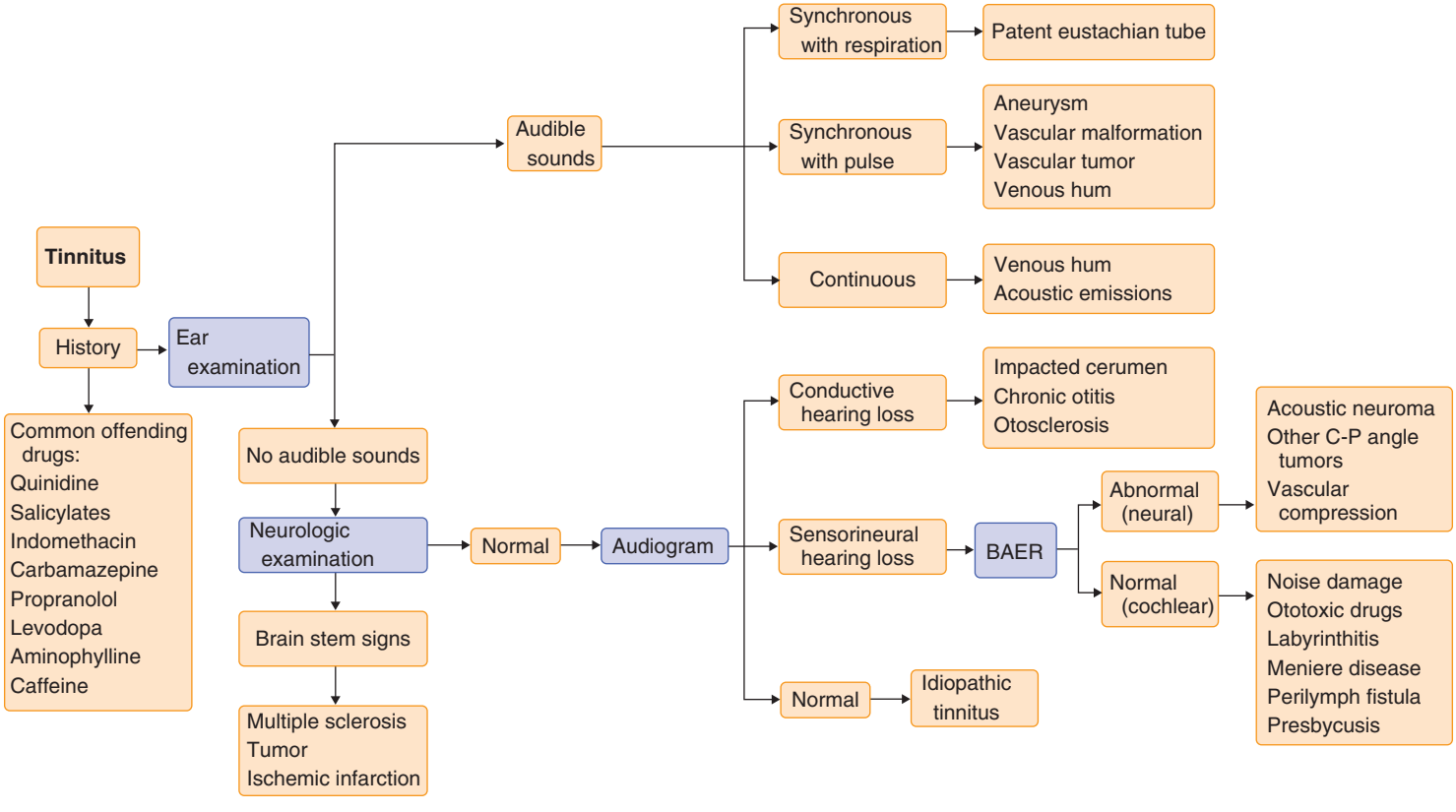

FIGURE 396-2. **Evaluation of tinnitus.** BAER = brain stem auditory evoked response; C-P = cerebellopontine.

EQUILIBRIUM–VESTIBULAR SYSTEM

PATHOBIOLOGY

Anatomy and Physiology of the Vestibular System

The paired vestibular end organs lie within the temporal bones next to the cochlea. Each organ consists of three semicircular canals that detect angular acceleration and two otolith structures, the utricle and saccule, that detect linear acceleration (including gravitational). Like the cochlea, these organs possess hair cells that act as force transducers, converting the forces associated with head acceleration into afferent nerve impulses. The hair cells of the three semicircular canals, each of which is oriented at right angles to the others, are located in the crista, where their cilia are embedded in a gelatinous mass called the *cupula*. Movement of the head causes the endolymph to flow either toward or away from the cupula, bending the cilia and, depending on the direction of endolymphatic movements, either exciting or inhibiting the afferent nerves at the base of the hair cells. The hair cells of the utricle and saccule are located in an area called the *macule*. The macule of the utricle lies approximately in the plane of the horizontal canal, and the macule of the saccule is approximately in the plane of the anterior canal. The hair cell cilia are embedded in a membrane that contains calcium carbonate crystals or otoliths; the density of otoliths is considerably greater than that of the endolymph. Linear accelerations of the head combine with the linear acceleration of gravity to distort the otolith membrane, thereby bending the cilia of the hair cells and modulating the activity of the afferent nerve terminals at the base of the hair cells.

The afferent vestibular nerves have their cell bodies in the Scarpa ganglion. The nerve fibers travel in the vestibular portion of the eighth cranial nerve contiguous to the acoustic portion. Fibers from different receptor organs terminate in different vestibular nuclei at the pontomedullary junction. There are also direct connections with many portions of the cerebellum, the greatest representation being in the flocculonodular lobe, the so-called vestibular cerebellum.

DIAGNOSIS

Evaluation

History

Most vestibular problems presented to the physician are episodic, and often there are neither symptoms nor signs when the physician examines the patient. The history therefore can become paramount for identifying vestibular dysfunction. The history should attempt to distinguish vertigo (the illusion of movement in space) from other types of dizziness (see later).

About 12% of patients with vertigo have a central cause, and about 88% have a problem with the peripheral vestibular apparatus. In general, peripheral vertigo is more severe, is more likely to be associated with hearing loss and tinnitus, and often leads to nausea and vomiting. Nystagmus associated with peripheral vertigo is usually inhibited by visual fixation. Central vertigo is generally less severe than peripheral vertigo and is often associated with other signs of central nervous system disease.[11] The nystagmus of central vertigo is not inhibited by visual fixation and frequently is prominent when vertigo is mild or absent.

Common Causes of Vertigo

Physiologic Vertigo

Physiologic vertigo includes common disorders that occur in healthy people, such as *motion sickness, space sickness,* and *height vertigo* (Fig. 396-3). In these conditions, vertigo (defined as an illusion of movement) is minimal whereas autonomic symptoms predominate. With height vertigo, patients may experience acute anxiety and panic reaction. Individuals with motion sickness and space sickness typically develop perspiration, nausea, vomiting, increased salivation, yawning, and generalized malaise. Gastric motility is reduced and digestion impaired. Even the sight or smell of food is distressing. Hyperventilation is a common sign, and the resulting hypocapnia leads to changes in blood volume, with pooling in the lower parts of the body predisposing to postural hypotension and syncope. An unusual variant of motion-induced dizziness occurs when the subject returns to stationary conditions after prolonged exposure to motion *(mal de débarquement syndrome)*. Typically, affected patients report that they feel the persistent rocking sensation of a boat long after returning to solid ground. Rarely, the syndrome can last for months to years after exposure to motion and can even be incapacitating. The cause is unknown.

Physiologic vertigo often can be suppressed by supplying sensory cues that help to match the signals originating from different sensory systems. Thus, motion sickness, which is caused by a mismatch of visual and vestibular signals, is exacerbated by sitting in a closed space or reading (giving the visual system the miscue that the environment is stationary). It may be improved by looking out at the horizon. Height vertigo, caused by a mismatch between sensation of normal body sway and lack of its visual detection, often can be relieved either by sitting or by visually fixating on a nearby stationary object.

Benign Paroxysmal Positional Vertigo (Canalithiasis)

Benign paroxysmal positional vertigo is by far the most common cause of vertigo.[12] Patients with this condition develop brief episodes of vertigo (<1 minute) with position change, typically when turning over in bed, getting in and out of bed, bending over and straightening up, or extending the neck to look up (so-called top-shelf vertigo). Benign paroxysmal positional vertigo results when otolith debris inadvertently enters one of the semicircular canals. It can occur after head trauma or inner ear infection but most commonly occurs spontaneously in older people and particularly in older women with osteoporosis. The diagnosis rests on finding characteristic positional nystagmus in the plane of the affected canal (see later). It is important to recognize this syndrome because, in most patients, it can be cured by simple bedside maneuvers (Fig. 396-4). If the history or findings are atypical, the condition must be distinguished from other causes of positional vertigo that may occur with tumors or infarcts of the posterior fossa.

Acute Peripheral Vestibulopathy (Vestibular Neuritis)

One of the most common clinical neurologic syndromes at any age is the acute onset of vertigo, nausea, and vomiting lasting for several days and not

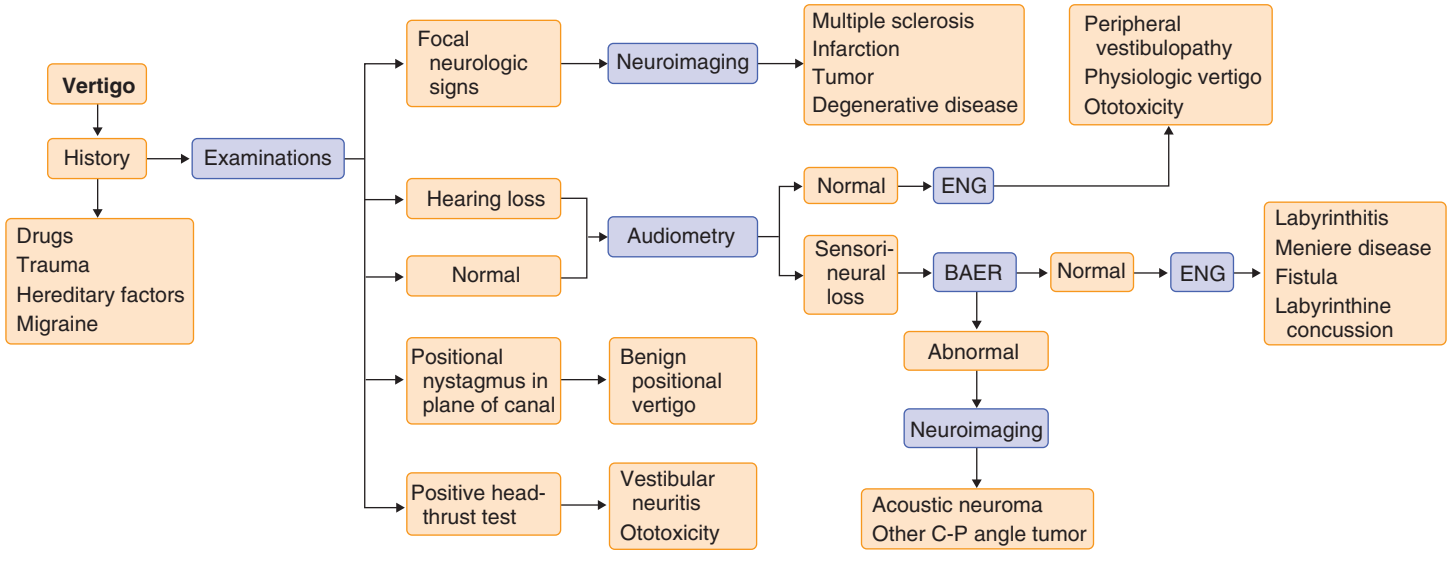

FIGURE 396-3. **Evaluation of vertigo.** BAER = brain stem auditory evoked response; C-P = cerebellopontine; ENG = electronystagmography.

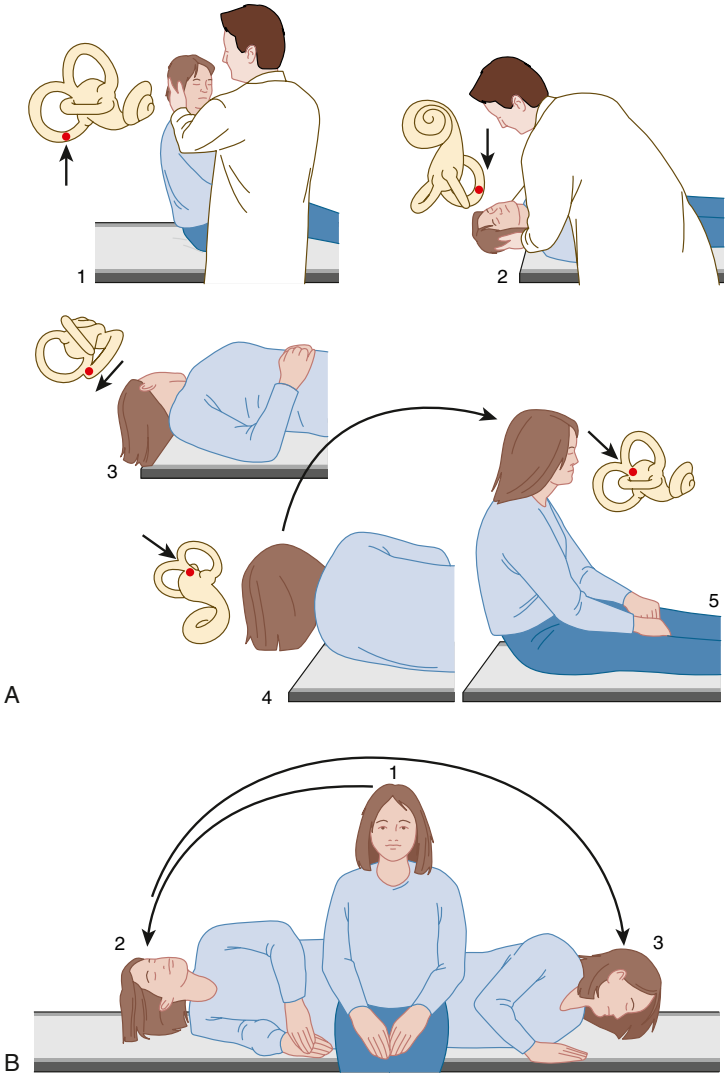

FIGURE 396-4. Modified Epley (A) and Semont (B) maneuvers for benign positional vertigo affecting the right posterior semicircular canal. The procedure is reversed to treat the left posterior semicircular canal. The entire sequence should be repeated until no nystagmus is elicited. (From Fife TD, Iverson DJ, Lempert T, et al. Practice parameter: therapies for benign paroxysmal positional vertigo [an evidence-based review]: report of the Quality Standards Subcommittee of the American Academy of Neurology. *Neurology*. 2008;70:2067-2074.)

associated with auditory or neurologic symptoms. A viral origin is suspected, but attempts to isolate an agent have been unsuccessful, except for occasional findings of a herpes zoster infection. Pathologic studies showing atrophy of one or more vestibular nerve trunks, with or without atrophy of their associated sense organs, are evidence of a vestibular nerve site and, probably, viral cause for most patients with this syndrome. Patients gradually improve during 1 to 2 weeks, but residual dizziness and imbalance can persist for months.

Meniere Disease

Meniere disease (see earlier) accounts for about 10% of all patients with vertigo. The diagnosis is based on documenting episodic severe attacks accompanied by fluctuating hearing levels on audiometric testing beginning in the low frequencies.

Migraine

Vertigo is a common symptom with migraine (Chapter 367). It can occur with headaches or in separate isolated episodes, and it can predate the onset of headache. So-called benign paroxysmal vertigo of childhood is often the first symptom of migraine. The mechanism of vertigo with migraine is not clear, but both peripheral and central types of nystagmus can occur with attacks. A few develop typical features of Meniere disease.

Post-traumatic Vertigo

Vertigo, hearing loss, and tinnitus often follow a blow to the head (Chapter 368) that does not result in temporal bone fracture, termed *labyrinthine concussion*. Blows to the occipital or mastoid region are particularly likely to produce labyrinthine damage. *Transverse fractures* of the temporal bone typically pass through the vestibule of the inner ear, tearing the membranous labyrinth and lacerating the vestibular and cochlear nerves. Complete loss of vestibular and cochlear function is the usual sequela, and the facial nerve is interrupted in approximately 50% of cases. Examination of the ear often reveals hemotympanum (see Fig. 394-15 in Chapter 394), but bleeding from the ear seldom occurs because the tympanic membrane usually remains intact. As noted earlier, *benign paroxysmal positional vertigo* is also a common sequela of head trauma. *Fistulas* of the oval and round windows can result from impact noise, deep-water diving, severe physical exertion, or blunt head injury without skull fracture. Clinically, the rupture leads to the sudden onset of vertigo or hearing loss, or both. Surgical exploration of the middle ear is warranted when there is a clear relationship between the onset of vertigo or hearing loss, or both, and the onset of severe exertion, barometric change, head injury, or impact noise.

Postconcussion Syndrome

The so-called postconcussion syndrome refers to a vague dizziness (not vertigo) associated with anxiety, difficulty in concentrating, headache, and photophobia induced by a head injury resulting in concussion (Chapter 368). On occasion, similar but less pronounced symptoms are associated with mild head injury judged to be trivial at the time. The cause is unknown, but animal studies indicate that small multifocal brain lesions (petechiae) commonly occur after concussive brain injury.

Other Peripheral Causes of Vertigo

Vertigo can be associated with *chronic bacterial otomastoiditis*, either from direct invasion of the inner ear by the bacteria or by erosion of the labyrinth by a cholesteatoma. Radiographic studies of the temporal bone readily identify these disorders. *Autoimmune inner ear disease* typically arises with episodic vertigo and fluctuating hearing levels similar to Meniere disease, but it is more fulminant with early bilateral involvement. It can occur in isolation or with other systemic features of autoimmune disease. About two thirds of patients have antibodies directed against heat shock protein 70. The aminoglycosides streptomycin and gentamicin are remarkably selective for vestibular ototoxicity. The patient may suffer acute vertigo if the toxic effect is asymmetrical. More often, there is a progressive symmetrical loss of vestibular function leading to imbalance but not vertigo. Unfortunately, many patients being treated with ototoxic drugs are initially bedridden and unaware of the vestibular impairment until they recover from their acute illness and try to walk. They then discover that they are unsteady on their feet and that the environment tends to jiggle in front of their eyes *(oscillopsia)*. The diagnosis can be made at the bedside with a head-thrust test (bilateral corrective saccades; see later). Caloric and rotational testing can confirm the vestibular loss. The best treatment is prevention. If the drug is discontinued early during the course of symptoms, the disorder may stabilize or improve.

Vascular Insufficiency

Vertebrobasilar insufficiency is a common cause of vertigo in older people. Whether the vertigo originates from ischemia of the labyrinth, brain stem, or both structures is not always clear because the blood supplies to the labyrinth, eighth cranial nerve, and vestibular nuclei originate from the same source, the basilar vertebral circulation (Chapter 375). Vertigo with *vertebrobasilar insufficiency* is abrupt in onset, usually lasting several minutes, and is frequently associated with nausea and vomiting. Associated symptoms resulting from ischemia in the remaining territory supplied by the posterior circulation include visual illusions and hallucinations, drop attacks and weakness, visceral sensations, visual field defects, diplopia, and headache. These symptoms occur in episodes either in combination with the vertigo or alone. Vertigo may be an isolated initial symptom of vertebrobasilar ischemia, but repeated episodes of vertigo without other symptoms should suggest another diagnosis. Vertebrobasilar insufficiency is usually caused by atherosclerosis of the subclavian, vertebral, and basilar arteries. MRI of the brain is usually normal because the vascular insufficiency is transient and function returns to normal between episodes. Magnetic resonance angiography can identify occlusive vascular disease most commonly involving the vertebral-basilar junction.

Vertigo is a common symptom with *infarction of the lateral brain stem* or *cerebellum* (Chapter 376), or both. The diagnosis is usually clear, based on the characteristic acute history and pattern of associated symptoms and neurologic findings. On occasion, cerebellar infarction or hemorrhage arises with

severe vertigo, vomiting, and ataxia without associated brain stem symptoms and signs that might suggest the erroneous diagnosis of an acute peripheral vestibular disorder. The key differential is the finding of clear cerebellar signs (extremity and gait ataxia); direction-changing, gaze-evoked nystagmus; and a normal head-thrust test. Such patients must be watched carefully for several days because they may develop progressive brain stem dysfunction as a result of compression by a swollen cerebellum.

Cerebellopontine Angle Tumors

Most tumors growing in the cerebellopontine angle (e.g., *acoustic neuroma, meningioma, epidermal cyst*) grow slowly, allowing the vestibular system to accommodate so that they produce only a vague sensation of disequilibrium rather than acute vertigo (Chapter 175). On occasion, however, episodic vertigo or positional vertigo heralds the presence of a cerebellopontine angle tumor. In virtually all patients, retrocochlear hearing loss is present, best identified by audiometric testing. MRI with contrast enhancement is the most sensitive diagnostic study for identifying a cerebellopontine angle tumor.

Other Central Causes of Vertigo

Acute vertigo may be the first symptom of *multiple sclerosis* (Chapter 380), although only a small percentage of young patients with acute vertigo eventually develop multiple sclerosis. Vertigo in multiple sclerosis is usually transient and often associated with other neurologic signs of brain stem disease, in particular, internuclear ophthalmoplegia or cerebellar dysfunction. Vertigo also may be a symptom of *parainfectious encephalomyelitis* or, rarely, *parainfectious cranial polyneuritis*. In this instance the accompanying neurologic signs establish the diagnosis. The *Ramsay Hunt syndrome* (geniculate ganglion herpes) is characterized by vertigo and hearing loss associated with facial paralysis and, sometimes, pain in the ear. The typical lesions of herpes zoster (Chapter 346), which may follow the appearance of neurologic signs, are found in the external auditory canal and over the palate in some patients. Rarely is herpes zoster responsible for vertigo in the absence of the full-blown syndrome. *Granulomatous meningitis* (Chapter 381) or *leptomeningeal metastasis* and cerebral or systemic *vasculitis* (Chapter 249) may involve the eighth nerve, producing vertigo as an early symptom. In these disorders, cerebrospinal fluid analysis usually suggests the diagnosis (Chapter 366). Patients suffering from *temporal lobe epilepsy* (Chapter 372) occasionally experience vertigo as the aura. Vertigo in the absence of other neurologic signs or symptoms is never caused by epilepsy or other diseases of the cerebral hemispheres.

Bedside Tests

Hyperventilation

If the history is not clear, bedside provocative tests to mimic the symptom may assist in making a pathophysiologic diagnosis. Hyperventilation, which lowers the arterial partial pressure of carbon dioxide ($Paco_2$) and decreases cerebral blood flow, causes a lightheaded sensation associated with syncope. Patients with compressive lesions of the vestibular nerve, such as with an acoustic neuroma or cholesteatoma, or with demyelination of the vestibular nerve root entry zone may develop vertigo and nystagmus after hyperventilation. Presumably, metabolic changes associated with hyperventilation trigger the partially damaged nerve to fire inappropriately.

Vestibulospinal Function

Bedside tests of vestibulospinal function are often insensitive because most patients can use vision and proprioceptive signals to compensate for any vestibular loss. Patients with acute unilateral peripheral vestibular lesions may past-point or fall toward the side of the lesion, but within a few days, balance returns to normal. Patients with bilateral peripheral vestibular loss have more difficulty compensating and usually show some imbalance on the Romberg and tandem walking tests (Chapter 366), particularly with eyes closed.

Doll's-Eye and Head-Thrust Tests

The vestibulo-ocular reflex can be tested at the bedside with the doll's-eye and head-thrust tests. In an alert human, rotating the head back and forth in the horizontal plane induces compensatory horizontal eye movements that are dependent on both the visual and vestibular systems. The doll's-eye test is a test of vestibular function in a comatose patient (Chapter 373) because such patients cannot generate pursuit or corrective fast components. In this setting, conjugate compensatory eye movements indicate normally functioning vestibulo-ocular pathways. Because the vestibulo-ocular reflex has a much higher frequency range than the smooth pursuit system, a qualitative bedside test of vestibular function can be made with the *head-thrust test*. It is performed by grasping the patient's head and applying brief, small-amplitude, high-acceleration head thrusts first to one side and then the other. The patient fixates on the examiner's nose and the examiner watches for corrective saccades, which are a sign of an inappropriate compensatory slow phase.

Caloric Test

The caloric test induces endolymphatic flow in the horizontal semicircular canal and horizontal nystagmus by creating a temperature gradient from one side of the canal to the other. With a cold caloric stimulus, the column of endolymph nearest the middle ear falls because of its increased density. This causes the cupula to deviate away from the utricle (ampullofugal flow) and produces horizontal nystagmus with the fast phase directed away from the stimulated ear. A warm stimulus produces the opposite effect, causing ampullopetal endolymph flow and nystagmus directed toward the stimulated ear (a mnemonic is COWS, meaning cold opposite, warm same). Because of its ready availability, ice water (approximately 0° C) can be used for bedside caloric testing. To bring the horizontal canal into the vertical plane, the patient lies in the supine position with head tilted 30 degrees forward. Infusion of 1 to 3 mL of ice water induces a burst of nystagmus usually lasting about a minute. Greater than a 20% asymmetry in nystagmus duration suggests a lesion on the side of the decreased response. The ice water caloric test is a useful way to test the integrity of the oculomotor pathways in a comatose patient. In this case ice water induces only a slow tonic deviation toward the side of stimulation.

Positional Tests

Examination for pathologic vestibular nystagmus should include a search for spontaneous and positional nystagmus (see Table 392-4 in Chapter 392). Because vestibular nystagmus secondary to peripheral vestibular lesions is inhibited with fixation, the yield is increased by impairing fixation with +30 lenses (Frenzel glasses) or infrared video recordings. Two types of positional testing are typically performed: moving the patient from the sitting to head-hanging-right and head-hanging-left positions (Dix-Hallpike test) and turning the head to the right and left while the patient lies supine.[13] Induced positional nystagmus may be paroxysmal or persistent, and it may be in the same direction in all positions or change directions in different positions. The most common cause of positional nystagmus is otolith debris in the semicircular canals, either free floating (paroxysmal) or attached to the cupula (persistent). This type of nystagmus always occurs in the plane of the affected canal—vertical torsional for the vertical canals and horizontal torsional for the horizontal canal. By contrast, central positional nystagmus is often pure vertical or horizontal and cannot be explained by stimulating a single semicircular canal.

Nystagmography

Nystagmography tests oculomotor control by inducing and recording eye movements. A standard test battery includes (1) tests of visual ocular control (saccades, smooth pursuit, and optokinetic nystagmus), (2) a careful search for pathologic nystagmus with fixation and with eyes open in darkness, and (3) the measurement of induced vestibular nystagmus (caloric and rotational). Nystagmography can be helpful in identifying a vestibular lesion and localizing it within the peripheral and central pathways.

Evaluating the "Dizzy" Patient

The history is key because it determines the type of dizziness (Table 396-1 and see Fig. 396-3), associated symptoms (neurologic, audiologic, cardiac, psychiatric), precipitating factors (position change, trauma, stress, drug ingestion), and predisposing illness (systemic viral infection, cardiac disease, cerebrovascular disease). The history provides direction for both the examination and the diagnostic evaluation. When focal neurologic signs are found, neuroimaging usually leads to a specific diagnosis. When vertigo is present without focal neurologic symptoms or signs, head-thrust and positional testing are key to localizing the lesion to the labyrinth or eighth nerve.[14] Audiometry and nystagmography are useful if the cause of vertigo is not clear after the history and examination. Patients with psychogenic dizziness (also called chronic subjective dizziness or persistent perceptual-postural dizziness) should be identified early so that needless tests are not obtained. A detailed cardiac evaluation (including loop monitoring) often identifies the cause of episodic near-fainting (Chapters 39 and 49). Experimental miniature video-oculography goggles can record spontaneous and positional nystagmus during a vertiginous attack and help distinguish among benign paroxysmal positional vertigo, Meniere disease, and vestibular migraines.[15]

TABLE 396-1 DESCRIPTION, MECHANISM, AND FOCUS OF DIAGNOSTIC WORK-UP FOR COMMON TYPES OF DIZZINESS

TYPE OF DIZZINESS	DESCRIPTION	MECHANISM	FOCUS OF DIAGNOSTIC EVALUATION
Vertigo	Spinning (environment moves), tilt, drunkenness	Imbalance in tonic vestibular activity	Auditory and vestibular systems
Near-faint	Lightheaded, swimming	Decreased blood flow to entire brain	Cardiovascular system
Psychogenic	Dissociated from body, spinning inside (environment still)	Impaired central integration of sensory signals	Psychiatric assessment
Disequilibrium	Off balance, unsteady on feet	Loss of vestibulospinal, proprioceptive, cerebellar, or motor function	Neurologic assessment

TREATMENT

Treatment of vertigo can be divided into three general categories: specific, symptomatic, and rehabilitative. When possible, treatment should be directed at the underlying disorder (Table 396-2). Specific therapies include particle repositioning maneuvers (the Epley and Semont maneuvers; see Fig. 396-4) for benign paroxysmal positional vertigo.[A9] For vestibular neuritis, steroids (e.g., methylprednisolone, 1 mg/kg/day for 5 days, then tapered during the next 15 days) are effective, at least for the short term, but antiviral agents are not. For Meniere disease, a low-salt diet and diuretics (e.g., 25 mg hydrochlorothiazide and 50 mg triamterene daily) are effective in some cases. Intratympanic methylprednisolone is comparable to intratympanic gentamicin injection in reducing vertiginous attacks in patients with refractory unilateral Meniere disease, but methylprednisolone preserves hearing.[A10] Endolymphatic duct blockage is a potential option for medically refractory Meniere disease. Limited data suggest that vitamin D (400 IU daily) plus calcium carbonate (500 mg twice daily) may reduce the risk of recurrent vertigo by about 25% in individuals who have benign paroxysmal positional vertigo and low vitamin D levels,[A11] but the findings of this single-blind trial require confirmation.

In many cases, however, symptomatic treatment either is combined with specific therapy or is the only treatment available. Many different classes of drugs have been found to have antivertiginous properties, and in most instances, the exact mechanism of action is uncertain. All these agents produce potentially unpleasant side effects, and the decision concerning which drug or combination to use is based on their known complications and on the severity and duration of the vertigo. An episode of prolonged, severe vertigo is one of the most distressing symptoms that a patient can experience. Affected patients prefer to lie still with eyes closed in a quiet, dark room. Antivertiginous drugs, such as dimenhydrinate (25 mg) or diazepam (5 mg), may be helpful. Promethazine suppositories (25 mg) are useful in patients with vomiting.

In more chronic vertiginous disorders, when the patient is trying to carry on normal activity, less sedating antivertiginous medications, such as meclizine (25 mg) or transdermal scopolamine (0.5 mg every 3 days), may provide relief. Chronic use of these drugs should be avoided.

Vestibular rehabilitation exercises are designed to help the patient compensate for permanent loss of vestibular function.[A12] As the acute stage of nausea and vomiting subsides, the patient should attempt to focus the eyes and to move and hold them in the direction that provokes the most dizziness. A useful exercise involves staring at a visual target while oscillating the head from side to side or up and down, slow at first and then fast. The patient should try to stand and walk, at first in contact with a wall or with an assistant, and make slow supported turns. As improvement occurs, head movements should be added while standing and walking. For refractory ototoxic or idiopathic chronic bilateral vestibular hypofunction, a vestibular implant that electrically stimulates the vestibular nerve is an experimental approach to improve posture, gait, and quality of life, although it may reduce hearing in the ear with the implant.[16]

PROGNOSIS

Vertigo commonly resolves, either because patients become truly asymptomatic or adjust to occasional symptoms. Among patients diagnosed with a peripheral cause of vertigo, the 30-day risk of accidental injury is less than 0.2%, as is the 30-day risk of stroke.

TABLE 396-2 TREATMENT OF COMMON VERTIGO SYNDROMES

SYNDROME	TREATMENT
Benign positional vertigo	
Posterior canal variant	Epley maneuver (see Fig. 396-4)
Horizontal canal variant	Barbecue roll toward normal side (side with less nystagmus), sleep with normal ear down
Vestibular neuritis	Methylprednisolone, 100 mg × 3 days, gradual taper during 22 days (must start within 3 days of onset)
Meniere disease	
Medical	Low salt (1-2 g salt/day) *and* either hydrochlorothiazide 25-50 mg/day *or* hydrochlorothiazide 25 mg/day plus triamterene 50 mg/day
Surgical	Intratympanic gentamicin, vestibular nerve section

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For the General References and other additional features, please visit Elsevier eBooks+ at https://ebooks.health.elsevier.com.

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397 THROAT DISORDERS

PAUL W. FLINT

Nearly every systemic and infectious disease results in head and neck manifestations, with the majority affecting the upper aerodigestive tract. Diseases of the upper aerodigestive system include infection (acute and chronic; viral, bacterial, and fungal), systemic disease, and neoplasm (Chapter 176), some of which require urgent care or referral to an otolaryngologist.[1]

Abnormalities of swallowing, respiratory function, voice, and speech are influenced by the anatomic site involved, the host's immune status and inflammatory response, the severity of the disease process, and the presence or absence of neurologic involvement.

In a patient with hoarseness, current clinical practice guidelines recommend visualization of the larynx for symptoms that persist for 3 months or longer; however, warning signs of a potentially serious or emergent throat condition warrant referral regardless of duration. These conditions include persistent throat pain with or without trismus, difficulty in swallowing, difficulty in breathing, hemoptysis, and ear pain with normal ear examination findings. Diagnostic testing options, which include fiberoptic examination, imaging, pulmonary function studies, and laboratory testing, are directed by history, symptoms, and physical findings.

ANATOMY OF THE UPPER AERODIGESTIVE TRACT

The pharynx is divided into three anatomic regions (Fig. 397-1). The *nasopharynx* is the region above the soft palate and uvula. Its anatomic components include the adenoids, the openings of the eustachian tubes, Rosenmüller fossa at the junction of the posterior and lateral walls, and the posterior aspect of the inferior turbinates of the nasal cavity. Diseases of the nasopharynx typically produce few symptoms until the process is well advanced and causes nasal obstruction (Chapter 394), epistaxis (Chapter 394), ear pain (Chapter 394), headache (Chapter 367), or cranial nerve abnormalities due to extension to the skull base. The *oropharynx* begins at the level of the soft palate and extends inferiorly to the tip of the epiglottis. This region includes the faucial tonsils, the base of the tongue, the lingual tonsils, the soft palate, the uvula, and part of the posterior pharyngeal wall. The *hypopharynx*, which extends from the tip of the epiglottis to the upper esophagus (the cricopharyngeus muscle) below, includes the larynx (epiglottis, arytenoids, glottis or true vocal cords), the piriform sinuses (pharyngeal folds lateral to the larynx), and the posterior pharyngeal wall. The tip of the epiglottis can be visualized by an experienced examiner with use of a laryngeal mirror or sometimes even on a routine oral examination with just a flashlight and tongue blade. The nasopharynx and hypopharynx are best visualized with a flexible fiberoptic nasopharyngoscope.

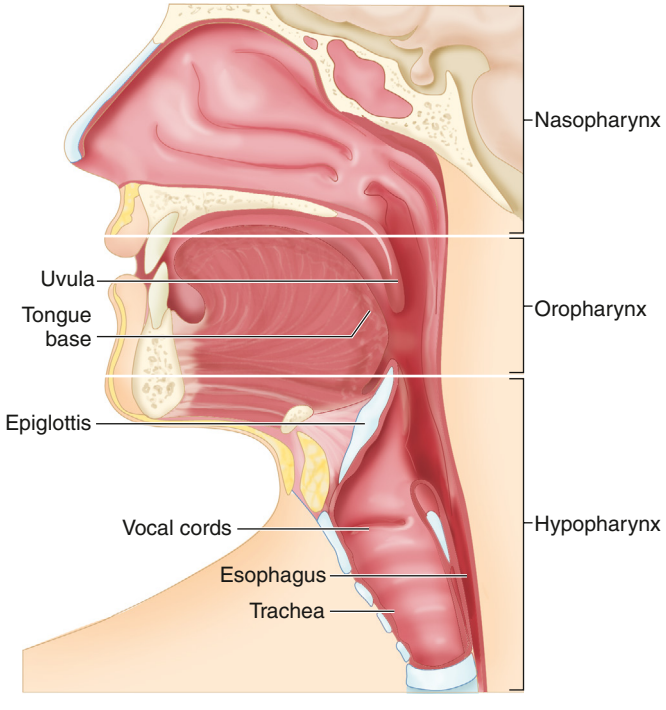

FIGURE 397-1. The pharynx (throat) is typically divided into three distinct anatomic regions (nasopharynx, oropharynx, and hypopharynx). (Courtesy Thomas A. Tami, MD.)

INFECTIOUS DISEASES OF THE UPPER AERODIGESTIVE SYSTEM

Infectious disorders of the upper aerodigestive tract typically are manifested as sore throat (pharyngitis),[2] changes in voice (laryngitis), or both.[3] The clinical evaluation must differentiate among bacterial (usually streptococcus [Chapter 269]), viral, and other infections and systemic causes (Table 397-1). Clinical differentiation of sore throat is critical to primary care and emergency management of the airway.

PHARYNGITIS

Bacterial infection accounts for approximately 5 to 10% of pharyngitis in adults compared with 30 to 40% in children. Unfortunately, as many as two thirds of adults with a sore throat are prescribed antibiotics.

STREPTOCOCCAL INFECTIONS

Group A β-hemolytic *Streptococcus pyogenes* (Chapter 269) is the most common cause of bacterial pharyngitis in adults, although it accounts for only 10% of all pharyngitis in adults. Infection is manifested with the rapid onset of sore throat, often accompanied by pain with swallowing, fever, chills, malaise, headache, mild neck stiffness, and anorexia. Hypertrophic tonsils with exudates, foul breath, and tender cervical adenopathy are hallmark findings. Some patients have palatal petechiae or a scarlatiniform rash. Rhinorrhea, hoarseness, cough, conjunctivitis, diarrhea, and ulcerative oral lesions are less common.

Untreated group A β-hemolytic *S. pyogenes* pharyngitis usually resolves within 3 to 7 days. The administration of antibiotics within 24 to 48 hours reduces pain by approximately 1 day,[A1] whereas both immediate and delayed antibiotics reduce the risk for suppurative complications.[A2] Antibiotics also reduce the contagious period from 2 weeks to 24 hours after administration. For prevention of rheumatic fever (Chapter 269), antibiotic therapy must be started within 10 days after the onset of symptoms. The risk for acute poststreptococcal glomerulonephritis (Chapter 107), however, is not affected by antibiotics.

To minimize the potential side effects and costs of unnecessary antibiotics, antibiotic therapy should be based on the presence of fever, tender anterior cervical adenopathy, tonsillar swelling or exudates, age, and the absence of cough. A rapid antigen test should be obtained in patients with three or more (or perhaps two or more) criteria (Table 397-2).[4] If the rapid antigen test result is negative but the clinical suspicion remains high, a throat culture specimen should be obtained for confirmation before starting antibiotics. Such a strategy can significantly reduce the unnecessary use of antibiotics.[A3]

Antibiotic options (Chapter 269) include penicillin (penicillin VK, 250 mg four times a day or 500 mg twice a day for 10 days), which is usually chosen to treat acute bacterial pharyngitis, although cefuroxime axetil (250 mg twice a day for 10 days) is even more effective for primary treatment and can be effective for persistent infection.[A4] In patients with proven recurrent infections, clindamycin (300 mg orally four times a day for 10 days) or amoxicillin–clavulanic acid (875 mg orally twice a day or 500 mg three times a day for 10 days) is recommended. For patients who are allergic to penicillin, azithromycin (500 mg/day for 3 days) is another alternative. Evidence also suggests that a single dose of oral or intramuscular corticosteroids given at the start of treatment will reduce the pain of severe pharyngitis, especially in children.[A5] In patients with recurrent symptomatic episodes despite appropriate antimicrobial therapy, tonsillectomy can decrease future throat infections, at least in the short term, compared with continued observation.[A6]

Non–group A β-hemolytic streptococcal infections (Chapter 269), including groups B, C, and G, can cause acute pharyngitis with a clinical picture that mirrors that of group A β-hemolytic streptococcal pharyngitis. Glomerulonephritis is a known sequela, whereas rheumatic fever is not. Penicillin or clindamycin, as prescribed for group A β-hemolytic streptococcus, provides adequate coverage.

NONSTREPTOCOCCAL BACTERIAL PHARYNGITIS

A variety of bacteria other than streptococci can infect the throat. For example, *Fusobacterium necrophorum*–positive pharyngitis, which clinically resembles

ABSTRACT

Nearly every systemic and infectious disease results in head and neck manifestations, with the majority affecting the upper aerodigestive tract. Diseases of the upper aerodigestive system include infection (acute and chronic; viral, bacterial, and fungal), systemic disease, and neoplasm, some of which require urgent care or referral to an otolaryngologist. Abnormalities of swallowing, respiratory function, voice, and speech are influenced by the anatomic site involved, the host's immune status and inflammatory response, the severity of the disease process, and the presence or absence of neurologic involvement. In a patient with hoarseness, current clinical practice guidelines recommend visualization of the larynx for symptoms that persist for 3 months or longer; however, warning signs of a potentially serious or emergent throat condition warrant referral regardless of duration. These conditions include persistent throat pain with or without trismus, difficulty in swallowing, difficulty in breathing, hemoptysis, and ear pain with normal findings on the ear examination. Diagnostic testing options, which include rigid and flexible fiberoptic laryngoscopy, imaging, pulmonary function studies, and laboratory testing, are directed by history, symptoms, and physical findings. This chapter introduces non-otolaryngologists to head and neck disorders that would likely present to a general practice. Emphasis is placed on diagnosis, testing, initial treatment, and criteria for referral to a specialist.

KEYWORDS

laryngitis
pharyngitis
hoarseness
odynophagia
vasculitis
laryngeal paralysis

TABLE 397-1 CLINICAL DIFFERENTIATION OF COMMON CONDITIONS ARISING AS SORE THROAT

FEATURE	VIRAL PHARYNGITIS	BACTERIAL TONSILLITIS	PERITONSILLAR ABSCESS	EPIGLOTTITIS
Tonsillar enlargement	Usual	Often	None	None
Tonsillar exudates	Occasional (infectious mononucleosis)	Usual	Often	None
Tonsillar asymmetry	None	None	Usual	None
Trismus (inability to open jaw)	None	None	Usual	None
Cervical adenopathy	Occasional	Usual (tender)	Usual (tender)	None
Tender larynx	Rare	None	None	Usual

From Tami TA. Throat disorders. In: Goldman L, Schafer AI, eds. *Goldman's Cecil Medicine*. 24th ed. Philadelphia: Elsevier Saunders; 2012.

TABLE 397-2 GUIDELINES FOR THE MANAGEMENT OF PHARYNGITIS

CENTOR SCORE*	PERCENTAGE POSITIVE FOR *STREPTOCOCCUS* INFECTION	ACP/CDC GUIDELINES†
0	7%	Do not test, do not treat
1	12%	Do not test, do not treat
2	21%	Treat if rapid test result positive
3	38%	
4	57%	

*Calculated as follows: 1 point each for temperature >38°C, absence of cough, presence of swollen and tender anterior cervical nodes, tonsillar swelling or exudate, or age 3 to 14 years; and −1 point for age ≥45 years.

†See Harris AM, Hicks LA, Qaseem A. Appropriate antibiotic use for acute respiratory tract infection in adults: advice for high-value care from the American College of Physicians and the Centers for Disease Control and Prevention. *Ann Intern Med*. 2016;164:425-434.

ACP = American College of Physicians; CDC = Centers for Disease Control.

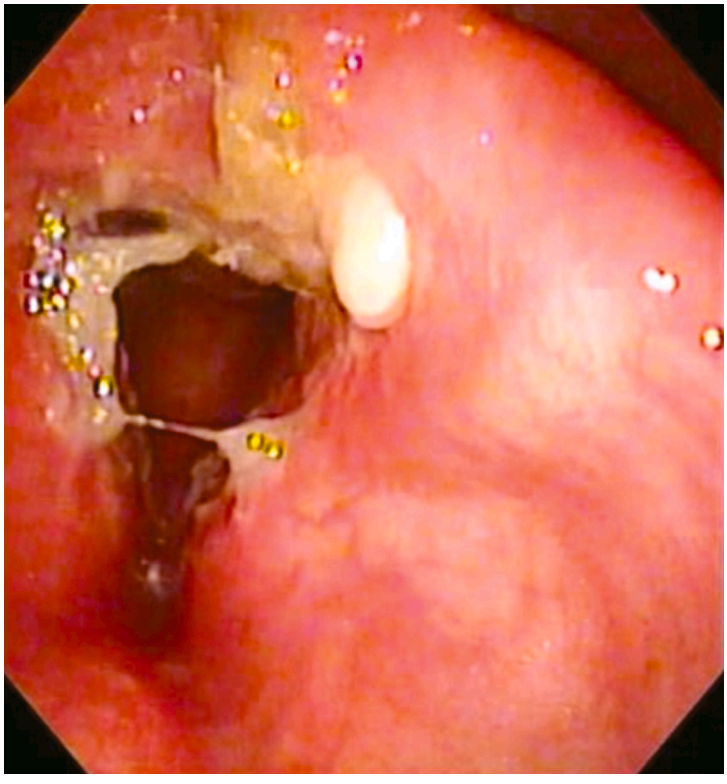

FIGURE 397-2. Fiberoptic laryngoscopy demonstrating chronic laryngitis secondary to methicillin-sensitive *Staphylococcus aureus* infection. Diagnosis is based on culture and biopsy.

streptococcal pharyngitis, occurs more frequently than group A β-hemolytic streptococcus–positive pharyngitis in a student population.[5] *Staphylococcus aureus* (Chapter 267) infections, whether caused by methicillin-resistant (MRSA) or methicillin-sensitive (MSSA) strains, usually are manifested with chronic hoarseness. About 30% of patients with bacterial laryngitis will have MRSA infection.[6] Laryngoscopy typically reveals thickened erythematous vocal folds with edema, whitish debris, and crusting, which may resemble leukoplakia (Fig. 397-2). Trimethoprim-sulfamethoxazole (160 mg/800 mg twice daily for 2 to 4 weeks) is generally effective, but treatment should be guided by antibiotic sensitivities.

Bordetella pertussis (Chapter 289) infections have become more common in adults because of their gradual loss of immune protection after vaccination. Adults typically present with cough, often but not always accompanied by nonspecific upper respiratory symptoms, fever, and leukocytosis. A *B. pertussis* serum immunoglobulin G titer higher than 27 IU/mL is highly predictive of recent infection. Erythromycin (500 mg four times a day for 14 days) or azithromycin (500 mg single dose orally on day 1, then 250 mg daily on days 2 through 5) is effective treatment.

Neisseria gonorrhoeae (Chapter 275) can cause sexually transmitted gingivitis, stomatitis, glossitis, and pharyngitis, especially in men who have sex with men. Treatment is the same as for urogenital disease and should include treatment for chlamydia. Options include ceftriaxone, 500 mg intramuscularly in a single dose, and doxycycline, 100 mg orally twice daily for 7 days. *Treponema pallidum* (Chapter 295) can cause oral and oropharyngeal ulcerations that involve the lips, tongue, and tonsil. Treatment is the same as that recommended for systemic disease. *Chlamydia* (Chapter 294), which is commonly associated with pneumonia and bronchitis, also can cause pharyngitis and hoarseness, sometimes as its presenting symptoms. *Mycoplasma pneumoniae* (Chapter 293), which frequently accounts for 15 to 20% of cases of community-acquired pneumonias, also can cause sore throat, nasal congestion, and coryza. Treatment of chlamydia and mycoplasma infections with tetracyclines, macrolides, and quinolones is the same as for the pneumonias they cause (Chapters 293 and 294).

Francisella tularensis (Chapter 287) is a gram-negative bacillus that causes tularemia. Oropharyngeal involvement is associated with fever, pharyngeal erythema, exudative tonsillitis, and tender lymphadenopathy. A false-positive monospot test result and atypical lymphocytosis can mimic infectious mononucleosis. The organism is sensitive to macrolides, fluoroquinolones, and tetracyclines.

Corynebacterium diphtheriae infection (Chapter 272) involves the mucosal surfaces of the upper respiratory tract, where it causes a patchy gray-black pseudomembrane in the nasopharynx, oropharynx, larynx, and trachea. About 75% of patients complain of throat pain. Airway obstruction and severe dysphagia are life-threatening sequelae. Antitoxin is given in combination with penicillin, erythromycin, tetracycline, clindamycin, or rifampin.

Arcanobacterium haemolyticum (Chapter 272) is a gram-positive bacillus that can cause pneumonia, meningitis, osteomyelitis, brain abscess, and peritonsillar abscess in both normal and immunocompromised patients. Uncomplicated pharyngitis may be treated with erythromycin (250 mg four times a day). Complicated infections require intravenous dosing with vancomycin, clindamycin, or cephalexin, with or without gentamicin (see Table 266-4 in Chapter 266).

PERITONSILLAR ABSCESS AND DEEP SPACE INFECTIONS

Only about 1% of patients with acute bacterial pharyngitis develop serious suppurative complications.[7] The best predictors are severe tonsillar inflammation and severe earache, but most complications occur in patients with neither of these findings. Peritonsillar abscesses usually can be diagnosed on physical examination (Fig. 397-3) and managed by an otolaryngologist in an outpatient setting by surgical drainage, needle drainage, or medical therapy. In uncomplicated patients without trismus, medical therapy appears to be equally safe and efficacious.[A7] Patients treated with medical therapy

FIGURE 397-3. Left peritonsillar abscess identified by bulging anterior pillar and soft palate with midline shift. (Courtesy Thomas A. Tami, MD.)

FIGURE 397-4. Mononucleosis with symmetrical exudative tonsillitis. (Courtesy Thomas A. Tami, MD.)

also experience less pain, use fewer opioids, and miss fewer days of work.[8] Oral antibiotics, such as clindamycin (300 to 450 mg four times a day for 14 days) or amoxicillin-clavulanate (875 mg orally twice a day for 10 days), are recommended. The addition of metronidazole does not add benefit in otherwise healthy adults who are treated with incision and drainage, and it can increase adverse events.

By comparison, patients with deep neck abscesses often have swelling of the external neck, trismus, torticollis, and even a compromised airway due to infection that has spread to the fascial planes of the neck and chest. These infections require urgent evaluation, usually with a computed tomography scan with contrast enhancement. Aggressive management includes incision and drainage as well as broad-spectrum intravenous antibiotics that cover aerobic and anaerobic bacteria (ampicillin-sulbactam, 3 g every 6 hours; ceftriaxone 2 g intravenously every 24 hours; levofloxacin 750 mg intravenously every 24 hours plus metronidazole 500 mg every 6 hours; or clindamycin 600 mg intravenously every 8 hours).

Severe infections of the pharynx can cause septic thrombophlebitis of the internal jugular vein (Lemierre syndrome), an uncommon but serious complication. Patients typically present with persistent fever, difficulty in swallowing, neck pain, and a neck mass due to an underlying peritonsillar, retropharyngeal, or parapharyngeal abscess. Diagnosis is best established with a contrast-enhanced computed tomography scan of the neck. This potentially life-threatening condition is almost always associated with anaerobic infection, especially with *F. necrophorum* or *A. haemolyticum* (Chapter 273). Infection can extend into the intrathoracic vasculature, and patients can develop bacteremia and septic pulmonary emboli. Treatment should be directed toward anaerobic coverage (empiric coverage with piperacillin-tazobactam 3.375 g intravenously every 6 hours, a carbapenem such as imipenem 500 mg intravenously every 6 hours, meropenem 1 g intravenously every 8 hours, ertapenem 1 g intravenously every 24 hours, or ceftriaxone 2 g intravenously every 24 hours plus metronidazole 500 mg intravenously every 8 hours). Anticoagulation with heparin is controversial and generally reserved for persistent septic emboli. Surgical intervention includes drainage of the abscess. Ligation or excision of the jugular vein may be indicated for persistent septic emboli unresponsive to medical management. Mortality rates can be as high as 5%.

VIRAL INFECTIONS

Prior to the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) pandemic (Chapter 336), the common cold (Chapter 329) caused 30 to 60% of cases of pharyngitis, with rhinovirus (Chapter 329) accounting for the majority of cases, followed by coronavirus (Chapter 334) and parainfluenza (Chapter 331) (see Table 397-2). U.S. adults experienced an average of 2.5 episodes per year of noninfluenza, non-coronavirus disease 2019 (COVID-19) upper respiratory infections, each with a 7.4-day average duration of symptoms. These 500 million episodes historically cost an estimated $40 billion annually, in part because of associated systemic symptoms such as fever, cough, and sinusitis and in part because of associated exacerbations of allergies, asthma, and chronic obstructive pulmonary disease. With COVID-19, the incidence of essentially every other viral pharyngeal infection declined markedly because of masking and social distancing, but their rates undoubtedly will increase back toward or to historic levels as such restrictions are lifted.

The viral infection that is most likely to be confused with a bacterial infection is mononucleosis. Mononucleosis is caused by Epstein-Barr virus (Chapter 348), which has a seroprevalence of 67% in U.S. children and adolescents aged 6 to 19 years. After an incubation period of 3 to 7 weeks, patients present with initial malaise, fever, and chills followed by sore throat, fever, and anorexia.[9] Some patients have associated abdominal discomfort due to splenomegaly or hepatomegaly, headache, stiff neck, and rash. On physical examination, patients have erythematous pharyngitis with exudative tonsillar hypertrophy (Fig. 397-4), prominent lingual tonsils, and adenoid hypertrophy (Waldeyer ring). Aphthous-type ulcerations and petechiae may be seen, especially at the junction of the hard and soft palate. Impressive cervical adenopathy is typical, and 50% of patients have splenomegaly. Lymphoid hyperplasia can cause some degree of upper airway obstruction in about 5% of patients.

A blood count will show lymphocytosis, usually with more than 10% atypical lymphocytes. The heterophil antibody test result is often positive, and Epstein-Barr virus–specific antibody tests are diagnostic. β-Lactam antibiotics, which may mistakenly be prescribed, will cause a maculopapular rash in 95% of patients. Laryngeal obstruction may require hospitalization and intravenous corticosteroids (e.g., dexamethasone, 8 mg intravenously three times a day).

Influenza virus infection can include nonexudative pharyngitis, but the predominant symptoms are tracheobronchial, usually accompanied by fever, headache, rhinorrhea, cough, and myalgia, without lymphadenopathy. Adenovirus (Chapter 333) can cause pharyngitis associated with fever, nonproductive cough, nasal congestion, myalgia, headache, nausea, vomiting, and diarrhea, especially in outbreaks, such as among military recruits or in immunocompromised patients.

Primary herpes simplex virus (Chapter 345) infection is characterized by pharyngitis with or without gingival stomatitis. Symptoms include sore throat, fever, and malaise; physical findings include erythema and hypertrophy of the tonsils with exudates, often with enlarged, tender cervical nodes. It may be difficult to distinguish clinically from group A β-hemolytic streptococcal pharyngitis unless patients have herpes-like lesions of the oral cavity or oropharynx.

Human immunodeficiency virus infection (Chapter 353) can be manifested as an acute retroviral syndrome that mimics infectious mononucleosis and resolves in 1 to 2 weeks. The diagnosis must be considered in febrile patients with known risk factors. Once infection is established, oral and oropharyngeal infectious ulcerations may be due to herpes simplex virus, cytomegalovirus, syphilis, cryptococcus, histoplasmosis, or mycobacteria. Large, painful, noninfectious aphthous ulcers also can involve the tonsillar fossa, floor of mouth, hypopharynx, and epiglottis (Chapter 393). In adults with a sore throat that does not warrant antibiotics, a single 10-mg oral dose of dexamethasone does not improve symptoms at 24 hours but does modestly improve symptoms at 48 hours.[A8]

FUNGAL INFECTIONS

By far, the most common fungal infection of the oropharynx and larynx is candidiasis. *Candida* (Chapter 310) is a normal commensal organism of the oral cavity and oropharynx, but it can be an opportunistic infectious agent

FIGURE 397-5. **Fiberoptic laryngoscopy demonstrating characteristic erythema and white pseudomembrane secondary to *Candida* infection.**

in immunocompromised patients, patients who have received prior head and neck irradiation, patients with xerostomia or diabetes, and immunocompetent patients who have been treated with antibiotics or with systemic or inhaled steroids. *Candida* infection is manifested with sore throat, burning of the mouth and tongue, dysgeusia, dysphagia, and hoarseness. White pseudomembranes characteristic of thrush (Fig. 397-5) may involve the oral cavity, oropharynx, hypopharynx, larynx, and esophagus. Treatment includes oral hygiene, probiotics, and topical antifungals (Chapter 310). Fluconazole (200 mg orally on the first day followed by 100 or 200 mg once a day for 14 to 21 days) is indicated for laryngeal and esophageal involvement and for recurrent disease. In patients who do not respond to fluconazole, resistant *Candida albicans* and non-*albicans Candida* species are likely causes and should be treated with itraconazole (200 mg orally once a day for 14 to 21 days).[10]

Other fungal infections may affect the oropharynx and larynx in isolation or as part of a systemic infection. *Blastomycosis* (Chapter 308) involves the larynx in less than 5% of cases, in which it produces pseudoepitheliomatous hyperplasia and clinically resembles squamous cell carcinoma. *Histoplasmosis* (Chapter 308), which is endemic to the Ohio and Mississippi river valleys, can involve the oral cavity, oropharynx, and larynx in immunocompromised patients. *Cryptococcosis* (Chapter 309) can involve the larynx and occurs most often in an immunocompromised host, in whom pseudoepitheliomatous hyperplasia may occur.

Paracoccidioidomycosis (Chapter 308) is the leading cause of fungal laryngitis in South America, especially among farmers. It causes pseudoepitheliomatous hyperplasia that can be misdiagnosed initially as squamous cell carcinoma. *Coccidioidomycosis* (Chapter 308), which is endemic to the southwestern United States, can involve the larynx, in which it results in hoarseness and throat pain and can progress to airway obstruction. For each of these fungal diseases, treatment is similar to what is recommended for the disseminated disease (Chapter 307) that usually accompanies pharyngeal and laryngeal disease.

MYCOBACTERIAL INFECTIONS

The risk that tuberculosis (Chapter 299) infection will involve the oropharynx and larynx is low, with only about 1 to 1.5% of infected tuberculosis patients having involvement of the tonsils or larynx. Tonsillar involvement, which most often occurs in the presence of systemic disease, is manifested as sore throat with exudative tonsillitis and cervical adenopathy. Other diseases that can have a similar clinical presentation include lymphoma (Chapter 171), squamous cell carcinoma (Chapter 176), and sarcoidosis (Chapter 83). Tuberculosis in the larynx is most likely to involve the vocal folds and supraglottis (false vocal folds). It is manifested with hoarseness and odynophagia, and its lesions mimic squamous cell carcinoma. Approximately 50% of cases occur in the presence of active disseminated disease, about one third occur with inactive disease, and the other 15% occur as primary laryngeal disease.

In contrast, *Mycobacterium leprae* infection (Chapter 301) is manifested with laryngeal disease in one third of patients with systemic disease. The clinical picture is indistinguishable from that of laryngeal tuberculosis. Atypical mycobacteria rarely involve the larynx, and infection most often is manifested as cervical adenopathy.

CHRONIC TONSILLITIS

Patients may develop deep tonsillar crypts that accumulate debris, such as food or sloughed mucosa, thereby providing an ideal environment for the growth of bacteria, especially anaerobes. Such patients commonly complain of whitish or yellow pieces of semisolid debris on or emanating from their tonsils. These tonsilliths often have a foul taste and odor, and they can cause halitosis. Some patients have chronic sore throats because of the persistent infection. Treatment includes frequent gargling of a hydrogen peroxide mouthwash and occasionally expressing this debris from the tonsil manually. Long-term amoxicillin (500 mg three times a day for 21 days) or clindamycin (300 mg orally three times a day for 21 days) may be effective; however, the presence of *Actinomyces*, a commensal organism of the oral cavity and oropharynx, is indicative of chronic infection that requires tonsillectomy because even long-term antibiotics are unlikely to be effective. Multiple episodes of acute tonsillitis, especially if accompanied by a peritonsillar abscess, can also be an indication for surgery. Adenotonsillectomy decreases the number of episodes of sore throat and days with sore throat in children in the first year after surgery, but its value in adults is less clear. Many adults improve spontaneously, and the potential benefit of surgery must be weighed against its risks,[11] including hemorrhage and pain, the latter of which is more prevalent in adults.

EPIGLOTTITIS

Epiglottitis (supraglottitis) is an uncommon problem in adults and has become even less common in children because of routine *Haemophilus influenzae* vaccination in children (Chapters 15 and 277). In adults, *Streptococcus pneumoniae* (Chapter 268) is now the most common organism, and adults present with a severe sore throat, odynophagia, fever, and "hot potato" voice. Airway obstruction occurs less frequently than in children, although it should be considered a possibility.[12] Palpation or movement of the larynx causes significant pain. On transnasal fiberoptic laryngoscopy, the larynx typically reveals swelling, erythema, and occasionally exudates of the epiglottis and other supraglottic structures. Patients with a confirmed diagnosis of epiglottitis require intravenous antibiotics (e.g., cefotaxime, 2 g every 6 hours, or ceftriaxone, 1 to 2 g/day, intravenously), and they should be observed in an intensive care unit setting until symptoms improve because of the risk for rapidly progressive airway obstruction.

NONINFECTIOUS PHARYNGITIS

LARYNGOPHARYNGEAL REFLUX

Patients with gastroesophageal reflux disease (Chapter 124) can develop laryngopharyngeal reflux with intermittent hoarseness, nighttime or chronic cough, postnasal drip, "globus" sensation, reactive airway disease, halitosis, and brackish or acid taste in the back of the mouth and throat. Findings on laryngoscopy, although nonspecific, may include posterior laryngitis, with swollen and erythematous arytenoid cartilages, thickening of the vocal folds, interarytenoid edema, and thickening of the mucosa. In severe cases, spasm or thickening of the cricopharyngeus muscle, also known as the upper esophageal sphincter (Chapter 124), can cause dysphagia as a result of poor pharyngeal emptying or even spillage of secretions into the larynx with aspiration.

Treatment should address dietary change, behavioral modification, elevation of the head of the bed at night, and a therapeutic trial of a proton pump inhibitor for up to 3 months (Chapter 124).[13] Empirical treatment without laryngoscopy is reasonable in patients with classic symptoms, but patients who do not respond within 3 months or patients with warning signs (e.g., ear pain, trismus, or odynophagia) require laryngoscopy to exclude more serious causes of hoarseness. In patients with persistent symptoms and a positive pH probe or with evidence of Barrett esophagitis, an antireflux procedure (Chapter 124) should be strongly considered.

SYSTEMIC DISEASES OF THE THROAT AND LARYNGITIS

About 80% of patients with *pemphigus* (Chapter 406) will have symptoms affecting the nasal cavity, oral cavity, and oropharynx, and half of these patients will have laryngeal involvement. Shallow ulcerations with fibrinous material and surrounding erythema are characteristic. Bullous lesions are less likely to be observed because the epithelial layer sloughs during swallowing. Laryngeal involvement may result in stenosis with airway obstruction due to scarring. Upper aerodigestive tract involvement occurs in 35% of patients with *pemphigoid* (Chapter 406), and 50% of these patients will have laryngeal involvement. Treatment in both disorders consists of high-dose steroids (prednisone, 75 to

100 mg orally per day until remission) during the attack phase and then tapered to a maintenance dose. Other immunosuppressive medications, such as azathioprine, cyclophosphamide, or cyclosporine (Chapter 28), may be required in the maintenance phase. Perilesional or intralesional triamcinolone acetonide injections are recommended during the maintenance phase for new lesions.

Granulomatosis with polyangiitis (Chapter 249) includes laryngeal involvement in 20% of patients, with a predilection for the subglottis (E-Fig. 397-1). Presenting symptoms may include hoarseness, cough, dyspnea, wheezing, and stridor. Flow-volume loops are useful and demonstrate flattening of both inspiratory and expiratory loops characteristic of a fixed extrathoracic obstruction. Patients presenting with airway obstruction require surgical intervention. Active disease with granulation tissue requiring airway management is treated with endoscopic dilation and steroid injection. Systemic immunosuppression is not effective for treatment of laryngeal involvement, so open resection may be required as the disease becomes chronic with the deposition of fibrous tissue.

Relapsing polychondritis involves cartilage in the ear, nose, and upper and lower airway as well as in the articular joints and costal cartilage. About 50% of patients will develop dyspnea, cough, hoarseness, stridor, or wheezing due to the destruction of cartilage and the resulting loss of structural support of the airway (E-Fig. 397-2). Airway obstruction may necessitate stenting or tracheostomy.

About 25 to 30% of patients with rheumatoid arthritis (Chapter 243) develop hoarseness, globus symptoms, and difficulty in swallowing. Hoarseness may result from acute inflammation or chronic nodular formation. Bilateral arytenoid joint involvement may impair vocal fold motion and cause airway obstruction with stridor. Surgical intervention may be necessary to open the airway. The role of steroids (systemic or injectable) for airway stenosis in rheumatoid arthritis has not been established.

About 1 to 5% of all patients with *sarcoidosis* (Chapter 83) develop laryngeal involvement, usually manifested as hoarseness. As the disease progresses, however, it can cause a conical stenosis due to thickening of the soft tissue (E-Fig. 397-3). Laryngeal paralysis can be caused by a mass effect or by adenopathy with peripheral nerve compression along the course of the vagus or recurrent laryngeal nerve. Vocal fold involvement responds to intralesional steroid injection, but endoscopic laser excision is recommended in patients with airway symptoms.

Amyloid (Chapter 174) can deposit anywhere in the upper aerodigestive tract. In patients with localized immunoglobulin light chain amyloidosis, the most common site is the larynx (about 14% of cases). Hoarseness and cough are the most common symptoms in patients with laryngeal involvement (E-Fig. 397-4), but pharyngeal involvement may be associated with pain. Airway obstruction is rare. Surgical debulking with or without external beam radiation may relieve symptoms and even resolve the lesions. Unfortunately, reports are anecdotal, and there are no large series to support treatment options.

NEUROLOGIC DISORDERS AFFECTING THE THROAT

Neurologic disorders of the oropharynx, hypopharynx, and larynx may be due to focal diseases or be a local manifestation of generalized neurologic disease. Head and neck manifestations of neurologic and neuromuscular disorders are classified as hyperfunctional and hypofunctional disorders. Hyperfunctional disorders include muscle tension dysphonia, dystonia (Chapter 379), essential tremor (Chapter 379), myoclonus, and stuttering. Hypofunctional neurologic disorders include Parkinson disease (Chapter 378), multiple sclerosis (Chapter 380), neuromuscular disorders (Chapters 387 and 390), postpolio syndrome (Chapter 349), myopathies (Chapter 389), medullary disorders, and laryngeal paralysis. Given the variety of disorders with head and neck manifestations, it is critical to identify and classify the physical findings and associated symptoms. For example, a patient who complains about the sound of the voice may in fact have a normal voice but actually have severe dysarthria and hypernasality secondary to amyotrophic lateral sclerosis. The site of the lesion associated with the neurologic disorder will result in characteristic physical findings and facilitate establishment of a correct diagnosis (Table 397-3).

Hyperfunctional Neurologic Disorders

In *dystonia* (Chapter 379), spasmodic dysphonia fluctuates moment to moment and day to day. Adductor spasms of the vocal folds produce strained, strangled vocal quality with pitch breaks. Abductor spasms produce breathy hypophonic word breaks. Nonspeech sounds (laughter) and singing voice may be normal. This condition responds well to botulinum toxin injections.

Muscle tension dysphonia, which may be difficult to distinguish from dystonia, can occur secondary to underlying weakness (paresis, aging) with compensatory hyperfunction. Speech has a rough strained quality, perhaps with pitch breaks, and does not fluctuate moment to moment. It generally responds to voice therapy.

Vocal tremor is seen in 30% of patients with *essential tremor* (Chapter 379) and may be associated with spastic dystonia. Patients have a tremulous, quavering vocal quality, with or without head or hand tremor. Because of involvement of pharyngeal and laryngeal muscles, botulinum toxin may not be effective.

Myoclonus (Chapter 379) causes rhythmic contraction of the palate, pharynx, or larynx at a rate of one or two per second. Patients may have audible clicking from the eustachian tube or larynx. Voice may or may not be affected. Palate and vocal folds may be treated with botulinum toxin.

Pseudobulbar palsy (Chapters 373 and 387) causes spasticity and hyperreflexia of the bulbar muscles (pharynx, palate, lips tongue, and larynx). Patients develop dysarthria, hypernasality, and a harsh, strident, strained vocal quality, which is more spastic than spasmodic.

TABLE 397-3 CORRELATING SITE OF LESION WITH PHYSICAL FINDINGS IN NEUROLOGIC DISORDERS AFFECTING THE THROAT

SITE OF LESION	SIGNS
Cortex	Aphasia Aphonia Dysarthria Dysphonia Stridor
Extrapyramidal system	Vocal strain and pitch breaks Tremor Hypophonia/tachyphemia Spasmodic movements Focal, regional, or generalized dystonia
Cerebellum	Ataxia Dysmetria Tremor Incoordination
Brain stem	Flaccid paralysis Associated dense sensory deficit
Peripheral	Focal paresis or paralysis Other cranial nerve ± Palate involvement defines location

Modified from Blitzer A, Alexander RE, Grant NN. Neurologic disorders of the larynx. In: Flint PW, Haughey BH, Lund VJ, et al., eds. *Cummings: Otolaryngology–Head and Neck Surgery*. 6th ed. Philadelphia: Mosby Elsevier; 2015.

Hypofunctional Neurologic Disorders

Parkinson disease affects speech and swallowing in more than 80% of patients. Patients have dysarthria, prosody of speech, hypophonia, tachyphemia, monotonous pitch, and absence of vocal tremor.

Laryngeal examination shows bilateral vocal fold bowing with incomplete glottic closure. In advanced disease, vocal fold motion becomes hypokinetic. Pooling of secretions occurs as swallowing dysfunction progresses. Patients benefit from early intervention by speech-language therapists to address both voice and swallowing symptoms. In *progressive supranuclear palsy*, bulbar symptoms progress more rapidly, with pronounced speech and swallowing difficulty (Chapter 378). In *multiple system atrophy* (Chapter 378), progressive airway obstruction from bilateral vocal fold motion impairment may necessitate tracheostomy. In *myasthenia gravis* (Chapter 390), hypernasal speech, palatal weakness, and hypophonia may be accompanied by difficulties with swallowing and respiration. Some patients with *amyotrophic lateral sclerosis* (Chapter 387) present with bulbar symptoms that result from buccal-labial-lingual weakness, which produces speech and swallowing dysfunction, before the definitive diagnosis is made. In *multiple sclerosis* (Chapter 380), dysphonia and dysarthria are common.

LUMP IN THE THROAT

The sensation of a lump in the throat, called *globus pharyngeus*,[14] should prompt a careful history and physical examination by an otolaryngologist to exclude a serious diagnosis. When no underlying anatomic disease is found, possible causes include gastroesophageal reflux and spasm of the cricopharyngeus. Cognitive-behavioral therapy may be helpful.

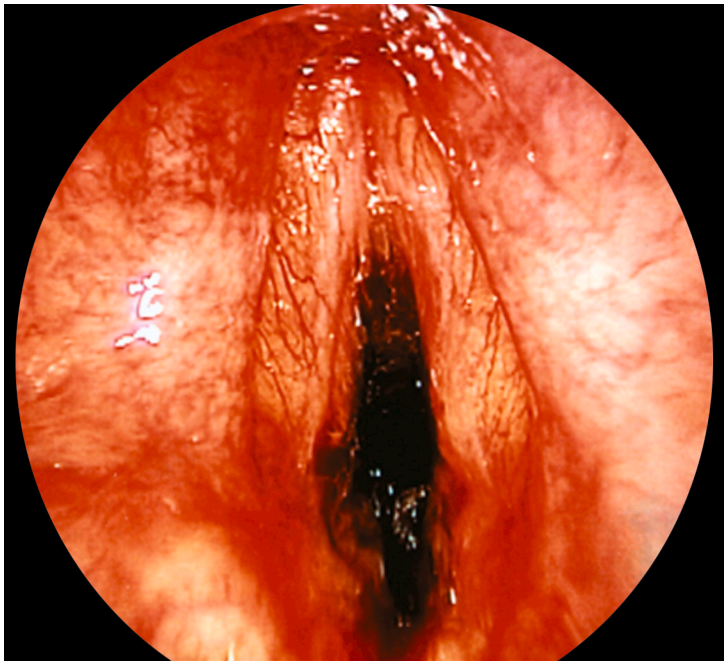

E-FIGURE 397-1. Fiberoptic examination of a patient with granulomatosis with angiitis demonstrating laryngeal involvement at the level of the vocal folds and subglottis.

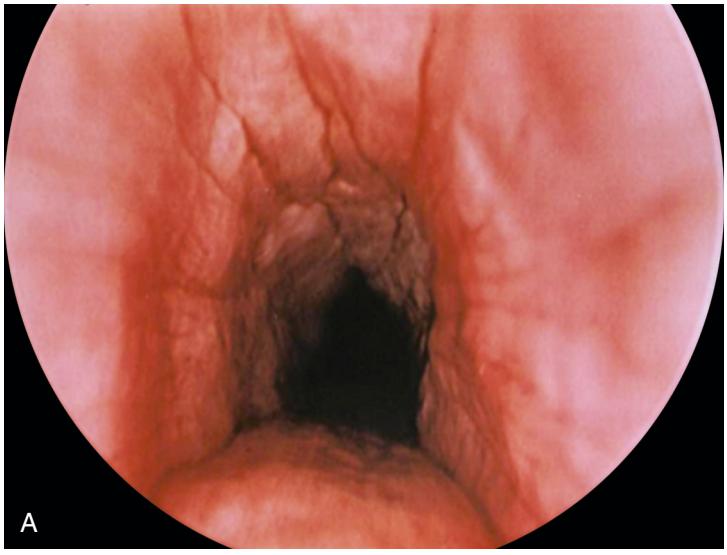

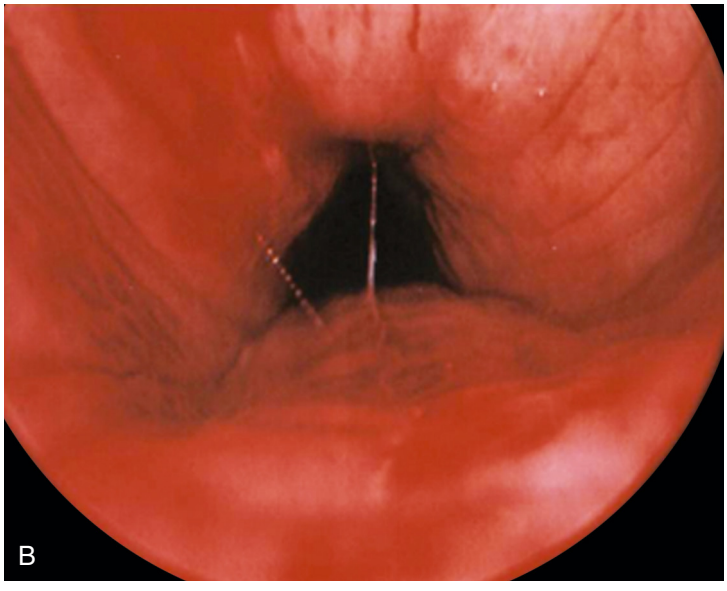

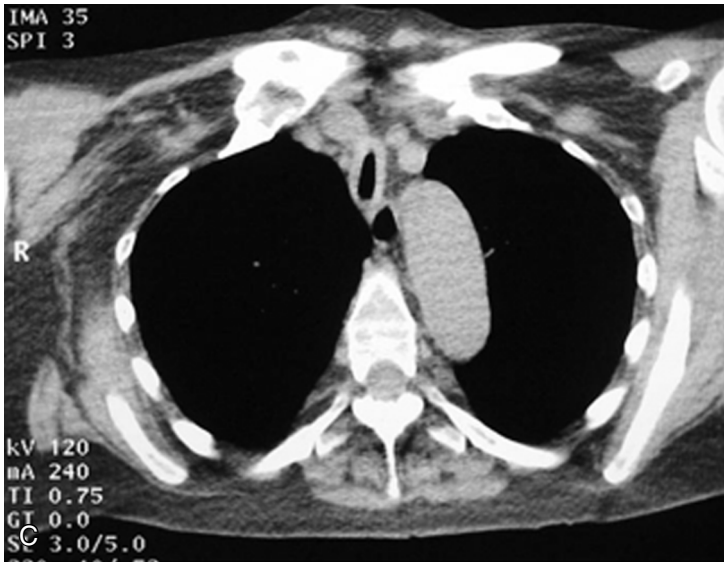

E-FIGURE 397-2. Tracheoscopy in a patient with relapsing polychondritis with tracheal involvement. **A**, On inspiration, negative intrathoracic pressure maintains a patent airway. **B**, During expiration, positive intrathoracic pressure collapses the airway because of loss of tracheal ring support. **C**, Computed tomography scan demonstrating thickening of the tracheal wall.

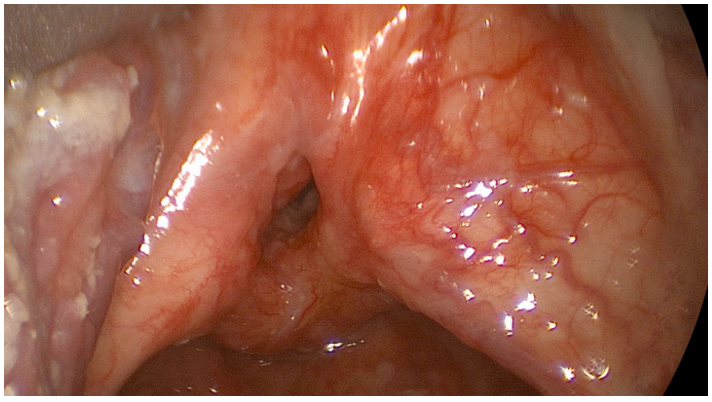

E-FIGURE 397-3. Supraglottic stenosis secondary to sarcoid demonstrating granulomatous destruction of epiglottis and aryepiglottic folds.

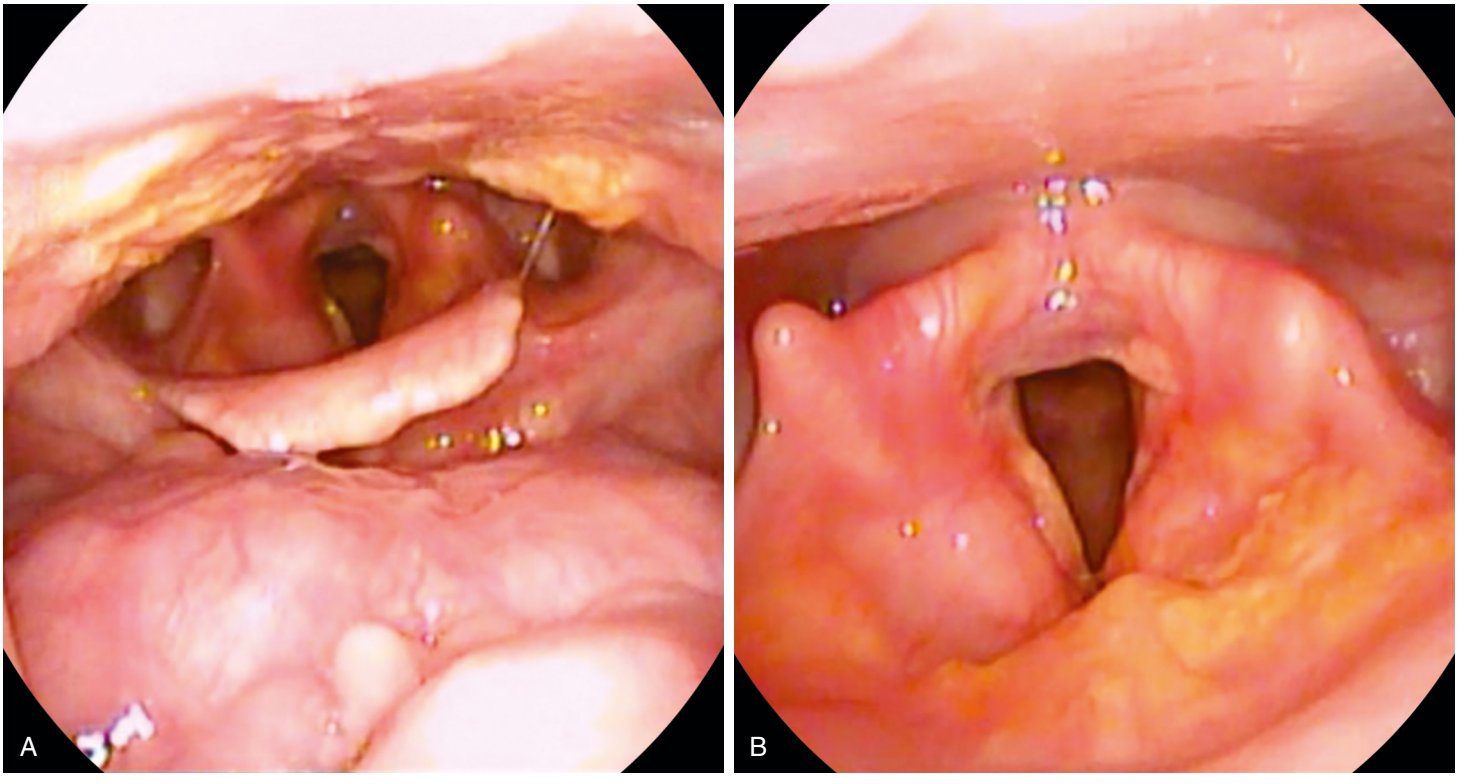

E-FIGURE 397-4. Amyloid deposition in the hypopharynx (A) and supraglottis and glottis (B).

HOARSENESS

Hoarseness, also called dysphonia, is characterized by altered voice quality, pitch, loudness, or vocal effort. Relevant history includes smoking status, occupation, and recent procedures involving the neck or affecting the recurrent laryngeal nerve. Symptomatic treatment should be considered in patients who have evidence suggesting a recent bacterial infectious process or gastroesophageal reflux without any historical features, such as ear pain, dysphagia, or odynophagia, or physical findings such as adenopathy or oral lesions suggestive of tumor. Additionally, there is no evidence to support the use of antibiotics or oral corticosteroids in patients with hoarseness unless otherwise indicated for a specific cause. Hoarseness that does not resolve within 4 weeks, or a history or physical examination suggesting a serious cause, should prompt referral to an otolaryngologist for laryngoscopy.

The symptom of hoarseness invariably points to the larynx as the site of disease. Benign lesions are most common, including vocal nodules (screamer's nodules), vocal cord cysts, vocal cord granulomas (usually resulting from intubation trauma or laryngeal hyperfunction), and vocal cord papillomas. Malignant neoplasms must be suspected (Chapter 176), especially in patients with a strong smoking history.[15]

Of the malignant tumors that can occur in the hypopharynx and larynx, squamous cell carcinoma is the most common and is usually associated with tobacco and ethanol use. However, the incidence of human papillomavirus–related oropharyngeal squamous cell carcinoma is increasing and should be considered in the nonsmoking population. Squamous cell carcinoma (Chapter 176) can occur on essentially any mucosal surface in the head and neck. Symptoms can range from mild sore throat to hoarseness, severe dysphagia, and odynophagia. Pain is often referred to the jaw or ear. Associated cervical lymph node enlargement is also common in advanced disease. Successful management depends on early detection by a careful examination of the entire upper aerodigestive tract, biopsy with histopathologic examination, and aggressive treatment based on the clinical stage and site of the lesion.

LARYNGEAL PARALYSIS

Laryngeal paralysis most often is manifested as a unilateral paralysis as a result of a mediastinal tumor; surgical trauma during thyroid, carotid, or anterior cervical spine surgery; blunt or penetrating trauma; aortic aneurysm; progressive neurologic disease; or viral or idiopathic causes. The severity of impairment can be determined from subjective criteria based on the patient's symptoms, such as breathiness, aspiration, and exertional intolerance.

Unilateral vocal fold paralysis with a favorable prognosis occurs after blunt trauma, endotracheal intubation, idiopathic vocal fold paralysis, and paralysis associated with viral pathogens (Ramsay Hunt syndrome). In this setting, the severity of aspiration, dysphonia, and electromyographic findings can be used to determine the choice of procedure and timing of intervention. Temporary medialization with collagen injection is warranted in patients with unilateral paralysis and a good prognosis. Patients who have poor prognosis for recovery include those with injury after complete section of the nerve during a surgical resection of tumor, invasion of cranial nerves by a tumor, paralysis associated with thoracic aneurysm, or paralysis due to progressive neurologic disorders. In patients with a low likelihood of recovery, permanent medialization of the paralyzed vocal fold is warranted.

Bilateral vocal fold motion impairment, which is less common, has the same causes. Its management is most often directed toward improving the airway because the predominant symptom is airway obstruction.

Laryngeal and Subglottic Stenosis

Airway injury may result in both glottic and subglottic stenosis. The most common causes of glottic stenosis are iatrogenic bilateral recurrent laryngeal nerve injury and intubation injury, which result in bilateral impairment of laryngeal motion. The most common causes of subglottic stenosis include prolonged intubation and tracheostomy. Early tracheostomy can reduce laryngeal trauma and the incidence of both laryngeal and subglottic stenosis.[16] With the acute respiratory compromise associated with COVID-19 infection (Chapter 336), the initial approach of delaying tracheostomy[17] was associated with airway injury and airway obstruction,[18] thereby reinforcing the adverse consequences of delaying tracheostomy, especially in patients who receive mechanical ventilation in the prone position.[19] However, changes in voice, most frequently caused by unilateral vocal fold paralysis, and swallowing issues were not reduced by earlier tracheostomy. Fortunately, however, most patients have improved speech and swallowing within the first week, especially with speech and swallowing therapy.

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398 PRINCIPLES OF MEDICAL CONSULTATION

GERALD W. SMETANA AND BARBARA A. SLAWSKI

APPROACH TO MEDICAL CONSULTATION

A general medical or subspecialty physician may receive a request to perform a consultation for a variety of purposes. In some settings, a single consultative encounter will be requested, or the consultant will determine that only one visit, either in the inpatient or in the outpatient setting, is necessary. More commonly, the approach will include one or more follow-up visits to meet the goals of the requesting physician, patient, and consultant. The consultant generally assumes one of four roles: (1) cognitive consultant, (2) procedural consultant, (3) comanager with shared care, or (4) comanager with principal care. The consultant as a comanager continues to care for a component of the patient's needs in an ongoing fashion while being careful to coordinate this comanagement with the requesting physician. Finally, in some situations, it may be most appropriate that the physician who initially requested the consultation no longer play an active role in the care of the patient but rather transfer ongoing care exclusively to the consultant. An example would be a referral to an oncologist for a new diagnosis of cancer that will require intensive chemotherapy and periodic restaging.

From a practical perspective, consulting physicians enter into the consultative mode in a relatively limited number of ways.[1] Surgeons may request a preoperative medical consultation to assess operative risk and obtain recommendations regarding perioperative care (Chapter 399) or, after surgery, to seek help in managing specific postoperative complications or assisting in the patient's long-term management. Both general medical physicians and medical subspecialists appropriately seek help from a subspecialist with particular knowledge in problems outside their own area of expertise to reduce uncertainty. Sometimes these requests are for specific medical procedures, but requests often seek cognitive guidance as well. Finally, noninternists may seek medical consultation for reasons other than perioperative care. For example, a psychiatrist may request a consultation to help determine whether the somatic symptoms of a particular patient represent important medical conditions (Chapter 402). In the peripartum setting, specific complications of pregnancy may require sophisticated medical consultation (Chapter 221).

Each of these settings raises different challenges for the medical consultant. In all settings, however, a number of general principles apply and can improve the effectiveness of consultations. In this chapter, we discuss these principles. Above, all, communication between physicians and other team members is critical to the process of consultation in all settings. The burgeoning patient safety movement has developed best practices for "hand-offs" that can be applied to consultations.

CONSULTATIVE SETTINGS

Consultations occur in both the outpatient and inpatient environment. In the inpatient environment, medical consultations are commonly performed by hospitalists in both the academic and community settings. Most hospitalists are trained in internal medicine or family medicine, but hospitalists specializing in fields such as neurology and obstetrics are becoming more common. The hospitalist may act as the primary physician who is seeking a consultation, as a consultant for medical or nonmedical physicians, or enter into a comanagement relationship with a nonhospitalist physician.

SETTING-SPECIFIC CONSULTATIVE ISSUES

An effective consultant must recognize the setting in which the consultation is requested and possess the required content knowledge. Distressingly, a number of studies have demonstrated that the requesting physician and the consultant often have substantially different views on the reasons that a consultation was requested. This initial disconnection, if present, will substantially decrease the efficacy of any medical consultation.

PREOPERATIVE SURGICAL CONSULTATION

In the preoperative setting, the medical consultant should not "clear" a patient for surgery and must avoid the temptation to do so even if asked. Clearance may incorrectly imply that the procedure or patient has no risk for adverse outcomes in the perioperative period. Instead, the medical consultant should help determine the inherent risk of the proposed procedure for the particular patient, whether the patient is in the best possible condition for surgery, and whether any generic or patient-specific interventions would reduce this risk (Chapter 399). Effective consultation also requires a specialized knowledge base, whether the consultation is focusing on a particular organ system or on overall perioperative risk (Chapter 399). The most important attributes of a preoperative medical consultation are a careful history and physical examination and an understanding of key literature and recommendations guiding perioperative care. Diagnostic testing plays a secondary role in this setting and may result in surgical delays, cancellations, or adverse patient outcomes if inappropriately ordered. The consultant can help avoid unnecessary and repetitive preoperative testing that is costly in the aggregate with essentially no benefit.[2]

POSTOPERATIVE SURGICAL CONSULTATION

Surgeons often request a postoperative medical consultation when a complication has developed that is beyond their area of expertise (Chapter 401). These problems are commonly urgent, so the goal is expeditious consultation and prompt intervention. Management of these problems does not usually differ from management of the same problem in nonoperative settings, but specific surgery-related risks must be considered. For example, the management of anticoagulation in the perioperative setting may vary from the nonoperative setting. As surgical patients become older with more comorbid conditions, surgeons increasingly request postoperative comanagement to help reduce the risk of complications. Consultants should aid in the transition to the outpatient or long-term care setting as appropriate.

MEDICAL-MEDICAL CONSULTATIONS

Cross-consultations between medical subspecialists or between a subspecialist and a generalist, in either direction, are quintessential examples of collaboration.[3] For all consultations, the key is to provide the requested expertise and benefit without overstepping into the domain of the expertise of the requesting physician.

Shared care, which is defined as truly joint participation of primary care physicians and specialist physicians in the delivery of care for patients with chronic conditions, can improve outcomes for hypertension, depression, and other medical conditions.[A1] For example, a randomized trial of shared care for patients with hypertension and chronic kidney disease demonstrated lower blood pressures and better use of lipid-lowering drugs in the shared care group. Rapid infectious disease consultations may result in improved outcomes, including shorter length of stay, fewer readmissions, and less inappropriate use of antibiotics.[4] For example, mandatory infectious disease consultation has been associated with a lower 30-day mortality and improved quality of care in patients with *Staphylococcus aureus* bacteremia.[5]

A common example of medical-medical consultation is the situation in which a hospitalist assumes principal responsibility for an inpatient admission and then returns the patient to the primary care physician after discharge from the hospital. In this consultative interaction, close communication is critical because primary responsibility for the patient's care has shifted from the outpatient medical physician to the inpatient physician. This transfer of responsibility is not dissimilar to that occurring when a patient is submitted to the care of a subspecialist for a procedure such as cardiac catheterization or gastrointestinal endoscopy. Similar issues also arise when a critically ill patient with a condition such as a complicated myocardial infarction (Chapter 58) or shock (Chapters 92, 93, and 94) is managed principally by a critical care medical specialist and is then expected to return to the care of the primary physician after hospital discharge. However, a key difference is that the inpatient hospitalist physician, unlike the consulting subspecialist, will not typically have an ongoing comanagement role. Because of the risk for discontinuity, effective communication at the time of hospitalization, whenever key issues arise during hospitalization, and at the time of discharge is even more important in the inpatient hospitalist model than in the other settings in which subspecialists may take on more of a comanagement role. Effective and comprehensive hand-offs at the time of hospital discharge improve continuity and reduce the potential for errors and medicolegal liability.

CONSULTATIONS FOR SPECIAL POPULATIONS

When consulting for psychiatrists or in the peripartum period, the consultant requires special expertise to understand the different expressions of

ABSTRACT

Medical consultation is a common activity for both generalists and specialists. In this chapter, we discuss the approach to medical consultation, including specific consultative settings, preoperative medical consultations, comanagement, telehealth, and strategies for effective consultation.

KEYWORDS

preoperative evaluation
medical consultation
telehealth
consultants
consultation
comanagement

TABLE 398-1 REASONS TO CONSIDER A SUBSPECIALTY CONSULTATION

To provide ongoing comanagement and become a partner in inpatient care • For an acute, unstable problem • For a chronic condition
To perform a procedure (or advise on whether to perform it) • Diagnostic • Therapeutic
To provide one-time or periodic advice • Diagnostic guidance • Therapeutic guidance • Reassurance • Medicolegal issues

TABLE 398-2 GUIDELINES TO HELP MAKE CONSULTATIONS EFFECTIVE

Determine whether the goal is to obtain advice (and, if so, specifically for what) or to aid in ongoing comanagement (see Table 398-1).
Understand the urgency of the consultation so that the consultation will be performed on a timely basis that meets the needs of the requesting physician and patient.
Perform a focused but careful history and physical examination—do not rely on information gathered by others.
Do not rehash information in an overly detailed note—emphasize the key issues your evaluation reinforced or discovered.
Be sure your recommendations are clearly listed and appropriately detailed—for example, indicate specific drugs, doses, and durations.
Limit the total number of recommendations to improve adherence.
Indicate how to monitor the effectiveness of your recommendations, as well as how to contact you urgently if problems arise.
Adjust your involvement (advice vs. comanagement) as appropriate, in concert with the requesting physician.
Serve as a peer—teach as appropriate but also seek to learn.
Remember that personal contact with the requesting physician, even if very brief, may be far more helpful than the best of written notes.
Do not disappear—follow the patient as frequently as appropriate, in coordination with the requesting physician.

For a more complete discussion of this topic, see Goldman L, Lee T, Rudd P. Ten commandments for effective consultations. *Arch Intern Med*. 1983;143:1753-1755; and Salerno SM, Hurst FP, Halvorson S, et al. Principles of effective consultation: an update for the 21st-century consultant. *Arch Intern Med*. 2007;167:271-275.

signs and symptoms in specific populations, as well as how and when to modify typical medical recommendations because of special circumstances (Chapters 221 and 402). Although these consultations occasionally result in long-term comanagement, more commonly they revolve around the resolution of an isolated problem or a perplexing condition.[6] In addition, the medical consultant should not make assumptions about the requesting physician's knowledge base regarding the specific medical issues that generate the consultation. The written report and verbal communications should be comprehensive and commonly include more basic medical content and specific recommendations than may be typical of a consultation for a medical subspecialist.

Subspecialty consultations requested by primary care physicians may be for advice, a technical procedure, or ongoing comanagement (Table 398-1). Consultations for general practitioners or family physicians generally follow the same guidelines as those for general internists. However, because both the training and ongoing practices of such physicians may or may not include the same spectrum and complexity of disease encountered by typical general internists, the subspecialty consultant must use judgment regarding both the initial consultation and the advisability of ongoing comanagement.

STRATEGIES FOR EFFECTIVE CONSULTATION

It is critical that requesting and consulting physicians agree about the reason for the consultative request. For example, the nature of a preoperative medical consultant's evaluation would differ substantially if the request were (1) routine, (2) for advice on perioperative insulin management in a patient with type 1 diabetes, or (3) to assist in determining the risks and benefits of proceeding to vascular surgery in a high-risk patient with coronary artery disease and a previous stroke. Effective communication at the time of the request will improve the value of the consultation and clarify the question. When there is doubt regarding the reason for the consultation, the consultant should speak directly to the referring physician before completing and documenting the evaluation of the patient.

Common reasons for medical consultation include assessment of perioperative risk; interpretation of a laboratory abnormality; help in performing a procedure, in obtaining advice, or in selecting therapy; and aid in providing long-term care. Prophylactic strategies (for example, venous thromboembolism, endocarditis, and surgical site infection) infrequently generate requests for medical consultation because they are commonly standardized to conform to practice guidelines at individual institutions.

Determining the question will also help narrow the scope of the consultant's advice and minimize the number of recommendations. Adherence by the requesting physician to any of the recommendations made by the consultant is higher for consultations with fewer recommendations. Another strategy to minimize the number of recommendations is to restrict advice to pertinent issues at the time, preferably in order of their importance.

Requesting physicians are also more likely to adhere to recommendations when the patient is sicker, the consultation is performed promptly, advice is given to institute specific therapy rather than perform more diagnostic testing, the consultant writes frequent follow-up notes, and computerized order entry support systems are used to convey recommendations. When giving advice about medications, consultants should indicate specific doses and duration of treatment. If a recommendation is likely to be controversial (e.g., postpone surgery), it is always preferable to speak directly to the requesting physician before writing a consultation note in the hope that direct conversation will provide an opportunity to develop a consensus that may then be reflected in the formal consultation note. In one study of 323 physicians, the three elements of greatest perceived importance for a high-quality consultation request were to frame the question, to indicate clearly whom to call with the response, and to establish urgency.

Consultants should be careful to restrict their advice to their particular area of expertise. For example, unless a particular antipsychotic medication is contraindicated because of a medical issue (Chapter 402), it is wisest to defer decision making regarding psychiatric management to the psychiatrist. A strongly worded consultation note that advises against a particular strategy will put another physician in a difficult medicolegal position if it differs from the physician's usual or recommended practice. The most important attributes of a consultative role are simple, concise recommendations and a clearly stated rationale for decision making. Detailed differential diagnosis is less important, and literature support is usually unnecessary.

Timely consultation reports improve physician satisfaction and patient care. For example, primary care physicians note that failure to receive timely reports from consultants limits their ability to provide high-quality care.

Salerno and colleagues have proposed modifications of Goldman's original "Ten Commandments" for effective consultations (Table 398-2). These recommendations serve as a helpful guide for consultants to improve adherence to their advice and, as a result, improve patient outcomes. Specific interactive training on the principles of consultation can increase the effectiveness of consultative communication.

SPECIAL CONSULTATIVE SITUATIONS

CURBSIDE CONSULTATION

Informal consultations are commonly called "curbside" consultations. In the current era, ready access to online medical references may potentially reduce curbside requests. Consultants in "cognitive" specialties such as infectious diseases, rheumatology, and endocrinology provide a disproportionate amount of informal (compared with formal) consultations. Informal consultations may occur by telephone, electronically, or in person. Curbside consultation is ingrained into the fabric of medical care.

Both generalists and specialists participate in an average of three to four curbside consultations per week. These consultations commonly involve questions about diagnostic tests, treatment plans, and the potential value of a formal consultation (which follows about one third of curbside consultations) in the future. To be effective, curbside consultations should be brief, involve a single question, and require no direct examination of the patient or medical records.

An important limitation of curbside consultations is that the consultant must rely on limited, secondhand information from the requesting physician rather than primary data from direct evaluation of the patient. Consultants report

that such indirect information is inaccurate in as many as half of curbside consultations. This reality, along with lack of financial compensation, leads to a greater degree of dissatisfaction with the curbside process by consultants than by requesting physicians. Salaried consultants may view a request for a curbside consultation more favorably than those whose livelihood depends on a fee-for-service model of care.

Although requesting physicians may perceive reduced medicolegal risk when they obtain and even document a curbside consultation, consultants may fear the risk for malpractice liability themselves when offering such advice. However, courts have consistently found that curbside consultants have no liability because no direct physician-patient relationship exists. Rather, the relationship is only between the requesting and consulting physicians.

ELECTRONIC CONSULTATIONS

Increasingly, physicians are using electronic communication, either as part of a shared electronic medical record or by e-mail, to supplement formal consultation requests.[7,8] An obvious advantage of this approach is that the requesting and consulting physician can communicate on their own schedules. Potential benefits include saving time, reducing costs, and improving continuity and access to specialty care. However, the lack of reimbursement for such activities may be a barrier to e-consultations.

MANDATORY CONSULTATIONS

In some situations, mandatory consultations may help enforce a standard of care. For example, mandatory inpatient infectious disease consultations, as part of an antimicrobial stewardship program, can improve the rational use of antimicrobial agents in the hospital and after discharge. Similarly, instituting routine consultation for patients with certain sentinel conditions, such as diabetes, may improve outcomes.

Telehealth Consultations

Historically, formal telehealth consultations were uncommon in large part because they were not a billable service. In 2020, driven by the coronavirus disease 2019 (COVID-19) pandemic, the Centers for Medicare & Medicaid Services relaxed previous constraints on billing for telehealth services as part of a declared public health emergency. As a result, telephone- and video-based telehealth services increased dramatically. Likely owing to convenience and safety, patients' satisfaction with telehealth services is surprisingly high despite the lack of an in-person physical examination.

This expansion has provided opportunities for creative and novel consultation strategies. Office-based specialists can provide telehealth consultations, even from a distance. Hospital medicine specialists also have used the expanded coverage of telehealth services in novel ways (Fig. 398-1),[9] including consultations at home, in post–acute care settings, and in emergency departments. Although the precise role of telehealth will likely evolve, especially if reimbursement regulations change, it can potentially change the landscape of medical visits (Fig. 398-2).[10]

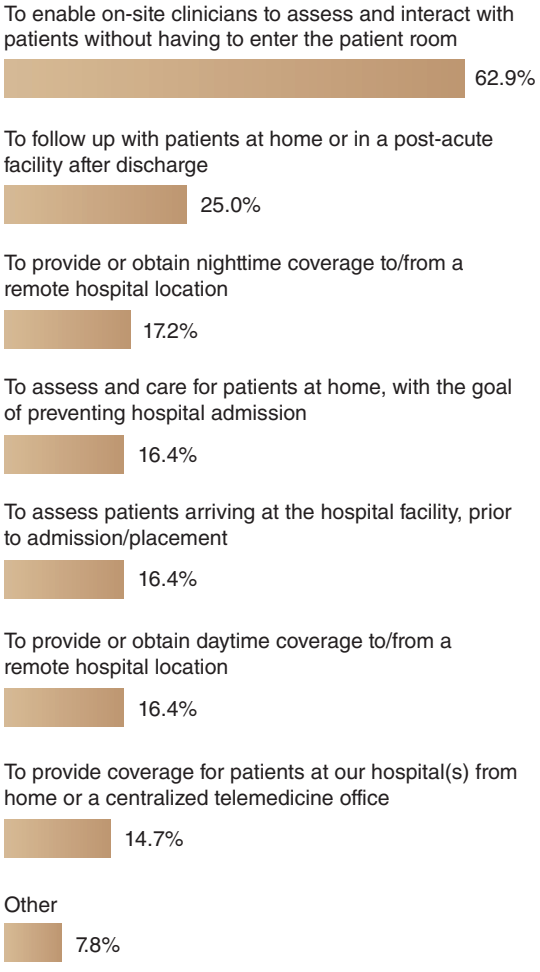

FIGURE 398-1. Use of telehealth technology among hospital medicine physicians. (From Society of Hospital Medicine. Hospital Medicine Groups Responding to the COVID-19 Pandemic: An Addendum to the 2020 State of Hospital Medicine report. https://www.hospitalmedicine.org/practice-management/shms-state-of-hospital-medicine. Accessed December 30, 2021.)

COMANAGEMENT

A consultation that begins with an initial encounter or a limited number of follow-up visits may evolve into ongoing comanagement. In such an arrangement, the physician initially serving in a consultative role becomes at least coequal to the requesting physician in the provision of ongoing care (see Table 398-1).

In some situations, the consultant may actually become the primary physician. This arrangement is obvious in situations in which the consultation was requested specifically for the provision of ongoing care. Other examples include situations in which an oncologist assumes principal care of a patient with a malignancy or a nephrologist assumes principal care of a patient with end-stage renal disease who is being maintained on dialysis. In some of these situations, a general internist who initially requested the consultation may now become the consultant and provide advice on preventive care and occasional help with intercurrent medical problems. This same transition in roles may occur temporarily in the inpatient setting when an outpatient primary care physician may retain a comanagement role even as a cardiologist cares for a patient with acute myocardial infarction, a pulmonologist cares for a patient in the ICU, a hospitalist cares for a patient in the general medical setting, or a noninternist addresses a specific problem.

More formal comanagement is now increasingly common in the hospital setting, where over 80% of hospitalists report that they comanage patients with specialists. Medical consultants may become comanagers of postoperative surgical patients, with a potential for improving outcomes. For example, hospitalist comanagement has been shown to improve quality and reduce costs for orthopedic, neurosurgical, and vascular surgery patients.[11,12]

In some institutions, comanagement for orthopedic or other surgical patients has become routine and does not require a specific request for consultation. In comanagement relationships, the comanaging specialist works as an active team member: writing orders; possibly rounding with the primary team; communicating with the staff, patient, and family; and participating in the coordination of care. Benefits of this model may include permitting the surgical team more uninterrupted time in the operating room, prevention and early diagnosis of medical complications, improved staff satisfaction, and improved outcomes. Because of the potential for gaps or duplication of care, comanagement relationships must develop and communicate specific interservice care agreements. These collaborative care agreements specify the care that will be delivered by each specialty to ensure optimal patient outcomes.

RESPONSIBILITIES OF THE CONSULTANT

The consultant is responsible to both the patient and the referring physician. A paternalistic approach is not desirable. The consultant should not limit communication to the referring physician and must not withhold discussion and recommendations from the patient. However, the consultant should not usurp the role of the referring physician, who remains responsible for assembling information and advice from varied sources, as well as for developing

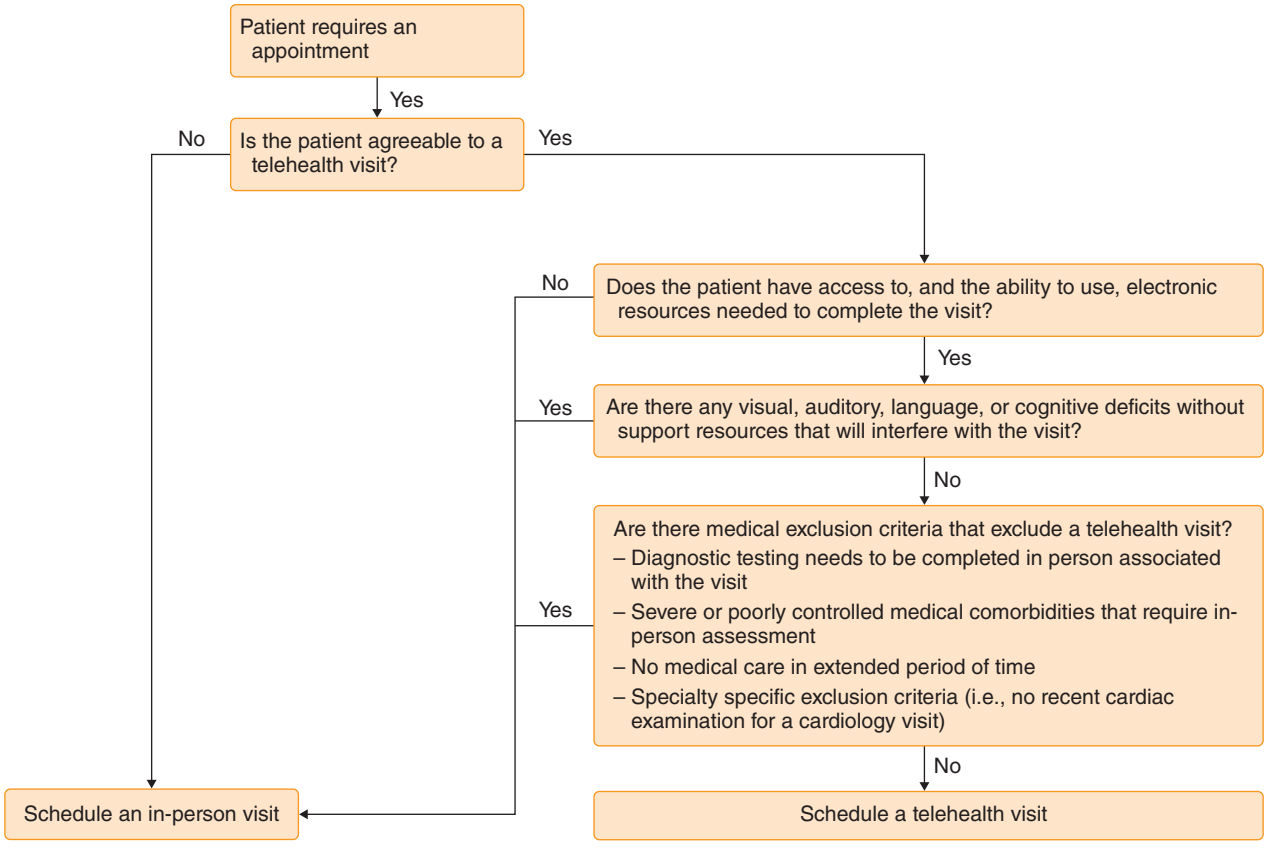

FIGURE 398-2. **Telehealth decision algorithm.**

an integrated plan with the patient. For example, in the preoperative setting, the consultant should not express a final opinion regarding the suitability of proceeding to surgery without first discussing all relevant considerations with the referring surgeon. Above all, the role of the consultant is to improve patient care and outcomes.

The consultant must execute his or her duty to the patient while acknowledging the collegial professional model of advising the primary physician. If, however, the patient's safety or welfare is at stake, the consultant's duty is foremost to be sure that the patient's needs always take precedence.

IMPACT OF CONSULTATIONS ON PATIENT OUTCOME

Few controlled trials have investigated the impact of medical consultations on outcomes. In one small study in the 1990s, an outpatient preoperative medical consultation reduced unnecessary admissions (those that did not result in surgery) compared with usual care (inpatient consultation at the discretion of the surgeon). In the outpatient setting, about 20% of diagnoses made by specialty consultants may be distinctly different than those made by referring physicians. Other reports indicate that anywhere from 5 to 50% of preoperative medical consultations result in changes in patient management. Comprehensive preoperative geriatric consultation can also reduce perioperative mortality among hip fracture patients.[A2]

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399 PREOPERATIVE EVALUATION

ANDREW D. AUERBACH

Every year, more than 7 million patients undergo inpatient surgical procedures, and almost 10 million more undergo ambulatory surgeries. Although the incidence rate of adverse events, morbidity, and mortality have continued to fall as surgical, anesthetic, and medical management techniques have improved, an aging patient population with increasing medical complexity is undergoing a growing number of more ambitious and extensive surgical procedures.

Planning surgical and perioperative care generally begins with a preoperative evaluation by the surgical team (e.g., surgeon, anesthesiologist). Medical consultants are primarily responsible for evaluating of comorbid medical conditions and helping to maximize the safety of the perioperative course.[1]

GENERAL PRINCIPLES

The preoperative medical evaluation is a potential opportunity to diagnose and treat asymptomatic disease or to optimize medical management of chronic problems. Occasionally, such issues are urgent, should preempt the primacy of the surgical procedure, or are important for perioperative outcomes. Usually, however, these issues should be reserved for postoperative consideration by the patient and their outpatient physician rather than becoming a priority for a consultant who will not be directly involved in the patient's ongoing care. The preoperative medical consultant's evaluation and recommendations should avoid low-value or extraneous tests or treatments, while emphasizing a coordinated approach to improve the efficiency, quality, and value of care. In this model of care, the preoperative medical consultant is increasingly a member of a comanagement team,[2] with an active role in the direct ordering of diagnostic tests and therapeutic interventions.

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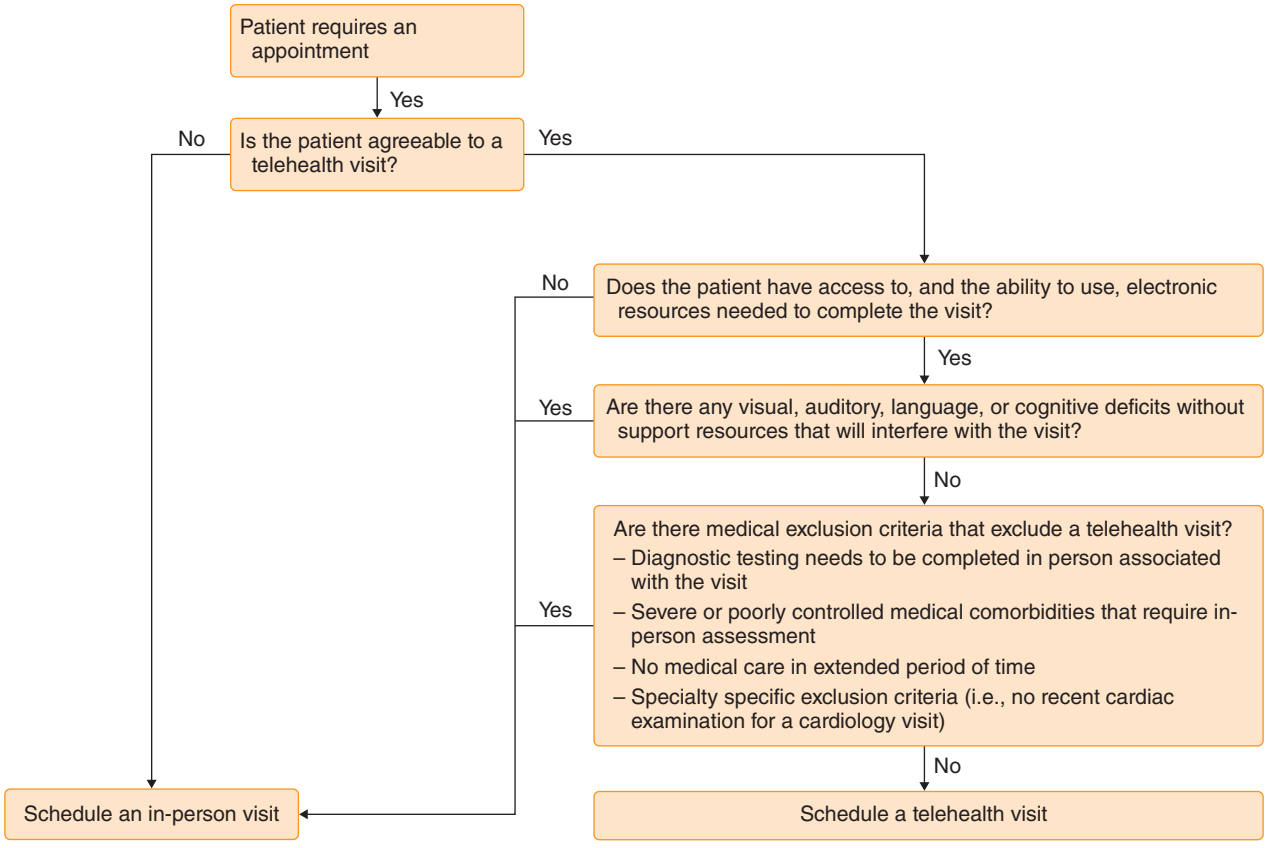

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Planning surgical and perioperative care generally begins with a preoperative evaluation by the surgical team (e.g., surgeon, anesthesiologist). Medical consultants are primarily responsible for evaluating of comorbid medical conditions and helping to maximize the safety of the perioperative course.[1]

GENERAL PRINCIPLES

The preoperative medical evaluation is a potential opportunity to diagnose and treat asymptomatic disease or to optimize medical management of chronic problems. Occasionally, such issues are urgent, should preempt the primacy of the surgical procedure, or are important for perioperative outcomes. Usually, however, these issues should be reserved for postoperative consideration by the patient and their outpatient physician rather than becoming a priority for a consultant who will not be directly involved in the patient's ongoing care. The preoperative medical consultant's evaluation and recommendations should avoid low-value or extraneous tests or treatments, while emphasizing a coordinated approach to improve the efficiency, quality, and value of care. In this model of care, the preoperative medical consultant is increasingly a member of a comanagement team,[2] with an active role in the direct ordering of diagnostic tests and therapeutic interventions.

ABSTRACT

In the past 10 years, the goals of preoperative evaluations have changed substantially. For elective and urgent procedures, the shift has been from focusing on identifying and "optimizing" medical conditions to identifying unstable medical problems, assessing functional status, and engaging a broad and interdisciplinary team so that perioperative care is coordinated safely and effectively. In situations in which surgery is needed to save a life or function emergently, preoperative evaluations are focused more narrowly on needs for postoperative management. Consultations should focus on gathering physical examination and historical data needed to use a validated risk calculator, with additional tests and procedures reserved for patients in whom these tests or procedures would be indicated regardless of the planned surgery. The incidence of major cardiac complications is relatively low and often secondary to other noncardiac complications. Common noncardiac complications include respiratory failure and pneumonia, delirium, venous thromboembolism, and hospital-acquired infections. Risks for these complications often also are linked to the risks for major cardiac outcomes (e.g., poor functional status, diabetes, baseline cognitive impairment), so preventive strategies recommended before surgery are likely to have broader benefit, particularly if coordinated with postoperative and posthospital care.

KEYWORDS

preoperative evaluation
risk stratification
medical consultation
hospital medicine
perioperative medicine
postoperative complications

TABLE 399-1 RISKS OF SURGICAL COMPLICATIONS AND IMPACT ON MORTALITY IN NONEMERGENT NON-CARDIAC SURGERY

	EVENT RATE IN ADULTS UNDERGOING NONCARDIAC SURGERY	30-DAY MORTALITY AMONG PATIENTS WITH COMPLICATION
Surgical site infection	6.9%	2.2%
Urinary tract infection	2.8%	3.8%
Venous thromboembolism or pulmonary embolism	1.5%	7.6%
Cerebrovascular accident	0.2%	24%
Myocardial infarction	0.2%	26%
Renal insufficiency	0.9%	27%
Pneumonia	2.4%	14%
Failure to wean from ventilator	2.6%	21%
Respiratory failure requiring reintubation	2.0%	26%
Combined respiratory complication (Pneumonia, failure to wean, or reintubation)	4.6%	19%
Any complication	16%	6.8%
Delirium	22%	11%

Adapted from Gajdos C, Kile D, Hawn MT, et al. Advancing age and 30-day adverse outcomes after nonemergent general surgeries. *J Am Geriatr Soc*. 2013;61:1608-1614; Silva AR, Regueira P, Albuquerque E, et al. Estimates of geriatric delirium frequency in noncardiac surgeries and its evaluation across the years: a systematic review and meta-analysis. *J Am Med Dir Assoc*. 2021;22:613-620 e619; Hamilton GM, Wheeler K, Di Michele J, et al. A systematic review and meta-analysis examining the impact of incident postoperative delirium on mortality. *Anesthesiology*. 2017;127:78–88; Marcantonio ER, Goldman L, Mangione CM, et al. A clinical prediction rule for delirium after elective noncardiac surgery. *JAMA*. 1994;271:134-139.

The spectrum of complications of surgery (Table 399-1) includes relatively common life-threatening issues, such as postoperative myocardial infarctions, but also a range of morbid events, such as delirium or preventable medical complications (e.g., urinary tract infections). Postoperative complications usually are not solo events but instead frequently develop as part of cascades or clusters that represent the effects of several comorbid conditions and acute insults that may accrue during or even after hospitalization. Overlapping and cascading complications, often beginning with a low-mortality event, require the preoperative consultant to take a global view, often including multicomponent and interdisciplinary recommendations.

The consultant's role and recommendations should encompass a holistic and multicomponent approach to reducing risk by:

- Assessing the impact of the surgery in terms of its urgency and impact on prognosis.
- Assessing the patient's burden of illness, with a focus on understanding comorbid conditions, functional limitations, or medications that require close attention.
- Helping to identify new or unstable symptoms, and judiciously recommending or even ordering diagnostic tests and therapeutic interventions.
- Planning medical care, particularly ensuring standard preventive measures and coordination of medications, through the perioperative time period. Anticipate potential need for higher level of care, such as in an intensive care unit (ICU).[3]
- Relating recommendations, plans for postoperative follow-up (including expectations around comanagement), and anticipated discharge needs to the surgical team and patient.

PROGNOSTIC IMPACT AND TIMING OF SURGERY

The need for surgery (emergent, urgent, or elective) is largely determined by the surgeon, who chooses the operative approach and coordinates the anesthetic approach with the anesthesiologist (Chapter 400). Emergency surgery (which is needed immediately to save life or function) largely precludes lengthy preoperative evaluations. Urgent surgery sometimes provides limited time to gather information about preoperative risks, but the focus of the evaluation, as with emergency surgery, is on anticipating likely complications and planning postoperative care. In emergency and urgent surgery where medical prognosis is very limited (e.g., patient with advanced dementia) and the risks of surgery are high, the medical consultant should also focus on ensuring that the patient's and family's goals of care are aligned with the risks of surgery. For elective surgery, delay has less direct impact on prognosis, so time is available to conduct a more comprehensive preoperative evaluation (Fig. 399-1).

Although certain surgical approaches (e.g., open vs. laparoscopic vs. intravascular) are associated with variations in risks for medical complications, the primary driver of these choices is the surgeon. Similarly, specific anesthetics or anesthetic approaches (Chapter 400) may be associated with lower risk for certain complications (e.g., dexmedetomidine may be associated with lower risk for delirium, or neuroaxial anesthetic approaches may reduce risk for pulmonary complications), but the route of anesthesia has minimal effect on most postoperative outcomes, and the anesthesiologist is responsible for these choices. Nevertheless, the result of a medical preoperative evaluation can sometimes provide critical information needed to plan a surgical procedure.

GENERAL PREOPERATIVE EVALUATION

PREOPERATIVE HISTORY AND PHYSICAL EXAMINATION

The history and physical examination remain the mainstays of effective preoperative evaluations and provide global information about patient baseline burden of illness, risks, and prognosis. Although an understanding of the patient's baseline symptoms is important for a general picture of comorbidity and prognosis, the decision to pursue additional preoperative tests or treatments will largely be driven by whether the consultant uncovers new, unstable, or progressive symptoms or signs that would warrant evaluation even in the absence of a planned surgery.

History taking should focus on key comorbid conditions (e.g., diabetes or a history of coronary artery disease) that pose known risks for complications or require specific attention before, during, or after surgery, especially any medical problems that have required more intensive recent management. A full review of systems should include an assessment of chest discomfort, dyspnea, and functional capacity, as well as all comorbid symptoms and conditions. The family history should focus on bleeding abnormalities or a history of malignant hyperthermia.

Functional capacity should be assessed by determining the patient's ability to undertake specific activities (Table 14-1) that represent discrete levels of physical capacity based on the number of metabolic equivalents required to complete them. Patients who are able to sustain activities of 4 metabolic equivalents or greater (such as climbing a flight of stairs briskly without stopping, walking up a hill, or running a short distance) are generally considered lower risk, even with existing medical illnesses. By comparison, patients who are frail[4] and unable to perform such activities are at higher risk. In some cases, however, functional status is not easily obtainable because of orthopedic problems or pain; in such situations, clinical assessment of comorbid conditions and specialized risk indices may be especially helpful.

The past surgical history can provide important information about the patient's ability to withstand the stress of surgery as well as experiences with anesthesia, particularly bleeding or cognitive complications of surgery. Certain habits, such as smoking or alcohol use, can be helpful in planning treatments (e.g., nicotine replacement) and avoiding unexpected withdrawal symptoms after surgery.

A complete medication history is a key aspect of the preoperative evaluation because many consultants' recommendations will relate to the longitudinal management of medications during the perioperative period. Patients should be explicitly questioned about use of opioids, illicit substances, and herbal supplements. A complete recent medication history should be obtained, including over-the-counter medications. A careful bleeding history should be obtained. Allergies to any medication, foods, or latex should be determined. The physical examination should include basic physiologic measures, such as pulse, blood pressure, and weight. All patients should have a careful cardiac evaluation, including auscultation to detect any murmurs, and volume assessment. Baseline mental status, particularly chronic cognitive impairment or past episodes of delirium during acute illness, should be determined. A general survey appropriate to the patient's age and gender should follow, with subsequent focus on organ systems relevant to the patient's history or review of symptoms. For example, patients with a history of chronic obstructive pulmonary disease should have their oxygen saturation measured, lungs assessed for wheezing, and presence or absence of peripheral edema noted. Evaluation of the airway or dentition is generally performed by the anesthesiologist, but any abnormalities noted by the medical consultant should be

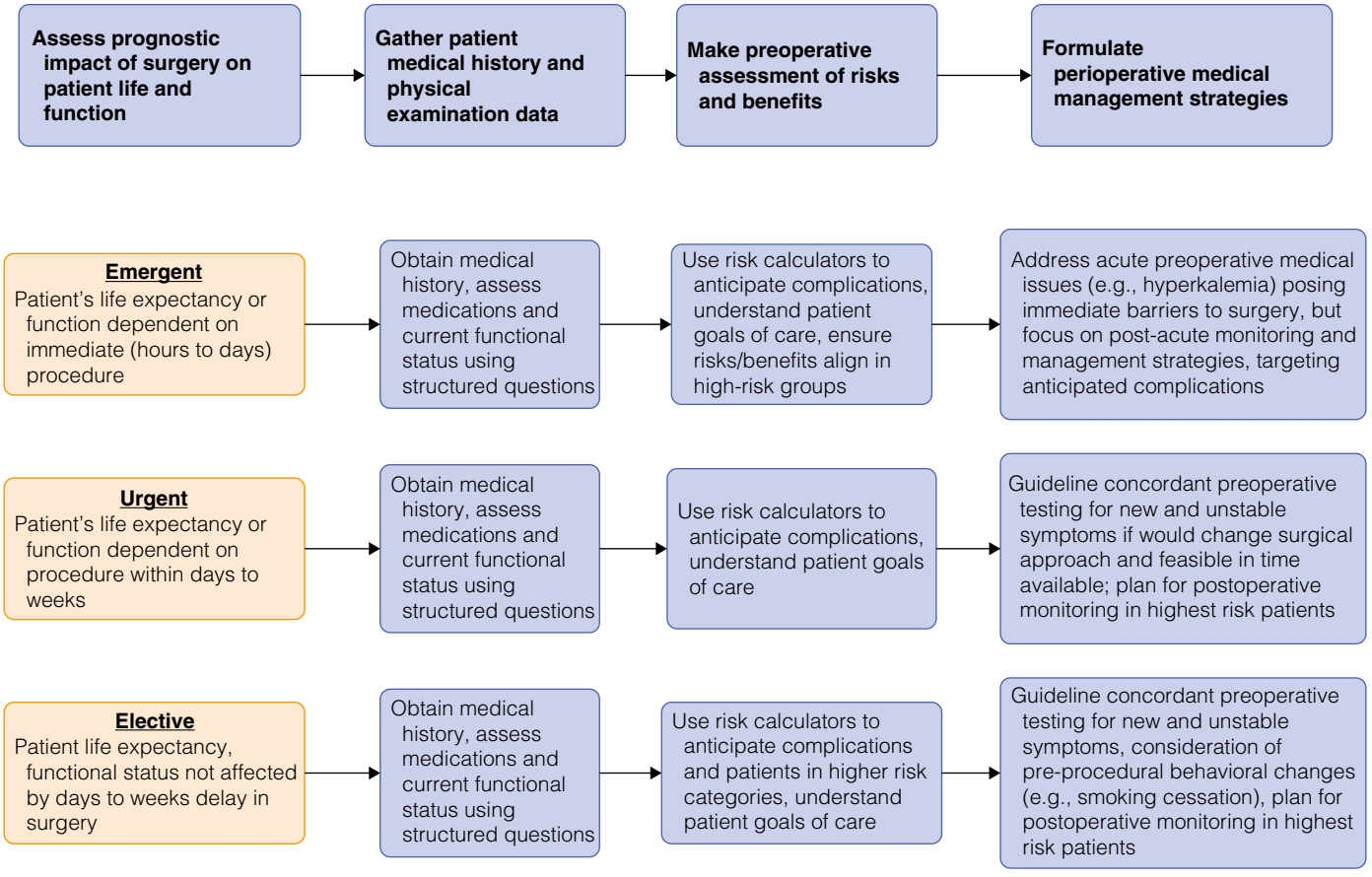

FIGURE 399-1. **Approach to preoperative evaluation according to surgical need.**

relayed. Point-of-care ultrasound, though potentially promising, is not part of a standard preoperative evaluation.

APPROACH TO PREOPERATIVE DIAGNOSTIC TESTING

Preoperative testing in asymptomatic patients rarely provides useful information, so most testing should be targeted based on the history or physical examination (Table 399-2), such as when a family history of bleeding prompts coagulation testing or a systolic murmur requires an echocardiogram to assess for possible aortic stenosis. In some situations, a preoperative test (e.g., an electrocardiogram in patients over age 40 years or with a history of cardiac disease and a chest radiograph for inpatients undergoing general anesthesia or with a history of lung disease) is also recommended as a baseline for comparison should postoperative problems (Chapter 401) occur. For patients with chronic illnesses or on chronic therapies that require monitoring (e.g., a creatinine level among patients with chronic kidney disease), a baseline perioperative value may prove useful.

ASSESSING RISK

In adult patients undergoing major inpatient noncardiac surgery, the combined risk of perioperative all-cause death, acute myocardial infarction, or acute ischemic stroke in the United States is about 3%. Overall surgical risk in an individual patient can be estimated using the American Society of Anesthesiologists' classification system. The risk of perioperative mortality is less than 0.03% in a normal healthy patient (class 1), but increases to 0.2% in patients with mild systemic disease (class 2), 1.2% in patients with severe systemic disease (class 3), 8% in patients who have severe systemic disease that is a constant threat to life (class 4), and 34% in a moribund patient who is not expected to survive for 24 hours without surgery (class 5). More detailed approaches can assess organ-specific risk, which is especially important in patients with underlying comorbid medical conditions.

CARDIOVASCULAR RISK

Risks vary by type of surgery (Table 399-3), with the highest risk for emergent operations and operations associated with prolonged anesthesia times, large fluid shifts, or bleeding. In these cases, risks are driven to a large degree by the underlying problem leading to the surgery, the circumstances of the surgery itself, and the patient's comorbid conditions. In high-risk surgeries, increased demand is placed on the cardiovascular system in the setting of a prothrombotic and inflammatory postoperative state, thereby leading to increased demand and subsequent ischemia, which in turn can lead to myocardial infarction (non-ST elevation or ST-elevation), arrhythmias, and sudden cardiac death.

The evaluation of a specific patient's risk for perioperative cardiovascular complications should focus on the patient's cardiovascular history, functional status, and cardiac physical examination.[5–7] Functional assessment should focus on the patient's metabolic equivalent (MET) level of activity, with the ability to perform 4 or more METs, suggesting that cardiac function can withstand the expected stress of surgery and, hence, is associated with a lower risk of perioperative cardiac complications. The presence of more than minimal aortic stenosis is not explicitly part of risk indices but should be specifically assessed on the cardiovascular evaluation.

Risk assessment prior to noncardiac surgery utilizes two separate strategies: assessing risk using a statistically validated risk index, and applying risk tools to consensus algorithms and guidelines. Two risk indices are widely used in clinical practice (Table 399-4). The Revised Cardiac Risk Index (RCRI) assigns single points for each risk factor category based on their importance as determined by prospective clinical evaluation and standardized follow-up. The National Surgical Quality Improvement Program (NSQIP) Myocardial Infarction and Cardiac Arrest index assigns points of varying weights for each individual factor identified by retrospective chart review. The Revised Cardiac Risk Index is potentially easier to remember and is not subject to biases in how patients may have been evaluated, whereas the Myocardial Infarction and Cardiac Arrest index uses web-based (https://riskcalculator.facs.org/RiskCalculator/) and spreadsheet-based tools. Either approach can guide additional risk stratification when the patient's estimated risk of cardiac events is greater than 1% (>1 Revised Cardiac Risk Index criteria).

Guidelines for applying these risk indices to patients who are scheduled to undergo elective or urgent noncardiac surgery begin with a clinical assessment for whether the patient is experiencing new or unstable symptoms that are indicative of an acute coronary syndrome (Fig. 399-2). This determination is followed by an estimation of cardiovascular risk combined with functional assessment to identify patients in whom additional testing is indicated.

TABLE 399-2 RECOMMENDATIONS FOR PREOPERATIVE LABORATORY TESTING

TEST	APPROXIMATE % ABNORMAL	APPROXIMATE % INFLUENCING MANAGEMENT	INDICATIONS
Hemoglobin	1.8	0.1	Expected major blood loss, symptoms of anemia, underlying cardiac or pulmonary disease, chronic kidney disease
White blood cell count	0.7	0.0	Suspected infection, myeloproliferative disorder, myelotoxic medications
Platelet count	0.9	0.02	Bleeding diathesis, myeloproliferative neoplasm, myelotoxic medications
Prothrombin time/INR	0.3	0.0	Bleeding diathesis, liver disease, malnutrition, antibiotic use, anticoagulants
Partial thromboplastin time	6.5	0.1	Bleeding diathesis, anticoagulant use
Electrolytes	13	1.8	Renal disease, medications affecting electrolytes (e.g., diuretics, digoxin, ACE inhibitor, ARBs)
Glucose	9	0.5	Known diabetes, taking glucocorticoids, morbid obesity
Renal function	8	2.6	Renal disease, diabetes, hypertension, major surgery, older age, medications affecting renal function
Liver function tests	0.4	0.1	Known liver disease, albumin level if at risk for needing postoperative parenteral nutrition
Urinalysis	19	1.4	No indication unless genitourinary symptoms or instrumentation planned (although often requested before joint replacement or spine surgery)
Electrocardiogram	25	2.6	Vascular surgery; intermediate-risk surgery with at least 1 RCRI risk factor; not indicated in asymptomatic patients undergoing low-risk procedures
Chest radiograph	20	3.0	Acute cardiopulmonary disease suspected based on history and physical examination, or surgery on heart or lungs

ACE = angiotensin-converting enzyme; ARB = angiotensin receptor blocker; INR = international normalized ratio; RCRI = Revised Cardiac Risk Index (1 point each for coronary artery disease; heart failure; prior cerebrovascular accident or transient ischemic attack; diabetes mellitus on insulin; creatinine >2.0; and abdominal, thoracic, or suprainguinal vascular surgery) (see Table 399-4).

Modified from Smetana GW, Macpherson DS. The case against routine preoperative laboratory testing. *Med Clin North Am*. 2003;87:7-40. Modified from Cohn SL. Preoperative evaluation. In: Goldman L, Schafer A, eds. *Goldman-Cecil Medicine*. 26th ed. Philadelphia: Elsevier; 2020.

TABLE 399-3 RISKS OF VARIOUS SURGICAL PROCEDURES

HIGH (VERY ELEVATED) RISK (CARDIAC RISK >5%)
Major vascular surgery
Emergency major operations
Prolonged procedures with large fluid shifts or significant blood loss
INTERMEDIATE (BUT ELEVATED) RISK (CARDIAC RISK 1-5%)
Intraperitoneal or intrathoracic procedures
Carotid endarterectomy
Endovascular aortic aneurysm repair
Head and neck surgery
Orthopedic procedures
Prostate surgery
LOW RISK (CARDIAC RISK <1%)
Superficial operations
Cataract surgery
Breast surgery
Ambulatory surgery

From Cohn SL. Preoperative evaluation. In: Goldman L, Schafer AI (Eds.). *Cecil-Goldman Medicine*, 26th ed. Philadelphia: Elsevier; 2020:2577-2583.

TABLE 399-4 TOOLS TO ESTIMATE PERIOPERATIVE CARDIAC RISK

NSQIP MICA*	REVISED CARDIAC RISK INDEX†
Age	History of ischemic heart disease (history of myocardial infarction, positive stress test, chest pain of cardiac origin, use of nitrates, Q waves on ECG)
Functional Status (independent, partially dependent, totally dependent)	History of heart failure (pulmonary edema, S_3 gallop or rales noted on physical examination, paroxysmal nocturnal dyspnea, chest radiograph showing pulmonary edema)
ASA Class (normal healthy; mild systemic disease; severe systemic disease but not a constant threat to life; severe systemic risk that is a constant threat to life; moribund and not expected to survive without surgery)	History of cerebrovascular accident or transient ischemic attack
Serum creatinine level <1.5 mg/dL, >1.5 mg/dL, or unknown	Insulin-dependent diabetes mellitus
Surgery type (multiple types)	Serum creatinine level ≥2.0 mg/dL
	Intraperitoneal, intrathoracic, suprainguinal vascular surgery

*Adapted from Gupta PK, Gupta H, Sundaram A, et al. Development and validation of a risk calculator for prediction of cardiac risk after surgery. *Circulation*. 2011;124:381-387. To use, see https://riskcalculator.facs.org/RiskCalculator/.

†Adapted from Lee TH, Marcantonio ER, Mangione CM, et al. Derivation and prospective validation of a simple index for prediction of cardiac risk of major noncardiac surgery. *Circulation*. 1999;100:1043-1049. To use, assign 1 point for each attribute the patient has.

ASA = American Society of Anesthesiologists; ECG = electrocardiogram; NSQIP MICA = National Surgical Quality Improvement Program Myocardial Infarction and Cardiac Arrest index.

Preoperative stress testing is of low yield and generally not recommended unless patients meet guideline criteria for such testing (see Chapter 56) in the absence of a surgical procedure (as when a patient has new symptoms concerning for an acute coronary syndrome [Chapter 57]). In patients who have a greater than 1% estimated risk of a cardiovascular perioperative event, and who have poor functional capacity, additional risk stratification with noninvasive stress testing may be indicated if the patient is a candidate for revascularization and a delay in surgery is feasible. For such patients, pharmacologic (adenosine or dipyridamole) nuclear stress testing (Chapter 44) or dobutamine echocardiography (Chapter 43) are the recommended tests. The results of noninvasive stress tests correlate with cardiac risks of surgery but should be interpreted cautiously given that a strategy of preoperative coronary revascularization is not beneficial except in patients who have indications for percutaneous or surgical revascularization in the absence of the noncardiac surgery itself.

Preoperative biomarkers[8] (e.g., troponin levels, N-terminal pro-brain natriuretic peptide [NT-proBNP], and C-reactive protein) are included in some algorithms for preoperative evaluation (E-Fig. 399-1). Elevated NT-proBNP or BNP in patients with more than 1 Revised Cardiac Risk Index factor or known aortic stenosis may identify patients in whom more intensive postoperative monitoring is indicated. However, such an approach has not been prospectively validated, and it is not yet clear whether biomarkers can be used in a cost-effective manner to avoid unnecessary testing or postoperative monitoring.

TREATMENT

Risk Reduction Strategies

Medications

The routine use of perioperative β-blockers can reduce the risks of perioperative cardiac events (e.g., ischemia, atrial fibrillation, need for coronary interventions), but it increases overall mortality because of an excess of strokes and deaths

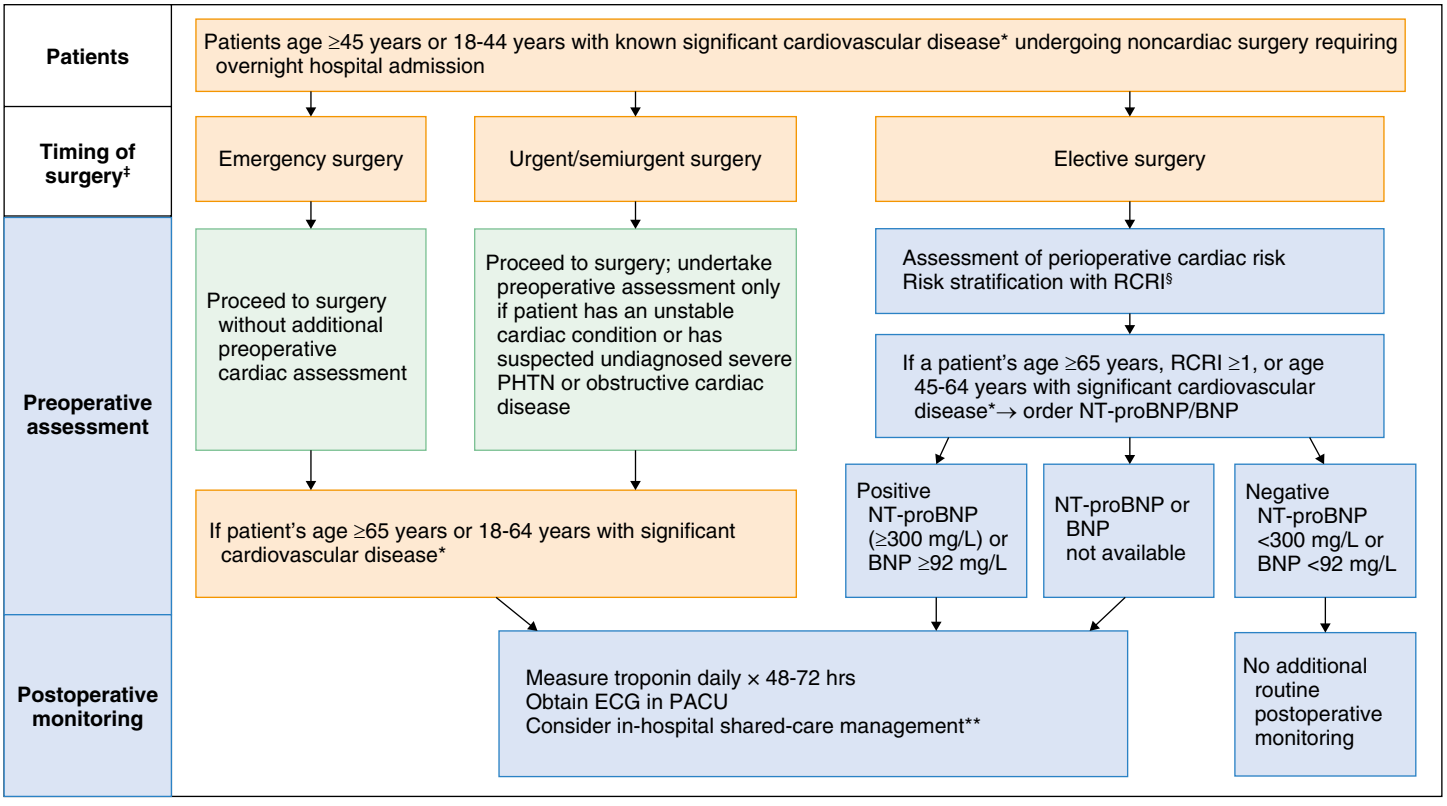

E-FIGURE 399-1. Canadian Association of Cardiology Algorithm. Preoperative risk assessment and postoperative monitoring flow diagram. *Significant cardiovascular disease includes known history of coronary artery disease, cerebral vascular disease, peripheral artery disease, heart failure, severe PHTN, or a severe obstructive intracardiac abnormality (e.g., severe aortic stenosis, severe mitral stenosis, or severe hypertrophic obstructive cardiomyopathy. †Timing of surgery refers to emergency surgery (e.g., severe trauma, ruptured aortic aneurysm), urgent surgery (e.g., hip fracture, bowel obstruction), semiurgent surgery (e.g., cancer with potential to metastasize), or elective surgery (e.g., knee arthroplasty). ‡If physical examination suggests there is an unknown severe obstructive intracardiac abnormality (e.g., severe aortic stenosis, severe mitral stenosis, or severe hypertrophic obstructive cardiomyopathy) or severe PHTN, then obtain an echocardiogram before surgery to inform the anesthesiologist, surgeon, and medical team of the type and degree of disease. If the history suggests the patient has an unstable cardiac condition (e.g., unstable angina), then discussion with the patient and surgical/medical team is required to decide whether to delay, cancel, or proceed with surgery. §RCRI score (each worth 1 point): history of coronary artery disease, cerebrovascular disease, congestive heart failure, preoperative insulin use, preoperative creatinine > 177 mmol/L, and high-risk surgery (i.e., intraperitoneal, intrathoracic, or suprainguinal vascular surgery). **Shared-care management refers to a multidisciplinary approach to inpatient postoperative care; this includes the surgeon and a medical specialist (e.g., internist, cardiologist, gerontologist), who will help with perioperative monitoring and management of cardiovascular complications. BNP = brain natriuretic peptide; ECG = electrocardiogram; NTproBNP = *N*-terminal pro-brain natriuretic peptide; PACU = post-anesthesia care unit; PHTN = pulmonary hypertension; RCRI = Revised Cardiac Risk Index. (From Duceppe E, Parlow J, MacDonald P, et al. Canadian Cardiovascular Society guidelines on perioperative cardiac risk assessment and management for patients who undergo noncardiac surgery. *Can J Cardiol*. 2017;33:17-32 and from Cohn SL. Preoperative evaluation. In: Goldman L, Schafer A, eds. *Goldman-Cecil Medicine*. 26th ed. Philadelphia: Elsevier; 2020.)

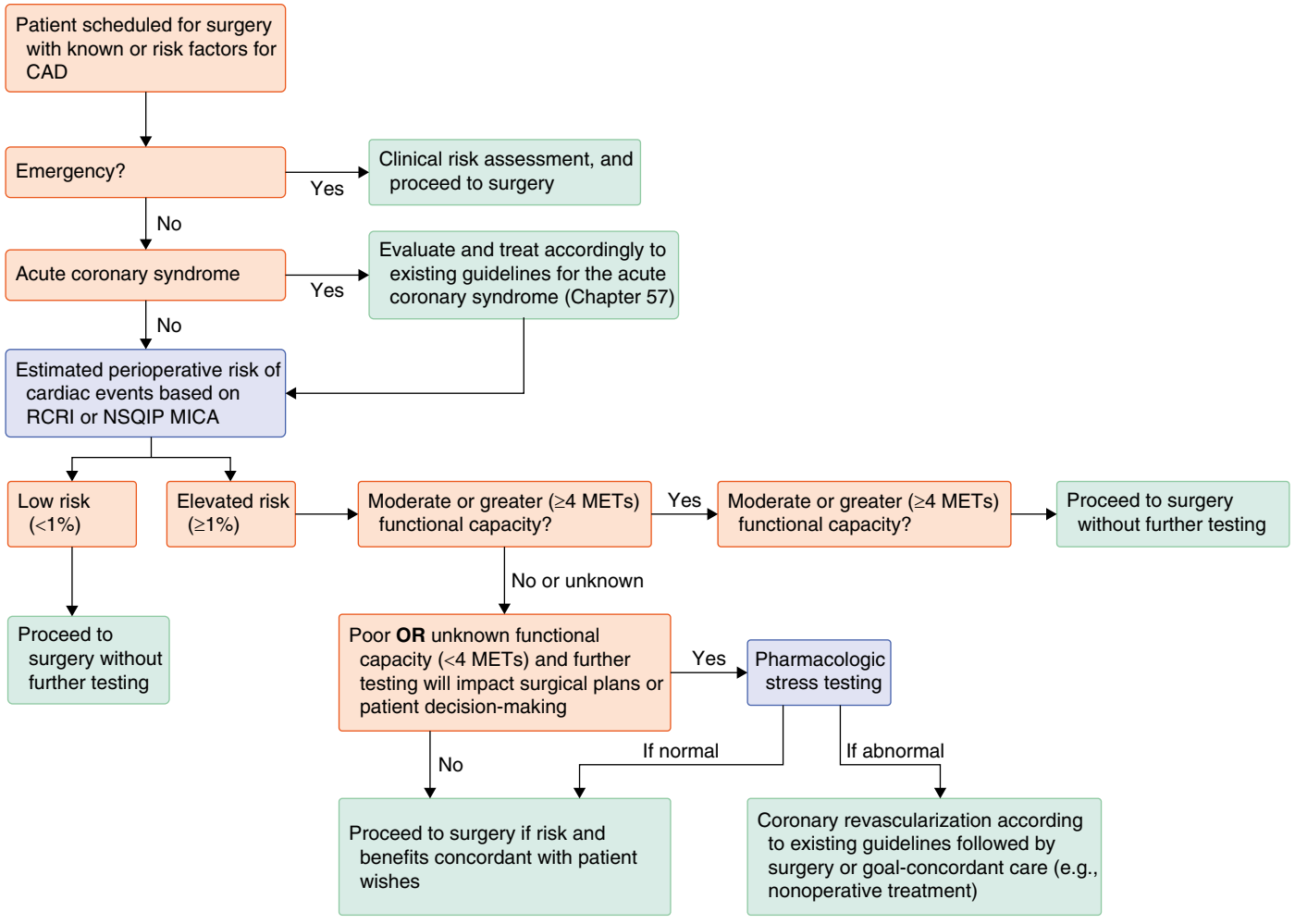

FIGURE 399-2. Approach to preoperative cardiac risk stratification. CAD = coronary artery disease; MET = metabolic equivalents (see Table 14-1); NSQIP MICA = National Surgical Quality Improvement Program Myocardial Infarction and Cardiac Arrest index; RCRI = Revised Cardiac Risk Index. (Adapted from Fleisher LA, Fleischmann KE, Auerbach AD, et al. 2014 ACC/AHA guideline on perioperative cardiovascular evaluation and management of patients undergoing noncardiac surgery: executive summary: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines. *Circulation*. 2014;130:2215-2245.)

from noncardiac complications.[A1–A3] Clonidine, aspirin, or the combination of the two also do not confer benefit.

Current recommendations are to continue chronic β-blockers but not to start β-blockers except in patients in whom a long-term indication exists. The drug should be started early, at least 7 days before surgery, optimally within a time period that will allow assessment for clinical effectiveness and dose adjustment if appropriate. β-Blockers should not be begun on the day of surgery, particularly at high initial doses. In patients who have vascular disease and who are undergoing noncardiac surgery, statins may be associated with a lower risk for postoperative cardiovascular complications,[A4] but no data support starting them anew before surgery unless the patient has longer-term indications. Patients on statins should continue them through surgery.

Coronary Revascularization

High-quality evidence recommends against prophylactic revascularization, whether percutaneous or surgical, as part of perioperative risk reduction, unless the patient has an indication for revascularization independent of the planned procedures. If a patient meets criteria for intervention, the noncardiac surgery ideally should be delayed between 3 and 6 months, and sometimes as long as 12 months depending on the type of stent placed (Chapter 59) and the attendant need for dual-antiplatelet therapy. Noncardiac surgery can be performed within 2 weeks of balloon angioplasty, but it is a temporizing approach that anticipates a later and more definitive coronary stent.

Postoperative Monitoring

Postoperative monitoring, in the form of continuous cardiac monitoring, periodic electrocardiograms (ECGs), or measurement of troponin-I levels, is usually recommended only in patients who have symptoms (e.g., dyspnea, chest pain) or signs (e.g., tachycardia) that provide a potential indication of myocardial injury. However, some guidelines suggest obtaining a one-time ECG when higher-risk patients (e.g., RCRI >1) are in the post-anesthesia care unit, with subsequent cardiac monitoring if abnormalities are noted.

Monitoring of troponin-I levels after surgery (Chapter 401) has prognostic importance as an indicator of myocardial injury. Elevations in troponin are associated with higher risk of cardiac events or death following surgery. Common protocols measure troponin I within 6 hours of surgery and then daily for up to 3 days afterward in high-risk patients. Although troponin elevations portend a worse prognosis, no intervention is of proven value in otherwise asymptomatic patients. However, optimization of medications, particularly statins, aspirin, and diabetes medications—according to guidelines for secondary prevention of myocardial infarction (Chapter 58), is a reasonable approach.

OTHER CARDIAC RISKS

Heart Failure

Heart failure (Chapter 46) and is associated with a higher risk for postoperative cardiac events.[9] Although no data from randomized trials are available, it seems reasonable to be sure heart failure is optimally controlled preoperatively, and perhaps guided by preoperative NT-pro-BNP or BNP levels. Patients' volume status and symptoms then should be monitored carefully after surgery.

Valvular Heart Disease

Aortic and mitral valvular diseases (Chapter 60) are associated with higher risks of postoperative cardiac events, but optimal approaches in patients who are otherwise asymptomatic and stable are undefined. Evidence suggests that careful attention to blood pressure and volume management during and after surgery may improve outcomes.[10] Transcatheter aortic valve replacement is a potential option for patients who meet criteria for valve replacement[11] and who need prompt noncardiac surgery.

Pulmonary Hypertension

Pulmonary hypertension (Chapter 69) is a risk for cardiac and respiratory complications of surgery, and it is increasingly noted as a comorbid condition in patients who are undergoing bariatric surgery and who often have obstructive sleep apnea. However, no specific interventions are of proven value.

Hypertension and Arrhythmias

Hypertension (Chapter 64) is a common preoperative and postoperative issue for the medical consultant but only very rarely is a reason for delaying or canceling surgery unless it is associated with acute symptoms or end-organ sequelae. Intensification of blood pressure medications during the acute hospital phase may be associated with worse post-hospital and long-term outcomes, so changing medications in patients with mild to moderate asymptomatic hypertension is rarely warranted.

Arrhythmias are often a marker of underlying heart disease, and patients with preoperative atrial fibrillation have about a 30% increased risk of stroke and all-cause mortality.[12] Patients with pacemakers or implanted cardioverter defibrillators also have increased risks based on their underlying cardiac disease. No changes in therapy are warranted preoperatively, unless the rhythm abnormality would require it otherwise, but electrocardiographic monitoring may sometimes be warranted preoperatively.

PULMONARY RISK

The evaluation of patients' risk for perioperative pulmonary complications (e.g., postoperative pneumonia, respiratory failure, or reintubation) should begin with a thorough medical history and physical examination, with the goal of gathering information, including symptoms and functional status, needed to estimate risks using a validated index.[13] However, sleep apnea (Chapter 374) is often asymptomatic or less well recognized than asthma or chronic bronchitis, so particular attention should be paid to determining whether it is present using validated approaches.

Chronic obstructive pulmonary disease (Chapter 76) increases postoperative pulmonary complications by about two-fold, but well-controlled asthma (Chapter 75) does not appreciably increase risk. Active smoking increases risk, and smoking cessation is recommended for 4 to 8 weeks prior to surgery.

Key predictors of complications include the use of general anesthesia and proximity of the surgical site to the diaphragm. Intrathoracic and upper abdominal procedures decrease pulmonary function by approximately 50% and lower abdominal surgery by about 25%, with function not fully returning to normal for several weeks. Laparoscopic procedures and epidural or spinal anesthesia appear to be associated with a somewhat decreased risk for pulmonary complications.

Several indices, each using similar clinical features, are available to predict postoperative pulmonary complications. The surgical approach and the duration of surgery are independent risk factors in each risk index. The most commonly used approach (Table 399-5) divides patients undergoing general anesthesia into three risk categories based on age, preoperative oxygen saturation, recent pulmonary infection, preoperative hemoglobin level, site of surgery, and expected duration of surgery.

Preoperative Testing

Pulmonary function tests, arterial blood gases, and chest radiography are generally not indicated to assess perioperative pulmonary risk, unless the patient has new or unstable respiratory symptoms. Pulmonary function tests are routinely recommended, however, in surgical planning for lung reduction or resection surgeries to identify residual lung reserve and the feasibility of the surgery itself.

When the respiratory risk is high, changes in surgical technique (e.g., laparoscopic vs. open) or anesthetic approach (e.g., regional versus general anesthesia) should be considered. Preoperative respiratory muscle training is promising[A5] but not widely available. Patients should be encouraged to discontinue smoking at least 8 weeks before surgery, and nicotine replacement therapy should be prescribed if they continue to experience cravings at the time of surgery. Courses of corticosteroids or antibiotics for patients with otherwise stable chronic bronchitis are not indicated and may worsen clinical outcomes.

Patients at higher risk (>2%) for major pulmonary complications may be candidates for further attention, particularly postoperatively. Patients with sleep apnea may be candidates for modified pain regimens or continuous pulse oximetry after surgery.

Inhaled β-agonists or anticholinergics agents may be useful in reducing bronchospasm and improving patients' ability to ventilate and clear secretions. Lung expansion maneuvers, such as incentive spirometry, are useful if performed several times per hour, so they are less effective in patients who are somnolent, in pain, or have difficulty managing the device because of drains or intravenous catheters. Methods for lung expansion and airway clearance using positive airway pressure should be considered when available. Medical consultants can also aid in management of respiratory risk by encouraging the use of nonopioid pain regimens (see Table 26-4), orders for positioning and activity, and consideration of more aggressive monitoring (e.g., step-down unit or continuous pulse oximetry) in selected patients.

TABLE 399-5 ARISCAT* RISK INDEX: INDEPENDENT PREDICTORS OF POSTOPERATIVE PULMONARY COMPLICATIONS

FACTOR	POINTS
AGE, YEARS	
<50	0
51-80	3
>80	16
PREOPERATIVE O_2 SATURATION	
≥96%	0
91-95%	8
≤90%	24
RESPIRATORY INFECTION IN THE LAST MONTH	17
PREOPERATIVE ANEMIA: HEMOGLOBIN ≤10 g/dL	11
SURGICAL INCISION	
Upper abdominal	15
Intrathoracic	24
DURATION OF SURGERY	
≤2 hours	0
2-3 hours	16
>3 hours	23
Emergency surgery	8

NUMBER OF POINTS	RISK CLASS	PULMONARY COMPLICATION RATE (%)
<26 points	Low	1.6%
26-44 points	Intermediate	13%
≥45 points	High	42%

*ARISCAT = Assess Respiratory Risk in Surgical Patients in Catalonia.
Adapted from Canet J, Gallart L, Gomar C, et al. Prediction of postoperative pulmonary complications in a population-based surgical cohort. *Anesthesiology*. 2010;113:1338-1350.

NEUROLOGIC RISK

STROKE

Postoperative stroke is infrequent in noncardiac surgery but highly morbid and associated with high mortality. Most postoperative strokes are ischemic in nature and result from emboli owing to the surgery itself (e.g., after carotid endarterectomy or cardiac surgery requiring cardiopulmonary bypass), intraoperative or postoperative hypotension,[14] or cardiac events (e.g., atrial fibrillation) that increase the risk of an embolic event. Though no risk index has been developed to target postoperative strokes per se, risk factors for stroke are similar to those for cardiac events.

Patients who have had a prior stroke have a markedly higher risk of postoperative strokes for 90 days[15] and perhaps for as long as 9 months after their initial cerebrovascular event, and elective surgery probably should be delayed in such patients. For patients who have asymptomatic high-grade extracranial carotid stenosis, guidelines for carotid revascularization (Chapter 376) should be followed before elective surgery. Thrombotic and embolic risks are the cornerstone of strategies around managing perioperative anticoagulants (covered elsewhere).

NEUROMUSCULAR DISEASE

Neuromuscular diseases (Chapters 386 to 390) have diverse underlying pathophysiologies but present with similar symptoms in terms of muscular

TABLE 399-6 RISK FACTORS FOR DELIRIUM

NONCARDIAC SURGERY	
Age > 70 years—1 point	
History of cognitive impairment—1 point	
Severe impairment in functional status*—1 point	
History of alcohol use disorder—1 point	
Abnormal preoperative sodium, potassium, or glucose level—1 point	
Aortic aneurysm surgery—2 points	
Noncardiac thoracic surgery—1 point	
TOTAL POINTS	**RISK OF DELIRIUM**
0	2%
1-2	11%
3+	50%

*Patient cannot perform any activity requiring 2 metabolic equivalents of activity (see Table 14-1).
Adapted from Marcantonio ER, Goldman L, Mangione CM, et al. A clinical prediction rule for delirium after elective noncardiac surgery. *JAMA*. 1994;271:134-139.

weakness or limited respiratory reserve. Some neuromuscular diseases involve other organs involvement (e.g., cardiac involvement Duchenne muscular dystrophy) that require specific monitoring. The complexity of these illnesses and the relationships among choices of anesthetics, the surgical approach, and the patient's baseline level of function require careful preoperative planning linked to postoperative monitoring, particularly for respiratory status.

DELIRIUM

Delirium (Chapter 361) is an important, common, and underrecognized complication of surgery. Delirium can lead to prolonged length of stay, additional in-hospital complications (e.g., pneumonia or thromboembolism), and worse post-hospital outcomes, including loss of independence, persistent cognitive impairment, and death. The medical consultant has a role in identifying patients at risk and recommending evidence-based strategies to reduce the incidence and severity of delirium.

Advancing age, functional status, and preoperative cognitive status are key features for predicting patients at increased risk of postoperative delirium (Table 399-6).[16] Patients with hip fractures are at particularly high risk largely because the risk factors for hip fracture (e.g., cognitive impairment, medical comorbidity, and functional decline) are closely associated with the risk of delirium.

Delirium, which is a clinical diagnosis (see Fig. 361-2), can range from agitation with active hallucinations to hypoactivity with somnolence. Furthermore, it waxes and wanes, thereby posing challenges for clinicians who see the patient at various times even during the same day. In the absence of traumatic head injury, falls in patients on anticoagulation, or newly noted focal neurologic findings, few tests are indicated for the diagnosis or evaluation of delirium in the preoperative time period. Laboratory risk factors for delirium (e.g., hyponatremia, hypercalcemia, or hypokalemia) should be corrected and monitored, but other tests (e.g., computed tomography of the brain, vitamin B_{12} levels) have no diagnostic or therapeutic role in the preoperative period.

TREATMENT AND PREVENTION

A key step in preventing and treating delirium is recognition of the disease itself and providing anticipatory guidance to the surgical team, patient, and family before surgery. Methods for prevention and treatment of delirium are multicomponent and multidisciplinary (Chapter 361),[A6] and the medical consultant has a key role in ensuring that effective treatments are used. Worthwhile intervention include active management of levels of serum electrolytes and glucose, use of supplemental oxygen if needed, implementing an effective bowel regimen, and ensuring that intravenous lines and catheters (particularly urinary catheters) are removed as early as feasible. Whenever possible, the consultant should attempt to discontinue medications that can worsen cognitive status (e.g., anticholinergic and antispasmodic medications). Nonopioid pain regimens (see Table 26-4), including scheduled acetaminophen and topical treatments (e.g., ice or warm compresses), can improve pain control without adding sedating medications.

Prehabilitation programs involving intensive presurgical physical therapy and comprehensive geriatric care programs[A7,A8] may improve functional recovery and may reduce the incidence and severity of delirium among older patients with functional limitations who are to undergo major surgery. Melatonin at low doses (2 to 5 mg) in the evening can aid with sleep and restore sleep–wake cycles that can be disturbed in the hospital setting. Ramelteon (a melatonin receptor/agonist at 8 mg nightly orally)[A9] or intravenous dexmedetomidine (0.1 μg/kg/hour) from intensive care unit admission on the day of surgery until 8 AM the next morning[A10] can reduce postoperative delirium. Prophylactic antipsychotic agents are not recommended, even in patients at risk for delirium.

Effective behavioral interventions can include instructing the nurses, care attendants, and patient's family to reorient the patient to day and time and to work to redirect the patient if the patient become agitated. Early and effective increases in mobility (e.g., getting the patient into a chair or walking every day) are helpful. In addition, many hospitals have specialized care units (sometimes called Acute Care for the Elderly units) for patients who have delirium and aging-related disorders; patients at high risk for postoperative delirium may benefit from care in these settings.

ENDOCRINE RISKS

DIABETES

Aggressive approaches to maintain a normal glucose level increase morbidity in most postoperative patients. The consultant's recommendations therefore should emphasize strategies that avoid in-hospital complications of diabetes, whether hypoglycemia or ketoacidosis, by targeting a blood sugar level between 80 and 140 mg/dL (Chapter 210).[17] Patients whose diabetes is controlled by diet alone can be managed with fingerstick blood glucose monitoring and short-acting insulin to correct hyperglycemia on an as-needed basis. Diabetic patients who take oral medications should not take them on the morning of surgery, with fingerstick monitoring and as-needed insulin in the immediate surgical period; postoperatively, such patients should continue with fingerstick monitoring and be treated with a combination of a short-acting insulin plus carefully titrated intermediate- or long-acting insulin, depending on daily basal insulin needs. Oral medications should be restarted prior to discharge if possible to ensure a smooth transition to home. Depending on their baseline blood glucose levels and the expected duration of surgery, patients with insulin-dependent diabetes typically should receive half to two thirds of their usual intermediate- or long-acting insulin dose prior to surgery, with a combination of their longer-acting insulin (usually at lower than home dose) and short-acting correctional insulin used in concert with frequent fingersticks to ensure good control after surgery. In patients who have insulin pumps, expert management by an endocrinologist is recommended.

GLUCOCORTICOIDS AND ADRENAL INSUFFICIENCY

Patients who are receiving less than 5 mg of prednisone (or its equivalent) daily or any dose of glucocorticoids for less than 3 weeks can continue this medication through the perioperative period (or forgo stress dose steroids). If the patient is to undergo a very low-risk procedure (e.g., dental extraction, cataract removal, arthroscopy), it is reasonable to continue the chronic glucocorticoid dose uninterrupted. Patients who have received higher doses for 3 weeks or longer or who are undergoing other surgeries are at increased risk for suppression of the hypothalamic–pituitary axis and should receive for stress dose corticosteroids, administered as hydrocortisone 50 to 100 mg IV prior to surgery. They then should receive either a 200-mg continuous infusion for 24 hours (Chapter 208)[18] or 50 to 100 mg every 8 hours for 1 day, followed by transition to their chronic dose (intravenously if required) on day 2.

THYROID DISORDERS

The major risks of thyroid disorders (Chapter 207) in the perioperative setting are for patients whose hypothyroidism or hyperthyroidism is poorly controlled or undiagnosed. Testing for thyroid disorders should be prompted by findings on the preoperative history and physical examination. If a patient has clinical hypothyroidism or hyperthyroidism and the surgery is elective, it is reasonable to delay the surgery to begin appropriate medical therapies needed to achieve euthyroidism before the surgery is performed. For urgent or emergent procedures, the hyperthyroid patient should be managed using accepted therapies for thyrotoxicosis (e.g., β-blockers, intravenous glucocorticoids; Chapter 207) with a goal of controlling the heart rate and reducing clinical signs of hyperthyroidism prior to surgery. For patients who have clinically apparent hypothyroidism prior to surgery, intravenous thyroxine (200 to 300 μg once, followed by 50 to 100 μg daily, with transition to oral maintenance dosing [see Chapter 207] at time of discharge) is a reasonable approach. Patients with clinically apparent hypothyroidism should also receive stress dose steroids for 24 hours after surgery.

RENAL, HEMATOLOGIC, AND LIVER DISORDERS

CHRONIC KIDNEY DISEASE

Patients with chronic kidney disease (Chapter 116) are at higher risk for a range of complications following surgery, in part because of the comorbid conditions that accompany chronic kidney disease, but also because of problems that result from chronic kidney disease itself (e.g., volume status, electrolyte management, anemia).[19] Few data support any approaches to reducing the risks of worsening renal function in patients with chronic kidney disease. The consultant should develop a plan to manage and monitor electrolytes in patients before and after surgery, with particular focus on diuretics and ensuring perioperative medications are dosed at levels that are appropriate for the degree of renal impairment. Patients on hemodialysis should have a dialysis treatment the morning of surgery to ensure adequate volume and electrolyte balance;[20] postoperative dialysis treatments can be performed as scheduled or tailored based on the patient's ability to produce urine, intrinsic renal function (e.g., ability manage electrolytes and acid-base status), and surgical factors (e.g., volume loss or administration during surgery).

ANEMIA AND CLOTTING PROBLEMS

Although preoperative anemia is a risk factor for 30-day complications, strong evidence supports a restrictive transfusion approach in patients who require surgery emergently or urgently. In these patients, transfusion should be triggered by a hemoglobin level of 7 g/dL if the patient is otherwise asymptomatic. For patients with cardiopulmonary symptoms, known cardiopulmonary disease, or undergoing major surgery, a transfusion threshold of 9 to 10 g/dL is appropriate.[A11] Preoperative iron therapy does not reduce risks.[A12] Patients who have significant anemia and who are scheduled for elective surgery should undergo routine evaluation (Chapter 144) prior to surgery, with the goal of ensuring that no life- or prognosis-limiting problems (e.g., active gastrointestinal bleeding or advanced gastrointestinal cancer) coexist with the surgical problem. In patients undergoing noncardiac surgery, tranexamic acid administered by the surgical team can reduce bleeding events.[A13]

LIVER DISEASE

Patients with asymptomatic or mild chronic hepatitis or other liver disease do not require specific preoperative testing beyond what is routinely indicated. However, such patients may be at higher risk for postoperative complications due in part to the causes of their liver disease (e.g., delirium in patients with alcohol-related hepatitis).[21] Outcomes of patients with cirrhosis tend to correlate with the severity of their liver disease as quantified by Model for End-Stage Liver Disease (MELD) score (Table 139-2). The focus in such patients should be on managing volume status (particularly ascites), clotting disorders, and potential encephalopathy (Chapter 139).

APPROACH TO MANAGING MEDICATIONS

CHRONIC MEDICATIONS

The management of medication is a key aspect of the preoperative consultation, with an emphasis on identifying which medications should have their doses modified or be discontinued (and if so, for how long) during the surgical period (Table 399-7) and being sure that needed medications be restarted before the patient is discharged or before the first postoperative visit. Medications should be stopped or have their doses modified if they have a direct relationship with surgical complications (e.g., warfarin and bleeding) or cannot be safely administered in the perioperative period (e.g., the patient is not eating, so modified doses of insulin are required).

Most medications should be continued as is feasible (based on patient's ability to take oral medications or their volume status) during the hospitalization. For insulin-dependent diabetes, adjustments in the insulin dose are critical (see earlier). For patients who are taking chronic glucocorticoids, stress doses are recommended (see earlier). Conversely, a subset of medications (e.g., angiotensin-converting enzyme inhibitors) are usually discontinued temporarily during the perioperative period because they can produce transient problems during the induction of anesthesia or while the patient is unable to eat. In these cases, the key goal is to ensure that medications are restarted prior to discharge.

The most challenging perioperative medication issue relates to antiplatelet agents and anticoagulants because the risk of perioperative bleeding must be balanced against the risk of thrombotic events. Most procedures outside of the central nervous system and spine can be performed safely while continuing

TABLE 399-7 APPROACH TO COMMON LONGITUDINAL MEDICATIONS IN THE PERIOPERATIVE PERIOD

	GENERAL APPROACH
CARDIOVASCULAR	
• β-Blockers and clonidine	Occasionally stopped by anesthesiologist on day of surgery based on concerns for hypotension during induction of anesthesia; medical consultant should focus on continuity through perioperative period
• Calcium channel blockers	No data to support holding or discontinuing; medical consultant should focus on continuity through perioperative period
• Angiotensin-converting enzyme inhibitors and angiotensin II receptor blockers	Occasionally stopped by anesthesiologist on day of surgery based on concerns for hypotension during induction of anesthesia; medical consultant should focus on continuity through perioperative period
• Statins	Some data suggest continuity can reduce risk for cardiovascular events; medical consultant should focus on continuity through perioperative period
• Diuretics	Can be held based on volume status or anticipated blood loss; medical consultant should focus on continuity through perioperative period
• Antiarrhythmic agents	No data to support holding or discontinuing; medical consultant should focus on continuity through perioperative period
GASTROINTESTINAL	
• Proton-pump inhibitors and histamine-2 blockers	No data to support holding or discontinuing; medical consultant should focus on continuity through perioperative period
PULMONARY	
• Inhaled medications	No data to support holding or discontinuing; medical consultant should focus on continuity through perioperative period
• Oral medications	No data to support holding or discontinuing; medical consultant should focus on continuity through perioperative period
ENDOCRINE	
• Oral hypoglycemic agents	Hold on day of surgery; replace with subcutaneous insulin until taking full diet (Chapter 210)
• Injected hypoglycemic agents	Exenatide, liraglutide: hold on day of surgery to avoid slowing gastric emptying; sitagliptin, linagliptin: can be continued (Chapter 210)
• Insulin	Type II diabetes: discontinue long-acting insulin 24 hours before surgery, administer reduced dose (usually half to two-thirds) of short-acting insulin on day of surgery, restart after surgery; type I diabetes: continue basal insulin through surgery (see Chapter 210 and text)
• Glucocorticoids	Consider stress dose corticosteroids if on chronic corticosteroids (see Chapter 208 and text)
• Estrogens	Consider discontinuation before surgery in patients at risk for thromboembolism
• Thyroid medications	Continue through surgery
HEMATOLOGIC AGENTS	
• Antiplatelet agents	See text and Fig. 399-3
• Anticoagulants	See text and Fig. 399-3
PSYCHIATRIC MEDICATIONS	In general, continue through surgical period. Monoamine oxidase inhibitors infrequent but should be held 10-14 days before surgery
OPIOIDS	No data to support holding or discontinuing; medical consultant should focus on continuity through perioperative period and anticipate an increment in the required dose due to acute postsurgical pain

Adapted from: Spell NO, 3rd. Stopping and restarting medications in the perioperative period. *Med Clin North Am*. 2001;85:1117-1128; Sudhakaran S, Surani SR. Guidelines for perioperative management of the diabetic patient. *Surg Res Pract*. 2015;2015:284063.

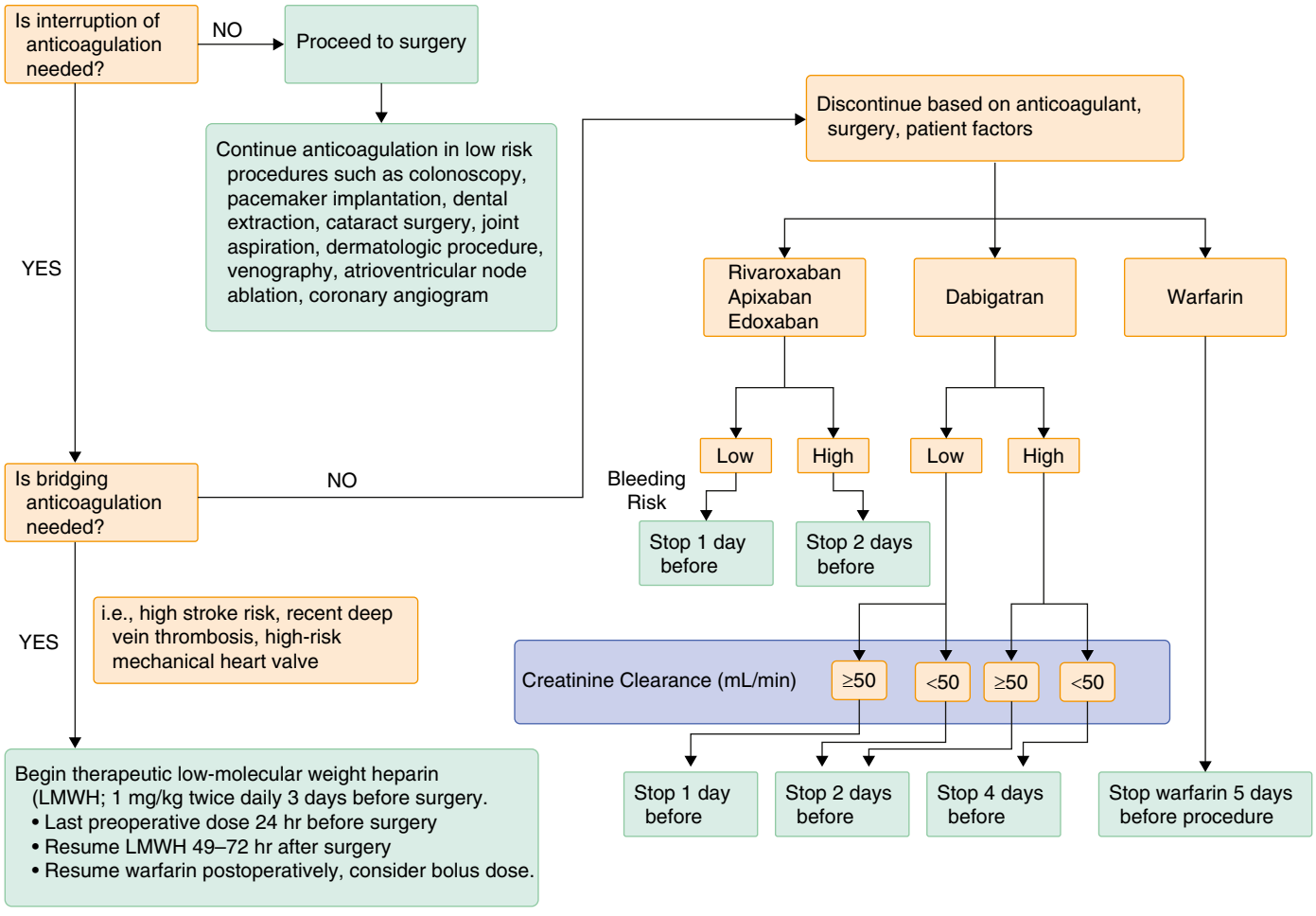

FIGURE 399-3. Anticoagulation management in the perioperative time period. DOAC = direct-acting oral anticoagulant; LMWH = low molecular weight heparin. (Adapted from Tafur A, Douketis J. Perioperative management of anticoagulant and antiplatelet therapy. *Heart*. 2018;104:1461-1467; and Douketis JD, Spyropoulos AC, Duncan J, et al. Perioperative management of patients with atrial fibrillation receiving a direct oral anticoagulant. *JAMA Intern Med*. 2019;179:1469-1478.)

low-dose (81 mg daily) aspirin through the perioperative period. The decision to hold other antiplatelet agents (see Table 70-8) such as clopidogrel (5 to 7 days before surgery), ticagrelor (5 days), or prasugrel (7 days) depends on risks of bleeding due to the procedure and the indication for the antiplatelet agent (e.g., cardiac stent). In cases in which P2Y12 inhibitors can be held (e.g., drug-eluting stent at least 6 and optimally 12 months old), aspirin should be continued, with the PY12 inhibitor restarted as soon as feasible after the procedure. If aspirin must be stopped, it should be discontinued 5 to 7 days before the planned procedure. If a drug-eluting cardiac stent is less than 6 months old, the patient is planned for urgent or emergent surgery, and dual antiplatelet therapy cannot be safely held for other reasons, few data exist to describe optimal management, though intravenous IIb/IIIa inhibitors could be considered as a bridge through the perioperative period (see Chapter 70 and Table 70-8).

For oral anticoagulants, low-risk patients (e.g., patients with distant history of thromboembolism) and patients with atrial fibrillation do not require bridging anticoagulation and should have their anticoagulant discontinued prior to surgery,[A14] with the time period depending on the medication, the patient's renal function, and the planned surgical procedure (see Fig. 399-2).[22,23] Even in the absence of data from randomized trials, patients who are at highest risk of thromboembolism while off anticoagulation (e.g., a mechanical mitral valve, known atrial appendage clot, or pulmonary embolism within the last 3 months) should have bridging anticoagulation with low-molecular-weight heparin (LMWH 1 mg/kg twice daily) or unfractionated heparin (Table 70-3), with these agents held for 24 hours (LMWH) or 6 hours (unfractionated heparin) prior to surgery.[24] Either agent should be restarted at therapeutic doses as soon as safe (optimally 24 hours) after surgery, with the patient's oral agent restarted soon thereafter. Many patients may have risks in between these two groups and will require a tailored approach, but the preponderance of evidence suggests that bridging anticoagulation strategies, though effective at reducing thrombosis and thromboembolism, are associated with excess bleeding and should not be used or must be used judiciously as part of a comprehensive plan. For example, if a patient has had a recent embolic event, it may be reasonable to delay the surgery until the patient has been on therapeutic anticoagulation for 12 or more weeks. If the surgery cannot be delayed, a temporary inferior vena cava filter may be indicated for patients with recent venous thromboembolism.

COMMUNICATING WITH THE SURGEON AND ANESTHESIOLOGIST

A consultant's recommendations should answer any specific questions posed by the consulting surgeon, while also relaying an overall assessment and key conclusions to the surgeon and the patient (Table 398-2). Terms such as "cleared for surgery" are nonspecific and unhelpful. Instead, the patient can be classified as being at "acceptable risk" when concerns are minimal, "elevated but acceptable risk" when additional preoperative recommendations are tailored to reduce risks, or "very high/concerning" when risks of complications are relatively high and intensified postoperative monitoring is required. The consultant should also use risk indices or disease-specific evaluations to describe the patient's primary sources of risk (e.g., cardiac risk, or pulmonary risk), followed by specific recommendations that correlate with the areas of risk as well as contingency plans should unexpected findings or events take place.

The consultant should also consider recommendations to ensure standard safety and quality steps are followed after surgery (e.g., thromboembolism prophylaxis, early removal of urinary catheters, and opioid-sparing pain regimens; see Chapter 401). Finally, the consultant should ensure close coordination of care by determining what postoperative role (e.g., continued consultation, active comanagement) is desired.

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For the General References and other additional features, please visit Elsevier eBooks+ at https://ebooks.health.elsevier.com.

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400 OVERVIEW OF ANESTHESIA

JEANINE P. WIENER-KRONISH AND LEE A. FLEISHER

Approximately 300 million interventional procedures are performed worldwide each year. Anesthetics and/or sedation and analgesia are utilized for most of these procedures, almost half of which are performed outside of a hospital operating room. Deaths attributed to anesthesia are very rare, estimated between 1:10,000 and 1:200,000.[1,2]

Risk reduction over recent decades has been a result of mandatory preoperative assessments, of functional status, cardiopulmonary disease, frailty,[3–5] and neuromuscular disease; attempts to achieve smoking cessation, alcohol abstinence, and control of opioid use; better intraoperative systems[6,7,A1]; and improved postoperative care. Preoperative fasting reduces the risk of aspiration, but clear liquids may be ingested up until arrival in the operating room without obvious adverse effects.[8] The location of care can also impact surgical outcomes, with teaching hospitals having superior outcomes in multimorbid patients.[9]

PREOPERATIVE ASSESSMENT

Essential aspects of total preoperative risk assessment (Chapter 399) include the type of surgery or procedure to be performed, the patient's underlying medical conditions, including dementia,[10] their functional state, and any specific issues related to the patient and the procedure.[11] Frailty, malnutrition, and sarcopenia are now recognized as important features that affect perioperative outcomes. Additionally, the preoperative evaluation can be used as a means to improve long-term health as part of a population health strategy.

AIRWAY ASSESSMENT

Assessment of the airway is always necessary, even if regional anesthesia or monitored anesthesia care (local anesthesia with sedation) is planned, because unexpected complications or compromise of airway reflexes may lead to an emergent need to support ventilation. The laryngeal mask airway device allows many patients to be ventilated easily, but it is important to assess the ability to intubate the patient as well as the ability to ventilate. The prevalence of difficult intubation is about 6% for nonobese patients, and reasons for difficulty include airway pathology (e.g., tumors, previous surgery), reduced mobility of the cervical spine, obstructive sleep apnea, or the anatomic relationship between the larynx and trachea. Although the videolaryngoscope offers improved views of the larynx and is used in many patients who need difficult or emergent intubation,[A2] the device does not improve success in nonexpert hands, nor does its use prevent complications.[A3] Difficult intubations can best be accomplished by clinicians who are expert in airways and who can personalize the choice among the various methods for intubation.[A4]

Criteria for extubation in postoperative patients are similar to those in other patients who receive mechanical ventilation (Chapter 91). Older patients with more severe, comorbid diseases, especially underlying cardiac or pulmonary disease, are more likely to require postoperative reintubation, which is associated with a nine-fold increase in mortality.

MEDICATION REACTIONS

MALIGNANT HYPERTHERMIA

Malignant hyperthermia (Chapter 402), which is a result of calcium dysregulation in skeletal muscle cells, leads to an increase in the production of carbon dioxide, increased oxygen consumption, and the production of heat during or immediately after exposure to triggering drugs, including halogenated volatile anesthetics and/or the depolarizing muscle relaxant, succinylcholine. Variations in the ryanodine receptors that regulate the duration and amplitude of calcium efflux from the sarcoplasmic reticulum are the leading cause of malignant hyperthermia, but variations in other genes (including *CACNA1S* and *STAC3*) also can predispose (Chapter 99).[12] Such genetic variants affect between 1:400 and 1:8500 people. Patients with mutations predisposing to malignant hyperthermia can function normally at resting conditions, but exposure to volatile anesthetics, or exposure to a succinylcholine, can precipitate life-threatening muscle contractures, increases in heart rate and body temperature, rhabdomyolysis, myoglobinuria, and metabolic acidosis. The mortality rate is 80% in untreated patients but about 5% with current treatment. Patients with malignant hyperthermia do not predictably respond to triggering agents, and some patients with malignant hyperthermia have had milder symptoms after the administration of nontriggering agents. Malignant hyperthermia now often occurs in muted forms, probably because of the decreased use of succinylcholine, the diagnostic awareness of malignant hyperthermia by anesthesiologists, the routine use of carbon dioxide monitors so that increases in end-expiratory carbon dioxide are detected quickly, and the availability of dantrolene. If malignant hyperthermia is suspected by obtaining a family history of adverse events with the administration of anesthesia or when a patient has a reaction suspicious for malignant hyperthermia, a muscle biopsy is usually obtained for in vitro contracture testing, which evaluates the muscle contracture responses to caffeine or halothane. Genetic investigations are also recommended, but malignant hyperthermia cannot be excluded on the basis of genetic testing alone because of the diversity of mutations and genes that can be involved in this syndrome. Medical personnel can get information 24 hours a day (www.mhaus.org or on the malignant hyperthermia hotline, 1-800-MHHYPER or 1-800-644-9737).

Rare congenital myopathies that are associated with mutations of the *RYR1* gene, which encodes the ryanodine receptor, and with the malignant hyperthermia syndrome include central core disease and multi/minicore disease, both of which present in early childhood. The clinical spectrum of *RYR1* mutations associated with malignant hyperthermia syndrome includes exertional myalgia associated with rhabdomyolysis, periodic paralysis, and a late-onset axial myopathy. Severe hyperkalemia and cardiac arrest also can be seen after the administration of succinylcholine in patients with other muscular dystrophies, such as Duchenne muscular dystrophy.

TREATMENT

Dantrolene, which is the drug of choice to prevent and reverse the symptoms of malignant hyperthermia, decreases muscle sensitivity to caffeine, reduces the release of calcium from the sarcoplasmic reticulum, and produces some muscle weakness. The dose of dantrolene should be 2 to 2.5 mg/kg, repeated

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400 OVERVIEW OF ANESTHESIA

JEANINE P. WIENER-KRONISH AND LEE A. FLEISHER

Approximately 300 million interventional procedures are performed worldwide each year. Anesthetics and/or sedation and analgesia are utilized for most of these procedures, almost half of which are performed outside of a hospital operating room. Deaths attributed to anesthesia are very rare, estimated between 1:10,000 and 1:200,000.[1,2]

Risk reduction over recent decades has been a result of mandatory preoperative assessments, of functional status, cardiopulmonary disease, frailty,[3–5] and neuromuscular disease; attempts to achieve smoking cessation, alcohol abstinence, and control of opioid use; better intraoperative systems[6,7,A1]; and improved postoperative care. Preoperative fasting reduces the risk of aspiration, but clear liquids may be ingested up until arrival in the operating room without obvious adverse effects.[8] The location of care can also impact surgical outcomes, with teaching hospitals having superior outcomes in multimorbid patients.[9]

PREOPERATIVE ASSESSMENT

Essential aspects of total preoperative risk assessment (Chapter 399) include the type of surgery or procedure to be performed, the patient's underlying medical conditions, including dementia,[10] their functional state, and any specific issues related to the patient and the procedure.[11] Frailty, malnutrition, and sarcopenia are now recognized as important features that affect perioperative outcomes. Additionally, the preoperative evaluation can be used as a means to improve long-term health as part of a population health strategy.

AIRWAY ASSESSMENT

Assessment of the airway is always necessary, even if regional anesthesia or monitored anesthesia care (local anesthesia with sedation) is planned, because unexpected complications or compromise of airway reflexes may lead to an emergent need to support ventilation. The laryngeal mask airway device allows many patients to be ventilated easily, but it is important to assess the ability to intubate the patient as well as the ability to ventilate. The prevalence of difficult intubation is about 6% for nonobese patients, and reasons for difficulty include airway pathology (e.g., tumors, previous surgery), reduced mobility of the cervical spine, obstructive sleep apnea, or the anatomic relationship between the larynx and trachea. Although the videolaryngoscope offers improved views of the larynx and is used in many patients who need difficult or emergent intubation,[A2] the device does not improve success in nonexpert hands, nor does its use prevent complications.[A3] Difficult intubations can best be accomplished by clinicians who are expert in airways and who can personalize the choice among the various methods for intubation.[A4]

Criteria for extubation in postoperative patients are similar to those in other patients who receive mechanical ventilation (Chapter 91). Older patients with more severe, comorbid diseases, especially underlying cardiac or pulmonary disease, are more likely to require postoperative reintubation, which is associated with a nine-fold increase in mortality.

MEDICATION REACTIONS

MALIGNANT HYPERTHERMIA

Malignant hyperthermia (Chapter 402), which is a result of calcium dysregulation in skeletal muscle cells, leads to an increase in the production of carbon dioxide, increased oxygen consumption, and the production of heat during or immediately after exposure to triggering drugs, including halogenated volatile anesthetics and/or the depolarizing muscle relaxant, succinylcholine. Variations in the ryanodine receptors that regulate the duration and amplitude of calcium efflux from the sarcoplasmic reticulum are the leading cause of malignant hyperthermia, but variations in other genes (including *CACNA1S* and *STAC3*) also can predispose (Chapter 99).[12] Such genetic variants affect between 1:400 and 1:8500 people. Patients with mutations predisposing to malignant hyperthermia can function normally at resting conditions, but exposure to volatile anesthetics, or exposure to a succinylcholine, can precipitate life-threatening muscle contractures, increases in heart rate and body temperature, rhabdomyolysis, myoglobinuria, and metabolic acidosis. The mortality rate is 80% in untreated patients but about 5% with current treatment. Patients with malignant hyperthermia do not predictably respond to triggering agents, and some patients with malignant hyperthermia have had milder symptoms after the administration of nontriggering agents. Malignant hyperthermia now often occurs in muted forms, probably because of the decreased use of succinylcholine, the diagnostic awareness of malignant hyperthermia by anesthesiologists, the routine use of carbon dioxide monitors so that increases in end-expiratory carbon dioxide are detected quickly, and the availability of dantrolene. If malignant hyperthermia is suspected by obtaining a family history of adverse events with the administration of anesthesia or when a patient has a reaction suspicious for malignant hyperthermia, a muscle biopsy is usually obtained for in vitro contracture testing, which evaluates the muscle contracture responses to caffeine or halothane. Genetic investigations are also recommended, but malignant hyperthermia cannot be excluded on the basis of genetic testing alone because of the diversity of mutations and genes that can be involved in this syndrome. Medical personnel can get information 24 hours a day (www.mhaus.org or on the malignant hyperthermia hotline, 1-800-MHHYPER or 1-800-644-9737).

Rare congenital myopathies that are associated with mutations of the *RYR1* gene, which encodes the ryanodine receptor, and with the malignant hyperthermia syndrome include central core disease and multi/minicore disease, both of which present in early childhood. The clinical spectrum of *RYR1* mutations associated with malignant hyperthermia syndrome includes exertional myalgia associated with rhabdomyolysis, periodic paralysis, and a late-onset axial myopathy. Severe hyperkalemia and cardiac arrest also can be seen after the administration of succinylcholine in patients with other muscular dystrophies, such as Duchenne muscular dystrophy.

TREATMENT

Dantrolene, which is the drug of choice to prevent and reverse the symptoms of malignant hyperthermia, decreases muscle sensitivity to caffeine, reduces the release of calcium from the sarcoplasmic reticulum, and produces some muscle weakness. The dose of dantrolene should be 2 to 2.5 mg/kg, repeated

ABSTRACT

In the United States, 40 million procedures per year require an anesthetic. This chapter reviews the ongoing evolution of risk assessment, the advantages and disadvantages of general compared with regional anesthesia, the major risk factors for adverse clinical outcomes, the medication reactions that can occur during anesthesia (including malignant hyperthermia and serotonin toxicity), and how the pharmacology and toxicity of common parenteral anesthetics and opioids can affect the postoperative course.

KEYWORDS

general anesthesia
airway assessment
malignant hyperthermia
serotonin toxicity
opioids
ketamine
dexmedetomidine

every 10 minutes until all signs regress, even if the dose exceeds 10 mg/kg. Dantrolene should be stopped when a normal minute ventilation is achieved and the core temperature is decreasing.

Other treatments for malignant hyperthermia include discontinuing the use of any volatile anesthetics; hyperventilating the patient and administering 100% oxygen; administering bicarbonate for severe acidosis; controlling fevers; and maintaining a temperature below 39° C without causing hypothermia by using iced fluids, surface cooling, and cooling of body cavities if necessary. The patient's temperature and vital signs, urinary output, muscle enzymes, glucose, coagulation studies, acid-base status, and gas exchange should be monitored for 48 hours and be observed for 72 hours to ensure there is no recrudescence.

MONOAMINE OXIDASE INHIBITORS AND SEROTONIN TOXICITY

The severe serotonin syndrome is usually precipitated when two or more serotonic drugs are administered, but the syndrome can occur with the administration of one such medication in a susceptible individual.[13] Serotonin toxicity has features similar to malignant hyperthermia and must be distinguished from it. Serotonin toxicity is characterized as a triad of neuromuscular hyperactivity (tremor, clonus, myoclonus, hyperreflexia, and pyramidal rigidity), autonomic hyperactivity (diaphoresis, fever, tachycardia, and tachypnea), and altered mental status (agitation, excitement, and confusion). It can be precipitated by the coadministration of monoamine oxidase inhibitors and selective serotonin reuptake inhibitors (SSRIs). Patients who are taking SSRIs have a higher overall perioperative mortality, a higher 30-day readmission rate, and a higher likelihood of bleeding. Rigidity, increasing arterial carbon dioxide levels, and fever above 38.5° C are associated with life-threatening toxicity. Ecstasy, or 3,4-methylenedioxymethamphetamine (MDMA), combined with monoamine oxidase inhibitors, including moclobemide, can be fatal because it acts as a serotonin releaser. Tramadol, used for pain relief, and venlafaxine, an antidepressant, act as serotonin releasers and are associated with toxicity when used in patients who are taking monoamine oxidase inhibitors. Patients with Parkinson disease are increasingly prescribed monoamine oxidase-B (MAO-B) inhibitors, and a dyskinesia-hyperpyrexia syndrome can occur in these patients.[14]

ANAPHYLAXIS IN THE PERIOPERATIVE PERIOD

The incidence of life-threatening hypersensitivity reactions during anesthesia is 1 : 4000 to 1 : 25,000. Anaphylaxis is caused by immunoglobulin E (IgE)–mediated reactions (Chapter 233), whereas anaphylactoid reactions produce the same clinical picture but are not mediated by IgE. Anaphylaxis during anesthesia can present as cardiovascular collapse, airway obstruction, flushing, or edema of the skin, singly or in combination, so a careful history of any previous allergic reactions to medications and the nature of the reaction must be obtained by the anesthesiologist and other members of the perioperative team. Neuromuscular blocking agents, such as succinylcholine, and opioid analgesics can cause nonimmunologic release of histamine from mast cells and produce a similar clinical syndrome. Antibiotics, protamine, and blood transfusions (Chapter 162), all given routinely during operations, also can elicit a variety of systemic reactions. About 75% of perioperative hypersensitivity reactions appear to be due to muscle relaxants, especially rocuronium and vecuronium, with a mortality rate of 3 to 6%. In patients with apparent allergic reactions, skin testing is usually performed, and IgE levels are usually obtained to determine whether the patient had an allergic reaction to a perioperative medication.

SODIUM-GLUCOSE COTRANSPORTER-2 INHIBITORS AND DIABETIC KETOACIDOSIS

Patients with type 2 diabetes and chronic kidney disease (Chapters 109, 116, and 210) or with heart failure (Chapter 46) have a lower risk of death from cardiovascular causes when treated with sodium-glucose cotransporter 2 inhibitors. The decreased fluid intake prior to and after anesthesia and surgery may predispose patients on these medications to dehydration, ketogenesis, and diabetic ketoacidosis. These drugs should be discontinued 3 to 4 days prior to major surgery, especially if bowel preparation is needed.[15]

LATEX ALLERGY

For sensitized patients (Chapter 233), exposure to even low amounts of latex-containing particles is sufficient to induce a severe anaphylactic reaction. A latex-free operating environment, in which no latex gloves or latex accessories are used, is key in patients with known allergy. Skin prick tests with latex extracts should be considered in patients at high risk for latex allergy. Early aggressive treatment with epinephrine is critical if severe anaphylaxis occurs.

TABLE 400-1 COMMON ANESTHETIC APPROACHES FOR VARIOUS TYPES OF SURGERY

SURGERY ON INTRA-ABDOMINAL OR INTRATHORACIC ORGANS
Examples: cardiac surgery, lung resections, gastric bypass
General anesthesia usually administered because mechanical ventilation is often required
Drugs include premedication for anxiety with midazolam, general anesthesia with volatile anesthetics (desflurane, sevoflurane, nitrous oxide), neuromuscular blockade, and opioid analgesics*
Epidural anesthesia and analgesia also used; examples include ropivacaine, lidocaine, with fentanyl
SURGERY ON LIMBS
Examples: hip replacement, knee replacement, foot or arm surgery
Can perform with epidural or spinal anesthesia, depending on the limb. Examples of medications would include tetracaine, lidocaine, ropivacaine, and fentanyl or morphine
Can perform axillary or scalene block; examples include lidocaine and ropivacaine
For postoperative pain control: can perform regional blocks that leave the catheter in place, including femoral nerve block, axillary nerve blocks
CATARACT SURGERY—LOCAL ANESTHESIA ON EYE WITH OR WITHOUT SEDATION†
Examples of drugs used for sedation include midazolam and fentanyl

*Includes the use of opioids given intraoperatively with effects that extend into the postanesthesia care unit (PACU) or postoperative period, opioids given in the PACU, or opioids given or intended to be given after discharge from the PACU.

†Anesthesia personnel are involved in the majority of cataract procedures, thereby suggesting that either blocks and/or local anesthesia with sedation are being utilized for the majority of cataract procedures.

INTRAOPERATIVE MANAGEMENT

There are three general classes of anesthesia: general, regional, and monitored anesthesia care. The same drugs are often used for general anesthesia and monitored anesthesia care; achievement of the two different conditions requires knowledge of the pharmacokinetics of the drugs (Table 400-1).

GENERAL ANESTHESIA

General anesthesia can be achieved with a balanced drug regimen that induces a loss of consciousness, which can range from a deep sedation requiring only airway support to states requiring full ventilatory support because of weakness and loss of respiratory drive. Both intravenous[16] and inhalational drugs can be used to induce and maintain general anesthesia. In contrast, monitored anesthesia care denotes a state in which patients can still control their airway, do not require ventilatory support, but are sleepy, have less pain, and may be amnestic. The quantity of anesthesia required to achieve unconsciousness varies depending on the patient's brain function and can be titrated by using electroencephalography.[17] Some data suggest that a lighter depth of anesthesia may be associated with less postoperative delirium[A5]

For general anesthesia, adequate and safe ventilation is critical. On average, there is no benefit from high as compared with low tidal volume or end-expiratory pressures,[A6,A7] so tidal volumes and end-expiratory pressures should be individualized for specific patients.[18]

Robotic-assisted laparoscopic surgeries, especially in obese patients, adversely affect respiratory mechanics intraoperatively because of abdominal insufflation and Trendelenburg positioning.[19,20] In patients undergoing these procedures, the use of electrical impedance tomography and of individualized positive end-expiratory pressures can improve the homogeneity of ventilation and reduce postoperative pulmonary complications.

PROPOFOL

Propofol, an alkylphenol, is perhaps the most frequently used intravenous anesthetic for induction of anesthesia and is often used for maintenance of anesthesia during short procedures or to achieve deep sedation during monitored anesthesia care. It is lipid soluble and quickly cleared from the central compartment, so it is rapidly eliminated even after long periods of continuous infusion. However, the clearance of propofol is changed by gender (men have lower clearance rates than women), size (children require higher doses), age (elderly patients have decreased clearance rates and experience increased effects with the drug), and narcotics, which decrease its clearance. Because of its predilection for causing apnea, propofol should be administered only

by someone with expertise in airway management. Propofol also decreases arterial blood pressure, causes pain with injection, and can precipitate myoclonus. Large quantities of propofol can cause propofol infusion syndrome, which is associated with cardiomyopathy, metabolic acidosis, skeletal myopathy, hyperkalemia, hepatomegaly, and lipemia. Despite these issues, propofol is frequently used because the recovery from propofol is within minutes, even after it is given as a prolonged continuous infusion, in contrast to the longer duration of drug effects seen after the administration of other intravenous sedatives. Propofol is commonly the preferred agent for healthy outpatients undergoing colonoscopy because it leads to earlier discharge and higher patient satisfaction compared with other agents.

MIDAZOLAM

Midazolam, a benzodiazepine that produces muscle relaxation through a central mechanism, is hypnotic, sedative, anxiolytic, amnesic, and anticonvulsant. Its amnesic and anticonvulsant effects are mediated through α_1-subunit–containing γ-aminobutyric acid A ($GABA_A$) receptors, and the anxiolytic and muscle relaxation are mediated through α_2-subunit–containing $GABA_A$ receptors. Only 20% receptor occupancy is needed to produce anxiolysis, whereas unconsciousness requires 60%. Long-term administration of benzodiazepines produces tolerance, which appears to decrease receptor binding and function. Benzodiazepines cause dose-related depression of the respiratory system, with a peak effect at 3 minutes and significant depression persisting for 60 to 120 minutes. The rate of administration of the drug affects the onset of depression: the faster the drug is given, the quicker the respiratory depression occurs. Benzodiazepines and opioids appear to produce additive respiratory depression, including apnea. Unlike propofol, benzodiazepines used alone decrease blood pressure only modestly. Other drugs, particularly drugs that affect the cytochrome P-450 3A4 enzyme (including azole antifungals, human immunodeficiency virus [HIV] protease inhibitors, and calcium-channel blockers), affect the clearance of midazolam and prolong its half-life significantly. There are several reports of prolonged amnesia in HIV patients who received midazolam for conscious sedation. Midazolam also has an active metabolite and is often associated with delirium in elderly patients (Chapter 361), perhaps because it impairs both implicit and relational memory.

OPIOIDS

Opioids are classified as naturally occurring (morphine, codeine), semisynthetic (heroin), and synthetic (methadone, fentanyl, remifentanil). They can be administered both intravenously and in the neuraxial space (epidural or spinal). There are four opiate receptors (mu, kappa, delta, and nociceptin receptors), which are G protein–coupled receptors. Chronic exposure to agonists leads to cellular adaptation mechanisms that probably are involved in tolerance, dependence, and withdrawal. Clinically, mu agonists are used almost exclusively; mu agonists include morphine, fentanyl, and meperidine. Opioid analgesics are administered because they relieve pain, but they have other important effects, including respiratory depression, decreased gastric emptying, nausea and vomiting, sedation, constipation, pruritus, dependence, and tolerance, when given repeatedly. When opioids are given with propofol or benzodiazepines, there is a synergistic depressive effect on respiration, hence the rationale for monitoring patients who receive medications for conscious sedation. The rate of prolonged opioid use after surgery is approximately 3%, and characteristics associated with prolonged use include younger age, lower household income, diabetes, heart failure, and pulmonary disease. The recent focus on pain management as a marker of patient satisfaction and putative hospital quality may be one driver of the recent opioid crisis. For example, 70% of opioid-naïve patients who undergo low-risk surgical procedures fill a prescription for hydrocodone/acetaminophen or oxycodone/acetaminophen within 7 days after discharge or the procedure date. Physicians should be careful to avoid unnecessary opiate prescriptions and to limit prescriptions to several days. Such limitations of perioperative opioid prescriptions have become a priority for both health systems and state regulators.

KETAMINE

Ketamine is unique among the intravenous agents because it has analgesic properties and decreases tolerance to opiates. The metabolism of [RS]-ketamine to [2,6 R]-hydroxynorketamine [HNK] is necessary and sufficient to exert antidepressant actions in mice; its antidepressant effects are *N*-methyl-D-aspartate (NMDA) receptor–independent but involve early and sustained activation of α-amino-3-hydroxy-5-methyl-4-isoxazole-propionic acid (AMPA) receptors. Ketamine produces dose-related analgesia, which may be profound even when patients can keep their eyes open, breathe spontaneously, and protect their own airway with conserved swallowing and cough reflex. Side effects include increased lacrimation, salivation, and muscle tone. Ketamine increases cerebral blood flow, can increase seizure activity, and can produce undesirable psychological reactions; these side effects are dose related and may be minimized by the concomitant use of benzodiazepines. Ketamine is also a bronchial smooth muscle relaxant and can prevent experimentally induced bronchospasm. Ketamine is usually associated with an increase in blood pressure, heart rate, and cardiac output. These features make ketamine a useful drug for sedating patients with hemodynamic instability and with depression. Intravenous ketamine under expert supervision also can provide significant short-term analgesic benefit in patients who have refractory chronic pain, but the optimal treatment protocol is not defined.

DEXMEDETOMIDINE

Dexmedetomidine is a highly selective α_2-agonist that is associated with less respiratory depression and more cooperative behavior than is propofol. Dexmedetomidine also causes hypnosis, analgesia, sympatholysis, and inhibition of insulin secretion. Dexmedetomidine induces sedation with a respiratory pattern and electroencephalographic changes similar to natural sleep. Even high concentrations of dexmedetomidine are associated with preservation of spontaneous respiration; however, when dexmedetomidine is administered in combination with sympatholytic or cholinergic agents, there is a high risk for extreme bradycardia and sinus arrest. Dexmedetomidine is associated with less amnesia than are benzodiazepines. Although propofol and benzodiazepines commonly have been used in critically ill patients to achieve sedation for procedures or for maintenance of mechanical ventilation, dexmedetomidine appears to have significant advantages over benzodiazepines because it can provide more comfort with a similar safety profile and decrease the time that critical care patients spend on ventilators. Dexmedetomidine also appears to help shorten the duration of perioperative delirium.[21]

VOLATILE ANESTHETICS

Volatile (inhalational) anesthetics include desflurane, sevoflurane, isoflurane, and nitrous oxide, as well as halothane, which now is rarely used in the United States. Inhaled anesthetics are absorbed through the respiratory epithelium and mucous membranes of the respiratory tract, and they are excreted mainly by exhalation. Access to the circulation is almost instantaneous, owing to the large pulmonary surface area. The pharmacologic effects of inhaled anesthetics depend primarily on alveolar ventilation, the ventilation-perfusion ratio, coadministered gases, gas flow, and the physicochemical properties of the anesthetic gas rather than on the quantity of drug administered, the extent and rate of absorption, protein binding, excretion, secretion, or metabolism.

All inhalational agents, with the exception of nitrous oxide, cause dose-dependent cardiovascular depression. Severe hepatotoxicity, which led to the discontinuation of the use of chloroform, carbon tetrachloride, and trichloroethylene anesthetics, is seen as fatal hepatic necrosis in 1 in 10,000 halothane anesthetics. This problem appears to occur much less frequently with isoflurane and desflurane. Mild halothane hepatoxicity is self-limited and can occur with a single exposure, whereas fulminant halothane hepatitis occurs only after multiple exposures to the drug, has a high mortality rate (50%), and is associated with antibodies to halothane-altered antigens. Volatile anesthetics, which are used in addition to or as a replacement for intravenous sedation in critically ill patients, may reduce the time to postoperative extubation.

Nitrous oxide, which is the only nonhalogenated agent still used, is not metabolized in human tissues. It irreversibly oxidizes the cobalt atom of vitamin B_{12}, thereby inhibiting the activity of the cobalamin-dependent enzyme methionine synthase. Individuals with vitamin B_{12} deficiency or with mutations of methionine synthase may be at risk for neurologic injury from nitrous oxide, which should not be used in patients at risk. Exposure to high concentrations of more than 10^3 ppm may be associated with an increased incidence of abortions and decreased fertility, so exposure should be avoided in patients and personnel at risk. Nitrous oxide is safe in major noncardiac surgery. General anesthesia can be achieved only by giving combinations of drugs along with nitrous oxide to achieve the desired effects. Based on the available evidence, no one general anesthetic appears to be superior to any other.

Volatile anesthetics are greenhouse gases, ozone-depleting agents, or both. As a result, the use of nitrous oxide and desflurane should be minimized if possible.[22]

NEUROMUSCULAR BLOCKERS

Neuromuscular blockers are used to paralyze muscles to facilitate endotracheal intubation and mechanical ventilation, to decrease shivering during induced hypothermia, or to improve conditions for optimal surgery. Succinylcholine

causes prolonged depolarization of the neuromuscular junction, thereby resulting in failure to generate an action potential. Within 9 to 13 minutes after 1 mg/kg of succinylcholine, 90% of muscle strength is restored. The very rapid onset and rapid return of muscle function make succinylcholine a useful drug for difficult intubations. Side effects of succinylcholine include hyperkalemia, myalgia, masseter spasm, sinus bradycardia and nodal rhythms, and increased intraocular pressure.

Most of the other neuromuscular drugs used by anesthesiologists are nondepolarizing in that they compete with acetylcholine for the neuromuscular junction and can be reversed by increasing the quantity of acetylcholine. These drugs are categorized by their chemical makeup: steroidal compounds, benzylisoquinolinium compounds, and other chemical compounds. Clinically, a drug is often chosen for its duration of action. Intermediate agents, which act for 20 to 50 minutes and are used most frequently, include vecuronium, rocuronium, atracurium, and cisatracurium. These drugs have different routes of metabolism, so the choice of agent depends in part on the presence of coexisting disease. The required dose of sugammadex to reverse the effects of neuromuscular blockade induced by rocuronium bromide and vecuronium bromide depends on the intensity of the neuromuscular blockade.[23]

The chronic administration of neuromuscular blocking agents is associated with prolonged paralysis, particularly in patients given concomitant steroids. Other notable interactions with nondepolarizing agents include that antibiotics can increase neuromuscular blockade; magnesium sulfate potentiates neuromuscular blockade; lithium can potentiate neuromuscular blockade with succinylcholine and with pipecuronium; antiepileptic drugs cause resistance to nondepolarizing muscle blockade so that larger doses must be administered to achieve paralysis; and patients receiving anticonvulsants have accelerated recovery from neuromuscular blockade.

Patients who have obstructive sleep apnea and who receive intraoperative neuromuscular blockers may be at higher risk for postoperative hypoxemia and respiratory failure. Reversal with sugammadex may reduce the risk of postoperative pulmonary complications.[24]

REGIONAL ANESTHESIA

Regional anesthesia involves the deposition of local anesthetics near nerves, including the deposition of local anesthetics in the epidural space and into the cerebrospinal fluid (CSF). Local anesthetics, which are aminoesters or aminoamides, affect cardiac function, as well as central nervous system function when administered systemically.

The binding of the local anesthetic to the sodium channels in the axoplasm prevents opening of the channels and conduction of nerve impulses. The rates of onset and recovery from nerve blockade are controlled by the diffusion of the local anesthetic into and out of the whole nerve.

Examples of regional anesthesia include neuraxial techniques, the deposition of local anesthetics near the brachial plexus to anesthetize the arms (axillary or intrascalene blocks), deposition near the femoral or sciatic nerves to anesthetize the legs, deposition near ulnar or radial nerves for lower arm blocks, deposition near the pudendal nerves for groin procedures, and deposition of local anesthesia in the caudal space for groin surgeries. Dentists employ this technique frequently when they inject local anesthesia near various nerves in the oral cavity. Many surgeries, including carotid surgery and the placement of fistulas for dialysis, can be performed with regional anesthesia. Regional anesthetics may also require supplementation with sedation or general anesthesia. Regional anesthesia can decrease postoperative pain and use of opioids.[25]

The dangers of regional anesthesia include the injection of local anesthesia into the systemic circulation. Systemic toxicity is manifested as convulsions and respiratory depression, which can require assisted ventilation. Tinnitus, visual and auditory disturbances, and dizziness are signs of milder central nervous toxicity. Cardiac toxicity can be manifested by decreases in heart rate, prolonged conduction times, and negative inotropic effects. Bupivacaine toxicity, which is associated with ventricular fibrillation, is more frequent in elderly patients. Treatment of local anesthetic systemic toxicity should include airway management, management of seizures, standard cardiovascular support, and lipid emulsion infusions.[26] Lower doses of epinephrine (<1 μg/kg) should be considered because the drug may interfere with the lipid resuscitation. Furthermore, the prolonged duration of many of the local anesthetics may require the institution of cardiopulmonary bypass until the drugs are metabolized.

NEURAXIAL (SPINAL AND EPIDURAL) ANESTHESIA AND ANALGESIA

Spinal anesthesia is the instillation of local anesthetics into the CSF. Epidural anesthesia is the instillation of larger volumes of local anesthetics into the epidural space, which is the potential space that exists just before the CSF. Spinal anesthesia is associated with an increased incidence of headache in younger patients, so epidural anesthesia is often used in younger patients. Complications of epidural and spinal anesthesia and analgesia include failed blocks, postdural puncture headaches, and toxicity from the local anesthetics. Another major concern of neuraxial anesthesia is that patients on antiplatelet agents may develop epidural hematomas, although epidural hematoma remains a rare event, occurring in fewer than 1 in 150,000 operations even in the presence of potent antiplatelet agents. Other, more rare complications of epidural and spinal anesthetics, in addition to the effects of local anesthesia outlined previously, include intracranial subdural hematoma, transverse myelitis, hypotension, and cardiac arrest.

Postoperative epidural analgesia, by which either local anesthesia or local anesthesia and narcotics are instilled into the epidural space for postoperative pain control, is associated with superior pain control, lower doses of opioids, improved bowel mobility, slightly decreased length of stay in the intensive care unit, and a slight decrease in the requirement for mechanical ventilation. The continuous intravenous infusion of perioperative lidocaine also may reduce pain and nausea, especially in the early postoperative period, but it is not as well studied as epidural anesthesia.[A8]

GENERAL VERSUS REGIONAL ANESTHESIA

Overall, there is no evidence that major postoperative cardiac events differ depending on whether non–cardiac surgery patients receive general, spinal, or epidural anesthesia.[A9,A10] When options are available, anesthesiologists and surgeons should offer patients the choice of less intensive anesthesia (i.e., spinal or epidural anesthesia or conscious sedation rather than general anesthesia, local anesthesia rather than conscious sedation), because such methods usually provide similar results.

However, the decision regarding what type of anesthesia should be administered often depends on the requirements of the surgery. For example, laparoscopic surgery requires general anesthesia because the insufflations of gases impair the ability to breathe adequately. General anesthesia is also required for surgeries on the airway or thorax because mechanical ventilation is usually needed to sustain adequate respiration. Procedures that do not allow any movement (e.g., precise procedures in the brain) often require general anesthesia and paralysis. For patients in whom the intraoperative technique could include general anesthesia, regional anesthesia, or a combination of the two, regional anesthesia may minimize pulmonary complications and modestly shorten hospital length of stay, but there currently is no evidence that it affects mortality.

Side effects of general anesthesia depend upon the drugs used to achieve anesthesia, whether neuromuscular blockade is administered, and whether mechanical ventilation is used. Complications of endotracheal intubation include local pain, trauma to the airway, swelling, vocal cord paralysis, increased bronchospasm, and death from improper placement. Volatile anesthetics are associated with postoperative atelectasis (Chapter 78), whereas regional anesthesia may help preserve respiratory dynamics. Postoperative cognitive dysfunction (Chapter 361) does not seem to depend on the type of anesthesia administered,[A11] but it may depend on the depth of accompanying sedation and severity of comorbid conditions.

NAUSEA AND VOMITING

Postoperative nausea and vomiting are more likely with volatile anesthetics but also are common when perioperative opioids are administered. Prophylactic ondansetron, dexamethasone, and droperidol each reduce postoperative nausea and vomiting, independently, by about 25%, with the main predictor for efficacy being the patient's risk for nausea and vomiting. It should be noted that droperidol has received a "black box" warning from the FDA, so it is not used very often in the United States. Total intravenous anesthesia with propofol reduces postoperative nausea and vomiting by only about 20%, often because narcotics are still administered. The use of spinal or epidural anesthesia may decrease the incidence of nausea and vomiting. In addition to general anesthesia, risk factors for postoperative nausea and vomiting include female gender, a prior history of nausea and vomiting, a history of motion sickness, nonsmoking, and intended administration of opioids for postoperative analgesia. If three or more risk factors are present, patients generally are recommended to receive at least two prophylactic pharmacologic antiemetic agents of different classes, selected among ondansetron (or ramosetron or granisetron), dexamethasone, or aprepitant preoperatively for the prevention of postoperative nausea and vomiting[A12] (Table 118-5).

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401 POSTOPERATIVE CARE AND COMPLICATIONS

DONALD A. REDELMEIER

POSTOPERATIVE CARE

OVERVIEW

Postoperative medical complications are common, potentially fatal, and variable across different settings. Over 99% of perioperative deaths occur after the surgery, and nearly half are related to potentially treatable bleeding, myocardial injury, or systemic sepsis.[1] Large national studies show about a two-fold difference in risk for mortality between high- and low-ranked hospitals. However, analyses disagree about how much these differences reflect a greater incidence of each complication (failure of prevention around the time of surgery), a heightened lethality of each complication (failure to rescue in the aftermath of surgery), differences in the severity of disease (inherent differences among patients), and surgical skill (technical excellence). Regardless of the explanation, the purpose of medical consultation is to relieve human suffering by preventing, detecting, and correcting postoperative complications. The main constraint is that the consultant often has limited ongoing direct contact with the patient before or after the perioperative interval.

EFFECTIVE TEAMWORK

The medical consultant (Chapter 398) in the postoperative setting must have both a knowledge of medicine and an appreciation of the team psychology that can improve outcomes of patients. In contrast to other settings, the internist is not the team leader, often does not maintain an ongoing relationship with the patient, and does not have the authority of the most responsible physician. Moreover, patients may be dispersed across diverse surgical services, each with its own orientation and culture. The challenges of coordination and communication are enormous, particularly given the many other health care professionals involved in complex surgical cases. Considerable tact is often needed to avoid antagonizing the surgeon, disrupting the team's dynamics, or inducing a cascade of cumbersome inopportune testing. The development and use of safety checklists may be one effective way to enhance teamwork and to improve outcomes.

FOCUSING ON RECOVERY

Facilitating the patient's recovery from surgery differs from managing patients with acute exacerbations or chronic diseases. In the postoperative setting, many therapies must be stopped when the patient has recovered, such as discontinuing a urinary catheter because the patient can now void spontaneously or discontinuing a major tranquilizer because the patient is now oriented and coherent. Discontinuation of many other interventions requires substantial judgment, such as the decision when to discontinue intravenous access, supplemental oxygen, and intermittent laxatives. Much depends on experience and reconsideration of the individual patient's recovery on a regular basis.

READING ANESTHESIA RECORDS

A focused review of the anesthesia record is essential because the consultant is rarely present during the operation. Perhaps the most basic information to identify is the date of surgery because the time elapsed helps when interpreting the patient's current state of recovery. Sometimes the date is not immediately evident if more than one surgery has been performed, a planned operation was delayed, or some misquotations have arisen. Data about the duration of surgery, type of anesthesia (e.g., regional, spinal, or general [Chapter 400]), and major intraoperative events can help to establish reasonable expectations about the future course as well as the possibility of specific complications (e.g., epidural hematoma after spinal anesthesia). Sharing some of the basic data with the patient is often helpful because many individuals either benefit from repetition or are not otherwise informed.

PATTERNS OF MISTAKES

Medical errors (Chapter 10) that arise in postoperative care often seem mundane in retrospect, yet can be lethal if missed. Some patterns of mistakes have the feature of "double trouble," such as when a patient has both a potassium level of 2.0 mEq/L and lithium level of 2.0 mEq/L, but care focuses on only one of these two metabolic abnormalities. Other mistakes occur because a problem arises at an awkward moment, such as when one patient develops acute dyspnea at the same time when another patient is having a seizure. Still other mistakes relate to the fallibility of human memory and attention, such as when a normal blood glucose value in the morning leads clinicians to presume that the level is still normal at night. These errors can result in substantial harm, failures of clinicians to learn from past mistakes, and unprofessional reactions related to lingering embarrassment. None of these patterns are unique to postoperative care, yet the fast and unfamiliar terrain of surgical settings can make even simple mistakes difficult to avoid.

CHECKING ORDERS

The first method for reducing errors after surgery is to check the postoperative orders already written for the patient. Such double-checking is a tedious task, and clinicians often direct insufficient attention to this review in the faulty belief that most of the work is already done. Ironically, checking orders written by another clinician requires more than customary attention because of the challenges of following someone else's legibility, sequencing, and preferences. The set of orders may need to be read twice: once for errors of commission (e.g., a calcium-channel blocker ordered at the wrong dose) and once for errors of omission (e.g., a β-blocker inadvertently not reordered after surgery). One classic mistake on postoperative orders is failure to follow through on interventions initiated immediately before surgery (e.g., delirium tremens prophylaxis). A particularly vexing issue is the need for repeated rechecking on subsequent days (e.g., new orders for unnecessary sedative medications).

RECOMMENDED PROPHYLAXIS

Some complications are sufficiently frequent and serious that routine prophylaxis is justified in the postoperative setting. For example, systemic anticoagulation is indicated for patients at risk for postoperative deep venous thrombosis (Chapters 68 and 70). Gastric acid suppression (Chapter 125) is justified for patients at high risk for postoperative gastric bleeding. Laxatives are indicated for patients who are receiving systemic opioids. In contrast, antibiotic prophylaxis is indicated only for selected patients who are at high risk for endocarditis (Chapter 61), and antibiotic prophylaxis to prevent surgical site infections can be discontinued immediately if best practice standards are followed.[A1]

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ABSTRACT

Postoperative care requires identifying and correcting medical complications in complex surgical patients. This chapter reviews the fundamentals of effective teamwork, interpretation of common patient symptoms, treatment of other abnormal signs or laboratory abnormalities, and selected nuances related to special situations. The goal of medical consultation is to relieve suffering by the prevention, detection, and treatment of postoperative complications.

KEYWORDS

postoperative complications
general internal medicine
medical consultation
surgical complications
shared patient management

The optimal method for gauging whether a patient is at high risk for each complication is contentious and thereby leads to variation in practice patterns across different settings.

FUTURE PREVENTION

A postoperative consultant who maintains communication, facilitates the patient's recovery, and avoids postoperative mistakes also has the chance to initiate medical interventions for general medical care. Such opportunities for prevention might include influenza vaccination, colon cancer screening, and cholesterol reduction. The main advantage of such comprehensive care is that it conforms to the ideal of providing all services possible to the individual. The main disadvantage of such comprehensive care is the potential for creating commotion, confusion, or misquotation (Chapter 398). Such unintended consequences distract the surgical team and also carry some risk for side effects at a time when the patient is trying to recover from surgery. Many effective postoperative consultants will defer such opportunities for prevention to the outpatient physicians who assume long-term responsibility for the patient's care.

COMPLICATIONS

SYMPTOMS

Chest Pain

Chest pain is a common problem after surgery and has an extensive differential diagnosis (Chapter 39). In the postoperative setting, the immediate consideration is an acute ischemic myocardial event. The diagnosis of a perioperative myocardial infarction (MI) differs somewhat from community-acquired MI (Table 401-1). Interpretation of a patient's symptoms, examination findings, and electrocardiogram is often problematic because of changes related to surgery and anesthesia. In particular, diagnosis is heavily dependent on biomarkers, such as an elevated troponin level, especially because many postoperative MIs are painless.

Management priorities include supplemental oxygen, heart rate control, and correction of severe anemia. Thrombolysis is often contraindicated, but percutaneous coronary intervention may be considered, especially because of the high 30-day mortality rate for postoperative MI, although data on its benefits are lacking. Dabigatran (110 mg twice daily) can reduce the risk of major vascular complications without increasing major bleeding in patients who develop evidence of myocardial injury after noncardiac surgery.[A2] Otherwise, therapies such as aspirin, clopidogrel, nitrates, statins, and angiotensin-converting enzyme inhibitors, should be considered on a case-by-case basis (Chapter 58).

Dyspnea

Shortness of breath (Chapter 71) after surgery has an extensive differential diagnosis (Table 401-2). The three key considerations are fluid overload from heart failure (Chapter 45), pulmonary embolism (Chapter 68), and air space disease (a continuum encompassing atelectasis [Chapter 78], bronchitis [Chapter 84], aspiration [Chapter 82], mucous plugging, and pneumonia). Distinguishing among these considerations requires focusing on the speed of onset, timing relative to surgery, vital sign abnormalities, findings on oximetry, and physical examination (Chapter 71). The evaluation should focus on a review of background comorbid conditions, an electrocardiogram, and a chest radiograph to assess for cardiac and pulmonary causes. Fluid overload is most commonly seen soon after the cessation of positive-pressure ventilation or vasodilating analgesia. It is also common 3 to 5 days postoperatively when fluid that had been extravasated into interstitial tissue is shifted back into the intravascular compartment. The results of the initial evaluation can guide further efforts to diagnose or confirm causes such as myocardial ischemia (Chapters 57 and 58), arrhythmias (Chapters 51 to 53), atelectasis (Chapter 78), pneumonia (Chapter 85), and venous thromboembolic disease (Chapter 68).

When no serious underlying cause is found, interventions that are safe in most situations include administration of oxygen and withholding of sedation. The use of noninvasive ventilation can reduce the rate of reintubation in hypoxemic postoperative patients compared with the use of oxygen alone.[A3] Other interventions that will be helpful or harmful, depending on the situation, include diuretics, opioids, and vigorous physiotherapy. Despite its common use, incentive spirometry is of little benefit.[A4]

TABLE 401-1 CRITERIA FOR DIAGNOSIS OF POSTOPERATIVE MYOCARDIAL INFARCTION

The diagnosis of perioperative MI requires any one of the following criteria.
Criterion 1: A typical rise in the troponin level or a typical fall in an elevated troponin level detected at its peak after surgery in a patient without a documented alternative explanation for an elevated troponin level (e.g., pulmonary embolism). This criterion requires that one of the following criteria be met: Ischemic signs or symptoms (e.g., chest, arm, or jaw discomfort; shortness of breath; pulmonary edema) Development of pathologic Q waves on an ECG Changes on an ECG indicative of ischemia Coronary artery intervention New or presumed new cardiac wall motion abnormality on echocardiography or new or presumed new fixed defect on radionuclide imaging
Criterion 2: Pathologic findings of acute or healing MI
Criterion 3: Development of new pathologic Q waves on an ECG if troponin levels were not obtained or were obtained at times that could have missed the clinical event

ECG = electrocardiogram; MI = myocardial infarction.

Adapted from Devereaux PJ, Goldman L, Yusuf S, et al. Surveillance and prevention of major perioperative ischemic cardiac events in patients undergoing noncardiac surgery: a review. *CMAJ*. 2005;173:779-788.

Anorexia

Loss of appetite (Chapter 118) after surgery has an extensive differential diagnosis that can be narrowed substantially if the patient was eating properly before surgery. The immediate priority is to search for and correct underlying contributors. Enteral or parenteral support is not the priority initially, although such support may eventually become indicated. Drug toxicity is a particularly common and rapidly reversible contributor to postoperative anorexia. Anatomic abnormalities are usually evident by medical imaging studies. Common metabolic contributors include abnormalities in potassium, bicarbonate, calcium, phosphorus, and magnesium. Acalculous cholecystitis (Chapter 141) is an important postoperative complication that must be considered in a patient with right upper quadrant tenderness. Constipation is another frequent contributor that often responds to increased laxatives.

Vomiting

Vomiting is the extreme form of nausea in the postoperative setting, and the two symptoms share the same differential diagnosis. In most patients, vomiting is unexpected and merits immediate attention. Initial management is to ensure that the patient's airway is protected, discontinue oral medications (and find parenteral substitutes if necessary), and consider insertion of a nasogastric tube. In patients after gastrointestinal surgery, the priority considerations include the possibility of an anastomotic leak, peritoneal abscess, or another anatomic abnormality. In patients after operations on more remote parts of the body, the priority considerations are emetogenic medications (such as postoperative chemotherapy), gastroparesis associated with autonomic neuropathy, and fecal impaction. Multiple antinausea medications are available for symptomatic relief (e.g., aprepitant, ramosetron, granisetron, prochlorperazine, ondansetron, and dexamethasone [which can be given safely without increasing the risk of surgical site infection[A5]], and droperidol; see Table 118-5)[A6] and act in an additive manner when they are used in combination (e.g., prochlorperazine 5 mg intramuscularly plus ondansetron 4 mg intramuscularly). If no reversible contributor is identified, the default diagnosis is prolonged idiopathic ileus, and a therapeutic trial of intravenous neostigmine can be considered (e.g., neostigmine 2.5 mg intravenously over 5 minutes).

Diarrhea

Diarrhea (Chapter 126) is rare after surgery and involves a limited number of possibilities if the patient's bowel movements were normal before surgery. In such cases, the situation represents an acute-onset diarrhea that is usually secretory in nature. An immediate priority is to exclude toxic megacolon, which is a potential emergency caused by overgrowth of toxigenic *Clostridioides difficile* (Chapter 271). Clinical evaluation for toxic megacolon requires assessment for tachycardia, hypotension, delirium, and other signs of sepsis rather than waiting on initial stool studies for confirmation of infection with *C. difficile*. Risk factors for antibiotic-associated diarrhea include advanced age, use of broad-spectrum antibiotics (e.g., third-generation cephalosporins), and unknown host susceptibility factors (e.g., past episodes of pseudomembranous colitis). A definitive diagnosis is frequently never established, and treatment focuses on feeding the patient a lactose-free diet while avoiding intestinal paralytics.

TABLE 401-2 DISTINGUISHING AMONG COMMON CAUSES OF ACUTE POSTOPERATIVE DYSPNEA

	PULMONARY AIR SPACE	FLUID OVERLOAD/HEART FAILURE	PULMONARY THROMBOEMBOLISM
CHARACTERISTICS OF TIMING			
Days since surgery	1-7 days	0-5 days	5-28 days
Speed of onset	1-3 days	1-24 hours	1-5 minutes
PREVIOUS HISTORY			
Previous lung disease	++		
Previous heart failure		++	
Previous venous thrombosis			++
ABNORMAL VITAL SIGNS			
Temperature	+		
Heart rate	+	+	+
Blood pressure	+	+	++
Respiratory rate	+	++	+
Oximetry	++	+	+
PHYSICAL EXAMINATION			
Jugular venous distention		+	+
Pulmonary rales	+	++	
S_3 gallop		++	
RESPONSE TO TREATMENT			
Oxygen	+	+	+
Anticholinergic bronchodilators	+	+	+
Withdrawal of sedatives	+	+	+
Aggressive physiotherapy	++		
Diuretics/afterload reduction		++	

Complete resolution is typical provided that adequate fluid and electrolyte levels are maintained.

Weakness

Generalized weakness after surgery is almost inevitable, but focal weakness may sometimes reflect nerve damage caused by intraoperative positioning (e.g., damage to the facial nerve after carotid endarterectomy) and only rarely indicates a new intracranial event (e.g., intracerebral bleeding [Chapter 377] due to anticoagulation). Focal neurologic deficits are often overlooked during the initial postoperative interval and may become apparent only after the patient has regained strength elsewhere in the body. Conversely, new deficits that are evident early after surgery and resolve rapidly thereafter may reflect unmasking of an old stroke that was fully compensated during less stressful circumstances. Medical imaging of the brain is worthwhile if no explanation is apparent on initial assessment. Diffuse neurologic weakness is usually due to deconditioning and commonly responds to physical therapy.

Delirium

Changes in mental status after surgery are common, especially in elderly patients (Chapter 361), and can be remarkably prolonged.[2] The immediate priorities are to determine whether the impairment is acute or chronic and to detect easily reversible contributors (such as infection, hypoglycemia, and alkalosis). An exhaustive assessment is often unnecessary if the patient had normal mental status before surgery because many dementia syndromes are thereby excluded (such as vitamin B_{12} deficiency, tertiary syphilis, or Alzheimer disease). Multicomponent interactions that can help prevent delirium in hospitalized patients[3] include discontinuation of medications (e.g., anticholinergics, opioids, and tranquilizers) and the continuous presence of friends or family members who can provide frequent orientation and constant attention.[A7] In one randomized trial, intravenous dexmedetomidine (0.1 µg/kg per hour, from intensive care unit admission on the day of surgery until 8 AM on postoperative day 1) decreased the occurrence of delirium by about two thirds during the first 7 days after noncardiac surgery,[A8] but it has not shown efficacy in other studies.[A9] Data on melatonin and ramelteon for the prevention of delirium are also mixed (Chapter 361).

Once delirium develops, a sense of patience is necessary because normalization rarely occurs instantly. Low-dose neuroleptics (e.g., risperidone, 0.5 mg by mouth twice daily) or haloperidol (0.25 to 0.5 mg intramuscularly, repeated up to every 30 minutes and no more than 3 to 5 mg over 24 hours) can be used to achieve sedation (Chapter 361). However, antipsychotic medications are generally unhelpful and may prolong the course of delirium.[A10] Delirium after surgery is associated with a significant decline in cognitive ability during the next year, with a trajectory characterized by an initial decline and prolonged impairment.

Seizures

The development of uncontrolled seizures (Chapter 372) after surgery is rare. The immediate priorities are to exclude status epilepticus, to uncover any history of seizures, and to identify provocative factors. Neurosurgical patients typically undergo a standardized treatment protocol, including steroids and anticonvulsants. Other conditions that can cause abnormal motor movements must be excluded, such as septic rigors, delirium tremens, Parkinson disease, major psychopathology, hypothermic shivering, and hypercapnic asterixis. Additional priorities include the detection and correction of underlying metabolic abnormalities such as hypocalcemia, hypoxemia, hyponatremia, hypophosphatemia, and drug toxicity. Treatment focuses primarily on reversing the underlying precipitating cause and providing nonspecific care with benzodiazepines, phenytoin, and ongoing monitoring.

SIGNS

Hypertension

Hypertension may reflect a variety of disorders and must be treated in a manner that neither overreacts nor underreacts to the situation. Hypertension is particularly common after neurosurgical procedures or carotid endarterectomy. The initial assessment focuses on whether the patient has chronic hypertension based on the past history, current electrocardiogram, or findings on fundoscopy. Other potential causes include undertreated pain, agitated delirium, fluid overload, alcohol withdrawal, and inadvertent discontinuation of chronic antihypertensive medications. In uncertain cases, systemic analgesia is often helpful, along with nitrates (e.g., nitroglycerin, 0.4 mg/hr transdermally) and β-blockers (e.g., metoprolol, 5 mg intravenously). The major complication of treatment is the potential for overcorrection and inadvertent hypotension; such errors are particularly common in patients with no evidence of past hypertension.

Hypotension

Hypotension (Chapter 7) after surgery is generally an emergency, and the immediate concern is internal bleeding, especially after intra-abdominal operations or when anticoagulation is initiated to prevent thrombosis. The early stages of hypotension are frequently unrecognized because of autonomic stress responses by patients, psychological denial by clinicians, and misattribution to the concurrent use of analgesia. Early hypotension is particularly easy to overlook if the patient has coexisting chronic hypertension and the apparently "normal" blood pressure is dismissed as unremarkable. Prompt echocardiography can almost always find the cause of undiagnosed hemodynamic instability. Treatment usually entails volume supplementation, vasopressors as needed (Chapters 93 and 94), serial assessments, and a search for underlying causes. An extensive differential diagnosis sometimes needs to be considered if no anatomic cause related to surgery is evident (Chapter 92). Routine use of pulmonary artery catheters to guide therapy is not helpful, and goal-directed fluid therapy does not reduce mortality beyond standard fluid resuscitation.[A11]

Hypoxemia

Postoperative hypoxemia is common after noncardiac surgery, with about 20% of patients having oxygen saturations below 90% averaged over the first 48 hours and about one third of patients having oxygen saturations below 90% for an hour or more. Many of these events are not clinically diagnosed but can be detected by continuous monitoring. The clinical implications of undiagnosed hypoxemia are uncertain, but they may contribute to anorexia, delirium, and cardiac sequelae. The evaluation is similar to the evaluation of dyspnea (see earlier). Treatment generally requires supplemental oxygen, encouragement of deep breathing, and specific treatment aimed at any underlying causes.[4] Inhaled bronchodilators have not been proven effective unless the patient has a clear history of reactive airway disease.

Tachycardia

Tachycardia after surgery can be caused by myriad arrhythmias (Chapters 52 and 53) and may contribute to postoperative cardiac ischemia. Distinguishing between newly detected and newly incident tachycardia can sometimes be accomplished by determining whether the patient does or does not complain of palpitations. An initial assessment also requires review of the electrocardiogram to distinguish atrial fibrillation from other disorders. The goal of treatment is to identify and correct precipitating factors such as pain, blood loss, hypoxia, electrolyte abnormalities, fluid overload, volume depletion, pulmonary embolism, and drug withdrawal. Most arrhythmias respond to correction of the underlying abnormality. Specific antiarrhythmic treatment, when needed, is generally similar to that used in the nonoperative setting (Chapters 52 and 53). For atrial fibrillation, anticoagulation is sometimes contraindicated; in such situations, cardioversion within 48 hours merits consideration. Postoperative atrial fibrillation portends an increased long-term risk of ischemic stroke.[5]

Fever

Fever (Chapter 259) after surgery is common,[6] frequently perplexing, and often multifactorial. Worrisome possibilities include transfusion reactions (Chapter 162), hospital-acquired pneumonia (Chapter 85), urinary tract infection (Chapter 263), line sepsis (Chapter 261), and surgical site infection. In many cases, no definitive cause is found, the patient recovers spontaneously, and the default diagnosis is atelectasis. Detailed evaluation, when necessary, requires cultures of blood, urine, and the surgical site to identify specific microbiologic organisms. Selection of empirical antibiotics is usually based on local practice patterns and hospital ecology, with the disadvantage of breeding resistant organisms. Hydration, nutrition, and general supportive care are important yet frequently neglected issues for patients with prolonged elevations in body temperature. Selective decontamination of the digestive tract and oropharynx appears to be beneficial, but chlorhexidine is not (Chapter 261).

Edema

Peripheral edema (Chapter 39), which is often first noticed by nursing staff after surgery, is rarely life threatening unless it is treated with excessive diuretics. The cause is usually multifactorial and includes increased hydrostatic pressure (including heart failure and gravity from intraoperative positioning), decreased oncotic pressure (related to hypoalbuminemia from decreased liver production or increased losses), and accentuated capillary leak (potentially caused by medications or tissue reactions). Treatment focuses on correction of underlying abnormalities, maintenance of nutrition, judicious use of diuretics, monitoring renal function, provision of systemic anticoagulation against deep venous thrombosis, and efforts toward mobilization of the patient. A low-salt diet, afterload reduction, and aldosterone antagonists (e.g., oral spironolactone, 25 mg once daily) may be helpful in patients in whom heart failure (Chapter 46) is the dominant mechanism.

LABORATORY

Leukocytosis

An elevated white blood cell count (Chapter 153) can have many causes, but the immediate priority is to exclude a life-threatening septic process (Chapters 92 and 94). Direct microscopic examination of the peripheral blood smear (Chapter 143) can be helpful to check for toxic granulations (see Fig. 143-18), Döhle bodies (see Fig. 143-19), and a shift toward primitive band cells. Many cases are due to noninfectious causes, including infarcted tissue (skin, heart, intestinal tract), inflammatory conditions (renal insufficiency, diabetic ketoacidosis, lupus erythematosus), and demargination stress reactions (dehydration, systemic corticosteroids, inotropic medications). In the absence of direct evidence, some clinicians may initiate antibiotics empirically, whereas others may elect waiting. Substantial controversy remains about the proper duration of an empirical trial of antibiotics when no cause is discovered and the patient is otherwise recovering.

Anemia

Anemia (Chapter 144) is common and sometimes underappreciated because coexisting volume depletion causes the blood hemoglobin concentration to underestimate the degree of blood loss. Major perioperative hemorrhage is associated with subsequent stroke, myocardial injury, and all-cause nonfatality[7] in patients undergoing noncardiac, non-neurologic surgery. The initial priority is to differentiate bleeding at the surgical site from other causes. In many cases, the exact cause is unclear and substantial uncertainty may arise over the need to initiate gastric acid suppression therapy or to interrupt systemic anticoagulation against venous thrombosis. In a large randomized trial, transfusion at a hemoglobin threshold of 10 g/dL was no better than transfusion for symptoms of anemia or at the physician's discretion for a hemoglobin level of below 8 g/dL.[8] Guidelines for transfusion therapy depend on the patient's cardiac reserve, hemodynamic stability, evidence of active postoperative bleeding, and the available blood bank supply at the particular medical center. A reasonable goal is to maintain a hemoglobin level of 7 to 9 mg/dL in patients who are hemodynamically stable, except in patients with cardiovascular disease or after orthopedic surgery, in whom a hemoglobin goal of 8 mg/dL is reasonable.[A12,A13] Other exceptional situations include patients with hemodynamic instability, ongoing myocardial ischemia, severe thrombocytopenia, or chronic transfusion-dependent anemia, in whom the threshold of 9 mg/dL is reasonable (Chapter 162).[9] The immediate postoperative interval is not usually the appropriate time to initiate erythropoietin, oral iron replacement, or detailed evaluations for other hematologic abnormalities.

Abnormalities in Platelet Count

Patients often have abnormal platelet counts after surgery yet rarely require further evaluation or treatment.[10] In most cases, the thrombocytopenia is mild, does not require transfusion therapy, resolves in a few weeks, and is not a sign of an ominous disorder (e.g., sepsis or heparin-induced thrombocytopenia). Platelet transfusions are indicated if the decrease in platelet count is extreme, accompanied by evidence of major blood loss, or related to recent surgery on the central nervous system (including the eye). Thrombocytosis is also common after surgery and is occasionally extreme. However, even postoperative thrombocytosis exceeding 1,000,000/mL rarely necessitates treatment, does not predispose patients to unwanted clotting complications, and typically resolves spontaneously after a few weeks.

Abnormal Sodium Concentration

Both hyponatremia and hypernatremia (Chapter 102) are frequent complications in the postoperative setting. The immediate priorities are to assess the patient's intravascular volume status and to correct possible volume depletion. The causes of hyponatremia are multifactorial, including excessive use of diuretics, high levels of intrinsic antidiuretic hormone (as a result of factors such as drugs, pain, mechanical ventilation), and unmeasured osmoles (e.g., intravenous contrast agents). The risk for postoperative hyponatremia may be reduced by the administration of isotonic saline rather than by water restriction. Once hyponatremia develops, vasopressin antagonists (Chapter 102) can be effective for both hypervolemic and euvolemic hyponatremia. Hypernatremia is always

due to free water deficiency, which may indicate severe cognitive impairment or other factors interfering with the ability to express thirst or to ingest water. Correction is similar to that in the nonoperative setting. Abnormalities in sodium concentration require careful follow-up, can recur at any point after an operation, yet are rarely the root cause of a patient's inability to recover from surgery.

Abnormal Serum Potassium Concentration

Hyperkalemia and hypokalemia (Chapter 103) are also frequent postoperative complications. The immediate priority is to assess the patient's electrocardiogram and to stabilize the patient's electrocardiophysiology. Hyperkalemia is usually due to cellular shifts, renal failure, and tissue destruction (including hemolysis). Hyperkalemia will generally be corrected with treatments that shift potassium into cells (e.g., intravenous glucose with or without insulin) and enhance total excretion (e.g., gastrointestinal binding agents). Hypokalemia is usually due to inadequate intake, excessive loss, or cellular shifts. Hypokalemia will generally be corrected with replacement therapy and rarely requires aldosterone antagonism. Both abnormalities can usually be treated as in the nonoperative setting (Chapter 103). The prognosis is favorable if the patient's electrocardiogram shows no major dysrhythmias and if renal function is preserved.

Alkalosis

Systemic alkalosis (Chapter 104) typically requires volume supplementation because the cause is generally intravascular volume depletion. Blood gas determinations may be necessary in some cases to exclude the possibility of concurrent carbon dioxide retention with compensatory metabolic alkalosis. Untreated, alkalosis can result in altered mentation, cardiac arrhythmias, and delayed mobilization. Most patients with postoperative alkalosis do not require carbonic anhydrase inhibitors or intravenous acid. The prognosis is usually favorable, with gradual correction during a period of several days. Rapid correction of alkalosis, unlike rapid correction of hyponatremia, is not known to cause neurologic injury.

Azotemia

The initial assessment of an elevated serum creatinine concentration (Chapter 100) focuses on reviewing previous values (to distinguish acute from chronic renal insufficiency) and identifying contributing factors (such as prerenal volume depletion, intrarenal nephrotoxins, or postrenal urethral obstruction). A trial of intravenous fluids may be useful on both a diagnostic and therapeutic basis. Treatment is the same as in the nonoperative setting. Subsequent monitoring is usually necessary, with serum creatinine measurements obtained on a once-daily basis. Serial measurements of urinary volume and body weight as well as a urine culture are occasionally helpful in selected cases. Postoperative acute kidney injury is strongly associated with poorer long-term outcomes.[11]

Hyperbilirubinemia

Elevations in serum bilirubin (Chapter 133) are rare after surgery, even though abnormalities in liver enzyme levels occur frequently with general anesthesia. The most benign explanation is Gilbert syndrome, but the immediate priority is to assess for possible hepatic failure (especially in patients who have received volatile agents). As in the nonoperative setting, treatment involves withdrawing potential hepatotoxins, supporting the patient, and allowing time for liver function to recover (Chapter 139). Treatment of hepatic encephalopathy is particularly important because of the concurrent constipation and generalized catabolic state that follow major surgery. Monitoring should include serial measurement of liver function on a daily basis because each component (e.g., bilirubin, albumin, prothrombin time) can be altered by factors unrelated to the liver. The prognosis is unfavorable if the patient's liver function fails to recover quickly.

Hypoalbuminemia

Reductions in serum albumin are common after surgery and are an ominous prognostic finding. The cause is rarely decreased production if the reduction in the albumin level occurs rapidly. Possible explanations include nephrotic syndrome, capillary leak into extravascular spaces, and occult catabolism in unrecognized sites. Treatment with albumin infusions does not usually normalize the metabolic abnormality and does not seem to improve patient survival. The main priorities are to continue nutritional support, preserve skin integrity, minimize the use of systemic diuretics, correct any contributing factors, and consider correlated serum protein deficiencies (such as reduced levels of immunoglobulins or antithrombin III). Hypoalbuminemia can also cause substantial indirect harm by the loss of carrier proteins, which thereby predisposes patients to potential drug toxicity. The long-term prognosis is favorable for survivors because the serum albumin level will eventually return to normal.

Abnormalities in Blood Glucose Concentration

In patients with diabetes mellitus (Chapter 210), serum blood glucose concentrations often become unstable after surgery because of altered dietary intake, decreased physical activity, and the release of counter-regulatory hormones. The priority is to avoid hypoglycemia, severe hyperglycemia, diabetic ketoacidosis, cerebral damage, and repeated events. Intensive control of the blood glucose level increases the risk for severe hypoglycemia and death, so a target glucose level of about 140 to 200 mg/dL is recommended. Rapid reversal of sepsis or focal infection can lead to a precipitous decrease in insulin requirements; in such cases, vigilance is required because unsuspected hypoglycemia may cause permanent damage or be fatal in a patient who may otherwise seem to be sleeping. Patients need to be forewarned that temporary doses of subcutaneous insulin may be required but do not commit the patient to chronic insulin therapy. Monitoring involves serial measurement of blood glucose concentration until the patient is eating in a reliable manner.

Troponin and Natriuretic Peptide Levels

Among patients undergoing noncardiac surgery, the peak postoperative troponin level during the first 3 days after surgery is significantly associated with 30-day mortality, even if patients do not have any other evidence of an acute MI.[12,13] The potential utility of routine postoperative troponin levels for patient management remains uncertain, but data support routine postoperative screening with a daily troponin level in patients who are over age 60 years and who underwent emergent surgery and in patients who underwent elective surgery with a Revised Cardiac Risk Index score (Table 399-4) of 3 or more.[14] The detection of an elevated troponin level should prompt a careful search for symptoms or signs of myocardial ischemia and trigger the use of a statin and, if associated with ischemic electrocardiographic changes, consideration of low-dose aspirin (81 mg daily) and perhaps dabigatran (110 mg twice daily; see Chest Pain, earlier).[15] Similarly, screening and monitoring levels of brain natriuretic peptides is favored in some guidelines and not in others.

SPECIAL SITUATIONS

Multiplicity

Some postoperative complications are difficult to classify because no single dominant problem is apparent by symptoms, signs, or laboratory test results. Instead, patients may have multiple problems that need to be addressed simultaneously. The immediate goal is to set priorities and to avoid the temptation to try to eliminate every possibility on the first day. The corollary is to continue to check progress during the subsequent days needed for a complete diagnosis and successful therapy. Because so many concerns require attention in the postoperative interval, the risk is that clinicians will lose track of a secondary issue and make an error that seems obvious in retrospect.

Redundancy

Postoperative complications sometimes generate multiple consultations with physicians who have overlapping abilities. An example might be a patient with a postoperative fever who prompts consultations from pulmonology, dermatology, general medicine, and infectious disease specialists. In theory, gathering a critical mass of medical experts together should increase the likelihood of accurate diagnosis, timely treatment, and foolproof follow-up. In reality, however, coordination and communication are never perfect. Personal rivalries, diffusion of responsibility, and many other psychological factors may impede interactions among consultants. Opportunities for miscommunication may be further accentuated if the patient has an exotic diagnosis that is a special draw on the consultant's attention (e.g., pheochromocytoma). Arguing in front of the patient, in view of other professionals, or in the medical record can be demoralizing. The priority is to communicate effectively with the surgical team responsible for the patient and to encourage that team to make final decisions.

Ambiguity

Another vexation occurs when an urgent request is not connected to a clear rationale (Chapter 398). Diplomacy is needed to establish whether the motivation reflects a medicolegal concern rather than a biologic change in the patient.

Sometimes the stimulus for the consultation can best be addressed by providing reassurance and confirmation. Sometimes the stimulus is an obscure preexisting disorder (e.g., Moyamoya disease), and the surgical team has neither the experience nor the time to investigate how this unrelated medical condition can influence recovery from surgery. Sometimes the stimulus is an unspoken political wish to transfer the care of a burdensome patient from one physician to another. A consultant should develop an understanding of how to interact with other clinicians under such ambiguous circumstances.

SETTING PRIORITIES

Requests for consultation often arrive outside conventional working hours, are usually tinged with a sense of urgency, and sometimes cluster to encompass more than one patient. Developing an effective method for prioritizing patients is a crucial clinical skill. One communication strategy is to provide an objective estimated time of arrival for the initial request from the surgical team. An often-helpful treatment strategy is to make some safe suggestions at the time of the initial request so that clear-cut recommendations can be instituted during the interval before the patient is seen and used later to help evaluate the patient's status and course.

AFTERMATH

In many postoperative cases, the original reason for consultation may resolve and no major issues remain. The situation now provides an opportunity to review the patient, particularly for the appropriate use of unrelated medications. The consultant may often detect excessive medications that were appropriate early in the hospital course but have ceased to be necessary, thereby justifying discontinuation (e.g., diuretics, antibiotics, bronchodilators). Discontinuing medications that have become superfluous requires initiative and wisdom, and the common mistake is to propagate unnecessary medications in stable patients under the rationale of "don't mess with success." The ability to watch the patient for several hours or for a day or two often presents an ideal opportunity for the safe withdrawal of medications. Ironically, discontinuing a treatment sometimes requires more skill, time, and initiative than starting it.

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402

MEDICAL CARE OF PATIENTS WITH PSYCHIATRIC DISEASES

MARSHA N. WITTINK AND S. RYAN GREYSEN

POPULATION HEALTH FOR PERSONS WITH SEVERE MENTAL ILLNESSES

Although patients with severe mental illnesses, such as schizophrenia, bipolar disorder, and debilitating depression and anxiety, constitute 6% of the U.S. population and are among the most complex and costly patients in the health care system. Patients with severe mental illness are nearly twice as likely to be readmitted to the hospital and have longer lengths of stay, thereby generating higher costs of care. These patients also have higher rates of chronic conditions, such as diabetes, lung disease, and cardiovascular disease that lead to declining function and to a premature mortality gap of 15 to 30 years compared with the general population.[1]

In this population, the complex interplay of medical, psychiatric, and psychosocial challenges (e.g., poor housing, transportation, and lack of access to preventive medical care) creates barriers to improving outcomes. Patients with severe mental illness are also affected by cognitive biases of providers, including a therapeutic pessimism that underestimates patients' interest in health care decision-making and assumes that patients will not be able to engage in care or adhere to a treatment. A clinician's pessimism, exacerbated by compassion fatigue and a desire for more collaboration with psychiatric and social services,[2,3] often results in reduced screening and missed opportunities for interventions earlier in the course of disease.[4] Another common bias is diagnostic overshadowing: the tendency to attribute symptoms to psychiatric causes rather than investigating medical causes that could be treated. Since the natural course of many psychiatric conditions tend towards improvement over time, the prevention and acute management of medical conditions present critical opportunities for clinicians to improve the outcomes of patients with severe mental illness.

SPECIFIC HEALTH CHALLENGES FOR PATIENTS WITH SEVERE MENTAL ILLNESS

CARDIOVASCULAR DISEASE

Cardiovascular disease, which is the leading cause of death for people with severe mental illness, is twice as common as compared with the general population. Contributing factors include a higher prevalence of cardiovascular risk factors, such as smoking, sedentary lifestyle, and poor nutrition (Chapter 40); structural disadvantages, including financial, housing, and transportation challenges (Chapter 4); delayed care-seeking; and mistrust of the health care system. Unfortunately, many psychotropic medications, in particular second-generation antipsychotic medications (Table 402-1), are associated with metabolic disorders, diabetes, and cardiovascular disease.

Beyond these patient factors, health care providers contribute to these disparities because patients with severe mental illness are less likely to receive adequate treatment. For example, when patients with severe mental illness suffer an acute myocardial infarction, they are less likely to receive aspirin, beta-blockers, coronary angioplasty, and coronary artery bypass grafting. Similarly, when patients with severe mental illness develop heart failure, they are less likely to have their left ventricular ejection fractions measured. These disparities, which persist even after adjusting for other comorbid illnesses, may be amplified by the use of alcohol (Chapter 364) and drugs of abuse (Chapter 365). Integrating medical and behavioral health in primary care and other settings may be one way to reduce these disparities.[A1]

AGING

The disproportionate burden of morbidity and mortality in the population with severe mental illness is exacerbated by aging, which accelerates the sensory, cognitive, physical, and functional challenges associated with mental illness. These challenges undermine the ability to comprehend and adhere to treatments and to access health information and services. For example, many patients with schizophrenia or major depression have greater cognitive and functional impairment than expected simply by their age or illness, and this

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402

MEDICAL CARE OF PATIENTS WITH PSYCHIATRIC DISEASES

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POPULATION HEALTH FOR PERSONS WITH SEVERE MENTAL ILLNESSES

Although patients with severe mental illnesses, such as schizophrenia, bipolar disorder, and debilitating depression and anxiety, constitute 6% of the U.S. population and are among the most complex and costly patients in the health care system. Patients with severe mental illness are nearly twice as likely to be readmitted to the hospital and have longer lengths of stay, thereby generating higher costs of care. These patients also have higher rates of chronic conditions, such as diabetes, lung disease, and cardiovascular disease that lead to declining function and to a premature mortality gap of 15 to 30 years compared with the general population.[1]

In this population, the complex interplay of medical, psychiatric, and psychosocial challenges (e.g., poor housing, transportation, and lack of access to preventive medical care) creates barriers to improving outcomes. Patients with severe mental illness are also affected by cognitive biases of providers, including a therapeutic pessimism that underestimates patients' interest in health care decision-making and assumes that patients will not be able to engage in care or adhere to a treatment. A clinician's pessimism, exacerbated by compassion fatigue and a desire for more collaboration with psychiatric and social services,[2,3] often results in reduced screening and missed opportunities for interventions earlier in the course of disease.[4] Another common bias is diagnostic overshadowing: the tendency to attribute symptoms to psychiatric causes rather than investigating medical causes that could be treated. Since the natural course of many psychiatric conditions tend towards improvement over time, the prevention and acute management of medical conditions present critical opportunities for clinicians to improve the outcomes of patients with severe mental illness.

SPECIFIC HEALTH CHALLENGES FOR PATIENTS WITH SEVERE MENTAL ILLNESS

CARDIOVASCULAR DISEASE

Cardiovascular disease, which is the leading cause of death for people with severe mental illness, is twice as common as compared with the general population. Contributing factors include a higher prevalence of cardiovascular risk factors, such as smoking, sedentary lifestyle, and poor nutrition (Chapter 40); structural disadvantages, including financial, housing, and transportation challenges (Chapter 4); delayed care-seeking; and mistrust of the health care system. Unfortunately, many psychotropic medications, in particular second-generation antipsychotic medications (Table 402-1), are associated with metabolic disorders, diabetes, and cardiovascular disease.

Beyond these patient factors, health care providers contribute to these disparities because patients with severe mental illness are less likely to receive adequate treatment. For example, when patients with severe mental illness suffer an acute myocardial infarction, they are less likely to receive aspirin, beta-blockers, coronary angioplasty, and coronary artery bypass grafting. Similarly, when patients with severe mental illness develop heart failure, they are less likely to have their left ventricular ejection fractions measured. These disparities, which persist even after adjusting for other comorbid illnesses, may be amplified by the use of alcohol (Chapter 364) and drugs of abuse (Chapter 365). Integrating medical and behavioral health in primary care and other settings may be one way to reduce these disparities.[A1]

AGING

The disproportionate burden of morbidity and mortality in the population with severe mental illness is exacerbated by aging, which accelerates the sensory, cognitive, physical, and functional challenges associated with mental illness. These challenges undermine the ability to comprehend and adhere to treatments and to access health information and services. For example, many patients with schizophrenia or major depression have greater cognitive and functional impairment than expected simply by their age or illness, and this

ABSTRACT

Medical conditions are far more prevalent in patients with severe mental illness and are associated with far worse outcomes, including disability and early mortality compared with the general population for several reasons. First, patient factors such as accelerated aging, poverty, social stigma, and unhealthy lifestyle are major contributors to disproportionate medical morbidity. Second, many of the treatment options for managing psychiatric disease (psychotropic medications) have significant side effects that worsen the burden of medical morbidity. Third, provider factors such as cognitive biases can contribute to worse outcomes by delaying the appropriate evaluation and care of medical conditions. This chapter outlines approaches to medical management of patients with severe mental illness in a variety of common settings and suggest strategies to overcome the factors that contribute to poor outcomes. The chapter also reviews common medical complications of psychiatric treatments, including cardiovascular effects (e.g., prolonged QT interval, myocarditis, and myositis), respiratory and swallowing effects (e.g., aspiration and asphyxia), and life-threatening syndromes (e.g., neuroleptic malignant syndrome, serotonin syndrome, and catatonia).

KEYWORDS

severe mental illness
adverse effects of psychotropic medications
disparities in care

TABLE 402-1 COMMON MEDICAL COMPLICATIONS OF PSYCHOTROPIC MEDICATIONS

MEDICAL COMPLICATIONS		PSYCHOTROPIC MEDICATION CLASS/COMMON MEDICATIONS	PROPOSED MECHANISMS
Cardiovascular	Prolonged QTc/arrhythmia	Antipsychotics SSRIs (citalopram/escitalopram) Tricyclics	Blocking delayed rectifier potassium ion channels
	Cardiotoxicity (myocarditis, cardiomyopathy)	Clozapine	Unknown, possible IgE-mediated hypersensitivity
	Orthostatic hypotension	Trazodone Antipsychotics Tricyclics	Alpha-1 adrenergic receptor antagonism
	Hypertension	Venlafaxine (dose-dependent)	Venlafaxine: norepinephrine reuptake inhibition (dose-dependent)
		MAO-inhibitors	MAO-inhibitors: excess norepinephrine and/or serotonin (mostly with drug-drug or drug-food interactions)
		Antipsychotics	Antipsychotics: unclear
Respiratory	Aspiration	Antipsychotics Tricyclics Benzodiazepines	Antimuscarinic, antihistaminic, anticholinergic: dry mouth, esophageal dilation, and hypomotility Sedation may also play a role.
	Respiratory Depression	Antipsychotics	Suppression of central respiratory drive
Gastrointestinal	Constipation (small bowel obstruction with clozapine)	Antipsychotics: clozapine, olanzapine, mirtazapine Tricyclics	Anticholinergic and possibly antiserotonergic properties
	Dysphagia; sialorrhea	See Table 402-3	See Table 402-3
	Hepatic impairment Hyperammonemia	Anticonvulsant; mood stabilizers: carbamazepine, valproate Antidepressants: mirtazapine Antipsychotics: olanzapine	Idiosyncratic: hypersensitivity reactions and toxin-induced
Renal and urinary tract	Renal insufficiency Urinary retention	Lithium Antipsychotics Tricyclics	Diabetes insipidus with hypernatremia Anticholinergic properties
Endocrine	Hyperprolactinemia	Antipsychotics: risperidone, haloperidol, fluphenazine	Dopamine blockade leads to increased prolactin levels
	Thyroid abnormalities	Lithium	Accumulation in the thyroid gland can alter synthesis and release of thyroid hormone
	Hyponatremia/SIADH	Antipsychotics: carbamazepine, oxcarbazepine	Antipsychotics: D2 receptor blockers
		Antidepressants (most commonly SSRIs/SNRIs)	Antidepressants: sustained release of ADH from the hypothalamus
Hematologic	Neutropenia Agranulocytosis	Clozapine, olanzapine, risperidone, quetiapine	A chemically reactive nitrenium ion, which is a metabolic product, causes direct toxicity or initiates an immune mechanism
	Leukocytosis	Lithium	Unclear cause
	Thrombocytopenia	Valproate, carbamazepine	Drug dependent autoantibodies and direct toxic effect on bone marrow
Skin	Stevens-Johnson syndrome	Lamotrigine Carbamazepine	Cytotoxic T-cell-mediated HLA-dependent drug hypersensitivity
Neurological	Extrapyramidal symptoms	First-generation antipsychotics > second-generation: especially clozapine, bupropion	Antagonism of dopamine D2 receptors
	Seizures	Tricyclics	Lower seizure threshold

ADH = antidiuretic hormone; HLA = human leukocyte antigen; MAO = monoamine oxidase; SIADH = syndrome of inappropriate antidiuretic hormone secretion; SNRI = serotonin-norepinephrine reuptake inhibitor; SSRI = selective serotonin reuptake inhibitor.

impairment can progress independently of psychiatric symptoms. Functional and cognitive assessment is imperative for all patients with severe mental illness, regardless of their chief complaint or age. Preventive efforts, such as encouraging engagement in community mental health services, referral for cognitive rehabilitation, and occupational therapy should be considered early. When more severe functional or cognitive impairment is present, planning for long-term support should be considered even while addressing the medical causes prompting acute care.

SUBSTANCE USE DISORDERS

As many as 50% of patients with severe mental illness have substance use disorders (Chapters 364 and 365). Rates of cigarette smoking (Chapter 363) are three-fold higher than in the general population, and patients with severe mental illness smoke more cigarettes for longer periods of time. Unfortunately, systems of care for severe mental illness and substance use disorders are often not integrated, so the likelihood that one of these issues may be undiagnosed or undertreated is higher than for either condition alone.[5] Despite these daunting odds, smoking cessation interventions have been successful when integrated into mental health settings and adapted to meet the needs of patients with severe mental illness.[A2] When caring for patients with a psychiatric diagnosis, it is critical to consider and screen for substance use, which may otherwise represent an added barrier to successful management of psychiatric symptoms. Similarly, when patients with severe mental illness present with agitation or a change in mental status, intoxication and substance abuse should be considered in the medical differential.

PROVIDING CARE IN DIFFERENT SETTINGS

All of the above factors lead to challenges for the physician who cares for patients who have concomitant medical and psychiatric needs. Depending on the psychiatric resources, the medical physician may be tasked with anything from identifying and separating the medical, psychiatric, and cognitive components of an acute change in mental status (Chapter 361) in the emergency department or on a medical service, to comanaging acute respiratory failure (Chapter 90) in a patient with active psychosis (Chapter 362), to providing consultation for chest pain (Chapter 39) to a patient admitted to a psychiatric hospital.

EVALUATION IN THE EMERGENCY DEPARTMENT

Some hospitals have emergency psychiatric resources, including dedicated areas for assessing acute psychiatric emergencies, but many do not. Although a true medical emergency (e.g., stroke [Chapters 376 and 377], coma [Chapter 373], sepsis [Chapter 94], substance overdose [Chapter 96]) must first be excluded in the patient with an altered level of consciousness, patients who have acute symptoms or decompensation of severe mental illness are often managed with the aid of a psychiatric consultation, particularly in hospitals that lack a dedicated psychiatric unit. Even in hospitals that do have psychiatric units, medical stabilization beyond what can be done in the emergency department might require initial admission to a medical unit. In making such determinations, physicians must understand that the criteria for acute admission to a psychiatric unit is often restricted to patients who are at risk for self-harm or harming others and have the potential for improvement on an inpatient psychiatric unit. For example, patients with neuropsychiatric sequelae of dementia may not meet criteria for admission to a psychiatric unit because they are unlikely to benefit from the therapeutic interventions provided there, whereas a bipolar patient with acute mania would potentially benefit. In patients who have relatively stable and chronic psychiatric issues, the key issue often is whether the patient can be safely discharged based on housing stability, social support structure, and transportation needs for follow-up medical care. Social work consultation and other resources can help with safety and the feasibility of outpatient options before a decision is made to discharge a patient.

CONSULTATIONS TO A PSYCHIATRIC UNIT OR HOSPITAL

Physicians who care for patients in psychiatric settings should have a general understanding of the environment and capabilities of the staff before arriving to see a patient. At the systems level, general familiarity with mental health regulatory, organizational, and insurance requirements can be helpful for understanding why patients were admitted, as well as the legal and supportive structures in place to protect the patient's rights. For example, medical and psychiatric beds are separated by regulatory oversight in many states, so transfer from one to the other requires a discharge and new admission. At the environmental level, it is useful to understand policies on locked doors and whether patients may have access to items such as oxygen and intravenous tubing that could pose a risk for self-harm or suicide. At the therapeutic level, it is important to understand how psychiatric units use their milieu to foster interactions among patients in preparation for returning to the community. This notion of using the milieu is often quite different than the environment on medical floors, where patients are rarely encouraged to interact with other patients as part of the care and rehabilitation process. Furthermore the staff and nurses in a psychiatric setting are focused on mental health therapy and are unlikely to be familiar with many medical interventions.

MEDICAL/SURGICAL FLOOR

For patients admitted to a medical unit, several key issues are important for the initial assessment.

Continue Outpatient Psychotropic Medication Regimens

It is very important not to interrupt or delay ongoing psychotropic medication therapy, especially in a patient who has been stable on a specific dose for months or longer. Abrupt discontinuation of some psychotropic medications can lead to withdrawal (also referred to as discontinuation syndrome), relapse of the psychiatric condition, or worsening of ongoing symptoms and behaviors.[6,7] If a reported medication was not taken regularly, however, restarting at the reported dose may lead to unexpected side effects from its rapid initiation. If a strong suspicion suggests that the acute medical problem is related to a known side effect of a psychotropic medication (e.g., see Table 402-1), it is reasonable to hold the medication temporarily while contacting the prescribing or consulting psychiatrist or pharmacist to discuss the relative risks and benefits of the particular medication, the alternative options, and how and when to restart the medication. If the psychotropic medication helps for more than a few days, dose titration may be required.

Obtaining the History of Smoking and Substance Use

Nicotine stimulates dopaminergic activity, which can reduce stress and enhance cognitive ability while stimulating the brain's reward centers. Nicotine withdrawal can exacerbate or lead to agitation. In addition, for patients who are heavy tobacco users, abrupt cessation of nicotine, which induces the CYP1A2 system that metabolizes clozapine and olanzapine, can increase the bioavailability of these drugs and result in over-sedation. For other known or suspected substance use, withdrawal symptoms should be anticipated and appropriate interventions begun (Chapters 364 and 365).

Communication and Building Trust

Somatic delusions and disorganized speech can make communication challenging. Nevertheless, an accurate history and physical examination are possible by observation and communication with others who are caring for the patient. Physicians should engage patients with severe mental illness with an empathetic and unbiased approach, being sure to obtain all relevant information (Chapter 6), but with a degree of flexibility. If patient declines part of the evaluation or treatment, it is important to recall the ethical imperative of do no harm. For example, restraining a patient to obtain a laboratory test or maintain an intravenous line would be warranted only in cases of imminent risk. Taking the time to understand a patient's priorities helps build trust and adherence. For example, a patient with paranoia may have difficulty understanding the importance of monitoring physical symptoms. Consulting with clinicians or other trusted persons who know the patient's preferences and communication style can be very helpful. A team-based care plan can help avoid a situation in which such patients may pit one clinician against another.

Physicians should also anticipate the potential for antagonism between patients and hospital staff owing to stress and unfamiliarity, especially on a medical unit, and proactively address sources of friction to prevent escalation. For example, minimizing nighttime blood drawing and medications can help reduce agitation for patients who are not accustomed to being medically hospitalized. Flexible plans can help build trust and encourage engagement in care. For example, a patient with diabetes may be more willing to engage in treatment if offered more dietary options, even if they are not ideal for glucose control.

Deescalation

The typical pitfall of clinicians is to become defensive when a patient becomes agitated or angry. A critical component of deescalation is recognizing one's own response to a patient. Reacting with fear or anger can lead the patient to become more agitated. An approach that can help deescalate a situation includes first controlling one's own emotional response and then using communication skills to engage the patient. The process is not unlike reacting to an emergency medical situation; in this case the way to control the emergent behavior is by building rapid rapport. A helpful first step is to take the time to show sympathy and ask open-ended questions to understand the patient's frustration. Other techniques include paying attention to body language, avoiding threatening postures, and setting boundaries and limits. Deescalation techniques are invaluable for reducing injuries to other patients or clinical staff and to reducing clinician burnout.

INTEGRATING MEDICINE AND PSYCHIATRY

Models of care that increase coordination between medical and psychiatric services in the outpatient setting, through co-location of primary care and psychiatry services or embedded primary care within specialty mental health settings, can improve outcomes, reduce costs, and improve staff satisfaction, particularly in the outpatient setting.[A3]

An inpatient model is the hybrid medical-psychiatry unit, in which medical and psychiatric physicians manage the treatment of patients admitted for acute medical needs in the context of their psychiatric complexity, or vice-versa.[8] Staff on such units should be skilled in caring for patients with both medical and behavioral health needs, including expertise in deescalation techniques. Medical-psychiatry units that provide comprehensive care and connections to integrated settings may hold the most promise for reducing the risk that patients will fall between the silos of mental and physical health.[9]

MEDICAL COMPLICATIONS OF PSYCHIATRIC TREATMENTS

BRIEF OVERVIEW OF PSYCHIATRIC DRUG CLASSES

Drugs for psychiatric conditions, including antipsychotics, antidepressants, anxiolytics, and mood stabilizers (Chapter 362), are often referred to broadly as psychotropic medications. The mainstay of modern pharmacologic treatment of severe mental illness is a family of drugs commonly known as antipsychotics: first generation (otherwise known as typical or neuroleptic) and second generation (otherwise known as atypical). Other drug classes commonly prescribed to patients with severe mental illness include antidepressants (selective serotonin reuptake inhibitors [SSRIs]; serotonin-norepinephrine reuptake inhibitors [SNRIs]; monoamine oxidase [MAO] inhibitors; and

tricyclic antidepressants), anxiolytics (benzodiazepines), and mood stabilizers (lithium, and anticonvulsant medications such as valproate). Medical consultation in patients with severe mental illness should be informed by knowledge about serious complications of these medications (see Table 402-1).

CARDIOVASCULAR COMPLICATIONS

In addition to the increased risk of atherosclerotic disease and coronary heart disease conferred by lifestyle factors and barriers to access to health care, several classes of psychotropic medications increase the risk for arrhythmias (through prolongation of the QT interval; Table 402-2),[10] cardiomyopathy, and myocarditis. Patients should have a baseline screening electrocardiogram (ECG) and serum electrolyte levels, as well as careful review of any history of syncope, arrhythmias, or early sudden death (before age 40) in first-degree relatives before beginning any antipsychotic medication regimen. If the baseline QTc is greater than 450 msec (men) or greater than 470 msec (women), significant hypokalemia (serum potassium level <3.5 mEq/L) or hypomagnesemia (serum magnesium level <1.5 mg/dL) should be repleted before starting psychotropic therapy. At the same time, a prolonged QTc should prompt reconsideration of risks and benefits before initiating psychotropic medications. After therapy is initiated, 12-lead ECG and electrolytes should be repeated at least annually, after any increase in the antipsychotic drug dosage, or after the addition of other drugs known to prolong the QT interval or cause electrolyte abnormalities, particularly of potassium or magnesium. Semi-annual monitoring may be indicated in older patients and patients with known structural or coronary arterial disease. An ECG also should be obtained immediately in any patient who develops the new onset of palpitations, syncope/near-syncope (Chapter 49), falls, or chest pain (Chapter 39) while taking antipsychotic medications.

QTc intervals less than 500 msec but longer than 450 msec in men and 470 msec in women should prompt reevaluation of the risks and benefits associated with the drugs in question, repletion of the potassium level to above 4.0 mEq/dL and magnesium level to above 2 mg/dL and a repeat ECG within 2 to 4 weeks.[11] A corrected QT (QTc) interval of 500 msec or longer should prompt cardiology consultation and immediate discontinuation of all medications known to prolong the QTc interval.

TABLE 402-2 COMMON PSYCHOTROPIC MEDICATIONS AND RISK OF QTc PROLONGATION

PSYCHOTROPIC MEDICATIONS (GENERIC)	BRAND NAME	AVERAGE AMOUNT OF PROLONGATION OF QTc (MSEC)
ANTIPSYCHOTICS		
Thioridazine	Mellaril	28-37
IV Haloperidol	Haldol	16
Ziprasidone	Geodon	16
Quetiapine	Seroquel	15
Risperidone	Risperdal	10
Clozapine	Clozaril	10
PO Haloperidol	Haldol	4-9
Olanzapine	Zyprexa	6
Lurasidone	Latuda	5
Paliperidone	Invega	4
Aripiprazole	Abilify	Negligible effect
Perphenazine	Trilafon	Negligible effect
ANTIDEPRESSANTS: SSRIS		
Citalopram	Celexa	10-20
Escitalopram	Lexapro	5-11
Fluoxetine	Prozac	Negligible effect
Fluvoxamine	Luvox	Negligible effect
Paroxetine	Paxil	Negligible effect
Sertraline	Zoloft	Negligible effect
ANTIDEPRESSANTS: SNRIS		
Desvenlafaxine	Pristiq	Negligible effect
Duloxetine	Cymbalta	Negligible effect
Venlafaxine	Effexor	Negligible effect
ATYPICAL ANTIDEPRESSANTS		
Trazodone	Desyrel	4-7
Bupropion	Wellbutrin	Negligible effect
Mirtazapine	Remeron	Negligible effect

IV = intravenous; PO = oral; SNRI = serotonin-norepinephrine reuptake inhibitor; SSRI = selective serotonin reuptake inhibitor.

Myocarditis and cardiomyopathy (Chapter 47) are also more common in patients who are treated with antipsychotic medications, especially clozapine.[12] The myocarditis often occurs unexpectedly within 3 weeks of starting therapy. Patients require close monitoring, especially after the initiation of therapy, with a low threshold to evaluate any new symptoms consistent with myocarditis, including fever, dyspnea, myalgias, fatigue, or chest pain with cardiac biomarkers (e.g., a troponin level) ECG, and transthoracic echocardiogram (Chapter 47). Symptoms often resolve or improve significantly with removal of the inciting agent, but mortality can be as high as 50%. Clozapine can also lead to dilated cardiomyopathy over longer periods of treatment (typically 6 to 9 months). Although the mortality is lower than for clozapine-induced myocarditis, clinicians should have a low threshold to pursue echocardiography in patients with new-onset symptoms of heart failure after starting antipsychotic therapy.

METABOLIC SYNDROME

Patients with severe mental illnesses have a sedentary lifestyle and are at high risk of developing the metabolic syndrome, which is characterized by insulin resistance, hypertension, dyslipidemia, and obesity and is associated with an increased risk for the development of diabetes and cardiovascular disease.[13] Up to 40% of patients receiving long-term treatment with antipsychotic medications have impaired glucose tolerance, and about 10% have diabetes. All antipsychotic medications are associated with weight gain, but the atypical or second-generation antipsychotic medications (Table 362-12) in particular appear to be a cause. Clozapine and olanzapine have the highest risk for weight gain and the development of metabolic syndrome, whereas quetiapine, risperidone, and paliperidone carry slightly lower risk. The lowest-risk antipsychotics appear to be the first-generation antipsychotics.

Because the glucose intolerance often seen in patients treated with antipsychotic agents is due to insulin resistance (Chapter 210), it is best treated by aggressive weight reduction (Chapter 201), increasing physical activity (Chapter 14), and metformin (Chapter 210) or a combination of these approaches. For example, metformin (850 mg twice daily) can significantly reduce the weight gain and reverse the metabolic abnormalities associated with the initiation of second-generation antipsychotic drugs,[A4] and a daily dose of 750 to 2500 mg for 12 to 16 weeks may prevent weight gain if it is initiated at the onset of olanzapine treatment. The administration of the glucagon-like peptide-1 receptor agonist liraglutide (starting with a dose of 0.6 mg administered subcutaneously daily and uptitrating to 1.2 mg daily after 1 week and to 1.8 mg daily in the third week) to overweight or obese patients treated with olanzapine or clozapine can lead to weight loss, decreased waist circumference and low-density lipoprotein cholesterol levels, and improved glucose tolerance.[A5]

Weight and body mass index should be tracked, particularly in the first 6 months after the initiation of or change in the dose of antipsychotic medications. Blood pressure and blood glucose levels should be monitored every 3 months. Reducing the risk of developing metabolic syndrome is a formidable challenge for physicians caring for patients with severe mental illnesses, but a structured approach can improve cardiovascular risk factors.[A6]

RESPIRATORY COMPLICATIONS: ASPIRATION AND DYSPHAGIA

Asphyxia deaths from choking are about 100 times greater in patients with severe mental illness than in the general population, and many patients who survive a choking incident will have silent aspiration. About 50% of patients with severe mental illness and dysphagia have a fast-eating syndrome with restlessness, poor chewing skills, food pocketing in the cheeks, and an attention deficit. Many medications used in psychiatric treatment also can lead to a range of conditions that affect a patient's ability to swallow and effectively protect their airway (Table 402-3). Furthermore, the anticholinergic properties of first-generation antipsychotics (and less commonly, second-generation antipsychotics) can cause xerostomia, bronchospasm, and even dyskinetic dysphagia,[14] which presents as extreme, often sudden pain and spasm in the anterior cervical region that can be associated with other extrapyramidal symptoms such as torticollis, trismus, or tongue protrusion.[15] Patients with asthma (Chapter 75) or chronic obstructive pulmonary disease (Chapter 76) may be at even higher risk of bronchospasm, pneumonia, and acute respiratory failure. Patients with severe mental illness also are at higher risk of stroke and vascular dementia (Chapter 371), which can predispose them to dysphagia, aspiration, and pneumonia. Interprofessional resources such as speech and language pathology therapists can be very helpful in managing patients who have aspiration or dysphagia.

TABLE 402-3 CAUSES OF ASPIRATION AND ASPHYXIA IN PATIENTS WITH SEVERE MENTAL ILLNESS

CONDITION	SYMPTOMS	ETIOLOGY	TREATMENT
Bradykinetic dysphagia	• Reduced lingual range of motion • Increased oral transit time • Decreased pharyngeal peristalsis • Delayed swallowing reflex	Antidopaminergic and anticholinergic effects of antipsychotic medications, especially haloperidol, lurasidone, and risperidone	Discontinuation or reduced dose of offending medication
Dyskinetic dysphagia	• Involuntary contractions of the tongue and perioral musculature • Clumsiness of voluntary movements of the tongue • Discontinuous propulsion of food bolus in the mouth	Extrapyramidal symptoms Acute dystonia (within 48 hours of starting or a rapid dose increase) or insidious onset of chronic symptoms with long-term use (>1 year) as part of tardive dyskinesia	Vesicular monoamine transporter inhibitors: (deutetrabenazine 6 mg orally twice daily or valbenazine 40 mg orally daily)
Laryngeal dystonia	• Clinical emergency, life-threatening • Laryngeal muscle spasms causing dysphonia, stridor, and respiratory distress	Antiepileptics, dopamine agonists, antipsychotics with anti-dopaminergic effects (first generation much more than second generation)	Prompt administration of intravenous diphenhydramine (25-50 mg intravenously) and discontinuation of offending medication
Sialorrhea	• Drooling and poor oromotor control	Cholinergic effect of phenothiazines, clozapine, olanzapine, and quetiapine	Anticholinergic agents: e.g., oral glycopyrrolate, 1 mg three times daily; oral hyoscyamine, 0.125 mg every 4-8 hours with immediate release or 0.375 mg every 8-12 hours with extended release; ipratropium (1-2 metered sprays of 21 µg per metered dose), or atropine (1-2 drops of 1% solution sublingually, up to twice a day)

CATATONIA, NEUROLEPTIC MALIGNANT SYNDROME, AND SEROTONIN SYNDROME

Catatonia and the related neuroleptic malignant syndrome and serotonin syndrome present with prominent motor and behavioral manifestations. Neuroleptic malignant syndrome and serotonin syndrome often present with features of catatonia and may lie on a spectrum (Table 402-4).

Catatonia

Catatonia is a psychomotor syndrome that can occur in association with primary psychiatric conditions or secondary to medical or neurologic conditions or substances. The incidence of catatonia in the acute inpatient psychiatric setting is 5 to 10%.[16] Although its pathogenesis remains unclear, patients with catatonia have increased cerebral blood flow in the supplementary motor cortex and reduced flow to frontal and insular gray matter. Catatonia can be hyperkinetic and excited (with impulsivity, restlessness and agitation) or hypokinetic and stuporous (with signs such as mutism and psychomotor slowing). Delayed recognition of catatonia can result in serious complications, including rhabdomyolysis, aspiration, thromboembolic disease, and even death. New-onset catatonia, especially when occurring in medical/surgical settings or in older adults, deserves a medical evaluation that prioritizes central nervous system causes such as inflammatory conditions (e.g., paraneoplastic and limbic encephalopathy) and seizures.[17] The diagnosis can be confirmed by improvement after a challenge dose of a benzodiazepine (typically 1 to 2 mg of lorazepam intravenously) under expert supervision. If no change in symptoms is noted within 5 minutes, an additional 1 to 2 mg of lorazepam can be given.

TREATMENT

Once the diagnosis is confirmed or strongly suspected based on initial improvement after the challenge dose, clinical management includes continued treatment with benzodiazepines (typically 2 mg lorazepam orally three to four times daily for 2 to 3 days). Even while managing symptoms, the concurrent identification and treatment of underlying medical or neurologic conditions that could have triggered the catatonia should be undertaken. If no improvement in symptoms is seen in several days, expert psychiatric consultation is required to consider options such as electroconvulsive therapy or amantadine. Frequent assessment of vital signs, pulse oximetry, and monitoring of the osmolar gap are appropriate. Flumazenil (0.2 mg intravenously can be increased to 0.3 mg and then 0.5 mg every minute) should be given when respiratory status is a concern and be continued until respiratory depression resolves. Adding a nonsedating glutamate antagonist agent, either memantine (10 mg daily) or amantadine (100 mg daily), may allow for lower benzodiazepine dosing.

Neuroleptic Malignant Syndrome

Although any dopamine D2 receptor blocking agent, including common antiemetics, can cause neuroleptic malignant syndrome, the risk is lower with second-generation antipsychotics as compared with first-generation antipsychotics. About one-third of cases may present within 48 hours after beginning the offending drug. Most other cases occur within 1 month, but the average time to onset is about 50 days for clozapine. Abrupt discontinuation of a dopaminergic agent may cause parkinsonism-hyperpyrexia syndrome, whose features are indistinguishable from neuroleptic malignant syndrome.

TREATMENT

Neuroleptic malignant syndrome is a serious condition requiring medical attention, often in an intensive care unit, with close monitoring and supportive care.[18] Causative agents should be discontinued, and any associated dehydration or electrolyte imbalances must be addressed. Symptomatic treatment of catatonic symptoms is with benzodiazepines (e.g., lorazepam 1 to 2 mg of IV every 4 to 6 hours). In more severe cases with rhabdomyolysis from muscle rigidity and autonomic instability, alternative medications include bromocriptine (2.5 mg orally or via nasogastric tube every 6 to 8 hours) or amantadine (100 mg orally or via nasogastric tube, daily). In patients with fulminant manifestations with malignant hyperthermia, dantrolene (1 to 2.5 mg/kg IV) may be added with caution given its potential risk of hepatotoxicity. Untreated, neuroleptic malignant syndrome has a reported mortality rate of 10 to 20%, but most deaths are avoidable with prompt diagnosis, early discontinuation of the offending medication, and assertive treatment

Serotonin Syndrome

Serotonin syndrome, which results from excess central and peripheral serotonergic agonism, may be an adverse effect of a single medication (e.g., overdose on a selective serotonin reuptake inhibitor) or due to an interaction among multiple serotonergic agents. The syndrome usually occurs in minutes to hours after starting the offending agent and nearly always occurs within 24 hours.

TREATMENT

Treatment includes immediate withdrawal of offending agents, treatment of catatonia with benzodiazepines, (e.g., lorazepam 1 to 2 mg IV) supportive therapy, and often treatment with the anti-serotonergic agent cyproheptadine (initial dose of 12 mg orally followed by 2 mg every 2 hours until a response is seen). Once the serotonin syndrome resolves, clinical indications for any discontinued medications should be reviewed to prevent relapse.

APPROACH TO COMMON SYMPTOMS AND FINDINGS

Patients with severe mental illness often have somatic complaints (Table 402-5) that frequently generate medical consultation or transfer from a psychiatric unit to a medical unit.

TABLE 402-4 CHARACTERISTICS OF NEUROLEPTIC MALIGNANT SYNDROME AND SEROTONIN SYNDROME

		NEUROLEPTIC MALIGNANT SYNDROME	SEROTONIN SYNDROME	CATATONIA
Precipitated By		Dopamine antagonists, particularly high-potency, first-generation antipsychotics (e.g., haloperidol, fluphenazine) and, to a lesser extent, second-generation agents (e.g., clozapine, risperidone, olanzapine) Metoclopramide, prochlorperazine	Serotonergic agents: consider with two or more serotonergic medications or concomitant substance use (e.g., MDMA) Decreased reuptake of serotonin: SSRIs, SNRIs, TCAs, trazodone, St. John's wort Inhibited serotonin metabolism: MAO inhibitors (including linezolid)	Medical, neurologic and psychiatric conditions
Onset		Variable, 1-3 days	Variable, <12 hours	Variable, days to weeks
Resolution		Days to weeks	<24 hours	Days to weeks
Identical Features	Vital signs	Hypertension, tachycardia, tachypnea, hyperthermia (>40° C)	Hypertension, tachycardia, tachypnea, hyperthermia (>40° C)	Hypertension, tachycardia, tachypnea, hyperthermia (>40° C); autonomic abnormalities may occur ("malignant catatonia")
	Mucosa	Hypersalivation	Hypersalivation	Variable
Overlapping Features	Skin	Diaphoresis, pallor	Diaphoresis	Variable
	Mental Status	Variable: from coma to alert (agitation rare)	Variable: from coma to agitation	Variable: from stupor to agitation
	Muscles	"Lead-pipe" rigidity in all muscle groups	Increased tone, especially in lower extremities	Rigidity, waxy flexibility or paratonic rigidity common
	Laboratory Findings	Elevated CK, WBCs	Elevated CK	Variable (low serum iron catatonia is a risk factor for neuroleptic malignant syndrome)
Distinct Features	Reflexes	Hyporeflexia	Hyperreflexia, clonus (unless masked by increased muscle tone)	Normal
	Pupils	Normal	Dilated	Normal
	Bowel Sounds	Normal or decreased	Hyperactive	Normal
Treatment		Remove offending agent Benzodiazepines (for catatonia) Supportive care Bromocriptine, dantrolene, or amantadine	Remove offending agent(s) Benzodiazepines (for catatonia) Supportive care Cyproheptadine (occasionally)	Benzodiazepines (first line) ECT for malignant or treatment-resistant cases Amantadine or memantine (second line) Treatment of underlying condition

CK = creatine kinase; ECT = electroconvulsive therapy; MAO = monoamine oxidase; MDMA = 3,4-methylenedioxymethamphetamine; SNRI = serotonin-norepinephrine reuptake inhibitor; SSRI = selective serotonin reuptake inhibitor; TCA = tricyclic antidepressant; WBC = white blood count.

Physicians should be aware that calls from a psychiatric unit about medical concerns may be different than those from other units in the hospital. At times, a nurse or other unit staff member may call for consultation directly, and some consultations may be driven by protocol (e.g., after a fall, altercation, or other trauma). Sometimes, the only observation is that the patient seems less well, without a traditional chief complaint. For example, a unit manager may call to say that a patient is noted to be breathing irregularly but denies dyspnea, cough, or other respiratory symptoms. These concerns, which require a personal visit and examination, should be managed thoughtfully; reassurance to staff and patients is often of high value when an evaluation finds no important underlying medical cause.

DISTINGUISHING AN ACUTE MEDICAL PROBLEM FROM A MEDICATION SIDE EFFECT

Patients with severe mental illnesses, particularly patients who have psychotic disorders, may have unique ways of articulating symptoms. Lower health literacy may result in difficulty communicating physical symptoms, and cognitive impairment and thought disorders can make it difficult for physicians to assess the history and course of illness. Associated lack of motivation can provide further obstacles for understanding a patient's needs. Patients may be vague or silent about physical suffering, or they may describe symptoms in ways that are unusual. The problem of overlapping symptoms (e.g., somatic manifestations of anxiety or anxiety due to physical disease) add to the complexity. Taking a systematic approach to the evaluation and using a structured method for considering the differential diagnosis is paramount. Collateral information from family members and others who know the patient becomes key in such situations. Close collaboration with the patient's mental health or social service providers is additionally helpful in ascertaining what is considered baseline behavior.

Physicians who provide medical care to patients who are taking psychotropic medications also must be aware of the extensive side effect profiles for these medications. Accordingly, the initial evaluation of an acute medical problem should always include the usual comprehensive history, physical examination, and laboratory testing, but also a higher index of suspicion for side effects of psychotropic medications[19] compared with other common classes of medications (e.g., statins, antihypertensive agents, antibiotics, etc.).

When careful evaluation results in a reasonable likelihood that a side effect of a psychotropic medication may be causing or contributing to an acute medical problem, the preferred strategy is usually to continue effective medications but to adjust their dosing or frequency if possible. An alternative strategy is to consider symptomatic management with pharmacologic or behavioral interventions. If these interventions are not successful, the psychotropic agent may need to be discontinued and replaced with an alternative under expert supervision.

GIVING RECOMMENDATIONS

Providing clear and actionable recommendations for the evaluation and management of medical conditions in patients with severe mental illness can improve the care of these patients. Consulting physicians should strive to follow common sense or "golden rules" of consultation; a non-exhaustive list of domains and examples are provided in Table 402-6.

The specific words used to document recommendations can have lasting impact on how patients are treated by current and subsequent clinicians. Medical physicians should strive to use patient-centered words that do not stigmatize: "declined" instead of "refused;" "substance use disorder" instead of "addiction;" "alcohol use disorder" instead of "alcoholic." Finally, consulting physicians should cultivate a sense of self-awareness and practice of examining their reactions and responses to encounters with patients with severe mental illness. Patients who have severe mental illness often have had prior traumatic experiences and interactions with providers and can, at times, be confrontational or otherwise uncomfortable. These interactions may evoke unhelpful emotional responses from providers and adversely influence their

TABLE 402-5 COMMON SYMPTOMS AND FINDINGS IN PATIENTS WITH SEVERE MENTAL ILLNESS

SYMPTOM	UNIQUE FACTORS TO CONSIDER IN PATIENTS WITH SEVERE MENTAL ILLNESS
Chest pain	• Increased risk of CVD in patients on psychotropic medications • Myocarditis and arrhythmias more prevalent
Pain	• Often have a higher pain threshold, so acute illness (e.g., appendicitis) may take longer to recognize • Reported pain may be incongruent with findings, physical examination, or laboratory data
Altered mental status	• Substance use disorders more prevalent • Psychotropic medications recently increased, added or restarted (when previously not adherent) or stopped in the hospital • More prone to cognitive decline, which can precipitate delirium in the hospital
Constipation/urinary retention	• Psychotropic medications can cause severe constipation, lower threshold for considering obstruction • Anticholinergic medications increase risk for constipation and urinary retention, leading to delirium
Hyperammonemia	• Valproic acid
Azotemia	• Psychotropic medications (e.g., quetiapine, risperidone, and olanzapine)
Anemia	• Lithium (microcytic) • Nutritional deficiencies common (iron and vitamin B_{12})
Fever	• Drug overdose (psychostimulants, antidepressants, lithium, anticholinergics) • Bacteremia in setting of intravenous drug use • Alcohol or drug withdrawal (benzothiazines, barbiturates, antiparkinsonian agents) • MAO inhibitors • Serotonin syndrome, neuroleptic malignant syndrome
Hyponatremia	• Polydipsia/water toxicity, SIADH (SSRIs, SNRIs, atypical antipsychotics, mood stabilizers)
Hypernatremia Diabetes insipidus	• Lithium
Trauma	• Higher incidence of trauma (falls, assault, abuse), which patient may minimize or not recall • Low threshold for plain films to assess for fractures, particularly of hands, arms (distal radius), face, spine
Seizure	• Bupropion, MAO inhibitors, tricyclic antidepressants, phenothiazines, clozapine
Hypoxemia	• Aspiration is common; consider aspiration pneumonia if acute or aspiration pneumonitis if chronic
Metabolic syndrome	• Atypical/second-generation antipsychotics • Sedentary lifestyle

CVD = cardiovascular disease; MAO = monoamine oxidase, SIADH = syndrome of inappropriate antidiuretic hormone secretion, SNRI = serotonin-norepinephrine reuptake inhibitor; SSRI = selective serotonin reuptake inhibitor.

TABLE 402-6 BEST-PRACTICE CONSIDERATIONS FOR MAKING RECOMMENDATIONS

DOMAIN	DO	DO NOT	EXAMPLE
Evaluation	Prioritize tests to exclude serious medical conditions, especially if acute signs or symptoms that may have an impact on inpatient care.	Recommend extensive evaluation to exclude less likely causes in the differential, especially in agitated patient.	Prioritize ECG for cardiac condition; avoid serial troponin levels or telemetry unless active myocardial infarction suspected.
Ongoing psychiatric treatment	Consider psychotropic medications as the potential cause or amplifier for new complaints.	Recommend significant modification of antipsychotic medications without consulting the psychiatry team.	Avoid pithy recommendations such as "Switch clozapine to aripiprazole."
Care setting	Align primary treatment goal (medical vs. psychiatric) with patient care setting; stabilize medical conditions to focus on psychiatric care.	Transfer the patient to another inpatient unit unless the primary goal has changed or the required evaluation or treatment cannot be delivered in the current setting.	Acute medical decompensation (e.g., myocardial infarction or acute respiratory failure) requires transfer to a medical unit, but stable angina or mild aspiration may be managed in a psychiatric unit.
Patient-centered documentation	Describe structural determinants of health, such as housing insecurity, transportation challenges, and mental distress.	Portray patient with severe mental illness as uncooperative, unreliable or difficult.	Instead of "poor historian," consider mentioning challenges the patient is having with communication or noting that the history is incomplete until further information can be gathered.
Follow-up care	Include anticipatory guidance, appropriate follow up with suggested time frame, and education for primary team.	Provide excessive details on mechanisms or pedantic statements that do not provide concrete guidance.	Provide specific guidance on what to do if symptoms reoccur or persist and/or when to repeat tests or consider new tests.

ECG = electrocardiogram.

recommendations. The goal is not to prevent or avoid emotional responses; rather the goal is to recognize and process these responses in the most nonjudgmental way.

ONGOING AMBULATORY MEDICAL CARE OF THE PSYCHIATRIC PATIENT

The ongoing medical care of patients who have severe mental illnesses typically is best achieved in community mental health settings that can provide tailored approaches to chronic medical conditions.[20] However, regardless of where patients with severe mental illnesses receive their medical care, close collaboration among all the patient's health care providers is critical.

Illness anxiety disorder (formerly known as hypochondriasis), is the persistent fear of a having a disorder despite normal medical workup and reassurance. For such patients, frequent preemptive office visits with a consistent and supportive medical team as well as engagement in mental health treatment are most effective in reducing the ineffective use of health care resources.[A7]

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403 APPROACH TO SKIN DISEASES

CHRISTINE J. KO

A thorough skin examination is about *sape vedere*, "knowing how to see" the skin. Although many nondermatologists often may feel limited to distinguishing a rash from a neoplastic process, it is important for all clinicians to recognize common as well as morbid and life-threatening skin diseases and to refer lesions suggestive of serious disease to a dermatologist.[1] Even as remote "tele-dermatology" has become increasingly available and useful, especially in rural settings,[2,3] data suggest that an in-person examination is still preferable, at least for potentially important diagnoses.[4]

The American Cancer Society and the American Academy of Dermatology advocate routine skin cancer screening for adults on an annual basis, but the U.S. Preventive Services Task Force does not, even for high-risk individuals. Lesion-directed examination of patient-identified abnormalities and screening of people with atypical moles or more than 50 moles may be a reasonable middle ground.[5] Regardless of the frequency of routine total body skin examination, all clinicians should recognize concerning skin lesions, including brown/black/blue/red lesions that are asymmetric and irregular, lesions that look different than others on a given patient, and new lesions that are not healing over 3 to 4 weeks of time (Chapter 188).

STRUCTURE AND FUNCTION OF THE SKIN

A basic understanding of the structure and function of the skin provides a framework for organizing skin diseases. The functions of the skin include physical and mechanical protection, thermoregulation, immunologic surveillance, and sensation. To achieve these goals, the skin is composed of the epidermis, dermis, and subcutaneous tissue. The epidermis is complex, primarily composed of keratinocytes in differentiated layers (E-Fig. 403-1). In addition to the epidermis, epithelial cells form important structures, including hair follicles, eccrine glands, apocrine glands, nails, and hair. Other cell types resident within the skin include melanocytes, Merkel cells, and immune cells. Melanocytes are critical for protecting against damage from ultraviolet light. Langerhans cells are resident immune cells that present antigens to circulating immune cells, which come in and out of the skin more transiently. Within the dermis, the fibroblast is a major cell responsible for forming collagen, which is the key structural protein. Vessels and nerves within the dermis are important for appropriate blood flow and sensation.

APPROACH TO A SKIN PROBLEM

Any new skin problem should be categorized as a tumor or a non-neoplastic process (rash). Although this distinction is often simple, with tumors being solitary and rashes being more diffuse with multiple lesions, there are many exceptions. For example, tinea corporis can present as a solitary, scaling, pink plaque, as can superficial basal cell carcinoma or squamous cell carcinoma in situ (E-Fig. 403-2). Cutaneous T-cell lymphoma can present as multiple, asymptomatic pink patches and plaques, and it can easily be mistaken for a benign rash (E-Fig. 403-3). Knowledge of these pitfalls can help avoid them, with a low threshold for biopsy as clinically indicated.

APPROACH TO DIAGNOSIS

THE SKIN EXAMINATION

Dermatology is an inherently visual specialty, in which subjective perceptions can lead to diagnostic errors,[6,7] which can be reduced by a systematic, orderly approach.[8,9] An observational checklist (Table 403-1) can help guide the skin examination, which is aided by optimal lighting, including side lighting. Magnification can be helpful, and a simple hand lens can be used. Polarized magnifiers (dermatoscopes) can sometimes be helpful for physicians with sufficient training and experience, especially for the diagnosis of possible melanoma.[10]

THE PATIENT

General and more specific characteristics of the patient should be observed. Age, gender, and skin type can all help direct the differential diagnosis. Skin type can be categorized (E-Table 403-1), and hair and eye color should also be noted. Red hair is associated with melanocortin-1 receptor mutations and an increased risk (about two-fold) of melanoma (Chapter 188). Occupational marks (e.g., linear burns on the arms of a baker) can sometimes be clues to job- or hobby-related diseases.

DISTRIBUTION

The bodily distribution (see Fig. 408-13 and Table 408-5) of lesions and the layers of skin (epidermis, dermis, subcutaneous) they involve can be helpful in creating a differential diagnosis (E-Fig. 403-4; Table 403-2). For example, involvement of much of the face, arms, and upper chest in a photodistribution (sparing the skin under the nose, mid-chin, body folds, clothed areas) can point to sun-exacerbated diseases such as lupus erythematosus

TABLE 403-2 LOCATION OF SKIN LESIONS AS A DIAGNOSTIC CLUE

LOCATION	POSSIBLE DIAGNOSES	
Unilateral	Herpes zoster Herpes simplex Deep vein thrombosis	Contact dermatitis where exposed Cellulitis Necrotizing fasciitis Solitary skin malignancies
Bilateral, widespread	Hematogenously spread process Severe drug eruption Disseminated viral, bacterial, or fungal infection Vasculitis Autoimmune disease	Psoriasis Cutaneous T-cell lymphoma Scabies Urticaria Atopic dermatitis (eczema) Other drug eruptions
Bilateral, limited sites	Stasis dermatitis Irritant contact dermatitis	Vasculitis Erythema multiforme Lipodermatosclerosis

TABLE 403-1 OBSERVATIONAL CHECKLIST

WHO?	WHERE?	WHAT?	WHEN?
The patient • General appearance • Age, degree of sun damage • Gender • Skin type, hair/eye color • Occupational marks	**Overall and local distribution** **Depth affected** (can use palpation) • Epidermal • Dermal • Subcutaneous	**Morphology of primary lesion** • Macule (Flat, <1 cm) • Patch (Flat, >1 cm) • Papule (Raised, <1 cm) • Plaque (Raised, >1 cm) • Nodule (Deeper than papule, <1 cm) • Tumor (Deeper than papule, >1 cm) • Vesicle (Fluid-filled, <1 cm) • Bulla (Fluid-filled, >1 cm) • Pustule (Pus-filled, <1 cm) **Configuration/pattern** **Color** **Secondary changes**	**Duration** • Acute • Chronic • Fixed vs. transient

An observational checklist can help guide the general skin examination (see text).

ABSTRACT

A thorough skin examination is about "knowing how to see" the skin. Although many nondermatologists focus on distinguishing a rash from a neoplastic process, it is important for all clinicians to recognize morbid or life-threatening skin diseases. To make the correct diagnosis, the clinician must consider the patient's general appearance; the distribution of skin findings; the morphology, configuration, and color of the skin changes themselves; and nonskin issues. Skin signs with a potential for high morbidity or mortality include generalized sloughing of the skin with red eyes and crusted lips, retiform purpura (concave, netlike, scalloped borders), and pigmented melanocytic lesions that are irregular in color and shape.

KEYWORDS

skin examination
toxic epidermal necrolysis
pruritus
retiform purpura
skin tumor
rash

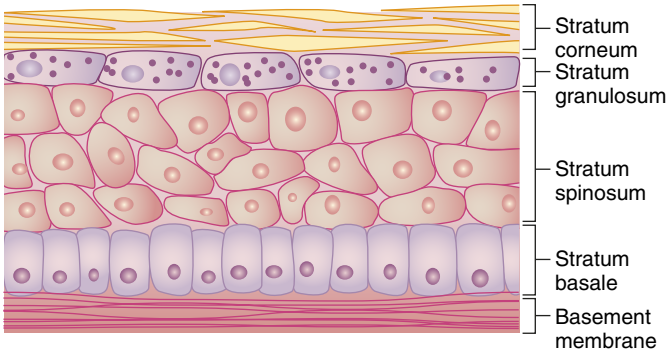

E-FIGURE 403-1. **The epidermis and its layers of differentiation.**

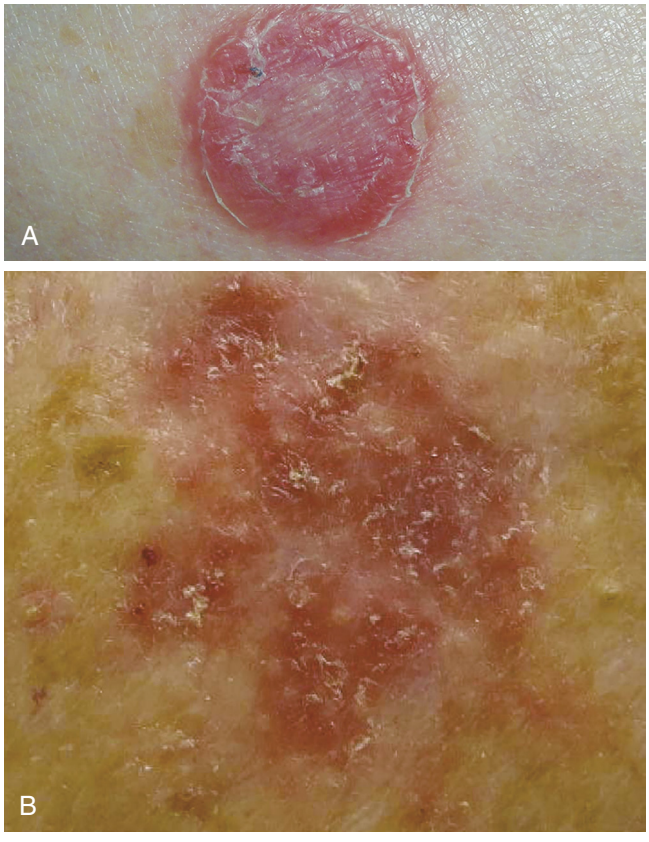

E-FIGURE 403-2. **Inflammatory processes can mimic tumors. A**, Tinea corporis, a superficial fungal infection, manifests as a solitary, pink, scaling plaque. The clinical presentation is similar to that of superficial basal cell carcinoma, also a solitary, pink plaque (**B**). (A, From Ko CJ. *Dermatology: Visual Recognition*. Elsevier; 2017.)

E-FIGURE 403-3. **Mycosis fungoides (cutaneous T-cell lymphoma).** Multiple pink patches over the buttocks, a typical site, with extension on the lower back. The atrophic area on the lower back is a clinical clue to the diagnosis. (Courtesy Yale Dermatology Residents' Collection.)

E-TABLE 403-1 FITZPATRICK SKIN TYPES

CATEGORY	DEFINITION
I	Always burns, never tans
II	Usually burns, then tans
III	Sometimes burns, often tans well
IV	Rarely burns, tans well
V	Very rarely burns, brown skin
VI	Very rarely burns, very dark skin

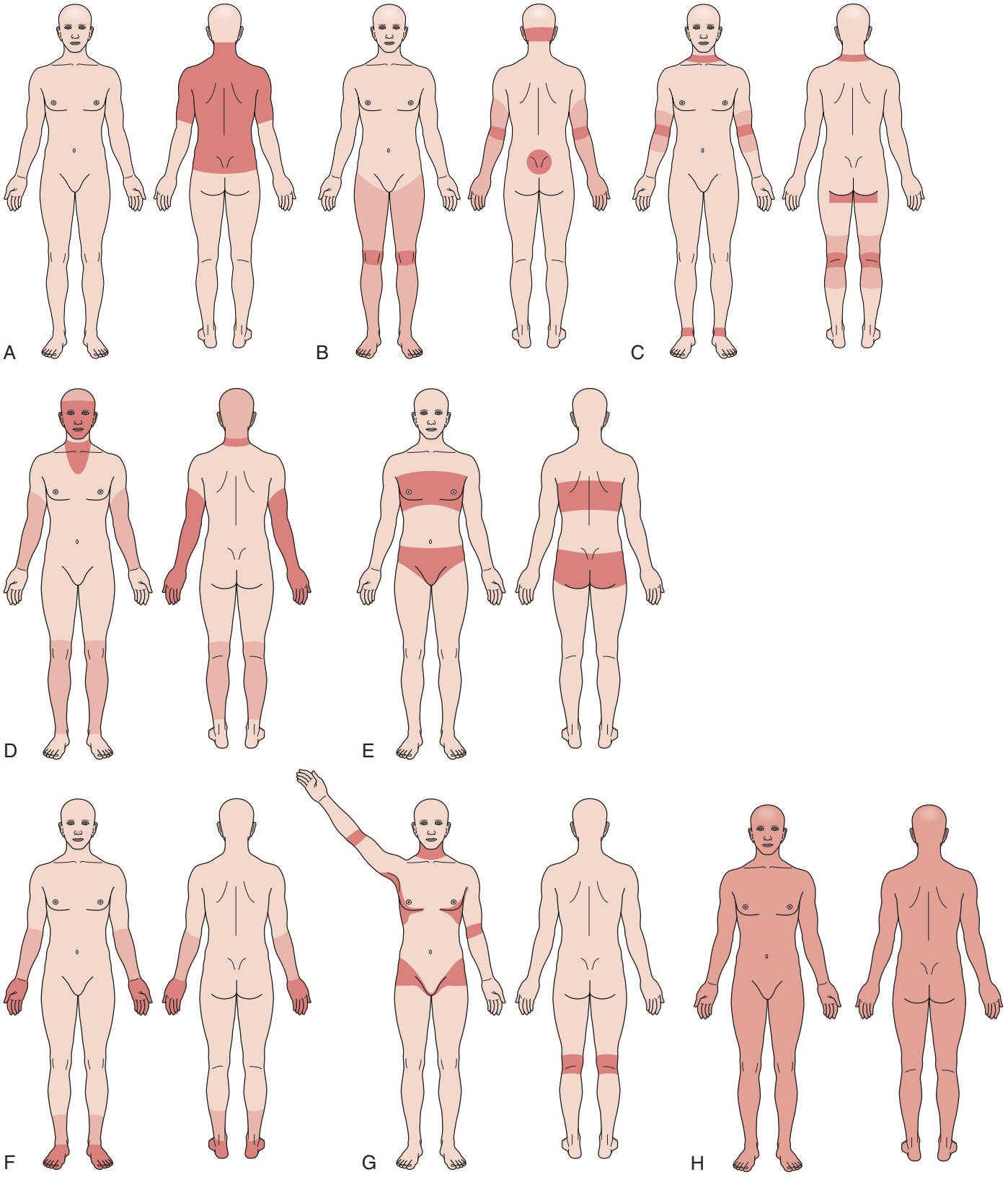

E-FIGURE 403-4. **Distribution (body sites affected). A,** Back. **B,** Extensor surfaces. **C,** Flexural surfaces. **D,** Photodistribution. **E,** Double-covered sites. **F,** Acral. **G,** Body folds. **H,** Generalized.

Continued

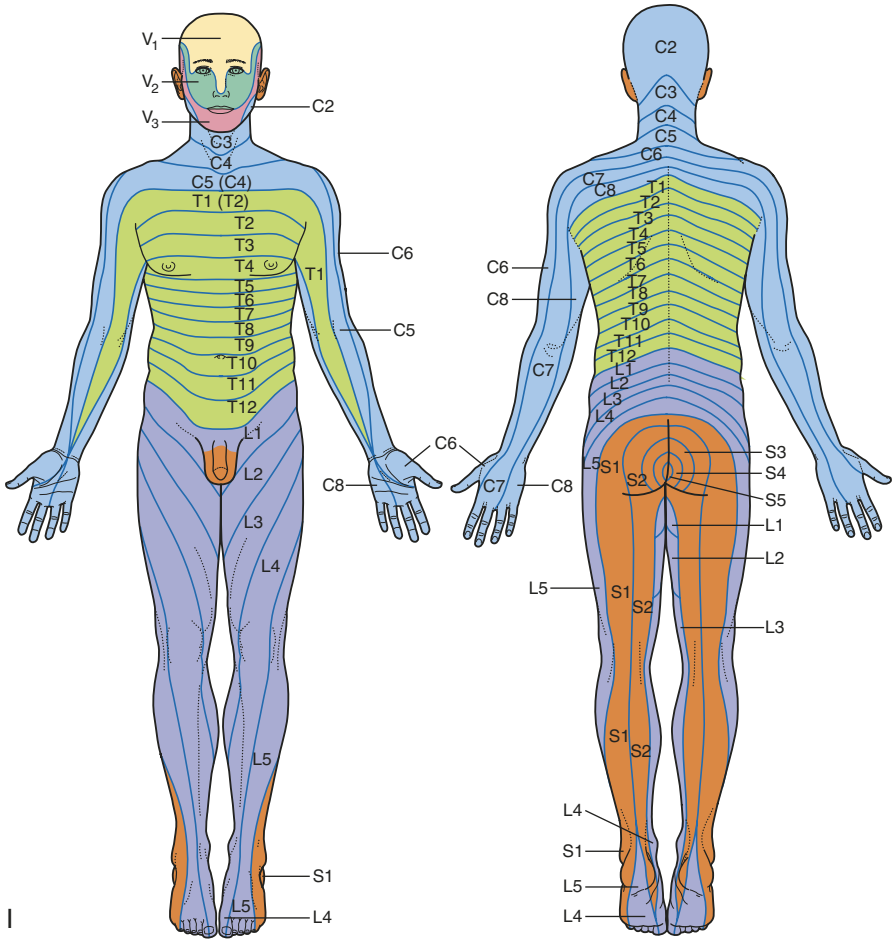

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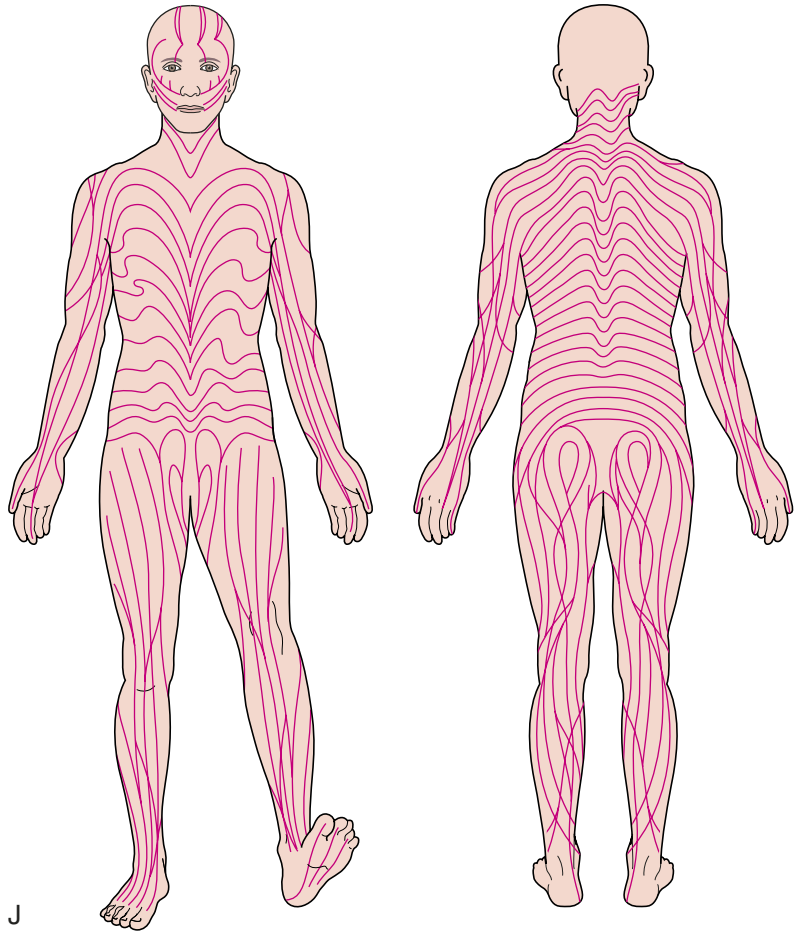

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E-FIGURE 403-4, cont'd. I, Dermatomal pattern. J, Blaschko lines. Areas *shaded in red* are classically involved. *Light pink areas* may also be involved. (A to E, From Ko CJ. *Dermatology: Visual Recognition*. Elsevier; 2017. I and J, From Bolognia JL, Jorizzo JL, Schaffer JV. *Dermatology*, 3rd ed. London: Saunders; 2012.)

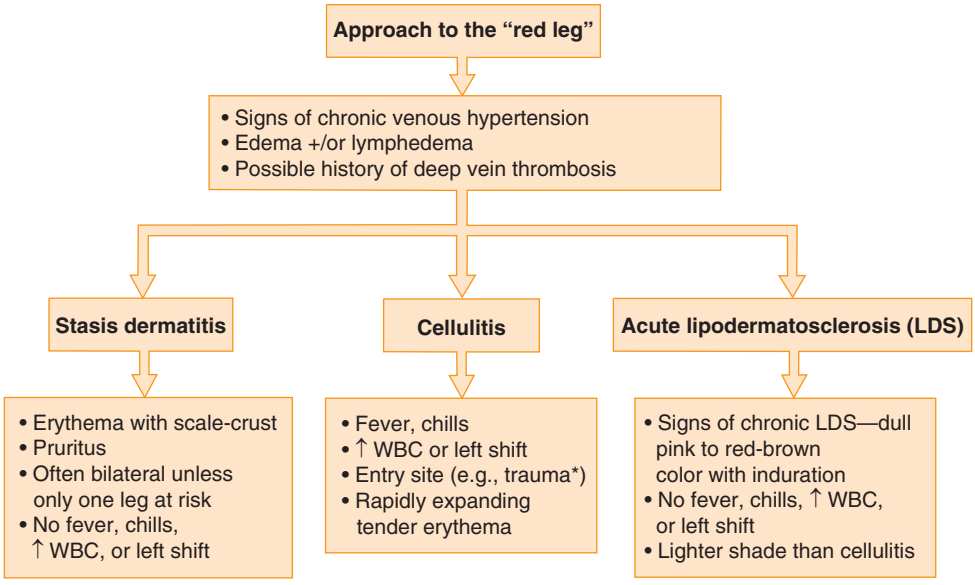

FIGURE 403-1. Approach to the "red leg." *May not have leg at risk. WBC = white blood cells. (From Bolognia JL, Jorizzo JL, Schaffer JV. *Dermatology*, 3rd ed. Philadelphia: Saunders; 2012.)

(Chapter 245) or a photo-induced drug reaction (Chapter 25). A unilateral, linear dermatomal distribution of vesicles is highly suggestive of herpes zoster (Chapter 346). Bilateral redness and swelling of the lower legs are highly unlikely to be cellulitis (Chapter 408), which is generally a unilateral disease (Fig. 403-1).

PALPATION

Palpation of lesions can discern the depth of involvement, whether something is more superficial (epidermal), deeper (dermal), or even deeper (subcutaneous) (Table 403-3). Fibrosis, heat, roughness, dimpling, and firmness can also be palpated. Epidermal processes may have associated scale. Dermal disorders can have a normal-appearing surface (a clue that the process is not epidermal) or have overlying epidermal changes as well. Similarly, subcutaneous disorders may affect only the subcutaneous tissue (e.g., erythema nodosum [Chapter 407], which is the most common panniculitis, generally affecting only the adipose tissue) or may affect the epidermis and/or dermis as well (e.g., lupus profundus, in which epidermal and dermal changes are similar to discoid lupus erythematosus [Chapter 245], with necrosis and lymphocytic inflammation within the fat).

MORPHOLOGY

Dermatology has its own vocabulary, and the most basic terms include those for morphology (Table 403-4; and see Table 403-1). The most important descriptions include macule, patch, papule, plaque, nodule, tumor, vesicle, bulla, and pustule. If the clinician is uncertain, descriptive language (e.g., "firm, raised bump about 0.4 cm in diameter" in place of "firm papule") is also effective for communicating among specialists.

Purpura (Fig. 403-2), which is caused by extravasation of red blood cells into the skin, results in a reddish to dark purple to black color. Small, pinpoint purpuric lesions are termed petechiae. Larger areas of purpura are termed ecchymoses. When purpura is palpable, it suggests small vessel leukocytoclastic vasculitis (Chapter 406). Larger vessel systemic vasculitis (Chapter 249) as well as occlusion of smaller vessels can produce retiform purpura, which can be a sign of a life-threatening disorder. The borders of retiform purpura form incomplete rings or nets in a concave outline rather than the smoother, convex, scalloped, and rounded outline of palpable purpura.

CONFIGURATION

The arrangement, or configuration—linear, target, annular/serpiginous, exogenous, small net, or large net—of primary lesions is a principal diagnostic feature, as is its topography—flat-topped, smooth dome-shaped, filiform, pedunculated, verrucous, or umbilicated (Table 403-5). Each of these patterns provides clues to the diagnosis.

COLOR

Color can be an important guide for the differential diagnosis and sometimes is diagnostic (Table 403-6). Importantly, the background skin color can substantially influence the appearance of color within a lesion. For example, inflammation, which usually imparts a pink to red color to the skin, can be masked in darker compared with lighter skin types (E-Fig. 403-5). Lighter skin is at higher risk for skin cancer.

SECONDARY CHANGES

Normal skin does not produce visible scale. The presence of scale indicates that the stratum corneum is abnormal, and different types of scale are clues to the correct diagnosis (E-Table 403-2). Scale is an important component of conditions such as psoriasis, tinea, and pityriasis rosea (Chapter 405). Other secondary characteristics include crusting, fissures, erosion, ulceration, excoriation, atrophy, and lichenification (E-Table 403-3). Certain secondary findings are expected for a given disease—for example, lichenification in atopic dermatitis (Chapter 405) and atrophy in lichen sclerosus (Chapter 407).

HISTORY

Because dermatologic diagnosis is, for the most part, visually based, the skin examination often precedes taking a history—or the two may be conducted simultaneously. Important factors (Table 403-7) to consider include onset/duration of the problem, systemic symptoms, and lesional symptoms including pruritus and/or pain. The past medical history, list of medications, and contactants, especially if recent or new, are important, as is a review of systems (Chapter 6).

The confidence in a diagnosis increases when the history and the skin findings point coherently to a single diagnostic entity. For example, allergic contact dermatitis (Chapter 405) seems highly likely for a new eczematous, excoriated rash that is seen on the margins of the scalp and extends slightly onto the forehead, especially if it is associated with pruritus and a recent switch to a new hairdresser and use of new hair dye. The differential diagnosis includes seborrheic dermatitis (Chapter 405), which commonly affects the scalp, though less often the forehead, and is often pruritic as well. In this specific example, patch testing (in which patches with specific allergens are placed on the patient's back for 24 to 48 hours before removal) and response to avoidance of hair dye can aid in differentiating the two disorders.

LIFE-THREATENING EMERGENCIES

The presence of an acute fever and rash should prompt exclusion of life-threatening diseases (Table 403-8; Figs. 403-3 to 403-8). Necrotizing fasciitis (Chapter 271) can also be a life-threatening emergency that may be deceptively limited to one extremity. Widespread retiform purpura, including on sites above the waist, in an ill-appearing patient should prompt consideration of

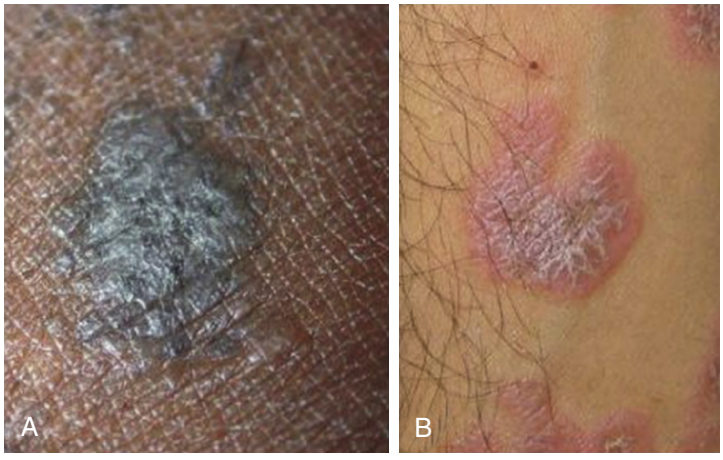

E-FIGURE 403-5. Background skin color. The same disorder, lichen planus, has a completely different color depending on the background darker (**A**) versus lighter (**B**) skin. The purplish tinge seen in **B** is more muted in **A**, which appears gray-purple. Wickham striae (lacy white surface scaling) are more easily seen in **B**. (From Bolognia JL, Jorizzo JL, Schaffer JV. *Dermatology,* 3rd ed. Philadelphia: Saunders; 2012:8.)

E-TABLE 403-2 TYPES OF SCALE

UNDERLYING ERYTHEMA

On advancing rim of a ring—e.g., Tinea corporis

Powdery (especially when lightly scraped)—e.g., Tinea versicolor

Greasy—e.g., Seborrheic dermatitis

Silvery to white-yellow—e.g., Psoriasis

Cornflake-like—e.g., Pemphigus foliaceus

Collarette ± central fine scale—e.g., Pityriasis rosea

Wickham striae (fine, net-like)—e.g., Lichen planus

Weeping—e.g., Nummular dermatitis

Lichenified—e.g., Lichen simplex chronicus

E-TABLE 403-2 TYPES OF SCALE—cont'd

WITHOUT UNDERLYING ERYTHEMA

Dry, small polygonal—e.g., Ichthyosis vulgaris

Corrugated, linear—e.g., Epidermolytic ichthyosis

Large, polygonal with lifting of edges—e.g., Lamellar ichthyosis (autosomal recessive congenital ichthyosis)

Scale that is often darker compared with surrounding skin—e.g., X-linked ichthyosis

Photographs from Ko CJ. Dermatology: *Visual Recognition*. Elsevier; 2017; Bolognia JL, Jorizzo JL, Schaffer JV. *Dermatology*, 3rd ed. London: Saunders; 2012, and the Yale Dermatology Residents' Collection.

E-TABLE 403-3 MORPHOLOGIC TERMS FOR SECONDARY FEATURES

Crust: Dried serum, yellow to hemorrhagic depending on number of cells in exudate

Impetigo

Fissure: Small linear splits in skin, usually superficial

Hailey-Hailey disease

Erosion: Loss of part of the epidermis

Staphylococcal bullous impetigo

Ulceration: Loss of epidermis into deep dermis or fat

Chronic ulcerated herpes simplex

E-TABLE 403-3 MORPHOLOGIC TERMS FOR SECONDARY FEATURES—cont'd

Excoriation: Self-inflicted erosion or ulcer

Factitial dermatitis (dermatitis artefacta)

Neurodermatitis; note inferior cutoff where patient cannot reach

Atrophy: Thinning or loss of dermal structures or fat usually; may apply to any tissue

Fat atrophy: lupus panniculitis

E-TABLE 403-3 MORPHOLOGIC TERMS FOR SECONDARY FEATURES—cont'd

Lichenification: Thickened skin from chronic rubbing. Poorly demarcated, skin lines accentuated

Lichen simplex chronicus

Courtesy James C. Shaw.

TABLE 403-3 REPRESENTATIVE DIAGNOSES BASED ON DEPTH OF PATHOLOGY IN THE SKIN

DEPTH	CHARACTERISTICS	DISORDERS		CLINICAL EXAMPLE
Epidermal	Distinct, even sharp margins Scaling Epidermal thickening Absence of induration May have mild erythema as well (some dermal involvement)	Seborrheic keratosis Warts In situ squamous cell carcinoma (Bowen disease) Ichthyosis Bullous impetigo Superficial basal cell carcinoma Acanthosis nigricans	Tinea versicolor Tinea corporis Actinic keratosis	 Seborrheic keratoses
Epidermal and dermal Most skin diseases will have some degree of dermal and epidermal involvement	Margins moderately well defined Scale can be present Inflammation (erythema) Usually palpable lesions (raised)	Lichen planus Systemic lupus erythematosus Chronic cutaneous lupus Nummular (discoid) dermatitis Mycosis fungoides Pyoderma gangrenosum	Atopic dermatitis Secondary syphilis Nodular basal cell carcinoma Squamous cell carcinoma Melanoma Most vesiculobullous diseases (HSV, autoimmune)	 Lichen planus, hypertrophic
Dermal Diseases with only dermal involvement usually consist of infiltrates with inflammatory or malignant cells that do not influence epidermal function	Margins moderately defined No scale Smooth surface No ulcer Variable inflammation Usually palpable	Urticaria Sarcoidosis Granuloma annulare Leprosy Necrobiosis lipoidica Morphea Scleroderma	Cutaneous metastases Most cysts Dermal melanocytic nevi Pretibial myxedema Other cutaneous lymphomas	 Sarcoidosis: Histiocyte collections in the upper dermis
Subcutaneous fat	Margins rounded and/or poorly defined Variable inflammation Smooth overlying skin	Lipoma Erythema nodosum Panniculitis of any etiology Some lymphomas		 Erythema nodosum

HSV = herpes simplex virus.
Courtesy James C. Shaw.

TABLE 403-4 MORPHOLOGIC TERMS FOR PRIMARY LESIONS

Macule: Flat, nonpalpable, <1 cm diameter

Lentigines. Brown to tan macules.

Papule: Superficial, raised, palpable, <1 cm diameter

Seborrheic keratosis. Gray-black stuck-on papule.

Patch: Large macules >1 cm diameter

Melasma. Light tan patch on the cheek.

Plaque: Raised, palpable, >1 cm diameter

Psoriasis. Pink-red well-demarcated plaques with adherent scale.

Nodule: Deeper than a papule, usually <1 cm diameter

Gout. Yellow-pink nodules over and near joints.

Tumor: Large mass, >1 cm diameter

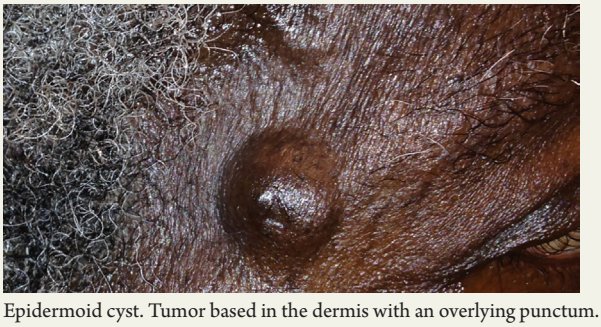

Epidermoid cyst. Tumor based in the dermis with an overlying punctum.

Vesicle: <1 cm fluid-filled, may be umbilicated or contain pus or blood

Herpes zoster. Small vesicles, some becoming confluent, with background erythema. The vesicles and erythema are unilateral in a dermatomal distribution.

Bulla: >1 cm, filled with clear fluid, pus, or blood

Bullous pemphigoid. Tense bullae (and some vesicles) on a pink background.

Pustule: White, pus-filled, small, raised, <1 cm diameter

Acute generalized exanthematous pustulosis (a type of drug reaction). Small pustules over confluent erythema.

Photographs courtesy Mary Tomayko, MD, PhD, and from Ko CJ. *Dermatology: Visual Recognition*. Elsevier; 2017; Bolognia JL, Jorizzo JL, Schaffer JV. *Dermatology,* 3rd ed. London: Saunders; 2012; Yale Dermatology Residents' Collection; and NYU Slide Collection.

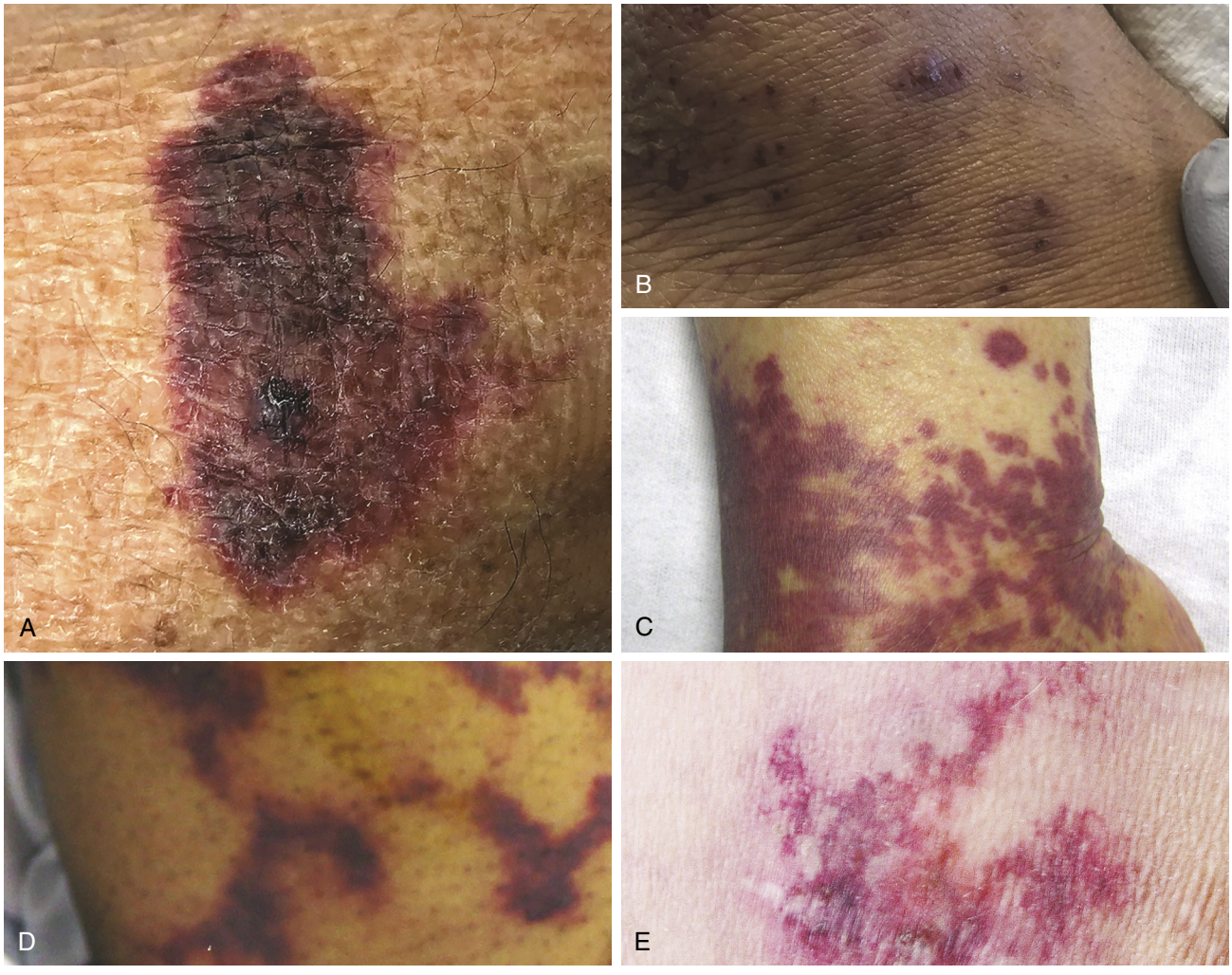

FIGURE 403-2. Purpura represents extravasated erythrocytes in the skin. A, Solar purpura. Bruises on the sun-exposed skin of older individuals are very common. **B, C**, Palpable purpura, which generally corresponds to leukocytoclastic vasculitis on biopsy. In darker skin (**B**), redness can be less obvious and appear more purple-gray in color. **D, E**, Retiform purpura. Note the jagged, netlike outlines. Purpura can vary in color depending on the background skin color. Retiform, or branching, purpura is often associated with larger vessel systemic vasculitis or coagulopathy. (B, Courtesy Yale Dermatology Residents' Slide Collection. C, From Ko CJ. *Dermatology: Visual Recognition*. Elsevier; 2017.)

disseminated intravascular coagulation (Fig. 403-9; Chapter 161), which is seen in severe systemic infections, such as meningococcemia (Chapter 274). The widespread distribution in a sick patient is in sharp contrast to localized purpura, which is less concerning and points to coagulation disorders, including reactions to warfarin or heparin, or the palpable purpura of small vessel leukocytoclastic vasculitis (see Fig. 403-2). Persistent skin mottling, principally in the fingers and toes, is a sign of poor circulation in a critically ill patient and is associated with increased mortality. Intense pruritus accompanying an acute blistering eruption points toward bullous pemphigoid or allergic contact dermatitis (Figs. 403-10 and 403-11; Chapter 405) rather than toxic epidermal necrolysis (Chapter 407).

DIAGNOSTIC TESTS

Pressing on the skin with something transparent (termed diascopy), such as a glass slide or tube, can help confirm the status of vessels, which normally blanch and then refill. Diascopy of red-pink erythema can confirm that the color is inflammatory—the red-pink color should fade completely with pressure. This finding is in contrast to purpura (blood within the skin), which has a deep red to purple to black color that does not fade with pressure.

Scale can always be gently scraped off onto a glass slide with a scalpel blade or even with another microscopic slide. A 10% solution of potassium hydroxide (KOH) can be applied onto the scale, then a cover slip can be placed over the scale and solution, with the bottom of the slide placed briefly over a flame (from a lighter or even a match). KOH dissolves keratin, with the heat accelerating the reaction, thereby allowing nonkeratinized structures such as fungal hyphae to be prominent on microscopic examination (E-Fig. 403-6). If scabies (Fig. 98-2) is suspected, skin lesions can be gently scraped, with scale and crust placed onto a slide covered with a small amount of mineral oil (E-Fig. 403-7).

Rapid diagnosis of herpes virus infection (without speciation) is possible with the Tzanck smear, by which vesicles are unroofed, with gentle scraping of the base of the lesion. Collected material is smeared onto a microscopic slide and briefly heated, with subsequent application of any nuclear stain (e.g., methylene blue, alanine, hematoxylin). After the slide is rinsed and blotted, microscopic examination can identify the pathognomonic multinucleated keratinocytes (E-Fig. 403-8). Other tests include direct fluorescent antibody staining, polymerase chain reaction testing, electron microscopy, and viral culture; local practice patterns often dictate which test is preferred. A Gram stain to look for bacteria is similar: pustular material is smeared and briefly heated on a slide, then four different stains are applied and rinsed (crystal violet, iodine, alcohol, safranin) in order. The slide is blotted, mounted under immersion or mineral oil, and examined under high magnification. Dermoscopy can magnify and/or polarize skin lesions, thereby aiding in visual diagnosis.

A skin biopsy entails taking a small piece of skin for fixation and microscopic examination. In general, the center of lesional tissue should be biopsied; the periphery should be biopsied only for ulcers, bullae, and normal skin for direct immunofluorescence studies.

PRURITUS

Pruritus is the medical term for itch. Pruritus, especially chronic pruritus, can be likened to pain (Chapter 26), as it can be extremely disruptive and life-changing.[11] Both pruritus and pain are mediated by the same nerve fibers, unmyelinated C fibers. Pruritus may originate in the skin (e.g., inflammatory skin diseases such as atopic dermatitis and psoriasis are the most common causes of chronic itching), afferent nerves (e.g., brachioradial pruritus), or the central nervous system (e.g., renal or liver failure, lymphoproliferative disorders, malignancy, delusions of parasitosis). When approaching a patient with

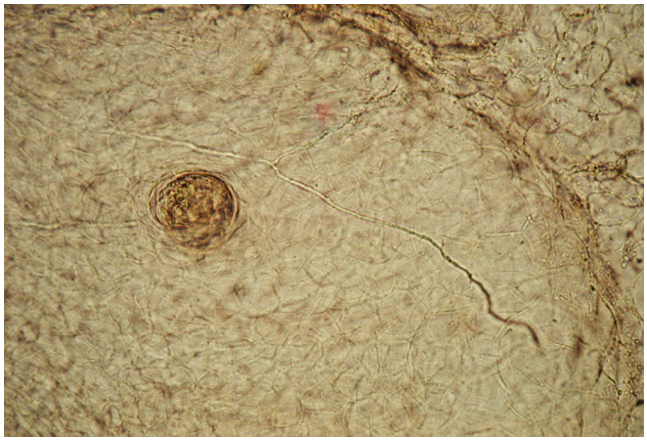

E-FIGURE 403-6. **Potassium hydroxide examination at 40× demonstrating linear fungal hyphae.**

E-FIGURE 403-7. **A scabies mite is seen on this microscopic examination of an oil mount of a scraping taken from the end of a small burrow on the wrist.**

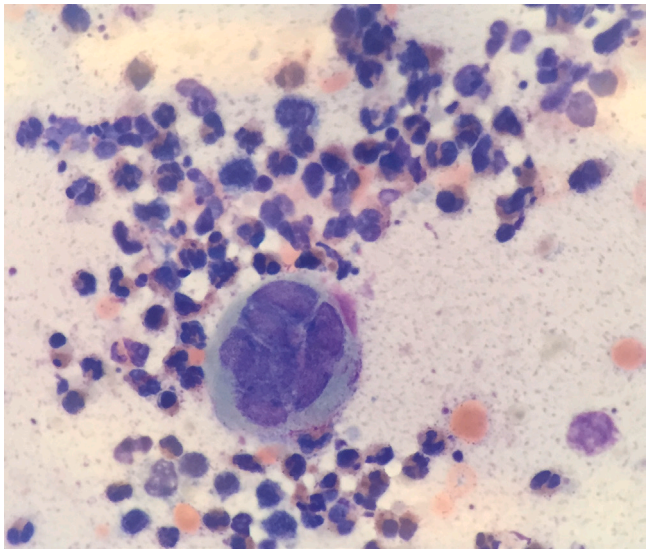

E-FIGURE 403-8. **Multinucleated keratinocyte in a Tzanck preparation for herpes simplex, zoster, or varicella.** Sample taken from the base of a vesicle (40×). (Courtesy Yale Dermatology Residents' Collection.)

TABLE 403-5 CONFIGURATION/PATTERN

CONFIGURATION/PATTERN/EXAMPLE

Linear

Externally induced
Dermatomal
Vascular
Blaschkoid

Poison ivy dermatitis

Herpes zoster

Exogenous

Allergic contact dermatitis

Small net

Livedo reticularis

Large net, irregular and incomplete

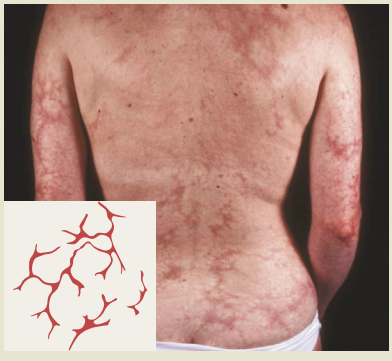

Livedo racemosa

Target (3 zones of color)

Erythema multiforme

Annular/serpiginous

Urticaria

TABLE 403-5 CONFIGURATION/PATTERN—cont'd

CONFIGURATION/PATTERN/EXAMPLE

Topography

Flat-topped

Dome-shaped, smooth

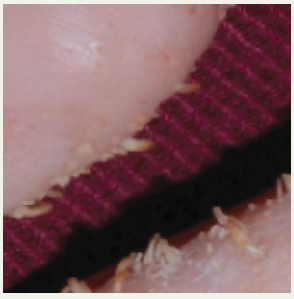

Filiform

Pedunculated

Verrucous

Umbilicated

Adapted from Bolognia JL, Schaffer JV, Duncan KO, Ko CJ. *Dermatology Essentials*. Elsevier; 2014. Photographs from Ko CJ. *Dermatology: Visual Recognition*. Elsevier; 2017; Bolognia JL, Jorizzo JL, Schaffer JV. *Dermatology*, 3rd ed. London: Saunders; 2012; Yale Dermatology Residents' Collection; and Kalman Watsky, MD, Peter Heald, MD, Christopher Baker, and Robert Kelly.

TABLE 403-6 COLOR CLUES IN DIAGNOSING SKIN DISEASE

COLOR

Black
Melanin
Erythrocytes (purpura)
Necrosis (can be gray early on)
Occluded vessels
Inflammation

Palpable purpura. Small vessel vasculitis with papules coalescing into a larger plaque.

Melanoma. Irregularly shaped black papules.

COLOR

Brown
Melanin
Hemosiderin

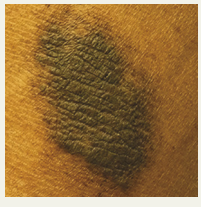

Medium-sized congenital nevus on the arm *(left)* and leg *(right)*.

TABLE 403-6 COLOR CLUES IN DIAGNOSING SKIN DISEASE—cont'd

COLOR

White
Decreased melanin
Vasospasm
Deposition (e.g., calcium)
Keratin (e.g., scale, cyst)
Sclerosis/scar

Tinea versicolor. White, powdery scale is typical with gentle scraping. The lesions are hypopigmented, thin plaques and papules.

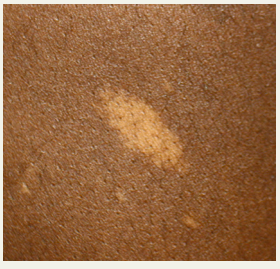

Ash-leaf macule of tuberous sclerosis.

COLOR

Blue
Melanin
Vessels

Varicose veins. Blue linear cords and papules.

Variations of pink

Pink (in lighter skin)
Vasodilation
Inflammation

Urticaria. Light pink papules.

Pink-red (in lighter skin)
Inflammation
Vasodilation

Psoriasis. Pink-red well-demarcated plaque with silvery, adherent scale.

Orange-red (in lighter skin)
Inflammation

Pityriasis rubra pilaris. Orange-pink plaques with areas of uninvolved skin on the back.

Red/pink-brown
Denser inflammation, often not just lymphocytes (e.g., lymphocytes and plasma cells in secondary syphilis, granulomatous/histiocytic disorders)

Sarcoidosis. Confluent pink-brown nodules.

Yellow to yellow-pink
Certain cell types (e.g., granulomatous/histiocytic)
Keratin (e.g., cyst)
Sebaceous lesion
Connective tissue
Lipid
Deposition (e.g., urate in gout, hemosiderin in bruise)

Xanthelasma. Yellow plaques on the eyelid.

Purple-pink (in lighter skin)
Dense lymphocytes
Vascular lesions

Lichen planus (pruritic purple polygonal papules; the wrist is a commonly affected site).

Photographs from Ko CJ. *Dermatology: Visual Recognition*. Elsevier; 2017; Bolognia JL, Jorizzo JL, Schaffer JV. *Dermatology,* 3rd ed. London: Saunders; 2012, and the Yale Dermatology Residents' Collection.

TABLE 403-7 IMPORTANT CLUES FROM THE HISTORY AND GENERAL HEALTH STATUS

CLUES	POSSIBLE DIAGNOSES	
Pruritus (itch)	Atopic dermatitis (eczema) Allergic contact dermatitis Urticaria Scabies	Bullous pemphigoid Lichen planus Dermatitis herpetiformis Inflammatory tinea pedis
Absence of pruritus	Acne vulgaris Rosacea Syphilis	Skin malignancies Lupus erythematosus Pemphigus vulgaris Erythema multiforme
Pain	Herpes zoster Ischemic necrosis from all causes Cellulitis Furunculosis	Carbuncles Pyoderma gangrenosum Severe systemic illnesses
Medications (especially new)	Severe drug eruptions Fixed drug eruptions Morbilliform drug eruptions Immunosuppression	Subacute cutaneous lupus Psoriasis exacerbation Urticaria Drug-induced hair loss
Cachexia/malnutrition	Paraneoplastic dermatoses Skin malignancy Alcohol exacerbated psoriasis	Nutritional deficiencies Metastatic disease Eating disorders leading to nutritional deficiencies
Obesity or weight gain	Dermatoses of diabetes Thyroid disease Cushing disease Polycystic ovarian syndrome Acne	Hirsutism Striae Acanthosis nigricans Eruptive xanthomas
Poor hygiene	Bacterial skin infections Infestations	Substance abuse
Psychiatric illness	Self-inflicted skin disease	Drug-induced dermatoses

TABLE 403-8 APPROACH TO THE ADULT WITH AN ACUTE FEVER AND RASH*

CATEGORY	DISEASES	CLUES ON SKIN EXAMINATION
Infectious	Potentially life-threatening systemic infection (viral, bacterial, fungal†, protozoal†) • Disseminated herpes zoster or herpes simplex† (see Fig. 403-3) • Meningococcemia (see Fig. 403-4) • Toxic shock syndrome (see Fig. 403-5) Disseminated fungal diseases (see Fig. 403-6)† Candidiasis Histoplasmosis Cryptococcosis • Protozoal† Strongyloidiasis Usually not immediately life-threatening • Viral exanthems due to enteroviruses, HHV-6, adenovirus; HIV, varicella; Kaposi varicelliform eruption • Bacterial: staphylococcal scalded skin syndrome, secondary syphilis, disseminated erythema migrans (Lyme disease)	Multiple (>2-3 to 100s), discrete lesions, scattered over body, suggesting hematogenous spread **Herpes viruses:** primary lesion is the vesicle **Meningococcemia:** retiform purpura affecting multiple different body sites, including above the waist **Toxic shock syndrome:** acute erythema of palms/soles **Strongyloidiasis:** periumbilical purpura
Inflammatory	Potentially life-threatening • Toxic epidermal necrolysis (see Fig. 403-7) Usually not immediately life-threatening • Drug reactions (severe drug reactions): morbilliform, serum sickness-like reaction, DRESS, AGEP, erythroderma • Erythema multiforme • Primary cutaneous disorders (e.g., pustular psoriasis) • Rheumatologic disorders (e.g., SLE, vasculitis, Still disease) • Graft-versus-host disease	Confluent erythema, scale peeling off in sheets, necrosis of skin (gray areas), widespread bullae, severe mucositis (see Fig. 403-8) **DRESS:** facial edema
Other	Potentially life-threatening • Disseminated intravascular coagulation (see Fig. 403-9) Usually not immediately life-threatening • Neoplastic (e.g., lymphoma) • Inherited (e.g., periodic fever syndromes)	Widespread retiform purpura, including above the waist

*Not a single site, as in cellulitis or necrotizing fasciitis.

†More likely in immunocompromised patient.

AGEP = acute generalized exanthematous pustulosis; DRESS = drug reaction with eosinophilia and systemic symptoms (also referred to as DIHS = drug-induced hypersensitivity syndrome); HHV = human herpes virus; HIV = human immunodeficiency virus; SLE = systemic lupus erythematosus.

Adapted from Bolognia JL, Schaffer JV, Duncan KO, Ko CJ. *Dermatology Essentials*. Elsevier; 2014.

FIGURE 403-3. Disseminated varicella-zoster virus. Widespread, individual papules and vesicles, many with hemorrhage. Note the absence of coalescence into larger bullae.

FIGURE 403-4. Acute meningococcemia. Retiform purpura with irregular outline and grayish-red color. (Courtesy Kalman Watsky, MD. From Bolognia JL, Jorizzo JL, Schaffer JV. *Dermatology,* 3rd ed. Philadelphia: Saunders; 2012.)

FIGURE 403-5. Toxic shock syndrome. Acute erythema in a swim-trunk distribution can be an early sign of toxic shock syndrome. Similar erythema occurs on dorsal hands and feet. Peeling of the skin in these areas occurs 1 to 2 weeks later.

FIGURE 403-6. Mucormycosis. Angioinvasive organisms led to extensive microvascular occlusion, with skin findings of purpura, necrosis, and sloughing.

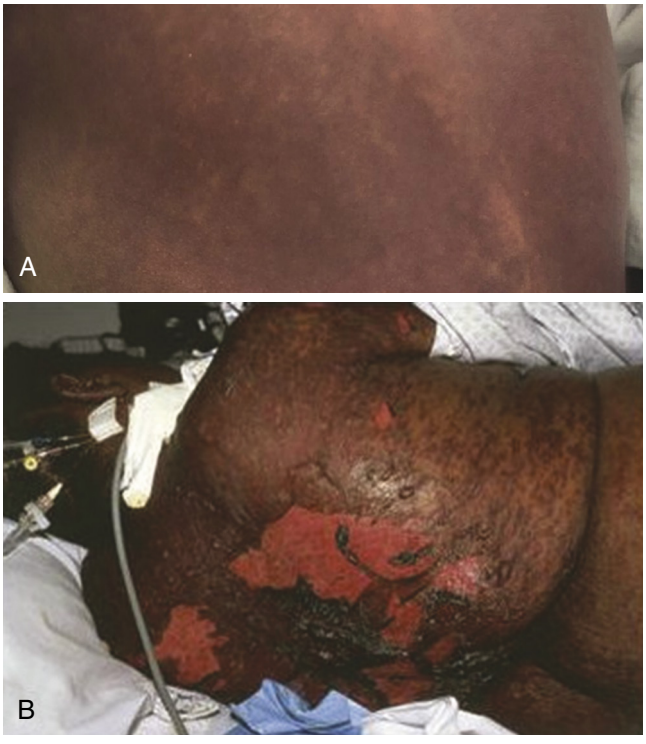

FIGURE 403-7. Toxic epidermal necrolysis. A, Early on, only erythema may be seen. **B,** Detachment of large sheets of necrolytic epidermis (>30% body surface area), leading to extensive areas of denuded skin. A few intact bullae are still present. (From Bolognia JL, Jorizzo JL, Schaffer JV. *Dermatology,* 3rd ed. Philadelphia: Saunders; 2012:328, Fig. 20.10A.)

FIGURE 403-8. Mucositis (Stevens-Johnson syndrome). Extensive erosive changes on lips and oral mucosa are highly suggestive of a severe drug eruption such as Stevens-Johnson syndrome or toxic epidermal necrolysis.

FIGURE 403-9. Disseminated intravascular coagulation. Noninflammatory (without underlying erythema) retiform purpura as well as hemorrhagic bullae in a patient with disseminated intravascular coagulation (DIC). (Courtesy Judit Stenn, MD. From Bolognia JL, Jorizzo JL, Schaffer JV. *Dermatology,* 3rd ed. Philadelphia: Saunders; 2012.)

FIGURE 403-10. Vesicles and bullae (bullous pemphigoid). Large bullae as well as smaller bullae and vesicles on a background of urticaria-like erythema.

FIGURE 403-11. Severe allergic contact dermatitis. Bullae and vesicles on a background of erythema. Severe cases such as this can be mistaken for the autoimmune disease bullous pemphigoid.

TABLE 403-9 APPROACH TO THE PATIENT WITH GENERALIZED PRURITUS AND NO OBVIOUS SKIN-SPECIFIC DISEASE

HISTORY
Complete history and review of systems • Consider risk factors for scabies (e.g., nursing home resident, close contact with recent diagnosis, symptoms in household contacts) • Ask about dermographism (exaggerated tendency to develop wheals with scratching of the skin—a type of physical urticaria), xerosis, irritants, occupational exposures • Review all medications (prescription,* OTC, supplements, illicit)
PHYSICAL EXAMINATION
Complete skin examination Lymph node examination
SCREENING LABORATORY TESTS
CBC with differential and platelets ESR and LDH TSH BUN/creatinine Liver function tests
ADDITIONAL EVALUATION (AS INDICATED BY AGE, HISTORY, COMORBID CONDITIONS, AND SCREENING TESTS)
Additional blood tests • Serum fasting glucose and Hgb A_{1c} • Serum calcium and phosphate levels • Albumin level • Ferritin, iron studies • Anti–tissue transglutaminase antibodies • Viral hepatitis screen • HIV testing Other tests • Chest radiograph • Age-appropriate cancer screening examinations • Stool exam for ova and parasites • Endoscopy

*Drug-induced pruritus: major culprits include calcium-channel blockers, proton pump inhibitors, narcotics, and amphetamines.

BUN = blood urea nitrogen; CBC = complete blood count; ESR = erythrocyte sedimentation rate; Hgb = hemoglobin; HIV = human immunodeficiency virus; LDH = lactate dehydrogenase; OTC = over-the-counter; TSH = thyroid-stimulating hormone.

Adapted from Bolognia JL, Schaffer JV, Duncan KO, Ko CJ. *Dermatology Essentials*. Elsevier; 2014.

pruritus and no signs of a specific skin disorder, a comprehensive diagnostic approach is indicated (Table 403-9)[12] to detect causes of pruritus as diverse as occult skin disease (scabies), medications (especially calcium-channel blockers, proton pump inhibitors, narcotics, and amphetamines), renal failure (Chapter 100),[13] cholestatic liver disease (Chapter 141),[14] hyperthyroidism (Chapter 207), myeloproliferative disorders (Chapter 152), parasitic infections, diabetes mellitus (Chapter 210), and celiac disease (Chapter 126). Anxiety and depression are often associated with chronic pruritus.[15]

TREATMENT

Treatment of pruritus can be tailored according to its probable cause. For primary dermatoses, such as eczema (Chapter 405), specific disease-related treatments will also reduce pruritis. For example, gabapentin is the preferred treatment for the pruritus of renal failure,[A1] bezafibrate is effective for the itch of cholestatic diseases,[A2] and ondansetron (4 mg intravenously) is effective for otherwise refractory morphine-induced pruritus.[A3] Itching from dry skin, such as eczema (Chapter 405), cholestatic jaundice (Chapter 141), hypothyroidism (Chapter 207), or myeloproliferative diseases (Chapter 152) may respond to over-the-counter emollients (Table 403-10). A mainstay of treatment of skin inflammation causing pruritus is topical corticosteroids or topical calcineurin inhibitors. Urticaria, which is an inflammatory disease of the skin with histamine release from mast cells in the dermis, can be treated with oral antihistamines.[16,A4] Other forms of pruritus may not respond directly to antihistamines (see Table 404-3), but antihistamines nevertheless may help the patient because of their sedative effects. For pruritus that originates in afferent nerves, capsaicin can be helpful over the long term because it depletes neural stimulatory peptides. Pruritus that is more centrally caused may respond to oral medications such as naltrexone or gabapentin, and mirtazapine may be helpful for patients in whom depression or anxiety play an important role.[17] For inflammatory skin disease as well as systemic causes of pruritus, ultraviolet light therapy also can be helpful.

TABLE 403-10 TREATMENT OF PRURITUS

TOPICAL AGENTS
Emollients
Eucerin (e.g, Skin Calming Crème), CeraVe (e.g., Itch Relief Moisturizing Cream), Aveeno (e.g. Eczema Therapy Moisturizing Cream) as needed daily
Corticosteroid ointment (corticosteroids should be discontinued following clinical response; medium- to high-potency steroids should not be used continuously for more than 2 weeks)
Low potency: hydrocortisone 2.5% cream, one to two times daily as needed
Medium potency: desoximetasone cream 0.05%, one to two times daily as needed
High potency: clobetasol cream 0.05%, one to two times daily as needed
Calcineurin inhibitors
Tacrolimus 0.03 and 0.1% ointment, one to two times daily as needed
Pimecrolimus 1% cream, one to two times daily as needed
Anesthetic agents (can be especially useful for neuropathic itch)
Capsaicin 0.025% cream, four times daily
Pramoxine 1%-hydrocortisone 2.5% lotion, cream, or ointment one to two times daily as needed
SYSTEMIC MEDICATIONS
Antihistamines (see Table 404-3)
Antidepressants
Mirtazapine 15 mg PO at bedtime
Opioids
Naltrexone 50 mg/day PO for cholestatic pruritus
Anticonvulsants
Gabapentin PO 300 mg three times/week after dialysis for pruritus in renal dialysis patients
Ultraviolet B radiation one to three times/week for six to eight exposures

PO = orally.

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404 PRINCIPLES OF THERAPY OF SKIN DISEASES

VICTORIA P. WERTH AND APRIL W. ARMSTRONG

The goal of therapy is to improve a skin condition with the least toxic and most specific approach. Because many treatments or medications can be applied directly to the skin, the option for topical therapy is attractive for treating many dermatologic diseases. However, many diseases require systemic therapy, particularly when patients have widespread involvement of the skin or a disease that cannot be improved with topical therapy. Therapies work by improving barrier function, removing scale, altering inflammation in the skin, altering blood flow, providing antimicrobial effects, or affecting proliferating cells. Recent advances in the understanding of cutaneous biology have not been routinely accompanied by evidence-based documentation of the benefits of many specific therapies.

PRINCIPLES OF TOPICAL THERAPY

SOAKS AND DRESSINGS

Water or saline applied by soaks and wet dressings can be beneficial for many skin conditions, including ulcers, by promoting healing of the epidermis and débridement of crusts. Soaked gauze is applied to involved areas for 15 to 30 minutes several times per day, and care should be taken not to allow the gauze to dry and adhere. If adherence occurs, the gauze should be soaked before the dressing is removed. Use of strong antiseptic solutions, including hydrogen peroxide, is not recommended because of toxicity to cells. Whirlpool action can enhance débridement. When large areas of skin are involved, baths are a convenient way to treat the skin with medications that reduce itching and inflammation. The best time to apply moisturizers that help trap water in the upper layers of skin is immediately after a bath or shower.

Wet-to-dry dressings are rarely used, except when initial vigorous wound débridement is necessary. Continued use after wounds are débrided traumatizes wounds and delays healing. Moist wound healing, which is often ideal, can be accomplished with a topical antibiotic such as a combination of polymyxin B and bacitracin (Polypore) or mupirocin (Bactrian), gauze impregnated with petrolatum (Vaseline), or an occlusive hydrocolloid dressing. Little evidence indicates that débriding enzymes are beneficial. Compression with an Unna or multilayered boot, which includes an elastic dressing such as Coban, can decrease local edema and facilitate wound healing. Polysporin/petrolatum gauze or occlusive dressings are placed underneath, an approach that is helpful for chronic venous, diabetic, and pressure ulcers, as well as for acute wounds. Closed wet dressings, in which gauze is soaked and then covered with an impervious material, can help when maceration and heat retention are needed. Biologic dressings with skin substitutes or keratinocytes can be beneficial for wounds that are resistant to healing.[A1] Skin grafts also can facilitate healing of otherwise nonhealing wounds. Platelet-derived growth factor, which is approved for use on diabetic ulcers, can modestly improve wound healing.

TOPICAL MEDICATIONS

Topical medications mix an active drug with preservatives, emulsifying agents, and an appropriate base or vehicle. Systemic absorption varies among patients, sites, and vehicles. Topically applied drugs are absorbed more readily through inflamed, thin skin. The base can be any of the following: a *powder*, which promotes dryness and is used to reduce maceration in intertriginous areas; a *lotion*, which is a suspension of oil in water; *solutions*, which include water, alcohol, and propylene glycol, but not oil; *gels*, which are solid at room temperature but melt on contact with the skin; a *cream*, which is an emulsion of oil in water that leaves a thin oil coating as the water evaporates; an *ointment*, which combines oils, such as petrolatum (Vaseline), with small amounts of water and which is more occlusive and hence increases the absorption of medication but also results in a greasier appearance; a *paste*, which is a mixture of powder and ointment; *foam*, which enables rapid deposition of active drug on the skin surface after the body heat evaporates inert contents; or a *spray*. Lotions, solutions, and gels provide less penetration than ointments do, but they are especially useful for the treatment of hair-bearing areas such as the scalp, where greasiness is displeasing. Creams are less greasy than ointments and are useful for the face, groin, and intertriginous areas. Ointments are often more effective for dry, scaly conditions such as eczema and psoriasis and are helpful in areas that have thick skin, such as the palms and soles, but they should be avoided in infected or intertriginous areas.[1] The choice of base is determined by the skin condition and location. Impregnated tapes are another delivery method to provide occlusion and protect the skin from manipulation. Active drugs with different optimal pH can now be combined with specialized bases.

ANTI-INFLAMMATORY AGENTS

GLUCOCORTICOIDS

Topical glucocorticoids work because of their effects on vasoconstriction, proliferation, immunosuppression, and inflammation. Assays related to the ability to vasoconstrict and clinical trials of efficacy have allowed glucocorticoids to be divided into various classes based on potency (Table 404-1). These

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ABSTRACT

The goal of therapy is to improve a skin condition with the least toxic and most specific approach. Because many treatments or medications can be applied directly to the skin, the option for topical therapy is attractive for treating many dermatologic diseases. However, many patients require systemic therapy, particularly when they have widespread involvement of the skin or a disease that cannot be improved with topical therapy. Therapies work by improving barrier function, removing scale, altering inflammation in the skin, altering blood flow, providing antimicrobial effects, or affecting proliferating cells.

KEYWORDS

therapy
topical therapy
glucocorticoids
anti-inflammatory agents
antiviral therapy
immunomodulatory therapy

TABLE 404-1 RANKING OF SOME COMMONLY USED TOPICAL STEROIDS BY POTENCY

Super potency	Clobetasol propionate (Temovate ointment and cream), betamethasone dipropionate (Diprolene cream and ointment), diflorasone diacetate (Psorcon E ointment), halobetasol propionate (Ultravate ointment)
High potency	Amcinonide, mometasone furoate ointment, diflorasone diacetate (Florone ointment), halcinonide 0.1% cream, fluocinonide, desoximetasone, triamcinolone acetonide, diflorasone diacetate ointment and cream, betamethasone dipropionate (Diprosone), betamethasone benzoate and valerate
Medium potency	Fluticasone propionate; mometasone furoate cream; halcinonide 0.25% ointment; triamcinolone acetonide 0.1% cream and lotion; fluocinolone acetonide 0.05%, and 0.1% cream, 0.1% and 0.25% ointment, and 0.5% solution; hydrocortisone valerate 0.2% ointment and cream; alclometasone dipropionate 0.5% ointment; betamethasone dipropionate 0.5% lotion; hydrocortisone butyrate 0.1% cream; betamethasone benzoate 0.25% cream; betamethasone valerate 0.1% cream and 0.5% lotion; flumethasone pivalate 0.3% cream; desonide 0.5% cream
Low potency	Hydrocortisone 1% cream

TABLE 404-2 CLINICAL APPLICATION OF TOPICAL GLUCOCORTICOIDS

Super potency and high potency	Plaque and palmoplantar psoriasis, lichen planus, dyshidrotic eczema, lichen simplex chronicus, granuloma annulare, sarcoidosis
Medium potency	Dermatitis: allergic contact, atopic, neurodermatitis
Low potency	Intertrigo, pruritus ani, seborrheic dermatitis

medications are typically used twice per day. Side effects include atrophy of the skin, telangiectases, purpura, striae, local skin infections (e.g., folliculitis, tinea, and candidiasis), hypopigmentation, hypertrichosis, systemic adrenal suppression when these agents are used on as little as 20% of the skin's surface area, and glaucoma when they are used around the eye. Side effects are especially prevalent when fluorinated steroids are used on thin skin (e.g., face, groin, or scrotum), and prolonged use on the face can result in facial dermatitis, acne, and an eruption resembling acne rosacea that is often exacerbated when use of the steroid is terminated. Certain conditions are more responsive to steroids, and the potency of the steroid chosen must be based on the condition and its location (Table 404-2). The superpotent class I agents should be restricted to patients with severe dermatoses, and their use normally should not exceed 2 weeks. Patients who receive these potent agents require frequent follow-up and must be carefully evaluated for the need to continue strong topical steroids. Use of any fluorinated steroid on the face requires an exact diagnosis and should be limited in the extent of application and duration of use. Intralesional glucocorticoids can be injected into individual lesions to improve delivery of the medication, and this method is commonly used to treat patients with acne cysts, hypertrophic scars, keloids, alopecia areata, granuloma annulare, discoid and panniculitic lupus erythematosus (Chapter 245), psoriasis, and lichen simplex chronicus. Triamcinolone acetonide is most frequently used, followed by the longer-acting triamcinolone hexacetonide. It is important to use proper dilutions, such as 1 to 2.5 mg/mL on the face and 5 mg/mL elsewhere, to avoid local skin atrophy. Because these drugs vary widely in price and often require at least some out-of-pocket patient payments, physicians can help their patients by being knowledgeable about their prices.

Systemic glucocorticoids are used for acute and chronic conditions in dermatology, but they should be avoided, if possible, or minimized because of their well-known side effects (Chapter 28). Acute conditions that commonly require systemic steroids include severe contact dermatitis such as poison ivy, photodermatitis, severe atopic dermatitis, and acute urticaria. Many skin conditions such as psoriasis and eczema become exacerbated when use of the steroids is tapered, so steroids should be avoided when possible in these conditions. The dose of steroid must be individualized to the condition and its severity. Steroid-sparing drugs, such as immunosuppressive or immunomodulatory agents, can be used to minimize the long-term use of steroids for selected conditions.

NONSTEROIDAL ANTI-INFLAMMATORY AGENTS

Psoriasis Therapies

Tars and anthralin are less commonly used for psoriasis (Chapter 405) than are other agents. Tars had been most commonly used in conjunction with ultraviolet B (UVB) light. Tars also are used in shampoos and bath oils to treat seborrhea and psoriasis. Anthralin is a synthetic hydroxyanthrone that inhibits keratinocyte proliferation; it stains and can be irritating, but it can be an effective therapy (Chapter 405).

Calcipotriol

Calcipotriol is a vitamin D derivative that has antiproliferative and immunomodulatory effects on skin. Hypercalcemia can occur if more than 100 g/week is used, so this agent cannot be used for widespread disease. It is applied twice daily, can be irritating on thin skin, and takes 6 to 8 weeks to be effective.

Retinoids

The retinoids are a group of compounds that include vitamin A and its derivatives. Their effects are mediated through several different classes of receptors, and the receptor-drug complex has effects on other regulatory proteins that affect growth factors, oncogenes, keratins, or transglutaminases. Retinoids affect cell growth, differentiation, and morphogenesis; inhibit tumor promotion and malignant cell growth; have immunomodulatory effects; and alter cell cohesion.

Topical retinoids include all-*trans*-retinoic acid (tretinoin), which is approved for acne (Retin-A) and photoaging (Renova 0.05% cream) and is also useful for hyperpigmentation, steroid-induced atrophy, and early stretch marks.[1] Tretinoin is available as a cream (0.025%, 0.05%, 0.1%), a gel (0.01%, 0.025%), and a solution (0.05%). Adapalene (Differin 0.1% gel) and tazarotene (Tazorac) are used for acne (Chapter 406). Tazarotene is also used for psoriasis, often in combination with topical steroids to minimize irritation and chronic photodamage. Bexarotene (Targretin) 1% gel is used for the topical treatment of cutaneous lesions in patients who have refractory or persistent stage IA or IB cutaneous T-cell lymphoma. Topical retinoids can be irritating and frequently cause an exacerbation before improvement. However, they should be used regularly on lesion-prone skin to produce improvement. Moisturizers may be needed to minimize drying effects.

Systemic retinoids commonly used for the skin include isotretinoin, acitretin, and bexarotene (Targretin). They have many applications, but most frequently isotretinoin (Accutane) is used for cystic and conglobate acne, acitretin for severe psoriasis (especially the erythrodermic and pustular forms), and bexarotene for cutaneous T-cell lymphoma. Isotretinoin and acitretin also have been used to treat several forms of ichthyosis and lupus erythematosus and for the chemoprevention of skin cancers, particularly in immunosuppressed transplant recipients. The many side effects of systemic retinoids include teratogenicity, cheilitis, hair loss, headaches, hyperlipidemia, abnormal liver enzyme levels, vertebral hyperostosis, tendon and ligament calcification, osteoporosis, and central hypothyroidism with bexarotene. Pregnancy must be avoided, and the use of retinoids in women of childbearing age therefore requires careful monitoring. Treatment of acne is reserved for cases of cystic acne not responding to less toxic therapies; in this setting, a 4- to 5-month course of Accutane, 0.5 to 1 mg/kg/day, is curative in 85 to 90% of patients.

OTHER AGENTS

Brimonidine and Oxymetazoline Hydrochloride

Brimonidine gel is a selective α_2-adrenergic receptor agonist. Oxymetazoline hydrochloride is an α_1-adrenergic receptor agonist. Both have vasoconstrictive activity and are used topically for rosacea.[A2] Crisaborole is a boron-based phosphodiesterase 4 inhibitor that increases intracellular cyclic adenosine monophosphate (cAMP) levels. It is applied as an ointment to treat atopic dermatitis.

Antimalarial and Antiparasitic Drugs

Aminoquinolines include hydroxychloroquine, quinacrine, and chloroquine. These agents have inhibitory effects on pro-inflammatory cytokine production, DNA replication, and chemotaxis. They are useful in patients with connective tissue diseases, polymorphous light eruption, sarcoidosis (Chapter 83), porphyria cutanea tarda (Chapters 194 and 406), sclerosing conditions,

and vasculitis. Side effects include diarrhea, headache, irritability, psychosis, skin dyspigmentation, and, rarely, retinopathy. Retinopathy is rare if doses of hydroxychloroquine are ≤5 mg/kg/day actual body weight or ≤2.3 mg/day for chloroquine. Combinations of hydroxychloroquine or chloroquine with quinacrine are frequently helpful when a solitary agent is inadequate. The combination of hydroxychloroquine and chloroquine should not be used because of the additive risk for retinopathy. Ivermectin cream is a broad-spectrum antiparasitic agent used for rosacea.[A3]

Dapsone

Dapsone is a sulfone that inhibits the response of neutrophils and possibly eosinophils to chemotactic stimuli. It is useful for dermatitis herpetiformis (Chapter 406), cutaneous vasculitis (Chapter 407), pyoderma gangrenosum (Chapter 407), bullous lupus erythematosus (Chapter 245), Behçet disease (Chapter 249), and autoimmune bullous diseases (Chapter 406). Topical 5% gel is approved for use in acne. Systemic use can be associated with side effects that include hemolysis, methemoglobinemia, peripheral neuropathy, agranulocytosis, and, rarely, a hypersensitivity syndrome with hepatitis, fevers, and rash. The glucose-6-dehydrogenase level should be checked before starting the drug, and it is common for patients with a normal glucose-6-dehydrogenase level to experience a 2-g/dL decrease in hemoglobin after achieving therapeutic doses of 100 to 200 mg/day.

Thalidomide and Lenalidomide

Thalidomide and lenalidomide have potent anti-inflammatory effects via their effects on two transcription factors that bind to cereblon. It also modifies adhesion molecules on circulating leukocytes. Thalidomide is a serious teratogen, and patients must comply with strict birth control and monitoring. It is effective at a dose of 50 to 100 mg/day, with improvement beginning in 2 weeks and a full clinical response seen in 2 to 3 months in patients with severe cutaneous lupus erythematosus (Chapter 245), erythema nodosum leprosum (Chapter 405), aphthae, Behçet disease (Chapter 249), scleromyxedema, actinic prurigo, chronic graft-versus-host disease (Chapter 163), multiple myeloma (Chapter 173), and numerous other inflammatory dermatoses. Besides teratogenesis, the main side effects include peripheral neuropathy, constipation, sedation, and, rarely, amenorrhea.

Colchicine

Colchicine, usually at a dose of 0.6 mg twice daily, is used for leukocytoclastic vasculitis (Chapter 406) and Behçet disease, as well as some patients with epidermolysis bullosa acquisita. The main side effect of this low oral dose is diarrhea.

ANTIMICROBIAL AGENTS

ANTIBACTERIALS

Topical antibiotics are used to treat superficial skin diseases, such as acne and folliculitis, as well as skin wounds and ulcers. They may work by decreasing neutrophil chemotaxis and other anti-inflammatory mechanisms. Topical solutions, gels, pledgets, and ointments are available, depending on the agent, and antibiotics include erythromycin, clindamycin, tetracycline, and metronidazole.[2] Benzoyl peroxide also has antibacterial properties and is quite effective for mild-to-moderate acne, while also minimizing bacterial resistance when topical antibiotics are also used (Chapter 406). Bacitracin and Polysporin ointments are typically used for wounds, but they can cause contact hypersensitivity; neomycin should be avoided because of the high incidence of allergic reactions. Mupirocin is particularly effective against *Staphylococcus* and *Streptococcus* spp., and it can be used in the nose for carriers of staphylococci. Systemic antibiotics such as penicillins, cephalosporins, and erythromycin are used in patients with soft tissue infections such as impetigo, folliculitis, furuncles, carbuncles, cellulitis, ecthyma, erysipelas, postoperative wound infections, and necrotizing fasciitis. Tetracycline, doxycycline, and minocycline are used for acne,[3,4] rosacea, and perioral dermatitis. Fluoroquinolones such as ciprofloxacin are useful for the treatment of gram-negative soft tissue infections.

ANTIFUNGALS

Topical antifungal agents are used in patients with limited superficial fungal infections of the skin (Chapter 405). The numerous topical antifungal drugs available include the azoles (clotrimazole, econazole, ketoconazole, oxiconazole, and miconazole), which are available as creams and lotions applied once or twice daily. The creams tend to be more effective. Topical agents used for dermatophytes, but not *Candida*, are haloprogin and tolnaftate. The newer allylamine antifungals naftifine and terbinafine have fungicidal effects. Ciclopirox 8%, efinaconazole, and tavaborole are used topically to treat and prevent relapses of onychomycosis, but they are not as efficacious as systemic therapy (Chapter 409).[A4] Nystatin creams, oral suspensions, and vaginal tablets are effective for the treatment of *Candida* infections. The combination of antifungals with potent topical steroids such as betamethasone dipropionate is not advised because of increased side effects from the steroid and decreased efficacy of the antifungal as a result of the concomitant steroid.

Systemic antifungal agents include griseofulvin, terbinafine (allylamine), ketoconazole (imidazole), itraconazole, and fluconazole. These agents are used for extensive or severe superficial skin fungal infections (Chapter 405) caused by dermatophytes, *Candida*, or *Malassezia furfur* or for local infections not responsive to topical drugs, such as those found in the nails and scalp. Itraconazole and terbinafine are the only oral antifungals approved in the United States for the treatment of onychomycosis,[A5] and griseofulvin is the only oral agent approved for tinea capitis. Griseofulvin is best taken with a fatty meal to improve absorption and is the only antifungal drug not requiring regular monitoring of liver enzymes. Griseofulvin shows weak affinity for keratin, and thus it must be used for 18 months for onychomycosis of the toenails and 6 months for the fingernails to achieve even relatively poor cure rates. Terbinafine is the only fungicidal drug; the rest are fungistatic. The number of interactions with medications is lower with terbinafine than with the triazole antifungals and ketoconazole because terbinafine does not inhibit or induce hepatic isoenzyme cytochrome P (CYP3A4) (Chapter 25). However, terbinafine affects CYP2D6, another hepatic isoenzyme, so it is relatively contraindicated in patients who are taking cyclosporine or rifampin. Itraconazole and fluconazole have been used in pulse-dosing regimens for the treatment of onychomycosis. Fluconazole and terbinafine are not dependent on gastric acidity for optimal gastrointestinal absorption. Overall, the side effects of the systemic antifungal agents are similar and include headache and gastrointestinal symptoms (griseofulvin, terbinafine), nausea and vomiting (itraconazole, fluconazole, ketoconazole), hepatitis, and lupus-like syndromes (terbinafine).

ANTIVIRALS

Verrucae are treated with various destructive modalities, including 50 to 80% dichloroacetic acid and trichloroacetic acid solutions, podophyllin resin, and podofilox.[5] Immunosuppressed patients may benefit from treatment with intralesional cidofovir. Topical antiviral creams such as penciclovir and acyclovir do not significantly shorten the course of herpes simplex. Systemic antiviral drugs include acyclovir, valacyclovir, famciclovir, and foscarnet, which are used to treat primary and recurrent herpes simplex (Chapter 345) and herpes zoster (Chapter 346). These agents specifically block the function of herpesvirus DNA polymerase. Valacyclovir and famciclovir are available only orally in the United States, but their prolonged intracellular half-life allows less frequent dosing than with acyclovir. Patients with herpes zoster require higher doses than do patients with herpes simplex. Side effects include nausea and headaches. The varicella-zoster vaccine has significantly decreased the incidence of herpes zoster in individuals older than 50 years of age, and current recommendation is for vaccination after the age of 50 with Shingrix (Chapter 15). If possible, it should be administered before starting oral immunosuppressive agents.

ANTIPARASITICS

Topical antiparasitic medications are used to treat pediculosis capitis, pediculosis pubis, and scabies. In addition, topical metronidazole has anti-inflammatory properties and is used to treat rosacea. For pediculosis and scabies, clothing and bedding must be washed and all family members must be treated. Effective treatment includes 1% γ-benzene hexachloride (lindane), a chlorinated hydrocarbon pesticide that should not be used on young children or on pregnant or lactating women. It is ineffective against nits and thus must be reapplied after 1 week. Permethrin 5% cream (Elimite) for scabies or 1% cream rinse is particularly effective for head lice and requires just one application; 10% crotamiton (Eurax) and 5% topical sulfur ointments are less effective. Malathion is a moderately toxic organophosphate insecticide, but it must be applied overnight to treat lice. Pyrethrins (RID, Nix) are best used twice, 1 week apart, to treat head lice and nits.

ANTIPRURITIC OR ANESTHETIC AGENTS

TOPICAL ANALGESICS

Capsaicin, an active ingredient of cayenne peppers and other plants of the genus *Capsicum*, is used for postherpetic neuralgia and other painful nerve-related

TABLE 404-3 OVERVIEW OF ANTIHISTAMINES

ANTIHISTAMINE GROUP	GENERIC NAME	AVERAGE ORAL ADULT DOSES
FIRST-GENERATION H_1-TYPE ANTIHISTAMINES		
Alkylamine	Brompheniramine (Dimetapp)	4 mg q4-6h
	Chlorpheniramine (Chlor-Trimeton)	4 mg q4-6h (short acting); 8-12 mg q8-12h (long acting)
Amino alkyl ether (ethanolamine)	Clemastine fumarate	1.34 mg bid or 2.68 mg qd-tid
	Diphenhydramine (Benadryl)	25-50 mg q4-6h
Ethylenediamine	Pyrilamine (Triaminic)	30 mg bid
Phenothiazine	Promethazine (Phenergan)	10-12.5 mg qid
	Trimeprazine (Temaril)	2.5 mg q6h
Piperidine	Azatadine	1-2 mg q8-12h
	Cyproheptadine	4 mg q8h
	Diphenylpyraline	2 mg tid-qid
Piperazine	Hydroxyzine (Atarax)	25-100 mg tid-qid
SECOND-GENERATION H_1-TYPE ANTIHISTAMINES		
Alkylamine	Acrivastine (combined with pseudoephedrine in allergy medication)	8 mg qid
Piperidine	Astemizole (Hismanal)	10 mg qd
	Loratadine (Claritin)	10 mg qd
	Fexofenadine (Allegra)	60 mg bid or 180 mg qd
Piperazine	Cetirizine (Zyrtec)	5-10 mg/day
H_2-TYPE ANTIHISTAMINES		
	Cimetidine (Tagamet)	400 mg bid
	Ranitidine (Zantac)	150 mg bid
	Famotidine	10 mg bid
	Nizatidine	300 mg hs
H_1- AND H_2-TYPE ANTIHISTAMINES		
	Doxepin (Sinequan)	10-25 mg hs

bid = twice daily; hs = at bedtime; qd = once daily; qid = four times daily; tid = three times daily.

conditions. It causes excitation of neural afferent C fibers and reduces substance P levels. Capsaicin causes a burning sensation and is applied four or five times daily for 5 to 6 weeks. Eutectic mixture of local anesthetic (EMLA) is a mixture of lidocaine and prilocaine that is used under occlusion to induce cutaneous anesthesia before a procedure. Lidocaine can be used as a topical anesthetic, but benzocaine should be avoided because it is a sensitizer.

ANTIPRURITIC AGENTS

Doxepin 5% cream is used for localized pruritus. Menthol is a cyclic terpene plant alcohol used for non–histamine-related itching. Pramoxine hydrochloride is a topical anesthetic used for mild-to-moderate itching. Oral antihistamines play an important role in controlling pruritus in many skin conditions (Table 404-3), especially those mediated by histamine, such as urticaria, angioedema, and urticaria pigmentosa. H_1-receptor antihistamines are the cornerstones of routine therapy. The sedating and anticholinergic properties of many H_1-receptor antihistamines probably account for some of their efficacy. Compared with the first-generation H_1-receptor antihistamines, second-generation H_1-receptor antihistamines are less sedating and therefore are now more commonly used as among the first-line agents.[A6] If an agent from one group of H_1-receptor antihistamines is ineffective at one dose, consider dose-escalating that agent. If dose escalation fails, an agent from a different class should be administered or combined. The combination of two different H_1-receptor antihistamines can be used when a solitary agent does not work; in particular, use of a sedating antihistamine at night and a second-generation antihistamine during the day can be helpful. The skin contains both H_1- and H_2-receptors, and occasionally combining H_1- and H_2-receptor antagonists can be beneficial. For example, first-generation agents (e.g., hydroxyzine, 10 to 25 mg every 6 hours) can be started at low doses and increased as tolerated, and regular continuous dosing is recommended. The tricyclic antidepressant doxepin, normally started at 10 to 25 mg at bedtime, has both anti–H_1- and H_2-receptor activity, but it interacts with drugs metabolized by the CYP-450 pathway. Side effects of commonly used first-generation antihistamines include sedation, dry mouth, blurred vision, constipation, and urinary retention, and lower doses may be required in elderly patients. The recommended dose for second-generation antihistamines (e.g., fexofenadine, 60 mg twice daily) should not be exceeded. Newer antipruritic agents target interleukins 4, 13, and 31 (e.g., dupilumab for eczema; Chapter 405), immunoglobulin E (e.g., omalizumab for urticaria; Chapter 407), Janus kinase inhibitors (e.g., abrocitinib for atopic dermatitis),[A7] and phosphodiesterase inhibitors.[6]

AGENTS THAT IMPROVE SURFACE FUNCTIONS (LUBRICATION, SCALE)

MOISTURIZERS

Moisturizers improve skin by diminishing scale and increasing water content. They usually contain mixtures of water and fatty substances such as petrolatum, lanolin, lanolin derivatives, and fatty alcohols. Greasy moisturizers tend to function better, but they are less acceptable cosmetically.

KERATOLYTICS

α-Hydroxy acids (lactic acid, glycolic acid, citric acid, glucuronic acid, pyruvic acid) are extremely effective keratolytics. They are helpful in treating disorders of keratinization and photoaging, as well as acne. Propylene glycol, used in 40 to 60% aqueous solutions, can decrease scaling. Salicylic acid, which works by decreasing keratinocyte adhesion and hydrating keratins, is used in a range of concentrations with many different bases to remove scale, to soften the stratum corneum, or as destructive therapy to remove warts and calluses. Urea is used in varying concentrations to treat scaling.

IMMUNE THERAPIES

HORMONAL THERAPIES

Systemic therapies to modulate androgen production can be beneficial in patients with acne and hidradenitis suppurativa. Such treatments for moderate acne include spironolactone and, in women, U.S. Food and Drug Administration (FDA)–approved combination oral contraceptives, such as Ortho Tri-Cyclen (norgestimate and ethinyl estradiol), Estrostep (norethindrone acetate and ethinyl estradiol), and Yaz (drospirenone and ethinyl estradiol), as they would be prescribed for contraception (Chapter 220).

IMMUNOSUPPRESSIVE AGENTS

Topical cytotoxic drugs include 5-fluorouracil, mechlorethamine (nitrogen mustard), carmustine (BCNU), bleomycin, and the calcineurin inhibitors tacrolimus and pimecrolimus. Topical 5-fluorouracil interferes with pyrimidine metabolism and action and blocks DNA synthesis. It is used to treat actinic keratosis, superficial basal cell cancer, Bowen disease, bowenoid papulosis, actinic cheilitis, and warts. Topical use does not cause systemic toxicity, but expected side effects include local irritation, erythema, and pain. Nitrogen mustard and BCNU, which have alkylating agents that inhibit DNA, RNA, and protein synthesis, are used to treat cutaneous T-cell lymphoma (Chapter 171); they can cause cutaneous reactions and myelosuppression, and nitrogen mustard commonly causes a cutaneous hypersensitivity reaction.

Intralesional bleomycin, which disrupts DNA synthesis, has been used to treat warts. Topical tacrolimus (Prograf) and pimecrolimus, immunosuppressive macrolides that act on T lymphocytes to inhibit interleukin-2 (IL-2) transcription, are used for atopic dermatitis, allergic contact dermatitis, psoriasis, and several other inflammatory skin conditions. They frequently cause a burning sensation in the skin; although systemic absorption is minimal, ongoing studies are assessing whether the risk for cancer is increased by their topical use. Systemic immunosuppressives such as methotrexate, azathioprine, thioguanine, hydroxyurea, mycophenolate (CellCept), cyclophosphamide, chlorambucil, rapamycin, and cyclosporine are used for numerous inflammatory or immunologically mediated skin conditions, particularly for widespread psoriasis (Chapter 405) and as glucocorticoid-sparing agents for autoimmune blistering diseases.

IMMUNOMODULATORY THERAPIES

Imiquimod, available as a 5% cream, is an imidazoquinolinamine that has antitumor and antiviral activity. It induces local production of interferon-γ and is used to treat warts and superficial skin cancers. Topical 3% diclofenac in hyaluronic acid, which blocks the induced cyclooxygenase-2 found in precancerous lesions, is approved to treat actinic keratosis. Many systemic immunomodulatory drugs are currently used in dermatology. These include interferons and tumor necrosis factor–α (TNF-α) inhibitors such as etanercept, adalimumab, and infliximab (Remicade). Anti-IL-12/23 therapy, anti-IL-17 therapy, anti-IL-17 receptor therapy, and IL-23 inhibitors are effective for psoriasis (Chapter 405).[A8]

Anti-CD20 antibodies have been effective in the treatment of autoimmune skin-blistering diseases, and rituximab is FDA approved for pemphigus vulgaris.[A9] Intravenous immunoglobulin, which is used to treat certain autoimmune skin diseases, including pemphigus vulgaris, cicatricial pemphigoid, and dermatomyositis, probably works through Fc receptor modulation and anti-idiotype interactions.

Interferon alfa-2b is used both intralesionally and subcutaneously to treat genital warts, high-risk melanoma, Kaposi sarcoma, hemangiomas, cutaneous T-cell lymphoma, keloids, Behçet disease, and cryoglobulinemia (Chapter 173), and perhaps basal cell and squamous cell carcinoma. Total interferon doses are generally 3 million IU or less per session, and systemic doses are usually administered 3 days per week. Side effects include flulike symptoms, leukopenia, anemia, and hepatitis. Denileukin diftitox is a fusion protein consisting of a fragment of diphtheria toxin genetically fused to IL-2. It targets IL-2 receptors on the surface of malignant cells and is approved for use in patients with resistant or recurrent cutaneous T-cell lymphoma.

Histone deacetylase inhibition increases acetylation of lysine residues that form the octomeric histone core of chromatin, thereby decreasing the ability of the histones to bind to DNA. This decreased binding allows chromatin expansion, permitting transcription of the tumor suppressor genes. However, histone deacetylase inhibitors affect acetylation globally and may have wider effects on various cellular functions. Two inhibitors (vorinostat and romidepsin) are approved by the FDA for use in patients with cutaneous T-cell lymphoma.

Extracorporeal photochemotherapy (photopheresis), which combines 8-methoxypsoralen and ultraviolet A (UVA) irradiation of lymphocytes, is used for Sézary syndrome, the leukemic form of cutaneous T-cell lymphoma (Chapter 171). Plasmapheresis, used in combination with other immunosuppressive therapies, can remove autoantibodies and immune complexes in patients in whom autoimmune disease or cryoglobulinemia is resistant to other therapies.

TREATMENT FOR SKIN CANCERS (SEE CHAPTER 188)

PHOTOTHERAPY AND LASER

Ultraviolet treatments are given with different wavelengths, depending on the condition and the response to treatment. Currently, clinicians use broad-band UVB (290 to 320 nm), narrow-band 311-nm UVB, PUVA (psoralen with 320- to 400-nm UVA), and UVA1 (340 to 400 nm). Both forms of UVB and PUVA are used for psoriasis and vitiligo, but other conditions such as nummular and atopic dermatitis, pruritus resulting from uremia, and cutaneous T-cell lymphoma are treated in this way. Because PUVA is associated with increased risk for skin cancers, including melanoma, UVB is generally preferred to treat psoriasis. High-dose UVA1 is used, mainly in Europe, to treat atopic dermatitis, localized scleroderma, and mastocytosis. The risks related to long-term UVA therapy are currently unknown, but photoaging is associated with UVA, and there have been reports of an increase in melanoma associated with use of suntanning beds, in which much of the exposure is to UVA. Laser therapy is used to treat vascular lesions such as port-wine stains, tattoos, psoriasis, benign skin tumors, and photodamage, as well as to remove hair. Photodynamic therapy involves activation of a photosensitizer by illumination with visible light, which leads to photochemical tissue destruction or immunomodulation. Photodynamic therapy can be used to treat actinic keratosis, Bowen disease, and superficial basal cell carcinoma by causing selective tissue necrosis and tumor destruction. Fractional lasers have been successfully used for treatment of actinic keratoses, photodamage, and scars.

DERMATOLOGIC SURGERY

Although approaches such as desiccation and curettage can be used for some skin tumors, others require excisional surgery or Mohs microscopic controlled surgery to ensure complete removal of lesions. If the tumors are recurrent, of a pathologic type that increases the likelihood for recurrence, or large and requiring clearance of the tumor before repair, the Mohs approach can provide rapid documentation of full removal while sparing as much normal tissue as possible. After the margins have been cleared of tumor, flaps and grafts can be used immediately for repair of the resultant defects.

Patients with extensive actinic damage resulting in either large numbers of actinic keratoses or photodamage can be treated with various ablative approaches that use either chemical peels or laser resurfacing with the carbon dioxide laser. Chemical peels can be performed at different depths and intensities, and agents can include glycolic acid, acetic acid, or even phenol. Lasers used to remove sun-induced lentigines include Q-switched lasers such as the neodymium:yttrium-aluminum-garnet, ruby, and alexandrite lasers. Many patients seek treatment of wrinkles with soft tissue augmentation that uses human-derived collagen and hyaluronic acid or with a muscle relaxer, botulinum type A exotoxin.

Hair transplants are a surgical approach to the problem of hair loss. The process includes harvesting hair grafts from the posterior of the scalp and placing the grafts in areas of alopecia.

SUNSCREEN

Transparent sunscreens, which absorb photons of light, are rated by the sun protection factor (SPF), which is determined by the ratio of ultraviolet exposure needed to cause erythema in protected versus unprotected skin. Most sunscreens work in the UVB range or shorter UVA wavelengths. Examples of UVB-absorptive compounds include aminobenzoates, cinnamates, salicylates, and benzophenones. Short-wavelength UVA-absorptive compounds include benzophenones and anthranilates. The best UVA blocking agent in the United States is avobenzone (Parsol 1789), which can be combined with UVB screens. Some sunscreens are water resistant or waterproof, as determined by the substantivity of the sunscreen, and these agents provide continued protection after sweating or swimming. Sunscreens can cause irritation and, rarely, contact allergic reactions. Physical sunscreens, such as zinc oxide and titanium dioxide, reflect light from the skin and include newer micronized reflecting powders that provide broad-spectrum (UVB and UVA) protection. Sunscreens decrease skin cancers and photodamage without compromising the synthesis of vitamin D or adversely affecting bone mineral density.[7] Although some active ingredients in sunscreen are absorbed into the systemic circulation, there is currently no evidence that such components represent a health hazard.[8,9] UVB is partially reflected by clothing, and sun-protective clothing can provide substantial protection (Solumbra, SPF of 30).

Visible light can cause redness in lighter-skinned individuals and pigmentation in darker-skinned individuals. Tinted sunscreens, which contain iron oxides and pigmentary titanium dioxide, protect against visible light[10] and are especially useful in patients with porphyria cutanea tarda and erythropoietic porphyria (Chapter 194).

COSMETICS: CAMOUFLAGE, BLEACHING, AND HAIR LOSS

Patients with numerous skin conditions benefit from camouflage cosmetics, which can also cause contact hypersensitivity. Products such as Dermablend can be blended to match skin colors, are thicker, can cover disfiguring lesions, and can be fixed with powder. Hydroquinones, topical retinoic acid, and azelaic acid (inhibits tyrosinase) are used to treat hyperpigmented conditions such as melasma and lentigines; these agents can be irritating and cause dyspigmentation. Topical minoxidil 2% (available over the counter) and 5% solutions are used for androgenic alopecia and alopecia areata. Finasteride, a 5α-reductase inhibitor, is effective in men with androgenic alopecia.

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405 ECZEMAS, PHOTODERMATOSES, PAPULOSQUAMOUS (INCLUDING FUNGAL) DISEASES, AND FIGURATE ERYTHEMAS

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ECZEMA

The more commonly encountered eczemas (Table 405-1) share similar histologic characteristics. They have edema within the epidermis (spongiosis) and infiltration with lymphocytes and macrophages in the superficial dermis.

NUMMULAR DERMATITIS

Nummular dermatitis occurs most frequently in patients who are in their 50s to 60s. Both sexes are affected, and it is most frequently seen in the winter. The condition tends to be more frequent and severe among East Asians. The pathogenesis is unclear, although xerosis plays a significant role.

Patients present with pruritic, coin-shaped, erythematous patches with some scales and occasionally with pinhead-sized vesicles (Figs. 405-1 and 405-2). Lesions may be excoriated and lichenified (i.e., thickened skin with accentuation of skin markings). Legs and arms are commonly affected, and the trunk is less frequently involved; facial involvement is uncommon. All patients should be educated about the use of emollients and moisturizing soaps, and avoidance of long, hot showers. Topical corticosteroid ointments (e.g., triamcinolone ointment, 0.1% twice daily for 1 to 2 weeks) are helpful for active lesions, and oral antihistamines (e.g., hydroxyzine 25 to 50 mg at bedtime) are useful for sedative effects when the patient's sleep is disturbed by pruritus. In severe cases, narrowband ultraviolet B (NB-UVB) phototherapy, and/or a short course of oral corticosteroids (prednisone, 0.5 to 1 mg/kg/day, with a maximal dose of 60 mg/day, for 1 to 2 weeks, then taper in 10 to 14 days) are beneficial. Some patients may require topical or oral antibiotics against *Staphylococcus aureus* if lesions become infected.

DYSHIDROSIS

Dyshidrosis manifests as pruritic, deep-seated, pinhead-sized vesicles, most commonly along the sides of the fingers (Figs. 405-3 and 405-4). Other features include xerosis, scaliness, and fissures. In severe cases, palms and soles also may be involved. Dyshidrosis is seen in individuals who wash their hands frequently, such as food industry workers, mothers of young infants, and increasingly in the general public during the severe acute respiratory syndrome coronavirus 2 pandemic. Treatment follows a sequential order: (1) replacing soap-and-water handwashing with hand sanitizers, (2) liberal use of emollients, and (3) topical corticosteroid ointments (e.g., fluocinonide ointment, 0.05% twice daily for 2 weeks). In some patients, a short course of oral prednisone (starting at 40 mg orally daily and tapering over 2 weeks) or longer term treatment with immune-suppressing medications (e.g., cyclosporine, 3 to 5 mg/kg daily for up to 12 months) may be needed.

ATOPIC DERMATITIS

Atopic dermatitis is most commonly seen among young children but may persist into adulthood or even begin in adulthood.[1] The prevalence has been estimated at between 15 and 23%.[2] Patients usually present with xerosis, erythematous scaly patches, small vesicles, excoriations, crusting, and, not infrequently, impetiginization (Fig. 405-5). In dark-skinned patients, a papular variant is commonly seen (Fig. 405-6). With chronic scratching and rubbing, hyperpigmentation and lichenification occur. Commonly affected sites include the periorbital area and flexor areas such as the neck, antecubital fossa, and popliteal fossa. In severe cases, the entire skin surface may be involved. Diagnosis is made by the typical morphology, the distribution of lesions, and family and personal history of atopy. The therapeutic ladder consists of (1) emollients; (2) topical corticosteroid ointments (e.g., triamcinolone ointment, 0.1% twice daily for 2 to 4 weeks), or topical calcineurin inhibitors (tacrolimus ointment,

TABLE 405-1 ECZEMAS

Nummular dermatitis
Dyshidrosis
Atopic dermatitis
Seborrheic dermatitis
Allergic contact dermatitis
Irritant contact dermatitis

FIGURE 405-1. Nummular dermatitis. Coin-shaped erythematous patches.

FIGURE 405-2. Nummular dermatitis. Coin-shaped erythematous patch.

FIGURE 405-3. Dyshidrosis. Deep-seated vesicles and scaliness on fingers.

ABSTRACT

Eczemas, photodermatoses, papulosquamous (including fungal) diseases, and figurate erythema have the common morphology of erythema, scaliness, papules, and vesicles. However, the pathophysiology, histology, and management are distinct for each of these diseases.

KEYWORDS

eczema
photodermatoses
lichen planus
tinea
mycosis fungoides

FIGURE 405-4. Dyshidrosis. Deep-seated vesicles and scaliness on fingers.

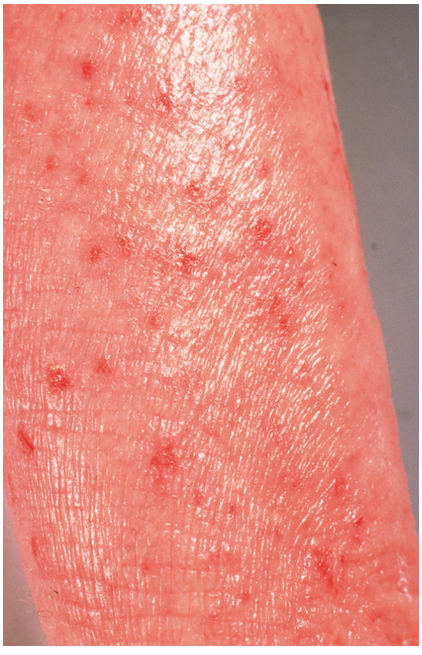

FIGURE 405-5. Atopic dermatitis. Note the erythema, excoriation, and lichenification.

FIGURE 405-6. Atopic dermatitis in a dark-skinned patient. Note the typical papular variant commonly seen in dark-skinned individuals.

0.1%, or pimecrolimus cream, 1% twice daily); (3) oral antihistamines (same dose range as nummular dermatitis); and (4) NB-UVB phototherapy.[3] Newer options for poorly responsive disease include crisaborole (a phosphodiesterase 4 inhibitor) 2% ointment applied twice daily,[A1] ruxolitinib (Janus kinase inhibitor) cream 1.5% twice daily, dupilumab (an interleukin-4 [IL-4] receptor α-antagonist) at 300 mg subcutaneously every other week,[A2,A3] tralokinumab (an IL-13 receptor blocker at 300 mg subcutaneously every other week to every 4 weeks)[A4], and two oral Janus kinase inhibitors (abrocitinib at 100 to 200 mg daily,[A5] and upadacitinib at 15 or 30 mg daily[A6]) are newer therapies especially for refractory disease.[A7] Cognitive behavioral therapy, even delivered over the internet, is also effective.[A8] Other traditional systemic treatments include oral prednisone (0.5 to 1 mg/kg/day), cyclosporine (3 to 5 mg/kg/day), and mycophenolate mofetil (1 to 2 g/day).

SEBORRHEIC DERMATITIS

Seborrheic dermatitis is a common condition that presents as erythematous patches with fine, greasy-appearing scales on the malar area, midforehead, midchest, and scalp (Fig. 405-7). In dark-skinned individuals, lesions may be hypopigmented (Fig. 405-8). The pathogenesis is unknown, although *Malassezia furfur* is believed to play a role. Lesions are common and more inflammatory in patients with human immunodeficiency virus (HIV) infection (Chapter 359) and may overlap with psoriasis. The diagnosis is made clinically. Topical corticosteroids (e.g., hydrocortisone cream 2.5%, twice daily for 1 to 2 weeks for facial lesions, fluocinolone acetonide 0.01% solution, gel, or ointment [depending on the patient's preference], twice daily for 3 to 4 weeks for the scalp) can rapidly reduce the inflammation; then topical ketoconazole cream, 2% twice daily, as needed (or shampoo 2% daily or every other day for the scalp), is safe for long-term treatment.[4]

FIGURE 405-7. Seborrheic dermatitis presenting as erythematous patches and plaques with fine scales on the malar area of an HIV-positive patient.

FIGURE 405-8. Seborrheic dermatitis. Hypopigmentation with fine scales on the forehead and scalp.

ALLERGIC CONTACT DERMATITIS AND IRRITANT CONTACT DERMATITIS

Allergic contact dermatitis is a delayed (occurring 24 to 48 hours after exposure) hypersensitivity response to external allergens,[5] whereas irritant contact dermatitis is a nonspecific toxic response to contact irritants. In both conditions, lesions occur in the exposed area. In severe cases, however, nonexposed areas may be involved, albeit less intensely. Allergic contact dermatitis presents with erythematous pruritic papules and vesicles in a pattern resembling the linear patches from poison ivy. Lesions resolve with fine scales. Postinflammatory hyperpigmentation may be observed. Histologically, epidermal edema and dermal histiocytic infiltrates are observed. The morphology of irritant contact dermatitis is similar to that of allergic contact dermatitis. However, irritant contact dermatitis is usually associated with a burning sensation rather than with pruritus. Postinflammatory hyperpigmentation is frequently observed. Histologic changes consist of necrotic keratinocytes, epidermal necrosis, and neutrophilic infiltrates. Management includes identification, which may require extensive patch testing, and removal of the offending agent, as well as symptomatic treatments such as topical corticosteroids and oral antihistamines.

PHOTODERMATOSES

Photodermatoses are cutaneous eruptions secondary to exposure to sunlight (Table 405-2). By convention, electromagnetic radiation in the ultraviolet (UV) region is divided into UVC (200 to 290 nm), UVB (290 to 320 nm), UVA-2 (320 to 340 nm), and UVA-1 (340 to 400 nm). Visible light extends from 400 to 700 nm. Because UVC emitted by the sun is absorbed by ozone in the stratosphere, UVC does not reach the earth's surface but is of medical interest as it is used for its germicidal effects (Chapter 18). UVB, UVA, and, less frequently, visible light are the relevant spectra in photodermatoses.

POLYMORPHIC LIGHT ERUPTION

Polymorphic light eruption is the most common immunologically mediated photodermatosis, occurring in 10 to 20% of the general population. It usually is seen in young adults, has a slight female predominance, and has been reported worldwide. Affected individuals are less susceptible to cutaneous photoimmunosuppression and hence have an enhanced response to UV-induced neoantigens in the skin. Lesions usually occur in early spring, within a few hours of exposure to sunlight. The lesions are mildly pruritic and manifest as pinhead papules (common among dark-skinned patients), papules, papulovesicles, or, less commonly, vesicles (Fig. 405-9). They persist for several days and resolve spontaneously. The condition tends to improve as the sunny season progresses, a phenomenon known as hardening.

The course is episodic but also chronic; only 11% of patients have complete resolution of the disease in 16 years and 24% in 32 years. Diagnosis is based on the typical history and morphology of the lesion. When lesions occur primarily on the face, a diagnosis of lupus must be excluded. Management consists of sun avoidance and the use of broad-spectrum sunscreens that cover both UVB and UVA with sun protection factor (SPF) of at least 30, topical corticosteroids, and oral antihistamines. In severe cases, desensitization treatment using NB-UVB is beneficial. Desensitization is usually performed in early spring by exposing patients to increasing doses of NB-UVB three times weekly for 15 to 20 treatments.

CHRONIC ACTINIC DERMATITIS

Chronic actinic dermatitis is a photodermatosis that occurs most commonly in men in their 60s and 70s. It occurs in patients of all ethnic groups, but in the United States it is more commonly seen in dark-skinned individuals. It is seen in 5 to 17% of patients referred for evaluation of photosensitivity. This condition has been postulated to represent a delayed hypersensitivity response to an unidentified antigen.

Patients present with lichenified plaques on sun-exposed areas (Figs. 405-10 and 405-11). Typically, sun-protected areas, such as the postauricular area, the area underneath the chin, the area above the eyes, and the trunk, are spared. Histologically, a dermal lymphohistiocytic infiltrate is seen, and atypical mononuclear cells may be observed. On phototesting, patients have increased sensitivity to UVB, UVA, and, less commonly, to visible light. In a study of

TABLE 405-2 SELECTED PHOTODERMATOSES

Polymorphic light eruption
Chronic actinic dermatitis
Phototoxicity and photoallergy
Cutaneous porphyrias

FIGURE 405-10. Chronic actinic dermatitis. Hyperpigmentation and lichenification; note sparing of the sun-protected areas of the neck and infra-auricular area.

FIGURE 405-9. Polymorphic light eruption. Erythematous papules a few hours after exposure to sunlight.

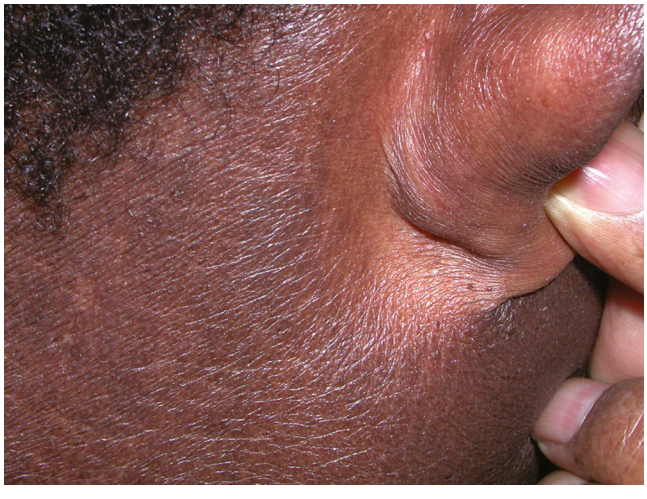

FIGURE 405-11. Hyperpigmentation and lichenification in a patient with chronic actinic dermatitis. Note sparing of the sun-protected postauricular area.

178 cases, 10% resolved in 5 years and 50% in 15 years. An association with HIV infection (Chapter 359) has been reported.

The diagnosis is based on the patient's history, morphology, and distribution of the lesions. It is confirmed by phototesting.

Management is challenging. Rigorous photoprotection is a must: staying in the shade, using broad-spectrum sunscreens with SPF 50 or more, and wearing photoprotective clothing, sunglasses, and a wide-brimmed hat. Other treatment modalities, in approximate sequential order, are topical corticosteroids (fluocinonide ointment 0.05% twice daily), tacrolimus ointment (0.1% twice daily), oral mycophenolate mofetil (1 to 2 g/day), oral cyclosporine (3 to 5 mg/kg/day), and azathioprine (up to 2 to 2.5 mg/kg/day). Treatment with oral corticosteroids (e.g., prednisone, 1 mg/kg/day) may be needed for acute flare. In recalcitrant cases, low-dose PUVA or NB-UVB in conjunction with oral corticosteroids may be helpful, and dupilumab (300 mg subcutaneously every other week) has been reported to be successful in some patients.[6]

PHOTOTOXICITY AND PHOTOALLERGY

The terms *phototoxicity* and *photoallergy* refer to the development of skin lesions after combined exposure to an oral or topical photosensitizer and electromagnetic radiation. Phototoxicity is a nonspecific cutaneous toxic reaction, whereas photoallergy is a delayed hypersensitivity response. For all photosensitizers, the action spectrum for both lies in the UVA range (Table 405-3).

CUTANEOUS PORPHYRIAS

The most common cutaneous porphyria is porphyria cutanea tarda, in which patients present with skin fragility and blisters on sun-exposed areas, most commonly the dorsum of the hands and the forearms (Fig. 405-12; Chapter 194).[7] Patients may have periorbital hypertrichosis and mottled hyper- and hypopigmentation, and infrequently, sclerodermoid skin changes. Sclerodermoid skin changes can occur in both sun-exposed and sun-protected areas. The defective enzyme is uroporphyrinogen decarboxylase. It is associated with excessive alcohol intake, exposure to estrogens, hepatitis C infection (Chapter 135), HIV infection (Chapter 359), and hemochromatosis (Chapter 196). Patients invariably have an elevated level of ferritin and frequently have elevated liver enzyme values.

TABLE 405-3 PHOTOTOXICITY AND PHOTOALLERGY

FEATURES	PHOTOTOXICITY	PHOTOALLERGY
Lesions after first exposure	Yes	No
Onset	Minutes after sun exposure	Delayed (24-48 hr after sun exposure)
Common offending agents	Systemic medications	Sunscreen agents
Morphology	Vesicles, bulla, hyperpigmentation	Eczematous (erythema, scaliness)
Management	Symptomatic (topical corticosteroids, antihistamine)	Removal of the offending agent

FIGURE 405-12. Erosion, crusting, and vesicles on the dorsum of the hand of a patient with porphyria cutanea tarda.

Laboratory findings are characterized by elevated levels of 8-, 7-, 6-, 5-, and 4-carboxyl porphyrins in the serum and urine, and isocoproporphyrin in feces (Chapter 194). Management consists of avoidance of precipitating factors (alcohol, iron-containing vitamins, estrogen-containing birth control pills) and weekly phlebotomy. In patients who are anemic, low-dose hydroxychloroquine (200 mg/week) is beneficial. In patients with concurrent chronic hepatitis C (Chapter 135), effective antiviral treatment of the hepatitis C can reduce the relapse rate of skin symptoms.

The second most common, albeit uncommon, porphyria is erythropoietic protoporphyria (Chapter 194). Defective ferrochelatase results in elevated protoporphyrin levels in erythrocytes and serum. Patients present with a life-long history of a stinging and deep-seated burning sensation upon sun exposure. A highly beneficial treatment is afamelanotide, an analogue of alpha-melanocyte–stimulating hormone, which is administered as a subcutaneous implant (16 mg) every 2 months.[8] The skin damage in porphyria cutanea tarda and erythropoietic protoporphyria is from the visible light range; therefore, topical sunscreens are not effective because they are designed to protect against only UV radiation. However, tinted sunscreens containing iron oxides and pigmentary titanium dioxide protect against visible light.

PAPULOSQUAMOUS (INCLUDING FUNGAL) DISEASES

Common papulosquamous diseases are listed in Table 405-4.

PSORIASIS

EPIDEMIOLOGY

Psoriasis occurs in about 3% of the general population,[9] with considerable variation in different parts of the world. It affects male and female patients equally. Approximately one third of the patients have a positive family history. Psoriasis has a bimodal peak of onset, at 22.5 years of age and again at age 55 years.

PATHOBIOLOGY

Psoriasis involves the innate and adaptive immune systems, with abnormal keratinocyte proliferation. Factors playing a role in the pathogenesis include activation of antigen-presenting cells and development of T_H1 and T_H17 cells. Mediators include IL-17, IL-23, and tumor necrosis factor-α (TNF-α).

Psoriasis has a complex, polygenetic inheritance. Cutaneous psoriasis is strongly associated with human leukocyte antigen–Cw6 (HLA-Cw6). To date, genome-wide studies have identified more than 85 non–major histocompatibility complex loci that may increase the risk for psoriasis.

CLINICAL MANIFESTATIONS

Several distinct forms of psoriasis are recognized.[10] *Psoriasis vulgaris,* the most common type, appears as a persistent erythematous plaques with silvery scales most commonly on elbows, knees, and scalp (Fig. 405-13). *Guttate psoriasis* usually occurs after viral or bacterial (most commonly streptococcal) infection; it appears as small, erythematous, scaly papules scattered over a large area of the body in a raindrop distribution (*guttate* means "droplike"). *Inverse psoriasis* refers to psoriasis that occurs in skinfold areas such as the groin, axilla, and inframammary folds. It appears as an erythematous, somewhat shiny patch; because of the constant friction in the involved areas, scales are absent. *Nail psoriasis* includes nail pittings, yellowish macules underneath the nail plate ("oil drop" sign), and thickening of the nail (onychodystrophy) (Fig. 405-14). *Erythrodermic psoriasis* appears as widespread erythroderma with fine silvery scales. *Palmoplantar psoriasis* manifests as keratotic scaly patches and plaques on the palms and soles, very frequently with accompanying fissures. *Pustular*

TABLE 405-4 PAPULOSQUAMOUS DISEASES

Psoriasis
Pityriasis rubra pilaris
Pityriasis rosea
Lichen planus
Lichen nitidus
Secondary syphilis
Pityriasis lichenoides
Parapsoriasis
Mycosis fungoides
Acrokeratosis paraneoplastica of Bazex
Necrolytic acral erythema
Dermatophytosis
Tinea versicolor

FIGURE 405-13. Psoriasis. Erythematous plaques with silvery scales.

FIGURE 405-14. Psoriasis. Thickening and crumbling of the nail plate (onychodystrophy). Note the erythematous patches with silvery scales in the periungual area.

psoriasis of von Zumbusch is a rare variant of psoriasis occurring with generalized pustules that are 2 to 3 mm in diameter (Fig. 405-15) and associated with the onset of fever.[11]

Of patients with psoriasis, 5 to 30% also may have psoriatic arthritis, which in about 20% of patients may precede the appearance of cutaneous lesions (Chapter 244). Psoriasis also is associated with chronic kidney disease, inflammatory bowel disease, hepatic disease, certain malignancies, infections, mood disorders, diabetes, major cardiovascular events, and mortality that warrant cholesterol reduction therapy analogous to what would be prescribed in high-risk primary prevention (Chapter 190). The association of psoriasis with HIV infection (Chapter 359) has been well documented.

DIAGNOSIS

The diagnosis usually can be made based on the history and physical examination alone. However, in patients with erythrodermic psoriasis, skin biopsy is needed to exclude other causes of generalized erythroderma, such as drug eruption, cutaneous T-cell lymphoma (Chapter 171), and pityriasis rubra pilaris.

TREATMENT

Treatment, which should be based on extent and areas involved with psoriasis, include topical therapy, phototherapy, oral agents, and injectable biologics (Table 405-5).[12] In general, biologics are more effective than oral treatments,[13] and newer biologics (e.g., ixekizumab, brodalumab, guselkumab, risankizumab, and bimekizumab) appear to be more effective than ustekinumab, etanercept, secukinumab, and adalimumab.[A9–A14] Roflumilast (a phosphodiesterase-4 inhibitor) cream and tapinarof cream (a topical aryl hydrocarbon receptor–modulator) are new FDA-approved topical agents.[A15]

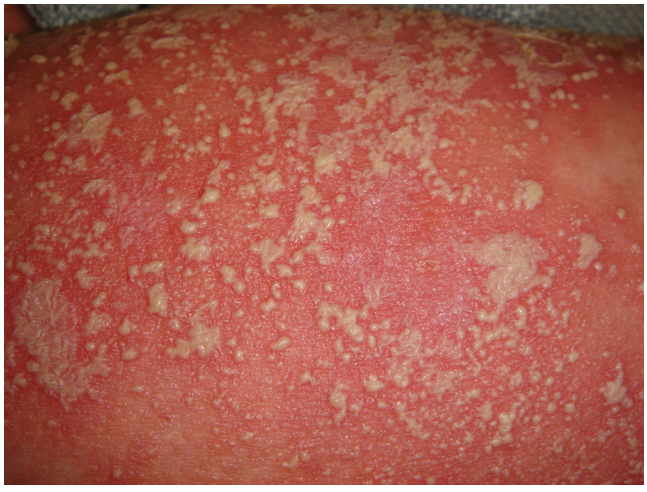

FIGURE 405-15. Pustular psoriasis. Erythematous patch with pustules in a patient with active disease.

TABLE 405-5 SEQUENTIAL THERAPEUTIC APPROACH IN PSORIASIS

Topical agents	Corticosteroids (e.g., triamcinolone ointment 0.1%) Vitamin D analogues (e.g., calcipotriene cream 0.005%) Retinoids (e.g., tazarotene cream 0.1%) Aryl hydrocarbon receptor agonist (tapinarof cream) Phosphodiesterase-4 inhibitor (roflumilast)
Phototherapy	Narrowband ultraviolet B (three times/wk)
Traditional systemic therapy	Methotrexate (10-20 mg/wk) Cyclosporine (3-5 mg/kg/day) Acitretin (25-50 mg/day)
Oral phosphodiesterase-4 inhibitor	Apremilast (30 mg twice/day)
Oral tyrosine kinase-2 inhibitor	Deucravacitinib (6 mg/day)
Biologics	TNF-α inhibitors • Etanercept (50 mg/wk SQ) • Adalimumab (40 mg every 2 wk SQ) • Certolizumab (400 mg SQ every 2 wk SQ) • Infliximab (5-10 mg/kg every 8 wk IV) IL-12/23 inhibitor • Ustekinumab (45-90 mg every 12 wk SQ) IL-17 inhibitors • Secukinumab (300 mg/wk for 5 weeks, followed by 300 mg every 4 wk SQ) • Ixekizumab (160 mg at wk 0, followed by 80 mg every 2 wk from week 2 to 12, then 80 mg every 4 wk SQ) IL-17 receptor antibody • Brodalumab (210 mg at wk 0, 1, 2, then every 2 wk SQ) IL-23 inhibitors • Guselkumab (100 mg wk 0, 4, then every 8 wk SQ) • Tildrakizumab (100 mg at wk 0, 4, then every 12 wk SQ) • Risankizumab (150 mg wk 0, 4, then every 12 wk SQ) IL-36 inhibitor • Spesolimab-sbzo (for flare of pustular psoriasis; 900 mg IV, may repeat 1 wk later)
Potential future treatments*	IL-17 inhibitor • Bimekizumab (320 mg every 4 weeks SQ)

*Doses may change if and when approved by the U.S. Food and Drug Administration.
IL = interleukin; IV = intravenously; SQ = subcutaneously; TNF = tumor necrosis factor; wk = week.

Biologics may increase the risk of infection, so patients should be screened for tuberculosis, HIV, and hepatitis before beginning therapy and not be started on them if such testing is positive unless these conditions are treated. Oral corticosteroids should not be used because psoriasis may worsen when they are discontinued. For the treatment of psoriatic arthritis, please see Chapter 244.

PITYRIASIS RUBRA PILARIS

EPIDEMIOLOGY

Pityriasis rubra pilaris occurs equally in men and women; the incidence ranges from 1 in 5000 new dermatology patients in Great Britain to 1 in 50,000 in India. This disease most frequently occurs as the acquired form, although a familial form (autosomal dominant with variable expression) occasionally has been reported. The pathophysiology is autoinflammatory in nature.

CLINICAL MANIFESTATIONS

The most common form of pityriasis rubra pilaris is type I, which is characterized by widespread salmon-colored plaques with fine scales, islands of sparing, scaliness on the scalp, waxy keratoderma of the palms and soles, and follicular hyperkeratosis (Figs. 405-16 and 405-17). In adult patients, the condition typically starts on the face and moves to the lower extremities; in the juvenile form, it usually starts in the lower half of the body. Ectropion and pruritus may occur.

DIAGNOSIS

Diagnosis is based on the clinical presentations and by the characteristic histologic findings of alternating vertical and horizontal parakeratosis in the stratum corneum.

TREATMENT

The most effective treatment is with oral retinoids (acitretin, 25 to 50 mg/day for 2 to 4 months). Some patients benefit from methotrexate (7.5 to 15 mg/week) or cyclosporine (3 to 5 mg/kg/day). Biologics targeting TNF, IL-12/23, IL-17, and IL-23, used at the same doses as for psoriasis, may be helpful for patients with recalcitrant type I disease. Topical keratolytic agents, such as ammonium lactate lotion 12%, twice daily, are helpful as adjunctive therapy.

PITYRIASIS ROSEA

EPIDEMIOLOGY AND PATHOBIOLOGY

The incidence of pityriasis rosea has been reported as 3 to 30 per 1000 patients. It occurs in all ethnic groups, most commonly in the third and fourth decades of life, with a slight female predominance. A possible association with human herpesvirus types 6 and 7 has been reported.

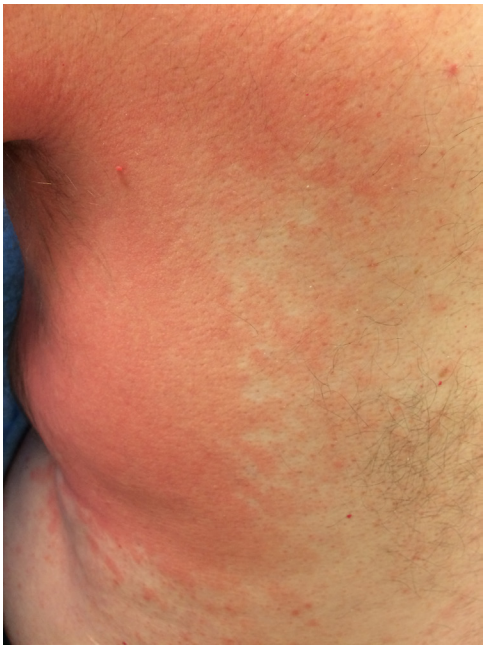

FIGURE 405-16. Pityriasis rubra pilaris. Note the erythematous orange patch with islands of sparing at the edge of the erythematous lesion.

CLINICAL MANIFESTATIONS

In 50 to 90% of patients, pityriasis rosea starts with a primary lesion (herald patch), which is an erythematous, scaly, oval patch a few centimeters in diameter (Fig. 405-18). This lesion is usually followed within a few days by smaller, minimally pruritic, erythematous scaly patches on the trunk, less commonly on the proximal extremities. As a rule, the palms and soles are spared. The distribution of the eruption, especially on the back, tends to follow the lines of cleavage of the skin, with a resulting "Christmas tree" distribution. The eruption is self-limited and resolves within 6 to 8 weeks. In rare instances, lesions may persist.

DIAGNOSIS

The diagnosis usually can be made clinically.[14] The most important differential diagnosis is secondary syphilis, which, in contrast to pityriasis rosea, usually involves the palms and soles. Serology testing to exclude syphilis (Chapter 295) is advisable.

TREATMENT

Treatment is primarily symptomatic, including topical corticosteroids and oral antihistamines.

LICHEN PLANUS

EPIDEMIOLOGY

Lichen planus occurs most commonly in patients between 30 and 60 years of age. Women are affected more frequently than men. The prevalence is less than 1%.

FIGURE 405-17. Pityriasis rubra pilaris. Palmar hyperkeratosis with waxy scales.

FIGURE 405-18. Pityriasis rosea. Large erythematous oval patch (herald patch) accompanied by smaller erythematous patches.

PATHOBIOLOGY

Histologically, lichen planus is characterized by dense T-cell infiltrate at the dermal-epidermal junction, suggesting the pathogenic role of cell-mediated immunity. Because lichen planus or lichen planus–like eruptions can occur after exposure to drugs or chemicals (e.g., color film developer), the role of drugs and chemicals in inducing a T-cell–mediated response against the epidermis has been postulated. Lichen planus may be associated with hepatitis C infection (Chapter 135).

CLINICAL MANIFESTATIONS

Patients present with pruritic erythematous-to-violaceous flat-topped papules, often with white lacy lines (Wickham striae) and most commonly on the wrists, hands, forearms, and genitalia (Fig. 405-19). *Oral lichen planus* occurs as white reticulated lines, most commonly along the bite line on the buccal mucosa. Similar lesions can be seen on the tongue (Fig. 405-20) and genital mucosa. Painful erosion may occur. *Hypertrophic lichen planus* usually occurs on the lower extremities as pruritic lichenified, violaceous plaques.

DIAGNOSIS

The diagnosis is made clinically and is confirmed by the characteristic histologic findings.

FIGURE 405-19. Lichen planus. Violaceous macules and papules on the lateral aspect of dorsum of a hand.

FIGURE 405-20. Lichen planus of the tongue. Note white plaques on dorsal surface of the tongue, with reticulated white line on the distal aspect of the tongue.

TREATMENT

Therapeutic options depend on the location of lesions (Table 405-6). Without treatment, cutaneous lesions usually resolve in approximately 1 year, whereas oral and hypertrophic lesions tend to be much more chronic, persisting for an average of 4.5 years and 8.5 years, respectively.

LICHEN NITIDUS

Lichen nitidus is a rather uncommon condition that usually occurs in dark-skinned children or young adults. The incidence has been estimated to be 3.4 cases per 10,000 persons. The cause is unclear.

The lesions are asymptomatic, 1- to 2-mm, shiny, skin-colored discrete papules, sometimes with fine scales on their surface, occurring most commonly on the genitalia or forearms and occasionally on the trunk (Fig. 405-21). Histologically, a dense, focal lymphocytic infiltrate is seen in the superficial dermis and at the dermal-epidermal junction.

The diagnosis can be confirmed from the typical clinical appearance and the characteristic histologic changes. The condition tends to remit spontaneously in a few years. Therapy with topical corticosteroids (e.g., triamcinolone ointment, 0.1% twice daily for 2 weeks) and oral antihistamines (e.g., fexofenadine, 180 mg every morning, and hydroxyzine, 25 to 50 mg at bedtime, as needed) should be reserved for symptomatic cases only.

TABLE 405-6 THERAPEUTIC OPTIONS FOR LICHEN PLANUS

CUTANEOUS LESIONS
Topical corticosteroids (triamcinolone ointment 0.1% twice/day)
HYPERTROPHIC LESIONS
Intralesional corticosteroids (triamcinolone suspension 3-5 mg/mL)
ORAL LESIONS
Corticosteroid paste (triamcinolone 0.1% paste twice/day) or cyclosporine solution (100 mg/mL, 2 mL, twice/day, swish and spit)
GENERALIZED LICHEN PLANUS, PAINFUL ORAL/GENITAL EROSIONS, RECALCITRANT DISEASE
Narrowband UVB phototherapy (two to three times/wk) Hydroxychloroquine 5 mg/kg daily Oral prednisone (0.5-1 mg/kg/day, taper in 6-8 wk) Mycophenolate mofetil (1-2 g/day) Cyclosporine (3-5 mg/kg/day) Tumor necrosis factor-α inhibitors (see Table 405-5)

UV = ultraviolet.

FIGURE 405-21. Lichen nitidus. Note skin-colored fine papules on the upper back.

SECONDARY SYPHILIS

Lesions typically occur 1 to 2 months after the development of a primary chancre lesion (Chapter 295). However, up to 25% of patients may not remember having a chancre. Once the eruption occurs, it lasts for 1 to 3 months.

Clinically, secondary syphilis results from widespread dissemination of *T. pallidum*, often accompanied by fever, fatigue, and lymphadenopathy. The rash may appear as erythematous macules (roseola syphilitica), erythematous-to-hyperpigmented oval or circular papules and plaques covered with scales, or a maculopapular eruption (Fig. 405-22). Nodular eruption also may occur occasionally. The lesions tend to be widespread, and the palms and soles are very frequently involved (Fig. 405-23). The diagnosis is made based on the history, physical examination, and a positive serology. Skin biopsy shows the proliferation of endothelial cells in the dermis and a dense dermal infiltrate containing many plasma cells. Intramuscular benzathine penicillin G (2.4 million U intramuscularly in a single dose) is currently the recommended treatment.

PITYRIASIS LICHENOIDES

Pityriasis lichenoides occurs as erythematous papules that may be minimally pruritic and covered with scales, scattered on all parts of the body. In the acute form (pityriasis lichenoides et varioliformis acuta [PLEVA]), the central part of the lesions develops vesicles, pustules, and hemorrhages, with eventual crusting of the lesions. The chronic form (pityriasis lichenoides chronica [PLC]) occurs as asymptomatic erythematous-to-hyperpigmented papules and plaques covered with fine scales; the trunk and extremities are common sites. Histologically, both PLEVA and PLC are characterized by dense lymphocytic infiltrates in the dermis, with CD8 lymphocytes predominating in PLEVA and CD4 lymphocytes in PLC.

PLEVA usually resolves in a few months, although it can persist. PLC usually lasts for a few years. Both disorders affect patients of all ages, with a slight male predominance.

Treatment generally follows a sequential order: (1) topical corticosteroids (e.g., triamcinolone ointment, 0.1% twice daily for 1 to 2 weeks) and antihistamines, (2) doxycycline (100 mg twice daily), (3) NB-UVB phototherapy (three times weekly for 8 to 10 weeks with increasing doses of NB-UVB),[15] and (4) methotrexate (7.5 to 15 mg/week).

FIGURE 405-22. Secondary syphilis. Papules with crust on elbow.

FIGURE 405-23. Secondary syphilis. Scaly papules and plaques on the palm.

PARAPSORIASIS

The two common variants of parapsoriasis are large plaque parapsoriasis and small plaque parapsoriasis. The peak incidence is in the fifth decade, although rare cases may begin in childhood. Large plaque parapsoriasis appears as minimally pruritic, oval-to-circular, erythematous-to-hyperpigmented macules and patches with fine scales and superficial atrophy (crinkling atrophy) scattered on all parts of the body (Fig. 405-24). These lesions are usually larger than 5 cm. Large plaque parapsoriasis is considered by some to be a variant of mycosis fungoides (see later). Small plaque parapsoriasis appears as circular-to-oval, erythematous-to-hyperpigmented patches or minimally elevated plaques, with lesions smaller than 5 cm in diameter and usually covered with fine scales. A distinct variant is digitate dermatosis, in which lesions appear along the lines of cleavage, usually on the lateral aspect of the trunk in the shape of fingerprints. Histologically, large plaque parapsoriasis is characterized by a dermal lymphocytic infiltrate, which may extend into the epidermis, whereas small plaque parapsoriasis is characterized by spongiotic dermatitis, with a mild superficial lymphocytic infiltrate in the dermis. In up to one third of patients, large plaque parapsoriasis may evolve into mycosis fungoides. As a result, treatment of large plaque parapsoriasis is similar to that of early-stage mycosis fungoides: high-potency topical corticosteroids, NB-UVB phototherapy, and psoralen and UVA (PUVA). By comparison, patients with small plaque parapsoriasis have a benign course, and management should be symptomatic only, with emollients, topical corticosteroids, and if needed, NB-UVB phototherapy.

MYCOSIS FUNGOIDES

Mycosis fungoides is the most common variant of cutaneous T-cell lymphoma (Chapter 171). The four types of cutaneous manifestations are patch, plaque, tumor, and erythrodermic.[16] Patch-stage disease manifests as asymptomatic or pruritic skin-colored or minimally erythematous patches with fine "cigarette paper" wrinkling of the epidermis (Fig. 405-25); hyperpigmented or hypopigmented lesions are frequently seen in dark-skinned patients. The patches can vary from a few millimeters to a few centimeters in diameter; they are more common on sun-protected areas such as the buttocks. Lesions may be present for years. As the disease progresses, some of the patches may become more indurated and may evolve into plaques (Fig. 405-26). Nodular lesions may occur in patients without any patch or plaque lesions, although

FIGURE 405-24. Large plaque parapsoriasis. Erythematous patches with fine scales.

FIGURE 405-25. Mycosis fungoides. Erythematous minimally elevated plaque with "cigarette paper" wrinkling of the epidermis.

FIGURE 405-26. Mycosis fungoides. Erythematous plaques with annular elevated borders.

more commonly these lesions occur in conjunction with patches and plaques. Erythrodermic mycosis fungoides occurs as a generalized erythroderma with significant scaling and pruritus. Hyperkeratosis of the palms and soles and fissuring of hands and feet are quite common.

The diagnosis is confirmed by histologic demonstration of atypical mononuclear cells both in the epidermis and in the dermis, as well as immunophenotypic markers showing predominance of CD4 cells in the infiltrate. Treatment options are summarized in Table 405-7.[17]

BAZEX SYNDROME AND NECROLYTIC ACRAL ERYTHEMA

Patients with Bazex syndrome (acrokeratosis neoplastica) present with symmetrical, scaly, erythematous-to-violaceous hyperkeratotic plaques on acral areas, such as digits, palms, soles, nose, and ears. Almost all have involvement of the ears and ridging of the nails. Bazex syndrome is associated with malignancy, especially of lips, tongue, larynx, pharynx, and esophagus, perhaps because of cross-reactivity between tumor antigens and normal keratinocytic antigens.

TABLE 405-7 TREATMENT FOR MYCOSIS FUNGOIDES

CLINICAL TYPE	TREATMENT
Patch and localized plaque	Topical corticosteroids (e.g., triamcinolone ointment 0.1% q12h) Topical retinoids (e.g., bexarotene gel 1%, one to four times/day) Imiquimod cream three times/wk Topical mechlorethamine gel 0.016% daily Narrowband UVB (two to three times/wk)
Extensive plaques and tumors	Psoralen and UVA (PUVA; two to three times/wk) Oral bexarotene (300 mg/m^2/day) Methotrexate (15-25 mg/wk SQ) Pegylated interferon-α2A (180 μg SQ weekly) Total skin electron beam therapy Histone deacetylase inhibitors: vorinostat (400 mg/day PO); romidepsin (14 mg/m^2 IV on days 1, 8, and 15 of a 28-day cycle) Low-dose pralatrexate (15 mg/m^2 IV, weekly for 6 wk in a 7-wk cycle) Brentuximab vedotin (1.2-1.8 mg/kg, maximum dose: 150 mg IV every 3 wk) Mogamulizumab (1 mg/kg IV on days 1, 8, 15, 22 [cycle 1]; then days 1 and 15 on subsequent cycles, every 28 days) Alemtuzumab (30 mg IV three times weekly for 10-12 wk) Gemcitabine (750-1000 mg/m^2, IV, weekly for 3 wk cycles) Pegylated liposomal doxorubicin (20 mg/m^2, IV, every 2-4 wk) Radiation therapy for localized tumors
Erythrodermic	Extracorporeal photopheresis (2 consecutive days every 2-4 wk)

IV = intravenously; PO = orally; SQ = subcutaneously; UVA = ultraviolet A; UVB = ultraviolet B; wk = week.

FIGURE 405-27. Necrolytic acral erythema. Lichenified plaques with fine scales on anterior lateral ankle.

Necrolytic acral erythema is a marker of chronic hepatitis C infection (Chapter 135). It manifests with well-defined hyperkeratotic, lichenified plaques on the dorsum of the hands and feet (Fig. 405-27). Low serum zinc levels have been reported in some patients whose disease improved after oral zinc therapy.

DERMATOPHYTOSES

Fungal infections that occur as papulosquamous eruptions include tinea corporis, tinea manuum, tinea cruris, and tinea pedis. *Tinea corporis* manifests as a polycyclic erythematous scaly patch that has elevated borders consisting of papules and pustules; the border advances centrifugally. The trunk is the most common site. *Tinea cruris* has similar morphology, except it is located in the inguinal folds (Fig. 405-28). *Tinea manuum* presents as an erythematous

FIGURE 405-28. Tinea cruris. Erythematous patch with erythematous papules and scales at the periphery.

FIGURE 405-29. Tinea versicolor. Hypopigmented patches on the trunk.

scaly patch with an advancing active border, usually located on the dorsum of the hands, or it may occur as diffuse scaly patches with mild hyperkeratosis involving part or the entire surface of the palm and palmar aspect of the fingers. *Tinea pedis* can occur as scaly macerated lesions with erythema in the toe webs, or as patchy or diffuse scaliness on the sole extending to the medial and lateral aspect of the foot (moccasin distribution). The latter presentation can be associated with diffuse scaliness of one but not both palms, a condition known as the "one-hand, two-feet syndrome." The diagnosis can be confirmed by examination of skin scrapings using 10% potassium hydroxide preparation or by fungal culture. Treatment consists of topical or oral antifungal medications (e.g., clotrimazole cream, 1%, twice daily for 2 to 4 weeks, or terbinafine, 250 mg for 2 to 12 weeks), depending on the site involved. Nail involvement (Chapter 409) is best treated with systemic therapy, although typical therapies can be useful as well.

TINEA VERSICOLOR

Tinea versicolor is a fungal infection of the skin caused by *Malassezia globosa*. It occurs in otherwise healthy young individuals, especially in warm and moist environments during the summer. The prevalence is estimated to be 2 to 8% in the United States and up to 50% in the tropical countries. Clinically, it appears as asymptomatic macules and patches with very fine scales; the color can be hypopigmented, skin colored, minimally erythematous, or light brown (Fig. 405-29). The patches start as perifollicular macules, with the midchest and midback the most common sites. The diagnosis is confirmed by the characteristic appearance of the fungal elements on a 10% potassium hydroxide preparation—grapelike clusters of yeast and short, septate branching hyphae ("spaghetti and meatballs" appearance). Treatment is with zinc pyrithione 1% shampoo (applied for 5 minutes then washed off, daily for 2 weeks), topical antifungal preparations (e.g., clotrimazole cream, 1% twice daily for 4 weeks), or fluconazole 300 mg once weekly for 2 weeks.

FIGURATE ERYTHEMAS

The figurate erythemas (which include erythema annulare centrifugum, erythema gyratum repens, and erythema chronicum migrans) appear as erythematous circular or polycyclic plaques with central clearing and, frequently, a centrifugally migrating border. Occasionally, fine scaling also may be observed. The extremities are the most common sites. The diagnosis frequently can be made by the typical history and morphologic features.

Erythema annulare centrifugum is most commonly idiopathic; however, it also can be a manifestation of a hypersensitivity response to medications. Management includes identification of a precipitating agent (if possible) and treatment with topical or systemic corticosteroids. *Erythema gyratum repens* occurs as concentric erythematous plaques with fine scales, resembling a wood-grain pattern. This unusual form of figurate erythema has been associated with malignant hematologic diseases and with carcinomas of the breast, lung, gastrointestinal tract, prostate, and cervix. Treatment of the underlying malignant disease results in the resolution of the skin lesion in a few months. *Erythema chronicum migrans* is a cutaneous manifestation of Lyme disease and is caused by the spirochete *Borrelia burgdorferi* (Chapter 296); it appears as a concentric ring of erythema that progresses centrifugally from the site of a tick bite. Occasionally, it may appear as a circular erythematous patch. The diagnosis is made by a history of a tick bite, the characteristic cutaneous lesion, or elevated serum antibodies to *B. burgdorferi*. Management is the same as for Lyme disease.

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406 MACULAR, PAPULAR, PURPURIC, VESICULOBULLOUS, AND PUSTULAR DISEASES

DANIELA KROSHINSKY

MACULAR AND PAPULAR EXANTHEMS

An exanthem, which is an acute generalized eruption of the skin, can be scarlatiniform or morbilliform. Scarlatiniform eruptions consist of innumerable small papules that coalesce into confluent blanching erythema (Chapter 338). Morbilliform eruptions are erythematous macules and flat papules that resemble the eruption of measles. Morbilliform eruptions can be caused by viral infections or by hypersensitivity reactions to medications (Chapter 407) (Table 406-1).

TABLE 406-1 EXANTHEMS

SCARLATINIFORM ERUPTIONS
Scarlet fever (see below)
Toxic shock syndrome (Chapter 269)
Kawasaki disease (Chapter 249)
MORBILLIFORM ERUPTIONS
Measles (Chapter 338)
Rubella (Chapter 339)
Erythema infectiosum (Chapter 342)
Roseola (Chapter 345)

SCARLATINIFORM ERUPTIONS

SCARLET FEVER

Scarlet fever is a sequela of toxin-producing β-hemolytic streptococcal infection (Chapter 269) of the ears, nose, throat, or skin, although *Staphylococcus aureus* (Chapter 267), *Haemophilus influenzae* (Chapter 277), or *Clostridioides* spp. (Chapter 271) cause occasional cases. The skin lesions often are accompanied by fever, headache, malaise, chills, sore throat, and vomiting.

On physical examination, the mucous membranes are usually erythematous with petechiae. A white membrane is often seen on the tongue, and tonsillitis may be present. The rash, which appears after the fever, is typically fine erythematous papules, beginning on the upper torso and then spreading. The face is characteristically flushed, with circumoral pallor. The rash persists for 4 to 5 days and is followed by desquamation.

Treatment is oral penicillin V 500 mg two to three times daily for 10 days or a single dose of intramuscular benzathine penicillin G (1.2 million units). Clinical recovery may take only 4 to 5 days but the rash typically takes several weeks to resolve.

TOXIC SHOCK SYNDROME

Toxic shock syndrome is an acute febrile illness, usually caused by toxin-producing *S. aureus* (Chapter 267) but sometimes caused by *Streptococcus* spp. (toxic shock–like syndrome [Chapter 269]). Most cases are in previously healthy adults between 20 and 50 years of age.

CLINICAL MANIFESTATIONS

The clinical manifestations of toxic shock syndrome are a result of the massive release of tumor necrosis factor-α (TNF-α) and interleukin-1: fever, diffuse macular erythema (Fig. 403-5 in Chapter 403), severe conjunctival involvement, and erythema of the mucous membranes of the lungs, liver, gastrointestinal tract, and kidneys. Blood cultures are positive in about 5 to 15% of patients who have staphylococcal toxic shock syndrome and about 50% of patients who have streptococcal toxic shock–like syndrome.

TREATMENT

For staphylococcal toxic shock syndrome caused by methicillin-sensitive organisms, treatment is oxacillin or nafcillin (2 g IV every 4 hours) or cefazolin (2 g IV every 8 hours) in the setting of a true penicillin allergy plus clindamycin (900 mg IV every 8 hours). For staphylococcal toxic shock syndrome due to methicillin-resistant *S. aureus*, treatment is vancomycin (15 to 20 mg/kg every 8 to 12 hours, not to exceed 2 g per dose) plus clindamycin (900 mg IV every 8 hours).

Streptococcal toxic shock syndrome should be empirically treated with clindamycin (900 mg IV every 8 hours) plus penicillin G (4 million units IV every 4 hours) until susceptibilities return. Alternatives to penicillin are ceftriaxone (1 to 2 g IV every 12 hours), cefazolin (1 to 2 g IV every 8 hours), vancomycin (30 mg/kg/day IV in two divided doses) or daptomycin (6 mg/kg IV every 24 hours).

PROGNOSIS

Desquamation of the skin of the palms and soles typically occurs 1 to 2 weeks after the onset. Staphylococcal toxic shock syndrome has a mortality of 5 to 15%, whereas the mortality rate for streptococcal toxic shock–like syndrome can be five times higher.

KAWASAKI DISEASE

Kawasaki disease (Chapter 249), which is a systemic vasculitis of unknown etiology, is primarily an illness of children under age 5 years, but it also can occur in adults. It is far more common in patients of Northwestern Asian descent.[1]

CLINICAL MANIFESTATIONS

Patients typically present with very high fever and a scarlatiniform, morbilliform, urticarial, or targetoid rash. Other features include conjunctival infection, hemorrhagic and dry, fissured lips, a "strawberry tongue," and cervical lymphadenitis. Arthralgias, frank arthritis, urethritis, diarrhea, pneumonitis, and aseptic meningitis can occur, but the most serious complications in untreated patients are coronary artery aneurysms and myocarditis.

DIAGNOSIS

No diagnostic tests are helpful, so the diagnosis is clinical and is based on the typical rash and the development of myocarditis.

TREATMENT

Acute treatment is a single infusion of 2 g/kg of IV gamma globulin (IVIG) given over 8 to 12 hours within 10 days of the onset of fever. Aspirin (30 to 50 mg/kg/day divided into 4 daily doses until defervescence, then reduced to 3 to 5 mg/kg/day) is also indicated. The concomitant use of supplemental intravenous corticosteroids under expert supervision results in a lower incidence of coronary artery aneurysm in at-risk individuals.[2]

MORBILLIFORM ERUPTIONS

Acute viral infections that can cause morbilliform rashes include measles (Chapter 338), rubella (Chapter 339), erythema infectiosum (Chapter 342), and roseola (Chapter 345). With measles, the enanthem (Koplik spots; see Fig. 338-2 in Chapter 338) precedes the exanthem (Fig. 338-3 in Chapter 338) by 1 to 2 days and persists for 2 to 4 days. The exanthem begins on the fourth or fifth day, typically with papules on the face and behind the ears, with subsequent spread to the trunk and extremities. The exanthem of rubella (Fig. 339-1 in Chapter 339) starts as pink facial macules and papules that spread to the trunk and extremities and that persist for only 1 to 3 days. In erythema infectiosum (Chapter 342), a bright red erythema develops suddenly over the cheeks (Fig. 342-1 in Chapter 342), followed within 1 to 4 days by an erythematous morbilliform rash on the extremities (Fig. 406-1). In roseola (Chapter 345), 2 or so days of pink papules or blanchable macular erythema typically follow defervescence after a high fever.

These viruses are typically diagnosed on clinical grounds, but polymerase chain reaction testing is both sensitive and specific.[3] For each of these viruses, treatment is supportive because no antiviral therapy is efficacious.

PAPULAR ERUPTIONS

INFECTIOUS ERUPTIONS

Molluscum Contagiosum

In molluscum contagiosum (Chapter 343), patients develop individual, grouped, or widely disseminated, skin-colored or pink papules that are firm, smooth, frequently umbilicated, and usually 2 to 6 mm in diameter (Fig. 406-2). In patients who are infected with human immunodeficiency virus (HIV), hundreds of lesions may be seen. The diagnosis is clinical.

ABSTRACT

Macular, papular, purpuric, vesiculobullous, and pustular diseases include exanthems, toxin-mediated diseases, primary skin infections, vasculitis, embolic phenomena, thrombotic sequelae, autoimmune blistering diseases, and hypersensitivity reactions. By using a systematic morphologic approach, the general physician can generate a differential diagnosis for each type of skin lesion, understand the underlying pathogenesis, and decide on appropriate medical therapy or referral options.

KEYWORDS

morbilliform
exanthem
purpura
pemphigoid
pemphigus
warts
herpes
acne
rosacea
hidradenitis

FIGURE 406-1. Reticulate macular erythema on the thigh of a patient with erythema infectiosum. (Courtesy Neil J. Korman, MD.)

FIGURE 406-2. Pustular presentation of inflamed molluscum contagiosum. A culture revealed only normal skin flora. (From Mancini AJ, Shani-Adir A, Sidbury, R. Other viral diseases. In: Bolognia JL, Schaffer JV, Cerroni L, eds. *Dermatology*. 4th ed. Elsevier; 2018:1440.)

Treatment options include cryotherapy with liquid nitrogen, curettage, cantharidin, podophyllin, and oral cimetidine (up to 40 mg/kg/day).

Warts

Warts are benign skin and mucosal proliferations caused by over 150 types of human papillomaviruses (HPVs) (Chapter 344). Common warts, which can occur anywhere on the body, are firm, hyperkeratotic papules ranging in size from 1 mm to more than 1 cm (Fig. 406-3). Other variants include genital warts, flat warts, and deep palmoplantar warts. The diagnosis is clinical, but biopsy should be performed on larger or atypical lesions to exclude malignant transformation. Common topical treatments include liquid nitrogen, cantharidin, or podophyllin, as well as prescription-strength salicylic acid, imiquimod, 5-fluorouracil, or cidofovir. Over-the-counter liquid nitrogen is not as cold and, as a result, not as effective as in-office treatment. Repeat cryotherapy is usually required until clearance is achieved.

PURPURIC ERUPTIONS

Purpuric eruptions occur when the extravasation of blood results in visible skin or mucosal hemorrhage. They are classified based on: their size as petechiae (≤4 mm; Table 406-2; Fig. 406-4), macular purpura (>4 to 10 mm; Fig. 406-5), or ecchymoses (>10 mm); and their morphology as palpable purpura (Table 406-3), and inflammatory and noninflammatory retiform purpura (Table 406-4).

FIGURE 406-3. Hand of a patient with verruca vulgaris revealing many verrucous papules. (Courtesy Neil J. Korman, MD.)

TABLE 406-2 DIFFERENTIAL DIAGNOSIS OF MACULAR PETECHIAE, PURPURA, AND ECCHYMOSES

MACULAR PETECHIAE (≤4 mm IN DIAMETER)
Thrombocytopenia (platelets <50,000/μL) (Chapter 158)
Increased venous pressure
Trauma (Chapter 97)
Vitamin C deficiency (Chapter 199)
Pigmented purpuric eruptions
Waldenström macroglobulinemia (Chapter 173)
MACULAR PURPURA (5-9 mm)
Waldenström macroglobulinemia (Chapter 173)
Thrombocytopenia with infection or inflammation (Chapter 158)
Cutaneous small vessel vasculitis (Chapter 249)
MACULAR ECCHYMOSES (≥1 cm)
Anticoagulation (Chapter 70)
Hepatic insufficiency (Chapters 148 and 149)
Vitamin K deficiency (Chapter 161)
Disseminated intravascular coagulation (Chapter 161)
Actinic (solar, senile) purpura
Corticosteroid therapy, topical or systemic
Vitamin C deficiency (Chapter 199)
Systemic amyloidosis (Chapter 174)
Ehlers-Danlos syndrome (Chapter 239)
Thrombocytopenia (Chapter 158)
Platelet function defects (e.g., von Willebrand disease; Chapter 159)

NONPALPABLE PURPURA

Petechiae

A common cause of petechiae is Schamberg disease, which is a pigmented purpuric dermatitis in which petechiae result from idiopathic capillaritis. Most often seen in middle-aged to older adults, Schamberg disease presents with yellow-brown patches on the lower legs with overlying petechiae that are cayenne pepper colored. Lesions occasionally can be present on the trunk, buttocks, arms, and thighs. The lesions become hyperpigmented and then fade, with new lesions occurring over time. Topical steroids (see Table 403-10), ascorbic acid 500 mg twice daily, with or without rutoside 50 mg twice daily, can be helpful.

Systemic diseases that can result in petechiae include idiopathic thrombocytopenic purpura (Chapter 158), thrombocytopenia-caused diseases or medications that reduce platelet production (Chapter 158), abnormal platelet function as a result of renal or hepatic insufficiency (Chapters 116 and 139), and clotting factor abnormalities (Chapter 160). Treatment is for the underlying condition.

Macular Purpura

Waldenström macroglobulinemia (Chapter 173) presents with recurrent petechiae and macular purpura on the legs, typically associated with itching,

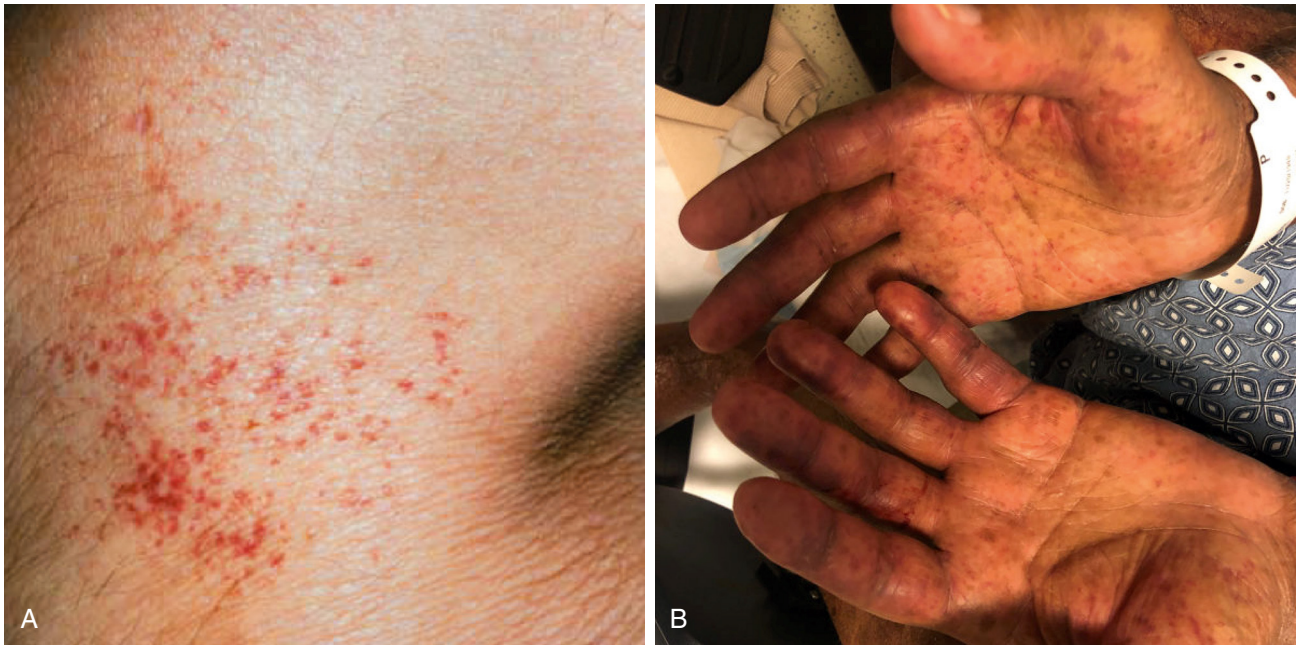

FIGURE 406-4. **Petechiae. A,** Round to oval petechiae, <3 mm in diameter. (From Piette WW. Purpura: mechanisms and differential diagnosis. In: Bolognia J, Schaffer J, Cerroni L, eds. *Dermatology*. 4th ed. Elsevier; 2018:377.) **B,** Petechiae and macular purpura on the palms. (Courtesy of Daniela Kroshinsky, MD MPH.)

FIGURE 406-5. **Palpable purpura due to cutaneous small vessel vasculitis (inflammation plus hemorrhage).** (From Piette WW. Purpura: mechanisms and differential diagnosis. In: Bolognia J, Schaffer J, Cerroni L, eds. *Dermatology*. 4th ed. Elsevier; 2018:377.)

stinging, or burning in the setting of a polyclonal hypergammaglobulinemia and high immunoglobulin G (IgG) or IgA rheumatoid factor titers. Some patients subsequently develop autoimmune connective tissue disease, especially Sjögren syndrome (Chapter 247) or lymphoma (Chapters 171 and 172).

Ecchymoses

Minor trauma in individuals who have lost dermal connective surrounding blood vessel tissue can result in macular ecchymoses. Solar purpura (Fig. 406-6), which is caused by aging and chronic sun exposure, is commonly seen on the forearms. Steroid purpura, which is related to prolonged treatment with topical or systemic corticosteroids, can develop anywhere on the skin (Chapter 28). Similar systemic examples include systemic amyloidosis (Chapter 174), scurvy (Chapter 199), and Ehlers-Danlos syndrome (Chapter 239).

PALPABLE PURPURA

Vasculitis

Palpable purpura is caused by inflammatory damage to small or small and medium-sized vessels, and the clinical findings depend on the size of the affected vessel.[4] Leukocytoclastic vasculitis, which is the most common form of small-vessel vasculitis (Fig. 406-7), may be idiopathic, but it also can be associated with infection, drug reactions, connective tissue disease, and underlying malignancy.[5] Some cases may be associated with systemic symptoms or systemic lupus erythematosus (Chapter 245).

TABLE 406-3 PALPABLE PURPURA: INFLAMMATORY PALPABLE PURPURA WITH PROMINENT EARLY ERYTHEMA

LEUKOCYTOCLASTIC VASCULITIS WITH IMMUNE COMPLEX DISEASE
Small Vessels Only
Idiopathic, infection-associated, or drug-associated
Waldenström macroglobulinemia (Chapter 173)
Urticarial vasculitis
IgA vasculitis (Henoch-Schönlein purpura)
Pustular vasculitis
Small- and Medium-Sized Vessels
Mixed cryoglobulinemia (Chapter 173)
Systemic lupus erythematosus (Chapter 245)
Rheumatoid arthritis (Chapter 243)
Sjögren syndrome (Chapter 247)
PAUCI-IMMUNE LEUKOCYTOCLASTIC VASCULITIS
Microscopic polyangiitis
Granulomatosis with polyangiitis (Chapter 249)
Eosinophilic granulomatosis with polyangiitis (Chapter 249)
Erythema elevatum diutinum
Sweet syndrome
OTHER
Erythema multiforme (see later)
Pityriasis lichenoides et varioliformis acuta
Pigmented purpuric eruptions (see above)
Waldenström macroglobulinemia (Chapter 173)

DIAGNOSIS

A complete blood count with differential, renal and liver function testing, and urinalysis with microscopy should be performed. Specialized tests should be ordered for idiopathic or chronic cases or based on a thorough review of systems (see Table 406-3) and can include cryoglobulins; rheumatoid factor; serologies for testing for hepatitis B and C, and HIV; levels of total complement, C3, C4; antineutrophil cytoplasmic antibodies (ANCAs); anti-nuclear antibody (ANA); double-stranded DNA (dsDNA); and anti-Ro, anti-La, anti-RNP, and anti-Sm antibodies.

Biopsy and clinical correlation are often required to confirm the clinical diagnosis (E-Fig. 406-1). Skin biopsy specimens taken from lesions within

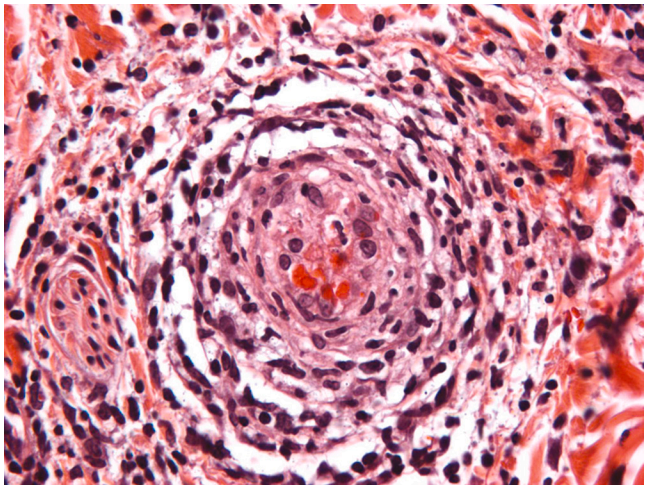

E-FIGURE 406-1. Leukocytoclastic vasculitis. Histologic evaluation reveals a smudged blood vessel in the dermis with neutrophils, neutrophilic dust, and red blood cells. (Courtesy Neil J. Korman, MD.)

TABLE 406-4 DIFFERENTIAL DIAGNOSIS OF RETIFORM (ANGULATED OR BRANCHED) PURPURA

NONINFLAMMATORY RETIFORM PURPURA
Protein C or protein S deficiency (Chapter 67)
Warfarin necrosis (Chapter 70)
Heparin necrosis
Thrombocytosis due to myeloproliferative neoplasms (Chapter 152)
Thrombotic thrombocytopenic purpura (Chapter 158)
Paroxysmal nocturnal hemoglobinuria (Chapter 146)
Cold agglutinins (Chapter 146)
Cryoglobulinemia (Chapter 173)
Cryofibrinogenemia (Chapter 66)
Vessel-invasive fungi (Chapter 311)
Ecthyma gangrenosum (Chapter 408)
Disseminated strongyloides (Chapter 327)
Postinfectious purpura fulminans
Antiphospholipid antibody (Chapter 67)
Livedoid vasculopathy (Chapter 66)
Malignant atrophic papulosis
Cholesterol emboli (Chapter 66)
Tumor emboli (Chapter 47)
Marantic endocarditis (Chapter 47)
Sickle cell disease (Chapter 149)
Malaria (Chapter 316)
Cutaneous calciphylaxis (Chapter 116)
Brown recluse spider bite (Chapter 98)
B-cell lymphoma (Chapter 171)
Calciphylaxis, oxalosis
INFLAMMATORY RETIFORM PURPURA
Vasculitis
Systemic lupus erythematosus (Chapter 245)
Polyarteritis nodosa (Chapter 249)
Rheumatoid arthritis (Chapter 243)
Mixed cryoglobulinemia (Chapter 173)
Granulomatosis with polyangiitis (Chapter 249)
Eosinophilic granulomatosis with polyangiitis (Chapter 249)
Chilblains (Chapter 66)
Pyoderma gangrenosum (Chapter 403)

FIGURE 406-6. Solar (actinic) purpura in sites of actinic damage plus trauma. (Courtesy Kalman Watsky, MD. From Piette WW. Purpura: mechanisms and differential diagnosis. In: Bolognia J, Schaffer J, Cerroni L, eds. *Dermatology*. 4th ed. Elsevier; 2018:377.)

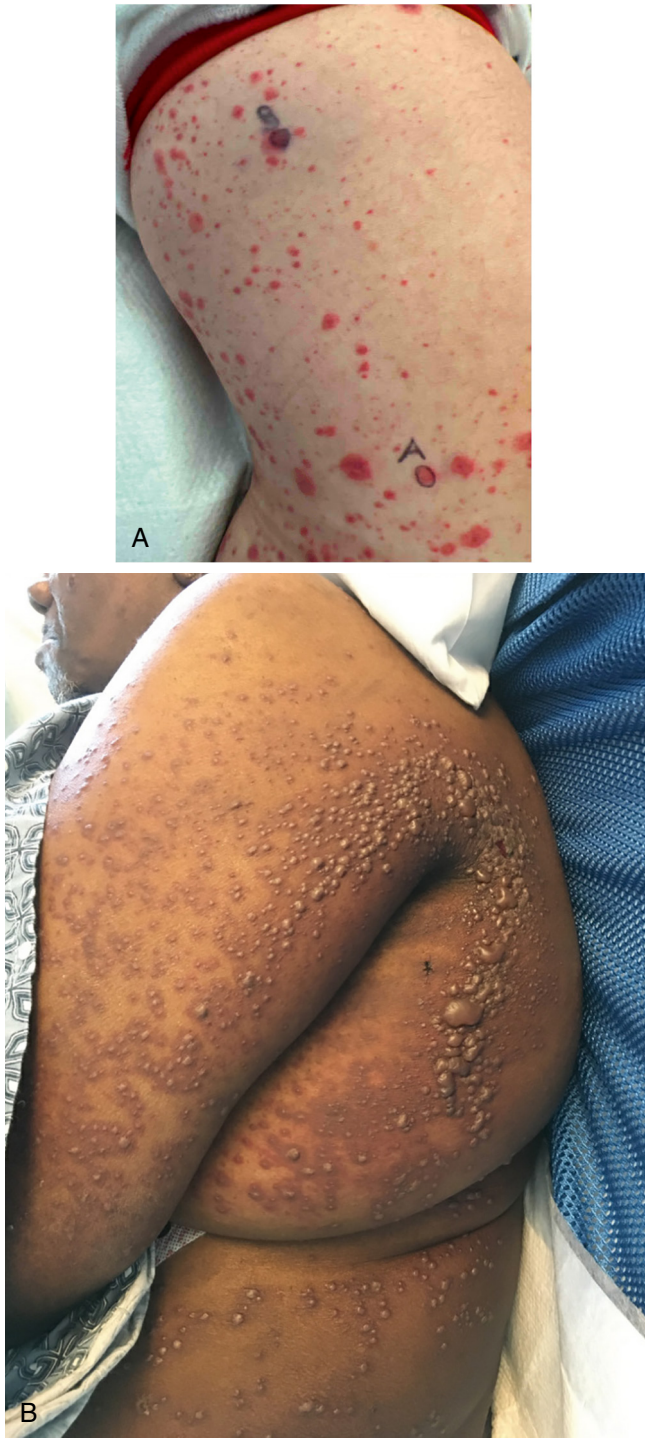

FIGURE 406-7. Palpable purpura. A, Leukocytoclastic vasculitis commonly causes raised purpuric and ulcerated lesions on the legs. **B,** Bullous leukocytoclastic vasculitis. (Courtesy Daniela Kroshinsky, MD MPH.)

48 hours of formation reveal a granular pattern of C3, IgG, IgM, and/or IgA deposits in blood vessel walls on direct immunofluorescence.

Patients with IgA vasculitis/Henoch-Schönlein purpura, which usually follows a streptococcal or staphylococcal infection in adults, have perivascular deposits of IgA and C3 on skin biopsy. Patients may have fever, arthralgias, and abdominal pain, and they are at risk for renal vasculitis (Chapter 107).

Urticarial or hypocomplementemic vasculitis (Chapter 249) generally persists for more than 24 hours and is associated with arthritis, facial and laryngeal edema, and low levels of serum complement. A clinical clue differentiating vasculitis from routine urticaria is that vasculitic lesions may heal with hyperpigmentation or purpura.

TREATMENT

Treatment is based on the diagnosis. For idiopathic leukocytoclastic vasculitis, oral treatment options include colchicine (0.6 mg twice daily); prednisone (1 mg/kg/day); or dapsone (up to 200 mg once daily). In severe cases, immunosuppressive options under expert supervision include mycophenolate mofetil (up to 45 mg/kg); azathioprine (up to 2.5 mg/kg); or cyclophosphamide (up to 2.5 mg/kg) can be continued until the disease becomes inactive.

RETIFORM PURPURA

Retiform purpura is defined as large patches of purpura, each with a netlike or angulated border. Retiform purpura can be inflammatory or noninflammatory but typically is not raised.

FIGURE 406-8. Polyarteritis nodosa. Retiform purpura of the dorsal foot in a patient with *systemic* polyarteritis nodosa. (From Wetter DA, Dutz JP, Shinkai K, et al. Cutaneous vasculitis. In: Bolognia JL, Schaffer JV, Cerroni L, eds. *Dermatology*. 4th ed. Elsevier; 2018:435.)

Inflammatory Retiform Purpura

Inflammatory retiform purpura is characterized by stellate or branching purpura, but early lesions also demonstrate prominent surrounding erythema (Fig. 406-8) and frequently reflect a vasculitic process. The skin lesions can be associated with microscopic polyangiitis (Chapter 249), granulomatosis with polyangiitis (Chapter 249), and eosinophilic granulomatosis with polyangiitis (Chapter 249).

In granulomatosis with polyangiitis, palpable purpura and oral ulcerations are the most common lesions, but patients may also develop painful subcutaneous nodules and ulcers that mimic pyoderma gangrenosum. In eosinophilic granulomatosis with polyangiitis, the skin disease usually presents as palpable purpura with necrosis on the legs, but retiform purpura, urticaria, subcutaneous nodules, livedo racemosa, and papulonecrotic lesions may be seen.

Skin biopsy and ANCA testing are often key to the diagnosis of these conditions, and treatment is for systemic disease (Chapter 249). The skin lesions generally resolve when the systemic disease responds to treatment.

Noninflammatory Retiform Purpura

Cutaneous Emboli

Cutaneous emboli, especially cholesterol emboli (Chapter 66) and infectious emboli (Chapter 61), can lead to retiform as well as palpable purpura. Cholesterol emboli, which tend to affect older patients with advanced atherosclerotic disease, can occur spontaneously upon fragmentation of an atheromatous plaque or, more commonly, acutely after catheterization, within hours to days after thrombolysis, or months after the initiation of systemic anticoagulation. Other symptoms and signs can include fever, altered mental status, myalgias, weight loss, acute kidney injury (Chapter 106), and new or worsened arterial hypertension. In addition to the acute onset of retiform purpura, patients may also develop cyanosis (Fig. 406-9), distal livedo reticularis, nodules, ulceration, and even gangrene. Up to 80% of patients have peripheral eosinophilia.

Emboli with retiform or palpable purpura can be seen in patients with infectious endocarditis (Chapter 61) and are most commonly seen in acute meningococcemia (Fig. 274-2 in Chapter 274) and disseminated gonococcal infection (Fig. 275-4 in Chapter 275). In ecthyma gangrenosum, patients infected with *Pseudomonas aeruginosa* (Chapter 282) or less commonly *Klebsiella* spp (Chapter 281), *Escherichia coli* (Chapter 280), or *Serratia* spp (Chapter 281) develop erythematous papules and plaques with central purpura and hemorrhagic necrosis. Fungal infections also have been implicated in immunocompromised patients.

Other emboli that may cause petechiae or purpura include fat emboli after bone trauma (Chapters 68 and 97), emboli from an atrial myxoma (Chapter 47) or ventricular thrombus, and emboli from nonbacterial thrombotic endocarditis (Chapter 47).

Thrombi

Noninflammatory retiform purpura can occur when patients with disseminated intravascular coagulation (DIC) (Chapter 161), thrombotic thrombocytopenic purpura (Chapter 158), monoclonal cryoglobulinemia (Chapter 173), calciphylaxis, and drug reactions to warfarin (Chapter 70) develop in situ thrombi. DIC also can be associated with hemorrhagic bullae and purpura fulminans (Fig. 406-10). Cryoglobulinemia (Chapter 173) may be associated with leukemia, lymphoma, multiple myeloma, and Waldenström macroglobulinemia (Chapter 173). Another thrombotic cause of purpura is thrombotic thrombocytopenic purpura (Chapter 158).

FIGURE 406-9. Cholesterol emboli. Both livedo reticularis and retiform purpura are seen distally. (Courtesy Norbert Sepp, MD. From Piette WW. Cutaneous manifestations of microvascular occlusion syndromes. In: Bolognia JL, Schaffer JV, Cerroni L, eds. *Dermatology*. 4th ed. Elsevier; 2018:399.)

FIGURE 406-10. Purpura fulminans. Purpura and hemorrhagic blisters are seen on the arm of this patient.

Warfarin skin necrosis (Chapter 70), which is an uncommon complication that typically occurs between the third and tenth day of therapy in patients who are not also receiving bridging heparin anticoagulation, presents as painful erythematous to purpuric plaques (especially on the breasts, thighs, and buttocks) that can progress to hemorrhagic bullae. The course of the disease is not dependent on whether or not warfarin therapy is continued.

VESICULOBULLOUS DISEASES

Vesicles are clear, fluid-filled lesions smaller than 1 cm, whereas bullae are similar lesions larger than 1 cm. Causes of vesiculobullous lesions include genetic and immunologic conditions, infections, hypersensitivity reactions, metabolic or physical disorders, and inherited genetic defects (Table 406-5).[6]

IMMUNOLOGICALLY MEDIATED BLISTERING DISEASES

Immunologically mediated blistering diseases are caused by autoantibodies that bind to components of the epidermal desmosome (pemphigoid) or

TABLE 406-5 VESICULOBULLOUS DISEASES

GENETIC AND IMMUNOLOGIC
Bullous pemphigoid
Pemphigoid gestationis
Mucous membrane pemphigoid
Epidermolysis bullosa acquisita
Dermatitis herpetiformis
Linear immunoglobulin A bullous dermatosis
Pemphigus
Vulgaris
Foliaceus
Paraneoplastic
INFECTIOUS DISEASES
Bullous impetigo
Herpes simplex
Varicella
Herpes zoster
HYPERSENSITIVITY
Erythema multiforme
Stevens-Johnson syndrome
Toxic epidermal necrolysis
METABOLIC/PHYSICAL
Porphyria cutanea tarda
Pseudoporphyria
Coma bulla
Bullous diabeticorum

Courtesy Neil J. Korman, MD.

FIGURE 406-11. Bullous pemphigoid. Tense subepidermal bullae are seen on an erythematous base. (Courtesy Neil J. Korman, MD.)

hemidesmosome (pemphigus), where they activate complement and precipitate inflammation. Inflammatory cell proteases can degrade basement membrane proteins, thereby leading to the formation of subepidermal (pemphigoid) or intraepidermal (pemphigus) blisters.

SUBEPIDERMAL BLISTERING DISORDERS

BULLOUS PEMPHIGOID

Bullous pemphigoid is an autoimmune blistering disease most commonly seen in elderly individuals or as an adverse effect of medications.[7] Patients develop pruritic, tense vesicles, bullae, and urticarial or eczematous plaques on the torso and extremities, including the palms and soles. Mucosal involvement can include the oral, laryngeal, and genital regions (Fig. 406-11). The diagnosis should also be considered in elderly patients who present with chronic, unexplained pruritic eruptions without bullae.

On skin biopsy, the subepidermal blisters have an eosinophilic infiltrate with linear IgG and C3 deposits at the basement membrane and IgG antibodies on the epidermal side. Indirect immunofluorescence, which has a lower sensitivity but higher specificity, can be helpful in assessing with clinically suspicious cases that are not evident on skin histology.[8]

TREATMENT

An ultrapotent (class 1) topical steroid can be used for patients with limited involvement, whereas oral prednisone (1 mg/kg/day) is rapidly effective in patients with moderate and severe disease.[9] Steroid-sparing agents should be initiated under expert supervision to allow steroids to be tapered over several weeks after the formation of new lesions has ceased; effective options include: dapsone (up to 200 mg/day), methotrexate (up to 25 mg weekly), azathioprine (up to 2.5 mg/kg as guided by the patient's thiopurine methyltransferase level), and mycophenolate mofetil (up to 4 g divided into two daily doses). Refractory cases or patients who have side effects from these standard treatments may benefit from IVIG (2 g/kg divided over 2 to 3 days), rituximab (375 mg/m^2 weekly for 4 weeks or 1000 mg given 2 weeks apart), omalizumab[10] (300 mg every 2 to 8 weeks or 375 mg every 2 to 4 weeks), or dupilumab (300 mg every other week) under expert supervision.[11] The duration of therapy is guided by the activity of the disease and its response to medication.

FIGURE 406-12. Pemphigoid gestationis. Multiple tense blisters and erosions on an erythematous base are present. (Courtesy Neil J. Korman, MD.)

PROGNOSIS

In most patients, treatment suppresses the disease until the process fully resolves several years later. Left untreated, bullous pemphigoid generally undergoes spontaneous remissions and exacerbations with a high risk of infection.

PEMPHIGOID GESTATIONIS

Pemphigoid gestationis is a rare autoimmune dermatosis predominantly arising in late pregnancy and/or immediately postpartum, although it can occur at any time during pregnancy. Intensely pruritic periumbilical urticarial plaques, which spread peripherally, progress to vesicles and blisters (Fig. 406-12). The face, palms, soles, and mucous membranes are typically spared. Skin biopsy shows bullous pemphigoid antigen II and linear C3 deposition in the basement membrane.

TREATMENT

Patients with mild disease should be treated with moderate or high-potency topical corticosteroids (see Table 403-10) twice daily to affected areas. Systemic corticosteroids (e.g., prednisone, 0.5 to 1 mg/kg once daily) should be reserved for patients who have extensive disease—usually 1 to 2 weeks of full-dose therapy, followed by a taper to the lowest effective dose. Antihistamines can be helpful in controlling itch. Women should be managed by experienced obstetricians because of the increased risk of premature labor and of the delivery of infants who are small for their gestational age.

MUCOUS MEMBRANE PEMPHIGOID

Mucous membrane pemphigoid presents as blisters on oral, nasopharyngeal, ocular, laryngeal, anogenital, and esophageal surfaces. The scarring associated with their healing can cause substantial morbidity (Fig. 406-13).

Some patients with mucous membrane pemphigoid have circulating IgG autoantibodies against laminin 332 on the dermal side of skin, others have pure ocular disease with IgG antibodies against β_4 integrin, others have mucosal and skin lesions, and yet others have oral but not skin lesions. Biopsy shows

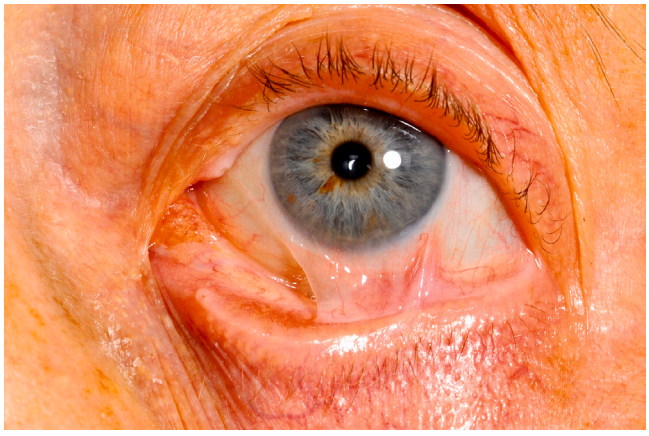

FIGURE 406-13. Mucous membrane (cicatricial) pemphigoid. Typical ocular involvement as manifested by fibrous tracts, representing partial or incomplete symblepharon. (From Bernard P, Borradori L. Pemphigoid group. In: Bolognia J, Schaffer J, Cerroni L, eds. *Dermatology*. 4th ed. Elsevier; 2018:521.)

subepidermal blister with basement membrane deposits of linear IgG, IgA, and C3, whereas circulating IgG and/or IgA antibodies are seen on indirect immunofluorescence.

TREATMENT

Treatment for mild disease is twice daily potent topical corticosteroids (or intralesional corticosteroids in patients with only oral disease). For ocular or significant oral disease, prednisone (1 mg/kg daily), cyclophosphamide (up to 2.5 mg/kg daily), rituximab (375 mg/m^2 weekly for 4 weeks or 1000 mg given 2 weeks apart), and IVIG (2 g/kg given over 2 to 3 days) may be required under expert supervision.[12]

Mucous membrane pemphigoid is a chronic condition, and untreated ocular disease may lead to blindness.

EPIDERMOLYSIS BULLOSA ACQUISITA

Epidermolysis bullosa acquisita, which is an acquired autoimmune blistering disease, generally occurs in middle age. It can present as noninflammatory acral blisters, which heal with scarring, or as generalized inflammatory vesiculobullous disease. Biopsy shows subepidermal blisters with linear basement membrane IgG deposits that target collagen VII.

TREATMENT

Epidermolysis bullosa acquisita is a chronic condition, and it can be refractory to treatment. Standard treatments, which are only occasionally successful, include colchicine (0.6 mg twice daily), dapsone (up to 200 mg/day), azathioprine (up to 2.5 mg/kg), or cyclophosphamide (2.5 mg/kg/day) alone or combined with prednisone (60 mg daily). For severe or refractory disease, options include cyclosporine (up to 5 mg/kg), rituximab (375 mg/m^2 weekly for 4 weeks or 1000 mg given 2 weeks apart), IVIG (2 g/kg given over 2 to 3 days), plasmapheresis, and extracorporeal photopheresis.

DERMATITIS HERPETIFORMIS

Dermatitis herpetiformis is an immune-mediated vesicular disease that occurs by middle age, almost always in patients who have a clinically known or subclinical gluten-sensitive enteropathy (Chapter 126). Skin lesions, which are very pruritic, can be grouped vesicles, papules, or erosions on the scalp, posterior neck, buttocks, and extensor surfaces of the elbows and knees (Fig. 406-14).[13] Many patients have other autoimmune medical conditions, such as diabetes or thyroid disease. Biopsy shows dermal papillary granular IgA deposits and neutrophilic microabscesses. In most patients, circulating IgA antibodies against tissue transglutaminase establish the diagnosis.

TREATMENT

The skin disease can sometimes be controlled by diet alone, but the condition is lifelong. Treatment options also include twice-daily high-potency topical steroids (see Table 403-10) and dapsone (up to 200 mg/day) given chronically.

FIGURE 406-14. Dermatitis herpetiformis. The elbow of a patient has erosions, erythematous papules and vesicles. (Courtesy Daniela Kroshinsky, MD MPH.)

LINEAR IMMUNOGLOBULIN A BULLOUS DERMATOSIS

Linear IgA bullous dermatosis is an acquired autoimmune blistering disease that is usually associated with medications, especially vancomycin. Primary vesicles and bullae develop mainly on the flexural regions, but they can involve the oral mucous membranes and become generalized. Biopsy shows a subepidermal vesicle with neutrophil predominance and linear IgA specific for a portion of bullous pemphigoid antigen II at the basement membrane. Circulating IgA antibodies are detected on indirect immunofluorescence.

TREATMENT

Patients usually respond to cessation of the offending medication and to dapsone (up to 200 mg/day). If the lesions do not respond or rapid control of severe disease is needed, prednisone (1 mg/kg once daily) can be prescribed.

INTRAEPIDERMAL BLISTERING DISORDERS

PEMPHIGUS

Pemphigus refers to a group of intraepidermal autoimmune blistering diseases that affect the skin and mucous membranes.[14] Pemphigus is seen most commonly in middle-age adults.

In *pemphigus vulgaris,* autoantibodies target desmoglein III. In *pemphigus foliaceus,* autoantibodies target desmoglein I. In *paraneoplastic pemphigus,* circulating antibodies react with a complex of proteins, including desmoplakin I and II, desmoglein I and III, bullous pemphigoid antigen I, envoplakin, and periplakin.

With pemphigus vulgaris, patients have flaccid blisters and erosions, which may be pruritic, in the oropharynx (Fig. 406-15), head, neck, and trunk. Patients with pemphigus foliaceus typically have erythema, scaling, and crusting on their scalp, face, and upper torso. Paraneoplastic pemphigus is characterized by ocular and oral blisters and erosions, as well as by polymorphous skin lesions that can resemble lichen planus, erythema multiforme, or pemphigoid. Associated malignancies include non-Hodgkin lymphoma (40%; Chapter 171); chronic lymphocytic leukemia (30%; Chapter 169); Castleman disease (10%; Chapters 171 and 359); thymomas (6%; Chapter 390); sarcomas (6%; Chapter 187); and Waldenström macroglobulinemia (6%; Chapter 173). Some patients can develop severe bronchiolitis obliterans.

In pemphigus vulgaris, biopsy shows suprabasilar acantholysis and deposits of IgG to desmoglein III. In pemphigus foliaceus, biopsy shows subcorneal acantholysis with IgG against desmoglein I. In patients with paraneoplastic pemphigus, biopsy shows suprabasilar acantholysis and dyskeratotic keratinocytes as well as antibodies to plakin proteins and IgG antibodies that are indistinguishable from those seen in pemphigus vulgaris.

TREATMENT

Treatment depends on the subtype and extent of pemphigus, as well as the rate of disease progression and the patient's age. Oral prednisone (e.g., 1 mg/kg once daily) is indicated for the initial treatment of pemphigus vulgaris; topical corticosteroids (e.g., 0.05% fluocinonide ointment applied twice daily to affected areas) sometimes can control pemphigus foliaceus. Adding rituximab (375 mg/m^2 weekly for 4 weeks or 1000 mg IV separated by 2 weeks) to short-term (3 to 6 months) prednisone appears to be safer and more effective than longer-term

prednisone alone,[A1] especially for extensive or recalcitrant disease, and it can induce remission. It is also superior to mycophenolate mofetil (35 to 45 mg/kg/day divided into two daily doses) for controlling the disease but at the expense of more adverse events.[A2] Other steroid-sparing agents for pemphigus vulgaris under expert supervision include azathioprine (up to 2.5 mg/kg), cyclophosphamide (up to 2.5 mg/kg), cyclosporine (3 to 5 mg/kg/day), and methotrexate (up to 25 mg/week). Plasmapheresis has been reported to be efficacious as well.

Systemic treatment of pemphigus foliaceus includes all of these same agents as well as dapsone (up to 200 mg/day) and hydroxychloroquine (total of <6 mg/kg of lean body mass in two divided daily doses). The duration of treatment varies with the level of disease activity.

When paraneoplastic pemphigus is caused by benign tumors, such as Castleman disease,[15] it can often be cured by removing the tumor (Chapter 171). Patients with associated malignant tumors should undergo treatment of their underlying condition but may have recalcitrant disease. Improvement has been reported with pulsed doses of corticosteroids (methylprednisolone, 1000 mg daily for 3 consecutive days) or cyclophosphamide (500 to 1000 mg monthly for 6 months to 1 year, often with varying doses of prednisone), rituximab (four weekly doses of 375 mg/m^2), plasmapheresis, and immunoablative doses of cyclophosphamide (50 mg/kg/day for 4 days).

Morbidity and mortality are related to complications from immunosuppressive therapy. In patients with malignant tumors, the prognosis is generally poor.

FIGURE 406-15. Pemphigus vulgaris—oral involvement. Essentially all patients develop painful oral mucosal erosions. The most common sites are the buccal and palatine mucosae, but lesions can also develop on the gingivae and tongue. (Courtesy Lorenzo Cerroni, MD. From Amagai M. Pemphigus. In: Bolognia JL, Schaffer JV, Cerroni L, eds. *Dermatology*. 4th ed. Elsevier; 2018:499.)

HYPERSENSITIVITY REACTIONS CAUSING BLISTERS

ERYTHEMA MULTIFORME

Erythema multiforme is a self-limiting hypersensitivity reaction that involves the skin and sometimes mucosal surfaces in response to infection or more infrequently medication.[16] The primary findings are target lesions, which are erythematous to violaceous macules with three zones: two concentric circles and a deeply erythematous to dusky or violaceous center. Target lesions are predominantly concentrated on the distal extremities (Fig. 406-16). The lesions can become bullous or erosive, and in more severe cases erosions occur in the oral, ocular, and/or genital mucosa. The most common infectious causes of erythema multiforme are herpes simplex virus (HSV; Chapter 345) and *Mycoplasma pneumoniae* (Chapter 293) followed by *Histoplasma capsulatum* (Chapter 308).

Biopsy demonstrates nonspecific keratinocyte necrosis, so the diagnosis is clinical.

TREATMENT

Mild cases of erythema multiforme can be treated symptomatically. Severe cases may require systemic corticosteroids (e.g., prednisone 0.5 to 1 mg/kg/day).

Lesions evolve, become fixed for up to 7 days, and then subside within 2 to 3 weeks. Recurrent episodes can occur. For recurrent erythema multiforme due to recurrent HSV, chronic suppressive antiviral treatment with valacyclovir should be considered (Chapter 328).

FIGURE 406-16. Erythema multiforme. Target or "bull's-eye" annular lesions with central vesicles and bullae are characteristic of erythema multiforme. (Courtesy Neil J. Korman, MD.)

FIGURE 406-17. Porphyria cutanea tarda. A blister and erosions are present on the dorsal surface of the hand. (Courtesy Neil J. Korman, MD.)

METABOLIC DISORDERS CAUSING BLISTERS

PORPHYRIA CUTANEA TARDA

Patients with porphyria cutanea tarda (Chapter 194) have skin fragility, painless blisters, and erosions in sun-exposed skin, especially of the face and the dorsal surface of the hands (Fig. 406-17) and the forearms. Healing is associated with scars, atrophic patches, hyperpigmentation, and hypopigmentation. Hypertrichosis is commonly found over the malar and temporal areas.

The cause is loss of activity of uroporphyrinogen decarboxylase (Chapter 194). Porphyria cutanea tarda can be hereditary, owing to a mutation in the *UROD* gene, or it can be acquired, owing to exogenous exposures such as alcohol consumption, hereditary hemochromatosis, hepatitis C, smoking, estrogen use, renal insufficiency, and/or chemical exposure.

Patients with hereditary porphyria cutanea tarda usually present between ages 30 to 50 years, whereas acquired disease usually manifests later. Both forms are associated with iron overload.

Diagnosis is based on elevated urinary porphyrin levels. Biopsy, though not necessary for the diagnosis, shows a minimal dermal infiltrate, subepidermal blistering, and deposition of immunoglobulin and complement at the basement membrane and in dermal capillaries.

TREATMENT

Depending on the type and cause, treatment options (Chapter 194) include avoiding triggers, phlebotomy (titrated so that the serum ferritin level declines to the lower limit of the normal range), hydroxychloroquine (100 mg twice weekly or 200 mg once weekly), or chloroquine (125 mg—half of a 250-mg tablet) orally twice per week until porphyrin excretion remains normal for several months.

PSEUDOPORPHYRIA

Pseudoporphyria, which is similar to porphyria cutanea tarda histologically and clinically but is not seen with any abnormalities of porphyrin, can be associated with chronic renal insufficiency (Chapter 116) or hemodialysis (Chapter 117). It can also occur as a reaction to medications, such as nonsteroidal anti-inflammatory drugs (NSAIDs), oral contraceptives, furosemide, tetracycline, ciprofloxacin, isotretinoin, amiodarone, cyclosporine, dapsone, isotretinoin, 5-fluorouracil, oral contraceptives, and flutamide. When the offending agent is discontinued, the prognosis is good, but skin lesions may persist or recur for several months.

BULLOSIS DIABETICORUM

Patients with diabetes mellitus (Chapter 210) can develop blisters on their distal extremities. The pathobiology is not understood, and there is no relationship of the skin lesions with the severity, duration, or complications of diabetes. Lesions present spontaneously as large, tense, noninflammatory bulla, often with irregular shapes. Lesions may leave erosions if traumatized. The lesions should be left in place or lanced and drained, leaving the roof in place to serve as a sterile physiologic dressing to reduce the risk of secondary infection. The condition is self-limiting.

INFECTIOUS DISEASES CAUSING BLISTERS

BULLOUS IMPETIGO

Impetigo, which is an epidermal bacterial infection, can be caused by *S. aureus* (Chapter 267) and group A β-hemolytic streptococcus (Chapter 269). Exfoliative toxins A and B target epidermal protein desmoglein 1 and cause cleavage below or within the stratum granulosum. Bullous impetigo presents with superficial vesicles and bulla that easily rupture, thereby resulting in a collarette of scale (Fig. 406-18). Lesions are commonly on the face, trunk, axillae, and perineum. Diagnosis is clinical, with culture of the lesions confirming the causative bacteria.

TREATMENT

Gentle washing is recommended to remove any crusts. Limited cases can be treated with topical 2% mupirocin ointment. Oral antibiotics (e.g., dicloxacillin 500 mg four times daily or cephalexin 500 mg three times daily) for 7 days are indicated for extensive disease and for patients who do not respond to topical antibiotics.

STAPHYLOCOCCAL SCALDED SKIN SYNDROME

Hematogenous dissemination of exfoliative staphylococcal toxins A and B can result in staphylococcal scalded skin syndrome (Chapter 267). In adults, it is usually seen with renal insufficiency (Chapter 116) or systemic immunosuppression. Patients present with the sudden onset of fever accompanied by blanchable, tender erythema that begins over the face, the neck, and intertriginous areas and then generalizes rapidly. Unlike toxic shock syndrome, the palms, soles, and mucous membranes are not affected. Flaccid blisters, which develop within 1 to 2 days, exfoliate in large sheets and leave behind superficially denuded skin (Fig. 406-19).[17] Skin biopsy can help to distinguish the periorificial fissuring and crusting of staphylococcal scalded skin syndrome from toxic epidermal necrolysis, which causes a subepidermal separation of the skin as well as mucosal involvement.

TREATMENT

Treatment for severe staphylococcal scalded skin syndrome is IV nafcillin or oxacillin 1 to 2 g every 4 hours for 7 to 14 days unless patients have methicillin-resistant staphylococci, in which case they should be treated with IV vancomycin (starting at 1 g every 12 hours, then adjusted based on the creatinine clearance). For mild disease, oral dicloxacillin (500 mg four times daily) for 10 to 14 days is often effective, but methicillin-resistant staphylococci require antibiotics shown to be effective by sensitivity testing.

HERPES SIMPLEX VIRUS INFECTION

Herpes simplex virus (HSV) infection (Chapter 345) commonly presents as a recurrent vesicular eruption on an erythematous base (Fig. 406-20). The location is typically oral and perioral with HSV-1 but genital or sacral with HSV-2.

Traumatized areas may appear as erosions with scalloped borders. Recurrent rash can be precipitated by other infections that suppress the immune system, cold or heat, skin trauma, and menstruation. Immunocompromised patients can develop chronic erosive ulcers.

Tzanck smear from the base of an unroofed vesicle or erosion can be helpful in rapidly confirming the diagnosis by identifying multinucleated giant cells with nuclear molding and margination (see E-Fig. 403-8 in Chapter 403), but the diagnostic "gold standard" is viral culture or direct fluorescent antibody testing. The direct fluorescent antibody test has both high sensitivity and specificity, can yield same-day results, and can distinguish among HSV-1, HSV-2, and varicella-zoster virus (VZV).

TREATMENT

HSV infection is self-limited in healthy individuals. Antiviral treatment with acyclovir, valacyclovir, or famciclovir (see Table 328-4 in Chapter 328) can shorten the initial attack and prevent recurrences. The dose and duration of antiviral therapy depend on whether the infection is disseminated or limited and on whether the patient is immunosuppressed.

VARICELLA

Varicella (chickenpox) caused by VZV (Chapter 346) usually occurs in childhood, but it is more severe when it occurs in adulthood. Erythematous macules on the face, scalp, trunk, and proximal limbs rapidly progress to

FIGURE 406-18. Bullous impetigo. Multiple crusted erosions, flaccid bullae, and pustules are present on the posterior leg of this patient.

FIGURE 406-19. Staphylococcal scalded skin syndrome. Confluent erythema with exfoliation of skin is seen on the trunk. (Courtesy Neil J. Korman, MD.)

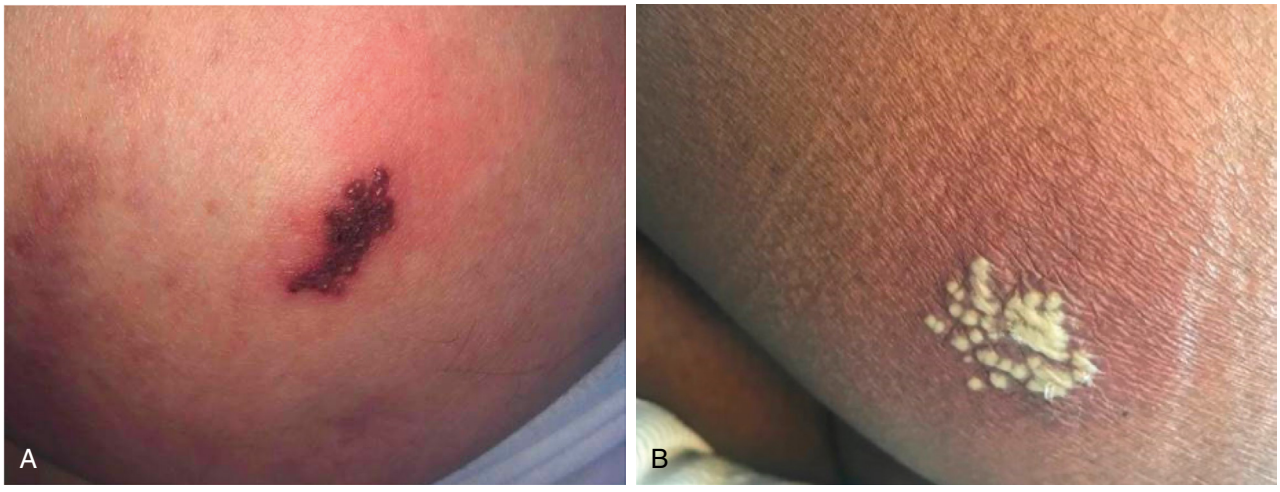

FIGURE 406-20. Recurrent genital herpes. A, Intact grouped vesicles with an erythematous base. **B,** Intact grouped pustules with an erythematous base. (Courtesy Daniela Kroshinsky, MD MPH.)

FIGURE 406-21. Erythematous macules and vesicles with crusted erosions on the chest of a patient with varicella. (Courtesy Neil J. Korman, MD.)

papules, vesicles, pustules, and crusting (Fig. 406-21) 10 to 21 days after exposure. The diagnosis is usually made clinically, with confirmation based on polymerase chain reaction (PCR) testing of the lesion because culture results are often delayed and less sensitive. Tzanck smear can be helpful but cannot distinguish HSV from VZV.

TREATMENT

Immunocompetent adults can be treated with oral valacyclovir (1 g three times daily) or oral acyclovir (800 mg five times daily) for 5 to 7 days with extended courses in cases of delayed crusting and dose adjustments as needed for reduced kidney function. The varicella vaccine is highly effective when given once to children or twice (4 to 8 weeks apart) to previously unvaccinated persons older than 13 years of age (Chapter 15).

HERPES ZOSTER

Herpes zoster (Chapter 346), which is caused by reactivation of VZV from prior primary varicella or following varicella vaccination, most often occurs in individuals who are older or immunocompromised. Patients typically develop grouped vesicles on an erythematous base in a dermatomal distribution (Fig. 406-22). The rash is usually preceded by pain, itching, tingling, or hyperesthesia. Cutaneous dissemination, defined as more than 20 vesicles outside the primary or adjacent dermatomes and/or visceral involvement, more commonly occurs in immunocompromised patients. Dysesthesia in the affected dermatome can persist in up to 20% of patients after resolution of the skin lesions (postherpetic neuralgia). The clinical diagnosis is usually obvious, but PCR testing can be used to confirm it.

FIGURE 406-22. Herpes zoster. A, Necrotic blisters and erosions in a dermatomal pattern are seen on the trunk. (Courtesy Neil J. Korman, MD.) **B,** Crusted herpes zoster of the face. (Courtesy Daniela Kroshinsky, MD MPH.)

TREATMENT

Immunocompetent adults can be treated with valacyclovir (1000 mg three times daily for 7 days), acyclovir (800 mg five times daily for 7 days), or famciclovir (500 mg three times daily for 7 days). In patients who are immunocompromised or have disseminated or visceral disease, intravenous acyclovir (10 mg/kg every 8 hours for 7 to 10 days) is indicated. The initiation of gabapentin with antiviral therapy also can decrease the incidence of postherpetic neuralgia. Varicella vaccination markedly reduces the incidences of both herpes zoster and postherpetic neuralgia (Chapter 346).

PUSTULAR ERUPTIONS

ACNE VULGARIS

Acne vulgaris affects up to 85% of teenagers, but it can persist until adulthood or even develop de novo in adults.[18] The sebum flow, which is stimulated by androgens, is physically impeded by abnormal keratinization in the pilosebaceous canal. The result is the formation of comedones, which can be open to air ("black heads"), or covered by epidermis ("white heads"). Proliferation of *Propionibacterium acnes* within the comedo can lead to rupture of the pilosebaceous unit, with resulting extravasation of its contents into the dermis, thereby creating inflammatory papules, pustules, and nodulocystic lesions.

Acne may be exacerbated or precipitated by oil-based cosmetics, hair preparations, systemic corticosteroids, and androgenic hormones. Other implicated medications include phenytoin, phenobarbital, lithium, and isoniazid. Endocrinologic conditions (e.g., polycystic ovary disease and ovarian or adrenal tumors) also may precipitate or worsen acne.

TREATMENT

Mild disease can be treated with topical benzoyl peroxide,[A3] erythromycin, or clindamycin, and/or a topical retinoid (e.g., adapalene, tretinoin, or tazarotene).[A4] Benzoyl peroxide and topical retinoids can help normalize follicular keratinization, whereas topical antibiotics help control inflammatory papules and pustules. For more serious disease, oral doxycycline or minocycline (50 to 100 mg twice daily) can be helpful.[19] In women, oral contraceptives (containing either ethinyl estradiol plus norgestimate or ethinyl estradiol plus drospirenone) and/or spironolactone can be particularly helpful in the treatment of hormonal acne that can predominantly affect the lower face, jawline, and upper neck. Isotretinoin (1.5 mg/kg given for 5 to 6 months) decreases the size of sebaceous glands as well as their production of sebum and is helpful for resistant disease, severe inflammatory cases, or extensive generalized comedonal involvement.[20]

ROSACEA

Rosacea, which is a chronic inflammatory disease, affects facial pilosebaceous units and blood vessels, generally in middle age.[21] Rosacea is more common in patients who have a tendency toward facial flushing, which can be caused by sun exposure or by other stimuli. (e.g., alcohol, spicy foods, hot liquids, or emotion). The four main types of rosacea are erythematotelangiectatic, papulopustular, phymatous, and ocular. Erythematotelangiectatic rosacea is characterized by persistent central facial erythema and telangiectasias. Papulopustular rosacea is characterized by erythematous papules and pustules in the absence of comedones. Phymatous rosacea is characterized by thickened skin and widened pores, usually of the nose but sometimes of the forehead, chin, ears, and eyelids (Fig. 406-23). Ocular rosacea, is characterized by dry, itchy, or gritty sensation of the eyes, conjunctivitis, blepharitis, and chalazia.

TREATMENT

Avoidance of precipitating causes, especially sun exposure, is recommended for all types of rosacea. Topical antibiotics (e.g., ivermectin 1% cream, azelaic acid 15% gel, or metronidazole 1% cream) are helpful in mild disease,[A5] whereas a low doxycycline dose (20 mg twice daily) is helpful for more inflamed cases.[22] For severe disease, full-dose doxycycline (100 mg twice daily) or minocycline (100 mg twice daily) are efficacious, as is low-dose isotretinoin 0.25 mg/kg.[A6] Ocular rosacea should be managed by an ophthalmologist.

PERIORIFICIAL DERMATITIS

In periorificial dermatitis, patients develop tiny, superficial erythematous papules and papulopustules, accompanied by occasional scaling patches around the mouth, eyes, and nose (Fig. 406-24). Patients often report an intolerance to topical agents and cosmetics, and many have inappropriately used chronic topical corticosteroids. Discontinuation of the corticosteroid often clears the rash, but a 2- to 4-week course of oral antibiotics (e.g., doxycycline 50 to 100 mg twice daily, minocycline 50 to 100 mg twice daily, erythromycin topical or 500 mg twice daily, or azithromycin 500 mg once followed by 250 mg for 4 days administered 2 weeks apart) can also clear the lesions.

ACUTE GENERALIZED EXANTHEMATOUS PUSTULOSIS

Acute generalized exanthematous pustulosis is most frequently caused by antibiotics (especially macrolides and β-lactams), calcium-channel blockers, and antimalarial agents. Edematous erythema and fever typically appear within 2 days after the drug is started, thereby suggesting a prior sensitization to the causative agent. Small sterile pustules subsequently develop on the face or in flexural areas, and they can then disseminate rapidly (Fig. 406-25). Superficial desquamation follows, and the condition usually resolves spontaneously within 2 weeks. Treatment includes discontinuation of the causative agent and the use of bland emollients. Topical corticosteroids (see Table 404-1) can be useful. Management of fluid and electrolyte status may be important in severe cases.

FIGURE 406-23. Rosacea dermatitis. When there is more severe disease, scaling and superficial crusting may be seen as on the cheek of this woman. (Courtesy Kalman Watsky, MD. From Powell FC, Raghallaigh SN. Rosacea and related disorders. In: Bolognia JL, Schaffer JV, Cerroni L, eds. *Dermatology*. 4th ed. Elsevier; 2018:607.)

FIGURE 406-24. Perioral dermatitis. Erythematous papules and pinpoint pustules are evident around the mouth. (Courtesy Neil J. Korman, MD.)

PUSTULAR PSORIASIS

Pustular psoriasis is a psoriatic variant (Chapter 405) that is triggered by pregnancy, infection, a rapid taper of corticosteroids, hypocalcemia, and medications such as lithium. It can be generalized (Fig. 406-26), localized to the palms and soles, annular, or acute and associated with fever and skin pain. Topical corticosteroids and/or calcipotriene may be sufficient, but systemic cyclosporine or TNF-α inhibitors such as infliximab are often needed for severe cases (Chapter 405).

FOLLICULITIS

Folliculitis, which is inflammation of the hair follicles caused by infection, presents as perifollicular pustules on an erythematous base. The most common cause is staphylococcal infection, but skin flora and gram-negative rods can

FIGURE 406-25. Acute generalized exanthematous pustulosis. Erythematous macules and numerous superficial pustules are present on the trunk of this patient. (Courtesy Neil J. Korman, MD.)

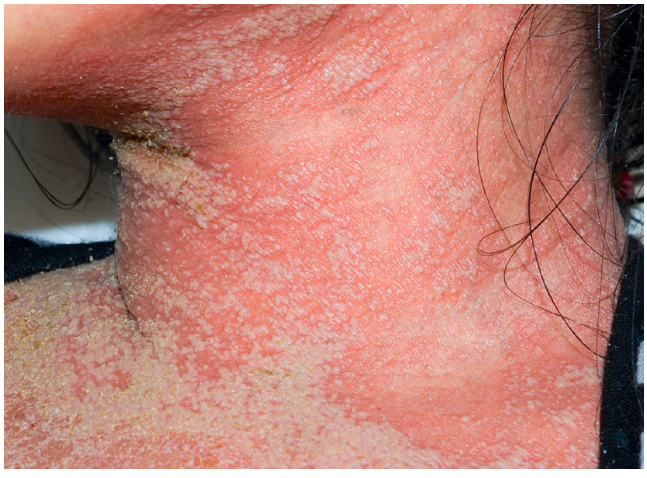

FIGURE 406-26. Generalized pustular psoriasis. Broad areas of erythema with numerous pustules and the formation of lakes of pus. (Courtesy Julie V. Schaffer, MD. From van de Kerkhof PCM, Nestlé FO. Psoriasis. In: Bolognia JL, Schaffer JV, Cerroni L, eds. *Dermatology*. 4th ed. Elsevier; 2018:145.)

be implicated. In addition, viral (HSV, VZV) and fungal folliculitis can occur. Folliculitis occurs more commonly in patients who are obese, are immunocompromised, or have diabetes mellitus. It most commonly affects follicles of the scalp, axilla, trunk, thighs, and inguinal area, but it also can extend deeper into the dermis where it can cause larger erythematous furuncles or carbuncles. Evaluation includes culture of the pustule's contents or base. Topical antibiotics (e.g., clindamycin solution twice daily for at least 2 weeks) and antibacterial washes (such as with benzoyl peroxide) are useful for mild disease, but antimicrobials (e.g., cephalexin, 500 mg twice daily for 14 days) based on culture results are needed for more extensive infection.

PSEUDOMONAS FOLLICULITIS

Pseudomonas folliculitis manifests 1 to 2 days after using hot tubs or whirlpools contaminated with *P. aeruginosa* (Chapter 282). The typical findings are pruritic papules and pustules, mostly on the torso and accentuated in any skin areas occluded by a bathing suit (Fig. 406-27).[23] The condition is usually self-limited in healthy individuals, but it can be treated with antibacterial soap. Ciprofloxacin (500 mg twice daily for 10 to 14 days) usually cures the infection.

PITYROSPORUM FOLLICULITIS

Pityrosporum ovale folliculitis is a pruritic, acne-like eruption that develops on the face, upper chest, and arms. It is most often seen in young adults, particularly in warm weather, after sweating, and in immunosuppressed individuals. Lesions appear as itchy, follicularly based papules and sometimes pustules over the torso and shoulders. Yeast forms are identifiable on a potassium hydroxide (KOH) preparation. Treatment consists of topical antifungal cream, selenium sulfide shampoo daily for 1 month, or oral itraconazole (200 mg daily for 1 week) or fluconazole (100 to 200 mg daily for 1 to 4 weeks or 300 mg once weekly for 1 to 2 months).

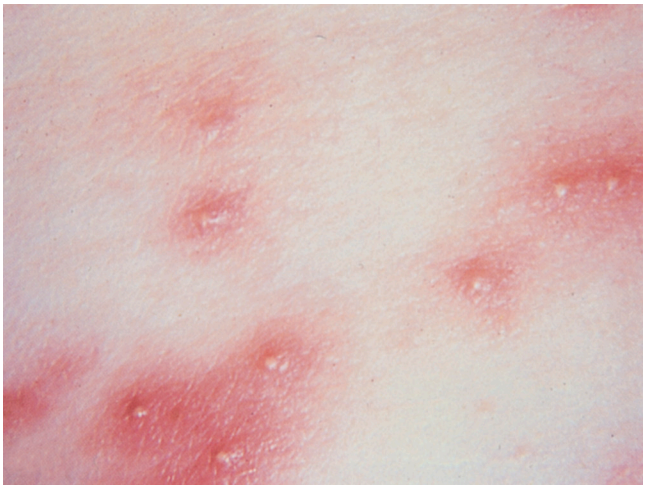

FIGURE 406-27. *Pseudomonas* species folliculitis. The trunk of this patient has numerous pustules on an erythematous base. (Courtesy Neil J. Korman, MD.)

EOSINOPHILIC PUSTULAR FOLLICULITIS

Eosinophilic pustular folliculitis, which is seen in HIV-positive patients, is a sterile but intensely pruritic folliculitis that is usually seen on the face and torso. It is accompanied by peripheral eosinophilia. Skin biopsy demonstrates eosinophils in and around the follicles. Treatment options include antihistamines, topical corticosteroids (see Table 403-10), and topical tacrolimus. Systemic options include indomethacin (50 mg/day), minocycline (100 mg twice daily), dapsone (100 to 200 mg/day), systemic corticosteroids, and colchicine (0.6 mg twice daily). Narrowband ultraviolet B phototherapy also can be helpful.

HIDRADENITIS SUPPURITIVA

Hidradenitis suppurativa, which is a chronic and recurrent inflammatory disease, is characterized by painful, deep-seated nodules and abscesses that result from occlusion of the follicular infundibula followed by inflammation.

Hidradenitis can begin in puberty but most commonly occurs in the early 20s, with its incidence declining substantially after age 50 years. Women predominate over men 3 : 1. The pathogenesis is poorly understood, but it appears to be an inflammatory or immune disease. Cigarette smoking and obesity are risk factors. Biopsy shows atrophy of the sebaceous glands, lymphocytic inflammation of the pilosebaceous unit, destruction of the hair follicles, and granulomas.

The clinical course is chronic, with periods of flares and remissions. The typical presentation is with painful, inflamed nodules and sterile abscesses in the axilla or the groin, but lesions also often occur in the inframammary, genital, and perineal areas. Sinus tracts can develop and be associated with purulent or bloody drainage; lesions may heal with scarring, sometimes cordlike. Flares are often related to menses. Lesions typically recur at the same or nearby sites despite prior incision and drainage and/or oral antibiotics (Fig. 406-28).

TREATMENT

Treatment options have variable success.[24] Weight loss and smoking cessation are encouraged. Moisture reduction through the use of topical aluminum chloride, powders, and loose-fitting clothing can be helpful. Antiseptic soaps and topical antibiotics (e.g., benzoyl peroxide or chlorhexidine washes or topical clindamycin/benzoyl peroxide combination products) may be beneficial for early or mild disease. Intralesional triamcinolone injections can reduce inflammation in early nodules. Systemic therapies include oral antibiotics (doxycycline, minocycline, clindamycin, rifampin, dapsone, trimethoprim-sulfamethoxazole), hormonal therapies (ethinyl estradiol plus cyproterone acetate, spironolactone, finasteride), the phosphodiesterase-4 inhibitor apremilast, TNF-α inhibitors (e.g., adalimumab[A7] 40 mg subcutaneously weekly or infliximab 7.5 to 10 mg/kg intravenously every 4 weeks),[25] and potentially the IgG1k monoclonal antibody secukinumab[A8] (300 mg subcutaneously every 2 to 4 weeks), sometimes combined with wide excision surgery.[A9]

FIGURE 406-28. Hidradenitis suppurativa. The axilla of this patient has several erythematous nodules with draining sinus tracts. (Courtesy Neil J. Korman, MD.)

FIGURE 406-29. Sweet syndrome. The edema can be quite marked as seen in these lesions on the upper back. (Courtesy Kalman Watsky, MD. From Davis MDP, Moschella SL. Neutrophilic dermatoses. In: Bolognia JL, Schaffer JV, Cerroni L, eds. *Dermatology*. 4th ed. Elsevier; 2018:456.)

SWEET SYNDROME

Sweet syndrome is an acute febrile neutrophilic dermatosis characterized by: fever; peripheral neutrophilia; and edematous, painful papules, nodules, or plaques. Sweet syndrome may be idiopathic, but it is more often seen with an underlying condition or exposure to medication.[26] In adults, Sweet syndrome is most commonly associated with hematologic malignancy, especially acute myelogenous leukemia (Chapter 168). It is also seen with inflammatory bowel disease (Chapter 127), infections, pregnancy, and exposure to medications such as all-*trans*-retinoic acid and granulocyte colony-stimulating factor. Sweet syndrome presents clinically with multiple firm, tender, deeply erythematous to violaceous papules, papulovesicles, or nodules, which may turn into edematous plaques. The most common locations are the head, neck, and upper and lower extremities (Fig. 406-29 and Chapter 407) The phenomenon of pathergy, which is the development of inflammatory lesions at sites of dermal injury, may be seen in sites such as IV insertion points and places of venipuncture. When the disease is active, patients may have fever, arthralgias, arthritis, and myalgias as well as a neutrophilic leukocytosis. Biopsy shows superficial edema and a deeper dense neutrophilic infiltrate.

TREATMENT AND PROGNOSIS

The skin lesions respond rapidly to oral corticosteroids (e.g., prednisone, 1 mg/kg/day). Steroid-sparing options include dapsone (100 to 200 mg/day), colchicine (0.6 mg three times daily), and potassium iodide (300 mg three times daily). For refractory disease, options such as cyclosporine, or TNF-α inhibitors may be used by specialists. Recurrent episodes can be a sign of recurrent cancer.

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407

URTICARIA, DRUG HYPERSENSITIVITY RASHES, NODULES AND TUMORS, AND ATROPHIC DISEASES

MADELEINE DUVIC AND SUSAN Y. CHON

URTICARIA

DEFINITION AND EPIDEMIOLOGY

Urticaria, or hives, is one of the most common cutaneous reaction patterns (Fig. 407-1). It is triggered by a wide variety of antigens or by physical stimuli, including cold, pressure, and sunlight (Table 407-1). Urticaria is a spectrum ranging from simple wheals to angioedema. Clinical distinction between acute and chronic urticaria is important for diagnosis and treatment. Chronic urticaria is defined by recurrence over a period of 6 weeks or more and is often of unknown cause.

Urticaria is common worldwide in persons of all ages, although certain types of urticaria have a predilection for certain age groups. For example, whereas acute urticaria is often seen in children with atopic dermatitis, chronic urticaria peaks in the third and fourth decade.

PATHOBIOLOGY

Urticaria can be caused by immunologic (autoimmune, immunoglobulin E [IgE]–dependent, immune complex–mediated, complement-kinin dependent) or nonimmunologic (direct mast cell–releasing agents, vasoactive stimuli, drugs) reactions. Local degranulation of mast cells with the release of histamine and other factors, such as slow-reacting substance of anaphylaxis, precipitates urticaria. Functional IgE autoantibodies, which release histamine from mast

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FIGURE 406-28. Hidradenitis suppurativa. The axilla of this patient has several erythematous nodules with draining sinus tracts. (Courtesy Neil J. Korman, MD.)

FIGURE 406-29. Sweet syndrome. The edema can be quite marked as seen in these lesions on the upper back. (Courtesy Kalman Watsky, MD. From Davis MDP, Moschella SL. Neutrophilic dermatoses. In: Bolognia JL, Schaffer JV, Cerroni L, eds. *Dermatology*. 4th ed. Elsevier; 2018:456.)

SWEET SYNDROME

Sweet syndrome is an acute febrile neutrophilic dermatosis characterized by: fever; peripheral neutrophilia; and edematous, painful papules, nodules, or plaques. Sweet syndrome may be idiopathic, but it is more often seen with an underlying condition or exposure to medication.[26] In adults, Sweet syndrome is most commonly associated with hematologic malignancy, especially acute myelogenous leukemia (Chapter 168). It is also seen with inflammatory bowel disease (Chapter 127), infections, pregnancy, and exposure to medications such as all-*trans*-retinoic acid and granulocyte colony-stimulating factor. Sweet syndrome presents clinically with multiple firm, tender, deeply erythematous to violaceous papules, papulovesicles, or nodules, which may turn into edematous plaques. The most common locations are the head, neck, and upper and lower extremities (Fig. 406-29 and Chapter 407) The phenomenon of pathergy, which is the development of inflammatory lesions at sites of dermal injury, may be seen in sites such as IV insertion points and places of venipuncture. When the disease is active, patients may have fever, arthralgias, arthritis, and myalgias as well as a neutrophilic leukocytosis. Biopsy shows superficial edema and a deeper dense neutrophilic infiltrate.

TREATMENT AND PROGNOSIS

The skin lesions respond rapidly to oral corticosteroids (e.g., prednisone, 1 mg/kg/day). Steroid-sparing options include dapsone (100 to 200 mg/day), colchicine (0.6 mg three times daily), and potassium iodide (300 mg three times daily). For refractory disease, options such as cyclosporine, or TNF-α inhibitors may be used by specialists. Recurrent episodes can be a sign of recurrent cancer.

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For the General References and other additional features, please visit Elsevier eBooks+ at https://ebooks.health.elsevier.com.

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407

URTICARIA, DRUG HYPERSENSITIVITY RASHES, NODULES AND TUMORS, AND ATROPHIC DISEASES

MADELEINE DUVIC AND SUSAN Y. CHON

URTICARIA

DEFINITION AND EPIDEMIOLOGY

Urticaria, or hives, is one of the most common cutaneous reaction patterns (Fig. 407-1). It is triggered by a wide variety of antigens or by physical stimuli, including cold, pressure, and sunlight (Table 407-1). Urticaria is a spectrum ranging from simple wheals to angioedema. Clinical distinction between acute and chronic urticaria is important for diagnosis and treatment. Chronic urticaria is defined by recurrence over a period of 6 weeks or more and is often of unknown cause.

Urticaria is common worldwide in persons of all ages, although certain types of urticaria have a predilection for certain age groups. For example, whereas acute urticaria is often seen in children with atopic dermatitis, chronic urticaria peaks in the third and fourth decade.

PATHOBIOLOGY

Urticaria can be caused by immunologic (autoimmune, immunoglobulin E [IgE]–dependent, immune complex–mediated, complement-kinin dependent) or nonimmunologic (direct mast cell–releasing agents, vasoactive stimuli, drugs) reactions. Local degranulation of mast cells with the release of histamine and other factors, such as slow-reacting substance of anaphylaxis, precipitates urticaria. Functional IgE autoantibodies, which release histamine from mast

ABSTRACT

Urticaria, or hives, is the most common cutaneous reaction pattern. The pink to light red blanching lesions are raised and pruritic. Management depends on the severity and duration of symptoms. For recurrent chronic spontaneous urticaria, cyclosporine or omalizumab therapy can be very effective. Drug rashes include rashes with eosinophilia, erythema multiforme, Stevens-Johnson syndrome, toxic epidermal necrolysis, leukocytoclastic vasculitis, drug eruptions, and contact dermatitis. Benign papules include actinic keratoses, seborrheic keratoses, and warts. Each of these lesions must be carefully diagnosed so that an effective topical and sometimes systemic therapy can be prescribed.

KEYWORDS

urticaria
drug rash
erythema multiforme
actinic keratosis
seborrheic keratosis

FIGURE 407-1. **Urticaria.** (From DermNet. Urticaria; 2014. http://www.dermnetnz.org/reactions/urticaria.html. Accessed October 23, 2014.)

TABLE 407-1 COMMON CAUSES OF URTICARIA

URTICARIA MAY BE ACCOMPANIED BY ANGIOEDEMA AND ANAPHYLAXIS
Blood products: red blood cells, platelets, gamma globulin
Drugs
Antibiotics: penicillins, cephalosporins, sulfonamides, isoniazid
Aspirin: salicylates, benzoates, phenylbutazone
Anticonvulsants: hydantoin
Chemotherapy: doxorubicin, daunorubicin, L-asparaginase, chlorambucil, cyclophosphamide, melphalan, methotrexate, nitrogen mustard, procarbazine
Dextran
Nonsteroidal anti-inflammatory drugs
Opiates
Quinidine
Radiocontrast dyes, iodine
Environmental: animal dander or proteins, formaldehyde, pollen, mold, plants, latex, plastic tubing, exercise, heat, cold, sunlight, dermal vibration
Foods: berries, eggs, milk, nuts, tomatoes, shellfish, soy
Food additives: sodium benzoate, tartrazine (yellow dye #5)
Hormones
Infections: streptococcal, staphylococcal, sinusitis or abscesses, viral hepatitis, Epstein-Barr virus mononucleosis, *Candida* spp
Insect bites or venom: Hymenoptera, mosquitoes, mites, scabies, bed bugs
Mechanical stimuli (dermographism, vibratory angioedema, delayed-pressure urticaria)
Vaccines
URTICARIA-LIKE ERUPTIONS AND REACTIVE ERYTHEMAS
Erythema multiforme: herpes simplex, DNA viruses, *Mycoplasma pneumoniae,* drugs
Erythema marginatum: streptococcal rheumatic fever
Juvenile rheumatoid arthritis
Erythema chronicum migrans: *Borrelia* spp infections
Erythema annulare centrifugum: tinea, drugs
Figurate erythemas: erythema repens (often with underlying carcinoma)
Urticaria pigmentosa (mastocytosis)

spp = species.

cells and basophils, are commonly found in the blood of patients with chronic urticaria. Additionally, basophils are recruited into the wheals, where they sustain the response by releasing histamine. Eosinophils also contribute through leukotriene C_4 (LTC_4), leukotriene D_4 (LTD_4), leukotriene E_4 (LTE_4), and major basic protein. Urticaria is typically transient and self-limited, without leakage of blood cells into the skin or damage to the blood vessels. Leakage of plasma into the dermis from capillaries and small postcapillary venules correlates clinically with development of a demarcated, pink, raised lesion (hive).

CLINICAL MANIFESTATIONS

Urticarial lesions are pink to light red, blanch with pressure, and are raised above the surface of the skin. The center of the lesions may be paler than the leading edge. By definition, an individual hive persists for less than 24 hours. A mosquito bite (Chapter 233) is the archetypal urticarial lesion. Individual hives can coalesce into giant plaques or annular rings, and in serum sickness they can be accompanied by arthralgias and fever. Confluent urticaria also may be accompanied by swelling of the underlying soft tissue or the mucous membranes (angioedema). Anaphylaxis with laryngeal edema is a life-threatening emergency. In otherwise normal individuals, pressure, scratching, or vibration on the skin will cause spontaneous local release of histamine, which induces a wheal-and-flare reaction or dermatographism. Deep swelling from sustained pressure may remain for days in delayed pressure urticaria. Affected individuals may develop lesions from tight-fitting clothing, shoes, socks, watches, or sexual intercourse.

Cold, heat, sun, pressure, or exercise may also induce urticaria. Cold urticaria may be precipitated by putting an ice cube on the skin; the interval until hives develop and the duration of the hives correlate with the severity of the condition. Cold urticaria can be life threatening if the patient is suddenly immersed in cold water. Heat, exercise, or exertion may be accompanied by small, 2- to 3-mm urticarial lesions in a condition called cholinergic urticaria. Exercise-induced anaphylaxis may be hereditary, but the defect is unknown. Patients with vibratory angioedema develop swelling and erythema within a few minutes of exposure to a vibratory stimulus. Lesions persist for about 30 minutes. Other forms of physically induced urticaria include solar urticaria and aquagenic urticaria (urticarial lesions caused by exposure to sun and water, respectively).

Food and exercise–induced anaphylaxis is a syndrome in which a few minutes of exercise after ingestion of specific foods results in angioedema or anaphylaxis. The cause of this syndrome is still controversial, but reduced gastric acid secretion may be involved in food and exercise–induced anaphylaxis.

DIAGNOSIS

A detailed history (e.g., duration, occupation, prescribed medications, over-the-counter supplements, frequency of episodes, associated illness) is critical. Urticaria typically results from exposure to antigen only minutes to a few hours before the onset of the lesions. In many cases, pruritus may precede onset of the rash. The most common triggers of IgE-mediated allergic urticarial reactions are drugs (especially penicillin, sulfa drugs, antibiotics, and contrast dye), foods (shellfish, salicylates in berries, tomatoes, yeast, and penicillin in blue cheese), food additives (sodium benzoate), nuts (especially peanuts), latex, and insect bites. Nonimmunologic mediators of urticaria include aspirin and opiates as well as physical agents that work through the prostaglandin pathway or degranulate mast cells.

Acute urticaria also can be triggered by skin contact with an antigen, such as latex, and can progress to anaphylaxis. In addition, urticaria can be a sign or prodrome of a latent infection, especially streptococcal pharyngitis in children or viral hepatitis in adults. The migratory urticarial rash accompanying rheumatic fever, erythema marginatum (Fig. 407-2), is characterized by evanescent, scalloped lesions that change location over the course of hours.

When urticarial lesions are present for more than 24 hours, underlying urticarial vasculitis should be suspected. A skin biopsy is required to distinguish urticarial vasculitis from urticaria in which no damage to the blood vessels is evident. When vascular damage is present, the lesion is termed *leukocytoclastic vasculitis*, the most severe expression of hypersensitivity reactions involving cutaneous blood vessels.

Chronic urticaria can be caused by occult infections (sinusitis, gallbladder disease, *Helicobacter pylori*, yeast infections, tooth abscesses, or silent hepatitis) as well as by collagen vascular diseases and tumors, especially Hodgkin lymphoma. Deficiency of the C1 esterase inhibitor can cause chronic urticaria with angioedema. Allergy testing is recommended if the history is unrevealing. If lesions persist for more than 24 hours, skin biopsy is indicated to determine whether vasculitis or mastocytosis is present (see Fig. 232-4). If infection, collagen vascular disease, or a tumor is suspected, a full serologic evaluation should be undertaken. Although a thorough medical evaluation may aid in diagnosis, the cause of chronic urticaria may remain uncertain. In the absence of a known antigen, stress is often invoked as the underlying cause of chronic recurrent idiopathic urticaria.

Systemic mastocytosis[1] (Chapter 235) may be accompanied by urticarial lesions and gastrointestinal symptoms. In the form of mastocytosis known as *urticaria pigmentosa*, stroking the lesions produces urticaria, known as the *Darier sign*. A skin biopsy shows an increased number of dermal mast cells. Serum tryptase and histamine levels may be elevated during an attack.

TREATMENT

Management of urticaria depends on its severity and the duration of the problem[2] (Chapter 232). For mild urticaria limited to the skin, traditional oral antihistamines (diphenhydramine) or the newer nonsedating agents (terfenadine, cetirizine, loratadine) can be administered intermittently as needed (Table 407-2).[A1] Acute urticaria is often treated with diphenhydramine orally. If the urticaria is severe, short-term corticosteroids, up to 1 mg/kg, can be used, but their efficacy is uncertain.[A2] For urticaria associated with wheezing or anaphylaxis, subcutaneous epinephrine, intravenous (IV) corticosteroids, and oxygen should be administered immediately.

Finding the cause and removing the antigen of chronic recurrent urticaria is highly preferable to chronic administration of corticosteroids or antihistamines. The patient should avoid aspirin compounds, nonsteroidal anti-inflammatory drugs (NSAIDs), and other drugs that could be the cause.

For chronic spontaneous urticaria that persists, omalizumab, an anti-IgE monoclonal antibody at 300 mg subcutaneously once per month,[A3] or cyclosporine (at doses of 3 mg/kg or higher for 8 to 16 weeks), is effective in 65 to 70% of patients who do not respond to H_1-antihistamines (Chapter 232). Prednisone is to be avoided because of long-term toxicity.

TABLE 407-2 TREATMENT OF URTICARIA

1. Avoid the inciting agent!
2. Medications based on severity
   - A. Mild to moderate, acute urticaria
     - Oral H_1-antihistamines (e.g., diphenhydramine, 25-50 mg PO q4-6h, or hydroxyzine, 10-25 mg PO q6h; nonsedating alternatives include cetirizine, 5-10 mg/day, levocetirizine 2.5-5 mg/day, fexofenadine 180 mg/day, or loratadine, 10 mg/day)
     - Omalizumab (an anti-IgE antibody) 150-300 mg subcutaneously monthly
   - B. Severe urticaria with or without angioedema
     - H_1-antihistamines (e.g., diphenhydramine, 25-50 mg PO q4-6h or 10-50 mg IV/IM q4-6h, not to exceed 400 mg/24 hr)
     - Corticosteroids (e.g., prednisone, 10-60 mg PO every morning with tapering over a 2-wk period; triamcinolone 40-60 mg IM for one dose; or dexamethasone, 4-20 mg/day IV/IM for one dose or divided doses q6-12h, depending on severity)
   - C. Anaphylaxis
     - A—Airway (intubation)
     - B—Breathing (oxygen)
     - C—Circulation: parenteral aqueous epinephrine, 1 : 1000 IV, saline or volume expanders
     - IV corticosteroids (e.g., methylprednisolone, 1-2 mg/kg/day; see Chapter 233)
     - Histamine H_1- and H_2-antagonists (diphenhydramine 25-50 mg IV and famotidine 20 mg IV; see Chapter 233)
   - D. Chronic idiopathic urticaria—combination therapy
     - Nonsedating PO H_1-antihistamine: cetirizine, 10 mg/day, or fexofenadine, 60-180 mg once or twice daily, alone or with leukotriene receptor antagonist: montelukast, 10 mg/day, or H_1 and H_2 antagonists (famotidine 20 mg twice daily or cimetidine 400 mg twice daily) and/or low-dose corticosteroids (if unavoidable)
     - Omalizumab (anti-IgE monoclonal antibody) at 150-300 mg subcutaneously once monthly and cyclosporine (doses of 3 mg/kg/day or higher for 8-16 weeks)

Ig = immunoglobulin; IM = intramuscularly; IV = intravenously; PO = orally.

FIGURE 407-2. Erythema marginatum. (From Medscape. Urticaria; n.d. http://www.medscape.com/content/1998/00/41/73/417394/art-m5649.fig2.jpg. http://www.dermnetnz.org/reactions/urticaria.html. Accessed October 23, 2014.)

DRUG RASHES

DEFINITION

Drugs have been associated with every type of cutaneous reaction pattern ranging from mild and self-limited to severe and life-threatening. Urticaria and exanthematous eruptions are common manifestations of cutaneous drug reactions. Less commonly seen are fixed drug, lichenoid, pustular, phototoxic, bullous, or vasculitic reactions, and the spectrum of erythema multiforme, Stevens-Johnson syndrome, and toxic epidermal necrolysis.

PATHOBIOLOGY

Drug rashes, which result from drug toxicity, overdose, drug-drug interactions, or products of metabolism, may be caused by immunologic or nonimmunologic mechanisms. Drugs or their metabolites can act as haptens and induce cell-mediated or humoral responses. Mechanisms include IgE-dependent anaphylaxis and urticaria, cytotoxic reactions resulting in thrombocytopenia and resultant petechiae, immune complex–mediated serum sickness, and delayed-type hypersensitivity resulting in exanthematous or fixed drug eruptions or Stevens-Johnson syndrome.

CLINICAL MANIFESTATIONS AND DIAGNOSIS

Drug rashes are either immediate (urticaria) or delayed hypersensitivity reactions (exanthems). Immediate reactions such as pruritus, hives, angioedema, and anaphylaxis occur within minutes to a few hours after the drug is taken. The most common drug-related rash (Table 407-3) is a $CD8^+$ T-cell–mediated hypersensitivity reaction manifested as a macular, bright pink to salmon–colored exanthem that appears as early as 7 to 10 days and as late as 14 days after a drug is first administered. Delayed hypersensitivity reactions can be macular or papular exanthems (or both), morbilliform eruptions, annular erythema, or confluent erythema (Fig. 407-3). After sensitization to a particular drug has occurred, readministration of the same drug may trigger an eruption within 24 to 72 hours. Drug hypersensitivity reactions are typically symmetrical. They characteristically begin on the face and upper trunk and progress to the lower extremities, where they may become purpuric. Exanthems secondary to drugs most often become confluent erythematous patches after several days.[3]

Pruritus is the most common symptom. The differential diagnosis for drug rashes includes viral exanthems (Chapter 406), graft-versus-host disease or the leukocyte recovery rash after allogeneic bone marrow transplantation, erythematous exanthems that accompany streptococcal (scarlet fever [Chapter 269]) or staphylococcal (toxic shock syndrome [Chapter 267]) infections, and the acute manifestation of collagen vascular diseases. A similar exanthem occurs when ampicillin is administered to patients who have infectious mononucleosis. A careful drug history is critical in diagnosis and treatment.

TREATMENT AND PROGNOSIS

After the offending drug is discontinued, delayed hypersensitivity reactions resolve in about 1 week. Therapy is mostly supportive. Corticosteroids, such as triamcinolone 0.01% cream applied several times per day to the affected area and antihistamines given orally three to four times daily are helpful in reducing the itching and shortening the course.

SPECIFIC SYNDROMES

DRUG RASH WITH EOSINOPHILIA AND SYSTEMIC SYMPTOMS

Drug-induced hypersensitivity rash and drug-induced hypersensitivity syndrome/drug reaction with eosinophilia and systemic symptoms (DRESS) is most frequently seen with sulfonamides and anticonvulsant medications[4] (Fig. 407-4). This condition is thought to be caused by an alteration in drug metabolism. Activated T lymphocytes release interleukin-5 (IL-5), leading to characteristic eosinophilia. DRESS involves activation of human herpes virus-6 and sometimes other DNA viruses. In some patients, there can be an overlap with cutaneous T-cell lymphoma or mycosis fungoides.

Eosinophilia and its systemic symptoms set DRESS apart from the usual delayed hypersensitivity drug rashes. DRESS may be delayed in onset by 2 to 6 weeks, persists longer than classic drug-induced eruptions, and becomes

TABLE 407-3 DELAYED HYPERSENSITIVITY DRUG RASHES BY CATEGORY

MACULOPAPULAR EXANTHEMS—ANY DRUG CAN PRODUCE A RASH 7-10 DAYS AFTER THE FIRST DOSE
Allopurinol Antibiotics: penicillin, sulfonamides Antiepileptics: phenytoin, phenobarbital Antihypertensives: captopril, thiazide diuretics Contrast dye: iodine Gold salts Hypoglycemic drugs Meprobamate Phenothiazines Quinine
DRUG RASH WITH EOSINOPHILIA AND SYSTEMIC SYMPTOMS (DRESS)
Anticonvulsants: phenytoin, phenobarbital, valproate, lamotrigine Antibiotics: sulfonamides, minocycline, dapsone, ampicillin, ethambutol, isoniazid, linezolid, metronidazole, rifampin, streptomycin, vancomycin Antihypertensives: amlodipine, captopril Antidepressants: bupropion, fluoxetine Allopurinol Celecoxib Ibuprofen Phenothiazines
ERYTHEMA MULTIFORME/STEVENS-JOHNSON SYNDROME/TOXIC EPIDERMAL NECROLYSIS SPECTRUM
Sulfonamides, phenytoin, barbiturates, carbamazepine, allopurinol, amikacin, phenothiazines Toxic epidermal necrolysis: same as for erythema multiforme but also acetazolamide, gold, nitrofurantoin, pentazocine, tetracycline, quinidine
ACUTE GENERALIZED EXANTHEMIC PUSTULOSIS (AGEP)
Antibiotics: penicillins, macrolides, cephalosporins, clindamycin, imipenem, fluoroquinolones, isoniazid, vancomycin, minocycline, doxycycline, linezolid Antimalarials: chloroquine, hydroxychloroquine Antifungals: terbinafine, nystatin Anticonvulsants: carbamazepine Calcium-channel blockers Furosemide Systemic corticosteroids Protease inhibitors
COLLAGEN VASCULAR OR LUPUS-LIKE REACTIONS
Procainamide, hydralazine, phenytoin, penicillamine, trimethadione, methyldopa, carbamazepine, griseofulvin, nalidixic acid, oral contraceptives, propranolol
ERYTHEMA NODOSUM
Oral contraceptives, penicillin, sulfonamides, diuretics, gold, clonidine, propranolol, opiates Fixed drug reactions: phenolphthalein, barbiturates, gold, sulfonamides, meprobamate, penicillin, tetracycline, analgesics

generalized and severe even when use of the agent is discontinued.[§] It typically begins as a morbilliform eruption, which later evolves into an edematous pustular eruption with erythroderma and purpura. The rash begins on the face, upper trunk, and extremities and later becomes generalized. Continued administration of the drug can result in exfoliative erythroderma; toxic necrolysis; and systemic hypersensitivity, including hepatitis (50%), nephritis (10%), or atypical lymphocytosis and lymphadenopathy mimicking mononucleosis or T-cell lymphoma. Less commonly seen are pneumonitis, myocarditis, and pericarditis. With visceral involvement, there is a 10% mortality rate, usually from hepatic failure.

TREATMENT

The initial step in management is the immediate withdrawal of the suspected drug. Systemic corticosteroids (e.g., oral prednisone at 1.0 mg/kg/day and tapered over 2 to 3 months) should be started as early as possible. For patients who develop exfoliative dermatitis, admission to a specialized unit such as a burn unit or intensive care unit is critical.

ERYTHEMA MULTIFORME, STEVENS-JOHNSON SYNDROME, AND TOXIC EPIDERMAL NECROLYSIS

Stevens-Johnson syndrome and toxic epidermal necrolysis represent a spectrum of the same disease, of which erythema multiforme (see Fig. 406-16 in Chapter 406) is the least severe, with less than 10% body surface area involvement. Intermediate involvement of 10 to 30% is called Stevens-Johnson syndrome, whereas toxic epidermal necrolysis is defined by extensive skin necrosis on greater than 30% of the body surface area.

Drugs (e.g., sulfonamides, seizure medications, NSAIDS, allopurinol, nevirapine, and chlormezanone) are almost always implicated when Stevens-Johnson syndrome or toxic epidermal necrolysis develops in adults (Fig. 407-5). The risk is also increased in patients infected with the human immunodeficiency virus.

The mildest form (erythema multiforme) is a hybrid of urticaria and vasculitis and consists of symmetrically distributed red macules or papules that

FIGURE 407-3. Morbilliform drug eruption due to trimethoprim-sulfamethoxazole (TMP-SMZ). This human immunodeficiency virus (HIV)–positive young man developed a widespread eruption of blanchable erythematous macules and papules 8 days after starting TMP-SMZ. Note the coalescence on the upper trunk. (From Bolognia. *Dermatology*, 4th ed.)

FIGURE 407-4. Hypersensitivity drug rash caused by phenytoin.

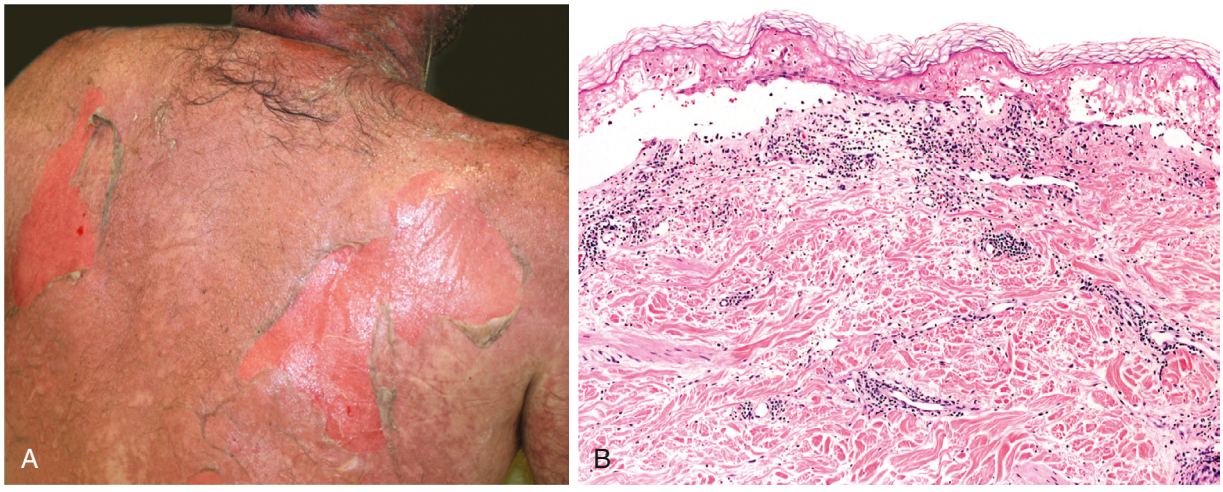

FIGURE 407-5. Toxic epidermal necrolysis. A, Detachment of necrolytic epidermis, leading to large areas of denuded skin. The glistening areas are exposed dermis. **B,** Full-thickness epidermal cell death results in a subepidermal separation. The normal stratum corneum points to the acute nature of the disease process. In the dermis, there is a lymphohistiocytic inflammatory infiltrate admixed with a few eosinophils. (From Bolognia. *Dermatology*, 4th ed.)

evolve into classic target or bull's-eye lesions with deep red centers and pink urticarial rims. Erythema multiforme is commonly precipitated by herpes simplex infections, other DNA viruses, or drugs.

Stevens-Johnson syndrome is characterized by flu like prodrome followed by development of characteristic flat hemorrhagic lesions on the mucosal membranes, trunk, and extremities. In toxic epidermal necrolysis, full-thickness keratinocyte necrosis or cell apoptosis leads to separation at the dermal-epidermal junction.[6] In the active phase of toxic epidermal necrolysis, skin blisters and erosions can be accompanied by pulmonary and hepatic involvement.

Each of these conditions may start as a morbilliform hypersensitivity drug rash and progress to skin necrosis. Symptoms include fever, severe pain, or sometimes asthenia. These conditions can progress rapidly, so it is critical to determine and discontinue the causative agent immediately.

TREATMENT

Management includes supportive care such as fluid and electrolyte replacement, transfer to a burn unit, wound care, treatment of infection, and ophthalmologic evaluation. Corticosteroids (e.g., IV methylprednisolone at 60 mg every 6 hours or 1 to 2 mg/kg for a short course) are frequently given, and IV immunoglobulin may decrease the duration of fever and slow eruptions.[7] Based on observational data, tumor necrosis factor–α inhibitors (e.g., etanercept) and cyclosporine (3 to 5 mg/kg per day) may be beneficial under the direction of a specialist.[8] Erythema multiforme can be inhibited by the chronic administration of oral acyclovir (400 mg twice daily).

PROGNOSIS

In toxic epidermal necrolysis, skin ulceration can lead to systemic sepsis (Chapter 94). Superinfection and fluid and electrolyte imbalances can lead to death in 5% of cases of Stevens-Johnson syndrome and 30% of cases of toxic epidermal necrolysis. Predictors of poor outcomes include older age, malignancy, and renal failure.

LEUKOCYTOCLASTIC VASCULITIS

Severe drug reactions can also be manifested as vasculitis, neutrophilic eruptions, and ulcerations. Vasculitis is further categorized by the size of the involved vessel and the nature of the cellular reaction and immune complexes. Leukocytoclastic vasculitis, which is the most common form of vasculitis induced by drugs, is manifested as palpable purpura, usually on the lower extremities (see Figs. 406-4 and 406-5 in Chapter 406).

NEUTROPHILIC DRUG REACTIONS

Neutrophilic drug reactions include iododermas, bromodermas, acute generalized exanthematous pustulosis, and acneiform folliculitis. Sweet syndrome (acute febrile neutrophilic dermatosis; see later) also can be drug related. Epidermal growth factor receptor inhibitors and protein kinase inhibitors cause an acneiform facial or chest eruption that is associated with drugs (Fig. 407-6).

FIGURE 407-6. Epidermal growth factor receptor inhibitor–associated rash.

Acute generalized exanthematous pustulosis is characterized by numerous (>100), small (<5 mm), nonfollicular subcorneal pustules that arise on erythematous skin, often beginning in skin creases or on the face. High fever and peripheral neutrophilia may precede or accompany the eruption. The pustules are sterile, present for 5 to 10 days, and followed by desquamation. They usually appear less than 2 days after the administration of the causative drug. Ninety percent of cases are due to drugs, most commonly β-lactam antibiotics, macrolides, and calcium channel blockers. This syndrome also has been called pustular drug rash, pustular psoriasis after corticosteroid withdrawal, and toxic pustuloderma. When severe, it may be confused with toxic epidermal necrolysis, but the mortality rate is only 1 to 2%. Skin patch testing is frequently positive.

FIXED DRUG ERUPTIONS

A fixed drug reaction appears at the same location 1 to 2 weeks after first drug exposure and within 24 hours of repeat exposure. The lips, hands, face, feet, and genitalia are most commonly involved. The lesion may begin as erythema and then become gray, brown, or violaceous. Trimethoprim-sulfamethoxazole, NSAIDs, tetracyclines, and pseudoephedrine are common causes.[9]

PHOTOSENSITIVITY AND WITHDRAWAL REACTIONS

Light combined with drugs (Table 407-4) can produce photosensitivity reactions that can be quite severe and mimic sunburn. Ultraviolet radiation interacts with a drug or its metabolite to generate reactive oxygen species, leading to cellular damage. Tetracyclines, sulfa drugs, NSAIDs, and fluoroquinolones are often implicated in photosensitivity reactions. Photosensitizing drugs may exacerbate lupus erythematosus (Chapter 245) or porphyria cutanea tarda (Chapter 194).[10]

TABLE 407-4 DRUGS ASSOCIATED WITH SUN SENSITIVITY

PHOTOTOXIC
Chlorpromazine
Hydralazine
Levaquin
Procainamide
Psoralens
Porphyrins
Sulfonamides
Tetracyclines
Thiazide diuretics
PHOTOALLERGIC
Chlorothiazide
Griseofulvin
Hypoglycemic drugs
Promethazine

CONTACT DERMATITIS

Allergic contact dermatitis is a T-cell–mediated delayed hypersensitivity reaction that occurs after topical drug application or exposure to poison ivy, oak, or sumac.[11] It is manifested by erythema and microvesiculation and may spread beyond the area of application (id reaction). Common contact sensitizers include Neosporin (polymyxin B, neomycin, and bacitracin), bacitracin, diphenhydramine, doxepin, lidocaine, lanolin, mercury, henna, ethyl cyanoacrylate (eyelash adhesive), nickel, hair dyes, latex, and *p*-aminobenzoic acid.

BENIGN PAPULES, NODULES, AND TUMORS

The skin is heterogeneous, composed of epidermis, dermis, subcutaneous compartments, and blood vessels. The skin hosts a number of migrating cells (Chapter 403), all of which can give rise to benign or malignant tumors. Lesions that arise from epidermal keratinocytes are usually papules (actinic keratoses, warts, seborrheic keratoses) or plaques (psoriasis, Bowen disease). Nodules are deeper dermal lesions that may be tender or asymptomatic and single or multiple, and they break down to form ulcers. Nodules are classified as inflammatory (granulomas, vasculitis, or panniculitis), infectious, vascular, metabolic, or neoplastic. Nodules can be benign or malignant tumors that arise from skin cells or migrant cells (Table 407-5). Nodules that are smaller and symmetrical are more likely to be benign than lesions that grow rapidly, are larger, or invade surrounding tissue. Any rapidly changing skin nodule should be investigated with an excisional biopsy to the level of fat and sent for histology as well as for bacterial, fungal, and acid-fast cultures.

BENIGN EPIDERMAL TUMORS

The top layer of skin is the avascular epidermis composed of keratinocytes that undergo apoptosis, thereby forming the stratum corneum. Melanocytes, Langerhans cells, and inflammatory cells may enter the epidermis. Epidermal stem cells form adnexal organs such as hair follicles and sebaceous, eccrine, and apocrine glands that can give rise to tumors.

ACTINIC KERATOSES

Actinic keratoses are pink, scaly macules composed of sun-damaged keratinocytes and are precursors of in situ squamous cell carcinomas (Bowen disease) or invasive squamous carcinomas (Chapter 188). Actinic keratoses are 0.1 cm to 1.0 cm in size and are found on sun-exposed areas such as the forearms, hands, face, and scalp (Fig. 407-7). Lesions with induration, thick crusts, ulceration, or pain should be excised for biopsy to exclude invasive squamous cell carcinoma.

TREATMENT

Tirbanibulin 1% ointment applied once daily for 5 days can result in complete clearance in about 50% of patients, but about 50% of responders will develop recurrent lesions in the next year.[A4] Other options include photodynamic therapy with topical aminolevulinate, cryotherapy, topical fluorouracil, retinoids, imiquimod, or ingenol mebutate gel.[A5–A8] To treat and prevent actinic keratoses, sun-exposed areas may be treated topically with 5-fluorouracil cream (5%) applied twice a day for 2 weeks or twice weekly for 8 weeks.[12] If needed, topical mupirocin ointment can used to prevent staphylococcal infection.

TABLE 407-5 TUMORS AND NODULES OF THE SKIN

Benign, nonpigmented tumors and nodules
Epidermal: warts, acrochordons, tricholemmomas, sebaceous hyperplasia
Adnexal: epidermal cysts, syringomas, follicular cysts, pilomatricoma, pilar cysts, apocrine or eccrine adenomas
Dermal and subcutaneous: lipomas, angiolipomas, neurofibromas, leiomyomas
Benign, pigmented tumors and nodules
Epidermal: seborrheic keratoses
Melanocytic compound nevi (junctional nevi are flat)
Spitz nevus
Blue nevus
Dermatofibromas
Malignant, nonpigmented tumors and nodules
Basal cell carcinoma (nodular, superficial, morpheaform, pigmented)
Squamous cell carcinoma (actinic keratoses, Bowen disease, keratoacanthomas)
Cutaneous T- and B-cell lymphomas
Amelanotic melanomas
Merkel cell carcinomas
Adnexal carcinomas of the sebaceous and/or apocrine glands
Malignant, pigmented tumors and nodules
Pigmented basal cell carcinoma
Malignant melanoma: in situ, superficial spreading, nodular, acral lentiginous
Dermatofibrosarcoma protuberans
Inflammatory nodules over joints
Gottron papules (dermatomyositis)
Gouty tophi
Heberden nodes (osteoarthritis)
Multicentric reticulohistiocytosis (paraneoplastic syndrome)
Rheumatoid nodules
Granuloma annulare
Inflammatory nodules of the lower extremities
Panniculitis
Vasculitis: periarteritis nodosa
Metabolic nodules of the skin
Amyloidosis
Gouty tophi
Xanthomas, necrobiotic xanthogranuloma
Xanthelasma
Vascular lesions
Benign: nevus flammeus, angiokeratomas, spider hemangiomas, capillary hemangiomas, cavernous hemangiomas, blue rubber bleb nevi, pyogenic granulomas
Malignant: Kaposi sarcoma, angiosarcoma

SEBORRHEIC KERATOSES

Seborrheic keratoses are common verrucous or stuck-on epidermal papules and plaques of various colors (Fig. 407-8).[13] They are common with advancing age, but a sudden eruption of seborrheic keratoses may be indicative of an internal malignancy. Seborrheic keratoses consist of a single clone of keratinocytes and are inherited as an autosomal dominant trait. Seborrheic keratoses have *FGFR3, PIK3CA, KRAS, EGFR, HRAS,* and *AKT* mutations but remain clinically benign. Their surface may be friable, and lesions can be scraped off. Seborrheic keratoses spare the palms, soles, and mucosal surfaces. Although benign, seborrheic keratoses must be differentiated from melanocytic nevi, melanomas, and pigmented basal cell carcinoma, usually by the presence of white to yellow horn cysts on their surface, best appreciated with dermoscopy. If needed, treatment options include cryotherapy, curettage, shave excision, or laser excision.[A9]

WARTY LESIONS

Epidermal papules include common warts (see Fig. 406-3 in Chapter 406) caused by human papillomavirus (HPV). HPV also can be detected in squamous carcinomas arising on the digits and in keratoacanthomas, which are low-grade, well-demarcated, dome-shaped papules or nodules that grow rapidly and spontaneously involute in 6 to 8 weeks. Acrodermatitis verruciformis is characterized by multiple warts with the appearance of seborrheic keratoses on the dorsal extremities and gives rise to squamous cell carcinomas. Molluscum contagiosum (Chapter 343) (Fig. 407-9), caused by a DNA virus, are small, shiny, domed-shaped, 1- to 5-mm papules with a central depression. Molluscum contagiosum lesions are common in children and immunocompromised patients. Treatment with anticancer BRAF inhibitors can cause warty papules, keratoacanthomas, and eruptive keratosis pilaris.

Cowden syndrome (Chapter 179), caused by mutations in the *PTEN* gene, is associated with warty papules (tricholemmomas; Fig. 407-10); cobblestone

FIGURE 407-7. Actinic keratoses. Numerous hypertrophic actinic keratoses on the bald scalp, with hypopigmentation at sites of previous treatment. (From Bolognia. *Dermatology*, 4th ed.)

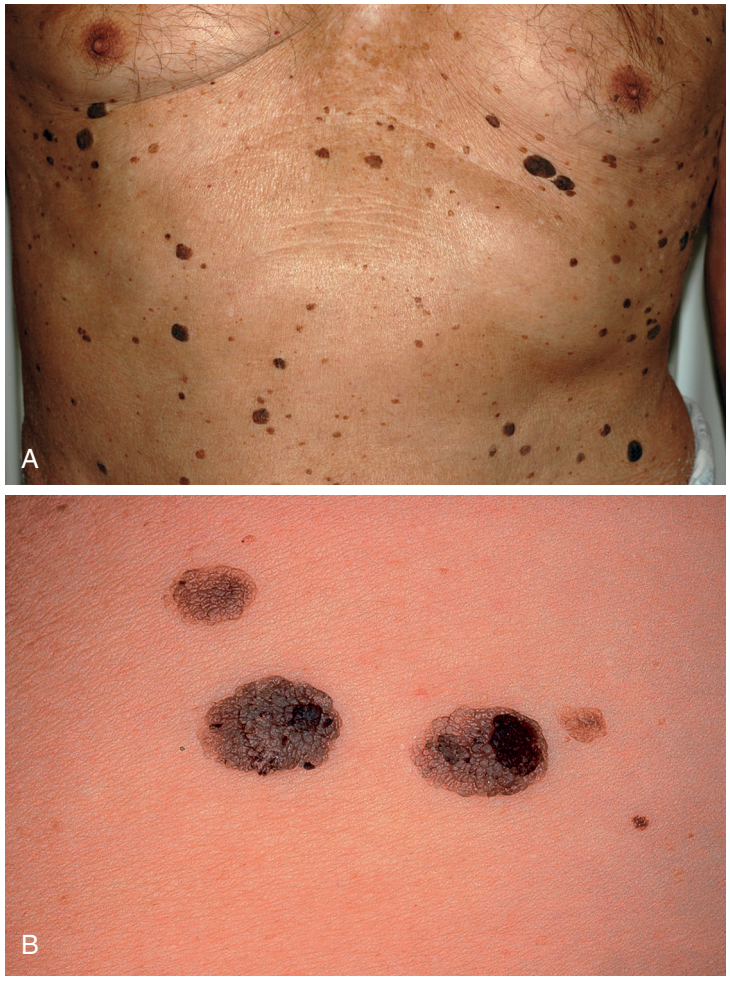

FIGURE 407-8. Seborrheic keratoses. A, Multiple seborrheic keratoses of the anterior trunk vary in size and color. **B,** Sharply demarcated, pigmented papules and plaques with a papillomatous surface and horn pseudocysts. Note the "stuck-on" appearance. (From Bolognia. *Dermatology*, 4th ed.)

papules on the gums and tongue; fibrous papules; and multiple hamartomas involving the breast, thyroid, intestines, ovary, and cerebellum.

ADNEXAL TUMORS

Adnexal tumors arise from hair follicles or glands and are commonly found on the face or scalp. Trichoepitheliomas resemble basal cell carcinomas. Sebaceous hyperplasia consists of small yellow papules with a central depression. Adnexal tumors of sebaceous origin, including sebaceous adenomas and sebaceous carcinomas, can also occur on the face, where they may be markers of the Muir-Torre syndrome of familial breast and colon cancer. Epidermal or sebaceous cysts, which are found in acne or as single firm nodules with a central pore, are filled with sebum or keratin. Epidermoid tumors of the scalp and a family history of colon cancer raise questions of a diagnosis of Gardner syndrome (Chapter 179).

DERMATOFIBROMAS AND COLLAGENOMAS

Fibroblasts, the resident cells of the dermis, produce collagen, elastin, and mucopolysaccharides. Accumulation of these products results in sclerosis, papules, or nodules. Fibroblasts in small, dense clusters form firm brown or tan papules known as dermatofibromas. Dermatofibromas are hypertrophic scars that are commonly found on the extremities and that may form after insect bites or trauma. They are firm and well-demarcated papules, and the skin dimples when lateral pressure is applied. Dermatofibromas can be treated, but increased scarring may occur. The malignant counterpart is dermatofibroma sarcoma protuberans, which is a poorly defined, rapidly expanding, dermal, malignant tumor. Overlying erythema or hyperpigmentation is often present.

Some individuals have more pronounced and hypertrophic scar formation known as keloids, with an autosomal dominant or autosomal recessive inheritance pattern. Keloids, which are shiny and firm in appearance, result from an overproduction of collagen. They are especially common on the anterior chest, neck, and earlobes. Treatment is discussed in Chapter 408.

Collagenomas and elastic tumors appear as small white to yellow papules and are found in the skin and bone of patients with Buschke-Ollendorff syndrome. *Pseudoxanthoma elasticum* (Chapter 239), an autosomal recessive disorder, typically manifests as cutaneous yellow plaques on the neck or antecubital fossa from damaged elastin tissue. Mucin cysts are gray, shiny, well-demarcated, round nodules that generally arise on the mucosa or on the digits, where they may have an underlying connection to the joint space.

NEURAL CREST CELL TUMORS

Benign tumors in the dermis arising from neural crest cells include neurofibromas (soft, flesh-colored papules; Fig. 407-11), schwannomas (larger subcutaneous soft tumors or plaques; Fig. 407-12), and melanocytic lesions. Although solitary neurofibromas may occur, multiple lesions with café-au-lait spots (tan macules) or axillary freckling (Crowe sign) are diagnostic of neurofibromatosis type I, an autosomal dominant disorder caused by mutations in neurofibromin (Chapter 385).[14] Schwannomas can become malignant and manifest as dermal nodules.

Merkel cell carcinoma, which is a neuroendocrine carcinoma of the skin, is a particularly aggressive small cell tumor arising from the cutaneous nerve endings or Meissner corpuscles. Merkel cell polyomavirus (Chapter 341) is associated with development of Merkel cell carcinoma. Merkel cell carcinoma may present as a solitary flesh-colored to purple dome-shaped papule on the head or neck (Fig. 407-13). Sentinel lymph node biopsy is recommended in all patients with primary Merkel cell carcinoma. Treatment requires full excision, radiation therapy, and often chemotherapy because the cancer tends to recur and metastasize. PD-1 axis checkpoint inhibitors, such as pembrolizumab (2 mg/kg every 3 weeks), avelumab (10 mg/kg every 2 weeks), and nivolumab (240 mg every 2 weeks), provide an objective response rate between about 55 to 70% in chemotherapy-naïve advanced Merkel cell carcinoma.[15]

MELANOCYTIC LESIONS

Benign melanocytic moles or nevi (new) are discrete nests of melanocytes acquired during childhood and young adulthood, stimulated by sun exposure. Nevi are benign and composed of melanocytes (Chapter 188). They regress with age and change in color during pregnancy. Benign melanocytic nevi are formed by nests of melanocytes at the epidermal junction (junctional nevi), in the dermis (intradermal nevi), or in both compartments (compound nevi). Their appearance depends on type and age of the lesion. Junctional nevi (Fig. 407-14) are small, flat, and light to dark brown. Intradermal nevi are soft, flesh-colored to pink papules with smooth regular borders and surface. Compound nevi are globular papules with brown pigmentation. Blue nevi (Fig. 407-15) are flat, grayish blue, and regular. Small congenital nevi are dark brown, dysplastic nevi (Fig. 407-16), have variegated colors, and may give rise to melanoma. More than 10 large, atypical moles with irregular borders and colors confer higher risk of developing melanoma, especially with a positive family history. Other recognized risk factors for melanoma include having more than 50

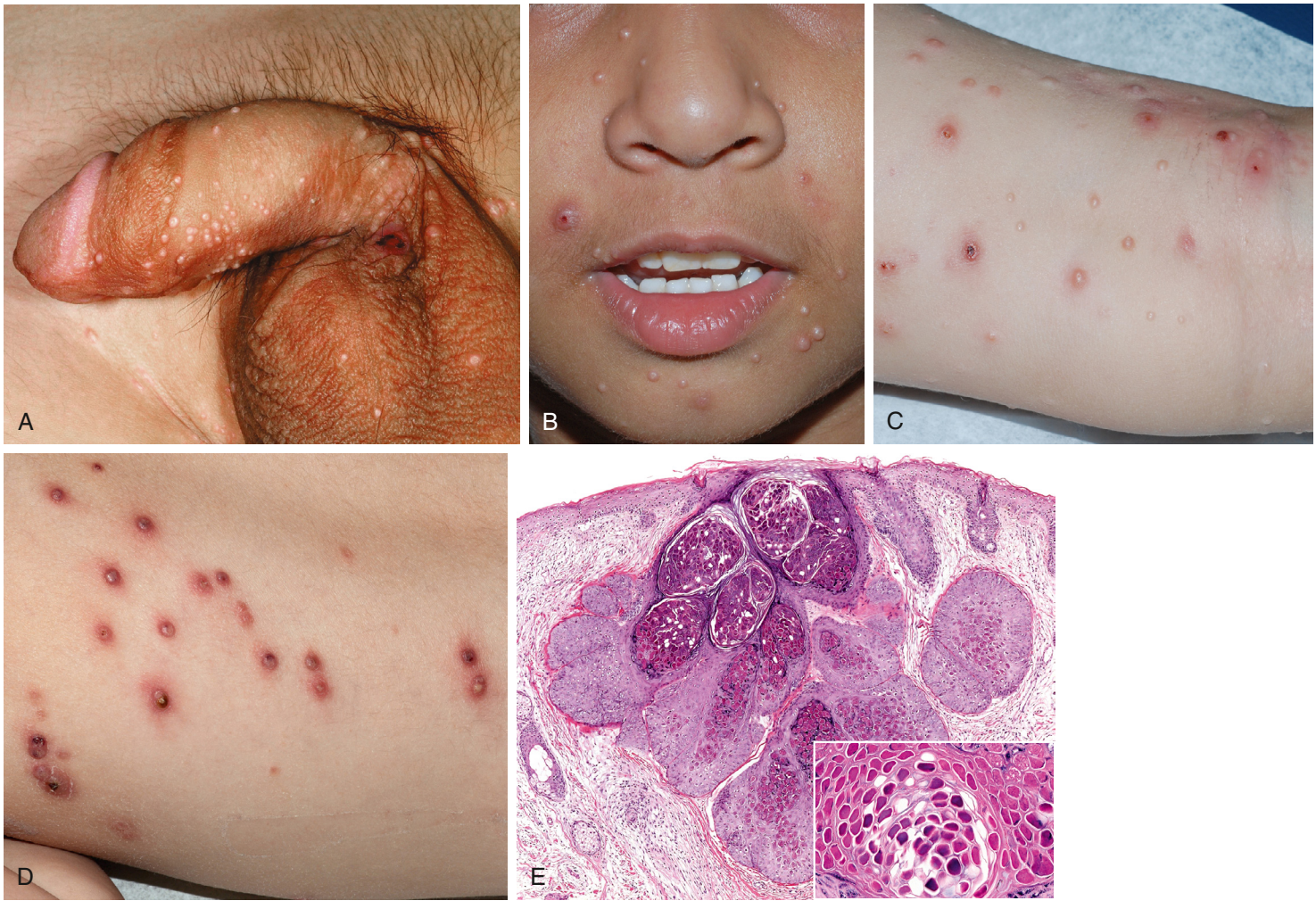

FIGURE 407-9. Molluscum contagiosum. Multiple pearly, umbilicated papules in the genital area (**A**) and on the face (**B**); note the inflamed lesion on the right cheek. Inflammatory reactions are a sign of the host immune response to the virus. **C**, Inflamed lesions surrounded by "molluscum dermatitis." **D**, Pustular presentation of an inflamed molluscum; culture revealed only normal skin flora. **E**, Histologic evaluation shows numerous molluscum bodies (*inset*). Demonstrating these bodies in a saline preparation of expressed lesional contents serves as a technique for making a bedside diagnosis. (B–D, Courtesy Julie V. Schaffer, MD. E, Courtesy Lorenzo Cerroni, MD.)

FIGURE 407-10. Cowden syndrome: cobblestone gums (*left*) and tricholemmoma (*right*).

small nevi, red or blonde hair, or fair skin that burns and a history of blistering sunburns as a child. Patients with higher risk for melanoma should have surveillance and regular skin examinations.[16]

LANGERHANS CELL HISTIOCYTOSIS

Skin surveillance is mediated by antigen-presenting cells: Langerhans cells, dermal dendritic cells, and skin-homing T lymphocytes.[17] Proliferation of Langerhans cells is called histiocytosis (Chapter 155). Childhood histiocytosis X is manifested as severe seborrheic dermatitis of the scalp and gluteal areas with underlying purpura and may result in the hemophagocytic syndrome. In adults, lesions appear in the intertriginous areas (Fig. 407-17). Patients with the non–Langerhans cell histiocytosis have lytic bone involvement (eosinophilic granulomas) or diabetes insipidus (Hand-Schüller-Christian syndrome).

VASCULAR LESIONS

HEMANGIOMAS

Benign capillary, or cherry, hemangiomas are bright cherry-red to purple papules, generally less than 5 mm in diameter. They appear on the trunk with

FIGURE 407-11. Multiple cutaneous neurofibromas. Soft, skin-colored to pinkish-tan, dome-shaped or polypoid, well-demarcated papules and nodules of various sizes (**A–C**) can occur in patients with neurofibromatosis. Neurofibromas may be superimposed on café-au-lait macules and lentigines (**B, C**). (A, B, Courtesy Julie V. Schaffer, MD.)

FIGURE 407-12. Solitary schwannoma. Skin-colored nodule on the plantar surface of the great toe. (Courtesy Julie V. Schaffer, MD.)

FIGURE 407-13. Merkel cell carcinoma (primary neuroendocrine carcinoma). A, A rapidly growing, violaceous nodule on the toe. **B**, Large, eroded, erythematous nodule arising within sun-damaged skin of the cheek. (B, Courtesy Lorenzo Cerroni, MD.)

FIGURE 407-14. Junctional nevus. (From Bolognia. *Dermatology*, 4th ed.)

FIGURE 407-15. Benign blue nevus. Well-circumscribed, dark blue, flat papule. (From Bolognia. *Dermatology*, 4th ed.)

FIGURE 407-16. Atypical melanocytic nevi. A, There is asymmetry as well as several shades of brown, simulating the clinical features seen in cutaneous melanoma. **B,** In addition to multiple atypical nevi, patients can have numerous typical nevi. (From Bolognia. *Dermatology*, 4th ed.)

aging and may be numerous (Fig. 407-18). Pyogenic granulomas can resemble hemangiomas but contain polymorphonuclear leukocytes, are friable, and bleed easily. Multiple pyogenic granulomas are seen in infectious bacillary angiomatosis (due to *Bartonella henselae* or *Bartonella quintana*) in immunocompromised hosts (Chapter 291). Cavernous or strawberry hemangiomas can also appear in the neonatal period as rapidly growing vascular tumors; they may obstruct the eye or the pharynx before regressing.

TREATMENT AND PROGNOSIS

Propranolol 2 to 3 mg/kg/day in two or three divided doses for 6 months may decrease the hemangioma's volume, color, and elevation in children younger than 5 years of age.[18] Corticosteroids, interferon, or antiangiogenic factors also can treat these lesions if propranolol is not successful. Cavernous hemangiomas are deeper and less likely to resolve than smaller lesions. When associated with platelet consumption and a risk for severe bleeding, the Kasabach-Merritt syndrome is present.

SARCOMAS

Kaposi sarcoma (Chapter 359) is a disseminated angiomatosis that arises from viral IL-8 production by herpesvirus 8. Lesions are symmetrical purple, red, gray, or brown patches, papules, nodules, or ulcers (Fig. 407-19). Mucosal involvement is more common in advanced disease. Kaposi sarcoma in young African adults and Kaposi sarcoma associated with human immunodeficiency virus (HIV) infection often have a more aggressive course than Kaposi sarcoma in elderly men of Mediterranean background, whose disease is indolent and often confined to the lower extremities. Treatment of HIV disease with highly active antiretroviral therapy has been associated with a marked decreased

FIGURE 407-17. Histiocytosis X in intertriginous areas.

incidence and severity of HIV-associated Kaposi sarcoma.[19] Treatment is described in Chapter 359.

Angiosarcomas are malignant purple to red vascular tumor nodules that are more common in elderly individuals or on the extremities of patients with chronic lymphedema. To help distinguish cutaneous angiosarcomas

FIGURE 407-18. Benign capillary hemangioma.

FIGURE 407-19. Kaposi sarcoma in a patient with AIDS. Violet-red papules or nodules are often oval to lanceolate and are usually more widely distributed than in classic Kaposi sarcoma. (From Bolognia. *Dermatology*, 4th ed.)

from benign histologic mimics, immunohistochemistry staining for the ERG protein, which is a member of the erythroblast transformation-specific family of transcription factors, is a specific and sensitive marker for endothelial differentiation. Treatment is described in Chapter 187.

INFLAMMATORY AND HEMATOPOIETIC PAPULES AND TUMORS

Inflammatory diseases of the skin involve the superficial or dermal vessels or subcutaneous tissue. Inflammatory infiltrates can be mixed or restricted in nature. Lymphocytes, polymorphonuclear leukocytes, histiocytes, eosinophils, and plasma cells are involved in the most common inflammatory reactions. Hematologic malignancies can present with secondary skin lesions, including patches, nodules, papules, or vasculitic lesions. Skin-homing $CD4^+$ T cells give rise to cutaneous T-cell lymphomas. Mycosis fungoides (Chapter 171) lesions are pleomorphic pink, white, or brown patches or plaques; alopecia; or diffuse erythroderma with blood involvement (Sézary syndrome). Early patch or plaque mycosis fungoides is indistinguishable from chronic eczematous or psoriasiform dermatitis. Tumors occur late in mycosis fungoides and

FIGURE 407-20. Cutaneous mucosa-associated lymphoid tissue (MALT) lymphoma.

can transform to a large cell lymphoma phenotype, with or without expression of CD30. Peripheral cutaneous T-cell lymphomas also may be found in subcutaneous tissue as panniculitic lesions. Lymphomatoid papulosis is characterized by crops of red to pink self-regressing papules with histologic findings similar to those of anaplastic large cell lymphoma (Chapter 171), including expression of CD30 antigen. Clinically, lymphomatoid papulosis presents as self-regressing papules, $CD3^+$ anaplastic T-cell lymphomas can present as tumors, and patients with transformed $CD30^+$ mycosis fungoides initially have patch or plaque stage disease before developing tumors. Treatment of lymphomatoid papulosis consists of topical corticosteroids, methotrexate, or bexarotene. For $CD30^+$ anaplastic T-cell lymphoma, therapeutic options include radiation therapy, methotrexate, bexarotene, brentuximab vedotin, and chemotherapy (Chapter 171). Natural killer T-cell lymphomas, immunoblastic lymphomas, and plasmacytoid dendritic cell tumors appear as brown to purple dermal nodules, often with purpura.

Cutaneous B-cell lymphomas present as pink, infiltrated, dome-shaped, shiny papules or tumors. Whereas follicular B-cell lymphoma is commonly located on the face, scalp, or upper part of the back, mucosa-associated B-cell tumors are more common on the trunk. With the exception of large B-cell lymphoma, follicular and mucosa-associated lymphoid tissue (MALT) B-cell lymphomas of the skin are indolent. Cutaneous MALT lymphomas (Fig. 407-20) have been associated with *Borrelia* spp infection (Chapter 296), *Helicobacter pylori* infection, and chronic inflammation. Plasmacytomas can arise in the skin, in bone, with multiple myeloma (Chapter 173), or independently. Extramedullary hematopoiesis or endometriosis can be associated with red or brown nodules in the dermis.

GRANULOMATOUS DISEASES

Sarcoidosis is an inflammatory granulomatous process manifested as ichthyosis, papules, plaques, or tumors with an apple-jelly color (Fig. 407-21). Patients with lepromatous leprosy also can have histiocytic plaques or tumors (Fig. 407-22); treatment of leprosy may induce an inflammatory reaction called erythema nodosum leprosum. Granulomatous mycosis fungoides, which is a variant of cutaneous T-cell lymphoma, is difficult to diagnose and treat. Granulomatous inflammation within the dermis can result in damage to collagen, as seen in granuloma annulare (ringlike pink to red infiltrated lesions, often on the hands or elbows), rheumatoid nodules that occur on the extensor surface of the arms, and necrobiosis lipoidica on the shins of patients with diabetes. All three lesions typically include fibrin deposits within dermal blood vessels. Multicentric reticulohistiocytosis is a rare paraneoplastic syndrome in which histiocytic nodules form over joints with associated arthritis.

INFLAMMATORY SKIN LESIONS AND NODULES

Inflammatory skin nodules arise from inflamed blood vessels (vasculitis) or adipose tissue (panniculitis). Either can arise in response to underlying infection or antigen stimulation with influx of inflammatory cells. Vasculitis is categorized by vessel size and circulating immune complexes. Damage to blood vessels results in leakage of red blood cells with the development of purpura (nonblanching red to purple lesions; Chapter 249).

Sweet syndrome, also called febrile neutrophilic dermatosis (Fig. 407-23), is accompanied by fever, leukocytosis, and tender reddish skin plaques.[20] Some

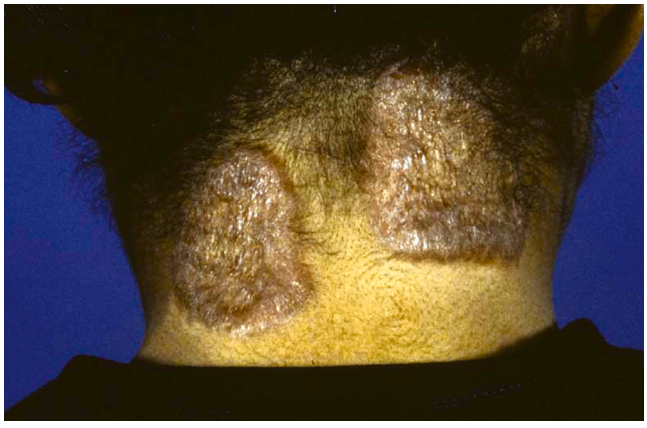

FIGURE 407-21. Cutaneous sarcoidosis.

FIGURE 407-22. Lepromatous leprosy. A, Numerous erythematous papules and nodules on the forearms and hands. **B,** Infiltrated nodules coalescing on the forehead with leonine facies and madarosis. Note the ocular involvement.

FIGURE 407-23. Sweet syndrome. A, Scattered tender, edematous pink papules, pustules, and plaques on the chest. **B,** The edema can be quite marked as seen in these lesions on the upper back. (B, Courtesy Kalman Watsky, MD.)

patients also have arthralgia. Biopsy shows sheets of leukocytes filling the upper dermis in the absence of infection. It can be idiopathic; drug induced; or associated with an underlying disease, typically with an underlying streptococcal infection, acute myelogenous leukemia, other malignancies, inflammatory bowel disease, or rheumatoid arthritis. Use of hematopoietic growth factors also can precipitate Sweet syndrome. Sweet syndrome, but not erythema elevatum diutinum, is highly responsive to corticosteroids (oral prednisone 1 to 2 mg/kg/day gradually tapered over 6 weeks to 3 months) or indomethacin (150 mg per day for 1 week; then 100 mg per day for 2 weeks), but oral dapsone (100 to 200 mg/day) can improve both conditions.

Pyoderma gangrenosum is a trauma-induced ulcer that is part of the spectrum of Sweet syndrome. Diagnosis requires skin biopsy, cultures, and serologic testing for other associated diseases. Treatment with prednisolone (0.75 mg/kg/day, maximum 75 mg/day) or cyclosporine (4 mg/kg/day, maximum 400mg/day) is equally effective.[A10] Decubitus ulcers require débridement, elimination of local pressure, and attention to nutrition.

Erythema elevatum diutinum is manifested as multiple, infiltrated pink, yellow, red, or violaceous nodules or papules that may be painful or asymptomatic. The lesions can coalesce to form gyrate lesions on the dorsum of the hands or extensor surfaces similar to granuloma annulare. Erythema elevatum diutinum is associated with upper respiratory infections (especially *Streptococcus* spp), HIV infection, and inflammatory bowel disease. Clinically, the lesions look similar to Sweet syndrome, but their underlying histopathology (a necrotizing vasculitis with neutrophils and hyalinization of the vessels) can be distinguished from the neutrophils seen in the upper dermis in Sweet syndrome on biopsy.

POLYARTERITIS NODOSA AND PANNICULITIS

Polyarteritis nodosa (Chapter 249) arises in larger arterioles and may be associated with hepatitis C infection, mesenteric aneurysms, cryoglobulinemia, cutaneous ulceration, and livedo reticularis. Polyarteritis nodosa is distinct from small vessel leukocytoclastic vasculitis, which is characterized by smaller areas (a few millimeters) of purpura.

In the clinical setting, *panniculitis* occurs more frequently than nodular vasculitis. The diagnosis of vasculitis versus septal or lobular panniculitis requires an excisional biopsy, including fat, with appropriate cultures and stains.

Erythema nodosum (Fig. 407-24) is a septal panniculitis characterized by tender nodules that are 1 to 2 cm in diameter with warm, pink, overlying epidermis. They appear in crops on the extremities. A perivascular inflammatory infiltrate is present around small intralobular vessels without vasculitis. Erythema nodosum arises frequently in response to sarcoidosis (Chapter 83), various infections, inflammatory bowel disease, or drug use and less commonly in patients with azathioprine-induced pancreatitis or primary biliary cirrhosis. Often, however, the underlying cause remains unknown (Table 407-6).[21]

Lobular panniculitis with necrosis and purpura is called nodular vasculitis or erythema induratum. Nodular vasculitis is characterized by painful, chronic, recurrent nodules on the shin or thigh that become bluish, ulcerate, and heal with scarring. Erythema induratum (Fig. 407-25) is exacerbated by cold exposure and is sometimes associated with *Mycobacterium tuberculosis* (Chapter 299).

True lobular panniculitis, with or without fat necrosis, is more frequent in men with underlying pancreatitis (Chapter 130) and may precede pancreatic cancer (Chapter 180). The lesions have a predilection for the anterior aspect of the shins and may be fluctuant as a result of fat necrosis. *Lupus panniculitis*, or lupus profundus, which involves the fat, is diagnosed by overlying granular immune complex deposition of IgM along the dermal-epidermal junction and is often difficult to distinguish from subcutaneous panniculitic T-cell lymphoma. Subcutaneous panniculitic γ/δ T-cell lymphoma is more aggressive and has a poor prognosis compared with α/β panniculitic T-cell lymphoma. Lupus panniculitis of the breast, which can be mistaken for adenocarcinoma, is treated with antimalarials or corticosteroids. Lobular panniculitis with calcification of the small arterioles, which occurs in the setting of renal failure with hyperparathyroidism, is called calciphylaxis (Chapter 116). Granulomatous lobular panniculitis may also arise in the setting of schistosomiasis (Chapter 326), Sjögren syndrome (Chapter 247), Crohn disease (Chapter 127), sarcoidosis (Chapter 83), ruptured epidermal cysts, atypical mycobacterial infection (Chapter 300), or tuberculosis (Chapter 299).

FUNGAL INFECTIONS

In immunocompromised patients, necrotic or granulomatous lobular panniculitis can be caused by disseminated fungal infections with *Candida* spp, *Sporothrix schenckii, Cryptococcus* spp, *Histoplasma* spp, *Nocardia* spp, *Rhizopus* spp, *Aspergillus* spp, *Fusarium* spp, or chromomycosis. Fungal mycelia invade vessel walls, where they produce purpuric and painful lesions that may ulcerate. Osler nodes, which are tender nodular vasculitic lesions on the extremities, occur in the setting of bacterial endocarditis (Chapter 61). Staphylococcal or streptococcal sepsis may be manifested as pustules, papules, or panniculitic lesions.

ATROPHIC AND SCLEROTIC LESIONS

ATROPHIC LESIONS

Atrophic lesions result from thinning or loss of the epidermal and dermal layers (Table 407-7).[22] Examples are photoaging caused by loss of epidermal thickness and collagen, discoid lupus, and genetic disorders of collagen production (e.g., Ehlers-Danlos syndrome; Fig. 407-26). Epidermal wrinkling can result in a cigarette paper appearance with prominence of the underlying blood vessels. High-potency topical corticosteroids cause loss of collagen, resulting in atrophy. In Cushing syndrome (Chapter 208), striae appear as red or purple streaks because the underlying dermis can be seen through the epidermis.

Aging skin is most pronounced in sun-exposed areas, but intrinsic aging beginning as early as 30 years of age is characterized by abnormalities in the formation of elastin fibers. Aging of the skin is accompanied by decreased rete ridges and diminished circulation. Sunlight ages the skin by inducing proteolytic enzymes that digest the underlying collagen and elastin (wrinkles). In addition, sun exposure induces pigment incontinence (freckling), increased junctional nevi, and proliferation of benign keratinocyte growths (seborrheic keratoses).

Atrophy can also result from ongoing inflammatory processes that cause scarring, such as collagen vascular disease or mycosis fungoides. The cutaneous and discoid forms of lupus erythematosus (Chapter 245) are manifested as scaly plaques with atrophy or alopecia on sun-exposed areas; the systemic form is characterized by malar rash, urticaria, or vasculitic lesions. Dermatomyositis (Chapter 248) can be associated with collagen vascular disease or malignancy; periorbital suffusion, telangiectasia of the nail beds, and Gottron papules or

FIGURE 407-25. Erythema induratum—clinical appearance. Inflamed nodular lesions on the lower leg, with evidence of ulceration. (Courtesy Kenneth E Greer, MD.)

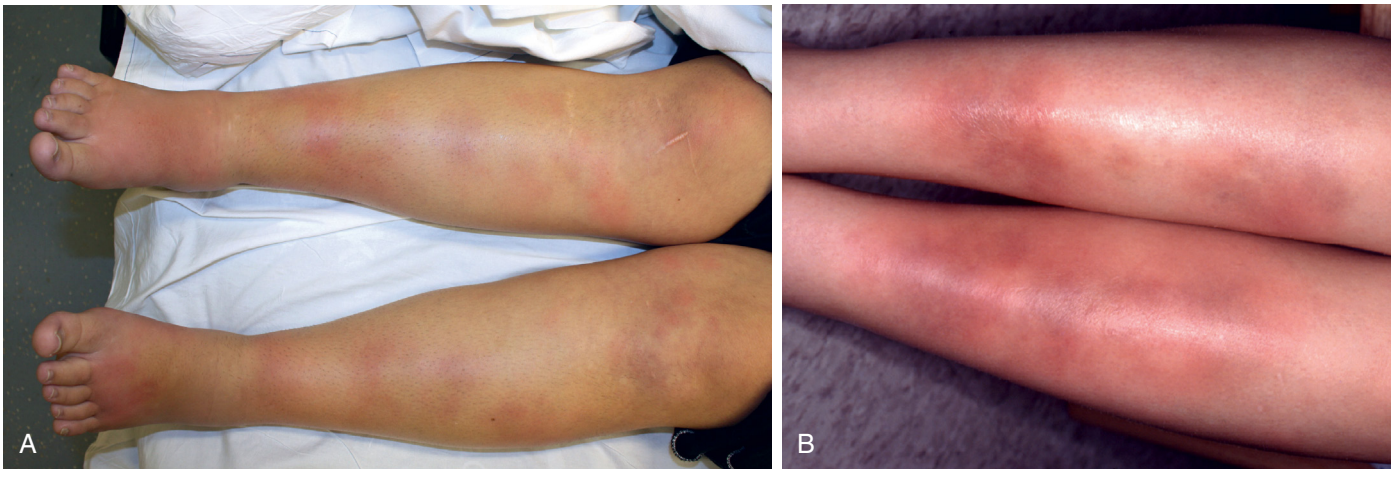

FIGURE 407-24. Erythema nodosum—clinical appearance. A, Erythematous, tender nodules bilaterally on the shins and dorsal feet. **B**, The nodules and plaques may develop a bruise-like appearance. (A, Courtesy Ian Odell, MD, PhD. B, Courtesy Kalman Watsky, MD.)

TABLE 407-7 ATROPHIC SKIN CONDITIONS WITH SCARRING, ULCERATIONS, OR TELANGIECTASES

ATROPHY
Epidermal: chronic corticosteroid use, photoaging, mycosis fungoides
Dermal elastin: anetoderma, cutis laxa, intrinsic aging
Dermal collagen: Ehlers-Danlos syndrome, aging
Subcutaneous: granulomatous slack skin (a mycosis fungoides variant)
Lipodystrophy (loss of fat)
SCARRING OR ATROPHY WITH TELANGIECTASIAS
Discoid and subacute cutaneous lupus erythematosus
Dermatomyositis
Keloid formation
Large plaque parapsoriasis (poikiloderma vasculare atrophicans variant of mycosis fungoides)
Photoaging
Necrobiosis lipoidica diabeticorum
Radiation dermatitis
Porphyrias
Thermal burns (erythema ab igne)
SCLEROSIS OR INFILTRATIVE PROCESSES
Amyloidosis
Systemic sclerosis, scleroderma
Localized sclerosis, morphea
Lichen sclerosis et atrophicus
Lichen myxedematosus or papular mucinosis (mucopolysaccharide deposition with paraproteinemia)
Myxedema (mucin deposits with anti–thyroid-stimulating hormone receptor antibodies)
ULCERATIONS
Secondary breakdown of any blister or nodule: infectious, inflammatory, tumor, vasculitis
Decubitus or pressure ulcers
Genital ulcers: syphilis, herpes simplex, chancroid, lymphogranuloma venereum, Behçet syndrome
Pyoderma gangrenosum, Sweet syndrome

FIGURE 407-26. Atrophic skin in Ehlers-Danlos syndrome type 2.

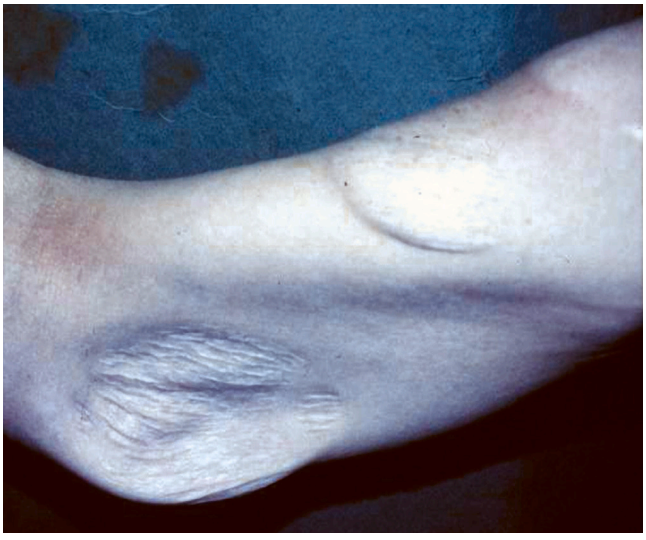

FIGURE 407-27. Anetoderma.

FIGURE 407-28. Lichen myxedematosus.

FIGURE 407-29. Nephrogenic systemic fibrosis.

scaly lesions over the joints are the skin manifestations. Anetodermas are localized sclerotic lesions (Fig. 407-27) with distinctive clinical features from underlying inflammation.

Eosinophilic fasciitis is accompanied by nodules or sclerosis of the lower extremities, myopathy, pulmonary disease, and eosinophilia. This syndrome, which follows the ingestion of L-tryptophan or its contaminants, resembles the panniculitis seen in systemic sclerosis, in which fat lobules are replaced by new collagen formation. Eosinophilic cellulitis, or Wells syndrome, is manifested as nodules, papules, or ulcerative lesions, as well as red plaques in which eosinophils infiltrate the area between collagen fibers.

SCLEROTIC LESIONS

Sclerotic lesions are accompanied by more collagen production, which results in skin with a glossy appearance. Sclerosis may also result from the accumulation of mucopolysaccharides in scleromyxedema (lichen myxedematosus) or from amyloid deposits. Papular mucinosis, lichen myxedematosus (Fig. 407-28), and scleromyxedema are a spectrum of diseases that are caused by deposition of hyaluronic acid. An entity associated with renal failure and gadolinium exposure, nephrogenic fibrosing dermopathy (Chapter 246; Fig. 407-29),

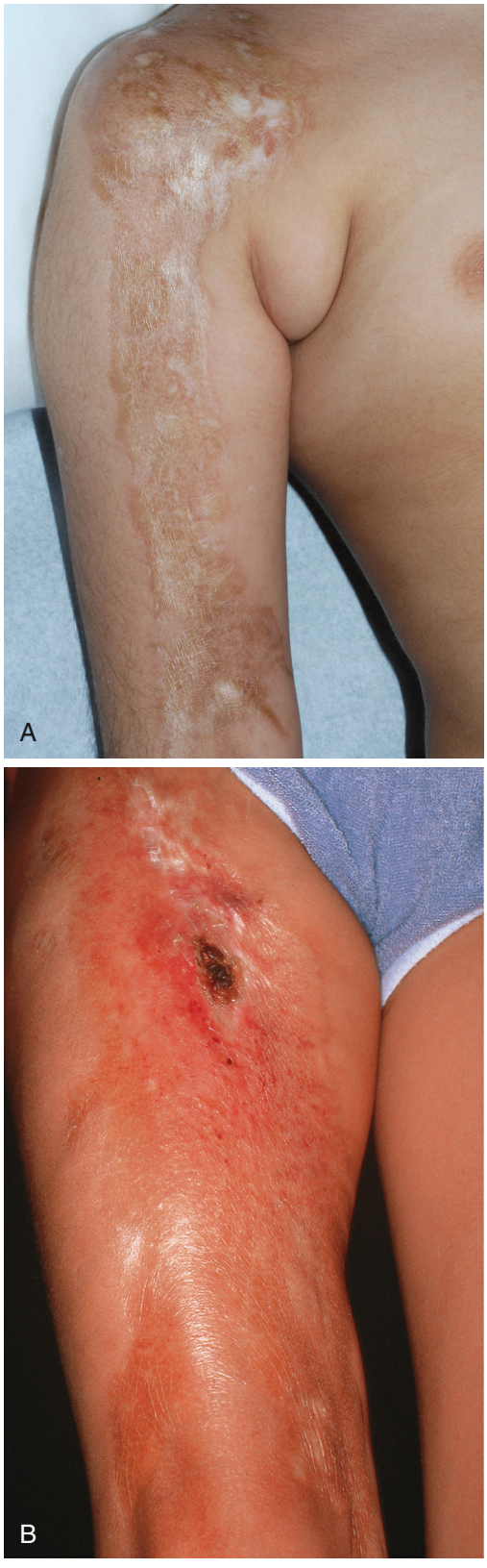

FIGURE 407-30. Linear morphea of an extremity. A, Linear sclerotic band of the arm with both hyperpigmentation and hypopigmentation. The majority of patients with linear morphea have unilateral involvement. **B,** More inflammatory phase with ulceration in addition to induration. (A, Courtesy Julie V. Schaffer, MD.)

is also characterized by acral fibrosis and deposition of hyaluronate in the skin. In scleroderma (Chapter 246), increased collagen deposition may be associated with Raynaud syndrome, calcinosis, and telangiectasia. A localized form of scleroderma, termed *morphea*, may occur down the center of the face (coup de sabre) or as plaques on the extremities (Fig. 407-30), after radiation exposure, or with *Borrelia* spp infection. Lichen sclerosis et atrophicus is a superficial inflammatory morphea characterized by white atrophic patches, especially in the genital region. Widespread systemic sclerosis may also follow bone marrow transplantation in the setting of chronic graft-versus-host disease.

TELANGIECTASIA

Telangiectasia is prominence of skin blood vessels that frequently accompanies atrophic as well as sclerotic processes and is common in photoaged skin and after radiation therapy. Telangiectasia of the mucous membranes is found in Osler-Weber-Rendu syndrome (Chapter 159), and vascular spiders are found both in α_1-antitrypsin deficiency and alcoholic liver disease. The presence of telangiectasia, hyperpigmentation, and hypopigmentation (poikiloderma) in sun-shielded areas of the body should alert the clinician to the diagnosis of early mycosis fungoides.

ULCERS

Ulcers are secondary skin lesions that may arise from trauma, loss of proper blood supply, aging, vasculitis, blister formation, infection, or underlying neoplasia. Ulcers may be shallow erosions (loss of the epidermis) or may be deeper and involve the dermis and underlying subcutaneous structures. Ulcers most commonly appear on the lower extremities, where they result from stasis dermatitis and venous insufficiency, arteriolar insufficiency, diabetic neuropathy, or vasculitis.

Venous stress ulcers are described Chapter 68, diabetic ulcers in Chapter 210, decubitus ulcers in Chapter 24, and genital ulcers in Chapter 264 (see Table 264-3).

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408 INFECTIONS, PIGMENTATION DISORDERS, REGIONAL DERMATOLOGY, AND DISTINCTIVE LESIONS IN BLACK SKIN

JEAN BOLOGNIA AND AMY MCMICHAEL

INFECTIONS, INCLUDING CELLULITIS

Cutaneous infections can be divided into four major categories: bacterial, fungal (Chapter 405), viral, and parasitic (Table 408-1).

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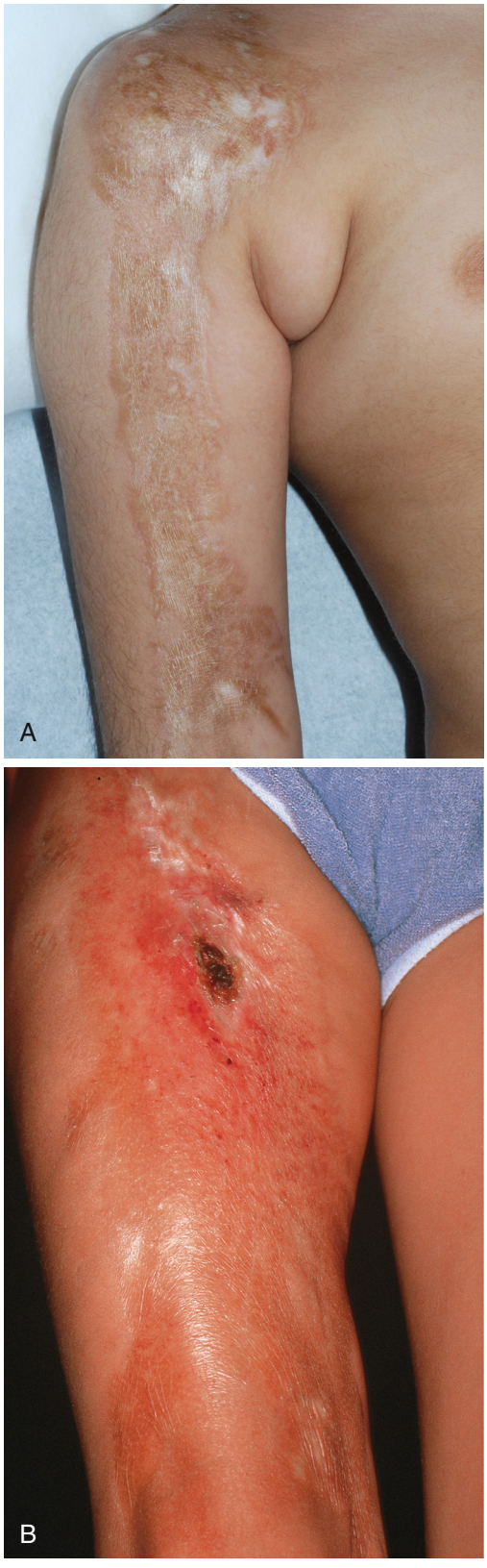

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JEAN BOLOGNIA AND AMY MCMICHAEL

INFECTIONS, INCLUDING CELLULITIS

Cutaneous infections can be divided into four major categories: bacterial, fungal (Chapter 405), viral, and parasitic (Table 408-1).

ABSTRACT

This chapter covers five major areas within dermatology: (1) cutaneous infections, including those that are bacterial, viral, fungal, and parasitic; (2) hypopigmentation; (3) hyperpigmentation; (4) distinctive lesions in Black skin; and (5) regional dermatoses. The disorders of hypopigmentation are divided into diffuse, circumscribed, linear, and guttate, whereas the disorders of hyperpigmentation are divided into diffuse, circumscribed, linear, and reticulated. Examples of disorders that are observed more commonly in Black skin include central centrifugal cicatricial alopecia, acne keloidalis nuchae, and pseudofolliculitis barbae. Distribution patterns are very helpful when generating differential diagnoses for skin diseases, and schematics of distribution patterns of several common disorders are provided, including those of psoriasis, atopic dermatitis, seborrheic dermatitis, acne, and vitiligo.

KEYWORDS

cutaneous infections
soft tissue infections
hypopigmentation
hyperpigmentation
acanthosis nigricans
regional dermatoses

TABLE 408-1 SKIN INFECTIONS

BACTERIAL DISEASES
Impetigo
Ecthyma
Folliculitis
Furuncle/carbuncle
Abscess
Erysipelas
Cellulitis
Necrotizing fasciitis
Ecthyma gangrenosum
Other
Gram-negative cocci: meningococcemia, gonococcemia
Gram-positive bacilli: erythrasma, anaerobic cellulitis
Spirochetes: Lyme disease, syphilis, endemic treponematoses
Mycobacterial infections
Rickettsial infections
VIRAL DISEASES
Herpes simplex virus: oral, genital, digital (whitlow)
Human papillomavirus: common warts, condyloma acuminata
Poxvirus: molluscum contagiosum, monkeypox (MPOX)
Varicella-zoster virus
Viral exanthems (e.g., enteroviruses, rubeola, rubella, parvovirus, Epstein-Barr virus, adenovirus, dengue virus, Zika virus, chikungunya virus, severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), human immunodeficiency virus [seroconversion])
FUNGAL DISEASES
Candidiasis
Tinea (dermatophytoses): pedis, corporis, cruris, manuum, capitis
Pityriasis (tinea) versicolor
Emboli (e.g., *Aspergillus, Mucor* spp)
ECTOPARASITES/PARASITES
Scabies
Lice: scalp, pubic, body
Leishmaniasis
Schistosomiasis, human and animal
Onchocerciasis
Strongyloidiasis
Gnathostomiasis
Amebiasis
Trypanosomiasis
Hookworm infections, human and animal
Filariasis
Acanthamoebiasis

BACTERIAL INFECTIONS

Of the cutaneous bacterial infections, impetigo, folliculitis, furuncles, and cellulitis are most commonly encountered.

IMPETIGO

Impetigo, which is caused by *Staphylococcus aureus* or group A β-hemolytic streptococci, is usually seen as honey-colored crusts (Fig. 408-1); less often, subcorneal (superficial) bullae are present. This infection is most commonly found on the face in children, but it can develop at any site where the cutaneous barrier has been disrupted (e.g., areas of dermatitis, sites of trauma, or arthropod bites). A deeper, but less common, bacterial infection of the skin is ecthyma, which is most frequently streptococcal in origin; it is characterized by thick hemorrhagic crusts overlying erosions or ulcerations, usually 0.5 to 1.5 cm in diameter. These lesions favor the extremities, especially in the setting of lymphedema. Ecthyma should not be confused with ecthyma gangrenosum, which represents an embolic phenomenon most often caused by bacteremia with gram-negative bacilli.

TREATMENT

Although mild cases of impetigo usually respond to topical 2% mupirocin three times daily, 1% retapamulin twice daily, or ozenoxacin 1% twice daily,[A1] more severe impetigo and ecthyma require oral antibiotics that cover *S. aureus* (e.g., dicloxacillin, 250 mg orally [PO] four times daily, or cephalexin, 250 mg PO four times daily). Compared with furuncles and abscesses, impetigo is less often due to methicillin-resistant *S. aureus* (MRSA).

FIGURE 408-1. Impetigo in an infant and marked involvement of the face with honey-colored crusts and superficial erosions. (Courtesy Yale Dermatology Residents' Slide Collection.)

FOLLICULITIS

The initial lesions of folliculitis are follicular pustules that are often surrounded by a rim of erythema (Chapter 406). Culture of pustular contents yields normal flora more often than *S. aureus* or gram-negative bacilli. *Pseudomonas* folliculitis, which favors the trunk, is usually associated with the use of hot tubs or whirlpools because their higher temperatures (vs. swimming pools) make eradication of *Pseudomonas* more difficult (see Fig. 406-27 in Chapter 406).

FURUNCLES

Furuncles, also called *boils*, represent *S. aureus* cutaneous infections that are localized primarily within the dermis. In contrast to folliculitis, the lesions are larger and manifest as tender erythematous nodules (Fig. 408-2). A central follicular structure may be noted, as may a central pustule ("pointing").

TREATMENT

Because a furuncle is an abscess, the preferred treatment is incision and drainage followed by oral antistaphylococcal antibiotics (e.g., dicloxacillin, 250 mg PO four times daily, or cephalexin, 250 mg PO four times daily); if MRSA is likely (e.g., use of health care facilities such as dialysis units, participation in skin-to-skin contact sports, an elevated prevalence of methicillin-resistant isolates in the local community), the antibiotic should be changed to doxycycline (100 mg PO twice daily), minocycline (100 mg PO twice daily), clindamycin (300 to 600 mg PO three times daily), trimethoprim-sulfamethoxazole (160 mg/800 mg PO twice daily), linezolid (600 mg PO twice daily), or omadacycline (450 mg PO on day 1 then 300 mg once daily),[A2] depending on local sensitivity patterns.[1] The duration of therapy is usually 10 to 14 days. Carbuncles, which are larger, more complex, and more extensive versions of furuncles, may be accompanied by systemic symptoms such as fever. In addition to incision and drainage, they may require a more prolonged course of antibiotic therapy.

CELLULITIS

Cellulitis is a fairly common cutaneous infection that occurs most often on the lower extremities. Locally, it manifests as erythema, edema, warmth, and tenderness; systemic findings can include fever, malaise, and leukocytosis. Most cases are bacterial in origin, but some are caused by fungal infections (e.g., *Cryptococcus* spp) or chemical reactions (e.g., extravasated oxacillin or calcium salts). Bacterial cellulitis is most commonly caused by group A β-hemolytic streptococci and *S. aureus*, with the former being associated with the more severe, necrotizing variant. Interestingly, the skin microbiome in the vicinity of the infection tends to be very similar to the contralateral microbiome, but both microbiomes typically differ from those of control patients. In patients who have diabetes or are immunocompromised, cellulitis can be caused by gram-negative bacilli or atypical

FIGURE 408-2. Furuncle with surrounding cellulitis. This common presentation of methicillin-resistant *Staphylococcus aureus* should be treated with incision and drainage as well as the administration of systemic antibiotics. (Courtesy Yale Dermatology Residents' Slide Collection.)

FIGURE 408-3. Bullous and hemorrhagic cellulitis of the shin. (Courtesy University of Southern California Dermatology Residents' Slide Collection.)

mycobacteria. Risk factors include a preceding break in the skin barrier, edema secondary to venous hypertension, lymphedema, and previous bouts of cellulitis.

Although the diagnosis of cellulitis is usually fairly straightforward (Fig. 408-3), it can sometimes be difficult and aided by dermatologic consultation in patients with chronic lower extremity edema, especially in patients who are afebrile and have persistent discoloration.[A3] One complication of chronic lower extremity edema is lipodermatosclerosis (i.e., inflammation followed by fibrosis of subcutaneous fat), which is seen acutely as erythema, warmth, and tenderness and is easily confused with cellulitis. The skin above the medial malleolus is often the initial site of involvement for lipodermatosclerosis, but the inflammation can extend onto the shin and calf. The chronic phase of lipodermatosclerosis is characterized by induration, a permanent brown-red to violet discoloration of the skin, and an "inverted wine bottle" appearance of the distal end of the lower extremity. It is important for the clinician to realize that in patients with chronic lipodermatosclerosis and superimposed cellulitis, the skin will never return to the color of uninvolved skin, even after adequate antibiotic therapy.

Unless there is an associated bacteremia, the diagnosis of cellulitis is primarily clinical. It also can be misdiagnosed when an abscess or a noninfectious condition, such as stasis dermatitis, is the cause.[2] In immunocompromised hosts, a saline injection followed by aspiration and culture can be helpful. Histologically, cellulitis is characterized by an infiltrate of neutrophils within the dermis. Skin biopsy can exclude disorders that may be confused with cellulitis, such as contact dermatitis, erythema migrans, inflammatory carcinoma, toxic erythema of chemotherapy, and Wells syndrome (an idiopathic disorder in which eosinophils infiltrate the dermis).

TREATMENT

Cellulitis resides in the middle of a spectrum of soft tissue infections that includes erysipelas (more superficial and more sharply demarcated; Fig. 408-4) at one end and necrotizing fasciitis (deeper, more necrotic, and undermining) at the other. In healthy adults, erysipelas can be treated with oral penicillin (200,000 units four times daily) or, if methicillin-sensitive *S. aureus* (MSSA) is of concern, oral dicloxacillin (500 mg four times daily) or oral cephalexin (250 to 500 mg four times daily) for a 10-day course.

Treatment for cellulitis should always cover *Streptococcus*[3] and MSSA, with coverage for MRSA recommended for children, athletes, residents of long-term care facilities, military recruits, prisoners, patients with prior MRSA exposure, men who have sex with men, and intravenous drug users. In general, oral antibiotic regimens are as effective as intravenous regimens.[A4] Options include oral cephalexin (250 to 500 mg four times daily for 10 to 14 days),[A5] clindamycin (300 mg three times daily for 10 days), or trimethoprim-sulfamethoxazole (160 mg/800 mg twice daily for 10 days),[A6] depending on the suspected pathogens, the host, and the severity of systemic toxicity. Penicillin (250 mg twice daily) can be effective in preventing recurrent cellulitis. Intravenous vancomycin plus intravenous cefepime (15 mg/kg twice daily and 2 g three times daily, respectively, until clinical response allows transition to oral medications) is reserved for severe infections and immunocompromised patients.

NECROTIZING FASCIITIS

Necrotizing fasciitis is usually caused by multiple organisms, including anaerobic streptococci. Its diagnosis requires a high index of suspicion, and it must be considered when patients have areas of painful violaceous induration or a foul-smelling discharge.[4]

FIGURE 408-4. Erysipelas of the face with well-demarcated erythematous plaques. (Courtesy Yale Dermatology Residents' Slide Collection.)

TREATMENT

Prompt surgical débridement and broad-spectrum systemic antibiotics (e.g., a β-lactam/β-lactamase inhibitor such as piperacillin-tazobactam, 4.5 g IV every 6 hours for a total of 18 g/day [16 g piperacillin/2 g tazobactam] plus vancomycin [15 mg/kg IV twice daily]) is required. For patients with a β-lactam allergy, ciprofloxacin (500 mg PO or 400 mg IV twice daily), metronidazole (500 mg IV three times daily), and vancomycin (15 mg/kg IV twice daily) is an alternative regimen. Unless only a single organism is seen on Gram stain and isolated on culture, broad-spectrum antibiotic coverage should be continued because of the polymicrobial nature of necrotizing fasciitis and the difficulty of culturing anaerobes.

ERYTHRASMA

Although *Clostridium perfringens* can cause anaerobic cellulitis and gas gangrene, the most common cutaneous infection by gram-positive bacilli is erythrasma, which manifests as interdigital toe web maceration with fissures as well as shiny or scaly brown-red patches in the axillae and groin. The latter is often confused with tinea cruris (Chapter 405) and seborrheic dermatitis. A diagnostic finding is the presence of coral (orange-pink) fluorescence on Wood lamp illumination (ultraviolet A). The responsible organism is *Corynebacterium minutissimum*.

TREATMENT

Treatment options include topical and oral erythromycin (e.g., 333 mg three times daily for 7 to 14 days).

TOXIC ERYTHEMAS

Eruptions caused by the release of toxins (e.g., exfoliative toxins ET-A and ET-B, erythrogenic toxin) produced by *S. aureus* and streptococci include

staphylococcal scalded skin syndrome (Chapters 267 and 406), scarlet fever (Chapter 269), and toxic shock syndrome (Chapter 406). Staphylococcal scalded skin syndrome (see Fig. 406-19 in Chapter 406) is characterized by large areas of tender erythema in which superficial desquamation (peeling) develops, often with scaling and crusting in a radial array around the mouth. The areas of erythema are sterile; the conjunctivae, nasopharynx, or a distant site on the skin is the usual site of the primary staphylococcal infection. A clue to the diagnosis of scarlet fever is the presence of a strawberry tongue with prominent red papillae. Management involves treatment of the systemic infection (Chapters 267 and 406).

NEISSERIA INFECTIONS

Both gonococcemia (Chapter 275) and meningococcemia (Chapter 274) can manifest with cutaneous lesions. The former gives rise to a small number of vesicopustules on an erythematous base, generally acral in location (Fig. 408-5); these lesions represent septic emboli and are accompanied by fever, arthritis, and tenosynovitis. The earliest lesions of acute meningococcemia may be subtle (macular areas of erythema), but central hemorrhage (petechiae and purpura) and necrosis (gun-metal gray color) soon follow (Fig. 408-6). When accompanied by disseminated intravascular coagulation, large areas of retiform purpura and severe peripheral ischemia may develop. Cutaneous involvement in chronic meningococcemia is a reflection of lymphocytic or leukocytoclastic vasculitis. Management is systemic treatment (Chapters 274 and 275).

FIGURE 408-5. Disseminated gonococcal infection with an acral pustule on a red-violet base. (Courtesy Yale Dermatology Residents' Slide Collection.)

FIGURE 408-6. Purpuric and necrotic embolic lesions of meningococcemia. (Courtesy Yale Dermatology Residents' Slide Collection.)

PSEUDOMONAS INFECTIONS

Pseudomonas infections of the skin vary from "hot tub" folliculitis (Chapter 406) to soft tissue infections of the external ear. Interdigital toe web infections that begin as simple tinea pedis can be complicated by superimposed *Pseudomonas* infection and result in erythema, swelling, tenderness, and drainage. Depending on its severity, treatment varies from topical antiseptics to oral or intravenous fluoroquinolones (e.g., ciprofloxacin, 500 mg PO twice daily for 7 to 14 days). In immunocompromised hosts, *Pseudomonas* and other gram-negative bacilli can produce cellulitis as well as secondary septic emboli in the skin. The latter begin as purpura or purpuric bullae in which central necrosis then develops. These lesions, which arise as a result of ischemic infarction of the skin, are termed *ecthyma gangrenosum*. Management is treatment of the systemic pseudomonal disease (Chapter 282).

SPIROCHETES

Spirochetal infections have a wide range of skin findings, from erythema migrans secondary to *Borrelia burgdorferi* (Chapter 296), to endemic treponematoses such as yaws and pinta (Chapter 295), to the cutaneous manifestations of the three stages of syphilis (Chapter 295). Syphilitic lesions include a firm, generally nontender ulceration (chancre) in primary syphilis; a generalized papulosquamous eruption plus alopecia, oral ulcers, and condylomata lata in secondary syphilis; and thick plaques and ulcers in tertiary disease (Chapter 405). Management involves treatment of the systemic disease.

MYCOBACTERIA INFECTIONS

Infections with *Mycobacterium tuberculosis* and mycobacteria other than *M. tuberculosis* (atypical mycobacteria) are associated with skin lesions, including verrucous or crusted papules, erythematous nodules, scarring granulomatous plaques, and draining ulcers. In immunocompetent hosts in high-income countries, *Mycobacterium marinum* (Chapter 300) is most commonly associated with skin disease, which usually manifests in a lymphocutaneous (i.e., sporotrichoid) pattern. Lower extremity furunculosis due to atypical mycobacteria can occur following pre-pedicure footbaths, and mesotherapy or injection of tattoo ink contaminated with *Mycobacterium chelonae* can lead to erythematous papules. Treatment of cutaneous mycobacterial disease is the same as for systemic disease (Chapters 299 and 300).

VIRAL INFECTIONS

The most common viral infections of the skin are verrucae (warts; see Fig. 406-3 in Chapter 406), recurrent oral and genital herpes simplex (Chapters 345 and 406), molluscum contagiosum (see Fig. 407-9 in Chapter 407), and exanthems (Chapter 406). Varicella and herpes zoster are seen less frequently (Chapter 346). Patients with severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection (Chapter 336) can develop alopecia, maculopapular eruptions, vesicles, urticarial lesions, or, with severe disease, even retiform purpura with necrosis.[5]

FUNGAL INFECTIONS

A variety of fungal infections involve the skin and nails and are most commonly due to dermatophytes (tinea), *Candida* spp, and *Malassezia* spp (pityriasis versicolor, also referred to as tinea versicolor) (Chapter 405; also see Table 408-1). Although both dermatophyte infections and pityriasis versicolor are associated with scaling, cutaneous candidiasis is characterized by erythema, a more erosive appearance, and satellite pustules. Treatment is described in Chapter 405.

Septic emboli caused by *Candida* or other opportunistic fungi such as *Aspergillus* (Chapter 311) or *Fusarium* often have a clinical appearance similar to that of ecthyma gangrenosum secondary to gram-negative bacilli such as *Pseudomonas*. The responsible organisms can be detected histologically in biopsy specimens or by bedside examination of dermal scrapings; culture confirms the specific organism. Although rare, cutaneous plaques secondary to *Pneumocystis jiroveci* favor the external ear canal. Treatment is for the underlying fungal infection.

ECTOPARASITES AND PARASITES

ECTOPARASITES: SCABIES AND LICE

The most common ectoparasitic cutaneous infestations are (1) scabies from the human variant of the *Sarcoptes* mite; and (2) lice, of which there are three subtypes: head, body, and pubic (Chapter 98). Scabies is characterized by pruritus in association with papules, papulovesicles, and linear burrows as well as signs of scratching, such as excoriations and areas of dermatitis. Sites of predilection include the wrists, ankles, fingers, and toes (including the web spaces), areolae, and genitalia (especially the penis) (Fig. 408-7). The number of mites living within the stratum corneum is limited in immunocompetent hosts; when scraped and examined microscopically,

FIGURE 408-7. Scabies with involvement of the penis. (From Bolognia JL, Jorizzo JL, Schaffer JV, eds. *Dermatology*, 3rd ed. London: Elsevier; 2012.)

linear burrows provide the highest yield of mites and eggs. In elderly and immunosuppressed patients, a form of scabies known as crusted (previously Norwegian) scabies manifests as multiple areas of scaling and crusting that are teeming with mites.

Infestations with scalp lice are seen most commonly in children, who may be symptom free or have marked pruritus. In addition to the lice, multiple egg casings ("nits") are attached to the proximal portions of scalp hairs. In high-income countries, body lice are seen primarily in homeless individuals; patients typically have multiple erythematous papules at the sites of bites as well as signs of scratching. The lice and their eggs are found in the patient's clothing. Pubic lice are sometimes called "crabs" because their bodies are shorter and broader than those of scalp or body lice and thus resemble the shape of a crab. Because of their leg span, these lice reside primarily on pubic hairs and less often on axillary hairs or eyelashes.

TREATMENT

First-line treatments for head lice, pubic lice, and routine scabies are topical 0.5% malathion lotion or gel, 5% permethrin cream, and 5% permethrin cream, respectively; each of these topical medications is applied for 8 to 12 hours on days 1 and 8. Topical ivermectin 0.5% lotion is also approved for the treatment of head lice. Two applications of a neem extract–containing shampoo is another potential option.[A7] For crusted scabies, epidemic outbreaks of scabies (e.g., in nursing homes), or difficult-to-treat head lice, oral ivermectin (200 to 400μg/kg; off-label use) can eradicate the infestation. Treatment of body lice involves discarding egg- and lice-infested clothing; for head lice, potential sources of reinfection, such as hairbrushes, should be discarded. Sexual and household contacts of patients with pubic lice and scabies, respectively, must be treated similarly to the patient who has symptoms.

OTHER PARASITES

Cutaneous lesions are seen in leishmaniasis (Chapter 319), amebiasis (Chapter 323), schistosomiasis (Chapter 326), onchocerciasis (Chapter 327), strongyloidiasis (Chapter 327), and hookworm infections (Chapter 327). Exposure to water infested with the cercariae of animal schistosomes results in multiple erythematous papules, which occur most commonly on the feet and are termed *swimmer's itch*. Dog and cat hookworm infections lead to cutaneous larva migrans, with serpiginous erythematous tracks that correspond to the path of migration of the hookworm larvae in sites where there has been direct contact with infected sand, most commonly the feet. Both of these infections are self-limited because the parasite's life cycle cannot be completed in humans. In immunocompromised hosts, cutaneous plaques can occasionally develop from free-living amebae such as *Acanthamoeba*.

TABLE 408-2 DISORDERS OF PIGMENTATION

HYPOPIGMENTATION
Diffuse (Pigmentary Dilution)
Oculocutaneous albinism Hermansky-Pudlak syndrome Chédiak-Higashi syndrome Generalized (total) vitiligo Inborn errors of metabolism (e.g., phenylketonuria)
Circumscribed
Decrease in pigment Acquired: postinflammatory hypopigmentation (e.g., atopic dermatitis, sarcoidosis, subacute cutaneous lupus erythematosus, mycosis fungoides), pityriasis (tinea) versicolor secondary to *Malassezia* spp infection Congenital: nevus depigmentosus, ash-leaf spots of tuberous sclerosis Absence of pigment Acquired: vitiligo, chemical or drug-induced leukoderma, leukoderma of scleroderma, leukoderma of melanoma* Congenital: piebaldism
Linear
Linear nevoid hypopigmentation, segmental pigmentation disorder
Guttate
Idiopathic guttate hypomelanosis Confetti macules of tuberous sclerosis
HYPERPIGMENTATION
Diffuse
Drug reactions (e.g., cyclophosphamide, busulfan) Addison disease Ectopic adrenocorticotropic hormone production (e.g., small cell lung cancer) Hemochromatosis Systemic sclerosis Primary biliary cirrhosis Hyperthyroidism Vitamin B_{12} or folate deficiency POEMS syndrome (see Table 408-3) Melanosis secondary to metastatic melanoma Argyria (gray hue)
Circumscribed
Postinflammatory hyperpigmentation (e.g., acne vulgaris, arthropod bites, dermatitis, lichen planus) Melasma Pityriasis (tinea) versicolor Mastocytosis Fixed drug reactions Deposits of drugs and their metabolites
Linear
Exposure to psoralen-containing plants (e.g., limes) plus ultraviolet A light Drug reactions (e.g., bleomycin) Linear nevoid hyperpigmentation Genodermatoses (e.g., incontinentia pigmenti)
Reticulated
Erythema ab igne Genodermatoses Confluent and reticulated papillomatosis

*Often referred to as *vitiligo* or *vitiligo-like* in the oncologic literature.
POEMS = *p*olyneuropathy, *o*rganomegaly, *e*ndocrinopathy, *m*onoclonal protein, *s*kin changes.

DISORDERS OF HYPOPIGMENTATION AND HYPERPIGMENTATION

Disorders of pigmentation can be divided into four major categories: diffuse, linear, circumscribed, and either reticulated (in the case of hyperpigmentation) or guttate (in the case of hypopigmentation) (Table 408-2).

HYPOPIGMENTATION

ALBINISM

For diffuse hypopigmentation, the primary disorder is oculocutaneous albinism, an autosomal recessive disorder in which there is a pigmentary dilution of melanin-containing structures (i.e., the eyes, hair, and skin). The phenotype varies from total absence of melanin pigment to a subtle decrease whose

recognition requires comparison with first-degree relatives; the density of melanocytes in skin is normal, but their ability to produce pigment is absent or decreased. Ninety percent of patients with oculocutaneous albinism have mutations in the genes that encode either tyrosinase (type I) or P protein (type II). Complications of oculocutaneous albinism include decreased visual acuity, nystagmus, photophobia, and an increase in cutaneous carcinomas, especially squamous cell carcinoma. These signs and symptoms are most severe in those who produce the least pigment and have the greatest amount of cumulative sun exposure. The differential diagnosis includes total vitiligo (absence of melanocytes histologically) and a few inborn errors of metabolism (e.g., phenylketonuria). Treatment consists of longitudinal ophthalmologic care and minimizing sun exposure.

LINEAR HYPOPIGMENTATION

Disorders of linear hypopigmentation consist primarily of nevoid conditions caused by somatic mosaicism (e.g., linear nevoid hypopigmentation, segmental pigmentation disorder), in which streaks of hypomelanosis follow the lines of Blaschko or patients have a blocklike configuration of hypopigmented patches. A minority of patients have associated central nervous system, musculoskeletal, or ocular abnormalities.

CIRCUMSCRIBED (PATCHY) HYPOPIGMENTATION

Vitiligo

Vitiligo (Fig. 408-8) is usually slowly progressive and occurs principally in periorificial areas (around the eyes, nose, lips, genitalia) and on the hands, feet, flexor surface of the wrists, ankles, elbows, and knees and in major body folds. Vitiligo, which is caused by a loss of melanocytes within the skin, is also associated with autoimmune endocrinopathies and alopecia areata.

The differential diagnosis is primarily chemical leukoderma secondary to compounds that are cytotoxic to melanocytes (e.g., catechols, phenols), drug-induced leukoderma (e.g., caused by imatinib), the leukoderma of melanoma (a good prognostic sign if seen in association with immunotherapy but an indication to exclude metastases if occurs spontaneously), and the leukoderma of scleroderma with retention of perifollicular pigmentation. In patients with vitiligo, T cells that recognize antigens on the surface of melanocytes (and melanoma cells) are found within the skin and in peripheral blood.

TREATMENT

Treatment of vitiligo includes topical corticosteroids, topical immunomodulators (e.g., ruxolitinib,[A8] tacrolimus), and photo-therapy.[A9] Combinations of follicular and epidermal stem cell suspensions are an experimental approach for difficult-to-treat disease.[A10,A11]

GUTTATE HYPOPIGMENTATION

Idiopathic guttate hypomelanosis, in which there are well-demarcated hypopigmented macules usually measuring 2 to 4 mm in diameter, is the most common cause of guttate ("raindrop") leukoderma (Fig. 408-9). The favored sites for this common age-related disorder, which may be related to chronic sun exposure, are the shins and the extensor surface of the forearms.

FIGURE 408-8. Striking leukoderma of the hand in a patient with vitiligo. In well-developed lesions, the skin is white, not tan, in color due to complete loss of melanin.

OTHER ACQUIRED CAUSES

Circumscribed hypomelanosis is seen in patients with pityriasis (tinea) versicolor (see Fig. 405-29 in Chapter 405) and postinflammatory hypopigmentation. Although postinflammatory hypopigmentation is most often associated with atopic dermatitis, it also can occur with sarcoidosis (Chapter 83), cutaneous lupus erythematosus (Chapter 245), and mycosis fungoides (Chapter 171).

CONGENITAL CAUSES

Congenital circumscribed areas of hypomelanosis include *nevus depigmentosus,* a common tan "birthmark" seen in 1 in 50 infants in whom there is a partial decrease in pigment; *piebaldism,* an unusual autosomal dominant disorder with areas of complete absence of pigment caused by mutations in the *KIT* gene; *nevus anemicus,* a localized area of vasoconstriction; and the *ash-leaf spots* of tuberous sclerosis (Chapter 385), with a partial decrease in pigment.

HYPERPIGMENTATION

DIFFUSE HYPERPIGMENTATION

Diffuse hyperpigmentation is most commonly due to drugs (e.g., cyclophosphamide, zidovudine) and endocrinopathies associated with increased circulating levels of adrenocorticotropic hormone (ACTH) (e.g., Addison disease [Chapter 208], ectopic ACTH production by tumors such as small cell lung carcinoma [Chapter 177]). ACTH, as well as melanocyte-stimulating hormone, can bind and activate the melanocortin-1 receptors on melanocytes, thereby leading to increased melanin production. Additional causes include hemochromatosis (Chapter 196), systemic sclerosis (Chapter 246), primary biliary cirrhosis (Chapter 141), POEMS syndrome (*p*olyneuropathy, *o*rganomegaly, *e*ndocrinopathy, *m*onoclonal protein, *s*kin changes) (Table 408-3), and hyperthyroidism (Chapter 207). Systemic exposure to silver (argyria; Chapter 20) can lead to a slate-gray color.

FIGURE 408-9. Idiopathic guttate hypomelanosis with small, well-demarcated hypopigmented macules on the shin.

TABLE 408-3 CUTANEOUS FINDINGS IN POEMS SYNDROME

Diffuse hyperpigmentation
Vascular tumors, including glomeruloid hemangiomas
Peripheral edema
Induration (sclerodermoid)
Hypertrichosis
Hyperhidrosis
Acrocyanosis
Clubbing and/or leukonychia
Acquired facial lipoatrophy
Livedo reticularis

POEMS = *p*olyneuropathy, *o*rganomegaly, *e*ndocrinopathy, *m*onoclonal (M) protein, *s*kin changes.

LINEAR AND RETICULATED HYPERPIGMENTATION

Linear streaks of hyperpigmentation can be due to nevoid conditions that reflect cutaneous mosaicism, as in linear hypopigmentation (see earlier) or several genodermatoses (e.g., incontinentia pigmenti, which is an X-linked dominant disorder caused by mutations in the gene *NEMO*), or they can be due to exposure to either plant-derived psoralens (e.g., from limes) plus ultraviolet A irradiation or systemic bleomycin (flagellate pigmentation). Reticulated hypermelanosis is also seen in several genodermatoses (e.g., dyskeratosis congenita) and after chronic exposure to heat (erythema ab igne). The latter corresponds to the cutaneous venous plexus and is seen most commonly in the lumbosacral region where heating pads have been applied or on the anterior thighs from laptop computers.

CIRCUMSCRIBED (PATCHY) HYPERPIGMENTATION

The most common causes of circumscribed hypermelanosis are pityriasis (tinea) versicolor (which can present as both hypopigmentation and hyperpigmentation, hence its name), postinflammatory hyperpigmentation, and melasma. Postinflammatory hyperpigmentation (Fig. 408-10) is observed more frequently in darkly pigmented individuals and often follows acne vulgaris, arthropod bites, chronic dermatitis, and lichen planus.[6] Additional causes of circumscribed darkening of the skin are cutaneous mastocytosis (urticaria pigmentosa; Chapter 235), deposits of drugs such as antimalarials and minocycline (blue-gray discoloration), and medications that produce fixed drug reactions, most frequently trimethoprim-sulfamethoxazole and nonsteroidal anti-inflammatory drugs. In melasma (Fig. 408-11), symmetrical hyperpigmented patches are seen on the lateral aspect of the forehead, upper part of the cheek, and mandibular area. At least 90% of patients with melasma are women. The lesions are exacerbated by ultraviolet light and estrogen (oral contraceptives, pregnancy).

TREATMENT

Melasma is treated with daily broad-spectrum sunscreens plus lightening agents such as hydroquinone (4% cream) and retinoic acid (0.025 to 0.1% cream) for 3 to 4 months, often in combination with mild topical corticosteroids to reduce irritation[7]; if irritation develops, the creams are discontinued temporarily and then restarted at a reduced frequency.

DISTINCTIVE LESIONS IN BLACK SKIN

Although some diseases are more common in patients of African ancestry (e.g., tinea capitis, pseudofolliculitis barbae, dissecting cellulitis), others are simply more noticeable (e.g., vitiligo and postinflammatory hypopigmentation) (Table 408-4). The explanation for the increased incidence is speculative in most instances, with the exception of curled hairs leading to pseudofolliculitis barbae. Individuals with polymorphisms in the gene that encodes KRT75 are more likely to develop this condition. Tightly curled hairs, when shaved, are usually cut at an oblique angle, which results in a sharp tip at the distal end of the hair shaft that allows penetration of the skin adjacent to the hair follicle and subsequent inflammation. The patient can apply topical anti-inflammatory agents, avoid shaving, or undergo laser hair removal. Some cutaneous disorders are seen less commonly in Black skin (e.g., acne rosacea and scabies).

Keloids

Another entity seen more commonly in individuals of African descent is keloids (Fig. 408-12). Keloids generally appear at sites of trauma (e.g., ear piercing) but may occasionally develop spontaneously, especially on the trunk. In the former situation, they are thought to represent an exaggerated response to wound healing, with increased formation of collagen not only at the site of the trauma (as in hypertrophic scars) but also in adjacent, previously uninvolved skin.

FIGURE 408-10. Postinflammatory hyperpigmentation secondary to arthropod bites. (Courtesy Yale Dermatology Residents' Slide Collection.)

FIGURE 408-11. Hyperpigmented patches on the cheek in a patient with melasma.

TABLE 408-4 DISORDERS SEEN MORE COMMONLY IN PATIENTS OF AFRICAN ANCESTRY

HEAD AND NECK
Follicultis decalvans/dissecting cellulitis
Tinea capitis due to *Trichophyton tonsurans*
Traction alopecia
Central centrifugal cicatricial alopecia*
Proximal trichorrhexis nodosa
Acne keloidalis nuchae
Pseudofolliculitis barbae
Acne cosmetica
Dermatosis papulosa nigra
Inherited patterned lentiginosis
Melasma
Discoid lupus erythematosus
PALMAR
Keratosis punctata of the palmar creases
LOWER EXTREMITIES
Ulcers secondary to sickle cell anemia
GENERALIZED
Post-inflammatory hyperpigmentation and hypopigmentation
Keloids
Cutaneous sarcoidosis, hypopigmented mycosis fungoides, lichen planus pigmentosus
Papular eczema and follicular-based inflammation

*Also previously termed follicular degeneration syndrome or hot comb alopecia.

FIGURE 408-12. Acne keloidalis in an African American man. (Courtesy Kalman Watsky, MD.)

TREATMENT

Treatment options include intralesional corticosteroids, intralesional 5-fluorouracil,[A12] intralesional interferon, pulsed dye laser, cryotherapy, or excision followed by low-dose radiation therapy.[8] Recently, verteporfin was found to block transcription of *En1* (engrailed-1) in murine dermal fibroblasts and to prevent wound-induced collagen deposition and scarring.[9] However, verteporfin may not be effective in keloids, which exhibit cellular proliferation not just enhanced production of extracellular matrix.

REGIONAL DERMATOSES

Some common dermatoses have a predilection for particular anatomic sites (Fig. 408-13 and Table 408-5). These locations can help narrow the differential and guide further diagnostic testing and therapy in many patients. The most common association is insulin resistance.

One regional dermatosis is acanthosis nigricans (Fig. 408-14).[10] Because of its potential systemic implications, careful medical evaluation is required (Table 408-6).

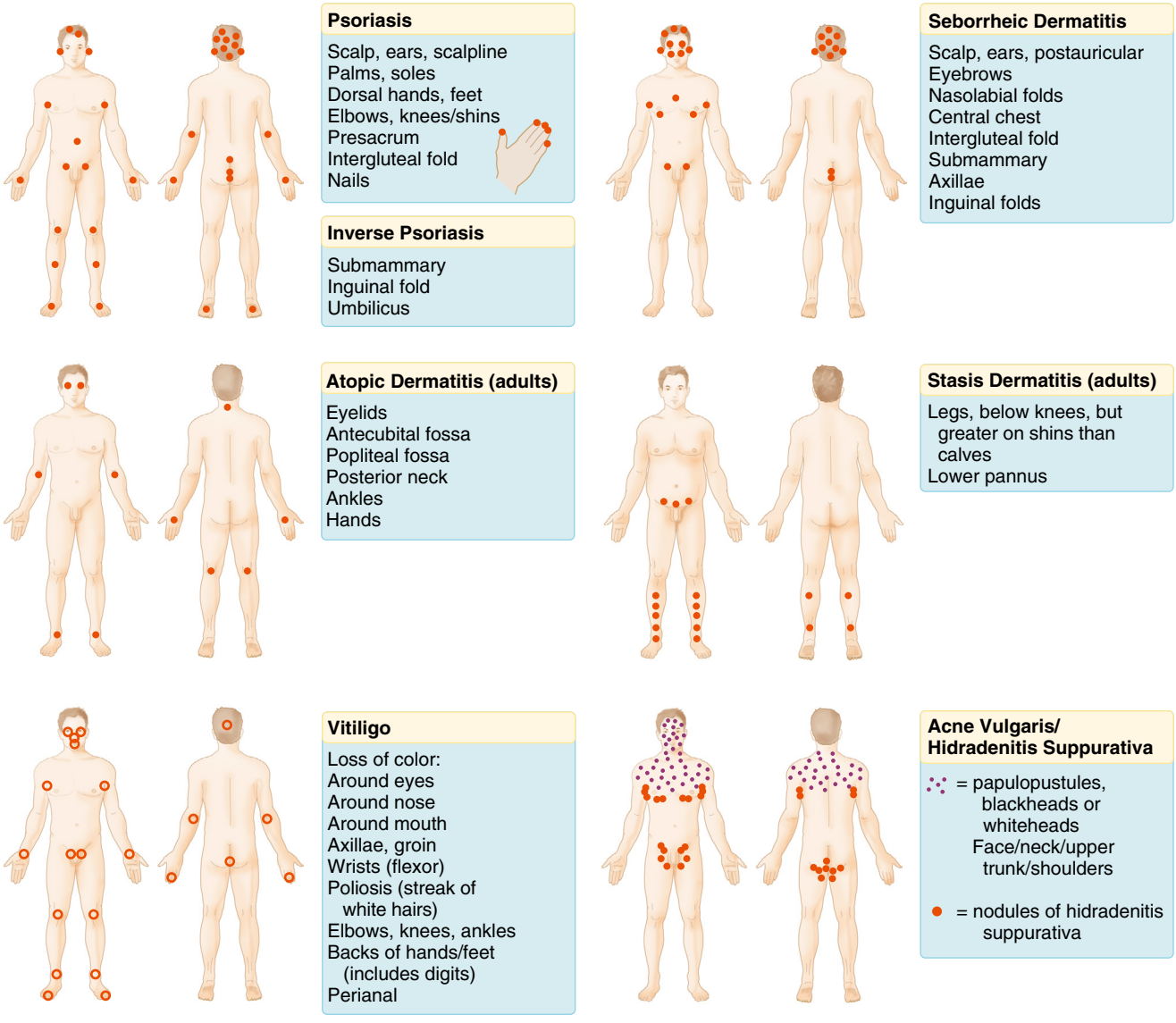

FIGURE 408-13. Regional involvement of specific skin diseases.

TABLE 408-5 REGIONAL DERMATOLOGY

REGION OF SKIN	TYPE OF SKIN LESION	DISEASE PROCESS
Scalp	Papulosquamous and eczematous	Seborrheic dermatitis, psoriasis, tinea capitis, eczema (atopic, contact [especially hairline])
	Pustular	Folliculitis, kerion
	Papulonodular	Melanocytic nevi, seborrheic keratoses, pilar cysts, verrucae, cherry angiomas, actinic keratoses (bald scalp)
Face	Pustular	Acne, rosacea, folliculitis (beard), tinea, demodicosis
	Papulosquamous and eczematous	Seborrheic dermatitis, psoriasis (hairline), contact dermatitis (e.g., cosmetics), atopic dermatitis, pityriasis alba, impetigo, systemic lupus erythematosus, photodermatitis
	Vesicular	Herpes simplex, herpes zoster, bullous impetigo
	Papulonodular	Melanocytic nevi, seborrheic keratoses, actinic keratoses, sebaceous hyperplasia, basal cell carcinomas, squamous cell carcinomas, melanomas
	Atrophic and telangiectatic	Discoid lupus erythematosus
Trunk	Papulosquamous and eczematous	Psoriasis, atopic dermatitis, contact dermatitis, tinea versicolor, pityriasis rosea, scabies, secondary syphilis, subacute cutaneous lupus (upper trunk)
	Vesiculobullous	Herpes zoster, bullous pemphigoid, pemphigus, erythema multiforme, Stevens-Johnson syndrome
	Maculopapular	Morbilliform drug reactions, viral exanthems
	Papulonodular	Melanocytic nevi, seborrheic keratoses, cherry angiomas, lipomas, epidermoid inclusion cysts, basal and squamous cell carcinomas, keloids, neurofibromas, melanoma
	Pustular	Acne, folliculitis
	Urticarial	Hives, drug reactions, early herpes zoster
Arms and forearms	Eczematous and papulosquamous	Contact dermatitis (e.g., plants), atopic dermatitis, psoriasis, lichen planus, photodermatitis (drugs, contactants, dermatomyositis, subacute cutaneous lupus)
	Papulonodular	Melanocytic nevi, verrucae, seborrheic keratoses, actinic keratoses, squamous cell carcinomas, polymorphic light eruption, rheumatoid nodules (elbows), xanthomas (elbows)
	Purpuric	Actinic (solar) purpura
	Annular	Granuloma annulare, subacute cutaneous lupus
Legs	Eczematous and papulosquamous	Stasis dermatitis, eczema craquelé (xerotic eczema), contact dermatitis, atopic dermatitis, psoriasis, lichen planus
	Papulonodular	Melanocytic nevi, dermatofibromas, erythema nodosum, melanoma, xanthomas (knees, Achilles tendon), Kaposi sarcoma
	Annular	Tinea, granuloma annulare
	Purpuric	Capillaritis, vasculitis
	Ulcerative	Stasis ulcers, arterial insufficiency, trauma, pyoderma gangrenosum, livedoid vasculopathy, squamous cell carcinoma, diffuse dermal angiomatosis
Genitalia and groin	Eczematous and papulosquamous	Seborrheic dermatitis, tinea, candidiasis, psoriasis, contact dermatitis, lichen simplex chronicus, scabies, reactive arthritis (Reiter syndrome), erythrasma, lichen planus
	Vesiculobullous	Herpes simplex
	Ulcerative	Herpes simplex, trauma, syphilis, chancroid, Behçet disease, squamous cell carcinoma
	Papulonodular	Angiokeratomas, epidermoid inclusion cysts, molluscum contagiosum, condyloma acuminata, hidradenitis suppurativa, squamous cell carcinoma
	Pustular	Folliculitis, candidiasis, hidradenitis suppurativa
Hands	Eczematous and papulosquamous	Irritant and allergic contact dermatitis, atopic dermatitis, tinea, scabies, secondary syphilis
	Vesiculobullous, pustular	Dyshidrotic eczema, psoriasis (palmar), hand-foot-and-mouth disease (palmar), herpetic whitlow, blistering dactylitis, porphyria cutanea tarda (dorsal), erythema multiforme, Stevens-Johnson syndrome, *Mycoplasma pneumoniae*/respiratory infection-induced rash and mucositis, epidermolysis bullosa acquisita
	Papulonodular	Warts, actinic keratoses (dorsal), digital mucous cysts (dorsal fingers), squamous cell carcinomas (dorsal), granuloma annulare, pyogenic granuloma
	Depigmentation	Vitiligo, chemical leukoderma
	Proximal nailfold telangiectases	Systemic sclerosis, dermatomyositis, systemic lupus erythematosus, Osler-Weber-Rendu disease
Feet	Eczematous and papulosquamous	Tinea, psoriasis, contact dermatitis, atopic dermatitis, syphilis (plantar)
	Vesiculobullous	Tinea, arthropod bites, epidermolysis bullosa (inherited and acquired), erythema multiforme, hand-foot-and mouth disease (plantar)
	Papules	Verrucae (plantar), corns, perniosis
	Ulcerative	Neuropathic ulcers (plantar)

FIGURE 408-14. Acanthosis nigricans of the axilla. Note the velvet-like appearance of the skin. (Courtesy Yale Dermatology Residents' Slide Collection.)

TABLE 408-6 CLUES TO UNDERLYING SYSTEMIC CONDITIONS ASSOCIATED WITH ACANTHOSIS NIGRICANS

Polycystic ovary syndrome	Women with acne, hirsutism, and/or menstrual irregularities
Malignancy	Sudden onset, weight loss, inflamed seborrheic keratoses, tripe palms
Endocrinopathy	Insulin resistance, type 2 diabetes, Cushing syndrome (striae, hypertension, central obesity, buffalo hump), hypothyroidism
Drug-induced	Especially niacin, human growth hormone, oral contraceptive agents, corticosteroids, protease inhibitors

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409 DISEASES OF HAIR AND NAILS

ANTONELLA TOSTI

HAIR DISORDERS

Normal Hair

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The hair follicle is formed by an upper permanent portion and a lower dynamic transient portion that migrates during the hair cycle. The transient portion includes the hair bulb, which is surrounded by the dermal papilla and contains the hair matrix that produces the hair shaft and its sheaths. The anatomic division between the permanent and the transient portion is just below the bulge region, which corresponds to the insertion of the erector pili muscle. The bulge region contains the epithelial stem cells that regenerate the follicle in each hair growth cycle; its damage results in stem cell destruction and cicatricial alopecia.

Hair Cycle

Hair follicles have a cyclic activity, characterized by alternating periods of hair shaft production and periods of resting (anagen, catagen, telogen). During the anagen phase, the follicles produce the hair shaft. Duration of anagen, which in the scalp ranges from 2 to 7 years, determines hair shaft length. Maximal length and growth rate of terminal hair varies in the different body regions. Scalp hair grows approximately 0.4 mm/day and may reach a length of more than 1 m. Maximal hair length decreases with age. During telogen, hair production is absent, even if the shaft remains within the follicle to be shed only when, after 3 months, the follicle reenters the anagen phase.

The hair cycle of adjacent scalp follicles is not synchronized. In normal conditions, approximately 85 to 90% of follicles are in anagen and 10 to 15% in telogen.

Hair Loss and Alopecias

Hair loss distresses most patients, independently from its severity and pattern. In some cases, the decrement in quality of life attributable to hair loss is comparable with that caused by major chronic diseases. Because some causes of hair loss are readily treatable, accurate diagnosis is critical.

The first diagnostic step is to assess family history, drug intake, systemic illness, and severity and duration of hair loss (Table 409-1). The second step is to establish whether the hair density is normal or decreased. The third step is to evaluate whether the rate of hair shedding is normal or increased. Acute and severe hair loss is typical of diseases that interrupt the mitotic activity of anagen follicles (drugs, alopecia areata). A normal hair density suggests telogen effluvium, which may be acute or chronic. A reduced hair density may involve the whole scalp (diffuse alopecia), may manifest with bald patches (patchy alopecia), or may be limited to specific scalp regions (patterned alopecia, marginal alopecia). In patchy alopecias, the scalp may show patches of alopecia that are completely devoid of hairs (alopecia areata, cicatricial alopecia) or have short broken hairs (trichotillomania, hair shaft disorders).[1] Dermatoscopy is a rapid, noninvasive technique that greatly improves the clinical diagnosis of alopecias and hair shaft disorders in adults and children (Table 409-2).

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Telogen effluvium (e.g., after illness or stress)
Anagen effluvium (e.g., after chemotherapy or radiation therapy)
Medications (see Table 409-3)
Nutritional deficiency
Hair treatments
Androgenetic alopecia (in women)
Hormonal changes (e.g., menopause, discontinuation of oral contraceptives, hypothyroidism)
PATCHY ALOPECIA
Alopecia areata (probably autoimmune)
Cicatricial (scarring) alopecia (e.g., lichen planopilaris, discoid lupus erythematosus, folliculitis decalvans, central centrifugal cicatricial alopecia)
Traction alopecia (e.g., excessive hair straightening or braiding)
Trichotillomania (hair pulling)
Scalp infection (e.g., ringworm)
MARGINAL ALOPECIA
Frontal fibrosing alopecia
Traction alopecia
Alopecia areata (ophiasis variant)

TABLE 409-2 DERMATOSCOPIC SIGNS IN HAIR AND SCALP DISORDERS

Alopecia areata	Yellow dots, exclamation mark hairs, broken hairs
Androgenetic alopecia	>20% variability in the hair diameter
Lichen planopilaris/frontal fibrosing alopecia	Peripilar casts; loss of follicular openings
Trichotillomania	Broken hairs, question mark hairs
Tinea capitis	Comma hairs, corkscrew hairs
Discoid lupus erythematosus	Red dots, follicular plugs
Folliculitis decalvans	Hair tufts
Scalp psoriasis	Coiled capillaries
Seborrheic dermatitis	Arborizing vessels

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ABSTRACT

This chapter reviews the most important diseases of hair and nails encountered in medical practice. The reader will be able to understand different types of non-scarring and scarring alopecias. Differential diagnosis and updated diagnostic methods are discussed in detail together with optimal treatment approaches. Hair manifestation of systemic disorders including drug-induced hair loss are also discussed. The part on nails describes traumatic, inflammatory, and infective nail disorders with tips for correct diagnosis and optimal treatment. Nail manifestation of systemic disorders are also discussed.

KEYWORDS

alopecia areata
androgenetic alopecia
telogen effluvium
anagen effluvium
frontal fibrosing alopecia
trichotillomania
scarring alopecias
hirsutism
clubbing
Beau lines
paronychia
onychomycosis

TELOGEN EFFLUVIUM

ACUTE TELOGEN EFFLUVIUM

Acute telogen effluvium results from noxious events that precipitate the entry of a large number of follicles into their resting phase (telogen). Possible causes include systemic diseases, drugs (Table 409-3), fever, stress, weight loss, delivery, iron deficiency, and inflammatory scalp disorders. Severe telogen effluvium also is common 2 to 3 months after infection with severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) and may be associated with scalp paresthesia or pain (trichodynia).[2,3] For drugs, the severity of hair loss depends on the drug, its dosage, and the patient's susceptibility.

Hair loss starts approximately 3 months after the causative event, a time frame that corresponds with the duration of the telogen phase. Telogen hairs are retained within the follicle during telogen, to be shed when the follicle produces a new anagen hair. Hair loss is severe when 100 to 200 hairs are shed daily. The patient usually remembers precisely when the increased shedding began. Acute telogen effluvium does not usually produce visible alopecia because approximately 50% of hairs need to be lost before reduction of hair density is evident.

CHRONIC TELOGEN EFFLUVIUM

Chronic telogen effluvium mostly affects middle-aged women and frequently remains unexplained. The daily shedding is mild (<100 hairs daily), but patients are distressed and complain of progressive temporal thinning as well as decreased hair mass and volume. Scalp pain (trichodynia) is frequently reported. Patients who have a high hair density may bring in envelopes of shed hairs to prove the amount of hair loss. There is no effective treatment. Chronic telogen effluvium has a chronic course with periodic exacerbations.

TREATMENT AND PROGNOSIS

Acute telogen effluvium subsides spontaneously in a few months after removal of the cause. It may, however, unmask or aggravate androgenetic alopecia.

DIFFUSE ALOPECIA

ANAGEN EFFLUVIUM

Acute hair shedding leading to diffuse alopecia is a typical side effect of cancer chemotherapy and scalp radiation. Hair loss is acute and severe and may produce loss of most of the scalp hair, eyebrows, and eyelashes; other body hairs are less commonly involved. Hair shedding usually starts 4 to 6 weeks after drug intake with up to 1000 hairs shed daily. Regrowth is usually fast after discontinuation of therapy, but hair shape and color may be different. Permanent alopecia may occur with high-dose radiation and certain drug regimens, such as busulfan and docetaxel.[4]

Scalp hypothermia prevents or reduces hair loss during chemotherapy,[A1] and can prevent permanent alopecia after docetaxel regimens[5] Topical minoxidil accelerates hair regrowth but does not prevent hair loss.

PATTERNED ALOPECIA (ANDROGENETIC ALOPECIA)

Androgenetic alopecia, which is the most common form of hair loss, affects up to 80% of men and 50% of women in the course of their life. Androgenetic alopecia is caused by a progressive reduction in the diameter, length, and pigmentation of the hair. Hair thinning is not diffuse, but rather is limited to the frontal, temporal, and vertex areas, where hair follicles are sensitive to the effects of the testosterone metabolite dehydrotestosterone (DHT). This sensitivity to DHT, which requires the 5α-reductase enzymes, is genetically determined. In men, androgenetic alopecia involves the frontotemporal areas and the vertex, following a pattern that corresponds to the Hamilton-Norwood scale. In women, androgenetic alopecia produces diffuse thinning of the crown region with maintenance of the frontal hairline (Ludwig pattern), a pattern that can easily be appreciated by making a central parting and comparing hair density at the top with hair density at the occipital region. In premenopausal women, androgenetic alopecia can be a sign of hyperandrogenism, together with hirsutism and acne. In most women, however, it occurs in the absence of biochemical and clinical evidence of androgen excess and may be due to excessive follicular sensitivity to androgens. Data also show that patients with androgenetic alopecia may be at increased risk for dying from diabetes and heart disease.

TABLE 409-3 DRUGS REPORTED TO INDUCE HAIR LOSS

ACE inhibitors (captopril, enalapril, moexipril, ramipril)
Allopurinol
Amiodarone
Amphetamines*,†
Analgesics, anti-inflammatories (ibuprofen, indomethacin, naproxen)
Androgens*,†
Anticoagulants (coumarin, dextran, heparin/heparinoids apixaban, dabigatran, rivaroxaban)*,†
Antiepileptics (carbamazepine, hydantoins, lamotrigine, troxidone, valproic acid, vigabatrin)*,†
Antipsychotics (flupenthixol decanoate, fluphenazine decanoate)
Antithyroid drugs (carbimazole, iodine, thiouracil)*
Appetite suppressants
Aromatase inhibitors (fadrozole, formestane [4-OHA], vorozole)*,†
Benzimidazoles (albendazole, mebendazole)
β-Blockers (levobunolol, metoprolol, nadolol, propranolol, timolol)*
Bromocriptine
Buspirone
Busulfan§
Butyrophenones
Cantharidin
Cholestyramine
Chloramphenicol
Cidofovir
Cimetidine
Clonazepam
Clotrimazole
Colchicine
Contraceptives (oral)
Danazol
Diclofenac
Dixyrazine
Diazoxide
Docetaxel§
Ethambutol
Ethionamide
Fibrates (clofibrate, fenofibrate)
Gentamicin
Gefitinib‖
Glatiramer acetate
Glibenclamide
Gold salts
Granulocyte colony-stimulating factor
Haloperidol
Immunoglobulins
Indanediones
Indinavir*
Interferons*,†
Isonicotinic acid hydrazide‖
Leflunomide*
Levodopa
Lithium*
Maprotiline
Mesalazine
Methyldopa
Methysergide
Metyrapone
Minoxidil¶
Nicotinic acid
Nitrofurantoin
Octreotide
Olanzapine
Paclitaxel§
Pentosan polysulfate
Phenindione
Piroxicam
Potassium thiocyanate
Pyridostigmine
Radiation (<700 Gy)*,‖
Retinol (vitamin A)*
Retinoids (acitretin, etretinate, isotretinoin)*,†
Risperidone
Salicylates
Serotonin reuptake inhibitors (fluoxetine, fluvoxamine, paroxetine, sertraline)*
Sonidegib*,†
Sorafenib
Spironolactone
Strontium ranelate*,†
Sulfasalazine
Tamoxifen
Terbinafine
Terfenadine
Thiamphenicol
Thyroxine
Tocopherol (vitamin E)
Trazodone
Triazoles (fluconazole, itraconazole)
Tricyclic antidepressants (amitriptyline, desipramine, doxepin, imipramine, maprotiline)
Trimethadione
Triparanol
Vasopressin
Vismodegib*,†

*Established by multiple reports or proved by rechallenge.
†Hair loss usually severe.
‡May produce androgenetic alopecia.
§May produce permanent alopecia.
‖May produce anagen effluvium.
¶May produce telogen effluvium 3 months after discontinuation.
ACE = angiotensin-converting enzyme inhibitor.

TREATMENT

Androgenetic alopecia is a progressive disease that tends to worsen with time. Medical treatments include 2% topical minoxidil in women and 5% topical minoxidil and/or oral finasteride, 1 mg/day, in men.[A2] Finasteride topical spray is as effective as oral finasteride with less impact on dihydrotestosterone levels.[A3] Oral dutasteride, 0.5 mg, approved in some countries, is more effective than finasteride with a similar safety profile.[A4] Clinical improvement is mostly due to thickening of the preexisting hair. Some men may report a post-finasteride syndrome characterized by persistent sexual dysfunction and depression occurring after treatment with 5α-reductase inhibitors. Low dose oral minoxidil (0.25 to 2.5 mg/day) is effective and usually well tolerated.[6,7]

Treatments for androgenetic alopecia should be continued for at least 6 months before assessing efficacy, and regular drug use is mandatory for

maintaining results. Interruption of minoxidil produces an acute telogen effluvium, which becomes evident 3 to 4 months after interruption and cannot be prevented by concomitant finasteride treatment. Interruption of finasteride is followed by gradual hair loss, with return to the pretreatment status after 1 year. Hair transplantation is a good option for men with severe androgenetic alopecia, and treatment with finasteride, 1 mg/day, improves the long-term results of surgery. Hair transplantation in women is more complicated because the hair thinning is often diffuse in the parietal and occipital regions, so there is not a good hair donor area.

PATCHY ALOPECIA

ALOPECIA AREATA

Alopecia areata is a common form of nonscarring, usually patchy hair loss affecting up to 2% of the population. The etiology is unknown, but evidence is consistent with an autoimmune disease to which both a genetic predisposition and environmental factors contribute. In genetically predisposed individuals, various triggering factors cause a predominantly CD8-driven, T_H1-type T-cell reaction against the hair follicles, and the Janus kinase and signal transducer and activator of transcription (JAK/STAT) pathway has a main role in sustaining the autoimmune reaction, thereby resulting in acute hair loss.

Alopecia areata can start at any age, but severe forms often start during childhood and are more frequent in males.[8] Clinical examination reveals one or multiple well-circumscribed smooth patches of nonscarring absence of hair that enlarge in a centrifugal way (Fig. 409-1). The margins of the patches often show 3-mm-long broken hairs with a pigmented tip (exclamation mark hairs), which indicates disease progression.

Alopecia areata may affect all hairy body areas, including the eyebrows and eyelashes (Fig. 409-2). Severe forms involve the entire scalp (alopecia totalis) or all body hair (alopecia universalis). Involvement of the scalp margins (ophiasis) is associated with a poor prognosis. Alopecia areata may be associated with other autoimmune diseases, most commonly thyroid diseases (Chapter 207). Other possible associations include anxiety, depression,[9] celiac disease (Chapter 126), vitiligo (Chapter 408), and atopy (Chapter 405). Nail abnormalities are common, especially in children.

The natural history of alopecia areata is unpredictable. Studies indicate that 34 to 50% of patients will recover within 1 year and 15 to 25% will progress to alopecia totalis/universalis, a condition from which full recovery is only approximately 10%.

TREATMENT

A variety of treatments may induce temporary hair regrowth but do not change the long-term prognosis.[10] In the absence of many head-to-head comparisons, the preferred order of treatment is still evolving.

Intralesional steroids can be used in localized areas, including the eyebrows. High-potency topical steroids can be applied under occlusion in acute or severe disease. High-dose pulse corticosteroid therapy is effective in acute alopecia areata but is not useful in ophiasis or long-standing alopecia totalis/universalis. Topical immunotherapy with diphenylcyclopropenone (DPCP) or squaric acid dibutylester (SADBE), which is not approved by the U.S. Food and Drug Administration (FDA), is an effective option in chronic alopecia areata. Oral Janus kinase inhibitors (e.g., baricitinib, 2 to 4 mg daily;[A5] ruxolitinib, 10 to 20 mg twice daily; tofacitinib, 5 to 10 mg twice daily; and ritlecitinib, optimal dose still not established)[A6] have been highly effective in inducing hair regrowth in severe alopecia areata,[11] although relapses often occur if drug treatment is interrupted. Baricitinib is FDA-approved for the treatment of severe alopecia areata, and two other JAK inhibitors (ritlecitinib and deuruxolitinib) are presently being reviewed for approval.

TRICHOTILLOMANIA

Trichotillomania is a compulsive disorder that is more common in children. Repetitive hair pulling and plucking produces patches of irregular alopecia. The scalp is not completely bald, but rather shows broken hairs of various lengths (Fig. 409-3). The frontal, parietal, and occipital scalp are most commonly affected, but other terminal hairs can be involved, especially the upper eyelashes.

Occasionally, patients develop the habit of chewing or eating the pulled hairs. Patients with trichotillomania frequently do not admit their habit, and parents of affected children may be recalcitrant to accept the diagnosis. Psychiatric referral is indicated in adults.

FIGURE 409-1. Alopecia areata: patchy hair loss. The alopecic area is devoid of hairs, and the scalp does not present inflammatory changes. Note diffuse thinning of the scalp surrounding the patch.

FIGURE 409-2. Alopecia areata: patchy hair loss. Hair loss involves the eyelashes and eyebrows.

CICATRICIAL ALOPECIAS (SCARRING ALOPECIA)

The hallmark of cicatricial alopecias is loss of follicular ostia. Cicatricial alopecias include diseases that primarily affect the hair follicles and diseases that affect the dermis and secondarily cause follicular destruction.

Primary cicatricial alopecias are classified as lymphocytic or neutrophilic, based on the principal inflammatory cell type seen on pathologic examination. Lymphocytic cicatricial alopecias include lichen planopilaris, frontal fibrosing alopecia, and discoid lupus erythematosus. Neutrophilic cicatricial alopecias include folliculitis decalvans and dissecting cellulitis.

Secondary cicatricial alopecias result from disorders that cause diffuse scarring of the dermis, including burns, radiation, severe skin infections, localized scleroderma, and scalp tumors. The diagnosis of primary scarring alopecia requires a scalp biopsy, which should be taken from areas with active evidence of inflammation because biopsy of atrophic scalp will typically show only follicular or dermal fibrosis. In scarring alopecias, hair loss is permanent; treatment can prevent progression but not induce hair regrowth.

LICHEN PLANOPILARIS/FRONTAL FIBROSING ALOPECIA

In lichen planopilaris, which is the most common form of cicatricial alopecia, the hair follicles surrounding the alopecic patches show perifollicular erythema and scaling. The patient usually complains of severe itching. A variant of lichen planopilaris is frontal fibrosing alopecia, which typically affects postmenopausal women, in which it causes recession of the frontotemporal hairline, often associated with loss of the eyebrows and hairs of the

FIGURE 409-3. Trichotillomania: patchy hair loss. Irregular areas of alopecia with hairs broken at different lengths.

arms and legs (Fig. 409-4). Frontal fibrosing alopecia is becoming increasingly common worldwide.[12] No therapy is consistently effective, but retrospective studies indicate that 5α-reductase inhibitors are effective in arresting disease progression in a high percentage of patients.

DISCOID LUPUS ERYTHEMATOSUS

In discoid lupus erythematosus, the alopecic area shows active inflammation with erythema, edema, scaling, and follicular plugging, as well as atrophy with variable degrees of telangiectasia and dyspigmentation (Fig. 409-5).

The disease is more common in African American women. Approximately 5 to 10% of adults with discoid lupus erythematosus will develop systemic lupus erythematosus (Chapter 245), especially those with widespread discoid lesions. In localized lesions, treatment with high-potency topical steroids (see Table 404-1 in Chapter 404) is usually effective. Antimalarials are a second-line treatment. Hair regrowth may occur when treatment is promptly started. Therapeutic strategy should include photoprotection of the involved area.

FOLLICULITIS DECALVANS

In folliculitis decalvans, the scalp shows papulopustular lesions that often coalesce to form exudative crusted areas that result in cicatricial alopecia. A typical finding is tufted folliculitis, in which tufts of 6 to 15 hairs emerge together from the scalp (Fig. 409-6). The cause is unknown, but the condition may reflect an abnormal host response to bacterial antigens. *Staphylococcus aureus* often is isolated from active lesions. Folliculitis decalvans responds to oral antibiotics (e.g., trimethoprim-sulfamethoxazole [one tablet, 160 mg/800 mg/day] or clindamycin [300 mg twice daily] with or without rifampin [300 mg twice daily] for 8 to 10 weeks) but usually relapses after interruption of therapy.

DISSECTING CELLULITIS

Dissecting cellulitis of the scalp is a follicular occlusion disorder that may progress to scarring alopecia. Patients typically complain of relapsing multifocal alopecic painful nodules, boggy plaques, and draining tracts. Possible treatments include systemic antibiotics, isotretinoin, and tumor necrosis factor–α inhibitors, but data are limited to small case series.

HAIR DISORDERS IN CHILDREN

Hereditary and congenital alopecias are present since birth or appear in the first years of life. Aplasia cutis congenita is the most common form of focal alopecia in newborns.

Hereditary hair shaft abnormalities associated with increased hair fragility produce diffuse or patchy alopecia that appears during childhood. The most common hereditary hair shaft disorder is monilethrix, in which hair

FIGURE 409-4. Alopecia. A, Frontal fibrosing alopecia. Scarring alopecia of the hair margin with recession of the frontal hairline. The alopecic area can be easily distinguished because it shows no photoaging compared with the normal forehead. **B,** Note alopecia of the eyebrows and facial papules.

FIGURE 409-5. Discoid lupus erythematosus. The alopecic patch shows erythema, scaling, and depigmentation.

shaft fragility is associated with follicular hyperkeratosis. The hair is dull and fragile and breaks easily, especially in the nape and occipital areas. Diagnosis is confirmed by finding hair beading on dermoscopy or microscopic examination.

Congenital triangular alopecia is usually noticed by the age of 6 years as an irregularly triangular patch of alopecia with vellus hairs on the frontotemporal region.

The loose anagen hair syndrome is characterized by a defective anchorage of the hair to the follicle, resulting in hairs that are easily and painlessly pulled out from the scalp. The condition is typical of children and may manifest with patchy hair loss due to hair pulling while playing.

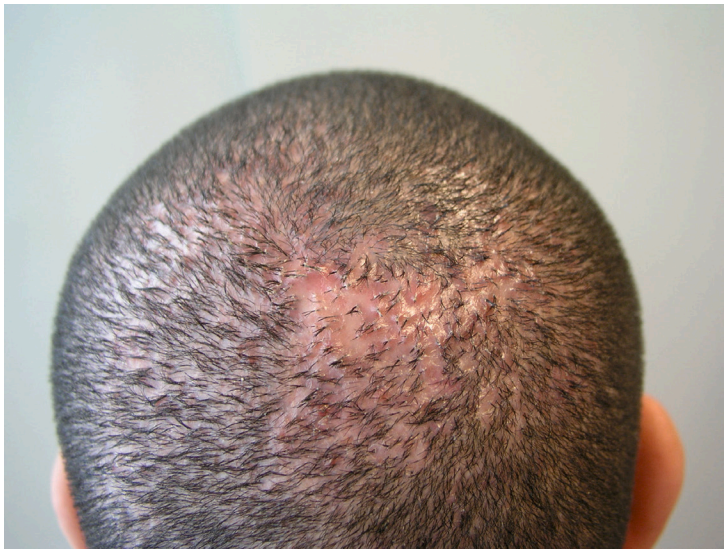

FIGURE 409-6. Folliculitis decalvans. Scarring alopecia with tufted folliculitis.

FIGURE 409-8. Central centrifugal cicatricial alopecia. The alopecic area involves the central portion of the scalp and expands centrifugally.

FIGURE 409-7. Traction alopecia. Hair loss involves the temporal scalp. Note presence of remaining hairs along the hairline (fringe sign).

Short anagen syndrome is a congenital disease characterized by short (<6 cm) fine hair and increased hair shedding. The condition is due to a decreased duration of the anagen phase.

RACIAL DIFFERENCES

The frequency and clinical aspects of hair disorders vary in different races. Androgenetic alopecia, for instance, is more frequent in Whites than in Blacks and Asians, whereas Black and Asian hair is more susceptible to weathering and fragility.

The Black hair shaft is flat, highly twisted, and difficult to manage without strong chemical or hair styling procedures, which often cause considerable damage. Hair straightening and braiding are responsible for traction alopecia, which is common and typically produces cicatricial alopecia of the frontal and lateral margins (Fig. 409-7). Central centrifugal cicatricial alopecia is a very common cause of scarring alopecia in Black women (Fig. 409-8). It manifests as slowly progressive scarring hair loss in the vertex or crown that spreads in a centrifugal pattern.[13]

In Asians, the hair shaft is round, thick, robust, and straight. Asian hair is very difficult to style and dye, and it is often damaged by its treatment with high concentrations or long exposure to chemicals.

EXCESSIVE HAIR GROWTH

Hirsutism describes excessive terminal hair with male distribution in a female. Hirsutism should be distinguished from hypertrichosis, which is characterized by the presence of an excessive amount of hair in a non–androgen-dependent area.

HIRSUTISM

Hirsutism is a common condition that affects up to about 8% of women[14] and is more frequent in Hispanic and Mediterranean women. Hirsutism may be associated with hyperandrogenism and polycystic ovary syndrome (Chapters 217 and 218), but it is idiopathic in approximately 15% of cases. Effective treatments include oral contraceptive agents, flutamide (62.5 to 500 mg/day), and spironolactone (100 mg daily) for severe cases.[A7]

HYPERTRICHOSIS

Hypertrichosis results from the presence of terminal hairs in anatomic areas that are normally characterized by vellus hair. Hypertrichoses can be congenital or acquired, localized or generalized. Acquired hypertrichoses are most commonly iatrogenic, metabolic (e.g., Cushing syndrome, porphyria, hyperthyroidism), nutritional (e.g., anorexia nervosa), or paraneoplastic (Chapter 164).

NAIL DISORDERS

Normal Nail

The nail plate is a keratinized hard structure produced by the nail matrix, which is a specialized epithelium located above the distal phalanx of the finger. In longitudinal sections, the matrix consists of a dorsal, an apical, and a ventral portion. The proximal matrix (dorsal portion and apex) produces the dorsal nail plate (two thirds upper plate), and the distal matrix (ventral portion) produces the ventral plate (one third lower plate). The nail plate is produced continuously throughout life. Nails grow slowly, and the nail plate can reflect illnesses that occurred several months earlier. Complete replacement takes approximately 6 months for fingernails and 12 to 18 months for toenails. Many medications (e.g., anticonvulsants, neuroleptics, antifungals), drugs (e.g., amphetamine, cocaine, doping substances), and poisons (e.g., mercury, arsenic) are retained in the nails, whose fragments (nail clippings) can be used to monitor previous exposure.

Nail abnormalities can be congenital or acquired and may be caused by developmental, traumatic, inflammatory, infective, and neoplastic disorders or by medications.[15,16] The diagnosis of nail dystrophies usually relies on a careful clinical examination and an accurate history, but radiographic or magnetic resonance imaging investigation of the digit and pathology may be required to guide treatment.[17]

KOILONYCHIA (SPOON NAILS)

In koilonychias (Fig. 409-9), which is also called spooning of the nails, the nail plate is thin and has a concave appearance. Koilonychia is physiologic in children. In adults, it can be occupational or, more rarely, a sign of iron deficiency (Chapter 145).

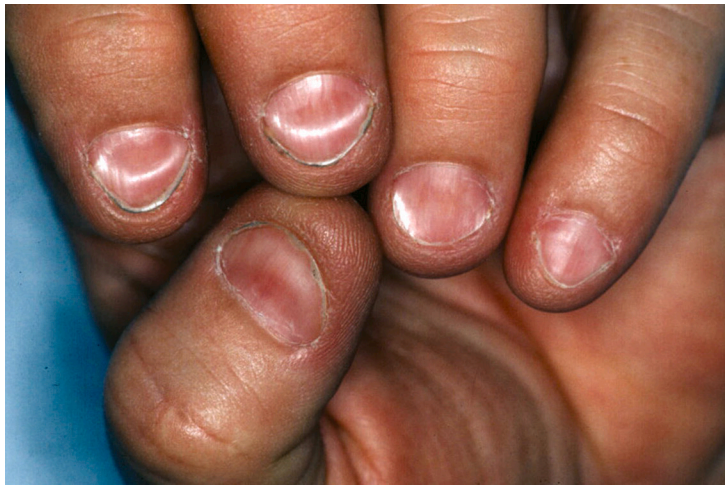

FIGURE 409-9. Spooning.

FIGURE 409-10. Clubbing.

CLUBBING

Clubbing (Fig. 409-10) develops when enlargement of the soft tissue of the distal digit causes a bulbous digit with an enlarged and overcurved nail plate. The angle between the proximal nail fold and the nail plate (Lovibond angle) is greater than 180 degrees. Clubbing may be congenital (i.e., in congenital heart disease; Chapter 55) or acquired. Other causes of acquired clubbing include intrathoracic (Chapter 177) and gastrointestinal neoplasms (Chapters 178 to 181), chronic intrathoracic suppurative disease (Chapter 78), inflammatory bowel disease (Chapter 127), and liver disorders.[18]

BEAU LINES AND ONYCHOMADESIS

Beau lines (Fig. 409-11) and onychomadesis are due to a temporary reduction or arrest of nail growth. Beau lines appear as transverse grooves of various depth; onychomadesis as a full-thickness transverse groove of the proximal nail plate. Causes include trauma, skin diseases involving the proximal nail fold and the matrix, drugs, and systemic diseases (Table 409-4), as well as SARS-CoV-2 infection, which can also cause a "red half moon sign" characterized by an erythematous half moon–shaped band surrounding the distal margin of the lunula (Table 409-5).[19] In systemic disease, Beau lines or onychomadesis involve all the nails and are localized at the same level.

PITTING

Pitting (Fig. 409-12) appears as punctate depressions of the dorsal nail plate, with variable size and depth. Pitting is caused by inflammatory skin disorders such as psoriasis (Chapter 405), alopecia areata, and eczema (Chapter 405).

FIGURE 409-11. Beau lines due to chemotherapy. The lines affect all the nails at the same level.

TABLE 409-4 CAUSES OF BEAU LINES AND ONYCHOMADESIS

SYSTEMIC
Acrodermatitis enteropathica
Severe metabolic stress
High fever
Viral infections (severe acute respiratory syndrome coronavirus 2, Kawasaki disease, measles, hand-foot-and-mouth syndrome)
Typhus
Stevens-Johnson syndrome
Drugs
Bullous disorders (pemphigus, pemphigoids)
Deep saturation, high altitude
Hemodialysis
Myocardial infarction
LOCAL
Trauma (including manicure)
Paronychia
Congenital malalignment (big toenails)

TABLE 409-5 NAIL SIGNS OF SEVERE ACUTE RESPIRATORY SYNDROME CORONAVIRUS 2 INFECTION

Chilblain-like lesions, most commonly on toenails (see Chapters 66 and 336)
Beau lines
Onychomadesis
Transverse true leukonychia (Mee lines)
Transverse orange discoloration
Red half-moon sign (erythematous band surrounding distal margin of the lunula)

LONGITUDINAL GROOVES AND STRIATIONS

Normal nails often show superficial thin longitudinal ridges that increase in number with aging. Deep longitudinal fissures, which indicate damage to the proximal matrix, can be caused by nail lichen planus, vascular insufficiency, trauma, and tumors involving or compressing the matrix.

LEUKONYCHIA

Leukonychia describes a whitish discoloration of the nail, which may be due to persistence of nuclei in the cells of the ventral nail plate (true leukonychia) or to a pallor of the nail bed (apparent leukonychia). True leukonychia, including the Mees lines of arsenic exposure (Chapter 20), does not fade with pressure and moves distally with nail growth; it is most commonly caused by trauma.

FIGURE 409-12. Pitting. Multiple punctate depressions on the nail plate surface.

FIGURE 409-13. Muehrcke lines. Note two parallel lines of apparent leukonychia.

Apparent leukonychia, which does not follow nail growth and fades with pressure, may be a sign of systemic diseases such as liver cirrhosis (Terry nails; Chapter 132), chronic renal diseases (half-and-half nails, characterized by apparent leukonychia of the proximal half of the nail; Chapter 116), hypoalbuminemia (Chapter 107), and systemic chemotherapy (Muehrcke lines; Fig. 409-13).

YELLOW NAIL SYNDROME

The yellow nail syndrome is a chronic nail disorder characterized by an arrest or a reduction of nail growth, resulting in nail thickening and hardening and yellow discoloration. Fingernails and toenails are excessively curved from side to side, and cuticles are absent (Fig. 409-14). Yellow nail syndrome occasionally may be paraneoplastic (Chapter 164). The pathogenesis of yellow nail syndrome is unknown, but a congenital abnormality of the lymphatic vessels may be involved.[20] Typical cases have associated lymphedema or respiratory disturbances. The nail abnormalities improve with treatment of the associated respiratory disorders. Oral vitamin E (1200 mg/day for several months) is useful in some cases.

SPLINTER HEMORRHAGES

Splinter hemorrhages (see Fig. 39-10 in Chapter 39) appear as longitudinal thin red-brown lines of variable length. Splinter hemorrhages are usually localized in the distal nail and are commonly seen in inflammatory diseases, including eczema (Chapter 405), psoriasis (Chapter 405), and onychomycosis (Table 409-6). Multiple splinter hemorrhages localized in the proximal nail plate can be a sign of systemic diseases, including infectious or marantic endocarditis (Chapter 61), trichinosis (Chapter 327), and the antiphospholipid syndrome.

FIGURE 409-14. Yellow nail syndrome. The nails are yellow, are overcurved, and do not grow.

TABLE 409-6 CONDITIONS ASSOCIATED WITH SPLINTER HEMORRHAGE

DERMATOSIS
Psoriasis
Lichen planus
Eczema
VASCULITIS
Antiphospholipid syndrome
Thromboangiitis obliterans
Granulomatosis with polyangiitis
Other small- and medium-vessel vasculitides
DRUGS
Antiangiogenic kinase inhibitors (e.g., sunitinib, sorafenib)
INFECTION
Infectious endocarditis
Psittacosis
Histoplasmosis
Meningococcemia
OTHER
Renal failure
Elderly
Amyloidosis
Marantic endocarditis
Hypereosinophilic syndrome
Langerhans cell histiocytosis
Onychomatricoma

Adapted from Haber R, Khoury R, Kechichian E, et al. Splinter hemorrhages of the nails: a systematic review of clinical features and associated conditions. *Int J Dermatol*. 2016;55:1304-1310.

ONYCHOLYSIS

Onycholysis (Fig. 409-15) describes detachment of the nail plate from the bed. The detachment usually occurs at the free lateral margins of the nail. The onycholytic area is white owing to the presence of air, but it may acquire a green-brown color if the space is colonized by bacteria, such as *Pseudomonas aeruginosa*.

Onycholysis of the fingernails is a common sign of nail psoriasis (Chapter 405). It also may be due to prolonged and frequent contact with water, detergents, or irritants (idiopathic onycholysis). Toenail onycholysis is almost exclusively caused by trauma or onychomycosis. When onycholysis is limited to one digit, the possibility of a nail tumor always should be considered.

PARONYCHIA

Paronychia, which describes the acute or chronic inflammation of the proximal and lateral nail folds, is common in the fingernails at any age. In acute paronychia, the affected digit is painful, with erythema, swelling, and pus

FIGURE 409-15. Onycholysis. The detached nail plate is white in color.

discharge localized to one corner of the proximal nail fold. Acute paronychia usually follows a trauma to the nail fold, as in children who pick or bite the cuticles or in women after a manicure.

In chronic paronychia, prolonged mechanical or environmental trauma (such as contact with water and irritants) damages the cuticle, allowing penetration of dirt, bacteria, and other particles under the proximal nail fold. The result is an inflammatory reaction of the proximal nail fold and nail matrix, with edema and redness of the fold, absence of the cuticles, Beau lines, and abnormalities of the nail plate surface. Treatment includes protective measures, such as use of cotton and rubber gloves to avoid contact with irritants, as well as topical steroids and topical antimicrobials. Acute paronychia, often associated with periungual pyogenic granuloma-like lesions, is a common side effect of treatment with epidermal growth factor receptor (EGFR) inhibitors.

ONYCHOMYCOSIS

Fungal nail infections most commonly affect the toenails of adults. Dermatophytes (particularly *Trichophyton rubrum*) are responsible for most infections. The clinical presentation varies depending on the modality of the nail invasion. In distal subungual onychomycosis, the most common form, fungi spread from plantar skin and invade the nail bed. The affected nail shows subungual hyperkeratosis, onycholysis, and yellow streaks (Fig. 409-16). In white superficial onychomycosis, which only affects toenails, fungi colonize the surface of the nail plate, where they cause multiple white friable patches (Fig. 409-17). Proximal subungual onychomycosis produces a true leukonychia, owing to the presence of fungal hyphae in the deep layers of the plate. Proximal subungual onychomycosis caused by *T. rubrum* is typical in immunosuppressed patients. Diagnosis of onychomycosis must always be confirmed by mycologic examination.

TREATMENT

Treatment depends on clinical type, number of affected nails, and severity of nail involvement.[21] A systemic treatment is preferred for proximal subungual onychomycosis and for distal subungual onychomycosis involving the proximal nail. Terbinafine (250 mg/day) for 2 months (fingernails) or 3 months (toenails) is the most effective treatment for dermatophyte infections.[A8] Topical efinaconazole[A9,A10] and tavaborole,[A11] usually used daily for 6 months, are FDA approved for mild/moderate onychomycosis of the toenails, but these antifungal medications are not as effective as oral terbinafine.

INGROWING TOENAILS

Ingrown toenails are a common condition, especially in young patients. Nail ingrowing most commonly affects one or both the big toes and is related to

FIGURE 409-16. Distal subungual onychomycosis. The nail shows subungual hyperkeratosis and a yellow streak.

FIGURE 409-17. White superficial onychomycosis. The affected nail shows white superficial patches.

genetic factors, hyperhidrosis, and poorly fitting shoes. Ingrowing is usually precipitated by incorrect nail trimming, with formation of a sharp edge (spicule) of the lateral nail plate that penetrates and injures the soft tissues of the lateral nail fold (Fig. 409-18). Depending on severity, treatment varies from simple disembedding of the spicule to chemical destruction of the lateral nail matrix by phenolization.

NAIL PIGMENTATION

Nail pigmentation is usually caused by staining from external agents, such as nicotine or hair dyes. It rarely may be due to drug deposition in the nail plate or into the nail bed (i.e., antimalarials) or systemic diseases (argyria). In these cases, the proximal margin of the pigmentation follows the shape of the lunula.

MELANONYCHIA

Melanonychia is defined by the presence of melanin within the nail plate. It appears more often as a longitudinal brown-black band starting from the matrix and extending to the free edge of the nail plate (Fig. 409-19).

Melanonychia results from production of melanin by melanocytes of the nail matrix. Melanonychia has three main causes: simple melanocytic activation, benign melanocyte proliferations (lentigo, nevus), and malignant melanocyte proliferation (melanoma; Chapter 188).

Common causes of longitudinal melanonychia due to melanocytic activation include inflammatory and traumatic nail disorders, drugs (chemotherapy,

FIGURE 409-18. Ingrowing toenail. Penetration of the nail spicule causes inflammation and granulomatous reaction.

FIGURE 409-20. Nail melanoma. Melanonychia and periungual pigmentation (Hutchinson sign).

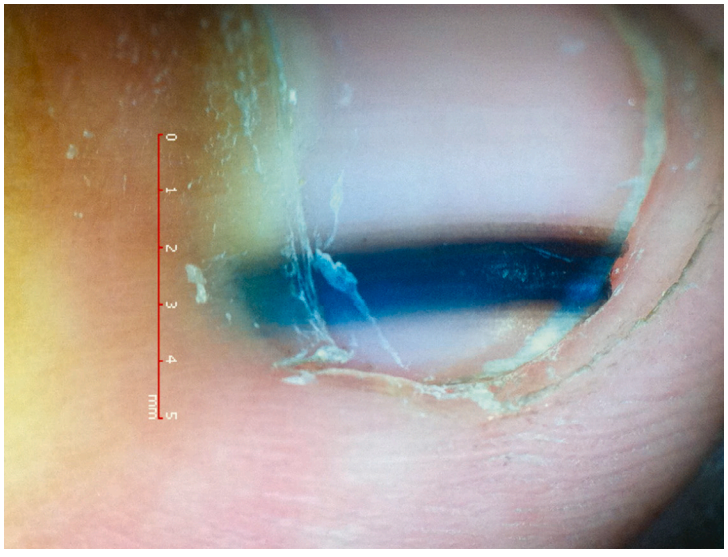

FIGURE 409-19. Longitudinal melanonychia. Black longitudinal pigmented band extending from the proximal nail fold to the free edge.

azidothymidine, antimalarials, or psoralen and ultraviolet A [PUVA] therapy), and systemic diseases (acquired immunodeficiency syndrome [Chapter 359]; Addison disease [Chapter 208]).

Nail melanoma is rare and most frequently involves the thumb of middle-aged individuals. Diagnosis is often delayed, and the 5-year survival rate is only 15%. Hutchinson sign, extension of the pigmentation to the proximal or lateral nail folds, is an important indicator of nail melanoma (Fig. 409-20).

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APPENDIX

REFERENCE INTERVALS AND LABORATORY VALUES

JORGE SEPULVEDA

This Appendix contains tables of reference values for common laboratory tests used in the practice of internal medicine. This information can provide important guidelines for the clinician but should not be used as absolute indicators of health and disease. For essentially every test, significant overlap exists between healthy and diseased populations.

A variety of factors can influence reference values. Such variables include the population studied, the duration and means of specimen transport, laboratory methods and instrumentation, and even the type of container used for the collection of the specimen. The reference or "normal" ranges given in this Appendix may therefore not be appropriate for all laboratories, and these values should only be used as general guidelines. Whenever possible, the reference values provided by the laboratory performing the testing should be utilized in the interpretation of laboratory data.

Values supplied in this Appendix reflect typical reference ranges in nonpregnant adults.[1] Values for older adults (e.g., >60 years old) and other age groups are provided when relevant. Pediatric reference ranges and values in pregnant patients may vary significantly from the data presented in the Appendix. Pediatric reference ranges can be obtained from the Canadian Laboratory Initiative on Pediatric Reference Intervals (CALIPER) study.[2]

In preparing the Appendix, the author has taken into account the fact that the system of international units (SI, système international d'unités) is used in most countries and in some medical journals. However, clinical laboratories may continue to report values in "traditional" or conventional units. Therefore, both systems are provided in the Appendix. If the value and units for a reference interval are the same for conventional and international units, the interval is listed only in the column for international units. The dual system is also used in the text except for those instances in which the numbers remain the same and only the terminology is changed (mmol/L for mEq/L or IU/L for mIU/mL), when only the SI units are given. In some cases (e.g., cholesterol, triglycerides, glucose), guideline-based recommendations for desirable values or medical decision levels are provided instead of the reference range, which may vary markedly among populations and environmental settings.

TABLE APPENDIX-1 PREFIXES AND ABBREVIATIONS

PREFIXES DENOTING DECIMAL FACTORS

PREFIX	SYMBOL	FACTOR
mega	M	10^{6}
kilo	k	10^{3}
hecto	h	10^{2}
deca	da	10^{1}
deci	d	10^{-1}
centi	c	10^{-2}
milli	m	10^{-3}
micro	μ	10^{-6}
nano	n	10^{-9}
pico	p	10^{-12}
femto	f	10^{-15}

ABBREVIATIONS

ADA	American Diabetes Association
AU	Arbitrary units
CSF	Cerebrospinal fluid
DDU	D-dimer units
EDTA	Ethylenediaminetetraacetic acid
EU	Ehrlich unit
F	Female
Hb	Hemoglobin
hpf	High-power field
IFA	Immunofluorescent assay
IFCC	International Federation of Clinical Chemistry
IU	International unit (of hormone activity)
Kat	Katal
KDIGO	Kidney Disease Improving Global Outcomes
M	Male
Pa	Pascal
RBC	Red blood cell
RID	Radial immunodiffusion
S	Substrate
U	International unit (of enzyme activity)
WBC	White blood cell

TABLE APPENDIX-2 CLINICAL CHEMISTRY, TOXICOLOGY, AND SEROLOGY

			REFERENCE INTERVAL (CONVENTIONAL UNITS)			*REFERENCE INTERVAL (INTERNATIONAL UNITS)*		
TEST	**SPECIMEN**	**CONDITION**	***LOWER***	***UPPER***	***UNITS***	***LOWER***	***UPPER***	***UNITS***
Acetoacetate, semiquantitative	Serum or plasma		0.5	3.0	mg/dL	49	298	μmol/L
Acetone, quantitative	Serum or plasma	Undetected if < lower limit	0.5	100	mg/dL	0.09	17.2	μmol/L
	Urine	Toxic if ≥ upper limit	10	100	mg/dL	1.7	17.2	mmol/L
Adrenocorticotropic hormone (ACTH)	Plasma (EDTA)	Morning	7	63	pg/mL	1.5	13.5	pmol/L
Alanine aminotransferase (ALT, SGPT)	Serum or plasma		9	50	U/L	0.15	0.85	μKat/L
Albumin	Serum or plasma		3.9	5.2	g/dL	39	52	g/L
	CSF		0	35	mg/dL	0	350	mg/L
	Urine		0	29.9	mg/g creatinine	0.00	3.38	mg/mmol creatinine
Aldosterone	Serum or plasma	Adults, average sodium diet						
		Supine	0	16	ng/dL	0	0.44	nmol/L
		Upright	4	31	ng/dL	0.12	0.86	nmol/L

TABLE APPENDIX-2 CLINICAL CHEMISTRY, TOXICOLOGY, AND SEROLOGY—cont'd

			REFERENCE INTERVAL (CONVENTIONAL UNITS)			REFERENCE INTERVAL (INTERNATIONAL UNITS)		
TEST	**SPECIMEN**	**CONDITION**	***LOWER***	***UPPER***	***UNITS***	***LOWER***	***UPPER***	***UNITS***
Alkaline phosphatase, IFCC	Serum or plasma	M, F (>19 yr)	40	129	U/L	0.68	2.19	μKat/L
Aluminum	Serum, metal-free tube		0	15	μg/L	0	0.56	μmol/L
		On hemodialysis	0	55	μg/L	0	2.1	μmol/L
δ-Aminolevulinic acid (δ-ALA)	Urine		0	7.9	mg/day	0	60	μmol/day
Ammonia	Plasma (Na or lithium-heparin)		15	45	μg/dL	8.8	26.4	μmol/L
	Urine, 24 hr		5	111	mg/day	0.3	6.5	mmol /day
Amylase	Serum or plasma		37	137	U/L	0.62	2.28	μKat/L
	Urine, random	F	21	447	U/L	0.36	7.60	μKat/L
		M	16	491	U/L	0.27	8.35	μKat/L
Angiotensin I	Plasma (EDTA)		0	25	pg/mL	0	25	ng/L
Angiotensin II	Plasma (EDTA)		0	52	pg/mL	0	52	ng/L
Angiotensin-converting enzyme	Serum		9	67	U/L	0.15	1.14	mcKat/L
Anion gap $[Na^+ - (Cl^- + HCO_3^-)]$	Serum or plasma		6	14	mEq/L	6	14	mmol/L
Antidiuretic hormone (ADH, arginine vasopressin)	Plasma (EDTA)		0	5.9	pg/mL	0.00	5.4	pmol/L
Antimüllerian hormone	Serum or plasma	F, 18-29 yr	0.40	16.0	ng/mL	2.9	114.3	pmol/L
		F, 30-39 yr	0.18	11.705	ng/mL	1.3	83.6	pmol/L
		F, 40-45 yr	0	6.28	ng/mL	0.0	44.9	pmol/L
		F, 46-50 yr	0	0.064	ng/mL	0.0	0.46	pmol/L
		F, postmenopausal	0	0.003	ng/mL	0.0	0.02	pmol/L
		M, 13 and older	2.08	30.66	ng/mL	14.9	219.0	pmol/L
α_1-Antitrypsin	Serum		90	200	mg/dL	0.9	2	g/L
Arsenic	Whole blood (metal-free EDTA)		0	12	μg/L	0	0.16	μmol/L
		Toxic if ≥ upper limit		600	μg/L		7.98	μmol/L
Ascorbic acid (see Vitamin C)								
Aspartate aminotransferase (AST, SGOT)	Serum or plasma		10	37	U/L	0.17	0.63	μKat/L
Base excess	Whole blood, arterial					–4	3	mmol/L
β_2-Microglobulin	Serum or plasma					1.1	2.4	mg/L
Bicarbonate (calculated)	Whole blood, arterial		21	28	mEq/L	21	28	mmol/L
Bilirubin, conjugated (direct)	Serum or plasma		0	0.3	mg/dL	0	5.1	μmol/L
Bilirubin, total	Serum or plasma		0.2	1.3	mg/dL	3.4	22.2	μmol/L
	Urine						Negative	
B-type natriuretic peptide (BNP)	Plasma (EDTA)	FDA-approved cutoff		100	pg/mL		100	ng/L
		F, <45 yr; upper limit increases with age, up to 167 pg/mL at >83 yr		64	pg/mL		64	ng/L
		M, <45 yr; upper limit increases with age, up to 93 pg/mL at >83 yr		35	pg/mL		35	ng/L
Cadmium	Whole blood (metal-free EDTA tube)	Nonsmoker	0.3	1.2	μg/L	2.7	10.7	nmol/L
		Smoker	0.6	3.9	μg/L	5.3	34.7	nmol/L
	Urine, 24 hr		0	3.2	μg/day	0	28.5	nmol/day
Calcitonin	Serum or plasma	F	0	5.1	pg/mL	0	5.1	ng/L
		M	0	7.5	pg/mL	0	7.5	ng/L
Calcium, ionized (iCa)	Serum or plasma (lithium heparin)		4.48	5.28	mg/dL	1.12	1.32	mmol/L
Calcium, total	Serum or plasma		8.3	10.3	mg/dL	2.08	2.58	mmol/L
	Urine, 24 hr	Average calcium diet	100	250	mg/day	2.5	6.3	mmol/day
Cancer antigen 125 (CA 125)	Serum or plasma		0	35	U/mL	0	35	kU/L

TABLE APPENDIX-2 CLINICAL CHEMISTRY, TOXICOLOGY, AND SEROLOGY—cont'd

			REFERENCE INTERVAL (CONVENTIONAL UNITS)			REFERENCE INTERVAL (INTERNATIONAL UNITS)		
TEST	**SPECIMEN**	**CONDITION**	***LOWER***	***UPPER***	***UNITS***	***LOWER***	***UPPER***	***UNITS***
Cancer antigen 15-3 (CA 15-3)	Serum or plasma		0	36	U/mL	0	36	kU/L
Cancer antigen 19-9 (CA 19-9)	Serum or plasma		0	35	U/mL	0	35	kU/L
Carbon dioxide, partial pressure (P_{CO_2})	Whole blood, arterial (heparin)		32	45	mm Hg	4.26	5.99	kPa
Carbon dioxide, total (T_{CO_2})	Serum or plasma, venous		19	27	mEq/L	19	27	mmol/L
	Whole blood, arterial		19	24	mEq/L	19	24	mmol/L
	Whole blood, venous		22	26	mEq/L	22	26	mmol/L
Carboxyhemoglobin	Whole blood	Nonsmokers	0	2	%	0	0.02	HbCO fraction
		Smokers	4	9	%	0.04	0.09	HbCO fraction
Carcinoembryonic antigen (CEA)	Serum	All	0.6	4.7	ng/mL	0.6	4.7	µg/L
		Nonsmokers	0	3	ng/mL	0	3	µg/L
β-Carotene	Serum		3	91	µg/dL	0.06	1.68	µmol/L
Catecholamines	Urine, 24 hr							
Dopamine			71	485	µg/day	464	3167	nmol/day
Epinephrine			1	14	µg/day	5	76	nmol/day
Norepinephrine			14	120	µg/day	83	709	nmol/day
Ceruloplasmin	Serum or plasma		17	54	mg/dL	0.17	0.54	g/L
Chloride (Cl)	Serum or plasma		98	107	mEq/L	98	107	mmol/L
	Urine, 24 hr		110	250	mEq/day	110	250	mmol/day
Cholesterol, total	Serum or plasma	Recommended		200	mg/dL		5.18	mmol/L
		Moderate risk	200	239	mg/dL	5.18	6.19	mmol/L
		High risk	239		mg/dL	6.19		mmol/L
Chorionic gonadotropin, intact + beta subunit	Serum or plasma (heparin)	F, nonpregnant, premenopausal	0	5.0	mIU/mL	0	5.0	IU/L
		F, postmenopausal	0	7.0	mIU/mL	0	7.0	IU/L
		M	0	3.0	mIU/mL	0	3.0	IU/L
Complement C3	Serum or plasma		80	162	mg/dL	0.80	1.60	g/L
Complement C4	Serum or plasma		14	47	mg/dL	0.14	0.47	g/L
Copper	Serum, metal-free tube	F	80	155	µg/dL	12.6	24.3	µmol/L
		M	70	140	µg/dL	11.0	22.0	µmol/L
	Urine, 24 hr		0	60	µg/day	0	9.4	µmol/day
Cortisol, total	Serum	6-10 AM	4.8	19.3	µg/dL	132	533	nmol/L
		4-8 PM	2.3	11.9	µg/dL	63	328	nmol/L
Cortisol, free	Urine, 24 hr	M	0	60	µg/day	0	166	nmol/day
		F	0	45	µg/day	0	124	nmol/day
C-peptide	Serum		0.5	3.3	ng/mL	0.2	1.0	nmol/L
C-reactive protein (CRP)	Serum or plasma (heparin)		0	0.8	mg/dL	0	8	mg/L
C-reactive protein, by high-sensitivity method (hs-CRP)	Serum or plasma (heparin)	Cardiac risk:						
		Low				0	1	mg/L
		Average				1.0	3.0	mg/L
		High				3.1	10.0	mg/L
Creatine kinase (CK)	Serum or plasma	F	40	308	U/L	0.68	5.24	µKat/L
		M	64	499	U/L	1.09	8.48	µKat/L
Creatinine	Serum or plasma	F	0.50	0.95	mg/dL	44	84	µmol/L
		M	0.70	1.30	mg/dL	62	115	µmol/L
	Urine, 24 hr	F	11	20	mg/kg/day	97	177	µmol/kg/day
		M	14	26	mg/kg/day	124	230	µmol/kg/day
Creatinine clearance	See Glomerular Filtration Rate							
Cystatin C	Serum or plasma		0.5	1.2		0.5	1.2	mg/L
Dehydroepiandrosterone (DHEA), unconjugated	Serum	F	1.3	9.8	ng/mL	4.51	34	nmol/L
		M	1.8	12.5	ng/mL	6.25	43.4	nmol/L
Dehydroepiandrosterone sulfate (DHEA-S)	Serum or plasma	Reference ranges are highly dependent on sex, age, and Tanner stage						
11-Deoxycortisol (compound S)	Serum or plasma		20	158	ng/dL	0.6	4.6	nmol/L
Erythropoietin	Serum or plasma		2.6	18.5	mIU/mL	2.6	18.5	IU/L

TABLE APPENDIX-2 CLINICAL CHEMISTRY, TOXICOLOGY, AND SEROLOGY—cont'd

			REFERENCE INTERVAL (CONVENTIONAL UNITS)			REFERENCE INTERVAL (INTERNATIONAL UNITS)		
TEST	**SPECIMEN**	**CONDITION**	***LOWER***	***UPPER***	***UNITS***	***LOWER***	***UPPER***	***UNITS***
Estradiol, by immunoassay	Serum or plasma	F, follicular phase	12.4	33	pg/mL	46	122	pmol/L
		F, ovulation phase	41.0	398	pg/mL	151	1469	pmol/L
		F, luteal phase	22.3	341	pg/mL	82	1258	pmol/L
		F, postmenopausal	0	138	pg/mL	0	509	pmol/L
		M	0	42.6	pg/mL	0	157	pmol/L
Fat, fecal	Feces, 72-hr		0	7.1	g/day	0	7.1	g/day
Fatty acids, nonesterified (free)	Serum	Age and sex dependent				0	1.1	mmol/L
Ferritin	Serum or plasma	F	13	150	ng/mL	13	150	µg/L
		M	30	400	ng/mL	30	400	µg/L
α-Fetoprotein (AFP)	Serum		0.7	9.3	ng/mL	0.7	9.3	µg/L
Fibrinogen (see Table Appendix-3)								
Folate	Serum		4.8		ng/mL	10.9		nmol/L
	Erythrocytes (EDTA)		366		ng/mL packed cells	829		nmol/L packed cells
Follitropin (FSH)	Serum or plasma	F, follicular phase	3.5	12.5	mIU/mL	3.5	12.5	IU/L
		F, midcycle	4.7	21.5	mIU/mL	4.7	21.5	IU/L
		F, luteal phase	1.7	7.7	mIU/mL	1.7	7.7	IU/L
		F, postmenopausal	25.8	134.8	mIU/mL	25.8	134.8	IU/L
		M	1.5	12.4	mIU/mL	1.5	12.4	IU/L
Fructosamine	Serum or plasma					205	285	µmol/L
Gastrin	Serum		0	100	pg/mL	0	100	ng/L
Glomerular filtration rate (estimated)	Serum or plasma	KDIGO normal or high	90		mL/min/1.73m^2	0.87		mL/sec/m^2
Glucose	Serum or plasma	Fasting	74	99	mg/dL	4.1	5.5	mmol/L
		Random, postprandial or 2 hr after 75-g glucose oral load	70	139	mg/dL	3.9	7.7	mmol/L
		DIABETES DECISION LIMITS (consider diagnosis if ≥ lower limit)						
		Fasting	126		mg/dL	0.0		mmol/L
		Random, postprandial or 2 hr after 75-g glucose oral load	200		mg/dL	0.0		mmol/L
	Whole blood (heparin)		65	95	mg/dL	3.6	5.3	mmol/L
	CSF		40	70	mg/dL	2.2	3.9	mmol/L
	Urine (quantitative, enzymatic)		0	0.5	g/day	0.0	2.8	mmol/day
	Urine (qualitative)						Negative	
Glucose tolerance test (GTT), 2-hour ADA-recommended screening test for gestational diabetes	Serum or plasma	NORMAL						
		Fasting	65	91	mg/dL	3.6	5.1	mmol/L
		60 min	65	179	mg/dL	3.6	9.9	mmol/L
		120 min	65	152	mg/dL	3.6	8.4	mmol/L
		DIABETIC						
		Fasting	126		mg/dL	7.0		mmol/L
		120 min	200		mg/dL	11.1		mmol/L
γ-Glutamyltransferase (GGT) IFCC	Serum or plasma	F	10	54	U/L	0.17	0.92	µKat/L
		M	13	109	U/L	0.22	1.85	µKat/L
Glycated hemoglobin (HbA_{1c})	Whole blood (EDTA or heparin)	Decreased risk for diabetes		5.7	%		0.057	Hb fraction
		Prediabetes	5.7	6.4	%	0.057	0.064	Hb fraction
		Consistent with diagnosis of diabetes	6.5		%	0.065		Hb fraction
Growth hormone (hGH, somatotropin)	Serum or plasma	Adult, F	0.05	8	ng/mL	0.05	8	µg/L
		Adult, M	0.05	3	ng/mL	0.05	3	µg/L
Haptoglobin	Serum, avoid hemolysis		16	206	mg/dL	160	2060	mg/L
HDL cholesterol (HDLC)	Serum or plasma	Desirable	40	60	mg/dL	1.0	1.5	mmol/L
β-Hydroxybutyrate	Serum or plasma		0	2.81	mg/dL	0	0.27	mmol/L
5-Hydroxyindole acetic acid (5-HIAA)	Plasma		0	22	ng/mL	0	115	µmol/L
	Urine		0	14	mg/g creatinine	0	8.3	mmol/mol creatinine

TABLE APPENDIX-2 CLINICAL CHEMISTRY, TOXICOLOGY, AND SEROLOGY—cont'd

			REFERENCE INTERVAL (CONVENTIONAL UNITS)			REFERENCE INTERVAL (INTERNATIONAL UNITS)		
TEST	**SPECIMEN**	**CONDITION**	***LOWER***	***UPPER***	***UNITS***	***LOWER***	***UPPER***	***UNITS***
17-Hydroxyprogesterone (17-OHP)	Serum or plasma	F, follicular phase	15	70	ng/dL	0.4	2.1	nmol/L
		F, luteal phase	35	290	ng/dL	1	8.7	nmol/L
		F, postmenopausal	0	70	ng/dL	0	2.1	nmol/L
		M	0	139	ng/dL	0	4.2	nmol/L
Immunoglobulin A (IgA)	Serum or plasma		103	501	mg/dL	1.0	5.0	g/L
Immunoglobulin D (IgD)	Serum or plasma		0	15.3	mg/dL	0	153	mg/L
Immunoglobulin E (IgE)	Serum or plasma		0	160	kIU/L	0	380	µg/L
Immunoglobulin G (IgG)	Serum or plasma		700	1600	mg/dL	7	16	g/L
	CSF		0	6.0	mg/dL	0	60	mg/L
Immunoglobulin M (IgM)	Serum or plasma		40	230	mg/dL	0.4	2.3	g/L
Insulin	Serum	Fasting	3	25	µIU/mL	18	150	pmol/L
Intrinsic factor (see Vitamin B_{12})								
Iron	Serum or plasma	F	37	145	µg/dL	6.6	25.9	µmol/L
		M	59	158	µg/dL	10.6	28.3	µmol/L
Iron-binding capacity, total (TIBC)	Serum or plasma	F	149	492	µg/dL	26.7	88.0	µmol/L
		M	171	505	µg/dL	30.6	90.3	µmol/L
Iron saturation	Serum or plasma	F	15	45	%	0.15	0.45	Fraction of iron saturation
		M	20	50	%	0.2	0.50	
Ketone bodies	Serum or plasma						Not detected	
	Urine, random						Not detected	
Light chains (free)	Serum or plasma	Kappa chains	0.33	1.94	mg/dL	3.3	19.4	mg/L
		Lambda chains	0.57	2.63	mg/dL	5.7	26.3	mg/L
		Kappa/lambda ratio				0.26	1.68	ratio
L-Lactate	Whole blood, venous (heparin)		4.5	19.8	mg/dL	0.5	2.2	mmol/L
	Whole blood, arterial (heparin)		4.5	14.4	mg/dL	0.5	1.6	mmol/L
Lactate dehydrogenase (LDH)	Serum or plasma		135	225	U/L	2.3	3.8	µKat/L
Lead	Whole blood, lead-free tube		0	4.9	µg/dL	0	0.24	µmol/L
		Toxic if ≥ upper limit		25	µg/dL		1.21	µmol/L
Lipase	Serum or plasma		16	95	U/L	0.27	1.58	µKat/L
Low-density lipoprotein cholesterol (LDLC)	Serum or plasma	Recommended for secondary prevention		70	mg/dL	0	1.81	mmol/L
		Recommended for primary prevention		100	mg/dL	0	2.59	mmol/L
		Mild risk	100	129	mg/dL	2.59	3.34	mmol/L
		Moderate risk	130	159	mg/dL	3.37	4.12	mmol/L
		High risk	160		mg/dL	4.14		mmol/L
Luteinizing hormone (LH)	Serum or plasma (heparin)	F, follicular phase	2.4	12.6	mIU/mL	2.4	12.6	IU/L
		F, midcycle	14.0	95.6	mIU/mL	14.0	95.6	IU/L
		F, luteal phase	1.0	11.4	mIU/mL	1.0	11.4	IU/L
		F, postmenopausal	7.7	58.5	mIU/mL	7.7	58.5	IU/L
		M	1.7	8.6	mIU/mL	1.7	8.6	IU/L
Magnesium	Serum or plasma		1.6	2.6	mg/dL	0.66	1.07	mmol/L
	Urine, 24 hr		72.9	121.5	mg/day	3.0	5.0	mmol/day
Magnesium, free	Serum or plasma					0.45	0.60	mmol/L
Manganese	Whole blood (EDTA)		4	15	µg/L	72	270	nmol/L
	Serum (metal-free tube)		0	2.0	µg/L	0	36	nmol/L
	Urine		0	5.0	µg/L	0	90	nmol/L
Mercury	Whole blood (EDTA)		0	10	µg/dL	0	50	µmol/L
	Urine, 24 hr		0	5	µg/L	0	25	µmol/L
		Toxic if ≥ upper limit		20	µg/L		100	µmol/L
Methemoglobin (MetHb)	Whole blood		0	1.5	% of total Hb	0	0.015	Fraction of total Hb

TABLE APPENDIX-2 CLINICAL CHEMISTRY, TOXICOLOGY, AND SEROLOGY—cont'd

			REFERENCE INTERVAL (CONVENTIONAL UNITS)			REFERENCE INTERVAL (INTERNATIONAL UNITS)		
TEST	**SPECIMEN**	**CONDITION**	***LOWER***	***UPPER***	***UNITS***	***LOWER***	***UPPER***	***UNITS***
Nickel	Serum (metal-free tube)		0	10	µg/L	0	170	nmol/L
	Urine, 24 hr		0	14	µg/day	0	238	nmol/day
NT-pro-BNP	Serum or plasma	F, 18-19 yr	6	207	pg/mL	1.7	59.8	pmol/L
		F, 19-45 yr	0	178	pg/mL	0	51.4	pmol/L
		F, 45-55 yr	0	192	pg/mL	0	55.5	pmol/L
		F, 55-65 yr	0	226	pg/mL	0	65.3	pmol/L
		F, 65-75 yr	0	353	pg/mL	0	102	pmol/L
		F, >75 yr	0	624	pg/mL	0	180.3	pmol/L
		M, 18-19 yr	6	207	pg/mL	1.7	59.8	pmol/L
		M, 19-45 yr	0	93	pg/mL	0	26.9	pmol/L
		M, 45-55 yr	0	138	pg/mL	0	39.9	pmol/L
		M, 55-65 yr	0	177	pg/mL	0	51.2	pmol/L
		M, 65-75 yr	0	229	pg/mL	0	66.2	pmol/L
		M, >75 yr	0	852	pg/mL	0	246.2	pmol/L
Osmolality	Serum or plasma					275	295	mOsmol/kg
Oxalate	Plasma		0	0.18	µg/mL	0	2.0	µmol/L
	Urine, 24 hr	M, 13 and older	16	49	mg/day	0.18	0.56	mmol/day
		F, 13 and older	13	40	mg/day	0.15	0.45	mmol/day
Oxygen (Po_2)	Whole blood, arterial (heparin)		72	104	mm Hg	9.6	13.8	kPa
Oxygen saturation (sea level)	Whole blood, arterial (heparin)		95	99	%	0.95	0.99	Fraction saturated
Parathyroid hormone, intact	Serum or plasma		15	65	pg/mL	1.6	6.9	pmol/L
pH (37° C)	Whole blood, arterial (heparin)					7.35	7.45	
Phosphate (inorganic)	Serum or plasma		2.5	4.5	mg/dL	0.81	1.45	nmol/L
	Urine, 24 hr		0.4	1.3	g/day	12.93	42	mmol/day
Porphobilinogen (PBG)	Urine, 24 hr	Quantitative	0	2.5	mg/day	0	11	µmol/day
	Urine, fresh random	Qualitative					Negative	
Potassium (K)	Serum		3.5	5.1	mEq/L	3.5	5.1	mmol/L
	Plasma (heparin)		3.4	4.5	mEq/L	3.5	4.5	mmol/L
	Urine, 24 hr		25	125	mEq/day	25	125	mmol/day
Procalcitonin	Serum or plasma		0	0.10	ng/mL	0	0.10	µg/L
Proinsulin, intact	Serum or plasma					0	8.0	pmol/L
Prolactin	Serum or plasma	F, nonlactating	3.1	22.5	ng/mL	3.1	22.5	µg/L
		M	3.5	16.9	ng/mL	3.5	16.9	µg/L
Prostate-specific antigen (PSA)	Serum or plasma	M, 40-49 yr	0	2.5	ng/mL	0	2.5	µg/L
		M, 50-59 yr	0	3.5	ng/mL	0	3.5	µg/L
		M, 60-69 yr	0	4.5	ng/mL	0	4.5	µg/L
		M, 70-79 yr	0	6.5	ng/mL	0	6.5	µg/L
Total protein	Serum		6.5	8.1	g/dL	65	81	g/L
Albumin		By electrophoresis (cellulose acetate)	3.6	4.8	g/dL	36	48	g/L
α1-Globulins			0.2	0.4	g/dL	2	4	g/L
α2-Globulins			0.6	0.9	g/dL	6	9	g/L
β-Globulins			0.6	1.1	g/dL	6	11	g/L
γ-Globulins			0.8	1.8	g/dL	8	18	g/L
Total protein	Urine, 24 hr		30	150	mg/day	0.03	0.15	g/day
	CSF, by lumbar puncture		14	45	mg/dL	140	450	mg/L
Pyruvic acid	Whole blood (heparin)		0.3	0.9	mg/dL	0.030	0.107	mmol/L
Renin (normal diet)	Plasma (EDTA)	Supine	0.2	1.6	ng/mL/hr	0.2	1.6	µg/L/hr
		Standing	0.5	4.0	ng/mL/hr	0.5	4.0	µg/L/hr
Riboflavin (see Vitamin B_2)								
Sediment	Urine, fresh, random	Hyaline casts				occasional (0-1)		casts/hpf
		RBC casts				not seen		
		WBC casts				not seen		
		Tubular epithelial casts				not seen		
		Transitional and squamous epithelial casts				not seen		
		RBCs				0	2	/hpf
		WBCs, Female				0	5	/hpf
		WBCs, Male				0	3	/hpf
		Epithelial cells				0	few	/hpf
		Bacteria: unspun					no organisms	
		Bacteria: spun				0	20	/hpf
Selenium	Serum or plasma (metal-free tube)		23	190	µg/L	0.29	2.38	µmol/L
	RBC, whole blood (metal-free tube)		110	330	µg/L of RBC	1.40	4.19	µmol/L of RBC
	Urine, 24 hr		12	40	µg/L	0.15	0.51	µmol/L

TABLE APPENDIX-2 CLINICAL CHEMISTRY, TOXICOLOGY, AND SEROLOGY—cont'd

			REFERENCE INTERVAL (CONVENTIONAL UNITS)			REFERENCE INTERVAL (INTERNATIONAL UNITS)		
TEST	**SPECIMEN**	**CONDITION**	***LOWER***	***UPPER***	***UNITS***	***LOWER***	***UPPER***	***UNITS***
Sodium (Na)	Serum or plasma Urine, 24 hr		137 40	145 220	mEq/L mEq/day	137 40	145 220	mmol/L mmol/day
Specific gravity	Urine					1.001	1.035	
Sulfhemoglobin	Whole blood		0	0.4	% of total Hb	0	0.004	Fraction of total Hb
Testosterone, free	Serum or plasma	F M	0.8 47	9.2 244	pg/mL pg/mL	2.8 163	31.9 847	pmol/L pmol/L
Testosterone, total	Serum or plasma	F, 17-50 yr F, >50 yr M, 17-50 yr M, >50 yr	8.4 2.9 249 193	48.1 40.1 836 740	ng/dL ng/dL ng/dL ng/dL	0.3 0.1 8.6 6.7	1.7 1.4 29.0 25.7	nmol/L nmol/L nmol/L nmol/L
Thiamine (see Vitamin B_1)								
Thyroglobulin (Tg)	Serum		1.3	31.8	ng/mL	1.3	31.8	µg/L
Thyroglobulin antibodies	Serum	Very method dependent				0	4.0	IU/mL
Thyrotropin (hTSH)	Serum or plasma		0.4	4.8	µIU/mL	0.4	4.8	mIU/L
Thyroxine, free (FT_4)	Serum or plasma		0.8	1.9	ng/dL	10.3	24.5	pmol/L
Thyroxine, total (T_4)	Serum or plasma	F M	5.5 4.6	11.0 10.5	µg/dL µg/dL	71 59	142 135	nmol/L nmol/L
Thyroxine-binding globulin (TBG)	Serum		13	30	µg/mL	13	30	mg/L
Transcortin (corticosteroid-binding globulin)	Serum	F M	14.9 18.8	22.9 25.2	mg/L mg/L	256 323	393 433	nmol/L nmol/L
Transferrin	Serum or plasma	 >60 yr	200 160	360 340	mg/dL mg/dL	2 1.6	3.6 3.4	g/L g/L
Transthyretin (prealbumin)	Serum or plasma		19.6	41.8	mg/dL	196	418	mg/L
Triglycerides (TG)	Serum or plasma, after ≥12-hr fast	Recommended < upper limit		150	mg/dL		1.7	mmol/L
Triiodothyronine, free (FT_3)	Serum or plasma		210	440	pg/dL	3.2	6.8	pmol/L
Triiodothyronine, total (T_3)	Serum or plasma		78	158	ng/dL	1.2	2.4	mmol/L
Troponin-I	Serum or plasma	99th percentile of a healthy population; reference values highly dependent on specific assay						
Troponin-T	Serum or plasma	F M	0 0	14 22	ng/L ng/L			
Urea nitrogen	Serum or plasma Urine, 24 hr		7 26	26 43	mg/dL g/day	2.5 0.9	9.3 1.5	mmol/L mol/day
Urea nitrogen/creatinine ratio	Serum or plasma					6:1	22:1	
Uric acid	Serum or plasma Urine, 24 hr	F M	3.0 4.0 250	7.1 8.6 750	mg/dL mg/dL mg/day	178 238 1487	422 512 4461	mmol/L mmol/L mmol/day
Urinary sediment (see Sediment)								
Vanillylmandelic acid (VMA)	Urine, 24 hr		0	7	mg/day	0	35.4	µmol/L
Viscosity	Serum					1.1	1.9	centipoise
Vitamin A (retinol)	Serum or plasma		30	120	µg/dL	1.1	4.2	µmol/L
Vitamin B_1 (thiamine diphosphate)	Whole blood					70	180	nmol/L
Vitamin B_2 (riboflavin)	Plasma		1.9	18.8	µg/L	5	50	nmol/L
Vitamin B_6	Serum or plasma		5	31	ng/mL	20	125	nmol/L
Vitamin B_{12}	Serum or plasma		299	1054	pg/mL	219	773	pmol/L
Vitamin C (ascorbic acid)	Serum or plasma		0.4	2.0	mg/dL	23	114	µmol/L
Vitamin D, 1,25-dihydroxy, total	Serum or plasma		20	79	pg/mL	48	190	pmol/L
Vitamin D, 25-hydroxy, total	Serum or plasma	Optimum level	30	80	ng/mL	75	200	nmol/L

TABLE APPENDIX-2 CLINICAL CHEMISTRY, TOXICOLOGY, AND SEROLOGY—cont'd

			REFERENCE INTERVAL (CONVENTIONAL UNITS)			REFERENCE INTERVAL (INTERNATIONAL UNITS)		
TEST	SPECIMEN	CONDITION	LOWER	UPPER	UNITS	LOWER	UPPER	UNITS
Vitamin E (alpha-tocopherol)	Serum or plasma		5.5	18.0	µg/mL	13	42	µmol/L
Vitamin E (gamma-tocopherol)	Serum or plasma		0.0	6.0	µg/mL	0	13	µmol/L
Zinc	Serum or plasma (metal-free tube)		60	120	µg/dL	9.2	18.0	µmol/L
Zinc protoporphyrin	Whole blood		0	60	µg/dL	0	600	µg/L

CSF = cerebrospinal fluid; EDTA = ethylenediaminetetraacetic acid; F = female; FDA = U.S. Food and Drug Administration; KIDGO = kidney disease improving global outcomes; M = male; RBC = red blood count; WBC = white blood count.

TABLE APPENDIX-3 HEMATOLOGY AND COAGULATION

TEST	SPECIMEN	REFERENCE INTERVAL (CONVENTIONAL UNITS)	REFERENCE INTERVAL (INTERNATIONAL UNITS)
Activated partial thromboplastin time (APTT)	Plasma (Na citrate)	Very dependent on reagent lot	23.9-34.7 sec
ADAMTS-13 activity	Plasma (Na citrate)	68-163%	0.68-1.63 activity ratio
Antithrombin III	Plasma (Na citrate)		
Antigenic		22-39 mg/dL	220-390 mg/L
Functional		70-130%	0.70-1.30
Blood volume	Whole blood (heparin)		F: 69-75 mL/kg body weight M: 69 mL/kg body weight
Bone marrow	Bone marrow aspirate		
Differential count		% (mean)	Number fraction (mean)
Myeloblasts		0.3-5.0 (2.0)	0.003-0.05 (0.02)
Promyelocytes		1.0-8.0 (5.0)	0.01-0.08 (0.05)
Myelocytes			
Neutrophilic		5.0-19.0 (12.0)	0.05-0.19 (0.12)
Eosinophilic		0.5-3.0 (1.5)	0.005-0.03 (0.015)
Basophilic		0.0-0.5 (0.3)	0.00-0.005 (0.003)
Metamyelocytes		13.0-32.0 (22.0)	0.13-0.32 (0.22)
Polymorphonuclear neutrophils		0.7-3.0 (2.0)	0.007-0.03 (0.02)
Polymorphonuclear eosinophils		0.5-4.0 (2.0)	0.005-0.04 (0.02)
Polymorphonuclear basophils		0.0-0.7 (0.2)	0.0-0.007 (0.002)
Lymphocytes		3.0-17.0 (10.0)	0.03-0.17 (0.10)
Plasma cells		0.0-2.0 (0.4)	0.00-0.02 (0.004)
Monocytes		0.5-5.0 (2.0)	0.005-0.05 (0.02)
Reticulocytes		0.1-2.0 (0.2)	0.001-0.02 (0.002)
Megakaryocytes		0.3-3.0 (1.0)	0.003-0.03 (0.01)
Pronormoblasts		1.0-8.0 (4.0)	0.01-0.08 (0.04)
Normoblasts		7.0-32.0 (18.0)	0.07-0.32 (0.18)
D-dimer	Plasma (Na citrate)	0.0-0.5 µg/mL DDU	0-500 µg/L DDU
Differential count (see bone marrow differential count or leukocyte differential count)			
Erythrocyte count (RBC count)	Whole blood (EDTA)	$\times 10^6$ cells/µL F: 3.8-5.1 M: 4.2-5.7	$\times 10^{12}$ cells/L 3.8-5.1 4.2-5.7
Erythrocyte sedimentation rate (ESR), Westergren	Whole blood (EDTA)		F: <50 y: 0-25 mm/hr >50 y: 0-30 mm/hr M: <50 y: 0-15 mm/hr >50 y: 0-20 mm/hr
Fibrin degradation products	Plasma (Na citrate)	0-1 µg/mL	0-1 mg/L
Fibrinogen	Plasma (Na citrate)	191-430 mg/dL	1.91-4.30 g/L
Glucose-6-phosphate dehydrogenase (G6PD) in erythrocytes	Whole blood (ACD, EDTA, or heparin)	≤39 minutes	≤2400
Hematocrit (HCT)	Whole blood (EDTA)	F: 33.8-43.3% M: 37.2-47.9%	0.34-0.43 volume fraction 0.37-0.48 volume fraction
Hemoglobin (Hb)	Whole blood (EDTA)	F: 11.2-14.7 g/dL M: 12.6-17.0 g/dL	112-147 g/L 126-170 g/L
Hemoglobin electrophoresis	Whole blood (EDTA, citrate, or heparin)	HbA: >95% HbA_2: 1.5-3.5% HbF: <2%	>0.95 0.015-0.035 <0.02
Immature platelet fraction (IPF)	Whole blood (EDTA)	F: 0.9-7.9% M: 1.3-8.2%	0.009-0.079 0.013-0.082
Immature reticulocyte fraction (IRF)		2.8-13.1%	0.028-0.131

TABLE APPENDIX-3 HEMATOLOGY AND COAGULATION—cont'd

TEST	SPECIMEN	REFERENCE INTERVAL (CONVENTIONAL UNITS)		REFERENCE INTERVAL (INTERNATIONAL UNITS)	
International normalized ratio (INR)	Plasma (Na citrate)	Relevant only in patients on warfarin $INR = \left[\frac{\text{Patient PT}}{\text{Normal mean PT}}\right]^{ISI}$ ISI = International sensitivity index of thromboplastin		INR 2.0-3.0 (for most indications)	
Leukocyte count (WBC count)	Whole blood (EDTA) CSF	F: 3.5-9.4 × 10^3 cells/μL M: 3.1-8.4 × 10^3 cells/μL 0.5 mononuclear cells/μL		3.5-9.4 × 10^9 cells/L 3.1-8.4 × 10^9 cells/L 0.5 × 10^6 cells/L	
Leukocyte Differential count:	Whole blood (EDTA)	*% cells*	*Cells (counts/μL)*	*Fraction of cells counted*	*Cells (×10^9/L)*
Neutrophils		43-75	1400-5800	0.43-0.75	1.4-5.8
Lymphocytes		17-45	950-3070	0.17-0.45	0.95-3.07
Monocytes		4.0-9.4	260-810	0.040-0.094	0.26-0.81
Eosinophils		0.2-4.9	30-480	0.002-0.049	0.03-0.48
Basophils		0.2-1.6	10-80	0.002-0.016	0.01-0.08
Immature granulocytes		0-0.5	0-30	0-0.005	0-0.03
Nucleated red blood cells		0	0	0	0
Leukocyte Differential count	CSF	*% cells*		*Number fraction*	
Lymphocytes		62 ± 34		0.62 ± 0.34	
Monocytes (includes pia-arachnoid mesothelial cells)		36 ± 20		0.36 ± 0.20	
Neutrophils		2 ± 5		0.02 ± 0.05	
Histiocytes				Rare	
Ependymal cells				Rare	
Eosinophils				Rare	
Mean corpuscular hemoglobin (MCH)	Whole blood (EDTA)	F: 26-33 pg/cell M: 27-33 pg/cell		0.26-0.33 fmol/cell 0.27-0.33 fmol/cell	
Mean corpuscular hemoglobin concentration (MCHC)	Whole blood (EDTA)	31-37% Hb/cell or g Hb/dL RBC		4.81-5.74 mmol Hb/L RBC	
Mean corpuscular volume (MCV)	Whole blood (EDTA)			F: 78.6-94.2 fL M: 79.4-94.7 fL	
Mean platelet volume (MPV)	Whole blood (EDTA)			F: 8.7-12.5 fL M: 9.0-12.1 fL	
Plasma volume	Whole blood (heparin)	F: 28-45 mL/kg M: 25-43 mL/kg		0.028-0.045 L/kg 0.025-0.043 L/kg	
Platelet count (thrombocyte count)	Whole blood (EDTA)	167-374 × 10^3/μL (μL) 159-325 × 10^3/μL (μL)		167-374 × 10^9/L 159-325 × 10^9/L	
Prothrombin time, one-stage	Plasma (Na citrate)	Reference values will vary with the type of thromboplastin		In general: 11-16 sec	
Red cell volume	Whole blood (heparin)	F: 19-31 mL/kg M: 20-36 mL/kg		0.019-0.031 L/kg 0.020-0.036 L/kg	
Red cell distribution width, coefficient of variation (RDW-CV)	Whole blood (heparin)	F: 11.4 14.7% M: 11.3 13.9%		0.114-0.147 0.113-0.139	
Reticulocyte count	Whole blood (EDTA, heparin, or oxalate)	0.77-2.26% of erythrocytes		0.0077-0.0226 (number fraction)	
Reticulocyte count, absolute	Whole blood (EDTA, heparin, or oxalate)	25,000-100,000/μL		25-100 × 10^9/L	
Reticulocyte hemoglobin	Whole blood (EDTA, heparin, or oxalate)			F: 29.2-37.8 pg M: 31.2-38.8 pg	
Thrombin time	Plasma (Na citrate)	15.0-18.9 seconds		15.0-18.9 seconds	
von Willebrand factor activity	Plasma (Na citrate)	51-215%		0.51-2.15 activity ratio	
von Willebrand factor antigen	Plasma (Na citrate)	52-214%		0.52-2.14 activity ratio	

ACD = acid citric dextrose; CSF = cerebrospinal fluid; EDTA = ethylenediaminetetraacetic acid; F = female; M = male; PT = prothrombin time; RBC = red blood count; WBC = white blood count.

TABLE APPENDIX-4 DRUGS: THERAPEUTIC AND TOXIC

			CONVENTIONAL UNITS				INTERNATIONAL UNITS			
			THERAPEUTIC RANGE				THERAPEUTIC RANGE			
DRUG	SPECIMEN	CONDITION	LOW	HIGH	TOXIC if >	UNITS	LOW	HIGH	TOXIC if >	UNITS
Acetaminophen	S/P	4-6 hr after dose	10	30	150	µg/mL	66	199	993	µmol/L
Amikacin	S/P	Peak	20	25	35	µg/mL	34	43	60	µmol/L
		Peak, urinary tract infection and gram-negative infections	25	30	35	µg/mL	45	51	60	µmol/L
		Trough	5	10	10	µg/mL	9	17	17	µmol/L
Amiodarone	S/P		0.5	2.0	2.5	µg/mL	0.7	2.9	3.7	µmol/L
Amitriptyline + nortriptyline	S/P		95	250	500	ng/mL	343	903	1805	nmol/L
Caffeine	S/P		8	20	20	µg/mL	41	103	103	µmol/L
Carbamazepine	S/P		4	12	15	µg/mL	17	51	64	µmol/L
Chloramphenicol	S/P		10	20	25	µg/mL	31	62	77	µmol/L
Chlorpromazine	S/P		30	300	750	ng/mL	94	942	2355	nmol/L
Cyclosporine A	WB	Trough (12 hr after dose)	25	525	700	ng/mL	21	436	581	nmol/L
Diazepam + nordiazepam	S/P		200	2500	3000	ng/mL	0.70	8.78	10.53	µmol/L
Digitoxin	S/P	8-12 hr after dose	10	30	45	ng/mL	13	39	59	nmol/L
Digoxin	S/P	>6 hr after dose	0.8	2.0	2.4	ng/mL	1.0	2.6	3.1	nmol/L
Diphenylhydantoin (see Phenytoin)										
Disopyramide	S/P		2.0	5.0	5.0	µg/mL	5.9	14.8	14.8	µmol/L
Doxepin + nordoxepin	S/P		100	300	500	ng/mL	358	1074	1790	nmol/L
Ephedrine	S/P		35	80	200	ng/mL	0.2	0.5	1.2	µmol/L
Ethanol	S/P	Impairment,			50	mg/mL	11	22		mmol/L
		CNS depression			100	mg/mL			22	mmol/L
		Life-threatening			400	mg/mL			87	mmol/L
Ethosuximide	S/P		40	100	150	µg/mL	283	708	1062	µmol/L
Everolimus	WB		3	8	15	ng/mL	3.0	8.6	16	nmol/L
Flecainide	S/P		0.2	1.0	1.0	µg/mL	0.5	2.0	2.0	µmol/L
Gabapentin	S/P		2	20	25	µg/mL	12.0	117	70	µmol/L
Gentamicin	S/P	Peak	5	10	12	µg/mL	10	21	25	µmol/L
		Trough	0.5	2	2	µg/mL	1	4	4	µmol/L
Haloperidol	S/P		5	17	42	ng/mL	13	45	112	nmol/L
Imatinib	P	GIST or CML	1000	1999	3200	ng/mL	2028	4054	6491	mmol/L
Imipramine + Desipramine	S/P		150	300	400	ng/mL	536	1071	1428	nmol/L
Itraconazole + hydroxyitraconazole	S/P		1.5		10	µg/mL	2		13	µmol/L
Lamotrigine	S/P		2.5	15		µg/mL	9.8	59		µmol/L
Levetiracetam	S/P		12	46		µg/dL	71	270		µmol/L
Lidocaine	S/P	>45 min post-bolus dose	1.2	5.0	9.0	µg/mL	5	21	38	µmol/L
Lithium	S/P	Trough (12 hr post dose)	0.5	1.2	1.6	mEq/L	0.5	1.2	1.6	mmol/L
Methotrexate	S/P	Low dose					0.5	1.0	1.0	µmol/L
		High dose (24 hr post)						5.0	5.0	µmol/L
		High dose (48 hr post)						0.5	0.5	µmol/L
		High dose (72 hr post)						0.1	0.1	µmol/L
Morphine	S/P		10	80	200	ng/mL	35	280	700	nmol/L
Mycophenolate	S/P		1.0	3.5	25	µg/mL	3.1	10.9	78	µmol/L
Nicotine	S/P	Use of or exposure to tobacco/ nicotine products	2.0	10.0		ng/mL	12	62		µmol/L
	Ur		17	700		ng/mL	105	4312		µmol/L

TABLE APPENDIX-4 DRUGS: THERAPEUTIC AND TOXIC—cont'd

			CONVENTIONAL UNITS				INTERNATIONAL UNITS			
			THERAPEUTIC RANGE				THERAPEUTIC RANGE			
DRUG	SPECIMEN	CONDITION	LOW	HIGH	TOXIC if >	UNITS	LOW	HIGH	TOXIC if >	UNITS
Nicotine metabolite (Cotinine)	S/P Ur		8 20	145 8000		ng/mL ng/mL	45 114	824 45440		µmol/L µmol/L
Oxcarbazepine	S/P		3	35	40	µg/mL	12	139	159	µmol/L
Paroxetine	S/P		30	120	120	ng/mL	91	365	365	nmol/L
Perphenazine	S/P	Low dose High dose	0.6 5	2.4 30	50 50	ng/mL ng/mL	2 17	6 75	125 125	µmol/L µmol/L
Phenobarbital	S/P		15	40	50	µg/mL	65	173	216	µmol/L
Phenytoin, total	S/P		10	20	30	µg/mL	40	79	119	µmol/L
Phenytoin, free	S/P		1.0	2.5	2.5	µg/mL	4.0	9.9	9.9	µmol/L
Primidone + phenobarbital	S/P		5	12	15	µg/mL	23	55	69	µmol/L
Procainamide	S/P		4	10	12.1	µg/mL	17	42	51	µmol/L
Procainamide + N-Acetyl (NAPA)	S/P		6	20	35.1	µg/mL	22	72	127	µmol/L
Propranolol	S/P		10	150		ng/mL	39	579		nmol/L
Protriptyline	S/P		70	260	500	ng/mL	266	988	1900	nmol/L
Quinidine	S/P		2	5	6	µg/mL	6	14	19	µmol/L
Salicylates	S/P		20	290	300	µg/mL	145	2103	2175	µmol/L
Sertraline	S/P		30	200	300	ng/mL	98	654	981	nmol/L
Sirolimus (Rapamycin)	WB		4	14	20	ng/mL	4	15	22	nmol/L
Tacrolimus	WB		5	25	25	ng/mL	6	30	30	nmol/L
Theophylline	S/P		8	20	20	µg/mL	44	111	111	µmol/L
Tobramycin	S/P	Peak Trough	5 0	10 2	10 2	µg/mL µg/mL	11 0	21 4	21 4	µmol/L µmol/L
Valproic acid	S/P		50	100	150	µg/mL	347	693	1040	µmol/L
Vancomycin	S/P	Combination therapy Aggressive therapy	10 15	15 20	28 28	µg/mL µg/mL	7 10	10 14	19 19	µmol/L µmol/L
Voriconazole	S/P		1.0	5.5	6.0	µg/mL	2.9	15.7	17.1	µmol/L
Warfarin	S/P		1.0	10	10	µg/mL	3	32	32	µmol/L
Zonisamide	S/P		10	40	80	µg/mL	47	188	376	µmol/L

CNS = central nervous system; CML = chronic myelogenous leukemia; GIST = gastrointestinal stromal tumor; S/P = serum or plasma; Ur = urine; WB = whole blood.

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GUIDE TO THE APPROACH TO COMMON SYMPTOMS, SIGNS, LABORATORY ABNORMALITIES, SCREENING, AND TREATMENTS

	CHAPTER	SPECIFIC TABLES OR FIGURES
SYMPTOMS		
Constitutional		
Poor appetite	118	Table 118-1
Fever	259, 260	Figures 260-1, 260-2, 260-3, 260-4; Tables 259-1, 259-2, 259-3, 259-4, 259-5, 259-6, 259-7
Obesity	201	Figure 201-1; Table 201-4
Snoring, sleep disturbances	374	Figures 374-5, 374-6
Weight loss	118, 200	Figure 118-4; Table 118-4
Head, Eyes, Ears, Nose, Throat		
Headache	367	Tables 367-1, 367-2, 367-3
Visual loss, transient	391, 392	Tables 391-2, 392-1
Ear pain	394	Table 394-8
Hearing loss	396	Figure 396-1
Ringing in ears (tinnitus)	396	Figure 396-2
Vertigo	396	Figure 396-3
Loss of smell or taste	395	Table 395-1
Nasal congestion, rhinitis, or sneezing	394	Figure 394-5; Tables 394-3, 394-5, 394-7
Dry mouth	393	Table 393-7
Hoarseness	397	
Sore throat	397	Tables 397-1, 397-2
Cardiopulmonary		
Cardiac arrest	50	Figures 50-2, 50-3; Table 50-1
Chest pain	39, 123	Tables 39-2, 123-8, 123-9
Cough	71	Figure 71-1; Tables 71-2, 71-3
Dizziness	39, 49, 396	Figure 49-1; Table 396-1
Hemoptysis	71	Figure 71-3; Tables 71-6, 71-7
Palpitations	39, 49	Figure 49-1; Tables 39-4, 49-8
Shortness of breath	39, 71	Figure 71-2; Table 71-5
Syncope	49	Figure 49-1; Tables 49-1, 49-2, 49-3, 49-4, 49-6, 49-7, 49-8
Gastrointestinal		
Abdominal pain		
Acute	118, 128	Figures 118-1, 118-2; Tables 118-2, 118-3, 128-1
Chronic	118, 123	Figure 118-3; Table 118-2
Anal pain	131	
Constipation	122, 123	Figures 122-3, 123-1; Table 122-2
Diarrhea	123, 126	Figures 123-1, 126-1, 126-2, 126-3, 126-4
Dysphagia, odynophagia	118, 124	Table 118-1
Fecal incontinence	131	Figure 131-5
Heartburn/dyspepsia	118, 123, 124, 125	Figures 118-6, 124-2; Tables 123-3, 123-4, 125-1
Hematemesis	121, 139	Figure 121-3; Table 121-1
Melena, blood in stool	121	Figures 121-3, 121-4, 121-6; Table 121-4
Nausea and vomiting	118	Figure 118-5; Table 118-5
Genitourinary		
Dysuria	263, 264	Tables 263-3, 263-5, 264-2
Erectile dysfunction	216	Figure 216-4; Table 216-9
Frequency	263	Table 263-3
Genital ulcers or warts	264	Table 264-1
Hematuria	100	Figure 100-3
Hot flashes	222	Tables 222-3, 222-4
Incontinence	115	Tables 115-1, 115-2, 115-3
Infertility, female	218, 222	Table 218-5
Infertility, male	216	Figures 216-2, 216-3; Table 216-7
Menstrual irregularities	218	Figure 218-3; Tables 218-4, 218-5, 218-6

GUIDE TO THE APPROACH TO COMMON SYMPTOMS, SIGNS, LABORATORY ABNORMALITIES, SCREENING, AND TREATMENTS—cont'd

	CHAPTER	SPECIFIC TABLES OR FIGURES
Polyuria	102	Figure 102-5; Table 102-10
Renal colic	111	Figure 111-1
Scrotal mass	185	Figure 185-1
Vaginal discharge	264	
Musculoskeletal		
Neck pain	369	Figures 369-4, 369-7; Tables 369-3, 369-4
Back pain	369	Figures 369-4, 369-5, 369-6; Tables 369-3, 369-5
Joint pain	236	Figures 236-1, 236-3; Tables 236-1, 236-3
Extremities		
Edema		
Bilateral	39	Figure 39-7
Unilateral	68	Figure 68-2; Table 68-2
Claudication	65	Tables 65-3, 65-4
Limb ischemia (acute)	65	Figure 65-4; Table 65-2
Neurologic		
Gait abnormalities	366	Table 366-2
Memory loss	371	Figures 371-1, 371-2; Tables 371-1, 371-2, 371-3, 371-4, 371-5, 371-6, 371-7, 371-8
Seizures	372	Tables 372-1, 372-2, 372-3, 372-4, 372-5, 372-6
Sensory loss	366, 388	Figure 388-1; Tables 388-1, 388-3
Weakness	366, 388, 389, 390	Tables 366-1, 388-2, 389-1, 389-2, 389-4
Integumentary		
Alopecia	409	Tables 409-1, 409-3
Bleeding abnormalities	157	Tables 157-1, 157-2, 157-3
Hirsutism	409	
Hives	232, 407	Figure 232-2; Tables 232-1, 407-1, 407-2
Nail disorders	409	Table 409-4
Pigmentation abnormalities	408	Table 408-2
Rash	259, 403, 408	Figure 403-1; Tables 259-2, 403-1, 403-2, 403-3, 403-4, 403-5, 403-6, 403-8, 408-5
SIGNS		
Vital Signs		
Abnormal vital signs	7	Tables 7-1, 7-2, 7-3
Fever	259, 260	Figures 260-1, 260-2, 260-3, 260-4; Tables 259-1, 259-2, 259-3, 259-4, 259-5, 259-6, 259-7, 260-2
Heat illness/hyperthermia	95	Tables 95-1, 95-2, 95-3
Hypothermia	7, 95	Tables 95-4, 95-5, 95-6
Bradycardia	7, 49, 51	Figures 49-2, 49-3; Tables 51-1, 51-2, 51-3
Tachycardia	7, 49, 52, 53	Figures 49-2, 49-3; Tables 52-1, 52-2, 52-3, 53-2
Hypertension	64	Tables 64-4, 64-5, 64-6, 64-7, 64-8, 64-9, 64-10, 64-11, 64-12
Hypotension/shock	7, 92	Figures 92-1, 92-2, 92-3, 93-2, 94-1; Tables 92-1, 93-1, 93-2, 93-3
Respiration alteration	7, 74, 90	Tables 74-1, 74-2, 90-2
Head, Eyes, Ears, Nose, Throat		
Eye pain	391	Table 391-3
Jaundice	133	Figure 133-1; Tables 133-1, 133-2, 133-3
Nystagmus	392	Table 392-4
Papilledema	391, 392	Figure 391-25; Table 392-2
Pupillary dilatation	392	Figure 392-4
Red eye	391	Tables 391-4, 391-6
Strabismus	392	Figure 392-6
Rhinitis	394	Tables 394-1, 394-3
Sinusitis	394	Tables 394-2, 394-4, 394-5
Oral ulcers and discolorations	393	Tables 393-1, 393-2, 393-3, 393-4
Salivary gland enlargement	393	Table 393-6

GUIDE TO THE APPROACH TO COMMON SYMPTOMS, SIGNS, LABORATORY ABNORMALITIES, SCREENING, AND TREATMENTS—cont'd

	CHAPTER	SPECIFIC TABLES OR FIGURES
Neck		
Lymphadenopathy	154	Tables 154-1, 154-2, 154-3, 154-4
Neck mass	176	Figure 176-2
Thyroid nodule	207	Figure 207-5
Thyromegaly/goiter	207	Figures 207-1, 207-3
Breast		
Breast mass	183	
Lungs		
Wheezes	71	Table 71-4
Cardiac		
Carotid pulse abnormalities	39	Figure 39-4
Heart murmur or extra sounds	39	Figure 39-5; Tables 39-7, 39-8
Jugular venous distention	39	Table 39-6
Abdomen		
Abdominal swelling/ascites	128, 139	Table 139-3
Acute abdomen	118, 128	Figure 118-2; Table 128-1
Hemorrhoids	131	Figures 131-1, 131-2; Table 131-1
Hepatomegaly	132	Figure 132-5
Rectal bleeding/positive stool	121, 179	Figures 121-3, 121-4, 121-6; Table 121-4
Splenomegaly	154	Table 154-5
Musculoskeletal/Extremities		
Arthritis	236	Figures 236-1, 236-2; Table 236-3
Clubbing	39, 254	Figures 39-9, 254-1
Cyanosis	39, 66	Figures 39-8, 66-12
Edema	39	Figure 39-7
Raynaud phenomenon	66	Figure 66-9
Neurologic		
Autism spectrum	385	Table 385-1
Coma	373	Tables 373-1, 373-2, 373-3, 373-4, 373-5, 373-6
Delirium	361	Figure 361-1; Tables 361-1, 361-2, 361-3
Movement disorders	378, 379	Tables 378-1, 378-2, 378-3, 378-4, 379-1, 379-2, 379-3, 379-4, 379-5, 379-6, 379-7, 379-8
Neuropathy	388	Figure 388-1; Tables 388-1, 388-2, 388-3, 388-4
Psychiatric disturbances	362	Tables 362-1, 362-2, 362-3, 362-4, 362-5, 362-6, 362-7, 362-8, 362-9, 362-10, 362-11, 362-12, 362-13, 362-14
Stroke	376, 377	Figure 376-1; Tables 376-2, 376-5, 376-6, 377-5, 377-6
Skin and Nails		
Mole	188	Table 188-1
Nail diseases	409	Table 409-4
COMMON LABORATORY ABNORMALITIES		
Hematology/Urinalysis		
Anemia	144	Figure 144-3; Tables 144-2, 144-3, 144-4, 144-5, 144-6, 144-7, 144-8, 144-9
Eosinophilia	156	Figure 156-1; Tables 156-1, 156-2
Leukocytosis	153	Figure 153-4; Table 153-1
Lymphocytosis	153	Table 153-3
Monocytosis	153	Table 153-2
Neutropenia	153	Figure 153-7; Tables 153-4 and 153-5
Neutropenia with fever	260	Figures 260-1, 260-2, 260-3, 260-4
Polycythemia	152	Table 152-4
PT or PTT prolongation	157	Figure 157-4
Thrombocytopenia	158	Figure 158-1; Tables 158-1, 158-3
Thrombocytosis	152	Table 152-5
Urinalysis	100, 106	Figure 100-3; Tables 100-2, 106-5

GUIDE TO THE APPROACH TO COMMON SYMPTOMS, SIGNS, LABORATORY ABNORMALITIES, SCREENING, AND TREATMENTS—cont'd

	CHAPTER	SPECIFIC TABLES OR FIGURES
Chemistries		
Acid-base disturbances	104	Figures 104-1, 104-2, 104-3; Tables 104-1, 104-2, 104-3, 104-4, 104-5, 104-6, 104-7
BUN/creatinine elevation		
Acute	106	Figure 106-1; Tables 106-1, 106-2, 106-3, 106-4, 106-5, 106-6
Chronic	116	Table 116-1
Hypercalcemia	227	Figure 227-2; Tables 227-2, 227-3, 227-4
Hyperglycemia	210	Tables 210-1, 210-2
Hypocalcemia	227	Figure 227-3; Table 227-6
Hypoglycemia	211	Figure 211-3; Tables 211-1, 211-2
Hypo- and hyperkalemia	103	Figure 103-3; Tables 103-2, 103-3
Hypo- and hypernatremia	102	Figure 102-3; Tables 102-5, 102-6, 102-7, 102-8, 102-9
Hypo- and hyperphosphatemia	105	Figures 105-1, 105-2; Tables 105-2, 105-3
Hypo- and hyperthyroidism	207	Figures 207-1, 207-3; Tables 207-1, 207-2, 207-3
Liver enzymes	133	Figures 133-1, 133-2, 133-3; Tables 133-1, 133-3
Magnesium deficiency	105	Table 105-1
Pco_2 elevation	74	Figure 74-2
ECG/Chest Radiograph		
ECG abnormalities	42	Tables 42-2, 42-3, 42-4, 42-5
Incidental masses		
Adrenal incidentaloma	208	
Hepatic mass	132	Figure 132-6
Mediastinal mass	86	Table 86-6
Renal mass	182	
Pleural effusion	86	Tables 86-3, 86-4, 86-5
Solitary pulmonary nodule	177	Figure 177-2

BUN = blood urea nitrogen; ECG = electrocardiogram; PT = prothrombin time; PTT = partial thromboplastin time.

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INDEX

Page numbers followed by "*f*" indicate figures, "*t*" indicate tables, and "*b*" indicate boxes.

A

AA amyloid, 788
AA (secondary) amyloidosis, 1306*t*
AB2 M variant amyloidosis, 1306*t*
AB2 M wild-type (dialysis-related) amyloidosis, 1306*t*
Abacavir, 2301*t*, 2319
Abaloparatide, for osteoporosis, 1643*b*–1646*b*, 1644*t*
Abatacept (Orencia)
  for rheumatoid arthritis, 1756*t*–1757*t*
  for total knee arthroplasty, 1830.*e*1*t*
Abciximab, 375*t*, 387*t*
Abdominal abscess, abdominal pain and, 854*t*
Abdominal actinomycosis, 2068
Abdominal aortic aneurysm
  clinical manifestations of, 436
  diagnosis of, 437–438, 438*f*
  epidemiology of, 436
  risk factors for, 436
  screening for, 53
  treatment of, 438*b*, 438.*e*1*f*
Abdominal compartment syndrome, 700*b*–703*b*
Abdominal distention, with ascites, 988
Abdominal emergencies, acute, characteristics of, 2270*t*
Abdominal examination, 31, 258
  in cardiovascular disease, 215
  in gastrointestinal disease, 851
  in liver disease, 988
Abdominal imaging, for liver disease, 990
Abdominal injuries, 700*b*, 701*f*
Abdominal pain, 854–858
  acute, 854–858
    clinical manifestations of, 854–857, 854*t*
    diagnosis of, 857–858, 858*f*
    history of, 854–857
    in hospital, 857
    imaging for, 857–858
    location of, 856, 856*f*
    physical examination for, 857, 857*t*
    special populations of, 857
    treatment of, 858*b*
  acute pancreatitis and, 969–970, 970
  chronic, 858, 859*f*
  chronic pancreatitis and, 974
  colon ischemia and, 964
  liver disease and, 986, 989*t*
  pathobiology of, 854
  from peptic ulcer, 1562–1563
  signs and symptoms of, approach to, 852*t*
Abdominal radiographs, description of, 866, 866*f*–868*f*, 867*f*, 868*f*
Abdominal ultrasonography, for acute pancreatitis, 971
Abelson *(ABL)* gene, 1272, 1273*f*
Abemaciclib, for breast cancer, 1369*b*–1373*b*
Abetalipoproteinemia, 939
Abiraterone acetate (Zytiga), 1215*t*
Ablation, for hepatocellular carcinoma, 1360*b*–1362*b*
Abnormal automaticity, 301
Abnormal thyroid function, 265*b*–278*b*
Abnormal uterine bleeding, 1597–1598, 1597*b*–1598*b*
ABO antigens, 205
Abortion, medical, 1617
  description of, 1610
  Paeniclostridium sordellii associated with, 1927
Abraxane. *See* Paclitaxel, protein bound
ABri amyloidosis, 1306*t*
Abscess
  amebic liver, 1022*t*, 1024–1025, 1025*b*, 1025*f*
  brain. *See* Brain abscess
  in Crohn disease, 945*b*–950*b*
Abscess *(Continued)*
  dental, pathogens and empirical therapy for, 2526*t*
  perianal, 978–979, 979*b*
  spinal epidural, 2527–2528, 2527*f*, 2527.*e*1*t*, 2528*b*
  subdural, 2528*f*
  temporal lobe, 2525
Absence seizures, 2428*t*, 2429–2430
Absolute hypovolemia, 735*b*, 735*t*
Absolute intensity, 61, 62*t*
Absolute refractoriness, 300
Absolute reticulocyte count, 1076*t*–1077*t*, 1076*t*
Absolute scarcity, 9
Abstainers, 2353
Abt-Letterer-Siwe disease, 1155
Abuse
  alcohol, 2353
  drugs of, 143
  in older adults, 118
Abused patient, management of, 1634*b*–1635*b*
Abusive patient, management of, 1634*b*
Acalabrutinib (Calquence), 1215*t*
  for chronic lymphocytic leukemia, 1269*t*–1270*t*, 1270*t*
Acamprosate
  for alcohol-associated liver disease, 1032*b*
  for alcohol use disorders, 2357*b*–2359*b*, 2358*t*–2359*t*
Acanthamoeba, 2150, 2150*t*
Acanthocytes, 1072*t*, 1074*t*
Acanthosis, 2241
Acanthosis nigricans, 987–988, 1239, 2745, 2746*f*, 2746*t*
Acarbose
  for orthostatic hypotension, 2559*t*
  for type 2 diabetes mellitus, 1541*t*
Accelerated gastric emptying, 890
Accelerated osteopenia, in liver disease, 987
Accessory pathway tachycardias, 324*f*, 326, 326*b*, 328*f*
Accidental infection, 2238
Accidents
  radiologic, 92, 92*t*
  "Swiss cheese" model of, 45
Accountability, medical profession, 4–5
Accutane. *See* Isotretinoin
ACE. *See* Angiotensin-converting enzyme
Acebutolol, 451*t*
Acetaminophen, *e*10*t*–*e*11*t*
  adverse reactions of, 132
  in blood pressure, 455
  for chronic pain, 138*t*
  toxicity, 686*t*, 690*t*, 1018, 1018.*e*1*f*
  for varicella, 2249*b*
Acetazolamide
  for action myoclonus, 2495*b*
  for altitude illness, 1889
  for Andersen-Tawil syndrome, 2585
  for high-altitude diseases, 593*t*
  for hypervolemia, 736*b*–737*b*
  for hypokalemia, 749, 749*t*, 752*b*
  for salicylate intoxication, 759
Acetoacetate, semiquantitative, *e*1*t*–*e*8*t*
Acetone, quantitative, *e*1*t*–*e*8*t*
Acetylcholine, 143, 2553
Acetylcholinesterase inhibitors, for Parkinson disease, 2487*t*
Acetylsalicylic acid
  for chronic pain, 138*t*
  pharmacokinetic parameters for, 127.*e*1*t*
Achalasia, 908, 908*b*, 908*f*, 908.*e*1*f*, 1337–1338
Achilles tendinosis, 1747–1749, 1748*b*
Achilles tendon rupture, 1748, 1748*b*
Achondroplasia, 1669–1670
Acid-base balance, kidney in, 754, 754.*e*1*f*
Acid-base disorders, 752–765
  clinical manifestations of, 755–756
  definition of, 752–756
  diagnosis of, 755, 755*f*, 756*t*
  epidemiology of, 752, 753*t*
  metabolic acidosis as, 756–762
  metabolic alkalosis as, 762–764
  pathobiology of, 752–755
  respiratory acidosis as, 765
  respiratory alkalosis as, 765
Acid maltase deficiency, 2586
Acid peptic disease, 913–923. *See also* Peptic ulcer
  anatomic diagnosis of, 917–918
  clinical manifestations of, 917
  definition of, 913–923
  diagnosis of, 917–919, 918*t*
  etiologic diagnosis of, 918–919
  Helicobacter pylori-associated, 920*f*
  hypersecretory syndromes causing, 918–919
  pathobiology of, 914–917
  physical examination of, 917
  prognosis for, 923
Acidemia, 752, 755*f*
Acidosis
  distal renal tubular, 749*t*
  hyperchloremic, 752*b*
  hypochlorhydric, 760
  lactic. *See* Lactic acidosis
  metabolic. *See* Metabolic acidosis
  respiratory. *See* Respiratory acidosis
  uremic, 757
Aciduria
  argininosuccinic, 1398*t*, 1402*t*
  glutaric, type I, 1398*t*, 1403*t*
  isobutyric, 1403*t*
  isovaleric, 1403*t*
  methylmalonic, 1398*t*, 1403, 1403*t*
  mevalonic, 1403*t*
  organic, 1403, 1403*f*, 1403*t*, 1404*b*
  propionic, 1398*t*, 1403, 1403*t*
Acinetobacter albensis, 1973.*e*3*t*
Acinetobacter apis, 1973.*e*3*t*
Acinetobacter baumannii, 1864*t*, 1973.*e*3*t*
Acinetobacter baylyi, 1973.*e*3*t*
Acinetobacter beijerinckii, 1973.*e*3*t*
Acinetobacter bereziniae, 1973.*e*3*t*
Acinetobacter bohemicus, 1973.*e*3*t*
Acinetobacter bouvetii, 1973.*e*3*t*
Acinetobacter calcoaceticus, 1973.*e*3*t*
Acinetobacter colistiniresistens, 1973.*e*3*t*
Acinetobacter courvalinii, 1973.*e*3*t*
Acinetobacter disperses, 1973.*e*3*t*
Acinetobacter genomospecies 6, 1973.*e*3*t*
Acinetobacter genomospecies 15BJ, 1973.*e*3*t*
Acinetobacter genomospecies 16BJ, 1973.*e*3*t*
Acinetobacter gerneri, 1973.*e*3*t*
Acinetobacter guillouiae, 1973.*e*3*t*
Acinetobacter haemolyticus, 1973.*e*3*t*
Acinetobacter johnsonii, 1973.*e*3*t*
Acinetobacter junii, 1973.*e*3*t*
Acinetobacter lwoffii, 1973.*e*3*t*
Acinetobacter nosocomialis, 1973.*e*3*t*
Acinetobacter parvus, 1973.*e*3*t*
Acinetobacter pittii, 1973.*e*3*t*
Acinetobacter radioresistens, 1973.*e*3*t*
Acinetobacter schindleri, 1973.*e*3*t*
Acinetobacter seifert, 1973.*e*3*t*
Acinetobacter spp., 1973–1975
  bacteremia caused by, 1973
  burn infection caused by, 1973
  clinical manifestations of, 1973–1974
  definition of, 1973
  diagnosis of, 1974
Acinetobacter spp. *(Continued)*
  epidemiology of, 1973
  pathobiology of, 1973
  pathogen causing, 1973, 1973.*e*3*t*
  prevention of, 1974
  prognosis of, 1974–1975
  representative members of, 1973.*e*3*t*
  skin and soft tissue infections caused by, 1973, 1974*f*
  treatment of, 1974*b*
  urinary tract infection caused by, 1973
  wound infection caused by, 1973
Acinetobacter tandoii, 1973.*e*3*t*
Acinetobacter tjernbergiae, 1973.*e*3*t*
Acinetobacter townerii, 1973.*e*3*t*
Acinetobacter ursingii, 1973.*e*3*t*
Acinetobacter variabilis, 1973.*e*3*t*
Acinetobacter venetianus, 1973.*e*3*t*
ACIP. *See* Advisory Committee on Immunization Practices
ACKD. *See* Acquired cystic kidney disease
Aclidinium bromide, 553*t*
ACLS. *See* Advanced cardiac life support
Acne, in women, medications for, 1608*t*
Acne keloidalis, 2744, 2745*f*
Acne vulgaris, 2722, 2722*b*, 2745*f*–2746*f*
Acoustic neuroma, 1312*b*–1313*b*, 2642
ACPA. *See* Anti-citrullinated peptide antibodies
Acquired angioedema
  clinical manifestations of, 1688*f*, 1690
  epidemiology of, 1690
  pathobiology of, 1690
  treatment and prevention of, 1690*b*–1691*b*
Acquired cystic kidney disease (ACKD), 808, 809*t*, 815, 815*b*
Acquired cystic lung diseases, 565
Acquired factor V deficiency, 1193
Acquired hemophilias, 1191, 1191*b*
Acquired hypogonadotropic disorders, 1584
Acquired hypoventilation syndrome, 536–537
  clinical manifestations of, 536–537, 537*f*
  definition of, 536
  epidemiology of, 535*t*, 536
  pathobiology of, 536
  prognosis for, 536*b*
  treatment of, 536*b*
Acquired immunodeficiency syndrome (AIDS). *See also* Human immunodeficiency virus
  candidiasis in, 2089
  cryptococcosis associated with, 2087
  cytomegalovirus in, 2251–2252
  epidemiology and diagnosis of, 2286–2291
  Hodgkin lymphoma and, 1292*b*–1293*b*
  immunization for, 65*t*–66*t*
  non-Hodgkin lymphoma and, 1287, 1287*b*
Acquired neuromyotonia, 2589*t*
Acquired platelet dysfunction, 1185, 1185*b*–1186*b*, 1185*t*
Acquired resistance, in Enterobacterales, 1965, 1966*t*
Acquired rhabdomyolysis, 714*t*, 715
Acquired von Willebrand disease, 1184, 1184*b*
Acral gangrene, plague and, 1991, 1991*f*
Acral lentiginous melanoma, 1391
Acrocyanosis, 474–475, 475*b*, 475*f*
Acrodermatitis chronica atrophicans, 2023, 2023*f*, 2025
Acrodermatitis verruciformis, 2729
Acrodynia, 103
Acrokeratosis neoplastica. *See* Bazex syndrome
Acromegaly, 1489–1490, 1489*b*–1490*b*, 1490*f*, 1823
Acroparesthesia, 1422
Acrylates, 88*t*

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Actemra. *See* Tocilizumab
ACTH. *See* Adrenocorticotropic hormone
ACTHoma, 1561*t*, 1566
Actigraphy, 2447*f*
Actinic keratoses, 2729, 2729*b*, 2730*f*
Actinobacillus actinomycetemcomitans, 2068
Actinomyces spp., 2066–2067
Actinomycetoma, 2110
Actinomycosis, 2066–2069, 2621*t*
  abdominal, 2068
  central nervous system infections and, 2068
  cervicofacial, 2067, 2067*f*
  clinical manifestations of, 2067–2068
  definition of, 2066–2069
  diagnosis of, 2068–2069
  epidemiology of, 2067
  pathobiology of, 2067
  pathogen that causes, 2066–2067
  pelvic, 2068
  prognosis of, 2069
  thoracic, 2067–2068, 2068*f*
  treatment for, 2069*b*
Action potential, 298–299
  cardiac, 223, 223*f*, 299–300, 299*f*, 333.e1*f*
  premature, 333.e1*f*
Action potential duration adaptation, 300
Action tremors, 2489
Actionability, of drugs, 167
Activated charcoal, for acute poisoning, 691*b*–693*b*
Activated partial thromboplastin time (APTT), *e8t*–*e9t*, 1166–1167, 1169, 1169*f*, 1195
Activated protein C resistance, 476
Activating *Kit* mutations, 1693
Activator protein-1 (AP1), 144
Active immunization, 64
Active myocarditis, 284–285
Active surveillance testing, for health care-associated infections, 1867–1868
Active tuberculosis, 2039–2040, 2040*b*–2043*b*
Activia, for irritable bowel syndrome, 896*t*
Activin, 1477
Activities of daily living (ADLs), 117
Acupuncture, 154
Acute abdominal emergencies, characteristics of, 2270*t*
Acute abdominal pain, 854
  clinical manifestations of, 854, 854*t*
  diagnosis of, 857, 858*f*
  history of, 854
  in hospital, 857
  imaging for, 857
  location of, 856, 856*f*
  physical examination for, 857, 857*t*
  special populations of, 857
  treatment of, 858*b*
Acute acalculous cholecystitis, 1053
Acute adrenal insufficiency, 1527, 1528*b*
Acute allograft rejection, 1049.e1*f*
Acute angle-closure glaucoma, 2608, 2608*f*
Acute aortic dissection
  diagnosis of, 440–441, 440*f*–441*f*
  evaluation for, 440*f*–441*f*
  high-risk characteristics for, 440*t*
  incidence of, 439
  management pathway for, 442*f*
  pathobiology of, 439
  prognosis of, 442.e1*f*, 443
  TEE findings, 440*f*
  type A, 441*b*–442*b*
  type B, 441*b*
Acute aortic regurgitation, 409
Acute aortic syndromes, 439–443, 439*f*
Acute bacterial prostatitis, treatment of, 825*b*
Acute bronchitis, 605–606, 605.e2*f*, 606*b*
Acute calcific periarthritis, 1815
Acute calculous cholecystitis
  clinical manifestations of, 1050, 1051*f*
  complications of, 1053
  pathobiology of, 1050
  treatment of, 1052*b*
Acute chest syndrome, in sickle cell disease, 1113
Acute cholecystitis, ultrasound of, 869*f*–870*f*
Acute compartment syndrome, causing envenomation, 705*b*–706*b*
Acute coronary syndrome, 370–380
  antiplatelet therapy for, 507
  clinical manifestations of, 371
  complications of, 374*t*–375*t*
  definition of, 370–380, 371*f*
  diagnosis of, 372–378
  differential diagnosis of, 373–378
Acute coronary syndrome *(Continued)*
  ECG findings, 372
  epidemiology of, 370
  initial treatment strategy, 378*t*
  integrated approach to, 374*t*
  non-ST elevation, 379*f*
  noninvasive testing for, 372
  pathobiology of, 370–371
  prognosis for, 378–380
  risk assessment in, 372, 373*f*, 375*t*
  risk score calculator in, 384.e1*f*
  serum biomarkers, 372
  symptoms, 371
  treatment of
    antianginal therapy, 374*t*
    strategies for, 375*t*
  triage for, 372, 373*f*
Acute cough, 512, 513*t*
Acute decompensated heart failure, 255, 255*t*
Acute dental infections, 2627
Acute diarrhea, 924–928
  clinical manifestations of, 924–928
  definition of, 923
  diagnosis of, 926, 927*f*
  epidemiology of, 925*t*
  prevention of, 928
  treatment of, 926*b*–927*b*
Acute disseminated encephalomyelitis, 2405, 2509
  Mycoplasma pneumoniae in, 2007
Acute dystonic reactions, 2495
Acute encephalitis, 2221
Acute exacerbation of COPD, in hypercapnic disease, 535*t*
Acute fatty liver, 998
  of pregnancy, 1625*t*, 1626, 1627*b*, 1627*t*
Acute febrile illness, 2030
Acute febrile neutrophilic dermatosis, 1857
Acute febrile syndrome, 590, 591*t*, 1869*t*
  clinical manifestations of, 590
  diagnosis of, 590
  treatment for, 591*b*
Acute fever, 2694*t*
Acute flaccid myelitis, 2258, 2258*b*
Acute flaccid paralysis, 1928, 2258, 2258*b*
Acute gallstone pancreatitis, 1055*b*
Acute generalized exanthematous pustulosis (AGEP), 2689*t*, 2722, 2723*f*, 2728
Acute glaucoma, characteristics of, 2270*t*
Acute glomerulonephritis, 783
Acute gouty arthritis, 1812*f*
Acute hemolytic transfusion reaction, 1201, 1202*b*
Acute hemorrhagic conjunctivitis, enteroviruses causing, 2260, 2260*b*
Acute hemorrhagic stroke, in sickle cell disease, 1113
Acute hepatic porphyrias, 1429, 1432
Acute hyperglycemic states, 1547–1549
  clinical manifestations of, 1547
  diagnosis of, 1547–1548
  epidemiology of, 1547
  pathobiology of, 1547, 1547*t*
  prevention of, 1549
  prognosis of, 1549
  treatment for, 1548*b*
Acute hypocalcemia, 1659*b*–1660*b*
Acute idiopathic interstitial pneumonias, 571*t*, 578–579
Acute infection, Whipple disease and, 2070
Acute injuries, occupational and environmental, 85–87, 86*t*
Acute intermittent porphyria (AIP), 1428*t*
Acute interstitial nephritis, 771, 771*t*
  biopsy of, 792, 792*t*, 793*f*
  causes of, 790*t*
  characteristics of, 790
  clinical manifestations of, 792–793, 792*t*
  diagnosis of, 792
  differential diagnosis of, 792
  drugs that cause, 790
  epidemiology of, 790
  granuloma formation in, 792
  prognosis for, 793
  proteinuria in, 792
  treatment of, 792*b*
Acute interstitial pneumonia, 566*t*, 567–568, 574*t*, 578, 579*f*
  clinical manifestations of, 568, 568*f*, 568.e1*f*
  definition of, 567–568
  diagnosis of, 568
  pathobiology of, 568
  treatment for, 568*b*
Acute ischemic stroke
  fibrinolytic therapy for, 509
  radiographic changes of, 2373–2374, 2373.e1*f*
  in sickle cell disease, 1113
Acute kidney injury (AKI), 725–726, 770–775
  categories of, 770*f*
  clinical manifestations of, 773
  critical care for, 636
  definition of, 770–775, 770*t*
  diagnosis of, 725–726, 773–774, 774*t*
  epidemiology of, 770–772
  imaging of, 726, 726*f*–727*f*
  intrarenal, 771*t*, 773–774
  intrinsic, 770–771, 771*t*
  laboratory testing of, 725–726
  pathobiology of, 772–773, 772*f*
  phases of, 775*f*
  postrenal, 771–774, 774
  prerenal, 772–773, 772*t*
  prevention of, 775
  prognosis of, 775
  rhabdomyolysis-induced, 717, 717*t*
  serum creatinine in, rapid resolution of, 771*f*
  in setting of SARS-CoV-2, 773
  in sickle cell disease, 1114
  treatment of, 774*b*–775*b*
  vascular disease in, 773
Acute leukemias, 1259–1266
  of ambiguous lineage, 1260*t*, 1261
  classification of, 1260, 1260*t*
  clinical manifestations of, 1262
  clonality and cell of origin of, 1260
  cytogenetics and molecular biology of, 1261–1262
  definition of, 1259–1266
  determinants of, 1259
    chemicals and drugs, 1259
    genetic predisposition, 1259
    oncogenic viruses, 1259
    radiation, 1259
  diagnosis of, 1260*f*, 1261*t*, 1262–1266
  differential diagnosis of, 1262–1266
  epidemiology of, 1259
  immunophenotyping of, 1260–1261
  incidence of, 1259
  management of complications of, 1262*b*–1266*b*
  morphology of, 1260, 1260*f*
  pathobiology of, 1260–1262
  treatment and prognosis of, 1262*b*, 1263*t*
Acute limb ischemia
  clinical categories of, 462*t*
  clinical manifestations of, 462
  diagnosis of, 462–463
  pathobiology of, 461–462
  treatment of, 464*b*–465*b*, 465*f*
Acute liver failure, liver transplantation for, 1044–1045
Acute lung injury, transfusion-related, 1200
Acute lymphoblastic leukemia (ALL), 1260*f*
  in adolescents, 111
  B-cell, 1260*t*
  Burkitt-like, 1262*b*
  cytogenetics and molecular biology of, 1262
  hematopoietic cell transplantation for, 1208
  immunophenotyping of, 1261
  morphology of, 1260
  mutations in, 1262
  peripheral blood smear of, 1073, 1073*f*–1074*f*
  Philadelphia chromosome-negative, 1263*t*
  Philadelphia chromosome-positive, 1262*b*
  prognosis of, 1262*b*, 1264*f*
  translocation in, 1262
  treatment of, 1262*b*, 1263*t*
Acute malnutrition, 1444, 1445.e1*f*, 1446*t*
Acute medical therapy, for aortic dissection, 443*t*
Acute mesenteric arterial occlusive disease, 960
Acute mesenteric ischemia, 959
  clinical manifestations of, 959
  diagnosis of, 960, 960*f*
  prognosis of, 960
  superior mesenteric artery embolism, 962, 962.e1*f*
  superior mesenteric artery thrombosis, 960
  treatment of, 960*b*, 961*f*
Acute motor axonal neuropathy (AMAN), 2564*t*
Acute motor sensory axonal neuropathy, 2571
Acute mountain sickness, 592*t*, 593*b*
Acute myeloid leukemia (AML), 1260*f*, 1260*t*
  cytogenetics and molecular biology of, 1261–1262
  mutations, 1261–1262, 1261*t*
Acute myeloid leukemia (AML) *(Continued)*
  translocations, 1261
  hematopoietic cell transplantation for, 1208–1209
  Hodgkin lymphoma and, 1292*b*
  immunophenotyping of, 1260–1261
  morphology of, 1260
  prognosis of, 1262*b*
  treatment of, 1262*b*, 1264*t*
Acute myocardial infarction, 395
  acute hospital phase, 384*b*–392*b*
  antiplatelet therapy for, 507
  causes of, 381*t*
  clinical manifestations of, 334–335
  coronary angioplasty for, 397*f*
  definition of, 380–392
  diagnosis of, 381–384
  early acute phase, 382
  echocardiographic findings, 242*t*
  electrocardiography in, 382–383, 382*f*
  evolved acute phase, 382–383
  hemodynamic subsets of, 389*t*
  pathobiology of, 380–381
  physical examination in, 381
  in presence of bundle branch block, 383
  ST-elevation, 380–393
    antiplatelet therapy for, 384*b*, 387*f*
    CABG for, 398
    clinical manifestations of, 381
    conditions that can mimic, 383*t*
    coronary intensive care for, 384*b*
    diagnosis of, 381
    differential diagnosis of, 383
    discharge, 384*b*
    echocardiography in, 384
    emergency department care for, 384*b*
    epidemiology of, 380–381
    general medical management of, 384*b*
    history in, 381
    hospital care for, 384*b*
    imaging in, 384
    late hospital phase, 384*b*
    management of complications of, 384*b*
    mechanical complications of, 384*b*
    patient education for, 384*b*
    physical examination in, 381
    post-hospital phase, 384*b*
    prehospital phase, 384*b*
    prognosis for, 392
    rehabilitation after, 384*b*
    reperfusion therapy for, 384*b*, 385*f*
    sample admission orders for, 388*t*
    secondary prevention of, 384*b*
    selection of ICD for, 389*f*
    thromboembolic complications of, 384*b*
    treatment of, 384*b*
Acute myopericarditis, 285*f*
Acute neurologic disorders, diagnosis and treatment of, 2369
Acute normovolemic hemodilution, 1205
Acute pain, 135, 1113
Acute pancreatitis, 969–973
  alcohol and, 969–970
  causes of, 970*t*
  clinical manifestations of, 970
  complications of, 972*t*
  definition of, 969
  determining severity of, 971–972, 972*f*
  diagnosis of, 970–972
  drugs, toxins, and metabolic factors, 970
  epidemiology of, 969
  etiology of, 971
  gallstones and, 969
  genetics of, 970
  imaging studies for, 971, 971*f*–972*f*
  infections and, 970
  laboratory tests for, 971
  pancreatic duct obstruction and, 970
  pathobiology of, 969–970
  prognosis of, 973
  risk stratification of, 972
  systemic complications of, 972*t*
  trauma and, 970
  treatment for, 972*b*–973*b*
Acute pericarditis, 423–425
  cardiac magnetic resonance image of, 427*f*
  clinical manifestations of, 423
  diagnosis of, 423
  diagnostic tests for, 425*t*
  electrocardiogram for, 426*f*
  epidemiology of, 423–425
  pathobiology of, 423

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Acute pericarditis *(Continued)*
prognosis for, 425
treatment of, 424*b*–425*b*
Acute peripheral vestibulopathy, 2644–2645
Acute phase response, 1712
Acute poisoning, 682–698
antidotes for, 691*b*, 693*t*
blood tests for, 690–691
cardiopulmonary effects of, 684
decontamination of, 691*b*
dermatologic signs of, 685
diagnosis of, 682–691
diagnostic tests for, 685–691, 689*t*–690*t*
elimination of, 691*b*
epidemiology of, 682–698
gastrointestinal effects of, 684–685
history of, 682
imaging for, 691
neurologic signs of, 683–684, 685*t*
physical examination for, 682–685, 683*t*
specific toxicants in, 685, 686*t*
stabilization of, initial, 691*b*
treatment of, 691*b*, 692*f*
vital signs for, 682–683
Acute progressive multiple sclerosis, 2501
Acute promyelocytic leukemia, 1262*b*, 1263*t*
Acute pulmonary edema, 273*f*
Acute radiation injury, 956
Acute radiation syndromes, 93, 94*f*
Acute radicular pain, 2398
Acute rejection, in renal transplantation, 845
Acute respiratory distress syndrome (ARDS), 591, 650–652, 700*b*
clinical manifestations of, 651
definition of, 650, 650*t*
diagnosis of, 651, 651*t*
disorders associated with, 650*t*
epidemiology of, 650
influenza and, 2200
mechanical ventilation for, 655–656
pathobiology of, 650–651
pathology of, 650
pathophysiology of, 651
prognosis of, 651–652
treatment of, 651*b*, 652*t*
Acute respiratory failure, 642–652
acute respiratory distress syndrome as, 650
chronic obstructive pulmonary disease as, 649–650
clinical evaluation of, 645, 645*t*
clinical manifestations of, 644
definition of, 642–645, 642*t*
diagnosis of, 643*t*, 644–645
pathobiology of, 642–644, 643*t*
pathophysiology of, 643–644, 644*f*
physiologic abnormalities in, assessment of, 645
treatment of, 647*b*–649*b*, 648*f*
without lung disease, 643*t*, 652
Acute respiratory tract infections, *Pseudomonas* infections causing, 1969
Acute retroviral syndrome, 2295
Acute rheumatic fever, *Streptococcus pyogenes* causing, 1917, 1917*b*, 1917*t*
Acute sarcoid arthritis, 602
Acute severe asthma, in hypercapnic disease, 535*t*
Acute sigmoid diverticulitis, with abscess, computed tomography of, 870*f*
Acute sinusitis, aspergillosis and, 2094
Acute spinal cord compression, 2369
Acute stress disorder, 2340*t*, 2344–2345, 2345*b*
Acute subdural hematoma, 2390
clinical manifestations of, 2391
diagnosis of, 2386*t*, 2387*f*, 2391
epidemiology of, 2390
pathobiology of, 2390
prognosis of, 2391*b*
treatment of, 2391*b*
Acute symptomatic hyponatremia, 741*b*–742*b*
Acute symptomatic seizures, 2434*b*–2436*b*
Acute telogen effluvium, 2748, 2748*b*, 2748*t*
Acute thyroiditis. *See* Infectious thyroiditis
Acute tubular injury (ATI), 773
Acute tubular necrosis (ATN), 773
Acute urticaria, 1674, 1687, 1689*b*, 2725
Acute viral hepatitis, 1002–1009, 1002*t*
clinical manifestations of, 1002–1003, 1003*f*, 1003*t*
diagnosis of, 1003, 1003*t*
general features of, 1002–1009
Acute viral hepatitis *(Continued)*
other types of, 1009
pathobiology of, 1002–1003
prognosis for, 1003
treatment of, 1003*b*
viruses that cause, 1002*t*
Acute viral respiratory illness, 585*t*
Acute watery diarrhea, 1869*t*
Acyclovir
for herpes simplex encephalitis, 2533*b*
for herpes simplex virus, 2521*b*
for herpes simplex virus infections, 2246
for herpesvirus infections, 2186, 2187*t*–2188*t*
for varicella, 2249*b*
for zoster, 2249*b*
Acyclovir-resistant varicella-zoster virus, treatment of, 2249*b*
ACys amyloidosis, 1306*t*
ADA2. *See* Adenosine deaminase-2
Adacel (Sanofi Pasteur), 81
Adalimumab (Humira)
description of, 151*t*
for inflammatory bowel disease, 945*b*, 946*t*
for rheumatoid arthritis, 1756*t*
for total knee arthroplasty, 1830.*e*1*t*
Adams forward bend test, 621
ADAMTS-13, *e*8*t*–*e*9*t*, 789, 1176–1177, 1180
Adapalene (Differin), 2698
Adaptive immune response, 192–195
Adaptive immune system, 182–191
cell differentiation of, 189–190
effector mediators of, 189
pathogenesis of disease and, 191
principles of activation of, 187–191
signaling pathways of, 189
Adaptive immunity, 671
ADC. *See* Apparent diffusion coefficient
Adcetris. *See* Brentuximab vedotin
Addiction
biology of, 142–143
definition of, 142
drug-induced neural plasticity relevant to, 143
neural substrate of, 142–143
in nicotine, complication of, 42
reward circuitry, 142, 143.*e*1*f*
risk factors for, 142
Addictive drugs, 142*t*, 143
Addison disease, in autoimmune polyglandular syndromes, 1560
Adefovir, for hepatitis B virus infections, 2181*t*–2182*t*, 2182*t*, 2183
Adenocarcinoma. *See also* Carcinoma
colon, 1349–1354
colorectal, 1346
diagnosis of, 1241*t*
esophageal, 1338–1339
gallbladder, 1358
gastric, 1339–1342
intraepidermal, 980
lung, 1329, 1329.*e*2*t*
pancreatic, 1354
rectal, 1350*b*–1352*b*
rectum, 1349
small bowel, 1343–1344
treatment of, 1241*b*–1242*b*, 1242*t*
Adenocarcinoma in situ, 1329
Adenoid cystic carcinoma, 2625
Adenomas
adrenal, 1522, 1524*b*
benign hepatocellular, 1615
hepatic, 991–992, 992*f*
large intestine, 1349
pituitary, 1524*b*
description of, 1486–1487, 1489
inherited syndromes of, 1487*t*
nonfunctioning, 1497–1498
prolactin-secreting, 1481
stomach, 1343
villous, 939
Adenomatoid malformation, congenital cystic, 565
Adenomatous polyposis coli *(APC)* gene, 1348
Adenomatous polyps, 1348–1349, 1349, 1349*b*, 1349*t*
Adenomyosis, 1054
Adenopathy, cervical, treatment of, 1241*b*
Adenosine, 325*t*
Adenosine deaminase-2 (ADA2), deficiency of, 1731*t*, 1733*t*, 1737
Adenosine deaminase deficiency, 174, 1676.*e*3*t*, 1678
Adenosine testing, 306
Adenosine triphosphatase, sodium-potassium, 745
Adenosine triphosphate (ATP), 2580
Adenoviral conjunctivitis, 2604, 2605*f*, 2605*t*
Adenoviral vectors, 175
Adenovirus
in acute bronchitis and tracheitis, 605
definition of, 2204
immunization for, 66*t*
manifestations of, 2205
pathobiology of, 2204
serotype distribution of, 2204.*e*2*f*
structure of, 2204*f*
subgroup of, 2204*t*
Adenovirus diseases, 2204–2206
clinical manifestations of, 2204–2205
definitions of, 2204–2205
diagnosis of, 2205
epidemiology of, 2204, 2204*f*, 2204.*e*1*f*
gastrointestinal tract infections, 2205
genitourinary tract infections, 2205
in immunocompromised patients, 2205
ocular infections, 2205
outbreaks of, 2204
pathobiology of, 2204
prevention of, 2205
prognosis of, 2205
respiratory tract infections, 2204–2205
treatment of, 2205*b*
Adenovirus vector vaccines, for COVID-19, 2219
Adenylate cyclase toxin, 1995
ADH. *See* Antidiuretic hormone
ADH1. *See* Autosomal dominant hypocalcemia type 1
ADH2. *See* Autosomal dominant hypocalcemia type 2
Adherence, drug, 265*b*
Adhesion molecules, 152
Adhesions, peritoneal, 957, 958*f*
Adhesive capsulitis. *See* Frozen shoulder
Adie pupil, 2555, 2600, 2617, 2617*f*
Adipocytes, 1464
Adipokines, 1464
Adiponectin, 1464
Adipose tissue
glucocorticoids metabolism in, 145
lipolysis of, 1465
Adjunctive antiandrogen therapy, for transgender women, 1578*b*–1580*b*
Adjunctive corticosteroids
for *Pneumocystis* pneumonia, 2103*b*
for tuberculosis, 2040*b*
Adjustment, in health delivery systems, 47, 48*f*
Adjuvant analgesics, 136*b*–141*b*
Adjuvant chemotherapy, for cancer, 1232*b*–1237*b*, 1234*t*
Adjuvant therapy
for melanoma, 1393*b*–1394*b*
for pain, in chronic pancreatitis, 975*t*
for systemic lupus erythematosus, 1772*b*–1775*b*
ADLs. *See* Activities of daily living
Admission orders, ICU, 637, 637*t*
Adnexal tumors, 2730
Adolescent(s), 110
approach to, 111–112
chronic illness and transition in, 113
confidentiality in, 111
eating disorders in, 113
health visit, 111–112
medical history of, 111
mental health of, 112–113
obesity in, 112
physical examination in, 111–112
physical growth and development of, normal, 110
preventive health care for, 111
primary malnutrition in, 1445*b*–1446*b*
psychosocial development of, normal, 110
sexual and reproductive health of, 112
substance use and substance use disorders in, 113
vital statistics of, 110–111
Adolescent medicine, 110–113
ADPKD. *See* Autosomal dominant polycystic kidney disease
Adrenal adenoma, 1522, 1524*b*
Adrenal cortex, 1520–1529, 1520*f*–1521*f*
anatomy of, 1520
disorders of, 1520–1529
adrenal incidentaloma, 1524
adrenal insufficiency. *See* Adrenal insufficiency
androgen excess, 1526, 1526*b*
Cushing syndrome. *See* Cushing syndrome
mineralocorticoid deficiency, 1529
mineralocorticoid excess, 1524–1526
function of, 1520
Adrenal cortical cancer, 1523
Adrenal cortical deficiency, complete, 750
Adrenal function, in HIV, 2317
Adrenal glands
histologic section of, 1521*f*
magnetic resonance imaging of, 1520*f*
weight of, 1520
Adrenal incidentaloma, 1524
Adrenal insufficiency, 1526–1529, 2665
acute, 1527, 1528*b*
ancillary tests for, 1527*t*
causes of, 1527*t*
chronic, 1527, 1528*b*
clinical manifestations of, 1527
diagnosis of, 1527–1528
differential diagnosis of, 1528
epidemiology of, 1526
glucocorticoids for, 1528*b*
pathobiology of, 1526–1527
primary, 1526, 1527*t*, 1528*f*
prognosis for, 1529
secondary, 1526–1527, 1527*t*, 1528*f*
treatment of, 1528*b*
Adrenal masses, 1591–1592
Adrenal medulla, 1529–1533
Adrenal steroidogenesis, 1569, 1569.*e*1*f*
Adrenal tissue, replacement of, 1526
Adrenal tumor or hyperplasia, 749*t*
Adrenalectomy, bilateral, role of, 1524*b*
Adrenarche, 110, 1581–1582, 1582*t*
α-Adrenergic blockers
for benign prostatic hyperplasia, 822*b*
clinical use of, 454–455
for hypertension, 454–455
for male lower urinary tract symptoms, 824*t*
mechanism of action of, 454
side effects of, 453*t*, 454
β-Adrenergic blockers, 264*b*
central nervous system effects of, 685*t*
for hypertension, 454
mechanism of action of, 454
side effects of, 453*t*, 454
toxicity, 686*t*
β_2-Adrenergic agents, for asthma, 541*b*–547*b*
β_3-Adrenergic receptor activator, for male lower urinary tract symptoms, 824*t*
Adrenergic toxidromes, 683*t*
Adrenocortical carcinoma, medical therapy for, 1524*b*
Adrenocorticotropic hormone (ACTH), *e*1*t*–*e*8*t*, 1492–1496
corticotropin-releasing hormone effects on, 1492
Cushing disease. *See* Cushing disease
deficiency of, 1481, 1492–1493, 1493*b*
definition of, 1492
ectopic, secretion of, 1523, 1523*t*, 1524*b*
endocrine diseases caused by, 1475*t*–1476*t*
excess of, 1523–1524
insufficiency tests of, 1484*t*
for multiple sclerosis, 2505*t*
Nelson syndrome, 1495–1496
plasma, 1496, 1522
pulsatile secretion of, 1492
reserve testing for, 1493
tests of, 1488*t*
24-hour secretion profile of, 1478.*e*1*f*
vasopressin and, 1499
Adrenoleukodystrophy, 1526, 2509
Adrenomyeloneuropathy, 2509, 2509*b*
Adriamycin. *See* Doxorubicin
Adrucil. *See* 5-Fluorouracil
ADTKD. *See* Autosomal dominant tubulointerstitial kidney disease
Adult inclusion conjunctivitis, 2604
Adult-onset diabetes, 1534
Adult-onset Still disease, 1731*t*, 1732
Adult polyglucosan body disease (APBD), 1416*b*–1418*b*, 1417*t*

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Adult T-cell leukemia/lymphoma, 2326–2327, 2327*t*
  clinical manifestations of, 2326, 2327*f*, 2327*t*
  diagnosis of, 2326, 2326*f*
  epidemiology and pathobiology of, 2326
  pathogenesis of, 2325, 2326*f*
  prognosis of, 2327
  treatment for, 2326*b*–2327*b*
Adult T-cell lymphoma/leukemia, 1286, 1286*b*
Adulterants, 2361
Adults
  congenital heart disease in, 347–356
  physical activity for, 62*t*, 63*b*–64*b*
  travel-related vaccines of, 1886*t*
Advanced cardiac life support (ACLS)
  for acute poisoning, 691*b*
  after cardiac arrest, 313*b*–316*b*, 315*f*–316*f*, 316*f*
Advanced endoscopy, 880–881
  combined procedures in, 881
  for creating anastomoses, 881
  esophageal varices in, 881, 881*f*
  imaging in, 880
  for remodeling organs, 881
  for surgical complications, 881
  tissue resection in, 880
Advanced gout, 1811–1812, 1812*f*
Adverse drug reactions, 131–133
  diagnosis and prevention of, 133
  epidemiology of, 131–132
  pathobiology of, 132–133
  predictable toxic responses, 132, 132*t*
  unpredictable toxic responses, 132–133
Adverse events, 45
Advisory Committee on Immunization Practices (ACIP), 76
Advocacy, in health delivery systems, 47, 48*f*
Aedes aegypti, 2266
Aedes albopictus, 90
Aerobic activity
  absolute intensity of, 62*t*
  for osteoarthritis, 1741*t*
Aerosols, 88*t*
Afatinib (Gilotrif), 1215*t*, 1251*t*
Afebrile neutropenia, 1147*b*–1148*b*
Affect, geriatric assessment of, 117
Afferent baroreflex failure, 2555
Afferent limb mechanisms, 734
Afferent visual system, examination of, 2615
AFib amyloidosis, 1306*t*
Afibrinogenemia, 1189*t*, 1192–1193, 1193*b*
Afinitor. *See* Everolimus
Aflatoxins, 59, 2093
Africa, arterial hypertension in, 445, 445.*e1f*
African Americans
  normal physical growth and development of, 110
  risks for atherosclerotic cardiovascular disease, 1*f*–2*f*
African drought, climate-related hazards, 91*t*
African sleeping sickness, 2123–2126
  clinical manifestations of, 2124–2125
  definition of, 2123–2126
  diagnosis of, 2125, 2125*f*
  East, 2124–2125
  epidemiology of, 2124, 2124.*e1f*
  pathobiology of, 2124
  pathogen of, 2123–2124
  prevention of, 2125–2126
  prognosis of, 2126
  treatment of, 2125*b*, 2125*t*
  West, 2124
African tick-bite fever, 2055*t*, 2057
African trypanosomiasis, 2115–2116. *See also* African sleeping sickness
  characteristics of, 2270*t*
  in travelers, 1889.*e1t*
Afterdepolarizations, 302
  delayed, 333, 333.*e1f*
  early, 333, 333.*e1f*
Afterload, 226
Agammaglobulinemia
  autosomal forms of, 1681*t*
  lack of B cells leading to, 1680
Agatston score, 249
Age, antimicrobial therapy affected by, 1843
Age-related changes
  cardiovascular disease and, 219
  cellular, 120
  molecular, 120
  physiologic system dysregulation, 120, 120.*e2f*
Age-related macular degeneration, 1731*t*, 2608, 2609*f*
  complement system and, 201*t*
AGel (Finnish hereditary) amyloidosis, 1306*t*
Agency for Healthcare Research and Quality (AHRQ), 41.*e1t*
  National Quality Measures Clearinghouse, 41–42
AGEP. *See* Acute generalized exanthematous pustulosis
Aggregatibacter aphrophilus, 2068
Aggressive fibromatosis, 1390, 1390*b*
Aggressive systemic mastocytosis, 1703, 1703*f*
Aging
  arterial hypertension and, 444, 444*f*
  bone loss related to, 1640–1641
  clinical manifestations of, 120
  clinical sequelae of, 120–124
    frailty, 122, 123*b*, 123*f*, 123*t*
    pressure sores, 122, 122*b*, 122*f*
    senile purpura, 121, 122*f*
  demography of, 114
  effects of, 121–123
  epidemiology of, 114–116, 120, 120*f*
  healthy, 115–116
  osteoarthritis and, 1738
  pathobiology of, 120
  pharmacology of, 122
  pubertal development and, 1581–1582
  pulse pressure and, 445.*e1f*
  responses to stressors, 226
  severe mental illness and, 2677–2678
α-Agonists, for alcohol withdrawal, 2358*t*
Agoraphobia, 2342*t*, 2343
Agranulocytosis, psychotropic medications and, 2678*t*
AHRQ. *See* Agency for Healthcare Research and Quality
Aicardi-Goutières syndrome, 1731*t*, 1735, 1768
AIDS. *See* Acquired immunodeficiency syndrome
AIDS-defining malignancies, 2315–2316
AIDS-defining non-Hodgkin lymphomas, 2315
AIHA. *See* Autoimmune hemolytic anemia
AIN. *See* Anal intraepithelial neoplasia
AIP. *See* Acute intermittent porphyria
Air bronchograms, 520
Air trapping, 530
AIRE-1. *See* Autoimmune regulator-1
Airway, radiofrequency ablation of, 541*b*
Airway clearance, for cystic fibrosis, 558*b*–559*b*
Airway closure, 654–655, 654.*e1f*
Airway obstruction, 513–515, 516*t*
  central, 630, 630*t*
    clinical manifestations of, 630, 630*f*–631*f*, 631*f*
    prognosis, 631
    treatment for, 630*b*
  congenital pulmonary malformations, 564–565
  diagnosis of, 513–515, 514*f*
  inflammation, 561*b*–562*b*
  mechanical ventilation for, 657
  prognosis for, 515*b*
  reversible, with heart failure, 265*b*
  treatment of, 515*b*
Airway responsiveness, assessing, 532
AJCC. *See* American Joint Committee on Cancer
Akathisia, 2495
Akinesia, in parkinsonism, 2484
Akinetic-rigid syndrome, 2486–2489
AL amyloid, 788
AL (heavy chain) amyloidosis, 1306*t*
AL (light chain) amyloidosis, 1306*t*
ALADP. *See* 5-Aminolevulinate dehydratase porphyria
Alafenamide, 2301*t*
Alanine aminotransferase (ALT), *e1t*–*e8t*, 998, 1017
Alastrim variola minor infection, 2238
Albendazole, 2112*t*, 2116–2117
  for ascariasis, 2172*b*
  for cystic echinococcosis, 2161
  for echinococcosis, 1029*b*
  for strongyloidiasis, 2173*b*
Albers-Schönberg disease, 1667
Albinism, 2742–2743
Albumin, *e1t*–*e8t*, 994
  description of, 1581
  in liver disease, 989–990
  urinary excretion of, 776
Albuminuria, 832–836, 834*t*, 836
Albuterol
  for asthma, 541*b*
  for hyperkalemia, 751*b*–752*b*
Alcohol
  acute pancreatitis and, 969
  cancer and, 1244–1245
  chronic pancreatitis and, 973
  consumption of, blood pressure and, 445
  coronary heart disease and, 58
  dietary guidelines for, 57.*e3t*
  folate deficiency and, 1120
  heart failure and, 265*b*
  intoxication levels, 2543
  liver cancer and, 59
  neuropathies, 2544–2545
  properties of, 142*t*
  rhabdomyolysis caused by, 715
Alcohol-associated liver disease, 1031–1033, 1031*t*, 1032*b*, 1032*f*
Alcohol intoxication, 2354
Alcohol-related cirrhosis, 2355
Alcohol-related diarrhea, 939
Alcohol-related disorders
  description of, 2543–2545
  hepatic encephalopathy, 2543
  liver toxicity, 2543
  neurologic disorders, 2537–2545
  seizures, 2543–2545, 2543*b*, 2543*f*
Alcohol-soluble protein fraction, of wheat gluten, 935
Alcohol use, 55
  in adolescents, 113, 113*t*
  in women, 1609
Alcohol use disorders, 2353–2359
  acute effects of, 2354
  cardiovascular disease and, 220
  chronic effects of, 2354–2356
  clinical manifestations of, 2354–2356
  complications of, 2355*t*
  criteria for, 2353*t*
  definition of, 2353–2359
  diagnosis of, 2356–2357, 2356*t*
  epidemiology of, 2353
  history of, 2356–2357
  laboratory findings in, 2357
  neurologic effects of, 2353–2354
  pathobiology of, 2353–2354, 2353*f*
  physical examination for, 2355*t*, 2357
  prevention of, 2357*b*
  prognosis of, 2359, 2359*t*
  treatment of, 2357*b*, 2358*t*, 2359*t*
Alcohol withdrawal syndrome, 2354, 2354*f*, 2357*b*, 2358*t*
Alcoholic cardiomyopathy, 287–288, 2355
Alcoholic ketoacidosis, 759
  clinical manifestations of, 759
  diagnosis of, 753*t*, 759
  epidemiology of, 759
  pathobiology of, 759
  prognosis of, 759–760
  treatment of, 759*b*
Alcoholic myopathy, 2544–2545
Alcoholic peripheral neuropathy, in liver disease, 987
Alcoholic steatohepatitis, 1031–1034
Alcoholism, 2353
Aldo-trastuzumab emtansine (Kadcyla), 1215*t*
Aldosterone, *e1t*–*e8t*, 732, 734
Aldosterone antagonists, 265*b*
  for hypertension, 451*t*
  for primary aldosteronism, 448*b*
Aldosterone paradox, 746
Aldosterone secretion, 1525
Aldosteronism, primary, 447–448, 1525*f*
Aldurazyme. *See* Laronidase
Alecensa. *See* Alectinib
ALECT2 amyloidosis, 1306*t*
Alectinib (Alecensa), 1215*t*
Alemtuzumab (Lemtrada)
  characteristics of, 152
  for multiple sclerosis, 2505*t*
  in renal transplantation, 845*t*
Alendronate, for osteoporosis, 1644*t*
Alendronic acid, for Paget disease, 1664*t*
Alexandrite lasers, 2701
Alexia, 2409–2410
Alfuzosin, 824*t*
Alginate, 1968
Alignment, in health delivery systems, 47, 48*f*
Alimta. *See* Pemetrexed
Aliphatic hydrocarbon-n-hexane, 88*t*
Aliqopa. *See* Copanlisib
Aliskiren, 451*t*
Aliskiren/HCTZ, 451*t*
ALK. *See* Anaplastic lymphoma kinase
Alkalemia, 752
Alkaline phosphatase, *e1t*–*e8t*, 999, 1010
  elevation, 1001, 1002*f*
  in liver disease, 989
Alkalosis
  metabolic. *See* Metabolic alkalosis
  postoperative, 2676
  respiratory. *See* Respiratory alkalosis
Alkaptonuria, 1825
Alkhurma hemorrhagic fever, 2265*t*, 2268*t*
Alkylamine, 2700*t*
Alkylating agents, 149
ALL. *See* Acute lymphoblastic leukemia
"All of Us" research program, 165–166
All-*trans*-retinoic acid (ATRA), for acute promyelocytic leukemia, 1262*b*, 1263*t*
Allelic imbalance, 1321
Allergen-specific IgE (sIgE), 1675
Allergens, anaphylaxis caused by, 1692–1693
Allergic *Aspergillus* sinusitis, 2095
Allergic asthma, 538, 1673*t*, 1674
Allergic bronchopulmonary aspergillosis, 541*b*
  clinical manifestations of, 2095
  diagnosis of, 2096, 2096*f*
  increased eosinophils counts in, 533
  pathobiology of, 2094
  treatment of, 2096
Allergic conjunctivitis, 1674, 2604, 2605*t*
Allergic contact dermatitis, 2704, 2729
  description of, 1674
  illustration of, 2691*t*, 2696*f*
Allergic disease
  approach to the patient with, 1672–1676
  definition of, 1672
  diagnosis of, 1675, 1675*t*
  epidemiology of, 1672
  IgE-mediated, 1672, 1672*f*, 1673*t*, 1673.*e1f*
  inborn errors of immunity, 1676
  laboratory evaluation of, 1675
  mixed, 1673*t*
  non-IgE mediated, 1672, 1673*t*
  pathobiology of, 1672–1673
  patient history of, 1675
  physical examination of, 1675
  prevention of, 1675*b*
  of skin, 1674
  treatment of, 1675*b*
Allergic reactions, 193
Allergic rhinitis, 1673*t*, 1674, 2193, 2631
Allergic transfusion reaction, 1202, 1202*b*
Allergy
  to antimicrobial therapy, 1842
  drug. *See* Drug allergy
  environmental, 1673
  food, 1673, 1673*t*
  gastrointestinal tract, 1674
  lower airway, 1674
  occupational, 1673
  upper airway, 1674
Allergy skin-prick tests, for sensitizer-induced occupational asthma, 586
Alloantibodies, 1171*b*–1173*b*
Alloantibody inhibitors
  for factor XI deficiency, 1192*b*
  for hemophilia, 1188*b*–1190*b*
Allodynia, 134
Allogeneic hematopoietic stem cell transplantation, 1207–1208, 1207*f*
  for aplastic anemia, 1126*b*
  for chronic myeloid leukemia, 1274*b*–1277*b*
  for myelodysplastic syndromes, 1255–1256
  for short telomere syndromes, 1129*b*
Allograft rejection, 205–206
AlloMap, 168
Allotransplants, 203
Allylamine. *See* Terbinafine
Almotriptan, 2380*t*
Alobar holoprosencephaly, 2547
Alogliptin, for type 2 diabetes mellitus, 1541*t*
Alongshan virus, 2282
Alopecia, 2747, 2747*t*
  androgenetic, 2748
  central centrifugal cicatricial, 2751, 2751*f*
  cicatricial, 2749–2750
  diffuse, 2747*t*, 2748
  frontal fibrosing, 2749–2750, 2750*f*
  marginal, 2747*t*
  patchy, 2747*t*, 2749–2750
  patterned, 2748

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Alopecia *(Continued)*
scarring, 2749
thallium and, 106, 106*b*
traction, 2751, 2751*f*
Alopecia areata, 2747*t*, 2749, 2749*b*, 2749*f*
Alosetron, for irritable bowel syndrome, 895*b*–898*b*, 896*t*
Alphacoronavirus, 2209*t*
Alphavirus, 2270*t*, 2278, 2520
Alprazolam, for anxiety disorders, 2344*t*
Alprostadil, for erectile dysfunction, 1589
ALPS. *See* Autoimmune lymphoproliferative syndrome
ALS. *See* Amyotrophic lateral sclerosis
ALT. *See* Alanine aminotransferase
Alteplase (t-PA), 386*t*, 509
Altered fat distribution, in HIV, 2317–2318, 2318*b*
Altered immunocompetence, immunization and, 76–77, 76.*e2t*
Altered mental status, severe mental illness and, 2683*t*
Altitude illness, in travelers, 1889
Altitude sickness, treatment of, 593*t*
Altruism, 4
Aluminum, *e*1*t*–*e*8*t*
dialysis dementia and, 101*t*–102*t*, 105, 105*b*
Alunbrig. *See* Brigatinib
Alveolar-arterial oxygen gradient, 639, 639*t*
Alveolar disease, 520
Alveolar filling disorders, 566–570, 566*t*, 582
acute interstitial pneumonia as, 567
classification of, 571*t*
definition of, 566
general approach to, 566*f*
invasive mucinous adenocarcinoma as, 569–570
lepidic predominant nonmucinous adenocarcinoma as, 569
pulmonary alveolar proteinosis as, 566–567
Alveolar hemorrhage, diffuse, 566*t*, 568–569
clinical manifestations of, 568, 568.*e*1*f*
definition of, 568
diagnosis of, 569, 569*f*, 569.*e*1*f*
pathobiology of, 568
prognosis of, 569
treatment for, 569*b*
Alveolar hydatid disease, 2162, 2162*b*
Alveolar hyperventilation, leading to respiratory alkalosis, 765
Alveolar macrophages, 2204
Alveolar proteinosis, 585*t*
Alveolar ventilation, 640–641
Alveolar volume, 530
ALYS amyloidosis, 1306*t*
Alzheimer disease, 2414–2417
amyloidosis and, 1310
anterograde amnesia in, 2408, 2416
clinical features of, 2485*t*
clinical manifestations of, 2415–2416
definition of, 2414
diagnosis of, 2416, 2416*t*, 2418*f*
epidemiology of, 2414
evidence-based treatments for, 2416*b*–2417*b*
genetics of, 2415
magnetic resonance imaging of, 2414–2415, 2415*f*
mortality from, 115
neuritic plaques in, 2414
neurofibrillary tangles in, 2414
pathobiology of, 2414–2415
pathophysiology of, 2414–2415
positron emission tomography of, 2416, 2417*f*–2418*f*, 2418*f*
posterior cortical atrophy caused by, 2410*f*
prevention of, 2416*b*
prognosis for, 2417
risk factors for, 2414
treatment of, 2416*b*
AMAN. *See* Acute motor axonal neuropathy
Amantadine, 2189–2190, 2189*t*, 2203*t*, 2487*t*
Amaurosis fugax, 2465
Ambient hypoxia, 1075
Ambiguous genitalia, surgery for, 1575*b*–1576*b*
Amblyomma americanum, 2025
Amblyopia, 2598
Ambulatory electrocardiography, 235
Ambulatory monitoring
in arrhythmias, 306–307
blood pressure, 446*t*, 447, 447.*e*1*f*
Ambulatory monitoring *(Continued)*
indications for, 212*t*
of psychiatric patient, 2683
Amebiasis, 2146–2150
asymptomatic intraluminal, 2147
characteristics of, 2270*t*
clinical manifestations of, 2147–2148
definition of, 2146–2150, 2147*f*
diagnosis of, 2148–2149, 2149*t*–2150*t*
diarrhea, 2147
dysentery or colitis, 2147–2148, 2148*f*
epidemiology of, 2146
liver abscess, 2148, 2149*f*
pathobiology of, 2146–2147
pathogen of, 2146
prevention of, 2149
prognosis of, 2150
thoracic, 2148
treatment of, 2149*b*, 2150*t*
Amebic dysentery, in travelers, 1891*t*
Amebic liver abscess, 1022*t*, 1024, 1025*b*, 1025*f*
Amebic trogocytosis, 2146
Amenorrhea, 1598–1600
biochemical evaluation of, 1599*f*
causes of, 1599*t*
clinical evaluation of, 1598–1600
diagnosis of, 1598–1600
hypergonadotropic, 1600, 1600*b*
laboratory findings of, 1599–1600
provocative testing of, 1598–1599
American Board of Internal Medicine, 41
American College of Radiology Thyroid Imaging, Reporting and Data System (ACR TI-RADS), 1516.*e*1*f*
American College of Rheumatology/European League Against Rheumatism (ACR/EULAR) classification criteria, 1755*f*
American human monocytic ehrlichiosis, 2060–2061, 2060*t*, 2061*b*, 2061*f*
American Joint Committee on Cancer staging system, 1232, 1333*t*
American Society of Anesthesiologist, 2661
American Spinal Injury Association Impairment Scale, 2390*t*
American Thoracic Society, 612*t*
American trypanosomiasis. *See* Chagas disease
Americas, cystic fibrosis in, 556
Amifostine, 597*b*
Amikacin, *e*10*t*–*e*11*t*
for bacterial meningitis, 2518*t*
dosage of, 1895*t*
for nontuberculous mycobacterial disease, 2046*t*
for pyelonephritis and urosepsis, 1877*t*
in renal failure, 129.*e*1*t*
Amiloride, 451*t*
for Gitelman syndrome, 817*b*
for hypervolemia, 736*b*, 737*t*
Amiloride/HCTZ, 451*t*
Amino acid solutions, in parenteral nutrition, 1450
Amino alkyl ether (ethanolamine), 2700*t*
Aminoglycosides
AUC exposures, 1894–1898, 1899*f*
for bacterial meningitis, 2518*t*
for cystic fibrosis, 1970*b*–1971*b*
dosage of, 1895*t*
for endocarditis, 419*t*
mechanism of action, 1895*t*
middle ear toxicity of, 1898
nephrotoxicity of, 1898
resistance mechanisms, 1893*t*
for *Stenotrophomonas maltophilia*, 1975*b*, 1976*t*
toxicities of, 1901*t*
for yersiniosis, 1994*b*
Aminohydroxypropylidene diphosphonate, 1215*t*
5-Aminolevulinate dehydratase porphyria (ALADP), 1428*t*, 1429, 1429.*e*1*f*
δ-Aminolevulinic acid (δ–ALA), *e*1*t*–*e*8*t*
Aminoquinolines, 2121*b*–2122*b*, 2698–2699
5-aminosalicylate, for inflammatory bowel disease, 945*b*, 946*t*
Aminotransferases, 998–999
asymptomatic abnormalities of, 1001, 1001*f*
Amiodarone, *e*10*t*–*e*11*t*, 325*t*
for advanced cardiac life support, 315*f*
for arrhythmias, 313*b*
for atrial fibrillation, 384*b*
Amiodarone *(Continued)*
for electrical storm, 338*b*–340*b*
induced hypothyroidism, 1507
for supraventricular arrhythmia, 282*b*–283*b*
thyroiditis caused by, 1514
Amitriptyline
for chronic pain, 138*t*–139*t*
for depression, 2340*t*
for irritable bowel syndrome, 896*t*
for tinnitus, 2643*b*
Amitriptyline + nortriptyline, *e*10*t*–*e*11*t*
Amivantamab-vmjw (Rybrevant), 1215*t*
AML. *See* Acute myeloid leukemia
Amlodipine, 451*t*
for acute STEMI, 384*b*
for ischemic heart disease, 470*b*
properties of, 367*t*
for Raynaud phenomenon, 473*b*
Amlodipine/benazepril, 451*t*
Amlodipine/olmesartan, 451*t*
Amlodipine/perindopril, 451*t*
Amlodipine/telmisartan, 451*t*
Amlodipine/valsartan, 451*t*
Ammonia, *e*1*t*–*e*8*t*, 88*t*, 999
Ammoniagenesis, 754
Ammonium, 755
Amnesic disorders, 2407–2408
Amnesic mild cognitive impairment, 2412*t*
Amnesic shellfish poisoning, 713
Amniotic fluid embolism, 492, 492*b*, 492.*e*1*f*
Amoebic encephalitis, 2112*t*, 2115
Amoxicillin
for cystitis, 1876*t*–1877*t*
dosage of, 1895*t*
for leptospirosis, 2031*b*
for Lyme disease, 2026*t*
pharmacokinetic parameters for, 127.*e*1*t*
Amoxicillin-clavulanate
for *H. influenzae* infections, 1954*b*
for *Moraxella catarrhalis* infections, 1955*b*
for peritonsillar abscess and deep space infections, 2649–2650
for *Streptococcus pneumoniae* pulmonary infections, 1912.*e*1*t*
for urinary tract infection, 1876*t*, 1877*t*
Amoxicillin-clavulanic acid
dosage of, 1895*t*
for pneumonia, 613*t*
AMP-activating protein kinase (AMPK), aging and, 115–116
AmpC β-lactamases, 1966
Amphetamines. *See also* Psychostimulants
central nervous system effects of, 685*t*
screening for, 689*t*
toxicity, 686*t*
Amphetamines, toxicity, 2363
clinical manifestations and diagnosis of, 2363
epidemiology of, 2363
pathobiology of, 2363
treatment of, 2363*b*
Amphotericin B
adverse effects of, 2078
drug interactions of, 2077
formulations and pharmacology of, 2077
for hepatosplenic candidiasis, 1024*b*
indications and dosage of, 2077
mechanism of action, 2077–2078
for mucormycosis, 2100*b*
for paracoccidioidomycosis, 2087*b*
preparations of, 2077–2078
for visceral leishmaniasis, 2132*b*–2133*b*
Amphotericin B deoxycholate, for cryptococcosis, 2088*b*
Ampicillin
for bacterial meningitis, 2518*t*
dosage of, 1895*t*
for endocarditis, 419*t*
for leptospirosis, 2031*b*
for listeriosis, 1938*b*
for vancomycin-resistant enterococci, 1922*t*
Ampicillin-sulbactam
for pneumonia, 613*t*
for pyogenic liver abscess, 1023*b*
AMPK. *See* AMP-activating protein kinase
Amplatzer devices, 250.*e*1*f*
Ampullary tumors, 1060, 1060.*e*1*f*
Ampyra. *See* Dalfampridine
Amsterdam criteria, for HNPCC, 1347
Amylase, *e*1*t*–*e*8*t*
in acute pancreatitis, 971
Amyloid, 2652, 2652.*e*2*f*
Amyloid arthropathy, 1822
Amyloidosis, 292, 1305–1310, 2560, 2560*b*, 2626
arthritis associated with, 1822
ATTRwt, 1309
cardiomyopathy with, 292
definition of, 1305
diagnosis of, 293, 294*f*
dialysis-associated, 842
epidemiology of, 292–293
of esophagus, 911
factor deficiency in, 1193
familial, 1306*t*, 1309
in familial Mediterranean fever, 1732
glomerular diseases in, 788
light chain, 2575–2576, 2576*b*
localized, 1310
pathobiology of, 292
prognosis for, 293*b*–294*b*
systemic, 1305, 1306*t*
light chain, 1305–1309
secondary, 1310
treatment of, 293*b*
β-Amyloidosis, 2414
Amyotrophic lateral sclerosis (ALS), 2543, 2562–2565, 2652
Awaji-Shima consensus criteria for, 2563*t*–2564*t*
clinical manifestations of, 2562–2563
definition of, 2561
diagnosis of, 2563, 2563*t*, 2564*t*
epidemiology of, 2562–2565
mimic syndromes of, 2564*t*
pathobiology of, 2562
pathology of, 2562
prognosis of, 2565
treatment of, 2563*b*–2565*b*
Anabolic agents, for osteoporosis, 1643*b*
Anabolic-androgenic steroids, 2365
Anaerobic bacteria, non-spore forming, 1938–1941
antimicrobial susceptibility patterns for, 1941*t*
bacteremia caused by, 1938
central nervous system infections caused by, 1938–1939
clinical manifestations of, 1938–1940
definition of, 1938–1941, 1939*f*, 1939*t*
diagnosis of, 1940–1941, 1940*t*
head infections caused by, 1939
intra-abdominal infections caused by, 1939
neck infections caused by, 1939
obstetric-gynecologic infections causing, 1939
osteomyelitis caused by, 1940
pathobiology of, 1938, 1938.*e*3*t*
pathogen that cause, 1938, 1938.*e*3*t*
prevention of, 1941
prognosis for, 1941
septic arthritis caused by, 1940
skin and soft tissue infections caused by, 1939–1940
taxonomy of, 1938.*e*3*t*
treatment of, 1940*b*, 1940*t*–1941*t*
Anagen effluvium, 2748
Anakinra (Kineret)
for cryopyrin-associated periodic syndromes, 1735*b*
description of, 150–151, 151*t*
for total knee arthroplasty, 1830.*e*1*t*
Anal cancer, 982
clinical manifestations of, 982
diagnosis of, 982
in HIV, 2316
treatment for, 983*b*
Anal dysplasia, 982
Anal endoscopic ultrasonography, 981
Anal fissure, 979–980, 979*f*
Anal fistula, 979, 979*b*–980*b*, 980*f*
Anal intraepithelial neoplasia (AIN), 982
Anal warts, 982, 982*b*, 982*f*
Analgesia
for critical care, 636
for postoperative pain, 1829
Analgesic nephropathy, 793, 794*f*
Analgesics
adjuvant, 136*b*, 138*t*
antipyretic, 136*b*, 138*t*
chronic interstitial nephritis caused by, 793
for common cold, 2193*b*
for fibromyalgia, 1819*b*–1820*b*

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Analgesics *(Continued)*
opioid, 136*b*, 138*t*, 141*t*
for pain, in chronic pancreatitis, 975*b*–976*b*, 975*t*
for skin diseases, 2699–2700
Anaphylatoxins, 201–202
distribution of, 202*t*
Anaphylaxis, 132–133, 1673*t*, 1674–1675, 1691–1695
allergens causing, 1692
aspirin causing, 1692–1693
clinical manifestations of, 1693
definition of, 1691–1695
diagnosis of, 1693–1694
differential diagnosis of, 1694
distinguishing features of, 515*t*
drugs associated with, 1698*t*
epidemiology of, 1691–1692
food allergy-associated exercise-induced, 1692
food causing, 1692
insect sting venom causing, 1692
latex causing, 1692
latex-induced, 1691–1692
medications causing, 1692
non-IgE-dependent agonists causing, 1692
nonsteroidal anti-inflammatory drugs causing, 1692
pathobiology of, 1692–1693
prevention of, 1694–1695
prognosis for, 1695
systemic
acute treatment of, 1694*f*
causes of, 1691*t*
diagnosing, 1693*f*
treatment of, 1694*b*
vaccines causing, 1692
Anaplasma phagocytophilum, 2025, 2060*t*, 2061
Anaplasmoses, 2060, 2060*t*
Anaplastic large cell lymphoma, 1287, 1287*b*
Anaplastic lymphoma, treatment of, 1241*b*
Anaplastic lymphoma kinase (ALK), lung cancer and, 1330
Anaplastic thyroid cancer, 1519, 1519*b*
ANAs. *See* Antinuclear antibodies
Anastomoses, endoscopy for, 881
Anastomotic ulceration, 916
Anastrozole (Arimidex), 1215*t*
for breast cancer, 1369*b*
Anatomic distribution, of disease, 523–524
ANCA. *See* Antineutrophil cytoplasmic antibodies; Antineutrophil cytoplasmic antibody
Ancylostoma duodenale, 2169
Andersen disease, 1417*t*
Andersen-Tawil syndrome, 2583.*e1t*, 2585
Andexanet alfa, 506*t*
Andres virus, 2265*t*
Androgen(s)
adrenal secretion of, 1572
biosynthesis, defects of, 1572
cancer and, 1245–1246
excess of, 1526, 1526*b*
Androgen insensitivity, 1573
Androgen receptor, 1384
Androgen replacement therapy, 1585*b*, 1585*t*
Androgen resistance, 1583
Androgenetic alopecia, 2747*t*, 2748, 2748*b*–2749*b*
Androstenedione, 1569, 1581
Anemia, 1074–1082
acute leukemias and, 1262
of aging, 1082
alcohol use disorders and, 2355
aplastic. *See* Aplastic anemia
associated with inadequate reticulocyte response, 1079–1080, 1080*t*, 1081*f*
associated with increased reticulocyte production, 1078, 1079*f*
blood loss causing, 1078
in chronic interstitial nephritis, 793
of chronic kidney disease, 836, 1080–1082, 1081*b*
clinical manifestations of, 1075–1076
Cooley, 1106
definition of, 1074
diagnosis of, 1076–1077
blood smear examination, 1077
bone marrow examination, 1077
complete blood counts, 1076–1077, 1076*t*, 1077*t*
medical history, 1076, 1076*t*, 1077*t*
physical examination, 1076–1077, 1077*t*
Anemia *(Continued)*
reticulocyte count, 1076*t*, 1077
dialysis-associated, 842
Diamond-Blackfan, 1127.*e1t*, 1129–1130, 1130*b*
differential diagnosis of, blood smear in, 1068–1070
of endocrine deficiency, 1081
Fanconi, 1127.*e1t*, 1129, 1129*b*, 1145
in heart failure, 265*b*
hemolysis causing, 1078, 1079*f*, 1079*t*–1080*t*, 1080*t*
hemolytic. *See* Hemolytic anemia
in HIV/AIDS, 2314, 2315*t*
of inflammation, 1079
initial laboratory approach to, 1078, 1078*t*
iron deficiency. *See* Iron deficiency anemia
of liver disease, 1081
macrocytic, 1079–1080, 1082–1086
malaria and, 2120
megaloblastic, 1080, 1117–1125
causes of, 1117*t*
clinical manifestations of, 1120–1122
complications of, 1120–1122, 1121*f*
definition of, 1117–1125, 1117*t*
diagnosis of, 1122–1123
epidemiology of, 1117–1118
pathobiology of, 1118–1120
peripheral blood smear of, 1069, 1072*t*
prevention of, 1124
prognosis of, 1124
treatment of, 1123*b*–1124*b*
methemoglobin and, 1075
microcytic, 1079
peripheral blood smear of, 1068–1069
normocytic, 1080
normocytic normochromic, peripheral blood smear of, 1069–1070
oxygen delivery and, 1074–1075, 1075*f*
pathobiology of, 1074–1078
pernicious
diagnosis of, 1123
incidence of, 1117
malabsorption of cobalamin and, 1119
physical findings of, 1076
physiologic, of pregnancy, 1081
postoperative, 2666, 2675
in pulmonary tuberculosis, 2035
regulation of red cell production in, 1075
in Rocky Mountain spotted fever, 2054
severe mental illness and, 2683*t*
sickle cell disease and, 1114*b*–1116*b*
sideroblastic, 1072*t*, 1084, 1086
acquired, 1086
clinical manifestations of, 1086
diagnosis of, 1086, 1086*f*
prognosis of, 1086*b*
treatment of, 1086*b*
symptoms of, 1075–1076
Anemia of chronic disease, 1085, 1086*b*
Anemia of inflammation, 1085, 1086*b*
Anergy, 207
Anesthesia, 2668–2672
airway assessment before, 2668
anaphylaxis in, 2669
dexmedetomidine for, 2670
diabetic ketoacidosis and, 2669
epidural, 2671
general, 2669, 2671
intraoperative management of, 2669–2671, 2669*t*
ketamine for, 2670
latex allergy and, 2669
malignant hyperthermia and, 2668, 2668*b*–2669*b*
medication reactions in, 2668–2669
midazolam for, 2670
monoamine oxidase inhibitors and, 2669
nausea and vomiting after, 2671
neuraxial, 2671
neuromuscular blockers for, 2670–2671
opioids for, 2670
in orthopedic patient, 1827
preoperative assessment, 2668
propofol for, 2669–2670
records of, in postoperative care, 2672
regional, 2671
serotonin toxicity and, 2669
for skin diseases, 2699–2700
sodium-glucose cotransporter-2 inhibitor and, 2669
spinal, 2671
volatile anesthetics for, 2670
Anetoderma, 2736–2737, 2737*f*
Aneuploidy, of sex chromosomes, 1574
Aneurysms
aortic, 436–439
abdominal, 436
clinical manifestations of, 436–437
definition of, 436–439, 437*t*
diagnosis of, 437–438
epidemiology of, 436
pathobiology of, 436
prognosis for, 438–439
risk factors of, 436
thoracoabdominal, 436
fusiform, 2478
hypothalamus and, 1480
left ventricular, 384*b*
mycotic, 2478
sinus of Valsalva, 352
visceral arterial, 969
Angina, 352
Angina pectoris, 211*t*, 356–370
in aortic stenosis, 400–404
chronic
diagnostic coronary angiography in, 363*t*
evaluation of, 361*f*
chronic stable, 398
definition of, 356–364
differential diagnosis of, 359
echocardiographic findings, 242*t*
epidemiology of, 356
exercise ECG in, 361
exercise test protocol for, 361–362
grading of, 356
history in, 357–358
microvascular, 369
noninvasive testing for, 359–363, 362*f*
pathobiology of, 356–357
Prinzmetal, 357, 368–369
prognosis for, 369
recommendations for myocardial revascularization in, 364*t*
rest or unstable, 211*t*
risk stratification of, 363–364
suspected, 360*f*
treatment of, 265*b*, 364*b*–368*b*, 364*t*, 365*f*
unstable, 370
in acute coronary syndrome, 370
definition of, 370, 371*f*
recurrent or refractory, 374*t*
treatment of, 374*t*
variant, 368
vasospastic, 357
Anginal equivalents, 357
Angioectasia, 965, 966*b*, 966*f*, 966.*e1*
Angioedema, 1674, 1687–1691
classification of, 1690*t*
clinical manifestations of, 1687, 1688*f*
definition of, 1687
hereditary, 1690–1691
visceral, 956
Angiography
in chronic stable angina, 361*f*
computed tomography
in atherosclerotic PAD, 463, 463*f*–464*f*
coronary, 249–250, 249.*e2f*, 250*f*
in coronary artery disease, 360–361
coronary
in acute coronary syndrome, 372–373, 375*t*
in chronic angina and stable ischemic heart disease, 363*t*
in coronary artery disease, 393
diagnostic, 363, 363*t*
technique, 395–396, 395*f*
digital subtraction, in atherosclerotic PAD, 463–465, 463*f*
in heart failure, 261
magnetic resonance, in atherosclerotic PAD, 463, 463*f*
subarachnoid hemorrhage on, 2476
Angioimmunoblastic T-cell lymphoma, 1287
Angiokeratomas, 1421*f*, 1422
Angioplasty
coronary
for acute MI, 397*f*
for atherosclerotic PAD, 467*b*
medical therapy *versus*, 397
percutaneous transluminal, 464.*e1f*, 468*b*
for fibromuscular dysplasia, 800*b*–801*b*
indications for, 385*t*
for renovascular hypertension, 449*b*
Angiosarcoma, 967, 2733–2734
Angiostrongyliasis, 2174*t*, 2175–2176, 2176*b*
Angiostrongylus cantonensis, 2175, 2524
Angiostrongylus costaricensis, 2175
Angiotensin, 730
Angiotensin-converting enzyme (ACE), *e1t*–*e8t*
Angiotensin-converting enzyme (ACE) inhibitors, 264*b*, 364*b*
for acute STEMI, 391*t*
for autosomal dominant polycystic kidney disease, 812*b*
for chronic interstitial nephritis, 795*b*
clinical benefits of, 265*b*
clinical use of, 452
for hypertension, 452–453
inducing angioedema, 1690–1691, 1690*b*
mechanism of action, 265*b*
mechanisms of action of, 452
practical use of, 265*b*, 266*t*
side effects of, 452–453, 453*t*
Angiotensin I, *e1t*–*e8t*
Angiotensin II, *e1t*–*e8t*, 730, 734
prostaglandins and, 734
Angiotensin receptor blockers (ARBs), 264*b*
for acute STEMI, 384*b*, 391*t*
clinical benefits of, 265*b*
clinical use of, 452
for hypertension, 451*t*, 452
mechanism of action of, 265*b*, 452
practical use of, 265*b*, 266*t*
side effects of, 452, 453*t*
Angiotensinogen, 730
Angle-closure glaucoma, 2608, 2608*f*
Angular cheilitis, 2624
Anhidrosis, 2555
Anhidrotic ectodermal dysplasia, with immunodeficiency, 1685, 1686*t*
Anidulafungin, 2078–2079
adverse effects of, 2079
drug interactions of, 2079
formulations and pharmacology of, 2078
for hepatosplenic candidiasis, 1024*b*
indications and dosage of, 2075*t*, 2078–2079
Anifrolumab (Saphnelo), for total knee arthroplasty, 1830.*e1t*
Anion gap, *e1t*–*e8t*
delta, 756–757
metabolic acidosis, 690–691, 757–760, 757*t*
Anisakiasis, 2173
Anisocytosis, peripheral blood smear of, 1067*f*
Ankle
disorders of, 1747–1749
fusion of, 1827
injury of, occupational, 86*t*
sprain, 1748
surgical treatment of, 1828–1829
Ankle-brachial index (ABI), 461, 461*f*
Ankylosing spondylitis, 622, 1708, 1717*t*, 1761–1762
clinical manifestations of, 622, 1761–1762, 1761*t*
diagnosis of, 622, 1762
differential diagnosis of, 1761*t*
epidemiology of, 622, 1761
exercise for, 1765*b*–1766*b*
HLA-B27 and, 1760, 1760*f*
imaging of, 1762, 1762*f*–1763*f*
interstitial lung disease associated with, 581
pathobiology of, 622, 1761
prognosis of, 622*b*, 1766–1767
treatment of, 622*b*, 1765*b*
Ankyrin, 1094
Anogenital warts, 2242
Anomalous pancreaticobiliary duct junction, 1058–1059, 1059.*e1f*
Anomalous pulmonary venous return, 247.*e1f*, 354
Anomia, 2408
Anorexia
abdominal pain and, 856
hypothalamic, 1481
liver disease and, 986
management of, approaches to, 13*t*
postoperative, 2673
signs and symptoms of, approach to, 852*t*
weight loss and, 860*t*
Anorexia nervosa
clinical manifestations of, 1461
definition of, 1461
hypogonadotropic hypogonadism and, 1584
hypothalamic chronic anovulation associated with, 1601
pathobiology of, 1461
prognosis of, 1462
treatment of, 1462*b*

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Anorgasmic state, 1590
Anovulatory bleeding, 1597
Anoxic brain injury, 591–592
Anserine bursitis. *See* Pes anserinus syndrome
Antalgic gait, 2373*t*
Anterior cerebral arteries, 2456–2457, 2458*f*
Anterior chamber, 2596
Anterior choroidal artery, 2457, 2459*f*, 2465, 2465*t*
Anterior communicating artery, 2463
Anterior cord syndrome, 2386, 2403
Anterior horn cell disease, 2581*t*
Anterior mediastinotomy, 1331
Anterior mediastinum, 527
Anterior pituitary, 1482–1498, 1482*f*
  adrenocorticotropic hormone. *See* Adrenocorticotropic hormone
  carcinomas of, 1498, 1498*f*
  definition of, 1482
  growth hormone. *See* Growth hormone
  insufficiency tests of, 1484*t*
  pathobiology of, 1482
  primary diseases of, 1483–1486
    empty sella, 1486, 1486*f*
    hypophysitis, 1483
    hypopituitarism. *See* Hypopituitarism
    pituitary apoplexy, 1485, 1485*t*–1486*t*, 1486*b*, 1486*t*
  prolactin. *See* Prolactin
  thyroid-stimulating hormone. *See* Thyroid-stimulating hormone
  tumors of, 1486–1488
    clinical manifestations of, 1487
    functioning, 1488*t*
    medical therapy for, 1487*b*
    pathobiology of, 1486–1488
    prognosis for, 1488
    radiation therapy for, 1487*b*
    surgery for, 1487*b*
    treatment of, 1487*b*
Anterior segment, 2596
Anterograde amnesia, 2407
  in Alzheimer disease, 2408
  clinical manifestations of, 2408
  residual deficit after, 2408
Anthelminthic drugs, 2116–2118
Anthracycline-induced dilated cardiomyopathy, 288
Anthralin, for psoriasis, 2698
Anthrax, 1930
  characteristics of, 2270*t*
  clinical manifestations of, 96–97, 1931
  cutaneous, 1932, 1932*b*
  description of, 96–97
  diagnosis of, 97
  epidemiology of, 96, 1930
  immunization for, 66*t*, 83–84
  inhalational, 1931, 1931*f*, 1932*b*
  pathobiology of, 96
  prevention of, 97
  prognosis of, 97
  treatment of, 97*b*
Anti-C5, 203
Anti-CD20 antibodies, 2701
Anti-citrullinated peptide antibodies (ACPA), 1750
Anti-cyclic citrullinated peptide antibody, 1707
Anti-endothelial cell antibodies, vasculitides and, 1794
Anti-epidermal growth factor antibodies, for colorectal cancer, 1350*b*
Anti-glomerular basement membrane (anti-GBM) disease, 784, 784*b*–785*b*, 784*f*, 784*t*, 1798
Anti-HER2 therapy, for breast cancer, 1369*b*
Anti-HMGCR myopathy, 1787–1789
Anti-IgA, 1202
Anti-IL2R monoclonal antibodies, in renal transplantation, 845*t*
Anti-infective therapy, principles of, 1840–1845. *See also* Antimicrobial therapy
Anti-inflammatory agents
  for acute STEMI, 384*b*
  for COVID-19, 2217
  for cystic fibrosis, 558*b*
  for radiation enteritis, 940*b*–941*b*
  for skin diseases, 2697–2699
Anti-ischemic therapies, for acute STEMI, 384*b*
Anti-La antibodies, 1715
Anti-La/SSB antibodies, in Sjögren syndrome, 1784
Anti-Parkinsonism medications, for Parkinson disease, 2486*b*
Anti-RNP antibodies, 1714
Anti-Ro antibodies, 1715
Anti-Ro/SSA antibodies, in Sjögren syndrome, 1784
Anti-*Saccharomyces cerevisiae* antibodies (ASCA), 945
Anti-Sm antibodies, 1714
Anti-tubular basement membrane disease, 790
Anti-tumor necrosis factor-α agents, for inflammatory bowel disease, 945*b*
Anti-vascular endothelial growth factor antibodies, for colorectal cancer, 1350*b*
Antianginal therapy, 374*t*
Antiarrhythmic drugs, 313*b*, 325*t*, 338*b*
  for acute STEMI, 384*b*
Antibacterial activity, synergism in, 1843–1844
Antibacterial chemotherapy, 1891–1902
  antibiotic selection, 1891–1892
  bacterial burden, 1893
  correct drug dose of, 1892
  culture, 1892
  dosages, 1891
  drug, classes and properties of, 1898–1900
  duration of therapy, 1900
  failure of, 1900–1902
  Gram stain, 1892
  infection site and, 1892, 1892*t*
  infection susceptibility to, 1892
  mechanism of action, 1894, 1895*t*
  pharmacokinetic of, changes of, 1894–1898, 1895*t*
  principles of, 1891
  resistance, 1892–1894, 1893*t*
  toxicities of, 1900, 1901*t*
Antibacterials, 1845*t*
  for skin diseases, 2699
Antibiotic(s)
  for acute bacterial prostatitis, 825*b*
  for acute bronchitis and tracheitis, 606*b*
  for acute mesenteric ischemia, 960*b*
  for asthma, 541*b*
  into cerebrospinal fluid, 2516*t*
  for common cold, 2193*b*
  for cystic fibrosis, 558*b*
  for diarrhea, 926*b*
  for diphtheria, 1935*b*
  for diverticulitis, 955*b*
  for *E. coli*, 1963*b*–1964*b*
  for esophagitis, 907*t*
  for inflammatory bowel disease, 945*b*
  for irritable bowel syndrome, 896*t*
  for malaria, 2121*b*
  for neutropenia, 1147*b*
  for perianal abscess, 979*b*
  for pyogenic liver abscess, 1023*b*
  reactions to, 1697–1698
  for relapsing fever, 2028*b*
  for shigellosis, 1981*b*–1982*b*
  for skin diseases, 2699
  for spondylitis, 1765*b*
  for *Stenotrophomonas maltophilia*, 1975*b*
  for *Streptococcus pneumoniae*, 1912*b*
  for viral hemorrhagic fevers, 2269*b*–2272*b*
Antibiotic-associated diarrhea, 926
Antibiotic resistance, mechanisms of, in Enterobacterales, 1965, 1966*t*
Antibodies, 152, 188, 192, 197
  for cancer, 1232*b*
  to citrullinated proteins, 1713
  monoclonal, for asthma, 541*b*
  specificities of, 188–189
Antibody deficiency, 1680–1682, 1681*t*
  clinical manifestations of, 1680–1682
  diagnosis of, 1682
  epidemiology and pathobiology of, 1680–1682, 1681*t*
  with normal immunoglobulins, 1682
  prognosis of, 1682
  treatment of, 1682*b*
Antibody-drug conjugates, 150*t*
Anticatabolic agents, for osteoporosis, 1643*b*
Anticholinergic agents
  central nervous system effects of, 685*t*
  toxidromes, 683*t*
Anticholinergic-antihistamine agents, for nausea and vomiting, 863*t*
Anticipatory anxiety, 2343
Anticoagulants, 364*b*, 501–506, 503*t*, 2666*t*, 2667*f*
  for giant cell arteritis, 1803*b*
  long-term use of, 487*b*–489*b*
  oral, 502*t*, 503–506
  parenteral, 501–503, 501*t*
  side effects of, 487*b*
Anticoagulation
  for acute coronary syndrome, 374*t*
  for acute STEMI, 384*b*, 387*f*
  for COVID-19, 2217
  in functional tests, 477–478
  for intracerebral hemorrhage, 2480*b*–2482*b*
  postoperative, 2667
  with warfarin, for portal vein thrombosis, 968*b*
Anticonvulsants
  central nervous system effects of, 685*t*
  for fibromyalgia, 1819*b*
  for myoclonus, 2493*b*–2494*b*
Antidepressants, 2679–2680, 2680*t*
  for anorexia nervosa, 1462*b*
  central nervous system effects of, 685*t*
  cyclic, toxicity, 686*t*
  in pregnancy, 1610
  tricyclic
    for chronic pain, 138*t*
    for depression, 2340*t*
    for fibromyalgia, 1819*b*
    screening for, 689*t*
Antidiarrheal agents, 940*b*, 941*b*
Antidiuresis, 1499
Antidiuretic hormone (ADH), *e*1*t*–*e*8*t*, 730–731, 738
Antidotes, for acute poisoning, 691*b*
Antidromic tachycardia, 323*t*, 326
Antiemetic regimens, for nausea and vomiting, 863*t*
Antiemetics, for intestinal pseudo-obstruction, 889*b*–890*b*
Antiepileptics, for alcohol withdrawal, 2358*t*
Antifibrinolytic agents, for disseminated intravascular coagulation, 1196*b*–1197*b*
Antifungal agents, 2074–2080, 2699
  amphotericin preparations as, 2077
  for aspergillosis, 2096
  azole, 2074–2077
    fluconazole as, 2075–2076
    indications and dosage of, 2075
    isavuconazole as, 2077
    itraconazole as, 2074–2075
    mechanisms of action, 2074
    posaconazole as, 2076–2077
    voriconazole as, 2076
  for coccidioidomycosis, 2085*b*
  dosing overview for, 2075*t*
  echinocandin, 2078–2079
    anidulafungin as, 2078
    caspofungin as, 2078
    mechanisms of action, 2078
    micafungin as, 2078
  flucytosine as, 2079
    adverse effects of, 2079
    drug interactions of, 2079
    formulation and pharmacology of, 2079
    indications and dosage of, 2075*t*, 2079
    mechanisms of action, 2079
  ibrexafungerp as, 2079
    adverse effects of, 2079
    drug interactions of, 2079
    indications and dosage of, 2075*t*, 2079
    mechanisms of action, 2079
  for mucormycosis, 2100*b*
  other, 2079
Antigen(s), 193*t*
  processing and presentation of, 188, 188*f*
  in transplantation, 203–205, 204*t*
Antigen-based testing, for COVID-19, 2214
Antigen detection, for malaria, 2120
Antigen-specific effector T cells, 193
Antigen-specific receptors, 188–189
Anti-glomerular basement membrane (anti-GBM), for glomerular syndromes, 727
Antihemophilic factor, 1189*t*
Antihistamines
  for acute bronchitis and tracheitis, 606*b*
  central nervous system effects of, 685*t*
  for rhinitis, 2632*b*–2634*b*
  for skin diseases, 2700, 2700*t*
Antihypertensive drugs, 1620*b*–1621*b*, 1621*t*
  classes of, 451–455
  interactions of, 455
  side effects of, 453*t*
  for specific condition, 454*t*
Antileukotrienes, 541*b*
Antimalarial drugs, 2698–2699
  for rheumatoid arthritis, 1755*b*–1758*b*
  for systemic lupus erythematosus, 1772*b*
Antimetabolites, for liver transplantation, 1048*t*
Antimicrobial resistance, 1834, 1965, 1966*t*
Antimicrobial therapy
  for *Acinetobacter* infection, 1974*b*
  administration of, 1844
  administrative aspects of, 1844–1845
  age and, 1843
  allergies to, 1842
  bactericidal activity of, 1842
  for bronchiectasis, 561*b*
  for *Campylobacter* infections, 1959*b*
  for cholera, 1956*b*–1957*b*
  combinations of, 1843
  definitive, 1841
  drug-drug interactions in, 1843
  drug resistance of, emergence of, 1843
  duration of, 1844
  empirical, 1840–1841
  failure of, 610*b*–611*b*, 1900
  for food poisoning, 1932*b*
  formularies for, 1844
  health care-associated infections and, 1863
  hepatic function in, 1843
  host factors, 1842–1844
  infection treated with, nature of, 1842
  pathogen of, identification of, 1841
  pharmacodynamic considerations in, 1844
  for plague, 1992*t*, 1993
  for pneumonia, 610*b*, 613*t*
  for polymicrobial infections, 1843
  in pregnancy, 1842–1843, 1842*t*
  renal function in, 1843
  resistance in, 1843
  route of administration, 1844
  selection of, 1840–1844
  for skin diseases, 2699
  stewardship for, 1844–1845, 1845*t*, 1865.*e*1*t*, 1867
  susceptibility testing of, 1836, 1840, 1916*b*
  toxicity of, 1843
Antimotility agents, for cholera, 1956*b*
Antimüllerian hormone, *e*1*t*–*e*8*t*, 1630
Antimuscarinics
  asthma and, 541*b*
  for benign prostatic hyperplasia, 822*b*
  for male lower urinary tract symptoms, 824*t*
Antineutrophil cytoplasmic antibodies (ANCA), 727, 1716, 1793–1794
Antineutrophil cytoplasmic antibody (ANCA)-associated vasculitis, 965, 1707–1708
Antineutrophil cytoplasmic antibody-associated vasculitides, 1796–1798
Antinuclear antibodies (ANAs), 727, 1714–1716, 1714*f*, 1785
  in pulmonary hypertension, 495
  systemic sclerosis, 1780
Antioxidants, 196, 975*t*
Antiparasitic therapy, 2111–2118, 2698
  for African trypanosomiasis, 2115
  for amoebic encephalitis, 2115
  for babesiosis, 2115
  for Chagas disease, 2116, 2128*b*
  for helminthic diseases, 2116–2118
  for intestinal protozoa, 2115
  for leishmaniasis, 2116
  for protozoal diseases, 2111–2116
  for skin diseases, 2699
  for toxoplasmosis, 2115
  for trypanosomiasis, 2115–2116
  for vaginal protozoa, 2115
Antiphospholipid antibody syndrome, 480–481, 481*b*, 1193, 1194*b*, 1715, 1770
Antiplatelet agents, 364*b*, 506–509, 506*t*, 2666–2667, 2666*t*, 2667*f*
  for acute coronary syndrome, 374*t*
  for acute STEMI, 384*b*, 387*f*
  for atherosclerotic PAD, 464*b*
  diabetes mellitus and, 1550
  for intracardiac procedures, 507–508
    adverse effects of, 508

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Antiplatelet agents *(Continued)*
combination of anticoagulant and, 508, 508*f*
pharmacology of, 507–509
α_1-Antiprotease, 548
Antipruritic agents, for skin diseases, 2700
Antipsychotics, 2679, 2680*t*
central nervous system effects of, 685*t*
Antipyretic analgesics, 136*b*
Antireflux surgery, 904*b*–905*b*
Antiretroviral therapy
corticosteroids and, 2317
for cryptosporidiosis, 2143*b*
gastrointestinal side effects of, 2319
for HIV infection, 2294, 2294*f*, 2297*b*, 2300–2305
for acute opportunistic infection, 2304–2305
available drugs for, 2300–2302, 2301*f*, 2301*t*
changing of, 2302–2303
for coinfection with hepatitis B, 2304
for coinfection with hepatitis C, 2304–2305
immunologic failure of, 2303
opportunistic infections associated with, 2307*b*–2308*b*
pregnancy and, 2305
recommended, 2303*t*–2304*t*
side effects and toxicity of, 2303–2304, 2304*t*
for special populations, 2304–2305
starting of, 2302
timing of, 2302, 2302*t*
toxic neuropathy caused by, 2313*b*
what to monitor, 2302
for *Pneumocystis* pneumonia, 2103*b*
to prevent sexual transmission, 2298–2299
Anti-SARS-CoV-2 monoclonal antibodies, 2216–2217, 2216*f*, 2219
Antiseizure medication
characteristics of, 2434*t*
discontinuation of, 2434*b*
selection of, 2433*t*, 2434*b*
Antisense oligonucleotides, 176–178
Antisocial personality disorder, 2348*t*
Antispasmodics, for irritable bowel syndrome, 895*b*, 896*t*
Antithrombin, 478*b*
Antithrombin III, *e8t*–*e9t*
deficiency, 475–476, 475*t*–477*t*
for disseminated intravascular coagulation, 1196*b*
for renal vein thrombosis, 802
Antithrombotic therapy, 501–509
for atherosclerotic PAD, 464*b*
for chronic kidney disease, 839*b*–840*b*
for gastrointestinal endoscopy, 875*t*
in-hospital dosing of, 387*t*
Antithyroid drugs, 1511*b*–1512*b*
α_1-Antitrypsin, *e1t*–*e8t*, 549, 551*b*–554*b*
α_1-Antitrypsin deficiency, 560, 993, 993*f*
Antituberculous agents, dosage of, 1895*t*
Antitumor cytotoxicity, 176
Antivenom, 708*b*–709*b*, 709*b*
for acute poisoning, 693*t*
for envenomation, 705*b*
for viperid bites, 708
Antiviral therapy, 2181–2191
for common cold, 2193*b*
for coronavirus infections, 2190–2191
for COVID-19, 2216–2217, 2217, 2217*f*
for cytomegalovirus, 2187*t*–2188*t*
for esophagitis, 907*t*
for hepatitis B virus infections, 2181–2183, 2181*t*
for hepatitis C virus infections, 2181*t*, 2182*t*, 2183–2186
for herpesvirus infections, 2186–2189, 2187*t*, 2188*t*
for influenza virus infections, 2189–2190, 2189*t*
for poxvirus infections, 2240*b*
for skin diseases, 2699
for varicella-zoster virus, 2187*t*
for viral hemorrhagic fevers, 2269*b*
Anton syndrome, 2616
Antral G-cell hyperplasia, 918
Anus
anatomy of, 977
diseases of, 977–983
anal fissure as, 979, 980*f*
anal fistula as, 979, 979*f*
Anus *(Continued)*
cancer as, 982
fecal incontinence as, 981, 981*f*
hemorrhoids as, 977–980, 978*f*
human papillomavirus as, 982–983
perianal abscess as, 978
pruritus ani as, 980
rectal prolapse as, 981*f*
sexually transmitted anorectal diseases, 983
warts as, 982, 982*f*
Anxiety
in adolescents, 112
chest pain in, 211*t*
management of, approaches to, 13*t*
in palliative care, 12
Anxiety disorders, 2337*t*, 2342–2343, 2683
clinical manifestations of, 2342–2343, 2343*t*
definition of, 2342–2343, 2342*t*
diagnosis of, 2343
epidemiology of, 2342
generalized, 2343
panic disorder, 2343
pathobiology of, 2342
phobias, 2343
prognosis of, 2343
social, 2343
treatment for, 2340*t*, 2343*b*, 2344*t*
in women, 1608*t*, 1609
Anxiolytic drugs, 926*b*, 2363, 2363*b*–2364*b*, 2679
Aorta
anatomy of, 437*f*
diseases of, 436
layers of, 436
normal, 436
Aortic aneurysm, 436
abdominal
clinical manifestations of, 436
diagnosis of, 437, 438*f*
epidemiology of, 436
risk factors for, 436
treatment of, 438*b*
clinical manifestations of, 436
definition of, 436, 437*t*
diagnosis of, 437
epidemiology of, 436
pathobiology of, 436
prognosis for, 438
risk factors of, 436
thoracic
diagnosis of, 438, 439*f*
treatment of, 438*b*
thoracoabdominal, 436
Aortic arch
anatomy of, 2454–2455, 2455*f*
magnetic resonance angiogram of, 2455*f*
Aortic diseases, 252, 253*f*
antihypertensive drug for, 454*t*
Aortic dissection, 211*t*, 439, 441*f*
acute. *See* Acute aortic dissection
acute medical therapy for, 443*t*
echocardiographic findings, 242*t*
stroke caused by, 2470.*e1t*
Aortic regurgitation, 240, 409–410
acute, 409, 410*b*
asymptomatic, with normal left ventricular function, 407*b*–408*b*
chronic, 410*b*
clinical manifestations of, 409–410
definition of, 409
diagnosis of, 410
echocardiographic findings, 410*f*
with left ventricular dysfunction, 410–411
noninvasive evaluation of, 410
pathobiology of, 409
physical examination of, 410
Aortic root dilation, 242*t*, 1725–1726
Aortic stenosis, 400
bicuspid, 400
clinical manifestations of, 402
congenital valvular, 351, 351*b*
diagnosis of, 402–403
Doppler echocardiogram from, 403*f*
epidemiology of, 400
exercise recommendations for, 355.*e2t*
low flow, low gradient, 403
measurement of, 239, 241*f*
medical therapy for, 405*b*–406*b*
pathobiology of, 400, 400.*e2f*
pathology of, 402*f*
prognosis for, 404
treatment of, 277*f*, 403*b*–404*b*
tricuspid, 400
Aortic valve, 224
bicuspid, 347
congenitally abnormal, 400
Aortic valve area (AVA), calculation of, 239
Aortic valve replacement, 402
transcatheter, 403*b*, 404*f*
Aortic vasculitis, 442.*e2f*, 443–444
Aortitis, asymptomatic, 2019
Aortoenteric fistulas, 967
Aortography, 463*f*
AP1. *See* Activator protein-1
Apalutamide (Erleada), 1215*t*
Apatite (basic calcium phosphate)-associated arthropathy, 1815, 1815*b*, 1815*t*
APBD. *See* Adult polyglucosan body disease
APBs. *See* Atrial premature beats
APECED. *See* Autoimmune polyendocrinopathy-candidiasis-ectodermal dystrophy
Aphasia
cause of, 2409
clinical manifestations of, 2408, 2409*f*
definition of, 2408
diagnosis of, 2408–2409
in frontotemporal lobar degeneration, 2421
language comprehension difficulties in, 2408
pathobiology of, 2408
primary progressive, 2409
treatment of, 2409*b*
Apheresis platelets, 1200
Aphthous stomatitis, 2620, 2621*f*, 2621*t*
Aphthous ulcer, oral, 2320*f*, 2322*t*
Apical lung disease, 524*f*
Apicomplexa species, 2141
Apixaban, 502*t*, 505, 505*t*
administration of, 506*t*
dosage and monitoring of, 505–506
for venous thromboembolism, 478*b*, 487*b*
Aplasia cutis, 2750
Aplastic anemia
Camitta criteria for, 1128*t*
clinical features of, 1127.*e1t*
drugs and toxins associated with, 1125.*e2t*
idiopathic, 1125–1126
large granular lymphocyte leukemia in, 1126–1128
myelodysplastic syndromes *versus*, 1255
paroxysmal nocturnal hemoglobinuria in, 1126
pure red cell aplasia in, 1128–1129, 1129*b*
related bone marrow failure states and, 1125–1130
Apnea, 2442–2443
Apo A lipoproteins, metabolism of, 1406, 1407*f*
ApoAI amyloidosis, 1306*t*
ApoAII amyloidosis, 1306*t*
ApoAIV amyloidosis, 1306*t*
ApoCII amyloidosis, 1306*t*
ApoCIII amyloidosis, 1306*t*
Apomorphine, for Parkinson disease, 2487*t*
Apoptosis, 671
Apparent diffusion coefficient (ADC), 1722
Apparent mineralocorticoid excess, 816*t*
Appearance, general, 212, 257–258
Appendectomy, 953*b*–954*b*
Appendiceal neuroendocrine neoplasms, 1566–1567
Appendicitis, 953
acute, abdominal pain and, 854*t*
clinical manifestations of, 953, 954*f*, 954*t*
differential diagnosis of, 953*t*
peritonitis caused by, 957
prognosis of, 953*b*
treatment of, 953*b*
Appetite, central nervous system regulation of, 1464.*e1f*, 1464.*e1t*
Applied energy, tissue effects of, 346
Apraxia
constructional, 989
oculomotor, 2619
Apremilast (Otezla), for total knee arthroplasty, 1830.*e1t*
Aprepitant, for nausea and vomiting, 863*t*
Aptamers, 177, 177*f*
aPTT. *See* Activated partial thromboplastin time
Aquagenic urticaria, 2725
Aquaporin 2, 730
Aqueous humor, 2607
Arachnia propionica, 2066
Arachnoid cysts, 1314
Arachnoiditis, 2398
Arava. *See* Leflunomide
Arboviruses, 2274–2284, 2520
characteristics of, 2270*t*
clinical manifestations of, 2274, 2275*t*–2276*t*, 2276*t*
definition of, 2274
diagnosis of, 2274
encephalitis syndrome and, 2280–2284
infectious process of, 2274
pathobiology of, 2274
phylogeny of, 2274
in travelers, 1890*t*
treatment of, 2276*b*
vector transmission of, 2274
ARBs. *See* Angiotensin receptor blockers
Arcanobacterium haemolyticum, 2649
Ardeparin, 503*t*
ARDS. *See* Acute respiratory distress syndrome
Area under the concentration-time curve, 1891–1892
Aredia. *See* Pamidronate
Arenaviruses, 2264
Argatroban, 501*t*, 503
Argentine hemorrhagic fever, 100*b*
Argininemia, 1398*t*, 1402*t*
Argininosuccinic aciduria, 1398*t*, 1402*t*
Argon, 88*t*
Argyll Robertson pupils, 2017, 2617
Argyria, 106, 106*b*, 106*f*
Arimidex. *See* Anastrozole
Aripiprazole
for psychotic disorders, 2346*t*
for Tourette syndrome, 2494*b*–2495*b*
ARISCAT Risk Index, 2664*t*
Aristolochic acid nephropathy, chronic interstitial nephritis caused by, 793
Armed spiders, envenomation of, 710
Armodafinil
description of, 2449*t*
for narcolepsy, 2446*b*
Aromasin. *See* Exemestane
Aromatase deficiency, 1573
Aromatase inhibitors, for breast cancer, 1369*b*
ARPKD. *See* Autosomal recessive polycystic kidney disease
Array-based comparative genomic hybridization, 164
Arrhythmias
alcohol use and, 2355
approach to, 303–312, 313*b*
bradyarrhythmias, 305, 318–319
cardiac, 301
causes of palpitations and syncope, 310*t*
clinical manifestations of, 303–312
diagnosis of, 305–309
diagnostic tests, 306–309
driving in patients with, 312*t*
life-threatening, 312–317, 313*b*
pharmacotherapy for, 313*b*
preoperative evaluation considerations, 2664
psychotropic medications and, 2678*t*
re-entrant, 301, 302.*e1f*
sinus, 318, 318*f*
supraventricular, 282*b*, 322
surgery for, 347
tachyarrhythmias, 305
treatment of, 264*b*
ventricular, 332–340, 333*f*–334*f*
Arrhythmogenesis, mechanisms of, 301–302
Arrhythmogenic right ventricular cardiomyopathy, 288–291, 337, 338*f*
clinical manifestations of, 289
definition of, 288
diagnosis of, 289–290, 289*f*, 290*t*
differential diagnosis of, 290
epidemiology of, 288
in first-degree relatives, 291*t*
pathobiology of, 288–289
pathology of, 288
prognosis of, 291
treatment of, 290*b*–291*b*
Arsenic toxicity, *e1t*–*e8t*, 87, 103–104, 690*t*
clinical manifestations of, 104
diagnosis of, 101*t*, 104
epidemiology of, 103–104
pathobiology of, 104
prognosis of, 104
treatment of, 102*t*, 104*b*
Arsenic trioxide (Trisenox), 1215*t*
Arsine gas, 104
Artemether-lumefantrine, 2112*t*, 2114, 2121*t*
Artemisinin, 2114, 2121*b*

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Arterial blood gases
in asthma, 540
in pulmonary function tests, 528*t*
systemic analysis of, 639, 639*f*
Arterial blood temperature, 678
Arterial CO_2 partial pressure ($Paco_2$), 642–643
Arterial dissection, 2464
Arterial gas embolism, 593–594, 594*b*
Arterial gas embolism syndrome, 593
Arterial hypertension, 439, 444–460
cardiovascular disease risk factors in, 447, 448*t*
clinical manifestations of, 445
definition of, 444–445
diagnosis of, 445, 446*f*
epidemiology of, 444–445
essential, 445, 448*t*
first-line drugs for, 451–454
identification and treatment of, 447–450, 448*t*, 450*b*
lifestyle modification for, 450, 450*t*
management of, 450*b*
medical therapy for, 450–455
pathobiology of, 445
secondary causes of, 450
Arterial oxygen content, 640
Arterial oxygenation, 644*f*
Arterial switch operation, 354
Arterial thromboembolism, 2667
Arteriovenous malformation, 2480*f*, 2482
Artery of Adamkiewicz, 2405
Artesunate, 2112*t*, 2114
Artesunate-amodiaquine (ASAQ), for malaria, 2121*t*
Arthralgia, 2274
arbovirus that cause, 2275*t*
arthritis *versus*, 1710
Whipple disease and, 2070
Arthritis, 1712–1713
acromegaly and, 1823
amyloidosis and, 1822
arthralgia *versus*, 1710
associated with treatments, for malignant diseases, 1823
autoimmune hepatitis and, 1820
carcinomatous polyarthritis and, 1823
diabetes mellitus and, 1822
enteropathic. *See* Enteropathic arthritis
epidemiology of, 1826
in familial Mediterranean fever, 1732
fungal, 1808
granulomatous, 1736
hemoglobinopathies and, 1822
in hemophilia, 1188, 1188*f*
hemophilia and, 1822
hyperlipoproteinemia and, 1823
hypertrophic osteoarthropathy and, 1823, 1824*f*–1825*f*
hypogammaglobulinemia and, 1822
inflammatory bowel disease and, 1821
leukemia and, 1823
Lyme, 1808, 2024
lymphoma and, 1823
Mycoplasma, 1808
in older adults, 115
osteoarthritis. *See* Osteoarthritis
pathobiology of, 1826, 1826*f*
perioperative, medication for, 1830, 1830.*e1t*
reactive. *See* Reactive arthritis
rheumatoid. *See* Rheumatoid arthritis
rheumatoid factor in, 1712–1713
septic, 1804–1807
systemic diseases associated with, 1820–1826, 1821*t*, 1824*f*, 1825*f*
thyroid disorders, 1822–1823
tuberculous, 1808
ureaplasma, 1808
viral, 1807
Whipple disease and, 2070
Arthrodesis, 1827
Arthrogryposis, 2589*t*
Arthropathy
apatite (basic calcium phosphate)-associated, 1815, 1815*b*, 1815*t*
hemochromatosis and, 1440, 1824*f*
Arthropods, 710–711
centipedes, 711
lice, 711
millipedes, 711
mites, 710–711
scorpion, 710
Arthropods *(Continued)*
ticks, 710
venomous, 710.*e1f*
Arthroscopy, 1827
Articular damage, 1751
Arylsulfatase B, for mucopolysaccharidosis type VI, 1420*t*
Asbestos, exposure to, 88*t*
lung cancer and, 1329
pleural effusions after, 626
Asbestos-related diseases, 589–590, 590*f*
Asbestosis, 590, 590*f*
ASCA. *See* Anti-*Saccharomyces cerevisiae* antibodies
Ascariasis, 2169–2170
clinical manifestations of, 2169–2170
diagnosis of, 2170
epidemiology of, 2169
pathobiology of, 2169, 2169*f*
prevention of, 2170
treatment of, 2170*b*, 2170*t*
Ascaris lumbricoides, 1026*t*, 2169
acute pancreatitis and, 970
treatment for, 2170*t*
Ascites, 736, 988, 988*f*, 989*t*, 990
in cancer, management of, 1232*b*
cirrhosis and, 1036, 1038
diagnosis of, 1039, 1040*t*
malignant, 957, 958*b*
treatment of, 1040*b*–1042*b*
Ascorbic acid, *e1t*–*e8t*, 1453*t*
ASCT. *See* Autologous stem cell transplant
ASDs. *See* Atrial septal defects
Asenapine, for psychotic disorders, 2346*t*
Aseptic meningitis
cerebrospinal fluid examination in, 2521
definition of, 2519
description of, 2030–2031
differential diagnosis of, 2521
enterovirus causing, 2520
epidemiology of, 2519–2520
herpes simplex virus causing, 2521
lymphocytic choriomeningitis causing, 2521
mumps causing, 2226, 2521
Mycoplasma pneumoniae in, 2007
noninfectious causes of, 2522
nonviral infectious causes of, 2522, 2522*t*
polymerase chain reaction for, 2521
prognosis for, 2522
Ash-leaf spots, of tuberous sclerosis, 2743
Asherman syndrome, 1598
Asia, HIV/AIDS in, 2289, 2289.*e2f*
Asian taeniasis, 2159
Ask-Tell-Ask approach, 12–13, 16*t*
Aspartate aminotransferase (AST), *e1t*–*e8t*, 998, 1017
Aspartylglucosaminuria, 1423–1424
Aspergilloma, 2094, 2095*f*
Aspergillosis, 2093
acute invasive, 2094
allergic forms of, 2095
caspofungin for, 2078
chronic pulmonary, 2094
classification of, 2094*t*
clinical manifestations of, 2094
definition of, 2093
diagnosis of, 2095
epidemiology of, 2093
extrapulmonary, 2094
invasive pulmonary, 2094
itraconazole for, 2075
pathobiology of, 2094
pathogens of, 2093
prevention of, 2097
prognosis of, 2098
treatment of, 2096
voriconazole for, 2076
Aspergillus flavus, 2093
Aspergillus fumigatus, 1857–1858, 2093
Aspergillus niger, 2093
Aspergillus spp.
endocarditis caused by, 417*t*
health care-associated infections caused by, 1865
otomycosis caused by, 2095
Aspergillus terreus, 2093
Asphyxia, psychotropic medications and, 2680
Aspiration, 597
distinguishing features of, 515*t*
psychotropic medications and, 2678*t*, 2680
Aspiration injury, 597–598
clinical manifestations of, 597
definition of, 597
diagnosis of, 597
pathobiology of, 597
prevention of, 598
prognosis of, 598
treatment of, 598*b*
Aspiration pneumonia, 615–616
clinical manifestations of, 615
diagnosis of, 615–616
epidemiology of, 615
pathobiology of, 615
prognosis of, 615, 616
treatment of, 616*b*
Aspirin, 387*t*, 506–507
for acute coronary syndrome, 374*t*
for acute STEMI, 384*b*, 391*t*
anaphylaxis caused by, 1692
for atherosclerotic PAD, 464*b*
for Fabry disease, 1423*b*
for frostbite, 474*b*
gastric ulcers and, 914–915
for homocystinuria, 1427
for ischemic heart disease, 470*b*
after PCI, 397
pharmacokinetic parameters for, 127.*e1t*
for postoperative care with substitute heart valves, 411–412
as preventive medications, 56
reactions to, 1698, 1698*t*
in renal failure, 129.*e1t*
Aspirin-exacerbated respiratory disease, 541*b*
Aspirin-induced asthma, 541*b*
Asplenia, immunization and, 76.*e2t*
Assessment, geriatric, 116–119
Assistance, in health delivery systems, 47, 48*f*
Assisted mechanical ventilation, 653
Assisted reproductive technologies
for infertility, 1603*b*–1604*b*
venous thromboembolism and, 481
Assisted suicide, 8–9
definition of, 8, 8*t*
empirical data for, 8–9
history of, 8
justification of, 8
practical considerations, 9
AST. *See* Aspartate aminotransferase
Asterixis, 989
Asthma, 537–547
allergic, 1673*t*, 1674
aspirin-induced, 541*b*
blood findings, 540
Chlamydia pneumoniae and, 2013
chronic obstructive pulmonary disease *versus*, 550
clinical manifestations of, 539
Crohn disease and, 943
cystic fibrosis and, 557
definition of, 537–547
diagnosis of, 539–541
differential diagnosis of, 541
ECG findings, 541
in emergency department, 541*b*
epidemiology of, 537–538
genetics of, 538
with heart failure, 265*b*
history in, 539
human microbiome and, 1840
increased eosinophils counts in, 533
laboratory findings of, 539–540
medications, 541*b*, 546*t*
obesity and, 533
occupational and environmental, 86, 86*t*
as occupational lung disease, 585*t*
pathobiology of, 538–539
physical examination of, 539
in pregnancy, 541*b*, 1619*t*
prevalence of, 538
prevention of, 541*b*
prognosis for, 547
pulmonary function findings, 539, 539*t*, 540*f*
with pulmonary infection, 541*b*
radiographic findings of, 540–541, 541*f*
rescue treatments for, 541*b*
in sickle cell disease, 1113–1114
sputum findings of, 541
treatment of, 541*b*, 542*f*
in women, medications for, 1608*t*
Astigmatism, 2598
Astra-Zeneca, 2219
Astrakhan fever, 2055*t*, 2057
Asymmetrical perfusion, 522–523
Asymptomatic bacteriuria, 1873, 1875*b*–1877*b*
Asymptomatic hyperuricemia, 1811
Asymptomatic hypoglycemia, 1546*t*
Asymptomatic infection, Whipple disease and, 2069
Asymptomatic intraluminal amebiasis, 2147
Asynchronous pubertal development, 1594
Asystole, 313*b*
At-risk drinking, 2353, 2353*t*
Ataxia
cerebellar, 2497–2498, 2497*b*, 2497*t*
Friedreich, 279–280, 2497
in multiple sclerosis, 2501
spinocerebellar, 2497
treatment of, 758*b*
Ataxia telangiectasia, 1250*t*, 2550*t*–2551*t*
Ataxia-telangiectasia, 1679, 1679*b*, 1679*t*
Ataxic breathing, 2438, 2439*t*
Atazanavir, 2301*t*, 2303, 2313
Atelectasis, 562–563, 563*b*, 563*f*
clinical manifestations of, 563
definition of, 562–563
diagnosis of, 563, 563*f*
epidemiology of, 563
pathobiology of, 563
rounded, 563, 563*f*
Atenolol, 451*t*
for alcohol withdrawal, 2358*t*
for premature ventricular contractions, 338*b*
for TSHomas, 1497*b*
Atenolol/chlorthalidone, 451*t*
Atezolizumab (Tecentriq), 1215*t*, 1394*t*
ATG16L1 gene, 942
Atheroembolic disease, 1142
Atherogenesis, 1406, 1407*f*
Atheromatous embolization, 469*t*–470*t*, 470*b*, 470*t*, 801, 801*b*, 802*f*
Atherosclerosis
cardiac risk factors associated with, 227
Chlamydia pneumoniae and, 2013
pathophysiology of, 227, 227.*e1f*
plaque activation of, 227, 227*f*, 227.*e1f*
regression of, 1406, 1406.*e1f*
Atherosclerotic cardiovascular disease (ASCVD), 1406, 1406.*e1f*, 1407*f*
prevention of, 1410
statin therapy for, 1411
Atherosclerotic peripheral arterial disease, 461–466
antiplatelet therapy for, 464*b*
antithrombotic therapy for, 464*b*
epidemiology of, 461
exercise therapy for, 464*b*
imaging of, 463–465, 463*f*, 464*f*
pathobiology of, 461–462
pharmacology of, 464*b*
prognosis for, 465
revascularization for, 464*b*, 464.*e1f*
risk factor modification for, 464*b*
Atherosclerotic renal artery stenosis, 800*b*, 800*t*
Atherosclerotic therapy, 227
Atherothrombosis, 2464
Athetosis, 2493
Athletes, electrocardiograms in, 234, 234*t*, 235*f*
Athlete's heart, 235*f*
ATI. *See* Acute tubular injury
ATN. *See* Acute tubular necrosis
Atomoxetine, for orthostatic hypotension, 2559*t*
Atopic asthma, 538
Atopic dermatitis, 1673*t*, 1674, 2702–2703, 2703*f*
Atopic diseases, 1672
Atopic keratoconjunctivitis, 1673*t*
Atorvastatin
for acute STEMI, 384*b*, 391*t*
for familial hypercholesterolemia, 1409*t*
for ischemic heart disease, 470*b*
Atovaquone, 2115
for amoebic encephalitis, 2112*t*
for babesiosis, 2112*t*, 2115, 2152*b*–2153*b*, 2152*t*
for *Pneumocystis* pneumonia, 2103*b*, 2106*t*, 2108*t*
for toxoplasmosis, 2112*t*, 2140*t*
Atovaquone-proguanil, 2115
for malaria, 1887–1888, 2112*t*, 2121*b*
ATRA. *See* All-*trans*-retinoic acid

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Atresia
  intestinal, 951
  tricuspid, 354–356
  vaginal, 1574
Atrial beats, complete heart block with, 321*f*
Atrial-esophageal fistulas, 912–913
Atrial fibrillation, 323*t*, 328–332, 328*f*
  antihypertensive drug for, 454*t*
  catheter ablation for, 346
  chronic persistent, 329*b*–332*b*
  clinical manifestations and diagnosis of, 329
  management of, 384*b*
  paroxysmal, 329*b*, 330*f*
  prognosis of, 331*t*, 332
  recent-onset, 329*b*, 330*f*
  renal infarction caused by, 802
  stroke caused by, 2464
  surgical ablation of, 347
  treatment of, 265*b*, 329*b*
  of uncertain duration, 329*b*, 330*f*
Atrial flutter, 323*t*, 326–327, 327*b*, 328*f*
Atrial myxoma, 2470.*e1t*
Atrial natriuretic peptide (ANP), 730, 734
Atrial premature beats (APBs), 322, 322*f*–323*f*
Atrial premature depolarizations, 328
Atrial septal defects (ASDs), 347
  classification of, 348–349
  color flow Doppler findings, 349.*e1f*
  diagnosis of, 349
  ECG findings, 349, 349*f*
  exercise recommendations for, 355.*e2t*
  prognosis for, 349*b*
  treatment of, 349*b*
Atrial tachycardias, 323*t*, 324, 324*f*
Atrioventricular (AV) block, 317*t*
  first-degree, 229, 320, 320*f*
  high-degree or advanced, 321, 321*f*
  Mobitz type I (Wenckebach), 306, 320, 320*f*
  third-degree, 321, 321*f*
Atrioventricular (AV) canal defect, 354
Atrioventricular (AV) conduction disturbances, 319–321, 321*b*
Atrioventricular (AV) dissociation, 321, 335
Atrioventricular nodal re-entrant tachycardia (AVNRT), 323*t*, 324, 324*b*, 324*f*, 327*f*
Atrioventricular (AV) node
  abnormalities, medications for, 319*t*
  two-to-one conduction in, 320*f*
Atrioventricular re-entrant tachycardia (AVRT), 323*t*, 326, 328*f*
Atrophic gastritis, 1340
Atrophic lesions, 2736–2737, 2737*f*, 2737*t*
Atrophic rhinitis, 2631
Atropine
  for acute poisoning, 693*t*
  for bradycardia, 313*b*, 316*f*, 384*b*
  for sinus node dysfunction and AV blocks, 321*b*
ATTRV50M, amyloidosis and, 1309
ATTRV122I, amyloidosis and, 1309
ATTRwt amyloidosis, 1306*t*, 1309, 1309*b*
Atypical absence seizures, 2430
Atypical adenomatous hyperplasia, 1329
Atypical bacterial pneumonia, characteristics of, 2270*t*
Atypical chronic myeloproliferative diseases, 1277–1278, 1278*b*
Atypical hemolytic-uremic syndrome, 201*t*, 1178
Atypical lymphocyte, 2253, 2254*f*
Atypical melanocytic nevi, 2733*f*
Atypical parkinsonism, 2486
Atypical squamous cells of undetermined significance (ASC-US), 1376
Aubagio. *See* Teriflunomide
Audiometry, for hearing loss, 2641
Auditory pathways, lesions within, localization of, 2641
Auditory system, disorders of, 2641–2643
  definition of, 2641–2643
  diagnosis of, 2641–2642
  epidemiology of, 2641
  pathobiology of, 2641
  tinnitus, 2643, 2643*b*, 2643*f*
  treatment of, 2642*b*
Auer rods, 1073, 1073*f*
Auerbach plexus, 887, 901
Augment clotting, for hemophilia, 1188*b*
Aura, 2376, 2378
Auscultation
  cardiac, 214, 215*f*, 216*t*
  lung, 512*t*
Auscultatory office blood pressure, 446–447, 446*t*
Autism spectrum disorders, 2548, 2548*b*, 2548*t*
Auto-PEEP, 654, 654.*e1f*
Autoantibodies, 194
  in rheumatic diseases, 1715*t*
  in systemic lupus erythematosus, 1768, 1768.*e2f*, 1772*t*
  in systemic sclerosis, 1776, 1777*t*
Autografts, 412*t*
Autoimmune acquired hypoparathyroidism, 1661
Autoimmune autonomic disorders, 2558–2560
Autoimmune conditions, in women, medications for, 1608*t*
Autoimmune cytopenias, in chronic lymphocytic leukemia, 1267
Autoimmune destruction, of adrenal gland, 1526
Autoimmune disease, 193
  bronchiectasis and, 560
  in pregnancy, 1619*t*
  treatment of, 1853*t*
Autoimmune encephalitis, 2535–2536
  clinical manifestations of, 2536
  diagnosis of, 2536
  epidemiology of, 2535–2536
  neural antigen targets and, 2536*t*
  pathobiology of, 2535
  prognosis of, 2536
  treatment of, 2536
Autoimmune ganglionopathies, 2554, 2554*t*
Autoimmune hemolytic anemia (AIHA), 1087–1089
  cold, 1088–1089, 1088*t*, 1090*f*
  corticosteroids for, 1089*b*–1091*b*
  diagnosis of, 1087–1089
  direct antiglobulin test for, 1087–1088
  epidemiology of, 1087
  folic acid supplementation for, 1089*b*
  laboratory test for, 1087
  pathobiology of, 1087
  rituximab for, 1089*b*
  signs and symptoms of, 1087
  splenomegaly associated with, 1152
  warm, 1087, 1089*t*
Autoimmune hepatitis, 1016–1017, 1017*b*
  acute manifestation of, 986
  arthritis associated with, 1820
  in pregnancy, 1625*t*
Autoimmune hypocalciuric hypercalcemia, 1658
Autoimmune hypophysitis, hypogonadotropic hypogonadism and, 1584
Autoimmune inner ear disease, 2645
Autoimmune lymphoproliferative syndrome (ALPS), 1684*t*
Autoimmune pancreatitis, 970, 970*t*
Autoimmune pericarditis, 424*t*, 432–433
Autoimmune polyendocrinopathy-candidiasis-ectodermal dystrophy (APECED), 1684*t*, 2090
Autoimmune polyglandular syndrome, 1559–1560
  clinical features of, 1559*t*
  type 1, 1559–1560, 1560*b*
  type 2, 1560, 1560*b*
  type 3, 1560, 1560*b*
  type 4, 1560, 1560*b*
Autoimmune regulator-1 (AIRE-1), 1559–1560
Autoimmune syndromes, chronic, 2510
Autoimmune testicular failure, 1584
Autoimmune thyroiditis, radiographic evaluation of, 1511*t*
Autoimmunity, 191, 1693
  complement system in, 197
  in systemic lupus erythematosus, 1768
  in systemic sclerosis, 1776
Autoinflammation, with arthritis and dyskeratosis, 1731*t*
Autoinflammation and PLCγ2-associated antibody deficiency and immune dysregulation (APLAID), 1731*t*
Autoinflammatory diseases, 1708
Autoinflammatory disorders, 1686
Autoinflammatory rheumatic diseases, 1708
Autologous hematopoietic cell transplantation, 1208
Autologous stem cell transplant (ASCT), for amyloidosis, 1308*f*–1309*f*
Autologous transplants, 203
Automated blood pressure machines, 33
Automated external defibrillators, 313*b*, 314*t*
Automatic junctional tachycardia, 323*t*
Automaticity, abnormal, 301
Autonomic disorders, 2553–2561
  autoimmune, 2558
  autonomic function tests for, 2556–2557
  classification of, 2554*t*
  clinical evaluation of, 2555–2556, 2556*f*, 2556*t*
  clinical manifestations of, 2554–2555
  definition of, 2553–2557
  diagnosis of, 2555–2557
  epidemiology of, 2553
  laboratory evaluation of, 2556, 2557*t*
  metabolic, toxic, and infectious causes of, 2560–2561
  pathobiology of, 2553–2554
  pathogenesis of, 2554, 2554*t*
  regional sympathetic dysfunction, 2561
  systemic, 2553–2557
  treatment for, 2557*b*–2558*b*
Autonomic failure, 2554–2555
Autonomic hyperactivity, 2555
Autonomic nervous system dysfunction, for tetanus, 1929*b*
Autonomic neuropathy
  in diabetes mellitus, 2577
  in HIV/AIDS, 2313
Autonomy, 4
Autosomal dominant hypocalcemia type 1 (ADH1), 1661
Autosomal dominant hypocalcemia type 2 (ADH2), 1661
Autosomal dominant hypophosphatemic rickets, 1648
Autosomal dominant inheritance, 160–161, 161*f*
Autosomal dominant polycystic kidney disease (ADPKD), 808–812
  clinical manifestations of, 811
  diagnosis of, 811–812, 811*f*
  gene products of, 810–811, 810.*e1f*
  genetics of, 808–810
  monitoring progressive renal disease in, 812
  pathobiology of, 808–811, 810*f*
  treatment of, 812*b*, 812.*e1f*
Autosomal dominant tubulointerstitial kidney disease (ADTKD), 795, 809*t*, 810*f*, 814, 814*b*, 818
Autosomal recessive inheritance, 161–162
Autosomal recessive polycystic kidney disease (ARPKD), 809*t*, 812–813
  clinical manifestations of, 813
  definition of, 812–813
  diagnosis of, 811*f*, 813
  epidemiology of, 812
  pathobiology of, 813
  prognosis of, 813
  treatment of, 813*b*
Autosomal recessive pseudohypoaldosteronism, type 1, 761–762
AV block. *See* Atrioventricular block
AV dissociation. *See* Atrioventricular dissociation
AV node. *See* Atrioventricular node
Avastin. *See* Bevacizumab
Avellis syndrome, 2465.*e2f*
Avelumab (Bavencio), 1215*t*
Avermectin, 2117
Avian influenza (H5N1), 2065*t*, 2199
AVNRT. *See* Atrioventricular nodal re-entrant tachycardia
Avoidant personality disorder, 2348*t*
Avoidant/restrictive food intake disorder, 1461, 1462*b*
Avonex. *See* Interferon Beta1*a*
AVRT. *See* Atrioventricular re-entrant tachycardia
Avulsion of flexor digitorum profundus, 1745–1746
Awaji-Shima consensus criteria, for amyotrophic lateral sclerosis, 2563*t*
Awareness, in health delivery systems, 47, 48*f*
Axial disease, 1710
Axillary buboes, 1991
Axillary lymph node metastases, treatment of, 1241*b*
Axitinib (Inlyta), 1215*t*, 1364*b*–1365*b*
Axonal injury, 2386, 2386.*e1f*
Azacitidine (Vidaza), 1215*t*, 1255
Azalides, mechanism of action, 1895*t*
Azathioprine, 148
  for Crohn disease, 945*b*, 946*t*
  for liver transplantation, 1048*t*
  for myocarditis, 286*b*
  in renal transplantation, 845*t*
  for rheumatoid arthritis, 1756*t*
  for systemic lupus erythematosus, 1772*b*
  for total knee arthroplasty, 1830.*e1t*
AZF. *See* Azoospermic factor
Azilsartan, 451*t*
Azilsartan/chlorthalidone, 451*t*
Azithromycin
  for acute bronchitis and tracheitis, 606*b*
  for babesiosis, 2112*t*, 2152*b*, 2152*t*
  for bronchiectasis, 561*b*
  for cat-scratch disease, 2003*b*
  for chancroid, 1951*b*
  for *Chlamydia trachomatis*, 2012*b*
  for cholera, 1956*b*
  for chronic obstructive pulmonary disease exacerbations, 555
  for COVID-19, 2217–2218
  for cystic fibrosis, 558*b*
  for diarrhea, 926*b*
  dosage of, 1895*t*
  for gonorrhea, 1948*b*
  for granuloma inguinale, 2004*b*
  for HIV/AIDS, opportunistic infections associated with, 2309*t*
  for legionnaires disease, 1999*t*
  for leptospirosis, 2031*b*
  for Lyme disease, 2026*t*
  for meningococcal disease, 1945*t*
  for nontuberculous mycobacterial disease, 2046*t*
  for pertussis, 1996
  for pneumonia, 613*t*
  for *Streptococcus pneumoniae* pulmonary infections, 1912.*e1t*
  for toxoplasmosis, 2140*t*
  for trachoma, 2010*b*
  for traveler's diarrhea, 1888, 1888*t*
  for typhoid fever, 1979*b*
  for urethritis, 1880*t*
  for yaws, 2021–2022, 2022*b*
Azole antifungal agents, 2074, 2085*b*
  fluconazole as, 2075
  indications and dosage of, 2075
  isavuconazole as, 2077
  itraconazole as, 2074
  mechanisms of action, 2074
  posaconazole as, 2076
  voriconazole as, 2076
Azoospermia, 1586
Azoospermic factor (AZF), 1586
Azotemia
  caused by amphotericin B, 2077
  postoperative, 2676
  severe mental illness and, 2683*t*
Aztreonam
  for bacterial meningitis, 2518*t*
  dosage of, 1895*t*
  for pneumonia, 613*t*
Azulfidine. *See* Sulfasalazine

B

B19 arthropathy, 2234. *See also* Parvovirus
B19 parvovirus, 2233, 2235*t*
Babesia, 1203
Babesia crassa, 2151
Babesia divergens, 2151
Babesia duncani, 2151
Babesia microti, 1026*t*, 2065*t*, 2151, 2152*f*–2153*f*
Babesia motasi, 2151
Babesia venatorum, 2151
Babesiosis, 1203, 2065*t*, 2115, 2151–2153
  clinical manifestations of, 2151
  diagnosis of, 2151–2152, 2152*f*, 2153*f*
  epidemiology of, 2151–2153
  pathobiology of, 2151
  prevention of, 2153
  prognosis of, 2153
  treatment of, 2112*t*, 2152*b*, 2152*t*
Baby boomers, 114
Bacillary angiomatosis, 2002–2003, 2002*f*, 2003*b*, 2003*t*
Bacillary dysentery, characteristics of, 2270*t*
Bacillus anthracis, infections caused by, 1930*f*, 2515*b*–2518*b*
  clinical manifestations of, 1931–1932, 1931*f*
  diagnosis of, 1932
  epidemiology of, 1930
  pathobiology of, 1931
  prevention of, 1932–1933
  treatment of, 1932*b*
Bacillus Calmette-Guérin (BCG) vaccine, 1215*t*, 2043, 2053

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Bacillus cereus, infections caused by, 1930
  clinical manifestations of, 1932
  diagnosis of, 1932
  pathobiology of, 1931
  prevention of, 1933
  treatment of, 1932*b*
Bacillus spp., infections caused by, 1930–1933
  clinical manifestations of, 1931–1932, 1931*f*
  definition of, 1930
  diagnosis of, 1932
  epidemiology of, 1930
  pathobiology of, 1931
  pathogen of, 1930, 1930*f*
  prevention of, 1932–1933
  prognosis of, 1933
  treatment of, 1932*b*
Bacillus thuringiensis, infections caused by, 1930
Bacitracin, for eye infection, 2605*t*
Back pain, 136*b*
Backwash ileitis, 944–945
Baclofen
  for chronic pain, 138*t*
  for spastic paraplegias, 2498*b*
Bacteremia, 2001*t*, 2002
  Acinetobacter causing, 1973
  anaerobic bacteria causing, 1938
  Campylobacter jejuni causing, 1959
  cellulitis caused by, 2740
  clinical manifestations of, 2002
  definition of, 669
  diagnosis of, laboratory methods for, 2003*t*
  in endoscopy, 876*t*
  enteric infections and, 1870*t*
  enterococci causing, 1921
  epidemiology and pathobiology of, 2002
  intraerythrocytic, 2000–2001, 2001*t*
  meningococcal, 1943*f*
  Pseudomonas infections causing, 1969, 1970*b*
  Salmonella causing, 1978
  Staphylococcus aureus causing, 1902, 1906*t*
  Streptococcus pyogenes causing, 1915
  systemic, hepatobiliary abnormalities affected by, 1023
  treatment of, 1921*b*–1924*b*, 1922*t*
Bacteria
  anaerobic. *See* Anaerobic bacteria
  peripheral blood smear of, 1074*t*
  in subarachnoid spaces, 2512
Bacterial ascites, in endoscopy, 876*t*
Bacterial conjunctivitis, 2604, 2605*f*, 2605*t*
Bacterial endocarditis, 2515, 2609, 2610*f*
  definitive therapy of, 419*t*
  pathogens and empirical therapy for, 2526*t*
  subacute, 195
Bacterial esophagitis, 912
Bacterial infections
  of liver, 1022–1023
  neutrophilia and, 1140–1141
  non-abscess hepatic, 1023
  of skin, 2739–2741, 2739*t*
    cellulitis as, 2739–2740, 2740*f*
    folliculitis as, 2739
    furuncles as, 2739, 2740*f*
    impetigo as, 2739, 2739*f*
    mycobacterial infections as, 2741
    Neisseria infections as, 2741, 2741*f*
    Pseudomonas infections as, 2741
    spirochetes as, 2741
    toxic erythemas as, 2740–2741
  in women, medications for, 1608*t*
Bacterial liver abscess, 1022*t*
Bacterial meningitis
  antimicrobial agents for, 2515*b*
  blood and respiratory tract cultures, 2514
  brain swelling in, 2515*b*
  cerebral blood flow in, 2512
  cerebrospinal fluid examination in, 2374*t*, 2513–2514, 2513*t*
  chemoprophylaxis for, 2519
  in children, 2511
  clinical manifestations of, 2512–2513
  coagulopathies associated with, 2518
  complications of, 2513, 2518
  corticosteroids for, 2515*b*
  definition of, 2510–2519
  diagnosis of, 2513–2519
  differential diagnosis of, 2514–2515
  epidemiology of, 2510–2511
  genetics of, 2512
  hypotension, 2515*b*
Bacterial meningitis *(Continued)*
  laboratory findings in, 2513–2514
  lactic acid in, 2514
  magnetic resonance imaging of, 2511
  neurologic findings in, 2513
  nosocomial, 2517*t*
  pathobiology of, 2511–2512
  pathogenesis of, 2511–2512
  pathology of, 2511
  physical findings in, 2512–2513
  prevention of, 2519
  prognosis for, 2519
  radiologic studies for, 2514
  recurrent, 2518–2519
  seizures in, 2513
  signs and symptoms of, 2512*t*
  supportive care for, 2515*b*
  surgery for, 2515*b*
  treatment of, 2519*b*
  vaccination for, 2519
Bacterial overgrowth
  antibiotics for, 889*b*
  gastrointestinal motility disorders and, 889
  intestinal, 932*t*, 934
    clinical manifestations of, 934
    diagnosis of, 931*t*–932*t*, 932*t*, 934
    treatment of, 934*b*
  tests for, 931*t*
Bacterial pericarditis, 426*t*, 431
Bacterial pneumonia, 566
  in left upper lobe, computed tomographic scan of, 521*f*
  in travelers, 1891*t*
Bacterial superinfection, of skin lesions, varicella and, 2248
Bacterial tonsillitis, 2649*t*
Bacterial vaginosis
  characteristics of, 1882
  organisms causing, 1879*t*
  treatment of, 1882*b*
Bactericidal, defined, 1894
Bactericidal antibiotics, for anthrax, 1932*b*
Bacteriology, for nocardiosis, 2073–2074
Bacteriostatic, defined, 1894
Bacteroides, 2068
Bacteroides fragilis, 1833
Bactrian. *See* Mupirocin
BAFF. *See* B-cell-activating factor
Bafiertam. *See* Monomethylfumarate
Baker cyst, 1752, 1752.*e*1*f*. *See also* Popliteal cysts
Balamuthia mandrillaris, 2150*t*
Balance activity, 63*b*
Balance training, 63*b*
Balancing professional responsibilities, 4–5
Balantidium coli, 2156, 2156*t*
Ballism, 2491–2492, 2492*t*
Balloon catheters, 395, 395*f*
Balloon-expandable coronary stents, 395.*e*1*f*
Balloon pumps, intra-aortic, 667*b*–669*b*
Baloxavir, for influenza, 2202*b*–2203*b*, 2203*t*
Baloxavir marboxil, for influenza virus infections, 2189, 2189*t*
Balsalazide (Colazal), for inflammatory bowel disease, 946*t*
Balversa. *See* Erdafitinib
Bamlanivimab/etesevimab, for coronavirus infections, 2190
Banana spiders, envenomation of, 710
BAP1. *See* BRCA1- associated protein
Barbiturates
  central nervous system effects of, 685*t*
  reactions to, 1698*t*
Bardet-Biedl syndrome, 809*t*
Bariatric surgery
  for obesity, 1467*b*–1469*b*
  for type 2 diabetes mellitus, 1540*b*–1544*b*
Baricitinib (Olumiant), 153*t*, 1755*b*, 1756*t*
  for total knee arthroplasty, 1830.*e*1*t*
Barium radiograph, of peptic stricture, 904*f*
Barlow type valve, 406.*e*1*f*
Barotrauma, 593
  clinical manifestations of, 594
  definition of, 593–594
  diagnosis of, 594
  epidemiology of, 593
  to middle ear, 2641
  pathobiology of, 594, 594.*e*1*f*
  prevention of, 594
  treatment of, 594*b*
Barrett esophagus, 905–906, 1338–1339
  clinical manifestations of, 905
  diagnosis of, 904*f*, 905–906
  epidemiology of, 905
  fluoroscopy of, 869*f*
  pathobiology of, 905
  prognosis of, 906
  treatment of, 904*t*, 906*b*, 906*f*
Barrier methods, for disseminated gonococcal infection, 1950
Barth syndrome, 1145
Bartonella alsatica, 2000, 2000*t*
Bartonella ancashensis, 2000, 2000*t*
Bartonella bacilliformis, 2000, 2000*t*
Bartonella clarridgeiae, 2000, 2000*t*
Bartonella elizabethae, 2000, 2000*t*
Bartonella grahamii, 2000, 2000*t*
Bartonella henselae, 1142, 1150, 2000, 2000*t*
Bartonella infections, 2000–2003
  bacillary angiomatosis as, 2002
  bacteremia and endocarditis as, 2002
  cat-scratch disease as, 2001–2002
  clinical manifestations of, 2000, 2001*t*
  definition of, 2000
  diagnosis of, 2002–2003
    alternative methods in, 2001*f*, 2002, 2003*t*
    mass spectrometry in, 2002
    molecular detection methods in, 2002
  differential diagnosis of, 2003
  endocarditis caused by, 417*t*
  epidemiology of, 2000, 2000*t*
  Oroya fever and trench fever as, 2000
  pathobiology of, 2000
  peliosis hepatis as, 2002
  prevention of, 2003
  prognosis of, 2003
  treatment for, 2003*b*
  verruga peruana as, 2002
Bartonella koehlerae, 2000, 2000*t*
Bartonella mayotimonensis, 2000, 2000*t*
Bartonella quintana, 2000, 2000*t*
Bartonella rochalimae, 2000, 2000*t*
Bartonella tamiae, 2000, 2000*t*
Bartonella vinsonii arupensis, 2000, 2000*t*
Bartonella vinsonii berkhoffii, 2000, 2000*t*
Bartonella washoensis, 2000, 2000*t*
Bartter syndrome, 749, 749*t*, 816*t*, 817, 817*b*, 817.*e*1*f*
Barttin, 817
Basal cell skin cancer, 1395–1396, 1395*f*, 1396*b*
Basal lung disease, 523–524, 523*t*
Basal metabolic rate (BMR), 1465
Basal pulmonary disease, 524*f*
Basaloid, 977
Basaloid squamous cell carcinoma, 1324*f*
Base excess, *e*1*t*–*e*8*t*
Basic calcium phosphate arthropathy, 1815, 1815*b*, 1815*t*
Basic life support (BLS), after cardiac arrest, 313*b*
Basilar artery, 2465
  anatomy of, 2456
  occlusion of, 2465
Basilar skull fracture, 2513
Basiliximab, in renal transplantation, 845*t*
Basophilic stippling
  conditions associated with, 1072*t*
  peripheral blood smear of, 1070*f*
Basophilopenia, 1148
Basophils, 183
Bat-borne viruses, 2264
Batteries, pacemaker, 342
Battering, 1633
Bavencio. *See* Avelumab
Bayes theorem, 38, 38.*e*1*t*
Baylisascariasis, 2065*t*, 2174
Baylisascaris spp., 2065*t*
Bazedoxifene, for osteoporosis, 1644*t*
Bazett's formula, 230
Bazex syndrome, 2710
B-cell(s), 204*t*
  development, 187, 187*f*
  differentiation of, 190
  stimulation and accessory molecules of, 189
B-cell-activating factor (BAFF), 151, 185–186
B-cell lymphoma
  diffuse large, 1279, 1284–1285, 1285*b*
    subtypes of, 1285, 1285*b*
  marginal, in Sjögren syndrome, 1785
  mature, 1283–1286
B-cell lymphoma *(Continued)*
  precursor, 1281–1282, 1282*b*
  primary mediastinal large, 1285
  rare types of, 1286
B-cell receptor
  in chronic lymphocytic leukemia, 1267
  genetic defects of, 1680, 1681*t*
BCG. *See* Bacillus Calmette-Guérin
B-complex vitamins, for malabsorption, 937*t*
Beau lines, 2752, 2752*f*, 2752*t*
Bebtelovimab, for coronavirus infections, 2190–2191
Becker disease, 2583.*e*1*t*
Becker muscular dystrophy, 2584, 2584*b*
Beclomethasone, 543*t*, 553*t*
Bedaquiline, dosage of, 1895*t*
Bedbugs, 711, 712*f*
Bedside radiography, 519
Beer potomania syndrome, 738
Behavior
  alcohol use disorders and, 2355*t*, 2356
  modification of, for obesity, 1467*b*
Behavioral determinants, of human blood pressure variation, 445
Behavioral intervention
  for alcohol use disorders, 2357*b*
  for disseminated gonococcal infection, 1950
  for urinary incontinence, 829*b*–830*b*
Behçet disease, 1731*t*, 1799, 2621*t*
  epidemiology of, 1793*t*
  of esophagus, 911
  intestinal ulcers associated with, 956
  prognosis of, 1799*b*
  treatment of, 1799*b*
Belatacept, in renal transplantation, 845*t*
Belching, 858
Beleodaq. *See* Belinostat
Belimumab (Benlysta), 1714, 1772*b*, 1830.*e*1*t*
Belinostat (Beleodaq), 1215*t*
Bell palsy, 1322, 2579, 2579*f*
Bempedoic acid, 1413
Benazepril, 451*t*
Benazepril/HCTZ, 451*t*
Bence Jones protein, 1294
Bendamustine (Treanda), 1215*t*
  for chronic lymphocytic leukemia, 1269*b*–1271*b*, 1269*t*, 1270*t*
  for mantle cell lymphoma, 1284*b*
Bendopnea, 256, 265*b*
Benedikt syndrome, 2465.*e*1*f*
Beneficence, 8
Benign asbestos disease, 589–590
Benign biliary strictures, 1056–1058, 1057*f*–1058*f*, 1058*f*
Benign breast lesions, 1374
Benign capillary hemangioma, 2731–2733, 2734*f*
Benign cramp-fasciculation syndrome, 2564*t*
Benign epidermal tumors, 2729–2730
Benign familial neutropenia, 1143
Benign hepatocellular adenoma, 1615
Benign migratory glossitis, 2623
Benign papules, of skin, 2729–2736
Benign paroxysmal positional vertigo, 2644, 2645*f*, 2647*t*
Benign prostatic hyperplasia (BPH), 821–823
  clinical manifestations of, 822
  definition of, 821, 821*f*
  diagnosis of, 822–823, 823*f*
  epidemiology of, 821
  laboratory findings of, 822–823
  management of, algorithm of, 824*f*
  pathobiology of, 821–822
  prognosis of, 823
  treatment of, 822*b*
Benign recurrent intrahepatic cholestasis, 997
Benlysta. *See* Belimumab
Benralizumab, for eosinophilic syndromes, 1164*b*
Benzathine penicillin G
  for nonsyphilitic treponematoses, 2019
  for yaws, 2022*b*
Benzene, 88*t*
Benzimidazoles, 2161*b*
Benznidazole, for Chagas disease, 2112*t*, 2116, 2128*b*
Benzodiazepines
  for alcohol withdrawal, 2358*t*
  for anxiety disorders, 2344*t*
  for catatonia, 2681*b*
  central nervous system effects of, 685*t*
  misuse, 2363

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Benzodiazepines *(Continued)*
for nausea and vomiting, 863*t*
for neuroleptic malignant syndrome, 2681*b*
screening for, 689*t*
for tetanus, 1929*b*
Benzoyl peroxide, for skin diseases, 2699
Benzyl alcohol, for lice, 711*b*
Benzyl benzoate, for scabies, 711*b*
Bepridil, 367*t*
Bereavement services, in hospice, 16
Berger disease, 969
Beri-beri, 2537
Bernard-Soulier syndrome, 1183*b*, 1184*f*, 1185
Bernoulli equation, simplified, 238
Beryllium, 88*t*
Beryllium disease, chronic, 589
Best Case/Worst Case communication framework, 15–16, 16.e1*f*
"Best-corrected visual acuity", 2615
"Best practices", 43–44
Betacoronavirus, 2209*t*
Betaine, 1427*b*
Betaseron. *See* Interferon Beta1b
Betaxolol, 451*t*
Bethesda criteria, for HNPCC, 1347
Bevacizumab (Avastin), 1186*b*, 1215*t*, 1251*t*, 1315*b*, 1369*b*
Bexarotene (Targretin), 2698
Bezlotoxumab, 1845*t*
Bicalutamide (Casodex), 1215*t*
Bicarbonate, *e1t–e8t*, 754
description of, 639
regulation of, 731–732, 731.e1*f*, 732*f*
for rhabdomyolysis, 717*b*, 717*t*
for salicylate intoxication, 759
Bicipital tendinosis, 1744, 1744*b*
Biclonal gammopathies, 1297
Bictegravir, 2301*t*
Bicuspid aortic valve, 347
Bifidobacterium dentium, 2066
Bifidobacterium infantis, for irritable bowel syndrome, 896*t*
Big-K channels, 746
Biguanides, for type 2 diabetes mellitus, 1541*t*
Bilateral primary adrenal disease, 1523
Bilateral subpulmonic pleural effusions, 525*f*
Bilateral violence, 1633
Bilateral vocal fold motion impairment, 2653
Bile, bilirubin in, 994
Bile acid diarrhea, 939, 939*b*
Bile acid sequestrants, 1413
for irritable bowel syndrome, 895*b*, 896*t*
Bile duct stones, 1054–1056. *See also* Choledocholithiasis
clinical manifestations of, 1054
complications of, 1055*b*, 1056*f*
diagnosis of, 1049.e1*f*, 1055, 1055*f*
pathobiology of, 1054
prevention of, 1056
treatment of, 1055*b*
Bile duct tumors, 1060
Bile salt, synthesis and delivery of, decreased, 933–934
Biliary and pancreatic ductal dilatation, magnetic resonance imaging of, 873*f*
Biliary cholangitis, 987
Biliary fistula, 1059
Biliary sphincterotomy, 1055*b*, 1056*f*
Biliary tract
anatomy of, 1358*f*
cystic fibrosis and, 556
Biliary tract cancers
clinical manifestations of, 1359
diagnosis of, 1360, 1360*f*
epidemiology of, 1358
pathobiology of, 1359, 1359*f*
prevention of, 1362
primary, 1357.e3*t*
prognosis of, 1362
treatment of, 1360*b*
Biliary tract disease, 996–1000, 998*f*
Bilirubin, 1429.e1*f*
acquired conjugation defects of, 997–998
in bile, 994
conjugated (direct), *e1t–e8t*
decreased uptake of, 995
excretion of, 994
genetic disorders of, 995
heme conversion to, 994
hepatic translocation of, 994
increased production of, 995
"indirect"-reacting, 994
Bilirubin *(Continued)*
liver deposition of, 994, 994.e1*f*
in liver disease, 986, 989
metabolism of, 994
plasma measurement of, 994–995
production of, 994, 994.e1*f*
total, *e1t–e8t*
unconjugated, 994
Biliverdin, 1429.e1*f*
Biliverdin reductase, 994
Binge drinking, 1609, 2353, 2543
Binge-eating disorder, 1461, 1462*b*
Binimetinib (Mektovi), 1215*t*, 1394*t*
Binocular vision loss, 2615
Bioassays, itraconazole, 2074–2075
Bioavailability, 126
Biochemical testing
for cobalamin and folate, 1122
for porphyrias, 1433–1434
Bioethics, in practice of medicine, 5–11
allocation of scarce medical resources, 9–10, 9*t*–10*t*, 10*t*
assisted suicide in, 8
euthanasia in, 8
financial conflicts of interest, 10–11
physician-patient relationship, informed consent in, 5–6
termination of medical interventions in, 6–7
Biologic agents, 149–153
adhesion molecules, 152
antibodies, 152
approved, 151*t*
B lymphocytes, 152
checkpoint molecules, 152
for chronic lymphocytic leukemia, 1269*t*
classes of, 150*t*
clinical applications of, 150*f*
complement, 152
costimulatory signals, 152
cytokines. *See* Cytokines
description of, 149–153
growth factor receptors, 152
for inflammatory bowel disease, 945*b*, 946*t*
for psoriatic arthritis, 1765*b*
specific types of, 151–153
for systemic lupus erythematosus, 1772*b*
T lymphocytes, 152
target cells, 152–153
targeted therapies as, 149
small molecule, 153
Biologic disease-modifying antirheumatic drugs, 1755*b*, 1756*t*
Biomarkers, for lysosomal storage diseases, 1419
Biopsy
for actinomycosis, 2068
for cancer of unknown primary origin, 1240
for chronic diarrhea, 930
for hepatocellular carcinoma, 1360
liver, 990
in α_1-antitrypsin deficiency, 993*f*
in hereditary hemochromatosis, 992, 993*f*
of lymph nodes, 1150
myocardial, 261
of pancreatic mass, 878*f*
of splenomegaly, 1153
Bioterrorism, 95–100
agents of concern, 96, 96*t*
epidemiologic clues to, 95–96, 96*t*
history of, 95
immunization against, 83–84
response to attack, 100
Biotin, 1453*t*
Biotin deficiency, 2541
Bipolar disorder, 2341–2342, 2341*b*–2342*b*, 2341*t*
Bipolar II disorder, 2342
Bipolar transurethral resection, for benign prostatic hyperplasia, 822*b*
Birt-Hogg-Dubé syndrome, 1363
Birthmark, 2743
Bismuth encephalopathy, 101*t*, 102*t*, 105, 105*b*
Bismuth subsalicylate
for diarrhea, 926*b*, 928
for traveler's diarrhea, 1888, 1888*t*
Bisoprolol
clinical use of, 451*t*
for heart failure, 267*t*
Bisoprolol/HCTZ, 451*t*
Bisphosphonates
for bone health, in breast cancer, 1369*b*
for esophagitis, 907*t*
for osteoporosis, 1608–1609, 1643*b*
for Paget disease of bone, 1664*b*–1665*b*, 1664*t*
Bitemporal hemianopia, 2616
Bites, 704–713
Crotalinae, 709*t*
snakebites
in Africa, 709
in Asia, 709
in Australia, 709
in Central America, 708–709
coral snake, 708, 708*b*
epidemiology of, 704–705
in Europe, 709
exotic, 710
in Mexico, 708
neurotoxic paralysis caused by, 707, 709.e1*t*
in New Guinea, 709
in North America, 708
signs of, 706*f*
in South America, 708
treatment of, in particular regions, 708–710, 708*b*
spider
envenomation of, 710
epidemiology of, 704
immunization for, 65*t*
signs of, 706*f*
viperid, 708
Bivalirudin, 387*t*, 501*t*, 503
for acute coronary syndrome, 374*t*
BK polyomavirus, 2228–2230, 2228*t*
hemorrhagic cystitis associated with, 2229, 2229*b*
nephropathy associated with, 2228–2229, 2229*b*, 2229.e1*f*
urothelial cancer associated with, 2229–2230, 2230*b*
Black Americans, 17–18
heart failure in, 254
hypertension in, 456
"Black box warning", 167
Black death, 96*t*, 1988
Black eschar, 1931, 1931*f*
Black skin, distinctive lesions in, 2744, 2744*t*
Black tar heroin, 1927
Blackheads, 2722
Bladder
neurogenic, 828
tumors of, 1362–1368
Bladder cancer, 1365–1367
clinical manifestations of, 1366
definition of, 1365
diagnosis of, 1366, 1367.e1*t*
epidemiology of, 1365
pathobiology of, 1365–1366
prevention of, 1367
prognosis of, 1367
treatment of, 1366*b*–1367*b*
Bladder diary, 829, 829.e1*f*
Bladder dysfunction, benign prostatic hyperplasia and, 822
Bladder exstrophy, 821, 821*b*
Bladder urgency, in multiple sclerosis, 2504*b*–2508*b*
Blast injury, 699*t*, 700, 700*f*
Blastic plasmacytoid dendritic cell neoplasm, 1260*t*, 1262*b*
Blastocystis hominis, 2156, 2156*t*
Blastomyces dermatitidis, 2080, 2080*f*, 2080*t*
Blastomyces spp., 2080
Blastomycosis, 2080–2081, 2080*t*, 2651
clinical manifestations of, 2080–2081
definition of, 2080
diagnosis of, 2081
disseminated infection in, 2081, 2081*f*
epidemiology of, 2080
pathobiology of, 2080
pathogen of, 2080, 2080*f*
prognosis of, 2081
pulmonary, 2080–2081
treatment of, 2081*b*
Blau syndrome, 1731*t*, 1736
Bleeding diathesis, of cyanotic congenital heart, 355.e1*f*
Bleeding disorder
alveolar hemorrhage and, 568
approach to, 1165–1170
in endoscopy, 876*t*
evaluation of, 1166–1169
history of, 1166, 1166*t*–1167*t*
laboratory screening for, 1166–1169
mechanisms of, 1165–1166
physical examination for, 1166
platelet
Bleeding disorder *(Continued)*
acquired, 1185
inherited, 1184–1185
preoperative evaluation of, 1169–1170
Bleeding score, 1166
Bleeding time, 1166, 1167
Blepharitis, 2601–2602, 2601*f*
Bloating
distention and, 859, 859*b*
gas and, 858–859
α-Blockers. *See* α-Adrenergic blockers
β-Blockers, 264*b*, 325*t*. *See also* β-Adrenergic blockers
for acute STEMI, 384*b*, 391*t*
for alcohol withdrawal, 2358*t*
for anxiety disorders, 2344*t*
for catecholaminergic polymorphic VT, 338*b*
clinical benefits of, 265*b*
clinical use of, 367*t*
for hypertension, 451*t*
mechanism of action, 265*b*
practical use of, 265*b*, 267*t*
Blocking anti-intrinsic factor antibodies, for pernicious anemia, 1123
Blood-borne viruses
health care-associated infections caused by, 1865, 1865.e1*t*
traveler exposure to, 1889
Blood-brain barrier, 2463
Blood cultures
for enteric infection, 1870*t*
for infection, 1834–1835
Blood-derived stem/progenitor cells, 172–174
Blood flow
coronary, 224
to digestive system, 959
Blood glucose concentration, abnormalities in, postoperative, 2676
Blood lipid levels, 219.e2*f*, 219–220
Blood pressure
abnormal, 34*t*
accurate measurement of, 445–447, 446*t*
aging and, 444*f*
ambulatory, 446*t*, 447, 447.e1*f*
cardiovascular disease and, 220
cardiovascular risk associated with, 444
control of
for chronic kidney disease, 839*b*
for diabetic nephropathy, 797*b*–798*b*
elevated, 35
in emergency department, 459–460
in heart failure, 257
low, 33*t*, 35, 455, 455.e1*t*
mean arterial pressure, 677*t*
measurement of, 29, 33, 461*f*
new-onset, evaluation of, 446*f*
normal range for, 32*t*
panic range for, 32*t*
stages of, 447*t*
systolic arterial pressure, 677*t*
variation
behavioral determinants of, 445
genetic determinants of, 445
Blood products, HIV transmission through, 2299
Blood-retinal barrier, 2596
Blood smears
for anemia, 1077
for malaria, 2120
Blood stream infections
central line-associated, 1862*t*, 1865–1866, 1865.e1*t*
Stenotrophomonas maltophilia and, 1975
Blood tests
for chronic diarrhea, 929–932, 929*f*
for Cushing disease, 1494
for gastrointestinal disease, 851–854
for toxicants, 690
Blood transfusion
ABO/D compatibility of, 1201
adverse effects of
allergic transfusion reaction, 1202, 1202*b*
Babesia transmission, 1203
bacterial contamination, 1203–1204
delayed hemolytic transfusion reaction, 1202–1203, 1203
delayed serologic transfusion reaction, 1202
febrile nonhemolytic transfusion reaction, 1202
hepatitis B virus transmission, 1203
hepatitis C virus transmission, 1203
human T-cell lymphotropic virus, 1203
hypotensive transfusion reactions, 1202

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Blood transfusion *(Continued)*
infectious complications of, 1203–1204
post-transfusion purpura, 1203
septic reactions, 1203
syphilis transmission, 1203
transfusion-associated circulatory overload, 1202, 1205
transfusion-associated dyspnea, 1202
transfusion-related acute lung injury, 1202, 1202*b*
Trypanosoma cruzi transmission, 1203
West Nile virus transmission, 1203
Zika virus transmission, 1203
allogeneic, 1205
autologous donation for, 1205
components of, 1199–1200, 1199*t*
directed donors, 1205
indications for, 1204–1205, 1204*t*
massive, 1205
safety of, 1201–1204, 1201*t*
for shock, 662*b*–665*b*
Blood urea nitrogen (BUN), 734
in acute kidney injury, 725
Blood volume, e8*t*–e9*t*
Bloody diarrhea, 1869*t*
Bloom syndrome, 1250*t*
BLS. *See* Basic life support
Blue nevi, 2730–2731, 2733*f*
Blue rubber bleb nevus syndrome, 969
Blunt injury, 699, 699*t*
B-lymphoblastic leukemia/lymphoma, 1260*t*
B lymphocytes, 152, 1784. *See also* B-cell(s)
BMAT. *See Brucella* microagglutination test
BMD. *See* Bone mineral density
BMI. *See* Body mass index
BMR. *See* Basal metabolic rate
Boceprevir, for hepatitis C infections, 2182*t*, 2185
Body fat, levels of, during adolescence, 110
Body fluid
osmolarity, 730–731, 732*f*
tonicity of
disorders of, 737–743
regulation of, 737–738, 737.e1*f*
Body lice, 711, 712*f*
Body mass index (BMI), 533, 1463
age and, 1582.e1*f*
of geriatric patient, 117
Body plethysmography, 530
Body temperature
abnormal, 34*t*
elevated, 34
low, 34
measurement, 33
measurement of, 29
normal, 32*t*, 34
panic range for, 32*t*
Body weight. *See also* Obesity
guidelines for management of, 63*b*
regulation of, 1464
Boerhaave syndrome, 912, 912*b*
Boils. *See* Furuncles
Bone
composition of, 803
glucocorticoids and, 145
peak mass, 1640, 1640.e1*f*–1640.e2*f*
remodeling of, 1640, 1640.e1*f*–1640.e2*f*
Bone densitometry, for celiac disease, 936*b*
Bone disorders
diffuse idiopathic skeletal hyperostosis, 1668
endosteal hyperostosis, 1666–1667, 1667*b*
fibrous dysplasia, 1668–1670, 1669*b*, 1669*f*
hereditary multiple exostoses, 1669
in HIV, 2318
hyperostosis, 1666–1668, 1666*t*
melorheostosis, 1668, 1668*b*
mixed sclerosing bone dystrophy, 1668
osteonecrosis, 1665
osteopathia striata, 1668
osteopetrosis, 1667, 1667*b*, 1668*f*
osteopoikilosis, 1668
osteosclerosis, 1665*f*, 1666, 1666*b*, 1666*t*
pachydermoperiostosis, 1667, 1667*b*
in sarcoidosis, 602, 604*t*
Bone edema, 1751
Bone infections, *Pseudomonas* infections causing, 1969, 1970*b*
Bone loss
aging-related, 1640
cause of, 1643
Bone loss *(Continued)*
drugs causing, 1641
mechanisms of, 1640–1641
secondary causes of, 1641, 1641*t*
Bone marrow
examination, for anemia, 1077
fibrosis, causes of, 1136*t*
myeloid maturation in, 1140*f*
transplantation, 1107*b*–1109*b*
Bone marrow-derived stem/progenitor cells, 172
Bone marrow failure defects, 1686
Bone marrow transplantation, for multiple myeloma, 1299*b*–1302*b*
Bone mass, regulation of, 1652*f*
Bone mineral density (BMD), 1638, 1642–1643, 1643.e1*f*–1643.e2*f*
Bone tumors, 1387–1389
chondrosarcoma, 1388, 1388*b*
clinical manifestations of, 1387–1388
diagnosis of, 1387
Ewing sarcoma, 1388, 1388*b*
metastatic, 1388–1389, 1388*b*
osteosarcoma, 1388, 1388*b*
primary, 1388
Bonferroni correction, 37
Bony osteonecrosis, 2621*t*
Boostrix (GlaxoSmithKline), 81
Borderline borderline leprosy, 2049, 2049*t*, 2049.e1*f*, 2050*f*
Borderline lepromatous leprosy, 2049, 2049*t*, 2050*f*, 2050.e1*f*
Borderline personality disorder, 2348*t*
Borderline tuberculoid leprosy, 2049, 2049*f*, 2049*t*
Bordetella ansorpii, 1994.e3*t*
Bordetella avium, 1994, 1994.e3*t*
Bordetella bronchiseptica, 1994, 1994.e3*t*
Bordetella hinzii, 1994, 1994.e3*t*
Bordetella holmesii, 1994.e3*t*
Bordetella parapertussis, 1994, 1994.e3*t*
Bordetella pertussis, 1994, 1994.e3*t*, 2649
Bordetella petrii, 1994.e3*t*
Bordetella species, 1994.e3*t*
Bordetella trematum, 1994.e3*t*
Borrelia afzelii, 2022
Borrelia burgdorferi, 1279, 2022, 2578, 2711
Borrelia duttonii, 2027
Borrelia garinii, 2022
Borrelia hermsii, 2027
Borrelia infections, relapsing fever as, 2027–2028
clinical manifestations of, 2028
definition of, 2027–2028
diagnosis of, 2028, 2028*f*
epidemiology of, 2027–2028
pathobiology of, 2028
prevention of, 2028
prognosis of, 2028
treatment for, 2028*b*
Borrelia miyamotoi, 2027
Borrelia parkeri, 2027
Borrelia turicatae, 2027
Borrelial lymphocytoma, 2024, 2024*f*
Bortezomib (Velcade), 1215*t*
for amyloidosis, 1308*b*
for multiple myeloma, 1299*b*, 1301*t*
Bosentan
for Eisenmenger syndrome, 355*b*
for Raynaud phenomenon, 473*b*
for systemic sclerosis, 1781*b*–1782*b*
Bosutinib, 1251*t*
for chronic myeloid leukemia, 1275*t*–1276*t*
Botulinum toxin, 1927
for achalasia, 908*b*
for anal fistula, 980*b*
Botulinum toxin A, for chronic pain, 138*t*
Botulism, 99, 1927–1928, 1928*b*, 2589*t*, 2592
clinical manifestations of, 99, 2592
diagnosis of, 99, 2592
immunization for, 65*t*
infant, 2571
pathobiology of, 2592
prognosis for, 99*b*, 2592*b*
treatment of, 99*b*, 2592*b*
Bourbon virus, 2065*t*
Bovine-associated vaccinia, 2238
Bowen disease, 980
Bowenoid papulosis, 2242
Box jellyfish, 712
Boyle's law, 594
BPH. *See* Benign prostatic hyperplasia
B-prolymphocytic leukemia, immunophenotype of, 1268*t*
Brachial plexopathy, 2368.e2*f*
Brachytherapy, for prostate cancer, 1385*b*–1387*b*
Bradyarrhythmias, 305, 313*b*, 318
Bradycardias, 34–35, 317–322, 317, 317*t*
acute poisoning and, 682
advanced cardiac life support response to, 316*f*
conditions associated with, 318*t*
definition of, 317–318
epidemiology of, 317
management of, 384*b*
pathobiology of, 317–318, 317.e3*f*
sinus, 319, 319*t*
Bradykinesia, 2484
Bradykinetic dysphagia, severe mental illness and, 2681*t*
Bradykinin-mediated hereditary angioedema, 1690, 1690*t*
clinical manifestations of, 1688*f*, 1690
diagnosis of, 1690–1691
epidemiology of, 1690
pathobiology of, 1690
prevention of, 1690*b*
prognosis of, 1691
treatment of, 1690*b*
BRAF inhibitors, for melanoma, 1393*b*
BRAF V600E inhibition, for colorectal cancer, 1350*b*
Brain, reward circuits, 143.e1*f*
Brain abscess, 2525–2530
clinical manifestations of, 2525
diagnosis of, 2525–2527
epidemiology of, 2525–2527
features of, 2525*t*
fungal, 2525
headache in, 2525
in immunocompromised host, 1861
magnetic resonance imaging of, 2526, 2526*f*
pathobiology of, 2525
pathogens that cause, 2526*t*
predisposing condition, 2525*t*
prognosis of, 2527
treatment of, 2526*b*
Brain death, 2437–2443, 2437*t*, 2442
clinical manifestations of, 2442–2443
diagnosis of, 2442, 2442*t*
epidemiology of, 2442
pathobiology of, 2442
tests for, 2442*t*
treatment of, 2443*b*
Brain infection, treatment of, 1970*b*
Brain malformations, 2547
Brain metastases, in melanoma, 1393*b*
Brain natriuretic peptide, 260, 403
Brain stem
abscess of, 2527*f*
blood supply to, 2458*f*
Brain stem auditory evoked responses, 2641
Brain stem dysfunction, *Mycoplasma pneumoniae* in, 2007
Brain stem encephalitis, 2531
Brain stem glioma, 1315–1316
Brain trauma, diabetes insipidus and, 1503
Brain tumors, 1310–1317
acoustic neuromas, 1312*b*
biopsy for, 1312
cerebrospinal fluid analysis of, 1312
chemotherapy for, 1313*t*
clinical manifestations of, 1310–1312, 1311*t*
diagnosis of, 1311–1312
differential diagnosis of, 1312, 1312*t*
electroencephalography of, 1312
extradural, 1318, 1318*b*
ganglioglioma, 1316
headache associated with, 1311
intra-axial, 1316
magnetic resonance imaging of, 1311, 1312*f*
medulloblastoma, 1316
meningiomas, 1313–1316
metastases, 1316–1317, 1317*b*, 1317*f*
pituitary adenomas, 1314
primary extra-axial, 1312*b*
radiation therapy for, 1312*b*
treatment of, 1312*b*
venous thromboembolism and, 1312*b*
Brainerd diarrhea, 932
Brainstem auditory evoked potentials, 2376
Brazilian purpuric fever, *H. influenzae* caused by, 1954
BRCA1- associated protein (BAP1), 1390–1391
BRCA1 mutations
in breast cancer, 1368, 1373
in ovarian cancer, 1379, 1379*t*
BRCA2 mutations
in breast cancer, 1369, 1373
in ovarian cancer, 1379, 1379*t*
Breakpoint cluster region *(BCR)* gene, 1272, 1273*f*
Breast
budding, 1591
development of, 1598, 1598*t*
female, 110.e2*f*
examination of, 30
Breast cancer, 1368–1375
adjuvant chemotherapy for, 1369*b*
anti-HER2 therapy for, 1369*b*
biologic agents for, 1369*b*
bone health in, 1369*b*
chemoprevention of, 1373
chemotherapy for, 1369*b*
clinical manifestations of, 1368
diagnosis of, 1368–1369
ductal, 1369, 1369*b*
early-stage, 1369*b*, 1370*t*–1371*t*, 1371*t*
endocrine therapy for, 1369*b*
epidemiology of, 1368–1374
hormone therapy for, 1369*b*
invasive, 1369*b*
lifestyle modification for, 1373
lobular, 1369*b*, 1370*t*
lymphedema associated with, 1369*b*
mammographic screening of, 1373–1374, 1373*t*
menopause associated with, 1630*b*–1631*b*
metastatic, 1369*b*
nutrition and, 59
pathobiology of, 1368
postmenopausal symptoms in, 1369*b*
in pregnancy, 1369*b*
prevention of, 1373–1374
preventive medications for, 56
prognosis for, 1374
prognostic and predictive markers of, 1369, 1369*t*–1370*t*
prophylactic mastectomy and oophorectomy for, 1373
radiotherapy for, 1369*b*
risk factors for, 1368*t*
screening for, 54, 1373, 1373*t*
selective estrogen receptor modifiers for, 1369*b*
stage III, 1369*b*
stage IV, 1369*b*, 1372*f*
staging of, 1369, 1369*t*
supportive care for, 1369
surgery for, 1369*b*
systemic therapy for, 1369*b*
tamoxifen for, 1369*b*
in women, 1607
Breast milk jaundice, 996
Breast pain, 1368
Breath sounds, bronchial, 512, 512*t*
Breathing
sleep-disordered, 257
spontaneous trial, 657
Brentuximab vedotin (Adcetris), 150, 1215*t*
Brief Pain Inventory, 12, 14*f*–15*f*
Brigatinib (Alunbrig), 1215*t*
Brill-Zinsser disease, 2055*t*, 2059
Brimonidine, for skin diseases, 2698
Bristol Stool Form Scale, 895*f*
Briumvi. *See* Ublituximab
Brivaracetam, for seizures, 2434*t*
Broad-spectrum antibiotic, for intestinal bacterial overgrowth, 934*b*
Brody disease, 2583.e1*t*, 2585
Bromocriptine
for hyperprolactinemia, 1491*b*–1492*b*
for neuroleptic malignant syndrome, 2681*b*
ovulation induction using, 1603*b*
for premenstrual syndrome, 1597*b*
Bronchial breath sounds, 512, 512*t*
Bronchial carcinoids, 1567
Bronchial thermoplasty, 630
Bronchiectasis, 560–562, 2327*t*
acute exacerbations of, 561*b*
anatomic causes of, 560
antimicrobial therapy for, 561*b*
central, 562*f*

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Bronchiectasis *(Continued)*
chronic obstructive pulmonary disease *versus*, 549–550
clinical manifestations of, 560
computed tomography findings of, 560, 560.e2*f*–560.e3*f*
cystic fibrosis with, 558, 558*f*
definition of, 560
diagnosis of, 560–561
diffuse, 522
distinguishing features of, 515*t*
epidemiology of, 560
"finger-in-glove" central bronchiectasis, 562*f*
genetics of, 560
imaging studies of, 560–561, 561*f*–564*f*, 561*f*, 562*f*, 563*f*, 564*f*
pathobiology of, 560
preventing exacerbations, 561*b*
prognosis for, 562
traction, 575, 575.e1*f*
treatment of, 561*b*, 562*t*
Bronchiolitis, 515*t*, 605, 2194
Bronchiolitis obliterans, 550
clinical manifestations of, 633
diagnosis of, 633
as occupational lung disease, 585*t*
pathobiology of, 633
prognosis for, 633–634
treatment for, 633*b*
Bronchiolitis obliterans organizing pneumonia of unknown cause, 578–579
Bronchioloalveolar cell carcinoma, 566*t*, 569
clinical manifestations of, 569
definition of, 569
diagnosis of, 569–570, 569.e1*f*, 570*f*
pathobiology of, 569
prognosis of, 570
treatment for, 570*b*
Bronchitis
acute, 605, 605.e1*f*, 606*b*
increased eosinophils counts in, 533
Bronchoalveolar lavage, 532–533
cellular constituents of, 533
fluid, 569.e1*f*
Bronchoconstriction, exercise-induced, 538
Bronchodilators, for cystic fibrosis, 558*b*
Bronchogenic carcinoma, 563.e1*f*
Bronchogenic cysts, 565
Bronchogenic lung cancer, 1329–1336
Bronchograms, air, 520
Bronchoscopy, 630–631
for acute interstitial pneumonia, 568
for alveolar filling disorders, 566*f*
for central airway obstruction, 630, 630*t*
for pulmonary alveolar proteinosis, 567
in surgical approach, 631
Bronzing, 1440
Brooke ileostomy, 945*b*
Brown classification, of drug reactions, 1696*t*
Brown fat, 1465
Brown-Séquard syndrome, 2386, 2404
Bruce protocol, 361
Brucella abortus, 1983
Brucella canis, 1983
Brucella endocarditis, 417*t*
Brucella melitensis, 1983
Brucella meningitis, 2515*b*
Brucella microagglutination test (BMAT), 1984
Brucella spp., 1804, 1983
Brucella suis, 1983
Brucellosis, 1983–1985
acute, 1889.e1*t*, 1984
clinical manifestations of, 1983–1984
clinical syndromes of, 1983–1984, 1984*t*
definition of, 1983–1985
diagnosis of, 1984
epidemiology of, 1983
immunity to, 1983
immunologic testing for, 1984
localized disease and complications of, 1984
pathobiology of, 1983
pathogen that causes, 1983
pathogenesis of, 1983
prevention of, 1985
prognosis of, 1985
relapsed infection of, 1985
strain-specific illness, 1983
subacute, 1984
subclinical illness of, 1983–1984
in travelers, 1891*t*
treatment of, 1984*b*, 1985*t*, 1987
Brudzinski sign, 2512
Brugada syndrome, 302–303, 303
cellular basis for, 302*f*
diagnosis of, 337–338, 338*f*
Bruns nystagmus, 2619–2620
Brush-border enzyme, mucosal malabsorption and, 934
Bruton tyrosine kinase inhibitors, 153, 1269*b*, 1284*b*
B-type natriuretic peptide (BNP), e1*t*–e8*t*
Bubonic plague, 1990*f*–1991*f*, 1990*f*, 1991, 1991*f*
Buckley-Job syndrome, 1679*t*, 1680
Budd-Chiari syndrome, 965*f*, 968, 968*b*, 986, 1170
Budesonide, 553*t*
for COVID-19, 2217
for ulcerative colitis, 945*b*, 946*t*
Budesonide MMX, for ulcerative colitis, 945*b*, 946*t*
Buerger disease, 468, 468*b*–469*b*, 469*f*, 1796
Bufadienolides, toxicity, 686*t*
Bulimia nervosa
clinical manifestations of, 1462
definition of, 1461
pathobiology of, 1461
prognosis of, 1462
treatment of, 1462*b*
weight loss and, 860*t*
Bulk-forming agents, 941*b*
Bulky Hodgkin disease, 1291*f*, 1292
Bullae, 2689*t*, 2696*f*
Bullectomy, 551*b*
Bullosis diabeticorum, 2720
Bullous impetigo, 2720, 2720*b*, 2720*f*
Bullous pemphigoid, 2689*t*, 2696*f*, 2717, 2717*b*, 2717*f*
Bumetanide, 451*t*, 737*t*
BUN. *See* Blood urea nitrogen
Bundle branch blocks, 231
diagnosis of acute MI in presence of, 383
left, 231, 231*t*, 232*f*–233*f*, 287.e1*f*
right, 231, 231*t*, 232*f*
Bundle branch re-entry, 334
Bunyavirales, 2274, 2279–2280, 2283–2284
Buprenorphine, 139*t*, 2362*b*–2363*b*
Bupropion
for depression, 2340*t*
for tobacco dependence, 2350*b*–2352*b*, 2351*t*
Burden of disease(s), global, 21*f*, 23
Burkholderia cepacia, 1972, 1972*b*
Burkholderia infections, 1972
Burkholderia mallei, 1972, 1972*b*
Burkholderia pseudomallei, 1972, 1972*b*
Burkholderia spp., cystic fibrosis and, 557
Burkitt-like acute lymphoblastic leukemia, 1262*b*
Burkitt lymphoma, 1286, 1286*b*, 2255, 2315
Burns
critical care of, 700*b*
early wound excision, 700*b*
infection, *Acinetobacter* causing, 1973
medical aspects of, 698–704
Pseudomonas infections causing, 1969
resuscitation formula, 702.e1*t*
Burosumab, for metabolic bone disease, 1639*b*
Bursae
definition of, 1804
infection of, 1804
superficial, 1804
Bursitis, 1747, 1747*b*
olecranon, 1804
septic, 1804
Bussuquara virus, 2275*t*
Busulfan, 1135*b*–1138*b*
Buthid scorpion venom, 710
Butorphanol, 136*b*, 139*t*
Bypass surgery. *See* Coronary artery bypass graft (CABG) surgery

C

C1 esterase inhibitor deficiency, 1694
C1-INH, 200*t*
C1 inhibitor deficiency, 1683, 1683*t*
C1*q* deficiency, 1683*t*
C1*r* deficiency, 1683*t*
C1*s* deficiency, 1683*t*
C2 deficiency, 1682, 1683*t*
C3 convertase, 199, 786
C3 deficiency, 1683*t*
C3 nephritic factor, 786
C3*a*, 201, 1768–1769
C3*a* receptor (C3*a*R), 202, 202*t*
C3*a*R. *See* C3*a* receptor
C4 deficiency, 1683*t*
C4*b*p (C4 binding protein), 200*t*
C5 convertase, 199
C5 deficiency, 1683*t*
C5*a*, 201
C5*a* receptor (C5*a*R), 202, 202*t*
C5*a*R. *See* C5*a* receptor
C5*b*-9, soluble, 200
C6 deficiency, 1683*t*
C7 deficiency, 1683*t*
C8 deficiency, 1683*t*
C9 deficiency, 1683*t*
Cabazitaxel (Jevtana), 1215*t*
Cabergoline
for acromegaly, 1489*b*
for Cushing syndrome, 1524*b*
ovulation induction using, 1603*b*
CABG. *See* Coronary artery bypass graft (CABG) surgery
Cabotegravir, 2301*t*
Cabozantinib, 1215*t*, 1364*b*
Cachexia
in cancer, 1239–1240, 1240*b*
cardiac, 257
management of, 13*t*
CACNA1A gene, 2376
Cadmium, e1*t*–e8*t*
Cadmium pneumonitis, 105
Cadmium toxicity, 88*t*, 104–105
chronic interstitial nephritis caused by, 794–795
clinical manifestations of, 105
diagnosis of, 101*t*, 105
epidemiology of, 104
pathobiology of, 104–105
prognosis of, 105
treatment of, 105*b*
Caffeine, e10*t*–e11*t*, 2449*t*
Caffeine halothane contracture test, 716
Calcific periarthritis, acute, 1815
Calcifications, in heart, 246, 247*f*
Calcified lesions, 2159
Calcineurin inhibitor-induced nephrotoxicity, in renal transplantation, 847
Calcineurin inhibitors, 148–149
for focal segmental glomerulosclerosis, 779*b*
for liver transplantation, 1048–1049, 1048*t*
in renal transplantation, 845*t*
for systemic lupus erythematosus, 1772*b*
Calcinosis cutis, in systemic sclerosis, 1777, 1779*f*
Calciphylaxis, 2735–2736
Calcipotriol, for skin diseases, 2698
Calcitonin, e1*t*–e8*t*
Calcitonin gene-related peptide (CGRP), 152
Calcitriol, 1650*t*–1651*t*, 1652
Calcium, 935, 937*t*
coronary artery scoring, 249, 249*f*
homeostasis of, 1652.e2*f*
intestinal actions of, 1654
ionized (iCa), e1*t*–e8*t*
metabolism of, 1652–1654
for narcolepsy, 2449*t*
for osteomalacia, 1651*t*
for osteoporosis, 1639*b*, 1643*b*
regulation of, 732, 732.e1*f*, 1652*f*
renal actions of, 1654
in sarcoidosis, 602
serum levels of, description, 1652
total, e1*t*–e8*t*
Calcium-channel blockers, 325*t*
for acute coronary syndrome, 374*t*
for acute STEMI, 384*b*
clinical use of, 452
for hypertension, 452
mechanism of action of, 452
properties of, 367*t*
for pulmonary hypertension, 496*b*–499*b*
side effects of, 452
Calcium channelopathies, 2585
Calcium channels, 300.e1*f*, 301, 305
Calcium deficiency, 288
Calcium gluconate, for arrhythmias, 313*b*
Calcium ion-sensing receptor, 817
Calcium oxalate crystals, 759–760
Calcium pyrophosphate dihydrate crystal deposition disease, 1713, 1717*t*, 1814, 1814*b*–1815*b*, 1815*f*
Calcium salt, for acute poisoning, 693*t*
Calcium-sensing receptor, 1652
Calcium stones, 803–804, 807*f*
California encephalitis virus, 2276*t*, 2283, 2284*b*
Caloric deprivation, 1430
Caloric test, 2646
Calquence. *See* Acalabrutinib
Calyceal diverticula, 819, 820*f*
Calymmatobacterium granulomatis, sexually transmitted anorectal diseases and, 983
Cameron ulcers, 916
Camitta criteria, for aplastic anemia, 1128*t*
Camptosar. *See* Irinotecan
Campylobacter concisus, 1960
Campylobacter fetus, 1960
Campylobacter hyointestinalis, 1960
Campylobacter infections, 1958–1960
clinical features of, 1959*t*
clinical manifestations of, 1959
definition of, 1958–1960
diagnosis of, 1959
differential diagnosis of, 1959
epidemiology of, 1958
gastroenteritis caused by, 1959
pathobiology of, 1958–1959
pathogen, 1958
prevention of, 1960
prognosis for, 1960
in travelers, 1889.e1*t*, 1891*t*
traveler's diarrhea caused by, 1888*t*
treatment of, 1959*b*
Campylobacter jejuni, 983, 1958
Campylobacter lari, 1960
Campylobacter upsaliensis, 1960
Camurati-Engelmann disease, 1666, 1666*b*
Canadian Association of Cardiology algorithm, 2662–2663, 2662.e1*f*
Canadian C-spine Rule, 2388, 2388*f*
Canadian Cardiovascular Society, angina grading scale, 356
Canadian Syncope Risk Score, 309*t*
Canagliflozin, for type 2 diabetes mellitus, 1541*t*
Canakinumab
description of, 151, 151*t*
for FMF, 1732*b*
for HIDS, 1734*b*
for TRAPS, 1734*b*
Canalithiasis, 2644
Canavan disease, 2510
Cancer
in adolescents, 111
anal. *See* Anal cancer
approach to, 1214–1243
biology, 1247–1252
breast. *See* Breast cancer
burden and trends, 1243
causes of death, 17
cell therapy, 175–176
cervical, 1375–1377, 1375*t*
clinical manifestations of, 1375
diagnosis of, 1375
epidemiology of, 1375, 2241
human papillomavirus and, 2241
loop electrosurgical excision procedure for, 1375*b*
pathobiology of, 1375
pelvic exenteration for, 1375*b*
prevention of, 1376
prognosis for, 1375*b*, 1377
risk factors for, 1375*t*
screening for, 1376, 1376*t*
treatment of, 1375*b*, 1376*t*
clonal evolution of, 1249–1250
colorectal. *See* Colorectal cancer
control, 1246, 1246*f*
diagnosis of, 1214–1232, 1214*t*
procedures for, 1214–1232, 1215*t*
staging and multidisciplinary evaluation for, 1232
diagnostic tests for, 1252
DNA alterations in, 1247–1250
ectopic hormone syndromes, 1237
endocrine manifestations of, 1237, 1237*t*
endometrial, 1377–1379
clinical manifestations, 1378
epidemiology, 1377
pathobiology, 1377–1378, 1377*f*, 1377*t*
prevention, 1379
prognosis, 1379
risk factors, 1377*t*
staging, 1378*t*
treatment, 1378*b*
epidemiology of, 1243–1247
fallopian tube, 1379–1381
clinical manifestations of, 1379–1380
definition of, 1379

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Cancer *(Continued)*
diagnosis of, 1379
epidemiology of, 1379, 1379*t*
pathobiology of, 1379
prevention of, 1380–1381
prognosis for, 1381, 1381*t*
risk factors for, 1379*t*
treatment of, 1380*t*–1381*t*, 1381*t*
familial cancer syndromes, 1250*t*
fever and cachexia in, 1239, 1240*b*
gene expression profiling, 1252
genetic instability of, 1249
genetics, 1247
germline DNA alterations in, 1248–1249, 1248*f*–1249*f*
global statistics, 1243, 1244*f*
hallmarks of, 1249*t*
head and neck, 1320–1328
hypercalcemia of, 1237, 1237*b*
lung. *See* Lung cancer
molecular and genetic epidemiology of, 1246
molecular diagnostics of, 166*t*
nutrition and, 58–60
obesity and, 1466
in older adults, 115
ovarian, 1379
clinical manifestations of, 1379
definition of, 1379
diagnosis of, 1379
epidemiology of, 1379, 1379*t*
pathobiology of, 1379
prevention of, 1380
prognosis for, 1381, 1381*t*
risk factors for, 1379*t*
treatment of, 1380*t*, 1381*t*
pancreactic. *See* Pancreatic cancer
prevention of, 1246–1247, 1246*f*
primary prevention of, 1246–1247
prostate. *See* Prostate cancer
of reproductive system, oral contraceptives and, 1615
risk factors of, 1243–1246
demographic factors, 1243, 1245*f*
environmental and lifestyle factors, 1244–1245
hormones, 1245–1246
ionizing radiation, 1246
secondary prevention of, 1247
somatic DNA alterations in, 1248, 1248*f*, 1249*f*
survivorship and follow-up in, 1243
systemic sclerosis and, 1780
targeted therapies for, 1250–1252, 1251*t*
therapeutic plan for, 1232*b*
thyroid. *See* Thyroid cancer
trajectories of, 12.*e1f*
treatment of, 1232*b*, 1234*t*, 1246, 1247*b*
adjuvant chemotherapy for, 1232*b*, 1234*t*
brachytherapy for, 1385*b*
combination therapy for, 1232*b*, 1234*t*
cytotoxic agents for, 1232*b*
diarrhea and, 926
epigenetic therapies for, 1232*b*
hematopoietic stem cell transplantation for, 1232*b*
hormonal therapies for, 1232*b*
immunotherapy for, 1232*b*
organ-sparing therapy for, 1232*b*, 1234*t*
targeted small molecules for, 1232*b*
tumor heterogeneity of, 1249
tumor lysis syndrome as, 1240, 1240*b*
United States statistics, 1243, 1245*f*
of unknown primary origin, 1240
biopsy and pathologic evaluation of, 1240
diagnosis of, 1240
search for, 1240, 1241*t*
treatment of, 1241*b*, 1242*t*
in women, 1607
Cancer antigen 15-3 (CA 15-3), *e1t*–*e8t*
Cancer antigen 19-9 (CA 19-9), *e1t*–*e8t*, 1356
Cancer antigen 125 (CA 125), *e1t*–*e8t*, 1379, 1591–1592
Cancer-associated venous thromboembolism, 487*b*
Cancer Genome Atlas, 167, 1377*f*
Cancer pharmacogenomics, 167
Candesartan, 451*t*
for heart failure, 266*t*
Candesartan/HCTZ, 451*t*
Candida albicans, 2089
Candida glabrata, 2089
Candida guilliermondii, 2089
Candida krusei, 2089
Candida lusitaniae, 2089
Candida parapsilosis, 2089, 2091
Candida tropicalis, 2089
Candidatus Neoehrlichia mikurensis, 2060*t*
Candidemia, 2090, 2091*f*
Candidiasis, 1882, 1882*b*, 1882*t*, 2650–2651, 2651*f*
caspofungin for, 2078
chronic disseminated, 2090, 2091*f*
chronic mucocutaneous, 2090
clinical manifestations of, 2090
definition of, 2089
diagnosis of, 2091
disseminated, 1861*f*
endophthalmitis caused by, 2091
epidemiology of, 2089
erythematous oral, 2623–2624, 2624*f*
of esophagus, 911, 912*f*
fluconazole for, 2075
hepatosplenic, 1023–1024, 1024*b*, 1024*f*, 2090
invasive, 2092
micafungin for, 2078
mucocutaneous, 2090, 2091
oral, 2320*f*, 2322*t*, 2623
oropharyngeal, 2090, 2090*f*
osteoarticular infections caused by, 2091
pathobiology of, 2089
pathogen that causes, 2089
peritonitis caused by, 2091
prevention of, 2093
prognosis for, 2093
treatment of, 2092*b*
urinary tract infections caused by, 2091
vulvovaginitis, 2090
CANDLE. *See* Chronic atypical neutrophilic dermatosis with lipodystrophy and elevated temperature
Cangrelor, 384*b*, 506*t*, 507
Canine monocytic ehrlichiosis, 2061
Canker sores, 2620, 2621*f*
Cannabidiol, for seizures, 2434*t*
Cannabinoids
for chronic pain, 136*b*
for nausea and vomiting, 863*t*
Cannabis sativa, 2364
Capecitabine (Xeloda), 1215*t*
for gallbladder cancer, 1054*b*
for gastric adenocarcinomas, 1341*b*–1342*b*
Capillaria hepatica, 1026*t*
Capillaria philippinensis, 2169, 2170*t*
Capillaritis, idiopathic pulmonary, 582
Capillary leak syndrome, 698
Capillary microcirculation, 1535
Caplacizumab, 152, 1177*b*–1178*b*
Capnocytophaga, 2068
Capnocytophaga canimorsus, characteristics of, 2270*t*
Capnometry, 640, 640.*e1f*
Caprelsa. *See* Vandetanib
CAPS. *See* Cryopyrin-associated periodic syndromes
Capsaicin, for skin diseases, 2699–2700
Capsule endoscopy, 880, 880*f*, 943, 1345
Captopril, 451*t*
for heart failure, 266*t*
for left ventricular dysfunction, 384*b*
Captopril/HCTZ, 451*t*
Caput medusae, 988*f*
CAR. *See* Chimeric antigen receptor
CAR-T cells. *See* Chimeric antigen receptor-T cells
Carbamates, toxicity, 88*t*, 686*t*
Carbamazepine, *e10t*–*e11t*
for action myoclonus, 2495*b*
for alcohol withdrawal, 2358*t*
for chronic pain, 138*t*
pharmacokinetic parameters for, 127.*e1t*
in renal failure, 129.*e1t*
for seizures, 2434*t*
toxicity, 690*t*
Carbapenem(s)
dosage of, 1895*t*
for pyogenic liver abscess, 1023*b*
toxicities of, 1901*t*
Carbapenem-resistant Enterobacterales, 1965
Carbapenem-resistant organisms, treatment of, 1966*b*–1967*b*
Carbapenemases, 1966
Carbohydrates
dietary guidelines for, 57.*e3t*
intestinal digestion and absorption of, 932.*e1f*
metabolism, disorders involving, 2586
Carbon-13 urea breath test, 918, 918*t*
Carbon-14 urea breath test, 918
Carbon dioxide
elimination of, by lung, 753–755
monitoring, 640
partial pressure (Pco_2), *e1t*–*e8t*
partial pressure of, 640
production of, 641
total (Tco_2), *e1t*–*e8t*
transcutaneous carbon dioxide measurement, 640
Carbon monoxide poisoning, 88*t*, 595–596, 596*b*, 700*b*
Carbonic acid, production of, 753
Carbonic anhydrase, 732
Carbonic anhydrase II deficiency, 816*t*, 1667
Carboplatin (Paraplatin), 1215*t*
Carboxyhemoglobin, toxicity, *e1t*–*e8t*, 690*t*
Carcinoembryonic antigen (CEA), *e1t*–*e8t*, 1360
Carcinogenesis
alcohol use disorders and, 2354
environmental, 1321
viral, 1321–1322
Carcinogens
of bladder cancer, 1365
environmental, 1321
Carcinoid heart disease, 1567
Carcinoid syndrome, 296, 1561*t*, 1567–1568
clinical manifestations of, 1567–1568
diagnosis of, 1567–1568
distinguishing features of, 515*t*
epidemiology of, 296
pathobiology of, 296
prognosis for, 296*b*
treatment of, 296*b*, 1568*b*
Carcinoid tumors, 1336
Carcinoma. *See also* Adenocarcinoma
bronchioloalveolar cell, 566*t*, 569
hepatocellular, 992*f*. *See also* Hepatocellular carcinoma
poorly differentiated, diagnosis of, 1241*t*
porphyrias and, 1432
renal cell, 1362–1365
squamous cell, of anus, 982
Carcinomatosis, peritoneal, treatment of, 1241*b*
Carcinomatous polyarthritis, 1823
Cardenolides, toxicity, 686*t*
Cardiac action potential, 223, 223*f*, 299, 299*f*, 333.*e1f*
Cardiac amyloidosis, 249, 249.*e2f*
Cardiac arrest, 312
AED rapid response to, 314*t*
bradycardic or asystolic, 316*f*
clinical manifestations of, 312–313
diagnosis of, 312
electrical mechanisms associated with, 313*f*
epidemiology of, 312–317
incidence of, 312
out-of-hospital, causes of, 313*t*
pathobiology of, 312
prognosis for, 316–317
sudden, 312
tachyarrhythmic, 313*b*
treatment of, 313*b*
Cardiac arrhythmias, 301
Cardiac cachexia, 257
Cardiac catheterization
for cardiovascular disease, 218
complications of, 393–395, 394*t*
contraindications to, 393, 394*t*
for mitral stenosis evaluation, 405
procedures performed in, 393.*e3t*
right-sided, in cardiogenic shock, 667
Cardiac cavities, extension of tumor into, 298
Cardiac cycle, 225, 225.*e1f*
filling phase, 225
pressure-volume loop, 225
Cardiac disease, in pregnancy, 1619*t*
Cardiac energetics, 225
Cardiac function, 223–227
Cardiac imaging
computed tomography, 249–251
echocardiography, 235–241
Cardiac imaging *(Continued)*
noninvasive, 244–254
radiography of, 244–247
stress MRI, 362–363
Cardiac implantable electronic devices, 340–345
Cardiac index, 677*t*
Cardiac inspection, 213–214
Cardiac masses
CMR imaging of, 252
echocardiographic findings, 242*t*
Cardiac output, 226, 677*t*
Cardiac resynchronization therapy (CRT), 265*b*, 344–345
complications of, 345
indications for, 345, 345*t*
Cardiac risk assessment, 2661–2664, 2662*t*, 2663*f*
Cardiac sarcoidosis, 249, 602, 603*b*–604*b*, 604*t*
Cardiac silhouette, 247
Cardiac syncope, 309*b*–311*b*
Cardiac syphilis, 2019
Cardiac tamponade
at cardiac catheterization, 429
echocardiography for, 426–427, 429*f*
treatment of, 427*b*–428*b*
Cardiac testing, noninvasive, 220–221
Cardiac toxicity, after hematopoietic cell transplantation, 1211
Cardiac transplantation, 265*b*
contraindication criteria for, 274*t*
heart-lung transplantation, 633
heart transplantation, 274*t*
Cardiac troponins, measured by a highly sensitive assay, 260.*e1t*
Cardiac tumors, 242*t*, 296–298, 297*f*, 297*t*
Cardioactive steroids, toxicity, 686*t*
Cardiogenic shock, 658–659, 659, 659*f*, 661*t*, 665–669
causes of, 666*t*
clinical manifestations of, 666, 666*f*, 667*t*
definition of, 665–669, 665*t*
diagnosis of, 665*t*, 666–667
epidemiology of, 665–666, 666*f*
inotropes for, 667*b*
management of, 384*b*
initial, 667*b*, 668*f*
vasopressors for, 667*b*
pathobiology of, 666
prognosis for, 669
Cardiology, nuclear, 247–249
in coronary artery disease, 362
in heart failure, 261
Cardiomyocytes, 224.*e1f*
Cardiomyopathy, 251–252, 253*f*
alcoholic, 287, 2355
arrhythmogenic right ventricular, 288, 337, 338*f*
causes of, 279.*e3t*
Chagas, 2127, 2127.*e1f*
chronic ischemic, 336*f*–337*f*
cirrhotic, 1037
classification of, 280*f*
CMR findings, 252
definition of, 279
dilated. *See* Dilated cardiomyopathy
genetic, causes of, 279.*e3t*
genetically inherited, 337
in HIV, 2317
Hodgkin lymphoma and, 1292*b*
hypertrophic, 279–284, 279.*e3t*, 337
apical, 281.*e1f*
echocardiographic findings, 242*t*
progressive, 281.*e2f*
hypertrophic obstructive, 282*f*
laboratory evaluation of, 287*t*
nonischemic dilated, 336–337
peripartum, 288, 1621–1622, 1622*b*, 1622*f*
psychotropic medications and, 2678*t*
rapidly reversing, 337
restrictive, 291–292
constrictive pericarditis *versus*, 429.*e1f*, 432*f*
differential diagnosis of, 433*t*
echocardiographic findings, 242*t*
overlap with dilated cardiomyopathy, 288
takotsubo (stress-induced), 294, 295*b*, 665
unclassified, 294–295
Cardiopulmonary arrest
electrical injury and, 703
lightning injury and, 704
Cardiopulmonary exercise tests, 532

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Cardiopulmonary resuscitation (CPR), after cardiac arrest, 313*b*
Cardiothoracic ratio, 244–245, 244*f*
Cardiotoxicity, psychotropic medications and, 2678*t*
Cardiovascular disease
  approach to, 210–218, 218
  atherosclerotic, 221.*e1f*
  autosomal dominant polycystic kidney disease and, 811
  in chronic kidney disease, 836
  complete medical history of, 212
  dialysis-associated, 842
  epidemiology of, 219–222
  future of, 221–222
  gene therapy for, 175
  global burden of, 219.*e2f*, 219
  hospitalization due to, 219
  hypertension and, 447, 448*t*
  laboratory studies, 216–218
  medical costs related to, 219
  molecular diagnostics and, 166*t*
  physical examination for signs, 212–218
  preoperative evaluation of, 2661, 2662*t*
  prevention of, 221
  rate of death due to, 219
  risk assessment, lifetime risk estimation, 221
  risk factors for, 219–222
    blood pressure, 439
    established, 219–220
    novel markers, 220–221
    screening for, 53
    short-term, 221
  in septic shock, 671–672
    clinical manifestations of, 672
    diagnosis of, 672–673, 673*f*
  severe mental illness and, 2677
  symptoms of, 212, 213*f*, 213*t*
    cardinal, 211*t*
    detection of, 210–212, 210*t*–211*t*
  US burden, 219
  in women, 1606–1607
Cardiovascular health, new paradigm for, 221, 222*t*
Cardiovascular magnetic resonance imaging (CMR), 251–253, 251*f*–252*f*
Cardiovascular risk, menopause associated with, 1632
Cardiovascular support, endocrine responses relevant to, 671
Cardiovascular syphilis, 2017, 2020*b*
Cardiovascular system
  age-related changes in, 121
  alcohol use disorders and, 2355, 2355*t*
  glucocorticoids and, 145
  metabolic regulation of, 224–225
  responses to stressors, 226, 226.*e1f*
  systemic lupus erythematosus manifestations of, 1769–1770
Cardioversion, transthoracic, 340
Caregivers, in heart failure management, 275*t*
Carfilzomib (Kyprolis), 1215*t*
Caribbean, HIV/AIDS in, 2289, 2289.*e4f*
Carney complex, 1487*t*, 1523, 1558, 1559*t*
Carnitine metabolism, disorders of, 1552*t*, 1555
Carnitine palmitoyltransferase I deficiency, 2586
Carnitine palmitoyltransferase II deficiency, 2586
Caroli disease, 990
β-Carotene, *e1t*–*e8t*, 59
Carotid body hypersensitivity, 306
Carotid duplex ultrasonography, 2468
Carotid endarterectomy, 2473
Carotid pulse, 30, 213, 215*f*
Carotid sinus massage, 324*b*
Carotid stenosis, 2473
Carpal tunnel syndrome, 1751, 1753*f*, 1779, 2579, 2579*b*
Carrier detection, for hemophilia, 1190–1191
Carrión disease, Oroya fever and, 2000–2001
Carteolol, 451*t*
Cartilage-hair hypoplasia, 1679*t*, 1680, 1680*b*
Cartilage-pannus junction, 1751
Carvajal syndrome, 288
Carvallo sign, 355
Carvedilol, 451*t*
  for acute STEMI, 384*b*, 391*t*
  for heart failure, 264*b*, 267*t*
Carvedilol phosphate, 451*t*
Case-control studies, 41
Case-mix adjustment methods, 41
Casirivimab/imdevimab, for coronavirus infections, 2191
Casodex. *See* Bicalutamide
Caspofungin
  adverse effects of, 2078
  drug interactions of, 2078
  formulations and pharmacology of, 2078
  for hepatosplenic candidiasis, 1024*b*
  indications and dosage of, 2075*t*, 2078
Cassava tubers (Konzo), 2541*t*
Cast nephropathy, in multiple myeloma, 794
Castleman disease, 1288, 1288*b*
Castration-resistant prostate cancer, 1385*b*
Casts, of urine, 722–724
Cat-scratch disease, 2001, 2003*b*, 2003*t*
Catabolism, 1429.*e1f*
Catalase, 196
Catamenial anaphylaxis, 1693
Cataract, 2606–2607
  congenital, 2612
  traumatic, 2604
Catastrophic antiphospholipid syndrome, 1770
Catathrenia, 2453*t*
Catatonia
  psychotropic medications and, 2681
  treatment for, 2681*b*
CATCH-22 syndromes, 347–348
Catecholamine(s), *e1t*–*e8t*, 1529, 1530.*e1f*
  half-life of, 1529
  synthesis of, 1529
  tyrosine synthesis of, 1529
Catecholamine-secreting tumors, 1529
  clinical manifestations of, 1530–1531
  complications of, 1533*b*
  definition of, 1529
  diagnosis of, 1531–1532, 1531*f*
  differential diagnosis of, 1531
  epidemiology of, 1530
  genetics of, 1530
  medical therapy for, 1533*b*
  pathobiology of, 1530
  signs and symptoms of, 1530*t*
  surgical therapy for, 1533*b*
  treatment of, 1533*b*
Catechol-*O* methyltransferase (COMT), 132*t*
Catheter ablation, 345–346, 345.*e1f*
  for atrial fibrillation, 329*b*, 346
  of supraventricular tachycardias, 346
  of ventricular arrhythmias, 346
  for ventricular tachycardia, 338*b*
Catheter-associated urinary tract infections, 1862*t*, 1866, 1873
Catheter-based adrenal ablation, for primary aldosteronism, 448*b*
Catheterization, cardiac
  for cardiovascular disease, 218
  complications of, 393, 394*t*
  contraindications to, 393, 394*t*
  for mitral stenosis evaluation, 405
  procedures performed in, 393.*e3t*
  right-sided, in cardiogenic shock, 667
Catheters, balloon angioplasty, 395, 395*f*
Cationic proteins, 183
Cationic trypsinogen gene *(PRSS1)*, mutations in, 970
Caucasian populations, cystic fibrosis in, 556
Cauda equina syndrome, 2402
Caudalization, 522
Causality, 37
Caustic injury, of esophagus, 907–908
Cavernous hemangioma, 2731
Cavernous sinus thrombosis, septic, 2528–2529
Cavitary disease, chronic, 2095
Cavitary lung diseases, 563–564, 564*b*, 564*t*
Cavitary tuberculosis, 2036*f*
Caya, 1611–1612
C-C chemokine receptor 2, 2089
CCKoma, 1561*t*, 1566
CCR5, 2291
CD4 cells, in opportunistic infections, 2306, 2306*f*
CD4 helper T (TH) cells, 2499
CD4+ T cells, 203–204, 204*t*
  depletion of, 2292–2293, 2292*f*
  micrographs of, 889.*e1f*
CD8+ T cells, 203, 204*t*
  micrographs of, 889.*e1f*
$CD8^+$T-cell-mediated hypersensitivity reaction, 2726
CD20, 152
$CD30^+$ anaplastic T-cell lymphoma, 2734
CD30+ cutaneous lymphoproliferative disorders, 1286
CD35, 200*t*
CD40 deficiency, 1681*t*
CD46, 200*t*
CD55, 200*t*
CD59, 200*t*
CD88, 202
CD207, 1154
CDC. *See* Centers for Disease Control and Prevention
CDKN2A, 1391
CEA. *See* Carcinoembryonic antigen
Cecal neuroendocrine neoplasms, 1566
Cefaclor, dosage of, 1895*t*
Cefadroxil, dosage of, 1895*t*
Cefazolin
  dosage of, 1895*t*
  for endocarditis, 422–423
Cefdinir, dosage of, 1895*t*
Cefditoren pivoxil, dosage of, 1895*t*
Cefepime
  for bacterial meningitis, 2518*t*
  dosage of, 1895*t*
  for pneumonia, 613*t*
  for pyelonephritis and urosepsis, 1877*t*
Cefiderocol, 1845*t*, 1970*b*
  Acinetobacter, 1974*b*
  dosage of, 1895*t*
Cefixime
  dosage of, 1895*t*
  for urinary tract infection, 1876*t*, 1877*t*
Cefotaxime
  for bacterial meningitis, 2518*t*
  dosage of, 1895*t*
  for *H. influenzae* infections, 1954*b*
  for meningococcal meningitis and meningococcemia, 1944*t*
  for pyelonephritis and urosepsis, 1877*t*
Cefotetan, for pelvic inflammatory disease, 1883*t*
Cefoxitin
  dosage of, 1895*t*
  for nontuberculous mycobacterial disease, 2046*t*
  for pelvic inflammatory disease, 1883*t*
Cefpodoxime proxetil
  for cystitis, 1876*t*
  dosage of, 1895*t*
Cefprozil, dosage of, 1895*t*
Ceftaroline
  for bacterial meningitis, 2518*t*
  dosage of, 1895*t*
  for pneumonia, 613*t*
  for *Streptococcus pneumoniae* pulmonary infections, 1912.*e1t*
Ceftazidime
  for bacterial meningitis, 2518*t*
  dosage of, 1895*t*
  for pneumonia, 613*t*
  for pyelonephritis and urosepsis, 1877*t*
  for *Stenotrophomonas maltophilia*, 1975*b*, 1976*t*
Ceftazidime-avibactam, dosage of, 1895*t*
Ceftibuten
  dosage of, 1895*t*
  for urinary tract infection, 1876*t*, 1877*t*
Ceftizoxime, dosage of, 1895*t*
Ceftolozane-tazobactam, dosage of, 1895*t*
Ceftriaxone
  for bacterial meningitis, 2518*t*
  disseminated gonococcal infection and, 1950*b*
  dosage of, 1895*t*
  for endocarditis, 419*t*
  for enteric fever, 1977
  for gonorrhea, 1948*b*
  for *H. influenzae* infections, 1954*b*
  for leptospirosis, 2031*b*
  for Lyme disease, 2026*t*
  for meningococcal disease, 1945*t*
  for meningococcal meningitis and meningococcemia, 1944*t*
  for pelvic inflammatory disease, 1883*t*
  for pneumonia, 613*t*
  for pyelonephritis and urosepsis, 1877*t*
  for *Streptococcus pneumoniae* pulmonary infections, 1912.*e1t*
  for urethritis, 1880*t*
  for Whipple disease, 2070*b*–2071*b*
Cefuroxime, dosage of, 1895*t*
Cefuroxime axetil
  dosage of, 1895*t*
  for Lyme disease, 2026*t*
  for urinary tract infection, 1876*t*, 1877*t*
Celecoxib
  for chronic pain, 138*t*
  for rheumatoid arthritis, 1756*t*
Celiac artery compression syndrome, 967, 967*f*
Celiac disease, 935, 1821
  clinical manifestations of, 935–936
  definition and epidemiology of, 935
  diagnosis of, 936, 936*f*
  osteomalacia and, 1649
  pathobiology of, 935
  prognosis of, 936–937
  treatment of, 936*b*
Cell-bound receptors, for immunoglobulin, 192
Cell count, in bacterial meningitis, 2514
Cell-free DNA, 1252
Cell therapy, 169–174
  definition of, 169–174
  for diabetes mellitus, 174
  disease application for, 174
  in mRNA anti-tumor vaccines, 177–178
  for neurodegenerative disorders, 174
  regenerative medicine approaches, 172–174, 173*f*
Cellular damage, in acute kidney injury, 773
Cellular immunity, in systemic sclerosis, 1776
Cellular mediators, 205
Cellular responses, 196
Cellulitis, 2739, 2740*f*
  Acinetobacter baumannii causing, 1973, 1974*f*
  H. influenzae causing, 1953
  Staphylococcus aureus causing, 1903
  Streptococcus pyogenes causing, 1915
Centers for Disease Control and Prevention (CDC), 41.*e1t*
  PulseNet, 1937
Centers for Medicare and Medicaid Services (CMS), 41.*e1t*, 44
Centipedes, 711
Central adiposity, 1629
Central Africa, HIV/AIDS in, 2289, 2289.*e1f*
Central Asia, HIV/AIDS in, 2289, 2289.*e2f*–2289.*e3f*
Central brain-gut neuromodulators, for irritable bowel syndrome, 895*b*, 896*t*
Central centrifugal cicatricial alopecia, 2751, 2751*f*
Central congenital hypoventilation syndrome, 534–536
  clinical manifestations of, 536
  definition of, 534
  epidemiology of, 534
  in hypercapnic disease, 535*t*
  pathobiology of, 534–536
  treatment of, 536*b*
Central cord syndrome, 2386, 2403
Central diabetes insipidus, 743
  clinical manifestations of, 1501, 1502*f*
  diagnosis of, 1502–1503
  pathobiology of, 1500
  treatment of, 1503*b*
Central Europe, HIV/AIDS in, 2289–2290, 2289.*e4f*, 2290.*e1f*
Central hearing disorders, 2641
Central hearing loss, 2642
Central hypothyroidism, 1497, 1497*b*
Central line-associated blood stream infections, 1862*t*, 1865, 1865.*e1t*
Central line bundle, 1866
Central nervous system (CNS)
  altered, irritable bowel syndrome and, 893
  brain tumors. *See* Brain tumors
  cobalamin deficiency of, 1124–1125
  glucocorticoids and, 145–146
  rhythms, 1478
  stimulants of, 2363
  toxicants and, 683
  tuberculosis, 2037
  tumors, 1310–1319, 1311*t*
  vasculitis, 1799–1800, 1800*t*
Central nervous system (CNS) infections
  actinomycosis and, 2068
  anaerobic bacteria causing, 1938
  cryptococcosis causing, 2087, 2088*b*
  enteroviruses causing, 2258–2259
  involvement, 2221
  nocardiosis and, 2073
  Pseudomonas infections causing, 1969
  Staphylococcus aureus causing, 1904
  subacute sclerosing panencephalitis, 2221
Central nervous system (CNS) lymphoma, 2255
  primary, 1316, 1316*b*, 1316*f*
Central neurogenic hyperventilation, 2438, 2439*t*
Central precocious puberty, 1481, 1582
Central retinal artery
  anatomy of, 2614
  occlusion, 2610, 2610*f*

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Central retinal vein occlusion, 2610, 2610*f*
Central sensitization, 134, 1816
Central sleep apnea, 534, 534*t*–535*t*, 2448, 2448.*e2f*
Central sympatholytics
  clinical use of, 455
  for hypertension, 455
  mechanism of action of, 455
  side effects of, 453*t*, 455
Central tendency, 36
Central venous catheter, in parenteral nutrition, 1450
Central venous pressure, 677*t*
Central venous thrombosis, in parenteral nutrition, 1450
Central vertigo, 2644
Centralization, 522
Centralized pain, 1816, 1817*t*
Centronuclear myopathy, 2585.*e1f*
CEP. *See* Congenital erythropoietic porphyria
Cephalexin
  for cellulitis, 2740*b*
  dosage of, 1895*t*
  for urinary tract infection, 1877*t*
Cephalic tetanus, 1928–1929
Cephalization, 522
Cephalosporins
  for bacterial meningitis, 2518*t*
  for chancroid, 1951*b*
  dosage of, 1895*t*
  for enteric fever, 1977
  for listeriosis, 1938*b*
  for *Moraxella catarrhalis* infections, 1955*b*
  toxicities of, 1901*t*
  for yersiniosis, 1994*b*
Cephradine, dosage of, 1895*t*
Cerebellar ataxia, 2373*t*, 2497, 2497*b*, 2497*t*
Cerebellar degeneration, 2544
Cerebellar hemorrhage, 2479
Cerebellopontine angle tumors, 2646
Cerebellum, infarction of, 2645–2646
Cerebral adrenoleukodystrophy, 1528
Cerebral amyloid angiopathy, 2419, 2478–2479
Cerebral aneurysms, 2476*f*
  autosomal dominant polycystic kidney disease and, 812
  description of, 2463
Cerebral arteries, 2465
Cerebral artery occlusion, 2465
Cerebral autosomal dominant arteriopathy with subcortical infarcts and leukoencephalopathy, 2419, 2472
Cerebral blood flow, 2459–2461
Cerebral edema, 2463–2464, 2464, 2511
  high-altitude, 592, 592*t*
Cerebral embolization, 2530
Cerebral hemorrhage, 2463
Cerebral infarct, 2530
Cerebral ischemia, 2462–2463
Cerebral malaria, 2120
Cerebral microbleeds, 2479*f*
Cerebral mucormycosis, 2099
Cerebral palsy, 2547, 2548*b*
Cerebral salt wasting, 739
Cerebral schistosomiasis, 2164
Cerebral venous thrombosis
  stroke caused by, 2471
  virally mediated, 2530
Cerebrospinal fluid (CSF)
  enteroviruses in, 2257–2258
  examination
    in bacterial meningitis, 2513, 2513*t*
    for cryptococcal meningitis, 2088
    for infection, 2110–2111
    lumbar puncture for, 2374, 2374*f*, 2374*t*
    in multiple sclerosis, 2503–2504
  in TB meningitis, 2040
Cerebrovascular diseases
  anatomy of
    anterior cerebral arteries, 2456, 2458*f*
    anterior choroidal artery, 2457, 2459*f*
    aortic arch, 2454, 2455*f*
    basilar artery, 2456
    circle of Willis, 2455.*e1f*, 2456
    external carotid arteries, 2455
    internal carotid arteries, 2455, 2456*f*
    middle cerebral artery, 2457, 2459*f*–2460*f*, 2460*f*
    posterior cerebral artery, 2457–2459
    venous system, 2459, 2461*f*–2462*f*
Cerebrovascular diseases *(Continued)*
    vertebral arteries, 2455–2456, 2457*f*
  approach to, 2454–2463
  blood-brain barrier, 2461
  cerebral ischemia, 2462
  cognitive impairment caused by
    clinical manifestations of, 2419
    definition of, 2417
    diagnosis of, 2419, 2419*t*
    epidemiology of, 2417–2418
    magnetic resonance imaging of, 2419*f*
    pathobiology of, 2418–2419
    prognosis for, 2420
    risk factors for, 2418
    treatment of, 2420*b*
  definition of, 2454–2461
  epidemiology of, 2454
  ischemic, 2464–2474
    clinical manifestations of, 2465–2466, 2465*t*
    diagnosis of, 2466–2469, 2466*f*
    differential diagnosis of, 2469
    epidemiology of, 2464
    pathobiology of, 2464
  neurovascular unit, 2461
  in older adults, 115
  pathobiology of, 2454–2461
  physiology of, 2459–2461
Cerebrovascular syncope, 306
Cerebrovascular syndrome, 93
Ceroid-lipofuscinoses, neuronal, 1420*t*, 1424
Certolizumab (Cimzia)
  for rheumatoid arthritis, 1756*t*
  for total knee arthroplasty, 1830.*e1t*
Certolizumab pegol
  description of, 151*t*
  for inflammatory bowel disease, 945*b*, 946*t*
Ceruloplasmin, *e1t*–*e8t*, 1436
Cerumen, impacted, 2641
Cervarix, 2243
Cervical adenopathy, treatment of, 1241*b*
Cervical artery dissection, 2470.*e1t*, 2471–2472
Cervical buboes, 1991
Cervical cancer, 1375, 1375*t*
  clinical manifestations of, 1375
  diagnosis of, 1375
  epidemiology of, 1375, 2241
  in HIV, 2316*b*
  human papillomavirus and, 1607, 2241, 2305–2306
  loop electrosurgical excision procedure for, 1375*b*
  oral contraceptives and, 1615
  pathobiology of, 1375
  pelvic exenteration for, 1375*b*
  prevention of, 1376
  prognosis for, 1375*b*, 1377
  risk factors for, 1375*t*
  screening for, 54, 112, 1376, 1376*t*
  treatment of, 1375*b*, 1376*t*
Cervical intraepithelial neoplasia, 1615, 2240, 2244
Cervical lymph nodes, nontuberculous mycobacteria causing, 2045
Cervical mediastinoscopy, 1331
Cervical mucus, in menstrual cycle, 1595
Cervical myelopathy, 2564*t*
Cervical neoplasia, organisms causing, 1879*t*
Cervical radiculopathy, 2394*t*, 2402–2403
Cervical spine, stenosis of, 2398*b*
Cervical spondylotic myelopathy, 2399–2401, 2401*b*, 2404*f*
Cervical squamous intraepithelial lesions, 2242–2243
Cervical vertebrae, 2392
Cervicitis, 1948
  characteristics of, 1883
  Chlamydia trachomatis causing, 2011
  clinical manifestations of, 1948, 1948*f*
  diagnosis of, 1948–1949, 1949
  organisms causing, 1879*t*
  treatment of, 1883*b*
Cervicofacial actinomycosis, 2067, 2067*f*
Cervix, menstrual cycle-related changes in, 1595
Cestodes, 2157
  cystic hydatid disease, 2161, 2161*b*, 2162*f*
  definition of, 2157
  Diphyllobothrium sp., 2157
  Dipylidium caninum, 2158, 2158*b*, 2158*t*
  Hymenolepis nana, 2157, 2158, 2158*b*
Cestodes *(Continued)*
  pathogens associated with, 2157
  Taenia asiatica, 2158*t*, 2159
  Taenia solium, 2158*t*, 2159, 2159*b*
Cetirizine, for mastocytosis, 1703*b*–1704*b*
Cetuximab (Erbitux), 1215*t*, 1251*t*
  for head and neck cancer, 1327*b*–1328*b*
CFTR. *See* Cystic fibrosis transmembrane conductance regulator
CFTR correctors, for cystic fibrosis, 558*b*
CFU. *See* Colony forming units
CGRP. *See* Calcitonin gene-related peptide
Chagas cardiomyopathy, 255, 2127, 2127.*e1f*
Chagas disease, 1203, 2065*t*, 2116, 2126–2130
  acute, 2127
  chronic, 2127
  clinical manifestations of, 2127–2128, 2127*t*
  constipation caused by, 890
  diagnosis of, 2127*t*, 2128, 2129*f*
  endemic, 2126
  epidemiology of, 2126
  infective myocarditis caused by, 284
  pathobiology of, 2126–2127, 2127*f*, 2127.*e1f*
  pathogen of, 2126
  prevention of, 2128
  prognosis of, 2129, 2129*t*
  symptomatic, management of, 2128*b*
  treatment of, 2128*b*
  in United States, 2126
  ventricular tachycardia in, 336–337
Chagoma, 2127
Chalazion, 2601, 2601*f*
Chamber hypertrophy, 233, 234*f*
Chancre, syphilitic, 1881, 2015
Chancroid, 1950–1952
  characteristics of, 1881
  clinical manifestations of, 1951, 1951*f*–1952*f*, 1952*f*
  definition of, 1950–1952
  diagnosis of, 1951
  epidemiology of, 1950–1951
  organisms causing, 1879*t*
  pathobiology of, 1951
  prevention of, 1952
  prognosis of, 1951–1952
  treatment of, 1881*b*, 1951*b*
Change, levers for, 44
Channelopathies
  description of, 2583.*e1t*
  genetically inherited, 333
Chapare virus, 2265*t*
Chaperones, 28–29
CHAPLE syndrome, 939
Charcot joint, 1822
Charcot-Leyden crystals, 2170
Charcot-Marie-Tooth disease, 2368.*e3f*, 2568–2570, 2570*b*, 2570*f*
Check for Safety: A Home Fall Prevention Checklist for Older Adults, 118
Checkpoint molecules, 152
Chédiak-Higashi syndrome, 1145, 1185, 1683, 1683.*e1t*, 1684*t*
Cheilitis, 943
Chelation therapy, for chronic poisoning of trace metals, 103*b*
Chemical injuries, to lung, 591–599
"Chemical" meningitis, 2515
Chemical peels, 2701
Chemical poisoning, industrial and agricultural, characteristics of, 2270*t*
Chemoimmunotherapy, for chronic lymphocytic leukemia, 1269*b*
Chemokine receptors, 184–185
Chemokines, hematopoiesis regulated by, 1065
Chemoprophylaxis, for common cold, 2193
Chemoradiotherapy, for anal cancer, 983*b*
Chemoreceptor proteins, 2639
Chemotherapy
  for brain metastases, 1317*b*
  for brain tumors, 1313*t*
  for breast cancer, 1369*b*
  for chronic lymphocytic leukemia, 1269*t*
  for cystic echinococcosis, 2161*b*
  for diffuse large B-cell lymphoma, 1285*b*
  for disseminated disease, 1383*b*, 1383*t*
  for esophagitis, 907*t*
  for Ewing sarcoma, 1388*b*
  neutropenia after, 1147*b*
  neutropenia induced by, 1854*t*
  reactions to, 1698
Chemotherapy *(Continued)*
  for schistosomiasis, 2165
  side effects of, 291
  ulcers associated with, 917
Chemotherapy-related myelodysplasia, Hodgkin lymphoma and, 1292*b*
Cherry hemangioma, 2731
Chest
  examination of, 30
  flail, 621–622, 621.*e1f*, 622*b*
  images of, evaluation of, 520–526
  injuries to, 700*b*
Chest pain, 210, 211*t*, 256–257, 394–395
  acute, 210
  cause of, 211*t*
  esophageal disease and, 902
  functional, 900–901
    clinical manifestations of, 900
    definition of, 900
    diagnosis of, 900
    differential diagnosis of, 901*t*
    epidemiology and pathobiology of, 900
    prognosis of, 901
    Rome IV diagnostic criteria for, 900*t*
    treatment of, 901*b*
  postoperative, 2673, 2673*t*
  recurrent, management of, 384*b*
  severe mental illness and, 2683*t*
Chest physical therapy, for viscid mucus, 558*b*
Chest radiography, 259, 358, 519
  of acute respiratory failure, 645, 645.*e1f*, 646*f*
  of apical lung disease, 524*f*
  of basal pulmonary disease, 524*f*
  of bilateral alveolar opacities
    with acute interstitial pneumonia, 568.*e1f*
    with diffuse alveolar hemorrhage, 568.*e1f*
  of bronchiectasis, 558*f*
  cardiac silhouette, 247
  of COVID-19, 520.*e1f*–520.*e2f*
  of cystic bronchiectasis, 557*f*–558*f*
  of cystic fibrosis with pulmonary hypertension and cor pulmonale, 558.*e1f*
  of diffuse alveolar damage, 520*f*
  of diffuse reticular lung disease, 522*f*
  double density sign, 245, 245*f*
  gooseneck sign, 247
  with implanted devices, 246
  in interstitial lung disease, 573–574, 573*t*
  of known transfusion reaction, 522*f*
  of left ventricular failure, 523*f*
  mediastinal findings on, 526–527, 526*f*–527*f*, 527*f*
  of multifocal pulmonary opacities, 524*f*
  of pleural effusion, 624, 624*f*
  pruned-tree sign, 246*f*
  of pulmonary alveolar proteinosis, 567, 567*f*
  of pulmonary arterial hypertension, 523*f*
  of pulmonary edema, 521*f*
  reversed figure-of-3 signs, 247
  scimitar sign, 247, 247.*e1f*
  of severe emphysema, 523*f*
  for signs of cardiovascular disease, 217
  of silicosis, 591*f*
  water-bottle sign, 245, 246*f*
Chest wall
  disorders of, 619*t*, 620–623
  imaging of, 519–527
Cheyne-Stokes breathing, 534, 534*b*, 534*t*, 2438, 2439*t*, 2448, 2448.*e1f*
Chiari I malformation, 2546, 2546*f*
Chiari II malformation, 2546
Chiari malformation, 2546, 2546*b*, 2546*f*
Chickenpox. *See also* Varicella
  immunization for, 65*t*, 82
  prophylaxis for, 2309*t*
Chigger mites, 711
Chikungunya virus, 1807, 2275*t*, 2278, 2278*b*, 2278.*e1f*
  in travelers, 1888, 1889.*e1t*, 1890*t*
Chilblains, 680, 1735
Childbirth, *Paeniclostridium sordellii* associated with, 1927
Children
  absence epilepsy in, 2432
  bacterial meningitis in, 2511
  cryptosporidiosis in, 2143
  histiocytosis X in, 2731
  meningococcal disease in, 1941
  obesity in, 1463–1464
  ovarian function in, 1591–1592

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Children *(Continued)*
primary malnutrition in, 1445*b*
recurrent parotitis in, 2626
reproductive axis development in, 1581–1582
Chills, caused by amphotericin B, 2078
Chimera, 162
Chimeric antigen receptor (CAR), 3, 207
Chimeric antigen receptor (CAR) T-cells
anticancer therapy uses of, 176, 176*f*
description of, 151
Chlamydia, 2649
definition of, 2009
developmental cycle of, 2009*f*
diseases caused by, 2009–2014
epidemiology of, 1879
pathobiology of, 2009
pathogens that cause, 2009
Chlamydia pneumoniae, 2010*t*
asthma and, 2013
atherosclerosis and, 2013
clinical manifestations of, 2013
description of, 2013
diagnosis of, 2013
epidemiology of, 2013
neurologic diseases and, 2013
prognosis of, 2013
treatment of, 2013*b*
Chlamydia psittaci, 2010*t*, 2013–2014, 2014*b*
Chlamydia trachomatis, 1879
annual screening for, 112
cervicitis caused by, 2011
conjunctivitis caused by, 2012
description of, 2009–2013
diagnosis of, 2010
diseases caused by, 2009–2014, 2010*t*
epididymitis caused by, 2011, 2012*b*
pelvic inflammatory disease caused by, 2011
in pregnancy, 2011–2012
prevalence of, 112
prevention of, 2012
proctitis caused by, 2012
prognosis of, 2012–2013
reactive arthritis caused by, 2012
serology of, 2012
sexually transmitted anorectal diseases and, 983
sexually transmitted infections caused by, 2010, 2011*f*
trachoma caused by, 2009
treatment of, 2012*b*
urethritis caused by, 2010–2011
Chlamydial conjunctivitis, 2604
Chlamydial infections, in adolescents, 112
Chlamydophila psittaci, 417*t*
Chlorambucil, for chronic lymphocytic leukemia, 1269*t*, 1270*t*
Chloramphenicol, e10*t*–e11*t*
for bacterial meningitis, 2518*t*
dosage of, 1895*t*
mechanism of action, 1895*t*
for meningococcal meningitis and meningococcemia, 1944*t*
for plague, 98*b*, 1992*t*
resistance mechanisms, 1893*t*
toxicities of, 1901*t*
Chlordiazepoxide
for alcohol withdrawal, 2358*t*
for anxiety disorders, 2344*t*
Chlorhexidine, reactions to, 1698*t*
Chlorhexidine-alcohol, for catheter-related infections, 1866
Chloride (Cl), e1*t*–e8*t*
Chloride channelopathies, 2585
Chloride-responsive metabolic alkalosis, 763
Chlorinated hydrocarbons, 88*t*
2-Chlorodeoxyadenosine (Mavenclad), for multiple sclerosis, 2505*t*
Chloromas, 1262
Chloroquine, 2114
for extraintestinal amebiasis, 2112*t*
for malaria, 1887, 2112*t*, 2121*b*
ocular effects of, 2613–2614
Chloroquine phosphate, for malaria, 2121*t*
Chlorpromazine, e10*t*–e11*t*, 2346*t*
Chlorthalidone, 451*t*
for hypervolemia, 737*t*
Cholangiocarcinoma, 1060
clinical manifestations of, 1359
definition of, 1357
histology of, 1359*f*
imaging of, 1360*f*
pathobiology of, 1359
Cholangiography, 1360
Cholangitis, 1055*b*
biliary, 987
in endoscopy, 876*t*
Cholecalciferol, 1650*t*
Cholecystectomy, 1052*b*, 1054*b*
Cholecystitis, acute
abdominal pain and, 854*t*
ultrasound of, 869*f*
Cholecystokinin, 1464–1465
Choledochal cysts, 1058, 1059*t*, 1059.e1*f*
Choledocholithiasis, 873*f*. *See also* Bile duct stones
Cholelithiasis, ultrasound of, 869*f*
Cholera, 1955–1957
clinical manifestations of, 1956
definition of, 1955
diagnosis of, 1956
epidemiology of, 1955, 1956*f*
immunization for, 66*t*, 83
pathobiology of, 1955–1956, 1957*t*
pathogen, 1955
prevention of, 1957
prognosis of, 1957
treatment of, 1956*b*, 1957*t*
vaccine, for traveler, 1886*t*, 1887
Cholescintigraphy, 1051
Cholesteatoma, 2641
Cholesterol, 1405, 1405*f*, 1405.e1*f*
dietary guidelines for, 57.e3*t*
dietary source of, 1405
metabolism of, 1406, 1407*f*
total, e1*t*–e8*t*
Cholesterol crystal embolization, 470
Cholesterol emboli, 2716, 2716*f*
Cholesterol gallstones, 1049
Cholesterol polyps, 1053–1054
Cholesterol reduction, 374*t*
Cholesteryl ester transfer protein, 1406
Cholestyramine, 941*b*, 1413, 1460*t*
for irritable bowel syndrome, 896*t*
for primary sclerosing cholangitis, 1058*b*
for small bowel rapid transit dysmotility, 890
Choline, 1451
Cholinergic urticaria, 2725
Cholinesterase, toxicity, 690*t*
Cholinesterase inhibitors
for Alzheimer disease, 2420*b*
for dementia with Lewy bodies, 2421*b*
Cholinomimetic toxidromes, 683*t*
Chondrocalcinosis, 1719, 1824
Chondrodystrophic myotonia, 2583.e1*t*
Chondrosarcoma, 1388, 1388*b*
Chordae tendineae, 224
Chordomas, 1314
Chorea
definition of, 2490–2492
differential diagnosis of, 2491*t*
Huntington disease, 2490–2491, 2490*b*–2491*b*, 2491*b*
Choreoathetosis, 2493
Choriomeningitis, lymphocytic, 2521
Chorionic gonadotropin, intact + beta subunit, e1*t*–e8*t*
Choroid, 2596
Choroid plexus papilloma, 1316
Choroidal dystrophy, 2611–2612
Christmas factor, 1189*t*
Chromaffin cells, 1529
Chromium, 88*t*, 1457*t*
Chromomycosis, 2109, 2109*f*, 2111*b*
Chromophobe renal cell cancer, 1363
Chromosomal aberrations, 164, 164.e1*f*
Chromosomal abnormalities, of chronic lymphocytic leukemia, 1267
Chromosomal deletions and duplications, 164
Chromosome 22q11.2 deletion syndrome, 1679*t*
Chronic abdominal pain, 854*t*, 858, 859*f*
Chronic actinic dermatitis, 2704–2705, 2704*f*
Chronic adrenal insufficiency, 1527, 1528*b*
Chronic adult T-cell leukemia/lymphoma, 2326, 2326*b*
Chronic alcohol use disorder, 1936
Chronic ambulatory peritoneal dialysis, 957
Chronic angina
coronary artery bypass graft for, 398
diagnostic coronary angiography in, 363*t*
Chronic anovulation, 1600–1602
causes of, 1601*t*
diagnosis of, 1601
endocrine causes of, 1602
hypothalamic, 1601–1602
Chronic anovulation *(Continued)*
inappropriate feedback causing, 1601
treatment of, 1601*b*
Chronic aortic regurgitation, 409
Chronic aspiration, cystic fibrosis *versus*, 558
Chronic atypical neutrophilic dermatosis with lipodystrophy and elevated temperature (CANDLE), 1731*t*, 1735
Chronic autoimmune syndromes, 2510
Chronic bacterial otomastoiditis, vertigo associated with, 2645
Chronic bacterial prostatitis, treatment of, 825*b*
Chronic beryllium disease, 589
clinical manifestations of, 589
diagnosis of, 589*b*, 589*f*
epidemiology of, 589
exposures to, 589*t*
pathobiology of, 589
treatment of, 589*b*
Chronic cavitary disease, 2095
Chronic coronary artery syndrome, antiplatelet therapy for, 507
Chronic cough, 512
diagnosis of, 512–513, 513*t*, 514*f*
management of, 514*f*
Chronic daily headache, 2378*t*, 2382, 2382*b*
Chronic diabetic kidney disease, 456
Chronic diarrhea, 928–932
causes of, 928*t*
clinical manifestations of, 928–932
diagnosis of, 928–932, 929*f*
Chronic disease
aging and, 120
prevention of, 57
Chronic disseminated candidiasis, 2092
Chronic dyspnea, 517*f*
Chronic eosinophilic pneumonia, 582
Chronic fatigue syndrome, 1816, 2372
Chronic fibrosing interstitial pneumonias, 571*t*, 575
Chronic granulomatous disease, 1683, 1683.e1*t*
Chronic hemodynamic monitors, 261
Chronic hemolytic anemia, 1072*t*
Chronic hepatitis B, 1010–1013
cirrhosis in, 1012–1013
clinical manifestations of, 1010–1011
diagnosis of, 1011, 1011*t*, 1012*f*
epidemiology of, 1010
pathobiology of, 1010
prevention of, 1011*b*–1012*b*, 1013*t*
prognosis for, 1012–1013
treatment of, 1011*b*, 1013*t*
Chronic hepatitis C, 1013–1014
clinical manifestations of, 1013–1014
diagnosis of, 1014
epidemiology of, 1013
human immunodeficiency virus and, 1014*b*
pathobiology of, 1013
prognosis for, 1014
recurrent, after liver transplantation, 1014*b*
treatment of, 1014*b*, 1015*t*
Chronic hepatitis D, 1015, 1015*b*
Chronic hepatitis E, 1016, 1016*b*
Chronic hypertension, in pregnancy, 1619*t*
Chronic hypocalcemia, 1659*b*
Chronic hyponatremia, 741*b*
Chronic idiopathic demyelinating polyneuropathy, 2564*t*
Chronic idiopathic neutropenia, 1146
Chronic idiopathic neutrophilia, 1141
Chronic idiopathic secretory diarrhea, 940
Chronic illness
in adolescents, 113
palliative care for, 11
Chronic immune demyelinating polyneuropathy (CIDP), immunization for, 65*t*
Chronic inflammation, neutrophilia and, 1141
Chronic inflammatory demyelinating polyneuropathy, 1296, 2313, 2375.e1*f*
Chronic inflammatory demyelinating polyradiculoneuropathy, 2572, 2572*b*
Chronic interstitial nephritis
analgesics causing, 793
anemia in, 793
cadmium toxicity causing, 794
causes of, 791*t*, 793–795
characteristics of, 790
clinical manifestations of, 793–795
diagnosis of, 793–795
granuloma formation in, 792
hypercalcemia causing, 794
lead toxicity causing, 794
Chronic interstitial nephritis *(Continued)*
myeloma causing, 794
obstruction causing, 794
pathology of, 791–792
primary, 790
vascular disease causing, 793
Chronic ischemic cardiomyopathy, 336*f*
Chronic ischemic heart disease, 336, 360*f*
Chronic kidney disease (CKD), 729, 729*f*, 831–840, 840
antihypertensive drug for, 454*t*
causes of, 831.e2*f*, 833*t*
clinical manifestations of, 834*t*, 836–837
conceptual model of, 831.e2*f*
criteria for, 837*t*
definition of, 831–840
diagnosis of, 837–839, 837*t*
disability-adjusted life years for, 831.e2*f*
epidemiology of, 831–832, 832*f*
evaluation of, 838*t*
cause, 839
duration, 837
glomerular filtration rate, 837–839, 839*t*
in hypertension, 448*t*
markers, 837
metabolic acidosis of, 757
pathobiology of, 832–836, 833*f*, 834*t*, 835*f*
porphyrias and, 1432
prevention of, 840.e1*f*, 840
prognosis of, 840
treatment of, 839*b*
Chronic limb ischemia, 462
Chronic limb ulceration syndrome, *H. ducreyi* and, 1951
Chronic liver failure, for liver transplantation, 1044
Chronic lower limb ischemia, 462*t*, 464*b*
Chronic lower respiratory disease
in adolescents, 110*t*
in older adults, 115
Chronic lung diseases, 1113–1114
occupational and environmental, 86
Chronic lymphocytic leukemia (CLL), 1266–1272, 1283, 1283*b*
autoimmune complications of, 1267, 1271
B-cell receptor in, 1267
chromosomal abnormalities in, 1267
clinical manifestations of, 1267–1268
definition of, 1266–1271
diagnosis of, 1268–1271, 1268*f*, 1268.e1*f*
differential diagnosis of, 1268–1269
disease-related complications of, 1267–1268, 1271
epidemiology of, 1266
epigenetics of, 1267
immunization for, 65*t*
pathobiology of, 1266–1267
peripheral blood smear of, 1074, 1074*f*
prognosis of, 1271
staging and prognostic factors of, 1269, 1269*t*
therapies used in, 1269*t*
treatment of, 1269*b*, 1270*f*, 1270*t*
Chronic medications, in preoperative evaluation, 2666–2667, 2666*t*
Chronic meningitis
infectious causes of, 2522–2524, 2523*t*–2524*t*
intermittent, 2524
noninfectious causes of, 2523–2524, 2524*t*
persistent, 2523*t*, 2524*t*
with predominantly neutrophilic pleocytosis, 2524, 2524.e1*t*
recurrent, 2523*t*
Chronic mesenteric ischemia, 916*f*, 963, 963*f*
clinical manifestations of, 963
diagnosis of, 963, 964*f*
treatment of, 964*b*
Chronic mitral regurgitation, asymptomatic, 407*b*
Chronic mountain sickness, 592, 592*t*, 593*b*
Chronic mucocutaneous candidiasis, 1686*t*, 2090
Chronic myelogenous leukemia (CML)
histamine hypersecretion, 917
neutrophilia and, 1142
Chronic myeloid leukemia (CML), 1272–1278
clinical manifestations of, 1274
cytogenetic abnormalities in, definition of, 1272–1277
diagnosis of, 1274, 1274*f*
epidemiology of, 1273
hematopoietic cell transplantation for, 1209
molecular response of, pathobiology of, 1273–1274, 1273*f*

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Chronic myeloid leukemia (CML) *(Continued)*
peripheral blood smear of, 1073, 1073*f*
prognosis of, 1277, 1277*t*
treatment of, 1274*b*, 1274*f*, 1275*t*, 1276*t*
Chronic myelomonocytic leukemia (CMML), 1277, 1278*b*
Chronic narcotic therapy, 534*t*
Chronic necrotizing pulmonary aspergillosis, 2095
Chronic neuropathy, porphyrias and, 1432
Chronic obstructive pulmonary disease (COPD), 547–556, 649, 2664
acute exacerbations of, 554–555
arterial blood gases of, 550
asthma *versus*, 550
bronchiectasis *versus*, 549
cigarette smoking and, 547
clinical manifestations of, 549, 649
computed tomography of, 548
cystic fibrosis and, 557
definition of, 547–554
diagnosis of, 549–550, 649
diagnostic testing of, 549–550, 550*t*
differential diagnosis of, 550
environmental air pollution and, 547–548
eosinophilic, 551*b*
epidemiology of, 547–548, 649
genetics of, 549
GOLD classification system for, 548*f*
history of, 549, 549*f*
in HIV, 2318
hospital management of exacerbations, 555*t*
imaging of, 550, 550*f*–551*f*, 551*f*
natural history of, 551*b*
as occupational lung disease, 585*t*, 588
in older adults, 114
oximetry of, 550
oxygen therapy for, 551*b*
pathobiology of, 548–549, 649
pathophysiology of, 548
pharmacotherapy for, 551*b*, 552*f*
physical examination of, 549, 549*f*
physical findings in, 549
prognosis of, 650
severe
contraindication for, 632*t*
decision guide for, 632*t*
indications for, 632, 632*t*
treatment of, 551*b*, 553*t*, 554*b*, 649*b*–650*b*, 649*t*
weight loss and, 860*t*
Chronic otitis media, 2526*t*, 2641
Chronic pain, 133
Chronic pancreatitis, 933, 973–976
abdominal pain and, 854*t*
alcohol and tobacco and, 973
causes of, 974
clinical manifestations of, 933, 974
definition of, 973
diagnosis of, 933, 974–975, 974*f*–975*f*, 974*t*, 975*f*
epidemiology of, 973
genetic of, 973
pancreatic duct obstruction and, 973–974
pathobiology of, 973–976
prevention of, 976
prognosis of, 976
treatment for, 975*b*, 975*t*
Chronic pelvic pain syndrome, treatment of, 825*b*
Chronic poisoning, of trace metals, 101–107
aluminum, 101*t*, 105, 105*b*
arsenic toxicity, 103
bismuth, 101*t*, 102*t*, 105, 105*b*
cadmium toxicity, 104
cobalt, 106, 106*b*
lead toxicity, 101
manganese, 101*t*, 107, 107*b*
mercury toxicity, 102–103
silver, 106, 106*b*, 106*f*
thallium, 106, 106*b*
zinc, 101*t*, 106, 107*b*
Chronic preexisting hypertension, 1620
Chronic progressive external ophthalmoplegia, 2586
Chronic Prostatitis Symptom Index, 826*f*
Chronic recurrent multifocal osteomyelitis (CRMO), 1731*t*
Chronic rejection, 206
in renal transplantation, 846
Chronic respiratory tract infections, *Pseudomonas* infections causing, 1969
Chronic rhinitis, 2627–2628
Chronic rhinosinusitis, 2628
cystic fibrosis and, 558
Chronic sarcoid arthritis, 602
Chronic sinusitis, 2627, 2633*t*
Chronic sleep-disordered breathing, 257
Chronic stable lower limb ischemia, 462
Chronic subdural hematoma, 2391, 2391*b*, 2391*f*
Chronic telogen effluvium, 2748
Chronic thromboembolic hypertension, 496*b*, 499.*e1f*
Chronic thromboembolic pulmonary hypertension, 490
Chronic tonsillitis, 2651
Chronic ulcerated herpes simplex, 2687.*e4t*
Chronic ulcerations, other, 2622
Chronic urate-lowering therapies, 1813*b*–1814*b*
Chronic urticaria, 1674, 1687, 2725
diagnosis of, 1688
diagnostic testing for, 1688
pathobiology of, 1687, 1687*f*
treatment of, 1689*b*
underlying causes of, 1688
Chronic viral hepatitis, 1009–1017
clinical manifestations of, 1009
definition of, 1009–1010
diagnosis of, 1010, 1010*t*
prognosis for, 1010*b*
treatment of, 1010*b*
Chronic wasting disease, 2422
Chronotropic incompetence, 319
Chrysotile asbestos, 589
Churg-Strauss syndrome, 2573. *See also* Eosinophilic granulomatosis with polyangiitis
Churg-Strauss vasculitis, 1142
Chvostek sign, 1648
Chylomicrons, 1405
Chylothorax, 626
Chylous effusions, 626–627, 626*b*
Cialis, 364*b*
CIAS1, 1734–1735
Cicatricial alopecia, 2749
Cicatricial pemphigoid, esophageal involvement in, 911
Cidofovir, 2187*t*, 2188*t*
for cytomegalovirus, 2252*b*
for molluscum contagiosum, 2240*b*
CIDP. *See* Chronic immune demyelinating polyneuropathy
Cigar-shaped elliptocytes, 1094*f*, 1097
Cigarette smoking, 2349–2352
behavioral treatment for, 2350*t*
bladder cancer and, 1365
blood pressure and, 445
cardiovascular disease and, 220
clinical manifestations of, 2349
COPD and, 547
definition of, 2349–2352
diagnosis of, 2349–2350
epidemiology of, 2349
lung cancer and, 1329
neutrophilia and, 1141
nicotine replacement therapy for, 2350*b*, 2351*t*
passive, 220
pathobiology of, 2349
pharmacologic treatment for, 2350*b*, 2351*t*
prevention of, 2352
prognosis for, 2352
psychosocial treatment for, 2350*b*, 2350*t*
second-hand, 220
treatment of, 2350*b*
vitamin levels affected by, 1459
in women, 1609
Ciguatera intoxication, in travelers, 1889.*e1t*
Ciguatera poisoning, 713
Ciguatoxin, 925
Ciliary body, 2596
Ciliary dyskinesia, primary, cystic fibrosis *versus*, 558
Cilofexor, for primary sclerosing cholangitis, 1058*b*
Cilostazol, 508–509
for atherosclerotic PAD, 464*b*
for ischemic heart disease, 470*b*
Cimzia. *See* Certolizumab
Ciprofloxacin
for anthrax, 97
for bacterial meningitis, 2518*t*
for *Campylobacter* infections, 1959*b*, 1960
for chancroid, 1951*b*
for cholera, 1956*b*
for cystoisosporiasis, 2112*t*
for diverticulitis, 955*b*
dosage of, 1895*t*
for eye infection, 2605*t*
for intestinal bacterial overgrowth, 934*b*
for lung disease, 558*b*
for meningococcal disease, 1945*t*
for nontuberculous mycobacterial disease, 2046*t*
for plague, 98*b*, 1992*t*
for skin diseases, 2699
for traveler's diarrhea, 926*b*, 1888, 1888*t*
for tularemia, 99*b*, 1987*b*–1988*b*
for urinary tract infection, 1876*t*, 1877*t*
for yersiniosis, 1994*b*
Circadian rhythm disorders
clinical manifestations of, 2452
definition of, 2451
diagnosis of, 2452
epidemiology of, 2451
graph of, 2452.*e1f*
pathobiology of, 2451
treatment of, 2452*b*
Circadian rhythms, 1478, 1478.*e1f*
description of, 2443–2444
Circle of Willis, 2455.*e1f*, 2456
Circulating vaccine-derived polioviruses, 2257
Circulation, 225
Circulatory support
for cardiogenic shock, 667*b*
mechanical, 265*b*
Circumcision
for chancroid, 1952
for HIV transmission prevention, 2298
male, 1884
Circumscribed hyperpigmentation, 2744, 2744*f*
Circumscribed hypopigmentation, 2743
Cirrhosis, 736, 988, 1035–1043, 1821
alcohol-related, 2355
causes of, 1036*t*
in chronic hepatitis B, 1013
clinical manifestations of, 1037–1038, 1037*f*
compensated, 1038, 1041*f*
complications of, 1036–1037, 1036*f*, 1039–1040
decompensated, 1014*b*, 1015*t*, 1038, 1041*f*
definition of, 1035–1043, 1035*f*
diagnosis of, 1038–1042
epidemiology of, 1035
with hepatocellular carcinoma, ultrasound of, 870*f*–871*f*
imaging studies for, 1039, 1039*f*
laboratory tests for, 1039
liver fibrosis and, 1035–1036
mesenteric venous thrombosis and, 963*t*
pathobiology of, 1035–1037
physical examination for, 1038–1039
portal pressure measurements for, 1039
prevention of, 1042
prognosis of, 1043
scoring systems in, 1038*t*
treatment of, 1040*b*, 1041*f*
weight loss and, 860*t*
in Wilson disease, 1436*f*–1437*f*
Cirrhotic cardiomyopathy, 1037
CISNE. *See* Clinical Index of Stable Febrile Neutropenia
Cisplatin (Platinol), 1215*t*
adverse reactions of, 132
for disseminated disease, 1383*b*
for head and neck cancer, 1327*b*
Cisternography, strengths and weaknesses of, 2373*t*
Citalopram
for depression, 2340*t*
for hot flashes, 1631*t*
for irritable bowel syndrome, 896*t*
Citrate, kidney stones, 803
Citrate-phosphate-dextrose, 1199
Citrullinated proteins, antibodies to, 1713
Citrulline, 1713
Citrullinemia, 1402*t*
CKD. *See* Chronic kidney disease
Cladribine, for multiple sclerosis, 2505*t*
Clarithromycin
dosage of, 1895*t*
for nontuberculous mycobacterial disease, 2046*t*
for pertussis, 1995*b*–1996*b*
Classic gout, 1811, 1812*f*
Classic heatstroke, 679*t*
Classic Hodgkin lymphoma, 1289–1290, 1290
Claude syndrome, 2465.*e1f*
Claudication
definition of, 462
intermittent, 465.*e1f*
Clear cell adenocarcinoma, of vagina, 1597
Clear cell renal cell carcinoma, 1363
Cleavage resistant RIPK1 induced autoinflammatory (CRIA) syndrome, 1731*t*
Clevidipine, for hypertensive emergencies, 460*t*
Climate change, 89–91
environmental impact from, 89
health care professionals and, 91.*e1f*, 91
how it affects health, 89–90, 90*f*, 91*t*
as occupational and environmental hazards, 87
recent evidence and projected impacts of, 90, 90*f*
research priorities for, 91
zoonoses and, 2064
Climate-related hazards, examples of, 91*t*
Climax, 1604
Clindamycin
for anthrax exposure, 97*b*
for babesiosis, 2112*t*, 2115, 2152*b*, 2152*t*
for cellulitis, 2740*b*
characteristics of, 1899–1900
dosage of, 1895*t*
for malaria, 2112*t*, 2121*t*
mechanism of action, 1895*t*
for peritonsillar abscess and deep space infections, 2649
for pneumonia, 616*b*
resistance mechanisms, 1893*t*
spectrum of activity, 1900
for *Streptococcus pneumoniae* pulmonary infections, 1912.*e1t*
toxicities of, 1901*t*
for toxoplasmosis, 2112*t*, 2140*t*
Clindamycin-primaquine, for *Pneumocystis* pneumonia, 2103*b*, 2106*t*
Clinical chemistry, reference intervals, *e1t*–*e8t*
Clinical decision support, 44, 169
Clinical genomics, 160–165
gene, 160–162, 161*f*
genetic test reports for, 165
genomic variations in, 162–165
assaying, 164–165
chromosomal aberrations in, 164, 164.*e1f*
copy number variants in, 164
deletion, insertion, and indels in, 163
structural aberrations in, 164
structural variants in, 164
tandem repeats in, 163–164
as normal part of medicine, 165
patterns of inheritance in, 160–162
mendelian inheritance, 160–162, 161*f*
mosaicism, 162, 163*f*
nonmendelian inheritance, 162
Clinical Index of Stable Febrile Neutropenia (CISNE), 1856*t*
Clinical pathways, 44
Clinical Pharmacogenomics Implementation Consortium, 167
Clinical syndromes, occupational and environmental, 85–87, 86*t*
Clinical transplantation, 203
Clitoromegaly, 1598
CLL. *See* Chronic lymphocytic leukemia
Clobazam, for seizures, 2434*t*
Clofazimine
for babesiosis, 2115
for leprosy, 2052*b*–2053*b*, 2053*t*
for nontuberculous mycobacterial disease, 2046*t*
Clomiphene citrate, for ovulation, 1603*b*
Clonal cytopenias, of undetermined significance, 1255
Clonal disorders, myelodysplastic syndromes as, 1253
Clonal expansion, in Enterobacterales, 1965, 1966*t*
Clonal hematopoiesis, 1064

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Clonazepam
for anxiety disorders, 2344*t*
for myoclonus, 2496*b*
Clonidine, 941*b*
for alcohol withdrawal, 2358*t*
for hot flashes, 1631*t*
oral, 451*t*
patch, 451*t*
perioperative cardiac events reduced using, 2662*b*–2663*b*
for small bowel rapid transit dysmotility, 890
for tobacco dependence, 2351*t*
for Tourette syndrome, 2494*b*
Clonorchiasis, 2166
Clonorchis, in travelers, 1889.*e1t*
Clonorchis sinensis, 1026*t*, 2166
Clopidogrel, 387*t*, 506*t*, 507
for acute coronary syndrome, 374*t*
for acute STEMI, 384*b*, 391*t*
for Fabry disease, 1423*b*
for stroke prevention, 397
Clorazepate, for anxiety disorders, 2344*t*
Closed pneumothorax, 526
Closed wet dressings, for skin diseases, 2697
Clostridial infections, 1924–1929
necrotizing, 1926–1927
botulism, 1927, 1928*b*
tetanus, 1928–1929, 1929*b*, 1929*t*
neurotoxic, 1927
Clostridial myonecrosis, 1926–1927, 1926*b*
Clostridioides difficile infection, 1833, 1839–1840, 1840.*e1f*, 1924–1926
antibiotic-induced, fever and, 1846
clinical manifestations of, 1925
colitis caused by, 1858–1859
definition of, 1924
diagnosis of, 1925
diarrhea caused by, 1836, 2673–2674
epidemiology of, 1924
health care-associated infections caused by, 1865
pathobiology of, 1924–1925
prevention of, 1925–1926
prognosis for, 1926
toxins A and B, 1927
treatment of, 1925*b*
Clostridioides difficile toxin A/B testing, for enteric infection, 1870*t*
Clostridium botulinum, 1833, 1927, 2592
Clostridium novyi infection, in injection drug users, 1927
Clostridium perfringens
cellulitis caused by, 2740
type A diarrhea, 1926, 1926*b*
type C enteritis, 1926, 1926*b*
Clostridium septicum, 1926
Clostridium tetani, 1833, 1928
Clot waveform analysis, 1169, 1198
Clotrimazole, for candidiasis, 2092*b*
Clotting factors, 1000, 1188*b*
Cloxacillin, dosage of, 1895*t*
Clozapine
for Parkinson disease, 2487*t*
for psychotic disorders, 2346*t*
weight gain and, 2680
CLPX-associated protoporphyria, 1428*t*
Clubbing, 216, 218*f*, 2752, 2752*f*
Cluster headache, 2377*t*, 2381–2382, 2381*t*, 2382*b*
Cluster randomized trials, 41
Clustered Regularly Interspaced Short Palindromic Repeats (CRISPR), 166
CML. *See* Chronic myeloid leukemia
CMML. *See* Chronic myelomonocytic leukemia
CMS. *See* Centers for Medicare and Medicaid Services
CMV. *See* Cytomegalovirus
CNS. *See* Central nervous system
CNS-acting drugs, for fibromyalgia, 1819*b*
Coagulase-negative staphylococci, 1909–1910
Coagulation, procoagulant response in sepsis, 671
Coagulation cascade, 1165*f*, 1167*f*
Coagulation disorders, 2470.*e1t*
Coagulation factor deficiencies, 1166*t*, 1167*t*, 1187–1194
coagulation abnormalities, 1193–1194
contact activation factors, deficiencies of, 1192, 1192*b*
dysfibrinogenemia and afibrinogenemia, 1192
factor V deficiency, 1193
factor XI deficiency, 1191
Coagulation factor deficiencies *(Continued)*
factor XIII, 1192, 1192*b*–1193*b*
hemophilias
acquired, 1191, 1191*b*
hereditary, 1187–1191
vitamin K-dependent coagulation, deficiencies of, 1193
von Willebrand disease, 1191
Coagulation factor IX, 476
Coagulation system, 1165
Coagulation tests, 999–1000
abnormal, evaluation of, 1169
albumin, 1000
for liver failure, 1198
prothrombin time, 999–1000
Coagulopathy
consumptive, 1195
cystic fibrosis and, 557
snake envenomation syndromes causing, 707
suspected, despite negative screening tests, 1167*f*, 1169
Coal, 88*t*
Coal workers' pneumoconiosis, 86
Coarctation of the aorta, 351–352, 352*b*, 352*f*, 450
evaluation of, 448*t*
exercise recommendations for, 355.*e2t*
Coarse atrial fibrillation, 328, 328*f*
Coartem, for malaria, 2121*t*
Cobalamin, 1117. *See also* Vitamin B_{12}
absorption of, 1117*t*, 1118–1119, 1118*f*
biochemical assays for, 1122
intracellular, metabolism pathway and defects of, 1425.*e2f*
malabsorption of, 1119
processes of, 1118*f*
processing of, 1425*t*–1426*t*
transport of, 1119, 1425*t*
Cobalamin deficiency, 2539–2540
of central nervous system, 1124
clinical manifestations of, 2539–2540
diagnosis of, 2540
due to drugs, 1119
epidemiology of, 1117, 1118*f*
megaloblastic anemia and, 1117*t*
metabolites for, 1124*t*
neurologic abnormalities due to, 1121–1122, 1122*f*
pathobiology of, 1118–1119
prevention of, 1124
prognosis for, 2540
treatment of, 1123*b*, 2540*b*
Cobalamins, 935
Cobalt, 1451
thyroid and cardiac toxicity, 106, 106*b*
toxicity, 88*t*
Cobb angle, 621, 621.*e1f*
Cobimetinib (Cotellic), 1215*t*, 1251*t*
for melanoma, 1394*t*
Cobra venom factor (CVF), 203
Cocaine. *See also* Psychostimulants
cardiomyopathy due to, 286
central nervous system effects of, 685*t*
screening for, 689*t*
toxicity, 2363, 2363*b*
Coccidian enteritis, 2155–2156
clinical manifestations of, 2155
diagnosis of, 2155–2156, 2155*f*
epidemiology of, 2155
pathobiology of, 2155
prevention of, 2156
prognosis of, 2156
treatment for, 2156*b*
Coccidioides immitis, 1024, 2083–2084
Coccidioides posadasii, 2083
Coccidioidomycosis, 2083–2085, 2084*t*, 2085*f*, 2651
clinical manifestations of, 2084
definition of, 2083–2084
diagnosis of, 2084–2085
epidemiology of, 2084
extrapulmonary dissemination in, 2084
pathobiology of, 2084
pathogen of, 2083–2084
pneumonia in, 520.*e2f*
primary pulmonary infections in, 2084
prognosis of, 2085
prophylaxis for, 2309*t*
treatment of, 2085*b*
Coccydynia, 1746, 1746*b*
Cochlear damage, 2641–2642
Cocoa, diet-related hyperoxaluria and, 806
Codeine, for hemarthroses, 1188*b*
Coenurosis, 2163
Coenzyme Q10 deficiency, 2586–2587
Coffin lid crystals, 723–724, 725*f*
Cogan syndrome, 1799, 1799*b*
Cognition, geriatric assessment of, 117
Cognitive behavioral therapy
for benzodiazepines, 2363*b*
for bulimia nervosa, 1462*b*
for drug use disorders, 2361*b*
for fibromyalgia, 1819*b*
Cognitive disorders, 2337*t*, 2548–2549
Cognitive dysfunction
amnesic disorders, 2407
in heart failure, 257
menopause associated with, 1630*b*
Cognitive impairments, 2412–2425
cerebrovascular disease causing
clinical manifestations of, 2419
definition of, 2417
diagnosis of, 2419, 2419*t*
epidemiology of, 2417
magnetic resonance imaging of, 2419*f*
pathobiology of, 2418
prognosis for, 2420
risk factors for, 2418
treatment of, 2420*b*
dementia. *See* Dementia
epidemiology of, 2412
management of, 2414
mild
amnesic, 2412*t*
cerebrospinal fluid findings in, 2416, 2417*f*
clinical manifestations of, 2415
diagnosis of, 2416, 2416*t*, 2418*f*
differential diagnosis of, 2416
genetics of, 2415
management of, 2414
prognosis for, 2417
neurologic diseases that cause, 2372–2373
in older adults, 114–115
screening for, 53
Cognitive psychotherapy, for depression, 2339*t*–2340*t*
Cohort studies, 41
Coitus interruptus, 1611
COL1A1, 1727
COL1A2, 1727
Colaspase, 1215*t*
Colazal. *See* Balsalazide
Colchicine
for acute pericarditis, 424*b*
for COVID-19, 2217
for pericardial constriction, 431*b*
for skin diseases, 2699
Cold agglutinin disease, 1087
Cold agglutinins, *Mycoplasma pneumoniae* in, 2007
Cold autoimmune hemolytic anemia, 1088, 1088*t*
Cold disorders, 678–682
Cold injury, 680–681
clinical manifestations and diagnosis of, 680, 681*f*, 681*t*
definition of, 680–681
epidemiology of, 680, 680*t*
factors predisposing to, 680*t*
as occupational and environmental hazards, 88*t*
prevention and treatment of, 681*b*, 681*t*
prognosis of, 681
Cold urticaria, 681, 2725
Colectomy, for ulcerative colitis, 945*b*
Colesevelam, for irritable bowel syndrome, 896*t*
Colistimethate, 2518*t*
Colistin, 1970*b*
Colitis
amebic, 2147, 2148*f*, 2149*t*, 2150*t*
cytomegalovirus, 2251
differential diagnosis of, 944*t*
hemorrhagic, *Escherichia coli* and, 1961, 1963
microscopic, 940
Collagen vascular disease
diffuse alveolar hemorrhage and, 568–569
treatment of, 1853*t*
Collagenomas, 2730
Collecting duct
disorder of, 817–818
diuretics, 736*b*
Collective dose, 91
Colloid cysts, 1316
Colloids, reactions to, 1698*t*
Colon
adenocarcinoma of, 1349
diverticulitis of, 954–955, 954.*e1f*, 955*b*, 955*f*
motility of, 887–888, 890–892
transit in, 887–888
Colon cancer
colonoscopy for, 879
human microbiome and, 1840
treatment of, 1241*b*
in ulcerative colitis, 945*b*
Colon ischemia, 964
algorithm of, 966*f*
clinical manifestations of, 964
conditions associated with, 964*t*
diagnosis of, 964, 965*f*, 965.*e1f*
medications associated with, 964*t*
treatment of, 965*b*
Colonoscopy, 879–880, 1349, 1349*t*, 1353
for colon ischemia, 965
indications for, 879, 879*f*–880*f*
instrument for, 879
for iron deficiency anemia, 887
for lower gastrointestinal bleeding, 885
preparation for, 879
procedure of, 879–880
Colony forming units (CFU), 1892
Colopathy, congestive, 967
Color blindness, 2598
Color flow Doppler imaging, 236
Colorado tick fever virus, 2276*t*, 2284, 2284*b*
Colorectal anastomotic leak, fluoroscopy of, 868*f*
Colorectal cancer, 1345–1346, 1346, 1346*f*
chemoprevention for, 1353
clinical manifestations of, 1349, 1349*f*
diagnosis of, 1350, 1350*f*
dietary prevention for, 1353
fecal occult blood tests for, 54
flexible sigmoidoscopy for, 54
follow-up for, 945*b*
in HIV, 2316
metastatic, 1350*b*, 1351.*e1f*
nutrition and, 59
prevention of, 1352–1353
prognosis of, 1353–1354, 1353*f*
screening for, 54, 1352–1353, 1352*t*
staging of, 1350, 1350*f*
stool DNA tests for, 54
treatment for, 1350*b*, 1351*t*
in women, 1607
Colostrum, for *E. coli*, 1963*b*
Colovesicular fistulas, in Crohn disease, 945*b*
Colpitis macularis, 1882–1883
Colposcope, 1376
Colposcopy, 2242
Coma, 2437
cause of, 2438*t*–2439*t*
clinical manifestations of, 2438
cranial nerve examination in, 2439
diagnosis of, 2438–2440, 2438*t*, 2439*t*
emergency management of, 2441*t*
epidemiology of, 2437, 2437*t*
grading of, 2440, 2440*t*
herniation causing, 2438
laboratory testing for, 2440
lightning injury and, 704
motor examination in, 2439–2440
pathobiology of, 2437–2438
prognosis for, 2440–2441, 2441*t*
treatment for, 2440*b*, 2441*t*
Comanagement, 2657*t*, 2658
Comatose patient, neurologic examination in, 2370
Combination dextroamphetamine/amphetamine, 2449*t*
Combination diuretic therapy, for hypervolemia, 736*b*
Combination T_4/T_3 therapy, for hypothyroidism, 1508*b*–1509*b*
Combination therapy
for cancer, 1232*b*, 1234*t*
for common cold, 2193*b*
for pulmonary hypertension, 496*b*, 499*f*
Combined resynchronization and cardioverter defibrillator therapy, 345
Common cold, 2192–2194
clinical manifestations of, 2192–2193
definition of, 2192–2194
diagnosis of, 2193
epidemiology of, 2192
pathobiology of, 2192
pathogens causing, 2192
prevention of, 2193–2194

Copyrighted material

Common cold *(Continued)*
prognosis of, 2194
treatment for, 2193*b*, 2193*t*
viruses associated with, 2192*t*
Common couple violence, 1633
Common variable immunodeficiency, 1681, 1681*t*, 1822
Common ventricle, 354
Commonwealth Foundation, 41.*e*1*t*
Commotio cordis, 700*b*
Communication, in psychiatric diseases, 2679
Community-acquired bacterial meningitis, 2516*t*
Community-acquired pneumonia, 606–613, 611*f*–612*f*, 612*f*, 1851*b*
antibiotic therapy for, 1912*b*
bacterial species that cause, 1892*t*
Staphylococcus aureus causing, 1904
Stenotrophomonas maltophilia and, 1975
Streptococcus pneumoniae causing, 1910
treatment of, 1998*b*–1999*b*
Comorbidity, heart failure and, 265*b*
Compartment syndrome, 716, 717*b*, 1188
Compensated cirrhosis, 1037–1038, 1038
Compensatory changes, in acid-base disorders, 755–756, 756*t*
Competency, geriatric assessment of, 117
Complement, 152, 1715–1716
activation of, 197–202, 202.*e*1*f*
alternative pathway of, 198–199, 198*f*–199*f*, 201*f*
classical pathway of, 197–198, 198*f*, 199*f*
lectin pathway of, 198, 198*f*, 199*f*
pathologic conditions associated with, 198*t*
regulators of, 197
tissue injury or degeneration and, 199*t*
levels, in nephritic syndrome, 778*t*
Complement C3, *e*1*t*–*e*8*t*
Complement C4, *e*1*t*–*e*8*t*
Complement disorders, 1682–1683, 1683*t*, 1731*t*
clinical manifestations of, 1683
diagnosis of, 1683
epidemiology of, 1682–1683
pathobiology of, 1682–1683
prognosis of, 1683
treatment of, 1683*b*
Complement fixation assays, for paracoccidioidomycosis, 2087
Complement inhibitors, 202–203
Complement-mediated membranoproliferative glomerulonephritis, 786, 786*t*
Complement receptor of the immunoglobulin superfamily (CRIg), 200*t*
Complement receptor type 1, 200*t*
Complement receptors, 184, 202
Complement system
in disease, 196–203, 201*t*
participation of, 198*t*
features of, 197*t*
function of, 197*f*
in host defense, 197*t*
regulating, 200*t*
Complementary and integrative medicine, 153–155
acupuncture, 154
definition of, 153–154
manual therapies, 154
meditation, 154
natural products, 154–155
for pain, 136*b*
tai chi, 154
traditional Chinese medicine, 154
use of, 154–155
yoga, 154
Complete blood counts, for anemia, 1076, 1076*t*, 1077*t*
Complete heart block, 321, 321*f*
Complex disorders, 533
Complex multimarker genomic tests, for disease diagnosis and prognosis, 168
Comportment, 2410–2411
Compound nevi, 2730
Comprehensive Environmental Response, Compensation, and Liability Act, 87
Compression-based ultrasound elastography, 1720
Compression-induced rhabdomyolysis, 715
Compression stockings, 490
Compression ultrasonography, description of, 484, 485*f*
Compressive focal motor neuropathies, 2564*t*
Compressive mononeuropathies, 2579
Compressive neuropathies, 2544
Compromised host
conditions and medical interactions in, 1853*t*
fever in, 1853–1861, 1854*b*–1855*b*
Computed tomographic pulmonary angiography, 484, 486*f*
Computed tomography (CT), 519
of acute kidney injury, 726, 727*f*
of acute mesenteric ischemia, 960
of acute pancreatitis, 969, 971, 971*f*
of bacterial pneumonia, 521*f*
of bronchiectasis, 558*f*
cardiac, 249
chronic obstructive pulmonary disease on, 548
of chronic pancreatitis, 974, 974*f*
of compensated cirrhosis, 1039, 1039*f*
of COVID-19, 520.*e*1*f*, 521*f*
of enterography, 871
in gastroenterology, 869–871, 870*f*, 871*f*
high-resolution, in interstitial lung disease, 574
of honeycombing, 522*f*
of hypoglycemia, 1557
of invasive mucinous adenocarcinoma, 569.*e*1*f*
of liver disease, 990
of lymphadenopathy, 1150
of mediastinum, 527
of metabolic bone disease, 1638–1639
of microscopic polyangiitis with pulmonary hemorrhage, 520.*e*1*f*
of mucormycosis, 520.*e*2*f*
of nephrolithiasis, 805, 805*f*
of neutropenic enterocolitis, 956, 956.*e*1*f*
of nocardiosis, 2073, 2073*f*–2074*f*, 2074*f*
of peritoneal carcinomatosis, 957*f*–958*f*, 958*f*
of primary coccidioidomycosis pneumonia, 520.*e*1*f*
of pulmonary alveolar proteinosis, 567, 567*f*
of pulmonary edema, 521*f*
of pyogenic liver abscess, 1022–1023, 1023*f*
of rheumatic disease, 1717–1718, 1719*f*
single-photon emission computed tomography. *See* Single-photon emission computed tomography
strengths and weaknesses of, 2373*t*
of stroke, 2464
Computed tomography angiography (CTA), 519, 870
in atherosclerotic PAD, 463, 463*f*
coronary, 249, 249.*e*2*f*, 250*f*
in coronary artery disease, 360
renal artery stenosis for, 800
Computed tomography colonography, 871, 871*f*, 1353
Computed tomography myelography, strengths and weaknesses of, 2373*t*
Computerized ECG readings, automated, 234
Concentration-mantra meditation, 154
Concussion, standardized assessment of, 2386*t*
Conditioning regimens, 1207, 1207*f*
Condoms, for HIV transmission prevention, 2298
Conduction, impulse, disorders of, 302
Conduction delays, management of, 384*b*
Conduction disorders, conditions associated with, 318*t*
Conduction system delays, 317
atrioventricular conduction disturbances, 319
conditions associated with, 318*t*
intraventricular blocks, 321–322, 322*b*
Conductive hearing loss, 2641
Condyloma, anal, 982*f*
Condylomata lata, 2014, 2015*f*, 2242, 2623
Cone snails, 713
Confabulation, 2539
Confidentiality, in adolescent medicine, 111
Confounding, 37
Confusion Assessment Method, 2331, 2331*f*
Confusional arousals, 2453*t*
Congenital abnormalities
of aortic valve, 400
cystic adenomatoid malformation of the lung, 565
of esophagus, 913
of pericardium, 433
pulmonary airway malformation, 565
Congenital adrenal hyperplasia, 1569–1572, 1569.*e*1*f*, 1594
description of, 749, 749*t*, 1520, 1526
diagnosis of, 1602
Congenital anomalies, in adolescents, 110*t*
Congenital cataract, 2612
Congenital coronary anomalies, 381*t*
Congenital disorders, cystic diseases, thoracic, 564
Congenital embryopathic disorders, 1478–1479
Congenital erythropoietic porphyria (CEP), 1428*t*, 1430, 1434*b*–1435*b*
Congenital factor V deficiency, 1193
Congenital heart disease, 253, 253*f*, 347
assessment of, 348*f*
clinical manifestations of, 348
CMR findings, 251, 251*f*, 252*f*
complex lesions, 353–356
echocardiographic findings, 242*t*
empirical therapy for, 2526*t*
epidemiology of, 347–348
exercise for, 355, 355.*e*2*t*
genetic determinants, 347–348
history of, 348
isolated shunt lesions, 348
laboratory investigations of, 348
pathobiology of, 347–348
physical examination for, 348
prognosis for, 355*b*
simple lesions, 348–353
treatment of, 347.*e*1*f*, 355*b*, 355.*e*1*f*
ventricular tachycardia in, 337
Congenital hyperinsulinemic hypoglycemia, 1554, 1557*b*–1558*b*
Congenital hypogonadotropic hypogonadism, 1584
Congenital infection, cytomegalovirus and, 2251
Congenital junctional ectopic tachycardia, 326
Congenital large hyperlucent lobe, 565
Congenital lobar emphysema, 565
Congenital muscular dystrophies, 2585–2587
Congenital myasthenic syndromes, 2591, 2591*b*
Congenital myopathies, 2585
Congenital neural tube defects, nutrition and, 60
Congenital nevus, 2692*t*
Congenital nonspherocytic hemolytic anemia, 1099
Congenital nystagmus, 2619
Congenital rubella syndrome, 2224
Congenital syndromes, with associated neutropenia, 1145
Congenital syphilis, 2018–2020, 2019, 2020*b*
Congenital thrombocytopenia, 1179
Congenital toxoplasmosis, 2136, 2138*t*, 2139
Congenital triangular alopecia, 2750
Congenital valvular aortic stenosis, 351, 351*b*
Congestion, 666
Congestive colopathy, 967
Congestive enteropathy, 967
Congestive gastropathy, 967
Congestive splenomegaly, 1152
Conidia, 2093
Conivaptan, for hypervolemia, 737*t*
Conjugate gaze disorders, 2619
Conjugated estrogen (Premarin), for genitourinary syndrome of menopause, 1632*t*
Conjunctiva
anatomy of, 2596
malignant melanoma of, 2612
Conjunctival suffusion, 2029–2030, 2030*f*
Conjunctivitis, 2600
acute hemorrhagic, enteroviruses causing, 2260, 2260*b*
adenoviral, 2604, 2605*f*, 2605*t*
allergic, 2604, 2605*t*
bacterial, 2604, 2605*f*, 2605*t*
Chlamydia trachomatis causing, 2012
chlamydial, 2604
follicular, 2009
Connective tissue, 1706
Connective tissue diseases, 1714, 1724–1729. *See also* Rheumatic diseases
clinical manifestations of, 1724–1725
cystic fibrosis *versus*, 558
diagnosis of, 1725
differential diagnosis of, 1725
Ehlers-Danlos syndromes, 1726–1727, 1727*b*, 1727*t*
interstitial lung disease associated with, 571*t*, 580–582
Marfan syndrome, 1725–1726, 1726*b*
mixed, 581
Connective tissue diseases *(Continued)*
mucopolysaccharidoses, 1724–1725, 1724*t*, 1725*b*
osteogenesis imperfecta, 1727–1729, 1728*b*, 1728*t*
pseudoxanthoma elasticum, 1729, 1729*b*
Connective tissue hyperplasia, 2624, 2625*t*
Consciousness, 2437, 2437*t*
Consolidation chemotherapy, 1262*b*
Constipation, 862
abdominal pain and, 856
algorithm for, 891*f*
diagnosis of, 890
epidemiology of, 890
evacuation disorder *versus*, 890*t*
irritable bowel syndrome in, 888
management of, 13*t*
pathobiology of, 890
psychotropic medications and, 2678*t*
severe mental illness and, 2683*t*
signs and symptoms of, approach to, 852*t*
slow-transit, 890
treatment of, 862*b*, 891*b*, 891*t*
Constitutional DNA, 1248
Constrictive pericarditis, 429.*e*1*f*, 431*f*–432*f*
Constructional apraxia, 989
Consultant, responsibilities of, 2658–2659
Consumer-based rhythm monitors, 308
Consumptive coagulopathy, 707, 1195
Contact activation factors, deficiencies of, 1192, 1192*b*
Contact activation (intrinsic) pathway, 1165
Contact dermatitis, 1673*t*, 2729
allergic
description of, 1674
illustration of, 2691*t*, 2696*f*
irritant, 2704
Contact hypersensitivity, 1692
Contemporary medical science, 2
Continence
geriatric assessment of, 118
physiology of, 888, 888*f*
Contingency management
for drug use disorders, 2361*b*
for stimulant use disorders, 2363*b*
Continuous data, 36
Continuous murmurs, 214
Contraception, 1610–1617
in adolescents, 112
barrier methods of, 1611–1613
diaphragm, 1611–1612
female condom, 1612–1613
intravaginal ring, 1615
male condom, 1612
oral contraceptives, 1613–1615
spermicides, 1611
transdermal patch, 1615
behavioral methods of, 1611
benefits of, 1611
contraindications for, 1611, 1616*t*
depot medroxyprogesterone acetate, 1615
emergency, 1615
hormonal (steroidal), 1613–1617
injectable steroid, 1615–1616
intrauterine devices for, 1617
natural method of, 1611
perfect use of, 1611, 1612*t*, 1613*f*
permanent, 1617
pregnancy and, 1772*b*
risks of, 1611
for sexually transmitted infections, 1884
sterilization for, 1617
subdermal implants for, 1616–1617
typical use of, 1611, 1612*t*, 1613*f*
unintended pregnancy and, 1611
vasectomy, 1617
venous thromboembolism and, 481
withdrawal method of, 1611
Contractile cells, 224
Contraction, 224, 224.*e*1*f*
Contraction coupling, 224.*e*1*f*
Contractures, 2370
Contrast echocardiography, 238, 240*f*
Contrast-induced acute kidney injury, 393–394
Contrast venography, 484
of venous thromboembolism, 490
Conus medullaris syndrome, 2404
Convalescent plasma, for COVID-19, 2216
Conventional angiography, strengths and weaknesses of, 2373*t*

Copyrighted material

Conventional disease-modifying antirheumatic drugs, 1755*b*, 1756*t*, 1757*t*
Convergence, 2618, 2619*f*
Conversion disorder, 2346–2347, 2347*t*
Cooley anemia, 1106
COPA (coatamer subunit α) syndrome, 1731*t*
Copanlisib (Aliqopa), 1215*t*
Copaxone. *See* Glatiramer acetate
COPD. *See* Chronic obstructive pulmonary disease
Copeptin, 260.*e1t*
Copper, *e1t–e8t*, 1457*t*
  deficiency of, 2538*t*, 2541*t*, 2542
  for malabsorption, 937*t*
  toxicity, 88*t*
Coproporphyrinogen III, 1429.*e1f*
Coproporphyrinuria, 1434
Copy number variants, 164
Cor pulmonale, cystic fibrosis with, 558.*e1f*
Cor triatriatum, 354
Coral snake bites, 708, 708*b*
Corals, 713
Cord blood hematopoietic stem/progenitor cells, 1206–1207
Core myopathy, 2585.*e1f*
Core temperature, 33
Cori disease, 1417*t*
Cornea
  abrasion of, 2602–2603
  anatomy of, 2596
Cornea verticillata, 2614
Corneal reflex, 2439
Corneal stromal dystrophy, 2611
Cornell voltage criterion hypertrophy, 233
Coronary angiography
  in acute coronary syndrome, 372
  in chronic angina and stable ischemic heart disease, 363*t*
  computed tomography, 249, 249.*e2f*, 250*f*, 360
  in coronary artery disease, 393
  diagnostic, 363, 363*t*
  in heart failure, 261
Coronary angioplasty
  medical therapy *versus*, 397
  percutaneous transluminal, 464.*e1f*, 468*b*
  technique, 395*f*
Coronary arteriography, 393–395
Coronary artery
  anomalous origin of, 249.*e2f*, 352–353, 353*f*
  calcium scoring, 249, 249*f*
Coronary artery bypass graft (CABG) surgery, 265*b*, 397
  for acute STEMI, 398
  antiplatelet therapy for, 507
  for chronic stable angina, 398
  for coexisting cardiac disease, 399
  for failed PCI, 399
  indications for, 398–399
  for ischemic heart disease, 364*b*
  late outcomes, 399
  for multivessel coronary artery disease, 364*b*
  for myocardial infarction, 398
  PCI *versus*, 399
  perioperative risks, 398–399
  reoperations, 399
  for survival, 398–399
  for symptom relief, 398
  types of grafts, 397–398, 398*f*
Coronary artery disease, 312
  detection of, 248
  diagnose, 357*f*, 362*t*
  echocardiographic findings, 242*t*
  Hodgkin lymphoma and, 1292*b*
  interventional diagnosis and treatment of, 393–399
  predicted risk for, 221.*e1f*
  risk for, blood pressure and, 440–441
  thrombotic, 381*t*
Coronary artery fistulas, 352
Coronary artery injuries, 700*b*
Coronary artery surgery, 397–399
Coronary blood flow, 224
Coronary emboli, 381*t*
Coronary heart disease
  in HIV, 2316–2317
  menopause associated with, 1630*b*
  nutrition and, 58
  in women, 1607
Coronary intensive care, 384*b*
Coronary intervention, percutaneous, 265*b*
Coronary ostial occlusion, 381*t*
Coronary revascularization, 374*t*, 2662*b*
Coronary stenosis
  assessment of, 393, 394*f*
  coronary arteriography for, 393
Coronary stents, 395, 2662*b*
  balloon-expandable, 395.*e1f*
Coronary vascular disease, infiltrative and degenerative, 381*t*
Coronary vasculitis, 381*t*
Coronary vessels, 394*f*
Coronavirus 2019 (COVID-19), 17, 25, 46, 2213–2215, 2639
  acute respiratory distress syndrome and, 650
  chest radiograph of, 520.*e1f*
  classification of, 2209*t*
  clinical manifestations of, 2213–2214, 2214*f*, 2214*t*
  community prevention of, 2215
  computed tomographic scan of, 520.*e1f*, 521*f*
  diagnosis of, 2214–2215, 2215*f*
  encephalitis and, 2535
  epidemiology of, 2213–2215
  genome of, 2210, 2210*f*
  hypercoagulable states and, 481
  immune response of, 2212
  immunization for, 66*t*, 77–78, 78*f*
    adverse reactions of, 78
    indications for, 78
    schedule of, 76.*e1t*, 77*f*–78*f*
  in older adults, 115
  physical examination and, 28
  in pregnancy, 1628
  prognosis of, 2215
  thrombocytopenia and, 1175
  transmission of, 2213
  treatment of, 2216–2220
    for contacts of infected person, 2219
    general care for, 2218
    general principles of, 2216–2218, 2216*f*
    for hospitalized patients, 2217–2218
    for outpatients with mild to moderate, 2216–2217
    overview of, 2216, 2216*f*
  tuberculosis and, 2032
  vaccination for, 2218*t*, 2219
    adverse effects of, 2219
    policy of, 2219
  variants of, 2212
  virology and pathology of, 2209–2212
Coronaviruses, 2206*f*
  in acute bronchitis and tracheitis, 605
  antiviral therapy for, 2190
    bamlanivimab/etesevimab as, 2190
    bebtelovimab as, 2190
    casirivimab/imdevimab as, 2191
    imiquimod as, 2191
    molnupiravir as, 2190
    nirmatrelvir boosted with ritonavir as, 2190
    remdesivir as, 2190
    sotrovimab as, 2191
  Middle East respiratory syndrome. *See* Middle East respiratory syndrome
  pneumonia, 608
  pre-2019, 2206–2209
  seasonal, 2206–2207
  severe acute respiratory syndrome. *See* Severe acute respiratory syndrome
Corpus callosum, agenesis of, 1479, 2547, 2547*f*
Corrected count increment, 1204
Corrigan pulse, 410
Cortical collecting duct, 754, 754.*e1f*
Cortical thrombophlebitis, 2511
Corticobasal degeneration, 2485*t*
Corticomedullary cysts, 814
Corticosteroids
  for acute interstitial pneumonia, 568
  antiretroviral therapy and, 2317
  for aspergillosis, 2094
  for autoimmune hemolytic anemia, 1089*b*
  for Bell palsy, 2579*b*
  for blastomycosis, 2081*b*
  for cancer, 1232*b*
  for chronic lymphocytic leukemia, 1269*t*
  for COVID-19, 2217
  for Crohn disease, 945*b*, 946*t*
  for diffuse alveolar hemorrhage, 569*b*
  for focal segmental glomerulosclerosis, 779*b*
  for giant cell arteritis, 1803*b*
  for HAM/TSP, 2328*b*
Corticosteroids *(Continued)*
  for hearing loss, 2642*b*
  for immune thrombocytopenic purpura, 1175*b*–1176*b*
  for interstitial lung disease, 575*b*, 575*t*
  for listeriosis, 1938*b*
  for liver transplantation, 1048*t*, 1049
  for membranoproliferative glomerulonephritis, 786*b*
  for membranous nephropathy, 780*b*
  for minimal change disease, 778*b*
  for multiple sclerosis, 2504*b*
  for nausea and vomiting, 863*t*
  for pulmonary alveolar proteinosis, 567*b*
  for rapidly progressive glomerulonephritis, 785*b*
  for rhinitis, 2632*b*, 2634*t*
  for spondylitis, 1765*b*
  for uveitis, 2604
  for zoster, 2249*b*
Corticotroph adenoma, 1493
Corticotropin-releasing hormone (CRH)
  adrenocorticotropic hormone secretion affected by, 1492
  cortisol release by, 1520
  description of, 1477
  stimulation test, for Cushing disease, 1494
Cortisol, 746, 749
  free, *e1t–e8t*
  gluconeogenesis and, 1552–1553
  late-night salivary measurement of, 1494
  plasma, 1522
  production of, 1520
  total, *e1t–e8t*
Corynebacterium, infections caused by, 1933–1935
  clinical manifestations of, 1933–1935
  community-acquired, 1934*t*
  diagnosis of, 1935
  epidemiology of, 1933
  health care-associated, 1934*t*
  pathobiology of, 1933
  pathogen of, 1933
  prevention of, 1935
  prognosis of, 1935
  treatment of, 1935*b*, 1935*t*
Corynebacterium diphtheriae, infections caused by, 1933, 2578, 2649
  clinical manifestations of, 1933–1934
  diagnosis of, 1935
  epidemiology of, 1933
  pathobiology of, 1933
  prevention of, 1935
  prognosis of, 1935
  treatment of, 1935*b*
Corynebacterium jeikeium, 1934–1935
Corynebacterium minutissimum, cellulitis caused by, 2740
Corynebacterium pseudodiphtheriticum, 1934
Corynebacterium pseudotuberculosis, 1934
Corynebacterium ulcerans, 1934
Cosmetics, for skin cancers, 2701
Costello syndrome, 1250*t*
Costimulation blockade
  for allograft rejection, 207
  in renal transplantation, 845, 845*t*
Costimulatory signals, 152
Costochondritis, 359
Costs, quality and, 46
Cotellic. *See* Cobimetinib
Cotswold modification, 1291, 1291*t*
Cotton, 88*t*
Cough, 2192
  acute, 512
  by acute bronchitis, 605, 606*b*
  approach to, 512–513, 513*t*
  chronic, 512
    diagnosis of, 512, 513*t*, 514*f*
    management of, 514*f*
  cystic fibrosis and, 557
  Mycoplasma pneumoniae in, 2005–2006
  pulmonary alveolar proteinosis and, 567
  treatment of, 513*b*, 2193*b*
Cough-related syncope, 306
Counseling
  drug, 275*t*
  medication use, 265*b*
Counter-regulatory hormones, to hypoglycemia, 1552–1553, 1554*f*
Couples therapy, 1634*b*
Covariate, 36
COVID-19. *See* Coronavirus 2019
COVID-19-associated nephropathy, 789
COVID encephalitis, 2535, 2535*b*
Cowden syndrome, 1250*t*, 2729–2730, 2731*f*
Cowdry type A bodies, 2245
Cowpox, 2237–2239, 2238
Cox proportional hazards model, 37
Coxiella burnetii, 417*t*, 2054, 2062, 2064, 2065*t*
Coxiellae, 2055*t*
C-peptide, *e1t–e8t*
CPIC, 169.*e1t*
CPN-1 (carboxypeptidase-N), 200*t*
CPR. *See* Cardiopulmonary resuscitation
Crab lice, 711
Crackles, 30, 512–513, 512*t*
CRAFFT screening tool, for drug and alcohol use, in adolescents, 113, 113*t*
Cranial autonomic dysfunction, 2555
Cranial nerve examination, in coma, 2439
Cranial neuropathies, 2577
Cranial parasympathetic failure, 2554–2555, 2555
Craniopharyngiomas, 1479
Crazy paving, 567, 567*f*, 567.*e1f*, 598
C-reactive protein (CRP), *e1t–e8t*, 186, 1712
  by high-sensitivity method (hs-CRP), *e1t–e8t*
Cream, 2697
Creatine kinase (CK), *e1t–e8t*
  muscle isoform of, 2581
Creatinine, *e1t–e8t*
Creatinine clearance (Cl_{cr}), *e1t–e8t*, 129–130, 721, 721*t*
Creon, for exocrine pancreatic insufficiency, 975*t*
Crepitus, 1710
Crescendo thyrotoxicosis, 1511*b*
CREST syndrome
  ectasias and, 967
  florid features of, 987
Creutzfeldt-Jakob disease, 1204
  magnetic resonance imaging of, 2424*f*
  sporadic, 2422
CRH. *See* Corticotropin-releasing hormone
CRIA syndrome. *See* Cleavage resistant RIPK1 induced autoinflammatory syndrome
Cricoarytenoid joint, rheumatoid arthritis of, 1752
Cricopharyngeal bars, 909
CRIg. *See* Complement receptor of the immunoglobulin superfamily
Crigler-Najjar syndrome, 994–996, 995
  clinical features of, 997*t*
  type 1, 995
  type 2, 995
Crimean-Congo hemorrhagic fever, 99, 99.*e1t*, 2265*t*, 2266, 2268*t*, 2275*t*
Crisaborole, for skin diseases, 2698
CRISPR. *See* Clustered Regularly Interspaced Short Palindromic Repeats
Critical care
  analgesia in, 636
  approach to, 636–638
  long-term outcomes, 636–637
  oxygen intubation in, 636
  predictions, 638
  preferences for, 638
  prevention of complications, 637
  respiratory monitoring in, 639–641
  sedation in, 636
Critical care physicians, 636
Critical illness neuropathy, 2578
Critical illness-associated hypoglycemia, 1553, 1557*b*
Critical limb ischemia, 465.*e1f*
Crizanlizumab
  for hereditary angioedema, 152
  for sickle cell disease, 1116*t*
Crizotinib (Xalkori), 1215*t*
CRMO. *See* Chronic recurrent multifocal osteomyelitis
Crofelemer, 941*b*
Crohn colitis, 1056
Crohn disease
  abscesses in, 945*b*
  algorithm for, 947*f*
  asthma and, 943
  clinical characteristics of, 942*t*
  complications of, 945*b*
  corticosteroids for, 945*b*, 946*t*
  cystic fibrosis *versus*, 558
  definition of, 941
  endoscopy of, 944, 944*f*

Copyrighted material

Crohn disease *(Continued)*
epidemiology of, 941
esophageal, 943
esophageal involvement in, 911
fistulae associated with, 943, 979, 979*f*
fistulizing, 945*b*
gastroduodenal ulcers associated with, 915–916
genetics of, 942
ileal disease and, 934
immunomodulators for, 945*b*
irritable bowel syndrome in, 889
medical therapy for, 945*b*
mild to moderate, 945*b*
moderate to severe, 945*b*
on MR enterography, 873*f*
obstruction in, 945*b*
pathology of, 942
perianal disease in, 945*b*
perianal fistulas associated with, 945*b*
physical examination in, 943
prognosis for, 950
radiology of, 945
rectovaginal fistulas associated with, 945*b*
serologic markers of, 945
surgical therapy for, 945*b*
symptoms of, 943
weight loss and, 860*t*
Crohn Disease Activity Index, 945.*e1t*
Cromolyn, 2632*b*
Cross-consultations, 2656
Cross-sectional studies, 41
Crotalinae bites, 709*t*
Crotamiton, for scabies, 711*b*
Croup, 2196
CRT. *See* Cardiac resynchronization therapy
Crush injury, 716
characteristics of, 699*t*, 700, 700*f*
management of, 717*b*
Crust, 2687.*e4t*
Crusted scabies, 2741–2742
Cryoglobulin, peripheral blood smear of, 1074*t*
Cryoglobulinemia, 681, 1304–1305, 1798, 1798*b*
essential mixed, 1716
mixed, 789, 1716
type I, 1304, 1304*b*, 1304*f*
type II, 1304–1305, 1305*b*
type III, 1305
Cryoglobulinemic vasculitis, 784*t*
Cryoglobulins, 1716
for glomerular syndromes, 727
Cryoprecipitate
HIV transmission through, 2299
transfusion, 1199*t*, 1200, 1205
Cryopyrin-associated periodic syndromes (CAPS), 1734–1735, 1735*b*
Cryopyrinopathies, 1734
Cryptic shock, 661
Cryptococcal meningitis
description of, 2087, 2523
fluconazole for, 2075–2076
Cryptococcal polysaccharide antigen (CRAG), 2088
Cryptococcosis, 2651
definition of, 2087
pathogens that cause, 2087
Cryptococcus neoformans, 1024, 1855–1857, 1861, 2087
Cryptogenic chronic liver disease, 1017
Cryptogenic fibrosing alveolitis, 2327*t*
Cryptogenic organizing pneumonia, 578–579
diagnosis of, 579–580, 579*f*–580*f*, 580*f*
increased lymphocyte counts in, 533
prognosis for, 579*b*
radiographic features of, 574*t*
treatment of, 579*b*
Cryptogenic stroke, 2472, 2472*f*
Cryptorchidism, surgical correction of, 1383–1384
Cryptosporidiosis, 2141–2143
childhood, 2143
clinical manifestations of, 2143
definition of, 2141–2143
diagnosis of, 2143
epidemiology of, 2141–2142
in immunocompetent host, 2143
in immunocompromised hosts, 2143
malabsorption and, 937
pathobiology of, 2142–2143
pathogen of, 2141, 2142*f*
Cryptosporidiosis *(Continued)*
prevention of, 2143
prognosis of, 2143
treatment for, 2143*b*
Cryptosporidium spp., 1026*t*
definition of, 2141
epidemiology of, 2141
life cycle of, 2141, 2142*f*
oocysts, 2141
outbreaks of, 925
pathobiology of, 2142
Crystal deposition diseases, 1810–1816
apatite (basic calcium phosphate)-associated arthropathy, 1815
calcium pyrophosphate dihydrate crystal deposition disease, 1814
gout, 1810–1813
hyperuricemia, 1810
Crystalline arthropathies, 1731*t*
Crystalline lens, 2596
Crystalloid solution, for shock, 662*b*
Crystals, of urine, 722, 724*f*–725*f*
CSF. *See* Cerebrospinal fluid
CT. *See* Computed tomography
CTA. *See* Computed tomography angiography
CTLA-4. *See* Cytotoxic T lymphocyte antigen-4
C-type lectin receptors, 183
Culture, of safety, 46
Culture-independent molecular stool testing, for enteric infection, 1870–1871, 1870*t*
Cultures, blood, for infection, 1834
Cumulative Deficit Frailty Model, in older adults, 123*t*
Cupula, 2644, 2646
Curbside consultation, 2657–2658
Cushing disease
blood tests for, 1494
clinical features of, 1493*t*, 1494*f*
clinical manifestations of, 1493–1494
CRH stimulation test for, 1494
definition of, 1493–1494
dexamethasone suppression testing for, 1494, 1495*t*
diagnosis of, 1494, 1495*f*
epidemiology of, 1493
inferior petrosal sinus sampling of, 1494
late-night salivary cortisol measurement for, 1494
magnetic resonance imaging for, 1494
pathobiology of, 1493
prognosis for, 1495*b*
treatment of, 1495*b*
24-hour urine for, collection of, 1494
Cushing reflex, 34
Cushing syndrome, 1520–1524
algorithm for, 1522*f*
clinical examination of, 1521
clinical manifestations of, 1520–1521
definition of, 1493
description of, 749, 749*t*, 1465
dexamethasone suppression tests for, 1522
diagnosis of, 1521–1524
differential diagnosis of, 1522–1524, 1523*f*
endogenous, 1522
epidemiology of, 1520
etiology of, 1522*t*
evaluation of, 448*t*
after hematopoietic cell transplantation, 1211–1212
hypercortisolism in, 1520–1521
laboratory findings in, 1521–1522
medical therapy for, 1524*b*
oligomenorrhea associated with, 1521
pathobiology of, 1520
prognosis for, 1524
pseudo-Cushing states *versus*, 1521*f*, 1522
radiation therapy for, 1524*b*
saliva cortisol measurements in, 1522
signs and symptoms of, 1520, 1521*t*
surgical therapy for, 1524*b*
treatment of, 1524*b*
urine free cortisol measurements in, 1522
Cutaneous anthrax, 1932, 1932*b*
Cutaneous atypical mycobacteria, in travelers, 1889.*e1t*
Cutaneous B-cell lymphoma, 2734
Cutaneous candidiasis, 2090
Cutaneous diphtheria, 1934
Cutaneous emboli, 2716, 2716*f*
Cutaneous human polyomavirus, 2232
Cutaneous infection, nocardiosis and, 2073
Cutaneous larva migrans, 2170, 2170*t*
in travelers, 1889.*e1t*
Cutaneous leishmaniasis, 2131
clinical manifestations of, 2133, 2134*f*
complex manifestations of, 2133–2135
diagnosis of, 2133
diffuse, 2133
disseminated, 2133
parasitology of, 2133, 2135*f*
prevention of, 2133
prognosis for, 2133–2135
recidivans, 2133
treatment of, 2133*b*, 2135*f*
Cutaneous lesions
blastomycosis and, 2081, 2081*f*
human immunodeficiency virus associated with, 2323*t*
Cutaneous leukocytoclastic angiitis, 1793*t*, 1799, 1799*b*
Cutaneous mastocytosis, 1699–1701, 1701
Cutaneous mucormycosis, 2099
Cutaneous mucosa-associated lymphoid tissue (MALT) lymphoma, 2734, 2734*f*
Cutaneous porphyrias, 1435, 2705, 2705*f*
Cutaneous psoriasis, 2705
Cutaneous T-cell lymphoma, 2686.*e2f*
Cutaneous ulcer, chancroid and, 1951, 1952*f*
CVF. *See* Cobra venom factor
CXCL4, 1065
CXCR2, 1065
CXCR4, 2291
Cyanide antidote kit, for acute poisoning, 693*t*
Cyanide poisoning, 596, 596*b*
Cyanosis, 215, 218*f*, 355, 639
CyberKnife stereotactic radiotherapy, for pituitary tumors, 1487*b*
CyBorD, for amyloidosis, 1308*f*
Cycad toxins, 2541*t*
Cyclic antidepressants, toxicity, 686*t*
Cyclic neutropenia, 1144, 1144*t*, 1683.*e1t*
Cyclizine, for nausea and vomiting, 863*t*
Cyclooxygenase-1 inhibitors, 914–915
Cyclooxygenase-2 inhibitors
description of, 914
for rheumatoid arthritis, 1755*b*
Cyclophosphamide, 149, 1215*t*
for amyloidosis, 1308*b*
cardiomyopathy due to, 288
for chronic lymphocytic leukemia, 1269*t*, 1270*t*
for granulomatosis with polyangiitis, 582
for membranous nephropathy, 780*b*
for rapidly progressive glomerulonephritis, 785*b*
for systemic lupus erythematosus, 1772*b*
for systemic sclerosis, 1781*b*
Cyclospora cayetanensis, 2155, 2155*f*, 2156*t*
Cyclosporiasis, 2155
Cyclosporine, 148–149
for acute graft-*versus*-host disease, 1210
for focal segmental glomerulosclerosis, 779*b*
hyperkalemic acidosis caused by, 751
for inflammatory bowel disease, 946*t*
for liver transplantation, 1048*t*
for membranous nephropathy, 780*b*
for minimal change disease, 778*b*
in renal transplantation, 845*t*
for total knee arthroplasty, 1830.*e1t*
Cyclosporine A, *e10t*–*e11t*
Cyclothymic disorder, 2342
CYP2B6 gene, 160*t*
CYP2C9 gene, 160*t*
CYP2C19 gene, 160*t*
CYP2D6 gene, 160*t*
CYP3A5 gene, 160*t*
CYP4F2 gene, 160*t*
Cyproterone acetate, for transgender women, 1579*t*
Cyramza. *See* Ramucirumab
Cyst(s)
benign pericardial, 433
bronchogenic, 565
echinococcal, 2161
hepatic, 990, 991*f*
thoracic, 564
Cystathionine β-synthase deficiency, 1425–1426, 1426*t*
Cystatin C, *e1t*–*e8t*, 260.*e1t*
Cysteamine bitartrate, 817*b*
l-Cysteinamide, 1215*t*
Cysteine proteinases, 227
Cystic bronchiectasis, chest radiograph of, 557*f*
Cystic diseases
adventitial, of lower extremity arteries, 467
congenital, of thorax, 564
Cystic echinococcosis, 2161, 2161*b*
Cystic fibrosis, 556–559, 993, 1825
associated variants of, 557*t*
classification of, 556*t*
clinical features of, 515*t*
clinical manifestations of, 557
definition of, 556–559
diagnosis of, 557–558, 557*f*, 558*f*, 558.*e1f*
differential diagnosis of, 558–559
epidemiology of, 556
gene therapy for, 177
genetics of, 556–557
in liver, 556
obstruction and, 532
in pancreas, 556
pathobiology of, 556–557
prevention of, 559
with pulmonary hypertension and cor pulmonale, 558.*e1f*
in sinuses and lungs, 556
in sweat glands, 556
treatment of, 558*b*, 1970*b*
Cystic fibrosis transmembrane conductance regulator (CFTR), 556, 1968
Cystic hydatid disease, 2161, 2161*b*, 2162*f*
Cystic kidney diseases, 808–815
acquired, 815, 815*b*
autosomal dominant polycystic kidney disease as, 808
autosomal dominant tubulointerstitial kidney disease as, 814
autosomal recessive polycystic kidney disease as, 812
clinical features of, comparison of, 809*t*
definition of, 808
epidemiology of, 808
gross pathology of, 808*f*
medullary sponge kidney as, 814, 814*b*
nephronophthisis as, 813–814
rare childhood syndromes as, 814, 815*b*
tuberous sclerosis as, 814, 814*b*
von Hippel-Lindau syndrome as, 814, 814*b*
Cystic medial necrosis, 1725
Cystic neoplasms, 1355–1356
Cysticercosis, 2158*t*, 2159
Cystine stones, 804–805, 815
Cystinosis, 815, 816*t*, 817*b*, 1420*t*, 1424
Cystinuria, 804–805, 815, 815*b*, 816*t*
Cystitis, 2091
antimicrobials for, 1876*t*
clinical manifestations of, 1874
description of, 1873
diagnosis of, 1876*t*
hemorrhagic, 2205
symptoms of, 1874*t*
treatment of, 1875*b*, 1876*t*
Cystoisospora belli, 2155, 2155*f*, 2156*t*
Cystoisosporiasis, 2155
Cystoscopy, for prostatitis, 825
Cytarabine, 1215*t*
Cytisine, for tobacco dependence, 2351*t*
Cytochrome oxidase inhibitors, central nervous system effects of, 685*t*
Cytochrome P-450 IIC (CYP2C), 132*t*
Cytochrome P-450 IID6 (CYP2D6), 132*t*
Cytochrome P-450 oxidoreductase deficiency, 1573
Cytogenetic abnormalities, of chronic myeloid leukemia, 1277
Cytogenomic microarray analysis, 158
Cytokine receptors, 184, 185*f*
Cytokines, 151–152, 189.*e1t*, 2079
in diabetic nephropathy, 796
interleukin-1, 151, 151*t*
interleukin-1β, 151
interleukin-2, 151
interleukin-4, 151
interleukin-5, 151
interleukin-6, 151, 151*t*
interleukin-12, 151
interleukin-13, 151
interleukin-17, 152
interleukin-23, 151
tumor necrosis factor-α, 151, 151*t*

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Cytolysin-hemolysin, 1920
Cytomegalovirus (CMV), 2250–2253, 2322*t*
  in acquired immunodeficiency syndrome, 2251
  antiviral therapy for, 2187*t*
  clinical manifestations of, 2251–2252
  colitis caused by, 2251
  congenital, 2251
  definition of, 2250–2253
  diagnosis of, 2252
  epidemiology of, 2250–2251
  of esophagus, 912
  gastrointestinal disease caused by, 1859
  hyperimmune globulin, 2252–2253
  immune response to, 2251
  immunization for, 65*t*
  in immunocompetent persons, 2251
  after lung transplantation, 633
  medications for, 2252*b*
  neonatal, 2251
  pathobiology of, 2251
  pathogen that causes, 2250
  pneumonia caused by, 2250*f*, 2251
  post-transplant, 2252*b*
  prevention of, 2252–2253
  prognosis for, 2253
  retinitis caused by, 2251, 2251*f*, 2307, 2606
  transfusion transmission of, 1200
  in transplant recipients, 2251
  treatment of, 2252*b*, 2252*t*
  ventriculitis, 2532*t*
Cytopenia, 2313–2314
  in hemophagocytic lymphohistiocytosis, 1160
Cytoplasmic nucleic acid sensors, 183, 184*f*
Cytotoxic agents
  for cancer, 1232*b*
  warm autoimmune hemolytic anemia treated with, 1089*b*
Cytotoxic T lymphocyte antigen-4 (CTLA-4), 152

D

D-dimer test, *e8t*–*e9t*, 483–484
D-Penicillamine, for Wilson disease, 1437*b*
Dabigatran, 502*t*, 504, 505*t*
  for atrial fibrillation, 397
  characteristics of, 487*b*
  for venous thromboembolism, 478*b*, 487*b*
Dabrafenib (Tafinlar), 1215*t*, 1251*t*
  for melanoma, 1394*t*
Daclatasvir, for hepatitis C infections, 2181*t*, 2182*t*, 2184–2185
Daclatasvir/asunaprevir, for hepatitis C infections, 2181*t*, 2185
Daclizumab, 151
Dacogen. *See* Decitabine
Dacrocytes, 1069*f*
Dactylitis, 1763
  in sickle cell disease, 1112–1113
DADA2. *See* Deficiency of adenosine deaminase-2
Dairy, dietary guidelines for, 57.*e3t*
Dalbavancin
  dosage of, 1895*t*
  mechanism of action, 1895*t*
  spectrum of activity, 1900
Dalfampridine (Ampyra), for multiple sclerosis, 2505*t*
Dalteparin, 503*t*
  for acute coronary syndrome, 374*t*
  for venous thromboembolism, 1624*t*
Damage-associated molecular patterns (DAMPs), 191, 192*f*
Damage control surgery, 700*b*
Damaged innervation, in lower urinary tract, 828
Damaging effectors, inhibitors of, 196
DAMPs. *See* Damage-associated molecular patterns
Danaparoid, 503*t*
Danazol
  for endometriosis, 1596*b*
  warm autoimmune hemolytic anemia treated with, 1089*b*
Danon disease, 1417*t*, 1418–1419
Dantrolene, for malignant hyperthermia, 679*b*–680*b*, 2668*b*
Dantrolene sodium, for malignant hyperthermia, 717*b*
Dapagliflozin
  for heart failure, 271*t*
  for type 1 diabetes mellitus, 1537*b*–1538*b*
  for type 2 diabetes mellitus, 1541*t*
Dapsone
  for HIV/AIDS, opportunistic infections associated with, 2309*t*
  hypersensitivity syndrome, 2052*b*
  for leprosy, 2052*b*, 2053*t*
  for *Pneumocystis* pneumonia, 2108*t*
  for skin diseases, 2699
  for toxoplasmosis, 2112*t*
Daptomycin
  for bacterial meningitis, 2518*t*
  characteristics of, 1900
  dosage of, 1895*t*
  for endocarditis, 419*t*
  mechanism of action, 1895*t*
  for methicillin-resistant *Staphylococcus aureus*, 1905
  resistance mechanisms, 1893*t*
  for vancomycin-resistant enterococci, 1922*t*
Daratumumab
  for amyloidosis, 1308*b*, 2560*b*
  for multiple myeloma, 1299*b*, 1301*t*
Darier sign, 2725
Darifenacin, 824*t*
Darunavir, 2301*t*
Dasatinib (Sprycel), 1215*t*, 1251*t*, 1275*t*
DASH. *See* Dietary Approaches to Stop Hypertension
DASH-sodium diet, for chronic kidney disease, 839*b*
Data
  characteristics, 36
  interpretation, 35–36
Daunorubicin, 1215*t*
Daycare diarrhea, 926
DCD. *See* Donation after cardiac death
DDAVP, for von Willebrand disease, 1183*b*
de Musset sign, 410
de Quervain tenosynovitis, 1745, 1745*b*, 1746*f*
de Quervain thyroiditis, 1513, 1514*b*
Dead space ventilation (V_D), 640–641
Deafness, hereditary, 2641
Death and dying
  causes of, in adolescents, 110, 110*t*
  in endoscopy, 876*t*
  leading causes of, 21, 22*f*, 57*t*
  in palliative care, 16
  sudden death, 282*b*
Deauville score, 1281
Debrisoquine-sparteine polymorphism, 132*t*
DEC. *See* Diethylcarbamazine
Decay-accelerating activity, 199
Decay-accelerating factor, 200*t*
Decision analysis, 39, 39.*e1f*
Decision making, 39
  aids to, 39
  decision analysis, 39, 39.*e1f*
  in geriatrics assessment, 117
  risk stratification with, 363*t*
  shared, 39
Decitabine (Dacogen), 1215*t*
  for myelodysplastic syndromes, 1255
Declarative episodic memory system, 2407
Decolonization therapy, for health care-associated infections, 1867
Decompensated cirrhosis, 1014*b*, 1015*t*, 1037, 1038
Decompression illness, 593
  clinical manifestations of, 594
  definition of, 593
  diagnosis of, 594
  epidemiology of, 593
  pathobiology of, 594, 594.*e1f*
  prevention of, 594
  treatment of, 594*b*
Decompression sickness, 593
  epidemiology of, 593
  type I, 593
  type II, 593
Decompressive surgery, 2401*b*
Decongestants, for rhinitis, 2632*b*
Decontamination, for acute poisoning, 691*b*
Decorticate posturing, 2439*t*, 2440
Decreased libido, 1587
Decubitus ulcers, spinal cord injury and, 2388*b*–2390*b*
Deep brain stimulation, for Parkinson disease, 2486
Deep enteroscopy techniques, 1345
Deep muscle necrosis, electrical injury and, 703
Deep mycoses, 2621*t*
Deep space infections, 2649–2650, 2650*f*
Deep venous thrombosis (DVT), 482
  algorithm for, 477*f*
  clinical manifestations of, 483, 483*f*
  diagnosis of, 483–487, 485*f*
  of lower extremities, 476
  in pregnancy, 1622
  therapy for, 478*b*
  treatment of, 487*b*
  of upper extremities, 490
Deescalation, in psychiatric diseases, 2679
DEET, 1889, 1988
Defecation, 888, 888*f*
Defecography, for rectal intussusception, 982
Deferiprone, chelation therapy with, 1822
Deferoxamine, for acute poisoning, 693*t*
Defibrillation, transthoracic, 340
Defibrination, 1195
Deficiency of adenosine deaminase-2 (DADA2), 1731*t*, 1733*t*
Deficiency of interleukin-1 receptor antagonist (DIRA), 1731*t*, 1735
Deficiency of the IL-36R antagonist (DITRA), 1731*t*, 1735
Degenerative disc disease, 1706*t*
Degos disease, 965, 969
Dehydrated hereditary stomatocytosis, 1097
Dehydration, signs of, 861
Dehydroascorbic acid, 1453*t*
Dehydroepiandrosterone (DHEA), 1520, 1581, 1585*b*, 1599–1600
  unconjugated, *e1t*–*e8t*
Dehydroepiandrosterone sulfate (DHEA-S), *e1t*–*e8t*
Dejerine syndrome, 2465.*e1f*
Delafloxacin, 1845*t*, 1895*t*
Delayed hemolytic transfusion reaction, 1202
Delayed puberty, 1593–1594, 1594*b*
Delayed serologic transfusion reaction, 1202
Delayed-type hypersensitivity reactions, 195, 2131
Deletion, 163, 207
Delirium, 2330–2336, 2336
  caregiver issues, 2334*b*–2335*b*
  clinical manifestations of, 2332–2334
  definition of, 2331–2336
  development of, 2332
  diagnosis of, 2334
  diagnostic criteria for, 2331*t*
  differential diagnosis of, 2334
  end-of-life care for, 2334*b*
  epidemiology of, 2331
  evaluation of, 2333*f*
  laboratory findings of, 2334
  management of, approaches to, 13*t*
  medical treatment, 2334*b*
  nonpharmacologic management, 2334*b*
  in older adults, 114, 2331
  in palliative care, 12
  pathobiology of, 2331–2332
  postoperative, 2674
  preoperative, 2665, 2665*b*, 2665*t*
  prevention of, 2335–2336, 2335*t*
  prognosis for, 2336
  treatment of, 2334*b*
Delta anion gap, 756
Delta check, 1067
Delta-delta, 756
Delusional disorder, 2345*t*–2346*t*, 2346
Dematiaceous fungal infections, 2108–2111
  associated diseases with, 2109*t*
  definition of, 2108–2111
  diagnosis of, 2110–2111
  differential diagnosis of, 2110–2111
  epidemiology of, 2108–2109
  pathobiology of, 2109
  pathogens causing, 2108
  prevention of, 2111
  prognosis for, 2111
  treatment of, 2111*b*
Dementia, 117, 2336, 2412, 2544
  clinical examination in, 2412–2413
  clinical manifestations of, 2412
  definition of, 2412, 2412*t*
  diagnosis of, 2412–2413, 2413*f*
  dialysis, 101*t*, 105, 105*b*
  differential diagnosis of, 2413, 2414*f*
  end-of-life care for, 2413
  epidemiology of, 2412
  HIV-associated, 2312
  multi-infarct, as arterial thrombotic complications, 481
  nutrition and, 60
Dementia *(Continued)*
  pathobiology of, 2412
  prognosis for, 2413
  rapidly progressive, 2424, 2424*t*
  semantic, 2421
  spectrum of mild cognitive impairment to, 2412–2413
  trajectories of, 12.*e1f*
Dementia with Lewy bodies, 2420–2421
  clinical manifestations of, 2420
  definition of, 2420
  diagnosis of, 2420–2421, 2420*t*
  differential diagnosis of, 2420–2421, 2485*t*
  epidemiology of, 2420
  pathobiology of, 2420
  prognosis of, 2421
  treatment of, 2421*b*
Demyelinating conditions, 2498–2510
  acute disseminated encephalomyelitis, 2509
  adrenoleukodystrophy, 2509
  adrenomyeloneuropathy, 2509, 2509*b*
  Canavan disease, 2510
  globoid cell leukodystrophy, 2510
  metachromatic leukodystrophy, 2509
  multiple sclerosis. *See* Multiple sclerosis
  neuromyelitis optica, 2508
  optic neuritis, 2500, 2508, 2508*b*
  Pelizaeus-Merzbacher disease, 2509
  transverse myelitis, 2406, 2508, 2509*b*
  vanishing white matter disease, 2510
Demyelinating neuropathies, 1238*t*
Demyelinating processes, monofocal and monophasic, 2508–2509
Dendritic cell-specific intracellular adhesion molecule-3 grabbing non-integrin (dendritic cell-SIGN), 183
Dendritic cells, 182
Dengue, 1*f*–2*f*, 2275*t*, 2277, 2277*b*, 2277.*e1f*
  in travelers, 1888, 1889.*e1t*, 1890*t*
Dengue hemorrhagic fever, 2268*t*
Dengue virus, 2265*t*, 2266
Denosumab (Xgeva), 1215*t*
  for osteoporosis, 1643*b*, 1644*t*
Dense connective tissue, 1707
Dent disease, 816*t*, 817, 817*b*
Dental abscess, pathogens and empirical therapy for, 2526*t*
Dental caries, Hodgkin lymphoma and, 1293*t*
Denture stomatitis, 2090
Denys-Drash syndrome, 1574
11-Deoxycortisol (compound S), *e1t*–*e8t*
Deoxyribonucleases (DNases), 1913
Department of Veterans Affairs, health care system in, 42
Dependent personality disorder, 2348*t*
Depot medroxyprogesterone acetate, 1615
Depression, 2337*t*
  in adolescents, 111–112, 112
  in heart failure, 265*b*
  intimate partner violence and, 1634
  management of, approaches to, 13*t*
  in palliative care, 12
  respiratory, psychotropic medications and, 2678*t*
  screening for, 53
  weight loss and, 860*t*
  in women, 1608*t*, 1609
Dermablend, 2701
Dermacentor andersoni, 1986, 2054
Dermacentor variabilis, 1986, 2054
Dermal depth, 2688*t*–2689*t*
Dermatitis, 1736
  allergic contact, 2704
  atopic, 2702, 2703*f*
  chronic actinic, 2704, 2704*f*
  disseminated gonococcal infection and, 1949
  irritant contact, 2704
  nummular, 2688*t*, 2702, 2702*f*
  occupational and environmental, 86*t*
  seborrheic, 2703, 2703*f*
Dermatitis herpetiformis, 2718, 2718*b*, 2718*f*
Dermatofibromas, 2730
Dermatofibrosis lenticularis disseminata, 1668
Dermatologic paraneoplastic syndromes, 1239
Dermatologic surgery, for skin cancers, 2701
Dermatomal zoster, 2248, 2249*f*
Dermatomes, 2395*f*
Dermatomyositis, 1238*t*, 2588*t*
  clinical features of, 1788*t*
  clinical findings of, 1788, 1790*f*
  cutaneous manifestations of, 1707
  diagnostic criteria for, 1790*t*

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Dermatomyositis *(Continued)*
epidemiology of, 1787
interstitial lung disease associated with, 581
pathobiology of, 1787
treatment of, 1790*b*
Dermatophytes, 2754
Dermatophytoses, 2710–2711, 2711*f*
Dermatoscopy, 2747
Dermographism, 1687, 1687*f*
Desensitization, for drug allergy, 1699*b*
Desipramine
for depression, 2340*t*
for irritable bowel syndrome, 896*t*
Desmoid tumors, 958, 1390, 1390*b*
Desmopressin
for central diabetes insipidus, 1503*b*
for gestational diabetes insipidus, 1503*b*
for subarachnoid hemorrhage, 2476*b*–2478*b*
Desquamative interstitial pneumonia, 578
diagnosis of, 578, 578*f*–579*f*, 578.e1*f*, 579*f*
prognosis for, 578*b*
radiographic features of, 574*t*
treatment of, 578*b*
Desvenlafaxine
for depression, 2340*t*
for hot flashes, 1631*t*
Detrusor hyperactivity with impaired contractility, 828
Detrusor overactivity, 827
Detrusor underactivity, 828
Deutetrabenazine, for tardive dyskinesia, 2496*b*
Developmental disorders, 2545–2553
Device-associated infections, 1865–1866, 1866
Dexamethasone
for bacterial meningitis, 2515*b*
for brain tumors, 1312*b*
for COVID-19, 2217
for *Haemophilus influenzae* type b meningitis, 1944*b*
for high-altitude diseases, 593*t*
for immune thrombocytopenic purpura, 1176*t*
for nausea and vomiting, 863*t*
Dexamethasone suppression testing
for Cushing disease, 1494, 1495*t*
for Cushing syndrome, 1522
Dexmedetomidine, 2670
Dexrazoxane (Zinecard), 1215*t*
Dextroamphetamine, 1460*t*, 2446*b*, 2449*t*
Dextrocardia, 354–355
DHEA. *See* Dehydroepiandrosterone
DHT. *See* Dihydrotestosterone
Diabetes foot, 1550, 1550*b*
Diabetes insipidus, 743–744, 1483, 1500–1504
central
clinical manifestations of, 1501, 1502*f*
diagnosis of, 1502
pathobiology of, 1500
treatment of, 1503*b*
clinical manifestations of, 1501
definition of, 1500
diagnosis of, 1501–1503, 1502*f*
epidemiology of, 1500
etiologic diagnosis of, 1502–1503
gestational
clinical manifestations of, 1501
pathobiology of, 1500
treatment of, 1503*b*
nephrogenic
clinical manifestations of, 1501
diagnosis of, 1503
pathobiology of, 1500
treatment of, 1503*b*
pathobiology of, 1500–1501
prognosis of, 1504.e1*f*, 1504
provocative testing for, 1501–1502
severe mental illness and, 2683*t*
Diabetes mellitus, 1534–1551, 1608*t*
acute hyperglycemic states, 1547
acute issues for individuals with, 1545–1549
antihypertensive drug for, 454*t*
arthritis associated with, 1822
autonomic neuropathies in, 2560
cardiomyopathy in, 294
cardiovascular disease and, 1550, 1550*b*
cell therapy for, 174
chronic complications of, 1549–1550
cystic fibrosis and, 557
definition of, 1534–1536, 1534*t*
diagnosis of, 1535–1536, 1536*t*
Diabetes mellitus *(Continued)*
diarrhea associated, 939
epidemiology of, 1549
gastroparesis associated with, 889
gestational, 1544–1545, 1624, 1624*b*
glomerular diseases in, 788
with heart failure, 265*b*
heart failure associated with, 262
after hematopoietic cell transplantation, 1211
in HIV, 2318, 2318*b*
hypoglycemia, 1545–1546
inpatient management of, 1538*t*, 1545
metabolic acidosis in, 747
microvascular complications of, 1549–1550
mucormycosis and, 2098
normal renal function and, 456
nutrition and, 60
pathobiology of, 1534–1535, 1534.e1*f*, 1535*f*, 1535*t*, 1549
in pregnancy, 1619*t*, 1624, 1624*b*
prevalence of, 18
screening for, 55
surgical risks associated with, 2665
type 1, 1534*t*, 1536–1539
clinical manifestations and diagnosis of, 1535*t*, 1536–1537, 1537*f*
diet and lifestyle treatment for, 1537*b*
epidemiology of, 1536–1539
insulin therapy for, 1537*b*, 1538*t*
pathobiology of, 1536
prevention of, 1538
prognosis of, 1539
treatment for, 1537*b*, 1538*t*
type 2, 1534*t*, 1539–1544
clinical manifestations of, 1540
diagnosis of, 1535*t*, 1539*t*, 1540
epidemiology of, 1539–1544
epigenetic risk of, 1539–1540
genetics of, 1539–1540
insulin action in, 1539
insulin secretion in, 1539
metabolic monitoring in, 1540*b*
obesity and, 1466, 1540
pathobiology of, 1539–1540, 1539*t*
pharmacologic therapy for, 1540*b*, 1541*t*, 1543*f*
polygenic risk of, 1539
prevention of, 1544, 1544*t*
prognosis of, 1544
self-management education and support for, 1540*b*
single-gene mutations, 1539
sleep deprivation and, 1540
smoking and, 1540
treatment for, 1540*b*
in women, 1607
Diabetic amyotrophy, 1822
Diabetic foot ulcer, 1892*t*
Diabetic ketoacidosis (DKA), 758
anesthesia and, 2669
clinical manifestations of, 758, 1547
diagnosis of, 758, 1547–1548, 1548*t*
epidemiology of, 758, 1547
pathobiology of, 758, 1547
prevention of, 1549
prognosis of, 758, 1549
treatment of, 758*b*, 1547*t*, 1548*b*
Diabetic lumbosacral radiculoplexus neuropathy, 2577
Diabetic nephropathy, 795–799, 1549
clinical manifestations of, 796
complications of, renal, 796
cytokines in, 796
diagnosis of, 796–797
epidemiology of, 795–799
genetics of, 796
hemodynamics in, 795–796
hormones in, 796
hyperglycemia in, 795
natural history of, 796
pathobiology of, 795–796
prognosis of, 798–799
renal biopsy for, 797
renal complications in, 796
stage I, 796, 797*f*
stage II, 796, 797*f*
stage III, 796, 797*f*
stage IV, 796, 797*f*
treatment of, 797*b*, 797*f*–798*f*
Diabetic neuropathy, 1550
acute focal neuropathies, 2577
definition of, 2577
diabetic lumbosacral radiculoplexus neuropathy, 2577
distal symmetrical and autonomic polyneuropathy, 2577, 2577*b*
epidemiology of, 2577
treatment-induced, 2577
Diabetic osteolysis, 1822
Diabetic retinopathy, 1549, 1549*b*, 1549*t*, 2609, 2609*f*
Diabetic stiff hand syndrome, 1822
Diagnostic and Statistical Manual of Mental Disorders, 5th edition (DSM-5)
on alcohol use disorders, 2353
on eating disorders, 1461
"Diagnostic dilemmas", 167
Dialysis
for acute kidney injury, 774*b*
for irreversible renal failure, 841–843
Dialysis dementia, 101*t*, 105, 105*b*
Dialysis-dependent chronic kidney disease, 842
Diamond-Blackfan anemia, 1127.e1*t*, 1129, 1130*b*
DIAPERS mnemonic, 828*t*
Diaphragm (contraceptive), 1611
Diaphragm (muscle), 619–620
Diaphragmatic disorders, 619–629
Diaphragmatic eventration, 620
Diaphragmatic weakness or paralysis, 619–620, 619*t*
causes of, 619*t*
chest radiography findings, 620, 620.e1*f*
clinical manifestations of, 619
diagnosis of, 619–620, 620*f*
epidemiology of, 619
pathobiology of, 619
sniff test for, 619–620
treatment of, 620*b*
Diarrhea, 865
abdominal pain and, 856
acute, 924
clinical manifestations of, 924
diagnosis of, 926
epidemiology of, 925*t*
prevention of, 928
alcohol-related, 939
amebic, 2147
approach to, 923–941
bile acid, 939, 939*b*
in carcinoid syndrome, 1567
chronic, 928
causes of, 928*t*, 932–938
clinical manifestations of, 928
diagnosis of, 924*t*, 927*f*, 928, 930*f*
chronic idiopathic secretory, 940
Clostridium perfringens type A, 1926, 1926*b*
congenital, 938–939
cryptosporidiosis and, 2143
definitions of, 923–924
diabetes mellitus-related, 939
in enteral nutrition, 1450
epidemiology of, 923–924
factitious, 940
in immunocompromised host, 1859
infectious, treatment of, 1872*t*
inflammatory, 924, 930*f*, 940
noninfectious, 1872*t*
pathobiology of, 924
persistent, 928
postoperative, 2673–2674
prolonged, 932
signs and symptoms of, approach to, 852*t*
treatment of, 926*b*, 941*b*
true secretory, 930*f*, 939–940
in VIPomas, 1564
watery, 760, 924, 930*f*, 939
Whipple disease and, 2070
in Zollinger-Ellison syndrome, 1563
Diarrheal syndromes, 1924–1926
Diastolic blood pressure
elevated, 33*t*
normal range for, 32*t*
panic range for, 32*t*
Diastolic ventricular function, 239
Diazepam
for alcohol withdrawal, 2358*t*
for anxiety disorders, 2344*t*
for diarrhea, 926*b*
Diazepam + nordiazepam, e10*t*–e11*t*
Diazoxide, for hypoglycemia, 1557*b*
DIC. *See* Disseminated intravascular coagulation
Dichlorphenamide, for hypokalemia, 752*b*
Diclofenac
for chronic pain, 138*t*
for dysmenorrhea, 1596*t*
for rheumatoid arthritis, 1756*t*
Dicloxacillin, dosage of, 1895*t*
Dicyclomine, for irritable bowel syndrome, 896*t*
Dientamoeba fragilis, 2156, 2156*t*
Diet. *See also* Nutrition
for arterial hypertension, 450*t*
behavioral interventions for, 55
cancer and, 1244
cardiovascular disease and, 220
for glycogen storage disease I, 1416*b*
for heart failure, 265*b*
for irritable bowel syndrome, 895*b*
micronutrient requirements, 1451
for obesity, 1467*b*
recommendations of, for chronic kidney disease, 839*b*
Dietary Approaches to Stop Hypertension (DASH) diet, 58, 59*t*, 450
Dietary deficiency, treatment of, 1123*b*
Dietary fat, intestinal digestion and absorption of, 932.e1*f*
Dietary Guidelines for Americans, 2020-2025, 57–58, 57.e3*t*, 58*t*
Dietary lipids, 932
Dietary oxaluria, 803
Dietary reference intakes, 57
Dietary Supplement Health and Education Act, 154
Dietary supplements, 60
Diethylcarbamazine (DEC), 2117–2118
for filariases, 2176*b*
for helminthic diseases, 2112*t*
for loiasis, 2179*b*–2180*b*
Dieulafoy lesion, 885*f*, 886, 918, 966, 967*f*
Dieulafoy ulcers, 913–914
Differential count, e8*t*–e9*t*
Differin. *See* Adapalene
Diffuse alopecia, 2747*t*, 2748
Diffuse alveolar damage, 650
chest radiograph of, 520*f*
Diffuse alveolar hemorrhage, 566*t*, 568
clinical manifestations of, 568, 568.e1*f*
definition of, 568
diagnosis of, 569, 569*f*, 569.e1*f*
pathobiology of, 568
prognosis of, 569
treatment for, 569*b*
Diffuse bronchiectasis, 522
Diffuse cutaneous leishmaniasis, 2133
Diffuse cutaneous systemic sclerosis, 1777, 1777*t*
Diffuse esophageal spasm, 909, 909*b*, 909*f*
Diffuse homogeneous opacities, 520–521
Diffuse hyperpigmentation, 2743
Diffuse hypoxic injury, 2462
Diffuse idiopathic skeletal hyperostosis (DISH), 1706*t*, 1815
Diffuse infiltrative lymphocytosis syndrome, 2323
Diffuse large B-cell lymphoma, 1279, 1284, 1285*b*, 2315
subtypes of, 1285, 1285*b*
Diffuse lung disease, 520–524
Diffuse pleural thickening, 526
Diffuse proliferative lupus nephritis, 787*f*–788*f*
Diffuse reticular lung disease, chest radiograph of, 522*f*
Diffuse-type gastric cancer, 1340
Diffusely adherent *E. coli*, 1961, 1962*t*
Diffusing capacity, in pulmonary function tests, 528*t*, 530–531, 531*f*
Diflunisal
for amyloidosis, 1309*b*, 2560*b*
for chronic pain, 138*t*
DiGeorge syndrome, 347, 1679–1680, 1679*b*, 1679*t*
hypoparathyroidism and, 1661
Digestive decontamination, for health care-associated infections, 1867
Digital rectal examination, for gastrointestinal disease, 851
Digital subtraction angiography, in atherosclerotic PAD, 463, 463*f*
Digitalis overdose, treatment of, 752*b*

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Digitoxin, e10t–e11t
Digoxin, e10t–e11t, 325t
  for atrial fibrillation, 384b
  for heart failure, 265b
  intoxication, immunization for, 65t
  toxicity, 686t, 690t
Digoxin-specific antibody fragments, for acute poisoning, 693t
Dihydroergotamine, 2378b–2379b
Dihydropyridines
  for hypertension, 451t
  side effects of, 453t
Dihydrotestosterone (DHT), 1581–1582
1,25-Dihydroxycholecalciferol, 732
1,25-Dihydroxyvitamin D, 1648–1649, 1652
Dilated cardiomyopathy
  acquired, 286
    clinical manifestations of, 287
    diagnosis of, 287
    prognosis for, 287–288
    treatment of, 287b
  characteristics of, 286–288
  definition of, 286
  echocardiographic findings, 242t
  epidemiology of, 286
  family screening for, 287b
  genetic, 286
  nonischemic, 265b, 336
  overlap with restrictive cardiomyopathy, 288
  pathobiology of, 286
Diloxanide furoate
  for amebiasis, 2150t
  for intestinal amebiasis, 2112t
Diltiazem
  for acute coronary syndrome, 374t
  for acute STEMI, 384b
  properties of, 367t
  for ventricular tachycardia, 338b
Diltiazem ER, 451t
Dilutional thrombocytopenia, 1179
Dimenhydrinate, for nausea and vomiting, 863t
Dimercaprol, for acute poisoning, 693t
Dimethylfumarate (Tecfidera), for multiple sclerosis, 2505t
Dipentum. See Olsalazine
Dipeptidyl peptidase 4 (DPP4), MERS and, 2208
Dipeptidyl peptidase 4 (DPP4) inhibitors, for type 2 diabetes mellitus, 1540b, 1541t
Diphenhydramine
  for intestinal pseudo-obstruction, 889b
  for nausea and vomiting, 863t
Diphenylhydantoin, e10t–e11t
Diphtheria, 1933
  clinical manifestations of, 1933
  cutaneous, 1934
  diagnosis of, 1935
  epidemiology of, 1933
  immunization for, 65t, 66t, 76.e1t, 77f, 78f, 82
  neuropathy associated with, 2578
  pathobiology of, 1933
  pathogen of, 1933
  prevention of, 1935
  prognosis of, 1935
  treatment of, 1935b, 1935t
  vaccinations, 1996
Diphtheria-tetanus-pertussis (DTaP) vaccine, 76
Diphtheria toxoid vaccine, 1935
Diphyllobothrium sp., 2157, 2158t
Dipylidium caninum, 2158, 2158b, 2158t
DIRA. See Deficiency of interleukin-1 receptor antagonist
Direct allorecognition, 205–206, 205f
Direct antiglobulin test, 1087
Direct factor Xa inhibitors, 505–506
  adverse effects of, 506
  anticoagulant effect, reversal of, 506, 506t
  dosage and monitoring of, 505–506
Direct fluorescent antibody test, of *Pneumocystis* pneumonia, 2105f
Direct/intrinsic hepatotoxicity, 1018–1019
  clinical manifestations of, 1018–1019, 1018.e2f
  diagnosis of, 1019, 1019t
  drugs and toxins that cause, 1018, 1019t
  pathobiology of, 1018
  prevention of, 1019
  prognosis of, 1019
  treatment for, 1019b
Direct MR arthrography, 1723
Direct oral anticoagulants (DOACs), 374t, 502t, 504–506, 505t
  for venous thromboembolism, 487b
Direct renin inhibitors, for hypertension, 452, 453t
Direct reprogramming, 173–174
Direct thrombin inhibitors, 502t, 504–505
  adverse effects of, 504
  anticoagulant effect of, reversal of, 504–505
  dosage and monitoring of, 504
  parenteral, 503
  vorapaxar as, 508–509
Direct-to-consumer genomic testing, 159
Dirofilaria immitis, 2180
Diroximel fumarate (Vumerity), for multiple sclerosis, 2505t
Dirty bomb, 92
Disability
  leading causes of, 21–23, 23f–24f, 24f
  in older adults, 115
Disaster management, in occupational and environmental medicine, 89
Discharge issues, 397
Discocyte, 1067f
Discoid lupus erythematosus, 2747t, 2750, 2750f
Disconjugate gaze-evoked nystagmus, 2619
Discordant thyroid tests, causes of, 1497t
Discrete data, 36
Discrimination, in health care, 42
Disease(s)
  anatomic distribution of, 523
  changing patterns of, 23
  complement system in, 196, 198t
  gene therapy for, 175–176
  genetic architecture of, 158, 158f
  global burden of, 21f, 23
  nutrition and, 57–60
  in older adults, 114–115
  stem cell-derived platforms for modeling of, 174
  trajectories of, 12.e1f
Disease-modifying antirheumatic drugs (DMARDs), 144, 1717, 1755b, 1756t, 1830.e1t
Disease-modifying medical therapy, for myelodysplastic syndromes, 1255
Disease-related malnutrition, 1447, 1447f
Disequilibrium dizziness, 2647t
DISH. See Diffuse idiopathic skeletal hyperostosis
Disoproxil fumarate, 2301t
Disopyramide, e10t–e11t, 283f, 325t
Dispersion, 36
Dissecting cellulitis, of scalp, 2750
Disseminated candidiasis, 1861f
Disseminated cutaneous leishmaniasis, 2133
Disseminated gonococcal infection, 1849, 1949–1950
  clinical manifestations of, 1949, 1949f
  diagnosis of, 1950
  prevention of, 1950
  prognosis of, 1950
  screening of, 1950
  treatment of, 1950b
Disseminated histoplasmosis, 2082, 2083b
Disseminated infections, 2090
Disseminated intravascular coagulation (DIC), 1178, 1195–1198
  causes of, 1195, 1195t
  clinical manifestations of, 1195–1196, 1196f
  definition of, 1195
  description of, 2696f
  diagnosis of, 1196
  management of, 2269b
  pathobiology of, 1195, 1196f
  treatment of, 1196b, 1197t
Disseminated mucormycosis, 2099
Disseminated nontuberculous mycobacterial disease, 2045
Distal acquired demyelinating symmetric neuropathy, 1296
Distal acquired demyelinating symmetric syndrome, 2576, 2576b
Distal acquired demyelinating syndrome, 2574, 2576b
Distal axonopathy, 683–684
Distal renal tubular acidosis, 749t, 761, 816t, 817, 818b, 818t
Distal subungual onychomycosis, 2754, 2754f
Distal symmetrical and autonomic polyneuropathy, 2577, 2577b
Distal symmetrical peripheral polyneuropathy, 2313
Distal tubule
  disorder of, 816t, 817
  diuretics, 736b
Distention
  abdominal pain and, 856
  bloating and, 859, 859b
Distinctive lesions, in black skin, 2744, 2744t
Distorted vision, 2599
Distributive shock, 658, 659, 659f, 661t
Disulfiram, for alcohol use disorders, 2357b, 2358t
DITRA. See Deficiency of the IL-36R antagonist
Diuretics
  for heart failure, 265b
  for hypertension, 454
  for hypervolemia, 736b, 736.e1f, 737t
  hypokalemia and, 749t
  for postpartum diuresis, 288b
Diverticular bleed, 884
Diverticular disease, 60, 954, 954.e1f, 955b, 955f
Diverticulitis, 955b, 955f
  abdominal pain and, 854t
  colitis, 956
  colonic, 954, 954.e1f, 955f
Diverticulosis, colonic, 954, 954.e1f, 955b, 955f
Dix-Hallpike test, 2646
Dizziness
  description of, 303, 2371, 2372f, 2646, 2647t
  evaluation of, 2646
  with palpitations, 303f
DKA. See Diabetic ketoacidosis
DMARDs. See Disease-modifying antirheumatic drugs
DNA hypomethylating agents, for myelodysplastic syndromes, 1255
DNA recombination, defects of, 1681t
DNA testing, 165
DNase, 625b
DOACs. See Direct oral anticoagulants
Dobrava-Belgrade virus, 2265t
Dobutamine
  for right ventricular infarction, 384b
  for shock, 664t, 667b, 672
Docetaxel (Taxotere), 1215t
  for head and neck cancer, 1327b
  for soft tissue sarcomas, 1389b
DOCK2 deficiency, 1678, 1678.e1t
DOCK8 deficiency, 1678, 1678.e1t
Docosanol, for herpesvirus infections, 2189
Doctoring, 3
Documented symptomatic hypoglycemia, 1546t
Doege-Potter syndrome, 526
Dofetilide, 325t
Döhle body, peripheral blood smear of, 1071f, 1072–1073
Dolasetron, for nausea and vomiting, 863t
Doll's eye test, 2646
Dolutegravir, 2301t
Domperidone, for intestinal pseudo-obstruction, 889b
Donabedian triad, 44, 44t
Donath Landsteiner test, 1088
Donation after cardiac death (DCD), 844
Donepezil
  for Alzheimer disease, 2416b
  for Parkinson disease, 2487t
Donor lymphocyte infusion, 1207
Donovanosis, 2004–2005, 2004b, 2004f
Dopa-responsive dystonia, 2493
Dopamine
  neurotransmitter, 143
  prolactin inhibition by, 1477–1478
  for shock, 662b, 664t, 673b–675b
  synthesis of, 1529
Dopamine agonist therapy, for Parkinson disease, 2486b
Dopamine receptor antagonists, for nausea and vomiting, 863t
Doppler echocardiography, 236–238
  color flow imaging, 236
  continuous-wave, 236
  modalities, 236
  principles of, 236
  pulsed, 236
  tissue, 236, 236.e1f
Doppler shift, 236
Doppler ultrasonography, 236
  continuous-wave, 236
  for gallbladder cancer, 1054
Doppler ultrasonography *(Continued)*
  pulsed, 236
  renal artery stenosis for, 800
Doravirine, 2301t
Doripenem
  dosage of, 1895t
  for pyelonephritis and urosepsis, 1877t
  for pyogenic liver abscess, 1023b
Dorsal midbrain syndrome, 2619
Dorsal root ganglionopathy, 2567t
Dot-in-circles sign, 2110–2111
Double-blinded controlled trial research design, 36
Double-contrast barium enema, 1353
Double density sign, 245, 245f
Double-hit and gray-zone lymphomas, 1285, 1285b
Double vision, 2598
Down syndrome, 164, 347, 2548f, 2549
  neutrophilia and, 1142
  treatment for, 2549b
Downbeat nystagmus, 2619
Doxazosin, 451t, 824t
Doxepin, 2452t
Doxepin + nordoxepin, e10t–e11t
Doxorubicin (Adriamycin, Rubex, Doxil), 1215t
Doxycycline, 2115
  for American monocytic ehrlichiosis, 2061b
  for anthrax exposure, 97
  for bacillary angiomatosis, 2003b
  for brucellosis, 1987b
  for cholera, 1956b, 1957t
  dosage of, 1895t
  for endocarditis, 2003b
  for granuloma inguinale, 2004b
  for intestinal bacterial overgrowth, 934b
  for leptospirosis, 2031b
  for Lyme disease, 2026t
  for malaria, 2112t, 2121t, 2123t
  for nontuberculous mycobacterial disease, 2046t
  for pelvic inflammatory disease, 1883t
  for plague, 98b, 1991b, 1992t
  for pneumonia, 613t
  for psittacosis, 2012b
  for Q fever, 2063b
  for relapsing fever, 2028b
  for rickettsialpox, 2060b
  for Rocky Mountain spotted fever, 2057b
  for scrub typhus, 2060b
  for syphilis, 2019
  for tick-borne rickettsioses, 2058b
  for total knee arthroplasty, 1830.e1t
  for tularemia, 99b
  for urethritis, 1880t
DPP4. See Dipeptidyl peptidase 4
DPYD gene, 160t
Dracunculiasis, 2180
DRB1*0301 allele, 204
DRESS. See Drug rash with eosinophilia and systemic symptoms
DRESS syndrome, 792
Dressings, for skin diseases, 2697
Dressler syndrome, 626
Driving, heart failure in, 265b
Dronabinol, for nausea and vomiting, 863t
Dronedarone, 325t
Droopy eyelid, 2600, 2600f
Droperidol, for nausea and vomiting, 863t
Dropped head syndrome, 2563
Drowning, 591–592, 592b
Droxidopa, for orthostatic hypotension, 2559t
Drug(s)
  absorption of, 126
  of abuse, 143
  acid peptic disease caused by, 917
  acquired platelet dysfunction caused by, 1185
  acute pancreatitis and, 970, 970t
  administration of, 126
  adverse reactions to, 131
  antiarrhythmic, 313b
  for atherosclerotic cardiovascular disease, 1410
  bioavailability of, 126
  bone loss as caused by, 1641
  classes of, 1898
  clearance, 127
  decreased excretion of, 131
  decreasing level of, 128
  determining accumulation of, 128, 128f
  distribution of, 126

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Drug(s) *(Continued)*
altered, 131
volume of, 126–127, 126*f*, 127.*e1t*
dose
adjustments of, 129–130
increase on, effects of, 128, 129*f*
drug monitoring as guide to, 128–129, 129*f*
in elderly patients, 130, 130*t*
elimination of, 127
for esophageal disease, 904*t*
first-pass effect of, 126
gastric ulcers caused by, 917
half-life of, 127, 127*f*
hearing loss caused by, 2642
for heart failure with reduced left ventricular ejection fraction, 265*b*
hypercalcemia caused by, 1659
for hypertriglyceridemia, 1414*b*
loading dose, 127–128
maintenance dose, 128, 128*f*
metabolism of
decreased, 131
increased, 131
ocular effects of, 2613–2614, 2613*t*
for pain, 136*b*
pharmacodynamics of, 1892
potential interactions with, 155
primary testicular hypogonadism caused by, 1583–1584
principles of, 126–133
problems with interpreting concentration of, 129
properties of, 1898
for septic shock, 673*b*
stem cell-derived platforms for, 174
stroke caused by, 2472
usefulness of genomic data in, 133
vitamin levels affected by, 1459
Drug- and toxin-induced hypoglycemia, 1552*t*, 1555, 1555*t*
Drug addiction, 142
Drug adherence, 265*b*
Drug allergy, 1695–1699
Brown classification of, 1696*t*
classification of, 1695.*e2f*
clinical manifestations of, 1696–1698, 1696.*e1f*, 1697*f*, 1698*t*
definition of, 1695–1699, 1696*f*
description of, 1673
diagnosis of, 1698–1699
epidemiology of, 1695–1696
pathobiology of, 1696, 1697*f*
prognosis of, 1699, 1699*f*
risk factors for, 1695–1696
treatment of, 1699*b*
type A, 1695.*e2f*
type B, 1696*f*
Drug counseling, 275*t*
Drug desensitization, for drug allergy, 1699*b*
Drug exposure, fetus and, 1573
Drug fever, 1846
Drug-induced gingival hyperplasia, 2625*f*
Drug-induced immune hemolytic anemia, 1089
Drug-induced interstitial lung disease, 572*t*, 582
Drug-induced liver injury, 986, 1017–1021
clinical manifestations of, 1018.*e1f*
definition of, 1017–1018, 1018*t*
direct/intrinsic, 1018
epidemiology of, 1017–1018
idiosyncratic, 1019–1021
indirect, 1021
international consensus criteria for, 1018*t*
pathobiology of, 1018, 1018*t*
Drug-induced movement disorders, 2495–2496
Drug-induced neutropenia, 1145–1146, 1145*f*
Drug-induced pancreatitis, 970
Drug-induced parkinsonism, 2485*t*
Drug-induced thrombocytopenia, 1173–1174, 1174*b*, 1174*t*
Drug-induced thyroiditis, 1514, 1515*b*
Drug interactions, 130–131
diagnosis of, 131, 132*t*
pharmacodynamic, 131
pharmacokinetic, 131
prevention of, 131
Drug-metabolizing enzymes, 132*t*
Drug overdose, 130, 2270*t*
Drug paraphernalia, 2361
Drug rash(es), 2726–2729
clinical manifestations of, 2726, 2727*f*, 2727*t*
Drug rash(es) *(Continued)*
definition of, 2726
diagnosis of, 2726
pathobiology of, 2726
prognosis of, 2726*b*
specific syndromes of, 2726–2729
treatment of, 2726*b*
Drug rash with eosinophilia and systemic symptoms (DRESS), 1697, 2726–2727, 2727*b*, 2727*f*, 2727*t*
Drug reaction, 2621*t*
Drug-related pericarditis, 424*t*
Drug-resistant hypertension, 456–457, 456*t*, 457*f*
Drug response, germline genetic variants and, 167, 167.*e1t*
Drug sensitivity, characteristics of, 2270*t*
Drug testing, 685–690
Drug use
in adolescents, 113
pathogens and empirical therapy for, 2526*t*
Drug use disorders, 2360–2365
agent of, 2360
clinical manifestations of, 2361
definition of, 2360–2361
diagnosis of, 2361
DSM-5 criteria for, 2360*t*
environment of, 2360–2361
epidemiology of, 2360
host of, 2360
major drugs in, 2361–2365
anabolic-androgenic steroids as, 2365
cocaine and amphetamines as, 2363
hallucinogens as, 2364
marijuana as, 2364
opioids as, 2361–2362
phencyclidine as, 2364–2365
sedative-hypnotic and anxiolytic drugs as, 2363
medical complications related to, 2361
pathobiology of, 2360–2361
treatment of, 2361*b*
Drusen, 2608
Dry eye syndrome, 2596, 2602, 2603*f*
DSM-5. *See Diagnostic and Statistical Manual of Mental Disorders, 5th edition*
Dual energy x-ray absorptiometry (DXA), 1638
Dual-energy x-ray absorptiometry (DXA), 1608
Dubin-Johnson syndrome, 994, 996
Duchenne muscular dystrophy
characteristics of, 2583, 2583*b*, 2583.*e2f*
dilated cardiomyopathy in, 286
Ductal carcinoma in situ, 1369*b*, 1369*t*, 1370*t*
Duffy A-B- individuals, normal neutrophil count for, 1143
Duffy antigen receptor, 1162
Dulaglutide, for type 2 diabetes mellitus, 1541*t*
Duloxetine
for chronic pain, 138*t*
for depression, 2340*t*
for distal symmetrical and autonomic polyneuropathy, 2577*b*
for fibromyalgia, 1819*b*
Dumping syndrome, 890, 932, 1554, 1557*b*
Duodenal biopsies, for Whipple disease, 2070, 2070*f*–2072*f*, 2071*f*
Duodenal histology, for Whipple disease, 2070, 2072*f*
Duodenal ulcers
with bleeding visible vessel, 882*f*
description of, 913
endoscopy of, 913*f*–914*f*
epidemiology of, 914
malignant, 915
Dupilumab, 151
Duplication cysts, 913
Dupuytren contractures, 987, 1032*f*, 1822
Dural arteriovenous fistulas, 2482
Duroziez sign, 410
Durvalumab (Imfinzi), 1215*t*
Dusts, 87, 88*t*
Dutasteride, 824*t*
Duvelisib, for chronic lymphocytic leukemia, 1269*t*
DVT. *See* Deep venous thrombosis
DXA. *See* Dual energy x-ray absorptiometry
Dyes, reactions to, 1698*t*
Dynamic hyperinflation, 654
Dynamic International Prognostic Scoring System-Plus, 1137*f*, 1139
Dysbarism, 88*t*
Dysbiosis, 1852
Dyschondroplasia, 1669
Dysentery, amebic, 2147, 2148*f*
Dysfibrinogenemia, 1189*t*, 1192, 1193*b*
Dysfunctional bleeding, 1597
Dysgenesis, gonadal, 1600
Dysgerminomas, suprasellar, 1479
Dyshidrosis, 2702, 2702*f*–2703*f*
Dyskaryosis, 2241
Dyskeratosis congenita, 1129, 1129*b*, 1145
Dyskinetic dysphagia, severe mental illness and, 2681*t*
Dyslipidemia
diabetes mellitus and, 1550
obesity caused by, 1466
Dysmenorrhea, 1596, 1596*b*, 1596*t*
Dysmorphic erythrocytes, 723*f*
Dysostosis multiplex, 1724
Dyspepsia
approach to, 865, 865*f*
direct thrombin inhibitors and, 504
functional, 898–899
alarm symptoms associated with, 899*t*
algorithm for, 899*f*
definition and epidemiology of, 898
pathobiology of, 898
prognosis of, 899
Rome IV diagnostic criteria for, 898, 898*t*–899*t*, 899*t*
treatment of, 899*b*
nonulcer, abdominal pain and, 854*t*
Dysphagia, 852*t*, 865
esophageal disease and, 902
psychotropic medications and, 2678*t*, 2680
Dysphagia lusoria, 913
Dysphonia, 2653
Dysplasia, in ulcerative colitis, 945*b*
Dysplastic hematopoiesis, myelodysplastic syndromes *versus*, 1255
Dysplastic nevi, 1390, 1391*f*, 1392*t*
Dyspnea, 210, 256
acute pancreatitis and, 970
alveolar hemorrhage and, 568
approach to, 513, 516*t*
chronic, 517*f*
diagnosis of, 513, 514*f*
hepatic dysfunction and, 987
obesity and, 533
paroxysmal nocturnal, 256
postoperative, 2673, 2674*t*
of pregnancy, 1622
prognosis for, 515*b*
pulmonary alveolar proteinosis and, 567
refractory, oxygen in, 12
severe, 256
transfusion-associated, 1202
treatment of, 515*b*
Dysregulated stress responsiveness, in irritable bowel syndrome, 893
Dystonia, 2652
adult-onset idiopathic, 2493
classification of, 2492*t*
clinical manifestations of, 2493
definition of, 2492–2493
diagnosis of, 2493
dopa-responsive, 2493
heredodegenerative, 2492*t*
myoclonus, 2493
pathobiology of, 2492
primary, 2492*t*, 2493
secondary, 2492*t*
treatment of, 2493*b*
Dystonia-plus, 2492*t*, 2493
Dystonic gait, 2373*t*
Dystonic tremor, 2493
Dystrophic epidermolysis bullosa, esophageal involvement in, 911
Dystrophin, 2580
Dystrophin-sarcoglycan complex, 2580
Dystrophinopathies
Becker muscular dystrophy, 2584, 2584*b*
Duchenne muscular dystrophy, 2583, 2583*b*, 2583.*e1f*
DYT6, 2493

E

EAD. *See* Early afterdepolarizations
Eagle-Barrett syndrome, 821
Ear(s)
acute poisoning and, 683
examination of, 29
Ear infections, *Pseudomonas* infections causing, 1969, 1970*b*
Ear injury, occupational, 86*t*
Ear pain, 2636–2638
cause of, 2636*t*
clinical manifestations of, 2636, 2637*f*
definition of, 2636–2638
diagnosis of, 2636–2638
differential diagnosis of, 2637–2638, 2638*f*
imaging of, 2637
laboratory findings in, 2637
pathobiology of, 2636
physical examination of, 2636–2637, 2637*f*–2638*f*
treatment of, 2638*b*
Early afterdepolarizations (EAD), 333, 333.*e1f*
Early childhood gigantism, 1487*t*
Early gastric cancer, 1340
Early infectious syphilis, 2020*b*
Early-onset protein-losing enteropathy, and thrombosis, intestinal lymphangiectasia, and intestinal inflammation, 1731*t*
Early-onset sarcoidosis, 1731*t*
Early-stage breast cancer, 1369*b*, 1370*t*, 1371*t*
East African sleeping sickness, 2124
Eastern Africa, HIV/AIDS in, 2288–2289, 2288.*e1f*
Eastern equine encephalitis virus, 2276*t*, 2283, 2283*b*
Eastern Europe, HIV/AIDS in, 2289, 2289.*e1f*
Eating disorders, 1461–1463, 2346
in adolescents, 113
clinical manifestations of, 1461–1462
definition of, 1461–1463
diagnosis of, 1462
epidemiology of, 1461
pathobiology of, 1461
prevention of, 1462
prognosis of, 1462–1463
treatment of, 1462*b*
EBNAs. *See* Epstein-Barr nuclear antigens
Ebola virus, 99, 99.*e1t*, 100*b*, 2264, 2265*t*, 2268*t*, 2269*f*, 2273
immunization for, 66*t*, 84
Ebselen, 2643
Ebstein anomaly, 354
chest radiography findings, 247
exercise recommendations for, 355.*e2t*
EBV. *See* Epstein-Barr virus
Ecchymoses, 2714, 2715*f*
ECG. *See* Electrocardiography
Echinocandin antifungal agents, 2078
anidulafungin as, 2078
caspofungin as, 2078
mechanisms of action, 2078
micafungin as, 2078
Echinococcosis, 1025–1029, 1029*b*, 1029*f*
cystic, 2161, 2161*b*
Echinococcus granulosus, 1026*t*
description of, 2161, 2162*f*
Echinococcus multilocularis, 1026*t*, 2162, 2162*b*
Echinococcus oligarthrus, 2163
Echinococcus vogeli, 2163
Echinoderm microtubule-associated protein-like 4 (EML4), lung cancer and, 1330
Echo dropout, 236
Echocardiographic-guided percutaneous pericardiocentesis, 427*b*, 430*f*
Echocardiography, 235
approaches, 238–239, 238*t*–239*t*, 238*t*, 239*f*, 239*t*
in arrhythmia, 309
cardiac measurements, 236, 237*f*, 239–241
for cardiac tamponade, 426, 428*f*
in cardiogenic shock, 667
contrast, 238, 240*f*
Doppler, 236
examination with, 241
in heart failure, 260–261
imaging, 236, 236*f*
indication for, 241, 242*t*, 243*f*
in infective endocarditis, 416–417, 418*f*
integrating with clinical findings, 241
intracardiac, 239
limitations of, 236
normal findings, 241
point-of-care, 238, 239*t*

Copyrighted material

Echocardiography *(Continued)*
principles of, 235
for pulmonary hypertension, 495
for signs of cardiovascular disease, 218
standard image planes, 236, 236*f*
stress, 238, 241*f*, 362
three-dimensional, 238, 240*f*–241*f*
transesophageal, 238, 238*t*, 239*f*
transthoracic, 238, 238*t*
E-cigarettes, in adolescents, 113
Ecologic model, intimate partner violence and, 1633
Ectasias, 967
Ecthyma, 1914–1915
Ecthyma gangrenosum, 1860*f*, 2239, 2741
Ectocervix, 2241
Ectoparasites
characteristics of, 1883
organisms causing, 1879*t*
of skin, 2739*t*, 2741–2742
Ectopia lentis, 1426
Ectopic ACTH secretion, 1523, 1523*t*, 1524*b*
Ectopic ACTH syndrome, Cushing disease *versus*, 1477
Ectopic atrial rhythm, 322, 323*f*
Ectopic hormone syndromes, 1237
Ectopic ureters, 819
Ectropion, 2601, 2601*f*
Eculizumab, for paroxysmal nocturnal hemoglobinuria, 1092*b*
Eczema, 2702–2704, 2702*t*
allergic contact dermatitis, 2704
atopic dermatitis, 2702, 2703*f*
dyshidrosis, 2702, 2702*f*, 2703*f*
irritant contact dermatitis, 2704
nummular dermatitis, 2702, 2702*f*
seborrheic dermatitis, 2703, 2703*f*
Eczema vaccinatum, 2238, 2240*b*
Edaravone, for amyotrophic lateral sclerosis, 2563*b*
Edema, 215
cerebral, 2464, 2511
high-altitude, 592*t*
due to heart failure, 258
postoperative, 2675
pulmonary
distinguishing features of, 515*t*
high-altitude, 592
subglottic, 2197*f*
wasting and, 1445
Edematous malnutrition, 1444–1445, 1445*f*
Edetate calcium disodium ($CaNa_2EDTA$), for acute poisoning, 693*t*
Edge Hill virus, 2275*t*
Edinburgh Hypoglycemia Scale, 1546*t*
Edmonton Symptom Assessment Scale, 12, 12.*e1f*
Edoxaban, 502*t*, 505*t*, 506
for venous thromboembolism, 478*b*, 487*b*
EDTA. *See* Ethylenediaminetetraacetic acid
Education, for heart failure, 265*b*
Edwards syndrome, 164
EEG. *See* Electroencephalography
Efavirenz, 2301*t*, 2303
for HIV/AIDS, 2312–2313
Effective dose, 91
Effector mechanisms, of rejection, 206
Effectors
of adaptive immune response, 192–193
damaging, inhibitors of, 196
of innate immune mechanisms, 191–192, 192*f*
Efferent limb mechanisms, 734–735
Effusion
in cancer, management of, 1232*b*
pericardial, 241, 243*f*, 425–428
causes of, 427*t*
chest radiography in, 245, 246*f*, 428*f*
clinical manifestations of, 425–426
diagnosis of, 426–427
epidemiology of, 425–428
management of, 429*f*
pathobiology of, 425
prognosis for, 428
treatment of, 427*b*
without tamponade, 427*b*
pleural, 623–625, 624*f*
Effusive-constrictive pericarditis, 431
Eflornithine, for African trypanosomiasis, 2112*t*, 2116, 2125*b*, 2125*t*
Efudex. *See* 5-Fluorouracil
EGAPP, 169.*e1t*
EGFR. *See* Epidermal growth factor receptor
eGFR. *See* Estimated glomerular filtration rate
Egg protein, in vaccines, 76
Egophony, 512
Ehlers-Danlos syndrome, 1186, 1726, 1727*b*, 1727*t*
esophageal involvement in, 911
type IV, 969
Ehrlichia canis, 2060*t*
Ehrlichia chaffeensis, 2060
Ehrlichia ewingii, 2060*t*
Ehrlichia muris-like, 2060*t*
Ehrlichia spp., 2061, 2061*b*
Ehrlichiae, 2055*t*
Ehrlichiosis, 2060, 2060*t*
American human monocytic, 2060, 2060*t*, 2061*b*, 2061*f*
characteristics of, 2270*t*
human granulocytic, 2060*t*, 2061, 2061*b*, 2062*f*
Japanese monocytic, 2060*t*
EIA. *See* Enzyme immunoassay
Eikenella corrodens, 2068
Eisenmenger complex, 350*b*
Eisenmenger syndrome, clinical manifestations of, 355, 355*b*
Ejaculatory failure, 1590, 1590*b*
Ejection, 225
Ejection fraction, 236
diminished, selection of ICD for, 389*f*
formula for, 236
preserved, heart failure with, 256, 256*t*
reduced, heart failure with, 255–256
three-dimensional echocardiography findings, 236, 237*f*
Elbow
disorders of, 1744–1745
injury of, occupational, 86*t*
surgical treatment of, 1828
Elderly. *See also* Older adults
epilepsies in, 2434*b*
gait disorder of, 2373*t*
non-Hodgkin lymphoma in, 1288
parainfluenza viral diseases in, 2196–2197
testosterone deficiency in, 1582, 1582*b*, 1582.*e1f*
urinary tract infection in, 1875*b*
Elective total hip, perioperative, medications for, 1830.*e1t*
Electrical alternans, 426, 428*f*
Electrical cells, 223
Electrical conduction
abnormalities, 231
of heart, 223–224, 228
Electrical injury, 699, 699*t*, 700*f*, 703
Electrical storm, treatment of, 338*b*
Electrocardiography (ECG), 228–235
abnormal, 231–233
in acute coronary syndrome, 372
in acute MI, 382, 382*f*
ambulatory, 235
approach to interpretation, 230–235, 231*t*
in arrhythmias, 306
in athletes, 234, 234*t*, 235*f*
automated computerized readings, 234
axes of electrical activation, 230, 230.*e1f*
axis deviation, 231, 231*t*, 232*f*
in chronic ischemic heart disease, 361–362
in COVID-19 disease, 234–235
exercise, 361
in heart failure, 258
leads, 230, 230.*e1f*
in narrow-complex tachycardia, 307*f*
normal, 228–231, 228*f*, 231, 231*f*
with pacemaker, 343*f*
resting, 358, 361*f*
screening, 235
standards, 228–229, 228*f*
waves, 228, 228*f*
in wide-complex tachycardia, 308*f*
Electroencephalography (EEG)
description of, 2374–2375, 2375*t*
for epilepsies, 2431
Electrolyte, intestinal transport of, 924, 924.*e1f*
Electromyography (EMG)
description of, 2375–2376, 2375*t*, 2399
muscle diseases on, 2581–2583
peripheral neuropathy evaluations, 2567
Electronic consultations, 2658
Electronic nicotine delivery systems (ENDS), 2352
Electrophysiologic procedures, 340–347
cardiac implantable electronic devices, 340
catheter ablation, 345, 345.*e1f*
of atrial fibrillation, 346
of supraventricular tachycardias, 346
of ventricular arrhythmias, 346
transthoracic cardioversion and defibrillation, 340
Electrophysiology, 298–302
in arrhythmia, 308–309
basic concepts of, 298–299
cardiac action potential, 299, 299*f*
impulse propagation, 300
ionic basis of, 299–300
molecular basis of, 300–301
calcium channels, 300.*e1f*, 301
gap junction channels, 300.*e1f*, 301
potassium channels, 300.*e1f*, 301
sodium channels, 300–301, 300.*e1f*
Elemental mercury, 103
Elephantiasis, 2177, 2177*f*
Eletriptan, 2380*t*
Elimination, enhanced, for acute poisoning, 691*b*
Elite controllers, 2294
Ellence. *See* Epirubicin
Elliptocyte
conditions associated with, 1072*t*
peripheral blood smear of, 1068*f*
Elliptocytosis, hereditary, peripheral blood smear of, 1068*f*
Eloxatin. *See* Oxaliplatin
Eltrombopag, 1175*b*, 2314*b*
characteristics of, 153
Elusive diarrhea, stool examination in, 931–932, 931*t*
Eluxadoline, for irritable bowel syndrome, 895*b*, 896*t*
Elvitegravir, 2301*t*
Embden-Meyerhof pathway
disorders of, 1099
of glycolysis, 1098–1099, 1098*f*
Embolic stroke, 2465, 2530
Embolism, superior mesenteric artery, 962, 962.*e1f*
Embolization
atheromatous, of renal arterial system, 801, 801*b*, 802*f*
for hepatocellular carcinoma, 1360*b*
Embryo, early, test of, 1603*b*
Embryopathic disorders, congenital, 1478
Emergency contraception, 1615
Emergency department care
for acute STEMI, 384*b*
psychiatric diseases in, 2679
Emergency Planning and Community Right-to-Know Act of 1986, 87
Emergency preparedness, in occupational and environmental medicine, 89
Emery-Dreifuss muscular dystrophy, 286, 302, 2584–2585
EMG. *See* Electromyography
Eminence-based medicine, 43
EML4. *See* Echinoderm microtubule-associated protein-like 4
EMLA. *See* Eutectic mixture of local anesthetic
Empagliflozin
for heart failure, 271*t*
for type 2 diabetes mellitus, 1541*t*
Empathic responses, in palliative care, 16
Emphysema, 548
congenital lobar, 565
severe, chest radiograph of, 523*f*
Empiric antibiotic therapy, for diarrhea and enteric infection, 1872*t*
Empiric chemotherapy, for cancer, 1241*b*
Empirical therapy
for community-acquired pneumonia, 1998*b*
for diffuse esophageal spasm, 909*b*
Empty sella, 1486, 1486*f*
Empyema, 625, 625*b*
subdural, 2528, 2528*b*
Emtricitabine, 2301*t*
Enalapril, 266*t*, 451*t*
Enalapril/HCTZ, 451*t*
Enalaprilat, for hypertensive emergencies, 460*t*
Enanthems, enteroviruses causing, 2259
Enasidenib (IDHIFA), 1215*t*
Enbrel. *See* Etanercept
Encephalitis, 2531–2536
acute, 2221, 2532
autoimmune, 2535
Encephalitis *(Continued)*
clinical manifestations of, 2536
diagnosis of, 2536
epidemiology of, 2535
neural antigen targets and, 2536*t*
pathobiology of, 2535
prognosis of, 2536
treatment of, 2536
brain stem, 2531
California, 2276*t*, 2283, 2284*b*
COVID, 2535, 2535*b*
definition of, 2531
diagnostic approach to, 2534*f*
eastern equine, 2276*t*, 2283, 2283*b*
enteroviruses causing, 2259, 2259*b*
granulomatous amebic, 2150
herpes simplex, 2247, 2247*b*, 2247*f*, 2520, 2532, 2532*t*, 2533*f*
Japanese, 66*t*, 83
limbic, 2532*t*
measles inclusion-body, 2221
mumps and, 2226*t*
Murray Valley, 2276*t*, 2283
neonatal, 2532*t*
parainfectious, 2532
rare viral causes of, 2535
relapsing, 2532*t*
specific viruses in, 2532–2535
St. Louis, 2276*t*, 2282, 2283*b*, 2520
subacute, 2221
tick-borne, 2276*t*, 2282, 2282*b*
toxoplasmic, 2136–2137, 2139, 2139*f*
Venezuelan equine, 2276*t*, 2283, 2283*b*
viral, 2531–2536
causes of, 2531*t*
cerebrospinal fluid findings in, 2374*t*
clinical manifestations of, 2531
diagnosis of, 2531–2532
differential diagnosis of, 2532
epidemiology of, 2531–2532
magnetic resonance imaging of, 2532
pathobiology of, 2531
prognosis for, 2532
rabies and, 2534, 2535*b*
spinal fluid analysis, 2532
tests for, 2532*t*
treatment of, 2532*b*
West Nile, 2532*t*
western equine, 2276*t*, 2283, 2283*b*
Encephalomyelitis
acute disseminated, 2509
description of, 2024–2025
paraneoplastic, 1238*t*
post-vaccination, 2238
Encephalopathy
bismuth, 101*t*, 102*t*, 105, 105*b*
cat-scratch disease and, 2001–2002
cirrhosis and, 1037–1038, 1038
coma and, 2438
diagnosis of, 1040–1042
hepatic, 986, 989*t*
hypertensive, 458
inborn errors of metabolism and, 1399
treatment of, 1040*b*
Enchondromatosis, 1669
Encorafenib, for melanoma, 1394*t*
End-diastolic pressure, 225
End-diastolic volume, 225
End-expiratory lung volume, 548
End-of-life care
for chronic kidney disease, 839*b*
in delirium, 2334*b*
for dementia, 2413
in heart failure, 278
for hepatobiliary cancers, 1360*b*
End-organ resistance, causes of, 1583*t*
End-plate development and maintenance, defects of, 2589*t*
End-stage heart failure, patients with, quality of life in, 12
End-stage liver disease, alcohol use disorders and, treatment of, 2357*b*
End-stage renal disease
in HIV/AIDS, 2313
renal transplantation for. *See* Renal transplantation
End-stage symptoms, treatment of, evidence for, 12
End-systolic volume, 225
Endemic countries, malaria in, 2118, 2122–2123

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Endemic mycoses, 2080–2087
blastomycosis as, 2080, 2080*t*
coccidioidomycosis as, 2083, 2084*t*, 2085*f*
histoplasmosis as, 2081–2083, 2081*t*
paracoccidioidomycosis as, 2086–2087
sporotrichosis as, 2085–2086
Endemic syphilis, 2021
Endobronchial sarcoidosis, 515*t*, 601
Endocannabinoids, 143
Endocardial diseases, 295
Endocarditis, 2001*t*, 2002, 2518
bacterial
definitive therapy of, 419*t*
subacute, 195
Candida, 2090
clinical manifestations of, 2002
continuing care for, 417*b*–422*b*
culture-negative, 416, 417*t*
diagnosis of, laboratory methods for, 2003*t*
echocardiographic findings, 242*t*
empiric therapy, 417*b*
empirical treatment of, 420*t*
in endoscopy, 876*t*
enterococci causing, 1921
epidemiology of, 2002
fungal, 416
glomerulonephritis with, 783–784
H. influenzae caused by, 1953–1954
indications for valve surgery in, 421*t*
infective, 413–423, 417*b*
Löffler fibroplastic endocarditis, 295
with negative blood cultures, 416
nonbacterial thrombotic, 296, 296*b*
pathobiology of, 2002
prophylaxis of, 355
prosthetic valve, 416, 416*t*
Q fever and, 2063
Staphylococcus aureus, 1903–1904
Stenotrophomonas maltophilia and, 1975
treatment of, 417*b*, 1921*b*, 1922*t*, 1970*b*, 2003*b*
zoonotic, 417*b*
Endocervix, 2241
Endocrine disease
approach to, 1472–1473
cardiomyopathy with, 288
genetic evaluation for, 1473
laboratory evaluation for, 1473
mechanisms of, 1474–1475, 1475*t*, 1476*t*
physical examination for, 1472, 1472*t*
in pregnancy, 1624–1625
response of, to treatment, 1473
surgical risks associated with, 2665
symptoms of, 1472, 1472*t*
thyroid disease, 2665
weight loss and, 860*t*
Endocrine dysfunction, after hematopoietic cell transplantation, 1211–1212
Endocrine insufficiency, chronic pancreatitis and, 975*b*
Endocrine system, age-related changes in, 121
Endocrinology, 1473–1476
Endocytosis, 730
Endodyogeny, 2136
Endofibrosis, iliac artery, 467, 468*b*
Endogenous acids, overproduction of, 757
Endogenous opioid peptides, 1478
Endoleaks, 438*b*, 438.*e*1*f*
Endometrial cancer, 1377
clinical manifestations of, 1378
epidemiology of, 1377
oral contraceptives and, 1615
pathobiology of, 1377, 1377*f*, 1377*t*
prevention of, 1379
prognosis for, 1379
risk factors for, 1377*t*
staging, 1378*t*
treatment of, 1378*b*
Endometrial clear cell carcinomas, 1378*b*
Endometriosis, 1596, 1596*b*, 1603*b*
Endometritis, 1949
Endometrium, menstrual cycle-related changes in, 1595–1596
Endomyocardial fibrosis, tropical, 296
Endophenotypes, 168
Endophthalmitis, 2604
Candida, 2091
fungal, 2606
Pseudomonas infections causing, 1969
Endoplasmic reticulum aminopeptidase gene, 1760
Endoscopic dilation, for peptic strictures, 905*b*
Endoscopic hemostasis, for upper gastrointestinal bleeding, 883*b*–884*b*
Endoscopic retrograde cholangiopancreatography (ERCP), 876–878
of acute pancreatitis, 970–971, 971
of benign biliary strictures, 1057*f*, 1058*f*
of chronic pancreatitis, 974, 975*f*
indications for, 878, 878*f*, 1000
instrument for, 876
preparation for, 876–878
procedure of, 878
Endoscopic therapy
for chronic pancreatitis, 975*b*
for obesity, 1467*b*
for pain, in chronic pancreatitis, 975*t*
for upper gastrointestinal bleeding, 883*b*, 883*t*
Endoscopic ultrasonography
of chronic pancreatitis, 974–975, 975*f*
of pancreatic cancer, 1355
Endoscopy
for chronic diarrhea, 930
Crohn disease on, 944, 944*f*
in emphysema, 632
gastritis on, 913*f*
gastrointestinal. *See* Gastrointestinal endoscopy
for gastrointestinal disease, 854
peptic ulcers on, 913, 913*f*, 914*f*
for pernicious anemia, 1123
Endosteal hyperostosis, 1666, 1667*b*
Endothelial injury, 671
Endothelin 1, 260.*e*1*t*
Endothelin B, 888
Endothelin receptor antagonists, for pulmonary hypertension, 496*b*
Endothelium, 670–671
Endovascular infections, *Pseudomonas* infections causing, 1969
Energy
balance, regulation of, 1464
depletion of, 1447*t*
requirements, estimation of, 1449
Energy expenditure, 1465
Energy intake, 1464–1465
Enfuvirtide, 2301*t*
Engineered cells, 150*t*, 151
Engraftment syndrome, after hematopoietic cell transplantation, 1211
Enhanced external counterpulsation, 364*b*
Enhertu. *See* Fam-trastuzumab deruxtecan-nxki
Enoxaparin, 387*t*, 503*t*
for acute coronary syndrome, 374*t*
for venous thromboembolism, 1624*t*
Entacapone, for Parkinson disease, 2487*t*
Entamoeba dispar infection, 2146
Entamoeba histolytica, 1024–1025, 1026*t*, 2146, 2147*f*
sexually transmitted anorectal diseases and, 983
in travelers, 1889.*e*1*t*, 1891*t*
Entecavir, for hepatitis B virus infections, 2181*t*, 2182–2183, 2182*t*
Enteral nutrition, 673*b*, 1449–1450
Enteral tube feeding, 1449, 1450*f*
Enteric fever
diagnosis of, 1978
differential diagnosis of, 1978
Salmonella causing, 1978
antimicrobial resistance of, 1977
asymptomatic intestinal carrier state of, 1977–1978
bacteremia caused by, 1978
carriers of, 1977–1978
clinical manifestations of, 1977–1978
contact with animals and their environments of, 1977
contact with infected persons of, 1977
contaminated animal products as source of, 1976–1977
in contaminated food and water, 1977
definition of, 1976–1980
diagnosis of, 1978
enterocolitis caused by, 1978
epidemiology of, 1976–1977
pathobiology of, 1977
pathogen description, 1976
prevention of, 1979
Enteric fever *(Continued)*
prognosis for, 1979–1980
treatment of, 1979*b*
in travelers, 1885–1886, 1889.*e*1*t*, 1890*t*
Enteric infection, 1868–1872
clinical manifestations of, 1869–1870, 1869*t*
complications and sequelae of, 1870*t*
definition of, 1868–1872
diagnosis of, 1870–1871
general approach, 1870
laboratory evaluation, 1870–1871, 1870*t*, 1871*f*
epidemiology of, 1868
etiology of, 1868, 1869*t*
pathobiology of, 1868–1869
prevention of, 1872
prognosis of, 1872, 1872*t*
treatment of, 1872*b*, 1872*t*
Enteric nervous system, 887
Enteric oxaluria, 803
Enteric protozoa, 2153–2157
amebiasis. *See* Amebiasis
coccidian enteritis, 2155
cryptosporidiosis. *See* Cryptosporidiosis
giardiasis. *See* Giardiasis
microsporidia, 2156
trichomoniasis, 2154–2155
Enteritis
Clostridium perfringens type C, 1926, 1926*b*
radiation, 940, 940*b*
in travelers, 1891*t*
Enteritis necroticans, 1926
Enteroaggregative *E. coli*, 1888*t*, 1961, 1962*t*
Enterobacterales, 1964–1967
carbapenem-resistant, 1965
clinical manifestations of, 1966
definition of, 1964–1967
diagnosis of, 1966
epidemiology of, 1964–1965
multidrug resistance, 1965, 1966*t*
pathobiology of, 1965–1966
pneumonia caused by, 1965
prevention of, 1967
prognosis for, 1967
treatment of, 1966*b*
Enterobiasis, 2172, 2172*b*
Enterobius vermicularis, 2169, 2170*t*
Enteroclysis, 951
Enterococcal infections, 1920–1924
bacteremia, 1921, 1922*t*
clinical manifestations of, 1920–1921
definition of, 1920–1924
diagnosis of, 1921
endocarditis caused by, 1921, 1922*t*
epidemiology of, 1920
intra-abdominal infections, 1921, 1921*b*
pathobiology of, 1920
pathogen associated with, 1920
primary prevention of, 1924
prognosis for, 1924
skin and soft tissue infections, 1921, 1921*b*
treatment of, 1921*b*, 1922*t*
urinary tract infections, 1920–1921, 1921*b*, 1922*t*
vancomycin-resistant enterococci
E. faecium causing, 1920
epidemiology, 1920
treatment, 1921*b*, 1922*t*
Enterococcus faecalis, 1920
Enterococcus faecium, 1864*t*, 1920
Enterocolitis, *Salmonella*, 1977
Enterocytozoon bieneusi, 2156
Enteroenteric fistulas, in Crohn disease, 945*b*
Enteroglucagon, pNEN secreting, 1561*t*
Enterohemorrhagic *E. coli*, 1961, 1962*t*
Enterohepatic circulations, 994
Enteroinvasive *E. coli*, 1961, 1962*t*
Enteropathic arthritis, 1763–1764
clinical manifestations of, 1764
diagnosis of, 1764
epidemiology of, 1763–1764, 1764*t*
pathobiology of, 1764
prognosis of, 1766
treatment of, 1765*b*
Enteropathogenic *E. coli*, 1961, 1962*t*
Enteropathy, congestive, 967
Enteropathy-type T-cell lymphoma, 1287
Enteroscopy, 878–879
Enterotoxigenic *E. coli*, 1868, 1888*t*, 1961, 1962*t*
Enterovesicular fistulas, in Crohn disease, 945*b*
Enteroviral meningitis, 2520–2521
Enteroviral myocarditis, 2257
Enteroviral pneumonia, 2260
Enteroviruses, 2256–2261
central nervous system infections caused by, 2258
classification of, 2256*t*
clinical manifestations of, 2257
clinical syndromes caused by, 2258–2261
definition of, 2256–2258
diagnosis of, 2257–2258
encephalitis caused by, 2259, 2259*b*
epidemiology of, 2257
ingestion of, 2257
meningitis caused by, 2259, 2259*b*, 2520
myopericarditis caused by, 2259, 2259*b*
myositis caused by, 2260
nonpolio, clinical manifestations of, 2258*t*
pathobiology of, 2257
pathogens that cause, 2256
prevention of, 2261
prognosis for, 2258*b*
respiratory tract syndromes caused by, 2260, 2260*b*
serotypes of, 2257*t*
in special populations, 2261
"summer cold" caused by, 2260
treatment of, 2258*b*
viral structure of, 2256
Enthesopathy, 1742
Entrectinib (Rozlytrek), 1215*t*
Entropion, 2601
Envenomation, 704, 2589*t*
acute coagulopathy associated with, 705*b*
antivenom for, 705*b*
arthropods, 710
centipedes, 711
lice, 711
millipedes, 711
mites, 710
scorpion, 710
ticks, 710
venomous, 710.*e*1*f*
clinical manifestations of, 704–705
diagnosis of, 704
epidemiology of, 704, 705*t*
first aid for, 705*b*
insects, 711–712
marine animals, 712–713, 712*b*
neurotoxic paralysis caused by, 707, 709.*e*1*t*
pathobiology of, 704
pressure bandage with immobilization for, 705*b*
signs of, 706*f*
snakebite. *See* Snakebites
spider bite. *See* Spider bites
syndromes of, 707–710
treatment of, 705*b*
Environmental carcinogenesis, 1321
Environmental carcinogens, 1321
Environmental contamination, health care-associated infections and, 1863
Environmental enteric dysfunction, 1444
Environmental enteropathy, enteric infections and, 1870*t*
Environmental head and neck squamous cell carcinoma, 1323, 1328
Environmental medicine
acute injuries in, 85, 86*t*
clinical implications of, 85–87
emergency preparedness and disaster management in, 89
hazards in, 88*t*
hierarchy of controls in, 87
history, salient features of, 1*f*–4*f*, 85
individual clinician in, role of, 89
medical surveillance in, 87
principles of, 84–89
regulatory environment of, 85
standards of, 87
syndromes in, 85, 86*t*
wellness and resiliency of, 87–89
work-related disability in, 85
worker's compensation in, 85
Environmental poisonings, diarrhea and, 925
Enzalutamide (Xtandi), 1215*t*
Enzootic cycle, of plague, 1988, 1990*f*

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Enzyme immunoassay (EIA)
for blastomycosis, 2081
for enteric infection, 1870*t*
for histoplasmosis, 2083
for paracoccidioidomycosis, 2087
Enzyme replacement therapy (ERT)
for Fabry disease, 1422*t*
for Gaucher disease, 1422*t*
for glycogen storage disease II, 1416*b*
for inborn errors of metabolism, 1401*b*
for mucopolysaccharidoses, 1424
Eosin-5-maleimide (EMA), 1095, 1096*f*
Eosinopenia, 1148
Eosinophil(s), 183, 538
acute inflammation and, 191–192
increased, 533
Eosinophilia, 1142
in mastocytosis, 1701
Eosinophilic cellulitis, 2737
Eosinophilic colitis, 1674
Eosinophilic esophagitis, 904*t*, 907, 907*b*, 907*f*, 907*t*
Eosinophilic fasciitis, 2737
Eosinophilic gastritis, 1674
Eosinophilic gastroenteritis, 940, 1674
Eosinophilic GI disorders, 1673*t*
Eosinophilic granuloma, 1155
Eosinophilic granulomatosis with polyangiitis, 573–574, 582, 1793*t*, 1797–1798, 1798*b*
Eosinophilic meningitis, 2523*t*, 2524
Eosinophilic myositis, 1788*t*
Eosinophilic pneumonia, chronic, 582
Eosinophilic pustular folliculitis, 2321, 2323*f*, 2723
Eosinophilic syndromes, 1162–1165
causes of, 1164*t*
clinical manifestations of, 1163
clinical subtypes of, 1163*t*
definitions of, 1162–1165
diagnosis of, 1163–1164
differential diagnosis of, 1163–1164, 1163*f*
epidemiology of, 1162
mutations in, 1163
pathobiology of, 1162–1163
prognosis of, 1165
treatment of, 1164*b*
Ependymoma, 1316
Ephedra alkaloids, central nervous system effects of, 685*t*
Ephedrine, *e*10*t*–*e*11*t*
Epidemic febrile polyarthritis, 2275*t*, 2279, 2279*b*
Epidemic influenza, 2199
Epidemic keratoconjunctivitis, 2205
Epidemic louse-borne typhus, 2059, 2059*b*
Epidemic typhus, 2055*t*
Epidermal depth, 2688*t*
Epidermal growth factor receptor (EGFR), 153
in bladder cancer, 1366
lung cancer and, 1330
Epidermal papules, 2729
Epidermis, 2686.*e*2*f*
Epidermodysplasia verruciformis, 2242
Epidermoid carcinomas, 1347
Epidermoid cyst, 2689*t*
Epidermolysis bullosa, 2621*t*
Epidermolysis bullosa acquisita, 2718, 2718*b*
Epidermolytic ichthyosis, 3*t*–4*t*
Epididymitis, *Chlamydia trachomatis* causing, 2011, 2012*b*
Epidural abscess, spinal, 2527, 2527*f*, 2527.*e*1*t*, 2528*b*
Epidural anesthesia, 2671
Epidural hematoma, 2391
Epigastric hernia, 952*b*–953*b*
Epigastric pain, 899*t*, 917, 917*t*
Epigenetics
for cancer, 1232*b*
of lung cancer, 1330
rheumatoid arthritis and, 1750
Epiglottitis, 2649*t*, 2651
description of, 2197*f*
distinguishing features of, 515*t*
H. influenzae caused by, 1953
Epilepsy, 2425–2436, 2547, 2547*b*
activity restrictions in, 2434*b*
childhood absence, 2432
definition of, 2425
diagnostic investigations of, 2431
in elderly, 2434*b*
electroencephalogram, 2431
Epilepsy *(Continued)*
epidemiology of, 2425–2427
with generalized tonic-clonic seizures alone, 2433
genetic testing for, 2431
genetics of, 2426–2427
headache associated with, 2425
idiopathic generalized, 2431–2433
imaging studies for, 2431, 2432*f*
incidence of, 2425
juvenile myoclonic, 2433
magnetoencephalography for, 2431
mesial temporal lobe, with hippocampal sclerosis, 2433
mortality risks, 2436
pathobiology of, 2426–2427
pathogenesis of, 2426
in pregnancy, 1619*t*
prevalence of, 2425
prognosis of, 2436
progressive myoclonus, 2433
reflex, 2433
risk factors for, 2425–2426
seizures *versus*, 2425
surgical treatment of, 2434*b*
syndromes, 2431–2433, 2431.*e*1*t*
temporal lobe, 2426*f*, 2646
treatment of, 2434*b*
Epinephrine
for pulseless electrical activity, 313*b*, 316*f*
for septic shock, 671
for shock, 664*t*
synthesis of, 1529
Epiphora, 2599–2600
Epiphrenic diverticula, 909–910, 910*f*
Epirubicin (Ellence), 1215*t*
Episcleritis, 2611
Epistaxis, 2635, 2635*f*–2636*f*, 2636*b*, 2636*f*
Epithelial cell apoptosis, 671
Epithelial cell infections, 1879*t*, 1881–1882
Epithelial sodium channel
activating mutations of, 749
description of, 746
Epitope spreading, in rheumatoid arthritis, 1750
Epizootic cycle, of plague, 1988, 1990*f*
Eplerenone, 451*t*
for Gitelman syndrome, 817*b*
for heart failure, 270*t*
for hypervolemia, 736*b*, 737*t*
Epley maneuver, 2645*f*
Epogen. *See* Erythropoietin
Eprosartan, 451*t*
Eprosartan/HCTZ, 451*t*
Epsilon-sarcoglycan gene, 2493
Epsilon waves, 338*f*
Epstein-Barr nuclear antigens (EBNAs), 2253
Epstein-Barr virus (EBV) infection, 1289, 2253–2256, 2650
acute infection of, 2253–2255
acute leukemias and, 1259
associated neoplasms with, 2256
Burkitt lymphoma and, 2255
central nervous system lymphoma and, 2255
chronic active, 2256
clinical manifestations of, 2253–2254, 2254*f*
clinical syndromes of, 2255–2256, 2256*b*
complications of, 2254
definition of, 2253
diagnosis of, 2254
epidemiology of, 2253
head and neck cancer and, 1320–1321
histiocytoses and, 2256
Hodgkin lymphoma and, 2255
lymphomatoid granulomatosis and, 2256
nasopharyngeal carcinoma and, 2256
non-Hodgkin lymphoma caused by, 1278–1279
oral hairy leukoplakia and, 2256
pathobiology of, 2253
post-transplant lymphoproliferative disorder and, 2255
prognosis of, 2255
related nasopharyngeal carcinoma, 1322
renal transplantation and, 847
treatment and prevention of, 2254*b*
X-linked lymphoproliferative syndrome and, 2254
Epstein-Barr virus pharyngitis, characteristics of, 2270*t*
Eptifibatide, 387*t*, 506*t*, 508
Epworth Sleepiness Scale, 2445, 2448*t*
Equalization, 522
Equilibrium, 2641–2647
Equivalent dose, 91
Eravacycline, 1845*t*, 1895*t*
Erbitux. *See* Cetuximab
ERCP. *See* Endoscopic retrograde cholangiopancreatography
Erdafitinib (Balversa), 1215*t*
Erdheim-Chester disease, 1155*f*, 1156–1157, 1157*b*
Erectile dysfunction, 1587–1589, 1589, 1589*t*, 1590*f*
Erectile physiology, 1581, 1581.*e*1*f*
Ergocalciferol, 1650*t*
Eribulin mesylate (Halaven), 1215*t*
Erivedge. *See* Vismodegib
Erleada. *See* Apalutamide
Erlenmeyer flask deformity, 1667
Erlotinib, 1251*t*
for pancreatic cancer, 1356*b*–1357*b*
Erosions, 913, 2687.*e*4*t*
Erosive gastritis, 913*f*
Errors, 45
ERT. *See* Enzyme replacement therapy
Ertapenem
dosage of, 1895*t*
for pneumonia, 616*t*
for pyelonephritis and urosepsis, 1877*t*
for pyogenic liver abscess, 1023*b*
Eructation, 858
ERV. *See* Expiratory reserve volume
Ervebo, 84
Erysipelas, 1903, 1915
Erysipeloid, 1936–1937, 1936*b*, 1936*f*
Erysipelothrix rhusiopathiae, 1936, 1936*b*, 1936*f*
Erythema, necrolytic migratory, 1564*f*
Erythema ab igne, 471*b*–472*b*, 472, 472*b*, 472*f*, 472.*e*1*f*
Erythema annulare centrifugum, 2711
Erythema chronicum migrans, 2711
Erythema elevatum diutinum, 2735
Erythema gyratum repens, 2711
Erythema induratum, 2735, 2736*f*
Erythema infectiosum, 2234, 2234*f*
Erythema marginatum, 2725, 2726*f*
Erythema migrans
clinical manifestations of, 2023–2025
differential diagnosis of, 2025
early localized infection associated with, 2023–2024, 2024*t*
illustration of, 2023*f*
laboratory tests for, 2025
single lesion, 2023–2024
treatment of, 2026*b*
Erythema multiforme, 2719, 2719*b*, 2719*f*, 2727–2728
description of, 2621*t*, 2691*t*
in parapoxvirus, 2239
prognosis of, 2728
treatment of, 2728*b*
Erythema nodosum, 601, 2688*t*, 2735, 2736*f*, 2736*t*
Erythema nodosum leprosum, 2050–2051, 2051.*e*1*f*
Erythema nodosum necroticans, 2050
Erythematotelangiectatic rosacea, 2722
Erythematous oral candidiasis, 2623, 2624*f*
Erythematous rashes, occupational and environmental, 87
Erythroblastosis fetalis, immunization for, 65*t*
Erythrocyte
disorders of, 724–725
dysmorphic, 723*f*
isomorphic, 723*f*
membrane of, 1093–1097, 1093*f*
disorders of, 1094–1097
function of, 1093–1094
lipids in, 1093–1094
proteins in, 1093–1094
metabolism of, 1098–1102
disorders of, 1099–1102
normal, 1098–1099
Erythrocyte count (RBC count), *e*8*t*–*e*9*t*
Erythrocyte sedimentation rate (ESR), 728, 1712
Westergren, *e*8*t*–*e*9*t*
Erythrocytosis, 355.*e*1*f*, 1134–1135, 1135*t*–1136*t*, 1135*t*, 1136*f*, 1136*t*
Erythrodermic mycosis fungoides, 2709–2710
Erythrodermic psoriasis, 2705–2706
Erythrogenic toxins, 1914
Erythromelalgia, 471, 471*f*, 471*t*, 480, 1133, 1133*f*
Erythromycin
for bacillary angiomatosis, 2003*b*
for bronchiectasis, 561*b*
for chancroid, 1951*b*
for *Chlamydia trachomatis*, 2012*b*
for cholera, 1956*b*, 1957*t*
dosage of, 1895*t*
for eye infection, 2605*t*
for intestinal pseudo-obstruction, 889*b*
for pertussis, 1995*b*
Erythrophagocytosis, conditions associated with, 1072*t*
Erythroplakia, 1321, 2623
Erythropoiesis, 2234
Erythropoietic porphyria, 1428
Erythropoietic protoporphyria, 1428*t*, 1430, 1433*f*, 2705
Erythropoietin (Epogen, Procrit), *e*1*t*–*e*8*t*, 1064–1065, 1215*t*
anemia and, 1075
for orthostatic hypotension, 2559*t*
pNEN secreting, 1561*t*
Escherichia coli, 1833
antimicrobial resistance of, 1864*t*
clinical manifestations of, 1963
definition of, 1960–1964
diagnosis of, 1963–1964
differential diagnosis of, 1963–1964
diffusely adherent, 1961, 1962*t*
enteric infections, 1960–1964, 1962*t*
enteroaggregative, 1961, 1962*t*
enterohemorrhagic, 1961, 1962*t*
enteroinvasive, 1961, 1962*t*
enteropathogenic, 1961, 1962*t*
enterotoxigenic, 1961, 1962*t*
epidemiology of, 1961
non-enterohemorrhagic, 1962*t*
pathobiology of, 1961–1963
pathogenesis of, 1961–1962
prevention of, 1964
prognosis for, 1964
septic bursitis caused by, 1804
shigatoxigenic, 1962*t*
traveler's diarrhea caused by, 1961
treatment of, 1963*b*
urinary tract infections caused by, 1873, 1965
Escitalopram
for depression, 2340*t*
for hot flashes, 1631*t*
Escobar syndrome, 2589*t*
Eslicarbazepine, for seizures, 2434*t*
Esmolol
for electrical storm, 338*b*
for hypertensive emergencies, 460*t*
Esomeprazole
for peptic ulcer disease, 921
for rheumatoid arthritis, 1756*t*
Esophageal adenocarcinoma, 1338
clinical manifestations of, 1339
diagnosis of, 1339
epidemiology of, 1338–1339
laboratory studies of, 1339
pathobiology of, 1339
physical examination for, 1339
prevention of, 1339
prognosis of, 1339
risk factors for, 1338–1339
symptoms and signs of, 1339
treatment for, 1339*b*
Esophageal atresia, 913
Esophageal Crohn disease, 943
Esophageal disease, 901–913
amyloidosis in, 911
anatomy and physiology of, normal, 901–902
bacterial esophagitis in, 912
Barrett esophagus as. *See* Barrett esophagus
candidiasis, 911, 912*f*
congenital abnormalities, 913
cricopharyngeal bars in, 909
cytomegalovirus in, 912
drug therapy for, 904*t*
esophageal diverticula, 909–910, 909*f*–910*f*
esophageal emergencies, 912–913
esophageal motor disorders as, 908–909
esophagitis as. *See* Esophagitis
gastroesophageal reflux disease as. *See* Gastroesophageal reflux disease
herpes simplex virus in, 911

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Esophageal disease *(Continued)*
hiatal hernia in, 910
human papillomavirus in, 912
peptic strictures as, 905
rings and webs, 910, 910*f*
scleroderma in, 911
skin disorders and, 911
symptoms of, 902
in systemic sclerosis, 1780
Esophageal diverticula, 909, 909*f*, 910*f*
Esophageal emergencies, 912
Esophageal fistula, 912–913
Esophageal functional testing, 901–902
Esophageal manometry, 904–905
Esophageal motor disorders, 908
achalasia in, 908
diffuse esophageal spasm in, 909
oropharyngeal dysfunction in, 908
Esophageal neoplasms, 1337–1339
adenocarcinoma, 1338
definition of, 1337
squamous cell carcinoma, 1337–1338
Esophageal reflux, 211*t*
Esophageal regurgitation, 852*t*, 865
Esophageal squamous cell carcinoma, 1337
clinical manifestations of, 1338
diagnosis of, 1338
epidemiology of, 1337–1338
laboratory studies for, 1338
medical therapy for, 1338*b*
pathobiology of, 1338
physical examination for, 1338
prognosis of, 1338
risk factors for, 1337–1338, 1337*t*
surgical therapy for, 1338*b*
symptoms and signs of, 1338
treatment for, 1338*b*
Esophageal varices, 912
endoscopy for, 881
Esophageal webs, 910, 910*f*
Esophagitis, 907–908
bacterial, 912
Candida, 2090
caustic injury, 907
clinical manifestations and diagnosis of, 907, 907*f*, 907*t*
eosinophilic, 907
pill-induced, 907, 907*t*
treatment and prognosis of, 904*t*, 907*b*
Esophagogastric junction outflow obstruction, 909
Esophagus, 901
alcohol use disorders and, 2355*t*
motor functions of, 901
Esotropia, 2598
ESR. *See* Erythrocyte sedimentation rate
Essential mixed cryoglobulinemia, 1716
Essential thrombocythemia, 1130–1139
anagrelide for, 1135*b*
aspirin for, 1135*b*
clinical manifestations of, 1133, 1133*f*
cytoreductive therapy for, 1135*b*
definition of, 1130–1139, 1130*t*
epidemiology of, 1130
erythromelalgia, 1133, 1133*f*
hydroxyurea for, 1135*b*
interferons for, 1135*b*
neutrophilia and, 1142
pathobiology of, 1130–1131, 1131*f*
ruxolitinib for, 1135*b*
treatment for, 1135*b*, 1136*t*
Essential tremor, 2490
Estimated glomerular filtration rate (eGFR), evaluation of, 837–839, 839*t*
Estradiol, 1581
for genitourinary syndrome of menopause, 1632*t*
by immunoassay, *e*1*t*–*e*8*t*
for transgender women, 1579*t*
Estradiol vaginal inserts (Imvexxy), for genitourinary syndrome of menopause, 1632*t*
Estradiol valerate, for transgender women, 1579*t*
Estrogen
cancer and, 1245
for osteoporosis, 1643*b*
for transgender women, 1578*b*, 1579*t*
Estrogen receptors, 1629
Estrogen replacement, hypertension associated with, 456
Eszopiclone, 2344*t*, 2452*t*
Etanercept (Enbrel)
description of, 150–151, 151*t*
for rheumatoid arthritis, 1756*t*
for total knee arthroplasty, 1830.*e*1*t*
Eteplirsen, 2583*b*
Ethacrynic acid, 451*t*
Ethambutol
dosage of, 1895*t*
for nontuberculous mycobacterial disease, 2046*t*
ocular effects of, 2614
for tuberculosis, 2040*b*, 2041*t*–2043*t*, 2041*t*, 2042*t*, 2043*t*
Ethanol, *e*10*t*–*e*11*t*
excess, 1072*t*
metabolism of, 2353*f*, 2354
toxicity, 690*t*
Ethanolamine. *See* Amino alkyl ether
Ethnic disparities, in health outcomes, 17–18
Ethnicity
age-adjusted drug overdose death rates by, 18*t*, 19*f*
arterial hypertension and, 444–445
Ethosuximide, *e*10*t*–*e*11*t*, 2434*t*
Ethylene glycol, 759–760
central nervous system effects of, 685*t*
toxicity, 686*t*, 690*t*, 698*t*
Ethylenediamine, 2700*t*
Ethylenediaminetetraacetic acid (EDTA), 1166–1167
Etodolac
for chronic pain, 138*t*
for rheumatoid arthritis, 1756*t*
Etopophos. *See* Etoposide phosphate
Etoposide (Vespid), 1215*t*
Etoposide phosphate (Etopophos), 1215*t*
Etoricoxib, for chronic pain, 138*t*
Etravirine, 2301*t*
Eulexin. *See* Flutamide
Eumycetoma, 2110
Europe
arterial hypertension in, 445, 445.*e*1*f*
Chagas disease in, 2126
European LeukemiaNet Cytogenetic/Molecular Risk Stratification of AML, 1261*t*
Eutectic mixture of local anesthetic (EMLA), for skin diseases, 2699
Euthanasia, 8, 8*t*
definition of, 8, 8*t*
empirical data for, 8
history of, 8
justification of, 8
practical considerations for, 9
safeguards, 8
Euthyroid sick syndrome, 1497
EV-A71, 2258
EV-D68, 2258
Evacuation disorder, constipation *versus*, 890, 890*t*
Event monitors, 307–308
Everolimus (Afinitor), *e*10*t*–*e*11*t*, 1215*t*
for liver transplantation, 1048*t*
in renal transplantation, 845*t*
Evidence-based medicine, 2
Evidence generation, 168–169, 168*t*
Evinacumab, 1413
Evoked potential tests
for multiple sclerosis, 2504
neurologic disease evaluations, 2376
Ewing sarcoma, 1388, 1388*b*
Ex vivo gene therapy, 175
Exanthems, 2712, 2712*t*
enteroviruses causing, 2259
macular, 2712–2716
papular, 2712
Excessive daytime sleepiness, 2444–2445, 2447*f*
Excitation-contraction coupling, 224.*e*1*f*
Excoriation, 2687.*e*4*t*
Executive cognitive dysfunction, 2410–2411, 2411*f*
Exemestane (Aromasin), 1215*t*
Exenatide, for type 2 diabetes mellitus, 1541*t*
Exercise
for atherosclerotic PAD, 464*b*
for congenital heart disease, 355, 355.*e*2*t*
definition of, 61
for heart failure, 265*b*, 275*t*
for osteoarthritis, 1741*t*
for pain, 136*b*
responses to stressors, 226
Exercise capacity, 261
Exercise electrocardiography, in angina pectoris, 361
Exercise-induced asthma, 541*b*
Exercise-induced bronchoconstriction, 538
Exercise-induced bronchospasm, 681
Exercise testing
in arrhythmia, 309
for hypoglycemia, 1557
for interstitial lung disease, 574
protocols, 212*t*
Exertional heat injury, 678.*e*2*f*
Exertional heatstroke, 678.*e*1*f*, 679*t*
Exertional rhabdomyolysis, 714, 715*t*
Exhaled nitric oxide, in asthma, 539–540
Exocrine insufficiency, chronic pancreatitis and, 975*b*
Exocytosis, 730
Exogenous hormones, cancer and, 1246
Exome sequencing, for inborn errors of metabolism, 1400
Exophthalmos, 2600, 2600*f*
Exotropia, 2598
Expanded volume, metabolic alkalosis with, 763–764
Expiratory flow, in pulmonary function tests, 528*t*
Expiratory reserve volume (ERV), 530
Exploding head syndrome, 2453*t*
Exposure Survey, 85, 85.*e*1*f*
Expressed genome, 168
complex multimarker genomic tests, for disease diagnosis and prognosis, 168
metabolic and protein profiling, 168
Expulsive therapy, for nephrolithiasis, 805*b*–806*b*
Exserohilum rostratum, 1865
Extavia. *See* Interferon Beta1*b*
Extended-spectrum β-lactamase-producing organisms, treatment of, 1966*b*
Extended-spectrum β-lactamases, 1966
Extensive urticaria, 1688*f*
External carotid arteries, 2455
External genitalia
abnormal differentiation of, 1572*f*
development of, 1569
Extra-axial brain tumors, 1313*t*
Extra-genital lesions, granuloma inguinale and, 2004
Extracellular fluid volume
control of, 733–734, 733*f*
depletion of, 738–739
disorders of, 733–736
pathobiology of, 733–735
regulation of, 730, 730.*e*1*f*
Extracellular pH, secretion, control of, 732
Extracellular vesicles, 172
Extracellular volume depletion, metabolic alkalosis with, 763
Extracorporeal photochemotherapy (photopheresis), 2701
Extracorporeal removal, for acute poisoning, 691*b*
Extracorporeal ultrafiltration, 736*b*
Extracranial carotid artery stenosis, 2464
Extradural brain tumors, 1318, 1318*b*
Extragenital lesions, chancroid and, 1951
Extraglandular disease, Sjögren syndrome and, 1785, 1786*b*–1787*b*
Extragonadal germ cell cancer syndrome, treatment of, 1241*b*
Extraintestinal infections, 2148
Extramedullary hematopoiesis, 527
pregnancy and, 1135*b*
in primary myelofibrosis, 1133
radiation therapy for, 1135*b*
Extramedullary plasmacytoma, 1303
Extranodal NK/T-cell lymphoma, 1287
Extrapulmonary aspergillosis, 2094
Extrapulmonary infections, legionellosis and, 1998
Extrapulmonary tuberculosis, 2035–2038, 2040, 2040*b*
Extrapyramidal symptoms, psychotropic medications and, 2678*t*
Extremities
due to heart failure, 258
for signs of cardiovascular disease, 215–216, 217*f*
Extrinsic allergic alveolitis, aspergillosis and, 2095
Extrinsic neuropathic disorders, 888
Extrinsic pathway, 1165
Exudates
characteristics of, 623–624
pleural
causes of, 626–627
fluid characteristics of, 625, 625*b*, 625*t*
Eye(s)
acute poisoning and, 683
anatomy of, 2597*f*
anterior chamber of, 2596
anterior segment of, 2596
ciliary body of, 2596
cornea of, 2596
crystalline lens of, 2596
examination of, 30
foreign body sensation in, 2599, 2600*f*
inflamed, 2599, 2599*t*
inflammatory disorders of, 2604
movements, examination of, 2618
onchocerciasis manifestations of, 2178
pain of, 2598–2599, 2599*t*
retina of, 2596
sclera of, 2596
syphilis involvement of, 2017
vision loss caused by, 2615
vitreous of, 2596
Eye disorders
Acanthamoeba keratitis, 2606
age-related macular degeneration, 2608, 2609*f*
autoimmune, 2611
in bacterial endocarditis, 2609, 2610*f*
cellulitis, 2604, 2605*f*
central retinal artery occlusion, 2610, 2610*f*
central retinal vein occlusion, 2610–2611, 2610*f*
choroidal dystrophy, 2611
conjunctivitis. *See* Conjunctivitis
corneal stromal dystrophy, 2611
cytomegalovirus retinitis, 2606
in diabetes mellitus, 2609, 2609*f*
endophthalmitis, 2604
fungal endophthalmitis, 2606
glaucoma. *See* Glaucoma
hemangioma of eyelid, 2612
herpes simplex keratitis, 2605, 2606*f*
herpes zoster ophthalmicus, 2605–2606
in hypertension, 2609, 2610*f*
idiopathic inflammatory, 2611
infectious, 2604–2606
keratoconjunctivitis sicca, 2611
lymphoma, 2613
pseudomonal keratitis, 2606
retinitis pigmentosa, 2612, 2612*f*
retinoblastoma, 2612
retinopathy of prematurity, 2612
in sarcoidosis, 601–602, 604*t*
scleritis, 2611
toxoplasmic retinitis, 2606
tuberculosis involvement, 2606
tumors, 2612–2613
uveitis, 2604
vascular abnormalities, 2610–2611, 2610*f*
Eye infections, *Pseudomonas* infections causing, 1969, 1970*b*
Eye injury, occupational, 85, 86*t*
Eyelids, 2596
abnormalities, 2601–2602
basal cell carcinoma of, 2602, 2602.*e*1*f*
benign neoplasms of, 2602
blepharitis of, 2601, 2601*f*
chalazion of, 2601, 2601*f*
ectropion of, 2601, 2601*f*
entropion of, 2601
hemangioma of, 2612
hordeolum of, 2601, 2601*f*
sebaceous carcinoma, 2602
squamous cell carcinoma of, 2602
twitching, 2600
Ezetimibe, 1413

F

Fabry disease, 787, 1398*t*, 1421–1423, 1825, 2560
cardiac involvement in, 282.*e*1*f*
clinical manifestations of, 1421*f*, 1422
definition of, 1421
diagnosis of, 1422–1423, 1422*t*
enzyme-specific treatments for, 1420*t*
epidemiology of, 1421

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Fabry disease *(Continued)*
female carriers of, 1422
pathobiology of, 1421–1422
stroke caused by, 2470.*e1t*
treatment of, 1423*b*
Face, examination of, 29
Facial injuries, in intimate partner violence, 1633–1634
Facial paralysis, 2579
Facioscapulohumeral dystrophy, 2368.*e3f*
Facioscapulohumeral muscular dystrophy, 2584, 2584*b*
Factitial dermatitis (dermatitis artefacta), 2687.*e4t*
Factitious diarrhea, 940
Factitious disorder, 2347, 2347*t*
Factor H, 200*t*
Factor I, description of, 200*t*
Factor II deficiency, 1189*t*, 1193, 1193*b*
Factor V deficiency, 1189*t*, 1193
Factor V Leiden, 476, 476*t*
Factor VII, 1000
Factor VII deficiency, 1189*t*, 1193
Factor VIII deficiency, 1189*t*
Factor IX deficiency, 1189*t*
Factor IX Padua, 476
Factor X deficiency, 1189*t*, 1193, 1193*b*
Factor XI deficiency, 1189*t*, 1191
clinical manifestations of, 1191
diagnosis of, 1191
epidemiology of, 1191
pathobiology of, 1191
treatment of, 1192*b*
Factor XI gene *(FXI)*, 1191
Factor XII deficiency, 1189*t*, 1192, 1192*b*, 1193*b*
Factor XIII deficiency, 1189*t*
Fainting. *See* Heat syncope
Fallopian tube cancer, 1379
clinical manifestations of, 1379
definition of, 1379
diagnosis of, 1379
epidemiology of, 1379, 1379*t*
pathobiology of, 1379
prevention of, 1380
prognosis for, 1381, 1381*t*
risk factors for, 1379*t*
treatment of, 1380*b*, 1380*t*, 1381*t*
Falls
frailty and, 123
multifactorial interventions for, 116
in older adults, 114
risk of, geriatric assessment, 118
Fam-trastuzumab deruxtecan-nxki (Enhertu), 1215*t*
Famciclovir
for herpes simplex virus infections, 2246
for herpesvirus infections, 2186, 2187*t*
for skin diseases, 2699
for zoster, 2249*b*
Familial adenomatous polyposis, 1250*t*, 1344, 1347*t*, 1348, 1348*f*
Familial amyloid polyneuropathy, 2560
description of, 2570–2571, 2570*b*
Familial amyloidosis, 1306*t*, 1309
clinical manifestations and diagnosis of, 1309
treatment and prognosis of, 1309*b*
Familial benign hypocalciuric hypercalcemia, 1658
Familial cancer syndromes, 1250*t*
Familial cholestasis syndromes, 997, 997.*e1t*
Familial cold autoinflammatory syndrome (FCAS), 1731*t*, 1733*t*
Familial cold urticaria, neutrophilia and, 1142
Familial colorectal cancer syndromes, 1347, 1347*t*
Familial combined hypercholesterolemia, 1409
Familial dysbetalipoproteinemia, 1409
Familial gastric carcinoma, 1250*t*
Familial hemophagocytic lymphohistiocytosis, 1159–1162, 1160*t*–1161*t*, 1161*b*–1162*b*, 1161*f*, 1161*t*, 1684*t*
Familial hypercholesterolemia, 160, 1398*t*, 1408
cascade screening for, 1409
clinical manifestations of, 1408
combined, 1409
diagnosis of, 1409
epidemiology of, 1408
pathobiology of, 1408
in pregnancy, 1409*b*
prognosis for, 1409
screening for, 1409
treatment of, 1409*b*, 1409*t*
Familial hypereosinophilic syndrome, 1162, 1163*t*
Familial hypokalemic periodic paralysis, 751–752
Familial hypomagnesemia with hypercalciuria, 816*t*
Familial intrahepatic cholestasis, 997
Familial isolated pituitary adenoma syndrome, 1487*t*
Familial juvenile polyposis, 1348
Familial keratosis lichenoides chronica, 1731*t*
Familial malignant melanoma, 1250*t*
Familial Mediterranean fever (FMF), 1730–1732, 1731*t*
clinical characteristics of, 1733*t*
clinical manifestations of, 1730–1732
definition of, 1730
diagnosis of, 1732
epidemiology of, 1730
pathobiology, 1730
prognosis for, 1732
treatment of, 1732*b*
Familial paraganglioma, 1530
Familial primary hyperparathyroidism, 1657
Familial pulmonary fibrosis, 570
Familial Wilms tumor, 1250*t*
Families
definition of, 12
in heart failure management, 275*t*
palliative care for, 12
Family history, 28, 2660
cardiovascular disease and, 220
Family screening, for dilated cardiomyopathy, 287*b*
Family testing, 2424–2425
Fanconi anemia, 1127.*e1t*, 1129, 1129*b*, 1145, 1250*t*, 1253
Fanconi-Bickel syndrome, 816*t*
Fanconi syndrome, 749*t*
in chronic interstitial nephritis, 793
Far-UVC radiation, 95
Farydak. *See* Panobinostat
Fascicular branch blocks, 231, 231*t*, 232*f*
Fasciculations, 2581*t*
Fasciola spp., 1026*t*
description of, 2166*t*
in travelers, 1889.*e1t*
Fascioliasis, 2165, 2168, 2168*b*
in travelers, 1891*t*
Fasciolopsis buski, 2166*t*
Faslodex. *See* Fulvestrant
FAST. *See* Focused abdominal sonography in trauma
Fasting
for hypoglycemia, 1556–1557, 1556*t*
rate of glucose during, 1552
Fasting glucose concentration, 1536*t*
Fasting hypertriglyceridemia, 1466
Fat
dietary guidelines for, 57.*e3t*
fecal, *e1t*–*e8t*
Fat atrophy, 2687.*e4t*
Fat embolism
in joint diseases, 1830
stroke caused by, 2472
Fat embolism syndrome, 491, 491.*e1f*
Fat-soluble vitamins, 1450–1451, 1451, 1453*t*
Fatal familial insomnia, 2423
Fatigue, 256
liver disease and, 986
management of, approaches to, 13*t*
multiple sclerosis and, 2501
neurologic diseases that cause, 2372
Fatty acid metabolism disorders, 2586, 2586*b*
Fatty acid oxidation, disorders of, 1404, 1404*b*, 1552*t*, 1555
Fatty acids
nonesterified, *e1t*–*e8t*
in parenteral nutrition, 1450
Favipiravir, 2202*b*, 2203*t*, 2269*b*
FBN1, mutations in, 1725
Fc receptors (FcRs), 184
FCAS. *See* Familial cold autoinflammatory syndrome
FcεR-bearing effectors, 193–194
FDA. *See* Food and Drug Administration
FDA Biomarkers, 169.*e1t*
18-FDG. *See* 18-Fluorine deoxyglucose
FDG-PET. *See* Fluorodeoxyglucose positron emission tomography
FDPs. *See* Fibrin degradation products
Febrile illnesses, 1851*b*
Febrile neutropenia, 1968–1969
syndrome of, 1855–1861
Febrile neutrophilic dermatosis. *See* Sweet syndrome
Febrile nonhemolytic transfusion reaction, 1202
Febrile seizures, prognosis after, 2436
Febrile syndromes, acute, 590, 591*t*
Fecal elastase-1 test, for malabsorption, 931*t*
Fecal incontinence, 865, 981
algorithm for, 981*f*
clinical manifestations and diagnosis of, 981
epidemiology and pathobiology of, 981
in older adults, 118
treatment for, 981*b*
Fecal microbiota transplantation, for *Clostridioides difficile*, 1925*b*
Fecal occult blood testing, 1352
Fecal transplantation, 1840
Fedratinib, 153*t*
Feeding, rate of glucose during, 1552
Feet, rheumatoid arthritis of, 1751
FEF. *See* Forced expiratory flow
Felodipine, 367*t*, 451*t*
Felty syndrome, 1146, 1152, 1754, 1755*b*
Female breast, development of, 110.*e1f*
Female condom, 1612
Female genital discharge, 1879*t*, 1882–1883
Femara. *See* Letrozole
Fenoldopam, for hypertensive emergencies, 460*t*
Fentanyl, 139*t*. *See also* Opioids
Fermentative *Corynebacteria*, 1934
Ferning, 1595
Ferric carboxymaltose, for iron deficiency anemia, 1085*t*
Ferric derisomaltose, for iron deficiency anemia, 1085*t*
Ferritin, *e1t*–*e8t*
Ferrous gluconate, for iron deficiency anemia, 1085*t*
Ferrous sulfate, for iron deficiency anemia, 1084*b*–1085*b*, 1085*t*
Fertility
in female, 1602
preservation of, in transgender individual, 1580
Fertility-awareness contraceptive method, 1611
Ferumoxytol, for iron deficiency anemia, 1085*t*
Fesoterodine, 824*t*
Fetal alcohol syndrome, 2545
Fetal hemoglobin, hereditary persistence of, 1106, 1107*f*
Fetal testicular regression syndrome, 1574
Fetal varicella syndrome, 2248
α-Fetoprotein (AFP), *e1t*–*e8t*
Fetor hepaticus, 1038
Fetus, maternal conditions affecting, 1573
FEV. *See* Forced expiratory volume
Fever
acute, 2694*t*
antibiotic therapy for, 1858*f*–1859*f*, 1859*f*
approach to, in normal host, 1845–1851
in cancer, 1239, 1240*b*
caused by amphotericin B, 2078
clinical manifestations of, 1846
in compromised host, 1853, 1854*b*
definition of, 1845–1846
diagnosis of, 1846–1847
drug, 1846
epidemiology of, 1846
in hemophagocytic lymphohistiocytosis, 1160
hepatosplenomegaly and, 1849
hospital-associated, 1846*t*
in immunocompromised host, 1851–1862
clinical manifestations of, 1854
definition of, 1851
diagnosis of, 1854
general concepts of, 1851–1852
treatment of, 1854*b*
infectious causes of, 1850*t*
in inpatients, 1846–1847
lymphadenopathy and, 1849, 1849*t*
management of, 1856*f*–1857*f*
musculoskeletal complaints and, 1849
in neutropenia, 1854
noninfectious causes of, 1851–1852
in outpatients, 1846
overview of, 1845–1847
pathobiology of, 1846
Pontiac, 1998–1999, 1999
postoperative, 1849, 2675
prolonged, in bacterial meningitis, 2518
Fever *(Continued)*
Q fever, 417*t*
rash and, 1847, 1848*t*
severe mental illness and, 2683*t*
syndromes, 1847–1851
travel associated with, 1890*t*
treatment of, 1851*b*
viral hemorrhagic, 99–100
vital signs in, 34
in women, medications for, 1608*t*
Fever of unknown origin (FUO), 1849–1850, 1850*f*, 1850*t*
Fexinidazole, for African trypanosomiasis, 2112*t*, 2115–2116, 2125*b*
FFP. *See* Fresh-frozen plasma
FGFR. *See* Fibroblast growth factor receptor
FHIT (fragile histidine triad) gene, lung cancer and, 1330
Fiber, dietary guidelines for, 57.*e3t*
Fibrates, for hypertriglyceridemia, 1414*b*
Fibrillary glomerulopathy-immunotactoid glomerulopathy, 788–789
Fibrin, 1165, 1165*f*
Fibrin degradation products (FDPs), *e8t*–*e9t*, 1195
Fibrin-stabilizing factor, 1189*t*, 1192, 1192*b*
Fibrinogen, *e1t*–*e8t*, *e8t*–*e9t*, 1167*t*, 1189*t*
Fibrinolysis, rare disorders of, 1169
Fibrinolytic therapy, 509
contraindications to, 487*t*
for STEMI, 384*b*, 386*t*
Fibroblast growth factor-23 (FG23), 732
Fibroblast growth factor receptor (FGFR), lung cancer and, 1330
Fibroblast-like synoviocytes, 1751
Fibrocystin, 813
Fibroelastomas, 296
Fibrogenesis imperfecta ossium, 1666
Fibromuscular dysplasia, 468, 468*f*
angioplasty for, 800*b*
clinical manifestations of, 468
diagnosis of, 468
epidemiology of, 799
renal artery stenosis caused by, 799
right renal arteriogram of, 801*f*
string of beads in, 449, 449*f*
"string of beads" lesion of, 468, 468*f*
treatment of, 800*b*
Fibromyalgia, 1708, 1769, 1816–1820, 2372
brain imaging studies for, 1817
clinical manifestations of, 1817–1818
comorbid, 1816
conditions that simulate, 1819*t*
definition of, 1816–1820, 1818*t*
diagnosis of, 1818–1819
epidemiology of, 1816
interventional therapies for, 1819*b*
nonpharmacologic therapies for, 1819*b*, 1819*t*
pain associated with
mechanistic characterization of, 1817*t*
processing, 1817
pathobiology of, 1816–1817
peripheral factors in, 1817
pharmacologic therapies for, 1819*t*
prognosis for, 1820
sensory processing in, 1817
stressors that cause, 1816, 1816*t*
symptom severity scale score for, 1818*f*
tricyclic agents for, 1819*b*
Fibronectin binding protein, 1913
Fibrosing mediastinitis, 629
Fibrosing mediastinitis, pulmonary histoplasmosis and, 2082
Fibrosis, in systemic sclerosis, 1776
Fibrous dysplasia, 1668, 1669*b*, 1669*f*
Fibrous tumors, of pleura, 526
FICA Spiritual Assessment Tool, 12, 16*t*
Fick equation, 640
Fidaxomicin, for *Clostridioides difficile*, 1925*b*
Fifth disease, 2234, 2234*f*
Figurate erythemas, 2711
Filamentous hemagglutinin, 1995
"Filarial dance sign", 2177
Filariases, 2176–2180, 2176*b*, 2176*t*
dracunculiasis, 2180
loiasis, 2179
lymphatics, 2176
Mansonella perstans, 2180
Mansonella streptocerca, 2180
onchocerciasis, 2178
in travelers, 1889.*e1t*
zoonotic, 2180

Copyrighted material

Filgotinib, 153*t*
Filgrastim (Neupogen), 1215*t*
Fimbriae, 1913
Final menstrual period, 1628
Financial assessment, geriatric, 118
Financial conflicts of interest, in bioethics, 10
  definition of, 10, 10*t*
  empirical data for, 10–11
  history of, 10
  justification of, 10
  practical consideration for, 11
Finasteride, 824*t*
Fine-needle aspiration biopsy, for thyroid nodules, 1516, 1516*t*
Fingolimod (Gilenya), for multiple sclerosis, 2505*t*
FIP1L1-PDGFRA fusion gene, 295, 1142
First-degree atrioventricular block, 229
"First-order" process, 127
First-pass effect, of drugs, 126
FISH. *See* Fluorescence in situ hybridization
Fissure, 2687.*e4t*
Fistula
  anal, 979, 979*b*, 980*b*, 980*f*
  aortoenteric, 967
  coronary artery, 352
  Crohn disease and, 943
  esophageal, 912
  from hepatic artery, 969
  pulmonary arteriovenous, 350–351
Fitness, physical, 61
Fitzpatrick skin types, 2686.*e2t*
Fixed airway obstruction, 532
Fixed drug eruptions, 2728
Flaccid blisters, 2720
Flagyl. *See* Metronidazole
Flail arm syndrome, amyotrophic lateral sclerosis and, 2563
Flail chest, 621, 621.*e1f*, 622*b*
FLAIR. *See* Fluid-attenuated inversion recovery
Flat smallpox, 2237, 2237*t*, 2270*t*
Flat warts, 2242
Flatus, 858–859
Flavin adenine dinucleotide, 1530
Flaviviridae, 2274, 2276*b*, 2280–2283
Flaviviruses, in travelers, 1891*t*
Flavonoids, 116
Flax, 88*t*
Flea-borne spotted fever, 2055*t*, 2059
  in travelers, 1889.*e1t*
Flea-transmitted diseases, 2058–2059
Flecainide, *e*10*t*–*e*11*t*, 325*t*
Fleischer ring, 987
Flexibility activity, 63*b*
Flexible sigmoidoscopy, 1349, 1353
  for colorectal cancer, 54
Flinders Island spotted fever, 2055*t*
Floaters, 2599
"Floating teeth", 1154
Flour dust, 88*t*
Flow cytometry, for anemia, 1077
Flow-volume curve, 528, 529*f*
"Flowers of Lichtenberg", 704, 704*f*
Fluconazole, 2075, 2699
  adverse effects of, 2076
  for candidiasis, 2093
  for cryptococcosis, 2089
  drug interactions of, 2076
  formulations and pharmacology of, 2075
  for hepatosplenic candidiasis, 1024*b*
  for histoplasmosis, 2083*b*
  indications and dosage of, 2075–2076, 2075*t*
  for mycoses, 2076
  for paracoccidioidomycosis, 2087*b*
  for sporotrichosis, 2086*b*
  for vulvovaginal candidiasis, 1882*b*
Flucytosine, 2079
  adverse effects of, 2079
  for cryptococcosis, 2088*b*
  drug interactions of, 2079
  formulation and pharmacology of, 2079
  indications and dosage of, 2075*t*, 2079
  mechanisms of action, 2079
Fludara. *See* Fludarabine
Fludarabine (Fludara), 1215*t*
  for autoimmune hemolytic anemia, 1089
  for chronic lymphocytic leukemia, 1269*t*, 1270*t*
Fludarabine/cyclophosphamide/rituximab, for chronic lymphocytic leukemia, 1269*b*
Fludrocortisone
  for orthostatic hypotension, 2559*t*
  for septic shock, 673*b*
Fluid(s)
  for acute kidney injury, 774*b*
  intestinal transport of, 924, 924.*e1f*
  for resuscitation, 636
Fluid-attenuated inversion recovery (FLAIR), for epilepsies, 2431, 2432*f*
Fluid replacement, for diarrhea, 926*b*
Flukes
  intestinal, 2166*t*, 2167
    approach to, 2168
  liver
    approach to, 2168
    description of, 2165–2167
    fascioliasis, 2168
    opisthorchiasis, 2168
    paragonimiasis, 2168
  lung, 2166*t*, 2168
  pulmonary, 2167–2168
Flumazenil
  for acute poisoning, 693*t*
  for catatonia, 2681*b*
Flunisolide, 553*t*
Fluorescence in situ hybridization (FISH)
  for anemia, 1077
  for chronic lymphocytic leukemia, 1267
Fluorinated hydrocarbons, 88*t*
Fluorine, 1457*t*
18-Fluorine deoxyglucose (18-FDG), 1723
Fluorochrome stains, for tuberculosis, 2039
Fluorodeoxyglucose positron emission tomography (FDG-PET), 519
  for Hodgkin lymphoma, 1291
Fluoropolymers, 88*t*
Fluoroquinolones, 1893
  for anthrax, 1932*b*
  for bacterial meningitis, 2518*t*
  for *Campylobacter* infections, 1959*b*, 1960
  for enteric fever, 1979*b*
  for Oroya fever, 2003*b*
  reactions to, 1698*t*
  Streptococcus pneumoniae resistance to, 1912*b*
Fluoroscopy
  description of, 866–868, 868*f*–869*f*, 868*f*, 869*f*
  for rheumatic disease, 1717
  water-soluble contrast for, 866–867
5-Fluorouracil (Adrucil, Efudex), 1215*t*
  cardiomyopathy due to, 288
  for gastric adenocarcinomas, 1341*b*
  for head and neck cancer, 1327*b*
Fluoxetine
  for cataplexy, 2449*t*
  for depression, 2340*t*
  for hot flashes, 1631*t*
  for irritable bowel syndrome, 896*t*
Fluphenazine, for psychotic disorders, 2346*t*
Flurazepam, for anxiety disorders, 2344*t*
Flutamide (Eulexin), 1215*t*
Fluticasone, 553*t*
Fluvastatin, for familial hypercholesterolemia, 1409*t*
Fluvoxamine, for COVID-19, 2217
FMF. *See* Familial Mediterranean fever
Foam, 2697
Focal central nervous system disorders, 2561
Focal invasive candidiasis, 2091
Focal ischemic injury, 2463, 2463*f*
Focal nodular hyperplasia, 992, 992*f*
Focal oligemia, with vascular deficiency, 522
Focal segmental glomerulosclerosis, 778, 779*b*, 779*f*, 779*t*
Focal segmental ischemia, 962*f*
Focused abdominal sonography in trauma (FAST), 700*b*, 701*f*
FODMAPs, 859
Folate, *e*1*t*–*e*8*t*, 935, 1119–1120, 1427*b*, 1453*t*
  absorption of, 1119–1120
  biochemical assays for, 1122
  cycle, 1425.*e2f*
  functions of, 2540
  homocysteine and, 1459, 2540
  malabsorption of, 1120, 1123
  metabolism of, 1119, 2121*b*
  supplementation of, 1453*t*
  transport of, 1119
Folate deficiency
  alcohol and, 1120
  description of, 2538*t*, 2540, 2540*b*
Folate deficiency *(Continued)*
  drugs that cause, 1117*t*, 1120
  epidemiology of, 1117–1118
  megaloblastic anemia caused by, 1117*t*, 2540
  metabolites for, 1124*t*
  prevention of, 1124
  treatment of, 1123*b*
Folex. *See* Methotrexate
FOLFOX chemotherapy, for gallbladder cancer, 1054*b*
Folic acid, 1119–1120
  for malabsorption, 937*t*
  for neural tube defect prevention, 1452
  supplementation
    for autoimmune hemolytic anemia, 1089*b*
    for hearing loss in elderly, 2642*b*
Folinic acid, 1427*b*
  for acute poisoning, 693*t*
  for toxoplasmosis, 2140*t*
Follicle-stimulating hormone (FSH), 1496
  description of, 1580–1581
  gonadotropin-releasing hormone effects on, 1476
  insufficiency tests of, 1484*t*
  menopause and, 1629
  pathobiology of, 1496
  in puberty, 1591, 1591*f*
  secretion of, 1582
  subunits of, 1581
  tests of, 1488*t*
  tumors that produce, 1496, 1496*b*
Follicular B-cell lymphoma, 2734
Follicular conjunctivitis, 2009
Follicular lymphoma, 1268*t*, 1283, 1283*b*–1284*b*
Follicular maturation, hypothalamic-pituitary-ovarian axis in, 1596*f*
Follicular (differentiated) thyroid cancer, 1517, 1517*b*–1518*b*, 1517*t*, 1518*f*
Folliculitis, 1903, 2722–2723, 2739
  eosinophilic pustular, 2321, 2323*f*, 2723
  hot tub, 1970*b*
Folliculitis decalvans, 2747*t*, 2750, 2751*f*
Folliculogenesis, chronology of, 1595–1596
Follistatin, 1477
Follitropin (FSH), *e*1*t*–*e*8*t*
Fomepizole, for acute poisoning, 693*t*
Fomivirsen, 174, 2189
Fondaparinux, 387*t*, 501*t*, 502–503
  for acute coronary syndrome, 374*t*, 375*t*
Fontaine's clinical classification, 462*t*
Fontan operation, 355, 355.*e2t*
Food
  Acinetobacter in, 1973
  anaphylaxis caused by, 1692
  intake, alterations in, hypothalamic disease and, 1481
  obesity and, 1464
Food allergies
  description of, 1675*t*
  diarrhea and, 940
Food allergy-associated exercise-induced anaphylaxis, 1692
Food and Drug Administration (FDA), on antiretroviral therapy, 2300, 2302*t*
Food and exercise-induced anaphylaxis, 2725
Food-borne bacterial pathogens, *Campylobacter* infections and, 1958
Food-borne infectious diarrhea, 924–926, 925*t*
Food impaction, esophageal disease and, 902
Food poisoning, 1930
  diarrhea and, 925
Food protein-induced allergic proctocolitis, 1673*t*
Food protein-induced enterocolitis syndrome, 1673*t*
Food protein-induced enteropathy, 1673*t*
Foodborne botulism, 1927, 2592
Foot
  disorders of, 1747
  Pseudomonas osteomyelitis of, 1969
Foramen ovale, patent, 348, 349, 349*b*
Forbes disease, 1417*t*
Forced expiratory flow (FEF), 528
Forced expiratory volume (FEV), 528
Forced expiratory volume in 1 second, 547
  and severity of asthmatic attacks, 539
Forced vital capacity (FVC), 528
Forearm exercise test, for rhabdomyolysis, 716
Foreign bodies, in esophagus, 912
Foreign body sensation, 2599, 2600*f*
Formoterol, 553*t*
Fosamprenavir, 2301*t*
Fosaprepitant, for nausea and vomiting, 863*t*
Foscarnet
  for cytomegalovirus, 2252*b*
  for herpesvirus infections, 2187*t*, 2188, 2188*t*
  for zoster, 2249*b*
Fosfomycin, for vancomycin-resistant enterococci, 1922*t*
Fosfomycin trometamol, for cystitis, 1876*t*
Fosinopril, 451*t*
Fosinopril/HCTZ, 451*t*
Fostemsavir, 2301*t*
Fovea, 2614
Foville syndrome, 2465.*e1f*
Fractional flow reserve, 250.*e1f*, 393
Fractional lasers, for skin cancers, 2701
Fracture Risk Assessment Tool (FRAX), 1642–1643, 2318
Fractures
  cystic fibrosis and, 557
  multifactorial interventions for, 116
  osteoporotic, 1639
  proximal femur, 1639
Fragile X syndrome, 2549, 2549*b*
Fragmentation injury, 699*t*, 700, 700*f*
Frailty, 114, 115, 122, 123*b*, 123*f*, 123*t*
  geriatric assessment of, 118
  trajectories of, 12.*e1f*
Frailty measure, in older adults, 123*t*
Francisella tularensis, 1985, 2649
  rhabdomyolysis caused by, 715
Frank psoriasis, 2321
Frank-Starling law, 225–226, 226*f*
Frank-Starling mechanism, 406
Frasier syndrome, 1574
FRAX. *See* Fracture Risk Assessment Tool
FRC. *See* Functional residual capacity
Free fatty acids, 1465
Free-living amebae, 2150, 2150*t*
Fresh-frozen plasma (FFP), 1200, 2269*b*
  HIV transmission through, 2299
Frey syndrome, 2555
Fridericia formula, 230
Friedreich ataxia, 279, 2497
Frontal fibrosing alopecia, 2747*t*, 2749, 2750*f*
Frontal lobe, 2460*f*
Frontal lobe seizures, 2430–2431
Frontotemporal dementia, amyotrophic lateral sclerosis and, 2563
Frontotemporal lobar degeneration, 2421–2422
  clinical manifestations of, 2422
  definition of, 2421
  diagnosis of, 2422
  diagnostic criteria for, 2421*t*
  epidemiology of, 2421
  magnetic resonance imaging of, 2423*f*
  pathobiology of, 2421–2422
  prognosis of, 2422
  treatment of, 2422*b*
Frostbite, 474, 474*f*, 680
Frovatriptan, 2380*t*
Frozen shoulder, 1744, 1744*b*
Fructosamine, *e*1*t*–*e*8*t*
Fructose, diarrhea and, 939
Fruits, dietary guidelines for, 57.*e3t*
FSH. *See* Follicle-stimulating hormone
Fulminant influenza viral pneumonia, 2202*b*
Fulvestrant (Faslodex), 1215*t*, 1369*b*
Fumigants, 88*t*
Functional chest pain, 900
  clinical manifestations of, 900
  definition of, 900
  diagnosis of, 900
  differential diagnosis of, 901*t*
  epidemiology and pathobiology of, 900
  prognosis of, 901
  Rome IV diagnostic criteria for, 900*t*
  treatment of, 901*b*
Functional dyspepsia, 898
  alarm symptoms associated with, 899*t*
  algorithm for, 899*f*
  definition and epidemiology of, 898
  pathobiology of, 898
  prognosis of, 899
  Rome IV diagnostic criteria for, 898, 898*t*, 899*t*
  treatment of, 899*b*
Functional gallbladder disorder, 1053, 1054*t*
Functional GI disorders, 850

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Functional heartburn, 899–900
  clinical manifestations of, 900
  diagnosis of, 900
  epidemiology of, 900
  pathobiology of, 900
  prognosis of, 900
  Rome IV diagnostic criteria for, 900*t*
  treatment of, 900*b*
Functional incontinence, 828
Functional luminal imaging probe, 902
Functional neurologic symptom disorder. *See* Conversion disorder
Functional outlet obstruction, 890, 890*t*
Functional pancreatic neuroendocrine neoplasms, 1561*t*
Functional residual capacity (FRC), 530
Functional status, geriatric assessment of, 117
Fundoscopic examination, for toxoplasmosis, 2138*t*
Fungal arthritis, 1808
Fungal brain abscesses, 2525
Fungal endocarditis, 416
  noncandidal, 417*t*
  treatment of, 417*b*
Fungal endophthalmitis, 2606
Fungal infections, 2650–2651, 2651*f*
  amphotericin B for, 2077
  after hematopoietic cell transplantation, 1211
  liver, 1023–1024, 1024*b*
  predisposition to, 1686*t*
  of skin, 2736, 2739*t*, 2741
Fungal keratitis, 2602–2603
Fungal meningitis, cerebrospinal fluid findings in, 2374*t*
Fungal pericarditis, 432
Fungi
  health care-associated infections caused by, 1865
  as occupational and environmental hazards, 88*t*
  peripheral blood smear of, 1074*t*
Fungicides, 88*t*
Funguria, 1875*b*
Fungus ball, 607–608, 609*f*
Funnel web spiders, envenomation of, 710
FUO. *See* Fever of unknown origin
Furosemide, 451*t*
  for amyloidosis, 293*b*
  for hypervolemia, 737*t*
  hypokalemia and, 749*t*
Furuncles, 1903, 2739, 2740*f*
Fusiform aneurysms, 2478
Fusion proteins, 150, 150*t*
Fusobacterium, 2068
Fusobacterium necrophorum, 2648–2649
FVC. *See* Forced vital capacity

G

G protein-coupled receptor (GPCR), 1652, 2639
G6PD deficiency. *See* Glucose-6-phosphate dehydrogenase (G6PD) deficiency
G6PD gene, 160*t*
Gabapentin, *e*10*t*–*e*11*t*
  for chronic pain, 138*t*
  for distal symmetrical and autonomic polyneuropathy, 2577*b*
  for fibromyalgia, 1819*b*
  for hot flashes, 1631*t*
  for seizures, 2434*t*
  for zoster, 2249*b*
Gabapentin enacarbil, for restless legs syndrome, 2496*b*
Gabapentinoid, for restless legs syndrome, 2453
Gadolinium-enhanced MRI, for spinal epidural abscess, 2527
Gadolinium toxicity, 463
GAGs. *See* Glycosaminoglycans
Gain-of-function mutations, 1476*t*
Gait, 117
  antalgic, 2373*t*
  disorders of, 2371, 2373*t*
  dystonic, 2373*t*
  hemiparetic, 2373*t*
  hysterical, 2373*t*
  parkinsonian, 2373*t*
  spastic, 2373*t*
  steppage, 2373*t*
  waddling, 2373*t*
Galactorrhea, 1491, 1601
α-Galactosidase, 787
  for Fabry disease, 1420*t*
Galantamine, for Alzheimer disease, 2416*b*
Galectin-3, 260.*e*1*t*
Gallavardin phenomenon, 402
Gallbladder
  adenocarcinomas, 1358
  adenomas, 1054
  cancer, 1054
Gallbladder diseases, 211*t*, 1049–1061
  acute acalculous cholecystitis, 1053
  acute calculous cholecystitis, 1050. *See also* Acute calculous cholecystitis
  functional gallbladder disorder, 1053
  gallstone. *See* Gallstone(s)
  gallstones, 1049–1053
  tumors, 1053–1054
Gallbladder tumors, 1053
  benign, 1053–1054
  malignancy, 1054
  prevention and treatment of, 1054*b*
Gallstone(s), 1049
  acute pancreatitis and, 969, 970*t*
  bilirubinate, 1095
  clinical manifestations of, 1050
  diagnosis of, 1050–1051, 1051*f*–1052*f*
  epidemiology of, 1049
  formation of, 1049–1050, 1050*t*
  liver disease and, 986
  pathobiology of, 1049–1050
  prevention of, 1052–1053
  treatment of, 1052*b*, 1053*f*
Gallstone ileus, 1053
Gamekeeper's thumb, 1745
Gamma-glutamyl transpeptidase (GGT), 999
Gammopathy, monoclonal, 727
Ganciclovir
  for cytomegalovirus, 2252, 2252*b*
  for herpesvirus infections, 2186–2188, 2187*t*, 2188*t*
Ganglioglioma, 1316
Ganglion, 1745–1746, 1745*b*
Ganglionopathies, 2554*t*
Gap junction channels, 300.*e*1*f*, 301
Gardasil-9, 2243
Gardner syndrome, 1348
Gas, bloating and, 858
Gas gangrene, 1926, 1926*b*, 1939
Gastric acid, suppression of, for asthma, 541*b*
Gastric adenocarcinoma, 1339
  clinical manifestations of, 1340–1341
  diagnosis of, 1341, 1341*f*
  epidemiology of, 1339–1340
  genetics, 1340
  laboratory studies of, 1341
  medical therapy for, 1341*b*
  pathobiology of, 1340
  physical examination for, 1341
  prevention of, 1342
  prognosis of, 1342
  risk factors for, 1340, 1340*t*
  surgical therapy for, 1341*b*
  symptoms and signs of, 1340–1341
  treatment for, 1341*b*, 1342*t*
Gastric adenomas, 1343
Gastric angioectasia, 966.*e*1*f*
Gastric band bariatric surgery, abdominal radiographs of, 868*f*
Gastric cancer, fluoroscopy of, 868*f*
Gastric disease, in systemic sclerosis, 1780
Gastric electrical stimulation, 889*b*
Gastric emptying
  accelerated, 889*b*
  for acute poisoning, 691*b*
Gastric lymphoma, 1342
  clinical manifestations of, 1342
  diagnosis of, 1342
  epidemiology of, 1342
  Helicobacter pylori and, 1279
  treatment for, 1342*b*
Gastric mucosal biopsy, for *Helicobacter pylori*, 918
Gastric outlet obstruction, 923
Gastric ulcers, 1341*f*
  aspirin and, 914
  Cameron ulcers, 916
  classification of, 913
  malignant, 915
  nonsteroidal anti-inflammatory drugs and, 914
  prevention of, 921–923
Gastrin, *e*1*t*–*e*8*t*, 1566
Gastrinomas, 1561*t*, 1562
  clinical manifestations of, 1562–1563
  diagnosis of, 1563
  differential diagnosis of, 1563
  pathobiology of, 1562
  prognosis of, 1563
  treatment of, 1563*b*
Gastritis
  alcohol use causing, 917
  definition of, 913
  endoscopy of, 913*f*
  epidemiology of, 914
  erosive, 913*f*, 917
  Helicobacter pylori, 913
  hypertrophic, 913
  microbial causes of, 917
  nodular, 913
Gastroduodenal ulcers
  causes of, 915, 919
  malignant causes of, 915
  systemic inflammatory disorders that cause, 915–916
Gastroenteritis, 1869*t*
  acute, treatment of, 1963*b*
  Campylobacter jejuni and, 1959
  cryptosporidiosis and, 2143
Gastroenterology, 866–874
  abdominal radiographs, 866, 866*f*, 867*f*, 868*f*
  computed tomography, 869, 870*f*, 871*f*
  fluoroscopy, 866, 868*f*, 869*f*
  magnetic resonance imaging, 871–872, 872*f*–873*f*
  radiographic plain films, 866
  ultrasound, 869, 869*f*, 870*f*
Gastroesophageal junction, Mallory-Weiss tear at, 882*f*
Gastroesophageal reflux disease (GERD), 902–906
  abdominal pain and, 854*t*
  clinical manifestations of, 903, 903*f*
  definition of, 902–905
  diagnosis of, 903–905, 903*f*–904*f*
  epidemiology of, 902
  laryngopharyngeal reflux and, 2651
  obesity and, 1466
  pathobiology of, 902
  prognosis of, 905
  treatment of, 904*b*, 904*t*
  in women, medications for, 1608*t*
Gastrointestinal agents, for cystic fibrosis, 558*b*
Gastrointestinal anthrax, 1931, 1932*b*
Gastrointestinal bleeding, 852*t*, 864–865
  of acute pancreatitis, 972*t*
  direct thrombin inhibitors and, 504
  lower, 882, 884–885. *See also* Hematochezia
    colonoscopy for, 885
    definition of, 884
    diagnosis of, 884–885
    epidemiology of, 884
    treatment of, 885*b*
  obscure and occult, 885–887, 886*f*, 886*t*
  upper, 882–883
    acute management of, 883*b*
    clinical manifestations of, 882, 882*f*, 882*t*
    diagnosis of, 882–883
    endoscopic therapy for, 883*b*, 883*t*
    Glasgow-Blatchford score for, 883*b*, 883*t*
    management of, 884*f*
    medical therapy for, 883*b*
    peptic ulcer disease causing, 882
    treatment of, 883*b*
Gastrointestinal disease
  chronic, Chagas disease and, 2127–2128
  chronic, in travelers, 1891*t*
  cystic fibrosis and, 557
  functional, 892
  in pregnancy, 1625–1627
  Pseudomonas infections causing, 1969
Gastrointestinal disease, approach to, 850–865
  abdominal examination in, 851
  abdominal pain in. *See* Abdominal pain
  belching, 858
  bloating and distention, 859, 859*b*
  clinical history in, 850–854
  constipation, 862, 862*b*
  digital rectal and pelvic examinations in, 851
  family history in, 851
  fecal incontinence, 865
  flatus, 858
Gastrointestinal disease, approach to *(Continued)*
  gas and bloating, 858
  gastrointestinal bleeding, 864
  involuntary weight loss, 860–861, 860*t*
  laboratory studies in, 851–854
  nausea and vomiting, 861–862, 862*b*, 862*f*–863*f*
  nonabdominal examination in, 851
  other, 865, 865*f*
  past medical history in, 850
  physical examination in, 851
  signs and symptoms of, 850–854, 852*t*
  social history in, 850–851
Gastrointestinal endoscopy, 875–881
  advanced, 880
  antithrombotic therapy for, 875*t*
  capsule, 880
  colonoscopy in, 879
  complications of, 876*t*
  diagnostic, 875–881
  endoscopic retrograde cholangiopancreatography in, 876
  enteroscopy in, 878
  standard, adjuncts to, 875
  ultrasonography, 876
  upper, 875
Gastrointestinal hemorrhage, 882–887
  clinical manifestations of, 882, 882*t*
  liver disease and, 986–987
  mortality risks, 922
  prophylaxis for, 700*b*
  upper. *See* Upper gastrointestinal bleeding
Gastrointestinal motility
  definition of, 887–888
  disorders of, 887–892
Gastrointestinal motility disorders
  accelerated gastric emptying, 890
  constipation. *See* Constipation
  definition of, 887
  dumping syndrome, 890
  enteric neuropathic disorders, 888
  extrinsic neuropathic disorders, 888
  intestinal pseudo-obstruction. *See* Intestinal pseudo-obstruction
  intrinsic neuropathic disorders, 888
  pathobiology of, 887–888
  rapid transit dysmotility, 890
  smooth muscle disorders, 888–889
  weight loss and, 860*t*
Gastrointestinal mucormycosis, 2099
Gastrointestinal neuroendocrine neoplasms, 1562, 1566–1567
Gastrointestinal stromal tumors (GISTs), 1342–1344, 1390, 1390*b*
Gastrointestinal syndrome, 93
Gastrointestinal system
  age-related changes in, 121
  systemic lupus erythematosus manifestations of, 1770
Gastrointestinal tract
  alcohol use disorders and, 2355, 2355*t*
  allergy of, 1674
  fluid reabsorption in, 888
  infections of, 2205
  neuroenteric control of, 887
  physiology of, 887–888
  systemic sclerosis involvement of, 1778
  vascular diseases of, 959
    acute mesenteric ischemia as, 959
    angioectasia as, 965
    aortoenteric fistulas as, 967
    Budd-Chiari syndrome as, 968
    celiac artery compression syndrome as, 967, 967*f*
    chronic mesenteric ischemia as, 963, 963*f*
    colon ischemia as, 964, 964*t*, 965*f*
    Dieulafoy lesion as, 966
    ectasias as, 967
    hemangiomas as, 967
    hepatic and splenic, 968
    hepatic and splenic arterial disease as, 969
    hereditary hemorrhagic telangiectasia as, 967
    intestinal ischemia as, 959
    portal vein thrombosis as, 968, 968*b*
    radiation proctopathy as, 968, 968*f*
    splenic vein thrombosis as, 968
    superior mesenteric artery syndrome as, 967
    vascular anomalies and disorders as, 965
    vasculitis as, 965

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Gastroparesis, 1778
  classification of, 888*t*
  clinical manifestations of, 888
  diagnosis of, 889
  differential diagnosis of, 889
  medical therapy for, 889*b*
  surgical therapy for, 891*b*
  treatment of, 889*b*
Gastroschisis, 951
Gastrostomy tube, for amyotrophic lateral sclerosis, 2563*b*
GATA1-associated CEP, 1428*t*
GATA2 deficiency, 1685–1686, 1686*t*
Gatifloxacin
  for bacterial meningitis, 2518*t*
  for eye infection, 2605*t*
Gaucher disease, 583, 1398*t*, 1420–1421
  clinical manifestations of, 1420–1421, 1421*f*
  definition of, 1420
  diagnosis of, 1421, 1421*f*, 1422*t*
  enzyme-specific treatments for, 1420*t*
  epidemiology of, 1420
  pathobiology of, 1420
  prognosis of, 1421*b*
  treatment of, 1421*b*, 1422*t*
Gaze-evoked nystagmus, 2619
Gazyva. *See* Obinutuzumab
Gefitinib, 1251*t*
Gels, 2697
Gemcitabine (Gemzar), 1215*t*
  for pancreatic cancer, 1356*b*
  for soft tissue sarcomas, 1389*b*
Gemzar. *See* Gemcitabine
Gender-affirming hormone therapy, 1578*b*
Gender identity, 1574–1575, 1577
Gender role, 1574
Gene, 160, 161*f*
Gene therapy, 174–178
  classification of, 175–178
  delivery methods, 175
  diseases treated by, 175
  ex vivo, 175
  for hemophilia, 1188*b*
  for herpes simplex virus infections, 2245
  human stem cell-based, 175–176
  indications for, 3
  liver involvement, 175
  mechanism of action, 175
  for sickle cell disease, 1114*b*
  suicide, 176
  for thalassemia, 1107*b*
  in vivo, 175
Gene transfer, horizontal, in Enterobacterales, 1965, 1966*t*
General advice, for heart failure, 275*t*
General anesthesia, 2669, 2671
General paresis, 2017
General risk assessment, 2661–2666
Generalized anxiety disorder, 2342*t*, 2343
Generalized morphea, 1782
Generalized pain syndromes, 1706
Generalized tetanus, 1928
Generalized vaccinia, 2238
Genetic bone marrow failure syndromes, 1253
"Genetic conditions", 158
Genetic counseling
  for cystic fibrosis, 559
  for inborn errors of metabolism, 1401*b*
Genetic dilated cardiomyopathy, 286
Genetic Information Nondiscrimination Act of 2008, 169
Genetic lipid disorders, 1408
Genetic polymorphisms, of drug-metabolizing enzymes, 132*t*
Genetic risk assessment, 159
Genetic test reports, 165
Genetic testing
  for endocrine disease, 1473
  for glomerular syndromes, 728, 728.*e1f*
  for monogenic common disorders, 159
  for porphyrias, 1434
Genetic Testing Registry, 169.*e1t*
Genetically inherited ventricular arrhythmias, 337–338
Genetics
  cystic fibrosis and, 556
  of diseases, 158, 158*f*
  principles of, 158–160
Genital herpes
  chancroid and, 1951
Genital herpes *(Continued)*
  characteristics of, 1880–1881, 2245–2246
  organisms causing, 1879*t*
  syphilis *versus*, 2019
Genital ulcers, 1880–1881
  organisms causing, 1879*t*
  treatment of, 1881*t*
Genital warts
  description of, 2242
  organisms causing, 1879*t*
Genitalia, male, examination of, 31
Genitourinary amyloidosis, 1310*b*
Genitourinary bleeding, hemophilia and, treatment of, 1188*b*
Genitourinary symptoms, of menopause, 1630, 1632*t*
Genitourinary tract infections
  adenovirus causing, 2205
  Pseudomonas infections causing, 1969
  Staphylococcus aureus causing, 1904–1905
Genome, expressed, 168
Genome editing, 178–179, 178*f*–179*f*
Genome sequencing, 158, 166–167
  of autoinflammatory syndromes, 1737
  cancer pharmacogenomics and, 167
  as driver of precision medicine, 166
  microbial, 167–168
  pharmacogenomics, 167, 167.*e1t*
  pre-conception carrier testing, 166
  prenatal diagnosis, 166
  for rare diseases and diagnostic dilemmas, 167
  for risk prediction, for common complex disease, 167
Genome-wide association studies (GWAS), 166
  description of, 159
  of rheumatoid arthritis, 1749
Genomic variations, 162
  assaying, 164
  chromosomal aberrations in, 164, 164.*e1f*
  copy number variants in, 164
  deletion, insertion, and indels in, 163
  single nucleotide, 162–163
  structural aberrations in, 164
  structural variants in, 164
  tandem repeats in, 163
Genomics, 1834
Gentamicin, *e10t*–*e11t*
  for bacterial meningitis, 2518*t*
  for bronchiectasis, 561*b*
  dosage of, 1895*t*
  for endocarditis, 417*b*, 419*t*
  for eye infection, 2605*t*
  for gonorrhea, 1948*b*
  for plague, 98*b*, 1992*t*
  for pyelonephritis and urosepsis, 1877*t*
  for trench fever, 2003*b*
  for tularemia, 99*b*, 1987*b*
Geographic tongue, 2623, 2623*f*
GERD. *See* Gastroesophageal reflux disease
Geriatric assessment, 116
  built and social environments in, 118
  cognition and competency in, 117
  continence in, 118
  financial assessment in, 118
  frailty in, 118
  function of, 116–118
  functional status in, 117
  goals and preferences of, 118–119
  hearing in, 117
  initial observation in, 117
  medication review in, 118
  mobility and life space in, 117–118
  mood and affect in, 117
  nutrition in, 117
  in practice, 119, 119*t*
  preventive services, 119, 119.*e1t*
  prognosis of, 118
  rationale of, 116
  risk of falls in, 118
  self-neglect and abuse in, 118
  sexuality in, 118
  social support in, 118
  vision in, 117
Geriatric Depression Scale, 2332*t*
Geriatric incontinence, 827
Geriatric syndromes, in older adults, 114
Germ cell tumors
  in adolescents, 111
  nonseminomatous, treatment of, 1383*b*
German measles. *See* Rubella
Germinomas, 1314
Germline DNA alterations, in cancer, 1248, 1248*f*, 1249*f*
Germline genetic variants, drug response and, 167, 167.*e1t*
Gerstmann-Sträussler-Scheinker syndrome, 2423
Gestational diabetes insipidus, 1501, 1503*b*
Gestational diabetes mellitus, 1544, 1545*b*
Gestational hypertension, 1620
Gestational rhinitis, 1618*t*–1619*t*
Gestational thrombocytopenia, 1178–1179
GFR. *See* Glomerular filtration rate
GFRomas. *See* Growth hormone-releasing factor secreting neuroendocrine neoplasms
GH. *See* Growth hormone
Ghon complex, 2034
Ghon focus, 2034
Ghrelin, 1477
Giant bullae, 631–632
Giant cell arteritis, 442.*e1f*, 443, 443*b*, 965, 1795, 1801–1804, 2383
  clinical manifestations of, 1801–1802, 1801*t*
  definition of, 1801–1803
  diagnosis of, 1802–1803
  differential diagnosis of, 1803
  epidemiology of, 1793*t*, 1801
  ischemic complications of, 1802
  ocular vascular abnormalities caused by, 2610
  pathobiology of, 1801
  prognosis for, 1803
  superficial temporal artery, assessment of, 1803
  survival rates for, 1803
  temporal artery biopsy for, 1803
  treatment of, 1803*b*
Giant cell myocarditis, 286
Giant platelets, 1073*f*
Giardia
  in travelers, 1889.*e1t*, 1891*t*
  traveler's diarrhea caused by, 1888*t*
Giardia lamblia infection, 937, 1858
  description of, 2144, 2144*f*
  sexually transmitted anorectal diseases and, 983
Giardiasis, 2115, 2144–2146
  characteristics of, 2270*t*
  clinical manifestations of, 2145
  diagnosis of, 2145
  epidemiology of, 2144
  pathobiology of, 2145
  pathogen that causes, 2144
  prevention of, 2146
  prognosis for, 2146
  treatment of, 2145*b*
Gigantism, 1489, 1489*b*
Gilbert syndrome, 994, 995, 997*t*, 2267
Gilenya. *See* Fingolimod
Gilotrif. *See* Afatinib
Gingival hyperplasia, 2624, 2625*f*
Gingival Kaposi sarcoma, 2320*f*, 2322*t*
Gingivostomatitis, characteristics of, 2245
GISTs. *See* Gastrointestinal stromal tumors
Gitelman syndrome, 749, 749*t*, 762–763, 816*t*, 817, 817*b*, 817.*e1f*
Give-way weakness, 2393
Glanders, 1972, 1972*b*
Glandular hypofunction, 1784
Glanzmann thrombasthenia, 1185
Glasgow-Blatchford score, for upper gastrointestinal bleeding, 883*b*, 883*t*
Glasgow Coma Scale, 2386, 2386*t*
Glatiramer acetate (Copaxone, Glatopa), for multiple sclerosis, 2505*t*
Glatopa. *See* Glatiramer acetate
Glaucoma, 2607–2608
  acute, characteristics of, 2270*t*
  angle-closure, 2608, 2608*f*
  drug-induced, 2613
  primary open-angle, 2607, 2607*f*
  secondary open-angle, 2607–2608
  visual loss caused by, 2615
Gleason scoring system, 1384*t*, 1387
Glecaprevir/pibrentasvir, 2181*t*, 2182*t*, 2184
Gleevec. *See* Imatinib
Gleich syndrome, 1162
Gliadins, 935
Glibenclamide, for type 2 diabetes mellitus, 1541*t*
Gliclazide, for type 2 diabetes mellitus, 1541*t*
Glimepiride, for type 2 diabetes mellitus, 1541*t*
Glinides, for type 2 diabetes mellitus, 1541*t*
Glioma, 1312*f*
  astrocytic, 1314
  brain stem, 1315
  clinical manifestations of, 1315–1316
  definition of, 1314
  diagnosis of, 1314–1316, 1315, 1315*f*
  epidemiology of, 1314
  optic, 1315
  pathobiology of, 1314–1315
  treatment of, 1315*b*
Glipizide, for type 2 diabetes mellitus, 1541*t*
Global coagulation laboratory, 1169
Global health, 21–25
  challenge, 23–25
  definition of, 21
  leading causes of deaths, 21, 22*f*
  leading causes of disabilities, 21, 23*f*, 24*f*
  leading underlying risk factors, 23, 24*f*
  life expectancy and, 21, 21*f*
Global ischemic injury, 2462
Global Partnership for Zero Leprosy, 2053
Global Registry of Acute Coronary Events (GRACE) risk score calculator, 373, 374*t*, 384.*e1f*
Global warming, 87
Globoid cell leukodystrophy, 2510
Globulin genes, 1113*f*
Globus pharyngeus, 2652
Glomerular basement membrane, 776
Glomerular capillaries, 729–730
Glomerular disorders/diseases, 776. *See also* Glomerulonephritis
  in amyloidosis, 788
  chronic kidney disease and, 833*t*
  clinical manifestations of, 776
  in COVID-19-associated nephropathy, 789
  definition of, 776
  in diabetes mellitus, 788
  diagnosis of, 776
  epidemiology of, 776
  in fibrillary glomerulopathy-immunotactoid glomerulopathy, 788
  with genetic defects, 786–787
  in human immunodeficiency virus-associated nephropathy, 789
  in light-chain deposition disease, 788, 788*f*
  in mixed cryoglobulinemia, 789
  in monoclonal gammopathy of renal significance, 788
  other, 787–789
  pathobiology of, 776
  proteinuria associated with, 776
  in systemic lupus erythematosus, 787–788, 787*b*–788*b*, 787*f*, 787*t*, 788*f*
  in thrombotic microangiopathies, 789
Glomerular filtration rate (GFR), *e1t*–*e8t*
  antiretroviral therapy and, 2302
  chronic kidney disease by, 833*t*, 835*f*
  complications of, treatment of, 839*b*
  evaluation of, 837, 839*t*
  plasma creatinine and, 721, 721*f*, 721*t*
  in sickle cell disease, 1114
Glomerular syndromes, 726–728
  diagnosis of, 727–728
  genetic testing for, 728, 728.*e1f*
  laboratory testing of, 727–728
  renal biopsy for, 728
  serologies for, 727–728
Glomerulonephritis, 736, 2164
  acute, 783
  Alport syndrome, 787
  complement-mediated membranoproliferative, 786, 786*t*
  immune complex, pneumonia with, 784*t*
  membranoproliferative, 785–786, 786*b*, 786*f*, 786*t*
  pauci-immune, 1716
  post-streptococcal, 783*b*, 1918, 1918*b*
  rapidly progressive, 784–786, 784*f*
    anti-glomerular basement membrane disease, 784, 784*b*, 784*f*, 784*t*
    classification of, 784*t*
    clinical manifestations of, 785
    diagnosis of, 785
    IgA nephropathy and, 781*b*
    immune complex, 785
    pauci-immune, 785–786
    prognosis for, 785
    treatment of, 785*b*, 785*f*
    vasculitis-associated, 785

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Glomerulosclerosis, focal segmental, 778, 779*b*, 779*f*, 779*t*
Glomerulus
  anatomy, 729
  renal pathologic processes that affect, 776
Glossomegaly, in amyloidosis, 1306*f*
Glossopharyngeal neuralgia, 2384
GLP-1. *See* Glucagon-like peptide-1
Glucagon
  for acute poisoning, 693*t*
  for hypoglycemia, 1557
  secretion of, 1552
Glucagon-like peptide-1 (GLP-1), 932
Glucagon-like peptide-1 (GLP-1) agonists, 262
  for chronic kidney disease, 839*b*
  for obesity, 1467*b*
  for type 2 diabetes mellitus, 1540*b*, 1541*t*
Glucagonomas, 1561*t*, 1563–1564, 1564*b*, 1564*f*
Glucocerebroside, for Gaucher disease, 1420*t*, 1421*b*
Glucocorticoid(s), 144*t*
  adipose tissue metabolism and, 145
  for adrenal insufficiency, 1528*b*
  bones and, 145
  cardiovascular system and, 145
  central nervous system and, 145
  clinical use of, 145–146
  endocrine diseases caused by, 1475*t*
  for eosinophilic syndromes, 1164*b*
  excess of, 1520
  history of, 144–146
  inflammation and, 144–145
  inhaled, for asthma, 541*b*
  liver metabolism and, 145
  monitoring of, 146
  muscle metabolism and, 145
  osteoporosis caused by, 145
  in pregnancy, 146
  for rheumatic diseases, 1712
  for rheumatoid arthritis, 1755*b*, 1756*t*
  for skin diseases, 2697–2698, 2698*t*
  systemic, for asthma, 541*b*
  tapering regimens for, 146
  toxicity of, 146
  withdrawal from, 146
Glucocorticoid deficiency, 739
Glucocorticoid-induced osteoporosis, 1643*b*
Glucocorticoid receptor, 144, 144*f*
Glucocorticoid-remediable hyperaldosteronism, 816*t*
Gluconeogenesis, hypoglycemia due to defects in, 1552*t*, 1555
Glucose, *e*1*t*–*e*8*t*, 1534–1535, 1534.*e*1*f*
  in bacterial meningitis, 2514
  blood, 1624
  cardiovascular disease and, 1550
  concentration of, 1551
  dipstick for, 722
  in parenteral nutrition, 1450
  physiology of, biochemical pathways in, 1553*f*
Glucose-6-phosphate dehydrogenase (G6PD), in erythrocytes, *e*8*t*–*e*9*t*
Glucose-6-phosphate dehydrogenase (G6PD) deficiency, 1100, 1398*t*
  adverse drug reactions and, 132
  clinical manifestations of, 1101–1102, 1101*t*
  diagnosis of, 1102
  epidemiology and pathobiology of, 1098*f*, 1100–1101
  features of, 1101*t*
  treatment of, 1102*b*
Glucose control, cardiovascular disease and, 220
Glucose intolerance, 1563
Glucose phosphate isomerase (GPI) deficiency, 1099–1100
Glucose tolerance test (GTT), *e*1*t*–*e*8*t*
Glucose transporter isotype 1 (Glut1), 2461
Glucose transporters (GLUT), 1415
α-1,4-Glucosidase, for Pompe disease, 1420*t*
α-Glucosidase inhibitor, for type 2 diabetes mellitus, 1540*b*, 1541*t*
GLUT. *See* Glucose transporters
γ-Glutamyl transpeptidase, 989, 1010
γ-Glutamyltransferase (GGT), *e*1*t*–*e*8*t*
Glutaric aciduria, type I, 1398*t*, 1403*t*
Glutathione metabolism, disorders of, 1102
Gluten-free diet, for celiac disease, 936*b*
Gluten-sensitive enteropathy, 1821
Glyburide, for type 2 diabetes mellitus, 1541*t*
Glycated hemoglobin (HbA1*c*), *e*1*t*–*e*8*t*, 1536*t*
Glycemic control
  for chronic kidney disease, 839*b*
  for diabetic nephropathy, 797*b*, 798*f*
Glycogen, 1415
  breakdown of, 1415, 1416*f*
  synthesis of, 1415
Glycogen storage diseases, 1415–1418
  clinical manifestations of, 1415, 1417*t*
  definition of, 1415–1418
  diagnosis of, 1415–1416
  differential diagnosis of, 1416
  epidemiology of, 1415
  pathobiology of, 1415, 1416*f*
  prognosis of, 1418
  treatment of, 1416*b*
  type Ib, 1145
Glycolic acid, 759
Glycolipids, 1093
Glycolysis, Embden-Meyerhof pathway of, 1098, 1098*f*
Glycophorin A, 1087
Glycophorins, 1094
Glycoprotein IIb/IIIa inhibitors, 374*t*
Glycopyrronium, 553*t*
Glycosaminoglycans (GAGs), 1724
Glycosylation defects, 2589*t*
Glycosylphosphatidylinositol, 1091
Glycylcyclines
  dosage of, 1895*t*
  mechanism of action, 1895*t*
  resistance mechanisms, 1893*t*
Glycyrrhizic acid, 749
GM-CSF. *See* Granulocyte-macrophage colony-stimulating factor
GNAS1 gene, 1661–1662
Gnathostoma spinigerum, 2176
Gnathostomiasis, 2176
  cutaneous or mucocutaneous, in travelers, 1889.*e*1*t*
GnRH. *See* Gonadotropin-releasing hormone
"God Committee", 9
Goiter, 1513*f*, 1515
  diagnosis of, 1508*f*, 1510*f*, 1515
  treatment for, 1515*b*
GOLD classification system, 548*f*
Golfer's elbow. *See* Medial epicondylitis
Goliath tarantula, 710
Golimumab
  description of, 151*t*
  for inflammatory bowel disease, 945*b*, 946*t*
  for rheumatoid arthritis, 1756*t*
Goltz syndrome, 1668
Gomori methenamine silver, for actinomycosis, 2068
Gonadal biopsies, 1575
Gonadal differentiation, 1569, 1571*f*
Gonadal dysgenesis, 1600
Gonadal steroidogenesis, 1569, 1569.*e*1*f*
Gonadotropin(s), 1496
  hypothalamic disease effects on, 1480–1481
Gonadotropin-releasing hormone (GnRH)
  description of, 1476–1477
  exogenous, 1477
  function of, 1476
Gonadotropin-releasing hormone (GnRH) agonists, for transgender women, 1578*b*, 1579*t*
Gonadotropin-releasing hormone (GnRH) analogs, for endometriosis, 1596*b*
Gonococcal keratitis, 2606
Gonococcal septic arthritis, 1807
  clinical manifestations of, 1807
  diagnosis of, 1807
  epidemiology of, 1807
  prognosis of, 1807
  treatment for, 1807*b*
Gonococcal urethritis, organisms causing, 1879*t*
Gonococcemia, 2741, 2741*f*
Gonorrhea, 2621*t*. *See also Neisseria gonorrhoeae*
  disseminated infection, 1949
    clinical manifestations of, 1949, 1949*f*
    diagnosis of, 1950
    prevention of, 1950
    prognosis of, 1950
    screening of, 1950
    treatment of, 1950*b*
  epidemiology of, 1879
  infectivity of, 1946
  in pregnancy, 1948–1949
Good syndrome, 1680, 1681*t*
Goodpasture syndrome, 784, 784*t*
  diffuse alveolar hemorrhage and, 568, 569
Gooseneck sign, 247
Gordon syndrome, 816*t*
Gorlin formula, 402–403
Goserelin acetate, for breast cancer, 1369*b*
Gout, 1708, 1717*t*, 1718*f*, 1810, 2689*t*
  advanced, 1811, 1812*f*
  alcohol use disorders and, 2356
  atypical presentations of, 1811*t*, 1812–1813
  classic, 1811, 1812*f*
  clinical manifestations of, 1811–1813
  definition of, 1810
  diagnosis of, 1813, 1813*f*
  epidemiology of, 1810
  flares of, 1811, 1813*b*
  monosodium urate monohydrate crystals and inflammation in, 1811
  pathobiology of, 1810–1811, 1810*t*–1811*t*, 1811*t*
  prevention of, 1813*b*, 1814*t*
  renal urate underexcretion in, 1810–1811, 1810.*e*3*f*
  treatment of, 265*b*, 1813*b*
  urate overproduction in, 1811
Gouty tophi, 1812*f*
Gowns, for HIV transmission prevention, 2300
GPCR. *See* G protein-coupled receptor
GPI. *See* Glucose phosphate isomerase
Graduate Medical Education (GME), 46
Graft rejection, after hematopoietic cell transplantation, 1211
Graft-*versus*-host disease (GVHD), 938, 1210–1212
  acute, 1210, 1210*b*, 1210*t*
  chronic, 1210, 1211*b*
  hematopoietic stem cell transplantation causing, 204–205, 1852–1853
  mechanisms of, 206
  strategies to prevent, 206–207
  transfusion-associated, 1203
Graft-*versus*-tumor (GVT), 206
Grafts, 397, 398*f*
Grains, dietary guidelines for, 57.*e*3*t*
Gram-negative bacillary meningitis, 2511, 2515*b*, 2519
Gram-negative organisms, 416, 419*t*
Gram-positive rod infections, 1930–1938
  caused by *Bacillus* species, 1930, 1930*f*, 1930*t*
  caused by *Corynebacterium*, 1933
  caused by *Erysipelothrix*, 1936
  caused by *Listeria monocytogenes*, 1937–1938
Gram stain, 1892
Gram-stained smear, in bacterial meningitis, 2513–2514
Granisetron, for nausea and vomiting, 863*t*
Granular cast, 722–723, 724*f*
Granulocyte colony-stimulating factor (G-CSF), 1065, 1200, 1206
  for febrile neutropenia, 1854*b*
Granulocyte-macrophage colony-stimulating factor (GM-CSF), pulmonary alveolar proteinosis and, 566–567
Granulocyte transfusion, 1200, 1205
Granuloma, 2033
  eosinophilic, 1155
  in sarcoidosis, 600
Granuloma inguinale, 2004
  chancroid and, 1951
  characteristics of, 1881
  clinical manifestations of, 2004, 2004*f*
  definition of, 2004–2005
  diagnosis of, 2004
  differential diagnosis of, 2004
  epidemiology of, 2004
  organisms causing, 1879*t*
  pathobiology of, 2004
  prognosis of, 2005
  treatment of, 1881*b*, 2004*b*
Granulomatosis with polyangiitis, 582, 1796–1797, 1797*f*, 2574*t*, 2652, 2652.*e*1*f*
  eosinophilic, 573, 582
  epidemiology of, 1793*t*
  flow-volume curve of, 529*f*
  pathologic characteristics of, 1793*t*
  prognosis of, 1797*b*
  treatment of, 1797*b*
Granulomatous amebic encephalitis, 2150
Granulomatous arthritis, 1736
Granulomatous disorders, 1659, 1659*b*, 2001*t*
Granulomatous liver diseases, 1029–1030, 1030*t*
Granulomatous lobular panniculitis, 2735
Granulomatous mediastinitis, pulmonary histoplasmosis and, 2082
Granulomatous meningitis, 2646
Granulomatous mycosis fungoides, 2734
Granulomatous myositis, 1788*t*
Granulomatous peritonitis, 957
Graves dermopathy, 1512
Graves disease, 1509
  clinical manifestations of, 1510*f*, 1512–1513
  diagnosis of, 1512
  hyperthyroidism and, 1472
  non-thyroid complications of, 1512
  radiographic evaluation of, 1511*t*
  treatment for, 1511*b*, 1511*t*, 1513*b*
Graves ophthalmopathy, 1510*f*, 1512
Gray platelet syndrome, 1185
Grazoprevir/elbasvir, for hepatitis C infections, 2181*t*, 2182*t*, 2185
Greater trochanter pain syndrome, 1746–1747, 1746*b*, 1746*f*
Greenhouse gas emission, 89
Griscelli syndrome II, 1145
Griseofulvin, 2699
Groin hernia, 952*b*
Gross hematuria, 856
Ground-glass opacities, 520
Group A β-hemolytic streptococci
  cellulitis caused by, 2739–2740
  impetigo caused by, 2739
Group A β-hemolytic *Streptococcus pyogenes*, causing pharyngitis, 2648
Group A streptococcus infections, 1913–1918
Growth differentiation factor-15, 260.*e*1*t*
Growth factors
  hematopoietic, 1064–1065
  receptors, 152
Growth hormone (GH), *e*1*t*–*e*8*t*, 1488–1490
  acromegaly and, 1489, 1489*b*, 1490*f*
  deficiency of, 1488–1489, 1489*b*
  endocrine diseases caused by, 1475*t*
  excess of, 1489, 1489*b*
  gigantism and, 1489, 1489*b*
  gluconeogenesis and, 1552
  hypothalamic disease effects on, 1480
  insufficiency tests of, 1484*t*
  metabolic effects of, 1488
  pathobiology of, 1488
  skeletal muscle functions of, 1488
  tests of, 1488*t*
Growth hormone-releasing factor secreting neuroendocrine neoplasms (GFRomas), 1561*t*, 1565, 1565*b*
Growth hormone-releasing hormone (GHRH), 1477
Growth hormone secretagogue receptor, 1477
Guanabenz, 451*t*
Guanarito virus, 2265*t*
Guanfacine, 451*t*
Guanylate cyclase stimulation, for pulmonary hypertension, 496*b*
Guillain-Barré syndrome, 106, 652, 2560
  botulism *versus*, 1928
  Campylobacter jejuni and, 1960
  cerebrospinal fluid findings in, 2374*t*
  clinical manifestations of, 2571
  definition of, 2571
  diagnosis of, 2571
  differential diagnosis of, 2571, 2572*t*
  enteric infections and, 1870*t*
  epidemiology of, 2571
  Mycoplasma pneumoniae in, 2007
  pathobiology of, 2571
  rhabdomyolysis *versus*, 716
  treatment of, 2571*b*
Gummas, 2017
Gummatous syphilis, 2014
Guselkumab (Tremfya), for total knee arthroplasty, 1830.*e*1*t*
Gustatory hyperhidrosis, 2555
Gut transit, irritable bowel syndrome and, 893
Guttate hypopigmentation, 2743, 2743*f*
Guttate psoriasis, 2705
GVHD. *See* Graft-*versus*-host disease
GVT. *See* Graft-*versus*-tumor
GWAS. *See* Genome-wide association studies
Gynecologic cancers, 1375–1382
  approach to survivors of, 1381
  cervical cancer, 1375, 1375*t*
  endometrial cancer, 1377, 1377*f*, 1377*t*, 1378*b*

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Gynecologic cancers *(Continued)*
fallopian tube cancer, 1379
ovarian cancer, 1379
uterine fibrosis, 1382, 1382*b*

H

H_1-receptor antihistamines, for skin diseases, 2700
H1N1, in travelers, 1889.*e1t*
H2-histamine antagonists, 1460*t*
HA20. *See* Haploinsufficiency of A20
HACEK gram-negative organisms, 416
Haemophilus ducreyi, 983, 1950. *See also* Chancroid
Haemophilus influenzae, 1952–1954
acute bronchitis and, 605
bacteremia caused by, 1953
Brazilian purpuric fever caused by, 1954
cellulitis caused by, 1953
clinical manifestations of, 1953–1954
definition of, 1952, 1952*t*
endocarditis caused by, 1953
epidemiology of, 1952–1953
epiglottitis caused by, 1953
gynecologic and urologic infection caused by, 1953
infectious caused by, 2510
meningitis caused by, 1953
otitis media caused by, 1953
pathobiology of, 1953
pericarditis caused by, 1953
pneumonia caused by, 1953
prevention of, 1954
prognosis of, 1954
purulent conjunctivitis caused by, 1954
septic arthritis caused by, 1954
sinusitis caused by, 1953
site of colonization of, 1952*t*
tracheobronchitis caused by, 1953
treatment of, 1954*b*, 2515*b*
Haemophilus influenzae aegyptius, 1954
Haemophilus influenzae type B vaccine, 66*t*, 76.*e1t*, 77*f*, 78–79, 1954
Haemophilus parainfluenzae, 1954
Hageman factor, 1189*t*
Hailey-Hailey disease, 2687.*e4t*
Hair
normal, 2747
toxicants and, 685
Hair cells, 2644
Hair cycle, 2747
Hair disorders, 2747
in children, 2750–2751
excessive hair growth, 2751
racial differences and, 2751, 2751*f*
Hair follicles, 2747
Hair loss, 2747, 2747*t*
Hair shaft, 2747
Hair transplants, 2701
Hairy cell leukemia, 1272, 1272*f*
Hairy leukoplakia, 2623, 2623*f*
Halaven. *See* Eribulin mesylate
Hallucinogens
abuse of, 2364
clinical manifestations and diagnosis of, 2364
epidemiology of, 2364
pathobiology of, 2364
treatment of, 2364*b*
central nervous system effects of, 685*t*
Halogenated hydrocarbons, 88*t*
Haloperidol, *e10t*–*e11t*
for psychotic disorders, 2346*t*
Halos around lights, 2599
HAM/TSP. *See* HLTV-associated myelopathy/tropical spastic paraparesis
Hamartoma, hypothalamic, 1479
Hamman-Rich syndrome, 578
Hand-foot-and-mouth disease, 2259–2260, 2260*b*, 2520–2521
Hand-Schüller-Christian disease, 1155
Hands
disorders of, 1745–1746
injury of, occupational, 86*t*
rheumatoid arthritis of, 1751, 1752*f*
Handwashing, for common cold, 2194
Hansen disease. *See* Leprosy
Hantaan virus, 2265*t*
Hantavirus, 99, 99.*e1t*, 2264
Hantavirus pulmonary syndrome, 2268*t*
Haploinsufficiency of A20 (HA20), 1731*t*, 1736
Haplotype, 204
Haptoglobin, *e1t*–*e8t*
Harlequin syndrome, 2555
Hartnup disease, 816*t*
Hashimoto encephalopathy, 2536
Hashimoto-Pritzker disease, 1156
Hashimoto thyroiditis, 1507
HAV. *See* Hepatitis A virus
Hax-1, 1144
Hay fever, 2628
HAZ. *See* Height-for-age Z-score
HbA1*c*. *See* Glycated hemoglobin
HBeAg-negative chronic hepatitis B, 1011
HBGAs. *See* Histo-blood group antigens
HBO. *See* Hyperbaric oxygen
HBV. *See* Hepatitis B virus
HC-cobalamin complex, 1118–1119
HCG. *See* Human chorionic gonadotropin
HCN channels, 300–301
HCoVs. *See* Human coronaviruses
HCP. *See* Hereditary coproporphyria
HCV. *See* Hepatitis C virus
HDCV. *See* Human diploid cell vaccine
HDL cholesterol (HDLC), *e1t*–*e8t*
Head and neck, examination of, 29–30
Head and neck cancer, 1320
clinical manifestations of, 1322
definition of, 1320–1328, 1320*f*
diagnosis of, 1322–1324
dietary factors for, 1321
environmental, 1328
environmental carcinogens and, 1321
epidemiology of, 1320–1321
Epstein-Barr virus and, 1320
human immunodeficiency virus and, 1321
human papillomavirus and, 1320, 1328
human papillomavirus-related, 2622
hypopharynx, 1320
immunology of, 1322
ionizing radiation and, 1321
larynx, 1320
leukoplakia and, 1321
nasopharynx, 1320
occupational exposures associated with, 1321
oral cavity, 1320
oropharynx, 1320
pathobiology of, 1321–1322
pathology of, 1323, 1324*f*
prevention of, 1328
prognosis of, 1328
radiation therapy for, 1327*b*
recurrent/metastatic, 1327*b*
salivary glands, 1320
sex and genetic risk factors of, 1321
staging of, 1323–1324, 1325*t*
supportive and palliative care for, 1327*b*
surgery for, 1327*b*
systemic therapies for, 1327*b*
treatment for, 1327*b*
viral carcinogenesis in, 1321
viruses and, 1320–1321
Head infection, 1939
Head injuries, 700*b*
Head lice, 711, 711*b*
Head pain, neurologic diseases that cause, 2371–2372
Head-thrust test, 2646
Head tremors, 2489
Headaches, 2376–2385
in acromegaly, 1489
in brain abscess, 2525
in brain tumors, 1311
chronic daily, 2382, 2382*b*
clinical manifestations of, 2376, 2377*t*
cluster, 2381, 2381*t*, 2382*b*
definition of, 2376–2378
diagnosis of, 2376–2377, 2377*t*
epidemiology of, 2376
in epilepsies, 2425
glossopharyngeal neuralgia causing, 2384
intracranial hypertension causing, 2383, 2383*b*
intracranial hypotension causing, 2383, 2384*b*, 2384*f*
migraine, 2378–2380
pathobiology of, 2376
prevention of, 2377
prognosis for, 2377–2378
Headaches *(Continued)*
pseudotumor cerebri causing, 2383, 2383*b*
secondary cause of, 2382–2384
sinus, 2382
temporal arteritis causing, 2383
tension-type, 2380–2381, 2380*b*
treatment of, 2377*b*
trigeminal neuralgia causing, 2384, 2384*b*
in women, medications for, 1608*t*
Health
cardiovascular, new paradigm for, 221, 222*t*
climate change effects on, 89
environmental impact from, 89
health care professionals and, 91.*e1f*, 91
how it affects health, 89, 90*f*, 91*t*
recent evidence and projected impacts of, 90, 90*f*
research priorities for, 91
global, 21
challenge, 23
definition of, 21
leading causes of deaths, 21, 22*f*
leading causes of disabilities, 21, 23*f*, 24*f*
leading underlying risk factors, 23, 24*f*
life expectancy and, 21, 21*f*
measures of, 40–43, 40*t*
attributes of, 42*t*
as parts of a system, 42–43, 43*f*
selecting, based on evidence, 41
sources of, 41.*e1t*
types of, 40.*e2f*
uses of, 41*t*
population, determinants of, 42
Health Access and Quality of Care Index, 23–25
Health care
access to, 19, 19*f*–20*f*, 20*f*
barriers to, 1606
costs of, 40
measures of, 40, 40*t*
attributes of, 42*t*
as parts of a system, 42, 43*f*
selecting, based on evidence, 41
sources of, 41.*e1t*
types of, 40.*e1f*
uses of, 41*t*
Health care expenditures, for cardiovascular diseases, 219
Health care professionals, climate change and, 91.*e1f*, 91
Health care quality, measures of, 40, 40*t*, 40.*e1f*
Health care resources, measures of, 40, 40*t*, 40.*e1f*
Health care workers, HIV transmission to, 2299–2300
Health care-associated infections, 1862–1868
active surveillance testing for, 1867
antimicrobial stewardship for, 1865.*e1t*, 1867
blood-borne viruses causing, 1865, 1865.*e1t*
burden of, 1862–1868
catheter-associated urinary tract infections, 1862*t*, 1866
central line-associated blood stream infections, 1862*t*, 1865, 1865.*e1t*
Clostridioides difficile causing, 1865
coagulase-negative staphylococci causing, 1909
decolonization therapy for, 1867
definition of, 1862
device-associated infections, 1865, 1866
due to *Corynebacteria*, 1934*t*
enterococcal infections causing, 1920
epidemiology of, 1862, 1862*t*
fungi causing, 1865
health care delivery-related factors, 1863
health care-related factors, 1863
host-related factors, 1863
incentives and penalties for, 1868
interfacility and regional collaboration for, 1868
multidrug-resistant bacteria and, 1864–1865, 1864*t*
pathobiology of, 1862–1867
pathogen-related factors, 1863
pathogens in, 1863–1865
prevention of, 1865.*e1t*, 1867–1868
respiratory viruses causing, 1865
surgical site infections, 1862*t*, 1866–1867
ventilator-associated pneumonia, 1862*t*, 1866
viruses causing, 1865
Health care-associated pneumonia, 616*t*
Health delivery systems, activities of, 47, 48*f*
Health disparities, definition of, 17
Health-enhancing physical activity, 61
Health equity, 17
Health insurance coverage, 19
Health outcomes
ethnic disparities in, 17
racial disparities in, 17
socioeconomic disparities in, 18–19
Health-related physical fitness, 61
Health span, 116
Healthcare-associated infections, *Pseudomonas aeruginosa* and, 1968
Healthcare Effectiveness Data and Information Set, 41
Hearing, 2641
geriatric assessment of, 117
screening for, 55
Hearing aids, 116
Hearing loss
acoustic neuroma causing, 2642
bedside test for, 2641
central, 2642
cochlear damage causing, 2641
conductive, 2641
diagnosis of, 2641
differential diagnosis of, 2641–2642
drugs as caused of, 2642
epidemiology of, 2641
evaluation of, 2641, 2642*f*
mumps and, 2226*t*
noise-induced, 2642
presbycusis causing, 2642
prevalence, 2641
prevention of, 2643
prognosis for, 2643
sensorineural, 2641–2642
tinnitus, 2643, 2643*b*, 2643*f*
treatment of, 2642*b*
Heart
anatomy of, 224–225
boot-shaped, 247
conduction abnormalities, 231, 231*t*, 232*f*
conduction system of, 223–224, 224*f*, 228, 228*f*
development of, 223, 223.*e2f*
energetics of, 225
examination of, 30, 258
Frank-Starling law of, 225, 226*f*
function of, 223
functional measurement of, 239
inspection of, 213
ion channels expressed in, 300.*e1f*
normal activation of, 228, 228*f*
physiology of, 225–226
pressure-volume area, 225–226, 226*f*
regeneration of, 226
remodeling of, 301
structure of, 223–224, 223.*e1f*
ultrastructure of, 224
univentricular, 354
work of, 226
Heart block
complete, 321, 321*f*
functional, 302
management of, 384*b*
Heart defects, congenital, 347
Heart disease
acquired, 299
in adolescents, 110*t*
asymptomatic structural or functional, 264
causes of death, 17
chronic ischemic, 336
coexisting, 399
congenital, 347. *See also* Congenital heart disease
diagnosis of, 335*t*
echocardiographic findings, 242*t*
hemochromatosis and, 1440
hypertensive, 456
impulse conduction, disorders of, 302
impulse formation, disorders of, 301–302
prognosis for, 248–249, 248.*e1f*
in sarcoidosis, 602
structural, treatment of, 338*b*
valvular, 400–413
Heart failure, 226, 254–279, 262, 287.*e1f*
acute decompensated, 255, 255*t*
antihypertensive drug for, 454*t*
in aortic stenosis, 400
biomarkers, 260, 260.*e1t*

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Heart failure *(Continued)*
causes of, 254–255, 255*t*, 272*t*
classification of, 254, 254*f*
clinical manifestations of, 256–258, 257*f*, 257*t*
comorbidity and, 265*b*
coronary angiography findings, 261
definition of, 254–261
diagnosis of, 258–261
diastolic, 226
disparities, 254
drugs to use with caution in, 265*b*
ECG findings, 258, 259*f*–260*f*
education for, 265*b*
end-of-life considerations in, 278
epidemiology of, 254–255
evaluation of, 30, 262
fluid retention in, 735.*e1f*
hemodynamic monitoring in, 261
in HIV, 2317, 2317*b*
hypertrophic cardiomyopathy causing, 265*b*
hypervolemia and, 735–736
invasive diagnostics for, 261
laboratory findings, 259–260
on left ventricular ejection fraction, 264
left ventricular systolic dysfunction causing, 265*b*
practical use of ACEIs and ARBs for, 265*b*, 266*t*
practical use of β–blockers for, 265*b*, 267*t*
practical use of mineralocorticoid receptor antagonists for, 265*b*, 270*t*
practical use of SGLT2 inhibitors for, 265*b*, 271*t*
management of, 262, 384*b*
with mildly reduced left ventricular ejection fraction, 265*b*, 277*f*
misdiagnosis of, 261
nonischemic dilated cardiomyopathy causing, 265*b*
nuclear cardiology findings, 261
obstruction and, 532
outpatient follow-up for, 265*b*
pathobiology of, 255–256, 255*t*, 255.*e1f*
patterns of presentation, 258, 259*f*, 260*f*
physical findings, 257–258
pre-heart failure, 264
preoperative evaluation considerations, 2663
with preserved ejection fraction, 256, 256*t*
with preserved left ventricular ejection fraction, 265*b*, 278*f*
prognosis for, 278
with reduced left ventricular ejection fraction, 255, 264, 265*f*
second-line treatments for, 265*b*, 272*f*
refractory, 265*b*
risk factors for, 262–264
stages of, 262–278, 263*f*
subtypes of, 265*b*
symptomatic, 264–278
symptoms of, 256–257
therapies for, 262*t*
trajectories of, 12.*e1f*
treatment of, 264*b*
valvular heart disease causing, 265*b*
ventricular tachycardia in, 337
weight loss and, 860*t*
Heart-lung transplantation, 633
Heart murmurs, 214
cause of, 216*t*
systolic, bedside identification of, 216*t*
Heart rate, 226
abnormal, 34*t*
elevated, 33*t*, 34
measurement of, 33
normal, 318
normal resting, 229, 229*t*
Heart size, 244–245
Heart sounds, 258
first, 214, 215*f*
second, 214
tumor plop, 298
Heart transplantation
for Chagas disease, 2128*b*
indications for, 274*t*
Heart valves
location of, 249*f*
prosthetic
advantages and disadvantages of, 412*t*
choices among, 411, 412*f*
postoperative care of, 411
Heartburn, 852*t*, 865
esophageal disease and, 902
functional, 899
clinical manifestations of, 900
diagnosis of, 900
epidemiology of, 900
pathobiology of, 900
prognosis of, 900
Rome IV diagnostic criteria for, 900*t*
treatment of, 900*b*
gastroesophageal reflux disease and, 903, 903*f*
peptic strictures and, 905
in Zollinger-Ellison syndrome, 1563
Heartland viruses, 2065*t*, 2275*t*
Heat, 88*t*
Heat disorders, 678
Heat exhaustion, 679, 679*t*
Heat illness, 678–680
clinical manifestations of, 679, 679*t*
definition of, 678–680
epidemiology of, 678, 678*t*
factors predisposing to, 678*t*
management of, 679*t*
pathobiology of, 678, 678.*e1f*
prevention and treatment of, 679*b*, 679*t*
prognosis of, 680
Heat injury, 678.*e1f*, 679
Heat-labile toxin, of enterotoxigenic *E. coli*, 1962, 1962*t*
Heat rash. *See* Miliaria rubra
Heat-stable toxin, of enterotoxigenic *E. coli*, 1962, 1962*t*
Heat syncope, 679
Heatstroke, 679, 679*t*
characteristics of, 2270*t*
exertional, 678.*e1f*, 679*t*
α-Heavy chain disease, 1304, 1304*b*
γ-Heavy chain disease, 1303–1304, 1304*b*
μ-Heavy chain disease, 1304, 1304*b*
Heavy chain diseases, 1303–1304
Heavy drinking, 2353
HEEADSSS assessment, for adolescents, 111
Height, cancer and, 1244
Height-for-age Z-score (HAZ), 1445
Height vertigo, 2644
Heimlich maneuver, CPR and, 313*b*
Heinz bodies, 1100, 1100*f*, 1116
Helicobacter cinaedi, 1960
Helicobacter fennelliae, 1960
Helicobacter pylori
cancer and, 1245
carbon-13/-14 urea breath test for, 919
epidemiology of, 914
gastric adenocarcinoma and, 1340
gastric lymphoma and, 1279
gastric mucosal biopsy for, 918
histology of, 914*f*
pathobiology of, 914, 914*f*
prevention of, 921
serology testing for, 918
stool antigen test for, 918*t*
testing for, 918
triple therapy for, 919*b*–920*b*
ulcers associated with, 919*b*, 920*t*
Helium, 88*t*
Heller myotomy, for achalasia, 908*b*
HELLP syndrome, 998, 1178–1179, 1627
Helmet cells, 1068*f*
Helminth infections, of liver, 1025–1029
Helminthic infections, 2116
of liver, 1024–1029, 1025
treatment of, 2112*t*
Hemangioblastoma, 1316
Hemangioendotheliomas, 967
Hemangiomas, 967, 2731–2733, 2733*b*, 2734*f*
of eyelid, 2612
hepatic, 991, 992*f*
Hemarthroses, acute, hemophilia and, 1187, 1187*f*–1188*f*, 1188*b*
Hematemesis, 856, 864–865
Hematochezia, 882
with abdominal pain, 856
colonic sources of, 885*t*
management algorithm for, 885*f*
Hematocrit (HCT), *e8t*–*e9t*, 1074, 1076*t*
Hematologic disorders, mesenteric venous thrombosis and, 963*t*
Hematologic malignant neoplasms, characteristics of, 2270*t*
Hematologic paraneoplastic syndromes, 1239
Hematologic system, systemic lupus erythematosus manifestations of, 1770
Hematoma
epidural, 2391
post-traumatic, 2390–2392
subdural, 2390
Hematopoiesis, 1064–1066
clonal, 1064
definition of, 1064
extramedullary, 527
Hematopoietic cell expansion, 1064
Hematopoietic cell grafts, T-cell depletion of, 206
Hematopoietic growth factors, 1064
for cancer, 1232*b*
clinical uses of, 1065–1066
Hematopoietic progenitor cells, 1064
Hematopoietic stem cell transplantation (HSCT), 1206–1212
for acute leukemias, 1262*b*
allogeneic, 1207, 1207*f*
for aplastic anemia, 1126*b*
autologous, 1208
for cancer, 1232*b*
complications after, 1209–1212
for follicular lymphoma, 1283*b*
future directions of, 1212
for hemophagocytic lymphohistiocytosis, 1161*b*
human microbiome and, 1840
in immunocompromised host, 1852–1853, 1853*t*
indications for, 1208–1209, 1208*f*
for less severe T-and B-cell combined defects, 1678*b*
for multiple myeloma, 1299*b*
for primary myelofibrosis, 1135*b*
risk of, for GVHD and marrow graft failure, 204
for sickle cell disease, 1114*b*
syngeneic, 1208
for Wiskott-Aldrich syndrome, 1678*b*
Hematopoietic stem cells, 1064, 1206
Hematopoietic syndrome, 93
Hematopoietic system
age-related changes in, 121
alcohol use disorders and, 2355
Hematoxic snake bite envenomation, characteristics of, 2270*t*
Hematuria, 722, 723*f*, 1366
gross, 856
microscopic, 776
in sickle cell disease, 1114
Heme
bilirubin conversion of, 994
biosynthesis, 1429, 1429*f*
catabolism of, 1429.*e1f*
dipstick for, 722
regulation of, 1429
Heme deficiency, 1430
Heme oxygenase, 995
Hemiballism, 2491–2492
Hemicrania continua, 2377*t*, 2380
Hemifacial spasm, 2496–2497
Hemiparetic gait, 2373*t*
Hemiptera, 711
Hemiscorpius lepturus, 710
Hemispatial neglect, 2409–2410, 2410*f*
Hemisphere infarction, 2468*f*
Hemochromatosis, 1438–1442
arthritis and, 1824, 1824*f*
classification of, 1438*t*
clinical manifestations of, 1439–1440, 1439*t*
definition of, 1438–1442
diagnosis of, 1440–1441, 1441*f*
epidemiology of, 1438
hereditary, 294, 294*b*
pathobiology of, 1438, 1439*f*
physical findings in, 1440*t*
prognosis of, 1442
quantifying, 1441
screening for, 1441
symptoms and signs of, 1440, 1440*t*
treatment of, 1441*b*
Hemodialysis, 130, 841
access issues in, 842
complications of, 841
optimal dialysis access for, 842
in septic shock, 673*b*
toxicants removed by, 698*t*
Hemodynamic compromise, 654
Hemodynamic disease, drug dose adjustment in, 130
Hemodynamics, in heart failure, 261
Hemoglobin, *e8t*–*e9t*, 1074
globin genes, 1113*f*
sickle, 1110
Hemoglobin A_{1c}, 1624
Hemoglobin C
description of, 1116
homozygous, peripheral blood smear of, 1070*f*
Hemoglobin concentration, 1076*t*
Hemoglobin E, 1106
Hemoglobin E thalassemias, 1106
Hemoglobin electrophoresis, *e8t*–*e9t*
Hemoglobin F synthesis, stimulation of, 1107*b*
Hemoglobin H disease, 1104, 1107*b*
Hemoglobin S, 1068*f*, 1110*f*
Hemoglobinopathies
arthritis associated with, 1822
high-oxygen-affinity, 1116
transfusion for, 1206
types of, 1114
unstable, 1109, 1116
Hemoglobinuria, paroxysmal nocturnal, 480, 480*b*
Hemolysis, 1070
Hemolysis, elevated liver enzymes, and low platelet count (HELLP), 1196
Hemolytic anemia, 1078, 1079*f*, 1079*t*, 1080*t*
autoimmune, 1087
cold, 1088, 1088*t*, 1090*f*
corticosteroids for, 1089*b*
diagnosis of, 1087
direct antiglobulin test for, 1087
epidemiology of, 1087
folic acid supplementation for, 1089*b*
laboratory test for, 1087
pathobiology of, 1087
rituximab for, 1089*b*
signs and symptoms of, 1087
warm, 1087, 1089*t*
cause of, 1072*t*
definition of, 1086, 1087*t*
Heinz body, 1116
microangiopathic, in thrombotic thrombocytopenic purpura, 1177
peripheral blood smear of, 1070
red blood cell membrane and metabolic defects, 1093–1102
splenomegaly associated with, 1152
Wilson disease and, 1437
Hemolytic transfusion reactions, 1092
Hemolytic-uremic syndrome, 728, 1178, 1731*t*, 1961
clinical manifestations of, 1178
definition of, 1178
enteric infections and, 1870*t*
pathobiology of, 1178
prevention of, 1178*b*
treatment of, 1178*b*
Hemoperfusion, 130
Hemophagocytic lymphohistiocytosis, 1159, 1160*t*, 1161*b*, 1161*f*, 1161*t*, 1684
Hemophilia
acquired, 1191, 1191*b*
arthritis associated with, 1822
hereditary, 1187
Hemoptysis
alveolar hemorrhage and, 568
in alveolar hemorrhagic disorders, 566
approach to, 515–519
causes of, 518*t*
diagnosis of, 516–519, 518*f*
invasive mucinous adenocarcinoma and lepidic predominant nonmucinous adenocarcinoma and, 569
special evaluation for, 519*t*
treatment of, 519*b*
Hemorrhage
alveolar, 566*t*, 568
clinical manifestations of, 568, 568.*e1f*
definition of, 568
diagnosis of, 569, 569*f*, 569.*e1f*
pathobiology of, 568
prognosis of, 569
treatment for, 569*b*
cerebral, 2463
gastrointestinal. *See* Gastrointestinal bleeding
peptic ulcer causing, 921–922, 922*t*
splinter, 216
subarachnoid. *See* Subarachnoid hemorrhage

Copyrighted material

Hemorrhagic cerebrovascular disease, 2474–2482
Hemorrhagic colitis, *Escherichia coli* and, 1961, 1963
Hemorrhagic cystitis, 2205
  BK polyomavirus-associated, 2229, 2229*b*
Hemorrhagic disorders, vascular
  acquired, 1186
  hereditary, 1186
Hemorrhagic fevers
  in travelers, 1890*t*
  viral, 99, 2264–2273
    antiviral therapy for, 2269*b*
    bat-borne viruses, 2264
    clinical management of, 2269*b*
    clinical manifestations of, 2267, 2268*t*
    contact tracing of, 2272
    definition of, 2264–2273
    diagnosis of, 2267–2269
    differential diagnosis of, 2270*t*
    epidemiology of, 2264–2266
    human-to-human transmission of, 2266
    infection prevention and control in, 2272
    laboratory testing for, 2269, 2271*t*
    maintenance in nature, 2264–2266
    mosquito-borne viruses, 2266
    nonspecific presentation of, 2268, 2272
    pathobiology of, 2266–2267
    pathogens that causes, 2264
    postexposure prophylaxis for, 2273
    in pregnancy, 2267, 2269*b*
    prevention of, 2272–2273
    prognosis for, 2273
    reservoir for, 2273
    ribavirin therapy for, 2272*t*
    rodent-borne viruses, 2264–2266
    sequelae of, 2273
    tick-borne viruses, 2266
    transmission to humans, 2264
    treatment of, 2269*b*
    vaccines for, 2272–2273
    vector control for, 2273
    viruses causing, 2265*t*
Hemorrhagic shock, 663*t*
  categorization of, 702*t*
  initial treatment of, 702*t*
Hemorrhagic smallpox, 2237, 2237*t*, 2270*t*
Hemorrhagic telangiectasia, hereditary, 1186, 1186*b*, 1186*f*, 1186*t*
Hemorrhoidectomy, operative, 978*b*
Hemorrhoids, 977
  clinical manifestations and diagnosis of, 977–978
  epidemiology and pathobiology of, 977
  external, 978, 978*f*
  internal, 977, 978*f*, 978*t*
  treatment for, 978*b*
Hemosiderinuria, 1092
Hemosiderosis, idiopathic pulmonary, 582
Hemostasis
  endoscopic, for upper gastrointestinal bleeding, 883*b*
  mechanisms of, 1165
  normal, 1165, 1165*f*
  point-of-care tests of, 1169
  screening tests of, 1166–1167, 1167*f*
    abnormal, 1167–1169, 1168*f*
Hemothorax, 626
Hemox-Analyzer, 1116
Hemp, 88*t*
Henderson-Hasselbalch equation, 639, 753
Hendra virus, 2065*t*
Henoch-Schönlein purpura, 965, 1798, 2715
  description of, 782
  pathologic characteristics of, 1793*t*
  treatment for, 1798*b*
Henry's law, 594
Heparin, 1165–1166
  for acute coronary syndrome, 374*t*
  bleeding caused by, 487*b*
  for disseminated intravascular coagulation, 1196*b*
  for hypercoagulable states, 477
  low-molecular-weight, 501*t*, 502, 503*t*
    for acute coronary syndrome, 374*t*
    in pregnancy, 1623*b*
  unfractionated, 501–502, 501*t*
    for acute coronary syndrome, 374*t*
    adverse effects of, 502
    dosage and monitoring of, 502
Heparin *(Continued)*
    effect of, reversing, 502
    in pregnancy, 1623*b*
  weight-based dosing of, 487*b*, 487*t*
Heparin-induced thrombocytopenia, 487*b*, 1174–1175
  clinical manifestations of, 1174–1175
  diagnosis of, 1174
  epidemiology of, 1174
  laboratory assays of, 1175*t*
  pathobiology of, 1174, 1174*f*
  prevention of, 1175*b*
  treatment of, 1175*b*
Heparin resistance, 478*b*
Hepatic adenomas, 991, 992*f*
Hepatic artery thrombosis, 969
Hepatic cirrhosis, in Wilson disease, 1436*f*
Hepatic cysts, 990, 991*f*
Hepatic disease, 968, 2246
Hepatic echinococcal cyst, 1029*f*
Hepatic encephalopathy, 986, 989*t*, 2544, 2544*b*
  alcohol causing, 2543
  cirrhosis and, 1037, 1038
  diagnosis of, 1040
  treatment of, 1040*b*
Hepatic fibrosis, autosomal recessive polycystic kidney disease and, 813
Hepatic glycogen release/storage, hypoglycemia due to, 1552*t*, 1555
Hepatic glycogenolysis, 1415
Hepatic hemangiomas, 991, 992*f*
Hepatic impairment, psychotropic medications and, 2678*t*
Hepatic mass, 989*t*
  approach to, 990–992, 991*f*
  solid, 990–992, 992*f*
Hepatic porphyria, 1428
Hepatic steatosis, with chemical shift imaging, 872*f*
Hepatitis
  acute, abdominal pain and, 854*t*
  acute viral. *See* Acute viral hepatitis
  autoimmune, 986, 1016, 1017*b*
Hepatitis A virus (HAV), 1004–1005
  clinical manifestations of, 1003*t*, 1004
  description of, 1002*t*, 1004
  diagnosis of, 1004, 1004*f*
  epidemiology of, 1004
  immunization for, 65*t*, 66*t*, 78*f*, 79
    adverse reactions of, 79
    indications for, 79
    schedule of, 76.*e*1*t*, 77*f*
    for traveler, 1886–1887, 1886*t*
  pathobiology of, 1004
  pathogen that cause, 1004
  prevention of, 1004
  prognosis of, 1004–1005
  prophylaxis for, 2309*t*
  in travelers, 1889.*e*1*t*
  treatment of, 1004*b*
Hepatitis B virus (HBV), 1245
  antiviral therapy for, 2181, 2181*t*
    adefovir as, 2183
    entecavir as, 2182
    interferons as, 2183
    lamivudine as, 2183
    telbivudine as, 2183
    tenofovir alafenamide as, 2181–2182
    tenofovir disoproxil fumarate as, 2181
  chronic, 1010
    cirrhosis in, 1012
    clinical manifestations of, 1010
    diagnosis of, 1011, 1011*t*, 1012*f*
    epidemiology of, 1010
    pathobiology of, 1010
    prevention of, 1011*b*, 1013*t*
    prognosis for, 1012
    treatment of, 1011*b*, 1013*t*
  clinical manifestations of, 1003*t*, 1005
  coinfection with, antiretroviral therapy for, 2304
  definition of, 1005
  description of, 1002*t*
  diagnosis of, 1005, 1005*t*, 1006*f*
  epidemiology of, 1005, 1358
  genotypes of, 1005
  immunization for, 65*t*, 66*t*, 78*f*, 79
    adverse reactions of, 79
    indications for, 76.*e*1*t*, 77*f*, 79
    schedule of, 76.*e*1*t*, 77*f*
    for traveler, 1886–1887, 1886*t*
Hepatitis B virus (HBV) *(Continued)*
  life cycle of, 1005
  pathobiology of, 1005
  pathogen that cause, 1005
  in pregnancy, 1626*b*
  prevention of, 1005–1006
  prognosis for, 1006
  prophylaxis for, 2309*t*
  screening for, 55
  transfusion-related transmission of, 1203
  transmission of, 1005
  treatment of, 1005*b*
Hepatitis C-associated cryoglobulinemia, 789
Hepatitis C virus (HCV)
  antiviral therapy for, 2181*t*, 2182*t*, 2183
    boceprevir as, 2185
    daclatasvir as, 2184
    daclatasvir/asunaprevir as, 2185
    glecaprevir/pibrentasvir as, 2184
    grazoprevir/elbasvir as, 2185
    ledipasvir/sofosbuvir as, 2184
    sofosbuvir as, 2185
    sofosbuvir/velpatasvir as, 2184
    sofosbuvir/velpatasvir/voxilaprevir as, 2184
  chronic, 986, 1013
    clinical manifestations of, 1013
    diagnosis of, 1014
    epidemiology of, 1013
    human immunodeficiency virus and, 1014*b*
    pathobiology of, 1013
    prognosis for, 1014
    recurrent, after liver transplantation, 1014*b*
    treatment of, 1014*b*, 1015*t*
  clinical manifestations of, 1007
  coinfection with, antiretroviral therapy for, 2304
  definition of, 1006
  description of, 1002*t*
  diagnosis of, 1007, 1007*f*, 1007*t*
  epidemiology of, 1006
  osteosclerosis associated with, 1668
  pathobiology of, 1007
  pathogen that cause, 1006
  in pregnancy, 1625–1626
  prevention of, 1008
  prognosis for, 1008
  screening for, 55
  transfusion-related transmission of, 1203
  transmission of, 1006
  treatment of, 1008*b*
Hepatitis D virus (HDV)
  chronic, 1015, 1015*b*
  clinical manifestations of, 1008
  definition of, 1008
  description of, 1002*t*
  diagnosis of, 1008
  epidemiology of, 1008
  pathobiology of, 1008
  pathogen that cause, 1008
  prevention of, 1008
  prognosis for, 1008
  treatment of, 1008*b*
Hepatitis E virus (HEV)
  chronic, 1016, 1016*b*
  clinical manifestations of, 1009
  definition of, 1008
  description of, 1002*t*
  diagnosis of, 1009
  epidemiology of, 1008–1009
  pathobiology of, 1008
  pathogen that cause, 1008
  prevention of, 1009
  prognosis for, 1009
  in travelers, 1889.*e*1*t*
  treatment of, 1009*b*
Hepatobiliary iminodiacetic acid (HIDA) scans, 1051
Hepatocellular carcinoma, 992, 992*f*, 1010, 1045
  clinical manifestations of, 1359
  diagnosis of, 1357.*e*3*t*, 1359–1360, 1360*f*–1361*f*, 1361*f*
  epidemiology of, 1357–1358
  hepatitis B virus causing, 1012
  magnetic resonance imaging of, 872*f*
  pathobiology of, 1359, 1359*f*
  risk factors for, 1357.*e*3*t*
  treatment of, 1360*b*
Hepatocellular necrosis, 1010
Hepatocyte dysfunction, 986
Hepatocytes, 986
Hepatojugular reflux, 215
Hepatomegaly
  diagnostic approach to, 989*f*
  glycogen storage disease *versus*, 1416
  hemochromatosis and, 1440
Hepatopulmonary syndrome
  cirrhosis and, 1038
  diagnosis of, 1040–1042
  treatment of, 1040*b*
Hepatorenal failure, 2031
Hepatorenal syndrome
  cirrhosis and, 1040
  treatment of, 1040*b*
Hepatosplenic candidiasis, 1023, 1024*b*, 1024*f*, 2090
Hepatosplenic T-cell lymphomas, 1287
Hepatosplenomegaly, fever and, 1849
Hepatotoxicity
  direct/intrinsic, 1018
  idiosyncratic, 1019
  indirect, 1021
Hepcidin, 1085, 1438, 1439*f*
Heptavalent botulinum antitoxin, 1928*b*
HER-2. *See* Human epidermal growth factor receptor 2
Herald patch, 2707, 2707*f*
Herald wave phenomenon, 2199
Herbicides, 88*t*
Herceptin. *See* Trastuzumab
Hereditary α-tryptasemia, 1693
Hereditary angioedema, 1690, 1731*t*
  acute attacks of, 1690*b*
  chronic therapy for, 1690*b*
  clinical manifestations of, 1688*f*, 1690
  complement system and, 201*t*
  diagnosis of, 1690
  epidemiology of, 1690
  pathobiology of, 1690
  prognosis of, 1691
  short-term prophylaxis for, 1690*b*
  treatment and prevention of, 1690*b*
Hereditary ATTR amyloidosis, 2560, 2560*b*
Hereditary breast cancer, 1250*t*
Hereditary coproporphyria (HCP), 1428*t*
Hereditary deafness, 2641
Hereditary elliptocytosis, 1096
  clinical manifestations of, 1097
  definition of, 1096
  epidemiology of, 1096
  pathobiology of, 1096–1097
  peripheral blood smear of, 1068*f*
Hereditary fructose intolerance, 816*t*
Hereditary hemochromatosis, 294, 294*b*, 992
Hereditary hemophilias, 1187
  clinical manifestations of, 1187–1188, 1187*f*, 1188*f*
  definition of, 1187
  diagnosis of, 1188
  epidemiology of, 1187
  genetics of, 1187
  pathobiology of, 1187
  prevention of, 1190–1191
  prognosis of, 1191
  treatment of, 1188*b*, 1189*t*
Hereditary hemorrhagic telangiectasia, 967, 1186, 1186*b*, 1186*f*, 1186*t*, 2550*t*
Hereditary leiomyomatosis, 1250*t*, 1363
Hereditary motor neuronopathy, 2565
Hereditary motor neuropathies, 2564*t*
Hereditary multiple exostoses, 1669
Hereditary nephropathies, 815–818, 816*t*
  cystinosis, 815
  cystinuria, 815
  Dent disease, 817
  distal renal tubular acidosis, 817, 818*b*, 818*t*
  distal tubule, 816*t*, 817
  Liddle syndrome, 817
  loop of Henle, 816*t*, 817
  proximal tubule, 815–817, 816*t*
Hereditary neutrophilia, 1141
Hereditary nonpolyposis colorectal cancer (HNPCC), 1250*t*, 1347, 1347*t*, 1377
Hereditary ovarian cancer, 1250*t*
Hereditary papillary renal cell carcinoma, 1250*t*
Hereditary paraganglioma, 1250*t*
Hereditary pyropoikilocytosis, 1094*f*, 1097
  diagnosis of, 1094*f*, 1097
  peripheral blood smear of, 1069*f*
  treatment of, 1097*b*

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Hereditary retinoblastoma, 1250*t*
Hereditary sensory and autonomic neuropathies, 2560
Hereditary spastic paraplegias, 2498, 2498*t*, 2564*t*
Hereditary spherocytosis, 1067*f*, 1094
  clinical manifestations of, 1095
  definition of, 1094, 1094*f*
  diagnosis of, 1094*f*, 1095–1096, 1095*t*, 1096*f*
  epidemiology of, 1094
  pathobiology of, 1094–1095
  treatment of, 1096*b*
Hereditary stomatocytosis, 1094*f*, 1097
Hermansky-Pudlak syndrome, 583
  type II, 1145
Hermaphroditism, true, 1574
Hernia, 952–953
  epigastric, 952*b*
  groin, 952*b*
  hiatal, 902, 910
  incisional, 952*b*
  inguinal, 952–953
  pelvic, 952*b*
  Spigelian, 953
  strangulated, abdominal pain and, 854*t*
  umbilical, 952*b*
Heroin. *See* Opioids
Herpangina, 2621*t*
  enteroviruses causing, 2259, 2260*b*
Herpes labialis, 2246*f*, 2621
Herpes simplex encephalitis, 1686*t*, 2247, 2247*b*, 2247*f*, 2408, 2532, 2532*t*, 2533*f*
Herpes simplex keratitis, 2605, 2606*f*
Herpes simplex virus (HSV) infections, 2244–2247, 2720, 2720*b*, 2721*f*
  aseptic meningitis caused by, 2521
  characteristics of, 2270*t*
  clinical manifestation of, 2245–2246
  definition of, 2244–2246
  diagnosis of, 2246
  of esophagus, 911
  gene therapy for, 2245
  genital, 2245
    characteristics of, 1880
    organisms causing, 1879*t*
    syphilis *versus*, 2019
  gingivostomatitis caused by, 2245
  in HIV, 2322*t*
  in immunocompromised hosts, 2246–2247, 2246*b*
  keratitis caused by, 2246, 2605, 2606*f*
  latency of, 2245, 2245.*e1f*
  meningitis caused by, 2246
  neonatal, 2247
  other cutaneous manifestations of, 2246
  pathobiology of, 2245
  pathogen that causes, 2244–2245
  pharyngitis and, 2650
  prevention of, 2246–2247
  primary, 2245.*e1f*, 2621*t*, 2622*f*
  primary prevention of, 2247
  recurrent, 2621*t*
  replication of, 2245.*e1f*
  secondary prevention of, 2246
  transmission of, 2245
  treatment of, 2246*b*
  type 1, 2532*t*
  type 2, 2532*t*
  virion of, 2245.*e1f*
Herpes zoster, 211*t*, 2689*t*, 2721, 2721*b*, 2721*f*
  immunization for, 66*t*
Herpes zoster ophthalmicus, keratitis caused by, 2605
Herpes zoster oticus, 2579
Herpesviridae, 2245
Herpesvirus infections, antiviral therapy for, 2186, 2187*t*, 2188*t*
  acyclovir as, 2186
  docosanol as, 2189
  famciclovir as, 2186
  fomivirsen as, 2189
  foscarnet as, 2188
  ganciclovir as, 2186
  letermovir as, 2188
  penciclovir as, 2186
  valacyclovir as, 2186
  valganciclovir as, 2186
Herpetic keratitis, 2246
Hers disease, 1417*t*
Heterochromia iridis, 2603
Heterosexual pubertal development, 1594
Heterotopic gastric mucosa, 913
Hexokinase deficiency, 1099
Hexose monophosphate shunt, 1098–1099
  disorders of, 1100
HFE mutations, 1438
Hiatal hernia, 902, 910
HIDA. *See* Hepatobiliary iminodiacetic acid
Hidradenitis suppurativa, 2723, 2723*b*, 2724*f*, 2745*f*
HIDS. *See* Hyperimmunoglobulinemia D with periodic fever syndrome
Hierarchy of hazard controls, 87
High-altitude diseases, 592–593
  clinical manifestations of, 593
  definition of, 592–593, 592*t*
  diagnosis of, 593
  epidemiology of, 592
  pathobiology of, 592–593
  prevention of, 593, 593*t*
  prognosis of, 593
  treatment of, 593*b*
High-altitude pulmonary edema, 592*t*
High-altitude retinal hemorrhage, 592*t*
High blood pressure, screening for, 53
High density lipoproteins, 1406, 1406.*e1f*
  high level of, 1410
  low level of, 1410
High-flow nasal oxygen, for acute respiratory failure, 647*b*
High-frequency ventilation, 653
High intensity statin, for acute STEMI, 391*t*
High-oxygen-affinity hemoglobinopathies, 1116
High-resolution computed tomography
  in interstitial lung disease, 574
  of lung parenchyma, 519
High-resolution esophageal manometry, 902
High-risk pulmonary embolism, 487*b*
High-throughput sequencing, 1169
Higher mental functions, 2407–2411
Hindbrain herniation, 2383
Hindgut neuroendocrine neoplasms, 1567
Hip
  disorders of, 1746–1747
  fractures of, osteoporosis and, 1607–1608
  injury of, occupational, 86*t*
  musculoskeletal anatomy of, 1743*f*
Hip, surgical treatment of, 1827–1828, 1828*f*
Hip fractures, surgery for, 1828
Hippocampal formation, 2407
Hippocampal sclerosis, mesial temporal lobe epilepsy with, 2433
Hirata disease, 1554
Hirschsprung disease, 862
  clinical manifestations of, 891–892
  definition of, 891
  diagnosis of, 892
  pathobiology of, 891
  treatment of, 892*b*
Hirsutism, 1598, 2751
Hispanic Americans, 18
  heart failure in, 254
Histamine, 193
  plasma, 1693–1694
Histamine-induced urticaria, 1687–1689, 1690*t*
Histiocyte, 1154
Histiocytoses, 1154–1162
  classification of, 1154*t*
  definition of, 1154
  Epstein-Barr virus and, 2256
  Erdheim-Chester disease, 1155*f*, 1156, 1157*b*
  hemophagocytic lymphohistiocytosis, 1159, 1160*t*, 1161*b*, 1161*f*, 1161*t*
  indeterminate cell, 1157
  Langerhans cell, 1154–1156
    clinical manifestations of, 1154–1156, 1155*f*, 1156*t*
    cutaneous features of, 1155*f*
    diagnosis of, 1156
    epidemiology of, 1154
    neurodegeneration associated with, 1156
    pathobiology of, 1154
    prognosis for, 1156
    treatment of, 1156*b*
  malignant, 1159, 1159*b*
  necrobiotic xanthogranuloma, 1158, 1158*b*
  Rosai-Dorfman disease, 1158, 1159*b*
Histiocytosis X, 1154
Histo-blood group antigens (HBGAs), noroviruses and, 2262
Histocompatibility antigens
  major, 203–205, 204*t*, 204.*e1f*, 204.*e1t*–204.*e2t*
  minor, 205
Histoid leprosy, 2051, 2052*f*
Histone deacetylase, 2701
Histoplasma capsulatum, 956, 1024
Histoplasma capsulatum var capsulatum, 2082
Histoplasmosis, 2081, 2081*t*, 2651
  acute pulmonary, 2082
  characteristics of, 2270*t*
  chronic pulmonary, 2082
  clinical manifestations of, 2082
  definition of, 2081–2082
  diagnosis of, 2082–2083
  disseminated, 2082
  epidemiology of, 2082
  identification of, 2082–2083, 2083*f*
  pathobiology of, 2082
  pathogen of, 2082
  prevention of, 2083
  prognosis of, 2083
  prophylaxis for, 2309*t*
  in travelers, 1889.*e1t*
  treatment of, 2083*b*
Histrionic personality disorder, 2348*t*
HIV. *See* Human immunodeficiency virus
HIV-1- specific antibodies, 2292
HIV-associated dementia, 2312
HIV-associated immune complex renal disease, 2313
HIV-associated lipodystrophy syndrome, 2317
HIV-associated nephropathy, 728, 2313
HIV-associated neurocognitive disorder, 2312
HLA. *See* Human leukocyte antigen
HLA-A gene, 160*t*
HLA-B gene, 160*t*
HLA-B27, 1760
HLA-DR3 allele group, 204
HLTV. *See* Human T-lymphotrophic virus
HLTV-associated myelopathy/tropical spastic paraparesis (HAM/TSP), 2327–2328
  clinical manifestations of, 2328
  diagnosis of, 2328
  epidemiology and pathobiology of, 2327–2328
  pathogenesis of, 2326
  prognosis of, 2328
  treatment for, 2328*b*
HNF1B nephropathy, 814
HNPCC. *See* Hereditary nonpolyposis colorectal cancer
Hoarseness, 2653
Hodgkin lymphoma, 1149, 1289–1294, 2255
  acquired immunodeficiency syndrome and, 1292*b*
  in adolescents, 111
  advanced-stage, 1292*b*
  classic, 1289, 1290
  clinical manifestations of, 1289
  definition of, 1289–1294
  diagnosis of, 1289–1292, 1290*f*
  differential diagnosis of, 1290
  in elderly population, 1292*b*
  epidemiology of, 1289
  Epstein-Barr virus and, 1289
  future directions of, 1293–1294
  genetic factors of, 1289
  hematopoietic cell transplantation for, 1209
  increased eosinophils counts in, 533
  limited-stage, 1292*b*
  management of complications of, 1292*b*, 1293*t*
  nodular lymphocyte-predominant, 1289, 1290
  nodular sclerosing, 1290, 1290*f*
  pathobiology of, 1289
  during pregnancy, 1291*t*, 1292*b*
  staging of, 1290–1291, 1291*t*
    imaging for, 1291, 1291*f*
    laboratory testing for, 1291
    physical examination for, 1290, 1290*f*, 1291*t*
    positron emission tomography for, 1291
  treatment for, 1292*b*, 1292*t*
  World Health Organization classification of, 1290*t*
"Holiday heart", 328
Holocarboxylase synthetase deficiency, 1403*t*
Holoprosencephaly, 2547
Holt-Oram syndrome, 302, 348
Holter monitors, 307
Home blood pressure, 446*t*, 447
Home HIV tests, 2297
Homicide, in adolescents, 110–111, 110*t*
Homocysteine, 1425
  folate and, 1459
  for megaloblastic anemias, 1122–1123, 1123
  metabolism of, 1425.*e1f*
Homocystinuria, 1402*t*, 1425–1427
  clinical manifestations of, 1425–1426
  definition of, 1425–1427, 1425.*e1f*
  diagnosis of, 1425*t*, 1426–1427, 1426*t*
  epidemiology of, 1425
  pathobiology of, 1425, 1425*t*, 1425.*e1f*
  prevention of, 1427
  prognosis of, 1427
  treatment of, 1427*b*
Homogeneous nucleation, 803
Homogeneous opacities, diffuse, 520
Homografts, advantages and disadvantages of, 412*t*
Homozygous acute porphyrias, 1433, 1433*f*
Homozygous cystathionine β-synthase deficiency, 479
Homozygous hemoglobin C, peripheral blood smear of, 1070*f*
Homozygous loss-of-function mutations, 939
Honeycombing, 522, 522*f*, 575.*e1f*
Hookworm
  clinical manifestations of, 2170*f*, 2171
  cutaneous larva migrans, 2170
  diagnosis of, 2171
  epidemiology of, 2170
  pathobiology of, 2171
  pathogen caused by, 2170, 2170*f*
  prevention of, 2171
  prognosis for, 2171
  treatment of, 2170*t*, 2171*b*
Hoover sign, 549
Hordeolum, 2601, 2601*f*
Hormonal change, in puberty, 1591, 1591*f*
Hormonal (steroidal) contraception, 1613
Hormonal therapies
  for cancer, 1232*b*
  menopausal
    discontinuation of, 1630*b*
    extended use of, 1630*b*
    vaginal symptoms and, 1630*b*
    venous thromboembolism and, 1630*b*
  for skin diseases, 2700
  for transgender men, 1578*b*, 1578*t*
  for transgender women, 1578*b*, 1579*t*
Hormone(s)
  cancer and, 1245
  in diabetic nephropathy, 796
  excess production of, hypoglycemia and, 1554
  exogenous, 1246
  mechanism of action, 1474, 1475*f*
  metabolism of, 1474
  synthesis and secretion of, 1474, 1474*f*
  transport of, 1474
Hormone deficiency, hypoglycemia due to, 1552*t*, 1555
Hormone insensitivity syndromes, 1573
Hormone replacement therapy
  for endocrine disease, 1473
  venous thromboembolism and, 481
Horner syndrome, 2555, 2618*f*, 2618*t*
Hospice, 16
Hospital-acquired pneumonia, 616*t*, 1965
  bacterial species that cause, 1892*t*
Hospital-associated fever, 1846*t*
Hospital-associated pneumonia, treatment of, 1970*b*
Hospitalist, medical consultations by, 2656
Hospitalization
  for cardiovascular disease, 219
  for pneumonia, 606
Host defense mechanisms, 191
Host-*versus*-graft (HVG), 203
Hot flashes, 1630*b*
Howell-Jolly bodies, 1152
  peripheral blood smear of, 1067*f*, 1074*t*, 1152
HPA axis. *See* Hypothalamic-pituitary-adrenal axis
HPV. *See* Human papillomavirus
HPV-associated oropharyngeal squamous cell carcinoma, 1320, 1322, 1324*f*, 1327*b*, 1328
HPV-unrelated oropharyngeal squamous cell carcinoma, 1322, 1327*b*
HSCT. *See* Hematopoietic stem cell transplantation
HSD3B2 gene, mutations in, 1571
HSV. *See* Herpes simplex virus
5-HT_3 receptor antagonists, for nausea and vomiting, 863*t*
HTLV-associated arthritis, 2327*t*
HTLV-associated myelopathy/tropical spastic paraparesis (HAM/TSP), 2327*t*
Human bone, 803

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Human chorionic gonadotropin (HCG), 1479
Human coronaviruses (HCoVs), 2206
  classification of, 2209, 2209*t*
Human cystic echinococcosis, 1025
Human diploid cell vaccine (HDCV), 82
Human epidermal growth factor receptor 2 (HER-2), 167
Human fetal tissue engraftment, 172–173
Human Gene Mutation Database, 1187
Human Genome Project, 165
Human granulocytic ehrlichiosis, 2060*t*, 2061, 2061*b*, 2062*f*
Human herpesvirus 6, 2532*t*
Human herpesvirus-8, 1279
Human immunodeficiency virus (HIV)
  acute, 2295–2297
    clinical manifestations, 2295–2297
    diagnosis of, 2296–2297
    infectivity, 2295–2296
    symptoms and signs of, 2295, 2295*t*
    in travelers, 1889.*e1t*
    viral load, 2295
  aging-related syndromes to, 2312
  antiretroviral therapy for, 2294, 2294*f*
    immune reconstitution using, 2307*b*
    toxic neuropathy caused by, 2313*b*
  associated with hypogonadism, 1583
  Campylobacter infections in, 1960
  candidiasis associated with, 2090
  cardiovascular manifestations of, 2316–2317
  chancroid and, 1950–1951
  characteristics of, 2270*t*
  chronic hepatitis C and, 1014*b*
  clinical consequences of, 2294
  cure for, 2305
  cutaneous lesions associated with, 2323*t*
  dermatologic manifestations of, 2321, 2323*t*
    approach to, 2323*t*
    inflammatory conditions, 2321
    pruritus, 2321
    skin malignancies, 2321
  diarrhea and, 937
  endocrine manifestations of, 2317–2318
  epidemiology and diagnosis of, 2286
  eradication of, 2294
  gastrointestinal manifestations of, 2319–2321, 2322*t*
    anorectal, 2321, 2322*t*
    biliary, 2321, 2322*t*
    esophageal, 2320, 2320*b*, 2322*t*
    gastric, 2322*t*
    hepatic, 2321, 2322*t*
    large bowel, 2320, 2320*b*–2321*b*, 2322*t*
    oral, 2319–2320, 2320*b*, 2322*t*
    small bowel, 2320, 2322*t*
  genes of, 2291, 2291.*e3f*
  global impact and response of, 2286–2288, 2286.*e3f*, 2287*f*–2288*f*, 2288*f*, 2288.*e1f*
  global statistics of, 2286, 2286*t*, 2286.*e2f*, 2287*f*
  head and neck cancer and, 1321
  hematology and, 2313–2316
    AIDS-defining malignancies, 2315
    anemia, 2314, 2315*t*
    cytopenia, 2313
    hypercoagulable state, 2315
    leukopenia, 2314
    thrombocytopenia, 2314, 2314*b*
    thrombotic microangiopathies, 2313
  HIV-1 replication, 2293–2294
  human papillomavirus and, 2241
  immune reconstitution inflammatory syndrome associated with, 2308–2313, 2311*b*, 2312*t*
  infected cells of, fate of, 2292–2293
  infertility associated with, 2318
  Leishmania donovani and, 2130
  Leishmania infantum and, 2133
  life cycle of, 2301*f*
  malaria and, 2121
  measles vaccination in, 2223
  meningitis caused by, 2521
  microbial complications of, 2305–2308
    clinical manifestations of, 2306–2307
    diagnosis of, 2307
    epidemiology of, 2305–2306
    pathobiology of, 2306
    prevention of, 2308, 2308.*e1f*
    treatment of, 2307*b*
Human immunodeficiency virus (HIV) *(Continued)*
  musculoskeletal manifestations of, 2321–2324
  nephropathy associated with, 789
  neuropsychiatric manifestations of, 2312–2313
  oncology and, 2313
    anal cancer, 2316
    cervical cancer, 2316*b*
    colorectal cancer, 2316
    Kaposi sarcoma, 2315, 2315*b*, 2316*f*
    lung cancer, 2316
    multicentric Castleman disease, 2316, 2316*b*
    non-AIDS-defining cancers, 2316, 2316*b*
    non-Hodgkin lymphoma, 2315
    prevention of, 2316
    primary effusion lymphoma, 2315
    screening for, 2316
  opportunistic infections associated with, 2305, 2306*t*
    antiretroviral therapy for, 2307*b*
    behavioral factors, 2306
    candidiasis, 2089
    CD4 cells in, 2306, 2306*f*
    clinical manifestations of, 2306
    cryptococcosis, 2087
    cytomegalovirus, 2307
    diagnosis of, 2307
    empiric management of, 2307*b*
    Mycobacterium tuberculosis, 2306
    natural histories of, 2306–2307
    pathobiology of, 2306
    prevention of, 2308, 2308.*e1f*
    prophylaxis for, 2309*t*
    treatment of, 2307*b*, 2307*t*
  oral lesions associated with, 2621*t*
  pathobiology of, 2291–2294
  pathogen that causes, 2291
  pharyngitis and, 2650
  physiology of, 2292–2294
  post-transcription events of, 2292.*e2f*
  preexposure prophylaxis for, 56, 1884
  prevention of, 2298–2300
    antiretroviral therapy for, 2298
    in blood products and other tissues, 2299
    development of, 2300
    in health care workers, 2299
    in injection drug users, 2299
    interventions in, 2300
    opportunities of, 2298*f*
    postexposure prophylaxis for, 2299, 2299*t*
    preexposure prophylaxis for, 2298–2299, 2299*t*
  pulmonary manifestations of, 2318–2319
  rapid tests and home testing options for, 2296–2297
  reactive arthritis and, 1763
  regional epidemics of, 2288–2291
    in Asia and the Pacific, 2289, 2289.*e1f*
    in Caribbean, 2289, 2289.*e1f*
    in Eastern and Southern Africa, 2288, 2288.*e1f*
    in Eastern Europe and Central Asia, 2289, 2289.*e1f*
    in Latin America, 2289, 2289.*e3f*
    in North Africa and the Middle East, 2289, 2289.*e1f*
    in United States, 2288*f*, 2290–2291, 2290*f*–2291*f*, 2291*f*
    in Western and Central Africa, 2289, 2289.*e1f*
    in Western and Central Europe and North America, 2289, 2289.*e1f*, 2290.*e1f*
  renal manifestations of, 2313
    end-stage renal disease, 2313
    immune complex renal disease, 2313
    nephropathy, 2313
    screening for, 2314*f*
    thrombotic microangiopathies, 2313
  replication of
    cycle, 2291–2292, 2292.*e1f*
    reverse transcription in, 2292, 2292.*e1f*
  RNA, 2292
  screening for, 55, 2297
  sexually transmitted infections and, 1880
  stages of early infection, 2296, 2297*t*
  syphilis and, 2017–2018
  systemic manifestations of, 2312–2324
Human immunodeficiency virus (HIV) *(Continued)*
  testing strategies, 2296, 2296*f*
  thrush in, 2090
  transcription of, 2292.*e1f*
  transmission
    modes of, 2298–2300, 2298*f*
    sexual, 2298–2299
  in travelers, 1889
  treated, 2294
  treatment of, 2297*b*
  tuberculosis and, treatment of, 2040*b*
  tubulointerstitial nephropathy in, 793
  untreated infection of, 2292–2294, 2293*f*
  virion structure of, 2291, 2291*f*
  weight loss and, 860*t*
  in women, 1609–1610
Human induced pluripotent stem cells (hiPSCs), 172, 172*f*
Human leukocyte antigen (HLA), 203
  associated with rheumatoid arthritis, 1749–1750, 1750.*e1t*
  diabetes mellitus and, 1536
  structural and functional features of, 1*t*–2*t*, 204
  two views of, 204.*e1f*
Human metapneumovirus, 2195, 2195*b*
Human microbiome, 1836–1840
  alteration of, 1837–1838, 1838*f*, 1838*t*
  definition of, 1836
  in developing precision medicine paradigm, 1840.*e2f*
  disease associations of, 1838–1840
    asthma, 1840
    C. difficile infection, 1839, 1840.*e1f*
    colon cancer, 1840
    hematopoietic stem cell transplantation, 1840
    inflammatory bowel disease, 1838–1839
    neurologic disorders, 1840
    obesity, 1838, 1839*f*
  environmental/iatrogenic factors of, 1838*t*
  establishment of, 1837, 1837*f*, 1837.*e1f*–1837.*e2f*
  host factors of, 1838*t*
  maternal factors of, 1837.*e1f*
  microbial factors of, 1838*t*
  postnatal factors of, 1837.*e1f*
  potential function of, 1838*f*
  structure and function relationships of, 1836
  studying of, 1837, 1837.*e1f*
  therapies targeting, 1840, 1840*t*
Human papillomavirus (HPV), 982
  anal cancer caused by, 2316
  cervical cancer and, 1375, 1607, 2241
  cervical carcinoma and, 2305
  characteristics of, 1881
  clinical manifestations of, 2241–2242
  definition of, 2240
  diagnosis of, 2242–2243
  epidemiology of, 2240–2241
  of esophagus, 912
  genital, 2240–2241, 2242*f*, 2244*f*
  genotypes of, 1881*b*
  head and neck cancer caused by, 1320, 2622
  human immunodeficiency virus and, 2241
  immune response to, 2241
  immunization for, 66*t*, 79
    adverse reactions of, 79
    indications for, 79
    schedule of, 76.*e1t*, 77*f*
  oncogenic risk of, 2241
  pathobiology of, 2241
  pathogen that causes, 2240
  plantar warts caused by, 2242
  prevention of, 2243–2244
  primary prevention of, 2243–2244, 2243*t*
  prognosis of, 2244
  prophylaxis for, 2309*t*
  secondary prevention of, 2244
  sexually transmitted, 1881
  treatment of, 2243*b*, 2243*t*
  vaccination for, 1376, 1884
  warts caused by, 2242
Human pluripotent stem cell lines, 174
Human polyomavirus, 2227–2228, 2228*t*
Human polyomavirus 6, 2232
Human polyomavirus 7, 2232
Human T-cell leukemia virus type 1, 2164
Human T-lymphotrophic virus (HLTV)
  -1, 2324, 2324*t*
  -2, 2324, 2324*t*
  adult-cell leukemia/lymphoma caused by, 2326
  associated diseases with, 2327*t*, 2328
  definition of, 2324–2326
  epidemiology of, 2324–2325
  pathobiology of, 2325–2326
  pathogens that cause, 2324
  prevention of, 2328
  transmission of, 2324–2325, 2324*t*
    by breast-feeding, 2324–2325
    by casual contact, 2325
    by coinfection with HIV, 2325
    by injection drug use, 2325
    sexual, 2324
    by solid organ transplantation, 2325
    by transfusion, 2325
  viral life cycle of, 2325
  virology of, 2325
Humira. *See* Adalimumab
Humoral hypercalcemia of malignancy, 1659
Humoral immunodeficiency, children with, 2261*b*
Hunt-Hess grading scale, 2477*t*
Hunter syndrome, 1724*t*
Huntington disease, 2411, 2416, 2420–2421, 2490, 2491*b*
Hurler syndrome, 1724*t*
Hutchinson sign, 2605–2606
HVG. *See* Host-*versus*-graft
Hyaline cast, 722, 724*f*
Hyaline thrombi, 1177
Hyaluronic acid capsule, 1913
Hyaluronidase, 1913–1914
Hycamptamine, 1215*t*
Hycamtin. *See* Topotecan
Hydatid cyst disease, 1025
Hydatid disease
  alveolar, 2162, 2162*b*
  cystic, 2161, 2161*b*, 2162*f*
Hydralazine, 451*t*
  for heart failure, 265*b*
  for preeclampsia, 1621*t*
Hydration
  for *E. coli*, 1963*b*
  for rhabdomyolysis, 717*b*
Hydrea. *See* Hydroxyurea
Hydrocalycosis, 819
Hydrocalyx, 819
Hydrocele, in bancroftian filariasis, 2177
Hydrocephalus, normal-pressure, 2421
Hydrochlorothiazide, 451*t*, 454
  for hypervolemia, 737*t*
Hydrocodone, 139*t*
Hydrocortisone
  for adrenocorticotropic hormone deficiency, 1493*b*
  for idiopathic pulmonary fibrosis, 576*b*
Hydrocytosis, 1094*f*, 1097
Hydrogen breath test, for malabsorption, 931*t*
Hydrogen cyanide, 88*t*
Hydrogen fluoride, 88*t*
Hydrogen ion concentration, in normal arterial blood pH, 753
Hydromorphone, 139*t*
  for erythromelalgia, 471*b*
  for frostbite, 474*b*
Hydrops fetalis, 1104, 1107*b*, 2235
Hydrostatic pulmonary edema, 566
Hydrothorax, in decompensated cirrhosis, 987
Hydroxocobalamin
  for acute poisoning, 693*t*
  for cyanide poisoning, 596*b*
α–Hydroxy acids, 2700
β-Hydroxybutyrate, e1*t*–e8*t*
γ-Hydroxybutyrate
  central nervous system effects of, 685*t*
  toxicity, 686*t*
Hydroxychloroquine, 2114
  for COVID-19, 2217
  development of, 146–147
  for malaria, 2112*t*
  ocular effects of, 2613
  for rheumatoid arthritis, 1755*b*, 1756*t*, 1757*t*
  for systemic lupus erythematosus, 1772*b*
Hydroxychloroquine, for total knee arthroplasty, 1830.*e1t*

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Hydroxydaunorubicin, 1215*t*
5-Hydroxyindole acetic acid (5-HIAA), *e1t–e8t*
11β–Hydroxylase deficiency, 1572
17α–Hydroxylase deficiency, 1571
21-Hydroxylase deficiency, 1571–1572, 1572*f*, 1593
Hydroxymethylbilane, 1429.*e1f*
17-Hydroxyprogesterone (17-OHP), *e1t–e8t*, 1593
3β–Hydroxysteroid dehydrogenase deficiency, 1571
Hydroxyurea (Hydrea), 1215*t*
  for essential thrombocythemia, 1135*b*
  for polycythemia vera, 1135*b*
  for sickle cell disease, 1114*b*
  sickle cell disease and, 1114*b*
25-Hydroxyvitamin D, 1453*t*, 1640–1641, 1648
Hydroxyzine, for mastocytosis, 1703*b*
Hymenolepis nana, 2157, 2158*t*
Hymenoptera, 522, 711
Hyoscyamine, for irritable bowel syndrome, 896*t*
Hyper-IgE syndrome, 1679*t*
Hyperacute rejection, 205, 845
Hyperaldosteronism, 746
Hyperaldosteronism, primary, 749, 1525, 1525*f*, 1525*t*
Hyperalgesia, 134
Hyperammonemia
  psychotropic medications and, 2678*t*
  severe mental illness and, 2683*t*
Hyperandrogenism, 1526, 1526*b*
Hyperbaric oxygen, 596*b*, 693*t*
Hyperbilirubinemia
  approach to, 995
  conjugated, 996, 997*t*
  definition of, 993–995
  differential diagnosis of, 996*t*
  intramedullary hemolysis and, 1121
  mixed, 996, 997*t*
  pathobiology of, 994–995
  postoperative, 2676
  unconjugated, 996
Hypercalcemia, 1652–1662, 1654
  autoimmune hypocalciuric, 1658
  causes of, 1655–1659, 1656*t*
  chromosomal locations of, 1653*t*
  chronic interstitial nephritis caused by, 794
  clinical features of, 1654*t*
  clinical manifestations of, 1654
  definition of, 1654
  diagnosis of, 1654, 1655*f*, 1656*t*
  drugs that cause, 1659
  endocrine causes of, 1658–1659
  epidemiology of, 1654
  familial benign hypocalciuric, 1658
  granulomatous disorders causing, 1659, 1659*b*
  of malignancy, 1237, 1237*b*, 1658–1659, 1659*b*
  pancreatic neuroendocrine neoplasms, 1561*t*
  pathobiology of, 1654
  in sarcoidosis, 603*b*
  symptomatic, 1654*b*–1655*b*, 1656
  thyrotoxicosis and, 1658
  treatment of, 1654
  Williams syndrome and, 1658
Hypercalcemia, for multiple myeloma, 1299*b*
Hypercalcemic disorders, nephrolithiasis and, 805*b*
Hypercapnia, 2461
  clinical manifestations of, 645*t*
  mechanisms of, 643*t*
Hypercapnic acute respiratory failure, causes of, 643*t*
Hypercapnic disease, 534, 535*t*
Hyperchloremic acidosis, 752*b*
Hyperchloremic metabolic acidoses, 753*t*, 760–762, 760*f*
  of nonrenal origin
    with hypokalemia, 760
    with normal or increased potassium level, 760
  of renal origin, with hyperkalemia, 761–762
Hypercholesterolemia, familial, 160, 1398*t*, 1408
  cascade screening for, 1409
  clinical manifestations of, 1408
  combined, 1409
  diagnosis of, 1409
  epidemiology of, 1408
  pathobiology of, 1408
  in pregnancy, 1409*b*
  prognosis for, 1409
  screening for, 1409
  treatment of, 1409*b*, 1409*t*
Hypercoagulable states, 475–482, 475.*e3f*, 2315
  evaluation of, 1166*t*, 1170, 1170*t*
  primary, 475–478, 475*t*, 476
    clinical manifestations of, 476–477, 476*t*, 477*t*
    diagnosis of, 477–478, 477*f*
    treatment of, 478*b*
  secondary, 478–482
    causes of, 479*t*
    definition of, 478
    prevention of, 480
    prognosis of, 480
    treatment of, 479*b*
Hypercortisolism, 1494, 1520
Hyperdynamic circulatory state, cirrhosis and, 1036, 1037*f*
Hyperemesis gravidarum, 1626, 1626*b*
Hypereosinophilic syndromes, 295–296, 296*b*, 1142, 1162
Hyperexplexia, 2495
Hyperfiltration, 795–796
Hyperfractionated radiation, for NSCLC, 1333*b*–1335*b*
Hyperfunctional neurologic disorders, 2652
Hypergastrinemia, peptic ulcers associated with, 916
Hyperglycemia, 795
  in acute pancreatitis, 971
  hypothalamic disease and, 1481
  in septic shock, 673*b*
  stroke-like symptoms associated with, 2467
Hyperglycinemia, nonketotic, 1398*t*
Hypergonadism, hypothalamic, 1481
Hypergonadotropic amenorrhea, 1600, 1600*b*
Hyperhemolytic transfusion reaction, 1203
Hyperhidrosis, 2555, 2557*b*
Hyperhistaminic syndromes, 917
Hyperhomocysteinemia, 479, 479.*e1f*, 1425, 1430–1433
  clinical manifestations of, 1425
  definition of, 1425, 1425.*e1f*
  diagnosis of, 1425*t*, 1426, 1426*t*
  epidemiology of, 1425
  pathobiology of, 1425, 1425*t*, 1425.*e1f*
  prevention of, 1427
  prognosis of, 1427
  treatment of, 1123*b*, 1427*b*
Hyperimmunoglobulin E syndrome, 1680, 1680*b*
Hyperimmunoglobulin M syndromes, 1681–1682, 1681*t*, 1686*t*
Hyperimmunoglobulinemia D with periodic fever syndrome (HIDS), 1731*t*, 1733–1734
  clinical characteristics of, 1733*t*
  clinical manifestations of, 1734
  prognosis for, 1734*b*
  treatment of, 1734*b*
Hyperinfection syndrome, 2173
Hyperinflation, dynamic, 654
Hyperinsulinemia, 1465
Hyperinsulinemic euglycemic therapy, for acute poisoning, 693*t*
Hyperinsulinemic hypoglycemia, 1552*t*
Hyperkalemia
  causes of, 750*t*
  in chronic kidney disease, 836
  chronic treatment of, 751*b*
  clinical manifestations of, 748
  definition of, 745
  disorders associated with, 750–751
  electrocardiographic manifestations, 748*f*
  emergent treatment of, 751*b*
  in hospitalized patients, 752
  hyperchloremic acidosis with, 761
  hypertensive syndromes, 751
  hypotensive syndromes, 750–751
  mortality associated with, 752
  normotensive syndromes, 750
  prognosis for, 752
  renin-angiotensin system inhibitors and, 453
  treatment of, 751*b*, 839*b*
Hyperkalemic periodic paralysis, 752*b*, 2583.*e1t*, 2585
Hyperlipidemia
  description of, 121
  in nephrotic syndrome, 777
  secondary cause of, 1408, 1408*t*
Hyperlipoproteinemia, 1823
Hyperlucent lungs, 565
Hypermagnesemia, 767, 767*b*
Hypermetabolic systemic response, to injury, 699
Hypernatremia, 733*t*, 742–743
  causes of, 743*t*
  clinical manifestations of, 742, 743*t*
  diagnosis of, 742
  prognosis of, 743
  severe mental illness and, 2683*t*
  treatment for, 743*b*
Hyperopia, 2598
Hyperosmolality, correction of, 1503*b*
Hyperosmolar hyperglycemic state
  clinical manifestations of, 1547
  diagnosis of, 1548
  epidemiology of, 1547
  pathobiology of, 1547
  prevention of, 1549
  prognosis of, 1549
  treatment for, 1547*t*, 1548*b*
Hyperosmolar nutrition solutions, 1450
Hyperostosis, 1666, 1666*t*
Hyperoxaluria, primary, 803
Hyperparathyroidism, 1655
  definition of, 1655
  magnesium deficiency and, 766
  primary, 1656
    clinical manifestations of, 1656
    description of, 1654
    diagnosis of, 1656–1657
    epidemiology of, 1656
    familial, 1657
    parathyroid surgery for, 1657*t*
    parathyroidectomy for, 1657*b*
    pathobiology of, 1656
    treatment of, 1657*b*
  secondary, 1658*t*
  uremic, 1657, 1658*b*
Hyperparathyroidism-jaw tumor syndrome, 1657
Hyperphosphatemia, 768–769
  causes of, 769*t*
  clinical manifestations of, 769
  diagnostic approach to, 769*f*
  dialysis-associated, 842
  pathobiology of, 768–769
  prognosis of, 769
  treatment of, 769*b*
Hyperpigmentation, 2742*t*, 2743–2744
  circumscribed, 2744, 2744*f*
  diffuse, 2743
  hemochromatosis and, 1440
  linear and reticulated, 2744
Hyperpolarization-activated cyclic nucleotide gated channels, 300
Hyperprolactinemia, 1479
  chronic anovulation caused by, 1601
  description of, 1491, 1491*b*, 1491*t*
  hypothalamic, 1481
  psychotropic medications and, 2678*t*
  treatment of, 1603*b*
Hyperpyrexia, severe, 1851
Hypersegmented neutrophils, 1072*f*
Hypersensitivity pneumonitis, 581, 581.*e1f*, 588
  chronic, 581.*e1f*
  classification of, 571*t*
  clinical features of, 581
  clinical manifestations of, 581, 588
  diagnosis of, 581, 588
  examples of, 588*t*
  increased lymphocyte counts in, 533
  pathobiology of, 581, 588
  prognosis for, 581*b*
  prognosis of, 589*b*
  treatment of, 581*b*, 589*b*
Hypersensitivity reactions, 193–195
  diarrhea and, 940
  type I, 193–194, 193*t*, 194*f*
  type II, 193*t*, 194, 194*f*
  type III, 193*t*, 194–195, 195*f*
  type IV, 193*t*, 195, 195*f*
  types I-IV, 1672*f*
  types of, 193*t*
Hypersensitivity vasculitis, 965. *See also* Cutaneous leukocytoclastic angiitis
Hypersomnia, 2444–2446
  diagnosis of, 2444–2445
  idiopathic, 2446
Hypersplenism, neutropenia due to, 1146
Hypertension, 220
  acute poisoning and, 683
  acute severe, 457–458, 458*b*–459*b*, 458*t*, 459*f*
  adrenocorticotropic hormone and, 1493
  arterial, 444
    cardiovascular disease risk factors in, 447, 448*t*
Hypertension *(Continued)*
    clinical manifestations of, 445
    definition of, 444
    diagnosis of, 445, 446*f*
    epidemiology of, 444
    essential, 445, 448*t*
    first-line drugs for, 451
    lifestyle modification for, 450, 450*t*
    management of, 450*b*
    medical therapy for, 450
    pathobiology of, 445
    secondary causes of, 450
  in Black Americans, 456
  chronic preexisting, 1620
  diabetes mellitus and, 1550
  drug-resistant, 456, 457*f*
  echocardiographic findings, 242*t*
  with estrogen replacement, 456
  gestational, 1620
  heart failure associated with, 262
  intracerebral hemorrhage related to, 2463
  intracranial, 2383, 2383*b*
  metabolic alkalosis with, 763
  nutrition and, 60
  obesity caused by, 1465
  ocular, 2609, 2610*f*
  with oral contraceptives, 456
  porphyrias and, 1432
  postoperative, 2674
  in pregnancy, 456
  preoperative evaluation considerations, 2664
  psychotropic medications and, 2678*t*
  pulmonary, 493–501
    arterial, in HIV, 2317, 2317*b*
    assessing response to therapy in, 496*b*, 500*t*
    background therapy for, 496*b*
    clinical classification of, 493*t*
    clinical manifestations of, 494–495
    collaborative care in, 496*b*
    complications of, 355
    cystic fibrosis with, 558.*e1f*
    definition of, 493–501, 493*t*
    diagnosis of, 495–496, 495*f*–499*f*, 496*f*, 497*f*, 498*f*, 499*f*
    differential diagnosis of, 359
    epidemiology of, 493–494
    history of, 494
    invasive therapies for, 496*b*
    medical therapy for, 496*b*, 500*t*
    pathobiology of, 494, 494.*e1f*
    physical examination for, 494–495
    primary lung disease, 493*t*, 496*b*
    prognosis for, 500–501
    special populations of, 496*b*
    thromboembolic hypertension, 493*t*, 496*b*, 499.*e1f*
    treatment of, 496*b*
    with unclear and/or multifactorial mechanisms, 493*t*
    venous hypertension, 496*b*
  renal artery causing, 799
  white coat and masked, 447, 447.*e1f*
  in women, medications for, 1608*t*
Hypertensive disorders of pregnancy, 1620–1621, 1620*b*, 1621*b*, 1621*t*
Hypertensive emergency, 35
Hypertensive encephalopathy, 458
Hypertensive nephrosclerosis, 839
Hypertensive peristalsis, 909
Hyperthermia, 34, 681–682
  acute poisoning and, 683
  malignant, 678, 715, 717*b*
  management of, 679*t*
  therapeutic, 682
Hyperthyroidism, 1509–1519
  cardiomyopathy with, 288
  clinical manifestations of, 1509–1510, 1510*f*
  definition of, 1509–1519
  diagnosis of, 1510–1512, 1510*f*, 1511*t*
  epidemiology of, 1509
  Graves disease and, 1472
  hypertension and, 450
  pathobiology of, 1506*t*, 1509
  subclinical, 1511*b*
  sustained, 1506*t*
  transient, 1506*t*
  treatment for, 1504.*e1f*, 1511*b*, 1511*t*
Hypertonic hyponatremia, 740
Hypertonic saline, for drowning, 592*b*
Hypertrichosis, 2751

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Hypertriglyceridemia, 1414, 1414*b*
  in acute pancreatitis, 971
  cause of, 1408
  diagnosis of, 1414
  drug therapy for, 1414*b*
  fasting, 1466
  severe, 1410
  statin therapy for, 1414*b*
  treatment of, 1410.*e1t*, 1414*b*
Hypertrophic cardiomyopathy, 281.*e1f*, 282
  apical, 281.*e1f*
  clinical manifestations of, 281
  definition of, 279
  diagnosis of, 281–282
  diagnostic criteria for, 282, 284*t*
  diagnostic testing of, 281
  echocardiographic findings, 281, 281.*e2f*
  epidemiology of, 279
  heart failure due to, 265*b*
  interventional therapy for, 282*b*
  management of, 283*f*
  medical therapy for, 282*b*
  pathobiology of, 279–281
  pathology of, 280–281
  pathophysiology of, 281
  prognosis for, 284, 284.*e1f*
  progressive, 281.*e2f*
  symptomatic management, 282*b*
  treatment of, 282*b*
  ventricular tachycardia in, 337
Hypertrophic gastritis, 913
Hypertrophic lichen planus, 2708
Hypertrophic obstructive cardiomyopathy, 282*f*
Hypertrophic osteoarthropathy, 1823, 1824*f*
Hyperuricemia, 1810–1813, 1810
  asymptomatic, 1811
  genetic causes of, 1811*t*
  nongenetic causes of, 1810*t*
  treatment of, 265*b*
Hyperuricosuria, 804
Hyperventilation
  vertigo and, 2646
  vital signs in, 34
Hyperviscosity symptoms, 355*b*
Hyperviscosity syndrome, 1303, 1303*b*, 1304*f*
Hypervolemia, 735–736, 735*t*
  clinical manifestations of, 736
  diagnosis of, 736
  pathobiology of, 735–736
  treatment for, 736*b*
Hypervolemic hypernatremia, 733*t*, 743
Hypervolemic hyponatremia, 733*t*, 741, 741*b*
Hyphae, 2093
Hyphema, 2603, 2604*f*
Hypnogram, 2443, 2444*f*
Hypnopompic hallucinations, 2446
Hypnotics, for insomnia, 2450*b*
Hypoadrenalism, 739
Hypoalbuminemia
  in nephrotic syndrome, 777
  postoperative, 2676
Hypoaldosteronism, 1529
  primary selective, 750, 750*t*
Hypocalcemia, 1652, 1659
  acute, 1659*b*
  in acute pancreatitis, 971
  causes of, 1658*t*, 1660–1662
  chromosomal locations of, 1653*t*
  chronic, 1659*b*
  clinical manifestations of, 1659, 1659*t*
  definition of, 1659
  diagnosis of, 1659, 1660*f*
  pathobiology of, 1659
  rhabdomyolysis and, 716
  treatment of, 1659*b*
Hypocapnia, 2461
  pulmonary embolism and, 487*b*
Hypochlorhydric acidosis, 760
Hypochondriasis, 2683
Hypochromia, 1067*f*
Hypocomplementemic urticarial vasculitis, 1798, 1798*b*, 2715
Hypodynamic variables, normal values, 677*t*
Hypofunctional neurologic disorders, 2652
Hypogammaglobulinemia
  arthritis associated with, 1822
  with B cells, 1681–1682
  immunization for, 65*t*
Hypoglycemia, 1545, 1551–1558
  causes of, 1552*t*, 1553–1555
Hypoglycemia *(Continued)*
  changes during fasting, 1552
  changes during feeding, 1552
  clinical manifestations of, 1546, 1546*t*, 1553
  counter-regulatory hormonal responses to, 1552, 1554*f*
  definition of, 1551–1558
  diagnosis of, 1546, 1546*t*, 1552*t*, 1555–1557, 1556*f*
  drug-and toxin-induced, 1552*t*, 1555, 1555*t*
  due to defects in gluconeogenesis, 1555
  due to defects in hepatic glycogen release/storage, 1555
  due to hormone deficiency, 1555
  epidemiology of, 1545, 1551, 1552*t*
  genetic studies for, 1557
  glycogen storage disease *versus*, 1416
  iatrogenic, 1546, 1546*t*
  insulin factitious, 1554
  metabolic diseases of, 1555
  nocturnal, 1546
  non-insulinoma pancreatogenous, 1554
  pathobiology of, 1545–1546, 1551–1553, 1553*f*
  prevention of, 1546
  prognosis of, 1546, 1558
  radiologic investigations of, 1557
  risk factors for, 1545*t*
  stroke-like symptoms associated with, 2467
  symptoms of, 1553
  treatment for, 1546*b*
  treatment of, 1557*b*
  tumor-associated, 1237, 1555
Hypogonadism, 1600
  definition of, 1582
  after hematopoietic cell transplantation, 1211
  hemochromatosis and, 1440
  hypogonadotropic, 1496, 1496*b*, 1573, 1584
    causes of, 1583*t*
    clinical manifestations of, 1584
    congenital, 1584
    diagnosis of, 1584–1585
    history of, 1584–1585
    laboratory studies in, 1584–1585
    physical examination of, 1584
    treatment of, 1585*b*
  hypothalamic, 1480–1481
  male, 1582–1585
    androgen preparations for, 1586*t*
    definition of, 1582–1585
    epidemiology of, 1582
    in HIV, 2318
    pathobiology of, 1583–1584
    testosterone delivery systems for, 1585*b*
    treatment of, 1585*b*
  primary testicular, 1583, 1583*t*
  systemic diseases associated with, 1584
Hypogonadotropic disorders, acquired, 1584
Hypogonadotropic hypogonadism, 1496, 1496*b*, 1573, 1584
  causes of, 1583*t*
  clinical manifestations of, 1584
  congenital, 1584
  diagnosis of, 1584
  history of, 1584
  isolated, 1601
  laboratory studies in, 1584
  physical examination of, 1584
  treatment of, 1585*b*
Hypokalemia
  causes of, 749, 749*t*, 750*f*
  clinical manifestations of, 747–748
  definition of, 745
  disorders associated with, 749–750
  electrocardiographic manifestations, 748*f*
  in Gitelman syndrome, 817*b*
  hyperchloremic metabolic acidoses with, 760
  hypertensive syndromes, 749
  hypomagnesemia and, 747
  hypotensive syndromes, 749–750
  mortality associated with, 752
  prognosis for, 752
  treatment of, 751*b*
Hypokalemic alkalosis, 749
Hypokalemic periodic paralysis, 751–752, 752*b*, 2583.*e1t*, 2585
Hypomagnesemia, hypokalemia and, 747
Hypomyelination, 2498
Hyponatremia, 733*t*, 738–742
  causes of, 739–740
  cirrhosis and, 1038
  clinical manifestations of, 738*t*, 740–741
  definition of, 738, 738*t*
  diagnosis of, 740, 740*f*
  epidemiology of, 738
  hypervolemic, 741
  hypovolemic, 741
  mechanisms of, 738*t*
  normovolemic, 741
  pathobiology of, 738–740, 738*t*
  prognosis of, 742
  psychotropic medications and, 2678*t*
  severe mental illness and, 2683*t*
  treatment of, 741*b*, 742*f*, 1040*b*
Hypoparathyroidism, 1658*t*, 1660–1661, 1823
  acquired forms of, 1660–1661
  autoimmune acquired, 1661
  in autoimmune polyglandular syndromes, 1560
  clinical manifestations of, 1662*t*
  complex syndromes associated with, 1661
  inherited of, 1661
  isolated, 1660–1661
  polyglandular autoimmune, 1661
  treatment of, 1661*b*
Hypoperfusion, 661
  epidemiology of, 770, 771*f*
Hypopharynx, 1320, 1320*f*, 2648
  cancer, 1322, 1325*t*, 1327*b*
Hypophosphatemia, 767–768
  cardiomyopathy with, 288
  causes of, 767*t*
  clinical manifestations of, 768
  diagnosis of, 768
  diagnostic approach to, 768*f*
  pathobiology of, 767–768
  prognosis of, 768
  treatment of, 768*b*
  X-linked, 1648
Hypophosphatemic rickets, 816*t*
Hypophysiotropic hormones
  corticotropin-releasing hormone, 1477
  functions of, 1476–1478
  gonadotropin-releasing hormone, 1476
  growth hormone-releasing hormone, 1477
  prolactin inhibitory factor, 1477–1478
  prolactin-releasing factor, 1478
  somatostatin, 1477
  thyrotropin-releasing hormone, 1476, 1477*f*
Hypophysitis, 1483
  clinical manifestations of, 1484
  diagnosis of, 1484
  empty sella causing, 1486, 1486*f*
  epidemiology of, 1483
  pathobiology of, 1483
  prognosis for, 1485*b*
  treatment of, 1485*b*
Hypopigmentation, 2742–2743, 2742*t*
  circumscribed, 2743
  congenital causes of, 2743
  guttate, 2743, 2743*f*
  linear, 2743
Hypopituitarism, 1482–1486
  acquired causes of, 1483*t*
  chronic anovulation caused by, 1601
  clinical manifestations of, 1483
  congenital causes of, 1483*t*
  diagnosis of, 1483
  epidemiology of, 1482–1483
  hormonal replacement therapy for, 1485*t*
  hypophysitis causing, 1483
  pathobiology of, 1482
  pituitary apoplexy causing, 1485, 1485*t*, 1486*b*, 1486*t*
  treatment of, 1483*b*
Hypopnea, 639
Hypotension
  acute pancreatitis and, 970
  acute poisoning and, 683
  in bacterial meningitis, 2515*b*
  intracranial, 2383, 2384*b*, 2384*f*
  orthostatic
    description of, 306
    psychotropic medications and, 2678*t*
  postoperative, 2675
  shock and, 660
Hypotensive transfusion reactions, 1202
"Hypothalamic" amenorrhea, 1480
Hypothalamic anorexia, 1481
Hypothalamic chronic anovulation, 1601
Hypothalamic hypergonadism, 1481
Hypothalamic hyperprolactinemia, 1481
Hypothalamic hypogonadism, 1480
Hypothalamic obesity, 1481
Hypothalamic-pituitary-adrenal (HPA) axis, 145, 1526–1527
Hypothalamic pituitary axis, 1483
Hypothalamic-pituitary axis, 1478
Hypothalamic-pituitary function, 1581–1582
Hypothalamic-pituitary-gonadal axis, 1580*f*
Hypothalamic-pituitary-ovarian axis, 1596*f*
Hypothalamic-pituitary thyroid axis, 1505, 1505.*e1f*
Hypothalamic-pituitary unit, failure of, 1601
Hypothalamic-pituitary axis, 2665
Hypothalamus
  disease of, 1478–1480
    congenital embryopathic disorders, 1478
    etiology of, 1479*t*
    gonadotropins affected by, 1480
    growth hormone affected by, 1480
    infiltrative, 1479–1480
    inflammatory, 1479
    irradiation affected by, 1480
    Langerhans cell histiocytosis, 1480, 1480*f*
    midline cleft syndromes, 1478
    optic nerve hypoplasia, 1478–1479
    on other neurometabolic functions, 1481
    pituitary function affected by, 1480–1481
    prolactin affected by, 1481
    sarcoidosis, 1479–1480
    thyroid-stimulating hormone affected by, 1476, 1481
    trauma and, 1480
    vascular, 1480
  dysfunction of, 1478
  lesions of, 1527
  neuroendocrine organization of, 1476*f*
  tumors of, 1479
Hypothermia, 34, 680, 681*f*
  acute poisoning and, 683
  stages and associated clinical manifestations of, 681*t*
  therapeutic, 681
  trauma, 681
  treatment of, 681*t*
Hypothermia thermometer, 33
Hypothermic syndromes, 681
Hypothesis testing, 36–37, 36*t*
Hypothyroidism, 739, 1465, 1506–1509, 2665
  cardiomyopathy with, 288
  central, 1497, 1497*b*
  clinical manifestations of, 1507
  definition of, 1506*t*
  diagnosis of, 1507–1508, 1508*f*
  epidemiology of, 1507
  Hodgkin lymphoma and, 1293*t*
  in older adults, 114
  overt, 1505, 1508*b*
  pathobiology of, 1506*t*, 1507
  primary, 1506–1507
  prognosis of, 1509
  subclinical, 1505, 1508*b*
  treatment for, 1508*b*, 1508*t*
Hypotonic hyponatremia, 740
Hypoventilation
  in acute respiratory failure, 643
  nocturnal, 619
  vital signs in, 34
Hypoventilation syndromes, 534–537, 534*t*, 535*f*, 535*t*
  acquired hypoventilation syndrome, 536
  central congenital hypoventilation syndrome, 534
  Cheyne-Stokes breathing, 534, 534*b*
Hypovolemia, 735
  absolute, 735*b*, 735*t*
  causes of, 735*t*
  clinical manifestations of, 735
  diagnosis of, 735
  relative, 735*t*
  signs of, 882
  treatment for, 735*b*
Hypovolemic hypernatremia, 733*t*, 743
Hypovolemic hyponatremia, 733*t*, 741
  treatment of, 741*b*
Hypovolemic shock, 658, 658–659, 659*f*, 661*t*

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Hypoxemia
and alveolar-arterial oxygen gradient, 639, 639*t*
clinical manifestations of, 645*t*
improving, methods for, 647*b*
mechanisms of, 643*t*
postoperative, 2675
pulmonary embolism and, 487*b*
severe mental illness and, 2683*t*
Hypoxemic acute respiratory failure, causes of, 643*t*
Hypoxemic respiratory failure, 596
Hypoxia, 595
ambient, 1075
tissue, 671
Hypoxia-induced factor (HIF) 1α, 1064
Hysterical gait, 2373*t*

I

I-cell disease, 1724, 1724*t*
IASLC. *See* International Association for the Study of Lung Cancer
Iatrogenic botulism, 1927
Iatrogenic hypoglycemia, 1546, 1546*t*
Iatrogenic interstitial lung disease, 572*t*
Iatrogenic perforation, 912
Ibalizumab, 2301*t*
for human immunodeficiency virus, 152
Ibandronate, for osteoporosis, 1644*t*
Ibrance. *See* Palbociclib
Ibrexafungerp, 2079
adverse effects of, 2079
drug interactions of, 2079
indications and dosage of, 2075*t*, 2079
mechanisms of action, 2079
Ibrutinib (Imbruvica), 1215*t*
for chronic lymphocytic leukemia, 1269*t*, 1270*t*
IBS. *See* Irritable bowel syndrome
Ibuprofen
for acute mountain sickness, 593
for chronic pain, 138*t*
for cystic fibrosis, 558*b*
for dysmenorrhea, 1596*t*
for patent ductus arteriosus, 350*b*
for pericardial constriction, 431*b*
for rheumatoid arthritis, 1756*t*
Ibutilide, 325*t*, 327*b*
ICDs. *See* Implantable cardioverter-defibrillators
Ichthyosis vulgaris, 2687.*e3t*
Iclusig. *See* Ponatinib
Icterus, 987, 987*f*–989*f*
Idarucizumab, 329*b*, 504–505
Idelalisib (Zydelig), 1215*t*
for chronic lymphocytic leukemia, 1269*t*
Ideomotor apraxia, 2408
Idiopathic and thrombotic thrombocytopenic purpura (ITP/TTP), characteristics of, 2270*t*
Idiopathic aplastic anemia, 1125
causes of, 1125*t*
clinical manifestations of, 1125
definition of, 1125–1126
diagnosis of, 1125, 1126*f*, 1127*t*
epidemiology of, 1125
pathobiology of, 1125
prognosis of, 1126
treatment of, 1126*b*
Idiopathic brachial plexitis, 2578
Idiopathic central apnea, 534*t*
Idiopathic cytopenias, of undetermined significance, 1255
Idiopathic generalized epilepsies, 2431
Idiopathic hypereosinophilic syndrome, 1162, 1163*t*
Idiopathic hypersomnia, 2446
Idiopathic megacolon, 890
Idiopathic nephrotic syndrome, 777–780, 777*t*
Idiopathic pulmonary arterial hypertension, 493
Idiopathic pulmonary capillaritis, 582
Idiopathic pulmonary fibrosis, 575
CT findings, 575.*e1f*
diagnosis criteria for, 577*t*
diagnosis of, 575–576, 576*f*
honeycombing in, 522*f*
as occupational lung disease, 585*t*
pathobiology of, 570
prognosis for, 577
radiographic features of, 574*t*
treatment of, 576*b*
Idiopathic pulmonary hemosiderosis, 582
Idiopathic thrombocytopenic purpura, 65*t*, 1770
Idiopathic tumoral calcinosis, 1815
Idiosyncratic hepatotoxicity, 1019
causes of, 1020*t*
clinical manifestations of, 1019*t*, 1019.*e1f*, 1020
diagnosis of, 1020–1021, 1021*t*
epidemiology of, 1019
factors that predispose to, 1020*t*
pathobiology, 1019–1020, 1019.*e1f*, 1020*t*
prevention of, 1021
prognosis of, 1021
treatment for, 1020*b*
Idioventricular rhythm, accelerated, 384*b*
Iduronate-2-sulfatase, for mucopolysaccharidosis type II, 1420*t*
α-l-Iduronidase, for mucopolysaccharidosis type I, 1420*t*
Ifex. *See* Ifosfamide
IFN-γ receptor 1 deficiency, 1686*t*
IFN-γ receptor 2 deficiency, 1686*t*
IFNL3 gene, 160*t*
Ifosfamide (Ifex), 1215*t*
cardiomyopathy due to, 288
IgA nephropathy. *See* Immunoglobulin A nephropathy
IgA vasculitis. *See* Immunoglobulin A (IgA) vasculitis
IgE. *See* Immunoglobulin E
IgE antibody, 193*t*
IGF-I. *See* Insulin-like growth factor-I
IgG4-related disease, 1288
IGNITE, 169.*e1t*
IGRA. *See* Interferon-gamma release assay
IL-1. *See* Interleukin-1
IL-1β. *See* Interleukin-1β
IL-2. *See* Interleukin-2
IL-4. *See* Interleukin-4
IL-5. *See* Interleukin-5
IL-6. *See* Interleukin-6
IL-12. *See* Interleukin-12
IL-13. *See* Interleukin-13
IL-17. *See* Interleukin-17
IL-23. *See* Interleukin-23
Ileal disease, 934
Ileal function, tests for, 931*t*
Ileitis, differential diagnosis of, 944*t*
Ileocecal syndrome, description of, 1860
Iliac artery endofibrosis, 467, 468*b*
Iliopectineal bursitis, 1746
Iliopsoas bursitis, 1746, 1747*b*
Iliotibial band syndrome, 1747, 1747*b*
Illness anxiety disorder, 2346, 2347*t*, 2683
Iloperidone, for psychotic disorders, 2346*t*
Iloprost, 468*b*, 473*b*
Imaging
cardiac, noninvasive, 244
myocardial perfusion, 248–249, 248*f*
pharmacologic stress myocardial perfusion, 248
speckle tracking strain imaging, 236, 236.*e1f*
of ventricular function, 249
Imatinib (Gleevec), *e10t*–*e11t*, 1215*t*, 1251*t*
for chronic myeloid leukemia, 1275*t*
for eosinophilic syndromes, 1164*b*
Imbruvica. *See* Ibrutinib
Imfinzi. *See* Durvalumab
Imidazole. *See* Ketoconazole
Imipenem, 1845*t*
for anthrax exposure, 97*b*
dosage of, 1895*t*
for nontuberculous mycobacterial disease, 2046*t*
for pneumonia, 613*t*
for *Stenotrophomonas maltophilia*, 1975*b*, 1976*t*
Imipenem-relebactam, dosage of, 1895*t*
Imipramine, for depression, 2340*t*
Imipramine + desipramine, *e10t*–*e11t*
Imiquimod, 2700
for anal warts, 982*b*
for coronavirus infections, 2191
Immature platelet fraction (IPF), *e8t*–*e9t*
Immature reticulocyte fraction (IRF), *e8t*–*e9t*
Immediate memory, 2407
Immobilization, thrombosis and, 481–482
Immune adherence or C4*b*/C3*b* receptor, 200*t*
Immune cells, 670
Immune checkpoint inhibitors, thyroiditis caused by, 1514
Immune complex glomerulonephritis, pneumonia with, 784*t*
Immune complex-mediated vasculitides, 1793, 1798
Immune complex rapidly progressive glomerulonephritis, 785
Immune complex renal disease, HIV-associated, 2313
Immune dysfunction, in chronic lymphocytic leukemia, 1267
Immune dysregulation syndromes, 1684–1685, 1684*t*
clinical manifestations of, 1685
diagnosis of, 1685
epidemiology of, 1684–1685
leading to colitis, 1684*t*
pathobiology of, 1684–1685
prognosis of, 1685
in systemic sclerosis, 1776
treatment of, 1685*b*
Immune globulin, defects of, 1680
clinical manifestations of, 1680
diagnosis of, 1682
epidemiology and pathobiology of, 1680, 1681*t*
prognosis of, 1682
treatment of, 1682*b*
Immune-mediated myocarditis, 286
Immune-mediated necrotizing myopathy, 1787, 1788, 1788*t*, 1790*t*
Immune-mediated thrombocytopenia, 1179
Immune neutropenia, 1146
Immune reconstitution inflammatory syndrome (IRIS), 2308, 2311*b*, 2312, 2312*t*
description of, 2088*b*
Immune-related adverse events, 1823
Immune response
to amebic infection, 2146
of COVID-19, 2212
innate, 670
Immune system
adaptive, 182
cell differentiation of, 189
effector mediators of, 189
pathogenesis of disease and, 191
principles of activation of, 187
signaling pathways of, 189
age-related changes in, 121
cells of, 182
components of, 1852*t*
evaluation of, approach to, 1676, 1677*f*, 1677*t*
in host defense, 182
innate, 182
activation of, 183–186
cell differentiation of, 185–186
cellular elements of, 182–183
effector mediators of, 185
localization of cells, 186
pathogenesis of disease and, 191
recognition receptors and triggers of, 183–186
role of, 186
signaling pathways of, 185
soluble products of, 185–186
transition to adaptive immune response, 186
in wound repair, 185*f*, 186
measles suppression of, 2220
overreactions of, 193
Immune therapies, for skin diseases, 2700–2701
Immune thrombocytopenic purpura (ITP), 1066, 1175, 1176*t*
Immune tolerance, 207
Immunity
adaptive, 671
inborn errors of, 1676
innate, 2108–2109
Immunization, 64–84. *See also* Vaccinations
active, 64
for adult, 66*t*, 76.*e1t*, 76.*e4t*
adverse reactions of, 76
altered immunocompetence in, 76, 76.*e2t*
for anthrax, 83
for chickenpox, 82
for cholera, 83
contraindications and precautions to, 75–76
for COVID-19, 77
for Ebola, 84
general characteristics of, 64–77
general considerations for, 76, 76.*e2t*, 77*f*, 78*f*
Haemophilus influenzae type b vaccine, 78
Immunization *(Continued)*
for heart failure, 275*t*
for hepatitis A, 79
adverse reactions of, 79
indications for, 79
for hepatitis B, 79
adverse reactions of, 79
indications for, 76.*e1t*, 77*f*, 79
for hepatitis B virus, 1006
for human papillomavirus, 79
adverse reactions of, 79
indications for, 79
for influenza, 79–80
adverse reactions of, 80
indications for, 79–80
for international travelers, 83
for Japanese encephalitis, 83
for measles, 80
for meningococcal disease, 80–81
adverse reactions of, 81
indications for, 80–81
for mumps, 81
passive, 64–75, 65*t*
pertussis, 1996
for pertussis, 81
for pneumococcal disease, 81
adverse reactions of, 81
indications for, 66*t*, 81
for poliomyelitis, 81–82
for possible bioterrorism agents, 83
for pregnancy, 76.*e2t*, 77
for rabies, 82
route and timing of, 75
for rubella, 82
schedule of, 76.*e1t*
for smallpox, 84
for tetanus and diphtheria, 82
for traveler
cholera, 1886*t*, 1887
description, 1885–1887
hepatitis A, 1886, 1886*t*, 1887
hepatitis B, 1886, 1886*t*, 1887
influenza, 1886*t*, 1887
Japanese encephalitis, 1886*t*, 1887
meningococcus, 1886*t*, 1887
polio, 1886*t*, 1887
rabies, 1886*t*, 1887
tetanus/diphtheria/acellular pertussis, 1886
typhoid, 1886*t*, 1887
update of, 1886–1887
varicella, 1886, 1886*t*
verification of, 1886
yellow fever, 1886*t*, 1887
for typhoid, 83
for varicella-zoster, 83
whooping cough, 1996
for yellow fever, 83
Immunocompetent donor T cells, role of, 1207
Immunocompromised hosts
adenovirus diseases in, 2205
approach to, 1852–1853
cutaneous syndromes in, 1855–1857, 1860*t*
diarrhea in, 1859
fever in, 1851, 1854*b*
gastrointestinal syndromes in, 1858–1860, 1860*t*
herpes simplex virus infections in, 2246, 2246*b*
infection in, 1851, 1854*b*
infectious syndromes in, 1860*t*
neurologic syndromes in, 1860*t*, 1861
noninfectious syndromes in, 1860*t*
parainfluenza viral diseases in, 2196
respiratory syncytial virus in, 2195
respiratory syndromes in, 1857–1858
sinopulmonary syndromes in, 1860*t*
Immunodeficiency, 191
autoinflammation, and amylopectinosis, 1731*t*
cystic fibrosis *versus*, 558
HLTV and, 2327*t*
inherited, 175
in solid organ transplant recipients, 1853
Immunoglobulin, intravenous, for autoimmune encephalitis, 2536
Immunoglobulin A (IgA), *e1t*–*e8t*
with IgG subclass deficiency, 1681*t*
Immunoglobulin A (IgA) nephropathy, 781, 783*f*
Immunoglobulin A (IgA) vasculitis, 782, 1798, 1798*b*, 2715
Immunoglobulin D (IgD), *e1t*–*e8t*
Immunoglobulin E (IgE), *e1t*–*e8t*, 1692

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Immunoglobulin G (IgG), *e1t–e8t*
antibody, 193*t*, 194
serologic tests, for toxoplasmosis, 2138*t*
subclass deficiency, 1681*t*, 1682
Immunoglobulin G4-related disease, 1825
Immunoglobulin G4-related interstitial nephritis, 793–794
Immunoglobulin-like domain-containing receptors, 183
Immunoglobulin-like killer inhibitory receptor (KIR), 183
Immunoglobulin M (IgM), *e1t–e8t*
antibody, 194
serologic tests, for toxoplasmosis, 2138*t*
Immunoglobulins
polyclonal, 1295, 1295*f*
serum, 1294
Immunologic disease, 1672
Immunologic failure, 2303
Immunologic testing, for brucellosis, 1984
Immunomodulatory drugs, 144–149, 146
azathioprine, 148
for Crohn disease, 945*b*, 946*t*
cyclophosphamide, 149
cyclosporine, 148
glucocorticoids, 144*t*
adipose tissue metabolism and, 145
bones and, 145
cardiovascular system and, 145
central nervous system and, 145
clinical use of, 145
history of, 144
inflammation and, 144
liver metabolism and, 145
monitoring of, 146
muscle metabolism and, 145
osteoporosis caused by, 145
in pregnancy, 146
tapering regimens for, 146
toxicity of, 146
withdrawal from, 146
hydroxychloroquine, 146
leflunomide, 147–148
6-mercaptopurine, 148
methotrexate, 147
mycophenolate mofetil, 147–148
for myelodysplastic syndromes, 1255
for retroperitoneal fibrosis, 1783*b*
sirolimus, 149
for skin diseases, 2700–2701
sulfasalazine, 146–147
tacrolimus, 148–149
Immunophilin-binding agents, 148
Immunoprophylaxis, for common cold, 2193
Immunosuppression
for acute kidney injury, 774*b*
Chagas disease and, 2128
for liver transplantation, 1048–1049, 1048*t*
net state of, 1853, 1853*t*
in renal transplantation, 844–845, 845*t*
reversal of, for aspergillosis, 2096
Immunosuppressive therapy, 147
for aplastic anemia, 1126*b*
for lung transplantation, 633
for myelodysplastic syndromes, 1255
for skin diseases, 2700
for systemic lupus erythematosus, 1772*b*
for systemic sclerosis, 1781*b*
Immunosuppressive therapy, warm autoimmune hemolytic anemia treated with, 1089*b*
Immunotherapy
for cancer, 1232*b*
for chronic lymphocytic leukemia, 1269*b*
for lung cancer, 1333*b*
for melanoma, 1393*b*
for rhinitis, 2634–2635
Impacted cerumen, 2641
Impaired lipolysis, 933
Impaired lymphatic drainage, 938
Impaired micelle formation, 933–934
Impaired mixing, 932
Impaired orgasm, 1590
Impetigo, 2687.*e4t*, 2720, 2739, 2739*f*
description of, 1903, 1914
Impingement syndrome. *See* Rotator cuff tendinosis
Implantable cardioverter-defibrillators (ICDs), 265*b*, 338*b*, 344
for acute STEMI, 384*b*
complications of, 345
Implantable cardioverter-defibrillators (ICDs) *(Continued)*
health care-associated infections and, 1866
indications for, 344, 344*t*
programming of, 344–345
pulse generators and leads for, 344, 344*f*, 344.*e1f*
selection of, 389*f*
Implantable electronic devices, cardiac, 340
Implantable loop recorders, 308
Impulse
conduction, disorders of, 302
formation, disorders of, 301
propagation, 300
Impulsivity, in eating disorders, 1461
IMRT. *See* Intensity-modulated radiation therapy
In vitro diagnostic multianalyte index assays, 168
In vitro fertilization (IVF), venous thromboembolism and, 481
In vivo gene therapy, 175
Inactivated hepatitis A vaccine, 66*t*
Inactivated Japanese encephalitis virus vaccine, 66*t*
Inactivated poliovirus vaccine (IPV), 66*t*, 81
Inactivated vaccine, 66*t*
Inactivated virus vaccine (IIV), 66*t*
Inborn errors of metabolism
approach to, 1398–1404
broad pathophysiologic mechanisms in, 1399*t*
characteristic signs of, 1399*t*
clinical manifestations of, 1399
definition of, 1398–1400
diagnosis of, 1399–1400, 1400*f*
epidemiology of, 1398, 1398*t*
fatty acid oxidation in, disorders of, 1404, 1404*b*
folate, 1120
micronutrients, 1452
pathobiology of, 1398–1399
protein metabolism in, disorders of, 1401–1404, 1402*t*
treatment of, 1401*b*, 1401*t*
Incidence, 35
"Incident reporting systems", 46
Incidental pulmonary nodule, as occupational lung disease, 585*t*
Incidentaloma, adrenal, 1524
Incisional hernia, 952*b*
Inclusion body myositis, 2368.*e4f*, 2564*t*, 2588*t*
clinical features of, 1788*t*
clinical manifestations of, 1789
diagnostic criteria for, 1790*t*
pathobiology of, 1787–1788
treatment of, 1790*b*
Incontinence
fecal, 865
stress. *See* Stress incontinence
urge. *See* Urge incontinence
urinary. *See* Urinary incontinence
Incontinentia pigmenti, 2550*t*
Indacaterol, 553*t*
Indapamide, 451*t*
Indels, 163
Indeterminate cell histiocytosis, 1157
Indian tick typhus, 2055*t*
Indinavir, 2301*t*, 2313
Indirect allorecognition, 205, 205*f*
Indirect euthanasia, 8*t*
Indirect hepatotoxicity, 1021, 1021*b*
Indirect magnetic resonance arthrography, 1722, 1722*f*
Individual clinician, role of, in occupational and environmental medicine, 89
Indolent systemic mastocytosis, 1703*b*
Indomethacin, for chronic pain, 138*t*
Inducible urticaria, chronic, 1687, 1690*t*
Induction therapy, in renal transplantation, 845
Industrial dusts, 88*t*
Inert gas dilution technique, 530
Infantile botulism, 1927, 2565
Infantile cystinosis, 816
Infantile febrile mucocutaneous lymph node syndrome, 965
Infants
with cystic fibrosis, 557
of diabetic mothers, 1464
micronutrient requirements for, 1452
Infection(s)
acute pancreatitis and, 970, 970*t*
of black skin, 2738–2742
blood cultures for, 1834
cancer and, 1245
cerebrospinal fluid testing for, 1835
chlamydial, in adolescents, 112
in chronic diseases, 1834–1836
in chronic lymphocytic leukemia, 1267
in chronic obstructive pulmonary disease, treatment of, 649*b*
coagulation response to, 671
and control, 2272
definition of, 1833
diagnosis of, 1834–1836
dialysis-associated, 843
early, 670
emerging, 1833–1834
in endoscopy, 876*t*
esophageal, 911–912
bacterial esophagitis in, 912
candidiasis in, 911, 912*f*
cytomegalovirus in, 912
herpes simplex virus in, 911
human papillomavirus in, 912
genetic susceptibility and response to, 1834
health care-associated, 1862
after hematopoietic cell transplantation, 1211
host reaction to, 1833
in immunocompromised host, 1851
clinical manifestations of, 1854
definition of, 1851
diagnosis of, 1854
general concepts of, 1851
treatment of, 1854*b*
in joints, 1717*t*
after lung transplantation, 633
microbiology testing of, 1834
nature of, antimicrobial therapy for, 1842
neutrophilia and, 1140–1141
occupational, 86*t*
parasitic, 515*t*
primary testicular hypogonadism caused by, 1583
prophylaxis for, 700*b*
pulmonary
and bronchiectasis, 560
pathogens and empirical therapy for, 2526*t*
Staphylococcus aureus causing, 1904
treatment of, 1970*b*
renal transplantation and, 846–847, 846*f*
respiratory specimen testing for, 1835–1836
sickle cell disease, 1114
stool testing for, 1836
treatment of, for cystic fibrosis, 558*b*
trematode, 2163–2168
urine testing for, 1836
Infection, periprosthetic joint, 1829
Infection-related neutropenia, 1145
Infections, extrapulmonary, legionellosis and, 1998
Infectious diseases
diagnostic testing for, 1834
historical description of, 1833
in pregnancy, 1627–1628
Infectious Diseases Society of America, guidelines for outpatient therapy for pneumonia, 612*t*
Infectious endocarditis, neurologic complications of, 2530, 2530*b*
Infectious enterocolitis, abdominal pain and, 854*t*
Infectious eruptions, 2712–2713
molluscum contagiosum, 2712–2713, 2713*f*
warts, 2713
Infectious myelopathy, 2406, 2406*b*
Infectious neuropathies, 2577–2578
Infectious pericarditis, 424*t*, 431–432
Infectious sacroiliitis, 1718, 1719*f*
Infectious sinusitis, 2631
Infectious thyroiditis, 1514, 1514*b*
Infective dermatitis, 2327*t*
Infective endocarditis, 413
causative organisms of, 415–416
clinical manifestations of, 414–415
complications of, 417*b*
definition of, 413–423
diagnosis of, 415–417, 415*t*
echocardiography in, 416, 418*f*
epidemiology of, 413–414
Infective endocarditis *(Continued)*
health care-associated, 414
history in, 414
incidence of, 413
laboratory findings of, 416
microbiology of, 415–416
modified Duke criteria for, 415, 415*t*
pathobiology of, 414
physical examination of, 414–415
predisposing conditions associated with increased risk of, 413*t*
prevention of, 422–423, 422*t*
prognosis of, 423
surgery for, 417*b*
Inferior petrosal sinus sampling, 1494, 1523–1524
Inferior vena cava filters, 487*b*
Infertility, 1580–1590
definition of, 1586
epidemiology of, 1586
female, 1602–1603
causes of, 1603*t*
definition of, 1602–1603
diagnosis of, 1602–1603
treatment of, 1603*b*
after hematopoietic cell transplantation, 1211
Hodgkin lymphoma and, 1293*t*
human immunodeficiency virus and, 2318
male, 1586
algorithm for, 1587*f*–1588*f*, 1588*f*
basic laboratory tests for, 1589*t*
clinical manifestations of, 1586
diagnosis of, 1586
treatment of, 1586*b*–1587*b*
pathobiology of, 1586
Infigratinib (Truseltiq), 1215*t*
Infiltrate, 520
Infiltrative cardiomyopathies, 249
Infiltrative disease, ventricular tachycardia in, 337
Inflamed eye, 2599, 2599*t*
Inflammasome, 183, 1735
Inflammation, 191
acute phase response, 1712
blood markers of, 220
glucocorticoids and, 144
markers of, 1712
in osteoarthritis, 1738
resolution of, 196, 196*f*
in sepsis, 670, 670.*e1f*–670.*e2f*
in systemic sclerosis, 1776
Inflammatory arthritis, pathobiology of, 1826, 1826*f*
Inflammatory bowel disease, 941–950
5-aminosalicylate for, 945*b*, 946*t*
antibiotics for, 945*b*
arthritis associated with, 1821
clinical manifestations of, 942–943
definition of, 941
diagnosis of, 943–945
diagnostic evaluation of, 943–945
differential diagnosis of, 944*t*
endoscopic evaluation of, 943
epidemiology of, 941
extraintestinal complications of, 943
extraintestinal manifestations of, 943, 943*t*
follow-up for, 945*b*
genetics of, 942
human microbiome and, 1838
laboratory findings in, 945
medical therapies for, 945*b*, 946*t*
nonsteroidal anti-inflammatory drugs and, 941
pathobiology of, 941–942
pathology of, 942
pathophysiology of, 942
physical examination of, 943
pregnancy in, 945*b*
prognosis for, 950
radiology of, 945
serologic markers of, 945
susceptibility gene in, 942
symptoms of, 943
treatment of, 945*b*
Inflammatory bowel disease-undetermined, 941
Inflammatory colitis, *E. coli* and, 1963
Inflammatory diarrhea, 924, 930*f*, 931, 940
Inflammatory disease, ventricular tachycardia in, 337
Inflammatory lung disorder, occupational and environmental, 86*t*
Inflammatory mediators, 183

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Inflammatory muscle diseases, 2587
Inflammatory myelopathy, 2406, 2406*b*
Inflammatory myopathies, 1787–1791, 2587.*e1t*, 2588*t*
  classification of, 1788*t*
  clinical manifestations of, 1788–1789
  definition of, 1787–1791
  diagnosis of, 1788
  diagnostic criteria for, 1790*t*
  epidemiology of, 1787
  pathobiology of, 1787–1788
  pathology of, 1789*f*
  prognosis for, 1791
  treatment of, 1790*b*, 1791*f*
Inflammatory myositis, 2260, 2260*b*
Inflammatory response
  adaptive, 192
  innate, 191–192, 192*f*
Inflammatory retiform purpura, 2715*t*, 2716, 2716*f*
Infliximab
  description of, 150, 151*t*
  for inflammatory bowel disease, 945*b*, 946*t*
  for rheumatoid arthritis, 1756*t*
  for sarcoidosis, 603*b*, 604*t*
Infliximab (Remicade), for total knee arthroplasty, 1830.*e1t*
Influenza, 2198–2203
  antigenic variation of, 2198–2199
  antiviral therapy for, 2189, 2189*t*
    amantadine, 2189
    baloxavir marboxil as, 2189
    oseltamivir as, 2189
    peramivir as, 2189
    rimantadine, 2189
    zanamivir as, 2189
  characteristics of, 2270*t*
  clinical manifestations of, 2200–2201
  definition of, 2198–2203, 2198.*e3t*
  diagnosis of, 2201
  epidemic, 2199
  epidemiology of, 2198–2199
  genetic variation of, 2198
  health care-associated infections and, 1865
  immunization for, 66*t*, 79
    adverse reactions of, 80
    indications for, 79
    schedule of, 76.*e1t*, 77*f*
  intrapandemic, 2199
  medications for chemoprophylaxis in, 2202, 2203*t*
  nonrespiratory complications of, 2200–2201
  pandemic, 2199
  pathobiology of, 2199–2200
  pathogen that causes, 2198, 2198.*e4f*, 2198.*e3t*
  precautions for, 2202
  prevention of, 2201–2202
  prognosis of, 2203
  respiratory complications of, 2200
  seasonal, 541*b*
  syndrome of, 2200, 2201*t*
  in travelers, 1889.*e1t*
  treatment for, 2201*t*, 2202*b*, 2203*t*
  vaccination, 2201–2202, 2201*t*, 2202.*e1t*
    prevention of, 555
    for traveler, 1886*t*, 1887
  virus structure, 2198.*e4f*
  zoonotic, 2199
Influenza A virus, 2198
  in acute bronchitis and tracheitis, 605
  antigenic subtypes of, 2198.*e3t*
  prophylaxis for, 2309*t*
  proteins of, 2198.*e3t*
Influenza B virus, 2198, 2309*t*
Influenza C virus, 2198
Influenza D virus, 2198
Information sharing, Ask-Tell-Ask, 12, 16*t*
Information technologies, advances in, 40
Informed consent, 5, 6*t*
Infradian rhythms, 1478
Infrapatellar bursa, 1747
Infrared radiation, 88*t*
Ingrowing toenails, 2754, 2755*f*
Inguinal adenopathy, treatment of, 1241*b*
Inguinal hernia, 952
Inhalation injury, 595–596, 703.*e1f*
  carbon monoxide poisoning, 595, 596*b*
  cyanide poisoning, 596, 596*b*
  e-cigarettes/vaping, 595
  oxygen toxicity, 596, 596*b*
  smoke inhalation, 595, 595*b*
  thermal injury, 595, 595*b*
Inhalational anthrax, 1931, 1931*f*, 1932*b*
Inhaled β-agonists, 551*b*
Inhaled glucocorticoids, 551*b*
Inhalers, 541*b*, 542*f*, 543*t*, 553*t*
Inheritance, patterns of, 160
  mendelian inheritance, 160, 161*f*
  mosaicism, 162, 163*f*
  nonmendelian inheritance, 162
Inherited autoinflammatory diseases, 1731*t*
Inherited bone marrow failure syndromes, 1129–1130
Inherited platelet bleeding disorder, 1184
Inherited renal tubular disorders, 815
Inherited rhabdomyolysis, 714*t*, 715
Inhibin, 1477
Inhibin B, 1586
Initiators
  of adaptive immune response, 192
  of innate immune mechanisms, 191, 192*f*
Injectable steroid contraceptives, 1615
Injection drug users
  Clostridium novyi infection in, 1927
  HIV transmission in, 2299
  infective endocarditis in, 413–414
Injury
  classes of, 699*t*
  clinical manifestations of, 699–703, 699*f*–700*f*, 699*f*, 700*f*
  critical care of, 700*b*, 703.*e1f*
  decompression procedures for, 700*b*, 702.*e1f*
  definitive surgical care for, 700*b*
  diagnosis of, 700*b*
  early response to, 698
  early systemic response to, 698
  emotional consequences of, 704
  epidemiology of, 698–703
  at extremes of age, 704, 704.*e1t*
  fluid resuscitation for, 700*b*
  initial evaluation for, 700*b*
  initial surgical care, 700*b*
  interhospital transport for, 700*b*
  late hypermetabolic systemic response to, 699
  late local response to, 698–699
  lung, 591
  pathobiology of, 698–699
  post-resuscitation metabolic issues, 700*b*, 703.*e1f*
  prehospital care of, 700*b*
  prevention, 55
  rehabilitation of, 700*b*, 703–704
  resuscitation for, 700*b*
  special considerations in, 703–704
  transfusion for, 700*b*
  treatment for, 700*b*
Inlet patches, 913
Inlyta. *See* Axitinib
Innate immune mechanisms, 191, 192*f*
Innate immune system, 182
  activation of, 183
  cell differentiation of, 185
  cellular elements of, 182
  effector mediators of, 185
  localization of cells, 186
  pathogenesis of disease and, 191
  recognition receptors and triggers of, 183
  role of, 186
  signaling pathways of, 185
  soluble products of, 185
  in systemic lupus erythematosus, 1768.*e2f*
  transition to adaptive immune response, 186
  in wound repair, 185*f*, 186
Innate immunity
  complement in, 196
  description of, 1834
Innate immunity, diseases of, 1685–1686, 1686*t*
  clinical manifestations of, 1685–1686
  diagnosis of, 1686
  epidemiology and pathobiology of, 1685–1686
  treatment and prognosis of, 1686*b*
Inorganic dusts, 88*t*
Inorganic mercury, 103
Inotersen, for amyloidosis, 1309*b*
Inotropes, 667*b*
Insects, envenomation of, 711
  anaphylaxis caused by, 1692
Insertion, 163
Insertional tendon. *See* Achilles tendon
Insoluble lipids, 938
Insomnia, 2450
  classification of, 2450*t*
Insomnia *(Continued)*
  clinical manifestations of, 2450
  definition of, 2450
  diagnosis of, 2450
  differential diagnosis of, 2451*f*
  epidemiology of, 2450
  medications for, 2452*t*
  nonpharmacologic therapies for, 2451*t*
  pathobiology of, 2450
  prognosis of, 2450
  treatment of, 2450*b*
Inspiratory capacity (IC), 530
Inspiratory hold maneuver, 640*f*
Inspiratory reserve volume (IRV), 530
INSTIs. *See* Integrase strand transfer inhibitors
Institute of Medicine (IOM), quality aims, 44*t*
Instrumental ADLs, 117
Insulin, *e1t*–*e8t*, 1534
  aging and, 115
  continuous infusion of, 1537*b*
  endocrine diseases caused by, 1475*t*
  intermittent subcutaneous, 1537*b*
  metabolic effects of, 1535*t*
  preparations, 1538*t*
  secretion of, 121
  in septic shock, 673*b*
  for type 1 diabetes mellitus, 1537*b*
  for type 2 diabetes mellitus, 1540*b*
Insulin antibodies, for hypoglycemia, 1557
Insulin autoimmune syndrome, 1554
Insulin deficiency, treatment of, 752*b*
Insulin-dependent diabetes, 1534
Insulin factitious hypoglycemia, 1554
Insulin-glucose, for acute poisoning, 693*t*
Insulin growth factor-1, aging and, 115
Insulin-like growth factor-I (IGF-I), 1474, 1477, 1488
Insulin-receptor mutations, hypoglycemia and, 1554
Insulin resistance
  HIV causing, 2318
  obesity and, 1465
  in pregnancy, 1624
Insulin secretagogues, for type 2 diabetes mellitus, 1534.*e1f*, 1540*b*, 1541*t*
Insulinoma, 1465, 1554, 1557*b*, 1561*t*
Insulitis, 1536
Insurance coverage, 19, 19*f*, 20*f*
Integral membrane proteins
  disorders, 1419*t*–1420*t*
  function, 1093–1094
Integrase strand transfer inhibitors (INSTIs), 2300–2302, 2303*t*, 2304*t*, 2319
Integrative medicine, complementary and, 153
Integumentary system, age-related changes in, 121–122
Intensity-modulated radiation therapy (IMRT), for cancer, 1232*b*
Intensive care
  admission orders, 637, 637*t*
  coronary, 384*b*
  long-term outcomes for survivors, 636
Intensivists, 636
Intentional injuries, in adolescents, 110–111, 110*t*
β-Intercalated cells, 754
Interdisciplinary team, in hospice, 16
Interferon (IFN)
  for hepatitis B virus infections, 2181*t*, 2182*t*, 2183
  thyroiditis caused by, 1514
  type I
    in COVID-19, 2212
    systemic lupus erythematosus and, 1768
Interferon-α
  cardiomyopathy due to, 288
  for chronic hepatitis B, 1011*b*
Interferon alfa-2*b*, 2701
Interferon-β, for COVID-19, 2217
Interferon beta1*a* (Avonex, Rebif), for multiple sclerosis, 2505*t*
Interferon beta1*a* pegylated (Plegridy), for multiple sclerosis, 2505*t*
Interferon beta1*b* (Betaseron, Extavia), for multiple sclerosis, 2505*t*
Interferon-gamma release assay (IGRA), 2039
  for nontuberculous mycobacteria, 2045
Interferon-related autoinflammatory syndromes, 1731*t*
Interferonopathies, 1731*t*, 1735–1736
  Aicardi-Goutières syndrome, 1731*t*, 1735
Interferonopathies *(Continued)*
  proteasome-associated autoinflammatory syndromes, 1731*t*, 1735–1736
  STING-associated autoinflammatory syndromes, 1736
Interleukin-1 (IL-1), 151, 151*t*
Interleukin-1 (IL-1) inhibitors, in familial Mediterranean fever, 1732
Interleukin 1 receptor associated kinase 4 (IRAK4), 1686*t*
Interleukin-1-related periodic fever syndromes, 1730–1735
Interleukin-1β (IL-β), 151
Interleukin-1-beta-related disorders, 1731*t*
Interleukin-2 (IL-2), 151
Interleukin-4 (IL-4), 151
Interleukin-5 (IL-5), 151
Interleukin-6 (IL-6), 151, 151*t*, 2217
Interleukin-6 (IL-6) receptor inhibitors, for rheumatoid arthritis, 1757*t*
Interleukin-7 (IL-7) deficiency, 1676.*e3t*
Interleukin-12 (IL-12), 151
Interleukin-12 (IL-12) receptor deficiency, 1686*t*
Interleukin-13 (IL-13), 151
Interleukin-17 (IL-17), 152
Interleukin-23 (IL-23), 151
Interleukin-23 (IL-23) receptor deficiency, 1686*t*
Intermediate density lipoproteins, 1405
Intermediate life support, 313*b*
Intermediate syndromes, hereditary stomatocytosis and, 1097
Intermittent claudication, 465.*e1f*
Intermittent infusions, 1449
Intermittent mandatory ventilation, 653
Internal carotid arteries, 2465
  anatomy of, 2455, 2456*f*
  bifurcation of, 2465
  magnetic resonance angiogram of, 2456*f*
International Association for the Study of Lung Cancer (IASLC), lymph node map, 1332*f*
International Cancer Genome Consortium, 167
International League Against Epilepsy Classification of Seizures, 2427*f*
International normalized ratio (INR), *e8t*–*e9t*
International Prognostic Index, 1281
International Prognostic Scoring System, for myelodysplastic syndromes, 1257–1258, 1258*f*
International Prostate Symptom Score (IPSS), 822, 823*f*
International travelers, vaccines for, 83
Internuclear ophthalmoplegia, 2500–2501, 2619, 2620*f*
Internuclear pathways, 2617–2618
Interpersonal behavior control, 2410, 2411*f*
Interpersonal psychotherapy, for depression, 2339*t*
Interprofessional team, in critical care, 636
Interrupted pregnancy, 1604
Interrupted time-series, 37
Interstitial cells of Cajal, 887
Interstitial disorder, occupational and environmental, 86*t*
Interstitial lung disease, 570–584
  chest radiograph in, 573, 573*t*
  classification of, 571*t*
  clinical manifestations of, 570–571
  connective tissue disease and, 571*t*, 580
  definition of, 570–575
  diagnosis of, 571–575, 572*f*
  drug-induced, 572*t*, 582
  epidemiology of, 570
  exercise testing for, 574
  forms of, 571*t*, 582–583
  high-resolution computed tomography in, 574
  history in, 572*f*
  iatrogenic, 572*t*
  incidence of, 570
  inherited disorders associated with, 583–584
  inherited forms of, 571*t*
  invasive evaluation of, 574–575
  laboratory testing for, 573
  noninvasive evaluation of, 573–574
  occupational, 582
  pathobiology of, 570
  physical examination for, 573
  prevalence of, 570
  pulmonary function tests for, 574
  pulmonary vasculitis and, 571*t*, 582
  respiratory bronchiolitis-associated, 574*t*, 577, 578*b*, 578*f*

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Interstitial lung disease *(Continued)*
in systemic sclerosis, 1779–1781, 1780, 1781*b*
treatment of, 575*b*, 575*t*
types of, 575–584
Interstitial nephritis, 790–795
acute
biopsy of, 792, 792*t*, 793*f*
causes of, 790*t*
characteristics of, 790
clinical manifestations of, 792, 792*t*
diagnosis of, 792
differential diagnosis of, 792
drugs that cause, 790
epidemiology of, 790
granuloma formation in, 792
prognosis for, 793
proteinuria in, 792
treatment of, 792*b*
characteristics of, 790
chronic
analgesics causing, 793
cadmium toxicity causing, 794
causes of, 791*t*, 793
characteristics of, 790
clinical manifestations of, 793
diagnosis of, 793
granuloma formation in, 792
hypercalcemia causing, 794
lead toxicity causing, 794
myeloma causing, 794
obstruction causing, 794
pathology of, 791
primary, 790
vascular disease causing, 793
definition of, 790–792
diagnosis of, 793
epidemiology of, 790
leptospirosis causing, 2029*f*
pathology of, 791–792
pathophysiology of, 790–791
prognosis of, 795
proteinuria in, 792
treatment of, 795*b*
Interstitial pneumonia
acute, 566*t*, 567, 574*t*, 578, 579*f*
clinical manifestations of, 568, 568*f*, 568.*e1f*
definition of, 567
diagnosis of, 568
pathobiology of, 568
treatment for, 568*b*
chronic fibrosing, 571*t*, 575
desquamative, 578
diagnosis of, 578, 578*f*, 578.*e1f*, 579*f*
prognosis for, 578*b*
radiographic features of, 574*t*
treatment of, 578*b*
honeycombing in, 522*f*
idiopathic, 575–580
acute, 571*t*, 578
radiographic features of, 574*t*
subacute, 571*t*, 578
lymphocytic, 579–580
diagnosis of, 580
prognosis for, 580*b*
radiographic features of, 574*t*
treatment of, 580*b*
lymphoid, 579, 580*b*, 580.*e1f*
nonspecific, 577
diagnosis of, 577, 577*f*
prognosis for, 577*b*
radiographic features of, 574*t*
treatment of, 577*b*
rare, 571*t*
smoking-related, 571*t*, 577
Interventional contrast pulmonary angiography, of venous thromboembolism, 486
Interventional procedures, 874
Interventional therapy, for aspergillosis, 2096
Interventricular septum, 224
Intestinal bacterial overgrowth, 932*t*, 934
clinical manifestations of, 934
diagnosis of, 931*t*, 932*t*, 934
treatment of, 934*b*
Intestinal diverticular disease, nutrition and, 60
Intestinal flukes, 2166*t*, 2167
Intestinal ischemia, 959
abdominal pain and, 854*t*
epidemiology of, 959
weight loss and, 860*t*
Intestinal metaplasia, 913
Intestinal perforation, enteric infections and, 1870*t*
Intestinal protozoa, 2112*t*, 2115
Intestinal pseudo-obstruction
clinical manifestations of, 888
diagnosis of, 889, 889*f*
medical therapy for, 889*b*
surgical therapy for, 889*b*
treatment of, 889*b*
Intestinal tuberculosis, 2037
Intestine
atresia, 951
blood flow to, 959
inflammatory diseases of, 951–959
malrotation, 951
Intimate partner violence (IPV), 1633–1636
abused patient, management of, 1634*b*
abusive patient, management of, 1634*b*
clinical manifestations of, 1633–1634
couples therapy in, 1634*b*
definition of, 1633–1636
diagnosis of, 1634–1635
epidemiology of, 1633
health care providers in, 1634*b*
pathobiology of, 1633, 1634*t*
prevention of, 1635–1636
prognosis of, 1636
treatment of, 1634*b*, 1635*t*
Intimate terrorism, 1633
Intoxication, 759
Intra-abdominal infections, 1921, 1921*b*
anaerobic bacteria causing, 1939
bacterial species that cause, 1892*t*
mesenteric venous thrombosis and, 963*t*
Pseudomonas infections causing, 1969, 1970*b*
Intra-abdominal testes, removal of, 1575*b*
Intra-aortic balloon pumps, 667*b*
Intra-axial brain tumors, 1316
Intracardiac echocardiography, 239
Intracardiac electrograms, 317.*e1f*
Intracavernosal injection, for erectile dysfunction, 1589
Intracavitary mycetoma, 607
Intracavitary tumors, 297–298
Intracerebral hemorrhage, 2479*f*
acute, 2481*t*
blood pressure control in, 2480*b*
causes of, 2479*t*
clinical manifestations of, 2479
definition of, 2478–2482
diagnosis of, 2479–2480, 2481*f*
epidemiology of, 2478–2482
hypertension-related, 2463
pathobiology of, 2478–2479
prevention of, 2480*b*
prognosis for, 2482
surgical treatment of, 2480*b*
treatment of, 2480*b*
Intracerebral Hemorrhage Score, 2481*t*
Intracerebral parenchymal brain hemorrhages, 2463
Intracranial aneurysm, autosomal dominant polycystic kidney disease and, 811
Intracranial epidural hematoma, 2391
clinical manifestations of, 2391
diagnosis of, 2387*f*, 2391
epidemiology of, 2391
pathobiology of, 2391
prognosis of, 2391*b*
treatment of, 2391*b*
Intracranial hypertension, 2383, 2383*b*
Intracranial hypotension, 2383, 2384*b*, 2384*f*
Intracranial leptomeningeal metastases, 1317, 1317*b*, 1317*f*, 1317.*e1f*
Intracranial plasmacytomas, 1299
Intracranial pressure, raised, treatment of, 2440*b*
Intradermal nevi, 2730
Intraductal papillary mucinous neoplasms, 1356
Intradural extramedullary tumors, 1318–1319, 1319*b*
Intraepidermal adenocarcinoma, 980
Intraepidermal blistering disorders, 2718
Intraepithelial neoplasia, cervical, oral contraceptives and, 1615
Intraepithelial neoplasias, 1376, 2242
Intraerythrocytic bacteremia, 2000, 2001*t*
Intrahepatic cholestasis of pregnancy, 1626, 1626*b*, 1627*t*
Intralesional bleomycin, 2700
Intraluminal digestion, impairment of, 932–934, 932.*e1f*
Intramedullary hemolysis, hyperbilirubinemia and, 1121
Intramedullary spinal cord tumors, 1319, 1319*b*, 1319*f*
Intramural hematoma, 439, 441*b*, 441*f*
Intramuscular hematomas, hemophilia and, 1188
Intramyocardial tumors, 298
Intraocular pressure, 2596
glaucoma and, 2607
Intrapandemic influenza, 2199
Intraperitoneal fibrosis, 1567
Intrarenal acute kidney injury, 773, 774
Intrathecal pumps, in palliative care, 12
Intrathecal tofersen, for amyotrophic lateral sclerosis, 2563*b*
Intrauterine devices (IUDs), for contraception, 1617
Intrauterine factors, 2641
Intravascular hemolysis, 1092
Intravascular large B-cell lymphoma, 1285
Intravenous access, for shock, 662*b*
Intravenous epoprostenol, 496*b*
Intravenous fluids
for cryptosporidiosis, 2143*b*
for shock, 662*b*
Intravenous gamma globulin, for systemic lupus erythematosus, 1772*b*
Intravenous GPIIb/IIIa receptor antagonists, 508
Intravenous hydration, for diarrhea and enteric infection, 1872*t*
Intravenous immunoglobulin, for Guillain-Barré syndrome, 2571*b*
Intravenous iron therapy, for iron deficiency anemia, 1084*b*
Intravenous medications, for hypertensive emergencies, 458*b*, 460*t*
Intraventricular blocks, 321, 322*b*
Intraventricular cysticerci, 2160*f*
Intraventricular hemorrhage, 2478
Intrinsic acute kidney injury, 770, 771*t*
Intrinsic factor, *e1t–e8t*
Intrinsic pathway, 1165
Intrinsic resistance, 1965, 1966*t*
Intubation, 654, 691*b*
Intussusception, 952, 952*b*
Invasive aspergillosis
clinical manifestations of, 2094
diagnosis of, 2095, 2095*f*
epidemiology of, 2094
treatment of, 2096
Invasive candidiasis, 2092
Invasive mucinous adenocarcinoma, 566*t*, 569, 569.*e1f*, 570*b*, 570*f*
Invasive procedures, diagnostic, 261
Inverse psoriasis, 2705
Involuntary active euthanasia, 8*t*
Involuntary bladder contraction, 827
Involuntary weight loss, 860
causes of, 860*t*
diagnosis of, 861, 862*f*
signs and symptoms of, 852*t*
Iodine, 1457*t*
for hyperthyroidism, 1511*b*
radioactive. *See* Radioactive iodine
Iodine deficiency, 1507, 2542–2543
Iodine-induced hyperthyroidism, 1511*t*
Iodine-induced thyrotoxicosis, 1514
Iodoquinol, for amebic liver abscess, 1025*b*
Ion channelopathies, 2585–2586
Ion channels, 223, 299*f*, 300
Ionizing radiation, 91–95
cancer and, 1246
definitions of, 91, 91*f*, 92*t*
exposure to, 88*t*
acute radiation syndromes, 93, 94*f*
clinical manifestations of, 93
diagnosis of, 93–94, 93*t*
epidemiology of, 91.*e1f*, 92
medical, 92
medical imaging of, 94–95
natural sources of, 92
organ-specific late effects after radiotherapy, 93, 93*t*
pathobiology of, 92
prevention of, 94–95
radiologic accidents, 92, 92*t*
Ionizing radiation *(Continued)*
radiologic terrorism, 92
stochastic effect, 93
head and neck cancer and, 1321
Ipilimumab (Yervoy), 1215*t*, 1251*t*
for melanoma, 1394*t*
for renal cell carcinoma, 1364*b*
Ipratropium bromide, 553*t*
IPSS. *See* International Prostate Symptom Score
IPV. *See* Intimate partner violence
Irbesartan, 451*t*
Irbesartan/HCTZ, 451*t*
Irinotecan (Camptosar), 1215*t*
IRIS. *See* Immune reconstitution inflammatory syndrome
Iris melanoma, 2612–2613, 2613*f*
Iritis, 2611
Iron, *e1t–e8t*, 1457*t*
for malabsorption, 937*t*
toxicity, 88*t*, 690*t*
Iron-binding capacity, total (TIBC), *e1t–e8t*
Iron bisglycinate, for iron deficiency anemia, 1085*t*
Iron chelation therapy, for myelodysplastic syndromes, 1255
Iron deficiency, 886
in heart failure, 265*b*
Iron deficiency anemia, 1082–1085
anemia of chronic disease *versus*, 1068–1069
cause of, 1083*t*
chronic hematuria as cause of, 1083–1084
clinical manifestations of, 1084
colonoscopy evaluations, 887
definition of, 1082
diagnosis of, 1084, 1084*f*, 1085*t*
differential diagnosis of, 1084
epidemiology of, 1082
gastrointestinal cause of, 1082–1083
pathobiology of, 1082–1084, 1083*f*, 1083*t*
prevention of, 1085
prognosis of, 1085
treatment of, 1084*b*
Iron overload, 1438
classification of, 1438*t*
clinical manifestations of, 1439, 1439*t*
definition of, 1438
diagnosis of, 1440, 1441*f*
epidemiology of, 1438
pathobiology of, 1438, 1439*f*
physical findings in, 1440*t*
prognosis of, 1442
quantifying, 1441
screening for, 1441
symptoms and signs of, 1440, 1440*t*
in thalassemia, 1107*b*
treatment of, 1441*b*
Iron saturation, *e1t–e8t*
Irradiation, hypothalamic disease effects on, 1480
Irregularly contracted cells, conditions associated with, 1072*t*
Irreversible renal failure, treatment of, 840–848
dialysis for, 841, 841*t*
hemodialysis for, 841
medical issues in, 842–843
peritoneal dialysis for, 841–842
prognosis of, 843, 843*t*
renal transplantation for, 843–848, 845*t*
Irritable bowel syndrome (IBS), 892–898
abdominal pain and, 854*t*
altered CNS processing and modulation in, 893
chronic diarrhea and, 928–929
clinical manifestations of, 893–894
definition of, 892
diagnosis of, 894–895
diagnostic criteria for, 895, 895*t*
dysregulated stress responsiveness in, 893
enteric infections and, 1870*t*
epidemiology of, 892
familial and genetic factors of, 892–893
gut transit and motility in, 893
increased visceral perception in, 893
pathobiology of, 892–893
peripheral gastrointestinal factors of, 893
postinfection, 893
prognosis of, 898
small bowel dysmotility in, 890
stressful life events and, 893

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Irritable bowel syndrome (IBS) *(Continued)*
symptom-based criteria for, 894–895, 894*f*, 894*t*
treatment of, 895*b*, 896*f*, 896*t*, 898*f*
weight loss and, 860*t*
Irritant contact dermatitis, 2704
Irritant dermatitis, 1692
Irritant exposure, 587–588
Irukandji syndrome, 712*b*
IRV. *See* Inspiratory reserve volume
Isavuconazole, 2077
adverse effects of, 2077
for aspergillosis, 2096
drug interactions of, 2077
formulations and pharmacology of, 2077
indications and dosage of, 2075*t*, 2077
for mucormycosis, 2100*b*
Ischemia
cerebral, 2462
colon, 964
algorithm of, 966*f*
clinical manifestations of, 964
conditions and medications associated with, 964*t*
diagnosis of, 964, 965*f*, 965.*e1f*
treatment of, 965*b*
focal segmental, 962*f*
intestinal, 959
epidemiology of, 959
pathobiology of, 959
limb
acute, 461, 462*t*, 465*f*
chronic, 462
lower limb
chronic, 462*t*, 464*b*
chronic critical, 462
chronic stable, 462
mesenteric
acute, 959
chronic, 963*f*
nonocclusive, 962, 962*f*
myocardial
differential diagnosis of, 424*t*
silent, 369
peptic ulcers caused by, 916
treatment of, 265*b*
Ischemic cardiomyopathy, chronic, 336*f*
Ischemic cerebrovascular disease, 2464
clinical manifestations of, 2465
definition of, 2464–2469
diagnosis of, 2466, 2466*f*
differential diagnosis of, 2469
epidemiology of, 2464
pathobiology of, 2464
physical examination of, 2466
Ischemic disease, end-stage, 242*t*
Ischemic heart disease
causes of, 358*t*
chronic, 356
blood tests in, 361*t*
epidemiology of, 356
noninvasive testing for, 359, 362*f*
pathobiology of, 356
symptoms of, 357*t*
diagnosis of, 358–364, 359*f*
diagnostic coronary angiography in, 363*t*
laboratory testing of, 358–359
physical examination of, 358
prognosis for, 369
risk stratification of, 363
stable, 356
treatment of, 364*b*
Ischemic nephropathy, 799
Ischemic optic neuropathy, 2615
Ischemic stroke
acute
fibrinolytic therapy for, 509
radiographic changes of, 2373, 2373.*e1f*
arterial hypertension in, 2471*f*
cerebral embolization causing, 2530
clinical manifestations of, 2465
definition of, 2464
diagnosis of, 2466
differential diagnosis of, 2469
endovascular therapy for, 2469*b*–2470*b*
epidemiology of, 2464
initial laboratory tests for, 2466–2469, 2467*t*
National Institutes of Health Stroke Scale, 2466, 2470*t*
physical examination of, 2466
recombinant tissue plasminogen activators for, 2469*b*, 2469*t*–2470*t*, 2469.*e1f*, 2470*t*
Ischemic stroke *(Continued)*
risk factors for, 2464*t*
treatment of, 2469*b*, 2469*t*
Ischial/ischiogluteal bursitis, 1747, 1747*b*
Isobutyric aciduria, 1403*t*
Isocarboxazid, for depression, 2340*t*
Isoimmune neonatal neutropenia, 1146
Isolated hypomagnesemia, 816*t*
Isolated hypoparathyroidism, 1660
Isomorphic erythrocytes, 723*f*
Isonatremia, 733*t*
Isoniazid, 1460*t*
dosage of, 1895*t*
for nontuberculous mycobacterial disease, 2046*t*
for tuberculosis, 2040*b*, 2041*t*, 2043*t*
Isopropyl alcohol, 760
Isoproterenol, 313*b*
Isosorbide-5-mononitrate, 368*t*
Isosorbide dinitrate, 265*b*, 368*t*
Isospora belli, sexually transmitted anorectal diseases and, 983
Isotonic hyponatremia, 740
Isotretinoin (Accutane), 2698, 2722*b*
Isovaleric aciduria, 1403*t*
Isovolumic contraction, 225
Isradipine, 367*t*, 451*t*
Israeli tick-bite fever, 2055*t*, 2057
Istradefylline, for Parkinson disease, 2487*t*
Ito cells, 1035–1036
Itraconazole, 2074, 2699
adverse effects of, 2075
for blastomycosis, 2081*b*
for chromomycosis, 2111*b*
drug interactions of, 2075
formulations and pharmacology of, 2074–2075
for histoplasmosis, 2083*b*
indications and dosage of, 2075, 2075*t*
for paracoccidioidomycosis, 2087*b*
for sporotrichosis, 2086*b*
Itraconazole + hydroxyitraconazole, *e*10*t*–*e*11*t*
IUDs. *See* Intrauterine devices
Ivabradine, 325*t*
for heart failure, 265*b*
for heart failure with reduced left ventricular ejection fraction, 265*b*
Ivermectin, 2117
for COVID-19, 2217
for helminthic diseases, 2112*t*
for lice, 711*b*
for onchocerciasis, 2179*b*
for strongyloidiasis, 2173*b*
IVF. *See* In vitro fertilization
Ixabepilone (Ixempra), 1215*t*
Ixazomib (Ninlaro), 1215*t*
Ixekizumab (Taltz), for total knee arthroplasty, 1830.*e1t*
Ixempra. *See* Ixabepilone
Ixodes dammini, 2151
Ixodes persulcatus, 2022
Ixodes ricinus, 2151
Ixodes scapularis, 2022, 2027
Ixodes spp., 710

J

J wave, 228, 229*f*, 680, 681*f*
J wave syndromes, 302, 302*f*
Jaccoud arthropathy, 1769
Jackhammer esophagus, 909
Jackson syndrome, 2465.*e1f*
Jacobsen/Paris-Trousseau syndrome, 1071
JAK inhibitors, for rheumatoid arthritis, 1757*t*
JAK2 V617f mutation, 1130–1131
JAK3 deficiency, 1676.*e3t*
Jakafi. *See* Ruxolitinib
JAKs. *See* Janus kinases
Jamestown Canyon virus, 2276*t*, 2283, 2284*b*
Janeway lesions, 216, 218*f*, 414–415, 414*t*
Janssen AD26 vector, 2218*t*, 2219
Janus kinase (JAK)-signal transducer, 185
Janus kinase-2, 1490
Janus kinase inhibitors
for COVID-19, 2217
for inflammatory bowel disease, 945*b*
Janus kinases (JAKs), 153, 153*t*
Japanese encephalitis, 2276*t*, 2280, 2280*b*
immunization for, 66*t*, 83
in travelers, 1891*t*
vaccine, for traveler, 1886*t*, 1887
Japanese monocytic ehrlichiosis, 2060*t*
Japanese spotted fever, 2055*t*, 2057
Jarisch-Herxheimer reactions
in leptospirosis, 2031*b*
in syphilis, 2020*b*
Jaundice
acute abdominal pain and, 856
approach to, 1000–1001, 1000*t*
cirrhosis and, 1037
definition of, 993
infectious causes of, 1849, 1850*t*
pathobiology of, 994
postoperative of, 998–1000
in pregnancy, 998
Jaw osteonecrosis, 1643*b*
JC polyomavirus, 2228*t*, 2230–2232, 2305
nephropathy associated with, 2231–2232
progressive multifocal leukoencephalopathy associated with, 2230–2231
Jejunostomy, nutritive, 1449
Jellyfish, 712
Jersey finger. *See* Avulsion of flexor digitorum profundus
Jervell and Lange-Nielsen syndrome, 348
Jet lag, traveler's, 1889
Jevtana. *See* Cabazitaxel
Johnson & Johnson's Janssen COVID-19 vaccine, 77–78
Joint(s)
infection of, 1804–1809
mobility and stability, for osteoarthritis, 1741*t*
rheumatoid arthritis of, 1751–1752, 1752.*e1f*, 1753*f*
Joint Commission, 46
Quality Check, 41.*e1t*
Joint diseases
in sarcoidosis, 602, 604*t*
surgical treatment of, 1826–1830
anesthesia in, 1827
complications of, 1829–1830
deciding upon, 1826–1827
epidemiology of, 1826
pathobiology of, 1826, 1826*f*
perioperative arthritis medication in, 1830, 1830.*e1t*
procedures for, 1827–1829
Joint fluid analysis, 1713, 1713*f*
Joint infections, *Pseudomonas* infections causing, 1969
Jugular veins, 212–213, 213*f*
distention of, 212–213, 214*f*
examination of, 30, 258, 259*f*, 260*f*
Jugular venous pressure, 212
Jumper's knee. *See* Patellar tendinitis
Junctional nevi, 2730, 2733*f*
Junctional premature beat, 322*f*
Junctional tachycardia, 324–326, 326*b*, 327*f*
Junin virus, 100*b*, 2265*t*
Juvenile myoclonic epilepsy, 2433
Juvenile-onset diabetes, 1534
Juvenile polyposis, 1347*t*, 1348
Juxtaglomerular apparatus, 734
Jynneos vaccine, 84

K

K complexes, 2443
Kadcyla. *See* Aldo-trastuzumab emtansine
Kallmann syndrome, 1480–1481, 1584, 1601
Kaplan-Meier analysis, 37
Kaposi sarcoma, 2624, 2733, 2734*f*
gingival, 2320*f*, 2322*t*
in HIV, 2315, 2315*b*, 2316*f*
Karnofsky and Zubrod performance scales, 1214*t*
Kawasaki disease, 965, 1793*t*, 1795, 1795*b*, 2712, 2712*b*
Kayser-Fleischer rings, 1436, 1437*f*, 2542
KDIGO. *See* Kidney Disease Improving Global Outcomes
KDPI. *See* Kidney Donor Profile Index
Kearns-Sayre syndrome, 2586
Keloids, 2730, 2744
Kennedy disease, 2564*t*, 2565–2566
Keratin pearls, 1323, 1324*f*
Keratinocyte, multinucleated, 2690.*e1f*
Keratitis
Acanthamoeba, 2606
gonococcal, 2606
herpes simplex, 2605, 2606*f*
herpetic, 2246
pseudomonal, 2606
Pseudomonas infections causing, 1969
Keratoconjunctivitis sicca, 1785, 1786*f*, 2327*t*, 2611
Keratoconus, 2598
Keratocytes, 1068*f*
Keratoderma blennorrhagicum, 1763
Keratolytics, 2700
Keraunoparalysis, 704
Kerley B lines, 245*f*, 405
Kerley lines, 521
Kernig sign, 2512
Kesimpta. *See* Ofatumumab
Ketamine
for anesthesia, 2670
for chronic pain, 138*t*
for erythromelalgia, 471*b*
properties of, 142*t*
Ketoacidosis
alcoholic, 759
cystic fibrosis and, 557
diabetic, 758
Ketoconazole, 2699
for Cushing syndrome, 1524*b*
for eumycetoma, 2111*b*
Ketolides
characteristics of, 1899
dosage of, 1895*t*
mechanism of action, 1895*t*
resistance mechanisms, 1893*t*
Ketone bodies, *e*1*t*–*e*8*t*
Ketone body synthesis/utilization, defects in, hypoglycemia and, 1552*t*
Ketoprofen
for chronic pain, 138*t*
for rheumatoid arthritis, 1756*t*
Ketorolac
for acute pericarditis, 424*b*
for chronic pain, 138*t*
17-Ketosteroid reductase deficiency, 1572
Keytruda. *See* Pembrolizumab
Kidney
in acid-base balance, 754, 754.*e1f*
agenesis, 818
calcium absorption by, 1652
development of, 818–821
dysfunction of
in septic shock, 673*b*
dysplasia, 818
ectopia, 819, 819*f*
function of, measuring, 720–721
hypoplasia, 818
malrotation, 819, 819*f*
potassium handling by, 746
production of acids and excretion by, 753
structure and function of, 729–733, 730*f*–731*f*, 730.*e1f*, 731*f*
body fluid osmolarity in, 730, 732*f*
extracellular fluid volume regulation in, 730, 730.*e1f*
plasma pH regulation in, 731, 731.*e1f*, 732*f*
plasma PO_4 and CA^{2+} in, 732, 732.*e1f*
plasma potassium regulation in, 732
systemic lupus erythematosus manifestations of, 1769
systemic sclerosis involvement of, 1779
transplantation. *See* Renal transplantation
tumors of, 1362
vascular disorders of, 728, 799–803
atheromatous embolization, of renal arterial system, 801, 801*b*, 802*f*
renal artery stenosis. *See* Renal artery stenosis
renal infarction, 801–802, 802*b*
renal vein thrombosis, 802, 802*b*
Kidney disease, drug dose adjustments in, 129–130, 129.*e1t*
loading dose in, 130
using clearance for, 130
Kidney Disease Improving Global Outcomes (KDIGO), on acute kidney injury, 770*t*
Kidney donation, in renal transplantation, 844
Kidney Donor Profile Index (KDPI), 844
Kidney failure, 738, 837
Kidney replacement therapy, for chronic kidney disease, 839*b*
Kidney stones, 803. *See also* Nephrolithiasis
Kikuchi disease, 1288, 1770
Kinase inhibitors, thyroiditis caused by, 1514
Kineret. *See* Anakinra
Kinesigenic, 2493
Kinetic tremor, 2484, 2489
Kisqali. *See* Ribociclib
Kissing bug, 2126

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Kisspeptin, 1477, 1592
Kisspeptin-neurokinin B-dynorphin neurons, 1580
KIT mutations, 1700
Klatskin tumors, 1357, 1360*f*
Klebsiella granulomatis, 2004
Klebsiella pneumoniae, 1022, 1965
  antimicrobial resistance of, 1864, 1864*t*
Klebsiella pneumoniae carbapenemase (KPC), 1966
Kleine-Levin syndrome, 2446
Klinefelter syndrome, 1574, 1582–1583
Klippel-Trenaunay syndrome, 969
Knee
  disorders of, 1747
  fusion of, 1827
  injury of, occupational, 86*t*
  surgical treatment of, 1828, 1828*f*–1829*f*, 1829*f*
Knudson's two-hit model of cancer development, 1248, 1248*f*
Koch-Weeks bacillus, 1954
Koilocytes, 2241
Koilocytosis, 2241
Koilonychia, 2751, 2752*f*
Koplik spots, 2220, 2221*f*, 2621
Korsakoff psychosis, 2539
Korsakoff syndrome, 2408, 2539
KPC. *See Klebsiella pneumoniae* carbapenemase
Krabbe disease, 2510
Krebs-Henseleit cycle, 999
Krukenberg tumor, 1341
Kupffer cells, 2204
Kussmaul sign, 384*b*, 428–429
Kwashiorkor, 1444, 1444*f*–1445*f*
Kyasanur Forest disease, 99.*e1t*, 2265*t*, 2268*t*
Kymriah. *See* Tisagenlecleucel
Kyphoplasty, 1643*b*
Kyphoscoliosis, 620–621
  clinical manifestations of, 621
  diagnosis of, 621
  epidemiology of, 620–621
  in hypercapnic disease, 535*t*
  pathobiology of, 620
  prognosis for, 621
  treatment of, 621*b*
Kyphosis, 622
Kyphotic deformity, 1642
Kyprolis. *See* Carfilzomib

L

L-carnitine, 693*t*, 1451–1452
L-glutamine, 1116*t*
La Crosse virus, 2276*t*, 2283, 2284*b*
Labetalol, 451*t*, 458*b*, 460*t*
  for preeclampsia, 1621*t*
Labile factor, 1189*t*
Laboratory testing
  anomalies, 3, 3.*e1t*
  cardiac catheterization. *See* Cardiac catheterization
Laboratory values, *e1*
  clinical chemistry, toxicology, and serology, *e1t*–*e8t*
  drugs: therapeutic and toxic, *e10t*–*e11t*
  hematology and coagulation, *e8t*–*e9t*
  prefixes and abbreviations, *e1t*
Labyrinthine concussion, 2645
Lacosamide, for seizures, 2434*t*
Lacrimal gland tumor, 2613
β-Lactamases
  AmpC, 1966
  extended-spectrum, 1966
  inhibitors, for multidrug-resistant Enterobacterales, 1967*t*
  narrow-spectrum, 1966
β-Lactams
  characteristics of, 1898–1900
  inhibitors of, for multidrug-resistant Enterobacterales, 1967*t*
  mechanism of action, 1895*t*
  reactions to, 1698*t*
  resistance mechanisms, 1893*t*
  for *Staphylococcus aureus*, 1909
  in *Stenotrophomonas maltophilia*, 1976*t*
Lactase deficiency, 935
L-Lactate, *e1t*–*e8t*
Lactate dehydrogenase (LDH), *e1t*–*e8t*, 999
Lactated Ringer solution, for cholera, 1956*b*
Lactation, familial hypercholesterolemia and, 1409*b*
Lactic acid, in bacterial meningitis, 2514
Lactic acidosis, 757
  causes of, 758*t*
  clinical manifestations of, 758
  diagnosis of, 758
  epidemiology of, 757–758
  pathobiology of, 757
  prognosis of, 758
  treatment of, 758*b*
Lactobacillus, for infectious gastroenteritis, 2263*b*–2264*b*
Lactobacillus acidophilus, 1882
Lactobacillus crispatus, 1882
Lactobacillus jensenii, 1882
Lactotrophs, 1490
Lactulose, for irritable bowel syndrome, 896*t*
Lacunar syndromes, 2465–2466, 2466*t*
Laguna Negra virus, 2265*t*
LAIV. *See* Live attenuated influenza virus
Lambert-Eaton myasthenic syndrome, 1238, 1238*t*, 2558–2560
Lambert-Eaton syndrome, 2589*t*, 2591
  clinical manifestations of, 2591
  diagnosis of, 2591
  pathobiology of, 2591
  prognosis of, 2591
  treatment for, 2591*b*
Lamellar ichthyosis, 2687.*e3t*
Lamivudine, 2181*t*, 2182*t*, 2183, 2301*t*
Lamotrigine, *e10t*–*e11t*
  for chronic pain, 138*t*
  for seizures, 2434*t*
Langerhans cell histiocytosis, 1154, 1480, 1480*f*, 2731, 2733*f*
  clinical manifestations of, 1154, 1155*f*, 1156*t*
  cutaneous features of, 1155*f*
  diagnosis of, 1156
  epidemiology of, 1154
  neurodegeneration associated with, 1156
  pathobiology of, 1154
  prognosis for, 1156
  pulmonary, 571, 582–583, 583.*e1f*
    clinical manifestations of, 583
    diagnosis of, 583
    prognosis for, 583*b*
    treatment of, 583*b*
  treatment of, 1156*b*
Lanifibranor, for nonalcoholic fatty liver disease, 1034*b*
Laninamivir, for influenza, 2203*t*
Lanreotide, for acromegaly, 1489*b*
Laparoscopic cholecystectomy, 1052*b*
Laparoscopic gastric banding, for obesity, 1467*b*
Laparoscopic ovarian surgery, for polycystic ovary syndrome, 1602*b*
Laparoscopy
  for endometriosis, 1596*b*
  for pelvic inflammatory disease, 1949
Lapatinib (Tykerb), 1215*t*, 1251*t*
Laplace equation, 400
Laplace's law, 225
LAR. *See* Lymphangitis-associated rickettsiosis
Large bowel adenocarcinoma, 1349*f*
Large bowel obstruction, abdominal pain and, 854*t*
Large bowel sarcomas, 1347
Large-cell B-cell lymphoma, 2613
Large cell carcinoma, 1329, 1329.*e2t*
Large cell neuroendocrine carcinoma, 1336
Large granular lymphocyte leukemia, 1126, 1272
  clinical manifestations of, 1127–1128
  definition and epidemiology of, 1126–1128
  diagnosis of, 1128, 1128*f*
  pathobiology of, 1126–1127
  prognosis of, 1128
  treatment of, 1128*b*
Large granular lymphocyte syndrome, 1146, 1754
Large intestine, neoplasms of, 1345–1354
  adenocarcinomas, 1346–1347, 1346*f*
  epidemiology of, 1345–1347
  epidermoid carcinomas, 1347
  lymphomas, 1347
  neuroendocrine cancers, 1347
  pathobiology of, 1346–1347
  risk factors of, 1346
  sarcomas, 1347
Large opacities, pulmonary, 520–521, 520*t*
Large pupil, 2600
Large vessel vasculitis, 965, 1792*t*, 1793, 1795, 2687.*e3t*
Laron dwarfism syndrome, 1488–1489
Laron-type dwarfism, IGF-I in, 1477
Laronidase (Aldurazyme), for mucopolysaccharidoses, 1725*b*
Larotrectinib (Vitrakvi), 1215*t*
Laryngeal amyloidosis, 1310
Laryngeal dystonia, severe mental illness and, 2681*t*
Laryngeal paralysis, 2653
Laryngeal stenosis, 2653
Laryngitis, 2651–2652
Laryngopharyngeal reflux, 2651–2653
Laryngotracheal injury, distinguishing features of, 515*t*
Larynx, 1320
  cancer, 1322, 1325*t*, 1327*b*
Lasers
  as occupational and environmental hazards, 88*t*
  for skin cancers, 2701
Lassa fever, 2268*t*, 2269*f*
Lassa virus, 99.*e1t*, 2265*t*
Late adolescence, 110
Late benign syphilis, 2017
Late neurologic Lyme disease, 2024–2025
Late-night salivary cortisol measurement, for Cushing disease, 1494
Late onset autoinflammatory disease, 1737
Late syphilis, 2017, 2017*t*
Latent syphilis, 2016
Latent tuberculosis, 2034
  skin testing for, 2038–2039
  treatment of, 2040*b*, 2041*t*
Lateral brain stem, infarction of, 2645
Lateral epicondylalgia, 1745, 1745*b*
Lateral flow analysis, 2088
Lateral sinus thrombosis, 2529–2530, 2529*b*, 2529*f*
Lateralization, of flow, 522
Latex allergy, 2669
Latex-induced anaphylaxis, 1691, 1692
Lathyrism, 2543
Latin America, HIV/AIDS in, 2289, 2289.*e1f*
Lauren classification, 1340
Laxatives
  for constipation, 862*b*
  for irritable bowel syndrome, 895*b*, 896*t*
LDL cholesterol. *See* Low-density lipoprotein cholesterol
Lead, *e1t*–*e8t*
Lead poisoning, 2564*t*
Lead toxicity, 87, 88*t*, 101, 690*t*
  chronic interstitial nephritis caused by, 794
  clinical manifestations of, 101
  diagnosis of, 101, 101*t*
  epidemiology of, 101
  pathobiology of, 101
  prognosis of, 101
  treatment of, 101*b*, 102*t*
Leading causes of death, 17, 18*t*
Leadless pacing system, 342, 342*f*
Lean or Six Sigma, 45
Leber hereditary optic neuropathy, 2586
Lecithin-cholesterol acyl transferase, 1406
Lectins, 197
Ledipasvir/sofosbuvir, for hepatitis C infections, 2181*t*, 2182*t*, 2184
Lefamulin, 1845*t*
  dosage of, 1895*t*
  mechanism of action, 1895*t*
  toxicities of, 1901*t*
Leflunomide (Arava), 147
  for rheumatoid arthritis, 1755*b*, 1756*t*, 1757*t*
  for total knee arthroplasty, 1830.*e1t*
Left anterior descending coronary artery, 397
Left anterior fascicular block, 231, 231*t*, 232*f*
Left atrial appendage, closure of, 347
Left bundle branch block, 231, 231*t*, 232*f*, 287.*e1f*
Left common carotid artery, 2454–2455
Left posterior fascicular block, 231, 231*t*, 232*f*
Left ventricular aneurysm, 384*b*
Left ventricular dysfunction
  aortic regurgitation with, 410
  management of, 384*b*
  mitral regurgitation with, 407
Left ventricular ejection fraction (LVEF)
  heart failure on, 264
  with mildly reduced, heart failure, 265*b*, 277*f*
  with preserved, heart failure, 265*b*, 278*f*
  with reduced, heart failure, 264, 265*f*
    second-line treatments for, 265*b*, 272*f*
  three-dimensional echocardiography of, 236, 237*f*
Left ventricular enlargement, 244, 245*f*
Left ventricular failure, chest radiograph of, 523*f*
Left ventricular hypertrophy, 233, 256–257
  concentric, 400
Left ventricular noncompaction, 294, 295*f*
Left ventricular outflow tract obstruction, 351–352, 351
Left ventricular stroke work index, 677*t*
Left ventricular systolic dysfunction, heart failure caused by, 265*b*
  ACEIs and ARBs for, 265*b*, 266*t*
  β–blockers for, 265*b*, 267*t*
  mineralocorticoid receptor antagonists for, 265*b*, 270*t*
  SGLT2 inhibitors for, 265*b*, 271*t*
Left ventricular thrombus, 242*t*
Left ventricular volume, 236, 237*f*
Legionella infections, 417*t*
Legionella pneumophila, epidemiology of, 1996.*e3f*, 1997
Legionella spp., 1996, 1998*f*
Legionellosis, 1996–1999
  clinical manifestations of, 1997–1998
  definition of, 1996–1999
  diagnosis of, 1998
  differential diagnosis of, 1998
  epidemiology of, 1996–1997, 1997.*e1f*
  pathobiology of, 1997, 1997.*e1f*
  pathogen of, 1996, 1996.*e1f*
  prevention of, 1999
  prognosis of, 1999
  in travelers, 1889.*e1t*
  treatment of, 1998*b*, 1999*t*
Legionnaires disease
  definition of, 1996
  pathology of, 1997.*e1f*, 1998
  treatment for, 1999*t*
Leiomyomas, 1343
Leiomyomatosis, hereditary, 1363
Leiomyosarcoma, 1342, 1389
Leishmania spp., 1026*t*, 2130
Leishmaniasis, 2116, 2130–2135
  characteristics of, 2130*t*
  cutaneous, 2131
    clinical manifestations of, 2133, 2134*f*
    complex manifestations of, 2133
    diagnosis of, 2133
    diffuse, 2133
    disseminated, 2133
    parasitology of, 2133, 2135*f*
    prevention of, 2133
    prognosis for, 2133
    recidivans, 2133
    treatment of, 2133*b*, 2135*f*
  cutaneous or mucocutaneous, in travelers, 1889.*e1t*
  definition of, 2130–2132
  epidemiology of, 2130–2131, 2130*t*, 2131*f*
  mucosal, 2133
  pathobiology of, 2131–2132
  pathogen that cause, 2130
  post-kala-azar dermal, 2131–2132, 2132
  treatment of, 2112*t*
  visceral, 2132
    antigen-based tests for, 2132
    clinical manifestations of, 2132
    complex manifestations of, 2132
    diagnosis of, 2132
    in immunodeficient patients, 2132*b*
    serologic tests of, 2132
    treatment of, 2132*b*
Leishmanin skin test, 2133
Lenalidomide (Revlimid), 1215*t*
  for multiple myeloma, 1299*b*
  for skin diseases, 2699
Lentigines, 2689*t*
Lentigo maligna melanoma, 1391, 1392*f*
Lentiviruses, 2291
Lenvatinib (Lenvima), 1215*t*
  for renal cell carcinoma, 1364*b*
Lenvima. *See* Lenvatinib

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Lepidic predominant nonmucinous adenocarcinoma, 566*t*, 569, 569.e1*f*, 570*b*, 570*f*
Lepromatous leprosy, 2049–2050, 2049*t*, 2050*f*–2051*f*, 2051*f*, 2734, 2735*f*
Leprosy, 1583, 2047–2053
  borderline borderline, 2049, 2049*t*, 2049.e1*f*, 2050*f*
  borderline lepromatous, 2049, 2049*t*, 2050*f*, 2050.e1*f*
  borderline tuberculoid, 2049, 2049*f*, 2049*t*
  classification of, 2048–2051, 2048*t*–2049*t*, 2049*t*
  clinical manifestations of, 2048–2051
  cutaneous or mucocutaneous, in travelers, 1889.e1*t*
  definition of, 2047–2053
  diagnosis of, 2052
  diagnostic criteria for, 2052
  drug resistance of, 2052*b*
  epidemiology of, 2047–2048
  global strategies for, 2053
  histoid, 2051, 2052*f*
  in immunocompromised hosts, 2051
  immunogenetics of, 2048
  immunotherapy for, 2052*b*
  laboratory testing for, 2052
  lepromatous, 2049, 2049*t*, 2050*f*, 2051*f*
  Lucio, 2051
  multibacillary, 2048, 2048*t*, 2048.e1*f*
  multidrug therapy for, 2052*b*, 2053*t*
  nerve damage in, pathogenesis of, 2048
  neuropathy caused by, 2578
  pathobiology of, 2048
  pathogen that causes, 2047
  pathogenesis of, 2048, 2048.e1*f*
  paucibacillary, 2048, 2048*t*, 2048.e1*f*
  pregnancy and, 2051
  prevention of, 2053, 2053*t*
  prognosis of, 2053
  pure neuritic, 2051
  reactions, 2050
  Ridley Jopling Classification of, 2048.e1*f*
  systemic involvement in, 2051
  treatment for, 2052*b*
  tuberculoid, 2048–2049, 2049*t*
  type 1 reactions, 2050, 2050.e1*f*
  type 2 reactions, 2050–2051, 2051.e1*f*
Leptin, 1464, 1475*t*
Leptomeningeal metastases, 1317, 1317*b*, 1317*f*, 1317.e1*f*, 2646
Leptospira interrogans, 2029, 2029*f*
Leptospirosis, 2029–2031, 2064
  aseptic meningitis associated with, 2030, 2522
  case definitions, 2030*t*
  characteristics of, 2270*t*
  clinical manifestations of, 2029–2030
  coagulation disorders associated with, 2029
  conjunctival suffusion associated with, 2029, 2030*f*
  definition of, 2029–2031
  diagnosis of, 2030–2031
  differential diagnosis of, 2031
  epidemiology of, 2029
  pathobiology of, 2029
  pathogen that causes, 2029, 2029*f*
  prevention of, 2031
  prognosis for, 2031
  signs and symptoms of, 2030*f*
  thrombocytopenia associated with, 2029
  in travelers, 1889.e1*t*, 1891*t*
  treatment of, 2031*b*
Letermovir, for herpesvirus infections, 2187*t*, 2188
Letrozole (Femara), 1215*t*
  for polycystic ovary syndrome, 1602*b*
Letterer-Siwe disease, 1155
Leucine sensitivity testing, for hypoglycemia, 1557
Leucovorin, for *Pneumocystis* pneumonia, 2108*t*
Leucovorin calcium (Wellcovorin), 1215*t*
Leukemia
  acute lymphoblastic. *See* Acute lymphoblastic leukemia
  acute myeloid. *See* Acute myeloid leukemia
  adult T-cell leukemia/lymphoma. *See* Adult T-cell leukemia/lymphoma
  arthritis associated with, 1823
  chronic myelogenous. *See* Chronic myelogenous leukemia
Leukemia *(Continued)*
  chronic myeloid. *See* Chronic myeloid leukemia
  peripheral blood smear of, 1073–1074, 1073*f*, 1074*f*
Leukemia cutis, 1262
Leukemoid reaction, 1140, 1141*f*, 1262–1266
Leukocoria, 2600, 2601*t*
Leukocyte, e8*t*–e9*t*
Leukocyte adhesion deficiency, 1142, 1683.e1*t*
Leukocyte count (WBC count), e8*t*–e9*t*
Leukocytoclastic vasculitis, 2714, 2715*f*, 2725, 2728
Leukocytosis, 1846
  due to expansion of other cell lines, 1142, 1143*t*
  peripheral blood smear of, 1072–1073
  postoperative, 2675
  psychotropic medications and, 2678*t*
  in pulmonary tuberculosis, 2035
Leukodystrophies, 2509
Leukoerythroblastic blood film, 1074*t*
Leukoerythroblastic reaction, 1141
Leukonychia, 2752–2753, 2753*f*
Leukopenia, 2314
  due to deficiency of other cell lines, 1148
  peripheral blood smear of, 1072
Leukoplakia, 1321, 2622–2623
Leukoreduction, 1200, 1205
Leukotriene modifiers, for rhinitis, 2632*b*
Leuprolide acetate (Lupron), 1215*t*
Levator ani muscle, 977
Levetiracetam, e10*t*–e11*t*
  for seizures, 2434*t*
Levitra, 364*b*
Levodopa, for Parkinson disease, 2486, 2486*b*
Levofloxacin
  dosage of, 1895*t*
  for *H. influenzae* infections, 1954*b*
  for legionnaires disease, 1999*t*
  for *Moraxella catarrhalis* infections, 1955*b*
  for plague, 98*b*, 1992*t*
  for pneumonia, 613*t*, 616*t*
  for *Streptococcus pneumoniae* pulmonary infections, 1912.e1*t*
  for urethritis, 1880*b*
  for urinary tract infection, 1876*t*, 1877*t*
Levoketoconazole, for Cushing syndrome, 1524*b*
Levorphanol, 139*t*
Lewy body dementia, 2558
Leydig cell agenesis, 1573
Leydig cells, steroid hormone synthesis of, 1581
LH. *See* Luteinizing hormone
Lhermitte sign, 2371, 2500
Li-Fraumeni syndrome, 1250*t*
Libido, decreased, 1587
Lice, 711, 2741
Lichen myxedematosus, 1296, 2737–2738, 2737*f*–2738*f*
Lichen nitidus, 2708, 2708*f*
Lichen planopilaris, 2747*t*, 2749, 2750*f*
Lichen planus, 2621*t*, 2707–2708
  characteristics of, 2623, 2623*f*, 2691*t*
  clinical manifestations of, 2708, 2708*f*
  diagnosis of, 2708
  epidemiology of, 2707
  esophageal involvement in, 911
  illustration of, 2687.e1*f*, 2687.e3*t*, 2688*t*
  pathobiology of, 2708
  treatment for, 2708*b*, 2708*t*
Lichen sclerosis et atrophicus, 2737
Lichen simplex chronicus, 2687.e3*t*, 2687.e4*t*
Lichenification, 2687.e4*t*
Lichenoid drug reaction, 2621*t*
Licorice, 749*t*
Liddle syndrome, 749*t*, 816*t*, 817
Lidocaine, e10*t*–e11*t*
  for electrical storm, 338*b*
Life expectancy, 17*f*, 21, 21*f*, 118, 118.e1*t*
Life-space mobility, 117
Life support, withdrawal of, 638, 638*t*, 638.e1*t*
Lifespan groups, for women's health, 1606, 1606*t*
Lifestyle modifications
  for arterial hypertension, 450, 450*t*
  for atherosclerotic cardiovascular disease, 1410, 1410*t*
  for chronic kidney disease, 839*b*
  drug use and, 2361
  for heart failure, 265*b*
  for heartburn, 900*b*
Lifestyle modifications *(Continued)*
  for hypertriglyceridemia, 1414*b*
  for ischemic heart disease, 366*f*
  for osteoporosis, 1643*b*
Ligamentous injury, spinal cord injury *versus*, 2388
Light chain amyloidosis, 2574
Light chain cast nephropathy, 1299
Light-chain deposition disease, glomerular diseases in, 788, 788*f*
Light chains, e1*t*–e8*t*
Light-near dissociation, 2616–2617
Light refraction, 2597, 2597*f*
Lightheadedness, 210*t*, 211–212, 211*t*
Lightning injury, 704
Likelihood ratio, 38
Limb-girdle muscular dystrophies, 2584
Limb ischemia
  acute
    clinical categories of, 462*t*
    clinical manifestations of, 462
    diagnosis of, 462
    pathobiology of, 461
    treatment of, 464*b*, 465*f*
  chronic, 463, 463*t*
  critical, 465.e1*f*
Limbic encephalitis, 2532*t*
Limbic encephalopathy, 1238*t*
Limbs, disorders of, occupational and environmental, 86*t*
Limited cutaneous systemic sclerosis, 1777, 1777*t*
Linaclotide, for irritable bowel syndrome, 895*b*, 896*t*
Linagliptin, for type 2 diabetes mellitus, 1541*t*
Lincosamides, dosage of, 1895*t*
Linear hypopigmentation, 2743
Linear immunoglobulin A bullous dermatosis, 2718, 2718*b*
Linezolid
  for bacterial meningitis, 97*b*, 2518*t*
  dosage of, 1895*t*
  mechanism of action, 1895*t*
  for nontuberculous mycobacterial disease, 2046*t*
  for pneumonia, 616*t*
  spectrum of activity, 1900
  for *Streptococcus pneumoniae* pulmonary infections, 1912.e1*t*
  for vancomycin-resistant enterococci, 1922*t*
Linkage disequilibrium, phenomenon of, 204
Lip cancer, 1325*t*
Lipase, e1*t*–e8*t*
  in acute pancreatitis, 971
Lipid(s)
  abnormal, screening for, 53
  blood levels, 219.e2*f*, 219
  insoluble, 938
  measurement of, 1407
  membrane, 1093
  metabolism of, 1405
    clinical disorder, 1408
Lipid disorders, 1404
  diagnosis, 1407
  genetic, 1408
  hyperlipidemia, 1408, 1408*t*
  pathobiology, 1405
  in women, medications for, 1608*t*
Lipid emulsion, for acute poisoning, 693*t*
Lipid-lowering therapy
  for acute MI, 384*b*
  for acute STEMI, 391*t*
  for chronic kidney disease, 839*b*
Lipid profile, fasting, 384*b*
Lipid storage disorders, 1419*t*
Lipoarabinomannan, 2040
Lipoatrophy, 2317
Lipoglycopeptides
  characteristics of, 1900
  resistance mechanisms, 1893*t*
  toxicities of, 1901*t*
Lipohypertrophy, 2318
Lipoid hyperplasia, 1571
Lipoid pneumonia, 598, 598*b*, 598*f*
Lipolysis, impaired, 933
Lipomas, 526, 1314
Lipophilic *Corynebacteria*, 1934–1935
Lipoproteins, 1406
  high density, 1406, 1406.e1*f*
  low density, 1405
  very low density, 1405
Liposomal amphotericin B, 2077, 2116
  indications and dosage of, 2075*t*
  for leishmaniasis, 2112*t*
Lipoteichoic acid, 1913
Liquid biopsy, 1252
Liraglutide
  for nonalcoholic fatty liver disease, 1034*b*
  for obesity, 1467*b*
  for type 2 diabetes mellitus, 1541*t*
Lirentelimab, 941*b*
Lisinopril, 451*t*
  for acute STEMI, 384*b*, 391*t*
  for heart failure, 266*t*
  for left ventricular dysfunction, 384*b*
Lisinopril/HCTZ, 451*t*
Lissencephaly, 2547
Listeria meningitis, 2515*b*
Listeria monocytogenes, 1861, 1937, 2510–2511
Listerial rhombencephalitis, 1937
Listeriosis, 1937
  clinical manifestations of, 1937
  definition of, 1937
  differential diagnosis of, 1937
  epidemiology of, 1937
  laboratory diagnosis of, 1937–1938
  pathobiology of, 1937
  pathogen of, 1937
  prevention of, 1938
  prognosis of, 1938
  treatment of, 1938*b*
Lithium, e10*t*–e11*t*
  causing hypothyroidism, 1507
  central nervous system effects of, 685*t*
  thyroiditis caused by, 1514
  toxicity, 686*t*, 690*t*, 698*t*
Lithium carbonate
  pharmacokinetic parameters for, 127.e1*t*
  in renal failure, 129.e1*t*
Lithotripsy, for chronic pancreatitis, 975*b*
Litifilimab, for cutaneous lupus erythematosus, 152
Live attenuated influenza virus (LAIV), 66*t*, 79
Live vaccinia virus, 66*t*
Live virus vaccine, 66*t*
  for measles, 2222
Livedo racemosa, 469–470, 469*f*, 470*b*, 2691*t*
Livedo reticularis, 469, 469*f*, 681, 2691*t*
Liver
  alcohol use disorders and, 2354–2355, 2355, 2355*t*
  anatomy of, 1358*f*
  cystic fibrosis and, 556
  examination of, 31
  function of, 986
  glucocorticoids metabolism in, 145
  infections of, 1022–1029
    bacterial, 1022
    helminthic, 1024, 1025
    parasitic, 1024, 1026*t*
    protozoal, 1024
  mass lesion in, approach to, 991*f*
  percussion of, 988
  ultrasound of, 1000
Liver abscess
  amebic, 1022*t*, 1024, 1025*b*, 1025*f*, 2148, 2149*f*, 2149*t*, 2150*t*
  bacterial, 1022*t*
  pyogenic, 1022–1023, 1023*b*, 1023*f*
Liver biopsy, 990
  for alcohol-associated liver disease, 1032, 1034*f*
  in α_1-antitrypsin deficiency, 993*f*
  for chronic viral hepatitis, 1010
  for hemochromatosis, 1441
  in hereditary hemochromatosis, 992, 993*f*
  indication of, 1001, 1001*f*
  Schistosoma mansoni on, 1029.e1*f*
Liver cancers
  epidemiology of, 1358–1359, 1358*f*
  nutrition and, 59
  prevention of, 1362
  primary, 1357.e3*t*
  prognosis of, 1362
Liver cirrhosis, mesenteric venous thrombosis and, 963*t*
Liver disease, 1072*t*, 2666
  abdominal examination in, 988, 988*f*
  abdominal imaging for, 990
  alcohol-associated, 1031
  approach to patient with, 986–993

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Liver disease *(Continued)*
bacterial, 1022
biliary tract disease and, 996
biopsy for, 990
diagnostic studies for, 989–990, 989*t*
drug dose adjustment in, 130
duration of, assessing, 987
family history of, 987
fungal, 1023, 1024*b*
general condition of, 987
granulomatous, 1029, 1030*t*
hematologic tests in, 1000
hemochromatosis and, 1440
hepatic mass in, approach to, 990, 991*f*
history of, 986–987
inherited, approach to, 992–993, 993*f*
laboratory studies for, 989–990
mucocutaneous findings in, 987–988, 987*f*, 988*f*
organ system review in, 987
parasitic, 1024
physical examination of, 987–989, 987*f*, 988–989, 988*f*, 989*f*
in pregnancy, 1625, 1625*t*
protozoal, 1025
risk factors for, 987
in sarcoidosis, 602, 604*t*
transjugular pressure in, measurement of, 990
Liver failure, 1043–1049, 1197–1198
acute, 1044
chronic, 1044
clinical manifestations of, 1043, 1197
diagnosis of, 1043, 1197–1198
epidemiology of, 1043
pathobiology of, 1043, 1197
prognosis for, 1044
treatment of, 1043*b*–1044*b*, 1198*b*
Liver fibrosis, cirrhosis and, 1035
Liver flukes
approach to, 2168
description of, 2165
fascioliasis, 2168
opisthorchiasis, 2168
paragonimiasis, 2168
Liver function tests
alkaline phosphatases, 999
aminotransferases, 998
hepatic enzymes, 999
hepatic synthetic function, 999–1000
metabolites and drugs, 999
for pulmonary hypertension, 495
Liver metastases, pancreatic neuroendocrine tumor with, magnetic resonance imaging of, 872*f*
Liver toxicity, after hematopoietic cell transplantation, 1211
Liver transplantation, 1044–1049, 1044*f*–1045*f*, 1045*f*
for acute liver failure, 1044
chronic, 1044
for chronic liver failure, 1044
for cirrhosis, 1040*b*
coagulation system and, 1043
complications of, 1047–1049, 1047*f*
contraindications to, 1046*t*
for hemochromatosis, 1441*b*
for hepatocellular carcinoma, 1045
immunosuppression for, 1048, 1048*t*
indications for, 1044–1045, 1045*f*
infectious complications of, 1047–1048, 1048*f*
listing for, 1046, 1048*t*
for liver failure, 1197
long-term management for, 1049
metabolic disorders associated with, 1045
for metastatic neuroendocrine tumor, 1568*b*
for porphyrias, 1434*b*
preoperative medical assessment for, 1046
preoperative psychosocial assessment for, 1046
for primary sclerosing cholangitis, 1058*b*
procedure, 1046–1047, 1046*f*–1047*f*
recurrent hepatitis C after, 1014*b*
rejection in, 1048, 1048*t*
selection for, 1045–1046, 1046*t*
surgical complications of, 1047
for Wilson disease, 1437*b*
Living donor lobar transplantation, 633
Living kidney donors, 844
Lixisenatide, for type 2 diabetes mellitus, 1541*t*
LMWHs. *See* Low-molecular-weight heparins
Loa loa, 2179
Loading dose, in renal insufficiency, 130
Lobar emphysema, congenital, 565
Lobar hemorrhages, 2479
Lobar holoprosencephaly, 2547
Lobar opacities, 520
Lobectomy, for lung cancer, 1333*b*
Lobular carcinoma in situ, 1369*b*, 1370*t*
Local tetanus, 1928
Localized amyloidosis, 1310, 1310*b*
Localized scleroderma, 1782
Locked-in syndrome, 2437*t*, 2442, 2465
Lockjaw, 1928–1929
Locoregional staging, of head and neck cancer, 1323
Loculated pleural effusions, 525, 525*f*
Locus heterogeneity, 1399
Loeys-Dietz syndrome, 1726
Löffler fibroplastic endocarditis, 295
Löfgren syndrome, 600, 604
Loiasis, 2179, 2179*f*
Lomentospora (Scedosporium) prolificans, infections by, voriconazole for, 2076
Lone Star tick, 2060
Long-acting β-agonists (LABA), for asthma, 541*b*
Long-chain fatty acids, 934–935
Long QT syndrome, 301, 303, 337, 338*f*
type 3 (LQT3), 300
Long-segment Barrett esophagus, 1339
Longevity, in older adults, 115–116, 116*t*
Longitudinal grooves and striations, of nails, 2752
Longitudinal melanonychia, 2754–2755, 2755*f*
Loop diuretics, 736*b*
for hypertension, side effects of, 453*t*
for hypervolemia, 737*t*
nephrolithiasis and, 805*b*
Loop electrosurgical excision procedure, 1375*b*
Loop of Henle disorder, 816*t*, 817
Loop recorders, implantable, 308
Loose anagen hair syndrome, 2750
Loose connective tissue, 1707
Loperamide
for diarrhea, 940
for irritable bowel syndrome, 895*b*, 896*t*
for small bowel rapid transit dysmotility, 890
for traveler's diarrhea, 1888, 1888*t*
Lopinavir/ritonavir, 2217, 2301*t*
Loratadine, for mastocytosis, 1703*b*
Lorazepam
for alcohol withdrawal, 2358*t*
for anxiety disorders, 2344*t*
for heatstroke, 679*b*
for nausea and vomiting, 863*t*
Losartan, 451*t*
for acute STEMI, 391*t*
for heart failure, 266*t*
Losartan/HCTZ, 451*t*
Loss of consciousness, transient, 305, 305*t*
Lotion, 2697
Louping ill virus, 2276*t*, 2282
Louse-borne epidemic relapsing fever, 2027
Lovastatin, for familial hypercholesterolemia, 1409*t*
Low back pain, 2393–2399
ancillary testing for, 2397
clinical examination of, 2396–2397
clinical manifestations of, 2395–2396
computed tomography of, 2397
corticosteroids for, 2398*b*
definition of, 2393
diagnosis of, 2396–2398, 2396*f*
differential diagnosis of, 2397–2398, 2397*t*, 2398*f*, 2403*t*
epidemiology of, 2393–2395
history-taking for, 2396
mechanical, 2399
medications for, 2398*b*
myocardial ischemia associated with, 2398
occupational and environmental, 86
pathobiology of, 2395
prognosis for, 2399
surgery for, 2398*b*
treatment of, 2398*b*
Low-density lipoprotein cholesterol (LDLC), *e*1*t*–*e*8*t*, 57–58
Low density lipoproteins, 1405
low level of, 1410
Low dietary solute, 738
Low-intensity vibration, 1643*b*
Low-molecular-weight heparins (LMWHs), 501*t*, 502, 503*t*
for acute coronary syndrome, 374*t*
in pregnancy, 1623*b*
weight-based dosing of, 487*b*
Low molecular weight iron dextran, for iron deficiency anemia, 1085*t*
Low-output states, management of, 384*b*
Lowe oculocerebrorenal syndrome, 817
Lowe syndrome, 816*t*
Lower abdominal pain, gonorrhea and, 1947
Lower airway allergy, 1674
Lower extremity, cystic adventitial disease of arteries in, 467
Lower gastrointestinal bleeding, 882, 884
colonoscopy for, 885
definition of, 884
diagnosis of, 884
epidemiology of, 884
treatment of, 885*b*
Lower gastrointestinal tract, systemic sclerosis involvement of, 1778
Lower limb ischemia, chronic
classification of, 462*t*
critical, 462
stable, 462
treatment of, 464*b*
Lower lobe predominant fibrosis, 575.*e*1*f*
Lower urinary tract, abnormalities of, 821
LRRK2, 2483
Lubiprostone, for irritable bowel syndrome, 895*b*, 896*t*
Lubrication, for skin diseases, 2700
Lucio leprosy, 2051
Lucio phenomenon, 2051
Lujo hemorrhagic fever, 2268*t*
Lujo virus, 2265*t*
Lumakras. *See* Sotorasib
Lumbar puncture
cryptococcal meningitis associated with, 2088
description of, 2374, 2374*f*, 2374*t*
stroke evaluations, 2468
subarachnoid hemorrhage evaluations, 2475
Lumbar radiculopathy, 2402
Lumbar spinal stenosis, 2399, 2399*b*
Lumbar vertebrae, 2392
Lumbosacral radiculopathy, 2394*t*
Lumefantrine, for malaria, 2121*b*
Lump, in throat, 2652
Lung(s)
congenital cystic adenomatoid malformation, 565
cystic fibrosis and, 556
examination of, 30, 258
hyperlucent, 565
imaging of, 519
shrinking, 580–581
systemic sclerosis involvement of, 1778–1779
Lung abscess, 1904
Lung auscultation, 512*t*
Lung cancer, 1329–1337
adenocarcinomas, 1329, 1329.*e*2*t*
bronchogenic, 1329
clinical manifestations of, 1330
definition of, 1329
diagnosis of, 1330–1335
diagnostic imaging for, 1331–1332
epidemiology of, 1329
epigenetics of, 1330
in HIV, 2316
initial evaluation, 1331–1332, 1332*f*
invasive diagnostic procedures, 1331
large cell carcinoma, 1329, 1329.*e*2*t*
metastatic, 631
molecular pathology of, 1330
molecular testing for, 1333–1335
non-small cell. *See* Non-small cell lung cancer
nutrition and, 59
as occupational lung disease, 585*t*, 591
oncogenes associated with, 1330, 1330.*e*1*f*
pathobiology of, 1329–1330
pathology of, 1329
pleural invasion by, 526
prevention of, 1335–1336
primary prevention of, 1335
prognosis of, 1336
risk factors for, 1329
screening for, 54–55, 1247
secondary prevention of, 1336
Lung cancer *(Continued)*
small cell, 1329–1330. *See also* Small cell lung cancer
solitary pulmonary nodule in, 1330–1331, 1331*f*
squamous cell carcinoma, 1329, 1329.*e*2*t*
staging of, 1332–1333, 1333*t*
supportive care for, 1333*b*
surgery for, 631
surveillance and follow-up for, 1333*b*
treatment for, 1333*b*
tumor suppressor genes associated with, 1330
in women, 1607
Lung disease
acute respiratory failure without, 652
apical, 524*f*
basal, 523, 523*t*
cystic fibrosis and, 557, 557*f*
diffuse, 520
interstitial. *See* Interstitial lung disease
interventional approaches to, 630–634
malignant, 631
surgery for, 631
occupational, 584–591
restrictive, cases of, 533
surgical approaches to, 630
Lung expansion maneuvers, 2664
Lung failure, trajectories of, 12.*e*1*f*
Lung flukes, 2165–2168
Lung function, 547.*e*3*f*
abnormality, common changes associated with, 532*t*
measures of, 528
Lung function tests, interpretation of, 531–532
Lung injury, 597–599
acute, transfusion-related, 598–599, 599*b*
aspiration injury, 597
chemical, 591
lipoid pneumonia, 598
physical, 591
radiation, 597, 597*b*
ventilator-induced, 655, 655.*e*1*f*
Lung neuroendocrine neoplasms, 1567
Lung transplantation, 551*b*, 632–634
acute rejection of, 633
bilateral, 632–633
chronic rejection of, 633
complications of, 633–634
for cystic fibrosis, 558*b*
decision guide for, 632*t*
heart-lung transplantation, 633
indications for, 632, 632*t*
living donor lobar transplantation, 633
post-transplantation issues, 633
prophylaxis after, 633
recipients, evaluation of, 633
single-lung, 633
survival estimates, 634.*e*1*f*
types of procedures, 632–633
Lung volume, 523
absolute, 530
body plethysmography for, 530
conditions associated with, 523*t*
inert gas dilution technique for, 530
nitrogen washout technique for, 530
in pulmonary function tests, 528*t*, 530, 530*f*
reduced, 533
Lung volume reduction, 551*b*
Lung volume reduction surgery, 631–632
decision guide for, 632*t*
inclusion and exclusion criteria for, 632*t*
mortality of, 631.*e*1*f*
Lupkynis. *See* Voclosporin
Lupron. *See* Leuprolide acetate
Lupus, during pregnancy, 1770
Lupus anticoagulant, 1193, 1715
clinical manifestations of, 1194
diagnosis of, 1194
epidemiology of, 1193
pathobiology of, 1193
treatment of, 1194*b*
Lupus erythematosus, 2621*t*
Lupus nephritis, 1769, 1771–1772, 1773*f*–1774*f*
classification of, 787–788, 787*t*
Lupus panniculitis, 2687.*e*4*t*, 2735
Lupus pernio, 601, 602*f*
Lurasidone, for psychotic disorders, 2346*t*
Lurbinectedin (Zepzelca), 1215*t*
Lutein, 1452

Copyrighted material

Luteinization, 1595–1596
Luteinizing hormone (LH), *e1t–e8t*, 1496
  description of, 1580
  gonadotropin-releasing hormone effects on, 1476
  insufficiency tests of, 1484*t*
  pathobiology of, 1496
  in puberty, 1591
  secretion of, 1582
  subunits of, 1581
  syndrome, 1561*t*
  tests of, 1488*t*
  tumors that produce, 1496, 1496*b*
Lutembacher syndrome, 348
Luteogenesis, 1595–1596
Luteomas, of pregnancy, 1573
LVEF. *See* Left ventricular ejection fraction
17,20 Lyase deficiency, 1571
Lyme arthritis, 1808, 2024, 2026*b*
Lyme borrelia, 2022
Lyme borreliosis, 2022
Lyme disease, 286, 318–319
  Borrelia burgdorferi and, 1279
  cardiac, 2024, 2027
  chemoprophylaxis for, 2027
  chronic, 2027
  clinical manifestations of, 2023, 2023*f*
  coinfections, 2026*b*
  definition of, 2022–2027
  diagnosis of, 2025–2026, 2025*t*
  differential diagnosis of, 2025–2026
  early neurologic, 2024
  epidemiology of, 2022, 2023*f*
  extracutaneous, 2025–2026
  late, 2024–2025
  late neurologic, 2024
  neurologic manifestations of, 2024
  pathobiology of, 2022–2023
  pathogen that causes, 2022
  post-Lyme disease and syndrome, 2027
  in pregnancy, 2026*b*
  prevention of, 2026–2027
  prognosis of, 2027
  reinfection of, 2026*b*
  serologic testing for, 2027
  in travelers, 1889.*e1t*
  treatment of, 2026*b*
Lyme myocarditis, 2026*b*
Lymph nodes, 1148
  biopsy of, 1150
  on chest images, 524
  enlarged, 524, 524*t*
  enlargement of, 1148
  regional, treatment of, 1393*b*
Lymphadenitis
  acute, 2177
  chancroid and, 1951*f*
  tuberculosis, 2037
Lymphadenopathy, 1148–1151, 2001
  autoimmune disorders associated with, 1150
  biopsy of, 1151
  blood testing for, 1150
  clinical manifestations of, 1148
  computed tomography of, 1150
  diagnosis of, 1149–1151
  differential diagnosis of, 1149–1150, 1149*t*, 1150*f*
  evaluation of, 1151
  fever and, 1849, 1849*t*
  generalized, 1151
  history of, 1149
  imaging of, 1150–1151, 1150*f*
  localized, 1149–1150
  malignancy presenting as, 1150, 1150*f*
  in parapoxvirus, 2239
  physical examination of, 1149, 1149*t*
  in systemic lupus erythematosus, 1770
  treatment of, 1151*b*
  West African sleeping sickness and, 2124
Lymphangioleiomyomatosis, 583, 583*b*, 583.*e1f*
Lymphangitic carcinomatosis, distinguishing features of, 515*t*
Lymphangitis, in parapoxvirus, 2239
Lymphangitis-associated rickettsiosis (LAR), 2055*t*
Lymphatic drainage, impaired, 938
Lymphatic filariasis, 2176, 2177*b*–2178*b*, 2177*f*
Lymphatic system, examination of, 30
Lymphedema, 1369*b*
Lymphocutaneous disease, 2073
Lymphocutaneous sporotrichosis, 2086, 2086*f*
Lymphocyte apoptosis, defects in, 1685
Lymphocytes, 187–191
Lymphocytic choriomeningitis, 2521, 2535
Lymphocytic hypereosinophilic syndrome, 1162, 1163*t*
Lymphocytic hypophysitis, 1483–1484
Lymphocytic infundibuloneurohypophysitis, 1503
Lymphocytic interstitial pneumonia, 574*t*, 579, 580*b*
Lymphocytic interstitial pneumonitis, 2319
Lymphocytic phlebitis, 916
Lymphocytoma, borrelial, 2024
Lymphocytosis, 1142, 1143*t*
Lymphogranuloma venereum, 2012, 2019
  chancroid and, 1951
  characteristics of, 1881
  organisms causing, 1879*t*
Lymphohematopoiesis, hierarchical model of, 1064*f*
Lymphohistiocytosis, hemophagocytic, 1684
Lymphoid diseases, in chronic lymphocytic leukemia, 1268–1269
Lymphoid follicle, from airway submucosa, 556.*e3f*
Lymphoid interstitial pneumonia, 579, 580*b*, 580.*e1f*
Lymphoid polyps, 1348
Lymphoid tissue, 187
Lymphoma
  adult T-cell leukemia/lymphoma. *See* Adult T-cell leukemia/lymphoma
  arthritis associated with, 1823
  Burkitt, 1286, 1286*b*
  diffuse large B-cell, 1279, 1284, 1285*b*
  Hodgkin. *See* Hodgkin lymphoma
  non-Hodgkin. *See* Non-Hodgkin lymphoma
  peripheral blood smear of, 1073
  primary central nervous system, 1316, 1316*b*, 1316*f*
  primary lung, 1336
  Sjögren syndrome and, 1785
  stomach, 1342
Lymphomatoid granulomatosis, 2256
Lymphomatoid papulosis, 1286, 2734
Lymphoplasmacytic lymphoma, 1088–1089, 1279–1280, 1280, 1286, 1286*b*
Lymphoproliferative disorders, increased lymphocyte counts in, 533
Lymphoproliferative syndromes, 1684*t*
Lynch syndrome, 162, 1249, 1250*t*, 1377
Lynparza. *See* Olaparib
Lysinuric protein intolerance, 816*t*, 1398*t*
Lysis, osmotic, 199
Lysosomal acid lipase deficiency, 1420*t*, 1424
Lysosomal storage diseases, 1418–1424, 1419*t*
  aspartylglucosaminuria as, 1423
  classification of, 1419*t*
  clinical manifestations of, 1419, 1420*t*
  cystinosis as, 1420*t*, 1424
  diagnosis of, 1419
  epidemiology of, 1418–1419
  Fabry disease as, 1421
  Gaucher disease as, 1420
  lysosomal acid lipase deficiency as, 1420*t*, 1424
  metachromatic leukodystrophy as, 1423
  mucopolysaccharidoses as, 1420*t*, 1424
  neuronal ceroid-lipofuscinoses as, 1420*t*, 1424
  Niemann-Pick disease type C as, 1420*t*, 1423
  pathobiology of, 1418
  Pompe disease as, 1424
  prognosis of, 1419*b*
  Tay-Sachs disease as, 1423
  treatment of, 1419*b*, 1420*t*

M

M-BCR. *See* Major breakpoint cluster region
m-iodobenzylguanidine, 261
M proteins, 1913–1914
M-type immunoglobulins (IgM), 2005
MAC. *See* Membrane attack complex
Machine learning, 37
Machupo virus, 99.*e1t*, 2265*t*
Macro-ovalocytes, 1067*f*
Macroadenoma, 1523
Macrocyte, 1067*f*
Macrocytic anemia, 1079, 1082
  cause of, 1072*t*
  peripheral blood smear of, 1067*f*, 1069
Macrocytic hypochromic anemia, 1083*t*
Macrocytosis
  causes of, 1117*t*, 1120
  definition of, 1120
Macroglossia, in amyloidosis, 1306*f*
Macrolides
  for chancroid, 1951*b*
  characteristics of, 1899
  for cystic fibrosis, 558*b*
  dosage of, 1895*t*
  mechanism of action, 1895*t*
  resistance mechanisms, 1893*t*
  toxicities of, 1901*t*
Macrophage activation syndrome, 1159
Macrophage-derived cytokines, rheumatoid arthritis and, 1750–1751
Macrophages, 182–183, 191
Macroprolactin, 1490
Macroprolactinoma, 1492*f*
Macrovesicular steatosis, 1031, 1031*t*
Maculae ceruleae, 712*f*
Macular edema, 1549*t*
Macular exanthems, 2712
Macular purpura, 2713–2714, 2713*t*–2714*t*, 2714*f*–2715*f*
Maculatum rickettsiosis, 2065*t*
Macule, 2644, 2689*t*
Maculopapular exanthems, 1857
Maculopapular rash
  measles-related, 2220
  in rubella, 2224, 2224*f*
Maffucci syndrome, 1669
Magnesium, *e1t–e8t*
  deficiency, 766–767, 766*b*–767*b*, 766*t*
  deficiency of, 2538*t*
  depletion, 288
  diarrhea and, 939
  free, *e1t–e8t*
  for malabsorption, 937*t*
  metabolism, 766
  for narcolepsy, 2449*t*
  as occupational and environmental hazards, 88*t*
Magnesium ammonium phosphate stones, 804
Magnesium sulfate
  for advanced cardiac life support, 315*f*
  for arrhythmias, 313*b*
  for torsades de pointes, 338*b*
Magnetic coils, 519
Magnetic resonance angiography (MRA)
  in atherosclerotic PAD, 463, 463*f*
  description of, 872
  of renal artery stenosis, 800
  strengths and weaknesses of, 2373*t*
Magnetic resonance cholangiopancreatography (MRCP), 872, 1055
  for pancreatic duct obstruction, 970
  secretin-enhanced, for malabsorption, 931*t*
Magnetic resonance (MR) elastography, 872–873
Magnetic resonance (MR) enterography, description of, 872, 873*f*
Magnetic resonance imaging (MRI), 519
  acute MI on, 384
  acute pancreatitis on, 970–971, 971
  Alzheimer disease on, 2414, 2415*f*
  anterior pituitary on, 1483, 1484*f*–1485*f*, 1485*f*
  brain abscess on, 2526, 2526*f*
  brain tumors on, 1311, 1312*f*
  breast cancer screening uses of, 1373–1374
  cardiac
    in heart failure, 261
    stress, 362
  cardiovascular, 251, 251*f*
  cerebral microbleeds on, 2479*f*
  cervical spine on, 2401*f*
  chronic pancreatitis on, 974
  Creutzfeldt-Jakob disease on, 2424*f*
  Cushing disease on, 1494
  empty sella on, 1486*f*
  epilepsies on, 2431
  frontotemporal lobar degeneration on, 2423*f*
  gadolinium-enhanced, 2527
  in gastroenterology, 871, 872*f*, 873*f*
  herpes simplex encephalitis on, 2533, 2533*f*
  hippocampal formation on, 2407
  hypoglycemia on, 1557
  infectious endocarditis on, 2530
  liver disease on, 990
  lumbar spinal stenosis on, 2400*f*, 2402*f*
  macroprolactinoma on, 1492*f*
  meningiomas on, 1313, 1313*f*–1314*f*, 1314*f*
Magnetic resonance imaging (MRI) *(Continued)*
  metabolic bone disease on, 1638
  multiple sclerosis on, 2501–2503, 2502*f*–2503*f*, 2502*f*, 2502*t*, 2503*f*
  pancreatic duct obstruction on, 970
  paralytic rabies on, 2535
  pelvic inflammatory disease on, 1949
  pituitary tumors on, 1487
  rheumatic disease on, 1720–1723, 1721*f*–1722*f*
  strengths and weaknesses of, 2373*t*
  stroke on, 2467*f*, 2471*f*
  subdural empyema on, 2528, 2528*f*
  vasculitis on, 728, 729*f*
  venous thromboembolism on, 485–486
Magnetic resonance spectroscopy (MRS), strengths and weaknesses of, 2373*t*
Magnetoencephalography, for epilepsies, 2431
Magnocellular neurons, 1498
Mahvash disease, 1564
Major breakpoint cluster region (M-BCR), 1273
Major depressive disorder, 2337–2341
  clinical manifestations of, 2338, 2338*t*
  continuation and maintenance therapies for, 2338*b*–2341*b*
  definition of, 2337–2341
  diagnosis of, 2338
  epidemiology of, 2337–2338
  pathobiology of, 2338
  prognosis of, 2341
  symptoms/signs of, 2338*t*
  treatment for, 2338*b*, 2339*f*, 2339*t*, 2340*t*, 2346*t*
Major histocompatibility antigens
  class I deficiency, 1678, 1678.*e1t*
  class II deficiency, 1678, 1678.*e1t*
Major histocompatibility complex (MHC), 1*t*–2*t*, 203, 204*t*, 204.*e1f*, 204.*e2t*, 1760
Mal de débarquement syndrome, 2644
Malabsorption, 932, 932.*e1f*, 933*f*, 2145
  causes of, 928*t*
  clinical consequences of, 929*t*
  congenital, 938
  evaluation of, test for, 931*t*
  laboratory tests for, 930, 931*t*, 932*t*
  micronutrient deficiency caused by, 1452
  vitamin deficiency caused by, 2537
  weight loss and, 860*t*
Malaise, liver disease and, 986
Malakoplakia, 791
Malar rash, in systemic lupus erythematosus, 1770*f*
Malaria, 2065*t*, 2111–2115, 2118–2123
  anemia caused by, 2314
  characteristics of, 2270*t*
  chemoprophylaxis for, 1887–1888, 1890*t*, 2123*t*
  clinical features of, 2120
  clinical manifestations of, 2119–2120
  complications of, 2120
  definition of, 2118–2123
  diagnosis of, 2120–2121
  in endemic countries, 2118
  epidemiology of, 2118
  parasite of
    host immunity and genetics of, 2119
    life cycle of, 2118–2119, 2119*f*
    pathogenic features of, 2119
  pathobiology of, 2118–2119
  pathogen of, 2118
  prevention of, 2112*t*, 2122–2123
  prognosis of, 2123
  prophylaxis for, 2309*t*
  severe, 2120
  splenomegaly associated with, 1152
  transmission of, 2118
  in travelers, 2118
  treatment of, 2112*t*, 2121*b*, 2121*t*
  uncomplicated, 2119–2120
Malarone, for malaria, 2121*b*, 2121*t*, 2123*t*
Malassezia furfur, 2703
Malassezia globosa, 2711
Malathion
  for lice, 2742*b*
  for scabies, 711*b*
Maldigestion, micronutrient deficiency caused by, 1452
Male circumcision, 1884
Male condom, 1612
Male genitalia, examination of, 31

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Male hypogonadism, 1582
androgen preparations for, 1586*t*
definition of, 1582
epidemiology of, 1582
in HIV, 2318
pathobiology of, 1583
testosterone delivery systems for, 1585*b*
treatment of, 1585*b*
Male infertility, 1586
algorithm for, 1587*f*, 1588*f*
basic laboratory tests for, 1589*t*
clinical manifestations of, 1586
diagnosis of, 1586
treatment of, 1586*b*
Male osteoporosis, 1646, 1646*b*
Male reproductive axis, 1580
Male reproductive physiology, 1580–1582, 1580*f*
Male senescence, 1582
Malignancy
in chronic lymphocytic leukemia, 1271
in chronic pancreatitis, 975*b*
hypercalcemia of, 1658, 1659*b*
Malignant ascites, 957, 958*b*
Malignant atrophic papulosis, 965, 969
Malignant diseases
arthritis associated with treatments for, 1823
in hypercoagulable states, 479–480, 479*b*, 480*f*
Malignant effusions, 625–626, 625*b*–626*b*
Malignant histiocytosis, 1159, 1159*b*
Malignant hyperthermia, 678, 715, 717*b*, 2583.*e1t*
anesthesia and, 2668, 2668*b*
Malignant melanoma, in adolescents, 111
Malignant mesothelioma, 1336
treatment and prognosis of, 1336*b*
Malignant neoplasms
in adolescents, 110*t*
alcohol use disorders and, 2355–2356
in renal transplantation, 847
with venous thromboembolism, 479, 480*f*
Malignant otitis externa, 1969
Malignant pericarditis, 432
Mallory-Weiss tear, 856, 882*f*, 912
Malnutrition
acute, 1444, 1445.*e1f*, 1446*t*
assessment and support for, 1446–1451
clinical manifestations of, 1447
common causes of, 1447*t*
definition of, 1446–1451
diagnosis of, 1447–1448, 1448*f*, 1449*t*
epidemiology of, 1446–1447
in older adults, 114
pathobiology of, 1447, 1447*f*
primary, in children and adolescents, 1445*b*
prognosis of, 1450–1451
screening for, 1447, 1448*t*
secondary, 1445, 1445*b*
severe, 1444–1446
clinical manifestations of, 1444–1445
definition of, 1444–1446
diagnosis of, 1445
epidemiology of, 1444
kwashiorkor, 1444, 1444*f*, 1445*f*
marasmus, 1444, 1444*f*
pathobiology of, 1444
prevention of, 1446
prognosis for, 1446
secondary, 1444
stunting, 1445
treatment of, 1445*b*
wasting, 1445
therapy for, 1448–1450, 1450*f*
vitamin deficiency caused by, 2537
MALT. *See* Mucosa-associated lymphoid tissue
Malta fever. *See* Brucellosis
Mammalian target of rapamycin (mTOR)
aging and, 115
inhibitors
for liver transplantation, 1048, 1048*t*
for renal transplantation, 845*t*
for renal cell carcinoma, 1364*b*
MammaPrint, 168
Mammillary bodies, 2407
Mammography, for breast cancer screening, 1373, 1373*t*
Mandatory consultations, 2658
Manganese, *e1t*–*e8t*, 1457*t*
hazards, 88*t*
parkinsonism and, 101*t*, 107, 107*b*
Manganism, 107
Mangled Extremity Severity Score, 717*b*
Mania, 2337*t*, 2341*t*
Manic-depressive illness, weight loss and, 860*t*
Mannitol
for drowning, 592*b*
for rhabdomyolysis, 717*b*, 717*t*
Mannose-binding lectin, 186
Mansonella ozzardi, 2180
Mansonella perstans, 2180
Mansonella streptocerca, 2180
Mantle cell lymphoma, 1284, 1284*b*
immunophenotype of, 1268*t*
Mantoux tuberculin skin test, 2039
Manual therapies, 154
MAOIs. *See* Monoamine oxidase inhibitors
MAP kinase pathway, 1251–1252, 1251.*e1f*
MAPK. *See* Mitogen activated protein kinase pathway
Maple syrup urine disease, 1398*t*, 1402*t*
Marasmus, 1444, 1444*f*
Maraviroc, 2301*t*
Marburg disease, 2501
Marburg virus, 99.*e1t*, 2264, 2265*t*, 2268*t*
March fracture. *See* Stress fracture
Marchiafava-Bignami syndrome, 2545
Marcus-Gunn pupil, 2500
Marfan syndrome, 210, 439, 1641
description of, 158, 1725, 1726*b*
Marginal alopecia, 2747*t*
Marginal micronutrient deficiencies, 1459–1460
Marginal ulcer, 913
Marginal zone lymphoma, 1268*t*, 1269, 1283, 1283*b*, 1284*t*
Margination, neutropenia due to, 1146
Marijuana, 2364
on cancer pain, 12
clinical manifestations and diagnosis of, 2364
epidemiology of, 2364
in palliative care, 16
pathobiology of, 2364
properties of, 142*t*
treatment of, 2364*b*
Marine animals, envenomation of, 712, 712*b*
Marine dinoflagellates, as source of food poisoning, 925
Marine omega-3 fatty acid, for hypertriglyceridemia, 1414*b*
Maroteaux-Lamy syndrome, 1724*t*
Marrow graft failure, hematopoietic cell transplantation and, 204
Marrow injury, neutropenia due to, 1145, 1145*f*
Marrow stimulation, neutrophilia and, 1141
MASCC Index. *See* Multinational Association for Supportive Care in Cancer Index
Masked hypertension, 447, 447.*e1f*
Masks, for HIV transmission prevention, 2300
Mass spectrometry, for *Bartonella* infection, 2002
Massage therapy, 154
Masses, mediastinal, 628–629
Massive pulmonary embolism, 487*b*
Massive transfusion, 1205
Mast cell(s), 183
acute inflammation and, 191
description of, 538
mediators released by, 1691
Mast cell activation syndrome, 1693
Mast cell leukemia, 1702
Mastalgia, 1374
Mastitis, 1374, 2226, 2226*t*
Mastocytomas, 1700–1701
Mastocytosis, 1699–1704
biopsy for, 1701–1702, 1702*f*
clinical manifestations of, 1700–1701
cutaneous, 1699, 1700, 1700*f*, 1701
cytoreductive therapy for, 1703*b*
definition of, 1699–1704, 1699*t*
diagnosis of, 1701–1703, 1701*f*
eosinophilia in, 1701
epidemiology of, 1700
gastrointestinal symptoms of, 1701
genetics of, 1700
hematologic manifestations of, 1701
medical therapy for, 1703*b*
musculoskeletal symptoms of, 1701
pathobiology of, 1700
prognosis for, 1704
protean clinical manifestations of, 1700
symptoms of, 1700, 1700*f*
systemic, 917, 1694, 1701–1703, 1703*f*
treatment of, 1703*b*
venom immunotherapy for, 1703*b*
Matrix-assisted laser desorption, for *Bartonella* infection, 2002
Matrix metalloproteinases, 227
Maturation arrest, 1143–1144
Maturity-onset diabetes of the young (MODY), 1539
Mavenclad. *See* 2-Chlorodeoxyadenosine
Maxi-K channels, 746
Maximal medical improvement, 85
Maximal mid-expiratory flow rate (MMEFR), 539, 539*t*
Maximal voluntary ventilation (MVV), 528, 531, 531*f*
Maximum surgical blood order schedule, 1200
May-Hegglin anomaly, 1071, 1179
Mayaro virus, 2275*t*, 2279, 2279*b*
Mayer-Rokitansky-Küster-Hauser (MRKH) syndrome, 1574
Mayzent. *See* Siponimod
Maze procedure, 329*b*
MC1R. *See* Melanocortin-1 receptor
McArdle disease, 1417*t*, 2586
McCune-Albright syndrome, 1487*t*, 1523, 1558, 1559*t*, 1668
MCH. *See* Mean corpuscular hemoglobin
MCHC. *See* Mean corpuscular hemoglobin concentration
McMahon Score Calculation, 717.*e1t*
MCP. *See* Membrane cofactor protein
MCTD. *See* Mixed connective tissue disease
MCV. *See* Mean corpuscular volume
MDI. *See* Methylene diphenyl diisocyanate
Mean arterial pressure, 677*t*
Mean corpuscular hemoglobin (MCH), *e8t*–*e9t*, 1076*t*
Mean corpuscular hemoglobin concentration (MCHC), *e8t*–*e9t*, 1076*t*, 1095
Mean corpuscular volume (MCV), *e8t*–*e9t*, 1076*t*, 1081*f*, 1095
Mean platelet volume (MPV), *e8t*–*e9t*
Meaningful Use standards, 46
Measles, 2220–2223, 2621*t*
characteristics of, 2270*t*
clinical manifestations of, 2221, 2222*f*
clinical progression of, 2221*f*
complications of, 2221
definition of, 2220–2223
diagnosis of, 2221–2222, 2223*t*
epidemiology of, 2220
German. *See* Rubella
global strategies, 2223
immunization for, 65*t*, 66*t*, 78*f*, 80
adverse reactions of, 80
indications for, 80
schedule of, 76.*e1t*, 77*f*
incidence of, 2220
Koplik spots associated with, 2220
pathobiology of, 2220–2221
prevention of, 2222–2223
prognosis for, 2223
rash associated with, 1847, 2221
in travelers, 1889.*e1t*
treatment of, 2222*b*
vaccination for, 2223
vaccine safety for, 2222–2223
vitamin A supplementation for, 2222*b*
Measles inclusion-body encephalitis, 2221
Measles-mumps-rubella (MMR) vaccine, 2225, 2249
Meat, dietary guidelines for, 57.*e3t*
Mebendazole, 2112*t*, 2117
Mecamylamine, for tobacco dependence, 2351*t*
Mechanical circulatory support, 265*b*, 667*b*
Mechanical load, in osteoarthritis, 1738
Mechanical reperfusion, for pulmonary embolism, 487*b*
Mechanical valves, 412*t*
Mechanical ventilation, 652–658
for acute respiratory distress syndrome, 655
assisted, 653
for chronic obstructive pulmonary disease, 649*b*
complications of, 654–655
discontinuation of, 657–658, 657*f*
high-frequency ventilation, 653
initiation of, 655, 655*t*
intermittent mandatory ventilation, 653
lung-protection strategies, 656
negative-pressure ventilators, 653
neurally adjusted ventilatory assist, 653
Mechanical ventilation *(Continued)*
noninvasive, 620.*e1t*
for obstructive airway disease, 657
positive end-expiratory pressure, 653–654
positive-pressure ventilators, 652–654
pressure-controlled ventilation, 653
pressure-support ventilation, 653
proportional assist ventilation, 653
for shock, 673*b*
specific common treatment scenarios, 655–657
for thermal injury, 595*b*
volume-controlled ventilation, 653
Meckel diverticulum, 951, 951*b*, 951*f*
Meclizine, for nausea and vomiting, 863*t*
Meclofenamate, for dysmenorrhea, 1596*t*
Medial epicondylitis, 1745, 1745*b*
Medial infarction, 2465.*e1f*
Median arcuate ligament syndrome, 967
Mediastinal masses, 628
anterior, 628–629
causes of, 628*t*
clinical manifestations of, 628, 628*f*
diagnosis of, 628–629
pathobiology of, 628
treatment of, 629*b*
Mediastinitis, 629
Mediastinoscopy, 1331
Mediastinum, 628–629
anterior compartment lesions, 628, 628*f*
compartments of, 527, 527*f*, 628.*e1f*
imaging of, 519, 526, 526*t*
techniques for, 526–527, 526*f*
pneumomediastinum, 629
Medicaid, 19
Medical abortion, 1617
description of, 1610
Paeniclostridium sordellii associated with, 1927
Medical care
coordination between, and community, 64
viewing, 42
Medical consultation
approach to, 2656
comanagement, 2657*t*, 2658
consultant in, 2658
curbside, 2657
electronic, 2658
impact of, on patient outcome, 2659
issues about, setting-specific, 2656–2657
mandatory, 2658
medical-medical consultations, 2656
postoperative surgical consultation, 2656
preoperative surgical consultation, 2656
principles of, 2656–2659
settings of, 2656
special consultative situations, 2657–2658
for special populations, 2656–2657
strategies for, 2657, 2657*t*
subspecialty, 2657, 2657*t*
telehealth, 2658, 2658*f*–2659*f*
Medical errors, in postoperative care, 2672
Medical exposures, of radiation, 92
Medical expulsive therapy, for nephrolithiasis, 805*b*
Medical history, 28, 29*t*, 2660–2661
complete, 212
family history, 28
history of the present illness, 28
past medical history, 28
review of systems, 28, 29*t*
surgical history, 28
Medical issues
alcohol use disorders and, 2356
in renal replacement therapy, 842
Medical marijuana
on cancer pain, 12
in palliative care, 16
Medical-medical consultations, 2656
Medical oncologist, 1232
Medical practice, changes in, 2
Medical profession, 4
Medical professionalism, 4
Medical resources, allocation of scarce, 9
definition of, 9
empirical data for, 10, 10*t*
ethical values for, 9*t*
history of, 9
justification of, 9
practical consideration for, 10

Copyrighted material

Medical rhythm control, for atrial fibrillation, 329*b*, 330*t*
Medical surveillance, 87
Medical therapy
  for chronic pancreatitis, 975*b*
  conventional, for systemic lupus erythematosus, 1772*b*
  for hypertension, 450
  for nephrolithiasis, 805*b*
  for pain, in chronic pancreatitis, 975*t*
  for pituitary tumors, 1487*b*
  for primary hyperparathyroidism, 1657*b*
  for upper gastrointestinal bleeding, 883*b*
  for Zollinger-Ellison syndrome, 1563*b*
Medical unit, psychiatric diseases in, 2679
Medicare, 19
  Value-based Purchasing program, 46
Medicare Hospice Benefit, 12
Medication-related diarrhea, 926
Medication review, in geriatric assessment, 118
Medication use counseling, 265*b*
Medicine
  accountability, 4
  anaphylaxis caused by, 1692
  approach to, 2–3, 3.e1*t*
  balancing professional responsibilities, 4
  changes in medical practice, 2
  clinical reasoning and decision-making, 3–4
  evidence-based, 2
  historic evolution of, 2–3
  incorporating a public health focus, 4
  internal, 2
  as learned and humane profession, 2–5
  new therapeutics, 3
  obesity caused by, 1465, 1466*t*
  psychiatry and, 2679
  social justice, 4
  societal implications, 3
  standard, 4
  teamwork, 4
  treatment, 3.e1*t*
  vitamin levels affected by, 1452, 1460*t*
Meditation, 154
Mediterranean diet, 58, 58*f*, 450
Mediterranean fever. *See* Brucellosis
Mediterranean spotted fever, 2055*t*, 2057
Mediterranean-type diet, for chronic kidney disease, 839*b*
Medium-chain acyl-CoA dehydrogenase deficiency, 2586
Medium vessel vasculitis, 965, 1792*t*, 1793–1794, 1795
Medullary collecting duct, 754, 754.e1*f*
Medullary sponge kidney, 814, 814*b*
Medullary stroke syndromes, 2465.e1*f*
Medullary thyroid cancer, 1518–1519, 1519*b*
Medulloblastomas, 1316, 1316*b*
Mees lines, 104
Mefenamic acid
  for chronic pain, 138*t*
  for dysmenorrhea, 1596*t*
Mefloquine, for malaria, 1887, 2112*t*, 2114, 2121*b*, 2121*t*, 2123*t*
Megacolon
  idiopathic, 890
  toxic, in ulcerative colitis, 945*b*
Megadisease, Chagas disease and, 2127
Megakaryoblasts, 1073
Megaloblastic anemia, 1080, 1117
  causes of, 1117*t*
  clinical manifestations of, 1120
  complications of, 1120, 1121*f*
  definition of, 1117, 1117*t*
  diagnosis of, 1122
  epidemiology of, 1117
  pathobiology of, 1118
  peripheral blood smear of, 1069, 1072*t*
  prevention of, 1124
  prognosis of, 1124
  treatment of, 1123*b*
Meibomian glands, 2596
Meigs syndrome, 626
Meissner plexus, 887, 901
MEK inhibitors, for melanoma, 1393*b*
Mekinist. *See* Trametinib
Mektovi. *See* Binimetinib
Melanocortin-1 receptor (MC1R), 1391
Melanocortin 4, endocrine diseases caused by, 1475*t*
Melanocytes, 1390
Melanocytic lesions, 2730–2731, 2733*f*
Melanoma, 1390–1395, 2691*t*
  acral lentiginous, 1391
  adjuvant therapy for, 1393*b*
  advanced, 1393*b*
  algorithm for, 1393*f*
  characteristics of, 1392*t*
  in chronic lymphocytic leukemia, 1268
  clinical manifestations of, 1391
  diagnosis of, 1391–1392
  dysplastic nevi associated with, 1390, 1391*f*, 1392*t*
  epidemiology of, 1390
  evaluation of, 1392
  follow-up for, 1393*b*
  immunotherapy for, 1393*b*
  inherited genetics of, 1391
  lentigo maligna, 1391, 1392*f*
  malignant, in adolescents, 111
  metastatic, 1393*b*
  mucosal, 1391
  nodular, 1391, 1392*f*
  ocular, 1391
  pathobiology of, 1390–1391
  prevention of, 1394
  primary, 1393*b*
  primary lesion in, biopsy of, 1391–1392
  prognosis for, 1394–1395
  regional lymph nodes and, 1393*b*
  risk factors for, 1390
  sentinel lymph node biopsy for, 1392
  somatic mutations in, 1390
  staging for, 1392
  superficial spreading, 1391, 1392*f*
  surveillance of, 1393*b*
  treatment of, 1393*b*, 1393*f*
Melanonychia, 2754–2755, 2755*f*
Melarsoprol, for African trypanosomiasis, 2112*t*, 2116, 2125*t*
Melasma, 2689*t*, 2744*b*
MELD. *See* Model for End-Stage Liver Disease; Model for End-stage Liver Disease
Melena, 864
Melioidosis, 1972, 1972*b*
  characteristics of, 2270*t*
  in travelers, 1889.e1*t*, 1891*t*
Melorheostosis, 1668, 1668*b*
Meloxicam, for chronic pain, 138*t*
Melphalan, for amyloidosis, 1308*b*
Memantine, for Alzheimer disease, 2416*b*
Membrane attack complex, 1091–1092
Membrane attack complex (MAC), 199–200
  activation of, 199.e1*f*, 201*t*
  regulation of, 200, 202*f*
Membrane cofactor protein (MCP), 200*t*
Membrane lipids, 1093
Membrane proteins, 1093
Membranoproliferative glomerulonephritis, 785, 786*b*, 786*f*, 786*t*
Membranous glomerulopathy, 781*f*
Membranous nephropathy, 727–728, 779–780
  clinical manifestations of, 780
  diagnosis of, 780, 780*f*–781*f*
  prognosis for, 780
  treatment of, 780*b*, 782*f*
Memory
  immune system and, 190–191
  loss of, neurologic diseases that cause, 2372
MEN. *See* Multiple endocrine neoplasia
MenACWY vaccine, 80
Menarche, 110
MenB vaccines, 80
Mendelian inheritance, 160, 161*f*
Mendelian Inheritance in Man, 158
Meniere disease
  hearing loss caused by, 2642
  treatment of, 2647*t*
  vertigo caused by, 2645
Meningiomas, 1313
  clinical manifestations of, 1313
  diagnosis of, 1313, 1313*f*, 1314*f*
  epidemiology of, 1313
  pathobiology of, 1313
  prognosis of, 1313*b*
  treatment of, 1313*b*
Meningitis, 2510–2524
  Acinetobacter causing, 1974
  Actinomyces causing, 2068
  anaerobic bacteria causing, 1938–1939
  anthrax and, 1931–1932, 1931
  aseptic
Meningitis *(Continued)*
  cerebrospinal fluid examination in, 2521
  definition of, 2519
  description of, 2030
  differential diagnosis of, 2521
  enterovirus causing, 2520
  epidemiology of, 2519
  herpes simplex virus causing, 2521
  lymphocytic choriomeningitis causing, 2521
  mumps causing, 2521
  noninfectious causes of, 2522, 2522*t*
  nonviral infectious causes of, 2522, 2522*t*
  polymerase chain reaction for, 2521
  prognosis for, 2522
  bacterial species that cause, 1892*t*
  by brain abscesses, 1937
  Brucella, 2515*b*
  Candida, 2091
  cerebral blood flow in, 2512
  cerebrospinal fluid findings in, 2374*t*
  "chemical", 2515
  chronic
    infectious causes of, 2522–2524, 2522, 2523*t*
    intermittent, 2524
    noninfectious causes of, 2523, 2524*t*
    persistent, 2523*t*, 2524*t*
    with predominantly neutrophilic pleocytosis, 2524, 2524.e1*t*
    recurrent, 2523*t*
  cryptococcal, 2087
  enteric infections and, 1870*t*
  enteroviruses causing, 2259, 2259*b*
  eosinophilic, 2523*t*, 2524
  gram-negative bacillary, 2515*b*
  H. influenzae caused by, 1953
  herpes, 2246, 2520
  in immunocompromised host, 1861
  Listeria, 2510, 2515*b*
  meningococcal, 1943, 1944*b*, 1944*t*, 2512, 2515*b*
  mumps and, 2226*t*
  nocardial, cerebrospinal fluid in, 2073
  non-nosocomial causes of, 2514*t*
  nosocomial, 2517*t*
  pneumococcal, 2511, 2514, 2515*b*
  purulent, 2516*t*
  staphylococcal, 2515*b*
  Staphylococcus aureus causing, 2511
  syphilitic, 2017
  in travelers, 1891*t*
  treatment of, 1970*b*
  viral, 2519–2522
    agents of, 2520*t*
    arboviruses causing, 2520
    cerebrospinal fluid findings in, 2521
    clinical manifestations of, 2520–2521
    definition of, 2519–2522
    differential diagnosis of, 2521
    enterovirus, 2520
    epidemiology of, 2519
    herpes simplex virus causing, 2521
    human immunodeficiency virus of, 2521
    lymphocytic choriomeningitis causing, 2521
    pathobiology of, 2520
    polymerase chain reaction for, 2521
  zoonotic, 2515*b*
Meningococcal colonization, initiation of, steps in, 1942.e1*f*
Meningococcal conjugate vaccines, 66*t*
Meningococcal disease, 2511
  chemoprophylaxis against, 1945*t*
  in children, 1941
  clinical manifestations of, 1943, 1943*f*
  epidemiology of, 1942*f*
  immunization for, 66*t*, 80
    adverse reactions of, 81
    indications for, 80
    schedule of, 76.e1*t*, 77*f*
  meningitis caused by, 1943, 1944*b*, 1944*t*, 2519
  necrotic purpura associated with, 1946
  polymerase chain reaction for, 1943–1944
  predisposing risk factor for, 1942
  prevention of, 1944–1945
  prognosis for, 1945–1946
  treatment of, 1944*b*, 1944*t*
  vaccination for, 1944–1945
Meningococcal septicemia, fulminant, 2512–2513
Meningococcemia, 1942, 2741, 2741*f*
  acute, 2695*f*
  characteristics of, 2270*t*
  treatment of, 1944*b*, 1944*t*
Meningococci, 1942
Meningococcus, vaccine, for traveler, 1886*t*, 1887
Meningoencephalitis, 2532*t*
  Chagas disease and, 2127
  definition of, 2531
  diagnosis of, laboratory methods for, 2003*t*
Meningovascular syphilis, 2017
Meniscal tears, 1747, 1747*b*
Menkes disease/syndrome, 1728–1729, 2542, 2550*t*
Menopausal hormone therapy
  discontinuation of, 1630*b*
  extended use of, 1630*b*
  vaginal symptoms and, 1630*b*
  venous thromboembolism and, 1630*b*
Menopausal transition, 1629
  bone health in, 1629
Menopause, 1628–1633
  breast cancer associated with, 1630*b*
  clinical manifestations of, 1629–1632
  cognitive dysfunction associated with, 1630*b*
  coronary heart disease associated with, 1630*b*
  definition of, 1628–1633
  diagnosis of, 1630
  epidemiology of, 1628–1629, 1628*t*–1629*t*
  final menstrual period, 1628
  genitourinary symptoms of, 1630, 1632*t*
  hormonal therapy for, 1630*b*
  mood disorders associated with, 1630, 1630*b*
  pathobiology of, 1629
  prevention of, 1632
  prognosis for, 1632
  restless legs syndrome associated with, 1630
  sleep disturbances in, 1630, 1630*b*
  treatment of, 1630*b*
  vasomotor symptoms of, 1629–1632, 1631*t*
  weight gain after, 1629
Menstrual attacks, porphyrias and, treatment of, 1434*b*
Menstrual cycle, 1595–1596
  cervical mucus, 1595
  cervix, 1595
  cytologic changes in, 1595, 1595*f*
  endometrium, 1595
  luteogenesis, 1595
  ovary changes in, 1595
  ovulation, 1595
  selection, 1595
  vagina in, 1595
Menstrual symptoms, 1596–1597
Mental health
  of adolescents, 112
  in pregnancy, 1623–1624, 1624*b*
Mental illnesses, severe
  health challenges for, 2677–2678
  population health for, 2677
  symptoms and findings in, approach to, 2681–2682, 2683*t*
Mental status, changes in, 2330–2336
  caregiver issues, 2334*b*
  clinical manifestations of, 2332
  definition of, 2331
  development of, 2332
  diagnosis of, 2334
  diagnostic criteria for, 2331*t*
  differential diagnosis of, 2330*t*, 2334
  end-of-life care for, 2334*b*
  epidemiology of, 2331
  evaluation of, 2330, 2330*t*, 2333*f*
  laboratory findings of, 2334
  medical treatment, 2334*b*
  nonpharmacologic management, 2334*b*
  in older adults, 2331
  pathobiology of, 2331
  prevention of, 2335, 2335*t*
  prognosis for, 2336
  treatment of, 2334*b*
Meperidine, 139*t*
Mephenytoin polymorphism, 132*t*
Mepolizumab, 541*b*, 1164*b*
6-Mercaptopurine, 148
  for inflammatory bowel disease, 945*b*, 946*t*
Mercury toxicity, e1*t*–e8*t*, 102, 690*t*
  clinical manifestations of, 103
  diagnosis of, 101*t*, 103
  epidemiology, 102

Copyrighted material

Mercury toxicity *(Continued)*
as hazard, 88*t*
pathobiology of, 102–103
treatment of, 102*t*, 103*b*
Merkel cell carcinoma, 2232, 2232*b*, 2233*f*, 2730, 2732*f*
Merkel cell polyomavirus, 2228*t*, 2231
Meropenem, 1845*t*
Acinetobacter, 1974*b*
for bacterial meningitis, 97*b*, 2516*t*
dosage of, 1895*t*
for meningococcal meningitis and meningococcemia, 1944*t*
for pneumonia, 613*t*, 616*t*
for pyelonephritis and urosepsis, 1877*t*
for pyogenic liver abscess, 1023*b*
Meropenem-vaborbactam, dosage of, 1895*t*
Merozoites, 2141
MERS. *See* Middle east respiratory syndrome
Mesalamine, 945*b*, 946*t*
Mesenchymal stromal cells, 172, 1640
Mesenteric arterial occlusive disease, acute, 960
Mesenteric cysts, 958
Mesenteric fibromatosis, 958
Mesenteric ischemia
acute, 959
clinical manifestations of, 959
diagnosis of, 960, 960*f*
prognosis of, 960
specific, 960
treatment of, 960*b*, 961*f*
chronic, 963, 963*f*
clinical manifestations of, 963
diagnosis of, 963, 964*f*
treatment of, 964*b*
nonocclusive, 962, 962*f*
Mesenteric panniculitis, 958
Mesenteric venous thrombosis, 962, 963*f*, 963*t*
Mesentery, anatomic diseases of, 958, 958*t*
Mesial temporal lobe epilepsy, with hippocampal sclerosis, 2433
Mesial temporal sclerosis, 2433
Mesocardia, 354
Mesonephric duct, 818
Mesothelioma, 590, 627
clinical manifestations of, 627
computed tomography of, 627*f*
diagnosis of, 627
epidemiology of, 627
pathobiology of, 627
prognosis of, 627*b*
treatment of, 627*b*
Messenger RNA-based therapeutics, 177
MET level requirements, 61*t*
Meta-analysis, 37
Metabolic acidosis, 754–762, 756
anion gap, 757, 757*t*
in chronic kidney disease, 836
clinical manifestations of, 757
epidemiology of, 756–757
expected compensation of, 755, 756*t*
hyperchloremic, 760, 760*f*
pathobiology of, 756
potassium levels affected by, 747
prognosis of, 762
treatment of, 762*b*
Metabolic alkalosis, 753*t*, 762
associated with extracellular volume depletion, 763
associated with normal or expanded volume, 763
associated with volume depletion, 762–763
associated with volume expansion and hypertension, 763
clinical manifestations of, 763
diagnosis of, 753*t*, 763–764, 764*f*
epidemiology of, 762
expected compensation of, 755–756, 756*t*
pathobiology of, 762
treatment of, 764*b*
Metabolic bone disease, 1638–1639
diagnosis of, 1638–1639
dialysis-associated, 842
laboratory and radiologic investigation of, 1638–1639
physical examination of, 1638
treatment of, 839*b*, 1639*b*
Metabolic disease
cardiomyopathy with, 288
hypoglycemia due to, 1555
Metabolic equivalents (METs), 61, 1465
Metabolic myelopathy, 2406, 2406*b*
Metabolic myopathies, 2583.*e2t*, 2586–2587
Metabolic pericarditis, 424*t*
Metabolic profiling, 168
Metabolic syndrome
in obesity, 60
psychotropic medications and, 2680
severe mental illness and, 2683*t*
Metabolism, 1447
cardiovascular, 224
of magnesium, 766
microbiota and, 1839*f*
of phosphorus, 767
Metabolomics, 168
Metachromatic leukodystrophy, 1423, 2509
Metals
as occupational and environmental hazards, 87, 88*t*
trace, chronic poisoning, 101
Metamorphopsia, 2599
Metamyelocyte, 1140*f*
Metastases
bone tumors, 1388, 1388*b*
brain, 1316, 1317*b*, 1317*f*
breast cancer, 1369*b*
ocular, 2613
to spinal leptomeninges, 1318*f*, 1319
Metastatic differentiated thyroid cancer, 1511*t*
Metastatic disease
of bladder, treatment of, 1366*b*
in lungs, 631
on positron emission tomography/computed tomography, 874*f*
of renal cell carcinoma, treatment of, 1364*b*
in Zollinger-Ellison syndrome, treatment of, 1563*b*
Metastatic extraintestinal infection, enteric infections and, 1870*t*
Metastatic neuroendocrine tumor, computed tomography of, 871*f*
Metastatic spinal cord compression, 2406, 2406*b*
Metformin, 1460*t*
for polycystic ovary syndrome, 1602*b*
for type 2 diabetes mellitus, 1540*b*, 1541*t*
Methacrylates, 88*t*
Methadone, 139*t*
for opioid use disorders, 2362*b*
Methanol, 760
central nervous system effects of, 685*t*
toxicity, 686*t*, 690*t*, 698*t*
Methemoglobin, toxicity, *e1t–e8t*, 690*t*
Methemoglobin reductase deficiency, adverse drug reactions and, 132
Methemoglobinemia, 215, 1075, 1075*t*
Methicillin-resistant *Staphylococcus aureus* (MRSA), 1865, 1902, 1902.*e3t*
Methimazole
for Graves disease, 1511*t*
for hyperthyroidism, 1511*b*
Methionine, oral, 1427*b*
Methotrexate (Mexate, Folex), *e10t–e11t*, 147, 1215*t*
for Crohn disease, 945*b*, 946*t*
for rapidly progressive glomerulonephritis, 785*b*
for rheumatoid arthritis, 1755*b*, 1756*t*, 1757*t*, 1765*b*
for systemic lupus erythematosus, 1772*b*
for systemic sclerosis, 1781*b*
for total knee arthroplasty, 1830.*e1t*
1-Methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP), 2483
Methyl conjugation polymorphism, 132*t*
Methyl mercury, 102
Methyl-tetrahydrofolate, 1118
Methyldopa, 451*t*
Methylene blue, for acute poisoning, 693*t*
Methylene diphenyl diisocyanate (MDI), 588
5,10-Methylenetetrahydrofolate reductase (MTHFR) deficiency, 1425, 1426*t*
Methylmalonic acid, for megaloblastic anemias, 1122
Methylmalonic aciduria, 1398*t*, 1403, 1403*t*
Methylphenidate, 2446*b*, 2449*t*
Methylphenidate ER, 2449*t*
Methylprednisolone
for acute rejection, 633
for diffuse alveolar hemorrhage, 569*b*
for idiopathic pulmonary fibrosis, 576*b*
Methylprednisolone *(Continued)*
intravenous, for autoimmune encephalitis, 2536
for membranous nephropathy, 780*b*
for *Pneumocystis* pneumonia, 2106*t*
for rapidly progressive glomerulonephritis, 785*b*
in renal transplantation, 845*t*
for status asthmaticus, 541*b*
for ulcerative colitis, 945*b*, 946*t*
for vestibular neuritis, 2647*b*
Metoclopramide
for intestinal pseudo-obstruction, 889*b*
for nausea and vomiting, 863*t*
Metolazone, 451*t*
for hypervolemia, 736*b*, 737*t*
Metoprolol, 460*t*
for acute STEMI, 384*b*, 391*t*
for aortic dissection, 441*b*
for arrhythmias, 313*b*
for atrial fibrillation, 384*b*
for heart failure, 267*t*
for premature ventricular contractions, 338*b*
Metoprolol succinate, 451*t*
Metoprolol succinate/HCTZ, 451*t*
Metoprolol tartrate, 451*t*
Metoprolol tartrate/HCTZ, 451*t*
Metronidazole (Flagyl), 2115
for amebiasis, 2150*t*
for amebic liver abscess, 1025*b*
for *Clostridioides difficile*, 1925*b*
dosage of, 1895*t*
for giardiasis, 2145*b*
for intestinal amebiasis, 2112*t*
for intestinal protozoa, 2112*t*
mechanism of action, 1895*t*
toxicities of, 1901*t*
for trichomoniasis, 2154*b*
for urethritis, 1880*t*
METs. *See* Metabolic equivalents
Metyrapone, for Cushing syndrome, 1524*b*
Mevalonate kinase deficiency (MKD), 1731*t*, 1733
Mevalonic acid, 1734
Mevalonic aciduria, 1403*t*
Mexate. *See* Methotrexate
Mexiletine
for amyotrophic lateral sclerosis, 2563*b*
for erythromelalgia, 471*b*
MHC. *See* Major histocompatibility complex
MHC class I-related chain A (MICA), 205
MI. *See* Myocardial infarction
MIC. *See* Minimal inhibitory concentration
Micafungin, 2078
adverse effects of, 2078
drug interactions of, 2078
formulations and pharmacology of, 2078
indications and dosage of, 2075*t*, 2078
Micelle formation, impaired, 933
Micro breakpoint cluster region (μ-bcr), 1273
Microalbuminuria, 722
Microangiopathic hemolytic anemia
hemolytic-uremic syndrome causing, 1178
in thrombotic thrombocytopenic purpura, 1177
Microbial disease, 1833–1836
Microbial prophylaxis, for disseminated gonococcal infection, 1950
Microbial sequencing, 167
Microbiome, human, 1836
alteration of, 1837, 1838*f*, 1838*t*
definition of, 1836
in developing precision medicine paradigm, 1840.*e2f*
disease associations of, 1838
asthma, 1840
C. difficile infection, 1839, 1840.*e1f*
colon cancer, 1840
hematopoietic stem cell transplantation, 1840
inflammatory bowel disease, 1838
neurologic disorders, 1840
obesity, 1838, 1839*f*
environmental/iatrogenic factors of, 1838*t*
establishment of, 1837, 1837*f*, 1837.*e1f*
host factors of, 1838*t*
maternal factors of, 1837.*e1f*
microbial factors of, 1838*t*
postnatal factors of, 1837.*e1f*
potential function of, 1838*f*
Microbiome, human *(Continued)*
structure and function relationships of, 1836
studying of, 1837, 1837.*e1f*
therapies targeting, 1840, 1840*t*
Microconidia, inhalation of, 2082
Microcyte, 1067*f*
Microcytic anemia, 1079
peripheral blood smear of, 1068
β_2-Microglobulin, *e1t–e8t*
Micronodular abscesses, with minimal capsular formation, 2073
Micronutrients, 1451
depletion of, malnutrition and, 1447*t*
dietary requirements for, 1451
medications, 1452, 1460*t*
older adults, 1452
pathophysiologic, 1452–1459
pharmacologic, 1452
toxins, 1459
women of childbearing age, 1452
function of, 1451–1452, 1453*t*
optimal intake of, 1451, 1452*t*
trace elements, 1451
types of, 1451
Micropenis, 1570*t*
MicroRNa (miRNA) inhibitors, 177
MicroRNa (miRNA) mimics, 177
Microsatellite instability, 1377
Microscopic colitis, 940
Microscopic polyangiitis, 520.*e2f*, 1797, 1797*b*
Microsomal transfer protein, 1405
Microsporidia, 1026*t*, 2156, 2156*b*, 2156*t*
Microtophi, 1811
Microvesicular steatosis, 1031, 1031*t*
Mid-esophageal diverticula, 909
Midazolam, for anesthesia, 2670
Midbrain stroke syndromes, 2465.*e1f*
Middle adolescence, 110
Middle cerebral artery
anatomy of, 2457, 2459*f*, 2460*f*
occlusion of, 2465
Middle East, HIV/AIDS in, 2289, 2289.*e1f*
Middle East respiratory syndrome (MERS), 2207–2209
clinical manifestations of, 2208
diagnosis of, 2208
epidemiology of, 2207*t*, 2208
pathobiology of, 2208
prevention of, 2208–2209
prognosis of, 2209
treatment for, 2208*b*
Middle mediastinum, 527
Midline cleft syndromes, 1478
Midline (lethal) granuloma, 2621*t*
Midodrine, for orthostatic hypotension, 2559*t*
Midostaurin (Rydapt), 1215*t*
Mifepristone, 1524*b*, 1610, 1617
Miglustat, for Niemann-Pick disease type C, 1423
Migraine headaches, 2378, 2464
clinical manifestations of, 2378
definition of, 2378–2380
description of, 2599, 2645
diagnosis of, 2377*t*, 2378, 2379*f*
differential diagnosis of, 2377*t*
pathobiology of, 2378
prevention of, 2379–2380
prognosis for, 2380
treatment of, 2378*b*, 2378*t*
Migrating motor complex, 887, 887.*e3f*
Mild hypothermia, 681*t*
Miliaria rubra, 679
Miliary tuberculosis, 2035, 2037*f*
Military service, history of, 29*t*
Millard-Gubler syndrome, 2465.*e1f*
Millennials, 114
Miller-Fisher syndrome, 2571
Millipedes, 711
Milnacipran, for fibromyalgia, 1819*b*
Milrinone, 667*b*
for shock, 664*t*
Miltefosine, 2116
for amoebic encephalitis, 2112*t*
for leishmaniasis, 2112*t*
for visceral leishmaniasis, 2132*b*
Milwaukee shoulder, 1815
Minamata disease, 103
Mind and body practices, 154–155
Mindfulness-based cognitive therapy, 154
Mineral supplementation, 56

Copyrighted material

Mineral supplements, 155
Mineral toxicity, 2541*t*
Mineralocorticoid receptor antagonists (MRAS)
  clinical benefits of, 265*b*
  mechanism of action, 265*b*
  practical use of, 265*b*, 270*t*
Mineralocorticoids
  deficiency of, 1529
  excess of, 1524
    algorithm for, 1525*f*
    causes of, 1525*t*
    clinical manifestations of, 1525
    description of, 749, 749*t*
    diagnosis of, 1525–1526
    differential diagnosis of, 1525–1526
    epidemiology of, 1524
    pathobiology of, 1525
    treatment of, 1526*b*
Mini-Cog test, 117, 2331*t*
Mini Nutritional Assessment - Short Form score, 1447
Minimal change disease, 777, 778*b*, 778*f*
Minimal inhibitory concentration (MIC), 1892, 1892*f*
Minimally conscious state, 2437*t*, 2441–2442, 2442*b*, 2442*t*
Minimally invasive adenocarcinoma, 1329
Minimally symptomatic patients, 541*b*
Minocycline
  dosage of, 1895*t*
  for rheumatoid arthritis, 1755*b*, 1756*t*
Minor histocompatibility antigens, 205
Minoxidil, 451*t*
Minute ventilation, 640
Mirabegron, 824*t*
Mirtazapine, 2340*t*, 2452*t*, 2696*b*
Misoprostol, 1610, 1617, 1756*t*
Mites
  description of, 710
  as vectors of zoonotic disease, 2064
Mitochondrial DNA depletion syndromes, 2586
Mitochondrial encephalomyopathy with lactic acidosis and strokelike episodes (MELAS), 2586
Mitochondrial myopathies, 2583.*e2t*
Mitochondrial oxidative phosphorylation disorders, 2586
Mitogen activated protein kinase pathway (MAPK), 1390
Mitoxantrone (Novantrone), for multiple sclerosis, 2505*t*
Mitral regurgitation, 240
  acute, severe, 406
  asymptomatic
    chronic, 407*b*
    with left ventricular dysfunction, 407*b*
    with normal left ventricular function, 407*b*
  chronic symptomatic, 407*b*
  echocardiography in, 407, 407*f*
  functional (secondary), 409
  pathophysiology of, 406, 406*f*
  primary (organic)
    clinical manifestations of, 407
    diagnosis of, 407
    epidemiology of, 406
    medical therapy for, 407*b*
    pathobiology of, 406–407
    surgical therapy for, 407*b*
  secondary (functional), 409
    clinical manifestations of, 409
    definition of, 409
    diagnosis of, 409
    epidemiology of, 409
    pathobiology of, 409
    prognosis of, 409*b*
    treatment of, 409*b*
  treatment of, 265*b*
Mitral stenosis, 404–405, 404.*e1f*
  clinical manifestations of, 404–405
  diagnosis of, 405, 405*f*
  epidemiology of, 404
  evaluation of, 239–240
  invasive evaluation of, 405
  mechanical therapy for, 405*b*
  medical therapy for, 405*b*
  pathobiology of, 404
  physical examination of, 404–405
Mitral valve, 224
Mitral valve prolapse, 408–409
  definition of, 408
  diagnosis of, 408–409
Mitral valve prolapse *(Continued)*
  history in, 408
  noninvasive evaluation of, 408–409
  physical examination of, 408
  prognosis for, 409
  treatment of, 409*b*
Mitral valve regurgitation, 1918
Mitral valve repair, 245*f*, 407*b*, 408*f*
Mitral valve replacement, transcatheter, 407*b*
Mixed connective tissue disease (MCTD), 581, 1782, 1782*b*
Mixed cryoglobulinemia, 789, 1716
Mixed cryoglobulins, 1798
Mixed disorder, 533
Mixed gonadal dysgenesis, 1574, 1594
Mixed incontinence, 829
Mixed-meal test, for hypoglycemia, 1557, 1557*t*
Mixed neuroendocrine-non-neuroendocrine neoplasms, 1567
Mixed pain, 134–135, 135*t*
Mixed sclerosing bone dystrophy, 1668
MKD. *See* Mevalonate kinase deficiency
MMR vaccine. *See* Measles-mumps-rubella
Mobile cardiac outpatient telemetry, 307
Mobility, geriatric assessment of, 117
Mobitz type I AV block (Wenckebach block), 306, 320
Modafinil, 2446*b*, 2449*t*
Model for End-stage Liver Disease (MELD) score, 1032*b*, 1197, 2666
Moderate aplastic anemia, 1125
Moderate drinking, 2353
Moderate hypothermia, 681*t*
Moderna COVID-19 vaccine, 77, 2218*t*, 2219
Modified acid-fast staining, for enteric infection, 1870*t*
Modified Ann Arbor staging system, 1291, 1291*t*
Modified barium swallow, 868
Modified Bruce protocol, 212*t*
Modified Fisher CT rating scale, 2478*t*
Modified Harris-Benedict equation, 703.*e1t*
Modified smallpox, 2237, 2237*t*
MODY. *See* Maturity-onset diabetes of the young
Moexipril, 451*t*
Moexipril/HCTZ, 451*t*
Mogamulizumab, for adult T-cell leukemia/lymphoma, 2326*b*
Mohs surgery
  for skin cancers, 2701
  for squamous cell skin cancer, 1396*b*
Moisturizers, 2700
Molds, 87
Molecular detection methods, for *Bartonella* infection, 2002
Molecular imaging, 1717
Molecular technologies, 165–169
  continuum from health to disease, 165–166, 166*f*, 166*t*
  expressed genome in, 168
  genomes, disease, and treatment, 166–168
  precision medicine, 168–169, 168*t*
Molecular testing, for cancer, 1214
Molecular tumor profiling, site-specific therapy directed by, 1241*b*
Moles, characteristics of, 1392*t*
Mollaret meningitis, 2524
Molluscipoxvirus, epidemiology of, 2237
Molluscum contagiosum, 1882, 2242, 2712, 2713*f*, 2729, 2731*f*
  clinical manifestations of, 2239
  diagnosis of, 2239
  epidemiology of, 2237
  organisms causing, 1879*t*
  prevention of, 2240*b*
  treatment of, 2240*b*
Mollusks, venomous, 712–713
Molnupiravir
  for coronavirus infections, 2190
  for COVID-19, 2216
Molybdenum, 1457*t*
Mometasone, 553*t*
Monge disease, 592
Monkeypox, 2236, 2238, 2239*f*
Monoamine oxidase inhibitors (MAOIs)
  anesthesia and, 2669
  central nervous system effects of, 685*t*
  for depression, 2340*t*
Monoarthritis, 1710
  joint fluid analysis for, 1713
Monobactams, dosage of, 1895*t*
Monoblasts, 1073
Monoclonal antibodies, 150, 150*t*
  anti-SARS-CoV-2, 2216, 2216*f*, 2219
  anti-spike, for SARS-CoV-2, 153
  for asthma, 541*b*
  for COVID-19, 2217
  reactions to, 1698
  therapeutic targets engaged by, 152–153
Monoclonal B-cell lymphocytosis, in chronic lymphocytic leukemia, 1268
Monoclonal gammopathy, 727
Monoclonal gammopathy of renal significance, 788
Monoclonal gammopathy of undetermined significance (MGUS), 1295–1297, 2574–2575
  clinical manifestations of, 1295
  definition of, 1295–1297, 1296*t*
  diagnosis of, 2575
  diseases associated with, 1296
  epidemiology of, 1295, 1295.*e2f*, 1295.*e2t*, 2574
  multiple myeloma *versus*, 1295
  pathobiology of, 1295, 2575
  prevalence of, 1295.*e2t*
  prognosis of, 1297
  smoldering multiple myeloma *versus*, 1295
  treatment of, 1297*b*, 1297*f*, 1297*t*, 2575*b*
Monoclonal proteins
  identification of, 1294–1295, 1295*f*, 1295.*e1f*
  polyclonal immunoglobulin *versus*, 1295, 1295*f*
  serum protein electrophoresis of, 1294, 1295*f*
Monocytes, 182
Monocytopenia, 1148
Monocytosis, 1142, 1143*t*
Monogenic defects, 1684–1685
Monogenic disorders, 158
  high-penetrance, 158
  inborn errors of metabolism as, 1399
  versions of common disorders, 159
Monomethylfumarate (Bafiertam), for multiple sclerosis, 2505*t*
Monomorphic ventricular tachycardia, in myocardial infarction, 334*f*
Mononeuritis multiplex, 2313, 2567, 2567*t*, 2573
Mononucleosis, 2650
Monosodium urate monohydrate crystals, 1811
Monosomy X, 164
Monosulfiram, for scabies, 711*b*
Monotherapy, for hepatocellular carcinoma, 1360*b*
Monoxide, carbon, 595, 596*b*
Montreal classification, of gastroesophageal reflux disease, 903*f*
Montreal Cognitive Assessment, 2332*f*
Mood, geriatric assessment of, 117
Mood disorders, 257, 2337
  bipolar disorder, 2341, 2341*b*, 2341*t*
  major depressive disorder, 2337
  menopause associated with, 1630, 1630*b*
Mood stabilizers, 2679
Mooren ulcer, 2611
Moraxella catarrhalis, 1954–1955
  clinical manifestations of, 1955
  definition of, 1954
  epidemiology of, 1954–1955
  infections, 1954
  pathobiology of, 1954
  as pathogen, 1954, 1954*t*
  prognosis of, 1955
  sites of colonization of, 1954*t*
  treatment of, 1955*b*
Moraxella lacunata, 1954*t*, 1955
Morbidity
  causes of, in women's health, 1609–1610
  changes in, 23
  of older adults, 114–115
Morbilliform eruptions, 1857, 2712, 2712*t*, 2713*f*
Morning stiffness, 1751
Morphea, 1782, 2737, 2738*f*
Morphine, e10*t*–e11*t*, 139*t*. *See also* Opioids
Morphine sulfate, for left ventricular dysfunction, 384*b*
Morquio syndrome, 1724*t*
Mortality
  causes of, in women's health, 1606–1609
  changes in, 23
  of older adults, 114*t*, 115, 115*f*
  socioeconomic disparities in, 18
Morton neuroma, 1748, 1748*b*, 1749*f*
Mosaicism, 162, 163*f*
Mosquito-borne viruses, 2266
Mosquito protection, 1889
Motility
  colonic, 887
  defects of, 1683, 1683.*e1t*
  gastric, 887
  of irritable bowel syndrome, 893
  small bowel, 887, 888*f*
Motion sickness, 2644
Motivational enhancement therapy, for drug use disorders, 2361*b*
Motivational incentive, for drug use disorders, 2361*b*
Motor examination, in coma, 2439
Motor neuron diseases, 1238*t*, 2561–2566
  amyotrophic lateral sclerosis. *See* Amyotrophic lateral sclerosis
  classification of, 2562*t*
  definition of, 2561
Motor unit, 2580
Mounier-Kuhn syndrome, 560
Mountain sickness
  acute, 592, 592*t*
  chronic, 592, 592*t*
Mouse spiders, envenomation of, 710
Mouth, examination of, 29
Movement disorders, 2489–2498
  akathisia, 2495
  cerebellar ataxia, 2497, 2497*b*, 2497*t*
  clinical manifestations of, 2489
  definition of, 2489
  diagnostic approach to, 2489
  hyperkinetic, 2489, 2489*t*
  hypokinetic, 2489
  neuroleptic malignant syndrome, 2496
  painful legs and moving toes, 2496
  spastic paraplegias, 2498*b*, 2498*t*
  tardive dyskinesia, 2496, 2496*b*
Moxidectin, for helminthic diseases, 2112*t*, 2117
Moxifloxacin
  for bacterial meningitis, 2518*t*
  dosage of, 1895*t*
  for eye infection, 2605*t*
  for *H. influenzae* infections, 1954*b*
  for *Moraxella catarrhalis* infections, 1955*b*
  for nontuberculous mycobacterial disease, 2046*t*
  for plague, 98*b*, 1991*b*, 1992*t*
  for pneumonia, 613*t*, 616*t*
  for *Streptococcus pneumoniae* pulmonary infections, 1912*b*
Moyamoya disease, 2470.*e1t*
Mozambique cyclones, climate-related hazards, 91*t*
MPO-ANCA, 1716
MRA. *See* Magnetic resonance angiography
MRAS. *See* Mineralocorticoid receptor antagonists
MRCP. *See* Magnetic resonance cholangiopancreatography
MRI. *See* Magnetic resonance imaging
MRKH. *See* Mayer-Rokitansky-Küster-Hauser
mRNA anti-tumor vaccines, 177
MRS. *See* Magnetic resonance spectroscopy
MRSA. *See* Methicillin-resistant *Staphylococcus aureus*
MTHFR. *See* 5,10-methylenetetrahydrofolate reductase
mTOR. *See* Mammalian target of rapamycin
Mucin cysts, 2730
Mucinous cancer, 1346
Mucinous cystadenomas, 1355
Mucinous cystic neoplasms, 1356
Muckle-Wells syndrome (MWS), 1731*t*, 1733*t*
Mucoceles, 2625
Mucocutaneous candidiasis, 1560, 2090
Mucocutaneous lymph node syndrome. *See* Kawasaki disease
Mucoid impaction, 522
Mucolipidoses, 1419*t*, 1724, 1724*t*
Mucopolysaccharidoses, 1419*t*, 1420*t*, 1424, 1724, 1724*t*, 1725*b*
Mucorales fungi, 2098
Mucormycosis, 2098, 2695*f*
  adjunct treatments for, 2100*b*
  antifungal therapy for, 2100*b*
  clinical manifestations of, 2098
  clinical specimens of, 2099
  computed tomographic scan of, 520.*e1f*
  culture of, 2100
  definition of, 2098

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Mucormycosis *(Continued)*
diagnosis of, 2100*f*
disseminated, 2099
epidemiology of, 2098
gastrointestinal, 2099
histopathology of, 2099, 2100*f*
management of comorbidity of, 2100*b*
pathobiology of, 2098
prognosis of, 2101
pulmonary, 2099, 2100*f*
radiology of, 2099, 2100*f*
rare clinical presentations of, 2099
rhinocerebral, 2099
skin and soft tissue, 2099
surgery for, 2100*b*
treatment of, 2100*b*, 2101*f*, 2523
Mucosa, 901
Mucosa-associated lymphoid tissue (MALT) lymphoma, 1283, 1283*b*, 1284*t*, 1342
Mucosal disease, tests for, 931*t*
Mucosal leishmaniasis, 2116, 2133
Mucosal malabsorption, impairment of, 934–938
Mucosal melanomas, 1391
Mucosal telangiectasia, 880*f*
Mucositis, 2621–2622, 2695*f*
Mucous membrane pemphigoid, 911, 2621*t*, 2624, 2717–2718, 2718*b*, 2718*f*
Mucous membranes, 1769
Mucus retention cyst, 2631–2632
Muehrcke lines, 2753*f*
Muir-Torre syndrome, 1347
Müllerian ducts, anomaly of, 1594
Multibacillary leprosy, 2048, 2048*t*, 2048.*e1f*
Multicentric Castleman disease, 2316, 2316*b*
Multicentric reticulohistiocytosis, 1824, 2734
Multidrug hypersensitivity, 1695–1696
Multidrug resistance, mechanisms of, Enterobacterales and, 1965, 1966*t*
Multidrug-resistant bacteria, health care-associated infections and, 1864, 1864*t*
Multifactorial disorders, 159
Multifocal atrial tachycardia, 324, 324*b*, 326*f*
Multifocal motor neuropathy, 65*t*, 2564*t*, 2572–2573, 2573*b*
Multifocal patchy opacities, 520
Multifocal pulmonary opacities, chest radiograph of, 524*f*
Multilevel spinal cord and root compression, 2564*t*
Multimarker genomic tests, for disease diagnosis and prognosis, 168
Multimineral supplementation, 1460
Multimorbidity, of older adults, 114, 114*t*
Multinational Association for Supportive Care in Cancer (MASCC) Index, 1854*b*, 1855*t*
Multiple chemical sensitivities, occupational and environmental, 86*t*
Multiple comparisons, 37
Multiple endocrine neoplasia (MEN), 1530
pituitary adenomas and, 1487*t*
type 1 (MEN 1), 1250*t*, 1558, 1559*t*
type 2 (MEN 2), 1250*t*, 1558, 1559*t*
type 4 (MEN 4), 1558, 1559*t*
type 5 (MEN 5), 1558, 1559*t*
Multiple enzyme deficiency disorders, 1419*t*
Multiple erythema migrans skin lesions, 2024
Multiple gadolinium-enhanced brain lesions, caused by Nocardia infection, 2074*f*
Multiple myeloma, 1297–1302
allogeneic bone marrow transplantation for, 1299*b*
autologous stem cell transplantation for, 1299*b*, 1301*t*
clinical manifestations of, 1298
complications of, 1299*b*
cytogenetic abnormalities of, 1298
diagnosis of, 1298–1299
epidemiology of, 1298
hematopoietic cell transplantation for, 1209
history of, 1298
hypercalcemia associated with, 1299*b*
infections and, 1299*b*
laboratory findings of, 1298, 1298.*e1f*, 1299*f*
monoclonal gammopathy of undetermined significance *versus*, 1295
neurologic involvement, 1299
neuropathies associated with, 2574–2576
pathobiology of, 1298
physical examination of, 1298
prognosis for, 1298*t*, 1302
Multiple myeloma *(Continued)*
radiation therapy for, 1299*b*
radiologic findings of, 1299, 1299*f*
relapsed refractory, 1299*b*
renal insufficiency associated with, 1299*b*
renal involvement, 1299
skeletal lesions and, 1299*b*
smoldering
monoclonal gammopathy of undetermined significance *versus*, 1295
treatment of, 1299*b*, 1300*f*
treatment of, 1299*b*, 1300*f*
variant forms of, 1302–1303
Multiple nodules, as occupational lung disease, 585*t*
Multiple parenchymal cysticerci, 2159
Multiple pterygium, 2589*t*
Multiple sclerosis, 2411, 2498–2508, 2564*t*, 2652
acute progressive, 2501
ataxia in, 2501
behavioral symptoms of, 2501
bladder urgency in, 2504*b*
cerebrospinal fluid in, examination of, 2503
clinical manifestations of, 2500–2501
cognitive symptoms of, 2501
corticosteroids for, 2504*b*
definition of, 2498–2508
diagnosis of, 2501–2504
diagnostic criteria for, 2502*t*
differential diagnosis of, 2504
disease-modifying treatments for, 2504*b*
epidemiology of, 2498–2499
evoked potential tests for, 2504
fatigue associated with, 2501
genetics of, 2499
incidence of, 2498–2499
magnetic resonance imaging of, 2501, 2502*f*, 2502*t*, 2503*f*
medications for, 2505*t*
motor symptoms of, 2501
optic neuritis caused by, 2615
optical coherence tomography for, 2504, 2504.*e1f*
organ dysfunction in, 2501
pathobiology of, 2499–2500
pathogenesis of, 2500
pathology of, 2499–2500
plaques associated with, 2499
in pregnancy, 2501
presenting symptoms of, 2499*t*–2500*t*, 2500, 2500*t*
prevention of, 2504*b*
primary progressive, 2501
prognosis for, 2508
relapsing-remitting, 2501
secondary progressive, 2501
sensory abnormalities of, 2500
sexual dysfunction in, 2504*b*
spasticity in, 2504*b*
systemic symptoms of, 2501
treatment of, 2504*b*
types of, 2501
vertigo caused by, 2646
visual effects of, 2500–2501
well-being in, 2504*b*
Multiple self-healing palmoplantar carcinoma, 1731*t*
Multiple sleep latency test, 2444
Multiple system atrophy (MSA), 2485*t*, 2558, 2652
Multislice CT scanners, S19
Multisystem inflammatory syndrome, with COVID-19, 2218
Multivariable statistics, 37
Multivitamin supplementation, 1460
Mumps, 2225–2227
aseptic meningitis caused by, 2521
clinical manifestations of, 2226, 2226*f*, 2226*t*
definition of, 2225–2227
description of, 1583
diagnosis of, 2226–2227
encephalitis caused by, 2535
epidemiology of, 2225–2226
immunization for, 66*t*, 76.*e1t*, 77*f*, 78*f*, 81
pathobiology of, 2226
pathogen of, 2225
prevention of, 2227
prognosis of, 2227
in travelers, 1889.*e1t*
treatment of, 2227*b*
Munchausen syndrome. *See* Factitious disorder
Mupirocin (Bactrian), for skin diseases, 2697, 2699
Mural thrombosis, 384*b*
Murine typhus, 2055*t*, 2058, 2059*b*
Murphy sign, 988
Murray Valley encephalitis virus, 2276*t*, 2283
Muscarinic antagonists, 551*b*
Muscle(s)
fiber structure of, 2580
glucocorticoids metabolism in, 145
strength testing of, 2581, 2582*t*
structure of, 2580.*e2f*
Muscle biopsy, for rhabdomyolysis, 716
Muscle cramps, 2581
Muscle diseases, 2580–2588
assessment of, 2583*t*
classification of, 2580*t*
clinical manifestations of, 2580–2581
definition of, 2580–2583
diagnosis of, 2581–2583
electromyography of, 2581
epidemiology of, 2580
genetic testing of, 2582
history-taking for, 2580–2581
inherited, 2583
muscle biopsy of, 2582–2583
physical examination of, 2581, 2582*f*
Muscle-invasive tumors, of bladder, treatment of, 1366*b*
Muscle pain, 2370–2371, 2580–2581
Muscle strengthening, 61
Muscle stretch reflexes, 2370
Muscle symptoms, statins and, 1412, 1412*t*
Muscle tension dysphonia, 2652
Muscle wasting, 2587
Muscular dystrophies, 2583–2584
Becker, 2584, 2584*b*
congenital, 2585
Duchenne, 2583, 2583*b*, 2583.*e1f*
Emery-Dreifuss, 2584
facioscapulohumeral, 2584, 2584*b*
limb-girdle, 2584
oculopharyngeal, 2585
types of, 2583.*e1t*
Muscular rings, 910
Musculoskeletal conditions
chest pain, 211*t*
fever and, 1849
Musculoskeletal disorders, occupational and environmental, 86–87, 86*t*
Musculoskeletal injuries
in intimate partner violence, 1633
occupational, 86*t*
Musculoskeletal system
age-related changes in, 122
examination of, 31
systemic lupus erythematosus manifestations of, 1769
systemic sclerosis complications of, 1779
Mustard or Senning repair, exercise recommendations for, 355.*e2t*
Mutation, 162–164
MUTYH-associated polyposis, 1347*t*, 1348
MVV. *See* Maximal voluntary ventilation
MWS. *See* Muckle-Wells syndrome
Myasthenia gravis, 2589–2591, 2589*t*, 2652
clinical manifestations of, 2590, 2590*f*
complement system and, 201*t*
diagnosis of, 2590
pathobiology of, 2589–2590, 2589.*e1f*
prognosis of, 2591
treatment for, 2590*b*
Mycetoma, 2108
clinical manifestations of, 2110, 2110*f*
diagnosis of, 2110
differential diagnosis of, 2110
epidemiology of, 2108
intracavitary, 607
pathobiology of, 2109
predominant agents of, 2109.*e1f*
prevention of, 2111
prognosis for, 2111
treatment of, 2111*b*
Mycobacterial infections, 1686*t*, 2651, 2741
Mycobacterium abscessus, 2044, 2044*t*
Mycobacterium africanum, 2031
Mycobacterium avium, 2044, 2044*t*
Mycobacterium avium complex, 2307, 2309*t*
Mycobacterium bovis, 2031
Mycobacterium canettii, 2031
Mycobacterium caprae, 2031
Mycobacterium celatum, 2044*t*
Mycobacterium chelonae, 2044*t*, 2741
Mycobacterium fortuitum, 2044*t*, 2045
Mycobacterium genavense, 2044, 2044*t*
Mycobacterium gordonae, 2044*t*
Mycobacterium haemophilum, 2044*t*
Mycobacterium kansasii, 2044*t*, 2045
Mycobacterium leprae, 2047, 2651. *See also* Leprosy
Mycobacterium malmoense, 2044*t*
Mycobacterium marinum, 1861*f*, 2044*t*
Mycobacterium marinum, infections with, 2741
Mycobacterium massiliense, 2044
Mycobacterium microti, 2031
Mycobacterium neoaurum, 2044*t*
Mycobacterium pinnipedii, 2031
Mycobacterium scrofulaceum, 2044*t*
Mycobacterium simiae, 2044*t*
Mycobacterium smegmatis, 2044*t*
Mycobacterium szulgai, 2044*t*
Mycobacterium terrae, 2044*t*
Mycobacterium tuberculosis, 1145, 2031. *See also* Tuberculosis
intestinal ulcers associated with, 956
prophylaxis for, 2309*t*
pulmonary infection caused by, 1855
septic bursitis caused by, 1804
tuberculosis caused by, 2306
Mycobacterium ulcerans, 2044*t*
Mycobacterium xenopi, 2044*t*
Mycophenolate, e10*t*–e11*t*
Mycophenolate mofetil, 147
for liver transplantation, 1048*t*
for systemic lupus erythematosus, 1772*b*
for total knee arthroplasty, 1830.*e1t*
Mycophenolic acid, 147, 845, 845*t*
Mycoplasma arthritis, 1808
Mycoplasma fermentans, 2008, 2008*t*
Mycoplasma genitalium, 2008, 2008*b*, 2008*t*
Mycoplasma hominis, 1808, 2008, 2008*b*, 2008*t*
Mycoplasma orale, 2008*t*
Mycoplasma pneumoniae, 2005–2008, 2649
cardiovascular complications of, 2007
clinical manifestations of, 2005–2007
definition of, 2005
dermatologic involvement of, 2006–2007, 2007*f*
diagnosis of, 2007
epidemiology of, 2005
extrapulmonary involvement of, 2006–2007
hematologic complications of, 2007
musculoskeletal complications of, 2007
neurologic complications of, 2007
pathobiology of, 2005, 2006*f*
prevention of, 2008
prognosis of, 2008
renal complications of, 2007
as respiratory infection, 2005–2006, 2006*f*
treatment of, 2007*b*
Mycoplasma salivarium, 2008, 2008*t*
Mycoses, endemic, 2080
blastomycosis as, 2080
coccidioidomycosis as, 2083, 2085*f*
histoplasmosis as, 2081
paracoccidioidomycosis as, 2086
sporotrichosis as, 2085
Mycosis fungoides, 1286, 1286*b*, 2686.*e1f*, 2709–2710, 2710*f*, 2710*t*, 2734
Mycotic aneurysms, 2478, 2530
Mydriasis, 684*f*
Mydriatic drugs, 2617
Myelin, diseases of, 2499*t*, 2508–2510
Myelin-associated glycoprotein, 2568
Myeloblastomas, 1262
Myeloblasts, 1073, 1140*f*
Myelocele, 2545, 2545*f*
Myelocyte, 1140*f*
Myelodysplastic syndromes, 1072*t*, 1252–1259, 1259
clinical manifestations of, 1253
definition of, 1252–1258
diagnosis of, 1253–1256
diagnostic criteria for, 1255
differential diagnosis of, 1255–1256
epidemiology of, 1252–1253
gene mutations associated with, 1254*t*
hematopoietic cell transplantation for, 1209

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Myelodysplastic syndromes *(Continued)*
International Prognostic Scoring System for, 1258*f*
pathobiology of, 1253, 1255*f*
prevention of, 1259
prognosis of, 1257–1258
treatment of, 1255, 1257*f*
variants of, 1255–1256, 1256*t*
Myelofibrosis, primary, 1130, 1130*t*
allogeneic hematopoietic stem cell transplantation for, 1135*b*
clinical manifestations of, 1133–1134
definition of, 1130, 1130*t*
diagnostic criteria for, 1134–1135, 1134*t*
Dynamic International Prognostic Scoring System-Plus for, 1137*f*, 1139
epidemiology of, 1130
extramedullary hematopoiesis in, 1133
pathobiology of, 1130, 1131*f*
peripheral blood smear of, 1134–1135
in pregnancy, 1135*b*
prognosis for, 1138–1139
ruxolitinib for, 1135*b*, 1138*f*
splenomegaly in, 1134
survival in, 1139, 1139*f*
treatment of, 1135*b*, 1136*t*
Myeloid dendritic cells, 182–183
Myeloid hypereosinophilic syndrome, 1162, 1163*t*
Myeloid maturation, in bone marrow, 1140*f*
Myeloid sarcomas, 1262
Myelokathexis, neutropenia of, 1145
Myeloma defining events, 1300*f*
Myelomeningocele, 2545, 2545*f*, 2546*b*
Myelopathy
causes of, 2403*t*
in HIV/AIDS, 2313, 2313*b*
infectious, 2406, 2406*b*
inflammatory, 2406, 2406*b*
metabolic, 2406, 2406*b*
necrotizing, 1238*t*
vascular, 2405, 2406*b*
Myelophthisis, 1141
Myeloproliferative neoplasms, 480, 480*b*, 1130
genotype-phenotype correlations, 1131
hematopoietic cell transplantation for, 1209
molecular abnormalities in, 1131, 1132*t*
neutrophilia and, 1142
risk factors of, 1130
Myelosuppression, for chronic myeloid leukemia, 1274*b*
Myenteric plexus, 888
MYH-associated polyposis, 1250*t*
Myiasis, cutaneous or mucocutaneous, in travelers, 1889.*e1t*
Myocardial biopsy, 261
Myocardial contractility, 226
Myocardial contusion, 700*b*
Myocardial depression, 287–288
Myocardial disease, 279–295, 280*t*, 281.*e3f*
Myocardial infarction (MI), 211*t*
acute
acute hospital phase, 384*b*
antiplatelet therapy for, 507
causes of, 381*t*
clinical manifestations of, 334
coronary angioplasty for, 397*f*
definition of, 380
diagnosis of, 381
early acute phase, 382
electrocardiography in, 382, 382*f*
evolved acute phase, 382
hemodynamic subsets of, 389*t*
key echocardiographic findings, 242*t*
pathobiology of, 380
physical examination in, 381
in presence of bundle branch block, 383
ST-elevation, 380
chronic phase, 383
complications of, 380, 384*b*
differential diagnosis of, 424*t*
discharge medication checklist after, 391*t*
epidemiology of, 380
left circumflex patterns, 383
monomorphic ventricular tachycardia in, 334*f*
neutrophilia and, 1141
non-ST-elevation, 380
nonfatal, 221.*e1f*
oral contraceptives and, 1614–1615
pathobiology of, 380–381
post-myocardial infarction pericarditis, 426*t*
post-myocardial infarction ventricular tachycardia, 336
Myocardial infarction (MI) *(Continued)*
postoperative, 2673*t*
risk stratification after, 384*b*
true posterior, 383
universal definition of, 374*t*
Myocardial ischemia, differential diagnosis of, 424*t*
Myocardial necrosis
pathobiology of, 380
serum cardiac biomarkers of, 383
Myocardial perfusion imaging, 248, 248*f*
clinical applications of, 248–249
determination of, 249
imaging agents for, 248
SPECT, 248–249
Myocardial revascularization, 364*b*, 364*t*
Myocardial tumors, 296
Myocarditis
active, 284–285
borderline, 284
causes of, 284*t*
definition of, 284
enteroviral, 2257
epidemiology of, 284
giant cell, 286
immune-mediated, 286
pathobiology of, 284–285
patterns of, 284
persistent, 284
psychotropic medications and, 2678*t*
resolving or resolved, 284
toxoplasmosis, 286
treatment of, 286*b*
viral, 285–286
Myoclonic epilepsy with ragged-red fibers (MERRF), 2586
Myoclonic seizures, 2428*t*, 2430
Myoclonus, 2495, 2495.*e1t*, 2652
Myoclonus dystonia, 2493
Myofibrillar myopathies, 2584, 2584.*e1f*
Myofibrils, 2580
Myoglobinuria, rhabdomyolysis and, 716
Myokymia, 2501
Myonecrosis, *Streptococcus pyogenes* causing, 1915
Myopathies
centronuclear, 2585.*e1f*
classification of, 2580*t*
clinical findings of, 2581*t*
congenital, 2583.*e1t*, 2585
core, 2585.*e1f*
definition of, 2580
flow-volume curve of, 529*f*
in HIV/AIDS, 2313, 2313*b*
inclusion-body myositis, 2588*t*
inflammatory, 1787, 2587.*e1t*, 2588*t*
classification of, 1788*t*
clinical manifestations of, 1788
definition of, 1787
diagnosis of, 1788
diagnostic criteria for, 1790*t*
epidemiology of, 1787
pathobiology of, 1787
pathology of, 1789*f*
prognosis for, 1791
treatment of, 1790*b*, 1791*f*
metabolic, 2583.*e2t*, 2586
mitochondrial, 2583.*e2t*
myofibrillar, 2584, 2584.*e1f*
necrotizing autoimmune, 2588*t*
nemaline rod, 2585.*e1f*
pathobiology of, 2580
polymyositis, 2588*t*
prevalence of, 2580
steroid-induced, 2587
toxic, 2587, 2587*t*
Myopericarditis, 433
acute, 285*f*
enteroviruses causing, 2259, 2259*b*
Myopia, 2597–2598, 2597*f*
Myositis, 1849, 2260
Myotonia, 2581
Myotonic dystrophies, 2581, 2582*f*, 2584–2585, 2584*b*
Myotonic dystrophy, 1600, 2368.*e3f*
MyPlate, 60, 61*f*
Myxedema coma, hypothyroidism and, 1508*b*
Myxoma, 297
clinical manifestations of, 297–298
definition of, 297
diagnosis of, 298
epidemiology of, 297
treatment of, 298*b*

N

N-acetyl cysteine (NAC)
for acetaminophen overdose, 1019*b*
for acute poisoning, 693*t*
N-acetyl-p-benzoquinone imine (NAPQI), 1018
N-acetylation polymorphism, 132*t*
N-acetyltransferase (NAT2), 132*t*
NAATs. *See* Nucleic acid amplification tests
Nabilone, for nausea and vomiting, 863*t*
Nabumetone, for chronic pain, 138*t*
Nadolol, 451*t*
for torsades de pointes, 338*b*
Nadroparin, 503*t*
Naegleria fowleri, 2150, 2150*t*
Nafcillin
for bacterial meningitis, 2518*t*
dosage of, 1895*t*
NAFLD. *See* Nonalcoholic fatty liver disease
Nail
normal, 2751
pigmentation, 2754
toxicants and, 685
Nail disorders, 2751–2755
Beau lines, 2752, 2752*f*, 2752*t*
clubbing, 2752, 2752*f*
ingrowing toenails, 2754, 2755*f*
koilonychia, 2751, 2752*f*
leukonychia, 2752, 2753*f*
longitudinal grooves and striations, 2752
melanoma, 2755, 2755*f*
melanonychia, 2754, 2755*f*
nail pigmentation, 2754
onycholysis, 2753, 2754*f*
onychomadesis, 2752, 2752*f*, 2752*t*
onychomycosis, 2754, 2754*b*, 2754*f*
paronychia, 2753–2754
pitting, 2752, 2753*f*
splinter hemorrhages, 2753, 2753*t*
yellow nail syndrome, 2753, 2753*f*
Nail-patella syndrome, 787
Na^+,K^+-ATPase, 745–746, 746
Nalbuphine, 136*b*, 139*t*
Nalmefene, for alcohol-associated liver disease, 1032*b*
Naloxone, for acute poisoning, 693*t*
Naltrexone
for alcohol-associated liver disease, 1032*b*
for alcohol use disorders, 2357*b*, 2358*t*
for opioid use disorders, 2362*b*
for tobacco dependence, 2351*t*
NAPQI. *See* N-acetyl-p-benzoquinone imine
Naproxen
for chronic pain, 138*t*
for rheumatoid arthritis, 1756*t*
Naproxen sodium, for dysmenorrhea, 1596*t*
Naratriptan, 2380*t*
Narcissistic personality disorder, 2348*t*
Narcolepsy, 2371, 2445–2446, 2449*t*
Narcotic analgesics, for hemarthroses, 1188*b*
Narcotic overdose, in hypercapnic disease, 535*t*
Narrow-spectrum β-lactamases, 1966
Nasal and face mask oxygen, for acute respiratory failure, 647*b*
Nasal calcitonin, 1643*b*
Nasal congestion, treatment for, 2193*b*
Nasal obstruction, 2192
Nasal polyps, 2629, 2629*f*–2630*f*, 2630*f*, 2635, 2635*b*, 2635*f*
NASH. *See* Nonalcoholic steatohepatitis
Nasolacrimal duct, 2596
Nasopharyngeal carcinoma, 1322, 1327*b*, 1328, 2256
Nasopharynx, 1320, 1320*f*, 1942.*e1f*, 2648
Natalizumab (Tysabri)
definition of, 152
for inflammatory bowel disease, 945*b*, 946*t*
for multiple sclerosis, 2505*t*
Nateglinide, for type 2 diabetes mellitus, 1541*t*
National Academy of Medicine, 17
National Clinicians' Post-Exposure Prophylaxis Hotline, 2300
National Committee for Quality Assurance, 41
National Healthcare Safety Network, 1863
National Human Genome Research Institute's Undiagnosed Diseases Program, 167
National Institute of Occupational Safety and Health (NIOSH), 87
National Institutes of Health (NIH)
Chronic Prostatitis Symptom Index, 826*f*
Patient Reported Outcomes Measurement Information System, 41
National Quality Forum (NQF), 41, 41.*e1t*
National Surgical Quality Improvement, 2661
National Vaccine Injury Compensation Program, 76
Natriuretic medications, 737*t*
Natriuretic peptide levels, postoperative, 2676
Natural killer (NK) cells, 182, 204*t*, 205, 206.*e2f*
Natural products, 154
Naughton protocol, 212*t*
Nausea and vomiting, 861
abdominal pain and, 856
acute pancreatitis and, 969, 970
after anesthesia, 2671
in cancer, management of, 1232*b*
diagnosis of, 861–862, 863*f*
in enteral nutrition, 1449–1450
management of, approaches to, 13*t*
signs and symptoms of, approach to, 852*t*
treatment of, 862*b*, 863*t*
Navelbine. *See* Vinorelbine
Naxos disease, 288
NDM. *See* New Delhi metallo-β-lactamase
Near-drowning, 591
Near-faint dizziness, 2647*t*
Nebivolol, 267*t*, 451*t*
Necator americanus, 2169
Neck
examination of, 30
infection, 1939
mass, 1322–1323, 1323*f*
rheumatoid arthritis of, 1752, 1752*f*
Neck pain, 2393
ancillary testing for, 2397
clinical examination of, 2396
clinical manifestations of, 2395
computed tomography of, 2397
definition of, 2393
diagnosis of, 2396, 2396*f*
differential diagnosis of, 2397, 2397*t*
epidemiology of, 2393
history-taking for, 2396
medications for, 2398*b*
myocardial ischemia associated with, 2398
pathobiology of, 2395
surgery for, 2398*b*
treatment of, 2398*b*
Necrobiosis lipoidica, 2688*t*
Necrobiotic xanthogranuloma, 1158, 1158*b*
Necrolytic acral erythema, 2710, 2710*f*
Necrolytic migratory erythema, 1564, 1564*f*
Necrosis
in pancreatitis, 969
papillary, 728–729
Necrotizing autoimmune myopathy, 2588*t*
Necrotizing clostridial infection, 1926
botulism, 1927, 1928*b*
tetanus, 1928, 1929*b*, 1929*t*
Necrotizing fasciitis, 1847, 1903, 1915, 2740
Necrotizing myelopathy, 1238*t*
Necrotizing pulmonary aspergillosis, chronic, 2095
Necrotizing sialometaplasia, 2621*t*
Negative blood cultures
endocarditis with, 416
Negative concordance, 335
Negative predictive value, 38
Negative-pressure ventilators, 653
Negative selection, 204
Neisseria gonorrhoeae, 1946–1950, 2649. *See also* Gonorrhea
annual screening for, 112
cervicitis caused by, 1948, 1948*f*
clinical manifestations of, 1946–1947
definition of, 1946–1947
diagnosis of, 1947, 1947*f*
epidemiology of, 1946
keratitis caused by, 2606
pathobiology of, 1946
pelvic inflammatory disease due to, 1949, 1949*b*
pharyngitis caused by, 1948
in pregnancy, 1948
prevalence of, 112
proctitis caused by, 1948
septic arthritis caused by, 1807
sexually transmitted anorectal diseases and, 983
urethritis caused by, 1947, 1947*f*
Neisseria infections, 2741, 2741*f*
Neisseria lactamica, 1943

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Neisseria meningitidis, 1941–1946
bacteremia, 1847, 1891*t*
clinical manifestations of, 1943, 1943*f*
definition of, 1941–1946
description of, 1880
diagnosis of, 1943–1944
epidemiology of, 1941–1942, 1942*f*
pathobiology of, 1942–1943, 1942.*e*1*f*
prevention of, 1944
prognosis for, 1945
recurrent, 2518–2519
serogroups of, 1941
in sub-Saharan Africa, 1941
treatment of, 1944*b*, 1944*t*
Nelfinavir, 2301*t*
Nelson syndrome, 1495
Nemaline rod myopathy, 2585.*e*1*f*
Nematodes, 2169–2180
angiostrongyliasis, 2175
anisakiasis, 2173
ascariasis, 2169
baylisascariasis, 2174
Capillaria philippinensis, 2173
definition of, 2169
enterobiasis, 2172
gnathostomiasis, 2176
pathogen caused by, 2169, 2169*f*
prognosis for, 2170
strongyloidiasis, 2172–2173
tissue, 2173–2180
toxocariasis, 2174, 2174*b*, 2174*t*
treatment of, 2170*t*
trichinellosis, 2174–2175
Trichostrongylus, 2173
trichuriasis, 2171–2172
NEMO deleted exon 5 autoinflammatory syndrome (NDAS), 1731*t*
Neoadjuvant chemotherapy, for muscle-invasive bladder cancer, 1366*b*
Neoadjuvant therapy, for cancer, 1232*b*, 1234*t*
Neodymium:yttrium-aluminum-garnet, 2701
Neonatal alloimmune thrombocytopenia, 1179
Neonatal encephalitis, 2532*t*
Neonatal herpes simplex virus infection, 2247
Neonatal infection, cytomegalovirus and, 2251
Neonatal-onset multisystem inflammatory disease (NOMID), 1731*t*, 1733*t*
Neonatal onset pancytopenia, autoinflammation, rash, and hemophagocytic lymphohistiocytosis (NOCARH syndrome), 1731*t*
Neonatal tetanus, 1929
Neoplasms
distinguishing features of, 515*t*
esophagus, 1337
large intestine, 1345
pulmonary, 1329
small intestine, 1343
stomach, 1339–1343
Neoplastic disease, patients with, 1852–1853, 1853*t*
Neoplastic pericarditis, 424*t*
Neorickettsia sennetsu, 2060*t*
Neovascularization, 2608, 2609*f*
Nephrectomy, for autosomal dominant polycystic kidney disease, 812*b*
Nephritic syndrome, 780–784
clinical manifestations of, 781
complement levels in, 778*t*
diagnosis of, 781
epidemiology of, 780–781
mechanisms of, 782*f*
pathobiology of, 780
Nephritis
interstitial. *See* Interstitial nephritis
nephrotic syndrome *versus*, 777*t*
Nephrocalcinosis, 794, 803
Nephrogenic diabetes insipidus, 744, 816*t*
clinical manifestations of, 1501
diagnosis of, 1503
gestational, 1501
pathobiology of, 1500
treatment of, 1503*b*
Nephrogenic sclerosing dermopathy, 463
Nephrogenic syndrome of inappropriate antidiuresis, 739
Nephrogenic systemic fibrosis, 463, 1782, 2737, 2737*f*
Nephrolithiasis, 803–808
calcium stones, 803
clinical manifestations of, 804*f*, 805
cystine stones, 804
diagnosis of, 805, 805*f*
epidemiology of, 803–808
pathobiology of, 803–805
prevention of, 806–807, 807*f*
prognosis of, 808
struvite stones, 804
treatment of, 805*b*, 806*t*
uric acid stones, 804
Nephron, 729, 731*f*
Nephronophthisis, 809*t*, 813, 814*b*
Nephropathy
BK polyomavirus-associated, 2228, 2229*b*
HIV-associated, 2313
human immunodeficiency virus-associated, 789
immunoglobulin A, 781, 783*f*
membranous, 727, 779
clinical manifestations of, 780
diagnosis of, 780, 780*f*, 781*f*
prognosis for, 780
treatment of, 780*b*, 782*f*
in systemic sclerosis, 1781
Nephrosclerosis, hypertensive, 839
Nephrotic-range proteinuria, 792
Nephrotic syndromes, 726, 736, 776–780
causes of, 777*t*
clinical manifestations of, 777
definition of, 776–777
diagnosis of, 777
epidemiology of, 776–777
focal segmental glomerulosclerosis, 778, 779*b*, 779*f*, 779*t*
idiopathic, 777, 777*t*
membranous nephropathy, 779
minimal change disease, 777, 778*b*, 778*f*
nephritis *versus*, 777*t*
pathobiology of, 777
primary, 777
renal diseases associated with, 784*t*
salt retention in, 777
secondary, 777*t*
treatment of, 777*b*
volume retention in, 777
warfarin in, 777*b*
Nephrotoxicity, calcineurin inhibitor-induced, in renal transplantation, 847
Neprilysin, inhibition of, 265*b*
Neratinib (Nerlynx), 1215*t*, 1251*t*
Neridronate, for Paget disease, 1664*t*
Nerlynx. *See* Neratinib
Nernst equation, 299
Nerve biopsy, for peripheral neuropathy, 2567–2568
Nerve blocks, 136*b*, 975*t*
Nerve conduction study, 2375, 2375*t*, 2375.*e*1*f*
Nerve root disorders, 2401–2403, 2402*f*, 2403*b*
Nerve sheath tumors, 1319
Nervous system, alcohol use disorders and, 2355, 2355*t*
Nesiritide, intravenous, for heart failure, 265*b*
Netherlands, euthanasia and physician-assisted suicide in, 8
Netilmicin, dosage of, 1895*t*
NETs. *See* Neutrophil extracellular traps
Netupitant, for nausea and vomiting, 863*t*
Neupogen. *See* Filgrastim
Neural antigen targets, autoimmune encephalitis and, 2536*t*
Neural crest cell tumors, 2730, 2732*f*
Neural tube defects, 2545–2547
congenital, nutrition and, 60
folic acid supplementation for, 1452
Neuralgic amyotrophy, 2578
Neurally adjusted ventilatory assist, 653
Neuraxial anesthesia, 2671
Neuregulin 1, 260.*e*1*t*
Neuritis, leprosy and, 2050
Neuro-ophthalmology, 2614–2620
oculomotor control, 2617–2620, 2618.*e*1*t*
pupillary control, 2616–2617
vision, 2614–2616
Neurobrucellosis, 2515*b*, 2522
Neurocardiogenic syncope, 305–306, 309*b*
Neurocognitive disorders, 2312–2313, 2337*t*
Neurocutaneous disorders, 2549–2553, 2550*t*
Neurocutaneous melanosis, 2550*t*
Neurocysticercosis
description of, 2159
in travelers, 1889.*e*1*t*
Neurodegenerative disorders, 174
Neurodegenerative synucleinopathies, 2554, 2558
Neurodermatitis, 2687.*e*4*t*
Neuroendocrine neoplasms, 1347, 1561–1568
clinical manifestations of, 1562
definition of, 1561–1562
epidemiology of, 1561
of gastrointestinal tract and thorax, 1566
metastatic, principles for controlling growth of, 1568
molecular pathogenesis of, 1562
pancreatic, 1561*t*, 1562
pathobiology of, 1561–1562
pathology/classification of, 1561–1562
treatment of, 1241*b*, 1242*t*, 1562*b*
type 2, 1566
type 3, 1566
Neuroendocrine system, 1476–1481
central nervous system rhythms, 1478
disease of, 1478–1481
endogenous opioid peptides, 1478
feedback loops of, 1476
function of, 1478
hypophysiotropic hormones
corticotropin-releasing hormone, 1477
functions of, 1476
gonadotropin-releasing hormone, 1476
growth hormone-releasing hormone, 1477
prolactin inhibitory factor, 1477
prolactin-releasing factor, 1478
somatostatin, 1477
thyrotropin-releasing hormone, 1476, 1477*f*
regulation by, 1476–1478
Neuroendocrinology, 1476
Neurofibrillary tangles, 2414
Neurofibromas, 2730, 2732*f*
Neurofibromatosis, 583, 1530
stroke caused by, 2472
type 1, 1250*t*, 2550, 2550*t*, 2551*f*–2552*f*, 2552*f*
treatment for, 2550*b*, 2552*t*
type 2, 1250*t*, 2550*t*, 2551, 2552*f*
treatment for, 2551*b*
Neurogenic bladder, 828
Neurogenic tumors, 526
Neurokinin-1 receptor antagonists, for nausea and vomiting, 863*t*
Neuroleptic malignant syndrome, 678, 2496
characteristics of, 2682*t*
psychotropic medications and, 2681
treatment for, 2681*b*
Neuroleptics, for chronic prostatitis/chronic pelvic pain syndrome, 825*b*
Neurologic disease, 2368–2376
acute, diagnosis and treatment of, 2369
clinical manifestations of, 2368
complaints commonly caused by, 2370–2373
cognitive impairment, 2372
dizziness, 2371, 2372*f*
episodic weakness, 2371
fatigue, 2372
gait disorders, 2371, 2373*t*
head pain, 2371
intermittent weakness, 2371
memory loss, 2372
muscle pain, 2370
pain, 2371
sensory symptoms, 2371
spontaneous movements, 2370
weakness, 2371
cytomegalovirus and, 2252*b*
diagnosis of, 2368–2369
electroencephalography, 2374, 2375*t*
electromyography, 2375, 2375*t*
imaging, 2373–2374, 2373*t*
lumbar puncture, 2374, 2374*f*, 2374*t*
nerve conduction study, 2375, 2375*t*, 2375.*e*1*f*
repetitive stimulation study, 2375
history of, 2368–2369
human microbiome and, 1840
hyperfunctional, 2652
hypofunctional, 2652
neurologic examination for, 2369–2370
neurologic findings for, 2368.*e*5*f*
in sarcoidosis, 602, 602*t*
symptoms of, 2368
of throat, 2652, 2652*t*
Neurologic examination, 2369
Neurologic Lyme disease, 2026*b*
Neurologic paraneoplastic syndromes, 1238–1239, 1238*t*
Neurologic syndromes, 2222
Neurologic testing, 309
Neurologic toxicity, diphtheria and, 1934
Neurological syncope, 309*b*
Neurolytic blocks, in palliative care, 12
Neuromodulators, central brain-gut, for irritable bowel syndrome, 895*b*, 896*t*
Neuromuscular and balance exercises, for osteoarthritis, 1741*t*
Neuromuscular blockers
for anesthesia, 2670
reactions to, 1698*t*
Neuromuscular disorders, 620.*e*1*f*
in hypercapnic disease, 535*t*
preoperative, 2664–2665
Neuromuscular junction disease, 2581*t*
Neuromuscular transmission, disorders of, 2588–2593
definition of, 2588–2589, 2589*t*
drugs that worsen or induce, 2592*t*
epidemiology of, 2588
pathobiology of, 2588–2589, 2588.*e*2*f*
Neuromyelitis optica, 2508
Neuromyelitis optica spectrum disorder, 201*t*, 2560
Neuromyotonia, 1238*t*, 2591–2592
acquired, 2589*t*
clinical manifestations of, 2591–2592
definition and epidemiology of, 2591
description of, 2585–2586
diagnosis of, 2592
pathobiology of, 2591
prognosis of, 2592
treatment for, 2592*b*
Neuronal ceroid-lipofuscinoses, 1420*t*, 1424
Neuronal migration, disorders of, 2547, 2547*b*
Neuropathic arthropathy, 1822
Neuropathic pain, 134, 135*t*, 136, 1817*t*
Neuropathy
amyloidosis and, 1307
associated with monoclonal gammopathies, 2574
critical illness, 2578
herpes zoster-related, 2578
HIV-associated, 2577–2578
infectious, 2577
leprosy-associated, 2578
Lyme disease-associated, 2578
peripheral. *See* Peripheral neuropathy
thallium and, 106, 106*b*
toxic, 2578
Neurophysins, 1498, 1499*f*
Neuropsychiatric lupus, 1772
Neuropsychiatric syncope, 306
Neuroretinitis, cat-scratch disease and, 2001
Neurosarcoidosis, 602, 602*t*, 603*b*, 604*t*
Neurosyphilis, 1881, 2017, 2019, 2020*b*
Neurotoxic clostridial infections, 1927
Neurotoxic paralysis, 707, 709.*e*1*t*
Neurotoxic poisoning, in travelers, 1889.*e*1*t*
Neurotoxic shellfish poisoning, 713
Neurotoxins, 2589*t*, 2592–2593, 2592*t*
Neurovascular unit, 2461
Neutropenia, 1142–1148
afebrile, 1147*b*
after chemotherapy, 1147*b*
chemotherapy-induced, 1854*t*
chronic idiopathic, 1146
clinical manifestations and diagnosis of, 1146–1147, 1147*f*
congenital syndromes with, 1145
cyclic, 1144
cytotoxic therapy causing, 1065–1066
differential diagnosis of, 1144*t*
drug-induced, 1145, 1145*f*
due to increased margination and hypersplenism, 1146
due to nutritional deficiency, 1146, 1146*f*
epidemiology and pathobiology of, 1143–1148
febrile, 1855, 1968
fever in, 1854
immune, 1146
infection-related, 1145
management of, 1856*f*, 1857*f*
peripheral blood smear of, 1073

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Neutropenia *(Continued)*
primary causes of, 1143–1145
psychotropic medications and, 2678*t*
secondary causes of, 1145–1146
severe congenital, 1143–1144, 1144*t*
treatment of, 1147*b*
Neutropenic enterocolitis
description of, 1860, 1926
intestinal ulcers associated with, 956, 956.*e1f*
Neutrophil differentiation, defects of, 1683.*e1t*
Neutrophil elastase (ELANE), 1144
Neutrophil extracellular traps (NETs), 1811
Neutrophil gelatinase-associated lipocalin, 260.*e1t*
Neutrophil production system, 1065*f*
Neutrophilia, 1140–1142
chronic idiopathic, 1141
clinical manifestations and diagnosis of, 1142, 1143*f*
differential diagnosis of, 1140*t*
epidemiology and pathobiology of, 1140–1142
hereditary, 1141
primary causes of, 1141–1142
secondary causes of, 1140–1141
Neutrophilic drug reactions, 2728, 2728*f*
Neutrophils, 182–183
acute inflammation and, 191
hypersegmented, 1072*f*
increased, 533
normal, dynamics of, 1140, 1140*f*
Nevi, 2730
Nevirapine, 2301*t*, 2303
Nevus
benign, 1391*f*
characteristics of, 1392*t*
dermal, 1391*f*
dysplastic, 1390, 1391*f*, 1392*t*
Nevus anemicus, 2743
Nevus depigmentosus, 2743
New Delhi metallo-β-lactamase (NDM), 1966
New-onset diabetes, in renal transplantation, 847
Newborn screening, 166, 1404
Nexavar. *See* Sorafenib
Next-generation sequencing, 164–165
for hereditary spherocytosis, 1096
for inborn errors of metabolism, 1400
NF-kappa-B-related autoinflammatory syndromes, 1731*t*
NFAT. *See* Nuclear factor of activated T cells
Niacin, 1413, 1453*t*
for hypertriglyceridemia, 1414*b*
Nicardipine
for hypertensive emergencies, 460*t*
properties of, 367*t*
Nicardipine SR, 451*t*
Nickel, *e1t–e8t*, 88*t*
Niclosamide
for *Diphyllobothrium*, 2157*b*, 2158*t*
for helminthic diseases, 2118
Nicotine, *e10t–e11t*
addiction, complication of, 42
dopaminergic activity and, 2679
properties of, 142*t*
Nicotine adenine dinucleotidase, 1913
Nicotine gum, 2350*b*
Nicotine inhaler, 2350*b*, 2351*t*
Nicotine lozenge, 2350*b*, 2351*t*
Nicotine metabolite (Cotinine), *e10t–e11t*
Nicotine nasal spray, 2350*b*, 2351*t*
Nicotine replacement therapy, 1609
Nicotine vaccine, for tobacco dependence, 2351*t*
Niemann-Pick disease, 583
type C, 1420*t*, 1423
Nifedipine
for high-altitude diseases, 593*t*
for livedo reticularis, 470*b*
for preeclampsia, 1621*t*
properties of, 367*t*
for Raynaud phenomenon, 473*b*
Nifedipine LA, 451*t*
Nifurtimox
for African trypanosomiasis, 2112*t*, 2125*b*, 2125*t*
for Chagas disease, 2116, 2128*b*
Night blindness, 2500, 2599
Nightmares, 2453, 2453*t*
NIH. *See* National Institutes of Health
Nilotinib (Tasigna), 1215*t*, 1251*t*
for chronic myeloid leukemia, 1274*b*, 1275*t*
Ninlaro. *See* Ixazomib
NIOSH. *See* National Institute of Occupational Safety and Health
Nipah virus, 2065*t*
Nipple discharge, 1368
Niraparib (Zejula), 1215*t*, 1251*t*
Nirmatrelvir
boosted with ritonavir, for coronavirus infections, 2190
for COVID-19, 2216
Nisoldipine, 367*t*, 451*t*
Nitazoxanide, 2115
for amebiasis, 2150*t*
for amebic liver abscess, 1025*b*
for cryptosporidiosis, 2112*t*, 2143*b*
for giardiasis, 2112*t*, 2145*b*
for helminthic diseases, 2118
for infectious gastroenteritis, 2263*b*
for tapeworm infections, 2158*t*
Nitrates, 357, 368*t*
Nitrendipine, 367*t*
Nitric oxide, 1581
Nitrofurantoin
for complicated urinary tract infection, 1875*b*
for cystitis, 1875*b*, 1876*t*
dosage of, 1895*t*
for urinary tract infection, 1877*t*
Nitrogen, 88*t*
Nitrogen washout technique, 530
Nitroglycerin, 368*t*
for acute coronary syndrome, 374*t*
for acute STEMI, 384*b*, 391*t*
for hypertensive emergencies, 460*t*
Nitroimidazoles, for amebiasis, 2149*b*
Nitroprusside, for hypertensive emergencies, 460*t*
Nitrous oxide
for anesthesia, 2670
for homocystinuria, 1427
Nivolumab (Opdivo), 1215*t*, 1251*t*
for melanoma, 1394*t*
for renal cell carcinoma, 1364*b*
NK. *See* Natural killer
NKCC2. *See* Sodium-potassium-2 chloride cotransporter
NLR. *See* Nucleotide-binding oligomerization domain (NOD)-like receptor
NLRP3, 1734, 1735
NMDA-receptor, autoimmune encephalitis and, 2536
NNRTIs. *See* Non-nucleoside analogue reverse transcriptase inhibitors
No-reflow phenomenon, 2463
Nocardia spp., 1855, 2072
Nocardial meningitis, cerebrospinal fluid in, 2073
Nocardiosis, 2072–2074
central nervous system infection and, 2073
clinical manifestations of, 2073
cutaneous infection and, 2073
definition of, 2072–2074
diagnosis of, 2073–2074
bacteriology for, 2073
procedure, 2073
radiology for, 2073, 2073*f*, 2074*f*
epidemiology of, 2072–2073
pathobiology of, 2073
pathogen causing, 2072
prognosis of, 2074
pulmonary, 2073
treatment for, 2074*b*
NOCARH syndrome. *See* Neonatal onset pancytopenia, autoinflammation, rash, and hemophagocytic lymphohistiocytosis
Nociceptive pain, 134, 135*t*, 1817*t*
Nociplastic pain, 134, 135*t*, 1817*t*
Nocturia, autosomal dominant polycystic kidney disease, 811
Nocturnal dyspnea, paroxysmal, 256
Nocturnal hypoglycemia, 1546
Nocturnal hypoventilation, 619
NOD2/CARD15, 942
Nodal marginal zone B-cell lymphoma, 1286
Nodular gastritis, 913
Nodular lymphocyte-predominant Hodgkin lymphoma, 1289, 1290
Nodular melanoma, 1391, 1392*f*
Nodular pulmonary amyloidosis, 1310
Nodular sclerosing Hodgkin lymphoma, 1290, 1290*f*
Nodular vasculitis, 2735
Nodules, 2689*t*
of skin, 2729, 2729*t*
Noise
hazard, 88*t*
hearing loss caused by, 2642
Noise-induced hearing loss, 2642
Nolvadex. *See* Tamoxifen
Non-abscess hepatic bacterial infections, of liver, 1023
Non-AIDS-defining cancers, 2316, 2316*b*
Non-enterohemorrhagic *E. coli*, 1962*t*
Non-group A β–hemolytic streptococcal infections, causing acute pharyngitis, 2648
Non-Hispanic White Americans, 17
Non-Hodgkin lymphoma, 1150, 1278–1288, 2315
in adolescents, 111
in AIDS patients, 1287, 1287*b*
B-cell lymphomas
diffuse large, 1279, 1284, 1285*b*
mature, 1283
precursor, 1281, 1282*b*
primary mediastinal large, 1285
rare types of, 1286
Burkitt lymphoma, 1286, 1286*b*
clinical manifestations of, 1280, 1282*f*
definition of, 1278–1281
diagnosis of, 1280–1281, 1282*t*
diseases confused with, 1288
in elderly patient, 1288
environmental exposure causing, 1279
epidemiology of, 1278
factors associated with development of, 1279*t*
familial, 1278
follicular lymphoma, 1283, 1283*b*
gastric mucosa-associated lymphoid tissue lymphomas, 1283, 1283*b*, 1284*t*, 1285*b*
genetic factors, 1278–1279
hematopoietic cell transplantation for, 1209
immunologic abnormalities, 1278–1279, 1279*t*
infectious agents associated with, 1279
occupational exposure causing, 1279
pathobiology of, 1278–1280, 1279*t*
pathology of, 1279, 1279.*e1f*, 1280*t*
posttransplant, 1287, 1287*b*
in pregnancy, 1288, 1288*b*
prognostic systems for, 1281, 1283*t*
Sjögren syndrome and, 1785
staging of, 1281, 1282*t*
T-cell lymphomas, 1281, 1282*b*
treatment, 1281*b*
World Health Organization classification of, 1279–1280, 1281*t*–1282*t*, 1282*t*
Non-homologous end-joining, 178
Non-IgE-dependent agonists, anaphylaxis caused by, 1692
Non-insulin-dependent diabetes, 1534
Non-insulinoma pancreatogenous hypoglycemia syndrome, 1554
Non-ionizing radiation, 91, 95
clinical manifestations of, 95
pathobiology of, 95
prevention of, 95
FAR-UV radiation, 95
radiofrequency radiations, 95.*e1f*, 95
ultraviolet radiation, 95
Non-muscle-invasive disease, of bladder, treatment of, 1366*b*
Non-neoplastic polyps, 1348
Non-nucleoside analogue reverse transcriptase inhibitors (NNRTIs), 2300, 2304*t*
Non-replicating adenovirus vector vaccine, 66*t*
Non-small cell lung cancer (NSCLC), 1329
chemotherapy regimens in, 1334*t*
histologic markers in, 1329.*e2t*
treatment for, 1333*b*
Non-spore forming anaerobic bacteria, 1938
antimicrobial susceptibility patterns for, 1941*t*
bacteremia caused by, 1938
central nervous system infections caused by, 1938
clinical manifestations of, 1938
definition of, 1938, 1939*f*, 1939*t*
diagnosis of, 1940, 1940*t*
head infections caused by, 1939
intra-abdominal infections caused by, 1939
neck infections caused by, 1939
obstetric-gynecologic infections causing, 1939
osteomyelitis caused by, 1940
pathobiology of, 1938, 1938.*e3t*
pathogen that cause, 1938, 1938.*e3t*
prevention of, 1941
prognosis for, 1941
septic arthritis caused by, 1940
skin and soft tissue infections caused by, 1939
taxonomy of, 1938.*e3t*
treatment of, 1940*b*, 1940*t*, 1941*t*
Nonabdominal examination, for gastrointestinal disease, 851
Nonacute porphyrias, 1429–1430
Nonalcoholic fatty liver disease (NAFLD), 986, 1033–1034, 1358
alanine aminotransferase levels in, 999
clinical manifestations of, 1033, 1033*f*–1034*f*
definitions of, 1033
diagnosis of, 1033–1034, 1033*f*, 1034*f*
epidemiology of, 1033
pathobiology of, 1033
prevention of, 1034
prognosis of, 1034
risk factors of, 1031*t*
treatment for, 1034*b*
Nonalcoholic steatohepatitis (NASH), 1031, 1466
Nonallergic rhinitis with eosinophilia syndrome, 2630*f*–2632*f*, 2631
Nonarteritic ischemic optic neuropathy, 2611
Nonarticular pain syndromes
definition of, 1742*t*
diagnosis of, 1742
epidemiology of, 1742
by region, 1742*t*
sports medicine injuries, 1742, 1744*t*
treatment of, 1742*b*
Nonarticular rheumatism, 1742
Nonbacterial thrombotic endocarditis, 414
Noncarbonic acids, 753
Noncardiogenic interstitial pulmonary edema, bilateral, 2267
Noncaseating granulomas, 942
Noncatastrophic disability, 115
Noncognitive psychiatric syndrome, 2336
Nonconvulsive status epilepticus, ECG findings in, 2429, 2429*f*
Noncoronary sinus, 352
Nondihydropyridines, for hypertension, 451*t*, 453*t*
Nonexercise activity thermogenesis, 1465
Nonfermentative *Corynebacteria*, 1934
Nonfunctional pancreatic neuroendocrine neoplasms, 1565–1566, 1566*b*
Nonfunctional PPoma, 1561*t*
Nongonococcal septic arthritis, 1805
clinical manifestations of, 1805
diagnosis of, 1805–1806, 1806*f*
differential diagnosis of, 1806
epidemiology of, 1805
pathobiology of, 1805, 1805*t*
prevention of, 1807
prognosis of, 1807
treatment for, 1806*b*, 1807*t*
Nongonococcal urethritis, organisms causing, 1879*t*
Nonhematologic malignancy, neutrophilia and, 1141, 1141*f*
Noninfectious pericarditis, 424*t*
Noninfectious pharyngitis, 2651–2653
Noninfectious recombinant vaccine, 66*t*
Noninferiority trials, 37
Noninflammatory retiform purpura, 2715*t*, 2716
Noninvasive mechanical ventilation, 620.*e1f*
Noninvasive positive-pressure ventilation, 620*b*, 653–654
Nonischemic dilated cardiomyopathy, 265*b*, 336
Nonketotic hyperglycinemia, 1398*t*
Nonmaleficence, 5
Nonmalignant conditions, hematopoietic cell transplantation for, 1209
Nonmelanoma skin cancers, 1390–1396
basal cell skin cancer, 1395, 1395*f*, 1396*b*
squamous cell skin cancer, 1395, 1395*f*, 1396*b*
Nonmendelian inheritance, 162
Nonocclusive mesenteric ischemia, 962, 962*f*
Nonpalpable purpura, 2713–2714
Nonparoxysmal junctional tachycardia, 323*t*, 326
Nonpneumococcal streptococcal infections, 1913–1919
Streptococcus agalactiae, 1918, 1918*b*
Streptococcus anginosus, 1919, 1919*b*
Streptococcus canis, 1919
Streptococcus dysgalactiae subspecies *equisimilis*, 1919, 1919*b*
Streptococcus gallolyticus, 1919
Streptococcus iniae, 1919
Streptococcus milleri, 1919
Streptococcus pyogenes, 1913
acute infections, 1913–1917
acute rheumatic fever caused by, 1917, 1917*b*, 1917*t*
bacteremia caused by, 1915

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Nonpneumococcal streptococcal infections *(Continued)*
cell wall of, 1913
cellulitis caused by, 1915
clinical manifestations of, 1914–1916
definition of, 1913
deoxyribonucleases, 1913
diagnosis of, 1914
ecthyma caused by, 1914
epidemiology of, 1913
erysipelas caused by, 1915
fibronectin binding protein, 1913
fimbriae, 1913
hyaluronic acid capsule, 1913
hyaluronidase, 1913
impetigo caused by, 1914
lipoteichoic acid, 1913
M proteins, 1913
myonecrosis caused by, 1915
necrotizing fasciitis caused by, 1915
nicotine adenine dinucleotidase, 1913
pathobiology of, 1913–1914
pharyngitis caused by, 1914, 1914*f*, 1914*t*
pneumonia caused by, 1916
post-streptococcal glomerulonephritis caused by, 1918
prevention of, 1917
prognosis for, 1916*b*
puerperal sepsis caused by, 1915
pyrogenic exotoxins, 1914, 1914*f*
rheumatic heart disease caused by, 1917–1918
scarlet fever caused by, 1914
streptolysin O, 1913
streptolysin S, 1913
treatment of, 1916*b*
Nonproliferative benign breast lesions, 1374
Nonproliferative diabetic retinopathy (NPDR), 1549*t*
Nonreplicative persister, 1900
Nonsecretory myeloma, 1302
Nonseminomatous germ cell tumors, treatment of, 1383*b*
Nonspecialist, in management
in rare genetic disorders, 158
role of, 159
Nonspecific building-related illness, occupational and environmental, 86*t*
Nonspecific immunosuppression, for allograft rejection, 207
Nonspecific interstitial pneumonia, 577
diagnosis of, 577, 577*f*
prognosis for, 577*b*
radiographic features of, 574*t*
treatment of, 577*b*
Nonsteroidal anti-inflammatory drugs (NSAIDs), 1460*t*
for acute pancreatitis, 972*b*
anaphylaxis caused by, 1692
in blood pressure, 455
for dysmenorrhea, 1596*t*
for esophagitis, 907*t*
for fibromyalgia, 1819*b*
gastric ulcers associated with, 914
hyponatremia and, 739–740
inflammatory bowel disease and, 941
for osteoarthritis, 1740*b*–1741*b*
in palliative care, 12
peptic ulcers caused by, 918, 919*b*
for postoperative pain, 1829
reactions to, 1698, 1698*t*
for rheumatoid arthritis, 1755*b*, 1756*t*
for skin diseases, 2698
for spondyloarthritis, 1765*b*
Nonsteroidal mineralocorticoid antagonism, for diabetic nephropathy, 797*b*
Nonstreptococcal bacterial pharyngitis, 2648–2649, 2649*f*
Nonsyphilitic treponematoses
definition of, 2021
pathogens that cause, 2021
Nontuberculous mycobacteria, 2040, 2044–2047
cervical lymph nodes in, 2045
clinical manifestations of, 2045
definition of, 2044–2047
diagnosis of, 2045–2046
diagnostic criteria for, 2046
disseminated disease in, 2045
epidemiology of, 2044
pathobiology of, 2044–2045, 2045.*e1f*
Nontuberculous mycobacteria *(Continued)*
pathogens that cause, 2044, 2044*t*
prevention of, 2047
prognosis of, 2047
pulmonary disease in, 2045
radiology for, 2045–2046, 2045*f*
rapidly growing, 2044*t*
skin and soft tissue disease, 2045
slowly growing, 2044*t*
treatment for, 2046*b*–2047*b*, 2046*t*
Nonulcer dyspepsia, abdominal pain and, 854*t*
Nonvariceal hemorrhage, treatment of, 883*b*
Nonviral vectors, 175
Nonvoluntary active euthanasia, 8*t*
Noonan syndrome, 348, 1250*t*
5'-noranhydrovinblastine, 1215*t*
Norepinephrine, 2553
for septic shock, 671
for shock, 662*b*, 664*t*, 667*b*
synthesis of, 1529
Norfloxacin
for cholera, 1956*b*
for urinary tract infection, 1876*t*, 1877*t*
Normal-pressure hydrocephalus, 2421, 2485*t*
Normocytic anemia, 1080
Normocytic normochromic anemia, peripheral blood smear of, 1069
Normothermia, 681*t*
Normovolemic hyponatremia, 733*t*, 741, 741*b*
Noroviruses, 1868, 2261–2264
clinical manifestations of, 2263
definition of, 2261–2264
diagnosis of, 2263
epidemiology of, 2262, 2262*t*
pathobiology of, 2262
as pathogen, 2261
prevention of, 2263
traveler's diarrhea caused by, 1888*t*
treatment of, 2263*b*
North Africa, HIV/AIDS in, 2289, 2289.*e1f*
North America, HIV/AIDS in, 2289, 2289.*e1f*, 2290.*e1f*
North American blastomycosis, 2080
Northern Europe, cystic fibrosis in, 556
Nortriptyline
for chronic pain, 138*t*
for depression, 2340*t*
for erythromelalgia, 471*b*
for irritable bowel syndrome, 896*t*
for tobacco dependence, 2351*t*
for zoster, 2249*b*
Norwalk virus, 2261
Nose
acute poisoning and, 683
examination of, 29
Nosocomial hospital diarrhea, 926
Nosocomial infections, 1997
suspected, 1851
Nosocomial meningitis, 2517*t*
Novantrone. *See* Mitoxantrone
Novavax, 77, 2218*t*, 2219
Novichok, 2592
Noxious gases, 88*t*
NPDR. *See* Nonproliferative diabetic retinopathy
NQF. *See* National Quality Forum
NRTIs. *See* Nucleoside analogue reverse transcriptase inhibitors
NSAIDs. *See* Nonsteroidal anti-inflammatory drugs
NSCLC. *See* Non-small cell lung cancer
NT-pro-BNP, *e1t*–*e8t*
Nuclear cardiology, 247
in coronary artery disease, 362
in heart failure, 261
Nuclear factor κ light chain enhancer of activated B cells (NF-κB) pathway, 185
Nuclear factor-kappa B (NF-κB)
activation of, autoinflammatory disease associated with, 1736
regulation, disorders of, 1736
transcription factor complex, 1730
Nuclear factor of activated T cells (NFAT), 148
Nuclear medicine, 872–874, 874*f*
Nuclear pathways, 2617–2618
Nucleation, 803
Nucleic acid amplification tests (NAATs)
for *Chlamydia trachomatis*, 2012
for *Clostridioides difficile*, 1925
for COVID-19, 2214
description of, 1834
Nucleic acid amplification tests (NAATs) *(Continued)*
for influenza, 2201
for sexually transmitted infections, 1879
Nucleoside analogue reverse transcriptase inhibitors (NRTIs), 2300, 2304*t*
Nucleoside analogues, for chronic hepatitis B, 1011*b*
Nucleoside reverse transcriptase inhibitors, 2577
Nucleosome, 1714
5'-Nucleotidase, 999
Nucleotide-binding oligomerization domain (NOD)-like receptor (NLR), 183
Nucleus accumbens, of brain, 142–143
NUDT15 gene, 160*t*
Nuedexta, for amyotrophic lateral sclerosis, 2563*b*
Null hypothesis, 36
Nummular dermatitis, 2687.*e3t*, 2702, 2702*f*
Nursing homes, death in, 16
Nusinersen, for spinal muscular atrophy, 2565*b*
Nutrient deficiency, 2542–2543
Nutrition, 57–61
breast cancer and, 59
for cancer, 58, 1232*b*
cardiovascular disease and, 57
colorectal cancer and, 59
congenital neural tube defects and, 60
coronary heart disease and, 58
dementia and, 60
diabetes mellitus and, 60
dietary change, translating evidence into, 60
dietary guidelines, 57, 57.*e3t*, 58*t*
dietary requirements in, 57, 57*t*
dietary supplements, 60
diseases and, 57
geriatric assessment of, 117
for heart failure, 265*b*
hypertension and, 60
for inborn errors of metabolism, 1401*b*
influence of, on mortality and morbidity, 57–60
intestinal diverticular disease and, 60
liver cancer and, 59
lung cancer and, 59
obesity and, 60
osteoporosis and, 60
pancreas cancer and, 59
prostate cancer and, 59
in renal replacement therapy, 842
Nutrition Risk Screening 2002, 1447, 1448*t*
Nutritional assessment, 1448
Nutritional deficiency, neutropenia due to, 1146, 1146*f*
Nutritional folate deficiency, causes of, 1120
Nutritional neurologic disorders, 2537
Nutritive jejunostomy, 1449
Nuts, diet-related hyperoxaluria and, 806
Nyctalopia, 2500
Nystagmography, 2646
Nystagmus, 2619–2620, 2620*t*

O

Obesity, 623, 1446, 1463–1470
in adolescents, 111, 112
blood pressure and, 445
body mass index and, 1463
body weight regulation, 1464
cancer and, 59, 1232*b*, 1244, 1466
cardiomyopathy and, 288
cardiovascular disease and, 220
in children, 1463
cholesterol gallstones and, 1049
classification of, 1463*t*
constitutional influences on, 1464
definition of, 1463–1470
diabetes and, 1540
diabetes mellitus and, 60
diagnosis of, 1466
dyslipidemia causing, 1466
endocrine manifestations of, 1466
energy balance regulation, 1464
energy expenditure and, 1465
energy intake and, 1464
environmental contributors to, 1464, 1464*t*
epidemiology of, 1463
evaluation of, 1466
flow diagram for, 1467*f*
food and, 1464
Obesity *(Continued)*
genetic aspects of, 1463–1464
human microbiome and, 1838, 1839*f*
hypertension caused by, 60, 1465
hypothalamic, 1481
increased intra-abdominal fat associated with, 902
insulin resistance and, 1465
kidney stone and, 803
medications causing, 1465, 1466*t*
metabolic complications of, 1465–1466
mortality rates for, 1463
nutrition and, 60
in older adults, 114, 117
osteoarthritis and, 1738
pathobiology of, 1463–1466
physical activity and, 1464, 1467*b*
prevalence of, 1463
prevention of, 1470
prognosis for, 1470
pulmonary function in, 533
secondary causes of, 1465
sleep apnea and, 1466
systemic complications of, 1466
testosterone affected by, 1583
treatment of, 1467*b*
bariatric surgery, 1467*b*
behavior modification, 1467*b*
diet, 1467*b*
endoscopic treatment, 1467*b*
laparoscopic gastric banding, 1467*b*
pharmacotherapy, 1467*b*, 1468*t*
physical activity, 1467*b*
very low calorie diets, 1467*b*
type 2 diabetes mellitus and, 1466
in women, 1609
Obesity-hypoventilation syndrome, in hypercapnic disease, 535*t*
Obeticholic acid
for nonalcoholic fatty liver disease, 1034*b*
for primary biliary cholangitis, 1058*b*
Obinutuzumab (Gazyva), 1215*t*
for chronic lymphocytic leukemia, 1269*b*, 1269*t*, 1270*t*
Object agnosia, 2409
Objective tinnitus, 2643
Obscure gastrointestinal bleeding, 885, 886*f*, 886*t*
Observation, 257–258
Observational studies, 41
Obsessive-compulsive disorder (OCD), 2343–2344, 2344*t*, 2348*t*
prognosis of, 2344*b*
treatment of, 2340*t*, 2344*b*, 2346*t*
Obstetric-gynecologic infections, 1939
Obstructive airway disease, 657
Obstructive jaundice, cholestatic liver disease *versus*, 1000*t*
Obstructive shock, 658, 659, 659*f*, 661*t*
Obstructive sleep apnea
characteristics of, 2448
clinical manifestations of, 2448
polysomnography of, 2444, 2445*f*
treatment of, 2449*b*
Occipital lobe, 2460*f*
Occlusive hydrocolloid dressing, for skin diseases, 2697
Occult gastrointestinal bleeding, 885, 886*f*, 886*t*
Occupational asthma, 541*b*
Occupational interstitial lung diseases, 582
Occupational lung disease, 584
acute febrile syndromes as, 590, 591*t*
asbestos-related diseases as, 589, 590*f*
cancer as, 591
chronic beryllium disease as, 589
chronic obstructive pulmonary disease as, 588
epidemiology of, 584
examples of, 585*t*
hypersensitivity pneumonitis as, 588
pneumoconioses as, 590, 590*t*, 591*f*
silicosis, 590, 590*t*, 591*f*
specific, 584–588
work-related asthma as, 585–588, 586*t*, 587*f*
Occupational medicine
acute injuries in, 85, 86*t*
clinical implications of, 85
clinical syndromes in, 85, 86*t*
emergency preparedness and disaster management in, 89
hazards in, 88*t*

Copyrighted material

Occupational medicine *(Continued)*
hierarchy of controls in, 87
history, salient features of, 85, 85.*e1f*
individual clinician in, role of, 89
medical surveillance in, 87
principles of, 84
safety standards of, 87
wellness and resiliency in, 87
work-related disability in, 85
worker's compensation in, 85
Occupational Safety and Health Administration (OSHA), 87
OCD. *See* Obsessive-compulsive disorder
Ochronosis, 1825
Ocrelizumab (Ocrevus), for multiple sclerosis, 152, 2505*t*
Ocrevus. *See* Ocrelizumab
Octopus species, 712–713
Octreotide, 941*b*, 1215*t*
for acromegaly, 1489*b*
for acute poisoning, 693*t*
for carcinoid syndrome, 1568*b*
for GFRomas, 1565*b*
for glucagonomas, 1564*b*
for intestinal bacterial overgrowth, 934*b*
for intestinal pseudo-obstruction, 889*b*
for orthostatic hypotension, 2559*t*
Ocular adenovirus infection, 2205
Ocular allergies, 1674
Ocular bobbing, 2439, 2620
Ocular dysmetria, 2620
Ocular flutter, 2620
Ocular hypertension, 2607
Ocular infections, adenovirus causing, 2205
Ocular larva migrans, 2174
Ocular melanomas, 1391
Ocular metastases, 2613
Ocular myoclonus, 2620
Ocular rosacea, 2722
Ocular syphilis, 1881, 2017, 2020*b*, 2606
Ocular toxoplasmosis, 2136
diagnosis of, 2138*t*, 2139, 2139*f*
treatment for, 2140*b*, 2140*t*
Ocular trauma, 2603–2604
Oculomotor apraxia, 2619
Oculomotor control, 2617, 2618*t*
Oculopharyngeal muscular dystrophy, 2585
Odomzo. *See* Sonidegib
Odynophagia, 852*t*, 865
Ofatumumab (Kesimpta), for multiple sclerosis, 2505*t*
"Off-the-midline" fissures, 980
Ofloxacin, for eye infection, 2605*t*
OGTT. *See* Oral glucose tolerance test
Ointment, 2697
Olanzapine
for nausea and vomiting, 863*t*
for psychotic disorders, 2346*t*
weight gain and, 2680
Olaparib (Lynparza), 1215*t*, 1251*t*
Older adults. *See also* Elderly
cancer in, treatment of, 1232*b*
congenital heart disease in, 355–356
delirium in, 2331
dietary requirements for, 1452
disease and disability in, 114
frail, 122–123, 123*f*
frailty in, 114*t*, 115
geriatric syndromes in, 114
health expectancy in, 116*t*
life expectancy in, 116*t*
mental status change in, 2331
morbidity in, 114
mortality of, 115, 115*f*
multimorbidity in, 114
obesity in, 114
pain management in, 136*b*
physical activity for, 63*b*
psychosocial and physiologic considerations in, 704.*e1t*
subclinical disease in, 114
Olecranon bursitis, 1744–1745, 1745*b*, 1745*f*
Olfactogenital dysplasia, 1601
Olfactory dysfunction, 2640*b*
Olfactory receptors, 2639
Oligoarthritis, peripheral, 1762
Oligodendrogliomas, 1315*b*
Oligomeganephronia, 818
Oligomenorrhea, 1598
in Cushing syndrome, 1521
Oligosaccharidoses, 1419*t*
Oligozoospermia, 1586
Ollier disease, 1669
Olmesartan, 451*t*, 926
Olmesartan/amlodipine/HCTZ, 451*t*
Olmesartan/HCTZ, 451*t*
Olodaterol, 553*t*
Olsalazine (Dipentum), for inflammatory bowel disease, 946*t*
Olumiant. *See* Baricitinib
Omacetaxine, for chronic myeloid leukemia, 1275*t*
Omadacycline, 1845*t*, 1895*t*
Omalizumab
for asthma, 541*b*
description of, 152
dosing calculators, 541*b*
Omega-3 polyunsaturated fatty acids, for heart failure, 265*b*
"Omega" sign, 951, 952*f*
Omental cysts, 958
Omentum, anatomic diseases of, 958, 958*t*
Omeprazole
for acute pericarditis, 424*b*
for functional chest pain, 901*b*
Omphalocele, 951
Omsk hemorrhagic fever, 99.*e1t*, 2265*t*, 2268*t*, 2275*t*
Onchocerca volvulus, 2178
Onchocerciasis, 2178
Onchodermatitis, 2178
Oncogenes, 1247
DNA alterations in, 1247–1248, 1248*f*
in lung cancer, 1330, 1330.*e1f*
Oncogenic osteomalacia, 768
Oncogenic viruses, 1259
Ondansetron
for infectious gastroenteritis, 2263*b*
for nausea and vomiting, 863*t*
Ondine's curse, 534
"One-hand, two-feet syndrome", 2710–2711
Onxol. *See* Paclitaxel
Onycholysis, 2753, 2754*f*
Onychomadesis, 2752, 2752*f*, 2752*t*
Onychomycosis, 2754, 2754*b*, 2754*f*
Candida, 2090
O'nyong-nyong virus, 2275*t*, 2278, 2279*b*
Oocytes, 1591
Oophorectomy, 1373
Oophoritis, 1949
mumps and, 2226, 2226*t*
Opdivo. *See* Nivolumab
Open-angle glaucoma
primary, 2607, 2607*f*
secondary, 2607
Open pneumothorax, 526
Operative hemorrhoidectomy, 978*b*
Ophthalmologic examination, 212
Ophthalmoplegia, supranuclear, Whipple disease and, 2070
Opiates, 941*b*
Opicapone, for Parkinson disease, 2487*t*
Opioid peptides, endogenous, 1478
Opioids
abuse of, 2361
clinical manifestations and diagnosis of, 2362
epidemiology of, 2361
medical complications of, 2362
pathobiology of, 2361
physical dependence on, 2362
treatment of, 2362*b*
for anesthesia, 2670
central nervous system effects of, 685*t*
for irritable bowel syndrome, 895*b*, 896*t*
in palliative care, 12
properties of, 142*t*
reactions to, 1698*t*
screening for, 689*t*
toxicity, 686*t*
toxidromes, 683*t*
Opisthorchiasis, 2166, 2166*t*, 2168
Opisthorchis felineus, 2166
Opisthorchis spp, 1026*t*
Opisthorchis viverrini, 2166
Opportunistic infections
associated with candidiasis, 2089
cryptococcosis, 2087
description of, 1857
in HIV/AIDS, 2305, 2306*t*
antiretroviral therapy for, 2304, 2307*b*
behavioral factors, 2306
CD4 cells in, 2306, 2306*f*
Opportunistic infections *(Continued)*
clinical manifestations of, 2306
cytomegalovirus, 2307
diagnosis of, 2307
empiric management of, 2307*b*
Mycobacterium tuberculosis, 2306
natural histories of, 2306
pathobiology of, 2306
prevention of, 2308, 2308.*e1f*
prophylaxis against, 2304
prophylaxis for, 2309*t*
treatment of, 2307*b*, 2307*t*
Opsoclonus, 2620
Opsonization, 202
Optic chiasm, 2616
Optic disc abnormalities, 30
Optic glioma, 1315
Optic nerve, 2596
arteries of, 2614
vision loss caused by, 2615–2616
Optic nerve hypoplasia, 1478
Optic neuritis, 2500, 2508, 2508*b*, 2615
Optic neuropathy, 2542, 2544
Optic tract, 2616
Optical coherence tomography, for multiple sclerosis, 2504, 2504.*e1f*
Opticospinal multiple sclerosis, 2509
OPV. *See* Oral poliovirus vaccine
Oral allergy syndrome, 1673*t*
Oral anticoagulants, 503
Oral aphthous ulcer, 2320*f*, 2322*t*
Oral candidiasis, 2320*f*, 2322*t*
Oral cavity
anatomy of, 1320
cancer of, 1322, 1325*t*, 1327*b*
Oral contraceptives, 1613
for abnormal uterine bleeding, 1597*b*
benign hepatocellular adenoma and, 1615
cancer and, 1246
cervical cancer and, 1615
combined, 1614
complications of, 1614–1615
contraindications for, 1610, 1615, 1616*t*
endometrial cancer and, 1615
formulations of, 1613–1614, 1614*t*
hypertension associated with, 456
management of, 1615
missed, 1615
myocardial infarction and, 1614
for polycystic ovary syndrome, 1602*b*
reproductive system cancers and, 1615
rheumatoid arthritis and, 1750
risk factors for, 1614
side effects, 1614
stroke and, 1614
thrombosis caused by, 1614
venous thromboembolism and, 481
Oral-facial digital syndrome-1, 809*t*
Oral glucose tolerance test (OGTT), 1535, 1536*t*
Oral hairy leukoplakia, 2256, 2319*f*, 2322*t*
Oral iron supplement, for iron deficiency anemia, 1084*b*
Oral lichen planus, 2708, 2708*f*
Oral mucosal diseases
angular cheilitis, 2624
candidiasis, 2623
erythema multiforme, 2622
erythematous oral candidiasis, 2623, 2624*f*
geographic tongue, 2623, 2623*f*
hairy leukoplakia, 2623, 2623*f*
lichen planus, 2623, 2623*f*
mucocutaneous diseases, 2624
pigmentations associated with, 2624, 2624*t*
squamous cell carcinoma, 2622
ulcers, 2621*t*
viral ulcers, 2621
white lesions, 2622–2623
Oral poliovirus vaccine (OPV), 81
Oral potentially malignant disorders, 1321
Oral rehydration salts solution, for infectious gastroenteritis, 2263*b*
Oral rehydration therapy
for cholera, 1956*b*
for cryptosporidiosis, 2143*b*
for diarrhea and enteric infection, 1872*t*
Oral soft tissue tumors, 2624–2625, 2625*t*
connective tissue hyperplasia, 2624, 2625*t*
epithelial proliferations, 2625
mucoceles, 2625
papillary epithelial tumors, 2625*f*
reactive hyperplasias, 2625, 2625*t*
Oral temperature, 29, 33
Orbit, 2596
metastases to, 2615
pseudotumor, 2611
tumors, 2613
Orbital floor, 2597
Orbital restrictive disease, 2618–2619
Orchitis, 1583
mumps and, 2226, 2226*t*
Order sets, 44
Ordinary confluent smallpox, 2237, 2237*t*
Ordinary discrete smallpox, 2237, 2237*t*
Ordinary semiconfluent smallpox, 2237, 2237*t*
Oregon, physician-assisted suicide in, 8
Orencia. *See* Abatacept
Organ dysfunction, cancer and, treatment of, 1232*b*
Organ-restricted eosinophilic disease, 295
Organ-sparing therapy, for cancer, 1232*b*, 1234*t*
Organ support, during critical illness, with COVID-19, 2218
Organ transplantation, for inborn errors of metabolism, 1401*b*
Organic acidurias, 1403, 1403*f*, 1403*t*, 1404*b*
Organic compounds, 88*t*
Organic mercury, 103
Organophosphate poisoning, 88*t*, 2592
Organophosphorus compounds
central nervous system effects of, 685*t*
toxicity, 686*t*
Orgasm, 1604
impaired, 1590
Oriental cholangiohepatitis, 1056
Oriental rat flea, plague and, 1988
Orientia tsutsugamushi. *See also* Scrub typhus
diseases caused by, 2054–2060
in travelers, 1889.*e1t*, 1891*t*
Oritavancin
dosage of, 1895*t*
mechanism of action, 1895*t*
spectrum of activity, 1900
Orlistat, 1467*b*, 1609
Ornidazole
for amebiasis, 2150*t*
for amebic liver abscess, 1025*b*
Ornithine transcarbamylase deficiency, 1398*t*, 1402*t*
Ornithodoros hermsii, 2027–2028
Oropharyngeal candidiasis, 2090, 2090*f*
Oropharyngeal dysfunction, 908
Oropharyngeal infection, 2012
Oropharyngeal squamous cell carcinoma
HPV-associated, 1320, 1322, 1324*f*, 1327*b*, 1328
HPV-unrelated, 1322, 1327*b*
Oropharynx, 1320, 1320*f*, 2648
Acinetobacter in, 1973
cancer, 1325*t*
Oroya fever, 2000, 2001*f*, 2003*b*, 2003*t*
Orthodromic AV re-entrant tachycardia, 323*t*, 326
Orthopnea, 256
Orthopoxvirus
clinical manifestations of, 2237–2239
cowpox, 2237, 2238
diagnosis of, 2239–2240
epidemiology of, 2236
monkeypox, 2236, 2238, 2239*f*
prevention of, 2240*b*
smallpox, 2236–2240. *See also* Smallpox
treatment of, 2240*b*
vaccination for, 2240*b*
vaccinia
bovine-associated, 2238
clinical manifestations of, 2238
epidemiology of, 2236
generalized, 2238
post-vaccination, 2238
progressive, 2238
Orthopoxvirus variola, smallpox caused by, 2236
Orthostatic hypotension, 2554–2555
description of, 306
psychotropic medications and, 2678*t*
treatment for, 2557*b*, 2559*f*, 2559*t*
Orthostatic intolerance, without autonomic failure, 2554*t*, 2555
Orthostatic vital signs, 33
Osborne wave, 680, 681*f*
Oscillometric office blood pressure, 446*t*, 447
Oscillopsia, 2500, 2645

Copyrighted material

Oseltamivir
for influenza, 2189, 2189*t*, 2202*b*, 2203*t*
for pneumonia, 613*t*
OSHA. *See* Occupational Safety and Health Administration
Osilodrostat, for Cushing syndrome, 1524*b*
Osimertinib (Tagrisso), 1215*t*, 1251*t*
Osler nodes, 216, 414, 414*t*, 415*f*
Osler-Weber-Rendu disease, 348, 967, 1186
Osmolality, *e*1*t*–*e*8*t*
regulation of, vasopressin and, 1499
volume regulation and, interaction of, 1499
Osmolarity, body fluid, 730, 732*f*
Osmoreceptor dysfunction
clinical manifestations of, 1501
pathobiology of, 1499*f*, 1500
treatment of, 1503*b*
Osmostat, 1499
Osmotic demyelination, 741*b*, 2544*f*, 2545, 2545*b*
Osmotic diuresis, 744
Osmotic lysis, 199
Osmotic pressure, 737
Ospemifene, for genitourinary syndrome of menopause, 1632*t*
Osteitis fibrosa cystica, 1823
Osteoarthritis, 1706*t*, 1717*t*, 1718*f*, 1737–1741, 1751–1752, 1751*f*–1752*f*, 1753*f*
aging and, 1738
clinical manifestations of, 1739
comprehensive assessment of, 1740*t*
definition of, 1737–1741
diagnosis of, 1739–1740
disease-modifying drugs for, 1740*b*
endotypes of, 1739
epidemiology of, 1737–1738, 1826
exercises and physical activities for, 1741*t*
genetic contribution to, 1738–1739
holistic evaluation of, 1740, 1740*t*
imaging of, 1740
incidence of, 1738*f*
joint injury and, 1738
natural history of, 1739.*e*1*f*
nonsteroidal antiinflammatory drugs for, 1740*b*
obesity and, 1738
in older adults, 114
pain in, etiology of, 1739, 1739.*e*1*f*
pathobiology of, 1738–1739, 1826, 1826*f*
phenotypes of, 1739, 1739.*e*1*f*
prevention of, 1741
prognosis for, 1741
risk factors of, 1738–1739, 1739*f*
signaling pathways and structural changes in, 1738.*e*1*f*
signs of, 1739
symptoms of, 1739
treatment of, 1740*b*
in women, 1609
Osteoarticular candidiasis infections, 2091
Osteoarticular sporotrichosis, 2086
Osteoarticular tuberculosis, 2037, 2038*f*
Osteocartilaginous exostoses, 1669
Osteocytes, 1640
Osteogenesis imperfecta, 1641, 1727, 1728*b*, 1728*t*
Osteomalacia, 1453*t*, 1647–1651
cause of, 1647*t*
celiac disease and, 1649
clinical manifestations of, 1648
definition of, 1647–1651
diagnosis of, 1648–1651
differential diagnosis of, 1648*f*, 1649–1651
epidemiology of, 1647
hypophosphatemia causing, 1648, 1650*b*–1651*b*
oncogenic, 768
pathobiology of, 1647–1648, 1648*f*
prevention of, 1651
prognosis for, 1651
pseudofractures associated with, 1649
radiographic findings of, 1649, 1649*f*
treatment of, 1650*b*
tumor-induced, 1649
vitamin D deficiency causing, 1647, 1647*t*, 1650*b*, 1650*t*, 1651*t*
Osteomyelitis, 1809, 1849
Acinetobacter causing, 1973–1974
anaerobic bacteria causing, 1940
blastomycosis and, 2081
Osteomyelitis *(Continued)*
clinical manifestations of, 1809
definition of, 1809
diagnosis of, 1809
epidemiology of, 1809
microorganisms responsible for, 1805*t*
pathobiology of, 1809
prevention of, 1809
prognosis of, 1809
Pseudomonas, of foot, 1969
Staphylococcus aureus causing, 1904–1905
treatment for, 1807*t*, 1809*b*
vertebral, 1904, 1904*f*
Osteonecrosis, 1665, 1665*f*, 1665*t*, 1666*b*
of jaw, 1643*b*
pathobiology of, 1826
Osteopathia striata, 1668
Osteopenia, 1639
cystic fibrosis and, 557
Osteopetrosis, 1667, 1667*b*, 1668*f*, 1729
Osteopoikilosis, 1668
Osteoporosis, 1639–1647, 1706*t*, 1755*b*
anabolic agents for, 1643*b*
anticatabolic agents for, 1643*b*
antiresorptive and anabolic agents for, 116
bisphosphonates for, 1643*b*
bone loss mechanisms, 1640
bone mineral density
definition, 1639
measurement, 1642, 1643.*e*1*f*
testing of, 1638
calcium for, 1643*b*
clinical manifestations of, 1642
computed tomography of, 1641, 1641*f*
cystic fibrosis and, 557
definition of, 1639–1646
denosumab for, 1643*b*
diagnosis of, 1642–1646, 1642*f*
epidemiology of, 1639, 1640*f*
estrogen for, 1643*b*
exercise for, 1643*b*
femoral fracture caused by, 1643*b*
fractures associated with, 1639
fragility fractures in, 1641, 1641*f*
glucocorticoid-induced, 145, 1643*b*
hip fractures associated with, 1639
in HIV, 2318
laboratory workup of, 1638*t*
lifestyle modifications for, 1643*b*
male, 1646, 1646*b*
medications for, 1643*b*
menopause associated with, 1632
nutrition and, 60
pathobiology of, 1639–1641
prevention of, 1643*b*
prognosis, 1646
screening for, 55
secondary causes of, 1641, 1641*t*
selective estrogen receptor modulators for, 1643*b*
treatment of, 1639*b*, 1643*b*, 1643*t*–1644*t*
vertebral fractures associated with, 1642
vitamin D for, 1643*b*
Wilson disease and, 1437
in women, 1607–1609
Osteoprotegerin, 1298, 1640, 1654
Osteosarcoma, 1388, 1388*b*
Osteosclerosis, 1666
Osteosclerotic myeloma, 1302
Osteotomy, 1827
Otalgia, 2636
cause of, 2636*t*
clinical manifestations of, 2636, 2637*f*
definition of, 2636
diagnosis of, 2636
differential diagnosis of, 2637, 2638*f*
imaging of, 2637
laboratory findings in, 2637
pathobiology of, 2636
physical examination of, 2636, 2637*f*, 2638*f*
treatment of, 2638*b*
Otezla. *See* Apremilast
Otic barotrauma, 594
Otic syphilis, 2017
Otitis externa
malignant, 1969
treatment of, 2638*b*
Otitis media
chronic, 2641
Otitis media *(Continued)*
chronic suppurative, 1972
H. influenzae caused by, 1953
Otosclerosis, 2641
Ottawa Subarachnoid Hemorrhage Rule, 2475*f*
OTULIN deficiency (otulipenia), 1731*t*
Otulipenia. *See* OTULIN deficiency
Out-of-hospital cardiac arrest, causes of, 313*t*
Outpatient ambulatory setting, for fever, 1851*b*
Output-selective disorders, 2554*t*
Ova and parasite examination, for enteric infection, 1870*t*
Oval macrocytes
conditions associated with, 1072*t*
peripheral blood smear of, 1067*f*
Ovarian cancer, 1379
clinical manifestations of, 1379
definition of, 1379
diagnosis of, 1379
epidemiology of, 1379, 1379*t*
pathobiology of, 1379
prevention of, 1380
prognosis for, 1381, 1381*t*
risk factors for, 1379*t*
treatment of, 1380*b*, 1380*t*, 1381*t*
in women, 1607
Ovarian cysts, 1591
Ovarian epithelial malignancies, 1379
Ovarian function, in HIV, 2318
Ovaries, 1591–1594
definition of, 1591–1592
development, 1569
menstrual cycle-related changes in, 1595
pathobiology of, 1591–1592
Overactive bladder, 827
Overflow incontinence, 828, 830*t*
Overhydrated hereditary stomatocytosis, 1097
Overlap hypereosinophilic syndrome, 1162
Overlap syndromes, 1788, 1788*t*
Overt hypothyroidism, 1505, 1508*b*
Overt shock, 660
Overweight
cardiovascular disease and, 220
classification of, 1463*t*
flow diagram for, 1467*f*
Ovotesticular disorder, of sexual development, 1574
Ovulation
clomiphene citrate for, 1603*b*
in menstrual cycle, 1595
Oxacillin
for bacterial meningitis, 2518*t*
dosage of, 1895*t*
Oxalate crystals, *e*1*t*–*e*8*t*, 725*f*
Oxalate nephropathy, 795
Oxalate renal stones, 934
Oxaliplatin (Eloxatin), 1215*t*
Oxalyl diaminopropionic acid, 2541*t*
Oxamniquine, for schistosomiasis, 2165*b*
Oxantel pamoate, for helminthic diseases, 2117
Oxaprozin, for chronic pain, 138*t*
Oxazepam, for anxiety disorders, 2344*t*
Oxazolidinones
characteristics of, 1899
dosage of, 1895*t*
Oxcarbazepines, *e*10*t*–*e*11*t*
for chronic pain, 138*t*
for seizures, 2434*t*
Oximetry, pulse, 640
5-Oxoprolinuria, 759
Oxybutynin, 824*t*
Oxycodone, 139*t*
Oxygen
alveolar-arterial oxygen gradient, 639
arterial content, 640
myocardial requirements, 381*t*
partial pressure of, *e*1*t*–*e*8*t*, 639
normal values, 639
venous content, 640
Oxygen consumption, 677*t*
Oxygen consumption index, 677*t*
Oxygen delivery
normal value, 677*t*
systemic, 640
Oxygen delivery index, 677*t*
Oxygen extraction ratio, 677*t*
Oxygen intubation, 636
Oxygen saturation, *e*1*t*–*e*8*t*
abnormal, 34*t*
decreased, 35
Oxygen saturation *(Continued)*
low, 33*t*
measurement of, 33
normal range for, 32*t*
panic range for, 32*t*
Oxygen therapy, for carbon monoxide poisoning, 596*b*
Oxygen toxicity, 596
clinical manifestations of, 596
definition of, 596
diagnosis of, 596
pathobiology of, 596
prognosis of, 596
treatment of, 596*b*
Oxygen transport, systemic, 640
Oxygenation
therapy for, 647*b*
for viral hemorrhagic fevers, 2269*b*
Oxyhemoglobin association-dissociation curve, 643*f*, 1075*f*
Oxymetazoline hydrochloride, for skin diseases, 2698
Oxymorphone, 139*t*
Oxytocin, 1500
Ozanimod (Zeposia)
for inflammatory bowel disease, 945*b*, 946*t*
for multiple sclerosis, 2505*t*

P

P. falciparum erythrocyte membrane protein-1 (PfEMP-1), 2119
p-aminosalicylic acid, for actinomycosis, 2068
P values, 36
P wave, 228*f*, 229, 229*t*
p16, 1391
Pacemaker
complications of, 343–344
dual-chamber, 342*f*
electrocardiogram with, 343*f*
leadless, 342*f*
permanent, indications for, 341, 341*t*
programming of, 342–343
Pachydermoperiostosis, 1667, 1667*b*
Pachygyria, 2547
Pacific, HIV/AIDS in, 2289, 2289.*e*1*f*
Pacific Coast tick fever, 2055*t*, 2065*t*
Pacing
modes, 342
permanent, 341–343
indications for, 341, 341*t*
synchronous biventricular, 342, 342*f*
systems of, 341–342, 342*f*
temporary, 341
Paclitaxel (Taxol, Onxol), 1215*t*
protein bound (Abraxane), 1215*t*
PACNS. *See* Primary angiitis of the central nervous system
Paeniclostridium sordellii, 1927, 1927*b*
Paget disease of bone, 1662–1665
arthritis associated with, 1823
bisphosphonates for, 1664*b*, 1664*t*
clinical manifestations of, 1663–1664
definition of, 1662–1665
diagnosis of, 1663*f*, 1664
drug therapy for, 1664*b*
epidemiology of, 1662
monitoring disease activity of, 1664*b*
pathobiology of, 1662–1663, 1662.*e*1*f*, 1663*f*
prognosis for, 1665
surgery for, 1664*b*
treatment of, 1664*b*
Paget disease of nipple, 1368
Pain, 133–141
acute, 135, 1113
back pain, 136*b*
biopsychosocial model of, 133, 134*f*
in cancer, management of, 1232*b*
categorization of states, 135*t*
centralized, 1816, 1817*t*
chest, 210, 211*t*
chronic, 133, 1113
in chronic pancreatitis, treatment for, 975*b*, 975*t*
chronic widespread, 1816
clinical manifestations of, 135–136
definition of, 133–141
diagnosis of, 135
diagnostic tests, 136
ear, 2636

Copyrighted material

Pain *(Continued)*
epidemiology of, 133
eye, 2598, 2599*t*
fibromyalgia and
mechanistic characterization of, 1817*t*
processing, 1817
history of, 135–136
management of, approaches to, 13*t*
mixed, 134, 135*t*
nature *versus* nurture, 134–135
neurologic diseases that cause, 2371
neuropathic, 134, 135*t*, 1817*t*
nociceptive, 134, 135*t*, 1817*t*
nociplastic, 134, 135*t*, 1817*t*
in osteoarthritis, etiology of, 1739, 1739.*e1f*
pathobiology of, 133–135, 134*f*
pathologic, 133–134
physical examination of, 136
postoperative, in joint diseases, 1829
psychologic assessment of, 136, 136*t*
severe mental illness and, 2683*t*
in sickle cell disease, 1113, 1114*b*
somatic, 134, 135*t*
treatment of, 136*b*, 137*f*
visceral, 134, 135*t*
Pain management
combination therapy, 136*b*
complementary and alternative medical (CAM) therapy, 136*b*
future developments of, 141
interventional therapy, 136*b*
in older adults, 136*b*
pharmacologic therapy, 136*b*
psychologic treatment, 136*b*
in women, medications for, 1608*t*
Pain-related symptoms, treatment for, 2193*b*
Pain syndromes, 1708
Painful hunger, 917
Painful legs and moving toes, 2496
Pakistan monsoon flooding, climate-related hazards, 91*t*
Palbociclib (Ibrance), 1215*t*
for breast cancer, 1369*b*
Paliperidone, for psychotic disorders, 2346*t*
Palivizumab, 153
for respiratory syncytial virus, 2195
Palliative care, 11–17, 638
domains of, 12–16
for hepatobiliary cancers, 1360*b*
questions to address, 12
Palliative radiation, for cancer, 1232*b*
Pallor, anemia and, 1076
Palmar erythema, 987, 988*f*
Palmar fasciitis and arthritis syndrome, 1823–1824
Palmoplantar psoriasis, 2705
Palonosetron, for nausea and vomiting, 863*t*
Palpable purpura, 2690*f*, 2692*t*, 2714, 2714*f*, 2714*t*, 2715*f*
Palpation
cardiac, 213
skin, 2687
Palpitations, 210–212, 212*t*
anemia and, 1075–1076
definition of, 303–304
Palytoxin poisoning, 713
Pamidronate (Aredia), 1215*t*
for Paget disease, 1664*t*
PAMPs. *See* Pathogen-associated molecular patterns
pANCA. *See* Perinuclear antineutrophil cytoplasmic antibodies
Pancreas, alcohol use disorders and, 2354, 2355, 2355*t*
Pancreatic cancer, 1354–1357
adenocarcinomas, 1354
biomarkers of, 1356
clinical manifestations of, 1355
definition of, 1354–1357
diagnosis of, 1355–1357
differential diagnosis of, 1355
epidemiology of, 1354–1355
hypercoagulability and, 479
imaging of, 1356
metastatic, 1356*b*, 1357*t*
neoadjuvant therapy for, 1356*b*
nutrition and, 59
palliative care for, 1356*b*
pathobiology of, 1355, 1355*f*
prevention of, 1357
prognosis for, 1357
screening of, 1356
treatment of, 1356*b*, 1356*t*
Pancreatic cancer *(Continued)*
tumorigenesis of, 1355
unresectable, 1356*b*, 1357*t*
Pancreatic duct, obstruction of
acute pancreatitis and, 970, 970*t*
chronic pancreatitis and, 973
Pancreatic enzyme replacement therapy
chronic pancreatitis, 975*b*, 975*t*
for cystic fibrosis, 558*b*
Pancreatic function tests, 931*t*, 975
Pancreatic insufficiency, cystic fibrosis and, 557
Pancreatic islet cell transplantation, for type 1 diabetes mellitus, 1537*b*
Pancreatic neuroendocrine neoplasms (pNENs), 1561*t*, 1562
ACTHomas as, 1566
carcinoid syndrome as, 1567
functional, 1562–1563
glucagonomas as, 1563
growth hormone-releasing factor secreting neuroendocrine neoplasms as, 1565, 1565*b*
nonfunctional, 1565, 1566*b*
somatostatinomas as, 1565
VIPoma syndrome as, 1564–1565
Zollinger-Ellison syndrome as, 1562
Pancreatic neuroendocrine tumor, with liver metastases, magnetic resonance imaging of, 872*f*
Pancreatic panniculitis, 1821–1822
Pancreatic pseudocyst, 975*b*
Pancreatic structure, tests of, 974–975, 974*f*, 975*f*
Pancreatic tumors, hypoglycemia and, treatment of, 1557*b*
Pancreatitis, 969–977
acute, 969
abdominal pain and, 854*t*
causes of, 970*t*
clinical manifestations of, 970
complications of, 972*t*
definition of, 969
determining severity of, 971, 972*f*
diagnosis of, 970
epidemiology of, 969
etiology of, 971
imaging studies for, 971, 971*f*, 972*f*
laboratory tests for, 971
pathobiology of, 969
prognosis of, 973
treatment for, 972*b*
autoimmune, 970, 970*t*
chronic, 933, 973
clinical manifestations of, 933, 974
definition of, 973
diagnosis of, 933, 974, 974*f*, 974*t*, 975*f*
epidemiology of, 973
pathobiology of, 973
prevention of, 976
prognosis of, 976
treatment for, 975*b*, 975*t*
in endoscopy, 876*t*
mumps and, 2226*t*
pleural effusions in, 626–627, 626*b*
weight loss and, 860*t*
Pancreatitis-arthritis syndrome, 1821–1822
Pancreaze, for exocrine pancreatic insufficiency, 975*t*
Pandemic, quality and safety during, 46
Pandemic influenza, 2199
Panencephalitis, subacute sclerosing, 2221
Panhypopituitarism, 1479, 1483
Panic attacks, 2342
Panic disorder, 2342*t*, 2343
Panitumumab (Vectibix), 1215*t*, 1251*t*
Panmyelosis, neutrophilia and, 1142
Panniculitis, 2735–2736
Panobinostat (Farydak), 1215*t*
Pansystolic murmurs, 214
Pantothenic acid deficiency, 1453*t*
Panuveitis, 793
PAPA. *See* Pyogenic arthritis with pyoderma gangrenosum and acne
Papillary muscle, 224
Papillary necrosis, 728
Papillary renal cell carcinomas, 1363
Papillary (differentiated) thyroid cancer, 1517
clinical manifestations of, 1517
epidemiology of, 1517
pathobiology of, 1517
prognosis of, 1518–1519, 1518*f*
risk for persistence/recurrence of, 1517*t*
treatment for, 1517*b*
Papilledema, 2513, 2609, 2610*f*, 2616, 2616*t*
Papillomatosis, 2241
Papillomaviruses, 2240–2244
Pappenheimer bodies, peripheral blood smear of, 1069*f*
Papular eruptions, 2712–2713
Papular exanthems, 2712
Papule, 2689*t*
Papulopustular rosacea, 2722
Papulosis, malignant atrophic, 965, 969
Papulosquamous diseases, 2705–2711, 2705*t*
Bazex syndrome, 2710
dermatophytoses, 2710, 2711*f*
lichen nitidus, 2708, 2708*f*
lichen planus, 2707
mycosis fungoides, 2709, 2710*f*, 2710*t*
necrolytic acral erythema, 2710, 2710*f*
parapsoriasis, 2709, 2709*f*
pityriasis lichenoides, 2709
pityriasis rosea, 2707
pityriasis rubra pilaris, 2707
psoriasis, 2705–2706
secondary syphilis, 2709, 2709*f*
Paracellular pathway, 730
Paracetamol. *See* Acetaminophen
Paracoccidioides brasiliensis, 1024
Paracoccidioides spp., 2086
Paracoccidioidomycosis, 2086, 2087*b*, 2651
Paradoxical vocal fold movement, distinguishing features of, 515*t*
Paraesophageal hernia, 910
Parafibromin, 1657
Paraganglioma
epidemiology of, 1530
familial, 1530
hypertension and, 450, 450*b*
metastatic, 1533
pheochromocytoma *versus*, 1529–1533
in von Hippel-Lindau disease, 1530
Paragonimiasis, 2167
Paragonimus spp., 2166*t*
Paragonimus westermani, 524
Parainfectious encephalitis, 2532
Parainfectious encephalomyelitis, 2646
Parainfluenza viral diseases, 2196–2198
in acute bronchitis and tracheitis, 605
clinical manifestations of, 2196–2197
diagnosis of, 2197
in elderly, 2196
epidemiology of, 2196–2198
in immunocompromised patients, 2196
pathobiology of, 2196
prevention of, 2198
primary infection, 2196
prognosis of, 2198
reinfection of, 2196
treatment of, 2197*b*–2198*b*
Paralysis, diaphragmatic, 619, 620.*e1f*
Paralysis ticks, 710
Paralytic rabies, 2535
Paralytic shellfish, 713
Paralytic shellfish poisoning, in travelers, 1889.*e1t*
Parameningeal infections, 2515, 2523, 2525
cerebral venous thrombosis, virally mediated, 2530
infectious endocarditis, neurologic complications of, 2530, 2530*b*
sinus thrombosis
lateral, 2529, 2529*b*, 2529*f*
septic cavernous, 2528, 2529*b*
septic sagittal, 2530, 2530*b*
venous, 2528–2530
spinal epidural abscess, 2527, 2527*f*, 2527.*e1t*
clinical manifestations of, 2527
definition of, 2527–2528
diagnosis of, 2527
epidemiology of, 2527
pathobiology of, 2527
prognosis of, 2528
treatment of, 2528*b*
subdural empyema, 2528, 2528*b*
Paramyxoviridae family, 2225
Paraneoplastic cerebellar degeneration, 1238*t*
Paraneoplastic encephalomyelitis, 1238*t*
Paraneoplastic hypercalcemia, pancreatic neuroendocrine neoplasm, 1566
Paraneoplastic neuropathies, 2576–2577
Paraneoplastic pemphigus, 2718
Paraneoplastic syndromes, 1237–1240, 2564*t*
dermatologic, 1239
diagnosis of, 1238*t*
Paraneoplastic syndromes *(Continued)*
evaluation of, 1238*t*
hematologic, 1239
hepatic, 1239
neurologic, 1238, 1238*t*
renal, 1239
rheumatologic, 1239, 1239*b*, 1239*f*
Paranoid personality disorder, 2348*t*
Paraplatin. *See* Carboplatin
Parapoxvirus, 2239, 2240*b*
Parapsoriasis, 2709, 2709*f*
Parasites
peripheral blood smear of, 1074*t*
of skin, 2739*t*, 2742
Parasitic infections
distinguishing features of, 515*t*
of liver, 1024, 1026*t*
treatment of, 2112*t*
Parasomnias, 2452–2453, 2453*b*
Paraspinal region, of mediastinum, 527
Parathyroid disorders
arthritis associated with, 1823
chromosomal locations of, 1653*t*
hypercalcemia. *See* Hypercalcemia
Parathyroid glands, 1652
Parathyroid hormone, 1652–1654, 1652.*e1f*
actions of, 1653–1654
extracellular fluid calcium regulated by, 1652*f*
intact, *e1t*–*e8t*
PTH gene and, 1652–1654
skeletal actions of, 1654
Parathyroid surgery, for primary hyperparathyroidism, 1657*t*
Parathyroidectomy, for primary hyperparathyroidism, 1657*b*
Paraventricular nucleus, 1477*f*
Paravertebral compartment, of mediastinum, 527
Parenchymal disorder, occupational and environmental, 86*t*
Parenchymal lung disease, 494
Parenteral anticoagulants, 501, 501*t*
Parenteral nutrition, 1445*b*, 1450, 1450*f*, 1451*t*
Parietal lobe, 2460*f*
Parinaud oculoglandular syndrome, cat-scratch disease and, 2001
Parinaud syndrome, 1314, 2619
Parkinson disease, 173*f*, 174, 2483–2486, 2558
deep brain stimulation of, 2486
diagnosis of, 2484–2485
differential diagnosis of, 2485*t*
drugs for, 2487*t*
epidemiology of, 2483
late-stage, 2484*t*
levodopa for, 2486, 2486*b*
motor symptoms, 2483–2484
pathobiology of, 2483
pathology of, 2483
pramipexole for, 265*b*
signs and symptoms of, 2484*t*
Parkinsonian gait, 2373*t*
Parkinsonism, 2483–2489
akinesia in, 2484
clinical manifestations of, 2483–2484
complications of, 2484
definition of, 2483
differential diagnosis of, 2483*t*
drug-induced, 2485*t*
manganese and, 101*t*, 107, 107*b*
postural disturbances in, 2484
prognosis of, 2486
resting tremor of, 2484
rigidity associated with, 2484
secondary, 2483*t*
treatment of, 2486*b*
Paromomycin
for amebiasis, 2150*t*
for amebic liver abscess, 1025*b*
for cryptosporidiosis, 2112*t*
for giardiasis, 2145*b*
for intestinal amebiasis, 2112*t*
for visceral leishmaniasis, 2132*b*
Paronychia, 1969, 2753
Parotid gland, swelling of, 987
Parotitis
of childhood, 2626
mumps, 2521
mumps and, 2226
Paroxetine, *e10t*–*e11t*
for depression, 2340*t*
for irritable bowel syndrome, 896*t*
Paroxetine mesylate, for hot flashes, 1631*t*
Paroxysmal atrial fibrillation, 329*b*, 330*f*

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Paroxysmal hemicrania, 2377*t*, 2381
Paroxysmal hypothermia, 681
Paroxysmal nocturnal dyspnea, 256
Paroxysmal nocturnal hemoglobinuria (PNH), 480, 480*b*, 1091–1092, 1126
  clinical manifestations of, 1092
  complement system and, 201*t*
  definition of, 1091–1092
  epidemiology of, 1091
  pathobiology of, 1091–1092
PARP. *See* Poly(ADP-ribose) polymerase
Partial pressure of carbon dioxide ($PaCO_2$), 639
Partial pressure of oxygen (PaO_2), *e*1*t*–*e*8*t*, 639
  normal values of, 639
Particulate matter, 87
Parvoviridae, 2233
Parvovirus, 2233
  B19 arthropathy caused by, 2234
  clinical manifestations of, 2234–2235
  definition of, 2233
  diagnosis of, 2235
  epidemiology of, 2233
  fifth disease caused by, 2234, 2234*f*
  hydrops fetalis caused by, 2235
  other syndromes of, 2235
  pathobiology of, 2234
  persistent infection in, 2235
  prevention of, 2235
  prognosis of, 2236
  pure red cell aplasia caused by, 2235*f*
  transient aplastic crisis caused by, 2234, 2235*t*
  treatment of, 2235*b*
PASC. *See* Post-Acute Sequelae of SARS-CoV-2
Pasireotide, 1356*b*, 1489*b*
"Passenger" mutations, 1249
Passive euthanasia, 8*t*
Passive immunity, 64, 65*t*
  for COVID-19, 2216, 2216*f*, 2217
Passive oral immunotherapy, for infectious gastroenteritis, 2263*b*
Past medical history, 28
Paste, 2697
Pastia lines, 1914
Patau syndrome, 164
Patch, 2689*t*
Patchy alopecia, 2747*t*, 2749
Patellar tendinitis, 1747
Patent ductus arteriosus (PDA), 350
  anatomy of, 350.*e*1*f*
  diagnosis of, 350
  exercise recommendations for, 355.*e*2*t*
  prognosis for, 350*b*
  treatment of, 350*b*
Patent foramen ovale, 348, 349, 349*b*
Paterson-Brown Kelly syndrome, 1337
Pathogen-associated molecular patterns (PAMPs), 182, 183, 191, 192*f*
Pathogen lipid shuttling, 670.*e*1*f*
Pathologic bone fractures, prevention of, in cancer, 1232*b*
Pathologic fractures, bone tumors and, 1388*b*
Pathologic myopia, 2598
Pathologic pain, 133
Patient autonomy, 4
Patient blood management, 1206
Patient communication
  advances in, 40
  Ask-Tell-Ask, 12, 16*t*
  core skills for, 16*t*
Patient education, for acute STEMI, 384*b*
Patient Health Questionnaire-9 (PHQ-9), 54*t*, 257
Patient-level measures, 40
Patient-physician interaction, 4
Patient safety, 45–46
  epidemiology of, 45
  improvement of, 45–46
  modern approach to, 45
Patiromer, for hyperkalemia, 751*b*
Patisiran, for amyloidosis, 1309*b*
Pattern reversal visual evoked potentials, 2376.*e*1*f*, 2376
Patterned alopecia, 2748
Patterns of inheritance, 160
  mendelian inheritance, 160, 161*f*
  mosaicism, 162, 163*f*
  nonmendelian inheritance, 162
Pauci-immune glomerulonephritis, 1716
Pauci-immune rapidly progressive glomerulonephritis, 785, 1716
Paucibacillary leprosy, 2048, 2048*t*, 2048.*e*1*f*
Pay for performance, 44–45
Pazopanib (Votrient), 1215*t*
PBC. *See* Primary biliary cholangitis
PBGD. *See* Porphobilinogen deaminase
PCECV. *See* Purified chick embryo cell vaccine
PCFT. *See* Protein-coupled folate transporter
PCI. *See* Percutaneous coronary intervention
PCOS. *See* Polycystic ovary syndrome
PCP. *See Pneumocystis* pneumonia
PCR. *See* Polymerase chain reaction
PCSK9 monoclonal antibodies, 1413, 1413*t*
PCT. *See* Porphyria cutanea tarda
PDA. *See* Patent ductus arteriosus
PDR. *See* Proliferative diabetic retinopathy
Peak bone mass, 1640, 1640.*e*1*f*
Peak expiratory flow rate (PEFR), 539, 539*t*
Pearson syndrome, 2586
Pectus excavatum, 621, 621*b*, 622*f*
Pediatric autoimmune neuropsychiatric disorders associated with streptococcal infections (PANDAS), 1918
Pediculus humanus, 2027, 2059
Pedunculated polyps, 1343
Peficitinib, 153*t*
PEG. *See* Percutaneous endoscopic gastrostomy
Pegvisomant, for acromegaly, 1489*b*
Pegylated interferon-alfa-2*a*
  for chronic hepatitis B, 1011*b*
  for hepatitis C infections, 2181*t*
Pegylated interferon-alfa-2*b*, for hepatitis C infections, 2181*t*, 2182*t*, 2185–2186
Pegylated interferon lambda, for COVID-19, 2217
Pelger-Huët anomaly, 1071*f*, 1141–1142
Peliosis hepatis, 2002, 2003*b*, 2003*t*
Pelizaeus-Merzbacher disease, 2509
Pellagra, 2541
Pelvic examination
  description of, 31
  for gastrointestinal disease, 851
Pelvic exenteration, for cervical cancer, 1375*b*
Pelvic hernia, 952*b*
Pelvic infection, actinomycosis and, 2068
Pelvic inflammatory disease (PID), 1949
  characteristics of, 1883
  Chlamydia trachomatis causing, 2012
  clinical manifestations of, 1949
  diagnosis of, 1949
  organisms causing, 1879*t*
  prognosis for, 1883, 1949
  treatment of, 1883*b*, 1883*t*, 1949*b*
Pelviureteral abnormalities, 818–819, 820*f*
Pembrolizumab (Keytruda), 1215*t*, 1251*t*
  for melanoma, 1394*t*
  for renal cell carcinoma, 1364*b*
Pemetrexed (Alimta), 1215*t*
Pemphigoid gestationis, 2717, 2717*b*, 2717*f*
Pemphigus, 2651–2652, 2718, 2718*b*–2719*b*
Pemphigus foliaceus, 2687.*e*3*t*, 2718
Pemphigus vulgaris, 194, 2718, 2719*f*
  description of, 2621*t*, 2624
  esophageal involvement in, 911
Penbutolol, 451*t*
Penciclovir, for herpesvirus infections, 2186
Pencil cells, 1068, 1068*f*
Penetrating aortic ulcer, 439, 441*b*, 441*f*
Penetrating injury, 699*f*, 699*t*
Penetrating trauma, pathogens and empirical therapy for, 2526*t*
Penicillamine, 1460*t*
Penicillin
  adverse reactions of, 132
  dosage of, 1895*t*
  for endocarditis, 419*t*, 422
  for Oroya fever, 2003*b*
  for streptococcal infections, 2648
  for *Streptococcus pneumoniae* pulmonary infections, 1912.*e*1*t*
  for syphilis, 2020*b*, 2020*t*
  toxicities of, 1901*t*
Penicillin allergy, delabeling, 1699.*e*1*f*, 1699*b*
Penicillin-binding proteins, 1898
Penicillin G
  for actinomycosis, 2069*b*
  for bacterial meningitis, 2518*t*
  dosage of, 1895*t*
  for erysipeloid, 1936*b*
  for meningococcal meningitis and meningococcemia, 1944*t*
Penicillin V, dosage of, 1895*t*
Penicilliosis, prophylaxis for, 2309*t*
Penile prostheses, for erectile dysfunction, 1589
Pentamidine
  for African trypanosomiasis, 2112*t*, 2125*b*, 2125*t*
  for *Pneumocystis* pneumonia, 2103*b*, 2106*t*, 2108*t*
  for visceral leishmaniasis, 2132*b*
Pentazocine, 136*b*, 139*t*
Pentose phosphate pathway, 1098
Pentoxifylline
  for ischemic heart disease, 470*b*
  for nonalcoholic fatty liver disease, 1034*b*
PEP. *See* Postexposure prophylaxis
Peppermint oil, for irritable bowel syndrome, 895*b*, 896*t*
Peptic strictures, 905
  clinical manifestations and diagnosis of, 904*f*, 905
  prognosis of, 905
  treatment of, 904*t*, 905*b*
Peptic ulcer(s), 211*t*
  abdominal pain from, 1562
  at anastomoses, 916
  "clean base", 922
  clinical presentation of, 919
  complicated, 917*t*
  complications of
    hemorrhage, 921, 922*t*
    intractability, 923
    perforation, 922–923, 922*f*
    stenosis, 923
  definition of, 913
  diagnosis of, 917, 918*t*
  differential diagnosis of, 919
  endoscopy of, 918, 922*t*
  Helicobacter pylori associated with, 914
  Helicobacter pylori-negative, non-NSAID, 915
  hypergastrinemic syndromes causing, 916
  hypersecretory syndromes causing, 918
  ischemia causing, 916
  malignant, 915
  nonsteroidal anti-inflammatory drugs causing, 918
  pathobiology of, 914
  perforation of, 922, 922*f*
  prevention of, 921
  prognosis for, 923
  rebleeding of, 922
  signs and symptoms of, 917*t*
  uncomplicated, 917*t*
Peptic ulcer disease
  abdominal pain and, 854*t*
  differential diagnosis of, 915*t*
  etiologic diagnosis of, 918
  idiopathic, 915, 919*b*
  physical examination of, 917
  prevention of, 921
  upper gastrointestinal bleeding caused by, 882
Peptide-binding cleft, 204.*e*1*f*
Peptide hormone receptors, 1475*f*
Peptide receptor radionuclide therapy, for metastatic neuroendocrine tumor, 1568*b*
Pepto-Bismol, for diarrhea, 926*b*
Per-oral myotomy, 880
Peramivir, for influenza, 2189, 2189*t*, 2202*b*, 2203*t*
Perampanel, for seizures, 2434*t*
Percussion, of liver, 988
Percutaneous coronary intervention (PCI), 265*b*, 395–397
  advantages of, 384*b*
  antiplatelet therapy for, 507
  complications of, 395–396
  coronary artery bypass grafting *versus*, 399
  disadvantages of, 384*b*
  discharge issues of, 397
  failed, 399
  indications for, 384*b*
  for ischemic heart disease, 364*b*
  mechanisms of, 395–397, 395.*e*1*f*, 396*f*
  for multivessel coronary artery disease, 364*b*
  for myocardial infarction, 384*b*, 385*t*
  procedural success of, 395
  recommendations for, 364*t*
  restenosis after, 396
  selection of patients for, 395
  technical considerations of, 395, 395.*e*1*f*, 396*f*
  thrombosis after, 396
Percutaneous endoscopic gastrostomy (PEG), 1449
Percutaneous pericardiocentesis, echocardiographic-guided, 427*b*, 430*f*
Percutaneous transhepatic cholangiography, 1000
Percutaneous transluminal angioplasty, 464.*e*1*f*, 468*b*
Perfectionism, in eating disorders, 1461
Perforation
  in endoscopy, 876*t*
  iatrogenic, 912
Perfusion, asymmetrical, 522
Perfusion imaging, myocardial, 248, 248*f*
Perianal abscess, 978, 979*b*
Perianal disease, in Crohn disease, 945*b*
Perianal fistulas, Crohn disease associated with, 945*b*
Perianal warts, 2242
Pericardial constriction, 428–431
  clinical manifestations of, 428–429
  diagnosis of, 429–430
  differential diagnosis of, 429–430, 433*t*
  epidemiology of, 428–430
  pathobiology of, 428
  treatment of, 431*b*
Pericardial cysts, benign, 433
Pericardial diseases, 423–433
  CMR findings, 252, 253*f*
  echocardiographic findings, 242*t*
  in HIV, 2317, 2317*b*
  specific forms of, 431–433
Pericardial effusion, 241, 243*f*, 425
  in cancer, management of, 1232*b*
  causes of, 427*t*
  chest radiography in, 245, 246*f*, 428*f*
  clinical manifestations of, 425
  diagnosis of, 426
  epidemiology of, 425
  management of, 429*f*
  pathobiology of, 425
  prognosis for, 428
  treatment of, 427*b*
  tuberculosis, 2040
  without tamponade, 427*b*
Pericardial tamponade, 425
  clinical manifestations of, 425
  diagnosis of, 426
  epidemiology of, 425
  pathobiology of, 425
  prognosis for, 428
  treatment of, 427*b*
Pericardial tumors, 296–297
  clinical manifestations of, 296
  diagnosis of, 297
  prognosis for, 297
  treatment of, 297*b*
Pericardiocentesis, echocardiographic-guided percutaneous, 427*b*, 430*f*
Pericarditis, 211*t*, 1769
  acute, 423
    cardiac magnetic resonance image of, 427*f*
    characteristics of, 359
    clinical manifestations of, 423
    diagnosis of, 423
    diagnostic tests for, 425*t*
    electrocardiogram for, 426*f*
    epidemiology of, 423
    pathobiology of, 423
    prognosis for, 425
    treatment of, 424*b*
  autoimmune, 424*t*, 432
  bacterial, 426*t*, 431
  causes of, 424*t*
  constrictive, 429.*e*1*f*, 431*f*
  drug-related, 424*t*
  effusive-constrictive, 431
  fungal, 432
  H. influenzae caused by, 1953
  infectious, 424*t*, 431
  initial management of, 427*f*
  malignant, 432
  metabolic, 424*t*
  neoplastic, 424*t*
  noninfectious, 424*t*
  post-myocardial infarction, 426*t*
  presentation of, 426*t*
  Staphylococcus aureus causing, 1904
  traumatic, 424*t*
  tuberculous, 426*t*, 431, 2037
  uremic, 426*t*, 431
  viral, 426*t*

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Pericardium, congenital abnormalities of, 433
Perihilar opacities, 520
Perilymphatic fistula, 2642
Perindopril, 451*t*
Perinephric abscess, 1875*b*
Perinuclear antineutrophil cytoplasmic antibodies (pANCA), 945
Periodic fever with aphthous stomatitis, pharyngitis, and cervical adenopathy (PFAPA), syndrome of, 1731*t*
Periodic fever with immunodeficiency and thrombocytopenia (PFIT), syndrome of, 1731*t*
Periodic paralysis, 2583.*e1t*, 2585, 2585*t*
Periodontal disease, 2627
Perioperative anaphylaxis, reactions to, 1698
Periorbital purpura, in amyloidosis, 1305, 1306*f*
Periorbital xanthelasma, 1155*f*
Periorificial dermatitis, 2722, 2722*f*
Periostitis, 1667
Peripartum cardiomyopathy, 1621, 1622*b*, 1622*f*
Peripheral arterial disease (PAD), 467–475
  antiplatelet therapy for, 507
  approach to suspected, 466*f*
  atherosclerotic, 461
  cilostazol for, 508
  lower extremity, 461
  in older adults, 114
  patients at risk for, 461*t*
  prognosis for, 468*b*
Peripheral arthritis, 1710
Peripheral autonomic neuropathies, 2560–2561
Peripheral blood smear, 1066–1074
  acute lymphoblastic leukemia on, 1073, 1073*f*
  anisocytosis on, 1067*f*
  basophilic stippling on, 1070*f*
  chronic lymphocytic leukemia on, 1074, 1074*f*
  chronic myeloid leukemia on, 1073, 1073*f*
  clinically significant abnormalities in, incidental detection of, 1074, 1074*t*
  Döhle body on, 1071*f*, 1072
  elliptocyte on, 1068*f*
  "flags" on, 1066–1067
  hemolytic anemia on, 1070
  hereditary elliptocytosis on, 1068*f*
  hereditary pyropoikilocytosis on, 1069*f*
  hereditary spherocytosis on, 1067*f*
  homozygous hemoglobin C on, 1070*f*
  of Howell-Jolly bodies, 1067*f*, 1074*t*
  interpretation of, 1066
  leukemias on, 1073, 1073*f*, 1074*f*
  leukocytosis on, 1072
  leukopenia on, 1072
  lymphomas on, 1073
  macrocyte on, 1067*f*
  macrocytic anemia on, 1067*f*, 1069
  megaloblastic anemia on, 1069
  microcytic anemia on, 1068
  neutropenia on, 1073
  normal, 1066*f*
  normocytic normochromic anemia on, 1069
  Pappenheimer bodies on, 1069*f*
  Pelger-Huët anomaly, 1071*f*
  platelet morphology assessment, 1070–1072
  poikilocytosis on, 1067*f*
  polychromasia on, 1067*f*
  polychromatic cells on, 1067*f*
  polychromatic macrocytes on, 1067*f*
  reasons for performing, 1066–1068, 1071*t*
  red cell on
    agglutination, 1070*f*
    fragmentation, 1068*f*
  rouleaux formation on, 1070*f*
  sickle cells on, 1068*f*
  target cells on, 1068*f*, 1074*t*
  teardrop poikilocytes on, 1069*f*
  thalassemia minor on, 1067*f*
  thrombocytopenia assessment, 1070
  thrombocytosis assessment, 1070
  toxic granulation on, 1071*f*
Peripheral cold injuries, 680
Peripheral cutaneous T-cell lymphomas, 2734
Peripheral edema, anemia and, 1076
Peripheral lung disease, 523, 524*t*
Peripheral membrane proteins, 1094
Peripheral nerve entrapment syndromes, 1754
Peripheral nerve injuries, in joint diseases, 1829
Peripheral neuropathy, 2554*t*, 2564*t*
  alcoholism causing, 2544
  anatomic pattern of, 2568*t*
  characteristics of, 2581*t*
  Charcot-Marie-Tooth disease, 2568, 2570*b*, 2570*f*
Peripheral neuropathy *(Continued)*
  clinical manifestations of, 2566–2567
  definition of, 2566
  diagnosis of, 2567–2568, 2569*f*
  epidemiology of, 2566–2568
  familial amyloid polyneuropathy, 2570, 2570*b*
  in HIV/AIDS, 2313, 2313*b*
  inborn errors of metabolism and, 1399
  laboratory testing of, 2568
  in Lyme disease, 2025
  in multiple myeloma, 1299
  nerve biopsy of, 2567, 2569*f*–2570*f*
  nerve conduction studies for, 2571
  pathobiology of, 2566
  prevalence of, 2566
  skin biopsy of, 2567, 2569*f*, 2570*f*
Peripheral oligoarthritis, 1762
Peripheral polyneuropathy, 2566, 2567*t*, 2578
Peripheral spondyloarthritis, 1765–1767
Peripheral T-cell lymphomas, 1286–1287
Peripheral vertigo, 2644
Periprosthetic joint infection, 1829
Perisinusoidal cells, 1035
Peristalsis, defense mechanisms based on, 902
Peritendinitis, 1742
Peritoneal adhesions, 957, 958*f*
Peritoneal carcinomatosis, 957, 958*b*, 958*f*, 1241*b*
Peritoneal dialysis
  chronic ambulatory, 957
  for irreversible renal failure, 841
Peritoneum
  anatomic disease of, 951
  inflammatory diseases of, 951
Peritonitis, 956–958, 1949
  abdominal pain and, 854*t*, 856
  Candida, 2091
  chronic ambulatory peritoneal dialysis as cause, 957
  clinical manifestations of, 957, 957*f*
  diagnosis of, 957
  primary, 956–957
  prognosis for, 957*b*
  secondary, 957
  spontaneous bacterial, cirrhosis and, 1036–1038
  treatment of, 957*b*
  tuberculous, 957, 2037
Peritonsillar abscess, 2649, 2649*t*, 2650*f*
Perjeta. *See* Pertuzumab
Permanent contraception, 1617
Permanent partial disability, 85
Permanent total disability, 85
Permethrin
  for lice, 2742*b*
  for scabies, 711*b*
Pernicious anemia, 1340
  cobalamin malabsorption and, 1119
  diagnosis of, 1123
  incidence of, 1117
Pernio, 473–474, 474*f*
  lupus, 601, 602*f*
  proposed diagnostic criteria of, 473.*e1f*, 474*t*
Peroral endoscopic myotomy, for achalasia, 908*b*
Perphenazine, *e*10*t*–*e*11*t*, 2346*t*
Persistent infectious diarrheas, 932
Persistent müllerian duct syndrome (PMDS), 1573
Personal behavior control, 2410
Personal hygiene, shigellosis and, 1982
Personality disorders, 2346*t*, 2347, 2347*b*, 2348*t*
Personality pathology, 2337*t*
Personalized medicine, 174
Pertussis, 1994
  immunization for, 66*t*, 78*f*, 81
    schedule of, 76.*e1t*, 77*f*
  in travelers, 1889.*e1t*
Pertuzumab (Perjeta), 1215*t*, 1251*t*
Pertzye, for exocrine pancreatic insufficiency, 975*t*
Pes anserinus syndrome, 1747, 1747*b*
Pesticides, 88*t*
PET. *See* Positron emission tomography
PET/CT. *See* Positron emission tomography/computed tomography
Petechiae, 414, 414*f*, 1172*f*, 2713, 2713*t*, 2714*f*
Petrolatum (Vaseline), for skin diseases, 2697
Peutz-Jeghers syndrome, 1250*t*, 1344, 1347*t*, 1348
PFAPA. *See* Periodic fever with aphthous stomatitis, pharyngitis, and cervical adenopathy
PFIT. *See* Periodic fever with immunodeficiency and thrombocytopenia
Pfizer BioNTech COVID-19 vaccine, 77, 2218*t*, 2219
pH, *e*1*t*–*e*8*t*
  Henderson-Hasselbalch equation, 639
  kidney and, 731
  secretion, control of, 732
  of urine, 721–722
Ph chromosome, 1273
pH-sensitive intracellular processes, 752
PHACE syndrome, 2550*t*
Phaeohyphomycosis, 2109–2110, 2111*b*
Phagocytic defects, 1683–1684, 1683.*e1t*, 1684*b*
Phalen sign, 2578–2579
Pharmacodynamics
  changes with age, 130
  drug interactions, 131
Pharmacogenetic syndromes, 132
Pharmacogenetic testing, 159–160, 160*t*
Pharmacogenomics, 167
Pharmacokinetics
  changes with age, 130
  clinical application of, 127–128
  drug interactions, 131
  principles, 126–127
Pharmacology, of aging, 122
Pharmacotherapy
  for irritable bowel syndrome, 895*b*
  for obesity, 1467*b*, 1468*t*
  for resistant arrhythmias, 313*b*
  for urinary incontinence, 829*b*
PharmGKB, 169.*e1t*
Pharyngitis, 1948, 2648–2651
  clinical manifestations of, 1948
  diagnosis of, 1948
  management of, guidelines for, 2649*t*
  noninfectious, 2651
  Streptococcus pyogenes causing, 1914, 1914*f*, 1914*t*
  viral, sore throat and, 2649*t*
Pharynx, 2648, 2648*f*
Phase 2 re-entry, 302, 302*f*
Phencyclidine, 2364, 2365*b*
  properties of, 142*t*
  screening for, 689*t*
Phenelzine, for depression, 2340*t*
Phenobarbital, *e*10*t*–*e*11*t*
  for primary sclerosing cholangitis, 1058*b*
  for seizures, 2434*t*
  toxicity, 690*t*, 698*t*
Phenothiazine, 2700*t*
Phenotypes, 1674
Phenoxybenzamine, 451*t*, 1533*b*
Phentermine, for obesity, 1467*b*
Phentolamine, for hypertensive emergencies, 460*t*
Phenylephrine, 747
  for cardiogenic shock, 667*b*
  for shock, 664*t*
Phenylketonuria, 1398*t*, 1402, 1402*b*, 1402*t*
Phenytoin
  free, *e*10*t*–*e*11*t*
  pharmacokinetic parameters for, 127.*e1t*
  in renal failure, 129.*e1t*
  for seizures, 2434*t*
  total, *e*10*t*–*e*11*t*
  toxicity, 690*t*
Pheochromocytoma
  cardiomyopathy associated with, 1531
  clinical manifestations of, 1530, 1530*t*
  complications of, 1533*b*
  definition of, 1529
  diagnosis of, 1531, 1531*f*
  differential diagnosis of, 1531
  epidemiology of, 1530
  evaluation of, 448*t*
  in familial paraganglioma, 1530
  genetic testing of, 1532
  genetics of, 1530
  hypertension and, 450, 450*b*
  laboratory findings for, 1531, 1532*f*, 1532*t*
  localization of tumor in, 1531–1532
  medical therapy for, 1533*b*
  metastatic, 1533
  in multiple endocrine neoplasia, 1530
  in neurofibromatosis, 1530
  paraganglioma *versus*, 1529
  pathobiology of, 1530
  in pregnancy, 1533
  prognosis for, 1533
  signs and symptoms of, 1530*t*
  surgical therapy for, 1533*b*
  treatment of, 1533*b*
  in von Hippel-Lindau disease, 1530
Philadelphia chromosome-negative acute lymphoblastic leukemia, 1263*t*
Philadelphia chromosome-positive acute lymphoblastic leukemia, 1262*b*
Phlebitis, in hyperosmolar nutrition solutions, 1450
Phlebotomus, 90, 2280, 2280*b*
Phlebotomus fever virus, 2275*t*
Phlebotomy, for hemochromatosis, 1441*b*
Phosphate
  inorganic, *e*1*t*–*e*8*t*
  for osteomalacia, 1651*t*
  regulation of, 732, 732.*e1f*
Phosphate economy, regulation of, 1652*f*
Phosphatidylinositol 3-kinase (PI3K) δ inhibitors, for chronic lymphocytic leukemia, 1269*b*
Phosphatidylinositol glycan *(PIG-A)* gene, 1091
Phosphodiesterase 4 inhibitors, 551*b*
Phosphodiesterase inhibition, 508
  clinical uses of, 508
  pharmacology of, 508
Phosphodiesterase type 5 inhibitors
  for benign prostatic hyperplasia, 822*b*
  for erectile dysfunction, 1589
  for male lower urinary tract symptoms, 824*t*
  for pulmonary hypertension, 496*b*
Phospholamban, 224
Phospholipids, 1093, 1715
Phosphorus
  metabolism, 767
  for osteomalacia, 1639*b*
Phosphorylase deficiency, 2586
Photoallergy, 2705, 2705*t*
Photochemotherapy, for mastocytosis, 1703*b*
Photodermatoses, 2704–2705, 2704*t*
  chronic actinic dermatitis, 2704, 2704*f*
  cutaneous porphyrias, 2705, 2705*f*
  photoallergy, 2705, 2705*t*
  phototoxicity, 2705, 2705*t*
  polymorphic light eruption, 2704, 2704*f*
Photodynamic therapy, for skin cancers, 2701
Photophobia, 2599
Photopsia, 2599
Photosensitivity, 1430, 1433
Photosensitivity and withdrawal reactions, 2728, 2729*t*
Phototherapy, for skin cancers, 2701
Phototoxicity, 2705, 2705*t*
Phymatous rosacea, 2722
Physical abuse, neurologic diseases and, 2369
Physical activity, 61–64
  behavioral interventions for, 55
  cancer and, 1245
  definition of, 61
  dose-response, 62–63, 63*f*
  energy expenditure of, 1465
  guidelines
    for adults, 62*t*, 63*b*
    for older adults, 63*b*
    for weight management, 63*b*
  health-enhancing, 61
  health risks, 63*b*
  levels of, 62
  mechanisms of effect, 62, 63*f*
  for obesity, 1464, 1467*b*
  for osteoarthritis, 1741*t*
  preventive health benefits in adults, 62
  recommendations
    for clinical settings, 63*b*
    tailoring, 63*b*
  risk management of, 63*b*
  therapeutic health benefits of, 63*b*
  types of, 61
  volume of, 61
Physical change, in puberty, 1591, 1591*f*
Physical examination, 28–32, 28
  of abdomen, 31
  for acute poisoning, 682, 683*t*
  for adolescents, 111
  for alcohol use disorders, 2355*t*, 2357
  of breast, 30
  chaperones, 28
  of chest, 30
  for cirrhosis, 1038
  for endocrine disease, 1472
  findings on, as health measures, 40
  future directions for, 32
  for gastrointestinal disease, 851
  of head and neck, 29
  of heart, 30
  of liver, 31
  for liver disease, 988

Copyrighted material

Physical examination *(Continued)*
lungs, 30
of male genitalia, 31
of musculoskeletal system, 31
pelvic examination, 31
of rectum, 31
of respiratory system, 639
for signs of cardiovascular disease, 212
of skin, 31
of spleen, 31
summarizing findings for patients, 32
vital signs, 29
Physical fitness, health-related, 61
Physical frailty, in older adults, 123*t*
Physical inactivity, cardiovascular disease and, 220
Physical injuries, to lung, 591
Physical stimuli, 1693
Physical symptoms, management of, approaches to, 13*t*
Physician-assisted suicide, 8, 8*t*
definition of, 8, 8*t*
empirical data for, 8
history of, 8
justification of, 8
practical considerations for, 9
safeguards, 8
state laws regarding, 16
Physician-patient relationship, informed consent, 5, 6*t*
Physicians, in health resources, 43
Physiologic anisocoria, 2617
Physiologic system dysregulation, 120, 120.e1*f*
Physiologic tremor, enhanced, 2489–2490
Physiologic vertigo, 2644
Physiology
of circulatory control, 225
of heart, 225
Physostigmine, for acute poisoning, 693*t*
PI3 kinase/AKT signaling pathways, 1251.e1*f*
Pibrentasvir, for hepatitis C virus, 1008*b*
Pica, 1075, 1084, 1461, 1462*b*
Pick disease, 2421–2422
PID. *See* Pelvic inflammatory disease
Piebaldism, 2743
Pigmentary retinal degeneration, 2615
Pigmentation, disorders of, 2742–2744, 2742*t*
Pigmented granular casts, 722, 724*f*
Pill-induced esophagitis, 907, 907*t*
Pimavanserin, 2487*t*
Pindolol, 451*t*
Pineal gland tumors, 2617
Pinguecula, 2602, 2603*f*
Pink disease, 103
Pinta, 2021
Pinworm, 2172
Pioglitazone, for type 2 diabetes mellitus, 1541*t*
Piperacillin-tazobactam
for pyelonephritis and urosepsis, 1877*t*
for pyogenic liver abscess, 1023*b*
for *Stenotrophomonas maltophilia*, 1975*b*
Piperacillin/tazobactam
dosage of, 1895*t*
for pneumonia, 613*t*, 616*t*
Piperazine, 2700*t*
Piperidine, 2700*t*
Pirfenidone, 576*b*
Piroxicam
for chronic pain, 138*t*
for dysmenorrhea, 1596*t*
Pit vipers, 708
Pitavastatin, for familial hypercholesterolemia, 1409*t*
Pitolisant, 2449*t*
Pitting, 2752, 2753*f*
Pittsburgh Sleep Quality Index, 2444
Pituitary adenomas, 1314, 1524*b*
description of, 1486, 1489
inherited syndromes of, 1487*t*
nonfunctioning, 1497
Pituitary apoplexy, 1485, 1485*t*, 1486*b*, 1486*t*
Pituitary axis, 1482
Pituitary carcinomas, 1498, 1498*f*
Pituitary gland
intrinsic rhythm of, 1478
lesions of, 1527
neuroendocrine organization of, 1476*f*
Pituitary macroadenoma, 1485*f*
Pituitary tumors, 1486
clinical manifestations of, 1487
Pituitary tumors *(Continued)*
functioning, 1488*t*
hypogonadotropic hypogonadism and, 1584
medical therapy for, 1487*b*
pathobiology of, 1486
prognosis for, 1488
radiation therapy for, 1487*b*
surgery for, 1487*b*
treatment of, 1487*b*
Pityriasis (tinea), 2744
Pityriasis lichenoides, 2709
Pityriasis lichenoides chronica (PLC), 2709
Pityriasis lichenoides et varioliformis acuta (PLEVA), 2709
Pityriasis rosea, 2687.e3*t*, 2707, 2707*b*, 2707*f*
Pityriasis rubra pilaris, 2692*t*, 2707, 2707*b*, 2707*f*
Pityrosporum folliculitis, 2723
Pivmecillinam, for cystitis, 1876*t*
PKD1, 810
PKD2, 810
Placenta, 1569
Plague, 1988–1994, 2065*t*
bioterrorism uses of, 98–99
bubonic, 1990*f*, 1991, 1991*f*
clinical manifestations of, 98, 1991
definition of, 1988
diagnosis of, 98, 1991
differential diagnosis of, 1991
ecology and transmission of, 1990*f*
epidemiology of, 98, 1988–1989, 1988.e3*f*, 1989*f*–1990*f*
pathobiology of, 98, 1989–1991, 1990*f*
pathogen that causes, 1988, 1988*f*
pneumonic, 1990*f*, 1991
prevention of, 99, 1992–1993
prognosis of, 99, 1993
septicemic, 1991
treatment of, 98*b*, 1991*b*, 1992*t*
Plain radiographs, for acute mesenteric ischemia, 960
"Plan, do, study, act" (PDSA), 45
Plantar fasciitis, 1748, 1748*b*
Plantar warts, 2242, 2242*f*
Plaque, 2499
atherosclerotic, 227.e1*f*, 370
rupture, 370–371
skin, 2689*t*
Plasma, 1581
bilirubin measurement in, 994
pH regulation, 731, 731.e1*f*, 732*f*
potassium regulation, 732
transfusion, 1200, 1204–1205, 1204*t*
Plasma cell disorder, 1294–1305
definition of, 1294–1295, 1294*t*
heavy chain diseases, 1303
hyperviscosity syndrome, 1303, 1303*b*, 1304*f*
monoclonal gammopathy of undetermined significance. *See* Monoclonal gammopathy of undetermined significance
multiple myeloma. *See* Multiple myeloma
syndromes associated with, 1294
Waldenström macroglobulinemia. *See* Waldenström macroglobulinemia
Plasma cell leukemia, 1302, 1302*b*
Plasma exchange, for thrombotic thrombocytopenic purpura, 1177*b*
Plasma volume, *e8t*–*e9t*
Plasmablastic lymphoma, 1285, 2315
Plasmapheresis, 2701
for systemic lupus erythematosus, 1772*b*
for thrombotic thrombocytopenic purpura, 1177*b*
Plasminogen activator, tissue, for frostbite, 474*b*
Plasmodial parasites, 2120
Plasmodium brasilianum, 2118
Plasmodium falciparum, 2118. *See also* Malaria
malaria caused by, 2111
in travelers, 1889.e1*t*
Plasmodium knowlesi, 2065*t*, 2118
Plasmodium ovale, 2118
Plasmodium simium, 2118
Plasmodium spp, 1026*t*
Plasmodium vivax
malaria caused by, 2111
in travelers, 1889.e1*t*
Plastics, 88*t*
Plateau airway pressure, 652*t*
Plateau pressure, 640*f*, 655
Platelet(s)
activation, 1165
adhesion, 1165
aggregation of, 370
blood smear, 1071, 1072*f*
decreased production of, 1171
destruction of, 1171, 1171*t*
HIV transmission through, 2299
immune-mediated destruction of, 1171
morphology of, peripheral blood smear assessment of, 1070
sequestration of, 1171
Platelet-activating factor, 1694
Platelet concentrates, 1204
Platelet count, *e8t*–*e9t*, 1070–1071, 1166, 1173*t*
abnormalities in, postoperative, 2675
Platelet dysfunction, acquired, 1185, 1185*b*, 1185*t*
Platelet function, disorders involving, 1184–1185
Platelet granule defects, 1185
Platelet $P2Y_{12}$ receptor antagonists, 507
Platelet plugs, 371
Platelet-poor plasma (PPP), 1169
Platelet receptor defects, 1184
Platelet-rich plasma (PRP), 1169
Platelet transfusions
alloantibodies, 1171*b*
complications of, 1171*b*
components of, 1200
indications for, 1204, 1204*t*
prophylactic, 1171*b*, 1204
for thrombocytopenia, 1171*b*
for von Willebrand disease, 1183*b*
Platelet-vascular disorders, 1166*t*
Platinol. *See* Cisplatin
Plazomicin, 1845*t*, 1899
dosage of, 1895*t*
PLC. *See* Pityriasis lichenoides chronica
Plecanatide, for irritable bowel syndrome, 895*b*, 896*t*
Plegridy. *See* Interferon Beta1*a* pegylated
Pleomorphic adenoma, 2625
Plethysmography, body, 530
Pleura, 623–627
Pleural disease, 525–526
Pleural effusion, 623
clinical manifestations of, 624
conditions that cause, 623*t*
diagnosis of, 624–625, 624*f*
epidemiology of, 623–624
malignant, 625, 625*b*
Mycoplasma pneumoniae in, 2006
as occupational lung disease, 585*t*
parapneumonic, 625, 625*b*
pathobiology of, 623
recumbent studies on, 519
in systemic inflammatory disorders, 626
tuberculous, 626, 626*b*
Pleural empyema, *Staphylococcus aureus* causing, 1904
Pleural exudates, 626
Pleural fluid
disease characteristics, 625*t*
mechanisms that promote accumulation of, 623*t*
normal turnover, 623
Pleural friction rub, 512
Pleural plaques, 525–526, 525*f*
Pleural tuberculosis, 2035, 2036*f*
Pleural tumors, 526
Pleurisy, 211*t*, 1730–1732
Pleurodynia, enteroviruses causing, 2260, 2260*b*
Pleuropulmonary infections, 1939
PLEVA. *See* Pityriasis lichenoides et varioliformis acuta
Plicatic acid, 88*t*
Plummer-Vinson syndrome, 1084, 1337
Pluripotent stem cells, induced, 170*f*–172*f*, 171–172
PMA. *See* Progressive muscular atrophy
PMR. *See* Polymyalgia rheumatica
PMS. *See* Premenstrual syndrome
pNENs. *See* Pancreatic neuroendocrine neoplasms
Pneumatic dilation, for achalasia, 908*b*
Pneumatosis, 867*f*, 960*f*
Pneumococcal conjugate vaccine, 66*t*, 81, 612–613
Pneumococcal disease, immunization for, 66*t*, 81
adverse reactions of, 81
indications for, 66*t*, 81
schedule of, 76.e1*t*, 77*f*
Pneumococcal meningitis, 2511, 2514
Pneumococcal pneumonia
antimicrobial therapy for, 1912*t*
clinical manifestations of, 1911
complications of, 1911
diagnosis of, 1911
incidence of, 1910
prevention of, 1912
radiographic findings, 609
risk factors for, 1910
treatment of, 1912*b*
Pneumococcal polysaccharide vaccine (PPSV23), 66*t*, 81, 612
Pneumoconioses, 88*t*, 590, 590*t*, 591*f*
Pneumocystis jirovecii
definition of, 2101
as pathogen, 2101
Pneumocystis pneumonia (PCP), 520, 2101
adjunctive corticosteroid therapy for, 2103*b*
algorithm for, 2105*f*
alternative antimicrobial for, 2103*b*
antiretroviral therapy for, 2103*b*
clinical manifestations of, 2102, 2103.e1*f*
definition of, 2101
diagnosis of, 2103, 2104*f*, 2105*f*
drug regimens for, 2106*t*
epidemiology of, 2102
histopathology of, 2102.e1*f*, 2103.e1*f*
HIV/AIDS patients, 2106, 2107*t*
non-HIV patients, 2106, 2108*t*
pathobiology of, 2102, 2102.e1*f*
pathogen, 2101
prevention of, 2106
prognosis of, 2107
prophylaxis for, 2309*t*
treatment for, 2103*b*, 2106*t*
Pneumomediastinum, 541*f*, 629
Pneumonia, 700*b*, 1911*f*
Acinetobacter causing, 1973
acute interstitial, 566*t*
antimicrobial therapy for, 613*t*
in-hospital regimens, 610*b*
outpatient regimens, 610*b*
aspiration, 615
bacterial, 566, 610*b*
bronchiolitis obliterans organizing pneumonia of unknown cause, 578
causative agent of, 608–609, 609*t*
causes of, 610*t*
chronic eosinophilic, 582
clinical manifestations of, 607
community-acquired, 606, 611*f*, 612*f*, 1851*b*
antibiotic therapy for, 1912*b*
bacterial species that cause, 1892*t*
Staphylococcus aureus causing, 1904
Stenotrophomonas maltophilia and, 1975
Streptococcus pneumoniae causing, 1910
treatment of, 1998*b*
cryptogenic organizing, 578
diagnosis of, 579, 579*f*, 580*f*
prognosis for, 579*b*
radiographic features of, 574*t*
treatment of, 579*b*
curb-65 scoring system for, 610*t*
cytomegalovirus, 2250*f*, 2251
definition of, 606
diagnosis of, 607–610
differential diagnosis of, 609–610
Enterobacterales causing, 1965
enteroviral, 2260
epidemiology of, 606–607
H. influenzae caused by, 1953
health care-associated, 616*t*
hospital-acquired, 613–615, 615*b*, 616*t*
with immune complex glomerulonephritis, 784*t*
in immunocompromised hosts, 616–619, 617*b*, 617*t*, 618*f*
interstitial
acute, 574*t*, 578, 579*f*
chronic fibrosing, 571*t*, 575
desquamative, 578
idiopathic, 575
lymphocytic, 579
lymphoid, 579, 580*b*, 580.e1*f*
nonspecific, 577
rare, 571*t*
smoking-related, 571*t*, 577
laboratory testing of, 609
legionellosis and, 1997–1998, 1998*f*

Copyrighted material

Pneumonia *(Continued)*
lipoid, 598, 598*b*, 598*f*
as occupational lung disease, 585*t*
overview of, 606–619
patchy, 608*f*
pathobiology of, 607
physical examination of, 607
with pleurisy, 211*t*
Pneumocystis, 2101
prevention of, 612–613, 615
prognosis for, 613, 615
radiology of, 607–608, 608*f*
Streptococcus pyogenes causing, 1916
treatment of, 610*b*
ultrasonography for, 520
unusual causes of, 609
ventilator-associated, 614*t*, 1862*t*, 1866, 1969, 1970*b*
viral, 607
Pneumonia Severity Index, 611*t*
Pneumonic plague, 1990*f*, 1991, 2270*t*
Pneumonic tularemia, 1987
Pneumonitis, hypersensitivity, 581, 581.*e1f*, 588
chronic, 581.*e1f*
classification of, 571*t*
clinical features of, 581
clinical manifestations of, 581
diagnosis of, 581
pathobiology of, 581
prognosis for, 581*b*
treatment of, 581*b*
Pneumonitis, in HIV, 2319
Pneumoperitoneum, abdominal radiographs of, 867*f*
Pneumothorax, 526, 526.*e1f*, 627
clinical manifestations of, 627
diagnosis of, 627, 627*f*
epidemiology of, 627
pathobiology of, 627
right-sided, 624*f*
spontaneous, 211*t*, 631
surgery for, 631
tension, 627
treatment of, 628*b*
ultrasonography for, 520
PNH. *See* Paroxysmal nocturnal hemoglobinuria
PNH II erythrocytes, 1091
PNH III erythrocytes, 1091
PNP. *See* Purine nucleoside phosphorylase
Podocytes, 729, 779–780
Podophyllin, topical, for anal warts, 982*b*
POEMS syndrome, 2316, 2575, 2575*b*, 2575*f*, 2575*t*, 2743, 2743*t*
Poikilocytes, teardrop, 1069*f*
Poikilocytosis, peripheral blood smear of, 1067*f*
Poikilothermy, 1481
Point-of-care echocardiography, 238, 239*t*
Point-of-care tests, 1169
Poison ivy dermatitis, 2691*t*
Poisoning, 759–760, 2589*t*
acute, 682
antidotes for, 691*b*, 693*t*
blood tests for, 690
cardiopulmonary effects of, 684
decontamination of, 691*b*
dermatologic signs of, 685
diagnosis of, 682
diagnostic tests for, 685, 689*t*, 690*t*
elimination of, 691*b*
epidemiology of, 682
gastrointestinal effects of, 684
history of, 682
imaging for, 691
neurologic signs of, 683, 685*t*
physical examination for, 682, 683*t*
specific toxicants in, 685, 686*t*
stabilization of, initial, 691*b*
treatment of, 691*b*, 692*f*
vital signs for, 682
arsenic, 103
cadmium, 104
carbon monoxide, 595, 596*b*
cyanide and other gases, 596, 596*b*
lead, 101
by marine animals, 713
mercury, 102
trace metals, 101
Policymakers, criteria for, 42*t*
Polio, vaccine, for traveler, 1886*t*, 1887
Poliomyelitis, 2257
immunization for, 66*t*, 76.*e1t*, 81
Polioviruses, circulating vaccine-derived, 2257
Poly(A)-binding protein, 2585
Polyangiitis, granulomatosis with, 582
eosinophilic, 573, 582
Polyarteritis nodosa, 965, 1795, 1797*f*, 2716*f*, 2735
epidemiology of, 1793*t*
pathologic characteristics of, 1793*t*
prognosis of, 1795*b*
treatment of, 1795*b*
Polychondritis
flow-volume curve of, 529*f*
relapsing, 2652, 2652.*e1f*
Polychromasia, peripheral blood smear of, 1067*f*
Polychromatic cells, peripheral blood smear of, 1067*f*
Polychromatic macrocytes, peripheral blood smear of, 1067*f*
Polyclonal immunoglobulins, 1295, 1295*f*
Polycystic kidney diseases (PKDs)
autosomal dominant. *See* Autosomal dominant polycystic kidney disease
autosomal recessive. *See* Autosomal recessive polycystic kidney disease
Polycystic liver disease, 990
Polycystic ovary syndrome (PCOS), 1594, 1601, 1602*b*, 1608*t*
Polycystin-1 (PC1), 810.*e1f*
Polycystin-2 (PC2), 810.*e1f*
Polycythemia vera, 1130
anagrelide for, 1135*b*
aspirin for, 1135*b*
clinical manifestations of, 1133, 1133.*e1t*
definition of, 1130, 1130*t*
diagnostic criteria for, 1134, 1134*t*
epidemiology of, 1130
gender-stratified features, 1133.*e1t*
genotype-phenotype correlations, 1131
hydroxyurea for, 1135*b*
interferons for, 1135*b*
neutrophilia and, 1142
pathobiology of, 1130, 1131*f*
prognosis for, 1138
ruxolitinib for, 1135*b*
survival in, 1138–1139, 1138.*e1t*
treatment of, 1135*b*, 1136*t*
Polydipsia, primary
clinical manifestations of, 1501
diagnosis of, 1503
pathobiology of, 1500
treatment of, 1503*b*
Polyethylene glycol, for irritable bowel syndrome, 895*b*, 896*t*
Polygenic risk scores, 159, 159*f*, 167
Polyglandular autoimmune hypoparathyroidism, 1661
Polyglandular disorders, 1558–1560
autoimmune, 1559
clinical features of, 1559*t*
type 1, 1559
type 2, 1560, 1560*b*
type 3, 1560, 1560*b*
type 4, 1560, 1560*b*
definition of, 1558
epidemiology of, 1558
neoplastic, 1558–1559, 1559*b*, 1559*t*
Polymerase chain reaction (PCR), 1834, 1835*f*
for acute bronchitis and tracheitis, 605
for amebiasis, 2148
for anemia, 1077
for *Bartonella* infection, 2002
for *Campylobacter jejuni*, 1958–1959
for COVID-19, 2214, 2215*f*
for granuloma inguinale, 2004
for legionellosis, 1998
for meningococcal disease, 1943
for mumps, 2226
for nocardiosis, 2073
for relapsing fever, 2028
for toxoplasmosis, 2138*t*
for varicella-zoster virus, 2249
for Whipple disease, 2070
Polymicrobial endobronchial colonization, in cystic fibrosis, 557
Polymicrobial infections, for antimicrobial therapy, 1843
Polymicrogyria, 2547
Polymorphic light eruption, 2704, 2704*f*
Polymyalgia rheumatica (PMR), 1801
algorithm for, 1802*f*
clinical manifestations of, 1801
definition of, 1801
Polymyalgia rheumatica (PMR) *(Continued)*
diagnosis of, 1709, 1802
differential diagnosis of, 1803
epidemiology of, 1801
pathobiology of, 1801
prognosis for, 1803
superficial temporal artery, assessment of, 1803
survival rates for, 1803
treatment of, 1803*b*
Polymyositis, 1238*t*, 2327*t*, 2588*t*
clinical features of, 1788*t*
diagnosis of, 1788
diagnostic criteria for, 1790*t*
epidemiology of, 1787
interstitial lung disease associated with, 581
pathobiology of, 1787
treatment of, 1790*b*
Polymyxin B (Polypore)
for *Acinetobacter*, 1974*b*
for bacterial meningitis, 2518*t*
for skin diseases, 2697
for *Stenotrophomonas maltophilia*, 1975*b*
Polyomavirus, 2227–2233
Polypharmacy, 118
Polyploidies, 164
Polypoid lesion, CT colonography for, 871*f*
Poly(ADP-ribose) polymerase (PARP) inhibitors, 1251, 1252*f*
Polyps, 1347–1349
adenomatous, 1348
colonic, 1347
lymphoid, 1348
nasal, 2629, 2629*f*, 2630*f*, 2635, 2635*b*, 2635*f*
non-neoplastic, 1348
serrated, 1348
Polyradiculoneuropathy, chronic inflammatory demyelinating, 2572, 2572*b*
Polyradiculopathy, 2567*t*
Polysomnography
indications for, 2446*t*
for obstructive sleep apnea, 2444, 2445*f*
Polyunsaturated fatty acids, omega-3, for heart failure, 265*b*
Polyuria, 743–744, 743*t*, 744*b*, 744*f*
Pomalidomide (Pomalyst), 1215*t*
Pomalyst. *See* Pomalidomide
POMC. *See* Proopiomelanocortin
Pompe disease, 282*b*, 1417*t*, 1420*t*, 1424
Ponatinib (Iclusig), 1215*t*, 1251*t*, 1275*t*
Ponesimod (Ponvory), for multiple sclerosis, 2505*t*
Pontiac fever, 1998, 1999
Pontine hemorrhage, 2479
Pontomedullary and pontine stroke syndromes, 2465.*e1f*
Ponvory. *See* Ponesimod
Poor self-esteem, adolescents with, 113
Popliteal artery entrapment syndrome, 467, 467*b*, 467*f*
Popliteal cysts, 1747, 1747*b*
Population health, 47–49
management, 47
on severe mental illnesses, 2677
social determinants of health
activities of health delivery systems to address social needs and, 48*f*
interventions focused on, 47
relative contribution of clinical care, individual behaviors, 48*f*
Population screening, 159
Porcelain gallbladder, 1052*b*
Pork tapeworm, 2159
Porphobilinogen (PBG), *e1t*–*e8t*
Porphobilinogen deaminase (PBGD), 1428*t*, 1429, 1429.*e1f*
Porphyria cutanea tarda (PCT), 1428*t*, 1434*b*, 2705, 2705*f*, 2719–2720, 2719*b*, 2719*f*
Porphyrias, 1428–1435, 1428*t*, 2564*t*
acquired, somatic mutations resulting in, 1430
acute attack of, 1430, 1431*f*
clinical manifestations of, 1430–1432, 1431*f*
diagnosis of, 1433
differential diagnosis of, 1434
prognosis of, 1435
treatment of, 1434*b*
acute hepatic, 1429
clinical manifestations of, 1430
congenital erythropoietic, 1430
definition of, 1428–1435
diagnosis of, 1433–1434
Porphyrias *(Continued)*
differential diagnosis of, 1434
epidemiology of, 1428–1429
genetic testing for, 1434
nonacute, 1429
pathobiology of, 1429–1430, 1429*f*
pathogenesis of, 1430
prevention of, 1435
prognosis of, 1435
recurrent attacks, 1432, 1434*b*
treatment of, 1434*b*
Porphyrogenic medication, 1430
Portal hypertension, cirrhosis and, 1036, 1037*f*
Portal vein, 986
Portal vein thrombosis, 968
clinical manifestations and diagnosis of, 968
prognosis of, 968
treatment of, 968*b*
Portopulmonary hypertension, cirrhosis and, 1037, 1040
Posaconazole, 2076
adverse effects of, 2077
drug interactions of, 2076
formulations and pharmacology of, 2076
for hepatosplenic candidiasis, 1024*b*
for histoplasmosis, 2083*b*
indications and dosage of, 2075*t*, 2076
for mucormycosis, 2100*b*
for sporotrichosis, 2086*b*
Positive concordance, 335
Positive end-expiratory pressure, 653
for acute respiratory distress syndrome, 656, 656*f*
auto-PEEP, 654, 654.*e1f*
Positive predictive value, 38
Positive-pressure ventilation, 652
noninvasive, 620*b*, 653
Positive selection, 204
Positron emission tomography (PET), 519
for Hodgkin lymphoma, 1291
for lung cancer, 1331
for rheumatic diseases, 1723
strengths and weaknesses of, 2373*t*
Positron emission tomography/computed tomography (PET/CT), metastatic disease on, 874*f*
Post-Acute Sequelae of SARS-CoV-2 (PASC), 2208
Post-herpetic neuralgia, zoster and, 2248–2249
Post-kala-azar dermal leishmaniasis, 2131, 2132
Post-myocardial infarction ventricular tachycardia, 336
Post-polio syndrome, 2564*t*
Post-radiotherapy sequelae, 94
Post-splenectomy, neutrophilia and, 1142
Post-streptococcal glomerulonephritis, 783, 783*b*, 783*f*, 1918, 1918*b*, 2270*t*
Post-streptococcal immunologic phenomena, 1917–1918
Post-thrombotic syndrome, 490
Post-transfusion purpura, 1203
Post-transfusion thrombocytopenia, 1179
Post-transplant lymphoproliferative disorder (PTLD), 1287, 1287*b*, 2255
clinical manifestations of, 2255
diagnosis of, 2255
epidemiology of, 2255
pathobiology of, 2255
treatment and prevention of, 2255*b*
Post-traumatic hematoma, 2390
Post-traumatic stress disorder (PTSD), 2344
history of, 29*t*
intimate partner violence and, 1634
prognosis of, 2345*b*
treatment of, 2340*t*, 2345*b*
Post-traumatic vertigo, 2645
Post-vaccination encephalomyelitis, 2238
Post-vaccination vaccinia, 2238
Postanoxic action myoclonus, 2495*b*
Postbulbar ulcers, 913
Postconcussion syndrome, 2645
Posterior cerebral artery, 2457
Posterior choroidal melanoma, 2613*f*
Posterior cortical atrophy, 2410, 2410*f*
Posterior leukoencephalopathy syndrome, 2616
Posterior pituitary, 1498–1504
anatomy of, 1498–1500, 1499*f*
hormone synthesis in, 1498
oxytocin in, 1500
vasopressin in, 1499
Posterior reversible encephalopathy syndrome, 1861

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Posterior tibial tendinitis, 1748, 1748*b*
Posterior tibialis tendon rupture, 1748, 1748*b*
Posterior urethral valves, 821
Postexposure prophylaxis (PEP), to prevent sexual transmission, 2299, 2299*t*
Post-Lyme disease, 2027
Postmenopausal hormone therapy, 56
Postmenopausal osteoporosis, 1644*f*
Postnasal drip syndrome, distinguishing features of, 515*t*
Postoperative care, 2672–2673
  checking orders in, 2672
  effective teamwork in, 2672
  focusing on recovery, 2672
  future prevention in, 2673
  overview of, 2672
  patterns of mistake in, 2672
  reading anesthesia records, 2672
  recommended prophylaxis for, 2672–2673
Postoperative complications, 2673–2677
  abnormal serum potassium concentration, 2676
  abnormal sodium concentration, 2675–2676
  abnormalities in blood glucose concentration, 2676
  abnormalities in platelet count, 2675
  aftermath of, 2677
  alkalosis, 2676
  ambiguity of, 2676–2677
  anemia, 2675
  anorexia, 2673
  azotemia, 2676
  chest pain, 2673, 2673*t*
  delirium, 2674
  diarrhea, 2673
  dyspnea, 2673, 2674*t*
  edema, 2675
  fever, 2675
  hyperbilirubinemia, 2676
  hypertension, 2674
  hypoalbuminemia, 2676
  hypotension, 2675
  hypoxemia, 2675
  laboratory, 2675–2676
  leukocytosis, 2675
  multiplicity of, 2676
  redundancy of, 2676
  seizures, 2674
  setting priorities, 2677
  signs of, 2674–2675
  special situations, 2676–2677
  symptoms of, 2673–2674
  tachycardia, 2675
  troponin and natriuretic peptide levels, 2676
  vomiting, 2673
  weakness, 2674
Postoperative diuresis, 1501
Postoperative fever, 1849
Postoperative surgical consultation, 2656
Postpartum thyroiditis, 1513, 1513*b*, 1513*f*
Postpericardiotomy syndrome, 431
Postpoliomyelitis muscle atrophy, 2258*b*
Postprandial distress syndrome, 899*t*
Postprandial hypoglycemia, 1554, 1557*b*
Postradiation pericarditis, 432
Postrenal acute kidney injury, 771, 773, 774
Postural disturbances, in parkinsonism, 2484
Postural hypotension, 306
Postural tachycardia syndrome (POTS), 2555
Potassium, *e*1*t*–*e*8*t*
  adaptation of, 745
  balance of, 745
  body amount of, 745
  in cortical collecting duct, 746.*e*1*f*
  deficiency of, 2538*t*
  definition of, 745
  depletion of, 745
  excess of, 745
  excretion of, 745–747
  external balance of, 747
  function of, 746
  hormonal effects of, 747
  importance of, 745
  internal balance of, 747, 747*t*
  level of, 745
  metabolic acidosis on, effects of, 747
  for narcolepsy, 2449*t*
  regulation of, 726*f*
  renal handling of, 746
  secretion of, 746
Potassium *(Continued)*
  secretory channels of, 746
  tubular flow rate of, 746
Potassium channels, 300.*e*1*f*, 301
Potassium chloride, 313*b*
Potassium citrate
  for hypercalciuria, 806
  for hypokalemia, 751*b*
Potassium disorders, 745–752
  clinical manifestations of, 747–748
  definition of, 745–752
  diagnosis of, 748–751
  epidemiology of, 745
  pathobiology of, 745–747
  prognosis for, 752
  treatment of, 751*b*, 752*b*
Potassium hydroxide, 2690.*e*1*f*
Potassium-sparing diuretics
  for hypertension, 451*t*, 454
  for hypervolemia, 737*t*
  side effects of, 453*t*, 454
Potentiators, for cystic fibrosis, 558*b*
POTS. *See* Postural tachycardia syndrome
Pott disease, 2038*f*
Potter phenotype, 818
Powassan virus, 2276*t*, 2282, 2282*b*
Powder, 2697
Power analysis, 36
Poxvirus infections, 2236
  clinical manifestations of, 2237–2239
  definition of, 2236
  diagnosis of, 2239
  epidemiology of, 2236
  molluscipoxvirus, epidemiology of, 2237
  molluscum contagiosum virus. *See* Molluscum contagiosum
  orthopoxvirus. *See* Orthopoxvirus
  parapoxvirus, 2239, 2240*b*
  pathobiology of, 2237
  pathogens that causes, 2236
  prevention of, 2240*b*
  prognosis for, 2240
  taxonomy of, 2236*t*
  treatment of, 2240*b*
  yatapoxvirus, 2237, 2239
PP interval, 229
PPNAD. *See* Primary pigmented nodular adrenocortical disease
PPP. *See* Platelet-poor plasma
PR interval, 229, 229*t*
PR3-ANCA, 1716
PRAAS. *See* Proteasome-associated autoinflammatory syndromes
Practice guidelines, 44
Pralidoxime chloride, for acute poisoning, 693*t*
Pramipexole
  for Parkinson disease, 265*b*, 2487*t*
  for restless legs syndrome, 2453, 2496*b*
Pramlintide, for type 1 diabetes mellitus, 1537*b*
Pramoxine hydrochloride, for skin diseases, 2700
Prasterone, for genitourinary syndrome of menopause, 1632*t*
Prasugrel, 387*t*, 506*t*, 507
  for acute coronary syndrome, 374*t*, 375*t*
  for acute MI, 397
  for acute STEMI, 384*b*, 391*t*
Pravastatin, for familial hypercholesterolemia, 1409*t*
Praziquantel, 2117
  for *Diphyllobothrium*, 2157*b*
  for helminthic diseases, 2112*t*
  for schistosomiasis, 2165*b*
  for tapeworm infections, 2158*t*
Prazosin, 451*t*
Pre-2019 coronaviruses, 2206
  definition of, 2206
  Middle East respiratory syndrome, 2208
  pathogen causing, 2206, 2206*f*
  seasonal coronavirus, 2206
  severe acute respiratory syndrome, 2208
Pre-conception carrier testing, 166
Pre-heart failure, 264
Pre-mutation, 163–164
Pre-rheumatoid arthritis, 1750
Prebiotics, 155
Precision medicine, 168, 168*t*
  data ownership, privacy, and sharing in, 168*t*, 169, 169.*e*1*t*
  evidence generation in, 168, 168*t*
Precision medicine *(Continued)*
  implementation of, in health care systems, 168–169, 168*t*
  participant engagement and trust in, 168*t*, 169
Precision Medicine Initiative, 165
Precocious puberty, 1592–1593
  in boys, 1481, 1582
  clinical manifestations of, 1593
  definition of, 1592
  diagnosis of, 1582, 1593
  diagnostic tests for, 1593
  epidemiology of, 1592
  pathobiology of, 1592
  peptide hormones in, 1593
  steroid hormones in, 1593
  treatment of, 1582*b*, 1593*b*, 1594*t*
Precordial thump, 313*b*
Prediction rules, 39
Prednisolone
  for alcohol-associated liver disease, 1032*b*
  for myocarditis, 286*b*
Prednisone
  for acute pericarditis, 424*b*
  for autoimmune hemolytic anemia, 1089*b*
  for focal segmental glomerulosclerosis, 779*b*
  for giant cell arteritis, 443*b*
  for granulomatosis with polyangiitis, 582
  for immune thrombocytopenic purpura, 1175*b*, 1176*t*
  for liver transplantation, 1048*t*
  for membranous nephropathy, 780*b*
  for minimal change disease, 778*b*
  for *Pneumocystis* pneumonia, 2106*t*
  for radiation lung injury, 597*b*
  for rapidly progressive glomerulonephritis, 785*b*
  in renal transplantation, 845, 845*t*
  for respiratory bronchiolitis-associated interstitial lung disease, 578*b*
  for retroperitoneal fibrosis, 1783*b*
  for rheumatoid arthritis, 1755*b*, 1756*t*, 1757*t*
  for sarcoidosis, 603*b*, 604*t*
  for systemic lupus erythematosus, 1772*b*
  for ulcerative colitis, 945*b*, 946*t*
  for vasculitis neuropathy, 2572*b*
  for zoster, 2249*b*
Predominant febrile illness, 1869*t*
Preeclampsia, 1178–1179, 1618, 1621*t*
Preexposure prophylaxis (PrEP), to prevent sexual transmission, 2298, 2299*t*
Pregabalin
  for chronic pain, 138*t*
  for distal symmetrical and autonomic polyneuropathy, 2577*b*
  for erythromelalgia, 471*b*
  for restless legs syndrome, 2453
  for zoster, 2249*b*
Preganglionic neurons, 2553
Pregnancy
  antidepressant medications in, 1610
  antihypertensive drug for, 454*t*
  antimicrobial therapy in, 1842, 1842*t*
  aplastic anemia during, 1126*b*
  asthma in, 541*b*
  cancer and, treatment of, 1232*b*
  cardiopulmonary resuscitation in, 1619–1620, 1619.*e*1*f*
  Chlamydia trachomatis in, 2011
  congenital rubella syndrome and, 2224
  contraception and, 1772*b*
  endocrine disorders in, 1624
  extramedullary hematopoiesis and, 1135*b*
  familial hypercholesterolemia and, 1409*b*
  gastrointestinal and liver diseases unique to, 1626
  general principles of, 1618–1620
  glucocorticoids in, 146
  gonorrhea in, 1948
  HIV in, antiretroviral therapy for, 2305
  Hodgkin lymphoma during, 1291*t*, 1292*b*
  hypercoagulable states in, treatment of, 478*b*, 481
  hypertension in, 456
  hypertensive disorders unique to, 1620, 1621*b*, 1621*t*
  hyperthyroidism and, 1511*b*
  hypothyroidism and, 1508*b*
  immunization and, 76.*e*2*t*, 77
  infectious disease in, 1627
  in inflammatory bowel disease, 945*b*
Pregnancy *(Continued)*
  interrupted, 1604
  jaundice in, 998
  laboratory test results in, 1619, 1620*t*
  lupus during, 1770
  luteomas of, 1573
  Lyme disease in, 2026*b*
  medical issues in, 1618–1628, 1618.*e*2*f*
    acute fatty liver of pregnancy, 1626, 1627*b*, 1627*t*
    asthma, 1619*t*
    deep vein thrombosis, 1622
    diabetes mellitus, 1624, 1624*b*
    eclampsia, 1620
    hyperemesis gravidarum, 1626, 1626*b*
    hypertensive disorders, 1620–1621, 1620*b*, 1621*t*
    intrahepatic cholestasis of, 1626, 1626*b*
    liver disease, 1625, 1625*t*
    thrombophilia, 1622
    venous thromboembolism, 1619*f*, 1622–1623, 1623*b*, 1623*f*, 1624*t*
    viral hepatitis, 1625, 1626*b*
  medications for, 1618–1620, 1619*t*
  mental health in, 1623, 1624*b*
  multiple sclerosis in, 2501
  non-Hodgkin lymphoma in, 1288, 1288*b*
  pheochromocytoma in, 1533
  physiologic changes in, 1618, 1618*f*
  polycystic ovary syndrome in, 1602*b*
  prolactin levels in, 1490
  radiation exposure in, 1618, 1618*t*, 1619*t*
  relapsing fever in, 2028
  renin-angiotensin system inhibitors and, 452–453
  seizures in, 2434*b*
  sickle cell disease in, 1114, 1114*b*
  syphilis in, 2020*b*
  in thrombocytopenia, 1178–1179
  tubal, 1604
  undernutrition in, 1464
  unintended, 1611
  urinary tract infection in, 1878
  venous thromboembolism in, 487*b*
  in viral hemorrhagic fevers, 2267
Preload, 226
Premature action potential, 333.*e*1*f*
Premature atherosclerotic disease, 1775
Premature ovarian failure, X chromosome mutation in, 1600
Premature ventricular contractions (PVCs), 333
Premenstrual dysphoric disorder, 2342
Premenstrual syndrome (PMS), 1596–1597, 1597*b*, 1597*t*
Premenstrual tension, 1596
Prenatal diagnosis, 166
Preoperative evaluation, 2659–2668
  anesthesiologist and, 2667
  assessing risk in, 2661
  cardiovascular diseases, 2663–2664
  cardiovascular risk assessment, 2661, 2662*t*
  endocrine conditions, 2665
  general principles of, 2659–2660, 2660*t*
  hematologic problems, 2666
  history of, 2660
  liver disease, 2666
  neurologic problems, 2664–2665
  perioperative medications, 2666–2667
  physical examination of, 2660
  prognostic impact of, 2660
  pulmonary risk assessment, 2664, 2664*t*
  renal disorders, 2666
  tests, 2661, 2662*t*
  timing of surgery, 2660, 2661*f*
Preoperative surgical consultation, 2656
PrEP. *See* Preexposure prophylaxis
Prepatellar bursitis, 1747
Prerenal acute kidney injury, pathobiology of, 772, 772*t*
Prerenal azotemia
  diagnosis of, 772*f*, 774
  epidemiology of, 770, 771*f*
  for hypokalemia, 751*b*
Presbycusis, 117
  hearing loss caused by, 2642
Presbyopia, 2598
Presenilin 1, 2415
Presenilin 2, 2415
Preseptal cellulitis, 2596, 2604, 2605*f*

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Pressure-assisted ventilation, for acute respiratory failure, 647*b*
Pressure bandage with immobilization, for envenomation, 705*b*
Pressure-controlled ventilation, 653
Pressure sores, 122, 122*b*, 122*f*
Pressure-support ventilation, 653
Pressure ulcers, in older adults, 114
Pressure-volume area, 225
Pressure-volume loop, 225, 225*t*, 225.*e1f*
Pressure-volume relationships, 225, 226*f*
Presyncope (dizziness), 304–305, 304*t*
Presystemic effect, of drugs, 126
Pretibial myxedema. *See* Graves dermopathy
Pretomanid, 1845*t*
Pretomanid, dosage of, 1895*t*
Prevalence, 35, 38
Preventive health care
  for adolescents, 111
  visit, 52
    asymptomatic risk factors, 52–55, 52*t*–53*t*
    behavioral interventions, 55
    history of, 52
    immunizations, 55–56
    preventive medications and supplements, 56
    risk assessment of, 52
    screening for early disease, 52, 52*t*, 53*t*
Preventive services, geriatric assessment, 119, 119.*e1t*
Priapism, 1114
Primaquine
  for malaria, 2112*t*, 2114, 2121*b*, 2121*t*, 2123*t*
  for *Pneumocystis* pneumonia, 2106*t*
Primary adrenal disorders, 1522–1523
Primary adrenal insufficiency, 1526, 1527*t*, 1528*f*
Primary aldosteronism, 447, 448*b*, 448*t*, 1525*f*
Primary amenorrhea, 1598
Primary amyloidosis. *See* AL (light chain) amyloidosis
Primary angiitis of the central nervous system (PACNS), 1799–1800, 1800*b*, 1800*t*
Primary biliary cholangitis (PBC), 1059, 1821
  clinical manifestations of, 1059
  diagnosis of, 1059
  epidemiology of, 1059
  pathobiology of, 1059
  prognosis of, 1059–1060
  treatment of, 1059*b*
Primary biliary cirrhosis. *See* Primary biliary cholangitis
Primary bone tumors, 1388
Primary carnitine deficiency, 2586
Primary central nervous system lymphoma, 1316, 1316*b*, 1316*f*, 2315
Primary ciliary dyskinesia, 560
Primary CNS lymphoma, 1285, 1285*b*
Primary coenzyme Q10 deficiency, 2586
Primary cutaneous anaplastic large cell lymphoma, 1286
Primary cutaneous diffuse large B-cell lymphoma, 1285
Primary debulking surgery, for metastatic neuroendocrine tumor, 1568*b*
Primary dystonia, 2492*t*, 2493
Primary effusion lymphoma, 1285, 2315
Primary extra-axial brain tumors, 1312*b*
Primary hyperaldosteronism, 749, 1525, 1525*f*, 1525*t*, 1526*b*
Primary hyperoxaluria, 807
Primary hyperparathyroidism, 1656
  clinical manifestations of, 1656
  description of, 1654
  diagnosis of, 1656
  epidemiology of, 1656
  familial, 1657
  parathyroid surgery for, 1657*t*
  parathyroidectomy for, 1657*b*
  pathobiology of, 1656
  treatment of, 1657*b*
Primary hypodipsia, 742
Primary immunodeficiency diseases, 1676, 1676–1686
  autoinflammatory disorders as, 1686
  bone marrow failure defects as, 1686
  C1 inhibitor deficiency as, 1683
  categories of, 1676*t*
  complement disorders as, 1682, 1683*b*, 1683*t*
  immune dysregulation syndromes as, 1684, 1684*t*, 1685*b*
Primary immunodeficiency diseases *(Continued)*
  immune globulin and antibody production in, defects of, 1680, 1681*t*, 1682*b*
  intrinsic and inate immunity in, diseases of, 1685, 1686*b*, 1686*t*
  phagocytic defects as, 1683, 1683.*e1t*, 1684*b*
  T-and B-cell combined defects as
    less, 1678, 1678.*e1t*
    severe, 1676–1678, 1676.*e3t*, 1678*b*
    with syndromic features, 1678–1680, 1678*b*, 1679*t*
Primary junctional tachycardia, 324
Primary large intestinal lymphomas, 1347
Primary lateral sclerosis, 2564*t*
Primary lesion, biopsy of, 1391
Primary lung disease, 496*b*
Primary lung sarcoma, 1336
Primary mediastinal large B-cell lymphoma, 1285
Primary myelofibrosis, 1130, 1130*t*
  allogeneic hematopoietic stem cell transplantation for, 1135*b*
  clinical manifestations of, 1133
  definition of, 1130, 1130*t*
  diagnostic criteria for, 1134, 1134*t*
  Dynamic International Prognostic Scoring System-Plus for, 1137*f*, 1139
  epidemiology of, 1130
  extramedullary hematopoiesis in, 1133
  pathobiology of, 1130, 1131*f*
  peripheral blood smear of, 1134
  in pregnancy, 1135*b*
  prognosis for, 1138
  ruxolitinib for, 1135*b*, 1138*f*
  splenomegaly in, 1134
  survival in, 1139, 1139*f*
  treatment of, 1135*b*, 1136*t*
Primary open-angle glaucoma, 2607, 2607*f*
Primary ovarian insufficiency, 1600
Primary peritonitis, 956
Primary pigmented nodular adrenocortical disease (PPNAD), 1487*t*, 1523
Primary polydipsia, 738, 1503*b*
Primary progressive aphasia, 2409, 2422
Primary progressive multiple sclerosis, 2501
Primary sclerosing cholangitis, 1056
  clinical manifestations of, 1057
  definition of, 1056
  diagnosis of, 1057, 1058*f*
  epidemiology of, 1056
  pathobiology of, 1056
  prognosis of, 1058
  treatment of, 1058*b*
Primary selective hypoaldosteronism, 750, 750*t*
Primary Sjögren syndrome, 2558
Primary syphilis, 2015, 2015*f*
Primary testicular hypogonadism, 1583, 1583*t*
Primary thyroid lymphoma, 1519, 1519*b*
Primary vesicoureteral reflux, 819–820, 820*b*
Primidone + phenobarbital, *e*10*t*–*e*11*t*
Prinzmetal angina, 357
Prion diseases
  clinical manifestations of, 2422–2423
  diagnosis of, 2423
  other classic, 2422–2423
  pathobiology of, 2422
  prevention of, 2423
  prognosis of, 2423
  treatment of, 2423
"Private" mutations, 1249
Pro-adrenomedullin, mid-regional (MR-proADM), 260.*e1t*
Pro-oxytocin, 1498
Probiotics, 155
  for *E. coli*, 1963*b*
  for irritable bowel syndrome, 895*b*, 896*t*
  for microbiota, 1840
Problem-solving therapy, for depression, 2339*t*
Procainamide, *e*10*t*–*e*11*t*, 325*t*
  for advanced cardiac life support, 315*f*
  for arrhythmias, 313*b*
Procainamide + N-Acetyl (NAPA), *e*10*t*–*e*11*t*
Procalcitonin, *e*1*t*–*e*8*t*, 1851*b*
Processed food, dietary guidelines for, 57.*e3t*
Prochlorperazine, for nausea and vomiting, 863*t*
Procrit. *See* Erythropoietin
Proctitis, 1948
  Chlamydia trachomatis causing, 2012
  clinical manifestations of, 1948
  description of, 943
  diagnosis of, 1948
  treatment of, 945*b*
Proctopathy, radiation, 968, 968*f*
Proctosigmoiditis, description of, 943
Professionalism, 4*t*
Profound hypothermia, 681*t*
Progenitor cells, 172
Progestogen hypersensitivity, 1693
Proglottids, 2157
Prognostication, 12
Prograf. *See* Tacrolimus
Programmed death 1 (PD-1) blockade, for colorectal cancer, 1350*b*
Progressive diaphyseal dysplasia, 1666, 1666*b*
Progressive external ophthalmoplegia, 2618
Progressive multifocal leukoencephalopathy, 1861, 2230, 2230*b*–2231*b*, 2231*f*, 2532*t*
Progressive muscular atrophy (PMA), 2564*t*
Progressive myoclonus epilepsies, 2433
Progressive supranuclear palsy, 2411, 2416, 2485*t*, 2652
Progressive systemic sclerosis, interstitial lung disease associated with, 580
Progressive vaccinia, 2238
Proguanil, 2115
Proinsulin, intact, *e*1*t*–*e*8*t*
Prolactin, *e*1*t*–*e*8*t*, 1490–1491, 1498, 1500
  deficiency of, 1491
  hyperprolactinemia and, 1491, 1491*b*, 1491*t*
  hypothalamic disease effects on, 1481
  insufficiency tests of, 1484*t*
  lactotroph regulation of, 1490
  pregnancy levels in, 1490
  tests of, 1488*t*
Prolactin inhibitory factor, 1477
Prolactin receptor, 1490
Prolactin-releasing factor, 1478
Prolactin-secreting adenoma, 1481
Prolactinomas, 1487, 1491, 1584
Proliferative benign breast lesions, 1374
Proliferative diabetic retinopathy (PDR), 1549*t*
Prolonged infectious diarrheas, 932
Prolymphocytic leukemia, 1272
Promethazine, for nausea and vomiting, 863*t*
Promyelocyte, 1140*f*
Proopiomelanocortin (POMC), 1478, 1492
Propafenone, 325*t*
Propensity score, 37
Properdin, 1942
Prophylactic mastectomy, 1373
Prophylaxis, recommended, in postoperative care, 2672
Propionibacterium acnes, 2722
Propionic aciduria, 1398*t*, 1403, 1403*t*
Propofol, for anesthesia, 2669
Proportional assist ventilation, 653
Propoxyphene, 139*t*
Propranolol, *e*10*t*–*e*11*t*
  for alcohol withdrawal, 2358*t*
  for anxiety disorders, 2344*t*
  for arrhythmias, 313*b*
  for hyperthyroidism, 1511*b*
  for hypertrophic cardiomyopathy, 282*b*
Propranolol IR, 451*t*
Propranolol LA, 451*t*
Proprotein convertase subtilisin kexin type 9 antibodies, 227
Proprotein convertase subtilisin kexin type 9 gene, 221–222
Proptosis, 2600, 2600*f*
Propylene glycol, 760
Propylthiouracil
  for Graves disease, 1511*t*
  for hyperthyroidism, 1511*b*
Prostacyclin, 468*b*
Prostaglandin synthetase inhibitors, 1595
Prostaglandins, angiotensin II and, 734
Prostanoids, for pulmonary hypertension, 496*b*
Prostate cancer, 1384–1387
  androgen receptor expression by, 1385*b*
  brachytherapy for, 1385*b*
  castration-resistant, 1385*b*
  chemoprevention for, 1387
  clinical manifestations of, 1384
  diagnosis of, 1384–1385, 1384*t*
  epidemiology of, 1384–1387
  Gleason score for, 1384*t*
  localized, 1385*b*
  metastasis, 1385*b*, 1385*t*
  nutrition and, 59
  pathobiology of, 1384
  prevention of, 1387
  prognosis for, 1387
Prostate cancer *(Continued)*
  prostate-specific antigen screening for, 1384
  radiation therapy for, 1385*b*, 1385*t*
  recurrent, 1385*b*
  screening for, 54, 1387
  staging of, 1385, 1385*t*
  supportive care for, 1385*b*
  treatment of, 1385*b*, 1385*t*
Prostate gland, 821, 821*f*
Prostate-specific antigen (PSA), *e*1*t*–*e*8*t*, 1384
Prostatic hyperplasia, benign, 821
  clinical manifestations of, 822
  definition of, 821, 821*f*
  diagnosis of, 822, 823*f*
  epidemiology of, 821
  laboratory findings of, 822
  management of, algorithm of, 824*f*
  pathobiology of, 821
  prognosis of, 823
  treatment of, 822*b*
Prostatic obstruction, in heart failure, 265*b*
Prostatitis, 823–826
  bacterial species that cause, 1892*t*
  classification of, 825*t*
  clinical manifestations of, 823
  diagnosis of, 823–825, 826*f*
  epidemiology of, 823
  laboratory evaluation for, 825
  pathobiology of, 823
  prognosis of, 825–826
  treatment of, 825*b*
Prosthetic heart valves
  advantages and disadvantages of, 412*t*
  choices among, 412*f*
  echocardiographic findings, 242*t*
  postoperative care for, 411
Prosthetic joint infection, 1808
  clinical manifestations and diagnosis of, 1808
  prevention of, 1808–1809
  treatment for, 1808*b*
Prosthetic valve endocarditis, 416
  causes of, 416*t*
  Staphylococcus aureus causing, 1903–1904
Protease inhibitors, 196, 2319
  for HIV, 2300, 2304*t*
Proteasome-associated autoinflammatory syndromes (PRAAS), 1731*t*, 1735
Protectin, 200*t*
Protective eyewear, for HIV transmission prevention, 2300
Protein
  in bacterial meningitis, 2514
  depletion of, 1447*t*
  dietary guidelines for, 57.*e3t*
  dipstick for, 722
  intestinal digestion and absorption of, 932.*e1f*
  membrane, 1093
  requirements, estimation of, 1449
Protein binding, 129
Protein-bound cobalamin malabsorption, 1119
Protein C deficiency, 476, 476*t*
Protein-energy malnutrition, acute malnutrition and, 1444
Protein F, 1913
Protein-losing gastroenteropathy, 940
Protein metabolism, disorders of, 1401, 1402*t*
Protein profiling, 168
Protein S, 200*t*
  deficiency, 476, 476*t*
Protein sensitivity, for hypoglycemia, 1557
Protein subunit vaccine, 66*t*
Protein tyrosine phosphatase nonreceptor 22 (PTPN22), functional polymorphism in, 1750
Protein-coupled folate transporter (PCFT), 1119
Proteinosis, pulmonary alveolar, 566, 566*t*, 585*t*
  clinical manifestations of, 567
  diagnosis of, 567, 567*f*, 567.*e1f*
  epidemiology of, 566
  pathobiology of, 566–567
  treatment for, 567*b*
Proteinuria, 727, 832, 833*f*
  glomerular disorders and, 776
  nephrotic-range, 792
Proteoglycans, 1724
Proteomics, 168
Proteus mirabilis, 804, 1874, 1965
Prothrombin, 1189*t*
Prothrombin complex concentrates, 1204
Prothrombin G20210A mutation, 476, 476*t*

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Prothrombin time (PT), 999, 1166, 1167, 1167*f*, 1167*t*, 1169*f*, 1195, 1453*t*
  one-stage, *e8t*–*e9t*
Prothrombotic factors, increased, 475*t*
Prothrombotic states, mesenteric venous thrombosis and, 963*t*
Proton pump inhibitors, 1460*t*
  for Barrett esophagus, 906*b*
  for peptic ulcer disease, 921
  reactions to, 1698*t*
  for upper gastrointestinal bleeding, 883*b*
Protoporphyria, 1428*t*, 1432–1433, 1432*f*, 1434*b*
Protoporphyrin IX, 1429.*e1f*
Protoporphyrinogen IX, 1429.*e1f*
Protozoal diseases, treatment of, 2111
Protozoal liver diseases, 1025
Protracted diarrhea, 1869*t*
Protriptyline, *e10t*–*e11t*
  for cataplexy, 2449*t*
Provasopressin, 1498
Providers, criteria for, 42*t*
Provocative testing, 532
  for diabetes insipidus, 1501
Proximal femur fractures, 1639
Proximal renal tubular acidosis, 761, 816*t*
Proximal subungual onychomycosis, 2754
Proximal tubular dysfunction, Wilson disease and, 1437
Proximal tubule, 731.*e1f*, 754, 754.*e1f*
Proximal tubule disorder, 815, 816*t*
Proximal tubule diuretics, 736*b*
PRP. *See* Platelet-rich plasma
Prune-belly syndrome, 821
Pruned-tree sign, 246*f*
Prurigo nodularis, 2321
Pruritus, 2690–2696, 2694*t*, 2697*t*, 2726
  in HIV, 2321
  West African sleeping sickness and, 2124
Pruritus ani, 980, 980*b*
Prussian blue staining, for anemia, 1077
Pseudo-Cushing states, Cushing syndrome *versus*, 1521*f*, 1522
Pseudo-delta wave, 335
Pseudo-Hurler polydystrophy, 1724*t*
Pseudo-hypoglycemia, 1546*t*
Pseudo-obstruction
  classification of, 888*t*
  description of, 888
Pseudo-osteoarthritis, 1814
Pseudo-precocious puberty, 1582
Pseudo-pseudogout, 1815
Pseudoaldosteronism, 817
Pseudoappendicitis, enteric infections and, 1870*t*
Pseudobulbar palsy, 2562, 2652
Pseudoclaudication, 2399
Pseudocyst, 971–972, 972*f*
Pseudofractures, osteomalacia in, 1649
Pseudogout, calcium pyrophosphate dihydrate crystals in, 1713
Pseudohemoptysis, 515
Pseudohyperkalemia, 748
Pseudohyperphosphatemia, 768–769
Pseudohypoaldosteronism
  autosomal recessive, type 1, 761
  type 1, 816*t*
  type 2, 816*t*
Pseudohyponatremia, 738
Pseudohypoparathyroidism, 1661, 1662*t*
Pseudomembranous candidiasis, 2623
Pseudomembranous colitis, 1865, 1925
Pseudomonal keratitis, 2606
Pseudomonas aeruginosa, 1968
  antimicrobial resistance of, 1864*t*
  community-acquired, 1968
  cystic fibrosis and, 557
  description of, 1894
  epidemiology of, 1968
  keratitis caused by, 2606
  multidrug-resistant, 1968
  treatment of, 1970*b*
  urinary tract infection and, 1874
  virulence factors in, 1968.*e2t*
Pseudomonas fluorescens, 1970
Pseudomonas folliculitis, 2723, 2723*f*
Pseudomonas infections, 1968–1972, 2741
  acute respiratory tract infections caused by, 1969
  bacteremia caused by, 1969, 1970*b*
  bacterial factors in, 1968
  bone infections caused by, 1969, 1970*b*
Pseudomonas infections *(Continued)*
  central nervous system infections caused by, 1969
  chronic respiratory tract infections caused by, 1969
  clinical manifestations of, 1968–1970
  cystic fibrosis and, 556
  definition of, 1968–1972
  diagnosis of, 1970
  ear infections caused by, 1969, 1970*b*
  endophthalmitis caused by, 1969
  endovascular infections caused by, 1969
  epidemiology of, 1968
  eye infections caused by, 1969, 1970*b*
  in febrile neutropenia, 1968
  gastrointestinal infections caused by, 1969
  genital tract infections caused by, 1969
  intra-abdominal infections caused by, 1969, 1970*b*
  joint infections caused by, 1969
  keratitis caused by, 1969
  pathobiology of, 1968
  pathogenesis of, 1968
  pathogens, 1968
  pathology of, 1968
  pathophysiology of, 1968
  prevention of, 1971–1972
  prognosis for, 1972
  skin and soft tissue infections caused by, 1969, 1970*b*
  treatment of, 1970*b*
  uncommon, 1969
  urinary tract infections caused by, 1969, 1970*b*
  ventilator-associated pneumonia caused by, 1969, 1970*b*
  virulence factors in, 1968.*e2t*
Pseudomonas stutzeri, 1970
Pseudopolyps, 942
Pseudoporphyria, 2720
Pseudopropionibacterium propionicum, 2066
Pseudothrombocytopenia, 1166
Pseudotumor cerebri, 2383, 2383*b*
Pseudotumors, 624
Pseudoxanthoma elasticum, 1729, 2550*t*, 2609, 2730
Psittacosis, 2013
Psoriasiform dermatitis, 2321
Psoriasis, 1707, 2689*t*, 2705
  clinical manifestations of, 2705–2706, 2706*f*
  description of, 2687.*e3t*, 2692*t*
  diagnosis of, 2706
  epidemiology of, 2705
  pathobiology of, 2705
  pustular, 2722, 2723*f*
  regional involvement of, 2745*f*
  therapies for, 2698
  treatment for, 2706*b*–2707*b*, 2706*t*
Psoriasis vulgaris, 2705
Psoriatic arthritis, 1717*t*, 1764
  clinical manifestations of, 1764
  diagnosis of, 1764, 1765*f*
  differential diagnosis of, 1764
  epidemiology of, 1764
  pathobiology of, 1764
  prognosis of, 1766
  radiographs of, 1764
  treatment of, 1765*b*
Psychedelics, in palliative care, 16
Psychiatric diseases
  aging and, 2677
  alcohol use disorders and, 2355*t*, 2356
  ambulatory medical care for, 2683
  cardiovascular disease and, 2677
  giving recommendations in, 2682–2683, 2683*t*
  health challenges with, 2677, 2678*t*
  medical care for, 2677–2684
  population health for, 2677
  providing care in different settings for, 2678–2679
  substance use disorders and, 2678
  symptoms and findings of, approach to, 2681, 2683*t*
  treatments for, medical complications of, 2679–2681, 2680*t*
Psychiatric disorders, 2336–2349
  acute stress disorder, 2344
  anxiety disorders, 2342
  bipolar disorder, 2341
  categories of, 2337*t*
Psychiatric disorders *(Continued)*
  causes of, 2336*t*
  comorbid conditions in, 2337
  definition of, 2336
  delusional disorder, 2346
  eating disorders, 2346
  evaluation for, 2347–2348, 2348*t*
  major depressive disorder, 2337
  obsessive-compulsive disorder, 2343, 2344*t*
  personality disorders, 2347
  post-traumatic stress disorder, 2344
  schizophrenia, 2345–2346
  somatic symptom and related disorders, 2346–2347, 2347*t*
  suicide, 2347, 2348*t*
  treatments in, 2337
Psychiatric evaluation, 31
Psychiatric illness
  substance use disorder and, 2360
  weight loss and, 860*t*
Psychiatric unit, consultations to, 2679
Psychiatry, medicine and, 2679
Psychodynamic psychotherapy, for depression, 2339*t*
Psychogenic dizziness, 2646, 2647*t*
Psychogenic eating disorders, weight loss and, 860*t*
Psychogenic nonepileptic seizures, 2431
Psychological symptoms, management of, approaches to, 13*t*
Psychological therapies, for irritable bowel syndrome, 895*b*
Psychomotor speed, 2411
Psychopathology, intimate partner violence and, 1633
Psychosocial issues
  alcohol use disorders and, 2355*t*, 2356
  in heart failure, 275*t*
Psychosocial support
  for cancer, 1232*b*
  for sexual development, 1575*b*
Psychostimulants, properties of, 142*t*
Psychotherapy, for pain, 136*b*
Psychotic disorders, 2337*t*, 2345–2346
Psychotropic medications
  brief overview of, 2679–2680
  cardiovascular complications of, 2678*t*, 2680, 2680*t*
  regimens, continue outpatient, 2679
  respiratory complications of, 2680
PT. *See* Prothrombin time
Pterygium, 2602, 2603*f*
PTH gene, parathyroid hormone and, 1652
PTH-related peptide (PTHrP), 1653
PTHrP. *See* PTH-related peptide
PTLD. *See* Post-transplant lymphoproliferative disorder
Ptosis, 2600, 2600*f*
PTSD. *See* Post-traumatic stress disorder
Pubarche, premature, 1593
Pubertal development, 1591
Pubertal maturation, Tanner stages during, 1598*t*
Puberty, 110
  aberrations in, 1592–1594, 1592*t*
  adrenarche and, 1581, 1582*t*, 1593
  asynchronous development, 1594
  breast budding in, 1591
  central precocious, 1582
  delayed, 1582, 1582*b*, 1593, 1594*b*
  in girls, 1591
  heterosexual development, 1594
  hormonal changes of, 1591, 1591*f*
  ovarian function in, 1591
  physical changes at, 1591, 1591*f*
  precocious, 1592
    in boys, 1481, 1582
    clinical manifestations of, 1593
    definition of, 1592
    diagnosis of, 1582, 1593
    diagnostic tests for, 1593
    epidemiology of, 1592
    pathobiology of, 1592
    peptide hormones in, 1593
    steroid hormones in, 1593
    treatment of, 1582*b*, 1593*b*, 1594*t*
  pseudo-precocious, 1582
  reproductive axis development in, 1581
  timing of, aberrations of, 1582
  weight gain, 110
Pubic hair
  development of, 110.*e2f*
  at puberty, 1573
  Tanner stages of, 1598*t*
Pubic lice
  organisms causing, 1879*t*
  treatment of, 1884*t*
Puerperal sepsis, 1915
Puerto Rican, 583
Pulmonary airway malformation, congenital, 565
Pulmonary alveolar proteinosis, 566, 566*t*
  clinical manifestations of, 567
  diagnosis of, 567, 567*f*, 567.*e1f*
  epidemiology of, 566
  pathobiology of, 566
  treatment for, 567*b*
Pulmonary arterial hypertension, 211*t*, 493*t*
  chest radiograph of, 523*f*
  echocardiographic findings, 242*t*
  group 1, 493*t*, 494
  group 2, 493–494, 493*t*
  group 3, 493*t*, 494
  group 4, 493*t*, 494
  in HIV, 2317, 2317*b*
  in systemic sclerosis, 1779, 1781*b*
Pulmonary arteriovenous fistulas, 350
Pulmonary artery obliterative vasculopathy, 1776.*e1f*
Pulmonary artery occlusion pressure, 677*t*
Pulmonary artery pressure
  normal value, 677*t*
  systolic, 240–241
Pulmonary artery wedge pressure, 677*t*
Pulmonary atresia, 247.*e1f*
Pulmonary atypical mycobacteria, in travelers, 1889.*e1t*
Pulmonary barotrauma, 594
Pulmonary capillaritis, idiopathic, 582
Pulmonary chest infections, as occupational lung disease, 585*t*
Pulmonary congestion, 256, 256.*e1f*, 394
Pulmonary cryptococcal infection, 2088, 2088*b*
Pulmonary disease
  basal, 524*f*
  chronic obstructive, 541*b*
  imaging in, 519–527
  nontuberculous mycobacteria causing, 2045
Pulmonary edema, 245*f*, 265*b*
  acute, 273*f*
  distinguishing features of, 515*t*
  hydrostatic, 566
  interstitial, 245*f*
  photographic negative of, 582
  ultrasonography for, 520, 521*f*
Pulmonary embolism, 211*t*
  algorithm for, 477*f*
  chronic, 246*f*
  classic electrocardiogram findings with, 486*f*
  definition of, 482
  differential diagnosis of, 424*t*
  distinguishing features of, 515*t*
  high-risk, 487*b*
  hypocapnia and, 487*b*
  hypoxemia and, 487*b*
  low-risk, 487*b*
  massive, 487*b*
  mechanical reperfusion for, 487*b*
  nonthrombotic, 491–492
  in pregnancy, 1622, 1624*t*
  severe, 487*t*
Pulmonary emphysema, 246*f*
Pulmonary examination, 258
Pulmonary fibrosis
  idiopathic, 575
    CT findings, 575.*e1f*
    diagnosis criteria for, 577*t*
    diagnosis of, 575, 576*f*
    pathobiology of, 570
    prognosis for, 577
    radiographic features of, 574*t*
    treatment of, 576*b*
  as occupational lung disease, 585*t*
Pulmonary flukes, 2167
Pulmonary function tests, 528, 528*t*, 2664
  bronchoalveolar lavage in, 532
  cardiopulmonary exercise tests in, 532
  for complex disorders, 533
  diffusing capacity in, 530
  for interstitial lung disease, 574
  lung volumes in, 530, 530*f*

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Pulmonary function tests *(Continued)*
maximal respiratory pressures in, 531, 531*f*
in obesity, 533
provocative testing in, 532
reference equations in, 530
spirometry in, 528
of ventilation, 528
Pulmonary hemorrhage, 2029
microscopic polyangiitis with, 520.*e1f*
Pulmonary hemosiderosis, idiopathic, 582
Pulmonary histoplasmosis
acute, 2082
chronic, 2082
complications of, 2082
treatment of, 2083*b*
Pulmonary hypertension, 211*t*, 493
assessing response to therapy in, 496*b*, 500*t*
background therapy for, 496*b*
chronic thromboembolic, 490
clinical classification of, 493*t*
clinical manifestations of, 494
collaborative care in, 496*b*
complications of, 355
cystic fibrosis with, 558.*e1f*
definition of, 493, 493*t*
diagnosis of, 495, 495*f*–499*f*
differential diagnosis of, 359
epidemiology of, 493
history of, 494
invasive therapies for, 496*b*
medical therapy for, 496*b*, 500*t*
pathobiology of, 494, 494.*e1f*
physical examination for, 494
primary lung disease, 493*t*, 496*b*
prognosis for, 500
in sickle cell disease, 1113
special populations of, 496*b*
in systemic sclerosis, 1781
thromboembolic hypertension, 493*t*, 496*b*
treatment of, 496*b*
with unclear and/or multifactorial mechanisms, 493*t*
venous hypertension, 496*b*
Pulmonary infections
and bronchiectasis, 560
pathogens and empirical therapy for, 2526*t*
Staphylococcus aureus causing, 1904
treatment of, 1970*b*
Pulmonary Langerhans cell histiocytosis, 571, 582, 583*b*, 583.*e1f*
Pulmonary lymphocyte alveolitis, 2327*t*
Pulmonary mucormycosis, 2099, 2100*f*
Pulmonary neoplasms, 1329
Pulmonary nocardiosis, 2073
Pulmonary nodules
on chest images, 524, 524*f*
solitary
description of, 1330, 1331*f*
surgery for, 631
Pulmonary opacities, 520
alveolar pattern of, 522
bronchial patterns of, 522
honeycombing, 522, 522*f*
linear patterns of, 521, 522*f*
nodular patterns of, 521
reticular patterns of, 522, 522*f*
vascular patterns of, 522–523, 523*f*
Pulmonary pressures, 240
Pulmonary rehabilitation, 551*b*
Pulmonary risk assessment, 2664*t*
Pulmonary sarcoidosis, 603*b*
Pulmonary sequestration, 565, 565*f*
Pulmonary stenosis (PS)
exercise recommendations for, 355.*e2t*
valvular, 351, 351*b*
Pulmonary system, systemic lupus erythematosus manifestations of, 1770
Pulmonary toxicities, after hematopoietic cell transplantation, 1211
Pulmonary toxoplasmosis, 2136
Pulmonary tuberculosis
clinical manifestations of, 2034–2035, 2036*f*
diagnosis of, 2039–2040
Pulmonary valve, 224
Pulmonary vascular resistance, 677*t*
Pulmonary vascular resistance index, 677*t*
Pulmonary vasculature, 246, 247*f*
Pulmonary vasculitis, interstitial lung disease associated with, 571*t*, 582
Pulmonary venous hypertension, 496*b*
Pulmonary venous return, anomalous, 247.*e1f*, 354–355
Pulmonic stenosis, 411
Pulse
abnormalities of, 214*t*
carotid, 30, 213, 215*f*
Corrigan, 410
irregular rapid, 33*t*
low, 33*t*, 34–35
measurement of, 33
normal range for, 32*t*
panic range for, 32*t*
Quincke, 410
Pulse oximetry, 32, 640, 683
Pulse pressure
aging and, 444, 445.*e1f*
narrow, 257
Pulsed Doppler, 236
Pulseless disease. *See* Takayasu arteritis
Pulseless electrical activity, 313*b*, 316*f*
Pulseless ventricular tachycardia, 315*f*
Pulsus alternans, 257
Punctate basophilia, 1070*f*
Pupil(s)
abnormalities of, 2617
Argyll Robertson, 2017, 2617
dilated, 2618*f*
examination of, 2616–2617
Pupillary control, 2616
Pupillary pathways, 2616, 2617*f*
Pure gonadal dysgenesis, 1600
Pure neuritic leprosy, 2051
Pure red cell aplasia, 1128, 1129*b*, 2235, 2235*f*
Pure tone testing, 2641
Purified chick embryo cell vaccine (PCECV), 82
Purine inhibitors, 147–148
Purine nucleoside phosphorylase (PNP) deficiency, 1679*t*
Purine synthesis inhibitors
in renal transplantation, 845*t*
for systemic lupus erythematosus, 1772*b*
Purpura
causes of, 2687
Henoch-Schönlein, 2715
inflammatory retiform, 2715*t*, 2716, 2716*f*
macular, 2713, 2713*t*, 2714*f*
noninflammatory retiform, 2715*t*, 2716
nonpalpable, 2713
palpable, 2690*f*, 2692*t*, 2714, 2714*f*, 2714*t*, 2715*f*
retiform, 2715–2716, 2715*t*
solar, 2690*f*, 2714, 2715*f*
steroid, 2714
Purpura fulminans, 2716*f*
Purpuric eruptions, 2713–2716, 2713*t*, 2714*f*, 2714*t*
Purulent conjunctivitis, *H. influenzae* caused by, 1954
Purulent meningitis, 2516*t*
Pustular eruptions, 2722
Pustular lesions, of smallpox, 2238*f*
Pustular psoriasis, 2722, 2723*f*
Pustular psoriasis of von Zumbusch, 2705, 2706*f*
Pustule, 2689*t*
Puumala virus, 2265*t*
PVCs. *See* Premature ventricular contractions
Pyelonephritis, 2091
antimicrobials for, 1877*t*
characteristics of, 2270*t*
clinical manifestations of, 1874
description of, 1873
diagnosis of, 1876*t*
in pregnancy, 1627–1628, 1628*b*
symptoms of, 1874*t*
treatment of, 1875*b*, 1876*t*
Pyknodysostosis, 1668, 1668*b*, 1729
Pyoderma gangrenosum, 2735
Pyogenic arthritis, 2518
Pyogenic arthritis with pyoderma gangrenosum and acne (PAPA), syndrome of, 1731*t*, 1736–1737
Pyogenic liver abscess, 1022, 1023*b*, 1023*f*
Pyogenic meningitis, 2513–2514
Pyomyositis, 1903
Pyrantel pamoate, 2112*t*, 2117
Pyrazinamide
dosage of, 1895*t*
for tuberculosis, 2040*b*, 2041*t*–2043*t*
Pyrethrins, 88*t*
Pyridostigmine, for orthostatic hypotension, 2559*t*
Pyridoxal-5-phosphate, 1453*t*
Pyridoxine
for acute poisoning, 693*t*
Pyridoxine *(Continued)*
deficiency of, 2540–2541, 2540*b*
toxicity, 2540
for type 1 primary hyperoxaluria, 807
for Wilson disease, 1437*b*
Pyrimethamine
for cystoisosporiasis, 2112*t*
for *Pneumocystis* pneumonia, 2108*t*
for toxoplasmosis, 2112*t*, 2115, 2140*t*
Pyrimidine 5′-nucleotidase deficiency, 1100, 1100*f*
Pyrimidine inhibitors, 147
Pyrogenic exotoxins, 1914, 1914*f*
Pyronaridine, for malaria, 2121*b*
Pyrophosphate arthropathy, 1814
Pyropoikilocytosis, hereditary, peripheral blood smear of, 1069*f*
Pyruvate kinase deficiency, 1099, 1099*b*, 1100*f*
Pyruvic acid, *e1t*–*e8t*
Pyuria, 722, 724*t*
urinary tract infection and, 1875

Q

Q fever, 417*t*, 2062–2063, 2065*t*
characteristics of, 2270*t*
clinical manifestations of, 2062–2063, 2062*t*
diagnosis of, 2063
epidemiology of, 2062–2063
pathobiology of, 2062
prevention of, 2063
prognosis of, 2063
treatment of, 2063*b*
Q-switched lasers, 2701
QRS complex, 228*f*, 229–230, 229*t*
QRS voltage, low, 233, 234*t*
QT interval, 230
corrected, 230
long QT syndrome, 337, 338*f*
Qualitative stool fat test, for malabsorption, 931*t*
Quality, changing environment for, 44–45
Quality-adjusted life years (QALYs), 39
Quality improvement, strategies, 45
Quality measures, 44*t*
Quality of care, 19–20, 43–45
Quality-related problems, epidemiology of, 44
Quantitative culture, of small intestinal aspirate, for malabsorption, 931*t*
Quantitative proteomics, 168
Quantitative stool fat test, for malabsorption, 931*t*
Quasi-experimental study designs, 37
Queensland tick typhus, 2055*t*
Quetiapine
for Parkinson disease, 2487*t*
for psychotic disorders, 2346*t*
Quinapril, 451*t*
Quinapril/HCTZ, 451*t*
Quincke pulse, 410
Quinidine, *e10t*–*e11t*, 325*t*
Quinidine gluconate, 2112*t*, 2114–2115
Quinine, 2114–2115
for babesiosis, 2152*b*, 2152*t*
for malaria, 2121*b*, 2121*t*
Quinine sulfate, 2114
for babesiosis, 2112*t*
for malaria, 2112*t*
Quinolones, 1899
for chancroid, 1951*b*
for cholera, 1957*t*
dosage of, 1895*t*
mechanism of action, 1895*t*
resistance mechanisms, 1893*t*
toxicities of, 1901*t*
Quinupristin, resistance mechanisms, 1893*t*
Quinupristin-dalfopristin
characteristics of, 1900
dosage of, 1895*t*
mechanism of action, 1895*t*

R

Rabies
encephalitis caused by, 2534, 2535*b*
immunization for, 65*t*, 66*t*, 82
in travelers, 1889.*e1t*, 1891*t*
vaccine, for traveler, 1886*t*, 1887
Rac 2 deficiency, 1683.*e1t*
Race
age-adjusted drug overdose death rates by, 18*t*, 19*f*
arterial hypertension and, 444
Racecadotril, for infectious gastroenteritis, 2263*b*
Racial differences, in cardiovascular disease, 219
Racial disparities, in health outcomes, 17
Radiation
acute leukemias and, 1259
marrow injury and, 1146
as occupational and environmental hazards, 87
Radiation biodosimetry, 94
Radiation carcinogenesis, 93
Radiation cataractogenesis, 93
Radiation enteritis, 940, 940*b*
intestinal ulcers associated with, 956
Radiation injury, 91–95
ionizing radiation in
clinical manifestations of, 93
diagnosis of, 93, 93*t*
ionizing radiation in, 91
medical imaging of, 94
pathobiology of, 92
prevention of, 94
lung, 597, 597*b*
non-ionizing, 95
Radiation myelopathy, 2564*t*
Radiation pneumonitis, increased lymphocyte counts in, 533
Radiation proctopathy, 968, 968*f*
Radiation therapy
for brain tumors, 1312*b*
for breast cancer, 1369*b*
for cancer, 1232*b*
for Cushing syndrome, 1524*b*
for extramedullary hematopoiesis, 1135*b*
for multiple myeloma, 1299*b*
for NSCLC, 1333*b*
organ-specific late effects after, 93, 93*t*
for pituitary tumors, 1487*b*
for prostate cancer, 1385*b*, 1385*t*
sequelae, treatment of, 94*b*
Radical nephrectomy, for renal cell carcinoma, 1364*b*
Radio frequency coils, 519
Radioablation, for ventricular tachycardia, 338*b*
Radioactive iodine
for Graves disease, 1511*t*
for hyperthyroidism, 1511*b*
Radioactivity, 91
Radiocontrast media, reactions to, 1698*t*
Radiofrequency radiation, 88*t*, 95.*e1f*, 95
Radiography
bedside, 519
chest, 519
in gastroenterology, 866
of heart, 244
for rheumatic disease, 1717, 1717*t*, 1718*f*
Radiologic accidents, 92, 92*t*
Radiologic terrorism, 92
counter measures after, 94
Radiology
for gastrointestinal disease, 854
for nocardiosis, 2073, 2073*f*, 2074*f*
Radionuclide imaging, in acute MI, 384
Radium 223, 1385*b*
Radon, exposure to, lung cancer and, 1329
Rales, 512
Raloxifene
for breast cancer, 1373
for osteoporosis, 1608
Raltegravir, 2301*t*
Ramelteon, 2452*t*
Ramipril, 451*t*
for acute STEMI, 384*b*, 391*t*
for heart failure, 266*t*
Ramsay Hunt syndrome, 2646
Ramucirumab (Cyramza), 1215*t*, 1341*b*
Randall plaques, 803–804
Random donor platelets, 1200
Randomized research design, 36
RANK ligand, 145
RANKL, 151
Ranolazine, 364*b*
Rapid bacteriologic diagnosis, in bacterial meningitis, 2514
Rapid intestinal transit, 939
Rapid plasma reagin test, 2018
Rapid ultrasound in shock (RUSH) protocol, 661*t*
Rapidly progressing myopia, 2597–2598
Rapidly progressive dementia, 2424, 2424*t*
Rapidly progressive glomerulonephritis, 784, 784*f*
anti-glomerular basement membrane disease, 784, 784*b*, 784*f*, 784*t*

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Rapidly progressive glomerulonephritis (*Continued*)
classification of, 784*t*
clinical manifestations of, 785
diagnosis of, 785
IgA nephropathy and, 781*b*
immune complex, 785
pauci-immune, 785
prognosis for, 785
treatment of, 785*b*, 785*f*
vasculitis-associated, 785
Rapidly reversing cardiomyopathy, 337
Rare childhood syndromes, 814, 815*b*
Rasagiline, for Parkinson disease, 2487*t*
Rash
acute, 2694*t*
fever and, 1847, 1848*t*
infectious entities associated with, 1849*t*
in Rocky Mountain spotted fever, 2054
Rate control, for atrial fibrillation, 329*b*
RaTG13, 2210
Rathke cleft cyst, 1479
Rationale, for heart failure, 275*t*
Raxibacumab, 97, 153
Raymond syndrome, 2465.e1*f*
Raynaud phenomenon, 472–473, 472*t*–473*t*, 681
bilateral, 473.e1*f*
in *Mycoplasma pneumoniae*, 2007
in systemic lupus erythematosus, 1770
in systemic sclerosis, 1776–1778
unilateral, 473*f*
RBBB. *See* Right bundle branch block
RBC. *See* Red blood cell
RBC size distribution width (RDW), 1076*t*
RCVS. *See* Reversible cerebral vasoconstriction syndrome
RDW. *See* RBC size distribution width
Re-entrant arrhythmias, 301, 302.e1*f*
Re-entry, 302, 302*f*
Reactivation pneumonitis, 1858
Reactive airways dysfunction syndrome, 587
Reactive arthritis, 1750, 1762–1763
Chlamydia trachomatis causing, 2012
clinical manifestations of, 1763, 1763*f*
definition of, 1762–1763
diagnosis of, 1763, 1764*f*
enteric infections and, 1870*t*
epidemiology of, 1762
human immunodeficiency virus and, 1763
pathobiology of, 1763
prognosis of, 1766
treatment of, 1765*b*
Reactive hyperplasias, 2625, 2625*t*
Ready-to-use therapeutic food (RUTF), for severe acute malnutrition, 1445*b*, 1446*t*
Rebif. *See* Interferon Beta1*a*
Rebound nystagmus, 2619
Receiver operator characteristic (ROC) curve, 38, 39*f*
Receptor activator of nuclear factor-κB ligand, 1640, 1640.e1*f*
Receptor editing, 187
Receptor-mediated signaling pathways, 185–186
Recidivans cutaneous leishmaniasis, 2133
Recluse spiders, envenomation of, 710
Recombinant human von Willebrand factor (rVWF), 1183*b*
Recombinant meningococcal B protein vaccines, 66*t*
Recombinant proteins, 149, 150*t*
Recombinant S protein vaccine, for COVID-19, 2219
Recombinant tissue plasminogen activators (rtPA), for ischemic stroke, 2469*b*, 2469*t*, 2469.e1*f*, 2470*t*
Recombinant zoster vaccine (RZV), 66*t*, 83
Recommended dietary allowances, 57, 1451
Rectal adenocarcinoma, 1349, 1350*b*
Rectal bleeding, 978
Rectal infection, diagnosis of, 1949
Rectal neuroendocrine tumors, 1567
Rectal prolapse, 981–982, 981*f*, 982*b*
Rectal temperature, 33, 678
Rectovaginal fistulas, Crohn disease-related, 945*b*
Rectum
anatomy of, 977
diseases of, 977
anal fissure as, 979, 980*f*
anal fistula as, 979, 979*f*
Rectum (*Continued*)
cancer as, 982
fecal incontinence as, 981, 981*f*
hemorrhoids as, 977, 978*f*
human papillomavirus as, 982
perianal abscess as, 978
pruritus ani as, 980
rectal prolapse as, 981, 981*f*
sexually transmitted anorectal diseases, 983
warts as, 982, 982*f*
distention of, 888
examination of, 31
Recurrent artery of Heubner, 2456–2457
Recurrent corneal erosion, 2602
Recurrent pregnancy loss, in hypercoagulable states, 476
Recurrent somatic mutations, in chronic lymphocytic leukemia, 1267
Recurrent unstable angina, 374*t*
Recurrent venous thromboembolism, 490
Red blood cell (RBC), 1076*t*
packed, HIV transmission through, 2299
transfusion of, 1199–1200
cryopreservation of, 1200
indications for, 1204
irradiation of, 1200, 1205
leukoreduction, 1205
modification of, 1199–1200, 1205
pathogen reduction in, 1200, 1205
for septic shock, 673*b*
Red cell agglutination
conditions associated with, 1072*t*
peripheral blood smear of, 1070*f*
Red cell distribution width, coefficient of variation (RDW-CV), e8*t*–e9*t*
Red cell distribution width (RDW), 1076–1077
Red cell fragmentation
conditions associated with, 1072*t*
peripheral blood smear of, 1068*f*
Red cell indices, 1076, 1076*t*
Red cell release, increasing, 1107*b*
Red cell volume, e8*t*–e9*t*
Red eye, 2599, 2599*t*
Red lesions, 2622*t*, 2623–2624
"Red man syndrome", 1692
5α-Reductase deficiency, 1572
5α-Reductase inhibitors
for benign prostatic hyperplasia, 822*b*
for male lower urinary tract symptoms, 824*t*
Refeeding syndrome, 1450
Reference intervals, e1
clinical chemistry, toxicology, and serology, e1*t*–e8*t*
drugs: therapeutic and toxic, e10*t*–e11*t*
hematology and coagulation, e8*t*–e9*t*
prefixes and abbreviations, e1*t*
Referred pain, 2393
Reflex epilepsies, 2433
Reflux, esophageal, 211*t*
Refractoriness
absolute, 300
dispersion of, 302
relative, 300
Refractory angina, 364*b*
Refractory disease, treatment of, 1269*b*
Refractory dyspnea, oxygen in, 12
Refractory heart failure, 265*b*
Refractory/relapsed Hodgkin lymphoma, management of, 1292*b*
Refractory unstable angina, 374*t*
Regenerative medicine, 169–179
Regional anesthesia, 1827, 2671
Regional dermatoses, 2745, 2745*f*, 2746*f*, 2746*t*
Regional pain syndrome, 1708
Regional rheumatic pain syndromes, 1742
Regional sympathetic dysfunction, 2561
Regional therapy, for metastatic neuroendocrine tumor, 1568*b*
Regorafenib (Stivarga), 1215*t*
for colorectal cancer, 1350*b*
Regulators of complement activation, 197
at C3 and C5 steps, 199
Regulatory cell therapy, 207
Regurgitation
esophageal disease and, 902
gastroesophageal reflux disease and, 903, 903*f*
peptic strictures and, 905
Rehabilitation, for acute STEMI, 384*b*
Rehydration, for cholera, 1956*b*
Reifenstein syndrome, 1573
RELA haploinsufficiency, 1731*t*, 1736
Relapsing encephalitis, 2532*t*
Relapsing fever, 2027, 2059
characteristics of, 2270*t*
clinical manifestations of, 2028
definition of, 2027
diagnosis of, 2028, 2028*f*
epidemiology of, 2027
pathobiology of, 2028
prevention of, 2028
prognosis of, 2028
in travelers, 1889.e1*t*, 1891*t*
treatment for, 2028*b*
Relapsing pancreatitis, prevention of, 972*b*
Relapsing polychondritis, 1825, 2652, 2652.e1*f*
Relapsing-remitting multiple sclerosis, 2501
Relapsing syphilis, 2016
Relative hypovolemia, 735*b*, 735*t*
Relative intensity, 61
Relative refractoriness, 300
Relative scarcity, 9
Relatlimab, for melanoma, 1394*t*
Relaxation, isovolumic, 225
Release reaction, 1165
Relebactam, 1845*t*
REM. *See* Rapid eye movement
REM sleep behavior disorder, 2420, 2452, 2453*t*
Remdesivir, 2190, 2216–2217
Remethylation disorders, 1425*t*, 1426
Remicade. *See* Infliximab
Remodeling organs, endoscopy for, 881
Renal acidification, mechanisms of, 754.e1*f*
Renal agenesis, 818
Renal allograft dysfunction
causes of, 847*t*
evaluation of, 847*t*
Renal arterial system, atheromatous embolization of, 801, 801*b*, 802*f*
Renal arteriography, for vasculitis, 728
Renal artery stenosis, 749*t*, 799–801
atherosclerosis causing, 799
atherosclerotic, 800*b*, 800*t*
clinical manifestations of, 800
definition of, 799
diabetes and, 796
diagnosis of, 800, 800*f*
epidemiology of, 799
fibromuscular dysplasia causing, 799
pathobiology of, 799
prognosis for, 801
Renal biopsy
for acute interstitial nephritis, 792, 792*t*, 793*f*
for diabetic nephropathy, 797
for glomerular syndromes, 728
Renal cell carcinoma, 1362
classification of, 1363*t*
clinical manifestations of, 1363, 1364*t*
definition of, 1362
diagnosis of, 1364
epidemiology of, 1362
pathobiology of, 1362–1363, 1363*t*
prevention of, 1365
prognosis of, 1365
TNM staging of, 1364*t*
treatment of, 1364*b*
Renal colic, evaluation of, algorithm of, 804*f*
Renal dialysis, 673*b*, 677*f*
Renal disease
acute kidney injury as, 725
approach to, 720–729, 720*f*
diagnosis of, 720–725
measuring kidney function in, 720, 721*f*
pathobiology of, 720–725
chronic kidney disease as, 729, 729*f*
glomerular syndromes as, 726
papillary necrosis as, 728
in pregnancy, 1619*t*
sickle cell disease and, 1114*b*
tubulointerstitial diseases as, 728, 728*t*
vasculitis and vascular diseases of kidney as, 728
Renal drug clearance, 129
Renal dysfunction
for septic shock, 673*b*, 677*f*
treatment of, 265*b*
Renal dysplasia, 818
Renal failure
bleeding and, 1166
chronic, weight loss and, 860*t*
drug dose adjustments in, 129.e1*t*
Renal function, normal, diabetes and, 456
Renal glycosuria, 816*t*
Renal hypoplasia, 818
Renal hypouricemia, 816*t*
Renal infarction, 801, 802*b*
Renal insufficiency
drug dosage in, 130
loading dose in, 130
psychotropic medications and, 2678*t*
Renal interstitium, injury to, 771
Renal involvement, in sarcoidosis, 602
Renal malrotation, 819, 819*f*
Renal nerves, 734–735
Renal osteodystrophy, 1657–1658
Renal outer medullary potassium channel (ROMK), 746
Renal parenchymal hypertension, 449, 449*b*
Renal pelvis, cancers of, 1367
Renal replacement therapy, 840–841, 841*t*
for diabetic nephropathy, 797*b*
hemodialysis. *See* Hemodialysis
peritoneal dialysis. *See* Peritoneal dialysis
Renal sodium, imbalances in, 724–725
Renal syndrome, hemorrhagic fever with, 2268*t*
Renal system, systemic lupus erythematosus manifestations of, 1769
Renal toxicity, after hematopoietic cell transplantation, 1211
Renal transplantation, 843
allocation of, 844
antihypertensive drug for, 454*t*
candidate for, 844
complications of, 846–847
epidemiology of, 843–844
immunosuppression in, 844, 845*t*
kidney donation in, 844
management after, 847
prognosis of, 847–848, 847*t*
rejection of, treatment of, 845–846
success rates of, 844
Renal tubular acidosis (RTA)
causes of, 761*t*
clinical manifestations of, 762
diagnosis of, 762
distal, 749*t*, 761
prognosis of, 762
proximal, 761
treatment of, 762*b*
Renal tubular disorders
cystinuria, 815
inherited, 815
Renal tumors, 1363
Renal vein thrombosis, 802, 802*b*
Renin, e1*t*–e8*t*, 730, 734, 1561*t*
Renin-angiotensin II-aldosterone, 734
Renin-angiotensin system, 225
Renin-angiotensin system inhibitors, for hypertension, 452
Renin-secreting tumor, 749*t*
Renomegaly, autosomal dominant polycystic kidney disease and, 811
Renova, for acne, 2698
Renovascular disease, hypertension and, 448*t*, 449, 449*b*, 449*f*
Reoviridae, 2274, 2284
Repaglinide, for type 2 diabetes mellitus, 1541*t*
Reperfusion injury, rhabdomyolysis and, 715
Reperfusion therapy
for acute STEMI, 384*b*, 385*f*
for shock, 667*b*
Repetitive stimulation study, 2375
Repetitive transcranial magnetic stimulation (rTMS), for fibromyalgia, 1819*b*
Repetitive use syndromes, 1742
Repolarization abnormalities, 233, 234*t*
Reproductive axis development, in childhood and puberty, 1581
Reproductive endocrinology, 1595–1604
abnormal uterine bleeding and, 1597, 1597*b*
amenorrhea and, 1598
chronic anovulation and, 1600
dysmenorrhea and, 1596, 1596*b*, 1596*t*
endometriosis and, 1596, 1596*b*, 1603*b*
menstrual cycle, 1595
premenstrual syndrome and, 1596, 1597*b*, 1597*t*
Reproductive health, of adolescents, 112
Reproductive issues
cystic fibrosis and, 557
in women, 1610

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Reproductive system
cancers of, 1615
syndromes affecting, 1570*t*
Reproductive tracts, male and female, development of, 1569, 1571*f*
Reprogramming, direct, 173
Reserpine, 451*t*
Residual volume (RV), 528
Resiliency, in occupational and environmental medicine, 87
Reslizumab, for eosinophilic syndromes, 1164*b*
Resource Conservation and Recovery Act, 87
Respiration, assessment of, 30
Respiratory acidosis, 765
clinical manifestations of, 765
diagnosis of, 765
expected compensation of, 756, 756*t*
toxicants and, 691*b*
treatment of, 765*b*
Respiratory alkalosis, 765
clinical manifestations of, 765
diagnosis of, 765
epidemiology of, 765
expected compensation of, 756, 756*t*
pathobiology of, 765
treatment of, 765*b*
Respiratory bronchiolitis-associated interstitial lung disease, 574*t*, 577, 578*b*, 578*f*
Respiratory burst, defects of, 1683.*e1t*
Respiratory cancers, occupational and environmental, 86
Respiratory compliance
measurement of, 641
static (Crs), 641
Respiratory depression, psychotropic medications and, 2678*t*
Respiratory diphtheria, 1933–1934
Respiratory disease, 512–519, 512*t*
aspirin-exacerbated, 541*b*
chronic lower, in adolescents, 110*t*
Respiratory drive, measurement of, 641
Respiratory failure
hypoxemic, 596
obesity and, 533
Respiratory function, testing, 528–533
Respiratory infections
cryptosporidiosis and, 2143
Mycoplasma pneumoniae in, 2005, 2006*f*
prevention of, in travelers, 1889
Respiratory monitoring, in critical care, 639
Respiratory muscle strength, measurement of, 641
Respiratory rate
abnormal, 34*t*
decreased, 35
increased, 35
measurement of, 33
normal, 639
normal range for, 32*t*
panic range for, 32*t*
Respiratory specimen testing, for infection, 1835
Respiratory support
for acute poisoning, 691*b*
for shock, 662*b*
Respiratory syncytial virus, 2194–2195
in acute bronchitis and tracheitis, 605
clinical manifestations of, 2194–2195
definition of, 2194
diagnosis of, 2195
epidemiology of, 2194
pathobiology of, 2194
pathogen that causes, 2194
prevention of, 2195
prognosis for, 2195
treatment of, 2195*b*
Respiratory system
age-related changes in, 121
disease, in sarcoidosis, 600–601, 601*f*, 601*t*
physical examination of, 639
Respiratory tract, cancer of, occupational and environmental, 86*t*
Respiratory tract infections
adenovirus causing, 2204
Stenotrophomonas maltophilia in, 1975
Respiratory tract syndromes, enteroviruses causing, 2260, 2260*b*
Respiratory viruses
health care-associated infections caused by, 1865
in travelers, 1891*t*
Rest, for heart failure, 275*t*
Resting membrane potential, 299
Resting metabolic rate (RMR), 1465
Resting tremor, 2484, 2489
Restless legs syndrome, 1630, 2496
anemia and, 1075
characteristics of, 2453
clinical manifestations of, 2496
diagnosis of, 2496
epidemiology of, 2496
pathobiology of, 2496
Restrictive cardiomyopathy, 291
causes of, 291*t*
clinical manifestations of, 291
constrictive pericarditis *versus*, 429.*e1f*, 432*f*
definition of, 291
diagnosis of, 291–292, 292.*e1f*, 293*f*
differential diagnosis of, 433*t*
epidemiology of, 291
idiopathic, 292*f*
overlap with dilated cardiomyopathy, 288
pathobiology of, 291
prognosis of, 292
treatment of, 292*b*
Restrictive disorder, 530
Resuscitation
postresuscitation care, 313*b*
for shock, 662*b*
RET defects, 888
Reteplase (r-PA), 386*t*
Reticular activating system, 2443, 2443.*e3f*
Reticulate macular erythema, 2713*f*
Reticulocyte count, *e8t–e9t*
absolute, *e8t–e9t*
Reticulocyte hemoglobin, *e8t–e9t*
Reticulocyte percentage, 1076*t*
Reticulocyte production index (RPI), 1076*t*, 1077
Retiform purpura, 2687, 2715, 2715*t*
Retin-A, for acne, 2698
Retina, 2596
arteries of, 2614
tears of, 2615
Retinal artery occlusion, as arterial thrombotic complications, 481
Retinal detachment, 2596, 2608
Retinal dystrophy, optic nerve edema, splenomegaly, anhidrosis, migraine headache (ROSAH) syndrome, 1731*t*
Retinal involvement, 2091*f*
Retinal necrosis, zoster and, 2249
Retinitis
diagnosis of, laboratory methods for, 2003*t*
Retinitis, cytomegalovirus, 2251, 2251*f*
Retinitis pigmentosa, 2612, 2612*f*
Retinoblastoma, 2612
Retinoic acid inducible gene I (*RIG-1*), influenza and, 2199–2200
Retinoids, for skin diseases, 2698
Retinopathy, diabetic, 2609
Retinopathy of prematurity, 2612
Retrocalcaneal bursitis, 1748
Retroperitoneal fibrosis, 1567, 1782–1783, 1783*b*
Retroperitoneal sarcomas, 1389*b*
Retropharyngeal abscess, distinguishing features of, 515*t*
Retrotracheal region, of mediastinum, 527
Retroviral vectors, 175
Retroviruses, 2324–2328
Rett syndrome, 2548, 2549*b*
Reverse transcriptase inhibitors, 2319
Reverse transcription polymerase chain reaction (RT-PCR)
for noroviruses, 2263
for rotaviruses, 2263
for rubella virus, 2224
Reversed figure-of-3 signs, 247
Reversible airway obstruction, with heart failure, 265*b*
Reversible cerebral vasoconstriction syndrome (RCVS), 1800, 1800*b*, 1800*t*, 2384
Reversible posterior leukoencephalopathy syndrome, 2616
Review of systems, 28, 29*t*, 2660
Revised Cardiac Risk Index (RCRI), 2661, 2662*t*
Revised El Escorial criteria, for amyotrophic lateral sclerosis, 2563*t*
Revlimid. *See* Lenalidomide
Reward, operational definition of, 142
Reward circuitry, 142, 143.*e1f*
Reye syndrome, influenza and, 2200–2201
Rhabdomyolysis, 714–717
acquired, 714*t*, 715
Rhabdomyolysis *(Continued)*
clinical manifestations of, 716
compression-induced, 715
creatinine kinase levels in, 716
definition of, 714–717, 2581
diagnosis of, 716
differential diagnosis of, 716
drugs and toxins causing, 714–715
epidemiology of, 714, 714*t*
exertional, 714, 715*t*
Guillain-Barré syndrome *versus*, 716
hydration for, 717*b*
infections causing, 715
inherited, 714*t*, 715
laboratory tests for, 716
Mycoplasma pneumoniae in, 2007
myoglobin testing for, 716
pathobiology of, 714–716
pathophysiology of, 714–715, 714.*e2f*
periodic paralysis *versus*, 716
prevention of, 716, 717*t*
prognosis of, 717, 717.*e1t*
statin-induced, 714
trauma causing, 715–716, 715*t*
treatment for, 717*b*, 717*t*
treatment of, 705*b*
Rhabdomyosarcoma, chemotherapy for, 1389*b*
Rheumatic diseases, 1706–1712
autoimmune, 1708
classification of, 1706, 1706*t*
clinical manifestations of, 1707–1709
crepitus associated with, 1710
cutaneous manifestation of, 1707–1708
definition of, 1706–1712
degenerative, 1708
diagnosis of, 1709–1712, 1709*t*, 1711*f*
epidemiology of, 1706–1707
glucocorticoid for, 1712
imaging studies in, 1711–1712, 1717–1723
computed tomography, 1717, 1719*f*
magnetic resonance imaging, 1720, 1721*f*, 1722*f*
radiographic evaluation, 1717, 1717*t*, 1718*f*
scintigraphy, 1723, 1723*f*
ultrasonography, 1718–1720, 1719*f*–1720*f*
joint symptoms associated with, 1707, 1708*f*
laboratory testing for, 1712–1716
anti-DNA, 1714
anti-La antibodies, 1715
anti-RNP antibodies, 1714
anti-Ro antibodies, 1715
anti-Sm antibodies, 1714
antibodies to citrullinated proteins, 1713
antibodies to phospholipids, 1715
antineutrophil cytoplasmic antibodies, 1716
antinuclear antibodies, 1714, 1714*f*
complement, 1715
cryoglobulins, 1716
erythrocyte sedimentation rate, 1712
joint fluid analysis, 1713, 1713*f*
to manage therapy, 1716
rheumatoid factor, 1712
laboratory testing in, 1711
medical history of, 1709–1710
nonspecific clinical presentation of, 1707
pain associated with, 1708–1709
pathobiology of, 1707
pattern of onset, 1710
physical examination of, 1710
range of motion assessment, 1710
specific joint symptoms and, 1710
stiffness associated with, 1710
systemic manifestations of, 1708
treatment of, 1712*b*
Rheumatic fever, 1913
acute, *Streptococcus pyogenes* causing, 1917, 1917*b*, 1917*t*
Rheumatic heart disease, *Streptococcus pyogenes* causing, 1917
Rheumatic valvular heart disease, 400
Rheumatoid arthritis, 1717*t*, 1718*f*, 1721*f*, 1749–1758
articular manifestations of, 1751–1752, 1751*f*, 1752*f*
cardiovascular involvement in, 1753
classification of, 1754, 1755*f*
clinical features of, 2574*t*
clinical manifestations of, 1751–1754
cutaneous manifestations of, 1707
cystic fibrosis *versus*, 558
definition of, 1749–1758
Rheumatoid arthritis *(Continued)*
diagnosis of, 1754–1758
differential diagnosis of, 1755–1758, 1755*t*
epidemiology of, 1749
etiology of, 1750, 1750.*e1f*
extra-articular manifestations of, 1752–1754, 1753*t*
of feet, 1751
Felty syndrome, 1754
gender predilection of, 1709
genetics of, 1749–1750, 1750.*e1t*
of hands, 1751, 1752*f*
hoarseness in, 2652
human leukocyte antigens and, 1750.*e1t*
hydroxychloroquine for, 146
initiation of, 1750.*e1f*
interstitial lung disease associated with, 580, 580*f*
juvenile, 2611
laboratory findings in, 1754–1755, 1755*t*
of large joints, 1751, 1752.*e1f*, 1753*f*
of neck, 1752, 1752*f*
neurologic manifestations of, 1754
ophthalmologic manifestations of, 1753
of other joints, 1752
pathobiology of, 1749–1751
pathogenesis and tissue pathology of, 1750–1751, 1750.*e2f*
pattern of onset, 1710
prognosis of, 1759
pulmonary manifestations of, 1753, 1754*f*
skin involvement in, 1752–1753, 1753*f*–1754*f*
splenomegaly associated with, 1152
treatment of, 1755*b*, 1756*t*–1757*t*, 1758*f*
of wrists, 1751, 1753*f*
Rheumatoid factor, 1712, 1751, 1754
in pleural fluid, 626
Rheumatoid nodules, 1752–1753, 1753*f*
Rheumatoid nodulosis, 1754*f*
Rheumatoid synovitis, 1750, 1750.*e1f*
Rheumatologic paraneoplastic syndromes, 1239, 1239*b*, 1239*f*
Rhinitis, 2627–2635
antihistamines for, 2632*b*
cause of, 2628*t*
characteristics of, 2628
chronic, 2627
clinical manifestations of, 2628–2629
corticosteroids for, 2632*b*, 2634*t*
cromolyn for, 2632*b*
decongestants for, 2632*b*
definition of, 2627
diagnosis of, 2629–2632
differential diagnosis of, 2630*f*, 2631, 2633*t*
epidemiology of, 2627
gestational, 1618*t*
imaging of, 2630–2631, 2630*f*–2632*f*
infectious, 2632*b*
laboratory findings in, 2630
leukotriene modifiers for, 2632*b*
medical therapy for, 2632*b*
nonallergic, with eosinophilia syndrome, 2630*f*, 2631
pathobiology of, 2627–2628
physical examination of, 2629–2630, 2629*f*–2630*f*
treatment of, 2632*b*, 2634*t*
Rhinocerebral mucormycosis, 2099
Rhinorrhea, 2193*b*, 2519
Rhinosinusitis, 2628
chronic, 2627, 2628
chronic, cystic fibrosis and, 558
definition of, 2627
diagnosis of, 2629
differential diagnosis of, 2631, 2633*t*
epidemiology of, 2627
imaging of, 2630, 2630*f*, 2631*f*, 2632*f*
laboratory findings in, 2630
pathobiology of, 2627
physical examination of, 2629, 2629*f*, 2630*f*
symptoms of, 2628*t*
Rhinoviruses, 605, 609, 2192
Rhonchus, 512, 512*t*
Rhythm disturbances, management of, 384*b*
Rhythmic movement disorder, 2452
Rib-pelvis distance, 1638*f*
Ribavirin
for hepatitis C, 1014*b*, 2182*t*, 2185
for respiratory syncytial virus, 2195*b*
for viral hemorrhagic fevers, 2272*t*

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Ribociclib (Kisqali), 1215*t*
for breast cancer, 1369*b*
Riboflavin, *e*1*t*–*e*8*t*, 1453*t*
Richter syndrome, 1283*b*
Richter transformation, in chronic lymphocytic leukemia, 1268, 1271
Rickets, 1453*t*, 1647
definition of, 1647
epidemiology of, 1647
Wilson disease and, 1437
Rickettsia akari, 2060
Rickettsia felis, 2058–2059
Rickettsia parkeri, 2065*t*
Rickettsia philipii 364D, 2065*t*
Rickettsia prowazekii, 2054
Rickettsia rickettsii, 1847
Rickettsia spp., diseases caused by, 2054
Rickettsia typhi, 2058
in travelers, 1889.*e*1*t*
Rickettsiae, 2055*t*
Rickettsial infections, 2054–2063
definition of, 2054
ehrlichioses and anaplasmoses, 2060–2062, 2060*t*
flea-transmitted diseases, 2058
genetic classification of, 2055*t*
in human beings, 2055*t*
louse and mite infections, 2059–2060
pathogens of, 2054
Q fever, 2062
rickettsioses, 2054
Rickettsialpox, 2055*t*, 2060, 2060*b*
Rickettsioses, 2054
lymphangitis-associated, 2055*t*
tick-borne, 2054–2058, 2055*t*
Riedel thyroiditis, 1515, 1515*b*
Rifabutin
for nontuberculous mycobacterial disease, 2046*t*
for tuberculosis, 2040*b*
Rifampicin
for leprosy, 2052*b*, 2053, 2053*t*
for primary sclerosing cholangitis, 1058*b*
Rifampin
for bacterial meningitis, 2518*t*
dosage of, 1895*t*
for endocarditis, 417*b*
for *H. influenzae* type B disease, 1954
mechanism of action, 1895*t*
for meningococcal disease, 1945*t*
for nontuberculous mycobacterial disease, 2046*t*
resistance mechanisms, 1893*t*
for tuberculosis, 2040*b*, 2041*t*–2042*t*, 2043*t*
Rifamycin, 1845*t*
Rifapentine, for tuberculosis, 2040*b*, 2041*t*
Rifaximin
for bloating, 859*b*
for irritable bowel syndrome, 895*b*, 896*t*
for traveler's diarrhea, 1888, 1888*t*
Rift Valley fever, 99, 99.*e*1*t*, 2265*t*, 2266, 2268*t*, 2275*t*, 2279, 2280*b*
RIG-1. *See* Retinoic acid inducible gene I
Right atrial pressure, 240
Right bundle branch block (RBBB), 231, 231*t*, 232*f*, 334
Right ventricular enlargement, 245
Right ventricular failure, 494
Right ventricular hypertrophy, 233
Right ventricular infarction
ECG findings, 383
management of, 384*b*
Right ventricular outflow tract obstruction, 351
Rigidity, in parkinsonism, 2484
Rilonacept, description of, 151, 151*t*
Rilpivirine, 2301*t*
Riluzole, for amyotrophic lateral sclerosis, 2563*b*
Rimantadine, for influenza, 2189, 2189*t*, 2203*t*
Ringed sideroblasts, 1086, 1086*f*
Rings, esophageal, abnormalities of, 910, 910*f*
Rinne test, 2641
Rinvoq. *See* Upadacitinib
Riociguat, for pulmonary hypertension, 496*b*
Rippling muscle disease, 2583.*e*1*t*, 2585
Risankizumab, for inflammatory bowel disease, 945*b*, 946*t*
Risdiplam, for spinal muscular atrophy, 2565*b*
Risedronate
for osteogenesis imperfecta, 1728*b*
for osteoporosis, 1644*t*
for Paget disease, 1664*t*
Risk assessment
cardiovascular, 2661, 2662*t*, 2663*f*
general, 2661
genetic, 159
Risk factors, 28
Risk prediction, for common complex disease, 167
Risk-reducing bilateral mastectomy, for cancer, 1232*b*
Risk stratification, 363
for decision making, 363*t*
after myocardial infarction, 384*b*
Risperidone, 2346*t*, 2496*b*
Ristocetin cofactor activity, 1181
Ritonavir, 2301*t*
Rituxan. *See* Rituximab
Rituximab (Rituxan), 1215*t*
for autoimmune hemolytic anemia, 1089*b*
for chronic lymphocytic leukemia, 1269*t*, 1270*t*
description of, 152
for immune thrombocytopenic purpura, 1175*b*, 1176*t*
for minimal change disease, 778*b*
for rapidly progressive glomerulonephritis, 785*b*
for rheumatoid arthritis, 1756*t*
for systemic lupus erythematosus, 1772*b*
for total knee arthroplasty, 1830.*e*1*t*
Rivaroxaban, 502*t*, 505, 505*t*
administration of, 506*t*
description of, 364*b*
dosage and monitoring of, 505
for venous thromboembolism, 478*b*, 487*b*
Rivastigmine
for Alzheimer disease, 2416*b*
for Parkinson disease, 2487*t*
Rizatriptan, 2380*t*
RMR. *See* Resting metabolic rate
RMSF. *See* Rocky Mountain spotted fever
RNA-based therapeutics, 176–178
RNA interference (RNAi), 176–177
Ro60, 1768
Robotic-assisted cholecystectomy, 1052*b*
Robotic resection, of lung cancer, 1333*b*
Rocio virus, 2276*t*, 2283
Rock of Gibraltar sign, 525
Rocky Mountain spotted fever (RMSF), 2054, 2055*t*
clinical manifestations of, 2054, 2057*f*
diagnosis of, 2054–2057
epidemiology and pathobiology of, 2054
prevention of, 2057, 2057*f*
prognosis of, 2057
reported cases of, 2056*f*
treatment of, 2057*b*
Rodent-borne viruses, 2264
Rodent flea, plague and, 1988, 1990*f*
Roflumilast, 553*t*
Rokitansky-Aschoff sinuses, 1054
Rolapitant, for nausea and vomiting, 863*t*
Romano-Ward syndrome, 348
Romhilt-Estes criteria, 233
Romiplostim, 1175*b*, 2314*b*
ROMK. *See* Renal outer medullary potassium channel
Romosozumab, for osteoporosis, 1643*b*, 1644*t*
Ropinirole
for Parkinson disease, 2487*t*
for restless legs syndrome, 2453, 2496*b*
Rosacea, 2722, 2722*b*, 2722*f*
ROSAH syndrome. *See* Retinal dystrophy, optic nerve edema, splenomegaly, anhidrosis, migraine headache syndrome
Rosai-Dorfman disease, 1158, 1159*b*
Rosiglitazone, for type 2 diabetes mellitus, 1541*t*
Ross River virus, 2275*t*, 2279, 2279*b*
in travelers, 1889.*e*1*t*
Rosuvastatin
for acute STEMI, 391*t*
for familial hypercholesterolemia, 1409*t*
for ischemic heart disease, 470*b*
lipid metabolism affected by, 364*b*
Rotational thromboelastometry (ROTEM), 1169
Rotator cuff tear, 1744, 1744*b*
Rotator cuff tendinosis, 1743–1744, 1743*f*, 1744*b*
Rotaviral NSP4, 2262–2263
Rotaviruses, 2261
clinical manifestations of, 2263
definition of, 2261
diagnosis of, 2263
epidemiology of, 2262, 2262*t*
pathobiology of, 2262–2263
as pathogen, 2261
prevention of, 2263–2264
traveler's diarrhea caused by, 1888*t*
treatment of, 2263*b*
vaccination, 928
ROTEM. *See* Rotational thromboelastometry
Roth spots, 2610*f*
Rotigotine
for Parkinson disease, 2487*t*
for restless legs syndrome, 2453
Rouleaux formation, peripheral blood smear of, 1070*f*
Roussel Uclaf Causality Assessment Method (RUCAM), 1020, 1021*t*
Roux-en-Y gastric bypass, 1467*b*
Rozlytrek. *See* Entrectinib
RPI. *See* Reticulocyte production index
R-protein, 1118
RR interval, 229, 229*t*
RT-PCR. *See* Reverse transcription polymerase chain reaction
RTA. *See* Renal tubular acidosis
rTMS. *See* Repetitive transcranial magnetic stimulation
rTPA. *See* Recombinant tissue plasminogen activators
Rubella, 2224–2225
characteristics of, 2270*t*
clinical manifestations of, 2224, 2224*f*, 2225*t*
definition of, 2224–2225
diagnosis of, 2224
epidemiology of, 2224
immunization for, 66*t*, 78*f*, 82
schedule of, 76.*e*1*t*, 77*f*
pathobiology of, 2224
pathogen of, 2224
prevention of, 2225
prognosis of, 2225
in travelers, 1889.*e*1*t*
treatment of, 2224*b*
Rubex. *See* Doxorubicin
Rubivirus, 2224
Rubraca. *See* Rucaparib
Rubulavirus, 2225
Ruby, 2701
RUCAM. *See* Roussel Uclaf Causality Assessment Method
Rucaparib (Rubraca), 1215*t*, 1251*t*
Rufinamide, for seizures, 2434*t*
Rumination disorder, 1461, 1462*b*
Runner's diarrhea, 926
Ruptured viscus, abdominal pain and, 854*t*
RUSH. *See* Rapid ultrasound in shock
Russell viper venom, 707–708
RUTF. *See* Ready-to-use therapeutic food
Rutherford's clinical classification, 462*t*
Ruxolitinib (Jakafi), 153, 153*t*, 1135*b*, 1138*f*, 1161*b*, 1215*t*
RV. *See* Residual volume
Ryanodine receptor 2, 224
Rybrevant. *See* Amivantamab-vmjw
Rydapt. *See* Midostaurin
RZV. *See* Recombinant zoster vaccine

S

S1PR1. *See* Sphingosine-1-phosphate receptor
Sabiá virus, 2265*t*
Saccades, 2618, 2618.*e*1*t*
Saccular aneurysms, 2475*f*
Sacituzumab govitecan-hziy (Trodelvy), 1215*t*
Sacral nerve modulation, for fecal incontinence, 981*b*
Sacral promontory, 977
Sacroiliitis, 1708
Sacubitril/valsartan, 265*b*, 269*t*, 451*t*
Safety
and cost, 46
culture of, 46
patient, 45
Safety data sheet (SDS), in occupational and environmental medicine history, 85
Safety factor, 300
Safinamide, for Parkinson disease, 2487*t*
Sail sound, 354
Salicylate intoxication, 686*t*, 690*t*, 698*t*, 758
clinical manifestations of, 759
diagnosis of, 759
epidemiology of, 758–759
pathobiology of, 758
prognosis of, 759
treatment of, 759
Salicylates, *e*10*t*–*e*11*t*
central nervous system effects of, 685*t*
Saliva cortisol, measurements of, 1522
Salivary gland, 1320
cancer, 1322, 1328
malignancies, 1327*b*
tumors of, 1322
Salivary gland carcinomas, 1336
Salivary gland diseases
enlargement, causes of, 2626*t*
impaired, without gland enlargement, 2626, 2626*b*
primary, 2625
secondary, 2625–2626
secretion, causes of, 2626*t*
sialolithiasis, 2625
Warthin tumor, 2625
Salmeterol
description of, 553*t*
for high-altitude diseases, 593*t*
Salmonella
nontyphoidal, in travelers, 1891*t*
in travelers, 1891*t*
traveler's diarrhea caused by, 1888*t*
Salmonella enterica, 1833
Salmonella enteritis, in travelers, 1889.*e*1*t*
Salmonella paratyphi, in travelers, 1887, 1891*t*
Salmonella sp.
antimicrobial resistance of, 1977
asymptomatic intestinal carrier state of, 1977
bacteremia caused by, 1978
carriers of, 1977
clinical manifestations of, 1977
contact with animals and their environments of, 1977
contact with infected persons of, 1977
contaminated animal products as source of, 1976
in contaminated food and water, 1977
definition of, 1976
diagnosis of, 1978
enterocolitis caused by, 1978
epidemiology of, 1976
pathobiology of, 1977
pathogen description, 1976
prevention of, 1979
prognosis for, 1979
treatment of, 1979*b*
Salmonella typhi, in travelers, 1891*t*
Salp15, 2023
Salpingitis, 1883, 1949
Salt retention, in nephrotic syndrome, 777
Salvage, for lung cancer, 1333*b*
Salvage antifungal therapy, for aspergillosis, 2096
Salvage esophagectomy, for esophageal squamous cell carcinoma, 1338*b*
Sanfilippo syndrome, 1724*t*
Sanofi Pasteur, 2219
SAPHO. *See* Synovitis acne pustulosis hyperostosis osteitis syndrome
Sappinia, 2150*t*
Saquinavir, 2301*t*
Sarcocystis spp, 2155
Sarcocystosis, 2155
Sarcoid arthropathy, 1824
Sarcoidosis, 292, 292*b*, 582, 599–604, 1029–1030, 1030*b*, 1150, 2611, 2652, 2734, 2735*f*
bone and joint involvement, 602
calcium metabolism in, 602
cardiac disease, 602
cardiomyopathy with, 292
central nervous system involvement of, 1479
chest CT findings of, 600*f*
chest radiography of, 600*f*
clinical manifestations of, 600–602, 600*f*
definition of, 599–604
description of, 1824–1825, 1825*f*
diagnosis of, 602–603
drug-induced, 603
endobronchial, distinguishing features of, 515*t*
epidemiology of, 599–600
eye disease, 601

Copyrighted material

Sarcoidosis *(Continued)*
hepatic, 603
illustration of, 2688*t*, 2692*t*
increased lymphocyte counts in, 533
intestinal ulcers associated with, 956
liver disease, 602
neurologic disease, 602, 602*t*
obstruction and, 532
as occupational lung disease, 585*t*
pathobiology of, 600, 600.*e1f*
prognosis for, 604
renal involvement, 602
respiratory system disease, 600, 601*f*, 601*t*
skin disease, 601, 602*f*
splenic, 602
steroid-dependent, 603*b*
treatment for, 603*b*, 604*t*
Sarcoma, 2733–2734, 2734*f*
chondrosarcoma, 1388, 1388*b*
Ewing, 1388, 1388*b*
Kaposi, 2315, 2315*b*, 2316*f*, 2624
large bowel, 1347
leiomyosarcoma, 1389
osteosarcoma, 1388, 1388*b*
retroperitoneal, 1389*b*
rhabdomyosarcoma, 1389*b*
soft tissue, 1389, 1389*b*
Sarcomeres, 224, 224.*e1f*, 2580
Sarcopenia, 2587
Sarcoplasmic reticulum calcium ATPase, 175
Sarcoptes mite, 2741
Sarcoptes scabiei, 710
Sarecycline, 1845*t*
Sarilumab, description of, 151, 151*t*
SARS. *See* Severe acute respiratory syndrome
SARS-CoV-2. *See* Severe acute respiratory syndrome coronavirus-2
SAT. *See* Standard (tube) agglutination test
Satiation, 1464
Satiety, 1464
Saturated fats, dietary guidelines for, 57.*e3t*
Saturated solution of potassium iodide (SSKI), for sporotrichosis, 2086*b*
Savage syndrome, 1600
SAVI. *See* STING-associated vasculopathy with onset in infancy
Saxagliptin, 262
for type 2 diabetes mellitus, 1541*t*
Scabies, 710, 711*b*, 711*f*, 2687.*e1t*, 2741, 2742*f*
organisms causing, 1879*t*
treatment of, 1884*t*
Scalded skin syndrome, 1908
Scalp eschar, neck lymphadenopathy after tick bite (SENLAT), 2055*t*
Scalp psoriasis, 2747*t*
Scarlatina, 1914
Scarlatiniform eruptions, 2712, 2712*t*
Kawasaki disease, 2712
Scarlet fever, 2712
toxic shock syndrome, 2712
Scarlet fever, 1914, 2712
Scarpa ganglion, 2644
Scarring alopecia, 2749
Scavenger receptors, 183
SCC. *See* Squamous cell carcinoma
Scedosporium apiospermum, infections by, voriconazole for, 2076
Schamberg disease, 2713
Schatzki ring, 910, 910*f*
Scheie syndrome, 1724*t*
Schiff-Sherrington phenomenon, 2386
Schistocytes
conditions associated with, 1072*t*
peripheral blood smear of, 1068*f*
Schistosoma haematobium, 2163–2164, 2165*t*
Schistosoma intercalatum, 2165*t*
Schistosoma japonicum, 1029, 2163, 2164, 2165*t*
Schistosoma mansoni, 1029, 1029.*e1f*, 2163*f*, 2164, 2165*t*
Schistosoma mekongi, 2165*t*
Schistosoma spp., 1026*t*
etiology of, 2163–2164
life cycle of, 2163, 2163*f*
in travelers, 1891*t*
Schistosomes
dermatitis caused by, 2164
description of, 1029
Schistosomiasis, 1029, 1029*b*, 1029.*e1f*
acute, 2164
chronic, 2164
clinical manifestations of, 2164
Schistosomiasis *(Continued)*
definition of, 2163–2165
diagnosis of, 2164–2165, 2165*t*
epidemiology of, 2163–2164
pathobiology of, 2164
pathogen that causes, 2163
prevention of, 2165
prognosis of, 2165
in travelers, 1889.*e1t*
treatment of, 2165*b*
Schizoaffective disorder, 2340*t*, 2345*t*, 2346, 2346*t*
Schizoid personality disorder, 2348*t*
Schizonts, 2141
Schizophrenia, 2345
definition of, 2345
diagnosis of, 2345, 2345*t*
epidemiology of, 2345
pathobiology of, 2345
prognosis of, 2345–2346
symptoms and signs of, 2345*t*
treatment for, 2345*b*, 2346*t*
Schizotypal personality disorder, 2348*t*
Schnitzler syndrome, 1731*t*
Schwannoma, 2730, 2732*f*
Schwartz-Jampel syndrome, 2583.*e1t*
Sciatica, 2402
Scimitar sign, 247
Scintigraphy, for rheumatic disease, 1723, 1723*f*
SCLC. *See* Small cell lung cancer
Sclera, 2596
Scleral icterus, 987, 987*f*, 2030*f*
Scleritis, 2611
Scleroderma, 888, 2737. *See also* Systemic sclerosis
of esophagus, 911
florid features of, 987
Scleroderma, ectasias and, 967
Scleroderma renal crisis, 1779, 1781, 1781*b*
Sclerosing thyroiditis, 1515, 1515*b*
Sclerosis, 2737
multiple. *See* Multiple sclerosis
systemic. *See* Systemic sclerosis
tuberous, 583
Sclerostin, 1643*b*
Sclerotic lesions, 2737–2738, 2737*f*, 2738*f*
SCN4A gene, 2585
SCN5A gene, 337
Scoliosis, 620–621
Scombroid poisoning, in travelers, 1889.*e1t*
Scopolamine patch, for nausea and vomiting, 863*t*
Scorpion, envenomation of, 65*t*, 710
Screening
for abdominal aortic aneurysm, 53
cancer
breast, 1373, 1373*t*
cervical, 1376, 1376*t*
colorectal, 54
pancreatic, 1356
prostate, 1387
skin, 1394
electrocardiograms, 235
family, 287*b*
newborn, 166, 1404
Scrub typhus, 2055*t*, 2059, 2060*b*. *See also* *Orientia tsutsugamushi*
SDS. *See* Safety data sheet
Sea anemone stings, 713
Sea urchins, 713
Seafood, as source of food poisoning, 925
Seasonal allergic rhinitis, 1674
Seasonal coronavirus, 2206
clinical manifestations of, 2207
diagnosis of, 2207
epidemiology of, 2206, 2207*t*
pathobiology of, 2206, 2207*t*
prevention of, 2207
prognosis of, 2207
treatment for, 2207*b*
Seasonal influenza vaccination, 541*b*
Sebaceous carcinoma, of eyelids, 2602
Sebastian syndrome, 1179
Seborrheic blepharitis, 2602
Seborrheic dermatitis, 2321, 2687, 2687.*e3t*, 2703, 2703*f*, 2745*f*, 2747*t*
Seborrheic keratoses, 2602, 2688*t*, 2689*t*, 2729, 2730*f*
Secnidazole, 1845*t*, 2150*t*
Second-line agents, for eosinophilic syndromes, 1164*b*
"Second-wind" phenomenon, 2586
Secondary adrenal insufficiency, 1492, 1526, 1527*t*, 1528*f*
Secondary amenorrhea, 1598
Secondary autoimmune neutropenia, 1146
Secondary dystonia, 2492*t*
Secondary gonadal insufficiency, 1584
Secondary hyperaldosteronism, 1525*t*
Secondary hyperparathyroidism, 1658*t*
Secondary hypocortisolism, 1492
Secondary malignancies
in chronic lymphocytic leukemia, 1268
after hematopoietic cell transplantation, 1211
Secondary malnutrition, 1445, 1445*b*
Secondary open-angle glaucoma, 2607
Secondary parkinsonism, 2483*t*
Secondary peritonitis, 957
Secondary progressive multiple sclerosis, 2501
Secondary syphilis, 2015–2016, 2016*f*, 2709, 2709*f*
Secondary systemic amyloidosis, 1310, 1310*b*
Secretin, 1561*t*
Secretin stimulation test, for malabsorption, 931*t*
Secukinumab (Cosentyx)
for psoriatic arthritis, 1765*b*
for total knee arthroplasty, 1830.*e1t*
Sedation, 636
Sedative-hypnotics, 2363, 2363*b*
central nervous system effects of, 685*t*
toxidromes, 683*t*
Sedentary behavior, 63*b*
Sediment, *e1t–e8t*
^{75}SeHCAT test, for malabsorption, 931*t*
Seizures, 306
absence, 2428*t*, 2429
acute symptomatic, 2434*b*
alcohol-related, 2543, 2543*b*
atonic, 2428*t*, 2430
autonomic, 2428*t*
in bacterial meningitis, 2513
causes of, 2426*t*
classification of, 2427*f*
clinical manifestations of, 2427–2430
clonic, 2428*t*
cognitive, 2428*t*
convulsive, 2429
definition of, 2425–2436
diagnosis of, 2430–2433
differential diagnosis of, 2430*t*
drug-resistant, 2434*b*
dystonic, 2428*t*
emotional, 2428*t*
epilepsies *versus*, 2425
febrile, prognosis after, 2436
focal, 2427–2429, 2428*t*
frontal lobe, 2430
generalized, 2425, 2428*t*, 2429
gustatory, 2428*t*
impaired awareness, 2428*t*
inborn errors of metabolism and, 1399
myoclonic, 2428*t*, 2430
olfactory, 2428*t*
postoperative, 2674
in pregnancy, 2434*b*
prognosis of, 2436
psychogenic nonepileptic, 2431
psychotropic medications and, 2678*t*
severe mental illness and, 2683*t*
single, 2431
single unprovoked, 2434*b*, 2436
somatosensory, 2428*t*
after subarachnoid hemorrhage, 2476*b*
surgical treatment of, 2434*b*
syncope *versus*, 2430*t*
tonic, 2428*t*, 2430
tonic-clonic, 2428*t*, 2429
treatment of, 2434*b*
type of, antiseizure medication selection by, 2433*t*, 2434*b*
vestibular, 2428*t*
visual, 2428*t*
in women, medications for, 1608*t*
Selective estrogen receptor modulators
for breast cancer, 1369*b*
for osteoporosis, 1643*b*
Selective IgA deficiency, 1681*t*, 1682, 1822
Selective oropharyngeal decontamination, in health care-associated infections, 1867
Selective serotonin reuptake inhibitors (SSRIs)
for anorexia nervosa, 1462*b*
central nervous system effects of, 685*t*
for depression, 2340*t*
for fibromyalgia, 1819*b*
in pregnancy, 1610
toxicity, 686*t*
Selegiline
for depression, 2340*t*
for Parkinson disease, 2487*t*
Selenium, *e1t–e8t*, 1457*t*
Selexipag, for pulmonary hypertension, 496*b*
Self-help groups, for alcohol use disorders, 2357*b*
Self-identified race, 219
Self-neglect, geriatric assessment of, 118
Selinexor (Xpovio), 1215*t*
Semaglutide
for nonalcoholic fatty liver disease, 1034*b*
for type 2 diabetes mellitus, 1541*t*
Semantic dementia, 2422
Semen analysis, 1589*t*
Semidirect allorecognition, 205, 205*f*
Seminomas, treatment of, 1383*b*
Semont maneuver, 2645*f*
Senile cardiac amyloidosis. *See* ATTRwt amyloidosis
Senile purpura, 121, 122*f*
SENLAT. *See* Scalp eschar, neck lymphadenopathy after tick bite
Senolytics, 116
Sensitivity, 38
Sensitization, central, 134
Sensitizer-induced occupational asthma, 585
clinical manifestations of, 585–586
diagnosis of, 586
epidemiology of, 585
pathobiology of, 585
prevention of, 586*b*
prognosis of, 586
treatment of, 586*b*
Sensorineural hearing loss, 2641
occupational and environmental, 86, 86*t*
Sensory, age-related changes in, 122
Sensory ataxia, 2373*t*
Sensory neuronopathy, 2567*t*
Sensory receptor, 2639
"Sentinel events", 46
Sentinel lymph node biopsy, for melanoma, 1392
Sepsis
definition of, 669
immunodepression in, 671.*e2f*
lactate and, 757
mesenteric venous thrombosis and, 963*t*
procoagulant response in, 671.*e1f*
screening for, 670*t*
severe, 669
shock syndromes related to, 669–677
thrombocytopenia and, 1175
Septic abortion, characteristics of, 2270*t*
Septic arthritis, 1804
anaerobic bacteria causing, 1940
definition of, 1804–1805
gonococcal, 1807, 1807*b*
H. influenzae caused by, 1954
microorganisms responsible for, 1805*t*
nongonococcal, 1805
clinical manifestations of, 1805
diagnosis of, 1805, 1806*f*
differential diagnosis of, 1806
epidemiology of, 1805
pathobiology of, 1805, 1805*t*
prevention of, 1807
prognosis of, 1807
treatment for, 1806*b*, 1807*t*
Staphylococcus aureus causing, 1904–1905
Septic bursitis, 1804
clinical manifestations of, 1804
definition of, 1804
diagnosis of, 1804
differential diagnosis of, 1804
epidemiology of, 1804
pathobiology of, 1804
prevention of, 1804
prognosis of, 1804
treatment for, 1804*b*, 1805*t*, 1807*t*
Septic cavernous sinus thrombosis, 2528, 2529*b*
Septic emboli, 2741
Septic embolization, 1904*f*
Septic sagittal sinus thrombosis, 2530, 2530*b*
Septic shock, 658–659, 659
antibiotics for, 673*b*, 675*t*
cardiovascular dysfunction in, 671

Copyrighted material

Septic shock *(Continued)*
circulatory therapy for, 673*b*
definition of, 669
differential diagnosis of, 673
drugs for, 673*b*
endocrine response and therapies in, 671.*e1f*
epidemiology of, 669–670
intensive insulin therapy for, 673*b*
pathobiology of, 670–672
prevention of, 676
prognosis for, 676
respiratory therapy for, 673*b*
tissue hypoxia in, 671
Septic thrombophlebitis, 2650
Septicemia, meningococcal fulminant, 2512
Septicemic plague, 1991, 2270*t*
Septo-optic dysplasia, 2547
Serologic tests
for COVID-19, 2214–2215
for malaria, 2120
for toxoplasmosis, 2138*t*
Serology
for *Bartonella* infection, 2002
for glomerular syndromes, 727
for histoplasmosis, 2083
reference intervals, *e1t–e8t*
for rubella virus, 2224
Seronegative arthritis, 1721*f*
Serotonin and norepinephrine reuptake inhibitors (SNRIs)
central nervous system effects of, 685*t*
for depression, 2340*t*
for fibromyalgia, 1819*b*
Serotonin re-uptake inhibitors (SRIs)
central nervous system effects of, 685*t*
toxicity, 686*t*
Serotonin syndrome, 1921*b*
characteristics of, 2682*t*
psychotropic medications and, 2681
treatment for, 2681*b*
Serotonin toxicity, anesthesia and, 2669
Serous cystadenomas, 1355–1356
Serovar Typhi, *Salmonella*, in travelers, 1891*t*
SERPINA1 Z allele, 556
Serrated polyps, 1348
Sertraline, *e10t–e11t*
for depression, 2340*t*
for irritable bowel syndrome, 896*t*
Serum aminotransferases, in liver disease, 989
Serum-ascites albumin, 1039, 1040*t*
Serum-ascites albumin gradient, 990
Serum cardiac biomarkers, 383
Serum creatinine, 721, 721*f*
Serum ferritin, in gastrointestinal disease, 851–854
Serum free light chain assay, 1295
Serum immunoelectrophoresis, for glomerular syndromes, 727
Serum potassium concentration, abnormal, postoperative, 2676
Serum protein electrophoresis, of monoclonal proteins, 1294, 1295*f*
Serum sickness, 195, 705*b*, 1694
Serum trypsinogen, in chronic pancreatitis, 974
Serum tryptase, 1675, 1693
Serum TSH, 1505
SeSAME syndrome (EAST syndrome), 816*t*
Severe acute respiratory syndrome (SARS), 2208
clinical manifestations of, 2208
diagnosis of, 2208
epidemiology of, 2207–2208, 2207*t*
pathobiology of, 2208
prevention of, 2209
prognosis of, 2209
treatment for, 2208*b*
Severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2), 286, 2213
acute kidney injury in, 773, 774*t*
acute respiratory distress syndrome and, 650
in adolescents, 111
clinical manifestations of, 2213, 2214*f*, 2214*t*
community prevention of, 2215
diagnosis of, 2214, 2215*f*
epidemiology of, 2213
functional domains of, 2211*f*
hypercoagulable states and, 481
infection of cells in, 2210–2211, 2210*f*
myocarditis and, 2259
nail signs of, 2752*t*
Severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2) *(Continued)*
origin of, 2210
prognosis of, 2215
rapid identification of, 40
schematic drawing of, 2210*f*
spill-back infections of wildlife, 2212
transmission electron micrograph of, 2209*f*
transmission of, 2213
in travelers, 1888
variants of, 2212, 2212*t*
virus and genome of, 2209–2210, 2209*t*
in women, 1610
Severe aplastic anemia, 1125, 1128*f*
Severe combined immunodeficiency
gene therapy, 174
X-linked, 175
Severe congenital neutropenia, 1143, 1144*t*, 1683.*e1t*
Severe fever with thrombocytopenia syndrome virus, 2275*t*
Severe hyperpyrexia, 1851
Severe hypoglycemia, 1546*t*
Severe malnutrition, 1444
clinical manifestations of, 1444
definition of, 1444
diagnosis of, 1445
epidemiology of, 1444
kwashiorkor, 1444, 1444*f*, 1445*f*
marasmus, 1444, 1444*f*
pathobiology of, 1444
prevention of, 1446
prognosis for, 1446
secondary, 1444
stunting, 1445
treatment of, 1445*b*
wasting, 1445
Severe parenchymal lung disease, in hypercapnic disease, 535*t*
Sex
arterial hypertension and, 444
in travelers, 1889
Sex chromosomes, aneuploidy of, 164, 1574
Sex hormone-binding globulin, 1581, 2318
Sex-linked inheritance, 162
Sex steroids, 1591
Sexual activity, heart failure in, 265*b*
Sexual assault, survivors of, regimen for, 1884*t*
Sexual development, 1569–1576
definition of, 1569
differences of, 1569–1573, 1570*t*
considerations related to sex assignment, 1575*b*
diagnosis of, 1575
initial medical management of, 1575*b*
surgical management of, 1575*b*
treatment of, 1575*b*
fetus in, maternal conditions affecting, 1573
hormone insensitivity syndromes, hormone deficiencies and, 1573
ovotesticular disorder of, 1574
Sexual differentiation
normal, 1569
prenatal, course of, 1571*f*
Sexual dysfunction, 1587–1590, 1604, 1604*b*
decreased libido, 1587
ejaculatory failure, 1590, 1590*b*
erectile dysfunction, 1587, 1589, 1589*t*, 1590*f*
impaired orgasm, 1590
in multiple sclerosis, 2504*b*
Sexual function, 1581, 1604
Sexual health, of adolescents, 112
Sexual maturity ratings (SMRs), 110, 110.*e1f*
Sexual orientation, 1574
Sexual transmission, of human immunodeficiency virus, 2298, 2298*f*
Sexuality, geriatric assessment of, 118
Sexually transmitted infections (STIs), 1878–1885
in adolescents, 112
bacterial vaginosis, 1882
barrier methods for, 1884
behavioral interventions for, 1883–1884
candidiasis, 1882, 1882*b*, 1882*t*
chlamydia, epidemiology of, 1879
Chlamydia trachomatis, 1879, 2010, 2011*f*
contraception for, 1884
counseling for, 1883–1884
definition of, 1878–1880
diagnosis of, 1879–1880
donovanosis as, 2004
Sexually transmitted infections (STIs) *(Continued)*
epidemiology of, 1878–1879
epithelial cell infections, 1881
general approach to, 1880*b*
genital herpes, 1880
genital ulcers, 1880
HIV infection and, 1880
human papillomavirus, 1881
lymphogranuloma venereum, 1881
male circumcision and, 1884
partner services for, 1884
pathobiology of, 1879
pelvic inflammatory disease, 1883
postexposure prophylaxis for, 1884, 1884*t*
preexposure interventions for, 1884
prevention of, 1883–1884
screening for, 55
screening of, for adolescents, 112
syndromes of, 1879*t*, 1880–1883
syndromic strategies to, 1879–1880
syphilis. *See* Syphilis
in travelers, 1889
treatment of, 1880*b*
trichomoniasis, 1882–1883, 1883*b*
urethritis, 1880
SGLT2. *See* Sodium-glucose cotransporter-2
Shared care, 2656
Shared decision making, 39
Shared epitope, 1749, 1750.*e1t*
Shear wave elastography, 1720
Shellfish poisoning, 713
in travelers, 1889.*e1t*
Shiga toxin-producing E. coli, 1178
Shigatoxigenic *E. coli*, 1962*t*
Shigella, 1980
epidemiology of, 1980
sexually transmitted anorectal diseases and, 983
transmission of, 1980
in travelers, 1889.*e1t*, 1891*t*
traveler's diarrhea caused by, 1888*t*
virulence of, 1981
Shigella boydii, 1980
Shigella dysenteriae, 1980
Shigella flexneri, 1980
Shigella sonnei, 1980
Shigellosis, 1980–1982
antibiotics for, 1981*b*
clinical manifestations of, 1981
complications of, 1981*t*
definition of, 1980–1982
diagnosis of, 1981
diarrhea caused by, 1981*t*
epidemiology of, 1980
incidence of, 1980
pathobiology of, 1980–1981
pathogen that causes, 1980
prevention of, 1982
prognosis of, 1982
treatment of, 1981*b*, 1982*f*
Shock, 658–665, 2518
blood and blood products for, 662*b*
body positioning for, 662*b*
cardiogenic, 659, 665
causes of, 666*t*
clinical manifestations of, 666, 666*f*, 667*t*
definition of, 665, 665*t*
diagnosis of, 665*t*, 666
epidemiology of, 665, 666*f*
inotropes for, 667*b*
management of, 384*b*
pathobiology of, 666
prognosis for, 669
cardiovascular pathophysiology of, 658–659
cellular pathobiology of, 659–660
clinical manifestations of, 660–661
cryptic, 661
definition of, 658–665, 659*f*
diagnosis of, 660*t*, 661–665
differential diagnosis of, 661
distributive, 659
early manifestations of, 660
emergency procedures for, 662*b*
epidemiology of, 658
genetic susceptibility of, 660
hemorrhagic, 663*t*
hypovolemic, 658
intravenous access for, 662*b*
intravenous fluids for, 662*b*
obstructive, 659
Shock *(Continued)*
organ pathobiology of, 659
overt, 660, 660*t*
pathobiology of, 658–660
physical examinations and laboratory signs in, 660*t*
prevention of, 665
prognosis of, 665
progression of treated or partially treated, 661
respiratory support for, 662*b*
resuscitation for, 662*b*
septic, 669
supportive care for, 662*b*
treatment of, 662*b*, 662*f*
type of, 661–665, 661*t*
untreated, 661
vasoactive agents for, 662*b*
vasopressors for, 662*b*, 664*t*
Short-acting β-adrenergic agents (SABA), for asthma, 541*b*, 544*t*
Short anagen syndrome, 2751
Short-bowel syndrome, 937*t*, 938, 938*b*
Short Nutritional Assessment Questionnaire (SNAQ), 1447, 1448*t*
Short Portable Mental Status Questionnaire, 2334*t*
Short-segment Barrett esophagus, 1339
Short telomere syndromes, 584, 1127.*e1t*, 1129, 1129*b*
Short unilateral headache, with conjunctival injection and tearing, 2377*t*, 2381
Shortness of breath
alveolar hemorrhage and, 568
invasive mucinous adenocarcinoma and lepidic predominant nonmucinous adenocarcinoma and, 569
management of, approaches to, 13*t*
after surgery, 2673
Shoulder
disorders of, 1742–1744
surgical treatment of, 1828
Shwachman-Diamond syndrome, 1145, 1253, 1683, 1683.*e1t*
SIADH. *See* Syndrome of inappropriate antidiuretic hormone secretion
Sialadenosis, 2626
Sialolithiasis, 2625
Sialorrhea
psychotropic medications and, 2678*t*
severe mental illness and, 2681*t*
Sialosis, 2626
Siberian tick typhus, 2055*t*, 2057
Sicca syndrome, 1786*b*
Sick building syndrome, 87
Sick sinus syndrome, 319
Sickle cell(s)
conditions associated with, 1072*t*
peripheral blood smear of, 1068*f*
Sickle cell anemia, 1113
genetics of, 1112*t*
laboratory features of, 1112*t*
Sickle cell carrier, 1111–1112
Sickle cell disease, 1109–1116
acute chest syndrome in, 1113
acute hemorrhagic stroke associated with, 1113
acute ischemic stroke associated with, 1113
acute kidney injury in, 1114
anemia associated with, 1113
asthma in, 1113
blood tests for, 1114
blood transfusion for, 1114*b*
cardiorespiratory complications of, 1113–1114
carriers of, 1111
chronic sickle lung disease in, 1113
clinical manifestations of, 1111–1114
complications of, 1112*t*
crizanlizumab for, 1116*t*
dactylitis associated with, 1112
definition of, 1109
diagnosis of, 1111*f*, 1114
epidemiology of, 1109–1110
gene therapy for, 1114*b*
genetics of, 1112*t*
glomerular filtration rate in, 1114
hematopoietic stem cell transplantation for, 1114*b*
high-pressure liquid chromatography of, 1111*f*, 1114

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Sickle cell disease *(Continued)*
hydroxyurea for, 1114*b*
infection, 1114
infection prophylaxis in, 1114*b*
laboratory features of, 1112*t*
multiorgan disease associated with, 1112–1113
Mycoplasma pneumoniae in, 2007
pain associated with, 1113
pathobiology of, 1110–1111
pathophysiology of, 1110*f*
in pregnancy, 1114
prevalence of, 1110
prevention of, 1114*b*
priapism in, 1114, 1114*b*
primary stroke prevention in, 1112
prognosis for, 1116
pulmonary hypertension in, 1113
red flags for, 1114*t*
renal complications of, 1114
screening of, 1114
silent cerebral infarction in, 1113
sleep-disordered breathing in, 1113
stem cell therapy for, 1114*b*
stroke caused by, 2470.*e1t*, 2472
transfusion for, 1114*b*, 1206
treatment of, 1114*b*
urologic complications of, 1114
vaso-occlusive crises associated with, 1113
Sickle cell trait, 1110*f*, 1111
Sickle hemoglobin, 1110
Sideroblastic anemia, 1072*t*, 1084, 1086
acquired, 1086
clinical manifestations of, 1086
diagnosis of, 1086, 1086*f*
prognosis of, 1086*b*
treatment of, 1086*b*
Signal aliasing, 236
Signal transduction, 1474
Signaling inhibitors, 149, 153
clinical applications of, 150*f*
Janus kinases, 153, 153*t*
Signaling pathways, genetic defects of, 1680, 1681*t*
Signet ring abnormality, 560.*e2f*
Sildenafil, 364*b*, 824*t*
for erectile dysfunction, 1589
for idiopathic pulmonary fibrosis, 576*b*
Silent cerebral infarction, in sickle cell disease, 1113
Silent gallstones, 1052*b*
Silent myocardial ischemia, 358, 369
Silica, 88*t*
Silicosis, 590, 590*t*, 591*f*
Silver, argyria and, 106, 106*b*, 106*f*
Silver deposition, 106, 106*f*
Simple cysts, 809*t*
Simple virilizers, 1572
Simvastatin, for familial hypercholesterolemia, 1409*t*
Sin Nombre virus, 2265*t*
Sindbis virus, 2275*t*, 2279, 2279*b*
Single-lung transplantation, 633
Single metastatic lesion, treatment of, 1241*b*
Single nucleotide variants, 162
Single-organ vasculitides, 1792*t*, 1799–1800
Single-photon emission computed tomography (SPECT)
for epilepsies, 2431, 2432*f*
myocardial perfusion imaging, 248, 249.*e1f*
strengths and weaknesses of, 2373*t*
Single seizures, 2431
Single stripe sign, 965.*e1f*
Single unprovoked seizures, 2434*b*, 2436
Single ventricle, 354
Sinoatrial block, 320*f*
Sinus arrhythmia, 318, 318*f*
Sinus bradycardia, 319, 319*f*, 319*t*
Sinus headache, 2382
Sinus histiocytosis with massive lymphadenopathy, 1288
Sinus node dysfunction, 317*t*, 319
treatment of, 321*b*
Sinus node inhibitors, for heart failure with reduced left ventricular ejection fraction, 265*b*
Sinus node re-entry, 323*t*, 324
Sinus of Valsalva aneurysms, 352
Sinus of Valsalva anomalies, 352–353
Sinus tachycardia, 323–324, 323*t*, 324*b*, 324*f*
Sinus thrombosis
lateral, 2529, 2529*b*, 2529*f*
septic cavernous, 2528, 2529*b*
septic sagittal, 2530, 2530*b*
venous, 2528
Sinuses, cystic fibrosis and, 556
Sinusitis. *See also* Rhinosinusitis
allergic *Aspergillus*, 2095
H. influenzae caused by, 1953
pathogens and empirical therapy for, 2526*t*
Sinusoidal obstruction syndrome, 1019
Siponimod (Mayzent), for multiple sclerosis, 2505*t*
Sirolimus (Rapamycin), e10*t*–e11*t*, 149
for liver transplantation, 1048*t*
for lymphangioleiomyomatosis, 583*b*
in renal transplantation, 845*t*
Sirtuins, aging and, 115
Sister Mary Joseph node, 1341
Sitagliptin, for type 2 diabetes mellitus, 1541*t*
Site-specific therapy, directed by molecular tumor profiling, 1241*b*
Sitosterolemia, 1410
Six Sigma, 45
6-minute walk test, 532
Sixth nerve palsy, 2618
Sjögren syndrome, 1783–1787, 2327*t*, 2564*t*
anti-La/SSB antibodies in, 1784
anti-Ro/SSA antibodies in, 1784
clinical manifestations of, 1707, 1707*t*, 1784–1785
cystic fibrosis *versus*, 558
definition of, 1783–1787
diagnosis of, 1785, 2626
differential diagnosis of, 1785
epidemiology of, 1783
extraglandular disease and, 1785, 1786*b*
genetics of, 1783
glandular (sicca) features of, 1784
glandular manifestations of, 1786*t*
immune mechanisms of, 1784
interstitial lung disease associated with, 581
labial salivary glands in, histopathology of, 1784.*e2f*
laboratory testing for, 1785
lymphoma and, 1785
pathobiology of, 1783–1784
prognosis for, 1787
rheumatology classification for, 1785*t*
sensory neuropathy of, 2573
treatment of, 1786*b*
Skeletal metastases, treatment of, 1241*b*
Skeletal muscle
composition of, 2580
growth hormone effects on, 1488
Skier's thumb. *See* Gamekeeper's thumb
Skin
allergic disease of, 1674
atrophy of, 2687.*e4t*
Candida infection of, 2090
color of, 2687
complicated, bacterial species that cause, 1892*t*
configuration of, 2687, 2691*t*
diagnostic tests of, 2688*t*, 2690, 2692*t*
examination of, 31, 2686–2687, 2686.*e3f*–2686.*e4f*, 2687*f*
Fitzpatrick types, 2686.*e1f*
function of, 2686
fungal infections of, 2736
granulomatous diseases of, 2734, 2735*f*
history, 2687, 2694*t*
inflammatory diseases of, 2734, 2734*f*
inflammatory lesion and nodules of, 2734–2735, 2735*f*
life-threatening emergencies of, 2687–2690
morphology of, 2687, 2689*t*
observational checklist, 2686*t*
onchocerciasis manifestations of, 2178
pruritus of, 2690, 2694*t*
secondary changes of, 2687
structure of, 2686
systemic lupus erythematosus manifestations of, 1769
systemic sclerosis involvement of, 1777, 1781*b*
toxicants and, 685
ulcers, 2738
Skin and soft tissue infections
Acinetobacter causing, 1973
anaerobic bacteria causing, 1939
enterococcus causing, 1921, 1921*b*
Pseudomonas infections causing, 1969, 1970*b*
Staphylococcus aureus causing, 1903
Skin biopsy, for peripheral neuropathy, 2567, 2569*f*, 2570*f*
Skin cancer
basal cell, 1395, 1395*f*, 1396*b*
screening for, 1394
squamous cell, 1395, 1395*f*, 1396*b*
Skin cancers, treatment for, 2701
cosmetics, 2701
dermatologic surgery, 2701
phototherapy and laser, 2701
sunscreen, 2701
Skin diseases
approach to, 2686–2697, 2696*t*
associated with immediate photosensitivity, 1432–1433
atrophy of, 2687.*e4t*
color of, 2687
configuration of, 2687, 2691*t*
diagnostic tests of, 2688*t*, 2690, 2692*t*
esophageal diseases and, 911
examination of, 2686, 2686.*e1f*, 2687*f*
Fitzpatrick types, 2686.*e1f*
function of, 2686
history, 2687, 2694*t*
life-threatening emergencies of, 2687
morphology of, 2687, 2689*t*
observational checklist, 2686*t*
porphyrias *versus*, 1434
protection against, in travelers, 1889
pruritus of, 2690, 2694*t*
in sarcoidosis, 601, 602*f*, 604*t*
secondary changes of, 2687
structure of, 2686
therapy for, 2697–2701
anti-inflammatory agents, 2697
antibacterials, 2699
antifungals, 2699
antihistamines, 2700*t*
antimalarial and antiparasitic drugs, 2698
antimicrobial agents, 2699
antiparasitics, 2699
antipruritic or anesthetic agents, 2699
antivirals, 2699
brimonidine and oxymetazoline hydrochloride, 2698
calcipotriol, 2698
colchicine, 2699
dapsone, 2699
glucocorticoids, 2697, 2698*t*
hormonal therapies, 2700
immune therapies, 2700
immunomodulatory therapies, 2700
immunosuppressive agents, 2700
keratolytics, 2700
moisturizers, 2700
nonsteroidal anti-inflammatory agents, 2698
psoriasis therapies, 2698
retinoids, 2698
soaks and dressings, 2697
thalidomide and lenalidomide, 2699
topical, 2697
topical analgesics, 2699
treatment of, 1434*b*
Skin infections, 2738, 2739*t*
bacterial, 2739
cellulitis as, 2739, 2740*f*
ectoparasites in, 2741, 2742*f*
folliculitis as, 2739
fungal, 2741
furuncles as, 2739, 2740*f*
impetigo as, 2739, 2739*f*
mycobacteria infections as, 2741
Neisseria infections as, 2741, 2741*f*
parasites in, 2742
Pseudomonas infections as, 2741
spirochetes as, 2741
toxic erythemas as, 2740
viral, 2741
Skin lesions, 2686*t*
of bacillary angiomatosis, 2002, 2002*f*
SENLAT with, diagnosis of, laboratory methods for, 2003*t*
Skin malignancies, in HIV, 2321
Skin manifestations
occupational, 86*t*
occupational and environmental, 87
Skin necrosis, warfarin-induced, 478*b*, 478*f*
Skin pigmentation, hemochromatosis and, 1440
Skin rash, drug allergy and, 1695
Skin tags, 2602
Skin testing, for latent TB infection, 2038
Skull fracture, 2513
"Slapped cheek" rash, 2234, 2234*f*
SLC3A1, 815
SLCO1B1 gene, 160*t*
SLE. *See* Systemic lupus erythematosus
Sleep
age-related changes in, 122
definition of, 2443
diary, 2445*f*
graph of, 2444.*e1f*
hypnogram of, 2443
NREM, 2448.*e1f*, 2452
pathobiology of, 2443–2444
REM, 2443, 2443.*e3f*, 2444*t*
stage N1, 2444*t*
stage N2, 2443, 2444*t*
stage N3, 2444*t*
Sleep apnea, 2446–2449
central, 2448, 2448.*e1f*
in heart failure, 265*b*
obesity and, 1466
Sleep-disordered breathing, 257
in sickle cell disease, 1113
Sleep disorders, 2443–2454
clinical manifestations of, 2444
definition of, 2443–2444
diagnosis of, 2444
with heart failure, 257
pathobiology of, 2443
Sleep disturbances, menopause and, 1630, 1630*b*
Sleep hypoventilation syndromes, 534*t*
Sleep-related breathing disorders
circadian rhythm disorders. *See* Circadian rhythm disorders
description of, 2446–2453
parasomnia, 2452, 2453*b*
Sleep-related eating, 2453*t*
Sleep-related hypoventilation, 2448
Sleep spindles, 2443
Sleep terrors, 2453*t*
Sleep transition apneas, 534*t*
Sleeping sickness. *See* African trypanosomiasis
Sleepwalking, 2453*t*
Slit lamp biomicroscope, 2597
Slow-transit constipation, 890
Sly syndrome, 1724*t*
SM1 gene, 2164
SMA. *See* Spinal muscular atrophies
Small bowel
adenocarcinomas, 1343
biopsy, for malabsorption, 931*t*
functions of, 888
motility of, 887, 887.*e1f*
neuroendocrine neoplasms of, 1566, 1566*b*
slow-transit disorders involving pathobiology of, 888
Small bowel carcinoids, 1344
Small bowel obstruction
abdominal pain and, 854*t*
abdominal radiographs of, 866*f*
computed tomography of, 870*f*
Small cell lung cancer (SCLC), 1329
treatment for, 1333*b*, 1335*t*
Small congenital nevi, 2730, 2733*f*
Small fiber neuropathies, 2554
Small interfering RNA (siRNA), 176, 177*f*
Small intestinal immunoproliferative disease, 1286
Small intestinal ulcers, 955–956, 956*f*, 956*t*
Small intestine, neoplasms of, 1343
adjuvant therapy for, 1345*b*
clinical manifestations of, 1344
diagnosis of, 1344–1345
epidemiology of, 1343–1345
metastatic disease of, 1345*b*
pathobiology of, 1343–1344, 1344*f*
predisposing conditions of, 1344
prevention of, 1345
prognosis of, 1345
staging of, 1345
surgery for, 1345*b*
treatment for, 1345*b*
Small lymphocytic lymphoma, 1268, 1283, 1283*b*
Small molecule targeted therapies, 153
Small opacities, pulmonary, 521–523, 521*t*
Small pupil, 2600
Small vessel vasculitis, 784*t*, 965, 1753, 1754*f*, 1792*t*, 1793
Smallpox, 97–98, 98*f*, 2236
clinical manifestations of, 97, 2237–2238
diagnosis of, 97, 2239
epidemiology of, 97, 2236
flat, 2237, 2237*t*
hemorrhagic, 2237, 2237*t*
immunization for, 66*t*, 84
modified, 2237, 2237*t*

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Smallpox *(Continued)*
ordinary confluent, 2237, 2237*t*
ordinary discrete, 2237, 2237*t*
ordinary semiconfluent, 2237, 2237*t*
Orthopoxvirus variola causing, 2236
pathobiology of, 97, 2237
prevention of, 97–98
prognosis for, 98
pustular lesions of, 2238*f*
treatment of, 97*b*
types of, 2237*t*
SMCHD1 gene, 2584
Smell, 2639–2640, 2640*b*, 2640*t*
Smith-Lemli-Opitz syndrome, 1573
SMN. *See* Survival motor neuron
Smoke inhalation, 595
Smoking
cessation of, 384*b*
heart failure in, 265*b*
history of, obtaining, 2679
rates of, 18, 18*f*
rheumatoid arthritis and, 1750
vitamin levels affected by, 1459
in women, 1609
Smoking-related interstitial pneumonias, 571*t*, 577
Smoldering adult T-cell leukemia/lymphoma, 2326, 2326*b*
Smoldering multiple myeloma
monoclonal gammopathy of undetermined significance *versus*, 1295
treatment of, 1299*b*, 1300*f*
Smooth muscle, airway, 541*b*
Smooth pursuit, 2618, 2618.e1*t*
SMV thrombosis. *See* Superior mesenteric vein thrombosis
Snake handlers, 710
Snakebites
in Africa, 709
in Asia, 709
in Australia, 709
in Central America, 708
coral snake, 708, 708*b*
envenomation syndromes of, 707–708
clinical manifestations of, 707–708, 707.e1*t*
coagulopathy associated with, 707
Colubridae, 707.e1*t*
Crotalinae, 707.e1*t*
Elapidae, 707.e1*t*
hematologic effects of, 708
Hydrophiinae, 707.e1*t*
Lamprophiidae, 707.e1*t*
local tissue injury associated with, 707
myotoxicity associated with, 707
Natricidae, 707.e1*t*
treatment of, 708*b*
Viperinae, 707.e1*t*
epidemiology of, 704
in Europe, 709
exotic, 710
immunization for, 65*t*
in Mexico, 708
neurotoxic paralysis caused by, 707, 709.e1*t*
in New Guinea, 709
in North America, 708
signs of, 706*f*
in South America, 708
treatment of, in particular regions, 708, 708*b*
venomous, 708.e1*f*
SNAQ. *See* Short Nutritional Assessment Questionnaire
Snellen eye chart, 117
"Sniff test", 619
SNRIs. *See* Serotonin and norepinephrine reuptake inhibitors
Soaks, for skin diseases, 2697
Social anxiety disorder, 2342*t*, 2343
Social determinants of health
activities of health delivery systems to address social needs and, 48*f*
interventions focused on, 47
relative contribution of clinical care, individual behaviors, 48*f*
Social environments, geriatric assessment of, 118
Social history, 28, 85
Social justice, 4
Social learning theory, intimate partner violence and, 1633
Social phobia, 2342*t*
Social support, geriatric assessment of, 118
Societal implications, 3
Socioeconomic disparities
in health outcomes, 18
magnitude of, 19
Socioeconomic factors, 21
Sodium, e1*t*–e8*t*
dietary guidelines for, 57.e3*t*
reabsorption of, 746
regulation of, 730, 730.e1*f*
Sodium bicarbonate
for acute poisoning, 693*t*
for hyperkalemia, 751*b*
for lactic acidosis, 758*b*
for postresuscitation care, 313*b*
for pulseless electrical activity, 316*f*
Sodium channelopathies, 2585
Sodium channels, 300, 300.e1*f*
Sodium concentration
abnormal, postoperative, 2675
of body fluids, 737
Sodium disorders, 733–744
epidemiology of, 733, 733*t*
pathobiology of, 733
Sodium-glucose cotransporter-2 (SGLT2) inhibitors
anesthesia and, 2669
for chronic kidney disease, 839*b*
clinical benefits of, 265*b*
mechanism of action, 265*b*
practical use of, 265*b*, 271*t*
for type 2 diabetes mellitus, 1540*b*, 1541*t*
Sodium-iodide symporter, 1504, 1504.e3*f*
Sodium nitrite, 596*b*
Sodium oxybate, 2446*b*, 2449*t*
for narcolepsy, 2449*t*
Sodium phenylbutyrate, for amyotrophic lateral sclerosis, 2563*b*
Sodium phosphate, diarrhea and, 939
Sodium-potassium adenosine triphosphatase, 300.e1*f*
Sodium thiosulfate, 596*b*, 693*t*
Sodium-potassium-2 chloride cotransporter (NKCC2), 746
Sofosbuvir, for hepatitis C, 1008*b*, 2181*t*, 2182*t*, 2185
Sofosbuvir/velpatasvir, for hepatitis C infections, 2181*t*, 2182*t*, 2184
Sofosbuvir/velpatasvir/voxilaprevir, for hepatitis C infections, 2181*t*, 2184
Soft tissue diseases, 1742
Soft tissue sarcomas, 1389, 1389*b*
SOJIA. *See* Systemic-onset juvenile idiopathic arthritis
Sokolow-Lyon criterion, 233
Solar purpura, 2690*f*, 2714, 2715*f*
Solar urticaria, 2725
Solid organ transplant recipients, in immunocompromised host, 1852, 1853*t*
Solid tumors, hematopoietic cell transplantation for, 1209
Solifenacin, 824*t*
Solitary plasmacytoma, 1302–1303
Solitary pulmonary nodule
description of, 1330, 1331*f*
surgery for, 631
Solriamfetol, 2449*t*
Soluble C5b-9, 200
Soluble fiber, for irritable bowel syndrome, 895*b*
Soluble guanylate cyclase stimulator, for heart failure with reduced left ventricular ejection fraction, 265*b*
Soluble mediators, 196
Soluble transferrin receptor, 1084
Solute diuresis, 743*t*
Solutions, 2697
Somatic DNA alterations, in cancer, 1248, 1248*f*, 1249*f*
Somatic mutations
in autoinflammatory disease, 1737
in melanoma, 1390
in pancreatic neuroendocrine neoplasms, 1562
resulting in acquired porphyria, 1430
Somatic pain, 134, 135*t*
Somatic sequencing, of tumor DNA, 167
Somatic symptom and related disorders, 2337*t*, 2346, 2347*b*, 2347*t*
Somatoform disorders. *See* Somatic symptom and related disorders
Somatosensory evoked potentials, 2376
Somatostatin, 1477
Somatostatin analogs
for acromegaly, 1489*b*
for glucagonomas, 1564*b*
for metastatic neuroendocrine tumor, 1568*b*
Somatostatinomas, 1561*t*, 1565, 1565*b*
Somatotrophs, 1487
Somatotropin release-inhibiting factor. *See* Somatostatin
Sonidegib (Odomzo), 1215*t*
Sorafenib (Nexavar), 1215*t*
Sorbitol, diarrhea and, 939
Sore throat, common conditions arising as, clinical differentiation of, 2649*t*
Sotalol, 325*t*
Sotatercept, for pulmonary hypertension, 496*b*
Sotorasib (Lumakras), 133, 1215*t*, 1251*t*
Sotrovimab, for coronavirus infections, 2191
South Africa, HIV/AIDS in, 2288, 2288.e1*f*
South American blastomycosis, 2086
South American hemorrhagic fever, 2268*t*
Southern tick-associated rash illness (STAR), 2025
Sowda, 2178
Space sickness, 2644
Spastic gait, 2373*t*
Spastic paraplegias, 2498*b*, 2498*t*
Spasticity, in multiple sclerosis, 2504*b*
Special populations, consultations for, 2656
Specialized acute care unit, 16
Specific gravity, e1*t*–e8*t*, 721
Specificity, 38
Specificity spillover, 1474–1475
Speckle tracking strain imaging, 236, 236.e1*f*
SPECT. *See* Single-photon emission computed tomography
Spectinomycin, dosage of, 1895*t*
Spectrin, 1094
Speech discrimination test, 2641
Speech reception threshold, 2641
Spermatogenesis, 1496, 1581
Spermicides, 1611
SPF. *See* Sun protection factor
Spherocytes
conditions associated with, 1072*t*
peripheral blood smear of, 1067*f*
Spherocytosis, hereditary, 1067*f*, 1094
clinical manifestations of, 1095
definition of, 1094, 1094*f*
diagnosis of, 1094*f*, 1095, 1095*t*, 1096*f*
epidemiology of, 1094
pathobiology of, 1094
treatment of, 1096*b*
Spheroschistocytes, 1068*f*
Sphincter muscle, external, 977
Sphincter of Oddi dysfunction, 1060
Sphincter relaxants, topical, for anal fistula, 980*b*
Sphingolipidoses, 1419*t*
Sphingosine-1-phosphate receptor (S1PR1), 153
Spider bites
envenomation of, 710
epidemiology of, 704
immunization for, 65*t*
signs of, 706*f*
Spider nevi, on face and thorax, 987
Spigelian hernia, 953
Spin-lattice relaxation (T1), in MRI, 1720, 1721*f*
Spina bifida, 2545, 2545*f*, 2546*b*
Spinach, diet-related hyperoxaluria and, 806
Spinal anesthesia, 2671
Spinal cord
anatomy of, 2393*f*
astrocytoma, 1319*f*
blood supply of, 2405*f*
compression of, metastatic, 2406, 2406*b*
fiber tracts of, 2404*f*
segments of, 2392–2393
Spinal cord disorders, 2403–2406
ancillary testing for, 2404
clinical manifestations of, 2403–2404
definition of, 2403–2405
diagnosis of, 2404–2405
differential diagnosis of, 2404–2405
epidemiology of, 2403
overview of, 2403
pathobiology of, 2403
prognosis of, 2405*b*
treatment of, 2405*b*
Spinal cord injury, 2385–2392
clinical manifestations of, 2386
decubitus ulcers and, 2388*b*
diagnosis of, 2387–2388
epidemiology of, 2385
ligamentous injury *versus*, 2388
pathobiology of, 2385–2386
primary injury phase of, 2385
prognosis of, 2390
secondary injury phase of, 2386
spine imaging for, 2388
thromboembolic disease and, 2388*b*
treatment for, 2388*b*
ventilatory support for, 2388*b*
visceral function and nutrition for, 2388*b*
Spinal cord ischemia, 2406*b*
Spinal cord lesions, 2371
Spinal cord stimulation, 136*b*
Spinal dural arteriovenous fistulas, 2405
Spinal epidural abscess, 2527, 2527*f*, 2527.e1*t*, 2528*b*
Spinal fluid analysis, for herpes simplex encephalitis, 2533
Spinal fluid PCR analyses, for viral encephalitis, 2532*b*
Spinal malformations, 2545–2547
Spinal manipulation, 154
Spinal meningiomas, 1318–1319
Spinal muscular atrophies (SMA), 2564*t*, 2565, 2565*b*
Spinal nerves, 2392
Spinal poliomyelitis, 2258*b*
Spinal stenosis, 1706*t*
cervical, 2399, 2401*b*, 2401*f*
lumbar, 2399, 2399*b*
Spinal tumors
classification of, 1318–1319, 1318*t*
intramedullary, 1319, 1319*b*, 1319*f*
Spine
anatomy of, 2393*f*
injuries, 700*b*
pain, 2397*t*
surgical treatment of, 1829
Spine disorders, 2392
clinical manifestations of, 2393
diagnosis of, 2393
pathobiology of, 2392–2393
Spinobulbar muscular atrophy, 2565, 2566*b*
Spinocerebellar ataxia, 2497
Spiny venomous fish, 712
Spiramycin, for toxoplasmosis, 2112*t*, 2115, 2140*t*
Spiritual distress, management of, approaches to, 13*t*
Spirituality, in palliative care, 12
Spirochetes, 2027, 2028*f*, 2741
Spirometry, 528
Spironolactone, 265*b*, 270*t*, 451*t*
for hypervolemia, 736*b*, 737*t*
for transgender women, 1578*b*, 1579*t*
Spironolactone/HCTZ, 451*t*
Spitting cobra venom, 709*b*
Spleen, 1151
examination of, 31
in hereditary spherocytosis, 1095
platelet sequestration in, 1171
red pulp of, 1151
white pulp of, 1151
Splenectomy
for autoimmune hemolytic anemia, 1089*b*
for immune thrombocytopenic purpura, 1176*t*
laparoscopic, 1089*b*
Splenic disease, 968
in sarcoidosis, 602
Splenic marginal zone lymphoma, 1286, 1286*b*
Splenic vein thrombosis, 968
Splenomegaly, 988, 1151–1153
autoimmune disorders associated of, 1152
biopsy of, 1153, 1153*t*
clinical manifestations of, 1151
congestive, 1152
diagnosis of, 1151–1153
differential diagnosis of, 1151*t*, 1152
evaluation of, 1152, 1152*f*
Gaucher disease and, 1421
history of, 1152
imaging of, 1152–1153, 1153*f*
infectious causes of, 1152
physical examination of, 1152
primary myelofibrosis in, 1134

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Splenomegaly *(Continued)*
prognosis for, 1153
in sarcoidosis, 602
in systemic lupus erythematosus, 1770
treatment of, 1153*b*
Splinter hemorrhages, 216, 414, 2753, 2753*t*
Spondyloarthritis, 1760–1767
biologic therapies for, 1765*b*
clinical manifestations of, 1760
corticosteroids for, 1765*b*
definition of, 1760–1761, 1760*f*
diagnosis of, 1760–1761, 1761*t*
epidemiology of, 1760
genetic susceptibility of, 1760
nonsteroidal anti-inflammatory drugs for, 1765*b*
pathobiology of, 1760
sulfasalazine for, 1765*b*
treatment of, 1765*b*, 1766*f*
Spondyloarthropathies, 1708
ankylosing spondylitis. *See* Ankylosing spondylitis
enteropathic arthritis. *See* Enteropathic arthritis
psoriatic arthritis. *See* Psoriatic arthritis
undifferentiated, 1710
Spondylosis
cervical, 2399
description of, 2395, 2402
Spontaneous bacterial peritonitis
cirrhosis and, 1036, 1038
diagnosis of, 1040
treatment of, 1040*b*
Spontaneous nystagmus, 2619
Spontaneous subarachnoid hemorrhage, 2474–2478
clinical manifestations of, 2475
diagnosis of, 2475–2476, 2476*f*
epidemiology of, 2474–2478
Hunt-Hess grading scale for, 2477*t*
laboratory testing for, 2475–2476
prevention of, 2478
prognosis for, 2478
"thunderclap" headache associated with, 2475
Spontaneous tension hydropneumothorax, 526*f*
Spontaneous urticaria, chronic, 1687, 1690*t*
Spoon nails, 2751, 2752*f*
Sporadic colorectal cancer, 1346
Sporadic inclusion body myositis, 2327*t*
Sporadic painless thyroiditis, 1513, 1513*b*, 1513*f*
Sporothrix spp., 2085
Sporotrichoid disease, 2073
Sporotrichosis, 2085, 2086*f*
Sports medicine injuries, 1742, 1744*t*
Spotted fever rickettsiosis, 2065*t*
characteristics of, 2270*t*
in travelers, 1889.*e1t*, 1891*t*
Spray, 2697
S protein, 2210
Sprycel. *See* Dasatinib
Spurling maneuver, 2396
Squamocolumnar junction, 1375
Squamous cell carcinoma (SCC), 2621*t*
of anus, 982
diagnosis of, 1241*t*
esophageal, 1337
of eyelids, 2602
lung, 1329, 1329.*e2t*
oral, 2622, 2622*f*
skin, 1395, 1395*f*, 1396*b*
treatment of, 1241*b*
Squamous intraepithelial lesion, 982
Src homology (SH)2 domains, 1065
SRH. *See* Stigmata of recent hemorrhage
SRIs. *See* Serotonin re-uptake inhibitors
SSKI. *See* Saturated solution of potassium iodide
SSRIs. *See* Selective serotonin reuptake inhibitors
St. John's wort, 155
St. Jude valve, 250.*e1f*
St. Louis encephalitis, 2276*t*, 2282, 2283*b*, 2520
ST segment, 228, 228*f*, 233
ST_2, 260, 260.*e1t*
Stable de-repression, 1894
Stable ischemic heart disease, antihypertensive drug for, 454*t*
Staging hypertension, 447, 447*t*
Standard (tube) agglutination test (SAT), for brucellosis, 1984
Standard exposure history, in occupational and environmental medicine history, 85, 85.*e1f*
Standards, medical profession, 4
Staphylococcal bullous impetigo, 2687.*e4t*
Staphylococcal food poisoning, 1906, 1906*b*
Staphylococcal infections, 1902–1910
Staphylococcal meningitis, 2515*b*
Staphylococcal scalded skin syndrome, 2720, 2720*b*, 2720*f*
Staphylococcal septicemia, disseminated intravascular coagulation from, 1196*f*
Staphylococcal toxic shock syndrome, 1906
Staphylococcemia, characteristics of, 2270*t*
Staphylococcus aureus, 416
antimicrobial resistance of, 1864*t*
bacteremia caused by, 1903
biofilm formation in, 1903
blepharitis caused by, 2601–2602
cellulitis caused by, 1903
clinical manifestations of, 1903–1905
CNS infections, 1905
cystic fibrosis and, 557
decolonization procedures for, 1908–1909
definition of, 1902–1909
diagnosis of, 1905
endocarditis, 783
epidemiology of, 1902
in exit site and tunnel infections, 843
genitourinary infections caused by, 1904, 1905
host defenses against, 1903
infections caused by, 1903
mechanisms of disease of, 1903
methicillin-resistant, 1902, 1902.*e3t*
orthopedic device-related infections, 1904–1905, 1905
osteomyelitis caused by, 1904, 1905
pathobiology of, 1902–1903
pericarditis caused by, 1904
pneumonia caused by, 606, 1905
prevention of, 1908–1909
prognosis of, 1909
prosthetic valve endocarditis caused by, 1903
pulmonary infections caused by, 1904
scalded skin syndrome, 1908, 1908*f*
septic arthritis caused by, 1904, 1905
septic bursitis caused by, 1804
skin and soft tissue infections caused by, 1903
spinal epidural abscess and, 2527
susceptibility testing for, 1905
toxin-mediated syndromes caused by, 1903
treatment of, 1905*b*–1906*b*, 1907*t*
virulence factors of, 1902–1903, 1902.*e3t*
Staphylococcus epidermidis, 1909
Staphylococcus lugdunensis, 1909
Staphylococcus saprophyticus, 1874
Starch blockers, for type 2 diabetes mellitus, 1541*t*
Stasis dermatitis, regional involvement of, 2745*f*
STAT proteins, 1065
Statin-induced rhabdomyolysis, 714
Statins, 1411
for acute coronary syndrome, 375*t*
hepatotoxicity, 1018
for hypertriglyceridemia, 1414*b*
indication for, 1411, 1411*f*
monitoring of, 1411.*e1f*, 1413
for nonalcoholic fatty liver disease, 1034*b*
rhabdomyolysis caused by, 715
risk estimation for, 1411, 1412*t*
safety of, 1412
Statistical interpretation of data, 35–39
causality in, 37
confounding in, 37
data characteristics in, 36
hypothesis testing in, 36, 36*t*
incidence in, 35
interpreting data in, 35
machine learning in, 37
noninferiority trials in, 37
prevalence in, 35
statistical approaches and challenges in, 37
study design in, 36–37
theories and principles for decision making, 38–39, 38*f*–39*f*, 39*f*
time to event data in, 37
using data for clinical decision making, 37–39, 38*t*
Status asthmaticus, 541*b*
Status epilepticus
alcohol-related, 2543, 2543*b*
nonconvulsive, ECG findings in, 2429, 2429*f*
treatment of, 2434*b*
Steatohepatitis
alcoholic, 1031
nonalcoholic, 1031, 1466
Steatorrhea
infants with, 558
signs and symptoms of, approach to, 852*t*
Stelara. *See* Ustekinumab
Stem cell(s), 170–172, 170*f*, 1206
adult (postnatal), 170–172, 170*f*
delivery of, 172
embryonic, 171, 171*f*, 172*f*
pluripotent
ex vivo differentiation of, 173
induced, 171, 171*f*
for sickle cell disease, 1114*b*
tissue-specific, 172
Stem cell transplantation
hematopoietic. *See* Hematopoietic stem cell transplantation
for inborn errors of metabolism, 1401*b*
for myelodysplastic syndromes, 1255
for neutropenia, 1147*b*
Stenotrophomonas maltophilia, 1969, 1975–1976
clinical manifestations and diagnosis of, 1975
definition of, 1975
epidemiology of, 1975
pathobiology of, 1975
prevention of, 1976
prognosis of, 1976
resistance in, mechanisms of, 1976*t*
risk factors for, 1975*t*
treatment of, 1975*b*
Stents/stenting
for atherosclerotic renal artery stenosis, 800*t*
choices related to, 396–397
Steppage gait, 2373*t*
Stepped wedge design, 37
Stereotactic body radiation therapy, for NSCLC, 1333*b*
Sterilization, 1617
Steroid acute regulatory protein, 1581, 1581.*e1f*
Steroid-dependent sarcoidosis, 603*b*
Steroid hormone receptor, 1475*f*
Steroid-induced myopathies, 2587
Steroid purpura, 2714
Steroidal contraception, 1613
Steroidogenesis
adrenal, 1569, 1569.*e1f*
defects of, 1569–1573, 1573
gonadal, 1569, 1569.*e1f*
hypothalamic-pituitary-ovarian axis in, 1596*f*
Steroids
for acute pericarditis, 424*b*
anabolic-androgenic, 2365
ranking of, 2698*t*
in renal transplantation, 845*t*
Stevens-Johnson syndrome, 1847, 2303, 2727
Mycoplasma pneumoniae in, 2007, 2007*f*
prognosis of, 2728
psychotropic medications and, 2678*t*
treatment of, 2728*b*
Stibogluconate sodium, 2112*t*, 2116
Stiff-person syndrome, 1238*t*
Stiffness, in rheumatic diseases, 1710
Stigmata of recent hemorrhage (SRH), endoscopic, for peptic ulcer bleeds, 883*t*
Still disease, adult-onset, 1731*t*, 1732
Stimulants, for narcolepsy, 2449*t*
Stimuli, of intestinal secretion, 924*t*
STING-associated autoinflammatory syndromes, 1736
STING-associated vasculopathy with onset in infancy (SAVI), 1731*t*
Stingrays, venomous, 712
Stings, 704
sea anemone stings, 713
spiny venomous fish, 712
venomous stingrays, 712
STIs. *See* Sexually transmitted infections
Stivarga. *See* Regorafenib
STK11/LKB1 gene, lung cancer and, 1330
Stomach
alcohol use disorders and, 2355*t*
slow-transit disorders involving
gastroparesis. *See* Gastroparesis
intestinal pseudo-obstruction. *See* Intestinal pseudo-obstruction
pathobiology of, 888
systemic sclerosis involvement of, 1778
Stomach neoplasms, 1339
adenocarcinoma, 1339
adenomas, 1343
benign tumors, 1343
definition of, 1339
Stomach neoplasms *(Continued)*
leiomyomas, 1343
lymphoma, 1342
malignant tumors, 1342–1343
Stomach neuroendocrine tumors, 1566
Stomatocyte
conditions associated with, 1072*t*
peripheral blood smear of, 1069*f*
Stomatocytosis, 1069*f*
hereditary, 1094*f*, 1097
Stool cultures, for enteric infection, 1870*t*
Stool DNA testing, 1353
Stool examination
in elusive diarrhea, 931, 931*t*
for gastrointestinal disease, 854
for infection, 1836
Storage diseases, 1150
Strabismus, 2598, 2618–2619, 2619*f*
Strangulated hernia, abdominal pain and, 854*t*
"Strawberry cervix", 1882
Strawberry hemangioma, 2731
Strengthening, for osteoarthritis, 1741*t*
Streptococcal infections, 2648, 2649*t*
glomerulonephritis after, 783, 783*b*, 783*f*
Streptococcal pharyngitis, characteristics of, 2270*t*
Streptococcal toxic shock syndrome, 1914–1916, 1915, 1915*t*
Streptococcus
classification of, 1913
group A, 1913
severe, 1915–1916
group B, 1918
group C, 1919*b*
group G, 1919*b*
identification of, 1913
nutritionally variant, 417*t*
viridans group, 415–416, 1919
zoonotic, 1919
Streptococcus agalactiae, 1918, 1918*b*
Streptococcus anginosus, 1919, 1919*b*
Streptococcus canis, 1919
Streptococcus dysgalactiae subspecies *equisimilis*, 1919, 1919*b*
Streptococcus gallolyticus, 1919
Streptococcus iniae, 1919
Streptococcus milleri, 1919
Streptococcus pneumoniae, 1910–1912, 1953
antibiotics for, 1912*b*
blood cultures of, 1911
clinical manifestations of, 1911
community-acquired pneumonia caused by, 1910
definition of, 1910–1912
diagnosis of, 1911
drug-resistant, 1912*b*
epidemiology of, 1910
Gram stain of, 1910*f*
immunochromatography of, 1911
pathobiology of, 1910–1911
pathogen, 1910
prognosis of, 1912
prophylaxis for, 2309*t*
rhabdomyolysis caused by, 715
sputum Gram stain for, 1911
transmission of, 1910–1911
treatment of, 1912*b*, 2516*t*
Streptococcus pyogenes, 1913
acute infections, 1913
acute rheumatic fever caused by, 1917, 1917*b*, 1917*t*
bacteremia caused by, 1915
cell wall of, 1913
cellulitis caused by, 1915
clinical manifestations of, 1914
definition of, 1913
deoxyribonucleases, 1913
diagnosis of, 1914
ecthyma caused by, 1914
epidemiology of, 1913
erysipelas caused by, 1915
fibronectin binding protein, 1913
fimbriae, 1913
hyaluronic acid capsule, 1913
hyaluronidase, 1913
impetigo caused by, 1914
lipoteichoic acid, 1913
M proteins, 1913
myonecrosis caused by, 1915
necrotizing fasciitis caused by, 1915
nicotine adenine dinucleotidase, 1913

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Streptococcus pyogenes (Continued)
pathobiology of, 1913
pharyngitis caused by, 1914, 1914*f*, 1914*t*
pneumonia caused by, 1916
post-streptococcal glomerulonephritis caused by, 1918
prevention of, 1917
prognosis for, 1916*b*
puerperal sepsis caused by, 1915
pyrogenic exotoxins, 1914, 1914*f*
rheumatic heart disease caused by, 1917
scarlet fever caused by, 1914
streptolysin O, 1913
streptolysin S, 1913
treatment of, 1916*b*
Streptococcus suis, 1919, 2515*b*
Streptococcus viridans endocarditis, 783
Streptokinase (SK), 386*t*
Streptolysin O, 1913
Streptolysin S, 1913
Streptomycin
for nontuberculous mycobacterial disease, 2046*t*
for plague, 98*b*, 1991*b*, 1992*t*
for tularemia, 1987*b*
for verruga peruana, 2003*b*
Stress
dysregulation of responses, 120, 120.*e1f*
hypogonadotropic hypogonadism and, 1584
neutrophilia and, 1141
responses to stressors, 226, 226.*e1f*
Stress cardiac magnetic resonance imaging, 362
Stress echocardiography, 238, 241*f*, 362
Stress fracture, 1748–1749, 1749*b*
Stress incontinence, 827–828
clinical manifestations of, 829
in men, 830
treatment of, 829*b*, 830*t*
in women, 1609
Stress-induced (takotsubo) cardiomyopathy, 665
Stress syndromes, 1747, 1747*b*
Stress testing
for chronic stable angina, 359–360, 361*f*
for signs of cardiovascular disease, 218
Stress ulcers, 916
Stressful life events, irritable bowel syndrome and, 893
Stridor, 512, 512*t*
Stroke
acute ischemic
fibrinolytic therapy for, 509
radiographic changes of, 2373, 2373.*e1f*
in sickle cell disease, 1113
as arterial thrombotic complications, 481
as asymptomatic carotid stenosis, 2473
atrial fibrillation causing, 2464
brain imaging of, 2467–2468, 2468*f*
carotid duplex ultrasonography of, 2468
catheter angiography of, 2469
cerebral venous thrombosis causing, 2471
cervical artery dissection causing, 2470.*e1t*
coagulation disorders causing, 2470.*e1t*
computed tomography of, 2464
cryptogenic, 2472, 2472*f*
devices for, 2473
differential diagnosis of, 2469
disabling deficits, 2473.*e1t*
endovascular therapy for, 2469*b*
epidemiology of, 2454
Fabry disease causing, 2470.*e1t*
fat embolism causing, 2472
history of, 2466
in HIV/AIDS, 2313
hyperviscosity causing, 2470.*e1t*
incidence of, 284
ischemic
arterial hypertension in, 2471*f*
cerebral embolization causing, 2530
clinical manifestations of, 2465
definition of, 2464
differential diagnosis of, 2469
endovascular therapy for, 2469*b*
epidemiology of, 2464
initial laboratory tests for, 2466, 2467*t*
prevention of, 2473
primary prevention of, 2473
risk factors for, 2464*t*
sickle cell disease causing, 2470.*e1t*, 2472
lumbar puncture of, 2468
mortality rates for, 2474
Stroke *(Continued)*
oral contraceptives and, 1614
postoperative, 2664
predicted risks for, 221.*e1f*
prevalence of, 2454
procedures for, 2473
prognosis for, 2473–2474
rare genetic causes, 2472
recovery/rehabilitation from, 2469*b*
risk for, 2454
secondary prevention after, 456, 2473
sickle cell disease causing, 1114*b*, 2470.*e1t*, 2472
after transient ischemic attack, 2473
unusual causes of, 2470–2474, 2470.*e1t*
vasculitis causing, 2470.*e1t*, 2472
Stroke volume, 238
calculation of, 238
formula of, 238
Strongyloides spp., 2172
in travelers, 1889.*e1t*, 1891*t*
Strongyloides stercoralis, 1026*t*, 2170*t*
Strongyloidiasis, 2172, 2173*b*
Strontium ranelate, for osteoporosis, 1643*b*
Structural aberrations, 164
Structural lesion, of bulbar region, 2564*t*
Structural variants, in genomics, 164
Struvite stones, 804
prevention of, 807
Stuart-Prower factor, 1189*t*
Study design, 36
Stunting, 1445
Stupor, cause of, 2437*t*
Sturge-Weber syndrome, 2550*t*, 2551–2552, 2552*b*, 2552*f*
Stuttering, 2408
Stye, 2601, 2601*f*
Subacromial bursa, 1743*f*
Subacute encephalitis, 2221
Subacute idiopathic interstitial pneumonias, 571*t*, 578
Subacute sclerosing panencephalitis, 2221
Subacute sensory neuropathy, 1238*t*, 2576, 2577*b*
Subacute thyroiditis, 1513, 1514*b*
Subarachnoid cysticerci, 2160, 2160*f*
Subarachnoid hemorrhage
angiography for, 2476
bacterial meningitis *versus*, 2515
causes of, 2476
cerebrospinal fluid findings in, 2374*t*
definition of, 2463
fusiform aneurysms causing, 2478
hydrocephalus after, 2476*b*
management of, 2477*t*
medical complications of, 2476*b*
mycotic aneurysms causing, 2478
non-aneurysmal causes of, 2475*t*
seizures after, 2476*b*
spontaneous, 2474
clinical manifestations of, 2475
diagnosis of, 2475, 2476*f*
epidemiology of, 2474
Hunt-Hess grading scale for, 2477*t*
laboratory testing for, 2475
prevention of, 2478
prognosis for, 2478
"thunderclap" headache associated with, 2475
treatment of, 2476*b*
Subclavian artery stenosis, 306
Subclinical disease, in older adults, 114
Subclinical hyperthyroidism, 1511*b*
Subclinical hypothyroidism, 1505, 1508*b*
Subcutaneous fat, 2688*t*
Subcutaneous nodules, 2178
Subcutaneous onchocercomas, 2178
Subcutaneous panniculitis-like T-cell lymphoma, 1287
Subcutaneous phaeohyphomycosis, 2110
Subcutaneous tophus, 1812
Subcutaneous treprostinil, for pulmonary hypertension, 496*b*
Subdermal implants, for contraception, 1616
Subdural abscess, 2528*f*
Subdural effusions, 2511
Subdural empyema, 2528, 2528*b*
Subdural hematoma, 2390
acute, 2390
chronic, 2391
Subfrontal craniotomy, 1487*b*
Subglottic edema, 2197*f*
Subglottic stenosis, 2653
Subjective tinnitus, 2643
Sublobar resections, of lung cancer, 1333*b*
Submersion incidents, 591, 592*b*
Subpleural reticulations, 575.*e1f*
Subpulmonic pleural effusions, 525, 525*f*
Subspecialty consultations, 2657, 2657*t*
Substance abuse
neurologic diseases and, 2369
psychiatric disorders and, 2337
weight loss and, 860*t*
Substance use
in adolescents, 113
in women, 1609
Substance use disorder, 2360
in adolescents, 113
agent of, 2360
clinical manifestations of, 2361
definition of, 2360
diagnosis of, 2361
DSM-5 criteria for, 2360*t*
environment of, 2360
epidemiology of, 2360
history of, obtaining, 2679
host of, 2360
major drugs in, 2361
anabolic-androgenic steroids as, 2365
cocaine and amphetamines as, 2363
hallucinogens as, 2364
marijuana as, 2364
opioids as, 2361
phencyclidine as, 2364
sedative-hypnotic and anxiolytic drugs as, 2363
medical complications related to, 2361
pathobiology of, 2360
severe mental illness and, 2678
treatment of, 2361*b*
Substituted judgment, 6
Substrate reduction therapy, for Gaucher disease, 1421*b*
Succimer, for acute poisoning, 693*t*
Succinate dehydrogenase, 1530
Succinylcholine
for anesthesia, 2670–2671
toxicants and, 691*b*
Sudden cardiac arrest, 312
prevention of, 316
Sudden cardiac death, 333
Sudomotor dysfunction. *See* Sweating disorders
Sufentanil, 139*t*
Sugammadex, reactions to, 1698*t*
Sugar, dietary guidelines for, 57.*e3t*
Sugar cane, 88*t*
Sugar monomers, 938
Suicide, 2347, 2348*t*
in adolescents, 110, 110*t*
assisted, 8
Suicide genes, 176
Sulbactam, for pneumonia, 616*t*
Sulfadiazine
dosage of, 1895*t*
for toxoplasmosis, 2112*t*, 2115, 2140*t*
Sulfamethoxazole, dosage of, 1895*t*
Sulfamethoxazole-trimethoprim, for granuloma inguinale, 2004*b*
Sulfasalazine (Azulfidine), 146
for inflammatory bowel disease, 945*b*, 946*t*
for psoriatic arthritis, 1765*b*
for rheumatoid arthritis, 1755*b*, 1756*t*, 1757*t*
for total knee arthroplasty, 1830.*e1t*
Sulfate, diarrhea and, 939
Sulfhemoglobin, *e1t–e8t*
Sulfonamides
dosage of, 1895*t*
mechanism of action, 1895*t*
reactions to, 1698
resistance mechanisms, 1893*t*
toxicities of, 1901*t*
for toxoplasmosis, 2115
Sulfonylureas, for type 2 diabetes mellitus, 1541*t*
Sulindac, for chronic pain, 138*t*
Sumatriptan, 2380*t*
Sun protection factor (SPF), 2701
Sunitinib maleate (Sutent), 1215*t*
Sunitinib monotherapy, for renal cell carcinoma, 1364*b*
Sunscreen, for skin cancers, 2701
Superantigen model, vasculitides and, 1794
Superficial bursae, 1804
Superficial phaeohyphomycosis, 2109–2110
Superficial spreading melanoma, 1391, 1392*f*
Superficial temporal artery, assessment of, 1803
Superficial vein thrombosis, 490–491
Superior mesenteric artery embolism, 962, 962.*e1f*
Superior mesenteric artery syndrome, 967
Superior mesenteric artery thrombosis, 960
Superior mesenteric vein thrombosis, computed tomography for, 871*f*
Superior sulcus sign, 627
Superior vena cava obstruction, 628, 628*f*
Superoxide dismutase, 196
Supersaturation, 803
Supine hypertension, 2554
Supportive care
for acute kidney injury, 774*b*, 775*f*
for acute pancreatitis, 972*b*
for acute respiratory failure, 647*b*
for cancer, 1232*b*
for myelodysplastic syndromes, 1255
Suppression, 207
Suppurative thyroiditis. *See* Infectious thyroiditis
Suprachiasmatic nucleus, 1478
Supraglottic stenosis, 2652.*e2f*
Supraglottitis, 2651
Supranuclear ophthalmoplegia, Whipple disease and, 2070
Supranuclear pathways, 2618
Suprasellar dysgerminomas, 1479
Supraventricular arrhythmias, 291
with normal rate, 322, 322*f*, 323*b*, 323*f*
Supraventricular ectopy, 322–332
Supraventricular tachyarrhythmias, 323–332, 323*t*, 384*b*
Supraventricular tachycardia (SVT)
catheter ablation of, 346
differential diagnosis of, 335, 335*t*
Suramin
for African trypanosomiasis, 2112*t*, 2125*b*, 2125*t*
Surface electrocardiogram, 317.*e1f*
Surface functions, agents for, 2700
Surgery, 340
for ambiguous genitalia, 1575*b*
for aortic regurgitation, 409
aortic valve replacement, 403*b*
for arrhythmia, 347
for aspergillosis, 2096
for benign prostatic hyperplasia, 822*b*
for biliary tract cancers, 1360*b*
for brain tumors, 1312*b*
for breast cancer, 1369*b*
for bronchiectasis, 561*b*
bronchoscopic approaches, 630
coronary artery, 397. *See also* Coronary artery bypass graft (CABG) surgery
for gastrointestinal stromal tumors, 1390*b*
for heart failure, 265*b*
for hepatocellular carcinoma, 1360*b*
for infective endocarditis, 417*b*
for lung disease, 631
minimally invasive approaches, 631
open approaches, 631
lung volume reduction, 631
decision guide for, 632*t*
inclusion and exclusion criteria for, 632*t*
for malignant lung disease, 631
for mitral regurgitation, 407*b*
mitral valve, 407*b*
for nephrolithiasis, 805*b*
for Paget disease of bone, 1664*b*
patient treated with, 136*b*
for pectus excavatum, 621*b*
for pheochromocytoma, 1533*b*
for pituitary tumors, 1487*b*
for primary lung cancer, 631
for renal cell carcinoma, 1364*b*
for sickle cell disease, 1114*b*
video-assisted thoracoscopic, 631
Surgical floor, psychiatric diseases in, 2679
Surgical history, 28
Surgical procedures, for urinary incontinence, 829*b*
Surgical resection, for coccidioidomycosis, 2085*b*
Surgical revascularization, for atherosclerotic renal artery stenosis, 800*t*
Surgical site infections, 1862*t*, 1866
Staphylococcus aureus causing, 1903

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Surgical therapy
Acinetobacter, 1974*b*
for cancer, 1232*b*
for chronic pancreatitis, 975*b*
for cirrhosis, 1040*b*
for Cushing syndrome, 1524*b*
for pain, in chronic pancreatitis, 975*t*
for premenstrual syndrome, 1597*b*
for Zollinger-Ellison syndrome, 1563*b*
Surgical total thyroidectomy, for Graves disease, 1511*t*
Survival motor neuron *(SMN)*, 2565
Suspected infection, approach to, in normal host, 1845
fever, 1845
nosocomial, 1851
Sutent. *See* Sunitinib maleate
Suvorexant, 2452*t*
SVT. *See* Supraventricular tachycardia
Sweat glands, cystic fibrosis and, 556
Sweating disorders, 2555
Sweet syndrome, 1857, 2724, 2724*b*, 2724*f*, 2734–2735, 2735*f*
Swimmer's itch, 2742
Swine H3N2 viruses, 2199
"Swiss cheese" model of accidents, 45
Switch maintenance, for lung cancer, 1333*b*
Swollen belly syndrome, 2173
Swyer-James-McLeod syndrome, 522
Swyer-James syndrome, 565
Swyer syndrome, 1574
Sydenham chorea, 2491
Sylvatic typhus, 2059
Sympathetic ophthalmia, 2611
Sympathoadrenal system, 747
Sympatholytics, central, for hypertension, 455
Symptom temporality, in occupational and environmental medicine history, 85
Symptomatic gallstones, 1052*b*
Symptomatic hypercalcemia, 1654*b*, 1656
Symptomatic hyponatremia, 741*b*
Symptomatic therapies, for diarrhea and enteric infection, 1872*t*
Symptoms
as health measures, 40
review of, 28
Synchronous biventricular pacing, 342, 342*f*
Syncope, 210*t*, 211, 211*t*, 304, 304*t*
in aortic stenosis, 400
cardiac, 309*b*
causes of, 304*t*
cerebrovascular, 306
cough-related, 306
neurocardiogenic, 305, 309*b*
neurological, 309*b*
neuropsychiatric, 306
prognosis of, 311–312
seizures *versus*, 2430*t*
treatment of, 309*b*, 310*t*
vasovagal, 304*t*
Syndrome of inappropriate antidiuretic hormone secretion (SIADH), 739, 1500
causes of, 739*t*
criteria for the diagnosis of, 739*t*
Syndromes, 3
Synergism, in antibacterial activity, 1843
Syngeneic hematopoietic cell transplantation, 1208
Synovectomy, 1827
Synovial cysts, 1752, 1752.*e1f*
Synovial hypertrophy, chronic, bleeds in, 1188
Synovitis, 1718, 1719*f*
Synovitis acne pustulosis hyperostosis osteitis syndrome (SAPHO), 1731*t*
Synthetic lethality, in BRCA null cells, 1251, 1252*f*
α-Synuclein, 2420
Syphilis, 1808, 2014–2021
algorithm for, 1881.*e1f*
cardiovascular, 2017
chancres associated with, 1881, 2015
chancroid and, 1951
characteristics of, 1881
chemiluminescence immunoassays for, 2018
clinical manifestations of, 2015–2018
condylomata lata associated with, 2015*f*, 2016
congenital, 2018, 2019
cutaneous manifestations of, 2015
dark-field examination for, 2018
definition of, 2014
diagnosis of, 2018–2019
differential diagnosis of, 2019
Syphilis *(Continued)*
early infectious, 2020*b*
endemic, 2021
enzyme immunoassays for, 2018
epidemiology of, 1879, 2014
false-positive serologic test results for, 2019
follow-up examinations for, 2021
gummatous, 2014
incidence of, 2014
Jarisch-Herxheimer reactions, 2020*b*
late, 2017, 2017*t*
late benign, 2017
latent, 2016
meningovascular, 2017
more than 1 year in duration, 2020*b*
natural history of, 2015
neurosyphilis, 1881, 2017, 2019
nontreponemal tests for, 2018
ocular, 1881, 2017, 2606
organisms causing, 1879*t*
otic, 2017
pathobiology of, 2014–2015
pathogen that causes, 2014
penicillin for, 2020*b*, 2020*t*
in pregnancy, 2020*b*
prevention of, 2019–2020
primary, 2015, 2015*f*, 2621*t*
prognosis for, 2021
prophylaxis for, 2309*t*
rapid plasma reagin test for, 2018
relapsing, 2016
screening for, 2019
secondary, 2015, 2016*f*, 2623
serologic tests for, 2018–2019, 2018*t*
tabes dorsalis, 2017, 2019
transfusion-related transmission of, 1203
treatment of, 2020*b*
treponemal tests for, 2018–2019
Syphilitic lesions, 2741
Syphilitic meningitis, 2017
Syringomyelia, 2546*f*, 2547, 2547*b*
Systemic amyloidosis, 1305, 1306*t*
Systemic anaphylaxis
acute treatment of, 1694*f*
causes of, 1691*t*
diagnosing, 1693*f*
Systemic antifungal agents, 2074
amphotericin preparations as, 2077
adverse effects of, 2078
drug interactions of, 2077
formulations and pharmacology of, 2077
indications and dosage of, 2077
mechanism of action, 2077
azole, 2074
fluconazole as, 2075
indications and dosage of, 2075
isavuconazole as, 2077
itraconazole as, 2074
mechanisms of action, 2074
posaconazole as, 2076
voriconazole as, 2076
dosing overview for, 2075*t*
echinocandin, 2078
anidulafungin as, 2078
caspofungin as, 2078
mechanisms of action, 2078
micafungin as, 2078
flucytosine as, 2079
adverse effects of, 2079
drug interactions of, 2079
formulation and pharmacology of, 2079
indications and dosage of, 2075*t*, 2079
mechanisms of action, 2079
ibrexafungerp as, 2079
adverse effects of, 2079
drug interactions of, 2079
indications and dosage of, 2075*t*, 2079
mechanisms of action, 2079
other, 2079
Systemic autoinflammatory diseases, 1730–1737, 1731*t*
adenosine deaminase-2, deficiency of, 1731*t*, 1733*t*, 1737
associated with activation of NF-$_{\kappa}$B, 1736
associated with *NLRC4* mutations, 1731*t*
clinical characteristics of, 1733*t*
cryopyrin-associated periodic syndromes, 1734, 1735*b*
deficiency of interleukin-1 receptor antagonist, 1731*t*, 1735
deficiency of the IL-36R antagonist, 1731*t*, 1735
Systemic autoinflammatory diseases *(Continued)*
definition of, 1730
discovery of, 1737
familial cold autoinflammatory syndrome, 1731*t*, 1733*t*
familial Mediterranean fever, 1730, 1731*t*
clinical characteristics of, 1733*t*
clinical manifestations of, 1730
definition of, 1730
diagnosis of, 1732
epidemiology of, 1730
pathobiology, 1730
prognosis for, 1732
treatment of, 1732*b*
genome sequencing of, 1737
hyperimmunoglobulinemia D with periodic fever syndrome, 1731*t*, 1733
clinical characteristics of, 1733*t*
clinical manifestations of, 1734
prognosis for, 1734*b*
treatment of, 1734*b*
inherited, 1731*t*, 1736–1737
innate immune pathways in, 1737
interferon-related, 1731*t*
late onset, 1737
Muckle-Wells syndrome, 1731*t*, 1733*t*
neonatal-onset multisystem inflammatory disease, 1731*t*, 1733*t*
proteasome-associated autoinflammatory syndromes, 1731*t*, 1735
pyogenic arthritis with pyoderma gangrenosum and acne, syndrome of, 1731*t*, 1736
somatic mutation in, 1737
tumor necrosis factor receptor-associated periodic syndrome, 1731*t*, 1733*t*, 1734
diagnosis of, 1734
epidemiology of, 1734
pathobiology of, 1734
prognosis for, 1734
treatment of, 1734*b*
type I interferon-associated, 1735
Systemic autonomic disorders, 2553
autonomic function tests for, 2556
clinical evaluation of, 2555, 2556*f*, 2556*t*
clinical manifestations of, 2554
definition of, 2553
diagnosis of, 2555
epidemiology of, 2553
laboratory evaluation of, 2556, 2557*t*
pathobiology of, 2553
pathogenesis of, 2554, 2554*t*
treatment for, 2557*b*
Systemic circulation, nutrient delivery to, impairment of, 924.*e1f*, 938
Systemic diseases
arthritis and, 1820, 1821*t*, 1824*f*, 1825*f*
of hemostasis, 1166*t*
inflammatory, with pleural effusions, 626
of throat, 2651
Systemic glucocorticoids, for skin diseases, 2698
Systemic inflammation, hypercoagulable states and, 481
Systemic inflammatory disorders, weight loss and, 860*t*
Systemic light chain amyloidosis, 1305
cardiac involvement in, 1306
clinical manifestations of, 1305–1307, 1306*f*, 1306*t*
definitive testing for, 1307*f*, 1308
diagnosis of, 1307–1308
differential diagnosis, 1308
gastrointestinal/liver and, 1307
initial testing for, 1307, 1307*f*
neuropathy and, 1307
pathobiology of, 1305–1309
prognosis of, 1309
renal involvement and, 1305–1306
treatment for, 1308*b*, 1308*f*, 1309*f*
Systemic lupus erythematosus (SLE), 195, 784*t*, 965, 1767–1775
adjunctive therapies for, 1772*b*
alkylating agents for, 1772*b*
anti-DNA, 1714
antinuclear antibody test for, 1768
antiphospholipid antibody syndrome in, 1770
autoantibodies associated with, 1768, 1768.*e1f*, 1772*t*
biologic therapies for, 1772*b*
cardiovascular system manifestations of, 1769
classification of, 1770–1771, 1771*t*, 1772*f*
clinical manifestations of, 1769–1770, 1769*t*
Systemic lupus erythematosus (SLE) *(Continued)*
complement associated with, 1768–1769
constitutional symptoms of, 1769
conventional medical therapy for, 1772*b*
cutaneous membranes involvement, 1769
definition of, 1767–1775
diagnosis of, 1770–1772
differential diagnosis of, 1771
diffuse alveolar hemorrhage and, 568
discoid skin lesions in, 1769
environmental triggers of, 1768
epidemiology of, 1767
of esophagus, 911
flares of, 1768
gastrointestinal system manifestations of, 1770
gender predilection of, 1709
genetics of, 1768
genomic region of, 1768.*e1t*
glomerular diseases in, 787, 787*b*, 787*f*, 787*t*, 788*f*
hematologic system manifestations of, 1770
immune complexes associated with, 1768
immunologic triggers of, 1768
immunosuppressive therapies for, 1772*b*
innate immune system of, 1768.*e1f*
intravenous gamma globulin for, 1772*b*
laboratory findings in, 1771
lupus nephritis, 1769, 1771, 1773*f*, 1774*f*
lymphadenopathy in, 1770
malar rash associated with, 1770*f*
mucous membranes involvement, 1769
musculoskeletal system manifestations of, 1769
neuropsychiatric involvement in, 1770
ocular manifestations of, 2611, 2624
organ-system disease in, management of, 1772*b*
pathobiology of, 1767–1769
plasmapheresis for, 1772*b*
in pregnancy, 1619*t*
prevalence of, 1767
prognosis for, 1775
pulmonary involvement, 580–581
pulmonary system manifestations of, 1770
Raynaud phenomenon in, 1770
renal system manifestations of, 1769
skin manifestations of, 1769
splenomegaly associated with, 1152
splenomegaly in, 1770
symptoms and signs of, 1769–1770
treatment of, 1772*b*
type I interferon and, 1768
vasculopathy in, 1769
Systemic mastocytosis, 917, 1694, 1701
Systemic-onset juvenile idiopathic arthritis (SOJIA), 1731*t*
Systemic sclerosis, 1775–1783
antinuclear autoantibodies in, 1780
autoantibodies associated with, 1776, 1777*t*
B cells in, 1776
calcinosis cutis in, 1777, 1779*f*
cancer and, 1780
cardiac involvement in, 1779, 1781
cellular immunity in, 1776
classification of, 1777*t*, 1780*t*
clinical manifestations of, 1777–1780
conditions associated with, 1780*t*
definition of, 1775–1782
diagnosing systemic involvement in, 1780–1781
diagnosis of, 1780–1781
epidemiology of, 1706–1707, 1775
facial features in, 1778*f*
fibrosis in, 1776
gastrointestinal complications in, 1781*b*
gastrointestinal tract involvement in, 1778
genetic factors, 1775–1776
humoral immunity in, 1776
immune dysregulation in, 1776
immunosuppressive agents for, 1781*b*
incidence of, 1707*t*
initial clinical presentation of, 1777
interstitial lung disease in, 1779, 1780, 1781*b*
kidney involvement in, 1779
laboratory features of, 1780
lower gastrointestinal tract involvement in, 1778
lung involvement in, 1778
microangiopathy of, 1780
mortality ratios for, 1782
musculoskeletal complications in, 1779
occupational exposure for, 1775

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Systemic sclerosis *(Continued)*
organ involvement in, 1777–1780
pathobiology of, 1775–1776
pathogenesis of, 1776.e1*f*
prevention of, 1781*b*
prognosis for, 1782
progressive, interstitial lung disease associated with, 580
pulmonary arterial hypertension in, 1779, 1781*b*
Raynaud phenomenon in, 1776, 1777
skin involvement in, 1777, 1781*b*
treatment of, 1781*b*
upper gastrointestinal tract involvement in, 1778
vascular complications of, 1778*f*
vasculopathy in, 1776
Systemic therapy
for cancer, 1232*b*
for hepatocellular carcinoma, 1360*b*
for lung cancer, 1333*b*, 1334*t*
Systemic vascular resistance, 677*t*
Systemic vascular resistance index, 677*t*
Systemic vasculitides, 1791–1800. *See also* Vasculitides
Systems thinking, 45
Systolic blood pressure
in industrialized societies, 444
normal range for, 32*t*
panic range for, 32*t*
Systolic hypertension, in elderly patients, 455, 455.e2*f*
Systolic murmurs, quiet, 30
Systolic thrill, 30
Systolic ventricular function, 239

T

T-and B-cell combined defects
less severe, 1678, 1678.e1*t*
severe, 1676, 1676.e3*t*, 1678*b*
with syndromic features, 1678, 1678*b*, 1679*t*
T-cell(s), 152, 186–187
development of, 186, 186*f*
differentiation of, 189–190, 189.e1*t*
homeostasis of, 190
regulatory, 190
stimulation and accessory molecules of, 189
T-cell depletion, 1207
disadvantage of, 206, 206.e2*f*
of hematopoietic cell grafts, 206, 206.e1*t*
T-cell lymphoma
adult, 1286, 1286*b*
anaplastic large cell lymphoma, 1287
angioimmunoblastic, 1287
enteropathy-type, 1287
extranodal NK/T-cell lymphoma, 1287
hepatosplenic, 1287
mature, 1286
mycosis fungoides, 1286, 1286*b*
precursor, 1281, 1282*b*
subcutaneous panniculitis-like, 1287
T-cell receptor chain defects, 1676.e3*t*, 1678
T-cell receptor excision circles (TRECs), 1679
T-cell receptors (TCRs), 188–189, 206
specificities of, 188
T-cell trafficking, role of, 206
T cell-depleting antibodies, in renal transplantation, 845*t*
T-lymphoblastic leukemia/lymphoma, 1260*t*
T lymphocytes, 152
t-PA. *See* Alteplase
T-regulatory cells, genetic defects of, 1684*t*, 1685
T wave, 228, 228*f*, 233
Tabes dorsalis, 2017, 2019
Tachy-brady syndrome, 319, 319*f*
Tachyarrhythmia, 34, 305, 322
supraventricular, 323, 323*t*, 384*b*
Tachyarrhythmic cardiac arrest, 313*b*
Tachycardia, 34
accessory pathway, 326, 326*b*, 328*f*
acute pancreatitis and, 970
in acute poisoning, 682
antidromic, 323*t*, 326
atrial, 323*t*, 324, 324*f*
atrioventricular nodal re-entrant, 323*t*, 324, 324*f*, 327*f*
atrioventricular re-entrant, 323*t*, 326, 328*f*
automatic junctional, 323*t*
monomorphic wide-complex, 335
postoperative, 2675
Tachycardia-induced cardiomyopathy, atrial fibrillation and, 329
Tachypnea, 35
acute pancreatitis and, 970
caused by amphotericin B, 2078
Tacrolimus (Prograf), e10*t*–e11*t*, 148, 2700
for focal segmental glomerulosclerosis, 779*b*
hyperkalemic acidosis caused by, 751
for liver transplantation, 1048*t*
for membranous nephropathy, 780*b*
for minimal change disease, 778*b*
in renal transplantation, 845, 845*t*
for total knee arthroplasty, 1830.e1*t*
Tactile fremitus, 512
Tadalafil, 364*b*, 824*t*
for erectile dysfunction, 1589
for high-altitude diseases, 593*t*
Taenia asiatica, 2158*t*
Taenia saginata, 2158, 2158*t*, 2159*b*
Taenia solium, 2158*t*, 2159
Taeniasis, 2158, 2159*b*
Tafamidis, for amyloidosis, 1309*b*, 2560*b*
Tafenoquine, 2114
for malaria, 2112*t*, 2121*b*, 2121*t*, 2123*t*
Tafinlar. *See* Dabrafenib
Tagrisso. *See* Osimertinib
Tai chi, 154, 1741*t*
Takayasu arteritis, 442.e1*f*, 443–444, 1795, 1796*f*
epidemiology of, 1793*t*
pathologic characteristics of, 1793*t*
prognosis of, 1795*b*
treatment of, 1795*b*
Takayasu disease, 965
Takayasu retinopathy, 1795
Takotsubo cardiomyopathy, 665
Talaromyces (Penicillium) marneffei, 2065*t*
Talaromycosis, 2065*t*, 2309*t*
Talazoparib (Talzenna), 1215*t*, 1251*t*
Talcott group classification, 1856*t*
TALENs. *See* Transcription activator-like effector nucleases
Talimogene laherparepvec, for melanoma, 1394*t*
Taltz. *See* Ixekizumab
Talzenna. *See* Talazoparib
Tamm-Horsfall proteins, 794
Tamoxifen (Nolvadex), 1215*t*
for breast cancer, 1369*b*
Tamponade, pericardial, 425
clinical manifestations of, 425
diagnosis of, 426
epidemiology of, 425
pathobiology of, 425
prognosis for, 428
treatment of, 427*b*
Tamsulosin, 824*t*
Tanapox virus, 2237
Tandem repeats, in genomics, 163
Tanner stages, 110
Tanycytes, 1476
Tapentadol, 136*b*, 139*t*
Tapeworm infections
Diphyllobothrium sp., 2158, 2158*b*, 2158*t*
Dipylidium caninum, 2158
Hymenolepis nana, 2158, 2158*b*, 2158*t*
Taenia asiatica, 2158*t*, 2159
Taenia saginata, 2158, 2159*b*
Taenia solium, 2158*t*, 2159, 2159*b*
treatment of, 2157*b*
Tarantula, goliath, 710
Tardive dyskinesia, 2496, 2496*b*
Target cells
conditions associated with, 1072*t*
peripheral blood smear of, 1068*f*, 1074*t*
Targeted small molecules, for cancer, 1232*b*
Targeted synthetic disease-modifying antirheumatic drugs, 1755*b*, 1756*t*
Targeted therapies
as biologic agents, 149
for chronic lymphocytic leukemia, 1269*t*
for eosinophilic syndromes, 1164*b*
for pulmonary hypertension, 496*b*
small molecule, 153
Targretin. *See* Bexarotene
Tarui disease, 1417*t*
TAS-102, for colorectal cancer, 1350*b*
Tasigna. *See* Nilotinib
Taste, 2639, 2640*b*, 2640*t*
Taste bud, 2639
Taste pathways, 2640*f*
Taurursodiol, for amyotrophic lateral sclerosis, 2563*b*
Taxol. *See* Paclitaxel
Taxotere. *See* Docetaxel
Tay-Sachs disease, 1399, 1423
Tazarotene (Tazorac), 2698
Tazemetostat (Tazverik), 1215*t*
Tazorac. *See* Tazarotene
Tazverik. *See* Tazemetostat
TB. *See* Tuberculosis
TBK1 deficiency, 1731*t*
Tc-MDP. *See* Technetium-99*m* methylene diphosphate
TCAs. *See* Tricyclic antidepressants
TCD. *See* Transcranial Doppler
TCRs. *See* T-cell receptors
Teamwork, medical profession, 4
Teardrop poikilocytes, 1069*f*
Tecentriq. *See* Atezolizumab
Tecfidera. *See* Dimethylfumarate
Technetium-99*m* methylene diphosphate (Tc-MDP), 1723
Tecovirimat, 2240*b*
Tedizolid
dosage of, 1895*t*
mechanism of action, 1895*t*
spectrum of activity, 1900
Tegaserod, for irritable bowel syndrome, 896*t*
Teicoplanin, mechanism of action, 1895*t*
Telangiectasia, 1778*f*, 2738
hereditary hemorrhagic, 967
Telangiectasia macularis eruptiva perstans, 1701
Telavancin
dosage of, 1895*t*
mechanism of action, 1895*t*
spectrum of activity, 1900
Telbivudine, for hepatitis B virus infections, 2181*t*, 2182*t*, 2183
Telehealth
consultations, 2658, 2658*f*, 2659*f*
for COVID-19, 31–32
for quality of care, 42
Teletherapy, 1232*b*
Telithromycin, dosage of, 1895*t*
Telmisartan, 451*t*
Telmisartan/HCTZ, 451*t*
Telogen effluvium, 2748
acute, 2748, 2748*b*, 2748*t*
chronic, 2748
Temazepam, 2344*t*, 2452*t*
Temodar. *See* Temozolomide
Temozolomide (Temodar), 1215*t*
Temperature
definition of, 1845–1846
regulation, 678, 1481
Temporal arteritis, 1801, 2383
Temporal artery biopsy, for giant cell arteritis, 1803
Temporal bone fracture, 2645
Temporal lobe
anatomy of, 2460*f*
epilepsy, 2426*f*, 2646
herniation of, 2511
Temporary partial disability, 85
Temporary total disability, 85
Temsirolimus (Torisel), 1215*t*
Ten Commandments, for effective consultations, 2657, 2657*t*
Tenapanor, for irritable bowel syndrome, 895*b*, 896*t*
Tendinitis, 1747, 1747*b*. *See also* Tendinosis
Tendinosis, 1742
Tendon rupture, of knee, 1747, 1747*b*
Tenecteplase (TNK-t-PA), 386*t*
Tennis elbow. *See* Lateral epicondylalgia
Tenofovir, 2301*t*
for chronic hepatitis B, 1011*b*
Tenofovir alafenamide, for hepatitis B virus infections, 2181, 2181*t*, 2182*t*
Tenofovir disoproxil fumarate
for chronic hepatitis B, 1011*b*
for hepatitis B, 1006, 2181, 2181*t*, 2182*t*
nephrotoxicity caused by, 2313
Tenosynovial giant cell tumor, diffuse type of, 1825–1826
Tenosynovitis, 1742
Tenosynovitis, disseminated gonococcal infection and, 1949
TENS. *See* Transcutaneous electrical nerve stimulation
Tension pneumothorax, 526, 627
Tension-type headache, 2377*t*, 2380, 2380*b*
Tepmetko. *See* Tepotinib
Tepotinib (Tepmetko), 1215*t*
Terazosin, 451*t*, 824*t*
Terbinafine, 2111*b*, 2699
Teriflunomide (Aubagio), for multiple sclerosis, 2505*t*
Teriparatide, for osteoporosis, 1643*b*, 1644*t*
Terminal follicles, 2747
Termination of medical interventions, 6
definition of, 6–7
empirical data for, 7
history of, 6
justification of, 6
practical considerations for, 7, 7*t*
Terrorism
bioterrorism, 95
radiologic, 92
Tesamorelin, 2318*b*
Testicular cancer, 1382–1384
clinical manifestations of, 1382
diagnosis of, 1382–1383, 1383*f*
epidemiology of, 1382–1384
pathobiology of, 1382
prevention of, 1383–1384
prognosis of, 1384
treatment of, 1383*b*, 1383*t*
Testicular feminization syndrome, 1573
Testicular ultrasound, for testicular cancer, 1383
Testis, 1580
irradiation to, 1583
physiology of, 1580
trauma to, 1583
Testosterone, 2365
benefits and risks of, 1585*b*
deficiency of, in elderly, 1582, 1582*b*, 1582.e1*f*
delivery systems for, 1585*b*
description of, 1496*b*
free, e1*t*–e8*t*
plasma proteins and, 1581
at puberty, 1573
secretion of, 1581
total, e1*t*–e8*t*
transdermal delivery for, 1585*b*
for transgender men, 1578*t*
Testosterone buccal patch, for transgender men, 1578*t*
Testosterone cypionate, for transgender men, 1578*t*
Testosterone enanthate, for transgender men, 1578*t*
Testosterone gel, for transgender men, 1578*t*
Testosterone patch, for transgender men, 1578*t*
Testosterone undecanoate, for transgender men, 1578*t*
Tetanospasmin, 1928
Tetanus
description of, 1928, 1929*b*, 1929*t*
immunization for, 65*t*, 66*t*, 78*f*, 82
schedule of, 76.e1*t*, 77*f*
Tetanus/diphtheria/acellular pertussis (Tdap) vaccination
description of, 1996
for traveler, 1886
Tetanus immune globulin, 1929
Tetanus toxoid vaccination, 1929
Tetany, 2581
Tethered spinal cord, 2546, 2546*b*
Tetrabenazine
description of, 2491
for tardive dyskinesia, 2496*b*
Tetracyclines, 2115
characteristics of, 1899
dosage of, 1895*t*
for intestinal bacterial overgrowth, 934*b*
mechanism of action, 1895*t*
resistance mechanisms, 1893*t*
spectrum of activity, 1900
for *Streptococcus pneumoniae* pulmonary infections, 1912.e1*t*
toxicities of, 1901*t*
Tetrahydrocannabinol, screening for, 689*t*
Tetralogy of Fallot (TOF), 353–354
chest radiography findings, 247.e1*f*
exercise recommendations for, 355.e2*t*
incidence and prevalence of, 347
repair of, 353, 353*f*
Tetrathiomolybdate, for Wilson disease, 1437*b*
Tetrodotoxin poisoning, 713

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TGF-β receptor, 185
T_H1-mediated hypersensitivity reactions, 195
α-Thalassemia, 1102–1104, 1103*t*, 1104
  minor, 1104
β-Thalassemia, 1103*t*, 1104–1106
  clinical classification of, 1105*f*
  genetics of, 1112*t*
  intermedia, 1104–1106
  laboratory features of, 1112*t*
  major, 1106
  minor, 1104
  pathophysiology of, 1106*f*
δβ-Thalassemia, 1103*t*, 1106, 1107*f*
Thalassemia(s), 1102–1109, 1103*t*
  clinical manifestations of, 1104–1106
  definition of, 1102–1107
  diagnosis of, 1106–1107
  diagnostic approach to, 1108*f*
  epidemiology of, 1102
  genetics of, 1102–1103
  hemoglobin E, 1106
  molecular basis of, 1103–1104
  pathobiology of, 1102–1104
  prognosis of, 1107*b*
  transfusion for, 1206
  treatment of, 1107*b*
  unstable hemoglobinopathies, 1109
Thalassemia intermedia, 1104, 1107*b*
Thalassemia major, 1104, 1107*b*
Thalassemia minor, 1107*b*
  peripheral blood smear of, 1067*f*
Thalidomide, for skin diseases, 2699
Thallium
  neuropathy and alopecia, 106, 106*b*
  toxicity, 690*t*
Theophylline, *e*10*t*–*e*11*t*
  for asthma, 541*b*
  toxicity, 690*t*
Therapeutic hyperthermia, 682
Therapeutic hypothermia, 681, 2462
Therapeutic index, 128–129, 1232*b*
Therapeutic paradigm, in oncology, 1232*b*
Therapeutic window, 128
Thermal disorders, 471–475, 471*f*
Thermal injury, 699, 699*f*, 699*t*
  to lungs, 595
  to upper airway
    clinical manifestations, 595
    diagnosis, 595
    pathogenesis, 595
    prognosis, 595
    treatment, 595*b*
Thermometers, 29
Thermoplasty, bronchial, 630
Thiamin, 1453*t*
Thiamine, *e*1*t*–*e*8*t*
  for alcoholic ketoacidosis, 759*b*
  deficiency of
    cardiomyopathy with, 288
    description of, 2537–2539, 2538*t*
Thiazide diuretics, 736*b*
  for hypercalciuria, 806
  for hypertension, 451*t*
  for hypervolemia, 737*t*
  hypokalemia and, 749*t*
  side effects of, 453*t*
Thiazide-induced hyponatremia, 739, 741
Thiazide-sensitive NaCl cotransport, 746–747
Thiazolidinediones
  description of, 262
  for nonalcoholic fatty liver disease, 1034*b*
  for type 2 diabetes mellitus, 1540*b*, 1541*t*
Thick ascending limb, 754.*e*1*f*, 817.*e*1*f*
Thioridazine, for psychotic disorders, 2346*t*
Thiothixene, for psychotic disorders, 2346*t*
Third nerve palsy, isolated, 2618
Thomsen disease, 2583.*e*1*t*
Thoracic actinomycosis, 2067, 2068*f*
Thoracic amebiasis, 2148
Thoracic aortic aneurysm, 437, 438*b*, 439*f*
Thoracic cysts, 564
Thoracic kyphosis, 1638
Thoracic radiation therapy, for NSCLC, 1333*b*
Thoracic radiculopathy, 2394*t*
Thoracic vertebrae
  anatomy of, 2394*f*
  description of, 2392
Thoracoabdominal aortic aneurysms, 436
Thoracoscopic surgery, video-assisted, 631
Thorax, neuroendocrine tumors of, 1566
Three-dimensional echocardiography, 238, 240*f*
Throat
  acute poisoning and, 683
  lump in, 2652
  neurologic disorders affecting, 2652, 2652*t*
  systemic diseases of, 2651
Throat disorders, 2648–2653
  clinical differentiation of, 2649*t*
  epiglottitis as, 2651
  laryngopharyngeal reflux as, 2651
  pharyngitis as, 2648
    chronic tonsillitis, 2651
    fungal infections, 2650, 2651*f*
    management of, guidelines for, 2649*t*
    mycobacterial infections, 2651
    noninfectious, 2651
    nonstreptococcal bacterial, 2648, 2649*f*
    peritonsillar abscess and deep space infections, 2649, 2650*f*
    streptococcal infections, 2648
    viral infections, 2650, 2650*f*
Thrombelastography, for liver failure, 1198
Thrombi, 2716
Thrombin, 1165
Thrombin generation tests, 1169
Thrombin time, *e*8*t*–*e*9*t*, 1166
Thromboangiitis obliterans, 468, 468*b*, 969
Thrombocytopenia, 1166, 1170–1179, 1196, 2314, 2314*b*
  clinical manifestations of, 1171
  congenital, 1179
  COVID-19 and, 1175
  definition of, 1170–1171
  diagnosis of, 1171, 1172*f*
  dilutional, 1179
  disorders that cause of, 1171*t*
  drug-induced, 1173, 1174*b*, 1174*t*
  epidemiology of, 1170–1171
  gestational, 1178
  heparin-induced, 487*b*, 1174, 1174*f*, 1175*b*, 1175*t*
  immune, 1179
  immune thrombocytopenic purpura, 1175
  in leptospirosis, 2029
  neonatal alloimmune, 1179
  pathobiology of, 1171
  peripheral blood smear of, 1070
  platelet transfusions for, 1171*b*
  post-transfusion, 1179
  in pregnancy, 1178
  psychotropic medications and, 2678*t*
  Q fever and, 2063
  sepsis causing, 1175
  thrombotic thrombocytopenic purpura, 1176–1177, 1177*b*, 1177*f*
  treatment of, 1171*b*
  vasculitis causing, 1179
Thrombocytopenic purpura, idiopathic, immunization for, 65*t*
Thrombocytosis, 1134, 1135*t*, 1136*f*, 1136*t*
  peripheral blood smear of, 1070
Thromboelastography, 1169
Thromboembolic disease
  in pregnancy, 1619*t*
  spinal cord injury and, 2388*b*
Thromboembolic prophylaxis, for atrial fibrillation, 329*b*, 331*f*, 331*t*
Thromboembolism
  atrial fibrillation and, 329
  in nephrotic syndrome, 777
  vision loss caused by, 2616*t*
Thrombolysis, 384*b*
Thrombolysis in Myocardial Infarction (TIMI) risk algorithm, 373
Thrombophilias, 476*t*, 477*f*
Thrombophlebitis, septic, 2650
Thrombopoietin, 1066
  description of, 1065
  for immune thrombocytopenic purpura, 1176*t*
Thrombopoietin receptor agents, for immune thrombocytopenic purpura, 1176*t*
Thrombosis, 1138.*e*1*t*, 1139, 1139*f*
  in acute coronary syndrome, 370
  approach to, 1165
  central venous, in parenteral nutrition, 1450
  deep vein, 482
  evaluation of, preoperative, 1169
  hepatic artery, 969
  history and physical examination for, 1166, 1166*t*, 1167*t*
  laboratory testing for, 1166
  mechanisms of, 1165
Thrombosis *(Continued)*
  mesenteric venous, 962, 963*f*, 963*t*
  oral contraceptives and, 1614
  pathogenesis of, general scheme of, 475.*e*1*f*
  after PCI, 396
  portal vein, 968, 968*b*
  postoperative, 481
  prototypical systemic inflammatory states and, 481*t*
  in superficial veins, 482
  superior mesenteric artery, 960
  traveler's, 1889
Thrombosis threshold, 482.*e*3*f*
Thrombospondin type-1 domain containing 7A, 779
Thrombotic coronary artery disease, 381*t*
Thrombotic disorders, hypercoagulable states, 475
Thrombotic endocarditis, nonbacterial (marantic), 296
Thrombotic microangiopathies, 728, 789, 2313
Thrombotic thrombocytopenic purpura, 728, 1176, 1177*b*, 1177*f*
Thrombus formation, in acute coronary syndrome, 371
Thrush, 2090, 2090*f*
Thymic stromal lymphopoietin (TSLP), 152
Thymocytes, 204
Thymoglobulin, in renal transplantation, 845*t*
Thymus neuroendocrine neoplasm, 1567
Thyroglobulin (Tg), *e*1*t*–*e*8*t*
Thyroglobulin antibodies, *e*1*t*–*e*8*t*
Thyroid acropachy, 1822–1823
Thyroid cancer, 1517
  in adolescents, 111
  anaplastic, 1519
  medullary, 1518
  papillary and follicular, 1517
  primary thyroid lymphoma, 1519
Thyroid disease/disorders, 1504–1505
  arthritis associated with, 1822
  clinical manifestations of, 1505
  diagnosis of, 1505
  differential diagnosis of, 1505, 1506*t*
  goiter, 1515
  in HIV, 2317
  hyperthyroidism, 1509
  hypothyroidism, 1506
  imaging for, 1505
  laboratory testing for, 1505, 1506*t*
  pathobiology of, 1504
  physical examination for, 1505
  in pregnancy, 1619*t*, 1624, 1625*b*
  preoperative evaluation, 2665
  psychotropic medications and, 2678*t*
  screening for, 55
Thyroid gland, 1504–1519
  abnormal function, 265*b*
  examination of, 30
  follicular cells, 1504, 1504.*e*1*f*
Thyroid hormone
  endocrine diseases caused by, 1475*t*
  set points of, 1505, 1505.*e*1*f*
  synthesis and secretion of, 1504, 1504.*e*1*f*
  transport and metabolism of, 1504, 1504.*e*3*f*
Thyroid nodules, 1515
  diagnosis of, 1515–1516, 1516*f*
  fine-needle aspiration biopsy for, 1516, 1516*t*
  imaging for, 1516
  treatment for, 1517*b*
Thyroid-stimulating hormone (TSH), 1505
  in amenorrhea, 1599
  central hypothyroidism, 1497, 1497*b*
  function of, 1497
  hypothalamic disease effects on, 1476, 1481
  insufficiency tests of, 1484*t*
  tests of, 1488*t*
  tumors that secrete, 1497, 1497*b*, 1497*t*
Thyroid storm, 1511*b*
Thyroiditis, 1513
  drug-induced, 1514
  infectious, 1514
  postpartum, 1513
  sclerosing (Riedel), 1515
  sporadic painless, 1513
  subacute (de Quervain), 1513
Thyrotoxicosis, 1509, 2564*t*
  assessment of, 1510*f*
  hypercalcemia and, 1658
  radiographic evaluation of, 1511*t*
Thyrotropin (hTSH), *e*1*t*–*e*8*t*
Thyrotropin-releasing hormone (TRH)
  description of, 1476, 1477*f*
  prolactin secretion regulated by, 1490–1491
Thyroxine, 1497, 1504
  free (FT_4), *e*1*t*–*e*8*t*
  for hypothyroidism, 1508*b*, 1508*t*
  total (T_4), *e*1*t*–*e*8*t*
Thyroxine-binding globulin (TBG), *e*1*t*–*e*8*t*
Tic douloureux. *See* Trigeminal neuralgia
Ticagrelor, 387*t*, 506*t*, 507
  for acute coronary syndrome, 375*t*
  for acute STEMI, 384*b*, 391*t*
Ticarcillin/clavulanate, dosage of, 1895*t*
Tick-bite hypersensitivity reactions, 2025
Tick-borne encephalitis, 2276*t*, 2282, 2282*b*
  in travelers, 1891*t*
Tick-borne relapsing fever, 2027
Tick-borne rickettsioses, 2054, 2055*t*, 2057, 2058*b*, 2058*f*
Tick-borne viruses, 2266
Tickover, 198
Ticks
  description of, 710
  as vectors of zoonotic disease, 2064
  viruses caused by, 2266
Tics
  clinical manifestations of, 2494
  diagnosis of, 2494
  epidemiology of, 2494
  etiology of, 2494*t*
  pathobiology of, 2494
  Tourette syndrome causing, 2494–2495
Tidal volume (TV), 530, 652*t*
Tigecycline
  Acinetobacter, 1974*b*
  dosage of, 1895*t*
  for nontuberculous mycobacterial disease, 2046*t*
Tilt table testing, 308
Time to event data, 37
Time Up and Go approach, 118
Timolol, 451*t*
Tin, 88*t*
Tinea capitis, 2747*t*
Tinea corporis, 2686.*e*2*f*, 2687.*e*3*t*, 2710
Tinea cruris, 2710, 2711*f*
Tinea manuum, 2710
Tinea pedis, 2710
Tinea versicolor, 2687.*e*3*t*, 2692*t*, 2711, 2711*f*
Tinel sign, 2578
Tinidazole (Tindamax), 2115
  for amebiasis, 2150*t*
  for amebic liver abscess, 1025*b*
  for giardiasis, 2112*t*, 2145*b*
  for intestinal amebiasis, 2112*t*
  for trichomoniasis, 2112*t*, 2154*b*
  for urethritis, 1880*t*
Tinnitus, 2643, 2643*b*, 2643*f*
Tinzaparin, 503*t*
  for venous thromboembolism, 1624*t*
Tiotropium bromide, 553*t*
Tipranavir, 2301*t*
TIPS. *See* Transjugular intrahepatic portosystemic shunt
Tirofiban, 375*t*, 387*t*, 506*t*, 508
Tirzepatide, for type 2 diabetes mellitus, 1540*b*, 1541*t*
Tisagenlecleucel (Kymriah), 1215*t*
Tissue cestode (cyst) infection, 2159, 2160*b*
Tissue damage, mediators of, 1162–1163
Tissue Doppler, 236, 236.*e*1*f*
Tissue engineering, 174
Tissue factor (extrinsic) pathway, 1165
Tissue hypoxia, in septic shock, 671
Tissue injury, 191–196
Tissue plasminogen activator, for frostbite, 474*b*
Tissue repair, 191
Tissue-resident macrophages, 182
Tissue-specific stem/progenitor cells, 172
TLC. *See* Total lung capacity
TLR. *See* Toll-like receptor; Toll-like receptors
TLR-4. *See* Toll-like receptor 4
TLRs. *See* Toll-like receptors
TMP-SMX. *See* Trimethoprim-sulfamethoxazole
TNF-α. *See* Tumor necrosis factor-α
TNF receptor-associated death domain (TRADD), 185
TNK-t-PA. *See* Tenecteplase
Tobacco history, 28
Tobacco smoking, 55, 2349
  behavioral treatment for, 2350*t*

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Tobacco smoking *(Continued)*
cancer and, 1244
chronic pancreatitis and, 973
clinical manifestations of, 2349
definition of, 2349
diagnosis of, 2349
epidemiology of, 2349
nicotine replacement therapy for, 2350*b*, 2351*t*
pathobiology of, 2349
pharmacologic treatment for, 2350*b*, 2351*t*
prevention of, 2352
prognosis for, 2352
psychosocial treatment for, 2350*b*, 2350*t*
treatment of, 2350*b*
in women, medications for, 1608*t*
Tobramycin, *e10t–e11t*
for bacterial meningitis, 2518*t*
for bronchiectasis, 561*b*
dosage of, 1895*t*
for eye infection, 2605*t*
for pulmonary infection, 1970*b*
for pyelonephritis and urosepsis, 1877*t*
in renal failure, 129.*e1t*
Tocilizumab (Actemra)
for COVID-19, 2217
description of, 151, 151*t*
for giant cell arteritis, 1803*b*, 2383
for rheumatoid arthritis, 1756*t*
for total knee arthroplasty, 1830.*e1t*
α-Tocopherol, 1453*t*
TOF. *See* Tetralogy of Fallot
Tofacitinib (Xeljanz), 153*t*
for inflammatory bowel disease, 945*b*, 946*t*
for psoriatic arthritis, 1765*b*
for rheumatoid arthritis, 1755*b*, 1756*t*
for total knee arthroplasty, 1830.*e1t*
Togaviridae, 2224, 2274, 2278–2279, 2283
Tolbutamide, for type 2 diabetes mellitus, 1541*t*
Tolcapone, for Parkinson disease, 2487*t*
Tolerable upper limits, 1451
Tolerance, 129
immune system and, 190–191
Tolerance signatures, 207
Toll-like receptor 4 (TLR-4), activation of, 1942
Toll-like receptors (TLR), 183–185, 191, 1801
Tolmetin, for rheumatoid arthritis, 1756*t*
Tolterodine, 824*t*
Tolvaptan
for autosomal dominant polycystic kidney disease, 812*b*
for hypervolemia, 737*t*
Tonicity, 737
Tonsillitis
bacterial, 2649*t*
chronic, 2651
Topical analgesics, for skin diseases, 2699
Topical corticosteroid, 474*b*
Topical cytotoxic drugs, for skin diseases, 2700
Topical decolonization therapy, for health care-associated infections, 1867
Topical podophyllin, for anal warts, 982*b*
Topical sphincter relaxants, for anal fistula, 980*b*
Topical therapy, principles of, 2697
Topiramate
for obesity, 1467*b*
for seizures, 2434*t*
Topotecan (Hycamtin), 1215*t*
Torisel. *See* Temsirolimus
Torsades de pointes, 302, 336*f*
diagnosis of, 335
pathobiology of, 334
treatment of, 338*b*
Torsemide, 451*t*, 737*t*
Toscana virus, 2276*t*
Total energy, dietary guidelines for, 57.*e3t*
Total hip replacement, 1827–1828, 1828*f*
Total iron-binding capacity, 1457*t*
Total joint arthroplasty, 1827–1829
Total knee replacement, 1828, 1828*f*, 1829*f*, 1830.*e1t*
Total lung capacity (TLC), 528
Total peripheral resistance (TPR), 226
Total protein, *e1t–e8t*
Tourette syndrome, 2494, 2494*b*
Touton cells, 1157
Toxic adenoma, 1511*t*
Toxic epidermal necrolysis, 1847, 2695*f*, 2727, 2728*f*
prognosis of, 2728
treatment of, 2728*b*
Toxic erythemas, 2740
Toxic granulation, peripheral blood smear of, 1071*f*
Toxic megacolon
enteric infections and, 1870*t*
in ulcerative colitis, 945*b*
Toxic multinodular goiter
radiographic evaluation of, 1511*t*
treatment for, 1511*b*
Toxic myopathies, 2587, 2587*t*
Toxic neuropathy, 2313*b*, 2568*t*, 2578
Toxic pneumonitis, acute, 589
Toxic shock syndrome, 2695*f*, 2712
clinical manifestations of, 2712
influenza and, 2200
staphylococcal, 1906–1908, 1908*b*
streptococcal, 1914, 1915, 1915*t*
treatment for, 2712*b*
Toxic shock syndrome toxin-1, 1906
Toxicant-induced bilateral miosis, 683, 684*f*
Toxicants, 682, 683*t*
removed by hemodialysis, 698*t*
Toxicology, reference intervals, *e1t–e8t*
Toxidromes, 682, 683*t*
Toxin(s)
acute pancreatitis and, 970, 970*t*
primary testicular hypogonadism caused by, 1583
vitamin levels affected by, 1459
Toxin-mediated disease
diphtheria and, 1934
Staphylococcus aureus causing, 1906–1908
Toxocara canis, 2174
Toxocara cati, 2174
Toxocara spp., 1026*t*, 2174
Toxocariasis, 2174
Toxoid, administration of, 64
Toxoplasma gondii, 1026*t*, 2136, 2137*f*
prophylaxis for, 2309*t*
retinitis caused by, 2606
Toxoplasmic encephalitis, 2136, 2139, 2139*f*
Toxoplasmic retinitis, 2606
Toxoplasmosis, 2136–2141
clinical manifestations of, 2137–2138, 2138*t*
congenital infection in, 2137–2138
definition of, 2136–2141
diagnosis of, 2138–2139, 2138*t*
epidemiology of, 2136
human pathology findings of, 2136–2137
in immunocompetent patients, 2137, 2139
in immunocompromised patients, 2137, 2139, 2141
after organ transplantation, 2137, 2141
pathobiology of, 2136–2137
pathogen that causes, 2136, 2137*f*
in patients on immunosuppressive medications, 2137
in patients with HIV/AIDS, 2137
in pregnant women, 2140*b*
prevention of, 2140–2141
in primary infection, 2140–2141
prognosis of, 2141
reactivation disease, 2141
serologic tests for, 2138*t*
treatment of, 2112*t*, 2140*b*, 2140*t*
TPMT gene, 160*t*
Trabectedin (Yondelis), 1215*t*
Trace elements, 1451, 1457*t*
Trace metals, chronic poisoning of, 101
aluminum, 101*t*, 105, 105*b*
arsenic toxicity, 103
bismuth, 101*t*, 102*t*, 105, 105*b*
cadmium toxicity, 104
cobalt, 106, 106*b*
lead toxicity, 101
manganese, 101*t*, 107, 107*b*
mercury toxicity, 102
silver, 106, 106*b*, 106*f*
thallium, 106, 106*b*
zinc, 101*t*, 106, 107*b*
Tracheal plateau, 529*f*, 532
Tracheal stenosis, 532
flow-volume curve of, 529*f*
Tracheitis, 605, 605.*e1f*, 606*b*
Tracheobronchial amyloidosis, 1310
Tracheobronchitis, 700*b*
H. influenzae caused by, 1953
Tracheoesophageal fistulas, 913
Tracheostomy tubes, *Acinetobacter* in, 1973
Trachoma
clinical manifestations of, 2010
diagnosis of, 2010
epidemiology of, 2009–2010
prevention of, 2010
Traction alopecia, 2751, 2751*f*
Traction bronchiectasis, 575, 575.*e1f*
TRADD. *See* TNF receptor-associated death domain
Traditional Chinese medicine, 154
Tramadol, 136*b*, 138*t*, 139*t*
Trametinib (Mekinist), 1215*t*, 1251*t*
for melanoma, 1394*t*
Trandolapril, 266*t*, 451*t*
Trandolapril/verapamil, 451*t*
Tranexamic acid, for von Willebrand disease, 1183*b*
Trans fats, 57
dietary guidelines for, 57.*e3t*
Trans-sulfuration, 479.*e1f*, 1425*t*
Transabdominal ultrasound, 1050, 1051*f*
Transbronchial needle aspiration, 1331
Transcobalamin, 1426*t*
Transcortin (corticosteroid-binding globulin), *e1t–e8t*
Transcranial Doppler (TCD), strengths and weaknesses of, 2373*t*
Transcription activator-like effector nucleases (TALENs), 166, 178
Transcutaneous bilirubinometry, 994
Transcutaneous carbon dioxide measurement, 640
Transcutaneous electrical nerve stimulation (TENS), for fibromyalgia, 1819*b*
Transdermal nicotine patch, 2350*b*, 2351*t*
Transdiaphragmatic pressure, 620
Transduction, 175
Transepithelial transport, 730
Transesophageal echocardiography, 238, 238*t*, 239*f*
in aortic dissection, 440, 440*f*, 441*f*
in infective endocarditis, 416–417
Transfer factor, 530
Transferrin, *e1t–e8t*
Transfusion(s), 1199–1206
ABO/D compatibility of, 1201
adverse effects of
allergic transfusion reaction, 1202, 1202*b*
Babesia transmission, 1203
bacterial contamination, 1203
delayed hemolytic transfusion reaction, 1202
delayed serologic transfusion reaction, 1202
febrile nonhemolytic transfusion reaction, 1202
hepatitis B virus transmission, 1203
hepatitis C virus transmission, 1203
human T-cell lymphotropic virus, 1203
hypotensive transfusion reactions, 1202
post-transfusion purpura, 1203
septic reactions, 1203
syphilis transmission, 1203
transfusion-associated circulatory overload, 1202
transfusion-associated dyspnea, 1202
transfusion-related acute lung injury, 1202, 1202*b*
Trypanosoma cruzi transmission, 1203
West Nile virus transmission, 1203
Zika virus transmission, 1203
blood components of, 1199, 1199*t*
cryoprecipitate, 1199*t*, 1200, 1205
cytomegalovirus transmission via, 1200
granulocytes, 1200, 1205
for hemoglobinopathies, 1206
indications for, 1204, 1204*t*
massive, 1205
patient blood management, 1206
plasma, 1199*t*, 1200, 1204, 1204*t*
platelet
alloantibodies, 1171*b*
complications of, 1171*b*
components, 1200
indication, 1204, 1204*t*
prophylactic, 1171*b*
for thrombocytopenia, 1171*b*
red blood cell, 1199
cryopreservation of, 1200
indications for, 1204, 1204*t*
irradiation for, 1200, 1205
Transfusion(s) *(Continued)*
leukoreduction, 1205
modification of, 1199, 1205
pathogen reduction in, 1200, 1205
for septic shock, 673*b*
safety of, 1201, 1201*t*
for sickle cell disease, 1114*b*, 1206
whole blood, 1199
Transfusion-associated circulatory overload, 1202
Transfusion-associated dyspnea, 1202
Transfusion-associated graft-*versus*-host disease, 1203
Transfusion reactions
allergic, 1202, 1202*b*
delayed hemolytic, 1202
febrile nonhemolytic, 1202
hemolytic, 1092
hyperhemolytic, 1203
hypotensive, 1202
Transfusion-related acute lung injury (TRALI), 598, 599*b*, 1200, 1202, 1202*b*
Transgender, 1575
Transgender medicine, 1577–1580
clinical manifestations of, 1577
definition of, 1577–1580, 1577*t*
diagnosis of, 1577
epidemiology of, 1577
pathobiology of, 1577
prognosis for, 1580
treatment in, 1578*b*
Transgender men
hormone therapy for, 1578*b*, 1578*t*
surgeries for, 1578*b*
Transgender women
hormone therapy for, 1578*b*, 1579*t*
surgeries for, 1578*b*
Transient aplastic crisis, 2234
Transient elastography, for hepatic fibrosis, 990
Transient global amnesia, 2408
Transient incontinence, 827, 828*t*
Transient infection, Whipple disease and, 2070
Transient ischemic attack
as arterial thrombotic complications, 481
definition of, 2464
pathobiology of, 2464
prognosis of, 2473
secondary prevention after, 2473
stroke after, 2473
Transient neonatal myasthenia, 2589*t*
Transient receptor potential vanilloid 5 (TRPV5), 1654
Transjugular intrahepatic portosystemic shunt (TIPS), 1041*f*
Transjugular pressure, measurement of, 990
Translocator protein, 1581, 1581.*e1f*
Transmembrane cytoplasmic protein 43 gene, 288
Transplantation
bone marrow, for multiple myeloma, 1299*b*, 1301*t*
for bronchiectasis, 561*b*
Chagas disease and, 2128
of ex vivo differentiated human pluripotent stem cells, 173
heart-lung transplantation, 633
liver, 1044, 1044*f*, 1045*f*
for acute liver failure, 1044
for chronic liver failure, 1044
coagulation system and, 1043
complications of, 1047, 1047*f*
contraindications to, 1046*t*
for hepatocellular carcinoma, 1045
immunosuppression for, 1048, 1048*t*
indications for, 1044, 1045*f*
infectious complications of, 1047, 1048*f*
listing for, 1046, 1048*t*
long-term management for, 1049
metabolic disorders associated with, 1045
preoperative medical assessment for, 1046
preoperative psychosocial assessment for, 1046
procedure, 1046, 1046*f*, 1047*f*
recurrent hepatitis C after, 1014*b*
rejection in, 1048, 1048*t*
selection for, 1045, 1046*t*
surgical complications of, 1047
for Wilson disease, 1437*b*
lung, 632
bilateral, 632

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Transplantation *(Continued)*
complications of, 633
contraindication for, 632*t*
decision guide for, 632*t*
heart-lung transplantation, 633
indications for, 632, 632*t*
living donor lobar transplantation, 633
post-transplantation issues, 633
prophylaxis after, 633
recipients, evaluation of, 633
single-lung, 633
survival estimates, 634.*e1f*
types of procedures, 632
Transplantation immunology, 203–208
antigens in, 203, 204*t*
major, 1*t*–2*t*, 203, 204*t*, 204.*e1f*, 204.*e2f*, 204.*e2t*
minor, 205
other, 205
definition of, 203
graft-*versus*-host disease in
mechanisms of, 205
prevention of, strategies, 206, 206.*e2f*, 206.*e1t*
rejection in
mechanisms of, 205
prevention of, strategies, 207
Transportasome, 1810
Transposition of the great arteries
complete, 354, 355.*e2t*
congenitally corrected transposition, 354
Transsphenoidal hypophysectomy, 1487*b*
Transthoracic cardioversion and defibrillation, 340
Transthoracic echocardiography, 238, 238*t*, 416
Transthyretin (prealbumin), *e1t*–*e8t*
Transthyretin amyloid cardiomyopathy, 1309*b*
Transudates, 624–625
Transverse myelitis, 2406, 2508, 2509*b*, 2615
incomplete, 2500
Mycoplasma pneumoniae in, 2007
Transverse relaxation time (T2), in MRI, 1720, 1721*f*
Transverse sinuses, 2459
Trantas dots, 1674
Tranylcypromine, for depression, 2340*t*
TRAPS. *See* Tumor necrosis factor receptor-associated periodic syndrome
Trastuzumab (Herceptin), 167, 1215*t*, 1251*t*
for breast cancer, 1369*b*
cardiomyopathy due to, 288
for gastric adenocarcinomas, 1341*b*
Trastuzumab deruxtecan, 1251*t*, 1341*b*
Trastuzumab emtansine, 150, 1251*t*
Trauma, 381*t*
acute pancreatitis and, 970, 970*t*
causing subarachnoid hemorrhages, 2478
hypothalamic diseases associated with, 1480
hypothermia, 681
medical aspects of, 698
ocular, 2603
penetrating, pathogens and empirical therapy for, 2526*t*
severe mental illness and, 2683*t*
thrombosis and, 481
Traumatic brain injury, 2385
biomarkers for, 2387
clinical manifestations of, 2386, 2386*t*
diagnosis of, 2386–2387, 2386*t*
epidemiology of, 2385
imaging for, 2387, 2387*f*, 2387*t*
mild, 2388*b*, 2389*t*, 2390
moderate to severe, 2388*b*, 2390
pathobiology of, 2385
primary injury phase of, 2385
prognosis of, 2390
secondary injury phase of, 2386, 2386.*e1f*
treatment for, 2388*b*, 2389*t*
Traumatic pericarditis, 424*t*
Traumatic spinal epidural hematoma, 2391–2392, 2392, 2392*f*
Traumatic ulcers, 2621*t*
Travel
approach to the patient before and after, 1885–1891
travel-related vaccines, 1886*t*, 1887
fever associated with, 1890*t*
heart failure in, 265*b*
problems of, non-infectious, 1889
Travel-related vaccines, 1886*t*, 1887
Travelers
altitude illness in, 1889
blood-borne pathogen exposure risks, 1889
Travelers *(Continued)*
Chikungunya virus in, 1888, 1889.*e1t*, 1890*t*
Dengue fever in, 1888, 1889.*e1t*, 1890*t*
enteric fever in, 1885, 1889.*e1t*, 1890*t*
food precautions for, 1889
gastrointestinal diseases in, chronic, 1891*t*
HIV infection in, 1889
immunization for
cholera, 1886*t*, 1887
description, 1885
hepatitis A, 1886, 1886*t*, 1887
hepatitis B, 1886, 1886*t*, 1887
influenza, 1886*t*, 1887
Japanese encephalitis, 1886*t*, 1887
meningococcus, 1886*t*, 1887
polio, 1886*t*, 1887
rabies, 1886*t*, 1887
tetanus/diphtheria/acellular pertussis, 1886
typhoid, 1886*t*, 1887
update of, 1886
varicella, 1886, 1886*t*
verification of, 1886
yellow fever, 1886*t*, 1887
jet lag in, 1889
malaria chemoprophylaxis in, 1887, 1890*t*
malaria in, 2118, 2122
post-travel care for, 1889–1891
pretravel consultation for, 1885*t*
preventive behaviors for, 1888–1889
respiratory infections in, prevention of, 1889
SARS-CoV 2 in, 1888
sexually transmitted infections in, 1889
skin diseases in, protection against, 1889
swimming by, 1889
thrombosis in, 1889
water exposure by, 1889
water precautions for, 1889
Zika virus in, 1888, 1890*t*
Traveler's diarrhea, 925–926, 1888, 1888*t*
Escherichia coli and, 1961
Trazodone, for depression, 2340*t*
Treadmill testing, 362
Treanda. *See* Bendamustine
Treatment-induced neuropathy of diabetes, 2577
Treatment-related tumor flare, 1369*b*
TRECs. *See* T-cell receptor excision circles
TREM. *See* Triggering receptors expresses by myeloid cells
TREM2 gene, 2415
Trematode
clonorchiasis, 2166
fascioliasis, 2165, 2166*t*, 2168
infections, 2163
opisthorchiasis, 2166
paragonimiasis, 2167
Tremor
action, 2489
clinical manifestations of, 2489
definition of, 2489–2490
differential diagnosis of, 2490*t*
dystonic, 2493
essential, 2490
head, 2489
kinetic, 2489
physiologic, enhanced, 2489
postural, 2489
resting, 2484, 2489
vocal, 2652
Trench fever, 2000, 2001*f*, 2003*b*, 2003*t*, 2059
Trench foot, 680
Treponema carateum, 2021
Treponema pallidum, 2014, 2649
chancroid and, 1951
sexually transmitted anorectal diseases and, 983
Treponemal tests, 2018
Tretinoin, 2698
TRH. *See* Thyrotropin-releasing hormone
Triad syndrome, 821
Triamterene, 451*t*
for hypervolemia, 736*b*, 737*t*
Triamterene/HCTZ, 451*t*
Triazolam, for anxiety disorders, 2344*t*
Trichiasis, 2601
Trichinella spiralis, 2175
Trichinellosis, 2174
definition of, 2174–2175
diagnosis of, 2175
epidemiology of, 2175
pathobiology of, 2175, 2175*f*
prevention of, 2175
prognosis for, 2175
in travelers, 1889.*e1t*
treatment of, 2175*b*
Trichodynia, 2748
Trichodysplasia spinulosa polyomavirus, 2228*t*, 2232
Trichoepitheliomas, 2730
Trichomonas vaginalis, 1879, 1882, 2154, 2154*f*
Trichomoniasis, 1882, 1883*b*, 2154, 2154*b*
Trichostrongylus spp., 2170*t*, 2173
Trichotillomania, 2747*t*, 2749, 2750*f*
Trichrome staining, for enteric infection, 1870*t*
Trichuriasis, 2171, 2172*b*
Trichuris trichiura, 2170*t*, 2172
Triclabendazole, for helminthic diseases, 2112*t*
Tricuspid atresia, 354
Tricuspid regurgitation, 410–411
definition of, 410–411
diagnosis of, 411
prognosis of, 411*b*
treatment of, 265*b*, 411*b*
Tricyclic antidepressants (TCAs)
for chronic pain, 138*t*
for depression, 2340*t*
for fibromyalgia, 1819*b*
screening for, 689*t*
Trifluoperazine, for psychotic disorders, 2346*t*
Trigeminal autonomic cephalalgias, 2381
Trigeminal neuralgia, 2384, 2384*b*, 2578–2579
Trigeminocervical complex, 2376
Trigger finger, 1745, 1745*b*, 1746*f*
Triggering receptors expresses by myeloid cells (TREM), 183
Triglycerides, *e1t*–*e8t*, 970, 1405, 1405*f*, 1405.*e1f*, 1410.*e1t*
Triiodothyronine, 1497, 1504
free (FT_3), *e1t*–*e8t*
total (T_3), *e1t*–*e8t*
Trimethobenzamide, for nausea and vomiting, 863*t*
Trimethoprim
dosage of, 1895*t*
mechanism of action, 1895*t*
resistance mechanisms, 1893*t*
for urinary tract infection, 1876*t*, 1877*t*
Trimethoprim-dapsone, for *Pneumocystis* pneumonia, 2106*t*
Trimethoprim-sulfamethoxazole (TMP-SMX)
for bacterial meningitis, 2518*t*
for cellulitis, 2740*b*
for HIV/AIDS, opportunistic infections associated with, 2309*t*
for nocardiosis, 2072–2073, 2074*b*
for plague, 1991*b*, 1992*t*
for *Pneumocystis* pneumonia, 2106*t*, 2108*t*
for *Stenotrophomonas maltophilia*, 1975*b*
for *Streptococcus pneumoniae* pulmonary infections, 1912.*e1t*
toxicities of, 1901*t*
for toxoplasmosis, 2112*t*, 2140*b*, 2140*t*
for urinary tract infection, 1876*t*, 1877*t*
Tripeptide thyrotropin-releasing hormone (TRH), 1505
Triple-negative breast cancer, 1369
Triple phosphate stones, 804
Tripod sign, 639, 639.*e2f*
Trisenox. *See* Arsenic trioxide
Trismus, 1928
Trisomy 21. *See* Down syndrome
Trisomy X, 1600
Trochanteric bursitis. *See* Greater trochanter pain syndrome
Trochlear nerve palsy, 2618
Trodelvy. *See* Sacituzumab govitecan-hziy
Trogocytosis, amebic, 2146
Tropheryma whipplei, 417*t*, 1821, 2069
Trophozoites, 2141
Tropical endomyocardial fibrosis, 296
Tropical fever virus, 2275*t*
Tropical myositis, 1903
Tropical sprue, 937, 1870*t*
Troponin(s)
elevated, 383, 383*t*
in heart failure, 260
measured by a highly sensitive assay (hs-cTn), 260.*e1t*
postoperative, 2676
Troponin-I, *e1t*–*e8t*
Troponin-T, *e1t*–*e8t*
Trospium, 824*t*
Trousseau syndrome, 1170, 1341, 1355, 1648
TRPV5. *See* Transient receptor potential vanilloid 5
True secretory diarrhea, 930*f*, 939
Truncal radiculopathy, 2577
Trunk, disorders of, occupational and environmental, 86*t*
Truseltiq. *See* Infigratinib
Trypanosoma brucei, 2126
Trypanosoma brucei gambiense, 2124
Trypanosoma brucei rhodesiense, 2123–2124, 2124, 2125*f*
Trypanosoma cruzi, 1203, 2065*t*, 2126, 2127*f*
Trypanosomiasis, 2115
in travelers, 1891*t*
treatment of, 2112*t*
Tryptase, serum, 1675, 1693
α-Tryptasemia, hereditary, 1693
TSH. *See* Thyroid-stimulating hormone
TSH-secreting pituitary adenoma, 1497
radiographic evaluation of, 1511*t*
TSH-suppressive levothyroxine, for thyroid cancer, 1517*b*
TSHomas, 1497
TSLP. *See* Thymic stromal lymphopoietin
Tubal pregnancy, 1604
Tube feeding, 1445*b*
Tuberculin skin test, 2039
Tuberculoid leprosy, 2048, 2049*t*
Tuberculoma, in travelers, 1889.*e1t*
Tuberculosis (TB), 2031–2044, 2621*t*
active, 2039, 2040*b*
cavitary, 2036*f*
central nervous system, 2037
characteristics of, 2270*t*
clinical manifestations of, 2034–2038
cystic fibrosis *versus*, 558
definition of, 2031–2043
diagnosis of, 2038–2040
drug-resistant, treatment of, 2040*b*
epidemiology of, 2032–2033, 2032*f*
extrapulmonary, 2035, 2040, 2040*b*
genitourinary, 2037
human immunodeficiency virus and, treatment of, 2040*b*
immunologic manifestations of, 2038
intestinal, 2037
latent, 2034
skin testing for, 2038
treatment of, 2040*b*, 2041*t*
lymphadenitis, 2037
miliary, 2035, 2037*f*
ocular involvement of, 2606
osteoarticular, 2037, 2038*f*
outcomes after, spectrum of, 2035*f*
pathobiology of, 2033, 2034*f*
pathogen of, 2031–2032
pericarditis, 2037
peritonitis, 2037
pleural, 2035, 2036*f*
prevention of, 2043
primary, 2034, 2036*f*
prognosis of, 2043
pulmonary
clinical manifestations of, 2034, 2036*f*
diagnosis of, 2039
risk factors for, 2033*t*
in travelers, 1889.*e1t*
treatment of, 2040*b*, 2041*t*, 2042*t*, 2043*t*
weight loss and, 860*t*
Tuberculous arthritis, 1808, 1808*b*
Tuberculous meningitis
cerebrospinal fluid findings in, 2374*t*
in travelers, 1889.*e1t*
Tuberculous pericarditis, 426*t*, 431
Tuberculous peritonitis, 957
Tuberculous pleural effusion, 626, 626*b*
Tuberous sclerosis, 583, 809*t*, 814, 814*b*
ash-leaf macule of, 2692*t*
Tuberous sclerosis complex, 2549, 2549*b*, 2550*t*, 2551*f*, 2551*t*
Tubular adenomas, 1349
Tubular cell cast, 722
Tubular necrosis, 720
Tubulointerstitial disease, 720, 728, 728*t*
autosomal dominant, 791
chronic kidney disease and, 833*t*
interstitial nephritis. *See* Interstitial nephritis
Tubulointerstitial nephritis, with uveitis syndrome, 793
Tubulointerstitial nephropathy, in human immunodeficiency virus infection, 793
Tubulovillous adenomas, 1349
Tucatinib (Tukysa), 1215*t*
Tukysa. *See* Tucatinib
Tularemia, 99, 1985–1988
characteristics of, 2270*t*
clinical manifestations of, 99, 1986–1987

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Tularemia *(Continued)*
definition of, 1985–1988
diagnosis of, 99, 1987
differential diagnosis of, 1987
epidemiology of, 1986, 1986.e1*f*
glandular disease caused by, 1986
oculoglandular disease caused by, 1986
oropharyngeal disease caused by, 1986
other clinical presentations, 1987
pathobiology of, 1986
pathogen of, 1985–1986
pneumonic disease caused by, 1986–1987
prevention of, 1988
prognosis for, 99*b*, 1988
treatment of, 99*b*, 1987*b*
typhoidal disease caused by, 1986
ulceroglandular disease caused by, 1986, 1987*f*
vectors of, 1986
Tumor(s)
cardiac, 296, 297*f*, 297*t*
of hypothalamus, 1479
intracavitary, 297
intramyocardial, 298
myocardial, 296
orbital, 2613
of skin, 2729, 2729*t*
Tumor-associated hypoglycemia, 1237, 1555
Tumor genetics, drug development and, 133
Tumor-induced osteomalacia, 1649
Tumor lysis syndrome, 1240, 1240*b*, 1262
Tumor mutation burden, 1249
Tumor necrosis factor-α (TNF-α), 151, 151*t*, 184–185
Tumor necrosis factor (TNF) inhibitors, for rheumatoid arthritis, 1757*t*
Tumor necrosis factor receptor-associated periodic syndrome (TRAPS), 1731*t*, 1733*t*, 1734, 1734*b*
Tumor plop, 298
Tumor suppressor genes, 1247
DNA alterations in, 1247, 1248*f*
in lung cancer, 1330
Tungiasis, cutaneous or mucocutaneous, in travelers, 1889.e1*t*
Tuning fork tests, 2641
Turcot syndrome, 1348
Turf toe, 1748, 1748*b*
Turner syndrome, 347, 967, 1574, 1600
TV. *See* Tidal volume
24-hour urine, collection of, for Cushing disease, 1494
Tykerb. *See* Lapatinib
Tylosis palmaris et plantaris, 1337
Tympanic membrane thermometer, 33
Type I interferon-associated autoinflammatory diseases, 1735
Type II error, 36
Typhlitis, description of, 1860
Typhoid fever
azithromycin for, 1979*b*
characteristics of, 2270*t*
immunization for, 66*t*, 83
vaccine, for traveler, 1886*t*, 1887
Tyrosine, catecholamine synthesis from, 1529
Tyrosine kinase inhibitors
cardiomyopathy due to, 288
for chronic myeloid leukemia, 1274*b*
toxicities of, 1274*b*, 1275*t*
Tyrosinemia
type I, 816*t*, 1398*t*, 1402*t*
type II, 1398*t*, 1402*t*
Tysabri. *See* Natalizumab
Tzanck smear, 2690

U

U wave, 228
Ublituximab (Briumvi), for multiple sclerosis, 2505*t*
"Ugly duckling" sign, 1391
UGT1A1 gene, 160*t*, 995
Ukoniq. *See* Umbralisib
Ulcer(s), 2738
anastomotic, 913
chancroid and, 1951
diabetic foot, 1892*t*
marginal, 913
pressure, in older adults, 114
Ulceration, 2687.e4*t*
Ulcerative colitis
acute flare of, 945*b*
algorithm for, 948*f*
budesonide for, 945*b*, 946*t*
budesonide MMX for, 945*b*
clinical characteristics of, 942*t*
colectomy for, 945*b*
colon cancer in, 945*b*
complications of, 945*b*
definition of, 941
diagnosis of, 943
dysplasia in, 945*b*
early, 942
endoscopy of, 944–945, 944*f*
epidemiology of, 941
extensive, 945*b*
maintenance therapy for, 945*b*
medical management of, 945*b*
medical therapy for, 945*b*
pathology of, 942
prognosis for, 950
radiology of, 945
severe, 945*b*
surgical therapy for, 945*b*
symptoms of, 943
Ulcerative jejunoileitis, 955
Ulcerative lesions, of granuloma inguinale, 2004, 2004*f*
Ulceroglandular disease, 1986, 1987*f*
Ulesfia lotion, 711*b*
Ultradian rhythms, 1478
Ultrasonography, 520
abdominal, for acute pancreatitis, 971
for abdominal pain, 857–858
for acute kidney injury, 726, 726*f*
for acute pancreatitis, 970
for autosomal dominant polycystic kidney disease, 811–812, 811*f*
for chronic kidney disease, 837
compression, 484, 485*f*
Doppler, 236
continuous-wave, 236
pulsed, 236
endobronchial, 630, 630.e2*f*
endoscopic, 876, 974
for gallbladder cancer, 1054
in gastroenterology, 869, 869*f*, 870*f*
for kidney stones, 805
for liver disease, 990
for pelvic inflammatory disease, 1949
for rheumatic disease, 1718, 1719*f*, 1720*f*
strengths and weaknesses of, 2373*t*
testicular, for testicular cancer, 1383
for thyroid disease, 1505
Ultrasound elastography (USE), 1720
Ultraviolet radiation, 95
as hazard, 88*t*
for skin cancers, 2701
Umbilical cord blood hematopoietic stem/progenitor cells, 1207
Umbilical hernia, 952*b*
Umbralisib (Ukoniq), 1215*t*
Umeclidinium, 553*t*
Uncal herniation, 2385
Uncinaria stenocephala, 2170
Unconjugated bilirubin, 994
Unconjugated hyperbilirubinemia, 996
Undervirilization, 1570*t*
Undervirilized male, biochemical evaluation of, 1575
Undifferentiated inflammatory polyarthritis, 1710
Undifferentiated spondyloarthropathy, 1710
Undulant fever. *See* Brucellosis
Unfractionated heparin, 387*t*, 501, 501*t*
adverse effects of, 502
dosage and monitoring of, 502
effect of, reversing, 502
in pregnancy, 1623*b*
Unilateral obstruction, of pulmonary artery, 522
Unilateral vocal fold paralysis, 2653
Unintended pregnancy, 1611
Unintentional injuries, in adolescents, 110, 110*t*
Unipolar disorders, 2337
United States
acute pancreatitis in, 969
amebiasis in, 2146
arterial hypertension in, 444–445
cardiovascular disease burden, 219
Chagas disease in, 2126
United States *(Continued)*
demographic changes in, 17
endoscopy in, 875
HIV/AIDS in, 2288*f*, 2290, 2290*f*, 2291*f*
routine newborn screening for cystic fibrosis in, 557–558
tuberculosis in, 2032
United States Preventive Services Task Force
on preventive health care, 111
preventive services for older adults, 119, ~~119.e1*t*~~
Univentricular heart, 354
Universal screening, 117
Unresponsive wakefulness syndrome, 2441
clinical manifestations of, 2441
diagnosis of, 2441, 2441*t*
epidemiology of, 2441
pathobiology of, 2441
treatment of, 2441*b*
Unstable hemoglobinopathies, 1116
Upadacitinib (Rinvoq), 153*t*
for inflammatory bowel disease, 945*b*, 946*t*
for rheumatoid arthritis, 1756*t*
for total knee arthroplasty, 1830.e1*t*
Upper aerodigestive tract
anatomy of, 2648, 2648*f*
infectious diseases of, 2648–2651
Upper airway
allergy of, 1674
irritation, occupational and environmental, 86*t*
thermal injury
clinical manifestations, 595
diagnosis, 595
pathogenesis, 595
prognosis, 595
treatment, 595*b*
Upper gastrointestinal bleeding, 882
acute management of, 883*b*
AIMS65 scoring system for, 921*t*
Blatchford system for, 921*t*
clinical manifestations of, 882, 882*f*, 882*t*
diagnosis of, 882
endoscopic therapy for, 883*b*, 883*t*
Glasgow-Blatchford score for, 883*b*, 883*t*
management of, 884*f*
medical therapy for, 883*b*
peptic ulcer disease causing, 882
Rockall scoring system for, 921*t*
treatment of, 883*b*
Upper gastrointestinal tract, systemic sclerosis involvement of, 1778
Upper GI endoscopy, 875
indications for, 875, 876*t*
instrument for, 875
preparation for, 875
procedure for, 875, 877*f*
Upper mesenteric ischemia, 916, 916*f*
Upper zone lung disease, 523, 523*t*
Upshaw-Schulman syndrome, 1177
Urapidil, for hypertensive emergencies, 460*t*
URAT1, 1810
Urate, 1810
crystals, 723, 725*f*, 1813*f*
overproduction of, 1811
renal, underexcretion in, 1810, 1810.e1*f*
Urea, for hyponatremia, 741*b*
Urea cycle, disorders of, 1402, 1403*f*
clinical manifestations of, 1402
diagnosis of, 1402
prognosis of, 1403
treatment of, 1402*b*
Urea nitrogen, e1*t*–e8*t*
Urea nitrogen/creatinine ratio, e1*t*–e8*t*
Ureaplasma arthritis, 1808
Ureaplasma spp., 2008, 2008*b*, 2008*t*
Uremic acidosis, 757
Uremic hyperparathyroidism, 1657, 1658*b*
Uremic lung, 784*t*
Uremic pericarditis, 426*t*, 431
Uremic syndrome, 836
Uremic toxins, 841
Ureteric anomalies, 819
Ureterocele, 819
Ureteropelvic junction obstruction, 818
Ureterosigmoidostomies, 760
Ureters, cancers of, 1367
Urethral obstruction, 828
Urethritis, 1947
characteristics of, 1880
Chlamydia trachomatis causing, 2010
Urethritis *(Continued)*
clinical manifestations of, 1880, 1947, 1947*f*
diagnosis of, 1880, 1947–1948, 1948
gonococcal, organisms causing, 1879*t*
nongonococcal, organisms causing, 1879*t*
treatment of, 1880*b*, 1880*t*
Urge incontinence, 827
bladder relaxant agents for, 831*t*
clinical manifestations of, 828
treatment of, 829*b*, 830*t*
in women, 1609
Uric acid, e1*t*–e8*t*, 1810
secretion, regulation of, 754–755
stones, 804
Uridine 5'-diphospho-glucuronosyltransferase, 995
Urinalysis
for benign prostatic hyperplasia, 822
chronic interstitial nephritis findings, 793
for prostatitis, 825
for renal disease, 721–724, 722*t*
Urinary alkalinization, for acute poisoning, 691*b*
Urinary antigen testing, for legionellosis, 1998
Urinary buffers, 754
Urinary histamine, 1693
Urinary incontinence, 827–831
clinical evaluation of, 829*t*
definition of, 827–831
diagnosis of, 829–830
epidemiology of, 827
functional incontinence, 828
lower urinary tract and, 827–828
in men, 830
mixed incontinence, 829
in older adults, 114, 118
pathobiology of, 827–828
prevention of, 830
prognosis for, 831
transient incontinence, causes of, 827, 828*t*
treatment of, 829*b*
in women, 1609
Urinary obstruction, 1875*b*
chronic interstitial nephritis caused by, 794
Urinary oxalate, 803
Urinary retention
psychotropic medications and, 2678*t*
severe mental illness and, 2683*t*
Urinary sediment, e1*t*–e8*t*
Urinary system, age-related changes in, 121
Urinary tract
abnormalities of, 818
development of, 818
lower
abnormalities of, 821
causes of established incontinence related to, 827
Urinary tract infection (UTI), 1873–1878
Acinetobacter causing, 1973
bacterial species that cause, 1892*t*
candidiasis causing, 2091
catheter-associated, 1862*t*, 1866, 1873
clinical manifestations of, 1874
clinical presentation of, 1873
complicated, 1873, 1873*t*, 1875*b*
control of, 1877–1878
definition of, 1873–1878
diagnosis of, 1874–1875
differential diagnosis of, 1875
in elderly, 1875*b*
enterococcus causing, 1920
Escherichia coli causing, 1873, 1965
etiology of, 1874, 1874*t*
follow-up for, 1875*b*
imaging of, 1875
laboratory findings of, 1874–1875
pathobiology of, 1873–1874
in pregnancy, 1878
prevention of, 1877–1878, 1877*t*
prognosis for, 1878
Pseudomonas infections causing, 1969, 1970*b*
pyuria associated with, 1875
risk factors for, 1873
screening for, 1877
symptoms of, 1874*t*
treatment of, 1875*b*, 1876*f*, 1921*b*, 1922*t*, 1966*b*
uncomplicated, 1873
urine culture for, 1875*t*

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Urine
  macroscopic appearance of, 722*t*
  sediment of, 722–724
  specific gravity of, 721
  testing of, for infection, 1836
Urine culture, for urinary tract infection, 1875*t*
Urine dipstick, for renal disease, 721–722
Urine free cortisol, in Cushing syndrome, 1522
Urine immunoelectrophoresis, for glomerular syndromes, 727
Urine porphobilinogen testing, for porphyrias, 1433
Urine sediment, evaluation of, 837
Urodynamic methods, for prostatitis, 825
Urogenital sinus, 1572*f*
Urolithiasis, 1874
Urologic disease, sickle cell disease and, 1114*b*
Urologic infection, *H. influenzae* caused by, 1953
Uroporphyrinogen III, 1429.*e1f*
Urorectal fold, 818
UROS-associated CEP, 1428*t*
Urosepsis
  antimicrobials for, 1877*t*
  clinical manifestations of, 1874
  description of, 1873
  symptoms of, 1874*t*
  treatment of, 1875*b*
Urothelial cancer, BK polyomavirus-associated, 2229, 2230*b*
Urothelial tumors, 1365–1366
Ursodeoxycholic acid, for primary sclerosing cholangitis, 1058*b*
Urticaria, 1673*t*, 1687, 2692*t*, 2724–2725
  accompanied by angioedema and anaphylaxis, 2725*t*
  classification of, 1690*t*
  clinical manifestations of, 1687, 1688*f*, 2725
  definition of, 1687, 2724–2725, 2725*f*, 2725*t*
  diagnosis of, 1688, 1689*f*, 2725, 2726*f*
  epidemiology of, 1687, 2724
  familial cold, neutrophilia and, 1142
  histamine-induced, 1687
  illustration of, 2691*t*
  like eruptions and reactive erythemas, 2725*t*
  pathobiology of, 1687, 2724–2725
  prevention of, 1689
  prognosis of, 1689
  treatment of, 1689*b*, 2726*b*, 2726*t*
Urticaria pigmentosa, 1700*f*, 2725
Urticarial vasculitis, 2715
  hypocomplementemic, 1798
U.S. hurricane Katrina, climate-related hazards, 91*t*
USE. *See* Ultrasound elastography
Ustekinumab (Stelara), 151
  for inflammatory bowel disease, 946*t*
  for psoriatic arthritis, 1765*b*
  for total knee arthroplasty, 1830.*e1t*
Usutu virus, 2276*t*
Uterine carcinosarcomas, 1378
Uterine fibroids, 1382, 1382*b*
Uterine serous carcinomas, 1379
UTI. *See* Urinary tract infection
Utility, 39
Uveal tract, malignant melanoma of, 2612
Uveitis, 1736, 2327*t*, 2604
  diagnosis of, laboratory methods for, 2003*t*
  in sarcoidosis, 601–602

V

V2 vasopressin receptor, endocrine diseases caused by, 1475*t*
Vaborbactam, 1845*t*
Vaccinations. *See also* Immunization
  bacterial meningitis, 2519
  for cancer, 1246–1247
  for COVID-19, 2218*t*, 2219
  for disseminated gonococcal infection, 1950
  for heart failure, 275*t*
  for hepatitis A, 1004
  for hepatitis B, 1006
  hesitancy, 2223
  for human papillomavirus, 2243
  for influenza, 2201, 2201*t*, 2202.*e1t*
  for measles, 2223
  for meningococcal disease, 1944
  for mumps, 2227
  for older adults, 119
  for orthopoxvirus, 2240*b*
  pneumococcal, 541*b*
  for rubella, 2225
Vaccinations *(Continued)*
  for seasonal influenza, 541*b*
  tetanus toxoid, 1929
Vaccine Adverse Event Reporting System, 76
Vaccine-derived polioviruses, circulating, 2257
Vaccines
  administration of, 64
  for amebiasis, 2149
  anaphylaxis caused by, 1692
  for certain destinations, 1887
  consideration of, for world travelers, 1886–1887
  for human papillomavirus, 1884
  for international travelers, 83
  for possible bioterrorism agents, 83
  reactions to, 1698, 1698*t*
  travel-related, 1886*t*, 1887
Vaccinia
  autoinoculation, of eye, 2238*f*
  bovine-associated, 2238
  clinical manifestations of, 2238
  epidemiology of, 2236
  generalized, 2238
  immunization for, 65*t*
  post-vaccination, 2238
  progressive, 2238
Vaccinia immune globulin (VIG), 2240*b*
VACTERL syndrome, 818
Vacuolated lymphocytes, 1074*t*
Vacuoles, E1 ligase, X-linked, autoinflammatory, somatic (VEXAS) syndrome, 1731*t*
Vagal impairment, 2554
Vagina
  atresia, 1574
  menstrual cycle-related changes in, 1595
Vaginal protozoa, 2112*t*, 2115
Vaginal ring, 1615
Vaginal symptoms, 1630*b*, 1632*t*
Vaginismus, 1604
Vaginitis
  characteristics of, 1882–1883
  organisms causing, 1879*t*
Vagus nerve, 2553
Valacyclovir
  for herpes simplex virus infections, 2246
  for herpesvirus infections, 2186, 2187*t*
  for skin diseases, 2699
  for zoster, 2249*b*
Valganciclovir
  for cytomegalovirus, 2252, 2252*b*
  for herpesvirus infections, 2186, 2187*t*, 2188*t*
Valproate, for seizures, 2434*t*
Valproic acid, e10*t*–e11*t*
  toxicity, 690*t*, 698*t*
Valsartan, 451*t*
  for acute STEMI, 384*b*, 391*t*
  for heart failure, 266*t*
Valsartan/amlodipine/HCTZ, 451*t*
Valsartan/HCTZ, 451*t*
Value, 46
Valvular heart disease, 400, 2663
  echocardiographic findings, 242*t*
  heart failure due to, 265*b*
  rheumatic, 400
  severe, 401*t*
Valvular pulmonary stenosis, 351, 351*b*
Valvular regurgitation
  echocardiographic findings, 242*t*
  evaluation of, 240
Valvular stenosis
  echocardiographic findings, 242*t*
  measurement of, 239–240, 241*f*
Van Buchem disease, 1666–1667
Vanadium pentoxide, 88*t*
Vancomycin, e10*t*–e11*t*
  for anthrax exposure, 97*b*
  for bacterial meningitis, 2518*t*
  characteristics of, 1900
  for *Clostridioides difficile*, 1925–1926, 1925*b*
  dosage of, 1895*t*
  mechanism of action, 1895*t*
  for methicillin-resistant *Staphylococcus aureus*, 1905
  pharmacokinetic parameters for, 127.*e1t*
  for pneumonia, 613*t*, 616*t*
  reactions to, 1698*t*
  in renal failure, 129.*e1t*
  resistance mechanisms, 1893*t*
  for *Streptococcus pneumoniae* pulmonary infections, 1912.*e1t*
  toxicities of, 1901*t*
Vancomycin-resistant enterococci
  E. faecium causing, 1920
  epidemiology, 1920
  treatment of, 1921*b*
Vandetanib (Caprelsa), 1215*t*
Vanillylmandelic acid (VMA), *e1t*–*e8t*
Vanishing bile duct syndromes, 1059–1060
Vanishing white matter disease, 2510
Vaping, in adolescents, 113
Vaping-associated lung disease (E-VALI), 2352
Vapor inhaler, for tobacco dependence, 2351*t*
Vaptans
  for hypervolemia, 737*t*
  for hyponatremia, 741*b*
Vardenafil, 364*b*
  for erectile dysfunction, 1589
Varenicline
  for spinocerebellar ataxia, 2497*b*
  for tobacco dependence, 2351*t*
Varenicline tartarate, for tobacco dependence, 2350*b*
Variability, 36
Variable-vessel vasculitides, 1792*t*, 1798–1799
Variant angina, 368
Variant-specific proteins (VSPs), 2144
Variceal hemorrhage
  cirrhosis and, 1036, 1038, 1038*t*
  diagnosis of, 1039
  treatment of, 883*b*, 1040*b*, 1041*f*
Varicella, 2720–2721, 2721*b*, 2721*f*
  diagnosis of, 2249
  epidemiology of, 2248
  immunization for, 65*t*, 66*t*, 76.*e1t*, 77*f*, 78*f*
  pathobiology of, 2248
  postexposure prophylaxis, 2250
  prevention of, 2249–2250
  prophylaxis for, 2309*t*
  treatment of, 2249*b*
  vaccination for, 1886, 1886*t*, 2249
Varicella immune globulin. *See* VariZIG
Varicella-zoster virus, 2247–2250, 2532*t*, 2621*t*
  antiviral therapy for, 2187*t*
  characteristics of, 2270*t*
  clinical manifestations of, 2248–2249
  definition of, 2247–2250
  diagnosis of, 2249
  disseminated, 2695*f*
  epidemiology of, 2248
  immunization for, 76.*e1t*, 77*f*, 78*f*, 83
  pathobiology of, 2248
  as pathogen, 2247
  prevention of, 2249–2250
  prognosis of, 2250
  treatment of, 2249*b*
Varices
  cirrhosis and, 1036
  diagnosis of, 1039
  treatment of, 1040*b*
Varicose veins, 491*f*, 2692*t*
Variegate porphyria (VP), 1428*t*
Variola major, 98
Variola minor, 98
Variola sine eruptione, 2237, 2237*t*
VariZIG, 2250
Vascular diseases
  in acute kidney injury, 773
  chronic kidney disease and, 833*t*
  of gastrointestinal tract, 959
    acute mesenteric ischemia as, 959
    angioectasia as, 965
    aortoenteric fistulas as, 967
    Budd-Chiari syndrome as, 968
    celiac artery compression syndrome as, 967, 967*f*
    chronic mesenteric ischemia as, 963, 963*f*
    colon ischemia as, 964, 964*t*, 965*f*
    Dieulafoy lesion as, 966
    ectasias as, 967
    hemangiomas as, 967
    hepatic and splenic, 968
    hepatic and splenic arterial disease as, 969
    hereditary hemorrhagic telangiectasia as, 967
    intestinal ischemia as, 959
    portal vein thrombosis as, 968, 968*b*
    radiation proctopathy as, 968, 968*f*
    splenic vein thrombosis as, 968
    superior mesenteric artery syndrome as, 967
    vascular anomalies and disorders as, 965
    vasculitis as, 965
  of kidney, 728
  in systemic sclerosis, treatment of, 1781*b*
Vascular endothelial growth factor (VEGF), 152
Vascular hemorrhagic disorders
  acquired, 1186
  hereditary, 1186
Vascular injury, platelet activation at, 1165
Vascular insufficiency, 2645–2646
Vascular lesions, 2731–2734
Vascular malformations, brain, 2482, 2482*b*
Vascular myelopathy, 2405, 2406*b*
Vascular parkinsonism, 2485*t*
Vasculitic neuropathies, 2573–2574, 2574*b*, 2574*t*
Vasculitides, 1791
  antineutrophil cytoplasmic antibody-associated, 1796
  associated with probable etiology, 1792*t*
  associated with systemic disease, 1792*t*
  of central nervous system, 1799, 1800*t*
  classification of, 1791–1792
    considerations in, 1791–1792, 1792*t*
    by vessel size, 1791–1792, 1792*t*
  definition of, 1791–1795, 1792*t*
  diagnosis of, 1794, 1794*t*
  epidemiology of, 1792, 1793*t*
  immune complex-mediated, 1793, 1798
  large-vessel, 1792*t*, 1793, 1795
  medium-vessel, 1792*t*, 1793, 1795
  pathobiology of, 1792–1794, 1793*t*
  pathophysiology of, 1792–1794
  prognosis of, 1795
  selected single-organ, 1799
  single-organ, 1792*t*
  small-vessel, 1792*t*, 1793, 1796–1798
  treatment for, 1794*b*
  variable-vessel, 1792*t*, 1798
Vasculitis, 728, 965, 1708, 2714, 2715*f*, 2734
  aortic, 442.*e1f*, 443
  diagnosis of, 2714–2715, 2714*t*, 2714.*e1f*
  large vessel, 965
  medium vessel, 965
  small vessel, 965
  stroke caused by, 2470.*e1t*, 2472
  thrombocytopenia and, 1179
  treatment for, 2715*b*
  vision loss caused by, 2616*t*
Vasculitis-associated rapidly progressive glomerulonephritis, 785
Vasculopathy
  in systemic lupus erythematosus, 1769
  in systemic sclerosis, 1776
Vasculoproliferative disease, 2001*t*, 2002
Vasectomy, 1617
Vaso-occlusive crises, 1113
Vasoactive agents, for shock, 662*b*
Vasoactive intestinal peptide (VIP), prolactin secretion regulated by, 1490
Vasodilators
  mechanism of action of, 455
  side effects of, 453*t*, 455
Vasomotor tone, shock and, 658
Vasopressin, 730
  adrenocorticotropic hormone and, 1499
  for advanced cardiac life support, 315*f*
  osmotic and volume regulation in, interaction of, 1499
  pressure and, 1499
  regulation of osmolality and, 1499, 1499*f*, 1499.*e1f*
  for shock, 662*b*, 664*t*
  volume regulation and, 1499
Vasopressors
  for cardiogenic shock, 667*b*
  for shock, 662*b*, 664*t*
Vasospasm, vision loss caused by, 2616*t*
Vasospastic (or Prinzmetal) angina, 357
Vasovagal hypotension, 394
Vasovagal syncope, 304, 1694
VDRL test. *See* Venereal Disease Research Laboratory test
Vectibix. *See* Panitumumab
Vedolizumab, 152, 945*b*, 946*t*
Vegetable dusts, 88*t*
Vegetables, dietary guidelines for, 57.*e3t*
Vegetative state, 2441
  clinical manifestations of, 2441
  diagnosis of, 2441, 2441*t*
  epidemiology of, 2441
  pathobiology of, 2441
  treatment of, 2441*b*
VEGF. *See* Vascular endothelial growth factor
Velcade. *See* Bortezomib

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Vellus follicles, 2747
Velocardiofacial syndrome, 1679*t*
Velocity-time integral, 238
Vemurafenib (Zelboraf), 133, 1215*t*, 1251*t*, 1394*t*
Venclexta. *See* Venetoclax
Venereal Disease Research Laboratory (VDRL) test, 1881
Venereal infections, 2622
Venetoclax (Venclexta), 1215*t*
  for chronic lymphocytic leukemia, 1269*b*, 1269*t*, 1270*t*
Venezuelan equine encephalitis virus, 2276*t*, 2283, 2283*b*
Venlafaxine
  for cataplexy, 2449*t*
  for chronic pain, 138*t*
  for depression, 2340*t*
  for hot flashes, 1631*t*
Veno-occlusive disease. *See* Sinusoidal obstruction syndrome
Venom
  clinical effects of, 707*t*
  description of, 704
  immunotherapy, for mastocytosis, 1703*b*
Venomous arthropods, 710.*e1f*
Venomous insects, 711–712
Venomous mollusks, 712
Venomous snakes, 708.*e1f*
Venomous stingrays, 712
Venous air embolism, 491–492, 492*b*
Venous oxygen content (Cvo_2), 640
Venous pressure, abnormalities of, 214*t*
Venous sinus thrombosis, 2528
Venous sinuses, 2529*f*
Venous system, 2459, 2461*f*, 2462*f*
Venous thromboembolism (VTE), 1170
  anticoagulation for, 487*b*
  blood tests of, 486
  brain tumors, 1312*b*
  cancer-associated, 487*b*
  clinical manifestations of, 483, 483*f*, 483*t*
  compression ultrasonography of, 484, 485*f*
  computed tomographic pulmonary angiography of, 484, 486*f*
  contrast venography of, 484, 486*f*
  D-dimer tests for, 483
  definition of, 482
  diagnosis of, 483, 484*t*
  diagnostic approach to, 477, 477*f*
  direct oral anticoagulants for, 487*b*
  echocardiographic findings in, 487
  epidemiology and risk of, 476*t*
  epidemiology of, 482
  in HIV, 2318–2319, 2319*b*
  hormonal therapy and, 1630*b*
  interventional contrast pulmonary angiography of, 486
  in joint diseases, 1829–1830
  long-term complications of, 489–490
  magnetic resonance imaging of, 485
  pathobiology of, 482–483
  post-thrombotic syndrome caused by, 490
  in pregnancy, 1619*f*, 1622, 1623*b*, 1623*f*, 1624*t*
  prevention of, 491
  prognosis for, 489
  recurrent, 490
  of upper extremities, 490
  ventilation-perfusion lung scanning for, 484–485, 486*f*
Venous ulcers, 490
Ventilation, 657
  alveolar ventilation (Va), 640
  assessment of, 639
  dead space (Vd/Vt), 640
  measurement of, 640
  mechanical, 652
    assisted, 653
    negative-pressure ventilators, 653
    positive end-expiratory pressure, 653
    positive-pressure ventilators, 652
    pressure-controlled ventilation, 653
    volume-controlled ventilation, 653
  minute (V_E), 640
  for viral hemorrhagic fevers, 2269*b*
Ventilation-perfusion mismatch, in acute respiratory failure, 643
Ventilation-perfusion scanning, for venous thromboembolism, 484, 486*f*
Ventilator-associated pneumonia, 616*t*, 1862*t*, 1866
  antibacterial chemotherapy for, 1900
  Pseudomonas infections causing, 1969, 1970*b*
Ventilator-induced lung injury, 655, 655.*e1f*
Ventilatory control disorder, 534–537
Ventilatory maneuvers, for acute respiratory failure, 647*b*
Ventral epidural hematoma, 2392*f*
Ventral induction, disorders of, 2547
Ventral lateral preoptic nucleus, 2443.*e3f*
Ventral tegmental area, of brain, 142
Ventricular arrhythmias, 332, 333*f*
  catheter ablation of, 346
  causes of, 335–336
  clinical manifestations of, 334–335
  definition of, 332–340
  diagnosis of, 335–338
  epidemiology of, 333
  genetically inherited, 337
  management of, 384*b*
  pathobiology of, 333–334
  prognosis for, 340
  treatment of, 338*b*
Ventricular contractility, 226
Ventricular cysticerci, 2159
Ventricular empyema, 2511
Ventricular fibrillation (VF), 333*f*
  ACLS response to, 315*f*
  acute management of, 338*b*
  AED rapid response to cardiac arrests caused by, 314*t*
  definition of, 333
  diagnosis of, 313, 338
  late, 384*b*
  prognosis for, 340
  treatment of, 338*b*
Ventricular function
  diastolic, 239
  imaging of, 249
  systolic, 239
Ventricular septal defect (VSD), 347, 349–350
  diagnosis of, 349–350, 349
  exercise recommendations for, 355.*e2t*
  prognosis for, 350*b*
  treatment of, 350*b*
Ventricular tachycardia, 333.*e1f*, 336.*e1f*
  acute management of, 338*b*
  definition of, 332–333
  diagnosis of, 313, 335*t*
  differential diagnosis of, 335, 335*t*
  electrocardiographic parameters, 336*t*
  genetically acquired, treatment of, 338*b*
  iatrogenic, 338, 338*b*
  idiopathic, 336.*e1f*, 338*b*
  monomorphic, 333, 333*f*, 334*f*, 336*f*, 337*f*
  pleomorphic, 333
  polymorphic, 333, 334*f*
  post-myocardial infarction, 336
  prognosis for, 340
  pulseless, 315*f*
  surgery for, 347.*e1f*, 347
  sustained, 332
Ventriculitis, 2511
  cytomegalovirus, 2532*t*
Ventriculoperitoneal shunting, 1725*b*
VEPs. *See* Visual evoked potentials
Verapamil, 367*t*
  for acute coronary syndrome, 375*t*
  for hypertrophic cardiomyopathy, 282*b*
Verapamil IR, 451*t*
Verapamil SR, 451*t*
Verapamil-delayed-onset ER, 451*t*
Vericiguat, for heart failure with reduced left ventricular ejection fraction, 265*b*
Verner-Morrison syndrome. *See* VIPomas
Vero cell, vaccine, for traveler, 1886*t*
Verruca plana, 2242
Verrucae, 2699, 2741
Verruga peruana, 2002, 2003*b*, 2003*t*
Vertebral arteries, 2465
  anatomy of, 2455, 2457*f*
Vertebral fractures, 1642
Vertebral osteomyelitis, 1904, 1969
Vertebrobasilar insufficiency, 2645
Vertebroplasty, 1643*b*
Vertigo, 2371
  bedside tests for, 2646
  benign paroxysmal positional, 2644, 2645*f*, 2647*t*
Vertigo *(Continued)*
  caloric test for, 2646
  causes of, 2644–2645
  central, 2644
  central causes of, 2646
  description of, 2647*t*
  doll's eye test for, 2646
  evaluation of, 2644*f*
  head-thrust test for, 2646
  height, 2644
  hyperventilation and, 2646
  Meniere disease causing, 2645
  migraine and, 2645
  nystagmography of, 2646
  peripheral causes of, 2645–2646
  physiologic, 2644
  positional tests for, 2646
  post-traumatic, 2645
  prognosis for, 2647
  treatment of, 2647*b*, 2647*t*
  vascular insufficiency causing, 2645
  vestibular rehabilitation exercises for, 2647*b*
Very low calorie diets, 1467*b*
Very low density lipoproteins, 1405
Very severe aplastic anemia, 1125
VES-13. *See* Vulnerable Elders Survey
Vesicle, 2689*t*, 2696*f*
Vesicoureteral reflux, 791, 818–820, 819, 820*b*
Vesiculo-erosive skin disease, porphyrias and, 1432
Vesiculobullous diseases, 2716–2721, 2717*t*
  hypersensitivity reactions causing blisters, 2719
  immunologically mediated blistering diseases, 2716–2717
  infectious diseases causing blisters, 2720–2721
  intraepidermal blistering disorders, 2718
  metabolic disorders causing blisters, 2719
  mucous membrane pemphigoid, 2717, 2718*f*
  pemphigoid gestationis, 2717, 2717*f*
  subepidermal blistering disorders, 2717
Vespid. *See* Etoposide
Vestibular neuritis, 2644, 2647*t*
Vestibular rehabilitation exercises, 2647*b*
Vestibular schwannomas, 1314, 1314*b*, 1314*f*
Vestibular system, anatomy and physiology of, 2644
Vestibulo-ocular reflex, 2439, 2618
Vestibulospinal function, 2646
VEXAS syndrome. *See* Vacuoles, E1 ligase, X-linked, autoinflammatory, somatic syndrome
VF. *See* Ventricular fibrillation
VHL. *See* von Hippel-Lindau disease
Viagra (sildenafil), 364*b*
Vibegron, 824*t*
Vibration, 88*t*
Vibrio cholerae, 1955
  nontoxigenic, 1958
Vibrio infections, 1957–1958
  in travelers, 1889.*e1t*
Vibrio parahaemolyticus, 90, 1958
Vibrio vulnificus, 1958
Vicenza bleeding score, 1166
Vidaza. *See* Azacitidine
Video-assisted thoracoscopic surgery, 631
Video capsule endoscopy, 1345
VIG. *See* Vaccinia immune globulin
Vilazodone, for depression, 2340*t*
Vildagliptin, for type 2 diabetes mellitus, 1541*t*
Villous adenomas, 939, 1349
Villous atrophy, inflammation and, 935
Vinorelbine (Navelbine), 1215*t*
Vinyl chloride, 88*t*
Viokace, for exocrine pancreatic insufficiency, 975*t*
VIP. *See* Vasoactive intestinal peptide
Viperid bites, 708
VIPomas, 1561*t*, 1564, 1565*b*
Viral arthritis, 1807
Viral carcinogenesis, 1321
Viral conjunctivitis, 2604, 2605*f*
Viral encephalitis, 2531
  causes of, 2531*t*
  cerebrospinal fluid findings in, 2374*t*
  clinical manifestations of, 2531
  diagnosis of, 2531
  differential diagnosis of, 2532
  epidemiology of, 2531
  magnetic resonance imaging of, 2532
  pathobiology of, 2531
Viral encephalitis *(Continued)*
  prognosis for, 2532
  rabies and, 2534, 2535*b*
  spinal fluid analysis, 2532
  tests for, 2532*t*
  treatment of, 2532*b*
Viral hemorrhagic fevers, 99, 2264
  antiviral therapy for, 2269*b*
  bat-borne viruses, 2264
  clinical management of, 2269*b*
  clinical manifestations of, 99–100, 2267, 2268*t*
  contact tracing of, 2272
  definition of, 2264
  diagnosis of, 100, 2267
  differential diagnosis of, 2270*t*
  epidemiology of, 99, 2264
  human-to-human transmission of, 2266
  infection prevention and control in, 2272
  laboratory testing for, 2269, 2271*t*
  maintenance in nature, 2264
  mosquito-borne viruses, 2266
  nonspecific presentation of, 2268, 2272
  pathobiology of, 99, 2266
  pathogens that causes, 2264
  postexposure prophylaxis for, 2273
  in pregnancy, 2267, 2269*b*
  prevention of, 100, 2272
  prognosis of, 100, 2273
  reservoir for, 2273
  ribavirin therapy for, 2272*t*
  rodent-borne viruses, 2264
  sequelae of, 2273
  tick-borne viruses, 2266
  transmission to humans, 2264
  treatment of, 100*b*, 2269*b*
  vaccines for, 2272
  vector control for, 2273
  viruses causing, 99.*e1t*, 2265*t*
Viral hepatitis
  acute, 986
  characteristics of, 2270*t*
Viral infections, 2650, 2650*f*
  of skin, 2739*t*, 2741
Viral meningitis
  agents of, 2520*t*
  arboviruses causing, 2520
  cerebrospinal fluid findings in, 2374*t*, 2513*t*
  clinical manifestations of, 2520
  definition of, 2519
  differential diagnosis of, 2521
  enterovirus, 2520
  epidemiology of, 2519
  herpes simplex virus causing, 2521
  human immunodeficiency virus causing, 2521
  lymphocytic choriomeningitis causing, 2521
  pathobiology of, 2520
  polymerase chain reaction for, 2521
Viral myocarditis, 285
  clinical manifestations of, 285
  diagnosis of, 285–286
  prognosis for, 286
  specific causes of, 286
Viral pericarditis, 426*t*
Viral pneumonia, 607
Viral rhinitis, 2631
Viral vectors, 175
Virchow node, 1341
Viremia, zoster and, 2248
Viridans group streptococci, 415, 1919
Virilization, 1570*t*
Virilized female, biochemical evaluation of, 1575
Virologic failure, 2302–2303
Virtual colonoscopy, 1353
Viruses, health care-associated infections caused by, 1865
Visceral abscesses, glomerulonephritis with, 783
Visceral angioedema, 956
Visceral arterial aneurysms, 969
Visceral compartment, 527
Visceral larva migrans, 2174
  in travelers, 1889.*e1t*
Visceral leishmaniasis, 2116, 2132
  antigen-based tests for, 2132
  clinical manifestations of, 2132
  complex manifestations of, 2132
  diagnosis of, 2132
  in immunodeficient patients, 2132*b*
  serologic tests of, 2132
  in travelers, 1889.*e1t*
  treatment of, 2132*b*

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Visceral pain, 134, 135*t*
Visceral perception, increased, irritable bowel syndrome and, 893
Viscid mucus, clearance of, 558*b*
Viscosity, *e1t–e8t*
Vision
  change in, 2598, 2599*t*
  geriatric assessment of, 117
  loss of
    binocular, 2614–2615
    eye causing, 2615
    optic chiasm lesions causing, 2616
    optic nerve causing, 2615
    transient monocular, 2616*t*
  screening for, 55
Vismodegib (Erivedge), 1215*t*
Visual axis, 2596
Visual evoked potentials (VEPs)
  in multiple sclerosis, 2504
  pattern reversal, 2376.*e1f*, 2376
Visual fields, 2615, 2615*f*
Visual function disorders, 2409, 2410*f*
Visual pathways, lesions of, 2614–2615
Visual radiations, 2616
Visual-sensitive seizures, 2433
Visual system diseases, 2596–2614
  amblyopia, 2598
  anatomy of, 2597*f*
  astigmatism, 2598
  clinical manifestations of, 2597
  color vision change, 2598
  common clinical conditions of, 2597–2604
  conjunctivitis, 2600
  corneal abrasion, 2602
  diplopia, 2598
  dry eyes, 2602, 2603*f*
  endophthalmitis, 2604
  esotropia, 2598
  excessive tearing, 2599
  exotropia, 2598
  floaters, 2599
  foreign body sensation, 2599, 2600*f*
  functional evaluation of, 2597, 2597*f*, 2597*t*, 2597.*e1f*
  halos around lights, 2599
  hyperopia, 2598
  hyphema, 2603, 2604*f*
  keratoconus, 2598
  leukocoria, 2600, 2601*t*
  myopia, 2597
  night blindness, 2599
  ocular surface abnormalities, 2602–2604
  pain, 2598, 2599*t*
  photophobia, 2599
  photopsia, 2599
  pinguecula, 2602, 2603*f*
  presbyopia, 2598
  proptosis, 2600, 2600*f*
  pterygium, 2602, 2603*f*
  ptosis, 2600, 2600*f*
  recurrent corneal erosions, 2602
  red eye, 2599, 2599*t*
  strabismus, 2598
  uveitis, 2604
Vital capacity (VC), 530
Vital signs
  abnormal
    approach to patient with, 32–35
    differential diagnosis, 34
    multiple, 34
    in patients who appear to be ill, 33–34, 34*t*
    in patients who complain of systemic illness but do not appear to be very ill, 33
    in patients without systemic complaints, 33
    requiring rapid evaluation, 33*t*
    single, 34
    that require urgent evaluation, 34*t*
    treatment options, 34
  for acute poisoning, 682
  in asthma, 539
  as health measures, 40
  in heart failure, 257
  importance of, 32, 32*t*
  measurement of, 29
  measuring, 33
  normal ranges for, 32*t*
  panic ranges for, 32*t*
  predictive value, 32
  role of, 33–35, 33*t*
  as symptoms, 32
Vital statistics, of adolescent, 110
Vitamin(s)
  fat-soluble, 1451
  for inborn errors of metabolism, 1401*b*
  as supplements, 56, 155
  water-soluble, 1451
Vitamin A, *e1t–e8t*
  characteristics of, 1453*t*
  deficiency of, 1453*t*, 2222*b*, 2538*t*, 2542
  for malabsorption, 937*t*
  toxicity, 2541*t*
Vitamin B_1, *e1t–e8t*
  characteristics of, 1453*t*
  deficiency of, 1453*t*, 2538*t*, 2578
Vitamin B_2, *e1t–e8t*
  characteristics of, 1453*t*
  deficiency of, 1453*t*, 2541
Vitamin B_3
  characteristics of, 1453*t*
  deficiency of, 1453*t*, 2538*t*, 2541
  toxicity, 2541*t*
Vitamin B_5, deficiency of, 2538*t*, 2541
Vitamin B_6, *e1t–e8t*, 1427*b*
  characteristics of, 1453*t*
  deficiency, 1453*t*
  deficiency of, 2538*t*, 2540–2541
  toxicity, 2541*t*
Vitamin B_{12}, *e1t–e8t*, 1427*b*
  characteristics of, 1453*t*
  deficiency, 1453*t*
  deficiency of, 2538*t*, 2539
  for malabsorption, 937*t*
Vitamin C, *e1t–e8t*
  characteristics of, 1453*t*
  deficiency, 1453*t*
Vitamin D
  characteristics of, 1453*t*
  deficiency of, 1453*t*, 2538*t*, 2541–2542, 2542*b*
    causes of, 2541
    characteristics of, 2538*t*
    in HIV, 2318
    osteomalacia and, 1647, 1647*t*, 1650*b*, 1650*t*, 1651*t*
  1,25-dihydroxy, total, *e1t–e8t*
  endocrine diseases caused by, 1475*t*
  function of, 2541
  25-hydroxy, total, *e1t–e8t*
  for malabsorption, 937*t*
  for osteoporosis, 1639*b*, 1643*b*
  toxicity, 2541*t*
  in women, 1607
Vitamin D_3, excretion of, 732, 732.*e1f*
Vitamin deficiencies
  clinical manifestations of, 2537
  fat-soluble vitamins, 2541–2542
  thiamine, 2537, 2538*t*
  types of, 2538*t*
  water-soluble vitamins, 2537–2541
Vitamin E, *e1t–e8t*
  characteristics of, 1453*t*
  deficiency of, 1453*t*, 2538*t*, 2541, 2541*b*
  for malabsorption, 937*t*
  for nonalcoholic fatty liver disease, 1034*b*
  toxicity, 2541*t*
Vitamin K, 999–1000
  for acute poisoning, 693*t*
  characteristics of, 1453*t*
  deficiency of, 1198, 1453*t*, 2538*t*, 2542
  for malabsorption, 937*t*
Vitamin K antagonists, 503–504
  adverse effects of, 504
  anticoagulant effect of, reversing, 504, 504*t*
  dosage and monitoring of, 502*t*, 503–504, 504*t*
Vitamin K-dependent coagulation, deficiencies of, 1193
Vitamin K-dependent coagulation factors, 1167*t*
Vitamin K epoxide reductase C1, 503
Vitiligo, 2743, 2743*f*, 2745*f*
Vitrakvi. *See* Larotrectinib
Vitreous, 2596
Vitronectin, 200*t*
V(D)J recombination, defects of, 1676.*e3t*, 1678
VKORC1 gene, 160*t*
Vocal cord dysfunction syndrome, distinguishing features of, 515*t*
Vocal tremor, 2652
Voclosporin (Lupkynis), for total knee arthroplasty, 1830.*e1t*
Vogt-Koyanagi-Harada syndrome, 2524
Volanesorsen, for hypertriglyceridemia, 1414*b*
Volatile acid, 753
Volatile anesthetics, 2670
Volume-controlled ventilation, 653
Volume depletion
  management of, 384*b*
  metabolic alkalosis with, 762
Volume expansion, metabolic alkalosis with, 763
Volume-limited ventilation, 653
Volume regulation
  osmotic and, interaction of, 1499
  vasopressin and pressure and, 1499
Voluntary active euthanasia, 8*t*
Volvulus, 951
  clinical manifestations of, 951
  colonic, 952*b*
  diagnosis of, 951, 952*f*
  prognosis of, 951*b*–952*b*
  treatment of, 951*b*
Vomiting. *See also* Nausea and vomiting
  acute pancreatitis and, 969, 970
  in cancer, management of, 1232*b*
  characteristics of, 888
  in enteral nutrition, 1449
von Gierke disease, 1417*t*
von Hippel-Lindau disease (VHL), 1530, 1558, 1559*t*, 2552–2553, 2553*b*
von Hippel-Lindau syndrome, 809*t*, 814, 814*b*, 1250*t*
von Recklinghausen disease, 583
von Willebrand disease, 1180–1186, 1189*t*, 1191
  acquired, 1184, 1184*b*
  classification of, 1180*t*
  clinical assessment of, 1181, 1181*f*, 1182*t*
  clinical manifestations of, 1180–1181
  definition of, 1180–1184
  desmopressin for, 1180, 1182*t*
  diagnosis of, 1180*t*, 1181–1183
  epidemiology of, 1180
  factor replacement therapy for, 1183*t*
  laboratory evaluation of, 1181–1183, 1181*f*
  pathobiology of, 1180
  treatment of, 1183*b*
von Willebrand factor, 1180, 1183*t*
von Willebrand factor activity, *e8t–e9t*
von Willebrand factor antigen, *e8t–e9t*
Vorapaxar, 506*t*, 508
Voriconazole, *e10t–e11t*, 2076
  adverse effects of, 2076
  for aspergillosis, 2096
  for candidiasis, 2092*b*
  for chromomycosis, 2111*b*
  for cryptococcosis, 2088*b*
  drug interactions of, 2076
  formulations and pharmacology of, 2076
  for hepatosplenic candidiasis, 1024*b*
  indications and dosage of, 2075*t*, 2076
  for mycoses, 2076
  for paracoccidioidomycosis, 2087*b*
Vortioxetine, for depression, 2340*t*
Votrient. *See* Pazopanib
Voxelotor, for sickle cell disease, 1116*t*
Voxilaprevir, 2182*t*
VSD. *See* Ventricular septal defect
VSPs. *See* Variant-specific proteins
VT. *See* Ventricular tachycardia
VTE. *See* Venous thromboembolism
Vulnerability, in older adults, 122, 123*f*
Vulnerable Elders Survey (VES-13), in older adults, 123*t*
Vulvovaginal candidiasis, 1882
Vulvovaginitis, 2090
Vumerity. *See* Diroximel fumarate

W

Waddling gait, 2373*t*
Waist circumference, 1466
Wakefulness, 2443, 2443.*e1f*, 2444*t*
Wakefulness test, 2444
Waldenström macroglobulinemia, 1088, 1303, 2713–2714
  clinical manifestations of, 1303
  diagnosis of, 1303
  diagnostic criteria of, 1303
  differential diagnosis of, 1303
  laboratory evaluation of, 1303
  prognosis for, 1303*b*
  treatment of, 1303*b*
Walking pneumonia, 2006
Wallenberg syndrome, 2465.*e1f*
Wandering atrial pacemaker, 322, 323*f*
Warfarin, *e10t–e11t*, 502*t*, 503, 504*t*
  anticoagulation uses of, 487*b*
  for hypercoagulable states, 477, 478*b*
  in nephrotic syndrome, 777*b*
  parenteral anticoagulation after, 487*b*
  for portal vein thrombosis, 968*b*
  in pregnancy, 487*b*, 487*t*
  skin necrosis, 2716
  for vitamin K deficiency, 1198
Warfarin-induced skin necrosis, 478*b*, 478*f*
Warm autoimmune hemolytic anemia, 1087, 1089*t*
Warm sitz baths, for chronic prostatitis/chronic pelvic pain syndrome, 825*b*
Warthin tumor, 2625
Warts, 2713, 2713*f*, 2741
  anal, 982, 982*b*, 982*f*
  genital, 2242
  human papillomavirus causing, 2242
  plantar, 2242, 2242*f*
Warty lesions, 2729–2730, 2731*f*
WASP. *See* Wiskott-Aldrich syndrome protein
Wasting, 1445
Water
  hazards, 87
  imbalances in, 724
Water-based exercises, for osteoarthritis, 1741*t*
Water-based lubricants, for HIV transmission prevention, 2298
Water-borne infectious diarrhea, 924
Water-bottle sign, 245, 246*f*
Water content, regulation of, 730, 732*f*
Water disinfection, for *Legionella*, 1999
Water disorders, 733, 733*t*
Water diuresis, 743*t*
Water-soluble vitamins, 935, 1450, 1451, 1453*t*
Waterhouse-Friderichsen syndrome, 1944*b*
Watery diarrhea, 760, 924
  laboratory tests for, 930, 931*t*
WBC. *See* White blood cell count
WBC casts, 722
Weakness
  diaphragmatic, 619
  neurologic causes of, 2371, 2371*t*
  postoperative, 2674
Weapons of mass destruction, 96, 96*t*. *See also* Bioterrorism
Weaver's bottom. *See* Ischial/ischiogluteal bursitis
Weber syndrome, 2465.*e1f*
Weber test, 2641
Webs, esophageal, 910, 910*f*
Wegener granulomatosis, 727. *See also* Granulomatosis with polyangiitis
Weibel-Palade bodies, 1180
Weight loss
  causes of, 1447–1448
  energy intake reduction for, 1467*b*
  goals for, 1609
  hypogonadotropic hypogonadism and, 1584
  involuntary, 860
    causes of, 860*t*
    diagnosis of, 861, 862*f*
    in older adults, 117
    signs and symptoms of, 852*t*
Weil disease, 2030
Wellcovorin. *See* Leucovorin calcium
Wellness, in occupational and environmental medicine, 87
Wells syndrome. *See* Eosinophilic cellulitis
Wenckebach AV block. *See* Mobitz type I AV block
Werdnig-Hoffman disease, 2565
Wernicke encephalopathy, 2537, 2539*b*, 2539*f*, 2545
West African sleeping sickness, 2124
West Nile encephalitis, 2532*t*
West Nile virus, 1203, 2276*t*, 2281, 2281*f*, 2282*b*
  in travelers, 1889.*e1t*
Western Africa, HIV/AIDS in, 2289, 2289.*e1f*
Western equine encephalitis virus, 2276*t*, 2283, 2283*b*
Western Europe, HIV/AIDS in, 2289, 2289.*e1f*, 2290.*e1f*
Wet age-related macular degeneration, 2608, 2609*f*
Wet-to-dry dressings, for skin diseases, 2697
Wheat gluten, alcohol-soluble protein fraction of, 935
Wheezes, 512, 512*t*, 513, 513*b*, 513.*e1f*, 515*t*, 539, 557

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WHIM syndrome, 1145
Whiplash, 2395
Whipple disease, 417*t*, 937, 1821, 2069–2071
  classical, 2070, 2070*t*
  clinical manifestations of, 2069–2070
  definition of, 2069–2071
  diagnosis of, 2070, 2070*f*, 2071*f*, 2072*f*
  epidemiology of, 2069
  pathobiology of, 2069
  pathogen that causes, 2069
  prevention of, 2071
  prognosis of, 2071
  treatment for, 2070*b*
Whisper test, 117
White blood cell count (WBC), ranges of, 1140
White coat hypertension, 447
White heads, 2722
White superficial onychomycosis, 2754, 2754*f*
WHO. *See* World Health Organization
WHO/ISUP. *See* World Health Organization/International Society of Urologic Pathology
Whole blood, HIV transmission through, 2299
Whole-body exposure syndromes, treatment of, 94*b*, 94*f*
Whole bowel irrigation, for acute poisoning, 691*b*
Whole-lung lavage, for pulmonary alveolar proteinosis, 567*b*, 567.*e1f*
Whole pancreas transplantation, for type 1 diabetes mellitus, 1537*b*
Whooping cough
  chemoprophylaxis for, 1996
  clinical manifestations of, 1995
  complications of, 1995
  definition of, 1994–1996
  diagnosis of, 1995
  epidemiology of, 1994–1995
  immunizations for, 1996
  pathobiology of, 1995
  pathogens that cause, 1994
  prevention of, 1996
  prognosis for, 1996
  treatment of, 1995*b*
Widow spiders, envenomation of, 710
Wiggers diagram, 225.*e1f*
Williams syndrome, 348, 1658
Wilson disease, 816*t*, 993, 999, 1398*t*, 1436–1437
  clinical manifestations of, 1436–1437, 1436*f*, 1437*f*
  definition of, 1436–1437
  diagnosis of, 1437
  dystonia *versus*, 2493
  epidemiology of, 1436
  pathobiology of, 1436
  in pregnancy, 1625*t*
  prognosis of, 1437
  treatment of, 1437*b*
Wiskott-Aldrich syndrome, 1071, 1144, 1179, 1678–1679, 1678*b*, 1679*t*
Wiskott-Aldrich syndrome protein (WASP), 1736–1737
Withdrawal of life support, 638, 638*t*, 638.*e1t*
WNK kinases, 746
Wnt signaling pathway, 1640
Wohlfart-Kugelberg-Welander disease, 2565
Wolbachia bacteria, 2061–2062
Wolff-Parkinson-White syndrome, 229, 306, 326
Women's health, 1606–1610
  alcohol use, 1609
  anxiety disorders, 1608*t*, 1609
  cancer, 1607
  cardiovascular disease, 1606
Women's health *(Continued)*
  depression, 1608*t*, 1609
  health disparities in, 1606
  human immunodeficiency virus, 1609
  incontinence, 1609
  lifespan groups for, 1606, 1606*t*
  medications for, 1608*t*
  morbidity causes, 1609
  mortality causes, 1606
  obesity, 1609
  osteoarthritis, 1609
  osteoporosis, 1607
  risks for atherosclerotic cardiovascular disease, 221.*e1f*
  severe acute respiratory syndrome coronavirus 2, 1610
  smoking, 1609
  substance use, 1609
  type 2 diabetes, 1607
  urinary tract infection in, prophylactic regimens for, 1877*t*
Women's Health Initiative, 1630*b*
Wood alcohol, 760
Work-exacerbated asthma, 586
  clinical manifestations of, 586–588
  diagnosis of, 586*b*
  epidemiology of, 586
  treatment of, 586*b*
Work of breathing, 641, 641*f*
Work-related asthma, 585
  clinical evaluation of, 587*f*
  management of, 587*f*
  occupations at risk for, 586*t*
Work-related disability, 85
Workers' compensation, 85
World Health Organization (WHO)
  classification of Hodgkin lymphoma, 1290*t*
  mastocytosis
    classification of, 1699*t*
    disease categories, 1702, 1702*t*
  on myelodysplastic syndromes, 1252
  non-Hodgkin lymphoma, 1279
  rubella, 2224
  sexually transmitted infection estimates, 1879
  on tuberculosis, 2032
World Health Organization/International Society of Urologic Pathology (WHO/ISUP), 1366
Wound
  botulism of, 1927
  infection
    Acinetobacter causing, 1973
    in endoscopy, 876*t*
  tetanus prophylaxis in, 1929*t*
Wrist
  disorders of, 1745
  fractures of, osteoporosis and, 1607
  rheumatoid arthritis of, 1751, 1753*f*
  surgical treatment of, 1828
Wuchereria bancrofti, 2176

X

X chromosome mutation, in premature ovarian failure, 1600
X-inactivation, 162
X-linked agammaglobulinemia, 1681*t*
X-linked hypophosphatemia, 1648
X-linked ichthyosis, 2687.*e3t*
X-linked lymphoproliferative syndrome, 2254
X-linked proliferative disorder (XLP), 1684
X-linked protoporphyria (XLP), 1428*t*, 1433
X-linked severe combined immunodeficiency, 175, 1676.*e3t*, 1678
X-linked thrombophilia, 476
Xalkori. *See* Crizotinib
Xanthelasma, 987, 2692*t*
Xanthine oxidase, 1810
Xanthogranuloma family, 1157–1158, 1158*b*
Xanthogranulomatous pyelonephritis, 791
Xanthoma disseminatum, 1157
Xanthomas, 216, 216.*e1f*, 1823
Xeljanz. *See* Tofacitinib
Xeloda. *See* Capecitabine
XEN402, 471*b*
Xenografts, 203
Xenopsylla cheopis, 1988
Xenotransplantation, of genetically modified animals, 172
Xerocytosis, 1097
Xeroderma pigmentosum, 1250*t*
Xerostomia, 2626
Xgeva. *See* Denosumab
Xpovio. *See* Selinexor
Xtandi. *See* Enzalutamide
XX male syndrome, 1574
XY female syndromes, 1574

Y

Yatapoxvirus, 2237, 2239
Yaws, 2021
Yellow fever, 99.*e1t*, 2275*t*, 2276
  clinical manifestations of, 2277
  definition of, 2276
  description of, 2265*t*, 2266, 2268*t*
  diagnosis of, 2277
  epidemiology of, 2276
  immunization for, 66*t*, 83
  pathobiology of, 2277
  treatment of, 2277*b*
  vaccine, for traveler, 1886*t*, 1887
Yellow nail syndrome, 2753, 2753*f*
Yersinia enterocolitica, 1993
Yersinia frederiksenii, 1988
Yersinia intermedia, 1988
Yersinia pestis, 1150, 1988, 1988*f*, 2065*t*. *See also* Plague
Yersinia pseudotuberculosis, 1993
Yersiniosis, 1993–1994
  clinical manifestations of, 1993–1994
  definition of, 1993
  diagnosis of, 1994
  epidemiology of, 1993
  pathobiology of, 1993
  pathogens that cause, 1993
  prevention of, 1994
  prognosis of, 1994
  treatment for, 1994*b*
Yervoy. *See* Ipilimumab
Yoga, 154
  for osteoarthritis, 1741*t*
Yondelis. *See* Trabectedin
Young modulus, 1720

Z

Z discs, 2580
Zafirlukast, 541*b*
Zaleplon, 2344*t*, 2452*t*
Zanamivir, for influenza, 2189, 2189*t*, 2202*b*, 2203*t*
Zanubrutinib, for chronic lymphocytic leukemia, 1269*t*
ZAP-70 deficiency, 1678, 1678.*e1t*
Zeaxanthin, 1452
Zejula. *See* Niraparib
Zelboraf. *See* Vemurafenib
Zenker diverticulum, 909, 909*f*
Zenpep, for exocrine pancreatic insufficiency, 975*t*
Zeposia. *See* Ozanimod
Zepzelca. *See* Lurbinectedin
Zidovudine, 2301*t*, 2303
  toxic myopathy caused by, 2313
Zika virus, 1203, 2065*t*, 2275*t*, 2278, 2278*b*, 2571
  in travelers, 1888, 1890*t*
Zileuton, 541*b*
Zinc, *e1t–e8t*, 1457*t*
  for malabsorption, 937*t*
  myelopathy and, 101*t*, 106, 107*b*
  toxicity, 88*t*
Zinc finger nucleases, 178
Zinc oxide, for pruritus ani, 980*b*
Zinc protoporphyrin, *e1t–e8t*
Zinc supplementation, for infectious gastroenteritis, 2263*b*
Zinecard. *See* Dexrazoxane
Ziprasidone, for psychotic disorders, 2346*t*
Zirconium cyclosilicate, for hyperkalemia, 751*b*
Zoledronate, for osteoporosis, 1644*t*
Zoledronic acid (Zometa), 1215*t*
  jaw osteonecrosis caused by, 1643*b*
  for osteoporosis, 1643*b*
  for Paget disease, 1664*t*
Zollinger-Ellison syndrome, 763, 1561*t*, 1562
  clinical manifestations of, 1562
  description of, 917
  diagnosis of, 918, 1563
  diarrhea associated with, 917
  differential diagnosis of, 1563
  pathobiology of, 1562
  prognosis of, 1563
  treatment of, 1563*b*
Zolmitriptan, 2380*t*
Zolpidem, 2344*t*, 2363, 2452*t*
Zometa. *See* Zoledronic acid
Zonisamide, *e10t–e11t*
  for myoclonus, 2495*b*
  for seizures, 2434*t*
Zoonoses, 2063–2066
  clinical manifestations of, 2064
  definition of, 2063–2066
  diagnosis of, 2065
  emerged and reemerging, examples of, 2065*t*
  epidemiology and pathobiology of, 2063–2064, 2064*f*, 2066*f*
  prevention of, 2065–2066
  prognosis of, 2066
  transmission of, 2064
  treatment of, 2065*b*
Zoonotic endocarditis, 417*b*
Zoonotic filarial infections, 2180
Zoonotic influenza, 2199
Zoonotic malaria, 2065*t*
Zoonotic spillover, 2063–2064
Zoster, 2248–2249, 2249*f*
  diagnosis of, 2249
  epidemiology of, 2248
  neuropathies associated with, 2578
  pathobiology of, 2248
  prevention of, 2250
  prophylaxis for, 2309*t*
  treatment of, 2249*b*
Zoster vasculopathy, zoster and, 2248
Zydelig. *See* Idelalisib
Zytiga. *See* Abiraterone acetate

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